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Virtual, Nurse-Led Early Primary Palliative Care Intervention (ELICIT) for Community-Dwelling Older Adults With Cognitive Impairment: Protocol for a Randomized Controlled Trial

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Abstract

Background: Although dementia is a serious illness that progresses over many years, little is known about the primary palliative care needs of individuals who have it, especially those living in the community.

Objective: This trial aims to test the impact of a virtual, nurse-led early primary palliative care intervention (ELICIT) on older adults living in the community who are chronically ill and have a diagnosis of cognitive impairment or are at risk of it.

Methods: A total of 200 community-dwelling older adults who were chronically ill and had varying degrees of cognitive impairment were recruited and randomized to either usual care or usual care + a virtual, nurse-led ELICIT. For both arms, we will track the number of participants who (1) report supportive care needs to the blinded evaluators and (2) complete conversations on goals of care and document advance directives and the Physician Orders for Life-Sustaining Treatment form in the electronic health record. We will also track their end-of-life resource use and the percentage of participants who receive goal-concordant care. Changes in Edmonton Symptom Assessment Scale, Patient Activation Measure, and Quality of Life in Alzheimer's Disease scores will be tracked and analyzed.

Results: As of October 2025, we have recruited 200 participants. We are following all study participants on an ongoing basis to determine whether they received goal-concordant care at the end of life and their resource use patterns. We hypothesize that, compared to the usual care arm, more participants in the intervention arm will (1) express supportive care needs to the blinded evaluators, (2) complete goals of care conversations, document advance care planning, and (3) have higher levels of goal-concordant care and lower end-of-life resource use.

Conclusions: The identification of the primary palliative care needs of community-dwelling older adults who are chronically ill and have various levels of cognitive impairment will help refine the intervention and enable trained nurses to provide virtual early primary palliative care within the scope of nursing.

Trial Registration: ClinicalTrials.gov NCT03881579; https://www.clinicaltrials.gov/study/NCT03881579

International Registered Report Identifier (IRRID): DERR1-10.2196/75082

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KEYWORDS

primary palliative care; goals of care; advance care planning; serious illness; supportive care; nursing; cognitive impairment; dementia; MCI

Introduction

Background

The World Health Organization has declared dementia a public health crisis and issued a call for global nations to make dementia an international public health priority [1]. Although dementia is a serious illness that progresses over many years, little is known about the everyday suffering endured over time by patients in the early stages of the disease, as most research focuses on patients who are already institutionalized and at the end of life. However, patients early in the dementia trajectory are beset with distressing symptoms. An estimated 85% [2] of persons with dementia live in the community (eg, private residences or non–nursing home residential care facilities) with unmet needs [3]. Proactive, patient-centered primary palliative care will likely benefit early-stage patients living in the community. Implementing early palliative care (EPC) will facilitate ongoing assessment and management of the distressing symptoms experienced by persons with dementia from very early in the illness trajectory, result in identification and

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management of primary palliative care needs, and facilitate timely advance care planning [4].

Preliminary Studies Conducted in Shaping the Design of This Proposed Trial

Preliminary Study 1

Working with participants and families, we co-designed the What Matters Most letter advance directive (WMM) in a simple letter format written at a fifth-grade reading level in multiple languages (English, Chinese, Hindi, Russian, Spanish, Tagalog, Vietnamese, and Urdu). The WMM was then tested and validated through a large, randomized controlled trial (NCT02799537) [5]. Participants reported that this advance directive was easier to read, better reflected what mattered most to them, helped stimulate their thinking about the types of treatments they wanted at the end of life, and allowed them to describe how they made medical decisions in their family.

Preliminary Study 2

We demonstrated that the WMM facilitates patient-proxy collaboration in completing advance directives [6]. The participants and their proxies used the WMM to identify their points of agreement and disagreement about the participants' choices for end-of-life care. When the participants and proxies collaborated in completing the participants' WMM, they were able to identify their viewpoints and arrive at a consensus after discussing the items in the WMM. Notably, a structured participant-proxy discussion using the WMM helped them reconcile discordance, most often in favor of a participant's original wishes. All participants and their proxies reported that they very much preferred the WMM to traditional advance directive documents.

Health care providers too preferred the WMM over traditional advance directives [6]. We conducted a prospective cluster randomized controlled trial with 5 general medicine ward teams at Stanford Hospital in 2016. The WMM was very helpful to the physicians, who were better able to understand their participants' life goals and values and improve shared decision-making regarding goals of care and advance care planning. While this was important for all patients with chronic and serious illnesses, it was especially important for patients with cognitive impairment, who should complete advance care planning and provide anticipatory guidance while they still have the capacity to make informed decisions. These efforts are essential to ensure that their future care aligns with their values and goals.

Preliminary Study 3

To provide preference-sensitive care, it is important to routinely inquire about participants' bucket lists and discuss the impact of their medical treatments on their life goals. We conducted a study with 3016 patients and identified 6 common themes: the desire to travel (78.5%), accomplish a personal goal (78.3%), achieve specific life milestones (51%), spend quality time with friends and family (16.7%), achieve financial stability (24.3%), and do a daring activity (15%) [7]. This study resulted in a simple life goal list tool that can be used to engage patients in their health care decision-making.

Trial Objectives and Purpose

The aim of this study is to test the impact of a virtual, nurse-led early primary palliative care intervention (ELICIT) on older adults living in the community who are chronically ill and have a diagnosis of cognitive impairment or who are at risk of it. We hypothesize that, compared to the usual care (UC) arm, more participants in the intervention arm will (1) express supportive care needs to the blinded evaluators, (2) complete conversations on goals of care and advance care planning documentation, and (3) have lower end-of-life resource use (hospital admissions and days and emergency visits) and higher levels of goal-concordant care.

Methods

Study Design

Overview

This study aimed to recruit 200 community-dwelling older adults (Figure 1) who were chronically ill and at risk of cognitive impairment or already had it and had undergone a full assessment by a multidisciplinary neurology team. They were randomized (100 participants in each arm) to UC or UC + a virtual EPC intervention delivered by a nurse over a 12-month period.

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Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram.

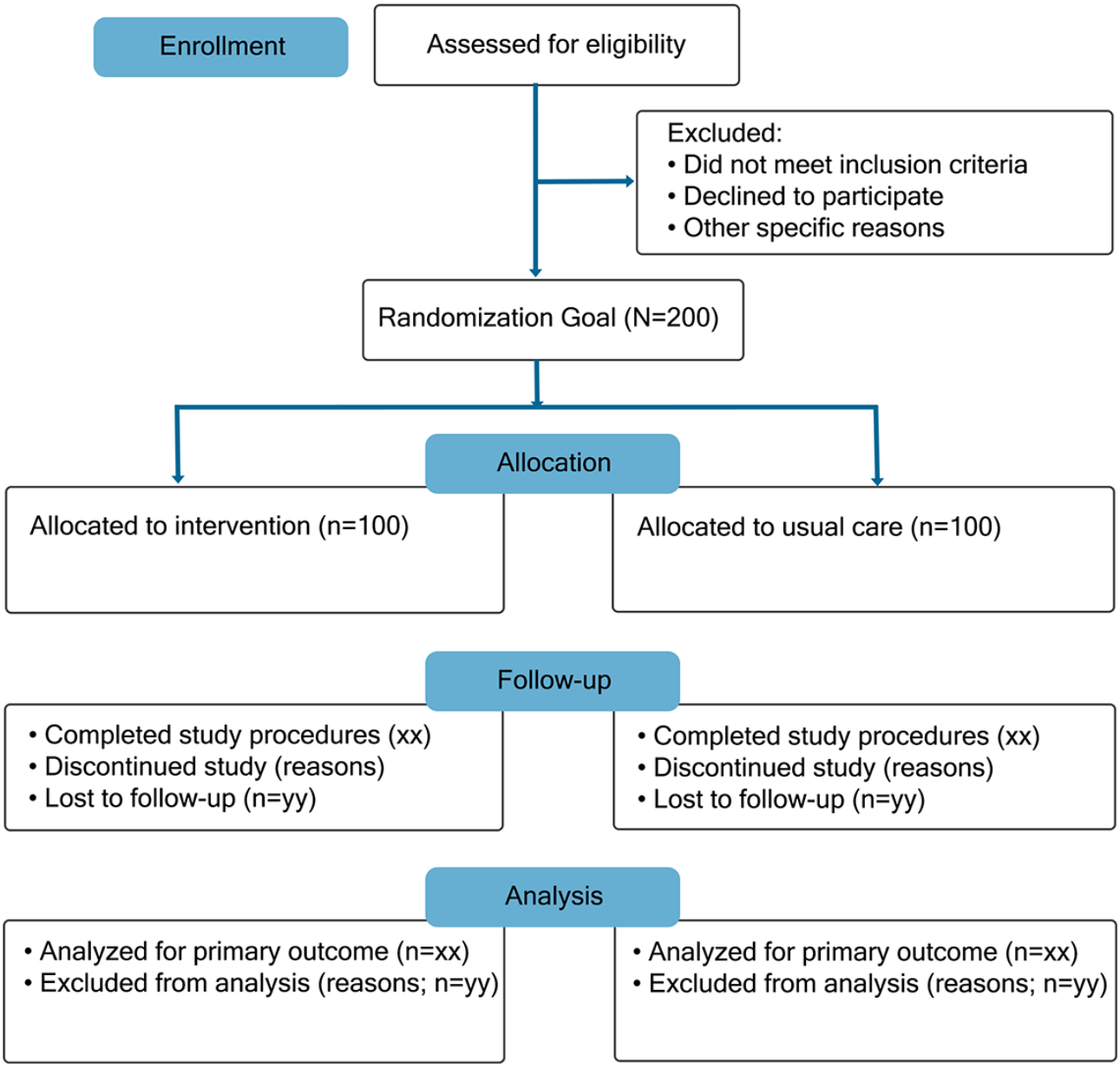

Impact of the COVID-19 Pandemic and Study Redesign

This study was originally designed to test the impact of an in-person nurse intervention to be delivered to the participants at their homes. Just as we were launching the study, the COVID-19 pandemic started in 2020, and the shelter-in-place orders were imposed. The study team had to adapt our study design to be able to proceed with the trial under the constraints imposed by COVID-19.

The following factors were key in shaping the study redesign:

1. All in-person research visits and face-to-face encounters were suspended due to the pandemic. Therefore, we had to change the study design to make it a virtual study.
2. In redesigning our study, we had to account for the technical challenges that our study participants (older adults) faced. In 2020, many older adults did not know how to participate in video encounters. We had to arrange for routine technical assistance before every encounter for participants who needed it.
3. We piloted the study survey outcome measures virtually. As the measures had Likert-scale responses with some reverse-worded items, it was challenging for the participants to respond over video or phone. On the basis of pilot participant feedback, the Likert measures became secondary outcome measures.
4. Originally, we wanted to observe the dyadic interactions between the participants and their care partners in person and track the caregivers' Zarit Burden Interview scores [8] over time. However, many of the caregivers were sheltered in place due to COVID-19 and not able to live with the participants. Due to COVID-19, many care partners were not available, and we could not track dyadic interactions.

Final Study Design

We converted the in-person nurse intervention to a virtual intervention.

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Control Condition (UC)

Participants randomized to the UC arm received care from their primary care provider (PCP) and their care team. In this case, UC refers to the standard or routine outpatient care that participants received from their primary care team. This included any appointments, consultations, and procedures that were standard for outpatient primary care.

Intervention Arm (EPC)

Participants in the intervention arm received UC + a virtual, nurse-led ELICIT.

Training of Study Nurses to Conduct the Virtual Intervention

All study nurses were trained using a training program provided through a learning management system followed by immersive simulation training with standardized patients. The feedback of the standardized patients and the preceptor was used to refine their skills. Ongoing training for skill building and education was provided through nurse peer support, weekly meetings with the study physician, and the weekly trial team meetings.

Four Components of Primary Palliative Care for the Nurse-Led Intervention

The nurse-led intervention was designed to focus on the four key components of primary palliative care: (1) assessing and palliating distressing physical symptoms; (2) assessing and supporting psychological, social, cultural, and spiritual aspects of care; (3) establishing goals of care, identifying a surrogate decision-maker, and completing advance care planning documentation; and (4) providing care coordination support.

The Intervention

It is important to note that the nurses delivering the intervention were registered nurses, and the care they provided was within their scope of practice. The nurses assessed the participants using several tools (Multimedia Appendix 1 [6-16]).

The intervention comprised 12 virtual encounters (1 per month) with the participants over a 1-year period, including an initial encounter (session 1) followed by 11 monthly encounters (sessions 2-12).

In session 1, a complete assessment of the participants' early primary palliative care needs using a set of measures (Table 1) and an assessment of participants' preferences for care were completed. During this session, the nurses introduced advance care planning and the concept of goals of care. The nurses worked with the participants (and their caregivers if present) to create a list of all the issues they needed help with.

Table . Protocol used by the nurses to deliver the early primary palliative care intervention over a 12-month period.

	Session type and duration	Agenda and measures
Session 1	Secure initial video encounter for up to 2 hours	• Conduct intervention visit and assess the participant using the following measures: Distress Thermometer [1], Katz Activities of Daily Living scale [2], spiritual assessment exploratory questions, social assessment exploratory questions, pain assessment, and depression assessment (Geriatric Depression Scale) • Introduction, advance care planning, and discussion on goals of care: life goal list [7], What Matters Most letter advance directive [6], and POLST[a] [5]
Sessions 2-11	Secure monthly video or audio encounter (based on participant preference) for up to 1 hour	• Follow up on supportive care needs (if any in the previous months), administer the Distress Thermometer and pain assessment, and assess for changes in health condition since the last visit • Follow up on goals of care and advance care planning • Schedule follow-up visit for the following month
Study exit (conducted at session 12)	Secure video or audio encounter (based on participant preference)	• Review and summarize the intervention encounters • Provide the study team's contact information for any follow-up

[a]POLST: Physician Orders for Life-Sustaining Treatment.

After session 1, the nurse presented the participant information and preferences to the study palliative care physician and worked to craft a personalized care plan based on the participants' needs and expressed wishes.

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In sessions 2 to 11, the nurse reviewed the participants' situation over the previous month and identified any concerns. They completed the Distress Thermometer and pain assessment, used these to explore any underlying issues to be palliated, and discussed those with the study palliative care physician. The study nurses worked with the PCP of each participant to implement the early primary palliative care plan. For example, if the participant reported pain and needed any medications, the study nurse would first consult with the study palliative care physician and then work with the participant to craft a personalized care plan. If the participant and their care partner wanted to contact their PCP, they could do so themselves. If the participant or caregiver wanted the study nurse to contact their PCP on their behalf, the nurse did so. All medical therapies could be prescribed by the individual participants' PCPs. The nurse continued the discussion about goals of care and advance care planning and helped complete the documentation. If the participant was interested, the nurse discussed the Physician Orders for Life-Sustaining Treatment (POLST) form choices with the participant and helped them identify their preferences. The participant was encouraged to discuss their goals of care with their PCP and finalize their choices. Once the participant and their PCP signed the POLST form, it was uploaded into the electronic medical record, and the original was sent to the participant to post on their refrigerator.

At the end of each encounter, the nurse worked with the participants to identify any issues that needed attention and make plans for follow-up in the next few days. The nurse also scheduled the date for the following month's session.

On the last follow-up visit (session 12), the nurse reviewed the intervention encounters over the previous year and summarized the issues identified (if any). They provided the study team's contact information to the participants in the event that they needed further assistance and thanked them for taking part in the study.

Participants and Recruitment

Potential eligible participants were identified by working with the neurology team. The study coordinators contacted the participants via phone to schedule a screening call to determine eligibility. If eligible, and if the participants and caregivers consented to take part in the study, we scheduled an appointment with the IT expert to help the participants access the video portal through their computer or smartphone. The blinded study evaluators consented all participants and completed all evaluation measures virtually. A total of 200 enrollees who met the inclusion criteria were randomly assigned to the intervention (UC + virtual, nurse-led EPC) or to UC. Consenting caregivers were also allowed to take part as observers along with the participants.

Inclusion Criteria

Participants were eligible to take part if they were older adults with chronic illnesses living in the community and they had undergone a full evaluation by a multidisciplinary neurology team of experts. The Stanford Alzheimer's Disease Research Center team assessed the participants' cognitive status and determined their Clinical Dementia Rating (CDR) scores through consensus. Participants with a composite CDR score of 0 (no symptoms), 0.5 (very mild), 1.0 (mild), or 2.0 (moderate) were eligible to take part in the study.

Exclusion Criteria

Participants were excluded from the study if they had severe dementia (CDR=3.0) or if they lived in an institutional setting.

Randomization

After obtaining informed consent, participants were randomized to either the intervention (UC + virtual, nurse-led EPC) or to UC. The study nurses worked with participants randomized to the EPC intervention or their proxies to schedule session 1 of the intervention as a secure virtual video encounter. Sessions 2 to 12 were scheduled monthly video or phone encounters based on participant preference. To the extent possible, the same nurse was assigned to each participant across all sessions to ensure continuity. Evaluators, blinded to the treatment condition, collected the outcome measures from participants in both arms at baseline (at the time of study enrollment) and months 4 and 12. Long-term observational follow-up is currently ongoing for all participants through the electronic health records to track their health care resource use and determine whether the participants received preference-sensitive care at the end of life.

Primary Outcome Measures

The first primary outcome measure is the number of participants who report supportive care needs in both arms to the blinded evaluators (time points: day 0 and months 4 and 12).

The second outcome measure is completion of conversations on goals of care and documentation of advance directives and the POLST [8] in the electronic health records (time points: daily during the intervention period).

The third outcome measure is end-of-life resource use (hospital admissions and days and emergency visits). We hypothesize that this will be lower for the participants in the intervention group and that, compared to those in the control group, the participants in the intervention group are more likely to receive goal-concordant care at the end of life. In both arms, blinded evaluators will track the participants' end-of-life outcomes by monitoring their electronic health records and through interviews with their caregivers after the death of the participants (time points: at 1 year and then annually).

Secondary Outcome Measures

Changes in Edmonton Symptom Assessment Scale Score

The Edmonton Symptom Assessment Scale [9] was designed to assist in the assessment of 9 symptoms common in patients: pain, tiredness, nausea, depression, anxiety, drowsiness, appetite, well-being, and shortness of breath. The severity at the time of assessment of each symptom is rated on a numerical scale from 0 to 10, with 0 meaning that the symptom was absent and 10 meaning that it was of the worst possible severity. The investigators hypothesize that participants with cognitive impairment will have higher scores than those with normal cognition (time points: day 0 and months 4 and 12).

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Changes in Patient Activation Measure Over Time

The Patient Activation Measure (PAM) [10] is a 3-item survey that assesses a person's underlying knowledge, skills, and confidence integral to managing their own health and health care. The PAM segments individuals into 1 of 4 activation levels along an empirically derived 100-point scale. Each level provides insight into health-related characteristics, including attitudes, motivators, and behaviors. Individuals in the lowest activation level do not yet understand the importance of their role in managing their own health and have significant knowledge gaps and limited self-management skills. Individuals in the highest activation level are proactive with their health, have developed strong self-management skills, and are resilient in times of stress or change (time points: day 0 and months 4 and 12).

Quality of Life in Alzheimer's Disease

The Quality of Life in Alzheimer's Disease (QOL-AD) scale [11] is a valid and reliable scale that is brief (13 items) and has good content validity, criterion concurrent validity, and construct validity. Interrater reliability was strong, with all Cohen κ values of >0.70. Internal consistency was good, with a Cronbach α of 0.82. Some people with severe dementia and a Mini-Mental State Examination score as low as 3 have been able to satisfactorily complete the QOL-AD (time points: day 0 and months 4 and 12).

Statistical Analysis

To compare the EPC intervention and UC groups, for ordinal outcome measures, we will use a hierarchical linear model that assumes that the outcome O for each participant p at a time t is a linear function with an intercept i and slope s: $O(p,t) = i(p) + s(p)\ln(t+1) + e(t,p)$, where t is the time of measurement (measured from baseline) and e is an error term. The intercept for each participant ($i[p]$) is the true baseline response, with randomization having the same distribution in both groups. The slopes of the groups reflect the impact of the intervention or of UC over the course of treatment. Both intercepts and slopes are assumed to have a bivariate distribution in the population of participants, and the error terms within participants are assumed to be intercorrelated according to an autoregressive covariance function (outcomes closer together are assumed to be more highly correlated than those more distal to each other). In addition, $\ln(t+1)$ is used rather than t because outcomes in randomized clinical trials are more likely to have a "fishhook" relationship to time t, with more rapid changes early on than later.

For the power calculation, the null hypothesis to be tested is that the slopes in the EPC group have the same distribution as those in the UC group (ie, that there is no effect of EPC relative to UC). The significance level is 5%, with no adjustment for multiple testing because the outcomes chosen tend to be independent of each other. For 80% power to detect a moderate effect size with a 2-tailed 5% test, the sample size per group is approximately 63. However, we recruited a total of 100 participants per arm (200 in total) as we anticipated that the number of participants with a CDR score of 0 and at risk of cognitive impairment and those with a CDR of 0.5, 1, or 2 would be similar, allowing for within-group analysis.

Ethical Considerations

Ethics Approval and Informed Consent

This study was approved by the Administrative Panel on Human Subjects in Medical Research at Stanford University. Informed consent was obtained by the study evaluators at the start of participation.

Planned Procedures for Protection of Confidentiality

All data will be coded using participant number to ensure anonymity of participation. Data will be kept in locked cabinets and secured computer files. Online data will be hosted on a secure server at Stanford University and available through a double authorization protocol for maximal security. Research records will be kept confidential to the level allowed by law. The findings of this research may be published; however, neither the name nor identity of the participants or their caregivers will be used in any publications. Only the study manager and database manager had access to the research database.

Compensation Details

All participants in both arms will receive a US $25 stipend after they complete the evaluation measures at each time point (baseline and months 4 and 12).

Potential Risks of the Proposed Study to the Participants

Primary palliative care consultation is known to be beneficial and not risky. We highlight that all the medical treatments will be conducted by the individual participants' PCPs, ensuring careful care coordination. The participants' PCPs served as the attending physicians and signed the POLST form based on the participants' goals of care. As the participants' care partners (if available) were involved in the early primary palliative care plan, and as the individual participants' PCPs provided all medical therapies, there was minimal risk to the participants.

Potential Benefits of the Proposed Study to the Participants and Others

It is expected that the risk-to-benefit ratio of this project will be favorable. At worst, participants could drop out and receive UC. All study participants were provided with a courtesy stipend for taking part in the study. Beyond the benefit for the individual participants, this study has a transformational potential as it could identify the common early primary palliative care needs of participants with mild cognitive impairment and mild and moderate dementia living in the community. If successful, this is a scalable, low-risk virtual intervention that is participant-centered and family-oriented, with minimal risks to participants.

Monitoring Procedures and Treatment for Adverse Reactions

Any adverse reactions must be reported to the Stanford Institutional Review Board as per our standard protocol. At any point in the protocol, a treatment failure may be declared, and the participants can opt out of the intervention at any time. Participants were free to withdraw their consent and discontinue

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participation at any time without prejudice to them or effect on their (the participants') medical care.

Results

This trial was initiated in December 2019. As of October 2025, we have recruited 200 participants, and 100 (50%) have completed the intervention. We are tracking the participants in the study on an ongoing basis. We anticipate that the participants in the intervention arm will receive goal-concordant care at the end of life, and their health care resource use will be lower than that of the participants in the UC arm.

Discussion

Expected Findings

There is a growing shortage of palliative care workers. There is also an escalating need for early implementation of primary palliative care for older adults in the community with dementia and other serious illnesses. The registered nurse workforce can be trained using the ELICIT intervention model to provide early primary palliative care within the scope of nursing.

Our trial is notable because most existing research focuses on the palliative needs of patients who have severe dementia or are in an institutional setting [17-21]. To our knowledge, this is the first nurse-led, virtual intervention that provides early primary palliative care for older adults with cognitive impairment living in the community. Registered nurses provide the bulk of care for patients enrolled in hospice. However, currently, registered nurses do not provide early primary palliative care to patients. While a registered nurse cannot function as an independent provider, trained nurses are well able to provide early primary palliative care in collaboration with a patient's PCP. Once we identify the scope of practice for registered nurses in providing early primary palliative care, nurses can be trained using our intervention. Training the nurse workforce to provide early primary palliative care will greatly expand access to these services and enable patients to receive primary palliative care early in their illness trajectory.

Older adults are often excluded [22] from randomized clinical trials. This randomized controlled trial has recruited 200 community-dwelling older adults with chronic illnesses and varying levels of cognitive impairment, and currently, we are following the participants on an ongoing basis.

There is limited research and understanding regarding the primary palliative care needs of patients in the early stages of cognitive impairment, making it difficult to provide timely and effective care interventions. Experts have noted that primary palliative care is a fundamental aspect of high-quality care for patients with dementia [23]. While primary palliative care is appropriate for persons living with dementia at any stage, challenges exist in identifying and assessing their unique physical, psychological, social, and spiritual needs, particularly due to the delayed diagnoses, uncertain prognosis, and difficulties in communication and decision-making. In this trial, we tracked the supportive care needs expressed by all the participants to the blinded evaluators. On completion of this study, we will have a better understanding of the primary palliative care needs of patients with mild and moderate cognitive impairment who are living in the community.

Older adults with moderate and severe dementia often lose their ability to participate in discussions on goals of care and shared decision-making. Eliciting the patients' values and goals of care and obtaining anticipatory guidance for their future care is an integral part of high-quality care [24]. Studies have shown that patients tend to choose less aggressive interventions when they have an opportunity to participate in shared decision-making and document their preferences [25-27]. It is also known that patient-designated and next-of-kin surrogates incorrectly predict patients' end-of-life treatment preferences [28]. There is a window of opportunity early in the trajectory of cognitive decline when the patient retains mental clarity and decisional capacity. Discussions on goals of care should be conducted during this window while patients are still able to voice their values and preferences for care [29]. While the patients' goals and preferences may change over time, documenting goals of care and completing advance care planning will serve to establish a baseline of their preferences while they still have the ability to express them.

Study Limitations

This study had the following limitations. First, the COVID-19 pandemic started at the exact time when we enrolled our very first participant, and we rapidly redesigned our trial into a virtual intervention. If COVID-19 had struck even a few months later, we would have been in the middle of our trial and forced to stop the study as our original intervention and evaluation were supposed to be in person. In preparation for the virtual study, we piloted all the study measures with a few participants before the start of enrollment. Our pilot participants reported challenges with completing the Edmonton Symptom Assessment Scale, PAM, and QOL-AD measures virtually as some questions had reverse wording and all had Likert-scale response options that made it hard for them to answer. As the measures were part of our original proposed study, we retained them as secondary measures. Second, in this study, early primary palliative care was provided by registered nurses. Trained registered nurses can assess participants and identify their medical and psychosocial needs, provide care coordination and education, and conduct conversations on goals of care; however, they cannot independently make a diagnosis or prescribe medications. While the nurses were able to fulfill the psychoeducation and care coordination needs of the participants, they had to work with the participants' PCPs to fulfill all their medical needs. This can be seen as a study limitation, but we believe that this is also a strength as defining the scope of registered nurses as encompassing the provision of primary palliative care will inform the path forward as we work to expand the primary palliative care workforce. If effective, this intervention might be an innovative solution to offset the growing shortage of palliative care workers. Nurses trained in this intervention may be able to become the backbone of the primary palliative care workforce in the future. Third, this study was a virtual, ELICIT instituted early in the trajectory of cognitive impairment, and its long-term impact is currently unknown. We are conducting long-term observational follow-up of study participants to better understand whether the intervention has any impact on the

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end-of-life care of the study participants and whether it resulted in goal-concordant care.

Importance of Knowledge to Be Gained

Currently, very little is known about the early primary palliative care needs of patients with cognitive impairment living in the community. If successful, this trial will delineate the common early primary palliative care needs of patients at risk of cognitive impairment and those with mild cognitive impairment and mild and moderate dementia. Such knowledge will allow future interventions to better support persons living with cognitive impairment in the community.

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Authors' Contributions

VSP, CVG, and HK conceptualized the study and designed the methodology.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Study protocol and study measures.
[DOCX File, 15862 KB - resprot_v14i1e75082_app1.docx]

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Abbreviations

CDR: Clinical Dementia Rating
ELICIT: early primary palliative care intervention
EPC: early palliative care
PAM: Patient Activation Measure
PCP: primary care provider
POLST: Physician Orders for Life-Sustaining Treatment
QOL-AD: Quality of Life in Alzheimer's Disease
UC: usual care
WMM: What Matters Most letter advance directive

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Using a Heuristic Tool to Improve Symptom Self-Management in Adolescents and Young Adults With Cancer: Protocol for a Randomized Controlled Trial

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Abstract

Background: Adolescents and young adults (AYAs) with cancer experience multiple distressing symptoms during treatment, yet few developmentally relevant resources have been developed to help them self-manage their symptoms. Empowering patients to have a more active role in self-management during cancer treatment may lessen their symptom severity and distress.

Objective: The aim of this study is to test an intervention designed to improve symptom self-management, the Computerized Symptom Capture Tool (C-SCAT), by helping AYAs understand their unique symptom experience and discuss it with their health care providers.

Methods: We are conducting a multisite, 2-group randomized controlled trial to evaluate the effects of the C-SCAT in improving symptom self-management versus usual care in 126 AYAs who are within the first 3 months of a cancer diagnosis and who are receiving chemotherapy. Participants are randomly assigned to either the C-SCAT intervention group or the usual care group. The primary aim is to determine the effects of the C-SCAT versus usual care on the primary outcomes of self-efficacy for symptom management and symptom self-management behaviors. The secondary aim is to examine the effects of the C-SCAT versus usual care on distal outcomes, including symptoms and quality of life. Participants complete measures of self-efficacy for symptom management, symptom self-management behaviors, symptom severity and distress, quality of life social function, and quality of life satisfaction of social function at baseline (time 0), immediately postintervention (time 1), and at follow-up 1 month later (time 2).

Results: Recruitment started on January 4, 2024, at the first site, and all sites were open by May 1, 2024. Thus far, accrual has been set at 73% of the quarterly benchmark goal. Linear mixed effects models will be used to test for group differences across time for the primary and secondary aims.

Conclusions: This randomized controlled trial is evaluating an innovative, point-of-care intervention designed to be used at a clinic visit with the provider to improve symptom self-management for AYAs with cancer.

Trial Registration: ClinicalTrials.gov NCT05958316; https://clinicaltrials.gov/study/NCT05958316

International Registered Report Identifier (IRRID): DERR1-10.2196/76667

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KEYWORDS

randomized clinical trial; cancer; adolescents and young adults; digital health; symptom management; mobile phone

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Introduction

Background

Approximately 90,000 adolescents and young adults (AYAs) are diagnosed with cancer yearly in the United States [1]. As a distinct subset of patients with cancer, AYAs are underserved, understudied, and at risk for inferior outcomes, both physical and psychosocial, compared to younger children and older adults [2]. The epidemiology of AYA cancers, the physical and psychosocial effects of the requisite treatments, and characteristics of the AYAs' developmental stage combine to create a distinctive cancer experience, including multiple distressing interrelated symptoms [3-5].

Undermanaged, persistent, and recurrent symptoms negatively affect quality of life, function, health care costs, morbidity, and survival [6]. Specifically, AYAs report a decline in both mental and physical aspects of quality of life with as few as 3 symptoms [7]. Symptoms can interfere with the AYA's ability to attend school, participate in sports, and develop and maintain romantic relationships [8]. AYAs with cancer desire personalized symptom management information [9], but communicating their symptom experience to health care providers (HCPs) can be difficult for multiple reasons. These include the AYA's lack of familiarity with the health care environment, inexperience in talking about symptoms, a lack of systematic symptom assessment in many clinical settings, and the HCP's focus on issues other than those important to the AYA [10]. One critical aspect of obtaining relief from symptoms is to enhance an individual's ability to self-manage symptoms.

Self-management is defined as the process by which individuals use knowledge, beliefs, skills, and abilities to achieve health-related outcomes [11]. A distinct component of self-management is symptom self-management, defined as "a dynamic, self-directed process of implementing behaviors that recognize, prevent, relieve, or decrease the timing, intensity, distress, concurrence, and unpleasant quality of symptoms to achieve optimal performance outcomes " [12]. Developing self-management abilities in general and symptom self-management abilities specifically may be challenging for AYAs with cancer for several reasons. They may be gaining autonomy but often will still be somewhat dependent on parents or guardians. They may be emotionally or physically unprepared for or incapable of executing the responsibilities they need to assume. Finally, they are basically novices at dealing with chronic illness, monitoring symptoms, and interacting with HCPs [12]. While effective interventions exist for AYAs to improve self-management of other chronic diseases, such as asthma and diabetes [13], nearly none exist for AYAs with cancer. Two aspects that are critical to improving symptom self-management are having self-efficacy to manage symptoms and engaging in effective symptom self-management behaviors.

The concept of self-efficacy is described as the confidence a person has in their ability to engage successfully in a behavior [14] and is essential to self-management [15]. Self-efficacy for symptom self-management is defined as the individual's belief in their "ability to implement behaviors to prevent, recognize, and relieve symptoms" [16]. In AYAs with cancer, evidence suggests that increased self-efficacy is associated with improved symptom self-management behaviors, in particular improved nutrition and physical activity [17,18]. Among adults with cancer, self-efficacy is a key predictor of symptom self-management behaviors and is associated with decreased symptom severity or distress, improved psychosocial function, and greater quality of life [19-23]. Targeting self-efficacy has been shown to be effective; however, interventions to increase AYAs' self-efficacy for symptom self-management are lacking.

Symptom self-management behaviors are those actions that individuals initiate to alleviate symptoms [24]. Mastering effective symptom self-management behaviors can be particularly challenging as AYAs transition from having their parents manage their health care to managing it on their own [25]. Studies addressing symptom self-management behaviors among AYAs receiving cancer treatment are largely cross-sectional and descriptive; however, they provide important insights into the strategies AYAs use. AYAs may initiate symptom self-management behaviors to target an individual symptom, such as taking an antiemetic medication to manage nausea or to target more than 1 symptom, such as allowing for rest periods to self-manage fatigue and pain [5,26]. AYAs have revealed their rationales for engaging in certain symptom self-management behaviors, which have included enduring a given symptom for the sake of avoiding another. For example, AYAs may opt to omit opioid analgesics to avoid side effects such as nausea and vomiting [5,27]. Symptom self-management behaviors may also be influenced by the AYA's own role-related responsibilities; for example, AYAs who are parenting may select or even forgo given symptom self-management strategies in deference to priorities for their children [28].

Collectively, these studies indicate the efforts that AYAs initiate to self-manage their symptoms. More significantly, they reveal challenges that AYAs face when deciding how to optimally manage their symptoms, and therefore, a person-centered approach to support symptom self-management is vital.

Interventions to improve symptom self-management for AYAs are sparse. Limitations in research to date include an emphasis on single symptoms [29], single-site studies with small samples that often include children along with AYAs [29], and early phase testing of interventions [29,30]. Furthermore, most of the interventions are not grounded in self-management theory that aims to target critical processes such as self-efficacy, self-regulation, and communication. Two technology-based interventions to improve cancer symptom self-management were found to be feasible and acceptable to AYAs, but rigorous testing of effectiveness has not been reported [29,30]. One is a mobile phone–based symptom management system for AYAs that was piloted to incorporate feedback from AYAs into the system [30]. The other is a smartphone app for self-managing cancer-related pain that showed improved pain outcomes [29,31,32]. In summary, the lack of randomized controlled trials (RCTs) that test the effectiveness of technology-based interventions to improve symptom self-management that are tailored to AYAs with cancer is a major weakness of previous research.

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To address this need, we developed and pilot tested the Computerized Symptom Capture Tool (C-SCAT), an innovative, inductive, heuristics-based symptom self-management intervention delivered via a tablet computer [33]. Heuristics are conscious or unconscious "mental models" used in decision-making and problem-solving. A heuristic approach is proposed to assist individuals in becoming more aware of their symptoms and the need to engage in symptom self-management behaviors.

The C-SCAT is a unique and efficient intervention because it is designed to be completed immediately before an HCP encounter to help AYAs better understand their symptom experience and plan how to discuss their symptoms with an HCP, including their priority symptoms and symptoms they may feel embarrassed about. In addition, the use of heuristics contrasts with typical checklist approaches to symptom assessment, which do not incorporate the patient's perspective to identify symptoms of high priority, defined as the symptoms that are most important to them, and to identify relationships among symptoms. Use of the C-SCAT prepares AYAs to have a more focused discussion about their symptoms and self-management strategies with their HCP. The C-SCAT is unique in leveraging digital technology in a novel, developmentally relevant way to advance a person-centered health care approach to symptom self-management [34].

Theoretical Framework

The Individual and Family Self-Management Theory (IFSMT) [11], which acknowledges the complex process of changing health behaviors to self-manage symptoms related to an illness, such as cancer, was used to develop the C-SCAT intervention. The theory proposes that context and process factors influence proximal and distal health outcomes. Individual contextual factors may add risk or provide protection for engagement in self-management, and process factors facilitate change in health behaviors. Interventions to improve symptom self-management can target context and process factors. This study uses a modified version of the IFSMT (Figure 1).

Figure 1. Conceptual framework. AYA: adolescent and young adult.

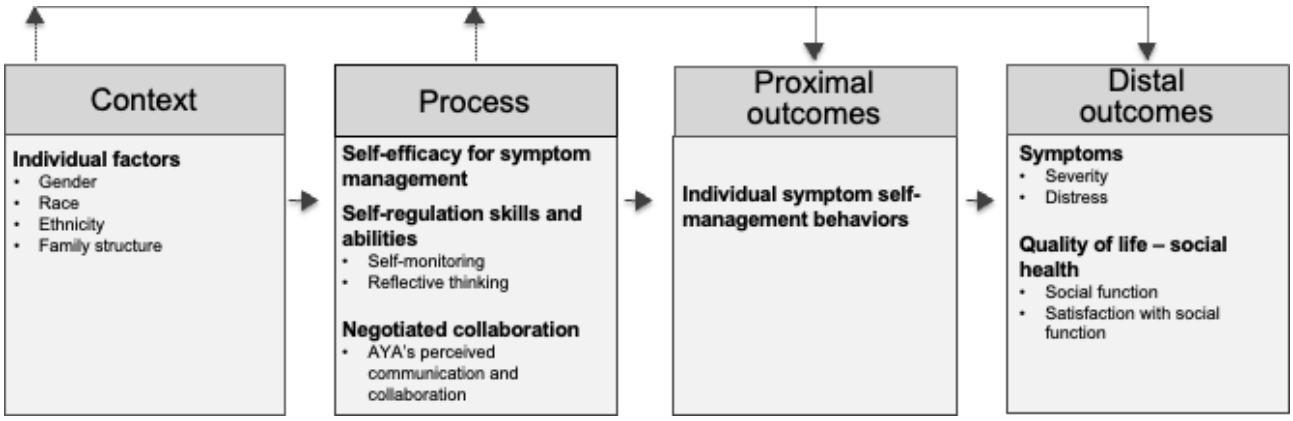

The C-SCAT targets three key process factors: (1) self-efficacy for symptom management, (2) self-regulation, and (3) negotiated collaboration. Self-efficacy for symptom management is enhanced by using the C-SCAT because creating the image facilitates the individual's interpretation of their symptoms. When individuals understand their symptoms' relationships and causes, they can engage more confidently in appropriate self-management behaviors [35]. The C-SCAT promotes self-regulation by facilitating individuals' understanding of their symptoms so that they can create a mental model that includes (1) which symptoms are deemed 'priority' and need priority management, (2) how their symptoms "cluster" together, and (3) how they might approach management options. These actions facilitate processes of self-regulation, including self-monitoring, reflective thinking, and self-evaluation [11,36]. Negotiated collaboration is facilitated by the C-SCAT because its use prepares AYAs for their discussion with an HCP and provides a strategy to efficiently communicate their priority symptom issues [37,38]. An advantage of the C-SCAT is that it is designed for AYAs to share information with any HCP who is involved with their symptom management (eg, physicians, advanced practice nurses, and staff nurses). The context factors include gender, race, ethnicity, and family structure. The proximal outcome, symptom self-management behaviors, is those activities used to prevent, monitor, manage, and communicate symptoms [39]. The distal outcomes are symptom severity and distress and quality of life–social health.

For this study, the primary outcomes are self-efficacy for symptom self-management and engagement in symptom self-management behaviors. While self-efficacy for symptom self-management is a process factor in the IFSMT, it is critical to improving symptom self-management and therefore is one of the primary outcomes. The secondary outcomes are symptom severity, symptom distress, social function, and satisfaction with social function.

Aims or Hypotheses

This RCT is testing a heuristics-based intervention designed to enhance symptom self-management in AYAs with cancer. Primary aim 1 is to determine the effects of the C-SCAT versus usual care on the primary outcomes of self-efficacy for symptom management and symptom self-management behaviors immediately postintervention (time 1) and at follow-up 1 month later (time 2). Aim 1 hypotheses are that AYAs using the C-SCAT will have higher self-efficacy for symptom self-management and higher scores on symptom self-management behaviors compared to AYAs receiving usual care. Primary aim 2 is to examine the effects of the C-SCAT

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versus usual care on secondary outcomes (eg, symptom severity, symptom distress, social function, and satisfaction with social function) immediately postintervention (time 1) and at follow-up 1 month later (time 2). Aim 2 hypotheses are that AYAs using the C-SCAT will have lower symptom distress and symptom severity and higher social function and satisfaction with social function compared to AYAs receiving usual care.

Methods

Ethical Considerations

This study was approved by Advarra on October 27, 2023 (Pro00070338), which serves as the single institutional review board of record and has received administrative approval from the institutional review boards at each study site. Privacy is protected with data stored in a secure, HIPAA (Health Insurance Portability and Accountability Act)-compliant server at the primary institution.

The informed consent process is conducted by study staff and includes verbally reviewing the consent form, answering questions, and obtaining signatures from the participant and 1 parent or legally authorized representative of participants who are minors. Obtaining informed consent or assent and parental permission occurs in person in a private setting in the inpatient or outpatient oncology setting. Assent is documented by the participant who is aged <18 years signing the informed consent, permission, or assent form. A reconsent process will occur for participants who are minors at enrollment but become adults during the study period and are reconsented as adults. Written informed consent or assent and parental permission, as appropriate, are obtained before completing baseline measures. After the informed consent process is complete, participants are considered enrolled and assigned a study identification number linked to their survey responses and intervention visits. Participants are compensated with a US $25 prepaid gift card after completing each of the first and second data collection visits and a US $30 prepaid gift card after completing the third data collection visit, for a total of US $80.

Recruitment

At each of the sites, recruitment occurs in both inpatient and outpatient oncology settings. Potential participants are approached in person. Sites using Epic are also able to provide a recruitment message through the electronic medical record.

Screening

At each site, oncology clinic schedules are reviewed at least weekly to identify potential participants. In addition, hospital staff in inpatient and outpatient oncology settings are asked to identify potentially eligible participants. A screening form is completed before enrollment to determine eligibility.

Trial Design

This study uses a multisite 2-group RCT design to evaluate the effects of the C-SCAT for improving symptom self-management versus usual care in AYAs who are within the first 3 months of a cancer diagnosis and who are receiving cancer treatment. For this study, cancer treatment is defined as a prescribed infusion (eg, chemotherapy or immunotherapy). Data collection occurs at 3 time points (times 0, 1, and 2). Time 0 (baseline, followed by randomization) occurs at or near the enrollment visit. The C-SCAT intervention period is approximately 12 weeks, depending on the participant's treatment schedule. Time 1 (postintervention) occurs approximately 2 weeks (±7 d) after completion of the intervention. Time 2 (follow-up) occurs approximately 4 weeks (±7 d) after time as seen in Figure 2.

Figure 2. Study schema. C-SCAT: Computerized Symptom Capture Tool.

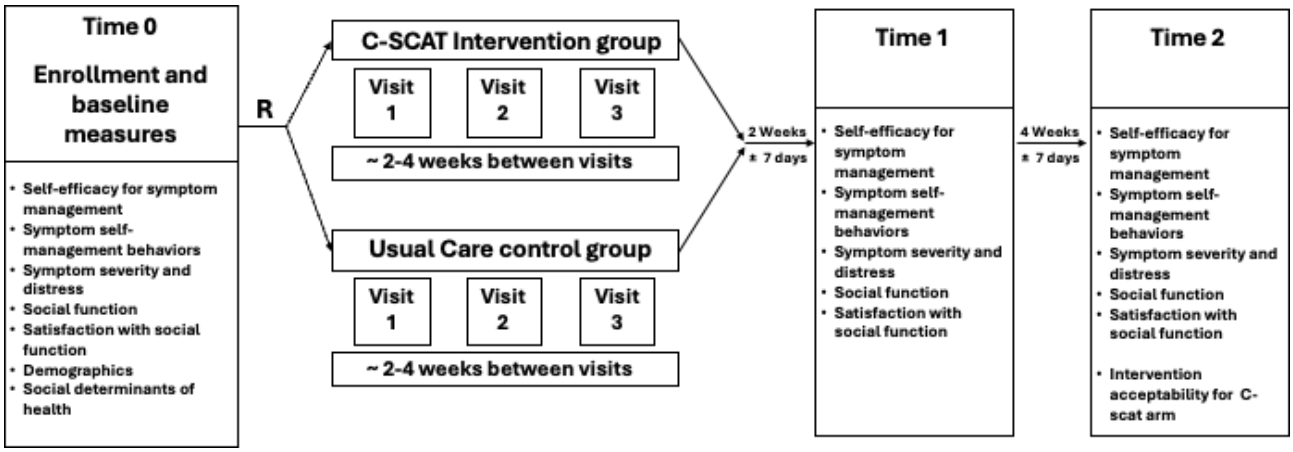

Participants and Setting

Recruitment and enrollment are conducted by trained study staff and take place at 4 institutions from the Northwest, Intermountain West, Midwest, and Southeast regions of the United States. Participants are AYAs with cancer who are in active treatment. The inclusion criteria are as follows: (1) ages 15 to 29 years; (2) has received at least one cycle of cancer treatment and is within 3 months of receiving that first cycle of treatment; (3) receiving regularly scheduled cancer treatment and will be receiving at least three more cycles; (4) reports at least one symptom related to cancer or its treatment; and (5) is able to speak, read, and write English as required for completion of the C-SCAT and study measures. The exclusion criterion is cognitive or physical inability to complete study measures.

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Randomization

Participants are randomized to either the C-SCAT intervention or usual care control group (UCCG). Study staff and participants are not blinded to treatment allocation due to the nature of the intervention. Thus, to reduce bias, deidentified data with dummy codes for assigned conditions are used in the database to ensure blinded data analysis. Using stratified randomization (a separate randomization at each clinical site), participants are randomized to the C-SCAT group or to the UCCG. Within each clinical site, a block randomization schema is generated with randomly selected block sizes of 2, 4, and 6. Stratified and block randomization with randomly selected block sizes are preferred in unblinded studies because they make it very difficult, if not impossible, for people enrolling participants to know what group assignment is next [40]. The biostatistician generates the various randomization schemas by clinical site, and the data manager uploads them into REDCap (Research Electronic Data Capture), allowing study staff at all sites to instantaneously receive the group assignment via computer.

Study Intervention

The C-SCAT is a symptom heuristic tool that is delivered via a tablet computer and was developed based on a symptom cluster heuristics interview guide created by Woods et al [41]. The heuristics approach is used because it promotes AYA's self-awareness of their symptoms, specifically it helps them visualize the 'big picture' of their unique symptom experience and be made aware of the need to engage in symptom self-management behaviors. Thus, the completion of the C-SCAT is the intervention.

The tool engages the AYA in creating a graphical image of the symptoms they experienced during the past week, designating relationships among symptoms and identifying priority symptoms. The C-SCAT includes the 32 symptoms from the Memorial Symptom Assessment Scale (MSAS) [42]. Users select symptoms they have experienced over the past week, rate each symptom's severity and distress, and name a perceived cause (Figure 3). They then identify temporal and causal relationships between symptoms using lines and arrows, designate groups, that is, "clusters" of symptoms, and give a name to each cluster (Figure 4). Users can designate up to 3 priority symptoms (symptoms most important to them). They are asked the reason for a symptom's designation as a priority symptom and what they do to alleviate that symptom (Figure 5). Next, they are asked to designate a priority cluster and finally to confirm whether the image accurately reflects their symptom experience (Figure 6).

The C-SCAT is completed just before an HCP visit to assist the AYA in understanding their symptom experience and communicating it effectively to the HCP to facilitate symptom self-management. Once they complete the C-SCAT, the image is printed out for them. Although they are encouraged to share the C-SCAT image with their providers, it is their decision as to whether they choose to share it.

Figure 3. The Computerized Symptom Capture Tool selection of symptoms screen.

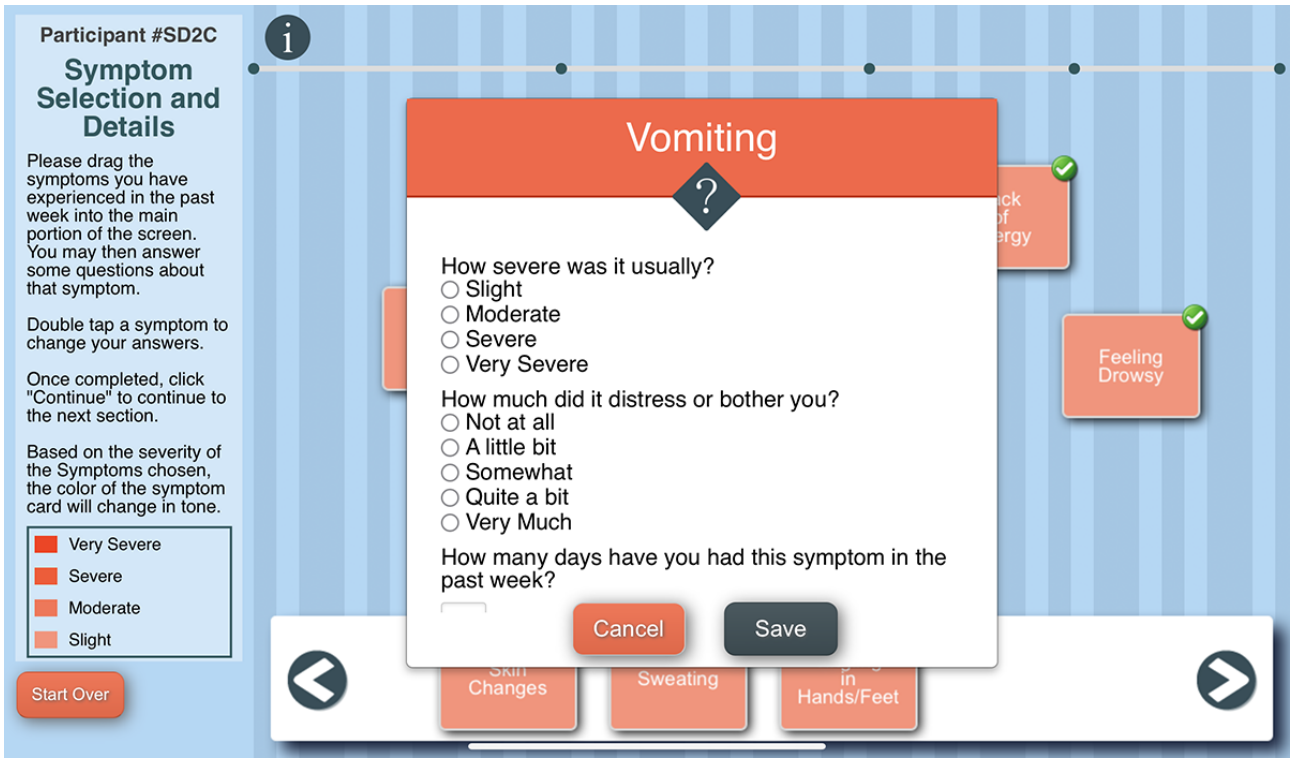

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Figure 4. The Computerized Symptom Capture Tool identification of groups screen.

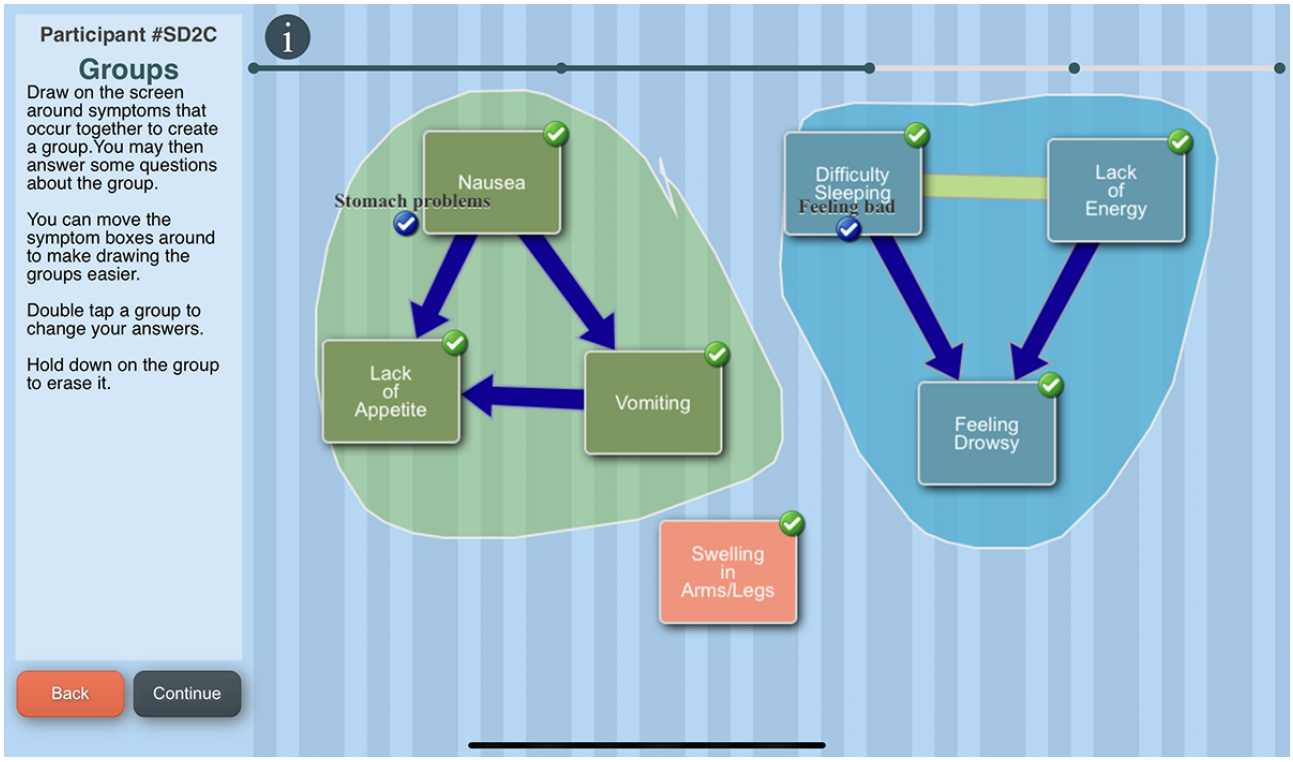

Figure 5. The Computerized Symptom Capture Tool identification of priority symptoms screen.

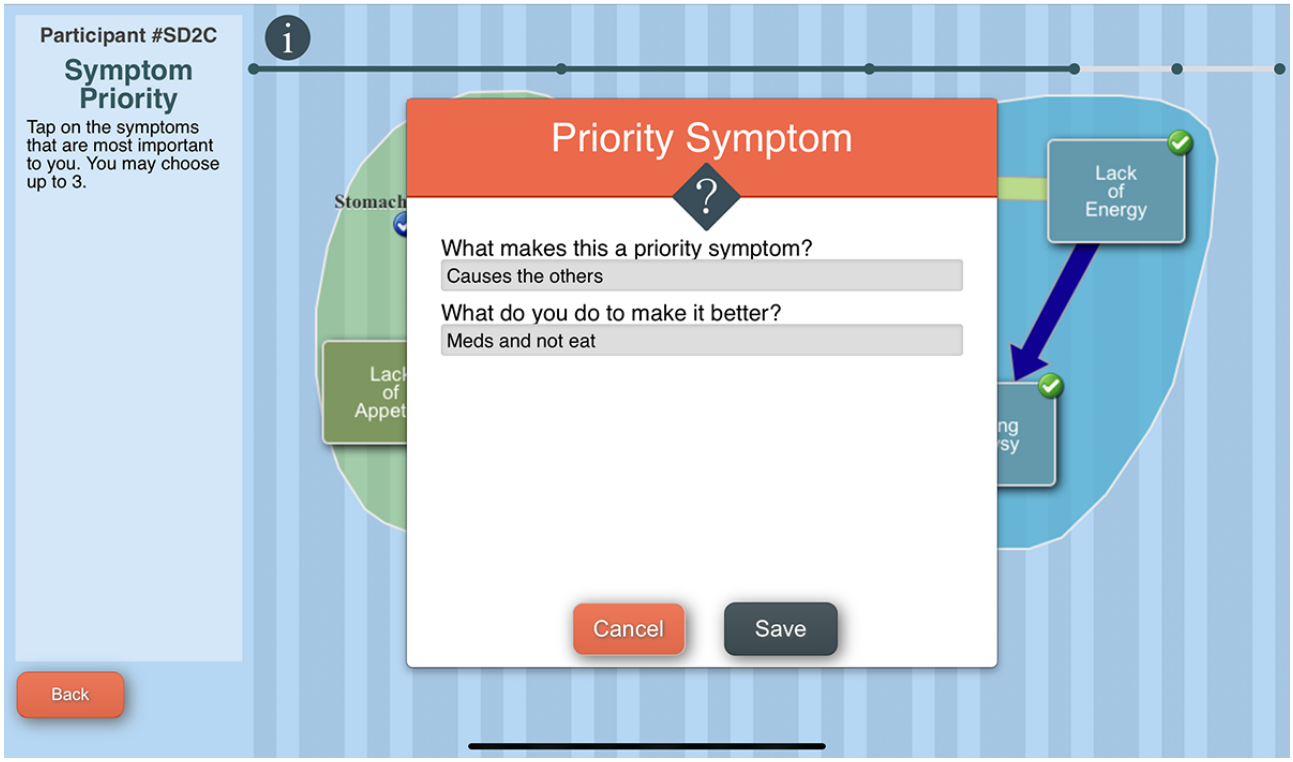

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Figure 6. The Computerized Symptom Capture Tool review of final image screen.

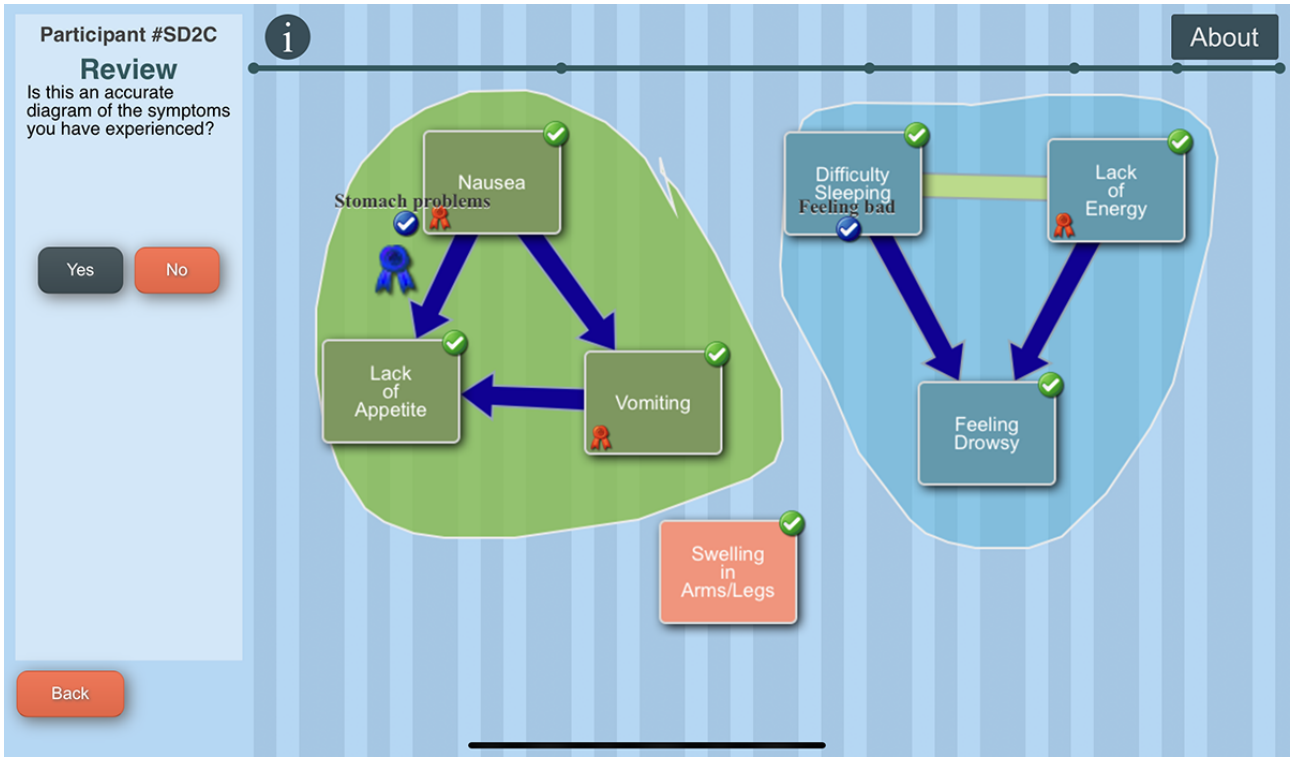

Description of the C-SCAT Intervention Group

Participants assigned to the C-SCAT intervention group complete the C-SCAT on a tablet computer in addition to their institution's usual care and processes for assessing symptoms before three of their scheduled clinic visits with their HCPs for their cancer treatment. Depending on the individual's treatment protocol, treatments are typically every 2 to 4 weeks. Before the AYA's first encounter with the HCP, study staff provide a short interactive practice session on how to use the C-SCAT that includes (1) an introduction to the C-SCAT as a tool that can be used to create a graphical image of the AYA's symptom experience that can be printed out and shared with the HCP, (2) a video that demonstrates how to complete the C-SCAT and how it can be used in an encounter with the HCP, (3) a practice session to ensure that the AYA is proficient and comfortable using the C-SCAT, and (4) a question and answer period. The practice session takes approximately 5 minutes. The AYA completes the C-SCAT at each of 3 HCP (intervention) visits, and the resulting image is printed out and given to the AYA to review and to share the image with the HCP as they wish. As this study is focused on improving symptom self-management and although study staff encourage the AYA to share the C-SCAT image with their HCP, ultimately, it is up to the AYA to decide whether they want to share the image. Before the start of the study, study staff gave in-services to the oncology clinics' HCPs on how to interpret the C-SCAT image and also supplied the HCP with a printed guide as to how to interpret the C-SCAT image at each participant intervention study visit.

Description of the UCCG

Participants assigned to the UCCG receive care based on the institution's usual approach to assessing symptoms during the HCP encounter. To provide attention control to the UCCG and help prevent disproportional attrition from that group, study staff make contact with UCCG participants 3 times during the intervention period (same as the intervention group) during scheduled clinic visits and communicate the following: (1) express appreciation for ongoing study participation, (2) ask how everything is going with their treatment, (3) ask if anything has changed with their treatment plan since the last study visit, and (4) confirm continued willingness to participate in the study. None of the recruitment sites use any standardized approach to assess multiple cancer symptoms, although all sites routinely assess for pain. Several sites use depression screening tools, but only for symptoms related to depression. Thus, it is not anticipated that elements of usual care will overlap with the C-SCAT intervention.

Intervention Fidelity and Training of Study Staff

Intervention fidelity is guided by recommendations from the National Institutes of Health Behavior Change Consortium [43], with attention to design, training, delivery, receipt, and enactment. Study staff at each site are involved in recruitment, retention, and data collection. Training addresses protection of human subjects, research compliance, study methods, data entry and management, roles and responsibilities, training on the C-SCAT intervention, and attention to the UCCG. All staff complete required human subjects and other relevant training at initiation of the project and throughout as appropriate.

To ensure that the intervention is delivered as intended within and across sites, we developed a standard operating procedure manual with core procedures for all sites and specific considerations within sites and ensured training for the study staff on procedures and interventions through review of the manual, didactic sessions, and demonstrations. To maintain consistency of training, study procedures based on the manual

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are regularly reviewed with the study staff. To mitigate bias by study staff during study visits for both arms, we have carefully scripted each study visit to support consistent delivery. The project coordinator monitors intervention delivery and receipt by routine random checking for any differences in study logs, completion of the C-SCAT, and completeness of measures. Retraining is instituted as needed. The research team holds twice monthly meetings (and ad hoc as needed) with study staff to discuss any issues with study procedures. To confirm intervention enactment, at the beginning of each intervention visit, study staff ask the participant what questions they have on how to complete the C-SCAT, and whether they want another practice session. These processes will ensure consistency of intervention delivery and integrity of data collection.

Outcome Measures

Primary Outcome Measures

Self-efficacy is measured with the Patient-Reported Outcomes Measurement Information System Self-efficacy of Symptom Management Scale (PROMIS S-E), a domain-based 28-item scale. Items assess the person's current level of confidence to manage or control symptoms, manage symptoms in different settings, and keep symptoms from interfering with work, sleep, relationships, or recreational activities [44]. Response options are on a 5-point Likert scale (1=*I am not confident at all* and 5=*I am very confident*). Scores are summed across items and can range from 28 to 140, and higher scores indicate greater self-efficacy. Cronbach α in our previous study with AYAs was 0.94 [45].

Symptom self-management is measured with the Symptom Self-management Behaviors Tool (SSMBT) [46]. The SSMBT contains 12 items with two subscales: manage symptoms (8 items) that address behaviors related to managing their symptoms and talk to health care provider (4 items) that address behaviors related to communicating with their HCP about their symptoms. Response options are on a 5-point Likert scale (0=*never* and 4=*always*). Scores are summed across all items. Higher scores indicate higher engagement in symptom self-management behaviors. The SSMBT was developed for AYAs with cancer and has evidence of being reliable and valid [46]. Reliability for the total scale was α= of .74. Construct validity was supported via principal component factor analysis and discriminant validity.

Secondary Outcome Measures

Symptom severity and distress in the past week are assessed using the MSAS [42]. Participants rate the severity on a 4-point Likert scale (1=*slightly* and 4=*very severe*) and the distress on a 5-point Likert scale (0=*none* and 4=*very much*). The adult version of the MSAS was used because it has 2 more symptoms (feeling bloated and problems with sexual interest or activity) than the MSAS 10‑18. In our previous study, AYAs indicated that these symptoms were relevant to them.

Two aspects of social function are assessed: quality of life related to social function and satisfaction with social function. Quality of life related to social function is assessed with the PROMIS SF (version 2.0) Ability to Participate in Social Roles and Activities. It contains 8 items, is scored on a 5-point Likert response scale (5=*never* and 1=*always*), and has strong evidence of reliability and validity in clinical populations, including individuals with cancer [47]. Satisfaction with social function is assessed with the PROMIS SF version 2.0 Satisfaction with Social Roles and Activities. It contains 8 items, is scored on a 5-point Likert response scale (1=*not at all* and 5=*very much*), has been validated in adults aged ≥18 years [48], and has been used in young adults with cerebral palsy [49].

Descriptive Measures

Self-reported demographic data are collected with the Biomedical Research Informatics Computing System, National Institute of Nursing Research [50] demographic form, including education, primary caregiver, employment, marital status, and household member count. Additional items assess household income, number of children, people living with the AYA, and living arrangement changes during treatment. Self-reported race and ethnicity are also being collected. Clinical and other descriptive variables are collected by study staff from the participant's electronic health record and include age, sex, cancer diagnosis, time since diagnosis, chemotherapy protocol start date, treatment protocol, comorbid conditions, insurance type, and ZIP code.

Intervention Acceptability

Participants in the intervention group are asked to complete the C-SCAT Intervention Acceptability Survey. This 7-item survey assesses the acceptability of various aspects of the intervention, such as "How much effort did it take to do the CSCAT? and "How confident did you feel that you could complete the C-SCAT as instructed?"

Data Collection

Data collection occurs at 3 time points (times 0, 1, and 2) at scheduled inpatient or outpatient visits (Figure 2). Baseline measures are collected at time 0, postintervention measures at time 1, and follow-up measures at time 2. Participants complete measures on a study-dedicated tablet computer using REDCap, or via a link to REDCap that is emailed to them. Study staff obtain clinical data from the electronic health record. The time 1 visit for the C-SCAT group is scheduled 2 weeks±7 days (to accommodate schedule changes) after completion of the intervention to allow time for the participant to have been at home (or outside the clinical setting) to self-manage their symptoms following chemotherapy. The time 1 visit for the UCCG group is scheduled 2 weeks±7 days (to accommodate schedule changes) after completion of the attention control visits. For both groups, the time 1 visit occurs during a scheduled inpatient or outpatient visit. Participants who are not scheduled for an inpatient or outpatient visit during the ±7-day window are contacted via telephone to complete the study measures and are sent a REDCap link via email. For both groups, the time 2 visit is scheduled 4 weeks±7 days from Time 1, and the same procedures for data collection as described earlier for time 1 are used.

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Safety

Data Safety Monitoring

This study carries less than minimal risk to participants. As this study is a multisite clinical trial and involves adolescents aged ≥15 years, we use a Safety Monitoring Committee to assess the safety of the study and monitor the data. The Safety Monitoring Committee consists of 2 members who have areas of expertise in AYAs with cancer and biostatistics. The Safety Monitoring Committee was established through the primary study site.

Monitoring Participant Safety

The research team uses a clearly defined protocol to monitor participant safety. Participant safety is monitored monthly and with each occurrence of a potential safety issue. The principal investigator, in collaboration with coinvestigators or site principal investigators, is responsible for monitoring the safety of participants at each site.

Data Analysis Plan

Overview

This study is a 2-group (C-SCAT vs control), longitudinal randomized multicenter (5 sites), clinical trial with data collected at 3 time points (times 0, 1, and 2). Two primary variables are being evaluated for group differences in aim 1: symptom self-efficacy as measured by the PROMIS Self-Efficacy of Symptom Management Scale (PROMIS S-E) and self-management behaviors as measured by the SSMBT. The secondary outcomes in aim 2 are symptom severity, symptom distress, social function, and satisfaction with social function. The plan is to enroll 126 AYAs with cancer in active treatment from 5 sites. The study biostatistician who was not involved with data collection and will be blinded to group affiliation will conduct all analyses.

Sample Size and Power

A mixed effects linear model is planned to test for group differences across time for aims 1 and 2. The co-primary outcome variables from aim 1 are the PROMIS S-E and the SSMBT. From the outset, we planned to take a more conservative approach to the power analysis due in part to the limited number of SSMBT samples observed from only one site. Thus, for both primary variables, power was estimated using a 20% inflated variance estimate and a target power of 90% (as opposed to the usual 10% inflated variance and 80% power). A 20% inflated estimate of the residual SE was estimated as 12.73 for PROMIS S-E and 6.35 for SSMBT. Assuming the smallest clinically significant difference between the groups of 10 for PROMIS S-E and 4.8 for SSMBT, a Bonferroni adjusted alpha of .05/2=.025 and a power of 90%, PASS (Power Analysis & Sample Size, PASS 2022; NCSS, LLC [51]) software estimated the total sample size to be 77 for PROMIS S-E and 83 for SSMBT. However, the proposed model will have effects for time (0, 1, and 2), group (C-SCAT vs usual care), time-by-group interaction, site (1, 2, 3, 4, and 5), site-by-group interaction, and population (adolescent vs young adult). Accounting for the 16 degrees of freedom necessary to fit these model effects, the total sample size will be 83+16=99 who complete time 2. Allowing for an attrition as high as 20%, the final sample size will be 126 AYAs or approximately 25 per site. Recruitment in our preliminary multisite studies demonstrated that this sample size is feasible within the proposed period of the project.

Descriptive statistics will be computed for demographic and all outcome variables. All data will be examined graphically to determine the distributional properties. In cases of nonnormally distributed data, transformations may be used for analyses.

Aims

Aim 1 is to determine the effects of the C-SCAT versus usual care on the primary outcomes of self-efficacy for symptom management and symptom self-management behaviors immediately postintervention (time 1) and at follow-up 1 month later (time 2). Self-efficacy for symptom management and symptom self-management behaviors will be assessed at times 0, 1, and 2 and will be compared between the C-SCAT intervention group and the UCCG. We anticipate using a linear mixed effects model to test the effect of the C-SCAT versus usual care. The general form of the mixed linear model [52-54] is given by y=XB+ZU+ e, where y is the observed data vector (PROMIS S-E and SSMBT), X is a known design matrix, B is a vector of unknown fixed effects, Z is a known design matrix, U is a vector of unknown random effects, and e is a vector of unknown random errors. This model will include a random effect for participant (represented by ZU in the equation) and fixed effects for group (C-SCAT and UCCG), time (0, 1, and 2), group-by-time interaction, site (1, 2, 3, 4, and 5), group-by-site interaction, and population (adolescent and young adult; represented by XB in the equation). The model is flexible enough to accommodate the potential cofactors of race (eg, Black and White), ethnicity (eg, Hispanic and non-Hispanic), and gender (eg, male and female). The first step in testing aim 1 will be to test each of the primary variables (PROMIS S-E and SSMBT) using a contrast on the group-by-time interaction to specifically test for an immediate effect of C-SCAT versus the UCCG at time 1. A Bonferroni correction (α=.05/2=.025) is planned to adjust for testing each of the 2 primary variables. All other tests, for example, testing for a sustained effect at time 2, are considered supportive and will be testing with an α of .05. Modeling assumptions such as normality and homoscedasticity will be checked for each model. In the case of positively skewed data, a transformation (such as a log transformation) will be used to normalize the data. It is anticipated that all analyses will be performed using JMP (JMP 18, 2025 JMP 18; JMP Statistical Discovery LLC [55]) and SAS/STAT (Statistical Analysis Software Institute [56]) software, specifically PROC MIXED.

Aim 2 is to examine the effects of the C-SCAT versus usual care on secondary outcomes (symptom severity, symptom distress, quality of life related to social function, and satisfaction with social function) immediately postintervention (time 1) and at follow-up 1 month later (time 2). The mixed effects linear model presented in the aim 1 analysis plan is anticipated to be sufficient for the analysis of the secondary outcomes in aim 2. The secondary outcomes are considered supportive of the tests of an immediate effect (aim 1) and will be tested with an α= of .05.

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Missing Data

In addition to strategies to prevent missing data, such as completion checks after study visits and reminders, we will monitor for patterns of missing data when data are merged on a quarterly schedule and determine reasons for missing data. We will use mean imputation for any missing data within a scale. Following an intention-to-treat principle, participants with any postintervention data will be included in the analysis.

Data Sharing Plan

Data will be shared with the scientific community via publishing results from the study in relevant peer-reviewed scientific journals and meetings. Analytic approaches will be available upon request.

Results

Recruitment began at the first site on January 4, 2024. All sites were open to recruitment by May 1, 2024. For the quarterly benchmark goal for recruitment, enrollment is at approximately 73%. We anticipate that the study will close to recruitment in Fall 2026, and the final participant will complete the study by Spring 2027. We anticipate publishing results in 2027.

Discussion

Anticipated Findings

We describe the protocol of a RCT that is testing the effectiveness of the C-SCAT intervention designed to improve symptom self-management by helping AYAs understand their unique symptom experience and discuss it with their HCPs. The intervention aims to increase self-efficacy for managing symptoms and engagement in effective symptom self-management behaviors. Empowering patients to adopt a more active role in self-management during cancer treatment may lessen their symptom severity and distress.

Limitations

The main limitations of this study center around reaching recruitment goals. Recruitment and retention are well-recognized challenges in any RCT with multiple data collection time points. However, beyond that, the nature of this study population poses additional challenges. Cancer in AYAs is fortunately considered rare, but this limits the number of eligible patients available. Recruiting minors (individuals aged <18 y) adds an extra layer of complexity to the consent process as both a parent or legally authorized representative and the eligible minor patient must be interested in study participation, the parent or legally authorized representative must give permission, and the patient must give assent. Sometimes the parent or legally authorized representative is interested, but the patient feels too ill or feels that the burden of participation is excessive. Sometimes the patient is interested, but the parent or legally authorized representative feels that the burden of participation may be excessive and wishes to protect the patient from that. Some potential participants may decline study participation because they do not perceive potential personal benefit even if randomized to the intervention arm, as they feel that their symptom experience is being well-managed and communication with their providers is already good. Alternatively, some potential participants may decline study participation because they feel too unwell from their symptom experience, or most commonly, express a sense of being overwhelmed, of ‘having a lot going on’ living a life that now includes cancer and cancer treatment. We aim to minimize recruitment challenges through our team’s expertise and experience with conducting several previous studies with this AYA population. In addition, we are recruiting from major cancer centers that have large catchment areas. To aid retention, both groups (C-SCAT and UCCG) participants receive personal contact with a study team member at least three times during the intervention period.

Conclusions

In conclusion, because undermanaged symptoms reduce quality of life and increase symptom severity and distress, effective person-centered symptom self-management is imperative for AYAs with cancer. A major barrier, however, is a lack of effective symptom self-management interventions that are tailored to this population. The proposed study addresses this gap by testing an intervention designed to improve symptom self-management behaviors in AYAs with cancer who are in active treatment. If shown to be effective, the C-SCAT could be incorporated into clinical settings at the point of care and potentially into the electronic health record as an efficient, low-cost approach to improve symptom self-management.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

AYA: adolescent and young adult
C-SCAT: Computerized Symptom Capture Tool
HCP: health care provider
HIPAA: Health Insurance Portability and Accountability Act
IFSMT: Individual and Family Self-Management Theory
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
S-E: PROMIS Self-efficacy of Symptom Management Scale
SSMBT: Symptom Self-management Behavior Tool
UCCG: usual care control group

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Wearable Continuous Vital Sign Monitoring Study (WARD-AMS) to Detect Clinical Deterioration in Postoperative General Surgery Patients: Protocol for a Randomized Controlled Trial

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Abstract

Background: Postoperative complications remain a major challenge in health care systems, with more than 70% of postoperative in-hospital mortality occurring in general wards. Current practice relies on intermittent spot-check monitoring of vital signs guided by track-and-trigger thresholds such as early warning scores. Evidence shows that, up to 4 hours before an adverse event, abnormal vital signs can be detected in up to 60% of patients. Continuous vital sign monitoring in general wards offers the potential to detect clinical deterioration earlier. However, prospective evaluations of continuous monitoring in general wards remain limited.

Objective: This study aims to prospectively evaluate the impact of continuous vital sign monitoring in adult postoperative patients in general wards. The primary objective is to determine whether continuous vital sign monitoring reduces the time from device-defined physiological deterioration to the first objective escalation event (acknowledgment or clinical action) by the health care team. Secondary objectives are to evaluate clinical outcomes, operational impact, and both staff and patient experiences.

Methods: We conducted a single-center, open-label randomized controlled trial of 200 general surgical patients, receiving continuous vital signs monitoring alongside standard care. Participants were randomized 1:1 to alerting or nonalerting groups, either real-time data and alerts visible or blinded to clinicians, respectively. The primary outcome is the time from the first device-defined physiological deterioration episode to the first objective escalation event (acknowledgment or clinical action). Exploratory outcomes evaluate time to treatment initiation, rapid response team activation, escalation of care, length of stay, mortality, alarm performance, and patient and staff experience.

Results: The Ward Alerting and Ambulatory Monitoring Study (WARD-AMS) trial received ethical approval in April 2024; recruitment commenced in October 2024 and was completed by December 2025 with 200 patients enrolled. Data analysis is ongoing, with results to be submitted for publication by mid-2026.

Conclusions: The WARD-AMS study is among the first prospective, randomized evaluations of continuous vital sign monitoring in real-world ward settings looking at clinical outcomes and user experience. By integrating clinical outcomes, alarm analytics, and stakeholder experiences, it aims to provide a comprehensive understanding of the benefits, limitations, and implementation challenges of continuous monitoring. Findings from this study will inform strategies to optimize response to early clinical deterioration, reducing alarm fatigue and embedding new technologies into existing routine ward practice.

Trial Registration: ISRCTN Registry ISRCTN15518094; https://www.isrctn.com/ISRCTN15518094

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KEYWORDS

ambulatory monitoring; continuous vital sign monitoring; patient deterioration; postoperative care; wearable sensors; health care technology; digital health

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Introduction

Despite significant advancements in surgical techniques and perioperative care, postoperative complications continue to present substantial clinical challenges, negatively impacting both patient health and health care systems. Findings from the European Surgical Outcomes Study revealed that 73% of patients who died in hospital were never admitted to an intensive care unit (ICU) [1], whereas another study added that general wards experienced the highest rate of adverse events, followed by operating theaters and ICUs at 48.8%, 26.1%, and 13%, respectively [2]. Additionally, it has been shown that, up to 4 hours before cardiorespiratory arrest, 59.4% of patients have at least one abnormal vital sign and there is a stepwise increase in mortality for patients with an increasing number of abnormal vital signs [3]. Current standard-of-care intermittent monitoring protocols suggest measuring vital signs every 4 to 8 hours in a general ward. There is a sharp drop in surveillance intensity from continuous monitoring intraoperatively and in ICUs to intermittent manual checks in the ward, where clinical deterioration may go undetected [4]. Despite repeated evidence highlighting the critical role of respiratory rate as a marker of clinical deterioration, inaccuracies in manual measurements persist, with no improvements in technology to support bedside nursing practice [5-7].

Continuous vital sign monitoring systems, successfully used in ICUs, offer a promising strategy to extend enhanced surveillance to general wards, addressing some of these issues. Recent innovations have led to the development of wireless, wearable continuous vital sign monitoring devices, mitigating previous barriers such as size and restrictive tethering [8]. It is known that early mobilization within the first 24 hours after surgery promotes improved lung function, reduces thromboembolic risk, and shortens hospital stay [9,10]. Wearable vital sign monitors facilitate this by allowing for continued surveillance without tethering patients to bedside monitors [11,12]. Nevertheless, early retrospective and limited prospective before-and-after analyses have reported modest clinical benefit of these technologies when applied in general wards [13]. These observations demonstrate significant barriers related to device implementation and integration into existing health care systems. A recent systematic review and meta-analysis of randomized controlled trials looking at the outcomes of patients with continuous monitoring of vital signs in general wards demonstrated nonsignificant trends for improvements in in-hospital mortality, major events or complications, or higher-level care admission, with pooled odds ratios of 0.95, 0.71, and 0.82, respectively, and a mean reduction in length of stay of 2.12 days [13]. The randomized controlled trials evaluated were constrained by the heterogeneity of monitoring technologies (devices measuring diverse combinations of vital signs and varying alert parameters) and the inconsistent definitions of major complications. In addition, by not comparing with a standardized escalation pathway (who is exposed to the alarms and data, at which thresholds, and how does staff intervene), the review overlooked the critical influence of response workflows, limiting insight into whether outcomes reflect technology performance or differences in clinical practice. Understanding of how nursing and health care staff navigate the challenges of increased data volume, alarm fatigue, and changes in workflow must be realized to successfully use these technologies to improve morbidity and mortality beyond the ICU [14,15]. Additionally, patient knowledge, attitude, and perceptions regarding digital devices have been incompletely explored, lacking validation and weakened by selection bias [16-18].

This study aims to evaluate whether continuous vital sign monitoring reduces the time from device-defined physiological deterioration (T_0) to the first objective escalation event (T_action), defined as acknowledgment or clinical action by the health care team, compared with the standard of care (intermittent monitoring) in postoperative adult patients in general surgical wards. Secondary aims are to evaluate the effect of continuous vital sign monitoring on escalation of care, timely intervention, and corresponding clinical outcomes. By capturing and analyzing the perspectives of nurses and patients, key stakeholders in device implementation, we seek to identify practical barriers and facilitators, thereby proposing actionable solutions to facilitate effective integration of continuous vital sign monitors into routine ward practice and enhance patient outcomes without imposing a burden upon health care professionals.

Methods

Study Design

A prospective, interventional randomized controlled trial will be conducted using a mixed methods approach. It is an open-label, 2-arm study that aims to recruit 200 patients over a 1-year period. Patients will be randomized using an online tool (Greenlight Guru Clinical) on a 1:1 basis into an alerting and nonalerting group (Figure S1 in Multimedia Appendix 1). This study will be conducted on 2 postsurgical wards at the West Middlesex University Hospital, London, with a capacity of 64 beds, providing orthopedic, general surgical, urological, gastroenterological, and gynecological care.

Patients are screened after the morning ward round, and those who are expected to remain in hospital for at least 1 night are approached by the research team for consent and assessment against the inclusion and exclusion criteria. Most of these patients are postoperative, although a small number are preoperative. All patients will be fitted with a continuous vital sign monitor (Portrait Mobile; GE HealthCare) from recruitment until either discharge from hospital or transfer to another unit. This CE-marked device (European Union certificate CR-03-1004-804-22) consists of 2 wearable sensors: a wrist-mounted saturation probe measuring both the oxygen saturation and pulse rate and a chest sensor measuring the respiratory rate. Both groups will have vital signs monitored as per the standard of care, intermittently acquired every 4 to 6 hours by health care staff using the National Early Warning Score 2 for identification and escalation of a deteriorating patient [19].

Only the alerting group will have their continuous vital signs transmitted to a visible central viewer dashboard located at the

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nursing station and have audible alarms enabled on both the bedside hub monitor and the central viewer. All ward health care staff have access to real-time patient data and alarms; however, the nurse in charge is responsible for recognizing alarms, logging them, and informing the bedside nurse to respond appropriately. The intervention in this trial is the activation of real-time alerting through the continuous vital sign monitor, and alarms are managed entirely by the usual ward clinical team. They follow standard hospital escalation protocols, escalating deteriorating patients to the ward physician during daytime hours, the on-call physician out of hours, or the critical care outreach team. The critical care outreach team (also known as the rapid response team [RRT]) is an existing hospital team of specialized nurses who respond to acutely unwell patients requiring urgent assessment or intervention outside of the ICU. In the nonalerting group, health care staff are blinded to the continuous monitoring data.

To address alarm fatigue, several considerations have been taken. The alerting thresholds and announcement delays were derived from the Continuous Vital Sign Monitoring in Surgical Wards (COSMOS) pilot study, which conducted its initial phase by analyzing alarm data (pulse rate of <45 beats per minute [bpm] or >130 bpm sustained for ≥30 seconds, respiratory rate of <4 breaths per minute sustained for ≥30 seconds or >30 breaths per minute sustained for ≥120 seconds, apnea sustained for ≥30 seconds, and peripheral oxygen saturation of <85% sustained for ≥90 seconds or <80% without delay) [20]. These clinically validated alarm thresholds and built-in delay minimize false alerts caused by artifacts or transiently deranged vital signs. The central viewer is stationed at the nursing bay, beside the desk of the nurse in charge, who triages alarms. In addition, all ward staff received structured device training from GE HealthCare representatives focusing on correct interpretation, prioritization, and escalation of alarms.

Blinding of clinicians was not feasible as the intervention requires visible and audible alarms in real time to be recognized and acted upon by ward teams. The purpose of this study is to evaluate continuous vital sign monitoring in existing ward workflows, where staff awareness of alarms is intrinsic to the intervention itself. Several design features were incorporated to minimize performance and detection bias: all patients will receive standard-of-care monitoring, staff training was delivered similarly across both trial arms, and the primary end points were derived objectively from either device or electronic patient record (EPR) time stamps rather than relying on subjective documentation. Although some degree of behavior modification is unavoidable, these measures attempt to minimize bias.

Sample Size

In a pilot study, approximately 15% of patients wearing the continuous vital sign monitor generated at least one physiological alarm, with an average response time of 154 minutes [21]. In this trial, we defined a clinically meaningful target as a reduction in response time from 154 minutes to 60 minutes, corresponding to an estimated hazard ratio of 2.6 for time to response between the alerting and nonalerting groups. Therefore, recruiting a minimum of 200 patients, 100 in each arm, yields at least 30 participants with analyzable alert events. This is sufficient in providing reasonable precision for estimating the primary effect size and to support analyses of secondary outcomes.

In a previous feasibility study, 969 respiratory rate alerts were generated from 276 patients, supporting the assumption that a sample size of 200 patients generates sufficient signal volume for detailed alarm analyses [21].

Participants

Patients are identified and assessed for eligibility based on several criteria. Inclusion criteria are patients aged >18 years who provide informed consent to be part of the study. Exclusion criteria are patients aged <18 years and those who are unable to provide informed consent, have an allergy to the electrocardiogram or sensor electrodes or skin conditions at the sensor site, have an implantable electronic cardiac device (which responds to minute ventilation and can interfere with respiratory rate measurement technology), or are already taking part in another study.

Nursing staff, including both registered nurses and health care assistants, are invited to participate in the study. After recruiting 100 patients, all staff on the delegation log will be invited to complete a structured questionnaire, and a subset who volunteer will be selected for a follow-up interview at the end of the study period.

Ethical Considerations

All participants will be required to provide informed consent. Ethics approval was granted by the Health Research Authority and Health and Care Research Wales (approval reference 24/YH/0073; Integrated Research Application System project ID 335808) on April 18, 2024. This study is conducted in accordance with the principles of good clinical practice, the UK policy framework for health and social care research, and the Declaration of Helsinki. All patient data will be anonymized, and patients will be assigned a unique study ID. No identifiable patient data will be shared with a third party.

Trial Registration

The trial is registered with the International Standard Registered Clinical/Social Study Number (ISRCTN15518094).

Outcomes

Despite the growing interest in continuous vital sign monitoring, most prospective trials are limited by assessing only feasibility and acceptability and are not always powered for patient-centered outcomes [20,22-29]. There is still a clear lack of understanding of how continuous physiological data translate into alerts, how these alerts influence clinician assessment and intervention, and whether these actions ultimately improve patient outcomes. The WARD-AMS study design assesses the full monitoring-alert-action-outcome pathway.

Primary End Point

The primary end point is the time (in minutes) from the first device-defined deterioration episode (T_0) to the first objective escalation event (T_action) among patients who experience at least one device-defined deterioration episode during the monitoring period.

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Definition of T_0 (Time Zero)

T_0 is defined as the time stamp of the first device-defined deterioration episode for each patient according to the prespecified WARD-AMS deterioration criteria: pulse rate of <45 bpm or >130 bpm sustained for ≥30 seconds, respiratory rate of <4 breaths per minute sustained for ≥30 seconds or >30 breaths per minute sustained for ≥120 seconds and apnea sustained for ≥30 seconds, and peripheral oxygen saturation of <85% sustained for ≥90 seconds or <80% without delay.

Definition of T_Action (Escalation Event)

T_action is defined as the earliest time stamp after T_0 at which any of the following prespecified escalation events occurs:

- Activation of an RRT call: time of official call log in the switchboard or outreach database
- Unplanned transfer to higher level of care: time of actual bed movement from the ward to the ICU, high-dependency unit (HDU), or critical care unit as recorded on the EPR
- New high-acuity treatment orders (time stamp of order entry on the EPR): new intravenous (IV) fluid; new start of vasopressor or inotrope; new start of high-flow oxygen, continuous positive airway pressure, or noninvasive ventilation; and new start of broad-spectrum IV antibiotics
- Time stamp of alarm acknowledgment on the nursing log

For each patient with at least one eligible deterioration episode, only the first deterioration episode (first T_0) will be included in the primary analysis. T_action is the earliest qualifying escalation event occurring after that T_0. If at least one escalation event occurs after T_0, the primary outcome is calculated as follows and expressed in minutes:

$$\text{Primary outcome} = \text{Taction} - \text{T0}$$

If no escalation event occurs before censoring, the observation is right censored at the prespecified censor time (eg, end of monitoring period, discharge, death, or withdrawal from the study).

Acknowledgment of clinical deterioration can occur through several legitimate pathways in routine ward practice; therefore, relying on a single indicator may risk meaningful clinical response detection. To address this, a composite definition of T_action is chosen to ensure that the earliest objective, time-stamped event is captured. The same criteria are applied across both trial arms.

Exploratory End Point

Exploratory end points will further evaluate a broader range of clinical, operational, alarm-related, and user experience outcomes. Time-to-event clinical end points include time from T_0 to initiation of key treatments, such as antibiotics, IV fluids, vasopressors, oxygen, or advanced respiratory support. Additional timing end points include the interval from T_0 to RRT activation and from T_0 to unplanned transfer to an HDU or ICU. Resource use outcomes will be explored, including length of hospital stay, rates of admission to higher-level care, frequency of RRT activation, and in-hospital mortality.

Analysis of alarms will include identifying the frequency, type, and clinical relevance of alerts triggered by the continuous vital sign monitor, as well as the proportion of alarms that are associated with escalation events. Patient and health care staff experience will be evaluated via structured questionnaires and semistructured interviews.

Health Care Staff Questionnaire and Interview

An adapted System Usability Scale questionnaire will be used to evaluate health care staff experiences with the Portrait Mobile system (Figure S2 in Multimedia Appendix 1). This adaptation is based on a validated framework designed to quantify user experience and acceptance [30]. Consent will be obtained before staff participation, and the questionnaire will be completed online on an electronic form via Greenlight Guru [31]. Responses will be captured using a 5-point Likert scale ranging from “strongly agree” to “strongly disagree,” allowing for precise measurement of attitudes toward regular use, complexity, integration of functions, and overall usability. Open-ended questions at the end will permit staff to share any specific experiences or suggestions for improvement, enhancing qualitative understanding of the quantitative findings.

Semistructured interviews will be conducted using a predefined guide of questions formulated following a literature review (Figure S3 in Multimedia Appendix 1). The guiding questions follow themes regarding system functionality, patient safety implications, effectiveness, adequacy in training, practical barriers and facilitators, technological challenges, and suggestions for system enhancements. These interviews will be audio recorded, anonymized, and transcribed verbatim, followed by analysis using NVivo (version 12; Lumivero) [32].

Patient Questionnaire and Interview

At least 24 hours after being recruited to the trial, patients will complete a questionnaire to assess their perceptions and experiences of the Portrait Mobile system (Figure S4 in Multimedia Appendix 1). This aims to collect information on comfort, usability, perceived impact on health care outcomes, and overall satisfaction with the monitoring device.

Additionally, a follow-up telephone interview will be conducted approximately 2 weeks after discharge to evaluate longer-term perceptions and outcomes (Figure S5 in Multimedia Appendix 1). These interviews are structured to capture detailed information on patient experiences and suggested improvements.

Statistical Analysis

Primary End Point Analysis

Among the 2 groups (blinded and unblinded), the primary comparison will be the time from device-defined deterioration to objective escalation. The primary analysis will be performed in the population of patients who experience at least one device-defined deterioration episode, restricted to only 1 episode per patient (the first). Time-to-event methods will be used, with Kaplan-Meier curves constructed for each arm to visualize the distribution of time to escalation. The primary hypothesis test will use a log-rank test comparing the survival curves between arms, and a Cox proportional hazard model will be fitted with the interventional arm as the main exposure to estimate the

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hazard ratio for escalation (intervention vs control) with corresponding 95% CIs. The Cox model will be adjusted for key baseline covariates (age, sex, and comorbidity burden [Charlson Comorbidity Index]).

Patients with a device-identified deterioration without an escalation event during follow-up until their censor time will be treated as right censored in all time-to-event analyses. Proportional hazard assumptions will be evaluated using standard diagnostics such as Schoenfeld residuals. If these assumptions are materially violated, alternative or supplementary summaries such as restricted mean time to escalation up to a predefined time horizon may be reported in sensitivity analyses.

Exploratory Analysis

Analysis of all clinical end points involving time-to-event data will be conducted using survival analysis methods, specifically Kaplan-Meier curves and log-rank tests to assess differences between the alerting and nonalerting arms.

Length of hospital stay will undergo additional analysis using nonparametric tests to evaluate differences in median length of stay between the 2 study arms. Secondary outcomes presented as categorical variables, such as frequency of HDU or ICU admission and RRT activation, will be compared using chi-square tests. These will be conducted using RStudio (Posit PBC) [33].

Quantitative data from both the health care staff and patient questionnaires will be analyzed to illustrate frequency distributions and central tendencies regarding system usability, satisfaction, and other outcome measures. Likert-scale responses will be numerically scored and statistically analyzed using RStudio [33].

Interview transcripts will be analyzed by generating a set of codes that will be predefined from existing literature and serve as initial labels to index relevant data segments. This will be refined through iterative coding and thematic consolidation to ensure accurate and meaningful categorization by merging similar codes and splitting overly broad codes. To enhance validity, this method will be performed by 2 independent researchers until thematic consensus and data saturation are reached.

The quantitative outcomes (time to acknowledgment of deterioration, time to treatment initiation, escalation of care, and alarm analyses) will be compared with qualitative themes from the staff and patient questionnaires and interviews using a triangulation approach for a better understanding of the effect and implementation of continuous vital sign monitoring. A joint display table will be developed aligning key quantitative results with corresponding qualitative findings, identifying areas of convergence, complementarity, or divergence.

This integrated mixed methods approach aims to facilitate a comprehensive understanding of the usability, acceptability, and practical implications of the Portrait Mobile system.

Data Governance and Management

The study data will be extracted by a staff member employed as a business intelligence research analyst at Chelsea and Westminster Hospital National Health Service Foundation Trust. These data are stored on secure trust servers, with access restricted to the core study team. These data will be retained for 15 years in accordance with trust policy. An audit trail is available in the EPR.

Each participant will be assigned a unique trial ID during randomization. Variables extracted will include demographics (eg, date of birth, sex, and ethnicity), medical and medication history, vital signs, blood tests, transfer of care, and length of stay. Missing data will not be imputed and will be analyzed as available.

Results

This manuscript reports the approved study protocol for the WARD-AMS trial, which received favorable ethics approval in April 2024. A total of 200 patients meeting the inclusion and exclusion criteria were successfully randomized, recruited, and completed the period of continuous vital signs monitoring. All patients completed the baseline questionnaire; as of December 2025, a total of 92 patients have participated in the telephone interview. In addition, 50 staff members completed the questionnaire, of whom 27 consented to participate in the interview. As of December 2025, 10 staff members have been interviewed. All data collection is projected to be completed by February 2026; thereafter, it will be cleaned, interviews transcribed, and prepared for data analysis. Results will be finalized with a manuscript submitted for publication by mid-2026.

Discussion

Expected Findings

The WARD-AMS study is expected to demonstrate that continuous vital sign monitoring of postoperative patients in a general surgical ward reduces the time from device-defined physiological deterioration to the first objective escalation event (acknowledgment or clinical action) compared to standard-of-care intermittent monitoring. Quantitative analysis will evaluate the changes in response latency, time to treatment, and escalation of care. Qualitative analysis will focus on contextualizing these outcomes by exploring staff and patient experiences. Together, these findings will clarify how continuous vital sign monitoring influences patient outcomes to understand better how to implement these technologies into existing clinical workflows.

Comparison With Prior Work

Previous observational and before-and-after studies have set a foundation to build on. These study designs and systematic reviews are limited by heterogeneity in device and sensor technologies, alerting protocols, escalation pathways, and staff engagement practices [12,13,34,35]. The COSMOS pilot prospective study evaluated alerting parameters; however, it was not powered for achieving statistical significance [20]. Our study allows for a more comprehensive assessment of the clinical benefit and implementation feasibility in a real-world setting.

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Alarm Fatigue and Implementation

A key area of analysis will involve alarm characteristics, including their frequency and clinical relevance and configuration of alarm thresholds. Understanding this will provide critical insights into addressing alarm fatigue, a known limitation of critical monitoring systems [12,13]. Qualitative data on staff perceptions and experiences will highlight reasons contributing to cognitive burden, such as a high number of false-positive alarms or unclear escalation pathways. These findings will further clarify and provide recommendations on how to integrate these technologies into general wards, improving usability, minimizing disruptions, and maximizing patient outcomes.

Strengths and Limitations

The strengths of the WARD-AMS study include the randomized design and prospective real-world deployment in an active general surgical ward. The study is being conducted in 2 separate wards, which captures variability in management and staff practices. In addition, both quantitative and qualitative data will be analyzed.

The limitations include the study being conducted in a single center with established escalation pathways. However, these are representative of a typical National Health Service surgical ward, which uses the National Early Warning Score 2 as a track-and-trigger threshold system supported by critical care outreach nurses, and therefore, the results are transferable to similar settings. Lack of blinding of clinicians in the alerting arm may introduce the possibility of performance and detection bias. However, as continuous vital sign monitoring is intended to modify clinical response behavior, staff awareness will reflect real-world practice in assessing implementation and effectiveness.

Future Directions and Dissemination

Overall, this study expects to lay a robust foundation for larger multicenter evaluation across diverse hospital settings and specialties. Results will be disseminated through peer-reviewed publications, conference presentations, and engagement with clinical innovation teams to support broader adoption and promote safer, more responsive, and equitable health care.

Acknowledgments

The authors declare the use of generative artificial intelligence (GAI) in the research and writing process. According to the Generative Artificial Intelligence Delegation Taxonomy (2025), the following tasks were delegated to GAI tools under full human supervision: literature search and systematization, evaluation of the novelty of the research and identification of gaps, proofreading and editing, summarizing text, and reformatting. The GAI tools used were ChatGPT-4o and ChatGPT-5 (OpenAI). Responsibility for the final manuscript lies entirely with the authors. GAI tools are not listed as authors and do not bear responsibility for the final outcomes.

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Data Availability

The data generated from this study remain under the ownership of Chelsea and Westminster Hospital National Health Service Foundation Trust (study sponsor), who retain full data storage and analysis. All data are stored on the trust's secure servers, with access granted on a case-by-case basis and in compliance with the General Data Protection Regulation. Deidentified patient data may be shared with qualified researchers for scientific work following approval from the Chelsea and Westminster Hospital National Health Service Foundation Trust's research and governance office. The subinvestigator or clinical investigator may be contacted for requests.

Authors' Contributions

JS, MJ, FSN, and SK developed the study protocol and coordinated study setup, regulatory approvals, and project management. JS and SK were involved in the writing of the manuscript. All authors reviewed and edited the manuscript. All authors approved the final version of this manuscript and agree to be accountable for all aspects of the work. JB and JA provided device-specific technical expertise and staff training support but are not involved in patient recruitment, data collection, or data analysis. All analyses are conducted independently by JS and the academic research team at Chelsea and Westminster Hospital National Health Service Foundation Trust and Imperial College London. All publications undergo internal institutional review before submission to ensure transparency and scientific integrity.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplementary figures, including the study design flowchart and patient and health care staff questionnaires and interview guided questions.
[DOCX File, 1181 KB - resprot_v14i1e81558_app1.docx]

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Abbreviations

bpm: beats per minute
COSMOS: Continuous Vital Sign Monitoring in Surgical Wards
EPR: electronic patient record
HDU: high-dependency unit
ICU: intensive care unit
IV: intravenous
RRT: rapid response team

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App-Based Myofunctional Therapy to Improve Adherence and Outcomes of Mandibular Advancement Devices in Moderate Obstructive Sleep Apnea: Multicenter Randomized Trial Protocol

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Abstract

Background: Mandibular advancement devices (MADs) are a valid alternative for patients with moderate obstructive sleep apnea (OSA) who do not tolerate continuous positive airway pressure. Despite their efficacy, both adherence and long-term results remain a challenge. Myofunctional therapy (MT) has shown potential to improve upper airway muscle tone and reduce OSA severity, but its role as an adjunct to MAD treatment is still unclear. This protocol evaluates whether app-based MT (Airway Gym) can improve adherence and clinical outcomes in patients with moderate OSA treated with MADs. We describe the study design.

Objective: This study aims to evaluate whether a mobile app–based MT program (Airway Gym) can improve adherence to MAD therapy and related sleep parameters in patients with moderate OSA treated with MADs.

Methods: This multicenter, prospective, randomized, controlled study included adults aged 18 - 75 years with moderate OSA (apnea–hypopnea index 15 - 30). Participants were randomized into four groups: (1) placebo exercises, (2) MT only, (3) MAD only, and (4) MAD plus MT. Outcomes included changes in the apnea–hypopnea index, oxygen desaturation index, sleep quality (Epworth and Pittsburgh scores), and tongue strength/endurance measured with the Iowa Oral Performance Instrument and a tongue digital spoon. Adherence was monitored via telemedicine and sleep diaries.

Results: Recruitment began in February 2024 across participating centers. Data collection was planned to continue until December 2025, after which the final analyses were performed. The protocol described the study procedures up to the most recent administrative review conducted in January 2025.

Conclusions: This protocol describes the rationale and methodology of a randomized trial evaluating app-based MT as an adjunct to MAD therapy in patients with moderate OSA. Full study results will be reported after the final analysis.

Trial Registration: ISRCTN Registry ISRCTN13128082; https://www.isrctn.com/ISRCTN13128082

International Registered Report Identifier (IRRID): DERR1-10.2196/80521

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KEYWORDS

obstructive sleep apnea; myofunctional therapy; mandibular advancement device; adherence; telemedicine; airway gym; digital health; IOPI; sleep quality; Iowa Oral Performance Instrument

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Introduction

Obstructive sleep apnea (OSA) is a multifactorial and prevalent condition that affects up to 20% of the adult population [1] and is characterized by repeated episodes of upper airway collapse during sleep [2]. This results in oxygen desaturation, fragmented sleep, and increased cardiovascular and neurocognitive risk [3]. Although continuous positive airway pressure (CPAP) remains the first-line treatment, many patients are unable or unwilling to adhere to long-term use, and alternative therapeutic strategies are needed [4].

Mandibular advancement devices (MADs) are a well-established option for patients with mild to moderate OSA [5]. These devices function by advancing the mandible and tongue forward, which thereby increases the patency of the upper airway and reduces its collapsibility [6]. Despite their efficacy, adherence to MAD therapy is inconsistent, and the long-term use rate is 60% - 70%. The long-term adherence depends on each patient's characteristics and device type [7], and significant morbidity is associated with its use. Studies [8-10] have described potential adverse effects associated with the long-term use of MADs, including gradual dental and skeletal changes such as decreased overjet and overbite, forward displacement of molars, and modifications of intercanine and intermolar relationships [11]. Some patients develop changes in dental inclination, including lingual tilting of the upper incisors and labial tilting of the lower incisors [12]. Skeletal alterations, such as posterior mandibular rotation, increased lower facial height, and vertical changes in the condylar position, have also been reported [10]. Although most studies have not reported significant structural damage to the temporomandibular joint, occasional reports of joint sounds, bite changes such as a posterior open bite, and mild discomfort highlight the need for regular monitoring [13]. In general, these side effects tend to be minor and develop slowly, especially when the appliance is properly adjusted and clinical supervision is maintained.

Myofunctional therapy (MT) is an emerging behavioral treatment based on oropharyngeal exercises aimed at improving the tone and coordination of muscles involved in breathing, swallowing, and speech [14]. Recent studies have shown that MT can significantly reduce the apnea–hypopnea index (AHI) and improve sleep quality in adults with OSA [15,16]. This study is in line with recent national evaluations in Spain that have endorsed the safety and usefulness of MT for treating OSA in selected patients [15]. For the first time, a mobile app—Airway Gym—[16] has been officially recognized by a national health authority as a valid therapeutic tool for OSA. This recognition places Spain at the forefront of integrating digital health into routine care for sleep-related breathing disorders. MT has also been proposed as a supportive intervention for improving tolerance to other treatments such as CPAP [17]. However, its potential role in improving adherence to and therapeutic efficacy of MADs has not been investigated.

The present protocol outlines a multicenter, randomized, prospective controlled study designed to assess whether combining MAD therapy with MT—delivered through the Airway Gym mobile app—can improve both adherence and treatment outcomes in patients with moderate OSA. In addition, the study will evaluate whether baseline oropharyngeal muscle performance, assessed using the Iowa Oral Performance Instrument (IOPI) and a tongue digital spoon (TDS) device, is associated with treatment success after the 3-month intervention period [18]. The primary objective is to assess whether app-based MT enhances adherence to MAD use in patients with moderate OSA. This protocol focuses on the early adaptation phase of MAD therapy, as short-term adherence during the first 3 months has been identified as a critical determinant of long-term treatment continuation and tolerance. Previous studies evaluating early adherence to CPAP and MAD therapy have shown that most barriers to sustained use emerge during this initial period [17].

Methods

Study Design

This protocol describes a multicenter, prospective, randomized controlled pilot clinical trial designed to assess the influence of MT on the adherence and efficacy of MAD in patients with moderate OSA. The study was conducted at the Departments of Otolaryngology and Pulmonology of Hospitales Quirónsalud Marbella, Malaga, and Campo de Gibraltar, Cadiz, Spain.

The protocol was approved by the Research Ethics Committee of the Hospital Provincial de Málaga (AWAGAP-2023 - 1) and complies with the Declaration of Helsinki and the General Data Protection Regulation (EU) 2016/679. The study is registered with ISRCTN (ISRCTN13128082) [19]. A flowchart summarizing the study design, group allocation, intervention, and follow-up is provided in Figure 1.

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Figure 1. Flowchart of the study design illustrating the random allocation of 48 patients into four parallel groups: (1) placebo orofacial exercises, (2) myofunctional therapy (MT) using the Airway Gym app, (3) mandibular advancement device (MAD) only, and (4) MAD combined with MT. All patients were evaluated at the baseline and after 3 months of intervention using telemedicine monitoring and standardized outcome assessments.

Patients aged 18 to 75 years with a confirmed diagnosis of moderate OSA, defined as an AHI between 15 and 30 events per hour, were eligible. All participants required a favorable indication for MAD therapy following drug-induced sleep endoscopy (DISE) [20] and had to provide written informed consent.

DISE-Based Selection Criteria

All participants underwent DISE as part of the preenrollment assessment to determine the suitability for MAD therapy. The procedure was performed under standardized sedation following the VOTE classification (Velum, Oropharynx, Tongue base, Epiglottis).

Candidates were considered eligible if DISE revealed a predominantly anteroposterior or concentric collapse at the velum or oropharyngeal level that improved with a mandibular advancement (jaw-thrust) maneuver. Subjects with complete concentric collapse at the velum that did not improve with jaw thrust, isolated epiglottic collapse, or predominant lateral wall collapse were excluded. This ensured that all enrolled participants had a favorable DISE pattern predictive of a good response to MAD therapy.

These selection criteria are consistent with previous studies showing that DISE findings, particularly improvement of anteroposterior collapse with a mandibular advancement maneuver, predict a favorable response to oral appliance therapy [21].

Patients were included only if they fulfilled all of the following inclusion criteria and none of the exclusion criteria.

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Inclusion Criteria

The study included the following inclusion criteria: (1) adults aged 18‑75 years, (2) a diagnosis of moderate OSA (AHI 15‑30) confirmed by polysomnography, (3) no prior treatment for OSA (CPAP, MAD, upper airway surgery, or MT), (4) a favorable anatomical indication for MAD use based on DISE findings, (5) anatomical conditions compatible with the use of an MAD, (6) access to a smartphone and ability to use mobile apps, (7) the willingness and ability to complete daily sleep diary and follow-up assessments, and (8) the provision of signed informed consent.

Exclusion Criteria

The study included the following exclusion criteria: (1) the presence of bad nasal patency and the presence of nasal obstruction: patients were excluded if nasal endoscopy revealed bilateral obstruction exceeding approximately 50% of the nasal airway (eg, severe septal deviation, turbinate hypertrophy, or nasal valve collapse) that could interfere with MAD fitting or with the performance of MT. (2) Neurological, neurodegenerative, or cognitive disorders affecting adherence, (3) malformations or edentulism impeding adaptation to the MAD, (4) temporomandibular joint dysfunction, (5) ankyloglossia or lingual restrictions preventing orofacial exercise performance, (6) the inability to follow instructions or participate in telemedicine sessions, (7) active oncological disease, (8) a history of alcohol dependence or other behavioral disorders, (9) uncontrolled psychiatric illness, (10) the lack of access to a reliable internet connection or inability to operate mobile apps, and (11) patients currently participating in a structured weight loss program or those with unintentional weight changes exceeding 5% of body weight within the previous 3 months.

All eligibility criteria were evaluated and confirmed by both an otolaryngologist and a dental sleep specialist before randomization.

Randomization and Groups

A total of 48 patients were randomized into the following four parallel groups (n=12 each): (1) Group 1: placebo (sham orofacial exercises); (2) Group 2: MT using the Airway Gym app; (3) Group 3: MAD only; and (4) Group 4: combined MAD+MT.

Patients were randomized using a computer-generated block randomization sequence with a 1:1:1:1 allocation ratio to ensure balanced distribution across the four intervention groups. The sequence was stratified by the study center to minimize intersite variability and was generated using an online tool (Sealedenvelope.com). Allocation concealment was achieved using sequentially numbered, opaque, sealed envelopes that had been prepared by an independent researcher not involved in patient enrollment or outcome assessment.

All MADs were custom-fitted (NOA device, OrthoApnea, Málaga, Spain) and adjusted to the maximum comfortable mandibular protrusion.

Interventions

Myofunctional Therapy

Participants in the MT groups followed a structured oropharyngeal exercise regimen using the Airway Gym app for 3 months, during which telemonitoring and weekly follow-up were performed [22] (Figure 2).

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Figure 2. Still image from the app-based myofunctional therapy video (Airway Gym) used during the intervention period. The image shows a patient performing an oropharyngeal exercise as part of the structured and remotely supervised myofunctional therapy protocol delivered via the Airway Gym mobile app.

Mandibular Advancement Device

Participants assigned to MAD therapy were fitted with the NOA device (OrthoApnea) [23], a custom-fabricated, two-piece appliance designed to optimize mandibular protrusion and patient comfort. The device allows for gradual titration and lateral movement and is custom manufactured to each patient's individual craniofacial anatomy. All devices used in the study were generously provided by OrthoApnea for research purposes. Devices were fitted by dental sleep medicine specialists and monitored periodically for side effects and adjustment (Figure 3).

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Figure 3. Mandibular advancement device used in the study.

Placebo Therapy

The placebo protocol consisted of simple, low-intensity oral and facial movements intentionally designed to avoid activation of the key oropharyngeal and tongue muscles involved in airway function. The exercises included gentle lip gestures, light tongue repositioning without resistance, and relaxed mandibular movements performed without sustained contraction. To ensure neutrality, the placebo sequence was developed in collaboration with experienced myofunctional therapists and ear, nose, and throat specialists. It was pilot-tested in a small group of volunteers to confirm that it produced no change in tongue strength measured by the IOPI and no subjective improvement in orofacial muscle tone. This process ensured that the placebo protocol provided a nontherapeutic control condition for the trial.

Outcome Measures

Primary Outcomes

The primary outcome of the study is adherence to MAD therapy, expressed as the mean hours of use per night and the number of nights per week the device is used.

Adherence was evaluated using structured sleep diaries, telemedicine follow-up, and digital monitoring data (for MT via the Airway Gym app).

This primary endpoint directly reflects the main objective of the study: to determine whether app-based MT improves adherence and acceptance of MAD treatment in patients with moderate OSA.

Secondary Outcomes

Secondary outcomes include changes in objective sleep parameters and functional measures, including (1) AHI (events per hour of recording); (2) oxygen desaturation index (ODI; events per hour of recording); (3) minimal nocturnal oxygen saturation (min SpO_2); (4) tongue and buccinator strength measured using the IOPI and TDS; (5) sleep quality and daytime sleepiness, assessed using the Pittsburgh Sleep Quality Index, Epworth Sleepiness Scale, and a visual analog scale (VAS) for discomfort; and (6) adverse effects associated with MAD and MT use.

Baseline and 3-month postintervention measurements included anthropometric data (BMI, neck and waist circumference), polygraphy, orofacial myofunctional evaluation with scores [24], IOPI score (kPa) [18] (Figure 4), and TDS (g/cm^2) [25] (Figure 5).

Polygraphy was performed for each participant using a type III sleep study device (SOMNOtouch, SOMNOmed). During polygraphy, the following parameters were evaluated for this study: mean oxygen saturation and lowest oxygen saturation, time of sleep spent with blood oxygen saturation <90% (SpO_2<90), and the AHI. The AHI is described as the total number of apnea and hypopnea events per hour of recording in an overnight sleep study. Apnea is defined as a ≥90% decrease in airflow for at least 10 s and hypopnea as a reduction of respiratory signals for ≥10 s, associated with a minimum of 3% of oxygen desaturation [26].

A structured daily sleep diary was used to monitor self-reported side effects, hours of device use, and perceived discomfort, including any mandibular, dental, or temporomandibular joint symptoms. Patients completed a VAS to rate their pain or discomfort and recorded any adverse events associated with the use of the MAD or MT.

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Figure 4. Measurement of tongue strength using the Iowa Oral Performance Instrument (IOPI). The IOPI is used to objectively assess tongue pressure in kPa during isometric compression of an air-filled bulb placed on the tongue.

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Figure 5. Assessment of anterior tongue pressure using a digital spoon. This tool allows low-cost quantification of anterior lingual force (g/cm²) and can detect changes in oropharyngeal muscle tone over time.

Study Procedures

At the baseline, all participants underwent an otorhinolaryngology examination, DISE, and functional orofacial evaluation. Devices and exercises were introduced at the initial visit. After 3 months, patients underwent a repeat sleep study and functional testing and completed the questionnaires.

Adherence was monitored using a structured sleep diary to record their daily MAD use, exercise compliance, and sleep-related variables (Table 1).

The schedule of enrollment, interventions, and assessments is summarized in Figure 4, following the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines.

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Table . SPIRIT[a] figure: schedule of enrollment, interventions, and assessments.

Timepoint	Enrollment	Allocation	Post-allocation (Week 0)	Week 1 - 11	Week 12 (End of intervention)	Close-out
Enrollment						
Eligibility screening	X					
Informed consent	X					
Baseline assessments (AHI[b], ODI[c], min $SatO_2$ [d], ESS[e], PSQI[f], IOPI[g], and TDS[h])	X					
Randomization		X				
Interventions						
Sham MT[i]			X	X	X	
MT alone			X	X	X	
MAD[j] alone			X	X	X	
MAD + MT			X	X	X	
Assessments						
Adherence (telemonitoring and diaries)				X	X	
Sleep study (AHI, ODI, and min $SatO_2$)			X		X	
IOPI and TDS			X		X	
ESS, PSQI, and VAS[k]			X		X	
Adverse events				X	X	
Close-out						X

[a]SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials.
[b]AHI: apnea–hypopnea index.
[c]ODI: oxygen desaturation index.
[d]$SatO_2$: saturated oxygen.
[e]ESS: Epworth Sleepiness Scale.
[f]PSQI: Pittsburgh Sleep Quality Index.
[g]IOPI: Iowa Oral Performance Instrument.
[h]TDS: tongue digital spoon.
[i]MT: myofunctional therapy.
[j]MAD: mandibular advancement device.
[k]VAS: visual analog scale.

Sample Size Calculation

The sample size calculation was primarily based on detecting moderate differences in adherence to MAD therapy (hours per night) between groups, which represents the primary outcome of this study. Secondary analyses explored changes in AHI, ODI, and other physiological measures as supportive efficacy end points. This study was conceived as a multicenter exploratory randomized trial including four parallel treatment groups with assessments at baseline and after 3 months.

These assumptions were informed by previous studies reporting mean reductions in AHI following MT [14] and variability in MAD response and adherence [5]. Considerations regarding the variability of AHI measurement were also based on Pevernagie et al [26].

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The power calculation was based on a repeated-measures design (4 groups×2 time points), assuming a two-sided α=.05 and within-subject correlations between 0.5 and 0.7. Under these conditions, a total sample of 48 participants provides approximately 80% to 87% power to detect a moderate interaction effect (Cohen *f*=0.30-0.34) for the primary outcome (adherence) and for exploratory analyses of AHI and related parameters. *Power estimation was performed using G* Power 3.1 software [27]. This analysis was powered primarily for adherence, while physiological end points (AHI, ODI, min SpO_2) were analyzed as exploratory secondary outcomes.

In practical terms, this sample size offers around 80% power to detect standardized mean differences (g=0.95 - 1.10) in change scores between groups. For AHI, this translates to a difference of roughly 8 to 10 events per hour, while for adherence (hours per night of MAD use), it allows the detection of differences of approximately ≥1.5 hours per night assuming a standard deviation of 1.8 hours. For the binary adherence outcome (≥4 hours per night on ≥70% of nights), the study retains ~80% power to identify group differences around 75% versus 35% to 40%.

Although modest in size, this design provides adequate sensitivity to identify meaningful changes and to yield variance estimates that will guide the power calculation of a future large-scale confirmatory trial.

Statistical Analysis

Descriptive statistics (mean and standard deviation or median and interquartile range) were used to characterize the study population. Between-group differences were analyzed using ANOVA for normally distributed continuous variables and Kruskal–Wallis tests for nonparametric data. For categorical variables, the chi-squared test or Fisher exact test was applied as appropriate.

A prespecified analytic framework was established prior to data analysis following the structure defined in the ISRCTN preregistration. Although a full statistical analysis plan was not separately published, all primary and secondary end points, analytic strategies, and handling of missing data were defined before unblinding.

When the overall group effect is significant, post hoc pairwise comparisons were performed using Bonferroni correction (or Dunn test for nonparametric data) to control for alpha inflation. Paired comparisons (baseline vs 3 mo within each group) were analyzed using the paired *t* test or Wilcoxon signed-rank test.

Correlations between adherence (primary outcome) and physiological parameters (AHI, ODI, min SpO_2 , IOPI, and TDS) were assessed using Spearman's rank correlation. All tests were 2-tailed, and statistical significance was set at $P<.05$ after correction for multiple comparisons.

The results were presented with adjusted *P* values and 95% CIs where applicable. Given the exploratory design and modest sample size, the analyses are intended to generate hypotheses for future confirmatory studies rather than establish definitive causal inferences.

Analyses were conducted using Epi Info (CDC) and IBM SPSS Statistics v.28.0 (IBM Corp).

Participants

Eligible participants were adults aged 18 to 75 years with moderate OSA (AHI 15 - 30), confirmed by polysomnography, with favorable anatomical features for MAD use based on DISE. Exclusion criteria included cognitive impairment, temporomandibular dysfunction, severe malocclusion, ankyloglossia, or inability to use mobile apps.

Randomization and Groups

Forty-eight patients are to be randomized into four groups (n=12 per group): (1) placebo exercises, (2) MT only, (3) MAD only, and (4) MAD+MT. Randomization is performed using computer-generated block sequences and stratified by site.

Interventions

The MAD used was the NOA device (OrthoApnea), fitted to each patient's maximum comfortable protrusion. MT was delivered via the Airway Gym mobile app, including structured oropharyngeal exercises for 12 weeks with weekly telemonitoring. The placebo group performed nonfunctional movements. Adherence to MAD and MT was recorded via sleep diaries.

Outcomes

Primary outcomes included changes in AHI, ODI, and min SpO_2 . Secondary outcomes were adherence to MAD (hours per night), tongue strength and endurance (measured by IOPI and TDS), and subjective sleep quality (Epworth Sleepiness Scale, Pittsburgh Sleep Quality Index, and VAS for discomfort).

Adherence Monitoring

Adherence to MT is monitored digitally through the Airway Gym app, which automatically records the number, duration, and completion of each exercise session for every participant. These data provide an objective record of engagement with the therapy. For participants using MADs, adherence is also verified through telemedicine follow-ups and structured clinical interviews.

In addition, participants complete daily sleep diaries to document their perceived use and sleep quality. While sleep diaries may be subject to recall bias and tend to overestimate adherence, their inclusion is consistent with prior studies in behavioral sleep medicine and provides complementary subjective data on patient perception and compliance.

Although sleep diaries are subject to recall bias, adherence to MT is objectively recorded through the Airway Gym app, which automatically logs daily session time, duration, and completion for each participant. Adherence to MAD use is further verified during structured telemedicine visits, providing an additional layer of supervision to minimize overestimation. At the time of study initiation, commercially available MADs with embedded objective adherence sensors were not yet widely accessible in our health care system; therefore, objective device-based adherence monitoring could not be implemented in this exploratory trial.

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Data Collection and Analysis

Assessments were performed at baseline and at 3 months. Polygraphy was used to assess sleep parameters. Orofacial function was evaluated using orofacial myofunctional evaluation with scores protocol (OMES), IOPI (in kPa), and TDS (g/cm²). Descriptive statistics and group comparisons were performed using ANOVA, Kruskal–Wallis, or nonparametric tests as appropriate. A significance level of $P<.05$ was applied.

Bias Control and Data Management

To prevent performance and detection bias, clinical investigators responsible for participant follow-up, MAD adjustments, and data entry were completely independent from the development of the Airway Gym app. All outcome assessors (polygraphy technicians, IOPI/TDS operators, and questionnaire administrators) were blinded to group allocation. Standardized telemedicine scripts and fixed follow-up schedules were used across all study sites to ensure procedural uniformity regardless of treatment arm.

All outcome data (polysomnographic variables, IOPI measurements, adherence records, and questionnaire scores) are collected and coded by local investigators who are not affiliated with the app's development. Data are entered into a centralized database managed by an independent statistician blinded to group allocation. Analyses of AHI, ODI, and adherence are performed using deidentified datasets.

Although one investigator is the inventor and scientific advisor of the Airway Gym app, he did not participate in recruitment, data collection, adherence verification, polygraphy interpretation, or statistical analysis. Data were stored in a centralized, access-restricted database managed by the institutional research office, which also performed routine external monitoring of data integrity. Statistical analyses were carried out by an independent biostatistician blinded to group allocation.

Ethical Considerations

The study was approved by the Ethics Committee of Hospital Provincial de Málaga (approval code: AWGAP-2023-1; date: January 17, 2023) and conducted in accordance with the Declaration of Helsinki. Written informed consent was obtained from all study participants prior to enrollment. Written informed consent for publication of the identifiable image included in Figure 2 was obtained from the individual depicted.

Results

Participant recruitment started in February 2024. As of January 2025, enrollment and follow-up assessments are progressing according to schedule. Data collection is expected to conclude in December 2025, after which the final analyses will be carried out once all participants have completed the 3-month intervention period.

Discussion

Principal Findings

This study primarily aims to determine whether combining app-based MT with MAD therapy improves adherence and tolerance, with secondary analyses exploring changes in AHI and oropharyngeal function. This protocol is expected to contribute new evidence on the potential of combining app-based MT (Airway Gym) with MAD treatment to enhance adherence and functional outcomes in moderate OSA.

We hypothesize that participants receiving both interventions will show greater adherence to MAD use and more pronounced functional improvement than those receiving either treatment alone or placebo exercises.

Comparison With Prior Work

This hypothesis is supported by previous studies suggesting that oropharyngeal exercises may enhance upper airway function by improving muscle tone and coordination [14,16,18,21,24,28-31]. The trial assessed changes in tongue strength and control through the IOPI and the TDS to determine whether these improvements are more pronounced in participants undergoing MT compared to those treated with MAD alone.

The study explored whether a potential interaction exists between passive mechanical support (via MAD) and active neuromuscular training (via MT), as suggested by prior research [14].

The study also examined whether the combination of MAD and MT may improve patient-reported tolerance and adherence, particularly in individuals with reduced baseline muscle tone or oral fatigue, which are known factors contributing to poor MAD tolerance [32].

Strengths and Limitations

An important aspect of this study is the use of a mobile app to deliver the MT protocol. This app-based platform is designed to allow remote supervision, daily monitoring, and structured progression of exercises without the need for in-person visits.

This telemedicine approach is expected to offer a scalable, accessible, and cost-effective model for supporting behavioral therapy in OSA, potentially facilitating better adherence to the intervention.

Previous reports have highlighted challenges in implementing MT in routine care—such as time constraints, cost, and low compliance—suggesting that digital tools may help overcome these barriers and promote broader adoption [16,19].

This digital health model may be particularly valuable in health care settings, with limited access to sleep specialists, such as rural or underserved areas, by facilitating the broader implementation of behavioral interventions.

Additionally, the study aims to objectively quantify oropharyngeal muscle changes resulting from MT to assess its potential functional impact.

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Increases in IOPI and TDS scores were analyzed to explore whether MT induces neurofunctional adaptations beyond symptomatic improvement [25].

Since discontinuation of MAD therapy in clinical practice is often due to discomfort rather than lack of efficacy, this study assessed whether strategies that promote neuromuscular adaptation, such as telemedicine MT, can enhance device acceptance.

To the best of our knowledge, this is the first randomized controlled trial designed to evaluate the combined use of an MAD and MT in patients with moderate OSA. It is also the first study to deliver MT through a mobile app–based telemedicine platform, allowing for remote supervision and structured progression of exercises.

This study contributed evidence on the value of a treatment model that integrates both anatomical and functional approaches to improve outcomes in patients with moderate OSA [31].

The study has several anticipated limitations. The sample size, while calculated to detect meaningful clinical effects, may still be affected by interindividual variability. Certain outcomes, such as adherence and discomfort, are based on patient-reported data and may be subject to bias. The 3-month follow-up duration was intentionally selected to capture early adherence patterns and short-term functional outcomes, as this period reflects the initial behavioral and neuromuscular adaptation to MAD and MT. Long-term adherence mechanisms were assessed in future longitudinal extensions of this trial once the full cohort completes extended observation.

Another potential limitation of this protocol is the use of self-reported sleep diaries, which are known to overestimate adherence. However, this limitation is common across most studies evaluating behavioral therapy or MT. In our case, adherence is also tracked digitally through the Airway Gym app and verified by telemedicine review, which mitigates the inherent subjectivity of diary-based reporting.

A further limitation is the absence of an embedded objective adherence sensor for the MAD. Although MT adherence is objectively logged through the Airway Gym platform, MAD use still relies partly on patient-reported sleep diaries, which may overestimate usage. This was mitigated through structured telemedicine verification, but future studies should integrate sensor-equipped MADs to provide fully objective adherence monitoring once such technology becomes more accessible.

Another limitation is that, although mechanisms were implemented to ensure independence in data handling and outcome assessment, the involvement of one investigator as the inventor of the Airway Gym app may raise concerns regarding potential performance bias. To mitigate this, data collection and statistical analysis were conducted entirely by independent personnel, and standardized procedures were applied uniformly across study arms.

Future Directions

If the combined therapy demonstrates greater adherence and functional benefit, this approach could be tested in larger, longer-term studies to assess sustained clinical impact, cost-effectiveness, and potential craniofacial adaptations. Further research also explored integration with wearable sleep-monitoring technologies to enhance remote follow-up.

Dissemination Plan

The results of this trial were disseminated through peer-reviewed publications and presentations at national and international otolaryngology and sleep medicine conferences. Summaries were also shared with participating centers and made accessible to patients and the public through institutional communication channels and the Airway Gym platform.

Conclusions

This multicenter trial aims to generate high-quality evidence on the feasibility and effectiveness of integrating app-based MT into standard mandibular advancement treatment for moderate OSA. The results are expected to inform future clinical guidelines and support the development of digital, patient-centered interventions that enhance adherence and treatment outcomes in sleep-disordered breathing.

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Data Availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

COCR is the inventor and scientific advisor of the Airway Gym app, which was used in the study. He received no financial compensation related to this project. All other authors declare no competing interests. Although one of the authors (COCR) is the inventor and scientific advisor of the Airway Gym app, all study procedures, data collection, and statistical analyses are

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conducted independently by investigators with no affiliation to the app's development. This conflict of interest was fully disclosed to the ethics committee and managed through independent data handling and blinded outcome assessment.

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Abbreviations

AHI: apnea–hypopnea index
CPAP: continuous positive airway pressure
DISE: drug-induced sleep endoscopy
IOPI: Iowa Oral Performance Instrument
MAD: mandibular advancement device
MT: myofunctional therapy
ODI: oxygen desaturation index
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TDS: tongue digital spoon
VAS: visual analog scale
VOTE: Velum, Oropharynx, Tongue base, Epiglottis

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Effectiveness of a Cardiovascular Management System on Triple Risk Factor Control in High-Risk Older Adults: Protocol for a Randomized Controlled Trial

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Abstract

Background: Cardiovascular disease (CVD) remains a leading cause of morbidity and mortality in China. Although the National Basic Public Health Services Program provides annual health checkups for older adults, postscreening management of CVD risk factors such as hypertension, dyslipidemia, and diabetes is often inadequate. The CardioCare system is a digital cardiovascular management platform that integrates risk prediction, personalized health interventions, and continuous engagement to address these gaps.

Objective: This trial aims to evaluate the effectiveness of the CardioCare system in improving triple risk factor control (simultaneous control of blood pressure, lipids, and glycemia) at 12 months among high-risk adults. Secondary objectives include assessing changes in estimated 10-year CVD risk, individual clinical parameters, medication adherence, lifestyle modification, system engagement, usability, satisfaction, and cost-effectiveness.

Methods: This is a single-center, parallel-group, superiority randomized controlled trial with a 1:1 allocation ratio. A total of 300 adults aged ≥50 years with an estimated 10-year CVD risk of >10% and no previous CVD diagnosis will be recruited from the Health Management Center of the First Affiliated Hospital of Sun Yat-sen University in Guangzhou, China. Participants will be randomized to receive either the CardioCare system intervention or minimal usual care for 12 months. The intervention includes risk stratification and communication, weekly personalized SMS text messages or WeChat messages, and cardiologist oversight. The primary outcome is the proportion of participants achieving triple risk factor control at 12 months. Secondary outcomes include clinical, behavioral, usability, and economic measures. Analyses will follow the intention-to-treat principle, with multiple imputation for missing data.

Results: This trial was funded on October 28, 2024. Recruitment is scheduled to begin in January 2026 and conclude in April 2026, with follow-up completed by June 2027. Data analysis will commence in mid-2027, and the main findings are expected to be published by the end of 2027. As of manuscript submission, recruitment has not yet started.

Conclusions: This trial will provide robust evidence on the clinical effectiveness and cost-effectiveness of the CardioCare system in managing multiple cardiovascular risk factors among high-risk adults. The findings will inform the potential for scaling this intervention within health checkup centers and integrating it into national chronic disease management strategies.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2500103369; https://www.chictr.org.cn/hvshowproject.html?id=277669

International Registered Report Identifier (IRRID): PRR1-10.2196/84428

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KEYWORDS

cardiovascular diseases; digital health; randomized controlled trial; risk factor control; medication adherence

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Introduction

The National Basic Public Health Services Program (NBPHSP) in China was launched in 2009 and has greatly improved access to annual health checkups for residents aged ≥65 years. This program aims to improve early detection and management of health issues among older adults, reaching approximately 173 million individuals, which constitutes approximately 12% of the population [1]. These checkups are designed to facilitate the early detection and management of various health conditions, particularly those prevalent in older adults, such as cardiovascular disease (CVD). Despite the extensive reach and potential benefits of this program, postcheckup management of health issues remains suboptimal [2].

Multiple systemic challenges contribute to these deficiencies. The fragmented nature of the health care system often results in poor coordination between primary care providers and specialists, leading to disjointed follow-up and inconsistent treatment [3]. Resource constraints, including shortages of trained personnel and limited funding, further limit the capacity for adequate postcheckup monitoring and support. Low patient engagement is another barrier; many patients fail to adhere to recommended treatments or lifestyle changes, diminishing the effectiveness of follow-up care [4,5]. Moreover, many individuals lack the necessary understanding of their condition and treatment plans, preventing effective self-management. Geographic and economic constraints, long waiting times, and inadequate electronic health record integration contribute to ongoing care fragmentation.

Screening alone is insufficient to improve disease awareness or management [6,7]. Many older adults in China have limited ability to comprehend screening results or the actions required in response [8,9]. Psychological barriers such as fear, denial, or anxiety may further reduce willingness to engage in follow-up care [10]. Infrastructure limitations, high costs, and poor physician-patient communication compound the problem [11,12]. Collectively, these factors underscore the need for a more integrated, patient-centered approach to postscreening management of chronic diseases, particularly CVD.

In light of these persistent challenges (ie, fragmented care, low patient engagement, and insufficient follow-up mechanisms), there is a clear need for innovative, scalable solutions that can support long-term cardiovascular risk management within routine care pathways. The CardioCare system was developed in response to these needs. It integrates an established CVD risk prediction model for risk stratification with personalized digital health management strategies, including tailored reminders, targeted lifestyle and medication interventions, and continuous feedback loops. By delivering individualized guidance and monitoring through a digital platform, the CardioCare system aims to enhance adherence to treatment plans and promote sustained behavior change, thereby improving control of key CVD risk factors. However, whether the implementation of the CardioCare system in routine health checkup services improves CVD management has yet to be examined.

Therefore, we will conduct a randomized controlled trial (RCT) to evaluate the effectiveness of the CardioCare system in improving triple risk factor control, defined as the simultaneous control of blood pressure, lipids, and glycemia, at 12 months among high-risk older adults identified through routine health checkups. Secondary objectives are to (1) assess changes in estimated 10-year CVD risk and individual clinical parameters, including systolic blood pressure (SBP), low-density lipoprotein cholesterol (LDL-C), and glycated hemoglobin (HbA_{1c}); (2) evaluate medication adherence, adoption of lifestyle modifications, and patient engagement with the system; (3) assess system usability and satisfaction among participants and health care providers; and (4) examine the potential cost-effectiveness of the intervention compared with minimal usual care.

Methods

Participants

This single-center, 2-arm, parallel-group RCT with a 1:1 allocation ratio will be conducted at the Health Management Center of the First Affiliated Hospital of Sun Yat-sen University in Guangzhou, China (Figure 1). The trial is designed within a superiority framework to determine whether the CardioCare system is more effective than minimal usual care in achieving triple risk factor control at 12 months among high-risk adults.

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Figure 1. Study flowchart. CVD: cardiovascular disease.

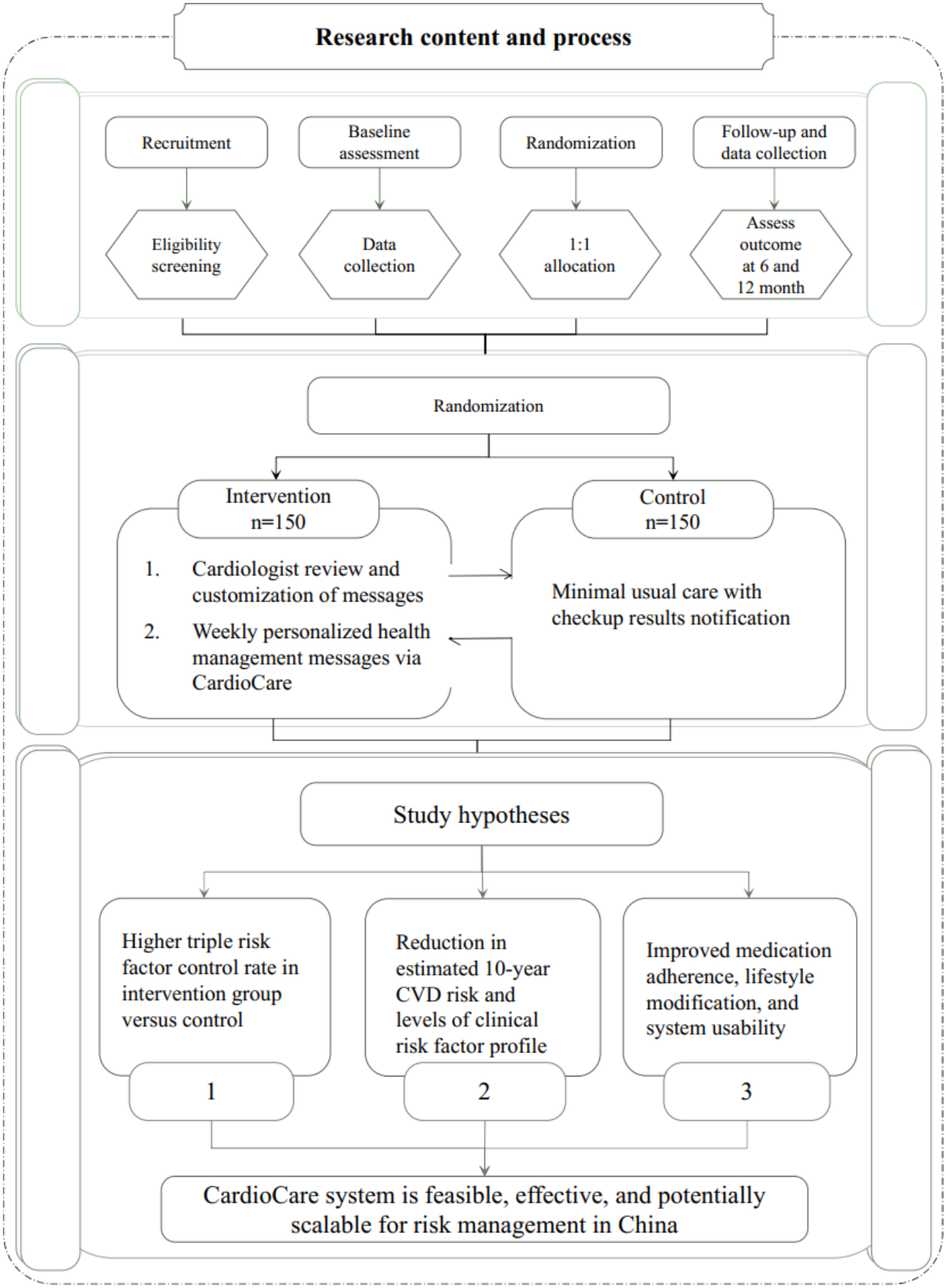

Eligible participants will be aged ≥50 years, have an estimated 10-year CVD risk greater than 10% calculated using the Guangzhou Biobank Cohort Study (GBCS) model [13], have no previous diagnosis of CVD, and own a mobile device capable of receiving messages from the CardioCare system. The GBCS model has been validated in a large urban Chinese cohort and

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is appropriate for identifying high-risk individuals in this population [13]. Participants must reside in Guangzhou for the duration of the study and provide written informed consent. Individuals will be excluded if they have severe comorbidities that preclude regular follow-up in the judgment of a study clinician based on medical record review, a life expectancy of less than 1 year, recent participation in similar CVD management programs, or any other condition judged by the investigators to interfere with safe participation.

Random Allocation and Allocation Concealment

A statistician not involved in participant recruitment will generate the random allocation sequence using computer-generated random numbers. Randomization will be stratified by sex, with random block sizes ranging from 4 to 12 undisclosed to the recruitment team to ensure unpredictability. Allocation concealment will be maintained using sequentially numbered opaque, sealed envelopes prepared by staff independent of the enrollment process.

Research assistants will identify eligible participants, send invitations, and obtain informed consent, after which the next available envelope will be opened to reveal allocation. Personnel enrolling participants will not have access to the allocation sequence.

Participants and care providers will not be blinded due to the nature of the intervention. Outcome assessors and statisticians will remain blinded to allocation. Group codes will be masked during analysis, and the randomization key will only be revealed after the primary analysis is completed. No emergency unblinding procedures are required given the nonpharmacological nature of the intervention.

Intervention and Control

The CardioCare system uses a structured message-tailoring algorithm that integrates clinical data, participant risk profiles, and previous engagement records to personalize message content and frequency. Cardiologists oversee message template development and conduct monthly reviews to ensure clinical relevance and appropriateness. Participant engagement is continuously monitored through automated system logs, which record message delivery and interaction. Predefined engagement thresholds trigger alerts to research staff for follow-up support. This operational framework follows the Template for Intervention Description and Replication guidance for intervention specification, ensuring reproducibility and transparency in intervention delivery.

The intervention group will receive a personalized intervention from the CardioCare system for 12 months. This system integrates CVD risk stratification using the GBCS model with tailored weekly SMS text messages or WeChat messages covering medication adherence, diet, exercise, and follow-up reminders. Messages will be reviewed by a cardiologist before dispatch and customized based on each participant's clinical profile and previous engagement. Message types will vary in intensity and content (eg, motivational, educational, or reminder based) depending on previous adherence and risk level. All messages are logged automatically, and participant engagement (eg, message reads, replies, and link clicks) is continuously monitored. Participants with declining engagement will be flagged for follow-up by the research assistant team, ensuring responsiveness. Cardiologist review takes place monthly or upon significant clinical change using an internal dashboard linked to participant records.

The control group will receive minimal usual care, consisting of notification of health checkup results and general recommendations to seek outpatient follow-up if indicated. After completing the 12-month follow-up, control group participants will be offered access to the CardioCare system. Participants may discontinue the intervention at any time or if advised by the study physician. No restrictions will be placed on concomitant medical care.

Outcomes

The primary outcome is the proportion of participants achieving simultaneous control of blood pressure, lipids, and glycemia at 12 months, defined as SBP of <130 mm Hg and diastolic blood pressure of <80 mm Hg, LDL-C of <2.6 mmol/L, fasting plasma glucose of <7.0 mmol/L, and HbA_{1c} of <7% (Table 1). Secondary outcomes include (1) clinical measures (changes in estimated 10-year CVD risk [GBCS model]; mean changes in SBP, LDL-C, triglycerides, fasting plasma glucose, and HbA_{1c}; and the proportion achieving control of individual risk factors at 12 months), (2) behavioral measures (medication adherence and adoption of lifestyle modifications), (3) system-level outcomes (participant engagement with the CardioCare system and usability and satisfaction among participants and physicians), and (4) economic outcomes (incremental cost-effectiveness expressed as cost per participant achieving triple risk factor control and per quality-adjusted life year [QALY] gained; Table 1).

Medication adherence and lifestyle modifications (diet, physical activity, and smoking) will be assessed using structured questionnaires adapted from previously validated tools applied in chronic disease studies in Chinese populations. Measurements for all primary and secondary outcomes will be taken at baseline and 6 and 12 months after enrollment. To assess feasibility and acceptability, we will evaluate (1) recruitment rate (participants enrolled and approached); (2) retention rate at 12 months; (3) system engagement metrics, including number of messages opened and responded to; and (4) participant-reported usability and satisfaction at 12 months. Usability will be assessed using the System Usability Scale, and satisfaction will be measured using a 5-point Likert scale. These data will inform scalability potential and guide future implementation strategies. Quantitative feasibility metrics will be summarized descriptively, and comparisons between groups will be exploratory.

In addition to formal clinical and behavioral assessments at baseline and 6 and 12 months, the CardioCare system captures weekly engagement data, including message delivery, read status, interaction frequency, and responsiveness. These metrics will be used to construct engagement trajectories and assess temporal patterns of system use. The economic evaluation will be conducted from the health care system perspective. Direct medical costs will include personnel time, digital intervention

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costs (eg, system maintenance and messaging), outpatient visits, medications, and laboratory tests. Cost-effectiveness will be assessed through incremental cost-effectiveness ratios reported as cost per participant achieving triple risk factor control and per QALY gained.

Table . Outcome measure summary.

Outcome	Definition and measure	Time point	Assessment method
Primary outcome	Triple risk factor control (SBP[a] of <130 mm Hg, DBP[b] of <80 mm Hg, LDL-C[c] of <2.6 mmol/L, and HbA_{1c}[d] of <7%)	12 months	Clinical measurements and laboratory assays
Secondary outcomes			
10-year CVD[e] risk	Estimated via GBCS[f] model	Baseline and 12 months	Model-based calculation
SBP, LDL-C, HbA_{1c}, FPG[g], and triglycerides	Individual clinical parameters	Baseline and 6 and 12 months	Hospital-certified laboratory and digital BP[h] monitor
Medication adherence	Self-reported adherence (structured questionnaire)	6 and 12 months	Validated adherence scale
Lifestyle modification	Diet, physical activity, and smoking status	6 and 12 months	Structured behavioral questionnaire
System engagement	Frequency of interactions with the CardioCare system	Continuous	Digital system logs
Usability	Perceived ease of use	12 months	SUS[i]
Satisfaction	Overall satisfaction with the system	12 months	5-point Likert scale questionnaire
Cost-effectiveness	Cost per case of triple risk factor control and QALYs[j] gained	Baseline and 12 months	Economic modeling using trial data

[a]SBP: systolic blood pressure.
[b]DBP: diastolic blood pressure.
[c]LDL-C: low-density lipoprotein cholesterol.
[d]HbA_{1c}: glycated hemoglobin.
[e]CVD: cardiovascular disease.
[f]GBCS: Guangzhou Biobank Cohort Study.
[g]FPG: fasting plasma glucose.
[h]BP: blood pressure.
[i]SUS: System Usability Scale.
[j]QALY: quality-adjusted life year.

Sample Size Estimation

The sample size was calculated to detect an absolute difference of 15 percentage points in the primary outcome (ie, 20% in the control group vs 35% in the intervention group), with 80% power and a 2-sided α of .05. This requires 126 participants per arm. Allowing for 15% attrition, the final target sample size is 300 participants (150 per group). This expected difference is based on previous studies in Chinese older adult populations showing triple risk factor control rates ranging from 15% to 25% under usual care and on effect sizes from similar multicomponent digital interventions, which have reported 10– to 20–percentage point improvements in risk factor control [14]. Recruitment will take place during routine health checkup visits, with eligible individuals identified from their health data and approached in person by a trained research assistant. Additional recruitment will be supported through study posters in the Health Management Center and announcements on the hospital's WeChat platform.

Data Collection and Management

Clinical and laboratory measurements will be collected at baseline and 6 and 12 months using standardized procedures. Blood pressure will be measured in duplicate using validated automated devices after 5 minutes of rest; the average reading will be recorded. Lipid profiles and glycemia will be measured in fasting venous samples analyzed at the hospital's certified laboratory. Medication adherence will be evaluated using a self-administered online questionnaire. Lifestyle modification and system engagement data will be collected through structured questionnaires. All data will be entered into a secure, password-protected database, and automated range checks will be conducted. Regular audits will be conducted to ensure accuracy. Personal identifiers will be stored separately from trial data accessible only to authorized personnel.

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Statistical Analysis

All analyses will follow the intention-to-treat principle, with all randomized participants included in the group to which they were assigned. The primary outcome will be compared between groups using a chi-square test, with risk differences and 95% CIs calculated. Secondary continuous outcomes will be analyzed using mixed-effects models adjusting for baseline values. Missing data patterns will be assessed visually and statistically (eg, the Little missing completely at random test) to inform appropriate imputation models. Multiple imputation using chained equations will be used under the assumption of the data being missing at random, and sensitivity analyses will include complete-case and worst-case scenarios. Prespecified subgroup analyses will examine potential effect modification by sex, age group, and baseline CVD risk. These subgroup analyses are exploratory in nature and will not be powered to detect statistically significant differences. Findings will be interpreted descriptively and used to inform hypothesis generation for future trials.

QALYs will be estimated using utility weights derived from published data on health-related quality of life in Chinese adults. A within-trial cost-effectiveness analysis will be conducted over the 12-month intervention period. Sensitivity analyses will be conducted to examine the robustness of the incremental cost-effectiveness ratio to variations in key cost and outcome inputs. All analyses will be conducted using Stata (version 18.0; StataCorp). A 2-sided P value of <.05 will be considered statistically significant.

Monitoring

A data monitoring committee comprising independent epidemiologists and cardiologists will oversee trial conduct, review adverse events, and provide recommendations regarding trial continuation. No interim analyses or formal stopping rules are planned. The trial will be monitored monthly by the study management team to ensure protocol adherence. The data monitoring committee will make recommendations regarding trial continuation or necessary modifications. Oversight procedures will follow International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use good clinical practice guidelines.

Ethical Considerations

Ethics approval has been obtained from the institutional review board of the School of Public Health, Sun Yat-sen University (2024-110). Written informed consent will be obtained from all participants by trained research assistants. Protocol amendments will be submitted to the institutional review board and communicated to trial staff and, if necessary, participants. Confidentiality will be maintained by assigning unique study IDs, with personal information stored separately from trial data. After the trial, control participants will receive access to the CardioCare system for 12 months. Participants who experience harm related to trial participation will receive appropriate medical care and compensation according to institutional policy.

Results

This trial was funded on October 28, 2024. Participant recruitment is scheduled to commence in October 2026 at the Health Management Center of the First Affiliated Hospital of Sun Yat-sen University and is expected to continue for approximately 9 months. Each participant will be followed up on for 12 months after randomization, with clinical assessments at baseline (0 months), 6 months, and 12 months. Data analysis is expected to begin shortly after the final 12-month assessments are completed. At the time of manuscript submission, recruitment has not yet commenced. Table 2 shows the trial schedule [15], with enrollment procedures at baseline; continuous delivery of the intervention up to 12 months; and timing of assessments at baseline and 6 and 12 months, with cost-effectiveness evaluated at baseline and 12 months.

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Table . Participant timeline: schedule of enrollment, intervention, and assessments.

	Trial period			
	Enrollment		Postrandomization closeout	
	−3 to 0 months	Baseline	6 months	12 months
Enrollment				
Eligibility screen	✓			
Informed consent	✓			
Randomization		✓		
Intervention and comparator				
Intervention		✓	✓	
Comparator		✓	✓	
Risk communication by cardiologists		✓		
Demographics, medical history, anthropometrics, blood pressure, laboratory tests, 10-year CVD[a] risk, and behavioral and psychosocial measures	✓	✓		
Primary outcome (triple risk factor control at 12 months [BP[b], LDL-C[c], FPG[d], and HbA_{1c}[e]]) and secondary outcomes (estimated 10-year CVD risk, individual clinical parameters, medication adherence, lifestyle modification, system engagement, usability, and satisfaction)			✓	✓
Cost-effectiveness (clinical assessments, laboratory tests, validated questionnaires, system logs, and economic analysis)				✓

[a]CVD: cardiovascular disease.

[b]BP: blood pressure.

[c]LDL-C: low-density lipoprotein cholesterol.

[d]FPG: fasting plasma glucose.

[e]HbA_{1c}: glycated hemoglobin.

Discussion

Expected Findings

CVD remains the leading cause of morbidity and mortality in China, particularly among older adults. Although the NBPHSP has greatly expanded access to routine health checkups, postscreening management of chronic conditions such as hypertension, dyslipidemia, and diabetes is often suboptimal [16]. The CardioCare system was designed to address these gaps by integrating CVD risk prediction, personalized health management, and continuous digital engagement into existing health care workflows. This RCT will be the first to evaluate whether such a system can improve simultaneous control of blood pressure, lipids, and glycemia among high-risk older adults in China.

This RCT has several strengths. First, it addresses a critical gap in postcheckup care by focusing on triple risk factor control, a clinically meaningful composite end point closely linked to CVD outcomes. Second, the intervention is built on an established risk prediction model (the GBCS model) and combines risk communication and evidence-based lifestyle and medication adherence strategies with personalized digital communication. Third, integration into an existing health checkup center ensures feasibility in a real-world setting, and the trial includes cost-effectiveness analysis to inform potential scalability.

There are also potential limitations. This trial is conducted in a single urban health management center, which may limit generalizability to rural or resource-limited settings where infrastructure and cardiovascular risk management practices

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differ. However, as an initial trial of the CardioCare system, this setting enables evaluation under conditions of high intervention fidelity. Future studies will be needed to assess adaptations for broader populations, particularly in underresourced areas or settings with lower digital capacity. The reliance on self-reported measures for some behavioral outcomes, such as medication adherence and lifestyle modification, introduces the possibility of reporting bias. Engagement with the digital intervention may vary between participants, potentially influencing its effectiveness. In addition, while the triple risk factor control outcome is clinically relevant, it may be more challenging to achieve than improvements in individual risk factors, potentially underestimating the system's benefit. If the trial demonstrates effectiveness, the CardioCare system could be scaled to other health checkup centers and integrated into national health programs, potentially improving chronic disease management for millions of older adults. Although mobile device access and digital communication literacy are eligibility requirements, these are unlikely to be significant sources of exclusion in the Chinese context, where smartphone ownership and WeChat use exceed 99% among Guangzhou residents, including those over the age of 50 years. Future research could explore adaptations for rural settings, automation of message delivery, integration with other chronic disease management modules, and long-term effects on CVD events and mortality. Finally, as the trial is conducted within a single health management center, there is a potential for contamination between intervention and control participants. Although the CardioCare intervention is delivered individually via private digital communication and participants do not engage in group sessions, the possibility of informal information sharing cannot be entirely excluded.

Conclusions

This RCT will evaluate the effectiveness of the CardioCare system, a digital cardiovascular management platform, in achieving simultaneous control of blood pressure, lipids, and glycemia among high-risk adults identified through routine health checkups. By integrating established risk prediction with personalized health management and continuous digital engagement, the intervention aims to address critical gaps in postscreening care within the Chinese health care system. The findings will provide robust evidence on both the clinical impact and cost-effectiveness of the CardioCare system, informing its potential for large-scale implementation in health checkup centers and integration into national chronic disease prevention strategies. If effective, the CardioCare system could be scaled through existing national platforms such as the NBPHSP and align with priorities outlined in Healthy China 2030. Its digital format supports integration into routine primary care and health checkup services, potentially strengthening chronic disease management at a population level.

Funding

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Data Availability

The datasets generated or analyzed during this study are not publicly available due to the protection of participant privacy but are available from the corresponding author on reasonable request.

Authors' Contributions

LX and HH are co–corresponding authors. HH can be reached via email at honghua@mail.sysu.edu.cn or phone at +86 133 8000 7226.

Conflicts of Interest

None declared.

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Abbreviations

CVD: cardiovascular disease
GBCS: Guangzhou Biobank Cohort Study
HbA_{1c}: glycated hemoglobin
LDL-C: low-density lipoprotein cholesterol
NBPHSP: National Basic Public Health Services Program
QALY: quality-adjusted life year
RCT: randomized controlled trial
SBP: systolic blood pressure

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Sitting Baduanjin Combined With Acupoint Massage on Frailty in Patients Undergoing Maintenance Hemodialysis: Protocol for a Randomized Controlled Trial

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Abstract

Background: Patients undergoing maintenance hemodialysis (MHD) endure weakness due to prolonged dialysis treatment, such as the continuous decline of muscle strength in patients, which will have varying degrees of impact on human physiological, psychological, and social functions. Effective nonpharmacological interventions can improve their mental health and quality of life (QoL).

Objective: This study aimed to investigate the effects of sitting Baduanjin combined with acupoint massage on improving the frailty status of patients undergoing MHD and evaluate whether it can significantly improve their physical activity, alleviate depressive emotions, and comprehensively improve their QoL.

Methods: This is a randomized controlled study to be conducted in the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine, comprising 114 patients to be treated using MHD. Patients who meet the inclusion and exclusion criteria will be randomly divided into 3 groups: the control group will receive only conventional hemodialysis and care, the acupoint massage group will receive acupoint massage treatment in addition to the control group treatment, and the sitting combined with acupoint massage group will receive sitting Baduanjin combined with acupoint massage and the control group treatment. We aim to comprehensively evaluate the clinical efficacy by comparing the FRAIL (Fatigue, Resistance, Ambulation, Illness, and Weight Loss) scale scores, grip strength, 10 times sit-to-stand test, Self-Rating Depression Scale scores, and QoL (Short Form Health Survey Questionnaire) scores before and after 8 weeks of treatment among the 3 groups. Statistical analysis will be conducted using the Statistical Package for the Social Sciences software (version 25.0; IBM Corporation).

Results: The first participant was enrolled on August 8, 2024. As of August 2025, a total of 52 participants have been fully registered, and the intervention is currently in progress. We expect the completion of this trial to occur within the year 2025.

Conclusions: The results of this study can provide a scientific basis for the future treatment of patients with asthenia in hemodialysis.

Trial Registration: International Traditional Medicine Clinical Trial Registry (ITMCTR) 2024000798; https://itmctr.ccebtcm.org.cn/mgt/project/view/6146572661308144719

International Registered Report Identifier (IRRID): DERR1-10.2196/72352

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KEYWORDS

maintenance hemodialysis; acupoint massage; sitting Baduanjin; quality of life; traditional Chinese medicine

Introduction

Background

Maintenance hemodialysis (MHD) is the primary treatment for end-stage renal disease. It effectively removes metabolic toxins from the body, prolongs patient survival, and improves quality of life (QoL) [1]. Frailty is a nonspecific state resulting from decreased physiological reserves or multisystem dysfunction, leading to increased vulnerability and reduced stress resistance. This makes individuals more susceptible to adverse clinical events, even in response to minor external stimuli [2]. It is a prevalent and debilitating clinical syndrome that significantly affects the QoL of patients undergoing MHD treatment [3]. Frailty is primarily characterized by unintentional weight loss, diminished grip strength, slowed walking speed, reduced

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physical activity, and self-reported exhaustion [4]. The presence of 1 or 2 of these criteria indicates a prefrail state, while the presence of 3 or more criteria can confirm frailty. A recent survey conducted in the United States revealed a 9% prevalence of frailty among the older population, with an even higher prevalence of 44% among those classified as prefrail [5]. A Chinese study revealed that 5.6% of individuals aged ≥60 years were classified as frail, while 49.3% exhibited characteristics indicative of prefrailty [6]. A review of international studies revealed that the prevalence of prefrailty among patients undergoing hemodialysis ranged from 50% to 63%, while the prevalence of frailty itself fluctuated between 33% and 47% [7-10]. A Chinese study revealed a prevalence of 60.7% for prefrailty and 44.8% for frailty in patients undergoing hemodialysis [11,12].

These findings indicate that all age groups of adults undergoing hemodialysis exhibited a significantly elevated prevalence of frailty, exceeding that observed in the general older population. This highlights the need for increased attention to this issue [7]. As the duration of dialysis increased, the patients exhibited a progressive decline in muscle strength, a reduction in activity levels, and the development of frailty. This condition can influence a range of physiological, psychological, and social functions, as well as self-care abilities. In addition, it increases the risk of falls, rehospitalization, and mortality, thereby reducing the QoL [13,14]. Frailty was identified as an independent predictor of all-cause mortality in patients undergoing MHD for more than 5 years [15].

Previous studies link frailty in patients undergoing MHD to physical function, depressive symptoms, and QoL [16]. Prolonged dialysis causes substantial amino acid and protein loss; patients with chronic renal failure with low protein intake (insufficient for bodily needs) have reduced muscle synthesis and impaired physical function [17]. In addition, calcium-phosphorus imbalance in patients undergoing MHD reduces skeletal muscle and joint function, while prolonged sitting and lying impairs muscle strength or mass and physical activity [16]. Due to irreversible progression and long treatment, patients often have anxiety and depression. A systematic review notes a bidirectional depression-frailty relationship: patients with depression face higher frailty risk, and patients with frailty are more likely to have depressive symptoms [17]. Declines in physical function and depression fuel frailty, creating a vicious cycle that lowers QoL, raises rehospitalization and death risks [18]. However, frailty is dynamic and reversible; timely detection or management can delay or reverse it, improving prognosis [19]. Sarcopenia is the core pathological basis of frailty in patients undergoing MHD, with most having low grip strength and activity levels [20]. MHD has a strong adverse association with frailty, with evidence from multiple studies. First, frailty is highly prevalent in patients undergoing MHD: a meta-analysis of 16 studies (2446 patients) reported a pooled frailty prevalence of 41% [21]. Second, frailty significantly elevates adverse outcomes in patients undergoing MHD. A systematic review including 23 studies (10,333 patients) showed patients with frailty undergoing MHD had higher all-cause mortality and all-cause hospitalization [22]. Third, specific factors mediate this association: xerostomia and poor nutrition correlate with frailty, jointly explaining 45.6% of frailty variance in older patients undergoing MHD [23]; age, hypoalbuminemia, depression, and malnutrition are independent frailty predictors in patients undergoing MHD [24]. This underscores frailty as a key clinical concern requiring attention in the management of patients undergoing MHD management. The prevalence of prefrailty is notably high among patients undergoing MHD. Prefrailty, an early and reversible condition between nonfrailty and frailty, can lead to adverse outcomes such as increased unplanned hospital admissions and a higher risk of other chronic diseases [24].

Early identification and treatment of frailty in patients with myocardial hypertrophy are critical for the management of this condition. Baduanjin, a low-to-moderate-intensity aerobic exercise, is based on traditional Chinese medicine (TCM) theories and integrates the yin-yang and meridian theories. Baduanjin comprises standing and sitting forms, distinguished by their gentle and slow movements. These are characterized by simplicity, ease of learning, safety, efficacy, and the absence of venue and time restrictions [25]. The practice of sitting Baduanjin has many beneficial effects, including regulation of the body, breath, and mind, as well as harmonization of the 5 viscera [26]. Furthermore, it mitigates the risk of falls and other mishaps resulting from muscle atrophy and diminished endurance, rendering it a suitable choice for patients with frailty undergoing MHD. Modern research has demonstrated that Baduanjin exhibits beneficial regulatory effects on multiple systems of the body, not only resisting aging but also significantly improving limb muscle strength, alleviating anxiety and depression, improving fatigue states, relieving pain, enhancing cardiopulmonary function, and, with long-term practice, strengthening the body and improving disease resistance [27-29].

Baduanjin can significantly improve sleep quality, alleviate anxiety and depression, and improve fatigue in patients undergoing MHD [29]. Another study indicated that 5-element music combined with Baduanjin helps reduce fatigue and alleviates frailty in patients undergoing MHD, improving the QoL [30]. From the perspective of TCM, frailty in MHD is mainly caused by a deficiency in organ functions, qi, blood, yin, and yang, with prolonged deficiency leading to fatigue. The core pathology involves spleen and kidney deficiencies. Sitting Baduanjin can harmonize qi and blood, balance yin and yang, and coordinate organ functions to achieve a balanced state, thereby improving physiological functions.

Furthermore, TCM emphasizes the overall regulatory role of the meridian system. Studies have demonstrated that acupoint massage can improve limb function, negative emotions, sleep quality, and fatigue [31,32]. Studies using acupoint massage on patients undergoing hemodialysis revealed significant improvements in fatigue and QoL with specific acupoints, including Zusanli (ST36), Sanyinjiao (SP6), Taixi (KI3), Yongquan (KI1), and Neiguan (PC6) being particularly effective [33].

Current Research Gap

Although studies have explored the effects of Baduanjin and acupoint massage on patients undergoing MHD, there are still

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knowledge gaps. Most studies focus on improving specific indicators, but there is a lack of assessment of the patients' frailty status. Baduanjin improves muscle function of patients undergoing hemodialysis, reduces systemic inflammation, and enhances skeletal muscle–related indices [34]. Massage relieves lower limb cramps [34] and boosts sleep quality via hot stone therapy [35]. Yet, massage only targets single symptoms (no effects on muscle mass and inflammation); Baduanjin needs nutritional support, covers a few frailty symptoms, and has limited skeletal muscle benefits [34,36]. Their combination could comprehensively address frailty, synergistically protect muscles, and improve frailty via multiple mechanisms. Regarding the effectiveness of combining sitting Baduanjin exercise and acupoint therapy in improving the frailty of patients undergoing MHD, there is also a lack of high-quality evidence.

Unique Contributions of This Study

This study aims to address these research gaps through a randomized controlled trial that systematically evaluated the effects of combining sitting aduanjin with acupoint massage on frailty in patients undergoing MHD treatment. This study makes several contributions to the field. First, it is the first to combine the sitting form of the 8-section brocade with acupoint massage to provide an 8-week comprehensive nonpharmacological intervention strategy with long-term follow-up. A systematic approach is used in this study to evaluate numerous indicators in patients undergoing MHD, including frailty, grip strength, lower limb function, depression status, and QoL. The findings contribute to the evidence base for effective and high-quality nonpharmacological interventions for patients with frailty undergoing MHD.

Purpose and Significance

This study aims to investigate the effects of various interventions on frailty. The primary objective is to investigate whether combining sitting Baduanjin with acupoint massage could improve frailty in individuals with mild-to-moderate heart disease, reduce muscle atrophy, inhibit physical function decline, and alleviate depressive symptoms. This approach is hypothesized to significantly improve patients' social life and QoL.

The following section outlines the foundation for further research on acupoint massage for MHD-induced frailty. This research will investigate clinically applicable TCM nondrug treatment strategies, providing new ideas for preventing and treating MHD-induced frailty using TCM. The intervention is low-cost and easily accessible. This combined intervention strategy is cost-effective, not venue- or equipment-specific, and has significant clinical implications.

Expected Outcomes

It is anticipated that the frailty status of patients undergoing MHD will improve significantly, with substantial enhancement of muscle strength and lower limb function. Depressive symptoms will be alleviated, and mental health and QoL will be enhanced. Furthermore, this study will serve as a reference for effective and convenient intervention measures to further improve frailty in patients undergoing MHD.

Methods

Research Design

A randomized controlled trial design is used to evaluate the impact of integrating Baduanjin exercise with acupoint massage on the prevalence of frailty in patients undergoing MHD treatment.

Participants

A total of 114 patients undergoing MHD who met the inclusion and exclusion criteria were selected from the Hemodialysis Center of the Affiliated Hospital of Chengdu University of TCM (Textbox 1).

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Textbox 1. Inclusion, exclusion, removal, withdrawal, and termination criteria for patients undergoing maintenance hemodialysis.

Inclusion criteria

- Age: 45 - 75 years with end-stage renal disease (uremia stage).
- Dialysis duration: receiving hemodialysis treatment ≥3 months, 3 times a week, and 4 hours per session, with stable vital signs.
- Frailty status: evaluated using the FRAIL (Fatigue, Resistance, Ambulation, Illness, and Weight Loss) scale, with scores of ≥1 indicating prefrailty or frailty.
- Cognitive and communication ability: clear consciousness, normal hearing, and ability to communicate normally.
- Physical function: no physical activity disorders, no regular exercise, able to understand and follow demonstration actions.
- Acupoint skin condition: intact skin at acupoint massage sites.
- Voluntary participation: willing to participate in the study.

Exclusion criteria

- Neurological disorders: presence of neurological diseases or other uncontrolled chronic diseases.
- Severe complications: severe arrhythmias, angina, severe infections, malignancies, and renal osteodystrophy.
- Noncooperation: refusal to cooperate or psychiatric abnormalities preventing collaboration.
- Concurrent clinical trials: simultaneous participation in another clinical trial.

Removal, dropout, and termination criteria

- Noncompliance: patients who did not follow the trial design methods or who were unable to cooperate due to illness were excluded.
- Data completeness: this was removed if the data completeness was <80% or the treatment period was less than 6 weeks.
- Voluntary withdrawal: patients who voluntarily withdrew were lost to follow-up or received a kidney transplant.
- Adverse events (AEs): the study was terminated if serious AEs or disease deterioration occurred.

Sample Size Calculation

The sample size calculation formula for the multigroup mean is as follows:

$$n=\phi 2(\sum isi2/g)/[\sum(X\bar{}l-X\bar{})2/(g-1)]$$

where n represents the requisite sample size for each group, g represents the number of groups, and Si is the mean (SD) for each group. The values of ϕ are obtained from tables α, β, ν1, and ν2, with α=.05, β=.1, ν1=2, ν2=∞, and ϕ=2.52. A 2-sided test was used in this study, which stipulates that the test level α=.05, the test efficiency 1-β=.90, and the probability of a type II error is 0.10. The FRAIL scale score was used to calculate the effect size, and the average number of patients in each group, as previously described [37], was as follows: 3.29, 2.67, and 2.58, with SD values of 0.96, 0.87, and 1.02, respectively. These data were entered into the formula to calculate n=34. Considering the shedding rate of 10%, the actual required sample size for the 3 groups was estimated to be 38 per group, totaling 114 patients.

Random Allocation Method

A randomized controlled trial design was used in this study, whereby participants were randomly allocated to the experimental and control groups. After generating the random numbers using SPSS 25.0 with the initial seed value 120983, the allocation sequence (Group A for participants 1 - 38, Group B for 39 - 76, and Group C for 77 - 114) was concealed using sequentially numbered, opaque, sealed envelopes. These envelopes were prepared by an independent statistician not involved in participant recruitment or assessment. Each envelope contained the group assignment for the corresponding participant and was only opened by the research coordinator after a participant had completed enrollment procedures, ensuring that neither the participants nor the recruiting researchers could predict or influence group allocation. This procedure was implemented to minimize the risk of selection bias.

Blinding

Given the nature of the interventions, blinding operators and patients was unfeasible. However, the individuals responsible for data collection and analysis were blinded to the group information to guarantee objective and impartial results.

Intervention Measures

Control Group

The patient received conventional hemodialysis treatment and care without any additional interventions.

Conventional hemodialysis treatment is the standard dialysis treatment regimen that includes general symptomatic support, including the selection of appropriate dialysis machines, fluids, and methods; blood pressure and blood sugar management; correction of anemia; and prevention of secondary hyperparathyroidism.

Conventional hemodialysis care consists of 3 distinct phases. First, predialysis care was administered, where patients were introduced to the dialysis room environment, and assistance was provided in assuming a comfortable position. Dialysis machines were checked for readiness, general condition was evaluated, and predialysis weight was measured. Second, during

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dialysis care, we closely monitored vital signs, observed the vascular access for swelling or bleeding, ensured tight connections of external blood circuits, and responded to dialysis machine alarms. Third, postdialysis care included managing the vascular access, assessing postdialysis conditions, providing health education on diet, re-examination, and daily protection of vascular access.

Acupoint Massage Group

Overview

In addition to conventional treatment and nursing, acupoint massage intervention was conducted 3 times a week, each lasting 15 minutes. Each acupoint was massaged for about 2‑3 minutes, focusing on specific acupoints, including Zusanli (ST36), Sanyin (SP 6), Taixi (KI3), and Yongquan (KI1).

Acupoints were selected based on an extensive literature review and expert consultation using the bone-degree measurement method in conjunction with finger-inch positioning. The location of the acupoints is based on the "National Standard of the People's Republic of China GB/T 12346‑2021 Acupoint Names and Locations" [38]. Here are the locations of the following acupoints: (1) Zusanli (ST36) located on the lateral side of the lower leg, 3 cun below Dubi (ST35), on the line connecting Dubi (ST35) and Jiaxi (ST41), (2) Sanyinjiao (SP6) located on the medial aspect of the lower leg, 3 cun above the tip of the medial malleolus at the posterior border of the tibia, (3) Taixi (KI3) located in the depression between the tip of the medial malleolus and Achilles tendon on the inner side of the ankle, (4) Neiguan (PC6, nonfistula side) located on the anterior aspect of the forearm, 2 cun above the transverse crease of the wrist on the palmar side, between the tendons of the palmaris longus and the flexor carpi radialis, and (5) Hegu (LI4, nonfistula side) located on the dorsum of the hand between the first and second metacarpal bones, approximately at the midpoint of the radial side of the second metacarpal bone.

Intervention Time and Frequency

Acupoint massage was administered 15 minutes before the end of dialysis [39]. Each acupoint was pressed and rubbed with the fingers for approximately 2 minutes, with 100 compressions each. The intervention was performed 3 times per week. Patient-reported sensations, such as soreness, numbness, and distension, indicated that the acupoints were accurately located. The applied pressure was maintained within the limits of patient tolerance.

Intervention Method

Before enrollment, the research team provided patients with a comprehensive introduction to the acupoints for pressing, including their functions and associated precautions. This ensured patient acceptance and cooperation. The acupoint pressing procedure was performed by trained members of the research team. Patients were reminded of the specific locations and functions of the acupoints during the procedure. The applied pressure was carefully adjusted to remain within the tolerance levels of the patients.

The force was applied uniformly and gently to prevent skin damage. The patient's subjective sensations were closely monitored throughout the procedure, and the patients were observed for any signs of injury, erythema, or edema on the skin. To avoid discomfort, massage should be avoided when the patient experiences anxiety, hunger, or over-satiation.

Sitting Baduanjin Combined With Acupoint Massage Group

In addition to conventional treatment and care, the patients received combined sitting Baduanjin exercise and acupoint massage thrice weekly. Each session comprised 30 minutes of Baduanjin exercise and 15 minutes of acupoint massage. The steps of Baduanjin are detailed in Table 1.

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Table . The steps of Baduanjin.

Steps	Exercise name	Key movements and steps	Duration and frequency	Body posture tips
First step	Sit with eyes closed to calm the mind	• Sit with eyes closed and back straight; fists on knees and tongue touching upper palate. • Abdominal breathing and gather qi at Dantian (3 - 5 min). • Tap teeth 36 times and swallow saliva in 3 mouthfuls. • Interlace hands to hold neck and breathe 9 times. • Flick back of head 24 times (such as drumming).	3 - 5 minutes (sitting quietly), 36 times (tooth tapping), 9 times (breathing), and 24 times (head flicking)	Cross-legged or legs hanging, back straight, and tongue against upper palate
Second step	Slightly swing and shake the "Tianzhu"	• Interlace hands (palms up) at thigh roots. • Lower head and twist neck to look left and right backward; swing shoulders with neck movement.	24 times per side	Keep upper body relaxed, coordinate neck, and shoulder movements
Third step	The "Red Dragon" stirring to produce saliva	• Stir tongue in mouth (up, down, left, and right) to make saliva. • Swirl saliva 36 times and swallow in 3 mouthfuls (with gurgling sound).	36 times (swirling) and 3 mouthfuls (swallowing)	Mouth closed, tongue movement gentle, and full
Fourth step	Hold breath, rub hands to warm them, and massage the back	• Inhale and hold breath; rub hands until warm and massage lower back sides while exhaling. • Repeat 24 times and then clench fists. • Inhale and hold breath; imagine fire burning Dantian and exhale.	24 times (massage cycle) and 1 round (breath-holding and imagination)	Keep waist straight during massage and focus on dantian when imagining fire
Fifth step	Single-side "Pulley" rotation	• Place 1 hand on corresponding waist (left hand on left waist and right hand on right waist). • Lower head and move arm in a circle (back to front) such as a pulley.	36 times per side (left arm first and then right arm)	Arm movement smooth and keep body stable without leaning
Sixth step	Double-side "Pulley" rotation	• Place both hands on waist. • Lower head and move shoulders and arms in a circle simultaneously, such as a pulley. • Straighten legs and rest 1 minute after movement.	36 times (circular movement) and 1 minute (rest)	Shoulders and arms move in sync and relax fully during rest

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Steps	Exercise name	Key movements and steps	Duration and frequency	Body posture tips
Seventh step	Cross-legged sitting with hands lifted above the head	• Rub hands and exhale on palms 5 times. • Interlace fingers, turn palms up, and lift hands over head; stretch waist upward. • Slowly lower arms.	9 times (lifting and lowering cycle)	Sit cross-legged and stretch body fully when lifting hands and lower arms slowly
Eighth step	Lower the head and reach for the feet frequently	• Palms facing each other and stretch hands forward. • Bend upper body forward, grasp foot soles, and lean forward and lower head. • Slowly sit up straight. • After 12 repetitions: cross-legged sit, clench fists, and calm mind; swirl saliva 36 times and swallow in 6 mouthfuls.	12 times (bending and sitting up), 36 times (saliva swirling), and 6 mouthfuls (swallowing)	Bend body slowly to avoid sudden force and keep breath natural during movement

Intervention Schedule and Frequency

The integrated intervention protocol involved conducting sessions 3 times per week, with each session lasting 45 minutes. The duration was allocated as follows: 30 minutes for sitting Baduanjin exercises and 15 minutes for acupoint massage.

Intervention Methods and Preparation

A comprehensive health promotion manual focusing on sitting Baduanjin exercises and acupoint massage was developed. The manual primarily included the benefits of this integrated therapy for patients undergoing dialysis, as well as detailed implementation plans and specific techniques, exercise principles, and protocols for managing any physical discomfort that may arise.

On the day of enrollment, the sitting Baduanjin technique and associated acupoints were explained to the patients. The purpose, methodology, expected outcomes, and precautions of this integrated therapy were elaborated to ensure their understanding and cooperation. After confirming through questioning that the patients had comprehended the relevant information, the necessary materials, including forms, brochures, and a recorded video demonstrating the sitting Baduanjin practice, were distributed.

Stage of Clinical Implementation

First, for the intervention content, a centralized intervention approach was implemented. The intervention sessions were conducted on dialysis days, 45 minutes before the start of dialysis, in the department's health education room. Participants engaged in group practice of sitting Baduanjin exercises. Each session was supervised by 2 research team members: one demonstrated and explained the movements and breathing techniques, while the other provided real-time corrections to ensure proper form. Efforts were made to standardize movements within the participants' physical capabilities to maximize exercise efficacy. The intervention was administered 3 times per week, with each session lasting 30 minutes and divided into 3 segments: a 3-minute warm-up focusing on joint mobility, a 25-minute main segment where sitting Baduanjin was practiced following standardized fitness qigong music instructions under the guidance of research team members, and a 2-minute cool-down period dedicated to relaxation and stretching exercises. In addition, 15 minutes before the end of dialysis, acupressure was applied to bilateral Zusanli (ST 36), Sanyinjiao (SP 6), Taixi (KI 3), and Neiguan (PC 6) on the nonfistula side, and Hegu (LI 4) on the nonfistula side. Following treatment, the participants rested for 15 minutes before leaving the dialysis room.

Second, the following precautions were taken: during the exercise regimen, if the patient experiences any of the following symptoms, which are severe fatigue, chest pain, hypoglycemic episodes, arrhythmia, shortness of breath, hypotension, or other abnormal conditions, the activity must be stopped immediately, and appropriate emergency protocols must be initiated.

As the closing form, the practitioner assumes a seated posture with their hands naturally hanging down and then adjusts their breathing.

Adverse Event Monitoring Plan

Trained nurses recorded adverse events (AEs; hypotension, arrhythmia, etc) via real-time vital sign monitoring (every 30 minutes during dialysis) and patient-reported symptoms. AEs were graded using Common Terminology Criteria for Adverse Events (version 5.0) and reported to the principal investigator within 2 hours; severe AEs were reported to the ethics committee within 24 hours.

Intervention Pause Criteria

Interventions were paused immediately if (1) systolic blood pressure was <90 mmHg (persistent after fluid resuscitation), (2) new-onset ventricular arrhythmia, and (3) patient-reported severe discomfort (eg, chest pain). The principal investigator

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would reassess within 1 hour to decide resumption or termination.

Evaluation Indicators

Overview

Data collection will be conducted in strict accordance with the established schedule to ensure the integrity and timeliness of information. Research team members must be trained in standardized measurement methods to minimize measurement bias. Furthermore, baseline data (including demographic characteristics, FRAIL scale scores, grip strength, 10 times sit-to-stand (STS-10) results, Self-Rating Depression Scale (SDS) scores, and QoL (Short Form Health Survey Questionnaire [SF-36]) scores must be collected before the intervention, and follow-up data for the same indicators must be collected after 8 weeks of treatment. The specific research program, including the timing of enrollment, intervention implementation, and indicator assessment, is detailed in Table 2.

Table . Enrollment schedule, interventions, and evaluation.

Research period	Registration phase (1 week)	Divide into groups (>1 week)	Intervene (8 weeks)
Point in time			
Join a group	✓		
Eligibility screening	✓		
Informed consent	✓		
Divide into groups		✓	
Intervene			
Control group			✓
Routine treatment and nursing			✓
Routine treatment and nursing+acupressure group			✓
Conventional treatment and nursing+sitting Baduanjin combined acupressure			✓
Assessment			
FRAIL[a] Scale score			✓
Grip strength			✓
STS-10[b]			✓
SDS[c]			✓
SF-36[d]			✓

[a]FRAIL: Fatigue, Resistance, Ambulation, Illness, and Weight Loss.

[b]STS-10: 10 times sit-to-stand.

[c]SDS: Self-Rating Depression Scale.

[d]SF-36: Short Form Health Survey Questionnaire.

Primary Evaluation Indicator (FRAIL Scale Score)

To assess the severity of frailty in patients, the scores before and after the intervention were compared as follows.

1. Decline: the FRAIL scale, a simple frailty measurement tool developed by the International Society for Nutrition and Aging in 2008 and derived from the Fried Frailty Scale, which has been widely used in different populations, is quick and easy to use and predicts the occurrence of adverse outcomes. The scale consists of 5 entries: fatigue, increased resistance or decreased endurance, decreased free mobility, disease conditions, and decreased body mass. Each entry was assigned 1 point, and the total score ranged from 0 to 5, with 0 indicating no debility, 1 - 2 indicating debilitating, and ≥3 indicating debilitating. A large foreign cohort study confirmed the good predictive validity of the FRAIL scale for impairment of daily activities and the occurrence of death [40]. Compared with other debilitation measurement tools, the FRAIL scale is most closely associated with dialysis-related complications and is useful for screening for debilitation in patients undergoing MHD [41]. It was standardized by Wei et al [42], and its reliability and validity were good, with a Cronbach coefficient of 0.826 and content validity of 0.98.
2. Indicators of somatic function: due to the lack of objective indicators on the FRAIL scale, secondary evaluation indicators related to physical function were selected for measurement based on the literature review.

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Secondary Evaluation Indicators

Grip Strength

Hand grip strength testing is the simplest and most widely used method for upper limb muscle strength testing. In this study, the EH101 electronic grip strength meter (Guangdong Xiangshan Company) was used to measure the grip strength. The patients were asked to hold the grip strength meter with maximum force using the noninternal fistula side of the limb in a standing position during measurement. Overall, 2 measurements were taken, with a 15-second interval between each measurement. The average value of the 2 measurements was taken.

STS-10

The 10 times sitting-stereotaxic position test (STS-10) is a common method for evaluating muscle strength and endurance of the lower limbs, which is easy to use, safe, and has high specificity [43]. Specific operation method where the patients were asked to cross their hands in front of their chest while sitting in the same standard-height chair so that they could withstand the speed of repeatedly standing up and sitting down 10 times. A stopwatch was used to note the time, and the 10th hip contact with the chair surface was considered the end of the exercise. A shorter time indicated better lower limb muscle strength.

SDS

The SDS, which was developed by Liu et al [44] in 1965, was primarily for patients' rating of the severity of their self-depression. It is widely used in clinical studies to observe changes in patients' depressive mood in response to interventions. The scale consists of 20 entries reflecting subjective feelings of depression, including 4 dimensions: psychotic affective symptoms, somatic disorders, psychomotor disorders, and depressive mental disorders. Each entry was scored on a 4-point scale according to the frequency of symptoms, and except for 10 entries that were scored on a 4 - 1 reverse scale, the other 10 entries were scored on a 1 - 4 positive scale. The total crude score was obtained by summing the entries, and the normal upper limit of the total crude score was 80, with a lower score indicating a better status. The standardized score was the integer obtained by multiplying the total crude score by 1.25. According to the Chinese normative results, the cutoff value of the SDS standardized score is 53, with no depression below 53, mild depression between 53 and 62, moderate depression between 63 and 72, and severe depression above 72.

SF-36

The QoL of the study participants was assessed using the SF-36, a concise health survey questionnaire developed by the Boston Health Research Institute in the United States. The Chinese version of the SF-36, developed by Prof. Jieqian Fang of Sun Yat-sen University of Medical Sciences was used in this study [45]. The scale contains 8 dimensions: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning, and mental health, comprehensively summarizing the respondents' QoL. The scale has 36 entries, each with a different scoring scale. Each dimension is scored as the ratio of the actual score for that dimension minus the difference between the lowest possible score for that dimension and the highest and lowest possible scores, with the ratio multiplied by a factor of 100 to give the final score for that dimension. The score for each dimension ranges from 0 to 100, and the scale total is the sum of the scores for each dimension, ranging from 0 to 800, with higher scores representing better QoL.

Data Collection

Research team members must be trained in standardized measurement methods. Furthermore, baseline data must be collected before and after 8 weeks of treatment. The specific research program is detailed in Figure 1.

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Figure 1. Study flowchart. FRAIL: Fatigue, Resistance, Ambulation, Illness, and Weight Loss; SDS: Self-Rating Depression Scale; SF-36: Short Form Health Survey Questionnaire; STS-10: 10 times sit-to-stand.

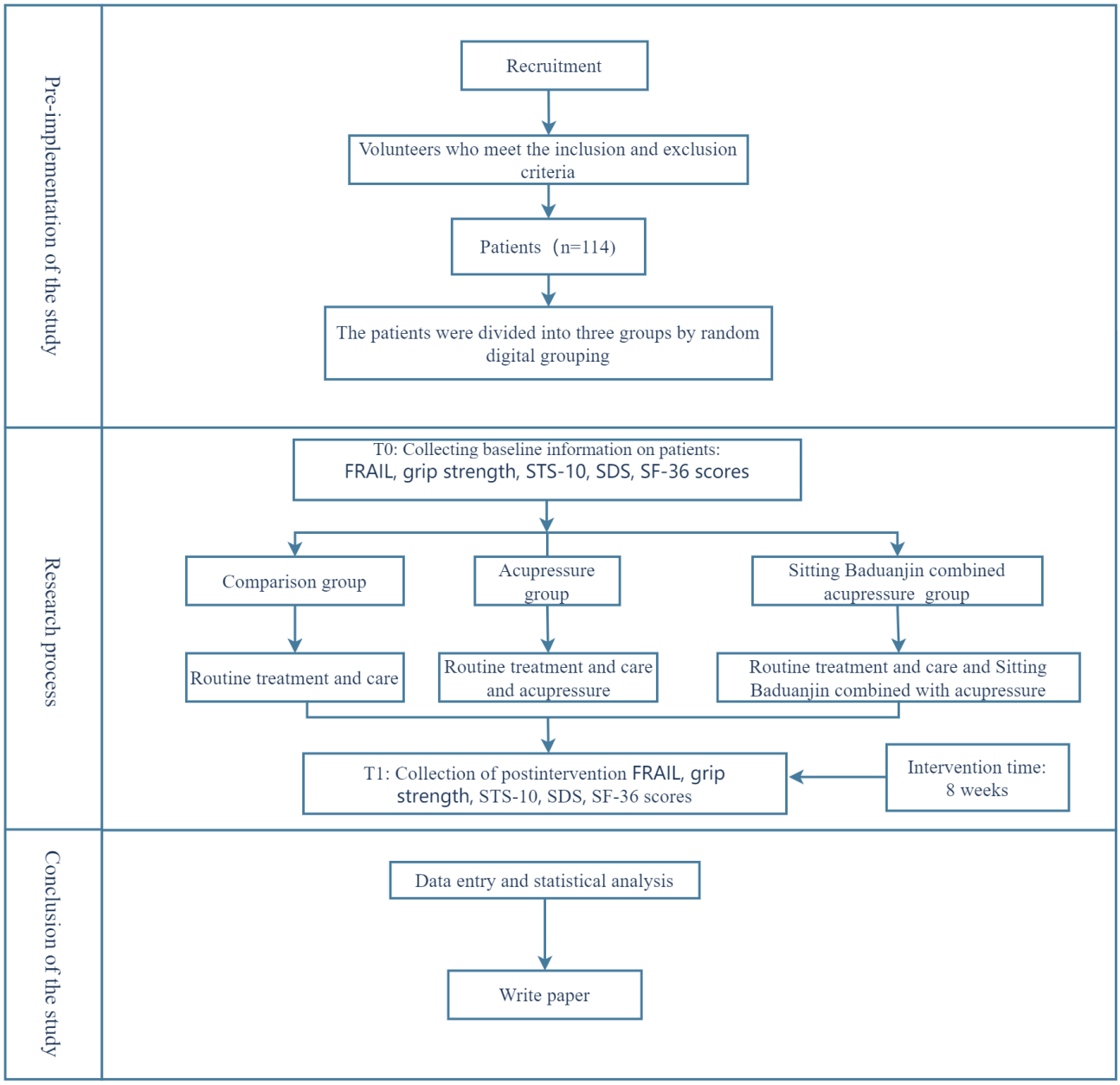

Quality Control

A preliminary trial plan should be developed, followed by pilot tests. It is critical to follow the established inclusion and exclusion criteria to ensure that baseline conditions across groups are balanced. Furthermore, compliance with the intervention measures and data integrity must be evaluated regularly. It is essential to provide comprehensive information regarding the advantages of the intervention, offer assistance and encouragement, and use WeChat groups for supervision to improve patient compliance.

Statistical Methods

Statistical Analysis

The database was established using Microsoft Excel software, and SPSS (version 25.0; IBM Corp) was used for statistical analysis and processing of all data. A bilateral test was used for statistical analysis; α=.05 was used as the test level, and P<.05 was considered statistically significant.

Descriptive Statistical Analysis

The measurement sample data that conform to a normal distribution are represented as mean (SD), and the measurement sample data that conform to a skewed distribution are represented as median (IQR). The frequency and composition ratio are used to describe the data of counting samples.

Statistical Inference

Baseline characteristics were comparable across groups. Continuous variables were analyzed using one-way ANOVA (normally distributed data) or rank-sum test; categorical data were assessed with chi-square tests. Within-group pre-post comparisons used paired 2-tailed t tests (normal data) or rank-sum tests. Between-group differences postintervention were evaluated using one-way ANOVA (with least significant

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difference post hoc testing if significant) or rank-sum tests, as appropriate. Categorical outcomes were compared using chi-square tests.

Ethical Considerations

The consent forms, participants' information sheets, and all other documentation provided to the participants have received approval from the Ethics Committee of the Affiliated Hospital of Chengdu University of Traditional Chinese Medicine (2024KL-109-01). This clinical trial has been retrospectively registered with the International Traditional Medicine Clinical Trial Registry on November 12, 2024 (ITMCTR 2024000798). All participants will be thoroughly informed about the details of the clinical trial. The consent of participants will be obtained in accordance with the ethical principles and standards based on the Declaration of Helsinki. All participants will have the right to withdraw their consent voluntarily at any time, and all personal information, such as name, gender, and age, will be anonymized or deidentified to ensure that individuals cannot be identified.

Sitting Baduanjin regulates qi, blood, yin and yang, dredges meridians, and adjusts zang-fu organs. It also boasts advantages such as moderate exercise intensity, high safety, and ease of practice. It has been proven safe and effective in previous clinical trials without toxic or side effects. However, acupressure involves external force application, and some patients may experience pain or discomfort. Researchers will make every effort to prevent and treat potential harms arising from this study. If participants experience any discomfort during the research, doctors will conduct evaluations and provide medical treatment accordingly. In the event of adverse events during the clinical trial, a committee of medical experts will assess whether they are related to the trial. For trial-related injuries, researchers will cover the medical treatment costs and provide corresponding economic compensation in accordance with relevant laws and regulations.

Results

This study was funded in December 2024, with data collection officially initiating on December 15, 2024, and projected to conclude in November 2025. As of the article submission date, 52 participants have been successfully enrolled, and all planned interventions are ongoing. Preliminary analysis of baseline demographic characteristics (eg, age, gender, dialysis duration) has been completed, confirming the balance of key variables across the 3 study groups, while full statistical analysis of intervention effects will be conducted immediately after the completion of all participant interventions and data collection. The trial is expected to be fully completed within 2025, with final study results anticipated to be published in Spring 2026.

Discussion

Anticipated Findings

The sitting-style Baduanjin can regulate respiration, adjust the body, and calm the mind. It can gently modulate the functions of internal organs [46]. This form of exercise is relatively less intense, easy to learn and practice, and is not constrained by location. Conversely, acupoint massage stimulates specific acupoints to regulate qi, blood, meridians, and internal organ functions. The procedure is simple and noninvasive, leading to a higher acceptance rate among patients. In addition, establishing community fitness and massage centers can reduce resource burdens and promote intervention applications.

The combination of Baduanjin and acupoint massage as a therapeutic modality within TCM is relatively less popular, and patient acceptance and preferences remain crucial factors that can influence the outcomes of this study. Beyond patient-related factors, the implementation of these TCM therapies also presents inherent complexity: both Baduanjin (the 8-section brocade) and acupoint massage require guidance and execution by individuals with specialized TCM knowledge, which necessitates substantial long-term investment in the training of skilled practitioners. For medical institutions that do not specialize in TCM, adopting and promoting these therapeutic methods thus becomes particularly challenging. Nevertheless, if health care providers and relevant stakeholders can learn and master the core theories and techniques of these TCM interventions, the benefits may extend beyond patients undergoing MHD, potentially benefiting individuals with various other chronic diseases as well.

Notably, this study has several limitations that warrant explicit acknowledgment. First, regarding the intervention duration and sample size: an 8-week intervention period may be insufficient to comprehensively elucidate the long-term therapeutic effects and patient compliance with TCM therapies. This initial time frame was determined based on the study's research design and resource constraints, which prioritized verifying short-term safety and preliminary efficacy; however, the small sample size further impacts the robustness and generalizability of our results. Second, in terms of study design, the control group only received conventional MHD treatment and care, while the intervention group additionally received either acupoint massage alone or a combined therapy of acupoint massage and seated Qigong. This imbalance in intervention content could easily lead to disparities in attention and participation between the groups, potentially introducing biases such as placebo effects. Furthermore, the combined intervention group lacked a separate control arm (eg, a group receiving only acupoint massage or only seated Qigong), making it impossible to distinguish the independent effects of each intervention component, a gap that may weaken the strength of our evidence. Third, the nature of TCM interventions, which involve active patient participation and a visible practitioner, makes it difficult to implement blinding for both operators and patients, further increasing the risk of bias.

Adding to these limitations, the single-center nature of our sample, recruited from a specific region (eg, North China), may restrict the representativeness of our findings to diverse hemodialysis populations globally. Importantly, TCM acceptance and familiarity vary significantly across different cultural contexts: in non-Chinese settings or regions with limited exposure to TCM, patient adherence to these interventions and the subsequent therapeutic outcomes may differ substantially from those observed in our study. This cultural variability further underscores the need to address generalizability in future research.

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To address these limitations and strengthen the evidence base for TCM interventions in MHD care, several future research directions are proposed. First, to improve generalizability, future studies should adopt a multicenter design involving diverse ethnicities, geographic regions, and health care systems. This will help validate whether the effects of Baduanjin and acupoint massage can be replicated across different patient populations and clinical settings. Second, conducting adaptability trials (eg, simplifying the movements of Baduanjin to enhance cultural acceptance or modifying intervention protocols to align with local health care practices) is essential for testing TCM modalities in populations with limited prior TCM exposure. Third, future research should also expand the intervention duration to assess long-term efficacy and compliance, increase the sample size to enhance statistical power, and refine the study design by including separate control arms for individual TCM components (eg, Baduanjin alone and acupoint massage alone). In addition, exploring innovative strategies to minimize bias, such as using objective outcome measures or implementing partial blinding where feasible, will further improve the rigor of future studies. Collectively, these efforts will provide a more robust validation of TCM-based interventions for patients undergoing MHD and support their potential integration into global hemodialysis care.

Significance for Clinical Practice

The findings of this study could provide effective nonpharmacological interventions to improve frailty status, mental health, and QoL in patients undergoing MHD. This combined intervention can effectively reduce the incidence of complications and readmissions and decrease medical costs and socioeconomic pressures. In addition, it can provide new evidence for integrating TCM nursing measures into chronic disease management.

Future Research Directions

Several strategies can be implemented to improve the reliability and comprehensiveness of studies on the effects of sit-to-stand Tai Chi combined with acupoint massage in patients undergoing MHD. First, expanding the sample size and study duration by conducting multicenter studies with larger sample sizes and extended intervention periods is essential. This would help to elucidate the long-term effects and improve generalizability accurately. Second, improving the research design by implementing stricter randomization and blinding methods is crucial to minimizing bias and ensuring the validity of the results. In addition, a comprehensive multidimensional evaluation that includes more aspects, such as social support and economic status, should be incorporated to provide a holistic view of the effects of the intervention. Third, optimizing intervention strategies by combining nutritional guidance, psychological counseling, and other relevant methods can improve the effectiveness of the intervention further. By combining these approaches, this study provides robust evidence of the efficacy of this combined TCM therapy in managing frailty in patients undergoing MHD.

Conclusions

This study protocol presents a randomized controlled trial evaluating the efficacy of sitting Baduanjin combined with acupoint massage in improving frailty among patients undergoing MHD, addressing the gap of insufficient high-quality evidence for combined nonpharmacological interventions in this group. Its core objective is to verify whether this integrated TCM intervention alleviates frailty, enhances physical function, reduces depressive symptoms, and improves QoL, compared to routine care alone or acupoint massage alone. A key strength is the comprehensive evaluation system, integrating the FRAIL scale (primary indicator), objective physical assessments (grip strength and STS-10), and patient-reported outcomes (SDS and SF-36), alongside rigorous design (random allocation, concealed grouping, and blinded data collection and analysis), standardized protocols (8-week and thrice-weekly sessions), and detailed safety monitoring, ensuring feasibility and reliability for patients undergoing MHD. Preliminary results confirm balanced baseline characteristics across groups and good intervention safety (only mild and reversible AEs), supporting clinical applicability. If final results (anticipated Spring 2026) validate efficacy, this study will provide a scientific, low-cost nonpharmacological strategy for MHD-related frailty, enrich evidence for TCM integration into chronic kidney care, and inform clinical guidelines. Future multicenter studies with larger samples and extended follow-up are recommended to verify long-term effects and generalizability.

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Authors' Contributions

WZ wrote the first draft of the article. SZ and HX conducted the field research management and collected field study data. JH, FW, JS, and SL critically reviewed and edited the article.

Conflicts of Interest

None declared.

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Abbreviations

AE: adverse event
FRAIL: Fatigue, Resistance, Ambulation, Illness, and Weight Loss
MHD: maintenance hemodialysis
QoL: quality of life
SDS: Self-Rating Depression Scale
SF-36: Short Form Health Survey Questionnaire
STS-10: 10 times sit-to-stand test
TCM: traditional Chinese medicine

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Effect of SMS Reminders, Telephone Calls, and Transport Incentives on Enhancing the Completion of Tuberculosis Diagnosis and Initiation of Treatment for Diagnosed Patients: Protocol for a Randomized Controlled Trial

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Abstract

Background: Globally, tuberculosis (TB) programs have enhanced efforts to improve case detection, treatment initiation, and monitoring of treatment outcomes. However, less attention has been given to reducing the number of persons with presumed TB who never get tested for TB or those with confirmed TB who never start treatment in endemic regions such as Uganda. Such losses hinder progress toward attaining the 2035 End TB goals. The World Health Organization recommends mobile health (mHealth) interventions such as SMS reminders, telephone calls, mobile apps, and digital monitoring devices to foster universal health coverage. To our knowledge, there is limited evidence on whether these mHealth interventions can increase linkage to care for persons with presumed TB, particularly in sub-Saharan Africa.

Objective: We aim to conduct a randomized controlled trial (MILEAGE4TB) whose aim is to assess the effect of SMS reminders, telephone calls, and transport incentives on improving completion of TB diagnosis among persons with presumed TB and initiation of treatment for diagnosed patients in Uganda.

Methods: This will be a 5-arm individual randomized controlled trial among persons with presumed TB aged 18 years or older who are referred for Xpert MTB/RIF testing. Participants will be randomly assigned (2:2:2:1:1) to (1) standard of care, (2) SMS reminders only, (3) telephone calls only, (4) SMS reminders and a transport incentive, and (5) telephone calls and a transport incentive. An estimated sample size of 2389 participants will be considered. The primary outcome will be completion of TB diagnosis, defined as submitting a sputum sample for Xpert MTB/RIF testing and receiving test results within 30 days of being identified as having presumptive TB. The secondary outcomes will include (1) TB treatment initiation, which will be defined as starting TB treatment within 30 days of being diagnosed; (2) median turnaround times for TB diagnosis and treatment initiation; and (3) acceptability and feasibility of the interventions. Participants will be followed for 30 days to check whether they have tested for TB and collected their results. Chi-square tests will be performed for categorical outcomes. Analysis will be by intention to treat. Modified Poisson regression models will be used to estimate the effects of the interventions on completion of TB diagnosis and treatment initiation.

Results: The study was funded in June 2020 and data collection for the trial started in August 2023. Results from this trial are not yet available. As of August 28, 2025, a total of 2355 participants had been recruited. Data from the preliminary analysis will be ready by December 2025 after all trial activities.

Conclusions: This randomized controlled trial will provide insights on the use of mHealth interventions to improve the completion of TB diagnosis among persons with presumed TB and initiation of treatment for diagnosed patients.

Trial Registration: ClinicalTrials.gov NCT05964842; https://www.clinicaltrials.gov/study/NCT05964842

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International Registered Report Identifier (IRRID): DERR1-10.2196/70325

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KEYWORDS

tuberculosis; TB; presumptive tuberculosis; SMS; telephone calls; transport incentives; linkage to TB care

Introduction

Background

Tuberculosis (TB) remains one of the leading causes of death from a single infectious agent despite the fact that it is preventable [1]. The End TB Strategy of the World Health Organization (WHO) calls for reduction of TB incidence by 90%, deaths by 95% and eliminating catastrophic costs for TB-affected households by 2035; however, progress is hindered by the loss to follow-up (LTFU) of patients along the continuum of care [2]. Patient LTFU can occur after they are identified with presumptive TB but are never tested, while those who are tested and are confirmed to have TB can also undergo LTFU and never initiate TB treatment. This is in addition to the number of patients who never access a TB diagnostic test [3]. In 2023, an estimated 10.84 million people fell ill with TB, of whom 8.16 million were diagnosed and notified to national TB programs, leaving out 2.7 million patients (25%) [1]. A study by Kim et al [4] on TB care cascades of 30 high TB burden countries found that 35% of people with TB did not receive a diagnosis, while 5% of people who were diagnosed did not initiate treatment.

The WHO recommends the use of mobile health (mHealth) for improved service delivery and continuation of health care, given its timeliness, popularity, and affordability [2,5]. SMS reminders, telephone calls, and mobile apps are some of the interventions being used to support TB care and reduce patient LTFU during the treatment phase [6-10]. These mHealth interventions have shown promise in improving adherence to TB treatment in previous studies [11-14]; therefore, they have the potential to also support persons with presumed TB to complete the diagnostic process. Incentives given to patients have also been found to improve health care outcomes elsewhere [15-19]. However, there is limited evidence on the application of mHealth interventions and incentives during the phase when one is being presumed for TB and on how they can improve completion of the diagnostic process.

Uganda's TB burden has persisted over the years, and the country is still ranked among the 30 countries in Africa with a high burden of both TB and HIV, with an incidence of 198 cases per 100,000 population [1]. Recent studies from Uganda have reported prediagnosis LTFU of up to 40% [20] and pretreatment LTFU of 19% [21]. Diagnosis and initiation of TB treatment are critical for controlling TB transmission and achieving good patient outcomes, particularly when medication adherence is maintained [2]. Therefore, this situation calls for bold actions and innovations to reduce the number of patients lost to follow-up before completing TB diagnosis (prediagnosis LTFU) and those lost to follow-up before initiating treatment when diagnosed (pretreatment LTFU). In Uganda, mHealth interventions have emerged as promising tools to enhance TB care by improving patient outcomes and health care processes. These mHealth interventions have been used to address challenges in TB care, including contact investigation, delivery of test results, adherence to appointments, linkage to care, and treatment adherence [6,22].

The consequences of prediagnosis and pretreatment LTFU are serious. Patients with untreated TB remain infectious and can transmit TB to others, while failure to initiate treatment contributes to increased morbidity and mortality [23-26]. Therefore, monitoring the outcomes of persons with presumed TB is an important aspect of TB control [5]. This study will thus assess the effect of SMS reminders, telephone calls, and transport incentives on enhancing completion of TB diagnosis and initiation of treatment in Uganda. Assessing the effect of these interventions will provide evidence on whether reminding patients using SMS reminders or telephone calls, with or without conditional cash incentives, can enhance completion of TB diagnosis and initiation of treatment for improved patient outcomes and hence aid in designing targeted interventions and policies.

Goal of the Study

This randomized controlled trial aims to assess the effect of SMS reminders, telephone calls, and transport incentives sent to persons with presumed TB and those with confirmed TB on enhancing completion of TB diagnosis and initiation of treatment for diagnosed patients. The TB care continuum comprises 4 steps: screening, diagnosis, treatment initiation, and treatment completion [3,4]. This study will address LTFU along the TB care continuum at 2 time points: before diagnosis and before treatment. Prediagnosis LTFU refers to the failure to test for TB and obtain results within 30 days from the date of being presumed. Pretreatment LTFU refers to failure to initiate treatment after TB has been confirmed. The proposed intervention will use SMS reminders and telephone calls to improve communication between patients and health care providers, while the transport incentives will help address the economic barriers to diagnosis completion and treatment initiation.

Objectives and Hypothesis

The primary objective is to assess the effect of SMS reminders, telephone calls, and transport incentives on completion of TB diagnosis among persons with presumed TB and initiation of treatment for diagnosed patients. The secondary objectives are to determine the median turnaround time for TB diagnosis and treatment initiation and to examine the acceptability and feasibility of the interventions. We hypothesize that compared to standard of care (SOC), each individual intervention—SMS reminders alone or telephone calls alone—will improve completion of TB diagnosis and initiation of treatment by reducing prediagnosis LTFU by a minimum of 40% (from 24%

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to 14.4%), while a combined intervention—SMS reminders or telephone calls coupled with transport incentives—will reduce prediagnosis LTFU by 50% (from 24% to 12%). This protocol follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) reporting guidelines [27].

Methods

Study Setting

The study will be conducted in 6 government health facilities in central Uganda: Kiruddu National Referral Hospital, Entebbe Regional Referral Hospital, Mukono General Hospital, Luwero General Hospital, Kawolo General Hospital, and Wakiso Health Center (HC) IV (a lower-level facility). The selection of these health facilities ensures a mix of urban and rural settings and different administrative levels to increase the generalizability of the findings. Uganda's government health system consists of national referral hospitals, regional referral hospitals, and the district health system [28]. The district health system is further divided into district general hospitals; HCs IV, III, and II; and village health teams [28,29]. National referral hospitals provide comprehensive specialist services, while regional referral hospitals have specialists in only some specific fields. District general hospitals and HC IVs have physicians. HCs are graded based on the administrative zone served, population size, and services offered. HC IVs serve a county or municipality with a population of approximately 100,000 people and provide emergency surgery, blood transfusion, and all general medical services offered at lower-level health facilities. HC IIIs serve a subcounty with a population of approximately 20,000 people and provide maternity, inpatient, and laboratory services in addition to all health services offered at an HC II. HC IIs provide health services to a parish, ward, or division with a population of approximately 5000 people and offer outpatient care, prenatal care, immunization, and community outreach services [29].

In the study facilities, patients presenting with symptoms suggestive of TB (eg, cough, fever, weight loss, and night sweats) are identified and their demographic, contact, and clinical details recorded in the registers for persons with presumed TB at the different facility entry points. Patients are evaluated for TB using Xpert MTB/RIF, urine lipoarabinomannan, or chest X-ray depending on their symptoms, with diagnosis primarily conducted via Xpert MTB/RIF as recommended by the Ministry of Health [30]. Persons with presumed TB are offered sputum testing using Xpert MTB/RIF or sputum smear microscopy, while those unable to produce sputum are offered alternative diagnostic tests (eg, chest X-ray, urine lipoarabinomannan, sonography, tissue biopsy, and cerebrospinal fluid analysis). Details of patients who complete the required investigations are subsequently recorded in the laboratory or radiology registers. Thereafter, patients confirmed to have TB are started on treatment and recorded in the unit TB register (Figure 1). Ideally, the results of Xpert MTB/RIF tests should be available within 2 hours, allowing persons with presumed TB to receive their results on the same day as sputum submission. However, challenges such as high patient loads, cartridge shortages, lack of on-site Xpert MTB/RIF equipment, and low staffing levels in laboratories, among others, often prevent same-day completion of the diagnostic process, contributing to a considerable proportion of patients being lost to follow-up [31-33].

Figure 1. Patient flow through the study facilities. LTFU: loss to follow-up; TB: tuberculosis.

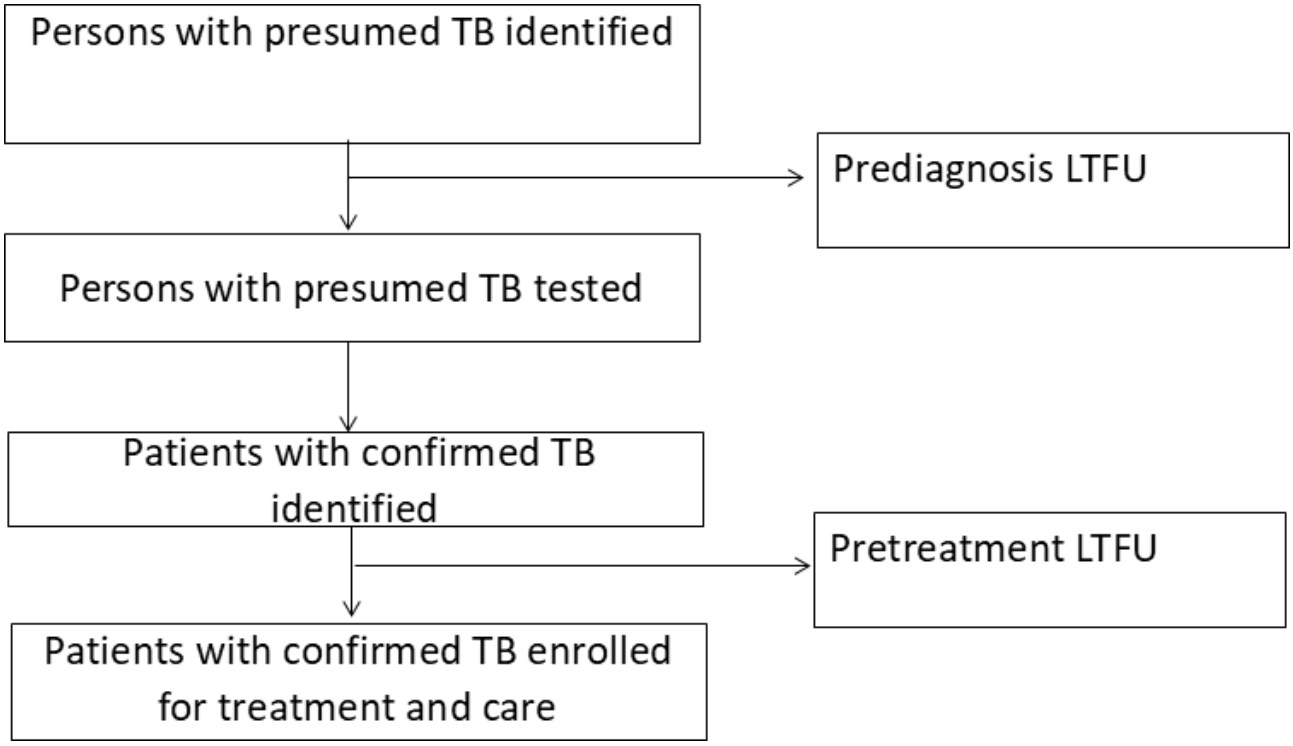

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Trial Design, Population, and Eligibility

This will be a multicenter individual randomized controlled trial with five arms: (1) SOC (control arm), (2) SMS reminders only, (3) telephone calls only, (4) SMS reminders and a transport incentive, and (5) telephone calls and a transport incentive. This intervention was designed and adapted through stakeholder engagements in a co-design workshop. The original design included SMS reminders only and a transport incentive [34]. However, based on stakeholder engagements, telephone calls were added to address the following concerns: (1) the risk of unintentional disclosure if someone other than the recipient reads the SMS text message; (2) existing SMS fatigue due to high volume of messages from telecom companies, leading to a likelihood of messages being ignored or deleted; (3) lack of real-time 2-way communication; and (4) lack of usefulness for patients who cannot read. Telephone calls were preferred because they offer privacy and foster 2-way communication in real time .

Description of the Study Arms

SOC Arm (Control)

Patients in the SOC arm (control) will continue to receive routine TB care, according to the Uganda Ministry of Health guidelines, including (1) screening individuals for TB, (2) identifying persons with presumed TB and recording their details in the TB register, (3) referring for testing, (4) receiving results, (5) irregular automated SMS text notification from the Xpert MTB/RIF machine to attending clinicians when results from the tests are ready, (6) irregular telephone calls to patients with positive TB test results to return to the health facility and start treatment, and (7) initiating treatment for patients with confirmed TB. There are irregularities in sending of SMS and making telephone calls due to inconsistencies in availability of funds, breakdown in the Xpert MTB/RIF server system, and limited human resource to support these processes.

Intervention Arms

The intervention will comprise 3 enhanced approaches to motivate participants to complete TB diagnosis: SMS reminders, telephone calls, and transport incentives. These interventions will be delivered in four arms: (1) SMS reminders only, (2) telephone calls only, (3) SMS reminders and a transport incentive, and (4) telephone calls and (5) a transport incentive.

SMS Reminders Only

Participants in this arm will receive up to 3 SMS reminders. The first reminder will be sent on day 0, the day of study enrollment. The second reminder will be sent once the patient's results are ready. If the patient does not return to complete the TB diagnostic process (ie, testing and receiving results) within 1 day of the second reminder, a third reminder will be sent. This third reminder will serve as a reinforcement, reminding participants to return and complete diagnosis or initiate treatment if they have not already done so. Standardized SMS reminders will be manually sent by the research team through the telecom service providers MTN and Airtel in either Luganda (the local language) or English, based on the participant's language preference determined at enrollment. The SMS reminders are planned to be 1-way (unidirectional) and the content neutral, excluding any mention of the word "TB" or the patient's name. The specific wording of the SMS reminders will be co-designed with stakeholders including persons with presumed TB and health workers. Quality control officers will verify the SMS reminders sent daily, checking for the correctness of recipient telephone numbers and ensuring that all reminders are sent on time as per the study procedures. Each day, quality control officers will randomly select at least 4 participants from the SMS reminder arm or from among those scheduled to receive the second or third reminder and cross-check their details on the study telephone to confirm that the participant received the appropriate SMS reminder and in the preferred language. They will also cross-check the correctness of the telephone number that received the SMS reminder vis-à-vis the one recorded in the register for persons with presumed TB. Successful transmission of reminders will be checked by requesting sample statements from the telecom companies to confirm SMS dispatch to patients. Moreover, at follow-up, participants will be asked whether they received either an SMS reminder or a telephone call and a transport incentive, further corroborating whether the participant received the SMS reminder.

Telephone Calls Only

In this arm, participants will receive up to 3 telephone calls as reminders, in addition to the usual SOC. The first telephone call will be made on the day of enrollment (day 0). The second telephone call will be made once the patient's results are ready. If the patient does not return to complete the TB diagnostic process within 1 day of the second call, a third telephone call will be made. The third telephone call will serve as a reinforcement, reminding participants to return and complete diagnosis or initiate treatment if they have not already done so. Telephone calls will be made in either Luganda (the local language) or English, based on the participant's language preference determined at enrollment.

Daily quality checks will be carried out to ensure delivery of the intervention to participants. At least 4 participants from the telephone call arm or from among those scheduled to receive the second or third telephone call will be randomly selected for the quality checks. Participant details will be cross-checked on the study telephone by the quality control officers at each study site to confirm that the participant received the appropriate telephone call. Call logs will also be checked to confirm the language used in the telephone call vis-à-vis the participant's preferred language and the correctness of the telephone number that received the call. Research assistants will continue attempting telephone calls if a patient does not answer the telephone, if another person answers, if it is not convenient for a patient to talk, or if the telephone is switched off until an effective call is made to the intended participant. A successful call will be defined as one in which a patient is reached, and a conversation takes place.

SMS Reminders and a Transport Incentive

Participants in this arm will receive the same SMS reminder package as those in the SMS reminder–only arm, along with a transport incentive of UGX 10,000 (approximately US $3). This transport incentive will be provided either after submitting a

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sputum sample in case the participant was unable to produce the sputum on the first day of the health facility visit or upon receiving their test results. The transport incentive will be disbursed through a prepaid mobile money system to ensure accountability for both the patient and the study team and to comply with the ongoing government campaign promoting the use of electronic cash [35]. These interventions will be administered in addition to the SOC provided at the health facility.

Telephone Calls and a Transport Incentive

The same telephone call package received by participants in the telephone call–only arm will be offered to those in this arm, along with a transport incentive of UGX 10,000 (approximately US$ 3). This will be in addition to the SOC received at the health facility. This transport incentive will be provided either after submitting a sputum sample in case a participant was unable to produce sputum on the first day of the hospital visit or upon receiving their test results. We will use the prepaid mobile money system to pay the transport incentive to participants in this study arm.

Sample Size Estimation

An estimated sample size of 2389 participants was determined to achieve 80% power at a type I error of 5%, adjusted for multiple comparisons using the Bonferroni correction. Four comparisons were considered according to the study objectives; therefore, the adjusted level of significance is 1.25%, with a corresponding 2-tailed Z value of 2.238. We also adjusted for a 24% LTFU among patients with TB, based on findings from the formative study that informed the design of these interventions. We assumed a 40% reduction in LTFU based on previous similar studies [36,37] for comparisons between SOC and either SMS reminders alone or telephone calls alone, resulting in an assumed proportion of LTFU of 14.4% in both these groups. For comparisons between SOC and combined interventions (SMS reminders or telephone calls with a transport incentive), a 50% reduction will be considered clinically significant, given the expected higher impact of the incentive. The sample size has been further adjusted for clustering using a design effect of 1.5 to account for the clustering anticipated at the health facility level and a postenrollment attrition rate of 20%.

Study Population

The study population will comprise persons with presumed TB who did not complete diagnosis on the same day as their health facility visit. Persons with presumed TB will be defined as those presenting with signs and symptoms suggestive of TB, including cough, fever, night sweats, and unexplained weight loss.

We will include (1) patients referred for Xpert MTB/RIF testing; (2) those aged 18 years or older; (3) those currently residing in the health facility's catchment area; (4) those willing to consent to the study procedures, including follow-ups, and able to sign an informed consent form; (5) those who own a mobile phone and have it in their possession on the day of recruitment; and (6) those able to read (a test SMS text message will be sent to the patient's mobile phone, and they will be asked to read it aloud). Participants planning to move out of the study area within 3 months after enrollment and those participating in other related studies (eg, those involving SMS reminders, telephone calls, or transport incentives) will be excluded.

Randomization and Blinding

Eligible participants will be randomly assigned by research assistants to 1 of the 5 study arms using permuted block randomization in a ratio of 2:2:2:1:1 via a predesigned mobile app (Figure 2). The block sizes will be varied to minimize predictability. A computer algorithm will be designed by the biostatistician together with the app designer to generate the allocation sequence in blocks of 8 and 16, assigning their order randomly. The allocation sequence will then be input into the predesigned mobile app for automatic randomization once the research assistants input the participant's unique study ID number. Due to the nature of the interventions, participants will not be blinded to their assigned study arm. Research assistants will also not be blinded, given their role in delivering the interventions. However, the outcome assessors and data analyst will remain blinded to the study arms.

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Figure 2. Flow diagram for randomization. SOC: standard of care; TB: tuberculosis.

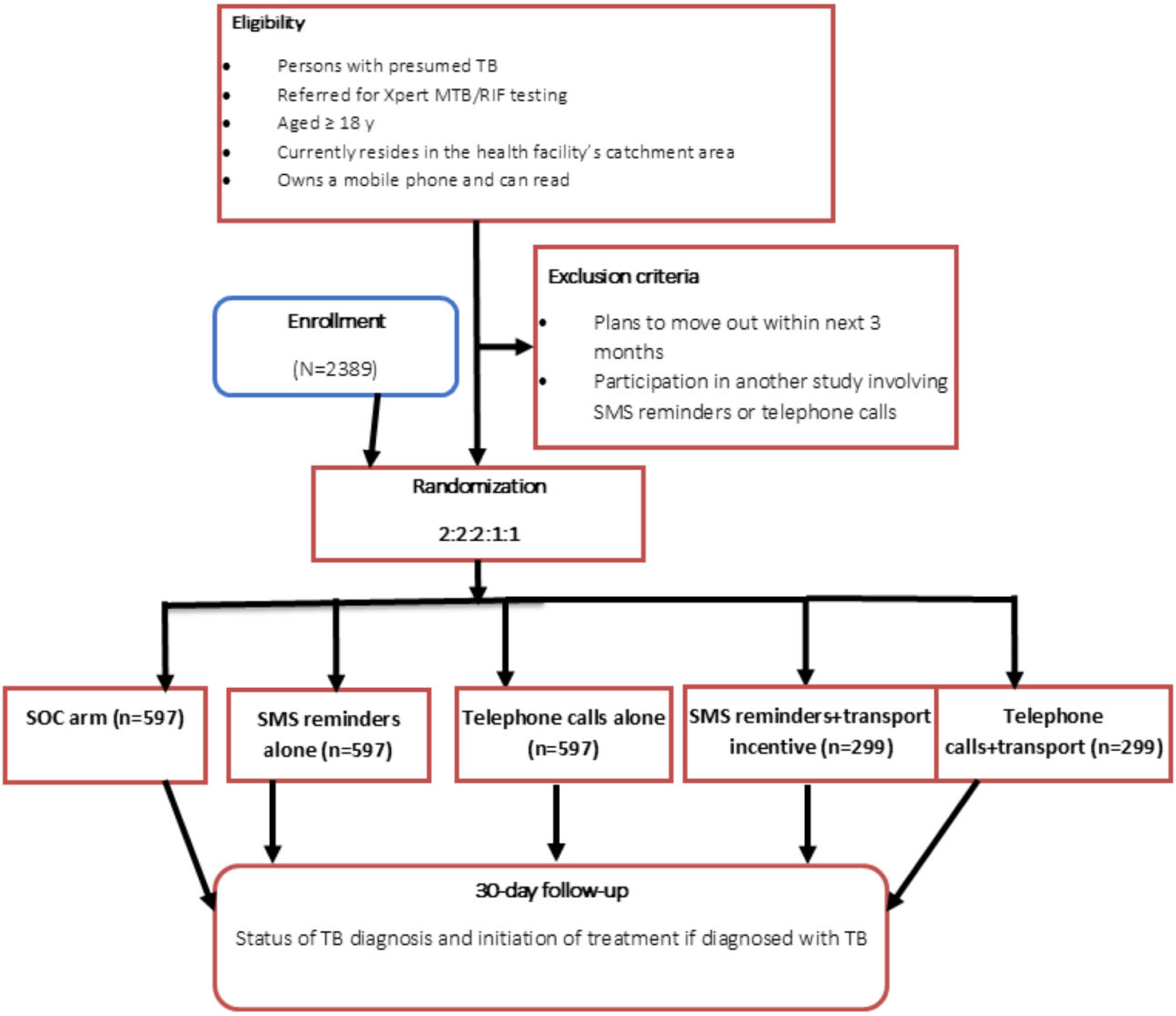

Recruitment Strategies for Study Participants

Two research assistants will be strategically positioned at different potential entry points for persons with presumed TB in each study health facility. The entry points will include the outpatient department, antiretroviral therapy (ART) clinic, prenatal clinic, and TB unit. The inpatient units will be excluded because admitted patients are less likely to be lost to follow-up, as they remain within the health facility throughout the testing process. In each study facility, we will hold entry meetings with health workers from the various departments involved in identifying persons with presumed TB to inform them about the study and solicit their support in referring eligible patients throughout the study period.

Referred patients will be introduced to the study team and asked whether they are interested in participating. Those who express interest will be given a card and requested to return to the study desk once they complete care seeking. The card will serve as a reminder not to leave the health facility before returning to the study desk. Patients who return after completing care seeking will be assessed for eligibility, and those who meet the criteria will be asked to provide informed consent by signing the consent form. Eligible participants will then be enrolled and randomly assigned to 1 of the 5 study arms using a smartphone preloaded with the randomization app. All participant details will be recorded in the study registers for persons with presumed TB in both electronic and hard-copy formats for backup.

Participant Follow-Up Procedures

Follow-up interviews will be conducted after 30 days from the day of recruitment for all participants primarily through face to face interviews at the health facility. Home visits will be conducted for patients who fail to turn up at the health facility. If still we can not access the patient, telephone calls will be made by research assistants to conduct the interview over the phone. At follow-up, data will be collected on whether the TB tests had been performed, along with the date of the TB test results, the date of registration for TB treatment, and the TB registration number. If a participant does not submit a sputum sample, receive test results, or initiate treatment after diagnosis, they will be asked to provide reasons for not undergoing testing, receiving results, or starting treatment.

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Data Collection Procedures

Participants will be enrolled in the study and assigned a unique ID number, which will be used for randomization using the mobile app. Once the participant has been randomly assigned, baseline measurements and tracking information will be collected and recorded using the Open Data Kit (ODK) platform (Get ODK Inc) and directly uploaded to the server. Data will be collected on age, sex, occupation, date when identified as a person with presumed TB, distance to the health facility of enrollment, test method used (ie, sputum smear microscopy or Xpert MTB/RIF), and knowledge and perceptions about the disease and treatment. We will train outcome assessors to objectively conduct interviews and assess outcomes at follow-up. This approach will minimize any biases associated with the team administering the intervention.

Trial End Points, Outcomes, and Timelines

The primary end point for the trial is completion of the TB diagnosis process within 30 days of being recruited. Completion of TB diagnosis will be defined as submitting a sputum sample for Xpert MTB/RIF testing and receiving test results within 30 days of being identified as a person with presumed TB. The 30-day follow-up period was selected based on previous studies for comparison [25,33]. Completion of TB diagnosis will be measured as the proportion of patients who completed TB diagnosis within 30 days out of all persons with presumed TB recruited into the study.

The secondary outcomes will include (1) TB treatment initiation, which will be defined as starting TB treatment within 30 days of being diagnosed (this will be measured as the proportion of patients diagnosed with TB who initiated treatment out of the total number of patients diagnosed with TB recruited into the study); (2) median turnaround times for TB diagnosis and treatment initiation; and (3) acceptability and feasibility of the study interventions. The detailed procedures and timelines are indicated in Table 1.

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Table . Study procedures and timelines.

Study procedure	Screening	Baseline	Day 0	Results available	Day after results reminder	Day 30
Enrollment						
Eligibility screening	✔					
Informed consent	✔					
Allocation	✔					
Sociodemographic information		✔				
Clinical history		✔				
Knowledge of and attitudes regarding TB[a]		✔				
Interventions						
SMS reminders			✔	✔	✔	
Telephone calls			✔	✔	✔	
Transport incentives				✔		
Assessments						
Sputum submission						✔
Receipt of results						✔
Receipt of interventions						✔
Treatment initiation for those diagnosed						✔
Acceptability assessment						✔
Qualitative study on perceptions and experiences of the interventions						✔

[a]TB: tuberculosis.

Data Management and Analysis

Overview

ODK data will be downloaded into Microsoft Excel and transferred to Stata 14 (StataCorp LLC) for cleaning and analysis. The primary analytical approach will follow the intention-to-treat principle, with participants in the intervention arm considered exposed to the intervention regardless of whether they received specific intervention services. We will assess for any contamination by conducting and comparing the results of the intention-to-treat and per-protocol analyses. Descriptive statistics (means, medians, and proportions) will be used to describe participant characteristics across the study arms. We will control for characteristics that are not balanced across the study arms in the fitted regression models. Chi-square tests will be performed for categorical outcomes. Log-binomial regression models using generalized linear modeling will be applied to assess associations between each intervention and the outcomes. A P value <.05 will be considered statistically significant.

Interim Analysis

Although this trial does not pose a significant risk to participants, we plan to conduct an interim analysis. Findings from the interim analysis will be shared with the data and safety monitoring board (DSMB) to determine whether the trial should continue based on the emerging results.

Ethical Considerations

The study was approved by the Makerere University School of Public Health Research and Ethics Committee (799) and the Uganda National Council of Science and Technology (HS993ES). The study will be conducted in accordance with the World Medical Association Declaration of Helsinki. Written informed consent will be obtained from all participants. Each participant will receive compensation of 10,000 Ugandan

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shillings (US $3) only for their time in the study at each level of data collection. All hard-copy study materials will be stored securely under lock and key, with access restricted to core project staff. Electronic data will be stored on a password-protected server hosted at Verton IT Ltd, with access similarly restricted to core project staff. To minimize the risk of inadvertent disclosure of presumptive TB status through SMS reminders or telephone calls received by unintended recipients, we will ensure that the SMS reminder content is neutral, with no mention of the word "TB," serving only as a reminder to the patient to return to the health facility. This approach was adopted based on feedback from the co-design workshop with stakeholders, who recommended avoiding the use of the word "TB" in the SMS reminder content. We will also only recruit participants who personally own a mobile phone and do not share it with others. Furthermore, at the beginning of each telephone call, participants will be asked to identify themselves to confirm that the data collectors are speaking with the correct individual. All enrolled participants will be assigned a unique ID number at recruitment, which will be used throughout the study period. All data will be deidentified before analysis. The trial has been registered at ClinicalTrials.gov (NCT05964842).

Study Oversight and Monitoring

The study investigators, coordinator, supervisors, and research assistants will meet daily during participant recruitment for quality control purposes. This trial will be monitored by an independent DSMB and a local steering committee (LSC). The DSMB will serve as the core technical team responsible for reviewing cumulative trial data, monitoring adherence to the trial protocol, and ensuring patient safety. It will also review any suggestions for protocol amendments. The DSMB will comprise 3 members (an epidemiologist, a clinical officer, and a senior researcher) and meet every 2 months to assess trial progress. The LSC will provide administrative oversight, ensuring adherence to study procedures, monitoring trial progress, and providing advice and guidance. It will comprise 7 members (a community advisory member, an IT specialist, 2 policymakers, a biostatistician, an epidemiologist, and a social worker) and meet every 6 months.

Adverse Events Monitoring and Reporting

The planned trial interventions pose minimal risk to participants; hence, we do not anticipate serious adverse events. However, we will continually conduct risk assessments to identify any incidents that may occur. The research assistants will be trained to monitor for adverse events, document them accurately, and follow established reporting procedures. All adverse events occurring during the study, whether or not considered related to the study, will be reported in writing to the study team, the LSC, the DSMB, and the Makerere University School of Public Health Research and Ethics Committee for assessment and further review. Each event will be recorded in the study registry, documenting the following information: description of the event, date of occurrence, participant details, onset and end dates, and severity. We will actively follow up each event until resolution or stabilization.

Dissemination Plan for Research Findings

All findings from the trial will be disseminated in workshops and conferences as oral or poster presentations. The target audience will include members of the Uganda National TB and Leprosy Program research forum, policymakers, TB program implementing partners, academic researchers, and the study participants. Policy briefs will be prepared, and a report of the study findings will be submitted to the participating health facilities and to the funder, the European and Developing Countries Clinical Trials Partnership. All findings will be published in open-access, peer-reviewed journals.

Results

The study was funded in June 2020 and data collection for this RCT started in August 2023. We encountered delays during the COVID-19 period hence the RCT started at a later date than anticipated. The results are not yet available. Results from the preliminary analysis will be ready by December 2025. As of August 28, 2025, a total of 2355 participants had been recruited, and preliminary analyses are ongoing. The final results are expected to be published by March 2026.

Discussion

Summary

The MILEAGE4TB study is an individual randomized controlled trial to determine the effect of SMS reminders, telephone calls, and transport incentives on enhancing completion of TB diagnosis among persons with presumed TB and initiation of treatment for diagnosed patients. The study hypothesizes that, compared to SOC, each individual intervention—SMS reminders alone, telephone calls alone, or a combined intervention of either SMS reminders or telephone calls with transport incentives—will reduce prediagnosis LTFU. Some of the factors contributing to patient LTFU are high patient loads, cartridge shortages, and low staffing levels in laboratories [31,32]. In addition, evidence indicates that even with improved diagnostic tools such as Xpert MTB/RIF, same-day results are often not feasible in low- and middle-income countries (LMICs) due to the unavailability of Xpert MTB/RIF equipment and thus the need to refer specimens for testing. These delays prevent same-day result delivery, increasing the likelihood of patient LTFU.

This study will address cascading patient LTFU along the TB care continuum, particularly at 2 time points: before diagnosis and after treatment. Prediagnosis and pretreatment LTFU are important because untreated patients with TB remain infectious and can continue to transmit TB in the community, while failure to initiate treatment results in poor patient outcomes, including death [6,24,38]. Studies have shown that timely diagnosis and treatment improve patient outcomes [39,40]. Effective TB case detection has been reported to lower TB incidence, prevalence, and mortality levels [41]. Therefore, routine follow-up of patients during the process of diagnosis and linkage to treatment is important. This is in line with the targets of the "End TB Strategy" and the United Nations' Sustainable Development Goals [42]. In addition, instances of pretreatment LTFU are not

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included in routine reporting by national TB programs, leading to an overestimation of program effectiveness [43].

The proposed intervention uses SMS reminders and telephone calls to improve communication between patients and health care providers, while transport incentives address the economic barriers associated with completion of TB diagnosis and treatment initiation. Telephone-based interventions such as SMS reminders and telephone calls have successfully improved adherence to TB treatment in Uganda [44-46] and increased the uptake of other health interventions, such as childhood immunization [47]. In addition, incentives have been found to improve health care outcomes [48-50]. However, there is limited data from LMICs on the role of SMS reminders, telephone calls, and transport incentives in interventions seeking to improve completion of TB diagnosis and initiation of treatment for diagnosed patients. This study will provide evidence on the use of mHealth strategies and incentives to improve completion of TB diagnosis and initiation of treatment for diagnosed patients.

Given that the phase of being presumed for TB offers an opportunity for early diagnosis and treatment initiation [51,52], this study, whose aim is to enhance completion of TB diagnosis and initiation of treatment for diagnosed patients, is critical to achieving the targets of the "End TB Strategy" [2]. In addition, our study will put into practice the "Find. Treat. All." initiative, which seeks to close gaps in TB detection and treatment. This initiative, launched in 2018 by the WHO in collaboration with the Stop TB Partnership and the Global Fund to Fight AIDS and Tuberculosis, focuses on improving the quality of TB services through assessment of the TB care cascade and identification of missing cases [53]. Furthermore, the provision of transport incentives is in line with the principles of social protection for patients and supports the attainment of universal health coverage, as outlined in Sustainable Development Goal 3 and the "End TB Strategy" [42].

Study Strengths and Limitations

This randomized controlled trial is expected to provide one of the highest levels of evidence for ways to enhance completion of the TB diagnostic process and treatment initiation. The study will be conducted across different levels of health facilities to enhance representativeness and increase the generalizability of the findings. In addition, we are implementing a multifaceted intervention comprising SMS reminders, telephone calls, and transport incentives, which is an approach that, to the best of our knowledge, has not been previously evaluated among persons with presumptive TB.

However, blinding will not be possible at all levels, particularly for participants, which may introduce some bias. This risk will be minimized through continual clarification of the study goal and methods. Moreover, individuals who share mobile phones will be excluded to avoid inadvertent disclosure of their testing status. This exclusion criterion may limit participation of certain populations that could have benefited from this intervention.

Conclusions

This study will assess the effect of SMS reminders, telephone calls, and transport incentives on enhancing completion of TB diagnosis among persons with presumed TB and treatment initiation for diagnosed patients within Uganda's health care system. The trial will provide evidence that can inform health care practice and policy related to the TB diagnosis process, which could ultimately improve patient care. The use of SMS reminders and telephone calls in the phase of being presumed for TB will provide insights on their effectiveness in this phase, which has not been extensively explored. Moreover, the application of these technologies will add to existing evidence on the effectiveness of mHealth in improving health service delivery.

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Authors' Contributions

RN led the manuscript writing and coordinated the writing process as well as ethical clearance of the protocol. IW, VK, and SK contributed to manuscript writing. RS provided technical support during study conceptualization, protocol development, and manuscript writing alongside NK, LA, JKN, and VN. EB conceptualized the study and provided overall technical guidance during protocol development and manuscript writing. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

DSMB: data and safety monitoring board
HC: health center
LMICs: low- and middle-income countries
LSC: local steering committee
LTFU: loss to follow-up
mHealth: mobile health
ODK: Open Data Kit
SOC: standard of care
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TB: tuberculosis
WHO: World Health Organization

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Efficacy of FiberMore, an AI-Based mHealth Intervention to Increase Dietary Fiber Intake Among Type 2 Diabetes Patients: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: A high intake of dietary fiber has been shown to improve glycemic control and decrease hyperinsulinemia in people living with type 2 diabetes (T2D). T2D patients in Japan consume less than the recommended amount of fiber. Based on findings from a formative study, we developed an artificial intelligence (AI)-powered mobile health (mHealth) intervention, FiberMore, that uses the theory of planned behavior to help T2D patients increase their dietary fiber intake by enhancing their perceived behavioral control and attitude toward fiber consumption.

Objective: We aimed to assess the efficacy of FiberMore in improving the dietary fiber intake of T2D patients by conducting a pilot randomized controlled trial. In addition, we want to explore the efficacy of FiberMore in reducing HbA_{1c} of T2D patients via improvement in dietary fiber intake.

Methods: This is a randomized, single-blinded, multicenter study targeting 80 T2D patients from 3 institutions in Japan with a 2-week run-in, a 12-week intervention, and a 12-week observation. The intervention group is given access to FiberMore throughout the 12-week intervention period. A core feature of FiberMore is AI-powered meal photo logging using a fine-tuned GPT-4o (OpenAI) model, which analyzes the nutrient content of meals and delivers personalized, real-time feedback on fiber content. In addition, FiberMore provides personalized fiber goal setting and supports participants in identifying barriers to increasing fiber intake, along with corresponding coping strategies (labeled as “solutions” to the participant), through an AI chatbot. The AI chatbot also assesses participants’ emotional attitudes toward eating more fiber and delivers relevant educational content on dietary fiber. The control group receives a sham intervention focused on salt reduction, consisting of educational content delivered at 3 time points during the intervention period and records their daily efforts in salt reduction in a diary. The 12-week intervention period will be followed by a 12-week observational period to investigate the sustainability of the intervention’s effects. The primary outcome is between-group difference in the change of dietary fiber intake at 12 weeks. The secondary outcomes include HbA1c, other clinical measures, measurements of behavior changes, and assessment of participants’ satisfaction and perceived usefulness of the intervention.

Results: Recruitment began on February 12, 2025, and ended on September 1, 2025. We anticipate that the intervention period will conclude in December 2025 and the observation period will conclude in March 2026. As of September 22, 2025, a total of 72 participants have been officially enrolled and randomized.

Conclusions:: There are currently no mHealth dietary interventions that specifically focus on increasing fiber intake in Japan, highlighting the novelty of this intervention. This trial will generate important evidence on the efficacy, feasibility, and safety of an AI-based mHealth intervention for enhancing dietary fiber intake and glycemic control in free-living individuals with T2D.

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Furthermore, as a pilot study, it will offer valuable insights into the development of AI as a promising tool for accurate, low-burden dietary assessment.

Trial Registration: Japan Registry of Clinical Trials jRCT2032240579; https://jrct.mhlw.go.jp/latest-detail/jRCT2032240579

International Registered Report Identifier (IRRID): DERR1-10.2196/78019

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KEYWORDS

digital therapeutics; behavior change; theory of planned behavior; dietary fiber; artificial intelligence; type 2 diabetes; randomized controlled trial

Introduction

Globally, approximately 462 million individuals are affected by type 2 diabetes (T2D) [1]. In Japan, the Ministry of Health, Labor, and Welfare estimated in 2019 that 11 million people are suspected of having diabetes, with a 19.7% prevalence in males and 10.8% in women [2]. T2D is associated with a variety of medical complications, including kidney failure, coronary heart disease, and stroke [3].

Dietary fiber is a macronutrient of importance in the nutrition management of diabetes patients [4]. A high intake of dietary fiber has been shown to improve glycemic control and decrease hyperinsulinemia in people living with T2D [5]. The impact of higher fiber content on reducing the glycemic index of foods has been a long-standing focus in diabetes treatment research [6]. Several meta-analyses have consistently demonstrated that increased dietary fiber intake leads to significant improvements in glycemic control, with reductions in HbA_{1c} of at least 0.3% [7-11].

Other benefits of high intake of dietary fiber include weight management, lowering of lipid levels, and lowering of blood pressure [12,13]. Additionally, T2D patients consuming more than 25 g of total dietary fiber per day had a notably low incidence rate of stroke (<0.90 per 1000 patient-years) [14]. In view of the benefits of increased dietary fiber intake, several clinical guidelines recommend daily fiber targets for individuals with diabetes: the Japan Diabetes Society (JDS) advises at least 20 g per day [15]; the European Association for the Study of Diabetes recommends 35 g or more per day [16]; and the American Diabetes Association suggests 25 - 38 g per day or a minimum of 14 g per 1000 kcal [17]. Nevertheless, T2D patients in Japan consume less than the recommended intake. In a cross-sectional study of 4399 Japanese patients with T2D, the average dietary fiber intake was about 13 g per day [18]. In addition, a cohort study of 1414 Japanese patients with T2D reported that approximately 75% of the cohort consumed less than 16 g of dietary fiber per day [14].

Mobile health (mHealth) lifestyle self-management interventions, typically targeting diet and physical activity, have been proven effective in achieving clinically meaningful glycemic control among T2D patients [19-21]. mHealth apps that support diet self-management improve diet quality and enhance adherence to self-monitoring more effectively than traditional pen-and-paper methods [22,23]. mHealth offers advantages such as delivering interventions anytime and anywhere, supporting extended engagement, and enabling personalized communication [24]. Nevertheless, previous research suggested that Japanese T2D patients who monitored their diet using an mHealth diabetes self-management app consumed less than the recommended 20 g of dietary fiber per day, despite engaging in self-monitoring through meal logging and receiving general nutritional feedback including dietary fiber [25]. This suggests a general diet management app is insufficient to help T2D patients increase their fiber intake. Additionally, many existing nutritional management apps are not grounded in behavior change theory [26], which hampers the understanding of the mechanisms through which the apps influence behavior [27]. Interventions based on behavior change theory have been shown to be more effective than non–theory-based interventions [28], with those using the theory of planned behavior (TPB) [29] being especially effective in understanding diet behaviors [30]. The inclusion of behavior change theory in mHealth apps has also been reported to enhance user engagement [31]. Given the well-established benefits of dietary fiber in glycemic control for T2D patients, there is a clear need for a fiber-focused mHealth dietary intervention among this population. Previous research has demonstrated that such interventions are effective in increasing fiber consumption [32-34].

A recent study based on the TPB revealed that while T2D patients in Japan are aware of the benefits of consuming more dietary fiber, the 2 main barriers they faced are a lack of knowledge about high-fiber foods and difficulty in estimating fiber content in meals [35]. Attitude and perceived behavioral control (PBC) were found to predict intention to increase 50% more dietary fiber than patients' usual intake [35]. This highlights the need for an intervention that provides real-time feedback on dietary fiber intake for each meal, along with educational information to support fiber consumption. Nevertheless, evidence has suggested that manual food logging in dietary apps can be burdensome, leading to reduced user engagement in diet self-monitoring over time [19,26]. Image-based dietary assessment, facilitated by artificial intelligence (AI), could address this issue by streamlining the process of food logging, thus reducing user burden [36]. This method has also been shown to potentially exceed the accuracy of human estimations of nutrient content based on digital food images [37], particularly in the assessment of dietary fiber [38,39]. Furthermore, AI is capable of offering personalized nutritional advice and meal plans [40]. Leveraging this strength of AI allows us to build a diet intervention in line with the JDS's recommendation to honor patients' personal diet preferences while administering medical nutrition therapy [15].

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Based on the above research findings, we developed FiberMore, an AI-powered diet intervention app that uses TPB to help T2D patients increase their dietary fiber intake by enhancing their PBC and attitude toward fiber consumption. To our knowledge, this is the first study to use an AI-based bot to deliver fiber-focused feedback based on the assessment of meal photos. While many nutrition apps focus on improving general health care concerns, apps that focus on specific chronic diseases and the nutrition involved in the disease state are limited [26]. Currently, dietary interventions specifically targeting improving dietary fiber intake among T2D patients have not been developed in Japan, thus highlighting the novelty and importance of this behavior change intervention. The purpose of this single-blind, randomized controlled trial is to examine the preliminary efficacy of an AI-assisted, app-based mHealth intervention to promote dietary fiber intake among T2D patients, leading to improved blood glucose control.

The specific research objectives and hypotheses are as follows:

1. Objective 1: To investigate the efficacy of FiberMore in improving dietary fiber intake.
   - We hypothesize that, at the end of the intervention, the intervention group will achieve statistically significant improvement in the primary outcome, dietary fiber intake, relative to the dietary fiber intake of the control group.
2. Objective 2: To investigate the preliminary efficacy of FiberMore in reducing HbA_{1c} levels.
   - We hypothesize that, at the end of the intervention, the intervention group will achieve a statistically significant reduction in the secondary outcome, HbA_{1c} levels, relative to HbA_{1c} levels in the control group.

Methods

Study Overview

This is a single-blind, parallel-group pilot randomized controlled trial targeting patients with T2D who consume less than 20 g of dietary fiber per day on average. Following a 2-week run-in period, study participants will undergo a 12-week intervention period, followed by a 12-week observation period, making the total study duration 26 weeks (with a maximum of 30 weeks, including allowable ranges in clinic visits; see Figure 1).

Figure 1. Overview of study timeline.

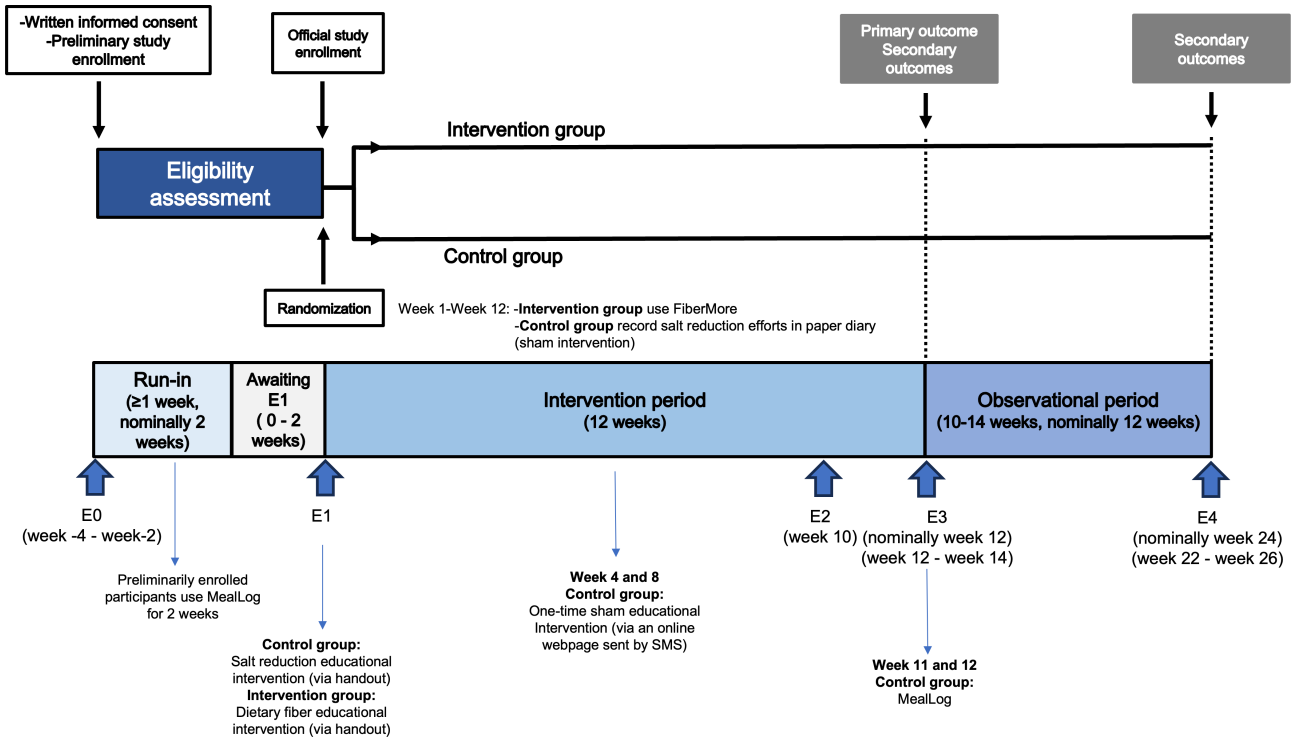

The intervention group is given access to an AI-powered dietary fiber intake support system named "FiberMore" throughout the 12-week intervention period. The intervention offers several features, including fiber content assessment of meals through meal photos and interacting with a chatbot, tailored feedback on logged meals, personalized fiber goal setting, barrier identification to eat more fiber and strategies (solutions) to overcome them, emotional attitude assessment toward eating more fiber, and access to educational information on dietary fiber via a chatbot.

The study will use a "sham intervention" related to dietary behavior change as control [41]. The main purpose of using a sham intervention is to achieve participant blinding and to control for the Hawthorne effect of receiving an intervention [42]. Salt reduction education aligns with dietary recommendation for T2D management. The educational content specifically focuses on reducing sodium intake through cooking methods and seasoning practices, without targeting food choices related to dietary fiber. The control group receives educational intervention on salt reduction at 3 time points: at official study enrollment (via an educational handout), at week 4 (through

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web-based educational information delivered via SMS), and at week 8 (through web-based educational information delivered via SMS). Additionally, participants in the control group will document their salt reduction efforts in a paper diary throughout the intervention period. They will use the meal logging app "MealLog" to record their meals at week 11 and 12, which allows for meal logging without providing any feedback or dietary intervention.

Setting and Participants

Patients are recruited at The University of Tokyo Hospital and Mitsui Memorial Hospital, both located in central Tokyo. Recruitment will be conducted by attending physicians during patients' regular consultations at outpatient clinics. In order to select patients who will benefit from the interventions in this study and can appropriately participate in this study, we apply the inclusion criteria (see Textbox 1). In order to exclude patients whose factors may affect the evaluation of this study's efficacy, and to ensure the intervention is safe for the participants, we apply the exclusion criteria (Textbox 2). Most of the criteria apply on the day of obtaining consent (at the E0 event), with some applying before randomization at the E1 event, based on results from the run-in period.

Textbox 1. Inclusion criteria of the study.

At the time of consent acquisition (E0):

- Diagnosed with type 2 diabetes (T2D) and attending the hospital for T2D treatment
- HbA_{1c} 7.5% and above and owns a smartphone with internet data connection (either an iPhone or an Android phone) and are able to receive SMS text messages
- Willing to take all meal photos with their smartphones and log them on an app
- Patients are able to attend research appointments at designated times during the research period
- Aged 18 years and older
- Fluent in spoken and written Japanese
- In the contemplation, preparation, and action stage to increase dietary fiber intake according to the transtheoretical model (TTM) of behavior change
- Determined by the recruiting researcher to have no cognitive impairment
- Determined by the recruiting researcher to be capable of receiving dietary fiber intervention
- Patients have received a thorough explanation about participation in this study, participants have provided voluntary, written consent based on a complete understanding of the study.

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Textbox 2. Exclusion criteria of the study.

At the time of consent acquisition (E0):

- Aged 76 years and older
- Judged by physicians to be an unsuitable candidate for dietary intervention
- Changed type 2 diabetes (T2D) medication within the past 8 weeks
- Currently participating in another clinical research program
- Undergoing a fiber-restricted diet as ordered by physicians
- History of eating disorder
- Currently taking fiber supplements
- Patients with fluid restriction
- Patients with Crohn disease, ulcerative colitis, irritable bowel disease, irritable bowel syndrome, and intestinal obstruction
- Patients who have taken bowel surgery within the last 3 months
- Patients with chronic kidney disease stage 4 and above
- Patients with hyperkalemia or hyponatremia
- Patients who are currently pregnant or actively trying to conceive
- Patients whose smartphones are incompatible with the app, either due to the inability to download or run it effectively, including smartphones with operating systems below Android 5.0 and iOS 14.0
- Any other reason determined by the physician that deems the patient unfit for participation

Before group allocation (after the run-in, before event E1):

- Takes a daily average of 20 g and above of dietary fiber, determined via app assessment over the 2 weeks run-in period
- Fail to log at least 2 eating occasions (either main meals or snacks) in the app per day for 7 or more days during the 2 weeks run-in period

Intervention design

The AI-based dietary fiber intake support system for the intervention group consists of a smartphone app (iOS and Android) that delivered intervention features to promote dietary fiber intake, named “FiberMore.” An AI-powered chatbot, named “EiYouBot,” uses Anthropic’s Claude Sonnet model with FiberMore-specific prompts. The image processing uses OpenAI’s GPT-4o (1-shot prompting, with fine-tuning). These 2 AI approaches are integrated within FiberMore (see Figure 2). GPT-4o and Claude Sonnet are state-of-the-art large language models that have undergone extensive pretraining on diverse multimodal data. We previously reported methodology and findings of an internal validation study, where the FiberMore image analysis model was benchmarked against registered dietitians using Japanese meal photos. We found that the base AI model without fine-tuning demonstrated better accuracy in fiber estimation than a dietitian [38,39]. Building on the same validation methodology, we fine-tuned the AI model using a data set of over 1269 Japanese meals that included a combination of weighed food records and dietitian-estimated nutritional values. The final fine-tuned AI model used in this study demonstrated improved performance, with intraclass correlation coefficients (ICC) of 0.79 for fiber, surpassing the earlier non–fine-tuned models and the dietitian benchmark (ICC=0.68).

Figure 2. System and equipment used in the intervention group during the intervention period (week 1 to week 12). AI: artificial intelligence.

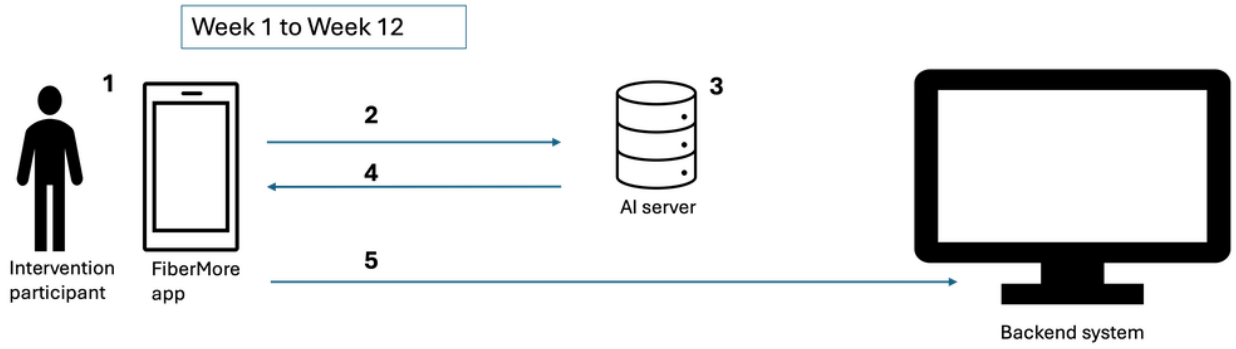

The FiberMore intervention design was guided by continuous, iterative discussions within the multidisciplinary research team, combined with repeated cycles of testing and refinement. The chatbot prompt was continuously improved through multiple rounds of testing with simulated and real-user inputs from individuals with T2D to ensure clarity, acceptability, and safety

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of the chatbot. The detailed full intervention features of FiberMore are listed in Table 1. Although FiberMore supports both Japanese and English, only the Japanese version will be used in this study.

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Table . Details of FiberMore features used by the intervention group.

FiberMore features	Description
Daily intervention features	
Meal logging options in FiberMore	
Snap a meal (or upload from phone gallery)	• Study participants log a meal via taking a photo with FiberMore. The meal photo is uploaded to the AI[a] server and analyzed for its fiber, energy, carbohydrates, protein, fat, and salt amounts. • If connectivity issues occur, study participants can take a meal photo using the native camera app of their smartphone and use the "Upload from gallery" function to upload the meal photo to FiberMore at a later time within the same day.
Chat a meal	• Study participants describe meals with the "Chat a meal" chatbot (EiYouBot) on FiberMore to log their meals. Based on the descriptions, the meal is analyzed by the AI server for its fiber, energy, carbohydrates, protein, fat, and salt amounts.
Snap a meal (or upload from phone gallery) followed by chat a meal	• Study participants first log a meal via taking a photo with FiberMore. The meal photo is uploaded to the AI server and analyzed for its fiber, energy, carbohydrates, protein, fat, and salt amount. Study participants then describe additional details about the meal with EiYouBot. Based on these extra details, the chatbot adjusts the estimates for the meal's fiber, energy, carbohydrates, protein, fat, and salt amounts.
Real-time feedback on logged meals	• For every meal logged onto FiberMore, study participants will receive 3 types of immediate feedback: • Real-time line graph showing progress toward reaching their daily fiber goal. • Feedback on the fiber amount of the meal in grams. • Feedback on the amount of dietary fiber in a meal compared to the number of calories it provides, whether it is low, moderate, good, and excellent (Multimedia Appendix 1).[b]
Daily feedback on fiber goal achievement	Once a day, study participants will receive feedback on the app of whether they achieved the goal for fiber intake for the previous day. This feedback occurs via a pop-up screen when they open the app for the first time during the day.
Coping strategy (solution) assessment	Once a day, when study participants open the app for the first time, a pop-up screen will prompt them to assess whether they implemented their chosen solution for their selected barrier to increasing fiber intake on the previous day.
Weekly intervention features	

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FiberMore features	Description
Goal setting	• Once a week, study participants will be prompted by app notification from FiberMore to set a new weekly fiber goal. EiYouBot suggests a new goal based on the number of days the fiber goal is met in the previous week. • Number of days fiber goal was met in the previous week: • 0, 1, or 2 days: decrease 1 g from previous week's goal. • 3 or 4 days: maintain previous week's goal. • 5 days: increase 1 g from previous week's goal. • 6 or 7 days: increase 2 g from previous week's goal. • Study participants will respond in the chat with EiYouBot whether they are confident to meet the suggested goal at least 5 days in the week. If they are confident, the fiber goal suggested by the chatbot will be set as the new goal of the week. If study participants are not confident that they can meet the suggested goal, the chatbot will propose to lower the goal by 1 g, as long as it is not lower than the minimum goal of the study participants.[c] • Study participants can also negotiate with EiYouBot for an easier goal by proposing a lower goal in the chat. The proposed lower goal can be set as the new goal as long as it is not lower than the participant's minimum goal.[c] • The maximum fiber goal that the chatbot can set is 30 g. • The initial fiber goal for study participants assigned to the intervention group during official enrollment will be based on the 10th highest daily fiber intake logged during the 14-day run-in period, with no-log days considered as "0." If the 10th highest value is 0, the smallest nonzero value logged during the run-in will be set as the initial goal.
Barrier and coping strategy setting	• Once a week, study participants will be prompted by an app notification to choose a main barrier to increasing their fiber intake and determine a solution (ie, a coping strategy) to overcome that barrier via the "Barrier and Solution" chatbot. Study participants can select the barriers and solutions from the list provided by EiYouBot, or they can write their own barriers and solutions in the chat.
Emotional attitude assessment	• Once a week, study participants will be prompted by an app notification to assess how they feel about increasing fiber intake via a chatbot, whether it is enjoyable, just okay, or not enjoyable. EiYouBot will provide positive and encouraging feedback based on the participant's response.
On-demand feature	

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FiberMore features	Description
Learn more	• Study participants can use the "Learn more" chatbot anytime to receive educational information on dietary fiber by writing their questions to EiYouBot.

[a]AI: artificial intelligence.

[b]Based on the calculation of fiber to energy ratio of the meal eaten scaled to the daily fiber goal and target energy intake: low (<0.5), moderate (0.5 - 0.89), good (0.9 - 1.2), and excellent (>1.2). Refer to Multimedia Appendix 1 for calculation of target energy intake.

[c]The minimum fiber goal will be the same as the initial fiber goal of the study participants.

FiberMore is designed in line with the JDS's guideline for T2D patients to consume 20 g and above of dietary fiber daily [15]. FiberMore uses intervention features such as goal setting, identifying barriers and coping strategies, and self-monitoring to help T2D patients reach this goal gradually. Furthermore, FiberMore uses AI to provide personalized feedback and advice for patients in line with JDS's recommendation to consider patients' personal dietary preferences when administering medical nutrition therapy [15].

The flow of interaction between the intervention participant, the app interface, the backend system, and the AI server is as follows, as illustrated in Figure 2: the intervention participant uploads a meal photo or engages with the chatbot feature in FiberMore (Step 1). Data provided by the participant is sent to the AI servers (Step 2). The AI servers process the uploaded meal photo or chatbot interaction and generate relevant feedback. Once the AI server completes processing, FiberMore receives relevant feedback by AI. This feedback is displayed to the user in real time within the app interface (Step 4). The app then securely transmits the feedback to the backend system via internet connection using a highly encrypted application programming interface (API) stored within the app (Step 5).

Description and app screenshots of participant interactions with FiberMore can be found in Multimedia Appendix 2.

The FiberMore intervention is mainly designed to enhance PBC by targeting and modifying participants' control beliefs, with the goal of influencing both intention and behavior (see Figure 3). This approach is informed by the findings from a formative study [35], which identified PBC as a significant predictor of participants' intention to increase fiber intake. The formative research revealed that many participants lacked the skills needed to effectively implement this dietary behavior change, highlighting the need for tailored support to improve their sense of control and confidence.

Figure 3. The theory of planned behavior (TPB) applied to the FiberMore intervention.

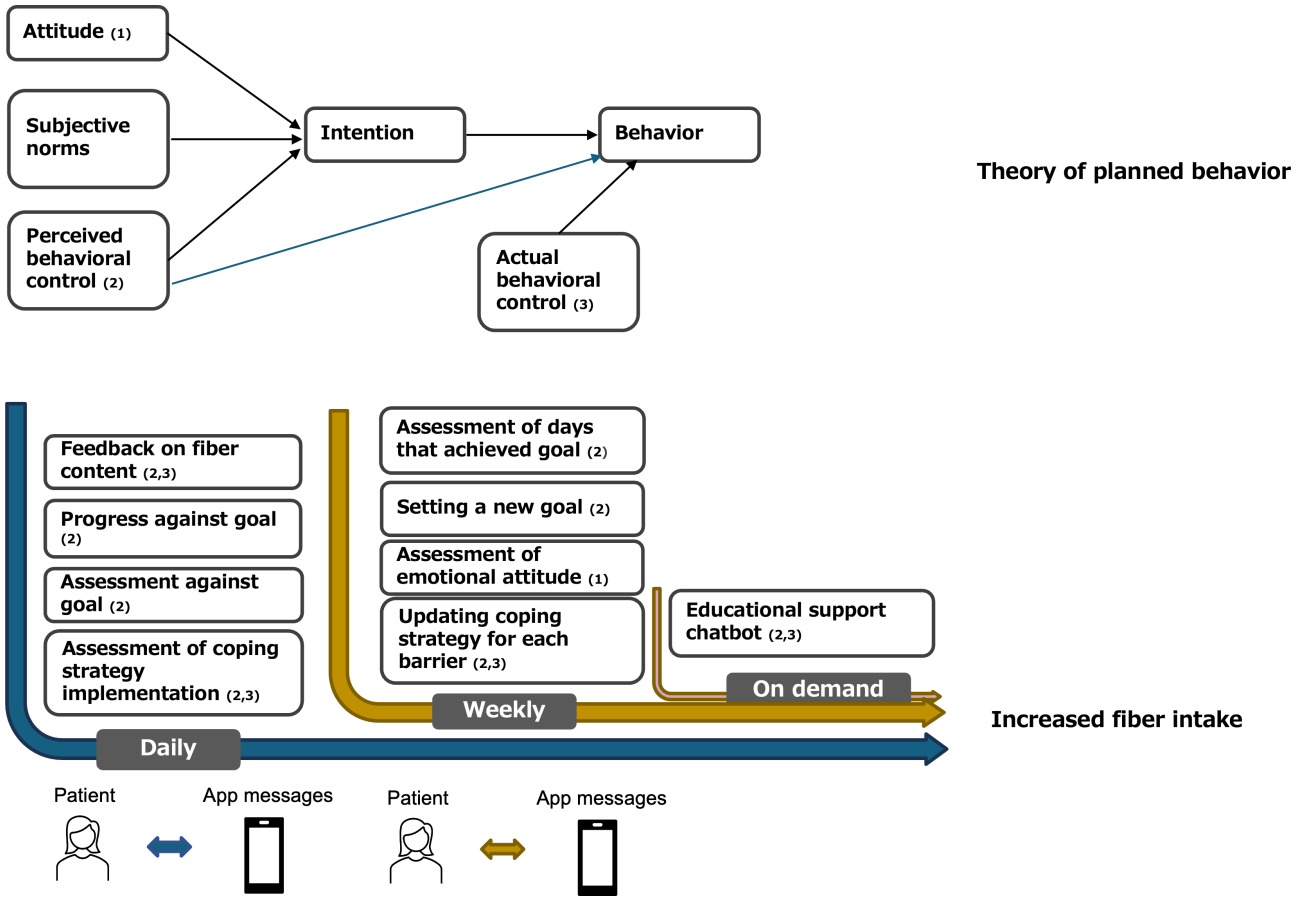

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The primary strategy involves the use of progressively challenging yet attainable goal-setting using a simple algorithm based on our previous work [20], which has been shown to enhance control beliefs and self-efficacy. Specifically, the chatbot suggests a new fiber intake goal each week, tailored to the participant's performance in the previous week based on the number of days the goal was met (see Table 1).

Participants can monitor their daily progress toward their fiber goal through a real-time update graph displayed on the app's home screen. Additionally, participants are able to view weekly goal achievement progress through this graph, supporting mastery experience and reinforcing a sense of achievement.

To further support PBC, participants receive personalized feedback on the fiber content and fiber-to-energy ratio of their meals. These feedback messages aim to increase participants' awareness and perceived ability to make appropriate dietary choices, thereby reinforcing control beliefs. A third mechanism enhances PBC via daily self-assessment of coping strategy implementation and weekly setting of new barriers and corresponding coping strategies. Setting coping strategies can enhance the optimistic beliefs about one's capability to cope with barriers that arise, leading to improved self-efficacy and a stronger sense of PBC when facing obstacles [43]. Another mechanism involves the "Learn More" chatbot, which provides useful information and tips on increasing fiber intake, aiming to enhance users' confidence and perceived control over increasing their dietary fiber.

Beyond influencing PBC, the FiberMore intervention may also impact actual behavioral control (ABC). ABC measures the extent to which a person has the skills, resources, and other prerequisites needed to perform the behavior [44]. FiberMore's provision of meal fiber values, daily fiber totals, and "Learn more" education on fiber may improve ABC by giving actionable information. To the extent that the solution offered to the barrier is new to the participant and effective, the barrier/solution process may increase ABC.

FiberMore also seeks to influence behavioral beliefs by shaping a positive emotional attitude toward the behavior, which in turn may increase users' motivation and intention to perform the behavior [44]. This is implemented through a weekly "checking in" chatbot that encourages users to reflect on what aspects of increasing fiber intake have been enjoyable or challenging. In response to user input, the chatbot delivers empathetic messages, validates users' experiences, and offers positive reinforcement to enhance emotional attitude toward increasing fiber intake.

We hypothesize that the FiberMore intervention will lead to improvements in participants' attitude and PBC toward increasing dietary fiber intake. These changes are expected to enhance their intention to consume more fiber, which in turn will result in an increase in fiber intake (see Figure 3).

We will measure the impact of the FiberMore intervention on TPB outcomes via a questionnaire of 20 direct TPB belief measures of intention (questions 1 - 5), attitude (questions 6 - 11), subjective norms (questions 12 - 14), and PBC (questions 15 - 20) regarding eating more fiber-rich foods than usual. The scoring of each scale for the belief measures is 7-point from 1 to 7. This TPB questionnaire was developed with reference to a previously validated instrument targeting high-fiber dietary intake [45], and was guided by the TPB questionnaire development manual by Francis et al [46]. It has been previously tested among the T2D population in Japan and content-validated by diabetes specialists and researchers experienced in health behavior change research [35].

Study Procedures and Participant Timeline

Preliminary Study Enrollment

The physicians at each research institution will conduct screening procedures to T2D patients who visited the outpatient clinic according to the inclusion and exclusion criteria of this study. A clinical research coordinator (CRC) will approach eligible patients to provide detailed information about this study and to obtain the patient's written consent to participate in this study. Once consent to participate in this study is obtained, the CRC will assist study participants to download MealLog onto participants' mobile phones and explain to study participants how to log meals through the app (see Table 2).

Table . Details of MealLog features.

Meal logging options in MealLog	Description
Snap a meal (or upload from phone gallery)	Study participants log a meal by taking a photo of the meal via the MealLog app. The meal photo is uploaded to the AI[a] server and analyzed for its fiber, energy, carbohydrates, protein, fat, and salt amounts. No feedback on the meal is provided to the user via the app.
Chat a meal	Study participants describe a meal with the "Chat a meal" chatbot (EiYouBot) on the MealLog app to log the meal. Based on the description, the meal is analyzed by the AI server for its fiber, energy, carbohydrates, protein, fat, and salt amounts. No feedback on the meal is provided to the user via the app.
Snap a meal (or upload from phone gallery) followed by Chat a meal	Study participants first log a meal by taking a photo via the MealLog app. The meal photo is uploaded to the AI server and analyzed for its fiber, energy, carbohydrates, protein, fat, and salt amounts. No feedback on the meal is provided to the user via the app. Study participants then describe additional details about the meal with EiYouBot. Nutrient values are updated according to their added details.

[a]AI: artificial intelligence.

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Run-in Period

During the run-in period, preliminarily enrolled study participants will use MealLog to log their meals so that the researchers can assess their average baseline fiber intake. A research co-investigator will contact the study participants via SMS text messages if participants do not log any meals or if only 1 meal is logged for 3 days consecutively since the start of the run-in period.

To be eligible for official study enrollment, study participants need to log at least 2 eating occasions (either main meals or snacks) in app per day for at least 7 days during the nominal 14-day run-in period and have an average baseline fiber intake of less than 20 g per day (after excluding days with 0 or 1 logged meal per day).

On the first 3 days of the run-in, at 11 AM, preliminarily enrolled study participants will receive an SMS containing a survey link for the TPB questionnaire (via Jotform). On day 1 of the run-in, study participants will receive a TPB questionnaire on increasing fiber intake. On day 2 of the run-in, they will receive a TPB questionnaire on reducing salt intake. On day 3 of the run-in, they will receive a TPB questionnaire on reducing saturated fat intake. Study participants are required to complete these surveys at home or at any convenient location with an internet connection. If the questionnaire submissions are not received by the 3rd day of the week, another SMS text message will be sent on the 4th day as a reminder to complete the missing questionnaire.

After completion of the run-in period, study participants will be contacted by the research office about their official study enrollment status.

Official Study Enrollment and Randomization

Randomization will be conducted using a dynamic allocation method based on minimization, with an allocation ratio of 1:1. The allocation adjustment factors will include the baseline dietary fiber intake during run-in (under 10 g, 10 g and above), sex (male and female), and HbA_{1c} level on the date of consent (less than 8.5% and 8.5% or higher). Random allocation will be performed online using the INDICE cloud system provided by the University Hospital Medical Information Network (UMIN). After randomization, a CRC will explain the details of the intervention according to the study participants' allocated group (intervention or control). Participants are blind to their group.

The Intervention Condition

A CRC will assist study participants assigned to the intervention group with downloading FiberMore onto their smartphones and input the initial fiber goal of the study participants to the backend system (refer to Table 2 for determination of the initial goal). The CRC will also assist the study participants to identify 1 barrier on increasing fiber intake and its corresponding solution via the "Barrier and Solution" chatbot within FiberMore. The CRC will also provide guidance and demonstration on using the intervention features of FiberMore.

The CRC will give study participants a handout on the benefits of increasing fiber intake as well as general tips and examples about eating more fiber. As some study participants depend on their family for meal preparation, the CRC will encourage the study participant to share the educational handout with their family members and communicate the weekly fiber goal as well as the feedback obtained from FiberMore with their family or person preparing their meals.

On the first three days during week 10, at 11 AM, study participants will receive an SMS text message containing a survey link for a TPB questionnaire (via Jotform). On day 1 of week 10, study participants will receive a TPB questionnaire about increasing fiber intake. On day 2, they will receive a TPB questionnaire about reducing salt intake. On day 3, they will receive a TPB questionnaire about reducing saturated fat intake. Study participants are required to complete these surveys at home or any convenient location with an internet connection.

The Control Condition

After randomization, the control group will receive an educational handout on salt intake reduction as well as a paper diary to record their efforts in reducing salt intake. They are encouraged to record any small effort to reduce salt intake in the diary on a daily basis. They will also receive web-based educational information via SMS text message once during week 4 and once during week 8 (see Figure 4). On the last day of week 10, the control group will receive SMS text message reminders from the research office to use MealLog to log their meals for 14 days during week 11 and week 12 (see Figure 5).

Figure 4. System and equipment used to send sham educational intervention to control participants by SMS text messaging (once during week 4 and once during week 8 of the intervention period).

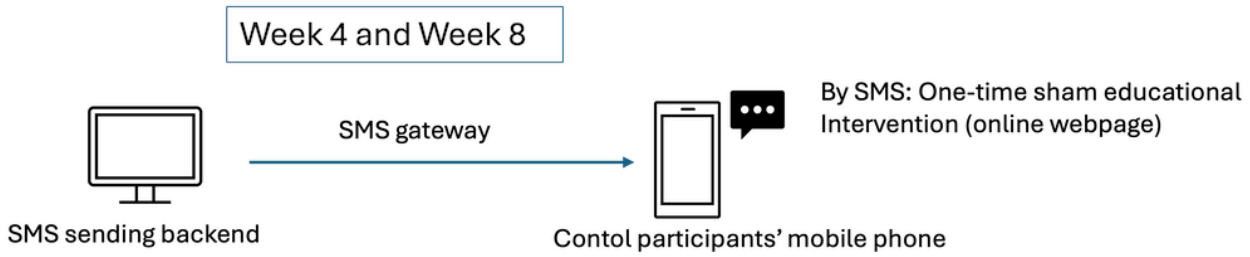

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Figure 5. System and equipment used by the control participants every day during weeks 11 and 12 of the intervention period. AI: artificial intelligence.

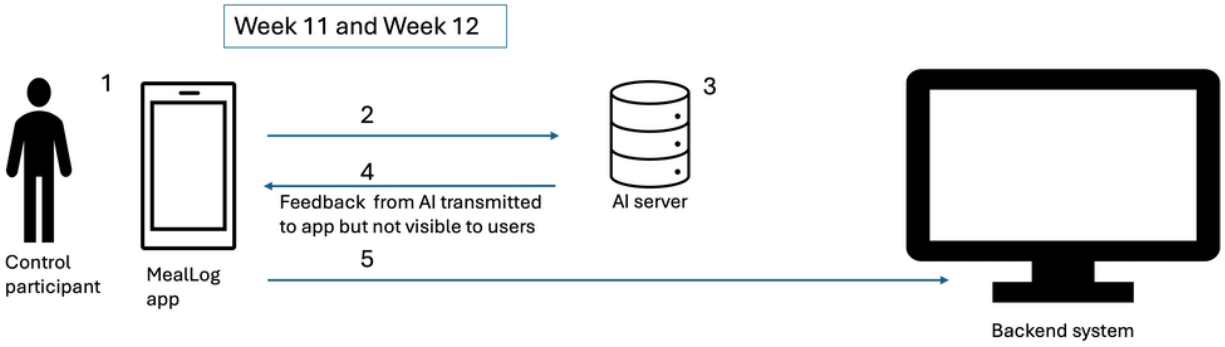

On the first 3 days during week 10, at 11 AM, study participants will receive an SMS text message containing a survey link for a TPB questionnaire (via Jotform). On day 1 of week 10, study participants will receive a TPB questionnaire about increasing fiber intake. On day 2, they will receive a TPB questionnaire about reducing salt intake. On day 3, they will receive a TPB questionnaire about reducing saturated fat intake. Study participants are required to complete these surveys at home or any convenient location with an internet connection.

The flow of interaction between the intervention participant, the app interface, the backend system, and the AI server is as follows, as illustrated in Figure 5: the control participant logs meal via “Snap a meal” function or “Chat a meal” function in MealLog app during week 11 and week 12 of the intervention period (Step 1). Data provided by the participant is sent to the AI servers (Step 2). The AI servers process the uploaded meal photo or chatbot interaction and generate information on fiber, energy, carbohydrates, protein, fat, and salt amount (Step 3). Once the AI server completes processing, the app receives relevant feedback and data generated by AI. This feedback is not visible to the user within the app interface (Step 4). The mobile app then securely transmits the feedback to the backend system via internet connection using a highly encrypted API stored within the app (Step 5).

Study Events

This study includes 5 events (E0-E4), a 2-week run-in period, a 12-week intervention period, and a 12-week observation period. Study participant experience and data collected in different stages of the study are described in Table 3.

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Table . Study events spanning approximately 26 weeks.

Event	Time	Key activities
E0	Preliminary study enrollment	• Participant experience: obtain consent to participate in study. • Data collected: Patient background[a], vital signs[b], hematological tests[c], biochemical tests[d], urinalysis[e], medication status survey, and the transtheoretical model (TTM) questionnaire for dietary behavior change[f].
Run-in period	From E0 for 2 weeks	• Participant experience: Log meals with MealLog app • Data collected: Number of days with at least 2 logged eating occasions (main meals or snacks), total fiber intake per day (grams), average fiber intake (excluding days with only 0 or 1 logged meal), theory of planned behavior (TPB) questionnaire for dietary fiber intake[g], TPB questionnaire for salt intake[g], and TPB questionnaire for saturated fat intake[g].
E1	At the time of official study enrollment	Intervention group: • Participant experience: Download FiberMore and receive educational handout on dietary fiber intake. • Data collected: Medication status and system defects. Control group: • Participant experience: Receive educational handout on salt reduction. • Data collected: Medication status and system defects.
Intervention period	From E1 for 12 weeks	Intervention group: • Participant experience: Interact with FiberMore. • Data collected: The number and percentage of days fiber goal is met out of 7 days, the number and percentage of implemented coping strategies per week, the average estimate of fiber intake per day (excluding days with only 0 or 1 logged meal), and the average estimate of energy intake per day (excluding days with only 0 or 1 logged meal). Control group: • Participant experience: Record salt reduction efforts in a paper diary (sham intervention), receive 1-time educational weblink on salt reduction via an SMS text message during week 4 and week 8, and use MealLog to log meals during week 11 and week 12. • Data collected: During week 11 and week 12—the average estimate of fiber intake per day (excluding days with only 0 or 1 logged meal) and the average estimate of energy intake per day (excluding days with only 0 or 1 logged meal).
E2	Week 10 of the intervention period	• Participant experience: receive a survey link of TPB questionnaires about dietary fiber, salt, and saturated fat on specified day via SMS text messages.[g] • Data collected: TPB questionnaire for dietary fiber intake, TPB questionnaire for salt intake, and TPB questionnaire for saturated fat intake.
E3	End of 12 weeks from E1 (end of the intervention period)	• Participant experience: attend regular outpatient clinic appointment and attend E3 meeting with a clinical research coordinator (CRC). • Data collected: vital signs, hematological examination, biochemical tests, urinalysis, medication status, system defect report, TTM questionnaire for dietary behavior change, and a survey on the participants' satisfaction and perceived usefulness of the intervention.

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Event	Time	Key activities
E4	End of 24 weeks from E1 (end of the observation period)	• Participant experience: attend regular outpatient clinic appointment, attend E4 meeting with CRC, receive survey link of TPB questionnaires for dietary fiber, salt, and saturated fat on specified day via SMS text messages. • Data collected: Vital signs, hematological examination, biochemical tests, urinalysis, medication status, and TTM questionnaire for dietary behavior change; TPB questionnaire for dietary fiber intake; TPB questionnaire for salt intake; TPB questionnaire for saturated fat intake; and a survey on the intention to improve eating habits using a generative artificial intelligence (AI)-enabled app.

[a]Definitions related to observation, investigation, and reporting items: Patient background: (1) Via self-administered questionnaire: Highest education level, annual income, marital status, living arrangement, employment status, meal arrangement methods, control over meal ingredients and menu, level of daily physical activity; (2) Via medical record: Age, sex, date of diabetes diagnosis, smoking and alcohol consumption at the time of consent acquisition; the presence of macrovascular disease, diabetic retinopathy, periodontal disease, tinea pedis, and diabetic neuropathy; and other medical history.

[b]Vital signs: Body height, body weight, and systolic and diastolic blood pressure.

[c]Hematological tests (Performed at least a week before each time point): hemoglobin level.

[d]Biochemical tests (performed at least a week before each time point): estimate glomerular filtration rate (eGFR), creatinine, fasting blood glucose, HbA_{1c}, low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides, albumin, blood urea nitrogen (BUN), and potassium.

[e]Urinalysis (performed at least a week before each time point): Urine protein and urine-albumin-creatine ratio (UACR).

[f]Transtheoretical model (TTM) questionnaire: Measure the 5 stages of dietary behavior change in TTM: Precontemplation, contemplation, preparation, action, and maintenance. Amount of dietary fiber intake: artificial intelligence (AI) assessment of dietary fiber intake via meals logged onto the app.

[g]The theory of planned behavior (TPB) questionnaire: Measure attitude, subjective norms, perceived behavioral control, and intention to improve dietary behavior.

Study Outcomes

Primary Outcome

The primary outcome of this study is the between-group difference in the change in daily intake of dietary fiber from the time of run-in to the end of the intervention period.

Secondary Outcomes

Secondary outcomes (see Table 4) include clinical and health measures, measurements of behavior changes, engagement measures with intervention features, and assessments of participants' satisfaction and perceived usefulness of the intervention. We will also assess the occurrence of adverse events via patient interviews.

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Table . Secondary outcome measures.

Measurements	Outcomes
Difference in changes	• HbA_{1c} (%)[a] • Weight (kg)[a] • BMI (kg/m^2)[a] • Systolic and diastolic blood pressure (mmHg)[a] • Estimate glomerular filtration rate (eGFR; ml/min/1.73m2)[a] • Fasting blood glucose (mg/dL)[a] • Low-density lipoprotein cholesterol (LDL-C; mg/dL)[a] • High-density lipoprotein cholesterol (HDL-C; mg/dL)[a] • Triglyceride (mg/dL)[a] • Theory of planned behavior (TPB) elements for dietary fiber, salt, and saturated fat intake (attitude, subjective norm, perceived behavioral control, and intention).[b]
Difference in proportions	• Transtheoretical model (TTM) stage of change questionnaire for dietary behavior.[a] • Changes in antidiabetic drugs since consent was obtained (intensified, unchanged, and weakened).[a] • Usage of each antidiabetic drug.[c]
Measured values	• Average estimate of fiber intake per day.[d] • Average estimate of energy intake per day.[d] • Number and percentage of days fiber goal is met out of 7 days.[d] • Number and percentage of implemented solutions in a week.[d] • Survey on participants' satisfaction and perceived usefulness of the intervention.[e] • Percentage of patients with HbA_{1c} less than 7%.[f] • Survey on intention to improve eating habits using a generative artificial intelligence (AI)-enabled app[g]

[a]Difference in change from the time consent was obtained to the end of the intervention period (12 weeks) and to the end of the observation period (24 weeks).

[b]Difference in change from the time of run-in to the end of 10 weeks and to the end of the observation period (24 weeks).

[c]Calculated at the time of consent acquisition, at the time of official study enrollment, after the end of the intervention period, and after the end of the observation period.

[d]Evaluated weekly from week 1 to 12 for the intervention group.

[e]Percentages of responses for each option on the Likert scale and for the Yes or No scale will be calculated after the end of the intervention period for the intervention group and control group.

[f]Evaluated at the end of week 12 and week 24 for both intervention group and control group.

[g]Percentages of responses for each option on the Likert scale will be calculated after the end of the observation period for the intervention group.

Sample Size Consideration

The primary outcome is the difference between the intervention group and the control group in the change in mean daily dietary fiber intake from the time of study enrollment to the end of the intervention period. We desired to detect a between-group difference in the mean change of 7 g of dietary fiber, drawing from a meta-analysis, which demonstrated a 9% risk reduction of cardiovascular disease events for 7 g increase in daily dietary fiber intake [47]. A previous RCT reported a 7.9 g/day increase in fiber intake at 3 months in the high-fiber group, supporting the use of a 7 g/day between-group difference as a realistic and meaningful target [33].

Based on the findings from a previous nutritional intervention research in Japan [48], we assumed a common SD of 9.85 g for the difference in dietary fiber change across both groups. Using a 2-sided significance level of 5% and a power of 80%, the required sample size calculated based on an independent *t* test is 33 participants per group. A study conducted in a similar population, which followed a similar study structure with a 2-week run-in phase, a 12-week intervention phase, and a subsequent 12-week observation phase by our research team showed minimal to no dropout throughout the study duration [49]. Nevertheless, as a conservative estimate to account for potential attrition, we aimed to enroll a minimum of 70 participants. The 2-week run-in phase also ensures that we enroll the participants who are able to use the app as instructed, thus minimizing drop-out risk.

Based on the findings from previous studies implemented in our research lab, we estimate a 10% dropout rate between

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preliminary and official study enrollment. Therefore, the target recruitment number for the preliminary study enrollment has been set at 77 participants.

Statistical Analysis Plan

In this study, we define 3 analysis populations: the full analysis set (FAS), the per protocol set (PPS), and the safety analysis set (SAS). The FAS is defined by all the study participants who had at least one primary outcome or secondary outcome obtained after randomization. We will follow the intention-to-treat (ITT) principle and analyze data based on the assigned group in the FAS analysis. The PPS is the FAS population with exclusion of patients who were found to have serious violations of the provisions of the research protocol:

1. Violation of inclusion and exclusion criteria
2. Study participants who log fewer than 2 meals per day on more than 7 days within any of the following 2-week intervals during the intervention period: Weeks 1 - 2, 3 - 4, 5 - 6, 7 - 8, 9 - 10, 11 - 12, or 13 - 14.
3. In the event of a medical condition that makes dietary fiber intake inappropriate for the study participants,

Major deviations from other provisions of the study protocol will be assessed through a blinded review process. The blinded review will be conducted according to the following procedures: assessment of whether individual participants or specific measurement data should be excluded from the PPS or FAS; evaluation of participants with significant protocol deviations to determine whether exclusion is warranted; and examination of efficacy outcomes, including consideration of potential variable transformations and identification of outliers.

The safety analysis set is the set of all patients who used either MealLog or FiberMore at least once after randomization. In the safety analysis using the SAS, we will analyze data based on the intervention actually used by patients regardless of allocation. The FAS will be the primary analysis population, and the PPS will provide supportive results. All safety analyses will be conducted in the SAS. Data on patients' characteristics will be presented as mean, minimum, SD, 25th percentile, median, 75th percentile, and maximum for continuous variables and as frequency and proportion for categorical variables.

Primary Outcome Analysis

We will perform analysis of covariance on the change in dietary fiber intake from the time of run-in to the end of the intervention period, with dietary fiber intake from the time of run-in as the covariate. The change in dietary fiber from the time of run-in and at the end of the intervention period will be calculated as ([average dietary fiber over week 11 and 12]-[average baseline dietary fiber during the run-in]). The estimated mean change in each group and its 2-sided 95% CI will be calculated. Additionally, the estimated difference between groups and its 2-sided 95% CI will be calculated.

To ensure reliable estimates of fiber intake, days with only 0 or 1 logged meal will be excluded from the analysis.

Secondary Outcomes Analysis

We will perform analysis of covariance on the change of HbA_{1c} from the time consent is obtained to the end of the intervention period (at 12 weeks) or the end of the observation period (at 24 weeks), using the measurements at the time consent is obtained as covariates. The estimated mean change in each group and its 2-sided 95% CI will be calculated. Additionally, the estimated difference between groups and its 2-sided 95% CI will be calculated. The proportion of HbA_{1c} less than 7% at week 12 (E3) and week 24 (E4; or point of discontinuation, if earlier) will be compared between groups by the Fisher exact test.

The change from baseline in the clinical laboratory test values stated below at week 12 (E3) and week 24 (E4) (or point of discontinuation, if earlier) will be analyzed as the secondary outcomes:

1. Weight (kg)
2. BMI (kg/m^2)
3. Systolic and diastolic blood pressure (mmHg)
4. Estimated glomerular filtration rate (ml/min/1.73 m^2)
5. Fasting blood glucose (mg/dL)
6. Low-density lipoproteincholesterol (LDL-C; mg/dL)
7. High-density lipoproteincholesterol (HDL-C; mg/dL)
8. Triglyceride (mg/dL)

The percentages of participants at each stage of the transtheoretical model (TTM) stage of change will be calculated for both groups at the end of the intervention period (week 12) and the end of the observation period (week 24) were compared between groups using the Cochran-Mantel-Haenszel test.

Between-group changes in all TPB survey elements for dietary fiber, salt, and saturated fat intake (attitude, subjective norms, PBC, and intention) will be analyzed from the time of run-in to the end of 10 weeks, and to the end of the observation period (24 weeks), using repeated measures ANOVA with time (Week 1, Week 10, and Week 24) as a within-subjects factor and group (control vs intervention) as a between-subjects factor.

Changes in diabetes medications since consent acquisition at the end of the intervention period (at 12 weeks) and at the end of the observation period (at 24 weeks; classified as intensified, unchanged, and weakened) will be calculated for each group and compared between groups using the Cochran-Mantel-Haenszel test. The proportion of new medications added will be compared between groups by the Fisher exact test.

We will also calculate the percentage of responses for each option on the Likert scale and for the "Yes or No" scale in "Survey on participants' satisfaction and perceived usefulness of the intervention" at the end of the intervention period for both intervention group and control group. For the "Survey on intention to improve eating habits using a Generative AI-enabled app", we will calculate the percentage of responses for each option on the Likert scale at the end of the observation period for the intervention group.

As part of our exploratory analysis, we will assess the reliability of the TPB questionnaire using the Cronbach α coefficient. Additionally, we will conduct multivariate regression analyses

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to examine various associations related to the TPB constructs. Specifically, we will investigate the relationship between changes in intention (INT) to increase fiber intake and changes in fiber intake outcomes both between and within groups. Furthermore, we will analyze the associations between changes in attitude (ATT), subjective norms (SN), and PBC with changes in intention to increase fiber intake, as well as the relationship between changes in PBC and changes in fiber intake outcomes at both the between-group and within-group levels. The impact of the intervention on INT via ATT, SN, and PBC will be evaluated through mediation analysis.

We will calculate the frequency and weekly percentages of the following measurements during the intervention period in the intervention: number and percentage of days fiber goal is met out of 7 days, the number and percentage of implemented solutions in a week, the average weekly fiber change in the intervention group from run-in, and the average weekly energy change in the intervention group from run-in. We will also evaluate the effects of changes in dietary fiber intake on changes in BMI and HbA_{1c} using the Pearson correlation test and simple regression analysis.

We will perform a statistical analysis of safety outcomes by calculating the number and percentage of individuals who experience adverse events during run-in, intervention, and observation periods. During the intervention and observation periods, data will be compiled separately for the intervention and control group, and the percentages will be compared between groups using the Fisher exact test.

We will not apply statistical adjustment for multiple comparisons in the analysis of secondary and exploratory outcomes. We will interpret these results as exploratory and use them to inform future hypotheses.

Monitoring, Quality Control, and Data Management

An independent auditor, separate from the departments involved in this clinical trial, will inspect the medical institution and other relevant facilities to ensure that the trial is conducted in compliance with established protocols and standards.

In accordance with the EU Artificial Intelligence Act [50], FiberMore falls under the limited-risk category, as it delivers dietary advice and behavioral support but does not make clinical diagnoses or treatment decisions. We implemented a few measures to ensure that the dietary advice and behavioral support offered in FiberMore is safe for T2D patients. FiberMore has undergone pretesting and has been reviewed by a diabetes specialist on the research team to ensure its suitability for providing dietary advice to individuals with diabetes. The intervention development team has implemented safeguards to ensure that the chatbot's conversations are suitable and reliable. For example, in the Learn More chatbot where users can get educational information, the chatbot discloses that "As I am a bot, I may rarely make mistakes, so please always use your common sense and follow your doctor's instructions." In addition, the chatbot conversations will be monitored by the study team daily to ensure that the advice given is safe and appropriate to T2D patients. If study participants encounter any unusual response from the chatbot at any time, they are advised to take a screenshot of the issue and send it to us by email, SMS text message, or Line, a popular social messaging app in Japan.

All data measured and provided through FiberMore will be securely transmitted to the research office's backend system, which is hosted on Firebase, a cloud-based platform developed by Google on a password-protected computer through an internet connection and stored on the backend system. Firebase complies with major regulatory frameworks such as the General Data Protection Regulation and the California Consumer Privacy Act, meets international security and privacy standards including ISO/IEC 27001 (information security management) and ISO/IEC 27018 (protection of personally identifiable information in the cloud), and aligns with requirements under Japan's Act on the Protection of Personal Information [51,52].

No personally identifiable information will be stored in the backend system alongside the study data, and all information will be pseudonymized using study participant ID. Data stored in the backend system include study participants' ID, meal photos taken by study participants and photo timestamp, chat logs generated in FiberMore and its timestamp, feedback on nutritional information generated by AI on each logged meals, total daily intake and average weekly intake of energy, dietary fiber, and other nutrients (eg, protein, fat, carbohydrates, salt), daily fiber goal achievement status, daily implementation status of coping strategies (solutions), and content of weekly chosen barrier and coping strategies to increase fiber intake. All data on the backend system will be automatically backed up once a day across Google Cloud's secure data centers. These backup copies can be restored in the event of system failure, accidental deletion, or data corruption.

Survey data from paper questionnaires are entered into the study database by a research co-investigator and independently verified by another research co-investigator to ensure data accuracy. Paper files are stored in locked cabinets within a locked room and are accessible only to authorized personnel. Paper questionnaires are stored in a locked room in locked cabinets and can be accessed only by authorized personnel.

TPB questionnaires administered using Jotform will be transmitted to the Jotform server, where the data is stored and accumulated. Jotform supports Health Insurance Portability and Accountability Act (HIPAA) compliance for managing sensitive health data, complies with GDPR for handling personal information, and aligns with the principles of Japan's Act on the Protection of Personal Information [53]. Surveys administered via Jotform are pseudonymized using study participant ID. A research co-investigator will download the survey responses from the Jotform server into a password-protected folder on a computer in the Department of Planning, Information, and Management of The University of Tokyo Hospital for data analysis. To maintain data quality, participants with missing responses or inconsistencies on the TPB questionnaire such as extreme or contradictory answers to items assessing the same underlying construct will be asked to recomplete the relevant survey items.

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Ethical Considerations

This trial will be conducted in compliance with the Declaration of Helsinki, the Pharmaceutical and Medical Device Act, the Ministerial Ordinance on Good Clinical Practice for Medical Devices, and all other guidelines in relation to these regulations (jRCT2032240579). This study was approved by the institutional review board of the University of Tokyo School of Medicine (approval 2024442NI).

Before the start of the study, we provide clear explanations to the study participants using the consent explanation document. Written consent, based on the study participant's free will, will be obtained. When obtaining consent, study participants will be given sufficient time and opportunities to ask questions, and all questions will be answered thoroughly. We also inform the study participants that their meal logs and chat conversations with the bot will be monitored by the research team for quality assurance and to improve the future iterations of the system. All patient data will be pseudonymized.

Study participants are free to withdraw consent at any point of the study, either pre- or postrandomization by contacting the research office in writing or via phone. We also inform the study participants that if consent is withdrawn before randomization, all the collected data will be discarded, while if consent is withdrawn after randomization, data collected up to the point of withdrawal will be retained.

As compensation for their participation, transportation costs to the research sites, phone internet data cost, and the time and effort required to complete the study procedures, study participants will receive a QUO card worth 30,000 yen (approximately US $200) after completing the 24-week observation period and the related questionnaires. This amount is considered reasonable for a 6-month clinical study in Japan. It is not intended as an inducement to participate but rather as a token of appreciation and to reduce financial barriers to participation.

All blood test and health examination results will be reviewed by the participant's primary physician (also the recruiting physician) during routine visits, with results communicated to the participant during their outpatient consultation. If a study participant reports any concerning symptoms to the CRC, the CRC will consult the principal investigator, who is a diabetes specialist. If deemed necessary, the participant will be referred to their primary physician for further evaluation or care.

To ensure equal educational opportunities for all participants without influencing study outcomes, participants in the intervention group will receive a handout on salt reduction strategies at the postobservation (E4) meeting, while those in the control group will receive, also at E4, a handout detailing the benefits of increased dietary fiber intake, general dietary tips, and examples of high-fiber foods.

Results

Recruitment began on February 12, 2025, and ended on September 1, 2025. We anticipate the intervention period will conclude in December 2025 and the observation period will conclude in March 2026.

As of September 22, 2025, 4947 patients have been screened for eligibility and 81 participants have been recruited to the study. A total of 72 participants have been officially enrolled and randomized. Progress through the phases of this planned randomized trial (enrollment, intervention allocation, follow-up, and data analysis) will be visually represented using the CONSORT (Consolidated Standards of Reporting Trials) flow diagram (see Figure 6).

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Figure 6. CONSORT flow diagram depicting enrollment, allocation, follow-up, and analysis phases as of September 22, 2025.

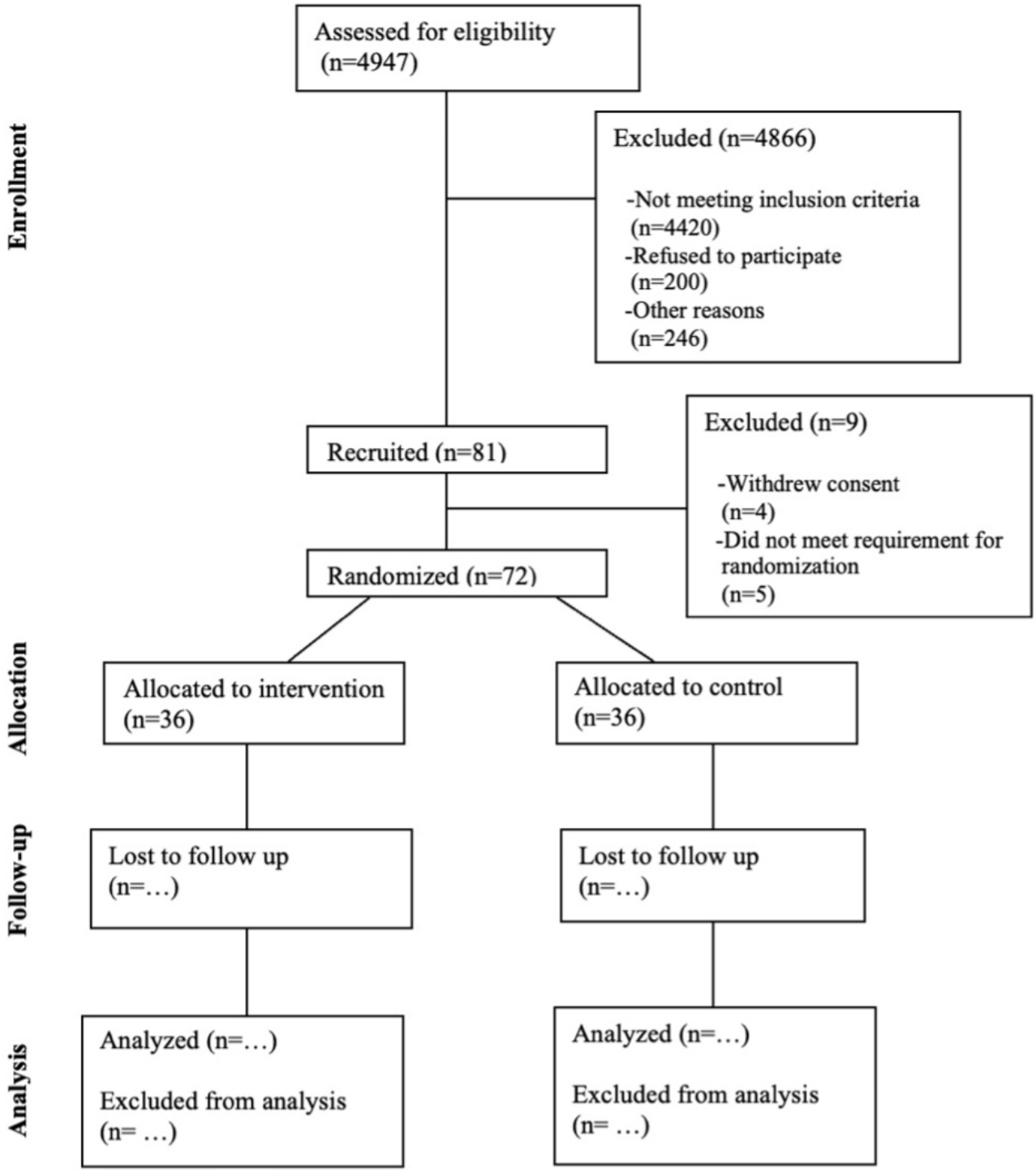

Discussion

This study proposes an mHealth intervention aiming to assist T2D patients in increasing their dietary fiber intake and possibly improving their glycemic control. In the management of diabetes, achieving glycemic control is critical for the prevention of complications, with a treatment goal of maintaining HbA_{1c} levels below 7% [15]. Despite advances in pharmacotherapy aimed at improving glycemic control, the increasing aging population with diabetes has raised concerns regarding the potential adverse effects and risks of polypharmacy associated with prolonged medication use [54]. The Diabetes Treatment Guide also specifies the need to continue lifestyle self-management such as diet and exercise regimens even when drug therapy is initiated [15]. This intervention could potentially enhance nutritional awareness and promote healthy eating habits among T2D patients.

The AI-assisted dietary fiber intervention was developed using a user-centered design approach, informed by recent formative research conducted before this study [35]. The formative research highlighted the usefulness of TPB in predicting intention to increase dietary fiber intake among individuals with T2D, with PBC and attitude emerging as significant predictors of this intention. These insights guided the design and

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refinement of the FiberMore intervention to better align with the needs and motivations of the target population. Previous meta-analyses have also demonstrated the capacity of the TPB to predict dietary behaviors [55,56]. We anticipate that the FiberMore intervention will increase PBC and attitude of patients toward fiber intake, which in turn will increase their intention and subsequently lead to increased fiber consumption.

The FiberMore intervention incorporates a personalized goal-setting approach, in which the user's fiber goal increases gradually based on the number of days in the current week that the goal is successfully achieved. This approach is modeled after the success demonstrated in a previous study that used this goal-setting strategy, where incremental increases in step count goals were achieved and accompanied by corresponding growth in actual step count throughout the intervention period [20]. Additionally, during the first week of the intervention, intervention group participants will be given an initial fiber goal based on the 10th highest daily fiber intake achieved during the run-in period, to ensure that the initial fiber goal is achievable. As repeated failure to meet a goal can result in diminished confidence over goal achievement [57], the intervention begins with an easily attainable goal to foster a sense of success and strengthen participants' perceived control over goal attainment. The goal-setting algorithm will then recommend gradual goal increments once participants successfully meet their fiber goals for at least 5 days in a week.

FiberMore allows users to add on additional information on the meal photos, such as the portion size of the food and details not visible in meal photos to enhance the accuracy of the nutrient estimation. Given that forgetting to photograph meals is a commonly reported issue in digital food logging using photography [58], the "chat a meal" feature provides an alternative way for participants to log their meals, thus reducing chances of missing meal records.

FiberMore is designed with patient safety in mind by minimizing gastrointestinal effects that may arise with increased dietary fiber intake. The intervention motivates study participants to increase their fiber in a gradual manner, rather than requiring a large amount of fiber intake all at once. This gradual approach allows the digestive system to adapt slowly to the increased fiber, thereby reducing the likelihood of gastrointestinal discomfort while allowing time to adjust to new eating habits. We have used prompt engineering to ensure that the maximum goal increase from the previous week's goal is 2 g and cap the maximum fiber goal that can be set to 30 g per day.

One of the key features of this study is the use of salt reduction educational intervention as a "sham intervention" for the control group. Salt reduction education is a widely accepted strategy in the management of T2D [41]. It is anticipated that participation in a study will introduce biases that influence participant behavior, a phenomenon known as the "Hawthorne effect." Intervention participants may be more conscious of their behavior if they believe that they are receiving a more beneficial intervention, while control participants may be less likely to comply with the trial protocol if they believe that they are not receiving active treatment [59]. Through the implementation of a sham intervention, the Hawthorne effect of receiving an intervention can be controlled [42]. We do not anticipate that the salt reduction educational intervention will have a significant impact on fiber consumption, as the educational content specifically focused on reducing sodium intake through cooking methods and seasoning practices, without targeting food choices related to dietary fiber.

To maintain blinding, participants will be informed that the study aims to assess the usefulness of a smartphone app in improving the eating habits of patients with type 2 diabetes. They will not be told that the intervention specifically targets increasing dietary fiber intake. Additionally, participants will remain unaware that they are randomly assigned to one of two groups. This approach helps mitigate social desirability bias, allowing for a more objective assessment of the intervention's effects and enhancing the overall validity of the study's findings.

Another key aspect of our approach is focusing exclusively on patients who are already motivated to change their behavior in dietary fiber intake. We achieve this by filtering participants based on their stage of change in TTM, targeting those in the contemplation, preparation, and action stages, which has shown to be effective [20,60]. Individuals who are already motivated to change need guidance and support to enhance their intentions and to translate their intentions into action, and they are more likely to engage with self-management tools [61]. In contrast, individuals with low motivation would require a fundamentally different intervention focused on enhancing motivation. Our strategy is supported by a study that reported 93.7% of T2D patients in Japan fall within these stages of dietary behavior change [62], suggesting that our intervention approach applies to a very large group of potential participants.

The study will maintain usual care practices for both the intervention and control groups. There will be no restrictions on medication adjustments or concurrent treatments during the study period. The intervention is aimed exclusively at improving dietary fiber intake, complementing the dietary counseling that T2D patients typically receive as a standard care practice in Japan.

This study is a multicenter randomized controlled trial, which enhances the generalizability of the findings to individuals with T2D across Japan. The elements of the intervention, such as the use of an AI-enabled chatbot to carry out personalized goal setting, barrier-solution planning, and meal logging are not unique to the Japanese context and can be adapted to other settings.

This study has several limitations. First, the findings may be specific to the studied population and may not fully generalize to other populations. Since the participants are likely to be older individuals of Japanese ethnicity, differences in lifestyles and the pathophysiology of T2D between Japanese and other populations may limit broader applicability. The cultural and dietary context of Japan may limit generalizability of the specific dietary patterns observed outside Japan. Additionally, the study is restricted to participants who can use smartphones; therefore, individuals with lower technological proficiency may be underrepresented. Individuals from lower socioeconomic backgrounds may have limited access to smartphones or may

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rely on older devices with limited functionality, which may result in selection bias that underrepresents these individuals.

AI performance in meal assessment can be significantly influenced by image quality, lighting conditions, and the angle at which the photo is taken [37]. Since participants use their own smartphones to capture meal images, variability in phone models and camera quality may introduce inconsistencies in photo quality. However, this approach closely mimics real-world conditions, making the findings more applicable to practical settings. To mitigate this variability, the study team provides detailed guidance and education to participants on how to take clear and well-angled photos to optimize AI performance.

Blinding of researchers is not considered in this study. Due to the complex nature of a dietary behavior change intervention that necessitates interactions between the researcher and participants, implementing researcher blinding is not feasible in this study, which may impose some degree of bias in the intervention delivery. The intervention content feedback and questionnaire reminders are delivered primarily by the app through prespecified algorithms and automated messages, thus minimizing researcher involvement in the intervention delivery. Furthermore, separate teams handle participant support and data management, and the statistician will remain blinded throughout the study.

The 24-week study involves multiple study events and intervention procedures, which may increase the risk of participant fatigue and dropout. We mitigate this by providing thorough explanation during study enrollment, along with a take-home manual containing detailed instructions on study procedures. To support adherence, we use SMS reminders and the LINE messaging app to notify participants of their hospital visits and intervention schedules. In addition, we align all study visits with routine hospital appointments, except for the single visit at official enrollment, thereby minimizing participant burden.

In this study, we will recruit T2D patients with an HbA_{1c} of at least 7.5%, thereby limiting the generalizability of the study findings to the broader T2D population. Nevertheless, as the treatment target for HbA1c is generally <7% according to the JDS guideline, this cut-off allows us to target patients who are most likely to benefit from additional dietary support. We also exclude patients with chronic kidney disease stage 4 and above to minimize the risk of potential hyperkalemia associated with fiber-rich foods, which may exclude a substantial portion of T2D patients.

Manual daily monitoring of the chatbot responses will be performed by the study team as a quality assurance measure, and to comply with ethics committee requirements. We acknowledge that this process may not be scalable in future larger-scale implementations. To address this limitation, future iterations of the system will explore the integration of automated monitoring features to reduce the burden on human resources.

The AI-based meal image analysis used to estimate dietary fiber and energy intake is not a validated gold-standard method, such as weighed food records, which may introduce bias in the dietary estimates. Nevertheless, our estimation approach is grounded in previous validation work comparing the AI model's outputs to dietitian assessments, which demonstrated acceptable accuracy for fiber and energy estimation [39]. Furthermore, the same assessment method is applied uniformly to both the intervention and control group, so that any potential measurement error introduced by the AI model is unlikely to cause a bias to between-group comparisons.

We acknowledge that AI may misclassify food items and also portion sizes, which may introduce bias in the dietary estimates. These image recognition models are typically trained on datasets featuring popular or standardized foods, which may limit their ability to accurately classify ingredients in less common meals, such as regional specialties, traditional home-cooked dishes, or foods from rural areas. Nevertheless, the AI model used in this study has been fine-tuned using a dataset of real-world meal photos, resulting in improved accuracy in estimating dietary fiber content. Our fine-tuned AI model demonstrates better accuracy in estimating fiber and energy content from meal photos than dietitians, whose estimation capabilities are widely regarded as an acceptable standard for validating dietary intake [55]. Since our AI model exceeds expert-level accuracy in estimating dietary fiber and energy content from meal images, we believe that the model is sufficiently reliable for the purposes of this intervention.

This pilot RCT will provide important evidence on the efficacy, feasibility, and safety of an AI-based mHealth intervention in improving dietary fiber intake and glycemic control among free-living T2D patients. This pilot study offers valuable insights and evidence on the development of AI as a promising method for accurate, low-burden dietary assessment [37], including how participants engage with AI-based meal logging and respond to AI-driven diet intervention. Additionally, this study has the potential to generate a large volume of meal photos taken in real-world conditions, which can be leveraged for further fine-tuning and improving the AI model's accuracy and performance in analyzing user-generated meal images.

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Data Availability

The datasets generated during and/or analyzed during this study, including the meal validation dataset, can be obtained from the corresponding author on reasonable request for noncommercial research purposes.

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Authors' Contributions

Conceptualization: DL, WTS, KW
Data curation: KH, RN, SI, WTS
Formal analysis: RN, SI
Funding acquisition: KW
Investigation: KW, TA, KM, YK, TK, YM, KM, NI, GT, SK, MI, MT, TY, MN, WTS, RN, SI, YJ
Methodology: WTS, DL, KW
Project administration: KW, WTS
Resources: KW
Software: KH, YJ, DL
Supervision: KW, TY, MN
Validation: KW
Visualization: RN, SI, WTS
Writing – original draft: WTS
Writing – review & editing: DL, KW, TA, KM, YK, TK, YM, KM, NI, GT, SK, MI, MT, TY, MN

Conflicts of Interest

None declared.

Multimedia Appendix 1
Calculation of target energy intake in FiberMore.
[DOCX File, 22 KB - resprot_v14i1e78019_app1.docx]

Multimedia Appendix 2
Overview of participant interaction with FiberMore.
[DOCX File, 3963 KB - resprot_v14i1e78019_app2.docx]

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Abbreviation

ABC: actual behavioral control
AI: artificial intelligence
CRC: clinical research coordinator
FAS: full analysis set
JDS: Japan Diabetes Society
PBC: perceived behavioral control
PPS: per protocol set
T2D: type 2 diabetes
TPB: theory of planned behavior

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Integration of Mindfulness and Acupuncture After Spine Surgery: Protocol for a Randomized Acceptability and Feasibility Trial

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Abstract

Background: Spine surgery is increasingly common in the United States, contributing substantially to spine-related health care costs. While many patients benefit, up to 25% experience chronic postsurgical pain, and the procedure is linked to high rates of opioid misuse. Key risk factors for persistent pain and opioid use include poorly controlled early postsurgical pain, high pain-sensitivity, and poor pain-coping. Clinical guidelines recommend multimodal treatment to address these risks, but such approaches are not well studied or widely implemented. Combining two safe and effective nonpharmacologic treatments, specifically mindfulness and acupuncture that target these factors, has the potential to improve postsurgical recovery and reduce the incidence of chronic pain and opioid use.

Objective: This paper describes the study protocol for the Integrating Mindfulness and Acupuncture after Spine Surgery (I-MASS), which is a single-site, 2-arm randomized controlled trial that will assess the feasibility and acceptability of a novel multicomponent program integrating mindfulness delivered via a mobile app, acupuncture, and education for patients undergoing single-level spine surgery.

Methods: A total of 50 participants will be randomized 1:1 to receive (1) mindfulness and acupuncture (ie, I-MASS program) plus enhanced education or (2) enhanced education alone. Mindfulness training will consist of a 4-week app-based program starting 1 week prior to surgery, and acupuncture will include up to 8 visits (1 visit prior to surgery and 7 after surgery) during the 13-week program. Enhanced education appropriate for each phase of recovery will be delivered through the mobile app. Primary outcomes are recruitment eligibility and enrollment rates, mindfulness module and acupuncture visit completion rates, questionnaire completion rates, and participant satisfaction. Secondary outcomes include physical function, fatigue, pain interference, depressive symptoms, anxiety, ability to participate in social roles and activities, sleep disturbance, fear avoidance beliefs, pain intensity, pain medication use, adverse events, hospital readmissions, and emergency department visits.

Results: Trial enrollment began in August 2024. As of May 9, 2025, 35 participants have been enrolled. Data analysis has not yet been performed. Enrollment is expected to be completed in the fall of 2025.

Conclusions: The I-MASS program addresses the need for mind and body treatments to improve recovery and reduce the risk of persistent pain and opioid use after spine surgery. This integrated model of care is designed to be user-friendly and scalable, enhancing its potential for implementation in real-world settings. A future pragmatic trial is planned to determine if the I-MASS program results in better outcomes compared to either treatment alone or usual care.

Trial Registration: ClinicalTrials.gov NCT06429072; https://clinicaltrials.gov/study/NCT06429072

(JMIR Res Protoc 2025;14:e77236) doi:10.2196/77236

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KEYWORDS

integrative; complementary; pain; chronic pain; opioids

Introduction

Spine-related pain, encompassing low back and neck pain, is a leading cause of disability and a major driver of health care expenditures in the United States [1,2]. Many patients undergo spine surgery to alleviate pain; however, up to 25% of patients continue to experience chronic postsurgical pain, defined as pain persisting for at least 3 months after surgery [3,4]. Chronic postsurgical pain not only exacerbates disability and diminishes quality of life but also increases the risk of prolonged opioid use, additional invasive procedures, and associated complications [5-8]. The management of chronic postsurgical pain is heavily dependent on opioids, which often fail to provide adequate pain relief [9,10] and carry serious risks related to misuse, addiction, and overdose [11]. Patients undergoing spine surgery are at high risk of long-term opioid use, with the cumulative dose of opioids prescribed in the immediate postoperative period being a strong predictor of prolonged use [12,13].

Chronic postsurgical pain develops through complex physiological and psychosocial mechanisms [14-18]. As a result, guidelines for postsurgical pain management advocate for a comprehensive, multimodal approach that targets modifiable risks for chronic pain [18,19], including depression, anxiety, and maladaptive pain-related beliefs like catastrophizing [20-23]. Multimodal treatment combines various analgesic medications and nonpharmacologic interventions to optimize pain relief [19,24]. Nonpharmacologic treatments, including mindfulness and cognitive behavioral therapies, are recommended to enhance pain coping mechanisms and reduce pain-related anxiety [25]. Despite these guidelines, multimodal care, especially the use of nonpharmacologic treatments, remains underused in clinical practice.

The Integrating Mindfulness and Acupuncture after Spine Surgery (I-MASS) study aims to address this gap by developing and assessing the feasibility of a novel program that integrates mindfulness, acupuncture, and education for patients undergoing spine surgery. Mindfulness is a psychological intervention that enhances coping and reduces pain-related anxiety, avoidance, and catastrophizing [26-28]. It involves techniques such as meditation, body awareness, and exploration of patterns of behavior, thinking, feeling, and action [29]. These techniques help moderate the influence of pain on stress, resulting in less pain-related stress arousal and a reduced desire for opioids [30,31]. Mindfulness also fosters long-term self-management and coping skills, contributing to improved emotional regulation and relaxation [32]. Acupuncture involves the insertion of thin needles into specific anatomical points on the body. The technique is used to alleviate pain, treat various health conditions, and promote overall well-being. Acupuncture provides physical therapeutic inputs that induce pain relief through neurochemical changes, such as endorphin production and autonomic mechanisms [33,34]. It reduces neuroinflammation and slows the development of chronic sensitization and pain through effects on endogenous opioid and inflammatory pathways [35-38].

Combining mindfulness and acupuncture offers a promising approach to preventing chronic postsurgical pain, reducing opioid use, and enhancing recovery following spine surgery. The distinct yet complementary mechanisms through which these interventions operate are hypothesized to yield additive and potentially synergistic effects [39], addressing both biological and psychological risk factors for the development of chronic pain [18,30,32-34,40,41]. While mindfulness helps patients respond more effectively to pain and develop long-term coping skills, acupuncture can provide short-term analgesia and reduce pain sensitivity [34]. Both treatments also share common mechanisms such as modulation of the autonomic nervous system and improvement of emotional regulation, further enhancing their combined efficacy [30,35]. Very few studies have fully integrated these treatments and aimed to assess their combined effects on pain and recovery following spine surgery [39].

This integrated model of care is designed to be user-friendly and scalable. In I-MASS, mindfulness training is delivered through a mobile app platform, enhancing its potential for implementation in real-world settings and providing an attractive option for postoperative pain management. Although highly promising, a rigorous, pragmatic trial is needed to determine if the I-MASS program results in lower rates of chronic pain, pain-related disability, and opioid use compared to either treatment alone or as an alternative to usual care following spine surgery. Trials of this size and scope require careful preparation, which includes feasibility testing of the novel intervention and research protocols, as outlined in the National Institutes of Health (NIH) Stage Model [42].

This paper describes the study protocol for a single-site, 2-arm randomized feasibility and acceptability trial of mindfulness and acupuncture (ie, the I-MASS program) plus enhanced patient education compared to enhanced patient education alone in patients undergoing spine surgery. Outcomes will focus on the feasibility and acceptability of I-MASS, the feasibility of recruitment and retention strategies, and data collection procedures through both the mobile app platform and electronic health record (EHR). Feasibility will be assessed through mindfulness module completion rates, acupuncture treatments attended, participant retention, and questionnaire completion rates. Acceptability will be assessed by patient-reported satisfaction, acceptability, and usability measures.

Methods

Study Design

This study uses a single-site, 2-arm, randomized controlled trial design to assess the feasibility and acceptability of the I-MASS program. The intervention arm will consist of the I-MASS program plus enhanced education, while the comparison arm will consist of enhanced education alone. Individual participants

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will be randomized 1:1 without stratification into each study arm. A target sample size of 50 participants has been established to determine the feasibility and acceptability of the protocol.

Setting

All participants in the study will be recruited from the Duke University Health System (DUHS). DUHS is based in Durham, North Carolina, and includes 3 hospitals and over 140 primary and specialty care clinics across central and eastern North Carolina. In the fiscal year 2023, DUHS served nearly 67,000 inpatient stays and 5 million outpatient visits. Acupuncture will be provided by licensed, study-approved acupuncturists at clinics in the surrounding geographic region, and patients will be free to choose their preferred site.

All mindfulness interventions, delivery of enhanced education in both arms, and collection of patient-reported outcomes in both arms will occur in a mobile app platform administered by Pattern Health, a software company based in Durham, North Carolina. Pattern Health provides an online dashboard for study teams to track all trial participants' activity in the app, including completion of questionnaires and access to educational and mindfulness content. The dashboard permits easy export of participant use data for analysis.

Data and Safety Monitoring

An independent monitoring committee (IMC) oversees this trial. All members are independent of the investigators involved in conducting the trial. IMC responsibilities include reviewing biannual reports to (1) ensure participant safety and (2) advise the principal investigators regarding scientific and ethical conduct. The IMC evaluates adverse event data, protocol deviations, reasons for exclusion, and participant accrual. IMC members make recommendations to the principal investigators and the funding agency regarding continuation, termination, or other modifications of the randomized controlled trial.

Regulatory Approvals

The trial protocol received ethical approval from the Duke University institutional review board (IRB; Pro00114814). The trial protocol was also approved by the National Center for Complementary and Integrative Health at NIH. All investigators and clinicians, including study acupuncturists outside the DUHS, completed training on the protection of human subjects.

Eligibility Criteria

To be included in the study, patients must meet all the following criteria: (1) be undergoing single-level fusion, discectomy, or laminectomy of the cervical or lumbar spine for pain management at DUHS; (2) be aged ≥18 years; and (3) have access to a smartphone or mobile device (with an Android or iOS operating system) and internet to complete training and questionnaires. The scope and complexity of spine procedures were limited to increase homogeneity within the cohort and to reduce potential confounding variables for this feasibility and acceptability study.

Patients will be excluded if they meet any of the following criteria: (1) having conditions that make consent, follow-up data collection, or use of the intervention prohibitive (eg, non-English speaking, serious psychiatric conditions such as schizophrenia, traumatic brain injury, or dementia-type illness); (2) undergoing surgery for neoplastic disease; (3) current daily opioid use greater than 100 mg morphine equivalents; (4) unable to receive acupuncture due to injury, infection, or other contraindication to the use of needles at acupuncture sites; (5) are unable to attend outpatient clinic for acupuncture follow-up (eg, from out-of-state); (6) currently practicing mindfulness or receiving acupuncture; or (7) being in hospice or receiving palliative care. Exclusion criteria are assessed using an initial self-report screen, and study personnel perform a medical record review to confirm criteria that can be assessed through the medical record (eg, prior diagnoses, opioid prescriptions, neoplastic disease, and planned surgery).

Identification, Recruitment, and Enrollment

We will use the following three strategies to identify and recruit participants:

1. Recruitment through Maestrocare: our primary form of recruitment will be through Maestrocare, Duke University's version of the Epic electronic health record system. A weekly customized report will be generated in Epic to identify potential participants based on searchable eligibility criteria. Automated messages will be sent through MyChart to patients meeting these criteria and scheduled for surgery in 21 to 42 days (3 - 6 wk). This timeframe allows adequate time to consent, randomize, and deliver preoperative interventions. The automated message informs them of their potential eligibility for the study and includes a link to alert our research coordinators of their initial interest. A reminder message will be sent after 5 days if the patient has not responded to the initial message. Patients who indicate interest will be prompted to complete a prescreen questionnaire in REDCap (Vanderbilt University) [43,44] to confirm eligibility. Those who meet the initial eligibility criteria will be contacted by phone by a research coordinator. All patient contacts will be recorded in a screening log, along with the outcome of the call.
2. Recruitment by phone: for patients who do not respond to the MyChart message, the research coordinator will contact them by phone, conduct screening for study participation, provide additional information on the study, and answer any questions.
3. Recruitment by clinic: patients may also be recruited in the clinic after they have decided to undergo surgery. Patients will be introduced to the study by their surgeon or another member of their health care team. The introduction will include basic study information, which may consist of distributing an IRB-approved study flyer, and patients will be asked if they are interested in learning more about the study. Those interested in learning more will be directed to the study flyer QR code that links to the REDCap screening form. The clinician may also contact the study coordinator with patient contact information if permitted by the patient. Those meeting the initial criteria will be contacted by phone by a research coordinator.

Recruitment through Maestrocare: our primary form of recruitment will be through Maestrocare, Duke University's version of the Epic electronic health record system. A weekly

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For all 3 recruitment strategies, calls to potential participants will include an explanation of the purpose of the study; what will be done during the study and length of participation; potential risks and benefits of participating; and verification that the participant has the right to leave the study at any time. Once informed, if the patient is willing to participate in the study, they will be sent a link to complete the eConsent via REDCap. The process for recruitment and enrollment is depicted in Figure 1.

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Figure 1. Participant flow through the Integrating Mindfulness and Acupuncture after Spine Surgery (I-MASS) trial.

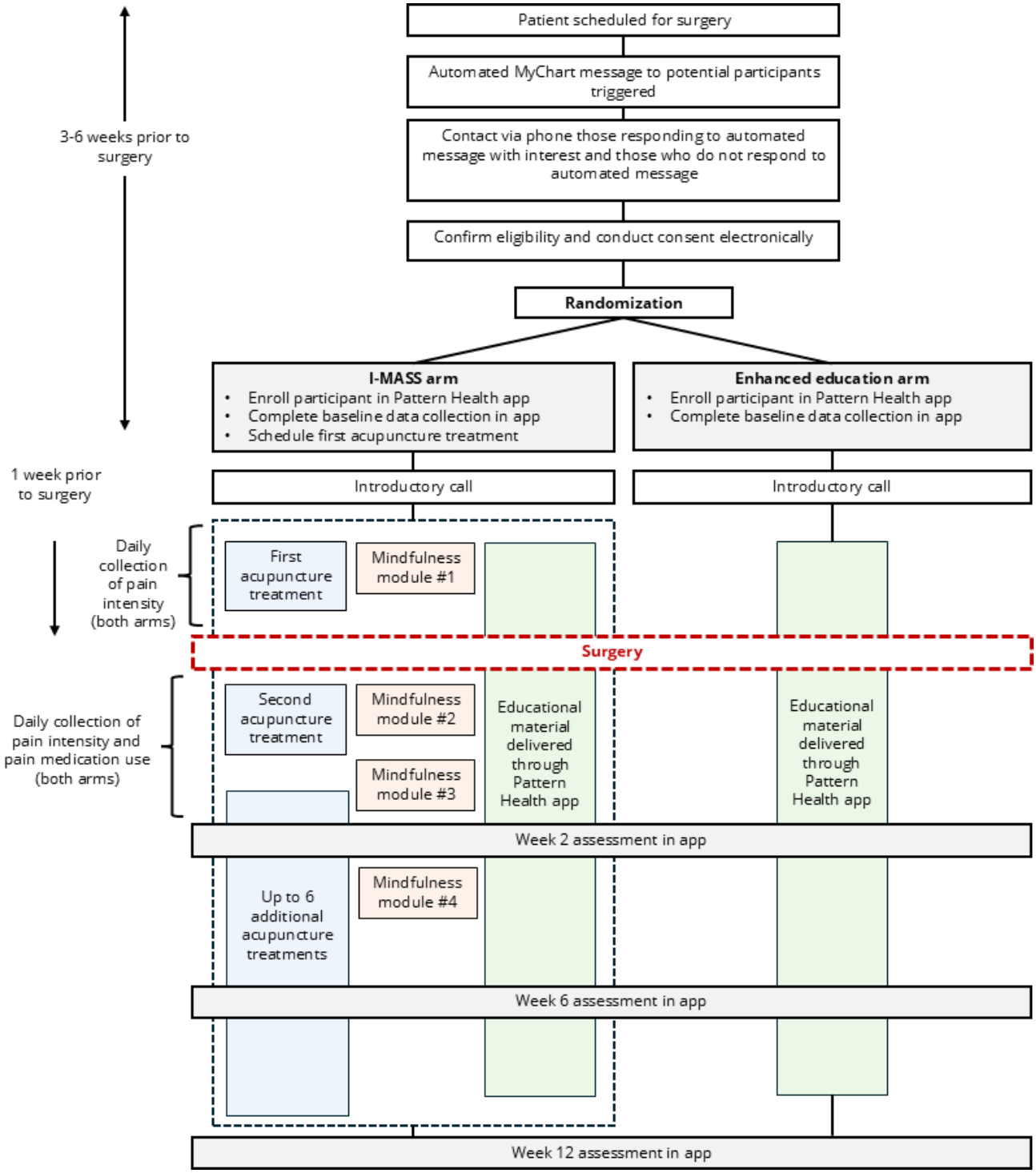

Allocation

The primary study biostatistician developed a 1:1 randomization schedule using a random number generator. Because this is a planning study, the principal investigators, research coordinators, and clinicians (ie, acupuncturists and orthopedic surgery teams) will not be blinded to the randomization. One of the 2 biostatisticians will be blinded. A study coordinator will randomize consented participants and inform them of their randomization group via telephone. During this call, the coordinator will schedule the participant's first acupuncture appointment (I-MASS plus education arm only) and send the participant a link to download the Pattern Health mobile app (both arms). Upon randomization, the participants' demographic details, contact information, and surgery date will be entered into the Pattern Health dashboard before the link is sent, allowing us to designate their allocation and start date in the app. The participant will be reminded to complete baseline surveys. They will also be reminded that a study team member will contact them approximately 1 week prior to their surgery (described in the "Introductory Call" section) to review their preoperative study tasks.

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Study Intervention

Overview

Participants will be randomized to one of two study arms: (1) mindfulness and acupuncture (ie, the I-MASS program) plus enhanced education or (2) enhanced education only (Figure 1).

Mindfulness

Participants will complete 4 week-long mindfulness modules using the Pattern Health mobile app (1 wk prior to surgery, 3 wk after surgery). Each module begins with a short (4 - 5 min) background video describing the mindfulness technique for that week. Participants then complete daily guided practice sessions (6 - 8 min each) that focus on that week's mindfulness technique (Table 1) [45,46]. Each module builds upon skills learned in the previous module. The preoperative module (module 1) discusses the rationale for incorporating mindfulness into the recovery process and teaches how to develop an awareness of breath. Awareness of breathing is a fundamental mindfulness technique that begins to cultivate skills of mindful nonreactive observation. Module 2 begins 2 days after surgery and focuses on building awareness of body systems. This module cultivates skills of observing, describing, and nonjudgmental attention. Module 3 focuses on awareness of emotion and mindful acceptance. This module aids in acknowledging difficult emotions and cultivating feelings of kindness and compassion towards oneself and others. The fourth and final module introduces awareness of the senses. It is designed to further build attention, concentration, observation, nonjudgment, and nonreactivity skills. The modules present mindfulness as a learned skill that participants are encouraged to continue using after completing the modules.

Table . Content of the mindfulness modules delivered through the Pattern Health app.

Module	Content	Purpose
Week 1	• Rationale for mindfulness • Learn to use awareness of breathing	Begin to cultivate skills of mindful nonreactive observation
Week 2	• Build awareness of body systems that are working well or less well	Continue to cultivate skills of observing, describing, and nonjudgmental attention
Week 3	• Practice awareness of emotion and mindful acceptance	Aids in acknowledging difficult emotions and cultivating feelings of kindness and compassion towards oneself and others
Week 4	• Introduce awareness of the senses	Build the skills of attention, concentration, observation, nonjudgment, and nonreactivity

Automated reminders in the app will alert the participant to complete each daily practice session. Participants can choose when they receive these push notifications. In the first week's introductory mindfulness video, they are encouraged to complete mindfulness sessions while in a comfortable location and during a time when they will not be interrupted. All participant activity in the app, including access to module content, can be tracked in the Pattern Health dashboard.

Acupuncture

Participants will receive up to 8 total acupuncture treatments at participating outpatient clinics. The initial acupuncture treatment will be scheduled to occur the week prior to surgery. The second acupuncture treatment will be planned to occur within 10 days of surgery, as soon as the participant can safely travel. Participants will have up to 12 weeks after surgery to complete their acupuncture treatments. We will take a pragmatic approach to the timing and cadence of acupuncture follow-up visits, aiming for visits to occur every 5 to 10 days at the discretion of the participant and their acupuncturist. Approximately every 2 weeks after surgery, participants are sent an automated reminder in the mobile app to make sure their next acupuncture treatment is scheduled.

Acupuncturists will also undergo a one-hour training session designed by the study psychologist to facilitate discussion about mindful awareness and nonjudgmental thoughts regarding pain, allowing participants to reflect on their experiences during the acupuncture session. We will not mandate a specific acupuncture protocol. Both body and auricular acupuncture techniques can be used during treatments. Because acupuncture is commonly delivered to support whole-person health, acupuncturists may target other needs (eg, reduce inflammation and aid in digestion) through treatment in support of postoperative recovery. Specific components of each acupuncture treatment will be recorded according to the revised STRICTA (Standards for Reporting Interventions in Clinical Trials of Acupuncture (Checklist 1) [47] to allow for post hoc assessment of treatment fidelity. Detailed acupuncture note templates will be developed with input and feedback from study acupuncturists, with the level of detail consistent with that needed to appropriately report the intervention content using STRICTA guidelines. All acupuncture charting will be done in study-specific REDCap forms. All acupuncturists involved in the study will undergo a screening process conducted by study personnel to ensure they hold valid licensure, maintain appropriate insurance coverage, and have completed relevant education and training. The study does not mandate a minimum number of years in practice.

Enhanced Education

Enhanced education consists of informational materials specially curated and delivered in the Pattern Health mobile app during the appropriate phase of recovery (Table 2). All educational content is from the Healthwise.net Duke Health Library. Educational topics include learning how to lift and sit when experiencing pain, proper precautions following surgery, how to ease back into daily activities following surgery, and ways

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to self-manage pain. Education is in the form of short reading materials or videos. Participants in both study arms will receive the same enhanced education, which starts in the preoperative week and continues for 6 weeks following surgery. Automated reminders in the app will alert the participant when new educational material is available. Once educational materials are first accessed, they remain available to participants in the app throughout the course of the trial.

Table . Educational content delivered in both trial arms.

Timing of delivery[a]	Content
The week prior to surgery	• Spine pain • Heat or ice for spine pain • Proper lifting • Stress and spine pain • Precautions after spine surgery
First week after surgery	• Getting in and out of bed • Self-massage • Spine pain: keeping it from coming back • Proper sitting for a healthy spine
Second week after surgery	• Easing back into your daily activities
Third week after surgery	• Getting support when you have spine pain • Spine pain and sex • Returning to work with spine pain
Sixth week after surgery	• Exercises to reduce pain • Keep moving

[a]After participants access materials for the first time, the content is made available in an education library within the app for the remainder of their time in the trial (through 12 wk after surgery).

Introductory Call

All participants will receive a telephone call from a study team member during the week before surgery. For participants in both study arms, the study team member will reinforce the importance of the enhanced education content, answer any questions about the program, remind participants of when questionnaires will be administered through the mobile app, and troubleshoot challenges with accessing or navigating the app. For participants in the I-MASS arm, the study team member will also reinforce mindfulness best practices (eg, find a comfortable place to practice, minimize distractions), review the benefits of combining mindfulness and acupuncture, and review how and when to schedule acupuncture treatments.

Other Treatments

Trial participation will not preclude the participant from receiving any other care deemed necessary by their health care team and surgeon, including the use of pain medication.

Assessments

Overview

All assessments presented below, except those indicated otherwise, will be collected at baseline (preintervention) and at 2 weeks, 6 weeks, and 12 weeks after surgery (Table 3). Sociodemographic and health history data will be collected through REDCap. All other self-reported measures will be collected in the Pattern Health app. The app will send an automated notification to the participant when a new assessment is due.

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Table . Primary and secondary outcome measures collected in Integrating Mindfulness and Acupuncture after Spine Surgery (I-MASS).

	Measure description	Time frame
Primary measures		
CSQ-8[a]	CSQ-8 assesses credibility and satisfaction with health-related services (8 items, 4-point Likert, with higher scores indicating higher credibility or satisfaction).	12 weeks after surgery
Recruitment	Percentage of contacted patients who are eligible and agree to participate	Baseline
Data collection	Percentage of participants who complete self-report follow-up questionnaires at each of the 4 timepoints.	Up to 12 weeks after surgery
Number of completed acupuncture visits	Percentage of acupuncture treatments completed out of 8 possible treatments	Up to 12 weeks after surgery
Number of completed mindfulness modules	Percentage of completed mindfulness modules out of 4 possible in the mobile app	Up to 12 weeks after surgery
Secondary measures		
PROMIS-29[b] version 2 0	This profile assesses pain intensity using a single 0 - 10 numeric rating item and 7 health domains (physical function, fatigue, pain interference, depressive symptoms, anxiety, ability to participate in social roles and activities, and sleep disturbance) using 4 items per domain and a 1-item measure of pain intensity.	Baseline (prior to surgery), 2 weeks, 6 weeks, and 12 weeks after surgery
Daily pain intensity	Daily pain intensity during the week prior to surgery and for 2 weeks following surgery will be measured with the following two questions: (1) please rate your worst pain in the last 24 hours on a scale from 0=no pain to 10=worst possible pain, and (2) please rate your average pain in the last 24 hours on a scale from 0=no pain to 10=worst possible pain.	Daily the week before surgery and for 2 weeks after surgery
SPARE-FA[c] Short form	The SPARE-FA short form is a 4-item questionnaire that measures characteristics of pain-related fear avoidance, catastrophizing, and kinesiophobia. Higher scores indicate higher levels of fear avoidance.	Baseline (prior to surgery), 2 weeks, 6 weeks, and 12 weeks after surgery
Medication Prescriptions	We will collect self-reported information on medication prescriptions for pain (eg, opioids, benzodiazepines, gabapentin or neurontin, and NSAIDs[d]) at baseline, 6 weeks, and 3 months. We will also collect self-reported pain medication use daily during the first 2 weeks following surgery.	Baseline (prior to surgery), 2 weeks, 6 weeks, 12 weeks after surgery
Number of hospital readmissions related to spine surgery	Identified through ADT[e] alerts in the Epic EHR[f] and periodic chart reviews through 12 weeks.	Up to 12 weeks after surgery
Number of emergency room visits related to spine	Identified through ADT alerts in the Epic EHR and periodic chart reviews through 12 weeks.	Up to 12 weeks after surgery
Adverse events	Identified through ADT alerts in the Epic EHR and periodic chart reviews through 12 weeks. Adverse events are also documented in acupuncture treatment notes.	Up to 12 weeks after surgery

[a]CSQ-8: 8-item Client Satisfaction Questionnaire.

[b]PROMIS-29: 29-item Patient-Reported Outcomes Measurement Information System.

[c]SPARE-FA: Screening for Pain Vulnerability and Resilience–Fear Avoidance.

[d]NSAID: nonsteroidal anti-inflammatory.

[e]ADT: Acceptance Determination Tool.

[f]EHR: electronic health record.

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Sociodemographic and Health History Information

A baseline questionnaire will be administered via REDCap. We will collect data regarding age, sex at birth, gender, race, ethnicity, education, employment status, annual household income, marital status, and disability insurance status. We will also collect zip codes, spinal surgical history (has the participant had prior spinal surgery and if so, list the dates), self-reported existing or comorbid medical diagnoses using the Charlson Comorbidity Index [48], self-reported overall current health status rated on a 5-point Likert scale from poor to excellent, the revised graded chronic pain scale [49], and previous acupuncture and mindfulness use ("Have you ever used these treatments in the past?").

Primary Outcomes

Consistent with the NIH stage model and feasibility and acceptability study guidelines, our primary outcomes are the following measures of feasibility, acceptability, appropriateness, satisfaction, and fidelity:

1. Feasibility of recruitment: we will calculate the percentage of contacted participants who were eligible for the study and who agreed to participate.
2. Feasibility of data collection: we will calculate the percentage of participants who complete the self-report questionnaires at 4 time points: baseline, 2 weeks, 6 weeks, and 12 weeks. We will also calculate the percentage of participants who complete the daily pain intensity and medication use questionnaires (described in the "Secondary Outcomes" section) on more than half the days in postoperative weeks 1 and 2.
3. Treatment satisfaction: we will assess satisfaction with the I-MASS program using the modified Client Satisfaction Questionnaire-8, an 8-item questionnaire designed to assess satisfaction with health-related services [50]. This measure has been modified to meet the needs of this study and includes questions regarding usability, satisfaction, and acceptability.
4. Number of completed acupuncture treatments: we will calculate the number and percentage of acupuncture treatments completed out of 8 possible treatments.
5. Number of completed mindfulness modules: we will calculate the number and percentage of mindfulness modules completed out of 4 possible modules in the mobile app.

Secondary Outcomes

Secondary outcomes included the following patient-reported outcomes, as well as health care use, including medication use, emergency department visits, and hospital readmissions:

1. 29-item Patient-Reported Outcomes Measurement Information System, version 2.0*:* this 29-item self-report questionnaire assesses pain intensity using a single 0 - 10 numeric rating item and 7 health domains (physical function, fatigue, pain interference, depressive symptoms, anxiety, the ability to participate in social roles and activities, and sleep disturbance) using 4 items per domain and 1 item for pain intensity [51]. Higher scores indicate more of the item being measured, which is positive for physical function and participation in social roles, and negative for all other scores.
2. Daily pain intensity: the following questions will be asked of patients daily during the week prior to surgery and in the 2 weeks following surgery: please rate your worst pain in the last 24 hours on a scale from 0=no pain to 10=worst possible pain, and please rate your average pain in the last 24 hours on a scale from 0=no pain to 10=worst possible pain [52]. Daily pain intensity will be collected in the 2 weeks following surgery because intensity and variability of pain during this timeframe are known to predict the persistence of postoperative pain [53]. Using multiple, repeated pain ratings provides a more ecologically valid and comprehensive assessment of the pain experience than single measures [54]. This method will also allow us to assess the feasibility and completeness of daily pain measure collection using the app, which will inform our decision to use this method in a future trial.
3. Screening for Pain Vulnerability and Resilience–Fear Avoidance Short-Form: this is a 4-item questionnaire that measures characteristics of pain-related fear avoidance, catastrophizing, and kinesiophobia [55]. Higher scores indicate worse outcomes.
4. Medication prescriptions: medication use for pain will be collected by self-report questionnaires. Medication prescriptions will also be extracted through an Epic chart review, and harmonized NIH Pain Management Pragmatic and Implementation Studies for the Management Initiative definitions [56] will be used to identify prescribed opioid medications. A standard formula from the Centers for Disease Control and Prevention Morphine Equivalent Factors will be used to compare opioid doses across classes. Medication use will be collected at baseline (before intervention) and daily during the 2 weeks following surgery. For each daily questionnaire, we will collect information on the type or name of medication, the number of pills taken in the last 24 hours, and the number of milligrams of each pill taken.
5. Number of hospital readmissions related to spine surgery from enrollment to study termination: collected through a Duke Acceptance Determination Tool alerts in the Epic EHR and periodic chart reviews through 12 weeks.
6. Number of emergency room visits related to spine surgery from enrollment to study termination: collected through Acceptance Determination Tool alerts in the Epic EHR and periodic chart reviews through 12 weeks.

Adverse Events

We will count the number of adverse events related to program participation among all enrolled participants, and the raw number of events will be reported by treatment arm.

Sample Size

We will enroll 50 participants (25/50, 50% per arm), which is suitable to achieve our feasibility and acceptability aims, including determining whether attrition rates will make a larger trial feasible. This approach and sample size are consistent with similar successful trial planning studies conducted on digital health and integrative medicine interventions, including

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multicomponent intervention studies [46,57-61]. Consistent with the design of our funding mechanism, this trial is neither powered for efficacy nor aimed to provide such information.

Statistical Methods

Demographic data will be reported as frequency and percentage of nonmissing values for categorical characteristics. Continuous demographic variables will be summarized as mean, SD, median, IQR, and range. We will enumerate the number of participants who meet the "Yes" definitions for all binary feasibility and acceptability outcomes. We will report the proportion of patients that met the definition at each time point with 95% CIs and descriptively compare these figures to benchmark values. For all secondary outcomes, we will report summary statistics (mean, SD for normal distributions; median, IQR for skewed outcomes) of all measures at all time points in which they are collected. This will be done overall and by treatment arm. Since we will not perform tests of efficacy and the rate of data missingness is a primary outcome, we will not have the need to use any techniques to account for missing data (eg, multiple imputation).

We set the following feasibility and acceptability benchmark values for primary outcomes based on similar pilot studies of technology-enabled behavioral interventions for musculoskeletal populations [46,57-61]:

- Feasibility of recruitment: overall, ≥60% of eligible and contacted patients will agree to participate
- Feasibility of data collection: among enrolled participants, ≥70% will complete self-report questionnaires at 4 time points: baselines, 2 weeks, 6 weeks, and 12 weeks.
- Treatment satisfaction: among enrolled participants, ≥70% will endorse a score higher than the midpoint on each of the 6 questions of the modified at 12 weeks. This will be a binary measure of "Yes" (scored a 3 or 4) or "No" (scored a 1 or 2).
- Feasibility of acupuncture: among enrolled participants, ≥70% will complete at least 4 acupuncture treatments out of 8 possible treatments.
- Feasibility of mindfulness: among enrolled participants, ≥70% will complete at least 3 mindfulness modules out of 4 possible modules.

Dissemination Plans

The results of our study will be presented at scientific conferences and manuscripts in the topical areas of orthopedics, pain management, and complementary and integrative health.

Ethical Considerations

The trial will be conducted in accordance with Good Clinical Practice guidelines. The trial was registered at ClinicalTrials.gov (NCT06429072), and the investigational plan was approved by the DUHS IRB on May 14, 2024 (approval: Pro00114814). All participants will sign the informed consent before joining the trial. Participation is voluntary, and participants may withdraw at any time without penalty or impact on their access to health care services. Participant data collected during the study will be entered into and stored in a secure REDCap database with access limited to authorized study personnel. Demographic, health-related, and health care use data extracted from the electronic health record will be transferred via Secure File Transfer Protocol portal managed by DUHS. Only authorized staff will have access to the data. Data files are immediately retrieved and subsequently managed within the internal secure computing environment. Only the minimal required information will be maintained in the dataset after project completion, but all identifiers will be destroyed once the IRB protocol is closed. All data collected through the Pattern Health app will be transferred via Secure File Transfer Protocol portal managed by Duke University. Pattern Health will populate the study-specific identification number into the patient-level participant Pattern Health data extract before providing it to the study investigators at Duke. Duke investigators will rely upon the study-specific identification number to integrate the participant Pattern Health data extract and the electronic health record REDCap dataset for reconciliation, reporting, and analysis. Only named members of the research team will have access to identifiable data. No personal identifying information will be included in the analytic extract. Only deidentified data will be used in publications and presentations. Nominal incentives will be provided for completing questionnaires at each time point: baseline, 2 weeks, 6 weeks, and 3 months. The total compensation will be up to $120 for completing all data collection in the study. This protocol has been prepared in accordance with the CONSORT (Consolidated Standards of Reporting Trials) guidelines Checklist 2.

Results

Trial enrollment began in August 2024. As of May 9, 2025, 35 participants have been enrolled. Enrollment is expected to be completed in the fall of 2025. Data analysis has not yet been performed. Results are expected to be published in the first half of 2026.

Discussion

Principal Findings

We anticipate that the I-MASS program will be acceptable and feasible for patients undergoing spine surgery. I-MASS is highly responsive to the need for mind and body treatments with strong potential to improve recovery and reduce risk for chronic pain and opioid use after spine surgery. Existing treatments have not adequately addressed this need. I-MASS takes a unique approach by using multicomponent treatments with distinct yet complementary therapeutic mechanisms. While acupuncture and mindfulness are commonly studied interventions, to our knowledge, no studies have fully integrated the two as a method of managing pain and improving recovery after spine surgery. Prior studies have found modest effects of acupuncture alone on pain intensity following spine surgery [62]; however, most of these studies have not assessed longer term results or outcomes like pain interference, pain-related disability, or changes in psychological distress. Likewise, mindfulness interventions have shown promising results after spine surgery [63-65], although many studies are limited by small sample size, and none to our knowledge use an asynchronous, entirely

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digital, self-directed mindfulness program delivered before and after surgery.

The I-MASS program is innovative because it is not simply 2 treatments provided concurrently, but rather an integrated program that includes both synchronous and asynchronous components. Using a mobile app for the delivery of mindfulness has great potential to make nonpharmacologic pain care more efficient and accessible to patients undergoing spine surgery. Importantly, modules teach mindfulness as a self-management strategy that participants can continue using after completing the study. Another important attribute of the program is that delivery of acupuncture is not confined to the academic medical setting. For this trial, we have developed a network of study-approved acupuncture clinics within a broad geographic region. The network allows us to enroll participants who receive surgery at DUHS but do not live in the immediate vicinity of a DUHS clinic. This is important because pain and fatigue that are common prior to and after surgery can limit the ability to travel long distances for treatment. We also take a pragmatic approach to the delivery of acupuncture where treatments are tailored to the unique needs of each participant with the intention of optimizing their postsurgical recovery. This approach closely mirrors usual care. The use of a network of I-MASS–trained acupuncturists and flexibility in treatment delivery are likely to enhance implementation potential for future pragmatic studies.

Limitations

This study has several limitations. First, we intentionally limited eligibility to patients undergoing single-level procedures of the spine. We did so to reduce the potential for confounding variables that could accompany larger and more complex procedures, like high complication rates. The approach is common for preliminary testing in feasibility and acceptability studies but could limit generalizability to patients with more complex procedures or clinical presentations. Second, acupuncture is delivered by acupuncturists trained in mindfulness and practicing within our I-MASS network. Because participants would need to receive acupuncture treatments from study-approved acupuncturists, we are limited to recruiting patients within a reasonable travel distance of our acupuncture clinics. This limits the number of people who can participate, and participation would be especially difficult for patients living in regions that do not have acupuncture services. Finally, the I-MASS program may not be appropriate for patients with low technical proficiency. Although we have worked closely with Pattern Health to make the app interface intuitive and easy to navigate, the program may not be accessible to patients who cannot access or use mobile apps.

Future Directions

The results of this feasibility and acceptability trial will provide the information needed to develop a rigorous pragmatic comparative effectiveness study of the I-MASS program for people undergoing spine surgery. If effective, this program has the potential to revolutionize spine care by providing a safe and effective alternative to reliance on medication, including opioids, for postoperative recovery.

Conclusions

This research aims to provide evidence for the feasibility and acceptability of integrating two effective integrative health interventions, mindfulness and acupuncture, to improve outcomes following spine surgery. The findings will not only contribute to the development of a future, fully powered pragmatic comparative effectiveness trial but also provide insight into the best methods for delivering this integrated program in real-world settings.

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Data Availability

The datasets used or analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

Conceptualization: TAL, LSP, CR, BR, TG, SAE, CLG, EP, AD, MM, CMG
Data curation: TAL, LM, CR, EKR, AD, MM, SF, CMG
Formal analysis: EP, CLG
Funding acquisition: TAL, CMG
Investigation: TAL, LSP, LM, CR, BR, TG, EKR, SAE, CLG, EP, AD, MM, SF, CMG
Methodology: TAL, LSP, CR, TG, EKR, SAE, CLG, EP, AD, MM, SF, CMG
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Writing—original draft: TAL, LM, CR, TG, EKR, CLG, EP, CMG
Writing—review and editing: TAL, LSP, LM, CR, BR, TG, EKR, SAE, CLG, EP, AD, MM, SF, CMG

Conflicts of Interest

None declared.

Checklist 1
STRICTA checklist.
[PDF File, 107 KB - resprot_v14i1e77236_app1.pdf]

Checklist 2
CONSORT checklist.
[DOC File, 233 KB - resprot_v14i1e77236_app2.doc]

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Abbreviations

DUHS: Duke University Health System
EHR: electronic health record
I-MASS: Integrating Mindfulness and Acupuncture after Spine Surgery
IMC: independent monitoring committee
IRB: institutional review board
NIH: National Institutes of Health

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Effects of Prevention Messages for Electronic Gambling Machines on Behaviors and Cognitions: Protocol for a Two-Arm Stratified Block: Randomized Controlled Study

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Abstract

Background: Electronic gambling machines and online gambling are the reputedly most damaging gambling type from a public health perspective. Pop-up messages are often used as a responsible gambling (RG) measure to prevent harm for these screen-based types of gambling. Despite some evidence of effectiveness in the literature for these messages, limitations persist, among which low ecological validity is of particular concern.

Objective: This study aims to test (1) the potential of pop-up messages as a prevention measure in a gambling setting and (2) whether this potential is moderated by characteristics of people exposed to the messages. Secondary objectives also tackle some fundamental assumptions of gambling studies conducted in a laboratory setting.

Methods: This is a 2-arm stratified block randomized controlled study. In total, 80 participants are recruited under the false pretense of evaluating the realism of a gambling session in a laboratory replicating a bar. Duplicity is also used to make participants believe that they are risking their own money during the experimentation (ie, winnings and losses are real). Participants are randomized to one of the two arms in a 1:1 ratio: (1) experimental group (regular gambling session with prevention pop-up messages presented on a fixed schedule) and (2) active control group (regular gambling session). Outcomes measures include behaviors and cognitive and emotional responses to the pop-up messages. The believability of the gambling session's realism is also evaluated.

Results: Recruitment began in February 2024 and concluded in December 2024. Results are expected to be published in 2026. No results are currently available.

Conclusions: This study will provide new insights on the efficacy of pop-up messages as a prevention measure for gambling as well as the appropriateness of laboratory studies as a substitute to a real-life setting.

Trial Registration: ClinicalTrials.gov NCT06341504; https://clinicaltrials.gov/study/NCT06341504

International Registered Report Identifier (IRRID): DERR1-10.2196/75068

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KEYWORDS

gambling prevention; responsible gambling; harmful gambling; pop-up messages; EGM; electronic gambling machine; primary prevention; preventive communication

Introduction

Background and Rationale

In the Diagnostic and Statistical Manual of Mental Disorders (DSM), gambling disorder refers to a persistent and recurrent problematic gambling behavior that disrupts several spheres of an individual's life [1]. Whereas the dichotomous approach of the DSM may be useful in a clinical setting, it can easily lead to problematic subclinical behaviors not being considered. From a prevention standpoint, a continuous conceptualization of problem gambling is more useful. While cutoffs and nomenclature vary between existing screening tools, they mostly overlap with "Recreational" or "Non-problem" on the lower bound and "Pathological" reserved for severe problem gambling

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meeting the clinical threshold [2-8]. In between are the designations “At risk” and “Problem gambling”. The former regroups people experiencing some adverse consequences from their gambling habits and exhibiting some signs of impaired control. The latter designates people experiencing significant harm from or impaired control over their gambling habits, but at a subclinical level [8]. Finally, recent developments in the literature have begun to shift the focus from counting people afflicted by them to counting harms (see the Conceptual Framework of Harmful Gambling for more information [9]). This framework allows for a more granular study of the impacts of gambling, notably the recognition that relatively small harms can be significant when experienced by a large population.

Data from a recent meta-analysis indicates that the worldwide prevalence in the adult population for any risk gambling (ie, anything higher than recreative or no problem gambling) is 8.7% and is 1.41% for problem gambling [10,11]. Problem gambling is associated with a range of negative effects encompassing multiple domains. For example, Cowlishaw and Kessler [12] found associations between problem gambling and poorer outcomes on mental health, psychosocial, and financial indicators. These effects are largely confirmed in a recent systematic review by Allami et al [13]. More generally, recent frameworks of gambling harms have been developed to classify and itemize different gambling harms across dimensions and temporal spans [14], among which the taxonomy of harms by Langham et al [15] is considered especially thorough. These frameworks of gambling harms are especially useful to show that harms are not limited to the individual gambler but can also affect their immediate surroundings and society at large. Furthermore, harms are not limited to pathological gamblers and can persist even after complete abstinence from gambling. To limit and prevent these harms, a wide range of measures grouped under the term “responsible gambling” (RG) have been put in place (see the study by Blaszczynski et al [16] for a detailed definition of the RG concept and see the study by Williams et al [17] for a review of different RG measures).

Among RG measures are pop-up messages. In the context of RG, pop-ups, dynamic warnings, or on-screen messages are presented during gambling activities to prevent or reduce gambling-related harm [18-20]. A common strategy used when designing such messages is providing factually accurate information used to correct cognitive distortions and irrational beliefs about gambling (eg, “The way you play will not increase your chances of winning” [21]). Other pop-up messages prompt gamblers to set limits on time or money allocated to gambling and then reappear when those limits are reached (eg, “You have reached your preset limit of 20 credits. You still have 60 credits in the slot machine…” [22]). Pop-up messages have also been used to remind gamblers about their behavior in-play (“You have now played 1000 slot games. Do you want to continue?” [23]) with the rationale that this combats compulsive play and dissociative-like state [24-27]. This strategy is sometimes coupled with normative feedback (eg, “…Only a few people play more than 1000 slot games” [28]). Finally, pop-up messages have used self-appraisal wording to foster self-awareness in gamblers by inducing a deeper and more personal processing of the information (eg, “Have you spent more than you can afford?” [29]).

The effectiveness of pop-up messages is still debated in the literature. On one hand, some results suggest that pop-up messages can be an effective and minimally invasive strategy for introducing responsible gambling information and reinforcing responsible gambling behaviors [18-20]. They also have the potential to reach a wide variety of gamblers at minimal cost and can be tailored to better fit their receiver’s characteristics (eg, age, sex, etc) and the context in which they are presented (eg, if the message is presented during a winning or a losing streak). Furthermore, the interest in pop-up messages is heightened by the fact that they serve as a prevention strategy for types of gambling regarded as the most damaging from a public health perspective, namely electronic gambling machines (EGMs) and online gambling [10,30-33]. On the other hand, numerous methodological limits affect the RG pop-up messages literature, including the paucity of replication studies for a same message parametrization [18-20], use of self-reported data instead of objective observations (eg, [29,34]), limited sample sizes (eg, [35]) and ecological validity flaws (eg, [36-38]). Thus, it is evident that more data is necessary to evaluate the effectiveness of RG pop-up messages and their potential moderators.

Designing Effective Prevention Pop-Up Messages

While the literature is not settled on the best design for effective RG pop-up messages, some elements are more supported than others. To synthesize available data in a useful manner, it is pertinent to start with an overarching model. For this paper, we based our strategy on Comprehensive Messaging Strategy For Sustained Behavior Change (CCSSBC) [39], a multitheoretical persuasive communication strategy combining both message tailoring strategy of the Transtheoretical Model (TTM) [40] and message framing strategy of the Self-Determination Theory (SDT) [41,42]. “Tailoring” is the adaptation of messages’ content to better fit the characteristics (eg, sociodemographics, psychological, etc) of its target individuals or populations [39]. On the other hand, “framing” refers to the way a message is conveyed, not its content per se [39].

The TTM describes the process of change in human behavior and proposes tailoring interventions to the stage of change of the receiver [40]. In their review, Pope et al [39] build on this model and propose 4 stages: detection (characterized by unawareness of a problem or failure, willfully or not, to acknowledge said problem); decision (characterized by acknowledging a problem exists, which leads to a state of uneasiness, and therefore higher receptiveness to information on potential solutions or reliefs); implementation (where the intentions about the problem are formed but have still not been enacted); and maintenance (where behavior is produced and the challenge is now about sustaining in the long term). Tailoring RG messages to gamblers’ stage of change would require some form of evaluation that would also need to be periodically updated. This could be done by a questionnaire via a gambling website or tied to an identity card required to play EGMs (eg, [43,44] for the use of a loyalty card to track behavior on EGMs). While this kind of evaluation would be desirable, it is not

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actually done by most, if any, gambling website, even less for offline play. Therefore, the next best option would be to tailor messages to the stage of change of gamblers that would benefit the most from it: gamblers at the detection stage. As said earlier, RG pop-up messages are a low-level prevention tool pushed to gamblers while in play, without any action needed on their part to receive them. This makes RG pop-up messages ideal for those who are the most oblivious to their own gambling behavior and are the least inclined to search for protective strategies by themselves. Gamblers at other stages of change could still benefit from these messages even though they are less tailored to them. This (presumably) reduced effectiveness is thought to be offset by the increased awareness of gamblers at higher stages of change, which in turn should make them more autonomous in protecting themselves and less reliant on the "imposed" protection of RG pop-up messages.

SDT describes how people regulate and act according to their social environment, goals, and motives [41]. Broadly speaking, both goals (what behavior is done) and motives (why said behavior is done) can be intrinsic (comes from the self, for their own sake) or extrinsic (determined by outside influences, like shame from peers). In their review, Pope et al [39] show that messages fostering both intrinsic goals and motives lead to better outcomes by almost every metric (ie, increased well-being and quality of life, less stress and anxiety, deeper processing of information, more commitment to positive change, and sustained positive behavior, etc). Whatever stage of change, messages should always strive to foster intrinsic-oriented goals and motives. This is readily compatible with the inclusion of self-appraisal statements in RG messages, which are the most promising feature in the literature for this specific prevention tool [28,29,45-47]. At the detection phase, Pope et al [39] suggest that messages should "(a) identify intrinsic risks or negative consequences associated with avoiding the behavior; (b) introduce small feasible options that serve as solutions to the problem; (c) provide a self-determined rationale; and finally, (d) use images/titles that reflect intrinsic goals, such as fitness and well-being, as opposed to appearance, social comparisons, or appealing to others."

Apart from the "content" portion of effective RG pop-up messages are the "container" features. These features refer to strategies aimed at better capturing the attention and maximizing readability and easiness of understanding. First is the necessity to periodically disrupt the game by forcing a pause. An explication for why EGMs are so much linked to problem gambling is their capacity to induce dissociative-like state, which makes gamblers lose track of time and money spent [24-27]. Therefore, a good pop-up message should be disruptive enough to break this mental state and give enough time to gamblers to think more rationally about their behavior. This is exemplified by Williams et al [17], who argue that smoking bans in public spaces could have been one of the more effective RG measures, because it forces gamblers, who are predominantly smokers, to take pauses outside gambling venues. Having a minimum duration between the appearance of the RG pop-up message and being allowed to continue is a common feature in the literature. Sometimes, the forced pause was as effective as the pause plus RG message condition to reduce gambling behavior [21,48]. The duration of the pop-up message should be sufficient, so gamblers have enough time to read and reflect on them, but still not be so long that they become excessively obstructing. Similarly, presentation frequency should be sufficient so that gamblers are exposed to them but not so much as they become harassing. There is much variation on these two parameters in the literature. On the higher end are studies like Ladouceur and Sevigny [48] with a 7s message each 15 games and on the lower end are studies, like Auer et al [23] or Schellink and Schrans [49], with a single message after a continuous hour of play and no minimum duration. A common observation by researchers was that few participants were exposed to their RG pop-up messages (eg, [23,28,49]). Schrans et al [50] tried a 30-minute presentation frequency that had the benefit of elevating the proportion of gamblers exposed to the RG pop-up messages but failed at lowering gambling behavior more than the 1-hour presentation frequency.

RG pop-up placement should be such that they are readily noticeable (other than the fact that they block the gambling activity). Gainsbury et al [34] compared the performance of RG pop-up messages presented in the center versus on the periphery of EGMs' screens. Pop-up messages at the center of the screen were more noticeable and remembered by participants and were perceived as more useful. Participants exposed to the centered pop-up messages also reported gambling less than those exposed to the peripheral ones.

The combination of a signal word [51] and a pictogram [51-53] can be useful to capture attention. Data on the subject mainly comes from the products safety literature where physical injuries are the main concerns. Because gambling deals with psychological and social harms which can nevertheless be devastating, the lower-level signal word "Notice" (prescribed by ANSI for practices not related to physical injury [54]) could be too tame to convey the proper level of danger. We argue that higher-level signal word "Caution" (prescribed by ANSI for hazardous situations which, if not avoided, could result in minor or moderate injury [54]) is more adequate for this purpose.

To improve readability, messages should be designed with an appropriate text-background contrast, font, font size, letter case, and text disposition [51,55]. Because people's perceptual abilities can vary, it is preferable to design messages to maximize the number of people that can read them easily. Messages accessible for disadvantaged people can still be easily read by the regular population, while the reverse is not necessarily true [56]. Good text-background makes the message stand out [51,55] and improves information processing [57]. Black characters on a white background are considered easier to read than white characters on a black background [57].

There is no consensus in the literature regarding which of serif or sans-serif fonts are optimal for readability [58-61]. However, a more recent study by Rello and Baeza-Yates [62] found that sans-serif fonts were easier to read for people with dyslexia. Current ANSI norms also recommend sans-serif fonts [54].

Font size should be optimized so that under normal reading conditions the message is entirely contained in one's field of vision [60,61]. Because readability tends to increase with font

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size [60,61,63], selected font size should err on the higher side of the recommended size [54].

Messages should be written with a mix of capital and lower-case letters. The general rule is that lower-case letters are more distinguishable from one another than capital letters [55]. Capital letters are more useful to mark the beginning of phrases or statements in the messages, or to emphasize the signal word in the message's header [54].

Wogalter et al [51] recommend segmenting messages by units of meaning written in a simpler telegraphic style and disposed of in a point-form manner. Text should be left-aligned. This disposition allows for an easier identification of each "argument" of the message and improves memorization. The ANSI proposes using bullet points to highlight even more each message segments [54].

Finally, designing effective messages necessitates accounting for habituation. Indeed, repeated exposure to prevention messages has the potential to lower their effectiveness because people pay less attention to them [64]. Hitchman et al. [64] suggest that an optimal strategy is to circulate different messages at the same time and periodically change the whole set of messages for a new one.

Ecological Validity

Ecological validity poses a more complex problem than parametrization of the "ideal" prevention pop-up message. Testing the effectiveness of RG pop-up messages in a natural environment poses major ethical, organizational, and financial challenges, mainly related to the need to reach an agreement with a gambling operator. Testing in a natural environment makes inevitable some sort of collaboration with a gambling operator to access their infrastructure and player base. This places the researchers at the mercy of the gambling operator who can interfere with the prevention measure tested or the research design itself. For example, in their study testing the effect of RG messages on EGMs in real gambling venues, Gainsbury et al [29] were asked by one of the venues' owners to reduce the presentation from 15 seconds four times per hour to 10 seconds once per hour. Even without such interference, these sorts of arrangements can incentivize researchers to self-censor to maintain access to their partnered gambling operator' infrastructure for future studies [65,66]. Finally, there are technical difficulties regarding gambling operators' proprietary software that can limit the possibilities of alterations to insert RG pop-up messages. For the aforementioned reasons, it is generally more practical to test RG measures in a laboratory setting, even if this approach comes with its own set of problems related to ecological validity. Indeed, recent systematic reviews evaluating the effect of RG pop-up messages show that most studies have been conducted in a laboratory environment, whereas only a few were conducted in a natural setting [18,19].

In laboratory settings, volunteers are typically invited to gamble by wagering virtual credits (eg, [47,67]) or their monetary compensation received for their participation in the study (eg, [21,35,36,48,68]). Their behavior in that setting is then deemed to resemble that of gamblers in a real gambling environment. Surprisingly, this proposition has received very little scientific verification. Data suggests that gamblers would be more emotionally engaged in play in a real gambling environment [69,70] but would take more risks in a laboratory setting [71]. These results could be explained in part by the fact that laboratory research in the field of gambling neglects a fundamental aspect of its definition: the wagering of money or an object of value, a wager which, once placed, cannot be taken back [72]. Indeed, a constant of laboratory studies is both the absence of monetary risk and low possible prizes. In the best of cases, wagering a certain amount of money provided upfront only risks participants losing something that was not in their possession before participating in the study. This is, by definition, enforcing some kind of preset limits as it is not possible for participants to bet money they cannot afford to lose. In cases where only virtual credits are gambled, the disconnect with risk is even greater. Prize money, for its part, is never really addressed in laboratory studies. Maximum winnable prizes are often quite low (eg, AU $40 [47], some chances to win a 19-inch TV [36], etc) compared to what is theoretically possible in a real gambling environment (eg, in Quebec, Canada, maximum jackpot per game on video lottery terminals, a subtype of EGMs, is CA $1000 [73]).

The absence or reduction of participants' sense of risk while gambling in a laboratory setting could reduce people's gambling inhibitions. This raises doubts about the seriousness with which they would take any warning message about the consequences of their actions. Indeed, without any serious motivation to gamble (eg, desire to win big, desire to make up for a major loss, etc), it is quite possible that participants would be more intensely subject to what Orne [74] calls "demand characteristics of the experimental situation," which are "…the totality of cues which convey an experimental hypothesis to the [participant and] become significant determinants of [participants'] behavior..." Participants exposed to RG measures in a laboratory setting could understand that they are being encouraged to moderate their gambling by the researchers. Participants could then modify their behavior mainly to either confirm or contradict the researchers' hypotheses. This bias could artificially inflate the effectiveness of certain RG measures when tested in the laboratory. These RG measures may subsequently fail to fulfill their protective role when deployed in the field.

Apart from the sense of risk, most laboratory studies on RG prevention messages were conducted in a significantly lesser immersive or restrictive environment. For example, in the study by McGivern et al [38], participants were proposed a computerized gambling task. In the study by Cloutier et al [21] and Ladouceur and Sevigny [48], participants gambled on real EGMs in a properly decorated gambling environment, but the gambling session was limited to how long it took to respectively spend CA $20 and CA $10. At this point, it is worth noting that Bjørseth et al [18] did not find a significant moderation effect of setting (real gambling setting vs laboratory). However, this absence of effect could as easily be explained by the extreme unexplained heterogeneity between studies. More studies are needed to determine the source of this heterogeneity.

This study addresses the aforementioned ecological validity concerns in multiple ways (see "Duplicity" and "Gambling session in the laboratory" subsections of the "Methods" section

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for details). First, the study' environment replicates as closely as possible a real gambling setting. This is done by using real EGMs and giving attention to decor and ambiance (eg, lighting, music, etc). Second, participants are allowed to behave in a more natural and unrestricted way. For example, they can take pauses from gambling without ending the study, they are not informed about the maximum duration that the protocol allows for gambling, and they are told they can gamble as much as they want. Finally, and most importantly, efforts are done to both elevate the perception of personal risk and provide a comparable incentive to gamble as a real gambling setting. The elevation of risk is done by use of duplicity to make participants believe they are betting their own money. Participants are also provided with a way to withdraw more money from their bank account to prevent situations where they would end their gambling session, not because they chose to, but because they did not bring enough money with them. An incentive to gamble is done by offering a comparable jackpot to the one offered in local gambling venues.

Aims and Objectives

This study aims to test (1) the potential of pop-up messages as a prevention measure in a gambling setting and (2) whether this potential is moderated by characteristics of people exposed to the messages. Secondary aims also tackle some fundamental assumptions of gambling studies conducted in a laboratory setting.

Specifically, the main objectives are to test to what extent prevention pop-up messages affect participants:

1. Gambling behaviors (eg, money betted, gambling session length, gambling intensity, etc).
2. Cognitions (eg, thoughts elicited by messages, perceived effectiveness of message, etc).
3. Emotions (eg, enjoyment of gambling, emotional response to messages, etc).

Secondary objectives are:

1. To test to what extent the main effects are moderated by participants' characteristics (eg, gender, age, education, Problem Gambling Severity Index [PGSI] category, etc) moderate the main effects found in objectives 1 - 3.
2. To examine the feasibility of studies conducted in a laboratory setting with the use of real money (or using deception to make the participants believe they are gambling their own money). This objective is accomplished with the use of five research questions:
   - 5.1. Is it possible to recruit enough participants for the study to conduct meaningful statistical analysis (ie, does the novel approach of risking one's own money in a study without guaranteed compensation deter too many people from participating)?
   - 5.2. Does the laboratory bar replicate adequately the overall "vibe" of a typical gambling venue with EGMs?
   - 5.3. Do the participants find their actual gambling activity in the bar replica as realistic as a real one?
   - 5.4. Do the participants believe they are gambling their own money during the study (ie, to what extent does the deception work)?
   - 5.5. Do outcomes, both self-reported (past 12 months) and measured in the laboratory, differ from each other?

Methods

Ethical Considerations

This study was approved by the Comités d'éthique de la recherche avec des êtres humains de l'Université Laval (CÉRUL; reference 2020-076 A-1 / 27-05-2024). Preliminary consent is obtained verbally during the intake interview and confirmed with a signature just before the gambling session in the laboratory. Some aspects of the study are withheld from the participants and are only revealed during debriefing after the gambling session has ended (see "Duplicity" and "Gambling session in the laboratory" subsections of the "Methods" section for details). After debriefing, participants are asked to confirm their consent one last time. Participants can remove consent at any point of the study without prejudice. After debriefing, participants who wish to quit without completing the study can ask that all their data be destroyed. Compensation for participation can vary between CA $30 and CA $500 depending on the results of the gambling session, which is completely random (see "Presentation of the Study and Verbal Consent" and "Duplicity" subsections of the "Methods" section for details). Some transportation expenses were also reimbursed on top of the compensation, namely transit fare, parking validation at the university, and taxi for the elderlies and people with mobility impairments. All data is kept in secured servers (files) and locked drawers (physical forms). Participants' data is anonymized with a nonsequential ID number.

This study exposes participants to potentially stressful situations. Notably, by gambling with their own money, participants risk gambling more than what they can afford and find themselves in a situation where they think they have lost a lot of money. This stress is a byproduct of the duplicity required to ensure maximal ecological validity of the study. It is mitigated by the fact that any potential stress is limited to a maximum of 2 h (the time limit for the study), after which debriefing ensues and they learn their "lost money" will be returned to them.

The use of duplicity poses some concerns over the importance of free and informed consent. While participants initially enroll in the study without knowing all the parameters, they have the option to retroactively remove their consent and ask for the destruction of their data during the debriefing. Some steps are also taken to minimize aspects of the study that are masked by duplicity. For example, even though losses are reimbursed to participants, gains are still paid as advertised. This prevents a potential situation where a participant who wins a lot of money and expects to leave with it is instead given a standardized (and lesser) amount.

It is also worth noting that this study does not expose participants to higher levels of risk and stress than what they already frequently experience in their own lives. Inclusion criteria target participants who regularly gamble on EGMs in their everyday lives. In the context of the study, participants are provided with the same incentives to gamble, but nothing is done to exacerbate these behaviors (eg, altering the EGMs'

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payout rate, offering loans to gamble, etc). On the contrary, half the participants are provided with prevention messages, and any money lost while gambling is reimbursed at the end of the session. Also, because this study is conducted in a psychology laboratory, people on site can provide crisis support should a participant feel unwell after a significant loss. This kind of support is not usually available where EGMs are situated. Finally, we chose not to recruit the most vulnerable gamblers (ie, people trying to reach or maintain abstinence). Despite those protections, the ethics committee felt that probable pathological gamblers should also be excluded from the study.

Study Design

This is a 2-arm stratified block randomized controlled study. Participants are randomized to one of the two arms in a 1:1 ratio:

- Experimental group: Regular gambling session with prevention pop-up messages presented on a fixed schedule.
- Active control group: Regular gambling session.

There are 3 assessment phases in this study (see Figure 1). Recruitment began in February 2024 and concluded in December 2024. Study completion is expected in February 2026. Study outcomes will be reported in line with the Consolidated Standards of Reporting Trials guidelines and the extension for social and psychological interventions trials (CONSORT-SPI) [75].

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Figure 1. Schematic overview of the 2-arm stratified block randomized controlled trial. EGM: electronic gambling machine; PGSI: Problem Gambling Severity Index.

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Sample Size Considerations

Using G*Power, we estimated the required sample size for an α level of 5% and ß level of 80% for a 2-tailed *t* test for a range of effect sizes (see Table 1). This was done both for testing differences in outcomes between 2 independent groups and for repeated measures.

Table . Required sample size for a range of effect sizes.

Effect size (*g*)[a]	Per group, n (%)	Total, N
0.2	394 (50)	788
0.3	176 (50)	352
0.4	100 (50)	200
0.5	64 (50)	128
0.6	45 (50)	90
0.7	34 (50)	68
0.8	26 (50)	52
0.9	16 (50)	32

[a]Calculated for an α level of 5% and ß level of 80% for a 2-tailed *t* test.

A recent meta-analysis by Bjørseth et al [18] on the effects of RG pop-up messages on gambling behaviors and cognitions reports effect sizes respectively of *g*=0.62 (95% CI 0.36-0.87 and *g* 0.58 (95% CI 0.33 - 0.83) when adjusting for publication bias. Based on those values, the total sample size would be between 86 and 96. Note that sample size requirements for 1-way analysis of covariances (ANCOVAs) and repeated measures analyses would be equal to or smaller. Considering the potential difficulty in recruiting participants accepting to play with their own money, we aimed at a sample size of 80. Therefore, we can expect a power range from 72.34% to 77.66% with effect sizes comparable to what is reported by Bjørseth et al [18].

Participants and Eligibility Criteria

We aim to recruit 80 participants in total. While many may refuse to participate when presented with the study's specifics, we do not anticipate a significant number of dropouts after consent is obtained. Textbox 1 shows the inclusion and exclusion criteria.

Textbox 1. Eligibility criteria.

Inclusion criteria:

- Aged 18 years and older.
- Functional literacy in French.
- Having played electronic gambling machines (EGMs) at least once every 2 weeks for the past 12 months. Note that this criterion was subsequently lowered to having played EGMs at least 6 times in the past 12 months to expand the recruiting pool. This change was done on May 27, 2024.

Exclusion criteria:

- Classified as a probable pathological gambler (score ≥8 on the Problem Gambling Severity Index, PGSI).
- Currently receiving treatment for problem gambling or trying to achieve or maintain abstinence from gambling.
- Currently under self-exclusion from a gambling venue or website.

The rationale for the age cut-off is that it is the legal age to gamble where the study is conducted (Quebec, Canada). The literacy requirement is justified by the fact that this study is conducted in French and requires being able to read and understand simple texts in that language. Questions are also asked and answered in French.

The age cut-off is the legal age to gamble where the study is conducted (Quebec, Canada).

The rationale for a floor limit on play frequency is that prevention pop-up messages are expected to produce a small effect that becomes more impactful when cumulated over multiple sessions. Therefore, these messages are thought to be more suited to people who gamble on a regular basis. Furthermore, regular EGM gamblers are more likely to feel compelled by a message warning about the dangers of excessive gambling than people who gamble very sporadically.

The rationale for a floor limit on play frequency is that prevention pop-up messages are expected to produce a small effect that becomes more impactful when cumulated over multiple sessions. Therefore, these messages are thought to be more suited to people who gamble on a regular basis. Furthermore, regular EGM gamblers are more likely to feel compelled by a message warning about the dangers of excessive gambling than people who gamble very sporadically.

The rationale for the exclusion criteria is ethical considerations. The first criterion is mandated by the ethics committee to

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prevent possible adverse effects on the most vulnerable gamblers. The other 2 criteria aim not to interfere with someone's recovery process or wishes to stop gambling.

Recruitment

From February 2024 and on, the study was advertised online via social media, our research team's website, and our university's mailing list. An email was also sent to participants from a previous study who agreed to be contacted again. The study was advertised offline via ads in a local newspaper 2 times in February 2024. Recruitment posters were placed in gambling venues in the same city of our university.

To boost recruitment, we started a second recruitment wave during the summer of 2024. This wave mainly used online ads targeted at people geolocated at gambling venues. Inclusion criteria were also relaxed on minimal gambling frequency (see the "Participants and Eligibility Criteria" section).

Preexperimentation Phase

Screening

Screening and following interview for the preexperimentation phase are done over the phone. Participants are asked questions to determine if they satisfy the inclusion and exclusion criteria. Not all criteria are communicated on the recruitment ads, and neither are the participants told beforehand what answer would disqualify them. The screening interview ends with the PGSI, which is a subscale of the Canadian Problem Gambling Index [6]. This instrument is designed to determine problem gambling severity and is the actual gold standard for problem gambling screening in the general population. The instrument is composed of nine items scored on a 5-point Likert scale. Scores range from 0‑27 and classify gamblers in four categories: (1) nonproblem (score of 0), (2) low risk (score of 1‑2), (3) moderate risk (score of 3‑7), and (4) problem gambling (score ≥8).

Presentation of the Study and Verbal Consent

After satisfying the screening criteria, participants are presented with the details of the study. Participants are recruited for a single gambling session in a bar replica equipped with EGMs. Recruitment is done under the false pretense of evaluating the realism of a gambling session in a laboratory replicating a bar. The main points communicated to the participants during the presentation of the study are:

- Gambling is done with your own money. You must bring the amount they wish to gamble the day of the experiment.
- Winnings are paid up to CA $500 more than the total amount inserted in the EGM over the course of the gambling session (eg, if you insert CA $60 in the EGM during your session, you could be paid up to CA $560). In turn, losses are real. There is no baseline compensation for participating in the study. The only compensation for participation is the potential winnings made while gambling. Overall, it is possible to end the study with less money than at the beginning, even to lose it all.
- The EGMs used in this study are of the same model currently in operation in Quebec, Canada. Their payout rate is the same (92%).
- You are free to gamble as much and for as long as you like.
- You are allowed to take breaks.
- Snacks and nonalcoholic beverages can be purchased with real money during the study via cash or electronic transactions.

Participants who give their verbal consent proceed with the intake interview.

Duplicity

In total, 4 aspects of this study are hidden from participants to emulate a realistic level of personal risk and prevent demand characteristics.

First, the main objectives of this study, namely "Evaluating the effect of prevention pop-up messages on behaviors and cognitions," are hidden from the participants. Instead, they are told that this study is about evaluating the bar replica (ie, the ambiance, look, functionality, etc) and the gambling session's realism. They are also told that this information will be used to inform future studies using the same bar replica. To prevent participants from mistaking the prevention pop-up messages for a bug or becoming skeptical about the study's true objectives, they are told that some characteristics of the EGMs could differ slightly from their typical experience. It is also specified that these differences are not guaranteed to be present (to account for participants in the control group). The explanation given to participants for potential differences is that our research team is conducting multiple parallel studies with the same EGMs and that it would not be practical to tinker with the EGMs between each participant. These potential differences are kept vague and presented to the participants as minor modifications, mostly affecting the user's interface (eg, change in fonts to improve readability) and never affecting the games' mechanics and payout rates.

Second, participants cannot lose their own money. All money inserted in the EGMs during the gambling session is given back at the end of the study, though winnings are paid as advertised (see Table 2). Also, participants who incur net losses or winnings less than CA $30 are reimbursed their money and given exactly CA $30. This ensures a floor limit on the compensation for participating in the study.

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Table . Examples of payments made to participants under different scenarios.

Amount inserted in the EGM[a] by the participant during the gambling session (CA $)	Amount left on the EGM at the end of the gambling session (CA $)	Net gains[b] (CA $)	Theoretical maximum amount payable to the participant[c] (CA $)	"New" money gained by the participant[d] (CA $)	Total amount given to participant at the end of the gambling session[e] (CA $)
60	120	+60	560	60	120
60	800	+740	560	500	560
60	65	+5	560	30	90
60	0	–60	560	30	90

[a]EGM: electronic gambling machine.

[b]Money remaining minus what was inserted in the EGM during the gambling session.

[c]Payable net gains are capped at CA $500. This amount is therefore CA $500+ money inserted in the EGM by the participant during the gambling session.

[d]Money gained by the participant that they did not have before the gambling session.

[e]The amount inserted in the EGM is returned to the participant (CA $60 in all examples) + stipulated compensation.

Third, the gambling session's duration is limited to 2 hours. The gambling session starts when the participant inserts money for the first time in the EGM. Breaks during the gambling session are permitted (eg, using the restroom, buying snacks from the bartender or barmaid, etc) but are included in the 2-hour time limit. If the participants have not yet ended their gambling session upon reaching the 2-hour time limit, they are offered to take a short break to answer some questions. They then proceed to the postexperiment phase. If the participant insists on continuing to play or tries to quit hastily (eg, because they are angry about losing money), they are prematurely debriefed before proceeding with the postexperiment phase.

Fourth, unbeknownst to them, participants are monitored through a secret camera hidden in the ceiling during their gambling session. Their gambling behavior is also recorded from the EGM they play on.

Intake Interview

The intake interview collects information on basic sociodemographic factors, gambling behaviors on EGMs (past 12 months), general level of fun while playing EGMs (past 12 months), and perceived self-control while playing EGMs. Participants then schedule a gambling session to be done in our laboratory on the university's campus. While free to choose any date and time they wish, participants are encouraged to select a moment that fits their usual gambling habits. There is no maximum or minimum time limit between the intake interview and the gambling session in the laboratory. Sessions are usually scheduled days to weeks after the intake interview.

Experimentation Phase

Randomization

Blocks are size 4 and strata are divided on problem gambling severity using PGSI categories. Randomization was done using RANDOM.ORG's list randomizer tool. The list within each block, "1, 1, 0, 0" (where "1" is experimental condition and "0" is control), was randomized 20 times for each PGSI category, excluding the probable pathological gambling category (see Figure 2). This arrangement of 80 places for the three lowest PGSI categories allows for any combination of levels of problem gambling among recruited participants while preventing major imbalance between the 2 groups on this characteristic.

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Figure 2. Randomization procedure. PGSI: Problem Gambling Severity Index.

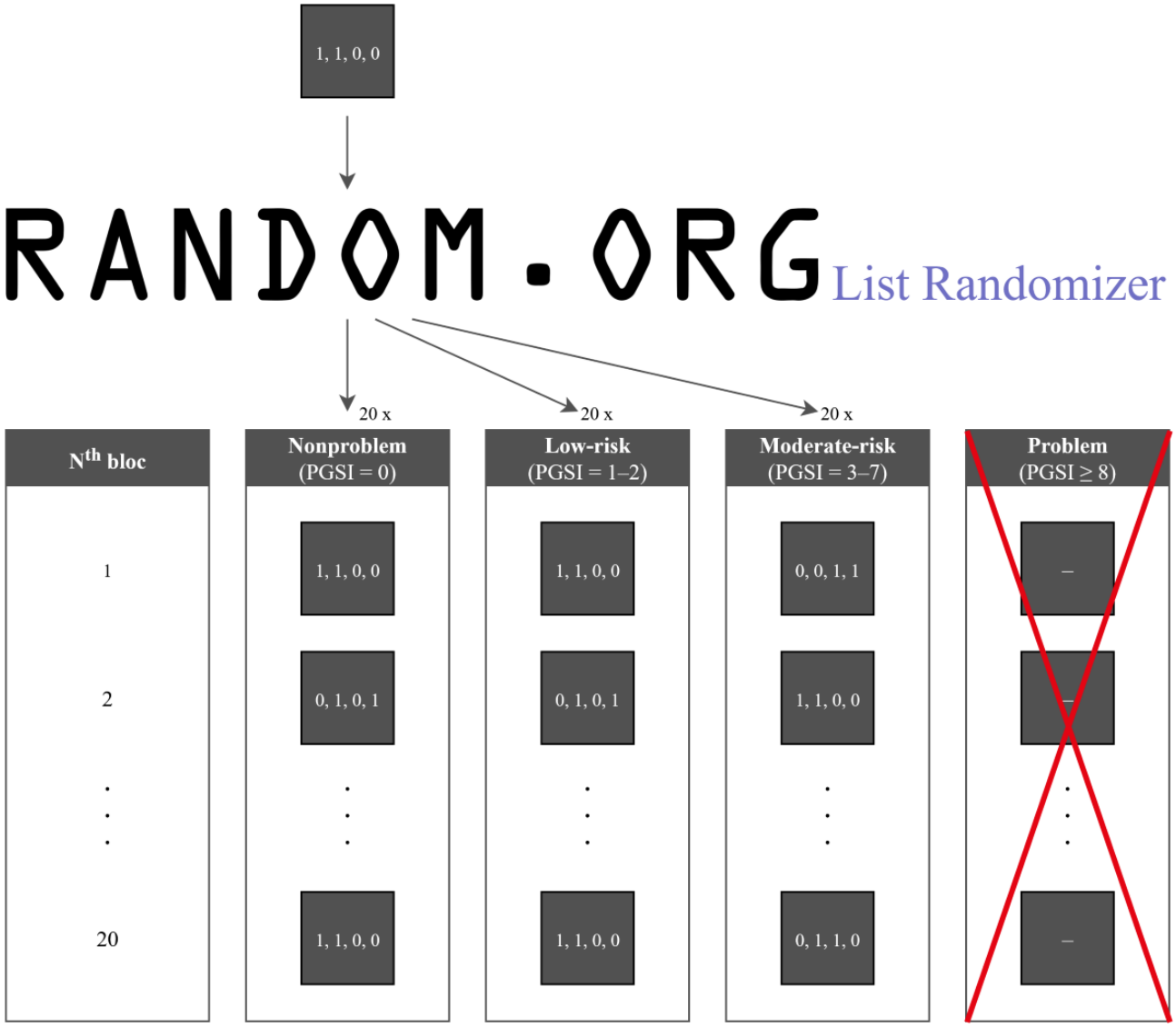

Allocation is done just before the participants arrive at the laboratory, on the day of the experiment. Participants are allocated to the first available spot from the top of the randomized list corresponding to their PGSI category (see Figure 3). Participants who complete the intake interview but do not show up at the scheduled appointment vacate their spot on the list. They may then be reassigned depending on whether they reschedule another gambling session. Meanwhile, the vacated spot becomes available for another participant who fits the same profile. The moment participants present themselves to the laboratory, their spot on the list cannot be reallocated, even if they desist later in the process.

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Figure 3. Allocation procedure. PGSI: Problem Gambling Severity Index; NPG: nonproblem gamer; LRG: low-risk gambler; Condition 1: Experimental; Condition 2: Control.

	Nonproblem gamblers (PGSI = 0)		Low-risk gamblers (PGSI = 1–2)	
N^{th} bloc	Condition	Participant ID	Condition	Participant ID
1	1	10159	1	10247
	1	10888	0	10663
	0	10232	0	[Next LRG participant]
	0	10956	1	
2	0	[Next NPG participant]	1	
	1		0	
	1		1	
	0		0	

- 1st nonproblem gambler participant to visit the laboratory was assigned to the experimental condition

- 2nd low-risk gambler participant to visit the laboratory was assigned to the control condition

- Next low-risk gambler participant to visit the laboratory will be assigned to the next available spot (control condition)

- Bloc 1 is full
- Filling of bloc 2 starts for nonproblem gambler participants
- Next nonproblem gambler participant to visit the laboratory will be assigned to the next available spot (control condition)

Concealment of Allocation and Blinding

While participants in the experimental group should notice the novel prevention pop-up messages, for all they know before debriefing, there is no “assignment” per se. This is because the study is presented as an opinion survey about the realism of the bar replica and the gambling session in it. No instruction suggests any type of comparison between conditions. Therefore, participants would not be aware that there are 2 different groups, nor that this study tests the effects of prevention pop-up messages.

Note that masking becomes “open label” after debriefing. Indeed, after being informed of the true goals of this study, participants are easily able to determine in which group they

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were allocated based on what occurred during their gambling session. Regardless, gambling behaviors are recorded before debriefing and would not be affected by unmasking. There is no functional way to mask group assignment to the research team. However, the randomization procedure ensures that allocation is purely random.

Gambling Session in the Laboratory

There is only a single participant at a time in the laboratory for the gambling session. Each participant arrives at the lab at a scheduled appointment. Then, a research assistant greets the participant and proceeds to refresh their memory about the important aspects of the study. The participant is then brought to a room replicating a typical bar with EGMs (eg, subdued light, music, bar paraphernalia, fake liquor on display, etc; see Figures 4 and 5 and Multimedia Appendix 1 for additional images).

Figure 4. Bar environment—electronic gambling machines and lounge.

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Figure 5. Bar environment—bar paraphernalia and music TV.

Upon entering the bar, the participant is greeted by another member of our research team who plays the role of bartender operating the cash register and ensuring the general safety of the session. The addition of this bartender is done to improve the general realism of the gambling setting. The bar replica has 3 EGMs, but only 1 can be played on and used to show the prevention pop-up messages. The other 2 EGMs are turned on for ambiance purposes, but their money collectors are disabled. Limiting play to only a single EGM eases the recording of gambling behaviors and proper showing of the prevention messages. The participant is told that the 2 unusable EGMs are awaiting servicing due to a malfunction with their money collector.

The participants are free to do as they please (eg, play EGMs, buy chips and nonalcoholic beverages, relax in the bar, etc). They are allowed to leave the bar if they need to go to the bathroom or smoke. They are accompanied by the bartender if they elect to do so. The reference time point of the experiment (ie, T+00:00:00) starts when the participant inserts money for the first time in the EGM. Note that breaks in play, no matter the motive, do not stop the experiment timer regarding the duration limit.

While the participant is in the bar, a second research assistant observes from an adjacent room and is responsible for recording all gambling behaviors using a computer connected to the EGM and operating the pop-up messages presentation schedule (see Figure 6). A live-feed spy camera disguised as a smoke detector is used to observe gambling-related behaviors that cannot be recorded by the EGM's computer (eg, taking a break).

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Figure 6. Observation post.

The session ends when one of the two following conditions is met: (1) the participant expresses, without ambiguity, that they wish to end the experiment, and (2) T+02:00:00 is reached. The procedure may slightly vary depending on how the gambling session ends. Under normal circumstances, the participants end their session by themselves, before reaching the T+02:00:00 time limit. In this scenario, the procedure continues normally, as described in the postexperimentation phase section. Alternative scenarios are:

- Alternative scenario 1: The participant reaches the T+02:00:00 time limit and continues to play. The member of the research team, playing the role of bartender, interrupts the participants and suggests taking a pause to answer some questions. If the participant agrees, the procedure continues normally, as described in the postexperimentation phase section. Unbeknownst to them, they will not be allowed to resume gambling after said questions.
- Alternative scenario 2: Same as "Alternative scenario 1," but the participant refuses and insists on continuing to play, and debriefing is done on the spot to end the play session. All questionnaires presented in the postexperimentation phase section are done, but contrary to the normal scenario, evaluation of participants' perception of the realism of the bar replica and of the gambling session is done after debriefing.
- Alternative scenario 3: The participants try to hastily quit the laboratory before we get a chance to debrief them (eg, because they are angry about losing a lot of money and do not wish to participate any longer). In this case, debriefing is done early to prevent them from quitting without receiving all the information to make an informed decision about their participation. All questionnaires presented in the postexperimentation phase section are done, but contrary to the normal scenario, evaluation of participants' perception of the realism of the bar replica and of the gambling session is done after debriefing.

Active Control Group: Regular Gambling Session

This condition is designed to closely replicate a typical gambling session in a natural setting.

Electronic Gambling Machines (EGMs)

Gambling is done on fully functional and unaltered EGMs, model IGT GL20. This is the model currently in use in Quebec, Canada, the location where this study is conducted. The wins and losses sequence is fully randomized and not determined beforehand. The payout rate is the same as what is prescribed by law (92%). These machines come equipped with basic responsible gambling features, the 2 main ones being a mandatory time limit reminder and a submenu containing responsible gambling information.

Mandatory Time Limit Reminder

The mandatory time limit reminder is activated either when (1) the previous time limit is up or (2) the player bank meter reaches CA $0. When the previous time limit is up, a pop-up takes up the upper third of the play screen and requires the player to set a new time limit using one of 5 choice buttons (first four buttons: 15, 30, 45, or 60 minutes; fifth button: cash out, which prints a receipt and ends the gambling session; see Figure 7). As the EGM cannot track who is playing, there are no limits on

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consecutive gambling sessions. When the player's bank meter reaches CA $0, the pop-up described above appears as soon as new money is inserted in the EGM, no matter if the previous time limit is up or not.

Figure 7. Mandatory time limit reminder.

Responsible Gambling Information

A submenu accessed through a button on the main touch screen opens a window, which contains basic information on randomness and responsible gambling advice. The information is presented in small white font on a black background (see Figure 8 for an example and Multimedia Appendix 2 for a complete overview).

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Figure 8. Responsible gambling information.

Food Purchases and Money Withdrawals

A payment terminal allows for buying nonalcoholic beverages (soft drinks or coffee) and chips during the experimentation. This is done to enhance the realism of the bar setting. It also allows for real cash withdrawal from a bank account during a gambling session. Quebec's code of conduct for EGM commercialization prohibits retailers from having an ATM near their EGMs. It also prohibits them from lending money to consumers or withdrawing cash for them to gamble. However, this rule is not always easy to enforce in practice. For this study, participants are allowed to withdraw from their bank account if they ask by themselves. This option is not communicated upfront to them.

Experimental Group: Regular Gambling Session With Prevention Pop-Up Messages

This condition is the same as the active control group with the addition of prevention pop-up messages delivered during the gambling session on a fixed presentation schedule.

Prevention Pop-Up Messages

Messages are shown full screen on the EGM's play screen on a fixed presentation schedule from the moment the participant inserts money for the first time in the EGM (ie, T+00:00:00). The first message is shown at T+00:10:00. Messages block the play screen for 15 seconds before automatically closing. This presentation frequency is thought to be a good compromise between a very high and potentially annoying frequency (eg, [21,48]) and a very low frequency where only a few participants are exposed (eg, [23]). The first message is presented sooner than the others so that every participant has a decent chance to see at least one. The subsequent presentation schedule is modeled on Schrans et al [50]. While it would have been ideal that messages stay on until participants close them, this was not possible due to hardware limitations on the EGMs' part. The 15-second presentation duration was chosen based on the mean reading speed of a typical francophone adult [76], so participants have enough time to read the messages.

Up to 4 different messages are presented during the gambling session. Order is determined by sortition without replacement. Variations were introduced to counter the possible habituation effect [19,64]. All messages follow the same template (see Textbox 2 and Figure 9 for an example and see Multimedia Appendix 3 for every message used in the study).

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Textbox 2. Prevention pop-up messages template.

- The message is written in black characters on a white box to maximize text-background contrast.
- The message box is placed on a blue background, which matches the EGMs' color palette. This is done so that messages appear native to the EGMs, not something introduced for a study. The background pattern behind the message box directs the eye toward the message. The signal word "Attention!" (ie, the French translation for "Caution!") is used conjointly with a warning pictogram (yellow triangle containing an exclamation mark). The signal word is written in capital letters.
- The bulk of the messages comprised 4 concise statements:
- The first statement is the time spent gambling since the beginning of the session. This portion is a factual statement to ground the participant in the present.
- The second statement is a warning that gambling could lead to serious monetary loss. This is a realistic risk associated with gambling. We choose to warn about monetary harms because they are relevant to every gambler (anyone can experience betting too much money, and this can have consequences even after a single session).
- The third statement is a self-appraisal question about current gambling behavior. This is the only part of the message that changes across versions. There are 4 different variations on this question. Self-appraisal questions drive participants to develop self-determined motivation and goals regarding their gambling behavior.
- The fourth statement is a simple piece of advice that a break could help choose what is best for oneself. This advice aims to foster participants' self-efficacy sentiment, enabling them to act in a way to protect themselves [77,78].
- Just below the message is a countdown indicating the time left before the message closes. This is to reassure participants that the message is not a bug of the EGM and that the only thing required of them is to wait and pay attention.
- The province's Health Department logo is shown in the lower right corner as a more neutral and expert endorsement of the messages. From a general standpoint, the more a source is considered expert and trustworthy, the more a message is susceptible to having an effect [79]. In gambling, Munoz et al [80] found that the participants trusted a source that gave more attention to prevention messages from a perceived independent source (governmental organization) than from a source perceived as having a conflict of interest (org. funded by the local gambling operator). Furthermore, Lemarié and Chebat [81] reported that antigambling ads led to more gambling when coming from a gambling operator.

Figure 9. The prevention pop-up message, as displayed on the electronic gambling machine (EGM).

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Note that due to hardware limitations on the EGMs' part, the prevention messages presented only alter what is shown on the

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play screen (they fill the screen completely, hiding the game), but cannot pause the game per se. The EGMs' buttons, sound, and music are still operational while the message is shown.

Postexperimentation Phase

The participant is brought in a separate office after the end of the gambling session for a series of questionnaires (outcomes listed in "Secondary Outcome" and "Other Outcomes" sections) which are, in order:

- Evaluation of participants' perception of the realism of the bar replica and of the gambling session.
- Evaluation of participants' ability to recall prevention pop-up messages. This includes multiple tasks of free recall (eg, describing the pop-up messages from memory) and cued recall (eg, selecting from a list the pop-up messages that were seen during the gambling session).
- Evaluation of participants' cognitive and emotional response to prevention pop-up messages.
- Evaluation of protocol credibility (ie, if the participant really believed they were gambling their own money and were really risking their own money).

These questionnaires are comprised of Likert scales, multiple-choice questions, and open-ended questions. Contrary to more standard qualitative designs, open-ended question responses are not recorded in an audio format, nor are they transcribed verbatim [82]. Instead, the interviewer takes notes, which the participant can see on a computer screen. Participants are then asked to confirm that the interviewer's notes accurately reflect their opinion. It has been suggested that note-taking is superior to audio recording for obtaining qualitative data [83].

Debriefing about the true goals of the study and final validation of consent to participate in the study are done between the evaluation of participants' perception of the realism and the evaluation of participants' ability to recall prevention pop-up messages.

Outcome Assessments

Table 3 shows the primary outcome measures.

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Table . Primary outcome measures.

Outcome category	Outcome number	Outcome	Description	Measurement time points
Gambling behavior: Money				
	1	Money betted (physical)	Cumulative amount of money physically inserted in the EGM[a] during the gambling session.	Assessed at the following time points from start of gambling session in the laboratory: [0] T+00:00:00, [1] T+00:10:00, [2] T+00:40:00, [3] T+01:10:00, [4] T+01:40:00, [5] end of gambling session (max T+02:00:00)
	2	Change in money betted (physical)	Change between self-reported measures (past 12 months) and observed data in the laboratory.	Past 12 months; end of the gambling session
Gambling behavior: Time				
	3	Gambling session's total duration	Time elapsed between the first time the participant puts money in the EGM (T+00:00:00) to the end of the gambling session. Session's duration is left for the participant to decide. While the participant is told they can play for as long as they like, there is a 2 h limit on the session duration. This limit is hidden from the participant. Session's duration includes any breaks taken from gambling on the EGM.	Assessed at the end of the gambling session.
	4	Total time effectively spent gambling	Time elapsed between the first time the participant puts money in the EGM (T+00:00:00) to the end of the gambling session, minus breaks taken from gambling on the EGM.	Assessed at the end of the gambling session.
	5	Change in total time effectively spent gambling	Change between self-reported measure (past 12 months) and observed data in the laboratory	Past 12 months; end of the gambling session.
Gambling behavior: Breaks				
	6	Number of breaks taken	Number of breaks taken from gambling on the EGM during the gambling session.	Assessed at the end of the gambling session.
	7	Mean breaks' duration	Average duration of breaks taken from gambling on the EGM over the gambling session's total duration.	Assessed at the end of the gambling session.
	8	Total breaks duration	Sum of breaks' duration taken from gambling on the EGM over the gambling session's total duration.	Assessed at the end of the gambling session.
	9	Mean time elapsed between breaks	Average time separating any two breaks taken from gambling on the EGM over the gambling session's total duration.	Assessed at the end of the gambling session.

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Outcome category	Outcome number	Outcome	Description	Measurement time points
Gambling behavior: Risk taking				
	10	Number of bets placed	Number of bets placed on the EGM during the gambling session.	Assessed at the following time points from start of the gambling session in the laboratory: [0] T+00:00:00, [1] T+00:10:00, [2] T+00:40:00, [3] T+01:10:00, [4] T+01:40:00, and [5] at the end of the gambling session (max T+02:00:00).
	11	Gambling speed	Number of bets placed on the EGM during the gambling session over a given amount of time (ie, bets/min).	Assessed at the following time points from start of the gambling session in the laboratory: [0] T+00:00:00, [1] T+00:10:00, [2] T+00:40:00, [3] T+01:10:00, [4] T+01:40:00, and [5] at the end of the gambling session (max T+02:00:00).
	12	Gambling intensity (physical)	Money physically inserted in the EGM during the gambling session over a given amount of time (ie, $/min).	Assessed at the following time points from the start of the gambling session in the laboratory: [0] T+00:00:00, [1] T+00:10:00, [2] T+00:40:00, [3] T+01:10:00, [4] T+01:40:00, and [5] end of the gambling session (max T+02:00:00).
	13	Gambling intensity (all)	Money betted on the EGM during the gambling session over a given amount of time (ie, $/min). This is money used to “buy rounds on the EGM,” whether it's money physically inserted in the EGM or money won while gambling and betted again.	Assessed at the following time points from the start of the gambling session in the laboratory: [0] T+00:00:00, [1] T+00:10:00, [2] T+00:40:00, [3] T+01:10:00, [4] T+01:40:00, [5] end of the gambling session (max T+02:00:00).
Cognitions				
	14	Perceived self-control while gambling on EGMs	Participant’s perceived ability to control their gambling behavior (eg, sticking to their predetermined limits) over the gambling session’s total duration. Evaluated with a 7-point Likert scale (1 = “I never had control” to 7 = “I always had control”).	Assessed at the end of the gambling session.
	15	Change in perceived self-control while gambling on EGMs	Change between self-reported measure (past 12 months) and observed data in the laboratory	Past 12 months; end of the gambling session.

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Outcome category	Outcome number	Outcome	Description	Measurement time points
	16	Perceived behavioral effectiveness of prevention pop-up messages	Participant's perceived effectiveness of prevention pop-up messages on modifying their gambling behavior during the gambling session. Evaluated with two 7-point Likert scales about the perceived effects of the prevention pop-up messages on money betted and time spent during the gambling session (1="lowered gambling behavior a lot" to 7="heightened gambling behavior a lot").	Assessed at the end of the gambling session.
Emotions				
	17	General level of fun while gambling on EGMs	Participant's general enjoyment of gambling on EGMs over the gambling session's total duration. Evaluated with a 7-point Likert scale (1="I hated it" to 7="I loved it").	Assessed at the end of the gambling session.
	18	Change in general level of fun while gambling on EGMs	Change between self-reported measures (past 12 months) and observed data in the laboratory.	Past 12 months; end of the gambling session.
	19	Psychological reactance to prevention pop-up messages (between group)	Evaluated based on Dillard and Shen [84] method: (1) Induction check (4 items, 7-point Likert scale, 1="Strongly disagree, 7="Strongly agree"); (2) Anger (4 items, 7-point Likert scale, 1="Strongly disagree, 7="Strongly agree"); (3) Cognitive response (count of negative thoughts in relation to the pop-up messages); and (4) Attitude (7 word pairs, 7-point semantic differential scale).	Assessed at the end of the gambling session.

[a]EGM: electronic gambling machine.

Secondary Outcome

Table 4 shows the secondary outcome measures.

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Table . Secondary outcome measures.

Outcome category	Outcome number	Outcome	Description	Measurement time points
Feasibility: Recruitment potential				
	20	Volunteers	Number of people that answered the recruitment ad and wanted to either participate or get more information on the study.	N/A[a]
	21	Recruited	Number of people that qualified and agreed to participate in the study.	N/A
	22	Rejected	Number of people that volunteered to participate but did not qualify according to the inclusion and exclusion criteria.	N/A
	23	Refusal	Number of people that qualified for participation in the study but refused to do so after hearing the details of it.	N/A
	24	Refusal reasons	N/A	N/A
	25	Attrition	Number of people that qualified and agreed to participate in the study but desisted during their participation.	N/A
	26	Attrition vs previous study	Conversion from recruitment list from a previous study	N/A
Feasibility: Perceived realism				
	27	Gambling location type most resembling the session in the laboratory	Among a predetermined list of gambling location type (eg, bar, restaurant, casino, etc), the participant chose which of the gambling sessions in the laboratory resembled the most.	Assessed at the end of the gambling session
	28	Session in the laboratory versus gambling on EGMs in a bar/restaurant	Level of resemblance between a gambling session on EGMs[b] in a bar or restaurant and the gambling session in the laboratory. Evaluated with a 7-point Likert scale (1="Almost 100% different" to 7="Almost 100% the same").	Assessed at the end of the gambling session
	29	Similarities between sessions in the laboratory versus gambling on EGMs in a bar/restaurant	Things that were the same or very alike when comparing a gambling session on EGMs in a bar or restaurant and the gambling session in the laboratory. Participant lists all the resemblances that come to their mind.	Assessed at the end of the gambling session

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Outcome category	Outcome number	Outcome	Description	Measurement time points
	30	Differences between session in the laboratory versus gambling on EGMs in a bar/restaurant	Things that were not the same or not very alike when comparing a gambling session on EGMs in a bar or restaurant and the gambling session in the laboratory. Participant lists all the differences that come to their mind.	Assessed at the end of the gambling session
	31	What could be done to heighten the realism of the session in the laboratory	Things or aspects of the study that could be changed in order for the gambling session in the laboratory to be more like a real gambling session on EGMs in a bar or restaurant. The participant lists all that come to their mind.	Assessed at the end of the gambling session
	32	Effect of using one's own money on realism	Effect of gambling one's own money in this study on the level of realism. Evaluated with a 7-point Likert scale (1="It lessened the realism a lot" to 7="It heightened the realism a lot").	Assessed at the end of the gambling session
	33	Effect of using one's own money on realism (open-ended)	Effect of gambling one's own money in this study on the level of realism. Participants freely explain their perception of the said effect.	Assessed at the end of the gambling session
	34	Perceived correspondence between habitual gambling behavior and gambling behavior during the session in the laboratory	Participant's perception of how much their gambling behavior during their gambling session in the laboratory was representative (ie, how much it was the same) of their gambling behavior on EGMs in the past 12 months. Evaluated with a 7-point Likert scale (1="Almost 100% different" to 7="Almost 100% the same").	Assessed at the end of the gambling session
	35	Perceived correspondence between habitual gambling behavior and gambling behavior during the session in the laboratory (open-ended)	Participants' perception of how much their gambling behavior during their gambling session in the laboratory was representative (ie, how much it was the same) of their gambling behavior on EGMs in the past 12 months. Participants freely explain their perception.	Assessed at the end of the gambling session
Feasibility: Duplicity check				

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Outcome category	Outcome number	Outcome	Description	Measurement time points
	36	Protocol credibility	Participant's level of certitude when they were betting their own money and that they could lose money for real during the study. Evaluated with a 7-point Likert scale (1="Almost 100% certain they were going to get their money back at the end of the study" to 7="Almost 100% certain winnings and losses were real").	Assessed at the end of the gambling session
	37	Protocol credibility (open-ended)	Participants comment freely on their level of certitude that they were betting their own money and that they could lose money for real during the study.	Assessed at the end of the gambling session

[a]N/A: not available.

[b]EGM: electronic gambling machine.

Other Outcomes

Table 5 shows other outcome measures.

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Table . Other outcome measures.

Outcome category	Outcome number	Outcome	Description	Measurement time points
Messages recall				
	38	Free recall (yes or no)	Participant is asked if they saw any prevention pop-up messages during their gambling session in the laboratory. This is a yes or no question.	Assessed at the end of the gambling session
	39	Free recall (number)	If the participant declared that they saw prevention pop-up messages during their gambling session in the laboratory, they are asked how many there were. The same message presented twice counts as “2”.	Assessed at the end of the gambling session
	40	Free recall (content)	If the participant declared they saw prevention pop-up messages during their gambling session in the laboratory, they are asked to freely describe them (ie, content, graphical appearance, etc).	Assessed at the end of the gambling session
	41	Cued recall (yes or no)	The participant is presented with a list of prevention pop-up messages that could have been shown during the study. For each of them, they are asked to identify if they saw it or not.	Assessed at the end of the gambling session
	42	Cued recall (number)	If the participant declared that they saw prevention pop-up messages during their gambling session in the laboratory, they are asked how many there were. The same message presented twice counts as “2”. This is different from outcome 39 because the participant might recognize a message they had forgotten about or a message they saw but did not consider it a “prevention message.”	Assessed at the end of the gambling session

Statistical Methods

Sociodemographic variables, past 12 months of gambling-related variables, and PGSI category will be presented in a table with appropriate central tendency estimates. This table will be divided by assignation group.

A total of 3 statistical models will be used to analyze the outcomes presented in Tables 3 and 4. All these models will control for the time-varying covariate “gains-losses differential” (ie, remaining balance on the EGM at measured time point minus money inserted in the EGM from the start of the study). All models will also test the moderation effect of the following variables: gender (men or women), age (continuous), education (5 categories), and PGSI category (nonproblem, low risk, and moderate risk). Holm-Bonferroni correction [85] will be used to counteract family-wise error rate due to multiple comparisons in each model for each statistically significant categorical variable (ie, time for repeated measures ANCOVAs; moderators with ≥3 categories).

The first model uses ANCOVAs to examine the differences between the two groups at the end of the gambling session on outcome variables 1, 3, 4, 6 - 9, 14, 16, 17, and 19, separately.

The second model uses repeated measures ANCOVAs to examine the differences between the two groups at specific time points during the experiment corresponding to the presentation of the prevention pop-up messages in the experimental group. This model is computed on outcome variables 1 and 10 - 13, separately.

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The third model uses repeated measures ANCOVAs to examine the differences between self-reported measures (past 12 months) and the observed behaviors during the experiment. This model is computed on outcome variables 2, 5, 15, and 18, separately.

Secondary and other outcomes will be documented but will not be statistically compared. Descriptive estimates will be provided for each quantitative variable. Open-ended questions will be analyzed in a manner inspired by the thematic analysis method (see Textbox 3) [86].

Textbox 3. The 5 steps in analysis of open-ended questions.

1. Interviewer's notes are regrouped in a Microsoft Word document.
2. Raw data is carefully read, both by main author and another member of the research team, to extract categories of similar content.
3. Categories are refined by both coders.
4. Raw data is independently categorized in appropriate categories by both coders.
5. Intercoder agreement is calculated on all categorizations to ensure reliability.

Results

Recruitment began in February 2024 and concluded in December 2024. Results are expected to be published in 2026. No results are currently available.

Discussion

Principal Findings

The main objective of this study is to test the potential of pop-up messages as a prevention measure in a gambling setting. Effects of messages are measured on behaviors, cognitions, and emotions. The optimal benefit from the messages would be observing a reduction in money bet during the gambling session. However, other behavioral effects, like reduction in gambling intensity or session lengths, are considered indirectly beneficial because they foster conditions for further preventive actions. For example, all things being equal, a reduction in gambling intensity reduces the amount of money lost per unit of time. This, in turn, gives more time to the person gambling to think about their behavior and potentially stop their session with some money left. The improved realism of our research design heightens the confidence that the effects observed in our study can successfully be transposed to a real gambling setting.

Similarly, cognitive and emotional responses to the pop-up messages are of interest for the ease of adoption and indirect protection. Modifying cognitions is among the first steps in initiating behavioral change. Even if exposure to pop-up messages does not cause immediate reduction in gambling behavior, it is possible that they initiate a reflection about one's gambling habits. This may lead to behavioral change at some point in the future or make the person more amenable to other gambling prevention strategies. Another aspect to consider regarding cognitive and emotional response to pop-up messages is psychological reactance, which is "the motivational state that is hypothesized to occur when a freedom is eliminated or threatened with elimination" [87]. In essence, the theory of reactance posits that, when a person's freedom is threatened or removed (eg, being exposed to an RG pop-up message they feel is telling them how to feel or to act), they are motivated to restore it, whether directly by rebelling against the instructions (eg, gambling more) or indirectly, where the rebellion is done cognitively (eg, derogating the source of the message, denying there is even a threat, etc) [84,87-89]. Measuring how people cognitively and emotionally react to the pop-up messages is useful for understanding their effect. Hypothetical negative results could be due to psychological reactance. Data collected in this study, namely open-ended questions, could help understand how to better design pop-up messages to reduce psychological reactance. Furthermore, observing that pop-up messages do not negatively affect the participants' level of pleasure could be a good argument to reduce potential reticence of the industry to broaden their usage [90].

Finally, this study will generate valuable data regarding the feasibility of studies conducted in a laboratory setting with the use of real money. Results will help determine if concerns are founded regarding participants' potential uneasiness with gambling their own money in the laboratory and choosing not to participate in the study. Furthermore, results will show if the use of duplicity was successful in making participants believe they were really at risk of losing money. Feedback from participants could help improve this aspect if necessary.

Comparison With Previous Work

While this study diverges from Auer and Griffiths [28] on certain theoretical underpinnings of the pop-up messages, their conceptualizations are mostly similar. This study has the advantages of measuring more thoroughly the effect of pop-up messages. This is reflected in the fact that this study records individual performance instead of a collection of gambling sessions (with the possibility that some of them have been done by the same individual). Furthermore, this study incorporates a variety of indicators, behavioral and psychological, whereas Auer and Griffiths [28] only evaluate the effect on ending of the gambling session immediately after the apparition of the pop-up messages.

This study also improves on other studies conducted in a real gambling setting using objective observed behavioral data instead of self-reported ones [29,34,49,50]. This limits the potential imprecision associated with the recollection of past events.

Finally, this study innovates by the level of ecological realism of the main task. To our knowledge, no other study conducted in the laboratory has so closely replicated the conditions of a real gambling setting.

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Strengths and Limitations

This study's main strengths are the use of a highly realistic setting for the gambling session and the use of duplicity to make participants believe that they are risking their own money. Furthermore, the maximal possible gain (CA $500) is sufficiently high to elicit an incentive to gamble seriously even though the (perceived) level of risk. This level of realism has seldom been achieved in a laboratory setting. Another strength is the diversity of outcomes observed. More specifically, the use of open-ended questions on multiple aspects heightens the chance to be able to interpret unexpected results.

On the other hand, limitations include potential difficulties in recruiting enough participants. First, regular EGM gamblers do not constitute a relatively small population in which this study is conducted. Furthermore, being a regular EGM player significantly overlaps with probable pathological gambling [91,92], which the ethics committee prohibits us from recruiting. The exclusion of probable pathological gamblers could affect the generalizability of the results. While pathological gamblers would be better served by more intensive prevention measures (or even therapy), they could still theoretically benefit from RG pop-up messages. Therefore, if this study goes well, it would be pertinent to repeat it while including this vulnerable population. In the meantime, it is possible that the pop-up messages observed in this study are higher than if deployed in a real setting due to the exclusion of pathological gamblers.

A second limitation is the impossibility of programming the same sequence of gains and losses for all participants. This is due to hardware limitations on the EGM. While randomness should provide balance between both groups, there is always the possibility that one group is significantly "luckier" than the other, altering how they respond to RG pop-up messages [45,93]. This could limit our ability to observe an effect. The gains-losses differential (see the "Statistical methods" section) is also used as a covariate in the analysis to mitigate this potential source of bias.

Third and finally, it is possible that the protection effect from pop-up messages is best observed over repeated exposure over multiple sessions. Therefore, a single gambling session as used in this study might not be enough to observe the full effect. Nevertheless, short of committing to operate a real gambling venue, there are no real feasible solutions to the "single session" in a laboratory setting with the use of real money. Indeed, duplicity works so long as participants do not know they will be reimbursed for their losses. In a study setting, it is not feasible to keep their money longer than a single session because (1) a participant might not come back for another session and be unreachable, making it impossible for the researchers to give them their money; and (2) even assuming all participants stay engaged in the study to the end, some of them might incur financial hardship that is not compensated by recuperating their money at a later date (eg, a participant might need to pay their rent now, a problem not fixed by getting their money back after months).

Conclusion

This study will provide new insights on the efficacy of pop-up messages as a prevention measure for gambling as well as the appropriateness of laboratory studies as a substitute to a real-life setting.

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Data Availability

The datasets generated during this study are not publicly available due to the ethics committee not approving their release in open access. Some portion of the datasets may be available from the corresponding author on reasonable request, within the constraints to be specified by the ethics committee.

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Authors' Contributions

Conceptualization: BG
Methodology: BG, IG, SS, CJ
Investigation: BG
Supervision: IG, SS, CJ
Project administration: BG
Validation: BG, IG, SS, CJ
Resources: IG, SS, CJ
Writing – original draft: BG
Writing – review & editing: BG, IG, SS, CJ

Conflicts of Interest

Loto-Québec (LQ), the state-owned gambling operator for the province of Québec (Canada), is lending, free of charge, electronic gambling machines (EGMs) to use in laboratory studies at the Centre québécois d'éxcellence pour la prévention et le traitement du jeu (CQEPTJ), to which all authors are affiliated. LQ also provides technical support for the EGMs through Moneris, a third-party provider. This equipment loan is made without any scrutiny rights from LQ. LQ cannot and does not suggest study designs or research ideas; intervene in or comment on ongoing studies; intervene in or comment on manuscripts; get a firsthand look at preprint manuscripts; or get privileged access to research results. All talks with Moneris have always been strictly about technical aspects pertaining to the EGMs' operation (eg, maintenance on broken modules, tutorials on usage of the EGMs' utilities, etc).

Multimedia Appendix 1
Bar environment.
[PDF File, 737 KB - resprot_v14i1e75068_app1.pdf]

Multimedia Appendix 2
Responsible gambling information.
[PDF File, 4145 KB - resprot_v14i1e75068_app2.pdf]

Multimedia Appendix 3
Prevention pop-up messages.
[PDF File, 463 KB - resprot_v14i1e75068_app3.pdf]

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Abbreviations

EGM: electronic gambling machines
PGSI: Problem Gambling Severity Index
RG: responsible gambling

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Comparative Study of the Quality of Life of Patients With Ototoxicity Due to Platinum-Based Chemotherapy, With Hearing Aid Versus Those Without: Study Protocol for a Randomized Pilot Study—The PROTOTOX Study

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Abstract

Background: Platinum salts are widely used for the treatment of cancers, including head and neck cancers. Despite their efficacy, platinum salts can induce neurosensory disorders such as ototoxicity, tinnitus, and decreased hearing acuity. These side effects can have a major impact on the quality of life of patients and are not often considered after treatment.

Objective: The PROTOTOX study aims to compare the quality of life of patients with hearing aids in the case of ototoxicity due to platinum salt-based chemotherapy, according to 2 treatments: standard management without equipment versus standard management with equipment.

Methods: The PROTOTOX study is an open pilot prospective monocentric and randomized study executed through collaboration of the Institut de Cancérologie de Lorraine (nonprofit comprehensive cancer institute). A total of 52 patients with head and neck cancer undergoing platinum-based chemotherapy and presenting with hypoacusis will be included and followed by an ear, nose, and throat specialist. Audiometric testing will be performed, and eligible participants who consent will be randomized to either receive or not receive hearing aids (groups 1 and 2). The primary endpoint of this study is to compare the quality of life of the patients undergoing platinum-based chemotherapy presenting with hypoacusis according to 2 ways of care: standard care without hearing aid versus standard care with hearing aid. Secondary outcomes are the evaluation of the hearing and the tinnitus, the evaluation of the patients' satisfaction at the end of the study, and the evaluation of the patients' adherence to hearing aid in case of ototoxicity due to platinum-based chemotherapy.

Results: The study protocol has been opened and is actively recruiting participants. The protocol was launched on November 23, 2023, and data collection is ongoing and will be completed once all patients have completed the protocol. At least 27 patients have been recruited to date. The date of publication of the results is not yet known.

Conclusions: The PROTOTOX study aims at demonstrating that the huge impact of platinum-based chemotherapy on hearing abilities must be managed to maintain the patients' quality of life. Hearing aid is the solution experimented here.

Trial Registration: ClinicalTrials.gov; NCT05936034; https://clinicaltrials.gov/study/NCT05936034

International Registered Report Identifier (IRRID): DERR1-10.2196/71562

(JMIR Res Protoc 2025;14:e71562) doi:10.2196/71562

KEYWORDS

chemotherapy; equipment; hearing aid; hypoacusis; platinum salts

Introduction

Background

Platinum salts (cisplatin, carboplatin, and oxaliplatin) are alkylating agents widely used for the treatment of several cancers: bladder, head and neck, lungs, ovary, cervix, endometrium, breast, brain, thyroid, bone, and testes. Although very effective, the adverse effects of platinum-based cancer treatments are numerous: kidney failure; thrombocytopenia; leukopenia; peripheral neuropathies; vomiting; nausea; and decreased plasma levels of magnesium, calcium, and potassium. In addition, the administration of anticancer treatments based on platinum salts induces neurosensory disorders such as ototoxicity, tinnitus, and decreased hearing acuity.

Hearing loss is very common (≥1/10) and is found in approximately 31% of patients treated with a dose of 50 mg

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cisplatin m^{-2} [1]. The ototoxic potential of cisplatin puts patients at risk of hearing loss and leads to additional negative impact on the patients' quality of life. Administration of cisplatin causes ototoxicity with a highly variable incidence rate. This variability depends on the duration of treatment, the dose received, the method of administration, and the treatment of the population. Textbox 1 shows some examples of the incidence rates observed depending on the treatment and dose and the audiology test performed [2].

Textbox 1. Incidence rates observed depended on the treatment, dose, and the audiology test performed.

- 100% of 34 patients with head and neck cancers receiving cisplatin-containing chemotherapy and concomitant radiotherapy
- 55.1% of 107 patients receiving cisplatin-containing chemotherapy, regardless of cancer type
- 31% up to 8 kHz and 47% up to 16 kHz with air and bone conduction tone audiometry (0.125-16 kHz) of 60 patients with locally advanced head and neck cancer, receiving cisplatin-containing chemotherapy and concomitant radiotherapy
- 15% of 60 patients receiving cisplatin-containing chemotherapy: 12% of 51 patients in the low-dose group; 33% of 9 patients in the high-dose group

A significant component of the acute hearing loss seen in patients undergoing chemotherapy relates to local inflammation, middle ear effusions, and eustachian tube obstruction. This tends to improve significantly, even resolving fully, over time as the inflammation resolves.

The cytotoxic effect of cisplatin is dose-dependent, and therefore less significant in multidrug therapy treatments, depending on the dosing used in the regimen [3]. There are multiagents that use cisplatin at a high dose. It is higher in patients receiving cumulative doses [4] or in a pediatric population [5]. The ototoxicity of cisplatin is often bilateral, symmetrical, and irreversible, mainly affecting high frequencies (4000-8000 Hz), whether or not associated with tinnitus [2]. Hearing impairment at frequencies between 250 and 6000 Hz (normal hearing range) is measured in 10%-15% of patients treated with cisplatin [6]. In rare cases, unilateral hearing loss has been reported depending on the location of the tumor and associated treatments [7]. Hearing loss caused by platinum agents is permanent [8].

Single or bilateral, ototoxicity becomes more frequent and more severe with the intensity and repetition of doses. It is increased by prior hearing loss and association with ototoxic drugs (loop diuretics like furosemide, or aminoglycoside antibiotics like gentamicin). Patients receiving carboplatin and oxaliplatin have lower ototoxicity, ranging from 15% of patients, with abnormalities located at the high frequencies (4000 - 8000 Hz).

A recent study estimated the prevalence of ototoxicity and its associated risk factors in a cohort of 145 testicular cancer survivors who received cisplatin-based first-line chemotherapy [9]. About 74% reported ototoxicity: 68% tinnitus, 59% hearing loss, and 52% both. Survivors with tinnitus were more likely to report hypercholesterolemia (P=.008) and hearing difficulties (P<.001). Tinnitus was also significantly related to age at the time of the survey (OR=1.79; P=.003) and the cumulative dose of cisplatin (OR=5.17; P<.001). Risk factors for hearing loss included age at the time of the survey (OR=1.57; P=.04), hypercholesterolemia (OR=3.45; P=.007), cumulative cisplatin dose (OR=1.94; P=.049) and family history of hearing loss (OR=2.87; P=.07). In conclusion, the authors recommend referring patients to audiologists before, during, and after cisplatin treatment.

Since then, clinical trials have been developed by offering drugs related to supportive care to limit the cytotoxic effect of cisplatin. Another proposes a thiosulfate treatment that results in a reduction in the neoplastic activity of cisplatin but does not show a significant result [10]. A study conducted in rats showed a decrease in the ototoxicity of cisplatin with the administration of a preventive treatment of diethyldithiocarbamate [11].

One review addressed 11 studies that looked at quality of life and chemotherapy-induced toxicities, such as hearing loss and tinnitus [12]. Overall, the results revealed that people treated with platinum-based chemotherapy, particularly cisplatin, had significantly more hearing loss and tinnitus than the population who did not receive it, and higher doses were correlated with persistent symptoms. These results are consistent with those in the literature as it is reported that, on average, 60% - 70% of adult patients experienced ototoxicity when treated with cisplatin [13-16]. This review found that people with tinnitus and hearing loss were more likely to have a lower quality of life.

According to an INSERM survey carried out in 2018 [17], hearing impairment due to cancer treatments is estimated at 39.7% of respondents, 5 years after a cancer diagnosis. A study summarized the impact of the long-term effects of hearing loss, tinnitus, and balance in children and adults treated with platinum-based chemotherapy [18]. The authors conclude that ototoxicity can lead to communication difficulties, subsequent social withdrawal, impaired cognitive functions, and repercussions on professional activity. Ototoxicity was linked to deficits in cognition, child development, and school performance. Employment and ease of daily life were disrupted by deafness and tinnitus. Depression and anxiety were linked to ototoxicity. The authors advocate early intervention for better management of ototoxicity, thereby improving the quality of life of affected patients. Similarly, tinnitus is associated with increased anxiety, depression, insomnia, and decreased concentration [19-22].

There is a clinical study on the ototoxic effects of chemotherapy on patients' quality of life [23]. In this study, 20 patients were asked about their perception of the ototoxic effect with semistructured interviews based on 2 main themes (ototoxicity-related quality of life and cancer-related quality of life). Subthemes included the impact of ototoxicity, hearing, tinnitus, clinical experience, audiological assessments, and the impact of treatment, cancer and chemotherapy, other toxicities, patient information, and reflections. Recruited patients describe

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fear of worsening symptoms, tinnitus-related fatigue, reduced sleep, and frustration. We can also note a decrease in their social interactions. It is described that patients would have liked to have had more information and follow-up on the ototoxicity of their chemotherapy. The study concludes that ototoxicity can have a negative impact on quality of life, especially on social life and fear of hearing loss and worsening tinnitus. The authors also report a lack of awareness among patients and clinicians about auditory monitoring and the management of patients receiving platinum-based chemotherapy. The main limitation of this study is that medical history was declared by the patients themselves and not by a collection of medical records due to lack of access. This can lead to unreliable data. The authors raised the issue where participants could not remember the type of chemotherapy they had received. Thus, their hearing loss could be related to age or noise, and not to ototoxic chemotherapy.

Need for the Study

An observational case-control study analyzed the audiological outcomes and quality of life of cancer and noncancer patients [24]. In the oncology group, 32 participants had to have an anatomopathological diagnosis of neoplasia and who had undergone radiotherapy and chemotherapy with cisplatin. Hearing loss was assessed by conventional tonal audiological examination and quality of life by the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36). It is a multidimensional questionnaire consisting of 36 questions divided into 8 domains: functional capacity, physical aspects, pain, general health, vitality, social aspects, emotional aspects, and mental health. The results were assessed by assigning scores for each question, which were transformed on a scale of 0-100, where 0 corresponded to a poorer quality of life and 100 to a better quality of life. The results indicate that 35.2% of patients had hearing loss in the oncology group. Textbox 2 shows the results of the analysis of the SF-36 questionnaires yielded scores.

Textbox 2. Results of the analysis of the 36-Item Short-Form Health Survey (SF-36) questionnaires yielded scores.

- 70.47: functional ability
- 56.25: physical aspects
- 48.91: pain
- 53.28: general health
- 40.69: vitality
- 72.13: social aspects
- 48.91: emotional aspects
- 49.44: mental health

A change greater than 5 points on a SF-36 subscale is generally considered clinically meaningful, indicating a noticeable improvement or decline in a patient's health status. Clinically, such a change may reflect enhanced physical functioning (eg, easier walking or daily activities), reduced pain, increased vitality, improved emotional well-being, or greater social participation. It represents a level of change that patients perceive as beneficial or impactful in their daily lives, beyond mere statistical significance. In a perfectly functional state, individuals typically score between 85 and 100 across all domains, reflecting full physical, emotional, and social well-being. A limited state, such as in chronic but manageable conditions, yields scores between 40 and 70, indicating moderate impairments in areas such as mobility, pain, or vitality. In contrast, a disabled or severely impaired state is characterized by scores below 40 in multiple domains, reflecting significant physical limitations, chronic pain, poor mental health, and reduced quality of life.

The SF-36 quality of life score is significantly different from the control group in these two domains: general health and mental health.

Unlike previous studies that focused primarily on pharmacological otoprotectants, which often present limitations in efficacy or interfere with chemotherapy's antitumor effects, this study explores a noninvasive, supportive approach through the early, systematic use of hearing aids—an area that remains largely unstudied. To date, no clinical trial has specifically evaluated the impact of proactive hearing aid use on quality of life outcomes in patients receiving platinum-based chemotherapy, despite growing evidence of the burden of ototoxicity. This pilot study addresses a critical gap by investigating a practical, immediately deployable intervention to manage chemotherapy-induced hearing loss, aiming to improve adherence and patient well-being without altering oncologic treatment protocols [25,26].

Our hypothesis is that a systematic hearing aid for patients suffering from ototoxicity of chemotherapy from the start of treatment would bring a benefit to these patients, by improving their quality of life. A hearing aid is a noninvasive intervention, and that is why we choose it over other interventions. The improvement in patients' quality of life is assessed by the SF-36 quality of life questionnaire. This questionnaire was used in a study to demonstrate a significant relationship between emotional aspects and the presence of tinnitus as well as hearing loss [24].

Regarding the collective benefit of this study, the generalization of the patients' equipment during their chemotherapy protocol would allow an increase in quality of life and better adherence to treatment.

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Objectives

The primary objective of the PROTOTOX study is to compare the quality of life of patients presenting with ototoxicity due to platinum-based chemotherapy following 2 different ways of care: standard management without hearing aid versus standard management with hearing aid. The secondary objectives are (1) to evaluate and compare hearing and tinnitus in patients with hearing aid and ototoxicity induced by platinum-based chemotherapy and patient satisfaction at the end of the study in the 2 groups (control and experimental), (2) to assess patients' adherence to hearing aid in case of ototoxicity due to platinum-based chemotherapy.

Methods

The PROTOTOX study is an open and prospective interventional monocentric pilot study with minimal risks and constraints. The study is registered on French Competent Authority (ID-RCB: 2023-A02141-44) and ClinicalTrials.gov (NCT05936034). The study is randomized into the control group, that is standard care without hearing aids, and the experimental group, standard care with hearing aids.

Standard care will entail an audiometric test and classical control visits.

Ethical Considerations

Regulatory Requirements

The study will be conducted in accordance with the ethical principles of the latest version of the Declaration of Helsinki, The Good Clinical Practice of 24 November 2006 defined by the International Conference on Harmonization (ICH-E6) [27], the Data Protection Act No. 78‑17 of 6 January 1978 as amended by Law No. 2004-801 of 6 August 6, 2004 on the protection of individuals regarding the processing of personal data [28], The Bioethics Law No. 2004‑800 of 6 August 2004 [29], Decree No. 2016‑1537 of 16 November 2016 on research involving human beings [30], the Decree of 7 May 2017 establishing the list of research mentioned in 2° of Article L. 1121‑1 of the Public Health Code [31], and the Decree of 9 May 2017 amending certain regulatory provisions relating to research involving human beings [32].

- Data Protection Act No. 78‑17 of 6 January 1978 as amended by Law No. 2004-801 of 6 August 6, 2004 on the protection of individuals regarding the processing of personal data [28]
- The Bioethics Law No. 2004‑800 of 6 August 2004 [29]
- Decree No. 2016‑1537 of 16 November 2016 on research involving human beings [30]
- Decree of 7 May 2017 establishing the list of research mentioned in 2° of Article L. 1121‑1 of the Public Health Code [31]
- Decree of 9 May 2017 amending certain regulatory provisions relating to research involving human beings [32]

Ethics Committee, Competent Authority, and CNIL (National Data Privacy Commission)

Before carrying out research on human beings, the sponsor is required to submit the project for approval to an Ethics Committee with the competence for the location in which the lead investigator practices and for information to the French health product safety agency (ANSM). The request for an opinion on the intervention research project with minimal risks and constraints is sent to the committee and the competent authority by the sponsor.

As such, the protocol was submitted to the Ethics Committee (Comité de Protection des Personnes Sud Est I) on November 11, 2023, which issued a favorable opinion (2023-A02141-44) and was sent to the ANSM for information, No. 23.03486.000352.

Requests for substantial changes to the initial projects will also be sent by the promoter to the committee for its opinion and to the competent authority for information.

The study complies with the MR-001 methodology published by CNIL (national data privacy commission) [33].

Insurance

In accordance with the current legislation of the Public Health Code [34], the sponsor (Institut de Cancérologie de Lorraine) has maintained liability insurance for the duration of the study to cover its liabilities and those of any other participating parties in accordance with the regulations in force under number B1339CTLICNWL22-73 with Lloyd's Insurance Company.

Patient Information and Informed Consent

Prior to carrying out intervention research with minimal risks and constraints on a person, the free, informed, and express consent (written or oral) of the person must be obtained after he or she has been exhaustively informed, by the investigator, during a consultation and after a sufficient period of reflection. The sponsor may ask the person participating in research at the time the person gives his or her informed consent when it is required to agree to the use of his or her data in subsequent research exclusively for scientific purposes. The person may withdraw his or her consent to this further use or exercise his or her right to object at any time.

Similarly, if an amendment to the protocol were to lead to a revision of the information forms intended for patients participating in the research and if it requires the collection of new consent, the request sent to the Ethics Committee concerned for opinion shall include a description of the procedures envisaged for obtaining this new consent.

For tests intended to perform genomics or proteomics analyses, the information form must specify the type of research that will be conducted. The use of these samples for a medical or scientific purpose other than that for which they were taken or collected is possible, unless the person from whom the sampling or collection was carried out, duly informed in advance of this other purpose, objects. The obligation to provide information may be waived when it is impossible to find the person concerned, or when one of the advisory Ethics Committees

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(Comité de Protection des Personnes) referred to in Article L. 1123‑1, consulted by the person responsible for the investigation, does not consider this information necessary [35].

This personal information must be kept in the file of the participating physician and treated in strict confidentiality but must be reviewable by the appropriate authorities and duly authorized people.

According to Article 1122-1-1, if the person taking part in research has withdrawn his or her consent, this withdrawal does not affect the activities carried out and the use of the data obtained based on the informed consent expressed before it was withdrawn [36].

Study Population

The PROTOTOX study is proposed to patients with head and neck cancer managed by a platinum-based chemotherapy at the Institut de Cancérologie de Lorraine. Textbox 3 includes the inclusion and exclusion criteria.

Textbox 3. Inclusion and exclusion criteria.

Inclusion criteria

- Patient aged 18 years or older
- Patient on treatment with platinum-based chemotherapy, with treatment-consistent hearing loss or with a worsening of existing hearing loss consistent with the start of platinum-based chemotherapy treatment
- Patient whose hearing loss is confirmed by audiometric testing
- Patient is able to and willing to follow all study procedures in accordance with the protocol
- Patient who understood, signed, and dated the consent form
- Patient affiliated with the social security scheme

Noninclusion criteria

- Pregnant or breastfeeding woman
- Persons deprived of liberty or under guardianship (including curatorship)
- Inability to undergo medical monitoring of the trial for geographical, social, or psychological reasons
- Patient with a contraindication to wearing hearing aid
- Patient already fitted with a hearing aid
- Patient already included in a protocol including an experimental molecule
- Patient who has not started treatment with platinum-based chemotherapy
- Tinnitus-only patient without hearing loss

Sample Size Calculation

A study estimated a mean quality of life score by the SF-36 questionnaire at 55 with a standard deviation of 20 in a population of 32 patients where the ototoxicity rate was 35.2% [24]. In our population with 100% ototoxicity, the expected SF-36 score in the control group would be lower (mean score less than 55) and less variable (standard deviation less than 20).

The justification for the number of subjects required is based on the size of the anticipated effect [37]. A comparison of the two groups (control and experimental) via an analysis of covariance (ANCOVA) adjusted to the baseline (estimated scores at baseline) will be performed to meet the primary objective.

Under the assumption of a common standard deviation of 15 points, an intra-group correlation coefficient r=0.8 (correlation between baseline and follow-up measures) [38], a statistical power level of 80%, and an alpha risk of 5%, a sample size of 26 patients per group will detect a minimum difference of 7 points between the control and experimental groups (7/15=0.46, an average effect size). If the effect size is smaller (difference less than 7 points), the results of the ANCOVA model will therefore not be statistically significant. In this case, we can use SF-36 estimates to accurately calculate the number of subjects for a larger study.

Statistical Analysis

Clinical-pathological characteristics of the patient, SF-36 scores, audiometric/acouphenometric measures, and patient satisfaction will be described in each group (control and experimental), in Baseline, M1, M3, and M6. Quantitative parameters will be described by mean (SD), median, min–max, and 1st and 3rd quartiles. Qualitative parameters will be described by frequency and percentage.

To meet the main objective, the overall SF-36 score of quality of life will be described in each group, and the normality of the data will be tested by the Shapiro-Wilk method. A comparison of the scores of the 2 groups in baseline and follow-up at the first month (M1), third month (M3), and sixth month (M6) via a Student t test will be used if the normality of the distribution has been verified; otherwise, a Wilcoxon Mann-Whitney U test will be used.

An ANCOVA will be performed to compare the scores of the 2 groups at the M1, M3, and M6 follow-ups by adjusting on the

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observed scores in baseline (initial state of the patient score). Given the limited sample size, stratification will be performed only on the type of treatment, which is most likely to influence both the severity of ototoxicity and the response to hearing rehabilitation. Other variables such as cancer type and cumulative dose will be included as covariates in the ANCOVA model or explored in sensitivity analyses.

To meet secondary objectives, the patients' hearing will be characterized by a binary qualitative variable (worsening or stagnation). It will be described in each group according to follow-up in M1, M3, and M6 and will be compared by a χ^2 test. The same analysis will be performed for the appearance of tinnitus measured by an incidence rate. A Student test will be used to compare patient satisfaction from the 2 groups if the data are normally distributed; otherwise, a Wilcoxon Mann-Whitney test will be used. The adherence rate is described by the proportion of patients who completed the 6 months of protocol follow-up with the wearing of the hearing aid among the patients randomized to the experimental group. Censored data (patients who died or were lost to follow-up before the end of follow-up) will be considered in estimating patient adherence rates.

Statistical analyses will be performed using RStudio software version 2022.07.2+576 (developed by Joseph Allaire). The materiality threshold is set at 5%.

Study Procedures

Information and Consent

Patients coming to the Institut de Cancérologie de Lorraine for cancer treatment with platinum-based chemotherapy and presenting with hearing loss will be referred to a clinical ear, nose, and throat (ENT) specialist (principal investigator of the study).

The ENT specialist will suggest that the patient undergo an audiometric and tinnitus test to confirm the hearing loss. If the audiometric and tinnitus test confirms the patient's hearing loss, and if all other eligibility criteria are verified, the principal investigator will present the PROTOTOX study to the patient.

After a period of reflection, the patient's free, informed, and signed consent will be collected, and the patient will be included in the study. Patients whose audiometric and tinnitus tests do not confirm hypoacusis will continue their usual care.

Inclusion and Randomization

Patients will be included in the study via the CleanWeb website. After signing consent and completing the V0 baseline visit, they will be randomly assigned (1:1 simple randomization) to the control or experimental group.

The inclusion assessment (V0) includes (Textbox 4):

- Control group: standard care without hearing aid
- Experimental group: standard care with hearing aid

Textbox 4. Proceedings of the inclusion assessment.

For all patients:

- A consultation with an ear, nose, and throat (ENT) specialist at the institute with an audiometric assessment carried out by an audiogram and a tinnitus assessment, according to the recommendations related to the treatment
- The collection of the 36-Item Short-Form Health Survey (SF-36) quality of life questionnaire completed by the patient
- The collection of treatments received with platinum salt: molecules, frequency, doses, and an inquiry about other ototoxic medications
- The collection of adverse events greater than 2 or having a significant impact on treatment (these include renal function and electrolyte derangements)
- The date of signing of consent and date of inclusion
- Randomization date and randomization arm

For experimental group only:

- The reference number of the hearing aid provided to the patient

Patients in the experimental group will be referred to certified hearing aid specialists from a preapproved network, who will follow a standardized fitting protocol, including device calibration, patient instruction, and adjustment follow-ups. Systematic use will be encouraged, targeting at least 6 hours/day, and adherence will be self-reported and recorded at each follow-up.

Simple randomization was chosen due to the exploratory nature and small sample size (n=52) of this pilot study, which primarily aims to assess feasibility and preliminary effects. While we acknowledge the risk of imbalance in key prognostic factors (eg, age, baseline hearing, cumulative cisplatin dose, prior ototoxic drugs), these variables will be collected and adjusted for in the planned ANCOVA analyses. Stratified or minimization techniques will be considered in future larger trials to enhance group comparability.

Follow-Up Visits

All follow-up visits will be scheduled during those taking place as part of the care in order to avoid the patient having to travel specifically for research.

Follow-up visits (V1 and V2) are carried out by the institute's clinical ENT specialist: for patients in the control group at 1 (V1) and 3 (V2) months after randomization and for patients in the experimental group at 1 (V1) and 3 (V2) months after randomization and equipment (M1 and M3).

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During these visits, and for all patients in the study, the institute's clinical ENT specialist will perform a clinical examination and an audiometric and tinnitus examination. The patient will complete the SF-36 quality of life questionnaire.

The follow-up reports (V1 and V2) are included in Textbox 5.

Textbox 5. Proceedings of the follow-up reports.

For all patients:

- An ear, nose, and throat (ENT) consultation with an ENT specialist from the institute with an audiometric assessment carried out by an audiogram and a tinnitus assessment, according to the recommendations related to the treatment
- The collection of the 36-Item Short-Form Health Survey (SF-36) quality of life questionnaire completed by the patient
- The collection of treatments received with platinum salt: molecule, frequency, and doses
- The collection of adverse events greater than 2 or having a significant impact on treatment

For the experimental group only:

- The collection of the time the hearing aid has been worn
- Adverse effects related to the wearing of the hearing aid: damage to the ear canal, embarrassment, autophony, occlusion, earwax plug, and need for hearing aid adjustment
- Possible dysfunctions of the hearing aid

End-of-Study Visit

The end-of-study visit (V3) is carried out by the institute's clinical ENT specialist: for patients in the control group 6 months after randomization and for patients in the experimental group 6 months after equipment (M6).

This visit will be scheduled when the patient arrives as part of his/her standard care.

During this visit, and for all patients in the study, the institute's clinical ENT specialist performs a clinical examination and an audiometric and tinnitus examination of the patient; the patient will complete the SF-36 quality of life questionnaire and a satisfaction questionnaire. At the end of the V3 visit, patients in group 2 only will give the hearing aid back to the clinician.

Following this visit, all patients are discharged from the study and go on with their care according to the recommendations specific to their pathology.

The end-of-treatment assessment (V3) is included in Textbox 6.

Textbox 6. Proceedings of the end-of-treatment assessment.

For all patients:

- An ear, nose, and throat (ENT) consultation with an ENT specialist from the institute with an audiometric assessment carried out by an audiogram and a tinnitus assessment, according to the recommendations related to the treatment
- The collection of the 36-Item Short-Form Health Survey (SF-36) quality of life questionnaire completed by the patient
- The collection of treatments received with platinum salt: molecule, frequency, and doses
- The collection of adverse events greater than 2 or having a significant impact on treatment

For the experimental group only:

- The collection of the time the hearing aid has been worn
- Adverse effects related to wearing the hearing aid: damage to the ear canal, embarrassment, autophony, occlusion, earwax plug, and need for hearing aid adjustment
- Possible dysfunctions of the hearing aid

Description of the SF-36 and Satisfaction Questionnaires

The quality of life questionnaire is based on the SF-36 self-questionnaire [39]. The items in SF-36 are divided into 8 different areas (Textbox 7).

Except for questions about the general change in health status, patients are asked to answer based on the last 4 weeks.

The SF-36 is a validated and widely used instrument for assessing health-related quality of life across diverse patient populations. Its inclusion in this clinical research protocol is justified by its ability to capture a broad range of physical, emotional, and social health domains through 8 subscales, including physical functioning, role limitations, bodily pain, vitality, general health perceptions, and mental well-being. This multidimensional structure allows for a comprehensive evaluation of the patient's perceived health status, which is especially relevant in conditions such as ototoxicity, where functional impairments may not be life-threatening but can significantly impact daily life. Moreover, the SF-36 is sensitive

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to clinical changes over time and enables the detection of both improvements and deteriorations in quality of life following an intervention, such as the use of hearing aids. Its standardized format also facilitates comparisons with normative data or across studies. Finally, the ability to compute both physical and mental component summary scores provides flexibility for both global and domain-specific analysis, making the SF-36 a robust and appropriate tool for evaluating the impact of this intervention on patients' overall well-being [40].

The satisfaction questionnaire is based on a numerical scale starting at 0 (not satisfied) to 10 (very satisfied).

Textbox 7. Items of the 36-Item Short-Form Health Survey (SF-36) questionnaire.

Physical component:

- Physical activity (10 items)
- Physical limitations (4 items)
- Physical pain (2 items)
- Perceived health (5 items)

Mental component:

- Life and relationships with others (2 items)
- Mental health (5 items)
- Limitations due to mental state (3 items)
- Vitality (4 items)

Other:

- Change in perceived health (1 question): The respondent is asked to rate his or her current health status by comparing it to his or her health status 1 year earlier

Study Stopping Rules

Research may be suspended or stopped by the sponsor in consultation with the coordinator or the Ethics Committee (Comité de Protection des Personnes) for insufficient patient recruitment.

Premature Withdrawal From the Study

Premature withdrawal exits may be justified by the following reasons: withdrawal of consent, lost from sight, patient no longer wishing to wear the hearing aid (considered a failure), death, and loss of hearing aid.

Patients participating in the research can withdraw their consent and ask to leave the trial at any time and for any reason, without having to justify themselves, without losing their right to be treated by their doctor.

Patients will continue to participate in the study whether the dose of platinum-based chemotherapy is modified following an adverse event and according to the recommendations of the patient's primary care physician, and whether the administration of platinum-based chemotherapy is permanently discontinued during the study.

Projected Study Schedule

The estimated duration of recruitment is 18 months. The estimated duration of each participant from the signing of the consent until 6 months after equipment is 8 months maximum. The estimated duration of the project is 36 months, including the recruitment period, the follow-up period, quality control (monitoring), and statistical analysis.

Data Collection

Data on hearing aid usage, adverse events, and satisfaction will be collected through standardized electronic case report forms and stored securely on the CleanWeb platform. Feasibility will be assessed by the proportion of patients who accept and adhere to the hearing aid intervention, while acceptability will be evaluated using patient-reported satisfaction scores and qualitative feedback collected during the final visit (V3).

Figure 1 describes the timeline of the study. Table 1 gives a summary of the investigations performed during the study.

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Figure 1. Timeline of the study.

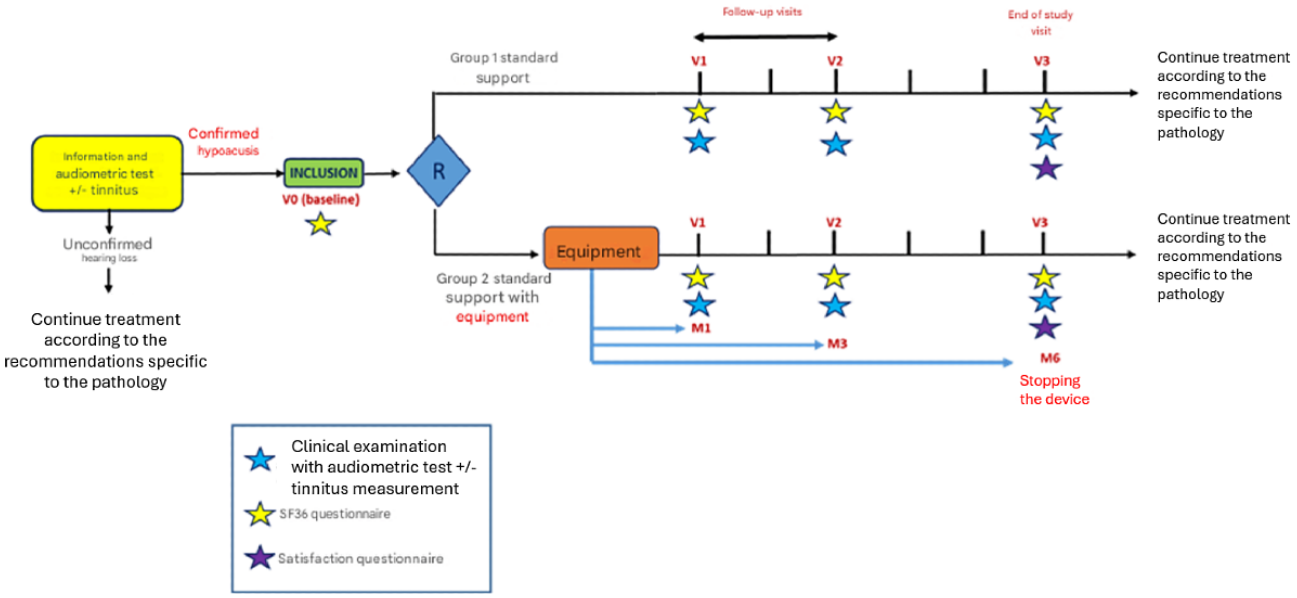

Table . Summary table of investigations.

Visits	Assessment of inclusion (visit 0)	Follow-up report (visit 1 at the 1-month follow-up)	Follow-up report (visit 2 at the 3-month follow-up)	End-of-study assessment (visit 3 at the 6-month follow-up)
Research data				
For all patients				
Inclusion/noninclusion criteria	X			
Signed informed consent	X			
Randomization	X			
SF-36[a] quality of life questionnaire	X	X	X	X
Satisfaction questionnaire				X
For group 2 patients only				
Hearing aid reference	X			
Worn time of the hearing aid		X	X	X
Adverse effects of wearing a hearing aid		X	X	X
Collection of hearing aid malfunctions		X	X	X
Data collected as part of care (for all patients)				
ENT[b] consultation	X	X	X	X
Audiogram	X	X	X	X
Tinnitus	X	X	X	X
Adverse events		X	X	X
Administration of platinum salt treatment		X	X	X

[a]SF-36: 36-Item Short-Form Health Survey.

[b]ENT: ear nose and throat.

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Primary Outcomes

The quality of life of patients with ototoxicity due to platinum-based chemotherapy treatment will be assessed using the SF-36 score. The questionnaire consists of 36 questions divided into 8 domains: functional capacity, physical aspects, pain, general health, vitality, social aspects, emotional aspects, and mental health. The calculation of the score is a scale from 0 to 100, where 0 corresponds to a worse quality of life and 100 to a better quality of life [39,41].

In this study, quality of life will be assessed by an overall score calculated by the average of the observed scores across the 8 domains. It will be assessed at baseline before randomization in order to measure the initial score of the patient's quality of life, then during the follow-up after randomization: M1, M3, and M6 of follow-up.

Secondary Outcomes

Hearing and tinnitus occurrence in patients with chemotherapy-induced ototoxicity will be assessed by Hertz/Decibel encryption using the Interacoustics Diagnostic Audiometer AD229b.

The hearing of patients will be characterized by 2 modalities: aggravation or stagnation. The appearance of tinnitus will be measured by an incidence rate.

Satisfaction will be measured at 6 months (end of the study) by a numerical scale from 0 to 10 (0: not satisfied; 10: very satisfied).

Patients' adherence to hearing aid use in cases of ototoxicity due to chemotherapy treatment will be assessed by an adherence rate which is defined by the proportion of patients who have completed the 6 months of protocol follow-up with hearing aid use among patients randomized to the experimental group (hearing aid).

Results

Experiments are underway with patients already enrolled, but the study is actively recruiting other participants. The protocol was launched on November 23, 2023, and data collection is ongoing and will be completed once all patients have completed the protocol. At least 27 patients have been recruited to date. The date of publication of the results is not yet known.

Discussion

The aim of this study is to determine if hearing aids improve quality of life in platinum-related hearing loss.

Numerous papers in the literature indicate that hearing loss can be followed by severe psychosocial consequences with a decrease in mood and quality of life [42]. In a general population, a study concludes that half of the 158 adults with hearing loss recruited before hearing aid fitting want to renew their hearing aid [43]. In addition, the authors note that the quality of life of patients with hearing loss was like that of the general population, but poorer than in many serious chronic diseases.

Improvement of hearing loss and tinnitus can significantly improve patients' daily lives and better tolerability and adherence to treatment [44,45]. In the long term, we can expect a proposal for systematic hearing aids for patients suffering from ototoxicity of chemotherapy. The aim of the study is to offer patients under chemotherapy a better quality of life. A study reveals that only 33% of health professionals know how to manage the ototoxic effects of chemotherapy [2]. The protocolization of care by hearing aid would allow a democratization of the practice in health institutes.

The heterogeneity of ototoxicity induced by platinum-based chemotherapy, along with potential clinical and environmental covariates, can significantly affect the outcomes and interpretation of a clinical study evaluating the effectiveness of hearing aids in affected patients. Variability in the severity and pattern of hearing loss—driven by factors such as cumulative dose, type of platinum agent, age, renal function, genetic susceptibility, and co-exposure to other ototoxic agents—may lead to wide interindividual differences in auditory deficits. This can increase data dispersion, reduce statistical power, and obscure the true impact of hearing aids. Additionally, confounding variables such as cognitive status, socioeconomic factors, comorbidities, prior hearing aid use, and time since treatment may influence both hearing loss severity and responsiveness to auditory rehabilitation, thereby threatening the study's internal validity. These factors also pose challenges to external validity, as generalizing findings for a broader patient population becomes more complex.

Ototoxicity induced by platinum-based chemotherapy is generally irreversible or only partially reversible. Hearing loss typically develops during or shortly after treatment and then stabilizes. Consequently, assessment intervals at 1 month (M1), 3 months (M3), and 6 months (M6) posttreatment are strategically chosen to capture the onset, progression, and plateau phases of ototoxicity. These points enable time evaluation of hearing impairment and the effectiveness of rehabilitative interventions such as hearing aids.

Extending follow-up to 12 months (M12) is considered less informative, as significant further recovery or deterioration is uncommon beyond 6 months. Additionally, longer follow-up periods may increase patient attrition and study burden without providing meaningful additional data. Therefore, focusing on the first 6 months posttreatment balances scientific rigor with practical considerations, ensuring robust and clinically relevant data collection.

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Data Availability

All data and information concerning the patient will be kept strictly confidential. Persons with direct access in accordance with the legislative and regulatory provisions in force, in particular Articles L. 1121-3 and R. 5121-13 of the Public Health Code (eg, investigators, persons in charge of quality control, monitors, clinical research assistants, auditors and any persons called upon to collaborate in the trials) shall take all necessary precautions to ensure the confidentiality of information relating to investigational medicinal products, the trials, the persons who are eligible for them, and in particular with regard to their identity and the results obtained. The data collected by these people during quality checks or audits are then anonymized.

Data properties

The investigator undertakes, for himself and for all those who may be required to follow the progress of the study, guarantee of the confidentiality of all information provided by the Institut de Cancérologie de Lorraine until the publication of the results of the trial. This obligation of confidentiality will not apply to information that the investigator may communicate to patients in the context of their participation in the study or to information already published.

The investigators undertake not to publish, disclose, or use, in any way whatsoever, directly or indirectly, scientific or technical information in connection with the study.

Nevertheless, in accordance with Article R. 5121-13 of the Public Health Code, the institute and the coordinating investigator may give information relating to the study to (1) Minister for Health and (2) Medical inspectors of public health.

All the data in the study are the property of the Lorraine Cancer Institute, which will be able to dispose of them freely.

Authors' Contributions

Data collection and analysis: RM, YF
Methodology: RM
Revision of the paper: RK
Study concept: GD, RM, YF

Conflicts of Interest

None declared.

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Abbreviations

ANCOVA: analysis of covariance
ENT: ear, nose, and throat
SF-36: 36-Item Short-Form Health Survey

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Promoting Physical Activity and Preventing Falls Among Older Adults in a Nursing Home Setting: Protocol for Development and Implementation of the BeSt Age Mobile App

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Abstract

Background: Most nursing home residents do not meet physical activity guidelines. Many interventions to promote physical activity and prevent falls in nursing home residents have low adherence rates, lack a theoretical foundation, or require much time from staff for preparation or delivery.

Objective: This study aims to describe the rationale, development, and implementation approach of the BeSt Age app through a cluster randomized controlled trial. We also provide baseline characteristics of the study sample and discuss possible implications for further app developments.

Methods: We iteratively developed a novel, tablet-based mobile app (BeSt Age) that enables nursing home staff to deliver individualized physical exercise training to residents with or without motor or cognitive impairments. The app was designed and developed based on an intervention-mapping approach. A needs assessment was performed, followed by defining objectives, theory-based methods, program development, implementation, and evaluation. We took several steps to ensure that the app was based on a sound theoretical background and considered limitations identified in prior research. For implementation and evaluation purposes, we conducted a study among 229 older adults from 19 nursing homes (171 females, 58 males; mean age 85, SD 7 years). Results will be used to examine the effectiveness of the app with regard to different outcomes. Primary outcomes among participating nursing home residents are quality of life, fall risk evaluated through 2 performance-oriented balance tests, and fall incidence. Secondary outcomes include motor performance, cognition, activities of daily living, physical activity behavior, and fall efficacy. In this paper, we examined differences between intervention group (IG) and control group (CG) participants at baseline using the chi-square test, the Mann-Whitney *U* test, or the *t* test.

Results: The IG (n=137 from 11 nursing homes) received a 12-week intervention with the BeSt Age app in small, homogenous groups of 5 - 7 nursing home residents, with 2 exercise sessions per week, each lasting 25 - 30 minutes. The CG (n=92 from 8 nursing homes) received usual care. At baseline, the IG had a statistically significantly larger number of females, participants had a higher BMI, and more participants rated attending physical activity programs as important. There were no further statistically significant differences between the groups. Results with regard to the effectiveness of the BeSt Age app are expected to be published in spring 2026.

Conclusions: If proven effective, the BeSt Age app may be a viable solution for physical activity promotion and fall prevention among older adults residing in nursing homes, thereby contributing to maintaining quality of life and overall well-being in this vulnerable population. The app can support nursing home staff in delivering exercise training to residents with minimal additional workload and without requiring specific resources.

Trial Registration: German Clinical Trials Register DRKS00032349; https://drks.de/search/en/trial/DRKS00032349

International Registered Report Identifier (IRRID): DERR1-10.2196/74174

(JMIR Res Protoc 2025;14:e74174) doi:10.2196/74174

KEYWORDS

mobile health; physical activity; fall prevention; older adults; nursing homes; cluster randomized controlled trial

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Introduction

Regular engagement in physical activity from young adulthood through middle into old adulthood is of high importance for an independent, self-determined life and maintained functional performance [1]. Research has shown that physical activity has various beneficial effects on physical as well as mental health and well-being in older adults [2] and may delay age-related cognitive decline [3]. Physical activity is also associated with a decreased risk of falls in community-dwelling older adults [4] and nursing home residents [5,6], albeit conflicting results for the latter group have been reported [7]. Nevertheless, it is well established that falls are very common among individuals residing in nursing homes [8] and are associated with adverse health outcomes, such as increased risk of morbidity and mortality [9].

The World Health Organization recommends 150-300 minutes of moderate- to high-intensity aerobic physical activity per week for adults and moderate strength training on 2 or more days per week that involves all major muscle groups of upper and lower extremities [10]. In addition, with regard to fall prevention, persons aged 65 years and older should perform activities that can improve functional balance and proprioception on at least 3 days per week [10]. A minimum of 4600 steps per day, averaged over a week of free-living behavior, has been recommended for older adults by an expert group [11]. Furthermore, another expert task force from the International Association of Gerontology and Geriatrics—Global Aging Research Network and the European Region Clinical Section has published physical activity recommendations for older adults residing in long-term care facilities [12]. They defined 2 different levels of recommendations, that is, a first set aiming at reducing sedentary behaviors for all residents in long-term care facilities and a second set aiming to establish specific, evidence-based guidelines for exercise training for well-defined subgroups of residents. To this end, they recommend multicomponent training, particularly focusing on strength, aerobic endurance, balance, and flexibility. This training should be of moderate intensity, carried out at a frequency of at least twice a week, and with a duration of 35-45 minutes per session.

However, despite the widely acknowledged benefits of physical activity, and despite many individuals having intentions to engage in physical activity, most fail to follow through, a phenomenon referred to by sports psychologists as the intention-behavior gap [13]. It is well known that older adults do not engage in a sufficient amount of physical activity, and this is particularly true for those residing in care facilities. For example, a literature review showed that care facility residents only engage in low levels and intensities of physical activity, with numbers of steps per day averaging between 385 and 3387 across studies, and that there is very little variation in movement patterns [14]. Another review reported daily sedentary times of 11.6 hours among residents in high-level care facilities, such as nursing homes [15]. Furthermore, a study conducted in German nursing homes using sensor-based assessment revealed that residents' movement space was mainly restricted to their personal rooms and the adjoining residential units during 90% of the daytime [16].

This lack of physical activity among nursing home residents is alarming, particularly since the negative consequences of sedentariness may be accelerated by age-related physical and cognitive decline, thereby further increasing care dependency and burden for caregivers and family members [17]. Different factors have been discussed in the literature that may impact physical inactivity and sedentariness. In community-dwelling older adults [18], main barriers to physical activity include personal characteristics of older adults (eg, poor physical and mental health status and lack of interest) and interpersonal aspects, such as lack of company or social network. For older adults residing in nursing and care homes [19,20], additional barriers may include physical environment (eg, lack of access to green spaces) or organizational barriers, such as nursing home staff shortages, time constraints, or insufficient communication of available exercise, as well as low awareness among residents. Recently, a systematic literature review of caregiver-provided exercise interventions for individuals with dementia residing in nursing homes reported that the main barriers to the implementation of interventions, such as physical exercise, care-integrated physical activity, outdoor or walking activity, technology-supported physical exercise, and dancing were a lack of knowledge about positive effects of physical activity, refusal of residents with dementia to participate, or insufficient time and resources for implementation among caregivers [21], albeit also acknowledging that all stakeholders considered physical activity interventions as useful and relevant.

To date, a growing body of interventions and programs aimed at promoting physical activity, preventing falls, or improving motor performance is being more widely implemented in care settings, and different literature reviews are available focusing on the effectiveness of such programs on various outcomes of interest, for example, quality of life and related factors in older adults in residential care facilities [22] or mental health, such as well-being and cognition in older persons residing in nursing homes [23]. However, there are still several challenges that need to be addressed. One challenge, for example, is low adherence. To this end, a French cross-sectional study revealed that only 1914 of 5402 older nursing home residents from a total of 163 different nursing homes participated in physical activity programs provided by their nursing homes and that classes were only offered once per week or less with a median duration of 45 (IQR 30-60) minutes, on average [24]. Of note, participation as well as exercise frequency and levels were increased among nursing home residents when an exercise instructor was present [24]. Another limitation is a lack of theory-based or derived interventions, such as interventions incorporating behavior change techniques. While a meta-analysis including 171 studies revealed no differences in overall effect sizes between theory-based and no-stated-theory interventions, it provided evidence that theory-based interventions incorporated a greater number of behavior change technique clusters, which may in turn be associated with better effects [25]. With regard to older adults in particular, a review examined behavior change techniques in interventions aimed at increasing physical activity using the theory of planned behavior. The investigators identified only 7 studies, and the most frequently used techniques were goal setting, action planning, and credible sources [26]. Another review including 70 physical activity

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interventions identified action planning, instructions on how to perform a behavior, graded tasks, and demonstration of behavior as the most common behavior change techniques and also showed that interventions carried out in older persons' homes used 9 behavior change techniques, whereas interventions conducted in a residential care facility used only 6 behavior change techniques on average [27]. Recently, researchers from Taiwan developed a motivation theory-based walking intervention and reported that it enhanced the self-efficacy of 30 older adults living in long-term care facilities and was perceived as helpful in increasing physical activity engagement [28]. Further limitations, as also mentioned above, include but are not limited to lack of knowledge among caregivers along with insufficient time and resources for implementation of physical exercise in nursing homes [20,21] or the use of "one-fits-all" physical exercise programs. To this end, it has been postulated that individualized exercise programs that are deliberately tailored to the needs and preferences of older adults residing in nursing homes may have higher effectiveness on physiological outcomes [29], variables related to brain health [30], physical activity [31], physical performance [32], or gait [33].

In light of these limitations and challenges of physical exercise implementation in care settings, different approaches and solutions have been discussed in the literature. Those include nontechnology-based approaches, such as exercise delivered by trained nursing home staff [34,35] or focus on environmental aspects that may impact physical activity in nursing home residents [36], as well as technology-based approaches, such as responsive surface technology [37], virtual reality–based systems [38,39], exergaming and other mobile health and eHealth–based interventions [40], and even social robots [41]. Indeed, one promising approach that is also rather simple to both develop and implement, cost-effective, and close to real life may be the use of mobile apps. Research has shown that digital, touchscreen-based technologies may be effectively used for person-centered care and engagement of nursing home residents [42], and can also support caregivers who may not have prior expertise or knowledge on physical activity training, or only have very limited time during their work routines in delivering exercise interventions to nursing home residents [43]. Moreover, a study examined the usability as well as the effects of an app-derived physical activity intervention for older adults with dementia residing in nursing homes, but the validity of results was limited by the small study sample size [43,44]. Other studies have shown that nursing staff are willing to use digital and assistive technologies, including mobile apps, but that access to such technologies, including Wi-Fi, is limited in nursing home settings, and that in order to maximize acceptance, it is crucial to involve nursing staff in the development process and provide adequate training and testing opportunities tailored to their experience and affinity for technology [43,45,46]. Overall, even though preliminary results regarding usability, acceptability, or effectiveness are promising, digital interventions for physical activity promotion in older adults remain understudied, and existing solutions are too heterogeneous for meaningful comparison of results [47], thereby limiting evidence. Furthermore, little is known about the practical application [48], accessibility, acceptability, and sustainability of such solutions [49], and many care institutions are thus still hesitant to adopt these innovations [50,51].

To address some of the challenges and limitations related to physical exercise implementation in care settings as outlined above, we have iteratively developed and implemented a mobile app called the BeSt Age app and examined its effectiveness in a cluster randomized controlled trial (cRCT). The aim of this paper is to describe the rationale, development steps, and implementation of the BeSt Age app, as well as to provide an overview of baseline characteristics of the cRCT study sample and discuss future implications.

Methods

Rationale for and Development of the BeSt Age App

To address gaps in prior research outlined above, the tablet-based BeSt Age app was designed with the overarching aim of supporting care staff in delivering an individualized physical exercise program to small, homogeneous groups of nursing home residents. Based on an intervention-mapping approach [52], a needs assessment was performed, followed by defining objectives, theory-based methods, program development, implementation, and evaluation. Thus, we took the following steps to ensure that the app was designed and developed based on a sound theoretical background and considered results and limitations identified in prior empirical research.

First, we conducted an online survey with 200 nursing home staff across Germany to examine previous experiences and willingness to use digital solutions, including but not limited to the purpose of physical activity promotion and fall prevention, as well as perceived possible risks, attitudes, and expectations in this regard [45,46]. We also inquired about affinity for technology or technical equipment available in nursing homes. We then conducted an interview study with stakeholders (ie, three managers, six employees providing care for residents, and ten residents) from seven different nursing homes to gather information about existing physical activity programs that they may have implemented in their institutions and to identify prior experience, needs, expectations, fears, and possible barriers to using digital technology. The results from both the internet-based survey and interview study were used to ensure that our app would have a high acceptability and feasibility.

Second, we defined the objectives of the BeSt Age app. Those included (1) the delivery of physical exercise tailored to the needs and preferences of nursing home residents (rather than "one-fits-all" exercise) by nursing home staff; (2) creation of small groups of residents with comparable motor and cognitive performance status using an in-built algorithm; (3) inclusion of a wide range of nursing home residents, for example, also those using a wheelchair or walking aids (we only excluded persons with very severe motor, neurological, or cognitive impairments and disorders); and (4) a multimodal exercise program, including both motor and cognitive stimulation.

Third, we took several theoretical considerations into account that have been the foundation of lifestyle interventions aimed at improving health-related outcomes, such as social cognitive

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theory [53], ensuring that our app is evidence-based, comprehensive, and tailored to meet the objectives as outlined above. Furthermore, app content was developed based on the self-determination theory [54], as it fosters intrinsic motivation by addressing three fundamental psychological needs, that is, autonomy (users choose activities), competence (activities are tailored to ability levels), and relatedness (social support through group activities). Also, the COM-B (Capability, Opportunity, Motivation, and Behavior) model [55] was considered for app development. According to this model, behavior change depends on capability (physical and psychological), opportunity (social and physical environment), and motivation. We designed the app in a way that it would target all 3 components by simplifying exercise selection, embedding social elements, and using gamification features to enhance motivation. Moreover, basic theories on enhancing acceptance of technology, such as the Technology Acceptance Model [56], as well as published physical activity recommendations for older adults residing in long-term care facilities [12], were taken into account.

Fourth, regarding the exercise program development, we drew on our expertise from the InCoPE app (Individualized Cognitive and Physical Exercise; Institute of Sports and Sports Science, Karlsruhe Institute of Technology) that our group had developed and evaluated prior to the BeSt Age app. Briefly, the InCoPE app was designed to enable nursing home staff to deliver an individualized exercise program to small, homogenous groups of nursing home residents with dementia [43,44,57]. In contrast, the BeSt Age app was developed to enable nursing home staff to deliver an individualized exercise program to nursing home residents regardless of their cognitive impairment status. Thus, we consider the BeSt Age to be more inclusive than our previously developed InCoPE app. When designing and developing the BeSt Age app, we also considered results from a systematic literature review performed by our group, which examined the effectiveness and acceptability of eHealth and mobile health interventions to promote physical activity and prevent falls in nursing homes [40].

As a fifth and last step, evaluation planning involved the design of a cRCT to examine the effectiveness of the app with regard to different outcomes of interest. Subsequently, the app prototype was developed and tested in a 2-week pilot study in 2 nursing homes to examine its feasibility, usability, and user experience. Feedback obtained during the pilot study was incorporated into the final version of the app, which was then used in the cRCT.

To conclude, we developed the app in an iterative manner, that is, the app was continuously revised and improved based on the several steps we took, to ensure that the final version would fulfill both expectations and needs of the users, that is, nursing home staff and residents. We adopted a 3-component user-centered design strategy to guide the development of our interface, and this approach yielded comprehensive user feedback through direct stakeholder engagement and contextual testing in the target environment. First, our interview study provided us with insights on workflow integration, usability requirements, and practical implementation considerations, which informed our initial design decisions and feature prioritization. Second, we collaborated with a usability and user experience expert from the software company that developed the app to ensure adherence to established usability principles and best practices for apps serving older adults. Third, the pilot study allowed us to observe actual user interactions, identify usability issues, and collect feedback from both staff and residents in authentic care settings, and it also enabled us to validate and refine the interface based on actual usage patterns.

Features and Functionality of the BeSt Age App

In general, as mentioned above, the purpose of the app is to assist nursing home staff in delivering individualized exercise training programs to small, homogenous groups of nursing home residents. Training with a single individual is also possible but less feasible given the restricted time and personnel resources in many care facilities [44]. A distinctive feature of the app is that it takes the cognitive and motor performance status of an individual into account, that is, exercises that align with the motor and cognitive capabilities of the small group of residents are selected through a distinctively developed algorithm. To this end, the app contains a large selection of about 150 different exercises and movements, and also different variations for most of them in terms of intensity or motor requirements needed to perform the exercise, thereby allowing for maximal variety in the training. Furthermore, the app creates a detailed plan for each exercise session, thereby reducing the workload of staff for preparing and providing exercise sessions.

The app workflow requires nursing home staff to create an overall profile for their facility (eg, by providing the name and indicating which materials are available) as well as a personal profile for each resident by inserting subjective information, as outlined in Textbox 1.

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Textbox 1. Subjective information.

Motor performance (multiple selection)

- The person is able to get up from a chair with or without aids.
- The person is able to walk with or without aids.
- The person is not able to get up from a chair or walk.

Cognitive performance level (single selection)

- The person has no or little cognitive impairment.
- The person has moderate cognitive impairment.
- The person has severe cognitive impairment.

Personal exercise preferences (multiple selection)

- The person likes to dance or exercise with music.
- The person likes to sing.
- The person likes to exercise with balls.

Once the profiles for all residents are created, matching algorithms implemented in the app create small, homogeneous groups of residents (up to 7 persons), with similar motor and cognitive performance status as well as personal exercise preferences. To this end, residents' characteristics and interests are matched by the algorithm with the requirements defined for each exercise (eg, the person must be able to stand for this exercise) and the materials available in the respective care facility.

Briefly, the matching algorithm was developed based on systematic feedback from nursing home staff collected during our interview study and pilot testing. It incorporates practical considerations identified by nursing home staff regarding the delivery of physical activity sessions. To validate its effectiveness, we tested the algorithm using simulated resident profiles with varying functional levels and confirmed that it successfully creates homogeneous groups. The app also features a calendar function, which can be used by nursing home staff to plan and schedule exercise sessions with different groups of residents for the entire week, month, or period of interest.

On the day of a given exercise session, nursing home staff operate the tablet and will be guided step-by-step through the entire exercise training program by following the on-screen instructions. On the starting screen, they are first shown an overview of all exercises included in the entire session, as well as any materials (eg, balls, chairs, and balloons) that may be needed, so that they can prepare the materials in advance. Once the program is started, each exercise will be shown and described in detail on a new screen, containing information about the name and purpose of the current exercise, any material needed (eg, a chair), potential risks or side effects (eg, pain), and duration or number of repetitions (eg, 2 times of 20 repetitions). A brief video clip showing an older person carrying out the exercise is also provided on the screen. In addition, the exercise program is accompanied by background music that can be turned on and off as needed.

The main exercise program contains 2-3 exercises for warm-up (ie, mobilization and coordinative exercises), 5-7 main exercises (ie, strength, balance, endurance, and gross motor coordination), and 2 exercises for cooldown (ie, relaxation and body perception), and takes approximately 25-30 minutes to complete. Please refer to Multimedia Appendix 1 for examples of warm-up, main, and cooldown exercises. The algorithm is trained to provide well-balanced sessions, including a comparable number of exercises for the strength of different body parts, mobility, and balance. If needed, nursing home staff can adapt the exercise sessions by skipping exercises while using the app (also, exercises can be removed or added before the program has been started on the app). After each session, nursing home staff can rate each exercise using a feedback feature. This feedback is also used to ensure progression with regard to intensity by suggesting more challenging versions of the exercises in upcoming sessions if and when an exercise has been rated positively several times. If an exercise is rated poorly, the app will exclude it and similar exercises from further sessions for this group. Furthermore, attendance of all individuals by group can be documented after the session, with the option of choosing reasons for not attending the program. Nursing home staff can also review the description of the upcoming session to identify any required materials and prepare them in advance. Of note, the app also features a gamification element for motivational purposes, that is, the group is awarded credit points for completed sessions, which can be used to purchase new items (eg, a bench and flowers) for a digital nursing home garden. Please refer to the screenshots (Figures 1-3) showcasing the main features of the app.

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Figure 1. Profiles of facilities and individuals. (A) Overall facility profile showing an overview of participants, training groups, and date and time of next training sessions. (B) Overview of individual profiles of participants with integrated search and filter function.

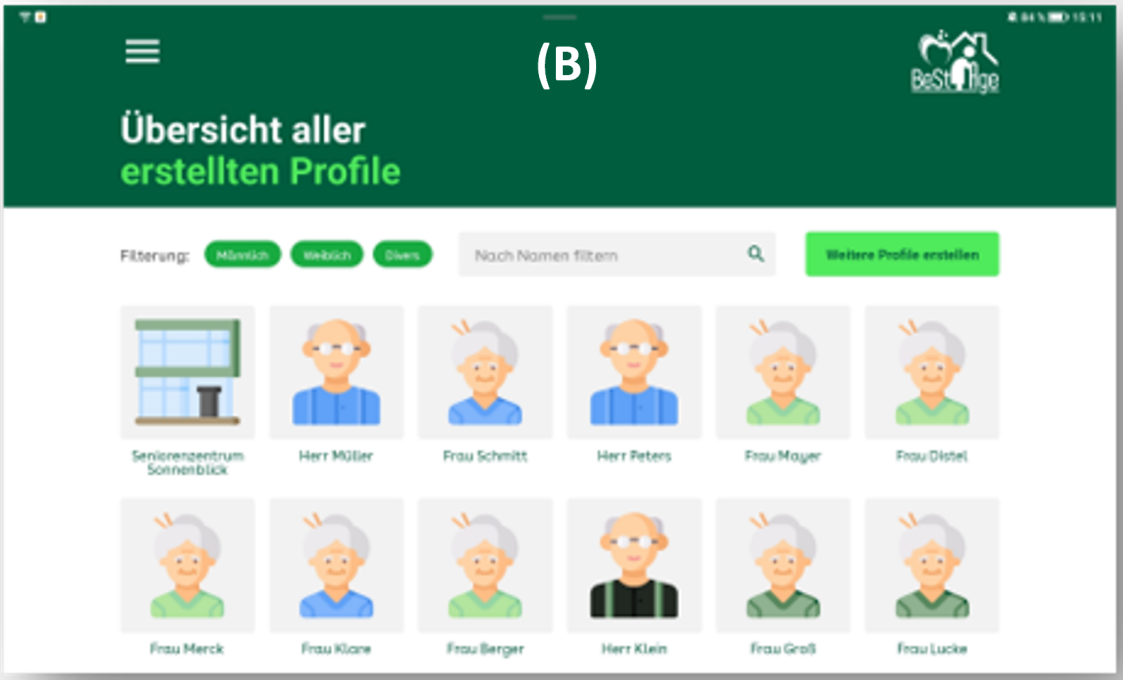

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Figure 2. Training sessions. (A) Overview of a training session including participants, duration of the session, material needed, and planned exercises. (B) Exercise screen, which includes material needed, possible risks, duration of the exercise, suggested repetitions, and a video of the exercise execution.

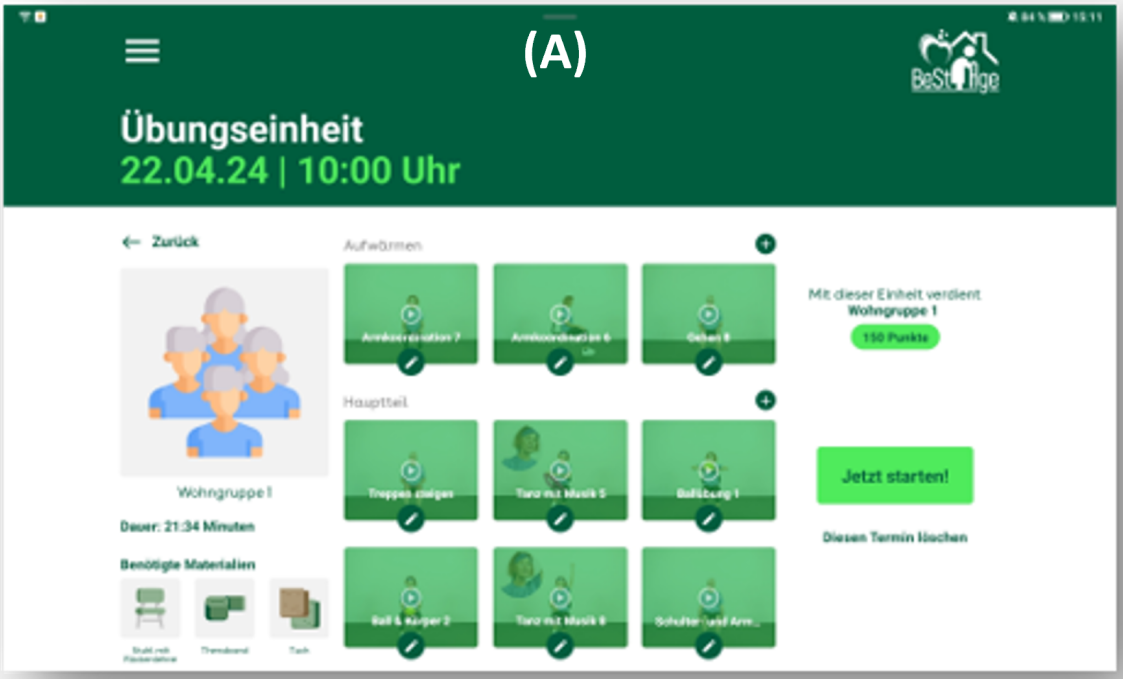

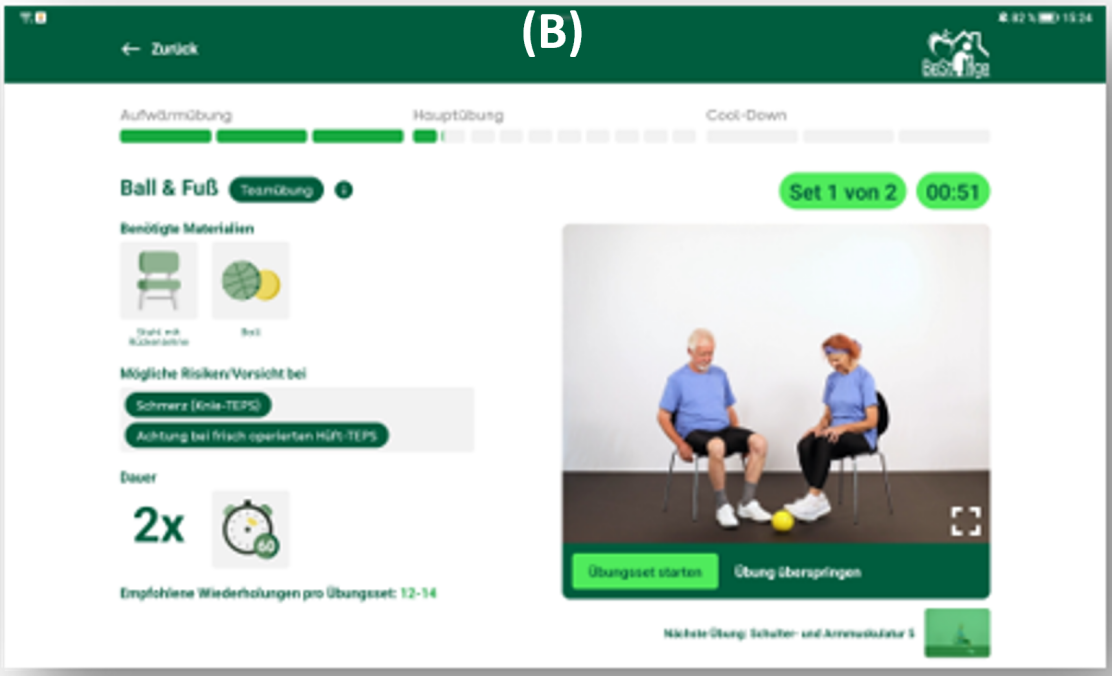

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Figure 3. Gamification within the BeSt Age app. (A) Nursing home garden as gamification element.

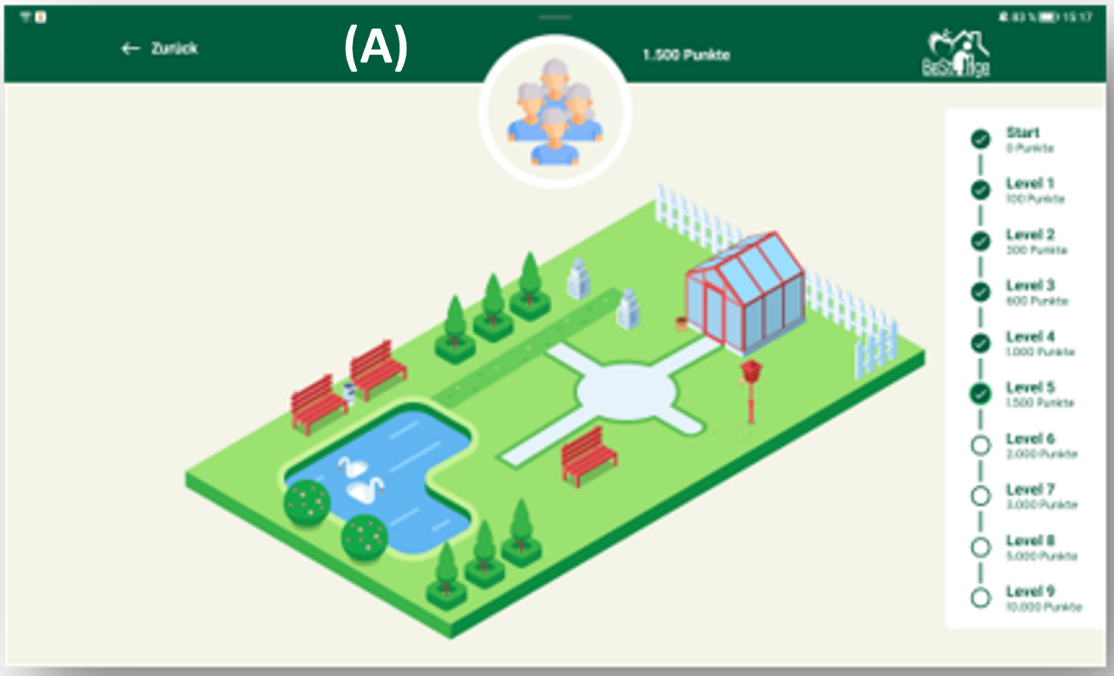

Overall, the following behavior change techniques were integrated into the app: (1) information on health, social, and environmental consequences, that is, health-related educational content, was presented to participants prior to each exercise session to enhance knowledge of fall prevention benefits; (2) demonstration of behavior, that is, video-based exercise demonstrations; (3) social comparison with other groups, that is, progress visualization via the digital nursing home garden enabled participants to compare their group's achievement with other participating groups; (4) prompts and cues, that is, audio-based reminder notifications were programmed to occur 15 minutes prior to scheduled exercise sessions; (5) habit formation, that is, the built-in calendar scheduling function enabled nursing home staff to establish consistent exercise sessions twice weekly at standardized times and days; (6) nonspecific reward, that is, a point-based reward system provided immediate positive reinforcement following completion of exercise sessions. Also, the app was designed to accommodate residents with varying degrees of cognitive impairment through several adaptive features. For example, educational content and exercise demonstrations used clear, simplified language and visual cues to enhance comprehension for persons with cognitive limitations. Given the cognitive challenges of the target population, nursing home staff served as primary facilitators and operated the app interface while guiding residents through the exercises, thereby reducing cognitive load on participants. In addition, audio prompts were combined with visual notifications to accommodate different cognitive processing abilities and ensure message reception across varying impairment levels. Furthermore, the digital garden visualization provided concrete, easily interpretable feedback that residents could understand regardless of cognitive status, with staff providing additional verbal explanations as needed. Also, the consistent scheduling and habit formation features embedded in the app were particularly beneficial for cognitively impaired residents, as establishing routines may compensate for memory deficits and reduce cognitive demands.

Implementation Approach: Cluster Randomized Controlled Trial

To test the effectiveness and acceptability of the BeSt Age app, we carried out a 12-week cRCT. Randomization into an intervention group and control group was done at the facility level in order to ensure a sufficient number of participants that would allow for the in-built matching algorithm to form homogenous groups for the exercise training program. To this end, a list of nursing homes in the city of Karlsruhe and the surrounding districts in the German state of Baden-Wuerttemberg was created, and we contacted the nursing homes by telephone and provided on-site informational meetings. Allocation of nursing homes to either the intervention or control group was performed using a computer-generated randomization procedure. If possible, investigators assessing gait, motor, and cognitive performance outcomes were blinded to group allocation. Blinding of participants or nursing home staff delivering the intervention was not possible.

Study Sample

An a priori power analysis was conducted using G*Power (version 3.1.9.7; Heinrich-Heine-Universität Düsseldorf [58]), based on the assumption that we would calculate 2-factor ANOVAs with repeated measurements, 2 groups, 2

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measurements, α=.05, 1-β=.80, and ²=0.02, and revealed a required total sample size of 100 participants. The effect size (²=0.02) used for the calculation of the required sample size was based on results presented in our literature review [40]. However, we will decide on the appropriate statistical approach based on the intraclass correlation coefficient (ICC) derived from the original data once data collection is completed. In the literature [59], an ICC of ≥0.05 has been suggested as a cutoff value for determining whether to use multilevel modeling. Since statistically significant differences between groups (eg, with regard to sex distribution, BMI, or perceived importance of physical activity) may confound outcomes, we will also consider those variables as covariates and adjust future analyses accordingly. Furthermore, in case of data missing at random according to the Little test, we plan to include multiple imputation procedures. To this end, we will use SPSS's (IBM Corp) multiple imputation procedure to generate multiple imputed datasets (typically 5 - 10 imputations) using the fully conditional specification method, which is appropriate for our dataset. Considering an estimated dropout rate of 20%, anticipated low adherence to the intervention, and adjustment to cluster randomization using a variance inflation factor [60], the sample size was set to 255 participants. The sample size calculation based on a priori power analysis was designed to detect overall intervention effects at the facility level rather than within specific subgroups, for example, based on cognitive function or mobility levels; however, subgroup analyses may be performed when suitable.

We defined the following inclusion criteria for nursing home residents: aged >65 years; ability to follow verbal instructions; and at least 50% functional capacity of extremities; that is, participants were required to have functional use of at least 50% of their extremities (at least 2 of 4 limbs: both arms, both legs, or 1 arm and 1 leg). We chose this criterion to ensure that the intervention would be rather inclusive, allowing, for example, wheelchair users to participate. Exclusion criteria were very severe cognitive, neurological, or motor impairments or disorders. We deliberately did not formulate any additional exclusion criteria in an attempt to be rather inclusive, particularly since prior studies had defined more strict inclusion and exclusion criteria that may not apply to many residents of nursing homes and may not be reflective of a real-world scenario [40]. Eligibility of participants was verified at baseline assessment and based on the aforementioned predefined criteria.

Intervention and Outcome Measures

The intervention group received a 12-week intervention with the BeSt Age app (including features as described above) in small, homogenous groups of about 5-7 participants, on average, with 2 exercise sessions per week, each lasting about 25 - 30 minutes. The control group received usual care. Baseline (T0) and postintervention (T1) assessments were carried out, and a follow-up survey (T2) was conducted 3 months after the end of the intervention to assess fall incidence. To ensure protocol adherence, all nursing home staff involved in the intervention received standardized training sessions covering app functionality, exercise session protocols, resident engagement strategies, and data collection procedures before the cRCT. Training materials also included detailed protocol manuals to ensure uniform understanding across facilities. To monitor intervention fidelity, we maintained regular contact with facility coordinators and provided ongoing technical support to address implementation issues. App usage analytics also provided objective data on session completion rates, feature usage, and timing of interventions across facilities. Furthermore, all assessments as part of the study were conducted and administered to nursing home residents and staff by trained members of the research team, and we also provided them with a detailed manual to enhance standardization of assessment and scoring procedures. Also, if and when possible, we assigned the same persons to administer the same tests in different nursing homes to ensure consistency in administration and scoring. Finally, our data handling procedures ensured full compliance with the European Union General Data Protection Regulation, including appropriate consent procedures and secure local storage protocols. All participant data were stored exclusively on local tablets without cloud-based storage or remote server connections, thereby eliminating risks associated with data transmission. Tablets were operated without internet connectivity, ensuring complete network isolation and preventing unauthorized external access to participant data. Please refer to Figure 4 for a graphical display of the study design. Please refer to Table 1 for an overview of all primary and secondary outcomes assessed at T_0, T_1, and T_2.

Figure 4. Study design.

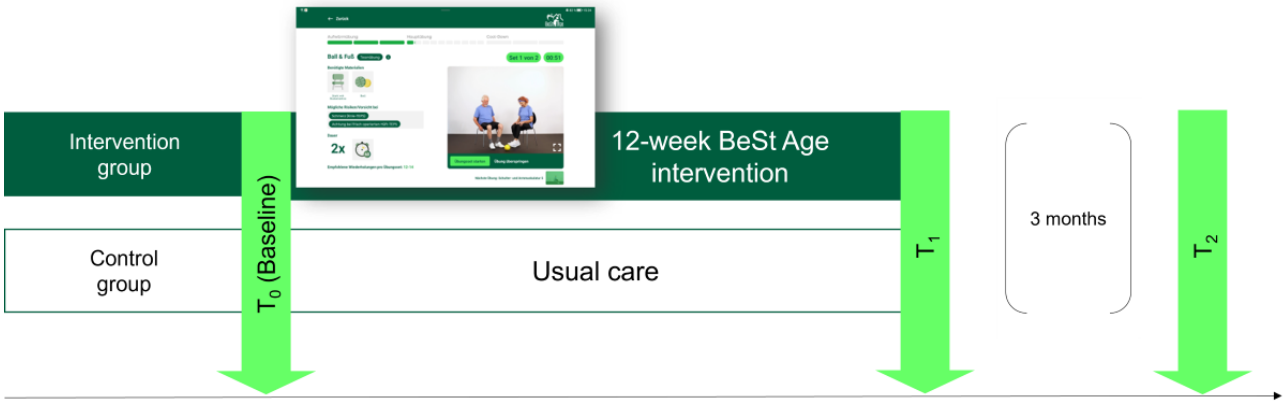

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Table . Overview of primary and secondary outcomes.

Dimension	Assessment	Time of measurement			Calculated variable or score used for analysis
		T_0	T_1	T_2	
Primary outcomes					
Quality of life	EUROHIS-QOL[a] questionnaire [61,62]	NHR[b]	NHR	N/A[c]	Total score (8-40)
Fall risk (performance-oriented balance tests)	Timed Up and Go [63]	NHR	NHR	N/A	Time (seconds)
	Berg Balance Scale [64]	NHR	NHR	N/A	Total score (0-56)
Falls	Fall incidence [65]	NHR	NHR	NHR	Number of falls
Secondary outcomes					
Grip strength	Digital hand dynamometer [66]	NHR	NHR	N/A	Best out of 6 trials in kg
Arm strength	30-seconds arm curl test [67]	NHR	NHR	N/A	Number of arm curls in 30 seconds
Walking speed	10-meter walking test [68]	NHR	NHR	N/A	m/s
Cognitive status	Montreal Cognitive Assessment [69,70]	NHR	NHR	N/A	Total score (0-30)
Anticipatory motor planning	Bar-transport task [71]	NHR	NHR	N/A	Number and percentage of end-state comfort grasps
Activities of daily living	Katz Index [72]	NHR	NHR	N/A	Total score (0-6)
Physical activity behavior	Life-Space Assessment in Institutionalized Settings (LSA-IS) [73,74]	NHR	NHR	N/A	Total score (0-90)
Fear of falling	7-item Short Falls Efficacy Scale-International [75]	NHR	NHR	N/A	Total score (7-28)
Digital competence	Single-item (Likert-Scale format)	NHR	NHR	N/A	Total score (1-5)
Reasons for and motivation to participate in physical activity in general	Open-ended questions	NHR	N/A	N/A	N/A
Motivation to continue using BeSt Age app	Open-ended questions	N/A	NHR	N/A	N/A
Influence of gamification	Open-ended questions	N/A	NHR	N/A	N/A
Reasons and motivation to work with BeSt Age app	Open-ended questions	NHS[d]	N/A	N/A	N/A
Usability of BeSt Age app	System Usability Scale [76]	N/A	NHS	N/A	Total score (0-100)
User experience	AttrakDiff [77]	N/A	NHS	N/A	4 dimensions scored –3 to 3
App usage	User statistics derived from app data	N/A	NHS	N/A	N/A
Enjoyment	Open-ended questions	N/A	NHS	N/A	N/A
Future app use	Open-ended question	N/A	NHS	N/A	N/A

[a]EUROHIS-QOL: European Health Interview Survey Quality of Life.

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[b]NHR: nursing home residents.

[c]Not applicable.

[d]NHS: nursing home staff.

Primary outcomes of interest among participating nursing home residents included quality of life assessed using the 8-item European Health Interview Survey Quality of Life (EUROHIS-QOL) questionnaire (calculated variable: total score ranging from 8 to 40 with a lower score indicating worse quality of life) [61,62] and fall risk evaluated through 2 performance-oriented balance tests, that is, the Timed Up and Go Test assessing lower extremity function and mobility (calculated variable: time in seconds to get up from chair, walk 3 meters, turn around, return 3 meters, and sit back down at chair; walking aids such as canes or rollators were permitted) [63] and the Berg Balance Scale assessing static and dynamic balance through a 14-item test battery, with each item rated from 0 to 4. Here, a lower score indicated greater balance impairment (calculated variable: total score ranging from 0 to 56) [64]. We also recorded fall incidence from nursing home staff at 6 months before the intervention, during the 12-week intervention period, and during the 3-month follow-up period postintervention. To this end, a fall was defined as "an event in which the individual unintentionally comes to rest on the ground or another lower level" according to the "Expert Standard for Fall Prevention in Nursing Care" of the German Network for Quality Development in Nursing Care [65].

Secondary outcomes of the cRCT included 3 motor performance tests, including grip strength assessed using a digital hand dynamometer according to the Southampton Protocol (calculated variable: best out of 6 trials, that is, 3 for each hand, in kg) [66], a 30-second arm curl test (calculated variable: number of performed arm curls in 30 seconds) [67], and a 10-meter walking test (2 trials at preferred pace; 2 trials at fast pace; walking aids such as canes or rollators were permitted) [68]. Additional outcomes included cognitive status assessed using the Montreal Cognitive Assessment (MoCA; calculated variable: score ranging from 0 to 30, with lower scores indicating greater cognitive impairment) [69,70], the end-state comfort effect as an indicator of anticipatory motor planning using the bar-transport task (calculated variables: number and percentage of end-state comfort trials in uncritical and critical conditions) [71], activities of daily living assessed using the Katz Index (calculated variable: score ranging from 0 to 6, with lower scores indicating lower function and dependence) [72], life space or physical activity behavior assessed using the Life-Space Assessment in Institutionalized Settings (LSA-IS; [73]) questionnaire (calculated variable: score ranging from 0 to 90 with a lower score indicating a greater degree of immobility) [74], and fear of falling which was assessed with the 7-item Short Falls Efficacy Scale-International (calculated variable: score ranging from 7 to 28, with higher scores indicating more severe concern about falling) [75]. All participants also rated their digital competence, and we created a score ranging from 1 (very low) to 5 (very high). In addition, participants were asked various questions, for example, about their reasons and motivation to participate in physical activity programs prior to the intervention period. After the 12-week intervention, participants of the intervention group were asked whether they were motivated to continue with the BeSt Age program and if the gamification element had influenced their motivation.

Assessments conducted among nursing home staff who delivered the physical exercise interventions included but were not limited to usability assessed using the System Usability Scale (calculated variable: score ranging from 0 to 100, with higher scores indicating better usability) [76], user experience using the AttrakDiff (calculated variables: pragmatic quality, hedonic quality divided into identity and stimulation, and attractiveness with scores ranging from –3 to 3) [77], affinity for technology, and app usage statistics. These considerations were based on implications derived from the RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) Framework [78]), which assesses reach (engagement among nursing home residents), effectiveness (health outcomes), adoption (nursing home staff willingness), implementation (consistency of use), and maintenance (long-term sustainability). Furthermore, nursing home staff were asked open-ended questions about reasons for offering physical activity programs and motivation to work with the BeSt Age app prior to the intervention period. After the 12-week intervention, they were additionally asked whether they enjoyed working with the app and whether they were motivated to use the BeSt Age app in the long term. Please refer to Table 1 for an overview of all primary and secondary outcomes. For all assessments, we used German language versions.

Ethical Considerations

The study adhered to the guidelines and recommendations outlined in the CONSORT (Consolidated Standards of Reporting Trials) statement [79,80] as well as the CONSORT extension to cluster randomized trials [81]. The study was preregistered in the German National Register of Clinical Trials (DRKS00032349), and adhered to the guidelines outlined in the Helsinki Declaration. Ethical approval was granted from the ethics committee of the Karlsruhe Institute of Technology, Karlsruhe, Germany following a review of the study methodology and data protection measures. Written informed consent was obtained from all participants or, in the case of participants unable to consent, their legal guardians prior to the study. All participants were informed about the nature, procedures, and possible benefits and risks of the study, and could withdraw from the study at any time without consequence. Collected data were de-identified by assigning a unique ID to each participant, and the full set of data was accessible only to authorized members of the research team. Participants did not receive compensation.

Results

Characteristics of Participants (Nursing Home Residents) at Baseline

A total of 229 persons (171 females and 58 males; 137 intervention group and 92 control group) from 19 different nursing homes (11 intervention group and 8 control group)

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participated in the baseline assessment. Please refer to Figure 5 for a flow diagram detailing cluster allocation, resident recruitment, and attrition through T_2. Mean age was 85.4 (SD 7.4) years, and participants rated their digital competency as low (mean score of 1.9, SD 1.1). The intervention group included a statistically significantly larger number of females, participants had a higher BMI, and more participants rated attending physical activity programs as important. There were no additional statistically significant differences between the intervention and control groups at baseline. Overall, 4 of 125 (3%) participants of the intervention group and 3 of 87 (3%) participants of the control group had a MoCA score of ≥26, indicating no cognitive impairment, while 40 of 125 (32%) participants of the intervention group and 33 of 87 (38%) participants of the control group had a score between 18 and 25, indicating mild cognitive impairment. Notably, 81 of 125 (65%) participants of the intervention group and 51 of 87 (59%) participants of the control group had a score ≤17, indicating moderate to severe cognitive impairment. Of note, MoCA data were missing for 17 participants, since we did not calculate a MoCA score for participants with visual or motor impairments or when German was not the mother tongue. With regard to mobility, 24 of 93 (26%) participants of the intervention group and 21 of 63 (33%) participants of the control group took 19 seconds or less to complete the Timed Up and Go test, indicating no mobility impairment, whereas 34 of 93 (37%) participants of the intervention group and 22 of 63 (35%) participants of the control group took between 20 and 29 seconds to complete, indicating impaired mobility, and 35 of 93 (38%) participants of the intervention group and 20 of 63 (32%) participants of the control group took ≥30 seconds, reflecting severe mobility impairment. Of note, 72 of 229 (31%) participants used no walking aid, 82 of 229 (36%) participants used a walker, and the remaining study participants used other tools, such as a walking stick or wheelchair. A total of 97 of 131 (74%) participants of the intervention group and 66 of 90 (73%) of the control group had no falls 6 months prior to the study baseline, 22 of 131 (17%) of the intervention group and 13 of 90 (14%) of the control group had 1 fall, and 12 of 131 (9%) participants of the intervention group and 11 of 90 (12%) of the control group had 2 or more falls. Please refer to Table 2 for an overview of participants' characteristics, stratified by group allocation.

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Figure 5. Flow diagram (modified according to Consolidated Standards of Reporting Trials). NH: nursing home. Single asterisk: Including some participants who did not attend postassessment (eg, due to illness and hospitalization). Double asterisk: Only number of falls assessed.

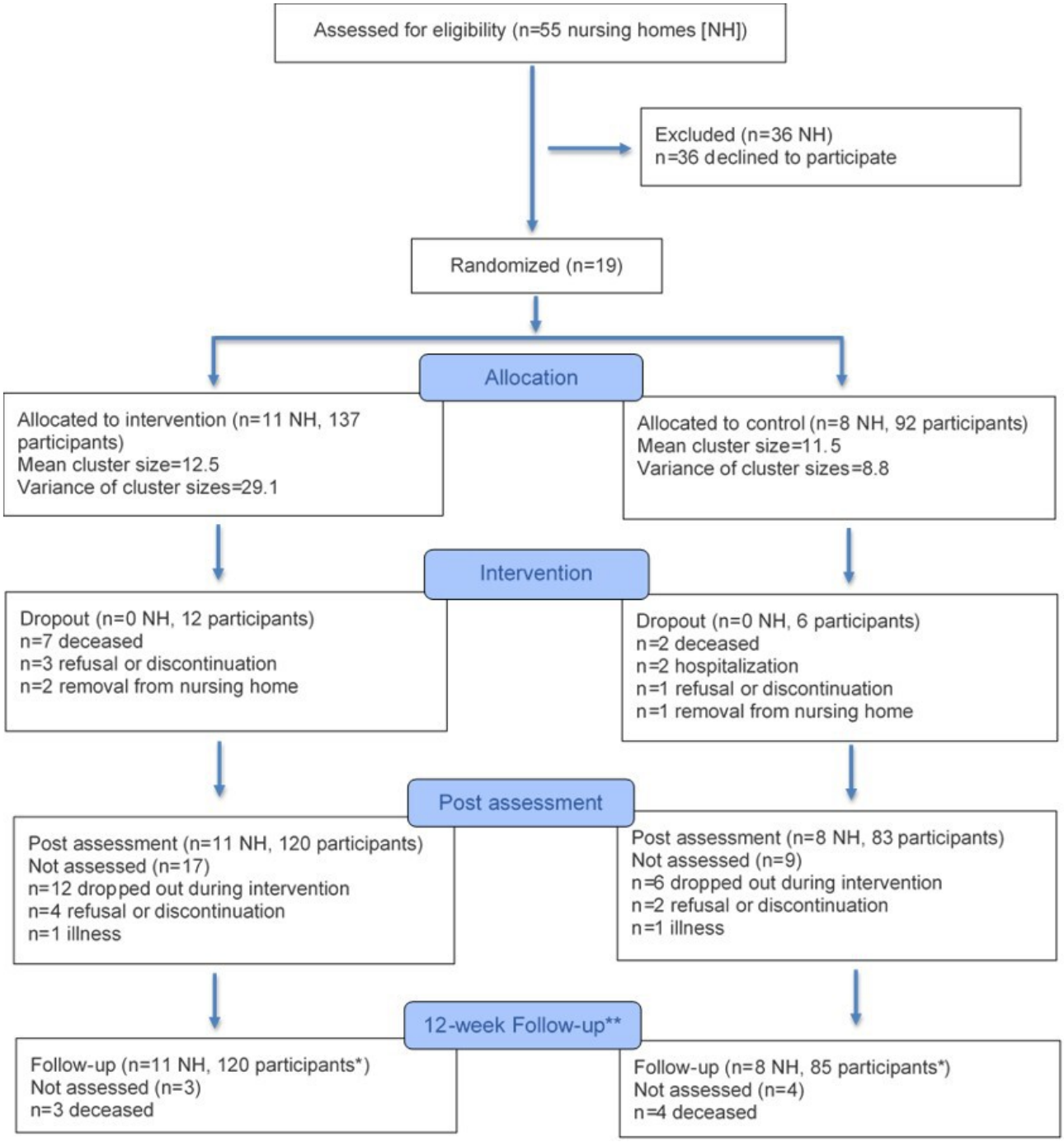

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Table . Participant characteristics (nursing home residents) at baseline.

Variable	Intervention group (n=137)	Participants with missing information	Control group (n=92)	Participants with missing information	Total (N=229)	Participants with missing information	*P* value
Female sex, n (%)	111 (81)	__[a]	60 (65.2)	—	171 (74.7)	—	<.01
Age in years, mean (SD)	85 (7.6)	2	85.9 (7.2)	—	85.4 (7.4)	—	.31[b]
School education, n (%)							.14
No school leaving certificate	13 (10.1)	8	3 (3.3)	3	16 (7.3)	11	
Basic secondary school-leaving certificate	71 (55)	8	53 (59.6)	3	124 (56.9)	11	
Intermediate secondary school-leaving certificate	29 (22.5)	8	16 (18)	3	45 (20.6)	11	
Higher education entrance qualification (A-levels)	16 (12.4)	8	17 (19.1)	3	33 (15.1)	11	
BMI (kg/m^2), mean (SD)	28.1 (5.8)	8	25.9 (5)	5	27.2 (5.6)	13	.02[b]
Digital competence score, mean (SD)	1.9 (1.1)	3	1.8 (1.2)	—	1.9 (1.1)	3	.43[b]
Quality of life and cognition							
EUROHIS[c]-Quality of life score, mean (SD)	30.5 (4)	8	29.9 (4.2)	1	30.3 (4.1)	9	.43[b]
Montreal Cognitive Assessment score, mean (SD)	13.9 (6.6)	12	15.1 (7.1)	5	14.4 (6.8)	17	.18[b]
Motor performance assessments							
Timed up and go test (time in seconds), mean (SD)	27.6 (11.7)	44	28.3 (16.5)	29	27.9 (13.8)	73	.53[b]
Grip strength (kg), mean (SD)	17.5 (6.7)	7	18.4 (8.7)	—	17.9 (7.6)[7]	7	.87[b]
10-meter walking test (m/s) at preferred pace, mean (SD)	0.61 (0.25)	25	0.58 (0.26)	10	0.60 (0.25)	35	.37[d]
Arm curl (number of curls in 30 seconds), mean (SD)	7.6 (4.5)	23	8.5 (5.8)	1	8 (5.1)	24	.23[b]
Berg Balance Scale score, mean (SD)	26.5 (16.3)	11	28.3 (16)	2	27.2 (16.2)	13	.41[b]

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Variable	Intervention group (n=137)	Participants with missing information	Control group (n=92)	Participants with missing information	Total (N=229)	Participants with missing information	*P* value
Short Falls Efficacy Scale score, mean (SD)	11.6 (4.5)	12	11.4 (4.2)	1	11.5 (4.4)	13	.75[b]
Number of falls (6 month before baseline), mean (SD)	0.54 (1.46)	6	0.60 (1.62)	2	0.57 (1.52)	8	.85[b]
Physical activity behavior and activities of daily living							
Life-Space Assessment in Institutionalized Settings score (participant-completed), mean (SD)	23.5 (14.7)	3	23.4 (13)	—	10.5 (5.2)	3	.77[b]
Life-Space Assessment in Institutionalized Settings score (nurse-completed), mean (SD)	28.1 (14.5)	6	29.2 (18.1)	13	28.6 (15.9)	19	.74[b]
Katz index, mean (SD)	3.7 (2)	13	4 (2)	11	3.8 (2)	24	.26[b]
Questions on physical activity							
Is it important for you to attend physical activity programs? n (%)							<.01
Yes	120 (88.9)	2	63 (70)	2	183 (81.3)	4	
No	15 (11.1)	2	27 (30)	2	42 (18.7)	4	
Are you motivated to attend the BeSt Age intervention? n (%)							
Yes	84 (62.7)	3	—	—	—	—	
No	18 (13.4)	3	—	—	—	—	
Undecided	32 (23.9)	3	—	—	—	—	
Did you participate in physical activity before the study? n (%)							.07
Yes	119 (90.2)	5	66 (81.5)	11	185 (86.9)	16	
No	13 (9.8)	5	15 (18.5)	11	28 (13.1)	16	

[a]Not applicable.

[b]Continuous, nonparametric data (Mann-Whitney *U* test).

[c]EUROHIS: European Health Interview Survey.

[d]Continuous, normally distributed data (2-tailed *t* test).

P values were calculated using the chi-square test (for categorical data) or the Mann-Whitney *U* test (for continuous, nonparametric data), or the 2-tailed *t* test (for continuous, normally distributed data). All percentages were computed relative to the sample with valid data (missing persons not included). An overview of the assessment tools and their scoring ranges is provided in Textbox 2.

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Textbox 2. Assessment tools, measures, and scoring criteria.

Digital competence score

- Possible range 1 - 5
- A lower score indicates lower competence

EUROHIS (European Health Interview Survey)-Quality of life score

- Possible range 8 - 40
- A lower score indicates a worse quality of life

Montreal Cognitive Assessment score

- Possible range 0 - 30
- A lower score indicates more severe cognitive impairment
- Persons with visual or motor impairments or for whom German was not the mother tongue were not considered

Berg Balance Scale score

- Possible range 0 - 56
- A lower score indicates greater balance impairment

Short Falls Efficacy Scale score

- Possible range: 7 - 28
- A higher score indicates more severe concern about falling

Life-Space Assessment in Institutionalized Settings score

- Possible range 0 - 90
- A lower score indicates a greater degree of immobility

Katz index

- Possible range 0 - 6
- A lower score indicates lower function and dependence

Selected Results Derived From Nursing Home Staff at Baseline

We included 37 nursing home staff with a mean age of 51.7 (SD 11.5) years. Notably, 20 reported having a certification to deliver physical activity, and mean (SD) years of experience with delivering physical activity were 7.9 (SD 7.2). Qualitative analyses on assessments conducted among nursing home staff revealed that the app was rated as very good based on the System Usability Scale (mean score 87, SD 15) and was perceived as easy to administer, well designed, including a good selection of effective and varied exercises, and limiting the time for preparation of the physical exercise program delivery to a minimum. Suggestions for improvement were mentioned with regard to the duration of exercises or breaks between exercises and the level of intensity and difficulty of exercises, among others.

Discussion

Principal Findings

The novel, innovative BeSt Age app has been developed and implemented in a cRCT among 229 older adults residing in 19 nursing homes in Germany. The app offers a unique approach to delivering physical exercise in nursing homes. It contains a comprehensive exercise library and uses an in-built algorithm to select appropriate exercises. This selection process considers residents' current motor and cognitive performance status, as well as their exercise preferences. Using the app, nursing home staff, regardless of their knowledge of physical exercise training, are enabled to deliver an individualized exercise program to nursing home residents. Of note, no or only minimal preparation is needed, which may be helpful to keep the burden for staff low.

The app contains a motivational feature, that is, credit points are awarded to a group for each completed training session. These points contribute to the growth and development of the group's digital nursing home garden, thereby creating a tangible visual representation of collective physical activity engagement. This immediate feedback loop was designed to reinforce exercise behavior through visible achievement markers that participants could observe and understand. Indeed, a recent systematic review emphasized that mobile health gamification strategies, including but not limited to points, may improve motivation and participation in physical activities, albeit the review focused on gamification effectiveness in general populations [82]. Thus, it must be noted that the specific

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effectiveness of our garden-based point system for motivating exercise behavior in nursing home residents with or without cognitive impairment requires further empirical validation.

Results on the effectiveness of the BeSt Age app for nursing home residents, including but not limited to falls and fall-related outcomes, motor performance and activities of daily living, as well as quality of life, will become available in the near future. These outcomes were chosen based on prior research, which provided evidence of associations between physical activity and those variables or constructs in older adults. For example, a 3-month RCT using an individually tailored physical activity intervention in more than 300 nursing home residents with a mean age of 85 (SD 8) years revealed effects on physical activity level, balance assessed through the Berg Balance Scale, 10-meter walking speed, or functional leg muscle strength assessed through the timed chair stand test [31]. In addition, moderate-intensity physical activity is known to be related to lower fear of falling in women aged ≥60 years [83] and quality of life among older adults in care facilities [22]. Furthermore, an increased step count over a 12-week intervention in older adults with mild cognitive impairment was associated with improved MoCA test performance [84]. Finally, we also built on prior studies from our team showing effects of an app-delivered physical activity intervention on mobility or balance-related outcomes [44].

Upon demonstrating effectiveness, we plan to implement the app across nursing homes in Germany. It is conceivable that the BeSt Age app may be scaled up beyond a nursing home setting to be also used in community-based senior centers, rehabilitation programs, or independent living facilities. Collaboration with health insurance providers and policymakers could further facilitate app adoption, for example, as a reimbursable intervention for fall prevention and mobility improvement. We may also provide an English version of the app to facilitate future use in research and practice on an international scale. However, there may be challenges and limitations when exporting the app to non-German health care systems. To mitigate some of these, we designed the app in a way that allows utmost flexibility to nursing home staff; for example, nursing home staff can conduct sessions with one or more persons and adapt exercise sessions by skipping exercises during usage or adding and removing exercises before starting the program, as needed. Nevertheless, challenges may exist related to regulatory or legal frameworks, data protection and safety, country-specific staffing ratios and workflow integration that may make it more challenging (or alternatively even more simple) to use the app, or cultural compatibility, including but not limited to aspects related to nursing home staff or resident acceptance.

Overall, the BeSt Age app may be a viable solution for addressing the intention-behavior gap related to physical activity among older adults. While many nursing home residents recognize the benefits of exercise, most older adults fail to meet recommended physical activity levels, and various barriers prevent them from engaging in physical activity, including but not limited to lack of motivation or inadequate staff resources. Our app may help in bridging the intention-behavior gap by incorporating behavior change techniques (eg, goal setting, feedback mechanisms, and positive reinforcement through gamification), thereby possibly increasing adherence to physical activity routines. This may also have implications for clinical practice. Furthermore, many countries face nursing home staff shortages, and our app may be valuable in nursing homes, as it can support nursing home staff in delivering exercise training to residents without adding additional workload or requiring specific resources.

Limitations

Our study has some limitations. Although an a priori power analysis was conducted, the sample size justification is built on assumptions from ANOVA that may not hold due to the cluster design and unvalidated ICC estimates, which may raise concerns about type II errors. Furthermore, the intervention group performed 2 sessions per week, and the duration for each session was only 25 - 30 minutes, which is rather low relative to World Health Organization and other guidelines for older adults. We decided on this duration based on experience from prior research and feedback we received from nursing home staff, indicating that any session duration longer than 30 minutes might not be realistic. Nevertheless, it must be acknowledged that both the duration and frequency of the intervention might have been too low to yield any effects on our primary and secondary outcome measures.

Another limitation pertains to the fact that we have not collected any cost-effectiveness or implementation-economics metrics to inform potential future scale-up decisions. Furthermore, we used several subjective outcomes that may be prone to assessment bias. However, to mitigate bias, we only used tests and questionnaires that have been validated and used in other studies in Germany or with the same or comparable target populations before. Also, in our study, blinding of participants (ie, nursing home residents and staff) was not possible, which may increase bias and compromise the validity of results. In addition, randomization at the facility level, combined with residents providing consent only after allocation, may introduce a potential selection bias. However, to address initial nonparticipation, multiple recruitment attempts within each facility over an extended period were carried out that allowed residents time to reconsider and potentially reduced selection bias.

Moreover, our analysis plan follows intention-to-treat principles, where facilities remain in their allocated groups regardless of individual resident participation rates, thus maintaining the integrity of the randomization. Furthermore, during interface design, we did not follow specific accessibility standards for residents with visual or motor limitations, since the app was designed to be used by nursing home staff. However, such adaptations may need to be made in the future. In addition, we did not implement a systematic adverse event capture system in our study. However, through our regular communication with facility coordinators across all participating nursing homes, no adverse events related to the intervention were reported to our research team.

Finally, we did not prespecify minimal clinically important difference thresholds for our primary outcomes, including the EUROHIS-QOL and Berg Balance Scale, and our sample size

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calculations were based on detecting statistically significant differences rather than clinically meaningful changes. This decision was made due to limited established minimal clinically important difference benchmarks for these instruments, specifically among nursing home residents with cognitive impairment. In addition, the heterogeneity of our target population in terms of baseline functional capacity and cognitive status made it challenging to establish universally applicable clinical significance thresholds.

Conclusions

We postulate that the BeSt Age app may be used to promote physical activity and prevent falls in nursing home residents, thereby ultimately contributing to maintaining quality of life and overall well-being in this vulnerable population. Many older adults face challenges in using digital interventions. By designing the app to be intuitive and staff-assisted, it can overcome digital literacy barriers, ensuring accessibility for residents with or without cognitive impairments. Future directions may include investigation of the long-term adherence to our digital exercise program, exploration of the role of gamification in sustained motivation, examination of the potential of the app to save time or decrease burden for nursing home staff, and conduct of comparative studies with other digital interventions to assess relative effectiveness.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

JKR, JD, JK, SR, AW, and KW conceptualized the study. JKR, JD, JK, SR, and KW collected the data and JKR performed the statistical analysis. JKR, JD, JK, and KW wrote the original draft. KW and AW supervised the research and were responsible for funding acquisition. All authors read, edited and approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Examples for exercises.
[PDF File, 357 KB - resprot_v14i1e74174_app1.pdf]

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ABBREVIATIONS

CG: control group
COM-B: Capability, Opportunity, Motivation, and Behavior
CONSORT: Consolidated Standards of Reporting Trials
cRCT: cluster randomized controlled trial
EUROHIS: E
EUROHIS-QOL: European Health Interview Survey-Quality of Life
ICC: intraclass correlation coefficient
IG: intervention group
InCoPE: Individualized Cognitive and Physical Exercise
LSA-IS: Life-Space Assessment in Institutionalized Settings
MoCA: Montreal Cognitive Assessment
RE-AIM: Reach, Effectiveness, Adoption, Implementation Maintenance

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A Culturally Tailored Digital Education Intervention to Improve Nutrition Among Older Adult Congregate Meal Participants During COVID-19: Protocol for a Stepped-Wedge Cluster Randomized Controlled Trial

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Abstract

Background: Inadequate nutrition and a lack of physical activity contribute to functional decline and complications from chronic diseases in older adults. The pandemic halted or altered necessary Older Americans Act (OAA) nutrition services provided to vulnerable, community-dwelling older adults in San Antonio, Texas. The “digital divide” or gap in technological access and knowledge further heightened the detrimental effect of the COVID-19 pandemic on older adults who may be “digitally excluded” from social, economic, and health-related interactions. During the pandemic, San Antonio congregate meal sites funded by OAA remained partially open biweekly to distribute meals but no longer offered in-person nutrition education, physical activity classes, and social activities. This project expands the current congregate meal programming infrastructure and partnerships with Older Adults Technology Services (OATS) to create a sustainable approach focused on improving the health of older adults.

Objective: The study aims (1) to test the impact of a digital nutrition education intervention on the primary outcomes of food security and diet quality; (2) to determine the effect of the intervention on secondary outcomes of technology knowledge and usage, physical activity, and social isolation and loneliness; and (3) to examine the long-term impact and sustainability of technology use on food security, diet quality, physical activity, social isolation, and loneliness.

Methods: This proposed digital nutrition education intervention study targets technologically limited older adults enrolled in the congregate meal program (CMP) using a stepped-wedge clustered randomized controlled trial. Key community partners, City of San Antonio Department of Health Services Senior Services Division and OATS, contributed to the study’s planning phase, research design, and implementation. The 20-week intervention included 5 weeks of in-person technology training, including internet access and technical support for 1 year and devices, followed by 15 weeks of a culturally tailored online nutrition education intervention. The study randomized 398 older adults from 12 congregate meal sites. Data collection took place at baseline, 3 months, 6 months, 9 months, 12 months, and 18 months. If successful, the impact of this program could be applied throughout the national OATS network and to similar CMPs to bridge the digital divide beyond the COVID-19 pandemic.

Results: Recruitment and enrollment of 398 older adults at 12 CMPs was completed in December 2022. Study CMPs were randomly assigned to Cohort 1 and 2: 164 completed Cohort 1 in August 2023 and 111 completed Cohort 2 in April 2024. Eighteen-month data collection is ongoing.

Conclusions: This study aims to determine the impact of a digital nutrition intervention on older adults’ nutrition status, physical activity, loneliness and isolation, and technology access and usage. Results from this study can inform future interventions with vulnerable populations and may serve as a basis for other OAA nutrition services.

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KEYWORDS

digital divide; older adults; elderly; nutrition; technology; digital education; United States; COVID-19

Introduction

According to the 2020 population estimates from the Census Bureau, the fastest-growing demographic consists of adults aged 65 years or older, totaling over 55 million nationwide. Texas has a large number of older adult residents (3.9 million), second only to California and Florida [1]. Nutrition is essential for healthy aging [2], the maintenance of health, and the prevention of chronic diseases. However, older adults are at an increased nutritional risk due to a unique set of circumstances that encompasses physiological, cognitive, and social factors, including loneliness, depression, lack of money for food and access to food, and physical impairments that hinder food procurement and preparation [3]. Factors such as food insecurity and malnutrition contribute to suboptimal nutrition and elevate the risk of chronic diseases [4]. Research indicates that food insecurity rates among older adults can be as high as 20% [5], with malnutrition rates reaching 27% among community-dwelling older adults [5,6]. Poor diet quality has been correlated with diminished functional capabilities, heightened susceptibility to falls [7], frailty [8], and increased mortality [9]. Therefore, addressing food security among older adults at risk is imperative for enhancing dietary standards, preventing malnutrition and its associated ramifications, and managing chronic conditions.

The goals of the congregate meal program (CMP) funded by the Older Americans Act (OAA) are to reduce hunger and food insecurity, promote health and socialization, and delay adverse health effects so community-dwelling older adults 60 years or older may remain independent in their homes, reducing institutionalization [10]. Socialization at congregate meal centers provides mental well-being benefits in addition to nutritional benefits. The CMP serves lunchtime meals for up to 5 days per week to over 1.5 million older adults in the United States and served over 60,000 older adults in Texas in 2018 [11]. Although the CMP meals provide one-third of the dietary reference intakes, allow for higher intakes of certain nutrients, and contribute to overall higher diet quality compared to nonparticipants, nutrient inadequacies still exist, especially among lower-income participants [12]. Gaps in technological access and knowledge referred to as the “digital divide” [13] disproportionally affect older adults, those who live in rural areas, the disabled, and the impoverished populations [14]. The COVID-19 pandemic heightened the awareness of the digital divide and deepened inequities in vulnerable populations [15]. In addition, the COVID-19 pandemic amplified existing challenges for older adults in maintaining their health. Marginalized and vulnerable older adults experiencing poverty, chronic conditions, financial instability, and limited technology access and knowledge before the pandemic shouldered much of the pandemic burden and risk [16-19]. Importantly, at-risk community-dwelling older adults who attend congregate meal sites lack digital nutrition interventions to address deficits in suspended services [20]. Eating alone is a nutritional risk factor and is associated with reduced food intake [21] and risk for malnutrition. With centers closed, those individuals who live alone are impacted by social isolation to a greater extent, and providing an online social environment during meal times can alleviate this risk factor and could potentially improve nutrient status. Thus, improving technology access and knowledge and delivering a virtual nutrition intervention can extend beyond the constraints of CMP participants to other vulnerable older adult populations. Although online services may never fully replace in-person interactions, the overall reliance and dependency on technology have become an integral part of our society.

Successful dietary behavioral change interventions with older adults have common features including using behavior change theories to promote self-efficacy, containing clear and repeated messages, incorporating incentives for motivation, and sufficient contact [22,23]. Positive behavior change has successfully increased fruit and vegetable intake and fiber in interventions targeting community-dwelling older adults [24]. Interventions at congregate meal sites have successfully increased participant fruit and vegetable intake after a 5-session program [25] or a 4-week intervention [26]. Additional studies have documented improvements in nutrition risk scores, a small improvement in food-related behaviors for both congregate and homebound meal participants [27], and improvements in dietary supplement knowledge and behaviors in congregate meal participants [28].

Limited studies on digital interventions for older adults impacting nutrition exist, and published studies focus on eHealth or Telehealth [29,30] and disease-specific interventions [31-35]. Successful digital interventions have been documented using “telemonitoring” for 4 months to improve nutritional status and increase vegetable, fruit, and dietary fiber intake in a Dutch population [30]. This study observed a high level of participant satisfaction, with an 80% completion rate. The majority of dropouts were older and had poorer cognition and physical function [29]. Another telemedicine intervention had positive outcomes of reduced malnutrition and improved protein intake [33]. In interventions targeting specific disease states, evidence supports “eHealth” interventions using the web and mobile-based technologies to improve diabetes care [34], and an 8-week program to increase calcium intake and exercise to improve bone health [35].

Therefore, to test the impact of a technology-based intervention on the primary outcomes of food security and diet quality, we hypothesize that older adult participants will report improved overall nutrition quality and a reduction in food security (Aim 1). To determine the effect of the intervention on secondary outcomes of technology knowledge and usage, physical activity, social isolation, and loneliness, we hypothesize that providing access and training to technologically disadvantaged older adults will increase accessibility, knowledge, and improved attitudes toward technology use (Aim 2). To examine the long-term

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impact and sustainability of technology use on food security, diet quality, physical activity, and social isolation, we will evaluate the sustainability of online programming integrated into the CMP, assessed via surveys and usage data (Aim 3).

Methods

Design

This study is a closed cohort stepped wedge design in which the timing of the intervention is randomized by cluster, with the sequential crossover of clusters from control to intervention until all clusters have received the intervention. With this design, each cluster contributes data when they are participating in the intervention and when they are not. Stepped wedge designs are useful for several reasons. First, they allow all participants to receive the intervention, and each intervention arm can serve as its control, which decreases the number of units needed. Second, the design is practical in a situation with limited resources where the intervention logistically cannot be carried out all at once. Third, the design allows researchers to examine any effects of time on the intervention's effectiveness [36,37]. Baseline data on current dietary intake, food security, malnutrition, technology use and attitudes, physical activity, social isolation, loneliness, and demographics were collected from all participants at Time 0. Each of the 12 centers was randomly assigned to one of 2 cohorts. Participants in Cohort 1 received the intervention first. Once Cohort 1 participants finished the intervention, a crossover occurred as Cohort 2 participants began the intervention. At the 12-month time point, the second cohort completed the intervention. Data will be collected for both groups each time point from T0 to T3 (Figure 1).

Figure 1. Stepped wedge cluster randomized trial schema depicting the staggered introduction of the intervention across clusters over time.

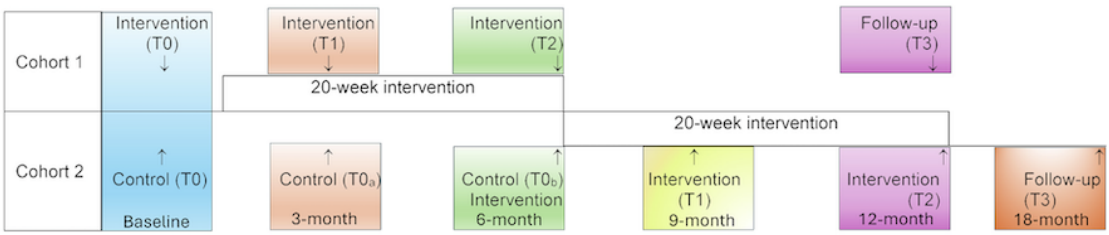

Recruitment and Procedures

Study Setting and Sample

Fifty-two congregate meal sites associated with the Department of Health Senior Services in San Antonio serve approximately 2400 older adults, 60 years or older in San Antonio. The sites vary by geographical location, services offered, number and demographics of older adults served, and setting. The comprehensive city-provided centers include meal service, exercise rooms and equipment, classes of varying topics from nutrition to crafts to technology, social activities, and other supportive services related to health care needs. Early in the pandemic, the congregate meal sites condensed to 11 main "hubs" that provided frozen meals twice per week to nearly 2000 older adults. Activity booklets distributed with the meals monthly provide nutritional educational materials, but this does not replace the lack of curriculum and resources normally available. San Antonio CMP participants are 73 years old, 63% female, and 70% Hispanic. Among them, 33% are categorized as impoverished based on national poverty income levels, and 15% are considered at high nutritional risk based on the DETERMINE (Disease, Eating Poorly, Tooth Loss, Economic Hardship, Reduced Social Contact, Multiple Medications, Involuntary Weight Loss, Needs Assistance, and Elderly Status) your risk nutritional screen, used to assess nutrition risk for all OAA nutrition services programs in Texas.

Participants were recruited from a total of 14 CMP sites. Flyers were used to advertise the study and information sessions. The research team conducted a comprehensive information session at each site, using a presentation describing the study's purpose, research methods, specific data to be collected, and reviewing the consent form. Interested participants signed the consent documents, completed screening forms, and received a US$5 grocery store gift card as a token of appreciation for their time and interest. Research staff were available during the screening process to answer questions and assist older adults as needed. This multifaceted recruitment approach proved effective in ensuring thorough participant engagement and enrollment.

Inclusion and Exclusion Criteria

Older adults with at least one of the following: (1) inadequate or no working technology device (computer, smartphone, or tablet), (2) no or poor internet connectivity at home, and (3) lack of knowledge and usage of technology AND at least one of the following (1) food insecurity or (2) low diet quality, were considered eligible for inclusion in the study. Technical inclusion criteria were measured by questionnaires adapted from the Attitudes Toward Computers Questionnaire and technology use questionnaire from the National Health and Aging Trends Study (NHATS). Food security was assessed using the 10-question US Adult Food Security Survey Module and diet quality was screened using the Dietary Screening Tool [38]. Older adults were excluded from the study if they had a terminal disease or illness, a diagnosis of dementia or Alzheimer disease, or were unable to read or write in English or Spanish.

Randomization and Allocation

Twelve out of the 14 centers participated in the study and were stratified by congregate meal participant enrollment and attendance as large (>100 participants), medium (50 - 100 participants), and small (<100 participants) and randomly

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assigned to one of 2 start times: immediately (Cohort 1) or 6 months later (Cohort 2). Site randomization by a statistician occurred after participant recruitment; however, the treatment condition was not revealed to the participants. Neither the study participants nor the study staff were blinded to the treatment conditions.

Participant Retention and Remuneration

Participants received compensation of a US $20 local grocery store gift card for each data collection event (T0, T1, T2, and T3). Additional rewards were built into the intervention to encourage participation and retention. Cohort 2 participants served as the active control group when not receiving the intervention. The active control consisted of monthly presentations on wellness topics not related to nutrition and bingo games led by our research team, in which they could win a US $5 local grocery store gift card. Furthermore, voluntary peer navigators, who were participants enrolled in the study and attending the center, were recruited from most sites to assist any participant requiring extra help with Zoom (Zoom Video Communications, Inc) session login, survey completion, or troubleshooting challenges within their capacity.

Intervention Design

The City of San Antonio Senior Services Division, which oversees the CMP in Bexar County, along with Older Adults Technology Services (OATS) and the University of Texas at San Antonio (UTSA), researchers with expertise in nutrition and physical activity devised the Digital Nutrition Education Intervention. The intervention included a 5-week technology intervention, designed to address defining features of the digital divide such as access, knowledge, and usage. The 15-week online nutrition course aimed to improve food security and increase overall diet quality, while providing accurate information about nutrition and physical activity through virtual sessions.

Formative Work

A pilot study (5 weeks) was conducted in June and July 2022 with 4 older adults who attended a local community center located in San Antonio and completed a technology class with OATS in May 2022. The community center does not have a congregate meal program. All baseline and posttesting measures and created the surveys for feedback were tested in the pilot study. Pilot data were used to inform the full 15-week intervention. All participants were satisfied with the nutrition topics, recipes, and resources provided, as well as the Friday lunch Zoom socials. A total of 75% were satisfied with the goal sheets and weekly surveys in Google Forms. All participants were satisfied with Google Classroom, but some preferred accessing the class materials by email. During the pilot study, only a single session was offered to participants. Based on their feedback, participants recommended that multiple sessions be provided to enhance scheduling, flexibility, and accommodate different availability. Process evaluation materials were finalized for the technology and nutrition intervention to document fidelity, knowledge gained, and participant satisfaction.

The creation of both the technology and nutrition intervention was informed by an advisory board consisting of UTSA researchers, key Department of Human Services (DHS) and OATS staff, and focus groups consisting of older adult CMP participants. Researchers conducted 14 focus groups with 109 CMP participants in Spring 2022 to determine the choice of technology device and nutrition topics to be incorporated into the nutrition intervention plan. Participants preferred iPads (Apple Inc) over LG tablets due to their big screen, brightness, and user-friendliness. The focus group informed the nutrition topics covered: food security and support resources, fruits and vegetables, whole grains, protein, lean meats, low-fat dairy, healthy snacks, hydration, sodium, healthy eating on a budget, reading food labels, dietary supplements, and food safety. Chronic disease-specific topics were not covered and were linked to the prevention and management of nutrition-related chronic conditions. Special emphasis on food security and the Supplemental Food Assistance Program, and other assistance programs that may help alleviate the cost of food. Three out of 5 older adults are eligible for assistance programs and do not apply for benefits [39]. Additional assistance was provided if food access was an issue. Many grocery stores and food delivery services require digital apps or online ordering, which was covered during the intervention.

Technology Intervention

OATS is a nonprofit organization established in 2004 with a mission to help older adults live better in the digital age. OATS focuses on key areas of financial security, health and wellness, civic engagement and advocacy, social engagement, creative expression, and lifelong learning. Based in New York, OATS expanded to 6 states, including Texas in 2018, with over 26 locations. OATS has served over 30,000 older adults and has engaged San Antonio's Mayor in the Aging Connected pledge to have 1 million seniors engage online. After participation in technology services, OATS reported 76% of participants felt more connected, 39% reported better health, 44% lost weight, 86% felt less lonely, and 94% felt more connected to the world around them. OATS has over 70 online courses and 45 online videos to support its programming.

The technology intervention addresses three key elements of the digital divide: (1) access to the internet and digital devices; (2) digital literacy or skills; and (3) internet usage and value. Access and use of the internet were reported by 67% of adults 65 years or older in the United States [19]. Although internet usage in older adults has increased significantly over the past 5 years [40], digital inequalities and disparities exist for at-risk populations. Digital inequalities can further describe the digital divide in terms of usage, skills, social support, and self-perception. Older adults who use the internet could have limitations in skill, social support, and attitudes that can further describe passive participation in our digital society [41]. Disparities in racial or ethnic minorities further expand the digital divide and are compounded by low socioeconomic status [42,43].

Using OATS' expertise in providing technology education and services, enrolled participants received a technology bundle. The technology bundle included a tablet computer device selected by the focus groups and covers 1 year of internet connectivity and technical support provided by OATS. The

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participants attended a 5-week iPad course that provides information on iPad essentials, introduction to digital culture, and physical activity resources in small groups of less than 15 in person at the CMP sites. In addition, peer navigators (participants who identified as being comfortable in technology skills) were recruited from CMP sites to assist those struggling with technology and having trouble completing weekly tasks in Google Classroom.

Nutrition Intervention

The nutrition intervention aims to restore and enhance nutrition programming for congregate meal participants online after bridging digital connectivity, access to devices, and the applied use of technology. Key intervention strategies to address technology and nutrition will be used to improve diet quality, food security, physical activity, technology use, and socialization (Figure 2). Long-term maintenance of the online curriculum will be managed by DHS Senior Services program, and the sustainability of the project will be measured after 6 months.

Figure 2. Conceptual framework outlining the digital nutrition study design and key components.

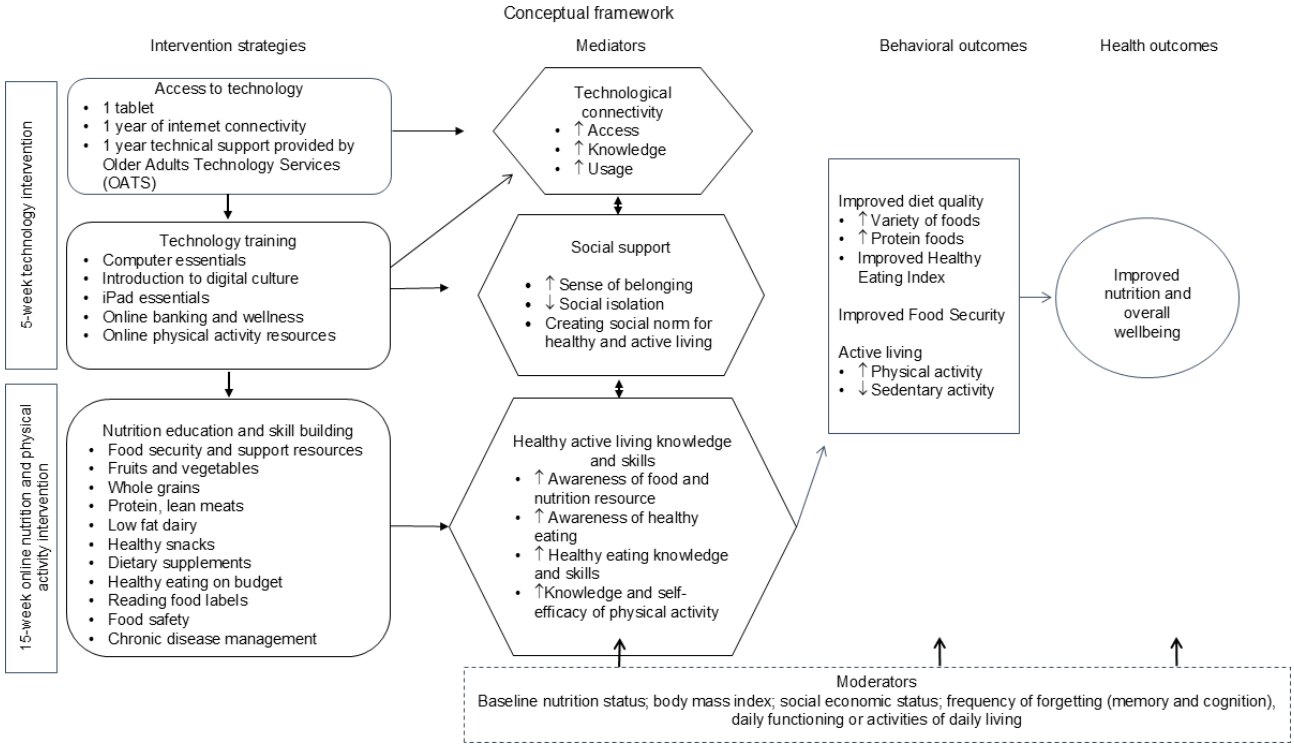

Suggestions from the literature recommend soliciting older adult participation in the technical intervention design and considering barriers to technological intervention [31]. Our nutrition intervention was developed in coordination with input from a subset of older adult CMP participants and the registered dietitian from DHS Senior Services. In addition, we designed the intervention based on successful dietary behavioral change interventions and successful digital interventions with older adults by the following: defined and clear topics relevant to older adult health and the population, using proven behavioral theories, using incentives, and sufficient contact. The intervention was informed by the Social Cognitive Theory that addresses intrapersonal and interpersonal influences on behavior change. Weekly goal setting and goal evaluation were incorporated to increase participants' self-efficacy in eating healthy. Social support systems embedded in the intervention encouraged and rewarded behavior changes. All materials were created at a sixth-grade reading level or below and made available in English and Spanish. Only 1 - 2 learning objectives for each topic were created. A digital reward-based program was created to provide incentives for participation and behavior change. Rewards were in the form of digital "badges" like what is used in online sites and applications for achievements [44,45]. The benefits of this system include a no-cost reward system that may motivate participation and signify progress in learning [45,46]. Weekly and monthly rewards were given for attendance and completing weekly tasks which were captured in a digital format. Graduates of the program were given a certificate at a graduation ceremony conducted at the centers in person.

Weekly modules in Google Classroom included nutrition, Microsoft PowerPoint presentations and supplementary resources, handouts, videos, and recipes to enhance learning and practical application. Physical activity resources such as prerecorded (<10 min) classes and resources, videos, and handouts were included to complement the nutrition intervention. The physical activity classes were designed to cater to the specific needs and abilities of older adults, including low-impact activities designed to be gentle on the joints and help improve cardiovascular health, strength, balance, and flexibility. The physical activity classes also provided information on the importance of nutrition and how it can enhance physical performance and recovery.

All sessions were conducted virtually using the Zoom videoconferencing platform. Email reminders for Zoom sessions and links were sent through Google Classroom and provided

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in Google Calendar. Each week, 3 sessions were conducted in English at different times of the day, and one session was conducted in Spanish, and participants were encouraged to attend live sessions conducted by a registered dietitian or a supervised dietetic student to provide sufficient contact and flexibility. Each session lasted between 40 minutes and an hour and included a Microsoft PowerPoint presentation based on the predetermined weekly topics (Table 1). Time was allocated at the end of each interactive session for questions and answers. One English session and 1 Spanish session were recorded and sent to all participants midway through the week for viewing if they missed attending the live session or if they would like to rewatch.

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Table . Specific topics, learning objectives, clear messaging, and rewards.

Week	Topic	Learning objectives	Clear messaging	Rewards[a]
1	Introduction	• Use the tablet to access live and recorded sessions. • List possible rewards. • Identify ways to document participation.	• Document participation and create goals each week. • Participate in 4 out of 5 activities per week to receive rewards.	• Digital reward • Content • Attendance
2	Nutrition and Physical Activity for Healthy Aging	• Define healthy aging. • List ways nutrition and physical activity can prevent or help manage certain diseases. • List the food groups of MyPlate.	• Good nutrition and regular physical activity can positively impact overall health. • MyPlate meals can help you eat healthy foods.	• Digital reward • Content • Attendance
3	Food security and support resources	• Define food security. • Identify resources that can help with food insecurity. • Assess qualifications for any resources to address food security.	• Use all the resources you qualify for to help with any food insecurity.	• Digital reward • Content • Attendance
4	Reading food labels	• Identify sections of the food label. • Identify nutrients that are high or low in a food product.	• Reading labels can identify healthy foods.	• Digital reward • Content • Attendance
5	Fruits and vegetables	• Describe the health benefits of fruits and vegetables. • List the fruit and vegetable recommendations for older adults. • Identify fruit and vegetable servings.	• Eat a rainbow of fruits and vegetables to gain a variety of nutrients. • Eat 2 servings of fruit and 3 servings of vegetables to gain maximum health benefits.	• Digital reward • Content • Attendance
6	Carbohydrates and grains	• List foods that contain carbohydrates. • Describe the difference between whole and refined grains. • Describe how foods with carbohydrates can affect my body.	• Many foods contain carbohydrates that are needed to fuel your body. • Make half your grains whole.	• Digital reward • Content • Attendance
7	Fats	• List foods that contain fats. • Describe the health benefits of fats. • List fats we need to limit or avoid in our diet.	• Healthy fats in our diet can help reduce the risk of certain diseases. • Limiting saturated fat and cholesterol is important for a healthy diet.	• Digital reward • Content • Attendance
8	Protein	• List foods high in protein. • Describe why dietary protein is important for healthy aging. • List the recommendations for protein for older adults.	• Including adequate protein in our diet can help maintain health. • Protein foods come from both plant and animal sources.	• Digital reward • Content • Attendance

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Week	Topic	Learning objectives	Clear messaging	Rewards[a]
9	Season food without salt	• Define sodium. • Describe how excess sodium relates to health. • Describe ways to flavor food without salt.	• Flavoring foods without salt can reduce excess sodium intake in the diet.	• Digital reward • Content • Attendance
10	Beverages	• Identify healthy beverage options. • Describe why hydration is important for older adults.	• Consuming beverages helps prevent dehydration. • Healthy beverages contain little to no sugar.	• Digital reward • Content • Attendance
11	Healthy snacks	• Describe the importance of consuming healthy snacks for older adults. • List 3 ways to make healthy snacks.	• Healthy snacks can help provide important nutrients in our diet. • Healthy snacks contain 2 or more food groups.	• Digital reward • Content • Attendance
12	Eating healthy on a budget	• Describe how planning meals helps optimize grocery store visits. • List inexpensive easy ways to eat healthy.	• Eating healthly on a budget is possible with adequate planning.	• Digital reward • Content • Attendance
13	Dietary supplements	• Define dietary supplements. • Describe why older adults may need to consume dietary supplements. • List ways dietary supplements may cause harm.	• Dietary supplements may be recommended in certain situations. • Dietary supplements can harm our health if not used appropriately.	• Digital reward • Content • Attendance
14	Food safety	• Define foodborne illness. Describe why older adults are more at-risk for foodborne illness. • Describe how to prevent foodborne illness.	• Older adults are at increased risk for foodborne illnesses. • Food may cause illness if not prepared, cooked, or stored properly.	• Digital reward • Content • Attendance
15	Celebration	• Celebrate goals achieved and knowledge gained.	• Making small changes can improve nutrition choices and healthy habits.	• Digital reward • Content • Attendance • Celebration

[a]Mapping of specific topics to corresponding learning objectives, with emphasis on clear messaging strategies and reinforcement through rewards, developed to support the Digital Nutrition Intervention study.

Participants were required to complete a weekly goal-setting survey, a goal check-in survey, and a week-specific survey. An optional satisfaction survey was sent each week to gather feedback. In addition, optional weekly Zoom social sessions hosted by dietetic and public health students were offered twice a week to facilitate social interaction in the digital space. This was mutually beneficial for the students and the older adults in providing cross-generational interactions to facilitate a greater understanding and empathy for other generations [47]. Older adults may also have added health benefits from this type of interaction [48]. Dietetic students benefited from the practical training experience, while older adults benefited from the socialization.

Measurements

Table 2 lists all the measurements incorporated in the study.

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Table . Overview of measurements applied in the digital nutrition intervention study.

Measurement	Data collection timeline	Outcomes
Diet Quality Score	Measured at all data collection timepoints.	• Developed to assess diet quality and nutrition risk [38]. • Completed within 15 minutes and used to assess the Diet Quality Score [49]. • Score based on overall diet quality (greater than 75=not at risk, between 60 - 75=possible risk, less than 60=at risk) [50].
Healthy Eating Index (ASA24 Food Recall)	Prior, during, and after the assigned cohort intervention.	• Measurement of dietary quality on recommendations from the Dietary Guidelines for Americans [51]. • Completed using the Automated Self-administered 24-Hour Dietary Assessment (ASA24) online tool developed by the National Cancer Institute [52]. • Research team will assist participants in the completion of the ASA24 food recall. • Scoring is on a scale of 1 to 100 for the following food groups: fruits, vegetables, greens, whole grains, dairy, protein, seafood, plant proteins, fatty acids, refined grains, sodium, added sugars, and saturated fats [51].
Food security	Measured at all data collection timepoints.	• Helps to determine financial barriers for safe access to food in the last 3 months [53]. • The 10-question US Adults Food Security Survey Module will be used to assess food security in the following categories and score: 0=high food security, 1 - 2=marginal food security, 3 - 5=low food security, ≥6=very low food security [54].
Physical Activity Scale for the Elderly (PASE)	Measured at all data collection timepoints.	• Used to assess self-reported physical activity in community-dwelling older adults over 7 days by adults aged 65 years and above [55]. • PASE scores range from 0 - 400 or more and are closely associated with grip strength and balance [55].

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Measurement	Data collection timeline	Outcomes
Short Physical Performance Battery (SPPB)	Prior, during, and after the assigned cohort intervention.	• Developed by the National Institute of Aging to assess lower extremity functioning in older adults. SPPB includes gait speed, chair stand, and balance tests [56]. • Overall scores can range from 0 (worst performance) to 12 (best performance) and are predictive of risk for frailty, mortality, nursing home admission, and disability [57].
Attitudes Toward Computers Questionnaire (ATCQ)	Measured at all data collection timepoints.	• 9-question Technology Attitudes Survey is used to measure a person's comfort and interest in tablet computers [43,58,59]. • Participants complete a 20-question survey rated on a 5-point Likert scale (strongly agree to strongly disagree). The final score is computed by adding scores from all questions.
Technology use questionnaire from the National Health and Aging Trends Study (NHATS)	Measured at all data collection timepoints.	• 9-question Technology Access and Usage Survey is used to measure technology comfort, typical daily use, and access in older adults [60]. • Overall scores range from 0 to 9. A score of 0 - 1 is classified as poor technology access and usage, scores of 2 - 5 indicate moderate access and usage, and a score of 6 - 9 signifies good technology access and usage.
OATS[a] technology survey	Administered before, during, and after the 5-week technology essentials class.	• Internal satisfaction survey following the completion of the 5-week technology essentials course administered by OATS. • The data obtained from this survey will be used to evaluate the participants' technology proficiency before and after the course, as well as to measure their satisfaction with the course materials, content, level of difficulty, and the instructor.
Social Disconnectedness Scale and Perceived Isolation Scale	Measured at all data collection timepoints.	• Scale measures the degree of social isolation using two scales. The Social Disconnectedness Scale includes 13 items including restricted social networks and social inactivity [61]. • The Perceived Isolation Scale includes 10 items including lack of support and loneliness [61].
3-item UCLA[b] Loneliness Scale		

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Measurement	Data collection timeline	Outcomes
	Measured at all data collection timepoints.	• The questionnaire assesses the degree of perceived loneliness using the 3-item UCLA Loneliness Survey (PhenX Toolkit) [62].
Malnutrition – Mini Nutrition Assessment (MNA)	Measured at baseline, 6 months, and 6-month postintervention.	• 5-question Mini Nutrition Assessment Short Form (MNA-SF) will be used as a screening tool to identify older adults who are malnourished or at risk for malnutrition [63]. • Score greater than or equal to 12 indicates normal nutritional status, a score between 11 and 8 suggests being at risk of malnutrition, and a score less than or equal to 7 indicates malnourishment [64].
Frequency of Forgetting questionnaire	Measured at baseline, 6 months, and 6-month postintervention.	• Assesses subjective memory impairments in older adult participants [65]. • Scoring is based on the following categories: major problems, some minor problems, and no problems.
Activities of daily living questionnaire	Measured at baseline, 6 months, and 6-month postintervention.	• The PhenX Toolkit was used to assess activities of daily living at baseline, 6 months, and 12 months [66]. • Participants completed a 16-question survey and ability to complete activities: bathing, grooming, dressing upper body, dressing lower body, feeding, using toilet, walking, and getting in/out of chair.
Height, weight, and BMI	Measured at baseline, 6 months, and 6-month postintervention.	• Measured without shoes and with lightweight clothing using a calibrated scale (Seca 876) and portable stadiometer (Seca 213). • BMI will be calculated from the measured height and weight and will be used as part of the MNA score calculation. • BMI categories are classified as follows: BMI less than 19=0, BMI 19 - 20.9=1, BMI 21 - 22.9=2, and BMI 23 or above =3 [67].
Demographic information and medical history	Gathered during screening.	

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Measurement	Data collection timeline	Outcomes
		• Gathered responses on age, sex, residence zip code, senior center attended, race/ethnicity, who lives in the household, how many people live in the household, annual household income, education (highest level attended), current employment status, history of smoking, whether receiving benefits such as social security, disability, Supplemental Food Assistance Program (SNAP) or retirement benefits, diagnosis of medical conditions, and medication list.

[a]OATS: Older Adults Technology Services.

[b]UCLA: University of California, Los Angeles

Process Evaluation

The process evaluation design is informed by the National Institutes of Health Behavior Change Consortium Treatment Fidelity Workgroup's best practice recommendations [68]. Multiple indicators will be used to evaluate the fidelity and completeness of the implementation of all intervention components and determine the contribution of each component to the primary and secondary outcomes. All process evaluation measures present a minimum participant burden. Three major aspects of process evaluation will be measured. First, the intervention dose delivered (ie, the extent to which the technology and nutrition intervention is delivered as planned to older adult participants) will be measured by: (1) technology use records that will measure the times the participant interacted with the intervention materials; (2) completion of delivery schedule from OATS staff to indicate technology equipment and support has been delivered to the participants; (3) evaluation of staff training; and (4) monthly auditing of intervention lesson delivery. Second, the intervention dose received (ie, the extent to which the older adult participants understand and learn the technology and nutrition knowledge and skills delivered in the intervention) will be assessed by: (1) attendance records collected when older adults log in to the intervention site; (2) pre and post knowledge test after each intervention activity; and (3) poststudy focus groups on program delivery process and feedback with intervention staff (n=10). Third, participants' responses to the intervention (ie, the extent to which the older adult participants use and apply the knowledge and skills learned in the intervention in daily life) will be evaluated by: (1) monthly surveys to gather feedback from older adults on their use and satisfaction with the intervention materials; and (2) poststudy focus groups with a subgroup of participants to assess their satisfaction with intervention components/activities and ideas for improving the intervention in the future.

Power Calculations and Estimation of Sample Size

Our sample size calculation was conducted based on examining the effect sizes of similar studies in the current literature [68]. Effect sizes for fruit and vegetable intake ranged from 0.41 to 0.8 [9,28]. Using the smaller effect sizes and considering the stepped wedge design as a clustered randomized trial, with an Interrelation Class Coefficient of 0.016 [37] estimated from the literature (thereby reducing our effective sample size), a total of 210 participants (105 per group) is required to reach 80% power. With an expected N=410 participants in the analytic sample (effective N=374), we will be able to detect an effect size of 0.30 with 80% power and 97.7% power to detect an effect of 0.41 [69]. To detect a difference with an effect size of 0.3 or greater with 80% power at an alpha level of 0.05, 352 participants are required in the analytic sample. Power was calculated using the stepped wedge command in STATA/SE (12.1; StataCorp LLC). The details are described in Hemming and Girling [36].

Data Analysis

Baseline Equivalency

Baseline characteristics for each cohort at the individual and cluster level will be used to determine if any imbalances exist in either demographic variable or baseline dietary intake and food security. Effect sizes (ES) for differences between cohorts will be assessed with Hedges *g* (for continuous variables) and Cox index (for dichotomous variables). Any variables with effect size between .05 and .25 will be added to models to adjust for pre-existing differences.

Missing Data

Missing data will be imputed using full information maximum likelihood. As with most longitudinal studies, participants leave the study at different times, with attrition commonly increasing over time. Traditional methods of handling missing data require the researcher to discard data or impute unknown values, which frequently causes estimation bias and loss of statistical power. These missing data concerns are ameliorated when using full information maximum likelihood, as it does not have the same limitations as other more common approaches (eg, listwise deletion and regression imputation methods).

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Statistical Models

Aim 1

Primary outcome data will be analyzed in Aim 1. For each of the 3 outcomes in Aim 1 (Dietary Quality Score and Food Security), at 3-month and 6-month periods, a 2-level multilevel model (MLM) will be constructed that examines change over time for individual participants within centers. MLMs consider that participants within a cluster (eg, a center) share characteristics that make them more like each other than participants at other centers. MLM has several distinct advantages over other modeling strategies: (1) MLM has greater statistical power given that the estimated standard errors are corrected for model dependency; (2) there is no need to assume or test for the homoscedasticity or sphericity assumptions, as these variance and covariance components are estimated within the MLM model. Depending on model complexity and whether the statistical assumptions are met, the models will be estimated via Bayesian estimation or maximum likelihood estimation with robust standard errors. For Level 1 (participant level), the outcome variable of interest will be modeled using pretest score on the outcome measure, treatment status (ie, control or experimental), and any nonequivalent baseline participant characteristics as covariates. Level 2 (center level) will model the cluster effect of centers on outcomes.

Aim 2

Data collected for Aim 2 represent our secondary research questions (eg, physical activity, technology knowledge and attitudes, social isolation, and loneliness). Data collected at all time points (Physical Activity Scale for the Elderly [PASE], technology knowledge and attitudes, social isolation, and loneliness) will be analyzed using MLM described in Aim 1. To minimize participant fatigue, data for this secondary research aim will be collected at defined intervals (T0, T1, and T2). These data will include the Healthy Eating Index and Short Physical Performance Battery (SPPB) to assess physical function. Differences between groups will be assessed at T2 for each outcome via 2-level covariate MLM models. Level 1 (participant level) will test whether treatment status (ie, control or experimental), pretest score on dietary quality, and food security, and any nonequivalent baseline participant characteristics predict outcomes. At Level 2 (center level), we will model the influence of the 7 centers.

Aim 3

To assess the long-term impacts of the program at T3, Level 1 (time) will model the change in the outcome variables throughout the study (T0, T1, T2, and T3) within each participant. Specifically, each participant's random intercept (eg, initial status) and the random slope over the 3 time periods will be calculated, and the time variable will represent the change in a particular outcome variable (ie, food security) over time within each participant. Level 2 (time nested within participant characteristics) will test whether treatment status (ie, control or experimental) and any nonequivalent baseline participant characteristics predict outcomes. If the ICC coefficient is greater than 0.10, a third level will be added to the model to control for clustering by center. Finally, participants will be clustered within centers (Level 3).

Ethical Considerations

This study is approved by the University of Texas at San Antonio Institutional Review Board (IRB protocol FY20-21-241). The baseline phase of the study involved obtaining institutional review board approval through a comprehensive review, followed by participant recruitment and baseline data collection. During this phase, participants also reviewed and signed consent forms in writing.

Data are collected using Research Electronic Data Capture (REDCap; Vanderbilt University) surveys and are managed and stored in REDCap and in a UTSA-secured site where only the study team has access to participant files. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture; (2) audit trails for tracking data manipulation and export procedures; (3) automated export procedures for seamless data downloads to common statistical packages; and (4) procedures for data integration and interoperability with external sources [70,71]. All data and records generated during this study comply with confidentiality procedures and protocols in accordance with UTSA and Health Insurance Portability and Accountability Act (HIPAA) policies. We will not share any identifiable data with outside study partners unless specified in the consent form. Data collection is the responsibility of the research study staff at the site under the supervision of the site investigator.

Participants receive a compensation of US $20 local grocery store gift card for each data collection event and the opportunity to win a US $5 local grocery store gift card during the bingo games.

Results

The project was funded in October 2022. As indicated in the study progress (Figure 3), recruitment and screening started in June 2022. The research team recruited and screened 150 participants by the end of August 2022 at the 7 original target centers. Due to the low recruitment numbers, the number of centers and recruitment time were extended. Seven additional centers for recruitment were incorporated starting in September 2022. Power analysis was completed to ensure adequate recruitment numbers were met with the 14 centers. NIH was notified in writing of these changes. Fourteen centers were condensed to 12 centers (1 closed because of structural damage and 1 smaller center merged with a larger sister center).

A total of 578 older adults completed the screening, of whom 507 participants were eligible to participate in the study (88%). The 12 centers were randomly assigned into 2 study cohorts, which consisted of a total of 398 older adult participants. Cohort 1 consisted of 226 eligible participants, of whom 164 participants graduated from the program. Cohort 2 had 172 eligible participants, of whom 111 participants graduated from the program (Figure 4). Monthly bingo and informative presentations (nonnutrition and nonphysical activity–related) were conducted with Cohort 2 centers for engagement and retention. Focus groups were conducted for Cohort 1 postintervention in October 2023 and for Cohort 2 in June 2024

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to assess the fidelity of the intervention. Data collection for Cohort 2 is currently ongoing. Preliminary data analysis is being conducted for all cohorts to evaluate the intervention's outcomes.

Figure 3. Study progress.

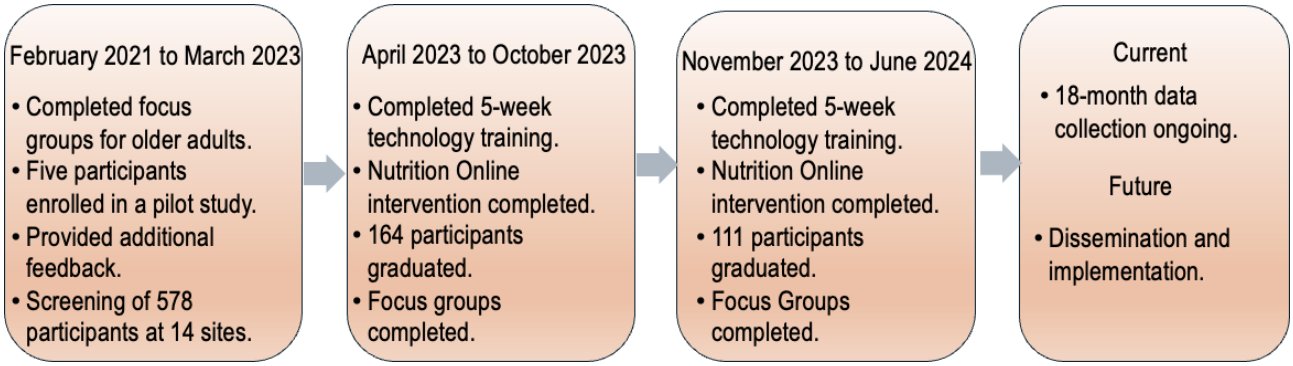

Figure 4. Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

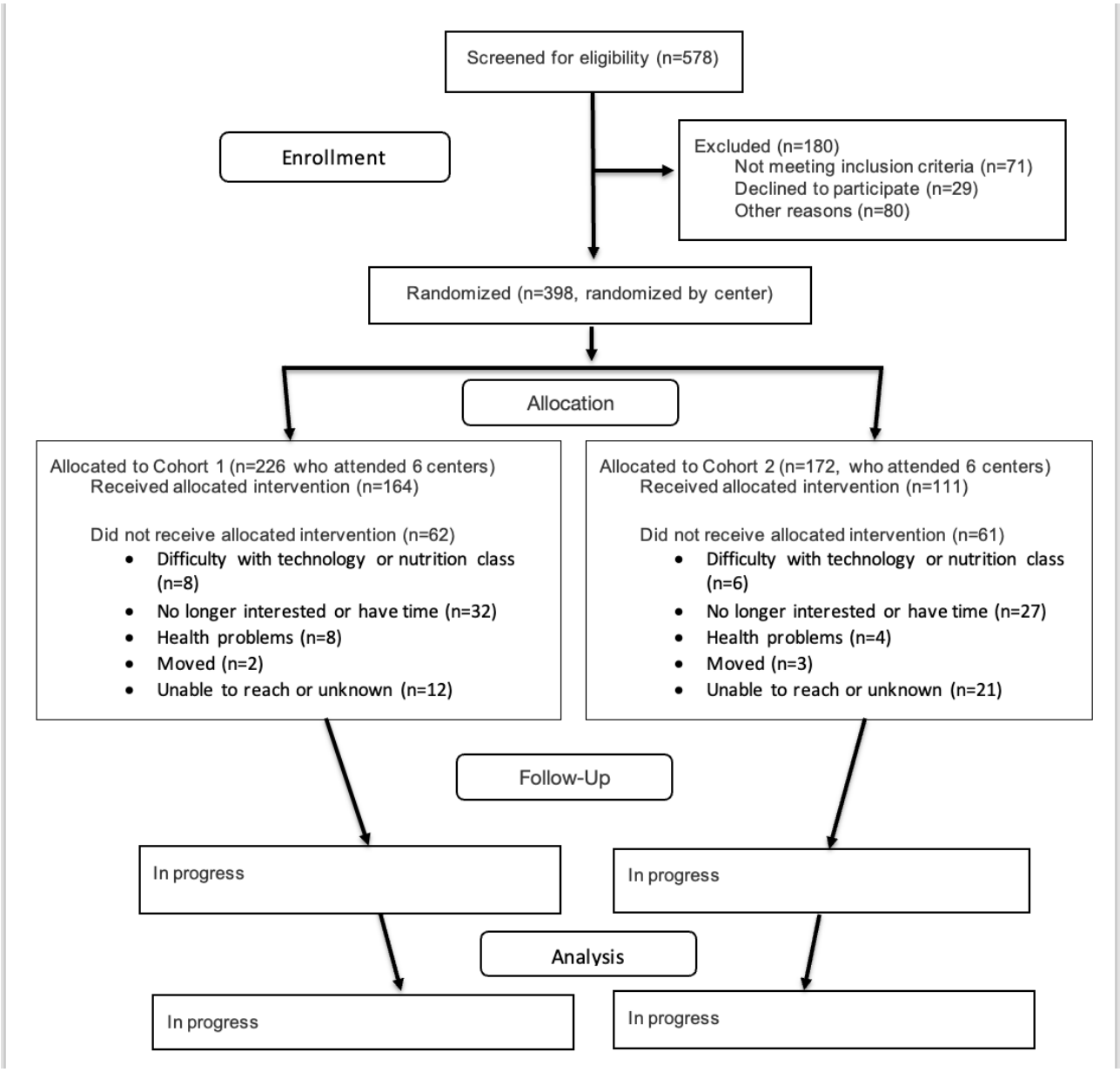

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Discussion

Principal Considerations

Inadequate nutrition and a lack of physical activity can lead to complications from chronic diseases in older adults and a decline in health [72,73]. The COVID-19 pandemic disrupted essential nutrition services like CMP sites in San Antonio, Texas [18]. The "digital divide" exacerbated the negative impact of the COVID-19 pandemic on older adults [18]. To address this, improving technology access and knowledge, and providing evidence-based online nutrition programs are essential and have the potential to benefit the vulnerable homebound population, thereby becoming an integral part of OAA-funded services.

Strengths and Limitations

The program's strengths lie in the potential for its integration into the existing CMP infrastructure, bolstering support and resources for participants most in need. The proposed intervention follows a community-based participatory research approach, seeking essential input and feedback from the DHS Senior Services, OATS, and older adult CMP participants to enhance the intervention's chances of success [74]. Seeking the assistance of the voluntary peer navigators at the centers provided additional in-person support to participants experiencing challenges in completing the intervention. The technology intervention addresses key barriers to older adults adopting technology by providing internet services and devices, offering support through a 5-week training program conducted by OATS, and providing continued technical support and internet access for one year [14,41]. In addition, OATS also provided practice Zoom sessions and in-person help to improve participant self-efficacy in navigating through the Zoom sessions and the nutrition modules in Google Classroom. The DHS team acted as a medium of communication between the study team and the participants.

A second strength of the study is the closed-cohort stepped-wedge design. In this approach, cohorts are randomly assigned the timing of the intervention, with a sequential transition from control to intervention for each cohort until all participants have received the intervention. This design ensures that all participants benefit from the intervention and allows each group to serve as its own control. It is practical when resources are limited and allows for the analysis of the influence of time on the intervention's effectiveness.

Given the increased reliance on technology post-COVID-19, offering a digital nutrition intervention has the potential to positively impact food security and diet quality among vulnerable populations [75]. Moreover, this project has the potential to enhance physical activity, improve socialization, and mitigate loneliness in an at-risk, predominantly Hispanic population in South Texas.

Although the proposed intervention offers technology training, support, and access to the internet and devices, some limitations exist. A few participants may continue to experience challenges in understanding and using technology to engage in the online nutrition sessions conducted via Zoom. Moreover, the technical support and internet access provided by OATS ceased after the one-year service period, thereby restricting participants from using their devices except at the CMP site or locations offering complimentary Wi-Fi connectivity. Furthermore, the accuracy of survey completion may be affected by recall bias and introspective ability. To enhance the long-term sustainability of the project, mitigate associated costs, and strengthen the scope of incorporation into OAA services, it is important to investigate alternative options that offer low-cost internet access and affordable devices.

Conclusions

This intervention study, conducted in collaboration with community partners and older adults, is focused on delivering a culturally tailored digital nutrition curriculum to at-risk older adults who frequently attend congregate meal sites. This initiative followed the allocation of technological resources and requisite support. The study's developed materials are designed for implementation across all senior center locations in San Antonio. If successful, the project has the potential to reach over 2000 older adult congregate meal participants throughout San Antonio. Furthermore, it could serve as a replicable model for other OAA-funded nutrition services. The study's outcomes will be disseminated through publication in high-impact journals and presentations at regional and national nutrition conferences dedicated to nutrition and aging.

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Data Availability

The data supporting the findings of this study are available from the corresponding author after primary and secondary outcome measures have been analyzed and published.

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Authors' Contributions

Conceptualization: SU, ES, MH, TZ, ZY
Data analysis: AH
Manuscript writing: VS, SA, MA, MMM, SU
Manuscript reviewing: VS, SU
Project administration: MMM

Conflicts of Interest

None declared.

Checklist 1
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File, 2514 KB - resprot_v14i1e65976_app1.pdf]

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Abbreviations

CMP: congreate meal program
DETERMINE: Disease, Eating Poorly, Tooth Loss, Economic Hardship, Reduced Social Contact, Multiple Medications, Involuntary Weight Loss, Needs Assistance, and Elderly Status
DHS: Department of Human Service
HIPAA: Health Insurance Portability and Accountability Act
MLM: multilevel model
NHATS: National Health and Aging Trends Study
OAA: Older Americans Act
OATS: Older Adults Technology Services
REDCap: Research Electronic Data Capture
UTSA: University of Texas at San Antonio

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Simulation Through Virtual Reality for the Management of Anxiety and Neuropathic Pain: Protocol for a Randomized Clinical Study

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Abstract

Background: Neuropathic pain is a complex chronic pain condition often accompanied by affective symptoms such as anxiety and depression. This comorbidity is associated with increased pain severity, disability, and diminished quality of life, complicating treatment. Virtual reality (VR) is an innovative non-pharmacological intervention that is gaining attention for its potential to alleviate pain and anxiety through immersive distraction. The Protocol Committee of the University of Salamanca (Spain) has approved the study protocol (approval code: ID.1243)

Objective: We aimed to evaluate the efficacy of VR in reducing pain and anxiety in patients with persistent neuropathic pain.

Methods: This randomized, controlled, multicenter, open-label trial involves two groups: an intervention group receiving VR sessions and a control group receiving standard pharmacological treatment. Participants are adults aged 30 - 61 years diagnosed with neuropathic pain, unresponsive to flexible doses of gabapentin. Pain and anxiety levels are assessed using the Pain Detect Questionnaire, Visual Analog Scale (VAS), and Goldberg Anxiety Scale at baseline and follow-up points. VR sessions are conducted weekly for 3 weeks, each lasting 30 - 35 minutes. Perceived time during VR sessions is recorded as an indirect measure of distraction effectiveness. The primary outcome is the reduction in pain intensity and anxiety levels post-intervention compared to baseline. A sample size of 30 patients (15 per group) was calculated to achieve 80% statistical power, considering a 2-point mean difference in VAS scores.

Results: A preliminary pilot study was completed with 16 patients, including 9 who received the virtual reality intervention. Initial findings showed reduced pain perception in 3 patients and decreased anxiety in 4 patients. These results informed the current protocol, which is scheduled to begin in 2025 and is currently in the preparatory phase.

Conclusions: This study hypothesizes that VR will significantly reduce pain and anxiety in patients with persistent neuropathic pain. By providing new insights into non-pharmacological pain management strategies, this research aims to enhance the quality of life for these patients. The findings could support the broader application of VR in clinical pain management.

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KEYWORDS

neuropathic pain; virtual reality; pain management; anxiety; randomized controlled trial; non-pharmacological intervention; neuropathic; chronic pain; disability; quality of life; innovative; alleviate pain; distraction; efficacy; pain reduction

Introduction

Pain is defined as a complex and multidimensional sensory experience that includes cognitive, behavioral, and psychological elements, often associated with unpleasant and subjective experiences. It has an adaptive function that initiates protective responses. Neuropathic pain is a form of chronic pain resulting from injury to the peripheral or central nervous systems. It is characterized as pain directly caused by an injury or disease affecting the somatosensory system [1].

Neuropathic pain frequently coexists with affective symptoms and negative emotions (anxiety, depression, fear, etc). It is estimated that 20% - 30% of patients with chronic pain also experience anxiety-depressive symptoms. Specifically, 50% of patients with chronic pain experience major anxiety-depression at some point, with 34% in the case of neuropathic pain [2,3].

The comorbidity of chronic pain and affective disorders is closely associated with higher pain severity, greater disability, and a substantial decline in patient quality of life [4], complicating treatment significantly. Persistent long-term pain

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and associated suffering seem to be key factors in developing secondary affective and emotional disorders. Long-term neuropathic pain has been shown to hyperactivate the LC-BLA pathway (that increases the activity of projections from the locus coeruleus [LC] to the basolateral amygdala [BLA]—a key noradrenergic circuit involved in arousal, emotional memory, and stress-related behaviors), responsible for anxiety symptoms secondary to the pain process [5].

Treating neuropathic pain is challenging. Pain management programs, therapeutic education, and physical training are fundamental for improving this type of pain. Therefore, it is crucial for patients to understand their pain process to change erroneous beliefs about it, as difficult-to-treat neuropathic pain is related to various psychosocial factors such as high stress or anxiety levels and various emotions caused by the pain.

Techniques aimed at reducing pain and anxiety are being introduced. One non-pharmacological, safe, and innovative technique that could potentially reduce pain and anxiety and is gaining interest in the scientific community in the "new technologies era" is virtual reality (VR). VR findings have helped to better understand the underlying processes of pain experiences and the analgesic role such strategies can play [6].

VR provides a three-dimensional, multisensory, and immersive environment that allows individuals to have modified reality experiences by creating a sense of "presence," making it an excellent candidate for distraction-based therapy. This is suggested to decrease attention to painful stimuli, which could affect the emotional interpretation associated with it, thus reducing perceived intensity.

Distractions help reduce anxiety by preventing painful stimuli from being transmitted to the thalamus (ie, the limbic system) or the sensory cortex as effectively, helping to focus attention on external and internal stimuli rather than nociceptive stimuli. Sometimes, distractions surpass the capability of local anesthetics to control pain and discomfort associated with medical interventions. Distractions can be active (immersive), involving patient participation by manipulating the environment, or passive (non-immersive), involving only observation [7].

Current technological advances, especially in the field of VR, have resulted in new types of distractions that can be used alongside traditional distractions to achieve better pain control in patients.

In VR technology, users interact with a computer-simulated three-dimensional environment. VR provides multisensory information (visual, auditory, tactile, and olfactory stimuli) that helps individuals interact in the simulated world. A literature review by Lopez-Valverde et al [8] concluded that VR has shown its utility in reducing chronic pain and related issues such as anxiety, hopelessness, time spent thinking about pain, and perceived time during a procedure.

The concept of "virtual reality" lacks a unique and homogeneous definition among authors who have worked on it. We believe the most appropriate definition is by Riva [9], who conceptualized VR as a communication interface based on interactive three-dimensional visualization capable of collecting and integrating different datasets into a single realistic experience. Various theories have been proposed regarding pain-modulating effects to explain VR's effects. To understand VR-induced hypoalgesia mechanisms, it is necessary to integrate neurobiological and neurochemical interactions with cognitive-attentional and affective-emotional aspects of the "painful experience" [10].

One of the main hypotheses states that humans have a limited capacity to pay attention to stimuli, so experiencing pain requires some attention to it [11]. Additionally, patients with both acute and chronic pain may experience excessive attention and vigilance towards pain, potentially increasing perceived intensity (or sensitivity to painful stimuli). VR could have an analgesic effect by distracting from the pain focus [12], producing a pain modulation response via neurophysiological activity in brain areas related to analgesia.

However, distraction is not the only proposed effect. The neuromatrix theory suggests that the pain experience results from a complex interaction between attentional, neurobiochemical, and emotional factors specific to each person. Therefore, pain depends on the interpretation and response of the brain matrix. In this context, VR could promote intercortical analgesia by modulating attentional and emotional networks, stimulating areas related to pain inhibition.

Many aspects remain unclear; however, VR use for pain treatment has shown significant benefits.

This study protocol aims to evaluate the outcomes in terms of pain and anxiety relief with VR application in this group of patients with persistent neuropathic pain.

Methods

Ethical Considerations

This study will adhere to the principles outlined in the Declaration of Helsinki and has been approved by the Institutional Review Board of the participating centers (University of Salamanca: approval code: ID.1243). Written informed consent (Multimedia Appendix 1) will be obtained from all participants before study enrollment.

Study Design

Trial Design

We will conduct a randomized, controlled, multicenter, open-label, parallel-group trial with two assigned groups (intervention group and control group).

Scope and Study Period

The study population will include adults aged 30 to 61 years. The study was started by the beginning of 2025, as shown in Figure 1.

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Figure 1. Temporal planning of the activity development during the project. VAS: visual analog scale; VR: virtual reality.

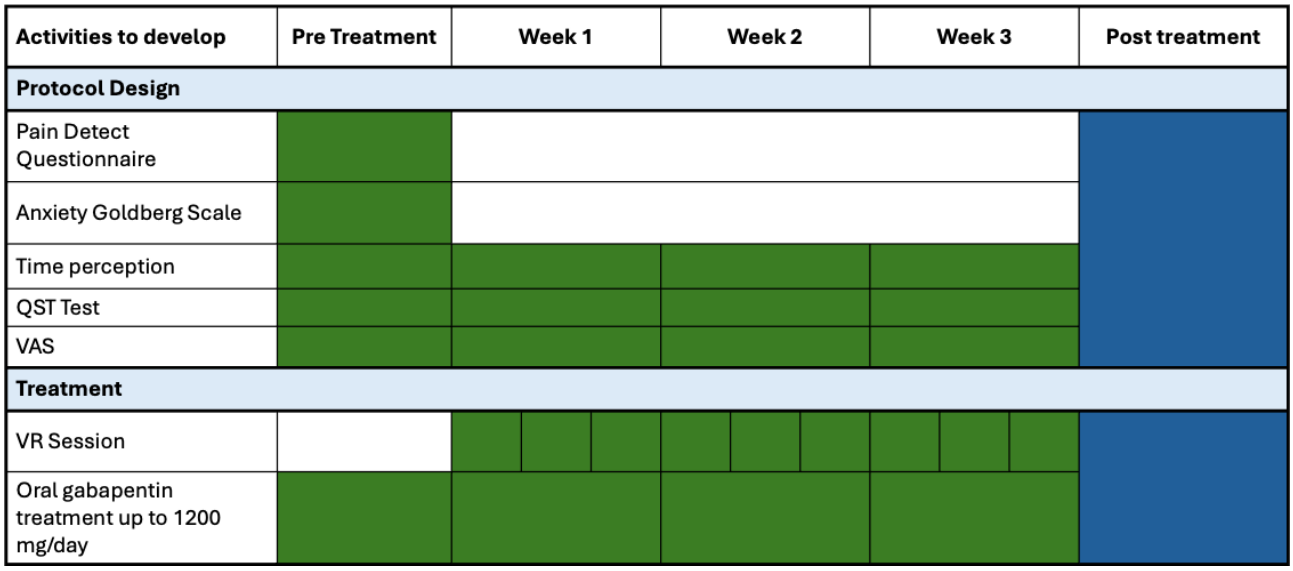

Participants

All patients will be evaluated and deemed suitable by a specialist in the Pain Unit. Neuropathic pain diagnosis was made using the Pain Detect Questionnaire [13].

Neuropathic pain symptoms and signs will be assessed, including sensitivity alterations history such as tingling, numbness, stabbing, burning, shooting, or electric-like pain, paresthesia, allodynia, hyperalgesia, hyperpathia, and motor dysfunction (foot or wrist drop, symmetric motor weakness, difficulty buttoning a shirt or holding a pencil), myalgia, or muscle cramps. Neurological assessment included motor evaluation (muscle strength in limbs), sensory evaluation (touch, pain [pinprick test], cold, heat, vibration, and position, and allodynia test for dynamic and static mechanical stimuli), balance test, coordination, and deep tendon reflexes.

After diagnosing persistent neuropathic pain, oral gabapentin treatment will be prescribed up to 1200 mg/day.

Inclusion Criteria

Patients will be included if they have moderate to severe pain intensity despite treatment with flexible doses of gabapentin for 3 months up to 1200 mg/24 h, understand VR operation and use of validated scales, and sign informed consent forms (Informed consent available as appendix).

Exclusion Criteria

The exclusion criteria include known hypersensitivity to gabapentin, inability to tolerate 1200 mg/24 h doses (dizziness and drowsiness), pregnant or lactating women, any relative or absolute contraindication to VR treatment, patients with unstable or poorly controlled hypertension, recent cardiovascular events (6 mo) before starting treatment, long-term diabetics with cardiovascular autonomic neuropathy, elderly patients, or those with cognitive deficits who cannot understand or apply the scales or answer the questions correctly.

Randomization

Sequence Generation

Randomization will be performed using the RandomizedR computer system (CRAN-R Project), a randomization tool in the R Studio program.

Implementation

Participants will be selected from a daily patient registry. Both the sequence and participant assignment to interventions will be generated by the RandomizedR computer system.

Masking

Due to the study's nature, it will not be possible to blind patients or health care professionals. Therefore, the trial will be open-label. However, a third-party blind evaluation will be conducted, as the data analysis responsible will not be involved in the intervention.

Data Collection, Sources of Information, and Intervention

Pain intensity will be measured using the PainDETECT Questionnaire [13], which is self-administered with 9 descriptors. It detects neuropathic pain intensity and discriminates between possible neuropathic pain (scores between 12 and 19) and definite neuropathic pain (scores above 19). The Visual Analog Scale (VAS) is a one-dimensional quantitative, effective, and easily reproducible scale. Patients mark a 100-mm segment with endpoints labeled as no pain (0 mm) and maximum pain (100 mm); the measure from 0 to the patient-marked point indicates pain intensity. A change of 20 mm (or 2 points on a 10-point pain intensity scale) is considered clinically significant.

Anxiety will be measured using the Goldberg Anxiety Scale [14], a test that not only guides diagnosis but also measures intensity. It contains 2 subscales with 9 questions each: anxiety subscale (questions 1 - 9). The first 4 questions of each subscale (questions 1 - 4) act as a precondition to determine if the rest of the questions should be answered. Specifically, if fewer than 2 questions of the first 4 are answered affirmatively, the rest of

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the first subscale questions should not be answered. For the second subscale, it is sufficient to answer one of the questions 10 - 13 affirmatively to proceed with the rest of the questions.

Time perception will be analyzed as an indirect measure of distraction, with less attention to pain, greater tolerance, and possibly an early sensation of completing the treatment time (or Tprogrammed).

At the end of each VR session (30 to 35 minutes), patients will be asked how much time they think remains. This is called "perceived time" (Tperceived) and will be recorded in 10 - 15-minute intervals based on their responses.

A "significant" difference is defined as a time difference (Tprogrammed - Tperceived) of ≥15 min and "no change" if ≤10 min. For patients who request to stop before completing the time, their "perceived time" is noted by adding the remaining time to the total programmed time.

The frequency and duration of the intervention—fifteen 30-minute VR sessions over 3 consecutive weeks (Monday to Friday)—were selected based on previous studies demonstrating that repeated short-duration sessions enhance user immersion and treatment adherence without inducing fatigue or diminishing attention [15]. This schedule allows for progressive desensitization to pain stimuli and anxiety reduction through consistent exposure to immersive distraction.

For the VR application, the Oculus Go VR 32GB (Meta) model was used, featuring a head-mounted display. This headset provides a stereo visual image, thereby creating a sense of space and depth. A motion tracker in the headset's screen measures head position and adjusts the visual image accordingly. As a result, users perceive their surroundings and can move through the simulated environment. The headset is accompanied by headphones that provide sounds, further enhancing the user's immersion in the virtual world.

Participants in the control group underwent the usual pain assessment review during the 2-week study period.

Eligible patients will be invited to participate in the study continuously, and the assignment to study groups will be randomized.

Sample Size

To detect a difference of 1 point between the two groups on the pain level scales, a sample of 50 patients is required, with 25 in each group, assuming an SD of 3 points, a 95% confidence level, a Z-score of 1.96, a margin of error $\alpha<.05$, and an estimated 10% dropout rate [15].

Patient Recruitment for Study Participation

Patient Selection

Patients included in the study will be selected from individuals diagnosed with persistent neuropathic pain by Pain Units, with moderate to severe intensity. All will be duly informed about the nature and objectives of the study.

Twenty-five patients will be included, and their scores on the VAS, the Pain Detect Questionnaire, and perceived time will be analyzed.

Participants will be adults aged 30 to 61 years. This age range was selected to reduce clinical variability and cognitive interference associated with younger or older populations. Individuals aged under 30 years may not reflect the target patient population for chronic neuropathic pain in clinical practice, while individuals aged over 61 years may present comorbidities or age-related cognitive decline that could interfere with VR engagement or outcome assessments.

Control Selection

Controls will be selected from patients in the Pain Unit diagnosed with moderate to severe neuropathic pain. All will be duly informed about the nature and objectives of the study and asked to provide signed consent.

Before the study begins, training on the use of the devices will be provided to all health care personnel involved.

Data Collection, Information Sources, and Intervention

Data collection will begin once the patient has provided written informed consent. Patient assignment to a study group will be randomized using the RandomizedR computer system.

The data collector will record the patients' age, sex, study group, and type of intervention performed. Before contacting the patient with the virtual reality device, the patient's status and heart rate will be recorded upon arrival at the clinic, regardless of the assigned study group.

Patients in Group 1 will be the intervention group. They will undergo 10 virtual reality pain treatment sessions (Monday to Friday for 2 weeks), with each session lasting 30 minutes, while maintaining treatment with gabapentin at a dose of 1200 mg/24 h. Their clinical history, pain situation, and anxiety will be assessed in each session.

Patients in Group 2 will be the control group. Their clinical history, pain situation, and anxiety will be assessed in each session. They will receive pain treatment with oral gabapentin at a dose of 1200 mg/24 h. The control group will receive standard care without any VR exposure. Participants will remain in a quiet room with standard analgesic treatment as prescribed. No additional relaxation stimuli will be provided. Outcome data will be collected in parallel with the intervention group.

Figure 2 shows the CONSORT diagram.

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Figure 2. CONSORT diagram used in clinical trial reporting to track the flow of participants through a trial, showing how many were screened, eligible, randomized, and completed each stage of the study.

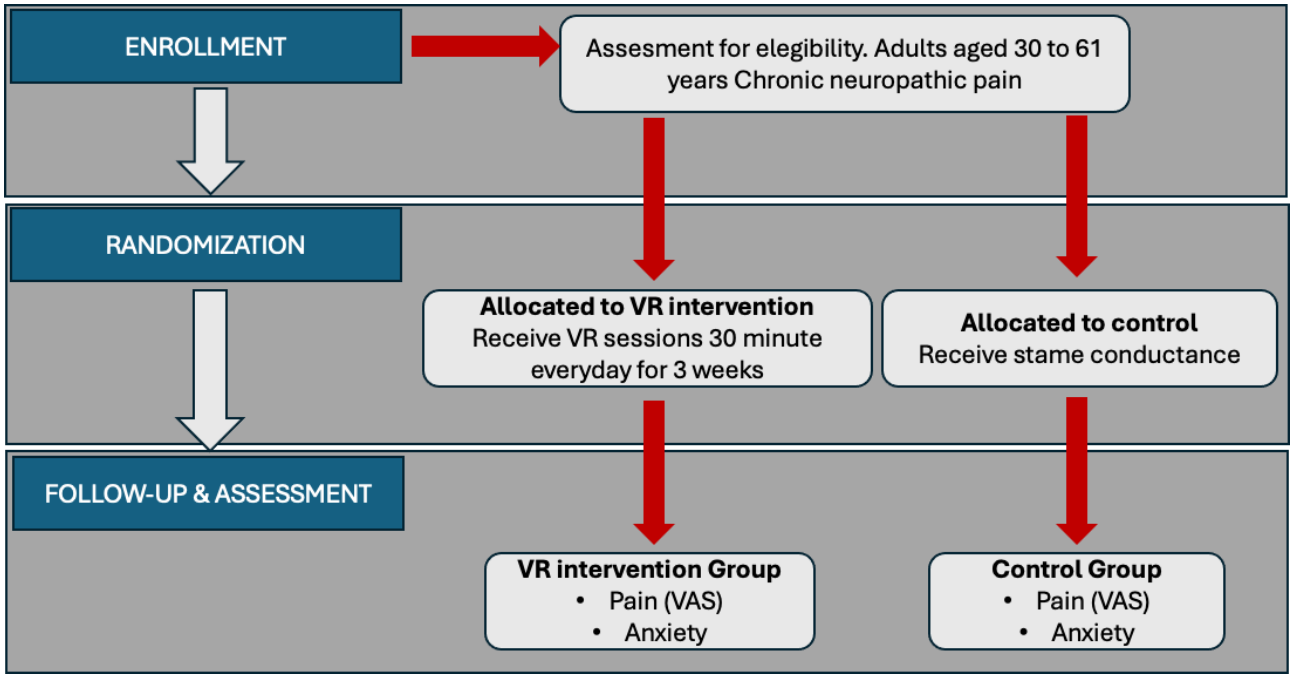

Data Analysis

Data entry for anxiety and pain test scores through VAS, Pain Project, and perceived time will be performed using Microsoft Excel and analyzed using SPSS statistical software (version 16.0).

A sample *t* test will be used. Before applying the *t* test, the Kolmogorov-Smirnov test will be used to evaluate the normality of the mean scores obtained.

Likert-type statements will be analyzed such that a score below 3 indicates disagreement and a score above 3 indicates agreement with a positive statement and vice versa for a negative statement.

Intervention group patients will be informed that they can use the VR device. They will be assisted in putting on the device and given a brief explanation of the content to be displayed.

Data collected from the control group will be compared with those from the intervention group (heart rate, pain perception level, anxiety level).

The mentioned data will be collected by an IT professional through a web questionnaire generated by Microsoft Forms on a tablet and will be stored on a computer server.

Statistical Analysis

Subjects will be analyzed according to the group to which they were assigned.

Data will be collected through Microsoft Forms (an application included in Office 365 by Microsoft Corporation that allows for creating customized questionnaires, surveys, and records) and analyzed with R software (version 4.0.3). Categorical variables will be described using absolute frequencies and percentages, and continuous variables will be described using means and standard deviations or medians and quartiles. A two-tailed *t* test will be used to compare values related to pain, anxiety, and satisfaction between the two groups. Correlations between pain perception and anxiety values reported by patients will be assessed using Pearson's correlation. The significance level will be set at 5%, and all confidence intervals will be set at 95%.

Data will be stored in a database. Pearson's χ^2 test will be used to calculate statistical significance.

Results

The current study began in April 2025 and is currently in the preparatory phase. Previously, a preliminary pilot study was conducted in which 16 patients were recruited, of whom 9 received the VR intervention [16].

In this pilot study, using a distraction chosen by each participant, a significant reduction in pain (defined as a decrease of ≥2 points on the VAS compared to previous experience) was observed in 3 patients. Five patients reported no noticeable change (VAS difference of 0 or 1 points), and 1 patient experienced worsening symptoms and discontinued participation.

Additionally, anxiety, measured using the Goldberg Scale, decreased during the session in 4 patients, with "significant anxiety" defined as a score >2 points.

Regarding time perception, 50% of participants reported a notable difference in their perception of time passage 30 days after the intervention (considered significant if the treatment duration was perceived as 30 min).

These preliminary results provided the rationale for the current full-scale randomized controlled trial, which aims to evaluate whether the use of virtual reality is effective in reducing anxiety and chronic neuropathic pain. In the current protocol, a statistically significant reduction in heart rate and pain intensity

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in the intervention group compared to the control group will be considered a satisfactory outcome.

If the hypotheses are confirmed, this intervention could be implemented in routine care and extended to other procedures involving difficult-to-manage pain.

Discussion

Principal Findings

This protocol outlines a randomized controlled trial aimed at evaluating the impact of VR on reducing anxiety and chronic neuropathic pain. Based on a previous pilot study and literature supporting the use of immersive distraction therapies [6,8,10], we hypothesize that VR will significantly improve patient-reported outcomes in terms of pain perception, anxiety levels, and treatment satisfaction.

Comparison With Prior Work

Several previous studies have demonstrated the analgesic and anxiolytic effects of VR in clinical contexts such as dental procedures, burn care, and pediatric interventions [7,8,17-19]. However, there is a scarcity of research targeting adults with pharmacoresistant neuropathic pain, a population with limited treatment options [20]. Our protocol addresses this gap and builds upon evidence showing that immersive experiences can activate cortical regions involved in pain modulation [12].

Strengths and Limitations

A strength of this study is the integration of immersive VR with standard pharmacologic therapy in a structured and replicable design. Limitations include the lack of home-use devices, potential biases in self-reported outcomes, and the absence of personalization in VR content. Additionally, the exclusion of older adults limits generalizability.

Future Directions and Dissemination

Future studies should explore the feasibility of home-based VR systems and allow patients to select content tailored to their preferences to maximize engagement. Results of this study will be disseminated through peer-reviewed journals, clinical conferences, and institutional briefings, supporting broader implementation in pain management strategies.

Conclusion

If the expected outcomes are confirmed, VR could represent a scalable, non-pharmacological adjunct for managing chronic pain and anxiety, potentially transforming routine clinical practices.

Acknowledgments

This study has not received any external funding. All participants will provide written informed consent prior to study enrollment. They will be informed about the study's objectives, procedures, potential risks, and their right to withdraw at any time without consequences to their standard care. All collected data will be anonymized and stored in a secure database accessible only to authorized personnel. Patient identifiers will be replaced with unique codes to protect confidentiality. No personal information will be used in any publication or presentation of the study results. Participants will not receive monetary compensation. However, they will benefit from increased monitoring and follow-up of their clinical status throughout the study. No identifiable images of participants will be used in the manuscript or supplementary materials. In the event that identifiable images are necessary for publication purposes, explicit consent will be obtained and corresponding consent forms will be uploaded as supplementary files.

Data Availability

The datasets used and analyzed during the current study available from the corresponding author on reasonable request.

Authors' Contributions

All authors contributed to the design and content of the study protocol. JMF is responsible for coordinating the study. JMLM, JMGE, JGS, and CMV are responsible for designing and drafting the initial manuscript. JMF is responsible for data collection, processing, and analysis. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Informed Consent.
[DOCX File, 558 KB - researchprotocols_v14i1e64781_app1.docx]

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Abbreviations

VAS: visual analog scale
VR: virtual reality

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Protocol

Impact of Remote Symptom Management on Exercise Adherence After Video-Assisted Thoracic Surgery for Lung Cancer in a Tertiary Hospital in China: Protocol for a Prospective Randomized Controlled Trial

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Abstract

Background: Regular pulmonary rehabilitation exercises are crucial for patients with lung cancer after surgery. However, poor adherence to outpatient exercises is difficult to address due to inadequate supervision. The integration of remote symptom management through electronic patient-reported outcomes (ePROs) offers a potential solution to improve adherence by enabling more effective monitoring and intervention.

Objective: This study aims to evaluate the impact of ePRO-based remote symptom management on enhancing adherence to outpatient pulmonary rehabilitation exercises following video-assisted thoracic surgery for lung cancer.

Methods: In this single-center, prospective, randomized controlled trial, 736 patients undergoing minimally invasive lung resection will be recruited. All patients will use a smartphone app for perioperative management, allowing periodic PRO measurement and recording of exercise participation. Upon discharge, patients will be randomly assigned 1:1 into either an intervention or control group. The intervention group will complete the Perioperative Symptom Assessment for Patients Undergoing Lung Surgery (PSA-Lung) scale on the day of discharge and postdischarge days 3, 7, 14, 21, and 28. Alerts will be triggered at the provider side if any of the 5 core symptoms (pain, cough, shortness of breath, sleep disturbance, and fatigue) scored ≥4, prompting remote symptom management. The control group will complete the PRO measures without triggering alerts. The primary outcome is the rehabilitation exercise adherence rate. Secondary outcomes include postdischarge pulmonary complication rate, 30-day readmission rate, trajectory of symptom severity changes, exercise participation rate, and patient satisfaction.

Results: The enrollment of study participants started in December 2023 and is expected to end in March 2025. The final comprehensive analysis of the results is planned for May 2025, after all data have been collected and thoroughly reviewed.

Conclusions: This study is among the first to investigate the feasibility and effectiveness of ePRO-based remote symptom management in enhancing rehabilitation adherence after video-assisted thoracic surgery for lung cancer. If successful, this approach could significantly influence postoperative care practices and potentially be adopted in similar settings.

Trial Registration: ClinicalTrials.gov NCT05990946; https://clinicaltrials.gov/study/NCT05990946

International Registered Report Identifier (IRRID): DERR1-10.2196/60420

(JMIR Res Protoc 2025;14:e60420) doi:10.2196/60420

KEYWORDS

thoracic surgery; rehabilitation medicine; patient-reported outcome measures; patient participation; telemedicine; eHealth; mobile phone

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Introduction

Lung cancer remains a predominant cause of cancer-related morbidity and mortality worldwide. Specifically in China, the incidence rate reached 828,000 cases in 2016 [1]. Non–small cell lung cancer is the most prevalent subtype. With the increasing adoption of lung cancer screening, more patients are being diagnosed at early stages. Surgical resection is the gold standard for treating early-stage, non–small cell lung cancer, and the paradigm of enhanced recovery after surgery has been widely adopted in perioperative care [2].

While enhanced recovery after surgery effectively shortens inpatient stays, its benefits are often offset by inadequate outpatient management stemming from limited resources, which can adversely affect clinical outcomes and postdischarge quality of life [3]. One critical factor in postoperative recovery is adherence to pulmonary rehabilitation exercises. However, adherence rates are suboptimal due to insufficient supervision and guidance.

Following discharge, many patients face decreased exercise adherence rates, ranging from 50% to 70% according to studies focusing on patients with musculoskeletal disorders [4-6]. Several factors influence adherence, including self-efficacy, personal beliefs, sense of self-control, physical and psychological condition, clinical symptoms like pain, and perceived forgetfulness [7-11].

Moreover, many patients continue to experience symptoms such as coughing, pain, poor sleep, and breathlessness after discharge, which may substantially undermine their exercise adherence [12]. In the era of patient-centered care, remote symptom management through electronic patient-reported outcomes (ePROs) is emerging as a promising approach to improve outpatient quality of life and reduce postoperative complications [13-16]. By providing effective strategies for timely monitoring and managing patients' symptoms, ePRO-based interventions may help patients overcome barriers to exercise and enhance their self-efficacy and motivation, thus promoting exercise adherence [17].

There is a pressing need for research to investigate the impact of postoperative symptoms on exercise adherence and to evaluate whether ePRO-based remote symptom management can effectively improve adherence to outpatient rehabilitation exercises [18,19].

Therefore, this study aims to assess the feasibility and preliminary effects of remote symptom management based on ePROs on enhancing adherence to outpatient rehabilitation exercises after video-assisted thoracic surgery (VATS) for lung cancer. A prospective, randomized controlled trial study design is adopted to provide new strategies for rehabilitation management in patients with lung cancer. We hypothesize that remote symptom management based on ePROs can improve exercise adherence in patients with lung cancer after VATS compared with usual care.

Methods

Study Setting

This is a single-center, prospective, superiority, randomized controlled trial, consistent with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [20]. Participants will be recruited from the Department of Thoracic Surgery, Zhongshan City People's Hospital, Guangdong, China, which performs approximately 600 lung cancer surgeries annually. The findings will be reported based on the CONSORT (Consolidated Standards of Reporting Trials) guidelines [21]. The study flowchart is shown in Figure 1. This trial has been registered on ClinicalTrials.gov (NCT05990946), where detailed information about the study protocol, inclusion and exclusion criteria, interventions, outcomes, and ethical approval can be found. The trial registration process was completed before the enrollment of the first participant.

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Figure 1. Flowchart of this parallel-group randomized controlled trial. ePRO: electronic patient-reported outcome; PPC: postdischarge pulmonary complication.

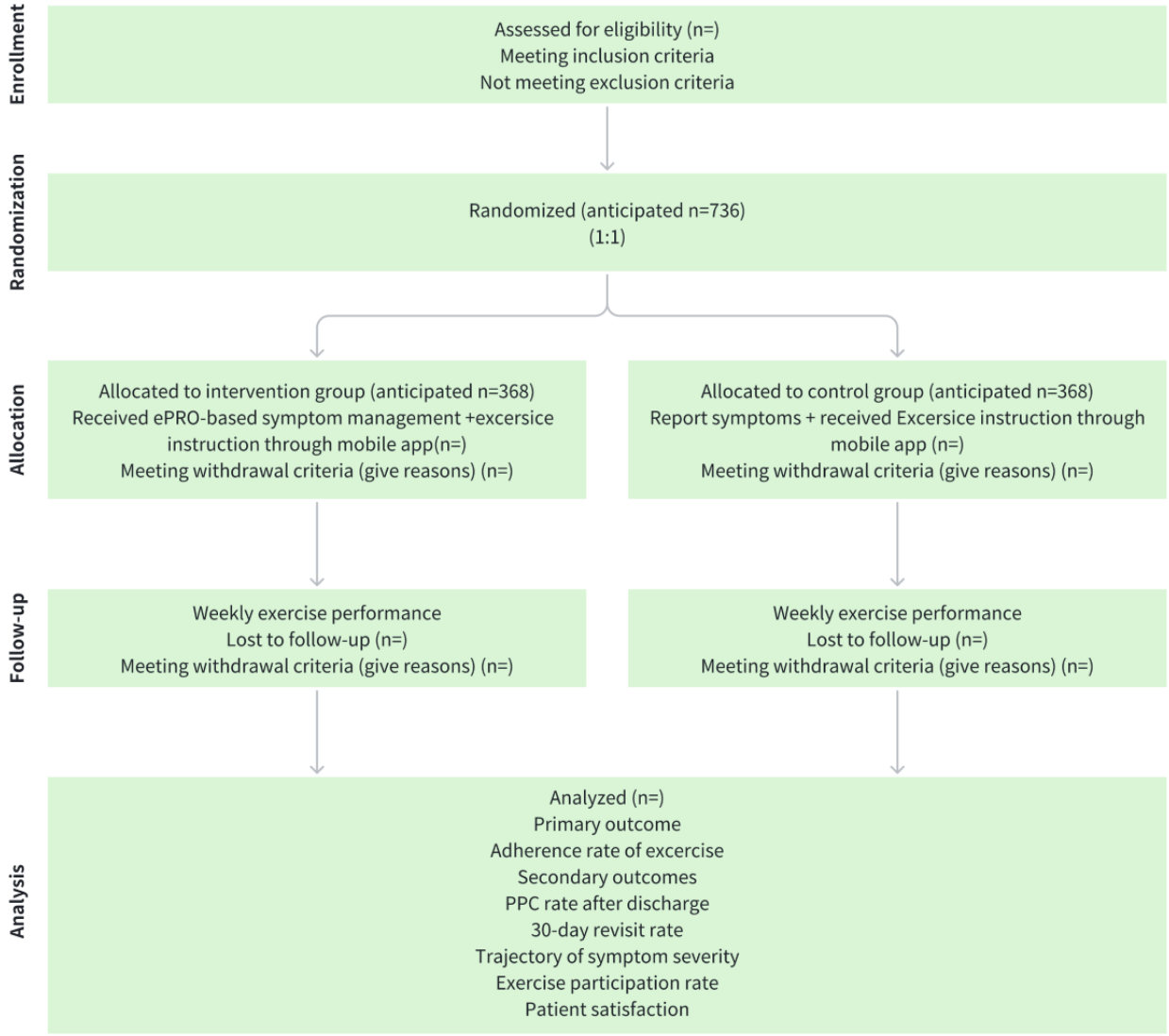

Eligibility Criteria

Inclusion criteria for the participants are (1) being aged 18-75 years; (2) undergoing VATS, including lobectomy or segmentectomy; (3) being able to use smart devices and completing electronic questionnaires; and (4) providing informed consent. The exclusion criteria are (1) conversions to open thoracotomy during surgery, (2) preoperative Eastern Cooperative Oncology Group score >1, (3) received neoadjuvant therapy, (4) previous thoracic surgery history, (5) unable to exercise due to physical impairments, (6) continuous systemic corticosteroid use within 1 month, (7) unresolved toxicity above grade 1, (8) significant medical history, (9) uncontrolled comorbidities, (10) postoperative length of stay >14 days, and (11) other unsuitable conditions in the investigator's judgment.

Participant Recruitment

Patient recruitment will commence before discharge, including preoperative patients awaiting scheduled surgery. Eligible patients will be randomly assigned before discharge after confirming they can properly operate the smartphone app. After discharge, patients will be reminded to use the app for symptom and exercise logging. The app provides an incentive for participating in the 4-week rehabilitation program between discharge and the first postoperative clinic visit.

Randomization and Allocation Concealment

Each potential participant will be assigned a unique 3-digit screening number in sequence. Eligible participants will be randomly allocated 1:1 to the intervention and control groups.

Randomization will be performed using a central Interactive Web Response System (IWRS), which is deployed on a third-party platform (Huawei Cloud) and was developed by the Shuyu app development team. The IWRS uses a block randomization algorithm to generate the allocation sequence and ensure balance between the treatment groups. After confirming eligibility, the study site will enter participant information into the IWRS and receive the allocation. Withdrawn participants will retain their randomization number without re-enrollment. The randomization code will be securely stored in the IWRS throughout the study.

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Blinding

Due to the nature of interventions, blinding of participants and care providers is not feasible. However, data collectors and statisticians will be blinded to group allocation. The data collectors, who are research nurses, will be trained to administer questionnaires and collect data consistently according to the study protocol. They will collect data at baseline through in-person interviews and then weekly for 4 weeks after discharge through telephone interviews.

Interventions

Participants will use the app "Shuyu" (Module type: TH001, Developed by Shanghai CinoCore Health Technology Co) for perioperative management.

Preoperatively, nurses will instruct app use and provide education. The app will assign individualized exercises and prompt logging. Patients will complete baseline PRO measurements. The Perioperative Symptom Assessment for Lung Surgery (PSA-Lung) was used for PRO assessments. The PSA-Lung scale includes 7 symptom items (pain, coughing, shortness of breath, disturbed sleep, fatigue, drowsiness, and distress) and 2 functional items (interference of activity and walking). Each symptom's severity was rated between 0 (the absence of symptom) and 10 (the worst imaginable symptom). Similarly, functional items were also rated on a scale between 0 (no interference) and 10 (complete interference). The PSA-Lung scale development team has verified its reliability and validity in patients who undergo lung cancer surgery, and the research results suggested adequate reliability and validity. The relevant articles have been submitted for publishing, and the preliminary results were announced at the 28th Annual Conference of the International Society for Quality-of-Life Research [22]. Permission to use the PSA-Lung scale in this study has been obtained from the scale development team.

Postoperatively during hospitalization, nurses will guide app-based rehabilitation, doctors will supervise exercises and PROs, and patients will complete daily PROs without alerts.

Before discharge, the care team will evaluate if patients can properly operate the app. Eligible patients will be randomly allocated into groups by the nurse entering the patient's screening number and discharge date in the provider app. Based on the pregenerated randomization code from the central system, this process will automatically allocate patients into the intervention or control group, unlocking the corresponding outpatient module.

After discharge, the app continues to offer postoperative education and exercise logging, sending daily reminders at 9 AM and follow-ups at 5 PM if logs are incomplete. Weekly phone checks by staff will confirm exercise log accuracy. Noncompliance or inaccessibility after 3 phone attempts will result in protocol violation and withdrawal.

Reminders for PRO assessments are set for 9 AM on the day of discharge and on postdischarge days 3, 7, 14, 21, and 28. A follow-up reminder will be sent at 5 PM if the assessment remains uncompleted. These assessments must be completed on the specified days, and the analysis will include patients who have logged exercises but have not submitted PRO assessments. For participants who are unable to continue using the ePRO system, a manual follow-up plan will be implemented to collect PRO data through telephone or email on the day following the scheduled assessment days to avoid conflict with system reminders.

Comparison

Intervention Group

The intervention group will be notified to complete the PRO measures on the designated days.

If any of the 5 core symptoms (pain, cough, shortness of breath, sleep disturbance, and fatigue) scored ≥4 in the ePRO questionnaire, alerts will be triggered on the provider end, prompting the assigned doctor and nurse to initiate remote guidance and intervention through the app through text or phone call within 24 hours following standardized procedures in the operation manual. Interventions will be based on PRO scores and include recommendations for self-management, medications, and clinic visits. In addition, patients who report any of the 5 core symptoms will immediately receive automated internet-based self-management suggestions generated by the system after submitting the PRO questionnaire.

The intervention will focus on the management of these 5 core symptoms since they were identified as critical symptoms for postoperative management in previous studies on remote PRO-based symptom management after lung cancer surgery in China [16]. Based on recommendations from the National Comprehensive Cancer Network and published studies, symptom scores ≥4 are considered moderate severity or above [23,24]. Therefore, a symptom score of 4 is set as the threshold for triggering alerts. Details of the patient self-reporting process and health care provider alert interface are shown in Figure 2.

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Figure 2. Workflow of patient self-reporting via the shuyu app and healthcare provider alert interface.

Symptom management in the intervention arm will adhere to the latest guidelines and be standardized across providers through standard operating procedure manuals, as shown in Multimedia Appendix 1. In cases of severe symptoms, physicians may advise patients to temporarily pause or adjust their exercise plans to ensure safety.

Control Group

The control group will complete PRO measures on the same days without triggered alerts or self-management suggestions.

All patients, regardless of group assignment, will receive guidance on seeking medical attention through conventional means for severe symptoms. Severe symptoms are defined as individual symptom scores ≥6 on the PSA-Lung scale.

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Withdrawal Criteria

Participants meeting the following withdrawal criteria will be removed from the analysis: (1) no primary lung cancer on pathology, (2) non-microscopically complete resection, (3) stage IV disease, (4) initiation of adjuvant therapy during follow-up, (5) severe protocol violation (nonadherence to instructions, random responses, etc), and (6) voluntary withdrawal.

Study Outcomes

Primary Outcome

The primary outcome is the rehabilitation exercise adherence rate over 4 weeks after discharge, defined as the proportion of patients completing the prescribed outpatient exercise regimen. Exercise completion will be ascertained based on patient self-reports through the app and verified through weekly phone follow-ups. Referencing exercise guidelines for cancer survivors from the American Cancer Society, ≥150 minutes of moderate to vigorous intensity physical activity per week (equivalent to 150 minutes of brisk walking) is considered adherent [25].

Secondary Outcomes

Secondary outcomes are listed in Textbox 1.

Textbox 1. Secondary outcomes and their measurement criteria.

- Postdischarge pulmonary complication (PPC) rate
  - Proportion of patients experiencing pulmonary complications within 30 days after discharge. Complications will be graded using the Clavien-Dindo classification [26], categorizing PPCs into 5 grades, as shown in Multimedia Appendix 2.
- 30-day revisit rate
  - Proportion of nonscheduled revisits within 30 days after discharge.
- Trajectory of symptom severity
  - Changes in symptom and interference scores on the electronic patient-reported outcome questionnaire from discharge to 30 days after discharge.
- Exercise participation rate
  - Number of days with exercise logged within 4 weeks after discharge. Any day with exercise logged is considered participation, regardless of whether the target duration is achieved.
- Patient satisfaction: score on the 4-item questionnaire including
  - Whether the app helped with rehabilitation and symptom control;
  - Overall satisfaction rating;
  - Whether the app caused daily life disruption; and
  - Likelihood of recommending the app to others. Each item is rated from 0 to 10.

Other Data

The study will record time intervals from alert to provider intervention in the app backend. Questionnaires and interviews will also survey provider acceptance of the app. Participant demographic information, tumor characteristics, clinical management, treatment outcomes, adverse events, and follow-up data will be collected at different time points. All adverse events will be evaluated and managed by thoracic surgeons.

Sample Size

The primary outcome is the rehabilitation exercise adherence rate, defined as the proportion of patients completing the prescribed exercise regimen. Adherence is defined as completing the prescribed exercise regimen, calculated from self-reported app data and verified through weekly follow-ups.

The sample size was calculated to detect a 10% difference in adherence rates between the intervention and control groups, with 80% power and a 2-sided significance level of .05. The control group adherence rate was assumed as 70% based on previous studies [27-30]. The 10% clinically important difference was determined through expert consultation, considering their practical experience and the potential impact on patient outcomes, despite limited direct literature support. The dropout rate was estimated as 20% from previous digital intervention trials (from 3.75% to 18.3%) [31-33]. Dropouts include discontinuation of app use and loss of follow-up.

Using a z test with a 10% proportion difference, 80% power, 5% type I error, and 20% dropout rate, the required sample size is 368 per group, 736 in total.

Data Analysis

Statistical analyses will be performed based on both the intention-to-treat principle and the per-protocol principle. The intention-to-treat population will include all randomly assigned participants, while the per-protocol population will include participants who provide baseline PRO data and measures for at least 2 additional time points, with at least 1 calculable weekly exercise duration logged. Participants meeting withdrawal criteria will be excluded from all analyses. Statistical inferences

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will adopt 2-sided tests at a significance level of .05, with 2-sided 95% CI for estimation. The primary outcome, exercise adherence rate, will be compared between groups using the Pearson χ^2 test or Fisher exact test. Secondary outcomes will be analyzed as follows: PPC rate and 30-day revisit rate will be compared using χ^2 test or Fisher exact test; symptom severity trajectory, which involves repeated measurements, will be assessed using linear mixed effects models to account for within-subject correlation; exercise participation rate will be compared using Wilcoxon rank sum test; and patient satisfaction scores will be compared using the Student 2-tailed *t* test or Wilcoxon rank sum test. The time from alert to intervention and provider acceptance will be summarized descriptively. Baseline characteristics will be compared using 2-tailed *t* test, Wilcoxon rank sum test, χ^2 test, or Fisher exact test, as appropriate. Missing data will be handled through multiple imputation or maximum likelihood estimation methods.

Data Monitoring and Interim Analysis

A Data Safety Monitoring Board will be set up, including 1 clinical physician and 1 data manager, to conduct independent data monitoring. No interim analysis is planned considering the low-risk nature and short study duration.

Patient and Public Involvement Statement

Patients and the public will not be involved in the design, recruitment, or implementation of this study. Study results will be disseminated to applicants. As disseminating results to participants is not standard practice in China, we have no plans for participant-directed dissemination. Study participants will be informed that final results can be accessed through our future publications.

Ethics Considerations

The study protocol was approved by the Ethics Committee of Zhongshan City People's Hospital in December 2022 (approval K2022-285). All recruited patients will be required to give written informed consent. Any subsequent amendments to the protocol will be submitted for further review and approval. Study findings will be disseminated through peer-reviewed publications and conference presentations.

Results

The enrollment of study participants started in December 2023 and is expected to end in March 2025. An interim analysis is planned to assess the feasibility and preliminary effects of the intervention. The final comprehensive analysis of the results is planned for May 2025, after all data have been collected and thoroughly reviewed.

Discussion

Conclusions

This study primarily investigates the impact of outpatient symptom management on exercise adherence after minimally invasive lung surgery. Remote symptom monitoring based on ePROs provides an innovative approach to improve patient self-management and rehabilitation compliance. While previous digital interventions have focused on education and coaching, this study explores a new precision rehabilitation model that actively monitors patient-reported symptoms and provides timely medical feedback. Although symptom-related exercise interruptions may occur in both groups, the ePRO-based interventions are designed to help manage symptoms and provide personalized exercise guidance, which may potentially mitigate the impact of symptoms on exercise adherence.

Potential findings from this preliminary study include (1) providing initial evidence on whether ePRO-based remote symptom management can improve outpatient exercise adherence, which has been a neglected area in previous research; (2) demonstrating the feasibility and acceptability of implementing such a personalized symptom-exercise comanagement model in local patients; and (3) exploring its potential to reduce patient symptom burden and postoperative complications. The findings from this study will provide valuable insights into the barriers and facilitators of implementing ePRO-based symptom management in real-world settings, informing future efforts to expand and optimize outpatient care for postoperative patients. The planned analyses will also help elucidate the complex relationships between symptom alerts, symptom management, and exercise adherence in this context. Understanding these relationships is crucial for optimizing the design and implementation of integrated symptom-exercise management interventions for postoperative patients. If the findings support the feasibility and potential effectiveness of this innovative rehabilitation approach, it could inform future larger-scale studies and efforts to improve postoperative care for a broader patient population. The research framework and findings will contribute to advancing telehealth for patient-centered and digitally enabled care models.

Limitations

This study also has some limitations. First, the single-center design may limit generalizability. Second, the strict inclusion or exclusion criteria may restrict the eligible population, such as excluding patients unable to use smartphones or with poorer reading comprehension. Third, the eligibility criteria may cause selection bias and limit external validity, although stringent criteria and verification of exercise data are adopted. Further pragmatic trials in more heterogeneous populations are warranted to validate broader generalizability and effectiveness. Fourth, the lack of blinding for researchers and participants may introduce bias into the results. Fifth, the short follow-up precludes evaluation of potential long-term impacts on exercise habits.

In summary, this unblinded randomized controlled trial aims primarily to provide preliminary evidence on the effects of ePRO-based symptom management on outpatient exercise behaviors, evaluating the feasibility of this management approach. Larger studies in real-world diverse populations are needed to further validate its generalizability and effectiveness.

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Acknowledgments

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Data Availability

The data sets generated during and/or analyzed during this study are available in the ClinicalTrials.gov repository. The protocol will be published on an open-access repository.

Authors' Contributions

All authors contributed to the design of this protocol. XY and JS initiated the project. XY drafted the protocol and will be responsible for manuscript preparation. JS, YL, and CY contributed to the study design and methodology and will provide critical revision of the manuscript. QZ was involved in the statistical design and will be responsible for data management and analysis. WJ, GL, and YC will contribute to research coordination, ongoing patient enrollment, outpatient research follow-ups, and data collection. All authors have read, refined, and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Standard operating manual for symptom intervention.
[PDF File (Adobe PDF File), 127 KB - resprot_v14i1e60420_app1.pdf]

Multimedia Appendix 2
Clavien-Dindo classification of surgical complications.
[DOCX File , 14 KB - resprot_v14i1e60420_app2.docx]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
ePRO: electronic patient-reported outcome
IWRS: Interactive Web Response System
PPC: postdischarge pulmonary complication
PSA-Lung: Perioperative Symptom Assessment for Patients Undergoing Lung Surgery
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
VATS: video-assisted thoracic surgery

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Protocol

Effectiveness of the User-Centered "Healthcare CEO" App for Patients With Type 1 Diabetes Transitioning From Adolescence to Early Adulthood: Protocol for a Randomized Controlled Trial

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Abstract

Background: Young patients aged 16 to 25 years with type 1 diabetes (T1D) often encounter challenges related to deteriorating disease control and accelerated complications. Mobile apps have shown promise in enhancing self-care among youth with diabetes. However, inconsistent findings suggest that further evidence is necessary to confirm the effectiveness of app-based interventions.

Objective: This study aims to evaluate the effectiveness of the Healthcare CEO app in patients with T1D transitioning from adolescence to early adulthood.

Methods: A 2 arms, double-blind, randomized controlled trial will be conducted over a 9-month period, with strategies designed to enhance treatment fidelity. The study expects to enroll 96 patients with T1D, aged 16 to 25 years. Participants will be randomly assigned to either the experimental or control group through central randomization. The intervention will be implemented using the Healthcare CEO app, which consists of 11 interfaces. The research will compare differences in disease control outcomes, confidence in self-management, self-care behaviors, emotional distress, quality of life, and specific diabetes-related knowledge between the 2 groups at baseline and 3, 6, and 9 months after intervention. Additionally, changes within the experimental group will be analyzed before and after the intervention.

Results: The study was funded in August 2020. It was originally scheduled from August 2020 to July 2022 but was interrupted by the COVID-19 pandemic after enrolling 38 participants, with preliminary results anticipated for publication by November 2024. Recruitment resumed in August 2023, with findings expected to be finalized by July 2025.

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Conclusions: The Healthcare CEO app is a comprehensive solution tailored specifically for individuals with T1D transitioning from adolescence to early adulthood. This innovative app has the potential to improve the quality of care for adolescents with T1D during this critical stage and may serve as valuable evidence in support of app-based intervention strategies.

Trial Registration: ClinicalTrials.gov NCT05022875; https://www.clinicaltrials.gov/study/NCT05022875

International Registered Report Identifier (IRRID): DERR1-10.2196/59871

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KEYWORDS

type 1 diabetes; transition; mobile health; treatment fidelity; diabetes; user-centered; adolescence; teenager; app; adolescent patients; early adulthood

Introduction

Overview

Type 1 diabetes (T1D) is the most common type of diabetes among youth younger than 18 years [1]. The incidence of T1D has exhibited a decline in the 0-9 years age group and an increasing trend in the 10-14 years age group [2,3]. Notably, T1D accounts for approximately 0.59% of all diabetes cases in Taiwan, and its incidence in patients aged 19 years or younger is 5.17 out of 100,000 while its prevalence is 0.05%. The prevalence and incidence of T1D in patients aged 19 years or younger increased significantly from 2005 to 2014 [4]. With this increase, the demand for care during the transition phase between adolescence and early adulthood is also expected to increase [5]. Therefore, understanding the life experiences and health care needs of adolescents with T1D in this transition phase and comprehending the customization of interventions to meet these needs is crucial in T1D care.

Background

Encounters and Challenges of Patients With T1D in the Transition Phase From Adolescence to Early Adulthood

A transition phase is when an individual encounters significant life events or environmental changes. It is fraught with uncertainty and requires adaptation by learning new skills and strategies [6]. In nursing, the antecedents of the transition process are transition events that can be classified into 4 categories: developmental, situational, health‐illness, and organizational transitions [6]. Moreover, providing nursing support to patients in transition may contribute to role mastery and maintenance of physical and emotional well-being [7].

The encounters and challenges of patients with T1D transitioning from adolescence to early adulthood are wide-ranging and possess unique characteristics. The developmental transition from adolescence to early adulthood is often characterized by a rapid increase in height and body weight, as well as dramatic hormonal changes. Therefore, individuals with T1D in this transition commonly face the physiological challenge of maintaining stable blood glucose levels [5,8] and are at a high risk of poor disease control [9,10]. A study of individuals registered in the T1D Exchange Clinic Registry (a large-scale registry of patients with T1D in the United States) revealed that the mean hemoglobin A_{1c} (HbA_{1c}) level in 18- to 25-year-olds was 8.7% (SD 1.9%) [11], which is higher than the average. The inability to achieve optimum blood glucose control is one of the greatest stressors faced by patients with T1D and may even cause anticipatory nervousness, which in turn affects sleep quality [12]. Other key stressors include the quest for independence, the burden of disease-related self-care, and the implementation of disease self-management [13,14]. Challenges faced by young patients with T1D in situational transition include the deconstruction of peer relationships caused by education system transition, establishment of sexual relationships, worries regarding the health and genetic inheritance of offspring, and reconstruction of physician-patient relationships due to workplace changes or home relocation [13,15,16]. During health-illness transition, especially from late adolescence to early adulthood, patients often become hospitalized owing to acute complications such as ketoacidosis and hypoglycemia. The need for frequent blood glucose monitoring and the transition from hospitalization to discharge often causes disruptions to life routines [5,16,17]. Young patients with T1D often experience an organizational transition, from family-centered care to patient-centered care, at 16-25 years [18,19]. Difficulties faced during this transition period often include the lack of a comprehensive transition-phase care plan that meets patient requirements, negative health care–seeking experiences in adult care systems, termination of health insurance, and loss to follow-up [10,20,21]. In Taiwan, the pediatric care model is adopted for most patients with T1D transitioning from adolescence to early adulthood. Many patients consider the transition from pediatric to adult care unnecessary owing to trust in physician-patient relationships and the familiarity of medical environments. Moreover, approximately 25% of patients reported that physicians should engage in active discussions with patients and provide assistance for referrals to adult care [5].

Needs and Effectiveness of App-Based Interventions Among Patients With T1D in the Transition Phase From Adolescence to Early Adulthood

Support from health care providers and primary caregivers is crucial for patients with T1D in the transition phase [14,22]. Patients with T1D, their primary caregivers, and health care providers agree that the provision of technology-based care and the development of specific apps for T1D self-management are important health care needs that should be addressed [23,24]. Studies have shown that diabetes-related knowledge, diabetes-specific and general life stress, and emotional disorders can affect self-care behaviors, disease management effectiveness, and HbA_{1c} control among patients in the transition phase [25-28], with higher severity of emotional distress

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associated with poorer HbA_{1c} control and quality of life (QoL) [29,30]. Therefore, app-based intervention measures should aim to address these factors.

Among the studies on the use of app-based interventions for youth with T1D or those in the transition phase, Goyal et al [31] and Veazie et al [32] reported that app-based interventions improved HbA_{1c} levels. Additionally, Frøisland et al [33] found that app-based interventions resulted in a better understanding of disease-related knowledge, whereas app usage seemed to positively affect diabetes self-care. However, some longitudinal studies have revealed that app interventions had no significant effects on HbA_{1c} levels [34,35], frequency of hypoglycemic events [31], diabetes-related QoL [31,34], self-perceived diabetes management ability, and diabetes-related emotional distress [35]. Although young patients with T1D generally provide positive ratings for the usability and feasibility of user-centered apps [35,36], these inconsistent results indicate that further evidence is necessary to support the effectiveness of app-based interventions.

Knowledge Gaps

Currently, the available apps for diabetes management can be broadly classified into 5 categories: nutrition, physical activity, blood glucose monitoring, insulin titration, and insulin injection. Most apps merely possess a single function, although there is an increasing trend toward integration [37]. Additionally, the majority of Chinese-language apps provide general diabetes knowledge, which may not be applicable to adolescents or young adults, and do not cater to the specific needs of patients with T1D in the transition phase [5]. Furthermore, the effectiveness of such apps should be validated by long-term empirical evidence [24,38], and few studies have mentioned the adoption of strategies to enhance treatment fidelity [31,35]. Health apps developed for intervention should incorporate evidence-based content while fulfilling the needs and protecting the privacy of the target age groups to enhance effective disease self-management [39]. To address the specific needs of patients in the transition phase, we developed the Healthcare CEO app using a user-centered approach. This app targets challenges such as poor glycemic control; pressures related to self-care; effective disease self-management; and interpersonal issues, including the establishment of romantic relationships, concerns about the health and heredity of future generations, workplace adaptation, parent-child conflicts, and enhancing QoL. This study aims to present a comprehensive protocol for evaluating the efficacy of the Healthcare CEO app. This will involve a series of detailed analyses, including (1) comparing disease control outcomes, confidence in self-management, self-care behaviors, emotional distress, and QoL between the experimental and control groups, and (2) a comparison of differences in preintervention and postintervention disease control outcomes, confidence in self-management, self-care behaviors, emotional distress, and QoL in the experimental group.

Conceptual Framework of the Study

Based on the literature described above, the transition phase theory was used as the framework of this study [6,40]. According to the transition phase theory, antecedents that trigger transition can be classified into 4 categories: developmental, situational, health illness, and organizational transitions. The Healthcare CEO app will be used as an intervention measure for patients with T1D transitioning from adolescence to early adulthood, and the effectiveness of the intervention in improving disease control outcomes, confidence in disease self-management, self-care behaviors, emotional distress, and QoL will be investigated, as shown in Figure 1.

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Figure 1. Conceptual framework of the study. HbA_{1c}: hemoglobin A_{1c}; QoL: quality of life.

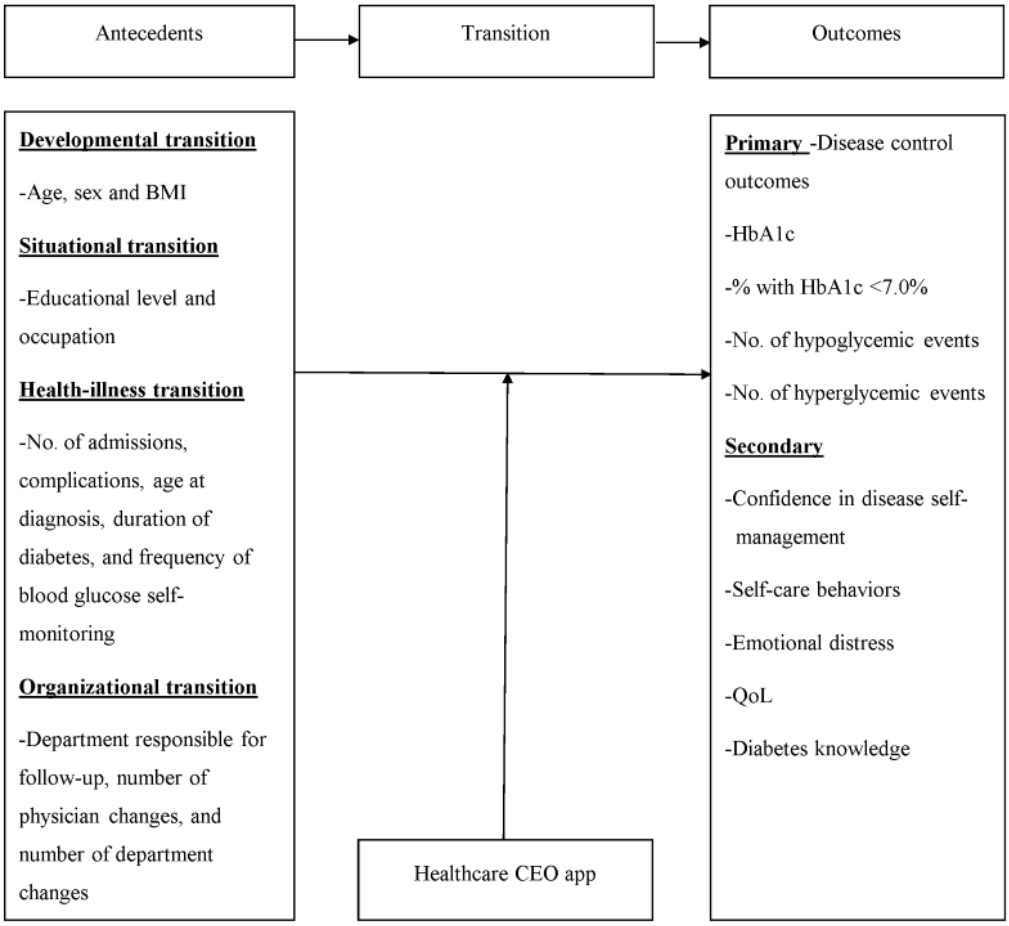

Methods

Design

A 9-month, 2-arm, parallel-group, double-blind, randomized controlled trial will be conducted. Participants will be randomly assigned to the experimental or control groups, and treatment fidelity monitoring strategies will be adopted to enhance the consistency and fidelity of intervention measures.

Participants

Inclusion and Exclusion Criteria

Participants will be enrolled from the outpatient clinic and wards of the Department of Pediatric Endocrinology and Metabolism, at a medical center in Northern Taiwan. The inclusion criteria are as follows: (1) a confirmed diagnosis of T1D from an endocrinologist before the age of 16 years and a disease duration of >6 months; (2) aged 16-25 years; (3) mean HbA_{1c} level ≥7.5% one year before inclusion; (4) ability to communicate in Chinese or Mandarin; (5) owning a smartphone with internet access; (6) agreeing to voice recording while explaining the treatment process; and (7) signing the informed consent sheet prior to participation—for minors, a legal representative must provide consent and sign the informed consent sheet. Patients with T1D with concomitant metabolic diseases, chromosomal aberrations, major illnesses, and cognitive impairment will be excluded from the study because their health care needs during the transition phase may differ from those who experience T1D only.

Sample Size

The required sample size was estimated using the G*Power program (Heinrich-Heine-Universität Düsseldorf) for repeated measures with 2 groups, 9 measured variables, power of 0.80, α set at .05, an estimated Cohen effect size of 0.25, and a correlation coefficient of 0.5. The sample size for each group was calculated as 36. By allowing for a potential 25% dropout rate, as suggested by Goyal et al [31], a final sample size of 96 participants (48 participants in each group) was established.

Sample Accessibility

The cumulative number of patients in the transition phase, aged 16-25 years, at the study site is expected to exceed 300. For each enrolled participant, the study explanation and data collection process is expected to last approximately 1 hour. Based on our research team's qualitative research experience, the on-site interview length for each participant was 1-1.5 hour, whereas the refusal rate is expected to be approximately 10%. Therefore, each week, approximately 8 patients who fulfill the inclusion criteria will participate in the study. Thus, the number of valid samples expected each month is roughly 28-32.

Randomization and Blinding

Randomization of the participants will be performed by a statistician, using the central randomization method in SPSS (IBM Corp). During participant enrollment, participants will

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be randomly assigned to the experimental or control groups in accordance with the instructions provided on the phone by the statistician; the participants and data collectors will be blinded to allocation. Blinding strategies include the following. First, the statistician will not be allowed to disclose the randomization results to others. Second, once a physician referral is received, the participant will be promptly taken to a private room. The data collection assistant will complete their duties and leave the room, and then 2 research assistants will come in and take over to administer the intervention phase. Third, participants of both the experimental and control groups will download the app, but the app content will differ. Fourth, to avoid differential demand characteristics, research assistants will emphasize to all participants that app usage is potentially beneficial for disease management.

Description of the Intervention

Overview

The Healthcare CEO app was developed guided by the user-centered information systems research framework and comprised 3 key cycles: Relevance, Rigor, and Design [41]. It was named after the self-expectations of patients in diabetes management, as patients with T1D often wished to become the "Chief Executive Officers" of their disease. The development and testing process of the Healthcare CEO app is detailed in published articles [42]. The app content was designed based on the results of previous qualitative and Delphi studies [5,23] and consisted of 11 interfaces (as shown in Figure 2): CEO's Profile; Health Tracking; CEO Knowledge Base; Barrier-free Communication; See Here: Diet and Exercise; Help Me, Detective!; CEO Chat Room; CEO's Secretary; Who's the Best CEO; SOS Calls; and Q&A. The evidence-based content aims to enhance disease knowledge among individuals in the transitional phase, improve self-care behaviors, and bolster confidence in disease self-management. These were combined with interpersonal communication skills training, to alleviate disease-related emotional distress, ultimately improving disease control outcomes and QoL. The content, objectives, and expected outcomes of each interface are detailed in Table 1.

Figure 2. Interfaces of the Healthcare CEO app. CEO: chief executive officer.

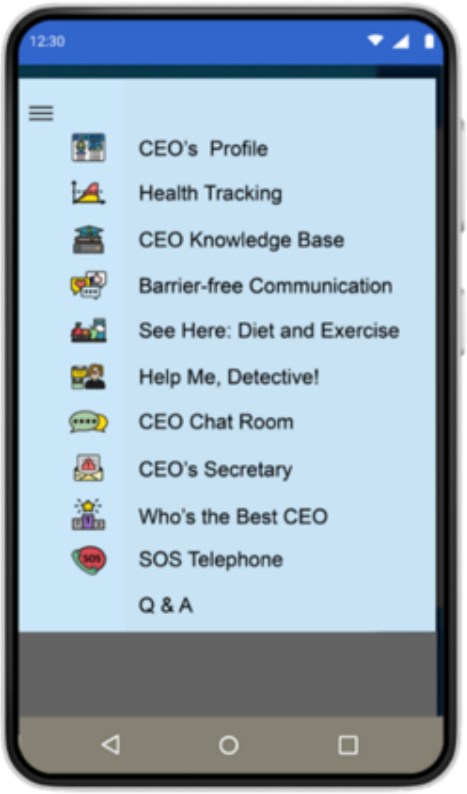

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Table 1. Content of Healthcare CEO app.

Interface	Description of content	Purposes and expected outcomes
CEO's Profile	Personal and disease data, including the following: name, nickname, date of birth, occupation, duration of disease, hospital, and attending physician. The patient can select the data to be openly displayed.	1. Establish basic data 2. Review and confirm basic disease information through data entry
Health Tracking	Upload or enter data on blood glucose level, blood pressure, body weight, and insulin dosage. HbA_{1c}[a] targets can be set, and changes in HbA_{1c} can be analyzed and displayed as trends.	1. The status of HbA_{1c} control can be checked to enhance self-care motivation and confidence in disease self-management
CEO Knowledge Base	Basic and advanced knowledge of interest to patients with T1D[b] in the transition phase is provided in the e-book format. Examples of basic knowledge include the following: impact of secondary sex characteristic development on blood glucose; blood glucose control targets in T1D; and tips for dieting, exercise, and travel during puberty. Examples of advanced knowledge are as follows: matters related to sex, genetics, gestation, and employment among patients with T1D. Both a pretest and posttest must be completed to determine the learning effectiveness of each article before the next article can be accessed.	1. Patients can enhance T1D-related knowledge on a need basis 2. Patients can boost their confidence in disease management by accumulating disease-related knowledge. This will enhance self-care behaviors, disease control outcomes, and disease-related QoLc
Barrier-free Communication	Guidance for techniques in parent-child, peer, and workplace interactions is provided through video and e-book links. Questions and scenarios are designed to prompt patients to reflect on their communication methods and think about/enact their strategies for effective interaction.	1. Improve communication skills, enhance ability to deal with interpersonal difficulties, and reduce emotional distress
See Here: Diet and Exercise	Carbohydrate and calorie calculators and a food swap guide are provided. The calorie contents of preferred foods and calories burned in preferred exercises of patients in the transition phase are displayed in images. Patients can keep records using the handy checkbox interface or uploading photos.	1. Assist in disease management and self-care, which will in turn improve disease control outcomes and disease-related QoL
Help Me, Detective!	When the blood glucose level is not within the expected range or emergency complications occur, this interface allows for the recording of the time of event occurrence, uploading of blood glucose readings, photographs of the patient's diet, exercise, or patient condition during the event, and documentation of the treatment measures adopted. These data can serve as a reference for discussion with the physician during outpatient visits, and physician advice can be input into the interface to guide the handling of future emergencies.	1. By recording and analyzing the causes of acute complications, the patient may devise improvement measures to enhance disease control, which will gradually enhance confidence in disease self-management and improve disease control outcomes
CEO Chat Room	An optional second password can be set to achieve 2 levels of privacy protection, which may be very important to patients in the transition phase. Two chat rooms named the "insider chat room" and "outsider chat room" have been designed. The insider chat room is reserved for patients using the app, with 2 themed chats organized monthly. Patients may invite individuals whom they trust (eg, attending physicians, close friends, or primary caregivers) and can engage in heart-to-heart talk using the outsider chat room, to develop their interpersonal networks and exchange views and ideas.	1. Provide interpersonal support and enhance disease-related knowledge and management strategies through experience sharing, which will alleviate emotional distress and strengthen disease self-management ability
CEO's Secretary	This consists of 2 functions, namely "Reminders" and "Online consultations." (1) Reminders: When trends of exceedances related to blood glucose occur, such as excessively high postdinner blood glucose level for 3 consecutive days, noninput of health data for ≥3 days, fewer blood glucose measurements than the required number of measurements for 3 days, and on the day before a scheduled outpatient visit, patients and app administrators will receive notifications and text message reminding them to perform relevant tracking actions. Reminders can also be set based on the needs of the patients; (2) Online consultations: The timing and theme of online consultation sessions can be booked in advance. Online consultations involve the clarification of doubts related to disease care through interactions with health care professionals.	1. Assist in disease management and provide individualized knowledge to enhance disease-related knowledge and confidence in self-care, thereby alleviating emotional distress and improving disease-related QoL 2. Conditions for reminders can be set to reduce annoying reminders, to prevent resentment of app use

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Interface	Description of content	Purposes and expected outcomes
Who's the Best CEO	One point is awarded every time the user performs data input on time, reads an article, devises a communication technique, and correctly enters data into the Help Me, Detective! interface, or enquires about online consultation. Ten points are awarded when the target HbA_{1c} level is reached. The patients with the highest number of points are listed weekly. At the end of each month in our study, the top 3 patients with the highest number of points will each receive an NT $300 (approximately US $9.24) voucher. Moreover, at the end of the study, the top 3 patients with the highest number of points will receive an NT $1000 (approximately US $30.79) voucher.	1. Enhance motivation and effort in self-care
SOS calls	Patients can set up 3 contact numbers to call for help quickly when necessary.	1. Assist in disease management and self-care, thereby improving disease control outcomes
Q&A	Patients who may be unaccustomed to asking questions in the chat room can have their queries answered via the provided email account.	1. Assist in disease management and self-care to improve outcomes

[a]HbA_{1c}: hemoglobin A_{1c}.

[b]T1D: type 1 diabetes.

[c]QoL: quality of life.

Experimental App Intervention

The complete Healthcare CEO app will be used to intervene in the experimental group. Two trained research assistants will supervise each other to guide the participants in the following aspects, according to the standard treatment manual: (1) account setup; (2) viewing of operation guidance videos; (3) demonstration of all app functions, getting participants to perform app operations, and clarifying doubts about app usage; (4) explaining troubleshooting methods; (5) providing contact information of app administrators; and (6) setting a HbA_{1c} control target. Between every 2 rounds of data collection, the research assistants will contact the participants to check if they have encountered issues or difficulties when using the app, although they will not exchange disease care-related information. After the completion of data collection, the app will be remotely uninstalled by the administrators at the backend.

Control App Intervention

Participants in the control group will only install the "CEO's Profile" and "Health Tracking" interfaces of the Healthcare CEO app. In addition to explanations for the account setup and the use of the 2 interfaces, the research assistants will not provide any app-related information to the control participants. The status and difficulties of app use will also not be tracked. After the last round of data collection, the full version of the Healthcare CEO app will be provided to the control group participants, according to their preferences. The app will be remotely uninstalled at the backend by the administrators after 9 months.

Measures

Overview

All survey questionnaires will be accessed via QR codes and answered online, with all fields set as mandatory to prevent nonresponses. The tools to be used in this study are as follows.

Demographic Questionnaire

This self-designed questionnaire has been developed based on the conceptual framework of this study. It includes questions on age, sex, BMI, educational level, occupation, number of hospital stays, complications, age at diagnosis, duration of diabetes, frequency of blood glucose self-monitoring, department responsible for follow-up, number of physician changes, and number of department changes.

Primary Outcomes

These include HbA_{1c} levels, percentage with HbA_{1c} <7.0%, and the number of hyperglycemic and hypoglycemic events.

HbA1c

HbA_{1c} will be recorded as a percentage; data will be obtained through venous blood analysis.

Percentage With HbA1c <7.0%

The percentage of HbA_{1c} readings below 7.0% for each participant will be calculated.

Hyperglycemic Events

The number of events with blood glucose >200 mg/dL or "high" on the glucometer or diagnosed ketoacidosis will be calculated for each participant.

Hypoglycemic Events

The number of events with blood glucose <60 mg/dL or "low" on glucometer or diagnosed hypoglycemia will be calculated for each participant.

For hyperglycemic and hypoglycemic events, during the data collection period, the blood glucose readings will be downloaded from the blood glucose meters of the participants, and the number of hyperglycemic and hypoglycemic events will be calculated. Considering that changes in blood glucose levels may be tracked only after adopting treatment measures, 2 researchers will perform a manual inspection of the data simultaneously. Only the first recorded reading, among all

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readings taken within the same measurement period, will be analyzed.

Secondary Outcomes

Perceived Diabetes Self-Management Scale

The original questionnaire was developed by Wallston et al [43]. It consists of 8 items scored on a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree), of which items 1, 2, 6, and 7 are reverse scored. The total score ranges from 8 to 40, with higher scores indicating higher confidence in diabetes self-management. Lin et al [44] translated the scale into Chinese to assess 168 patients with T1D and type 2 diabetes (T2D). The translated questionnaire has content validity, Cronbach α, and test-retest reliability values of 0.75, 0.93, and 0.97, respectively.

Self-Care Behavior Assessment Scale

This scale was originally developed in Chinese by Wang [45] to measure self-care behaviors of adolescents with T1D. It comprises 7 dimensions: pharmacological treatment–insulin injections; healthy diet–diet control; blood glucose monitoring–self-monitoring; physical activity and exercise–regular exercise; problem-solving–risk reduction; healthy coping–psychological and social adaptation; and stress adaptation. A total of 39 items are scored on a 5-point Likert scale ranging from 1 (not achieved at all) to 5 (completely achieved), of which items 26 to 35 are reverse scored. The total score ranges from 39 to 195, with higher scores indicating better self-care behaviors. Cronbach α and the content validity value are 0.87 and 0.92, respectively.

Diabetes Distress Scale

The original scale was developed by Polonsky et al [46]. The Chinese version consists of 17 items across 4 subscales: emotional burden, physician-related distress, regimen-related distress, and diabetes-related interpersonal distress. Items are scored on a 4-point Likert scale ranging from 1 (no distress) to 4 (severely distressed), with higher scores indicating more severe emotional distress. Cronbach α and test-retest reliability values of the Diabetes Distress Scale are 0.89 and 0.81, respectively [47].

Diabetes Quality of Life

The original scale was developed for use in the Diabetes Control and Complications Trial and translated into Chinese by Cheng et al [48]. The Chinese version consists of 42 items with the following subscales: satisfaction, impact, and diabetes-related worry. Each item is scored on a 5-point Likert scale, with 1 and 5 representing “very dissatisfied” and “very satisfied” in the satisfaction subscale, “never” and “always” in the impact subscale, and “never worried” and “always worried” in the diabetes-related worry subscale, respectively. Higher scores are indicative of a higher QoL. The Cronbach α and test-retest reliability values of the scale and subscales are within the ranges of 0.76-0.92 and 0.94-0.99, respectively.

Diabetes Knowledge Questionnaire

The original questionnaire was developed by Garcia et al [49]. The Chinese version comprises 24 items that are answered “Yes,” “No,” or “I don’t know”; 1 point is awarded for each correct answer. The total score ranges from 0 to 24 points, with higher scores indicating more excellent knowledge of diabetes. In a study that adopted the 24-item Diabetes Knowledge Questionnaire (DKQ) for assessing 108 patients with T2D, the results indicated reliability and Cronbach α values of 0.78 and 0.89, respectively [50]. Currently, the DKQ is used chiefly for patients with T2D. However, when we sequentially inspected all items of the DKQ to determine its applicability to patients with T1D, it was found that the correct answer for Item 6, “If I am diabetic, my children have a higher chance of being diabetic,” needs to be changed to “No,” and for Item 13, “Medication is more important than diet and exercise to control my diabetes,” needs to be changed to “Yes.” In contrast, the remaining items and answers remain applicable to patients with T1D and are considered essential knowledge among such patients. Therefore, the DKQ will be used in this study following the above-mentioned modifications.

App Use Data

During the data collection period, the administrators will also download app-use data at the backend. Such data include log-ins to the Healthcare CEO app, the number of e-books read in the CEO Knowledge Base, the number of online consultations with the CEO’s Secretary, and the content of the chats in the CEO Chat Rooms.

Data Collection

Three research assistants with a background in health care, who have a basic understanding of T1D, have undergone training, and are not involved in the provision of health care, will be responsible for the data collection. Attending physicians of patients with T1D will provide referrals of patients who meet the inclusion criteria. One research assistant in charge of data collection will then approach the patients to explain the purposes of the study and the research process. Patients who agree to participate will subsequently fill out the informed consent sheet and undergo the preintervention test (T0) in an undisturbed environment. The second research assistant will obtain the randomization results from the statistician by phone and assist participants in downloading the Healthcare CEO app onto their smartphones based on their group assignment. The third research assistant will check and remind the second research assistant of the intervention steps to ensure the accuracy and completeness of the intervention. Considering that HbA_{1c}, the critical indicator of blood glucose control, is measured once every 3 months, the time points for the postintervention data collection for both groups are set at 3 months (T1), 6 months (T2), and 9 months (T3) after the intervention.

Treatment Fidelity

Overview

To monitor the faithfulness and fidelity of the intervention process and enhance intervention effectiveness evaluation, we formulated strategies for the inspection of treatment fidelity in the 5 areas proposed by Bellg et al [51] at the National Institution of Health Behavior Change Consortium.

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Treatment Design

A standard treatment manual was formulated to explain the purpose of the study, the processes, and the details. Standardized interaction content of the interventions was established.

Training Provider

Research assistants received 16 hours of standardized training in accordance with the roles they will serve in the study. The standard training sessions attended by all research assistants included treatment of patients with T1D in the transition phase, research ethics, and 2 observational visits to the outpatient clinic for familiarization with the study settings. Individual training sessions included data collection techniques or the development, methods of use, and troubleshooting of the Healthcare CEO app. In addition, during the data collection process for the first 10 participants, the research assistants will be accompanied by senior researchers to confirm their techniques and abilities in participant inclusion and ensure faithfulness in the implementation of the intervention measures, and strategies for improvement will be provided after observation.

Delivery of Treatment

An intervention step checklist has been formulated and will be provided to research assistants for the sequential inspection and confirmation of the level of completion and completeness of the intervention measures. Another assistant will inspect the fidelity and faithfulness of the intervention process using an intervention process checklist and perform voice recordings of the entire treatment process for researchers to conduct random analyses, evaluations, and feedback.

Receipt of Treatment

Participants will be asked to perform operations in the app and discuss and clarify any doubts that they may have. An intervention content checklist will be provided to the participants after the completion of the intervention to confirm that they have received the complete intervention and determine their level of understanding and app use abilities.

Enactment of Treatment Skill

To ensure that participants are capable of using the app in everyday life, the following will be carried out: weekly monitoring of the frequency of app content usage and the level to which app usage has been correctly completed, documenting usage issues and suggestions highlighted by participants during routine telephone follow-up, and downloading and analyzing app use data during each round of data collection.

Data Analysis

Statistical Analysis

The intention-to-treat principle will be used for the data analysis; that is, all participants will be included in their initially assigned groups for analysis, regardless of whether they withdraw from the study for any reason or are lost to follow-up. Data will be analyzed using IBM SPSS 26.0 for Windows, with differences considered statistically significant at $P<.05$. Demographic and disease status data, including age, gender, BMI, age at diagnosis, disease duration, and HbA_{1c}, along with metrics on the app usage to evaluate treatment fidelity, such as the log-ins to the app, frequency of use for each interface, number of e-books read in the CEO Knowledge Base, and number of online consultations in CEO's Secretary, will be presented through descriptive statistics. This will include frequency distributions, percentages, means, SDs, and maximum and minimum scores. Homogeneity in the essential attributes of the 2 groups will be compared and analyzed using inferential statistics, such as the chi-square test and ANOVA. Owing to the longitudinal nature of this study, repeated data measurements will be taken. Dependencies may exist among the data at different time points, and data loss may also occur. Using generalized estimating equation models, repeated measurements can be simultaneously included in the regression analysis. Through the variance correction process, consistent estimates of the regression parameters and their variance can be provided to correct for dependencies, and participants with missing values can still be included in the analysis [52]. Therefore, a generalized estimating equation will be used for data analysis to compare the differences between the experimental and control groups at both preintervention and postintervention time points, as well as the differences in the scores of the experimental group before and after intervention.

Healthcare CEO App Chat Room Data Analysis

Chats in the CEO Chat Rooms will first undergo thematic categorization, beginning with a review of the chat content to gain an initial understanding. Relevant patterns will then be identified and labeled through initial coding, and similar codes will be grouped to form broader themes. These themes will be reviewed and refined for relevance and consistency with the data, and each theme will be clearly defined. Finally, the frequency of each identified theme will be calculated.

Ethical Considerations

The study will follow the Declaration of Helsinki and has received approval from the Ethics Committee of the Chang Gung Foundation Institutional Review Board (submission reference: 202100050B0; March 9, 2021). It will uphold key ethical principles, including informed consent, with participants receiving comprehensive information about the study. For minors, consent will be obtained from a legal guardian simultaneously, and efforts will be made to minimize any undue influence from guardians or family members to guarantee voluntary participation. Participants may withdraw at any time without impacting their medical care. The study prioritizes participant safety through self-reported questionnaires and a mobile app that poses no risks. Justice is maintained by ensuring equal medical care for all participants, with the control group accessing the app after the study. Privacy is protected with data secured in locked storage and coded identifiers used in publications to ensure anonymity. Participants will receive a voucher worth NT $300 (approximately US $9.34) for each completed questionnaire as an appreciation for their time and effort.

Validity and Reliability

The study design and participant enrollment process were formulated in accordance with the recommendations of the CONSORT (Consolidated Standards of Reporting Trials)

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statement. We also formulated strategies based on the National Institution of Health Behavior Change Consortium guidelines to monitor the faithfulness and fidelity of the intervention process. The research tools used in this study also exhibit good validity and reliability. In the measurement of the primary outcome variables, this study differs from previous works on diabetes management apps in that "% with HbA_{1c} <7.0%" data will be calculated for the first time for analysis. This allows for greater objectivity and rigor in evaluating the effectiveness of the Healthcare CEO app.

Results

After a comprehensive review, the National Science and Technology Council, Republic of China (MOST 109-2314-B-182-057-MY2), and Chang Gung University (NMRPD1K1021) provided financial support for this research project. The project was initially scheduled to run from August 1, 2020, to July 31, 2022. However, owing to the widespread impact of the COVID-19 pandemic, the study was abruptly halted after the enrollment of 38 participants. Details of the recruitment and randomization processes can be found in the CONSORT flowchart (Figure 3). We anticipate that the preliminary results will be compiled and submitted for publication by November 2024. The recruitment of participants resumed in August 2023, with findings expected to be finalized by July 2025. At present, each experimental and control group includes 13 participants.

Figure 3. CONSORT (Consolidated Standards of Reporting Trials) flowchart of preliminary results of the trial. HbA_{1c}: hemoglobin A_{1c}.

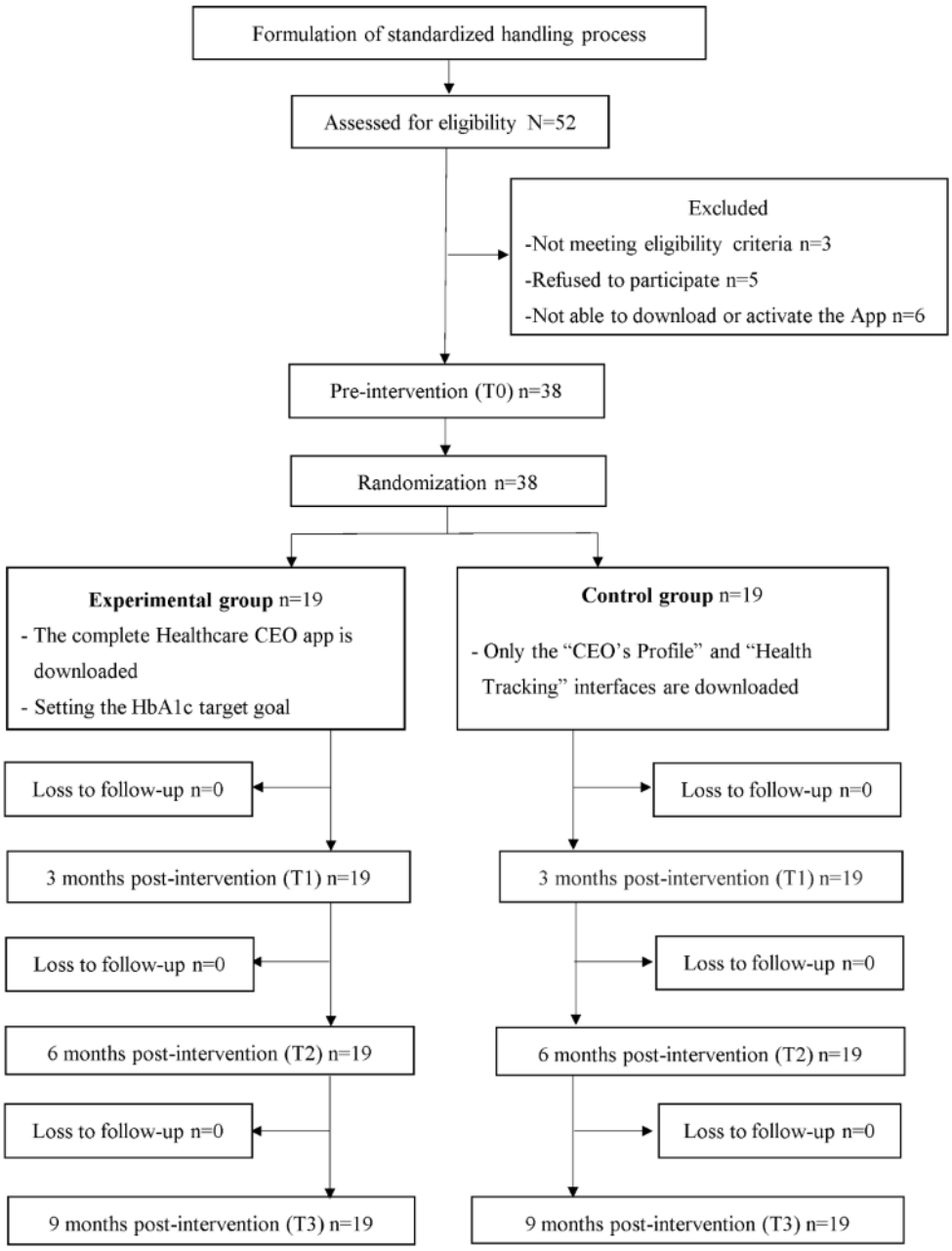

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Discussion

Principal Findings

The Healthcare CEO app distinguishes itself as one of the few evidence-based, multifunctional integrated apps specifically designed for individuals aged 16-25 years managing T1D. This study uses a double-blind, randomized controlled trial intervention, with anticipated outcomes aimed at enhancing disease knowledge, improving self-care skills, and strengthening self-efficacy in disease management. Additionally, training in effective communication skills is intended to reduce interpersonal and emotional distress, enhance QoL, and ultimately improve glycemic control outcomes. The strengths and limitations of this study are elaborated in the following sections.

Strengths

The 6 major aspects of diabetes self-management are physical activity, nutrition, blood glucose testing, medications or insulin injections, health feedback, and education. However, existing diabetes management apps focus only on 2 to 3 of these aspects on average. App developers should work closely with health care providers and patients to ensure that the developed apps address patients' health care needs [53]. Our app differs from the majority of commercially available apps in that it contains the following distinctive features: (1) the app content has been designed based on a series of empirical studies [5,23,42] to ensure that it fulfills the needs of the users; (2) the app contains diverse content across 11 interfaces instead of being limited to 2 or 3 aspects; (3) the See Here: Diet and Exercise interface allows for easy and convenient recording of carbohydrate and calorie intake and exercise intensity; (4) the CEO Knowledge Base contains specific content targeted at patients in the transition phase, which is divided into basic and advanced knowledge, for perusal on a need basis; (5) themed discussions can be organized in the CEO Chat Rooms interface, during which users can discuss their needs and expert suggestions can be provided; (6) an SOS Calls function is provided for users transitioning from the dependence to independence phases, so that they can seek help from trusted individuals when needed; and (7) a points system, in which points can be exchanged for gift vouchers, is used to reward users for app use. With the above features and added emphasis on enhancing treatment fidelity, we anticipate that our results will indicate high effectiveness in diabetes self-management among patients with T1D in the transition phase due to our app-based intervention.

Limitations

This study design has several limitations. First, the app usage may be limited by an unstable internet connection, which could impact the effectiveness of our app-based intervention. Second, in addition to providing gift vouchers to enhance the motivation and efforts of the participants, we also factored in an allowance during sample size estimation to minimize the effects of participant withdrawals. Third, because of the nature of the study, the researchers cannot be blinded during the study implementation, which may lead to potential biases. To address this issue, researchers must adhere to strict intervention principles to minimize the impact on the study results. Finally, the Healthcare CEO app was developed and will be evaluated based on Taiwanese participants with T1D in the transition phase. Therefore, caution will have to be exercised, and cultural differences will be considered when interpreting the study results.

Conclusions

Patients with T1D transitioning from adolescence to early adulthood are in extreme need of support from health care providers and primary caregivers. The Healthcare CEO app developed in this study differs from current commercially available apps in that the functions desired by transitioning adolescent patients, as indicated by the empirical results obtained from previous qualitative and quantitative studies, have been integrated into the app to the best of our ability. In other words, this app is the first multifunctional app targeted at the needs of patients with T1D in the transition phase from adolescence to early adulthood. Our study protocol consisted of strategies formulated to enhance the treatment accuracy of the intervention measures. Such strategies make it possible to increase the objectivity of intervention effectiveness evaluation. The findings can serve as a reference for further applications to the clinical care of patients in the transition phase.

Acknowledgments

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Data Availability

The datasets produced or analyzed in this study can be obtained from the corresponding author upon reasonable request.

Authors' Contributions

YTC, PKT, CW Chen, CLH, FSL, and PM contributed to the conception of the study. YTC, HYY, CW Chang, and CW Chen contributed to the study design. YTC and PKT performed statistical planning and data analysis. YTC, HYY, PKT, and CLH performed implementation and process evaluation planning. YTC, HYY, and FSL performed data collection. YTC, HYY, and PM contributed to the manuscript writing. YTC, HYY, PKT, CW Chen, JGE, CW Chang, CLH, FSL, and PM performed the article review.

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Conflicts of Interest

None declared.

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
DKQ: Diabetes Knowledge Questionnaire
HbA1c: hemoglobin A_{1c}
QoL: quality of life
T1D: type 1 diabetes
T2D: type 2 diabetes

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Protocol

Digital Health Intervention (SANGYAN Podcast) to Enhance Knowledge Related to COVID-19 and Other Health Conditions: Protocol for an Implementation and Evaluation Study

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Abstract

Background: Podcasts are an unconventional method of disseminating information through audio to the masses. They are an emerging portable technology and a valuable resource that provides unlimited access for promoting health among participants. Podcasts related to health care have been used as a source of medical education, but there is a dearth of studies on the use of podcasts as a source of health information. This study will provide new perspectives by implementing the SANGYAN podcast, which contains information about COVID-19 and other health conditions.

Objective: The study aims to determine the usefulness and effectiveness of the SANGYAN podcast as a digital health intervention to address misinformation related to COVID-19 and other health conditions among individuals in Chennai, Tamil Nadu, India.

Methods: An implementation and evaluation study will be conducted with 500 participants from the Panimalar Medical College Hospital & Research Institute (PMCHRI) and Rural Health Training Centre in Chennai. Among individuals aged 18 years and older, those residing in the selected urban and rural settings who visit the outpatient department of the PMCHRI and Rural Health Training Centre will be recruited. For participants who consent to the study, their sociodemographic details will be noted and their health literacy will be assessed using the Rapid Estimate of Adult Literacy in Medicine scale. Once the participants have listened to the podcast, the usability, acceptance, and user satisfaction of the podcast will be assessed. Descriptive analysis will be used for continuous variables, and frequency analysis will be used for categorical variables. Bivariate analysis will be conducted to understand the correlation of sociodemographic features in response to perception, usefulness, acceptance, and user satisfaction of the podcast. All analysis will be performed using SPSS (version 24), and the results will be reported with 95% CIs and $P<.05$.

Results: As of December 2024, the SANGYAN podcast has been launched for voluntary usage in the PMCHRI.

Conclusions: The finding from this research project will aid in the development and implementation of data-driven, evidence-based, and human-centered behavior change interventions using podcasts to address public health challenges among populations living in diverse settings. This would also help in enhancing the acceptability of podcasts as a source of health-related information.

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KEYWORDS

podcast; human-centered behavior; pandemic; coronavirus; intervention; digital health; usefulness; effectiveness; usability

Introduction

Background

The term "podcast," coined in 2004, is derived from the terms iPod and broadcast. It was chosen as the word of the year by the New Oxford American Dictionary in 2005 [1,2]. It is an unconventional means of distributing information to the general public via audio. Podcasting is a relatively new portable technology. It has established itself as a reliable channel for knowledge and information exchange. Podcasts are classified under Web 2.0 tools among other tools such as wikis and blogs, which comprise the latest generation of web-based collaboration [3]. Technology-enabled approaches to managing lifestyle have begun to emerge with the increased development and use of electronic media. Public health practitioners are now using mobile health technology to deliver health-related interventions [4]. However, there are hurdles to offering web-based interventions since they often need research participants to have a mobile phone, a certain level of education, and the capability of properly comprehending textual material [5]. The development of audio or video material for an audience that wants to listen to what they want, when they want, where they want, and how they want is the heart of podcasting [6].

India has reported a significant shift in the number of podcast users over the years. A report states that India holds the third-largest podcast user population after China and the United States, with over 57.6 million users [7]. Podcasting is becoming increasingly popular due to its ability to communicate health-related data and information for educational reasons [3]. Podcasting represents a largely untapped conduit for promoting health information to the general public with internet access and those who are not comfortable seeking face-to-face knowledge, treatment, and guidance. The COVID-19 pandemic played a significant role in increasing the consumption of podcasts by 29.3% in India [8]. Podcast use in entertainment, lifestyle, health, society, and culture is widespread according to a Spotify report. While in regard to health care [9-11], podcasts in India have seen increasing use in medical education and training, but not in other aspects of health care [12]. There is a dearth of research showing the use of podcasts to address misinformation, especially in an Indian context. A medium like a podcast provides screen-free alternatives even during the COVID-19 pandemic's restrictive environment. Podcasts are becoming increasingly popular among the younger population as a source of entertainment, self-improvement, and awareness.

Why Use a "Podcast" to Deliver Public Health Intervention?

According to user control theory, allowing flexibility boosts learning as compared to traditional instruction such as print. Podcasting may be more effective than the web because such a platform can decrease cognitive load [13]. Podcasts can encourage users' positive knowledge, attitude, and practice by allowing them to listen to the podcast anywhere, anytime. Podcasts promote knowledge dissemination by allowing podcast channel owners to communicate knowledge even when movement is restricted (eg, during a pandemic). The most prominent reason for the podcast boom is the connection between the host and listener. Podcast technology is a valuable resource that provides unlimited access for promoting health among participants. It also plays a significant role in public health and global health, where challenging and critical situations demand simple, effective, and concise information delivery. Numerous studies have examined the acceptability or feasibility of this modality for learning; however, limited studies have focused on podcast use for knowledge sharing [14]. Also, journals such as The *New England Journal of Medicine* [13] and *Lancet* [15] currently use podcasts to support medical and nonmedical information dissemination.

Need for the Study

The COVID-19 pandemic has shown that misinformation spread via social media and other digital platforms is a more significant threat to global public health than the virus itself [16]. Studies show that female individuals are more likely to accept misinformation than male individuals. A higher education level also decreases the possibility of accepting misinformation. Thus, older people with a higher level of education are less likely to accept misinformation [17,18].

This research will provide new perspectives through implementing the SANGYAN podcast, which contains information about the COVID-19 pandemic and other health conditions. The research project's findings will directly benefit individuals and researchers in developing tailored intervention models aimed at addressing misinformation.

Study Objectives

The study aims to determine the usefulness and effectiveness of the SANGYAN podcast as a digital health intervention to address misinformation related to COVID-19 and other health conditions among individuals in Chennai, Tamil Nadu, India.

Methods

Study Design and Population

An implementation and evaluation study will be conducted at the outpatient department of the Panimalar Medical College Hospital & Research Institute (PMCHRI) and Rural Health Training Center (RHTC) in Chennai. The participants will be recruited through convenience sampling in a paper-based format, by the researchers or trained data collection team from the RHTC and PMCHRI. A total of 500 individuals (250 each from the PMCHRI and RHTC) will be enrolled for the study. The data will be collected at a single time point by administering the study questionnaire to the eligible study participants. For participants who consent to the study, their sociodemographic details will be noted and their health literacy will be assessed

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using the Rapid Estimate of Adult Literacy in Medicine (REALM) scale. Once the participants have listened to the podcast, the usability, acceptance, and user satisfaction will be assessed.

The eligible study participants will comprise individuals (1) aged 18 years and older, (2) residing in the selected urban and rural settings who visit the outpatient department of the PMCHRI and RHTC, and (3) consenting to participate in the study. Individuals with any mental or physical challenges that might affect their ability to participate in the study will be excluded.

Variable Assessment

Sociodemographic Profile

Sociodemographic data will be gathered, including participants' age, gender, income level, education level, employment status, occupation, region of residence, marital status, parenthood, and religion.

Health Literacy

The REALM scale is one of the most widely used tools to measure health literacy. Statistically, the REALM scale appears to provide a highly reliable data [19]. The study will use this scale as a screening instrument to assess an adult patient's ability to read common medical words. It is designed to assist medical professionals in identifying patients with poor literacy skills [20].

Use of Podcast or Other Mediums for Health Information

This measure will help us gather data on prior use of podcasts or other sources by participants to gather health data.

Usability

A Likert-scale System Usability Scale (SUS) survey will assess user acceptance. The SUS is a 10-item questionnaire with 5 response options, ranging from strong agreement to strong disagreement on a scale of 0 to 4, for each question. The total score will be calculated by adding the converted responses for each user and multiplying that total by 2.5. This will restore the range of possible values to 0-100 instead of 0-40 [21].

Client Satisfaction Questionnaire-8

The Client Satisfaction Questionnaire-8 (CSQ-8) is an 8-item measure of client satisfaction with services. The items for the CSQ-8 were selected on the following basis: ratings on information seeking by participants for a number of items that could be related to client satisfaction and a subsequent factor analysis. The CSQ-8 is unidimensional, yielding a homogenous estimate of general satisfaction with services [22].

SANGYAN Podcast

The SANGYAN podcast comprises audio content that will be delivered over a network via a free subscription.

The steps for developing the SANGYAN podcast are as follows: (1) file production, (2) podcast publication, (3) podcast delivery, and (4) podcast playback. File production involves planning, writing, recording and editing content, and file compression. Recording requires hardware like a recording microphone, and editing requires software like Audacity (The Audacity Team) and Premiere Adobe Pro (Adobe). The feed would be a simple XML file that lists the location of the podcast's COVID-19 episodes. The meta-tagging will have file information like the producer details, date of publication, title, and description of each episode. The RSS feed then will be posted to the web server of SMAART Rapid Tracker [23]. The podcast is hosted by the Foundation of Healthcare Technologies Society with a team of researchers that curate evidence-based content. Listeners will be able to subscribe, access, and download the podcast file.

Data Collection, Data Entry, and Quality Assurance

Data will be collected using a structured questionnaire. The questionnaire will be presented to the participants in the local Indian dialects to help increase the usefulness and generalizability of the study data. Data collection and data entry will be performed by a team of data collectors and data management personnel. To ensure efficiency and high-quality data collection and processing, the following data management protocol is in place: a clearly defined study manual, a well-trained team of data collectors, weekly meetings with the research team, weekly data checks, maintenance of study participants contacts, and data instrument logs.

Expected Outcomes

The proposed research study will help explore the usability and acceptability of a health-related podcast. Further, it will help evaluate the SANGYAN podcast's usability as well as satisfaction toward information delivery through a podcast. The results of the study will help design and develop a podcast platform that can deliver health educational information to facilitate podcast acceptance in varied settings. The expected study outcomes include the acceptability of using a digital health podcast to obtain tailored and evidence-based health information related to COVID-19 and other health conditions.

Data Analysis Plan

The gathered data will be presented in tables comprising the recorded characteristics of all variables. These tables will serve the purpose of data quality control to find inconsistencies in the data patterns and outliers or any missing data. Descriptive analysis will be conducted to report the means and SDs of the continuous variables (such as SUS scores), and frequency analysis will be conducted for the categorical variables (such as CSQ-8 scores and data on the use of podcasts and other mediums for health information). Bivariate analysis will be conducted to understand the correlation of sociodemographic features in response to perception, usefulness, acceptance, and user satisfaction of the podcast. All analysis will be performed using SPSS (version 24; IBM Corp), and the results will be reported with 95% CIs and $P<.05$.

Project Timeline and Milestones

A detailed study timeline is presented in Table 1.

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Table 1. Project timeline and milestones.

Task	Month														
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15
Review of the literature, initial designing, and planning of the study	✓														
Development of study proposal and ethical approval	✓														
Approval of the study proposal	✓														
Development of survey items and the questionnaire	✓														
Review and revision of the questionnaire by the research team		✓													
Recruitment and training of the data collector team		✓													
Recruitment of the target sample		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Data analysis														✓	
Results write-up and preparation of the manuscript														✓	
Dissemination														✓	✓

Ethical Considerations

This study (protocol PMCHRI-IHEC-056) gained approval from the PMCHRI Institutional Human Ethics Committee (Central Drugs Standard Control Organization Registration ECR/1399/Inst/TN/2020) in February 2022, with approval PMCH&RI/IHEC/2021/078 (dated February 18, 2022).

The institutional review board–approved informed consent form will be administered by the research team to the eligible individuals for the study. The research team will explain the study, the time commitment necessary, and the advantages of the study results to participants. Those willing to participate and give their consent will be enrolled in the study. Written informed consent will be obtained in both English and local Indian dialects. The data gathered will be stored securely, ensuring data privacy and confidentiality. No compensation will be provided.

Dissemination

The study's findings will be disseminated through peer-reviewed publications and national and international conference presentations. Results will also be disseminated to the local community health leaders, state officials, and policy makers for data-driven, evidence-based, and informed decision-making.

Results

As of December 2024, the SANGYAN podcast has been launched for voluntary usage in the PMCHRI.

Discussion

Podcasts are rapidly being used as a tool for information distribution by a wide range of organizations and associations, including medical and dentistry schools, research institutes, and scientific journals. There is a need for robust strategies to boost podcast acceptability and provide community-specific information on misconceptions about public health concerns. The study would help assess the acceptability of podcasts as a source to obtain tailored and evidence-based health information.

The study findings will elucidate the association of the acceptance and usability of podcasts with various sociodemographic factors such as education level, gender, and occupation, for which there is a dearth of data in the Indian context. The findings will also provide insight into people's awareness of podcasts and other digital sources of health information prior to the study.

The rollout of the protocol may see some limitations, in that it is a one-time implementation of the SANGYAN podcast and adherence is not assessed. Another limitation could be in its implementation within a limited geographical setting; thus, future studies regarding the usability, acceptance, and adherence can be carried out at a larger scale across various states in India.

Studying the spread of misinformation (or infodemics) in India remains critical considering the booming use of social media in the wake of the COVID-19 pandemic. India, along with 132 member states of the United Nations, has endorsed fighting infodemics especially during COVID-19 [24]. This study relevant to this endorsement, as the study findings will contribute to the development and implementation of data-driven, evidence-based, and human-centered behavior change interventions using podcasts to address public health challenges among populations living in diverse settings. Further, this study would aim to expand the use of the SANGYAN podcast as source of evidence-based health information for the public.

Data Availability

The data supporting this study's findings are available on request from the corresponding author.

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Authors' Contributions

All authors have contributed to the study's design, development of the questionnaire, and preparation of the manuscript and have approved the manuscript for publication.

Conflicts of Interest

None declared.

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Abbreviations

CSQ-8: Client Satisfaction Questionnaire-8
PMCHRI: Panimalar Medical College Hospital & Research Institute
REALM: Rapid Estimate of Adult Literacy in Medicine
RHTC: Rural Health Training Centre
SUS: System Usability Scale

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Protocol

LoVE4MUM Mobile App to Prevent Postpartum Depression: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Postpartum depression remains a significant concern, posing substantial challenges to maternal well-being, infant health, and the mother-infant bond, particularly in the face of barriers to traditional support and interventions. Previous studies have shown that mobile health (mHealth) interventions offer an accessible means to facilitate early detection and management of mental health issues while at the same time promoting preventive care.

Objective: This study aims to evaluate the effectiveness of the Leveraging on Virtual Engagement for Maternal Understanding & Mood-enhancement (LoVE4MUM) mobile app, which was developed based on the principles of cognitive behavioral therapy and psychoeducation and serves as an intervention to prevent postpartum depression.

Methods: This single-blinded, pilot randomized controlled trial includes 64 mothers recruited from the postnatal ward and randomized using a 1:1 ratio to receive either postpartum care (treatment as usual) or postpartum care (treatment as usual) plus the self-guided LoVE4MUM mobile app. The primary outcome is the effectiveness of the mobile app at improving postpartum depression. Secondary outcomes are changes in the mental health literacy score and negative automatic thoughts, which are collected using a self-reported questionnaire.

Results: Patient recruitment began on September 1, 2024. As of January 1, 2025, recruitment was successfully completed, with a total of 72 participants enrolled: 36 in the intervention group and 36 in the control group . The final results are anticipated to be available by March 2025, and publication is expected by the end of 2025.

Conclusions: By examining the LoVE4MUM app alongside standard postpartum care, this pilot randomized controlled trial seeks to offer preliminary evidence on the potential of mHealth tools to improve maternal mental health as well as to reduce postpartum depression symptoms. The findings are expected to contribute to the future development of effective, accessible, and scalable interventions for mothers.

Trial Registration: ClinicalTrials.gov NCT06366035; https://clinicaltrials.gov/study/NCT06366035

International Registered Report Identifier (IRRID): PRR1-10.2196/63564

(JMIR Res Protoc 2025;14:e63564) doi:10.2196/63564

KEYWORDS

postpartum depression; mHealth intervention; mobile phone; prevention; self-guided; virtual engagement; engagement; maternal; protocol; randomized controlled trial; postpartum; depression; maternal; well-being; mobile health; preventive care; mobile app; mental health literacy; postpartum care

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Introduction

The global pooled prevalence of postpartum depression (PPD) was as high as 34% in a recent systematic review [1]. In Malaysia, the National Morbidity and Health Survey 2022 reported that 11.2% of mothers had depression [2] and an alarming 90% were unaware of their symptoms. Moreover, PPD results in detrimental consequences not only for the mother but also for the baby and their future bonding and relationship [3,4].

Meeting the increasing demand for mental health care is particularly challenging. These challenges encompass issues such as a lack of privacy, limited access to mental health experts, insufficient knowledge, and cultural stigma [5-8]. Consequently, mothers do not receive the necessary assistance that they require [5]. Mobile health (mHealth), a component of eHealth [9], has emerged as a crucial means to provide accessible health care solutions, especially with the advent of technologies like smartphones, web-based platforms, and text messaging [10,11]. These tools have become helpful for offering health care services and making health care more flexible, private, and readily available. This is particularly relevant in countries with high mobile internet penetration rates, such as Malaysia where rates of mobile internet coverage reached 128% in 2021 [12].

Interventions for depression range from pharmacotherapy to psychotherapy as well as lifestyle modifications [13]. Over the years, service delivery has evolved with the use of smartphone apps, web-based applications, and text messaging services to deliver therapeutic content [14,15]. Psychotherapies such as cognitive behavioral therapy (CBT) [16-18], mindfulness [19], and psychoeducation [20,21] using these technologies have previously been reported. A systematic review found that mHealth interventions can significantly improve depressive symptoms, highlighting their potential as accessible and cost-effective treatment options [22]. Additionally, more recent reviews concurred that mHealth interventions can effectively reduce PPD, as evidenced by improvements in Edinburgh Postnatal Depression Scale (EPDS) scores among these mothers [23,24].

Women in the perinatal period are less likely to seek help for mental health issues than women at other life stages due to lower postpartum mental health literacy [25]. Mental health literacy has evolved from being defined merely as knowledge and beliefs about mental disorders to attitudes toward these disorders and efficacy in seeking help [26,27]. Kutcher et al [27] highlighted that poor mental health literacy leads to underutilization of mental health services, noting the critical role of help-seeking attitudes. mHealth platforms can boost mental health literacy by offering resources that heighten awareness of mental health issues, treatments, and self-care. For example, Chan et al [28] showed that mHealth is effective at enhancing mental health knowledge, attitudes, and behaviors, thus bridging the educational gap and reducing stigma. A systematic review emphasized the need for interventions to improve mental health literacy among perinatal women, due to a widespread lack of awareness about PPD symptoms, hesitance toward seeking professional help, a preference for informal support, and numerous other obstacles to accessing care, which are further compounded by marked stigma surrounding mental health issues [29].

Within the CBT framework, our thought processes are usually framed by our beliefs, which have a profound impact on how we feel and act in response to life's challenges [30]. Past experiences shape beliefs that can distort interpretations of events, leading to emotional disorders. In stress-triggering situations like the postpartum period, these beliefs trigger automatic negative thoughts and worsen depressive symptoms, underscoring the need to target these thoughts through depression management. By altering negative thought processes and maladaptive behaviors into more positive emotional outcomes, CBT offers improvements for depression management [31,32]. In addition, digital interventions, including exercises, thought diaries, and educational materials, facilitate the identification, confrontation, and modification of these negative cognitive patterns. A study demonstrated that smartphone-based CBT interventions could significantly reduce negative automatic thoughts and improve cognitive restructuring skills for users [33]. Mental health experts also advocate for short-term preventive CBT interventions, tailored for perinatal concerns, as a robust therapeutic strategy [34-36].

CBT's traditional reliance on mental health professionals is challenged by cost and availability barriers. Due to health care personnel limitations, Mohammad-Alizadeh-Charandabi et al [37] highlighted the shortcomings of midwife-led phone interventions due to inconsistent quality and time constraints. In contrast, Niksalehi et al [38] effectively deployed structured automatic text messages with optional phone support, significantly enhancing depression scores and showcasing the potential of accessible, self-guided support. Complementing this, Carona et al [39] introduced a low-intensity, self-guided CBT program as an effective firstline intervention to help perinatal women, resulting in more improved depression scores in the intervention group than in the control group. Another study that used internet-based CBT [40] reported significant differences between the intervention and control groups.

It is noteworthy that the majority of studies on mHealth interventions were conducted in urban and academic settings in high-income countries [14]. Therefore, the generalizability of the outcomes is limited to the local population and might not apply to other settings such as Malaysia, which has a diverse cultural and religious background. Furthermore, these technologies frequently lack a user-centered design [41] and are primarily developed in western countries, which impacts their adaptability and sustainability in local contexts [14]. To culturally tailor appropriate mHealth interventions, meticulous development is required, engaging not only health care professionals to shape evidence-informed intervention priorities but also patients to enhance the effectiveness and widespread adoption of these interventions [42].

Initiatives in Malaysia include the TIARA MURNI project [43], which involves health care workers for its delivery. However, there is a notable absence of self-guided mental care solutions for mothers during the postpartum period especially in the Asian setting. This highlights an opportunity to improve mental health care access especially in areas with limited resources [38,44,45].

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This study protocol intends to assess a user-centered, self-guided mental health app and compare it with standard postpartum care. It aims to determine the app's preliminary effectiveness at improving depression and mental health literacy and addressing negative thoughts among mothers in the postpartum period.

Methods

Type and Design

This study is a single-blind, pilot randomized controlled trial with participants randomized using a 1:1 ratio.

Study Location

The study includes postpartum mothers located in the postnatal ward of tertiary hospitals in the Selangor state of Malaysia. According to the Department of Statistics Malaysia, Selangor has the highest birth rate in the country, with a total of 95,211 live births in 2019 [46]. The National Morbidity and Health Survey 2022 survey indicated that urban mothers have a higher risk of depression. Considering Selangor's birth statistics and status as a highly urbanized state, we considered it to be the ideal location for our research. We selected 2 hospitals from urban locations using a computerized random number generator.

Ethics Approval and Ethical Considerations

Approval to conduct the study was obtained from the Medical Research and Ethics Committee, Ministry of Health Malays (ref number 24-00924-HPO, dated April 04, 2024). Written informed consent was obtained from all participants prior to their involvement in the study. Participants are fully informed of their right to opt out at any time without any consequences. All participant data are anonymized to ensure privacy and confidentiality. No identifiable information is collected nor stored during the study. Protective measures, including secure data storage, were implemented to safeguard participant information. Participants are compensated MYR 10 (US $2.15) for each questionnaire returned, to acknowledge their time and effort. Participation is entirely voluntary, without any form of coercion.

Recruitment

Mothers were recruited from the obstetric wards by the investigators. Mothers received comprehensive information about the study, including its aims, procedures, risks, and benefits. Sufficient time was given to ensure informed consent was obtained in the ward. Those agreeing to participate were enrolled in the pilot randomized controlled trial, and reasons for refusal were documented.

Patients were screened for eligibility based on the study criteria. Mothers (1) scoring between 9 and 11 on the EPDS, (2) who had access to a smartphone, (3) who possessed home wireless internet or could access internet connectivity, (4) who planned to continue routine postpartum care in the government primary health facility, and (5) who were literate in both English and Malay were included in the study. Mothers (1) with a history of drug abuse; (2) who had been diagnosed with depressive illness in the current pregnancy; (3) who were undergoing treatment for depression, bipolar disorder, or any other psychiatric disease at the time of participation; and (5) whose infant experienced intrauterine death or death immediately after birth were excluded from the study.

Randomization and Blinding

Participants were randomized (1:1) into 2 groups (ie, intervention and control groups). The researchers were blinded to the randomization process. Randomization was conducted by an independent assistant using a prearranged sealed opaque envelope. The envelopes contained a QR code linking to either a mobile app (the intervention group) or a WhatsApp communication channel (the control group). Both groups continue to receive treatment as usual (TAU) postpartum care.

Intervention Group

The intervention group receives TAU postpartum care and the Leveraging on Virtual Engagement for Maternal Understanding & Mood-enhancement (LoVE4MUM) mobile app intervention.

The LoVE4MUM app represents an innovative self-guided approach to postpartum mental health care and offers a comprehensive, tailored intervention for maternal mental health during the postpartum period. It is available in English and the local Malay language. It was developed using a prior rigorous research process that included in-depth interviews with mothers who had symptoms of PPD and guidance from a multidisciplinary expert panel including clinical psychologists, psychiatrists, obstetricians, family health specialists, public health specialists, and epidemiologists with further input from previous literature [13,47-50]. This app-based intervention is grounded in psychoeducation, intrapersonal therapy, and CBT principles.

The app was validated by a panel of 4 experts. The content underwent detailed item-by-item validation to ensure its relevancy and clarity. In this face validation process, the majority of the items garnered unanimous approval, which was reflected in a content validity index and kappa coefficient of 1.00. Nevertheless, items 12 and 16 had content validity index and kappa scores <0.7, necessitating their revision to enhance relevancy within the module content. Additionally, item 18 was modified to provide better clarity. The expert panel reviewed the revisions and subsequently approved the finalized module. See Multimedia Appendix 1 for details of the validation process.

A linguistic expert translated the content into the Malay language to ensure that it was culturally and contextually appropriate. The app was developed on a self-developed website platform using a mobile phone interface. Snippets of the mobile app are available in Multimedia Appendix 2 and Multimedia Appendix 3.

The app is structured around 5 main modules that provide flexible and accessible support over a 6-week period. It does not require sequential module completion and allows for personalized pacing. Each module targets critical aspects of postpartum mental well-being and is delivered in several formats including video, infographics, notes, and worksheets. Each module takes approximately 20 minutes to 30 minutes to complete. Automated reminders incorporated into the app and

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linked to users' emails encourage regular user engagement with app. The modules are described in Table 1.

Table 1.

Module	Module description	Skills learned	Worksheet
Module 1: Learn to Love Yourself	This module emphasizes self-care, establishing goals, and navigating social comparisons while addressing typical challenges like managing expectations, hospital admissions, and handling baby feeding and care. It aims to empower mothers to prioritize their well-being.	Self-care practices, goal formulation, effective communication for seeking help, and strategies for tackling common issues	Setting goals and listing things you love
Module 2: Understanding Postpartum Depression	This module offers foundational knowledge about postpartum depression, aiming to increase awareness and reduce stigma.	Identifying postpartum depression, seeking help, treatment options, and assertive communication with partners and family	—[a]
Module 3: Addressing Unhelpful Thinking	This module integrates cognitive behavioral therapy (CBT) concepts, guiding mothers to recognize and question negative thinking and understand how thoughts influence behaviors.	Identifying unhelpful thinking habits and mechanisms to improve thought patterns	Encourages describing specific situations and working on improving the associated thoughts
Module 4: Mood Tracker	This module engages mothers in monitoring their mood and provides strategies for mood improvement.	Identifying emotions, identifying healthier responses, and learning how to perform deep breathing	—
Module 5: I Need Help Now	This module guides users in accessing immediate calming techniques, help, and essential information for assertive communication with health care providers.	Calm breathing, communication with health providers, and information on seeking help	—

[a]Not applicable.

All data in the mobile app are stored in a password-protected, secured data cloud handled by the app developer. To register to use the app, participants must create a password that is requested after every time they sign in. Only administrative personnel have access to the encrypted password data.

Control Group

Both groups receive TAU postpartum care during the study. According to The Malaysian Perinatal Care Manual (fourth edition), at least 5 postnatal home visits and 1 clinic visit are conducted for normal cases, and the frequency increases for high-risk mothers and babies [51,52]. Routine postnatal care services include lactation consultation in the ward and postnatal visits by health care workers at home. Each postnatal check should assess the mother's overall, psychological, and emotional health, asking about any concerns, and evaluate the baby's well-being, feeding, and development to promptly identify any issues [53]. Participants are advised that they are free to withdraw from the study at any point for any reason.

Measurements

The study uses a questionnaire delivered online (Google form) and divided into 3 outcome measurement tools.

Primary Outcome Measurement

The EPDS is a 10-item questionnaire extensively used to assess postnatal depression in both international and local contexts. It uses a 4-point Likert scale for responses, with higher scores indicating greater depressive symptoms. The scale has been translated into the Malay language [54], where a score of 11.5 was the optimum cut-off for 72.7% sensitivity, 95% specificity, and a positive predictive value of 80%. In our study, participants with an EPDS score ≥12 are categorized as having postpartum depressive symptoms.

Secondary Outcome Measurements

Postpartum Depression Literacy Scale (PoDLiS)

The Postpartum Depression Literacy Scale (PoDLiS) is a 31-item, self-administered questionnaire developed by Mirsalimi et al [55] to assess the understanding of PPD. It evaluates 7 attributes of PPD literacy, including recognition, knowledge of risk factors and causes, self-care activities, available professional help, attitudes toward recognition and help-seeking, and information sources. Responses are scored on a 5-point scale, with attribute scores calculated by averaging related item scores. The Malay version of PoDLiS has acceptable reliability, with a Cronbach α of 0.73.

Automatic Thought Questionnaire (ATQ)

The Automatic Thought Questionnaire (ATQ), which is available in the Malay language [56], assesses the frequency of negative automatic thoughts linked to depression and anxiety. This 17-item scale asks respondents to rate the occurrence of specific negative thoughts over the past week on a scale from 1 to 5. Higher total scores indicate more frequent negative thinking. The scale's internal consistency ranges from 0.83 to 0.93 [56]. The total score ranges from 17 to 85, with a higher score reflecting a higher frequency of negative thinking.

Data are conducted at baseline, 1 week postpartum, and 6 weeks postpartum using the Google form, which is delivered via either the mobile app or a Whatsapp number. The self-reported survey takes approximately 15 minutes to 20 minutes to complete. All answers are automatically storied in the Google drive, and only

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the research team has access to the data. The schedule of enrollment, interventions, and assessments is summarized in Multimedia Appendix 4 and Multimedia Appendix 5.

Sample Size

Based on the recommendations of Whitehead et al [57], for a pilot trial with 90% power and a 2-sided significance level of 5%, the suggested sample size per treatment arm based on previous literature with a medium effect size (0.43) [58] is 25. Hence, a total of 72 participants (36 participants per arm) was required after taking into consideration a 30% nonresponse rate.

Statistical Analysis

Data will be analyzed using SPSS version 26, and significance is set at $P<.05$. Intention-to-treat analysis will be used. Categorical variables will be presented as the frequency and percent values, while continuous data will be presented as mean (SD). Baseline between-group comparisons will be conducted using Pearson chi square and Fisher exact tests for categorical data. Meanwhile, independent *t* tests will be used for continuous data. Repeated measures ANOVA will be used for within-group (time effect) and between-group (treatment effect) comparisons at 6 weeks. The mean difference and its corresponding 95% CI will be reported, with the significant level set at $P<.05$.

Risk Management

All participants were informed that the intervention serves as a supplementary self-help program and does not replace professional health care services. They are strongly encouraged to seek advice from their doctors or general practitioners regarding any concerns related to their mental or general health. Participants who experience symptoms of depression during the pilot trial are urged to promptly consult health care professionals and inform the research team of their condition. These measures allow for the appropriate management of any adverse effects and ensure the well-being of participants throughout the study.

For those screened and found ineligible for the trial, comprehensive support information was provided through a brochure containing information on PPD, immediate assistance, and emergency contact details. These individuals are also advised to consult their health care providers if they have concerns about their mental health. Specifically, mothers with an EPDS score ≥12 were excluded and referred to specialists for further evaluation and intervention in line with the Malaysian guideline for managing PPD.

Moreover, all participants continue to receive postpartum care by attending health care professionals at the Malaysia's Ministry of Health facilities, with care adhering to the standards set forth in the Perinatal Care Manual (fourth edition) [51].

Results

Participant recruitment began on September 1, 2024. As of January 1, 2025, recruitment was complete, resulting in a total of 72 participants enrolled: 36 in the intervention group and 36 in the control group. Data analysis and results are anticipated to be available by March 2025. The trial results are expected to be published by the end of 2025.

Discussion

Overview

PPD is influenced by a combination of intrapersonal, environmental, and physical factors that necessitates multifaceted interventions. The LoVE4MUM app represents a potential intervention for PPD prevention and uses an innovative approach that integrates the complexity of PPD with the unique cultural and societal contexts of Malaysia. The app combines psychosocial interventions, including CBT components, to address negative automatic thoughts and improve mental health literacy through engaging, educational content. The authors anticipate that participants receiving the LoVE4MUM app will demonstrate improvements in depressive symptoms, as measured by EPDS, compared with those receiving only standard postpartum care. Previous studies highlight the potential of mobile apps to improve mental health in perinatal populations [59]. Several reviews on mHealth interventions have revealed significant reductions in EPDS scores among postpartum mothers using mobile apps [23,60-62]. The LoVE4MUM app is designed to provide culturally relevant content. It also considers the barriers postpartum mothers in Malaysia face, such as limited access to face-to-face care and social stigma surrounding mental health.

The COVID-19 pandemic amplified the global prevalence of PPD, with rates within middle-income countries increasing from 20.8% before the pandemic to 34% during the pandemic [1,63] . This surge emphasizes the urgent need for remote health care solutions. The LoVE4MUM app leverages this shift by offering a self-guided platform that empowers mothers to engage in self-care from the convenience of their smartphones, circumventing the limitations of in-person care.

Lin et al [64] demonstrated that digital interventions promoting psychological empowerment and hedonic well-being are effective at driving these behavioral changes. In line with these findings, the LoVE4MM app encourages mothers to engage in activities that enhance their well-being while offering tools for cognitive restructuring. This approach is particularly crucial in a cultural context like Malaysia, where mental health stigma may prevent mothers from seeking professional therapy. Compared with the control group, we expect that mothers using the app will have improved EPDS scores; better scores for mental health literacy, as measured by the PoDLiS tool; and reductions in automatic negative thoughts.

Additionally, mHealth interventions alleviate depressive symptoms by improving social support [65,66]. Enhancing environmental support through assertive communication enables mothers to seek effective help from spouses and family members, reducing stress and improving mental health [67-69]. Similar to the CareMom app, which demonstrated a significant reduction in depressive symptoms through communication exercises, assertive requests within the CBT framework in the LoVE4MUM app are expected to improve emotional well-being during the postpartum period [70].

Anto et al [71] and Hartnup et al [72] showed that postpartum mothers often experience social risk and pressure through social

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media, which can exacerbate stress by promoting unrealistic comparisons and idealized identities of motherhood. Many mothers feel pressured to project a “perfect” image, leading to feelings of inadequacy and increased mental strain. By addressing these concerns, the LoVE4MUM app emphasizes the importance of self-compassion and reinforces a supportive, nonjudgmental digital environment, encouraging mothers to focus on doing their best rather than striving for perfection, which is crucial for improving mental well-being in this vulnerable period.

The strength of this pilot trial lies in its integration of validated measurement tools—EPDS, PoDLIiS, and ATQ—which offer a comprehensive view of maternal mental health. We expect the LoVE4MUM app's CBT-based interventions to demonstrate the success seen in similar applications, such as the CareMom, MumMoodBoster, Sunnyside, and Mother and Babies Course apps, which have successfully used structured exercises and personalized feedback to reduce depressive symptoms [18,70,73-76].

Nevertheless, certain challenges remain. First, the reliance on self-reported measures may introduce bias, as participants may underreport symptoms due to stigma or discomfort. Second, as demonstrated with other mHealth interventions like the Happy Mother app, user engagement can be inconsistent, and low adherence rates may diminish the overall effectiveness of the intervention[77]. To address this, the LoVE4MUM app incorporates strategies to enhance user engagement, such as push notifications, scripts, and personalized feedback. Another critical aspect to consider is the influence of cultural factors on app engagement and perception, which may affect how Malaysian mothers interact with the app. Ensuring that the app’s content is culturally sensitive and tackles common misconceptions about PPD will be essential in maximizing its impact. Moreover, as a pilot trial, the sample size may not allow for definitive conclusions, and the study’s findings should be interpreted as preliminary evidence of the app's potential.

Conclusion

The LoVE4MUM app represents a promising, scalable solution to address PPD among Malaysian mothers. If successful, this app could serve as a model for culturally adapted digital interventions that empower mothers to manage their mental health, ultimately reducing the prevalence and impact of PPD. Future studies will be necessary to further refine the app’s features and evaluate its long-term impact on maternal mental health outcomes.

Acknowledgments

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Data Availability

The data sets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

SSK, IBI, SS, and NA contributed to the conception, design, and methods. SSK and IBI drafted the manuscript. IBI, SS, and NA provided study supervision and critically revised the paper. All authors revised and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Expert validation of LoVE4MUM module content.
[PNG File , 302 KB - resprot_v14i1e63564_app1.png]

Multimedia Appendix 2
Snippets from LoVE4MUM mobile app login interface.
[PNG File , 460 KB - resprot_v14i1e63564_app2.png]

Multimedia Appendix 3
Snippets from LoVE4MUM mobile app module Postpartum Depression.
[PNG File , 795 KB - resprot_v14i1e63564_app3.png]

Multimedia Appendix 4
Patient visit schedule.
[PNG File , 25 KB - resprot_v14i1e63564_app4.png]

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Multimedia Appendix 5
Consolidated standard of reporting trials flow diagram of the LoVE4MUM pilot trial.
[PNG File , 130 KB - resprot_v14i1e63564_app5.png]

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Abbreviations

ATQ: Automatic Thought Questionnaire
CBT: cognitive behavioral therapy
EPDS: Edinburgh Postpartum Depression Scale
LoVE4MUM: Leveraging on Virtual Engagement for Maternal Understanding & Mood-enhancement
mHealth: mobile health
PoDLiS: Postpartum Depression Literacy Scale
PPD: postpartum depression
TAU: treatment as usual

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Protocol

Increasing Access to Mental Health Supports for 18- to 25-Year-Old Indigenous Youth With the JoyPop Mobile Mental Health App: Study Protocol for a Randomized Controlled Trial

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Abstract

Background: Transitional-aged youth have a high burden of mental health difficulties in Canada, with Indigenous youth, in particular, experiencing additional circumstances that challenge their well-being. Mobile health (mHealth) approaches hold promise for supporting individuals in areas with less access to services such as Northern Ontario.

Objective: The primary objective of this study is to evaluate the effectiveness of the JoyPop app in increasing emotion regulation skills for Indigenous transitional-aged youth (aged 18-25 years) on a waitlist for mental health services when compared with usual practice (UP). The secondary objectives are to (1) evaluate the impact of the app on general mental health symptoms and treatment readiness and (2) evaluate whether using the app is associated with a reduction in the use (and therefore cost) of other services while one is waiting for mental health services.

Methods: The study is a pragmatic, parallel-arm randomized controlled superiority trial design spanning a 4-week period. All participants will receive UP, which involves waitlist monitoring practices at the study site, which includes regular check-in phone calls to obtain any updates regarding functioning. Participants will be allocated to the intervention (JoyPop+UP) or control (UP) condition in a 1:1 ratio using stratified block randomization. Participants will complete self-report measures of emotion regulation (primary outcome), mental health, treatment readiness, and service use during 3 assessments (baseline, second [after 2 weeks], and third [after 4 weeks]). Descriptive statistics pertaining to baseline variables and app usage will be reported. Linear mixed modeling will be used to analyze change in outcomes over time as a function of condition assignment, while a cost-consequence analysis will be used to evaluate the association between app use and service use.

Results: Recruitment began September 1, 2023, and is ongoing. In total, 2 participants have completed the study.

Conclusions: This study will assess whether the JoyPop app is effective for Indigenous transitional-aged youth on a waitlist for mental health services. Positive findings may support the integration of the app into mental health services as a waitlist management tool.

Trial Registration: ClinicalTrials.gov NCT05991154; https://clinicaltrials.gov/study/NCT05991154

International Registered Report Identifier (IRRID): DERR1-10.2196/64745

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(JMIR Res Protoc 2025;14:e64745) doi:10.2196/64745

KEYWORDS

mental health; youth; Indigenous; First Nations; eHealth; mHealth; JoyPop; protocol; mobile mental health app; mobile app; Canada; mobile health; emotion regulation

Introduction

Background

Transitional-aged youth refer to individuals aged roughly 15-26 years who are transitioning from childhood to adulthood, a time of developing independence and increased challenges [1]. In Canada, mental health difficulties among transitional-aged youth have increased across the past decade and during the COVID-19 pandemic [2,3]. Indigenous individuals within this age range experience a greater burden of mental health difficulties compared to their non-Indigenous peers [4,5], partly attributed to distal factors such as a family history of residential school attendance [6] and more proximal factors such as experiences of childhood adversity [7]. Stressors such as substance use, loss of culture, racism, socioeconomic status, and family instability also impact the well-being and mental health of Indigenous youth [8].

Mental health services are less accessible for youth living in remote and rural locations [9]. For instance, there is less use of outpatient-based mental health care and psychiatry services and higher rates of emergency department visits and hospital admissions for mental health-related reasons in Northern Ontario, a region of many different Indigenous communities [10]. In general, long wait times in Northern Ontario are similar to those experienced in other regions of the province [10]; however, wait times for counseling and therapy are particularly long in Thunder Bay compared to many other communities, with an average of 348 days [11]. Services that consider and incorporate culture are even more sparse. Long wait times for services not only delay care and contribute to prolonged distress and suffering but also affect interest and engagement in services once they are offered [12,13].

Mobile health (mHealth) innovations can increase access to mental health support. Specifically, smartphone apps can be an effective medium for improving mental health symptoms and quality of life [14,15] and for youth specifically [16]. Knowledge gaps exist, however, with respect to app effectiveness for those on a waitlist for services and for Indigenous youth. For instance, a recent review of waitlist interventions for youth did not include any app-based interventions [17]. Further, until recently, app evaluation studies seldom included Indigenous youth in the evaluations [18]. A review published in 2024 highlights several initial evaluations of apps with Indigenous youth that were focused on a variety of health-related outcomes, with a few of these focused on general mental health or coping and well-being [19]. Most of this research has been conducted with Indigenous populations outside of Canada, whose cultural values related to well-being may differ [20]. While there are apps geared toward Indigenous populations in Canada [21], they have not been evaluated among treatment-seeking youth, and some are primarily informational in nature or used for data collection only [22,23]. More research is needed to test the effectiveness of apps for addressing mental health among Indigenous youth [24].

In collaboration with an Indigenous-led agency informed by Anishinabek culture and located in Northern Ontario (Dilico Anishinabek Family Care; Dilico), in this study, the JoyPop app will be evaluated as a tool for supporting the mental health needs of Indigenous youth currently waiting for mental health services. The app was developed by researchers in collaboration with youth and service providers [25], and input from these stakeholders continues to inform its implementation and evaluation [26,27]. The app was designed to promote resilience to stress and adversity [25], targeting emotion regulation as part of this goal since it is linked to strengthening resilience [28]. Rather than targeting specific mental health diagnoses, focusing on emotion regulation is also in line with recommendations that apps target “transdiagnostic factors” to make the best use of resources [24], since difficulty with emotion regulation is common among different mental health concerns [29,30]. To accomplish this goal, app features include a mood rating feature to promote emotional awareness [31], breathing exercises to help with relaxation [32], relaxing sounds to help with sleep [33], a game and art feature helpful for distracting oneself from stressful situations [34,35], a journal focused on positive topics to promote well-being [36], and connection to one’s support network and professional helplines, if needed [37].

An initial evaluation of the JoyPop app showed that app use was associated with improvements in emotion regulation and depressive symptoms for transitional-aged youth starting university [38], who shared that they valued the opportunity to build awareness and regulation of emotions [39]. Another study conducted with an Indigenous community in Southern Ontario identified the potential utility of the app for youth in the community while also gathering knowledge on how cultural values were connected to the app features [26,27]. Prior to developing the current protocol, a pilot study was also conducted with Dilico and another local organization, in which youth identified benefits of using the app related to coping and mental health [40]. Service providers also expressed positive feelings about the app’s ease of use and how the app could be helpful for youth who are on the waitlist for services (eg, by increasing their comfort levels before services begin) [40].

In sum, it is important to identify beneficial transdiagnostic mental health supports for Indigenous transitional-aged youth in Northern Ontario. Considering past findings with the JoyPop app have been promising [26,27,38-40], a larger scale randomized controlled trial is warranted to more robustly evaluate its effectiveness. Providing this intervention while youth are on a waitlist for services may help reduce disengagement and the need to seek other services during this time.

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Objectives

The objectives of the study are in response to the goals and needs identified by the community partner, Dilico. Specifically, the primary objective is to determine the effectiveness of the JoyPop app compared to usual practice (UP) in improving emotion regulation among Indigenous transitional-aged youth (aged 18-25 years) who are awaiting mental health services. We hypothesize that youth receiving the app will show improvement in emotion regulation (small to medium effect) greater than that observed for youth receiving only UP.

The secondary objectives are to (1) compare change in mental health difficulties and treatment readiness between youth in each condition to better understand the app's broader impact as a waitlist tool and (2) conduct an economic analysis to determine whether using the app while waiting for mental health services reduces other health service use and associated costs.

Methods

Overview of Study Design

This protocol was developed in collaboration with Dilico management and frontline staff to answer research questions of importance to the organization and the youth they serve. It was designed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement [41] (see Multimedia Appendix 1 for completed checklist). A pragmatic, parallel-arm randomized controlled superiority trial design will be used. Participants will be randomly assigned to the control (UP) or intervention (UP+JoyPop) condition in a 1:1 ratio using stratified block randomization. UP will involve waitlist monitoring practices at the study site, which include regular check-in phone calls to obtain any updates regarding functioning. In addition to UP, participants allocated to the intervention condition will receive the JoyPop app for 4 weeks and be asked to use it at least twice daily. Outcome measures will be administered to participants in both conditions during 3 assessments (first [baseline], second [after 2 weeks], and third [after 4 weeks]).

Setting and Participants

Data collection will take place at Dilico Anishinabek Family Care, an Indigenous-led organization that provides culturally informed child welfare, mental health and addictions, and health services to Anishinabek children and adults. Programs and services are provided at individual, family, and community levels. This self-governed organization is situated in Fort William First Nation in Northern Ontario.

Youth will be informed about the study by waitlist case managers and with flyers and letters mailed and emailed to them. Youth will be eligible for trial participation if they are on the waitlist for mental health services at Dilico and between the ages of 18-25 years.

Study Procedure

Table 1 describes participant progression through the study. A research assistant will contact interested youth by phone, text, or email to provide a brief description of the study. If a youth is interested and meets eligibility criteria, the research assistant will schedule their study orientation (as part of the baseline assessment). The research assistant will obtain informed consent during this orientation. As part of the informed consent process, youth will be made aware of local support services they can access should they experience distress during the study. They will also be made aware of the possibility that they are assigned to the control group so that they can make an informed decision about participation in light of this possibility.

Table 1. Participant timeline.

	–1	T1	T2	T3
Activity/assessment	Pre-study screening	Orientation/baseline assessment	2 Weeks/second assessment	4 Weeks/third assessment
Eligibility screen	✓			
Informed consent and condition allocation		✓		
Intervention (UP+JoyPop; or UP only)				
Outcomes measured: emotion regulation, mental health, treatment readiness, and service usage		✓	✓	✓
Outcome measured: app quality				✓—intervention group only
Control group participants given access to app				✓

Following consent, participants will complete the baseline assessment measures. They will be encouraged to respond as honestly and accurately as possible and not how they think researchers might want them to. Any participant that endorses suicidal thoughts during the first assessment will see an onsite counselor who will conduct a risk assessment and intervene as needed. Following completion of the assessment measures, the research assistant will access the allocation envelope from the locked filing cabinet, open it to determine the allocation, inform the participant, and proceed with associated study tasks. Participants allocated to the intervention condition will be supported in accessing and learning about the app. All participants will return to Dilico after 2 and 4 weeks to complete the second and third assessments. Once they have finished the

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study at the end of their third assessment, participants in the control condition will learn about and receive access to the app.

To promote retention, participants will receive reminders about upcoming assessments via text and email. To incentivize completion [42,43], participants will receive cash compensation (CAD $20 [US $13.89] for baseline assessment; CAD $25 [US $17.36] for second assessment (after 2 weeks); CAD $30 [US $20.83] for third assessment (after 4 weeks); and an additional CAD $25 [US $17.36] if all assessments are completed). We will arrange transportation (taxis, bus fare) if required for participants. Promising retention rates were observed using these methods in a pilot study [44].

Description of Intervention and Control Conditions

Participants in the intervention condition will be able to use the JoyPop app by downloading it onto their own device (if suitable). Participants who do not have an iPhone will be given a refurbished one containing only the app to use for the duration of the study. Participants will be asked to use the app at least twice daily for 4 weeks. The JoyPop app has features that allow participants to rate their mood, engage in relaxation exercises (ie, breathing), prepare for sleep, journal, play a Tetris-like game, create art, and reach out to their support system or suitable helplines. Figure 1 further describes these features. Internet connection is not required to use the app.

Figure 1. JoyPop features. LGBTQ: lesbian, gay, bisexual, transgender, and queer/questioning.

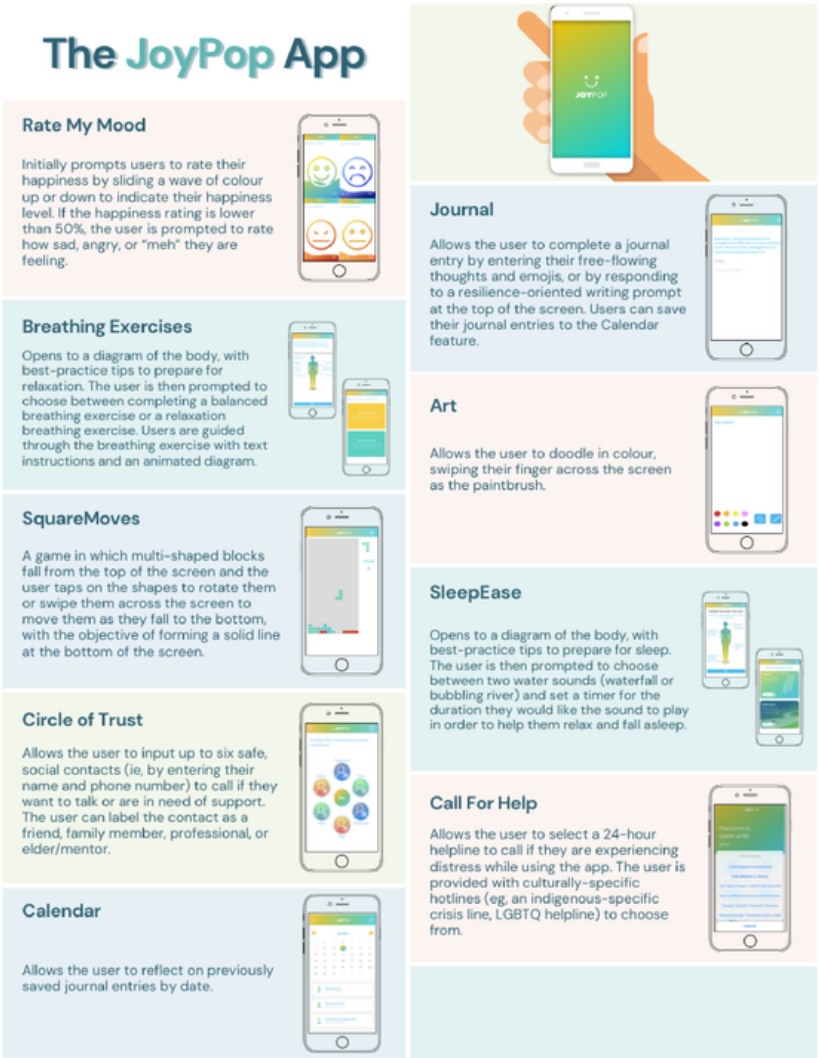

To promote engagement, youth will receive an email and SMS text message twice per day (at 8 am and 8 pm) reminding them to use the app. Outside of recommending using the app near the start and end of their day, we will not instruct or prescribe participants to engage with the app for any specific duration or pattern. Our intention is to evaluate the effects of using the app under real-world conditions in which users choose when and how often to use the app. Prior research suggests youth do use the app for the majority of the 4-week period [38,39]. Youth will also receive the usual waitlist management practice (UP).

Participants allocated to the control condition will only receive the UP. We chose this comparator to assess whether the JoyPop app could be a complementary support for individuals waiting for mental health services. This comparison creates the opportunity to test whether those who receive the app experience improved outcomes compared to those who do not receive it, representing "true" change after accounting for the regression to the mean phenomenon likely to affect both groups [45]. The use of a control condition addresses the limitations of our

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previous research in which all participants received the app [38].

Randomization and Blinding

Stratified block randomization will be used to randomize participants to the control or intervention condition in a 1:1 ratio. An independent researcher outside of the research team will create the randomization sequence using a computer-generated sequencing tool [46] and then place allocations into numbered, opaque, sealed envelopes. These will be stored in a locked filing cabinet and only accessed by the research assistant who is with the participant.

To protect against bias, the principal and coinvestigators and the statistician conducting the analyses will be blinded to conditions. Trial participants cannot be blinded given the nature of this trial in which they are actively using the app or not. Research assistants will also not be blinded, as the condition assignment determines study procedures such as showing the participant how to use the app and providing them with the correct measures.

Outcomes

The primary outcome is change in emotion regulation from the baseline assessment to the second assessment (after 2 weeks) and to the third assessment (after 4 weeks). Secondary outcomes are changes in mental health symptoms, readiness for treatment, and service usage from the baseline assessment to the second assessment and to the third assessment.

Measures

Descriptive Measures

During the baseline assessment, participants will complete a demographics measure asking about their age, ethnicity, family composition, highest level of education, gender, sex at birth, sexual orientation, and living situation. Demographic variables that could change over time (ie, gender, sexual orientation, family composition, and living situation) will be reassessed at subsequent assessments. We will also measure symptom presentation during the baseline assessment using a modified version of the *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) Self-Rated Level 1 Cross-Cutting Symptoms Measures (DSM-5-CCSM) [47] to characterize symptoms across 12 psychiatric domains (ie, depression, anger, irritability, mania, anxiety, somatic symptoms, inattention, suicidal ideation, psychosis, sleep disturbance, repetitive thoughts and behaviors, and substance use). One item pertaining to past suicide attempts was removed at the request of Dilico partners. Using the DSM-5-CCSM measure, respondents will report how much (or how often) they have been bothered by symptoms during the past 2 weeks. Items are rated on a 5-point scale (from 0=none at all to 4=severe or nearly every day) with the exception of items related to suicidal ideation and substance abuse, which are rated as either “Yes” or “No.” In a sample of adults receiving mental health services, most items in this measure except for the mania items have good test-retest reliability (intraclass correlation range=0.53-0.97) [48]. The measure also has good internal consistency (α=0.96) and criterion validity in terms of severity of impairment across life domains (r=0.84) in a community sample [49]. App usage data will be recorded in the JoyPop app with a timestamped record created each time the participant uses a feature.

Primary Outcome Measure

Emotion regulation will be measured with the Difficulties in Emotion Regulation Scale-Short Form (DERS-SF) [50,51], an 18-item self-report measure that asks respondents how often statements regarding their emotions have applied to them over the previous 2 weeks. Items are rated on a 5-point scale (ranging from 1=“almost never” to 5=“almost always”). Total scores range from 18 to 90, and subscale (strategy use, nonacceptance of emotion, impulsivity, ability to maintain focus on goals, awareness of emotions, and clarity of emotions) scores range from 3 to 15, with higher scores indicating greater difficulty regulating emotion. The DERS-SF demonstrates convergent validity via associations with symptoms of emotional disorders (eg, r=0.66 with the Beck Depression Inventory) [51,52]. In our pilot sample of Indigenous youth from Dilico, internal consistency for the total score ranged from α=0.87 to α=0.91 [53].

Secondary Outcome Measures

Mental health difficulties will be assessed with 2 measures: the Depression, Anxiety, and Stress Scale 21 (DASS-21) [54] and the Strengths and Difficulties Questionnaire (SDQ) [55,56]. The DASS-21 is a 21-item self-report measure that asks respondents how much specific statements regarding psychological distress applied to them over the past week. Items are rated on a 4-point scale (from 0=“never” to 3=“almost always”). Total scores range from 0 to 63, and subscale scores range from 0 to 21, with higher scores indicating greater distress. In clinical samples, this measure demonstrates convergent validity via correlations with other mental health measures (eg, r=0.85 between the Anxiety subscale and Beck Anxiety Inventory; r=–0.66 between the Depression subscale and Mental Health Questionnaire) [57,58]. In our pilot sample, internal consistency ranged from α=0.95 to α=0.96 across subscales. The SDQ is a 25-item self-report measure that asks respondents how true various statements have been for them. Items are rated on a 3-point scale (from 0=“not true” to 2=“certainly true”). Total scores range from 0 to 40, and subscale (emotional problems, conduct problems, hyperactivity, peer problems, and prosocial behavior) scores range from 0 to 10, with higher scores indicating greater difficulty (except for the prosocial scale for which the reverse applies). The SDQ has satisfactory internal consistency (α=0.80) and validity via its association with clinical diagnoses [56,59]. In our pilot sample, internal consistency was variable [53]; thus, we will ensure adequate psychometric performance in this study with a larger sample prior to analyses.

Treatment readiness will be assessed with the 4-item treatment readiness subscale of the Motivation for Youth’s Treatment Scale (MYTS) [60]. Items are rated on a 5-point scale (from 1=“strongly disagree” to 5=“strongly agree”), with the total subscale score calculated as the mean of item scores; higher scores indicate greater readiness. Groups with prior mental health service use and higher symptom severity tend to have

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higher average scores [60]. In our pilot sample, internal consistency ranged from α=0.80 to α=0.90.

Service usage will be assessed with 5 items generated by the research team that ask respondents how many times they accessed various health care services (ie, walk-in clinic, family doctor or nurse practitioner, emergency department, mental health counselor, and mental health hotline or phone support) over the previous 2 weeks.

Statistical Analyses

Descriptives

We will describe the sample by calculating means and frequencies across demographic variables such as gender. We will also calculate mean scores on the DSM-5-CCSM to describe presenting mental health across 12 psychiatric domains. We will report internal consistency estimates and correlations between all measures to provide an indication of their reliability and convergent validity in the sample, given a lack of prior validation with Indigenous samples. With respect to app use among the intervention group, we will calculate the average frequency and duration of app use both in general and for each feature.

Primary Outcome

We will calculate the change in overall emotion regulation using the DERS-SF total score and the change in specific domains via the DERS-SF subscale scores. An independent statistician will use linear mixed modeling to test whether the change in emotion regulation is greater for those in the intervention condition relative to those in the control condition by including an interaction term between time and group [61]. We will evaluate the final sample to determine whether it is also feasible to analyze gender and baseline mental health symptoms as subgroup effects via interaction terms [62,63]. Analyses will be conducted with an intent-to-treat approach. Missing data will be handled with full information maximum likelihood estimation, which is recommended for avoiding bias in parameter estimates [64,65].

Secondary Outcomes

We will calculate change in mental health using total scores from the DASS-21 and SDQ, while we will calculate change in specific domains using the DASS-21 and SDQ subscale scores. We will calculate change in treatment readiness using the treatment readiness subscale from the MYTS as described. Similar to the primary outcome analyses, linear mixed modeling will be used to test whether the change in mental health symptoms and treatment readiness is greater for those in the intervention condition relative to those in the control condition by including an interaction term between time and group [61]. Covariates of gender and baseline mental health symptoms will again be included. With respect to service usage, we will estimate the costs of services used among participants in each condition and conduct a cost-consequence analysis to determine the incremental costs or savings associated with receiving the app [66].

Sample Size

We calculated the required sample size for a 2 (between subjects; treatment condition) by 3 (within subjects; time) mixed design, roughly estimating the statistical power needed for the planned linear mixed model for the primary outcome under the assumption of compound symmetry. We used parameters of f=0.2 (small to medium effect), =0.05, and power=0.95, resulting in a suggested sample size of 66 to achieve necessary power. We estimate 60% retention throughout the study (40% attrition) based on our initial research [53]; as such, an initial sample of 110 will be recruited.

Ethical Considerations

Ethics Approval

The study protocol (version 1) was approved on December 16, 2022, by the Research Ethics Board at the Thunder Bay Regional Health Sciences Centre (file #100157). This Research Ethics Board acts as the Board of Record for clinical research projects led by Lakehead University researchers. The Research Advisory Committee at Dilico reviewed and approved all procedures. All participants will provide informed consent and will be made aware that they will receive counseling regardless of their choice to participate. Any required amendments would be reviewed by the Research Ethics Board, and participants would be informed by phone or email if such amendments directly impacted their experience in the study. We would also update the ClinicalTrials.gov registry (NCT05991154).

Mitigation of Harms

The risk of harm due to study participation is minimal. Participants may withdraw at any time by contacting the research team via phone or email. Any concerns or adverse events experienced or reported by participants to a research assistant would be reported immediately to the principal investigator (author ARM). The research team also meets weekly and will discuss any issues or concerns as they arise. All serious adverse events will be reported to the Thunder Bay Regional Health Sciences Centre Research Ethics Board using the Research Ethics Local Serious Adverse Event Reporting Form.

As described earlier, we will provide participants with contact information for local support services during the orientation, including walk-in counseling services and a local crisis line. Additionally, if recent suicidal thoughts are endorsed, an onsite counsellor will conduct a risk assessment with the participant and intervene as needed. As part of this risk assessment, the participant and counsellor will discuss whether continued study participation is recommended. Finally, as participants are on the waitlist for mental health services, they will be offered counseling services at some point following study completion (exact timing based on waitlist at the time).

Data Management and Confidentiality

Practices related to confidentiality follow the Canadian Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans [44] and ethical guidelines at the Thunder Bay Regional Health Sciences Centre and Lakehead University. During recruitment, names and contact information of potential participants will be kept in a list only accessed by the research

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team. Once enrolled, the research assistant will assign each participant an ID number; both self-report and app data will contain only this ID number and no identifying information. The list connecting participant IDs to their names and contact information will be deleted upon study completion. The research assistant leading the orientation will inform participants about confidentiality and its limits during the informed consent procedure, including the procedure for notifying a staff member if recent suicidal ideation is endorsed; we will also provide this information in the information letter that is given to participants.

With respect to data management, a research assistant will enter responses from the hard-copy measures into a version of the measures hosted by Survey Monkey. Survey Monkey has SOC 2-accredited data centers [67] with physical security, including 24×7 monitoring, cameras, visitor logs, entry limitations, as well as dedicated cages for Survey Monkey hardware. Data in transit is encrypted using secure TLS cryptographic protocols. Usage data from the JoyPop app will be stored on a password-protected server within Canada and encrypted during transmission. In accordance with the Ownership, Control, Access, and Possession (OCAP) standards set by the First Nations Information Governance Centre [68], all data will be stored at Dilico; electronic measures and app data will be stored on a password-protected computer while hard-copy data will be stored in a locked filing cabinet. Data will not be shared with the public or outside third parties. Data will be retained for at least 7 years after study completion following Lakehead University policy.

Oversight and Monitoring

Author ARM, as the principal investigator, will oversee all trial activities and hold weekly meetings with research assistants to discuss the day-to-day running of the trial. Author ARM will consult with coinvestigators and meet on a quarterly basis to discuss the trial status and plan for future trial activities. Author ARM will also meet with collaborators from the local community partner (Dilico) to discuss ongoing implementation of the trial. Retention will be discussed on an ongoing basis with further strategies implemented if needed.

Results

This research is funded through a Brain Canada—2021 Future Leaders in Canadian Brain Research grant, which began in October 2022. Recruitment began September 1, 2023, and is ongoing. As of July 2024, two participants have completed the study and attended all assessments. When the trial is complete, our community partner, Dilico, will review the findings via their research advisory committee, which is in line with OCAP principles [68]. Pending approval by the committee, results will be disseminated through academic conferences and publications as well as media interviews to reach the broader community. We will also share a summary of findings with participants who selected that they would like to receive this, as well as with staff at Dilico who are interested in the information. Pending positive results, avenues for future funding to support scalability will also be discussed with community partners.

Discussion

Overview

The current research will explore the impact of the JoyPop app on emotion regulation, mental health, and treatment readiness among Indigenous youth waiting for mental health services. Positive change among these variables and demonstrated cost-effectiveness associated with using the app would support adopting the app into routine waitlist management practices within the current partner organization. The degree and magnitude of findings within this clinical sample of Indigenous youth will be compared to prior work within a non-clinical sample in which use was associated with positive change in emotion regulation and depression symptoms [38]. We will also compare findings to another trial studying the effectiveness of the app among younger Indigenous youth [69] and another with non-Indigenous youth [70]. Such comparisons will allow identifying how to best use the JoyPop app as a supportive tool. Finally, positive findings would also be consistent with a growing emphasis on transdiagnostic approaches to mental health care. Specifically, findings may increase our knowledge about the link between emotion regulation and various mental health–related difficulties among Indigenous youth [29].

Dissemination of Findings

When the trial is complete, our community partner, Dilico, will review the findings via their research advisory committee, which is in line with OCAP principles [68]. Pending approval by the committee, results will be disseminated through academic conferences and publications. We will also create infographics and videos to be shared broadly through team members' networks, on social media, and through public presentations, which we will invite youth from the study to help develop and participate in. We will use media interviews to reach the broader community. We will share a summary of findings with participants who selected that they would like to receive this, as well as with staff at Dilico who are interested in the information. Pending positive results, we will discuss further scalability and potential integration of e-mental health solutions into services with the community partner, such as seeking funding to conduct a hybrid implementation/effectiveness study. We will also share findings with decision makers from other organizations who are similarly seeking solutions to meet youth mental health needs.

Strengths and Limitations

Study strengths include the randomized controlled trial design, methods to promote retention and uptake of the intervention (eg, reminders and provision of phones and transportation), and evaluation of diverse outcomes, including both clinical outcomes and an analysis of service usage to understand the broader impact of the app within the health care system. The experimental design specifically improves upon the limitation of non-randomized earlier work [38]. An inherent study limitation is that participants are not blinded to condition assignment. A further limitation is that although the study was designed with few requirements surrounding app usage to allow for a more naturalistic examination, it is possible that in potential future nonresearch clinical settings, participants may engage

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with the app to a lesser extent when they are not actively involved in attending research sessions.

Given the nature of the intervention, an additional consideration is whether implementing an app-based intervention may contribute to problematic mobile device use. While this is an important consideration, the app does differ from social media and communication apps, which some research indicates are among those identified as the most "addictive" [71]. Future research, however, could evaluate whether accessing an app such as JoyPop encourages greater smartphone use overall. Future research could also incorporate scales assessing the risk of smartphone app addiction [eg, 72].

Conclusions

Transitional-aged youth in Canada experience a heightened burden of mental health difficulties relative to adult populations, and Indigenous youth in this age range may be especially at risk [4,5]. Individuals who live in more remote or rural locations, such as in Northern Ontario, have less access to mental health care, which has negative impacts on well-being and engagement in future services [10,12]. This study, conducted in partnership with Dilico Anishinabek Family Care, will speak to whether adopting the JoyPop app as part of routine waitlist management practices may benefit Indigenous youth mental health and reduce additional service use during the waiting period. While an app is unlikely to remedy all mental health symptoms, it may be a useful tool for helping youth build skills and readiness in advance of formal counseling services.

Acknowledgments

This study was funded through a Brain Canada—2021 Future Leaders in Canadian Brain Research grant (ARM). The study was also supported through a Tier 1 Canada Research Chair in Addictions and Mental Health (SHS) and in-kind contributions by Dilico Anishinabek Family Care. ARM is the principal investigator and led the design of the study and protocol, while ASN, ET, FS, JVO, and SHS provided substantial contributions to the study design. ARM, ASN, AO, ET, FS, JVO, and SHS sought funding for the study. CD, ET, FS, KS, and TB provided guidance regarding implementing the study locally and recruiting and retaining participants at the local site. TN led the trial coordination and data collection with supervision from ARM and support from ET and IM. AM drafted the manuscript. ARM provided supervision and revisions on the manuscript. All authors reviewed and approved the final manuscript.

We would like to thank Dilico staff whose knowledge and experiences have informed the study design and who have supported the onsite implementation of the trial. We also thank the youth who have participated in our research and shaped the ongoing design of the JoyPop app and associated research projects.

Conflicts of Interest

The majority of the authors have no conflicts of interest to declare. The principal investigator (ARM) recently acquired intellectual property ownership rights for the JoyPop app (in June 2024). Prior to this time, intellectual property rights were owned by another researcher or institution. ARM did not own any intellectual property rights when applying for funding for this study, when creating the protocol, or when initiating the study. To mitigate any risk related to ARM's new intellectual property ownership rights, ARM will not be involved in collecting or analyzing the data, will be blinded to participant condition assignment, and will consult with coinvestigators throughout the study.

Multimedia Appendix 1
SRIRIT (Standard Protocol Items: Recommendations for Intervention Trials) checklist.
[PDF File (Adobe PDF File), 90 KB - resprot_v14i1e64745_app1.pdf]

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Abbreviations

DASS-21: Depression, Anxiety, and Stress Scale 21
DERS-SF: Difficulties in Emotion Regulation Scale-Short Form

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Dilico: Dilico Anisinabek Family Care
DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)
DSM-5-CCSM: DSM-5 Self-Rated Level 1 Cross-Cutting Symptoms Measures
mHealth: mobile health
MYTS: Motivation for Youth's Treatment Scale
OCAP: Ownership, Control, Access and Possession Standards
SPIRIT: Standard Protocol Items: Recommendations for Intervention Trials
SDQ: Strengths and Difficulties Questionnaire
UP: usual practice

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Protocol

Effect of an Internet-Based Pilates Telerehabilitation Intervention in People With Multiple Sclerosis: Protocol for a Randomized Controlled Trial

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Abstract

Background: Physical activity (PA) has been recommended in multiple sclerosis (MS) to maintain good physical fitness and mental health, reduce the severity of symptoms and risk of relapse, and improve quality of life. Pilates has been suggested as an ideal PA to manage physical, cognitive, and psychological symptoms of MS and a useful method to maintain and improve balance and gait.

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Objective: This paper presents the protocol for a study that aims to evaluate the efficacy on the physical domain (specifically balance and gait) of a home-based, self-managed PA intervention delivered through the MS-FIT exergame (HELAGLOBE Società a responsabilità limitata). In addition, measures of cognitive performance, quality of life, and well-being will be considered.

Methods: This is a 2-arm, multicenter, randomized controlled trial with 3 assessment points (baseline, 12 weeks postintervention, and 6 weeks follow-up). People with MS with mild disability, low risk of falling, preserved cognitive functions, and low anxiety and depression are potential eligible participants. The experimental group (MS-FIT) will self-administer the MS-FIT exergame at home in addition to their leisure-time physical activities. MS-FIT is an internet- and Pilates-based tool that uses the Microsoft Kinect Sensor V2. Participants in the control group will only have access to their leisure-time physical activities. Participants in the MS-FIT group will train at home with MS-FIT for 12 weeks and will be required to perform the exercises for a total of 30 minutes/day for at least 3 days/week. The primary outcome is the Timed Up and Go, a test designed to assess walking. We will also administer additional tests for motor function (visual analog scale 0-10, Timed 25-Foot Walk, Ambulation Index, 2-minute walk test, Twelve Item Multiple Sclerosis Walking Scale, Nine-Hole Peg Test), cognition (Brief International Cognitive Assessment for Multiple Sclerosis), fatigue (Modified Fatigue Impact Scale), quality of life (Multiple Sclerosis Quality of Life-54), well-being (Psychological Well-Being Scales), and PA (International Physical Activity Questionnaire and Minnesota Leisure Time Physical Activity Questionnaire). Acceptance and satisfaction with the intervention received (Client Satisfaction Questionnaire and an adapted version of the Tele-healthcare Satisfaction Questionnaire – Wearable Technology) and subjective impressions of changes in performance (Patients' Global Impression of Change) will also be assessed.

Results: Recruitment for the trial started on March 16, 2022, and the first participant was randomized the same day. Data analysis and results are expected to be published in 2025.

Conclusions: Pilates has proven beneficial in several neurological diseases such as MS. With this study, we will provide evidence for the use in clinical practice of a digital tool for self-administered Pilates exercises at home as a complement to rehabilitation and for the continuity of care in MS.

Trial Registration: ClinicalTrials.gov NCT04011579; https://tinyurl.com/2p9n4d2t

International Registered Report Identifier (IRRID): DERR1-10.2196/58026

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KEYWORDS

exergame; MS-FIT; Pilates; Kinect; multiple sclerosis; exercise; physical activity; leisure time physical activity; Timed Up and Go

Introduction

Multiple sclerosis (MS) is a chronic inflammatory neurodegenerative disease with autoimmune demyelinating lesions of the central nervous system and one of the most common causes of neurological disability in young adults. Clinically, MS progressively worsens over time, leading to cumulative physical disability, cognitive deficits, and neuropsychiatric and behavioral symptoms [1]. Physical impairments lead up to 85% of people with MS to complain of ambulation difficulties after typically 10-15 years of disease, and, after 20 years, over 66% of people with MS do not retain the ability to walk [1]. Several factors, such as weakness, spasticity, cerebellar ataxia, fatigue, and impaired attention, can cause imbalance and gait disorders [2,3]. They prevent people from performing daily activities properly and regularly, with negative effects on work status and social relationships. Rehabilitation is the main option to enhance recovery from disabling symptoms such as spasticity, ataxia, sensory loss, fatigue, pain, mood, and cognitive disorders [4]. More recently, people with MS have been recommended to engage in regular physical activity (PA).

PA, including leisure-time physical activity and exercise, comprises any bodily movement produced by skeletal muscles' contraction that results in a substantial increase in energy expenditure over resting levels [5]. Increasing PA and reducing sedentary behavior are general recommendations to improve health outcomes for all people with chronic diseases [6]. For people with MS, PA maintains good physical fitness and mental health, prevents or reduces the severity of symptoms and the risk of relapses, and improves quality of life [7-9]. Based on current evidence and experts' opinions, recent MS guidelines recommend "at least 150 minutes/week of exercise and/or 150 minutes/week of lifestyle PA" throughout the disease course [10]. However, Klaren et al [11] report that people with MS do not engage in sufficient PA amounts, with only approximately 20% of people with MS meeting recommended levels of moderate or vigorous daily activity compared with 40% of healthy participants. Although a recent survey study reported higher rates among people with MS, only 60% of the total sample met recommendations, with the lowest rate shown in the severely disabled group [12]. Furthermore, the benefits of PA may be limited if not incorporated into a structured, personalized, and supervised program.

Various mind-body fitness modalities, such as Pilates, yoga, Tai chi, and Qigong, are widely used by people who seek to achieve physical and mental health outcomes [13,14].

Pilates has been suggested as an ideal approach to managing physical, cognitive, and psychological symptoms of MS [15] and a popular alternative method for maintaining and improving balance and gait performance [16], as in other neurological conditions [17-19]. Indeed, it is a precise and controlled form

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of exercise that uses the body's stabilizing muscles and is based on the principles of concentration, control, centering, flowing movement, precision, and breathing. If followed correctly, they can improve flexibility, strength, core stability, muscle control, breathing, and posture, and increase body awareness with less ground impact and joint stress [20,21]. The research findings support the therapeutic use of Pilates in the management of MS because it is a safe, active treatment method (few adverse effects) with high adherence (low dropout rate), and it can improve important meaningful functions (eg, balance, gait, physical-functional capacities, and cognition) [22].

A possible perspective for delivering Pilates interventions could benefit significantly from the proliferation of exergames and new technologies for telerehabilitation [23]. Playing exergames is a form of whole-body physical exercise [24] that requires users to complete assigned tasks aimed at improving physical fitness and promoting an active lifestyle [25]. Furthermore, exergames have been demonstrated to be comparable with traditional therapies, may be more enjoyable and acceptable, and may improve the engagement of people with MS in PA [26]. Exergame-based telerehabilitation solutions represent an efficient alternative method to overcome barriers that prevent people with MS from accessing regular long-term rehabilitation interventions (ie, transportation and working time) and to provide effective treatments in a setting, matching the patient's circumstances (eg, at home), priorities (eg, during lunch break), and capabilities (eg, physical impairment) [27].

Recently, MS-FIT (HELAGLOBE Società a Relazioni Limitate), a Kinect-based playable exergame implementing Pilates exercises, has been developed by an Italian network of experts in the field of MS rehabilitation for future use in research and clinics [28]. It has been customized for people with MS, allows tailoring the intervention in order to potentiate the effects of an ongoing program, and has been conceived to be developed for asynchronous telerehabilitation purposes.

The aim of this study, promoted by the Italian Multiple Sclerosis Foundation, is to test in people with MS the efficacy on the mobility domain measured with the Timed Up and Go (TUG) test of a self-managed home intervention delivered through MS-FIT in addition to leisure-time physical activities, in comparison with leisure-time physical activities alone. Measures of balance, gait, upper limb functioning, PA, cognition, quality of life (QoL), well-being, acceptability, satisfaction with use, and adherence to the intervention will also be considered. In addition, a blood sample will be collected to investigate if genetic polymorphisms that are considered potential regulators of neural plasticity could influence the response to the proposed intervention [29].

Based on previous findings [30], we expect that the intervention, in addition to leisure-time physical activities, will be associated with a primary outcome of mobility (TUG) compared with leisure-time physical activities alone that are expected to worsen due to disease progression. Similar changes between groups are expected in secondary outcomes; furthermore, based on our previous findings [28], we expect high acceptability, satisfaction-to-use, and adherence to the MS-FIT intervention.

If results are positive, MS-FIT could be proposed in combination with rehabilitation to potentiate the effect of the rehabilitation intervention and ensure continuity of care for people with MS.

Methods

Study Design

We are conducting a multicenter 2-arm, superiority randomized controlled trial (RCT) with 3 assessment points (baseline, T0; postintervention at 12 weeks, T1; and follow-up at 6 weeks, T2). Participants will be allocated to the intervention (MS-FIT) or control group in a 1:1 ratio by simple randomization.

Participants in the MS-FIT group will have access to the MS-FIT exergame for at-home self-administration [28] (Multimedia Appendix 1) in addition to their leisure-time physical activities. Participants in the control group will have the possibility to perform only their leisure-time physical activities. Exercise will not be allowed and rehabilitation treatments, except for speech therapy, sphincter rehabilitation, and psychological support, must be suspended. The study design is illustrated in Figure 1.

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Figure 1. Study design.

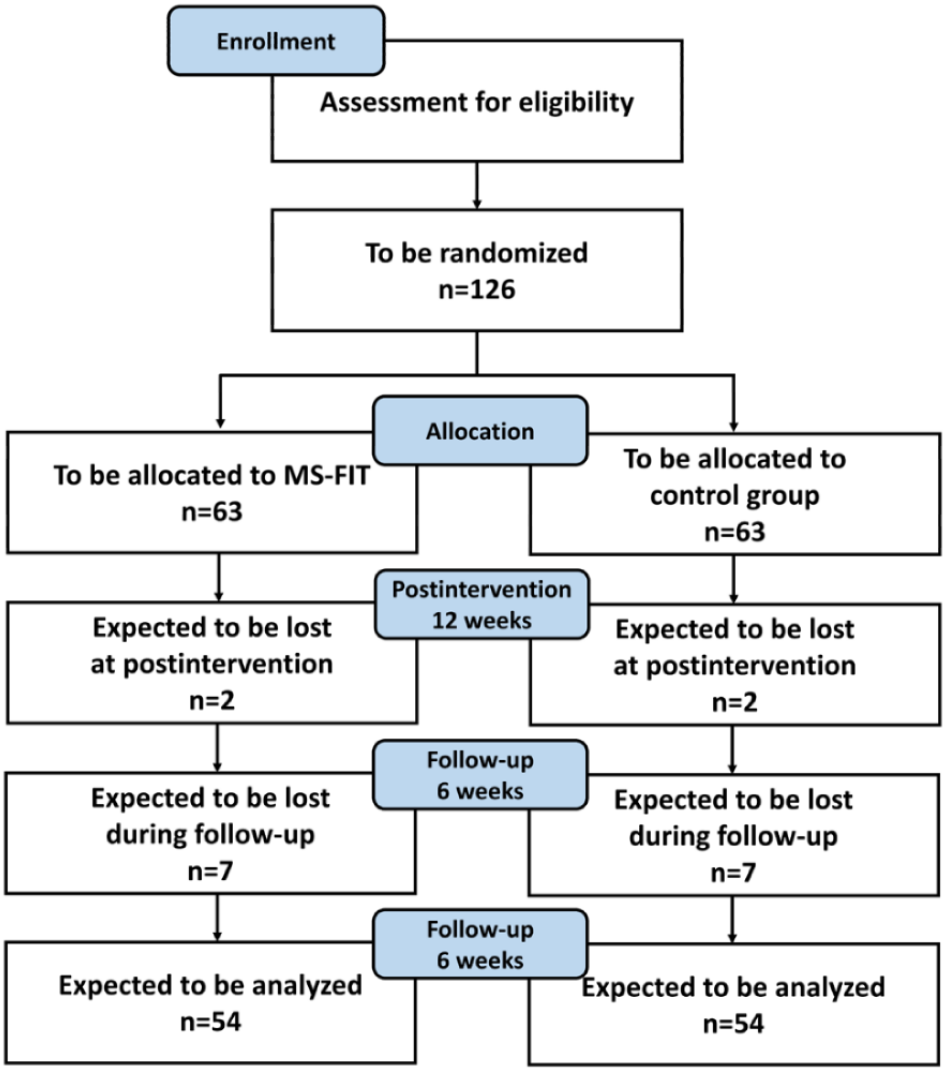

Setting

Participants will be recruited among those followed by 14 Italian neurorehabilitation centers; specifically, at the Italian Multiple Sclerosis Society Rehabilitation Services of Genoa and Padua, the Multiple Sclerosis Center of IRCCS (Istituto di Ricovero e Cura a Carattere Scientifico) Foundation "Carlo Besta" Neurological Institute (Milan), the Vita-Salute San Raffaele University (Milan), the Department of Neuroscience, Rehabilitation, Ophthalmology, Genetics, Maternal and Child Health (DINOGMI) of the University of Genoa, the Neurology Unit of IRCCS Neuromed (Pozzilli), the Department of Medical Science and Public health of the University of Cagliari, Department of Translational Biomedicine and Neurosciences (DiBraiN) of the University A. Moro (Bari), the IRCCS Fondazione Don Carlo Gnocchi ONLUS (Milan), the Uosi Multiple Sclerosis Rehabilitation of the IRCCS Istituto delle Scienze Neurologiche of Bologna, Department of Advanced Medical and Surgical Sciences (DAMSS) of the University of Campania Luigi Vanvitelli (Naples), the Department of Neurosciences of the S. Camillo-Forlanini Hospital (Rome), the Department of Medical and Surgical Sciences and Advanced Technologies "G.F. Ingrassia" (DGFI) of the University of Catania, and the IRCCS Centro Neurolesi "Bonino-Pulejo" (Messina).

The assessments will be carried out in person at the several centers. The intervention with MS-FIT will be performed at home.

Recruitment, Enrollment, and Randomization

People with MS along with mild disability, low risk of falling, preserved cognitive functions, and low anxiety and depression as reported in medical records are potential eligible participants. They will be contacted by telephone by the study manager of the related center (Multimedia Appendix 1), who will explain the study process in detail to ensure that patients understand the entire clinical trial; they will receive detailed information, including the purpose, procedures, follow-up content, data storage, benefits, and risks of the study, and will be given adequate time to consider participation. They will be informed that for the entire period of participation in the study, only leisure-time physical activities will be allowed, but not exercise and rehabilitation. They will also be informed verbally that their participation is voluntary and that they can withdraw their consent at any time without giving reasons and without depriving themselves of any treatment and care or other disadvantages.

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Patients who agree to participate will be scheduled for a screening visit with a therapist (Multimedia Appendix 1). First, they will be asked to sign the written informed consent (Multimedia Appendix 2) after carefully reading and understanding the information about the study procedures and data security measures (including information on how to contact the study team in case of questions) provided to them. This approach is compliant with the General Data Protection Regulation and has been approved by the ethics committees.

After consent, recruited patients will proceed to the screening evaluation, where inclusion and exclusion criteria are assessed, and they will immediately receive feedback on whether or not they can participate in the study. Enrolled patients will be randomized by the study manager through the electronic case record form (eCRF) (Multimedia Appendix 1) into one of the 2 groups (ie, MS-FIT and control) and informed of the result of the assignment.

Eligibility Criteria

Eligibility criteria were selected to ensure optimal fitness of the study sample with respect to the subsequent implementation of the MS-FIT intervention in the health care setting, to minimize the impact of confounding variables (eg, rehabilitation outcomes), and to ensure comparability with other studies on similar interventions.

Inclusion Criteria

The study includes people with a diagnosis of MS according to McDonald's criteria [31] and aged ≥18 years; all disease courses are eligible (relapsing-remitting, primary progressive, and secondary progressive) [32]. Patients will be included if their disability level based on the Expanded Disability Status Scale (EDSS) [33] is between 2 and 4. Indeed, we expect that in people with MS with a lower EDSS, the proposed intervention might not be effective and other forms of PA based mainly on exercise should be considered. For people with MS with a higher EDSS, Pilates could be recommended as a complement but not as a replacement for rehabilitation; also, for this reason, we considered it unethical to include patients who should suspend their treatments for the aims of the study. Furthermore, asynchronous telerehabilitation tools for self-administered balance training should be proposed when the patient's ability to maintain balance safely is preserved (eg, pregnant women will be excluded until after giving birth). In any case, we included patients with preserved balance evaluated with the Berg Balance Scale score >46 [34].

To ensure the ability to use the MS-FIT exergame, normal cognitive functioning determined by a Mini-Mental Status Examination score >24 [35] is required; a Hospital Anxiety and Depression Scale score <10 in the 2 subsets of anxiety and depression [36] could prevent a loss of adherence due to mood disorders.

Exclusion Criteria

The study excludes individuals who have received at least 1 rehabilitation treatment (except speech therapy, sphincter rehabilitation, and psychological support) in the last month before being contacted. Other exclusion criteria are visual deficits that could compromise the use of the MS-FIT exergame and relapses in the last 3 months. Participants with relapses during the period of involvement in the study will be considered dropouts.

All hardware and software components will be provided to the participants in the MS-FIT group; training provided by the study manager will ensure ease of use. For this reason, technology will not be an exclusion criterion.

Intervention

All participants will be allowed to continue their leisure-time physical activities.

Participants in the MS-FIT group will receive the MS-FIT exergame [28]. They will be required to train at home with MS-FIT for 12 weeks by performing the exercises for a total of 30 minutes/day for at least 3 days/week.

While gaming, participants will choose their favorite and most useful exercises; the difficulty of the exercise will increase based on the user's performance. In this way, the exercise selection and the reward structure will ensure the personalization of the intervention.

Before starting the intervention, each participant will be trained in the use of the tool by the study manager.

Participants in the control group will not receive MS-FIT; however, as a reward for their participation, we will offer them the MS-FIT intervention at the end of their study involvement.

All participants will be assessed at T0, T1, and T2.

Assessment

The assessment will consist of clinical tests measuring the domains most relevant to MS. The primary outcome will always be administered first; the order of the secondary outcomes will be randomized across participants; however, the same order will be maintained for the individual participant. We assume that the administration of all tests will take, on average, about 60 minutes.

Multimedia Appendix 3 summarizes when the different outcome measures should be collected.

Primary Outcome

The primary outcome of the study is TUG [37], commonly used to measure dynamic balance and to assess activity limitations by examining the patient's ability to ambulate and perform transfers. The TUG was originally created to predict the risk of falling in geriatric patients.

At the "go" signal, the participant must rise from a chair, walk 3 m, turn around, return to the chair, and sit down as quickly but safely as possible. The participant starts with the back against the chair and the arms resting on the armrests and is timed from the moment he or she lifts the pelvis from the chair until he returns with the pelvis on the chair [34]. The participant wears his or her regular footwear and uses his or her customary walking aid (none, cane, or walker); however, due to the eligibility criteria adopted in this study, participants will not

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use assistive devices for walking. No physical assistance is given.

Secondary Outcomes

Secondary outcomes will evaluate the effects of the intervention on the following:

1. Motor function: visual analog scale (VAS; 0-10) for balance subjective disability improvement [38], Timed 25-Foot Walk (T25FW) [39], Ambulation Index [40], 2-minute walk test (2MWT) [41], Twelve Item Multiple Sclerosis Walking Scale (MSWS-12) [42,43], and Nine-Hole Peg Test (9HPT) [44].
2. Cognition: Brief International Cognitive Assessment for Brief International Cognitive Assessment for Multiple Sclerosis (BICAMS), which consists of the Symbol Digit Modalities Test (SDMT), the California Verbal Learning Test-II (CVLT-II), and the Brief Visuospatial Memory Test-Revised (BVMT-R) [45].
3. Fatigue: Modified Fatigue Impact Scale (MFIS) [46,47].
4. QoL: Multiple Sclerosis Quality of Life-54 (MSQoL-54) [48,49].
5. Well-being: Psychological Well-Being Scales (PWB) [50,51].
6. PA: International Physical Activity Questionnaire (IPAQ) [52,53], the Minnesota Leisure-Time Physical Activity Questionnaire [54] which provides a general evaluation of the total energy expenditure in leisure time physical activity.
7. Perceived intervention effect: 7-point Patients' Global Impression of Change (PGIC; from 1="no change or worse" to 7="a great deal better") scale.

Technology

Furthermore, acceptance of the used technology will be evaluated with an ad-hoc questionnaire on patients' expectations; satisfaction with the intervention will be evaluated with the Client Satisfaction Questionnaire (CSQ-8) [55,56] and the Tele-healthcare Satisfaction Questionnaire (TSQ-WT) [57].

Blood Sample

If the participant consents, a peripheral blood sample will be collected at T0 in vacutainer tubes containing ethylenediaminetetraacetic acid. According to previous studies [29], participants will be divided into subgroups with respect to polymorphism. All blood samples will be genotyped for a total of 55 genetic polymorphisms of 23 potential regulators, such as Homer1, AKT1, RAPTOR, D2R, GAPD, CHAT, p53, BRCA2, LIG4, XRCC5, CYP3A4, NBS1, MDM2, CNR1, ATTn, CNR2, GRIN1, GRIN2B, TRPV1, FAAH, COMPT, and BDNF.

For example, CNR1 region containing AAT repetitions will be amplified by polymerase chain reaction from genomic DNA; sequencing products will be purified using a rapid, high-performance dye-terminator removal kit and will be subjected to electrophoresis; AAT repetitions will be counted on the resulting electropherograms (short AAT: homozygous or heterozygous for an allele with ≤11 repeats of AAT triplets; long AAT: homozygous for an allele with ≥12 repeats of AAT triplets). For the TRPV1 and FAAH, the iPLEX Gold technology and MassARRAY high-throughput DNA analysis will be performed.

The blood sample will be collected early in the morning after awakening (8:00 AM). To synchronize the sample with lifestyle variables, participants were requested to avoid excessive physical activity in the last 3 days before blood sampling, to sleep for 7-8 hours the night before the study, to avoid starvation, and to have a normal breakfast in the morning [29]. The samples will be analyzed in the center of DC.

Other Measures

Adherence to the intervention will be provided by the number of sessions actually performed as automatically recorded by the MS-FIT tool and the number of dropouts.

Safety will be assessed by the number of potential issues (ie, number of falls). The severity of adverse events will be graded according to the Common Terminology Criteria for Adverse Events v 4.0 on a 5-point scale (grade 1, mild discomfort; grade 2, moderate discomfort; grade 3, severe inability; grade 4, life-threatening or disabling; grade 5, death) and reported in detail on the eCRF. A grade higher than grade 2 will be considered as a condition for dropout.

We will also collect information on the pharmacological treatments (specific and nonspecific for MS) followed by participants, comorbidities, and the type of PA practiced during participation in the study.

Criteria for Premature Withdrawal

In addition to withdrawal of consent at any time, the study manager at each site may also consider as criteria for premature withdrawal any medical conditions that could jeopardize the safety of the patient if she or he continues the study, changes in the disease treatment during the study, and noncompliance of the participants to the study procedures.

Sample Size

The sample size was calculated by referring to the TUG change after a Pilates intervention found by Kalron et al [30] in a group of people with MS. The authors found no difference between the group receiving the Pilates intervention and the control group receiving an intervention of physical therapy. The Pilates group improved the TUG performance by about 1.8 seconds, which is clinically relevant for people with MS. Considering a variability of about 3.4 seconds, a power of 80%, a significance level (2-sided) of 5%, and a potential loss of 15% of patients at follow-up, the estimation of the necessary sample size consists of approximately 63 participants for the experimental group (a total of 126).

Data Collection and Management

Data entry, including quality checks and double entry validation, will be performed through eCRF (Multimedia Appendix 1). Missing data from the unit record will be compared with the corresponding handwriting case record form and corrected accordingly.

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Statistical Analysis

Descriptive statistics will be used to evaluate differences between the 2 groups of participants. The study hypotheses will be tested using an intention-to-treat analysis, where all consenting patients who were randomized during the accrual period will be included in the analysis.

Continuous data will be summarized using count, mean, median, SD, and IQRs, whereas categorical measures will be described using frequencies. The assumption of normality will be tested with the Shapiro-Wilk test. Pre-post effects within groups will be investigated using the paired *t* test or the Wilcoxon matched-pairs signed-rank test. Between-group proportions will be compared by chi-square or Fisher exact test, while between-group comparisons for continuous variables will be done using either the unpaired 2-sided *t* test or the 2-sided Wilcoxon 2-sample test for nonnormal data. Correlations will be computed using Pearson or Spearman coefficients.

The primary analysis will be performed by comparing mean changes from T0 to T1 in the primary and secondary study outcomes. In particular, the MS-FIT group will be compared with the control group with analyses of covariance. The model includes change as the dependent variable, with the intervention group as the main effect and baseline and number of sessions as additional covariates. Finally, generalized estimating equation models will be performed to assess the persistence of the intervention effect; here the mean effect of the intervention at the time points T0, T1, and T2 on all outcomes, adjusted for the baseline value, will be evaluated between the 2 groups.

Differences in the outcome measures between subgroups defined by different polymorphisms will be analyzed using the analysis of variance or the Kruskal-Wallis test, as appropriate.

Statistical analysis will be performed using STATISTICA 7.1 software (StatSoft GmbH). Significance will be recognized for $P<.05$.

Ethical Considerations

This trial is conducted in accordance with the protocol (version 1, July 27, 2018), the Declaration of Helsinki, and good clinical practice. It has been approved by the Ethics Committee of San Martino Hospital (134/2018) and registered before patient enrollment at ClinicalTrials.gov (NCT04011579).

Any change to this protocol must be agreed upon by all the study investigators. Each amendment must be signed by the principal investigator at each site, and amendment forms will be submitted to the local Ethics Committee for approval. The amendment will be updated in the clinical trial registry.

Participants will be asked to sign the written informed consent, and their data will be deidentified. Participants will not receive any compensation for participating in the study.

A formal audit process at the end of the study is proposed for this trial.

Patient and Public Involvement

Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of our research, although patient feedback was an important source for the development and improvement of the MS-FIT tool investigated in this trial [28]. Published results will be disseminated to study participants upon request.

Dissemination

The results of this RCT study will be disseminated. Dissemination includes communication and promotion of the project activities and results to participants, people with MS, and their stakeholders (eg, caregivers, health care professionals, and the scientific community). Dissemination activities will begin at launch and will continue throughout the duration of the study. Specific activities include dissemination through materials such as flyers and videos to be distributed through the internet, social networks, forums, or at local, national, and international events, and specific meetings with end users; dissemination through presentation of results in national and international peer-reviewed scientific journals; dissemination through presentation of research results at major national and international health care conferences and annual meetings; and dissemination through the ClinicalTrials website registry.

Results

Recruitment for the trial started on March 16, 2022, and the first participant was randomized on the same day. As of March 2022, we enrolled 126 participants who received a T0 visit; up to now, 108 received a T1 visit and 103 received a T2 visit. Data analysis and results will be published in early 2025.

Discussion

Summary

Cumulative data suggest that the Pilates method has proven beneficial in several neurological diseases and may be a PA tool for people with MS. A recent review [22] in MS showed that Pilates improves balance, gait, physical-functional conditions (muscle strength, core stability, aerobic capacity, and body composition), and cognitive functions; in contrast, fatigue, QoL, and psychological function did not show a clear improvement. Furthermore, high adherence (average adherence ≥80%) and few adverse effects were reported. For these reasons, future research is needed to develop clinical protocols that can maximize the therapeutic effects of Pilates for people with MS. In this context, novel devices and technologies for home-based interventions could provide solutions to overcome limitations due to urban barriers (eg, transportation), daily activities (eg, working time), and clinical conditions (eg, level of disability) and to ensure continuity of care. Therefore, practicing Pilates at home through eHealth tools could help people with MS to regularly engage in PA and to successfully maintain their physical, cognitive, and emotional status.

Here, we describe the RCT protocol designed to test the efficacy of a home-based PA intervention delivered through the MS-FIT exergame on balance and gait. In addition, we will also assess the effects on cognition, QoL, and well-being.

The present RCT protocol was designed taking into account previous studies in the MS scientific literature in terms of the

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number of weeks of intervention, weekly frequency, session duration, outcomes, setting, and control group [22]. Because only one study evaluated long-term monitoring after the intervention [58] and it is unclear whether the obtained results are maintained, as an additional element of novelty, we propose to schedule a follow-up assessment in order to define whether the effects of Pilates persist.

Limitations

The first limitation of this study is that we will only have evidence of the effectiveness of a Pilates exergame for people with MS with mild disability. However, even people with MS at more advanced disease stages benefit from regular PA to maintain fitness, prevent pain and secondary complications of inactivity, and treat or reduce symptoms. Thus, as specific prescriptions should be tailored to clinical conditions, a dedicated trial for patients with a higher level of disability should be considered. Second, due to the discontinuation of the Kinect Sensor V2 adopted in MS-FIT, for the successful translation of the exergame into clinical practice, a new compatible commercial sensor will be identified, and the app will be adapted; Microsoft Azure Kinect and Mentor Age (Wita Società a responabilità limitata) are valid and comparable systems already taken into account by other researchers [28,59,60]. Third, although the MS-FIT tool was not developed to pursue rehabilitation purposes, it would be helpful to analyze the MS-FIT intervention as a complement to the work of health care professionals and evaluate if it is able to potentiate the effect of a rehabilitation intervention, possibly also in people with MS with a higher level of disability. Finally, direct evidence, such as MRI acquisition, will not be considered to reveal which microstructural changes are due to the MS-FIT intervention.

Future Directions and Conclusions

MS-FIT is a usable and accepted digital health tool for telerehabilitation implementing Pilates exercises and aims at supporting the self-administration of Pilates training at home. This study will provide evidence for the use of the MS-FIT tool in clinical practice as a complement to rehabilitation and for the continuity of care of people with MS. However, a feasibility protocol involving patients with moderate disability (EDSS between 4 and 6) should be designed and tested, followed by a multicenter trial that assesses the effectiveness of the tool and paves the way for more extensive use in MS.

Acknowledgments

The authors would like to thank the Italian Multiple Sclerosis Foundation and Roche Società per Azioni (Società per azioni) for supporting this study.

Data Availability

The data sets generated and analyzed during this study will be available from the corresponding author on reasonable request.

Conflicts of Interest

AT, MP, PC, LL, EC, MR, LS, GT, LP, FP, ES, EP, MAB, and GB have no conflicts of interest to disclose. MI is coeditor for MSJ; she has received honoraria for participation in advisory boards from Biogen, Bristol Myers Squibb, Merck, Novartis, Roche, Sanofi, and Janssen. DC is an advisory board member of Almirall, Bayer Schering, Biogen, GW Pharmaceuticals, Merck Serono, Novartis, Roche, Sanofi-Genzyme, and Teva and received honoraria for speaking or consultation fees from Almirall, Bayer Schering, Biogen, GW Pharmaceuticals, Merck Serono, Novartis, Roche, Sanofi-Genzyme, and Teva; he is also the principal investigator in clinical trials for Bayer Schering, Biogen, Merck Serono, Mitsubishi, Novartis, Roche, Sanofi-Genzyme, and Teva; his preclinical and clinical research was supported by grants from Bayer Schering, Biogen Idec, Celgene, Merck Serono, Novartis, Roche, Sanofi-Genzyme, and Teva. DP received advisory board membership, speaker's honoraria, travel support, research grants, consulting fees, or clinical trial support from Almirall, Biogen, BMS-Celgene, Sanofi-Genzyme, Merck Serono, Novartis, Roche, and Alexion. PG is an advisory board member of Biogen, Bayer-Shering, Roche, Merck-Serono, Novartis Pharma, Sanofi-Genzyme, Teva; he received honoraria for speaking or consultation fees from Biogen, Bayer-Shering, Roche, Merck-Serono, Novartis Pharma, Sanofi-Genzyme, Teva, Almirall, Sandoz; he is the principal investigator in Phase I, II and III clinical trials for Biogen, Bayer-Shering, Roche, Merck-Serono, Novartis Pharma, Sanofi-Genzyme, Teva; he received research funds from Biogen, Bayer-Shering, Roche, Merck-Serono, Novartis Pharma, Sanofi-Genzyme.

Multimedia Appendix 1
Description of the digital tools used in the study and of the personnel involved in the study activities.
[DOCX File , 24 KB - resprot_v14i1e58026_app1.docx]

Multimedia Appendix 2
Original Italian version of the information sheet and its English translation.
[DOC File , 74 KB - resprot_v14i1e58026_app2.doc]

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Multimedia Appendix 3
The collection of the outcome measures occurs at different time points depending on the considered measure.
[DOCX File , 25 KB - resprot_v14i1e58026_app3.docx]

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Abbreviations

2MWT: 2-minute walk test
9HPT: 9-Hole Peg Test
BICAMS: Brief International Cognitive Assessment for Multiple Sclerosis
CSQ-8: Client Satisfaction Questionnaire
eCRF: electronic case record form
EDSS: Expanded Disability Status Scale
IPAQ: International Physical Activity Questionnaire
IRCCS: Istituto di Ricovero e Cura a Carattere Scientifico
LTPA-Q: Leisure Time Physical Activity Questionnaire
MFIS: Modified Fatigue Impact Scale
MS: multiple sclerosis
MSQoL-54: Multiple Sclerosis Quality of Life-54
MSWS-12: 12-Item Multiple Sclerosis Walking Scale
PA: physical activity
PGIC: Patients' Global Impression of Change

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PWB: Psychological Well-Being Scales
QoL: quality of life
RCT: randomized controlled trial
T25FW: Timed 25-Foot Walk
TSQ-WT: Tele-healthcare Satisfaction Questionnaire – Wearable Technology
TUG: Timed Up and Go
VAS: visual analog scale

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Protocol

Swasthya Pahal (Health for All) Using a Sustainable, Multisector, Accessible, Affordable, Reimbursable, and Tailored Informatics Framework in Rural and Urban Areas of Chennai, Tamil Nadu: Protocol for a Quantitative Study

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Abstract

Background: Noncommunicable diseases (NCDs) require a longer period of care, for which health care systems must acquire technologically advanced solutions to enhance patient care. Swasthya Pahal (health for all) is an innovative, interactive, multilingual, stand-alone, internet-enabled computer-based program that aims to improve the self-management of NCDs.

Objective: This study aims to enhance the self-management of chronic NCDs (diabetes, hypertension, high cholesterol, and obesity) by determining the usefulness, acceptance, and effectiveness of the Swasthya Pahal program in hospital and community settings in both rural and urban areas of Chennai, Tamil Nadu. This objective can be met by generating risk factor profiles of individuals enrolled and enhancing their self-management of NCDs using a portable health information kiosk that uses the Sustainable, Multisector, Accessible, Affordable, Reimbursable, and Tailored (SMAART) model.

Methods: A quantitative study will be conducted on a convenient sample of 2800 individuals from selected hospital and community settings in rural (n=1400) and urban areas (n=1400) in Chennai, Tamil Nadu. Data will be collected on sociodemographics, health behaviors, and clinical status, as well as knowledge, attitudes, and practices. Objective assessments such as weight, blood pressure, and random blood sugar levels will be measured. In addition, the usefulness, acceptance, and effectiveness of the Swasthya Pahal program will be determined.

Results: Results will be summarized using descriptive analysis. Appropriate bivariate and multivariate regression analysis will be performed to determine the predictors of the outcome variables of usefulness, acceptance, and effectiveness of Swasthya Pahal in wider settings. All analyses will be performed using SAS (version 9.1; SAS Institute), and the results will be reported as 95% CI values and $P<.05$.

Conclusions: The study proposes to enhance the self-management of NCDs in both rural and urban community settings through the implementation of the Swasthya Pahal program based on the SMAART informatics framework. The study aims to understand the implementation, acceptability, and usability of Swasthya Pahal among a diverse sample of people in urban and rural settings.

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KEYWORDS

interventions; Swasthya Pahal; acceptance; health behavior; NCDs risks; self-management; healthcare; noncommunicable disease

Introduction

Background

Noncommunicable diseases (NCDs), which include heart disease, stroke, cancer, diabetes, and chronic lung disease, are the leading causes of illness worldwide. This has been identified as one of the most significant challenges to sustainable development in the 21st century [1]. According to the World Health Organization, NCDs account for approximately 38 million (68%) of all deaths worldwide and approximately 5.87 million (60%) of all deaths in India [2]. The Sustainable Development Goal target 3.4 is to reduce premature mortality from NCDs by one-third by 2030 relative to 2015, as well as to promote mental health and well-being [3]. India faces a significant burden of NCDs, which poses a challenge in achieving Sustainable Development Goal 3 Good Health and Well-Being. In recent years, India has experienced demographic and epidemiological shifts, resulting in a shift from infectious diseases to NCDs. The World Health Organization reports that 1 in every 4 Indians is at risk of dying from an NCD before the age of 70 years [4]. If timely NCD prevention and control measures are not implemented, the total annual number of NCD deaths will rise to 55 million by 2030 [5].

In the current era, information and communication technologies (ICTs) serve as health systems, promoting, restoring, or maintaining health. They should be used for the prevention and control of both communicable and NCDs at multiple levels and in a variety of ways [4]. The use of ICT in a health-promoting lifestyle behavior program improves health behaviors that are crucial in the prevention of both communicable and noncommunicable diseases. eHealth is defined as the application of ICT in the world of health care. It includes mobile health, telemedicine, health information systems, electronic health records, and many more [6]. These technologies can be presented and accessed in a variety of ways, including web-based applications, mobile phone and alert systems, and phone and videoconferencing. They have been identified as effective measures for improving patient skills and knowledge, increasing the likelihood of healthy behavior [7]. It can provide both low-cost and high-quality services. Health information products can be designed to suit the needs of the community by incorporating high levels of interaction and accessibility. Technological solutions play an important role in health care systems by assisting individuals in self-checking their health status and providing low-cost, accessible, and affordable solutions to meet the demands of local communities across geographical locations, particularly those in resource-poor settings [8]. Studies have shown that the use of ICT through mobile health in India has benefitted both urban and rural healthy and unhealthy ("disease") population groups. [9-11] Health kiosks will continue to play an important role in the digital health scene for the foreseeable future. One of the advantages of telehealth kiosks is that they bring medical and expert care to remote locations that medical practitioners rarely visit. In nations such as India, these locations could be distant rural areas with inadequate infrastructure [12]. A pilot study of the Swasthya Pahal (health for all) program, which is an advanced community-based program facilitated by an interactive, multilingual, standalone, and internet-enabled program, has highlighted the improvement of self-management of NCDs among police personnel [13]. The program was implemented through a digital, interactive touch screen platform Sustainable, Multisector, Accessible, Affordable, Reimbursable, and Tailored (SMAART) model. The potential outcome of the SMAART platform is that it is a personalized self-management action plan that enables easier self-management and that is backed up by continuous monitoring, interactive health information, and collaborative decision-making [8]. The pilot study had significant findings: the applicability of the study and its use beyond a purposive population group needed to be further studied. The program is based on the Population Health Informatics framework; to the best of our knowledge, this framework is now used to address the burden of NCDs in both urban and rural economic groups. This study aims to evaluate the usability of a portable health information kiosk that uses the SMAART framework to address the burden of NCDs by determining the usefulness, acceptance, and effectiveness of Swasthya Pahal in hospital and community settings of both rural and urban areas of Chennai, Tamil Nadu.

Objectives

The objectives of the research are as follows:

1. To use the digital health intervention Swasthya Pahal to assess the risk factor profile of NCDs in individuals from hospital and community settings in rural and urban areas of Chennai, Tamil Nadu.
2. To assess individuals' Knowledge, Attitudes, and Practices (KAP) of their health status and self-management of chronic NCDs (diabetes, hypertension, high cholesterol, and obesity) through the Swasthya Pahal program among individuals from hospitals and community settings in rural and urban areas of Chennai, Tamil Nadu.
3. To investigate the usefulness and acceptance of the Swasthya Pahal program among individuals from the hospital and community settings in rural and urban areas of Chennai to enhance self-management of NCDs.

Methods

Study Design

The quantitative pre-post study will recruit 2800 study participants from the community and hospital settings in urban and rural areas of Chennai, Tamil Nadu. Individuals will have access to a touch screen device to register their health data in their respective languages. Subjective data on sociodemographic details, health behaviors, clinical status, and KAP will be gathered. Objective data will include measurements of height, weight, blood pressure, and blood glucose levels. Individuals will be randomly assigned to the intervention and control group. A total of 20% of the rural and urban samples will be assigned

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to the control group (total N=560; n=280 from each urban and rural area) and intervention group (total N=560; n=280 from each urban and rural area). Those in the intervention group will have access to tailored messages through the use of multiple interactive digital formats using podcasts and SMS. Those in the control group will have access to standard of care and will be provided with a booklet in English and in the local dialect to self-manage the burden of NCDs. Individuals will receive interactive messages for 3 months on a daily or weekly basis. The message content and delivery will be tailored (based on sociodemographics, KAP, user preferences, and disease conditions) to meet the specific needs of the individuals. Monthly assessments will be done at month(s) 1, 2, and 3. At 6 months, retention analysis will be done for Knowledge. In addition, the usefulness, acceptance, and effectiveness of Swasthya Pahal will be assessed postintervention.

Study Setting and Study Population

The study population will be from hospital and community settings of selected rural and urban areas of Chennai, Tamil Nadu, namely Kannur, Pannur, Thirumanikuppam, Thodukadu, Kottaiyur, Nemili, Mannur, Kiloy, Ulundai, Narasamangalam, Karanai, Panimalar Medical College Hospital and the Research Institute and Rural Health Training Centre Chennai, and Maligaipattu village.

Sampling and Recruitment

Participants will be recruited using the nonprobability convenience sampling method from selected urban and rural sites of Chennai, Tamil Nadu. Data will be gathered from 2800 participants (1400 each from urban and rural sites).

Inclusion criteria were participants above the age of 18 years and those consenting to participate and exclusion criteria were individuals below the age of 18 years and those who would not give their consent.

Data Collection—Structured and Semistructured Questionnaire

Overview

A structured questionnaire will be used to determine the risk factor profile of NCDs in individuals from selected rural and urban areas of Chennai, Tamil Nadu. For objectives 1 and 2, data will be collected on the portable health information kiosk. Individuals will be enrolled in the Swasthya Pahal program with a unique code that will generate a SMAART health card. Information will be recorded electronically, that is, subjective data that captures sociodemographic profile, clinical status, information on health behavior, KAP of individuals, and objective data such as BMI, blood pressure, and blood glucose levels will be measured. After 3 months of intervention, a posttest will be conducted on KAP, and then a crossover of intervention mode is done. For objective 3, after the dual intervention, KAP will be conducted and the acceptance and usability of the program will be assessed by 2 tools: the Client Satisfaction Questionnaire and System Usability Scale (annexures 2 and 3 in Multimedia Appendix 1). The tool will be translated into the local language (Tamil). A small group of respondents will pilot test the study tool in the local language to ensure the clarity of the questions asked.

Variables Assessed

The following variables will be assessed in the study: variables A1, A2, A3, and A4 will be assessed with respect to objectives 1 and 2, and variables B1 and B2 will be assessed with respect to objective 3.

A1—Sociodemographic Details

Data will be gathered on the study participant's age, gender, region of residence, and education level.

A2—Health Behavior

Data on history and current smoking and alcohol consumption will be compiled. Data on the family history of consumption will also be collected.

A3—Clinical Status Details

This will include information on anthropometric measurements such as height (as measured by a Stadiometer), weight (as measured by a standard technique), and BMI. A sphygmomanometer will be used to take blood pressure readings. A glucometer will be used to measure blood glucose levels.

A4—Knowledge, Attitudes, and Practices

These data will collect information on an individual's understanding of their BMI, blood pressure, and blood sugar level. The information gathered will determine whether the individual is currently receiving treatment for any disease risks and what treatments have already been followed (eg, diet, medicine, and physical activity). The tool also captures the individual's level of understanding of obesity, hypertension, and diabetic risk factors. It also acquires information on individuals receiving treatment for any of the illness risks and information on individuals' understanding of their family's health history.

B1—Tool for Acceptance: Client Satisfaction Questionnaire

This questionnaire includes a total of 8 questions on a 4-point Likert scale that contains questions related to the accessibility of the computer-based software Swasthya Pahal.

B2—Tool for Usability: System Usability Scale

The System Usability Scale consists of 10 questions on which individuals rate the system on a 5-point Likert scale based on their opinion of the system's usefulness.

Data Collection, Data Entry, and Quality Assurance

To ensure efficient and high-quality data collection and processing, the following data management protocol will be followed: a well-defined study manual will be prepared, and a well-trained data collection team will be in charge of data collection, data entry, and data security procedures. Each question will be explained clearly by the data collector, and any doubt or confusion regarding the question will be addressed immediately. The data will be electronically recorded using the Swasthya Pahal (Health for All) software.

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Data Security and Privacy

Regular backups will ensure data security by storing data files in one password-protected computer or laptop and deleted from other systems. The data files will have a unique password that only the concerned research team will be able to access. Data will be kept for 15 years after the study is completed in case it is needed to validate research findings, set priorities, or be re-analyzed by another researcher [14].

Data Analysis

The collected information will be entered in SAS (version 9.1; SAS Institute) and the results were reported as 95% CI values and $P<.05$. The data will be summarized by using frequency, percentage, mean, and SD values. Appropriate bivariate and multivariate analyses will be done. A *t* test to compare means between the continuous variables and a categorical dependent variable will be conducted. A chi-square analysis will be performed to determine whether the two independent variables are related.

Project Timeline and Milestones

A detailed research plan and schedule timeline of the tasks involved in the study are presented in Table 1.

Table 1. Scheduled timeline of the tasks in the Swasthya Pahal.

Task	Months									
	1	2	3	4	5-7	8-10	11-13	13-15	16-19	20-24
Review of the literature, initial design, and planning of the study	✓	✓								
Development of study protocol and ethical approval		✓								
Approval of the study		✓								
Development of the study tool		✓								
Review and revision of the study tool by the research team			✓							
Training of the data collection team			✓							
Pilot testing of Swasthya Pahal computer-based tool			✓							
Initial data analysis, results, discussion, and dissemination of the pilot study				✓						
Deployment of the Swasthya Pahal intervention and baseline data collection					✓					
Recruitment of the target sample and assignment into intervention and control groups					✓					
Post assessment at 1, 2, 3, and 6 months					✓	✓	✓			
Reviewing collected data by the research team								✓	✓	
Data analysis									✓	
Results and Discussion and Conclusion										✓
Dissemination										✓

Informed Consent

The research team will provide the informed consent form approved by the Institutional Review Board (IRB) to all eligible participants in the study (Multimedia Appendix 1). The team will explain the study details, the time commitment, and the benefits of the study results to the participants. Those who are willing to participate and provide consent will be enrolled in the study. If any participant is uneducated, ethical consent will be audio recorded. Furthermore, uneducated participants will be instructed on how to complete the questionnaire in the local Indian dialect, increasing the study's usefulness and generalizability. Data privacy and patient confidentiality will be assured. The study participants will have the right to withdraw from the study at any time.

Ethical Considerations

The study with protocol number PMCHRI-IHEC-058 gained approval from the Panimalar Medical College Hospital and Research Institute Institutional Human Ethics Committee (Central Drugs Standard Control Organization Registration number ECR/1399/Inst/TN/2020) in February 2022 with approval number PMCH&RI/IHEC/20221/021 dated February 18, 2022. The study will be conducted according to the Declaration of Helsinki, as it involves human participants [15].

Results

The program Swasthya Pahal aims to enhance the self-management of NCDs, including diabetes, hypertension, and obesity, in the rural and urban setting of Tamil Nadu, which will help in examining the individual's perception of NCDs and also help in behavioral changes among the general population. The data collected will determine the predictors of the outcome variables of usefulness, acceptance, and effectiveness of Swasthya Pahal and broaden the applicability of the Swasthya Pahal program among individuals from rural and urban settings.

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Discussion

Overview

NCDs claim the lives of 40 million people worldwide each year, accounting for 70% of all fatalities. Cardiovascular illnesses (17.7 million deaths), malignancies (8.8 million deaths), respiratory diseases (3.9 million deaths), and diabetes (1.6 million deaths) account for 81% of these deaths [16,17]. NCDs have become a serious public health problem in developing nations like India. NCD imposes financial consequences for India's poorer households, as well as high out-of-pocket costs for the acute and long-term impacts of NCDs. This results in catastrophic health expenditure for households [18]. As a result, it is critical to screen individuals for NCDs and provide health education. Tailored ICT-supported NCD management programs such as Swasthya Pahal (Health for All) can make a difference by ascertaining an individual's risk factor profile, as well as their perspective on NCDs and their health status. The critical need of the hour is the applicability of tailored NCD management interventions that can enhance knowledge and prognosis of the disease to the patient while also influencing policy decisions among low- and middle-income countries [19]. This digital platform intervention across a wider population group cannot only enhance the self-management or prevention of NCDs in individuals but its usefulness and acceptance may assist researchers and policymakers in health education and communication across the country.

The limitation of the study is that it is cross-sectional, needs to evaluate the long-term impact of the Swasthya Pahal program, and covers a large population group in the self-management of NCDs.

Conclusions

Swasthya Pahal offers a personalized self-management plan that is supported by continuous monitoring, interactive health data, and collaborative decision-making. It focuses on an individual's risk factor profile and helps us understand how they perceive NCDs and their health status. The research will help us understand the acceptability and usefulness of Swasthya Pahal among a large sample from urban and rural settings. It can be used to raise awareness and address the burden of NCDs. The program can be used for developing cost-effective interventions that can be used to educate populations from remote or unreached areas.

Acknowledgments

The authors are the only ones who contributed to this paper, and they are appreciated.

Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

AJ, SKM, SRS, and DO contributed to conceptualization. AJ and HK assisted with data curation. AJ and AG performed the formal analysis. SKM assisted with methodology. SKM, HK, and SRS conducted project administration. AJ and DO assisted with resources. SKM assisted with software. AJ contributed to supervision. HK, SRS, and DO assisted with writing–original draft. AJ, SKM, and AG contributed to writing–review & editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Study tools.
[DOCX File , 27 KB - resprot_v14i1e39950_app1.docx]

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Abbreviations

ICT: Information and Communication Technology
KAP: Knowledge, Attitudes, and Practices
NCD: noncommunicable diseases
SMAART: Sustainable, Multisector, Accessible, Affordable, Reimbursable, and Tailored framework

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Protocol

Effectiveness of Anti-Gravity Treadmill Exercise After Total Knee Arthroplasty: Protocol for a Randomized Controlled Trial

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Abstract

Background: Postoperative rehabilitation following total knee arthroplasty (TKA) varies worldwide. In Finland, patients receive guidance on safe walking and home exercises from a physiotherapist both before and after TKA. These are performed independently after surgery. However, a sedentary lifestyle is rather common among patients who have undergone TKA, with pain often limiting postoperative walking, training, and activities of daily living.

Objective: This randomized controlled trial aimed to investigate the effectiveness of anti-gravity exercise, precisely the AlterG anti-gravity treadmill, on postoperative rehabilitation following TKA and to obtain new knowledge on this form of rehabilitation to better use it in the future.

Methods: This randomized controlled trial study divided the patients into two groups: the intervention group and the control group. The follow-up period was 12 months. Research data were collected through questionnaires and functional tests. All patients in both groups responded to the questionnaires and participated in functional tests before surgery as well as 4 and 12 months after surgery. Patients in the intervention group exercised on the AlterG treadmill 10 times after the surgery. All the patients in this study performed the exercises as instructed when they were in the hospital. The primary outcomes were perceived pain, walking ability, and quality of life.

Results: The data collection process began in 2018 and concluded in 2022, intending to obtain valuable information regarding the effect of AlterG training after TKA and determine whether it, along with traditional exercises, could be an effective form of rehabilitation that can be performed at home. We hypothesized that AlterG training would lead to faster rehabilitation, better walking quality, improved quality of life, improved physical activity, and improved overall functioning. The results of this study will be analyzed in 2025 and 2026.

Conclusions: This study provides information on how AlterG training can be used in rehabilitation after TKA, further enhancing the rehabilitation program for patients undergoing TKA in general.

Trial Registration: ClinicalTrials.gov NCT03904030; https://clinicaltrials.gov/study/NCT03904030

International Registered Report Identifier (IRRID): DERR1-10.2196/59935

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KEYWORDS

total knee arthroplasty; AlterG; anti-gravity treadmill; postoperative rehabilitation; walking ability; quality of life; pain

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Introduction

Overview

Pre- and postoperative rehabilitation for total knee arthroplasty (TKA) varies worldwide [1-3]. There are guidelines for postoperative physiotherapy after TKA [4], and physiotherapy guidance for self-directed home exercises is recommended [5]. In Finland, the current care guidelines provide guidance for pre- and postoperative rehabilitation [6], but the practices associated with the rehabilitation vary among different hospitals. Previous studies have shown that both inpatient and home-based rehabilitation are effective after TKA [7] and that resistance training in water is a feasible mode of rehabilitation with a wide range of positive effects on patients undergoing TKA [8]. Reportedly, a sedentary lifestyle is rather common among patients who have undergone TKA, with pain or discomfort while standing being the greatest barrier to increasing physical activity [9]. Pain limits postoperative walking training and activities of daily living [10].

Anti-gravity exercises could help address these challenges. They enable a more objective analysis of walking, showing the entire picture of a patient's walking problems. AlterG (AlterG, Inc., Fremont, CA), a patented compressed air technology (NASA differential air pressure technology), can be used to lighten the user's body weight and the load of gravity with 1% accuracy, thereby enabling a less painful walking exercise compared to normal land-based training [11]. While there is limited research on the effects of AlterG training, randomized controlled trials (RCTs) with small sample sizes have been reported, particularly among patients with neurological disorders, such as cerebral palsy [12] and stroke [13,14]. These studies demonstrated that AlterG training positively affected walking speed and dynamic balance and reduced the risk of falls [12-14]. Similar results were reported in studies investigating the effects of AlterG training in rehabilitation after lower limb fractures [15,16]. Precisely, it was found that AlterG training increased muscle strength in the hip area [15] and enabled better walking [16].

A pilot study on AlterG training after TKA revealed that it increased functional ability and is thus overall a safe, useful, and effective rehabilitation method after TKA [17]. Although previous researchers [17] concluded that while functional outcomes improved over time with the use of anti-gravity gait training, further studies with a larger sample size are required to define the role of this device as an alternative or adjunct to established rehabilitation protocols [17]. Furthermore, AlterG training in the acute phase of postoperative knee rehabilitation after knee surgeries, such as TKA and anterior cruciate ligament reconstruction, demonstrated a positive effect on balance in patients experiencing increased pain in weight-bearing postures [18]. AlterG training also decreased pain, enhanced joint function, improved quality of life (QoL), and maintained thigh muscle strength gains in patients with knee osteoarthritis [19]. However, as previously mentioned, not much research has been conducted on postoperative rehabilitation including AlterG training after TKA [17,18], thereby warranting further studies in the future to obtain more knowledge regarding its effects on walking and functional capacity.

Aims and Objectives

The exposures under investigation were the effects of anti-gravity treadmill training in postoperative rehabilitation following TKA and the added value it offered compared to traditional exercise. We hypothesized that AlterG training after hospitalization leads to faster rehabilitation, better walking quality, improved QoL, improved physical activity, and enhanced balance management compared to traditional rehabilitation methods with instructions, where patients perform the exercises independently at home. In addition, we hypothesized that the differences, in terms of the above factors, between the groups in the study—intervention group and control group—were larger in the early phase of the rehabilitation but became smaller over time. The study has been registered on ClinicalTrials.gov (NCT03904030).

This study aimed to determine the effectiveness of the AlterG anti-gravity treadmill in postoperative rehabilitation after TKA. Primary outcomes were perceived pain, walking ability, and QoL. To this end, AlterG rehabilitation and traditional postoperative rehabilitation with instructions were compared.

In detail, we aimed to measure the effects of AlterG training on:

- a patient's walking ability and walking distance after TKA,
- a patient's perceived QoL and functional ability after TKA,
- a patient's perceived pain, and
- lower limb and step symmetry during gait and if it normalizes the patient's stepping and walking.

Methods

Participant Selection and Sampling Strategy

Participants for this RCT study were recruited from two hospitals in the capital region of Finland: Orton Orthopaedic Hospital and Peijas Hospital, both of which are part of the HUS Helsinki University Hospital. Patients with grades 3 and 4 primary knee osteoarthritis and with a scheduled unilateral TKA were included in the study. Those with rheumatoid arthritis, who have undergone hip or knee arthroplasties within the last year, or with a BMI >40 kg/m^2 were excluded. All eligible patients who came for a knee arthroplasty surgery at Orton Orthopaedic Hospital between 2018 and 2021 and at Peijas Hospital between 2020 and 2021 were asked to participate in the study. The patients were recruited through a nurse's preoperative visit or a phone call made to the patients attending the surgery. The nurse then checked whether they met the inclusion and exclusion criteria; those who met the criteria were provided with written information regarding the study. The included patients were asked to provide signed consent forms (Multimedia Appendix 1), which they forwarded to the research assistant. When the patient had consented to participate in the trial, the randomization envelope was opened after the surgery. However, due to the nature of the intervention under study (rehabilitation intervention), it was not possible to blind the patients. The patients were randomly allocated either to the treatment group or the control group using a random number generator (StatTrek) by an expert who did not execute the study in practice. All the patients had free access to the available

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health care services during the study. Overall, 62 patients (31 in each group) were recruited for the study.

Study Procedure

Patients in both groups underwent initial measurements 1-2 weeks before the surgery, which included questionnaires and functional tests performed by a physiotherapist. All the measurements were taken at Orton Orthopaedic Hospital. First, the patients were asked to complete the questionnaires, and functional tests were then performed. The questionnaires used were a visual analogue scale (measures perceived pain) [20], painDETECT [21], Tampa Scale of Kinesiophobia [22], RAND 36-item Health Survey 1.0 (RAND-36) [23], Oxford Knee Score [24,25], Western Ontario and McMaster Universities Osteoarthritis Index [26], Beck Depression Inventory [27], and State-Trait Anxiety Inventory [28] (Table 1). Functional tests performed were knee range of motion (ROM) [29], knee swelling [30], thigh circumference [31], single-leg stance test [32], Timed Up and Go test (TUG) [33,34], stair climbing test [35], and 6-minute walk test (6MWT) [36] (Table 1).

Patients were asked to complete the same questionnaires 6-8 weeks after surgery. The same questionnaires and functional tests were administered in the same order 4 and 12 months after the surgery at Orton Orthopaedic Hospital. This data can help obtain information regarding short-term (4 months) and long-term (12 months) changes. Then, 6 months after the surgery, the patients were sent a 6-month questionnaire regarding possible rehabilitation sessions, use of medication, and possible complications after TKA. The purpose of this questionnaire was to obtain information regarding their use of health care services and how their rehabilitation and recovery from the surgery have progressed.

After the surgery, the researcher informed each patient over the phone or face-to-face about their assigned group, either the intervention or control group. After that, the researcher booked training times on the AlterG for each member of the intervention group. Patients were sent a reminder through an SMS text message on the time reserved for them to ensure that the risk of forgetting was lower. If the time did not suit the patient, the physiotherapist was informed, and a new time was reserved accordingly. The patients in the intervention group exercised 10 times on the AlterG under the supervision of a registered physiotherapist. Both groups performed traditional postoperative exercises after TKA. The follow-up period was 12 months. Exercises began in the third week after surgery. In the third and fourth weeks after TKA, patients in the intervention group exercised twice a week on the AlterG and thrice a week in the fifth and sixth weeks considering individual variations. The AlterG training was recorded 3 out of 10 times—the first, fifth, and 10th training sessions. The recording began after the patient found a suitable walking speed and lightening. On average, the length of one recording was 2 minutes. The data obtained from the AlterG training was saved to a memory stick and then transferred to an electronic folder. The patient schedule of enrollment, interventions, and assessments are shown in Table 2. The study procedure is outlined in Figure 1.

The protocol has been developed using the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist [37] (Multimedia Appendix 2).

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Table 1. Questionnaires and functional tests.

Measurement	Explanation
Questionnaires	
Pain	
Severity of pain: VAS[a] [20]	The scale ranges from 0 to 100, where 0 indicates no pain at all and 100 indicates the worst possible pain.
Neuropathic pain: painDETECT [21]	The screening questionnaire identifies neuropathic components in patients with pain.
Fear of movement: TSK[b] [22]	The screening questionnaire detects fear of movement due to pain.
OKS[c] [24,25]	The 12-item questionnaire assesses knee pain and functionality.
WOMAC[d] [26]	The disease-specific questionnaire explores the effects of osteoarthritis treatment intervention.
Quality of life	
RAND-36[e] [23]	The questionnaire explores well-being and functional ability across eight dimensions: general health perceptions, physical functioning, emotional well-being, social functioning, energy, bodily pain, role functioning/physical, and role functioning/emotional.
Depression and anxiety	
BDI-21[f] [27]	The 21-item questionnaire measures depression.
STAI[g] [28]	The 40-item questionnaire measures trait and state anxiety.
Functional tests	
Knee ROM[h] in degrees (°) [29]	Knee ROM (flexion and extension) is measured using a goniometer.
Knee swelling (cm) [30]	Knee joint swelling is measured using a tape measure at the popliteal.
Thigh circumference (cm) [31]	The thigh circumference is measured using a tape measure 15 cm above the upper edge of the patella.
Single-leg stance (s) [32]	The balance test assesses static balance and upright posture control on a support surface narrower than a normal stance.
TUG[i] (s) [33,34]	The functional test measures an individual's mobility/ability to move.
Stair climbing test (s) [35]	The functional test measures the functionality of the lower extremities and balance control. Here, the test was systematically conducted on the same staircase, which had 11 steps. The depth of one step was 34 cm, and the height was 14.5 cm.
6MWT[j] (m) [36]	The functional test measures an individual's endurance and walking ability.

[a]VAS: visual analogue scale.
[b]TSK: Tampa Scale of Kinesiophobia.
[c]OKS: Oxford Knee Score.
[d]WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.
[e]RAND-36: RAND 36-item Health Survey 1.0.
[f]BDI-21: Beck Depression Inventory.
[g]STAI: State-Trait Anxiety Inventory.
[h]ROM: range of motion.
[i]TUG: Timed Up and Go test.
[j]6MWT: 6-minute walk test.

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Table 2. Patient schedule of enrollment, interventions, and assessments.

	Enrollment	Study period							
		Initial assessment	Allocation	Post-allocation					Closeout
	–2 to –3 weeks	–1 to –2 weeks	0 weeks	3-6 weeks	6-8 weeks	4 months	6 months	12 months	12 months
Enrollment									
Eligibility screen	✓								
Informed consent	✓								
Allocation			✓						
Interventions									
Intervention (AlterG)				✓[a,b]	✓[b]				
Control group (traditional exercises)				✓[b]	✓[b]				
Assessments									
Questionnaires (VAS[c], PainDETECT, TSK[d], RAND-36[e], OKS[f], WOMAC[g], BDI-21[h], and STAI[i])		✓			✓	✓		✓	✓
Functional tests (ROM[j], knee swelling, thigh circumference, single-leg stance, stair climbing test, and 6MWT[k])		✓				✓		✓	✓
6-month questionnaire							✓		

[a]AlterG training (10 times).

[b]Traditional home exercises that the patient was instructed to perform in the hospital after the total knee arthroplasty.

[c]VAS: visual analogue scale.

[d]TSK: Tampa Scale of Kinesiophobia.

[e]RAND-36: RAND 36-item Health Survey 1.0.

[f]OKS: Oxford Knee Score.

[g]WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

[h]BDI-21: Beck Depression Inventory.

[i]STAI: State-Trait Anxiety Inventory.

[j]ROM: range of motion.

[k]6MWT: 6-minute walk test.

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Figure 1. Study procedure.

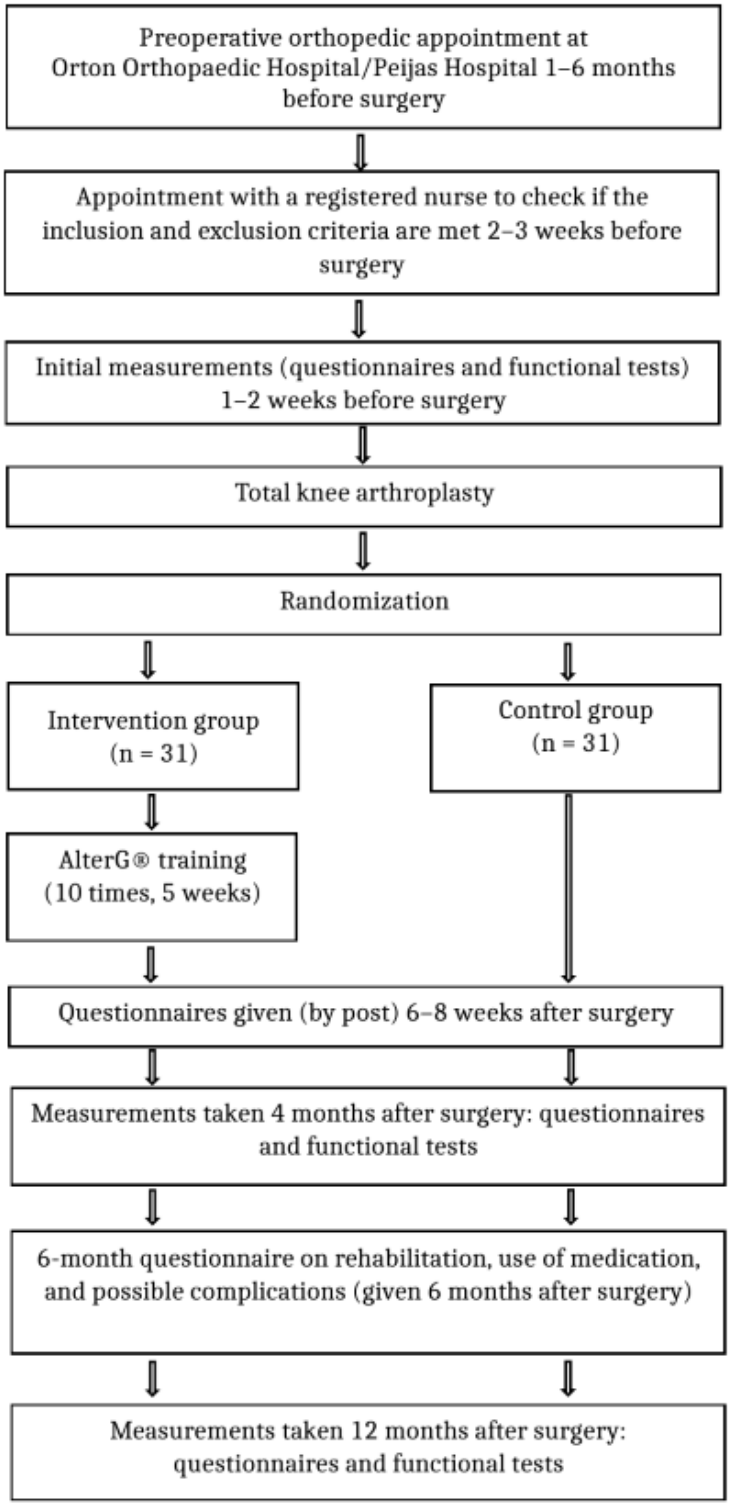

Postoperative Exercises

Furthermore, all the patients (intervention and control groups) in the study independently performed the postoperative exercises instructed by the hospital's physiotherapists. The exercises were aimed to improve knee ROM and quadriceps and hamstring muscle strength and to stimulate venous circulation. Patients also received guidance on walking with crutches. They were instructed to perform home exercises for approximately 2 months after surgery. However, the researchers do not have information on how actively the patients were engaged with home exercises. The home exercises are described in Table 3.

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Table 3. Traditional home exercises.

Exercise	Description	Aim
Knee flexion (sitting/supine position)	Sitting on a chair or in the supine position, the patient flexes the knee as much as possible, sliding the sole of the foot backward on the ground. The patient keeps the knee flexed for a while and then returns the lower limb to the starting position, sliding the sole of the foot forward.	To increase knee mobility in the direction of flexion
Knee flexion (standing position)	In the standing position, the patient brings the operated foot on a stair and shifts the weight forward, stretching the knee in the direction of flexion.	To increase knee mobility in the direction of flexion
Quadriceps strengthening (sitting/supine position)	In the sitting or supine position on a bed, the patient extends the knee and presses it against the platform or a towel roll by activating the quadriceps muscles. When performing this in the supine position, at the end of the movement, the patient can lift the straight leg off the ground. Quadriceps strengthening can also be done by sitting on a chair and lifting the straight leg off the ground.	To activate and strengthen the quadriceps muscles and the end-extension of the knee
Ankle pump movements (flexion and extension)	In the supine position, the patient flexes and extends the ankles in turns.	To stimulate and enhance venous blood circulation
Dynamic calf stretching	In the standing position, the patient performs a dynamic calf stretch, taking a step backward with the operated leg and pressing the heel on the ground while extending the knee and then lifting the heel off the ground and letting the knee flex.	To stretch the calf muscles
Hamstring stretching	In the sitting position and with the operated leg straight on the bed, the patient bends the upper body forward and stretches the hamstring muscles.	To stretch the hamstring muscles
Toe raises	In the standing position, the patient takes support from the back of the chair with their hands and rises to their toes and then returns to the starting position.	To activate the calf muscles
Walking with crutches	The patient is instructed on how to walk with crutches after the surgery, using either three-point walking or alternating walking, or with only one crutch. The patient is also instructed to walk on stairs with a crutch/crutches.	To guide the patient on how to use crutches after the surgery

Outcome Assessment and Measurements

The primary outcomes were walking ability measured with the 6MWT, health-related QoL measured with RAND-36, and perceived pain measured with VAS. All outcomes were measured before the TKA and 4 and 12 months after the TKA. In addition to this, the patients were asked to complete the same questionnaires 6-8 weeks after the TKA. The initial measurements were performed 1-2 weeks before the TKA. Depending on the patient, it took a total of 1.5-2 hours to complete the questionnaires and execute the functional tests. The same measurements were performed 4 and 12 months after the surgery, and the time required for these was the same as in the initial measurements (1.5-2 hours). Regarding the functional tests, the test scores were not calculated within the testing situation; however, the physiotherapist noted the measurement results on the test form, which were then saved in an electronic format. The results obtained from the tests were compared throughout the study between the patient's own results and between the intervention and control groups; no comparisons were made with the general reference values of the tests. The knee ROM and swelling, thigh muscle circumference, TUG, stair climbing test, and 6MWT were performed only once. The tests were performed twice only in the static balance test, and the best test result was recorded (the maximum time was 60 seconds).

All the measures of the study are presented in Table 1. During the AlterG training, the weight-bearing symmetry, step length, stance time symmetry, and cadence during walking were measured (Textbox 1).

Textbox 1. AlterG measurements.

Weight-bearing symmetry

- Weight-bearing symmetry gives information about the symmetry of the stance phase. In pathological situations, the stance phase is shorter on the weaker side [38].

Step length symmetry

- Step length is the distance from the back of one heel to the back of the other heel [38].

Stance phase symmetry

- Stance phase is the period when the foot is on the ground [38].

Cadence (steps/min)

- Cadence is the number of steps taken per minute [38].

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Data Collection and Statistical Analysis

We estimated that a difference of 30 m in the 6MWT between the two groups would represent a clinically relevant difference [39,40]. To identify such a difference with 2-sided testing (α=.05 and power of 85%), the study required 31 participants in each group, with the assumption of 20% loss to follow-up.

The analysis will use the intention-to-treat principle, which will include all randomized patients. Summary statistics will be described using mean and SD, median and IQR, or numbers and percentages. Statistical comparison between the groups will be performed using the *t* test, Mann-Whitney test, χ^2 test, or Fisher-Freeman-Halton test, as appropriate. A linear mixed model or generalized estimating equation model with appropriate distribution and link function for repeated measurements will be used for analysis. In case of a violation of the test assumptions, a bootstrap-type method or Monte Carlo method will be used. Normal distributions will be graphically evaluated using the Shapiro-Wilk W test. Stata 18 (StataCorp LP) will be used for the analysis. Access to data will be granted to the research team of this study.

Ethical Considerations

The study protocol was approved by the ethics committee of the Hospital District of Helsinki and Uusimaa in 2017 (HUS/3117/2017). Helsinki University Hospital, Peijas Hospital, was also included in the study in 2020, and updated ethical permission and research permission were received from HUS (HUS 234/2020). Good research ethics practices were maintained in the study in accordance with the Declaration of Helsinki. Before participating in the study, every patient was given an information letter that would help them decide whether they wanted to participate in the study; once the decision was made, they were asked to sign a written consent form. The patients had the right to discontinue the trial whenever they wanted without giving any reason. However, the data collected before the discontinuation can be used for research purposes (Multimedia Appendix 1).

There was no inclusion of vulnerable groups such as children, prisoners, or individuals with mental disability. No participant reimbursement was provided to prevent economic factors from impacting the recruitment process.

If there were any changes to the protocol, the ethics committee and other relevant parties were informed.

Ensuring Data Quality

Anonymity and confidentiality were ensured by using numerical codes for the participants. Only the research group members had access to the participants' names. Data protection and storage security were ensured by storing the participant information and questionnaires in a locked cabinet at Orton Orthopaedic Hospital. Data were securely stored with electronic passwords on the hospital's server.

Results

The data collection began in 2018 and concluded in 2022. This study aimed to obtain valuable information on the effect of AlterG training after TKA. AlterG, along with traditional exercises, could be an effective form of rehabilitation that can be performed at home. We hypothesized that AlterG training leads to faster rehabilitation, better walking quality, improved QoL, improved physical activity, and improved overall functioning. At baseline, there were 62 participants in the study, with 31 in each group. Of these, 35 (56%) were women, and 27 (44%) were men, with a mean age of 66 (SD 7) years. The results of this study will be analyzed in 2025 and 2026. Results from this study will be submitted for publication in peer-reviewed international scientific journals and presented at scientific meetings.

Discussion

Expected Findings

The expected findings were related to walking ability, health-related QoL, and perceived pain. The expectations were that pain would decrease, walking distance would be longer, and health-related QoL would improve. In addition, we expected that the differences between the groups would be larger in the short term and eventually level out in 12 months.

Comparisons With Prior Work

Studies on postoperative rehabilitation after TKA including AlterG training are scarce [17,18]. To our knowledge, Bugbee et al [17] were the only ones who investigated the effects of AlterG training in patients who underwent TKA in an RCT. Hence, the present study was conducted to further investigate and obtain more information on the effects of AlterG training in patients who underwent TKA.

Limitations and Strengths of the Protocol

One of the limitations of this study was the risk of dropouts when patients heard that they were not included in the intervention group. Second, not all patients were committed to the 12-month follow-up. Third, the implementation of the study coincided with the COVID-19 pandemic, impacting the progress of the study and leading to dropouts.

However, this study also has some strengths. First, this is an RCT study. Second, to the best of our knowledge, there has been only one pilot and feasibility study [17] that directly focused on this issue thus far. With this relatively novel study, it is possible to collect more valuable information on how anti-gravity exercise can be used in rehabilitation after TKA. Third, it investigated aspects of a patient's physical functioning, perceived QoL, and pain rather extensively, thereby providing an opportunity to control various sources of bias such as state of depression and neuropathic pain. Lastly, the study design was planned in a multi-professional manner.

Study Significance and Feasibility

The results of this study provided information on how AlterG can be used in rehabilitation after TKA. With this knowledge, hospitals may potentially develop and enhance the rehabilitation program for patients who undergo knee arthroplasty. It is also possible to use the research results more widely with other patient groups, such as those with lower limb problems and athletes.

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Conclusion

The results of this study provided information on how AlterG training can be used in rehabilitation after TKA. This information may enable the enhancement and development of a rehabilitation program for patients undergoing TKA.

Acknowledgments

We would like to thank physiotherapist Iiris Vanhanen for helping to acquire the data needed for the study. We would also like to thank research assistant Arja Mäkelä and registered nurse Leene Torri, both of whom played a key role in recruiting the patients for this study.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

All authors made substantial contributions to the conception or design of the study; the acquisition, analysis, or interpretation of data for the study; the drafting or critical revision of the manuscript for important intellectual content; final approval of the version to be published; and agreement to be accountable for all aspects of the study in ensuring that questions related to the accuracy or integrity of any part of the study are appropriately investigated and resolved.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Consent form.
[PDF File (Adobe PDF File), 58 KB - resprot_v14i1e59935_app1.pdf]

Multimedia Appendix 2
CONSERVE (CONSORT and SPIRIT Extension for RCTs Revised in Extenuating Circumstances)–SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 119 KB - resprot_v14i1e59935_app2.pdf]

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Abbreviations

QoL: quality of life
RAND-36: RAND 36-item Health Survey 1.0
RCT: randomized controlled trial
ROM: range of motion
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TKA: total knee arthroplasty
TUG: Timed Up and Go test
6MWT: 6-minute walk test

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Protocol

Blended Care Intervention for Cancer Aftercare in General Practice Centers: Protocol for a Randomized Controlled Trial

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Abstract

Background: Combining effective eHealth programs with face-to-face consultations in general practice may help general practitioners care for survivors of cancer.

Objective: This study protocol describes a 2-armed randomized controlled trial to evaluate the cost-effectiveness of a blended intervention integrating the Cancer Aftercare Guide in general practice centers (GPCs).

Methods: A parallel-group design will compare an intervention group with a waiting list control group. Participants will be nested within GPCs and randomization will occur at the GPC level. The participants in the intervention group will receive a blended care intervention. In contrast, the participants in the waiting list control group will receive care as usual for the duration of this study and will receive the online intervention afterward. All participants will be asked to complete an online questionnaire at baseline, 6 months, and 12 months after baseline, measuring self-reported adherence to lifestyle recommendations, psychosocial well-being, and quality of life. A process evaluation and cost evaluation are also included in this study. The effects will be evaluated based on differences in residual change scores between intervention and control group participants, using multilevel linear regression analyses. Moreover, effect analyses will be supplemented with Bayes factor analyses. Finally, an economic evaluation will be conducted from a societal perspective and will include medical costs, productivity costs, and costs of the blended care intervention.

Results: This study was funded in July 2020. Data collection started in August 2022 and is likely to be completed by April 2025. As of December 2024, a total of 127 participants have been included in this study, recruited across 26 GPCs in the Netherlands. Data analysis will commence once data collection is completed. Data analysis is estimated to start in the spring of 2025. The results will likely be published in 2026.

Conclusions: The results will provide insight into the effectiveness of blended care and may be relevant to cancer aftercare, general practice, and the field of eHealth implementation in general. Potential challenges lie in recruitment due to the strain on the health care system since the COVID-19 pandemic.

Trial Registration: ISRCTN ISRCTN12451453; https://www.isrctn.com/ISRCTN12451453

International Registered Report Identifier (IRRID): DERR1-10.2196/64662

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KEYWORDS

cancer aftercare; general practice; blended care; eHealth; randomized controlled trial; cost effectiveness; general practitioners; online intervention

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Introduction

In the coming decades, the growing number of survivors of cancer will challenge health care worldwide. Global data show the increased incidence and survival rates, indicating an increase in the number of survivors of cancer worldwide [1]. Data for the Netherlands (total population of 17 million) predict that in 2032, a total of 1.4 million people will be receiving treatment for cancer or will have been successfully treated for cancer [2]. This underlines the urgency of studying the needs of survivors and finding ways to meet these needs to safeguard the quality of life (QoL) after disease and treatment.

After treatment, survivors of cancer may face physical, psychological, and psychosocial challenges that affect their transition to normal life. In addition, survivors of cancer must adhere to lifestyle recommendations regarding physical activity (PA), diet, smoking cessation, and alcohol consumption to prevent recurrence or the development of comorbidities [3]. In reality, however, many survivors of cancer find it difficult to adhere to these guidelines [4]. They seek support to help them recover and cope with the effects of their disease [5]. However, due to a shortage of health care professionals and increasing demand for care in the general population due to aging, survivors of cancer may not always receive the support they need.

Over the past decades, several eHealth interventions have been introduced to support survivors of cancer in their healthy recovery. The online Cancer Aftercare Guide (CAG) is an example of such an intervention [6,7]. The CAG is a web-based eHealth intervention that targets lifestyle and common psychological and psychosocial problems experienced by survivors by promoting self-management of these problems using evidence-based techniques, such as cognitive behavioral therapy and problem-solving therapy. Effectiveness evaluation has shown that the CAG is effective in reducing fatigue, depression, and anxiety and in increasing PA and healthy eating [8-11]. This shows that the CAG can help survivors cope with common cancer-related problems and can help reduce the risk of future disease by promoting a healthy lifestyle.

The use of eHealth for applications such as disease management and patient data sharing is encouraged [12,13], but in reality, effective eHealth interventions struggle to reach their target population [7,14,15]. For survivors of cancer in particular, it has been found that while they use the internet to search for health information, their use of eHealth self-help programs is not common [16]. One reason for this may be that many eHealth interventions are not implemented in everyday practice [17]. To improve the use of eHealth, the Dutch eHealth Monitor suggests that health care providers play an important role in informing patients about eHealth self-help programs and that health care workflows should be designed to facilitate the use of eHealth through blended care [18]. Similarly, in the case of the CAG, Willems et al [11] and Kanera [6] state that the online intervention could be offered in a blended approach, where patient-therapist interaction is provided, to promote patient engagement with the intervention.

Apart from a biyearly follow-up aimed at detecting recurrence, no structural care is currently provided for survivors of cancer in the Netherlands. For issues related to cancer survivorship, patients are referred to their general practitioner (GP) [19], resulting in on-demand care requests. In addition, GPs are responsible for tertiary prevention, which targets healthy lifestyle behaviors in survivors of cancer. With the increasing number of survivors of cancer, this demand will pose a significant challenge to general practice workflows. Therefore, a structured approach is essential for GPs to meet the needs of their patients. This is illustrated by the Dutch College of General Practitioners (in Dutch: *Nederlands Huisartsen Genootschap*), which stated that general practice could structurally provide cancer aftercare [20]. Implementing the CAG in general practice in a blended care setting could provide a solution to the growing demand for cancer aftercare by promoting healthy recovery and improving self-management of problems, ultimately reducing the care needs of survivors of cancer.

This study protocol outlines a randomized controlled trial (RCT) to investigate the cost-effectiveness and associated process evaluation of a blended care approach offering the CAG in general practice. The blended care intervention has been co-designed with GPs, practice nurses (PNs), and survivors in a separate study (MJM Smits, unpublished data, 2025) and has been tested in a pilot study before starting this RCT.

Methods

Study Design

An RCT will be conducted to compare the effectiveness of the blended CAG intervention between the intervention group and the waiting list control group. A general practice center (GPC) is usually run by at least 1 GP, supported by one or more medical assistants. In addition, many Dutch GPs are supported by PNs who are dedicated to patients with chronic disease, older adult care, and mental health care. The PNs provide additional care for identified health problems, such as asthma, chronic obstructive pulmonary disease, and diabetes (for the somatic nurse) or mental health problems (for the mental health nurse). The intervention protocol is implemented by either the GP or the PN (under the supervision of the GP). A full list of participating GPCs can be requested from the researchers.

Recruitment of GPCs

GPCs will be recruited through a variety of channels, including calls published in online primary care newsletters distributed by Regional Collaborative Care Groups or special interest groups dedicated to oncology care or lifestyle counseling in primary care. In addition, direct mail will also be sent out by the research team. If no response is received within 4 weeks, the direct mailing will be followed by telephone calls to discuss potential participation. GPCs are eligible to participate if they are located in the Netherlands. If the GPC agrees to participate in this study, an appointment will be made for the researcher to visit the GPC to give instructions on this study protocol.

Recruitment of Participants

Overview

Survivors of cancer will be recruited by general practice personnel (GPP: either GP, PN, or assistants). From the GP's

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electronic medical record (in Dutch: *Huisartsen Informatie Systeem*), the GPP will select patients who meet the following inclusion criteria: (1) patients who have completed primary treatment of cancer (eg, radiotherapy, chemotherapy, or surgery), with the last treatment having been between 6 weeks and 3 years ago, or who belong to a watchful waiting condition (eg, option for prostate cancer patients); (2) patients who are 18 years of age or older; (3) patients who are able to read and speak Dutch; (4) patients without a serious medical, psychiatric, or cognitive condition that would interfere with participation; (5) patients who have access to the internet and at least minimal experience of using it; and (6) patients who have access to a computer or a tablet.

If desired, the selection of participants can be assisted by the researcher (under the supervision of the GP).

Eligible patients will be invited to participate in this study using an invitation package distributed by the GPC. The information package consists of an information letter, an informed consent form (Multimedia Appendix 1), and a prepaid return envelope. Survivors of cancer who agree to participate will need to sign the consent form and return it to the research team with the return envelope. The researchers will notify the GPC when the consent form has been received and stored. Enrolled patients will receive a welcome email from the researchers, informing them of their randomization (intervention or control group) and providing a link to the first online self-report questionnaire (baseline measurement). Awareness of randomization can lead to selection bias, but studies on survivors of cancer have shown that this effect is minimal [8-11]. Informing patients about the group to which they are assigned is required in the Netherlands by the Medical Research Involving Subjects Act.

The CAG Intervention

The online CAG program provides personalized information in 8 modules covering healthy lifestyles and common psychosocial issues related to cancer survivorship (ie, PA, diet, smoking cessation, alcohol use, fatigue, anxiety and depression, return to work, and social relationships). The CAG will use data from the baseline assessment to create the Module Referral Advice (MRA; Multimedia Appendix 2). The MRA presents personal outcomes across the 8 subtopics featured in the CAG and advises the participant to visit the module that corresponds to their greatest need, as indicated by the MRA. The modules consist of textual information and advice, video clips (in which former cancer patients share their survivorship experiences), and tasks or exercises that the participants can complete independently.

Intervention Procedure

Participants in the intervention group will receive the CAG blended care intervention. This means that after completing the baseline measurement, they will be given access to the online CAG. Participants will use the online CAG program independently at home. In addition, they will be invited to 2 consultations with their GP or PN. Within the online CAG, the intervention group participants will receive personalized advice on 8 topics related to cancer survivorship based on their results at baseline. This is represented by the MRA. Participants are asked to share their MRA results with the GP or PN at their first consultation. During the first consultation, the GP or PN and the participant will discuss the MRA results. Through shared decision-making, the GP or PN will motivate the participant to choose at least 1 of the 8 subtopics to focus on for the next 4 to 6 weeks, after which the follow-up consultation will take place. During the follow-up consultation, the GP or PN will enquire about the participant's progress with the chosen topic or topics. Any questions or problems the participant may have in interpreting the (lifestyle) advice given by the program will be addressed in the personal consultation. After the follow-up consultation, the participant will retain access to the online CAG intervention for up to 6 months after the start of the baseline measurement.

After completing the baseline measurement, participants in the control group are directed to a message thanking them for completing the questionnaire, asking them to log out and return only for the next measurement. Per GP care, participants in the control group will receive care as usual, which is mostly initiated by patient request and is usually complaint-driven. At the end of this study, the researchers will actively inform and encourage control group participants to finally use the online CAG intervention. Study groups will have full access to other interventions during the trial, but only on their initiative. The use of cointervention will be assessed by questionnaires at all time points.

Measurements

All participants will be asked to complete an online questionnaire at baseline, 6 months, and 12 months after baseline. GPs and PNs will not be present during the self-report questionnaire (participants will complete this assessment digitally at home). Therefore, no influence of the GP or PN on the Patient Reported Outcome Measures is expected. The questionnaires will measure self-reported lifestyle behaviors, behavioral determinants, and experienced psychological problems (see the *Outcomes* section).

The second questionnaire, administered 6 months after baseline, will also include items measuring health-related costs and, for intervention group participants only, a process evaluation questionnaire. In addition, biomedical measurements will be taken from all participants at 6 months after baseline. Blood pressure, total cholesterol/high-density lipoprotein cholesterol, and blood glucose were originally planned for the biomedical measurement. However, due to current circumstances in Dutch primary care (see the *Discussion* section), total cholesterol/high-density lipoprotein cholesterol and blood glucose measurements will be discontinued in consultation with the funding agency.

Nonresponse will be prevented by using previously effective protocols, including automated reminders 1 week and again 3 weeks after the distribution of questionnaires to patients [7,21] and email reminders to GPCs to ensure blood pressure measurement at 6 months. The quality control procedures ensure that there will be little nonresponse [8-11]. To improve the engagement of GPCs, relationships will be maintained through regular emails or phone calls to the designated contact person. In addition, a Christmas card will be sent each year on behalf

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of the research team. In addition, the GPCs will be offered support in patient selection and patient contact by a researcher on several occasions during this study.

Outcomes

Overview

The primary outcomes of this study are changes in lifestyle behaviors, measured by validated self-report questionnaires. PA will be assessed using the self-report Short Questionnaire to Assess Health [22,23]. Smoking behavior will be assessed using a validated (self-report) abstinence scale [24,25]. Alcohol consumption will be measured using a standardized alcohol consumption scale [26]. Dietary behavior will be assessed using a food frequency questionnaire on saturated fat intake and fruit and vegetable consumption [27-29].

Secondary outcomes are changes in experienced psychosocial problems such as anxiety and depression, fatigue, health-related QoL, and health-related costs, which will be assessed using validated self-report questionnaires. Anxiety and depression will be assessed using the Hospital Anxiety and Depression Scale [30,31]. Fatigue is assessed using the Checklist Individual Strength [32,33]. Health-related QoL is measured using the abbreviated European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire [34,35]. Health-related costs are considered from a societal perspective and are measured as health care consumption in the last 3 months using the Institute for Medical Technology Assessment Medical Consumption Questionnaire, productivity losses in the last 4 weeks for both paid and unpaid labor using the Institute for Medical Technology Assessment Productivity Cost Questionnaire, and quality-adjusted life years (QALY) using the EQ-5D-5L [25,36-42]. All questionnaires used are validated, we do not conduct additional validation research as part of this research project.

Secondary outcomes are also blood pressure measurements, taken from all participants at 6 months postbaseline. Blood pressure will be assessed by clinical measurements performed by GPP.

In addition to outcome measures, relevant medical data (type of cancer, time since diagnosis, type of treatment, and recurrence) and social demographics (age, sex, level of education, income, living situation, comorbidities, and BMI), as well as intention toward PA, healthy diet, reduced alcohol consumption, and smoking cessation will be assessed at baseline. Items assessing recurrence, use of cointerventions, BMI, and lifestyle behavioral intentions will be repeated at the 6-month measurement and 12-month assessments.

In addition, the process evaluation will be measured by (1) dose delivered: the number of intended modules accessed; (2) dose received: the extent to which participants actively engage with the material in the module; (3) satisfaction with the program; (4) practice-patient interaction: perceptions of the level of collaboration, satisfaction, and active engagement with the blended care program; and (5) context: aspects of the environment that influenced program implementation, impact, or outcomes. In addition to self-report measurements, log data from the online CAG (use of the website and individual CAG modules) will be automatically collected throughout the intervention.

Process evaluation will also take place with GPs and PNs. During the interview session at the end of the trial, they will be asked to report on (1) their satisfaction with the blended care program; (2) the type of patients involved; (3) the number of consultations carried out by the GP or PN; (4) the practice-patient interaction: perceptions of the level of cooperation, satisfaction, and active engagement with the program; and (5) the context: aspects of the environment that influenced the implementation/impact or outcomes of the program.

Sample Size

The effect evaluation of the online CAG intervention showed small to medium effect sizes (ES=0.20-0.40) on lifestyle behaviors at 6 months. In the current design, we expect an ES of 0.40 at 6 months follow-up [8]. Based on previous research on computer-tailored lifestyle interventions, we estimate an ES of 0.30 at 12 months [8,43-48]. Based on CAG data and other research in the primary care setting [49], we estimate an intracluster correlation of 0.03 to account for the multilevel design. Sample size calculation (ES=0.30; power=0.80; intracluster correlation=0.03, design effect 1.27) indicates that 282 participants are required for the effect study (141 in each condition). From 2 previous RCTs of online lifestyle interventions in patients or survivors of cancer, we know that dropout is 20%-25% [8,48]. Accounting for a 25% dropout, 376 survivors of cancer need to start in the RCT (188 per condition).

Furthermore, based on cancer prevalence figures, cancer survival rates, and the number of GPCs in the Netherlands, we expect that a standard GPC (consisting of 1-4 GPs and additional PNs) will have at least 20-40 survivors of cancer who meet the inclusion criteria. Therefore, to achieve a sufficient sample size, we aim to recruit approximately 40 GPCs, each of which will recruit 10 participants.

Randomization

A cluster-randomized design is used, which means that randomization to either the intervention or control condition takes place at the GPC level, and that all participants in a GPC are assigned to the same condition. Neither GPCs nor participants are blinded to their assigned condition during the trial. However, during recruitment, both GPCs and the researcher are unaware of the randomization outcome to ensure that participation is not influenced by assigned conditions. The randomization outcome will be defined by a computer-generated randomization list using simple randomization (1:1), which was generated before the start of recruitment and stored with a third person.

Statistical Methods

Overview

The first 2 steps of the analysis will test for statistical differences at baseline in lifestyle behaviors, QoL, demographics, and psychosocial and medical symptoms between the 2 study groups. Blinding of the analyst will be applied for primary outcomes.

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Patterns and mechanisms of missing data will be explored. Thereby, special attention will be paid to dropouts. Randomization of the GPCs should account for an even distribution between the experimental and control conditions of socioeconomic factors or other confounding factors that may skew our results. However, in case conditions are unbalanced, these factors will be adjusted for in the analysis. If necessary, other statistical adjustment procedures will be applied to minimize the impact of any bias.

Multilevel linear regression analyses will be conducted to test for differences in residual change scores between the intervention and control groups on the primary and secondary outcomes at the 6-month follow-up and the 6- and 12-month follow-up combined. Intention-to-treat (ITT) analyses with multiple imputations will be applied. Participants will be nested within GPCs to account for potential interdependence between participants. Multilevel linear regression analyses with a random intercept for GPC level will be performed to account for possible interdependence in the effect analyses. The effects on the population will be assessed via CIs.

The primary outcome measures will be the residual change scores in lifestyle behaviors, but also differences in the secondary outcomes (anxiety and depression, fatigue, [health-related] QoL, and health-related costs). Blood pressure at 6 months will be compared between the intervention and control groups. In addition, moderation analyses will be conducted to examine different potential moderators such as age, gender, type of treatment, and level of education [8-11]. Subanalyses may be performed to explore individual differences that may be attributed to the degree of participation in the intervention. Besides factors on the level of participants, factors on the level of GPCs will be considered for further analysis. Finally, process evaluation data will be analyzed and summarized descriptively.

In addition, Bayes factor analyses will complement the primary analysis of the effects of the blended CAG intervention on the primary and secondary outcomes. A Bayes factor analysis expresses the relative strength of the evidence supporting competing hypotheses. This study examines support for the hypothesis that the blended CAG intervention has greater effects than care as usual as opposed to support for the hypothesis that the conditions do not differ or that the blended CAG intervention has a smaller effect than care as usual. In addition, the strength of support for the hypothesis that the blended CAG intervention has no smaller effects than care as usual will be compared to the support for the hypothesis that the blended CAG intervention has smaller effects than the effects found in the online-only CAG intervention, as studied in previous research [8-11]. In principle, default prior distributions will be used. It will be verified that these prior distributions are sufficiently diffuse, do not overwhelm the data, and do not destabilize the analysis.

Economic Evaluation

To calculate QALYs, utility scores will be obtained from the EQ-5D-5L scores and multiplied by the duration of follow-up (12 months). The economic evaluation will be conducted from a societal perspective and will therefore include medical costs (as measured by the Institute for Medical Technology Assessment Medical Consumption Questionnaire at T1), productivity costs (as measured by the Institute for Medical Technology Assessment Productivity Cost Questionnaire at T1), and costs of the blended care intervention. Intervention program costs include GP and PN training time, time for 2 consultations in the GPC, costs for program updates, and user licenses divided by a conservative number of potential annual users. Costs for the development of the intervention as well as research-specific costs were excluded.

Incremental cost-effectiveness ratios and incremental cost-utility ratios will be calculated by comparing the costs and effects (probability of maintaining a healthy lifestyle and QALYs) of the usual care group with those of the intervention group. Statistical differences in nonnormally distributed costs and QALYs will be tested using bootstrapped 1-tailed *t* tests. A cost-effectiveness acceptability curve will be constructed with the bootstrapped incremental cost-effectiveness ratio to visualize the probability that the blended care intervention is cost-effective at specific willingness-to-pay thresholds. The ceiling ratio for the cost-utility of the interventions will be set at €20,000 (US $20,900.80) per QALY. This is an accepted Dutch cutoff point for the willingness to pay for each QALY gained by preventive interventions and is commonly used to evaluate this type of intervention in the Netherlands [46,50-52].

Data Management

Data will be collected and handled according to the Data Management Plan that has been drafted for this project on the Data Management Plan online portal [53] and approved by ZonMw (ie, the grant provider). The progress of this study will be described in an annual report to the Medical Research Ethics Committee of Zuyderland Hospital and Zuyd University of Applied Sciences (in Dutch: *medisch-ethische toetsingscommissie van Zuyderland en Zuyd Hogeschool* [METC Z]) and the grant provider. Data will be password-protected and stored on hard disks on systems equipped with power-failure backup devices and automatic backup systems. All data will be kept confidential and anonymous. Each participant will be given a unique respondent number, not linked to a name or personal details, under which the data will be stored. Only researchers working on this project will have access to the data.

Potential Benefits and Risks

There are no risks or adverse effects associated with the trial. The participants in the intervention group can decide for themselves if, when, and how often they use the intervention. In addition, all the participants (intervention and control) can withdraw from this study at any time. It is expected that the use of the intervention will contribute to a healthier lifestyle, improve self-management, and have a positive impact on participants' QoL. During this study, the control group will only participate in the online self-report questionnaires and blood pressure measurements at the GPC. They will not be denied medical care and will be able to seek additional professional support if they wish to do so. Insurance was not compulsory for this trial, as assessed by the medical ethics committee.

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Ethical Considerations

This study was approved by the METC Z before patient enrollment (NL806166.096.21, version 4.0; April 25, 2023). Informed consent (Multimedia Appendix 1) will be obtained from all the participants or legal guardians for this study. All patients will be required to provide written informed consent to participate. Participation can be discontinued at the request of the participants. Participants will receive a €10,- (10,31 USD) book voucher after completing the study. Modifications to this study protocol will be communicated to the METC Z through amendments. The METC Z has revised the informed consent materials to be given to participants and adapted them to accord with the Medical Research Involving Subjects Act. The protocol was amended to version 6.0 as of April 2023. This study conforms to the Declaration of Helsinki and is registered with the ISRCTN (International Standard Randomised Controlled Trial Number; ISRCTN12451453; registration date: December 15, 2021; last edited: September 12, 2023). All data will be kept confidential and anonymous.

Results

This study was funded in July 2020. Data collection started in August 2022 and is likely to be completed by April 2025. As of December 2024, this study is still ongoing. Data analysis is estimated to start in the spring of 2025. A total of 127 participants have been recruited across 26 GPCs in the Netherlands. The first results are expected to be published in 2026.

Discussion

Overview

This study protocol describes an RCT to evaluate the effects on self-reported lifestyle behavior, psychosocial well-being, (health-related) QoL, medical consumption, and productivity costs of the blended CAG intervention integrated into general practice.

Principal Findings

Overview

Previous research has investigated the effectiveness of the CAG in an online-only format [8-11]. This research found effects on PA, diet, fatigue, depression, and QoL, suggesting that the CAG is an appropriate eHealth intervention to support cancer survivorship. If similar results are found in this study, this would confirm that the online-only intervention has been appropriately adapted to the blended care context, maintaining its effectiveness. It would also suggest that the CAG could be integrated into the GPC workflow to facilitate the integration of cancer aftercare into general practice, as was proposed by the Dutch College of General Practitioners [20].

Comparison to Prior Work

Delivering the CAG in a blended care format improves the personalization of the care provided. This may strengthen the intervention and allow it to be better tailored to the individual recipient. Moreover, the integration of eHealth in general practice to facilitate cancer aftercare may address barriers to the uptake of cancer aftercare by general practice, as previously identified by Duineveld et al [54]. These barriers consisted of time constraints and a lack of expertise in cancer survivorship. Both of these can be complemented by effective eHealth tools such as the CAG.

Strengths and Limitations

Overview

This paper describes the study protocol for an RCT of the effectiveness of a blended care intervention for cancer aftercare in general practice. Conducting an RCT strengthens our interpretation of the results by controlling for confounding through randomization. In addition, the current research is very similar to the previous research evaluating the effectiveness of the online-only CAG intervention, which allows the results to be compared and the added value of blended care to be identified. The blended care format is being added to increase the reach of our intervention, specifically targeting a population that would not access an online-only intervention on their own. The blended care protocol has been developed in cocreation with survivors, GPs, and PNs to ensure the best fit with the general practice context and the needs of survivors (MJM Smits, unpublished data, 2025). However, some challenges cannot be foreseen. Conducting the RCT in a period following the global COVID-19 pandemic may place limitations on our study protocol. For example, it may be difficult to achieve our target sample size due to recruitment problems with both GPCs and survivors of cancer. In the aftermath of COVID-19, the health care sector is facing a workforce shortage, partly due to the retirement of a large proportion of the working population [55,56]. In primary care, this is leading to the closure of GPCs as owners are not being replaced by a new generation. Meanwhile, the COVID-19 pandemic has resulted in a high rate of delayed care, further increasing the demand for GPCs and leaving little room for trial participation and research activities such as patient recruitment. This resulted in a difference in the number of GPCs recruited compared to our target. We aimed to recruit 40 GPCs, but in reality, only 26 GPCs were recruited.

Future Directions

Future research could further investigate the implementation of eHealth for survivors of cancer in general practice or, depending on the results of this study, in different practice contexts. Emphasis should be placed on reaching survivors who are at risk of developing comorbidities or recurrence, or who have a high burden of disease that translates into medical costs or loss of productivity.

Dissemination of Research Findings

Research findings will be discussed with the consortium partners and published in academic journals. This study is the next step in disseminating the CAG in a practical context. However, to translate our findings to the real world, further research should be conducted to investigate how the intervention is sustained outside of the research protocol. Depending on our findings, the RCT will be followed by an implementation study in which survivors, GPs, and other stakeholders will be invited to share

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their views on the integration of blended CAG into regular cancer care.

Implications and Relevance

The number of survivors of cancer is expected to increase in the coming decades [2]. These survivors consult their GP with issues related to cancer survivorship, resulting in a high demand for general practice [19]. To support survivors of cancer in maintaining a healthy lifestyle and managing psychosocial needs, the online CAG program was developed [57]. The program was shown to be effective in promoting healthy lifestyle behaviors and reducing fatigue, depression, and anxiety [8-11]. Structurally embedding the CAG in general practice could support GPs and PNs in caring for their patients and help reach more survivors who need support after treatment. The expected ESs are small but arguably clinically relevant given the affordability, minimal associated risks, and widespread implementability of the blended CAG intervention [58,59]. The results of this study may have implications for cancer aftercare and general practice, and may also be relevant to the wider field of eHealth implementation.

Conclusion

The research described in this study protocol will investigate the effectiveness (and cost-effectiveness) of a blended care intervention for survivors of cancer in general practice. The blended care intervention combines the use of a proven effective eHealth program (CAG) with face-to-face consultations with a GP or PN. Integrating eHealth for cancer aftercare into general practice may help GPs and PNs in caring for the growing number of survivors of cancer and may effectively improve their QoL, leading to reduced care needs in the future. The results of this study may be relevant to the field of cancer aftercare and general practice and will add to the literature on eHealth implementation.

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Data Availability

The datasets will be available from the corresponding author upon reasonable request.

Authors' Contributions

LL is the principal investigator, CAWB and IM are coapplicators, and MJMS is the PhD candidate on this research project. LL, CAWB, and IM contributed to the conceptualization, funding acquisition, and supervision. MJMS was responsible for the project administration and writing of the original draft of this paper. All authors contributed equally to the investigation, methodology, validation, and writing (review and editing) of this paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Informed consent form.
[DOCX File , 16 KB - resprot_v14i1e64662_app1.docx]

Multimedia Appendix 2
Example of the Module Referral Advice (MRA).
[PDF File (Adobe PDF File), 322 KB - resprot_v14i1e64662_app2.pdf]

Multimedia Appendix 3
SPIRIT checklist. SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials.
[PDF File (Adobe PDF File), 138 KB - resprot_v14i1e64662_app3.pdf]

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Abbreviations

CAG: Cancer Aftercare Guide
ES: effect size
GP: general practitioner
GPC: general practice center
GPP: general practice personnel
ISRCTN: International Standard Randomised Controlled Trial Number
ITT: intention-to-treat
METC Z: Medical Research Ethics Committee of Zuyderland hospital and Zuyd University of Applied Sciences (medisch-ethische toetsingscommissie van Zuyderland en Zuyd Hogeschool)
MRA: Module Referral Advice

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PA: physical activity
PN: practice nurse
QALY: quality-adjusted life year
QoL: quality of life
RCT: randomized controlled trial

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Protocol

Improving the Health and Well-Being of Individuals by Addressing Social, Economic, and Health Inequities (Healthy Eating Active Living): Protocol for a Cohort Study

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Abstract

Background: Health inequity is interlinked with the good health and well-being of an individual. Health inequity can be due to various socioeconomic factors like income levels or social status. Digital health interventions have the potential to reduce the existing health inequities.

Objective: This study aims to identify determinants of social, economic, and health inequity in diverse settings to enhance healthy eating and active living. It further aims to design and develop a digital health intervention HEAL (Healthy Eating Active Living) that incorporates a human-centered design framework in order to improve healthy eating and active living among rural and urban population groups in Chennai, Tamil Nadu, India.

Methods: A prospective, 3-year cohort study will be conducted. This study aims to recruit 6350 individuals across rural and urban settings of Chennai. A total of 11 sites have been selected for participation in the study. Data on sociodemographic characteristics; economic inequity; HEAL profile; depression, anxiety, and stress; well-being; sources of health information; perceived access to health care; health literacy; navigation of health literacy; and satisfaction with the health system will be gathered. This study would help to explore the determinants of social, economic, and health inequity across multiple sites. SAS (version 9.3; SAS Institute Inc) will be used for data analysis, and results will be reported as 95% CI and *P* values. This study's findings will guide the design and development of a tailored, human-centered digital health intervention to enhance the health and well-being of Chennai's population groups.

Results: As of December 2024, the literature review for the development of the intervention has been completed. The recruitment for the baseline data collection will begin shortly, followed by the development of HEAL intervention.

Conclusions: The proposed study will help in examining the role of the proposed HEAL intervention to enhance the health and well-being of the population groups of Chennai.

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KEYWORDS

health inequity; health; well-being; digital interventions; social health; lifestyle

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Introduction

Background and Rationale

The World Health Organization (WHO) identifies health inequities as "systematic differences in the health status of different population groups" [1]. Further, the WHO refers to health as "a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity" [2]. Consequently, research on health inequity is a central agenda component of the 2030 Sustainable Development Goals and various government and development dialogues [3,4]. Despite this, the WHO reports that health inequalities exist at varying degrees around the world, both within and between countries [5]. These inequalities further exacerbate health disparities between high-income and low-income, urban and rural, employed and unemployed populations, as well as between low-, middle-, and high-income countries [6] due to socioeconomic factors such as social status or income levels [7].

According to the Centers for Disease Control and Prevention, health equity can be attained when every individual can "attain his or her full health potential" and no one is "disadvantaged from achieving this potential because of social position or other socially determined circumstances" [8]. This also emphasizes the significance of measuring health inequity, promoting opportunities and monitoring the progress in health and intersectoral strategies. Additionally, measuring the interrelationship between health and its social determinants is vital to promoting effective interventions for health equity [9].

Inequalities are unfair, affect everyone, and are avoidable; however, the underlying factors causing inequality are imperfectly understood, and evidence on the effectiveness of interventions to reduce inequalities is limited [10]. Prior research has further highlighted the issue of good health for socioeconomically vulnerable groups and the need for targeted public health interventions in India [11]. A study indicated that health inequity in India is favored toward high-income populations and that despite services being available to people, there was a lack of awareness around it, especially in the rural region [12]. Considering the diversity in India and the prevalent social inequalities, the literature also emphasizes on the importance of research on health inequalities for monitoring health policies and programs [11].

Equity was also identified as one of the key principles of India's 2017 National Health Policy [13]. However, with a limited evidence base of health equity in India, there is a need to generate empirical data for the variables that create, sustain, and reinforce inequity. This would further help the policy makers to prioritize and strategize the limited resources available for the health system of the country [14].

However, the paucity of data on health inequalities in India and the subsequent research gap on critical issues related to health inequity in the country also underscore the probable impact of policies and strategies deployed to enhance the well-being of population groups. Moreover, the COVID-19 pandemic has exacerbated the health inequity worldwide [15]. In addition, eating habits are possibly determined by the socioeconomic status of the individuals [16]. Thus, this study aims to enrich the current understanding of health inequity with empirical research. The findings will also help with the design and development of digital health intervention HEAL (Healthy Eating Active Living) to improve the good health and well-being of individuals by addressing social, economic, and health inequities. Tamil Nadu, India, was the chosen region of study as it seems to be a state that has progressed in health care in recent years, and hence, this study aims to see the receptivity to digital intervention of the study population in these settings [12].

Study Objectives

This study aims (1) to identify determinants of social, economic, and health inequity to enhance healthy eating and active living among rural and urban population groups of Chennai, Tamil Nadu; (2) to design and develop a digital health intervention HEAL using the SMAART (Sustainable, Multi-Sector, Accessible, Affordable, Reimbursable, Tailored) model, targeted to enhance healthy eating and active living among rural and urban population groups of Chennai, Tamil Nadu; and (3) to evaluate impact of the proposed intervention to address burden of social, economic, and health inequity to enhance healthy eating and active living among rural and urban population groups of Chennai, Tamil Nadu.

Methods

Study Overview

The proposed research involves a multidisciplinary team with expertise in population health, epidemiology, sociobehavioral sciences, anthropology, and biochemical sciences.

Study Design and Population

The HEAL cohort study is a prospective, 3-year cohort study with the aim to recruit 6350 individuals across rural and urban settings of Chennai, Tamil Nadu. The study sample will be recruited from Kannur; Pannur; Thirumenikuppam; Thodukadu; Kottaiyur; Nemili; Mannur; Kiloy; Ulundai; Narasamangalam; Karanai; Panimalar Medical College Hospital and Research Institute; Rural Training Health Centre Chennai; and Maligaipaddu village of Chennai, Tamil Nadu. Baseline evaluation will be performed at the time of recruitment of study participants. The study participants will be recruited through convenience sampling. This will serve as cross-sectional data to estimate the prevalence of determinants of social, economic, and health inequity.

Study Intervention

The HEAL intervention will be designed based on the SMAART model to enhance healthy eating and active living for the individuals participating in the study. This intervention will ensure the coordination of social, economic, and health-related parameters to enhance the health and well-being status of the population. The SMAART model works on the principles of data, information, and knowledge; human-centered approach; information processing theory; and humanistic, behavioral, and learning theories [17]. The intervention stage will have two

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parallel groups (case and control) for comparison. Individuals in the intervention group will be provided access to the informatics-based intervention for enhancing their healthy eating and active living. The participants from the intervention stage will be included in the study based on participants from the baseline stage consenting to participate in the intervention. The participants will be assigned to the intervention or control group through randomization. They would be provided information on good dietary habits and the importance of regular physical exercise for maintaining good health and well-being. Individuals in the control group will be provided an educational booklet as standard care. The intervention will be a tailored multilingual digital health intervention. Both the groups will undergo a series of baseline and follow-up assessments for estimation of change in eating patterns, physical activity, and well-being to assess the impact of intervention. The study location includes both the urban and rural areas of selected sites, and the study duration is 3 years. The study population includes all adults aged 18 years and older. The inclusion criteria are (1) individuals aged 18 years and older, (2) individuals from both urban and rural areas, and (3) individuals who consent to participate in the study.

Efforts will be made to include individuals of varied age groups, gender, location, and socioeconomic status. The exclusion criteria consist of (1) individuals younger than 18 years of age, (2) individuals who would not give their consent, and (3) individuals who have impaired cognition.

Ethical Considerations

This study (protocol PMCHRI-IHEC-067) gained approval from the Panimalar Medical College Hospital and Research Institute Institutional Human Ethics Committee (Central Drugs Standard Control Organization Registration ECR/1399/Inst/TN/2020) in March 2022, with approval PMCH&RI/IHEC/2021/078 dated March 15, 2022. The study will be conducted according to the Declaration of Helsinki, as it involves human participants [18].

The institutional review board–approved informed consent form will be administered by the research team to the eligible individuals for the study. The research team will describe the study, time required, and benefits of the study results to the participants, and those willing to participate and give their consent will be enrolled in the study. Written informed consent will be obtained in both English and local Indian dialects at the time of data collection if the participants are able to read and understand the questionnaire. In the case of participants without formal education, an audio recording of the consent will be done. Study participants will be allowed to withdraw from the study at any time [19]. No compensation will be provided.

Data security will be ensured through regular backups in password-protected computers in the locked office of the principal investigator. Data will be stored for 5 years from the point of study completion, after which it will be destroyed. All the physical data files will be stored in a locked file cabinet in the office. The information will be accessible to members of the research team only.

Data Collection, Data Entry, and Quality Assurance

Data collection and data entry will be performed by a team of trained field data collectors and data management. Data will be gathered in the field on paper and then entered on the computer. The data will be entered into the computer using Excel (Microsoft Corp). For quality assurance, a clearly defined data collection and management protocol will be in place. This will include a well-defined study manual with all the relevant instructions. For quality assurance, we will have a trained team of data collectors, weekly meetings with the research team, weekly data checks, maintenance of study participant contact, and maintenance of study participant data instrument logs.

Variable Assessment

Sociodemographic Characteristics

Information will be collected on the participant's age, gender, educational status, migration status, disability status, occupation, household size, family size, income, and number of earning members in the household.

Economic Inequity

The wealth index is a division of households into 5 wealth quintiles to show the relationship between wealth, population, and health indicators [20].

HEAL Profile

Data will be collected on the respondent's health and lifestyle profile. We will use the WHO STEPwise approach to noncommunicable diseases risk factor surveillance questionnaire. It is a simple, standardized method for collecting, analyzing, and disseminating data on key noncommunicable disease risk factors in countries. The survey instrument covers key behavioral risk factors: tobacco use, alcohol use, physical inactivity, and unhealthy diet, as well as key biological risk factors: overweight and obesity, raised blood pressure, raised blood glucose, etc [21].

Depression, Anxiety, and Stress

Data will be gathered from the respondents about their mental and well-being. We will use the Depression, Anxiety, and Stress Scale (DASS). The DASS is a set of three self-report scales designed to measure the negative emotional states of depression, anxiety, and stress. Each of the three DASS scales contains 14 items, divided into subscales of 2-5 items with similar content [22].

Well-Being

The Short Warwick Edinburgh Mental Well-Being Scale is a shortened version of the Warwick-Edinburgh Mental Well-Being Scale. It measures both mental and emotional well-being (how "good" somebody feels) and psychological functioning (how well somebody thinks they are functioning). This scale is suitable for ages 13-74 years and works well as a "before" and "after" tool to measure the change in well-being during an intervention or specific program [23].

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Sources of Health Information, Social Media, Technology Access, and Familiarity

Information will be gathered about cell phone ownership in households, type of cell phone, access to the internet, and knowledge of SMS text messaging [24,25].

Perceived Access to Health Care

Information will be collected from the respondents regarding access to health care. We will use the Perceived Access to Health Care questionnaire. The questionnaire includes six dimensions: (1) availability, (2) accessibility, (3) affordability, (4) accommodation, (5) acceptability, and (6) awareness. In addition, the psychometric evaluation was conducted on the instrument's initial version with 31 items on a 5-point Likert scale (strongly agree to strongly disagree) [26].

Health Literacy

Rapid Estimate of Adult Literacy in Medicine will be used to assess the health literacy of the study participants. It is a quick screening tool to assist physicians in identifying patients with limited reading skills and in estimating patient reading levels. "At risk patients" are defined as those with a score of six or less [27].

Satisfaction With Health System

The Patient Satisfaction Questionnaire yields separate scores for each of seven different subscales: general satisfaction (2 items), technical quality (4 items), interpersonal manner (2 items), communication (2 items), financial aspects (2 items), time spent with the doctor (2 items), and accessibility and convenience (4 items). This questionnaire will be used both at baseline and postintervention [28,29].

Outcomes

The study outcomes include the identification of determinants of social, economic, and health inequity. The research would further help in identifying the key areas that need to be addressed through intervention to improve the health and well-being status of the general population. Additionally, the study would also help in developing tailored interventions targeted to reduce social, economic, and health inequities.

Data Analysis

Descriptive analysis will be conducted to report the mean and SD of the continuous variables and frequency analysis of the categorical variables. A 1-tailed *t* test will be performed to compare means between the continuous variables and a categorical dependent variable while a chi-square analysis will be performed for the categorical variables. Multivariate regression analysis will be performed to determine the determinants of social, economic, and health inequity. All analysis will be performed using SAS (version 9.1; SAS Institute Inc), and reporting of the results will be done at 95% CI and $P<.05$.

Projected Timelines and Milestones

A detailed research plan and scheduled timeline of the tasks involved in the study are presented in Table 1.

Table 1. Scheduled timeline of the tasks in the HEAL[a] study.

Variables	Month 1	Months 2-5	Months 6-7	Months 8-10	Months 11-18	Months 14-30	Months 31-33	Months 34-36
Stakeholder meeting	✓							
Baseline data collection		✓						
Design and development of human-centered intervention			✓					
Heuristic evaluation			✓					
Usability of the proposed system				✓				
Refine the proposed SMAART[b] informatics self-management intervention				✓				
Final deployment of the proposed SMAART informatics self-management intervention tool				✓				
Study recruitment (baseline data)					✓			
Follow-up data collection					✓	✓		
Statistical analysis					✓	✓	✓	
Report writing and paper preparation							✓	✓

[a]HEAL: Healthy Eating Active Living.

[b]SMAART: Sustainable, Multi-Sector, Accessible, Affordable, Reimbursable, Tailored.

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The study is in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guideline for case-control studies (Multimedia Appendix 1) [30].

Results

As of December 2024, the literature review for the development of the intervention has been completed. Recruitment for the baseline data collection is scheduled to begin in the upcoming months, followed by the development of HEAL intervention.

The findings of the study will be disseminated through peer-reviewed publications and national and international conference presentations.

Discussion

Expected Findings

In order to reduce the health inequity in India, it is imperative to have the requisite knowledge base. This study would help to fill the research and knowledge gap by identifying key areas that need to be addressed to improve the health status of the population. The baseline data will enable us to find the socioeconomic inequity faced by the participants, their health literacy, and their awareness regarding their health status and health care. These findings would also help to design and develop tailored population health interventions to enhance the healthy eating and active living of the population groups.

Health inequities have existed throughout time, as resonated by the concept of inverse care law (1971), which highlighted how good medical care is inversely related to people's needs in low- and middle-income countries [31]. Similarly, Cookson et al [32] recently proposed the law of disproportionate care (2021) where they argue that in high-income countries, socially disadvantaged groups receive more care but of worse quality to meet their health care needs. The available studies also reinstate the need to address health inequities by collecting and analyzing the relevant health equity data [33]. This study would therefore help in filling the requisite knowledge gaps by identifying the key determinants of health inequity. It would also help in contributing to the advancement of evidence-based strategic decisions on health inequity. The findings from this research project would also help in designing, developing, and implementing data-driven, evidence-based, and human-centered interventions to enhance the healthy eating and active living of the population groups.

Limitations

This study's limitations include that it is confined to one geographic region, and implementing it in diverse geographic and population settings would help to better understand and compare the impact of the HEAL intervention.

Conclusions

The HEAL intervention offers a model to enhance healthy eating and active living for the individuals participating in the study through the SMAART framework. The findings from the study will contribute to the understanding of the role of digital health interventions to enhance healthy eating and active living of the population groups, which will help in understanding and addressing determinants of health equity in the population.

Acknowledgments

The authors are the only contributors to this manuscript and are acknowledged.

Data Availability

The datasets generated during or analyzed during this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

All authors have contributed to the design of the study, development of the questionnaire, and preparation of the manuscript, and have approved the manuscript for publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1
STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist.
[DOCX File , 19 KB - resprot_v14i1e41169_app1.docx]

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Abbreviations

DASS: Depression Anxiety, and Stress Scale
HEAL: Healthy Eating Active Living
SMAART: Sustainable, Multi-Sector, Accessible, Affordable, Reimbursable, Tailored
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
WHO: World Health Organization

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Protocol

Future Patient—Telerehabilitation of Patients With Atrial Fibrillation: Protocol for a Multicenter, Mixed Methods, Randomized Controlled Trial

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Abstract

Background: Atrial fibrillation (AF) is a chronic cardiovascular condition with a lifetime risk of 1 in 3 and a prevalence of 3% among adults. AF's prevalence is predicted to more than double during the next 20 years due to better detection, increasing comorbidities, and an aging population. Due to increased AF prevalence, telerehabilitation has been developed to enhance patient engagement, health care accessibility, and compliance through digital technologies. A telerehabilitation program called "Future Patient—telerehabilitation of patients with AF (FP-AF)" has been developed to enhance rehabilitation for AF. The FP-AF program comprises two modules: (1) an education and monitoring module using telerehabilitation technologies (4 months) and (2) a follow-up module, where patients can measure steps and access a data and knowledge-sharing portal, HeartPortal, using their digital devices. Those patients in the FP-AF program measure their heart rhythm, pulse, blood pressure, weight, steps, and sleep. Patients also complete web-based questionnaires regarding their well-being and coping with AF. All recorded data are transmitted to the HeartPortal, accessible to patients, relatives, and health care professionals.

Objective: This paper aims to describe the research design, outcome measures, and data collection techniques in a clinical trial of the FP-AF program for patients with AF.

Methods: This is a multicenter, mixed methods, randomized controlled trial. Patients are recruited from AF clinics serving the North Jutland region of Denmark. The telerehabilitation group will participate in the FP-AF program, while the control group will follow the conventional care regime based on physical visits to the AF clinic. The primary outcome measure is AF-specific health-related quality of life, to be assessed using the Atrial Fibrillation Effect on Quality-of-Life Questionnaire. Secondary outcomes are knowledge of AF; measurement of vital parameters; level of anxiety and depression; degree of motivation; burden

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of AF; use of the HeartPortal; qualitative exploration of patients', relatives', and health care professionals' experiences of participating in the FP-AF program; cost-effectiveness evaluation of the program; and analysis of multiparametric monitoring data. Outcomes are assessed through data from digital technologies, interviews, and questionnaires.

Results: Patient enrollment began in January 2023 and will be completed by December 2024, with a total of 208 patients enrolled. Qualitative interviews conducted in spring 2024 will be analyzed and published in peer-reviewed journals in 2025. Data from questionnaires and digital technologies will be analyzed upon study completion and presented at international conferences and published in peer-reviewed journals by the fall of 2025.

Conclusions: Results from the FP-AF study will determine whether the FP-AF program can increase quality of life for patients with AF and increase their knowledge of symptoms and living with AF in everyday life compared to conventional AF care. The cost-effectiveness evaluation will determine whether telerehabilitation can be a viable alternative for rehabilitation of patients with AF.

Trial Registration: ClinicalTrials.gov NCT06101485; https://clinicaltrials.gov/study/NCT06101485

International Registered Report Identifier (IRRID): DERR1-10.2196/64259

(JMIR Res Protoc 2025;14:e64259) doi:10.2196/64259

KEYWORDS

atrial fibrillation; telerehabilitation; quality of life; research design; patient education; co-creation; randomized controlled trial; chronic; cardiovascular disease; adult; aging; prevalence; comorbidity; Future Patient; patient engagement; primary outcome; cost-effectiveness; monitoring; health care professional; digital health; remote therapy; telehealth

Introduction

Atrial fibrillation (AF) is a chronic cardiovascular condition occurring in 3% of the adult population, the prevalence of which is predicted to more than double over the next 20 years [1]. The increase in AF prevalence may be attributed to better opportunistic screening for silent AF, aging of the population, and an increase in conditions predisposing to AF, such as obesity, hypertension, diabetes, obstructive sleep apnea, and physical inactivity [2]. If untreated, AF is associated with a 5-fold increase in the risk of stroke; 20%-30% of all strokes are due to this type of arrhythmia [1,3].

AF imposes a substantial economic burden on the health care system, with 10%-40% of patients with AF being acutely hospitalized each year [1]. AF patients may experience a variety of symptoms, such as palpitations, fatigue, dyspnea, chest pain, sleeping difficulties, fear, and anxiety, although there is great variation in the individual symptom levels. While up to 40% of patients with AF are asymptomatic, others report severe or disabling symptoms [1]. Sleeping difficulties such as sleep apnea are also observed and may be associated with increased cardiovascular risk, further underscoring the importance of AF management [4,5]. Patients with AF trying to live with their disease can benefit from some form of effective, prolonged, and specialized cardiac rehabilitation (CR).

CR is an outpatient chronic disease management intervention that includes structured exercise. CR is based on a risk-factor assessment combined with health management interventions. Patients are educated and encouraged to quit smoking, attend vocational and nutritional counseling sessions, and seek psychosocial support. A review of CR aimed at patients with AF found gaps in the CR research, notably the need for more rigor in the reporting of intervention details, outcomes, and gender-based characteristics of CR and its effectiveness for patients with AF [6]. Many patients with AF do not feel that they have received sufficient knowledge regarding how to live with their disease [7], while other studies have shown that patients with AF often have poor knowledge about arrhythmia, its treatment, and self-management strategies [6]. In 2019, Denmark published the first national guidelines for CR for patients with AF [8], but actual rehabilitation programs have not yet been implemented. A new, innovative alternative to CR is cardiac telerehabilitation (CTR), in which certain elements of the CR program take place in the patient's home with the help of wearables and other technologies, such as a blood pressure monitor, and using remote communication between the patient and the health care professionals (HPs) [9]. Continuous monitoring, combined with the use of oral anticoagulation for stroke prevention and maintenance of normal sinus rhythm, has demonstrated benefits such as reduced hospitalization, limiting disease progression, and improving survival [10]. Reviews focusing on digital patient education for patients with AF found improvements in patient knowledge of AF [11]. For example, Desteghe et al [4] found that tailored web-based education was an effective strategy for improving AF knowledge and that patients were positive about using web-based patient education. These findings are in line with a review by Fredericks and Yau [12], who found that individualized patient education in heart surgery patients increases quality of life (QoL), improves performance of health behavior, and ameliorates psychological distress [12].

Psychological distress, such as anxiety and depressive symptoms, is prominent among patients with AF, with prevalence rates ranging from 28% to 38% [13]. Some studies have shown that AF may be a causal factor in the onset of depression, while a few studies find that depression may also cause AF [14-18]. Both anxiety and depression have been associated with recurrent AF [19], while anxiety is also described as a side effect of living with AF [15,20]. Overall, psychological distress has been associated with poorer QoL [19,21] and increased severity of AF symptoms [13,19], whereas QoL has been associated with AF severity [19]. This association highlights the importance of examining the impact of both AF

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severity and psychological distress on QoL. It should be noted that psychological distress may also impair the patient's motivation for engaging in rehabilitation, thus reducing participation in rehabilitation and self-care [22,23], whereas successful alleviation of AF symptoms is often associated with reduced emotional distress [24].

The educational CTR program "Future Patient—telerehabilitation of patients with AF" (FP-AF) was developed in Denmark through a cocreation process with patients with AF, their relatives, and researchers. The program was evaluated in a pilot study [25], which showed that patients with AF and their relatives found the FP-AF useful because it created an increased sense of security, increased knowledge about mastering symptoms, and a community of practice linking patients with AF and their relatives with HPs. These findings suggest that there is a potential for increasing the QoL of patients with AF by providing educational telerehabilitation programs that can permit sufficient individualization for patients (and relatives). Following the pilot study, the intention is for the FP-AF program to be evaluated in a multicenter, mixed-methods, randomized controlled trial (RCT). The development of the program is in line with the strategies of user involvement developed by the Danish Heart Association and with national strategies promoting digital health in Denmark, as well as current recommendations for AF rehabilitation [8].

The purpose of the FP-AF program (ClinicalTrials.gov NCT06101485) is to increase the QoL of patients with AF by providing both patients and their relatives additional knowledge about AF and practical guidance on how to live with AF in everyday life. The program aims to individualize the rehabilitation process by helping patients and their relatives develop their own self-management strategies using their own clinical data and enhanced knowledge about AF. This paper describes the research design, outcome measures, and data collection techniques used in the FP-AF research project.

Methods

Research Design

The FP-AF program will be evaluated in a multicenter, mixed methods, RCT study. The telerehabilitation group will participate in the FP-AF program, while the control group will follow the conventional care regime based on physical visits to the AF clinic. Enrollment of patients began in January 2023, and the RCT is expected to end in June 2025.

Ethical Considerations

The Future Patient project has been approved by The Scientific Ethics Committee for the North Denmark Region (N-20220056). The study is listed in ClinicalTrials.gov (NCT06101485). The study is being carried out in accordance with the Helsinki Declaration, and all participants have signed an informed consent form prior to enrollment in the study. Participants have been informed that they have the right to withdraw their consent at any point in time during the study, and the reason for their withdrawal will also be documented if the participant so wishes. The participants have not received any compensation for their participation in the study. Upon the randomization, all patients have been assigned an individual identification number so their data remain anonymous. The project team will then collect the equipment upon request.

Procedure and Eligibility Criteria

All patients diagnosed with AF at the Departments of Cardiology at Central Region Hospitals in Viborg, Skive, and Silkeborg will be assessed for eligibility in the study. The inclusion criteria are as follows: patients must be diagnosed with AF; they must be adults aged 18 years or older; they must live in Skive, Viborg, or Silkeborg municipalities; they must live at home and be capable of caring for themselves; and they must possess basic computer skills or have a relative or friend with basic computer skills.

Exclusion criteria are as follows: pregnancy; refusal or inability to cooperate; patient does not speak, read, or understand Danish; and patient has a life expectancy of less than a year.

A CONSORT (Consolidated Standards of Reporting Trials) diagram will be used to document all data pertaining to the recruitment process, as well as patient withdrawal or dropout.

Power Calculation

The primary outcome of this study is AF-specific health-related QoL (HRQoL) as measured by the Atrial Fibrillation Effect on Quality-of-Life Questionnaire (AFEQT) through the use of telerehabilitation compared to conventional rehabilitation. A clinically significant mean difference of 11 points between the intervention and control groups and an SD of 23 points were used in the study power calculation, based on prior literature [26]. A sample size of 184 patients would have 90% power to demonstrate a difference between the groups. This project estimates a dropout rate of about 10%. Thus, the total number of patients required in the study is 208, with 104 patients in the intervention group and 104 in the control group.

Randomization

Randomization of the patients will be conducted according to a randomized block design using random sized blocks of 4, 6, and 8 patients. The blocks will be stratified by center and appropriate age group and sex. The randomization will be digital and blinded for the project nurses who will be recruiting patients for the study.

Theoretical Framework

The FP-AF program is based upon self-determination theory (SDT), which describes motivation as an essential part of any successful rehabilitation [27]. SDT describes human motivation as the fulfillment of 3 basic needs: autonomy, competency, and relatedness. To ensure continuous motivation, it is necessary that this motivation is intrinsic to the patient, which requires that the patient feels that all 3 of these primary needs are being supported simultaneously [27]. As such, intrinsic motivation is achieved when a patient (1) experiences autonomy, that is, identifies with the goals of rehabilitation and values these as personally important; (2) experiences competency, that is, the patient believes that he or she has the necessary knowledge and skills to achieve the goal and receives guidance and feedback; and (3) experiences relatedness, that is, the HP's and the

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patient's social network create a milieu in which the patient feels respected, understood, and supported.

Future Patient Telerehabilitation Program

The FP-AF education program for patients with AF and relatives consists of two modules: (1) an education and monitoring module using telerehabilitation technologies (4 months) and (2) a follow-up module, where the patients use their own personal devices to measure steps and to access the HeartPortal (3 months).

After enrollment, those patients randomized to the intervention group meet individually with the project nurse. At this meeting, the patient (and relatives, if necessary) are instructed in the use of the technologies (see details below), and an individual plan is formulated for the AF patient's telerehabilitation program. The project nurses at the AF clinics (Regional Hospitals in Viborg and Silkeborg) review all the patients' measured values twice a week and have continuous contact with the patients during their enrollment in the project. For each patient, the physicians at the hospital set limit values for blood pressure, pulse, and weight. If patients register values that are out of range, they are instructed to contact the project nurse or the cardiology ward. Furthermore, the patients and relatives are invited to participate in an educational module at the local health care center, where offerings include topics such as living with AF, symptoms of AF, management of own disease using digital technologies, and how you as a relative can support your spouse or partner.

The HeartPortal

The HeartPortal (version 1.0), a web-based portal used by patients, relatives, and HPs at the hospitals and health care centers, functions as a digital toolbox and learning module. Patients and relatives in the telerehabilitation group will have access to the HeartPortal, where they can read texts and watch animations about AF, have access to visualization of the patients' measured data (steps, weight, pulse, blood pressure, and sleep), and communicate in video and chat with HPs at the hospitals and health care centers. The patients can access the data from the electrocardiogram (ECG) on a separate platform. Screen captures of the HeartPortal are shown in Figure 1, and the context of the Future Patient study is shown in Figure 2.

The HeartPortal consists of 4 elements (Textbox 1).

The technologies being used in the CTR group are listed in Textbox 2.

Figure 1. Screen captures from the HeartPortal. (A) The patients front page. (B) Measurement from the sleep sensor. (C) The information platform. (D) Measurement from the pedometer.

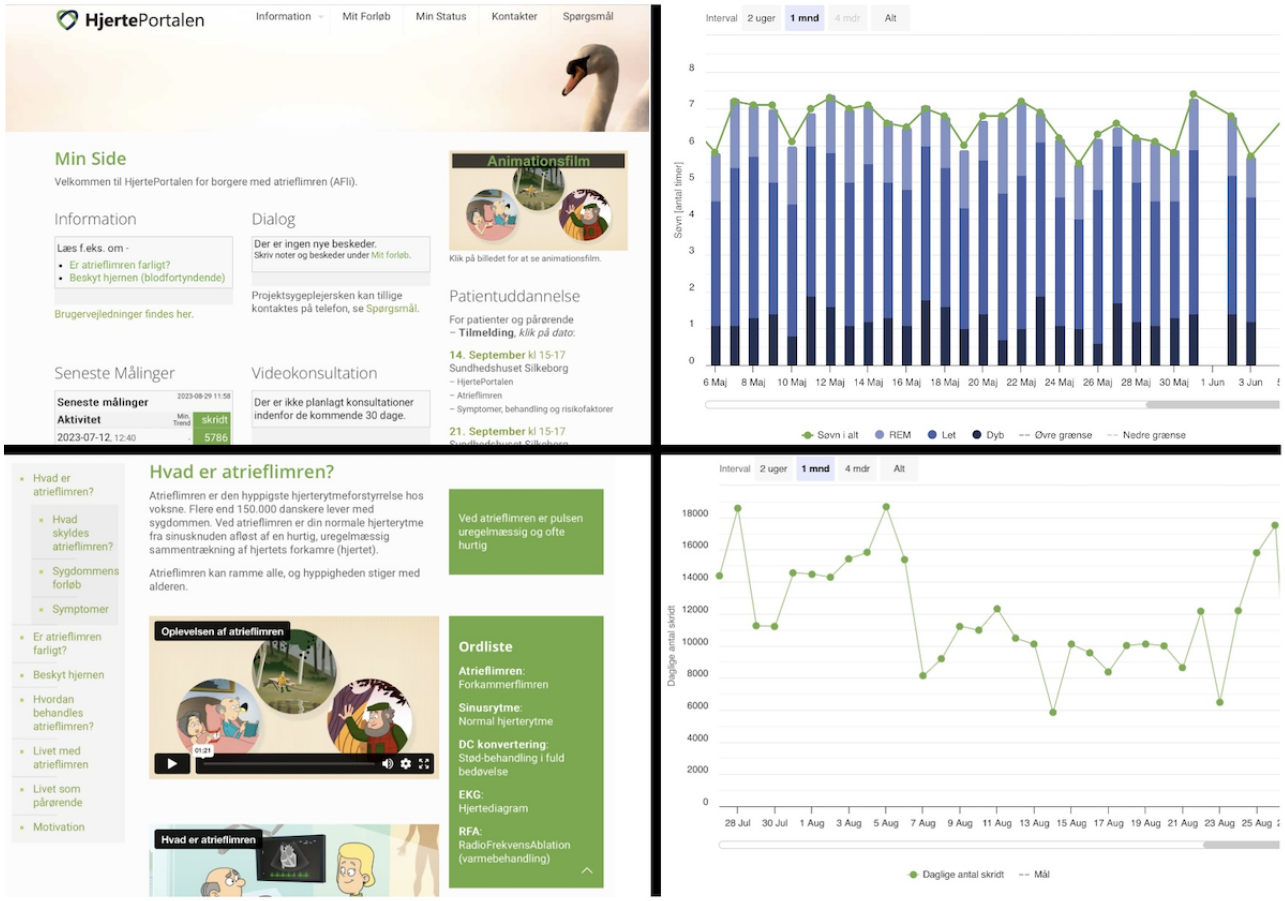

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Figure 2. The context of the Future Patient program.

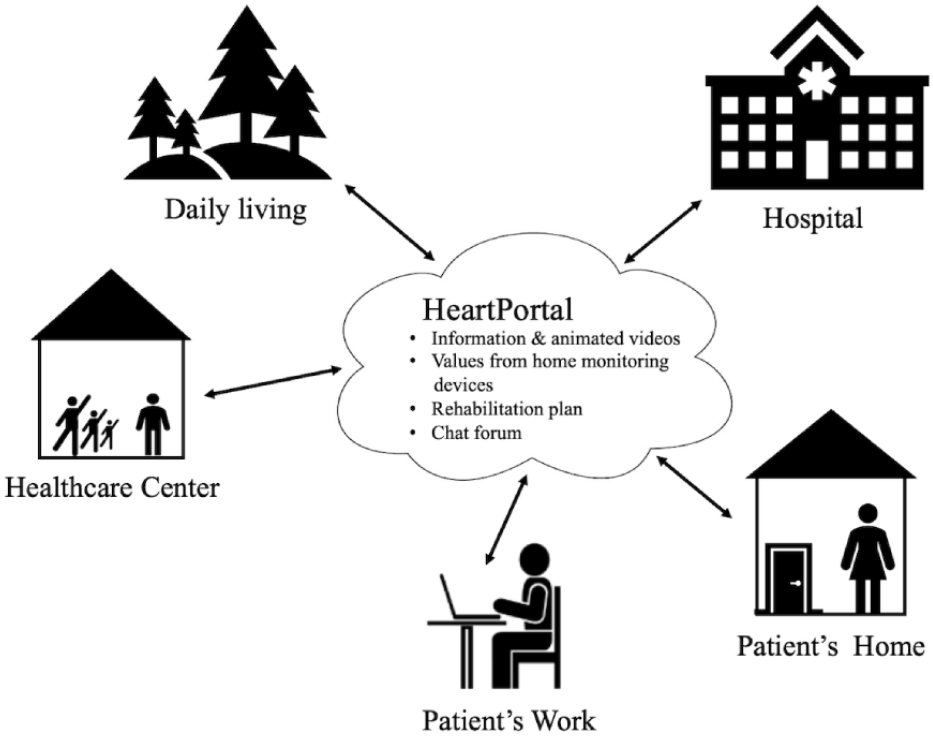

Textbox 1. Four elements of HeartPortal.

- A platform containing atrial fibrillation and rehabilitation related information pages (text, images or illustrations, animation, link to other validated sources, etc).
- Visualization of measured values (steps, weight, pulse, blood pressure, and sleep) in graphs that offer an easy overview and trends in data.
- A communication platform (video and chat) that enables patients to communicate directly with health care professionals. Video consultations will be conducted at 1 month and 4 months after enrollment in the study and additionally as needed on an individual basis.
- A rehabilitation plan. For each patient, an individualized rehabilitation plan is defined in a dialogue between the patient, the doctor, and a project nurse. The rehabilitation plan is formulated using individual parameters such as weight, physical status, pulse, and blood pressure. The patients write down their personal rehabilitation goals on the HeartPortal. The patients start the rehabilitation plan at the time of enrollment in the study. A project nurse monitors the patient's data twice a week and contacts the patients if the rehabilitation goals have not been met, data have not been transmitted to the HeartPortal, or in case data are not within the normal range set for the patient.

Textbox 2. Technologies used in the cardiac telerehabilitation group.

- Blood pressure monitor (iHealth Neo [BP5S]) [28]. Measurement of systolic and diastolic pressure and pulse. Connects to an app on the tablet to record the measurement and the tablet's internet connection to transfer the measured values. Blood pressure is measured twice a week.
- Weight scale (iHealth Lina) [29]. Allows the patient to follow his or her weight and observe weight loss or gain. Connects to an app on the tablet to record the weight, and the tablet's internet connection transfers the measured values to the HeartPortal. Weight is measured twice a week.
- Activity tracker (Fitbit Inspire 3|Health & Fitness Tracker) [30]. Measures physical activity, counted as steps and calories burned as well as pulse throughout the day. The activity tracker can also measure sleep if worn while sleeping. An app on the tablet is used for viewing and reviewing the tracked data and for data transfer. Activity, measured as steps, is measured every day and transmitted to the HeartPortal.
- Electrocardiography (ECG) monitor (KardiaMobile) [31]. Consists of a small device with touchpads, one for each hand. The monitor uses ultrasound to communicate with an app on the tablet. The app transfers the data to a General Data Protection Regulation-compliant system for clinicians, KardiaPro. ECG is carried out twice a week. The Kardia device includes an artificial intelligence–powered algorithm with an accuracy rate of 97% [31]. When patients measure their ECG, the device detects their heart rhythm. Patients have also been taught to interpret the results, such as the difference between sinus rhythm and AF.
- Sleep sensor (Emfit QS) [32]. Monitors pulse and respiration during sleep, sleep duration, stages, and sleep quality. Sleep is measured in hours every night, and the sensor data are transmitted to the HeartPortal.
- Video solution (VDX, Medcom) [33], a national video platform in Denmark within health care.

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Data and Network Security

The telerehabilitation program has a strong focus on data and network security and resiliency. Security and resiliency in eHealth is a general issue that requires special measures in an environment where data are generated both from a health system (pulled data) and from the users or patients (pushed data). The format of metadata for reliable integration (source traceability), encryption, and infrastructure reliability (VPNs, VLAN, centralized vs federated storage) will be addressed by including perspectives from the different endpoints in the system (home, workplace, health center, etc), the technology used (wired, wireless, and dual technology), and the classification of information. Standardization activities, such as those from ITU-T, Continua, ENISA, etc, will be monitored and applied where possible.

Usual Care Intervention

Patients in the control care group have received AF education as usual, with the standard 45-60 minutes of orientation in AF, symptoms, treatment, and management of their own disease delivered in person at the hospital and by consultancy if needed by their general practitioner.

Baseline Characteristics

Sociodemographic data, such as civil status, level of education, work status, and IT competences, will be collected from both groups at baseline using data from the patient's electronic medical record and questionnaires.

Clinical baseline data, such as clinical status, primary and secondary diagnoses, and prescribed medicine, will also be collected for both groups using the electronic patient record.

Outcome Measures

Table 1 presents an overview of the primary and secondary outcome measures, along with the scheduled data collection dates. Except for progression in clinical data, including adverse events and dropout, all outcome measures will be collected using packages of questionnaires relevant to the specific point in time. The patients answer questionnaires in a web-based version, or on paper if they prefer.

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Table 1. Primary and secondary outcome measures and data collection dates.

Outcomes	Time of measurement				End of tele- rehabilitation (at 4 months)	Follow-up at 7 months
	Baseline	Every day	Twice a week	As needed		
Primary						
Changes in AF[a]-specific quality of life	(I[b],C[c])				(I,C)	(I,C)
Secondary						
Changes in AF knowledge	(I,C)				(I,C)	(I,C)
Measurement of vital parameters						
Weight	(I,C)		(I)	(I)		
Blood pressure	(I,C)		(I)	(I)		
Pulse	(I,C)	(I)		(I)		
Steps	(I)	(I)			(I)	(I)
Sleep	(I)	(I)				
Electrocardiogram	(I,C)		(I)	(I)		
Changes in anxiety and depression	(I,C)				(I,C)	(I,C)
Changes in motivation	(I,C)				(I,C)	(I,C)
Burden of AF	(I,C)				(I,C)	(I,C)
Use of HeartPortal					(I)	
Patients' and relatives' perspective and experiences					(I)	
Health care professionals' perspective and experiences					(I)	
Cost-effectiveness evaluation					(I,C)	(I,C)
Trends and patterns in multiparametric clinical data					(I)	

[a]AF: atrial fibrillation.

[b]I: intervention group.

[c]C: control group.

Primary Outcome

Changes in AF-Specific Health-Related Quality of Life

AF-specific HRQoL is measured using the AFEQT [34]. The AFEQT is a 20-item self-administered questionnaire designed to assess the impact of AF on the patients' HRQoL across symptoms, daily activities, treatment concerns, and treatment satisfaction. Scores range from 0 to 100, with higher scores indicating better HRQoL.

Secondary Outcomes

Changes in AF Knowledge

The Jessa Atrial Fibrillation Knowledge Questionnaire (JAKQ) is a 16-item scale used to assess the knowledge of patients' AF about the arrhythmia illness [4]. For every item, false responses or "I don't know" responses are scored as 0, and the correct responses are scored as 1. The total score of the scale is calculated by adding up all item scores.

Measurement of Vital Parameters

Clinical data on weight, blood pressure, pulse, steps, sleep, and ECG in the intervention group will be collected as specified in Table 1.

Changes in Anxiety and Depression

Symptoms of anxiety and depression are measured using the Hospital Anxiety and Depression Scale (HADS) [35]. The HADS is a 14-item self-reported questionnaire often used for screening of psychological distress in patients with cardiac conditions. Each item is scored on a 4-point Likert scale ranging from 0 to 3. The 2 subscales, anxiety and depression, each comprise 7 items, and scores on these subscales range from 0 to 21, with higher scores indicating higher levels of anxiety or depressive symptoms.

Changes in Motivation

Motivation is measured by the Health-Care Self-Determination Theory Questionnaire Packet (HC-SDTQ). The HC-SDTQ

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includes 3 separate questionnaires: the Treatment Self-Regulation Questionnaire, which focuses on autonomy as stipulated by SDT [36]; the Perceived Competence Scale, which assesses patients' sense of competence about engaging in, or maintaining, a healthier behavior [37]; and the Health Care Climate Questionnaire, which assesses the patient's perception of autonomy support from their health care provider [38].

Burden of AF

The burden of AF is measured using the Arrhythmia-Specific Questionnaire in Tachycardia and Arrhythmia (ASTA) [39]. The ASTA measures symptoms and HRQoL in patients with different forms of arrhythmias, including AF. The ASTA is divided into 3 parts: Part I assesses demographic data, such as the most recent episode of arrhythmia, current medication, and the presence of arrhythmia at the time of follow-up; Part II measures the arrhythmia-specific symptom burden; and Part III measures HRQoL. Parts II and III are scored using a 4-point Likert-type scale (0="No" to 3="Yes, a lot"). The total score range is from 0 to 100, with a higher score indicating a higher symptom burden or a negative effect on HRQoL.

Use of HeartPortal

Time log files for login and logout of patients and relatives will be analyzed in order to identify which parts of the HeartPortal are being used and for how long. The patients will be asked for their consent prior to extracting their log files from the database for analysis.

Perspectives and Experiences From Participating in the FP-AF Program

Participant-observation [40,41] will be used in situations such as educating and counseling the patients and relatives in using the technologies at home and to observe how patients and relatives use the digital technologies and the HeartPortal.

Perspectives and experiences of patients, relatives, and HPs participating in the FP-AF program will be explored using semistructured qualitative interviews, inspired by Brinkmann and Kvale [42]. Interviews will be performed until data saturation is reached, with a minimum of 10 interviews conducted for each group: patients, relatives, and HPs. The interviews will be recorded, transcribed, and analyzed in themes inspired by Brinkmann and Kvale [42] and based on their phenomenological approach. The interviews will be coded by 2 researchers using NVivo (version 14.0) software [43].

Cost-Effectiveness Evaluation

Throughout the duration of the study, we will also collect information on unplanned admissions for any reason with at least 1 overnight stay, unplanned readmissions for any reason and length of stay, visits to outpatient clinics, rehabilitation activities, visits to the general practitioner, equipment used, driving distance, personnel use, and numbers of phone or video calls. The analysis will be based on the guidelines for economic evaluation elaborated by Drummond et al [44].

Data Storage

Demographic data are being stored within the Future Patient database, and the questionnaire data are stored in the REDCap (Research Electronic Data Capture; Vanderbilt University) software for quantitative analysis.

Adverse Events, Dropout, and Technical Issues

All adverse events, dropouts, and deaths, as well as any technical issues related to the equipment, will be registered. No preterm study stop criteria are planned.

Data Analysis

Statistical Analysis

Baseline characteristics will be presented as frequencies and percentages or as medians and IQRs, as appropriate, and the data will be stratified by randomization groups and by sex. Changes over time on the primary outcome will be analyzed in accordance with the intention-to-treat principle, using a mixed-effects model for repeated measures design with robust variance in order to relax the assumption of normally distributed residuals. In addition, margin plots will be produced in order to investigate the interaction of time and randomization group. A sensitivity analysis will be conducted in order to investigate the effects of missing data as a result of dropout by comparing baseline characteristics between complete cases and dropouts, followed by adjusted analyses of the primary outcome using appropriate baseline characteristics as adjustment parameters. Secondary outcomes will be analyzed in a manner similar to the primary outcome. We will also examine overlaps between and variations within groups of different sexes. In examining sex differences, we will adjust for possible confounding factors (eg, age).

Trends and Patterns in Multiparametric Clinical Data

Data will be analyzed in order to identify correlations in multiparametric data collected during the 4 months. Initial analysis of the multiparametric data will be carried out by assessing the architectural structures and complexities of the data design through basic statistical and distributive analysis. Differences in the multiparametric data between baseline and postintervention measurements will be tested with paired *t* tests. Correlations of multiparametric data will be compared with patient-reported symptoms of AF. Paired *t* tests will be performed for the multiparametric data between periods both with and without patient-reported symptoms of AF in patients experiencing symptoms. Also, *t* tests will be performed for multiparametric data between patients with and without symptoms of AF. Simplistic features will be developed based on the statistical analyses and correlations between data.

Qualitative Analysis

A research assistant will transcribe all interviews into text files. Data will be coded in NVivo (version 14.0; QSR International), drawing inspiration from the SDT theoretical framework and using methods developed by Brinkmann and Kvale [42]. Two different researchers will be responsible for conducting the interviews and analyzing the data. The data will be presented in terms of key themes and major findings.

Economic Evaluations

A cost-effectiveness analysis of the FP-AF telerehabilitation program compared to conventional care will be made at 7

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months after inclusion for both groups. The analysis will be based on the guidelines for economic evaluation elaborated by Drummond et al [44].

Results

The findings of the RCT will be analyzed during the spring of 2025 and subsequently published in peer-reviewed journals in the fields of telerehabilitation, clinical cardiology, and health economics. In addition, these results will be presented at relevant international scientific conferences. A total of 208 patients will be enrolled, 104 in the telerehabilitation group and 104 in the control group.

The evaluation of the FP-AF program comprises both clinical data recorded by the patients and data gathered through interviews and questionnaires. The evaluation involves quantitative analysis of primary and secondary outcomes (questionnaires) as well as qualitative exploration of the perspectives and experiences of patients with AF, their relatives, and HPs. Finally, a health economic evaluation will be conducted. Taken together, the data and the associated analyses will provide a comprehensive perspective on the effectiveness of the FP-AF program as seen from clinical, patient, relatives, psychological, organizational, and economic perspectives.

Discussion

Telerehabilitation Program

The aim of the study is to test an individualized CTR program for patients with AF. The primary outcome measure is to assess potential changes in QoL among those patients with AF using telerehabilitation. The secondary outcome measures are changes in AF knowledge, changes in anxiety and depression, changes in motivation, the burden of AF, patients' and relatives' perspectives and experiences, patients' and relatives' use of the HeartPortal, perspectives and experiences of HPs, the development of clinical data, and a cost-effectiveness analysis.

CR for patients with AF is a fairly new initiative, and national guidelines for AF CR have only recently been published [8]. In this study, we take this initiative further by examining the potential of a CTR program for patients with AF, as telerehabilitation provides a promising and innovative alternative to conventional rehabilitation. The potential advantage of telerehabilitation is that it can provide easier access to rehabilitation assistance and activities and may therefore be a means of overcoming some of the barriers to participation in CR that have been identified in other cardiac patient groups [45]. Use of telerehabilitation may be especially relevant for patients with AF, as this group is very diverse in terms of the subjective impact of their disease; hence, some patients may not feel the need to attend physical appointments at the clinic, but they may be willing or even positive about participating through digital communication and technology. The digital option offered by telerehabilitation may thus improve their QoL.

The FP-AF program will be tested in a multicenter study in order to increase the validity of the study. The FP-AF program is based upon SDT theory and the exploration of how patients, their relatives, and HPs use the HeartPortal. We will therefore analyze the linkages between motivation and use of the digital platform. In a previous study of patients with heart failure, we have documented that telerehabilitation motivates patients with heart failure just as effectively as conventional rehabilitation and that it does not lead to higher levels of psychological distress [46].

To obtain a more in-depth understanding of how patients, relatives, and HPs perceive CTR, we also plan to conduct qualitative interviews with all groups in order to learn more about how they experience the program as part of their everyday life and work, including their evaluation of the specific modules of the program. Using interviews together with questionnaire data will allow for a more holistic understanding of the usability, effect, and acceptance of the proposed program.

Limitations

The expected limitations for the interpretations of the results are as follows. The study relies heavily on commercial tracking devices that have been chosen for their ability to automatically transmit data to the HeartPortal. Any changes in device regulations during the study could make it necessary to replace these devices, potentially leading to inconsistency in the data. In addition, the proposed intervention is complex, consisting of a chain of events and interventions and based on multiple commercially available technologies that may become outdated. This complexity, including the rapidly changing nature of technology, may pose a challenge to future replication studies.

Conclusions

Analyzing data from primary and secondary outcomes will help determine whether the FP-AF program has the potential to increase QoL for patients living with AF and give them more knowledge of how to master the disease. The cost-effectiveness analysis will provide an assessment of the health economic sustainability of the FP-AF program and shed light on whether telerehabilitation can be a viable alternative for rehabilitation of patients with AF.

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Conflicts of Interest

None declared.

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Abbreviations

AF: atrial fibrillation
AFEQT: Atrial Fibrillation Effect on Quality-of-life Questionnaire
ASTA: Arrhythmia-Specific Questionnaire in Tachycardia and Arrhythmia
CONSORT: Consolidated Standards of Reporting Trials
CR: cardiac rehabilitation
CTR: cardiac telerehabilitation
ECG: electrocardiogram
FP-AF: Future Patient—Telerehabilitation of patients with atrial fibrillation
HADS: Hospital Anxiety and Depression Scale
HC-SDTQ: Health-Care Self-Determination Theory Questionnaire
HP: health care professional
HRQoL: health-related quality of life
JAKQ: Jessa Atrial Fibrillation Knowledge Questionnaire
QoL: quality of life
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SDT: self-determination theory

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Protocol

Cognitive Training for Emotion-Related Impulsivity and Rumination: Protocol for a Pilot Randomized Waitlist-Controlled Trial

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Abstract

Background: Inhibitory deficits are common in psychopathology. Emotion-related impulsivity (ERI) and rumination are general risk factors for psychiatric distress that are similarly associated with dysfunctional inhibition—particularly in affective contexts. A number of cognitive remediation procedures have been developed to improve inhibitory control; however, most remediation programs focus on “cold” cognition independent of affective processing. This pilot trial will gather preliminary evidence for a new cognitive training intervention targeting “hot” affective control (ie, inhibitory functions during elevated emotional arousal) in a transdiagnostic sample of adults who report heightened emotion dysregulation.

Objective: This manuscript describes a protocol for a pilot randomized waitlist-controlled trial to assess changes in ERI and rumination after neurobehavioral affective control training (N-ACT), an 8-week cognitive training intervention designed to improve emotional response inhibition and emotional working memory. Our primary aim is to evaluate the efficacy, feasibility, and acceptability of N-ACT in reducing rumination and ERI, which we respectively conceptualize as complementary cognitive and behavioral consequences of emotion dysregulation. Secondarily, we will examine whether N-ACT leads to improvements in inhibitory control and, more distally, psychopathology symptoms.

Methods: The final sample will comprise 80 adults who report high ERI or rumination. Participants will be randomized to (1) begin the N-ACT program without delay or (2) join a waitlist condition and then complete N-ACT. Exclusion criteria include active alcohol or substance use disorders, psychosis, and suicide risk. At the baseline and postintervention time points, participants will complete measures of emotion dysregulation and psychiatric symptoms, as well as a neuropsychological assessment of inhibitory control. Individuals assigned to the control group will undergo an identical assessment before joining the waitlist, followed by parallel assessments before and after N-ACT.

Results: This trial is funded by support from the University of California Board of Regents and the Peder Sather Foundation (funding period: October 2022-September 2025). Recruitment is scheduled to begin in spring 2025. We will begin data analysis once data collection is complete, which is planned to occur in fall 2025.

Conclusions: This pilot randomized waitlist-controlled trial is designed to assess the initial efficacy, feasibility, and acceptability of N-ACT, a novel cognitive remediation approach developed to address 2 key contributors to psychopathology: ERI and rumination. The N-ACT program uses computerized adaptive behavioral tasks to strengthen the affective control processes theoretically and empirically linked to ERI and rumination. We hope this work will help inform future studies with sufficient

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statistical power to ascertain whether enhancing affective control through cognitive training (N-ACT) produces downstream reductions in psychiatric symptoms via improved emotion regulation.

Trial Registration: ClinicalTrials.gov NCT06226467; https://www.clinicaltrials.gov/study/NCT06226467; Open Science Framework Registry rak5z; https://osf.io/rak5z

International Registered Report Identifier (IRRID): PRR1-10.2196/54221

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KEYWORDS

cognitive control; cognitive training; emotion regulation; emotional response inhibition; emotional working memory; executive function; impulsivity; rumination; transdiagnostic; urgency

Introduction

Background

Emotion dysregulation is an established risk factor for nearly all psychiatric syndromes, with particularly strong effects for anxiety and depression—the 2 most common psychological disorders [1,2].These links between emotion dysregulation and psychiatric dysfunction are well documented across ecological and laboratory studies, as well as in large-scale prospective work [3-5]. This research will evaluate a novel intervention, neurobehavioral affective control training (N-ACT), which is designed to target two trait-like facets of emotion dysregulation: (1) *rumination*, the tendency toward self-focused, past-oriented, repetitive negative thinking about the causes and consequences of negative affect [6,7]; and (2) *emotion-related impulsivity* (ERI; [8]), the tendency toward reduced behavioral control during states of high affective arousal [9], most commonly captured using measures of Urgency. These 2 aspects of emotional dysregulation reflect cognitive and behavioral responses, respectively, to negative affect. Robust associations have been documented of rumination and ERI with anxiety and depressive disorders as well as numerous other psychiatric conditions [6,7,10-18].

Inhibitory Control Deficits in Psychopathology

Rumination and ERI are both tied to problems with cognitive (inhibitory) control. Cognitive control is a multifaceted construct that includes (1) the ability to update and manipulate the contents of working memory; and (2) the inhibition of task-inappropriate behavior (ie, response inhibition), alongside closely related executive functions (eg, cognitive inhibition, set shifting or task switching). This project targets both working memory and response inhibition, which represent promising candidate mechanisms linking emotion regulation deficits to varied manifestations of psychopathology.

Cognitive difficulties associated with major depressive disorder (MDD) and other internalizing syndromes often have severe consequences for the individuals affected, likely through adverse influences on symptoms and role functioning. Systematic reviews of this literature suggest that cognitive control deficits in MDD are not simply epiphenomenal effects caused by symptoms—as some have recently suggested [19]—but rather often persist after remission, thereby exerting continued influence on everyday functioning and the likelihood of symptom recurrence [20,21]. Indeed, impaired cognitive control predicts relapse in patients with first-episode depression [22] up to 5 years after the index episode through its association with rumination [23,24]. One of the longest prospective studies of cognition in MDD revealed cognitive control impairment a full decade after symptom remission [25]. In sum, a substantial literature implicates poor cognitive control in prolonged vulnerability to depression recurrence and relapse.

Evidence for chronic neuropsychological deficits in MDD and other psychiatric disorders has generated interest in improving mental health through strengthening cognitive control and other executive functions. However, traditional psychotherapeutic interventions have limited effects on cognitive control; for example, meta-analyses indicate little to modest changes in cognitive control capacities after psychological [26] or pharmacological treatment for depression [27]. The recognition of the need for new approaches to enhancing executive functions has led to a growing focus on development of cognitive remediation or training programs that directly target inhibitory control [28-30].

However, many studies—of major depression or otherwise—rely on measures of “cold” cognitive control, in that the assessment procedures lack emotionally salient stimuli or probes. *Affective control* refers to the ability to exert inhibitory control in situations or tasks involving emotionally arousing content, often referred to as “hot” executive functions. Emotional contexts may be more likely to activate or aggravate symptoms compared to contexts without such affective components [31]. Rumination and ERI—as well as psychopathology more broadly—may be more closely linked to affective control deficits than to cold cognitive control deficits. For example, among people with remitted MDD compared to healthy controls, Ronold et al [32] observed working memory deficits (during high cognitive load) especially for negative compared to positive emotional content; moreover, in 2 independent samples, such impairment was tied to heightened rumination [33], which in turn predicted elevated risk for depressive relapse [32]. ERI is similarly associated with impaired inhibitory control, particularly during higher arousal states [34]. Moreover, poor affective control is associated with symptoms of eating disorders [35], nonsuicidal self-injury [36-40], and suicidal behaviors [31,41,42]. Thus, affective control is an empirically justified and theoretically informed target to remediate and prevent the recurrence of psychiatric symptoms.

A growing corpus of research has converged on 2 components of affective control, both of which are targeted by N-ACT: (1) *emotional working memory*, which involves the temporary

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storage and manipulation of emotional information in short-term memory; and (2) *emotional response inhibition*, or the ability to regulate motor impulses driven by automatic emotional reactions. Dysfunction in working memory or response inhibition—*specifically in the context of negative emotion*—is independently tied to rumination, ERI, and internalizing symptoms, as well as self-injurious thoughts and behaviors [39,41,43-46]. Several studies have shown that emotional response inhibition, as indexed by an emotional stop-signal task (ESST), shows significant correlations with measures of ERI and psychiatric severity [37,39,43]. Negative emotional response inhibition impairment is a strong predictor of symptoms, including increased risk of future suicide attempts [41].

Cognitive Remediation in Psychiatry

The goal of cognitive remediation is to improve dysfunctional neurocognitive processes. This improvement relies on the repeated practice of specialized cognitive training exercises using computer algorithms that adjust task difficulty according to user performance. A burgeoning literature suggests that cognitive remediation may be a promising transdiagnostic intervention approach [28,47-55]. Working memory training has been found to reduce the recurrence of mood episodes among patients with remitted MDD, with stronger protective effects—apparent up to 2 years after the intervention—for those who reported reduced rumination after training [52,56]. Although accumulating evidence supports the efficacy of cognitive remediation in psychiatric disorders, meta-analytic effect sizes tend to be small to medium [28], and a substantial proportion of individuals do not respond to existing training programs for symptom reduction [57].

Numerous issues likely contribute to the relatively modest treatment effects associated with standard cognitive remediation programs. N-ACT is novel in 3 ways. First, we focus on emotion regulation rather than psychiatric symptoms as our primary outcome. Second, extant literature shows considerable variability in the delivery methods of cognitive remediation. Following consensus recommendations from an expert working group [47], we will implement scaffolding techniques to facilitate the generalization and functional impacts of N-ACT. More specifically, we will follow recommendations to provide support to facilitate translation of skills into everyday activities, so as to enhance the ecological validity and effectiveness of cognitive training programs [47-55]. Participants will accordingly complete N-ACT intervention sessions guided by a "coach," who will deliver semistructured and (partially) personalized psychoeducational content. N-ACT coaching sessions will include the identification of compensatory problem-solving strategies for emotion regulation, skills practice, motivational enhancement, discussion of the ecological relevance of the cognitive skills being trained, and procedures to promote the transfer of training effects to real-world situations. Therefore, we will be testing the effects of repeated affective control exercises, coupled with therapeutic coaching. Our hope is that this combination of techniques will support generalization to improved functional outcomes.

Third, although the stimuli and parameters in many cognitive control training tasks (eg, those using geometric shapes and letters) lack inherent salience value, our trial builds from a smaller body of work on cognitive remediation using the affective variants of inhibitory control tasks as well as traditional tasks (with neutral stimuli) that may naturally induce emotional arousal [50]. As an example of the latter, the Paced Auditory Serial Addition Test [58], which uses numerical stimuli and has been extensively implemented as an adaptive training task [29,30,59], characteristically evokes frustration [58]. To our knowledge, the only direct comparison of cold versus hot cognitive remediation was performed in a pilot trial of emotional working memory training, which yielded promising results in symptoms and cognition (but not rumination) among patients with depressive symptoms [60]. This early work is consistent with recent meta-analytic findings suggesting that hot inhibitory control training may be more effective than nonaffective cognitive remediation procedures for psychopathology [61]. Accordingly, N-ACT incorporates affective stimuli (eg, naturalistic images with standardized emotional content) into traditional training tasks designed to improve cognition such that users learn to use these mental operations in socioemotional contexts that more closely match in vivo experiences. The inclusion of affective stimuli is particularly important, given a substantial body of work suggesting that difficulties sustaining inhibitory control during states of elevated arousal are particularly relevant to emotion regulation and psychiatric symptoms.

This Study

Overview

This pilot randomized waitlist-controlled trial will enroll adult participants with high rumination or ERI scores. The primary aim of this study is to examine the acceptability, feasibility, and efficacy of N-ACT as a novel therapeutic approach to reduce rumination and ERI by improving 2 facets of affective control: emotional working memory and emotional response inhibition. Secondarily, we will test the effects of N-ACT on behavioral indices of ability transfer as well as on other subjective measures of emotion dysregulation (beyond trait rumination and ERI) and psychopathology symptom severity (refer to Multimedia Appendix 1 for details). Finally, we will conduct exploratory analyses to examine the potential mechanisms that might influence predicted changes in emotion dysregulation, informing future work to systematically test these effects in a sufficiently powered sample. In addition to performing intent-to-treat analyses, we will conduct sensitivity analyses to evaluate the extent to which program adherence predicts the hypothesized effects.

Hypotheses

We propose the following hypotheses:

- H1: Participants will rate N-ACT as an acceptable intervention to reduce emotion dysregulation.
- H2: Participants will demonstrate adherence to the N-ACT program at levels comparable to those observed in established cognitive remediation protocols [33,52,62-64].
- H3 (primary): Compared to baseline, participants assigned to complete N-ACT (without a waitlist) will report greater decreases in rumination and ERI at the postintervention

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assessment than those assigned to the control condition at the postwaitlist assessment.

- H4 (secondary): Compared to baseline, participants assigned to complete N-ACT (without a waitlist) will demonstrate greater improvements in targeted affective control processes (ie, enhanced emotional working memory and emotional response inhibition) at the postintervention assessment than those assigned to the control condition at the postwaitlist assessment.
- H5 (secondary): Compared to baseline, participants assigned to complete N-ACT (without a waitlist) will demonstrate near (ie, enhanced hot affective flexibility) and far (ie, enhanced cold working memory and cold response inhibition) transfer of trained neurocognitive abilities at the postintervention assessment than those assigned to the control condition at the postwaitlist assessment.
- H6 (secondary): Compared to baseline, participants assigned to complete N-ACT (without a waitlist) will report greater decreases in self-rated psychopathology symptom severity (ie, reduced internalizing and externalizing symptoms) at the postintervention assessment than those assigned to the control condition at the postwaitlist assessment.

Methods

Overview

This research comprises a delayed intervention randomized waitlist-controlled trial with a mixed, 2-group (2 between-subject levels: active vs control), repeated measures (2 within-subject levels: T1=baseline or preintervention time point; T2=postwaitlist or postintervention time point) design, for which we will recruit English-speaking adults (aged 18-65 y) from the San Francisco Bay area of the United States. The inclusion criteria include high self-reported rumination or ERI. Eligible individuals will be invited to the university for an initial baseline session. At this session, they will complete informed consent procedures and an assessment battery consisting of computerized neuropsychological tasks with concurrent psychophysiological monitoring. After the baseline session, participants will complete a battery of questionnaires, followed by 1 week of baseline ecological momentary assessment (EMA) of real-world daily fluctuations in mood, rumination, and ERI.

After the baseline assessment (laboratory session, questionnaires, and EMA), we will randomly assign participants to receive active treatment (ie, N-ACT without delay) or the waitlist control condition, unblinded, using an asymptotic maximal procedure to achieve a maximally tolerated imbalance of 2, while maintaining a 1:1 allocation ratio between the 2 trial arms [63]. Participants in the active N-ACT group will begin the intervention, which consists of 8 weekly coached training sessions, within 1 week after baseline EMA. We will recontact waitlist control participants after a period equivalent to the intervention duration (ie, 2 months) to complete a second (postwaitlist) assessment session and EMA before starting the N-ACT program for the following 8 weeks. After the intervention, participants will be asked to complete a second week of EMA, and then a postintervention assessment session with comparable measures to baseline. We will recontact waitlist control participants approximately 10 weeks after their (prewaitlist) baseline assessment session to complete a second (postwaitlist) assessment and 1 week of EMA, parallel with the pre-intervention assessment procedures of the N-ACT group,. The waitlist group will then be offered 8 weeks of N-ACT, followed by a second week of postintervention EMA, and then a final assessment session. In sum, we will follow participants assigned to receive the intervention without delay for 12 weeks (3 mo) and those assigned to the waitlist control group for 22 weeks (5.5 mo). This delayed intervention randomized waitlist-controlled trial design enables us to offer all interested participants the opportunity to participate in the program and maximizes our ability to rapidly accrue a sufficiently sized sample for analyses. Figure 1 demonstrates the flow of potential participants through the study procedures.

Figure 1. Flow of participants through the trial with a delayed intervention randomized waitlist-controlled design. N-ACT: neurobehavioral affective control training. Assessments are indicated in gray.

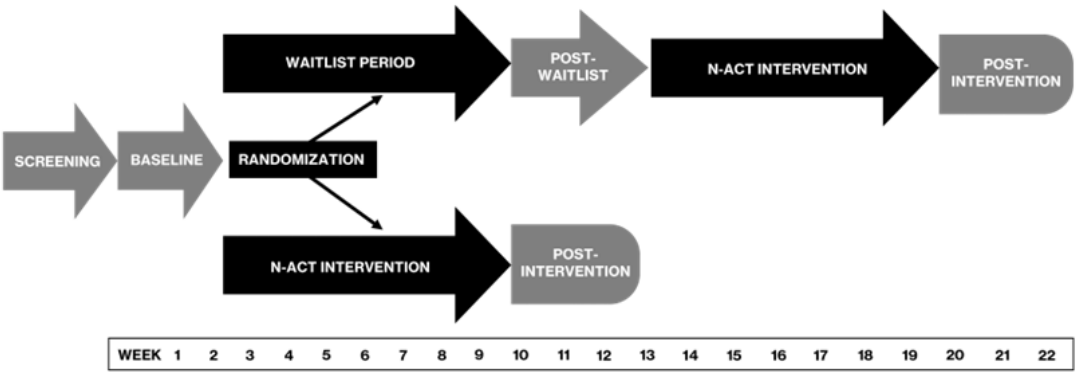

Hypotheses and analyses were preregistered at OSF. We plan to detail any changes to this protocol in future publications and disseminate our findings to the scientific community in accordance with the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist (V 1.6.1) [64].

Ethical Considerations

The University of California Berkeley Committee for Protection of Human Subjects granted approval for this research (2023-01-15949) before data collection. All participants will complete written informed consent before commencing study procedures.

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Participants will be assigned an ID number, which will be used in place of their name or other identifying information on all research materials. Data will be kept in secure, password-protected files. Although we plan to make data publicly available for reanalysis, we will carefully deidentify data before doing so. In publishing or presenting the results, we will not provide any information that could identify an individual participant.

Participants will receive course credit or monetary compensation for completing assessment procedures but will not be paid for time spent on screening or the intervention itself. Students will be able to earn credit toward required research hours in their psychology classes. We plan to increase the hourly payment rate slightly over the course of the trial to promote retention, from US $20/h for the baseline assessment to US $30/h for the postwaitlist and postintervention assessments. We will compensate participants up to US $60 (or 3 h of course credit) for completing the baseline assessment (2.5-h in-person session plus 30 min of questionnaires), a US $10 "bonus" for performance on an unrelated computer task during the baseline session, US $10 for each week of EMA if they complete at least 75% of the prompts, and US $60 for the postintervention assessment (1.5-h in-person session plus 30 min of questionnaires). Those randomized to the waitlist control condition will be eligible to receive up to an additional US $60 for completing the postwaitlist assessment (identical to the postintervention assessment).

In sum, participants assigned to complete N-ACT without the waitlist can earn up to US $150 (or 3 h of course credit plus up to US $90), while those in the waitlist control condition could earn up to US $70 in addition to those amounts. Payments will be prorated if participants complete only part of an assessment. We will remunerate participants within 1 week of each completed assessment via digital credit cards, which will be replenished as necessary.

Study Procedures

Recruitment and Screening

We will invite up to 500 adults to complete preliminary screening procedures and an estimated 100 participants to complete the initial baseline assessment session. After accounting for 20% expected attrition, we expect 40 participants in each condition to complete all study procedures.

Study advertisements will be posted locally in public spaces and distributed by web (eg, via email listserves, Craigslist, and social media sites). We will also administer a prescreening survey to students enrolled in psychology classes at the University of California Berkeley, and we will invite students who meet the preliminary inclusion criteria based on those responses to take part in the study. Potential participants (recruited either from the community or from the student participant pool) will be directed to our website, where they can view additional details about the trial. We intend to recruit only secondarily from the student participant pool to supplement community-based recruitment, which will constitute most of the targeted sample. All questionnaires, including screening items, will be administered through REDCap (Research Electronic Data Capture; Vanderbilt University) software [65], which will also be used for the secure storage of collected data.

After providing informed consent, interested individuals will complete the brief web-based screening via REDCap to assess preliminary eligibility. The inclusion and exclusion criteria are presented in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Current California residency
- Age 18 to 65 y
- Elevated scores on self-report measures of rumination (Mn >2 on the Brooding subscale of the Ruminative Responses Scale [13]) or emotion-related impulsivity (Mn >3 on the Feelings Trigger Action factor of the Three-Factor Impulsivity Index [9])

Exclusion criteria

- Insufficient English literacy to understand study procedures (as assessed by self-report) or careless responding as indicated by the following:
- Failing ≥50% of the attention check items embedded in the screening questionnaires
- Overly rapid responding (ie, mean response time of <2 s for multiple-choice items)
- Qualitative review of long strings of identical entries
- Positive history of brain tumors, neurological disorders, or head injuries accompanied by the following:
- Loss of consciousness of >5 min
- >2 separate instances of clinically significant head trauma
- Recent alcohol or other substance use disorder (in the past 6 mo) or current psychosis (in the past 2 wk) according to the Psychiatric Diagnostic Screening Questionnaire [66]
- Past-month active suicidal ideation paired with either of the following:
  - An identified method, specific plan, or intent
  - Lifetime history of suicide attempts as assessed by the screen version of the Columbia Suicide Severity Rating Scale [67]

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The exclusion criteria do not cover the presence of anxiety, depression, or other psychiatric symptoms, given our intention to target emotion dysregulation broadly and to assess the generalizability of effects across psychiatric diagnoses and severity, including participants with few or no symptoms and those without treatment history. However, the screening will include items from the self-rated screen version of the Columbia Suicide Severity Rating Scale (C-SSRS; for suicidal thoughts) as well as the alcohol, substance, and psychosis subscales from the Psychiatric Diagnostic Screening Questionnaire (PDSQ) [66]. Individuals who do not respond to the requisite screening items or do not meet eligibility requirements, including those whose responses to the psychiatric screening questions surpass established clinical thresholds, will be automatically informed that they will not be able to join the trial and will receive a list of mental health resources along with an invitation to contact our team should they desire additional referral assistance. We will provide further support for engaging with psychiatric care providers to respondents who endorse past-month active suicidal ideation with an identified method, specific plan, or intent on the C-SSRS.

Assessment

Overview

Each in-person assessment session will involve core measures expected to take 90 minutes, including a battery of computer-based behavioral tasks measuring cold and hot executive functions as well as the Positive and Negative Affect Schedule (PANAS) [68] to evaluate subjective mood before and after the neuropsychological examination. Within 24 hours of each session, participants will be asked to complete self-rated questionnaires to evaluate psychiatric symptoms and other variables of interest, which will require an additional 30 to 40 minutes. Table 1 presents key measures included at each assessment and intervention time point (refer to Multimedia Appendix 1 for a comprehensive list and additional details).

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Table 1. Administration schedule of core measuresa.

Domains and measures	Format	Screening	Baseline assessment	Postwaitlist assessment	N-ACT[a] assessment	Post–N-ACT assessment
Emotion dysregulation						
Ruminative Responses Scale–Brooding	Self-report	✓		✓		✓
Three-Factor Impulsivity Index–Feelings Trigger Action	Self-report	✓		✓		✓
Three-Factor Impulsivity Index–Pervasive Influence of Feelings	Self-report		✓	✓		✓
Psychiatric symptom severity						
Columbia Suicide Severity Rating Scale	Self-report	✓				
Demographic questionnaire or mental health history survey	Self-report	✓				
Psychiatric Diagnostic Screening Questionnaire–Alcohol Use Disorder or Substance Use Disorder or Psychosis	Self-report	✓				
Externalizing Spectrum Inventory–Revised	Self-report		✓	✓		✓
Inventory of Depression and Anxiety Symptoms, Expanded Version	Self-report		✓	✓		✓
Neuropsychological assessment battery						
Digit Span Backward	Behavioral		✓	✓		✓
Stop-signal task	Behavioral		✓	✓		✓
Trail-making test	Behavioral		✓	✓		✓
Wechsler Adult Intelligence Scale, Fourth Edition–Vocabulary	Interview		✓	✓		✓
Emotional stop-signal task	Behavioral		✓	✓		✓
Memory and affective flexibility task	Behavioral		✓	✓		✓
Affective control training (N-ACT)						
Adaptive emotional n-back task	Behavioral				✓	
Emotional stop-signal task–adaptive	Behavioral				✓	

[a]A comprehensive list of secondary measures and additional outcomes is available in Multimedia Appendix 1.

Neuropsychological Battery

At each assessment session, participants will perform 5 computerized neuropsychological tasks (in a pseudorandom order) to index the hypothesized effects of N-ACT on emotional working memory and emotional response inhibition as well as the transfer of targeted inhibitory control processes from T1 (baseline time point) to T2 (postwaitlist or postintervention time point). The assessment battery accordingly includes 3 widely used gold standard cold executive functioning tasks that measure key components of cognitive control: (1) Digit Span Backward [69], a working memory test that requires participants to select (using the computer cursor) a series of numbers in the opposite order from which the digits were presented (in numerical strings of increasing length); (2) the stop-signal task (SST) [70], a measure of prepotent response inhibition in which participants must quickly indicate (via keypress) the direction of rapidly presented arrow stimuli, except on trials that include an unpredictable buzzer tone, which require termination of the initiated motor response; and (3) the trail-making test [71], an assay of set-shifting or task-switching ability that involves using

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the computer cursor to draw a path connecting an array of alphanumeric stimuli in an alternating sequential pattern (eg, “A” to “1” to “B” to “2,” and so on) as quickly as possible. The neuropsychological battery additionally includes the administration of the Vocabulary subtest from the Wechsler Adult Intelligence Scale, Fourth Edition [72], to assess crystallized intelligence, which we will examine in exploratory analyses of the specificity of intervention effects.

Participants will also complete 2 tasks to confirm the efficacy of N-ACT in augmenting 2 core facets of affective control, emotional response inhibition and emotional working memory: (1) the ESST [37,39,43], which follows procedures parallel to those of the traditional SST but differs in that participants must rapidly categorize affective pictures according to perceived valence (ie, “positive or pleasant” vs “negative or unpleasant”) instead of indicating the direction of arrow stimuli, while still inhibiting prepotent motor responses on a subset of trials with an unpredictable auditory stop signal (buzzer or tone); and (2) the memory and affective flexibility task (MAFT) [73], a novel modified n-back procedure that provides indices of emotional working memory as well as affective flexibility (as captured by emotional set shifting or task switching trials) by asking participants to recall whether they have previously seen (1-3 trials earlier) serially presented images with affective content (ie, “n-level,” which varies by block), with occasional interspersed “switch” trials prompting them to respond instead to perceived image valence (identical to ESST go or no-signal trials).

Psychophysiology

During the administration of the computerized cognitive assessment tasks, we will gather 2 metrics of arousal—pupil dilation, which reflects phasic norepinephrine signaling; and skin conductance, an index of autonomic sympathetic nervous system activity—to evaluate the physiological correlates of cold and hot executive functioning. We will consider incorporating physiological reactivity variables gathered during the latter set of tasks as secondary indicators in exploratory mechanistic analyses of the hypothesized treatment effects (Multimedia Appendix 1).

Pupil measurements will be recorded noninvasively with a Tobii T-120 infrared eye tracker [74] using E-Prime Extensions for Tobii [75]. We will not gather pupillometry data from participants who report a history of epilepsy or seizures triggered by arcade or video games, computer or television screens, or flickering fluorescent bulbs. Skin conductance levels will be monitored by electrodes placed (by the participant) on the inner sole of the foot. Trained research staff will calibrate physiological recording hardware (eg, by ensuring proper electrode placement and adjusting a chin rest to limit movement-related artifacts) for maximum comfort and signal.

EMA Surveys

We will use EMA to capture the temporal dynamics of real-world affect and regulation using a probes delivered via REDCap. Each EMA survey will ask participants to complete (1) PANAS items to rate current levels of anxiety, irritability, and sadness on a 7-point Likert scale; (2) the Momentary Ruminative Self-Focus Inventory–Abbreviated [76], a 3-item questionnaire evaluating state-level fluctuations in rumination, each rated on a 7-point Likert scale; and (3) the Momentary Impulsivity Scale [77], a 4-item questionnaire measuring momentary impulsivity on a 5-point Likert-type scale. Our chief EMA emotion dysregulation indices, which we predict will decline from the preintervention assessment to the postintervention assessment, include the (1a) average levels of, and (1b) variability (ie, mean square of successive difference) in, daily negative affect (derived from mean scores on the mood probes); (2) average daily levels of rumination via the Momentary Ruminative Self-Focus Inventory–Abbreviated; and (3) average daily levels of ERI, as measured by Momentary Impulsivity Scale scores during periods of elevated momentary negative affect (ie, scores above the person-level mean).

We will provide an in-person tutorial at baseline to help familiarize participants with the structure and content of EMA surveys, and to facilitate the completion of practice items. Participants will use their personal mobile phones or other internet-capable devices to submit EMA responses. Specifically, participants will receive automatic “push” notifications to complete EMA surveys 5 times per day. We will randomize notifications by binning participants’ available waking hours into 5 equal windows and then randomly selecting a survey time within each bin, with an interval of at least 90 minutes between notifications. Surveys will be available for completion for 80 minutes, and reminder prompts will be sent within 40 minutes of missed survey notifications.

Questionnaires

After each in-person assessment session, we will ask participants to complete questionnaires administered via REDCap (Table 1) as promptly as possible. Each set of questionnaires includes primary and secondary outcome measures related to emotion dysregulation as well as measures of psychiatric symptom severity, perceived functional impairment in cognitive abilities and activities of daily living. The baseline assessment will also include potential moderators of treatment effects for exploratory analyses. We will ask participants who request premature withdrawal from the trial to complete an identical assessment of the major outcomes of interest (ie, self-rated emotion dysregulation, psychiatric symptom severity, cognitive deficits, quality of life, and treatment acceptability) at the time of discontinuation.

N-ACT Intervention

Overview

The N-ACT program comprises 8 in-person training sessions over 2 months. The intervention is limited to weekly 1 h sessions to maximize adherence and minimize attrition. Each N-ACT session is guided by a trained “coach” (supervised by a licensed clinician) who will explain intervention procedures and rationale, offer relevant psychoeducation, and use motivational interviewing principles to encourage and support participants. At each training session, participants will practice 2 computer-based adaptive tasks targeting affective control. Approximately half of each N-ACT session will be spent performing these exercises, and the other half will be dedicated to coaching and assessment. Coaches will discuss standard

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cognitive behavioral psychoeducational content regarding emotion regulation (drawn from established therapy protocols).

Psychoeducational Content

To begin each weekly N-ACT session, a coach will review information from the previous session and discuss the implementation of learned techniques over the prior week. Coaches will then present information from 1 psychoeducational module, adapted from empirically supported interventions, on the topics presented in Textbox 2. Modules 2 to 7 will also include theoretical justification for cognitive training to enhance emotion regulation.

Textbox 2. Topics covered in coaching sessions.

Coaching session sequence

1. Introduction and orientation, which includes an overview of session procedures and program structure, rationale, and personal goal setting
2. Cognitive behavioral approaches to emotion, which introduces fundamental concepts derived from cognitive behavioral therapy to elucidate links among affect, cognition, and behavior, plus an emotion regulation strategy (“STOP”) drawn from dialectical behavior therapy (DBT)
3. Environmental influences on feelings, in which participants identify risk and resilience factors that impede or facilitate emotional self-regulation, paired with distress tolerance skill adapted from DBT (“Self-soothing”)
4. Functional analysis of behavior, which involves functional analysis of problematic patterns of thought or behavior related to personal goals for emotion regulation
5. Mindfulness, involving a guided meditation practice
6. Psychological flexibility, which introduces key elements of acceptance and commitment therapy
7. Interpersonal skills, covering 2 closely related techniques (also borrowed from DBT) to promote adaptive emotional self-regulation and communication within relationships (“DEARMAN”)
8. Review, summary, and wrap-up, involving an examination of progress toward overarching treatment goals, review of key concepts, and solicitation of participant feedback on program components via interview and self-report

After engaging with psychoeducational content in each module, participants will complete the N-ACT tasks, and coaches will end each session with an informal debriefing to help consolidate learning and identify implementation intentions (ie, interim objectives toward participants’ identified treatment goal) for the coming week. Coaches will additionally administer the PANAS before and after the training tasks. We will audio record N-ACT training sessions (with participant consent) for regular review by independent raters to evaluate coach adherence and fidelity to the intervention guidelines using session-specific standardized forms created for this study.

N-ACT Task Battery

Overview

Participants will be asked to perform the same 2 computerized training tasks each week, in counterbalanced order: (1) an adaptive emotional n-back (AEnB) task targeting emotional working memory and (2) the ESST-adaptive (ESST-A), which targets emotional response inhibition. These are adaptive versions of the affective control behavioral measures completed during assessment sessions, modified to dynamically adjust the level of difficulty according to participant performance, which we expect to improve with additional training over time. Both training tasks include gamified graphical elements (eg, user-selected avatars) to facilitate user engagement (refer to Multimedia Appendix 1 for task instructions and other details).

The AEnB Task

The AEnB training task is an adaptive variant of procedures originally described by Levens and Gotlib [78,79], in which participants are instructed to indicate (as quickly and accurately as possible via keypress) whether a *target* affective picture stimulus is a “match” or a “mismatch” to a *cue* image shown *n* trials earlier, where *n* equals the number of interim trials between the presentation of the original cue and the to-be-evaluated target stimulus (ie, the “n-level”). The AEnB task additionally draws from an adaptive version of the dual-dimension emotional (n-back) working memory training task developed by Pan et al [53], such that cue-target pairs are only considered to match if the images are identical *and* spatially congruent, as each stimulus appears in 1 of 9 positions on an invisible 3×3 grid.

All AEnB task stimuli are pseudorandomly presented and counterbalanced to ensure equivalent numbers of matched and mismatched cue-target image pairs from 3 valence categories (neutral, negative, or positive) within each of 6 blocks, resulting in 36+n trials per block, or 216+n total trials. Image stimuli are shown for 1000 milliseconds on each trial, followed by a 2500-millisecond response window and a feedback screen shown for 1000 milliseconds. Trials are separated by a jittered intertrial interval of approximately 250 milliseconds (150-350 ms) assigned pseudorandomly on each trial.

The AEnB task involves 2 orthogonal adaptive components. The first is a tracking algorithm that adjusts the number of trials per condition (ie, emotional valence of cue-target pairs) to prioritize the encoding of spatial information (over affective content) into working memory for emotionally arousing images. Specifically, independent of the current n-level, higher accuracy for emotional (negative or positive) versus nonemotional (neutral) cue-target pairs will result in 2 fewer “match” trial pairs on the subsequent block. Crucially, the emotional images on these 2 trial pairs will remain identical but will be mismatched in spatial location. The algorithm will continue to swap matched emotional pairs with identical mismatched images until the participant achieves greater accuracy for neutral cue-target pairs (that are spatially congruent throughout the

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task), at which point the number of emotional trial pairs per condition returns to baseline, on a per-block basis, with 1 negative and 1 positive identical but spatially mismatched pair replaced by fully matched emotional cue-target pairs.

The second adaptive feature of the AEnB task is the n-level itself, which is adjusted after the first block either upward (n=3) or downward (n=2) at the start of each subsequent block (range: n=1-7), contingent on participants' accuracy and response times (with larger values indicating greater working memory load). Specifically, the n-level decreases if a participant is unable to achieve at least approximately 80% accuracy (ie, at least 30 correctly identified pairs out of 36+n trials) within a given block; conversely, once a participant surpasses this accuracy threshold, the n-level increases at the start of the next block but only if the mean reaction time during trials with neutral target stimuli is faster than that during trials with emotional stimuli (regardless of whether cue-target pairs are matched or mismatched, provided that responses are accurate). This training approach is intended to encourage the development of relatively more rapid—but equally accurate—evaluative responses to less arousing or salient images. In sum, the AEnB task involves multiple adaptive components designed to facilitate diminished stimulus reactivity or enhanced engagement of affective control when processing emotionally evocative stimuli (eg, via enhanced attentional focus on key perceptual features rather than affective information, per se) for immediate recall in working memory.

The ESST-A Task

The ESST-A is a training variant of the original ESST [37,39,43], with comparable design elements; however, the ESST-A is distinct in that emotional (negative or positive) image stimuli are presented exclusively on no-go or stop trials (n=60 per valence), and, conversely, neutral images are only shown on go or no-signal trials (n=90 per block over 4 blocks) without an inhibitory cue. Participants must accordingly terminate emotional reactions to the most arousing and evocative stimuli on the ESST-A. This unique design feature of the ESST-A is meant to facilitate implicit associative learning, wherein salient affective content serves as a reliable "cue" that predicts upcoming stop signals, while stimuli with neutral information are consistently delivered without accompanying inhibitory demand. Therefore, repeated training with the ESST-A is expected to promote more automatic, reflexive engagement of inhibitory control at earlier stages of emotional information processing.

Similar to the nonadaptive version, the ESST-A comprises 4 blocks of 120 trials each, with stimuli presented pseudorandomly and counterbalanced across blocks to ensure equivalent numbers of trials per condition. Each ESST-A trial spans 2000 milliseconds, which includes a fixed pretrial pause period of 500 milliseconds, followed by a central fixation cross displayed for approximately 250 milliseconds, depending on a jittered latency value assigned on a trial-by-trial basis (150-350 ms), comparable to the AEnB task. The target image stimulus replaces the fixation cross in the center of the screen, where it is displayed for 1250 milliseconds. The initial (50 ms) stop signal is presented 250 milliseconds after stimulus onset, separately for positive and negative stimuli.

The primary adaptive component of the ESST-A is identical to the assessment version of the ESST (and similar to other SSTs). Specifically, the ESST-A includes 2 independent staircase algorithms that adjust valence-specific stop-signal delay (SSD) values (ie, distinct tracking values for negative and positive images) in 50-millisecond increments depending on participant performance, such that successful inhibition results in a longer SSD on the next no-go or stop trial with the same type of image, thereby increasing inhibitory demand. By contrast, commission errors (ie, false alarms) shorten each SSD by 50 milliseconds on subsequent no-go or stop trials with images from the same emotional valence category. These 2 stepwise algorithms are programmed to maintain commission error rates at approximately 50% of the no-go or stop trials, separately for negative and positive images, which enables calculation of valence-specific indices of emotional response inhibition (ie, stop-signal reaction time).

Data Quality Assurance

The screening survey and assessment questionnaires will randomly incorporate simple "attention checks" (eg, "2 + 2 = ?" and "for our data quality checking, please answer '1' to this question") to identify patterns of careless responding, which we will supplement by manual review to confirm the validity of self-report data. As previously noted, we will exclude participants who demonstrate patterns of careless responding during the screening questionnaire. Before conducting statistical analyses, research staff will perform comprehensive data cleaning and processing procedures as needed (eg, ascertaining violations of distributional assumptions for parametric tests and comparison with published norms).

Training and Reliability

Our team has comprehensive preparation procedures for all staff members involved in data collection. Before study recruitment, N-ACT coaches will receive extensive training in each session-specific intervention module to promote protocol adherence. Coach training and group supervision will comprise regular team-based meetings led by clinically licensed investigators, with didactic instruction, role-play, the development of interrater reliability to evaluate coach fidelity, and a review of practice tapes by senior researchers. We will conduct session adherence evaluations (as a group) monthly and provide retraining as necessary to address drift.

Risk Management

Overview

Trial procedures are designed to balance respect for participants' autonomy with the need for safety. Study consent forms will provide contact information for crisis hotlines and other mental health resources. We will offer referral assistance to interested individuals. All team members with direct participant contact will receive training regarding psychiatric emergencies, suicide risk assessment, and crisis management. A detailed manual will provide assessment probes, decision rules, referral resources, and contact information for use during emergency situations. Training will emphasize procedures for providing feedback in a clinically sensitive manner, and senior investigators will use role-play to demonstrate fundamental principles related to

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assessment, obtaining supervision, providing referrals, and preparing documentation according to legal and ethical guidelines. This training will cover circumstances in which staff are permitted to breach confidentiality to contact emergency services.

Research assistants and coaches will be trained to carefully monitor cues indicating participant distress or discomfort, and we will offer breaks or opportunities to reschedule as warranted for fatigue or distress. Participants who endorse significant distress or endorse active suicidal ideation will be given the opportunity to speak with clinically licensed senior investigators, who will evaluate and determine the need for further follow-up. Research staff will work with these participants to develop a plan to obtain support, which may include strategies for discussing symptoms with their current provider, removing access to lethal means, and the provision of feedback or referrals. Our team has developed relationships with local sites to facilitate referral for individuals with insurance or those without; after referral, we will follow up with these participants as warranted to ensure that they received sufficient support.

Adverse Events

We will describe the limits of confidentiality as part of informed consent procedures to minimize the likelihood of study-related adverse events. During the consent process, we will also emphasize that our team is unable to provide emergency services or review research data in real time, and it is therefore important for participants to have access to other sources of care. Consent documents will encourage participants to contact the senior investigators with any concerns.

Throughout the trial, N-ACT coaches will also informally solicit information about potential issues at each training session. We will formally assess adverse events at the postintervention session. We will follow up with participants who show apparent clinical deterioration and will attempt to determine whether emergent symptoms or concerns might be somehow connected to study procedures. Adverse events will be reported to the university's Committee for the Protection of Human Subjects within 1 week.

Measures

Screening

The screening survey will include a demographic questionnaire to assess inclusion criteria in addition to the self-report measures outlined in the following subsections.

Mental Health History Survey

The mental health history survey includes items to identify individuals whose linguistic abilities or cognitive, neurological, or psychiatric condition might interfere with completing study procedures or fully engaging in the intervention.

C-SSRS, Screen Version

The screening includes the self-report screen version of the C-SSRS [67], a well-validated and widely used instrument designed to assess suicidal thoughts and behaviors. Endorsement of the C-SSRS ideation item (Have you actually had any thoughts of killing yourself?) will trigger 3 follow-up items, to cover past-month presence of an identified method, intent, and a specific plan. Responding affirmatively to any of these 3 items will result in automatic study exclusion. Regardless of their responses, all participants will be asked an item to evaluate lifetime history of suicidal behavior; those who endorse this item in addition to past-month active suicidal ideation will also be automatically excluded from study participation.

PDSQ Prompts

The screening survey includes the Psychosis, Alcohol Use Disorder, and Substance Use Disorder scales of the PDSQ (6 *yes* or *no* items per scale) [66]. Questions regarding psychosis refer to the previous 2 weeks, and substance-related questions cover the previous 6 months. Prospective participants who respond affirmatively to at least 1 of these prompts (on any of the 3 PDSQ scales) will be automatically excluded, based on established clinical cutoffs for this measure [62].

Ruminative Responses Scale–Brooding

The Ruminative Responses Scale–Brooding (RRS-B) [13] will be used to assess study inclusion criteria. The RRS-B comprises 5 items to evaluate the dispositional propensity to engage in past-oriented patterns of repetitive negative thinking. Respondents rate prompts on a scale ranging from 1 (*almost never*) to 4 (*almost always*) based on characteristic reactions to dysphoric mood described by each item.

Three-Factor Impulsivity Index

Eligibility will be further determined using the Feelings Trigger Action (FTA) scale of the Three-Factor Impulsivity Index (TFII) [9], a 54-item multidimensional measure of trait-like impulsiveness that asks respondents to rate their agreement with each prompt on a scale of 1 (*I disagree a LOT*) to 5 (*I agree a LOT*). FTA includes 26 items describing tendencies to engage in impulsive speech and action in response to emotional states. The TFII includes 2 additional scales derived from factor analysis: Pervasive Influence of Feelings, which comprises 9 items reflecting powerful cognitive and motivational responses to emotion; and Lack of Follow Through, which captures distractibility and lack of perseverance. Pervasive Influence of Feelings is included as a secondary measure of emotion dysregulation (assessed in conjunction with FTA, at baseline).

Emotion Dysregulation

Our primary measures of emotion dysregulation will comprise self-reported rumination (RRS-B) and ERI (FTA). The secondary indices of emotion dysregulation further include EMA indices of daily negative affect, rumination, and ERI, in addition to scores on questionnaires capturing conceptually related constructs (Multimedia Appendix 1).

Psychiatric Symptom Severity

Participants will complete the following questionnaires at baseline, postwaitlist, and postintervention time points to evaluate the hypothesized clinical effects of N-ACT (refer to Multimedia Appendix 1 for the secondary symptom outcome measures).

Externalizing Spectrum Inventory–Revised

The Externalizing Spectrum Inventory–Revised (ESI-R) [80] is a 100-item questionnaire that covers 23 facets of externalizing

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psychopathology, including aggression, alcohol and other substance use problems, and fraudulent behavior. Respondents rate each ESI-R item as *true*, *mostly true*, *mostly false*, or *false*. Items referring to impulsivity (ie, redundant with the TFII) will not be included in the scale totals.

Inventory of Depression and Anxiety Symptoms, Expanded Version

The 99-item Inventory of Depression and Anxiety Symptoms, Expanded Version [81], is a validated questionnaire that assesses various emotional syndromes across the internalizing spectrum of psychopathology (eg, anxiety, depression, obsessions and compulsions). This instrument produces scores on 3 major factors (distress, fear, and mania), which are each composed of multiple subfactors (18 in total).

Statistical Analysis Plan

Our final target sample size (n=80) was derived from power analysis (1-β>0.85), based on hypothesized medium between-groups effect sizes (Cohen d=0.35) for the main outcomes of interest (α=.05). Before conducting the analyses, data will be checked for errors, statistical assumptions, and potential confounding variables to examine as covariates. Missing data imputation will also be performed as appropriate; we will present the results with and without imputed values for comparison. Our primary analyses will follow the International Conference on Harmonization E9 statistical principles for clinical trials. In accordance with these principles, we will use intention-to-treat analyses to estimate the main effects of N-ACT, using the final assessment scores of all randomized participants. To augment these findings, we will conduct sensitivity analyses restricted to data from participants who complete preintervention and postintervention assessments and at least 6 of the 8 weekly N-ACT sessions.

Descriptive statistics will be calculated to address the preliminary hypotheses regarding N-ACT's acceptability and adherence. Mean scores on the Interest or Enjoyment and Value or Usefulness subscales of the adapted Intrinsic Motivation Inventory [82] will serve as our main indices of the N-ACT program's acceptability (H1); specifically, we predict that participants who complete the intervention will provide average ratings of at least 5 (out of 7) across both scales. We further hypothesize that N-ACT participant adherence and retention will be comparable to those observed in other cognitive remediation interventions (H2); specifically, we anticipate median person-level adherence levels between 70% and 75%, which we expect to decrease at the group level by approximately 5% each week [63,64], with most participants (ie, >66%) completing all 8 N-ACT training sessions [33,52]. Consistent with other cognitive remediation protocol procedures [63], we will calculate percentage adherence for each participant as a function of the number of *completed* N-ACT training task trials divided by the *total* number of trials, that is, individual differences in the "dosage" of training.

We will consider potential confounds before testing key hypothesized effects. Of particular import, we will examine whether participants differ significantly in treatment gains based on assignment to a specific training coach and control for this unintended influence as necessary. Specifically, we will use multivariate analysis of covariance (MANCOVA) to explore the effect of coach assignment (independent variable) on postintervention emotion dysregulation (ie, scores on the TFII-FTA and RRS-B; dependent variables), controlling for scores at initial screening.

The core aim of this pilot trial is to determine whether N-ACT significantly reduces ERI and rumination, as measured by the TFII-FTA and RRS-B, respectively (H3). To achieve this aim and the related objective to explore potential mechanisms, we will conduct parallel 2 (group: immediate N-ACT vs waitlist control condition; between-subjects factor)×2 (time: T1 vs T2; within-subjects factor) mixed MANCOVAs to evaluate whether N-ACT completion is associated with greater pre-postintervention improvement in these 2 primary outcomes compared to the waitlist control condition. Among all participants, T1 will represent data collected at the baseline assessment; for participants assigned to the immediate N-ACT group, T2 refers to the postintervention assessment, whereas for those assigned to the control condition, T2 refers to the postwaitlist assessment. Thus, these models will not include postintervention data for participants initially allocated to the waitlist, permitting direct comparisons of the slope of change over time associated with completing N-ACT or the waitlist period. The key index of treatment effect in all MANCOVA models will be the group×time interaction. We will also perform a parallel set of multivariate cluster-robust general linear models with time (T1: baseline time point vs T2: postintervention time point) as the sole regressor on key outcomes of interest, which will include all participants who complete N-ACT (regardless of initial group or condition assignment) to maximize statistical power.

In addition to testing the hypothesized effects on emotion dysregulation, mixed MANCOVA and multivariate cluster-robust general linear models will be used to evaluate performance changes over time on (1) 2 hot executive functioning tasks (ESST and MAFT), which will be used to assess the hypothesized effects on the targeted aspects of affective control (H4); and (2) one hot (MAFT) and 2 cold (Digit Span Backward and SST) executive functioning tasks, which will be used to ascertain transfer to the nontargeted cognitive processes (H5). We will specifically derive key dependent variables from the ESST (valence-specific indices of stop-signal reaction time) and the MAFT (valence-specific indices of accuracy) to assess intervention-related changes in emotional response inhibition and emotional working memory, respectively. We will similarly calculate summary metrics of hot affective flexibility from the MAFT (valence-specific indices of accuracy and reaction time on less frequent "switch" trials prompting emotional reactions instead of working memory recall [73]) as well as cold working memory, updating from the Digit Span Backward (mean span) and cold response inhibition from the traditional SST (stop-signal reaction time) to evaluate near and far transfer of hypothesized N-ACT training effects, respectively.

Finally, we will perform a complementary set of secondary analyses (ie, mixed MANCOVA and multivariate cluster-robust generalized linear models) to explore the hypothesized

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downstream effects of N-ACT on changes in psychiatric symptom severity (H6). We will use dimension-reduction techniques (eg, confirmatory factor analysis) to extract the summary indices of internalizing and externalizing symptoms from the Inventory of Depression and Anxiety Symptoms, Expanded Version and ESI-R, respectively. Statistical models will use these latent factors as dependent variables, potentially providing preliminary evidence for the efficacy of affective control training as a transdiagnostic intervention to address psychopathology (via diminished emotion dysregulation; refer to Multimedia Appendix 1 for more information). Support for this hypothesis will motivate future work to more directly and precisely examine the effectiveness of the N-ACT program in sufficiently powered samples of patients with psychiatric conditions.

Results

This trial is funded by support from the University of California Board of Regents and the Peder Sather Foundation (funding period: October 2022-September 2025). Recruitment is scheduled to begin in spring 2025. We will begin data analysis once data collection is complete, which is planned to occur in fall 2025. We anticipate publishing the findings in 2026.

Discussion

Summary

This randomized waitlist-controlled trial extends cognitive remediation research by testing a novel intervention program focused on facets of hot cognition typically unaddressed in this body of work. The trial will also be novel in testing a transdiagnostic sample comprising individuals with emotion regulation difficulties. Drawing on a substantial theoretical and empirical literature, we aim to modulate 2 aspects of affective control (ie, emotional working memory and emotional response inhibition) putatively underlying the problems with emotional self-regulation strongly implicated in common forms of psychopathology. Given the low cost, minimal coach training requirements, and relatively simple delivery of the N-ACT program, success in this project has major implications for reducing the public health burden associated with prevalent psychiatric conditions—as well as subclinical distress or dysfunction—involving tendencies toward rumination or ERI.

If our findings align with our hypotheses, this pilot trial will provide early data to support the further refinement and larger-scale deployment of N-ACT in a fully powered randomized clinical trial of patients with psychiatric conditions. Our findings will help identify the levels of interest and adherence and may suggest components that need to be refined for greater acceptability. Beyond the results concerning change in cognitive processes, we hope to learn more about how cognitive changes generalize to psychopathological outcomes. The profile of effects may help us understand which participants would be most likely to benefit from inclusion in future trials.

Limitations

The potential impact of this work should be considered in the context of several limitations. Regarding the study sample, we will make every effort to maximize participant diversity and, accordingly, the generalizability of our findings; however, the modest target sample size (n=80) for this pilot trial will constrain our ability to ensure adequate representation of all psychiatric symptom types and severity levels. Relatedly, patients with acute symptoms of alcohol or substance use disorders and psychosis will be excluded. Additional studies will thus be necessary to elucidate the putative mechanisms identified in this work. Although our protocol incorporates a variety of well-validated multimodal measures to assess key constructs, 1 of the 2 primary behavioral outcomes will be derived from the MAFT, which is a novel task developed for this study. This limitation is somewhat lessened in that the MAFT includes design elements drawn from existing tasks that are widely used to index working memory and shifting and switching (eg, other emotional n-back procedures [73]). Finally, we see 2 core needs for enhancing the N-ACT intervention if the initial findings are promising. The current N-ACT intervention is limited in its scope of training around transfer to real-world tasks. Others have more extensively integrated ecological elements into cognitive remediation programs, including simulated work situations [83] and compensatory transfer sessions to supplement computerized training procedures [84]. Future work might help clients practice their skills in the context of mood inductions as a method to facilitate skills transfer. It will also be important to consider gamification [85,86] and other techniques to enhance the appeal of training programs.

Conclusions

In conclusion, this study represents an important step in translating knowledge from basic affective science to produce interventions (with empirically informed treatment targets) that can be widely disseminated and easily implemented. This area of research is promising, given the need for alternative approaches to improve mental health because a substantial portion of patients do not seek nor respond to traditional treatment modalities. In addition, current rapid technological advancements, such as the proliferation of accessible and affordable mobile devices capable of delivering cognitive training, support the feasibility of digital therapeutics. Therefore, N-ACT has the potential to reduce barriers to mental health treatment, particularly among people from underserved groups or cultures with persistent stigma against talk-based psychotherapy as well as those who may be more amenable to computerized interventions for various reasons (eg, youth and patients with social phobia). Crucially, we expect N-ACT to have transdiagnostic applications, given that the program's central aim is to address emotion regulation problems, which include shared features across a broad range of psychopathologies. We hope that establishing efficient and cost-effective means of modulating these common risk factors might eventually facilitate prevention among individuals considered vulnerable before diagnosable psychiatric disorders emerge.

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Data Availability

The datasets generated and analyzed during this study will be available in this project's Open Science Framework repository [87].

Authors' Contributions

KJDA, MVE, EHR, AH, and SLJ were responsible for conceptualization. KJDA, EHR, AH, and SLJ were responsible for funding acquisition. KJDA, MVE, EHR, LM, AH, and SLJ were responsible for methodology. KJDA, NR, and SLJ were responsible for project administration. SLJ was responsible for resources. KJDA, MVE, and SLJ were responsible for supervision. KJDA and SLJ wrote the original draft of this manuscript. All authors reviewed the final manuscript.

Conflicts of Interest

KJDA is the director of Brain Health Consulting, which provides consultation on neurocognitive approaches to mental health assessment and intervention. The neurobehavioral affective control training program is not currently being offered through Brain Health Consulting.

Multimedia Appendix 1
Additional details on measures, tasks, and secondary analyses.
[DOCX File , 41 KB - resprot_v14i1e54221_app1.docx]

Multimedia Appendix 2
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 414 KB - resprot_v14i1e54221_app2.pdf]

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Abbreviations

AEnB: adaptive emotional n-back
C-SSRS: Columbia Suicide Severity Rating Scale
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
EMA: ecological momentary assessment
ERI: emotion-related impulsivity
ESI-R: Externalizing Spectrum Inventory–Revised
ESST: emotional stop-signal task
ESST-A: emotional stop-signal task–adaptive
MAFT: memory and affective flexibility task
MANCOVA: multivariate analysis of covariance
MDD: major depressive disorder
N-ACT: neurobehavioral affective control training
PANAS: Positive and Negative Affect Schedule
PDSQ: Psychiatric Diagnostic Screening Questionnaire
REDCap: Research Electronic Data Capture
RRS-B: Ruminative Responses Scale–Brooding
SSD: stop-signal delay
SST: stop-signal task
TFII: Three-Factor Impulsivity Index

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Protocol

Evaluation of Comparative Efficacy of Polyherbal Steam Inhalation Versus Polyherbal Nasal Fumigation (Dhoopana) in Children With Rhinitis (Pratishyaya): Protocol for an Open-Label Randomized Controlled Trial

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Abstract

Background: Rhinitis is a condition characterized by inflammation of the nasal mucosa. It causes obstruction and congestion in the nasal cavity. Clinically, it resembles *pratishyaya* (rhinitis) in Ayurveda, which is caused by accumulation and downward movement of the *tridoshas* (3 elements, named *vata*, *pitta*, and *kapha*) in the nasal cavity. Rhinitis is one of the most common diseases among children. There is no role for antibiotics in rhinitis, and nasal decongestants have also not been found to be effective in its management. In Ayurveda, *dhoopana* (nasal fumigation) is mentioned in the *pratishyaya* treatment protocol. However, we have found no previous study regarding its efficacy. The efficacy of *tulsi*, *vasa*, *nirgundi*, and *nilgiri* is already proven when they are used for steam inhalation in respiratory tract infections. Therefore, in this study, a *dhoopana* of a polyherbal formulation containing *tulsi*, *vasa*, *nirgundi*, and *nilgiri* will be compared with the inhalation of steam containing *arka* (a liquid obtained by distillation) of *tulsi*, *vasa*, *nirgundi*, and *nilgiri* leaves in children with *pratishyaya*.

Objective: We aim to evaluate the efficacy of polyherbal steam inhalation as a standard control against *dhoopana* in children aged 7 to 14 years with *pratishyaya*.

Methods: A total of 70 participants fulfilling the inclusion criteria were selected and distributed into 2 groups of 35 each. The intervention group received *dhoopana* and the control group received polyherbal steam inhalation, both twice daily for 7 days. The primary outcome measure was the change in Total Nasal Symptom Score and a modified cold spatula test. At the same time, the association between *prakriti* (body constitution) and the prevalence of *pratishyaya* in children was analyzed as a secondary outcome. Assessments were performed on days 3, 5, and 7, with a follow-up time of 28 days. Appropriate descriptive and inferential statistics will be used for data analysis.

Results: As of November 2024, we have completed our enrollment of 70 patients, with 35 patients in each group. Data analysis will be completed by February 2025, and we expect results to be published in March 2025.

Conclusions: We anticipate that polyherbal nasal fumigation will be found to be equally as effective as polyherbal steam inhalation in the management of acute rhinitis in the pediatric population. This study may provide a standardized, herbal, safe, and cost-effective treatment for rhinitis in children in the form of *dhoopana*.

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KEYWORDS

pratishyaya; Ayurveda; allergic rhinitis; rhinitis; dhoopana; nasal fumigation; steam inhalation; polyherbal; vasa; nirgundi; nilgiri; tulsi; sneezing; nasal cavity; nasal decongestants; evaluation; efficacy; child; adolescent; randomized controlled trial

Introduction

Overview

Rhinitis is defined as inflammation of the nasal mucosa due to any infection, allergy, or injury. Symptoms of rhinitis are sneezing, discharge from the nose, obstruction in the nasal cavity, irritation in the nasal cavity, body ache, a feverish sensation, and headache [1]. As per Ayurveda, a clinical picture of rhinitis is seen in the disease *pratishyaya*. It is one of the *nasagata roga* (nasal disorders) in which *kaphadi tridoshas* (the 3 elements of the body) are continuously eliminated through the nose. These vitiated *doshas* accumulate in the head, and their further movement toward the nose causes *pratishyaya* [2]. According to Acharya Charaka, the definition of *pratishyaya* is "*pratikshnam shyayatiitipratishyaya*," which means the "continuous outward movement of *vata*, *pitta*, and *kapha* doshas from the nostrils." The prevalence of nonallergic rhinitis is about 40% [3]. The prevalence of allergic rhinitis in India was reported as "11.3% in children aged 6-7 years and 24.4% in children aged 13-14 years" [4]. Acharya Videha explained the clinical presentation of *pratishyaya* as excessive secretions from the nasal cavity and eyes, fever, and generalized weakness with severe headache [2]. *Pratishyaya* is classified into 5 types: *vataja*, *pittaja*, *kaphaja*, *sannipataja*, and *raktaja pratishyaya* [2,5]. The nasal mucosa has a rich blood supply, and stimulation of the sympathetic nervous system causes vasoconstriction that results in shrinkage of the nasal mucosa on the other side, while stimulation of the parasympathetic nervous system is responsible for excessive secretion from the nasal mucosa along with dilatation of local vessels. Emotional disturbance also plays a significant role, as the autonomic nervous system innervation of the nasal mucosa is under the control of the hypothalamus [3]. If no treatment is given at an early stage, the condition may become complicated and lead to comorbid conditions like chronic rhinitis, cough, or breathing difficulty and debility [2]. There is no use of antibiotics in acute rhinitis [6]. Antihistamine decongestants are frequently used in cough and cold. However, in some studies, these were not found to be effective in the management of rhinitis [7]. There are limited data regarding the safety of pseudoephedrine and phenylephrine in rhinitis [8]. In Ayurveda, various oral medications are available for the management of this condition. However, it is difficult to administer Ayurvedic medicines orally to children. So, this study has been planned to find an effective way to manage the acute stage of rhinitis that can be administered locally in the nasal cavity. Various Ayurvedic interventions are mentioned in the Ayurveda classics as protocols for the management of *pratishyaya*, including *dhoopana* (nasal fumigation), an intervention that can effectively manage the disease. In this intervention, various herbs are made into a stick known as a *varti* (wick), and its fumes are used for local fumigation of the affected area. It can be considered an Ayurvedic therapy that delivers the medicines directly into the airways, providing relief and protection to the local region [9].

Pratishyaya treatment should be aimed at relieving the *avarodha* (obstruction) created by the dosha. Drugs having *ushna* (hot) and *tikshna* (pungent) properties are indicated in *dhoopana*. The efficacy of steam inhalation of *tulsi*, *vasa*, *nirgundi*, and *nilgiri* has already been shown in respiratory tract infections [10]. So, in this study, *dhoopana* of a polyherbal formulation containing *tulsi*, *vasa*, *nirgundi*, and *nilgiri* will be compared with a steam inhalation containing *arka* of *tulsi*, *vasa*, *nirgundi*, and *nilgiri* in *pratishyaya* in children. *Kashyapa Samhita* (an Ayurveda classical text) is mainly devoted to the Kaumarbhritya branch (Ayurvedic pediatrics) of Ashtanga Ayurveda, and *dhoopana* is described in the treatment protocol of *pratishyaya* [11]. There are many studies regarding the efficacy of oral medication in *pratishyaya* but there is no previous study available regarding the efficacy of local fumigation with medicated fumes in *pratishyaya* in children. Steam inhalation has a known soothing effect on the nasal mucosa in rhinitis. Herbal steam inhalation is more effective as compared to plain water steam inhalation [12], but steam inhalation is quite difficult to administer in children. So, in this study, we plan to compare the effect of polyherbal steam inhalation with polyherbal fumigation in children with *pratishyaya*. The herbs chosen for *dhoopana* were justified in previous studies, as steam inhalation of *tulsi*, *vasa*, *nirgundi*, and *nilgiri* was found to be effective for reducing local inflammation in the nostrils. A detailed description of previous articles and a research gap analysis with justification for this study is given in Table 1.

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Table 1. Previous studies and research gap analysis.

Reference	Conclusion	Remark
Memon [13]	*Vyoshadi vati* was found to be effective in reducing signs and symptoms of *pratishyaya* (rhinitis) in comparison with chlorpheniramine maleate in children aged 4-8 years.	Children tend to resist the intake of medicines orally in most cases, especially when they are sick. So, local fumes or steam inhalation could be a better choice.
Tarun and Anup [14]	*Nasya* with *tulasi swarasadi taila* and *haridrakhand* showed 100% results in objective as well as subjective parameters of *pratishyaya*. *Tulasi swarasadi taila nasya* and *haridrakhand* gave effective results in treating *pratishyaya*.	As *tulsi* has an anti-inflammatory effect and was found to be effective in the management of *pratishyaya*, and the *nasya* procedure is contraindicated in the acute stage, fume inhalation can be done with the use of *tulsi* in place of *nasya karma*. Local fume inhalation can provide instant relief for the symptoms of *pratishyaya*.
Rajput and Patni [15]	According to Acharya Charaka, any drug when instilled into the nostrils causes direct action in the brain; hence, it is highly effective in the treatment of various diseases related to the nervous system and supraclavicular region. The *nasya* procedure is indicated in *pratishyaya*. Standardization of *nasyakarma* with Ayurveda and modern scientific parameters with proper documentation is a current need.	*Nasya* is widely used in rhinitis but it is contraindicated in its acute stage. Moreover, it is quite difficult to administer to children. Direct contact with oil in the nostrils sometimes irritates children. In this study, acute cases were mentioned in the inclusion criteria, so local fumes could provide a better approach to the treatment of *pratishyaya*. Moreover, local nasal fumigation is described in the treatment protocol of *pratishyaya*, but no previous study has been done to determine its efficacy in rhinitis.
Kamble et al [16]	Steam inhalation of *tulsi* leaves was found to be more effective in reducing sign and symptoms of cough and cold in adults than steam inhalation of plain water.	*Tulsi* steam inhalation was found to be better than plain steam inhalation in the adult population. This shows that volatile herbs like *tulsi* have better efficacy when given locally in the form of vapors. Steam inhalation is also easier to administer in children. So in this study, *tulsi* was chosen as one of the herbs for fume as well as steam inhalation.
Kumar Dwibedi et al [17]	Initially, there was mild relief in symptoms. Gradually, improvement was seen in signs and symptoms at further appointments. In the last appointment, the patient felt relief and could perceive smells.	Atrophic rhinitis is a chronic stage of *pratishyaya*; hence, a combination of *nasya* and *dhoompana* was given to the patient. *Trikatu dhoompana* was found to be effective in the management of the disease in the chronic stage. Thus, *dhoopana* (nasal fumigation) should only be given to children in the acute stage of *pratishyaya*.
Gowrishankar et al [10]	Phytochemicals from selected plants were found to be effective against protein targets of COVID-19.	In an in silico study, the active components of *vasa*, *nirgundi*, and *nilgiri* were found to be effective against protein targets of SARS-CoV-2. Hence, these herbs were chosen for the intervention as well as the control group.
Swain and Sahu [18]	There was improvement in symptoms of COVID-19 after taking steam inhalation. The severity and duration of infection was reduced after steam inhalation. It was found to be a ray of hope in that pandemic.	This was a nonrandomized, nonclinical trial. The study was performed along with oral medications for COVID-19 without confirming the efficacy of steam inhalation alone. So there is a need for a study of herbs as a single therapy in children. This study is a randomized clinical trial with the use of polyherbal steam inhalation in the control group of children without oral medication.
Berger et al [19]	The intranasal formulation of azelastin and fluticasone propionate was found to be safe for administration in children, and it was well tolerated for 3 months by children with allergic rhinitis.	Epistaxis was reported as a treatment-related adverse effect in both groups, followed by headache and other adverse effects. Herbal procedures are quite safe and effective. Local polyherbal fume administration can be an alternative.
Sebastian and Sujatha [20]	The study showed that steam inhalation with *tulsi* leaves is effective in relieving symptoms of coryza compared to hot water steam inhalation in children aged 6-12 years.	The study was performed in a selected community with a small sample size, and no randomization was done. Steam inhalation was administered for only 3 days. The follow-up time was not mentioned in the article. This study is a randomized clinical trial, and *tulsi* along with *nilgiri*, *nirgundi* and *vasa* will be used for steam inhalation in the control group for 7 days with a follow-up of 28 days.
Macchi et al [21]	A statistically significant improvement was seen in ciliary motility in the first group, who received a nasal wash with sodium hyaluronate in saline solution ($P<.001$).	This was a pilot study with very small sample size. Moreover, the study included patients with recurrent upper respiratory tract infections; there was no specific disease chosen for the study. Aerosol use was indicated in lower respiratory tract infection, as there was a chance of the medicine entering the lungs. In our study, only *pratishyaya* cases will be included, rather than all patients with respiratory tract infections. Polyherbal fumes will be administered in the trial group, which could be a better alternative to aerosols.

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Reference	Conclusion	Remark
Baartmans et al [22]	Annually, on average 3 people are admitted to a Dutch burn center for burns resulting from steam inhalation therapy. Most patients are children, and they need skin grafting more often than adults. At burn centers in the Netherlands, 31 patients were admitted with burns caused by steam inhalation therapy in the 1998 to 2007 period.	These data show that steam inhalation can result in burns, especially in children. So, in our study, we plan to find if *dhoopana* can be an alternative.
Murphy et al [23]	Between July 1 and December 31, 2002, 7 children were admitted to the burn unit of a children's hospital in Dublin with scalds sustained during the course of steam inhalation. The children ranged in age from 9 months to 10 years. Techniques involving kettles or bowls of boiling water should be actively discouraged.	The common technique of steam inhalation is risky in children as it may cause burns. So, in our study, we plan to find an easier way to administer herbal effects to the nasal mucosa through *dhoopana*.

Aim

We aim to study the efficacy of polyherbal steam inhalation versus *dhoopana* in children with *pratishyaya*.

Primary Objectives

There are 3 primary objectives: first, to determine the efficacy of *dhoopana* in reducing signs and symptoms of *pratishyaya* compared to polyherbal steam inhalation; second, to study the duration of alleviation of Total Nasal Symptom Score (TNSS); and third, to determine the efficacy of *dhoopana* in the reduction of nasal obstruction in a modified cold spatula test.

Secondary Objectives

There are 2 secondary objectives: first, to study the prevalence of *pratishyaya*, its origin, and its causative factors, such as viruses, bacteria, or allergies; second, to analyze the association between *prakriti* (body constitution) and the prevalence of *pratishyaya* in children.

Hypothesis

The alternate hypothesis is that *dhoopana* has equivalent efficacy to polyherbal steam inhalation in reducing the signs and symptoms of *pratishyaya* in children aged 7-14 years. The null hypothesis is that *dhoopana* does not have equivalent efficacy as polyherbal steam inhalation in reducing the signs and symptoms of *pratishyaya* in children aged 7-14 years.

Trial Design

This will be a randomized, reference, controlled, open-label equivalence clinical study. A total of 70 patients have been recruited for the study.

Methods

Recruitment

The patients were selected from the outpatient and inpatient departments of the Department of Kaumarabhritya (Ayurvedic pediatrics) of Mahatma Gandhi Ayurveda College, Hospital & Research Centre and from the surrounding region. After initial screening, the patients were randomized using computer-generated random numbers into 2 groups; the control group (polyherbal steam inhalation) and the intervention group (polyherbal nasal fumigation). All baseline parameters were recorded at the start of the study. Both groups underwent treatment for 7 days. All the parameters were recorded on the third, fifth, and seventh days, with a follow-up of 28 days after the treatment period. Patients were advised to drink warm water and stay away from cold and sour items. Patients were given regular counseling and reminders through calls or messages to follow the rules and regulations of the trial.

Guidelines

This study used the Consolidated Standards of Reporting Trials (CONSORT) guidelines; Figure 1 shows a flow diagram of the study.

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Figure 1. Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

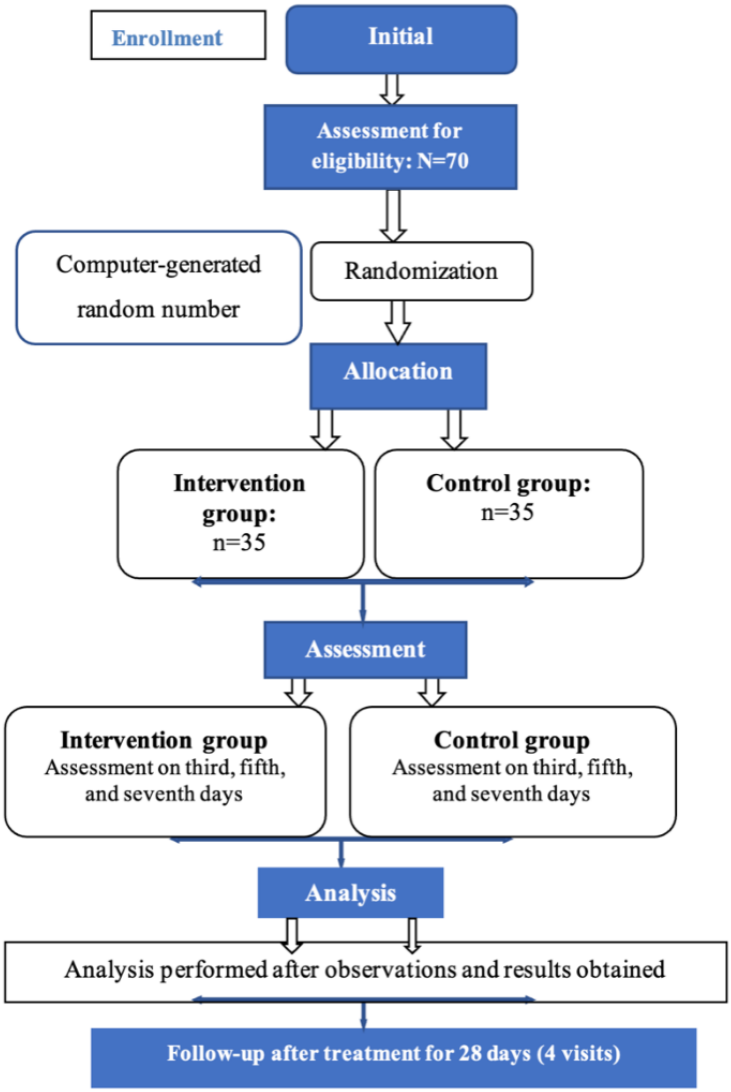

Grouping and Dosage

Grouping and dosage are described in Table 2.

Table 2. Grouping and dosage.

	Control group (polyherbal steam inhalation)	Intervention group (*dhoopana*; polyherbal nasal fumigation)
Participants, n	35	35
Name and details of the medication	*Arka* is prepared from *tulsi*, *vasa*, *nirgundi*, and *nilgiri*. In participants with mild symptoms, 2.5 ml *arka* is added to 500 ml of water, and in those with moderate to severe symptoms, 5 ml *arka* is added to 500 ml of water for steam inhalation.	*Dhoomvarti* (polyherbal wick) prepared from dry leaves of *tulsi*, *vasa*, *nirgundi*, and *nilgiri*.
Mechanism of delivery	Steam	Fumes
Duration	1 minute for mild symptoms and 1.5 minutes for moderate to severe symptoms.	1 minute for mild symptoms and 1.5 minutes for moderate to severe symptoms.
Route/mode of administration	Nostrils	Nostrils
Frequency	Twice daily	Twice daily

Inclusion Criteria

Children of either sex aged between 7 to 14 years whose parents provide written consent for enrolling their child in the study will be included if they have had the common cold with features of *pratishyaya* for 7-10 days.

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Exclusion Criteria

Patients will be excluded if they have had the common cold for more than 10 days or if they have chronic allergic rhinitis, *dushta pratishyaya* (chronic rhinitis with complications), *raktaja pratishyaya* (a type of rhinitis with dominance of the blood element), *sannipataja pratishyaya* (rhinitis with involvement of all 3 elements), or infectious diseases such as tuberculosis. Patients will also be excluded if they have a cleft palate, a deviated nasal septum, or nasal polyps, or if they are hypersensitive to the trial drug or any of its ingredients.

Drug Collection and Authentication

The raw material for the drug was purchased from a reliable source and authenticated and identified by the Department of Dravyaguna and Rasashastra. Details of the raw ingredients are provided in Table 3 and images are shown in Multimedia Appendix 1.

The *dhoomvarti* (polyherbal wick) for nasal fumigation and *arka* (for steam inhalation) from *tulsi*, *vasa*, *nirgundi*, and *nilgiri* leaves were prepared as per the classical methods and standard protocol at the Mahatma Gandhi Ayurveda College and Hospital and were analyzed in a pharmaceutical laboratory. The method of drug preparation is described in Figure 2.

Arka of the leaves of *tulsi*, *vasa*, *nirgundi*, and *nilgiri* was prepared by using a distillation process. Parents of the patients were counseled and trained regarding the administration of *dhoopana* and steam inhalation at their homes.

Table 3. Latin name and family name of the herbs used for nasal fumigation and steam inhalation

Serial No.	Drug	Latin name	Family
1	*Tulsi*	*Ocimum sanctum* Linn	Lamiaceae
6	*Nirgundi*	*Vitex negundo* Linn	Verbenaceae
7	*Vasa*	*Adhatoda vasica* Nees	Acanthaceae
8	*Nilgiri*	*Eucalyptus globules* Labill	Myrtaceae

Figure 2. Method of preparation of dhoomvarti.

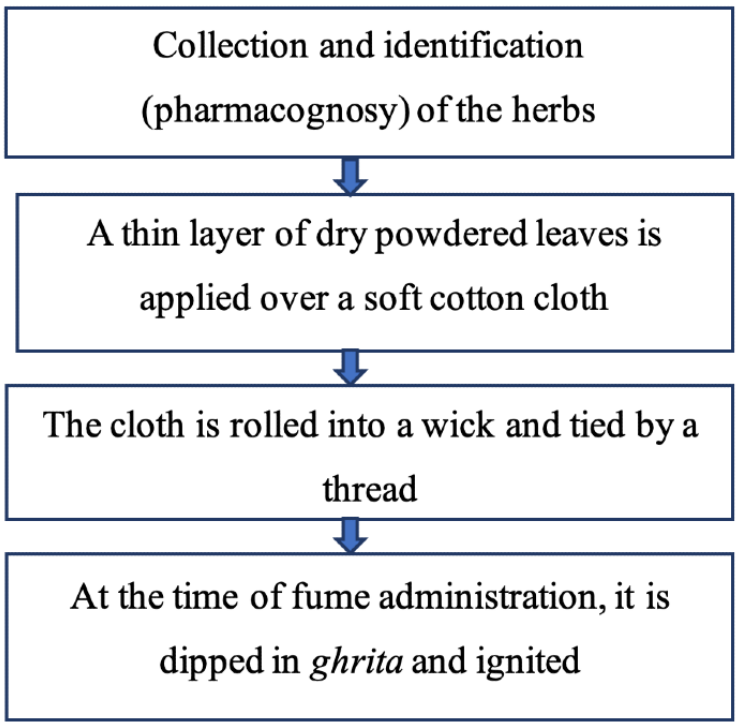

Outcomes

The outcomes are designed to compare the efficacy of *dhoopana* and polyherbal steam inhalation on *pratishyaya* with subjective and objective parameters.

Subjective Criteria

Signs and symptoms of *pratishyaya* will be evaluated with the TNSS, illustrated in Table 4.

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Table 4. Total Nasal Symptom Score (TNSS).

Symptom and domain	Score
Symptoms	
Rhinorrhoea	
No symptoms	0
Aware but not troubled (mild)	1
Troublesome but does not interfere with normal day-to-day activities or sleeping habits (moderate)	2
Interferes with normal day-to-day activities or sleeping habits (severe)	3
Nasal itching	
No symptoms	0
Aware but not troubled (mild)	1
Troublesome but does not interfere with normal day-to-day activities or sleeping habits (moderate)	2
Interferes with normal day-to-day activities or sleeping habits (severe)	3
Nasal obstruction	
No symptoms	0
Aware but not troubled (mild)	1
Troublesome but does not interfere with normal day-to-day activities or sleeping habits (moderate)	2
Interferes with normal day-to-day activities or sleeping habits (severe)	3
Sneezing	
No symptoms	0
Aware but not troubled (mild)	1
Troublesome but does not interfere with normal day-to-day activities or sleeping habits (moderate)	2
Interferes with normal day-to-day activities or sleeping habits (severe)	3
Additional symptoms as per Ayurveda texts	
***Sirashoola* (headache)**	
No headache	0
Occasional headache	1
Frequent headache	2
Continuous headache	3
***Aruchi* (loss of appetite)**	
Absent	0
Present	1
***Kasa* (cough)**	
No cough	0
Occasional cough	1
Moderate cough	2
Continuous cough with throat and chest pain	3

Objective Criteria

The modified cold spatula test will be used to measure nasal patency in rhinitis. The test is done to study the area of fogging associated with a nasal obstruction and compare the pre- and posttreatment outcomes. The patients are asked to breathe normally over a polished stainless steel plate, and the extent of fogging is marked with a marker pen. The magnitude of fogging is then measured with a transparent graph sheet marked with a central red line at 50 mm on the x-axis, dividing the graph into 2 equal parts with corresponding right and left areas of fogging.

Sample Size

A comparative pilot study was performed with 20 patients, including 10 patients in 2 groups, to evaluate the efficacy of *dhoopana* for rhinitis in comparison with polyherbal steam

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inhalation. Based on the results of that study, the minimum sample size for this study was calculated by using the following formula of proportion:

The parameters related to sample size were as follows: α=.05; β=.2; proportion in group 1=0.60; proportion in group 2=0.90; ratio (group 2/group 1)=1; minimum sample size needed for group 1=32; and minimum sample size needed for group 2=32. The minimum total sample size needed was 64, and the minimum total number of patients to be enrolled was 35 in each group (including a 10% withdrawal rate).

Data Collection Tools

This study will use the *Ayurveda Samhitas* (a textbook on Ayurveda), modern texts, and an online search of PubMed and Google Scholar. The polyherbal *dhoomvarti* will be prepared from a powder of *tulsi*, *vasa*, *nirgundi*, and *nilgiri*. The polyherbal *arka* will be prepared from *tulsi*, *vasa*, *nirgundi*, and *nilgiri*. The study will also use a case record form, patient information sheet, and written informed consent form.

Data Analysis

Data will be analyzed by using appropriate descriptive and inferential statistics. Quantitative variables will be analyzed with the Student *t* test and subjective parameters will be analyzed with the Wilcoxon signed test and Mann-Whitney *U* test. Alternate statistical methodologies may be applied if deemed necessary.

Ethical Considerations

The study obtained approval from the institutional ethics committee of Mahatma Gandhi Ayurved College Hospital and Research Centre (MGACHRC/IEC/JULY-2022/522). The committee will decide on the end point and oversee the trial as it progresses. The researchers will assess any adverse events and will report to the ethics committee. Consent from parents and assent from patients was obtained before conducting the trial in the local language while explaining every aspect of the study. The informed consent form included a patient information sheet (part 1) and a certificate of consent (part 2). Data will be anonymized and personal information of the participants will be kept confidential before, during, and after the trial. Physical data will be stored in a protected storage facility with access available only to the researchers. Computerized data will be held in a password-protected hard drive with access available only to the researchers. There was no need to provide any compensation to the patients in the trial. Identification of individual participants and users will not be possible in any images in the manuscript or supplementary files. If needed, prior consent will be obtained from identifiable individuals before the inclusion of such images.

Withdrawal Criteria and Stoppage

No adverse effects of the trial drug were noted during the treatment period. Thus, no cases were excluded from the study. A total of 4 patients, including 2 patients in each group, voluntarily stopped taking treatment during the trial and were counted as withdrawn.

Dissemination

This protocol will be published and disseminated as a thesis on *pratishyaya*. The study protocol provides a detailed overview of the study design, methodology, data collection procedures, data analysis plan, and ethical considerations. By disseminating this protocol, we hope to advance knowledge in the field and facilitate future research.

Results

As of November 2024, we completed the enrollment of 70 patients, with 35 patients in each group. A total of 4 patients voluntarily withdrew from the trial. Data analysis of 66 patients will be completed by February 2025, and we expect the results to be published in March 2025.

Discussion

Dhoopana is mentioned in the Ayurveda classics for the management of acute rhinitis, and we anticipate that it will be found to be equally effective as polyherbal steam inhalation in the management of acute rhinitis in children. Steam inhalation of the herbs that were chosen for this study has been found to be effective in the management of upper respiratory tract infections. Thus, fumes of the same ignited herbs (ie, *tulsi*, *vasa*, *nirgundi*, and *nilgiri*) should work just as well in the management of rhinitis. The disease *pratishyaya* is very common in the pediatric population, but no standardized Ayurvedic therapy is available that can be given locally in the nostrils in its acute stage. Locally given medicines are fast and effective compared to oral medication. Another classical procedure known as *nasya* (nasal instillation of oil) is recommended for rhinitis, and as per previous research, it is effective in the management of chronic and recurrent rhinitis, but as per the Ayurveda classics, it cannot be used in acute rhinitis. The herbs chosen for this study are hot and pungent in nature and can reach the minute *srotasa* (channels of the nostrils); thus, they promise to be beneficial in acute rhinitis. Polyherbal *dhoopana* is safe and easy to administer, and if it is found to be effective, it may be a better alternative to steam inhalation. Thus, it can be used in general pediatric practice for patients with acute rhinitis. A positive outcome of the study will facilitate further studies in a large population with standardization of the procedure for *dhoopana*. In this study, a polyherbal wick was prepared manually, and it takes some time to ignite the herbal powder. In the future, this can be improved by using a pocket-friendly herbal nasal fumigator that ignites the herbs in few seconds without any manual practice. This could be patented and copyrighted later and publicized for the benefit of the population.

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Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Images of intervention.
[DOCX File , 1159 KB - resprot_v14i1e58197_app1.docx]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
TNSS: Total Nasal Symptom Score

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Protocol

Examining the Implementation of the Italian Version of the Teen Online Problem-Solving Program Coupled With Remote Psychological Support: Protocol for a Randomized Controlled Trial

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Abstract

Background: Pediatric acquired brain injury (ABI) is frequently associated with cognitive and socioemotional alterations. Therefore, targeted rehabilitation to improve everyday functioning, particularly executive functioning (EF), is needed to limit the possible deterioration of cognitive abilities and behavior over time and the associated social and psychological costs.

Objective: In this paper, we present the protocol for a phase-2 randomized controlled trial (RCT) aimed at examining the feasibility and efficacy of a web-based intervention (ie, the Italian version of the Teen Online Problem-Solving [I-TOPS] intervention) to improve problem-solving abilities versus an active-control, web-based intervention (ie, wellness intervention) providing health and wellness content.

Methods: A double-blinded, phase-2 RCT will be conducted to guarantee controls on data quality and findings. In total, 42 adolescents will be recruited from a rehabilitation institute and individually randomly assigned in a 1:1 ratio to receive the I-TOPS intervention or the web-based wellness intervention. Both interventions will include 10 core sessions and will be delivered remotely using a web-based platform. Participants allocated to both interventions and their caregivers will independently complete the learning modules in an everyday setting using their computer. The I-TOPS intervention's core sessions will target the EF domain (eg, planning, emotion regulation, and social skills), while all the contents of the wellness intervention will be aimed at providing psychoeducation on ABI sequelae and supporting health and wellness. Participants assigned to the I-TOPS intervention will also receive bimonthly direct training in problem-solving coupled with remote support from a psychologist. Feasibility data and efficacy outcomes on both adolescents' and parents' functioning will be assessed. Cognitive abilities in the EF domain and behavioral and psychological functioning (ie, internalizing and externalizing symptoms) of the adolescents will be evaluated via performance-based measures, administered remotely using the Google Meet platform, and paper-and-pencil questionnaires; parents' well-being will be assessed through paper-and-pencil questionnaires. Efficacy will be evaluated immediately after training and at 6-month follow-up.

Results: This study started on February 26, 2021, and ended on February 28, 2023. A total of 42 adolescents were enrolled and randomly assigned to the 2 study groups, 34 (81%) completed the intervention and posttreatment evaluation (I-TOPS: n=19 and wellness intervention: n=15) and 31 performed follow-up evaluation (I-TOPS: n=18 and wellness intervention: n=13). Data analysis on feasibility and efficacy will be performed after protocol publication, and the results will be published in the form of a paper in a relevant journal in 2025.

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Conclusions: This double-blinded, phase-2 RCT could extend knowledge on the best rehabilitation practices to adopt with the survivors of pediatric ABI by providing evidence-based data currently lacking for the Italian context. If this study yields positive results, a larger, multicenter, phase-3 RCT could be planned and delivered to examine program cost-effectiveness in a larger sample.

Trial Registration: ClinicalTrials.gov NCT05169788; https://clinicaltrials.gov/study/NCT05169788

International Registered Report Identifier (IRRID): DERR1-10.2196/64178

(JMIR Res Protoc 2025;14:e64178) doi:10.2196/64178

KEYWORDS

telerehabilitation; acquired brain injury; executive functioning; pediatric; problem-solving; computer

Introduction

Background

Acquired brain injury (ABI), a condition of either traumatic (eg, traumatic brain injury [TBI]) or nontraumatic origin (eg, stroke, anoxia or hypoxia, and infections or inflammation to the brain), represents one of the leading causes of lifelong disability among children and adolescents [1-4]. Together with physical disabilities, the most common consequences of a pediatric ABI include cognitive impairment, reduced academic and vocational attainment, issues with emotional and behavioral regulation, and social problems, all negatively affecting the quality of life of patients [5-15]. Research has indicated that patients with pediatric ABI may be at high risk for substance misuse, mental health problems, criminal behavior, and unemployment in adulthood [5,9,12,15]. Pediatric ABI also substantially causes stress and burden for caregivers and families because children with these conditions experience neurocognitive, behavioral, and adaptive challenges that require relatives to change their lifestyle and develop additional skills to help their children, which often generates significant physical and emotional burden [16,17]. Therefore, pediatric ABI exerts adverse long-term effects on the individual, their family, and the society [6,9,12,15-17].

Specifically, executive functioning (EF) difficulties represent one of the core deficits of ABI, affecting not only cognitive abilities but also behavioral and social functioning [6,9,13,18-24]. EF deficits have been linked with socioemotional adaptation and psychological well-being, with several patients with these deficits exhibiting externalizing behaviors and temper outbursts [6,9,13,18-24]. Thus, there is a clear need for programs designed to rehabilitate EF during the chronic phase of an ABI. However, studies indicate that many children with ABI fail to receive the recommended treatments for optimal recovery after discharge from the hospitals or rehabilitation centers [25-29]. Research has also reported that numerous children with mental health issues do not obtain adequate support [30]. Barriers to receiving treatment have different origins, ranging from intervention accessibility (eg, geographical barriers and time and economic demands to health care facilities and families), poorly designed and grossly underresourced health services, to patients' and families' readiness to work on issues [26-31]. Therefore, numerous rehabilitation interventions for this population deliverable at a distance (ie, telerehabilitation) have been developed and offered over the years [31-38]. Telerehabilitation has diminished the financial and time burden on families typically associated with traditional rehabilitation, thereby allowing patients to receive higher therapy doses [31,39-41]. In the field of psychology, telerehabilitation has also been found to reduce the stigma of therapy, to have similar clinical outcomes to traditional face-to-face interventions, and to improve treatment utility and satisfaction [31,39-41].

In the United States, in the mid-2000s, Wade et al [42] developed a technology-assisted intervention for pediatric patients with TBI and, subsequently, with ABI, with the aim to address EF in everyday settings. The program targets problem-solving within the family context, combining the problem-solving framework by D'Zurilla and Nezu [43] and D'Zurilla et al [44] with the collaborative family problem-solving model by Robin and Foster [45]. The Teen Online Problem-Solving (TOPS) program was originally designed with the specific purpose of providing a contextualized treatment that addressed EF, self-regulation, and communication challenges in everyday settings. The web-based format of the intervention had the objective of increasing patients' participation in outpatient rehabilitation and improving retention rates. The TOPS-contextualized approach is in contrast with training programs that involve only drill-based exercises, which often suffer from a lack of generalization of the effects [37].

The TOPS program includes self-guided, web-based sessions that the child and their family complete at home and bimonthly videoconferences with a psychologist with expertise in cognitive behavioral therapy [42]. The sessions provide training in the steps of problem-solving, teaching adolescents and families to apply them to everyday challenges with organization and planning, social interactions, and emotion control. Metacognitive strategies to promote self-monitoring and self-regulation are also taught. Both the child and the family are required to complete the web-based learning modules, including reading or listening to the didactic information and performing exercises to reinforce understanding of what they read.

In randomized controlled trials (RCTs) of the TOPS program conducted in the United States, families have evaluated the web-based modules of the intervention as helpful, the length and structure as feasible, and the overall program as easy to follow and useful [46,47]. In addition, the web-based program was found to be convenient and beneficial as face-to-face therapy [48]. Regarding efficacy, previous studies have demonstrated the beneficial effects of the TOPS program on children (eg, EF and psychological well-being and behavior at home, school, and other settings); parents (eg, levels of

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depression and psychological well-being); and even parent-child conflicts [37,42,46,48-52]. In view of this success, recent guidelines acknowledged TOPS as an evidence-based treatment and a standard of care for executive dysfunction and behavioral issues following TBI in the United States [36].

In Italy, there is a great need to develop rehabilitation interventions accessible to large cohorts of patients with ABI, considering the substantial distance of many families from rehabilitation centers and, in some cases, the presence of geographical barriers (eg, living in remote rural areas, mountains, and islands), which make it difficult for many patients to receive treatments in the chronic phase [31,53]. At present, in Italy, telerehabilitation for cognitive and behavioral functions is still at an embryonic phase. The lack of remote interventions for young children with neurological conditions in this country has been highlighted by a review published in 2020 [53], reporting very limited research on the topic, with only one intervention for children with ABI conducted up to 2019 [54]. Importantly, no intervention focusing on everyday EF was detected. In 2020 and 2023, two papers on an RCT of our research group on the effects of a drill-based remote intervention for children with ABI were published, but also in this case, no focus on EF was given [55,56]; no other intervention delivered in Italy was found up to 2023 [57]. Nevertheless, the area of remote interventions is a matter of great interest for the Italian health care system, as suggested by the publication of 2 relatively recent documents on the following topics: the Italian State-Regions agreement on telemedicine delivery published in 2020 [58] and the guidelines for home assistance published in 2022 by the Italian Ministry of Health [59]. These documents report the national guidelines for the provision of remote services and identify the key elements required for the delivery of treatments at a distance.

To increase rehabilitation opportunities for young patients with ABI and embrace the push toward remote interventions in Italy, we translated and adapted the original American TOPS program to create an Italian version of the TOPS (I-TOPS) intervention [31]. The usability of the I-TOPS intervention and its potential positive effects on adolescents with ABI in Italy should be rigorously tested by conducting an RCT, with the aim to inform the Italian health care system on standardized methods to promote recovery and well-being among this population. A clear evaluation of the clinical impact and cost-effectiveness of the program should be provided to support recommendations for effective behavioral and neuropsychological interventions.

To this end, a single-center, double-blinded, phase-2 RCT will be conducted, comparing an experimental group receiving the I-TOPS (ie, I-TOPS intervention group) intervention with an active control group receiving a modified version of the program (ie, wellness intervention group), having the same structure but omitting problem-solving–related content. The sample size of the study was established through power analysis by considering data from a previous meta-analytic study on the effects of the original American TOPS program [37]. This paper describes the trial protocol; the steps required to conduct the study, including study procedures (ie, setting, participants' characteristics, sample size calculation, randomization and blinding, intervention and active control characteristics, and outcomes selected); and a discussion of the clinical implications of the study.

Objectives

In summary, the study objectives are to (1) examine I-TOPS intervention feasibility in a sample of adolescents with ABI aged 11 to 19 years—we will examine different feasibility outcomes taken from previous studies on remote cognitive rehabilitation interventions for pediatric patients with ABI, considering both the feasibility of the training (eg, accessibility, training adherence, technical smoothness, and training satisfaction) and the feasibility of study and procedures (eg, participation willingness, participation rates, assessment procedures, assessment timescale, and loss to follow-up) [54,60]—and (2) examine I-TOPS intervention efficacy—before training, after training, and at the 6-month follow-up, we will administer questionnaires and performance-based measures to participants and parents in the 2 study groups to assess neurocognitive and psychological or behavioral functioning of children as well as the psychological well-being of parents.

Methods

Trial Design

We will conduct a single-center, 2-arm, parallel-group RCT. The trial will apply a pre-post design, with a baseline preintervention assessment (T0), a postintervention assessment immediately after the 6-month intervention period (T1), and a long-term follow-up assessment conducted 6 months after the end of the intervention (T2). Participants will be randomly assigned to groups in a 1:1 ratio to receive the I-TOPS or the wellness intervention. The wellness intervention presents the same structure as the I-TOPS intervention but omits contents related to problem-solving. No change to the I-TOPS or wellness intervention content will be made during the trial; therefore, both interventions will be delivered in their initial Italian version. Eventual failures or system downtimes will be recorded and considered for the evaluation of the feasibility of the training, but no changes in functionality will be made. The trial was registered on ClinicalTrials.gov (NCT05169788) on December 23, 2021.

Study Setting

The I-TOPS and wellness interventions will be delivered remotely using a web-based platform including web-based learning modules. Participants will complete the intervention in an everyday setting, generally at home using a computer, as the program is not compatible with tablets and mobile phones. Every 2 weeks, a psychologist located in the rehabilitation center (ie, Scientific Institute IRCCS E. Medea in Bosisio Parini, Lecco, Italy) will contact patients and families using the Google Meet videoconference platform to provide remote monitoring, content discussion, and support on the problem-solving process for the I-TOPS intervention and remote monitoring and content discussion only for the wellness intervention.

Demographic, clinical, and outcome data will be collected and stored at the Scientific Institute IRCCS E. Medea.

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Eligibility Criteria

The inclusion criteria for the study, in accordance with those of the studies on the original American TOPS program [42,46,49-52], are as follows: a diagnosis of nonprogressive ABI (eg, TBI, stroke, brain inflammation or infection, and anoxia or hypoxia) in the chronic phase (ie, at least 1 year after the event); ages between 11 and 19 years at the time of the recruitment; full-scale IQ ≥70; proper comprehension and speaking abilities in the Italian language; having a PC and access to the internet in the everyday setting, and adolescent and family familiarity with basic computer and internet literacy to manage emails, access to the internet and websites, and video calls; and at least one parent or guardian living with the adolescent available to participate in the intervention.

Exclusion criteria, in accordance with those of the studies on the original American TOPS program [37,42,46,48-52], are as follows: presence of preinjury or comorbid conditions, such as sensory impairments and global developmental delay; a history of abuse; a history of psychiatric hospitalization; and receiving concomitant psychological intervention.

Participant Recruitment

The staff members responsible for the study (AB and CC), in conjunction with the referring physicians, will identify potentially eligible participants by reviewing medical records related to pediatric ABIs at the Scientific Institute IRCCS E. Medea. Families of all potentially eligible patients or the patients themselves, if of age, will be met face-to-face in the clinic or contacted by phone by a psychologist of the research team and provided with details about the aims and methods of the study. Parents and adolescents will be given the opportunity to ask questions about the study and to confirm whether they are interested in participating. No information on group allocation, and thus, on differences between the I-TOPS and the wellness intervention will be provided to limit user expectations and biased results; only general information on the structure of the program and its duration and aims will be discussed. If families are interested in participating, eligibility criteria will be checked with the parent to confirm suitability for the research and ascertain whether both parents or which parent will participate with the adolescent during the intervention. A summary of the informed consent will also be provided. To achieve adequate participant enrollment, research assistants will contact all adolescents meeting the inclusion criteria with up-to-date contact information until the target sample size is reached.

Randomization and Blinding

After completion of the informed consent and baseline measures, participants will be randomly assigned into one of 2 groups: G1, receiving the regular I-TOPS treatment, or G2, receiving the active control training, namely, the wellness treatment. In detail, the randomization will be conducted by a researcher of the Institute, independently from the research staff responsible for recruiting participants. Randomization of patient assignment to the groups will follow a coin flip procedure using the randomization tool of Microsoft Excel: an automated number will be randomly associated with any recruited patient and determine assignment to G1 (0-0.49) or G2 (0.50-1). No stratification will be used. The independent researcher will give the staff members responsible for the study (AB and CC) a sealed envelope containing the participant's group assignment to keep it concealed from the research staff. This is to avoid selection bias and to prevent the research staff from subverting the allocation sequence. In turn, the research staff will give this envelope to the psychotherapists supervising the interventions, who will contact parents of enrolled adolescents to provide information regarding the next study steps on the basis of the group allocation. Indeed, to allow for clinical supervision, treatment fidelity, and patient interactions, the supervising psychotherapist will be required to receive group allocation information. Other research staff, participants, and testers will remain blinded to group assignment. Given these considerations, this study will constitute a double-blinded RCT. Emergency unblinding will be used only in front of reasonable request by the patient or the referring physician due to clinical reasons.

Interventions

This study will have 2 treatment arms, that is, the I-TOPS (G1) and wellness (G2) interventions, described subsequently in Textbox 1. Participants will not have to pay or will not be paid to access the allocated intervention.

For both interventions, before starting the training, a psychologist, who will follow training administration, will contact the families via telephone and discuss how to access the treatment sessions on the interventions' website and how to connect to Google Meet calls. No recommendations on timing, frequency, or intensity of use will be provided; the only requirement will be the completion of each session within a 2-week window. Prompts to use the training will be provided via emails automatically sent by the program; however, participants will choose the frequency (ie, weekly, bimonthly, or monthly) of reminders by selecting a specific option included in the program website. In addition, bimonthly meetings with the psychologist will review content and promote adherence. To this aim, the psychologist will ensure flexibility and coordinate the timing of the sessions to allow families to have time for other commitments and holidays or breaks to be built into the schedule.

No possibility to modify allocated interventions for each trial participant will be given, but each adolescent could discontinue the intervention at any study time due to personal, family, medical, or other reasons.

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Textbox 1. Training sessions of the Italian version of the Teen Online Problem-Solving (I-TOPS) intervention and wellness intervention.

I-TOPS intervention

- Session 1 (*Inizio: essere positivi*; Getting started, staying positive, and handling stress): after an introduction on the I-TOPS program and its purposes, the session explains how it is important to develop and maintain a positive attitude in everyday life to better solve problems. The psychologist should review the differences between a positive versus negative approach to problems with the family, emphasizing why it is important to have a positive problem-solving orientation. The family should be encouraged to talk about how they feel when they have problems.
- Session 2 (*Problem-solving*; Problem-solving): the session introduces a 5-step strategy (ie, FAREI, which represents the corresponding acronym to the strategy ABCDE of the original version of the Teen Online Problem-Solving [TOPS] intervention) to solve practical and organizational problems; the 5 steps of problem-solving are as follows: A (ie, aim or focus on a goal), B (ie, brainstorm or analyze all the possible solutions), C (ie, choose a plan), D (ie, do or implement the plan), and E (ie, evaluate what works and what does not work). The psychologist helps the adolescent to apply the strategy by using examples.
- Session 3 (*Organizzarsi*; Getting organized): the session expounds the cognitive changes that occur following an acquired brain injury (ABI), for example, difficulties in memory and attention; the psychologist asks the teenager and the parent about problems with thinking or learning that they feel the teenager is having because of the ABI and about the strategies that they use to compensate for these difficulties. The psychologist helps the family to apply the F.A.R.E.I. strategy learned in session 2 to solve the everyday problems.
- Session 4 (*Lavorare con la scuola*; Working with the school): the session aims to provide parents with information regarding their rights as well as the rights of their adolescent in the education system, with materials and ideas to become advocates for their adolescent, and to create an optimal learning environment while respecting the school's ideas. In addition, parents are taught strategies to better communicate and work with teachers and are required to solve problems on this topic during the web-based session with the psychologist.
- Session 5 (*Mantenere il controllo*; Staying in control): the session describes the possible behavioral and emotional problems following ABI. The psychologist discusses with the adolescent and their caregivers their own problems to allow them to find a solution. During this session, the adolescent learns the 5-step SMART strategy (which is the same as the one reported in the original TOPS program) useful to empower them to manage their own behavior during social interactions. The 5 steps to stay in control are as follows: S (ie, stop and think), M (ie, monitor your behavior), A (ie, appraise and look at how others are reacting), R (ie, reflect), and T (ie, try a new or different behavior). The psychologist helps the adolescent to apply the strategy in the everyday setting.
- Session 6 (*Gestire la rabbia*; Controlling your anger): the session offers a 6-step strategy to manage anger (ie, SPACCA, which represents the corresponding acronym to the strategy STARRS of the original version of the TOPS intervention) and suggests how to become a good communicator by using *iMessages*. The 6 steps to control anger are as follows: S (ie, stop), T (ie, think about what is happening), A (ie, accept the situation), R (ie, relax), R (ie, reframe or look at the situation differently), and S (ie, solve). The psychologist discusses with the family why a person may have more problems with anger after ABI and helps the adolescent to apply the strategy in the everyday setting.
- Session 7 (*Ascoltare, parlare e leggere i segnali non verbali*; Verbal and nonverbal communication): the session helps the adolescents to focus on verbal and nonverbal communication skills and encourages them to focus on nonverbal signals from communication partners and their own nonverbal communication. The adolescent learns strategies for effective verbal communication. The psychologist supervises the exercises done by the adolescents on the web platform and helps them to identify some situations of everyday life in which the learned abilities could be implemented to improve social communication.
- Session 8 (*Comportamento sociale e di gruppo*; Social behavior and problem-solving): the session focuses on possible everyday difficulties in group settings, romantic relationships, web-based communication, and family context. The psychologist discusses with the adolescent and the family how friendships and social activities could change after an ABI and asks the adolescent to identify social situations that are challenging for them and to apply the strategies learned in sessions 5 and 6 to better deal with others.
- Session 9 (*Prendersi cura di sè*; Taking care of you): the session focuses on the relationship between sleep, nutrition, hydration, physical exercise, and cognitive functioning and wellness following an ABI; it also explains the consequences of feeling stressed and suggests different strategies to manage stress. The psychologist discusses with the family members their own habits and helps the adolescents to use the strategies presented in the session to face difficulties of everyday setting and to maintain an adequate routine to support wellness.
- Session 10 (*Conclusione: mettere insieme i pezzi*; Moving forward and planning for the future): this session recaps the 3 main strategies showed in previous sessions (FAREI, SMART, and SPACCA) and introduces a fourth strategy (FOCUS) devoted at helping adolescents to understand the possible steps to effectively ask for help whenever necessary in view of potential future problems in the everyday setting. This strategy is made of F (ie, flexibility when dealing with something), O (ie, optimism), C (ie, creativity to think about other ways to deal with something), U (ie, use your own resources), and S (ie, support or ask for help). The psychologist helps the adolescent to exercise this fourth strategy to use it in the everyday setting after the end of the training.

Wellness intervention

- Session 1 (*La strada verso il recupero*; Recovery and planning for the future): the session introduces the wellness intervention and focuses on the teenager's global difficulties and worries following an ABI. The psychologist provides psychoeducation on ABI sequelae and encourages the adolescent and their caregivers to describe their personal experience of the injury and related emotions and concerns.
- Session 2 (*Fare fatica è normale*; Acquired brain injuries: possible consequences): the session describes the cognitive changes that can occur following ABI, for example, difficulties in memory, attention, and executive functioning (EF) and includes video testimonials of adolescents with ABI discussing such difficulties. The psychologist encourages the teens and their caregivers to describe their personal experience of the injury and its consequences. The content is aimed at providing psychoeducation on ABI sequelae specifically related to the area of cognition.
- Session 3 (*Essere positivi*; Staying positive and handling stress): the session explains how it is important to hire and maintain a positive attitude in everyday life, but this is not specifically related to the problem-solving process, instead to wellness, reducing perceived stress. The psychologist investigates the family's use of humor in daily life and encourages them to talk about how they feel and how they react when problems occur.

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- Session 4 (*Lavorare con la scuola*; Working with the school): the session aims at providing parents with information regarding their rights as well as the rights of their adolescent in the education system and with materials and ideas to become advocates for their adolescent and to create an optimal learning environment for their adolescent while respecting the school's ideas.
- Session 5 (*Prendersi cura di sè*; Taking care of you): the session focuses on the relationship between sleep, nutrition, hydration, exercise, and cognitive and physical functioning following ABI. The psychologist investigates with the adolescent and their caregivers their habits in these areas. The aim is to support health and wellness.
- Session 6 (*Gestire lo stress*; Managing your stress): the session explains the consequences of feeling stressed on health and suggests some strategies to manage stress. The psychologist investigates how the adolescents usually cope with stress and helps them to learn the strategies to manage stress and to experiment them in daily life. The aim is to support health and wellness.
- Session 7 (*Il sonno*; Sleep): the session shows the possible sleep changes following ABI and gives advice to improve sleep quality to support health and wellness. The psychologist investigates the adolescent's sleeping habits and, if necessary, helps them to improve sleep quality. The aim is to support health and wellness.
- Session 8 (*Dopo la scuola superiore*; After high school): the session offers the adolescent an overview on the opportunities provided by the Italian system in terms of education and work activities after high school, with a primarily psychoeducational focus. The psychologist helps the adolescents to think about what they would like to be when they grow up and what paths they could follow.
- Session 9 (*Emozioni di chi si prende cura*; For parents: family coping): the session shows the possible emotional difficulties of caregivers of adolescents with ABI and offers strategies for managing stress within the family context. The psychologist reviews with the caregivers their unique responses to the injury, acknowledging that responses are as unique as they are, with a focus on normalizing their emotional reactions.
- Session 10 (*Parlare con i vostri ragazzi*; Talking with your teenager): the session helps the parents to become good listeners and good communicators to improve their communication with the adolescents and the families to support a calm family environment and overall family wellness. The psychologist engages the parents in role-playing to allow them to improve their communication abilities.

I-TOPS Intervention (ie, Experimental Intervention Group)

The qualitative data on the process of adaptation of the original TOPS program to the Italian context (ie, I-TOPS) are extensively reported as a case study in a paper published in 2021 [31]. In summary, the adaptation process comprised focus groups with parents of adolescents with TBI to understand the needs of Italian patients and their families; after a literacy translation of the original program into the Italian language, they were asked their opinions on the relevance and clarity of the program content. The main suggestions were related to the scripted videos, with recommendations to emphasizing nonverbal aspects of communication that are integral to the Italian culture. Furthermore, a clearer depiction of the consequences of negative behaviors in the videos was required. The translation of the original TOPS program text from the English language to the Italian language was completed by 3 different psychologists with expertise in the field of brain injury and cognitive behavioral therapy. Translations were subsequently produced by 1 bilingual expert via forward-backward methods, and discrepancies were discussed and resolved. The final text was checked by adolescents with TBI, their parents, physicians, and adolescents of a local school class. Any suggested changes were accepted if they did not alter the meaning of the original sentence. This process required 5 months of work, during which further content revisions were made to improve ease of comprehension and flow in the Italian language.

The regular version of the I-TOPS intervention consists of 10 core sessions focused on problem-solving, EF, behavioral strategies, and social skills and 10 supplemental sessions. Before starting the program, the psychologist will meet with the adolescents and their family to learn about the specific issues occurring in their everyday setting with respect to organization or planning, social interactions, and emotion control that they want to work on during the intervention. Thus, although the I-TOPS program is delivered according to a defined protocol and content, the problem-solving will focus on personalized, everyday issues that the adolescents and their families have identified. The 10 core modules consist of self-guided didactic content regarding the steps of problem-solving and strategies for managing everyday challenges, brief videos modeling these skills, and exercises to support implementation. The adolescents and their families will complete a new module approximately every 15 days. Each web-based session will take 30 to 45 minutes to complete depending on the adolescent's level of attention. The parent or parents will work with the adolescent to complete each module. The program will not provide any feedback on the activities completed. After the family has completed and reviewed the contents of each session, the trained psychologist will conduct a video meeting of approximately 1 hour with the adolescent and the parent to review the web-based content and practice the problem-solving skills, focusing on a problem identified by the family related to the intervention content from the web-based learning modules (ie, organization or planning, social interactions, and emotion control). Ideally, video meetings should be provided bimonthly, but this period can be slightly adjusted according to family commitments. Completion of all 10 sessions is expected to take each family 5 months. Supplemental sessions will be recommended if their specific content is determined to be potentially beneficial in addressing the ongoing problems of the adolescent or the family identified at the baseline assessment. Therefore, considering supplemental sessions (a maximum of 2 supplemental sessions will be scheduled for each adolescent and family), we anticipate that participants will take approximately 6 months to complete the program.

Wellness Intervention (ie, Active Control Training)

The active control wellness intervention was developed by translating the original TOPS program contents related to health and wellness into the Italian language, usually included in

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supplemental sessions, or contents included in original core sessions related to psychoeducation on TBI. In addition, in this case, the translation of the original TOPS program text from the English language to the Italian language was completed by 3 different psychologists having expertise in the field of brain injury and cognitive behavioral therapy. Translations were subsequently produced by 1 bilingual expert via forward-backward methods, and discrepancies were discussed and resolved.

Patients included in the wellness intervention will complete the treatment according to the same schedule as patients of the experimental group but will not receive direct intervention on EF nor support with respect to the problem-solving process. This control treatment focuses on health and wellness but omits contents on problem-solving, EF, behavioral strategies and social skills, and goal setting. The wellness intervention consists of 10 core sessions and 3 supplemental sessions to provide adolescents and their families with a program having the identical structure to the original I-TOPS intervention. The wellness intervention represents an active control training. No feedback will be automatically provided on the activities completed by the program. Bimonthly meetings of a brief duration (ie, about 15 minutes each) with the psychologist will focus on promoting knowledge regarding the consequences of ABI and on healthy lifestyle behaviors to improve wellness and will have the goal to sustain compliance. Completion of all 10 sessions and potentially supplemental ones (a maximum of 2 supplemental sessions will be scheduled for each adolescent and family) is expected to take each family a total of 6 months, similar to the experimental TOPS program. The active control group allows us to control for the placebo effects associated with being involved in a rehabilitation treatment and to isolate the effects of problem-solving training in the I-TOPS intervention.

Therapist Training

The I-TOPS intervention and the wellness treatment will be delivered by psychologists with expertise in psychotherapy. To ensure fidelity and quality assurance, all psychologists will receive training in recruitment strategies, interviewing techniques, questionnaire administration, and delivery of the I-TOPS and wellness interventions before beginning the program implementation; instructions for delivering each session are detailed in a treatment manual written by the TOPS program developer SLW and her research staff.

Treatment Fidelity

In relation to the I-TOPS intervention, psychologists will receive weekly supervision from a qualified psychotherapist with a master's in clinical psychology, a specialization in cognitive behavioral psychotherapy, and qualification in clinical neuropsychology to ensure treatment fidelity and quality assurance.

With respect to the wellness intervention, a supervising psychotherapist will conduct a random review of the sessions conducted by the psychologists every 2 weeks to ensure fidelity. The main topic of discussion will be how to focus on the ABI consequences without directly teaching problem-solving strategies to manage those consequences.

Data Collection

Following completion of the consent process, sociodemographic information (eg, age, sex, and socioeconomic status); details of past medical history; concurrent medication; the adolescent's age at the time of injury; and injury severity, measured using the Glasgow Coma Scale [61] will be collected from each patient's referring physician. Family compositions will be collected from parents via telephone for outpatients or directly in the clinic for hospitalized patients who are close to discharge.

At baseline (T0), after treatment (T1), and at 6-month follow-up (T2), adolescents and parents will be asked to complete study outcome measures, including questionnaires on cognitive and behavioral functioning of adolescents, and the psychological well-being of parents and adolescents will undergo remote cognitive performance–based evaluations. Questionnaires will be sent to adolescents and families in a sealed envelope; after completing them, adolescents and parents will be required to return them to the research staff using an envelope with a postmark included in the sealed envelope within 2 weeks. To promote participant retention, support from a member of the research team could be given for questionnaire fulfillment, if needed. In addition, performance-based measures on adolescents' cognitive functioning will be remotely administered, thus removing practical barriers to patient retention in the study, such as difficulties in transportation and reaching research centers.

Feasibility Outcomes

Outcome measures to assess study feasibility will be taken and adapted from previous studies on telerehabilitation interventions for adolescents with ABI, with the aim to use a priori–defined criteria and allow comparisons [54,60]. These measures have been developed for a previous study [60] based on the relevant literature on pilot feasibility studies [62,63]. A total of 9 measures will be used: 4 to assess the feasibility of the I-TOPS or the wellness intervention (ie, accessibility, training adherence, technical smoothness, and training motivation) and 5 to evaluate the study design and procedures (ie, participation willingness, participation rates, assessment procedures, and assessment length and loss to follow-up).

With respect to the feasibility of the I-TOPS or the wellness intervention, the outcomes outlined in Textbox 2 will be considered.

In relation to the feasibility of study design and procedures, the outcomes outlined in Textbox 3 will be considered.

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Textbox 2. Outcomes to be considered regarding the feasibility of the Italian version of Teen Online Problem-Solving (I-TOPS) or wellness intervention.

- Accessibility: number and percentage of participants who ask for further instructions to understand training content and session-related tasks when at home. This criterion refers to understanding how to access the training, how to enter a session, how to perform and save exercises, and how to print specific materials. The criterion for success: 90% of families understand training content and session-related tasks when at home, after the explanation of sessions' content and activities by the psychologist. For all families, the explanation of the content of sessions will be performed during each scheduled web-based meeting (ie, at the end of each session, the psychologist will briefly explain the content of the following one, also indicating to families the web-based activities they are expected to do for the next meeting), with instructions repeated if a family asks for further clarification. If ≥3 explanations are needed, requiring other remote calls, the criterion will be considered to not have been satisfied. The criterion for success was 100% in the paper presenting the original version of the feasibility criteria [60] and in a previous study of our research group [54], both focusing on remote cognitive interventions having a drill-based format. However, for this study, it was reduced to 90%, given the complexity and multiple requirements of navigating and completing content in the I-TOPS intervention.
- Training adherence: number and percentage of the 10 core sessions completed during the scheduled training period (ie, expected time for completion of the 10 core sessions is 5 months) by each patient, including dropouts. No data on the number of log-ins or average session length will be recorded, as, for both treatments, these data do not provide significant information on better training use and are not considered to be associated with improving target abilities. The criterion for success: average 80% of treatment core sessions is completed after 5 months by each treatment group; the remaining 20% (ie, 2 core sessions) should be completed in a maximum 1 further month (ie, 2 extra weeks for each session). To be adherent, participants needing an additional month to complete the training need to have agreed in advance with the psychologist to postpone sessions due to valid reasons (such as holidays or other family plans). The average completion rate per treatment group in the scheduled time frame, calculated as the sum of the percentage of sessions completed by each participant divided per the total number of participants, is considered.
- Technical smoothness: number and percentage of participants who encounter technical issues with the training material (eg, the platform does not work) that persist for 2 or more weeks, thereby generating a training interruption and possibly influencing total training duration. The criterion for success: all participants will be able to perform the training without technical issues; dropouts are included in the calculation, considering only sessions performed.
- Training satisfaction: training satisfaction will be assessed through a satisfaction questionnaire created ad hoc for the original Teen Online Problem-Solving program and already used in previous studies on its feasibility (Multimedia Appendix 1) [46,47]. The questionnaire assesses perceived helpfulness and usability of the program and improvements as a result of treatment, and for this study, it was translated into the Italian language. Item responses include 1 (ie, strongly disagree), 2 (ie, disagree), 3 (ie, agree), and 4 (ie, strongly agree) on a Likert scale. In particular, 5 items pertain to perceived changes in one's problem-solving abilities and psychological wellness, 10 items pertain to satisfaction with the overall program (ie, program helpfulness and enjoyment and relevance of contents), and 2 items focus on the website ease of use. The questionnaire generates a total score, with higher scores indicating greater perceived satisfaction. A total score of ≥57 reflects a positive outcome in terms of satisfaction. The criterion for success: 80% of participants have a neutral or positive global score on the questionnaire.

Textbox 3. Outcomes to be considered in relation to the feasibility of the study design and procedures.

- Willingness to participate: number of participants who accept to partake in the study among those who were contacted for study enrollment. The criterion for success: 75% of eligible participants agree to take part in the study; the criterion is considered on the whole group, as referred to prerandomization data.
- Participation rates: number and percentage of enrolled participants who complete ≥1 session of the interventions, not abandoning the study after baseline measurements and before the start of the training. The criterion for success: 80% of participants who agreed to partake actually participate in the study.
- Assessment procedures: number and percentage of participants for whom outcome data are collected without any problems (eg, missing data and technical issues of assessment tools) on the 3 assessment time points (ie, baseline [T0], after treatment [T1], and 6-month follow-up [T2]). The criterion for success: 90% of the outcome measures for each participant are collected at each time point.
- Assessment timescale: number of participants whose follow-up data are collected within a week after training completion, for posttraining assessment, and within 2 weeks after the 6-month period from training end, for follow-up evaluation. The criterion for success: for all participants, the interval between training end and immediate posttraining evaluation is ≤7 days; for the 6-month follow-up, the assessment is performed in a range of 0 to 14 days from the first day of the 6 months subsequent to training end. This criterion is calculated only for participants performing posttraining and follow-up evaluations, excluding dropouts.
- Loss to follow-up: number of patients who fail to complete all outcome measures at posttraining assessment and 6-month follow-up. The criterion for success: less than 20% of participants enrolled fail to complete all outcome measures on both posttraining assessment and 6-month follow-up. This criterion does not refer to the presence of evaluations with missing data for each participant, for which the criterion "assessment procedures" already provides such information.

Efficacy Outcomes

A total of 9 outcome measures will be used to test preliminary evidence of training efficacy. Specifically, 7 self-assessed outcome measures (ie, 5 questionnaires for parents and 2 questionnaires for adolescents), 2 performance-based tasks assessing social cognition taken from a standardized neuropsychological battery, and a virtual reality–based assessment of everyday setting EF will be used. Questionnaires will be sent to patients and families in a sealed envelope; after completing them, participants will be required to return them to the research staff using an envelope with a postmark included in the sealed envelope within 2 weeks. The performance-based subtests assessing social cognition and the virtual reality–based assessment will be administered remotely using the Google Meet videoconference platform.

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A detailed description of outcome measures is provided in Textbox 4. The sample of this study will include adolescents aged 11 to 19 years, but some measures and questionnaires have been standardized for populations having a lower maximum age range; however, they will be adopted for this study as no other measures with the same characteristics are available in the Italian language. The individual measures affected by this problem are clearly described in Textbox 4.

All outcome measures will be administered at T0 (ie, preintervention assessment), T1 (ie, immediately after the 6-month intervention), and T2 (ie, 6 months after the end of the intervention).

For the questionnaire outcomes, approaches to missing individual items will follow the guidelines for missing item procedures indicated in the manual for each questionnaire. If no guidelines for individual missing items are available, the mean of the completed items will be used to replace missing items if ≤10% are missing.

A summary of outcome measures to test training efficacy is presented in Textbox 5.

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Textbox 4. Description of outcome measures.

- Behavior Rating Inventory of Executive Function Second Edition (BRIEF-2)−parent form [64]: the BRIEF-2–parent form questionnaire is aimed at assessing executive functioning (EF) behaviors of children and adolescents (aged 5-18 years) in everyday life by considering their parents' perspectives. The questionnaire is composed of 63 items referred to 9 different clinical scales (ie, inhibit, self-monitor, shift, emotional control, initiate, working memory, plan or organize, task-monitor, and organization of materials) and 3 validity scales (ie, inconsistency, negativity, and infrequency). BRIEF 2–parent form is administered to parents, who rate the frequency of executive problems of their children on a 3-point Likert scale. Raw scores on the global scale range from 63 to 189. The *t* scores (mean 50, SD 10) are used to evaluate the level of EF behaviors relative to normative samples. Higher scores indicate a worse outcome. As this questionnaire covers the age range of 5 to 18 years, scores of adolescents of 19 years have been standardized by considering norms for adolescents of 14 to 18 years.
- BRIEF 2–self-report form [64]: the BRIEF 2–self-report form questionnaire is aimed at assessing self-reported EF in everyday life of adolescents aged 11 to 18 years. It is composed of 55 items belonging to 7 clinical scales (ie, inhibit, self-monitor, shift, emotional control, task-monitor, working memory, and plan or organize) and 3 validity scales (ie, inconsistency, negativity, and infrequency). Raw scores on the global scale range from 55 to 165. The *t* scores (mean 50, SD 10) are used to interpret the level of EF compared to normative sample. Higher scores represent a worse outcome. As this questionnaire covers the age range 5 to 18 years, scores of adolescents of 19 years have been standardized by considering norms for adolescents of 14 to 18 years.
- Child Behavior Checklist 6 to 18 (CBCL 6-18) [65]: the CBCL 6 to 18 is aimed at assessing psychological adjustment and behavioral functioning of children and adolescents aged 6 to 18 years, as rated by parents. The questionnaire includes 113 items. The scores of this instrument considered for this study are total problems, internalizing problems, and externalizing problems. Raw scores of the Total Problems Scale range from 0 to 226 and are converted to *t* scores (mean 50, SD 10) to interpret the level of behavioral functioning compared to normative sample. Higher scores indicate a worse outcome. As this questionnaire covers the age range 6 to 18 years, scores of adolescents aged 19 years have been standardized by considering norms for adolescents aged 12 to 18 years.
- Youth Self-Report 11 to 18 (YSR 11-18) [65]: YSR 11 to 18 is aimed at assessing self-reported psychological adjustment and behavioral functioning of adolescents aged 11 to 18 years. The questionnaire includes 112 items. The scores of this instrument considered for this study are total problems, internalizing problems, and externalizing problems. Raw scores of the Total Problems Scale range from 0 to 224 and are converted to *t* scores (mean 50, SD 10) to interpret the level of behavioral functioning compared to normative sample. Higher scores represent a worse outcome. As this questionnaire covers the age range 11 to 18 years, scores of adolescents aged 19 years have been standardized by considering norms for adolescents aged 11 to 18 years.
- Beck Anxiety Inventory (BAI) [66]: the BAI is a 21-item questionnaire aimed at assessing state and trait anxiety in adults. In this study, the questionnaire is administered to parents to evaluate their psychological functioning. The total score is calculated as the sum of the 21 items (4-point Likert scale, ranging 0-3), with a minimum score of 0 and a maximum score of 108. Higher scores indicate a worse outcome. Specifically, a score of 0 to 21 indicates low levels of anxiety, a score of 22 to 35 indicates moderate levels of anxiety, and a score of 36 to 108 indicates potentially concerning levels of anxiety.
- Symptom Checklist 90 (SCL-90) [67]: the SCL-90 is a self-report questionnaire for adults aimed at measuring psychiatric symptom intensity on 9 different subscales (ie, somatization, obsessive-compulsive, interpersonal sensitivity, depression, anxiety, anger-hostility, phobic anxiety, paranoid ideation, and psychoticism). The 90 items included in the questionnaire are scored on a 5-point Likert scale (ranging 0-4), indicating the rate of occurrence of the symptoms during the last 7 days. In this study, the questionnaire is administered to parents to assess their psychological well-being. The Global Severity Index (GSI) is considered, for which the score is reported as a ratio of the sum of all items to the number of items scored. Higher scores indicate higher psychiatric symptom intensity; consistent with recommendations [65], an average score corresponding to ≥1 on the GSI enters the clinical range.
- Parenting Stress Index (PSI)–Short Form [68]: PSI–Short Form is a 36-item questionnaire aimed at assessing levels of stress associated with parenting in relation to different areas: parenting competence, restrictions on life introduced by parenting, parental conflict, depression, and social support. The 36 items of the questionnaire are scored on a 5-point Likert scale. The global score (PSI-total) is considered for this study, for which clinical cutoff is established at 90. Higher scores indicate higher distress.
- Jansari assessment of Executive Functions for Adolescents (JEF-A) [69]: JEF-A is a computerized assessment based on nonimmersive virtual reality aimed at evaluating everyday EF in adolescents aged 10 to 18 years. It is a performance-based assessment administered to adolescents. Participants are asked to plan, set up, and run a birthday party through the completion of 16 tasks resembling real-world activities. JEF-A tasks evaluate 8 constructs related to EF: planning, prioritization, selective thinking, creative thinking, adaptive thinking, action-based prospective memory, event-based prospective memory, and time-based prospective memory. All tasks are scored on a 3-point scale: 0 for failure, 1 for a partial or nonoptimal completion, and 2 for satisfactory completion. The scores for the 2 tasks for any particular construct are summed (ie, maximum of 4 possible), and this score is converted to a percentage of achievement for this construct. In addition to the 8 individual module scores, an average total percentage is computed for the whole assessment. The final raw score ranges from 0 to 32. Higher scores and percentages indicate a better EF. Although this instrument has been tested on adolescents with acquired brain injury (ABI) who are aged 10 to 18 years, in this study, we adopted it for participants aged 19 years as well to ensure comparability and a task in line with tasks related to such an age instead of administering to those adolescents the task for adults involving a multiple errand task based around a business office [70].
- A Developmental Neuropsychological Assessment-2 (NEPSY-2; Theory of Mind and Affect Recognition subscales) [71]: the Theory of Mind and Affect Recognition subscales of NEPSY-2 are performance-based subtests administered to adolescents and aimed at evaluating their social perception and emotion recognition skills. Theory of Mind subscale–part A measures understanding of mental functions and other people's perspectives, and its raw scores range from 0 to 17; Theory of Mind subscale–part B examines the ability to match basic emotions (eg, happy, sad, angry, afraid, and disgusted) to specific situations, and its raw scores range from 0 to 8. The Affect Recognition subscale tests the ability to recognize emotions in facial expressions, and its raw scores range from 0 to 35. Raw scores are converted into scaled scores (mean 10, SD 3) based on age norms ranging from 1 to 19. Higher scores indicate better outcomes. As this battery covers the age range 3 to 16 years, scores of adolescents aged 17 to 19 years have been standardized by considering norms for adolescents aged 11 to 16 years.

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Textbox 5. Outcome measures to test training efficacy administered to adolescents and parents.

Cognitive outcomes

- Jansari assessment of Executive Functions for Adolescents (JEF-A; performed by the adolescent) [69]
- A Developmental Neuropsychological Assessment-2 (NEPSY-2; performed by the adolescent) [71]
- Behavior Rating Inventory of Executive function 2 (BRIEF 2-self-report form; related to self-functioning. filled by the adolescent) [64]
- Behavior Rating Inventory of Executive function 2 (BRIEF 2-parent form; related to the adolescent, filled by the parent) [64]

Behavioral or psychological outcomes

- Youth Self-Report 11 to 18 (YSR 11-18; related to self-functioning, filled by the adolescent) [65]
- Beck Anxiety Inventory (BAI; related to self-functioning; filled by the parent) [66]
- Child Behavior Checklists 6 to 18 (CBCL 6-18; related to the adolescent, filled by the parent) [65]
- Parenting Stress Index (PSI; related to self-functioning, filled by the parent) [68]
- Symptom Checklist-90 (SCL-90; related to self-functioning, filled by the parent) [67]

Sample Size and Power Calculation

A previous meta-analysis on the effects of the original American TOPS program on the various outcomes found a small-to-medium average effect size (Hedges g=0.37) [37]; however, high variability was found among the effect sizes of the different studies analyzed. This led us, to be conservative, to estimate a small effect size of f=0.2 for the evaluation of the power calculation in the present study. Power analysis was conducted using G*Power3 Software (Heinrich-Heine-Universität Düsseldorf) [72,73]. Assuming a correlation of 0.50 between repeated measures and setting the α level at P<.05, a sample size of 21 participants per group will be required to obtain 80% of power with our 2 group- and 3 time-point- design. Therefore, a whole sample of 42 participants will be required to be included in the study. Attrition was not considered in performing power calculation, as adherence rates will be a core outcome of this study, which is pioneering for the Italian context and, therefore, will be aimed at collecting data on feasibility. Therefore, any eventual dropouts will be accounted for in statistical analyses using intention-to-treat analysis procedures.

Data Analysis Plan

All randomized adolescents will be included in the analyses, irrespective of adherence to treatment in the I-TOPS or wellness intervention. No imputation of a missing baseline or follow-up data will be performed. The t tests and chi-square analyses will be performed to compare the I-TOPS (ie, experimental) and wellness (ie, control) intervention groups on continuous and dichotomous variables, respectively. Similar analyses will be performed to examine baseline differences between patients who will complete the study and those who will drop out. Frequencies and means related to feasibility outcomes will be calculated. Analyses will be performed using SPSS (version 29.0.1.0; IBM Corp) [74].

Efficacy outcome measures will be separately entered into linear mixed effect models with “time” (baseline vs immediately after treatment vs 6-month follow-up) and “treatment” (regular I-TOPS vs wellness intervention) and their interaction as fixed factors and “intercepts” and “participants” as random factors. In case of differences in any clinical or demographic variables between groups at baseline, those measures will be included in the analyses as covariates. Mixed model analysis allows flexible modeling of the pattern of change over time and uses all the data for a given participant, even if that participant is not seen at all assessments, allowing us to retain participants with missing assessments. Significant interaction effects (ie, time and group) or group effects will be analyzed by post hoc tests. The significance threshold will be set at <.05. No interim analysis will be planned.

Safety Reporting

The risks associated with participating in this trial are considered minimal. The exclusion of adolescents with photosensitive epilepsy reduces the possible risks associated with the prolonged use of a technological device. The interventions, both the original I-TOPS and the wellness interventions, could raise awareness of injury-related cognitive or behavioral problems, which could contribute to conflict between family members. Family communication and problem-solving in the I-TOPS group might increase family burden. Nevertheless, the purpose of the original I-TOPS program is ultimately to help families cope with these difficulties by teaching problem-solving and communication strategies. In addition, the psychologist supporting the web-based interventions (ie, both original I-TOPS and wellness intervention) is trained to handle any emerging problems. Should any issues arise, the psychologist will have the opportunity to discuss the situation during weekly group supervision meetings with the supervising psychotherapist who is qualified in psychotherapy (a minimum of 2 psychologists is scheduled to deliver the treatments). Thus, there is no requirement to report nonserious adverse events (SAEs) in this study; nevertheless, a monitoring of SAEs will be performed. SAEs may be reported by referring physicians of each patient or researchers, the I-TOPS intervention coaches, participants themselves, or any other informant. Adverse event data will be monitored by the Ethics Committee of the Scientific Institute, IRCCS E. Medea to ensure safety. All suspected SAEs will be reported within 24 hours of discovery to the chief investigator, who will be asked to inform the ethics committee contact person at our Institute. All SAEs will be followed up until resolution.

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Ethical Considerations

This study has been approved by the Ethics Committee of Scientific Institute, IRCCS E. Medea (08/21-CE, January 21, 2021). The trial will be conducted in accordance with the protocol and the principles of the 1964 Declaration of Helsinki. Any eventual amendments to the protocol will be submitted to the Ethics Committee of Scientific Institute, IRCCS E. Medea for approval. The principal investigator should make available, on request, relevant trial-related documents for monitoring and audit by the sponsor (Scientific Institute, IRCCS E. Medea) or the relevant research ethics committee.

The informed consent will be obtained face-to-face by staff members responsible for the study (AB and CC) when the adolescents and parents come to the clinic or remotely by using a sealed envelope for those families not able to reach the Institute. The consent process depends on the age of the participants; for participants aged 11 to 17 years, the parents or guardians will provide consent, while participants aged 18 or 19 years will provide their own signed consent. Families will be required to sign the "participant information sheet and informed consent for research participation." Participants will be given the opportunity to express their concerns and declare barriers to participating in the study at the time of enrollment. Participants will have the ability to opt out at any time during the study.

Parents of participants below the age of consent or participants of age will be required to sign a "privacy policy statement and consent." An Institute Data Protection Officer (DPO) will be available, representing a contact point between the Italian Data Protection Authority and the concerned parties. DPO email address is reported on the "privacy policy statement and consent" signed by the parents or the participants. In addition, using the email address of the DPO reported on the "privacy policy statement and consent," participants will have the possibility to provide feedback and express any concerns about the project.

Participants' personal data will be pseudonymized. A unique trial number will be provided to each participant consenting to participate in the study. Each participant will be identified in all study-related documentation by the trial number and initials. A record of names and addresses linked to participants' trial numbers will be maintained by the research team and stored securely. All data will be entered into a password-protected database and encrypted using a stored procedure. Data will be stored for 50 years, except in the case of extension by law, in accordance with information reported in the document on data management for scientific research.

To prevent problems with mislaid usernames and passwords, participants will access the web pages of the allocated training program through links emailed to them by the research team members. Once the program has been completed by the participant, it will be locked to prevent further data entry or change.

The trial database will be designed and maintained by 2 members of the research team responsible for data management (AB and CC); access to the database will be given to eventual research assistants involved in the research project by signaling their name to the specific privacy office of the Institute. Database access by researchers will be password protected.

All data will be collected and managed in accordance with Regulation (European Union) 2016/679 of the European Parliament and of the Council of April 27, 2016, on the protection of natural persons with regard to the processing of personal data and on the free movement of such data and repealing Directive 95/46/EC.

No compensation related to study participation will be provided.

Results

After the approval of the ethics committee, the study started on February 26, 2021, and ended on February 28, 2023. Recruitment started on December 27, 2021, and ended on February 25, 2022. The last patient evaluation was performed on February 22, 2023. A secular event, namely the COVID-19 emergency, fell into the first part of the study period, which could have increased the interest of adolescents and families in participating in a remotely delivered treatment. However, due to the need of the target population to receive neurocognitive treatment in the chronic phase, we consider this fact marginal and not influencing the adherence rate. At study protocol submission in *JMIR Research Protocols*, the study has been concluded; the expected 42 participants were randomly assigned into the 2 treatment groups, and 34 (81%) of them concluded the assigned intervention and underwent posttraining and 6-month follow-up evaluations. The total attrition rate was 19% (8/42).

Figure 1 depicts the CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

After the publication of the protocol, data analysis to test feasibility and efficacy will be performed, and final results are expected to be published in the form of a paper in a relevant scientific journal in 2025. In this paper, demographics associated with digital divide issues such as age, education, gender, family socioeconomic status, and computer or internet literacy will be reported.

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Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram. I-TOPS: Italian version of teen online problem-solving.

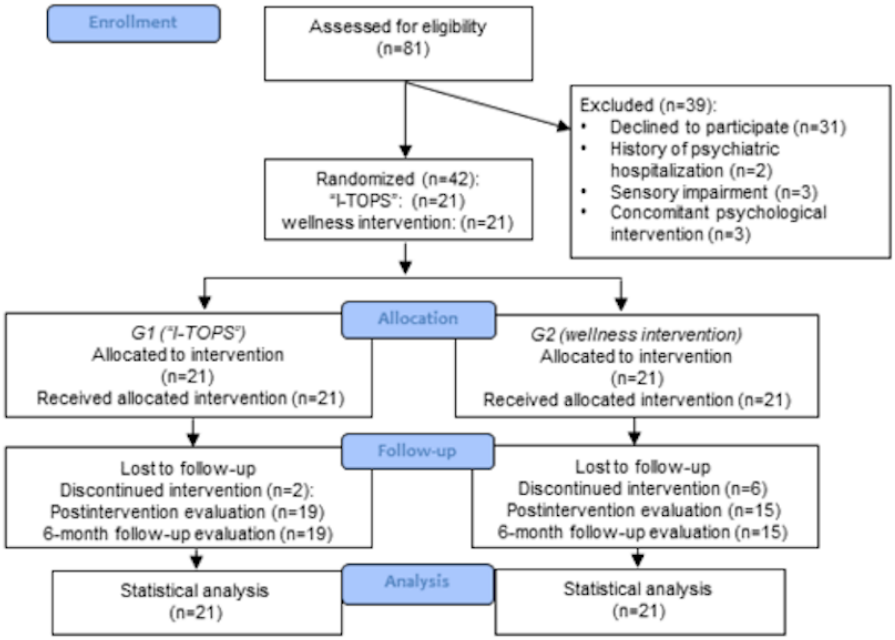

Discussion

Principal Findings

This RCT will evaluate the feasibility and efficacy of a web-based training aimed at improving EF and problem-solving abilities (ie, I-TOPS intervention) versus an active control web-based intervention providing health and wellness content (ie, wellness intervention) in adolescents with ABI. Substantial evidence on the feasibility and efficacy of the original TOPS program developed and delivered in the United States has been collected, while this RCT will be the first study providing data for the Italian context using the adapted Italian version of the intervention (ie, I-TOPS).

EF rehabilitation is highly recommended for pediatric patients with ABI to limit the progressive deterioration of behavior over time and to reduce associated social and psychological costs [31,75]. Telerehabilitation represents a new form of service that mitigates issues associated with face-to-face rehabilitation, such as limitations in access or elevated costs for families and hospitals, creating more care opportunities for patients. Until now, in Italy, no specific remote intervention for EF for this population is available [57]. Therefore, the TOPS program, originally developed in the United States to help teenagers with TBI and, subsequently, other types of ABI to improve problem-solving in the everyday setting, has been translated and adapted to the Italian cultural context with the name "I-TOPS." The I-TOPS intervention urgently needs to be administered in a rigorous RCT in Italy, allowing a test of its feasibility, clinical efficacy, and cost-effectiveness. Our research team has already conducted pilot trials on telerehabilitation treatments for children with ABI in recent years and has also concluded and published a phase-2 RCT on the effects of a drill-based cognitive training [55,56]. However, data on the efficacy of the program were promising only for visual-spatial working memory and not for other cognitive domains, including EF or behavioral and psychological measures [55,56]. Therefore, at a clinical level, the need remains to provide patients with a rehabilitation program to improve EF in everyday settings. This research is the first Italian study that will focus on this topic.

We will conduct a phase-2 RCT to guarantee adequate controls on data quality and findings, consistent with recommendations proposed for studies on rehabilitation interventions [75]. This RCT protocol is reported in accordance with the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist (version 1.6.1) [76] (Multimedia Appendix 2), which allows for improving the quality of reports of web-based intervention evaluations. Data from this RCT will help inform future directions for investments in the field of telerehabilitation in Italy.

Strengths and Limitations

The planned study possesses a number of strengths, including the use of an active control group (ie, wellness intervention) instead of a passive one, which allows controlling for placebo effects. Furthermore, although the I-TOPS program involves self-directed, web-based learning modules, the provision of active problem-solving therapy by a trained cognitive behavioral psychologist constitutes a key aspect for the success of this RCT. In support of this, a recent study highlighted the fundamental role of patient-therapist engagement in obtaining good results during the rehabilitation therapy [77]. Finally, the use of the computer, rather than a smartphone, for treatment delivery should allow adolescents to maintain an adequate level of commitment and concentration while performing the I-TOPS intervention, requiring them and their families to carry out the program in a quiet place at home and not in random places (eg, on the beach and means of transportation). However, at the same time, this requirement may restrict treatment access and preclude participation by families who do not have the financial means to buy a computer and the necessary equipment for the

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videoconferences. Furthermore, families who go on vacation during the 6-month intervention period will have to plan to bring a computer to continue the program or postpone appointments if they are unable to access a computer, which may cause problems with respect to the treatment schedule. At the same time, the long study duration could cause study adherence issues. Nevertheless, it will be the responsibility of our research team to indicate whether the postponement of the sessions is agreed in advance (ie, for holidays or other justified or warranted engagements of the family) or it is instead linked to other factors associated with feasibility issues (eg, forgetfulness, lack of desire or motivation, and failure to carry out tasks). An accurate examination of the feasibility associated with both the training and study design and procedures will be reported.

To limit the issues related to potential biases associated with subjective measures [37], this study examines efficacy as well by using performance-based measures. Furthermore, it adopts a virtual reality–based assessment [69] requiring adolescents with ABI to do errands typical of the everyday setting, which could provide important information on their actual functioning in activities similar to those of real life. Inclusion of these measures will provide further evidence regarding the utility of the intervention in improving various neuropsychological consequences, and thus, this information could be useful to provide the National Health Care System with recommendations for survivors of pediatric ABI.

In addition, the examination of training and study procedure feasibility will allow investigating the usability of the training and the adequateness and potential replicability of the study design, which could help addressing potential issues to intervention delivery in the clinical context and study replication by future research teams. This could also favor the evaluation of the generalizability of trial findings to the general patient population of adolescents with brain injury, addressing sources of potential bias and imprecision. In the clinical context outside of an RCT setting, the I-TOPS intervention would be delivered in the same exact way as in this study, in terms of content, prompts to use the training and human involvement, which increases the relevance of findings of this study to inform the clinical practice.

Conclusions

If this phase-2 RCT yields positive results, a larger, multicenter, phase-3 RCT could be planned and delivered to examine I-TOPS intervention efficacy and cost-effectiveness in a larger sample. Since 2020, Italy has a network for sharing the best practices related to rehabilitation for pediatric neurological children—Rete Pediatrica degli IRCCS [78]—with an important focus on telerehabilitation. This network could enroll in the phase-3 RCT, particularly given that the institute conducting the phase-2 RCT is part of this network.

If the phase-3 RCT demonstrates efficacy, future work will focus on broader implementation within the Italian health system. Beyond providing clinical benefits to adolescents with ABI and their families, the I-TOPS intervention might reduce longer-term health care service use, thus limiting rehabilitation costs. The program might also have broader societal benefits through improvements in educational and vocational outcomes and reductions in criminal behavior frequently associated with EF impairments following ABI [6,9,13,18-24]. Considering local policy making and treatment delivery, the I-TOPS intervention requires limited economic resources to be implemented due to its web-based format and allows for a centralized psychologist, with expertise in the program and pediatric ABI, to provide treatment throughout the country rather than limited to a single region. Therefore, I-TOPS intervention delivery does not necessarily need individuals with this expertise throughout Italy, especially in rural areas or islands, but could allow clinicians of specialized rehabilitation centers to take charge of a wide range of patients, also reaching those living in remote regions. In addition, with the program being accessible at any time that is convenient for the adolescents and their families, it could be less burdensome than traditional clinic appointments, which often require children to miss school lessons or parents to modify their work schedules. Using I-TOPS intervention materials, the National Healthcare System might routinely provide the program to adolescents with ABI and their families throughout the country using a single central therapist to support the needs of multiple families in disparate locations. The findings from this RCT will be disseminated through publications in peer-reviewed and popular science journals and presentations at scientific conferences with the aim to reach relevant research, clinical, health service, and patient communities.

Acknowledgments

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Authors' Contributions

CC, AB, CU, RB, and SLW defined the study design and method. CC, MP, and SLW wrote the manuscript. AB, AJ, FAS, GP, CU, RB, RR, and SS significantly revised the manuscript. CC, MP, and SLW prepared the tables and figures. All authors read and approved the final manuscript.

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Conflicts of Interest

SLW is the developer of the original Teen Online Problem-Solving program, which was adapted for the Italian context (Italian version of Teen Online Problem-Solving) by the first author, CC. In this regard, we declare that no conflict of interest exists in data reporting: CC was not responsible for patient enrollment and allocation and was masked with respect to participants' group allocation; SLW did not have access to any information on patients nor to the database. All other authors declare no other conflicts of interest.

Multimedia Appendix 1
Training satisfaction questionnaire.
[PDF File (Adobe PDF File), 476 KB - resprot_v14i1e64178_app1.pdf]

Multimedia Appendix 2
CONSORT-eHEALTH checklist (V 1.6.2).
[PDF File (Adobe PDF File), 97 KB - resprot_v14i1e64178_app2.pdf]

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Abbreviations

ABI: acquired brain injury

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CONSORT: Consolidated Standards of Reporting Trials
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
DPO: Data Protection Officer
EF: executive functioning
I-TOPS: Italian version of Teen Online Problem-Solving
RCT: randomized controlled trial
SAE: serious adverse event
TBI: traumatic brain injury
TOPS: Teen Online Problem-Solving

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Protocol

Effectiveness of Text Messaging Nudging to Increase Coverage of Influenza Vaccination Among Older Adults in Norway (InfluSMS Study): Protocol for a Randomized Controlled Trial

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Abstract

Background: The coverage of influenza vaccination among older adults in Norway is insufficient, especially in some immigrant groups. To improve public health, there is a need for an intervention that can increase influenza vaccination coverage. Further, interventions tailored to reduce potential barriers among immigrants can reduce health inequities.

Objective: InfluSMS aims to determine if SMS nudging increases vaccination coverage among those aged 65 years or older (1) in Norway's general population; (2) among immigrants born in Poland; and (3) among immigrants born in Ukraine; and evaluate the impact of SMS nudging in Norwegian versus in the official language of the native country of immigrants born in Poland or Ukraine.

Methods: InfluSMS is a pragmatic randomized controlled trial conducted among people aged 65 years or older residing in Norway. Influenza vaccination coverage is the main outcome, measured in control and intervention arms for each of the 3 populations listed earlier. In all 3 populations, the control arm is standard care, that is, no individual reminder for influenza vaccination. All populations have an intervention arm that will receive an SMS nudge in the Norwegian language. In addition, the Polish and Ukrainian immigrant populations include a second intervention arm that will receive an SMS nudge in Polish or Ukrainian, respectively. In the general population, at least 23,485 individuals will be randomized to the SMS intervention arm while the rest of the population constitutes the control arm. In each of the 2 immigrant populations, we will randomize all eligible individuals 1:1:1 into the 3 arms. The intervention will take place at the start of the 2025-2026 influenza season. All eligible individuals will be passively followed up through the National Immunisation Registry, SYSVAK, from which individual influenza vaccination status 3 months after the SMS nudge will be collected. Coverage rates between arms within each population and effect sizes between the populations will be compared. The cost-effectiveness of SMS nudging will also be assessed.

Results: The inclusion of participants will start in the third quarter of 2025, and the registry data will be available in the first quarter of 2026. Coverage rates of each strategy and coverage differences between strategies will be presented.

Conclusions: SMS nudging is a scalable, inexpensive, and nonintrusive intervention that could be integrated into the national influenza vaccination program if the trial shows it effectively increases influenza vaccination coverage among older adults.

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Further, the trial will establish whether language is a barrier to influenza vaccination uptake among recent immigrant groups that have low influenza vaccination coverage, and to what extent this potential barrier can be diminished by SMS nudging in the official language of their native country.

Trial Registration: ClinicalTrials.gov NCT06486766; https://clinicaltrials.gov/study/NCT06486766

International Registered Report Identifier (IRRID): PRR1-10.2196/63938

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KEYWORDS

influenza vaccination; coverage; uptake; behavioral nudging; vaccine hesitancy; randomized controlled trial; undervaccination; migrant health; mobile health; mHealth; smartphones; eHealth; SMS

Introduction

Background

Seasonal influenza has a high disease burden worldwide and may cause up to 5 million severe cases and 645,000 deaths annually [1]. Vaccination against influenza is generally safe and may be effective in reducing influenza-like illness and associated conditions [2-4]. It is a widely recommended public health intervention [5,6], especially for groups experiencing a disproportionately high influenza burden such as older adults, who have a higher risk of severe disease, hospitalization, and mortality [7,8]. However, influenza vaccination coverage generally falls far below the 75% target set by the World Health Organization [9], thus many older adults that could have benefitted from vaccination remain unprotected. Furthermore, vaccine hesitancy, defined as a “delay in acceptance or refusal of vaccination despite availability of vaccination services” [10], is widespread for influenza vaccination [11]. The World Health Organization has defined vaccine hesitancy as one of the 10 current threats to global health [12].

Several immigrant groups have shown a relatively low vaccination coverage in their adopted country and a relatively high burden of vaccine-preventable disease [13,14]. This may partly be related to differences in vaccine hesitancy, which may differ between countries [15,16]. It may also be associated with more limited access to vaccination among some immigrant groups, for instance, if immigrants do not understand the language in their adopted country. Whatever the reason, efforts are needed to narrow the gap in vaccination coverage and to promote public health as well as health equity. Tailored interventions addressing acceptability and access barriers faced by immigrants may be useful to achieve this end [14,17].

Vaccine hesitancy is a complex phenomenon that has several psychological components [18,19] that may be influenced by public health interventions that facilitate action and reduce barriers to uptake [20,21]. Behavioral nudges may improve compliance with the use of primary health care services [22], including influenza vaccination uptake among older adults [23]. However, the effectiveness of nudging varies substantially by mode, content, and population [24]. Nudging by reminding older adults to vaccinate against influenza has proven effective in increasing coverage but with far higher effectiveness for reminders sent by ordinary mail [25] than by a governmental electronic letter system [26]. SMS text message nudging may improve childhood vaccination [27], COVID-19 vaccination among health system employees [28], and influenza vaccination among patients due for a routine primary care visit [29]. However, a recent systematic review of randomized control trials (RCTs) on text messaging for improving vaccine uptake shows that very few trials have addressed influenza vaccination among older adults [30].

Norway’s influenza vaccination program recommends vaccination to people aged 65 years or older, as well as to other risk groups and health care personnel. Each municipality organizes local vaccination of risk groups. Vaccination is typically available at general practitioner’s offices, health clinics, and pharmacies, and is currently offered at an out-of-pocket cost ranging from NOK 150 to 500 (US $14 to $47). In general, vaccination at general practitioners requires the vaccinee to schedule an appointment, while vaccination at pharmacies can be drop-in or scheduled. There is no individual invitation, reminder, or scheduling for vaccination organized by the influenza vaccination program. COVID-19 vaccination is also recommended to the same age group at the same time of year. The same vaccination conditions apply to all residents of Norway, regardless of their citizenship or legal residency status.

InfluSMS is designed as a pragmatic, multiarmed, superiority RCT embedded in the Norwegian influenza vaccination program. In this trial, we aim to determine if sending a smartphone SMS nudge to be vaccinated against influenza can improve vaccination coverage in the general population aged 65 years or older in Norway, and further, to determine the impacts on vaccination coverage associated with providing an SMS nudge in the official language of the native countries of immigrants born in Poland or Ukraine. The Norwegian setting is well suited to conduct an RCT on SMS nudging among older adults, including in selected immigrant groups because there are nationwide administrative and health registries that can be used for this purpose.

An RCT on SMS nudging for influenza vaccination among older adults is warranted because the coverage is insufficient and because evidence on the effectiveness of this intervention is lacking [23,30]. Moreover, most older adults in Norway have a smartphone, thus an SMS intervention is likely to reach most of the eligible population. It is also a relatively nonintrusive and inexpensive intervention that is highly scalable, which thus could function as part of a national influenza vaccination program.

On average the influenza vaccination coverage among older individuals in Norway is 64%. However, the coverage among

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some immigrant groups is much lower. Immigrants born in Poland and Ukraine have especially low coverage rates with only 19% and 3% vaccinated in the 2023-2024 influenza season, respectively (Table 1). Poles and Ukrainians are the 2 largest immigrant groups in Norway. As of March 2024, there were 110,000 and 66,000 immigrants from Poland or Ukraine, respectively, accounting for 2.0% and 1.2%, of the entire Norwegian population. Even though the age profile of immigrants from Poland and Ukraine is younger than for some other country backgrounds, they still account for many older adult individuals (Table 1), and this demography is likely to increase in the coming years. Furthermore, Poles and Ukrainians are relatively recent immigrants and may as such have a limited proficiency in Norwegian. If this language barrier hinders their uptake of services, it could potentially be reduced by providing nudges in the official language of their native country.

Table 1. Nationwide coverage[a] of influenza and COVID-19 vaccine among individuals aged 65 years or older[b] during the 2023-2024 influenza season in Norway, stratified by country background[c].

	Total population	Influenza vaccine[d], n (%)	COVID-19 vaccine[e], n (%)
All	1,020,728	656,990 (64.4)	555,745 (54.4)
Born in Norway	941,657	623,598 (66.2)	530,923 (56.4)
Born in Sweden	7129	4520 (63.4)	3976 (55.8)
Born in Denmark	5966	3820 (64.0)	3372 (56.5)
Born in United Kingdom	4606	2888 (62.7)	2594 (56.3)
Born in Germany	3991	2000 (50.1)	1783 (44.7)
Born in Poland	3888	740 (19.0)	520 (13.4)
Born in Ukraine	3843	119 (3.1)	72 (1.9)

[a]Norwegian Immunisation Registry SYSVAK [31] data, extracted May 31, 2024.

[b]Age on December 31, 2023 (born 1958 or earlier).

[c]The most common country backgrounds among individuals aged 65 years or older.

[d]Received at least 1 dose of influenza vaccine between September 1, 2023, and May 29, 2024.

[e]Received at least 1 dose of COVID-19 vaccine between September 1, 2023, and May 29, 2024.

Poles and Ukrainians in Norway also had a very low uptake of the COVID-19 vaccine, both during [32] and after (Table 1) the pandemic, showing that low uptake of adult vaccines in these populations is not limited to influenza vaccination. Thus, interventions that may overcome vaccine hesitancy, which is prominent in Ukraine and Poland [15,16], as well as potential access barriers such as language, are likely to have a general relevance for vaccine uptake.

A recent systematic review highlighted language and tailored text message nudges for improving vaccine uptake as understudied [30]. We are not aware of any studies that have investigated the effectiveness of SMS nudging for influenza vaccination in several languages among immigrant populations.

Objectives

The primary objectives of the InfluSMS trial are to establish whether (1) influenza vaccination nudging by SMS in the Norwegian language increases influenza vaccine coverage compared to standard care, among the Norwegian population aged 65 years and older; (2) influenza vaccination nudging by SMS in Polish or Ukrainian language increases influenza vaccine coverage compared to standard care, among older adults of Polish or Ukrainian background, respectively; (3) influenza vaccination nudging by SMS in Norwegian language increases influenza vaccine coverage compared to standard care, among older adults of Polish or Ukrainian background, respectively; and (4) influenza vaccination nudging by SMS in Polish or Ukrainian language increases influenza vaccine coverage more than nudging by SMS in Norwegian language among older adults of Polish or Ukrainian background, respectively.

For primary objectives 1-3, we hypothesize that SMS nudging will increase coverage. If this hypothesis is not confirmed, the interventions investigated here are futile from a public health perspective, and the remaining study objectives will not be investigated. For primary objective 4, we hypothesize that an SMS in the official language of the native country of each immigrant population will be more effective in increasing coverage than an SMS in Norwegian.

The secondary objectives are to establish whether (1) the effect of SMS nudging in the Norwegian language differs by country background; (2) the effect of SMS nudging in the official language of their native country differs between older adults of Polish or Ukrainian background; (3) SMS nudging for influenza vaccination is cost-effective compared to standard care; (4) SMS nudging for influenza vaccination influences coverage of COVID-19 vaccination; and (5) the time to vaccination differs by the comparisons described in the primary objectives.

Secondary objectives 1-4 are exploratory and have no hypotheses. For secondary objective 5, we hypothesize that SMS nudging will shorten the time elapsed to vaccination.

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Methods

Participants

Overview

All Norwegian residents have a unique personal identification number, which is used in health and administrative national registries and can be used to merge data across different registries. In this study, we identify all eligible individuals based on information available from the National Population Register and the Norwegian Immunisation Registry SYSVAK.

The trial has 3 separate populations of individuals who are aged 65 years or older and who reside in Norway, namely (1) the entire Norwegian population (except immigrants born in Poland or Ukraine); (2) immigrants born in Poland; and (3) immigrants born in Ukraine.

Inclusion Criteria

- Aged 65 years and older (age at the end of 2025, ie, born in 1960 or earlier).
- Resident in Norway and have a valid ID number on September 1, 2025.
- Have a smartphone number in the common contact register.

Exclusion Criteria

- Have received the 2025 influenza vaccine prior to the SMS nudge dispatch date.
- Have emigrated or died before SMS nudge dispatch date.

Interventions

Participants in the intervention arms receive an SMS reminder for influenza vaccination in Norwegian, Polish, or Ukrainian. Participants in the control arm do not receive an SMS reminder for influenza vaccination, which is "standard care" in Norway. A description and overview of the InfluSMS study arms and participant flow are shown in Table 2 and Figure 1.

Table 2. InfluSMS study arms.

Study arm	Description	Population
Control	Standard care: Individuals do not receive an SMS reminder for influenza vaccination.	• General population • Immigrants born in Poland • Immigrants born in Ukraine
Intervention 1	Norwegian nudge: Individuals receive an SMS in Norwegian language at the start of the influenza season; to remind them they are recommended to get the influenza vaccine	• General population • Immigrants born in Poland • Immigrants born in Ukraine
Intervention 2	Polish or Ukrainian nudge: Individuals receive an SMS in the official language of their native country (ie, Polish or Ukrainian) at the start of the influenza season, to remind them they are recommended to get the influenza vaccine	• Immigrants born in Poland • Immigrants born in Ukraine

Figure 1. InfluSMS participant flowchart.

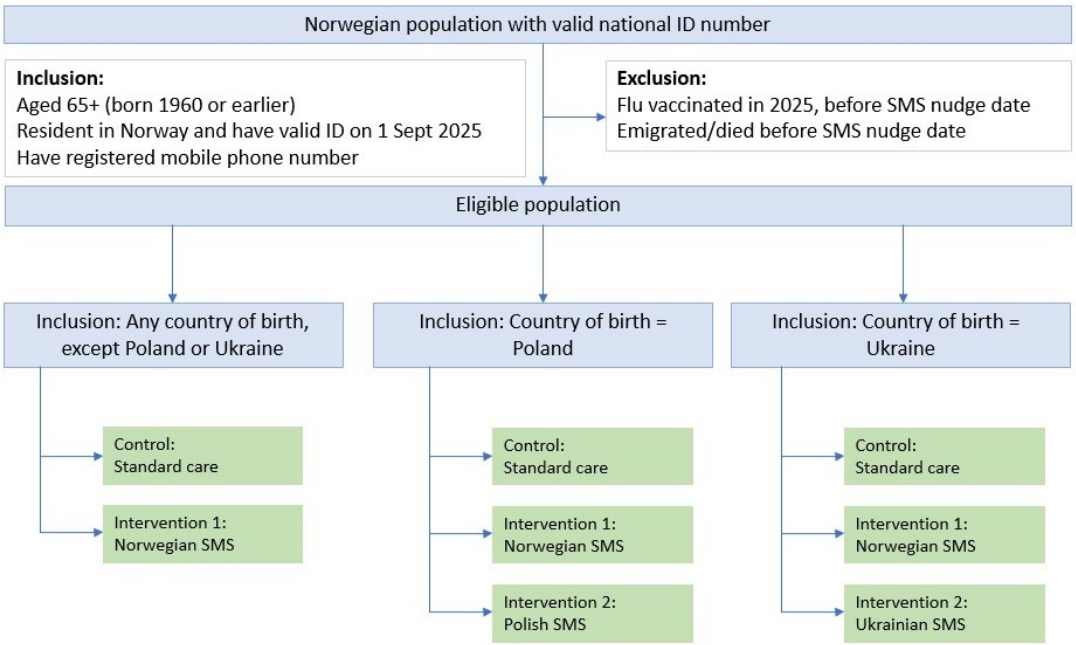

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Outcomes

The primary outcome measure is having been vaccinated against influenza during the 3 months following the SMS dispatch date in the 2025-2026 influenza season (yes or no, for each individual), as registered in the Norwegian Immunisation Registry SYSVAK [31]. Notification of influenza vaccination to SYSVAK is obligatory for vaccine administrators and does not require patient consent. Follow-up during this trial is passive and does not require any effort from the participants.

Effects will be assessed by influenza vaccination coverage, that is, percent uptake, which will be compared between strategies. SMS nudging will take place at the earliest timepoint at which vaccines for the upcoming influenza season become widely available across the country, which usually is around week 42. All SMS nudges will be dispatched within 1 week. Each individual will be followed up through SYSVAK for 3 months after their SMS dispatch date. We end follow-up at 3 months because we expect that the potential effect of an SMS nudge will be exhausted by then, and because most vaccinations in the influenza vaccination program will have occurred by the end of this period.

Time to influenza vaccination, that is, the number of days elapsed between the SMS dispatch date and the influenza vaccination date (as registered in SYSVAK), is a secondary outcome measure.

We will also address coverage of COVID-19 vaccination as an outcome in the exploratory analyses.

Sample Size

Primary Objective 1: General Population in Norway

We will identify all individuals in the National Population Register that fulfill the eligibility criteria, and among those, make a random selection to receive the Norwegian nudge (intervention 1). We power for a 1% point minimal detectable increase in uptake in the SMS arm compared to the control arm in the general population because the intervention is relatively inexpensive and might be cost-effective even with low effectiveness on coverage. To achieve this minimal detectable increase with a baseline uptake rate of 60%, a power of 0.8, and a 1-sided α of .05, we need to randomize 18,788 individuals to intervention 1. However, based on available statistics, some 20% of individuals may have received the influenza vaccine before the scheduled trial start date and will be excluded from the trial after randomization. We thus need to randomly sample at least 23,485 individuals aged 65 years or older from the entire Norwegian population (except those born in Poland or Ukraine) to be allocated to intervention 1 to be able to detect an increase of 1 percentage point (23,485×80/100=18,788). The control group will be the rest of the Norwegian population that fulfills the eligibility criteria. Currently, there are circa 1.1 million persons aged 65 years or older who reside in Norway. We use this large group as a control because it gives the study high power, the inclusion of individuals receiving standard care carries no cost, and it will provide real-world data on the entire older adult population in Norway.

Primary Objectives 2-4: Immigrants Born in Poland or Ukraine

To maximize power among individuals born in Poland or Ukraine, we will include all eligible individuals and randomly assign them 1:1:1 to each of the 3 study arms. The number we will be able to include in the trial will most likely be higher in 2025 than in 2023 (Table 1) due to the age structure in these immigrant populations and due to new migration. Based on current national demographic statistics, we anticipate there will be some 6000 individuals aged 65 years or older from each immigrant group at the start of the trial. However, some 10% may be excluded due to not having a registered phone number, and a further 1% and 6% (Table 1) may be excluded due to influenza vaccination before the scheduled SMS dispatch date among the Ukrainian and Polish immigrant populations, respectively. Thus, we expect to be able to randomize 5346 Ukrainian immigrants, giving 1782 individuals in each study arm. With a baseline uptake rate of 3% (Table 1), a power of 0.8, and a 1-sided α of .05, this gives a minimal detectable coverage increase of 2 percentage points, adjusted for 3 pairwise comparisons. Similarly, we expect to be able to randomize 5076 Polish immigrants, giving 1692 individuals in each study arm. With a baseline uptake rate of 19% (Table 1), a power of 0.8, and a 1-sided α of .05, this gives a minimal detectable coverage increase of 4% points, adjusted for 3 pairwise comparisons.

In conclusion, the minimal detectable coverage increases of this trial fall within the range of effect sizes reported for other modes of nudging investigated in neighboring countries that share a similar influenza vaccination policy. Specifically, a recent study from Denmark reported that nudging by electronic letters increased coverage by approximately 1% points [26], while a recent study from Finland reported that nudging by ordinary mail on average increased coverage by approximately 6% points [25].

Stratified Analyses

We will also perform analyses stratified by sex, broad categories of age, years of residency in Norway, and household composition. These analyses will have lower power to detect the differences indicated earlier because the sample size in each stratum will be lower than for the overall population.

Recruitment

The study uses data from all residents in Norway who meet the eligibility criteria. The data is retrieved from complete nationwide registries that contain routinely collected information. Therefore, recruitment and follow-up are entirely registry-based and do not require any action by the participants.

Assignment of Interventions

Assignment of treatment arm (control, intervention 1, and intervention 2) will be randomized, automated, and concealed. The identities of the participants will not be decipherable by the data managers.

We will use an external service provider to identify the eligible study population, perform the random selection and randomization procedures, and dispatch the SMS. The provider will be selected through a tendering process. All data

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management by the service provider will be done in close collaboration with and under the supervision of the project group. Data management, random selection, and randomization procedures will be performed with reproducible code that includes documented and adequate software functions, preferentially in R programming (R Foundation for Statistical Computing). For the Norwegian population, individuals in intervention arm 1 will be randomly selected from the whole eligible population, while the remainder of the eligible population will serve as the control arm. Similarly, we will use complete random assignment to treatment arm for the Polish and Ukrainian populations. Examples of R functions that serve these purposes are sample_n (from the *dplyr* package) and complete_ra (from the *randomizr* package). Random selection and randomization procedures will be performed after the assessment of the exclusion criteria. The project group will inspect the randomization code before dispatching the SMS.

Blinding

The outcome measure of the trial is based solely on routinely collected data and those reporting or registering this information will not be aware of whether a vaccinated individual has received an SMS nudge. Thus, the trial is blinded to the outcomes assessor. Moreover, treatment allocation is randomized and computer-generated, there is no interaction between the InfluSMS project team and study participants, and the InfluSMS researchers work with deidentified data and do not know the identity of any participant in the dataset. Due to the inherent characteristics of the intervention, treatment allocation cannot be blinded for participants.

Data Collection

The external service provider will be asked to prepare a key file that includes all individuals born in 1960 or earlier in the Norwegian population, with associated individual information including the individual national ID number, the household ID, a randomly generated study ID unique for each individual, and categorical variables indicating treatment arm and exclusion status. This key file will be shared with the National Population Register and SYSVAK. All registries involved will merge requested variables from their registry to this file by the national ID number, and forward the resulting file, excluding the national ID number, to the InfluSMS team. Using the study ID, InfluSMS researchers will then merge the deidentified files from the registries. The key linking the national ID numbers and the study ID numbers will be kept by the service provider and will never be accessible to the InfluSMS team. The procedure is illustrated in Figure 2.

Table 3 lists the variables that will be used in the trial. Note that the national ID will only be used to generate the dataset.

Figure 2. InfluSMS data flow and deidentification of registry data.

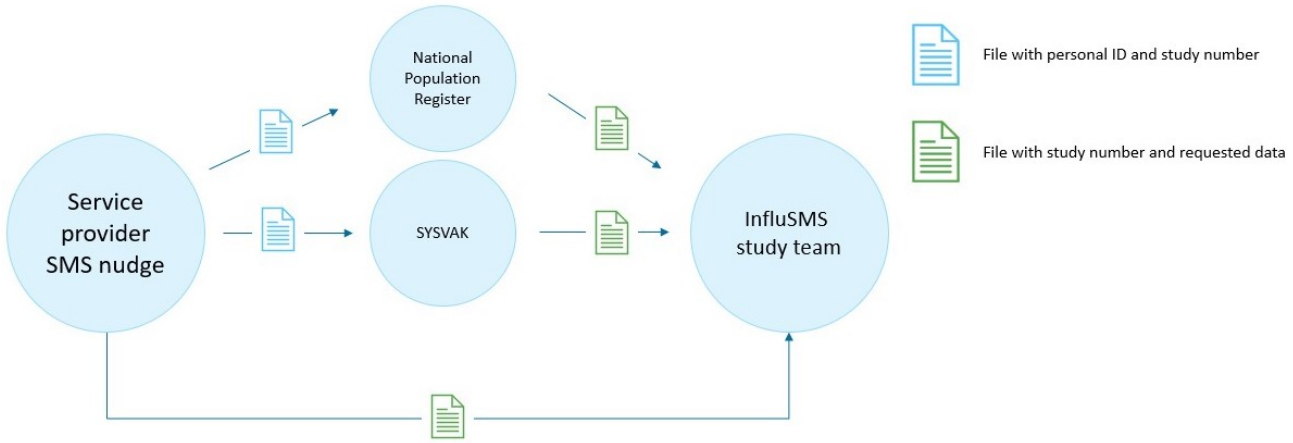

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Table 3. List of variables collected or generated in the trial.

Variable	Reason for inclusion
National Population Register	
National ID	Used to identify eligible individuals and link to study ID. Not shared with InfluSMS project group
Household composition	Variable identifying whether eligible individuals live in the same household, to enable sensitivity analyses
Year of birth	Potential confounder (age)
Sex	Potential confounder
Vital status, with date	Exclusion of individuals who died or emigrated
Country of birth	Determine if born in Poland or Ukraine
Immigration date	Determine time living in Norway (potential confounder)
SYSVAK	
National ID	Used to identify eligible individuals and link to study ID. Not shared with InfluSMS project group
Date of vaccination	Determine if date of vaccine was before/after nudge, and impact of vaccination
Disease against which the vaccine protects: • Influenza • COVID-19	Determine who received each vaccine, to calculate vaccination coverages
External service provider	
National ID	Used to identify eligible individuals and link to study ID. Not shared with InfluSMS project group
Demography: • General population • Born in Poland • Born in Ukraine	Study populations
Randomized, and received intervention (SMS): • Yes • No	Identify control or intervention groups
Date SMS was sent	Start of intervention
SMS language: • Norwegian • Polish • Ukrainian	Type of intervention
Excluded from study: • No • Yes, with code for reason	Quantify exclusions
SMS sending errors: • Yes: error in sending • No: no known error	Quantify errors with intervention or infrastructure

Data Management

All data management and analyses will be scripted in R code so that each step can be reproduced and quality assured. Range and other logical data checks will be performed for quality assurance. Programming will be validated by several team members. Data and scripts will be used and stored in a high-security data zone that will be accessible only to team members via login.

Statistical Methods

All individuals randomized will be analyzed, except individuals who die or emigrate during follow-up, who will be excluded from the analyses. We expect exclusions to be evenly distributed between treatment arms due to the randomized design.

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Additionally, we anticipate a low proportion of excluded individuals given the relatively short follow-up time of the trial. According to official statistics [33], we can expect approximately 2800 deaths and 100 emigrations per month among the nearly 1.1 million persons aged 65 years or older residing in Norway, which accounts for 0.3% of this population.

As recommended for binary RCT outcomes [34], coverage differences between treatment arms will be expressed on absolute and relative scales, that is, as percentage point differences and as relative risks, with associated 95% Wald CIs. The primary focus will be on absolute scale analyses because they may be most informative for public health decision-making. Absolute estimates will be derived from linear regressions [35], while relative estimates will be derived from generalized linear models with a log-binomial link function [36]. Overall interactions (specifically secondary objectives 1 and 2, where differences between treatment arms will be compared between country backgrounds) will be assessed by likelihood ratio tests and, if significant, further analyzed by the participation differences between factor levels of the variables that interact.

We will compare the time to vaccination (ie, the number of days elapsed between the SMS dispatch date and the influenza vaccination date) between trial arms by the Kaplan-Meier method and the log-rank test.

We assume the registry data for randomized individuals to be close to complete and thus will not impute missing values.

As sensitivity analyses, we will exclude households consisting of at least two or more people aged 65 or older. Comparing the results of these analyses with the main results will indicate whether there may be spillover effects of the SMS interventions within households. Moreover, it will exclude persons living in nursing homes, who may experience easier access and less autonomy regarding influenza vaccination. In exploratory analyses, we will also address the potential effects of SMS nudging for influenza vaccination on the coverage of COVID-19 vaccination. We will use the same statistical methods for these sensitivity and exploratory analyses as described for the main analyses.

We will develop a decision analytic model that can evaluate the potential cost-utility of each nudge compared to standard care and each other. The model will be based on coverage differences observed in the trial and will incorporate implications of increased coverage on the spread of influenza and its consequences for the use of health care resources. Data on reduced influenza from increased uptake will be based on effect estimates of vaccination from the best available scientific evidence. Costs associated with the intervention as well as with increased uptake of the vaccine will be recorded in detail during the project phase. Direct medical costs related to the downstream use of health care services will also be incorporated into the model. The cost-utility analysis will be based on Norwegian guidelines [37], conducted according to standard principles for health economic evaluation [38], and reported according to current guidelines [39].

Data Monitoring

The trial does not pose any harm to participants; thus, the project does not have a data monitoring committee or plans for auditing of trial conduct. Similarly, there will be no interim analyses before the end date of follow-up and no stopping guidelines for the trial.

Ethical Considerations

We have submitted the project for initial evaluation to the Regional Committees for Medical and Health Research Ethics, who recently determined that the project does not fall under the jurisdiction of the Health Research Act [40] (reference #787321). We will thus apply for exemption from the duty of confidentiality from the Health Directorate. The rationale for this decision was that the objective of the research is not to gain new knowledge on health and disease as such, with reference to paragraphs 2 and 4a of the Health Research Act. The application was considered by the REK sør-øst B committee.

This study cannot be performed based on informed consent. Exemption from the duty of confidentiality gives a permit to access and merge the personal registry data without obtaining informed consent. We have conducted several similar registry-based studies. It is our experience that exemption for the duty of confidentiality is granted for studies of this nature, that have large potential public health benefits and no direct consequence for participants [41-44]. The registries own their data and will grant the project data access based on the permits we supply in our data application (ie, exemption from the duty of confidentiality).

Smartphone numbers will be accessed through the Contact and Reservation Register, in which every Norwegian citizen who has logged into a Norwegian public service using an electronic ID is registered. Individuals can opt out of the register, and those who have done so will not receive an SMS as part of this study. About 95% of the adult Norwegian population is part of the Contact and Reservation Register. Opting out will not be considered in the analyses in this pragmatic trial because access to smartphone numbers would be through the same register if SMS reminders were part of the influenza vaccination program. We expect that the drop-out rate will be similar across treatment arms due to the randomized design.

We will submit the protocol and approvals together with a dedicated data protection impact assessment for assessment by the data protection officer at the National Institute of Public Health. The data protection officer oversees data processing in research projects to ensure it is in accordance with applicable data protection laws. The main principles regarding data protection and confidentiality in the project are described in the Data Collection and Data Management sections.

In case of protocol amendments, all stakeholders that have granted approvals to the project, as well as Clinicaltrials.gov, will be notified. None of the project members have any financial or other conflicting interests to declare.

Data access is contingent on the specific permits described above. Thus, data are only accessible to project members. To advise the project, users of Polish, Ukrainian, and Norwegian

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origin will be part of the project group. We will also have focus groups with users from each nationality to help formulate acceptable and adequate SMS nudges.

Dissemination

We plan to publish the protocol and the findings of the trial in international peer-reviewed scientific journals. Authorship will be granted according to the Vancouver Convention. Professional writers will not be used.

The findings will also be presented at national and international conferences. To inform the public, we will publish information about the trial on a project web page. Information aimed at the public will mainly be in Norwegian. Further, we will present the project to various stakeholder groups, notably the main user groups of the study (organizations for older adults and immigrant groups) and public health organizations.

Results

As of July 3, 2024, the project has received funding for protocol development from Foundation Dam (grant SDAM_FOR-558766) and we are in the process of obtaining permits, agreements, and access to the infrastructure needed to conduct the trial. Inclusion of participants will start in the third quarter of 2025 and the outcome registry data will be available in the first quarter of 2026. We plan to publish the results during the fourth quarter of 2026.

The results will be reported according to the Consolidated Standards of Reporting Trials (CONSORT) statement on eHealth [45,46]. We will present the baseline characteristics of the 3 study populations, and describe the coverage by treatment arm and population, for strata of age, sex, and duration of residency. We will present the absolute and relative coverage differences between the treatment arms as described in objectives 1-4. In addition, we present comparisons of effect sizes between populations as described in secondary objectives 1 and 2, on absolute and relative scales. The primary focus will be on absolute scale analyses for the coverage analyses (primary outcome measure). We also compare the time to vaccination between treatment arms (the secondary outcome measure). All effects are presented with 95% CIs. We also present the likelihood ratio test *P* value for interaction terms. Table shells for the analyses described earlier can be found in Multimedia Appendix 1. The main findings may also be illustrated in the figures.

Discussion

This pragmatic RCT will provide insights into the effectiveness of SMS reminders in improving influenza vaccination coverage among older adults, which was specifically mentioned as a knowledge gap in a recent review on this topic [23]. The trial will estimate the effectiveness in the older adult population in Norway at large, and among older adult immigrants from Poland or Ukraine, which are large immigrant populations that have a particularly low influenza vaccination coverage in Norway. For the immigrant populations, the trial will also address whether the language of their adopted country may represent a barrier to influenza vaccination uptake that can be reduced by SMS nudging in the official language of their native country. If SMS nudging is effective, it is a strategy that may be feasible for implementation in a nationwide influenza vaccination program because it is scalable, inexpensive, and non-intrusive. Since influenza vaccination protects against influenza and its sequelae, a higher influenza vaccination coverage will benefit society through lower health care costs, as well as the individuals who get vaccinated through direct protection against influenza.

Strengths of this trial include the use of data on nearly all individuals aged 65 years or older residing in Norway, whose health and administrative data are captured in nationwide registries without any loss to follow-up. This eliminates selection and response biases associated with surveys, ensures high quality of the main outcome measure of the trial, that is, influenza vaccination coverage, and yields results that are valid at the national level. Further characteristics that contribute to the high internal validity of this study include the randomized design, no experimenter bias, and standardized procedures for all participants. This trial also has high external validity since it is conducted in real life and will thus yield data that will be entirely representative of how these interventions would work should they become part of an adult vaccination program. Moreover, the results are likely to be of relevance internationally, both as a proof of concept of whether SMS interventions might be effective in increasing adult vaccination coverage and more directly for the immigrant groups addressed here, which likely experience similarly low coverage, for similar reasons, in other adopted countries. The trial will also establish the feasibility of implementing an SMS nudging intervention using the infrastructure available in Norway, for instance in terms of timely access to the necessary health and administrative registry data. Novelty is another strength of the study since we are not aware of other trials with similar interventions and objectives. The trial will also be informed by users, which may enhance its relevance to the populations targeted by the interventions.

The trial also has several limitations, most of which relate to the number of Polish and Ukrainian immigrants we will be able to randomize. First, the number of persons in the immigrant groups who are aged 65 years or older in the 2025-2026 influenza season is a moving target that will be influenced by the influx and outflux of people by that time, as well as the exact underlying age distribution of these immigrant populations. Second, our estimates of the fraction of people missing a registered smartphone number are based on statistics for the whole Norwegian population, and we do not know whether this fraction may be different for the Polish and Ukrainian sub-populations. Third, the minimum detectable effect size for the Polish and Ukrainian populations is approximately 4% and 2% points, respectively. This may be a limitation because even smaller effect sizes might be of public health interest for an inexpensive intervention. Finally, even though we will initiate the trial at the very start of the influenza season, some people will already have been vaccinated by this point, and they will be excluded from participation in the trial. The number of excluded individuals will depend on national vaccine distribution logistics and the epidemiology of influenza in the trial season, which are beyond our control.

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The current influenza vaccination program lacks an individual cue to action, which could potentially be more effective than a general recommendation that lacks personalization or direct communication. Sending SMS nudges for influenza vaccination is one way to make individual contact that is likely to reach a very large proportion of the eligible population. If sending SMS reminders is effective, even small effect sizes may benefit public health and be cost-effective. Furthermore, nudges tailored to immigrant groups that have very low uptake of influenza vaccine may reduce inequalities in the use of this preventive health care service and, thus, in health. Insights from the interventions investigated in the current trial can extend to other vaccination contexts and be of international relevance.

Acknowledgments

The authors wish to thank Suzanne Campbell from the National Immunisation Registry SYSVAK for providing background coverage estimates, and Folkehelseforeningen for administrative support and endorsement for project funding. The project was funded by Foundation Dam (grant SDAM_FOR-558766). The funder did not have any role or authority in the study design; collection, management, analysis, and interpretation of data; writing of the report; or decision to submit the report for publication.

Data Availability

The datasets generated in this study are not publicly available because the participants have not consented to it. The data are available from the corresponding author upon reasonable request with permission from the relevant Norwegian authorities.

Authors' Contributions

BTH, LEØ, and HM conceived the study. BTH acquired funding for the study and is the principal investigator. BTH and HM wrote the original draft of the manuscript. All authors contributed to the development of the methodology of the study, critically reviewed manuscript drafts, and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Table shells for statistical analyses.
[DOCX File , 27 KB - resprot_v14i1e63938_app1.docx]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
RCT: randomized controlled trial

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Protocol

Testing a Dashboard Intervention for Tracking Digital Social Media Activity in Clinical Care of Individuals With Mood and Anxiety Disorders: Protocol and Design Considerations for a Pragmatic Randomized Trial

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Abstract

Background: Mood and anxiety disorders are prevalent mental health diagnoses. Numerous studies have shown that measurement-based care, which is used to monitor patient symptoms, functioning, and treatment progress and help guide clinical decisions and collaboration on treatment goals, can improve outcomes in patients with these disorders. Including digital information regarding patients' electronic communications and social media activity is an innovative approach to augmenting measurement-based care. Recent data indicate interest and willingness from both mental health clinicians and patients to share this type of digital information in treatment sessions. However, the clinical benefit of systematically doing this has been minimally evaluated.

Objective: This study aims to develop an electronic dashboard for tracking patients' digital social activity and a protocol for a pragmatic randomized trial to test the feasibility and efficacy of using the dashboard in real-world clinical care of patients with depression or anxiety disorders.

Methods: We developed a personalized electronic dashboard that tracks patients' electronic communications and social media activity, visualizes data on these interactions through key graphics and figures, and provides a tool that can be readily integrated into routine clinical care for use by clinicians and patients during treatment sessions. We then designed a randomized trial to evaluate the feasibility and effectiveness of using the electronic dashboard in real-world care compared to treatment as usual. The trial included patients aged ≥12 years with a mood or anxiety disorder who were receiving treatment in outpatient psychiatry clinics in the Johns Hopkins Health System and the Kennedy Krieger Institute. The primary outcome includes changes in patient-rated depression symptoms. Secondary outcomes include changes in patient-rated anxiety symptoms and overall functioning. Exploratory analyses examine the impact of the intervention on measures of therapeutic alliance and the detection of clinically actionable targets.

Results: We successfully developed an electronic dashboard for tracking patients' electronic communications and social media activity, and we implemented a protocol for evaluating the feasibility and efficacy of using the dashboard in routine care for mood

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or anxiety disorders. The protocol was approved by the Johns Hopkins University School of Medicine Institutional Review Board. In this study, we report the technological, ethical, and pragmatic considerations in developing the dashboard and testing it in a real-world setting.

Conclusions: The integration of an electronic dashboard to monitor digital social activity in mental health care treatment is novel. This study examines the feasibility and effectiveness of the dashboard and the challenges in implementing this protocol. The lessons learned from developing and implementing the study will inform ongoing discussions about the value of gathering collateral information on patients' digital social activity and how to do so in a way that is acceptable and clinically effective.

Trial Registration: ClinicalTrials.gov NCT03925038; https://clinicaltrials.gov/study/NCT03925038

International Registered Report Identifier (IRRID): DERR1-10.2196/63279

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KEYWORDS

digital mental health; mental health; dashboards; psychiatry; measurement-based care; electronic communication; social media; depression; anxiety; personal health information

Introduction

Background

Mood and anxiety disorders are among the most common mental health disorders in the United States, and they are associated with significant morbidity, mortality, and overall impairment in functioning [1]. These disorders are prevalent across the lifetime, with an onset often in adolescence, and evidence suggests that their rates are increasing in this age group in the United States [2]. A tragic outcome of depression and anxiety is suicide, which has increased by 30% since 2000 and is a leading cause of death in individuals aged between 10 and 34 years [3].

There are treatments for mood and anxiety disorders, but these are not always effective. In a meta-analysis of 38 studies of patients with depression and anxiety receiving outpatient mental health therapy, >40% did not show a reliable change in symptom improvement [4]. Barriers to effective treatment include patient adherence to the treatment model, session attendance, and the alignment between patients' needs and clinicians' therapeutic modalities [5]. There is clearly an urgent need to provide improved mental health care and develop new approaches to treat patients with mood and anxiety disorders.

Measurement-based care (MBC) is a promising but underused approach to providing more effective care for patients with mood and anxiety disorders [6]. MBC refers to the systematic use of measurement tools to monitor patient symptoms, functioning, and treatment effects in care to guide clinical decision-making and promote collaborative treatment planning [7]. A wealth of evidence shows that, when properly implemented, MBC can significantly improve patient outcomes; however, clinicians have been slow to adopt MBC in routine practice [8]. MBC traditionally entails the regular collection of patient-rated or, less frequently, clinician-rated outcome measures during treatment. A significant barrier to adopting MBC is the burden on both patients and clinicians to collect the outcome measures during busy clinical encounters [7]. The emergence of digital technologies, such as smartphones and wearables, has the potential to dramatically broaden the scope of MBC by offering new sources of collateral information that can be more readily leveraged to achieve the goals of MBC [9]. Digital information from these devices can provide valuable insights into a patient's course of illness in real time beyond the point of care [10], and the information can be "passively" collected, which reduces the burden on patients and providers and facilitates downstream use as part of a more expansive approach to MBC [9].

A variety of information relevant to mental health can be gleaned from digital devices [9]. A particularly rich source of digital information is available from social media [10] and other forms of electronic communication, such as SMS text messages [11], collectively referred to as digital social activity in this study. Our social activity is crucial in shaping our mental health, and electronic communication and social media platforms have transformed the way people communicate and interact with one another daily. Indeed, they are typically the predominant form of communication, especially among adolescents and young adults [12,13].

A growing body of research has examined the potential for obtaining useful clinical insights into mental health from digital social activity. Multiple studies have shown that quantifiable signals derived from the language used and activity on different social media platforms are associated with and can be used to develop computational models that distinguish individuals with depression [14-17], postpartum depression [17], schizophrenia [18-20], posttraumatic stress disorder [21], and other serious mental illnesses [22,23]. Other studies have developed models that can predict clinically salient changes in the trajectories of mental illness, such as relapse leading to hospitalization in patients with psychotic disorders [22], the emergence of suicidal ideation or attempts [24,25], the occurrence of binge drinking [26], and clinical responses to antidepressant treatments [27]. Many earlier studies were limited by a reliance on self-report or inferences drawn from data available on social media platforms to establish "ground truth" about mental health end points. In addition, these studies typically analyzed data from only 1 social media platform, while individuals regularly engage with multiple platforms [28]. More recent studies have validated models using clinically documented samples with data from electronic health records [16,20], and another recent study specifically addressed the challenges of developing generalizable models based on diverse social media data sources [29].

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Together, these studies suggest that it is possible to reliably monitor digital social activity for actionable collateral information, sparking interest in using such information to improve clinical care for patients with mental illnesses.

Several recent surveys have found that clinicians ask about their patients' electronic communications and social media activity [30-32], and they believe that using this information is helpful in providing more effective treatment [32]. Both clinicians and patients have reported that they are comfortable with using and discussing social media and digital data in mental health therapy [31,33,34]. However, one study found that adult patients were less willing to share more personal data, such as their location or private communications, compared to less personal data, such as screen state (ie, phone screen on or off) and motion data [34]. Another study found that therapists were concerned about whether patients' online posts would accurately reflect their mood, while patients did not want their use of social media and content to be the sole focus of their therapy sessions [31]. In a different study, adolescent patients at risk of suicide, whose social media activity was being monitored by their therapists, expressed concern about the balance between privacy and safety, with some reporting that they may be less likely to seek peer online support [35].

Despite the promise, it remains unclear whether systematic monitoring of digital social activity in routine care of patients with mood or anxiety disorders is acceptable and feasible. Moreover, it has not been shown whether doing so is effective in improving patient outcomes. One group has reported on the design and development of an electronic dashboard for displaying the results of computational analyses of patients' digital social activity that can be used by clinicians and patients [36,37]; however, the use of this dashboard has not been formally tested in clinical practice. Another group has taken a simpler approach to incorporating collateral information from patients' digital social activity and tested this approach in an unblinded randomized trial [38]. They found that integrating insights about patients' social media use in clinical care is feasible; however, there was no significant difference in mental health outcomes between the intervention and treatment as usual (TAU) arms [38]. More research is needed to better understand the appropriate role of systematically monitoring digital social activity in routine clinical care of patients with mental illness.

Objectives

This study was initiated to address the aforementioned need. In this study, we report on the development of an electronic dashboard for tracking patients' digital social activity and a protocol for a pragmatic randomized trial to test the feasibility and efficacy of using the dashboard in real-world clinical care of patients with depression or anxiety disorders. We describe our guiding conceptual model and the decisions we made in designing the dashboard and protocol to test the dashboard, and we discuss the challenges we confronted and the solutions we implemented to launch the trial. The systematic monitoring of patients' digital social activity in clinical care is not only novel and promising but also presents several important challenges. This study informs discussions about translating the promise into clinical reality and sets the stage for reporting trial results in a subsequent paper, which will ultimately contribute to the evidence base on whether monitoring digital social activity in clinical care is warranted.

Methods

Conceptual Model

The conceptual model that guided our development and testing of a digital social media intervention in patients with depression or anxiety is shown in Figure 1.

It is grounded in the principles of MBC. We have an expansive view of MBC, which posits that systematically monitoring multiple sources of collateral information, in addition to patient- and clinician-rated outcomes measures, throughout the course of treatment can significantly improve clinical outcomes. In this case, the intervention is designed to gather collateral information about the patient's digital social activity, which growing evidence suggests can provide important real-time insights into the patient's mental health status. We hypothesize that such an intervention may improve downstream clinical outcomes through 2 mediating pathways. In the first pathway, routinely gathering collateral information on the patient's digital social activity may lead to better detection of clinically actionable targets. Clinically actionable targets may include the early detection of signals that the patient's course of illness is starting to worsen or of interpersonal struggles that may precipitate declines in the course of illness. Earlier detection of these clinically actionable targets can lead to more rapid treatment adjustments to address emerging issues before they become more intractable problems. The treatment adjustments may involve a wide variety of interventions, including changes in medication; frequency and duration of clinical visits; the focus of psychotherapy; and outreach to parents, the school, or other responsible parties in the patient's social support network. In the second pathway, the digital social media intervention may improve the therapeutic alliance by fostering more informed and open communication between the patient and clinician, and a substantial body of evidence indicates that a strong therapeutic alliance is crucial to the success of psychiatric treatment [39]. The conceptual model hypothesizes that through these 2 mediating pathways, the intervention may improve more proximal clinical outcomes on clinical symptomatology, which, in turn, leads to improvements in more distal outcomes, such as overall functioning. It is possible that routinely collecting information about the patient's digital social activity may lead to the false positive detection of clinically actionable targets, leading to unnecessary and perhaps harmful changes in treatment. Another possibility is that data collection may disrupt the therapeutic alliance between the patient and clinician by raising concerns over privacy and engendering distrust, which together could ultimately lead to worse clinical outcomes. These are empirical questions about the impact of the proposed intervention that need to be tested and are the focus of our randomized pragmatic trial.

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Figure 1. Conceptual model of the mediating pathways by which an intervention designed to monitor patients' digital social activity may impact proximal and distal patient outcomes. ED: emergency department; GAD-7: Generalized Anxiety Disorder-7; M-CICAS: McLean Collateral Information and Clinical Actionability Scale; PHQ-9: Patient Health Questionnaire-9; SES: Session Experience Scale; SF-36 MHC: Short Form-36 Health Survey Mental Health Component; WAI: Working Alliance Inventory.

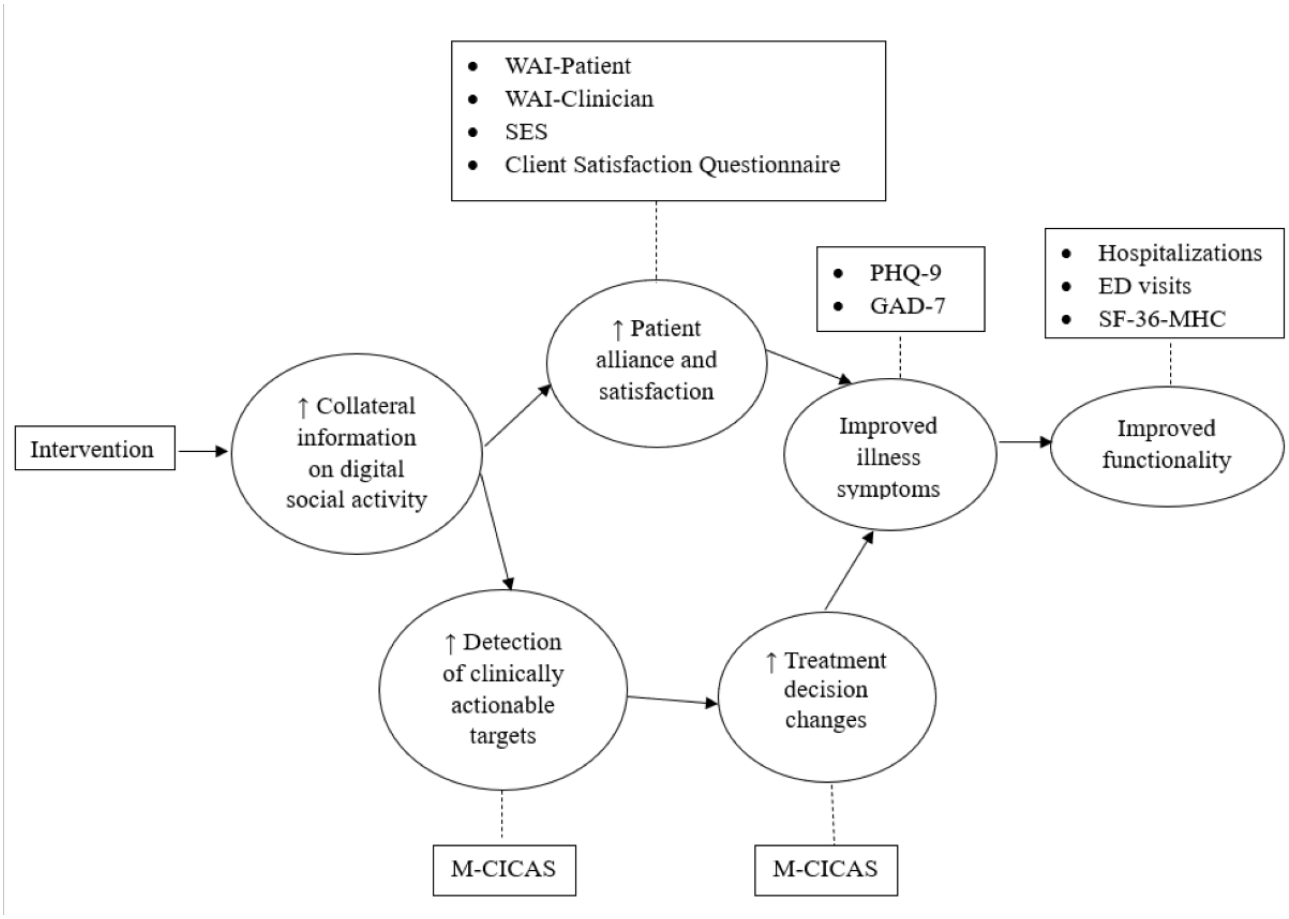

Electronic Dashboard

Overview

We developed an electronic dashboard to present information about our patient participants' digital social activity for review by their treating clinician in collaboration with the participants during routine clinical encounters. The creation of each personalized dashboard involves 4 steps. First, data from different social media and electronic communication platforms used by the participants, which they have identified for release, were collected using a commercially available app called Bark. Second, the gathered data were transferred to and processed at Johns Hopkins University. Third, the data were analyzed and translated into a set of key graphs and figures that can be rendered in an electronic dashboard format. Fourth, a patient-specific dashboard was delivered to the treating clinician. For each of these components, we implemented steps to ensure the privacy and security of the data as they were gathered and processed, which are detailed in the Data Collection and Data Processing sections.

Data Collection

Data from the patient participants' digital social activity were collected using Bark [40]. Bark is a commercially available app that is designed for use by parents or caregivers to monitor and manage their children's online activity by scanning >30 social apps, web browsers, emails, and SMS text messages. It provides alerts based on algorithms trained to detect online threats, such as cyberbullying, and offers personalized insights and recommendations regarding how to address these alerts. The app works with both iOS and Android mobile devices, but differences exist in how the app accesses certain communication platforms. Apple has stricter controls to prevent third-party apps' direct access to monitor iOS devices. Therefore, to access text messages on iOS devices, users install an app on a desktop computer, and text messages from the iOS device are "manually" transferred to the desktop via a cord connection and uploaded to Bark when the desktop is connected to the internet.

In partnership with Bark leadership, we modified the app for use in this research project by shutting down all features, including alerts, except those related to gathering data from participant activity on SMS text messages, email, and various social media platforms. As a result, the Bark app was used in our study as a data collection tool rather than an analytic tool. Textbox 1 shows the data types and platforms that are monitored by the app.

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Textbox 1. Overview of data types and platforms monitored by Bark.

Data type and data sources

- Email: AOL, Comcast, Gmail, iCloud, Outlook, and Yahoo
- Search engine: Microsoft Edge (Android), Firefox (Android), Google Chrome (Android), and Safari (iOS)
- Social media: Instagram, Twitter, Snapchat, Facebook, Pinterest, Reddit, Tumblr, and TikTok
- Text messaging: GroupMe, SMS text messages (Android and iOS), iMessage (iOS), Gmail Chat, WhatsApp, Discord, and Kik
- Miscellaneous: Google Drive (documents and comment or reply), iCloud Notes (iOS), YouTube (comment), and OneNote

Data Processing

Bark executes queries to their internal database at regular intervals (approximately every 30 min) that identify newly captured digital traces from all active participants in the study. These queries generated JSON-formatted data files, which were then automatically uploaded to a password-protected access point on Amazon Web Services Simple Storage Service (AWS S3). Data files were transferred through an encrypted https or transport layer security connection from AWS S3 to a remote network drive hosted at Johns Hopkins University using a scheduled job that executes hourly on a remote server. Microsoft Active Directory was used to restrict network drive access to a subset of study team members on a need-to-have basis. The study team did not provide Bark with any information about patient participants except for the unique signup codes. Data collected by Bark were not shared with guardians in the case of minor participants.

Bark does not apply any exclusion criteria to preemptively filter data uploaded to AWS S3. Instead, the study team used an intermediate processing stage to discard data that lacked natural language text, were unlikely to contain clinically relevant information (eg, promotional emails), or were of a nature that would be likely deemed too invasive by study participants. Images, videos, geolocation tags, and internet use (not including search engine queries) fell into the latter group. Text from the remaining data was passed through a toolkit, which replaced personally identifiable information (ie, phone numbers, social security numbers, zip codes, email addresses, and names) with grammatically appropriate synthetic alternatives [41].

Dashboard Generation

The research team developed several algorithms to analyze the electronic communication data (ie, messages) gathered via the Bark app and, in turn, created a patient participant–specific dashboard that highlighted patterns of patient electronic communication use relevant to their mental health. The choice of the information displayed on the dashboard was primarily based on previous empirical observations recorded in the literature regarding relationships among digital activity, language use, and mental health status (ie, anxiety and depression), and certain visual elements (ie, distribution of platforms used by the participant and the total number of messages sent) were included to contextualize the analyses. Some measures of use were included on the dashboard to facilitate clinician engagement with patient participants (eg, use by platform). Broadly, the type of information displayed to clinician participants about patient participants fell into the following 3 general categories: use statistics, content, and measures of content.

Use Statistics

The dashboard presented information regarding the frequency at which the patient participant had recently used electronic communication. To contextualize the information contained within the dashboard, digital cards located at the top of the dashboard indicated the number of messages a patient participant sent and received during the past week (with comparisons to a running weekly average), a list of platforms (eg, SMS text messages and Discord) used to send messages, and an indicator of the platform most frequently used to send messages [42,43]. To identify possible sleep disturbances or irregularities, a bar graph presented the daily distribution of messages sent during the daytime (6 AM to midnight) and late at night (midnight to 6 AM) over the past 7 days [44,45]. To provide an indication of social connectedness, a second bar graph displayed a weekly distribution of messages sent and received during the past 90 days [46]. A final bar graph displayed the weekly distribution of platforms used to send messages during the past 90 days, which was included primarily to engage participants and provide grounding to existing digital measurement tools (eg, iOS Screen Time).

Content

Language from messages sent by the patient participant during the past 7 days was displayed in multiple forms throughout the dashboard. First, to provide a general summary of the patient participant's communication patterns over the previous week, a word cloud displayed the 40 most frequently used words across all digital platforms, with the size of each word dependent on its use frequency. Second, to capture recent thoughts, interests, and personal challenges, search engine queries were semantically clustered using an external knowledge base derived from Wikipedia and then listed within a table [47,48]. To highlight specific psychologically relevant themes, all messages were processed by the Linguistic Inquiry and Word Count (version 2007) toolkit [49]. The most frequently used words for a set of predefined themes were identified as psychologically relevant in previous literature [16,50-54] and representative messages for those themes were displayed. These themes included the following: positive emotion, negative emotion, anxiety, anger, sadness, family, friendship, work, health, achievement, leisure, home, money, and death. Representative messages for each theme were those that contained the highest number of thematically relevant words. Importantly, as a privacy measure, representative messages were hidden behind a pop-up window until patient participants granted their clinician verbal

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permission to view them. In all the aforementioned cases, common "stop words," such as articles and pronouns, were excluded from consideration.

Measures of Content

Several numeric measures were also extracted from the content described earlier and visualized in the dashboard. A bar graph showed the proportion of messages sent over the previous 7 days that contained each theme from the Linguistic Inquiry and Word Count toolkit. To facilitate temporal comparisons, a heat map displayed this same measure computed weekly over the previous 90 days. A second heat map displayed the proportion of messages, aggregated weekly over the previous 90 days, containing different forms of pronouns (eg, personal vs impersonal and first person vs third person). The inclusion of the pronoun measures was based on multiple previous studies identifying correlations between the use of certain pronoun forms and mental health status [55-57].

Dashboard Delivery

Electronic dashboards for each patient participant were updated nightly using an automated script and stored as HTML in a password-protected relational database. Code hosted on a web server behind the Johns Hopkins University firewall was used to retrieve and display dashboards to the clinicians treating patient participants. Multiple guardrails were in place to control access to patient participant dashboards by the treating clinicians. The clinicians were allotted permission in our study's Microsoft Active Directory group and connected to the Johns Hopkins University virtual private network to access the dashboard's landing page. Upon reaching the dashboard's landing page, treating clinicians were prompted to authenticate themselves using Johns Hopkins single sign-on (with 2-factor authentication). A cookie generated by the single sign-on authentication procedure was used throughout the dashboard to ensure that clinicians could only access dashboards for their own patient participants. The list of appropriate patient participants (including a participant ID and name) was shown to the clinician to facilitate navigation around the dashboard.

Data Privacy

We worked closely with our technology team to implement several solutions that helped preserve the privacy of the data collected through the Bark app. We developed a coding system for patients to log into the Bark app so that Bark would not have direct access to any personally identifying information about the patients who were under our care and participating in the study. In addition, we transferred and processed all the collected data to servers behind the Johns Hopkins University firewall that could only be accessed by approved study team members using Johns Hopkins University's standard 2-factor authentication procedures. To further protect the privacy of the data collected through the app, we implemented a pipeline that minimized manual review of the data to only what was necessary to process the data and use it clinically. In addition, we instructed clinicians to review the appropriate dashboards only when they met with their patients, and at that time they could address any potential concerns that emerged from the collected data. We informed patients that the collected data would not be monitored in real time, so they were aware of the procedures.

Randomized Trial

Overview

Motivated by our conceptual model, we hypothesized that providing clinicians with an electronic dashboard of their patients' digital social activity before routine clinical encounters would aid the dialogue and exchange of relevant collateral information during those encounters and thereby improve patient outcomes. The goal was to test this hypothesis in a randomized pragmatic trial comparing patients who received care augmented by the electronic dashboard versus patients who received TAU. The primary research questions to be addressed by the trial were as follows: (1) Is the use of the electronic dashboard in routine care feasible and acceptable to both patients and their clinicians? and (2) Does the use of the electronic dashboard in routine care improve outcomes for patients with depression or anxiety disorders? The outcomes to be examined are described subsequently.

Study Sample

The study was carried out in outpatient psychiatry clinics across the Johns Hopkins Medical Institution and the Kennedy Krieger Institute, which is affiliated with but separate from the Johns Hopkins Medical Institution. We focused on clinics that use a collaborative care model in which patients see a psychiatrist for medication-assisted care as well as a master's level therapist or doctoral-level psychologist for ongoing psychotherapy. Both clinicians and patients were recruited to participate in the study. We first recruited clinicians in the selected clinics to participate in the study and then sought to enroll patients on their case rolls. Patients aged ≥12 years with a mood or anxiety disorder receiving ongoing care were eligible. To be pragmatic and stay as close to the real world as possible, there were no exclusion criteria other than if the treating clinician determined the patient was not able to provide informed consent. In addition, all patients who met the inclusion criteria were eligible, regardless of their current mental health status and scores on patient or clinician rating scales.

Study Procedures

All patient participants downloaded the Bark app and went through the process of connecting their social media and electronic communication platforms to the app. To promote trust and participation in the study, we allowed patients to decide which platforms to connect to the Bark app. While patients retained final control of the decision, we explained to them that their most frequently used apps would provide the most relevant information. Patients were randomized within strata formed by treating clinicians in a 1:1 ratio with blocks of size 2 to either the dashboard intervention or TAU. The purpose of stratified randomization in blocks was to promote balance in the number of patient participants in the 2 treatment arms seen by each clinician, thereby reducing the impact of differences between treating clinicians on comparisons of patient outcomes between the 2 arms. For patients in the intervention arm, the electronic dashboard was delivered to the treating clinician before scheduled clinical visits. The clinician and patient

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collaboratively decided when and how to use the dashboard in the session during each clinical encounter. For patients in the TAU arm, the clinician did not receive a clinical dashboard for review. After the initial visit to download the Bark app, there were no more study-specific research visits. To be pragmatic and stay as close to the real-world setting as possible, patients continued to be seen by their clinician as clinically indicated. The first regularly scheduled clinic visit with their clinician after the patient consented and downloaded the Bark app was considered the study's baseline visit. Patients were then followed through their clinical care for up to 6 months, and all study measures were completed during their regularly scheduled clinic visits.

Study Measures

Both the patient and clinician participants completed measures throughout the study follow-up. The measures were selected to address the primary research questions and (based on our conceptual model) to tap into potential mediating constructs. Table 1 provides the schedule of measures during the study follow-up.

Table 1. Schedule of participant measures.

Measures	Baseline	Every clinic visit	Every 3 months[a]
Patient and clinician			
Consent	✓		
Demographics	✓		
Patient			
CSQ[b]	✓		✓
SF-36 MHC[c]	✓		✓
WAI-SR[d]	✓		✓
SES[e]		✓	
PHQ-9[f] and GAD-7[g]		✓	
Patient questionnaire			✓
Clinician			
MFAS[h]	✓		
M-CICAS[i]		✓	
EDMH[j]		✓	
WAI-SRT[k]	✓		✓
Clinician questionnaire			✓

[a]These measures were collected every 3 months, coinciding with the nearest regularly scheduled clinic visit.
[b]CSQ: Client Satisfaction Questionnaire.
[c]SF-36 MHC: 36-Item Short Form Health Survey Mental Health Component.
[d]WAI-SR: Working Alliance Inventory-Short Revised.
[e]SES: Session Experience Scale.
[f]PHQ-9: Patient Health Questionnaire-9.
[g]GAD-7: Generalized Anxiety Disorder-7.
[h]MFAS: Monitoring and Feedback Attitudes Scale.
[i]M-CICAS: McLean Collateral Information and Clinical Actionability Scale.
[j]EDMH: Electronic Data and Mental Health.
[k]WAI-SRT: Working Alliance Inventory-Short Revised-Therapist.

Patient Measures

To measure proximal outcomes on mental health symptoms, participants completed the Patient Health Questionnaire-9 (PHQ-9) [58] and Generalized Anxiety Disorder-7 (GAD-7) [59] at the baseline and every subsequent clinic visit during follow-up. The PHQ-9 is a 9-item measure of current depressive symptoms ranging from 0 to 27, with higher scores representing greater levels of depression. The GAD-7 is a 7-item measure of current anxiety symptoms that ranges from 0 to 21, with higher scores representing greater levels of anxiety. In addition, to measure more distal outcomes on overall mental health–related quality of life, participants completed the Short Form-36 Health Survey Mental Health Component (SF-36 MHC) at baseline and every 3 months, coinciding with their nearest regularly scheduled clinic visit. This 13-item mental

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health component scoring ranges from 0 to 100, with higher scores indicating higher mental health–related quality of life [60]. We selected these measures as our primary (PHQ-9) and secondary (GAD-7 and SF-36 MHC) outcomes because they are brief, making them pragmatic to collect, and they are widely used with well-established psychometric properties for measuring important clinical outcomes that, based on the conceptual model we hypothesized, will improve with the proposed intervention.

To measure the overlapping constructs of therapeutic alliance and patient satisfaction, participants completed the Working Alliance Inventory-Short Revised (WAI-SR) and Client Satisfaction Questionnaire at baseline and every 3 months, coinciding with their nearest regularly scheduled clinic visit. The WAI-SR is a 12-item measure of the goal, task, and bond aspects of the therapeutic alliance, and each item ranges from 1 to 5, with higher scores indicating greater alliance [61]. The Client Satisfaction Questionnaire is an abbreviated 8-item measure of patient satisfaction with clinical therapy sessions, and each item ranges from 1 to 4, with higher scores reflecting greater satisfaction [62]. In addition, to further measure therapeutic alliance after every clinic visit, patients completed the Session Experience Scale. This is a 4-item scale that assesses key dimensions of effective therapeutic relationships [63]. Finally, at the end of the study follow-up, patients completed the patient questionnaire, which was a 4-item open-ended measure of the patient-clinician relationship that we developed to assess patient perception of the therapeutic relationship with their clinician and whether discussions about electronic communication had occurred and whether this was helpful.

Clinician Measures

At baseline, clinicians completed the Monitoring and Feedback Attitudes Scale. This is an 18-item measure of clinician attitudes toward treatment tracking and the usefulness of incorporating individualized progress measures. It is scored on a 5-point Likert scale, with higher scores indicating more positive attitudes [64]. To measure clinician perspectives on the therapeutic alliance, they completed the WAI-SR-Therapist at baseline and every 3 months, coinciding with the patient's nearest regularly scheduled clinic visit. This is a 10-item version of the WAI-SR, and each item is rated on a 0 to 5 scale, where higher scores represent a higher alliance [65]. In addition, at every clinic visit, clinicians completed the McLean Collateral Information and Clinical Actionability Scale (M-CICAS) and the Electronic Data and Mental Health (EDMH) Questionnaire. The M-CICAS [66] collects information on the collateral sources of information reviewed, clinical actions taken, and shared decisions made between a clinician and a patient in a clinical session. The EDMH Questionnaire is a 6-item assessment of electronic communication that was completed by clinicians after sessions with patients randomized to the dashboard arm. It includes three Likert-rated questions: (1) Did review of electronic communications affect topics discussed in sessions? (2) How helpful was the review of this information to patient care? and (3) How likely is the clinician to recommend reviewing electronic communication to other clinicians? The questionnaire also includes 3 open-ended questions to gather more context about responses to the first 3 questions. Finally, at the end of the study, clinicians completed the clinician questionnaire, which is a 2-item open-ended survey to measure the use of dashboard-prompted electronic communication in discussion and the usefulness of the dashboard on patient care. We developed the EDMH Questionnaire and clinician questionnaire, but these have not been validated. They were included to gather additional qualitative data on the experience of using the dashboard in clinical care for exploratory analyses.

Data Management

The PHQ-9 and GAD-7 were collected as part of an MBC program that has been implemented in our clinics. As part of this program, patients completed the PHQ-9 and GAD-7 before every clinic visit through the Epic electronic health record as part of routine care. All other measures were collected remotely at the scheduled times via text with a link to questionnaire forms developed in a REDCap (Research Electronic Data Capture; Vanderbilt University) database that is maintained by approved study team members at Johns Hopkins University. These data are to be joined and processed for downstream analyses after removing all patient identifiers except for dates of service.

Statistical Analysis

The primary outcome of the trial is the difference in depressive symptoms measured by the PHQ-9 total score over the course of follow-up between the dashboard intervention and TAU arms. Secondary outcomes include differences in anxiety symptoms measured by the GAD-7 total score and in the more distal outcome of functioning, as measured by the SF-36 MHC. Because the PHQ-9 and GAD-7 were collected at each clinic visit and the SF-36 MHC at baseline and end of the study, there are repeated measures over time for each scale within individual patients. We plan to use random effects linear regression models to test for differences in scores on these measures between the 2 treatment arms. We will include fixed effects terms for the treatment arm as well as for time. Furthermore, we will consider including fixed effects terms for potential confounders, such as demographics (eg, age, sex, and race), and clinical factors, such as primary diagnosis and the number of clinic visits as an indicator of clinical severity. We will also include random effects for individuals to account for the correlation in outcome measures within repeated measures of the same individual as well as for clinicians, if indicated, to account for the potential clustering effects of treatment within clinicians. The primary statistical test of interest will focus on the fixed effects term for treatment, which will provide an estimate of the mean differences in the outcome measures between the 2 treatment arms, controlling for time. We will consider different functional forms of the time covariate and use the one that provides the best fit to the data on changes in score over time. Given that patients will be enrolled in the study regardless of their current mental health status and scores on these outcome measures, we consider the model in which we control for time to be the most appropriate test of differences between the treatment arms. However, we may consider examining interactions between treatment and time to see whether changes in the scores over time differ between the 2 treatment arms. We will use the conventional threshold of $P<.05$ to declare differences statistically significant.

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In additional exploratory analyses, we will examine whether there are differences between the 2 treatment arms in measures of therapeutic alliance and detection of clinically actionable targets, both of which we hypothesize, based on our conceptual model, may mediate the therapeutic effect of the intervention. These analyses will provide important evidence as to whether the proposed intervention actually engages the targeted mechanisms of action. In particular, we will test whether there are differences between the 2 treatment arms on scores on the WAI-SR (which measures therapeutic alliance for both patients and clinicians) and the M-CICAS (which captures information about the detection of clinically actionable targets and whether subsequent treatment adjustments were made). For the WAI-SR score, which is a quantitative measure and was captured every 3 months, we will use the same modeling approach as statistical modeling for the primary and secondary outcomes. For the M-CICAS, which was captured after every clinic visit, we will tally the number of times issues related to the patient's social media activity or electronic communications were discussed in the clinical encounter and the number of times treatment adjustments were made. We will again use the same modeling approach as described earlier, except that we will use random effects logistic regression models to carry out separate tests of differences in the probability of these events occurring over time between the 2 treatment arms. Furthermore, we will use $P<.05$ as the threshold to declare findings significant even though multiple tests will be carried out because these analyses will be exploratory.

Finally, we will conduct a series of analyses to assess the feasibility and acceptability of the intervention. We will use several different approaches to do this. First, we will provide descriptive statistics on how many clinicians and patients whom we approached agreed to participate and the reasons why some declined. We are particularly interested in learning whether clinicians and patients decline due to concerns about privacy in sharing personal information obtained from their social media and electronic communication activity or due to the burden of collecting and sharing this information during busy clinical encounters. Second, we will examine descriptive statistics regarding which social media and electronic communications platforms patients agreed to share to assess whether patients were selective about what information they voluntarily provided. Third, we collected a qualitative survey from clinicians to describe the main themes on whether they found systematically discussing social media and electronic communications during treatment helpful, and, if so, what they found most useful.

Sample Size

We estimate that the study has 80% power to detect differences in the primary outcome measure described earlier between the 2 treatment arms with a Cohen *d* effect size of at least 0.5, given the prespecified sample size of 100 and at least 3 repeated outcome measures. We selected a planned sample size of 100 to balance pragmatics and novel treatment intervention, while ensuring a large enough sample size to detect clinically meaningful differences.

Ethical Considerations

The study protocol was approved by the Johns Hopkins University School of Medicine Institutional Review Board (#00184638). We obtained informed consent from both patients and clinicians who participated in the study, ensuring voluntary participation and understanding of objectives, procedures, and potential risks of the study. We obtained assent from patients who were aged <18 years and consent from their guardians. All personal data collected were anonymized and stored in encrypted electronic databases, accessible only to the research team members. To compensate participants for their time and effort, patients received US $100 at randomization and another US $100 at the completion of the study. Participants who shared iOS text data were compensated US $50 because of the extra work required from the participants to share these data. Therapists received US $100 for enrolling 5 patients, US $200 for enrolling 10 patients, and US $250 for enrolling ≥15 patients.

Results

The study was initiated in April 2019, but progress was delayed due to the onset of the COVID-19 pandemic. Data collection has been completed, and the study results will be reported in a separate manuscript. The study is registered on ClinicalTrials.gov (NCT03925038).

Discussion

Challenges

Overview

The goals of this study were to create an electronic communication dashboard and evaluate its use in routine mental health treatment for patients aged ≥12 years with mood or anxiety disorders. The integration of a dashboard to monitor social media use in routine mental health care is novel and promising. With the explosion in the use of electronic communications, it is increasingly relevant to consider social media activity in the therapy setting to aid in treatment planning. However, there are important challenges that merit consideration in deciding how to best achieve this and testing whether doing so is acceptable and effective. In this study, we report the decisions we made to address these challenges in designing and testing such an intervention. The challenges generally fall into 3 categories: technological, ethical, and pragmatic.

Technical Challenges

The most immediate questions to tackle are technological, including how to monitor social media and electronic communications and how to extract and present the information from these data for routine use in clinical care. Regarding the first question, we decided to collaborate with a private start-up company and use the Bark app as a tool for monitoring patients' digital social activity. Our patients typically use several social media and electronic communications platforms, and we wanted to simultaneously track as many as possible to obtain a more comprehensive picture of their digital social activity. The Bark app offers the best out-of-the-box solution that meets our needs for monitoring the widest array of platforms and working with

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both the iOS and Android operating systems, which are widely used by our patients. However, there are challenges in working with Bark. The app was not designed for our use case; therefore, we worked with the company to make certain modifications, to make it suitable for our purposes. To give an illustrative example, we had to shut down all alerts from the app, especially ones that promoted the product, because we did not want to be seen as endorsing it commercially. In addition, there are unavoidable challenges to making connections with the different social media and electronic communication platforms through the Bark app that are beyond its control. The iOS and Android operating systems each present their own challenges to work with, but Apple devices, in general, have stricter controls in place. Bark has implemented certain workarounds to these controls, such as for capturing SMS text messages; however, these solutions can add extra burden to patients in using the app, and it is important to learn whether this impacted their willingness to engage with the intervention. Moreover, different social media and electronic communications platforms are constantly evolving their rules and application programming interfaces for third-party access to their data, which could potentially disrupt the connections made by our patients through the Bark app. We will learn what impact, if any, this had on fidelity to the intervention throughout the course of the study. Finally, our incentives are not always aligned when working with Bark. They are a commercial enterprise and understandably motivated to focus on developing a product that will appeal to their target customers, which are parents. By contrast, we wanted to use a tool that can be seamlessly integrated into clinical care and would appeal to both our patients and their clinicians. There is clearly some but not complete overlap in our interests, and it is an open question whether working with the Bark app is sustainable beyond the life of this study.

Regarding a solution to digest and present information about the patient's digital social activity, we decided to develop a custom electronic dashboard. Bark has developed its own algorithms to analyze social media activity data and present alerts of concerning behavior to parents. However, we chose not to use Bark's alerts because their algorithms are proprietary, and we could not clinically validate them. As there were no other options that met our needs at the time, we decided to develop our own approach. As part of future work, we will conduct a qualitative assessment to gather stakeholder feedback on the dashboard, which can inform the next generation of development.

Ethical Challenges

The next set of challenges to consider are ethical challenges. A major concern is how to ethically manage personal information often exchanged on social media and other electronic communication platforms. This concern is especially heightened because we were dealing with patients as young as 12 years, and we were processing potentially sensitive information about their mental health through a third-party commercial app. We worked closely with our technology team to develop several solutions to securely gather and store data in a way that protected the privacy and confidentiality of our patients. However, these solutions raised competing concerns about how to manage scenarios where collected data might contain information that a patient was at risk of harming themselves or others. In weighing the competing concerns about privacy against responding to actionable findings revealed by the collected data, we decided to err on the side of privacy. We sought to inform patients when they joined the study that the information gathered through the Bark app was not monitored in real time and would be reviewed when they met with their clinicians. The clinicians were able to directly address any concerns about the risk of harm to the patient or others that emerged from reviewing their digital social activity during clinical sessions.

Furthermore, there was concern that social media and electronic communications may reveal information about third parties who did not consent to be in the study, such as friends, families, or acquaintances. To address this concern, we used automated procedures to anonymize the content by replacing identified names with fictitious substitutes. While no procedures for scrubbing identifiers in text are 100% effective, this step helps to minimize the chances of inadvertently revealing third-party identities. Consistent with this thinking, we also opted not to analyze data from videos or pictures. The videos and pictures are likely a rich source of information about a patient's mental health status; however, we decided to forgo such information again in favor of caution in protecting the patient's privacy.

Pragmatic Challenges

The final set of challenges to consider are pragmatic challenges. It is one thing to implement procedures that ensure the intervention is ethically sound, but it is another thing to ensure patients and providers are comfortable using those procedures. We anticipate that trust is an important factor in the adoption and success of the intervention. To respect the patient's choice and promote trust, we chose to let participants select which social media and electronic communications platforms they connected to the Bark app. We recognize that some patients may have decided not to connect to certain platforms they regularly use because they were uncomfortable sharing their activity on these platforms, and, as a result, we may have missed important information that is highly relevant to their mental health. However, we reasoned the potential risk was worth the benefit of giving patients control over participation in the study and building trust with the intervention. We sought to explain to the patients during the log-in process the value of sharing their commonly used platforms to encourage more complete engagement. Similar reasoning motivated our decision to mask any specific content (ie, SMS text messaging) that was extracted from the social media and electronic communication platforms and displayed on the dashboard. Moreover, we wanted to give patients a measure of control over how the intervention was used and allow them to decide when clinicians could review the content. Finally, we decided to let the clinicians and patients decide collaboratively whether and when to use the dashboard during the clinical encounter. We trained the clinicians on how to interpret and use the information on the dashboard, but we let them make the decisions with their patients on how it was used in actual care. We understand that this may result in variability across clinicians on how the intervention was used, but we opted to be pragmatic and give the clinicians and patients control over the use of the intervention to foster greater buy-in.

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Limitations

In addition to the challenges detailed earlier, there are several limitations to the study that will be important to consider when interpreting the findings that come from it. First, the dashboard we developed and tested is a first-generation product, which may have important limitations in functionality. For example, it is unable to distinguish sarcasm or specific kinds of speech, such as slang, that may be important to correctly interpret social interactions. In addition, it does not include nontext forms of communication, including images or emojis, which can be rich sources of information. It is possible that the functional limitations may negatively impact the efficacy of the intervention. It will be important in future work to continue improving the dashboard to address these functional limitations and achieve the full potential of its clinical utility. Second, there is potential for selection bias in the study participants and their sharing of social media and electronic communication data. Moreover, for those who agreed to participate, their use of social media may have been influenced if they knew it was being regularly monitored. These considerations may skew the findings and limit their generalizability. Information gathered during the conduct of the study from those who do and do not agree to participate may help inform the extent to which these biases influence the results.

Conclusions

We anticipate that this study will be an important step in advancing the use of novel tools for monitoring digital social activity in routine clinical care to improve outcomes for patients with mood or anxiety disorders. We will learn whether using such tools is acceptable and feasible and whether there is evidence that doing so provides clinical benefits. In addition, we will learn what works and what does not work when using this intervention approach, which will crucially inform how to improve upon it for real-world implementation.

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Data Availability

The datasets generated and analyzed during this study as well as the code for the dashboard will be available from the corresponding author upon reasonable request.

Conflicts of Interest

MD receives consulting fees from Good Analytics and Bloomberg LP.

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Abbreviations

AWS S3: Amazon Web Services Simple Storage Service
EDMH: Electronic Data and Mental Health
GAD-7: Generalized Anxiety Disorder-7
MBC: measurement-based care
M-CICAS: McLean Collateral Information and Clinical Actionability Scale
PHQ-9: Patient Health Questionnaire-9
REDCap: Research Electronic Data Capture
SF-36 MHC: Short Form-36 Health Survey Mental Health Component
TAU: treatment as usual
WAI-SR: Working Alliance Inventory-Short Revised

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Protocol

Efficacy of a Supervised Exercise Program on Pain, Physical Function, and Quality of Life in Patients With Breast Cancer: Protocol for a Randomized Clinical Trial

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Abstract

Background: Breast cancer is the second most common cancer in women worldwide. Treatments for this disease often result in side effects such as pain, fatigue, loss of muscle mass, and reduced quality of life. Physical exercise has been shown to effectively mitigate these side effects and improve the quality of life in patients with breast cancer.

Objective: This randomized clinical trial aims to evaluate the efficacy of a 12-week supervised exercise program on pain, physical function, and quality of life in female patients with cancer.

Methods: This randomized, double-blind clinical trial will recruit 325 participants, divided into an intervention group receiving the exercise program and a control group receiving standard care recommendations. Outcome measures, including pain (assessed via the Brief Pain Inventory), physical function (Disability of the Arm, Shoulder, and Hand Questionnaire), and quality of life (European Organization for Research and Treatment of Cancer QLQ-C30 and European Organization for Research and Treatment of Cancer QLQ-BR23), will be evaluated at baseline, immediately post intervention, and 12 weeks post intervention. Statistical analysis will involve repeated measures of ANOVA and MANOVA to determine the significance of the intervention's effects across time points.

Results: Recruitment and data collection will commence in February of 2025, and data analysis is scheduled for completion at the end of 2025. No results are currently available

Conclusions: Physical exercise is anticipated to play a significant role in alleviating pain, enhancing physical function, and improving the quality of life in female patients with cancer. This study will provide robust evidence to support the integration of supervised exercise into standard care protocols for this population.

Trial Registration: ClinicalTrials.gov NCT06618690; https://clinicaltrials.gov/ct2/show/NCT06618690

International Registered Report Identifier (IRRID): PRR1-10.2196/63891

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KEYWORDS

breast cancer; exercise; quality of life; muscle strength; pain; efficacy; protocol; physical exercise; fatigue; loss of muscle; physical function; randomized clinical trial; patients with cancer

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Introduction

Background

The World Health Organization (WHO) defines breast cancer as a pathology in which cells present in the breast reproduce uncontrollably and form tumors [1]. It is the second most common type of cancer worldwide, with an incidence in 2022 of 2.3 million. Similarly, in 2022, its mortality rate ranked fourth in the world with a rate of 669,418 [2]. Women are the most affected by this disease, with only 0.5% to 1% of cases in men [1].

Genetic mutations play a key role in cancer development. Mutations in *BRCA1* and *BRCA2* increase the risk of breast [3], ovarian, and prostate cancers, while *TP53* is linked to multiple cancers like breast and colon due to its role in cell cycle regulation [4]. *PTEN* mutations are found in breast and thyroid cancers [5], and APC is associated with colorectal cancer [6]. *MLH1* and *MSH2* mutations cause Lynch syndrome, increasing colorectal cancer risk [7]. *KRAS* mutations are common in lung, colon, and pancreatic cancers [8].

Other causes of the disease are diverse: on the one hand, advanced age at motherhood and late menopause are also considered risk factors. On the other hand, breastfeeding, physical exercise and not consuming alcohol are considered protective factors against the disease [9,10].

Treatment will be selected according to the characteristics of the tumor. Generally, it is based on neoadjuvant or adjuvant chemotherapy, radiotherapy, surgery, and hormonal therapy [11].

The prognosis of the disease has improved due to early diagnosis and therapeutic advances. The mortality rate, in turn, has decreased significantly [12,13]. Because of this increase in survival, scientific society is becoming interested in the treatment of the side effects that these patients may suffer, which include both physical and psychological symptoms [14]. Associated physical symptoms that may appear include lymphedema, decreased movement and strength of the upper limb, decreased mobility and strength of the upper limb [15], pain [16], bone loss [17], and sarcopenia [18].

These side effects have a direct impact on the health-related quality of life of patients with cancer [14]. The WHO defines quality of life as the individual's perception of his or her social and cultural way of life, as well as his or her expectations and goals. This is a very open concept that encompasses different aspects of the person from physical health, psychological state, level of independence, social relationships, and personal beliefs [19]. Quality of life measurement is frequently used in breast cancer studies to evaluate the effectiveness and outcomes of treatments [20].

Exercise and Breast Cancer

It has been observed that patients with breast cancer present atrophy of the skeletal muscle apparatus, which is associated with the mitotoxic effects of chemotherapy. Anthracyclines, substances that play a leading role in chemotherapy against breast cancer, have an affinity for the inner membrane of the mitochondria, the place where the body's energy is produced; therefore, this mechanism explains fatigue, atrophy, and muscle pain [21,22].

Various treatments are currently being studied to alleviate these side effects, including therapeutic exercise. Exercise provides short- and long-term benefits to reduce the symptoms that may appear during treatment in each patient. Here, therapeutic exercise specialists play an important role in helping patients overcome their fear and improve their physical abilities [23]. The American College of Sports Medicine says exercise is associated with improved survival after developing cancer [24].

The health professionals in charge of applying this type of therapy must evaluate each patient individually and adapt the exercise prescription to each one of them. The ideal type of exercise for these patients is one that includes a combination of aerobic and resistance exercise, the intensity of each of these parts will be determined by the characteristics of the patient [25,26].

There is evidence that professionally supervised physical exercise has positive results compared to unsupervised exercise. Research has shown evidence that it positively influences decreases anxiety, depressive symptoms, and fatigue, improves quality of life and physical function, and there is no risk of exacerbating upper limb lymphedema. Even people who have already developed lymphedema can perform resistance exercises. In 2000, Harris and Niesen-Vertommen [27] were the first to start strength studies with people with lymphedema, as the existing recommendations so far were the rest of the affected limb [27-30].

The objective of this project is to develop a randomized clinical trial to determine the efficacy of a supervised exercise program on pain, physical function, and quality of life in female patients with cancer.

Methods

Hypothesis

- A supervised exercise program reduces pain and improves physical function and quality of life in female patients with cancer compared to a control group not receiving the exercise program.
- The beneficial effects of the supervised exercise program are maintained over time at least 12 weeks after the end of the program.

Study Design

This study will be a single-blind, randomized clinical trial. To determine the efficacy of a therapeutic exercise program on the different dimensions of quality of life, physical function, and pain in patients with cancer. Once the participants have been recruited, they will be randomly assigned to 2 groups (intervention group and control group). Three assessments will be made: initial assessment, assessment after the end of the intervention, and assessment 12 weeks after the end of treatment. The intervention group will follow a 12-week therapeutic exercise plan, and the control group will follow the usual recommendations for this type of patient. After this last

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assessment, the participants in the control group will be offered the intervention. (Figure 1). Approval will be sought from the ethics committee of the University Hospital of Torrecárdenas.

Figure 1. Untitled.

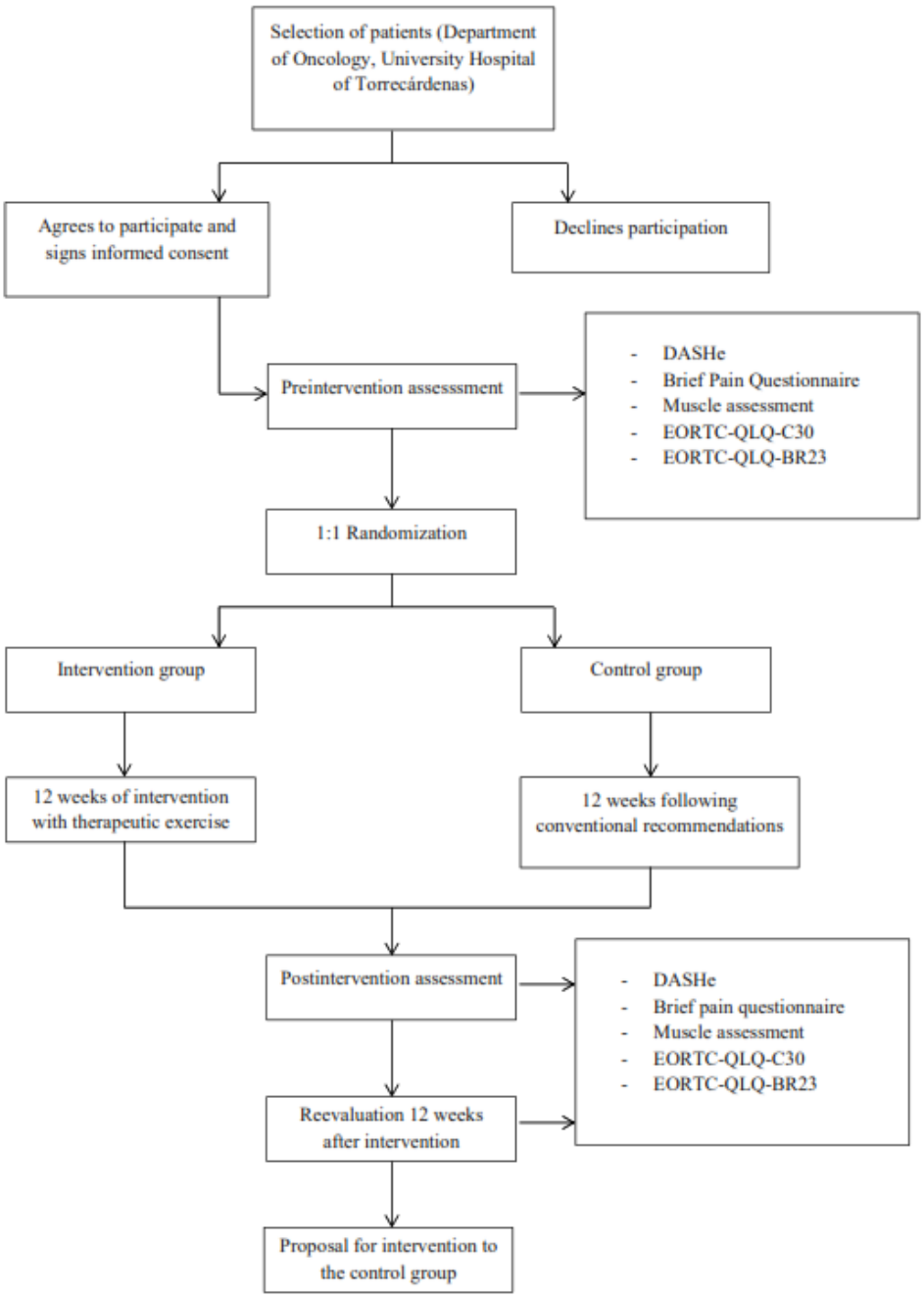

Study Population

The participants will be recruited through the oncologists of the University Hospital of Torrecárdenas. The inclusion criteria will be the following: women aged between 45 and 65 years (age range with the highest incidence in Spain), with oncologic treatment completed less than 3 months ago, without metastasis, without pathologies that contraindicate exercise, and who have agreed to sign the informed consent form. The exclusion criteria will include: not attending scheduled sessions to instruct on the exercises to be performed, being part of other studies, undergoing another type of therapy, and pregnant patients.

The selected age range of 45 to 65 years for participants is based on epidemiological data indicating that this demographic encompasses the highest incidence of breast cancer in Spain. This range ensures a representative sample for evaluating the intervention's efficacy while excluding populations less likely to face similar diseases and treatment dynamics. Additionally, menopause is included as an independent variable in the analysis due to its significant influence on both physiological and psychological responses to breast cancer treatment and exercise interventions. Hormonal changes associated with menopause can affect musculoskeletal health, fatigue levels, and overall quality of life, making it a critical factor to consider when evaluating the intervention's outcomes on pain, physical

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function, and quality of life [31]. By accounting for these variables, the study aims to provide a nuanced understanding of how menopausal status may modulate the benefits of supervised exercise in patients with cancer.

Sample

To calculate the sample size, the QuestionPro software (QuestionPro Inc) was used [32]. It consists of software that, among other functions, incorporates a sample calculator for research.

Based on breast cancer morbidity data in the province of Almeria for 2022, published by the National Institute of Statistics [33], the calculation assumed a moderate effect size of 0.5, based on prior research on exercise interventions in similar populations. To ensure sufficient sensitivity to detect meaningful differences, the significance level (α) was set at .05 (2-tailed), and the study power (1–β) was set at 80%. Considering these assumptions, an initial sample size of 280 participants was determined. However, recognizing the potential for participant dropout, which is common in exercise-based trials, we accounted for an estimated attrition rate of 15%. To compensate for this and maintain statistical power, the final sample size was adjusted to 325 participants.

This approach ensures that the study is adequately powered to detect significant differences between the intervention and control groups for the primary outcomes. If further specifics or expanded parameters are required, we are happy to provide additional details. This explanation aims to address editorial concerns and clarify the robustness of our calculation methodology.

In the beginning, an attempt will be made to recruit the estimated size of participants; if this cannot be done, a smaller sample size will be used, assuming a decrease in the confidence level of the results.

Randomization

All participants have the same probability of belonging to either group. Assignments will be randomized with a 1:1 ratio using the OxMaR software (OxMaR Inc) in its Spanish version [34].

Measuring Tools for Evaluation

Disability of the Arm, Shoulder, and Hand Questionnaire

Self-administered and validated questionnaire in Spanish, the original questionnaire was first published in 1996 [35]. This measuring instrument assesses the impact of processes occurring in the upper limb. This questionnaire consists of 30 items and 2 optional modules. The score obtained is transformed to a scale from 0 to 100, where higher scores show a worse result. It shows a high internal consistency (Cronbach α=0.96) [36].

Brief Pain Questionnaire

This questionnaire is a pain assessment instrument used to measure pain intensity and its impact on the patient's daily life; the original questionnaire was developed at McGill University in 1971, with an internal consistency of 0.7 [37]. The questionnaire used in the study was validated in Spanish in patients with neoplastic pain. It consists of 11 items on a Likert-type scale from 0 to 10 (where 0=no pain and 10=worst possible pain) and 15 additional items that assess the impact of treatment on pain relief. It presents a high internal consistency, with Cronbach α being higher than 0.7 in all dimensions (0.89 for pain intensity and 0.87 for impact on daily life) [38].

Muscle Assessment

Muscle strength will be assessed using a 1 maximum repetition (MR) protocol for the chest press in the horizontal plane and the leg press, as this is the most commonly used muscle assessment test in similar studies, according to the meta-analysis by Hasenoehrl et al [39]. One RM is defined as the maximum weight at which only 1 repetition can be performed [40].

For the evaluation, we will start with an initial warm-up series with 6 repetitions, the initial weight will be 2.5 kg and 18 kg for the upper and lower limbs, respectively. According to the perceived effort of each participant, we will start with an approximate weight for the one RM test, until it increases according to tolerance to find out the 1 RM weight of each participant. This is the strategy followed by Brown and Schmitz [41]. The assessment of the upper limb will be performed unilaterally in order to objectively evaluate the difference between the affected and healthy upper limb, as was done by Hagstrom et al [42]. Thus, we will start with 1.25 kg for each upper limb.

EORTC-QLQ-C30 Quality of Life Questionnaire

A questionnaire was created by the European Organization for Research and Treatment of Cancer (EORTC) to assess the quality of life in patients with cancer. The organization provides the questionnaire translated into several languages, including Spanish. It consists of 30 Likert-type questions that assess various aspects of quality of life, including the ability to perform activities, symptom control, general perception of health, and other relevant aspects such as difficulty breathing, insomnia, anorexia, constipation, diarrhea, and economic impact [43].

The EORTC-QLQ-C30 presents in most of the studies performed a good internal consistency (Cronbach α=0.7 for most of the scales). This questionnaire, based on a specific formula, obtains results on a scale from 0 to 100, where a higher score indicates a better quality of life. The scores for each question within each dimension (physical, emotional, and social functioning) are summed [44]. Within this questionnaire, there are specific modules that complement it for some types of cancer, for breast cancer they have created the EORTC QLQ-BR23 [44].

EORTC Quality of Life Questionnaire, QLQ-BR23

This questionnaire is a specific module for breast cancer that complements the previous questionnaire. Two main aspects are assessed here: functional scale (body image, sexuality, and concern for the future) and symptom scale (breast symptoms, arm, and side effects of treatment). It presents in most of the studies carried out a good internal consistency (Cronbach α=0.7) [44]. Like the general module, this questionnaire has a score from 0 to 100, where they are transformed according to a formula by specific dimensions.

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Ethical Considerations

In this study, clinical investigations involving medical devices are conducted on human participants. In order to safeguard the integrity, well-being, and privacy rights of the participants, the study is carried out in accordance with the guidelines set forth by the Declaration of Helsinki of the World Medical Association (64th General Assembly, Fortaleza, Brazil, October 2013), the Council of Europe Convention on Human Rights and Biomedicine, Good Clinical Practice standards, Royal Decree 1090/2015 of December 4, which regulates clinical trials with medicinal products, the Research Ethics Committees for Medicinal Products and the Spanish Registry of Clinical Studies, and Royal Decree 1591/2009 of October 16th, which regulates medical devices [45,46].

The study protocol will be submitted to the Bioethics Committee at the University Hospital of Torrecárdenas for review and approval in February 2025, during the preparatory phase. Ethical approval will be obtained before the initiation of any participant recruitment or data collection activities, in compliance with ethical standards. Recruitment is scheduled to begin in February 2025, contingent on receiving ethical approval. The ethical approval number will be provided in the final manuscript once it is obtained.

Before the study commences, explicit informed consent will be requested from participants via a digital form, clearly explaining the study's objectives and participation details (Multimedia Appendix 1). Participants will have the ability to opt out at any stage without consequences. For any secondary data analyses, it will be confirmed that prior institutional review board–approved consent covers reuse without requiring additional consent. Compliance with Spanish Organic Law 3/2018 of December 5, 2018, on the Protection of Personal Data and the guarantee of digital rights [47], will also be ensured. Participant privacy will be rigorously protected, and all collected data will be anonymized or deidentified to prevent the disclosure of personal information. The data will be securely stored and used exclusively for this research project and any resulting publications. If any identifiable data is included in images or supplementary materials, explicit consent will be obtained and the necessary documentation will be submitted as supplementary files.

Participants will not receive any financial compensation for their participation in the study. However, they will be provided with detailed information about the study's objectives, potential benefits, and their rights as participants to ensure transparency and fairness in the research process. These measures ensure that the study adheres to the highest ethical standards and prioritizes participant safety, confidentiality, and informed consent in compliance with national and international research ethical regulations.

Intervention

The proposal will be carried out in the intervention group (group 1), while the control group (group 2) will undergo the conventional recommendations indicated for this type of patient.

A supervised training plan will be carried out for 12 weeks with a frequency of 3 sessions per week with a duration of 60 minutes, an ideal estimate according to the meta-analysis of Montaño-Rojas et al [48]. In first 2 weeks, the group exercises will be performed to familiarize the participants with the exercises and then each participant will perform them at home with a review every 2 weeks to assess the increase of the load.

The exercises and loads included in this treatment plan have been designed and modified based on previous clinical trials [39,49-51]. The training plan will work the upper limbs, lower limbs, and trunk. All sessions begin with a general warm-up, which will be previously instructed to the participants, in which the heart rate will be increased (Multimedia Appendix 2). After a 2-minute break, the specific block of each session will begin (Textbox 1 and Multimedia Appendix 2). All exercises will be performed with dumbbells, elastic bands, and a ball. We will consider the age of each participant, making minor adjustments to the initial exercise program as needed.

Three sets of all exercises will be performed with 10-12 repetitions at 50%-60% 1 MR (previously calculated for each participant in each of the exercises) with 1 minute of rest between sets. Finally, we will conclude with general stretching previously instructed (Multimedia Appendix 2). The control group will participate in a general education and wellness program designed to promote overall well-being and maintain a basic level of activity. This program, matched in duration to the experimental group, will include regular counseling sessions covering topics such as nutrition, stress management, sleep quality, and relapse prevention. In addition, participants will be encouraged to engage in low-impact physical activities, such as short walks and gentle mobility exercises. For the experimental group, the supervised exercise program aims to improve pain, physical function, and quality of life through a variety of carefully selected exercises tailored to each participant's needs. These include stretching exercises, such as pectoral stretches for chest mobility and shoulder and arm stretch to enhance the range of motion and relieve tension. Strength training exercises using resistance bands or light weights will focus on improving upper limb and core strength to enhance posture and stability. Aerobic activities like walking or stationary cycling will be incorporated to boost cardiovascular endurance and mobility. Flexibility exercises, including range-of-motion activities, will help maintain and improve overall flexibility, while balance and coordination exercises will enhance stability and prevent falls. Muscle endurance will also be developed through lightweight or resistance band exercises. The program's design emphasizes a personalized approach, guided by physiotherapists or exercise specialists, to ensure safety and maximize benefits for patients with cancer.

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Textbox 1. Strength exercises included in the training plan.

Session 1

- Squats
- Biceps curl
- Superman in quadruped
- Dumbbell chest press in horizontal plane
- Shoulder rotators with elastic band
- Dumbbell rowing

Session 2

- Proprioceptive shoulder exercises with ball on wall
- Static stride
- Upper limb flexion with ball on wall
- Isometric abduction with ball (elbow 90º)
- Prone spine extension
- Quadruped hip abduction

Session 3

- Dumbbell triceps extension
- Quadruped gluteal kick
- Triceps kick with dumbbell
- Lateral shoulder raises with dumbbells
- Dead weight with dumbbells
- Rowing with elastic band

Data Management and Analysis

Once all the measurements included in the measuring instruments section have been taken, they will be recorded and analyzed using SPSS (version 28.0; IBM Corp) [52].

The quantitative data of the sample will be described by number, mean, and SD.

A result is understood to be significant when $P \leq .05$. In statistics, significance or internal consistency indicates that there is congruence between the different results obtained [53].

For the statistical analysis of the results of this test, 2 tests will be performed as follows.

- Repeated measures ANOVA: This analysis allows us to evaluate whether the differences between the results of the same test in a participant are statistically significant. If so, it also determines what percentage of the effect is attributable to the intervention and not to other factors [53]. Two ANOVA analyses will be performed: one comparing the preintervention assessment with the postintervention assessment, and the other comparing the postintervention with the assessment 12 weeks later. This test will check if there is a significant improvement in the different measures of pain, physical function, and quality of life. Finally, the paired comparison table will tell us in which measurement periods the differences are found [53].
- ANOVA of differences: In this case, the differences between the results of the intervention group and the control group will be compared [53]. With the results obtained from this statistical analysis, it will be possible to verify whether the differences between groups in terms of pain, physical function, and quality of life are significant between the participants receiving the intervention and those belonging to the control group.
- MANOVA: To assess the overall effect of the intervention and determine whether the hypotheses can be accepted or refuted, the following hypotheses will be tested [53].

These statistical analyses described the significance between the test results of the same individual and the significance between the different results of both groups of the test that will be tested.

Results

Recruitment and data collection will begin in the third quarter of 2024. Data analysis will be conducted between the first and second quarters of 2025. No results are available at the time of this intervention protocol.

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Discussion

Principal Findings

This randomized clinical trial is intended to test the efficacy of an exercise program applied to patients with cancer.

Most of the patients present a deterioration of their quality of life and physical function after suffering breast cancer, physical exercise can be a great ally to counteract these negative effects [23-30]. Therefore, the results obtained in the intervention group are expected to be significantly better than those of the control group. It is likely that there will be benefits to the intervention in some aspects and not in all the variables measured in the study. In addition, the benefits provided are expected to be maintained in the long term, hence the reassessment 12 weeks after the end of the intervention.

A compelling finding emerges from the systematic review by Montaño-Rojas et al [48], which demonstrates significant muscle strengthening benefits, even with low-intensity and short-duration exercise programs. Participants in these programs showed notable improvements in muscle strength compared to those who did not engage in physical activity. This aligns with the meta-analysis by Shen et al [54], which reported improvements in pain and joint amplitude of the upper limb following physical exercise after radiotherapy in breast cancer. These findings complement international guidelines, such as those from the Clinical Oncology Society of Australia (COSA), which recommend at least 150 minutes of moderate aerobic exercise and 2 resistance training sessions per week, tailored to the individual's health and treatment phase. Like the protocol in this study, COSA highlights the benefits of exercise in reducing fatigue, improving musculoskeletal health, and enhancing quality of life [30]. However, COSA also emphasizes the routine integration of exercise into oncology care, a practice that remains inconsistently implemented across European health care systems. This comparison underscores the universal importance of exercise in patients with cancer and highlights the need for tailored adaptations to local health care systems and cultural contexts to maximize accessibility and impact [29].

In line with the aforementioned, Zengin Alpozgen et al [55] obtained positive results in their clinical trials for pain relief. In contrast, the results of Loudon et al [56] are not significant in terms of pain reduction. This difference may be due to the fact that the first two use exercises that involve greater resistance and dosage; in contrast, the latter performs an intervention of a single session per week based exclusively on yoga exercises.

On the one hand, Aydin et al [57] in their clinical trial, show that physical exercise not only has a positive influence on the physical condition of the participants but is also strongly related to the improvement of mental health. In her study with 48 participants, she used the EORTC-QLQ-C30 and WHO Quality of Life–Brief Version scales to measure the quality of life of the sample. On the other hand, Koevoets et al [58] used the EORTC-QLQ-C30 scale to measure the impact of exercise on cognitive function in patients with breast cancer after chemotherapy. Reporting positive results in the participants of the intervention group. On the contrary, Bruce et al [59] in a clinical trial with 392 participants, found no significant differences in the improvement of mental health in participants who had performed physical exercise and those who had followed the usual recommendations. These differences may be due to the sample size as the latter study presents a significantly larger sample than the previous ones. They may also be due to the dosage and type of exercises proposed in the intervention; since Aydin et al [57] and Koevoets et al [58] perform aerobic and general strength exercises of all muscle groups, while Bruce et al [59] only perform a shoulder strengthening program in flexion, abduction, and external rotation.

Regarding when to start the exercise program, authors such as Carayol et al [60] recommend starting a supervised exercise program during chemotherapy or radiotherapy treatment, combined with an adequate diet to improve health status and the consequences of these treatments.

Vincent et al [61] compared in a randomized clinical trial the results obtained in a group that started the intervention with exercise during chemotherapy and in another group that started it after the end of chemotherapy, not observing significant differences between the two and highlighting the importance of performing them either during or after.

From another point of view, not only is the impact of physical exercise after breast cancer being investigated but there is already research that is beginning to show positive results in the prevention of breast cancer through exercise in populations with risk factors. An example of this is the studies by Coletta et al [62] and Khosravi et al [63] where they performed interventions with physical exercise in postmenopausal participants and with various other risk factors to see the impact of this training with leptin and myokine levels. Prevention of both first-time disease onset and recurrence, aided by physical exercise could be a future line of research that will gain more momentum.

The strengths of this study are randomization, as well as the use of previously validated assessment tools, some of them specific to breast cancer, such as the EORTC QLQ-BR23. The variables analyzed range from pain to physical function and quality of life. In addition, it is based on a protocol of resistance exercises, which, according to previously cited research, provides better benefits.

The main limitation of this study is that the intervention will be carried out through patients recruited from a single referral hospital, although a large sample is achieved, it would be interesting for future studies to have a variety of more heterogeneous participants and better generalize the results. In addition to making longer-term measurements to see how the possible improvements acquired are maintained. Furthermore, the study's results may be influenced by factors like hormonal variables, age, and treatment responses. Hormonal changes, such as menopause, can affect treatment effectiveness and side effects. Additionally, younger patients may experience different side effects or treatment responses due to metabolism, health, and comorbid conditions.

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Conclusions

Oncology research is advancing at a very fast pace. Therefore, addressing the side effects of the disease is a great success for these patients, who today have a high survival rate. Therapeutic exercise is a great ally in improving strength, pain, and joint mobility after breast cancer, as well as positively influencing the improvement of quality of life.

Acknowledgments

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Data Availability

The data that will support the findings of this study will be derived from patient medical record data. The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

JGM was responsible for conceptualization, formal analysis, investigation, methodology, software, visualization, and drafting as well as reviewing and editing the manuscript. OSV contributed to conceptualization, data curation, formal analysis, investigation, methodology, project administration, resource management, supervision, validation, visualization, and both drafting and revising the manuscript. MSV took charge of the methodology and the preparation and review of the manuscript. JHOH played a role in conceptualization, data curation, formal analysis, investigation, methodology, project administration, supervision, validation, visualization, and manuscript preparation, including drafting and revisions. All authors reviewed and approved the final manuscript and took full accountability for all aspects of the work.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Informant consent.
[DOCX File , 25 KB - resprot_v14i1e63891_app1.docx]

Multimedia Appendix 2
Exercises session.
[DOCX File , 706 KB - resprot_v14i1e63891_app2.docx]

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Abbreviations

COSA: Clinical Oncology Society of Australia
EORTC: European Organization for Research and Treatment of Cancer
MR: maximum repetition
WHO: World Health Organization

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Protocol

Demonstrating Tactical Combat Casualty Care in Simulated Environments to Enable Passive, Autonomous Documentation: Protocol for a Prospective Simulation-Based Study

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Abstract

Background: The Telemedicine & Advanced Technology Research Center (TATRC) commenced a new research portfolio specifically addressing Autonomous Casualty Care (AC2) in 2023. The first project within this portfolio addresses the current and historical challenges of capturing tactical combat casualty care (TCCC) data in operational settings.

Objective: The initial autonomous casualty care effort, the Passive Data Collection using Autonomous Documentation research project, conducts systematic, simulated patient and casualty care scenarios, leveraging suites of passive sensor inputs to populate a data repository that will automate future combat care.

Methods: To obtain the required datasets, TATRC will engage care provider participants who provided consent in one of 6 randomized simulated TCCC scenarios leveraging an institutional review board–approved office protocol (#M-11057). These simulations will leverage mannikins (low and high fidelity) and live simulated patients (eg, human actors who provided consent). All consenting participants (eg, both the care providers and live simulated patients) will be equipped with suites of sensors that will passively collect data on care delivery actions and patient physiology. Simulated data is being collected at Fort Detrick, Maryland; Fort Sam Houston, Texas; Fort Indiantown Gap, Pennsylvania; Fort Liberty, North Carolina; and a commercial site in Greenville, North Carolina.

Results: Across all research locations, TATRC will collect and annotate approximately 2500 simulation procedures tasks by March 2025. These study data will generate the first machine learning and artificial intelligence algorithms to populate Department of Defense (DD) Form 1380 fields accurately and reliably. Additional data collected past March 2025 will be used to continue to refine and mature the algorithm.

Conclusions: The military health care system (MHS) lacks real-world datasets for TCCC care at the point of injury. Developing a data repository of simulated TCCC data is required as an essential step toward automating TCCC care. If TATRC's research efforts result in the ability to automate care delivery documentation, this will alleviate the cognitive burden of TCCC care providers in austere, chaotic environments. By generating a TCCC data repository through this Autonomous Documentation research project, TATRC will have opportunities to leverage this research data to create machine learning and artificial intelligence models to advance passive, automated medical documentation across the health care continuum.

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KEYWORDS

tactical combat casualty care; TCCC, automation; medical documentation; DD form 1380; combat casualty care; artificial intelligence; AI; machine learning; ML; point of injury; POI; simulation; military health; passive data collection; sensors; algorithms; medical record

Introduction

The military health care system (MHS) is a Joint Service health care system that operates under the Defense Health Agency (DHA) [1]. Within this health care system, there is a diversified set of health care data ranging from routine preventative services for service members (SMs) and their families to battlefield casualty statuses. Due to the nature of its complexity, the MHS thrives in stable connected environments and languishes in operational settings where network communications are compromised or insecure. Thus, when our SMs are located in various tactical environments in multidomain operations, the MHS lacks a robust, accurate, and reliable methodology to collect, store, and track health data, often referred to as tactical combat casualty care (TCCC) data.

Historically, TCCC data has been manually collected using the DD Form 1380, also known as the TCCC card (Figure 1). The TCCC card is intended to be filled out by combat medics at point-of-injury (POI) and Role 1 and attached to the casualty's uniform.

Figure 1. DD Form 1380, the TCCC card.

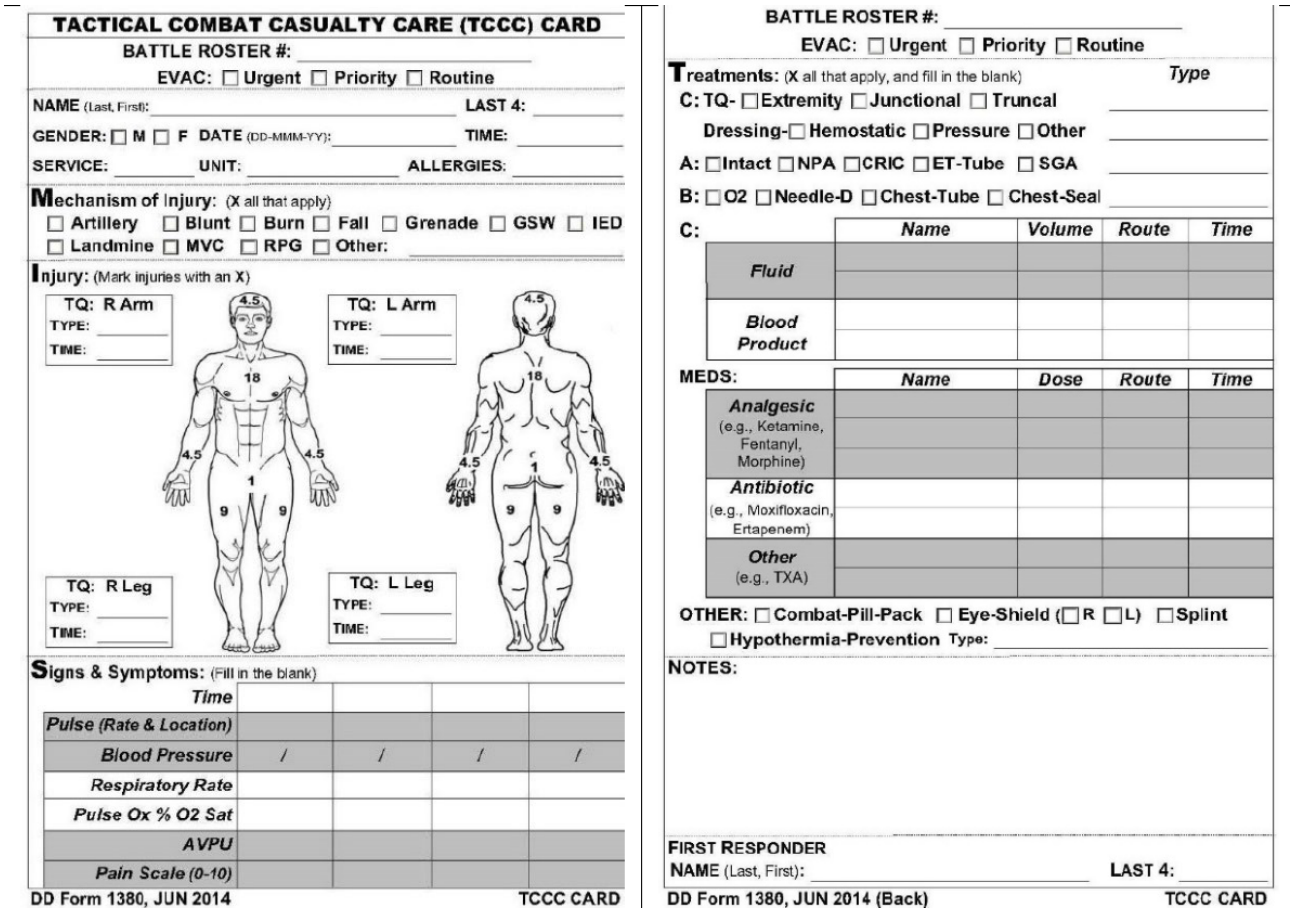

The intent is for this DD Form 1380 to travel with the casualty until they reach their final treatment destination where its contents will be populated into the electronic medical record in the MHS. Current assumptions, which constrain the success of the manual TCCC data capture process, include the following: (1) the DD Form 1380 will be present at the time of the SM's final treatment destination, (2) the DD Form 1380 will be undamaged and legible to transcribe into the medical record, and (3) there will be abundant resources to transcribe all DD Form 1380 data entries or fields into that record.

Due to the chaotic nature of conflict environments, most of the DD Form 1380s are either incorrectly or inadequately completed. Capturing the medical care provided in these austere venues is secondary to saving lives; however, the need for timely, accurate medical documentation remains for acute care and long-term care management [2-4]. In the near term, this data generates valuable information for higher echelons of care, medical resupply, and logistics systems, and command situational awareness. The long-term benefit is the ability to provide a basis for evaluating quality of care and benchmarking key metrics for quality improvement efforts and to leverage machine learning (ML) and artificial intelligence (AI) to enhance future care delivery in the tactical environment, as well as to inform clinical decision support systems and algorithms deployed in these settings [5].

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In May of 2023, the telemedicine and advanced Technology Research Center (TATRC) commenced a new Autonomous Casualty Care (AC2) research portfolio with the initial objective of creating an innovative, trustworthy, reliable solution to enhance TCCC and improve medical documentation in the MHS. TATRC intends to develop a passive (ie, with minimal human effort and distraction), autonomous documentation (AutoDoc) solution of medical care in operational environments comprising a system of sensor suites that passively collect accurate and reliable data about casualty status, care provider actions, and real-time resource usage.

The goal will be for the sensor suites to passively and autonomously document data for a digital DD Form 1380. To accomplish this, TATRC will (1) identify which commercial off-the-shelf (COTS) sensors are most suitable to collect TCCC data elements required to populate the DD Form 1380; (2) conduct human subjects research using participants who perform TCCC skills in controlled, simulated environments; and (3) annotate all sensor suite data collected to build a TCCC dataset for current and future ML and AI algorithms to leverage.

Methods

Overview

Since the AC2 mission realignment in May 2023, TATRC has worked in partnership with the United States Army Medical Research and Development Command (USAMRDC) Institutional Review Board Office (IRBO) to ensure optimal human participant protections can be achieved within the scope of our research study. The novelty of developing a study design that leverages sensor suites and simulated data across multiple locations and includes iterative improvements in the technology configuration features due to the agile development process is groundbreaking for the organization. TATRC received its initial human subjects research protocol approval (#M-11057) from the USAMRDC IRBO in February 2024 to conduct this research and will continue to amend the protocol as new collaborators onboard and new methodologies are adapted, as required. Study personnel will follow the protocol requirements including consenting mandates as directed by the IRBO.

Passive data collection using AutoDoc is a research, development, test, and evaluation (RDT and E) project that will be conducted in three separate stages: (1) selection and procurement of sensor suite components, (2) data collection via live human actor simulations, and (3) data annotation.

Sensor Suites

Individual COTS sensors were bundled into synchronized technology suites designed to capture both patient physiological data and care provider interventions. These passive sensor suites generate data that can be used to generate an electronic DD Form 1380. The categories of sensors used in this research project are listed in Table 1. The COTS sensors selected for the research project's suite were based on technology maturity level, National Defense Authorization Act compliance, suitability for the operational environment (eg, durability and ruggedization), and ability to extract data from the sensors (eg, nonproprietary data formats). Before leveraging the passive sensor suites in the AC2 research project, the technologies were systematically evaluated through a series of assessments. The sensor suites are worn by consented participants (eg, both the care providers and live simulated patients) in the simulated TCCC scenarios for data collection.

Table 1. Categories of commercial off-the-shelf sensors integrated into sensor suites.

Sensor category	Sensor type
Primary care providers	
Audio	Microphone clipped to a collar, lapel, or helmet
Identification readers	Near field Communication cards attached to items in the care provider's bag
Inertial measurement unit	Wrist-worn inertial measurement units to track hand movements
Mounted video	Traditional video and infrared video
Simulated Patients	
Vital signs monitor	Velcro blood pressure cuff and skin safe adhesive electrocardiogram electrodes leads, adhesive vitals monitoring patch (blood pressure, heart rate, respiration rate, temperature, and SpO_2[a]), and finger pulse oximeter

[a]SpO_2: oxygen saturation.

Data Collection

Live, controlled, simulated scenarios will be used for all passive sensor suite data collection activities. The purpose of conducting live simulation events is to observe participants performing TCCC-related activities. These structured data collection events allow the research team to obtain relevant data for future algorithm development. The purpose of the data collection events is research-specific, and not to educate, assess, or help caregivers self-identify knowledge gaps.

TATRC has identified Department of Defense (DoD) affiliated collaborators to generate the volume of data needed to train the ML and AI. TATRC personnel are currently collecting data at 5 different locations at Fort Detrick, Maryland; Fort Sam Houston, Texas; Fort Indiantown Gap, Pennsylvania; Fort Liberty, North Carolina; and a commercial site in Greenville, North Carolina.

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Settings

Live simulation data collection events are conducted at the 5 approved research locations. At each location, a series of physical spaces are dedicated to simulating the prehospital roles of care: POI (casualty collection point or equivalent), Role 1 (battalion aid station or equivalent), Evacuation to Role 2, and Role 2 (Forward Surgical Team or equivalent). In addition, the equipment and medical supplies that are available at each prehospital venue are accessible to the research participants. Data collection locations can create immersive virtual environments, sounds, or other environmental characteristics (smoke, smells, etc) to create a realistic combat environment. In addition, an audiovisual system (AVS) is leveraged to record and archive activities conducted during the data collection events. When data are collected in a formal laboratory venue, the AVS is fixed, but in other locations, a portable AVS is leveraged (Figure 2).

Figure 2. Staged simulation scenario of primary care provider triaging simulated patient (Mannikin).

Study Participants

Participants will be split into two groups: (1) care provider and embedded participant or (2) simulated patient, based on inclusion criteria. The research team is using video, audio, and kinematic recording equipment to collect first-person data from care providers and embedded participants during the TCCC scenarios. The first-person sensors will record casualty injury patterns, care and tasks provided by the care providers, equipment and supplies used, and other environmental factors. In addition, vital signs monitors, such as finger pulse oximeters, blood pressure cuffs, adhesive electrocardiography patches, and so on, will be placed on the simulated patient participants to record physiological data.

Inclusion Criteria

Care provider and embedded participants specific inclusion criteria. This research population group must be a certified provider, as defined below, to participate, ensuring that the simulated data collected reflects data that would be collected by a care provider in a real battle space (Textbox 1). Care provider participants will be split into 2 separate roles during a scenario:

1. Primary care provider (PCP): The PCP is the person providing care to the patient in the scenario and will be required to wear the system of sensors during the simulation.
2. Embedded participant (EP): The EP assists the PCP throughout the scenario by updating vitals, holding items, injecting added pressure onto the PCP, prompting the next steps, and so on.

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Textbox 1. Inclusion criteria and exclusion criteria by participant role.

Inclusion criteria

- Primary care provider or embedded participant
- Are between the ages of 18 and 65 years
- Must have one or more of the following:
  - Active tactical combat casualty care certifications for All Service Members, the Tier 1 course
  - Working knowledge of combat casualty care skills through medically related training (eg, combat medic or equivalent training)
  - Deployment with medical experience in the last 36 months
- There are no preexisting conditions that would negatively impact their ability to provide care for a 20-minute simulated trauma care scenario or work outside for prolonged periods of time (eg, extreme allergies or extreme reactions to sun exposure, etc)
- Simulated Patient
- Age 18 years or older
- Must have the ability to act injured and unconscious for the duration of a 20-minute patient care scenario. The range of injury acting will vary from a state of unconsciousness (ie, lying still) to yelling and writhing in pain

Exclusion criteria

- All participants
- Younger than 18 years
- Currently pregnant
- History of abnormal heart rate (eg, arrhythmias)
- Internal electric medical devices (eg, pacemakers)
- Uncontrolled high blood pressure disorders
- Uncontrolled breathing disorders
- Severe allergies
- Epilepsy
- Primary care provider or embedded participant
- Younger than 18 years or older than 65 years
- Do not hold an active certification for tactical combat casualty care Tier 1
- Simulated Patient
- Younger than 18 years
- Unable to meet the physical requirements of acting as an injured or unconscious patient, such as an inability to act in a predetermined way for up to 20 consecutive minutes or having an adverse response to prolonged time outdoors

Exclusion Criteria

For generalized and participant-specific exclusion criteria, please see Textbox 1.

Procedures

After recruitment, enrollment, and consent, each participant will be placed into one of 6 simulated scenarios that were scripted for this project. Participants will be paired based on similar levels of expertise described in Bloom's Taxonomy and then randomized into provider type groups [6].

A total of 6 combat casualty care scenarios were designed and written by TATRC's combat medic subject matter experts. The injury patterns were developed using common battlefield mechanisms of injury and real-world scenarios. The majority of the TCCC tasks in the scenario correspond to an Individual Critical Task List item for the 68W Combat Medical Specialist, with only a few exceptions. The severity of the casualties differs to capture all triage categories and levels of difficulty. Baseline simulations were developed for each scenario by selecting the appropriate patient mannikin, applying relevant moulage (medical makeup), and by selecting the applicable scene location for POI care. The six scenarios are as follows:

> *26-year-old male infantryman injured by small arms fire during dismounted patrol. Patient is unresponsive and has a massive hemorrhage from the face or neck and left inguinal area. Enemy threat has been eliminated, and combat lifesaver (CLS) has been attempting to control bleeding for several minutes unsuccessfully.*
>
> *29-year-old male SM involved in improvised explosive device (IED) explosion. Patient alert to verbal stimuli,*

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and complains of 10/10 pain all over. Obvious right leg below knee amputation. Bleeding from right chest and forehead.

23-year-old male SM injured by small arms fire during key leader engagement. Patient suffered multiple gunshot wounds to the left shoulder, left arm, and left leg. Patient presents with moderate bleeding but alert.

25-year-old male platoon leader injured by mounted IED explosion. Patient has shrapnel and burns to the left arm, leg, and torso with minimal bleeding. Patient is alert and complaining of 10/10 pain. Enemy threat in the area has been eliminated and CLS has been attempting to control bleeding for several minutes unsuccessfully.

35-year-old male platoon sergeant injured by mortar strike. Patient is alert and has right arm amputation below elbow and shrapnel wounds to the right side with moderate bleeding. Patient is alert and complaining of 10/10 pain.

31-year-old male involved in an IED explosion. Patient alert to verbal stimuli with complaints of 10/10 pain on left side of body. Patient has burns to neck and face with stridor. Left side "peppered" with minor shrapnel injuries. Patient is found extricated from vehicle and burning process has been stopped. Scene is absent of enemy activity and no percutaneous transluminal angioplasty treatment has been provided.

Before the simulation commences, the PCP is trained on how to use the sensor suite and if using a simulated patient, the appropriate moulage is applied. The participants are then taken to one of two locations, depending on their assigned scenario: (1) indoor laboratory or training facility: fully controlled environment; and (2) outdoor training facility: partially controlled environment, used for scenes with potential for care under fire.

After arriving at their assigned location, each participant is given a scenario brief. The scenario brief contains information on simulation tasks, conditions, and standards, and allows time for the participants to prep their equipment and supplies or ask any last-minute questions.

The data collected from each scripted scenario will differ based on each PCP. Each caregiver will manage the problem set differently based on their personal experiences and knowledge base resulting in individualized outcomes (Figure 3). Only one PCP will manage the simulated patient. The generalized process of how each scripted scenario occurs is as follows:

1. The simulated patient, PCP, and EP are all present at their assigned location.
2. The PCP is trained on the sensor suite technology while the simulated patient is reviewing the script and having moulage applied.
3. The simulated patient, PCP, and EP are given a scenario brief.
4. The start cue is given, and the scenario commences.
5. The simulated patient begins to act out their injuries.
6. The PCP begins performing care to treat the simulated patient, while the EP is standing by. The EP only intervenes if the PCP requests their assistance (eg, to hold equipment or to provide updated patient information), to troubleshoot equipment, or to prompt the PCP.
7. After a determined amount of time, the PCP is notified that evac has arrived.
8. The scenario ends.

From the beginning of the scenario brief to after action reporting, each participant will be engaged in the study for a maximum of 2.5 hours, where 50 minutes is the maximum amount of time a participant can participate in a simulation run.

Figure 3. Autonomous documentation flow diagram from simulation data collection to algorithm development. TATRC: Telemedicine & Advanced Technology Research Center.

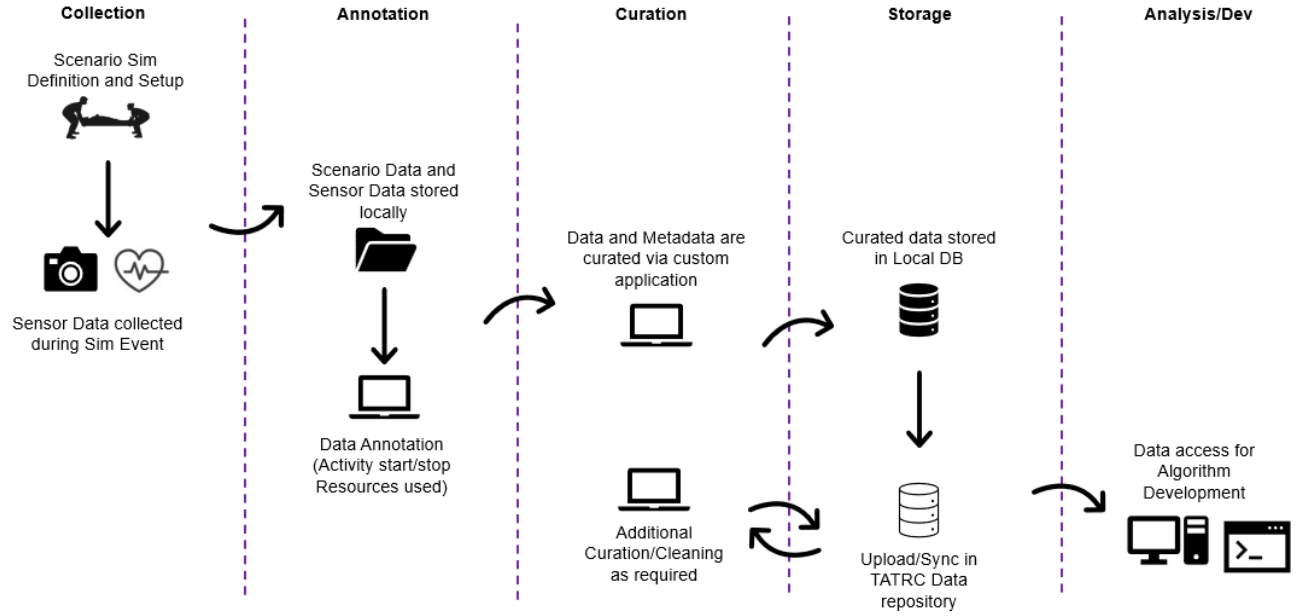

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Data Annotation

Following the simulation, all simulated TCCC data collected on the sensor suites will be uploaded into TATRC's secure, PIA-approved data repository. The data are considered "unlabeled" and will require annotation with "labels" for future use in algorithm development.

Unlabeled sensor data must be annotated with labels defining a specific action necessary for algorithm development or "training." In this case, the object is to build algorithms that, based on sensor data collected in each scenario (input), infer a specific treatment or procedure was performed by providers (output). For example, if a combat medic is placing a tourniquet, then the algorithm must be able to correctly label this specific act using sensor-generated data including start and stop times. Task start and stop times are recorded relative to the simulation start time. The annotation process can be summarized as follows: annotations are applied to each simulation, and 2 annotators review the video and audio resulting from the simulation.

Individually, the annotators record start and stop times for standardized TCCC tasks of interest. Start and stop time identification is guided by pre-established start and stop time markers specific to each task. Examples of the annotations and descriptions of the time points can be visualized in Table 2 below.

1. Comparison and review: task periods (bounded by start and stop times) are compared between the 2 annotators. Any task with less than 80% overlapping between the annotators must be discussed and reannotated by each annotator. If an 80% overlap is still not achieved, another annotator will annotate and review the data. This process will continue until >80% overlap is achieved.
2. Label combination: the final bounds for each task are defined as the outermost stop and start times between the 2 annotators (ie, the union of A and B). The original start and stop times each annotator records, will also be maintained for transparency.

All annotations will be stored in a spreadsheet linked to simulation metadata via a unique simulation ID. The goal of this project is to develop a cloud-based dataset that will enable ongoing and future ML and AI algorithm development for automatic, passive documentation of DD Form 1380 data fields.

Table 2. Examples of annotations and descriptions of time points.

Task	Start time (s)	Stop time (s)	Duration (s)
Start of scenario	0	76	76
Tourniquet application	85	142	57
Chest seal application	167	253	86
Nasopharyngeal airway	195	214	19
Treat a casualty for a cold injury	270	346	76
Uses sensor	355	465	110
Documentation	404	579	175
Administer medication	542	579	37
Chest needle decompression	583	612	29
Initiate an intravenous	652	717	65
Uses sensor	681	708	27
Uses sensor	715	738	23
Initiate an intravenous	739	848	109
Administer medication	854	917	63
Administer fluids through an infusion	884	980	96
Documentation	923	954	31
Administer tranexamic acid	956	1048	92
Uses sensor	1010	1050	40
Documentation	1053	1116	63
Bag-valve-mask assisted ventilation	1125	1294	169
Chest needle decompression	1143	1164	21
Documentation	1209	1294	85
End of scenario	1293	1303	10

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Ethical Considerations

Ethics Review Approvals or Exemption

This protocol was reviewed and approved by the USAMRDC IRBO, which included human subjects' ethics review. The approved protocol (#M-11057) was classified a minimal risk to human participants and undergoes annual continuing reviews by IRBO to ensure the safety and ethical considerations of research on all human participants in our research.

Informed Consent

Within 48 hours before the simulation scenarios are conducted, one of the research team members will provide the individual with a mailed hard copy or emailed electronic copy of the consent to review and contact them over either a secure telecommunication software or face-to-face, whichever is most convenient for the potential study participant. In either form of meeting, the ombudsperson is also present to explain that participation is voluntary and that the information provided about the research is consistent with the institutional review board (IRB)–approved materials. If over telecommunication software, the research staff member ensures the participant is in a private space and can adequately hear all explanations. If the consent process is in-person, the process takes place in a private area. The trained research effort staff members are completely trained on providing all necessary information to the potential participants and go through the consent form with them. This consent form explains the activities, potential risks, and data collection that the Principal Investigator would like to conduct. The consent form highlights that the data collected in this effort contains footage of the participant's faces or participants' voices. As the research team member reviews the consent form with the potential participants, they encourage the participants to ask questions about the data collection specifics.

After the review is complete, the participants are told they may review the consent information up until the day data are collected as the consent form describes and their decision to participate or does not negatively or positively affect their job. The potential participant also is given an opportunity to speak with the ombudsperson alone to discuss any concerns of participation they may have. If the potential participant agrees to participate, she is asked to sign the consent form. Participants will also be asked to sign an optional image release form for use in presentation, promotional, and marketing materials. The participants either sign in person or sign a virtual copy of the consent form and send this back to the research staff member, via methods such as DocuSign or in person. After signing, a copy of the signed consent form is provided to the study participant. The original consent forms are printed and stored in study files in a locked filing cabinet in the TATRC research office. Before leaving the consenting meeting, the volunteers will be reminded that they can reach out to the ombudsperson at any time if they have concerns about participating in this research effort.

Privacy and Confidentiality

Care providers and simulated patient participants are assigned a participant ID to be associated with collected demographics, video, and physiological signal recordings. All data are stored in DoD- and HIPAA (Health Insurance Portability and Accountability Act)-compliant safety and security compliant e-storage facilities. All hard copy documents including completed consent forms are stored in locked filing cabinets at TATRC.

The research team collects all video and physiological signal recordings. Following data collection sessions, all recordings are checked within 1-7 days and before media is removed to ensure no nonconsented individual's identifiable information was not recorded. If any inadvertent recordings were made, the PI or a study team member deletes these segments of recordings. All recordings are stored securely in a DoD-approved, TATRC maintained server or repository including a NAS at Fort Detrick, Maryland. The procedure for consent occurs prior to participants engaging in simulation scenarios. If a person does not consent to data collection, they will not participate in research activities.

One of the main aspects of the data that is collected is that the faces and physiological signatures of the simulated patients are included in the footage of the data. This is needed to be able to accurately train the algorithms and technology that is developing from this effort. This is made abundantly clear to the participants in the consenting process. If they do not consent to their faces being included in this data, they are not allowed to move forward with participating in the collection. Photo Release Waivers for image use in nonresearch activities accompany the consent forms at the start of participation but are entirely optional for participation in the study.

Compensation Details

Military volunteers who meet the eligibility requirements and consent to participate in the study have the opportunity to participate in volunteer hours as a participation incentive. After completion of their participation in the study, the participant may request a letter of participation from the research team. The eligibility for volunteer hours toward service recognition will be determined by the units or offices who grant the volunteer hours. The research team will provide the letter of participation in an electronic format to the participant's email address. This process will be mirrored at all data collection locations. There are no monetary incentives or compensation for this research effort for volunteers.

Results

TATRC is on track to collect and annotate approximately 2500 simulation procedures (or tasks) by March 2025. In addition to the data recorded at each TATRC-hosted simulation event, TATRC intends to continue to expand its data repository by acquiring data from similar recorded simulated events at other military and civilian organizations and creating or obtaining augmented or synthetic TCCC data through synthetic modeling environments (ie, digital twin systems). Synthetic modeling environments can generate novel TCCC data to increase the variety and complexity of the datasets. To furthermore diversify the datasets, TATRC plans to collect simulation data from non–TATRC sponsored events (ie, research conferences, operational exercises, etc). Combining both physical and augmented simulation data, TATRC's aspirational goal is to

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accumulate approximately 100,000 TCCC simulated procedure or task recordings to populate and generate DD Form 1380 elements by the end of September 2025 (Figure 4). As the annotated simulation procedures are aggregated into TATRC's data repository, contracted extramural partners will commence algorithm and software development to support TATRC's goal if automating combat casualty care scene interpretation and patient encounter documentation to significantly reduce manual data entry and enhance the capabilities of combat medics. By September 2025, the extramural algorithm partners intend to complete the machine perception algorithms and associated software to leverage data collected by the AutoDoc suite of sensors to auto-populate all DD Form 1380 elements into a digital XML or JSON format.

Figure 4. Primary care provider camera view while performing TCCC procedures on simulated patient (Mannikin). TCCC: tactical combat casualty care.

Discussion

TATRC's AC2 mission focuses on addressing and improving the current reality for combat medics:

> *A distracted, stressed combat medic managing their way through a chaotic battlefield with multiple casualties surrounds them, with only a bag full of supplies, including one permanent marker and several DD Form 1380 cards.*

There are minimal improvements in how the Joint Forces have documented health data beyond our borders, specifically in operational settings in times of conflict, despite the large advancements in data science and technology in the last decade. TATRC's goal is to replace the current, paper-based process, with modern, passive data collection and automated documentation. The aim is not only to create a more reliable, accurate method for collecting casualty care data but to alleviate the care provider's cognitive burden in the battle space of this strenuous additional duty.

The methodology for collecting TCCC data may raise questions on why our research team is not leveraging existing or available datasets from historical conflicts. The simple answer is that they do not exist. During the Afghanistan and Iraq conflicts, there were approximately 30,000 documented casualties but only 10% of those casualties had any documentation of prehospital care, and 1% or less had sufficient information to inform care at the next echelon [7]. Similarly, an unpublished 15-month review by the Joint Trauma System (JTS) found that from 172 submitted DD 1380 Forms from the field, more than 50% of them did not meet the criteria for completeness as measured by a quality checklist developed by the JTS. Furthermore, there is a lack of data granularity necessary in medical documentation from the POI based on an analysis of the JTS DOD Trauma Registry database in 2011 by Therien et al [8]. How, when, and where this data was stored remains unknown. These previous publications have illustrated the extreme, nearly impossible, expectation of documenting TCCC while in the battle space. Limiting TCCC data collection to just 1 form and expecting this 1 form to travel with the casualty from the POI to their final treatment destination, without being damaged or lost, is the reason why only less than 1% of DD Form 1380 during the Afghanistan and Iraq conflicts were sufficient to inform the next echelon of care. The result is that there are no existing combat casualty care datasets within the MHS.

TATRC's solution to this data limitation is using scripted, simulated TCCC scenarios to capture the data. TATRC has partnered with other DoD entities to provide an environment emulating specific battlefield conditions generating realistic TCCC data outcomes. Together, TATRC and partners, are testing and refining the sensor suites while simultaneously diversifying the TCCC dataset and generating the volume of

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data needed to create trustworthy solutions for care providers across the echelons of care. Although the AutoDoc project primarily focuses on building DD 1380 Forms, the data obtained across all research locations could be used to create an abundance of tools and capabilities, such as algorithms to automate personal health information documentation into an existing electronic health record (eg, MHS). The possibilities to use this data to benefit the warfighter are limitless as long as you can find a way. TATRC is devoted to having this data serve as a foundation for future research, development, test, and evaluation projects across the DoD to improve our understanding of TCCC and allow organizations across the DoD to build upon our work and create innovative tools to automate future healthcare and improve the current standard of care.

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Federal Disclaimer

The views expressed are those of the authors and do not reflect the official policy of the Department of the Army, the Department of Defense, the Defense Health Agency, or the US Federal Government.

There was no usage of generative AI tools throughout the entire manuscript ideation, planning, outlining, drafting, and submission process.

Data Availability

The data obtained in this study contains PII. According to our IRB protocol, in order to protect the confidentiality of our participants, the Headquarters, Medical Research and Development Command institutional review board (IRB) requires any institution to execute the proper agreements between HQ MRDC IRB and their respective local IRB.

Authors' Contributions

JL, TRN, and HP drafted the original manuscript. JL, EQ, JG, and ESB designed this research. JL, TRN, HP, OB, CY, JG, CD, CY, and TH edited the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ACC: autonomous casualty care
AI: artificial intelligence
AutoDoc: autonomous documentation
AVS: audiovisual system
COTS: commercial off-the-shelf
DoD: Department of Defense
EP: embedded participant
HIPAA: Health Insurance Portability and Accountability Act
IED: improvised explosive device
IRB: institutional review board
IRBO: Institutional Review Board Office
JTS: Joint Trauma System
MHS: military health care system
ML: machine learning
PCP: primary care provider
POI: point of injury
SM: service member
TATRC: Telemedicine & Advanced Technology Research Center
TCCC: tactical combat casualty care
USAMRDC: United States Army Medical Research and Development Command

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Protocol

Evaluation of a Smartphone-Based Weight Loss Intervention with Telephone Support for Merchant Women With Obesity in Côte d'Ivoire: Protocol for a Randomized Controlled Trial

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Abstract

Background: The obesity rate among women in Côte d'Ivoire is rising, particularly in urban areas. Merchantry is the leading occupation for women in the country, and merchant women face a high risk of obesity owing to their sedentary lifestyle. A previous survey indicated that the obesity rate among merchant women was 30%, double the national average. Furthermore, 82.2% of merchant women with obesity were unaware of their condition, and 40.1% expressed no interest in losing weight. While most weight loss programs target individuals ready to lose weight, community interventions should also address those with minimal readiness. Additionally, low-cost weight-loss interventions that do not require health professionals are needed in countries with limited medical resources. Smartphones could offer a cost-effective solution as they enable self-monitoring and remote communication.

Objective: This study will evaluate a low-cost smartphone-based intervention that targets individuals who are not ready to lose weight without the involvement of health professionals.

Methods: The intervention will run for 6 months, and its efficacy will be assessed in an unblinded, parallel-group, randomized controlled trial with 108 participants per group. All direct interventions for participants in this study will be carried out by staff without medical qualifications. The intervention group will receive weighing scales and be encouraged to record their weight with a smartphone app. Health education will be provided via weekly group messages and monthly phone calls. The evaluation will be conducted face-to-face. The primary outcome will be the weight change, and the secondary outcome will be differences in body fat percentage, abdominal circumference, and stage of behavioral change in weight loss behaviors from baseline to 3, 6, and 12 months.

Results: In accordance with this protocol, the recruitment of participants started on August 26, 2024. A total of 216 participants were allocated, with 108 in the intervention group and 108 in the control group. The baseline survey began on November 15, 2024, and is currently ongoing as of the end of November 2024.

Conclusions: This study will be the first in sub-Saharan African countries to implement a smartphone app-based weight loss program in sub-Saharan Africa that does not require direct intervention by health care professionals but specifically targets communities. Furthermore, if the effectiveness of this program is confirmed, it has the potential to serve as a low-cost sustainable weight loss model at the policy level.

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KEYWORDS

West Africa; sub-Saharan Africa; obesity; noncommunicable diseases; mHealth; mobile health; eHealth; randomized controlled trial; Côte d'Ivoire; weight loss program

Introduction

Background

Obesity caused an estimated 5 million deaths associated with noncommunicable diseases (NCDs) such as cardiovascular diseases, diabetes, cancers, and chronic respiratory diseases [1]. Additionally, its high prevalence in people 18 years and older is a critical issue, at 17.9% for women and 13.6% for men in 2022. In Africa, the obesity rate was 17% in women and 6.8% in men in 2022 [2]. This difference is particularly significant, making obesity among women an urgent issue. The percentage of women with obesity in Côte d'Ivoire has doubled compared to 20 years ago (7.3% in 2002 and 15.7% in 2022) [2].

The characteristics of the occupational style of African market traders indicate that these traders are at high risk of obesity due to long sedentary hours and easy access to food [3-5]. In Abidjan, the largest city in Côte d'Ivoire, 64.3% of working women are merchants [6], and merchant is a common occupation among women from lower- and middle-income groups. A survey of medical facilities in Abidjan also showed that merchantry was the most common occupation among patients with overweight and obesity [7]. Furthermore, our all-inclusive market survey showed that the obesity rate among merchant women is 30% [8], double the national average of 15.3%. This indicates an urgent need to address obesity among individuals in the merchant community.

Obesity is a substantial cause of NCDs such as heart disease and type 2 diabetes [9,10], and weight loss can reduce the risk of NCDs. However, in Côte d'Ivoire, there is no community-targeted weight loss program. In general, weight loss programs often target those who wish to lose weight. However, in African countries such as Côte d'Ivoire, where being plump is a symbol of wealth and power, many individuals with obesity have no desire to lose weight. Notably, 82.2% of merchant women with obesity who work at the targeted market were unaware that they had obesity, and 40.1% did not wish to lose weight (38.6% wished to maintain their current weight and 1.5% wished to gain weight) [8]. Thus, in an environment such as that in Côte d'Ivoire, developing measures to address obesity in communities that include those with minimal readiness for weight loss is necessary.

To increase the willingness of individuals with obesity to undergo weight loss, we must educate them on their condition and reasons to lose weight. Weighing is key to this; however, in our study, 53.3% of merchant women with obesity did not weigh themselves once a year, and 95.5% of them did not own a scale. Regular weighing is effective for weight loss even without interventions such as weight loss programs [11] and is one of the most cost-effective and easiest weight loss methods to implement. In this study, we aim to increase the awareness of one's own weight through regular weighing, promote awareness of health risks, and increase readiness for weight loss.

Noninvasive exercise and diet are the cornerstones of behavioral therapy as a treatment method for obesity [12]; overweight and obesity management guidelines [13] that include behavior change programs have been established in the United States. However, these are primarily conducted by primary care physicians in medical institutions and require advanced medical personnel and resources such as frequent counseling and elaborate individualized behavioral strategy planning. Therefore, implementing these behavior change programs as is in resource-limited countries such as Côte d'Ivoire is challenging [14,15].

Mobile health is cost-effective and impactful in supporting diet and exercise regimens [16-20]. Self-monitoring using smartphones is more effective than other methods of weight management [20]. Enhanced social support through online social networking services (SNSs) can also be effective. For example, Facebook groups have shown weight loss benefits [21]. In Côte d'Ivoire, WhatsApp is a popular private communication tool; however, studies on implementing behavior change using WhatsApp are limited [22]. Most studies that use smartphone apps and SNSs have been conducted in high-income countries. Such studies are limited in sub-Saharan Africa because sociocultural backgrounds and the use of smartphones and SNSs are different.

The prevalence of smartphones in sub-Saharan Africa was 45% in 2019 and is expected to steadily increase [23]. In our previous study, 77% of female traders in the target markets used smartphones [8], suggesting that interventions using smartphones are feasible. Smartphone use is important in areas requiring low-cost interventions.

Community-based weight loss interventions in sub-Saharan Africa include a group session intervention in South Africa [24] and a program initiated in Burkina Faso that includes multiple in-person dietary counseling sessions with experts [25]. These include multiple in-person sessions with health professionals, counseling, and health education.

Considering their feasibility in areas where medical resources are scarce, smartphone use that allows for remote intervention and methods that require less intervention by health care workers are required.

In this study, we aim to examine the effectiveness of a low-cost versatile weight loss intervention that can be implemented without intervention by health professionals in a community that comprises those with minimal readiness for weight loss. Specifically, this study will examine the effectiveness of a weight loss intervention that incorporates weight measurement promotion, the use of a smartphone app, and communication with non–health professionals among female merchants with

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obesity in Côte d'Ivoire. This will be an unblinded, parallel-group, randomized controlled trial.

This paper outlines the study protocol of a randomized controlled trial, describing the intervention and examining its effectiveness.

Hypothesis

This study hypothesizes that the intervention group will achieve a weight loss of at least 2% [13] from baseline to 6 months, significantly differing from the control group. We will consider 2% weight loss as a clinically meaningful value; since the average weight of women with obesity in the target market is 85.6 kg [8], the equivalent of 2% is –1.7 kg. Based on the results of previous studies [19], this goal was deemed feasible.

Methods

Research Design

This study will focus on market A in Abidjan, Côte d'Ivoire. The effectiveness of the weight loss intervention will be tested in a parallel-group (1:1) randomized controlled trial among Merchant women with obesity within this market. As standard treatment, the control group will be weighed and provided with their BMI based on physical measurements, whereas the intervention group will receive a scale and the weight loss intervention using a smartphone app, and the differences will be compared. The study will be unblinded, and the effectiveness of the program will be evaluated after 6 months. In addition, a follow-up evaluation will be conducted 12 months later to assess sustained changes after the intervention is complete. We followed the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 statement and CONSORT-eHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist (V 1.6.1).

Eligibility Criteria

The target population will be female merchants between 18 and 65 years of age working in market A with a BMI ≥30 who own a smartphone for personal use and who can use WhatsApp. The exclusion criteria included those who are pregnant or lactating, those who are found pregnant during the intervention period, those for whom weight loss is contraindicated (due to a cancer diagnosis, eating disorders, poorly controlled hypertension, diabetes, etc), and those using physician-prescribed weight loss medication. If they have medical records, we will review them for the eligibility assessment. If they do not, we will ask about their conditions in detail and make a judgment.

Recruitment

Four interviewers and supporters will visit the target market, approach potential participants, and screen them to see if they satisfy the inclusion criteria by asking a few questions and taking physical measurements (weight and height measurements). If the participants were eligible, we explained the purpose of the study, the intervention and procedures, and the eligibility and exclusion criteria in detail and returned at least half a day later to obtain their signatures on a consent form. We also explained that the participants would be randomly assigned to either the intervention or control group and would not be able to self-select. We explained that all participants would be weighed regularly at the beginning of the intervention as well as 3, 6, and 12 months later, and that their height would be measured at the beginning of the study so that their BMI would be known each time. We further explained that the control group will have access to free scales placed at several locations in market A 12 months after the end of the entire study, which they can use at their leisure. We also informed them that smartphone apps and other devices would be introduced to them at the end of the study.

Participants could withdraw from the study at any time before data collection at 6 months by submitting a consent withdrawal form to a member of the research team.

Intervention

The weight loss intervention implemented in this study will target communities, including those who have no desire to lose weight, and will be low-cost without direct intervention by health professionals. The basic framework will be based on the American Heart Association (AHA)/American College of Cardiology (ACC)/The Obesity Society (TOS) guidelines for the management of overweight and obesity in adults [13] and the Burkina Faso program [25], which is implemented in the sociocultural context of West Africa. However, since both of these programs include direct intervention by health professionals, which differs from the purpose of this study, the content of the intervention is adapted to the situation in Abidjan in this study (Table 1). The weight loss intervention will be conducted for 6 months. The intervention will be based on self-weighing [11], which has been shown to be beneficial for weight loss, and will include the use of a low-cost personalized support smartphone app [16]. In addition, direct contact with the intervention group will be conducted by Ivorian non–medical professional supporters who were selected based on their research experience within Côte d'Ivoire and have received training for this study.

The intervention consisted of the following three components: (1) promoting weight measurement and encouraging self-monitoring through a smartphone app; (2) health education using a messaging app; and (3) in-person or telephone health education based on the stage of behavior change [26]. Lose it! (FitNow, Inc.) is a weight management app that will be used for weight self-monitoring [27], which has been used in weight loss programs in previous studies [20,28] and is available for free. WhatsApp, which is widely used in Côte d'Ivoire [29], can send and receive images, videos, audio, and text [30], and can deliver a variety of health education messages at low cost [31,32]. In addition, a step-counting app, such as Google Fit (Google Inc) for Android users and Health Care (Apple Inc) for iPhone users, can be installed for weight change and step-count monitoring. These apps will be installed on the smartphones of the intervention group, and participants will receive an orientation on their use. Additionally, they will be able to contact their supporters via WhatsApp to inquire about the use of Lose It! and another app at any time.

Health education should include recommendations for and emphasize the importance of a healthy diet, exercise, and weight

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measurement. Diet and exercise content should be in line with the "Diet and Exercise" described in the "Obesity" chapter of the Côte d'Ivoire National Disease-Specific Cookbook Guidelines [33]. In-person or telephonic health education will be conducted once a month and tailored to the stages of behavioral change [26] (precontemplation, contemplation, preparation, action, and maintenance) of the target population. Interventions corresponding to the change process [34-36] of each stage are provided. The intervention stimulates interest in weight loss during the precontemplation stage, motivates implementation during the contemplation stage, supports implementation during the preparation stage, supports continuation during the action stage, and supports maintenance during the maintenance stage to maintain confidence in behavior. The intervention and evaluation schedules are shown in Table 2.

To maintain consistency among supporters in the intervention, a manual was developed on how to send health education material via WhatsApp. A manual for telephone interviews was developed, and supporters will conduct telephone interviews according to the manual and provide a report on the content of the interviews. Supporters will be trained on the content of the intervention and the survey to ensure the quality of the intervention and the survey.

No interventions are administered in the control group. For the control group, height and weight are measured at baseline and at data collection at 3, 6, and 12 months, and BMI is calculated and reported on the spot by the supporter. This allows participants in the control group to know their weight and BMI regularly. In addition, after the 12-month survey is completed, scales will be installed in the target markets free of charge so that participants can continue to measure their weights. In addition, we will introduce the app to those who wish to use it.

Table 1. Adaptations of the weight loss program following the American Heart Association (AHA)/American College of Cardiology (ACC)/The Obesity Society (TOS) guidelines for the management of overweight and obesity in adults.

Variable	AHA/ACC/TOS guidelines [13]	Intervention adapted to this study	Reason for adaptation
Participants and setting	Individual with obesity who contacted with general practitioner or another medical organization	Community recruitment	Many individuals with obesity are unaware of their obesity risk and do not feel the need to lose weight, making them less likely to visit a health care facility voluntarily.
Intervention method and frequency	In-person, high-intensity (≥14 sessions in 6 months) sessions and counseling for feedback (face-to-face or telephonic)	6 phone calls and 3 face-to-face health education sessions (focused on behavior change stages, not full medical counseling)	For nonmedical interventions, feasibility was considered.
Intervention duration	6 months	6 months	No change
Interventionist	Health professionals (registered dietitians, psychologists, exercise specialists, health counselors, or professionals in training) who adhered to formal protocols in weight management	Trained non–medical professionals over 3 days, covering coaching, intervention methods by behavior change stage, and diet/exercise per Côte d'Ivoire obesity guidelines	Côte d'Ivoire's limited medical personnel and resources were taken into consideration.
Weight loss goal	Loss of 5%-10% of baseline weight within 6 months	Loss of 2% of baseline weight within 6 months	It is a clinically meaningful minimum value and is feasible according to previous studies [8,19].
Physical activity	Advice by health professionals; increased aerobic physical activity (such as brisk walking) for ≥150 min	Recommend increasing the number of steps in one's daily routine and establish a step count goal	With limited facilities and resources for fitness programs, the plan recommends daily walking and using a smartphone app for exercise.
Dietary intervention	Advice by health professionals; daily energy deficit of 500 kcal typically achieved with dietary intake of 1200-1500 kcal/d for women	Advice from trained non–health professionals based on the National Recipe Guidelines: offer recommended local dishes and cooking tips	The method is feasible for non–health professionals, using guidelines adapted to local eating habits without calorie calculations, which are difficult for participants and interventionists.

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Table 2. Enrollment, intervention, and data collection timeline.

	–2 months	–1	0[a]	1	2	3	4	5	6	12
Enrollment										
Eligibility assessment	✓									
Informed consent	✓									
Allocation		✓								
Intervention										
Distribution of scales			✓	✓						
App installation and orientation			✓	✓						
Health education via message app (1 time/wk)				✓	✓	✓	✓	✓	✓	
In face-to-face health education (at the time of survey)			✓			✓			✓	
Health education by phone				✓	✓		✓	✓		
Data collection for intervention group										
Collect data at time of call (weight, stage of behavior change)				✓	✓		✓	✓		
Data collection for intervention group and control group										
Weight, body fat percentage, and abdominal circumference measurements	✓		✓			✓			✓	✓
Height measurement	✓									
Structured interview	✓		✓			✓			✓	✓

[a]The intervention lasted from months 0 to 6.

Outcome

The primary end point of the study is to compare weight changes from baseline to the end of the intervention (6 months later) between the intervention and control groups.

Secondary end points include the differences in body fat percentage, abdominal circumference, stage of behavioral change in weight loss behaviors such as diet and exercise, percentage of individuals with correct weight perception, degree of body pain (with visual analog scale [VAS]), and self-rated health at the end of the intervention (6 months later) compared to baseline. Simultaneously, the intervention group will be evaluated in terms of the frequency of inputs to the self-monitoring apps, degree of participation in WhatsApp groups, average number of steps taken, and degree of weight loss during the intervention period.

To evaluate the interim process of the intervention, the intervention and control groups will be compared and analyzed in the same manner as described above, 3 months after the start of the intervention. In addition, the intervention group will be evaluated for weight change at 1, 2, 4, and 5 months and for changes in the behavioral change stage of weight loss behaviors such as diet and exercise.

As a follow-up evaluation after the intervention, both groups will be evaluated at 12 months (6 months after the end of the intervention) in the same way.

Sample Size Calculation

For the sample size calculation, we relied on a meta-analysis [19] of a smartphone app–based weight loss intervention. We applied –1.5 (95% CI –2.09 to –1.09) kg as the clinically meaningful difference between the 6-month smartphone-only intervention without face-to-face motivational interviewing and the control group, as indicated in the meta-analysis. However, the meta-analysis did not provide SD values, so we used the SD (–1.8, SD 3.7) [37] value of the smartphone self-monitoring–only intervention results as a reference and set the expected value at –1.5 (SD 3.7) kg. Furthermore, the α error was set at 5% (95% CI=1.96), power (1 – β error) at 80% (0.842), and the dropout rate at 10%. Based on the above values and after consulting a statistical expert, the sample size was calculated to be 108 individuals for each group (N=216 in total).

Assignment, Allocation Concealment, and Blinding

The random assignment will be performed using the permuted block method. Stratification will be conducted based on BMI (threshold: 32 kg/m^2) and age (threshold: 45 years), which represent the median values reported in a previous study. The four resulting strata will be as follows: (1) BMI ≥32 and age ≥45 years, (2) BMI ≥32 and age <45 years, (3) BMI <32 and age ≥45 years, and (4) BMI <32 and age <45 years.

The list of potential participants recruited was sent to study member allocator 1 in Japan. Allocator 1 prepares a provisional ID list that does not contain attributes other than BMI and age to ensure concealment and sends it to allocator 2. Allocator 2 creates an allocation table with an allocation ratio of 1:1 and BMI and age as adjustment factors using software for randomized controlled trial–stratified substitution blocks and allocates the provisional IDs to each stratum in descending order of provisional ID numbers, from top to bottom.

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This study will be conducted in an unblinded manner. This is because the intervention group will be given a scale and an app to be installed; therefore, blinding of the participants will not be possible. In addition, the content of the questions asked during each evaluation differs between the intervention and control groups, making blinding difficult for supporters and research team members.

Data Collection Methods

Data will be obtained from supporters visiting the market to conduct face-to-face structured interviews (Multimedia Appendix 1) and anthropometric measurements. Body measurements will be taken at the time of recruitment to measure height and weight, and BMI will be calculated immediately. Subsequent data collection will include weight measurements, body fat percentage, and abdominal circumference. Height will be measured using a hardware SHUREMAN Lock Convex measuring tape (Kenoh Co, Ltd, Japan, model LC-5525) with a locking function, and an InBody (InBody Japan Inc, model H20N) will be used as the body composition scale. Structured interviews will be conducted using a questionnaire asking about sociodemographics, weight perception, behavioral change stages related to weight loss, behaviors related to weight management, body pain level (using the VAS scale), and the use of smartphone apps for weight management.

In addition, the intervention group will be asked about the weight and behavioral change stages of exercise and diet during the monthly telephone intervention.

Statistical Methods

The primary outcome will be evaluated by comparing the difference in weight change between the intervention and control groups 6 months after the intervention ended. In addition, the effectiveness of the weight loss intervention will be estimated using a linear regression model with weight change at 6 months as the dependent variable and the affiliation group, stratification variables, and other sociodemographic attributes as covariates.

Among the secondary outcomes, weight, body fat percentage, abdominal circumference, and degree of body pain (VAS scale) will be measured and compared in the same way as the primary outcome at all evaluation periods (3, 6, and 12 months). Other secondary outcomes will be compared to differences in rates at baseline and 3, 6, and 12 months. These analyses will follow the intention-to-treat principles. Additionally, intention-to-treat and per-protocol analyses will be performed and compared to address cases of protocol noncompliance.

Within the intervention groups, weight loss will be used as the dependent variable, and linear regression model analyses will be performed to estimate the impact of self-monitoring input frequency, WhatsApp group participation, and sociodemographic characteristics as covariates.

Data Management and Monitoring

All data will be collected on paper, entered into an Excel data entry format, and stored as digital data. The reason for this is that the intervention in this study involved self-monitoring of weight by app and encouraging behavioral change, so no significant safety issues are foreseen [38,39].

The research team will create a participant management sheet and continuously monitor the participants' health and weight loss status during the supporters' calls to identify any problems. During the study period, supporters will hold web-based meetings with the research team 1-6 times a month to share the participants' situation, which will facilitate the detection of unexpected adverse events.

Ethical Considerations

This protocol (version 6) and all related materials for this study were reviewed and approved by the Ethics Committee for Research on Life Sciences and Medicine Involving Human Subjects of Yokohama City University, Japan (approval General 2024-020) and by the National Ethics Committee in Health and Life Sciences of Côte d'Ivoire (RefNo 218-23/MSHPCMU/CNESVS-km). In the event of a protocol change, the ethics committee and UMIN Clinical Trials Registry will be notified.

After receiving a full explanation face-to-face, the participant will be asked to sign an informed consent form. At the same time, the participant will be informed that she can withdraw her consent (Multimedia Appendix 2). The collected digital data will be password-protected, and the paper-based data will be stored in a locked cabinet. Additionally, the data for this research will only be accessible to the research team members who have been instructed to maintain strict confidentiality. The results of this research will be published in a peer-reviewed international scientific journal.

The study was registered in the UMIN Clinical Trials Registry (ID 000055142) (Multimedia Appendix 3).

Results

In accordance with this protocol, the recruitment of participants started on August 26, 2024; by September 8, 2024, a total of 231 people were recruited. After reconfirming eligibility, one participant was excluded, and from 230 people, 108 were allocated to the intervention group and 108 were allocated to the control group. The baseline survey began on November 15, 2024, and is currently ongoing as of the end of November 2024.

Discussion

Expected Findings

The expected outcomes will analyze body weight, body fat percentage, and abdominal circumference. It is anticipated that the intervention group will achieve greater reductions in these three indicators compared to the control group. Additionally, the difference between the intervention and control groups is expected to be greater at 6 months and remain stable at 12 months.

Comparisons With Prior Work

There are fewer community-based weight loss programs in sub-Saharan Africa than those conducted within health care facilities. One such program is that of Herrmann et al [25];

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however, it primarily involves interventions led by health care professionals with specialized knowledge and does not use smartphones or web-based media.

In our study, we deliberately chose to use nonmedical staff as direct interventionists to evaluate the feasibility of implementing a weight loss program by those staff in sub-Saharan African countries where human resources in health care are particularly scarce.

Additionally, weight loss programs that use smartphone apps often recruit participants via web-based media, thereby primarily attracting individuals who are already motivated to lose weight [20]. Our study differs from previous research in that it targets communities with cultural norms that view being plump as a virtue, includes individuals who may not be aware of the need to lose weight, and recruits participants through face-to-face interactions.

To our knowledge, this is the first study to implement a smartphone app–based weight loss program in sub-Saharan Africa that does not require direct intervention by health care professionals and targets specific communities.

Study Significance and Feasibility

The findings of this study will provide information on the effectiveness and feasibility of a smartphone app–based weight loss program for communities in sub-Saharan Africa. Additionally, it will offer evidence on the extent to which interventions led by nonmedical individuals can be effective.

In Côte d'Ivoire and neighboring countries, the most common occupation among women is merchant [40-43]. If the feasibility of using smartphone apps within this community is demonstrated, it could pave the way for applying it to other health programs. Furthermore, if the effectiveness of this program is confirmed, it has the potential to serve as a low-cost, sustainable weight loss model at the policy level.

Limitations

First, the intervention cannot be blinded to the participants because those in the intervention group will receive a weighing scale. It is also difficult to make the supporters blinded because the questionnaires are different between the two groups. Second, it is not possible to perfectly prevent the participants from exchanging information with each other. However, we will try to understand the status of communications between the two groups by including a related question in the questionnaire. Third, the target population of the study may not represent all female merchants in Côte d'Ivoire as we only included those who have smartphones. However, as the smartphone ownership rate among female merchants in the market in the previous study was 77% [8], we judged this to be feasible.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

All authors made substantial contributions to the study concept, data analysis, and interpretation. RU drafted the manuscript, and MA, SK, SW, BTJS, KK, and YK critically revised it for important intellectual content. All authors have approved the final version of the manuscript for publication and agreed to be accountable for all aspects of this work.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Survey form (baseline, 3, 6, and 12 months later).
[PDF File (Adobe PDF File), 4621 KB - resprot_v14i1e69264_app1.pdf]

Multimedia Appendix 2
Consent form and related documents.
[PDF File (Adobe PDF File), 556 KB - resprot_v14i1e69264_app2.pdf]

Multimedia Appendix 3
Table of WHO Trial Registration Data Set.
[PDF File (Adobe PDF File), 116 KB - resprot_v14i1e69264_app3.pdf]

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Abbreviations

ACC: American College of Cardiology
AHA: American Heart Association
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
NCD: noncommunicable disease
SNS: social networking service
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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TOS: The Obesity Society
VAS: visual analog scale

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Protocol

Predicting Therapy Outcomes in Patients With Stress-Related Disorders: Protocol for a Predictive Modeling Study

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Abstract

Background: While cognitive behavioral therapy has shown efficacy in treating stress-related disorders, such as adjustment disorder and exhaustion disorder, knowledge about factors contributing to treatment response is limited. Improved identification of such factors could enhance assessment procedures and treatment strategies. In addition, evaluating how traditional prediction methods and machine learning can complement each other may help bridge gaps in understanding and predicting treatment response.

Objective: This study aims to (1) evaluate putative predictors of treatment response in patients with stress-related disorders using traditional prediction methods and (2) model treatment outcomes using a machine learning approach. This design combines the interpretability of traditional methods with the ability of machine learning to identify complex patterns.

Methods: We will analyze data from a randomized controlled trial comparing 2 internet-delivered treatments, cognitive behavioral therapy versus an active control treatment, for patients diagnosed with adjustment disorder or exhaustion disorder (N=300). Prediction models will be based on pooled data from both treatment arms due to the limited sample size and lack of knowledge on predictors of treatment effects. Putative predictors include sociodemographic and clinical information, clinician-assessed data, self-rated symptoms, and cognitive test scores. The primary outcome of interest is responder status on the Perceived Stress Scale-10, evaluated based on the reliable change index posttreatment. For the traditional approach, univariate logistic regressions will be conducted for each predictor, followed by an ablation study for significant predictors. For the machine learning approach, 4 classifiers (logistic regression with elastic net, random forest, support vector machine, and AdaBoost) will be trained and evaluated. The dataset will be split into training (70%) and testing (30%) sets. Hyperparameter tuning will be conducted using 5-fold cross-validation with randomized search. Model performance will be assessed using balanced accuracy, precision, recall, and area under the curve.

Results: All data were collected between April 2021 and September 2022. We hypothesize that key predictors will include younger age, education level, baseline symptom severity, treatment credibility, and history of sickness absence. We anticipate that the machine learning models will outperform a dummy model predicting the majority class and achieve a balanced accuracy of ≥67%, thus indicating clinical usefulness.

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Conclusions: This study will contribute to the limited research on predictors of treatment outcome in stress-related disorders. The findings could support the development of more personalized and effective treatments for individuals diagnosed with adjustment disorder or exhaustion disorder, potentially improving clinical practice and patient outcomes. If successful, this dual approach may encourage future studies with larger datasets and the implementation of machine learning models in clinical settings, ultimately enhancing precision in mental health care.

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KEYWORDS

adjustment disorder; cognitive behavioral therapy; exhaustion disorder; machine learning; predictive modeling; psychological stress; therapy outcome

Introduction

Background

Mental disorders have a negative effect on quality of life, often precipitating personal suffering and work disability [1]. Around 23% of all who receive a psychiatric diagnosis in Swedish primary care receive a stress-related diagnosis [2], and these account for most psychiatric long-term sickness absences [3]. In Sweden, disorders believed to stem from persistent or overwhelming subtraumatic life events are often categorized using the diagnostic labels adjustment disorder (AD) or exhaustion disorder (ED). Even though ED is only recognized as a medical diagnosis in the Swedish version of the *International Classification of Diseases, Tenth Revision*, the clinical picture of ED is similar to the internationally acknowledged burnout construct [4], a condition that is often associated with significant suffering and work disability [5].

According to diagnostic definitions of AD and ED, these conditions develop in the context of one or several subtraumatic life events (stressors), resulting in mixed symptoms of anxiety, depressed mood, disturbed sleep, fatigue, and impaired memory and concentration. They share symptomatology with other mental disorders, and their diagnostic validity is debated [6,7]. Despite evidence indicating the efficacy of cognitive behavioral therapy (CBT) [8-10] and problem-solving interventions [11] on symptoms of stress, many studies have suffered from significant attrition, and knowledge regarding the factors that contribute to treatment response is still limited [8,12]. Improved identification of such factors could facilitate development of improved assessment procedures and adaptive treatment strategies that might improve outcomes [13].

Research on predictors of psychiatric treatment outcomes is limited [14,15] but demographic factors (eg, age and education level) [16,17], clinical characteristics (eg, use of medication and symptom severity) [17-19], treatment-related factors (eg, treatment credibility and adherence) [16,18] and cognitive functioning [20] have been associated with treatment outcomes.

When it comes to studies investigating predictors of treatment for stress-related disorders, Kocalevent et al [15] found that symptoms of anxiety but not perceived stress, depressive symptoms, or demographic variables predicted self-rated mental health following treatment for patients diagnosed with AD. In a study investigating burnout, Pallich et al [21] identified emotional competence, but not demographic characteristics, as a predictor of treatment response. However, both of these studies suffer from limited generalizability due to their inadequate description of the treatment offered, the fact that the interventions were conducted in an inpatient setting, and the lack of control groups. In ED patients, one study identified several predictors of treatment outcome following multimodal rehabilitation, including younger age, baseline symptom severity (insomnia, anxiety, and depression), perfectionism, physical activity level, treatment credibility, and a history of sickness absence due to ED [22]. However, the effects of demographics and pretreatment symptoms were so small that they offered limited clinical utility. In sum, at the current stage of research, it is a challenge for clinicians to determine who will benefit from treatment, underscoring the imperative for more sophisticated predictive studies.

Traditionally, prediction in psychiatry has relied on interpretable linear or logistic regression models. The aim has been to identify variables explaining a statistically significant portion of the variance in outcome, under the premise that such variables should inform researchers and clinicians. For example, the presence of previous sickness absence and earlier unsuccessful treatment attempts might lead a psychologist to conclude that a patient requires additional support, possibly extending the treatment duration. Although this approach of identifying predictors has offered some clinical utility, it often falls short in practice; the predictive power of specific variables in isolation is typically inadequate to inform assessment, treatment selection, and adaptations of interventions. Given the inherent complexity of mental disorders, the likelihood of pinpointing strong predictors with clinical utility is small, thus limiting the practical value of this approach [23,24].

Machine learning (ML) represents a promising methodological shift in psychiatric prediction modeling, transitioning from the identification of statistically significant predictors to an emphasis on quantifiable model performance, characterized by ensemble methods and adaptability to new datasets. This approach often sacrifices explainability in favor of enhanced predictive performance but offers unique value in handling the complex, nonlinear, high-dimensional data characteristic of mental disorders [25]. With this approach, a model generates a prediction (eg, remission, yes or no) intended to be actionable for a clinician. For example, patients predicted to have low probability of treatment success could be offered additional psychological support or an alternative intervention, thus increasing the likelihood of remission [26,27].

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Forsell et al [28] have proposed a balanced accuracy (BACC) threshold of 67% as a benchmark for clinical utility in psychiatric applications, offering a tangible goal for ML implementation. However, the efficacy of ML in this domain remains an ongoing area of inquiry, and its capacity to surpass conventional methods in clinical usefulness is yet to be established [29].

Given the high prevalence and substantial societal costs associated with stress-related disorders, it is imperative to critically evaluate both the applicability and the limitations of ML within this specific context. Such an assessment will not only contribute to the broader understanding of the role of ML in precision psychiatry but also inform the development of more effective diagnostic and treatment strategies for stress-related disorders.

Objective of the Study

The overall objective of this study is to predict treatment outcomes in patients with stress-related disorders. Due to limitations in existing methods for prediction analyses, this study aims to first evaluate putative predictors using a traditional prediction paradigm, and second to model treatment outcomes using an ML approach. Our primary outcome of interest is responder status after treatment on the Perceived Stress Scale-10 (PSS-10), evaluated using the reliable change index (RCI; further described in the Planned Statistical Analysis and Data Cleaning and Preparation sections). On the basis of earlier research on predictors of treatment outcome, we hypothesize that key predictors will include younger age, education level, baseline symptom severity, treatment credibility, and history of sickness absence. Furthermore, we anticipate that the ML models will outperform a dummy model predicting the majority class and achieve a BACC of ≥67%, thus being indicated clinically useful [28].

Methods

Study Design

We will use collected data from a randomized controlled trial (RCT; N=300) of internet-delivered CBT for patients diagnosed with AD or ED compared to an active, internet-delivered control condition consisting of general health-promoting advice. A priori power analysis conducted for the main outcome in the RCT indicated that 300 study participants would be needed for a 90% power to detect a between-group effect size of Cohen d=0.4 with a significance level of .05 and an expected attrition rate of 10%. Due to the limited sample size and general lack of knowledge on predictors of treatment effect, prediction models in this study will be based on pooled data from both treatment arms. The study design is prospective, and predictors will include sociodemographic and clinical information, clinician-assessed data, self-rated symptoms, and results from cognitive test scores. The results will be reported in line with the TRIPOD+AI (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis+Artificial Intelligence) statement [30].

Ethical Considerations

The study was approved by the Swedish Ethical Review Authority (registration 2020–03198; 2023–06857-02) and was preregistered on ClinicalTrials.gov (NCT04797273). All participants provided written informed consent before inclusion, and their data are pseudonymized and securely stored on an encrypted server. Participants received no monetary compensation but accessed study interventions free of charge. No identifying information of participants will be included in the manuscript or supplementary materials.

Procedure

Participants

In total, 300 nationally recruited individuals were diagnosed with a primary diagnosis of AD (n=142, 47.3%) or ED (n=158, 52.7%) and were included in the RCT. Participant recruitment was carried out through social media, newspaper advertisements, and information provided to health care clinics. Participants self-referred to the study web page, where they signed digital informed consent and completed a screening battery consisting of sociodemographic and clinical background questions as well as self-report symptom questionnaires. Participants were subsequently clinically assessed by a psychologist using a structured diagnostic interview, including Mini International Neuropsychiatric Interview [31], self-rated ED [32], and the Adjustment Disorder New Module-8 (ADNM-8) [33]. For inclusion, participants needed to (1) fulfill the criteria for a primary diagnosis of AD or ED, (2) be aged between 18 and 65 years, (3) have regular access to a computer with internet access, and (4) be able to read and write in the Swedish language. Exclusion criteria included (1) drug use or addiction during the past 6 months, (2) current or past psychosis or bipolar disorder, (3) current risk of suicide, (4) changed psychopharmacological treatment in the past month, (5) other ongoing psychological treatment, and (6) previous experience of CBT for AD or ED in the past year.

Treatment

Patients were randomized to one out of two 12-week internet-delivered treatments (CBT and general health-promoting advice). They both consisted of web-based text-based modules with related exercises and assignments. Patients were guided sequentially through the modules by a therapist via a secure web-based platform. The therapists' primary role was to provide feedback on exercises, support in problem-solving, and to give emotional and technical support via weekly asynchronous text messages. Therapists were licensed clinical psychologists or clinical psychology students in their final year of training. Because this study will not evaluate the individual treatments, they will not be further described here. A full description of the treatments is described in the study by Sennerstam et al [34].

Outcomes

The primary outcome in this study and the original RCT is PSS-10 [35]. The PSS-10 is a self-report questionnaire developed to evaluate an individual's perception of life as unpredictable, uncontrollable, and overwhelming. Responses are recorded on an ordinal scale ranging from 0 *never* to 4 *very often*, reflecting the individual's feelings and thoughts over the

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past month. It contains statements, such as '*In the last month, how often have you been upset because of something that happened unexpectedly?*' and sum scores range from 0 to 40. The PSS is the most commonly used outcome measure of stress-management interventions globally [8,36,37]. For this study, a Swedish version of the PSS-10 was used. The PSS-10 has been found to exhibit high internal consistency (Cronbach α=0.84) and adequate construct validity [38]. The PSS-10 was administered digitally through the web-based study platform before randomization to treatment, every 3 weeks during the treatment phase, and at treatment completion (12 weeks). During treatment, the instructions for the PSS-10 were modified to have patients consider the last week instead of the last month. For this study, the sum score of the PSS-10 will be dichotomized into responder or nonresponder after treatment based on the RCI criteria [39] to differentiate between statistically significant change and those attributable to measurement error or natural variability. The PSS-10 baseline and 3-week measurement will also be used as predictors.

Putative Predictors

Overview

Predictors were gathered through self-report measures that were administered in the web-based study platform, clinical assessment conducted before inclusion to the study, and remote cognitive testing. Table 1 presents all predictors included in the study.

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Table 1. Putative predictors of treatment outcome in stress-related disorders

Predictor	Construct measured	Type	Clinician-rated	Scoring range
Sociodemographics				
Age (y)	—[a]	Interval		18-65
Sex	—	Categorical		Male or female
Relationship status	—	Categorical		3 categories
Number of children	—	Interval		0-∞
Educational attainment	—	Ordinal		9 categories
Employment status	—	Categorical		8 categories
Employment type	—	Categorical		11 categories
Self-rated computer skills	—	Ordinal		5 categories
Self-rated reading skills	—	Ordinal		5 categories
Swedish native speaker	—	Categorical		Yes or no
Clinical characteristics				
Number of medications	Medication	Interval	✓	0-4
Antidepressants	Medication	Categorical	✓	Yes or no
Sleep medication	Medication	Categorical	✓	Yes or no
Pain medication	Medication	Categorical	✓	Yes or no
Anxiolytics	Medication	Categorical	✓	Yes or no
Diagnosis	Primary diagnosis	Categorical	✓	2 categories
Secondary diagnosis	Secondary diagnosis	Interval	✓	0-4
Depression	Secondary diagnosis	Categorical	✓	Yes or no
Anxiety disorder	Secondary diagnosis	Categorical	✓	Yes or no
Insomnia	Secondary diagnosis	Categorical	✓	Yes or no
Other disorders	Secondary diagnosis	Categorical	✓	Yes or no
S-ED[b]	Exhaustion disorder	Ordinal	✓	3 categories
ADNM-8[c] criteria	Adjustment disorder	Categorical	✓	Yes or no
ADNM-8 number of stressors	Adjustment disorder	Interval	✓	0-11
ADNM-8 stressors	Adjustment disorder	Categorical	✓	16 categories
Duration of current episode	—	Interval	✓	0-∞
Age of first episode (y)	—	Interval	✓	0-65
Sick-leave status	Sickness absence	Interval		0%-100% 5 steps
Sick-leave duration	Sickness absence	Ordinal		5 categories
Self-rated symptoms				
AUDIT[d]	Alcohol consumption	Interval		0-40
GAD-7[e]	Anxiety symptoms	Interval		0-21
SMBQ[f] cognitive weariness	Burnout	Continuous		0-7
SMBQ exhaustion	Burnout	Continuous		0-7
SMBQ listlessness	Burnout	Continuous		0-7
MADRS-S[g]	Depression	Interval		0-54
KEDS[h]	Exhaustion disorder	Interval		0-54
WHODAS[i] 2.0	Functional disability	Continuous		0%-100%

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Predictor	Construct measured	Type	Clinician-rated	Scoring range
EQ-5D-5L	Quality of Life	Interval		5-25
BBQ[j]	Quality of life	Interval		0-96
ISI[k]	Insomnia severity	Interval		0-28
SRH-5[l]	Self-rated health	Interval		0-5
PSS-10[m]	Perceived stress	Interval		0-40
PHQ-15[n]	Somatoform symptoms	Interval		0-30
6-QEMP[o]	Subjective memory impairment	Interval		0-30
3-week measurement				
SMBQ cognitive weariness	Burnout	Continuous		0-7
SMBQ exhaustion	Burnout	Continuous		0-7
SMBQ listlessness	Burnout	Continuous		0-7
ISI	Insomnia severity	Interval		0-28
PSS-10	Perceived stress	Interval		0-40
Treatment-related predictors				
Clinician treatment expectancy	—	Interval	✓	0-10
Treatment credibility scale	—	Interval		0-10
Cognitive functioning				
SDMT[p]	Attention and processing speed	Interval		0-∞
FAS[q]	Executive functions	Interval		0-∞
Stroop index	Executive functions	Continuous		0-∞
Stroop inhibition	Executive functions	Continuous		0-∞
CERAD[r] learning	Memory	Interval		0-30
CERAD recognition	Memory	Interval		0-10
Corsi forward	Memory	Interval		0-9

[a]Not applicable.
[b]S-ED: self-rated exhaustion disorder.
[c]ADNM-8: The Adjustment Disorder New Module-8.
[d]AUDIT: Alcohol Use Disorder Identification Test.
[e]GAD-7: General Anxiety Disorder-7.
[f]SMBQ: Shirom-Melamed Burnout Questionnaire.
[g]MADRS-S: Montgomery-Åsberg Depression Rating Scale.
[h]KEDS: Karolinska Exhaustion Disorder Scale.
[i]WHODAS: World Health Organization Disability Assessment Schedule.
[j]BBQ: Brunnsviken Brief Quality of Life Scale.
[k]ISI: Insomnia Severity Index.
[l]SRH-5: Self-Rated Health-5.
[m]PSS-10: Perceived Stress Scale-10.
[n]PHQ-15: Patient Health Questionnaire-15.
[o]6-QEMP: 6-item Questionnaire of Everyday Memory Problems.
[p]SDMT: Symbol Digit Modality Test.
[q]FAS: Verbal Fluency Test.
[r]CERAD: Consortium to Establish a Registry for Alzheimer's Disease.

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Sociodemographic Variables

Information on age (interval), sex (male, female, other, or prefer not to disclose), relationship status (in relationship, single, or widowed), number of children, educational attainment (in 9 categories between <9 years of school to PhD), employment status (eg, student, unemployed, or full-time work), and employment type (in 11 categories, eg, employed in the private sector, by the municipality, or other) was gathered before the start of treatment using the web-based study platform. Self-rated reading and computer skills were rated separately on a 5-step ordinal scale from *poor* to *very good*. Patients also reported if they were Swedish native speakers.

Clinical Characteristics

During the clinical interview, patients reported their medication regimen, specifying both the number (0-4) and type of medication (antidepressants, anxiolytics, sleep medication, and pain medication and yes or no). Primary diagnosis (AD or ED), and possible secondary psychiatric diagnosis (eg, anxiety or depressive disorder) was assessed by the clinician using Mini International Neuropsychiatric Interview, self-rated ED (ordinal categories ranging from *no* to *yes—to a high degree*) [32], and the ADNM-8 [33]. Using ADNM-8, the patient was asked about which specific stressors had been present in the past 2 years (in 16 options, eg, *too much or too little work* or *financial difficulties*). The clinician assessed the length of the current episode (in months), and the age of the patients first episode (in years). Sick-leave status upon inclusion in the study (0%-100% in 5 steps), length of current sick-leave episode (*0-1 months* to *>12 months* in 5 categories) was self-reported.

Self-Rated Symptoms

Alcohol use was assessed using the Alcohol Use Disorder Identification Test [40,41]. This 10-item screening instrument evaluates alcohol consumption, drinking behavior, and alcohol-related problems over the past year. It contains items, such as *How often do you have six or more drinks on one occasion*? rated on various ordinal scales, typically ranging from 0 to 4.

Symptoms of anxiety were measured using the Generalized Anxiety Disorder-7 scale [42]. This screening tool assesses generalized anxiety symptoms over the past 2 weeks. It comprises 7 items, such as *not being able to stop or control worrying* rated on a 4-point ordinal scale ranging from 0 *not at all* to 3 *nearly every day*.

Symptoms of burnout were measured using the Shirom-Melamed Burnout Questionnaire [43,44]. It aims to measure 3 components of burnout; emotional and physical fatigue, cognitive weariness, and listlessness and contains statements such as *I have difficulty concentrating* rated on a 7-point scale ranging from 1 *never or almost never* to 7 *always or almost always* with some items using reversed scoring.

Symptoms of depression were measured using Montgomery-Åsberg Depression Rating Scale [45]. It is a 9-item questionnaire used to measure different aspects of depression such as concentration difficulties, suicidal thoughts, sadness, and affected appetite with answers rated on a 7-point ordinal scale from 0 to 6.

Symptoms of exhaustion disorder were measured using the 9-item Karolinska Exhaustion Disorder Scale [46]. Measuring different aspects of exhaustion such as fatigue, endurance, and sleep impairment, answers are rated on an ordinal scale from 0 to 6 (eg, ability to concentrate; ranging from 0 “I do not have any difficulty concentrating, and can read, watch TV and converse normally” to 6 “I cannot concentrate on anything at all.”)

Functional disability was measured using The World Health Organization Disability Assessment Schedule (2.0) [47], developed to assess functioning in the last 30 days in 6 different life domains, including cognition, mobility, self-care, relationships, life activities, and societal participation. It contains statements, such as “I have difficulty standing for longer periods such as 30 minutes.” Answers are rated on a 5-point ordinal scale ranging from 0 *never* to 4 *extreme or unable*. A 12-item version was used.

Quality of life was assessed using the EQ-5D-5L [48,49] and the Brunnsviken Brief Quality of Life Scale [50]. The EQ-5D-5L contains 5 dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression each rated on 5 levels of severity from *no problems* to *extreme problems*. The Brunnsviken Brief Quality of Life Scale is a 12-item questionnaire that assesses 6 life areas (leisure time, view on life, learning, creativity, view of self, and friends and friendship). Ratings range from 0 *strongly disagree*, to 4 *strongly agree*, on statements of the importance and satisfaction of each area.

Insomnia severity was measured using the Insomnia Severity Index [51]. The Insomnia Severity Index is a 7-item questionnaire designed to assess aspects of insomnia, including difficulty falling asleep, difficulty staying asleep, and satisfaction with sleep. Ratings are given using an ordinal scale ranging from 0 to 4.

Self-rated health was assessed using Self-Rated Health 5 asking patients to rate their general health on a scale of 1, *very bad* to 5 *very good* [52].

Somatoform symptoms were assessed using the Patient Health Questionnaire [53]. It consists of 15 questions covering somatic symptoms commonly seen in primary care, such as back pain, headache, and nausea. Answers are rated on a 3-point ordinal scale ranging from *not at all bothered* to *bothered a lot*.

Subjective memory impairment was measured using the 6-item Questionnaire of Everyday Memory Problems (6-QEMP) [54]. A 5-item version has previously been used to assess subjective memory problems in this patient population [55,56]. The present version was adapted by Stigsdotter Neely for use in patients with stress-related disorders with statements, such as “How do you think your memory functions now compared to before your stress-related mental health problems?.” The answers are rated on a 5-point ordinal scale.

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Treatment-Related Predictors

Clinician Treatment Expectancy was judged after patient assessment, upon inclusion in the study, by clinicians rating the probability of the patient improving after treatment on a scale of 0 *no improvement* to 10 *full remission*.

The *Treatment Credibility Scale* was administered 3 weeks after the start of treatment [57]. Patients were asked questions about their impression of the treatment and if they thought they would improve. It included statements such as "How logical do you think this treatment is?" and "How confidently would you recommend this treatment to a friend with the same problems as you?" on a scale of 0 *not at all* to 10 *very logical*, *very confidently.*

Cognitive Functioning

Attention and processing speed were measured using the Symbol Digit Modality Test. A test originally developed by Smith [58,59] that measures visual detection, attention, and processing speed. A key with 9 different symbols and matching numbers is shown on the upper part of the display. At the center one of these 9 symbols are shown and the task of the participant is to choose the corresponding number using the key as guidance. The test score is the number of correct entries in 90 seconds. Comparable substitution tasks are considered sensitive to treatment effects for patients with multiple sclerosis [60] and depression [61], and it has been used in patients with stress-related disorders [62].

Executive functioning was measured using the Verbal Fluency Test (FAS) Word Fluency Test and the Stroop test. FAS was first described by Spreen and Benton [63], and it measures spontaneous verbal fluency and selective attention and shifting. The participant is tasked with producing words beginning with a certain alphabet letter (F, A, and S). Names, numbers, or repeated words are not allowed. The test score is the number of correct words beginning with the letter. FAS and similar word fluency tasks have been shown to be impaired in patients with stress-related exhaustion [62].

The Stroop test, originally developed by Stroop [64] and described by Jensen and Rohwer [65], measures executive functioning, inhibition, as well as updating and processing speed [66]. The test has 2 parts, (1) 20 color words are presented (green, yellow, blue, or red) and they are colored congruent to their meaning (eg, the word red colored in red). In the bottom part of the display, the color words are displayed on 4 buttons. The task is to, as quickly and thoroughly as possible, click the correct button. (2) Twenty color words are presented but displayed in an incongruent color (eg, the word red colored in green). The task of the participant is to click the button containing the color of the word as quickly and thoroughly as possible. Test score is calculated as an index (number of correct answers in part 2 divided by average time in seconds from part 2) and for interference (average time in part one–average time in part one). Performance of Stroop in patients with stress-related disorders has been shown to be impaired in 2 studies [62,67], but not in others [68,69].

Memory and learning were assessed using the Consortium to Establish a Registry for Alzheimer's Disease (CERAD) Word List Learning Test and Corsi block-tapping test forward. CERAD was originally developed for use with Alzheimer disease [70] but is similar to other word-list tasks used in this patient population. It measures verbal learning and episodic memory. In the learning part of the test, a word list containing 10 words is presented over 3 trials and the task after every trial is to recall the words from the list. For every presentation the order is mixed. In the delayed recall part of the test (trial 4) that occurs after 5 to 10 minutes, the participant is asked to recall the words. Test score for the learning time is number of correct words in trial 1 to 3, and in the delayed recall part, number of correct words in trial 4. Similar word-list tasks have been used previously to assess memory functioning in patients with stress-related disorders [62,69].

Corsi block-tapping test forward gives information about visual ability of attention, short-term memory and working memory [71]. It contains 2 parts, but in this test battery, only the first part of the test is used. Nine blocks are displayed, and the testing platform starts by lighting up a sequence of blocks. The task is to repeat the sequence of blocks that the platform has displayed. The task starts out easy with only 2 blocks, but the difficulty increases by adding a longer sequence of blocks until the participant enters the incorrect sequence twice at the same number of blocks. The test score is the maximum number of correct repeated blocks. A cross-sectional study comparing patients with stress-related disorders to a healthy normative group found impaired performance on this test [62].

Planned Statistical Analysis

All data will be prepared and analyzed using the latest version of Python [72] and the libraries NumPy [73], Pandas [74], and scikit-learn [75] or equivalent statistical packages. A notebook containing the analysis in documented code will be made available on Open Science Framework [76] for research transparency following the analysis.

Data Cleaning and Preparation

We will transform categorical variables into a format suitable for numerical analysis. For binary categorical variables, we will use label encoding. For multinomial variables, we will apply one-hot encoding. In addition, for ordinal data, which have a natural order, we will transform the categories into integers.

Predictor variables with over 20% missing data will be excluded from the analysis. Categorical variables exhibiting low variance, as determined by predictors with <5% of a certain response will be removed. For instance, by removing the variable "Sleep medication" if it only occurs in 3 out of 300 patients. This approach aims to reduce unnecessary complexity in the predictions and to minimize the risk of overfitting. To control for multicollinearity, variables with a correlation coefficient ≥0.8 will be removed from the traditional prediction analysis but will be retained for the ML model development. Data that are highly skewed will be transformed if deemed appropriate.

Cognitive test results will be manually reviewed before model fitting to validate a proper result. Comments pertaining to technical difficulties and disturbances that may have affected the test result will be assessed by two of the authors and lead to exclusion if so judged. Participants who have noted during

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screening that Swedish is not their native language will be excluded from the analysis for CERAD and FAS. We will standardize the raw scores from the cognitive tests using normative regression models with age, education and sex as covariates. This standardization process will convert raw scores into *Z* scores, as previously described by Franke Foyen et al [62] and for a full overview of the multiple linear regression models used and how they were calculated, see the studies by Mindmore [77] and van den Hurk et al [78].

Patients who have missing data for the posttreatment PSS-10, ie, the missing outcome variable for the primary aim, will be replaced by a PSS-10 process measurement at week 10 if available; If not, the patient will be excluded from the analysis. The number of participants excluded from the final models will be described.

To prepare our primary outcome, RCI for the PSS-10 before to after treatment will be computed using the following formula [39]:

Cronbach α=0.83 from normative data will be used [38]. Patients exhibiting an RCI of −1.96 will be classified as responders.

Descriptive Statistics

Descriptive statistics will be used to summarize the sample characteristics and pretreatment variables, including mean or median, SDs and IQR for continuous variables, and proportions for categorical variables.

Predictor Analysis

For the traditional regression analysis, data will be imputed using the KNN imputer. The imputer, a nonparametric imputation method, works by imputing missing values based on the k-nearest neighbors; in this study *k* will be determined by cross-validation. It uses the Euclidean distance metric to find the nearest neighbors and can be used for both numerical and categorical data. Each missing value is imputed using values from its k-nearest neighbors. After imputation, we will run univariate logistic regressions for each predictor listed in Table 1 using RCI as a target variable. Predictors that are statistically significant in the univariate analyses will then be included in an ablation study, a systematic approach to evaluate feature importance. This method involves iteratively removing each significant predictor from a full model, measuring the change in explained variance, and then reinserting it, thereby quantifying each predictor's unique contribution to the model's explanatory power in the context of all other features.

ML Model Development

For an introduction on the technical terms introduced in this section, see the review article by Bzdok and Meyer-Lindenberg [13].

Train Test Split

As the ultimate goal of any model is to predict an outcome in unseen data, the ML models will be developed using a training set, and then evaluated on a test set stratified on main diagnosis (AD or ED) and responder status. In total, 70% of the data will be used for selecting predictor variables and training the models, and 30% for testing the prediction accuracy of the models. The choice of 70 to 30 was due to the limited size of our sample, as fewer observations in the testing data makes it difficult to use uncommon predictors. No external validation set is currently available at the time of writing.

Standardization and Imputation

Standardization and imputation will be applied on the training and test data separately to avoid data leakage. Numerical data will be standardized and all missing data will be imputed using the KNN imputer.

Model Descriptions

We will train and evaluate 4 different ML classifiers, a multiple logistic regression (LogReg) classifier using elastic net, a random forest (RF) classifier, a support vector machine (SVM) classifier, and an AdaBoost classifier. For a review of the models used, see the textbook by Geron [79]. In short, the LogReg classifier works by modeling the probability of a binary outcome based on one or more predictor variables, using the logistic function to ensure the output is between 0 and 1. We will use elastic net regularization to facilitate feature selection and prevent overfitting. Elastic net combines L1 (lasso) and L2 (ridge) penalties, encouraging sparsity and maintaining stability in the model. The RF classifier works by building multiple decision trees on random subsets of data and predictors. Each tree's prediction is based on splits that minimize variance in the target variable, with the final model ensembling these predictions. The SVM classifier works by finding the hyperplane that maximizes the margin between different classes in the feature space. SVM is particularly effective in high-dimensional spaces and when the number of dimensions exceeds the number of samples. AdaBoost, the final classifier, works by combining multiple weak classifiers, typically decision trees, into a single strong classifier. It sequentially fits these weak learners on repeatedly modified versions of the data, focusing more on misclassified instances to improve overall accuracy.

Hyperparameter Tuning

We will conduct 5-fold cross-validation using randomized search for hyperparameter tuning and training evaluation to enhance the external generalizability and robustness of the results. This process involves defining a hyperparameter space, then randomly selecting a predetermined number of samples—in this case, 10—from this space, and conducting 5-fold cross-validation for each selected set of hyperparameters. Fivefold cross-validation is done by partitioning the data into 5 subsets, training the model on 4 subsets, and validating it on the remaining subset. This process is repeated 5 times, with each subset used exactly once as the validation data. The best performing hyperparameters will be chosen for the final models that are trained and then evaluated on the test set.

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The hyperparameter ranges for the LogReg will include C values from 0.01 to 100 and l1_ratio values from 0 to 1. For RF, the parameter ranges will include the number of estimators from 5 to 1200, minimum samples required to split a node from 10 to 200, maximum depths from 5 to 750, and a binary indicator for bootstrapping. For SVM, the parameter range for the randomized search will include regularization parameter C values from 0.01 to 1 and for AdaBoost, the parameter ranges for the randomized search will include the number of estimators, ranging from 1 to 1500, and learning rates from 0.001 to 2.5.

Model Interpretation

The models developed to identify the responder status will be evaluated using BACC, precision and recall, both in the training set obtained through k-fold cross-validation and in the test set. Predictor importance in the RF model will be determined using Scikit-learn's Feature importance function, which quantifies each predictor's contribution to the model's balanced classification accuracy. Area under the curve will be used to assess the models' capability to distinguish between classes accurately. The approach will aim to provide a clear understanding of the models' effectiveness and the role of various predictors. Our primary outcome of interest for comparison will be BACC in each model in the test set with the aim that (1) the model should perform better than a dummy model that simply predicts the most common responder status, and (2) that the model should perform 67% BACC or above to be deemed clinically useful [28]. Furthermore, the models will be statistically compared using bootstrap sampling. Specifically, we will generate 5000 bootstrap samples from the test set, calculating the BACC for each model on each sample. The distributions of these bootstrap BACCs will be compared and we will conclude that there is a statistically significant difference between models if the CIs do not overlap.

Results

This study was funded by ALF medicin (20190148), Region Stockholm (SLSO 2022–1278; SLSO 2022–1276), and Region Stockholm in collaboration with Stockholm university (FoUI-939533). OF is supported by the Swedish innovation agency (No. 2022-00549). All data were collected (N=300) between April 2021 and September 2022. For a participant flow diagram throughout the study, see Figure 1.

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram showing participant flow through enrollment, allocation, follow-up, and analysis. CBT: cognitive behavioral therapy.

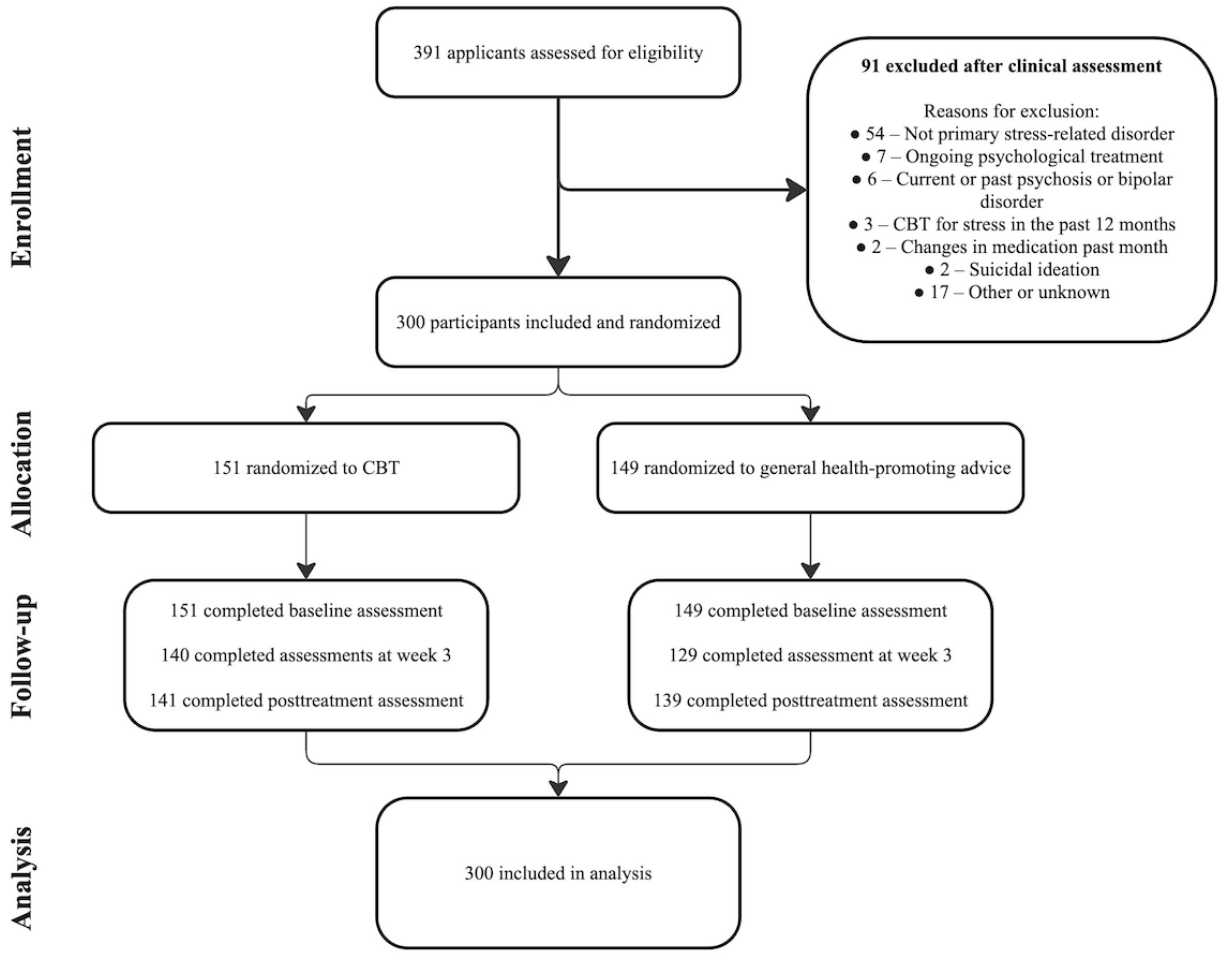

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A cross-sectional study investigating baseline cognitive functioning as compared with a healthy reference group has been published indicating small-to-moderate objective cognitive impairments [62], raising the question of whether objective cognitive function serves as a predictor of treatment response. In addition, an interim analysis of pre- and postcomparisons was presented at a conference in September 2022. These earlier analyses addressed separate research questions and did not influence the design, methods, or objectives of the current protocol. As of March 2025, data have not been analyzed for this study.

Discussion

Overview

This study will use a high-quality dataset from an RCT to investigate potential treatment predictors using both traditional prediction methods and an ML paradigm. This dual approach will enable the identification of predictors of treatment response in a patient population where prior research is limited. In addition, it will facilitate comparisons between different methodological approaches to prediction research.

Comparison to Prior Work

To the best of our knowledge, this is the first study to apply an ML approach to study predictors of treatment outcome in patients diagnosed with AD or ED. In line with previous traditional prediction research of treatment outcomes in stress-related disorders, we hypothesize that younger age, education level, symptom severity, treatment credibility, and history of sickness absence will predict treatment response [15,22]. Furthermore, we anticipate that the ML models will outperform a dummy model and achieve a BACC of 67% or higher, surpassing the benchmark indicated by Forsell and others [28]. If confirmed, our findings would support the notion that predictive models using sociodemographic, clinical, self-rated, treatment-related, and potentially cognitive variables are valuable when predicting therapy outcomes, as have been suggested in other patient populations [17,18,80]. In subsequent research, these models should be externally validated and tested in implementation trials to assess their utility as decision support tools. Such trials could evaluate whether integrating predictions into treatment planning improves outcomes and supports personalized care.

Strengths and Limitations

The study's strengths include the use of a multimodal dataset from an RCT, including objective cognitive functioning. By comparing traditional prediction methods with advanced ML models and employing techniques, such as cross-validation and hyperparameter tuning, the study has the potential to generate robust and generalizable insights into treatment outcomes, contributing to methodological advancements in prediction research.

A limitation is the modest sample size (N=300) which may increase the risk of overfitting. While smaller sample sizes have been used in previous ML studies [80-82], it is well established that limited sample sizes can hinder generalization [23]. The minimal sample size required for ML prediction in mental health research depends on the explanatory power of the predictors, with some researchers advocating for at least 300 observations [83], while others recommend a larger sample of 500 to 1500 for studies involving predictors with low explanatory power [84]. External validation is widely regarded as the gold standard to ensure model generalizability [85], but such data are not currently available for this study. However, ongoing data collection by the research group may enable external validation in the near future. In the meantime, k-fold cross-validation on the training set and validation on a separate test set will be used to estimate and mitigate overfitting, providing a basis for model evaluation within the study's constraints.

In addition, the recruitment strategy, which relied on social media, newspaper advertisements, and health care clinic referrals, may introduce selection bias and limit the generalizability of the findings. Participants recruited through these channels may not fully represent the broader population of individuals with stress-related disorders, potentially overrepresenting individuals with higher internet access, health literacy, or willingness to participate in internet-delivered interventions. These factors should be considered when interpreting the applicability of the study's results to other settings or populations.

Finally, ML models, such as RF, while effective at handling complex datasets, often prioritize predictive performance at the expense of interpretability. Unlike traditional statistical methods, their inclusion of numerous variables can make it challenging to understand the relationships between predictors and outcomes, limiting their integration into clinical practice where transparency is essential. Efforts to address this, such as using feature importance metrics, will be necessary to bridge this gap moving forward.

Implications for Clinical Practice

The study's findings could significantly impact clinical practice by contributing to the limited research on predictors of treatment outcome for stress-related disorders. Given the current lack of a gold standard treatment for AD and ED, this research is particularly timely and relevant. The investigation into ML models for treatment outcome prediction may encourage future larger-scale studies and, potentially, the implementation of these models in clinical settings as decision support tools. These could help clinicians tailor treatments by integrating complex data, such as patient demographics, symptom severity, and treatment history, to recommend evidence-based options, guiding therapy selection, and monitoring progress in real time. By operationalizing predictive insights, decision support tools could enhance clinical precision, reduce trial-and-error in treatment, and improve patient outcomes for individuals with stress-related disorders.

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Acknowledgments

The research team gratefully acknowledges the contributions of all study patients, without whom this work would not have been possible.

Data Availability

The data referenced in this study protocol are not yet available, as the study has not yet been conducted. Once the study is completed, data may be made available on reasonable request, subject to compliance with Swedish law (the Swedish Ethical Review Act: 2003:460). For such requests, please contact the corresponding author.

Conflicts of Interest

LFF was previously employed by the cognitive testing company Mindmore until 2023 and runs a small-scale clinical psychology practice. All other authors declare no other conflicts of interest or financial involvement.

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Abbreviations

AD: adjustment disorder
ADNM-8: Adjustment Disorder New Module-8

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BACC: balanced accuracy
CBT: cognitive behavioral therapy
CERAD: Consortium to Establish a Registry for Alzheimer's Disease
ED: exhaustion disorder
FAS: Verbal Fluency Test
ML: machine learning
PSS-10: Perceived Stress Scale-10
RCI: reliable change index
RCT: randomized controlled trial
RF: random forest
SVM: support vector machine
TRIPOD+AI: Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis+Artificial Intelligence

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Protocol

Feasibility, Acceptability, and Potential Effects of a Digital Oral Anticancer Agent Intervention: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Individuals taking oral anticancer agents (OAAs) often face important challenges, requiring more timely informational support, ongoing monitoring, and side effect management.

Objective: This study, guided by the Self-Efficacy Theory, aims to assess the feasibility, acceptability, and potential effects of a comprehensive, digital OAA intervention.

Methods: A 2-arm, mixed methods, pilot randomized controlled trial took place at a large university-affiliated cancer center in Montreal, Quebec, Canada. Participants (N=52) completed baseline self-report e-questionnaires and subsequently were randomly assigned to the experimental group (intervention plus usual care, n=26) or control group (usual care only, n=26). The study intervention, designed to increase medication adherence via medication adherence self-efficacy and decreased symptom distress, included (1) OAA informational videos, (2) OAA-related e-handouts and other supportive resources, (3) nurse-led follow-up calls, and (4) e-reminders to take OAAs. The e-questionnaires were completed once a week for the first month and every 2 weeks for the subsequent 4 months, or until OAA treatment was completed. A subset from both groups (n=20) participated in semistructured interviews once they completed the study requirements. Study feasibility is assessed using recruitment, retention, and response rates, as well as intervention uptake. Through e-questionnaires and exit interviews, intervention acceptability is to be assessed prospectively at baseline and retrospectively upon study completion. Potential effects are then assessed via medication adherence self-efficacy, medication adherence self-report, and symptom distress.

Results: Data collection was completed by December 2023 with a final sample size of 41. Results are expected to be published in 2025.

Conclusions: This study relies on a theoretically based, OAA digital intervention with modalities tailored to the needs and preferences of participants. The use of quantitative and qualitative methods enriches our understanding of the potential contributions of the intervention. In addition, following participants over the course of treatment captures potential changes in oral treatment–related processes and outcomes.

Trial Registration: ClinicalTrials.gov NCT04984850; https://www.clinicaltrials.gov/study/nct04984850

International Registered Report Identifier (IRRID): DERR1-10.2196/55475

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KEYWORDS

oral anticancer agent; supportive intervention; medication adherence; cancer; oncology; feasibility; acceptability; digital health; anticancer; adherence; compliance; RCT; randomized controlled trial; drug; pharmacy; pharmacology; pharmacotherapy; pharmaceutic; pharmaceutical; medication; mobile phone

Introduction

Background

It is estimated that 18.1 million new cancer diagnoses occur globally every year [1,2]. Whereas survival rates vary among cancer diagnoses and countries, mortality rates for the most prevalent cancers in high-income countries continue to decrease [2,3]. Individuals with cancer are living longer and with higher quality of life due to improvements in prevention, detection, and advancements in treatment [4]. More specifically, driven by cost-effectiveness, patient convenience, and the potential for improved patient outcomes, the use of orally administered anticancer drugs continues to grow. It is now estimated that 60% of all new cancer medications currently in development are oral, across all cancer types and stages [5].

Oral anticancer agents (OAAs), having grown in popularity in the past few years, demonstrate equivalent efficacy, safety, and outcomes as intravenous chemotherapy, while being less invasive and easier to administer [6]. As OAAs are taken at home rather than in cancer centers or hospitals, medication management resides with patients- requiring them to be active in their care [7]. For OAAs to be as effective as possible and demonstrate outcomes equivalent to those seen in clinical trials, patients must follow best practices for their treatment, resulting in added responsibilities for medication management [8]. These include attention to treatment adherence, as well as monitoring and management of side effects and adverse events, especially at OAA treatment onset when side effects and toxicity may be high [9,10]. However, the literature to date suggests that patients often report having unmet OAA-related needs, feeling helpless at home, receiving insufficient knowledge and support to manage their treatment, and having suboptimal medication adherence [10-13].

A Canadian survey conducted among individuals treated for cancer in the last 6 months (N=3300), for instance, found that only 62% of individuals on OAAs reported receiving information and guidance on potential side effects and how to manage them, compared to 74% for radiation and 76% for intravenous chemotherapy. In the same sample, only 67% of individuals on OAAs felt their care provider did everything they could to help with side effects, compared to 73% for radiation and 76% for intravenous chemotherapy [14]. Elsewhere, the lack of OAA information and monitoring for side effects were found to be significantly related to fatigue, nausea and vomiting; change of taste; and poorly managed mouth sores [15].

Medication adherence, the extent to which a person's medication-related "behavior corresponds with agreed-upon recommendations from their health care provider" [16], denotes a collaborative relationship between the health care provider and patient where the patient plays an active role in taking their prescribed treatment [17]. Medication adherence is construed as one of the primary determinants of treatment success, as unwanted alterations in dose and timing affect treatment-related outcomes [18,19]. However, medication adherence rates for OAAs vary significantly, with a systematic review across 63 studies reporting adherence rates ranging from 46% to 100% [20]. Lower OAA adherence is found to be related to decreased treatment effectiveness, increased health care utilization, and increased costs due to more physician visits, higher hospitalization rates, longer hospital stays, and in some cases, decreased survival [21-24].

As OAA development and use expands, medication adherence issues related to OAAs are increasingly of interest to multiple stakeholders, including policy makers, insurance companies, drug makers, health care providers, and researchers [25]. A systematic review of factors influencing adherence to oral anticancer drugs identified three potentially modifiable factors that interventions should address: (1) side effects and toxicities, (2) forgetfulness, and (3) the lack of timely information [26]. The American Society of Clinical Oncology and the Oncology Nursing Society jointly released evidence-based guidelines and OAA management standards. These emphasize patient education at OAA initiation and ongoing monitoring throughout treatment to enable early identification of side effects and toxicities, thus preventing complications [27,28]. Consequently, there is a need for more timely and more accessible patient support for individuals taking OAAs [28].

A comprehensive, personalized, digital OAA intervention was developed based on Bandura's [29] "Self-Efficacy Theory." One of the intervention goals is to increase medication adherence by increasing medication adherence self-efficacy (SE) and symptom distress. SE refers to individuals' beliefs in their own ability to successfully perform a specific task related to specific behavior, for instance, remembering to take medication on time to adhere to treatment, or effectively self-managing fatigue experienced from treatment [29,30]. A systematic review of the relationship between SE and medication adherence found a positive link between these two variables in 59 out of the 66 studies reviewed [31]. Behavior is influenced by the interaction between perceived SE and expectations surrounding the outcome of the behavior; thus, medication adherence is affected by a patient's belief in their capacity to consistently remember to take medication and the belief that consistently taking the medication, as prescribed, will be an effective treatment to kill cancer cells in their body. Knowledge and self-management skills of disease care can enhance SE through expectations [32]. In support of this, a standardized patient education and follow-up intervention for oral chemotherapy by Tokdemir and Kav [33] successfully increased medication adherence SE after the intervention (66.39 vs 71.04; $P<.05$). Herein, we tested a broader multimodal intervention that went beyond patient education.

Purpose of Study

The aim of this pilot randomized controlled trial (RCT) was to document the feasibility and acceptability of the experimental

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intervention. Pilot studies are critically important as a first step to address practical, logistical, and methodological issues that may arise. In addition, this pilot RCT seeks to determine whether study components can be executed and delivered to participants as planned and the intervention's potential impact on medication adherence SE, adherence, and symptom distress among participants on OAAs.

More specifically, the study's first aim was to establish feasibility, defined as "whether the intervention, study design, and procedures can be successfully executed by the researcher and delivered to the participants as planned" [34]. The constructs of feasibility herein include participant recruitment, retention, self-report questionnaire response, and uptake of the intervention. Predetermined objectives and measures of success for each are reviewed in the *Methods* section while Figure 1 provides an overview.

Figure 1. Study aims, objectives, and measures.

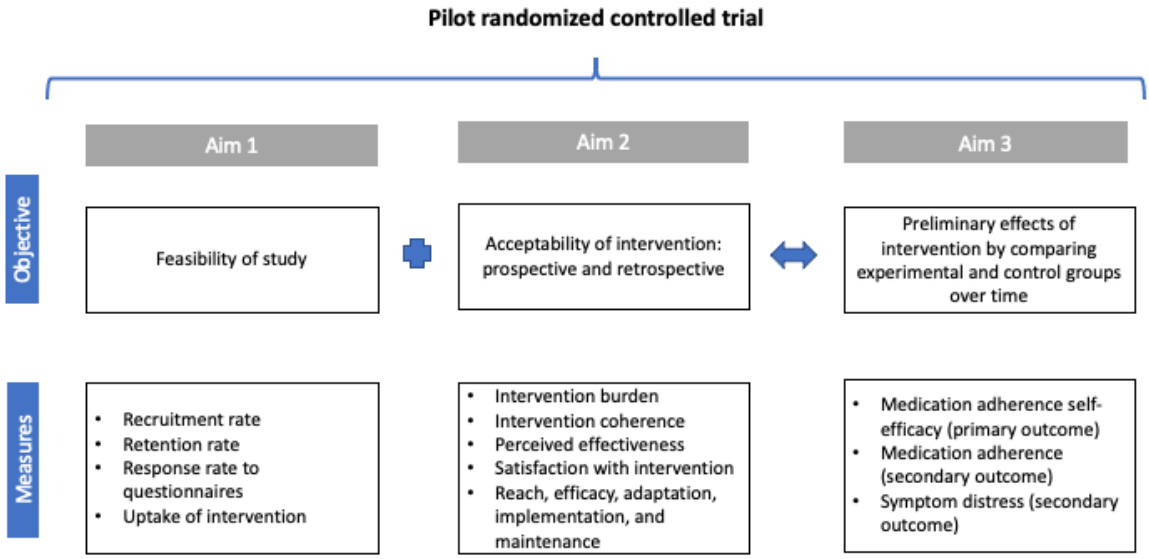

The second aim is to determine the acceptability of the intervention. The definition and measures of acceptability are based upon theoretical framework of acceptability of health care interventions by Sekhon et al [35], which defines acceptability as a multifaceted construct reflecting the appropriateness of the intervention. A key feature of this framework is the distinction between prospective, concurrent, and retrospective acceptability, emphasizing that acceptability can be assessed before, during, and after the intervention as all 3 can have an impact on participant use and access to the intervention. Although Sekhon et al [35] propose 7 concepts of intervention acceptability, only the 3 most relevant are included herein, namely intervention burden, coherence, and perceived effectiveness.

The third aim of the study focuses on documenting the potential effects of the intervention: As stated in the CONSORT (Consolidated Standards of Reporting Trials) on randomized pilot and feasibility trials [36], pilot trials may assess potential effectiveness using surrogate outcomes—substitute measures used as alternatives to clinical outcomes that may be challenging to assess directly [36]. Herein, potential intervention effects are assessed by comparing experimental and control groups over time, from baseline, every 2 weeks (depending on the outcome), and after the intervention. It is hypothesized that over time, compared to the control group, the experimental group will report higher medication adherence SE, higher medication adherence, and lower overall symptom distress.

Methods

Design

A prospective, mixed methods, 2-arm, pilot RCT is being conducted to address the study aims and hypothesis.

Setting

The study takes place at a large academic cancer center in a university-affiliated hospital in Montreal, Quebec, Canada.

Ethical Considerations

The study received approval from the Psychosocial Research Ethics Committee of CIUSSS West-Central Montreal Research Ethics Board (Project 2021-2861). Participants provided written informed consent. A randomly generated unique number (combination of numbers containing no identifiers) was generated and assigned to each participant such that all data collected were deidentified. As a token of appreciation for the time spent completing study e-questionnaires at baseline and follow-ups, participants received a CAD $10 (a currency exchange rate of CAD $1=US $0.69 is applicable) gift card at baseline as well as an additional one for each set of e-questionnaire completed. In sum, each participant could receive a maximum of CAD $120 in gift cards over the 5-month study period. If they withdrew from the study at any time, they receive a minimum of CAD $10 for the baseline e-questionnaire with an additional CAD $10 for each follow-up e-questionnaire completed.

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Sample

A sample of 52 participants (26 per arm) was to be recruited and randomly assigned, at any moment from the decision to start OAA therapy to the completion of their first oral medication cycle.

Sample Size

Sample size calculation was undertaken using procedures provided by the software program G*Power 3 [37]. As per our statistical consultant, the calculation was undertaken to determine adequate power in the determination of the potential effects of the intervention (aim 3), in which a repeated-measures ANOVA with a within-between interaction would be the statistical test used. The parameters for the power calculation included an effect size of 0.25 (standard medium effect size for ANOVA) [38], α of .01, and a power of 0.95. The sample size was further increased to account for a 30% attrition rate over the study duration, determined to be appropriate given a review of attrition rates in supportive oncology trials found a mean of 26% (95% CI 23%-28%) across 18 trials (ie, the original sample size was 36, total with added 30%, attrition is 52) [39].

Inclusion Criteria

The inclusion criteria were as follows: being 18 years or older; being seen at the study cancer center; having a diagnosis of cancer at any stage; and being about to start or within the first cycle of oral anticancer treatment (traditional cytotoxic, targeted therapy, or hormonal therapy as adjuvant treatment). Potential participants had to have access to a computer tablet or smartphone device with internet, as well as the ability to communicate, read, and write in English or French.

Exclusion Criteria

The exclusion criteria were as follows: receiving intravenous chemotherapy, immunotherapy, or oral hormonal therapy as long-term maintenance treatment for the prevention of cancer's return or growth of cancer cells after initial treatment, assisting in prolonged remission; any significant physical or cognitive limitations that would prevent the ability to fully participate in the study (as reported by the patient, primary health care provider, or research staff); and being at imminent "end-of-life," defined as a condition in rapid decline whereby active treatment is stopped and considered in the actual process of dying [40]. We also excluded patients who were already participating in an ongoing clinical trial.

OAA Experimental Intervention

All study intervention components were available remotely using a study-specific access code on Belong – Beating Cancer Together [41], a supportive digital platform with a closed community for patients, caregivers, and health care providers at the institution to create networks and connect with other patients [42]. Participants could access the platform on their smartphone or tablet and enter an access code for the study as a closed community in the platform. As opposed to a "one-size-fits-all" approach, the study intervention accords the choice to select the support received. Participants in the experimental group were provided access to all intervention components and chose which specific components to use at any time during study participation. The intervention was developed through rigorous multistakeholder consultation processes, beginning with a comprehensive review of existing OAA-related interventions and evidence by the senior author. Noting no published OAA-specific supportive interventions at the time, the senior author (CGL) secured funding from the Rossy Cancer Network to design and test an OAA intervention, including videos and e-handouts addressing potential side effects and complications related to OAA intake. After meeting with Precare, a company providing educational video resources to patients [43], the first and senior authors gathered initial intervention feedback from oncology nurses, oncologists, researchers, cancer community organizations, patient partners, and informal caregivers or family member representatives. More specifically, these stakeholders provided insights into the content, duration, and overall aspects of the videos and e-handouts, contributing to the refinement of the intervention format and delivery. The final version was thoroughly reviewed by the first and senior author and subsequently integrated into an app [41]. The multimodal OOA intervention components are mentioned in Textbox 1 and Figures 2-4 below.

Textbox 1. Multimodal oral anticancer agent intervention components.

1. Oral anticancer agent informational videos
   - Topics: General information, side effects, support, fertility and work, and symptoms
2. Symptom management tip sheets and additional web-based resources
   - Topics: Pain, fatigue, drowsiness, nausea and vomiting, lack of appetite, shortness of breath, depression, anxiety, well-being, insomnia, fear of cancer recurrence, and work
3. Call with a nurse navigator.
   - Support and dispatch
4. Medication reminders
   - Reminder notification pop-ups
5. Any combination of services above

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Figure 2. The multimodal OAA intervention contained OAA informational videos on general information (seen here), side effects, support, fertility and work, and symptoms. OAA: oral anticancer agent.

Figure 3. The multimodal OAA intervention contained symptom management tip sheets and additional web-based resources on pain, fatigue (seen here), drowsiness, nausea and vomiting, lack of appetite, shortness of breath, depression, anxiety, well-being, insomnia, fear of cancer recurrence, and work. OAA: oral anticancer agent.

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Figure 4. The multimodal OAA intervention contained medication reminders as reminder notification pop-ups. OAA: oral anticancer agent.

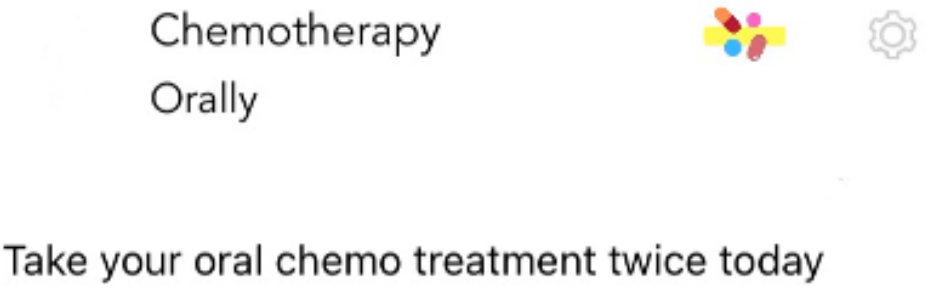

OAA Informational Video

In the context of this study, an evidence-based animated video was developed (Figure 2). The content of the video has been reviewed by multiple stakeholders, including health care providers, patients, and caregivers. The video is available to be watched in English or French, with subtitles available in 16 languages. The video contains 4 parts: general information on oral chemotherapy, side effects, support, fertility and work, and symptoms.

Symptom Management Tip Sheets and Additional Web-Based Resources Common Physical and Psychosocial Concerns of Oral Anticancer Therapy

These e-handouts provide knowledge, facts, tips, and additional or telephone resources (Figure 3). The content has been reviewed by multiple stakeholders, including health care providers, patients, and caregivers. The e-handouts are available in French and English on the following 12 topics: pain, fatigue, drowsiness, nausea, lack of appetite, shortness of breath, depression, anxiety, sleep, fear of cancer recurrence, and work. The e-handouts are available for download in PDF format.

Follow-up Calls From Oncology Nurse

Participants in the experimental group can receive a call from the oncology nurse specific to their tumor site. A participant may request a phone call at each follow-up e-questionnaire by selecting “I would like to receive a phone call from a nurse” and identifying the topic they would like to discuss. The study coordinator forwards the participant’s name and contact number to the nurse. The participant’s symptom scores from the e-questionnaire are shared with their nurse at this time. The nurse calls the participants and speaks to them on the topic of their choice, and the interaction is documented in the patient chart as a virtual encounter.

Medication Reminders

Participants can receive daily e-reminder notifications on their smartphones to take their OAA medication (Figure 4). The e-reminders use preconfigured templates tailored to a 21-day cycle (14 days on per 7 days off) or a 28-day cycle (21 days on and 7 days off) that users must select, with options for once or twice daily reminders. Upon the conclusion of each cycle, users receive a notification prompting them to refill their prescription and reload the 21-day or 28-day cycle template.

In sum, the study intervention was designed to increase SE for OAA adherence through direct mastery experiences (self-management and reminders), vicarious experiences (video), verbal persuasion (phone calls), and feedback (self-management and reminders).

Participants in the control group continued to receive care as usual. This includes follow-up care with their oncologist, contact with their pharmacist and nurse as needed, as well as access to any internal and external supportive services from other health care professionals (eg, psychosocial oncology, social services, physiotherapist, occupational therapist, etc).

Recruitment, Consent, and Randomization

Participant recruitment occurred at the cancer center in two ways. First, a member of the oncology clinical care team (oncologist, radiation oncologist, nurse, or administrative staff) briefly explained the study and asked patients if they were interested in hearing more about the study. If yes, a member of the study team was informed (in-person, email, or telephone) and contacted the patient. Second, a study poster placed at relevant locations within the cancer center contained the contact information (QR code, email, and telephone number) of the study team. The patients then contacted the team directly.

Interested individuals met with a member of the research team in person or communicated over email or telephone. Study details were provided, and eligibility was verified. If still interested and eligible, a secure link to an electronic consent form was emailed, followed immediately by the baseline questionnaire. Participants were randomly assigned to intervention plus usual care (experimental group, n=26) or usual care only (control group, n=26). Once initial consent was given, those in the experimental group reconsented. Participants in the control group were blinded to group assignment (Article 3.7A of Tri-Council Policy Statement 2) [44]. The randomization sequence was determined on R (R Core Team), a software program, using the randomized R package for clinical trials [45]. Diagram of study design, measurement points, and timeline is shown in Figure 5.

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Figure 5. Diagram of study design, measurement points, and timeline.

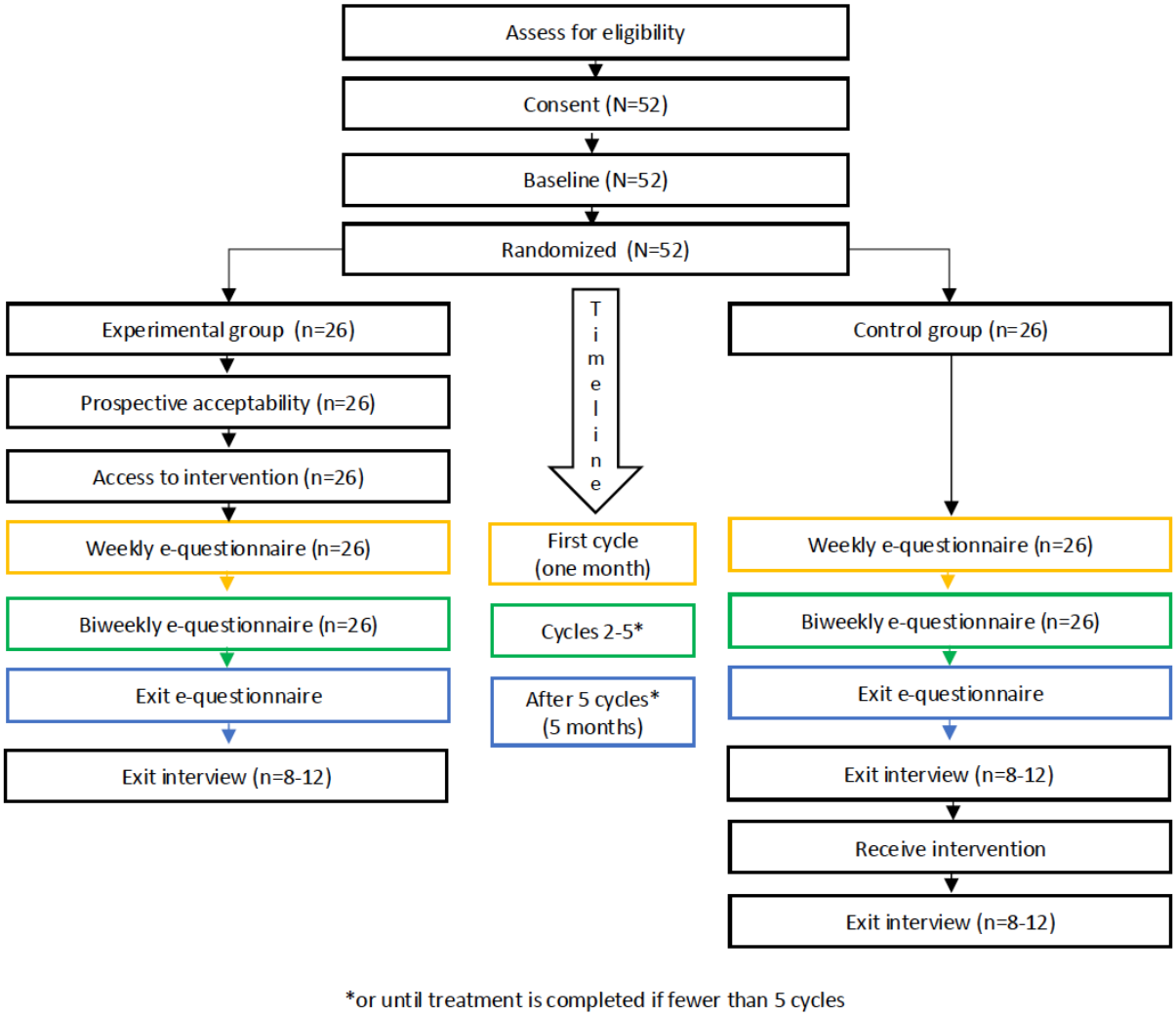

Data Collection

In both groups, follow-up e-questionnaires were completed every week for the first month and 2 weeks for the following 4 months, or until treatment was completed (if less than 5 months). Given the considerable variability in the duration of time patients may remain on OAAs, the study duration of 5 months was established as a long enough period in consultation with medical oncologists and pharmacists and was deemed appropriate for assessing the primary outcomes of feasibility and acceptability. Participants were monitored more closely during the first treatment cycle, as this period is critical for identifying potential toxicities and making necessary dosage adjustments. Furthermore, it is crucial to establish positive medication adherence behaviors early in the treatment process [46]. After 5 months or until OAA treatment was completed (if less than 5 months), participants completed the exit questionnaire, and a subset of participants in the experimental group (n=10) and control group (n=10) who had completed the study were invited to participate in a semistructured interview.

All e-questionnaires were completed on Qualtrics, a secure web-based electronic data capture system licensed through McGill University [47]. A data management plan between the university and the affiliated hospital was established for the study (Multimedia Appendix 1). Details of each measure and timepoint are provided in Table 1.

Baseline questionnaires completed by all participants included sociodemographic and medical characteristics, cancer information-seeking preferences, and OAA knowledge.

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Table 1. Study data collection.

Objective and measure	Instrument	Items, n	Time of collection				
			Baseline	Weekly for the first cycle	Every 2 weeks for cycles 2-5	Final questionnaire	Study completion
Baseline information							
Sociodemographics	__[a]	12	✓	—	—	—	—
Medical characteristics	—	7	✓	—	—	—	—
Oral anticancer agent knowledge	—	9	✓	—	—	✓	—
Cancer information-seeking preferences	Cancer information-seeking profiles	1	✓	—	—	✓	—
Feasibility of study							
Recruitment rate	—	—	—	—	—	—	✓
Retention rate	—	—	—	—	—	—	✓
Response to questionnaire	—	—	—	—	—	—	✓
Intervention uptake	—	—	—	—	—	—	✓
Prospective acceptability of intervention							
Intervention burden perceived effectiveness	Acceptability E-scale for web-based patient-reported outcomes in cancer care	3	✓	—	—	—	—
Retrospective acceptability of intervention							
Intervention burden, perceived effectiveness, and intervention coherence	Acceptability E-scale for web-based patient-reported outcomes in cancer care	5	—	—	—	✓	—
Exit interview	—	—	—	—	—	—	✓
Preliminary effects of the intervention							
Medication adherence	Proportion of days covered	Chart review	—	—	—	—	✓
Medication adherence	Medication Adherence Rating Scale (Professor Rob Horne)	5	—	✓	✓	—	—
Medication adherence self-efficacy	Medication Adherence Self-Efficacy Scale	20	✓	✓	✓	—	—
Symptom distress	Edmonton Assessment Scale revised	12	✓	✓	✓	—	—

[a]Not applicable.

Measures

Sociodemographics and Medical Characteristics

At baseline, participants completed a sociodemographic questionnaire identifying their sex, gender, age, marital status, work status, country of birth, languages spoken, education, and income. They were also asked to complete a medical questionnaire identifying their current diagnosis, cancer stage, coverage of their OAA medication, other medications they are taking on a regular basis, and treatment or treatments received.

Cancer Information-Seeking Preferences Scale

This brief, self-report questionnaire based on Self-Evaluation Theory [48] contains 5 statements related to distinct preferences for cancer information. Respondents select the one that best describes how they go about getting information about their cancer: (1) intense—"I seek as much information as possible about my cancer," (2) complementary—"I seek information about my cancer that adds to what I was told," (3) peer-focused—"I seek cancer information from others diagnosed with same cancer," (4) minimal—"I do not seek information about my cancer," and (5) guarded—"Cancer is stressful enough; I only seek information about my cancer that is hopeful."

In a large sample (N=2142), participants treated for cancer within the past 6 months responded to the Cancer Information-Seeking Preferences (CISP) scale and patient satisfaction survey (Ambulatory Oncology Patient Satisfaction Survey). A total of 50.2% (1076/2142) selected complementary, 25.2% (539/2142) selected minimal, 14.4% (309/2142) selected guarded, 6.4% (137/2142) selected peer-focused, and 3.8%

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(81/2142) selected intense, with intense seekers reporting lower satisfaction with cancer care [48,49]. The CISP provides context to the participants' preferences and uptake of the intervention.

Knowledge

The 7-item oral chemotherapy knowledge questionnaire was developed by SA and CGL for the purpose of this study. The scale contains 7 true or false items pertaining to OAA knowledge and self-management (eg, "If I forget to take my oral chemo, I should not double the next dose").

The study feasibility (aim 1) will be determined by the recruitment rate, retention rate, response rate to e-questionnaires, and uptake of the intervention (Textbox 2).

To assess the acceptability of the intervention (aim 2), intervention burden, intervention coherence, and perceived effectiveness were assessed prospectively at baseline and retrospectively at exit [35] by participants in the experimental group. They were asked to complete the Acceptability E-scale for web-based, patient-reported outcomes in cancer care by Tariman et al [56], requiring a mean score of 80% or higher as the objective. It evaluates the acceptability and usability of computerized health-related programs in oncology. The scale has a reliability of 0.757. It contains 6 items that are rated from 1 (very difficult) to 5 (easy to understand), with total scores ranging from 6 to 30. Table 2 presents constructs and definitions of acceptability as well as baseline and exit questions. In addition, postintervention acceptability was assessed in exit interviews with a subsample of participants (n=20, 10 per group) using an author-generated semistructured interview guide developed based on relevant questions using questions based on the RE-AIM (Reach, Efficacy, Adoption, Implementation, and Maintenance) framework by Glasgow et al [57] to evaluate health behavior interventions (Multimedia Appendix 2). Questions explored participants' perceptions of OAA information and support, such as "What are your general impressions of the information and support you received during your OAA treatment?" Participant selection for interviews was convenient. Participants were approached in person or over the telephone, and interviews took place in person or over the telephone by the first author, lasting between 30-60 minutes. Only the researchers and participants were present for the interview. After the total number of subsample participants (n=20) had been interviewed, the first author analyzed the interviews to ensure data saturation had been reached. No additional interviews were required.

The potential effects of the intervention (aim 3) will be assessed by comparing experimental and control groups over time, from baseline, every 2 weeks (depending on the outcome), and after the intervention in terms of the following outcomes: medication adherence SE, medication adherence (self-report and pharmacy records), and symptom distress.

Textbox 2. Study feasibility objectives.

Recruitment rate

- Calculated by dividing the total number of participants recruited throughout the study by the number of months recruitment occurred.
- Objective: Based on clinical estimates of eligible individuals, approximately 3 to 4 participants were recruited each month.

Retention rate

- Calculated by comparing the number of participants who complete baseline e-questionnaires to the number of participants who complete study exit e-questionnaires.
- Objective: Of participants who begin the study, ≥45% complete the study, and reasons for dropout are documented if participants wish to share [39,50].

Response rate to study e-questionnaires

- Determined by the number of completed follow-up e-questionnaire assessments for participants who complete the study.
- Objective: Of participants who complete the study, ≥70% complete outcome measures across all time points. This is slightly higher than the 60% minimum required by biomedical journals [51], typical for web-based questionnaires and patient acceptability and satisfaction research [52,53].

Uptake of intervention

- Nature of intervention access (modality, topics, and time points). Uptake of the intervention will be assessed by the number of participants who access the platform, and the number of times each modality was accessed throughout the study duration.
- Objective: Of participants in the experimental group, ≥85% will access at least one intervention modality [54,55].

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Table 2. Constructs and definitions of acceptability [35] as well as questions asked at baseline and exit [56].

Construct of acceptability	Definition	Question at baseline	Question at exit
Intervention burden	Perceived amount of effort required to participate in the intervention	• Do you anticipate the amount of time you will spend reading and watching video or videos in this study will be acceptable?	• Was the amount of time you spent reading the information on the e-handouts acceptable? • Was the amount of time you spent watching the video or videos acceptable? • How easy was it for you to access and use the information and support offered in the study? (overall)
Intervention coherence	Extent to which participant understands the intervention and how it works	__[a]	• How understandable was the information in the e-handouts? • How understandable was the information in the videos?
Perceived effectiveness	Extent to which the participants perceive the intervention as likely to achieve its purpose	• How helpful do you anticipate the information and support offered in this study will be in helping you manage your treatment? (treatment management) • How helpful do you anticipate the information and support offered in this study will be in reminding you to take your medication? (reminders)	• How helpful was the information and support offered in this study in helping you manage your treatment? (treatment management) • How helpful was the information and support offered in this study in reminding you to take your medication? (reminders)

[a]Not applicable.

Medication Adherence Self-Efficacy

The Medication Adherence Self-Efficacy Scale (MASES) [58] asks about participants' level of confidence in taking their medication. The original scale contains 25 items, each rated from 1 (not at all sure) to 3 (extremely sure), with a total score calculated by summing the responses. Initially developed within the context of antihypertensive medication, the scale has been modified and adapted into 24-items for oncology oral agents [33]. For this study, 4 items were removed, and 20 items were used. The 4 items removed were not deemed suitable for the study as they pertain to taking the medication for the rest of their life, coming home late from work, being in a public area, and being afraid of becoming dependent on the medication.

Medication Adherence via Proportion of Days Covered

Participants were asked to provide the name and telephone number of their pharmacy, as well as consent for the research team to contact the pharmacy for records to calculate the proportion of days covered (PDC), in order to obtain the average adherence of each participant over 5 cycles of OAAs. PDC is defined as the "sum of the days" supply for all fills of a given drug in a particular time period, divided by the number of days in the time period" [59]. PDC is preferred over the medication possession ratio as the medication possession ratio can overestimate adherence for patients who refill their prescriptions early [59]. PDC will be assessed as the mean PDC for each group.

Medication Adherence via the Medication Adherence Report Scale

The Medication Adherence Report Scale (MARS-5; Professor Rob Horne) [60] is a validated measure of medication adherence, with a Cronbach α of 0.67 [60,61]. It is the shorter version of the MARS-10. MARS-5 contains 5 items, each rated from 1 (always) to 5 (never). Total scores range from 5 to 25. In addition, participants are asked specifics about their OAA regimen such as timing, dose delays, interruptions, and stoppages [62].

Symptom Distress

Physical and psychosocial distress is measured using the Edmonton Symptom Assessment Scale Revised (ESAS-r). The current version, ESAS-r, has been revised to include psychosocial needs; depression, anxiety, and well-being [63,64]. Each item is rated from 0 (none) to 10 (worst possible). The scale has been tested in cancer populations (Cronbach α= 0.71).

Data Analysis

Statistical analyses to be performed rely on Microsoft Excel, SPSS (version 25; IBM Corp) [65], and R (R Project for Statistical Computing) software [66]. For PDC, independent sample 1-tailed *t* tests will be performed to calculate the difference between 2 independent means of the experimental and control groups at one time point—study completion. Changes over time in MARS-5, MASES, and ESAS-r will be assessed using repeated-measures ANOVA. Between-group analyses will be conducted to examine how each group changed over time, and within-group analyses will be conducted to examine how participants changed over time.

The relationship between objective (PDC) and subjective (MARS-5) measures of medication adherence will be assessed using Spearman correlation coefficients. Oral chemotherapy knowledge at baseline and study exit will be compared using paired sample 1-tailed *t* tests.

Interviews were conducted individually, audio recorded, and transcribed verbatim by the first author, a doctoral candidate at

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the time with experience in qualitative research in oncology working on her dissertation. A reflexive journal was kept to document thoughts and feelings to recognize, acknowledge, and mitigate the influence of her role as a researcher and as someone with lived experience as an informal caretaker for a parent. Interview data were analyzed by the same author using thematic analysis as described by Braun and Clarke [67,68], beginning with several thorough readings of participant verbatim content to familiarize the researcher with the data and the identification of significant statements relating to the phenomenon under investigation [69]. Next, significant statements were placed into initial categories and organized into broader themes and subthemes. Themes and subthemes were reviewed, redefined, renamed, and explored as needed until no new themes emerged from the data.

Results

Data collection was completed as of December 2023 with a final sample of 41 (experimental group, n=23; control group, n=18), considering 11 dropouts after consent. Results are expected to be published in 2025 in a separate manuscript. Figure 6 presents the CONSORT flow chart for the study.

Figure 6. CONSORT (Consolidated Standards of Reporting Trials) flow diagram for the study. IV: intravenous.

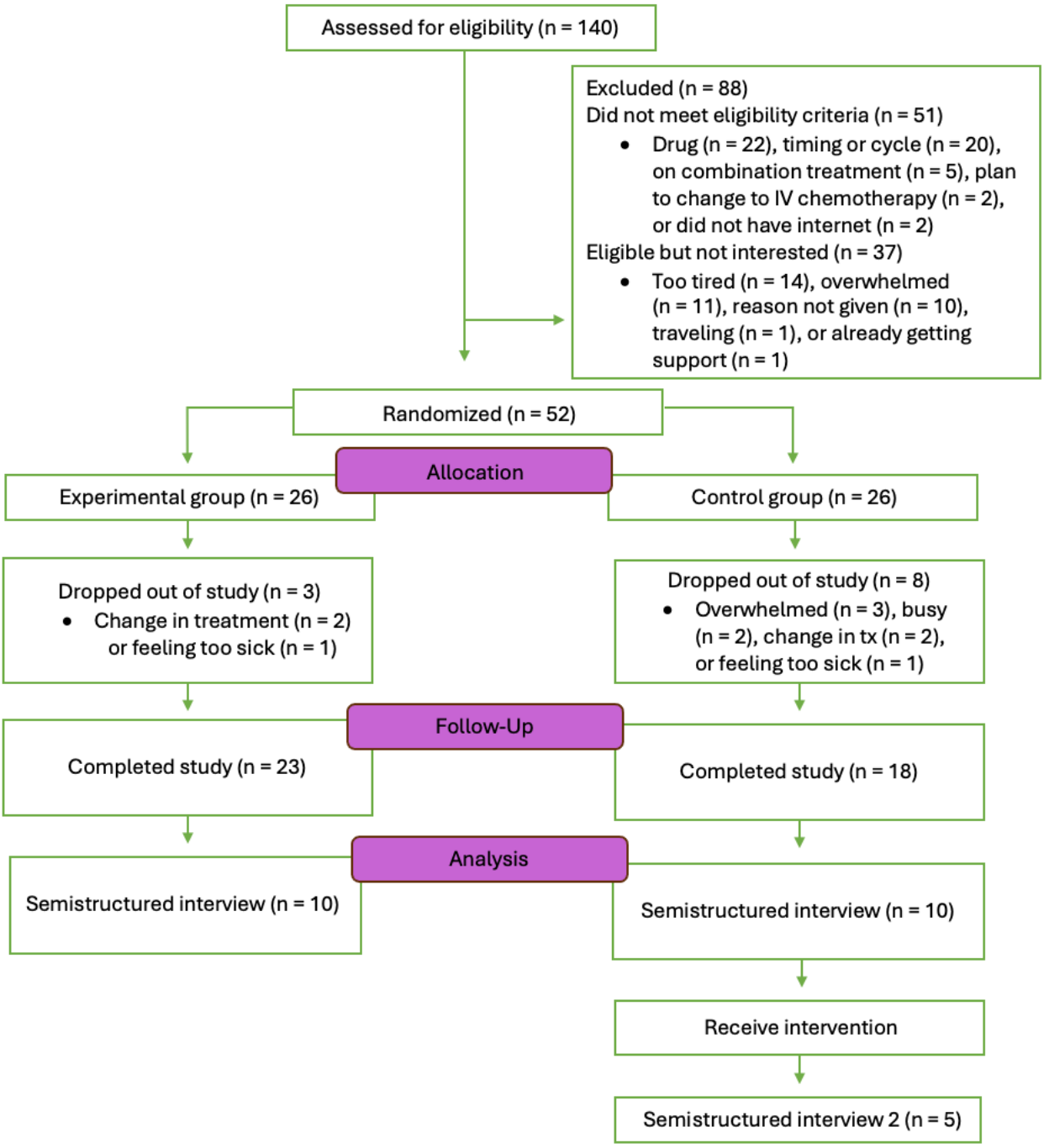

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Discussion

Principal Findings

Individuals taking OAAs face many challenges, ultimately impacting medication adherence. While studies have begun to test supportive interventions, there remains a lack of theory-based interventions supported by controlled studies that follow explicit reporting guidelines [70]. This pilot RCT sought to inform the study and intervention feasibility and acceptability from the perspective of patients. Given preliminary insights, it is anticipated that feasibility and acceptability objectives will be achieved. As such, the processes of the study and intervention testing will be successful, and the OAA intervention will be well received by participants. Exit interviews further explore OAA-related experiences and distinct narratives of the intervention, which quantitative measures do not capture. Study results will provide preliminary evidence to assess trends using the potential effects of the comprehensive, theory-based intervention when compared to usual care. The use of qualitative interviews will add further insight to study findings, providing context for the significance or nonsignificance of primary and secondary outcomes. As OAA use continues to grow in upcoming years, the study design and reporting of theory-based intervention will contribute much-needed insights toward how patients on these drugs can best be supported.

Of note, the testing of a remote multimodal intervention was particularly timely amid the COVID-19 pandemic, as oncology teams increasingly performed remote consultations, and patients who are immunocompromised were at higher risk for virus-related complications. Social distancing, isolation, and quarantine all further limited the support and resources available to them.

Conclusion

As remote consultations are still used for patients who are immunocompromised in the current period, the proposed intervention is still very relevant. Whether the COVID-19 pandemic may have acted as a confounding factor in this study remains unclear. In addition, since the study took place in a single setting, the next steps should include a multisite investigation to determine whether it is scalable and relevant across settings and geographical regions. The study sample is small, with 41 participants completing the study included in the final analysis for preliminary effects. Whereas the final sample is smaller than anticipated (41 vs 52), reliance on mixed methods provides complementary evidence. Dissemination activities related to the study results and its tested intervention include presentations at tumor boards, scientific publications, conference presentations, and diffusion through professional networks and webinars, as well as patient representative groups.

Acknowledgments

We are most grateful to all patients who participated in this study. We thank the oncologists, nurses, and clinical administrators who assisted in participant recruitment. We are indebted to patient partners, caregivers, and oncology team members who provided valuable feedback on the intervention. We thank Precare for making the educational videos and Belong for its assistance in making the oral anticancer agent intervention available on their app.

We would like to thank the Rossy Cancer Network for providing partial funding for this study (Cancer Care Quality and Innovation Program Research Fund—grant title: “Implementation and testing of a sustainable support program as a complement to an ongoing RCN patient-reported outcome initiative”). CGL’s work is supported by the Christine and Herschel Victor/Hope and Cope Research Chair in Psychosocial Oncology at McGill University. SA’s doctoral work was partially supported by the Maysie MacSporran Graduate Studentship and a studentship from Belong.

Data Availability

The datasets generated during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

SA and CGL are responsible for study and intervention design, operationalization, randomized controlled trial implementation, data analysis, and write-up of the manuscript. CGL wrote the initial study protocol, obtained funding, and supervised the first author during her doctoral studies. CM, WG, and GB provided ongoing feedback on the study protocol and study implementation.

Conflicts of Interest

WG sits on the board of the company that provided the digital patient education but does not receive any monetary benefits.

Multimedia Appendix 1
Study data management plan.
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Multimedia Appendix 2
Semistructured interview guide.

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[DOCX File , 16 KB - resprot_v14i1e55475_app2.docx]

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Abbreviations

CISP: Cancer Information-Seeking Preferences
CONSORT: Consolidated Standards of Reporting Trials
ESAS-r: Edmonton Symptom Assessment Scale revised
MARS: Medication Adherence Report Scale
MASES: Medication Adherence Self-Efficacy Scale

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OAA: oral anticancer agent
PDC: proportion of days covered
RE-AIM: Reach, Efficacy, Adoption, Implementation, and Maintenance
RCT: randomized controlled trial
SE: self-efficacy

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Protocol

Treatment of Substance Use Disorders With a Mobile Phone App Within Rural Collaborative Care Management (Senyo Health): Protocol for a Mixed Methods Randomized Controlled Trial

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Abstract

Background: COVID-19 worsened an already existing problem in substance use disorder (SUD) treatment. However, it helped transform the use of telehealth, which particularly benefits rural America. The lack of specialty addiction treatment in rural areas places the onus on primary care providers. Screening, brief intervention, and referral to treatment (SBIRT) is an evidenced-based strategy commonly used in primary care settings to target SUD outcomes and related behaviors. The integration of telehealth tools within the SBIRT pathway may better sustain the program in primary care. Building on Mayo Clinic's experience with collaborative care management (CoCM) for mental health treatment, we built a digitally native, integrated, behavioral health CoCM platform using a novel mobile app and web-based provider platform called Senyo Health.

Objective: This protocol describes a novel use of the SBIRT pathway using Senyo Health to complement existing CoCM integration within primary care to deliver SUD treatment to rural patients lacking other access. We hypothesize that this approach will improve SUD-related outcomes within rural primary care clinics.

Methods: Senyo Health is a digital tool to facilitate the use of SBIRT in primary care. It contains a web-based platform for clinician and staff use and a patient-facing mobile phone app. The app includes 16 learning modules along with data collection tools and a chat function for communicating directly with a licensed drug counselor. Beta-testing is currently underway to examine opportunities to improve Senyo Health prior to the start of the trial. We describe the development of Senyo Health and its therapeutic content and data collection instruments. We also describe our evaluation strategy including our measurement plan to assess implementation through a process guided by Consolidated Framework for Implementation Research methods and effectiveness through a waitlist control trial. A randomized controlled trial will occur where 30 participants are randomly assigned to immediately start the Senyo intervention compared to a waitlist control group of 30 participants who will start the active intervention after a 12-week delay.

Results: The Senyo Health app was launched in May 2023, and the most recent update was in August 2024. Our funding period began in September 2023 and will conclude in July 2027. This protocol defines a novel implementation strategy for leveraging a digitally native, clinical platform that enables the delivery of CoCM to target an SUD-specific patient population. Our trial will begin in June 2025.

Conclusions: We present a theory of change and study design to assess the impact of a novel and patient-centered mobile app to support the SBIRT approach to SUD in primary care settings.

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International Registered Report Identifier (IRRID): PRR1-10.2196/65693

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KEYWORDS

substance-related disorders; mobile apps; primary care; clinical trial; substance use disorder; SUD; addiction treatment; telemedicine; telepsychiatry; care management; community-based care; behavioral health program

Introduction

Limited access to substance use disorder (SUD) treatment was a problem long before COVID-19. Approximately 22 million American people needed SUD treatment in 2019, but only 13% received any intervention [1]. The COVID-19 pandemic coincided with an increase in SUD prevalence, as treatment programs were restricted or closed [2]. The National Institutes of Health described the compounding effects of the concurrent opioid epidemic and COVID-19 pandemic as a national emergency [3]. In response, the White House Office of National Drug Control Policy recommended increased funding for telehealth services and mobile phone apps.

Telehealth use has increased dramatically since the COVID-19 pandemic onset [4]. While numerous patients may benefit from its flexibility, rural patients and stigmatized populations, such as individuals with addiction, may be particularly aided [5]. Before COVID-19, rural patients already had fewer health care providers and mental health service offerings [6]. The pandemic was associated with an increased incidence of SUD in rural areas, where isolation, stress, and boredom exacerbate risks to psychological health [7]. The shortage of SUD providers impairs individuals from receiving specialty treatment and places increased pressure on primary care providers [8]. The incorporation of telehealth helps bridge this gap. We recently published a review showing that the synchronous delivery of care through video visits for SUD treatment has robust safety and efficacy evidence [2].

Screening, brief intervention, and referral to treatment (SBIRT) is the most common strategy to address problematic substance use in primary care. However, there have been significant barriers to translating it into treatment. Data combined from the 2015 to 2019 National Survey on Drug Use and Health found that only 69.9% of adults with alcohol use disorder were screened for alcohol use, with this leading to approximately 5% to 6% of adults who might benefit from treatment being referred to and eventually receiving treatment [9]. Known barriers to SBIRT use are limited clinician time, competing clinical priorities, providers' belief that the intervention will be ineffective, lack of training and experience with delivering the intervention, and the need for integration with the addiction care delivery model [10]. These factors can be addressed with adequate preimplementation support and training [11].

Collaborative care management (CoCM) is a system-based approach that integrates behavioral health care managers into primary care clinics with the support of psychiatrists to assist primary care providers in managing mental health disorders. This improves treatment access and outcomes while decreasing the need for independent psychiatric services [12]. Current evidence supports case management services delivered by various backgrounds (nursing, welfare or social workers, and mental health therapists) to strengthen service connections [13,14]. CoCM has demonstrated effectiveness in improving SUD treatment access, increasing resource efficiency, and reducing substance use [15-17]. However, addressing SUDs within CoCM poses several challenges, including organizational process and infrastructure capacity development for CoCM implementation, training behavioral health care managers, accessing specialty addiction consultation, a national shortage of SUD providers, and overcoming staff stigma [18]. CoCM also relies on symptom monitoring tools [12], and when used within addiction treatment, these must comply with federal and state confidentiality and consent regulations.

Digital CoCM adapts the traditional CoCM framework to a digital format, leveraging telemedicine platforms to overcome geographical and logistical barriers to care. Unlike traditional CoCM, which relies on in-person care teams embedded in clinics, digital CoCM uses digital tools to facilitate integration and communication between primary care providers, care managers, and consulting psychiatrists. Digital platforms allow for the integration of structured workflows, enabling asynchronous communication between providers and giving real-time updates on patient progress. This approach enhances flexibility while maintaining the core components of CoCM: care coordination, systematic case review, measurement-based care, and patient-centered outcomes [19].

Compared to stand-alone telehealth services or other SUD-focused apps, digital CoCM emphasizes integration across the care team rather than focusing solely on the patient-provider dyad. While telehealth visits allow for synchronous patient-provider interactions, they may lack systematic tracking of patient progress, team-based coordination, or integration of psychiatric consultation. SUD-focused apps typically provide self-management tools, such as cognitive behavioral therapy (CBT) modules or contingency management (CM), but they often operate outside the clinical care team and do not facilitate collaborative decision-making between primary care providers and care managers [20]. Digital CoCM bridges this gap by embedding app-based tools within a team-based care model, ensuring that technology supports both patient engagement and provider collaboration. Digitally delivered interventions can positively augment the patient-provider experience by incorporating new ways to interact [21,22], enabling the easy monitoring of clinically relevant measures of substance use and mental health symptoms, and supporting evidence-based practices. However, to our knowledge, no digital telemedicine platform has been tested to facilitate integrated SUD CoCM

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within primary care. This study aims to evaluate the implementation and clinical effectiveness of Senyo Health, a digitally native, addiction treatment and CoCM platform designed to address barriers to SUD treatment in rural primary care settings. Specifically, we aim to identify facilitators and barriers to implementation; improve the integration of SUD treatment into primary care workflows; and assess the platform's impact on substance use outcomes, treatment retention, and recovery trajectory. We hypothesize that this intervention will reduce the frequency and intensity of substance use, promote addiction recovery, and be well received by primary care staff. This protocol details the iterative design, development, pilot-testing, and randomized controlled trial study stages.

Methods

Study Design

This is a mixed methods study. The first stage is focused on implementing SBIRT into primary care and identifying barriers. During this stage, we will use Consolidated Framework for Implementation Research (CFIR) [23]. The CFIR's core domains include intervention characteristics, which focus on the attributes of the intervention itself, such as its complexity and adaptability. The outer and inner settings examine the external and internal contexts, including factors like patient needs, organizational culture, and readiness for implementation. Finally, the characteristics of individuals and the process domains address the roles of individuals involved and the steps taken to implement the intervention, such as planning and engaging stakeholders. The second stage is a waitlist randomized controlled trial studying the effectiveness of the Senyo Health platform in decreasing substance use over a 12-week period (Figure 1). The intervention will have 4 core components that will be iteratively improved based on stakeholder feedback. First, each patient will receive digitally native CoCM for SUD with weekly web-based check-ins with licensed alcohol and drug counselors (LADCs), who will be the main point of contact for patients enrolled in the study. Consistent with CoCM, standardized symptom monitoring and monthly reviews of all clinical cases will occur with the LADC and the overseeing psychiatrist. Second, the patient will be offered, initiated, or continued on medications to manage psychiatric and addiction diagnoses and symptoms. Third, the patients will use a digital clinical platform to complete a set of CBT and behavioral activation–based psychotherapeutic modules. Fourth, patients will use a digital CM platform through an app on their phones.

Figure 1. Study flow diagram. The study is an exploratory, sequential, mixed methods design. The initial study phase is qualitative (left, pink square) with a focus on interviewing clinical stakeholders (physicians, nursing, and medical support staff), training on SBIRT, and reassessing their understanding and experience to iteratively improve the process. The second study phase is quantitative (right, yellow rectangle) with outcomes noted. The first 10 patients will be recruited from ongoing CoCM for mental health services after screening positive on validated alcohol and drug use measures. We then will recruit an additional 60 patients, who will participate in a randomized controlled trial of a 12-week intervention with Senyo Health (active phase) or to a 12-week waitlist control group who will subsequently receive the active intervention. These results and feedback will be used to iteratively improve the intervention after study completion. CoCM: collaborative care management; SBIRT: screening, brief intervention, and referral to treatment.

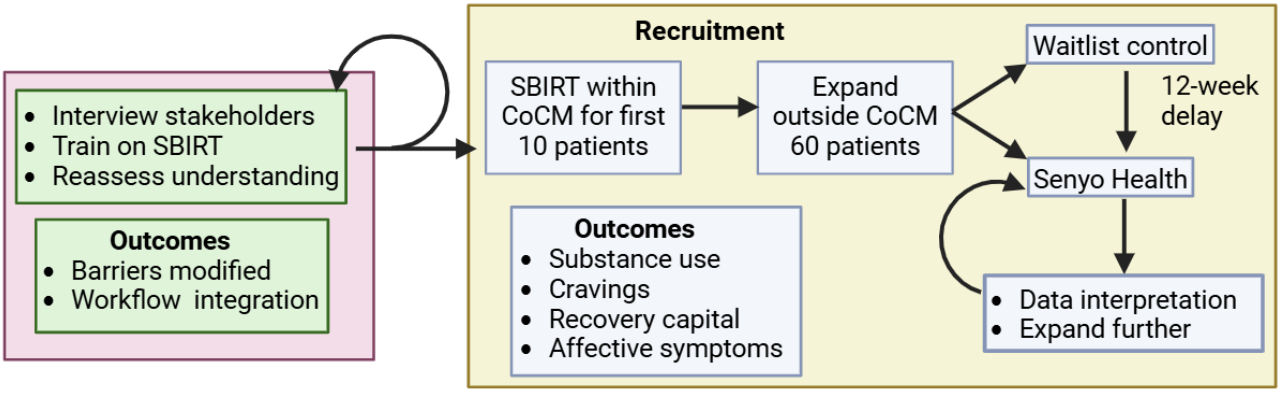

Ethical Considerations

This study was reviewed and approved by the Mayo Clinic Institutional Review Board (IRB) for human research (#24-007758) in accordance with institutional policies and federal regulations governing human participant research. The IRB determined that this study requires full board review, and no exemption or waiver was granted. Informed consent will be obtained directly from all participants prior to study enrollment, and participants will have the ability to opt out at any time without consequence. This study does not involve secondary data analysis requiring additional consent considerations. No identifiable patient information will be reported, ensuring participant confidentiality and data security. Data collected by the app system are securely transferred using industry-standard encryption to the "Backend Services" (ie, Mayo Clinic servers behind Health Insurance Portability and Accountability Act [HIPAA]–compliant firewall). This cloud-based infrastructure serves and communicates with the patient-facing app. The Backend Services contain all data and analytics specific to the app clients (participants, researchers, and providers). No protected health information is contained in the app itself. All data used by the app follow internationally recognized security standards, including the National Institute of Standards and Technology SP800-53 and HIPAA. All patient information is automatically encrypted when entered in the system, allowing for secure data transfer from the participant device to the provider interface and storage. The treatment phase of this project uses the CM method. Participants earn points for completing treatment tools within the Senyo app. They turn in those points for rewards of specified dollar amounts. These dollar amounts are loaded on a reloadable cash card (ClinCard).

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The app will notify study staff of the dollar amount, which will be loaded onto the card and documented in the research participant remuneration application system. The amount of points a participant can earn is approximately 1400 (converts to US $350), but this amount will vary depending on participation and points received. In the follow-up and waitlist phase, participants will receive US $25 for each visit where they complete interviews and questionnaires. Those assigned to the waitlist phase will have an additional 12 weeks of participation than those assigned to the intervention phase. Remuneration will not be provided during time on the waitlist.

Senyo Health Intervention

Overview

Senyo Health has several core features that enable it to deliver digital CoCM for SUD treatment. Senyo offers several well-studied, app-based components to users, including asynchronous CBT modules, CM, behavioral activation, and an interface to interact with the program LADC. We chose these features as our initial intervention based on our research that showed CBT and CM had significant effect sizes for improving substance use-related outcomes, with CM having a large effect [20]. A group of licensed drug counselors meeting an hour a week over the course of several months with a senior patient education specialist employed by Mayo Clinic took individual paper copies of patient education content that presented CBT-based concepts and combined them with CBT content found in National Institutes of Health CBT Content built for "Project MATCH" [24]. This process resulted in the production of 16 modules.

Traditional care coordinator and patient coordination visits involve a comprehensive assessment of the patient's physical, mental, and social health needs. It includes collaborative care planning with input from various health care providers, patient education, and regular follow-up. These visits are typically done in person or over the phone. To add digital care coordination, we incorporated the ability to communicate directly with a LADC care coordinator through the app. Furthermore, the Senyo platform enhances care coordination by providing the care coordinator with a desktop portal directly linked to the patient's mobile phone app. The care coordinators have immediate access to the patient's progress through an interface that showed the patient's use of the mobile phone app features, survey results, and activities. The platform also allows the care coordinator to do video-based conversations that more closely mimic in-person care coordination visits.

The app was designed to be simple and user-friendly. When first using the app, initial prompts are designed for the user to create personalization and review security or privacy settings. Figure 2 displays the patient's to-do list, a behavioral activation goal (walking), and the points received for completing that goal. Figure 3 displays the chat feature, which is a communication portal with the LADC. Modules and surveys can be assigned in response to current symptoms in real time.

Figure 2. Screenshots from Senyo Health app that the individual using the app sees. Panel (A) shows the initial personalization. Panel (B) shows the current "To-do List" and also displays the chat icon at the bottom of the panel. Panel (C) shows a behavioral activation task, and panel (D) showcases the points awarded for completing this task.

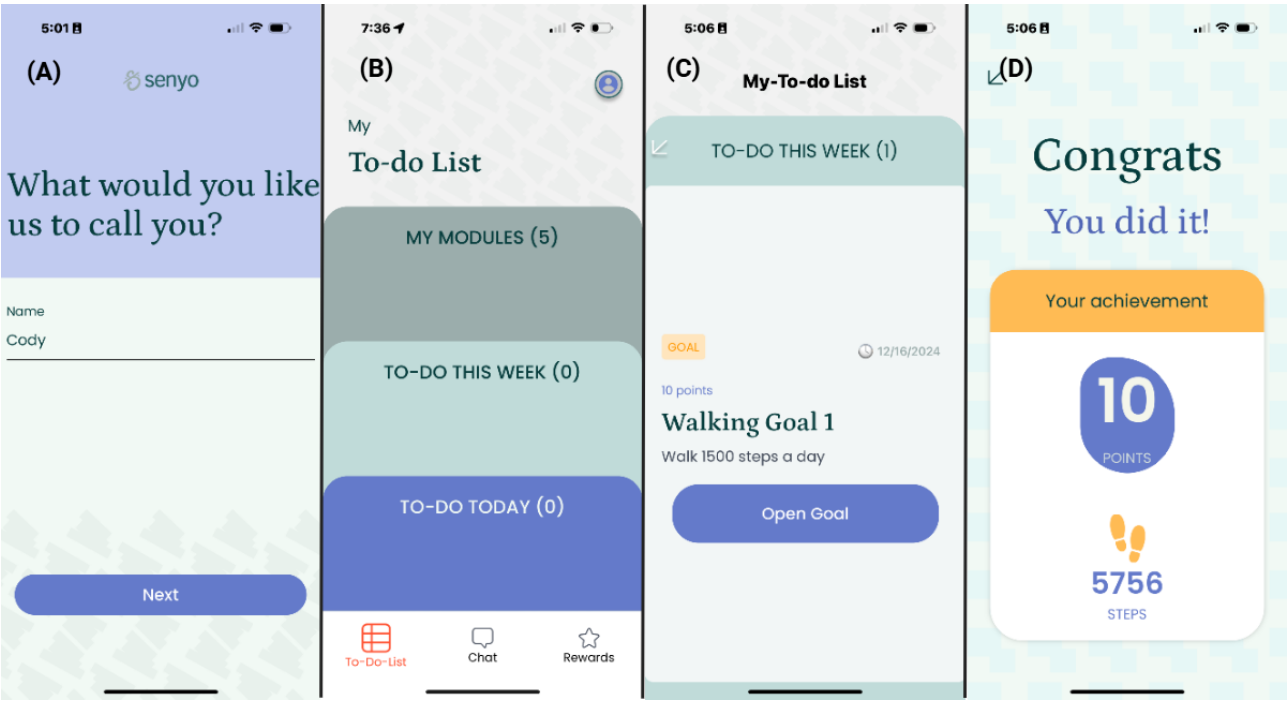

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Figure 3. Senyo Health chat feature being displayed from the perspective of the recovery coach. The left is conversations with multiple patients. Once selected, the full conversation appears in the center of the screen, with the recovery coach able to text back and forth. Surveys, modules, and activation tasks can also be assigned to the participant through the chat.

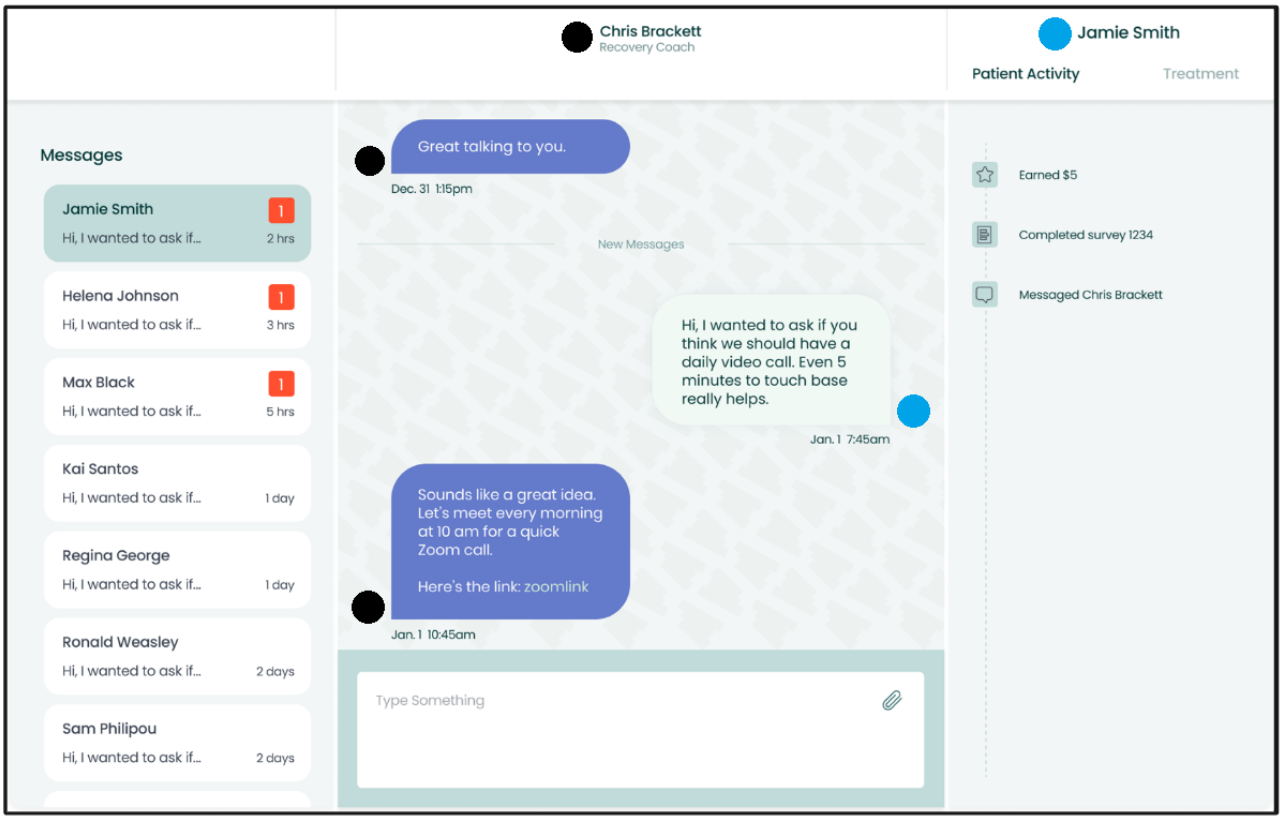

CBT Modules

Apps allow for the asynchronous delivery of therapeutic content that participants can use at any time. Current research supports delivering asynchronous content through "modules" or "activities." Psychotherapeutic modules within apps contain brief text-based content, videos, and related questions that patients can experience independently whenever convenient. CBT is the most researched content type for asynchronous modules [15,25,26]. "Activities" within apps are usually actions that the patient performs, such as filling out a survey, doing a mindfulness exercise, or being physically active [27]. Senyo Health currently contains 16 modules with content based on Mayo Clinic patient education pamphlets. Topics include "addictive thought patterns," "living with emotions in recovery," "self-esteem and relationships," "my recovery building blocks," "self-care in recovery," "cravings," and "relapse prevention."

CM Component

CM is a behavioral therapeutic intervention where monetary or prize-based rewards are "contingent" on objective evidence of drug abstinence and abstinence-promoting behaviors, such as attending mutual support meetings and counseling sessions [28]. Therefore, CM does not deliver education or concepts for individuals to learn; instead, it is a strategy to encourage positive behaviors. CM has decades of research representing hundreds of controlled trials demonstrating its safety and efficacy in assisting in-person SUD treatment [28,29]. It is arguably one of the most effective therapeutic strategies available to date but can be challenging to implement within conventional in-person treatment programs [30]. "ReSET" and "ReSET-O" are Food and Drug Administration–approved products that are available for prospective patients through a prescription that use CM to encourage the completion of in-app modules [25,26]. Digitally delivered CM through an app appears to improve engagement at a similar level to CM delivered in person [31].

The incorporation of CM-based token economy architecture into a CoCM platform makes Senyo Health unique [32]. The app awards points for completing surveys, modules, and activities. The points per action are customizable through the research interface, allowing for the adjustment of relative incentives associated with each task. Participants can use points to purchase rewards through a reloadable card (ClinCard). The purchased rewards will be tracked and documented in the research participant remuneration application. For this study, the point value is US $0.25 per point. One point is earned for each page of a module, minute of a video, and question in a survey.

Activity or Goals

Senyo Health was built to work with Apple and Google health kit wearable platforms to gather data from wearable device sensors. If a device is detected and the patient authorizes this, the wearable device sensor will track activity, heart rate, and oxygen saturation. These data will be used to encourage physical activity by connecting sensor data to CM rewards. These data will only be collected from participants who already have and wear a personal device; the study will not provide such device to participants.

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LADC to Patient User Interface

The LADC will use the provider portal to communicate through the app with their patients. Social rewards through apps, such as support from a clinician or peer via messaging or telephone, produce significantly greater user engagement than fully automated apps [32]. Typically, this support aims to maintain patient adherence with the app, monitor user progress through periodic symptom assessments, assist the patient in understanding therapeutic concepts or skills training, and triage patients who do not respond to app-based interventions [33].

Study Sample and Recruitment

Overview

The implementation phase will start with a pilot within a rural primary care site in the upper Midwest region of the United States that is familiar with the CoCM model for mental health treatment. After following the implementation strategy below at the initial location, we will expand to 2 additional primary care sites—1 for a rural service population and 1 for a nonrural service population. This staged rollout will allow for iterative improvements for the subsequent sites based on knowledge gained from the first site.

Provider Engagement and Implementation

Preimplementation

Clinic engagement efforts will start by recruiting a primary care champion at the primary care site. Other primary care clinic key stakeholders (physicians, nursing, CoCM staff, and medical support and administrative staff) will be included as appropriate. Focus groups and interviews with providers and staff engaged in the SBIRT workflow will assess attitudes and perceived barriers toward SBIRT, the use of medications for addiction treatment (buprenorphine, acamprosate, etc), and the use of digital delivery of SUD treatment within CoCM. Focus groups will be interviewed using a semistructured interview based on the CFIR interview guide. Please see Multimedia Appendix 1 for details.

Implementation: Training, Supervision, and Refinement

Research team members with experience treating SUD in primary care clinics will provide education to providers at the participating site. We will be scheduled as part of a regularly recurring staff education curriculum to provide didactic base education on the project (specifically the screening metrics, conducting a brief intervention, and how to refer to this study). The LADC will support voluntary follow-up training on brief interventions, motivational interviewing, and the referral process. Primary care champions at each participating site will encourage other site providers to attend training and initiate medications for addiction treatment for patients with confirmed moderate and severe SUD diagnoses. These champions will also liaise with the LADC.

Throughout the implementation approach described, we will gather feedback from the primary care team on SBIRT, the Senyo Health platform, the CoCM team, and LADC to evaluate the processes. Primary care providers, nurses, key administrators, and clinic staff from each of the sites will be identified for interviews. Feedback on these components will be used to iterate and refine our strategy.

SBIRT Protocol

Screening

Universal patient screening with the Drug Abuse Screening Test (DAST) [34] and the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C) [35] is an eventual goal. These instruments help determine the need for treatment referral using the SBIRT care pathway. The AUDIT-C is already frequently implemented across primary care; however, the DAST is not. Screening frequency will be explored in the feasibility stages based on feedback from clinic staff and leadership. While the US Preventive Services Task Force recommends all adults are screened for substance use, this may not be feasible in all clinic workflows. Stakeholder feedback will monitor excessive screening burden, and process iteration will attempt to minimize unnecessary rescreening to optimize overall results.

Brief Intervention

The brief intervention stage is where the SBIRT pathway often stalls out. Implementation of a brief intervention will be collaborative and iterative with the initial pilot site. FRAMES [36], which consists of feedback, responsibility, advice, menu for change, empathy, and enhancing self-efficacy, will be the primary component of this intervention. If granted permission by the patient in the screening stage, a LADC will provide a brief intervention to the patient (ie, personalized feedback, education, and motivational interviewing). The primary care provider is at liberty to provide some initial counseling to the patient, but the full FRAMES-based structure of the brief intervention is deferred to the LADC. In this modification of the traditional SBIRT framework, the goal is to minimize the additional clinical burden on the primary care providers and emphasize the value of the CoCM program in augmenting the capabilities and capacities of the primary care team. The primary goal of the brief intervention as conducted by the LADC is to facilitate patient enrollment in CoCM or referral to a higher level of care if needed.

Referral

Patients will be informed about local treatment options for treatment as usual and about the option to participate in this study by enrolling in the Senyo CoCM program. They will be allowed to choose which option they feel is best for them. Once the process runs smoothly at the pilot site, we will expand to the next selected site.

Treatment

All patients who consent to study participation will receive care through the Senyo Health platform. However, randomization will determine if this is provided immediately or if access is delayed by 12 weeks (ie, waitlist design). These patients will have outcomes closely monitored as described in the Study Procedures section. To ensure all eligible patients receive treatment regardless of trial participation, study coordinators will attempt to follow up with those who chose treatment as usual to monitor if they do ultimately receive treatment.

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Study Criteria

The intervention will be piloted to 10 patients who screen positive on the DAST or AUDIT-C and are already participating in CoCM for depression within primary care (no randomization). In addition to screening results, the clinical team will use their clinical judgment to determine eligibility, prioritizing patients for whom a SUD appears to be the primary psychiatric diagnosis rather than a mood or anxiety disorder. Once these patients have been recruited effectively and we have solidified our implementation strategy, we will broaden screening to primary care patients not currently in CoCM at the participating site. An additional 60 patients will be randomly assigned to immediate access to Senyo Health versus the waitlist. The 30 participants randomly assigned to the waitlist arm will be later added to the active arm (Senyo Health platform), for a total of 70 patients receiving active intervention by study conclusion. A computerized random assignment list will be generated by the study statistician for the study coordinator to assign enrollees sequentially, stratified by sex and restricted to every 10 cases, ensuring equal numbers per group. Due to the nature of the intervention and trial design, no one will be blinded. The study will recruit patients from Mayo Clinic primary care clinics at 3 sites after they have agreed to participate, with 2 serving primarily rural patients and 1 serving primarily nonrural patients.

Inclusion criteria are as follows: age 18 years and older; ability to read, write, and understand English; minimum DAST (1+) or AUDIT-C (3+) scores; and access and willingness to use a mobile device for asynchronous (text) and synchronous (video visits) engagement with care. Exclusion criteria are as follows: already participating in or about to initiate treatment in another structured addiction treatment program; diagnosed personality pathology as the primary presenting concern based on clinical judgment, severe cognitive impairment (eg, intellectual disability or dementia), or psychosis; inability to actively participate in and learn from psychotherapeutic interaction based on clinical evaluation and clinical judgment; needing a higher level of mental health care as demonstrated by American Society of Addiction Medicine assessment; and decline to answer suicidality questions.

Study Procedures

Overview

Once primary care patients have selected the study treatment path, the steps outlined below will occur. These include obtaining and signing informed consent, collecting medical and psychiatric history for comorbidities through patient interview, and answering validated questionnaires on mood, anxiety, and their overall strengths and resources to achieve substance use cessation (ie, recovery capital). Recovery capital is a biopsychosocial model of recovery from addiction, which encapsulates the interpersonal strengths and resources an individual can leverage in pursuit of substance use cessation [37]. Next, participants will be randomly assigned to the waitlist or active intervention. Once randomly assigned, participants will complete visits through a clinical treatment phase and a follow-up phase. The waitlist group will serve as a “waitlist” control and be asked to “cross over” and receive the active intervention after 12 weeks on the waitlist.

Study activities are listed in Textbox 1 and detailed in Table 1.

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Textbox 1. Study activities.

- Baseline visit
  - Obtain informed consent from the participant.
  - American Society of Addiction Medicine diagnostic interview [38] conducted by a licensed alcohol and drug counselor (LADC).
    - Participants must meet the criteria for outpatient treatment or indicate that outpatient is their preference.
  - Questionnaires: Brief Substance Craving Scale [39]; Brief Assessment of Recovery Capital [40]; self-reported substance use based on the Timeline Followback [41]; and psychiatric comorbidities measured via Generalized Anxiety Disorder-7 [42], Patient Health Questionnaire-9 [43], and Epworth Sleepiness Scale [44].
  - Treatment attendance monitoring questionnaire.
  - Urine drug test—check for certain drugs, including alcohol and illicit substances (ie, cocaine and methamphetamine).
  - Randomization to active intervention versus waitlist arms.
  - Set up active participants in the Senyo Health app.
- 12 weekly visits with LADC and pertinent study staff during the clinical treatment phase.
  - LADC will provide clinical counseling. The total number of counseling visits will be up to the discretion of the LADC, with a target goal of at least 1 hour weekly.
  - Questionnaires: Brief Substance Craving Scale [39], Timeline Followback [41], Generalized Anxiety Disorder-7 [42], Patient Health Questionnaire-9 [43], and Epworth Sleepiness Scale [44].
- Additional items monthly on weeks 4, 8, and 12.
  - Urine drug screen.
  - Brief Assessment of Recovery Capital [40].
- Final visit of active treatment (week 12).
  - Acceptability of Intervention Measure.
  - Intervention Appropriateness Measure.
  - Feasibility of Intervention Measure.
  - System Usability Scale [45].
- The follow-up phase begins immediately after completion of 12 weeks of active treatment. Visits will occur at weeks 4, 8, and 12, and at 1 year.
  - Questionnaires: Brief Substance Craving Scale [39], Timeline Followback [41], Generalized Anxiety Disorder-7 [42], Patient Health Questionnaire-9 [43], Epworth Sleepiness Scale [44], and Brief Assessment of Recovery Capital [40].
  - Urine drug screen.
- Individuals randomly assigned to the waitlist phase will follow the “follow-up phase” schedule during their 12 weeks prior to active intervention.

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Table 1. Study activities[a].

Assessment	Baseline	Active treatment phase (week)												Follow-up or waitlist phase (week)												1 year
		1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	
Consent	✓																									
Check-in		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				✓				✓				✓	✓
TLFB[b]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				✓				✓				✓	✓
BSCS[c]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				✓				✓				✓	✓
ESS[d]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				✓				✓				✓	✓
PHQ-9[e]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				✓				✓				✓	✓
GAD-7[f]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓				✓				✓				✓	✓
TAM[g]	✓				✓				✓				✓				✓				✓				✓	✓
Urine test	✓				✓				✓				✓				✓				✓				✓	✓
BARC[h]	✓				✓				✓				✓				✓				✓				✓	✓
SUS[i]													✓													
AIM[j]													✓													
IAM[k]													✓													
FIM[l]													✓													

[a]Participants will be randomly assigned to immediately start the 12-week study intervention or be put on a waitlist for 12 weeks and then start the study intervention. There will be long-term follow-up at 1 year.

[b]TLFB: Timeline Followback.

[c]BSCS: Brief Substance Craving Scale.

[d]ESS: Epworth Sleepiness Scale.

[e]PHQ-9: Patient Health Questionnaire-9.

[f]GAD-7: Generalized Anxiety Disorder-7.

[g]TAM: treatment attendance monitoring.

[h]BARC: Brief Assessment of Recovery Capital.

[i]SUS: System Usability Scale.

[j]AIM: Acceptability of Intervention Measure.

[k]IAM: Intervention Appropriateness Measure.

[l]FIM: Feasibility of Intervention Measure.

Outcomes

This protocol has 2 phases. For the initial implementation phase, the primary outcome will be a thematic analysis of coded structured interviews of clinic stakeholders, with a focus on whether noted SBIRT barriers were effectively modified during implementation. For the clinical trial phase, the study end point is the week 12 assessment of the primary outcome measure, overall substance use as measured by Timeline Followback. We anticipate that patient involvement in the active phase will lead to a significant reduction in substance use relative to the end of the waitlist period. Secondary outcomes will explore abstinence rates, treatment retention, along with treatment effects on craving, recovery capital, psychiatric well-being (Patient Health Questionnaire-9, Generalized Anxiety Disorder-7, and Epworth Sleepiness Scale), and use of clinical services throughout the intervention and follow-up periods.

Data Analysis

Qualitative interviews will be recorded, transcribed, and coded on a rolling basis using a rapid, template-based approach derived from the interview protocols [46]. Quantitative clinical treatment outcomes will be analyzed by comparing participant data at baseline, weekly during the intervention, and 12 weeks after the treatment (after completion of LADC visits). Our recent meta-analysis indicated that CM delivered through an app had a large effect size for improving substance use–related outcomes relative to control conditions [20]. Using this to inform our power calculation, there is greater than 0.80 power to see a large effect size between active and waitlist groups at the primary study end point. We will use information from this pilot to inform sample size calculations for a larger controlled efficacy trial. Several exploratory end points (eg, anxiety and depression) will be evaluated to contextualize the primary end-point effect. We will use likelihood methods (eg mixed models) that allow

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for data that are missing at random, so we will not impute any missing data. Intention-to-treat will be used.

Safety Monitoring

During the study, the LADC will be the first point of contact with the patient. Their app-based communications with the patient will focus on assessing symptoms, addressing clinical concerns, and providing brief encouragement to continue predetermined goals. The LADC will meet with the study psychiatrist and review the history obtained from the patient during their initial evaluation. The LADC will write a formal weekly update note on each patient, and monthly clinical tracking scores will be reviewed and reported to the consulting psychiatrist. Psychiatric recommendations for the management of addiction concerns and related mental health issues (ie, worsening mood or suicidality) will be reported back to the primary care providers, who will ultimately remain responsible for clinical decision-making and the treatment plan that may involve starting medications as a part of their clinical care. This patient review and consultation system will be managed through the provider portal, which will also serve as the patient population registry for quantitative tracking of clinical concerns with specific and quantitative end-point treatment goals.

Once a patient is enrolled in the study, the LADC and study staff will use the American Society of Addiction Medicine criteria to determine ongoing appropriateness for the current level of care [38]. To stay in the study, participants must remain eligible for outpatient SUD care. If the participant's American Society of Addiction Medicine criteria worsens enough that psychiatric recommendation is a higher level of care, they will be referred clinically to residential SUD treatment. The participant's active treatment phase will be stopped and moved into the follow-up phase for the schedule of visit. Adverse events will be reported to the psychiatrist for evaluation and reviewed for reporting requirements to the IRB.

Results

The Senyo Health app was launched in May 2023, and the most recent update was in August 2024. Our funding period began in September 2023 and will conclude in July 2027. This protocol defines a novel implementation strategy for leveraging a digitally native, clinical platform that enables the delivery of CoCM to target an SUD-specific patient population. Our trial will begin in June 2025.

We have not yet started enrollment in the primary study. In December 2024, focus group testing of the mobile app with people who have SUDs and are in treatment was completed. LADCs who reviewed the mobile and desktop apps were also interviewed. Their feedback has been used to improve the interface, design, and fix bugs, preparing for the primary study enrollment.

Discussion

Overview

This protocol builds from the large literature base that has described the positive effects of telehealth both before and after the COVID-19 pandemic [2,47]. Most treatment-seeking individuals report high patient satisfaction with telehealth [47]. Specific to alcohol use, digitally delivered interventions have been shown to significantly decrease heavy and binge drinking for both male and female patients and increase treatment retention at 1 year [48,49]. The use of telehealth among Medicare beneficiaries with an opioid use disorder was significantly associated with greater treatment retention and reduced odds of medically treated overdose [50]. App engagement, however, is typically low for traditional health-related apps. Individuals often use these apps for less than 1 week [31]. User time, effort, and attention can measure user engagement [51,52]. Greater engagement has been correlated with improved abstinence rates among apps incorporating CM and CBT modules [53]. Social rewards through apps, such as support from a health care provider via messaging, also produce significantly greater user engagement than fully automated apps [32]. These are core features of Senyo Health and help differentiate it from other interventions.

Additionally, the use of digital interventions to drive changes in recovery capital is largely unknown. A study of individuals engaging through a recovery-based web page noted that positive digital interactions help bind individuals within groups, supporting the overall recovery process [54]. This is reflecting community involvement and social connectedness, which are important aspects of recovery capital. Little else is known about the use of digital interventions in this space.

It is important to note that app creation is expensive. Additionally, apps are slow to create and typically costly to update. Senyo Health was created with sustainability in mind. It is owned solely by the Mayo Clinic, is fully operational, and is actively in use. New modules can be created within a desktop-based application directly linked to the app that we call the "researcher portal." The researcher portal allows for easy and rapid creation of new content without the need for changes to the app's code or new versions of the app to be pushed to the App Store. This allows for easy iterative improvements to existing content with no development costs. This feature dramatically reduces long-term costs and allows for real-time improvements based on user feedback.

Principal Findings

We will use mixed methods (interviews and questionnaires or scales) to evaluate implementation outcomes. We anticipate the identification of facilitators and barriers for the successful implementation of SBIRT and Senyo Health within a rural primary care workflow. Based on these findings, our hope is that through iterative enhancements, the rollout from site 1 to sites 2 and 3 will be increasingly streamlined.

While engaged in treatment services, substance use–related outcomes typically improve overall. Our proposed program is a combination of multiple evidence-based interventions, and as such, we expect a significant improvement in the active arm versus the waitlist control group. Additionally, we anticipate seeing recovery capital growth as individuals are engaged in treatment. As this growth has been significantly associated with decreased cravings [55] and past 30-day abstinence of alcohol and methamphetamine use [56,57], we hypothesize a significant

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correlation between substance use and recovery capital changes. As recovery capital growth for female patients has been reported as suppressed compared to male patients while in treatment [58], we will also explore possible sex differences.

Limitations

As with all pilot trials, there are potential barriers. This intervention relies on wireless internet or cellular data capabilities. Access to these is improving across the United States; however, residents in rural areas, which is our main target population, have disparities in internet access [6,59]. We do not anticipate that this will affect the app, as the media is cached or can be buffered; however, it may negatively impact live counseling sessions. This will need to be monitored and will be individual-specific. The study also relies on the willingness of primary care patients to participate in a novel addiction treatment paradigm. We suspect that the flexibility, convenience, and potential receipt of positive reinforcers through CM will aid in recruitment. Additionally, because patients in primary care often have an unmet need for specialty addiction treatment, we anticipate strong interest and engagement with this intervention. Finally, a lasting intervention will require clinical champions at primary care sites to help foster interest among treatment staff. If clinical providers are not interested, this will hamper dissemination to patients. The initial qualitative aspect of this trial, which focuses on facilitators and barriers, will be pivotal in maximizing the potential long-term success of this intervention.

Conclusions

Addiction is widely prevalent and negatively impacts health from both acute and chronic use. Treatments are available; however, uptake is low, and access is limited. Senyo Health is a digitally native platform that combines multiple evidence-based interventions to address and treat SUDs. Its flexibility is particularly useful for rural populations, who often experience severely limited access to treatment. Senyo Health is freely available for download to be used without CM, LADC, or CoCM components. However, we feel that these aspects are essential for the highest treatment efficacy.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are not publicly available due to patient confidentiality protections and institutional data-sharing policies but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Semistructured interview used in the clinical trial.
[PDF File (Adobe PDF File), 241 KB - resprot_v14i1e65693_app1.pdf]

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Abbreviations

AUDIT-C: Alcohol Use Disorders Identification Test-Consumption
CBT: cognitive behavioral therapy
CFIR: Consolidated Framework for Implementation Research
CM: contingency management
CoCM: collaborative care management
DAST: Drug Abuse Screening Test
HIPAA: Health Insurance Portability and Accountability Act
IRB: institutional review board
LADC: licensed alcohol and drug counselor
SBIRT: screening, brief intervention, and referral to treatment
SUD: substance use disorder

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Protocol

Efficacy of a Web-Based Integrated Growth Mindset Intervention on Reducing Anxiety Among Social Work and Counseling Practicum Trainees: Protocol for a 2-Arm Randomized Controlled Trial

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Abstract

Background: Practicum is indispensable for the development of professional practitioners; yet, trainees may encounter psychological distress, especially anxiety, brought on by new challenges. Research stated that a positive mindset promotes better learning and mental status. Well-designed interventions have been shown to relieve anxiety and help trainees thrive in their practicums and professions. The proposed study adapted an integrated intervention, We-SMILE (Web-Based Single-Session Intervention of Mindset on Intelligence, Failure, and Emotion), for improving prepracticum anxiety and coping. We-SMILE has the potential to be a low-intensity self-help prepracticum intervention to support students in adjusting their mindsets and overcoming the challenges in practicum.

Objective: Using a 2-arm randomized controlled trial, this study aims to examine the efficacy of We-SMILE on reducing anxiety (primary outcome) and enhancing psychological status, psychological well-being, learning orientation, academic self-efficacy, and confidence (secondary outcomes).

Methods: A total of 117 students will be recruited from the social work and counseling programs and randomly assigned to existing prepracticum training (training as usual [TAU]) or that plus the We-SMILE. Participants will be assessed repeatedly at 3 time points: baseline, 2 weeks post intervention, and 8 weeks post intervention. The outcomes will be measured by validated items and scales on anxiety, mindsets, psychological well-being, and the Failure Mindset Scale. Recruitment for the pilot study was initiated in May 2024 during social work and counseling prepracticum briefing sessions. Participants were randomly assigned to the intervention or TAU group. The intention-to-treat (ITT) analysis principle and linear regression–based maximum likelihood multilevel models will be used for data analysis.

Results: This study has received research ethics approval in May 2024. Participant recruitment started at the end of May 2024, and enrollment was ongoing as of when this protocol was submitted. Data collection and analyses are expected to be complete in 2025.

Conclusions: The randomized controlled trial will compare the efficacy of the We-SMILE intervention group and the TAU group. The results of this study will benefit practicum students, fieldwork supervisors, and social work and counseling programs.

Trial Registration: ClinicalTrials.gov NCT06509802; https://tinyurl.com/36vkwd63

International Registered Report Identifier (IRRID): DERR1-10.2196/67234

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KEYWORDS

implicit theory; growth mindset; social work students; counselling students; practicum; anxiety

Introduction

Prepracticum Anxiety

Practicum is an essential educational component of professional training [1,2], bridging the gap between theory and practice and enhancing the professional capacity and core competence of future practitioners [3,4]. The quality of fieldwork profoundly influences social work trainees' personal, intellectual, and professional development [4], per communication skills, critical reflection, professional growth, creativity, innovation, and self-efficacy [1,5]. Students and alumni frequently highlight their field experiences as pivotal in preparing them for their future roles [1]. Research indicated that continuous improvements in fieldwork training benefit the training of future practitioners, such as integration of resources, collaboration across sectors, and improvements in curriculum design [1,4,5]. Through practice and feedback, trainees gradually evolve from knowledge receivers to social workers and competent practitioners [6]. However, the process can be challenging and sometimes frustrating, with obstacles such as the rigorous training process and mental distress [4].

Research showed that students indeed face various challenges during practicums, which can be categorized into professional and individual levels [7]. At the professional level, anxiety and stress may rise when students experience issues with engagement, poor relationships, etc, related to trainers and supervisors [1,2,8,9] and are often exacerbated by the distinct cultural context and intense competition [6,7]. Moreover, although the programs usually prepare students for their placements, they may overlook the specific complexities of the work environment and the higher expectations of professional skills [4,10]. On the flip side, students probably encounter mental difficulties (eg, anxiety, stress, and compassion fatigue), financial pressures, maladaptive coping, physical problems, etc [7,11-15]. It has been noted that excessive anxiety and negative emotions can interfere with the practicum process [16]. Being adequately prepared to confront the challenges and difficulties in practicum is crucial for the learning outcomes and well-being of social work and counseling trainees.

Different coping mechanisms among students can lead to varied training outcomes. Clinical practicum students with the abilities to both manage their emotions and understand the emotions of the people around them have been shown to achieve better patient outcomes and patient satisfaction [2]. For example, dietitian students who effectively manage stress report the most supported feeling [10]. Conversely, students may doubt their abilities and talents if they find it tough to handle critical feedback and expectations from their supervisors and placement agency staff, besides the discrepancy between their preconceived notions before the practicum and the real situation [4,9]. Thus, fostering a positive attitude toward negative emotions, challenges, and feedback is essential to facilitate better learning outcomes and maintain trainees' mental health.

Existing Interventions and Gaps

The existing intervention approaches have broadly been delivered from 2 perspectives: the external perspective, such as transition support programs and peer group supervision [17-19], and the internal perspective, such as mindfulness training [20]. Transition support programs usually focus on supervisory support, transition-supportive learning activities, professional behavior and practice, and student internship responsibilities [4,18]. These programs are beneficial to students' mental health, specifically lowering anxiety, increasing confidence, improving preparation levels, and enhancing professional knowledge and skills [4,17]. Moreover, researchers examined the efficacy of peer group supervision in a practicum setting for counseling students [19] and found it was helpful to stimulate and bolster participants' professional self-efficacy, self-confidence, and feelings of pleasure and happiness [21]. However, several pertinent studies particularly highlighted mindfulness interventions for social work and counseling practicum trainees [22-24]. Mindfulness as a self-care practice was valuable for managing trainees' anxiety and strengthening self-care [20,25].

There is a notable lack of research evaluating the implementation of stress and anxiety management interventions in practicum settings for social work and counseling trainees. First, many studies usually develop and apply multiple-session interventions and must be led by professionals, expanding the trainers' workload [26]. More importantly, full-time employees and interns generally face different work tasks, challenges, and pressures [27]. However, existing interventions lack clear definitions and distinctions, so more evidence from interns' perspectives is needed. Lastly, the current interventions require more objective and reliable outcome indicators and well-designed randomized controlled trials. Thus, a low-intensity self-help prepracticum intervention to increase the preparation levels of social work and counseling trainees is desired.

Mindset Intervention

Mindset, which refers to implicit theory, means an individual's belief in the changeability of his or her attributes [28]. Individuals with growth mindsets believe that their attributes are changeable. Believing intelligence and emotion are temporary and evolving will prompt one to make efforts at learning and emotion regulation. In contrast, a fixed mindset indicates the belief that one's attributes are immutable [29-31]. The extant literature shows that the fixed mindset is related to more anxiety and stress, while the growth mindset contributes to proactive coping with anxiety and stress and resilience in the face of drawbacks [28,32]. Mindset is found to be a modifiable factor in intervention, which is essential in clinical psychology, therapy, prevention, and early intervention. These days, the growth mindset has been gradually introduced into practice and has yielded positive results [31,33,34].

Nevertheless, little research has been conducted on integrated mindset interventions, and there is very limited evidence for

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this initiative. As mindsets can be domain-specific, one may have different mindsets regarding various domains [35]. When one faces a challenge, multiple mindsets may interact and intervene in one's coping behaviors. As for prepracticum trainees, their anxiety is multifaceted. Instilling growth mindsets regarding intelligence, emotion, and failure-is-enhancing mindsets, respectively, is worthwhile in easing anxiety and stress coping [36]. An integrated mindset intervention may be more efficient in reducing anxiety related to practicum, thereby preparing for the challenges that may be encountered.

Integrated Mindset Intervention: We-SMILE

This research has adapted an existing integrated mindset intervention by the principal investigator (PI: SZ), that is, PC-SMILE (Parent-Child Single-Session Mindset Intervention on Intelligence, Failure, and Emotion) for secondary school students [37]. The design is grounded in implicit theory research and supported by emerging evidence of the effect of brief interventions [38-42]. PC-SMILE is a 45-minute intervention that aims to instill growth mindsets of intelligence, failure-is-enhancing, and belief-in-change of emotion using neuroplasticity and real-life examples among students. The efficacy of PC-SMILE is being examined with a 3-arm randomized controlled trial [37].

The current protocol endeavors to modify the child-version of PC-SMILE for practicum trainees in social work and counseling programs, namely, We-SMILE (Web-Based Single-Session Intervention of Mindset on Intelligence, Failure, and Emotion). We-SMILE adheres to the core concepts of PC-SMILE with specific adjustments to practicum trainees' circumstances, that is, intending to introduce growth mindsets about intelligence, failure, and negative emotion to prepracticum students. We-SMILE starts with stories mirroring scenarios from social work and counseling practicum, followed by key principles from implicit theory, learning mechanisms, and emotion regulation, and finally supports these conceptions with solid evidence from research. One highlight of We-SMILE is that it includes a session dedicated to time management, an issue that new practicum students often struggle with. In this section, students are introduced to effective time management tools and ways of enhancing awareness of allocating time without burning out. Then, transferred to self-care methods to manage emotions caused by practicum experiences.

Aims

The protocol aims to assess the efficacy of We-SMILE through a 2-arm randomized controlled trial.

The primary objective is to evaluate the efficacy of We-SMILE in reducing anxiety related to practicum among social work and counseling trainees compared to the training as usual (TAU) group.

The secondary objective is to evaluate the efficacy of We-SMILE on secondary outcomes, including (1) relieving depression, anxiety, and stress; (2) improving psychological well-being; (3) enhancing learning orientation; and (4) increasing academic self-efficacy and confidence related to practicum compared with the TAU group.

Methods

Design of We-SMILE and Implementation Strategies

Patient and public involvement is a key principle we adopted in the intervention design and implementation strategies. The intervention design was coproduced by the research team and student advisory group who have completed at least one practicum training.

The first step is preintervention development. The needs for prepracticum mindset training were identified through interviews with the students who completed their summer practicum in 2023. Second, during intervention development, a student advisory group of 3 social work students was invited to participate in pilot studies and provide suggestions on the initial questionnaires, videos, and the final intervention regarding content consistency, process clarity, ease of understanding, and intervention duration. Third, after the pilot study in May 2024, participants' open-ended feedback will be collected for intervention improvement. We also invited 3 participants to interview for detailed comments. Based on the feedback and comments, further improvements were made. Thematic analysis will be conducted to integrate participants' feedback to identify what they perceive as the most beneficial aspects of the intervention and those most in need of improvement. Coproduction is helpful to ensure the intervention's acceptability, feasibility, relevance, and effectiveness. Fourth, about implementation strategies. The implementation process was co-designed with the fieldwork coordinators. We collected feedback from supervisors and teachers in the social work program. They will help send invitations to upcoming prepracticum social work and counseling students during briefing sessions and share the research link with the students via WhatsApp group once this study begins. Our study adheres to the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist (version 1.6) and follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (see Multimedia Appendices 1 [43] and 2 for details).

The intervention is a 45-minute web-based course, finally consisting of five elements: (1) an introduction to a proactive mindset, including neuroplasticity, the malleability of intelligence and emotion, and the importance of failure and feedback in the learning process; (2) stories and testimonials during practicum, which emphasize the belief in change; (3) short videos about allegories of developing intelligence, emotion, and failure mindsets; (4) common questions and misconceptions about growth mindsets; and (5) self-persuasive writing exercises in which participants write down their thoughts and suggestions for others about growth mindsets. Figure 1 displays the intervention home page, Figure 2 provides an example of a story emphasizing the positive aspects of failure, and Figure 3 presents the neuroplasticity foundation linked to a growth mindset. Participants in the TAU group will be provided with the We-SMILE after completing the 8-week follow-up.

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Figure 1. Home page of We-SMILE. We-SMILE: Web-Based Single-Session Intervention of Mindset on Intelligence, Failure, and Emotion.

Figure 2. A screenshot from one of three short stories about failure. In the screenshot, Red Bean says, “If only I’d eaten the fourth vegetable and meat bao straight away, just one would have filled me up!”.

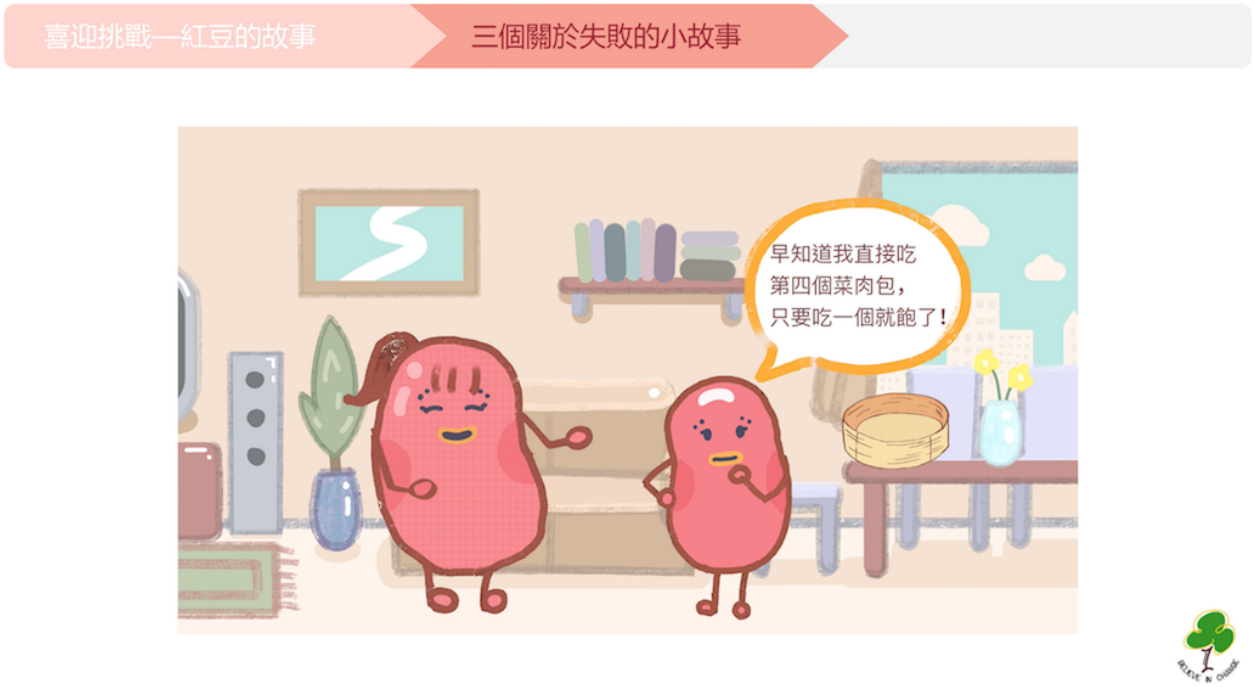

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Figure 3. A screenshot demonstrating the neural changes in a learner. The image and text indicate that "Through practice, the connections between neurons can be strengthened, establishing broader connections. We can see that as practice time increases, the neural network becomes progressively more enriched. This is the change that our brains undergo during the process of behavioral change. In fact, the changes in brain neurons go far beyond this. Let's continue to explore.".

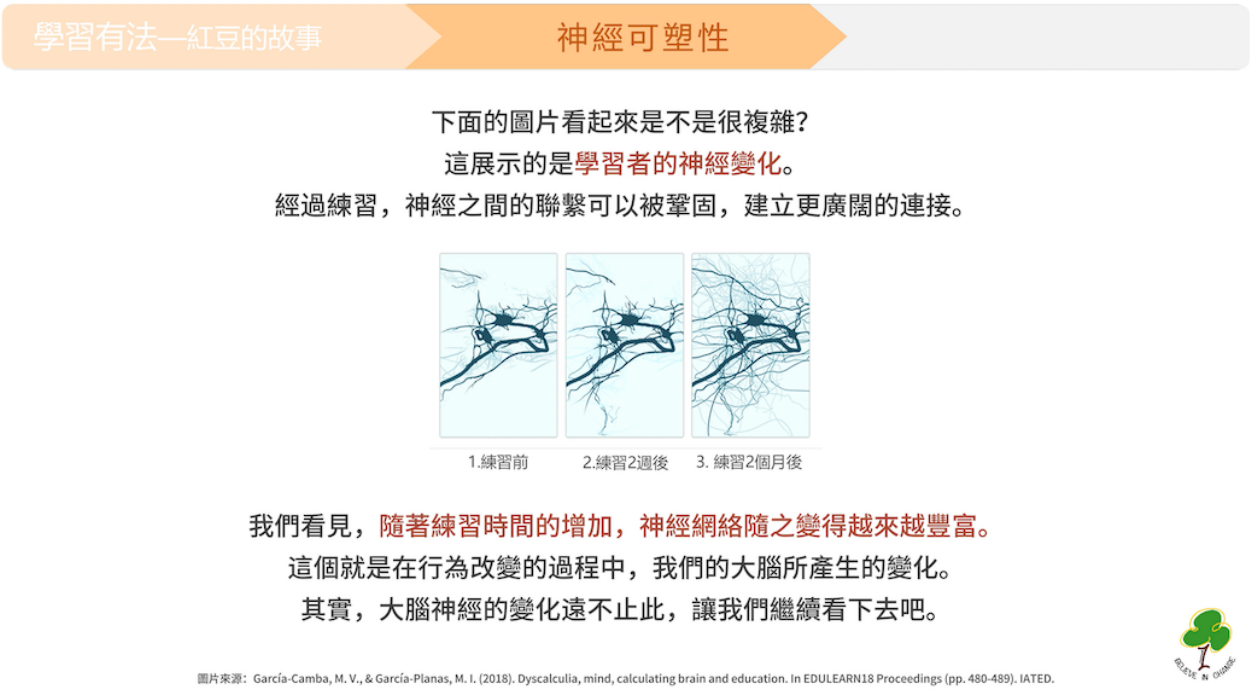

Randomization Process

Randomization will be performed via the randomization module of Qualtrics with a 1:1 allocation, whereby students will be allocated to either the We-SMILE group or the TAU group. Students assigned to the We-SMILE group will receive the intervention link immediately, while participants in the TAU group will be provided with the course 8 weeks later. Both groups will be taught by instructors with equivalent qualifications and expertise in the subject matter to ensure consistency in the teaching quality. Concealment can be ensured as participants complete the survey individually and randomization is set after the baseline assessment. The data will be collected at 3 intervals: baseline, 2 weeks after the intervention, and 8 weeks after the intervention; that is, the research team will send the link of follow-up questionnaires to participants at the corresponding time.

Sample Size and Power Analysis

This study targeted prepracticum social work and counseling students during the period 2024-2025. The sample size is 117, based on the number of trainees. The G*Power is used to determine the target sample size, achieving adequate efficacy to detect mean group differences of small (d=0.2), medium (d=0.5), and large (d=0.8) effect sizes using 2-tailed tests with α=.05. Although previous studies have indicated that the ideal is to detect small effects, the target sample of 117 in this study may reflect the ability to detect moderate to large effects (slightly greater than 0.5) due to limitations on the number of students in the programs [44].

Participant Eligibility

Undergraduate and postgraduate prepracticum students in social work and counseling programs from universities in Hong Kong and Mainland China are eligible. Inclusion criteria are students who (1) are about to start the practicum soon, (2) can read and write Chinese, and (3) consent to participate. Exclusion criteria are students who (1) do not consent to participate, (2) cannot concentrate for at least 45 minutes to complete the intervention and questionnaires, (3) have a disability or serious physical or mental illness resulting in poor condition, and (4) do not participate in the practicum.

Measurements

Figure 4 illustrates the specific research arrangements and measurement schedules.

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Figure 4. Study periods, arrangements, and measurement schedules. T: time point; TAU: training as usual.

	Study period						
	Enrollment	**Allocation**	**Postallocation**				**Close-out**
Time point	$-T_1$	0	T_0: week 1	T_1: week 1	T_2: Week 2	T_3: Week 8	T_x
Enrollment							
Eligibility screen	✓						
Informed consent	✓						
Allocation		✓					
Intervention							
Intervention group			◄	►			
TAU group						✓	
Assessments							
Intervention group			✓	✓	✓	✓	
TAU group			✓		✓	✓	
1. Demographics			✓		Student number	Student number	
2. Mindset about intelligence			✓	✓	✓	✓	
3. Mindset about failure			✓	✓	✓	✓	
4. Anxiety related to practicum			✓	✓	✓	✓	
5. Depression, anxiety, and stress			✓		✓	✓	
6. Psychological well-being			✓		✓	✓	
7. Learning and performance orientation			✓		✓	✓	
8. Academic self-efficacy			✓		✓	✓	
9. Confidence related to practicum			✓		✓	✓	
10. Intervention feedback (close-and open-ended)				✓			
11. Motivation				✓			

Demographics

Name, gender, ethnicity, year of birth, year of study, program type, program name, student number, practicum mode, previous social work experience, and other work experience will be collected at baseline. Students' university numbers will be collected again at 2 follow-ups for matching. Collected students' names and university numbers are solely for administrative purposes, such as matching pre- and postintervention data and ensuring accurate contact with participants for compensation after this study.

Fidelity Checking

Mindset about intelligence will be assessed by a 3-item Growth Mindset Scale developed by Dweck et al [45] with high internal reliability across studies, including "you have a certain amount of intelligence, and you can't really do much to change it," "your intelligence is something about you that you can't change very much," and "you can learn new things, but you can't really change your basic intelligence." Each item will be rated from 1=strongly disagree to 6=strongly agree. A higher average score means participants believe less that they can become smarter if they work at it. The reliability was reported in adolescents with Cronbach α of 0.71 [46].

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Mindset about failure will be measured by the 6-item Failure Mindset Scale [47,48]. The first 3 items indicate that failure can be a positive motivation (eg, "The effects of failure are positive and should be utilised"), while the last 3 items indicate that failure is a setback (eg, "The effects of failure are negative and should be avoided."). Each item will be rated from 1 (strongly disagree) to 6 (strongly agree). The Cronbach α was 0.76 [48].

Primary Outcome Variable

Anxiety related to practicum will be measured by 4 items proposed by Gelman which parallels with the evaluation often used in social work practice [16], including 1 direct measuring item: "level of anxiety about starting the practicum," and 3 indirect measuring items: "how much your anxiety will interfere with their learning," "how prepared you are for the practicum" and "how excited you are to participate in the practicum" [16,49]. Each statement will be rated on a 10-point Likert scale, ranging from 1=completely not anxious, very small, completely unprepared, and completely unexcited to 10=extremely anxious, very great, perfectly prepared, and extremely excited [16]. The Cronbach α was 0.70 [50].

Secondary Outcome Variables

Depression, anxiety, and stress will be assessed by the simplified 12-item Depression Anxiety Stress Scales (DASS-12) [51,52]. The items of DASS-12 were shortlisted from the DASS-21, such as "I found it hard to wind down" [51,52]. Each item will be rated from 0=never to 4=almost always according to the participant's status over the past week. A higher score indicates a higher level of recognition of one's recent mental distress symptoms. The Cronbach α was 0.90 [52].

Psychological well-being will be measured using the 7-item Short Warwick-Edinburgh Mental Well-Being Scale [53,54]. One example item is "I've been feeling optimistic about the future." Each item is rated from 1 (none of the time) to 5 (all of the time). Higher scores suggest better mental well-being. The Short Warwick-Edinburgh Mental Well-Being Scale was validated in Hong Kong, and the Cronbach α was 0.89 [55].

Learning and performance orientation will be assessed by 11 adapted items from learning orientation and performance orientation scale [56], with 5 items measuring the learning orientation (eg, "I like to learn new knowledge in practicums") and 6 items measuring performance orientation (eg, "I like to seek rewards in short term for my efforts"). Each item will be rated on a 5-point Likert scale from 1=strongly disagree to 5=strongly agree. Reliabilities were reported of Cronbach α with 0.65 and 0.56 [56].

Academic self-efficacy will be measured by 5 adapted items from the Bandura Self-Efficacy Scale [57]. Example items are "I believe that as long as I study diligently, I will be able to master practical skills" and "as long as I am diligent, I can master all of the skills learned during the internship." The items will be scored from 1=strongly disagree to 5=strongly agree and reported a Cronbach α of 0.84 [57].

Confidence related to practicum will be assessed by a 6-item self-developed scale. Items generated from interviews with social work students, such as "I am confident that I can listen to comments from supervisors/colleagues/service users with an open mind" and "I am confident that I can manage my time well and cope with my practicum work and schoolwork at the same time." Each item needs to be rated from 1=strongly disagree to 5=strongly agree. A higher total score represents a higher level of confidence.

Intervention Feedback

Intervention feedback contains both close-ended and open-ended questions. The close-ended intervention feedback will be measured using an adapted 12-item 5-point Likert scale based on the Theoretical Framework of Acceptability scale [36]. The items include affective attitude, burden, perceived effectiveness, opportunity costs, and specific acceptability. A sample item is "does this course affect your daily schedule?" The open-ended question invites participants to share their thoughts about the intervention: "Do you have any other suggestions or feedback about this programme?"

Motivation will be measured using 2 self-designed items: "How much do you want to improve your ability to cope with challenges?" and "how much do you want to use what you have learned in the course to cope with challenges in your current or future practicum?" The items will be measured on a 6-point scale from 1=extremely not willing to 6=extremely willing. Higher scores indicate that participants are more motivated to learn from the intervention, apply it to their practice, and are intrinsically more willing to improve their status.

Pilot Study

The pilot study is initiated at the end of May 2024, before the commencement of the first batch of social work and counseling students' practicum. An overview of the intervention study is incorporated into the prepracticum briefing to attract participants. Upon obtaining consent, program supervisors will distribute the intervention course link to the students. Alongside standardized questionnaires, participants are invited to offer open-ended feedback on the intervention to facilitate future revisions and enhancements after finishing. Examples of feedback we currently received include "The content and duration can be condensed. The principle about red beans' story is something I believe everyone understands. It's better to directly point it out" and "If the voiceover is done by a real person, it would feel more authentic. The sound effects in the stories are very interesting" In the next revised version, the intervention will be shortened and improved with human voice dubbing from a professional actress.

Follow-Up Plan for Distressed Participants

Follow-up plans have been established to support participants who experienced severe distress during the trial. Research staff have been trained to respond to reports of distress from participants. If severe distress is identified, participants will be referred to appropriate resources, including counseling services and crisis hotlines provided by schools, government agencies, and nongovernmental organizations. Additionally, guidance on seeking professional help is included in the information sheet given to participants. Ensuring the mental health and well-being of participants is always our top priority.

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Analytic Plan

Data analysis will be conducted according to the intention-to-treat (ITT) analysis principle, and missing data will be processed using multiple imputations. Descriptive analyses will be used for the distribution of demographics and all outcome variables. Analysis of covariance will be deployed to compare postintervention outcomes between the intervention and TAU groups, controlling for baseline differences. This approach ensures that the observed effects can be attributed to the intervention rather than preexisting differences, thereby enhancing the validity of the results. Generalized estimating equations will be applied to process data from repeated measures to initiate subgroup analyses and to assess differences in the efficacy of the intervention among participants with different work experiences, emotional states, and mindsets. Because of the cluster randomization, a 2-level analysis will be conducted [58]. Additionally, multilevel regressions will be used to test group effects, time effects, and their interactions on outcome variables. A P value of <.05 will be considered statistically significant, and all statistical analyses will be performed using SPSS (version 26; IBM Corp).

Data Quality Assurance

Respondents can review and change their answers through a "back" button. The investigators will be responsible for the quality control of the data. Data with response times that are too long or too short, as well as expired responses, will be excluded. Completion times from the pilot study will be used to determine thresholds for early or late submissions. The first entry will be kept to avoid duplicate entries. Two attention-checking items are embedded to identify careless responses.

Protocol Amendments

In general, the research will be conducted following the protocol. The protocol should be seriously and carefully revised and reapproved by the ethics committee of the PI's university if major modifications are necessary for any reason or if the change will impact the conduct of this study and the interests of the participants. Minor adjustments that do not have significant impacts on this study and participants will be recorded for subsequent supplementation of ethical and trial materials.

Ethical Considerations

This study has received research ethics approval from the institutional review board of the PI's university (HSEARS20240512001-01). Students who click the link sent by supervisors and teachers will first read the information sheet and sign the consent form. The participants can decide when to start and withdraw from the intervention. The primary investigators will be responsible for the management of research data. All identifying information of participants will be anonymized during the research process, including data analysis, results reporting, and publication. The data will be generated directly from the web-based survey platform and will be stored at the PI's university. All database files will be password-protected and can only be accessed by direct researchers. Researchers who have permission to access the data will be appropriately trained to maintain data confidentiality, integrity, and basic data security measures. All data and backups will be maintained till 5 years after the completion of the research. Each eligible participant will be contacted by the research team and receive HK $100 (US $12.87) supermarket vouchers after completing all the questionnaires.

Results

The project was funded by the Departmental Teaching and Learning Grant of the Department of Applied Social Sciences at PI's university (grant 8AL1). Recruitment began in May 2024, and data collection is expected to end in April 2025. Data collection is currently underway. The results are scheduled to be released in August 2025. We plan to issue a publication and may also disseminate the results at conferences. The flow of this study is shown in Figure 5.

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Figure 5. CONSORT diagram. CONSORT: Consolidated Standards of Reporting Trials; We-SMILE: Web-Based Single-Session Intervention of Mindset on Intelligence, Failure, and Emotion.

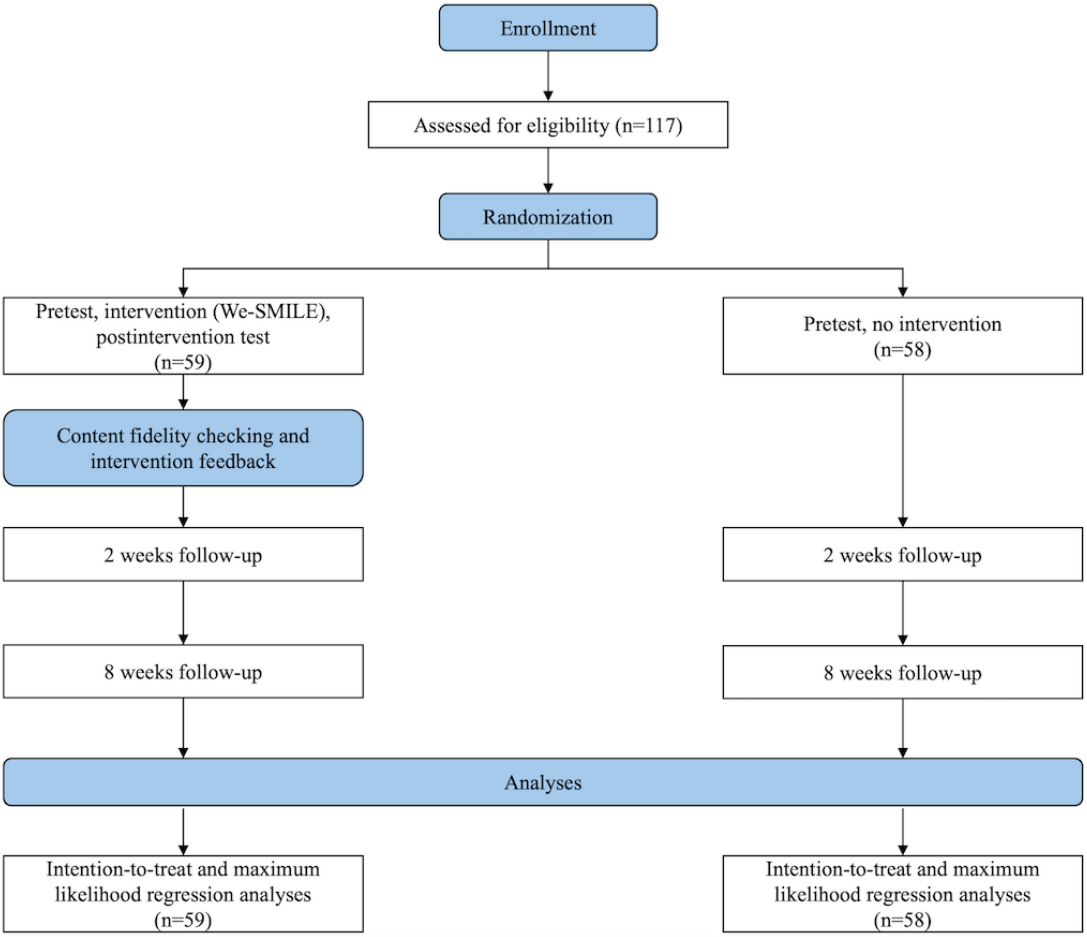

Discussion

Principal Findings

The purpose of this study is to initiate a randomized controlled trial among prepracticum social work and counseling students, assessing the efficacy and acceptability of a digital integrated growth mindset intervention (We-SMILE). It is expected that the We-SMILE group will present lower anxiety related to practicum and more positive secondary outcomes compared to the TAU group. Although this is a single-session, web-based self-help intervention, its efficacy, effectiveness, and sustainability should not be overlooked, as it may continue to serve a useful purpose beyond the project period [44].

We-SMILE is an innovative, convenient, and promising intervention for prepracticum training with a focus on the growth mindset. The We-SMILE will be the key deliverable of the proposed project and has several remarkable advantages. First, We-SMILE is theory-based. Extant interventions with similar core concepts from Western or local practice have been found effective in improving mental health [28,36,40]. Second, patient and public involvement and the coproduction process involving students and fieldwork supervisors ensure We-SMILE to be a tailor-made intervention for practicum trainees. Third, the web-based and nonstigmatizing natures increase accessibility and flexibility for young individuals. Once the efficacy of We-SMILE is established, the integrated mindset prepracticum intervention can help hundreds of students be psychologically prepared for fieldwork training. While providing mental support, it can also supplement practicum education as a readily accessible module to enhance the training outcomes of social work and counseling students. Additionally, this study will provide clear implementation protocols and strategies to increase transparency. The intervention study can be replicated, developed, and referenced as a basis for future research and the design of single-session growth mindset interventions.

Strengths

Based on previous research indicating the lack of interventions targeting prepracticum training, the proposed study fills this gap by focusing on improving the growth mindset in this particular population. The project will benefit multiple parties. The immediate beneficiaries will be social work and counseling students. The intervention is designed to tune trainees' mindsets regarding how they perceive the learning process, feedback, failure, and emotion. It could help prevent a high level of anxiety and fear about receiving negative feedback and facilitate students building resilience in fieldwork training. Second, it could benefit fieldwork supervisors. We-SMILE offers a flexible intervention option as a concise psychoeducational tool that seamlessly fits into prepracticum preparation. It does not require an extra workload for supervisors and can easily be distributed for students' needs and reference. Alternatively, the intervention can be used as a specialized component of the existing

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prepracticum training or incorporated into classroom teaching. Third, it may benefit the social work and counseling programs as a whole. We-SMILE provides an accessible intervention to assist social work and counseling students in transitioning into future workplaces with lower levels of distress, better self-efficacy, and becoming mentally prepared, which will in return improve the outcome and quality of education programs.

Limitations

Some limitations in this intervention require further consideration and refinement. First, this study only targets students in social work and counseling programs. The number of participants in each cohort will be limited. We may not be able to recruit a sufficient sample size if practicum trainees are occupied by coursework and internships and become too busy to complete the intervention course. There is a need to expand the scope of implementation by including a larger sample in the future to demonstrate that the intervention could be adapted into training for other education and health care domains. Second, as this study does not differentiate individuals with various levels of anxiety states, the effectiveness in reducing anxiety may not be significant for those students with no or low levels of anxiety, thus, it may affect the overall statistical significance. Therefore, we may conduct subgroup analyses to address this issue.

Conclusion

This study aims to develop a digital single-session integrated growth mindset intervention (We-SMILE) and to evaluate its efficacy and acceptability using a 2-arm randomized controlled trial among practicum trainees of social work and counseling programs. If proven effective, our study will provide a potential model for the implementation of a brief, low-dose, single-session intervention. In return, We-SMILE may also contribute to the development of accessible, highly adaptable, low-cost, and sustainable interventions in mental health education on a larger scale.

Acknowledgments

This work was supported by the Departmental Teaching and Learning Grant of the Department of Applied Social Sciences at The Hong Kong Polytechnic University (grant 8AL1). We thank social work students who served as student helpers in the coproduction of the intervention, including Oscar Cheung, Alfie Li, and Tim Lam. We also thank the students in the pilot study who provided helpful comments for intervention improvement. The social work or counseling program leader, supervisors, and student assistants contributed greatly to the development and conduct of the intervention and are gratefully acknowledged.

Data Availability

Data generated and analyzed during this study is not publicly available due to privacy and confidentiality issues but can be obtained by contacting the corresponding author upon reasonable request.

Authors' Contributions

SZ proposed this study concept, was responsible for the intervention design, funding acquisition, study supervision, paper writing, review, and revision. YW participated in the intervention design, data collection, paper writing, and revision. AX worked on the intervention design and paper revision. and SSKW, KY, and JTYL facilitated the data collection. All authors read and approved this paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-eHEALTH checklist (V1.6.1).
[PDF File (Adobe PDF File), 948 KB - resprot_v14i1e67234_app1.pdf]

Multimedia Appendix 2
SPIRIT checklist.
[DOC File , 119 KB - resprot_v14i1e67234_app2.doc]

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Abbreviations

CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
DASS: Depression Anxiety Stress Scales
ITT: intention-to-treat analysis
PC-SMILE: Parent-Child Single-Session Mindset Intervention on Intelligence, Failure, and Emotion
PI: principal investigator
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TAU: training as usual
We-SMILE: Web-Based Single-Session Intervention of Mindset on Intelligence, Failure, and Emotion

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Protocol

Ayurveda Management of Menorrhagia (Raktapradara): Protocol for a Randomized Controlled Trial

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Abstract

Background: In India, heavy menstrual bleeding or menorrhagia (*Raktapradara*) constitutes about 15% to 20% of all gynecological admissions in an institution. Of these, 43% of patients are aged 20-40 years. This condition is worsening because of the high prevalence of anemia among Indian women. Menorrhagia can have a significant impact on women's lives. Medical treatment is usually the first choice in excessive bleeding, but it reduces menstrual blood loss by only 50%, and up to 50% of women undergo surgical treatment within 5 years. However, none of these treatments proved their definite efficacy in spite of the high price and side effects. This condition presents a major financial burden on health care services. In Ayurveda, encouraging work has been done on the compound drug *Ashokarishta*, and the drug *Trinakantamani pishti* is indicated in Ayurvedic classics and the *Ayurvedic Formulary of India*. Also, these medicines have been used in Ayurvedic practice for a long time. However, no clinical trial has been carried out on these formulations.

Objective: The primary objective is to evaluate the efficacy of Ayurvedic intervention in the management of menorrhagia, and the secondary objective is to assess the efficacy of Ayurvedic intervention on the quality of life of the women with menorrhagia.

Methods: This ongoing study is an open-label, interventional, randomized controlled trial, with a sample size of 140 in the treatment and control groups combined (including 20% dropouts), and will be carried out within the duration of 36 months. Participants in the treatment group will receive Ayurvedic treatment, that is, 20 mL of *Ashokarishta*, 250 mg of *Trinakantamani pishti*, and 1 iron and folic acid tablet (100 mg of elemental iron and 1.5 mg of folic acid) twice a day orally for 3 months. Participants in the control group will receive a 500-mg tranexamic acid tablet thrice a day for 7 days from the first day of menses for 3 cycles and 1 iron and folic acid tablet twice a day orally for 3 months. The primary outcomes are changes in the amount of uterine bleeding evaluated by the Pictorial Blood Loss Assessment Chart, changes in the duration of bleeding, and attainment of a normal quantity of blood loss during the interval of cycles. The secondary outcome is changes in the Menorrhagia Impact Questionnaire.

Results: As of December 2024, a total of 79 patients have been enrolled. Data analysis should be completed by February 2026. The study will be reported following standard guidelines for reporting randomized controlled trials. Clinical results will be disseminated through conferences and peer-reviewed publications in a relevant journal.

Conclusions: The Ayurvedic approach may provide an evidence-based therapeutic tactic for the management of menorrhagia.

Trial Registration: Clinical Trial Registry India CTRI/2023/05/052929; https://tinyurl.com/3cd6mxrn

International Registered Report Identifier (IRRID): DERR1-10.2196/60801

(JMIR Res Protoc 2025;14:e60801) doi:10.2196/60801

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KEYWORDS

Ashokarishta; Trinakantamani pishti; tranexamic acid; menorrhagia; Raktapradara

Introduction

Normal menstrual bleeding is cyclical, with 3-5 days in durations and 50-60 mL of bleeding in normal color, as described in Ayurvedic classics. However, when the normal menstrual bleeding pattern is altered in reference to duration, amount, color, and cycle, the conditions are called *Artavadushti*; *Raktapradara* is one of them, and it is comparable to menorrhagia. In India, menorrhagia constitutes about 15% to 20% of all gynecological admissions in an institution. Of these, 43% of patients are aged 20-50 years. This condition is worsening because of the high prevalence of anemia among Indian women [1]. Heavy menstrual bleeding (HMB) can have a significant impact on women's lives. HMB or menorrhagia is clinically defined as greater than or equal to 80 mL blood loss per menstrual cycle [2,3]. It is, however, the woman's perception of her own menstrual loss that is the key determinant in a referral and, indeed, subsequent treatment. In allopathic medicine, various medical treatment options are available, but many women proceed to surgery due to treatment failure or hormonal side effects. Surgery introduces the risk of bowel, bladder, and ureteric damage, as well as hemorrhage, infection, and even death [4]. So, there is a clear unmet clinical need for better medical treatments for this benign but incapacitating condition. *Ashokarishta* is a compound drug, consisting of 14 drugs described in the *Stree rogadhikara* (female disorders) section of the *Bhaishajya Ratnavali* book of Ayurveda [5]. The *phalashruti* (benefits at the end of the composition) of this medicine says that, by using the medicine for more than one month, it cures pain due to menorrhagia, fever, several types of hemorrhages, hemorrhoids, etc. *Trinakantamani pishti* [6,7] is a drug also mentioned for *Raktapradara* (HMB or menorrhagia) in Ayurvedic classics. As the effect of this medicine is mainly in bleeding disorders, it was decided to evaluate its efficacy in *Raktapradara* (Table 1). Some encouraging work has been done on the effect of *Ashokarishta* [8-10] on *Raktapradara*, but no work has been carried out on *Trinakantamani pishti* along with *Ashokarishta*. Tranexamic acid is a safe and effective form of medical therapy in women with menorrhagia; it also increases the quality of life in these women [11]. So, this study is planned to evaluate the efficacy of Ayurvedic treatment modalities in the management of menorrhagia and to assess the efficacy of Ayurvedic intervention on the quality of life of the women with menorrhagia, compared to the control intervention (tranexamic acid).

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Table 1. Details of the investigational products.

Drug and components	Botanical name	Part used	Quantity
Trinakantamani pishti			
1. Trinakantamani	__[a]	—	1 part
2. Distilled rose water	—	—	As needed for *mardana* (triturate)
Ashokarishta			
1. Ashok	*Saraca asoca* L.	Stem bark	100 parts
2. Water for decoction (*kashaya*), reduced	—	—	256 parts
3. Guda (jaggery)	*Saccharum officinarum*	—	200 parts
4. *Dhataki*	*Woodfordia fruticosa* (L.) Kurz.	Flower	16 parts
5. *Ajaji*	*Nigella sativa* L.	Fruit	1 part
6. *Mustaka* (*musta*)	*Cyperus rotundus* Linn.	Rhizome	1 part
7. *Sunthi* (ginger)	*Zingiber officinale* Roxb.	Rhizome	1 part
8. *Darvi* (*daruharidra*)	*Berberis aristata* DC.	Stem	1 part
9. Utpala	*Nymphaea stellata* Willd.	Flower	1 part
10. *Haritaki*	*Terminalia chebula* Retz.	Whole plant	1 part
11. *Bibhitaka*	*Terminalia bellirica* (Gaertn.) Roxb.	Whole plant	1 part
12. *Amalaki*	*Phyllanthus emblica* L.	Whole plant	1 part
13. *Amrasthi* (*Amra*)	*Mangifera indica* L.	Endosperm	1 part
14. *Jiraka* (*sveta jiraka*)	*Cuminum cyminum* L.	Fruit	1 part
15. *Vasa*	*Adhatoda vasica* Nees.	Root	1 part
16. *Chandana* (*sveta candana*)	*Santalum album* Linn.	Heart wood	1 part

[a]Not applicable.

Methods

Study Setting

This study will be conducted at Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi, India.

Eligibility Criteria

Inclusion Criteria

Participants will include those aged 20-50 years with menorrhagia—that is, regular (21-35 days) cycle with HMB loss, subjectively or objectively defined (Pictorial Blood Assessment Chart [PBAC] score of more than 100 points) [12], or prolonged bleeding (bleeding more than >7 days) for 3 consecutive cycles—who are willing and able to participate in the study.

Exclusion Criteria

Participants with any of the following will be excluded: anemia (hemoglobin level <7%); hypertension; diabetes mellitus; hepatic or renal disease; cardiac disease; organic lesions of the reproductive tract due to conditions such as tuberculosis, carcinoma, and congenital deformities; pelvic inflammatory disease or cervicitis; evidence of malignancy, cervical intraepithelial neoplasia, or cervical carcinoma; history of untreated sexually transmitted disease or being HIV positive; past history of atrial fibrillation, acute coronary syndrome, myocardial infarction, stroke, or severe arrhythmia in the last 6 months; lactating women; current or previous use of oral contraceptive pills, glucocorticoids, antiandrogens, ovulation induction agents, antidiabetic drugs, antiobesity drugs, or other hormonal drugs recently (unless there is a washout period of 1 month); hypersensitivity to the trial drugs or any of their ingredients; currently participating in any other clinical trial or participated in past 6 months; or any other condition that the principal investigator thinks may jeopardize the study.

Study Interventions (Investigational Products)

Participants in the treatment group will receive 250 mg of *Trinakantamanipishti* twice a day orally before meals, 20 mL of *Ashokarishta* twice a day orally before meals, and 1 iron and folic acid tablet (100 mg of elemental iron and 1.5 mg of folic acid) twice a day orally after meals for 3 months. The treatment group's medicines (investigational products) will be procured from Good Manufacturing Practices–certified pharmacies, namely, Indian Medicines Pharmaceutical Corporation Ltd. and Central Ayurveda Research Institute, along with the Certificate of Analysis to ensure the quality and safety of the medicines. The study drugs will be kept in a secure place and will only be supplied to the participants under the guidance of the investigator. A record will be maintained for the drug dispensed.

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Any discrepancies between amounts dispensed and returned will be explained.

Participants in the control group will receive a 500-mg tranexamic acid tablet thrice a day for 7 days from the first day of menses for 3 cycles and 1 iron and folic acid tablet twice a day orally for 3 months.

Strategies to Improve Adherence to Study Protocol

The compliance of taking trial drugs will be assessed at each visit during the follow-ups (30-day intervals) by assessing the approximate quantity consumed. The participants will be asked to return the empty container of medicine at the time of each follow-up visit. Repeated reminders will be given over the phone or through family members and project staff for regular taking of medicine.

Outcome Measures

Primary Outcome Measures

Primary outcome measures are changes in the amount of uterine bleeding evaluated by the PBAC, changes in the duration of bleeding, and the attainment of a normal amount of blood loss during the interval of cycles, evaluated at baseline, the end of every cycle up to 3 cycles, and follow-up visits.

Secondary Outcome Measure

The secondary outcome measure is changes in the Menorrhagia Impact Questionnaire (MIQ) [13], evaluated at baseline, the end of intervention period, and follow-up visits.

Safety Outcomes

The safety of the trial intervention will be evaluated by recording the incidence of adverse events on every scheduled follow-up visit. All adverse events during the study timeline will be recorded and monitored per the Good Clinical Practice Guidelines. The investigator will report the same to the institutional ethics committee and the sponsors at the earliest opportunity. To assess the safety, hematological and biochemical investigations such as complete blood count and liver and kidney function tests will be done at baseline and the end of the intervention period.

Sample Size

To calculate the sample size, we anticipated a difference of 70 units in average PBAC score after treatment between the two groups (*Trinakantamanipishti* along with *Ashokarishta* vs tranexamic acid tablet), with an SD of 137 units based on the results of the previous study [14]. With 95% confidence level (α=.05) and 80% power, the number of patients to be enrolled in the study was calculated using the following formula:

where $Z_{1-\alpha/2}$=1.96, $Z_{1-\beta}$=0.84, σ=137, and δ=70.

Expecting a dropout rate of 15%, the number of patients is estimated to be 60 + 9 = 69. Thus, approximately 70 patients should be enrolled in each group.

Randomization and Allocation

A randomization chart will be generated with the help of computer-generated random numbers. Participants will be randomized in a ratio of 1:1 to either of the two groups. The randomization schedule will be strictly controlled and remain with the biostatistician/data analyst. Sequentially numbered, sealed, opaque envelopes will be used to conceal the allocation.

Study Procedure

The participants will be screened for menorrhagia as per the inclusion criteria. Prior to any trial-related activity, the investigator will give the verbal information and written information in a printed form about the trial to the participant, parents, or guardians to read and understand. The investigator would ensure that the participants are fully informed about the aims, procedures, discomforts, and expected benefits of the trial. It must be emphasized that participation is voluntary, and participants have the right to discontinue the trial at any time without any prejudice. A voluntary, signed informed consent will be obtained from the participants prior to any clinical trial–related procedure.

After the screening, if the participants are found to be suitable, then they shall be enrolled in the study after signing the consent form. The required investigations will be carried out, and subsequently, within one week or as soon as laboratory values are received and found to be within permissible limits, the participants will be enrolled in the study, and that day will be considered visit 1 or the baseline visit. The treatment will be given to the participants after fulfilling all the formalities as per the protocol. The subsequent follow-ups will be on the 30th day (visit 2), the 60th day (visit 3), the 90th day (visit 4), the 120th day (visit 5), and the 150th day (visit 6; ie, completion of active treatment). Participants will visit the study site 6 times during the trial. The details of the activity during each visit are presented in Table 2 and Figure 1.

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Table 2. Study schedule.

Components	Screening	Baseline (visit 1)	30th day (visit 2)	60th day (visit 3)	90th day (visit 4)	120th day (visit 5)	150th day (visit 6)
Informed consent	✓						
Demographics and medical history		✓					
Laboratory investigations	✓		✓		✓		
Assessment of clinical signs and symptoms		✓	✓	✓	✓	✓	✓
Assessment of the MIQ[a]		✓	✓	✓	✓	✓	✓
Clinical examination	✓						
Assessment of the PBAC[b]		✓	✓	✓	✓	✓	✓
Assessment of ADRs[c]			✓	✓	✓		
Assessment of drug compliance			✓	✓	✓		
Issue of trial drugs every 20 or 30 days							

[a]MIQ: Menorrhagia Impact Questionnaire.
[b]PBAC: Pictorial Blood Loss Assessment Chart.
[c]ADR: adverse drug reaction.

Figure 1. Flowchart of the study procedure.

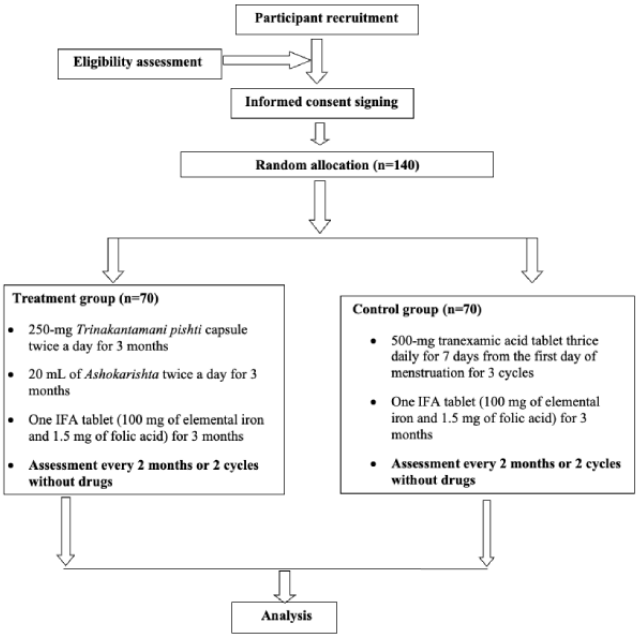

Timelines With Deliverables

The total study period spans 36 months and is divided into four distinct phases. During the initial phase, which lasts from months 1 to 6, efforts will focus on procuring standard trial drugs and finalizing laboratory arrangements. Additionally, tasks such as staff recruitment, equipment procurement, and finalization of case report forms (CRFs) will be undertaken. The second phase, covering months 7 to 23, will be dedicated to the recruitment of participants for the study. Subsequently, months 24 to 34 will constitute the treatment period, during which participants will undergo interventions as per the study protocol, with follow-up assessments conducted accordingly. Finally, in the last phase spanning months 35 to 36, data compilation, analysis, report preparation, and publication will be the primary activities, culminating in the dissemination of study findings.

Laboratory Tests

The laboratory tests (hematological tests, biochemical tests, and ultrasonography) will be conducted in a National Accreditation Board for Testing and Calibration Laboratories–accredited laboratory. Hematology (hemogram, lipid profile, fasting blood sugar and postprandial blood sugar levels, and hemoglobin A_{1c} level); liver function test; kidney function test; venereal disease research laboratory test; HIV test; hepatitis B surface antigen test; ultrasonography (transabdominal sonography or transvaginal sonography); coagulation profile; hormonal test like thyroid profile, serum prolactin test, serum follicle-stimulating hormone test, and serum luteinizing hormone

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test; routine urine culture; and microscopic urinalysis will be carried out at baseline and the end of the treatment (90th day). Coagulation profile will also be done at the middle of treatment (30th day).

Data Collection, Management, and Analysis

The data collection will include all information in the CRFs. All participants will be assigned an enrollment number, which will be used on CRFs and electronic databases. Consent forms and CRFs will be stored in locked cupboards, and electronic databases will be password protected. The data will be entered using the double-entry method for accuracy. All data will be accessible to the principal investigator and coinvestigators during and after the study has been completed and will be available to sponsors and monitors as required. Data will be stored for 5 years before being destroyed. In case of dropout, 10% data will be inserted through the imputation technique. Proper documentation will be done to ensure its accurate interpretation and verification. The analysis will be done by the Central Council for Research in Ayurvedic Sciences statistical unit.

Statistical Methods

Continuous variables will be presented as mean, SDs, medians, and ranges. Categorical variables will be summarized with frequencies and percentages. When inferential analyses will be conducted for continuous variables, they will be tested for normality. Nonparametric methods will be used to compare nonnormal data. Within-group comparison will be done using a paired *t* test (1- or 2-tailed, as suitable), while between-group comparisons will be done using an independent sample *t* test (1- or 2-tailed, as suitable) for the data following normal distribution. Nonnormal data within the group will be compared using the Wilcoxon sign rank test, while between groups comparison will be done by using the Mann-Whitney *U* test. Categorical data between groups will be compared using the chi-square or Fisher exact test. A 2-sided *P* value of <.05 will be considered statistically significant. Per-protocol and intention-to-treat analyses will be carried out at the end of the study. All data will be analyzed using Stata (version 16.1; Stata Corp).

Ethical Considerations

This research protocol had been reviewed and approved by the institutional ethics committee of Vardhman Mahavir Medical College and Safdarjung Hospital (S. No. IEC/VMCC/SJH/NOTE/2023-Feb/06). Participants will receive an information sheet with the research details given in two languages (Hindi and English). Voluntary signed informed consent will be obtained from the participants before any clinical trial–related procedure. The participants will be informed by the investigator that all trial data recorded will be treated with strict confidence. During documentation and analysis of the trial, the individual participant will only be identified by their enrollment number.

Participant confidentiality will be guaranteed, and only researchers will have access to the data. Participants are nominally compensated for their loss of wages and transportation costs by paying an amount of IND 100 (US $1.19) for every visit to the hospital during the study period.

Data Safety and Monitoring

The safety of the trial intervention will be evaluated by recording the incidence of adverse events on every scheduled follow-up visit. All adverse events during the study timeline will be recorded and monitored per the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use's Guideline for Good Clinical Practice. The investigator will report the same to the institutional ethics committee and the sponsors as soon as possible.

For facilitating appropriate reference standards for scientific, ethical, and safety issues before the trial begins, this protocol has been developed according to the 2013 SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) and CONSORT (Consolidated Standards of Reporting Trials) statements [15].

After completion of the study on 25% of the total participants, the data will be analyzed for the safety of the trial drugs. The project monitoring committee will monitor the trial's progress through review meetings and site visits as per the requirement to ensure strict adherence to the trial protocol and correct completion of the CRF.

Drug Compliance

The compliance of taking trial drugs will be assessed at each visit during the follow-ups (30-day intervals) by assessing the approximate quantity consumed. The participants with equal to or more than 80% compliance will continue in the study. The participants will be asked to return the empty container of medicine at the time of each follow-up visit. Repeated reminders will be given over the phone or through family members and project staff for the regular taking of medicine.

Prior and Concomitant Medication

Participants will receive clear instructions not to take any medication other than the trial drugs for any condition without prior consultation with the investigators. The investigator will advise participants to promptly report any additional signs, symptoms, or unusual occurrences and to seek guidance accordingly. Additionally, the investigator will diligently document any other medications taken by the participants for comprehensive recordkeeping.

Rescue Medication

Permission will be given for the use of rescue medication for alleviating any emergency condition as per the discretion of the investigator. It will be documented in detail in the CRF.

Results

As of December 2024, a total of 79 patients have been enrolled. Data analysis should be completed by February 2026. The study will be reported following standard guidelines for reporting randomized controlled trials. Clinical results will be disseminated to the public through conference presentations and peer-reviewed publications in a relevant, open-access journal.

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Discussion

Conclusion

Ayurveda scholars correlate *Raktapradara* with menorrhagia (National Ayurveda Morbidity Code: EL-4) based on the similarities in causes, clinical features, and treatment. This paper describes the protocol for the Ayurvedic management of menorrhagia. We undertook a randomized controlled trial to objectively assess the efficacy of Ayurvedic treatments for the management of menorrhagia and compared it with standard conventional treatment. The changes are assessed objectively by using the PBAC score and MIQ as the outcomes for participants with menorrhagia.

Studies have demonstrated promising results of some Ayurvedic interventions for managing *Raktapradara*. With this study, we aim to observe the effectiveness and safety of Ayurvedic management using the formulations of *Ashokarishta* and *Trinakantamani pishti* in reducing symptoms associated with menorrhagia, such as HMB. If beneficial, this study could contribute significantly to integrative approaches for managing menorrhagia.

Strengths and Limitations

The strengths of this study include its randomized design and the inclusion of enough participants to allow for adequate statistical power for subgroup analyses. This study uses the PBAC score and MIQ, which are well-validated instruments to assess menorrhagia.

One potential limitation of this study is that the investigators were aware of the participants' group assignment, and therefore, bias in favor of any particular group cannot be excluded. However, every effort was made to ensure blinding of the participants during the group allocation. An independent evaluator blind to study conditions was responsible for administering all study measures. The protocol may also serve as a reference for the planning of similar clinical trials.

Acknowledgments

The authors are thankful to the institutional ethics committee, for approving the protocol, and to the Vardhman Mahavir Medical College and Safdarjung Hospital, for allowing the study to be conducted at their facilities. The study was funded by the Central Council for Research in Ayurvedic Sciences, New Delhi, India. Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Data Availability

The findings will be disseminated to the public through conference presentations and published in open-access, peer-reviewed journals. Analyzed data will be made available for interested researchers with a reasonable request after the publication of the results.

Authors' Contributions

SR, SM, US, SO, and BG developed the protocol. SR and SM registered the protocol and generated the first draft of the manuscript. SM revised the manuscript according to suggestions. The manuscript was reviewed and approved by all authors.

Conflicts of Interest

None declared.

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
CRF: case report form
HMB: heavy menstrual bleeding
MIQ: Menorrhagia Impact Questionnaire
PBAC: Pictorial Blood Loss Assessment Chart
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Cooperative Virtual Reality Gaming for Anxiety and Pain Reduction in Pediatric Patients and Their Caregivers During Painful Medical Procedures: Protocol for a Randomized Controlled Trial

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Abstract

Background: The hospital experience is often marked by fear and pain, particularly for children undergoing medical procedures. Sedation is commonly used to alleviate patient anxiety, but it poses additional health risks. Caregivers, usually the parents, also experience emotional distress during the child's hospital stay, which can further exacerbate the child's anxiety and pain. While various interventions exist to ease patient distress, few consider the emotional well-being of caregivers.

Objective: This study aims to explore the effectiveness of a cooperative virtual reality (VR) game as a novel nonpharmacological solution to reduce anxiety and pain for both pediatric patients and their caregivers during medical procedures. Specifically, we aim to investigate whether the VR game "Sweet Dive VR" (SDVR), designed for children aged between 6 and 12 years to play with 1 caregiver, can alleviate anxiety and pain during different types of needle punctures and Kirschner-wire removal.

Methods: A prospective multicenter randomized clinical trial will be conducted. Eligible participants will be identified by scanning the hospital information system, and group allocation will follow stratified randomization. During the medical procedure, patients in the VR condition will play SDVR with a caregiver present, while patients in the control group will listen to a recording of gently crashing waves. Data collection will be carried out through self-reports of patients and caregivers using visual analog scales and questionnaires at 2 measurement time points: before and after the intervention. In addition, observation by the interviewers will occur during the intervention to capture emotional and pain reactions as well as interaction quality between patients and caregivers and smoothness of the procedure flow using a structured observation protocol. The measured variables will encompass patient affect and pain, caregiver affect, player experience, patient experience, and the flow of the procedure.

Results: As of November 2024, we enrolled 39 patients and caregivers, 28 of whom completed the study. Data collection is still ongoing.

Conclusions: Cooperative VR gaming, as exemplified by SDVR, emerges as a promising intervention to address anxiety and pain in pediatric patients while involving caregivers to support the emotional well-being of both parties. Our approach strives to foster positive shared experiences and to maintain trust between children and caregivers during emotionally challenging medical situations.

Trial Registration: German Clinical Trial Register (DRKS) DRKS00033544; https://drks.de/search/en/trial/DRKS00033544

International Registered Report Identifier (IRRID): DERR1-10.2196/63098

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KEYWORDS

virtual reality; extended reality; mixed reality; serious game; video game; pain; anxiety; stress; child; caregiver; patient experience; well-being; medical procedures; punctures; distraction; intervention

Introduction

Background

Fear and pain characterize the hospital experience. Children, due to a lack of understanding of the situation, often show extreme anxiety reactions even in objectively harmless situations such as magnetic resonance imaging [1]. Hence, the patient's anxiety and stress can complicate treatment procedures and interfere with the healing process [2-4]. As a result, it is a common practice to sedate patients by administering medication. However, the use of such medication is associated with additional health risks [5], particularly in the context of child development [6]. An additional factor that can influence the emotional experience of child patients is their caregivers, in most cases a parent. Caregivers are also under extraordinary emotional pressure during the child's stay in hospital. If a medical procedure causes intense fear or pain, it can strain the caregiver-child relationship, especially if the child perceives the caregivers as siding with medical staff instead of supporting them—for example, by helping to physically restrain the child [7]. As a result, anxiety, stress, and pain of patient and caregiver can mutually depend on and reinforce each other [8]. While there are numerous pharmacological and nonpharmacological options to ease the patient, the experience of the caregivers is rarely the focus of such interventions.

Therefore, it is advisable to explore nonpharmacological solutions to reduce anxiety and pain. Distracting patients from the medical situation in a controlled manner is an approach that has proven successful for a large variety of media such as movies, music, or toys [9]. The use of immersive technologies such as digital games and virtual reality (VR), in particular, has been shown to be effective in reducing anxiety and pain in a variety of medical situations in numerous studies, especially for needle-related procedures, burn care, and in dental medicine [9-13]. However, these solutions typically address only the patient, which may lead to patients and caregivers feeling disconnected from each other. VR has the potential to result in patients feeling separated from their caregivers due to the sensory shielding provided by wearing a head-mounted display (HMD), which is necessary to create the desired level of immersion. This, in turn, could have an unintended anxiety-increasing effect.

Approach

We are pursuing a new approach in our work: we have developed the cooperative, asymmetrical VR game "Sweet Dive VR" (SDVR) that involves the patient and a caregiver equally in the gameplay and promotes joint communication [14]. In this way, both parties are distracted from the intimidating medical situation without being artificially separated from each other. Involving caregivers in the game, thereby creating positive shared player experiences, can be a way of maintaining children's trust and reducing feelings of helplessness for both children and caregivers [15]. In addition to the game-related interaction with the child, the caregivers are given the task of reacting to certain steps of the medical procedure (eg, the application of a disinfectant or an oxygen cannula) by triggering in-game events. In this way, we achieve synchronization of the virtual world with the patient's real-world sensory impressions, which is intended to preserve and strengthen immersion for the patient on the one hand, while supporting the caregivers' sense of agency. SDVR was designed for children aged between 6 and 12 years and for application during needle-related procedures, in particular port punctures, bone marrow punctures, central and peripheral venous catheterization, and venipunctures. However, we are also planning to test our approach with more painful procedures, such as Kirschner-wire removal.

Objectives

While several different works have successfully used VR games as a distraction during painful procedures [14-16], SDVR is, to the best of our knowledge, the first game that involves both the patient and the caregiver and aims to enhance the emotional experience of both. This study aims to evaluate the effectiveness of using cooperative VR games during medical procedures to improve patient and caregiver experiences. Specifically, we examine whether SDVR can reduce patients' anxiety, pain, and agitation; improve cooperation; and positively influence caregivers' emotional states compared to a control condition in which a calming atmosphere is created by playing natural ocean wave sounds to promote relaxation.

Methods

Hypotheses

In this study, we investigate whether targeted distraction from anxiety- and pain-inducing medical procedures through cooperative VR gaming can reduce experienced pain and anxiety while fostering well-being for both the patients and their caregivers. A list of our hypotheses is presented in Textbox 1. Hence, the primary outcome of the study is a reduction in pain and anxiety ratings of the patient (hypothesis 1) as well as an improvement in the caregiver's emotional experience (hypothesis 2). Our intervention relies on targeted distraction through sensory immersion for the patient as well as cognitive immersion and game fun for the patient and caregiver. Thus, distraction from the medical procedure represents a further end point of the study (hypothesis 3 and hypothesis 5).

The smooth execution of the medical procedure, characterized by the cooperativeness of the patient and caregiver, the needlessness of sedation or fixation, and an uninterrupted flow, will be assessed as a secondary end point (hypothesis 4). Moreover, this study aims to evaluate the quality of SDVR with respect to the player experience of both patient and caregiver (hypothesis 5).

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Textbox 1. A list of hypotheses.

Hypothesis 1: patient affect and pain

a. Patients playing Sweet Dive VR (SDVR) during the procedure will report reduced levels of *anxiety* compared with those in the control group.

b. Patients playing SDVR during the procedure will report reduced levels of *pain* compared with those in the control group.

c. Patients playing SDVR during the procedure will exhibit decreased *motoric activity* compared with those in the control group.

d. *Observer's* ratings of *patient cooperation* during the procedure will be improved in the SDVR group compared with those in the control group.

e. *Caregivers'* ratings of patient *pain* will be lower in the SDVR condition than in the control condition.

f. *Caregivers'* ratings of patient *anxiety* will be lower in the SDVR condition than in the control condition.

g. *Observers'* ratings of patient *pain* will be lower in the SDVR condition than in the control condition.

h. *Observers'* ratings of patient *anxiety* will be lower in the SDVR condition than in the control condition.

Hypothesis 2: caregiver affect

a. Caregivers in the SDVR group will experience more *positive emotions* during the procedure compared with those in the control group.

b. Caregivers in the SDVR group will experience fewer *negative emotions* during the procedure compared with those in the control group.

c. *Observer's* ratings of *caregiver cooperation* during the procedure will be improved in the SDVR group compared with those in the control group.

Hypothesis 3: player experience

a. The more positive the player experience of the patients in the SDVR group is, the lower will be the *patients'* intensity of *anxiety* during the procedure.

b. The more positive the player experience of the patients in the SDVR group is, the lower will be the *patients'* intensity of *pain* during the procedure.

c. The more positive the playing experience of the *caregivers* in the SDVR group, the less negative will their *emotional experience* be.

Hypothesis 4: patient experience

a. In the SDVR condition, more patients will have a feeling of *being in control over the situation* than those in the control condition.

b. In the SDVR condition, more patients will report being *distracted* from the procedure than those in the control condition.

c. The number of *patients* reporting that SDVR reduced their *agitation* will be greater than those reporting that listening to ocean waves reduced their agitation.

d. *Patients* in the SDVR condition will be more *surprised by the pain* than those in the control condition.

Hypothesis 5: flow of the procedure

a. The *observers'* rating of the *overall quality of the procedure* will be higher in the SDVR condition than in the control condition.

As interviewing children about their emotional and physical experience is a methodological challenge due to various biases, and because we strive for an objective assessment of the patient's and caregiver's experience, we follow a comprehensive, holistic approach in our methodology and the instruments used. In addition to the patients' and caregivers' self-reported emotional experiences, we also ask the caregivers to assess the patient's anxiety and pain. In addition, the interviewers use a structured observation protocol to assess the patient's experience, the gaming situation, and the course of the medical procedure.

Potential Confounding and Influencing Factors

The meta-analysis carried out by Eijlers et al [11] indicates that VR-based distraction from anxiety and pain is more efficacious in younger children than in older children. Age and gender influence the perception of pain and anxiety during medical procedures. Younger children tend to report more pain during procedures such as venipuncture [16]. In self-reporting, girls tend to report more pain than boys [17]. However, older children and boys tend to rate pain and anxiety differently compared to younger children and girls [17]. Age and parental predictions of distress are substantial predictors of pain and anxiety on blood tests [18]. Therefore, age and gender will be considered as possible influencing factors in the analysis.

Our intervention addresses a range of medical procedures that have shown to be highly anxiety- and stress-inducing in pediatric patients but can generally be performed without anesthesia. It is possible that patient anxiety and pain ratings differ for different procedures and that these perceptions influence the effect of our intervention.

Fundamental anxiety as a patient characteristic (ie, trait anxiety) is also a likely influencing factor for anxiety and pain ratings [19]. Furthermore, there is evidence in the literature of a link between perceived anxiety and postoperative recall of pain [20], which could influence patients' retrospective assessment of their pain. Therefore, we will consider the assessment of the caregivers and the observation of the interviewers in our study.

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A well-documented phenomenon that negatively impacts the VR gaming experience is simulator sickness, which includes symptoms such as nausea, dizziness, headaches, and eye strain. There is evidence that children are less likely to react to VR exposure with these negative symptoms [21], but there have been few studies on the possible relationship between age and different forms of visually induced motion sickness. Nevertheless, we will record any indications of simulator sickness before and after the intervention as the described symptoms may relate to patients' general health state. We have elaborated more on that topic in the Methods section, under the Simulator Sickness subsection.

Previous hospital experience, particularly about the previous interventions of the same or similar nature, as well as needle-related phobias and trauma, can influence the patient's emotional response to the medical situation and will therefore be documented during screening. The actual diagnosis will also be recorded to assess the overall psychological situation of the patient and caregiver.

Ethical Considerations

This study was approved by the ethics committee of the medical faculty of the University of Duisburg-Essen (22-10873-BO). The ethics committees of the other study centers, Universitätsklinikum Hamburg-Eppendorf, Germany, Ethik-Kommission der Ärztekammer Hamburg (approval 2023-200739-BO-bet) and Ethikkommission des Universitätsklinikum Schleswig-Holstein, Lübeck, Germany (approval 2023-708), also saw no ethical or legal objections to this study.

All patients and caregivers will be fully informed about the background and procedure of the study during the recruitment process before they consent to participate in the study. Both the legal guardians and the children must give their written consent to participate in the study. They will be informed about the protection of their personal data and their digital rights in accordance with the European General Data Protection Regulation.

During the onboarding process, the collected data will be pseudonymized. An individual, random participant ID will be created during enrollment and stored with the patient ID separate from the survey answers. Once data collection is complete, the pseudonymization table will be deleted so that the data are anonymous from this point on. The children will be informed of the possibility that they might undergo the procedure in the control group without HMD and sedation or anesthesia. Participants in the control group will be allowed to try the game after completing the medical procedure.

Study Design

The study presented here is a prospective multicenter randomized nonblinded clinical trial. This study refers to protocol version 19 (March 1, 2023), which is registered in the German Clinical Trials Register (DRKS00033544). Any changes to the protocol will be submitted as an amendment to the responsible ethics committee of the University Hospital Essen for approval and filed in the DRKS. Data collection will take place at the University Hospital Essen, the University Hospital Schleswig-Holstein in Lübeck, and the University Hospital Hamburg-Eppendorf, all 3 located in Germany. Patients in the VR condition will play the game SDVR with 1 caregiver during the medical procedure. The beneficial effects of VR and digital games in distracting from anxiety and pain compared to the standard of care (ie, no intervention for distraction or sedation) have been demonstrated in numerous studies [9,11-13]. Therefore, our study particularly focuses on the effect of the shared gaming experience and addresses both the patient and the caregiver as recipients of the distraction and mood-enhancing intervention. Furthermore, to avoid the results being biased simply by the patient's experience of getting an "extra treatment" and additional attention from the medical staff during participation in the study, we will compare the experimental condition with a control condition in which the patients and caregivers will also receive special treatment. Acoustic relaxation techniques are straightforward and unobtrusive to implement in medical procedures, making it possible to address both patients and caregivers simultaneously. In contrast to guided imagery, which requires active mental engagement—often challenging in stressful or painful situations—nature sounds offer a passive form of relaxation. This passivity makes them more accessible and appealing across a range of ages and cognitive abilities. Another option could be passive music therapy; however, natural sounds present a more universally neutral and calming experience, as they bypass personal musical preferences and the emotional resonance often associated with music. Therefore, we chose to play a recording of ocean waves to foster a calming atmosphere during the procedure.

Procedure

A diagram of the study procedure is shown in Figure 1. Patients meeting the eligibility criteria (Textbox 2) will be identified in the hospital information system. Patients and their caregivers will then be contacted by telephone or during their next stay in the hospital. They will be fully informed about the background and aim of the study, the procedure, and the 2 experimental conditions. Patients and caregivers will then have at least 24 hours to consider whether they want to participate. Refusals and their reasons will be recorded anonymously.

If they agree to participate, patients and caregivers will be asked to give their written consent. During registration, the patients will then complete the screening questionnaire together with an interviewer, based on which the randomized, stratified group allocation will be automatically performed. All questionnaires aimed at patients will be completed together with the interviewers. The task of the interviewers is to read out the questions and items if necessary and to help with comprehension problems. The interviewers are trained accordingly so that they do not interfere with the patient's response behavior and do not suggest answers.

The participants will be requested to arrive 60 minutes before the actual appointment. During this time, the patients and caregivers will fill out the preexamination questionnaires in parallel. The participants will be reminded once again that participation is voluntary and that they can withdraw their participation at any time.

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Figure 1. Study procedure timeline. Participants are assigned to either the experimental group (ie, Sweet Dive VR; SDVR) or the control group (ie, ocean waves). Pre- and postexamination questionnaires are administered to patients and caregivers. The interviewers assess the situation during the intervention using an observation protocol. CG: control group; EG: experimental group.

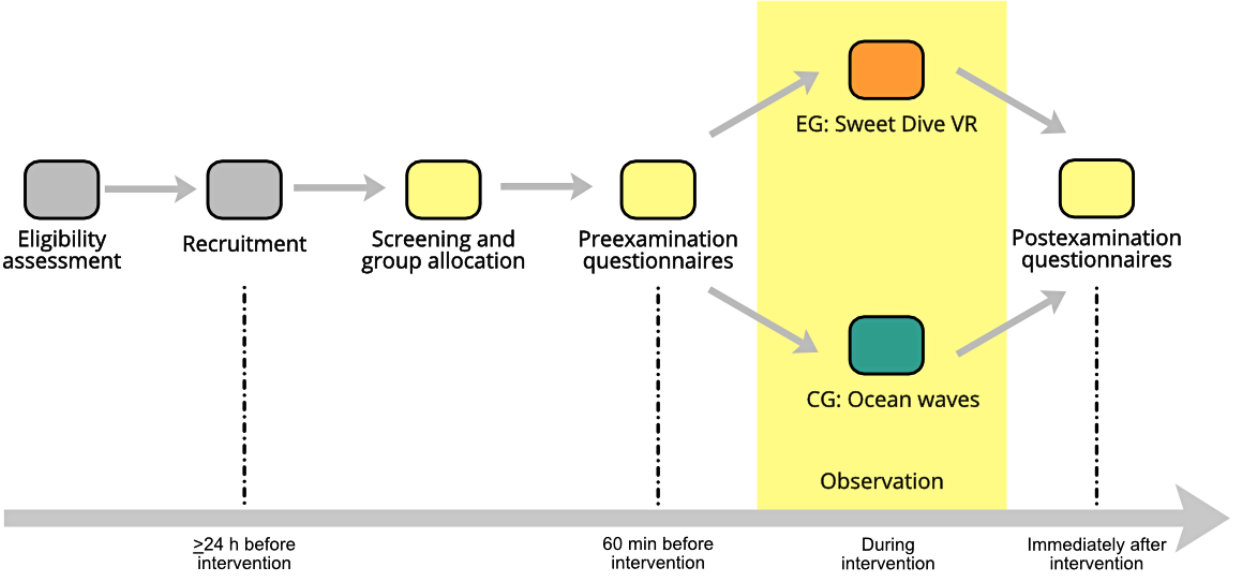

Textbox 2. Participant inclusion and exclusion criteria.

Inclusion criteria

- Age 6 to 12 years (applies for patients only)
- Procedure possible without sedation or anesthesia (applies for patients only)
- Sufficient knowledge of German (applies for patients and caregivers)
- Ability to hold and operate a game controller (applies for patients and caregivers)

Exclusion criteria

- Visual impairments (eg, lack of stereo vision and color blindness; applies for patients only)
- Severe cognitive impairments (as assessed by the caregivers and physicians; applies for patients and caregivers)
- Diagnosed with epilepsy (applies for patients only)

Termination criteria

- Desire to end participation (applies for patients and caregivers)
- Clear signs of severe simulator sickness (applies for patients only)
- Extreme pain (applies for patients only)
- Extreme anxiety (applies for patients only)
- Other adverse events (applies for patients and caregivers)

In the SDVR condition, patients and caregivers will receive a verbal, written, and illustrated explanation from the interviewer about the process, goal, and controls of the game as well as a brief introduction to the background story either as a short video or in the form of a short picture story. The caregivers will be instructed that they can start the game using the buttons on the controller and trigger events in the game that correspond to the treatment steps.

After the patients and caregivers have entered the examination room, in the SDVR group, the interviewer will help the patient put on the HMD and hand them the controller. The caregivers will receive the game controller and can then start the game session. In the control condition, the audio file will be played from a tablet or notebook.

We made special efforts to make the setup process as straightforward and quick as possible to enable noninvasive and seamless integration into the medical procedure. The VR app starts automatically as soon as the HMD is switched on (ie, the so-called “kiosk mode”). The necessary realignment of the perspective in the virtual world to the patient’s position can be triggered simply by pressing a button on the game controller. The technical setup process, including a functional test of all components (eg, Bluetooth connection to the game controller), takes just 5 minutes on average and can be prepared before the

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actual treatment. Setting up and adjusting the HMD for the patient and handing over the game controller to the caregiver takes a further 1 to 2 minutes on average.

During the procedure, the interviewer will observe the medical situation, the patient's reactions, and the interaction between the patients and the caregivers. The observations will be documented in an observation protocol.

At the end of the intervention, the postexamination questionnaires will be completed by the patients and caregivers. Interruptions and premature terminations of the intervention will be recorded, and the reasons will be noted. Children in the control condition will be allowed to try out the game after the end of the experiment.

If a participant wishes to terminate the intervention or if one of the termination criteria described in Textbox 2 is met, the intervention will be discontinued immediately, and the participant will return to the standard of care, and a note will be made in the observation protocol.

Participants

Sample

Patients requiring port puncture, lumbar puncture, peripheral or central venous catheter insertion, or Kirschner-wire removal will be enrolled, each with 1 caregiver. Given the complexity of the planned study setting and its integration into the clinical processes, we performed a sensitivity analysis to ensure an appropriate test strength and sample size. We anticipate that the recruitment of 78 patients and caregivers each is feasible. On the basis of a power analysis with the G*Power software [22] and starting from a 2-sided *t* test with a significance level of α=.05 and a test power of 80%, we determined that a medium-size effect of approximately Cohen *d*=0.64 can be achieved with a corresponding sample size of 39 participants per group. In view of these statistical parameters and considering the objectives of the study, we decided that recruiting 26 participants in each of the 3 participating study centers would provide an appropriate balance between practical feasibility and statistical power.

Randomization and Stratification

Assignment to the experimental conditions will be automated by a study management software. The recruiters will have no opportunity to influence the assignment at any time. Allocation will use the method of stratified randomization using a minimization algorithm. Consequently, the patient-related variables (ie, strata) used for sample stratification, are as follows: (1) trait anxiety (State-Trait Anxiety Inventory for Children–trait anxiety), (2) age, (3) type of intervention, (4) previous experience with the procedure, and (5) sex. The minimization algorithm attempts to allocate a new patient to a group in such a way that the difference between the 2 groups is minimal for each stratum. If no clear allocation can be achieved with this procedure, a random allocation will be made.

Material

Experimental Condition: SDVR

The players' mission will be to catch as many fish as possible for a medical examination after a cargo ship lost a container filled with candy. The patient and 1 caregiver will play the game cooperatively. The core mechanic of SDVR is attracting and catching fish. To attract a fish, the patient can drop a piece of candy into the water by pressing a button. A transport box moves horizontally on the upper edge of the screen from left to right and back. When the box is precisely above the fish, the patient must press another button at the right moment to bring it down and cover the fish. In the next step, the patient must inform the caregiver verbally so that the caregiver can press a button on the gamepad to move the box upward. The fish is then considered to be collected, and the process can start all over again. The number of fish collected will be shown to the VR player in a head-up display (Figure 2). The gameplay is infinite; that is, there is no fixed game end or goal. This way, we can respect the variable length of the treatment.

Figure 2. In "Sweet Dive VR," the patient must attract a fish with candy and move the box down in the right moment to collect it. Next, the caregiver must move the box up again. The head-up display in the upper-left corner indicates the number of collected fish (top row) and events associated with the medical procedure triggered by the caregiver (bottom row).

The game was designed to be played in a supine position (Figure 3). Consequently, the player's perspective has been adjusted so that, while lying on their back, they not only look up at the virtual sky (ie, the virtual water surface as in the case of SDVR) but can also see the horizon and the ground. By slightly shifting the virtual camera, a natural visual impression is possible, suggesting that the player is standing. In numerous previous

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tests, we have not registered any negative effects such as simulator sickness.

The key feature of our game design is the inclusion of a caregiver in the gameplay as a second player. Through the asymmetrical game design [23], we can distract both the patient and caregiver from the treatment and create a shared positive experience. While both players must cooperate to pursue their shared objective (ie, catching the fish), they have different mechanics at their disposal to achieve that objective. However, not only are the actions available to the 2 players different but also the information about the game world is different. While the patient can see the game world via the HMD, the caregiver lacks all visual and auditory cues about the current game state (Figure 3). Thus, the caregiver is completely dependent on the communication of their child. Consequently, a high degree of concentration on the game events and the verbal communication of both players is required, which thus becomes an essential mechanic of the game and enhances the immersion of both players [14]. With the children giving verbal instructions to their caregivers, the game is designed to support their feeling of being in control over the situation. Moreover, the strong focus on communication between caregivers and children should enhance the sense of familiarity, security, and connectedness within the emotionally challenging situation. In addition to interacting with the child through the game, caregivers are assigned the task of responding to specific steps of the medical procedure (eg, the application of a disinfectant or an oxygen cannula) by triggering corresponding in-game events. This approach synchronizes the virtual world with the patient's real-world sensory experiences, thereby preserving and enhancing the patient's immersion. Concurrently, it grants caregivers a sense of agency and participation in the medical situation, reinforcing their involvement in the process.

As this study focuses on the description of the research protocol for the clinical evaluation of our approach, we refrain from delving deeper into the design rationale here and refer to the planned publication elsewhere.

Figure 3. Schematic representation of the medical procedure and the patient-caregiver interaction in the asymmetric game design.

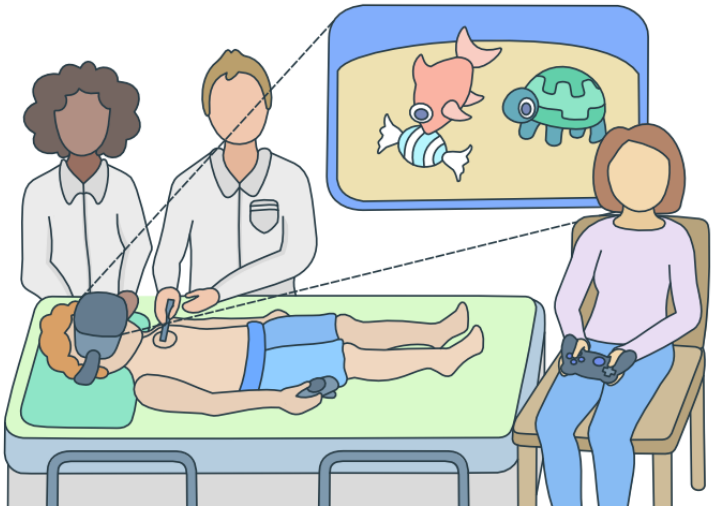

Control Condition: Audio Recordings of Ocean Waves

The research field of environmental psychology explores the positive effects of natural environments on human experience [24], including in medical contexts [25,26]. It has been shown that exposure to natural environments can reduce acute and anticipatory stress. Annerstedt et al [27] showed a stress-recovery–promoting effect of birdsong in a virtual forest scenario. Liszio et al [28] have shown that the audiovisual presentation of virtual underwater environments significantly reduces acute and anticipatory stress. However, research on the effect of solely auditive presentation of nature sounds on the emotional experience of patients in medical situations is scarce; however, there is some evidence in the literature. Moreover, several studies indicate a significant reduction of patient anxiety and agitation during percutaneous coronary intervention [29] and coronary artery bypass graft surgery [30,31] when listening to nature sounds.

In the control condition, a 30-minute recording of ocean waves will be played instead of the VR game. Recording will start with a 1-minute introduction by the same soothing voice that narrates the companion character "Turtle" in SDVR. From then on, only the sound of the waves will continue.

Hardware

Patients in the VR condition will play the game with a Pico G2 4K HMD (Figure 4, left). The device is a stand-alone HMD in which all calculations are performed on the device itself, so that no additional computer is required. The HMD has 3 df and can therefore only be used when sitting or lying down. User inputs are made via the associated controller, which resembles a simple remote control. A larger touchpad is located on the controller, which works like the directional pad on a typical game controller. In addition, the controller has a trigger button that is operated with the index finger. It can be controlled with 1 hand using either the left or right hand. We chose this hardware for the following reasons: the housing is comparatively easy to disinfect, as all external components are either hard plastic or rubber. Comparable devices from other manufacturers typically use foam covered with fabric for the face pad and elastic fabric for the headbands, which do not meet health care hygiene standards. Furthermore, no user account from third-party

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providers is required for operation. Apps can also be started in a so-called kiosk mode, that is, the corresponding app starts automatically when the device is switched on, which makes it much easier to use in the fast pace of everyday clinical practice. Finally, the standard controller's small design and reduced number of buttons simplify operation with small hands. Children have no problems holding the controller and reaching all the buttons with their fingers. The symmetrical design allows operating the controller with either the left or right hand.

For the caregiver, we will use a conventional gamepad as an input device for the game. The gamepad and HMD are connected via Bluetooth. The advantage of using a common gamepad is that many people are familiar with the layout of the buttons and the handling while the acquisition costs are low.

For data collection, we will use tablet PCs. These will also be used to play the recording of ocean waves in the control condition.

Figure 4. The Pico G2 4K head-mounted display with controller (left) and conventional gamepad (right) used in the experimental condition during the medical procedure.

Psychometric Assessment

Emotional Experience

State and Trait Anxiety

The State-Trait Anxiety Inventory is an established questionnaire for measuring anxiety [32] (Table 1). It was developed to measure both state anxiety and the personality characteristics of anxiety (ie, trait anxiety). The questionnaire consists of 2 scales, one for assessing state anxiety and one for assessing trait anxiety. In this study, we will use the German translation provided by Laux et al [33].

For the child survey, we will use the German translation of the adapted State-Trait Anxiety Inventory for Children [19]. This adaptation is characterized by a reduced number of 20 per scale items and a simplified response scale as compared to the original State-Trait Anxiety Inventory. In addition, the rating options are reduced to 3, ranging from 1 (low anxiety) to 3 (high anxiety).

In addition, we will implement a visual analog scale (VAS), which provides an effective method of assessing children's affective state as it offers a simple and easy to understand way of quantifying emotions. We will use the scale "Anxiety" by Gräßer et al [34]. This is based on a scale from 0 (not at all) to 10 (very strong). By simultaneously presenting an illustration the children can identify with and scaling the values from 0 to 10 on a line, children can express their emotional experience in a precise and differentiated way. For comparability between the children's self-report and the impressions of the caregivers and the interviewers, we will also ask the caregivers and the interviewers to rate the patients' pain perception on the same VAS.

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Table 1. Breakdown of the psychometric instruments administered (ie, questionnaires, visual analog scales, and self-designed questions) for each respondent group and measurement time.

Respondents and measurement time	Psychometric instrument
Children	
Screening	• STAIC-T[a]
Preintervention measurement	• STAIC-S[b] • VAS[c] anxiety • PANAS-K[d] • SSQ-C[e]
Postintervention measurement	• STAIC-S • VAS anxiety • PANAS-K • VAS pain • SSQ-C • Adapted PXI[f] for childreng • Patient experience • Presence
Caregivers	
Preintervention measurement	• PANAS • PANAS-C-P[g] • VAS anxiety (child)
Postintervention measurement	• PANAS • 0-P • VAS anxiety (child) • VAS pain (child) • PXI[h] • Player experienceg
Interviewers	
Observation	• CHEOPS[i] • Self-designed questions for assessing procedure flow

[a]STAIC-T: State-Trait Anxiety Inventory for children–trait anxiety.

[b]STAIC-S: State-Trait Anxiety Inventory for children–state anxiety.

[c]VAS: visual analog scale.

[d]PANAS-K: German translation of the Positive and Negative Affect Schedule for Children.

[e]SSQ-C: Child Simulator Sickness Questionnaire.

[f]PXI: Player Experience Inventory.

[g]PANAS-C-P: parent version of the Positive and Negative Affect Scale for Children.

[h]Sweet Dive VR only.

[i]CHEOPS: Children's Hospital of Eastern Ontario Pain Scale.

Positive and Negative Emotions

To assess the participants' affective state, we will use the positive affect negative affect schedule (PANAS) [35]. The questionnaire consists of 2 separate scales, one for positive affect (PA) and one for negative affect (NA). Each scale comprises a list of words that describe different emotions or moods. Respondents will be asked to indicate the extent to which they felt each of these words either "when thinking about the medical procedure" (before measurement) or "during the medical procedure" (after measurement).

For the caregivers, we will use the original questionnaire translated to German by Janke and Janke and Glöckner-Rist [36]. This version comprises 20 adjectives that describe emotional states. The rating scale describes the intensity with which these emotional states were experienced on a 5-point scale from 1 (not at all) to 5 (extremely). For the 2 dimensions PA and NA, the sum scores are formed from the intensity ratings of the corresponding items.

In addition to describing their own emotional experience, the caregivers assess the children's emotional states using the parent version of the Positive and Negative Affect Scale for Children, which we will use in the German translation provided by

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Großheinrich [37]. The scale consists of 2 subscales to determine the children's PA (12 items) and NA (15 items) according to the caregiver's impression on a 5-point scale from 1 (very little or not at all) to 5 (extremely).

The participating children will be administered an adapted version of the original PANAS (PANAS-C) developed by Laurent et al [38]. To our knowledge, because no official German translation of the children's version of the PANAS-C exists, we used this version as a starting point and compared the items with the German translations of the adjectives according to Janke and Glöckner-Rist [36]. As the PANAS-C comprises 30 items, rather than 20 items as in the version by Janke and Glöckner-Rist [36], additional adjectives for which no translation could be found were translated by the authors.

Pain

To measure the children's perceived pain, we will use the VAS "Pain" by Gräßer et al [34], equal to the measurement of anxiety (as mentioned earlier). Again, we will ask the patients, the caregivers, and the interviewers for a rating.

The interviewers will rate the observed pain-associated behavior of the child using the Children's Hospital of Eastern Ontario Pain Scale [39]. It can be used to monitor the effectiveness of interventions to reduce pain and discomfort in young children. The result is a pain score between 4 (no pain) and 13 (severe pain).

Player Experience

Overview

We will use the German translation of the Player Experience Inventory (PXI), which was developed by Graf et al [40], to assess the caregivers' experiences while they play SDVR. The PXI consists of 10 dimensions that describe aspects of the player experience, allowing for a systematic analysis of the game design. Each dimension comprises 3 items, which are rated on a 7-point scale ranging from –3 (strongly disagree) to 3 (strongly agree).

For evaluating the caregivers' experience, we will consider only the following constructs: "ease of control," "goals and rules," "challenge," "meaning," "curiosity," and "mastery and immersion." We will exclude the constructs "progress feedback," "audiovisual appeal," and "autonomy" from the evaluation of SDVR because the game does not have any audiovisual component for caregivers.

To date, there is no suitable and validated version of the PXI for children. As the PXI in its complete form is quite extensive and, in our experience, some item formulations are difficult for younger children to understand, we created a variant by selecting 1 item from each of the 10 dimensions that is clear and easy to understand. In the first round, 3 of the authors—an educator and health play specialist, a pediatric nurse with significant expertise in child-friendly medical language, and an entertainment computing specialist—independently selected 1 item per dimension that, in their opinion, met the criteria of representativeness for the dimension, child-appropriate concept complexity, and child-appropriate language. In the second step, the items for which there was no agreement between the 3 reviewers were discussed until consensus was reached. Moreover, we reduced the response options to a more child-friendly 5-point scale from −2 (strongly disagree) to +2 (strongly agree). It should be noted that this is a tentative, empirically unvalidated version. The data collected in the study may provide the basis for future efforts to develop a suitable player experience metric for children. For the sake of reproducibility and transparency, we included the final list of items in Multimedia Appendix 1.

The interviewers will be asked to assess the child's player experience by rating the statements "The child had fun playing."; "...was completely immersed in the play world."; "...gave the caregiver clear, game-related instructions."; "...understood what his role in the game was."; "...had no problems with the controls of the game"; and "...was optimally challenged by the game" on a 7-point Likert scale.

Presence

According to our assumptions, playing a VR game creates presence, which can be explained as a redirection of the user's attentional focus from the real to the virtual world. Hence, the experience of presence is an indicator of distraction from the medical situation. As there is no questionnaire designed for children to measure their sense of presence, we will use 5 items from the German Igroup Presence Questionnaire [41]. These 5 items describe how conscious the players were of the actual world and how real the virtual world seemed to them. The vocabulary used in these items is less abstract, which makes it easier for children to comprehend. The items are rated on a 7-point scale from 0 (strongly disagree) to 6 (strongly agree).

Simulator Sickness

Simulator sickness is a possible adverse side effect of VR exposure. To diagnose simulator sickness, we will use the Child Simulator Sickness Questionnaire adapted by Hoeft et al [42] and translated to German by us. The questionnaire comprises 7 items describing different symptoms summarized in dimensions "nausea," "oculomotor," and "disorientation." Each symptom is rated on a 3-point scale ranging between 0 ("not at all") and 3 ("very much").

However, it should be noted that our target group will consist of children who are sick. Thus, it is likely that some participants, due to their illness, will experience symptoms that are also associated with simulator sickness. Therefore, we will ask the participants to rate their symptoms before (ie, before measurement) and after (ie, after measurement) the VR exposure.

Patient Experience

We will use several simple self-designed questions to assess specific aspects of the patient experience from the perspective of the children, the caregivers, and the interviewers, including a sense of control, perceived distraction from the medical situation, excitement, and surprise at the onset of pain.

Procedure Flow

The interviewers will be asked to evaluate the course of the medical procedure using the statement "Please evaluate the willingness of the patient and the accompanying person to

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cooperate regarding the examination procedure" (1="very uncooperative"; 5="very cooperative"). In addition, they will be asked to rate the overall procedure on a 5-point star scale. We will also track all premature terminations of the intervention and the reasons given by participants, if any.

Data Collection and Analysis

All questionnaires will be completed electronically using the LimeSurvey (LimeSurvey GmbH) software to prevent data loss, incorrect data, or duplicate entries. Data will be stored anonymously on secured servers at the University Hospital Essen. The signed declarations of consent will be stored separately from the data collected. No identifying data will be stored in the dataset. The dataset will be stored separately from security-relevant patient data. Only the persons involved in the data analysis (SL and OB) will have access to the final dataset. Methods of descriptive and inferential statistics will be used to analyze quantitative data.

Results

Data collection is ongoing at the time of publication of this study. As of November 2024, we enrolled 39 patients and caregivers, 28 of whom completed the study (Multimedia Appendix 2 presents the participant flow diagram).

Discussion

Overview

Although anxiety and pain at the hospital cannot always be avoided, there are situations in which the emotional experiences of patients and their caregivers can be improved in a controlled and safe manner using comparatively simple means. VR gaming has proven to be a suitable, effective measure for distracting pediatric patients in pain and anxiety-ridden situations and thus as a nonpharmacological analgesic. We take this approach one step further and involve the caregivers in the game. Therefore, our aim is to make the medical procedure as pain-, anxiety-, and stress-free as possible for patients and their companions to enable the most positive patient experience possible. With our intervention, we aim to increase the cooperativeness of patients and caregivers and thus optimize the course of the medical procedure in terms of minimizing health risks for the patients as well as the necessary time and personnel resources. In the study presented here, we use the VR game SDVR, a cooperative multiplayer game based on cooperation between patient and companion specially designed for this use case.

Challenges

In our effort to enhance the experience for pediatric patients and their caregivers, we acknowledge the challenges associated with maintaining immersion and comfort during medical procedures, particularly when patients are visually and auditorily shielded from the real world; that is, some patients might feel uncomfortable when touched while visually and auditorily shielded from the real world [43]. In this context, it should be noted that there is currently no HMD that has been optimized for children's heads. All existing devices on the market are designed for adults in terms of weight, dimensions, lens distance, and so forth. Consequently, patients may perceive the HMD as a strain and wish to discontinue wearing it during the procedure. In the study, we record such cases and the patients' reasons.

Furthermore, unexpected real-world sensations (eg, phone calls, medical staff coming and going, and noises from medical equipment) that interfere with the virtual environment may "break" immersion and distraction [44]. Our approach addresses these concerns by integrating real-world stimuli into the VR gaming environment, thereby enhancing immersion and minimizing potential disruptions. By allowing the caregivers to trigger events in the game from the outside, real-world stimuli and game-related sensations can be aligned.

We might also encounter patients who are not eager to wear the HMD and engage in the game as they may perceive a sense of losing control over the situation. Previous adverse experiences with the same or similar medical procedures may have resulted in trauma and left patients so emotionally compromised that they perceive any additional treatment (ie, wearing the HMD) as an excessive burden. Reaching such patients with alternative interventions is generally very difficult.

As mentioned earlier, studies show that there is a relation between pain perception and age [16,17]. Against this background, the wide age range of our study is beneficial as it allows us to examine this relationship. In the results report, we will compare our findings with those of other studies to derive potential recommendations on the use of VR game–based pain distraction for pediatric patients of different age groups.

When designing our specific VR application SDVR, we already focused on seamless integration into medical treatment processes. Nevertheless, integrating VR into medical situations brings several challenges, and solutions and workflows must be found. These include the maintenance of the hardware (eg, system updates, battery charging, storage, and disinfection) but also the training of staff in the use of the technology. A VR solution can only provide real added value if it can be easily and safely integrated into the highly standardized processes of the hospital. It must be borne in mind that medical staff are primarily responsible for medical tasks, and experience has shown that, in many cases, they are already working to their capacity. In addition, previous experience and technological expertise cannot always be assumed. If a VR solution does not take these circumstances into account, there is a high risk that the technology will not be accepted and therefore not used. We tried to take these circumstances into account when developing SDVR and our intervention concept and want to use the planned study to check whether we have succeeded.

Limitations

There are some restrictions regarding the study design and methodology. Answering self-report questionnaires about their emotional and perceptual experience can be difficult for younger children. Although we use instruments specially adapted and, where available, validated for children. The interviewers are trained to assist the children in answering the questionnaires without influencing their answering behavior. However, bias cannot be completely ruled out due to children's psychoemotional and cognitive development including language

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skills, focus, and motivation. Sometimes the caregivers need to be kept from trying to influence the child when answering the questions. Given the nature of the matter, the study cannot be blinded. Therefore, it is not possible to fully objectify the interviewer's assessment during the intraoperative observation.

The duration of exposure to the alleged anxiety- and pain-reducing stimuli (ie, SDVR and recording of ocean waves) cannot be standardized due to the variable length of the medical procedure. Therefore, it is not possible to determine whether the duration of the intervention influences the experience of patients and caregivers. In addition, the reality of daily practice in the hospital does not allow for a fully standardized, perioperative measurement of the relevant experience-related variables. Therefore, our study protocol defines realistic time frames before and after the procedure, representing a reasonable compromise between temporal proximity to the events and feelings under investigation, integration into hospital operational processes, and standardization with sufficient time for the participants to complete the questionnaires.

Conclusions

This study represents a significant step forward in addressing the challenges of managing anxiety and pain in pediatric medical settings. By harnessing the immersive potential of VR gaming and actively involving caregivers in the process, we strive to create a supportive and stress-free environment for patients and their caregivers. Despite the complexity inherent in our presented study design, we are confident that our work contributes to advancing nonpharmacological interventions in pediatric health care.

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Data Availability

The datasets generated and analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Selection of items derived from the German version of the Player Experience Inventory used to assess player experience in children.
[PDF File (Adobe PDF File), 119 KB - resprot_v14i1e63098_app1.pdf]

Multimedia Appendix 2
CONSORT (Consolidated Standards of Reporting Trails) participant flow diagram.
[PDF File (Adobe PDF File), 56 KB - resprot_v14i1e63098_app2.pdf]

Multimedia Appendix 3
SPIRIT checklist.
[PDF File (Adobe PDF File), 147 KB - resprot_v14i1e63098_app3.pdf]

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Abbreviations

HMD: head-mounted display
PXI: Player Experience Inventory
SDVR: Sweet Dive VR
VAS: visual analog scale
VR: virtual reality

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Protocol

Assessing the Noninferiority of a Rhythm and Language Training Serious Game Combined With Speech Therapy Versus Speech Therapy Care for Children With Dyslexia: Protocol for an Investigator-Blinded Randomized Controlled Trial

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Abstract

Background: Specific learning disorder (SLD) of reading skills impacts approximately 7% of children. Speech and reading therapy is currently the gold-standard intervention for improving children's reading abilities. However, intensive interventions are difficult to implement. Recently, numerous studies have investigated the interest of game- and home-based training approaches to enhance children's motivation and facilitate intensive learning activities in home settings. The serious game Poppins Clinical integrates rhythm and specific written language exercises to improve reading skills in children with SLD.

Objective: This study aimed to assess the noninferiority of Poppins Clinical combined with a reading specialist session once every 2 weeks versus a reading specialist session every week, on the reading skills of children with SLD.

Methods: A total of 306 children with dyslexia will be recruited for this study and randomly assigned to either the experimental or control group. Children in the experimental group will use the serious game Poppins Clinical at home for 20 minutes, 5 days a week, and attend 1 reading therapy session every 2 weeks. The control group will participate in one reading therapy session per week. Poppins Clinical combines rhythm and language exercises integrated into an engaging game designed to maintain user motivation. We will use a noninferiority paradigm to assess the clinical impact of both interventions in terms of reading accuracy, reading speed, and reading comprehension. We will also investigate the evolution of phonological and visual-attentional skills. However, we will explore the impact of the protocol on parental stress and children's perception of their difficulties. Finally, we will also assess the cost of medical care and the impact of introducing the serious game Poppins Clinical on reading therapy. To facilitate recruitment and ensure the representativeness of our sample, the evaluation of the children will be conducted via videoconference using standardized tests that have been adapted for videoconference administration.

Results: Patient recruitment is expected to start in December 2024, with study completion by the end of August 2025.

Conclusions: This study should allow us to assess the interest in using the serious game Poppins Clinical in addition to reading therapy to improve reading abilities in children with SLD.

Trial Registration: ClinicalTrials.gov NCT06592911; https://clinicaltrials.gov/study/NCT06592911

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International Registered Report Identifier (IRRID): DERR1-10.2196/71326

(JMIR Res Protoc 2025;14:e71326) doi:10.2196/71326

KEYWORDS

dyslexia; serious game; rhythm; randomized controlled trial; non-inferiority protocol

Introduction

Specific learning disorder (SLD) with impairment in reading is a type of SLD classified as a neurodevelopmental disorder according to the *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]). The disorder affects reading and spelling abilities as well as related language processing skills such as phonological skills or auditory attention, despite adequate instruction, and in the absence of general cognitive or sensory deficits [1]. Yang et al [2] estimated the prevalence of SLD at around 7% in primary school children, suggesting that this disorder represents a considerable public health challenge.

It is now well established that SLD is caused by problems at the level of phonological representation, characterized by difficulty in accessing or manipulating speech sounds [1]. Recently, several studies revealed a deficit in the temporal processing of speech, which could explain the phonological deficit observed in people with SLD [3-5]. This deficit does not seem to be specific to the processing of speech but applies to the temporal treatment of the auditory signal in general. Effectively, the ability to process rhythm in music is linked with the processing of linguistic prosody in children and adults. However, musical rhythm perception skills predict metaphonological and reading skills [6,7]. People with SLD have difficulty estimating changes in the amplitude of the sound envelope over time [8], processing short durations [5], preattentive processing of vowel duration and voicing establishment [9], and also processing rhythmic information. This is particularly the case in the synchronization of simple rhythmic sequences, such as a metronome, or complex ones, such as music, where people with SLD are more variable [4,10,11]. They also have difficulty identifying whether a sequence is regular or not [11,12]. Rhythm perception and production skills even predict reading skills in children with SLD with reading deficits [12]. Regarding the strong link between rhythm perception and reading skills, several studies tried to improve reading skills in children with SLD through musical training [13]. Among them, some studies specifically focused on the training of rhythm skills. As an example, Flaugnacco et al [12] compared the impact of rhythm training to art training on phonological and reading skills in children with SLD. In this randomized controlled trial including 46 children with SLD, children receiving the rhythm training significantly improved their phonological and reading skills, more than the group of children receiving art training.

The “Recommendations for good practice in the assessment, prevention, and treatment of written language disorders in children and adults” by the Collège Français d’Orthophonie [14] describe three different modes of intervention for patients affected by SLD: (1) corrective treatment targets underlying cognitive deficits (eg, phonological or visual-attentional deficits) and various processes involved in identifying written words (eg, graphophonological conversion, phonological decoding, orthographic memory, and orthographic recoding), (2) adaptive treatment aims to reinforce the reader’s natural compensatory strategies (eg, lexical orthographic memory formation), and (3) compensatory treatment seeks to reduce written language disorders by replacing deficient cognitive functions (eg, using digital aids). These modes of intervention are not mutually exclusive and should be combined or alternated according to a treatment plan defined for each patient. However, when possible, corrective treatment should be the first option applied to a patient. For the intervention to be effective, it must be intensive (5 times a week). Achieving this intensity is not feasible in conventional in-person speech and reading therapy, where therapists are generally limited to scheduling 1-2 sessions per week [15]. Therefore, learning activities must also be carried out at home to ensure sufficient training frequency.

In recent years, there has been growing interest in digital technologies and game-based assessment, training, and rehabilitation methods for neurodevelopmental disorders [16,17]. As defined by Mayer [18], serious games have the motivational and playful characteristics of games, but their main objective is to achieve a measurable change in the player’s skills. The playful nature of these games leads to increased interest and attention from the player, which in turn encourages greater effort [18,19]. However, the digital tool appears to be a preferred learning tool for school-age children [20]. Digital tools also enable the multimodal, sequential, and simultaneous presentation of information, allowing the player to interact with the device in various ways [21]. A recent review of serious games for people with SLD supports their effectiveness in developing reading abilities, particularly those targeting sound and letter association and action video games [22]. In addition, serious gaming could be an ideal medium for training rhythmic skills, as rhythmic synchronization is one of the easiest musical skills to isolate [23]. Furthermore, serious games enable the use of an active musical framework in which body movements, emotions, and intentionality influence each other, maximizing the demands on the audio-motor loop and enhancing anticipatory and predictive processing [24]. Indeed, serious games provide an interesting medium to combine musical training with grapheme-phoneme correspondence, as recommended by recent guidelines [14]. The serious game Poppins Clinical was created to combine written language exercises and rhythm training, allowing children with SLD to practice at home and improve their reading skills. The rhythm training part is the most original component and has been used with children with neurodevelopmental disorders, showing improvement in rhythm skills within the game [25]. A randomized placebo-controlled trial involving 154 children with SLD tested the rhythm training part or a placebo game for 2 months [26]. The results showed improvement in reading accuracy and speed, supporting the

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efficacy of Poppins Clinical to improve reading skills in children with SLD. Written language exercises have been added to the rhythm training to match the most recent recommendations [14].

The use of new technologies, including serious games, raises several questions, notably regarding how these new technologies are used in the current health system [27]. Specifically, cost-effectiveness data is lacking. It is crucial to evaluate the impact of a technology compared with its cost [27]. In addition, the impact of a new treatment must also take into account other variables such as treatment adherence or safety. To assess these points, a number of trials use a noninferiority paradigm [28,29]. The objective of these trials is to evaluate if a new treatment can be considered not worse than the gold-standard treatment by an acceptably small amount, with a given degree of confidence [30]. In this type of trial, defining the noninferiority margin is crucial [30]. This margin represents the threshold below which any difference in efficacy is considered clinically acceptable. Elicited health costs can be considered to evaluate the gain of the treatment. These costs may be divided into three types of costs: direct costs related to resources used, indirect costs related to productivity loss, and intangible costs as costs related to pain and endurance [31]. As an example, Schmidt et al [32] identified 31 subcategories of "out-of-pocket" costs such as transportation, insurance, or technology-related costs, that could be considered when looking at health expenditures.

The objective of this paper is to present the methodology of a randomized controlled trial aimed at comparing the effectiveness of Poppins Clinical combined with one reading therapy session every 2 weeks to one reading therapy session per week, on the reading skills of children with SLD, using a noninferiority paradigm. Safety, treatment adherence, and cost will also be considered.

Methods

Study Design and Objectives

This study is an interventional, multicenter, noninferiority randomized trial with two arms. The main objective is to evaluate the noninferiority of Poppins Clinical combined with one reading therapy session every 2 weeks (experimental arm) compared with one reading therapy session every week (control arm) on the reading accuracy (the primary end point) of children with SLD and reading impairment.

Secondary objectives include comparing the experimental group to the control group in terms of safety, reading speed, reading skills, phonological awareness, parental stress, parent quality of life, and text comprehension (secondary end points). Costs related to medical care and therapy between the experimental and control groups are also investigated. This protocol follows SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (checklist provided in Multimedia Appendix 1).

Study Population

The study will include 306 participants. The justification for the sample size is given below in the *Statistical Justification of the Sample Size* section.

Inclusion criteria require participants to have a confirmed diagnosis of SLD with a reading deficit, as defined by a speech-language assessment. This diagnosis must align with the *DSM-5-TR* (*DSM-5*, Text Revision) definitions, with reading and/or transcription test scores showing an SD of at least –1.4 or below the 20th percentile, or –2 SD and below the 10th percentile on two such tests. Eligible participants will be children aged 7-11 years, enrolled from CE1 to CM2, who have been receiving reading therapy once a week for less than 2 years. Other criteria include fluency in French or bilingualism in French at home, at least 3 years of schooling in France, and access to a tablet or smartphone at home. In addition, participants must be affiliated with the French National Insurance system, and both the child and their legal guardians must provide informed consent and agree to follow the study protocol. Only one child per family will be enrolled.

Exclusion criteria will exclude individuals who have previously used Poppins Clinical or its earlier version, Mila-Learn (Poppins). Children with unstabilized chronic illnesses, autism spectrum disorders, or documented intellectual disabilities will not be eligible. Participants with vision or hearing impairments that would prevent the use of a tablet or smartphone, as well as those engaged in other interventional studies that may affect the trial's outcomes, will also be excluded.

Study Procedure

First, participants will be informed about the study either by their therapists or via web-based social media platforms. Two clinical sites in Paris and Poitiers, France, will be in charge of the screening and recruitment. Potentially eligible children and their legal representatives will receive study information during an informational visit. If interested, legal representatives will be asked to sign the informed consent form. Speech and reading therapists working with the participants will also be officially informed about the study, and their consent will be collected. The study investigator will then verify whether the participant meets the study criteria and determine their eligibility during an inclusion visit, which can be conducted either on-site or via videoconference. During this visit, verbal assent will also be obtained from the child. Following this, a baseline evaluation (T1) will be conducted by a speech therapist from the clinical site via videoconference, and questionnaires will be provided to both the patients and their legal guardians. These assessments will be performed under the same conditions as renewal evaluations, using standardized tests that have been adapted for videoconference administration.

Patients will then be randomized into one of two groups: the experimental arm or the control arm. Randomization will be carried out by the Contract Research Organization (CRO) using blocks of size six to maintain a 1:1 ratio, with stratification based on the participant's schooling level.

Patients assigned to the experimental arm will undergo 12 weeks of reading therapy, with one session every two weeks. In addition, they will use the medical device Poppins Clinical for 20 minutes per day, 5 days a week, over 12 weeks. The Poppins Clinical device is provided free of charge to families during the three-month training period. Each family must create an account in the game using a specially generated link designed to track

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study participants. The patient's playtime is recorded by Poppins Clinical—the time spent on each exercise is tracked, enabling the app to monitor the children's daily playtime. The patient will receive a notification on their tablet every Monday encouraging them to play, and another on Saturday to motivate them to reach the playtime goal. If they have not played during the week, the child will receive an additional notification the following Wednesday to encourage them to play. The first day of training in the Poppins Clinical group must be performed within 2 weeks after the baseline evaluation (T1). Patients in the control arm will continue to receive a weekly reading therapy session, as per common practice in France [15]. To control for potential bias related to the formation of speech and reading therapists, years of graduation and the training courses followed in the last 5 years will be recorded.

A second evaluation (T2) will take place via videoconference 12 weeks (+ or - 14 days) after the first day of training with Poppins Clinical for the experimental arm, or 12 weeks after the baseline evaluation for the control arm. Questionnaires for patients, their legal guardians, and speech and reading therapists will be collected at this time. Please refer to Figure 1 for a flowchart of the study procedures.

Throughout the trial, investigators and evaluators will remain blinded to the patients' group assignments. However, patients and their speech and reading therapists will not be blinded to the allocation. To maintain blinding of the investigators and evaluators, the CRO's safety department will be responsible for recording all adverse events and device deficiencies.

Figure 1. Study procedure flowchart. CONT: control group; EXPE: experimental group.

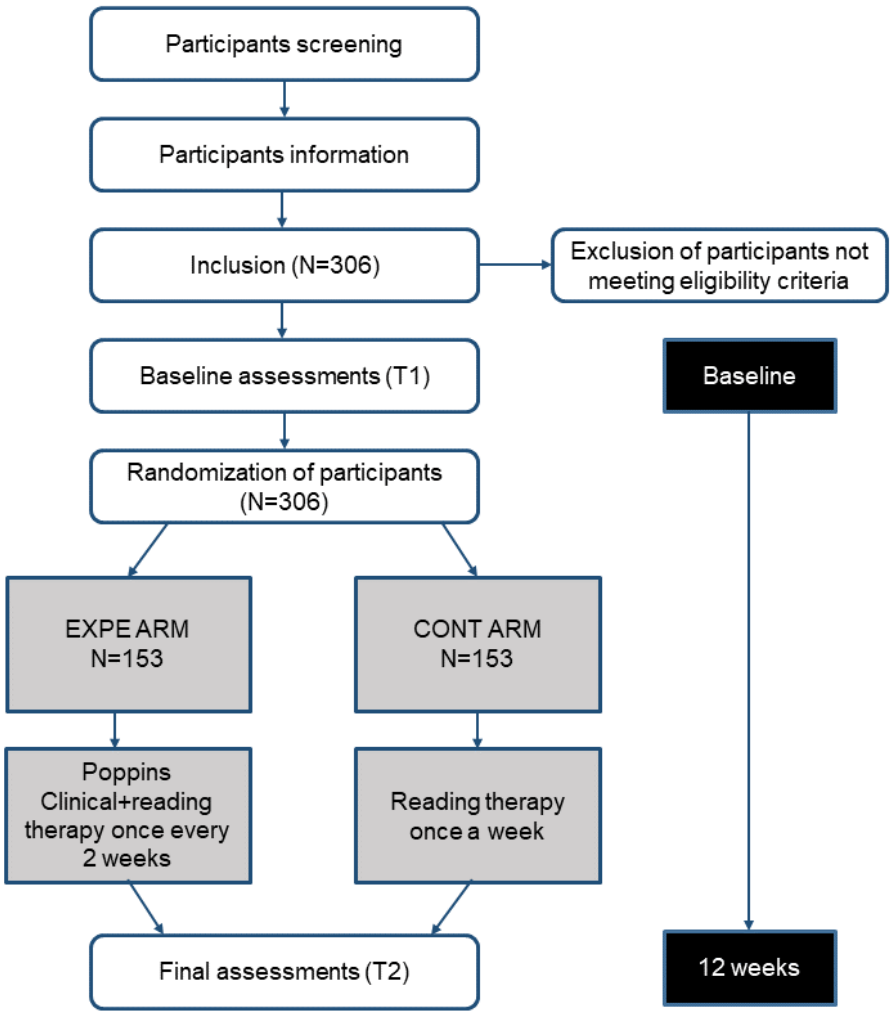

Experimental Intervention: Poppins Clinical

As aforementioned, we have already examined the impact of the first version of the digital medical device Poppins Clinical on the reading abilities of children with SLD. This version consisted of musical training in the form of a serious game [26]. Based on the new recommendation from the Collège Français d'Orthophonie [14], a new version of Poppins Clinical has been developed that combines the initial musical training program with a written language training program.

Poppins Clinical is now an app available on tablets and smartphones (iOS [Apple Inc] and Android), where children are led to carry out different activities divided into two categories: language activities and musical activities. Depending on the child's performance, the difficulty of the proposed activities is adapted. Poppins Clinical contains several short activities, allowing for a variety of activities within a single session. Each activity lasts an average of 1.40 minutes, ensuring that it does not demand too much sustained attention from the child [33,34]. This structure of short activities ensures a fluid,

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coherent, and continuous experience for the user. To offer an experience suitable for as many children as possible (aged 7-11 years, both gamers and nongamers, with a wide range of tastes), the visual and narrative aesthetics of Poppins Clinical align with mainstream video game standards such as Rayman (Ubisoft) and Mario games (Nintendo), which are designed for all audiences.

Musical Activities

The musical activities consist of rhythmic tasks described in a previous paper [25]. In summary, all these tasks were designed to work on rhythm, as rhythm appears to be directly related to reading skills, whereas melody is not [35]. However, children with SLD showed deficits in rhythm processing [8,9]. Each task also requires the mobilization of other skills such as attention, inhibition, working memory, and motor skills, which are often impaired in children with dyslexia [36].

Written Language Section

The written language section combines exercises to enhance phonological awareness, reading speed, and writing accuracy (Figure 2). All exercises are proposed to associate phoneme and grapheme as recommended by the College Français d'Orthophonie [14]. Words presented in the game were chosen from the Manulex database, considering their frequency, length, and orthographic difficulty. Syntactic difficulties and vocabulary frequencies were also considered in the selection of sentences and texts presented in the game.

Figure 2. Screenshots of written language tasks from Poppins Clinical.

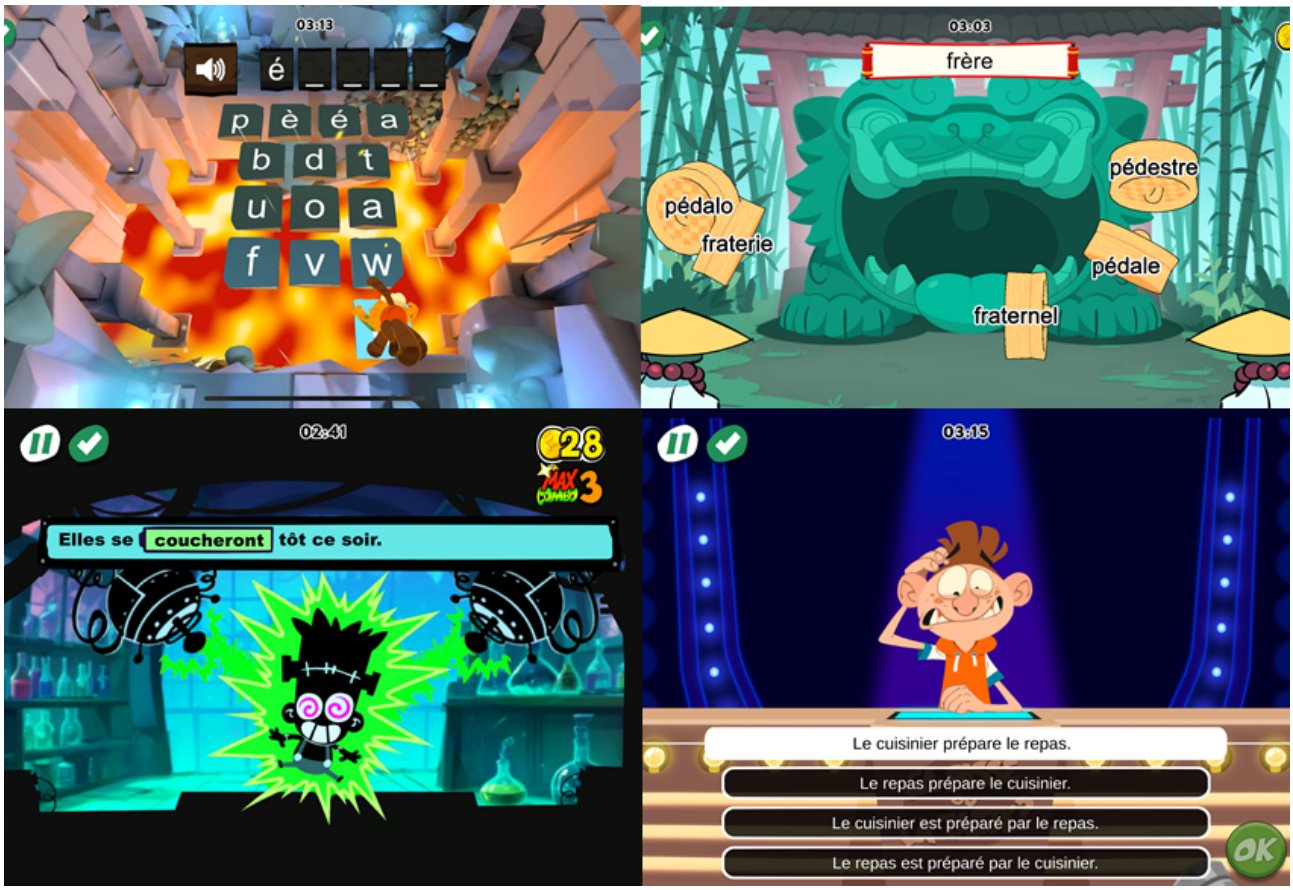

Four types of exercises have been developed to work on different skills used to access written language:

1. Underlying processes: In Poppins Clinical, various activities are based on the ability to identify the sounds contained in a word (phoneme or syllable), thus calling on phonological and meta-phonological skills. These include activities to classify words according to the sounds that make them up. However, the activities (language and music) are carried out in various forms and require interaction with the digital tool in several ways, calling on visual attention skills, executive functions, and praxis.
2. Graphophonology: Various activities are based on matching graphic representations with their corresponding sounds (syllables and words). The aim is to teach the player to link a graphic form to a phonological representation, in reading activities such as categorizing written words.
3. Orthographic skills: Transcription activities are based on the ability to write words by working on lexical spelling (eg, knowledge of spelling irregularities), grammatical spelling (eg, differentiation of "et" or "est"), inflectional morphology (eg, plural marks), and derivational morphology (eg, recognizing prefix-radical-suffix structures). Activities such as word completion are proposed here.
4. Semantics: Semantics activities are based on understanding written language. This involves knowing the vocabulary, understanding syntactic structures (eg, subordinate clauses) and textual structures (eg, organization of ideas in a text), and making inferences. This involves activities such as

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carrying out written instructions or putting a story in chronological order.

Outcomes

The primary outcome of this study is reading accuracy, which will be measured by the number of correctly read words using the EVALEO (Ortho Edition) [37] 2-minute word reading test (EVAL2M). Noninferiority will be evaluated 12 weeks after the start of training with Poppins Clinical for the experimental group or 12 weeks after the baseline evaluation for the control group.

Safety will be assessed by monitoring adverse events reported by patients during the 12-week study duration.

Seven secondary outcomes will also be investigated. Noninferiority in reading speed, measured by the number of words read using the EVAL2M [37], will also be evaluated. In addition, noninferiority in word reading skills (speed and accuracy) and meta-phonological skills will be assessed using respectively the Alouette-R [38] text reading test and the BALE Phoneme Suppression Test [39].

The impact of Poppins Clinical on parents' stress levels and quality of life will be measured using the Parenting Stress Index-Short Form (PSI-SF) and the EQ-5D-5L [40] quality of life questionnaire. Text comprehension will also be assessed through the computerized BMT-i test battery [41], evaluating correct answers to comprehension questions, as well as reading precision and speed. A cost evaluation will be conducted by administering a questionnaire to parents to evaluate the health and economic value of Poppins Clinical. The objective is to determine in each group the direct and indirect health care costs, including, treatment costs (eg, number of appointments and costs of each session) and work-related costs (eg, the number of days off used for health purposes).

A total of 5 exploratory end points will be investigated. The effect of Poppins Clinical on visual attention span will be assessed with the EVALEO test, using correct answer scores. The patient's quality of life and reading and writing difficulties will be evaluated using the PedsQL 4.0 CORE [42] young child report and a self-assessment grid for reading and writing difficulties [43]. The perceptions of parents and speech therapists regarding the study's impact on therapy will be captured via an adapted questionnaire. Finally, predictive factors of training effectiveness with Poppins Clinical will be explored to improve the individualization of the program and the use of the device through connection data.

All the outcomes are described in Table 1.

All outcomes will be evaluated 12 weeks after the start of training for the experimental group or 12 weeks after the baseline evaluation for the control group. Participants of the experimental group will have up to 14 calendar days to start training with Poppins Clinical once the baseline evaluation is completed. The results will be entered into an electronic case report form (eCRF) hosted on the web by the CRO, which will be responsible for data monitoring and treatment.

Table 1. Measured outcomes investigated in the protocol.

Outcome	Measure
Primary outcome	Reading accuracy is measured by the number of correctly read words (EVAL2M)
Safety secondary outcome	Number of adverse events reported during the study
Secondary outcome 1	Reading speed is measured by the number of read words (EVAL2M)
Secondary outcome 2	Word reading accuracy and speed (Alouette-R)
Secondary outcome 3	Cost evaluation
Secondary outcome 4	Phoneme suppression skills (BALE)
Secondary outcome 5	Parental stress levels measured using the Parenting Stress Index Short Form
Secondary outcome 6	Parent's quality of life measured using the EQ-5D-5L
Secondary outcome 7	Reading precision, speed, and comprehension (BMT-i)
Exploratory outcome 1	Visual attention span (EVALEO)
Exploratory outcome 2	Child's quality of life (PedsQL 4.0 CORE)
Exploratory outcome 3	Child's perception of reading and writing difficulties [43]
Exploratory outcome 4	Perception of parents and speech therapists on the impact of the protocol on the child (custom questionnaire)
Exploratory outcome 5	Evaluation of predictive factors of training effectiveness

Statistical Justification of the Sample Size

The sample size determination was based on the primary end point, which is to demonstrate the noninferiority of a follow-up with reading therapy every 2 weeks, in addition to the use of the digital medical device (Poppins Clinical), compared with a follow-up with reading therapy every week, on the evolution of reading accuracy over 12 weeks. The null (H0) and alternative (H1) hypotheses for noninferiority trials may take the following form:

1. H0: experimental (EXPE) is inferior in terms of the mean response, $\mu EXPE - \mu CONT \leq -\Delta NI$.
2. H1: experimental is noninferior in terms of the mean response, $\mu EXPE - \mu CONT > -\Delta NI$.

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Where μEXPE is the mean of the outcome in the experimental arm, and μCONT is the mean of the outcome in the control arm. The noninferiority limit, –ΔNI, is defined as the threshold at which the mean difference between the experimental arm and the control arm becomes clinically unacceptable.

The noninferiority margin was determined through a formal expert committee meeting, combining independent experts and investigators. The committee was structured to ensure both independence and relevant expertise. Two independent experts were selected for their complementary expertise: a neuropediatrician who pioneered diagnostic recommendations for learning disorders in France, and a speech therapist who codeveloped the standardized assessment tool used as the primary outcome in this study (EVALEO 6-15). The two investigators of the study, both professors in child psychiatry with extensive research experience in neurodevelopmental disorders, provided their methodological expertise. A fifth expert, a neuropsychologist with experience in written language rehabilitation guidelines and as a reviewer of good practice recommendations, was included as a scientific advisor. All experts were active clinicians and researchers in learning disabilities.

The committee's decision was informed by empirical data from the previous randomized controlled trial (ML-01), showing a natural progression of 7.7 (SD 12.9) correctly read words over 8 weeks in the placebo group [26]. Based on these data and their collective clinical experience, they established that a difference of 5 words or fewer between groups would represent a clinically acceptable margin of noninferiority. This threshold was unanimously approved by the full committee after a structured discussion of potential age-related variations in reading progression.

The SD of the outcome in each group was estimated at 12.7 words from the ML-01 study [26]. The maximum acceptable inferiority for experimental versus control on the primary outcome is therefore expected to be a standardized difference (Cohen d=0.39), which corresponds to a label between small or medium, depending on the guidelines (R effect size package) [44].

Considering a one-sided significance level of 2.5% and a power of 90%, it is necessary to include 137 participants per group (G*Power 3.1). Assuming a 10% drop-out rate, the final estimate is 306 participants in total (or 153 participants per arm).

Statistical Methods

This trial uses a noninferiority and possibly superiority hypothesis testing framework between groups for primary, secondary, and exploratory outcomes. We will report the results in accordance with the noninferiority trials extension of the CONSORT (Consolidated Standards of Reporting Trials) 2010 statement. Tests for noninferiority will be one-sided and performed using a 2.5% significance level. All other tests will be two-sided, performed using a 5% significance level. The type I error rate will be controlled using a hierarchical testing procedure for secondary end points. A subsequent end point will only be tested if the previous end point's test for noninferiority is statistically significant.

Criteria Analysis

According to CONSORT 2010, interpreting a noninferiority trial's results depends on where the CI for the treatment effect lies relative to the margin of noninferiority –ΔNI and the null effect. The lower bound of the one-sided (1–α)×100% CI for the treatment effect must be above the margin –ΔNI to declare that noninferiority has been shown [45].

Once noninferiority is evident, it is acceptable to assess whether the new follow-up appears superior to the reference follow-up, using an appropriate test or CI, with a significance level defined a priori and with an intention-to-treat (ITT) and a per-protocol (PP) analysis. All randomized patients will be included in the ITT analysis, including children assessed at T1 or T2, after the time allowed by the protocol. The PP population will include only participants without major deviations. These patients must have completed at least 50% of the prescribed training time and at least 50% of the reading therapy sessions outlined in the protocol.

In this context, if the noninferiority is shown (based on both ITT and PP analyses), superiority will then be tested for the same primary end point, as described in the European Medicines Agency (EMA) guidelines [46]. Superiority will be tested using a t test at a 2-sided 5% significance level.

The type I error rate will be controlled using a hierarchical testing procedure for secondary end points. A subsequent end point will only be tested if the previous end point's noninferiority test is statistically significant.

Safety Criterion Analysis

The safety population includes all participants who will use the DM Poppins device at least once. This safety population will be used for the safety analysis. Adverse events will be reported by the participant's parents to the CRO's Safety Department or the patient coordinator and will be recorded in the eCRF form. The form will contain all necessary variables to define the date, severity, and relationship to the study device, as evaluated by the investigator (see Textbox 1).

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Textbox 1. Summary of descriptive statistics of adverse events and device deficiencies.

For adverse events:

- Type of adverse event
- Severity
- Evolution
- Relationship with the device
- Number of episodes
- Time of onset of the adverse event (defined as the time from first use to the earliest date of the adverse event)
- Number of participants with at least one episode (and percentage)
- Discontinuations will also be summarized.

For device deficiency:

- Type of device deficiency
- Duration of the deficiency

Ethical Considerations

The study protocol was approved by the local ethics committee (Comité de protection des personnes for Sud-Est-1; number 2023-A02723-42) and national regulatory agencies (Agence nationale de sécurité du médicament et des produits de santé and Commission nationale de l'informatique et des libertés; N°IDRCB 2023-A02723-42).

Before consent, the patient and their parents will receive a patient information sheet via email. This document will provide the participant and legal guardian with a comprehensive explanation of the study, including its rationale, procedures, benefits, and risks. It will also emphasize that participation is voluntary and that the participant may withdraw from the study at any time without any negative consequences. In addition, a physician will discuss this information with the participant and legal guardian, allowing them sufficient time and opportunity to ask questions and make a decision about whether to participate in the study.

It will be clearly stated that the participant is free to withdraw from the study at any time and for any reason, without affecting their future care, legal rights, and the obligation to give a reason for withdrawal.

Written informed consent must be obtained from the legal guardian in accordance with local practices and regulations before any study assessments or tests are conducted. Written consent will be obtained by signing and dating the approved consent forms. No study assessments or procedures will be conducted until written informed consent has been provided. A description of the consent process must be documented in the participant's medical record.

The parents will provide their signature at the end of the consent form, and a delegated site team member will countersign it. Consent will be obtained either via an electronic signature or a wet ink signature. A copy of the fully executed informed consent form will be provided to both the participant and their parents (either in paper form or sent electronically via email), and a copy will be securely retained by the site in a restricted-access area.

Identifiable participant details (such as name and date of birth) will be held in a separate database from the research database after receiving the participant's consent. The research database will never hold personally identifiable information. Automatic reminders will be sent to participants by doing a one-time recall of identifiable information, matched with the unique study ID.

Given the patient's condition (specific learning disability with reading deficit) and their age thus potentially being unable to provide written consent, the child will provide verbal assent to participate in the trial. The investigator will read the content of the consent form during the information visit, clearly stating that the child is free to decline their participation at any moment. The consent form is adapted to an appropriate language to facilitate the children's understanding. An audio track of the consent form content will also be sent to the parents via email, in case the child would like to listen to it again. Once the child verbally agrees to participate in the trial, the investigator will sign the consent form (either electronically or wet ink) on their behalf and register it in the eCRF.

An information letter for the speech and reading therapist in charge of the participants will also be sent by email to the participant's parents. Parents will be asked to forward it to the speech and reading therapist to inform them of the study and that compensation is provided for them if the participant participates.

The compensation for the speech and reading therapist aims to cover their involvement in the study (they will receive by email the attribution group of their patient and might be asked to rearrange their session schedule to comply with the study protocol) and to compensate for missed sessions (for speech and reading therapist who follow up with patients in the experimental group). Compensation is disclosed to the speech and reading therapists only after the participant signs the informed consent and is detailed in an email that is directly sent to the speech and reading therapists. For further information, the speech and reading therapist can ask for an appointment

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with the dedicated support team (assured by an independent third party), if desired. Speech and reading therapists will be asked to agree to the collection of their personal data (name and email address) to receive information about the study via email and to complete a questionnaire at the end of the trial.

Results

We expect to enroll 306 patients within 6 months from the start of the inclusion phase. Considering that children's participation lasts 3 months, we expect to have the results of this study by the end of August 2025.

Discussion

Principal Findings

The objective of this study is to assess the noninferiority of the serious game Poppins Clinical combined with one reading therapy session every 2 weeks, compared with a reading therapy session every week. To achieve this, we will use a noninferiority trial to measure the acceptance of the new intervention with Poppins Clinical. Our primary outcome will be the number of correctly read words with the EVAL2M test, which is a standard and recent test used in reading therapy. We expect that the experimental group's outcomes will remain within the established noninferiority margin relative to the control group for reading tasks (speed, accuracy, and comprehension), visual span, phonology, and measures of quality of life and parental stress. In addition, we anticipate that the children will be able to adhere to the training program over 3 months when combined with speech therapy sessions, during which the speech therapist can monitor the child's progress. Finally, we expect parents and speech therapists to easily integrate Poppins Clinical–based training into their daily routines. Therefore, Poppins Clinical would demonstrate good integration into the child's care pathway, positively impacting the medico-economic aspects of the treatment, such as improving access to care or simplifying travel for families.

The noninferiority margin represents the maximum clinically acceptable difference between the new treatment and the active control that still allows concluding noninferiority. This margin should be based on a clinical basis, but methods for defining the noninferiority margin can vary widely [47]. The methods used to define the noninferiority margin are frequently not detailed in noninferiority trials, although the choice of the noninferiority margin may strongly impact the conclusion regarding noninferiority trials [47]. Currently, there is no consensus about the best method for defining the noninferiority margin. Previous trials and historical data should be considered if available, however, such data do not always exist. To our knowledge, there is no previous trial or historical evidence regarding the margin that could be clinically relevant in SLD therapy. In that case, the choice of the margin is often based on experts' opinions [29,47]. The clinically significant margin was determined through consultation with an independent expert committee. A threshold of –5 correctly read words was established as the noninferiority margin based on clinical data and expertise. This decision was based on data from a previous double-blind randomized controlled trial showing a natural progression of 7.7 (SD 12.7) correctly read words over 8 weeks [26] and was unanimously approved by a committee of experts combining clinical experience in learning disabilities with methodological expertise.

The choice of population and how to handle missing data may also affect trial results. ITT analyses may favor noninferiority results, while protocol violations may dilute potential differences between the treatment arms, favoring noninferiority results. Therefore, it is preferable to analyze noninferiority trials using both the ITT and PP approach [48]. We will conduct statistical analysis using both the ITT and PP populations. The PP population includes only participants who have completed at least 50% of the training time prescribed by the protocol. To ensure consistency in reading therapy care within the PP population, each participant must complete at least 50% of the reading therapy sessions outlined in the protocol.

We will also conduct noninferiority analysis for reading skills with texts with and those without meaning. The use of several reading tests will allow us to explore different aspects of reading such as accuracy, speed, and comprehension. The use of two texts, with and without meaning, should help us address the possible compensation that patients might use during reading by relying on the context of the text to increase their performance [49]. To avoid an effect between the test and retest for the evaluation of reading understanding, we will use two different texts between the pretest and posttest. Both texts come from the EVALEO 6-15 [37] and are equivalent in terms of syntactic complexity, word frequencies, and length.

However, we will look at the medical costs in both groups during the study. Effectively, the benefit of a new treatment may also be considered in terms of time consumption (eg, transportation and appointments), costs for the family and the patient, as well as costs for society, as speech and reading therapy are reimbursed by the social health insurance in France [28,29]. Gentili et al [50] conducted a literature review on the impact of medical costs of the use of digital health interventions. It appears that more and more evidence suggests a generally favorable effect of digital interventions in terms of costs and health outcomes. The findings show a positive impact, especially for studies that implemented a new mobile app or a web portal intervention, as is the case for Poppins Clinical. Benefits seem to be particularly important in rural areas [50].

Finally, we will perform questionnaires to assess the quality of life and perceived reading difficulties of the patient. Effectively, it is important to evaluate if the impact of an intervention is perceived by the patient and should have an impact on their daily life [51]. However, we will take into account parents' and speech therapists' perceptions of the impact of the protocol on reading therapy in terms of motivation, satisfaction, and time dedicated to work at home and in in-person therapy. We seek to evaluate if the introduction of home training with the serious game Poppins Clinical may negatively or positively affect family time and reading therapy. We will track the stress of parents, as the introduction of home training could be time-consuming and raise behavioral problems (such as rejection to use the device). However, most web- and game-based interventions used with patients with SLD are well accepted by patients and

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their parents [52,53]. Home training may benefit the link between the child and the parents, supporting their interaction and giving them a structured environment to help the child make new learning [54].

Some limitations can be identified in our study. First, the participants are not blinded to their group allocation. This was not feasible, as the protocol affects the frequency of reading therapy sessions, and it would have been unethical to reduce the number of reading therapy sessions to replace them with a placebo. In addition, we will conduct multiple analyses, which could increase the risk of a Type I error. To control for this, we will use a hierarchical testing procedure for secondary end points. A subsequent end point will be tested only if the previous end point's noninferiority test is statistically significant. Finally, we cannot control what reading therapists do during therapy sessions. However, we will monitor the training of the reading therapists by recording their year of certification and any recent training they have completed.

Conclusion

We plan to conduct a single-blind randomized controlled trial to compare the effect of the serious game Poppins Clinical, combined with a reading therapy session every 2 weeks, to reading therapy alone every week on reading skills in children with SLD. To compare the clinical impact of both interventions, we will use a noninferiority design. We will also explore phonological and visual-attentional skills and the impact of the intervention on children, parents, speech and reading therapists, and patient care organizations. The trial results will be submitted to a research journal and summarized for the study participants.

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Data Availability

The datasets generated or analyzed during this study are available upon reasonable request from the corresponding author.

Authors' Contributions

CG: methodology, writing—original draft; MD: methodology, statistical plan; SC, DC, FV, and JX: methodology, Writing—review & editing; HP and BF: methodology, Writing—review & editing.

Conflicts of Interest

FV is the CEO of Poppins, the company that developed Poppins Clinical. MD and CG are employees at Poppins. DC reports a relationship with Poppins that includes equity or stocks.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 242 KB - resprot_v14i1e71326_app1.pdf]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
CRO: Contract Research Organization
DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)
DSM-5-TR: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition, Text Revision)
eCRF: electronic case report form
EMA: European Medicines Agency
H0: null hypothesis
H1: alternative hypotheses
ITT: intention-to-treat
PP: per-protocol
PSI-SF: Parenting Stress Index-Short Form
SLD: specific learning disorder
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Testing a Machine Learning–Based Adaptive Motivational System for Socioeconomically Disadvantaged Smokers (Adapt2Quit): Protocol for a Randomized Controlled Trial

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This is a corrected version. See correction statement: https://www.researchprotocols.org/2025/1/e79873

Abstract

Background: Individuals who are socioeconomically disadvantaged have high smoking rates and face barriers to participating in smoking cessation interventions. Computer-tailored health communication, which is focused on finding the most relevant messages for an individual, has been shown to promote behavior change. We developed a machine learning approach (the Adapt2Quit recommender system), and our pilot work demonstrated the potential to increase message relevance and smoking cessation effectiveness among individuals who are socioeconomically disadvantaged.

Objective: This study protocol describes our randomized controlled trial to test whether the Adapt2Quit recommender system will increase smoking cessation among individuals from socioeconomically disadvantaged backgrounds who smoke.

Methods: Individuals from socioeconomically disadvantaged backgrounds who smoke were identified based on insurance tied to low income or from clinical settings (eg, community health centers) that provide care for low-income patients. They received text messages from the Adapt2Quit recommender system for 6 months. Participants received daily text messages for the first 30 days and every 14 days until the end of the study. Intervention participants also received biweekly texting facilitation messages, that is, text messages asking participants to respond (yes or no) if they were interested in being referred to the quitline. Interested participants were then actively referred to the quitline by study staff. Intervention participants also received biweekly text messages assessing their current smoking status. Control participants did not receive the recommender messages but received the biweekly texting facilitation and smoking status assessment messages. Our primary outcome is the 7-day point-prevalence smoking cessation at 6 months, verified by carbon monoxide testing. We will use an inverse probability weighting approach to test our primary

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outcome. This involves using a logistic regression model to predict nonmissingness, calculating the inverse probability of nonmissingness, and using it as a weight in a logistic regression model to compare cessation rates between the two groups.

Results: The Adapt2Quit study was funded in April 2020 and is still ongoing. We have completed the recruitment of individuals (N=757 participants). The 6-month follow-up of all participants was completed in November 2024. The sample consists of 64% (486/757) female participants, 35% (265/757) Black or African American individuals, 51.1% (387/757) White individuals, and 16% (121/757) Hispanic or Latino individuals. In total, 52.6% (398/757) of participants reported having a high school education or being a high school graduate; 70% (529/757) smoked their first cigarette within 30 minutes of waking, and half (379/757, 50%) had stopped smoking for at least one day in the past year. Moreover, 16.6% (126/757) had called the quitline before study participation.

Conclusions: We have recruited a diverse sample of individuals who are socioeconomically disadvantaged and designed a rigorous protocol to evaluate the Adapt2Quit recommender system. Future papers will present our main analysis of the trial.

Trial Registration: ClinicalTrials.gov NCT04720625; https://clinicaltrials.gov/study/NCT04720625

International Registered Report Identifier (IRRID): DERR1-10.2196/63693

(JMIR Res Protoc 2025;14:e63693) doi:10.2196/63693

KEYWORDS

smoking cessation; mHealth; socioeconomically disadvantaged, biochemical verification; machine learning

Introduction

Background

Cigarette smoking is a serious public health problem and the leading cause of preventable disease, disability, and death in the United States [1]. While overall smoking rates have decreased, smoking rates among individuals who are socioeconomically disadvantaged remain high [2-5]. Individuals who are socioeconomically disadvantaged are affected disproportionately from smoking-related diseases [2-5]. Individuals who are socioeconomically disadvantaged may be less likely to try to quit smoking (eg, due to lower self-efficacy and maladaptive beliefs) and are less likely to use evidence-based strategies (such as quitlines).

Computer-Tailored Health Communication via Texting: A Potential Approach

One strategy to engage these individuals is by using computer-tailored messages delivered via texting. Computer-tailored health communication involves the use of computer programs to select the best personalized message for an individual. This form of communication has been effective in enhancing motivation to quit and supporting cessation [6-12]. In a systematic review, computer-tailored messages showed higher cessation rates than nontailored messages (relative risk 1.17, 95% CI 0.97-1.41). Computer-tailored messages work because participants are more likely to engage and carefully process personally relevant messages [13]. Thus, methods to increase the relevance of the message may increase the effectiveness of the smoking cessation intervention. Computer-tailored messages delivered via texting over phones may be particularly attractive for individuals who are socioeconomically disadvantaged. Mobile phone ownership is now nearly universal (95%) [14], and these rates are consistent across socioeconomically disadvantaged groups (less than high school education, 92% and those earning <US $30,000, 92%). The texting app is the most commonly used app on mobile phones [14].

The Adapt2Quit Intervention: Leveraging Machine Learning for Tailored Cessation Support

In our National Institutes of Health–funded trial, we are testing Adapt2Quit, which uses machine learning algorithms (ie, recommender systems) to computer-tailor messages for an individual and deliver them via texting [15]. Recommender systems can be programmed to continuously learn from user feedback and improve personal relevance and customer engagement [15]. Adapt2Quit also includes proactive texting facilitation to the state quitline in which participants are asked if they want to be referred to the quitline, and those who agree are referred to the quitline. Quitlines are programs in the United States that offer evidence-based support (eg, counseling and medications) to individuals who smoke. These individuals can either directly contact quitlines using the number 1-800-QUIT-NOW or be referred by a health care provider or tobacco cessation programs. Although quitlines have been established in all 50 US states, they are vastly underused. The use of texting to promote quitline use could potentially increase quitline use, and thereby increase the effectiveness of the smoking cessation intervention for the participants.

Preliminary Evidence Supporting Adapt2Quit

In our preliminary studies, Adapt2Quit increased engagement and 30-day point-prevalence effectiveness over a standard messaging that randomly selected these messages [16]. In a subanalysis among those who reported lower education (n=49), the average rating of the messages was higher on more days than the average ratings of true comparison messages (77% vs 23%; $P<.01$). This pilot study showed the potential of the Adapt2Quit trial among individuals who are socioeconomically disadvantaged. Since the beginning of the trial, we have completed another randomized controlled trial that tested the machine learning algorithm compared to standard messaging among those who were recruited via social media [17]. In the other trial, there was no significant difference in 6-month point-prevalence smoking cessation (adjusted odds ratio 0.81, 95% CI 0.61-1.08) between the recommender system (146/412, 35.4% of participants with outcome data) and messages tailored

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by standard messaging based on participants' baseline readiness to quit groups (156/389, 40.1% of participants with outcome data). However, the other trial differs from the current trial being reported in that the messages were delivered via email, it did not target individuals who are socioeconomically disadvantaged, and the system did not facilitate referral to the quitline. Furthermore, another group has evaluated a similar recommender system approach for message selection in a pilot trial for self-reported smoking cessation [18]. However, additional studies testing recommender systems are needed to uncover the potential of these systems for increasing the effectiveness of computer-tailored smoking cessation interventions.

Theoretical Basis for the Adapt2Quit Intervention

The Adapt2Quit intervention is based on the self-determination theory (SDT). SDT-based interventions support autonomous decisions and are designed to increase intrinsic motivation and self-regulation and they have been shown to improve motivation and cessation outcomes among those who smoke [19-24]. Three innate psychological needs are theorized to promote self-motivation: autonomy, relatedness, and competence [19]. Autonomy reflects the need to engage in behaviors with a sense of choice or personal endorsement [25]. Autonomy support can be provided by acknowledging an individual's unique perspective and offering choice [25,26]. Relatedness reflects the degree to which an individual feels connected to and understood by others. Competence is a feeling of being capable and is akin to self-efficacy, the belief that one can bring about desired outcomes. By supporting autonomy, relatedness, and competence, health behaviors are more likely to be internalized and maintained. Specific examples of how Adapt2Quit supports the SDT are provided in Textboxes 1 [27] and 2. Our aims and hypotheses align with our proposed model, which suggests that relevant personal messages from the Adapt2Quit system will enhance system engagement. This increased engagement is expected to improve internal processes (ie, the SDT constructs measured using the Perceived Competence Scale [PCS]), leading participants to adopt cessation-supporting behaviors (external processes such as quitline and nicotine replacement therapy [NRT] use), ultimately resulting in smoking cessation.

Textbox 1. Examples of mapping the self-determination theory to Adapt2Quit.

- Autonomy: participants can control how often they want to rate the messages with the system. Autonomy increases as the participant's ratings influence the messages they receive, providing an enhanced feeling of control over the intervention. Furthermore, Adapt2Quit facilitates quitline access but does not impose it. Participants are asked if they want to contact the quitline. Only if the participant responds positively, our system will initiate a quitline referral. Autonomy is increased as the participant controls if and when they choose to interact with the quitline. Our messages will focus on persuading the smoker to use quitline.
- Relatedness: in addition to the smoker profile, Adapt2Quit's recommendations are based on feedback from thousands of smokers who previously engaged with the recommender system. Relatedness increases as the system learns and adapts to the ratings feedback of each new smoker. The Adapt2Quit messages database includes peer-written messages [27]. Messages from peers may enhance relatedness because they reflect shared experiences, allowing smokers to more easily identify with the message content [27].
- Competence: Adapt2Quit messages are designed to improve motivation, educate, and increase a smoker's confidence and skills related to smoking cessation. Content includes appropriate strategies and treatments, as cues and reminders to encourage use, which were developed based on current guidelines on smoking cessation. Our pilot showed that Adapt2Quit increased the adoption of cessation-supportive behavior.

Textbox 2. Specific aims.

Aim 1: Adapt2Quit engagement—heterogeneity of Adapt2Quit recommender system engagement

- Hypothesis 1a: among Adapt2Quit participants, those with higher engagement levels (ie, completed more ratings) will have greater scores on the Perceived Competence Scale (PCS).

Aim 2: behavioral processes—internal processes (self-determination theory constructs) and external "processes" or cessation-supportive actions comparing Adapt2Quit and the comparison group (texting facilitation to quitline)

- Hypothesis 2a: Adapt2Quit participants will have greater scores on the PCS than comparison participants.
- Hypothesis 2b: Adapt2Quit participants will adopt more cessation-supporting actions (quitline use and nicotine replacement therapy) than comparison smokers.

Aim 3: effectiveness—6-month smoking cessation in Adapt2Quit versus the comparison group

- Hypothesis 3a: (primary outcome) Adapt2Quit participants will have greater smoking cessation rates (6-month point-prevalence biochemically verified) than comparison participants.
- Hypothesis 3b: (mediation analysis) measured internal and external processes will mediate the effect of Adapt2Quit on smoking cessation.

Paper Objective

This paper describes the protocol and status of our ongoing randomized controlled trial testing the Adapt2Quit intervention among individuals from socioeconomically disadvantaged backgrounds who smoke. Our comparison participants receive the biweekly texting facilitation messages but do not receive the motivational messages recommended by the Adapt2Quit intervention. Our protocol description includes the intervention and comparison system as well as the description of the analyses

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of the primary and secondary hypotheses listed in the following sections. Since recruitment for our study has finished, we describe the demographics of the participants we have recruited. Our follow-up data collection is in progress.

Methods

Study Design and Setting

This study is a 2-arm randomized controlled trial comparing participants who received smoking cessation text messages selected by the Adapt2Quit recommender system plus a texting facilitation approach to connect participants to the quitline with participants who received the texting facilitation but no smoking cessation text messages. Study participants were blinded to group assignments. They were recruited from health systems in diverse geographic areas. Recruitment started in April 2020 and was completed in March 2024. Our target sample size was 750 individuals from socioeconomically disadvantaged backgrounds who smoke.

Ethical Considerations

The Adapt2Quit study has been approved by all participating institutions' institutional review boards (IRBs), including Baystate (BH-20-123) and Johns Hopkins (IRB00280942), with the University of Massachusetts Chan Medical School (UMass Chan) IRB (H00018991) being the central IRB. The study is listed in ClinicalTrials.gov (NCT04720625). It is being carried out in accordance with the Helsinki Declaration, and all participants have signed an informed consent form before enrollment in the study. Participants have been informed that they have the right to withdraw their consent at any point during the study, and the reason for their withdrawal will also be documented if the participant so wishes. The participants have received compensation for completing study activities. They received US $25 for completion of baseline, US $25 for the 6-month follow-up, US $50 for completing the carbon monoxide (CO) verification assessment, and an additional US $50 for participation in the qualitative interview. Upon randomization, all patients have been assigned an individual ID number so their data remain anonymous.

Inclusion and Exclusion Criteria

The inclusion criteria were as follows: an individual who smokes, comes from a socioeconomically disadvantaged background, speaks English, who is active in care (having at least 2 clinical visits in the past 2 years), and who has a texting-enabled mobile l phone. We used insurance status to identify participants as socioeconomically disadvantaged [28]. In the United States, people can receive health insurance or health care payment coverage from several sources including through their employer, other private health insurance companies, or through government-supported programs. Individuals who have these government-supported programs are more likely to be from socioeconomically disadvantaged groups. For our study, we used Medicare (a government-funded program for older adults and those with disabilities) and Medicaid (a state and federal program for low-income individuals) to identify individuals from socioeconomically disadvantaged backgrounds. We determined smoking status by asking participants if they had smoked at least 100 cigarettes and their current smoking frequency (Multimedia Appendix 1). Those who responded "yes" to 100 cigarettes and "some" or "every day" were included.

The exclusion criteria were as follows: adults who were unable to consent, individuals who were not yet adults (ie, aged <18 years), prisoners, people with Alzheimer disease, and pilot study participants.

Recruitment

Recruitment was spread over the 3.5 years of the study. Study participants were recruited at urban and rural health care settings across 3 health care systems in the United States (UMass Memorial Medical Center, Baystate Health, and Johns Hopkins University). We used an opt-out recruitment strategy, with some variations between the three sites. At all 3 sites, after obtaining a Health Insurance Portability and Accountability Act waiver, potential participants who met our inclusion criteria in the clinical data warehouse were identified. At the UMass Chan and Baystate Medical Center, an initial invitation letter with a self-addressed, stamped opt-out postcard was sent to those eligible from the local site principal investigator outlining the study's purpose. Johns Hopkins University's site used emailed study invitation letters with instructions to opt-out via email instead of or in addition to mailed letters and "opt-out" postcards for those without an email address. Instructions were provided on how to opt-out by email. At all sites, individuals who opted out or whose email was returned undelivered within 2 weeks were removed from the recruitment list.

Screening, Informed Consent, and Baseline Data Collection

Potential participants were phoned up to 4 times to determine their interest and were screened for eligibility. Before starting the first recruitment call, the research staff sent an automated introductory text message to potential participants who would be called that day. During the phone call, participant eligibility was assessed (Multimedia Appendix 1). Eligible participants were asked to provide informed consent for study participation, were asked to complete the baseline data, and were then randomized to treatment. The screening session, informed consent, and baseline data collection were conducted via Zoom (Zoom Communications, Inc) or by phone.

Once randomized, after completion of the baseline survey (Multimedia Appendix 1), the Adapt2Quit intervention participants received 5 initial motivation messages and were asked to provide a rating. The recruitment staff viewed the rating in real time to confirm whether the participant understood and was comfortable with the system. The staff emphasized the importance of rating their messages to intervention participants. The research staff explained the quitline facilitation process and smoking status texting assessment to both groups and reiterated the importance of completing the ratings to intervention participants. Those randomized to the control group received only the texting facilitation and smoking status but did not receive the motivational messages, and instructions were provided accordingly.

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Randomization

Separate randomization tables were created for each site to enhance the balance between the two groups. Participant allocation to study arms was based on a permuted block scheme in which treatment assignments were made within blocks so that numbers assigned to each treatment arm are equal after a block has been filled. Blocks of various sizes (2, 4, and 6) were used in random order to facilitate allocation concealment. As in our prior technology-based trials, we embedded randomization within the technology [29,30]. After completing the screening, informed consent, and baseline data collection, the research staff entered the participant ID and participant mobile phone number from the survey into a web-based system, which then assigned the allocation based on the randomization table. Using this technique, participants and staff were blinded to allocation during the initial session. The research staff were subsequently unblinded to provide personalized training for the intervention and control groups, as noted.

Intervention and Comparison

Intervention: The Adapt2Quit Recommender System

The Adapt2Quit recommender system uses a machine learning algorithm to select the best message for a participant from a motivational messaging database. We programmed Adapt2Quit to select messages based on the following: (1) the smoking status of the participant and (2) the ratings database (both from prior study participants and current participants) [16,31-33]. We discuss the recommender system components in subsequent sections. The system has multiple components.

Component 1: The Motivational Messages Database

The messages include 261 messages, including 206 expert- and 55 peer-written messages (Multimedia Appendix 2) [27]. We developed the expert-written messages through an iterative group review process guided by theoretical frameworks and existing smoking cessation guidelines [34]. Peer-written messages were written by current and former people who smoke, responding to a web-based survey. Our methods for developing this messaging database and its characteristics have been published [27]. Briefly, the expert messages written by smoking cessation providers and researchers were more “biomedical” (ie, avoidance, behavioral strategies, and health), while peer messages had more “social” and “real-life” content (ie, expectations, money, quality of life, attitudes, and friends) [27]. Our messages were assessed to be readable for someone with at least a fifth grade–level education (Flesch-Kincaid Grade level 5.5). In total, 19.9% (52/261) of the messages were peer messages. Overall, 52.9% (138/261) of the messages provided information about behavioral treatments (eg, substitution and distraction); 39.8% (104/261) contained motivational content, such as reasons to quit; 26.8% (70/261) included health-related information, such as the risks of smoking to physical and cognitive functioning; and 19.9% (52/261) addressed how seeking social support or smoking impacted social interactions with family and friends. Multimedia Appendix 2 lists example messages.

Component 2: Ratings Database

The algorithm uses 2 types of ratings data to generate the following recommendations.

First, ratings from prior study participants. More than 1000 participants have rated our messages using the influence rating question (see definition in the Data Elements, Statistical Analysis, and Power Calculation for Specific Aims section) resulting in 18,920 ratings [16,32,33]. We chose the influence rating question after a pilot test in which we asked participants to rate each message on 4 aspects: influence, emotional response, relevance, and preference [33]. We found that all these aspects were highly correlated. In developing the algorithms for the recommender system, we compared ratings by different user profile characteristics. Of the 20 messages rated most highly by participants with less than a high school education, only 3 messages were rated in the top 20 by college graduate participants. Adapt2Quit considers all these variations for message selection.

Second, current ratings from participants in the intervention group using 2-way texting. Adapt2Quit is also programmed to learn from the explicit ratings of participants receiving the messages. Thus, when a participant is sent a text message, it will be accompanied by a question (see definition in the Data Elements, Statistical Analysis, and Power Calculation for Specific Aims section) asking the participant to rate the text message using the influence ratings question. The participant can choose how frequently they wish to rate the text messages. In addition to improving the system, our participants in the pilot studies noted that rating the messages helped them to cognitively process the messages better and remember their content.

Component 3: Machine Learning Algorithm

In our prior publications, we have described our algorithm development in detail [16,32,33]. For the purpose of this paper, we describe our approach and the functioning of the system in brief. We used a strong generalization protocol that involved completely separating test users from train users, learning a model using all the train users’ ratings, freezing all non–user-specific parameters, and finally training the user-specific parameters on a subset of each test user’s observed ratings. We evaluated several recommender methods for accurate prediction, including K-nearest neighbors, probabilistic matrix factorization, collective matrix factorization, and the Bayesian probabilistic matrix factorization (BPMF) [33]. In evaluating rating prediction methods, we used a range of standard performance metrics including root mean squared error, Kendall tau-b, and normalized discounted cumulative gain. In all these tests, BPMF was identified as the best single model. For example, comparing the root mean squared error metric between the different algorithms, there was a small but statistically significant gap (P=.01) between the BPMF and other algorithms as determined by a paired t test with Bonferroni correction. The BPMF model estimates a probability distribution over a joint embedding of users and items into complementary latent spaces. The rating of the given user supplies for a given item is approximated by the expected value of the product of the latent user and item factor vectors representing the user-item

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pair, with the expectation taken over the uncertainty in embeddings.

The intervention participant experience is as follows: during baseline registration, the intervention participant will be asked to rate 5 messages. The recommender system will use these ratings to select the first message. As the intervention unfolds, the participant will be asked to rate each message, and the system will learn and adapt to these ratings [16,32,33]. In the backend, each time the program needs to select a message for an individual, the program sends all the prior ratings provided by the participant and the messages rated by the participant. The system also sends demographic information of the participant. The algorithm then selects the next messages based on these data from the list of messages that have not been sent to the participant. The algorithm was also programmed to choose only from among those messages that matched the participant's readiness to quit status. All participants will receive a new message every time. When they do not rate the message on a particular day, our system will have the 5 messages rated at baseline and the ratings of the prior participants to fall back upon to pick a new message. Because the machine learning algorithms operate as a black box, in our prior study, we conducted an analysis of our messages to uncover the black box of the algorithms and understand the message selection process and have published our results [35].

Flow of the Intervention

Participants in the intervention group receive motivational messages, texting quitline facilitation, and texting assessment of smoking status.

Motivational messages selected by the Adapt2Quit recommender system including ratings for user feedback. Participants receive daily motivational messages for the first 30 days and every 14 days until the end of the study. As noted, participants were asked to read these messages and provide their ratings. They were able to choose how frequently they rated messages.

For texting quitline facilitation, participants in both study arms were asked (via text message) if they were interested in being referred to the quitline every 14 days or until the participant responded "yes" to this question. We have followed current best practices in SMS text messaging to connect users to the quitline as described in the study by Krebs et al [36], who, after assessing multiple message frames, found that including a self-efficacy frame was the most effective. If participants request to be connected, a member of the study team refers them to quitline via a secure web form provided by the Massachusetts and Maryland quitline. As per their standard protocol, once quitline staff receive notice of participant interest, they proactively call the participant and engage in counseling.

For texting assessments of smoking status, participants were asked, "What is your current smoking status?" every 30 days over a 6-month period.

Comparison

To isolate the effect of the Adapt2Quit recommender system, comparison participants do not receive tailored motivational messages but receive the texting quitline facilitation and the texting assessment of smoking status with the same frequency as intervention participants.

Six-Month Data Collection Procedures

Overview

Six-month follow-up was conducted via telephone using the REDCap (Research Electronic Data Capture; Vanderbilt University) system to collect the data. Participants had the option to complete the REDCap survey on their own, with research staff sending the secure REDCap link by either email or text or mailing a paper survey to the participant. The system is designed to first collect the main outcome data and then branch into any intervention or control-specific questions. This way the staff is blinded to the participants' assignment when the primary outcome data are collected. To maximize retention, participants were asked upon enrollment to provide 2 alternate telephone numbers, their physical and email addresses, and any other contact information, as applicable. All this contact information was used in making multiple attempts to reach participants to complete their follow-up assessment, which includes sending a thank you letter and incentives for completing the 6-month visit. Participants in both groups will receive a US $25 incentive for completion of the 6-month follow-up and an additional US $50 for completing the CO verification assessment. A web-based tracking system was used to automatically alert staff about participants due for the 6-month follow-up measure to facilitate timely assessments.

Qualitative Interviews

After completion of the 6-month follow-up visit, intervention participants will be invited to complete the qualitative interview to deepen the understanding of potential mechanisms and ways to improve the next generation of the Adapt2Quit intervention (Multimedia Appendix 1). We are using a purposeful sampling approach to recruit interview participants (n=30). Purposeful sampling is a technique widely used in qualitative research for the identification and selection of information-rich cases for the most effective use of limited study resources [37]. We will select participants based on the extent of engagement with Adapt2Quit, use of the quitline, and eventual quitting success. Study coordinators will contact participants who agree to be interviewed to complete the audio-recorded qualitative interviews. The interviews will be conducted by phone and will examine a series of topics following the hypothesized path model presented in the research strategy (Adapt2Quit increases engagement, which results in external and internal processes causing the participant to implement smoking cessation–supporting behaviors; Multimedia Appendix 1). Across these topics, our goal is to understand what participants value most and to elicit recommendations for further system enhancement. Interviews are semistructured, allowing for natural conversation with opportunities to explore unanticipated issues, and will be no longer than 30 to 45 minutes in duration. All qualitative interview participants will be asked to provide verbal consent before participating in the interview and being audio recorded. For participation in the qualitative interview, participants will receive US $50.

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Data Elements, Statistical Analysis, and Power Calculation for Specific Aims

Data are collected throughout the study at several time points via text-based ratings, quitline use, assessments, questionnaires, and CO readings. Our main outcomes are described subsequently.

Completion of Ratings

Each Adapt2Quit message is accompanied by the influence ratings question as follows: "Please type the number below to indicate whether you agree with this statement—How much does this message influence you to quit smoking"—on a 5-point Likert scale (strongly disagree to strongly agree). Our program tracks the ratings completed for each participant.

Internal Processes

Perceived competence, a key SDT construct, will be measured using the previously validated PCS [23]. The 4-item scale assesses the participant's feelings of being able to stop smoking permanently ("I feel confident in my ability to not smoke," "I now feel capable of not smoking," "I am able to not smoke anymore," and "I am able to meet the challenge of not smoking"). Responses are scored on a 7-point scale from 1 (strongly disagree) to 7 (strongly agree), and individual items are averaged to create a scale mean. In prior work [23], PCS was reliable (α=.95) at the 6-month follow-up [23]. We will assess PCS at baseline and at the 6-month follow-up visit.

External Processes (Quitline and NRT)

Quitline use is assessed using data collected from the quitline. We will send a list of our users and ask quitline to provide data on these users, such as the number of contacts between the smoker and the counselor. We will use the time to first call completed with the quitline counselor as our primary quitline measure. NRT is self-reported (yes or no).

Six-Month Cessation

Assessment of the 6-month smoking cessation is collected using the 7-day point-prevalence question [38]: "Do you currently smoke cigarettes (smoked even 1 puff in the last 7 days)?" Point prevalence can capture an intervention's delayed effects. A psychometric analysis comparing continuous, prolonged, and point-prevalence outcomes found that point prevalence had the highest concurrent validity [38]. The 7-day window provides an appropriately stringent measure to account for a cross-sectional snapshot. Using the CoVita Smokerlyzer breath CO monitor, participants who self-report quitting at the 6-month follow-up will be asked to complete biochemical verification remotely (the device will be mailed to them) or in person. Because of the variability of the device, participants will be asked to repeat the test 3 times. The average of these values will be used for our analyses [39]. Participants will be classified as tobacco users if their CO measurement is >6 ppm [40]. Participants completing remotely will be asked to conduct the test over videoconference, where our staff will monitor and guide them. To complete the biochemical verification, whether in person or remotely, study participants will receive a US $50 gift card.

Data Analysis

Statistical Analysis and Power Calculations

To preserve randomization, all primary analyses will be on an intent-to-treat basis. Secondary analyses will explore dose-response effects among those with variable levels of adherence to the intervention. All analyses will be 2-sided, and the α error level will be set at .05. We will begin by examining univariate statistics (means, medians, SDs, frequencies, percentages, and 95% CIs) and distributions of the variable of interest. We will examine the balance of participant characteristics by study groups and account for any imbalances in our multivariable analysis. To address sex as a biological variable, we will stratify the analyses by male and female to evaluate whether the mechanisms and outcomes are modified by sex. We will test group differences either using chi-square tests of independence (categorical variables), *Z* test, or a 2-tailed *t* test (continuous variables), or the equivalent nonparametric tests depending on the distribution of the variables. Baseline differences between the intervention and control group will be established based on standardized differences, rather than on tests of statistical significance.

Aim 1: Adapt2Quit Engagement

Aim 1 is analyzed within the intervention group (N=375). Engagement will be defined as the number of daily ratings divided by the total number of rating opportunities (percentage of ratings completed).

Hypothesis 1a

Among Adapt2Quit participants, those with higher engagement levels (completed more ratings) will have greater scores on the PCS. For hypothesis 1a, we will explore the distribution of the PCS at baseline and the averaged PCS scores during follow-up. Furthermore, we will analyze the distribution of engagement. It is likely that these distributions will be nonnormally distributed. In this case, we will transform the distribution into something approximating normality or choose a nonparametric test to assess the correlation between engagement and the PCS. We will generate a generalized linear model with the averaged follow-up PCS score as the dependent variable and engagement as the independent variable, adjusting for demographic characteristics that vary between highly engaged and less-engaged individuals and for baseline PCS measurements.

Power for Hypothesis 1a

We have considerable *power* to detect relatively small correlations for secondary analyses. As a preliminary power estimate, if we assume a normal distribution and α=.05, we have 80% power to detect a correlation coefficient as small as 0.2 with 200 patients. For larger, more meaningful correlations, we have well over 90% power starting at a sample of 375.

Aim 2: Behavioral Processes

Hypothesis 2a

Adapt2Quit participants will have higher scores on the PCS than control participants. To analyze hypothesis 2a, we will first create a generalized linear model where the dependent variable is the averaged PCS score during follow-up (see the section

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Hypothesis 1a), the independent variable is randomization group, and the baseline PCS score is included as a covariate. Furthermore, to fully use the repeated measures of the PCS, we will develop a random effects interrupted time series model evaluating the change in slope of PCS over time, comparing the Adapt2Quit intervention and comparison group. This will be implemented using a segmented regression to evaluate changes in slope early in the intervention and sustain change over time in the latter months of the 6-month follow-up.

Power for Hypothesis 2a

In a prior smoking cessation study, the mean (SD) of PCS was 4.79 (1.96) [23]. On the basis of these results, for power calculations, we assumed a meaningful difference in the averaged PCS score to be equal to 1 SD, assumed the mean in control to be 4.79, and set α at .05. To detect a difference of 1 SD, we have 99% power with a sample of 120 participants per group, further demonstrating power for aims 1 and 2.

Hypothesis 2b

Adapt2Quit participants will adopt more cessation-supporting actions (quitline and NRT) than control participants. For hypothesis 2b, the independent variable is again the randomization group. Each dependent variable will be modeled separately. There are several ways to analyze quitline use, including time to first call completed (time from baseline when the first call with the counselor was conducted in a number of weeks) or whether the participant used the quitline and the number of contacts between the patient and counselor. We chose the time to first call completed with the quitline counselor because it matters how quickly the intervention succeeded in motivating participants to call the quitline (if the call happened in the first few days of the intervention or later). The participant may initiate the call, or the counselor can call the participant following a texting referral.

Power for Hypothesis 2b

Analysis and the power calculation for time to first call completed is similar to the hypothesis 3b analysis. The use of NRT will be assessed via self-report at the 6-month follow-up. To analyze NRT use, a dichotomous variable, we will create a logistic model with the use of NRT (yes or no) as the dependent variable and randomization as the independent variable.

Aim 3: Effectiveness

Hypothesis 3a: Primary Outcome

Adapt2Quit participants will have greater smoking cessation rates (6-month point-prevalence biochemically verified) than control participants. For our primary outcome, we will follow recommendations from the Society for Nicotine and Tobacco Research and other experts. While we will attempt to minimize dropout rates loss to follow-up (missing outcomes) in trials such as ours cannot be fully averted [41]. Penalized imputation (missing=still smoking) is not a conservative approach and can be biased (against a group), especially when there is a differential missing between the groups [41]. Thus, the recommended approach is to use inverse probability weighting [42]. In this approach, the first step is to develop a logistic regression model to predict nonmissingness using variables that are found to be different between study participants with and without missing data. The next step is to calculate the inverse probability of nonmissingness and use it as the weight in a logistic regression model to compare the cessation rate between two study groups [43]. Along with inverse probability weighting, we will present penalized imputation and a complete case analysis (limited to those with complete data) as sensitivity analyses. We propose to biochemically verify participants who self-report quitting smoking using a CO meter.

Power for Primary Outcome (Hypothesis 3a)

In our prior National Cancer Institute trial, we observed an absolute 9% difference in the standard messaging versus no-messaging control group [29]. We expect socioeconomically disadvantaged groups to have lower cessation rates than non–socioeconomically disadvantaged groups. Thus, we calculated power using a range of control cessation rates from 7% to 9%. We started at 7%, because it is the estimated rate at which the general population of all individuals who smoke quit without any intervention [34]. On the basis of the recommender enhancements (and further pilot data), we saw an additional marginal difference of 6% at 30 days (even higher for African American individuals who smoke) and expect this difference to continue and expand over time as the recommender system continues to learn and adapt to the individual; however, to be conservative and recognizing the potential difficulty in impacting behavior in this population, we chose to power for a small difference, namely 7%. Although our hypothesis is directional, we have chosen to adopt the commonly used conservative approach of 2-sided tests for all our power calculations. On the basis of a 2-sided chi-square test of equal proportions, α=.05, for all these base rates, we will have 80% power with 600 participants (N=300 per arm). Considering loss to follow-up, we plan to oversample by 25% and thus have budgeted for a total of 750 participants to complete baseline and be randomized. On the basis of our prior experience recruiting from clinical systems, we expect the dropout rate to be lower than the 25% we have assumed in our calculations.

Hypothesis 3b: Mediation Analysis

Measured internal and external processes will mediate the effect of Adapt2Quit on smoking cessation. Adapt2Quit is expected to result in several interconnected processes (Adapt2Quit increases personal relevance, thereby improving system engagement, which results in increasing the external and internal processes, causing the participant to implement cessation-supporting behaviors resulting in smoking cessation; Figure 1). We will explore the pathways using modern mediation and structural equation modeling (SEM) techniques. Mediation occurs when an independent variable (X) leads to a given outcome (Y) through an intervening process (M). In our case, the independent variable is the Adapt2Quit recommender (X), and the outcome will be 6 months of smoking cessation (Y). Perceived competence and adoption of cessation-facilitating behaviors (use of quitlines, use of NRT, and adoption of behavioral strategies) are all potential mediators (M). The mediation analyses will focus on each individual process variable, using the classic mediation principles modified from Barron and Kenny [44]. This approach requires 3 regression models and decomposes the total effect (*c*) of the independent

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variable (X) into a direct component (*c'*) and an indirect or mediated component (c-c'). Limitations to the modified Barron and Kenny approach include the fact that more complex mediation pathways with multiple steps are not allowed. Thus, we will implement SEM using Mplus as the covariance analysis software. SEM allows for the simultaneous estimation of multiple regression equations representing complex mediation pathways, allowing errors to be correlated across equations. Furthermore, constructs may be represented as latent variables to relax the assumption of no measurement error. An array of diagnostic tests (eg, root mean square error of approximation and comparative fit index) are available to examine model quality.

Figure 1. Hypothesized path model depicting associations among constructs. NRT: nicotine replacement therapy.

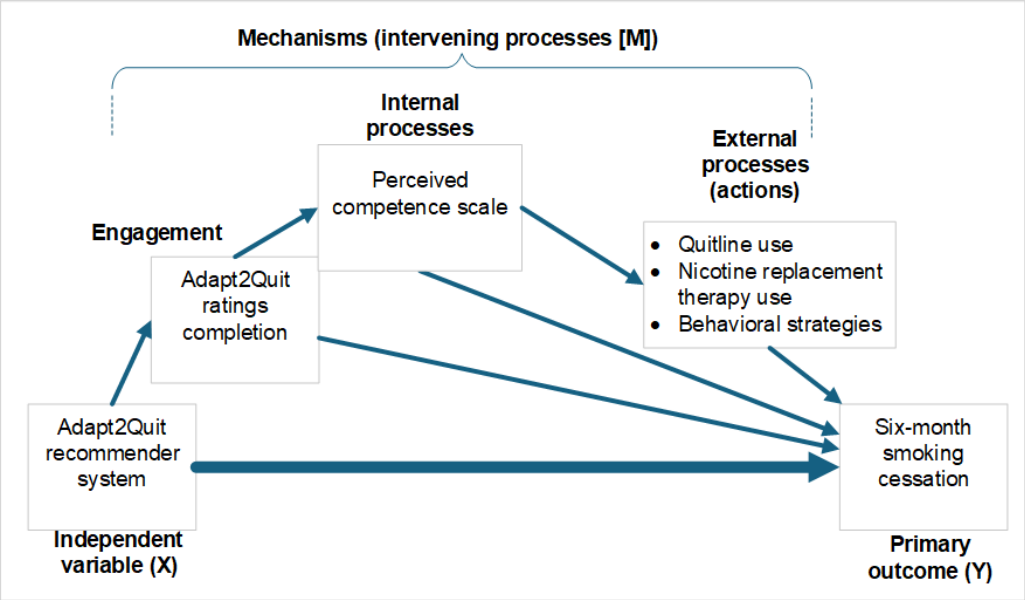

Qualitative Interview Analysis

We will transcribe the interviews verbatim and will use the rapid qualitative analysis method to code the transcripts. The rapid qualitative method uses triangulation and iterative data analysis to quickly develop a preliminary understanding of a situation from the insider's perspective [45-47]. In this method, primary topics or "domains" will be taken from the topics addressed in the interview guide to create summary templates. Two research team members will each code at least 10% of the interview transcripts, and coding checks will be completed to ensure interrater reliability. We will use the summary templates to create a matrix to analyze each domain's depth and breadth of data. From these, we will identify study themes and subthemes using the matrix. The research team will collaboratively and iteratively review, discuss, and sort the data to refine the initial themes and subthemes and highlight the most salient quotes. Recordings collected during interviews will be deidentified using subject ID numbers. No identifiable information, such as a full name, will be collected in the recording. Identifiers will be collected separately and will be stored in an encrypted form. Recordings will be transcribed and deidentified. They will be stored in a secured UMass Chan drive specified for the study within the UMass Chan IS regulated environment, where only UMass Chan study staff will have access to them. Recordings, and all other data collected in this study, will be retained and destroyed in accordance with Standard Operating Procedure Human Research Protection-800. Transcripts of audio or video recordings as well as the audio or video recordings themselves will be fully destroyed 6 years from the conclusion of the study period or at the request of the individual to whom that data belongs.

Results

This trial was funded in April 2020 and is currently ongoing. As of May 2024, we had enrolled 757 participants, and 591 (78.1%) of them had completed the 6-month follow-up interviews (Figure 2). We anticipate that data analysis and final manuscript preparation will occur in late 2025. Multimedia Appendix 3 provides the demographic and screening survey responses of 757 participants.

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Figure 2. CONSORT (Consolidated Standards of Reporting Trials) diagram. EMR: electronic medical record.

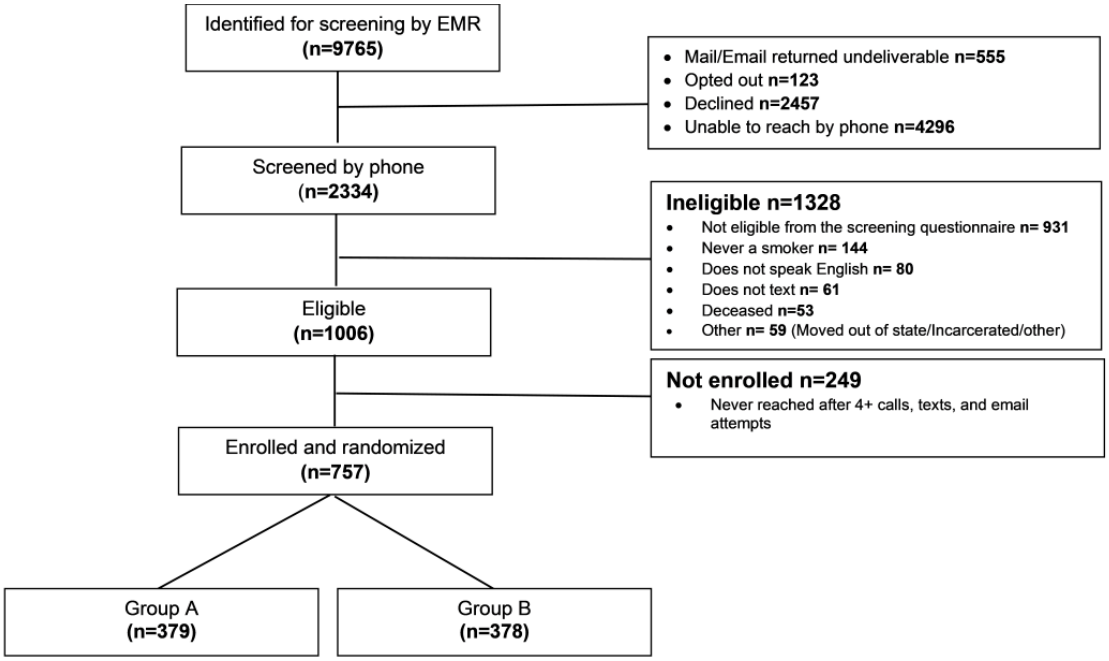

Discussion

Principal Findings

This study protocol describes a randomized controlled trial to test a machine learning algorithm–based, computer-tailored health communication system for smoking cessation. We hypothesized that the intervention will impact mechanisms of action—specifically engagement, competence (a theoretical construct), and adoption of cessation-supportive actions—as well as demonstrate effectiveness in promoting smoking cessation. Our system will test these hypotheses among individuals who are socioeconomically disadvantaged, a group disproportionately affected by smoking.

Because of the potential for wide reach and effectiveness, texting programs (especially texting) have been increasingly adopted in real-world settings worldwide (public health and within health care systems) [48-50]. For example, the World Health Organization has helped establish texting programs for smoking cessation in several countries, including Costa Rica, Tunisia, and India [51]. The US Department of Health and Human Services established a Text4Health Task Force in 2010 to promote health text messaging programs in the United States [48]. In 2017, 55% of state quitlines offered texting programs (up from 20% in 2012) [34,52]. There is now growing evidence that these programs can be effective. An evaluation of SmokefreeTXT (a free evidence-based smoking cessation program offered by the US National Cancer Institute) reported that point-prevalence abstinence for smokers who initiated treatment at completion of the 42-day program was 7.2% (3% at the 6-month follow-up) [53]. Leaders have called for continued innovations to increase the effectiveness of these health messaging programs, especially to increase effectiveness with smokers from socioeconomically disadvantaged backgrounds.

Our study will provide important evidence on whether a more personalized approach using machine learning can encourage quitline use and support smoking cessation, compared to a text-based referral to quitline. In previous papers, we described our pilot studies testing the Adapt2Quit intervention [16,35,54]. Furthermore, our prior large randomized controlled trial compared the Adapt2Quit intervention to a system that delivered messages based on participants' baseline readiness to quit [17]. In that trial, we recruited participants online as well as through referrals from friends and family. In addition, messages were delivered by email rather than by text, as is being done in this trial. The previous study also did not include biochemical verification of smoking cessation. Beyond the potential benefit of computer-tailored messaging, our system aims to actively engage participants with the quitline. Quitlines have proven to be effective in supporting people to quit smoking, yet using a quitline and attending counseling sessions is a significant step for individuals from socioeconomically disadvantaged backgrounds who smoke. Currently, only 2% to 3% of people who smoke use the quitline, with usage rates even lower among individuals from socioeconomically disadvantaged backgrounds [34]. Prior research has shown that it is possible to use a low-intensity intervention such as texting to increase motivation and the use of cessation resources among people who smoke [55].

In addition to our system, one group compared a similar recommender system in a pilot trial to a system that selected messages based on a knowledge base. They compared the message appreciation, engagement with the system, and one's own self-reported smoking cessation status (7-day point prevalence) [18]. Another group developed a recommender system for smoking cessation and promoting physical activity [56]. This group described an experiment they conducted to identify the optimal approach for selecting messages. In addition, a systematic review examined the potential of using another machine learning approach—reinforcement

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learning—for similar purposes [57]. Together, these approaches highlight the potential of the use of machine learning approaches to enhance a widely used behavioral intervention: computer-tailored health communication.

Because we have completed recruitment for our study, we also provide the characteristics of our participants. Our recruitment method, using an opt-out strategy at 3 different health care systems, was able to successfully recruit a diverse sample. A third of our sample (265/757, 35%) are Black, and 16% (121/757) self-identified as Hispanic or Latino. There may be several factors for our successes, including that our intervention is a low-intensity intervention using a texting model that is widely available. Furthermore, our procedures for screening, baseline, and follow-up are all remote, which may have reduced barriers to recruitment. Participants in our study indicated higher motivation levels than the general population. This is an artifact of our recruitment strategy that people who are more motivated participate in a study about tobacco cessation. This more representative sample implies that our study findings will be more generalizable to the US population.

Strengths and Limitations

We describe the protocol for a rigorous evaluation of behavioral intervention among individuals from socioeconomically disadvantaged backgrounds. Since recruitment for our study is complete, we also present participant characteristics. Using an opt-out recruitment strategy across 3 different health care systems, we successfully recruited a diverse sample, which has been challenging to achieve for clinical trials. Our fully remote procedures for screening, baseline, and follow-up may have reduced barriers to recruitment. Notably, 35% (265/757) of our sample identified as Black and 16% (121/757) as Hispanic or Latino. This more representative sample suggests that our study findings will be more generalizable to the US population. One limitation is that our participants reported higher motivation levels for quitting smoking than the general population, which is likely due to the recruitment strategy attracting those who were more motivated to participate in a tobacco cessation study. Because we only used insurance status to determine socioeconomically disadvantaged, some participants may not align with all characteristics that may describe socioeconomically disadvantaged.

Conclusions and Future Work

Our project is the first to rigorously test the use of a recommender system for smoking cessation among individuals from socioeconomically disadvantaged backgrounds who smoke. In this paper, we have reported on protocols for conducting a rigorous trial. In addition to our primary analyses for the 3 aims, we will conduct exploratory analyses to assess the heterogeneity of treatment effects across these subgroups, which could yield valuable insights for future tobacco cessation efforts. Our follow-up papers will report on the results of our trial following the analysis plans described in this paper. Future studies will also explore implementing texting interventions in various clinical and public health settings.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Telephone screening script, consent form, baseline survey, and 6-month follow-up survey.
[PDF File (Adobe PDF File), 716 KB - resprot_v14i1e63693_app1.pdf]

Multimedia Appendix 2
Example motivational messages (expert and peer).
[DOCX File , 22 KB - resprot_v14i1e63693_app2.docx]

Multimedia Appendix 3
Participant demographic and screening survey responses (N=757).
[DOCX File , 31 KB - resprot_v14i1e63693_app3.docx]

Multimedia Appendix 4
SPIRIT-AI checklist.
[XLSX File (Microsoft Excel File), 15 KB - resprot_v14i1e63693_app4.xlsx]

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Abbreviations

BPMF: Bayesian probabilistic matrix factorization
CO: carbon monoxide
IRB: institutional review board
NRT: nicotine replacement therapy
PCS: Perceived Competence Scale
REDCap: Research Electronic Data Capture
SDT: self-determination theory
SEM: structural equation modeling
UMass Chan: University of Massachusetts Chan Medical School

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Protocol

Text Message Intervention to Facilitate Secure Storage and Disposal of Prescription Opioids to Prevent Diversion and Misuse: Protocol for a Randomized Controlled Trial

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Abstract

Background: Nonmedical use of prescription opioids remains a critical public health issue; 8.5 million people in the United States misused opioids in 2022. Most people obtain prescription opioids for misuse from family or friends. Thus, facilitating secure storage and disposal of opioid medications during and after treatment is needed to prevent medication diversion and subsequent misuse.

Objective: The primary objective of this study is to test the feasibility and efficacy of a novel intervention that uses a persuasive, informational SMS text message reminder system to enhance the impact of secure storage and disposal of unused opioid medications. We hypothesize that the SMS text message intervention will increase secure storage during treatment and disposal of prescription opioids after treatment.

Methods: We will use a 2-arm randomized controlled trial to test the intervention for feasibility and efficacy. Participants (aged 18+ years who have received an opioid prescription in the past 2 weeks) will be randomly assigned to either receive the SMS text message intervention or standard-of-care educational materials. Participants in the intervention will receive 4 SMS text messages related to secure storage and 3 messages related to disposal. All participants will complete baseline, midpoint (day 25), and postintervention (day 45) evaluation surveys. We will test whether receipt of the intervention is associated with two primary outcomes, which are (1) secure storage of prescription opioid medication (locked vs unlocked) and (2) disposal of unused prescription opioid medication (disposed vs not disposed). We will use multiple logistic regression to test the main hypotheses that the intervention will be positively associated with secure storage (locked vs unlocked) and disposal (yes vs no) behaviors, which will allow us to control for demographic variables known to influence the outcomes. This protocol represents the entire structure of the randomized controlled trial.

Results: Recruitment for the randomized controlled trial was launched in April 2024, and data collection was completed in December 2024. The final sample size is 484. Data analyses for the main hypothesis will be completed by May 2025, and the main hypothesis manuscript will be submitted for publication by May 2025.

Conclusions: Results from this study will indicate whether a text message reminder system can increase secure storage and disposal behaviors for individuals who receive opioid medication. This type of intervention has the potential to be integrated into

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currently used health care delivery systems, such as prescription pickup reminders at pharmacies. Thus, the intervention is scalable across systems of care, thus expanding the reach of secure storage and disposal programs to prevent prescription opioid misuse.

Trial Registration: ClinicalTrials.gov NCT05503186; https://clinicaltrials.gov/study/NCT05503186

International Registered Report Identifier (IRRID): DERR1-10.2196/60332

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KEYWORDS

prescription opioid; storage; disposal; text message intervention; randomized controlled trial; mobile phone

Introduction

Statement of the Problem

Despite efforts in the United States to reduce the number of opioid prescriptions through prescribing guidelines [1,2] and drug monitoring programs [3,4], mortality rates due to the nonmedical use of prescription opioids have remained high since their peak in 2010 [5]. National data estimates that 6.1 million people met the criteria for opioid use disorder and 8.5 million (3%) misused prescription opioids in 2022 [6]. The majority of people obtain prescription opioids for misuse from family or friends, with or without their knowledge [6]. Furthermore, many opioid medications go unused; a meta-analysis of postoperative opioid consumption for acute pain by US adults found that 61% of medications [7] remain after treatment. Unused prescriptions can lead to medication diversion, which is the primary source of prescription opioids for misuse [6]. Facilitating secure storage and disposal of opioid medication during and after treatment is needed to prevent medication diversion.

In an early response to the opioid crisis, the Office of the National Drug Control Policy disseminated a plan that included secure storage and disposal of unused opioid medications as key strategies for prevention [8]. This plan specified the need to educate patients on the proper storage and disposal of prescription medications. The Centers for Disease Control and Prevention recommends that medication is stored out of reach of children and pets and opioid medications should be stored in a locked cabinet or drawer [9]. The US Food and Drug Administration (FDA) endorses multiple methods to dispose of unused prescription opioids when they are no longer needed, including medication take-back days, disposal boxes, mail-back programs, and deactivation kits [10,11]. Currently, the FDA also recommends flushing certain types of medications in the toilet or putting them in the trash if other options are not available [12]. The guidance on flushing unused medications is in contradiction to that provided by the US Environmental Protection Agency [13].

Despite the release of the Office of the National Drug Control Policy plan over a decade ago and guidance on secure storage and disposal from federal agencies [9,10,12,13], evidence suggests uptake of the simple behavior of secure storage and disposal is limited. For example, in a study of a nationally representative panel of 1032 adults who had been prescribed an opioid medication, only 8.6% (n=89) stored their medication in a locked location [14]. Similarly, in a study of 113 patients prescribed opioids for cancer pain, only 15% (n=17) locked their opioids while 36% (n=41) stored opioids in plain sight; however, 73% (n=82) indicated a willingness to store their medications in a locked location [15]. Across multiple studies of individuals prescribed opioids for chronic and acute pain, less than a third reported disposal of unused opioid medications [16-19]. Hence, there is significant room for improvement in opioid medication storage and disposal practices.

There is emerging evidence that a more targeted intervention at medical facilities may enhance the secure storage and disposal of unused opioid medications. Several studies have examined the provision of an educational pamphlet to patients who receive an opioid prescription for acute pain [20-23]. In general, the educational pamphlets contained brief information about nonmedical prescription opioid use and instructions for secure storage and disposal. All studies found statistically significant intervention effects on self-reported storage and disposal of unused prescription opioids [20-23]. That is, a targeted intervention to facilitate secure storage and disposal by patients receiving an opioid prescription improved the uptake of these preventive behaviors. However, the rates of utilization of these practices remained low. Across these studies, secure storage did not improve and 48% (45/86) to 78% (37/170) of patients who received an educational pamphlet still did not dispose of their unused opioid medications, which indicates that additional intervention is warranted.

The high prevalence of opioid prescriptions that are not fully used demands an intervention that can scale widely. The widespread adoption and instantaneous nature of mobile phones make them a promising vehicle for economical and systems-based interventions. Almost all (1442/1502, 96%) of US adults have a mobile phone with SMS capabilities [24], indicating that text interventions have the potential to serve as a universal intervention delivery method. Digital health systems have already been implemented in pharmacies. Many pharmacies have established systems that alert patients via text message when medications are ready to be picked up. Patients report that they prefer to receive health information from medical practices via SMS text messages over other forms of communication [25]. Half of pharmacy patrons already use existing pharmacy-based text reminders and smartphone apps [25]. Thus, delivering reminders about the secure storage and disposal of prescription opioids via SMS text messages represents a scalable intervention across systems of care.

Theoretical Frameworks

The study is informed by 2 theoretical frameworks (Figure 1). First, the Message Impact Framework [26] suggests that message characteristics affect the extent to which the message will be

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noticed and later recalled. An individual's reaction to the message impacts their knowledge, attitudes, and risk beliefs, which in turn impact intentions and actual behavior. Furthermore, exposure to messages can elicit interpersonal communication and social interactions which further spread and influence individuals' attitudes, beliefs, and reactions to the messages. Second, the Health Belief Model (HBM) [27] posits that messages will generate behavior change if they target perceived barriers, benefits, threats, and self-efficacy specific to the behavior. Specifically, attitudes and beliefs pertaining to perceived seriousness and susceptibility to harms result in the formation of a perceived threat. Along with perceived threats, beliefs about the benefits of and barriers to performing a behavior paired with self-efficacy to do so influence whether an individual will perform the behavior. A cue to action, such as an SMS intervention, serves as a trigger or motivator to perform the behavior, such as securely storing and disposing of prescription opioid medications.

Figure 1. Conceptual framework.

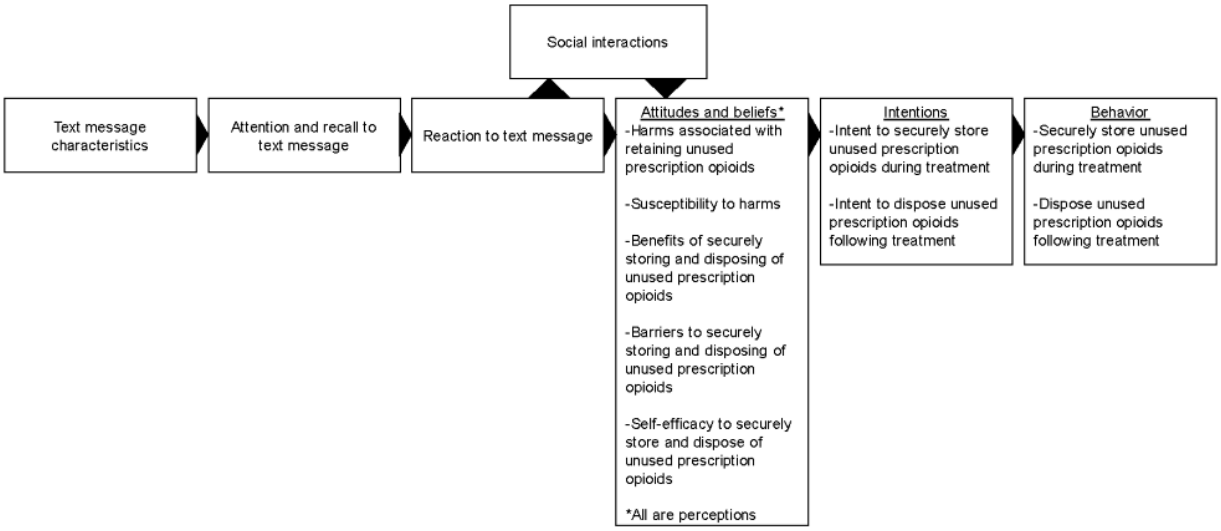

Objective

The overall objective of the study is to test the feasibility and efficacy of a novel, evidence-informed strategy that uses a persuasive, informational SMS text message reminder system to expand the impact of secure storage and disposal programs. Our central hypothesis is that the implementation of an SMS text message intervention will increase the secure storage of opioid analgesics during treatment and disposal following treatment.

Methods

Overview

This study uses a 2-arm, single-blinded, randomized controlled trial (RCT) design (Figure 2). Participants are randomly assigned into either the SMS text message intervention condition or a standard-of-care control group. Participants will complete baseline, midpoint (day 25), and postintervention (day 45) evaluation surveys, described further in this study. The primary trial site is Wake Forest University School of Medicine.

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Figure 2. Planned randomized controlled trial study design.

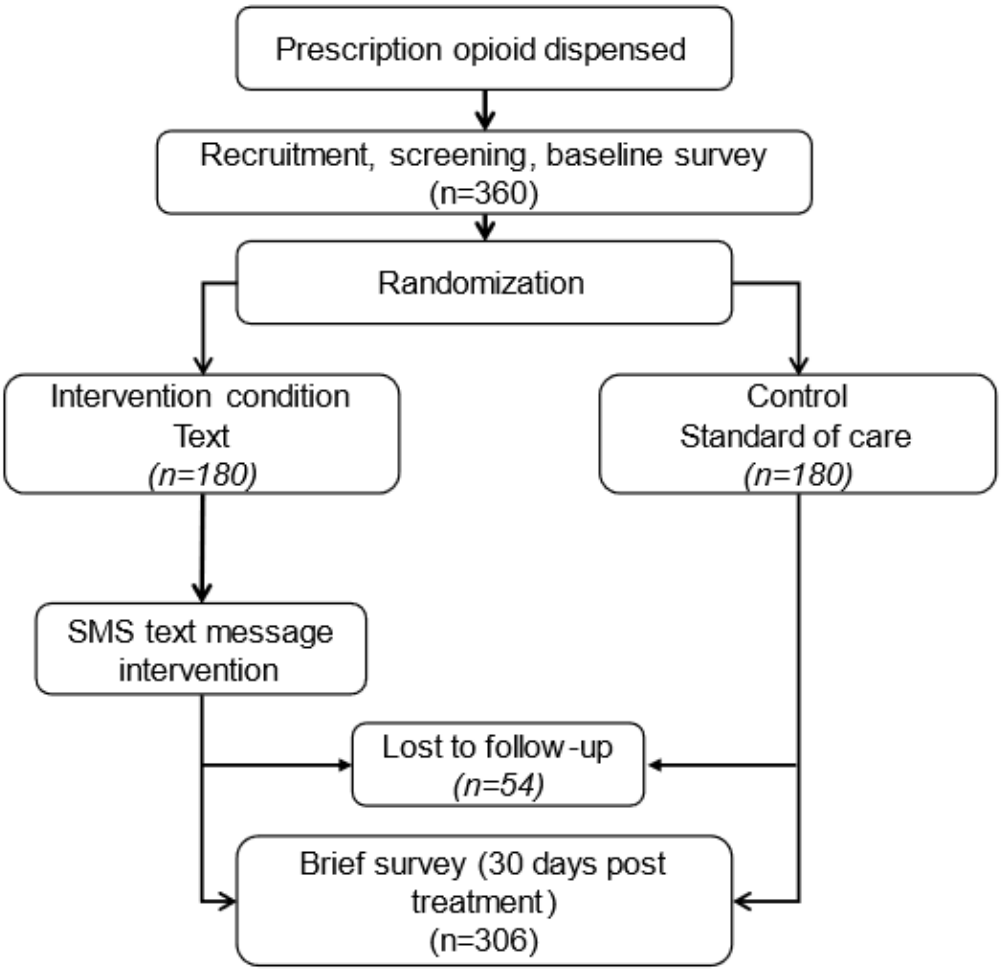

Ethical Considerations

This protocol has been approved by the Wake Forest University School of Medicine Institutional Review Board (IRB; IRB00102139).

The consent form will be self-administered on REDCap (Research Electronic Data Capture; Vanderbilt University). Potential participants will review the consent without the assistance of a study team member and will be directed to the study team if they have any questions. In lieu of a signature, participants will be informed that they should "click 'I agree to participate' at the end of the consent form" to provide their authorization to participate in the study. The consent form will use language approved by the Wake Forest University School of Medicine IRB that is designed for readability and includes the general topic of the study, the name of the principal investigator, the principal investigator's contact information, the IRB approval number, and the phone number of the IRB at Wake Forest University School of Medicine. Participants will be reminded that they are not required to answer questions (other than for eligibility), that they can end participation at any time, and that there is no obligation to participate. Given that participants for the RCT may be patients at a participating institution, they will be reminded during the consent process that participation will not impact their treatment or future access to medications.

To recruit participants, we will maintain a spreadsheet that has identifiable information of individuals who have met the study criteria stored electronically on a secured device and IRB-approved cloud system. The purpose of this spreadsheet is to ensure that potential participants are not invited to participate more than once. After ascertaining consent to participate, unique identifiers will be assigned to participants, and identifiers will be stored separately from the data. To minimize the likelihood of a breach in confidentiality, data will be collected and stored in REDCap, a secure web application for building and managing online surveys, and on a secure and encrypted storage system maintained by Wake Forest University School of Medicine IT security.

All participants in the RCT will be provided with incentives following completion of the baseline survey, midpoint survey, and postintervention surveys, in the form of an electronic US $25 Amazon gift card per survey. Participants will be asked if they are willing to upload a photo of their prescription opioid bottle or box for an additional US $5 Amazon gift card. The maximum amount of money that a participant may receive for participation in this study is US $80. Electronic gift cards will be provided via SMS text message to study participants.

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Participants

Eligibility

Individuals are eligible to participate if they are 18 years of age or older, able to read and speak English, own a cell phone with the capability of receiving SMS text messages, within 14 days of being dispensed a prescribed opioid medication, and have an opioid prescription that is for 30 days or less.

Sample Size

We plan to enroll 360 participants (n=180 per condition) based on assumptions from an RCT using a text intervention that encouraged parents to vaccinate their adolescent child [28] and an RCT that assessed the delivery of a deactivation product with educational material by medical staff on self-reported disposal of unused opioids [29]. Power calculations based on proportions of vaccine completion for the group exposed to the SMS text message intervention (0.49) and the unexposed group (0.30) [28] indicate a total of 230 participants will be needed to detect a difference in the impact of an SMS text message intervention. Power calculations based on the proportions of disposal for the group who received the deactivation product intervention (0.72) and the unexposed group (0.56) [29] indicate a total of 306 participants will be needed to detect a difference in the disposal of unused opioid medications. We based our sample size on the more conservative estimates [29]. To account for a 15% (12/79) loss to follow-up [21], we plan to recruit an additional 54 participants for a total of 360 participants.

Recruitment

We will use a multimethod approach to recruit participants for the RCT. Potential participants will be identified through the Advocate Health electronic health records. Biweekly, we will receive medical record numbers of Advocate Health patients who were recently prescribed an opioid medication. These individuals will be sent an SMS text message via their Advocate Health MyChart inviting them to participate in the RCT. We will also post flyers in local pharmacies with study information. Participants will be directed to a self-administered consent form programmed in REDCap. If the participant consents to participate, they will complete the self-directed web-based eligibility screener.

Screening and Randomization

If the individual is eligible to participate in the RCT, they will transition immediately from the eligibility screening questions to the baseline survey questions. Following completion of the baseline survey, a study team member will be notified so they can randomize the new participant to study condition. Randomization will occur within REDCap using simple randomization procedures to randomly assign participants to the intervention or control conditions. Randomization will be stratified by biological sex of the participant. An external module has been integrated into REDCap to confirm that each new participant is unique based on their phone number and email address.

Intervention

Procedures (Intervention Condition)

Participants in the intervention group will receive a series of SMS text messages to securely store prescription opioids during treatment and dispose of unused prescription opioids. Twilio will be used to deliver text messages to participants. Twilio is a third-party web service that integrates with REDCap, allowing users to send survey invitations and alerts or notifications to participants as SMS text messages or voice calls. It acts as a conduit between participants' mobile devices and the REDCap project. The intervention will last for 45 days and will start immediately following the completion of the baseline survey. All participants randomized to the intervention study condition will receive 7 identical SMS text messages over the course of the intervention. Participants will receive 4 SMS text messages about storing their medications before the midpoint survey which will take place on day 25 of the research study. SMS text messages about the disposal of unused medications will begin after day 31 of the intervention to ensure that all participants would have completed their treatment regimen. Participants will receive 3 SMS text messages about disposing of their unused medications before the postintervention survey, which will take place on day 45 of the research study. Participants will receive 1-2 SMS text messages about storing and disposing of their unused medications per week, reflecting participant feedback from the first phase of this study, which focused on the development of the SMS text message content (Textbox 1) [29]. The order in which all SMS text messages are delivered will be randomized. The recommendations for storing medications have been endorsed by the Centers for Disease Control and Prevention [9], and recommendations for disposal are currently endorsed by the FDA [10].

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Textbox 1. Participant-derived SMS text messages.

Storage messages

- It is your prescription, not theirs. Keep your medication hidden and out of reach.
- Locking up your prescription pain pills could save a life. Keep them in a locked location such as a cabinet or box.
- Your favorite hiding spot could save a life. Keep your pain pills where someone would not look for them.
- Your prescription can become someone else's addiction. Lock up your pain pills.

Disposal messages

- Dispose of your unused medications. You may save the life of someone you love. Dispose in a way that works best for you: Return them to the pharmacy, use a home disposal kit, or mix pills with an undesirable substance and put in your trash.
- Discarding your unused pain pills could save a life. Dispose in a way that works best for you: Return them to the pharmacy, use a home disposal kit, or mix pills with an undesirable substance and put in your trash.
- Your prescription can become someone else's addiction. Safely discard unused or expired medications. Dispose in a way that works best for you: Return them to the pharmacy, use a home disposal kit, or mix pills with an undesirable substance and put in your trash.

Control Condition

Individuals who are assigned to the study control condition will receive the standard of care provided to them from their prescribing physician and dispensing pharmacist. Immediately after completing the postintervention survey, participants will receive information on ways to securely store and dispose of unused opioid medication. This information will be provided in the REDCap survey.

Data Collection and Measures

Evaluation

Participants will complete 3 evaluation surveys. Each evaluation will be delivered via a secure link to a web-based REDCap survey. The baseline survey will be completed directly following study enrollment. A midpoint survey will be sent 25 days after study enrollment, and a final postintervention survey will be delivered 45 days after study enrollment. The baseline survey assesses sociodemographic characteristics, information about the prescribed opioid medication, and past medication storage and disposal behaviors. The midpoint and postintervention surveys ask about how the participant has been storing their opioid medication, if they are still using their opioid medication, if they have disposed of their medication, and their intent to dispose of their medication. Participants assigned to the intervention study condition will provide feedback on the SMS text message intervention in the postintervention survey. Those who were assigned to the control study condition will share what they would like to receive in an SMS text message intervention. All surveys will also query perceptions in alignment with the HBM (eg, perceived barriers, and benefits) [27] about securely storing and disposing of their opioid medications.

Primary Outcomes

We will use 2 primary outcomes based on data from the postintervention survey. Pertaining to storage of opioid medications, participants will be asked, "Where do you usually store your prescribed pain medication?" with response options of (1) in an unlocked box, closet, cabinet, or drawer; (2) in a locked box, closet, cabinet, or drawer; (3) in a purse, backpack, or other carrier; (4) out in the open; (5) other; or (6) unsure where kept. We will create a binary variable for storage of locked (in a locked box, closet, cabinet, or drawer) versus unlocked (all other responses) to test study hypotheses. Related to disposal behaviors, for participants that indicate they had no leftover medications, we will create a binary variable based on the disposal method of the medication (put in the trash, used deactivation product, used a prepaid mail-back envelope, flushed in the toilet, returned them to the pharmacy, or took them to law enforcement agency) versus not disposed (gave them to friend or family member or something else).

Secondary Outcome

For participants who indicate they have medication from their prescription leftover, we will create an intention to dispose variable based on the item "What do you intend to do with your remaining prescription pain medicine?" The binary variable will denote intent to dispose (put them in the trash, use deactivation product, use prepaid mail-back envelope, flush in the toilet, return to pharmacy, or take to law enforcement agency) versus do not intend to dispose (keep them, gave them to friend or family member, or something else).

Other Measures

At the baseline and postintervention time points, we will assess measures derived from the HBM including self-efficacy (eg, I know how to properly dispose my prescription medication), barriers (eg, I do not have access to a locked location where I can securely store my prescription pain medication), benefits (eg, disposing my unused prescription pain medications can stop someone else from taking them), perceived severity (eg, I think there are risks to having prescription pain medication in my home), and perceived susceptibility (eg, I worry about having prescription pain medication in my home). At the midpoint and postintervention time points, we will also assess the SMS text messages themselves using items derived from the Message Impact Framework, including whether the participant felt the SMS text messages grabbed their attention, were easy to understand, and made them think about the risks of having prescription pain medicines in their homes.

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Data Management

Before ascertaining consent to participate, we will maintain a spreadsheet stored electronically on a secured device and IRB-approved cloud system that has the name, phone number, and email address of individuals identified via Advocate Health electronic health records who have met study eligibility criteria. This spreadsheet will include the date we contacted the individual and the way in which we contacted them. The purpose of this spreadsheet is to ensure that an individual is not invited to participate more times than approved by the IRB. This spreadsheet will also have a unique identifier, which will be linked to data pertaining to their prescription number, medication list (ie, opioid prescription only), age, gender, and race or ethnicity. We will retain this information for use in the event that they consent to participate in the study. The spreadsheet will be destroyed once recruitment has closed. To minimize the likelihood of a breach in confidentiality, data will be collected and stored in REDCap, a secure web app for building and managing web-based surveys, and on a secure and encrypted storage system maintained by Wake Forest University School of Medicine IT security. Public access to deidentified data will be made public at the conclusion of the study.

Data Analysis

Design and Data Preparation

Analyses will be conducted to assess group differences on the two primary dichotomous outcomes, which are (1) secure storage of the opioid medication (locked vs unlocked) and (2) disposal of unused medication (disposed vs did not dispose). We will use a modified intention-to-treat (ITT) design. While an ITT design minimizes bias and type 1 error, it is often considered a conservative approach that may increase type 2 error [30]. A modified ITT design allows for the exclusion of some randomized subjects in a justified way to achieve the goal of minimizing both type 1 and 2 errors [30]. For this study, we will retain the ITT approach by including all participants regardless of their compliance with the SMS text message intervention. We will modify the ITT approach by excluding participants who do not have outcome data since we will not have a mechanism to assess their storage or disposal behaviors, which could inflate type 2 error if retained in analyses. We will first test for group equivalence in demographic and household characteristics of the participant, diagnosis and treatment, and information about the prescribed opioid (eg, type, number of pills, and duration of treatment). Group differences are not expected in the context of randomization; however, if one of these variables is associated with both a condition and an outcome variable, we will include it as a covariate in subsequent analyses using that outcome. Data will be compiled and screened for integrity, outliers, missing values, and violations of the assumptions of logistic regression. Missing values will be handled in regression analyses using full maximum likelihood estimation.

Statistical Analyses

We will use multiple logistic regression to test the main hypotheses that the intervention will be positively associated with secure storage (locked vs unlocked) and disposal (yes vs no) behaviors, which will allow us to control for demographic variables known to influence the outcomes. We will use a 2-step logistic regression to predict each outcome. In step 1, demographic variables will be entered into the model. We will retain variables significantly associated with the outcome at a significance threshold of $\alpha<.05$. In step 2, the intervention condition will be entered into the model.

Results

Recruitment for the RCT was launched in April 2024, and the first participant enrolled in the study in June 2024. The primary completion date, defined as the date on which the last participant in a clinical study completed the postintervention survey, was in December 2024. The final sample size is 484. Data analyses for the main hypothesis will be completed by May 2025, and the main hypothesis manuscript will be submitted for publication by May 2025.

Discussion

Contributions to the Literature

The overall objective of the study is to test the feasibility of a novel, evidence-informed strategy that uses a persuasive, informational SMS text message reminder system to expand the impact of secure storage and disposal programs. Our central hypothesis is that the implementation of an SMS text message intervention will increase the secure storage of opioid medication during treatment and disposal following treatment. The intervention will be tested with a 2-arm, single-blinded, RCT design. Participants in the intervention group will receive a series of 7 SMS text messages about securely storing prescription opioids during treatment and disposing of unused prescription opioids. The SMS text messages have been developed and refined by end users of the intervention [31].

The status quo is to encourage secure storage and disposal of unused prescription opioids with the implementation of disposal programs [28,29], community-wide awareness campaigns [32], educational pamphlets [20,21], and drug deactivation products [29,33] delivered by medical providers. Current research indicates the need for improved interventions that effectively facilitate secure storage and disposal of unused prescription opioids. Our study adopts an evidence-based intervention strategy, SMS text messages on mobile phones, for a novel purpose—facilitation of secure storage and disposal of prescription opioids. We use a theoretically driven and user-derived messaging delivered in an SMS text message intervention during a critical window of need following receipt of a prescription opioid medication. The findings from the proposed study have the potential to be scalable across multiple systems of care and expand new horizons for medical systems to use existing digital technologies to improve patient care.

Limitations

Several limitations may impact this study. Individuals will be eligible to participate within 14 days of receiving their opioid medications. Thus, individuals with shorter prescriptions may receive SMS text messages about secure storage after they have completed treatment and receive SMS text messages about

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disposal after they have already disposed of their unused medication. We will only recruit individuals who have an opioid prescription for 30 days or less, so findings may not be generalizable to patients who have more than a 30-day prescription. We will not be able to control exposure to external messaging about storing or disposing of opioid medications, but we will be assessing self-reported exposure to messaging. While we will be able to track the delivery of all SMS text messages, we cannot assess if they are received or read by the study participants. A systematic, 2-phase approach was used to refine the text messages for the SMS text message intervention using both focus groups and a Qualtrics (Silver Lake) panel [31]. It is possible, but unlikely, that the SMS text messages will not resonate with or be well received by the participants in the RCT. The RCT is being conducted during an election cycle. Participants may be getting more SMS text messages than usual during this period, which may detract from their attention to the study text messages.

Conclusion

Upon successful completion of the study, we will have developed and pretested a systems-level, scalable intervention using mobile technology for the secure storage and disposal of unused prescription opioids, which could be implemented in pharmacies and other medical systems. This contribution is expected to be significant in that facilitating secure storage and disposal of unused prescription opioids should reduce the accumulation of these medications that would otherwise be accessible for nonmedical use. Due to the decreased availability of unused prescription opioids, we would expect to see a decline in the prevalence of nonmedical prescription opioid use and associated consequences. Without the identification of strategies that effectively and universally facilitate secure storage and disposal of unused opioid medications, opioid medications with misuse potential will remain in communities, increasing the likelihood for nonmedical prescription opioid-related morbidity and mortality.

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Data Availability

Deidentified data collected during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

KLE contributed to conceptualization, methodology, investigation, resources, writing – original draft, writing – review and editing, supervision, project administration, and funding acquisition. MJC contributed to conceptualization, methodology, investigation, writing – original draft, writing – review and editing, and funding acquisition. DWH contributed to conceptualization, methodology, investigation, writing – review and editing, and funding acquisition. JTJ contributed to conceptualization, methodology, investigation, resources, writing – review and editing, and funding acquisition. ARR contributed to conceptualization, methodology, investigation, writing – review and editing, and funding acquisition.

Conflicts of Interest

None declared.

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Abbreviations

FDA: US Food and Drug Administration
HBM: Health Belief Model
IRB: institutional review board
ITT: intent-to-treat
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture

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Protocol

The Effectiveness of a Race-Based Stress Reduction Intervention on Improving Stress-Related Symptoms and Inflammation in African American Women at Risk for Cardiometabolic Disease: Protocol for Recruitment and Intervention for a Randomized Controlled Trial

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Abstract

Background: In recent years, the prevalence of cardiometabolic disease (CMD) in African American women has risen; the risk also increases with age, in comparison to men. Evidence demonstrates that stressful life events, including experiences of racism and perceived discrimination, contribute substantially to inflammatory diseases, such as CMD. Despite this evidence, few evidence-based interventions are available to assist individuals from minoritized communities in coping with the chronic stress related to their racial or ethnic identity.

Objective: Our proposed randomized controlled trial will test a novel, race-based intervention tailored to African American women, called Resilience, Stress, and Ethnicity (RiSE).

Methods: In this randomized controlled trial, we will randomize participants 1:1 to the 8-week, group-based RiSE program (intervention) or a health education program (active control group). Both programs will consist of synchronous classes on Zoom and will be led by experts. The primary end point will be stress at 6 months after the intervention, and the efficacy of RiSE will be evaluated for improving stress-related symptoms (current perceived stress, depressive symptoms, fatigue, and sleep disturbance), improving coping strategies, and reducing inflammatory burden in African American women at risk for CMD. Validated survey measures and inflammatory biomarkers will be assessed at baseline, midintervention, intervention completion, and 6 months after the intervention, and differences over time by intervention will be evaluated using mixed effects models.

Results: This study was funded by the National Institute on Aging on March 30, 2023, with recruitment and enrollment beginning in October 2023. The study is underway, with 120 participants enrolled as of March 2025.

Conclusions: This study will be one of the first to examine a race-based stress reduction intervention in African American women and has the potential to improve the health of minoritized groups faced with chronic stress associated with experiencing

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racism and discrimination. We anticipate that RiSE will reduce stress-related symptoms, enhance adaptive coping, and reduce inflammation.

Trial Registration: ClinicalTrials.gov NCT05902741; https://www.clinicaltrials.gov/study/NCT05902741

(JMIR Res Protoc 2025;14:e65649) doi:10.2196/65649

KEYWORDS

cardiometabolic disease; stress; Resilience, Stress, and Ethnicity; RiSE intervention; health of minoritized groups

Introduction

Cardiometabolic Disease Among African American Women

Cardiometabolic disease (CMD) is a complex pathophysiological syndrome characterized by progressive abdominal adiposity, dyslipidemia, hypertension, and insulin resistance [1,2]. It is well established that CMD heightens the risk for cardiovascular disease (CVD) [3]. Individuals with CMD have a 2-fold risk of mortality from coronary artery disease and a twice greater risk of stroke [4]. In recent years, the prevalence of CMD in women has risen drastically in comparison to men [3], and the risk increases with age [5]. Studies demonstrate that females experience more sex-specific risk factors that increase adiposity [6], resulting in greater risk for CMD [7,8]. Furthermore, CMD is disturbingly prevalent in African American women; for example, 55% of non-Hispanic Black women in the United States are obese [9], 43% have hypertension [10], and 13% have been diagnosed with diabetes mellitus [11]. While CVD mortality has declined in the United States, these same reductions have not been seen in African American women who continue to experience a disproportionate CVD burden compared to their White counterparts, even after controlling for traditional risk factors, such as smoking and weight [12].

Psychosocial Stressors, Psychobiological Response, and CMD

Numerous studies link higher levels of psychosocial stress to both CMD and CVD [13-17]. Recent evidence demonstrates that stressful life events, including experiencing racism and perceived discrimination, play a substantial role in contributing to inflammatory diseases, such as CMD [18,19]. African Americans who reported a history of experiencing racism had a significantly greater incidence of carotid artery plaque [20] and hypertension [21] than those who did not. African American women experience greater social stress from exposure to both racism and sexism [22,23]. Furthermore, low socioeconomic status may contribute to chronic stress in African American women, thereby increasing the risk of CMD [24]. Adaptive coping (seeking social support, problem-solving, and resistance to racism) may reduce stress-related symptoms (current perceived stress, depressive symptoms, fatigue, and sleep disturbance) and inflammatory burden [25-27] and moderate the impact of racism on well-being and health [28-30]. Furthermore, evidence demonstrates that there are sex differences in the types of coping strategies used, particularly in response to racial discrimination; for example, while men tend to use suppression and distraction, women are more prone to rumination [31]. Importantly, individuals can learn adaptive coping strategies that result in decreased stress-related symptoms [32], inflammatory burden (ie, proinflammatory cytokines) [33], and CVD [34].

The Need for a Novel Intervention to Ameliorate Psychobiological Stress and Empower African American Women

Despite evidence that chronic stress associated with experiencing racism, discrimination, and sexism increases the inflammatory response, few evidence-based interventions are available to assist individuals from minoritized communities in coping with the chronic stress related to their racial or ethnic identity. Interventions to assist individuals in managing chronic stress, such as mindfulness-based stress reduction (MBSR) and cognitive behavioral therapy (CBT) do not address trauma related to experiencing racism and discrimination [35]. Furthermore, MBSR and CBT do not specifically address race-based stressors. To date, only 3 published interventions address coping with discrimination; 2 interventions focus on coping related to discrimination experienced by individuals positive for HIV [36], and the other addresses racial socialization within Black families [37]. However, none of these interventions specifically address racism and discrimination experienced by African American women at risk for CMD. As research related to discrimination grows, there is a significant need for evidence-based interventions to address the psychobiological and health consequences of discrimination at the individual level [38].

Our proposed randomized controlled trial (RCT) will test a race-based intervention tailored to African American women, called Resilience, Stress, and Ethnicity (RiSE) [35] (Motley D, unpublished data, November 2017). In this group-based, 8-week intervention, cognitive behavioral and stress reduction strategies will be integrated [39] focusing on the biopsychosocial effect of racism [40,41], racial identity development [42-44], and empowerment [45]. Table 1 presents the schedule of enrollment, interventions, and assessments for the study.

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Table 1. Study schedule of enrollment, interventions, and assessments.

	Enrollment	Baseline (T0)	Midintervention (T1)	Intervention completion (T2)	6 months after intervention completion (T3)
Eligibility screen	✓				
Informed consent		✓			
First DNA sample		✓			
Allocation		✓			
Health measures		✓	✓	✓	✓
Audio computer-assisted self-interview		✓	✓	✓	✓
Second DNA sample					✓
Final assessment					✓

Our previous pilot study found that RiSE improved the ability of African American women to cope with racism and increased the use of adaptive coping strategies through emotional validation and cognitive restructuring of the response to racism and discrimination [35]. However, no research has examined RiSE as an intervention for the reduction of stress-related symptoms and inflammation in African American women at risk for CMD. The psychobiological impact of RiSE and its potential to reduce health risks may improve the health of many minoritized groups who endure chronic discrimination and racism [35]. Importantly, our study addresses the impact of racism on the individual that has not previously been addressed by other interventions.

On the basis of our preliminary data as well as evidence from other stress reduction interventions [46,47], we propose that RiSE will improve stress-related symptoms by providing access to coping strategies that may decrease inflammation (as indicated by biomarkers such as C-reactive protein [CRP], interleukin-6 [IL-6], tumor necrosis factor–alpha [TNF-α], interleukin-1beta [IL-1β], and interferon-gamma [IFN-γ]). Our pilot data indicate that RiSE attenuates maladaptive coping [48]. Adaptive coping, such as seeking social support and active coping, has been found to lessen the harmful effects of perceived discrimination and racism on the health of minoritized groups [49,50]. Furthermore, adaptive coping is related to well-being and lower levels of inflammation [51].

Conceptual Model

Our conceptual model (Figure 1) is based on allostatic load theory [52], which posits that chronic stressors produce wear and tear on the body through prolonged hyperactivity or hypoactivity of adaptive physiological systems.

Figure 1. Conceptual model. CMD: cardiometabolic disease; RiSE: Resilience, Stress, and Ethnicity; SES: socioeconomic status.

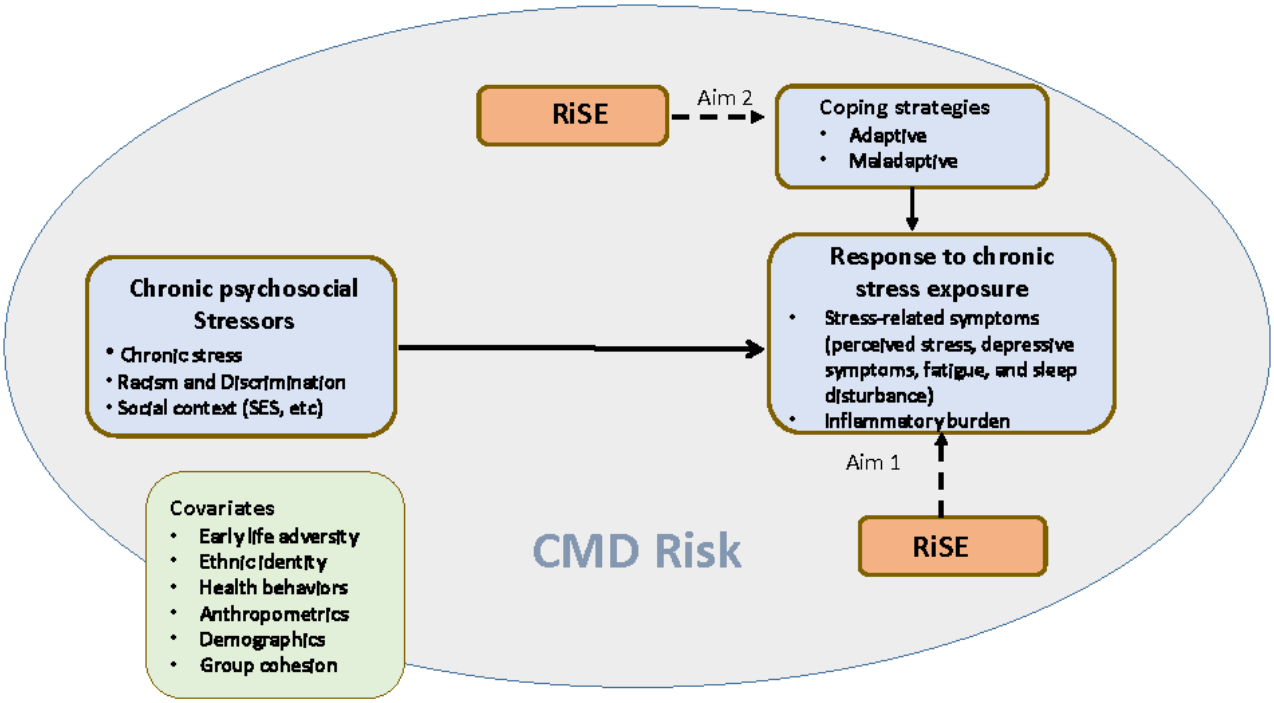

There are 3 types of responses to stressors: frequent activation of the stress response (eg, responding to the frequency and severity of a stressor), failed response (eg, chronic response where the body is unable to stop reacting to the stressor), and

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inadequate response (eg, the body has little to no response to the stressor) [52]. Our model proposes that psychosocial stressors, such as discrimination, racism, and social context (eg, socioeconomic precarity) when chronic, repeated, and overbearing, may heighten inflammation [53-55].

In this paper, we present a research protocol for the primary aim: to investigate the impact of RiSE on the response to chronic psychosocial stressors and inflammation. The subaim is to explore the impact of RiSE on adaptive coping (ie, problem- and emotion-focused coping strategies, such as positive mindset reframing and venting) versus maladaptive coping strategies) [55]. We hypothesize that women who participate in the RiSE intervention will exhibit decreases in stress-related symptoms (current perceived stress, depressive symptoms, fatigue, and sleep disturbance) as well as decreases in inflammatory burden (as indicated by biomarkers such as IL-6, TNF-α, IL-1β, IFN-γ, and CRP) compared to women in the health education program (HEP), which is the active control arm. For the subaim, we anticipate that women who participate in the RiSE intervention will report an increase in the use of adaptive coping strategies (seeking social support, problem-solving, and resistance to racism) and a decrease in the use of maladaptive coping strategies (avoidance and internalizing racism). This work is innovative because we are working to add resources to the toolbox of minoritized groups to increase resiliency in the face of racism at the interpersonal level. Although successful in some populations and types of stress-related conditions, CBT and MBSR were not specifically developed to reduce the impact of racism and discrimination [35]. RiSE has the potential to reduce the psychobiological consequences of racism and discrimination. This research study should aid in the continuing efforts of researchers to provide tools, which can be implemented as necessary, to groups considered marginalized.

Methods

Ethical Considerations

This study was approved by the Loyola University Chicago Health Sciences Institutional Review Board (LU214133) and the WCG Institutional Review Board (20230283). Eligible and willing participants will provide written informed consent. Participants can choose to opt out at any point during the study. All data are deidentified. Given the extent of participant involvement, we ensured fairness in the compensation process. The participants can be compensated up to US $500 in electronic Amazon gift cards. Compensation transparency is ensured. The recruitment flyers, telephone screen, and consent form all contain the mode of compensation and the amount. The study has been registered at ClinicalTrials.gov (NCT05902741).

Design

In this RCT (stage II [traditional efficacy testing] of the National Institutes of Health Stage Model for Behavioral Intervention Development [56,57]), we will determine the effectiveness of the 8-week, group-based RiSE program (intervention) in improving stress-related symptoms (current perceived stress, depressive symptoms, fatigue, and sleep disturbance), reducing inflammatory burden, and improving coping strategies from baseline to after the intervention in African American women aged 50 to 75 years at risk for CMD. This age range was chosen because women develop a higher risk for CMD [58] during perimenopause [59]. We are excluding women aged >75 years to control for the effects of older age on inflammation and DNA methylation [60,61]. Outcomes from the intervention group (RiSE) will be compared to those from the active control group (HEP). Figure 2 presents the overview of the study design.

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Figure 2. Overview of the study design. HEP: health education program; RiSE: Resilience, Stress, and Ethnicity.

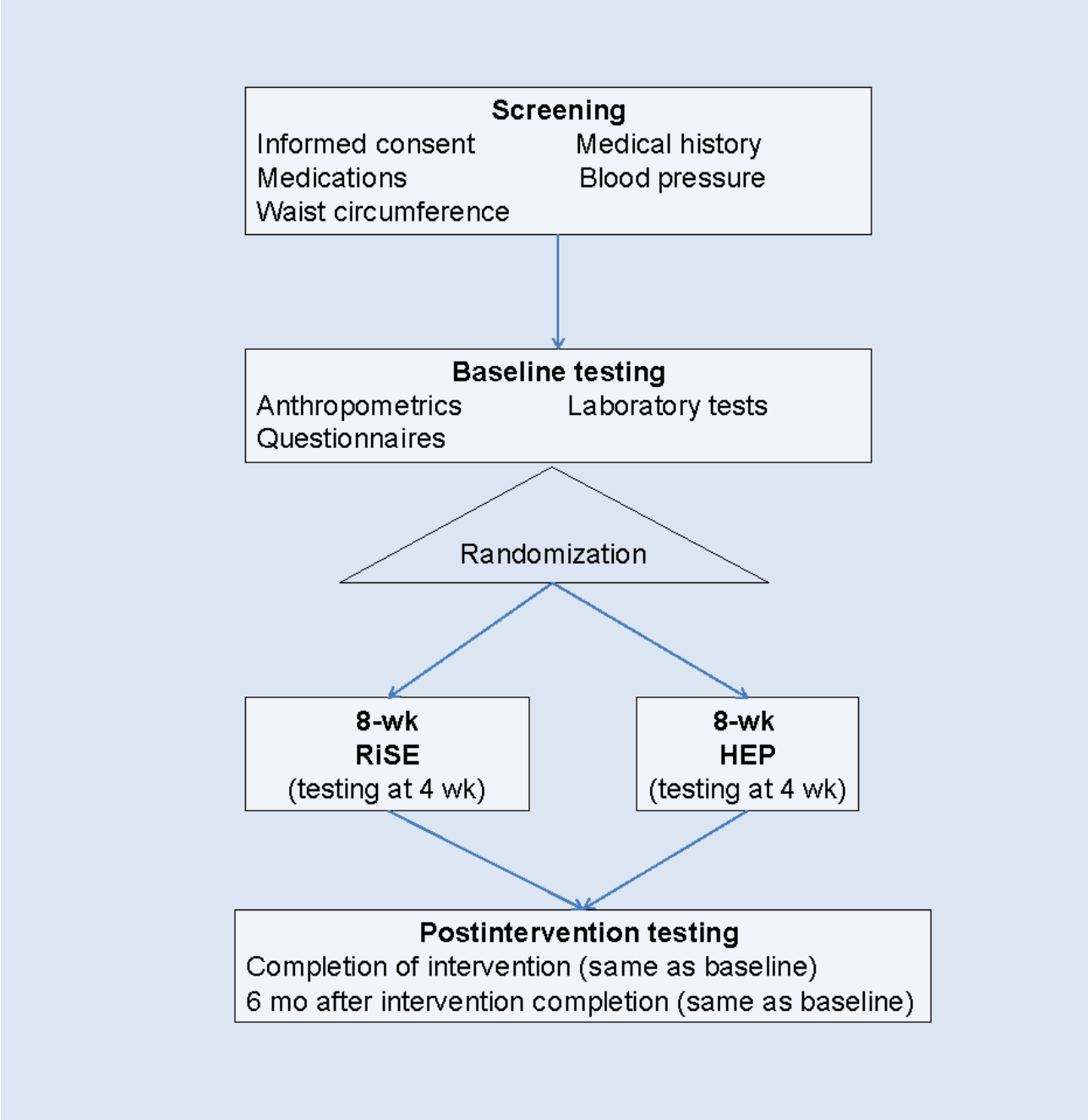

Procedures

We will recruit 300 African American women at risk for CMD from 2 large metropolitan cities in the United States (Chicago and New York City). Both communities are ethnically and racially diverse with relatively large African American populations [62,63].

We will use several recruitment strategies. First, we will work closely with key trusted community leaders (eg, church leaders) to promote the study. This strategy is particularly effective in recruiting people from minoritized communities in clinical trials [64,65]. In addition, we will meet regularly with our community advisory board, made up of individuals from the surrounding community, for suggestions on how best to recruit potential participants. We will send recruitment letters describing the study to African American women (aged 50-75 y) who broadly meet eligibility criteria (eg, no history of myocardial infarction or ischemic stroke) from our respective hospital databases. In addition, we will recruit women through community clinics, churches, health fairs, hair salons, social media, newspaper advertisements, and word of mouth. The use of proven recruitment and retention strategies for research participants from minoritized communities [64,66,67] will also be advantageous for this study. These efforts include sharing health information about CMD, engaging community representatives through the sharing of health information, and providing cultural sensitivity training for the study team [68-70]. Potential study participants will be prescreened for eligibility over the telephone. An appointment will be scheduled for further screening for those meeting the study eligibility criteria. Textbox 1 presents detailed inclusion and exclusion criteria.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Aged between 50 and 75 years
- Woman
- Postmenopausal stage (without menstrual periods for at least 12 consecutive months)
- Self-identify as African American
- Able to read, write, and speak English
- At least one of any of the following: waist circumference >88 cm; systolic blood pressure >130 mm Hg and diastolic blood pressure >88 mm Hg, or use of antihypertensive medications; diagnosed and receiving treated for hypercholesterolemia; history of type 2 diabetes

Exclusion criteria

- History of myocardial infarction or ischemic heart disease and angina pectoris, stent placement, coronary artery bypass, left ventricular hypertrophy, congestive heart failure, or ischemic stroke
- Any major immune-related disease (eg, rheumatoid arthritis or lupus)
- Use of immune-altering medications, such as glucocorticoids
- Periodontal disease, bleeding gums, and dental work in the past 72 h
- Current smoker or has smoked in the past 3 mo
- Active cancer
- Active infection
- Substance abuse
- Cognitive or psychiatric disorder that would affect the ability to participate in program classes (Brief Screen for Cognitive Impairment total score of ≥8)

Participants will be assessed for CMD risk. They will also be assessed for cognitive impairment using the 3-item Brief Screen for Cognitive Impairment [71]: a total score of ≥8, which suggests cognitive impairment, will lead to the exclusion of the participant from the study. All ineligible participants will receive a gift card (US $10) after the screening. Baseline measures will be collected after the screening.

After the baseline interview (T0), eligible participants will be randomized 1:1 to RiSE or HEP, with each wave of enrollment treated as a block. The randomization plan (PROC PLAN) generated in SAS 9.4 (SAS Institute Inc) includes the site as a stratifying variable, and we plan for each site to have at least 6 RiSE and 6 control participants per wave. Patient registration data, group assignment, and self-report survey data will be managed via a single REDCap (Research Electronic Data Capture; Vanderbilt University) server with access for both sites.

Assessments are completed face-to-face in a private room of our research building. At each of the 4 assessment points (T0: baseline, T1: midintervention; 4 wk, T2: intervention completion; 8 wk, and T3: 6 mo after intervention completion), trained interviewers will collect the following anthropometric measurements: 3 blood pressure readings, waist and hip circumference, weight, height, body fat percentage, and body water percentage. Data on psychosocial factors, health behaviors, and medical history will be collected using an audio computer-assisted self-interview system [72] and REDCap surveys. In addition, we will collect saliva samples using a passive drool kit to measure participants' inflammatory burden (as indicated by biomarkers such as CRP, IL-6, TNF-α, IL-1β, and IFN-γ) [46,51,73-82]. At T0 and T3 (ie, baseline and final assessment; 6 mo after intervention completion, respectively), we will collect participants' saliva samples using the Oragene DNA kit (DNA Genotek) to measure DNA methylation [68]. Study participants will receive a gift card (US $50) after the completion of each interview (T0-T3).

Intervention

Overview

Both RiSE and HEP groups will meet weekly on Zoom (Zoom Communications, Inc) for 8 consecutive weeks for approximately 2 hours per session. In addition, 2 sessions will occur 1 month and 2 months after the completion of the interventions. These booster sessions will include a brief review of information covered during the programs and will allow the participants the opportunity to discuss and ask questions about how they applied what they learned in their lives. For every class attended, participants will receive a US $30 gift card. Participants will be sent an SMS text message or email reminder before each class. The RiSE and HEP classes will meet synchronously over Zoom and will be led by experts in the area. The study staff will review how to access Zoom with research participants at the baseline data collection appointment and will answer any questions they may have. The topics of each session are detailed in Table 2. Written educational materials will be provided to support the classes in both interventions.

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Table 2. Overview of the Resilience, Stress, and Ethnicity (RiSE) intervention and health education program (HEP) topics.

Session	RiSE program (intervention)	HEP (active control)
1	Introduction to RiSE; establish group as safe place for dialogue about racism and oppression	Introduction to HEP
2	Explore issues related to being a woman from a minoritized community and impact of intersectionality; discuss insidious forms of racism	Caring for your skin cleansers and makeup
3	Explore challenges in having conversations about race and racism and discuss how defensiveness makes conversations unproductive	Cooking organically
4	Identify both overt and covert racism; reflect how racism can affect emotions and esteem	Finding credible health care information on the web
5	Identify aversive racism, institutional racism, and the role of White privilege; reflect on how these forms of racism can affect emotions and esteem	Immunizations for adults—what is available and what do you need?
6	Describe the use of cognitive behavioral theory to conceptualize emotional reactions to race-based stress	Over-the-counter medications: potential hazards
7	Review physical reactions to stress; practice strategies to cope with stress	Growing an herb garden
8	Review resilience, coping, and empowerment in response to race-based stress	Communicating with the health care team
Booster 1	Discuss challenges and successes in coping with chronic stressors; reinforce the use of adaptive coping skills	Review of health education topics, questions, and answers
Booster 2	Discuss challenges and successes; reinforce the use of adaptive coping skills	Review of health education topics, questions, and answers

RiSE Intervention

The RiSE intervention was adapted by Motley and Shawahin (Motley D, unpublished data, November 2017) for a behavioral health setting using components from an open-ended intervention developed by Carlson et al [35]. During our pilot work, the intervention was provided face-to-face and was tailored to help African American women address the unique challenges of navigating >1 marginalized identity (ie, intersectionality) [83]. RiSE includes three main components: (1) processing and sharing experiences associated with race-based stress, (2) psychoeducation related to the biopsychosocial impacts of racism, and (3) skill building and empowerment [48]. The intervention is feasible and well accepted among African American women [55]. In the first several sessions, RiSE provides participants with a safe place to share the emotional impact of race-based stress and to offer supportive listening among others in the group. Participants discuss their experiences as African American women, considering the ways in which the interaction between their racial and gender identities shapes their experiences. Facilitators promote discussion related to addressing racism and the unique experiences of Black women (eg, being stereotyped as angry and being expected to embody the “strong Black woman” archetype) [84-86] at interpersonal and structural levels. The facilitators share evidence of strategies to promote effective communication and internal emotional regulation regarding experiences of racism. Next, participants are provided with information on how racism can be manifested and are encouraged to use a common language with which to discuss their experiences. The facilitators provide psychoeducation on intersectionality, structural racism [87], overt racism [88], microaggressions [89], and internalized racism [90]. In addition, the facilitators assist participants in using cognitive behavioral strategies to understand thoughts, feelings, and actions associated with their experiences. Finally, the facilitators teach participants about stress, anxiety, and the “alarm” system [91] as they pertain to race-based stressors and other chronic stressors. Participants are encouraged to use adaptive coping strategies as well as community-based and cultural coping strategies. Throughout the program, participants engage in self-monitoring of the practice of skills discussed during the group sessions. Participants are sequentially introduced to the empowerment process steps [45] through journaling homework. Several mechanisms are key to the RiSE intervention in alleviating stress-related symptoms [48]. First, the group-based format allows participants to share their experiences with others and verbally process traumatic events [92]. Shame is believed to be a key barrier to overcoming race-based trauma [93]. Allowing participants to share their inner thoughts and concerns in a safe environment permits them to process their experiences and gain emotional validation from their peers. In addition, cognitive restructuring surrounding race-based trauma is used. This helps the participants reshape the maladaptive beliefs, such as self-blame, internalized stigma, and hopelessness, associated with their experiences. Participants learn that they do not cause racial and gender-based discrimination; rather, their experiences are related to systemic racism [35]. Participants are also encouraged to discuss their methods of coping with discrimination and are taught the difference between unhealthy and healthy coping strategies. The facilitators share approaches, such as mindfulness, cognitive restructuring, and advocacy, that

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participants can use to cope with their experiences [35]. Finally, participants are empowered to identify the meaning of their experiences and celebrate successes in using adaptive coping strategies. Classes are facilitated by 2 clinical psychologists trained in RiSE and who have >5 years of experience facilitating the RiSE program. In addition, they are experienced in leading and managing group dynamics and will develop ground rules with participants in the first session, including how to ensure that all participants can participate in the discussion.

HEP Intervention

Topics for the HEP (active control group) sessions were identified so that they would not confound the overall objectives of the RiSE program [94]. Experienced speakers (eg, dietitian, pharmacist, and aesthetician) will facilitate the HEP classes in their area of expertise. Classes will focus on wellness promotion with topics that will include cooking organically, immunizations, and skincare.

Importantly, the RiSE intervention will be delivered using standardized materials by the same 2 experienced RiSE interventionists for all cohorts [95]. Participants are assigned weekly homework and maintain logs of their practice time. Strategies to monitor participant understanding and application of treatment include a weekly review of participant self-monitoring logs that document weekly practice. Facilitators will assess the understanding of RiSE skills by asking questions, discussing material with participants, and monitoring skills development during in-class practice. Participants complete a brief post-RiSE evaluation form to provide feedback regarding the use of RiSE skills during appropriate life situations. We will assess and control for group cohesion using the 5-item Engaged Scale from the Group Climate Questionnaire–Short Form [96,97]. The fidelity of the HEP control intervention will follow the methods proposed by Stanton et al [98] and will be similar to that of the treatment group. Session content will be reviewed and approved by principal investigators. Standardized PowerPoint (Microsoft Corporation) presentations and class materials will be used. Multiple mechanisms will be used to ensure the integrity of the RiSE and control interventions. These mechanisms support the 5 dimensions of intervention integrity formulated by Dane and Schneider [99]: adherence (the extent to which program objectives are met), quality of delivery (interventionist effectiveness), exposure (dosage), participant responsiveness (engagement), and program differentiation. Adherence to program objectives will be monitored using multiple informants and methods to collect integrity data. Interventionists will complete a self-evaluation checklist after each weekly session identifying the extent to which session objectives were met. The study team will review notes for patterns or any areas that need to be addressed.

Outcome Variables

The outcome variables for the trial include stress-related symptoms (current perceived stress, depressive symptoms, fatigue, and sleep disturbance) and inflammatory burden (as indicated by biomarkers such as IL-6, TNF-α, IL-1β, IFN-γ, and salivary CRP; Table 3). Each of these variables will be collected at 4 time points: T0, T1, T2, and T3.

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Table 3. Study measures.

	Enrollment	T0[a]	T1[b]	T2[c]	T3[d]
Eligibility					
Eligibility screening questions	✓				
Brief Screen for Cognitive Impairment [71]	✓				
Aim 1: psychosocial stressors					
Chronic stress: Adult Stress and Adversity Inventory [100]		✓	✓	✓	✓
Perceived discrimination: Detroit Area Study Discrimination Scale [101]		✓	✓	✓	✓
Perceived racism: Index of Race-Related Stress–Brief Version B [102]		✓	✓	✓	✓
Subjective social status: MacArthur Scale of Subjective Social Status [103]		✓	✓	✓	✓
Aim 1: response to chronic stress exposure					
Current perceived stress: Perceived Stress Scale [104] and Stress Overload Scale [105]		✓	✓	✓	✓
Depressive symptoms: Beck Depression Inventory (Motley D, unpublished data, November 2017); depressive symptoms: Patient Health Questionnaire-9 [106]		✓	✓	✓	✓
Anxiety: General Anxiety Disorder-7 [107]					
Fatigue: PROMIS[e] Fatigue Short Form 8a [108]		✓	✓	✓	✓
Sleep disturbance: PROMIS Short Form v1.0 [109]		✓	✓	✓	✓
Inflammatory burden: salivary CRP[f], TNF-α[g], IL-6[h], IL-1β[i], IFN-γ[j], and CRP[k] (Human High Sensitivity Cytokine B Premixed Magnetic Luminex Performance Assay [R&D Systems])		✓	✓	✓	✓
Aim 2: Coping strategies					
Coping: Ways of Coping Questionnaire [110]		✓	✓	✓	✓
Coping with discrimination: Coping with Discrimination Scale [111]		✓	✓	✓	✓
Internalizing racism: Appropriated Racial Oppression Scale [112]		✓	✓	✓	✓
Resistance and empowerment: Resistance and Empowerment Against Racism Scale [113]		✓	✓	✓	✓
Covariates and descriptive measures					
Early life adversity: Childhood Trauma Questionnaire [114]		✓			
Ethnic identity: Vancouver Index of Acculturation [115]		✓			
Health behaviors, anthropometrics, and brief medical history: Block Brief 2000 Food Frequency Questionnaire [116]; National Institute of Nursing Research Social Determinants of Health Survey [117]; Self-Administered Comorbidity Questionnaire [118]; blood pressure, height and weight, body fat percentage, and body water percentage [119]; Alcohol, Smoking, and Substance Involvement Screening Test [120]; Life Events Checklist-7 [121]; and Race-Related Events Scale [122], health behaviors, anthropometrics, brief medical history, and demographics		✓	✓	✓	✓
Intervention and active control group cohesion: 5-Item Engaged Scale from Group Climate Questionnaire [96]			✓	✓	✓

[a]T0: baseline.

[b]T1: midintervention.

[c]T2: intervention completion.

[d]T3: 6 months after intervention completion.

[e]PROMIS: Patient-Reported Outcomes Measurement Information System.

[f]CRP: C-reactive protein.

[g]TNF-α: tumor necrosis factor–alpha.

[h]IL-6: interleukin-6.

[i]IL-1β: interleukin-1beta.

[j]IFN-γ: interferon-gamma.

[k]CRP is not measured using the Luminex Performance High Sensitivity. Cytokine Magnetic Panel B MultiPlex but rather an Enzyme-Linked Immunosorbent Assay kit from R&D Systems.

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Inflammatory Biomarker Procedures

Saliva samples will be collected to measure inflammatory biomarkers because this method is less invasive than blood draws. Salivary CRP and proinflammatory cytokines (eg, IL-6, TNF-α, IL-1β, and IFN-γ) are associated with stress-related symptoms [46,82]. We will follow recent best practice recommendations for collecting salivary cytokines [123], including the use of the passive drool method for sample collection and returning specimens overnight on dry ice between sites. Saliva samples will be kept frozen at −80 °C before batch analysis.

Exposure Variables

Measurements of chronic stress (Adult Stress and Adversity Inventory), perceived discrimination (Detroit Area Study Discrimination Scale), perceived racism (Index of Race-Related Stress–Brief Version B), and subjective social status (MacArthur Scale of Subjective Social Status; Table 3) will be collected and analyzed as exposure variables. Trained interviewers will collect these data using an audio computer-assisted self-interview system [72].

Covariates

Several variables may influence or moderate the relationship between the intervention group and chronic stressors, stress-related symptoms, and inflammatory burden and coping mechanisms. For this reason, data on age, education, income, employment, height and weight, blood pressure, health behaviors, and early life adversities, as well as a brief medical history, will be collected at baseline and considered as covariates.

Analytic Plan

Data Quality

Before data analysis, we will ensure the accuracy and integrity of the data by regularly reviewing and cleaning the data from both sites using frequency distribution to identify data entry errors. In addition, 50% of the data will be manually checked for accuracy. If the coding or entry error rate is higher than 2% for any individual test or instrument, all data for that particular test or instrument will be manually checked. Monitoring logs will be maintained for the following: (1) patients screened for participation (basic demographic information and reason for nonparticipation [for nonparticipants only]), (2) patient entry into the study, (3) timeliness of data collection, and (4) missing data. Regarding missing items from the psychometric measurements, each tool will be assessed for missing data, and, if appropriate, participants will be contacted to complete the missing items.

Statistical Analysis

Baseline demographics and clinical characteristics will be reported according to the CONSORT (Consolidated Standards of Reporting Trials) guidelines. The size of any chance group imbalances will be described, but no formal significance testing of group differences will be performed [124]. Generalized linear mixed models (GLMMs) will be used for analyses of outcomes due to their flexibility regarding the distribution of dependent variables (DVs) and their superiority over alternative approaches such as repeated measures ANOVA for longitudinal modeling with missing data. Data will be collected from participants at 4 time points (T0: baseline, T1: midintervention; 4 wk, T2: intervention completion; 8 wk, and T3: 6 mo after intervention completion). Time will be modeled as a fixed effect, and random intercepts and random slopes will be considered to account for within-individual differences and trends. The primary DVs include stress-related symptoms (current perceived stress, depressive symptoms, fatigue, and sleep disturbance) and biomarkers (ie, IL-6, TNF-α, IL-1β, IFN-γ, and CRP) to be modeled using GLMM. Before modeling, DVs will be plotted to choose an optimal distribution and link function for GLMMs and to identify potential floor or ceiling effects. For each DV, a GLMM will regress the follow-up DV on a group×time interaction, the baseline value of the DV, and covariates. Treatment assignment (group) will be a fixed effect, and adjusted means with SEs will be used to describe group differences. Random effects will be evaluated for site and cohort. Exploratory end points include coping (Ways of Coping Questionnaire and Coping with Discrimination Scale), internalizing racism (Appropriated Racial Oppression Scale), and resistance to racism (Resistance and Empowerment Against Racism), which will be DVs in separate GLMMs, as described earlier.

Covariate adjustment will be performed to account for explained variation in outcome variables [125]. Not all covariates considered may be necessary to include in the models to explain the bulk of the variation in DVs; therefore, a parsimonious subset will be chosen concerning multicollinearity, the strength of associations, and appropriateness for total sample size. Residual plots will be examined to determine whether transformations or other regression remedial measures are required to satisfy model assumptions. Although sample size calculations have accounted for potential attrition, analyses of end points will be conducted under the intent-to-treat principle. While every attempt will be made to capture all available data on participants, we may consider sensitivity analyses using model-based approaches (eg, multiple imputation) for missing data [126]. A detailed statistical analysis plan will be prepared and finalized by the study biostatistician before the database lock to promote the reproducibility and transparency of the analytic approach. Analyses will be performed using SAS (version 9.4; SAS Institute) and R (version 4.0.2 or later; R Foundation for Statistical Computing). Results reporting will include all preplanned analyses, and any post hoc analyses will be clearly labeled as such when we disseminate this work.

Sample Size

We will enroll 300 participants and anticipate that at least 250 (n=125, 50% per arm) will have the 6-month postintervention follow-up data. For the primary end point of the Perceived Stress Scale (PSS), this sample size has >80% power to detect a 3-point difference in mean PSS scores at follow-up using an F test in an analysis of covariance. This assumes the R-squared value of 5 covariates, including baseline PSS, to be 0.3 and uses a significance level of α=.05. This calculation conservatively estimates the SD of PSS to be 10 points. Initial psychometric studies and norm groups analysis of the PSS reported SDs of 7.2 points in African Americans; relevant to the RiSE study,

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group SDs ranged from 6 to 10 points from a pilot trial involving African Americans with hypertension [127]. At this sample size and with similar design assumptions, effect sizes were estimated using the RiSE pilot study for the hypothesized mediator of coping as well as biomarkers [48]. The estimates from the analysis of covariance (Table 4) represent the lower limits for power because the mixed model approach that incorporates all time points may be more powerful in detecting meaningful differences.

Table 4. Pilot study estimates and effect sizes.

Outcome evaluated at 6 months	RiSE[a] group, mean	Control group, mean	|Δ|, mean	Pooled SD	Observed effect size	Mean difference required for 80% power[b]
WCQ[c]: active coping	23.76	24.77	1.01	8.24	0.06	2.45
WCQ: avoidance coping	8.14	14.38	6.24	5.25	0.59	1.56
WCQ: minimize situation	11.21	14.04	2.83	4.36	0.32	1.30
TNF-α[d]	0.95	1.00	0.05	0.36	0.07	0.11
hsCRP[e]	3.83	7.24	3.41	6.30	0.27	1.88

[a]RiSE: Resilience, Stress, and Ethnicity.

[b]Assumes n=125 per group and α=.05; R-squared value of 5 covariates is 0.30.

[c]WCQ: Ways of Coping Questionnaire.

[d]TNF-α: tumor necrosis factor–alpha.

[e]hsCRP: high-sensitivity C-reactive protein.

Results

This study was funded by the National Institute on Aging on March 30, 2023, with a project end date of January 31, 2028. Recruitment and enrollment began in October 2023 and is ongoing. As of March 2025, we enrolled 120 participants. Figure 3 depicts the CONSORT flow diagram for study participants as of March 2025.

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Figure 3. CONSORT (Consolidated Standards of Reporting Trials) flow diagram for the study. RiSE: Resilience, Stress, and Ethnicity.

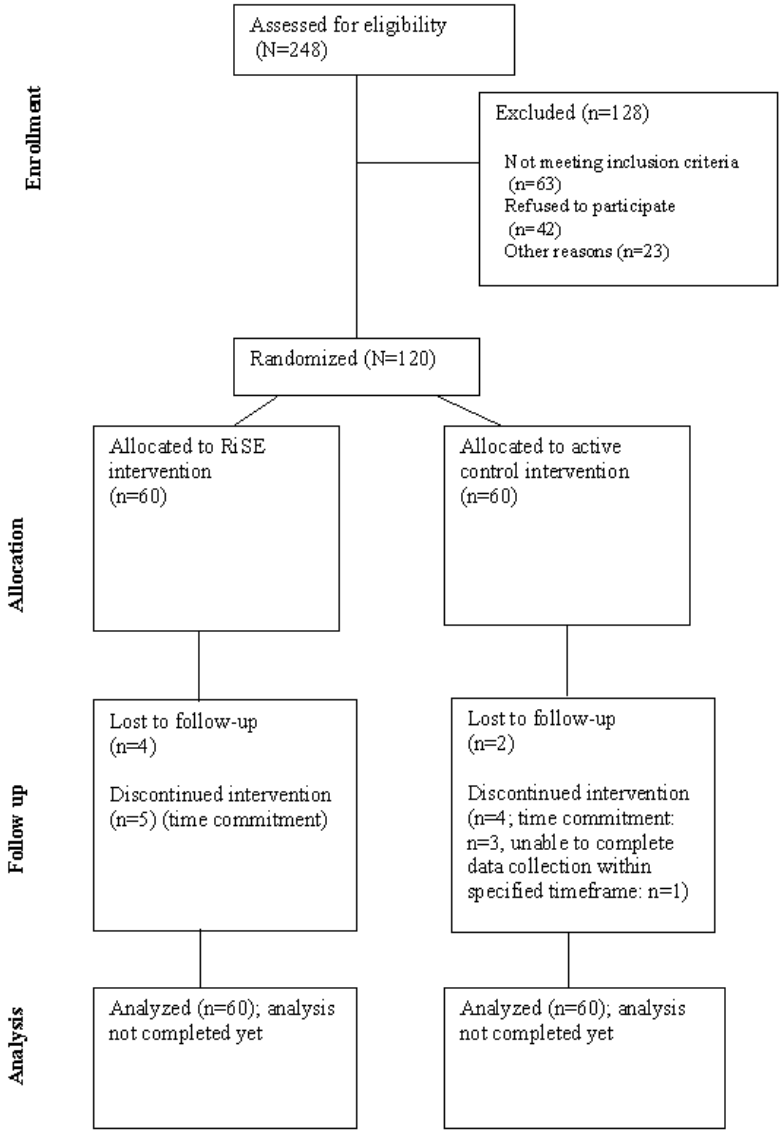

Table 5 presents the start dates and enrollment for each cohort. We plan to enroll 3 cohorts each year with anticipated enrollment completed in 2027. In addition, retention (defined as attending at least 5 of the 8 program classes) has been 95% (38/40) for the RiSE intervention and 91% (41/45) for the HEP active control intervention. We began preliminary analysis of baseline data in March 2025.

Table 5. Cohort start dates and enrollment size (n=120).

Cohort	Start date	Participants, n (%)
1	October 30, 2023	23 (19.2)
2	February 26, 2024	23 (19.2)
3	May 7, 2024	26 (21.7)
4	September 16, 2024	26 (21.7)
5	February 17, 2025	22 (18.3)

Discussion

Principal Findings

This study proposes to examine the effect of a race-based stress reduction intervention, called RiSE, on stress-related symptoms, coping, and inflammation in older African American women at risk for CMD. We anticipate that participants completing the RiSE program will have decreased stress-related symptoms, improved adaptive coping, and decreased inflammatory burden compared to those randomized to the active control group (HEP).

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Racism is dangerous, pervasive, and unfortunately a growing problem in the United States. A third of African Americans report experiencing a race-related incident in the past year [128]. Undeniably, racism needs to be addressed at the interpersonal, community, and societal levels. However, until such time, ways to reduce the impact of racism on psychological and physical health at the individual level must be developed and tested. The RiSE intervention may accomplish this goal. It reduces stress and has the potential to reduce the psychobiological consequences of racism and discrimination, leading to decreased inflammation and ultimately contributing to lowered CMD and CVD risk in African American women. In sum, despite evidence that experiencing racism and perceived discrimination heightens the inflammatory response and CMD [19,53], few evidence-based interventions are available to help individuals from minoritized communities cope with unique stressors related to their racial or ethnic identity. There is evidence that health behaviors [129], early life adversity [130,131], and ethnic identity [132-134] may impact the relationships among chronic stressors (perceived discrimination, racism, and subjective social status) and the psychological and inflammatory response to stress.

Limitations and Strengths

The proposed study has some limitations that should be recognized. As with most RCTs, challenges related to recruitment and retention are anticipated. In response, we have developed a detailed recruitment plan supported by our community advisory board as well as strategies to minimize attrition, including immediately contacting participants who miss program classes or data collection visits as well as providing fair compensation. In addition, generalizability is a potential limitation of this study. Future work will examine RiSE in additional populations. Despite these challenges, this study will be one of the first to examine a race-based stress reduction intervention in African American women and has the potential to improve the health of minoritized groups faced with the chronic stress associated with experiencing racism and discrimination [35,39-45,48,55] (Motley D, unpublished data, November 2017). In addition, RiSE is being offered via Zoom, which may allow participants who cannot travel or have caregiving responsibilities the opportunity to participate in the program. If RiSE is found to be effective in older African American women, future research may consider evaluating RiSE in other populations, such as younger African American women as well as men.

Acknowledgments

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Data Availability

This study is in the data collection phase. Datasets will be made available at a later time upon request from the corresponding author.

Authors' Contributions

KLS, JYT, and LJ conceptualized the study. KLS, CJ, and JYT were responsible for data curation and formal analysis. KLS and JYT were responsible for funding acquisition, investigation methodology, supervision, validation, and visualization. KLS, DM, LS, and JYT were responsible for project administration resources. KLS, CJ, AN, LJ, DT, PdlP, DM, LS, LP, SP-T, and JYT wrote the original draft. KLS, CJ, AN, LJ, DT, PdlP, DM, LS, LP, SP-T, and JYT reviewed and edited the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CBT: cognitive behavioral therapy
CMD: cardiometabolic disease
CONSORT: Consolidated Standards of Reporting Trials
CRP: C-reactive protein
CVD: cardiovascular disease
DV: dependent variable
GLMM: generalized linear mixed model
HEP: health education program
IFN-γ: interferon-gamma
IL-1β: interleukin-1beta
IL-6: interleukin-6
MBSR: mindfulness-based stress reduction
PSS: Perceived Stress Scale
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
RiSE: Resilience, Stress, and Ethnicity
TNF-α: tumor necrosis factor–alpha

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Protocol

Efficacy And Safety of Acupoint Catgut Embedding for Perennial Allergic Rhinitis: Protocol for a Randomized Clinical Trial

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Abstract

Background: Allergic rhinitis (AR) is a noninfectious chronic inflammatory disease of the nasal mucosa characterized mainly by itching, sneezing, nasal congestion, and rhinorrhea. It is mediated by immunoglobulin E (IgE). AR is one of the most common allergic diseases globally, affecting 10% to 20% of the population worldwide, with some regions even reaching rates as high as 50%, posing a global health issue. The prevalence of AR has been increasing since the 1960s, with a significant increase in recent years. At present, modern medicine—including desensitization therapy, the use of antiallergic drugs, antihistamines, hormones, and other treatments—can improve symptoms or regulate the immune system. However, both short- and long-term efficacy remain limited, as symptoms often recur after treatment cessation, and long-term drug use is associated with toxicity and side effects.

Objective: Acupoint catgut embedding (ACE) therapy is widely used to treat AR in China. ACE therapy has been reported to be effective in managing the symptoms of AR, but the evidence faces methodological limitations. Therefore, we designed a parallel-arm, randomized controlled, multicentered, placebo-controlled, and single-blinded trial to evaluate the efficacy and safety of ACE therapy for AR.

Methods: This study will be a parallel-group, patient-blind, placebo-controlled randomized controlled trial conducted in the Third Affiliated Hospital of Sun Yat-sen University, Ningxia Chinese Medicine Research Center, and the Affiliated Hospital of Shanxi University of Traditional Chinese Medicine. The trial consists of a 4-week treatment period, along with a 3-month follow-up. After providing written informed consent, eligible participants will be randomized at a ratio of 1: 1 into one of 2 groups: the ACE group receiving treatment and the sham ACE group. Both groups will receive conventional loratadine treatment.

Results: The funding began in January 2022. The study was initiated on February 1, 2025, and will end in February 2026. Patient recruitment has already started, and the study results will be released in March 2026.

Conclusions: We expect that this research will provide important insights into the efficacy of ACE treatment for AR and generate robust data for the foundation of future research in this field.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2500095634; https://www.chictr.org.cn/historyversionpubEN.html?regno=ChiCTR2500095634

International Registered Report Identifier (IRRID): PRR1-10.2196/63933

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KEYWORDS

acupoint thread embedding; catgut embedding; allergic rhinitis; loratadine

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Introduction

Allergic rhinitis (AR) is a noninfectious chronic inflammatory disease of the nasal mucosa characterized mainly by itching, sneezing, nasal congestion, and rhinorrhea. AR is mediated by immunoglobulin E (IgE). It is one of the most common allergic diseases, affecting between 10% and 20% of the population worldwide [1], with some regions even reaching rates as high as 50%, posing a global health issue. The prevalence of AR has been increasing since the 1960s [2], with a significant increase in recent years [3]. At present, modern medicine—including desensitization therapy, antiallergic drugs, antihistamines, and hormones—helps improve symptoms and regulate the immune system. However, the short- and long-term efficacy is limited, as symptoms often recur after treatment cessation, and long-term drug use is associated with toxicity and side effects [4]. Allergen-specific immunotherapy (AIT) is the only means of altering the natural immunological course of allergic diseases and achieving long-term remission. Pharmacological measures can suppress the immune response and ameliorate symptoms, but there is a risk of relapse soon after stopping these measures [5]. Currently, the main drugs for treating AR are H1 antihistamines, nasal steroid hormones, and leukotriene receptor antagonists. The control and safety of nasal symptoms have been verified; however, limitations remain in preventing the recurrence of AR [6]. Catgut implantation at the acupoints is a subtype of acupuncture, in which a catgut is embedded in the acupoint using a special needle. The catgut is absorbed by the tissue over a period of time. Therapeutic effects can be achieved by continuing stimulation caused by the catgut at the acupoint. Therefore, catgut implantation at the acupoint may be effective in treating some chronic diseases such as AR. Although acupoint catgut embedding (ACE) therapy has been used to treat diseases for thousands of years in China, there have been very few clinical trials strictly designed to verify the efficacy and safety of this treatment for AR [7]. It is necessary to obtain stronger evidence for catgut implantation at the acupoints for treating AR. Research on ACE therapy for AR primarily focuses on regulating cytokines, influencing neurotransmitters, and inhibiting immune molecules such as IgE. At the cytokine regulation level, acupoint embedding research concentrates on interventions targeting inflammatory factors and transforming factors. Inflammatory factors include interleukin-17(IL-17), interleukin-4 (IL-4), and interferon-gamma (IFN-γ), and transforming growth factors include transforming growth factor β1, among others [8-12]. ACE therapy intervenes in neurotransmitters mainly by participating in the release of various immunologically active substances, such as substance P. Research has found that embedding therapy can alleviate rhinitis-related symptoms by regulating substance P and nitric oxide levels [13-15]. The process begins with mechanical stimulation, followed by biological and chemical stimulation. The gradual softening, decomposition, liquefaction, and absorption of the catgut thread within the acupoint provides prolonged stimulation, reducing the likelihood of recurrence. Therefore, the treatment interval can be extended to once every 10 days, greatly improving patient compliance. Moreover, catgut thread, as an allogeneic protein stimulus, can better regulate the relative balance of the body's internal environment, enhance immune function and stress resistance, and reduce allergic reactions. Therefore, it is considered an excellent method for treating AR [16].

A recently published systematic review confirmed the effect of ACE therapy. However, it also pointed out that previous randomized controlled trials (RCTs) faced a variety of methodological limitations, including the absence of sample size calculation, inappropriate control groups, and multicenter RCTs and blind designs [17]. Therefore, it is necessary to conduct large-scale and rigorously designed RCTs to overcome the identified methodological issues. The primary objective of this study is to evaluate the efficacy of ACE therapy for AR, with a focus on reducing recurrence. Secondary objectives include assessing whether ACE therapy can (1) improve patients' quality of life and (2) change the dosage of the relief medication (RM).

Methods

Study Design

This study will be a parallel-group, patient-blind, placebo-controlled RCT conducted in the Third Affiliated Hospital of Sun Yat-sen University, Ningxia Chinese Medicine Research Center, and the future Affiliated Hospital of Shanxi University of Traditional Chinese Medicine. The flowchart of this trial is shown in Figure 1. The trial consists of a 4-week treatment conducted along with a 3-month follow-up. After providing written informed consent, eligible participants will be randomized at a ratio of 1: 1 into one of 2 groups: an ACE group receiving ACE treatment or a sham ACE group receiving sham ACE treatments. Both groups will receive conventional loratadine treatment.

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Figure 1. Trial flow diagram. ACE: acupoint catgut embedding; AE: adverse event; BRE: blood routine examination; FU: follow-up; RCAT: Rhinitis Control Assessment Test; RM: relief medication; TNSS: Total Nasal Symptom Score; TOSS: Total Ocular Symptom Score.

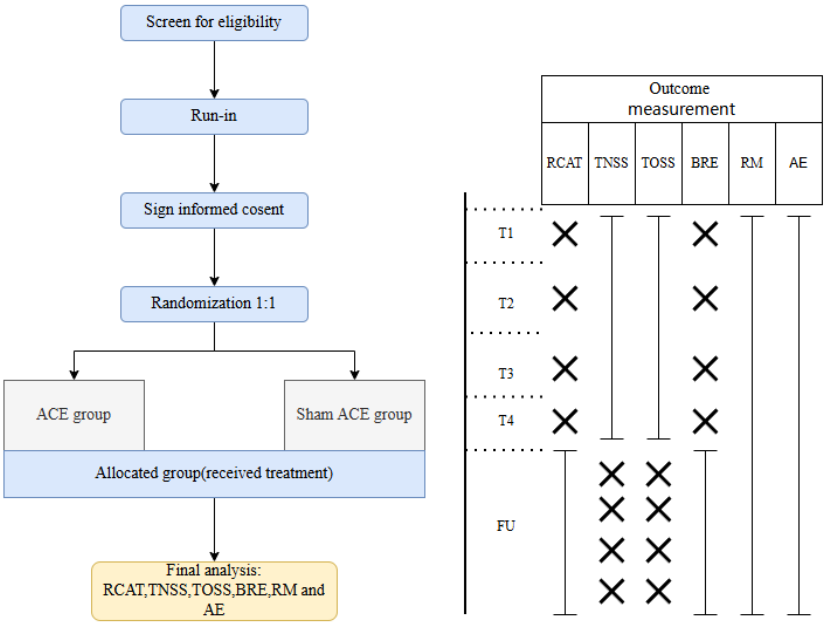

Patient Information

Participants will be recruited via advertisements, posters, leaflets about the trial, and doctor referrals from otorhinolaryngology clinics in the 3 study hospitals. Interested individuals will need to contact research assistants by phone or email. Trial information and consent forms will be sent to them to read before scheduling their first visit. In the first visit, screening evaluations will be conducted and recorded to ensure eligibility. For each participant who is eligible and willing to participate in the trial, research assistants will provide a signed consent form. The inclusion criteria for this trial are: (1) age between 18 and 65 years old; (2) meeting the diagnostic criteria for perennial AR; and (3) currently experiencing symptomatic attacks, able to accurately describe their condition, and willing to provide informed consent and participate in the clinical study.

Patients with AR were diagnosed based on the following criteria: (1) the presence of 2 or more symptoms including sneezing, clear watery nasal discharge, itchy nose, or nasal congestion that persists or occurs for more than 1 hour per day; (2) ocular symptoms such as itchy, watery, or red eyes; (3) nasal endoscopy showing pallor and edema of the nasal mucosa; and (4) a positive seasonal allergen test result for serum-specific IgE [18]. The exclusion criteria included: (1) recent respiratory infection or acute paranasal sinusitis within the past 14 days; (2) evidence of inflammation on chest X-ray; (3) history of chronic paranasal sinusitis or current diagnosis via X-ray examination; (4) the presence of organic lesions in the nasal cavity or recent nasal surgery; (5) diagnosis of paroxysmal respiratory diseases such as asthma; (6) recent use of H1-antihistamines, steroids, decongestants, or other medications affecting the respiratory system within the past 14 days; (7) specific immunotherapy or systemic hormone therapy within the last year; (8) recent use of acupuncture, moxibustion, cupping, nasal inhalation of traditional Chinese medicine, or other traditional therapies within the past 14 days; and (9) determination by clinical investigators that the patient is unable to adhere to the treatment regimen.

Randomization and Allocation Concealment

A block randomization sequence was generated by SAS software (version 9.2; SAS Institute Inc), which was performed by Guangdong Provincial Hospital of Chinese Medicine's Key Unit of Methodology in Clinical Research. Eligible participants will be randomly assigned to either the ACE group or the sham ACE group at a ratio of 1:1. An independent researcher will prepare treatment cards, on which a serial number and one of 2 names are printed, each representing one of the 2 groups. This independent researcher will be responsible for selecting and adding intestinal thread to the injection needles according to the respective groups. Treatment allocations will be stored in password-protected files and held independently by staff of the Key Unit of Methodology in Clinical Research. While receiving the first treatment, the participants will be given sequential treatment cards from independent researchers to ensure adequate concealment. The participants will be allocated into one of 2 groups according to the name printed on their treatment card.

Blinding

The researchers will assign intervention measures to the participants according to their allocated groups. The participants will be blinded to their group allocations in this single-blind study, whereas the researchers and acupuncturists will be aware of the group allocations. To minimize bias, outcome assessors will be blinded throughout the study.

A first-level blind base will be established for data statistics, ensuring the statistician is unaware of the group assignments. All operations will be performed in accordance with established standard operation procedures. After each treatment session, the participants in the ACE and sham ACE groups will complete a questionnaire on whether they believe they received ACE treatment and how certain they are that active treatment was received on a 0-to-10 numeric rating scale, where 10 represents

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absolute certainty [18]. Both the block randomization and the blinding questionnaire will be exclusively administered by a single external party.

Intervention

To ensure operational consistency, all patients will receive unified treatment set by the same doctor. The research assistant will add intestinal threads to the injection needles according to the respective groups. The ACE group will undergo ACE. The bilateral YingXiang (LI20), QuChi (LI11), JianJing(GB21), YinTang(GV24+), and DanZhong (CV17) points will be disinfected. Detailed positioning data are shown in Table 1 and Figure 2. The patient will assume a supine position, and acupoints will be located, marked with a marker, and disinfected with iodophor cotton swabs.

Table 1. Location of acupoints from the World Health Organization (WHO) 2014 Standard Acupuncture Point Locations in the Western Pacific Region (SPAR) study.

Acupoint	Location
YingXiang (LI20)	On the face, next to the midpoint of the outer edge of the alar, in the nasolabial groove
QuChi (LI11)	On the lateral aspect of the elbow, at the midpoint of the line connecting LU5 with the lateral epicondyle of the humerus
DanZhon (CV17)	In the anterior thoracic region, at the same level as the fourth intercostal space, on the anterior median line
JianJing (GB21)	In the posterior region of the neck, at the midpoint of the line connecting the spinous process of the seventh cervical vertebra (C7) with the lateral end of the acromion
YinTang (EX-HN3)	At the midpoint of the line connecting the 2 medial ends of the eyebrows

Figure 2. Diagram of the prescribed acupoints from the World Health Organization (WHO) 2014 Standard Acupuncture Point Locations in the Western Pacific Region (SPAR) study.

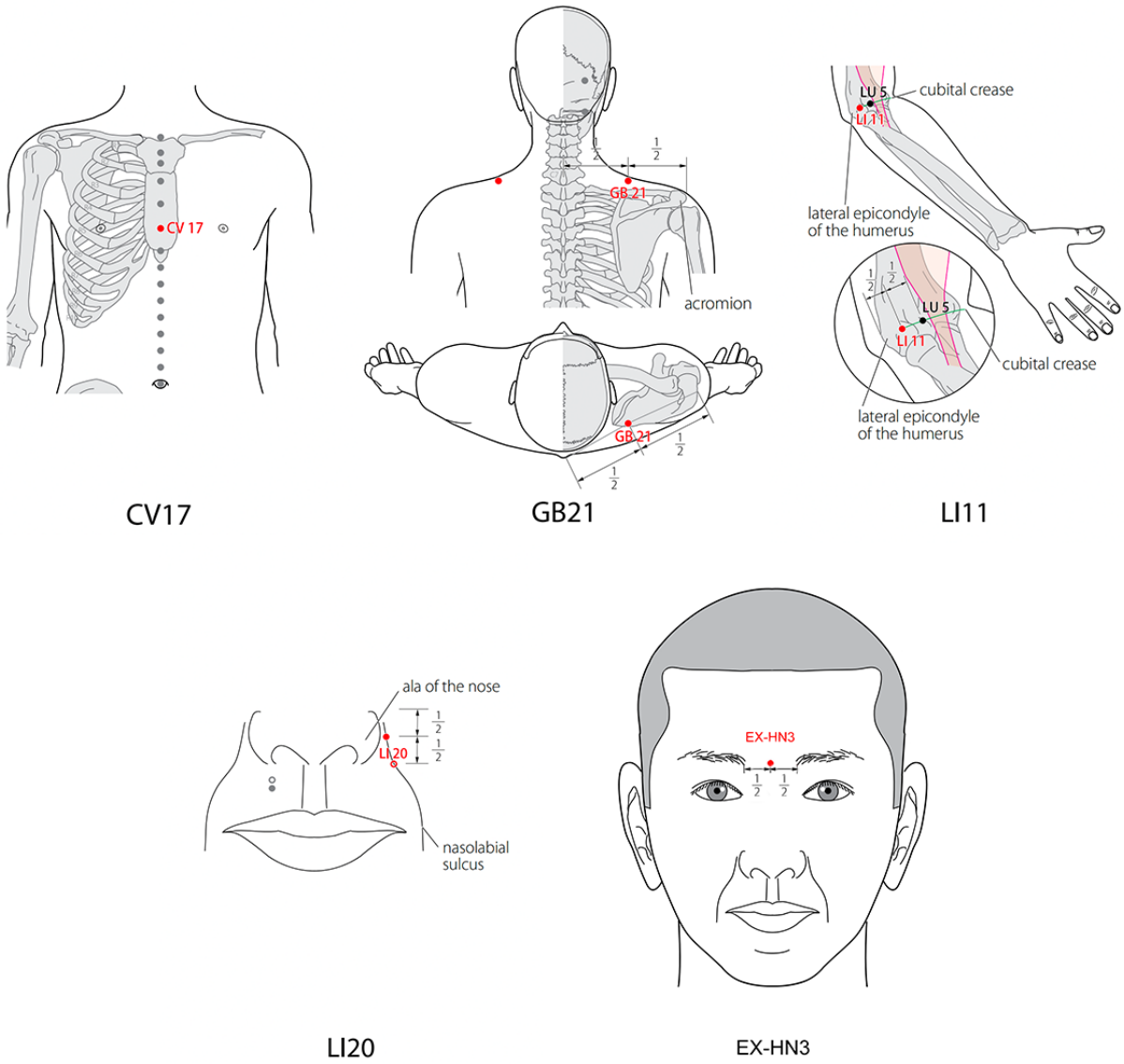

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The practitioner will wear aseptic gloves, cut the absorbable surgical suture around 5 mm, and place it into the front end of the needle tube. The structure of the acupuncture needle is illustrated in Figure 3. The doctor's left thumb and index finger will tighten the skin around the operation site, and the needle will be inserted vertically with a catgut-burying needle in their right hand at a depth of 0.5 cm. The needle will be slightly lifted to stimulate the acupoints, and after getting qi, the left hand will push the needle core inward while the right hand withdraws the needle tube outward, embedding the surgical suture in the acupoint. After the stitches are placed, the pinhole will be pressed with aseptic gauze for a while and covered with a bandage or infusion paste.

Figure 3. The process of acupoint catgut embedding (ACE) and the structure of the needle. a: Needles and absorbable surgical sutures. b: Specific cut-to-length. c: Insert the thread end into the needle eye. d: Insert the stylet into the needle. e: Insert the suture end into the acupoint.

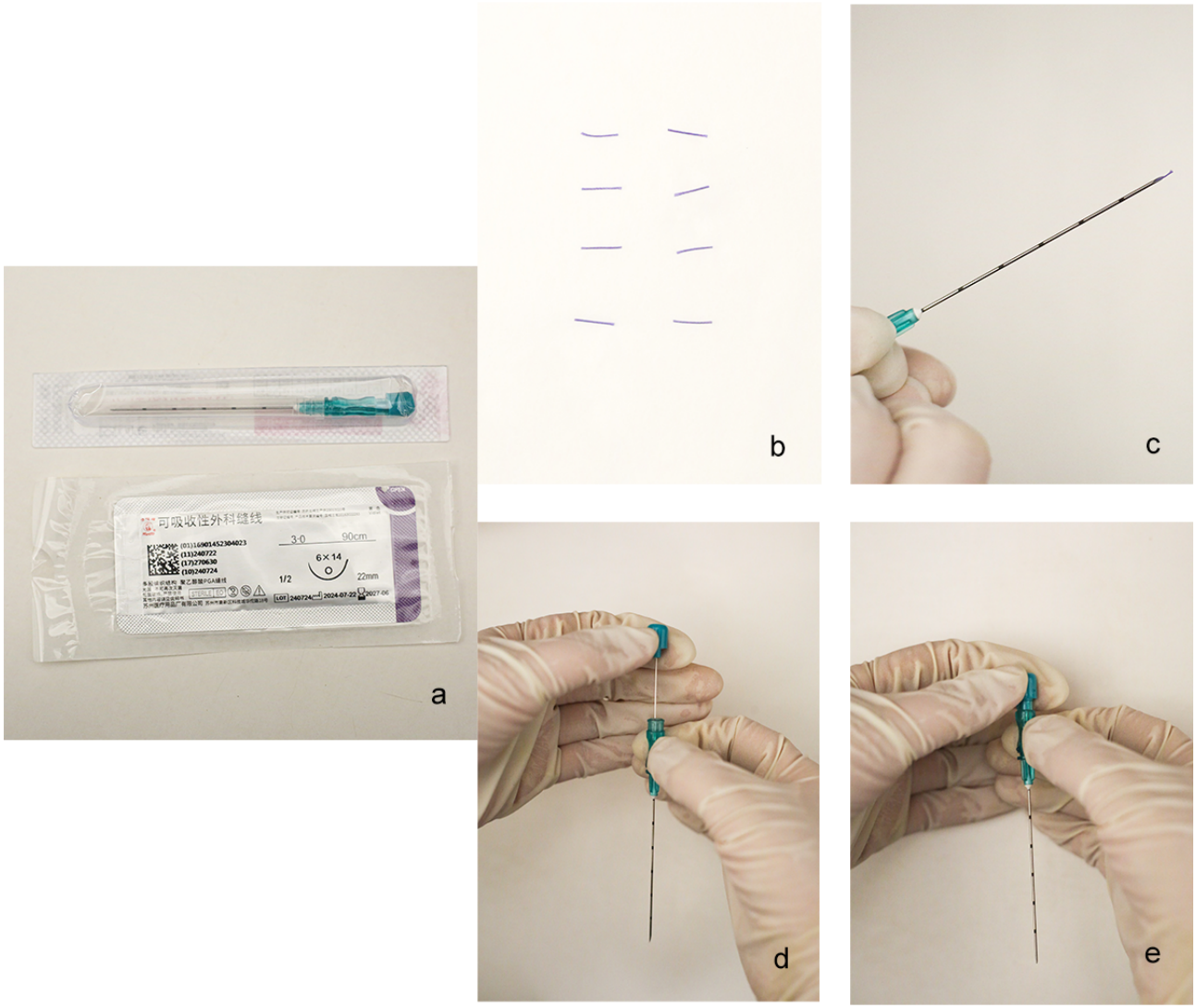

Catguts will be implanted once every 7 days for a total of 28 days, and each participant will take a prescribed dose of loratadine orally every day. In the sham ACE group, participants will be placed in a supine position, and the acupoints will be located, marked with a marker, and disinfected with an iodophor cotton swab. The practitioner will wear sterile gloves and insert the needle into the skin. The doctor's left thumb and index finger will tighten the skin around the operation site, and the needle will be inserted vertically with a catgut-burying needle in their right hand, at a depth of 0.5 cm. The needle will be slightly lifted to stimulate the acupoints, and after getting qi, the left hand will push the needle core inward. However, no absorbable surgical suture will be placed into the front end of the needle tube. After the procedure, the pinhole will be pressed with aseptic gauze for a while and covered with a bandage or infusion paste. This procedure will also be conducted once a week for 4 consecutive weeks. Each participant will take a prescribed dose of loratadine orally every day. Participants from both groups will be instructed to stop symptomatic RMs during the 1-week run-in and treatment periods. However, they will be allowed to take RMs if needed during the follow-up period. The use of RMs will need to be documented in the participants' diaries.

Outcome Measurement

For an evaluation of the primary and secondary outcome measures, the participants are required to complete 2 questionnaires, the Total Ocular Symptom Score (TOSS) and the Total Nasal Symptom Score (TNSS) [19]. These questionnaires will be completed at the beginning of each of the 4 treatment sessions (from week 2 to week 5) and in weeks

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8, 12, and 16 during each follow-up session. During the follow-up process, the participants need to independently record their Rhinitis Control Assessment Test (RCAT) scores weekly [20]. In addition, the participants will be asked to complete diaries throughout the trial. The primary outcome is the recurrence rate 3 months after discontinuation. Once the treatment-effective participants discontinue the medication (RCAT score less than 21 points), they will immediately enter the follow-up period. If a relapse occurs, the relapse time will be promptly recorded, and the follow-up will conclude. Otherwise, the participants will continue to be monitored until 3 months after discontinuation of medication. RCAT is one of the most commonly used rhinitis control scales, and its reliability, validity, and responsiveness have been widely verified [21,22]. A score of 21 corresponds to the validated RCAT score of 25, which determines the controlled state of rhinitis. When RACT ≤21, it indicates an uncontrolled state of AR and the starting point for treatment [23]. RCAT is a simple self-rating scale that allows patients to assess their AR control at home and helps assess the success of long-term repeated treatment interventions [20,24]. TNSS evaluates 4 nasal symptoms: nasal obstruction, sneezing, rhinorrhea, and nasal itch. The symptoms are self-assessed and recorded by participants using a 5-point scale (0=no symptoms; 1=mild symptoms; 2=moderate symptoms; 3=severe symptoms; 4=very severe symptoms) [23]. TNSS scores range from 0 to 16, with low scores indicating lighter nasal symptoms. TOSS assesses eye symptoms, including redness, itchiness, and tearing. Each symptom is assessed on a scale between 0 and 3 (absent to most severe), with a total score from 0 to 9 [19,25]. The score represents an average for both eyes. The secondary outcomes include (1) changes in TNSS and TOSS score from baseline to weeks 8, 12, and 16; (2) response to interventions, defined as participants with a change in TNSS score of ≥0.5 from baseline; (3) and serum levels of tumor necrosis factor-alpha (TNF-α), IFN-γ, IL-4, IL-17, and IgE, measured by enzyme-linked immunosorbent assay according to the manufacturer's protocol (Bio-Techne).

Serum Acquisition

The participants' venous blood samples will be collected using blood collection tubes, symmetrically placed in the centrifuge sample bin, and covered. The rotation speed will be set to 4000 rpm, and the centrifuge time will be 10 minutes. The machine will be turned off after centrifugation, the sample bin opened, the sample carefully taken out, and the separation of the sample observed. If it is unsatisfactory, the sample will be centrifuged again. The serum will be carefully sucked from the upper layer with a 1-ml pipette, moved to an Eppendorf tube, and stored in a refrigerator at –80 °C degrees for inspection. Serum TNF-a, INF- γ, IL-17, IL-4, and IgE levels will be measured using enzyme-linked immunosorbent assay [26].

Basic Characteristic Variables

Demographics such as age, sex, height, body mass, and BMI will be obtained. Vital signs including temperature, blood pressure, heart rate, and breathing will also be measured. Data on patient medical history, family history, risk factors, and dietary history will be collected.

Statistical Analyses

Intentional therapeutic analysis will be adopted, with missing values estimated using the last observation carried forward method. Mean and SD (for continuous variables that obey normal distribution), median and quartile (for continuous variables that do not obey normal distribution), and frequency and percentage (for classified variables) will be used for the statistical description. According to the numerical characteristics of the variables, quantitative data such as age, height, and weight of the 2 groups will be compared using a *t* test or the Wilcoxon rank sum test. The chi-square test or Fisher exact probability method will be used to compare qualitative variables, such as sex and nationality between the 2 groups. Cox regression analysis will be carried out with recurrence outcome and time of first recurrence as dependent variables, and the differences in survival curves between both groups will be compared. SPSS software (version 23.0; IBM Corp) will be used for statistical analysis. A 2-sided test will be used for all statistical inferences, and $P<.05$ will be considered statistically significant.

Safety Assessment

An independent data and safety monitoring committee evaluates the progress of the trial and assesses the safety data that may be requested during the trial. An adverse event (AE) is defined as any undesirable experience that participants undergo during the trial period, whether it is associated with the intervention or not. Participants will be instructed to report any AEs to the research team at any time. All details of AEs such as time of occurrence, severity, management, and causality to the intervention will be recorded on case report forms (CRFs). There are nine common AEs related to ACE: (1) lingering discomfort; (2) local hematoma or subcutaneous bleeding; (3) local swelling; (4) local induration; (5) severe pain; (6) thread extrusion; (7) local itching; (8) elevated body temperature after embedding the thread; and (9) local redness, swelling, heat, and pain after embedding the thread [27]. All AEs will be followed up from the date they are brought to the investigator's attention until the AE is resolved. In the event of an emergency medical situation, the individual's randomization code and group allocation will be identified via a standard operational procedure.

Quality Control

Before recruitment, the entire research team including acupuncturists, operational assistants, and research nurses were required to attend a training workshop. This was done before the trial to ensure their strict adherence to the study protocol and familiarity with the trial administration process. They were also provided with a written protocol and standard operation procedure documents. The 2 acupuncturists who will administer the treatment each have acupuncture licenses from the Chinese Ministry of Health and have over 5 years of experience in ACE application. The data collected in this trial comprise information recorded in CRFs and information on the RCAT, TNSS, TOSS, and blood routine examinations. Data will be entered using the double-entry method. The data quality will be checked regularly by research assistants and overseen by monitors. Data monitoring will be conducted regularly following standard operation procedures set by the Guangdong International Clinical Research Center of Chinese Medicine (Guangzhou,

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China). Audits will be performed regularly by the Department of Science Research at the Guangzhou University of Chinese Medicine. All modifications will be marked on the CRFs. Data managers will then recheck the data before logging them and promptly notify the research team if any discrepancy is found. The database will be locked after all data have been cleaned. If participants withdraw from the trial either during the treatment period or the follow-up phase, they are not required to provide any reasons. The withdrawal rate will be analyzed via statistics.

Sample Size Calculation

Our preliminary study [28] indicated that the 3-month recurrence rate of the ACE group should be at least 5% lower than that of the Sham ACE group to be clinically significant. Using α=0.025 (unilateral), β=0.2, $\triangle$=5%, and K=1, the sample size was estimated based on the comparison of two sample rates in the optimization test. The sample size in each group was calculated to be 52. Since the effectiveness of any treatment was not 100%, patients with ineffective treatment in this study could not be included in the assessment of recurrence, so the loss of follow-up rate in this study was 20%, which amounted to 126 cases. The \following equation is used to calculate the sample size, which refers to the estimated number of patients to be enrolled in the study:

Ethical Considerations

This study protocol has been approved by the Ethics Committee of the Guangzhou University of Chinese Medicine (B2014-014-01). It is explicitly outlined to all participants that the trial involves a waiting-list group and that informed consent to participate includes an agreement to undergo 3 months of clinical monitoring. All participants are provided with enough time to decide whether to sign the informed consent. This clinical study will adhere to the ethical principles outlined in the Declaration of Helsinki (2024) and relevant national regulations. Prior to study initiation, the trial protocol underwent rigorous review and approval by the Ethics Committee of Ningxia Medical University (2024-075). Written informed consent must be obtained from each participant before randomization.

Results

The study funding began in January 2022. The study was initiated on February 1, 2025, and will end in February 2026. Participant recruitment is underway, and the results will be released in March 2026.

Discussion

Presently, there are many limitations in the treatment of AR. The main drugs for treating AR are H1 antihistamines, nasal steroid hormones, and leukotriene receptor antagonists. The control and safety of nasal symptoms have been verified, but there are still deficiencies in controlling the recurrence of AR [6]. AIT is the only means of altering the natural immunological course of allergic diseases and achieving long-term remission. Pharmacological measures can suppress the immune response and/or alleviate the symptoms, but there is a risk of relapsing soon after these measures are withdrawn. The current AIT approaches depend on the administration of intact allergens, often comprising crude extracts of the allergen. In contrast, ACE has many advantages, involving mechanical stimulation and later biological and chemical stimulation [29]. The process of softening, decomposing, liquefying, and absorbing the catgut thread within the acupoint generates long-lasting stimulation, making it less prone to recurrence. Therefore, the treatment interval can be extended to once every 10 days, greatly improving patient compliance. Moreover, the catgut thread, as an allogeneic protein stimulus, can better regulate the relative balance of the body's internal environment, enhance immune function and stress resistance, and reduce allergic reactions [16]. Currently, the research on ACE therapy for AR primarily focuses on regulating cytokines, influencing neurotransmitters, and inhibiting immune molecules such as IgE. At the cytokine regulation level, acupoint embedding research concentrates on interventions targeting inflammatory factors and transforming factors. Inflammatory factors include IL-17, IL-4, and IFN-γ [30], and transforming growth factors include transforming growth factor β1, among others [8-12]. ACE therapy intervenes in neurotransmitters by participating in the release of various immunologically active substances, such as substance P. Research has found that embedding therapy can alleviate rhinitis-related symptoms by regulating substance P and nitric oxide levels [13-15]. Importantly, a study found that ACE therapy decreased the release of immunoglobulin G (IgG) in vivo in mice, which was accompanied by a decrease in IgG1, histamine, and interleukin. The symptoms of AR in mice were likewise alleviated during this process [25].

The purpose of this trial is to reduce the recurrence of rhinitis, relieve symptoms, and achieve clinical benefit by using ACE as a nondrug therapy. Previous articles about ACE for the treatment of AR lack placebo-controlled, high-quality research [26]. Therefore, it is necessary to provide high-quality research in this domain. We designed this RCT to examine whether ACE treatment decreases recurrence and improves symptoms such as sneezing, clear watery nasal discharge, itchy nose, and nasal congestion in patients with AR. The main limitation of this study is its single-blind design. Another potential limitation is the possibility of patient attrition due to the requirement of undergoing treatment over 4 weeks, totaling 4 times. Another limitation is our inability to design double-blind trials due to the material and design of the embedding needles. Moving forward, our aim is to develop improved embedding needles that align more closely with the requirements of double-blind testing, thereby enhancing the international promotion of this therapy. The strengths of this study include the use of a randomized controlled design, with all patients being followed up. Both subjective and objective data will be collected in this study to examine the effectiveness of ACE in treating AR. Another advantage is that it focuses on decreasing recurrence. The results of this study could improve the treatment outcomes of patients with AR. We posit that this research will provide important insights into the efficacy of ACE treatment for AR and generate robust data for the foundation of future research in this field.

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Acknowledgments

We are grateful to Bin Guo for his assistance with the design of the trial phase.

This study would not have been possible without the support of Ningxia Medical University. We thank Prof ChunZhi Tang for assistance with data analysis and processing.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed for this article. The data sets analyzed during this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

ZC and CXM wrote the initial draft of the manuscript, contributing equally to it. We would like to include CZT as one of the corresponding authors, but BG is the primary corresponding author. All authors have reviewed and edited the manuscript and approved the manuscript for publication.

Conflicts of Interest

None declared.

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Abbreviations

ACE: acupoint catgut embedding
AE: adverse event
AIT: allergen-specific immunotherapy
AR: allergic rhinitis
CRF: case report form
IgE: immunoglobulin E
IgG: immunoglobulin G
INF-γ: interferon-gamma
IL-17: interleukin-17
IL-4: interleukin-4
RCAT: Rhinitis Control Assessment Test
RM: relief medication

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TNF-α: tumor necrosis factor-alpha
TNSS: Total Nasal Symptom Score
TOSS: Total Ocular Symptom Score

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Protocol

Feasibility of Using Resting Heart Rate and Step Counts From Patient-Held Sensors During Clinical Assessment of Medical Emergencies (FUSE): Protocol for Prospective Observational Study in European Hospitals

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Abstract

Background: Abnormalities of vital signs are quantified by comparison with normal ranges, which are those observed in resting healthy populations. It might be more appropriate to compare the vital sign values of an individual in distress with their own usual values recorded when they were stable and well. Sensors from smartwatches or smartphones might make this possible at scale, but the proportion of patients using them is not known.

Objective: This study aimed to assess the feasibility of using heart rate and mobility data from patients' own wearable sensors as part of clinical assessments at the time of presentation to hospitals with medical emergencies, and to quantify the difference between heart rate and the change in daily steps taken by the patient on admission to acute care compared with the previously recorded values at home.

Methods: This is an international, multicenter observational study using the flashmob research design. The study will recruit patients aged 18 years and older who present to emergency departments, acute medical departments, or ambulatory emergency care with an acute medical complaint. Main end points of the study include the proportion of patients assessed for an acute complaint who use wearable devices to record vital signs. The study will describe the population that uses devices that collect vital signs in terms of sex, age group, digital literacy, and the severity of illness on presentation (as measured by a standard set of vital signs and frailty). Trends in heart rate and step counts measured in the month before presentation to acute care services will be reported according to discharge or admission status. Data will be collected during a pilot phase and during a single week in centers across Europe.

Results: The study has been registered and passed the required approvals in the Netherlands Medical Ethics Committee (MEC-2022-0795) and the United Kingdom Integrated Research Application System (IRAS 321129). Based on the results of a pilot study performed at a single site in the United Kingdom, a flashmob study has been concluded in hospitals throughout Europe in May 2024 and reported in 2025.

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Conclusions: With the increasing availability of consumer held devices able to record medically relevant information this study will provide information about the availability of these data for clinical use in a number of European settings.

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KEYWORDS

mHealth; emergencies; heart rate; step count; hospital admission; intensive care; medical emergency; smart watch; feasibility; clinical assessment; wearables; vital signs; distress; wearable sensors; mobility; device; mobility data

Introduction

Background

The decision about the need of an individual to require hospital admission relies on the assessment of patients' symptoms, signs, past medical history, medication use, diagnosis, social support at home [1-3], and a judgment about the severity of illness based on estimated risk of deterioration in the subsequent hours and days [4].

Abnormalities of vital signs are quantified by comparison with normal measurements on healthy individuals recorded during periods of physiological stability. Within these individuals, the normal measurements vary and are influenced by age, sex, body composition, medication use, and physical condition [5-7]. There is a relation between the size of change from a physiologically normal range and the number of vital signs affected by abnormality and the frequency of adverse events [8]. Abnormality might be scored with generic tools that can be applied to the majority of patients, such as the National Early Warning Score [9], or tools that are disease-specific, such as the CURB65 [10], Blatchford [11], and DECAF (Dyspnea, Eosinopenia Consolidation, Acidemia, and Atrial Fibrillation) [12]. However, these scores can under- or overestimate risk in individual patients [13].

Knowing the values of an individual patient's vital signs while well might help clinicians to better understand and interpret their changes or trends [14], their relative degree of deviation from the patient's own normal and get a better estimate of their personal severity of illness. Similarly, mobility has been suggested to be a vital sign [15] and could be easily quantified by step counts. Normal mobility has been shown to be a protective factor [15]. Therefore, the assessment and comparison of step count during illness might be of value.

The general public are increasingly using devices such as smartwatches and mobile telephones that can potentially measure and record vital signs such as heart rate, heart rhythm, and oxygen saturation. Currently, approximately 90% of the population in the United States [16] and 94% in the United Kingdom [17] are smartphone users. Vital signs are also increasingly being recorded at home using conventional sphygmomanometers and pulse oximeters, and these values, if recorded, might also be available.

The aim of this study is to assess the feasibility of using a patient as their own reference for vital signs by assessing the difference between vital signs on admission to acute care with their own vital sign values recorded by his or her wearable device when they are at home and well (Textbox 1).

Objectives

The primary and secondary study objectives are described in Textbox 1.

Textbox 1. Primary and secondary objectives.

Primary objectives

- To assess the feasibility of using data from patients' own wearable sensors for assessments in acute care. Feasibility will be assessed by eligibility, recruitment, retention rates, and patients' acceptability.

Secondary objectives

- To explore the proportion of patients assessed for an acute complaint who are wearing or carrying a device that collects data on vital signs (eg, smartwatch or other wearables).
- To describe the population who wear or carry devices that collect data on vital signs.
- To quantify the change in heart rate in patients admitted to acute care between measurements taken on presentation and previously recorded vital signs by a consumer-grade wearable while patients were stable and well.
- To quantify the change in step count in patients admitted to acute care between measurements taken shortly before presentation and previously recorded step counts by a consumer-grade wearable while patients were stable and well.
- To explore the association between trends in in vital signs with the disposition of patients (admission to a general ward, critical care area, or discharge home within 24 hours from assessment).

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Methods

Study Design

A pilot study was performed at a single site in the United Kingdom to develop and test procedures for data collection and reporting during the previous 6 months. Based on the learning from this pilot a prospective, international, multicenter, observational study using the flashmob research design will be conducted [18]. Participating units will collect data from patients presenting with acute medical emergencies to emergency departments, acute medical units, and ambulatory emergency care. There will be no randomization, blinding, and treatment allocation.

Population

Patients who present at the emergency department, acute medical department, and ambulatory emergency care unit in secondary and tertiary hospitals in a sample of hospitals in the Netherlands, United Kingdom, Denmark, and Switzerland with an acute medical complaint. Acute medical complaints are nonsurgical admissions commonly treated by internists such as acute physicians, cardiologists, pulmonologists, gastroenterologists, endocrinologists, geriatricians, and similar (Textbox 2).

Textbox 2. Inclusion and exclusion criteria.

Inclusion criteria

Participants in this study must be able to give informed consent, have an acute presenting complaint, be aged 18 years or older, and use any of the following: smartwatch, activity tracker, or other wearable monitoring devices, or a smartphone that collects step counts or data from other wearable devices.

Exclusion criteria

Patients who are unable to give informed consent or endure an imminently life-threatening illness.

Main study end point

To quantify the proportion of patients assessed for an acute complaint who are wearing a device that collects data on vital signs (ie, heart rate and step count).

Secondary study end points

Secondary end points will focus on four areas of interest:

- The difference between the heart rate at rest from the wearable device 24 hours, 1 week, and 1 month before assessment by emergency practitioners compared with the first set of vital sign parameters measured on admission to acute care.
- The change in daily steps taken in the month before admission to acute care.
- To describe the population that is wearing devices that collect data on vital signs in terms of gender, age group, severity of illness as measured by a standard set of vital signs, level of education, and digital literacy and frailty.
- To explore the association of changes in heart rate from the community to assessment in acute care services with clinical end points such as admission to a general ward or admission to a critical care area or discharge home within 24 hours from the time of clinical assessment.

Study Procedures

All patients aged 18 years and older who present to acute care will be asked if they wear a smartwatch, activity tracker, or wearable that measures heart rate.

Patients will be asked to give informed consent in line with the guidance from the participating countries. This is likely to include written informed consent in the Netherlands, Denmark, and the United Kingdom. Informed consent will be explicit about accessing data from patient-held wearables (Multimedia Appendix 1). Once consent has been obtained, initial data will be entered into the case report form, and the remaining items of the case report form will be completed on the day after the initial presentation or later (Textbox 3). Study documentation will include a guide for investigators to interrogate commonly used wearable devices (Multimedia Appendix 2). Parameters recorded will vary according to the different devices used but should at least include heart rate and step count.

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Textbox 3. Data items were collected as part of the "Feasibility of Using resting heart rate and step counts from patient-held Sensors during clinical assessment of medical Emergencies" (FUSE) study.

- Site ID is the unique number for each site.
- Participant ID is a consecutive number (no identifiable information is collected).
- Location is the location where the patient is included in the study (ie, emergency department, medical admissions unit, ambulatory emergency care, or other).
- Sex as reported by the patient (ie, men, women nonbinary, or unknown).
- Date of birth, which will be used to compute an age category.
- Date and time of first presentation, defined as the time that a patient presents at the location.
- Highest level of education is the patient finished highest level of education or the level of education the patient is currently following (ie, primary school, secondary school, and higher education).
- Digital literacy is assessed using 2 questions asking for confidence of using the internet and confidence of using mobile apps, which patients can answer using a 5-point Likert scale.
- Device is the device used to measure heart rate, and the brand and type will be recorded.
- Phone is the phone that patients use, and this will be used to retrieve the step count and heart rate data. The brand and type will be recorded.
- Heart rate on the device is the heart rate that is stored and measured by the device, and the resting heart rate (as presented by the device), the minimum, maximum, and mean or median (depending on the device) will be retrieved on three-time points, namely on presentation, within 24 hours before presentation and within 1 week (plus or minus 1 day) before presentation.
- Walking distance is the number of steps of exact distance (in kilometers or miles), either measured by the device of the phone. The daily walking distance of the 7 days before the presentation will be recorded.
- Frailty as quantified through the Clinical Frailty Scale [19].
- Mobility will be assessed as either normal or impaired. Mobility is considered impaired if the patient is unable to get onto the bed unaided, either from the ambulance gurney or whichever way they arrive.
- Date and time of the first set of vital signs is defined as the time that the first set of vital signs are measured.
- Heart rate on admission is the first heart rate measured during clinical examination.
- National Early Warning Score [9] as a standardized assessment of the severity of illness, based on the first full measurements of respiratory rate (per minute), oxygen saturation (in %), temperature (in °C), heart rate (per minute), systolic blood pressure (in mm Hg), AVPU (alert, verbal, pain, and unresponsive) score, and the use of any supplemental oxygen.
- Outcome is assessed at midday on the day after the initial assessment and can be (ie, discharged, admitted to hospital, admitted to high care or intensive care, or deceased).

Withdrawal of Individual Participants

If they wish, participants can leave the study at any time for any reason without any consequences. The investigator can withdraw a participant from the study if they consider it is in the participant's best interests, such as avoiding delay or compromise of urgent medical care.

Statistical Analysis

Sample Size Calculation

Due to the use of the Flash Mob Research design a formal sample size calculation is not possible. We assume that a number of 40 participating hospitals in Europe screening up to 50 patients each would result in a sample size of at least 2000 patients screened. This sample size should be able to answer questions about the proportion of the number of patients presenting with wearable devices and about changes in key vital signs between assessment in the hospital and a period 24 hours 1 week or 1 month previous.

Data Analysis

Data will be analyzed using SPSS (version 28; IBM Statistics). All variables will be assessed for normality. This study will use basic epidemiological data to determine if patient-owned monitoring devices can be used in an emergency care setting to assess the patient's current severity of illness and compare it with their usual state of health.

Continuous data will be analyzed using the unpaired *t* test (if the data are normally distributed) or the Wilcoxon rank sum test (if the data are not normally distributed). Changes between measurements will be described as percentage change from the first measurement taken at home before admission as the assumed baseline and as an absolute change. Categorical data will be analyzed using chi-square test. Basic statistics and descriptives will be used to identify the distribution of patient and device characteristics. Missing data will not be imputed.

Associations between the baseline measurements and the specified clinical end points and the absolute and proportional change of physiological measurements and the specified clinical end points will be assessed using linear regression and logistic regression.

Patient characteristics will be expressed as absolute numbers per (sub)category for the total patient population, the discharged patients, and the admitted patients. The heart rate and step count

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data will be compared for their respective average or median for the different time points. Both will be tested for significant interaction between time, disposition, and change in either heart rate or step count using a generalized linear model.

For secondary exploratory analyses, the correlation between potential outcomes will be tested using Pearson coefficient correlation analysis (r), where the following interpretation will be used: below 0.10 negligible, between 0.10 and 0.39 weakly correlated, between 0.40 and 0.69 moderately correlated, between 0.70 and 0.89 strongly correlated, and above 0.89 very strongly correlated. The percentile change in heart rate and step count will be calculated in comparison to the baseline, which will be assumed to be at 30 days before a hospital visit.

Primary Outcome Measures

The primary outcome of the study will be feasibility as assessed by the proportion of eligible patients with emergency presentations who have devices as well as recruitment and retention rates.

Secondary Outcome Measures

Secondary outcomes measures include measures of epidemiology and physiology:

We will report trends for heart rate and step count, specifically the difference between the heart rate at home 24 hours, 1 week, and 1 month before clinical assessment from the wearable device compared with the first vital signs measured on admission to acute care as both an absolute and a proportional change.

We will also describe the degree of association between changes to vital signs from the community to assessment in acute care services with admission to a general ward or admission to a critical care area or discharge home within 24 hours from the time of the first hospital assessment.

The population wearing or carrying devices will be described in terms of gender, age, ethnicity, level of education, and digital literacy and contrasted with data from national surveys.

Administrative Aspects, Monitoring, and Publication

Handling and Storage of Data and Documents

Data will be anonymously recorded in a research database (ie, Castor Electronic Data Capture System) in line with local data protection regulations, including but not limited to European General Data Protection Regulations (GDPR).

The collected data will be subsequently stored on a digital research environment from the Erasmus MC, a secure server with 2-factor authentication. There are no patient identifiers within the data. Only selected investigators of this study will have access to the server with the data. Data will be stored for 15 years.

Amendments

Amendments are changes made to the research after a favorable opinion by the accredited MEC has been given. All amendments will be notified to the ethics committee that gives a favorable opinion.

Annual Progress Report

The sponsor or investigator will submit a summary of the progress of the trial to the accredited MEC (Medisch Ethische Toetsings Commissie, METC) once the study is completed or, at the latest, after 1 year. Information will be provided on the date of inclusion of the first participant, the numbers of participants included and the numbers of participants that have completed the trial, serious adverse events or serious adverse reactions, other problems, and amendments.

Temporary Halt and (Premature) End of Study Report

The investigator or sponsor will notify the accredited METC of the end of the study within a period of 8 weeks. The end of the study is defined as the last patient's last visit.

The sponsor will notify the METC immediately of a temporary halt of the study, including the reason of such an action.

In case the study is ended prematurely, the sponsor will notify the accredited METC within 15 days, including the reasons for the premature termination.

Within 1 year after the end of the study, the investigator or sponsor will submit a final study report with the results of the study, including any publications or abstracts of the study, to the accredited METC.

Public Disclosure and Publication Policy

The results of this study will be published in one or more peer-reviewed articles. Publications will be coordinated by the investigators or sponsors. Authorship of publications will be determined in accordance with the requirements published by the International Committee of Medical Journal Editors and in accordance with the requirements of the respective medical journal.

Benefits and Risks Assessment and Group Relatedness

There are no benefits or risks for participants of this study. The burden of participation in this study is low.

Ethical Considerations

Regulation Statement

The study will be conducted in compliance with the principles of the Declaration of Helsinki (version 10, October 19, 2013) and the principal of Good Clinical Practice. Participants are not subject to procedures or required to follow rules of behavior and, as no additional data are collected the Medical Research Involving Human Subjects Act (also known by its Dutch abbreviation WMO) is not applicable to this study. Each principal investigator is responsible for ensuring that the study is performed in accordance with the protocol and Good Clinical Practice.

The review board of the Erasmus University Medical Center, Erasmus MC in Rotterdam, the Netherlands, has reviewed the research proposal. It confirmed that the rules laid down in the WMO, do not apply to this research proposal Medical Ethics Committee (MEC-2022-0795). The protocol (V1.2 17 February 2025) passed the required approvals in the United Kingdom Integrated Research Application System (IRAS 321129).

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Recruitment and Consent

Patients eligible for inclusion are asked if they use a smartwatch or other wearables that measure heart rate by a collaborator of the study. If they do they fulfill the inclusion criteria, and they will then be informed about the study procedures and asked to participate after they have read the patient information form. After receiving this form patients will be asked if they will agree to sign written informed consent.

Governance

Hospitals will be recruited across Europe and coordinated by the study steering board. The study steering board consists of the principal investigators and members of the Safer home consortium. Centers are encouraged to collect data on a small cohort of patients before the main study week (May 10-22, 2024). During the main study week, all participating units are asked to collect data on all patients presenting in the study areas during a 24-hour period.

Participating countries will be responsible for their own submission for approval and coordination of research.

Results

Approvals have been completed in 11 sites in Denmark, 17 sites in the Netherlands, 1 site in Switzerland, and 7 sites in the United Kingdom.

The main FUSE study has gone live on the May 15, 2024, in 34 hospitals in the Netherlands (n=17), the United Kingdom (n=7), Denmark (n=9), and Switzerland (n=1). A total of 1137 patients were screened, of these, 452 patients were included and 209 patients had data on at least 2 collection points, allowing for an analysis of trends.

Preliminary analysis will be completed by December 31, 2024, and the main manuscript will be submitted for publication by the end of March 2025.

Discussion

Anticipated Findings

While sensors that can be carried or worn are in widespread use with a project market size in 2023 of in excess of US $4 billion [20], previous research has found little evidence of their use in emergency care [21]. This study aims to determine if there are opportunities to use the data generated by these consumer-held devices to improve patient care. Trends in vital signs and mobility are used to quantify risks to patients and are likely to become more important as the proportion of patients with chronic conditions (and abnormal vital signs during signs of clinical stability) is increasing. For clinical use we anticipate a number of use cases: Assessing patients whose vital signs have not changed in the week previous presentation in an acute care setting might reassure clinicians that the condition is overall stable and that treatment in the community is likely to be safe. Assessing patients whose vital signs have significantly changed in the days or hours before presentation might increase the confidence of clinicians to admit for observation and treatment in the hospital. This type of decision-making is commonly undertaken during an initial observation phase in emergency departments or acute medical unit with patients being observed for a night before committing to a decision about admission or discharge. We anticipate that this type of decision-making could be undertaken during the initial presentation if data on markers of physiological instability is available already at this point.

Limitations

The distribution of wearables in the population might point toward the exclusion of a significant proportion of the population from this type of support: patients who are less financially well off or not sufficiently digitally or health literate might be disadvantaged in a future health care. This data will hence be collected as part of FUSE. While this study focuses on readily available data and will require in future supplementation by detailed qualitative data.

The study is conducted by a group of secondary care clinicians with expertise in medical emergencies. Many of the patients who will be screened and included will have previously presented in primary care. There is no theoretical reason that the results from this study might not be applicable to those presenting in primary care, but this might require future research.

In preparation of the study, we reviewed sales for the top 20 devices in the Dutch and British markets. For these devices, we have created a data dictionary for investigators that will enable them to assist patients in the location of relevant data. With new devices coming online and changes in consumer habits, the frequency distribution of these devices might however be soon outdated.

The study will explicitly not address the quality of data collected in wearables. We will, however, report on the distribution of devices and approval for medical use where applicable. In the same vein, we anticipate that the duration of usage by individuals will affect the measurements. This is something that we might not be able to evaluate in the current setup.

Given that patients will use a range of devices with different methods for data acquisition and different usage patterns our analysis will focus on the comparison of relative changes in parameters for individuals (intraindividual variation). This relies on the assumption that individuals will have a pattern of usage that is constant over time. Further research will be required, especially if it turns out that the variation between the collected parameters turns out to be large in the days before deterioration and presentation to the hospital.

Finally, future health care needs to be equitable. FUSE will include data that will allow us to gauge some aspects of equity, diversity, and inclusion which are crucial for the development of policy and strategy in this field.

Study Impact

Given the funding shortfall in most health economies consumer-owned monitoring will represent a tempting addition for health care providers in primary and secondary care. The supporting tools such as the wearable device dictionary (Multimedia Appendix 2) might be useful to clinicians even without the data from the study.

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Conclusions

This article describes a feasibility study. The results should aid power calculations and the design of more definitive observational and ultimately interventional trials.

From a health policy point of view, there is concern that, at present, device ownership might be more common in those who are younger and well off, thus potentially amplifying problems around equitable access to health care and emphasizing the inverse care law. The FUSE study and subsequent research should provide data that might direct manufacturers toward the design of devices that are suitable for the widest range of users. We hope that FUSE will help policymakers and clinical teams in the design of better and safer services around digitally enabled patients and for those who are not (yet) connected to mHealth systems.

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Funding has been secured through a grant from the Society for Acute Medicine. This means that the study is a portfolio study for the United Kingdom.

Authors' Contributions

The study was conceived by JA. All authors have been equally involved in the development of the trial protocol and this publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Sample consent form.
[PDF File (Adobe PDF File), 135 KB - resprot_v14i1e55975_app1.pdf]

Multimedia Appendix 2
Wearable devices data guide for investigators of the FUSE study.
[PDF File (Adobe PDF File), 4259 KB - resprot_v14i1e55975_app2.pdf]

Multimedia Appendix 3
Spirit checklist for study protocols.
[PDF File (Adobe PDF File), 138 KB - resprot_v14i1e55975_app3.pdf]

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Abbreviations

DECAF: Dyspnea, Eosinopenia Consolidation, Acidemia, and Atrial Fibrillation
GDPR: General Data Protection Regulations
IRAS: Integrated Research Application System
MEC: Medical Ethics Committee
WMO: Medical Research Involving Human Subjects Act

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Protocol

Mobile Health–Based Motivational Interviewing to Promote SARS-CoV-2 Vaccination in Rural Adults: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Despite documented effectiveness, the public health impact of vaccinations is severely limited by misperceptions, hesitancy, and poor acceptance. Messaging from health care providers has not yet been optimized to overcome these barriers and has not been tailored to groups that face health disparities, such as rural Americans. Because vaccines have become controversial, as illustrated by the public response to the SARS-CoV-2 vaccines, traditional approaches that use persuasive education or advice to change perspectives are unlikely to have long-term effects and may even be counterproductive. Alternatively, motivational interviewing (MI) is a conversational approach to address modifiable behavior and its empathic nature can be useful when navigating challenging topics. Although MI has been found to be efficacious in improving vaccination rates among children and adolescents, it is unknown whether MI can reduce vaccine hesitancy and health disparities among underserved rural adults. Further, the ideal mode of delivery for MI is unknown, especially “dose,” “intensity,” and integration with mobile health (mHealth). Therefore, it is essential to investigate the efficacy of MI in promoting vaccine uptake in rural populations to reduce health disparities.

Objective: This study aims to develop and evaluate the feasibility, acceptability, and preliminary efficacy of our mHealth-based MI intervention to diminish SARS-CoV-2 vaccine hesitancy (MOTIVACC).

Methods: This pilot study uses mixed methods. A 2-phase study will be conducted: convening a community advisory panel to understand barriers and facilitators to vaccination and mHealth uptake among adults (phase 1, n=16-20), and a pilot 3-group single-blind randomized controlled trial (RCT) for 8 weeks (phase 2, N=60). In the RCT, we recruit adults who have received no previous dose of the COVID-19 vaccine and randomize them into one of three arms: standard MI (SMI; n=20), intensive MI (IMI; n=20), or mHealth-based MOTIVACC (n=20). The primary RCT outcomes are positive change in vaccine hesitancy and intention to obtain the vaccines, measured on Likert scales. The secondary RCT outcome is the actual vaccine receipt.

Results: Phase 1 of this study was approved by the ethics committees of both the University of Oklahoma and Oklahoma State University in July 2022, and was completed in June 2023. Phase 2 of this study was approved by the ethics committee at the University of Oklahoma in April 2024.

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Conclusions: This randomized trial will evaluate the preliminary efficacy of MI for targeting SARS-CoV-2 vaccine hesitancy, as well as compare traditional MI versus mHealth-based MI. This will provide pivotal data on scalable strategies to assist in navigating vaccine hesitancy, including in rural populations.

Trial Registration: ClinicalTrials.gov NCT05977192; https://clinicaltrials.gov/study/NCT05977192

International Registered Report Identifier (IRRID): DERR1-10.2196/64010

(JMIR Res Protoc 2025;14:e64010) doi:10.2196/64010

KEYWORDS

motivational interviewing; vaccination hesitancy; community-based participatory research; rural health; mobile health; mHealth

Introduction

Throughout the COVID-19 pandemic, rural populations have had lower rates of SARS-CoV-2 vaccination, increased vaccine hesitancy, and higher risks of morbidity and mortality associated with active infection than urban populations [1]. Increased likelihood of vaccine hesitancy has been associated with rural residence, low household income, and less education [2]. While some strides have been made in rural vaccination, it has been estimated that those who remain unvaccinated and currently reside in rural areas are less likely to consider vaccination (eg, will "definitely not" get vaccinated) [3]. In Oklahoma specifically, as of May 10, 2023, 68% of Oklahomans aged 18–35 years and 57% of Oklahomans aged 36-49 years had not received any dose of a SARS-CoV-2 vaccine [4]. However, in urban counties, 76%-95% of adults had received at least one dose, while the rates in rural counties ranged from 37%-65% [5]. Further, it has been estimated that as many as two-fifths of rural Oklahoman residents are hesitant to receive the vaccine [6].

Health communication has been consistently identified as a key element in promoting vaccine uptake and addressing vaccine hesitancy. Historically, approaches taken to communication vary [7] but may focus on attempts to craft persuasive informational messages [8]. The effect of these messages is likely minimized, as many individuals who are vaccine-hesitant perceive the source of information (eg, health care providers) as misinformed [8], thus a fundamental shift in the purpose of vaccine-related communication is essential. Such approaches may instead focus on honoring individual autonomy and navigating information and perceptions of information, versus relaying of information itself [9]. Data also suggest the advantage of using messages that emphasize the personal benefits of vaccination rather than prosocial benefits in reducing vaccine hesitancy; however, this may differ according to individual values [10]. Thus, it is critical to align individual priorities with intervention content, a key feature of motivational interviewing (MI) [11]. No studies have examined the effects of MI on vaccination rates among adults most vaccine-hesitant. MI has documented efficacy in vaccine-hesitant parents (eg, child HPV vaccines): vaccine intention rose by 12%, hesitancy decreased by 40% [12], and vaccine coverage in infants increased by 3.2%, 4.9%, and 7.3% at 3, 5, and 7 months of age, respectively [13]. MI has also been used to promote HPV vaccination in high-risk adults with promising results [14], but not necessarily in those who are vaccine-hesitant. While promising, MI delivery can be laborious, limiting scalability. Alternatively, mobile health (mHealth)–based interventions have been used to promote vaccination [15]. Thus, integrating MI into automated platforms is essential for scalability to improve public health.

The World Health Organization (WHO) acknowledges mHealth as a cost-effective, scalable, and sustainable way to improve public health [16]. A limiting factor in MI's effectiveness is scalability due to the intensity of provider training and evaluation. Further, smartphone ownership in the United States increased from 35% in 2011 to 90% in 2023 [17] with similar rates across urban and rural groups (91% and 87%, respectively). Near-universal smartphone ownership provides an ideal yet untapped mechanism to deliver MI-based vaccine interventions to rural populations.

In summary, there is a critical need for improving SARS-CoV-2 vaccination rates among rural populations in Oklahoma and nationwide. To address this need, we will test the efficacy of an mHealth-based MI intervention to diminish SARS-CoV-2 vaccine hesitancy (MOTIVACC). This protocol paper aims to describe our mixed-methods approach to develop and pilot test the MOTIVACC. This study and subsequent course of research will contribute significantly to reducing vaccine-preventable morbidity and mortality in rural populations.

Methods

Study Design

This pilot study uses a mixed-methods, empathy-driven, user-centered intervention design strategy with two phases: (1) convening a community advisory panel (CAP) to understand emerging and current barriers and facilitators to vaccination and mHealth uptake among rural adults and (2) a pilot 3-group, 8-week-long randomized controlled trial (RCT) to examine the feasibility, acceptability, and preliminary efficacy of MOTIVACC. The CONSORT (Consolidated Standards of Reporting Trials) and SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklists were used.

Conceptual Framework

Our study (particularly qualitative data analysis, MI interventions, and RCT measures) is guided by social cognitive theory (SCT), which posits that an individual's cognition and health behavior change in a social context with dynamic and reciprocal interactions with other people and the environment [18]. Key constructs of SCT include expectations (eg, vaccination benefits or consequences of not being vaccinated),

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observational learning (eg, seeing the vaccine's effectiveness), self-efficacy (eg, vaccine confidence), reciprocal determinism (eg, the dynamic and reciprocal interactions of the person with other people and the environment, that leads to vaccine acceptance, including eliminating stigma), reinforcements (ie, internal or external processes to vaccine acceptance or uptake), and behavioral capability (ie, the ability to obtain the vaccine through sufficient knowledge and skills) [19]. Interactions within the MI intervention will help to address reciprocal determinism and reinforcements, as it will entail direct interactions with personnel to address ambivalence toward vaccination, identify discrepancies between vaccination decisions and individual values, and provide information to participants in an empathetic and value-driven manner [11,19].

Phase 1: Intervention Development

Panel Development

We convene the rural CAP using the "broad community" model to capture participants' opinions about vaccination [20]. We work directly with Cooperative Extension Educators at Oklahoma State University (OSU) to identify and partner with (1) key stakeholders (eg, community leaders) and (2) members of the community for panel development. Cooperative Extension is a key branch of the land-grant system and includes community outreach and health-related engagement with populations across the state, including rural adults [21]. We use purposive sampling to identify, with educators' input, and recruit key partners within rural counties with the lowest vaccination rates at the time of recruitment. We recruit a minimum of two individuals in the bottom 10% of vaccinated counties across Oklahoma to participate in the CAP. Our target total sample size for phase 1 is 15-20 CAP participants in order to achieve this benchmark, which is consistent with existing recommendations in qualitative research [22].

Eligibility Criteria

Inclusion criteria include being ≥18 years of age, residing in a target county and being identified as a key stakeholder, and willingness to provide informed consent and complete a semistructured interview. There are no exclusion criteria.

Interview Procedure

We conduct one-on-one semistructured interviews with each participant (see Multimedia Appendix 1). Interviews include open-ended questions to gauge barriers and facilitators to vaccination. To promote the diversity of opinions, research personnel are trained in using open-ended questions that are developed with empathy-driven, user-centered principles [23] and in using MI-consistent prompts (eg, "Please tell us about the impressions of vaccines in your community" or "Please share your experience with vaccinations"). For individuals who express vaccine resistance, questions focus on their perspectives (eg, "Tell me what you don't like about vaccines") and hypotheticals (eg, "Imagine you were to get the vaccine, what would those circumstances look like?"). For those who have been vaccinated, questions similarly focus on community perceptions and participants' own experiences (eg, "Tell me about your decision to get the vaccine"). Lastly, questions also center on mHealth (eg, "Imagine you were to use an app to help you make health care decisions – what would that look like to you?"). All interviews are about 30-45 minutes via phone, video call, or in-person if preferred. Interviews are recorded and transcribed verbatim for analysis.

Qualitative Data Analysis

Interviews conducted with the CAP are transcribed verbatim and triple-coded by 3 separate members of the research team to inductively identify themes classified broadly as barriers to and facilitators of receiving the COVID-19 vaccine as well as the use of mHealth using content analysis. In addition, all transcripts are reviewed for identification of SCT constructs and opportunities for the use of MI relational skills, technical skills, and existing empirical evidence [24,25]. This approach uses a reflexive strategy to integrate three different researchers' perspectives into the data set (eg, experience in SCT versus MI) [26]. Coding matrices are used to match MI- and SCT-specific elements to barriers to and facilitators of vaccination to design potential mHealth-specific messages. Discrepancies in coding are discussed to achieve intercoder agreement, and inductive thematic saturation is achieved at the time of analysis by iteratively reviewing the emergence of new themes during triple coding [27]. If saturation is not achieved in that new themes emerge at the time of analysis that are not well integrated into the codebook, additional community members will be recruited to complete interviews (maximum total n=20) [28]. The final data set is entered into the NVivo software (Lumivero, LLC) package [29]. Codes are organized into barriers and facilitators; other categories can be created as they emerge during the coding process.

Phase 2: Pilot RCT

Participant Recruitment

We leverage multiple recruitment strategies in an intentional effort to reach historically underrepresented areas across Oklahoma. For phase 2, we partner with OSU Cooperative Extension and TrialFacts to target primarily rural counties to recruit a total of 60 participants. Around 60 participants are selected as consistent with recommendations for pilot studies, taking into consideration the focus on evaluating feasibility, as well as practical restraints [30]. TrialFacts is a participant recruitment service company that provides targeted recruitment of specific populations of interest.

Eligibility Criteria

Eligible adults are (1) aged ≥18 years, (2) living in a rural area (based on Rural-Urban Commuting Area codes; rural, codes 4-10) [31,32], (3) self-report of never having received any dose of a SARS-CoV-2 vaccine, (4) able to speak English, and (5) able to provide written informed consent. Exclusion criteria include (1) a cognitive or other disability that inhibits smartphone use, (2) inability to participate because of medical or psychiatric conditions diagnosed by a physician or clinician, or (3) enrollment in other COVID-19 research.

Procedure

RCT participants (N=60) are randomized to one of the 3 treatment groups using simple randomization in the REDCap (Research Electronic Data Capture; Vanderbilt University)

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program [33,34]. These groups include standard MI (SMI; n=20), intensive MI (IMI; n=20), or mHealth-based MOTIVACC (n=20). SMI consists of one MI session at least 20 minutes in length [35-38] delivered by a trained counselor at the baseline and provision of printed self-help materials. IMI consists of the SMI component plus 3 additional MI sessions delivered by a trained counselor via telephone or video calls at weeks 2, 4, and 6 post enrollment. MOTIVACC consists of an empathy-driven, fully automated, smartphone-based MI program that involves proactive, interactive, and individually tailored messages, plus some embedded images or videos, delivered by our Insight app [39]. MOTIVACC will begin immediately after enrollment and data collection and continue for an 8-week period (about 2-5 messages or questions per day, depending on participants' interaction and responses). The intervention content in all groups is adapted from the team's previous work and existing empirical evidence for in-person MI [25], is informed by Phase 1 outcomes, and is designed to tap SCT mechanisms. Insight for Android is used and any participants enrolled in MOTIVACC who do not have an Android phone will be loaned one for the duration of the study. All participants are followed up at week 8 post enrollment via individualized REDCap survey links sent via email [33,34].

Outcomes and Measures

Primary assessments (self-reported data) are conducted at baseline (after completing informed consent) and 8 weeks (after completion of the intervention if applicable). Additional data regarding the completion of the intervention contacts is recorded at the time of delivery in REDCap by study personnel (ie, for MI) or consistently and automatically in Insight (ie, for MOTIVACC). Table 1 displays the assessments and measures. The primary RCT outcomes are positive changes in the vaccine hesitancy scale [40,41] and intention to obtain the vaccine [42,43]. The secondary outcome is actual vaccination.

Table 1. Trial assessments at baseline and 8-week follow-up.

Variable type	Measure
Descriptors and potential moderators	• Demographics [44], health literacy [45] • COVID-19–related experience [46,47], health conditions, or diagnoses
Feasibility/ Adherence to MOTIVACC[a]	• Numbers of messages/images/videos opened and completed; weekly EMAs[b] opened and completed
Social Cognitive Theory– and motivational interviewing–related mechanisms	• Expectations (eg, vaccination benefits or consequences of not being vaccinated) [42,48] • Ambivalence regarding vaccination [49,50] • Behavioral capability (eg, perceived barriers) [48]
Qualitative, open-ended assessment	• An in-app participant-initiated assessment—"Share your thoughts with us"—with an open text field to capture the participant's thoughts and feelings
Primary outcomes	• Vaccine hesitancy and confidence [40,41] • Intention to receive the vaccines [42,43]
Secondary outcomes	• SARS-CoV-2 vaccine receipt

[a]MOTIVACC: mHealth-based motivational interviewing intervention to promote SARS-CoV-2 vaccination.

[b]EMAs: Ecological momentary assessment.

Compensation

All clinical trial participants receive one US $30 gift card as compensation for completion of baseline and 8-week follow-up data collection.

Statistical Analysis

This pilot study was designed to test feasibility, acceptability, and preliminary efficacy; thus, existing recommendations regarding sample sizes for pilot studies were used [30] versus a formal power calculation. Descriptive statistics will be used to assess the feasibility and acceptability of MOTIVACC, including the proportion of individuals who met inclusion criteria, the proportion of eligible participants who agreed to participate, the proportion of prescheduled events (intervention messages and interactive open-ended questions) delivered, viewed, or completed, and attrition rate at 8-week follow-up. The preliminary efficacy of IMI or MOTIVACC vs. SMI in changing participants' vaccine hesitancy and uptake intention will be evaluated using generalized linear mixed models, controlling for selected covariates such as sex and education level. Secondary outcomes will be examined using log-binomial regression with an intent-to-treat approach (ie, missing=no vaccine receipt) to compare the effect of IMI or MOTIVACC on the dichotomous 1st-dose vaccine receipt outcome at 8 weeks post enrollment. As aforementioned, given the preliminary nature of the RCT, we do not expect to have sufficient power for full hypothesis testing. For missing data, we will consider a multiple imputation approach based on participants' demographics at baseline to account for potential missing-at-random mechanisms. We also will explore pattern-mixture and selection models to account for potential (and likely) missing-not-at-random mechanisms [51].

Ethical Considerations

All study procedures were approved by the Oklahoma State University (IRB-22-282-STW) and University of Oklahoma Health Sciences' institutional review boards (14893). Electronic

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informed consent was obtained from all study participants. All CAP participants who completed an interview received one US $30 Amazon gift card distributed via phone or e-mail. All clinical trial participants receive one US $30 gift card as compensation for completion of baseline and 8-week follow-up data collection.

Results

This project is funded by the Oklahoma Shared Clinical & Translational Resources Pilot Grant Program, which is funded by the National Institute of General Medical Sciences, a part of the National Institutes of Health (U54GM104938). The study is approved by the institutional review boards of both University of Oklahoma Health Sciences and OSU. As of April 2024, data collection for phase 1 was complete with a total of 16 individuals recruited to participate in the CAP. Qualitative data analysis for phase 1 contributed to the MOTIVACC intervention development and testing (Figure 1). As of December 2024, the planned recruitment goal has been met (ie, n=60, 20/arm) and follow-up assessments are underway. The CONSORT flow diagram is shown in Figure 2, and the SPIRIT checklist is uploaded in Multimedia Appendix 2.

Figure 1. Screenshot of the Insight app.

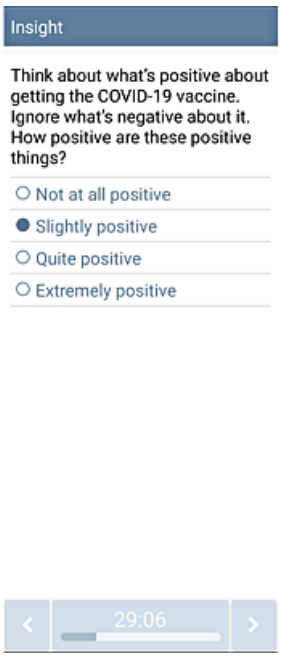

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Figure 2. CONSORT (Consolidated Standards of Reporting Trials) flow diagram. MI: motivational interviewing; MOTIVACC: mHealth-based motivational interviewing intervention to promote SARS-CoV-2 vaccination.

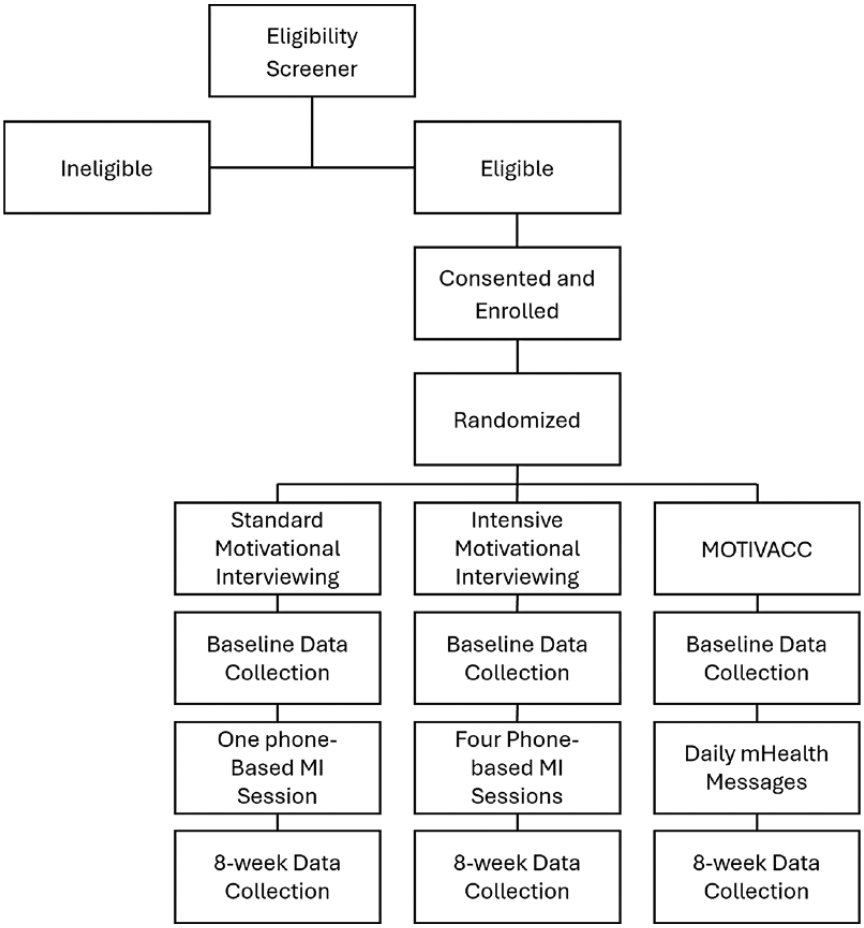

Discussion

Anticipated Findings

The results of this study will provide critical data regarding the utility of MI and MI-based mHealth interventions in targeting vaccine-related hesitancy and intention. Despite documented effectiveness, the public health impact of vaccinations is severely limited by misperceptions, hesitancy, and poor acceptance [52]. Messaging from health care providers has not yet been optimized to overcome these barriers [53-55] and has not been tailored to groups that face health disparities, such as rural Americans. Understanding the utility of different communication strategies, including those rooted in empathy, is important to navigate conversations surrounding SARS-CoV-2 vaccines, and others, as alternatives to education or advice. Motivational interviewing is a logical candidate given it is thoroughly operationalized and clearly defined, though questions regarding dose, intensity, and scalability remain. It is essential to investigate the efficacy of MI in promoting vaccine uptake in rural populations to reduce health disparities. Our study will address this need and will contribute to filling the gap in evidence regarding the dose and intensity at which MI can be (cost-) effective. While an app-based mHealth intervention does not allow for two-way or interpersonal communication (a hallmark of MI), careful design of mHealth messages, as well as the ability to share input (eg, “Share your thoughts with us”) could prove sufficient. Conversely, the use of mHealth could help alleviate common concerns that exist in MI-based studies (eg, drift in provider skills), which can be addressed via ongoing evaluation, but this is not overly scalable.

This project will be one of the first to test the use of MI, including via mHealth, to address vaccine hesitancy in adults residing in primarily rural areas. MI has long been acknowledged as a key candidate in helping to navigate difficult conversations, including conversations around general vaccine hesitancy. Although MI’s efficacy has been demonstrated in parents to vaccinate their children, its efficacy among adults, particularly rural ones, to receive vaccines for themselves is unknown. Given the convoluted nature of vaccine hesitancy secondary to the COVID-19 pandemic, autonomy-supportive and empathetic intervention strategies are essential, thus it is critical to evaluate the use of MI in this context.

Conclusion

Results from this pilot project will be critical for future robust fully-powered clinical trials to examine the efficacy of different MI approaches in promoting vaccination. If MOTIVACC is found to be acceptable and effective, it could be an affordable and scalable stand-alone MI intervention that can be easily and widely implemented with minimal human involvement to reduce the disease in rural populations. The long-term goal of our research is to establish a scalable, automatic, interactive, mHealth-based MI intervention that can be tailored to individuals or groups to decrease vaccine hesitancy for any type

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of vaccine (not just SARS-CoV-2 vaccine) and increase vaccination rates. Therefore, if successful, MOTIVACC may be adapted to be used in reducing vaccine hesitancy and promoting the uptake of other vaccines. Therefore, this study, together with our subsequent course of research, will help to reduce vaccine-preventable morbidity and mortality in rural populations.

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Data Availability

Data are deposited in publicly available repositories (where available and appropriate).

Authors' Contributions

AB handled conceptualization, fund acquisition, investigation, methodology, project administration, supervision, writing—original draft. SC contributed to investigation, data curation, formal analysis, writing–review and editing. KD performed data curation, investigation, writing—review and editing. CJ handled investigation, data curation, formal analysis, writing–review and editing. CM contributed to investigation, project administration, writing—review and editing. MB performed conceptualization, fund acquisition, investigation, writing–review and editing. TB handled conceptualization, fund acquisition, investigation, methodology, project administration, supervision, writing–review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guide.
[DOCX File , 41 KB - resprot_v14i1e64010_app1.docx]

Multimedia Appendix 2
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 109 KB - resprot_v14i1e64010_app2.pdf]

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Abbreviations

CAP: community advisory panel
CONSORT: Consolidated Standards of Reporting Trials
IMI: intensive motivational interviewing
mHealth: mobile health
MI: motivational interviewing
MOTIVACC: mHealth-based motivational interviewing intervention to promote SARS-CoV-2 vaccination
OSU: Oklahoma State University
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SCT: Social Cognitive Theory
SMI: standard motivational interviewing
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
WHO: World Health Organization

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Protocol

Improving Diet Quality of People Living With Obesity by Building Effective Dietetic Service Delivery Using Technology in a Primary Health Care Setting: Protocol for a Randomized Controlled Trial

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Abstract

Background: Almost a third of Australian adults are living with obesity, yet most cannot access medical nutrition therapy from dietitians, that is, the health professionals trained in dietary weight management services. Across the health system, primary care doctors readily identify people who may benefit from weight management services, but there are limited referral options in the community. Dietitians are trained to provide evidence-informed dietary treatment of overweight and obesity but are underutilized and underresourced. The chat2 (Connecting Health and Technology 2) trial will test combining new technologies for dietary assessment with behavior change techniques to improve outcomes for people living with obesity.

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Objective: This study aimed to compare the effectiveness of a 1-year digital dietary intervention, with standard care on body weight reduction and improved diet quality, in adults living with obesity delivered by dietitians in a primary care setting.

Methods: This randomized controlled trial will compare a 1-year, digitally tailored, feedback dietary intervention with a control group in 430 adults living with obesity (BMI≥30 to ≤45 kg/m^2). Participants will be recruited by letters sent to individuals randomly selected from the electoral roll and supplemented by hospital site posters, newsletters, and unaddressed mailbox delivery postcards sent to residential street points. The primary outcome is change in body weight, measured face-to-face at a baseline, 6 months, and 12 months. A 4-day, image-based dietary assessment tool (mobile Food Record) will be used to measure diet quality score. Secondary outcomes include diet quality score; dual-energy absorptiometry body composition; and total cholesterol, triglyceride, low-density lipoprotein, high-density lipoprotein, glycated hemoglobin, and fasting glucose levels. The intervention group will receive 8 video counseling sessions with a trained dietitian delivered over 12 months to support dietary behavior change and relapse prevention. The trial is unblinded. Both groups will receive feedback on their clinical chemistry and dual-energy absorptiometry scans at each time point.

Results: Participant recruitment commenced in July 2023 and ended in August 2024. Data analysis will commence in 2025, with the anticipated publication of results in 2026.

Conclusions: If found to be effective, the results of this randomized controlled trial will support the delivery of effective, evidence-based weight management advice using new technologies. Improving community access to high-quality dietetic services will ensure more effective use of the dietetic workforce to improve outcomes for people living with obesity.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12622000803796; https://anzctr.org.au/Trial/Registration/TrialReview.aspx?id=383838

International Registered Report Identifier (IRRID): DERR1-10.2196/64735

(JMIR Res Protoc 2025;14:e64735) doi:10.2196/64735

KEYWORDS

obesity; diet; diet quality; digital behavioral interventions; health behavior change; mHealth; mobile health; eHealth; mobile food record; telemedicine; weight management; obese; RCT; randomized controlled trial; Australia; adult; nutrition; dietitians; access; dietary management; intervention; digital health

Introduction

The high and increasing prevalence of obesity across the world is a major challenge for health care delivery and confers a substantial burden on individuals and the health care sector. The effects of obesity are widely recognized as one of the leading health concerns, affecting all age and socioeconomic groups [1]. For example, in Australia, overweight and obesity and dietary risks collectively account for nearly half of the 38% of the preventable burden of disease, with overweight and obesity being the leading contributor to nonfatal burden [2]. In tandem, direct health care costs associated with obesity-related conditions, such as cardiovascular disease, respiratory disease, type 2 diabetes, and some cancers, are rising with an unequal distribution corresponding to the level of socioeconomic disadvantage [3,4]. Almost a third (31%) of Australian adults are living with obesity, yet most are unable to access weight management services. An urgent priority for health service delivery is to identify the most cost-effective approach to delivering evidence-based weight management.

Primary care is a critical component of addressing obesity and requires a person-centered approach to treatment [5]. This includes changing the weight-stigmatizing narrative among health professionals working with people living with obesity [6]. Treatment guidelines for obesity are evaluated by the person's BMI and the severity of obesity-related complications [5]. Intensive interventions involving very low-energy diets, pharmacology, or bariatric surgery are indicated with BMI≥40 kg/m^2 and obesity-related complications [5]. Whereas, for people with BMIs between 30 and 40 kg/m^2 without complications, supervised lifestyle interventions to achieve 10% initial weight loss are recommended [5]. However, unfortunately in Australia, there are limited referral options for weight management in the community. Publicly supported bariatric surgery waiting lists are long and triaged to those with a BMI≥40 kg/m^2 with obesity-related complications, and while recently pharmacological treatments have been increasingly used in the treatment of obesity [7], issues with availability and cost limit the access to these pharmacological treatments. In addition, not everyone has access to or wishes to choose the pharmacological pathway. Therefore, continued research on behavioral lifestyle interventions is needed as they remain the first-line treatment for people living with obesity [7].

Lifestyle modification is a fundamental component of weight management. The most effective interventions to date have used behavioral strategies to support people to achieve energy reduction [8]. Guidelines for comprehensive weight management interventions identify the importance of personal counseling to achieve a clinically significant 5% weight loss to confer health benefits, including lowering blood pressure or delaying progression to type 2 diabetes [9]. In a review of primary care interventions for obesity, intensive counseling (≥12 sessions per year), delivered face-to-face, by phone, or electronically, produced weight loss of 4-7 kg, compared with low-dose counseling (≤12 sessions per year) without behavioral strategies, which only resulted in only modest losses of 1-2 kg [8], supporting the value of higher intensity behavioral interventions.

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Behavioral interventions for weight management are complex and may include a range of components and modes of delivery. Factors associated with greater effectiveness include changes in diet, provision of meal replacements, and whether the program was delivered by a dietitian or psychologist [10]. A systematic review of weight management interventions demonstrated that those provided by a dietitian resulted in improvements in BMI and other cardiometabolic outcomes compared with control conditions [11]. Behavioral strategies of these weight management interventions, however, were not explored. Teasing out the behavioral components of interventions is important to discover the most effective behavior change techniques. In a review of behavioral interventions in type 2 diabetes, frequent feedback and support were associated with weight reduction [12].

To date, few studies have examined the combined effectiveness of behavior change techniques with new cutting-edge digital technologies and medical nutrition therapy. Digital technologies are effective in supporting weight loss, particularly when combined with personalized feedback [13]. One of the challenges for dietitians in working with individuals living with obesity is the ability to easily and accurately assess diet and dietary behaviors—an important component of personalized advice. Another consideration is people's willingness to record their dietary intake. An image-based dietary record app with time and date stamp data, termed the mobile food record (mFR), has been shown to be feasible for dietary assessment and feedback, a key component for changing dietary behaviors [14,15]. The content of the images is confirmed either by the participant or by novel automated methods using computer vision and machine learning techniques under development [16,17]. An additional technological intervention feature is the use of videoconferencing. Improving access to weight management advice, through videoconferencing, may assist people in managing their weight, but is yet to be fully evaluated. This study will provide the first test of these digital technologies in people living with obesity in Australia. The study is designed based on key components of effective weight management interventions that include behavioral strategies guided by the (1) capability, opportunity, motivation, and behavior (COM-B) model [18]; (2) the behavior change techniques; and (3) self-monitoring, goal setting, and individually tailored feedback on dietary behaviors [15,19-21]. The objective is to compare the effectiveness of a 1-year digital dietary intervention on body weight reduction and improved diet quality, in adults living with obesity delivered by dietitians in a primary care setting, with a control group.

Methods

Study Design

The chat2 (Connecting Health and Technology 2) study is a 1-year randomized controlled trial (RCT). Consenting participants will be randomly assigned (1:1) to an intervention or minimal intervention control group. Figure 1 shows the CONSORT (Consolidated Standards of Reporting Trials) study design. Assessments will occur at 0, 6, and 12 months with the primary outcome assessed at 12 months.

Figure 1. Study design with randomization to two groups: intervention and control groups.

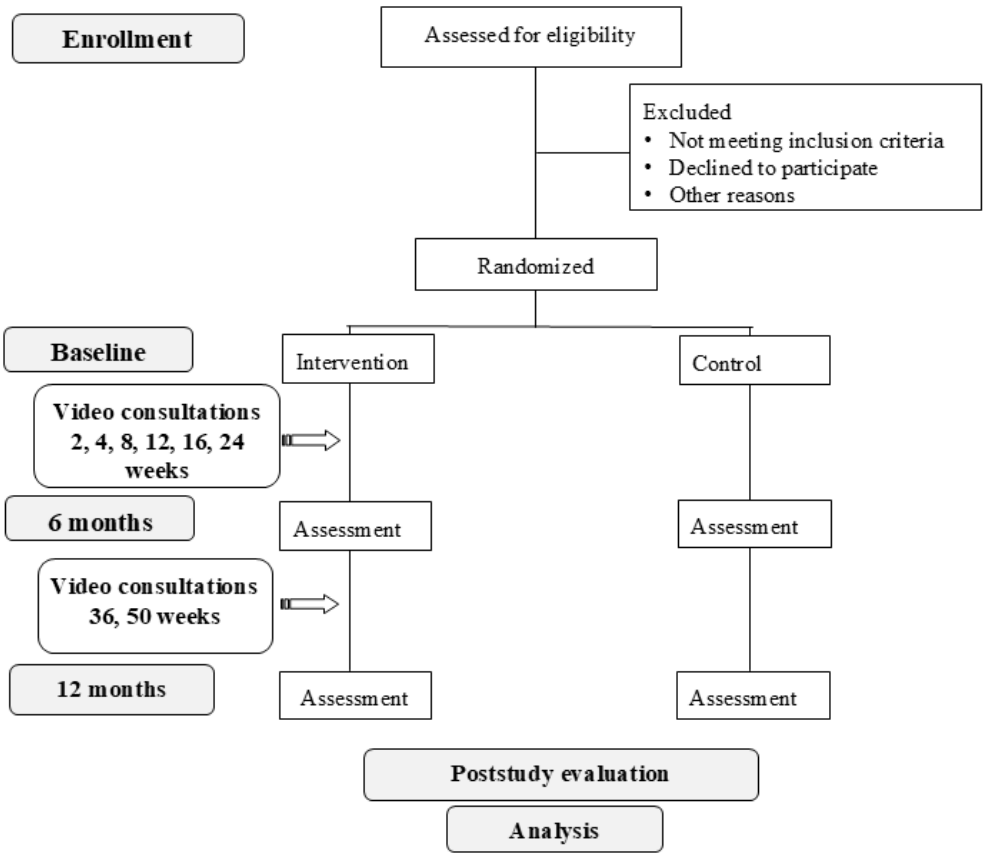

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Consumer Engagement

Engaging with health consumers alongside doctors and health professionals in weight management is a novel and strategic approach to this complex health issue. Using a systems approach provides opportunities for people with lived experience, health professionals, and policy makers to work together to take positive action to address the complex issue of weight management. A systems science group model–building approach was used to develop the East Metropolitan Health Service (EMHS) Obesity Prevention Strategy, to cocreate a shared understanding of the complex issue of obesity, its causes and consequences, and feasible solutions [22]. Health service executives; clinicians; allied health professionals; and representatives from community service providers, government, and nongovernment agencies identified the gap in services for people living with obesity and prioritized action to address this.

This intervention design was developed in partnership with EMHS and informed by the Western Australian Healthy Weight Action Plan, led by the Western Australian Health Department's partnership with the Western Australian Primary Health Alliance and the Western Australian Health Consumers' Council [23]. This partnership ensured that peoples' lived experiences were central to the research. Since 2018, the Western Australian Health Consumers' Council has conducted several engagement activities to ensure the voices of people with lived experience of overweight and obesity were key drivers of change. A review of weight-management services by this group identified gaps in service delivery, including the lack of supported behavior change programs for weight management, the absence of clear referral pathways, and limited access to a skilled workforce in weight-management care. This study will recruit a panel of health consumers who have lived experiences of overweight and obesity as members of the project advisory board to ensure that their perspectives and voices are considered at all stages of the project. Their role will include reviewing all study materials, including ethics documents, study website design, and recruitment strategies and materials. In addition, the project team and consumers will work to ensure that the trial is respectful, recognizing that participants are likely to have experienced the negative consequences of weight stigma on their health [6].

Setting

The study setting will target recruitment in the EMHS catchment, 1 of 4 publicly funded health service areas in Perth, Western Australia. EMHS is responsible for the maintenance and improvement of the well-being and health of 725,000 people residing within its catchment, approximately one-third of the population of Western Australia. This is achieved through the provision of an extensive health network including tertiary, secondary, specialist, community, and population health services. The EMHS catchment has the highest prevalence of overweight and obesity in the Perth metropolitan area, where 77% of adults live with overweight or obesity (43% live with obesity) [24,25].

Recruitment

Overview

Participants will be recruited by letters sent to individuals randomly selected from the electoral roll in Perth to provide representation across all socioeconomic status groups. Electoral roll recruitment is a feasible and effective recruitment method previously used by the research team [15]. The mailout will be staggered so that recruitment occurs over 12 to 18 months with a target of 25 participants per month. This will ensure adequate resourcing and staffing for the study. Other recruitment methods will supplement the mail out and will include EMHS hospital sites displaying posters and recruitment postcards; newsletters sent to primary care doctors and practice managers; EMHS and university newsletters; and unaddressed mailbox delivery to residential street points in suburbs located in the EMHS catchment area. Quota sampling will ensure equal numbers between study groups and genders. After receiving the letter of invitation, those who wish to take part in the study will contact the research team by email, mobile telephone (text or voice), or the study website, where they will be directed to read the information statement and consent online, and complete an online screening questionnaire. Computer literacy was not an explicit criterion to be eligible for the study.

To be eligible, participants must be aged 18-65 years, have a self-reported BMI≥30 to ≤45 kg/m^2, own a mobile telephone with internet access, and be able to attend the study center in metropolitan Perth for all 4 visits. Participants will be excluded on the basis of serious illness or medical conditions including diabetes requiring insulin; medical dietary restrictions (eg, low potassium diet for renal failure); receiving counseling from a dietitian; had or planned to have a surgical intervention for weight management in the next year; severe heart conditions (eg, cardiac failure requiring fluid restriction and a stroke or myocardial infarction in the previous 6 months); severe life-limiting illness receiving palliative treatment (eg, cancer, cirrhosis, and pulmonary disease or heart failure); currently taking or plan to take weight loss medication in the next 12 months; pregnancy or breastfeeding, or planning to become pregnant or breastfeed in the next year; receiving treatment for an eating disorder; or unable to participate in telehealth dietary consultations.

Randomization

Block randomization will be used with allocation concealment from the active research team via the use of sealed opaque envelopes. The randomization will be in blocks of 4, with stratification by gender (men, women, and other), where participants will be assigned to either the intervention or minimal intervention control groups (1:1). Sequence generation will be conducted before the commencement of the study by a statistician using a randomization table created in Stata (version 18, StataCorp). The electronic file will be kept in a secure password-protected server by the statistician. Randomization will occur at the second study visit to assign participants to either the intervention or control groups. On opening the randomization envelope, the participant will inform the research staff which group they are allocated to. The trial is unblinded due to the nature of the intervention; it is not possible to blind

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participants or researchers to the intervention group after allocation.

Data Collection Procedures

Eligible participants will be notified via email and invited to attend 2 baseline in-person visits 1 week apart at the Curtin University study center. Before the first visit, participants will be asked to complete an online questionnaire (including ethnicity, education, employment, postcode, alcohol use, smoking, physical activity, eating and dietary habits, motivation, and weight loss history), as detailed in Table 1. At the baseline visit, participants will be asked to fast overnight before a blood test, whole-body composition dual-energy absorptiometry (DXA) scan, and height and weight measurement. They will receive training on how to record their dietary intake by taking images using the mFR app, a mobile app developed by Purdue University. The mFR app will be installed on participants' mobile devices (Android [Google] or iPhone [Apple Inc]) at no cost. They will be asked to return approximately 1 week later, where they will receive a copy of their DXA scan and blood tests. They will be interviewed by the research dietitian to clarify the content of their mFR images and probe for missing data. Participants will undergo random allocation to the intervention or control groups. The assessments will be repeated for both groups at 6 and 12 months (Table 1). Participants will be asked to keep an adverse events diary (eg, hospital admissions, illness, or changes to medications) for the duration of the study that will be reviewed at the 6- and 12-month study assessment visits. Participants will be encouraged to discuss their involvement with their primary care doctor, who will be notified by the research team that their patient has volunteered and has been provided with blood test results, information about the trial, and contact details of the research team via a secure facsimile. Before each appointment, participants will be sent an email with details of their visit, along with a text message reminder the day before. Both intervention and control group participants will be provided with a study booklet with information on healthy eating from the Australian Dietary Guidelines (ADG) website [26]. This will include healthy eating information on food groups, serving sizes, links to recipes, and label reading.

Table 1. Frequency of assessment variables for the chat2 (Connecting Health and Technology 2) study intervention and control groups.

Variables	Group	Baseline	6 months	12 months
Height and weight (measured at clinic visit)	I[a] and C[b]	Yes	Yes	Yes
Body composition: whole body dual-X-ray-absorptiometry scan of regional or total body fat (including visceral body fat)	I and C	Yes	Yes	Yes
Adverse events diary	I and C	Yes	Yes	Yes
Dietary intake: 4-day mFR[c]	I and C	Yes	Yes	Yes
mFR usability to assess user feedback and method preference [14,27]	I and C	Yes	Yes	Yes
Blood sample: total cholesterol, triglyceride, LDL[d] and HDL[e] cholesterol, fasting glucose, and glycated hemoglobin	I and C	Yes	Yes	Yes
Health status EQ-5D, a 5-item scale to assess utility and health-related quality of life [28]	I and C	Yes	Yes	Yes
Sociodemographic and personal characteristics assessed via questions on sex, age, eating behavior, educational level, country of birth, ethnicity, socioeconomic status, and financial status	I and C	Yes	Yes	Yes
18-item Food Insecurity [29]	I and C	Yes	No[f]	No[f]
Self-report Habit Index Score [30]	I and C	Yes	Yes	Yes
Creature of Habit questionnaire [31]	I and C	Yes	Yes	Yes
Self-reported physical activity assessed via the International Physical Activity Questionnaire (short form) [32]	I and C	Yes	Yes	Yes
Depression, Anxiety, Stress Scale, with 21 self-report items to assess severity of depression, anxiety, and stress [33]	I and C	Yes	Yes	Yes
Weight-Loss History, an 8-item tool to assess previous weight-loss history [34]	I and C	Yes	No[f]	No[f]
The Health Care Climate Questionnaire [35]	I	No[f]	No[f]	Yes
Personalized Nutrition Questionnaire [21]	I	Yes	Yes	Yes

[a]I: intervention.

[b]C: control.

[c]mFR: mobile Food Record.

[d]LDL: low-density lipoprotein.

[e]HDL: high-density lipoprotein.

[f]Data not collected.

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Dietary Assessment and Analysis

Participants will be provided with access to the mFR app on their mobile device to record their dietary intake at baseline, 6 months, and 12 months (Figure 2) [16,36]. They will be asked to take "before eating" and "after eating" images of all foods and beverages consumed over 4 consecutive days, including 1 weekend day. The mFR app communicates with a dedicated cloud-based server for the storage and processing of images via Wi-Fi or 4G and 5G networks. A fiducial marker is included in the image to allow improved accuracy for quantifying dietary intake [37-39]. The mFR app will be updated regularly in response to operating systems updates (Android and iPhone). Participants will label the content of their images, referred to as mini labels. When the participant starts typing the word, a list of foods will appear where they can select from a list of approximately 800 food and beverage items. These labels link to a food composition database (not visible to the participant) with the food code, detailed description, and energy and nutrient composition [40]. These mini labels will be linked to a code for estimating food group servings to enable a food-based assessment. At the study visit, the research dietitian will review the images with participants through the web and probe for food and beverage items not recorded (Figure 2). The data from the mFR will be entered into a purpose-built Microsoft Access database platform to assess the food group servings.

Figure 2. Review process for viewing a labeled eating occasion, with colored labels identifying the foods and the time and date stamp displayed.

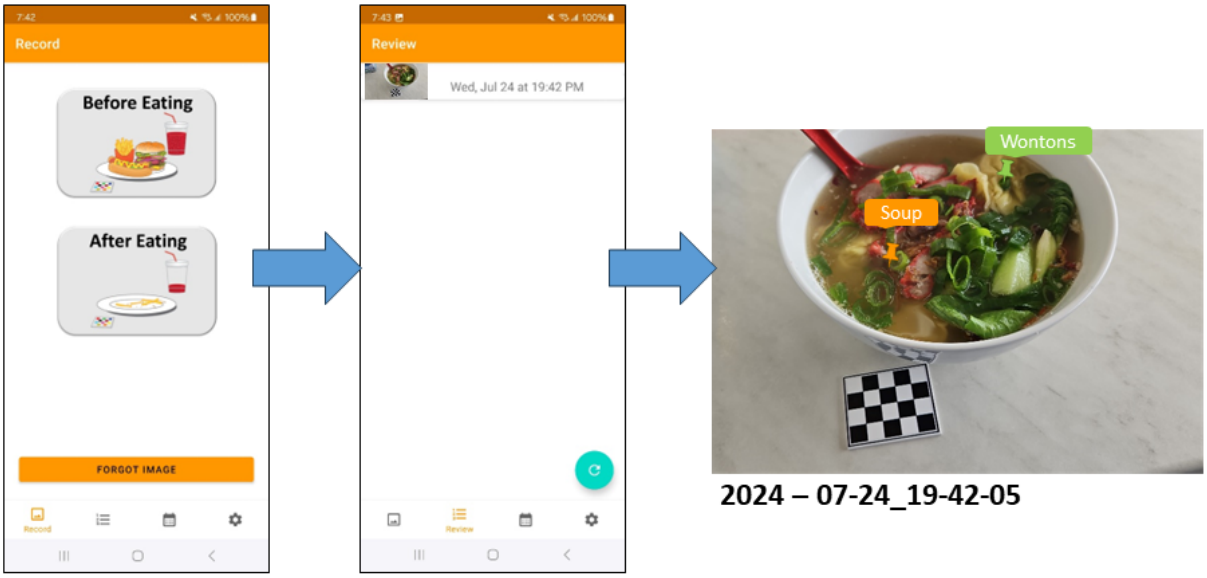

Diet Quality Scoring

Analysis of the 4-day mFR will be undertaken by the research dietitian, and a food-based diet quality score (DQS) will be calculated (Table 2). In addition to energy reduction, this study will assess diet quality, as there is emerging evidence that diet quality, particularly reduced ultraprocessed foods, have a role in energy balance [41,42]. The 11-component DQS is based on the ADG [26] and adapted from 2 food-based indexes developed for Australian adults [43,44]. The DQS uses a continuous weighting system based on increments of food group servings, or proportions of total intake for behaviors without set recommendations, such as variety of fruits and vegetables. For core food groups, such as fruits and vegetables, the maximum weighting assigned to the item is determined by the ADG-recommended daily servings. To achieve weight reduction consistent with study goals, discretionary foods and beverages will be split into separate components. Reverse scoring is assigned for discretionary (energy-dense and nutrient-poor) foods, sugar-sweetened beverages, and alcoholic beverages, where a maximum score of 10 points is achieved with zero servings. The DQS at baseline and 6 months will be provided to the study dietitians to be relayed to intervention group participants in the video consultations.

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Table 2. Diet quality scoring calculated from average daily servings based on the Dietary Guidelines for Australia. Total maximum score of 100 points from 11 components.

Item Description	Minimum score	Composite scores	Maximum score
Fruit	0 to <0.5 servings (0 points)	• ≥0.5 to <1.0 serving (2.5 points) • ≥1.0 to <1.5 servings (5 points) • ≥1.5 to <2.0 servings (7.5 points)	• ≥2 servings (10 points)
Vegetables and legumes or beans	0 to <1.0 serving (0 points)	• ≥1.0 to <2.0 (2 point) • ≥2.0 to <3.0 servings (4 points) • ≥3.0 to <4.0 servings (6 points) • ≥4.0 to <5.0 servings (8 points)	• ≥5 servings (10 points)
Variety of fruits	0 type (0 points)	• 1 type (1 point) • 2 types (2 points) • 3 types (3 points) • 4 types (4 points)	• 5 or more types (5 points)
Variety of vegetables	0 type (0 points)	• 1 type (1 point) • 2 types (2 points) • 3 types (3 points) • 4 types (4 points)	• 5 or more types (5 points)
Lean meat, poultry, fish, eggs, nuts, seeds, legumes, or beans (women)	>2.5 servings or <0.5 servings (0 points)	• ≥0.5 to <1.0 (2 points) • ≥1.0 to <1.5 (4 points) • ≥1.5 to <2.0 (6 points) • ≥2.0 to <2.5 (8 point)	• 2.5 servings (10 points)
Lean meat, poultry, fish, eggs, nuts, seeds, legumes, or beans (men)	>3 servings or <1.0 serving (0 points)	• ≥1.0 to <1.5 servings (2 points) ≥1.5 to <2.0 servings (4 points) • ≥2.0 to <2.5 servings (6 points) • ≥2.5 to <3.0 servings (8 point)	• 3 servings (10 points)
Milk, yoghurt, cheese, and alternatives	<0.5 servings (0 points)	• ≥0.5 <1.0 servings (2 points) • ≥1 to <1.5 servings (4 points) • ≥1.5 to <2.0 servings (6 points) • ≥2 to <2.5 servings (8 points)	• ≥ 2.5 servings (10 points)
Grain (cereal) foods, mostly wholegrain, and high cereal fiber varieties	<1.0 serving or >6.0 servings (0 points)	• ≥1.0 to <2.0 servings (1 point) • ≥2.0 to <3 servings (2 points) • ≥3.0 to <4 servings (5 points) • ≥4.0 to <5 servings (6 points) • ≥5.0 to <6 servings (8 points)	• 6.0 servings (10 points)
Discretionary foods	≥2.75 servings (0 points)	• ≥1.75 to <2.75 servings (2 points) • ≥0.75 to <1.75 servings (4 points) • >0 to <0.75 servings (8 points)	• 0 servings (10 points)
Sugar-sweetened beverages	≥2 servings (0 points)	• ≥1.25 to <2 servings (2 points) • ≥0.5 to <1.25 servings (4 points) • >0 to <0.50 servings (8 points)	• 0 servings (10 points)
Alcoholic beverages	≥2 servings (0 points)	• ≥1.25 to <2 servings (2 points) • ≥0.5 to <1.25 servings (4 points) • >0 to <0.50 servings (8 points)	• 0 servings (10 points)
Plain water	<1 cup (0 points)	• ≥1 to 3 cups (2 points) • ≥3 to 5 cups (6 points) • ≥5 to <8 cups (8 points)	• ≥8 cups (10 points; women) • ≥10 cups (10 points; men)

Intervention Features

The intervention features, content, and behavior change techniques to be implemented are shown in Table 3. The selection of intervention features and strategies is guided by the COM-B model [18]. The COM-B model identifies behavioral targets when developing interventions and focuses on 3 factors required to change behavior: capability, opportunity, and motivation. Performing a behavior requires individuals to be

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capable or have physical and psychological abilities (eg, nutrition knowledge and cooking skills). Opportunity includes both practical and social aspects (eg, access to healthy foods, supportive environments, and social norms). Motivation comprises automatic drivers like habits as well as beliefs, emotions, impulses, and reflective processes such as intentions and planning. Behavior change techniques will include feedback, self-monitoring, feedback on performance, goals or planning, repetition, and substitution or habit formation [20].

Table 3. Overview of the study goals and intervention features, content, and behavior change techniques.

Goal	How to achieve	Behavior change techniques [20]
1. Achieve a reduction in body weight by at least 5% in 12 months	• Avoid or limit discretionary foods, sugary drinks, and alcohol • Eating less at meals and snacks (except for vegetables and salad) • Eating less often (avoid snacking—except for vegetables and salads)	• Feedback—DQS[a] from mFR[b]
2. Improve DQS	• Eat from each of these five food groups with more variety (especially vegetables and fruit) every day • Vegetables and legumes/beans, including different types and colors • Fruit—choose fresh fruit as much as possible • Grains (cereal) foods, mostly wholegrain and high cereal fiber varieties • Lean meats and poultry, fish, eggs, tofu, nuts, and seeds, and legumes/beans (eg, kidney beans, chickpeas, lentils, and other beans) • Milk, cheese, yoghurt, and alternatives, mostly reduced fat • Drink more plain water (no added flavors); 2.1-2.6 L/day (8-10 cups)	• Feedback and self-monitoring—DQS from mFR
3. Behavior change	• Find your motivation • Plan to make changes • Set SMART[c] goals • Build healthy habits	• Questionnaire for current barriers and enablers to eating behavior change and some goals (PNQ[d]) • Goals and planning—action planning, commitment, goal setting, problem solving • Goals and planning—action planning, commitment, goal setting problem solving, coping planning, implementation intentions • Repetition and substitution—habit formation

[a]DQS: diet quality score.

[b]mFR: mobile food record.

[c]SMART: Specific, Measurable, Achievable, Relevant, and Time-Bound.

[b]PNQ: Personalized Nutrition Questionnaire.

Intervention Group

Participants allocated to the intervention group will be offered 8 video consultations (approximately 20 to 45 minutes based on intervention stage) with a dietitian for the first 6 months (at 2, 4, 8, 12, 16, and 24 weeks) to provide support and guidance for unhelpful behaviors (eg, emotional eating) and additional maintenance calls (relapse prevention and coping planning) at 9 and 12 months (8 in total). This number of individual contacts was chosen as a balance between recommendations [9] and practical service delivery costs. Before selecting telehealth consultations, participants complete the Personalized Nutrition Questionnaire (PNQ) to identify and prioritize self-perceived factors impacting on their eating behaviors [21]. The PNQ is a tool designed to support the dietitian during consultations by collecting information on barriers before the session. Based on the COM-B framework [18], the PNQ has been used with a variety of groups to support dietitian-led telehealth consultations [45-47]. The medical nutrition therapy consultation will cover dietary feedback focusing on their DQS, goal setting, and behavioral strategies. Feedback will be formulated from the analysis of the mFR and will focus on key dietary messages (Table 3). The content will address each participant's personal barriers to changing dietary behaviors, reinforce capability, motivation, and guide adoption of health-enhancing habits.

Control Group

The control group will complete all measures and will be provided with a standard care study booklet using information from the ADG website [26]. At the end of the study, control group participants will receive personalized feedback on their outcomes, including their dietary feedback report.

Dietetics Training and Consultations

Research dietitians will undertake 8 hours of in-person training, before their consultations with participants. The training will

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include approximately 2 hours of self-paced, recorded, online training in the dietitian's own time and 6 hours of online or in-person workshops. The training will include current evidence-based practice for people living with obesity, addressing weight bias or stigma, study design, ethics, mFR technology or study systems, documentation, and fidelity of implementation adherence. Study dietitians will complete online training in motivational interviewing in health care [48]. The behavior change training conducted by the health psychology team will be guided by the COM-B model, and embedded with behavior change techniques [49]. A follow-up booster session will be conducted midway through the intervention. Standard guides will be developed for each of the 8 consultation sessions by the research team. Dietitians will use the consultation guide for each session, record attendance, and contact participants for missed sessions. The style of communication will be consistent with self-determination theory and motivational interviewing principles [15,50,51]. Fidelity of implementation adherence will be guided by a conceptual framework for implementation fidelity [52] (ie, adherence to the guide as prescribed and quality of delivery) and will be assessed for dietitians using measures of fidelity and engagement [53]. Practice management software for allied health professionals [54] will be used to manage appointments; send text appointment reminders; document attendance; record treatment notes; and access anthropometry, DQS, PNQ, and blood test results. Study dietitians will document each of the 8 sessions according to the nutrition care process: nutrition assessment, nutrition diagnosis, nutrition intervention, nutrition monitoring, and evaluation [55,56]. They will also document behavior change techniques implemented according to the COM-B model [20].

Process Evaluation

Overview

A process evaluation will be undertaken to evaluate the implementation and impact of the intervention (ie, fidelity, dose, and reach) using the UK Medical Research Council evaluation framework [57]. Adherence to the intervention will be assessed by attendance at sessions as documented in the practice management software and set at 75% attendance. Delivery of behavior change elements will be assessed by reviewing the dietitian's documentation of behavior change techniques. Additional components relevant for digital interventions will assess acceptability, engagement, effectiveness, and sustainability. A questionnaire will be used to evaluate participants' perception of the intervention (ie, dietetic video consults, feedback, usefulness of advice, suitability, and relevance to age group). Both intervention and control participants will evaluate their perceptions of intervention features (ie, receiving results of blood tests and whole-body DXA scans).

Poststudy Qualitative Interviews

At the completion of the study, approximately 20 semistructured interviews will be conducted with intervention and control participants using videoconferencing. The interviews aim to assess participant experiences, the intervention impact, and perceptions of various strategies and study materials. The interview topic guide will be developed using the COM-B model as a theoretical framework to explore participants' capability, opportunity, and motivation to change their eating behaviors [18]. The interviews will be audio recorded and transcribed verbatim. Data will be analyzed using framework analysis, a systematic approach that provides a structured method for managing and interpreting interview data [58,59]. While the COM-B model will be used to inform the development of the topic guide, the analysis will take an inductive approach to ensure that themes generated from participants' experiences are captured beyond the predefined theoretical framework. The procedure for analysis will involve (1) verbatim transcription, (2) familiarization with the data through reading of transcripts, (3) open coding data segments from transcripts, (4) developing an analytical framework based on generated codes, (5) coding all transcripts using the analytical framework, (6) charting the data into a framework matrix, and (7) interpreting the data through pattern mapping and theme generation. The analysis will be facilitated using NVivo (Lumivero) qualitative data analysis software. Several strategies will be implemented to ensure qualitative rigor. A reflexive journal will be maintained throughout data collection and analysis to document assumptions, potential biases, and evolving interpretations. Regular team debriefing sessions will offer opportunities to discuss and challenge interpretations. Participants will be offered the opportunity to review their interview transcripts and provide feedback on initial interpretations through member checking. Together, these strategies will support the credibility and confirmability of the findings [60]. Dependability will be enhanced through clear documentation of the analytical process in NVivo, with an audit trail capturing analytical decisions and interpretation development [60]. To support transferability, detailed descriptions of the context, participant characteristics, and the RCT will be provided. Findings will be reported using the Consolidated COREQ (Criteria for Reporting Qualitative Research) checklist to ensure comprehensive and transparent reporting of the research process [61].

Statistical Analysis

Overview

The primary outcome is a change in weight at 12 months for both groups. Secondary outcome variables are changes in DQS, body fat (DXA derived), total cholesterol, triglyceride, low-density lipoprotein and high-density lipoprotein cholesterol, fasting glucose, and glycated hemoglobin. It is hypothesized that at 12 months the intervention group will achieve at least a 5% reduction in body weight. Data on change in outcome variables in each of the 2 groups will be compared using general linear models after adjusting for covariates. Assumptions of the analyses will be assessed by examining residuals. Data will be transformed if the assumptions of the analyses are not satisfied. Possible covariates will include age, sex, country of birth, ethnicity, highest education level, socioeconomic index for area, and baseline value of the variable analyzed. P values <.05 will be considered statistically significant. Effect size of differences between groups will be expressed as adjusted mean difference and associated 95% CIs. Data on change in outcome variables postintervention and follow-up time points will also be converted into binary categorical variables and analyzed using multivariable logistic regression and generalized estimating

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equations. The odds ratio and associated 95% CIs will be reported.

Sample Size

A sample size of 342 participants (n=171 per group) will have 90% power to detect a difference in change between arms of at least 5% of body weight at 12 months between groups, using a conservative estimate of SD, at 90% power and 5% level of significance. Assuming 20% (n=86) of participants are not followed up, this would necessitate 430 (215 in each group) participants to be recruited. Difficulties in obtaining a sufficient number of participants in weight management trials are well documented [11]. Assuming an 8% change in weight and 20% dropout would require 170 participants. Estimates of means and SDs, including percentage dropout, were obtained from existing trial data for this study's power calculation.

Economic Evaluation

A stepped cost-effectiveness analysis of the 2 arms (intervention with control) will be conducted. The economic evaluation will consider the relative costs and outcomes of the intervention from the health and social care perspective. For the final step, to facilitate a cost-utility analysis, the EQ-5D will be administered to capture the quality of life [28]. The 5-level version more sensitively captures changes in health-related quality of life. Incremental quality-adjusted life years will be estimated for both groups. Incremental costs, collating the time needed to provide tailored advice, medication, and self-estimated weekly food expenditure will allow economic evaluation from the perspective of the health system and the broader society (by considering all costs). Univariate and multivariate sensitivity analyses will be undertaken. In particular, the impact of different methods of extrapolating costs and outcomes beyond the horizon of the trial will be assessed. The costing model will include resources required to assess ongoing maintenance of the mFR, including changes because of upgrades to operating systems. The major cost of the intervention is likely to be the provision of dietetic counseling (research personnel and research platform costs). This will be estimated by recording time spent deconstructing the mFR data and then interpreting data and constructing appropriate feedback.

Ethical Considerations

The project protocol has been approved by the Curtin University Human Research Ethics Committee (approval HRE2022-0059) and the Department of Health WA Human Research Ethics Committee (PRN RGS0000005490). The trial was registered with the Australian New Zealand Clinical Trials Registry (ACTRN12622000803796).

Informed consent to participate in the study will be received during the initial recruitment stage before any data collection. Volunteers who are interested in participating will follow a Qualtrics survey link to the participant information sheet that details their involvement in the trial. Participants will be provided with a copy of the participant information sheet at their first face-to-face visit. Following this information, participants will be asked to consent to participate in the study and informed that they have the right to withdraw from the study at any time without penalty. Participants will receive an Aus $20 (~US $12.70) grocery store voucher at each face-to-face visit.

Results

Participant recruitment commenced in July 2023 and ended in August 2024. Recruitment was staggered over 12 to 14 months. Data analysis will commence in 2025, with the anticipated publication of results in 2026.

Discussion

Principal Outcomes

This RCT will compare the effectiveness of a 1-year, digitally tailored, dietitian-delivered, feedback dietary intervention with standard care in adults living with obesity (BMI≥30 kg/m^2) in a primary care setting. Specifically, this project addresses a gap in dietetics service for the delivery of telehealth weight management care in the community. A key outcome of this research is to improve the primary care referral pathway for patients living with obesity by improving community access to high-quality dietetic services. This includes resourcing dietitians with a digital platform, incorporating an image-based dietary assessment and tailored feedback system. This research could enhance the capability and capacity of dietitians by improving the effectiveness of dietetics weight management services, resourcing dietitians with an innovative, time-saving digital platform that will provide a comprehensive state-of-the-art technology in dietary assessment and feedback. This study will provide the first test of the technology alongside dietetic counseling conducted by videoconferencing in people living with obesity in Australia.

Clinical practice guidelines for the management of obesity have focused on reducing energy intake [62]. While this approach is effective, the "thinking beyond calories" concept indicates that various dietary components and patterns may negatively affect energy balance leading to obesity [63] and recidivism post intervention. This novel concept is supported by a crossover trial where inpatients were fed ad libitum either an ultraprocessed or an unprocessed diet [41]. Energy intake was greater during the ultraprocessed diet, suggesting improving diet quality and reducing consumption of ultraprocessed foods may play an important role in energy balance. Dietitian-led interventions lead to statistically significant changes, but the effect sizes do not always show clinically significant improvements in health outcomes [11]. This may be due to the inconsistent use of behavior change techniques in dietitian-led interventions. Their focus on education alone may be insufficient to facilitate behavior change [64]. For dietary interventions, the inclusion of behavior change techniques is more effective for improving health outcomes [65]. However, many studies to date have not specified the behavioral theory used nor have they measured changes in psychological variables. This study will address this gap through the comprehensive assessment of both dietary and psychological parameters, to comprehensively test the effectiveness of behavior change strategies for weight management.

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Strengths and Limitations

A strength of the study is the intervention design comparing a dietitian-led intervention with minimal intervention control. The intervention is underpinned by the COM-B model, delivered by dietitians trained in behavior change techniques [49]. In addition, the study will use the electoral roll, a compulsory enrollment system for Australians aged more than 18 years, for the recruitment of participants to provide representation across socioeconomic groups. The results will be potentially useful in clinical decision-making to inform weight management advice. A limitation is the self-selecting sample, meaning that the findings may not be generalizable to the wider population or priority groups. Therefore, the findings of this study may not be generalizable outside the Australian context, and application of the findings across different cultures may be limited. Furthermore, there may be challenges in recruiting volunteers to meet recruitment targets and ensuring representation from a diverse background for socioeconomic status and ethnicity.

Conclusions

This research aims to improve outcomes for people living with obesity and addresses a gap in telehealth dietetics services for the delivery of weight management care. This RCT will compare a 12-month, digitally tailored, feedback dietary intervention with standard care in people living with obesity, where the feedback uses new cutting-edge technologies to automate an otherwise lengthy process. Consistent with a patient-centered model of care, the chat2 intervention incorporates video counseling by trained dietitians to support dietary behavior change and relapse prevention. This model of care will build capacity for dietitians to deliver effective evidence-based weight management advice using new technologies, potentially creating a paradigm change in the management of obesity, a common condition that is associated with a substantial disease burden.

Acknowledgments

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Data Availability

The datasets generated and analyzed during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

The study was conceived and designed by DAK, CMP, CEC, AB, SSD, CEP, FZ, RLP, PA, HM, JG-S, MER, and CM-S. The paper was drafted by DAK, CMP, BM, HB, and AH. The paper was revised for intellectual content by all authors who approved the final content of the paper.

Conflicts of Interest

DAK collaborates with FZ (principal investigator) on the mobile Food Record app.

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Abbreviations

ADG: Australian Dietary Guidelines
chat2: Connecting Health and Technology 2
COM-B: capability, opportunity, motivation, and behavior
CONSORT: Consolidated Standards of Reporting Trials
COREQ: Criteria for Reporting Qualitative Research
DQS: diet quality score
DXA: dual-energy absorptiometry
EMHS: East Metropolitan Health Service

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mFR: mobile Food Record
PNQ: Personalized Nutrition Questionnaire
RCT: randomized controlled trial

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Protocol

An In-Person and Online Intervention for Parkinson Disease (UPGRADE-PD): Protocol for a Patient-Centered and Culturally Tailored 3-Arm Crossover Trial

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Abstract

Background: Dance for Parkinson's Disease (DfPD) is a dance program for individuals with Parkinson disease (PD). There is a lack of knowledge about the effect of this program on frailty and sarcopenia experienced by patients with PD. In addition, no randomized controlled trial to date has investigated either the possible differential effects of in-person versus online DfPD or the possible effects of DfPD on clinical parameters in Greek patients with PD.

Objective: We aimed to assess the efficacy, safety, and feasibility of a culturally tailored and patient-centered DfPD program offered both in-person and online to Greek patients with early- to midstage PD.

Methods: This is a 3-arm crossover randomized controlled trial (in-person DfPD vs online DfPD vs control) of UPGRADE-PD (Upbeating Greek Application of Dance in Parkinson's Disease). The experimental period will be 10 months, including three 2-month interventional periods of two 60-minute dance classes per week for each group (in-person DfPD vs online DfPD) versus a control group (nonintervention group), and two 2-month washout periods between each group for 40 Greek patients with early- to midstage PD. Assessments will be performed face-to-face at baseline and at the end of each study period and will include quality of life, fatigue, depressive symptoms, stress, anxiety, sarcopenia, frailty, balance, cognitive functions, movement and nonmovement PD symptoms, and BMI. Safety, feasibility, and patient satisfaction for each dance intervention (in-person DfPD vs online DfPD) will be assessed as well.

Results: The study protocol was approved by the Medical Ethics Committee of the Eginition University Hospital in September 2022 and the Research and Ethics Committee of the University of West Attica in October 2023 and funded in September 2023. The first participant was enrolled in April 2023, and the trial is currently ongoing and will conclude in September 2024.

Conclusions: The results of this study are expected to show the possible differential effect of a patient-centered and culturally tailored in-person vs online DfPD intervention on several movement and nonmovement symptoms, as well as on quality of life, sarcopenia, and frailty in people living with PD in Greece.

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Trial Registration: ClinicalTrials.gov NCT06220084; https://clinicaltrials.gov/study/NCT06220084
International Registered Report Identifier (IRRID): DERR1-10.2196/65490

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KEYWORDS
Parkinson disease; dance; cultural tailoring; patient-centeredness; quality of life; frailty; sarcopenia

Introduction

Background

Parkinson disease (PD), an idiopathic, neurodegenerative, and progressive movement disorder, is accompanied by movement and nonmovement symptoms, such as bradykinesia, postural instability, and cognitive and mood disorders, which all negatively affect the quality of life (QoL) [1]. Furthermore, all the aforementioned PD symptoms seem to relate to the reduction of physical activity, muscle mass, and strength levels, as well as movement performance of patients with PD, thus increasing sarcopenia and frailty [2-4]. It is well accepted that systematic physical exercise enhances neuroplasticity [5]; prevents or delays frailty [4,6]; and improves symptoms such as balance, gait, and QoL in people with PD [7].

In dance, the human body and its purposefully selected movements are the basic tools for expression in various rhythmical and cultural contexts, whether artistic, educational, training, recreational, therapeutic, or religious [8,9]. As an art form expressed through movement, dance is a physical activity accompanied by musical stimuli that seems to activate the reward system [1] and has the potential to improve QoL of participants across various age groups [10], while the targeted use of auditory rhythmical information itself seems to be therapeutic for movement and nonmovement symptoms, as well as for QoL, in people with PD [11].

Humans, as social animals, have a fundamental need to belong [12], and dance-based interventions seem to reduce social isolation and loneliness among older people [13], while also facilitating their social inclusion [14], even during the social isolation caused by the COVID-19 pandemic [15]. Positive memories directly connected with dance experiences from a young age, as well as the supportive nature of dance, which enhances social interaction, and the emotional experiences that accompany the dance process, may be some of the reasons older adults prefer dance to other physical activities [16-18].

While physical exercise seems to induce neuroplasticity in people with PD [5], dance has been associated with favorable changes in the corticospinal tract, the corpus callosum, the superior longitudinal fasciculus, the dorsolateral prefrontal cortex, the bilateral putamen, the mirror neuron system, and sensorimotor pathways of healthy dancers [9,19]. Following the aforementioned effects of dance in neuroplasticity, dance in PD seems to enhance psychological flexibility (thus the person tends to adapt to environmental changes more efficiently) and creative self-efficacy (thus the person tends to think creatively and execute these thoughts) [20]. Dance, compared to other types of exercise, improves PD symptoms, such as balance, functional mobility, and cognition [21-24]. Moreover, dance is a substantial motivational means of exercise for patients with PD, enhancing their adherence rates to exercise programs [25,26], as well as a safe, feasible, and enjoyable intervention for patients with early- to midstage PD [27], even when the classes are remotely conducted [28].

Dance for Parkinson's Disease (DfPD) is a structured dance program under appropriate care and supervision especially designed for people with PD, which integrates different dance genres [29]. Various studies have already described the content of the DfPD class that was followed [30-32]. To our knowledge, there is no published study investigating the effect of DfPD on the frailty and sarcopenia experienced by patients with PD. In addition, no randomized controlled trial to date has been conducted to investigate either the effect of this program on any clinical parameter in Greek patients with PD or the possible differential effect of in-person versus online DfPD. Furthermore, there is no published protocol of any patient-centered or culturally tailored dance intervention for the PD population showing the exact methodology that was followed and the content of the dance intervention. This study aims to fill the above gaps by publishing all the aforementioned data of our research protocol.

Objective

The primary aim of this study is to investigate the possible effectiveness of a patient-centered and culturally tailored dance intervention delivered both in-person (in-person DfPD) and remotely (online DfPD) on QoL of Greek patients with early- to midstage PD. The key secondary aim is to investigate the safety and feasibility of the aforementioned interventions (ie, in-person DfPD and online DfPD) and its possible effectiveness on fatigue, depressive symptoms, stress, anxiety, sarcopenia, frailty, balance, cognitive functions, movement and nonmovement PD symptoms, and BMI of Greek patients with early- to midstage PD.

Methods

Study Design

This is a single-centered 3-arm crossover and open-label randomized controlled trial (in-person DfPD vs online DfPD vs control) of UPGRADE-PD (Upbeating Greek Application of Dance in Parkinson's Disease). Blinding among participants and researchers is not possible due to the nature of the study. There are 6 possible research sequences, as shown in Table 1, and 3 possible carryover effects (1, 2, and 3) for each period from the prior intervention, as shown in Table 2. The study will last 10 months for each participant, including three 2-month research periods and two 2-month washout periods. Assessments will be conducted at enrollment (T_{-0}=week −1), baseline periods

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(T_0=week 0, T_2=week 18, and T_4=week 36), and postinterventional periods (T_1=week 9, T_3=week 27, and T_5=week 45), as shown in Table 3. Allocation to each of the 6 possible sequences will occur after the completion of the first baseline assessment, as shown in the participant flow in Figure 1.

Table 1. The UPGRADE-PD (Upbeating Greek Application of Dance in Parkinson's Disease) study design.

Sequence	Period		
	First	Second	Third
ABC	A[a]	B[b]	C[c]
BCA	B	C	A
CAB	C	A	B
ACB	A	C	B
BAC	B	A	C
CBA	C	B	A

[a]Intervention A (in-person Dance for Parkinson's Disease combined with usual medical care).
[b]Intervention B (online Dance for Parkinson's Disease combined with usual medical care).
[c]Control group (usual medical care without Dance for Parkinson's Disease).

Table 2. The UPGRADE-PD (Upbeating Greek Application of Dance in Parkinson's Disease) study's code for the possible carryover effect.

Sequence	First period		Second period		Third period	
	Trial	Carryover effect	Trial	Carryover effect	Trial	Carryover effect
ABC	A[a]	0[b]	B[c]	1[d]	C[e]	2[f]
BCA	B	0	C	2	A	3[g]
CAB	C	0	A	3	B	1
ACB	A	0	C	1	B	3
BAC	B	0	A	2	C	1
CBA	C	0	B	3	A	2

[a]Intervention A (in-person Dance for Parkinson's Disease combined with usual medical care).
[b]Noneffect.
[c]Intervention B (online Dance for Parkinson's Disease combined with usual medical care).
[d]Effect from intervention A.
[e]Control group (usual medical care without Dance for Parkinson's Disease).
[f]Effect from intervention B.
[g]Effect from the control group.

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Table 3. The UPGRADE-PD (Upbeating Greek Application of Dance in Parkinson's Disease) schedule of enrollment, interventions, and assessments for participants.

Time point (wk)	Study period									
	Enrollment (T_{-0}=wk –1)	Baseline 1 (T_0 =wk 0)	Allocation (T_0 =wk 0)	Postintervention 1 (T_1 =wk 9)	Wash-out 1 (T_1 =wk 9)	Baseline 2 (T_2 =wk 18)	Postintervention 2 (T_3 =wk 27)	Wash-out 2 (T_3 =wk 27)	Baseline 3 (T_4 =wk 36)	Postintervention 3 (T_5 =wk 45)
Enrollment										
Eligibility screen	✓									
Informed consent	✓									
Allocation			✓							
Interventions										
In-person DfPD[a]			A[b]	B[c]						
Online DfPD						A	B			
Control group									A	B
Wash-out					A	B		A	B	
Assessments										
SD[d] and MH[e]		✓								
AE[f] and SAE[g]										✓
Adherence rates										✓
Attrition rates										✓
Recruitment rates										✓
Patient satisfaction										✓
PDQ-8[h]		✓		✓		✓	✓		✓	✓
PFS-16[i]		✓		✓		✓	✓		✓	✓
MFIS[j]		✓		✓		✓	✓		✓	✓
DASS-21[k]		✓		✓		✓	✓		✓	✓
SARC-F[l]		✓		✓		✓	✓		✓	✓
EWGSOP2[m]		✓		✓		✓	✓		✓	✓
FP[n]		✓		✓		✓	✓		✓	✓
BBS[o]		✓		✓		✓	✓		✓	✓
MoCA[p]		✓		✓		✓	✓		✓	✓
MDS-UPDRS[q]		✓		✓		✓	✓		✓	✓
BMI		✓		✓		✓	✓		✓	✓
Music preferences	✓									

[a]DfPD: Dance for Parkinson's Disease.

[b]A: starting point of the period.

[c]B: ending point of the period.

[d]SD: sociodemographics.

[e]MH: medical history.

[f]AE: adverse event.

[g]SAE: serious adverse event.

[h]PDQ-8: Parkinson's Disease Questionnaire-8.

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[i]PFS-16: Parkinson Fatigue Scale-16.
[j]MFIS: Modified Fatigue Impact Scale.
[k]DASS-21: Depression, Anxiety, and Stress Scale-21.
[l]SARC-F: Strength, Assistance in walking, Rise from a chair, Climb stairs, and Falls Scale.
[m]EWGSOP2: European Working Group on Sarcopenia in Older People.
[n]FP: Frailty Phenotype.
[o]BBS: Berg Balance Scale.
[p]MoCA: Montreal Cognitive Assessment.
[q]MDS-UPDRS: Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale.

Figure 1. Flow diagram of the study.

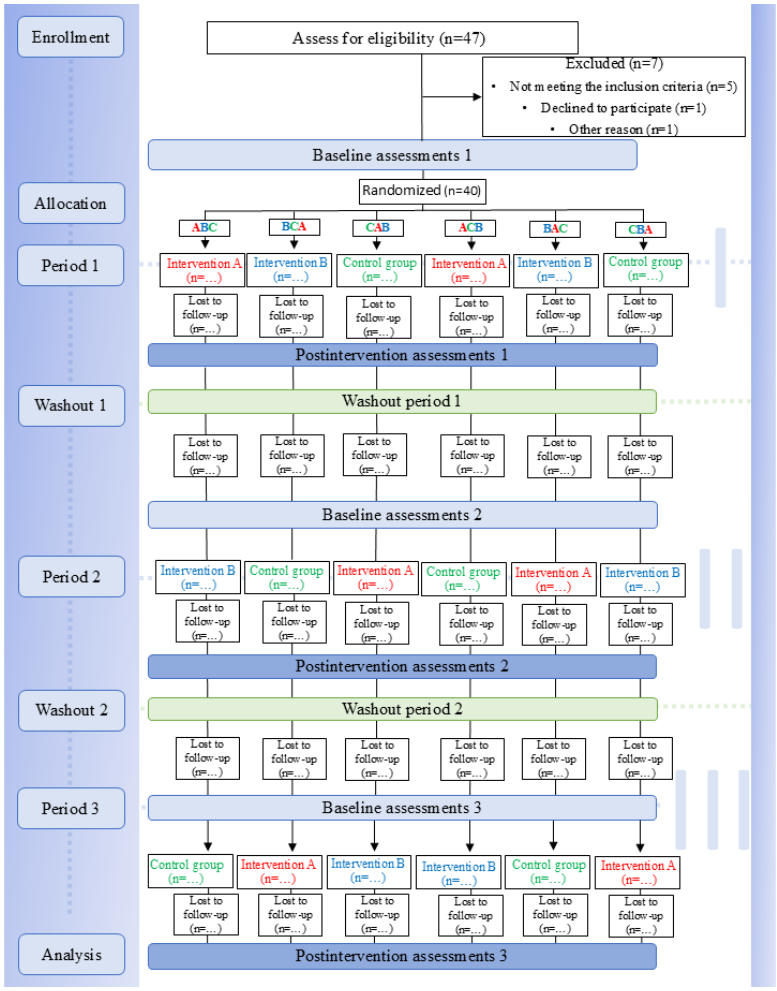

Study Setting

We aim at examining whether following a twice per week DfPD class in-person or remotely for 8 weeks improves the study clinical parameters compared to usual care alone. A total of 40 patients with early- to midstage PD have been randomized to undergo a total of sixteen 60-minute DfPD classes twice weekly for more than 8 weeks, both in-person and online. The study will be conducted following the ethical principles of the Declaration of Helsinki and its later amendments [33], and the Pre-emptive Pharmacogenomic Testing for Preventing Adverse Drug Reactions (PREPARE) trial guide [34], and will conform with the CONSORT (Consolidated Standards of Reporting Trials) guidelines for randomized crossover trials [35], as shown in Figure 1, and the Standard Protocol Items Recommendations for Interventional Trials (SPIRIT) [36-38]. Eginition University Hospital Neurological Outpatient PD Clinic is the participating center, and the first participant was enrolled in April 2023.

Ethical Considerations

The study protocol was approved by the Medical Ethics Committee of the Eginition University Hospital (approval 688/07.09.2022) and the Research and Ethics Committee of the University of West Attica (approval 92282/10/10/2023) and registered at ClinicalTrials.gov (NCT06220084). Written informed consent will be obtained from all participants. At the time of manuscript submission, recruitment has been concluded, but the trial is ongoing.

Eligibility Criteria

The inclusion criteria for patients were set as follows: (1) age ≥18 years; (2) established diagnosis of idiopathic early to

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moderate PD, from 0 to 2.5 according to Hoehn and Yahr stages [39]; (3) being patient of the Eginition University Hospital Neurological Outpatient PD Clinic and under a stable medication for ≥4 weeks; (4) absence of other comorbidities or conditions that seriously affect or may affect mobility (eg, musculoskeletal or cardiovascular issues, pregnancy, terminal illnesses—such as cancer) according to attending physician's discretion; (5) ability to understand, write, and speak in Greek; (6) written consent for participating in the study; (7) a consent of attending physician for participating in an exercise program, given they are totally aware of the patient's clinical and physical status and medications; (8) smart device (either smartphone or tablet, laptop, or computer) access for the dance intervention that will be conducted remotely; (9) absence of serious cognitive impairment, according to attending physician's discretion.

The exclusion criteria for patients were set as follows: (1) a non-PD tremor disorder diagnosis; (2) moderate to severe PD (≥3 Hoehn and Yahr stages) [39] because of a high fall risk [40]; (3) serious health or disability issues (either physical or mental, including pregnancy), because of which exercise is not permitted or exercise instructions cannot be followed; (4) hearing issues for which patient cannot follow music or verbal guidance; (5) non-PD related mental or mobility disorder; (6) any electronic internal medical device or implant, such as a pacemaker or a deep brain stimulation, due to contraindication in the use of bio-electrical impedance analysis [41]; (7) no access of the participant or patient's carer to any smart device (either smart phone or tablet, laptop, or computer).

Interventions

Explanation for the Choice of Comparators

The COVID-19 pandemic placed significant restrictions on the social circulation and exercise of patients with PD and highlighted the necessity of finding alternative forms of therapeutic exercise, such as telerehabilitation [42,43]. The use of telerehabilitation in neurological diseases is constantly expanding [44]. Online attendance in therapeutic dance classes for patients with PD is feasible and safe and is characterized by high compliance rates; it enables training of participants in new technologies and it is easy, fast, and inexpensive [27,28]. While we have already presented evidence that in-person DfPD is safe, feasible, and potentially effective in improving several movement and nonmovement symptoms of Greek patients with PD [45], there are no data regarding a related study conducted online.

Intervention Description

A total of sixteen 60-minute DfPD classes will be conducted twice weekly for 8 weeks, both in-person and online, in a physiotherapy facility in Athens, Greece (in-person DfPD), and via Zoom platform (online DfPD; Zoom Communications, Inc), which will be free for the participants; the facility is licensed for the establishment and operation of physiotherapy activities. All the dance classes will be instructed by the main investigator (ME), who holds the approval to use DfPD for research reasons and is a licensed neurological physiotherapist, adapted physical educator, and dance educator. The exact structure and content of the program are described in Table 4. Participants will be instructed individually on how to use the Zoom platform before their program entry. Frequency and duration of the program are in accordance with past exercise and dance programs in patients with PD [30,45-48].

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Table 4. UPGRADE-PD (Upbeating Greek Application of Dance in Parkinson's Disease) study's DfPD structure and content.

Part (category) and track number	Type of activity	Type of exercise	Primal goals	Song title, album title (release date), composer
1 (seated warm-up)				
1	Introduction: "The Sun Salutation"	Breathing exercises and gradual early mobilization	General warm-up, increase of concentration, and general mobilization	"Love in the Heart" (remastered 2004), *30 Nocturnes* (1987), Manos Hadjidakis
2	Introduction to flow: legato	Gradual moderate intensity and limp and torso mobilization	Specific warm-up and introduction to contemporary dance	"By the Sea," *Eternity and a Day* (1998), Eleni Karaindrou
3	Storytelling: "The Outside the Window Travel"	Introduction to spine twist movements and arm waves	Aesthetics, fantasy stimulation, and visualization	"The Young Rallou" (remastered 2004), *30 Nocturnes* (1987), Manos Hadjidakis
4	Introduction to upper limb velocity: staccato	Tapping movements, rotational arm movements, gestures, and visual contact	Coordination, diadochokinesia, and group dynamics	"The River," *The River* (1959), Manos Hadjidakis
5	Story telling: "The Ocean Dive"	Torso and upper extremities "waving"	Fantasy and imagination stimulation and visualization, successive movement	"Two," *Two* (2006), Konstantinos Vita
6	Limb and torso mobilization	"Flex point"	Coordination and seated posture	"Who Pays the Ferryman," *Who Pays the Ferryman* (1977), Yannis Markopoulos
7	Storytelling: "High Five"	Arm waves, stretch side to side, high five in pairs interaction, and spine rotation	Social interaction, spine mobilization, and group dynamics	"When the Clouds Come," *Gioconda's Smile* (1965), Manos Hadjidakis
8	Introduction to velocity: staccato	Rhythmical walking on the spot and transition of weight	Rhythm, speed switching, and coordination	"Rain," *Gioconda's Smile* (1965), Manos Hadjidakis
9	Storytelling: "Opa"	Staccato-and-legato body movements	Social interaction, speed switching, and movement dynamics (staccato-legato transitions)	"I Hartaetoi" (remastered), *I Gitonia Ton Aggelon* (2004), Mikis Theodorakis
2 (supported by chairs—standing position)				
10	Ballet barre exercises	"Pliés relevés" in 1st and 2nd foot position, coordinated arms and legs movements, and "port de bras" movements	Introduction to basic ballet steps, balance, coordination, and posture	Movement 9, *Mythodea—Nocturne* (2019), Vangelis Papathanasiou (Vangelis)
11	Introduction to the standing coordinated movement	Transition of weight side to side, on-spot walking, coordinated limb movements	Coordination, rhythm, and balance	"Kemal (O Mithos Tou Sevah)," *30 Nocturnes* (1987), Manos Hadjidakis
12	"Sirtaki"	Transition of weight side to side, on-spot running	Introduction to basic *sirtaki* steps, coordination, balance, and stamina	"The Original Sirtaki Zorbas," *Zorba the Greek* 1964, Mikis Theodorakis
3 (nonsupported standing position)				
13	"Zeibekiko"	Forward-backward-side transfer of weight, turns, and free improvisation	Rhythm, creativity, and introduction to basic *zeibekiko* steps	"Evdokia's Zeibekiko," *Evdokia* (1972), Manos Loizos
14	"La Révérence": the goodbye section	Movement in a circle and one-leg balance positions with open and closed eyes	Balance, group dynamics, cooldown, and finish of the class	"A Stroll to the Moon," *30 Nocturnes* (1987), Manos Hadjidakis

Strategies for Improved Adherence to Interventions

Although it has already been shown that dance interventions have higher adherence rates and lower attrition rates than other types of exercise in people with PD [49,50], we have implemented several actions within a more patient-centered and culturally tailored approach, as described in subsequent sections, to further increase patient continued participation.

Patient-Centered Dance Therapeutic Intervention

During the last decades, biomechanical-based therapeutic models in physiotherapy [51,52] have been progressively replaced by more "embodied" therapeutic approaches, in which each diversity and difference is accepted in a more inclusive attitude, which considers patient's bodily and movement image [53]. This approach can be seen as part of a more personalized patient-centered physiotherapeutic approach, which is

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considered as a practical application of the biopsychosocial model [54,55] in terms of integrating the "patient world" in a comprehensive, empathic, and individualized tailored approach [56], and has been already used by physiotherapists, as a more holistic therapeutic approach in neurological patients [57]. The above model takes into serious consideration patients' preferences, needs, and values [58], while it seems to enhance power, responsibility, and therapeutic alliance [59], and relates to better outcomes and QoL in patients with PD [60].

As there are many models and conceptualizations around patient-centeredness in physiotherapy [61], we proposed an 8-number domain of patient-centeredness in therapeutic dance interventions for PD patients with PD (Textbox 1, adapted from the studies by Stewart [55], Brown et al [62], Little et al [63], Stewart [64], Langendoen [56], Dukhu et al [65], and van der Eijk et al [58]), which was adapted from the patient-centeredness approach in medicine [55,62-64], the aspects of patient-centeredness in physiotherapy [56], the person-centered physiotherapeutic management of long-term conditions [65], and the patient-centered health care aspects for patients with PD [58].

The procedures that will be performed during our study according to this proposal are outlined in Textbox 2.

Textbox 1. Domains of patient-centeredness in therapeutic dance interventions for patients with Parkinson disease.

1. A multidimensional and empathic assessment by a trained therapeutic dance health care professional with experience in Parkinson disease for a holistic understanding of the patients' issues, concerns, preferences, and need for tailored information
2. A comprehensive planning and explaining of the physical assessment and the therapist's hypotheses
3. Mutual agreement between patient and therapist on the multidimensional characteristics of the patient's tailored issue after a holistic and valid assessment and interdisciplinary scientific collaboration
4. Mutual agreement between patient and therapist on the therapeutic intervention's goals
5. Building of a high-confidence environment, accompanied by emotional support, empathy, and respect, between patient and therapist for enhancing the patient's levels of self-responsibility, self-management, and independence
6. Treatment adaptations and modifications during possible circumstances differentiation
7. Individualization of exercises, dance combinations and techniques, and teaching methods
8. Sufficient and realistic use of resources and time and continuous health care accessibility

Textbox 2. Procedures that will be performed during the study.

1. The assessment is structured, for research reasons; it is characterized by empathy, and includes multiple movement and nonmovement aspects of Parkinson disease (PD), giving a full informative description of the study's procedures and goals to participants by the main researcher (ME), who is a specialized neurological diseases physiotherapist, and an adapted physical and dance educator. Although ME is responsible for the whole communication with patients, assessments before and after each research period will be performed by an independent researcher who is specialist in the use of the specific tools to eliminate possible detection bias. Part of the assessment (Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale [MDS-UPDRS] and Montreal Cognitive Assessment [MoCA] tests) will be performed by specialized neurologists of the Eginition Neurological Outpatient Clinic (domains 1 and 3).
2. Each step of the assessment procedure before and after each research period is explained; the necessity that each patient gives continuous feedback about possible adverse events is emphasized (domain 2).
3. Translated and validated scientific tools are used, and a continuous multidisciplinary scientific collaboration between physicians, nurses, and physiotherapists is ensured as part of this study (domain 3).
4. Therapeutic intervention goals were based on past research; however, personal patient needs were adapted in the dance combination's design, based on our past pilot study [45], while individual music preferences were considered for the dance intervention's design [66] (domain 4).
5. A high-confidence environment, accompanied by emotional support, empathy, and respect between participants and the physiotherapist, will be ensured (domain 5).
6. Although the early- to midstage severity stage of PD of participants usually does not demand specific modifications for each participant, due to the related motor independence with low fall risk [40], we are prepared to adapt our dance intervention following possible individual circumstances (domain 6).
7. Dance for Parkinson's Disease (DfPD) classes are generally characterized by supportive instruction in a way that participants feel free to perform each dance combination in their individual level of functionality [67]; thus, inclusion, adaptability, and accessibility to all are promoted during each dance class [68] (domain 7).
8. The dance intervention is being conducted in a facility that is offered for free. Classes will be conducted solely by the main researcher (ME), while the trial will be partially funded by a charitable association, and continuous accessibility of patients to the research team will be provided (domain 8).

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Culturally Tailored Therapeutic Dance Intervention

Most nation states were created during the 19th century, when cultural elements were used as potent symbols to serve each national identity [69], such as music and dance [70]. Dance has been used as a powerful tool in the creation of national identity [71] and as a national symbol that seems to emotionally empower members of a community [72]. Particularly in Greece, events involving dance are used for entertainment, socializing, and escape from everyday routine, as well as a sign of well-being that underpins the Greek national identity [73,74].

Dance is a physical activity in which the basic tool is the human body and its purposefully selected movements in a potentially varied rhythmical and cultural context [8]. Dance can be defined as ethnic, where movement types and motivation agree with the way of life and socially accepted norms of a period, and theatrical, where movement patterns are consciously designed to be shown to an audience that is not necessarily familiar with its context [75], even considering that every dance in any context contains ethnic elements [76]. Each person, even unconsciously, dances, bringing to bear all their past intra- and interpersonal experiences and cultural values within the specific socioeconomical environment they live [77], we decided to examine the effect of our dance intervention practice taking into consideration the cultural background of the targeted individuals, who in our case were Greek patients with PD.

DfPD is a dance intervention specially designed for patients with PD, which integrates different dance genres, encourages dance exploration, and focuses on dancing individually and in groups rather than in pairs [45]. For culturally adjusting this intervention to our population, we proceeded with several actions, as noted subsequently. First, we adopted the term “culturally tailored,” instead of “culturally adjusted,” as it has been already proposed in past research and it refers to the total sum of adaptations that must be done in terms of content, symbolisms, and strategies in an intervention to best suit specific cultural characteristics, and thus positively affect health behavior and cultural expression [78].

To incorporate Greek culture elements into our dance intervention, we focused on both surface structure (culturally matched music and dance movements or steps) and deep structure (social and historical influences) as prerequisites for feasibility and efficacy or impact of the dance intervention accordingly [79]. Although collecting participant needs and experiences through exploratory focus groups may better inform both the surface and deep structure of the intervention [79], we based our intervention on past research and participants’ music preferences [66], as described subsequently, to reduce the cost and duration of the study (domain 8, Textbox 1).

All the 14 selected music pieces were composed by Greek artists, and they have been chosen for their capability to serve the idea of Greekness or “Hellinikotita” and being well known in most of the Greek population. While Greek folk dances can be used as a therapeutic tool for older adults at risk of neurodegeneration [80], and they seem to improve functional and psychological characteristics leading to better outcomes in terms of QoL in patients with chronic diseases [81], 2 of the earlier mentioned dances (tracks 12 and 13) were selected for the aforementioned reasons. Furthermore, they seem to have several semiotic cultural references; thus, they may involve symbolic signals for the Greek population [82,83]. The explanation for each music selection is noted below (Table 5).

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Table 5. Explanation for each musical selection in terms of cultural tailoring.

Tracks	Composer	Explanation for each music selection
1, 3, 4, 7, 8, 11, and 14	Manos Hadjidakis	Manos Hadjidakis was a well-known Oscar-winning Greek composer whose work led to the development of a musical language combining popular musical elements directly connected with the Greek cultural memory [84].
9, 12	Mikis Theodorakis	Mikis Theodorakis' work, along with that of Hadjidakis, influenced the idea of Greekness or "Hellinikotita" in the music of the 20th century, while he was characterized by his political influence on late 20th century in Greece [85]. Especially, the 12th track refers to the internationally well-known Greek folk dance "syrtaki," which has been the most famous Greek melody since its birth in 1964, and as part of the film "Zorba the Greek" has been included as a musical semiosis to the Greek cultural identity [82,86].
2	Eleni Karaindrou	Eleni Karaindrou is a Greek artist established for her works in the cinema [87]. The music piece has been chosen from the film *Eternity and a Day* by Theo Angelopoulos, a movie that influenced Greek filmography of the past century and managed in an artistically abstract way to reconstruct the history of Greece, the Balkans, and Europe in a context full of historical and political allegories [88].
13	Manos Loizos	This track refers to the most well-known music that accompanies the "zeibekiko" dance ("Evdokia's Zeibekiko"), a mostly improvisational Greek folk dance directly connected with "rebetiko" culture, and which, from 1980 onwards, has been defined as a pan-Hellenic semiotic dance, leading someone to nonverbally express their emotions [83].
6	Yannis Markopoulos	Yannis Markopoulos is an internationally well-known Greek composer. The selected musical piece was composed for the British Broadcasting Corporation (BBC) television series "Who Pays the Ferryman?" a drama series with great success in Great Britain, Europe, Canada, and Australia [89].
5	Konstantinos Vita (known as K.BHTA)	K.BHTA is the founder of the well-known Stereo Nova Greek electronic music band (1992-1996), while the selected music piece was produced to accompany the dance performance 2 of Dimitris Papaioannou (2006), an internationally well-known Greek choreographer, and artistic director of the opening and closing ceremonies of the 2004 Athens Summer Olympic Games.
10	Evangelos Odysseas Papathanassiou or Vangelis Papathanasiou (known as Vangelis)	Vangelis was a well-known Oscar-winning Greek composer, and the selected music piece is part of the internationally well-known music album *Mythodea—Music for the NASA Mission: 2001 Mars Odyssey*.

Music Preferences

People seem to develop musical identities from an early age in the context of constructing a more general self-identity [90], either as individuals (personal identity) or as members of larger social groups (social identity) [91,92]. Music preferences play a key role in both personal and social parameters of self-identity by participating in the construction of (1) self-image, (2) self-definition, (3) sense of belonging and acceptance by a certain social group, and (4) specific personal values' reflection [66].

In the "musical preferences" scale by Gardikiotis and Baltzis [66], 24 music genres are included on a 6-point scale (0=I do not know this music genre and 1=I do not like it at all, to 5=I like it very much) [93], and divided into 5 factors: (1) "sentimental and sensational," (2) "sophisticated and complex," (3) "nonmainstream dissonant," (4) "established rebellious," and (5) "native-Greek traditional."

During the enrollment phase (Table 3), music preferences of all the participants were registered, and taking in serious consideration the strong music preference frequency ("I like it very much") of most participants (>50%), we compiled the list of selected music titles of the intervention (Table 4). As it is shown in Table 6, the first 4 categories of strong music preferences frequency were formed by music genres of the "established rebellious," which includes Greek art popular (*entechno*), and "native Greek traditional" scale's factors, which includes *rebetika*, *laika* (Greek urban popular), and Greek folk (traditional) music.

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Table 6. Strong music preference frequency ("I like it very much") based on a 6-point scale.

Music genre	Frequency "I like it very much," n (%)
Greek art-popular (*entechno*)	24 (60)
Greek urban-popular (*laika*)	24 (60)
Rebetika	24 (60)
Greek folk (traditional)	23 (57.5)
Classical	19 (47.5)
Greek rock	18 (45)
Greek pop	18 (45)
Pop (contemporary and Western-style)	18 (45)
Jazz	18 (45)
Rock 'n' roll	18 (45)
Blues	17 (42.5)
Greek *laika* pop	14 (35)
Rock	14 (35)
World (ethnic) music	13 (32.5)
Reggae	9 (22.5)
Soul or rhythm and blues	8 (20)
Hard rock or metal	6 (15)
Greek rap or hip-hop	4 (10)
Rap or hip-hop	3 (7.5)
Funk	3 (7.5)
Punk	3 (7.5)
House	3 (7.5)
Alternative	2 (5)
Trance	1 (2.5)

Criteria for Discontinuing or Modifying Allocated Interventions

Participants are free to withdraw from the study at any time and for any reason. As it has been previously mentioned, according to the patient-centered approach that we follow, we have been prepared to adapt our dance intervention following possible differentiation in circumstances (domain 6, Textbox 1). DfPD classes are generally characterized by supportive instruction in a way that participants feel free to perform each dance combination at their individual level of functionality [67]; thus, any personal modification or interpretation is always encouraged to be performed by each participant (domain 7, Textbox 1).

Outcomes

Primary Outcomes

Patients' QoL before and after each research period will be assessed by the change in total score of the Greek version [94] of Parkinson's Disease Questionnaire-8 [95], which is a 0-to-100-point scale with a higher score indicating worse QoL.

Key Secondary Outcomes

The expected key secondary outcomes are outlined in Textbox 3.

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Textbox 3. Key secondary outcomes.

Safety (occurrence of adverse events and serious adverse events)

The occurrence of adverse events such as possible falls, injuries, muscle soreness, and excessive fatigue [96] will be assessed by recording after the end of the program, as has been done in our past pilot clinical study [45], for each participant. The following are considered as serious adverse events [96,97], and they will be recorded after the end of the program: death, threat to life, hospitalization, persistent or significant disability or incapacity, and necessity of surgical operation for any of the aforementioned events.

Feasibility

Adherence rates: an adherence rate of ≥70% is considered as high in older patients with functional limitations [98], and it will be used to assess adherence to each dance intervention following the appropriate formula after the end of the program:

Attrition rates: an attrition rate of ≤15% is considered as acceptable by the Physiotherapy Evidence Database Scale [99], and will be used to assess attrition to each dance intervention following the appropriate formula after the end of the program:

Recruitment rates: for the assessment of the recruitment rates, a target of up to 5 months for 40 participants will be accepted according to past studies [45,100] after the end of the program.

Patient satisfaction

Willingness to continue the program after the intervention: a verbal statement for continuing the program after the end of the intervention in a 6-point Likert scale (0=I don't know if I'd like to continue the program, 1=I don't want to continue the program at all, 2=I don't want to continue the program, 3=I might want to continue the program, 4=I want to continue the program, and 5=I want to continue the program very much) after the end of the program.

Advantages and disadvantages of the program: there will be a total of 2 open questions: (1) Could you please list all the positive and negative points of the in-person Dance for Parkinson's Disease (DfPD) intervention? and (2) Could you please list all the positive and negative points of the online DfPD intervention? These will be asked in a one-to-one interview of each participant by the principal investigator (ME) after the end of the program for the qualitative recording of advantages and disadvantages of each dance intervention from the patient's perspective.

Secondary Outcomes

The other expected secondary outcomes are outlined in Textbox 4.

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Textbox 4. Other secondary outcomes.

Fatigue

- Parkinson Fatigue Scale-16 (PFS-16): fatigue will be assessed before and after each research period by the change in total score of the Greek version [101] of PFS-16 [102], which is a 1- to 5-point scale with a higher score indicating more fatigue.
- Modified Fatigue Impact Scale: fatigue will be also assessed before and after each period by the change in total score of the Greek version [103] of the Modified Fatigue Impact Scale [104], which is validated in the population with Parkinson disease (PD) [105] 0- to 84-point scale, with a higher score indicating more fatigue.

Depressive symptoms

- Depressive symptoms will be assessed before and after each research period by the change in total score of the Greek version [106,107] of the depression subscale score of Depression, Anxiety, and Stress Scale-21 (DASS-21) [108], which is a validated in the population with PD [109] 0-to-42-point scale with 0 to 9 indicating no symptomatology, 10 to 12 indicating mild symptomatology, 13 to 20 indicating moderate symptomatology, 21 to 27 severe symptomatology, and 28 to 42 extremely severe symptomatology.

Stress

- Stress will be assessed before and after each research period by the change in total score of the Greek version [106,107] of the stress subscale score of DASS-21 [108], which is validated in the population with PD [109] 0-to-42-point scale, with 0 to 10 indicating no stress, 11 to 18 indicating mild stress, 19 to 26 indicating moderate stress, 27 to 34 severe stress, and 35 to 42 extremely severe stress.

Anxiety

- Anxiety will be assessed before and after each research period by the change in total score of the Greek version [106,107] of the anxiety subscale score of DASS-21 [108], which is validated in the population with PD [109] 0- to 42-point scale, with 0 to 6 indicating no anxiety, 7 to 9 indicating mild anxiety, 10 to 14 indicating moderate anxiety, 15 to 19 severe anxiety, and 20 to 42 extremely severe anxiety.

Sarcopenia

- Sarcopenia risk will be assessed before and after each research period by the change of total score of the Greek version [110] of Strength, Assistance in walking, Rise from a chair, Climb stairs, and Falls Scale [111], which is a 0 to 10 self-reporting screening tool of five 0- to 2-point components (strength, assistance walking, rise from a chair, climb stairs, and number of falls) with 0 to 3 indicating no risk for sarcopenia, and ≥4 indicating risk of sarcopenia.
- Sarcopenia status will be assessed before and after each research period by the change of European Working Group on Sarcopenia in Older People criteria [112], as has been previously assessed in the PD population [113]. According to the European Working Group on Sarcopenia in Older People, sarcopenia is (1) probable in an individual with low muscle strength (hand grip strength [HGS] for men: <27 kg and women: <16 kg), (2) confirmed in an individual with the above criteria combined with low muscle quantity (appendicular skeletal muscle mass index for men: <7 kg/m^2 and women: <5.5 kg/m^2), and (3) severe in an individual with the 2 above criteria combined with low physical performance (4 m usual walking speed test≤0.8 m/s). HGS will be assessed by a calibrated digital handheld dynamometer, appendicular skeletal muscle mass index by a bioelectrical impedance analysis equipment, and physical performance by the4-m usual walking speed test.

Frailty

- Frailty will be assessed before and after each research period according to the most often used frailty scale in PD [4] frailty phenotype (FP) status [114], in which 5 criteria have to be assessed: (1) unintentional weight loss >5 kg the last year, (2) weakness (HSG for men: <27 kg and women: <16 kg), (3) slow walking speed (10-m usual walking speed test ≤0.8 m/s), (4) exhaustion (PFS-16 total score ≥3, which indicates moderate to severe fatigue), and low levels of physical activity (a total score <600 MET/min/week^{-1} indicates inactivity in the Greek version of International Physical Activity Questionnaire-Short Form [115]). The FP score ranges from 0 to 5 (1 point for each criterion; 0: best score to 5: worst score), and defines as frail an individual with a score of ≥3, as prefrail an individual with a score of 1 to 2, and as nonfrail or robust an individual with a score of 0.

Balance

- Balance will be assessed before and after each research period by the Greek version [116] of Berg Balance Scale [117], which is a 14-item validated in PD [118] scale with a minimum score of 0, and a maximum score of 56, while lower scores indicate worse balance (0-20: high fall risk, 21-40: medium fall risk, and 41-56: low fall risk).

Cognitive functions

- Cognition will be assessed before and after each research period by the Greek version [119,120] of Montreal Cognitive Assessment (MoCA) [121], which is a 0- to 30-point scale with lower scores indicating cognitive impairment.

Movement and nonmovement PD symptoms

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Movement and nonmovement PD symptoms will be assessed before and after each research period by the Greek version of Movement Disorder Society–sponsored revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS) [122], which is a 4 parts scale. Part I assesses nonmotor experiences of daily living (13 items, score range: 0-52), part II assesses motor experiences of daily living (13 items, score ranges: 0-52), part III assesses motor signs (33 items, score ranges: 0-132), and part IV assesses motor complications, namely dyskinesias and motor fluctuations (6 items, score ranges: 0-24). Each item score ranges from 0 (normal) to 4 (severe), and higher scores indicate a greater impact of PD signs.

BMI

- BMI will be assessed before and after each research period by the score from the equation kg/m^2, with <18,5 indicating underweight, 18.5 to 24.9 indicating normal weight, 25 to 29.9 indicating overweight, and ≥30 indicating obesity (3 obesity subcategories exist: Class I scores of 30-34, Class II scores of 35-39, and Class III scores of ≥40) [123].

Sample Size

A prospective, nonrandomized, uncontrolled, open-label pilot study has already been conducted in a Greek population of 16 patients with early- to midstage PD, showing that in-person DfPD is safe and feasible, and can improve QoL, as well as several movement and nonmovement PD symptoms [45]. According to the results of the above pilot clinical trial for our primary outcome (QoL), the Cohen equations for sample size calculation [124], and considering the power of the study equal to 80% and the level of statistical significance of the controls equal to the conventional limit of statistical significance (α=.05), a power analysis was applied with the a priori formula for the *F* test statistical control through analysis of variance with repeated measures using G*Power software (version 3.1) [125].

Taking in consideration that the number of experimental groups will be 3, the number of repeated measurements for each participant will be 6, and the average correlation coefficient between repeated measurements will be 0.64, it was estimated that for this study, which has a 1:1:1:1:1:1 distribution ratio of participants to the groups, at least 6 participants are required in each group (18 in total). On the basis of the equations that adjust the sample size to the expected dropout rate [126], which is expected to be up to the 15% acceptable value, based on the Physiotherapy Evidence Database Scale [99], the minimum sample size required to achieve the study's primary end point (QoL) is 21 participants.

Recruitment

Recruitment started 6 months before the starting date of the program via relevant printed information material and health care practitioners (neurologists and nurses) of the Eginition University Hospital Neurological Outpatient Clinic. All study procedures have been discussed face-to-face individually with each potential participant before screening for eligibility by the primary researcher. The primary researcher (ME) has obtained written informed consent from the potential clinical trial participants before the study's inclusion.

Assignment of Interventions: Allocation

A block randomization will be conducted after the completion of the first baseline assessment (Figure 1) in equal ratio (1:1:1:1:1:1) to 1 of the 6 study sequences (ABC, BCA, CAB, ACB, BAC, or CBA), as further shown in Table 1 [127]. Concealment is ensured by keeping study material in sealed, opaque envelopes and by using paper assignment. After baseline 1 assessment completion (Figure 1), each participant will be randomized to 1 of the 6 study sequences by the data analyst, and the document with the final groups' formation will be delivered in a sealed envelope to the principal investigator, who is the responsible for participants' enrollment.

Data Collection and Management

All assessments will be conducted face-to-face by an independent investigator to eliminate possible detection bias, except of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale and Montreal Cognitive Assessment, which will be conducted face-to-face by specialized neurologists of the Eginition University Hospital Neurological Outpatient Clinic.

Participants are free to quit at any time if they wish to discontinue the study. In that case, reasons for withdrawal will be recorded, if this is possible. Participant's enrollment will be followed by the research team's assistance during the entire study period, including scheduling of data collection appointments, reminding of intervention's appointments, and communicating the starting time of each research period.

Data, including consent forms, completed paper-based data files, and study notes, will be securely stored in the main investigator's office, which will be locked. Raw data will be encrypted and stored digitally on a local computer with access rights to the main investigator. All original data will be archived for 5 years after the completion of the research and then destroyed, according to local regulations. All written data will be stored in a locked cabinet of the main investigator's locked office for 5 years and then destroyed. Digital data will be stored on a password-protected local computer.

Statistical Analysis

The primary analysis will evaluate the between group differences in total score of the Greek version of Parkinson's Disease Questionnaire-8 after each research period. Mean (SD) or summary statistics appropriate to the distribution of the QoL total score will be reported by study group (in-person DfPD vs online DfPD vs control). Study groups will be compared in terms of QoL using mixed model repeated measures considering the correlated data from the same patient [128]. Mixed model repeated measures are robust in small sample size studies; thus, a decreased risk of type II errors occurs [129]. For all secondary end points, summary statistics will be tabulated by study group, and study groups will be compared with a statistical method appropriate to the type of the end point (eg, continuous and

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categorical end point). Bonferroni correction will be used to account for multiple comparisons of secondary outcomes.

A secondary analysis of the primary end point will adjust for those prerandomization variables which might reasonably be expected to be predictive of favorable QoL total score. Any deviations from the protocol will be recorded and agreed by the investigators. Missing data will not be imputed neither for primary nor secondary analyses, and no interim analyses will be conducted in this study. All the *P* values are 2-sided at an α level of .05. Analyses will be conducted with SPSS (version 20.0; IBM Corp) and R (version 4.4.1; R Foundation for Statistical Computing).

Results

The study is a 3-arm crossover and open-label randomized controlled trial (in-person DfPD vs online DfPD vs control), and was partially funded in September 2023. The first participant was enrolled in April 2023. The trial is currently ongoing, and will conclude in September 2024. A total of 47 patients were enrolled during the recruitment period, of whom 7 have been excluded (Figure 1). A total of 40 patients were randomized equally to the study's 6 sequences to undergo sixteen 60-minute culturally tailored DfPD classes both in-person and online during a 10-month experimental period following a patient-centered approach. The data analyst will analyze all the data after the final participant exists the study. We expect that by the second quarter of 2025, the study's results will have been published.

Discussion

Principal Findings

This is a 3-arm crossover and open-label randomized controlled trial (in-person DfPD vs online DfPD vs control), which aims to evaluate the efficacy, safety, and feasibility of a patient-centered and culturally tailored DfPD intervention delivered both in-person and online as a complementary therapy for a series of movement and nonmovement PD symptoms, as well as for QoL, sarcopenia, and frailty of Greek patients with PD.

Frailty is a state most common in older people, characterized by high vulnerability to acute stressors, such as falls, which are associated with increased hospitalization and mortality risk as well as disease severity or progress [130]. Patients with PD, accompanied by sarcopenia and frailty, seem to have lower cognitive function, movement performance, and QoL; recurrent falls; and higher fatigue, orthostatic hypotension, and inpatient mortality. Physical exercise programs seem to reduce or prevent the risk of both conditions; thus, they may improve the QoL of patients with PD [2,4,6,131]. The possible effect of DfPD on sarcopenia and frailty of Greek patients with early-to-midstage PD has not been examined. Furthermore, there is no controlled study investigating any possible differential effect of in-person and remote delivery of the aforementioned program on the QoL of patients with PD, fatigue, depressive symptoms, stress, anxiety, sarcopenia, frailty, balance, cognitive functions, movement and nonmovement PD symptoms, and BMI. We expect that our results will aid in the implementation of well-organized patient-centered and culturally tailored dance programs for patients with PD, thus providing reliable evidence for better recommendations for clinical practice.

Conclusions

The results of this study are expected to show the possible differential effect of a patient-centered and culturally tailored DfPD intervention, delivered in-person versus online, on several movement and nonmovement symptoms, as well as on QoL, sarcopenia, and frailty in people living with PD in Greece.

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Authors' Contributions

ME was responsible for conceptualization, visualization, methodology, investigation, data collection, project administration, and writing (original draft). IG was responsible for software, methodology, sample calculation, and data analysis. MP was responsible for methodology, validation, and writing (review). NP, AB, AMS, ES, I Alexandratou, I Alefanti, RA, CK, and IM were responsible for data collection. CC was responsible for data curation. LS was responsible for writing (review and editing), methodology, validation, and conceptualization. DB was responsible for conceptualization, validation, writing (review), and supervision.

Conflicts of Interest

None declared.

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
DfPD: Dance for Parkinson’s Disease
PD: Parkinson disease
QoL: quality of life
UPGRADE-PD: Upbeating Greek Application of Dance in Parkinson’s Disease

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Protocol

Short, Animated Storytelling Video to Reduce Addiction Stigma in 13,500 Participants Across Multiple Countries Through an Online Approach: Protocol for a Randomized Controlled Trial

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Abstract

Background: Stigma toward people with addiction is a well-documented phenomenon that dramatically impacts help-seeking, treatment, and recovery. Interventions aimed at reducing stigma toward those with addiction must overcome the frequent mischaracterization of addiction as a failure of judgment rather than a chronic, treatable illness. Previous research has demonstrated that social contact with people recovering from addiction can promote empathy and reduce stigma, but social contact is difficult to scale. Short, animated storytelling (SAS) is a novel health communication approach that scales easily because it can leapfrog barriers associated with language, culture, literacy, and education levels.

Objective: This study will investigate the effect of a cross-culturally accessible SAS video intervention aimed at reducing stigma and increasing empathy toward people with addiction. We also seek to gain insight into the mechanisms of action of this SAS intervention by measuring the contribution of sound design to their effect.

Methods: We will conduct a randomized controlled trial with 13,500 adult participants from the United States, the United Kingdom, and South Africa, recruited online via Prolific Academic and randomized into 3 arms, per country. The 2 intervention arms will receive a wordless, social contact–based SAS video, one arm with a soundtrack and one without. The third arm will receive an educational video about addiction. Validated questionnaires will be used to assess our primary outcome, addiction stigma, and secondary outcomes, optimism, warmth toward the subject, and hopefulness, at baseline, immediately post exposure, and 2 weeks later. Ethics clearance was obtained on August 15, 2024, from the Stanford University institutional review board (protocol 76457).

Results: This trial was funded in January 2025 by the Heidelberg Institute of Global Health, the Faculty of Medicine at Heidelberg University, in Germany. As of March 2025, no data have been collected. The estimated start date for this trial is May 15, 2025. We expect to complete data collection by July 1, 2025, and expect results to be published in the spring of 2026.

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Conclusions: Here, we present the protocol for an online, multicountry, randomized controlled trial. This trial is designed to measure the effect of an innovative approach to global health communication (wordless, short, and animated storytelling) on addiction stigma in 3 global regions. These findings will inform the design of future scalable, digital health storytelling interventions for global audiences while exploring the capacity of SAS to shift public health attitudes and perceptions. Furthermore, if effective, the intervention described here could be disseminated broadly via social media and other online platforms.

Trial Registration: ClinicalTrials.gov NCT06705205; https://clinicaltrials.gov/study/NCT06705205

International Registered Report Identifier (IRRID): PRR1-10.2196/73382

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KEYWORDS

stigma reduction; addiction; health communication; social media; animation; video; storytelling.

Introduction

Stigma toward people with addiction is a well-documented phenomenon that dramatically impacts recovery by discouraging help-seeking behavior, isolating those affected, and increasing the likelihood of shame-related comorbidities such as anxiety and depression [1]. Similar to stigma in other domains, stigma toward people with addiction involves prejudice and discrimination, leading to compounding sequelae such as avoidance, self-stigmatization, and failure to seek treatment [2]. These effects have been documented cross-culturally and globally, worsening an already challenging public health issue [1,2]. The World Health Organization estimates that approximately 400 million people aged 15 years and older live with alcohol use disorders globally [3]. In addition, an estimated 39.5 million people aged 15-64 years are affected by drug use disorders [4]. Recent research suggests that the COVID-19 pandemic dramatically exacerbated these problems, particularly in low- and middle-income countries [5]. In addition, the pandemic aggravated social isolation and loneliness, exacerbating self-stigmatization, especially for underresourced populations that are at a greater risk of addiction [6-8]. Stigma can thus significantly widen health disparities, underscoring the need for effective interventions to ameliorate it.

Reducing addiction stigma is challenging because addiction is often viewed as a failure of judgment and lack of morality rather than a chronic illness, with complex causes (genetic and environmental) that require both medical and psychological intervention. Interventions aimed at reducing public stigma toward those with addiction must address this frequent mischaracterization of addiction [9]. Evidence of stigma has even been documented among health care professionals with observed negative impacts on quality of care [10]. Previous research has demonstrated that social contact with people recovering from substance use disorders can promote empathy and reduce stigma, but these interventions often require extended face-to-face interaction and are difficult to scale [11]. Intergroup social contact interventions, despite their promise for reducing stigma, can also be limited by individual selection bias, due to the very prejudice the intervention aims to reduce [12]. A further challenge lies in the fact that public health communication interventions often result in the systematic exclusion of non–English speakers and non-Western cultural groups [13]. Even scalable virtual interventions for stigma reduction and empathy building have produced mixed findings beyond high-income and homogeneous populations [14]. As a result, there is an urgent need for novel approaches that focus on broadly disseminating accessible, positive stories related to addiction to promote empathy and understanding. The major challenge lies in making them accessible across languages, cultures, education, and literacy levels.

Short, animated storytelling (SAS) is a novel health communication approach developed in response to the need for rapid, global dissemination of public health messaging across various languages, cultures, literacy, and education levels during the COVID-19 pandemic [15,16]. SAS interventions boost cross-cultural relevance through accessible character designs [17], and they support the engagement of diverse audiences through the use of wordless visual storytelling and compelling soundtracks [18,19]. These interventions are specifically designed for online environments, namely social media platforms, where people readily consume short video content and increasingly seek health information [20]. Social media has become a critical tool for public health communication, with a growing body of research evaluating these interventions [21]. The global reach of many social media platforms enhances their potential utility for scaling health communication interventions, including those aimed at reducing addiction stigma. However, such interventions must be rigorously tested in different global regions and their mechanisms of action must be better understood in order to inform the ongoing development of effective, scalable, and cross-culturally accessible interventions.

This study will investigate the effect of a globally accessible SAS video intervention aimed at reducing stigma and increasing empathy toward people with addiction. In addition, we will attempt to isolate and quantify the contribution of sound design to the effect of the intervention. This wordless, animated SAS intervention was co-created with a multidisciplinary team of experts who are trained in health communication, addiction medicine, animation, sound design, screenwriting, and digital storytelling. The video was designed to resonate globally, across cultures, and traverse linguistic, literacy, and educational barriers. We hypothesize that a single exposure to the 2.5-minute intervention video will measurably reduce addiction stigma and boost hope, optimism, and empathy toward people with addiction in three culturally distinct global settings: the United States, the United Kingdom, and South Africa. We also hypothesize that this effect will persist at a 2-week follow-up and that sound design will enhance the magnitude and durability of the observed effect.

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Methods

Study Setting, Participants, and Recruitment Procedure

This study will be conducted online. Adult participants from the United States, the United Kingdom, and South Africa will be recruited and randomized through the platform Prolific Academic (ProA). These 3 countries were chosen because Prolific has a large enough number of participants in each of these countries to make it feasible to reach our desired sample size. The video intervention and questionnaires will be delivered to participants through the secure, online survey platform, Qualtrics, an experiment builder that provides users with the tools for undertaking online behavioral research.

We will enroll 4500 participants in the United States, 4500 participants in the United Kingdom and 4500 participants in South Africa using ProA, a crowdsourcing platform frequently used to conduct rigorous academic research [22]. Participants in this study will be adults aged 18-49 years. This age group is selected because they reflect our target audience: adults who are likely to seek information and regularly engage on social media [23]. Broad eligibility criteria reflect our interest in evaluating the intervention as it would be delivered outside of experimental conditions: online, widely available via social media or the Internet, and not targeted toward any specific audience. Before enrolling in the study, all participants will read an information sheet on ProA that has been approved by the Stanford Ethics Committee. Those who agree to participate will be directed by Prolific to complete the study activities on Qualtrics.com, a secure online data-collection platform.

Randomization, Consent, and Study Design

After reviewing the Institutional Review Board-approved information sheet, delivered to prospective participants online via ProA, those who indicate their consent to take part in the study will then be randomly assigned to one of three groups:

1. Intervention A: receiving the SAS video full intervention group.
2. Intervention B: receiving the SAS video partial intervention (without sound) group.
3. Control Group: receiving written information about addiction prevalence.

A baseline survey will be used to collect demographic information as well as baseline data on our primary and secondary outcomes. Thereafter, the Intervention A group will watch the 2.5-minute video, the Intervention B group will watch the 2.5-minute video without sound, and the control group will read a fact sheet about the global burden of addiction. Following this, all groups will complete a series of validated questionnaires to assess our primary outcome: addiction stigma, and secondary outcomes: optimism, warmth toward the subject, and hopefulness.

We will conduct the first round of surveys immediately post exposure of the intervention groups to the SAS video interventions and the control group to their written fact sheet. Follow-up assessments, using the same surveys, will be conducted 2 weeks later. To ensure the accuracy and validity of the results, we will include attention checks and exclude participants who fail these checks. Each participant will spend approximately 8 minutes watching the intervention and completing the surveys and will receive US $4.80 for completing the study. Figure 1 represents the trial design and flow.

Figure 1. Trial design and flow.

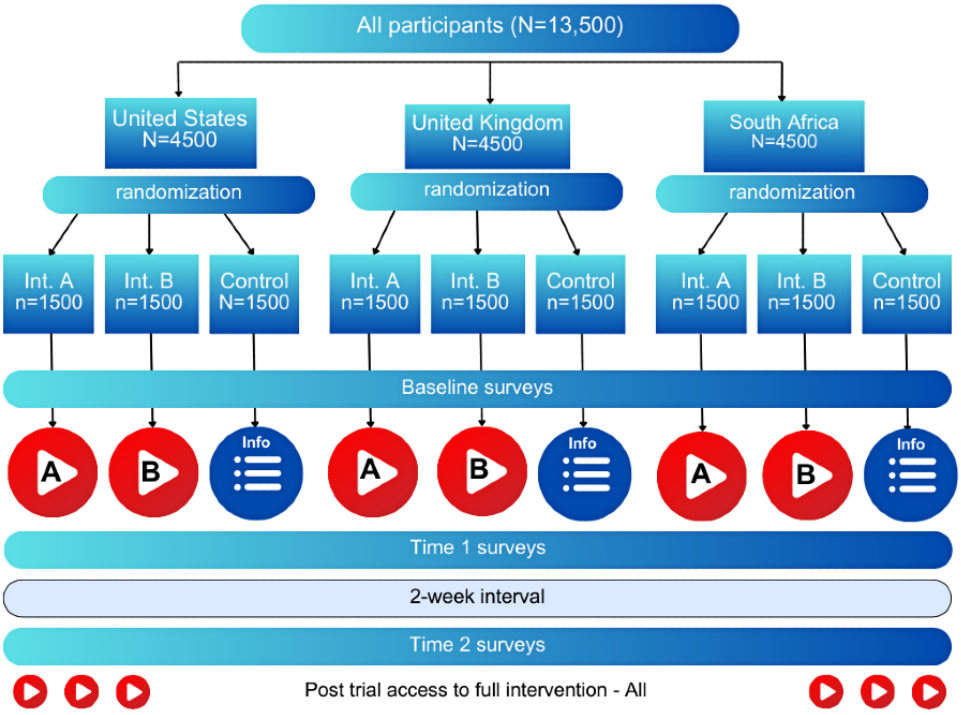

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Intervention

This short, animated story video was co-created by a global health communication specialist with formal training in screenwriting and story development, an addiction medicine specialist, a professional animator living in South Africa, an adolescent composer and sound designer, and a group of high school student advisors at Avenues the World School in New York City. The intervention follows a classical 3-act story structure, with an inciting event, rising action, a midpoint, climax, and resolution. Figure 2 displays selected scenes from the SAS intervention video, with corresponding timestamps and descriptions of the story "beats" that propel the narrative forward. The main character is a fish who discovers and tries a foreign substance, ignoring the warnings of a more senior fish character. The young fish soon becomes addicted to the substance, and we see the negative impact on his underwater life. He injures others around him while under the influence and, finally, injures himself in his desperate pursuit of the next high. In this way, the video visually conveys the concept of drug tolerance. In the second half of Act 2, the main character, in desperation, gulps down the remaining dose of the addictive substance before realizing that he is (literally) hooked. A fishing line drags him off-screen and it seems that all is lost until the senior fish reappears and helps him break free of the hook. This leaves a deep gash in the young fish's mouth. In the young fish's moment of deepest pain and shame, the senior fish reveals his identical gash (the unexpected story twist). The 2 fish share a moment of painful empathy, then swim off-screen together. The only words in this video appear as text on the final, "call-to-action" screen: "Hooked on something that's hurting you? Speak up. There's help." The video can be viewed on YouTube [24].

Figure 2. Selected scenes from short, animated storytelling intervention with timestamps.

Primary Outcome

The primary outcome is stigma toward people with addiction, which we will measure using an abbreviated, 18-item version of the Attribution Questionnaire (AQ-18) [25,26]. This version (AQ-18) includes the blame, pity, help, dangerousness, fear, and avoidance subscales of the original questionnaire, as these subscales are most appropriate, in scope and topic area, to detect a potential effect of our short video "micro-intervention." The AQ-18 will be scored along a 9-point Likert scale indicating the extent to which participants agree with the item ranging from "not at all" (1) to "very much" to (9) with a maximum score of 27 for each 3-item construct. Higher scores indicate greater stigma. The AQ-18 is highly reliable and subscales have Cronbach α ranging from fair (0.6, responsibility) to good (0.93, fear/dangerousness) [25,26]. Participants responding to the AQ-18 may score between 12 and 108. Like the longer version, the AQ-18 offers a brief vignette, which we modified to be (1) gender-neutral and (2) about addiction rather than general mental illness. All participants will read the following vignette before completing the questionnaire. A gender-neutral name (Alex) was chosen to eliminate potential gender bias:

> *Alex is a 30-year-old with a history of addiction. Alex's substance use problem has harmed Alex's health and hurt others. Alex has been hospitalized several times for addiction-related health problems.*

Secondary Outcomes

Optimism

We will measure optimism using the Brief García's Interactive Optimism Scale (BIOS-G) [27]. The BIOS-G is an instrument

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designed to assess an individual's level of general optimism toward their life and other people. The scale includes 4 statements for which respondents indicate their level of agreement from 1 ("Of course not") to 4 ("Yes, of course"). Higher scores indicate a greater level of optimism. Participants may score between 4, (indicating low optimism) and 16, (indicating high optimism). The BIOS-G has demonstrated reliability and validity across diverse populations, with a reported Cronbach α of 0.86 [27].

Attitude

We will also measure attitudes toward those with addiction using a "stigma thermometer," a tool we previously developed to assess attitudes regarding sexual orientation and gender diversity [28]. The thermometer provides the following prompt:

> *Using a scale from zero to 100, please tell us about your personal feelings toward people who are addicted to substances such as drugs or alcohol. As you do this task, think of an imaginary thermometer. The warmer or more favorable you feel toward people who are addicted to substances such as drugs or alcohol, the higher the number you should give it. The colder or less favorable you feel, the lower the number. If you feel neither warm nor cold toward people who are addicted to substances such as drugs or alcohol, rate it 50.*

Researchers in the fields of political science and psychology have frequently used feeling thermometers to assess attitudes toward stigmatized groups [29].

Finally, we will measure subjective levels of hope using a visual analog scale (VAS), a longstanding, validated tool for assessing related constructs of stress and subjective well-being [30]. The VAS provides the following prompt:

> *Using a scale from zero to 100, please tell us about how hopeful you feel after watching the video [control group participant instructions will reference the fact sheet in the AQ-27 instead]. As you do this task, think of an imaginary thermometer. The more hopeful you feel, the higher the number you should give it. The less hopeful you feel, the lower the number. If you feel neither hopeful nor hopeless, rate it 50.*

Analysis

At the first time point (T1), we will compare addiction stigma, optimism, hope, and warmth toward subject scores between the 2 intervention groups and the control group. This comparison is intended to establish the immediate effect of watching the intervention videos on addiction stigma, optimism, hope, and warmth toward people with addiction. At the second time point (T2), we will once again compare our primary and secondary outcomes between the intervention and control groups. This will allow us to detect potential short-term effects of watching the intervention video on addiction stigma, optimism, hope, and warmth toward people with addiction. By comparing the outcomes of the 2 intervention arms at the 2 time points, we will be able to measure the contribution of sound design to the effect of the SAS video intervention.

Sample Size

We calculated the sample size needed for comparing mean scores between the 3 arms, as detailed in the trial design. This was performed independently for the primary and secondary outcomes based on the score of each survey, upon which we selected the most conservative sample size for our study.

We assume that a significant, sustainable change in addiction stigma from watching the SAS video could be achieved by multiple exposures to the video or similar SAS interventions in a series of "micro-doses." As our study measures the effect of a single exposure to a single SAS video, we aim to measure a small change in our mean outcome scores, presuming that these small changes could yield larger ones following repeated exposures (microdoses). Thus, we have powered this trial to detect a small effect size for comparing the mean scores between trial arms, that is, d=0.1, smaller than the generally recommended threshold for detecting a small effect size [31].

We used the sample size formula for a 1-tailed comparison of the mean scores with equal variance, a Type I error of 0.01 to account for multiple comparisons, and a power of 80% to detect changes in the mean scores. This resulted in a sample size of 1128 individuals per arm. Accounting for a potential attrition rate of 20% (personal communication with ProA), this yields 1410 individuals per arm. For this study, we will recruit 1500 participants per arm in each of the 3 countries. This gives us a total sample size of 13,500 participants, which allows us to detect the potential effects of the intervention with a power higher than 80%.

Recruitment and Strategies to Improve Adherence to Interventions, Promote Participant Retention, and Complete Follow-Up

Reaching adequate participant enrollment for our target sample size relies on our choice of ProA as a recruitment platform. ProA has a sufficiently large database of registered prospective trial participants in the United States, the United Kingdom, and South Africa. To improve survey completion rates in this trial, we offer payment to all participants. Participants will receive half of their payment after Step 1 of the study and the remaining half after completing Step 2 of the study. If participants spend more than 45 minutes on any phase of the trial, they will be timed out of the experiment. This prevents participants from bottlenecking the survey platform with partially completed questionnaires. We also conducted a pilot trial with 600 participants in the United States only to verify participant retention. In this pilot study, 88% (526/598) of participants returned to complete the follow-up surveys, underscoring the feasibility of this trial [32].

Sequence Generation, Allocation Concealment, and Implementation

This 3-arm individual, parallel-group randomized controlled online trial will be hosted and implemented by the Qualtrics survey platform. The platform uses a computer-generated allocation sequence to randomly allocate participants 1:1:1 to the 3 trial arms. The investigators will remain unaware of individual trial arm allocations.

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Blinding

All co-investigators and researchers involved in the data analyses will remain blinded to the trial arm allocation for the entire duration of the study. Statisticians will also be blinded to the study hypotheses, minimizing the risk of bias.

Participant Timeline

Participants will be enrolled over a period of 4 weeks via the ProA platform. Step 1 of the trial (baseline data collection, video viewing, and T1 surveys) will occur on a rolling basis, with Phase 2 (follow-up surveys) taking place 2 weeks later across all arms. After both study phases have been completed, all participants will be offered posttrial access to the intervention video. Their voluntary view times will be recorded as a measure of participant engagement with this health education medium (Table 1).

Table 1. Schedule of enrollment, interventions, and assessments.

Trial Information	Enrollment	Allocation	Close-out				
Time point	$-t_1$	0	Intervention videos (t_1)	Surveys (t_1)	2-week interval	Surveys (t_2)	Posttrial SAS[a] video access
Enrollment procedure							
Eligibility screen	✓						
Informed consent	✓						
Allocation		✓					
Intervention and assessments by arm							
Intervention arms			✓	✓	✓	✓	✓
Control arm				✓	✓	✓	✓

[a]SAS: short, animated storytelling.

Relevant Concomitant Care Permitted or Prohibited During the Trial

There is no relevant concomitant care, permitted or prohibited during this trial.

Criteria for Discontinuing or Modifying Allocated Interventions

Participants can withdraw their consent to participate at any time, before or during the study. Incomplete survey data will not be used in the primary analysis, except at a meta-level to report the aggregate number of incomplete surveys.

Provisions for Posttrial Care

This trial involves the viewing of a short, animated storytelling video featuring fish, after which a collection of validated surveys will be completed by participants in both groups. The trial will be conducted purely online.

There are no foreseeable risks associated with participating in this study. Participants volunteer and consent to participate in the study and are aware that they can withdraw at any time. The study investigators can be contacted at any time after the study, should the participants wish to follow up.

Plans for Assessment and Collection of Outcomes

The Qualtrics platform will collect data submitted by individual participants as they select their responses to the surveys used in this trial. We anticipate completing all data collection within a 6-week period.

Data Management

Qualtrics uses Transport Layer Security encryption for transmitted data. Qualtrics' services are hosted by trusted data centers that are independently audited using the industry-standard Statement on Standards for Attestation Engagements 18 (SSAE-18) method. The research team conducting this study can access only anonymized data and, for statistical analysis purposes, we will download and safely store this data on secure computers maintained by our coinvestigators.

Statistical Methods for Analyzing Primary and Secondary Outcomes

Descriptive Statistics

We will use descriptive statistics to summarize the distribution of our outcomes by demographic factors, including age, gender, race/ethnicity, political affiliation, socioeconomic status, and previous experience with both addiction and childhood trauma, since these factors could affect scores.

Primary Outcomes

For each participant, stigma scores will be calculated individually. The mean score for each study arm at T1 and T2 will be calculated and compared between the intervention arms and the control arm at T1, and between the intervention arms and the control arm at T2, using repeated measure ANOVAs. This will be done at the study level and the country level to identify differential effectiveness across geographic conditions. We will also use multilevel regression analyses to control for demographic factors and other potential variables as needed. All analyses will be conducted in R (R Core Team, 2021).

Secondary Outcomes

For the evaluation of secondary outcomes, we will use the statistical methods described above to evaluate both the immediate and medium-term effects of the SAS video intervention. The methods include, but are not limited to, *t* tests

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for independent groups, matched *t* tests for dependent groups, repeated measure ANOVAs, and multilevel regression models. For that, we will analyze the mean scores of the stigma surveys at T1 and T2, with a focus on the impact of the SAS video intervention on the score outcomes. All analyses will be conducted in R.

Methods for Additional Analyses (eg, Subgroup Analyses)

Exploratory subgroup analyses will be conducted to understand the extent to which demographic characteristics and country location moderate the effects of the intervention on stigmatization and secondary outcomes.

We will also use regression models to describe the potential effects of demographic factors on participant engagement. To quantify this engagement, we will use Qualtrics to offer participants voluntary posttrial access to the SAS video intervention. We will record a timestamp when the participant reaches the end of the second time point, the moment when a participant chooses to play the video and the moment when they end the study. Participants who skip the video or watch it for less than 3 seconds will be considered as not having engaged with the video. For the participants who watch the video, we will record the length of time spent watching it.

Methods in Analysis to Handle Protocol Nonadherence and Any Statistical Methods to Handle Missing Data

Participants in the study will have 45 minutes to watch the short, animated storytelling video and answer their surveys. All items of each survey are designed such that individual items must be answered before moving forward. This will guarantee that there will be no missing values in the datasets of participants included in the analyses. All participants who have completed the first part of the study (T1) will be included in the second part (T2). If a participant, who submitted a completed survey at T1, fails to complete a survey at T2, their data will be included only in the immediate effect analysis. Participants who do not watch the videos or answer the questionnaire items at either time point will be excluded from the analysis.

Access to Data

All researchers listed as co-authors on this study will have access to the full dataset. We have no contractual agreements with any other parties regarding the collection, evaluation, or use of the data collected as part of this study.

Data Monitoring and Trial Steering Committees

A trial steering committee (TSC) made up of an independent chairperson, additional members, and study collaborators will oversee this trial. A total of 2 TSC meetings will be conducted during the planning and data collection periods. Because this is a minimal-risk study with a very short study period, no additional data monitoring committee will be required. For the same reason, no interim analyses are planned, and no specific stopping rules are needed.

Adverse Event Reporting and Harms

This is a minimal-risk study. We do not anticipate any adverse events. The TSC will monitor study conduct during data collection. When providing consent, participants will be given a way to report adverse events should they occur during the trial.

Dissemination Plans

We anticipate the data collection to be completed by the end of July 2025. We aim to publish our findings in peer-reviewed academic journals, in the Spring of 2026, as well as presenting these at scientific conferences. Authorship will be considered according to the International Committee of Medical Journal Editors (ICMJE) criteria.

Plans to Give Access to the Full Protocol, Participant Level-Data, and Statistical Code

This document is the full protocol. Individuals interested in additional information or documentation should contact the corresponding author. The R code for the analyses will be published together with the planned publications on Github.com, as appropriate.

Ethical Considerations

This study will be performed according to the ethical standards laid down in the 1964 Declaration of Helsinki and has been approved by the Stanford University Institutional Review Board (Protocol number 76457, approved on 8/15/2024.) We will follow the CONSORT (Consolidated Standards of Reporting Trials) guidelines [33] and the study has been registered in ClinicalTrials.gov (NCT06705205).

Results

This trial was funded in January 2025 by the Heidelberg Institute of Global Health, at the Heidelberg University Faculty of Medicine, in Germany. As of March 2025, no data have been collected. The projected start date for this trial is May 15, 2025. We expect to have completed data collection by July 1, 2025, and we expect results to be published in the Spring of 2026. This is version 1.0 of the trial protocol and recruitment has not started for this trial. We anticipate beginning to recruit participants in March 2025. We anticipate that recruitment will be completed by May 1, 2025.

Discussion

Here, we present the protocol for an online, multicountry, randomized controlled trial. This trial is designed to measure the effect of an innovative approach to global health communication (wordless, short, animated storytelling) on addiction stigma in 3 diverse global regions. Our hypothesis is that the SAS intervention tested here will measurably reduce stigma toward people with addiction, boost optimism, and improve attitudes toward people with addiction in 3 countries. We also hypothesize that the soundtrack will augment the effects of the intervention and will enhance the durability of those effects. Societal stigma toward individuals with addiction reduces help-seeking and impedes treatment and recovery from an increasingly prevalent global public health problem. During the design of this trial, we carefully considered the following potential limitations of our study. First, because not all countries have adequate numbers of potential participants enrolled on

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Prolific, and because our outcome measures are only validated in English, we were limited to three countries, in only three global regions: the United States, the United Kingdom, and South Africa. This subset is not representative of all global regions, so we will need to interpret our findings with caution, without overstating them. However, if our findings are promising, future studies could explore the effect of this intervention in other global regions, for example, in Asian countries where patterns and attitudes toward drug addiction differ from the global regions examined here [34]. Second, we acknowledge that our participant population may not be entirely representative of the general population in each country. Previous studies have shown that people registered on ProA tend to be younger and more educated than country averages [35]. However, the benefits of using ProA include providing concurrent access to large, geographically dispersed, adult test populations in different global regions, with minimal loss to follow-up [35].

Conclusion

The findings can help establish future approaches to using short, animated storytelling interventions in cross-cultural settings, as well as characterize the extent to which these interventions can affect attitudes and perceptions. Furthermore, if effective, the intervention described here would be delivered via social media and other online platforms; therefore, we suggest that testing it with an online community is a reasonable approach for gauging its true effectiveness.

Acknowledgments

We wish to thank our talented creative partners and co-creators, Matt Torode who animated the Intervention video under the direction of the first author, and with input from the students of the Avenues Media Innovation Hub, and co-author MS who composed the original soundtrack. We thank our addiction medicine expert, Dr. Chwen-Yuen Chen, as well as Jennifer Gates Nassar, TB, and the Stanford Medicine Office of Communications, for their support in developing this intervention. This protocol was reviewed and funding for the trial was awarded from the Alexander von Humboldt Professor Prize of TB and the Stanford Center for Digital Health.

Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

MA led the conceptualization, funding acquisition, project administration, visualization, and writing–original draft. MK, MG, JKR, DA, and TB assisted with conceptualization, investigation methodology, review and editing of the manuscript. MS led the online trial set-up, intervention development, assisted with investigation methodology and manuscript editing. AG assisted with investigation methodology and manuscript review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT Checklist.
[PDF File (Adobe PDF File), 82 KB - resprot_v14i1e73382_app1.pdf]

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Abbreviations

AQ-18: Attribution Questionnaire
BIOS-G: Brief García's Interactive Optimism Scale
CONSORT: Consolidated Standards of Reporting Trials
ICMJE: International Committee of Medical Journal Editors
ProA: Prolific Academic
SAS: Short, animated storytelling
SSAE-18: Standards for Attestation Engagements 18
TSC: Trial Steering Committee
VAS: visual analog scale

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Protocol

Enhancing Adherence to Continuous Positive Airway Pressure Therapy in Patients With Obstructive Sleep Apnea Using Augmented Reality: Protocol for a Randomized Controlled Trial

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Abstract

Background: Continuous positive airway pressure (CPAP) therapy is the gold standard treatment for treating obstructive sleep apnea (OSA). However, patient adherence to CPAP therapy remains a critical challenge, with many individuals finding it difficult to maintain consistent use due to discomfort, lack of understanding, or perceived inconvenience. Augmented reality (AR) offers a novel approach to overcoming these barriers by providing interactive real-time guidance to users, potentially enhancing adherence rates.

Objective: This clinical trial aims to examine the feasibility of AR implementation and the effect of AR on improving CPAP adherence in patients with OSA.

Methods: A randomized controlled trial with a parallel assignment will be conducted. Participants will be randomly assigned to either an experimental group receiving AR-guided CPAP therapy or a control group receiving standard care. The study will span 6 months, with assessments at baseline (T0), and with follow-ups at 1 month (T1), 3 months (T2), and 6 months (T3) post intervention. The primary outcome measure is CPAP adherence, defined as using the CPAP device for more than 70% of sleep time, with a minimum of 4 hours per night. Secondary outcomes will evaluate the common adverse effects associated with CPAP therapy, device usability, and time required for CPAP machine use education.

Results: This study is funded by the Ministry of Science and Technology, Taiwan (August 2023 to July 2026) and was registered in August 2024 (ClinicalTrials.gov NCT06520592). Participant recruitment is scheduled to begin in April 2025, and by September 2025, we expect to have enrolled 40 participants (50% of the target sample of 80). Preliminary analyses of CPAP adherence at 1 month and usability data are currently underway. Final data collection is anticipated to be completed by December 2025, with results expected to be published by Fall 2026.

Conclusions: Anticipated findings suggest that AR-guided CPAP therapy may significantly enhance patient adherence by improving mask fitting and providing effective, interactive education. If validated, this innovative approach could pave the way for more personalized technology-driven interventions in OSA management and other chronic conditions requiring long-term therapy adherence.

Trial Registration: ClinicalTrials.gov NCT06520592; https://clinicaltrials.gov/study/NCT06520592

International Registered Report Identifier (IRRID): PRR1-10.2196/69757

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(JMIR Res Protoc 2025;14:e69757) doi:10.2196/69757

KEYWORDS

obstructive sleep apnea; continuous positive airway pressure; augmented reality; adherence; feasibility

Introduction

Obstructive sleep apnea (OSA) is a prevalent sleep disorder characterized by repetitive episodes of upper airway obstruction during sleep, which results in low oxygen saturation or frequent awakenings [1]. It has been associated with significant health risks, including cardiovascular diseases [2], cognitive impairment [3], and decreased quality of life [4]. Continuous positive airway pressure (CPAP) therapy is a strongly recommended treatment for OSA according to the clinical practice guidelines of the American Academy of Sleep Medicine. It effectively mitigates the associated risks by maintaining airway patency during sleep [5]. However, adherence to CPAP therapy remains a significant challenge, as many patients struggle to use the device consistently due to physical discomfort [6] and lack of proper guidance or without follow-up care [7].

Guiding patients in disease-related knowledge through educational materials to change their adherence to medical treatment is a commonly used method in clinical practice [8]. However, the effectiveness of guiding middle-aged and older individuals through printed educational materials is often limited. Kim and Oh [9] conducted qualitative interviews with 16 frontline nurses in South Korea and attempted to examine the situation of older adults in receiving health education and health literacy through their perspective. The study found that older adults struggle to understand educational content due to declines in physical and cognitive functions.

The Information-Motivation-Behavioral Skills model suggests that patients' adherence behavior is driven by their level of information, motivation, and behavioral skills [10]. Augmented reality (AR) applications have the potential to significantly enhance patient adherence to therapeutic regimens through engagement and understanding [9,11]. AR applications can provide personalized real-time information in an engaging format. A systematic review and meta-analysis, which included 11 articles, found that AR can be a tool in physiotherapy to improve older adults' balance, especially in patients with Parkinson disease [11]. In addition, AR can enhance motivation through interactive features, such as progress tracking and gamification, which make the therapy experience more rewarding [12]. Ideally, by guiding patients in the correct use of their devices, AR can also enhance the behavioral skills necessary for successful adherence.

Previous studies have explored various interventions to improve CPAP adherence, including standardized care procedures [13], cognitive behavioral therapy [14], troubleshooting [15], and telemonitoring [16]. However, the integration of AR technology into CPAP management is a novel approach. Limited research has been conducted on the application of AR in this context, making this study one of the first to investigate its potential impact on OSA management. By addressing the gap in the literature, this study aims to contribute to the growing body of knowledge on innovative strategies to enhance adherence to CPAP therapy.

This study hypothesizes that AR-guided CPAP therapy can enhance patient engagement and understanding of CPAP therapy among patients with OSA, and patients receiving AR-guided CPAP therapy will show higher adherence rates compared to those receiving standard care.

Methods

Study Design

This parallel group randomized controlled trial is designed to evaluate the effectiveness of AR-guided CPAP therapy on patient adherence among individuals diagnosed with OSA. Participants will be randomly assigned to either the experimental group (AR-guided therapy) or the control group (standard care) by the blocking sample method. Aside from the AR component, both groups will receive identical standard care. An assistant researcher (Ms Ng) generated the random allocation sequence, case managers enrolled participants with OSA, and an assistant researcher (Ms Jhong) assigned participants to interventions. In this study, we will blind assessors and investigators. The study will follow participants over 6 months, with data collection points at baseline (T0), and follow-ups at 1 month (T1), 3 months (T2), and 6 months (T3) post intervention.

Participants

Patients with OSA will be randomly assigned to either the experimental group or the standard care group.

Inclusion Criteria

Our study will enroll adults 20 years or older diagnosed with moderate to severe OSA (Apnea-Hypopnea Index ≥15) confirmed by polysomnography who are CPAP therapy naive at the time of enrollment.

Exclusion Criteria

We will exclude those with previous use of positive pressure ventilators, a diagnosis of central sleep apnea, a presence of uncontrolled acute mental illness, or a terminal illness.

Sample Size

The sample size was determined based on a power analysis conducted for the CPAP adherence rate. Effect sizes were estimated to be 0.32 based on our previous findings, which indicated that 32.25% of CPAP-related side effects were associated with the CPAP interface [17]. A power of 0.85 was used to detect a significant difference at P=.05 (2-sided). Given the highly variable dropout rate for CPAP therapy, we aimed to accommodate a 20% dropout rate, which necessitated recruiting 80 participants, with 40 participants in each group.

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Experimental Group Receiving AR-Guided CPAP Therapy: Proposed System

Figure 1 illustrates the proposed system architecture, consisting of a camera module, an Edge-AI computing module, and a display module. The camera module captures the user's facial and hand images, while the Edge-AI computing module processes these images to detect relevant features and perform calculations to ensure a proper nasal mask fit and verify the accuracy of the wearing procedure. The display module presents the measurement results and offers real-time feedback on the recommended nasal mask size, following the mask sizing guidelines provided by ResMed [18].

Figure 1. Proposed system architecture.

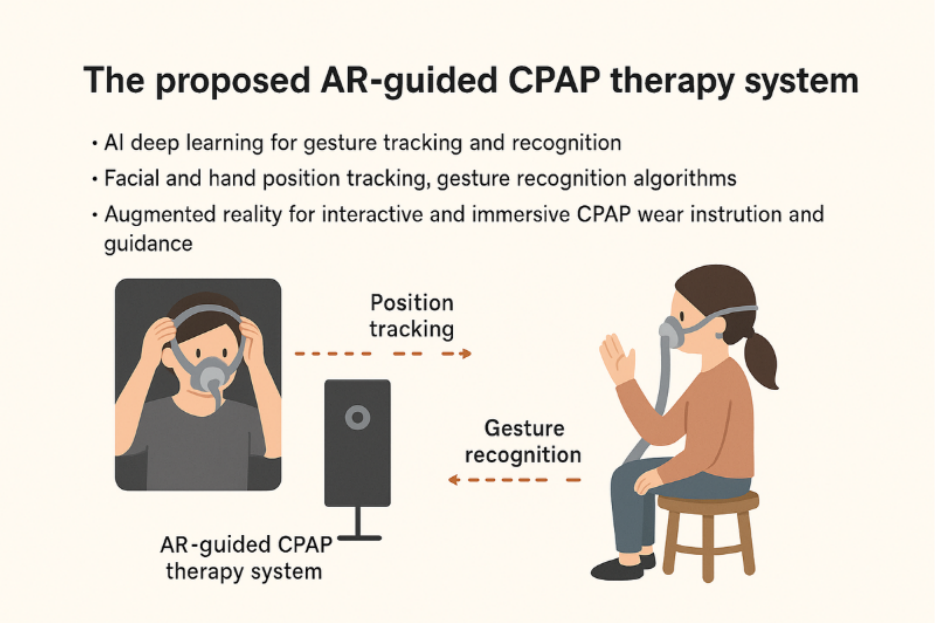

Standard Care Group

Participants assigned to the standard care group will have their mask size visually checked by a case manager, who will also teach them how to use the CPAP machine.

Primary Outcomes

Objective Measure: Adherence to CPAP Therapy

CPAP adherence will be monitored daily using AirView, a cloud-based remote monitoring system. The research team will explain the study objectives to participants and obtain their written consent to authorize ResMed to grant access to their CPAP cloud data. This approval will enable the research team to retrieve and analyze adherence data with company authorization.

Data from CPAP devices (eg, AirSense 10 AutoSet) will be collected at T1, T2, and T3, tracking the percentage of nights meeting adherence criteria. Adherence refers to the patient's adherence to CPAP therapy, which means using CPAP for more than 70% of the total sleep time during the night, with a minimum duration of 4 hours. The calculation method involves dividing the number of days with CPAP use exceeding 4 hours by the total number of days and multiplying by 100 to obtain the average percentage of CPAP use [19].

Subjective Measure: Adherence to CPAP Therapy Questionnaire

We developed a self-assessed CPAP adherence and comfort levels questionnaire to allow participants to track their daily adherence and comfort levels, providing a comprehensive overview of their subjective CPAP experience.

- Adherence is defined as using CPAP for at least 70% of total sleep time per night, with a minimum duration of 4 hours.
- Comfort levels are self-rated on a 0 to 10 scale, where 0 is extremely uncomfortable and 10 is extremely comfortable.
- If participants experience discomfort, they will be asked to document the specific reasons contributing to their discomfort (Multimedia Appendix 1).

This structured daily assessment enables a detailed evaluation of patient experiences, helping to identify potential barriers to CPAP use and providing valuable insights into factors influencing adherence and comfort over time.

Secondary Outcomes

Common Adverse Effects Associated With CPAP

Common discomforts of using CPAP were collected and categorized based on symptoms identified by Australian scholars Ghadiri and Grunstein [6].

Device Usability

At the end of the study, participants will fill out a system usability scale (Multimedia Appendix 2) to evaluate system usability. This scale is a questionnaire assessing the usability of emerging technologies or systems, consisting of 10 items scored from 0 to 4 (from strongly disagree to strongly agree). The overall score is then multiplied by 2.5, with a maximum score of 100. According to Sauro [20], based on nearly 500 studies, a score of 68 is used as the benchmark for the system

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usability assessment: if the score is greater than 68, it indicates that the system's usability is above 50%; if it is less than 68, the opposite is true.

Accuracy of Estimated Nasal Size

The AR system's recommended nasal size compared to the case manager's estimation shows an agreement rate approaching 95% at T0.

Time Required for CPAP Machine Use Education

We will calculate the time during the initial education session, hands-on training, patient questions and answers, and troubleshooting guidance at T1.

Covariates

Demographic Data

We will collect participants' gender, height, weight, waist circumference, blood pressure values, education level, presence of other comorbidities (eg, hypertension, diabetes, cardiovascular diseases, chronic obstructive pulmonary disease, asthma, cancer), smoking habits (none, once a week, once a month, once a year), drinking habits (none, once a week, once a month, once a year), exercise habits (none, once a week, once a month, once a year), history of being diagnosed with mental health disorders, napping habits, and the approximate duration of naps.

Clinical Indicators

The Apnea-Hypopnea Index, average blood oxygen saturation, and minimum blood oxygen saturation will be measured through polysomnography and a CPAP machine.

Procedure

Participants diagnosed with moderate to severe OSA through polysomnography will be assessed for their willingness to participate in the study by the principal investigator. Patients who agree to undergo CPAP therapy and sign the institutional review board permit will be referred to the clinical trial. A research assistant will then contact potential participants via telephone to reconfirm their willingness to enroll. Upon confirmation, the research assistant will assist in scheduling the clinical trial and coordinating regular follow-ups at T1, T2, and T3 to assess CPAP adherence and evaluate treatment-related adverse effects (Figure 2).

Figure 2. AR-guided CPAP therapy procedure followed in both the experimental group and the standard care group during the study. Data collection points were at baseline (T0), and follow-ups at 1 month (T1), 3 months (T2), and 6 months (T3) post intervention. AR: augmented reality; CPAP: continuously positive airway pressure; IRB: institutional review board; OSA: obstructive sleep apnea; Q&A: questions and answers.

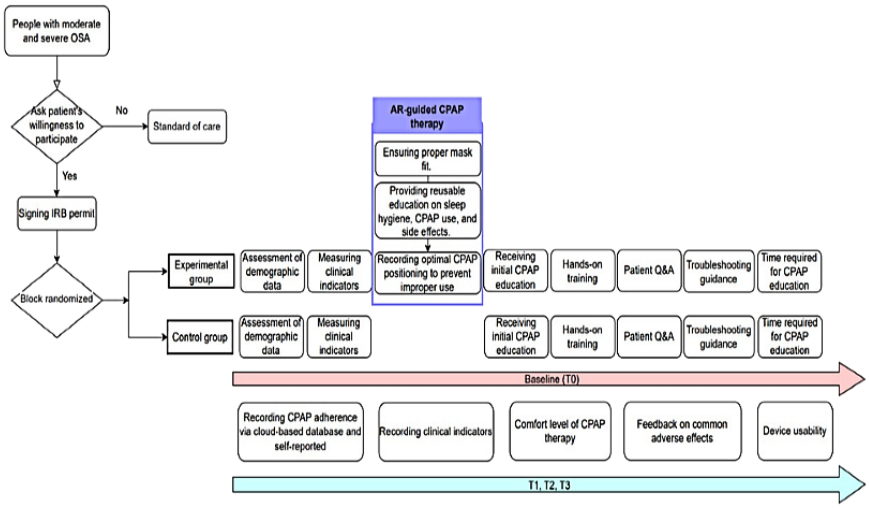

Ethical Considerations

Human Subject Ethics Review

This study was approved by the Institutional Review Board of National Cheng Kung University on March 1, 2023 (approval A-ER-111-531). The study adheres to all institutional guidelines and ethical principles outlined in the Declaration of Helsinki.

Informed Consent

All participants will provide written informed consent before enrollment. They will receive detailed explanations regarding the study objectives, procedures, and potential risks and benefits. Participants will have the right to withdraw from the study at any time without consequences.

Privacy and Confidentiality

All collected data will be anonymized and deidentified to protect participant privacy. Identifiable information will be securely stored and accessed only by authorized research personnel. Data will be reported in an aggregate format, ensuring that individual participants cannot be identified.

Compensation Details

Participants will receive financial compensation (US $6) for T2 and T3 participation. Besides that, they will be provided with comprehensive CPAP education and follow-up support as part of the study. No additional costs will be incurred by participants for their involvement.

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No Identifiable Features of Research Participants

We confirm that no identifiable information of individual participants or users is present in any images included in the manuscript or supplementary materials.

Data Analysis

To evaluate the effectiveness of AR-guided CPAP therapy on telemonitored adherence rates and self-reported CPAP adherence, a mixed-effects model for repeated measures will be used. This model accounts for missing data and enables comparisons of adherence rates between the two groups at T0, T1, T2, and T3. Correlation analyses will be conducted between objective CPAP adherence and the subjective adherence assessment. Data analysis was performed using SPSS version 22.0 (IBM Corp).

Results

This randomized controlled trial is funded by the Ministry of Science and Technology Council, Taiwan, from August 2023 to July 2026. The trial was registered in August 2024 (ClinicalTrials.gov NCT06520592). Participant recruitment is scheduled to commence in April 2025, with follow-up assessments planned at 1 month (T1), 3 months (T2), and 6 months (T3) post intervention.

We plan to enroll 40 participants by September 2025, representing 50% of the targeted sample size of 80. Preliminary analyses of baseline adherence and usability data are underway. The trial remains on schedule, with the final data collection anticipated in December 2025 and results expected to be published by Fall 2026.

Discussion

Summary of Principal Findings

This prospective observational study is anticipated to yield valuable insights into the effectiveness of AR-guided CPAP therapy in improving adherence among patients with OSA. Specifically, the study focuses on facilitating the selection of appropriately fitting mask sizes, providing hands-on training on proper mask use, and offering troubleshooting support. If the hypothesis is validated, AR technology could emerge as a powerful tool to enhance patient engagement and address machine interface barriers to CPAP adherence, such as discomfort, leakage, and lack of motivation. The study's results could have broader implications for the management of OSA and other chronic conditions that require long-term adherence to therapeutic regimens.

Comparison to Prior Work

Previous studies have explored telemonitoring and cognitive behavioral therapy to improve CPAP adherence, but research integrating AR technology into CPAP management remains limited. By addressing this gap, our study contributes to the growing evidence on technology-assisted interventions for chronic disease management.

Strengths and Limitations

A strength of this study is the comprehensive assessment of adherence, incorporating both objective adherence tracking and subjective self-reported adherence evaluation. This multidimensional approach enhances the study's ability to identify barriers to CPAP adherence and potential intervention strategies to improve long-term compliance. Additionally, this study has a randomized controlled design, which enhances the validity and reliability of the findings. Another strength is that the integration of AR technology allows for real-time patient education and support, which has the potential to improve CPAP adherence through enhanced engagement and interactive learning.

However, some potential limitations should be considered. First, generalizability may be limited due to the specific population studied. Since the study is conducted in a single region with a particular demographic profile, findings may not be fully applicable to other populations with different cultural, socioeconomic, or health care structures. Second, the novelty of AR technology may present implementation challenges, particularly among older adults or patients with low technology literacy, potentially limiting the accessibility and effectiveness of the intervention. Lastly, variations in AR device compatibility across different CPAP models could pose practical barriers to widespread adoption.

Future Directions

To address these limitations, future research should explore multicenter studies across diverse populations and investigate strategies to enhance AR accessibility for less tech-savvy users, such as simplified interfaces or additional training modules.

Dissemination Plan

The results of this study will be disseminated through peer-reviewed publications, conference presentations, and clinical workshops. Additionally, findings may inform the development of AR-based educational modules for sleep medicine practitioners.

Conclusions

This study is expected to provide valuable insights into the role of AR-guided CPAP therapy in improving adherence among patients with OSA. By integrating real-time interactive guidance, the intervention aims to enhance patient engagement, improve mask fitting, and address adherence barriers such as discomfort and lack of motivation. While findings from this study may support the use of technology-driven interventions in CPAP management, further research will be needed to explore long-term effectiveness, broader applicability across different populations, and strategies to optimize accessibility for patients with lower technology literacy. If validated, this study could inform future clinical practice by integrating AR-based patient education and support tools into standard CPAP care, potentially improving adherence and long-term treatment outcomes for patients with OSA.

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Acknowledgments

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Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' Contributions

Conceptualization: MCC, YCC, CYL
Data curation: MCC, YCC
Formal analysis: MCC, YCC
Writing – original draft: MCC
Methodology: YCC
Supervision: YCC
Validation: YCC
Writing – review and editing: YCC, CYL
Investigation: CYL
Resources: CYL
Visualization: CYL
All authors have read and agreed to the published version of the manuscript. We confirm that generative artificial intelligence tools, specifically ChatGPT, were used solely to assist with language editing and improving sentence clarity. The authors developed all core content, including study design, data analysis, interpretation, and conclusions.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Subjective Questionnaire: CPAP Adherence and Comfort Assessment.
[DOCX File , 18 KB - resprot_v14i1e69757_app1.docx]

Multimedia Appendix 2
System Usability Scale.
[DOCX File , 15 KB - resprot_v14i1e69757_app2.docx]

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Abbreviations

AR: augmented reality
CPAP: continuous positive airway pressure
OSA: obstructive sleep apnea

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Protocol

Cognitive Behavioral Immersion for Depression: Protocol for a Three-Arm Randomized Controlled Trial of Peer-Based Coaching in the Metaverse

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Abstract

Background: Depression and anxiety are among the most common mental health concerns globally. Efficacious treatments such as cognitive behavioral therapy exist but remain difficult to access and scale. Cognitive behavioral immersion (CBI)—a cognitive behavioral skills training intervention delivered by peer coaches in the metaverse—has been developed to address these barriers. CBI can be used through a virtual reality headset or via flat-screen devices such as phones, tablets, or computers. Pilot data have established its usability among participants with clinical levels of depression and anxiety. However, more research is needed to determine whether CBI causes decreases in these symptoms and how delivery via virtual reality compares to flat-screen devices.

Objective: This protocol aims to conduct a randomized controlled trial evaluating the efficacy of immersive CBI accessed via a virtual reality headset (CBI-VR) as compared to a less immersive (but more accessible) CBI condition accessed via a flat-screen device (CBI-FS) and each to a delayed access control (DAC).

Methods: A total of 306 adults experiencing clinical levels of depressive symptoms are being recruited nationally to participate in this web-based trial. Participants will be randomized according to a 1:1:1 ratio to one of three conditions: (1) CBI-VR, (2) CBI-FS, and (3) DAC. The CBI program consists of eight weekly 60-minute group sessions led by trained peer coaches who teach cognitive behavioral skills. The acute period of each condition will last 8 weeks with a follow-up period of 6 months. The primary outcome is depressive symptoms; secondary outcomes are anxiety symptoms and quality of life. Outcomes will be assessed once at baseline, weekly during the course of the intervention, and monthly during follow-ups. We will use hierarchical linear models to assess differences in the rate of symptom change among conditions. We will also explore potential prognostic (demographics and immersion) and prescriptive (cognitive behavioral skills, group alliance, and program engagement) predictors, as well as potential mechanisms (cognitive change and social support) of response.

Results: We hypothesize that participants randomized to either CBI group will experience greater symptom improvement than those in DAC and that CBI-VR participants will improve more than CBI-FS participants. This study was funded in September 2023. Data collection began in February 2024. As of January 2025, all 306 participants have been enrolled. Data collection should conclude by September 2025. Data have not yet been analyzed. Expected results to be submitted for publication in the winter of 2025.

Conclusions: This trial will determine if CBI via either device is efficacious as compared to DAC and whether virtual reality enhances outcomes. Findings will contribute to the literature on using the metaverse and virtual reality to facilitate effective accessible mental health interventions, particularly for depression.

Trial Registration: ClinicalTrials.gov NCT06418997; https://clinicaltrials.gov/study/NCT06418997

International Registered Report Identifier (IRRID): DERR1-10.2196/65970

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(JMIR Res Protoc 2025;14:e65970) doi:10.2196/65970

KEYWORDS

cognitive behavioral immersion; virtual reality; anxiety; mental health; depression; stress; protocol; randomized controlled trial; RCT; coaching; metaverse; behavioral therapy; skills training intervention

Introduction

Background

Approximately 280 million people worldwide are experiencing depression [1], and nearly half of those people also experience comorbid anxiety [2]. Symptoms of either disorder can cause substantial distress and impair functioning across all domains of life. Worse yet, the prevalence and severity of these disorders are growing [3]. Despite the increasing evidence base of effective interventions, including cognitive behavioral therapy (CBT), the prevalence of depression and other mental health disorders continues to rise [4]. Accordingly, there is a demand for effective, accessible, and scalable interventions to manage these mental health conditions.

CBT is one of the most effective interventions for depression and anxiety [5]. The model underlying this intervention describes how one's cognitions influence and are influenced by their emotional, behavioral, and even physiological consequences [6]. Based on this model, CBT teaches clients a variety of cognitive behavioral skills to identify, evaluate, and change maladaptive thoughts and behavioral patterns to indirectly change emotions. CBT has been deemed an empirically supported treatment through direct comparisons to waitlist controls and other bona fide interventions such as antidepressant medications [7]. Not only is CBT generally effective during its acute phase but it also has an enduring effect on symptoms that lasts beyond the end of treatment [8]. Despite its many strengths, CBT-oriented care is often difficult to access and scale due to the lack of trained providers, high costs, and stigma associated with seeking mental health care [9].

Two major innovations in the mental health care field could help to address the aforementioned problems of accessibility—the deployment of lay therapists and the use of technology. First, nonprofessional lay therapists (hereafter referred to as "coaches") can be trained to provide peer support and teach cognitive behavioral skills. A primary driver of the effects seen in CBT is clients' use of the specific cognitive behavioral skills taught [10,11], suggesting that cognitive behavioral skills may be a worthwhile training target for mental health support. Prior research has shown that individuals without any prior formal professional training can be taught to deliver effective cognitive behavioral interventions [12], therefore, reducing the burden on and expense of the limited workforce of highly trained, specialized therapists.

Second, digital mental health interventions can deliver cognitive behavioral skills training nearly anywhere at any time and have outcomes comparable to face-to-face CBT [13-18]. Although technology can remove the need for therapists (eg, through completely self-guided interventions or provided through the use of artificial intelligence–based computerized cognitive behavioral programs), digital CBT programs have experienced high dropout rates, with reviews reporting average dropout rates of 32%-74% depending on dropout definition and level of support [19-21]. Fortunately, human support provided via peers or coaches can help improve accountability, engagement, and efficacy [22]. Furthermore, human-mediated digital mental health interventions can help promote nonspecific effects that may contribute to outcomes [23]. Social connection has been posited as a key contributor to engagement in digital mental health interventions [24], indicating that digital interventions must strike a balance between accessibility and human interaction in order to be scalable while remaining effective. While existing CBT programs have aimed to leverage lay therapists and digital modalities to deliver interventions remotely, at scale, and at a lower cost, their uptake and effectiveness remain inconsistent. This highlights the clear need for innovative approaches that can enhance both engagement and efficacy.

Recently, the technology of the metaverse, defined as internet-connected social digital environments that allow end users to interact as avatars, has been adopted to facilitate digital mental health interventions delivered by humans [25]. The metaverse can transport an individual into a personalized 3D digital world that promotes immersion, the extent to which an individual perceives, experiences, and interacts with a digital environment as if it were a real environment [26]. Individuals can create an anonymous avatar and become immersed in a world where they communicate by speaking to other people, each of whom is also represented by an avatar. This technology affords a unique opportunity to deliver an intervention that is simultaneously immersive and anonymous, potentially allowing individuals to feel more comfortable being vulnerable [25]. The level of anonymity that accompanies the use of avatars may also attract end users who typically do not seek out mental health care, whether due to shyness or stigma [25,27]. Finally, the digital nature of the metaverse can reduce barriers to access related to cost, lack of trained providers, or other physical hurdles. Metaverse environments can be accessed through commonly owned flat-screen devices (eg, computer or phone) or through virtual reality technology (ie, head-mounted displays that generate graphics in real time that simulate a 360° view of an environment that one can interact with using hand-held controllers). Virtual reality enables end users to feel strongly immersed in a 3D space, which can increase the sense of presence in a particular environment despite being physically situated in a different place [28]. The metaverse is a suitable setting for coach-based mental health interventions designed to facilitate cognitive behavioral skills training, integrating digital facilitation of effective mental health interventions with realistic anonymous interpersonal interactions. Despite growing interest in virtual reality and metaverse apps for mental health, research on integrating virtual reality and the metaverse with coach-supported CBT skills remains limited.

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Cognitive behavioral immersion (CBI), a synchronous cognitive behavioral skills group training program delivered by coaches in the metaverse developed by Innerworld, Inc, is the first app to our knowledge that bridges virtual reality, the metaverse, and CBT skills in the pursuit of delivering efficacious, accessible, and scalable mental health care [25]. A pilot study provided support for its feasibility among a group of individuals in recovery from a substance use disorder [25]. A second study on this intervention demonstrated improvement in depression and anxiety symptoms associated with CBI engagement [29]. That study found that internet-based social support was associated with depressive symptom improvement, while the use of virtual reality (vs a flat-screen device) with the intervention was associated with greater anxiety symptom improvement. While this preliminary support for the use of CBI is promising, a direct comparison of this modality against a control has not yet been conducted, and its absolute efficacy is unknown. In addition, it is unknown whether accessing CBI via immersive virtual reality confers any advantage over more readily accessible, less immersive flat-screen devices.

Objectives

This study is designed to address the following research questions: (1) is CBI efficacious (better than its absence)? and (2) does immersive virtual reality confer any advantage over and above accessing CBI via less immersive flat-screen devices? In line with these questions, this study aims to compare immersive CBI accessed via virtual reality (CBI-VR) to a delayed access control (DAC) condition and less immersive CBI accessed via flat-screen devices (CBI-FS) in a randomized controlled trial. We predict that participants randomized to CBI-VR will experience greater clinical and functional improvement than participants randomized to the other conditions. In addition to this primary aim, we plan to explore predictors of response regardless of condition (prognostic), prescriptive indices that predict differential program response (moderators), and causal mechanisms of clinical and functional change across conditions (mediators).

Methods

Study Design

This study is a three-arm unblinded randomized controlled trial (NCT06418997). Participants are randomly assigned to one of three groups in a 1:1:1 ratio: CBI-VR, CBI-FS, or DAC. In the CBI-VR and CBI-FS conditions, participants participate in up to eight weekly intervention sessions. Those in the CBI-VR condition will be mailed Meta Quest 3 headsets to participate in the intervention, while those in the CBI-FS condition will use their own existing flat-screen device (such as a personal computer, tablet, or smartphone) to participate in the intervention. Participants in the DAC condition will be asked not to access the intervention for 8 weeks but will then be provided with information on and encouraged to access the same intervention. Outcomes will be monitored weekly throughout the 8-week acute phase and monthly for 6 months during follow-ups. All procedures will be conducted on web-based platforms. See Figure 1 for a flowchart of study procedures. Reporting in the protocol was based on the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) and SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklists (Multimedia Appendices 1 and 2).

Figure 1. Flowchart of study procedures. CBI: cognitive behavioral immersion.

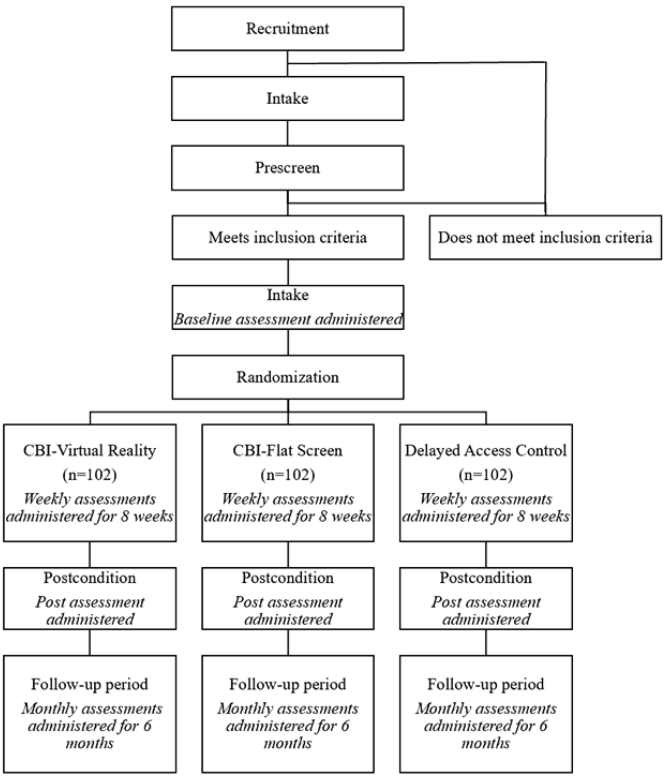

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Ethical Considerations

All study procedures received human participant ethics review approval from the University of Southern California's (USC) Institutional Review Board (UP-23-00491). As part of the approved procedures, all participants will provide informed consent prior to beginning the study and be made aware that they can stop their participation in the study at any time. All data will be collected securely through REDCap (Research Electronic Data Capture; Vanderbilt University) [30,31]. After the study is completed, all data will be deidentified. Participants will be compensated with electronic gift cards sent to their email for completion of study surveys. Participants across all conditions will also receive a new Meta Quest 3 virtual reality headset to keep as part of study participation. Distribution of the headset is dependent on study randomization; those randomized to the CBI-VR condition receive a headset prior to starting their 8-week condition, whereas participants in the other two conditions receive the headset after completion of the 8-week acute condition.

Participants

We are recruiting a sample of 306 individuals from across the United States who endorse clinical levels of depression symptoms. Participants are recruited through paid advertisements on popular social media apps (eg, Facebook and Instagram), posts on clinical trial or research study registries (eg, ClinicalTrials.gov), through our research lab's website, and by word of mouth.

Inclusion and Exclusion Criteria

The inclusion criteria for this study are (1) clinical level of depressive symptoms (indicated by a score of ≥10 on the 9-item Patient Health Questionnaire [PHQ-9] [32]), (2) 18 years or older, (3) able and willing to give informed consent, (4) personal computer with a stable internet connection that can run the CBI application, and (5) able to speak and read English. The exclusion criterion for this study is elevated suicide risk at the baseline assessment that precludes inclusion in the study (see Safety Monitoring section for more information).

Prescreening and Intake Procedures

All prescreening and intake procedures will be managed by a research team at USC. Interested individuals will be directed to a link where they will complete an initial prescreening questionnaire hosted on REDCap containing a brief description of the study, eligibility questions, and the PHQ-9. Those who meet initial inclusion criteria will be emailed a link to schedule a 20-minute intake session conducted via Zoom (Zoom Video Communications).

Prior to attending their intake session, each individual will be asked to sign the study consent form via the REDCap eConsent module and to complete a set of intake measures via a secure REDCap link. During the intake session, study personnel will explain the study; answer any questions; confirm participant eligibility; record the participant's name, address, and mobile phone number for verifying identity and for mailing the virtual reality headset; collect the participant's availability for attending a CBI intervention group, and secure informed consent. After completing the intake session, participants will be randomized to one of three conditions.

Participants randomized to the CBI-VR or CBI-FS conditions will be sent an email alerting them of their study conditions and providing directions on how to access the application hosting the CBI intervention. Prior to their first intervention session, participants will take part in a web-based tutorial about how to navigate the CBI intervention and may attend an optional onboarding session with study personnel if additional support is needed navigating the CBI intervention (and virtual reality headset if randomized to the CBI-VR condition). DAC participants will also be emailed to inform them of their study condition, when they can expect to begin receiving surveys, and when they can expect to receive compensation.

Randomization

Participants are randomized to one of the three groups in a 1:1:1 ratio using a random number generation Python script. The seed Python uses to perform random generation is predetermined for each "wave" of participants to aid replicability. Once the number of recruited participants in a wave has reached the cap indicated by coach and researcher availability, recruitment will be paused, and that wave of participants will be randomly assigned to a group and commence their 8-week condition. This process will repeat every few weeks until the planned sample size of 306 is reached. Randomization will be done in blocks so that participant distribution across each group per wave is equated to ensure CBI classes during each wave have sufficient scheduled participants. The randomization procedures are conducted by the research team at USC.

Intervention

The CBI intervention will be hosted on the Innerworld app. Innerworld is an English language app freely available for download across several platforms (eg, Windows, Meta Quest headsets, iOS, and Android). Innerworld trains adults who do not necessarily have prior professional training to serve as CBI coaches. Each coach undergoes an intensive 20-hour training program spread over 5 days led by Innerworld support staff to learn how to facilitate cognitive behavioral skills groups. Coaches will be trained to lead an 8-week CBI for depression course, which was developed by investigators who are experts in CBT. See Table 1 for a condensed outline of the coach training program. After completion of the fifth training session, each coach must cofacilitate at least one real meeting in the presence of a trainer (ie, a coach who has extensive experience leading Innerworld groups). The coach is evaluated by the trainer and provided with feedback. To maintain coach adherence to the intervention throughout the trial, coaches will be required to attend weekly supervision led by Innerworld support staff and team investigators. We will also ask participants to complete the Group Session Rating Scale to assess group quality.

The CBI for depression intervention involves participants meeting in groups of up to 10 in which they learn lessons on various strategies to cope with depression based on cognitive behavioral theory [6]. Each group meets for 1 hour once a week for 8 weeks. In addition, user feedback during pilot testing led

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to the implementation of an "a la carte" model that allows participants to attend a rotating schedule of makeup sessions. Peer coaches will follow a detailed manual describing the content to be followed for each session. See Table 2 for a condensed outline of the session content. Behavioral strategies include but are not limited to activity scheduling, problem-solving, and assertion training. Each session begins with setting the agenda and reviewing homework from the previous session. Cognitive strategies include but are not limited to identifying the connections between thoughts, feelings, physiology, and behaviors, and catching and examining negative automatic thoughts. Each session ends with a session summary, homework assignment, and feedback about the session. If participants cannot attend their assigned session, participants are encouraged to attend a makeup for that session via email prompts sent by the research team. If participants need support navigating the app or using their virtual reality headset after beginning the intervention, they will be directed to connect with the app support staff, who are available as avatars in the app 24/7.

Table 1. Outline of coach training.

	Training content	Training methods	Homework	Hours
1	Introductions; therapy versus peer support; types of meetings; CBI[a] model; motivational interviewing; motivational interviewing roleplays	Group-based discussion; roleplays	Shadow two Innerworld meetings and send summaries to trainer	4
2	Review session 1 homework; intro to leading a meeting; overview of CBI tools	Didactics; live demonstrations; partner role-plays; group-based Q&A	Shadow two meetings; practice skills at home	4
3	Review session 2 homework; how to lead a meeting; how to teach the tools; continue to practice CBI tools	Live demonstrations; partner role-plays; group based Q&A	Shadow two meetings; practice skills with partner	4
4	Review session 3 homework; how to deal with trolls or minors; moderation tools; crisis situations; how to administer surveys	Live demonstrations; group-based Q&A; partner role-plays	Shadow two meetings; review crisis protocol	4
5	Review session 4 homework; practice roleplays and check-ins; discuss next steps to facilitating meetings	Group-based Q&A; group role-plays	Set up meeting for facilitation evaluation	4

[a]CBI: cognitive behavioral immersion.

Table 2. Outline of session content.

Session	Topic	Homework
1	Introduction to CBI[a] model: icebreakers, practice with CBI conceptualization	Mood tracking
2	Behavioral activation and mood tracking: psychoeducation on mood tracking, behavioral activation, SMART[b] goals	SMART goals
3	Identifying automatic thoughts: psychoeducation on automatic thoughts, cognitive distortions, introduction to thought record	Three-column thought record
4	Reframing automatic thoughts: catching distortions and reframing beliefs, individual practice with thought record and review as a group	Four-column thought record
5	Identifying and reframing core beliefs: psychoeducation on core beliefs, continued practice with thought record	Four-column thought record
6	Assertion training: psychoeducation on assertiveness curve tool and group role-plays to practice assertion skills	Assertion practice
7	Performance and arousal: overview of Yerkes-Dodson curve and how to target optimal arousal	Yerkes-Dodson practice
8	Relapse prevention plan and next steps: completing relapse prevention plan, course feedback, discuss key takeaways	Relapse prevention

[a]CBI: cognitive behavioral immersion.

[b]SMART: Specific, Measurable, Achievable, Relevant, and Time-Bound.

Safety Monitoring

We will take precautions to monitor the safety of the study participants. First, all coaches and study investigators at USC will undergo training on how to manage crisis situations. During each CBI session, coaches will also monitor any discussion participants share regarding their safety in relation to themselves and others. We will also establish automatic thresholds on REDCap for PHQ-9 and 7-item Generalized Anxiety Disorder (GAD-7) assessments completed before, during, and after baseline. If a participant meets the criteria for suicidality (a 2 or above on the PHQ-9 suicide item), crisis resources will be automatically displayed and participants will be prompted to complete the Columbia-Suicide Severity Rating Scale (C-SSRS) Self-Report [33]. High-risk participants (scoring 4 or above on the C-SSRS Self Report) will be contacted by the research team

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via email to schedule a Zoom call for further assessment using the C-SSRS interview. Participants scoring a 4 or above on the C-SSRS interview will be excluded from the study due to sufficiently elevated suicide risk and will be provided with crisis and mental health resources. If imminent risk is present (C-SSRS interview score of 5), a lead study investigator (IDE) will evaluate the situation and contact local emergency services if deemed necessary. Participants with significantly worsening symptoms (a 20% increase on PHQ-9 or GAD-7 and a score of 15 or above) will be contacted by USC study personnel via email for a brief check-in and provided with mental health referrals. A copy of these referrals will also be publicly posted in the Innerworld app at all times.

All adverse incidents will be documented and immediately reported to lead study investigators, who will then follow them to a satisfactory resolution. They will distinguish serious adverse events from adverse events not judged to be serious using the guidance and definitions provided by the National Institutes of Health notices. All serious adverse events will be reported to the USC Institutional Review Board and the study's independent Data and Safety Monitoring Board.

Measures

Primary Outcome Measures

PHQ-9 will be used to assess depressive symptoms. The PHQ-9 [32] is a 9-item self-report measure with strong psychometric properties that mirrors the nine criteria for major depressive disorder in the Diagnostic and Statistical Manual, 4th edition. Scores range from 0 to 27, with higher scores indicating great severity.

The GAD-7 [34] will be used to assess participants' generalized anxiety symptoms. The GAD-7 is a psychometrically strong 7-item self-report measure based on the diagnostic criteria for generalized anxiety disorder from the *Diagnostic and Statistical Manual of Mental Disorders* (Fourth Edition). Scores range from 0 to 21, with higher scores indicating greater severity.

Exploratory Measures

Outcomes

The World Health Organization Quality of Life-Brief [35] is a 26-item self-report measure of the quality of life within the domains of physical health, psychological health, social relationships, and environment. During the follow-up period, we will use only the first item to assess overall quality of life. Scores are transformed on a scale from 0 to 100, with higher scores indicating a higher quality of life. This measure has strong psychometric properties.

Prognostic Indices

The Competencies of Cognitive Therapy Scale is a 29-item self-report measure of three areas of cognitive behavioral skill competency: behavioral activation, automatic thoughts, and core beliefs [10]. Items are measured on 7-point scales, with higher scores indicating greater skill use. This measure has demonstrated strong psychometric properties.

The Group Session Rating Scale [36] is a 4-item measure that assesses group alliance and the quality of helper skills. Total scores range from 4 to 40 with higher scores indicating greater group alliance. This measure has demonstrated strong psychometric properties.

The Innerworld app will measure program engagement using passive user platform engagement (eg, sessions attended, minutes logged in, and type of device).

Prescriptive Indices

The Demographics Questionnaire is a basic demographic information survey that includes age, sex, gender identity, sexual orientation, race, ethnicity, educational attainment, employment or occupation, technology experience, past therapy experience, and prior diagnosis, among other variables.

The Immersion Questionnaire, adapted from a 3-item measure of social presence from Bailenson et al [37] and a 5-item measure of environmental presence from Fox et al [38], will be used to assess the degree to which the participant feels immersed in the metaverse.

Mechanisms

The Cognitive Change Immediate Scale [11] is a 5-item measure designed to assess participants' experience of cognitive change and use of cognitive skills during sessions. Items are measured on a 7-point Likert scale, where lower scores indicate less agreement. This measure has demonstrated acceptable psychometric properties.

The Online Social Support Scale [39] is a 40-item scale with strong psychometric properties that assesses the level of social support participants receive from web-based sessions. We plan to use a 30-item version of the scale, measuring constructs of esteem or emotional support, social companionship, and informational support. Each item is scored from 1 to 5, with higher scores indicating a greater sense of social support.

Storage and Timing of Assessments

All assessments will be managed by a research team at USC and securely collected using REDCap. All participants regardless of condition will receive the same set of web-based surveys at the same time points apart from the two session-related assessments (Group Session Rating Scale and Competencies of Cognitive Therapy Scale). These two session assessments will not be given to the DAC participants because they do not complete sessions during their 8-week condition. In the case that a participant does not complete a survey, study personnel will send up to three reminder emails over the course of 1 week post survey invitation to complete the uncompleted survey. See Table 3 for the assessment schedule.

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Table 3. Assessment schedule.

Measures	Prescreen	Intake	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Week 8	Post	Follow up
Screen												
Prescreen	✓											
Outcome												
PHQ-9[a]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
GAD-7[b]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
WHO[c] Quality of Life-Brief		✓									✓	✓[d]
Prognostic												
Competencies of Cognitive Therapy Scale		✓									✓	
Group Session Rating Scale			✓	✓	✓	✓	✓	✓	✓	✓		
Program engagement[e]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Prescriptive												
Demographics Questionnaire		✓										✓[f]
Immersion Questionnaire						✓					✓	
Mechanism												
Cognitive Change Immediate Scale			✓	✓	✓	✓	✓	✓	✓	✓		
Online Social Support Scale		✓				✓					✓	

[a]PHQ-9: 9-item Patient Health Questionnaire.

[b]GAD-7: 7-item Generalized Anxiety Disorder.

[c]WHO: World Health Organization.

[d]Only the first item from this measure is administered during the follow-up period.

[e]Continuous passive data collection.

[f]Participants will only be asked questions pertaining to changes in psychiatric medication or other psychological treatment during the follow-up period.

Statistical Analysis

Descriptive Statistics

Data analysis will primarily use R statistical software (version 4.4.2; R Foundation for Statistical Computing) supplemented with other programs as needed. Theory-driven procedures (ie, inferential statistics) will use 2-tailed tests, $\alpha<.05$, and power >80%. Descriptive statistics, including histograms, will be computed for each study variable, along with 95% bootstrap CIs. Data transformations will be made as needed. Depending on the distributional properties of variables, it may be necessary to use nonparametric statistics or generalized models with a link function to accommodate nonnormal distributions.

Primary Analysis

The main analytic approach will be a longitudinal random coefficients slope-as-outcome hierarchical linear model (HLM) conducted on the intent-to-treat sample. HLM is required for exploring the longitudinal nature of the data because repeated measurement of participants violates ANOVA's assumption of independent errors. To control for correlated errors within participants, the model estimates an individual growth curve for each participant [40]. Advantages of this method over classical approaches include (1) repeated measurements increase statistical power, (2) shape of change over time is described, (3) missing values and unequal time intervals between measures for different participants can be handled, and (4) psychometric problems with change scores are avoided.

This study requires a 2-level HLM to represent multiple time points for each individual. Level 1, within participant, represents each participant's time-varying symptoms as an individual linear trajectory. Level 2 uses individual fixed characteristics (eg, condition arm) to predict individual growth parameters (ie, participant's intercept and slope). In this regression framework, we can then add covariates to ask more nuanced questions, observe interaction effects, and increase power by reducing error variance. We expect to estimate distinct linear slopes during the 8-week period (from baseline to postcondition) and the 6-month follow-up period (from postcondition to 6-month follow-up). Therefore, we plan to specify time in a piecewise manner to allow for separate slope estimates for the active condition and follow-up periods within the same regression model. This allows us to assess acute and long-term condition effects across the full duration of the trial.

Under the HLM framework, we will examine whether CBI-VR produces better clinical and functional outcomes compared to

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the CBI-FS and DAC conditions in terms of differences in trajectories (ie, slopes) and outcomes at each timepoint (ie, least-squares means and pairwise contrasts). Separate regression models will be used for each of the outcome variables (depression, anxiety, and quality of life). To examine differences in slopes, the primary effect of interest in the HLM model will be the Condition (CBI-VR, CBI-FS, and DAC) × Time (active condition and follow up) interaction effect. Using a piecewise specification of time, the models will yield estimates for the Condition × Time interaction effect during the acute condition and follow-up periods, corresponding to detecting acute and long-term differences in condition response (ie, slopes). We will also examine absolute change in outcome variables and differences in outcome variables by the condition at each timepoint through estimation of marginal or least-squares means and pairwise contrasts at each timepoint. This analysis will inform when outcomes start to differ during the active condition and the subsequent follow-up.

Exploratory Analysis

To explore baseline indices that predict general program response, we will enter proposed prognostic variables as predictors (ie, covariates) in HLM models using a stepwise approach.

To explore baseline indices that predict differential condition response, hypothesized prescriptive variables will be entered as potential moderators of program response in the HLM models. Specifically, separate Prescriptive Variable × Time interaction effects will be assessed in each HLM model. Again, the piecewise specification of time will allow for the prescriptive variables to be tested and identified during the active condition and follow-up periods.

To identify mechanisms of change of clinical and functional change across conditions, we will test for mediation of proposed mechanisms in the longitudinal framework by specifying hypothesized mediators as time-varying random effects. Estimation and inference for this time-varying mediation model will allow mediation effects to vary as a function of time. This method is suitable for detecting processes by which the intervention affects outcomes, as proposed mediators will be collected at multiple timepoints throughout the trial.

Sample Size

A longitudinal power analysis was conducted using the "powerlmm" package in R Statistical Software with $\alpha<.05$, 2-tailed, and power >80%. Power analyses were focused on the ability to detect a medium effect size (Cohen d=0.50) at postcondition in the context of a 2-level random coefficients HLM. Given that the primary contrast of interest would be that between CBI and the other study conditions, calculations were focused on detecting significant differences between two active conditions. Where study parameters in this 2-level model were not yet known, we used standard values and varied parameters to approximate an effective sample size. We specified eight equally spaced timepoints, the amount of baseline variance at the subject level at 0.50, and allowed the ratio of the random slope variance to the within-subject variance to vary from 0.02 to 0.05 in increments of 0.01. Based on typical rates of drop out in digital CBT treatment, the rate of drop out was set at 25%. With anticipated missing data, the sample size estimate in each study arm varied from 65 to 138, yielding an average of 102. It is also recommended that power calculations should be based on the minimum detectable effect size or smallest difference between conditions that one would be willing to fail to detect [41]. We assessed this using the "PowerUpR" package (v1.1.0) [42] in R Statistical Software. Using the parameters specified above, we estimated a minimum detectable effect size of 0.26 (95% CI 0.08-0.44) with 102 in each study arm and a minimum detectable effect size of 0.22 (95% CI 0.07-0.37) with 138 in each study arm. With findings from Ezawa et al [29], we anticipate differences between conditions that will be considerably larger. Thus, a total sample size of 306 (n=102 in each study arm) will be effective for detecting meaningful differences in outcomes between CBI and the other conditions.

Results

This study was funded in September 2023. Recruitment of study participants began in February 2024. As of January 2025, 306 participants have been enrolled. Data collection is expected to be completed by September 2025. Data have not yet been analyzed. We plan to submit initial results for publication in a peer-reviewed scientific journal and share them with ClinicalTrials.gov in the winter of 2025.

Discussion

Overview

This study will be the first randomized controlled trial to test the efficacy of CBI. While the cognitive behavioral skills being taught and the therapeutic framework of peer support are each supported empirically, this study investigates an intervention that integrates these components in a novel environment (the metaverse) and compares its efficacy to a minimal treatment control condition. This study will also examine the relative efficacy of accessing the coach-led cognitive behavioral skills training program via immersive virtual reality technology versus less immersive flat-screen devices. We anticipate that participants randomized to both CBI conditions will experience improvements in depression symptoms, anxiety symptoms, and quality of life. We also predict that participants who access the program through virtual reality will experience more positive outcomes than those who access the program through flat-screen devices. Furthermore, we will explore a variety of prognostic variables (ie, cognitive behavioral skills, group alliance, and program engagement), prescriptive variables (ie, demographics and immersion), and mechanisms (ie, cognitive change and social support) of program response.

The findings from this study will test the efficacy of this intervention relative to its absence and determine if and how the access platform affects efficacy. This study will also help to determine if there is a benefit to the increased cost of disseminating CBI through virtual reality headsets versus through devices that many people may already own. If deemed efficacious, this intervention can be promoted to scale and subsequently increase access to effective mental health interventions.

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Potential Challenges

We anticipate some potential challenges. The primary challenge we foresee is a high dropout rate given an elevated dropout rate among digital interventions in prior research [43]. To help reduce the risk of drop out, we have designed a comprehensive onboarding process to get study participants comfortable with the study procedures and address any anticipated technical barriers to study completion. We did incorporate an expected dropout rate of 25% into our power analysis to avoid low statistical power in the event of sizeable attrition rates. We will monitor participant engagement with the sessions and assessments, as well as send electronic reminders of intervention sessions and study assessments. If a participant misses any session or assessment, we will send follow-up reminders and inquire about barriers to completing the study. If any barriers are noted, we will work with the participant to address them. Given that this intervention is delivered on a web-based platform by nonprofessional coaches, there exists the chance that technical or personal issues related to Innerworld, or its coaches, may interfere with the delivery of the intervention to participants. To mitigate this risk, Innerworld provides 24/7 access to live coaches (who are trained on how to detect if a person is in crisis and provide the proper resources) and technical support to address any unexpected obstacles. Finally, we were unable to implement blinding due to differences between interventions (such as the device used to access the intervention) that would be obvious to participants, as well as coaches. This could introduce bias in how participants or coaches behave or perceive their symptoms and the intervention.

Conclusions

If we find a significant difference in favor of CBI versus the DAC condition, this will provide evidence that CBI is efficacious for individuals with depression. If we find a significant difference in favor of CBI accessed via virtual reality headsets over the less immersive CBI accessed via flat-screen devices, this may suggest that the immersive quality of CBI strengthens the program. If we find no such difference, this will suggest that CBI may be effectively implemented with either virtual reality or flat-screen devices (ie, computer or handheld mobile devices), significantly reducing the cost of access since most people have a flat-screen device. This study will produce valuable information on whether CBI can effectively serve as a scalable and accessible mental health intervention among a growing, diverse population of help-seekers. In addition, knowledge of the differential benefit (or lack thereof) of immersive technology will help researchers develop other virtual reality and metaverse interventions, as well as funding agencies in determining whether virtual reality equipment is worthwhile or necessary in clinical studies.

Acknowledgments

We would like to thank our Data and Safety Monitoring Board (Drs Kimberly Hieftje, Clara Hill, Robert Gallop, and Zachary Cohen) for their contributions to ensuring the safety and integrity of this trial. This research was funded by the National Institute of Mental Health (R44 MH132202-02A1). The funder did not play a role in the study design, collection, or analysis.

Data Availability

Data sharing is not applicable to this article as no datasets have yet been analyzed during this study.

Conflicts of Interest

NR is the chief executive officer of Innerworld, Inc, the company that developed the Innerworld platform.

Multimedia Appendix 1
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1144 KB - resprot_v14i1e65970_app1.pdf]

Multimedia Appendix 2
SPIRIT Checklist.
[PDF File (Adobe PDF File), 264 KB - resprot_v14i1e65970_app2.pdf]

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Abbreviations

CBI: cognitive behavioral immersion
CBI-FS: cognitive behavioral immersion accessed via a flat-screen device
CBI-VR: cognitive behavioral immersion accessed via a virtual reality
CBT: cognitive behavioral therapy
CONSORT E-HEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
C-SSRS: Columbia-Suicide Severity Rating Scale
DAC: delayed access control
GAD-7: 7-item Generalized Anxiety Disorder

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HLM: hierarchical linear modeling
PHQ-9: 9-item Patient Health Questionnaire
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
USC: University of Southern California

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Protocol

Virtual Reality for the Prevention and Cessation of Nicotine Vaping in Youths: Protocol for a Randomized Controlled Trial

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Abstract

Background: Only a few trials target high school-aged teens with vaping interventions, typically focusing on prevention rather than cessation, with content limited to vaping harms and refusal skills. Given the co-occurrence and increasing incidence of vaping and mental health issues in teens, both must be simultaneously addressed by vaping interventions.

Objective: This randomized controlled trial aimed to evaluate the feasibility and preliminary efficacy of a virtual reality (VR) intervention for teens that targets both determinants of vaping (eg, mood and stress) and vaping prevention and cessation skills.

Methods: The participants are 150 students attending 1 of 2 racially and ethnically diverse Boston-area high schools. Health classes are randomly assigned to VR or control (assessment only). Students are eligible if not opted out by their parents, provided assent, and did not have health issues that preclude participation. While control classes (and ineligible students within them) have their regular classroom activity, VR classes are provided with Oculus Meta Quest 2 headsets and engage with the intervention during 3 class periods, once per week. Players solve a mystery with a vaping subplot and play a series of minigames to teach emotional regulation, coping strategies, and building resilience. A mobile app connects to the VR game, providing a home-based experience to reinforce skills learned. VR and control classes complete baseline and postintervention surveys on the same schedule. Primary outcome measures include feasibility, satisfaction and engagement with game play, and vaping awareness, knowledge, attitudes, and intentions to avoid or quit vaping. Secondary outcomes include vaping quit attempts, 7- and 30-day point prevalence abstinence, motivation and self-efficacy to quit or avoid vaping, positive and negative affect, emotional regulation and coping, and motion sickness.

Results: The project was approved by the institutional review board on April 2, 2024, and data collection began in April 2024 and concluded in June 2024, and 150 participants were recruited (98 intervention and 52 control). Although freshmen and sophomore classes were targeted in this study, there were several juniors and seniors (n=5) in these classes due to school transfers and the need for them to take the mandatory curriculum. Data cleaning has been completed, and analyses are ongoing. The results are expected to be submitted for publication in August of 2025.

Conclusions: As VR is visual, auditory, and tactile, it is ideal for practicing skills, facilitating memory, and increasing the likelihood of transfer to real-world settings. The immersion of VR promotes engagement with the intervention, rather than external digital temptations. Our study is innovative due to the cluster-randomized design, focus on both prevention and cessation, integration of mood management, and implementation among racially and ethnically diverse teens. Incorporation into school-based health curricula allows for proactive reach.

Trial Registration: ClinicalTrials.gov NCT06003439; https://clinicaltrials.gov/study/NCT06003439

International Registered Report Identifier (IRRID): DERR1-10.2196/71961

(JMIR Res Protoc 2025;14:e71961) doi:10.2196/71961

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KEYWORDS

vaping; teens; virtual reality; prevention; nicotine; coping; mood management; depression

Introduction

The prevalence of e-cigarette or vaping product use among teenagers is a substantial concern, with 10% of middle and high school students in the United States self-reporting current e-cigarette use in 2023, which is approximately 2.8 million students [1]. Moreover, 34.7% of current e-cigarette users report use on at least 20 of the past 30 days [1]. Though many teens believe e-cigarettes are a safer alternative to combustible cigarettes [2], studies suggest e-cigarette use has negative physiological, cognitive, and behavioral effects for teenagers [3]. E-cigarette use is associated with a variety of mental health issues, including depression, internalizing problems, perceived stress, and suicidality [4-6]. Moreover, the percentage of high school students experiencing persistent feelings of sadness or hopelessness (for at least 2 consecutive weeks) increased from 28% in 2011 to 42% in 2021 [7,8]. Therefore, e-cigarette interventions should include emotional regulation and coping in addition to typical approaches that involve teaching vaping refusal skills and managing cravings.

Several intervention approaches have been developed and tested with older adolescents, such as text messaging [9], contingency management [10], and social media approaches [11], but few studies have tested vaping interventions for high school-aged teens [12]. One trial among high school-age teens randomly assigned participants to watch Food and Drug Administration “Real Cost” advertisements (on either health harms of vaping or addiction potential) or a control group (neutral videos about vaping) with results showing that both intervention groups had lower self-reported likelihood of future vaping, less positive attitudes toward vaping and vaped fewer days per week compared to those in the control group [13]. In a small pilot study (n=69), text messages regarding the harms of e-cigarettes were sent to teens for 6 days. Outcomes were measured on day 7, with participants reporting increased knowledge and worry regarding the risks of e-cigarette use [14].

Another intervention approach used with high school-aged children is virtual reality (VR). VR is an immersive, computer-generated simulation that enables users to navigate within a 3D environment and interact with objects within the environment. One study used a pre-post design to test a VR program that focused on teaching vaping refusal skills (n=47) during 2 play sessions [15]. The results demonstrated a significant increase in knowledge and perceptions of e-cigarette harm, and a significant decrease in perceived likelihood of using e-cigarettes in the future, but there were no significant changes in attitudes toward e-cigarettes, social norm perceptions, or refusal self-efficacy. However, this study was not randomized, and 38 of the 47 study participants were boys. A follow-up study that randomized students by class tested the efficacy of the program in 285 middle school students aged 11 to 14 years [16]. The results showed that the VR program significantly increased e-cigarette knowledge and perceived addictiveness of e-cigarette at the 6-month follow-up, but there were no differences in e-cigarette behaviors between the control group and the VR group [16].

There are several advantages to VR interventions. VR is a 360-degree experience, so distractions by external stimuli are limited (eg, temptations to check social media). The immersive nature of VR also promotes learning and behavior change by increasing attention [17] and by creating meaningful emotions and experiences [18]. In VR, skills are not only learned auditorily and visually but also through tactile interaction. These multiple modes of skill acquisition increase memory retention. Finally, VR is an engaging medium for teens [16].

We describe the protocol for a randomized controlled trial that evaluates the feasibility, engagement, satisfaction, and acceptability of a VR program aimed at the prevention and cessation of vaping among high schoolers, delivered as part of their regular health curriculum throughout 3 classes (Clinical Trial Registration NCT06003439). A secondary aim is to assess the preliminary impact of the intervention on the determinants of vaping and vaping behavior. Distinct from the prior VR studies that focused solely on refusal skills for vaping [15], the intervention developed for this study focuses on the determinants of vaping (emotional regulation, coping strategies, and resilience) in addition to prevention and cessation skills (refusal skills, craving management, and cessation resources). A mobile app was also developed for use by students at home to reinforce the skills learned during the VR experience and to continue interactions with game characters in between VR sessions. Our study also expands upon prior literature by including a randomized controlled trial design and by including an ethnically and racially diverse sample. Our overall aim was to test the feasibility, acceptability, and preliminary efficacy of a VR-based prevention and cessation intervention program for high school-age students. We hypothesize that the intervention will be feasible (eg, high rate of student assent), satisfactory to students, and that most students will engage with the intervention (eg, complete all 3 sessions). Although the trial is not fully powered, we further hypothesize that the intervention will have promising effects in the desired direction on vaping attitudes and behaviors.

Methods

Participants

Eligible participants are assenting students enrolled at 1 of 2 high schools in the Greater Boston Area of Massachusetts. Exclusion criteria are (1) prone to seizures or severe motion sickness; (2) visual impairments that would prevent them from playing VR or using the VR device; (3) parent or guardian opt out; and (4) indication by school staff that participation is inappropriate (eg, heart condition, visual or auditory disability, psychiatric disorder, pacemaker, hearing aid, implanted medical device, or any other medical reasons).

Opt-out forms were distributed to eligible students’ parents or guardians that detailed this study’s procedures, potential risks,

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as well as how to opt their child out of this study. The opt-out form was translated into languages spoken by the families of the children who attended the schools and distributed approximately 3 weeks before obtaining assent from students. Parents or guardians were able to contact either the school or research staff to opt out their child. During their health class, electronic assent forms are given to all students who have not been opted out. Human subjects approval was obtained from our institutional review board (H-43102), and subsequent protocol modifications were submitted to the institutional review board. After assent, students complete a baseline survey, and data are stored in REDCap (Research Electronic Data Capture; Vanderbilt University), a secure, web-based app designed to support data capture and features to support cleaning, storage, and analysis.

Study Design and Random Assignment

Health education classes in the 2 high schools were randomized to either intervention (VR) or control (assessment only) by a statistician external to this study, using a 1:3 threshold probability. Three classes were randomized in 1 high school, and 4 classes in the other high school. Regarding the latter high school, 2 classes were "yoked" during randomization due to small class sizes. After completing a baseline survey, classes randomized to VR engage with the VR intervention once per week for 3-4 weeks, followed by a follow-up survey. Classes randomized to control complete baseline and follow-up surveys only, on the same schedule as the VR group. All study procedures take place during regular health classes. Students in control classes, as well as ineligible and nonassenting students in the VR classes, engage in alternative assignments regarding vaping or substance use from their respective teachers while study procedures are conducted. Only eligible participants who assented to be in this study completed pre- and post-assessments. As randomization occurs at the class level, teachers cannot be masked to the condition. Due to the nature of the intervention, study staff and participants were also not masked to the condition.

Equipment

Participants in the VR condition are provided with Meta Quest 2 VR headsets, which do not need to be tethered to computers. Each headset has adjustable head straps and lens spacing, and 3D positional audio. The headset is equipped with cameras to track the movement of the head and body and read hand gestures, so that hand controllers are not needed for navigation through the digital world, to execute game play, or to interact with the digital environment (eg, grabbing or throwing objects). Head straps and the facial interfaces are disinfected with antibacterial wipes after each use.

VR Intervention

Overview

Our prior mixed methods studies informed the structure and content of the intervention, in which we conducted focus groups and surveys to identify: teens' intrinsic and extrinsic motivators to initiate and maintain vaping; the methods teens currently use to quit vaping and perception of extant vaping cessation treatments; and intervention delivery methods and components that are acceptable to teens [19,20]. We also conducted usability testing with teens that consisted of playing progressive iterations of the VR program and interviewing them about their play experiences. This helped to identify bugs, ensure functionality, and make content changes.

VR Play Session Procedure

There are 3 VR play sessions, and each is 30-40 minutes in duration (approximately 1 class period) and played while seated. Four class periods are reserved for game play so that absent students can "make up" missed sessions. The VR sessions occur in large areas that allow for entire classes of students to use the VR headsets simultaneously (ie, school gymnasium or open space in library) without injury (eg, chairs that are not attached to desks).

Students download the study's mobile app onto their personal devices to obtain a login for the VR program and also to engage with game content at home. Students who do not have compatible devices can be logged into the VR game via study devices. Students are assisted with donning the VR headsets, including adjustment of the head straps and the interpupillary distance of the lenses, and providing spacers for eyeglasses, if needed. Students are given a brief overview of VR, including how to navigate through a digital environment (eg, teleporting), how to interact with objects in the environment (eg, grab, place, and throw objects), how to interact with characters in the environment (eg, waving to initiate communication with characters), and an overview of the minigames.

VR Play Sessions

The 3 play sessions are connected by a narrative arc that has a main storyline (the player solves a mystery at a fictional high school) and a vaping subplot. During the vaping subplot, the player chooses a friend at the high school, and the player discovers that the friend has a history of being caught vaping at school. During the story, the friend experiences triggers to vape, struggles with the decision of whether or not to quit vaping, tries to quit unsuccessfully, and finally applies a constellation of coping and motivational strategies to successfully quit. The player tries to help his or her friend quit vaping through various means, including playing 5 minigames to learn about how to cope with negative moods, reduce the friend's craving to vape, and identify treatments for vaping cessation. The minigames also go beyond vaping to teach general coping skills and building resilience, so that these skills have broad applicability to a wide range of risk behaviors and mood problems. At the end of each play session, the player and friend go to a secret cabin in the woods behind the high school, which has an "art wall" with additional intervention strategies for at-home practice. A friendly robot, ARAL, guides players through the overall game. A mobile app is connected to the game, where players can view their scores and send text messages with their in-game friend, providing a home-based experience (outside of class time) to reinforce skills learned in the classroom-based VR game. No new intervention strategies are presented in the mobile app; rather, the text message conversations relate to the events occurring in the VR game, as well as topics discussed with their fictional friend during game play (eg, the friend fighting urges to vape and what coping skills

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they used). Due to technical issues, actual use of the mobile app was not measured. Figure 1 depicts the player's journey throughout the intervention.

This image depicts the player's journey throughout the intervention. The VR app is divided into 3 play sessions. Each session ends at an "art wall" that reviews the content learned in that session and how to bring coping skills into the "real world." Between VR sessions, there is a home-based component where the player can interact with a mobile app that is connected to the game, so they can see their scores and interact with their friend from the game, reinforcing the skills learned in the game.

The first VR session introduces the player to ARAL the robot, has the player select a friend and play the first minigame together, and introduces the main plot (the mystery) and the subplot (the friend uses vapes). In the second VR play session, the player and friend try to solve the mystery and interview suspects in different locations (school cafeteria and movie theater), and 2 more minigames are played to further develop coping skills and build resilience. Play session 3 delivers content via 2 more minigames, the players solve the mystery, and also engage in an art wall activity that involves the discovery of different options for vaping cessation.

Figure 1. Player journey in the VR intervention. VR: virtual reality.

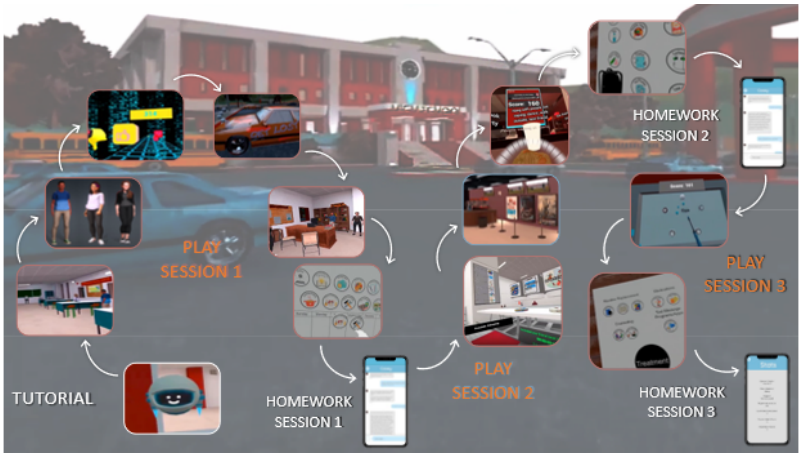

VR Intervention Content: VR Minigames and Art Wall Experiences

Rhythm Game

The player learns that physical activity helps reduce stress and cravings to vape. The objective is to hit boxes that fly toward the player to the beat of high-energy music while making the correct gesture (thumbs up, thumbs down, or OK symbol) with the correct hand, with gameplay becoming progressively more difficult throughout 3 rounds.

Lunch Line Game

The player identifies ways to cope with cravings to vape and also helps their friend reduce their cravings to vape (higher points lead to lower cravings on their friend's craving meter). The player grabs the correct coping strategy from the cafeteria shelf to destroy different cravings as they appear on lunch trays that are continuously moving with increasing speed down the lunch line conveyor belt.

Popcorn Game

The player identifies their own triggers (for vaping, and for negative moods and stress) and learns coping skills (eg, refusal skills, options for quitting vaping, and stress management). While the player and friend are in a movie theater to search for a suspect, ARAL shrinks them down into a popcorn machine. Kernels pop, and each one is labeled with a trigger. The player grabs each kernel and throws it into 1 of 2 popcorn buckets labeled "applies to me" or "does not apply to me." In the next round, 3 popcorn buckets appear, each labeled with a coping strategy, and the player must throw the kernel with the trigger on it into the bucket with the correct coping strategy before the "shot clock" runs out.

Vision Board Game

Players identify their personal goals (how they envision their future selves) by grabbing and placing them on a vision board, and then they learn how vaping may hinder those goals because a vape cloud appears and moves around the board with increasing speed, attempting to remove the goals. Players must use a spray hose to remove the vape cloud before it erases their goals, and then they must grab and quickly replace the goals that have been destroyed.

Art Walls

Intervention strategies include Behavioral Activation [21] (planning and scheduling activities, even if you feel sad), developing a crisis survival kit [22], engaging in a deep breathing exercise with ARAL, and learning about treatment options for vaping. Intervention strategies are delivered by having the player interact with objects (eg, grabbing and placing) and practice them in real time (eg, deep breathing).

Control Classes

These classes complete baseline assessments and post-assessments on the same schedule as the classes randomized to VR, but do not receive the VR intervention or vaping prevention or cessation. Instead, they receive their regular health education curriculum from their teachers, which includes required reading and in-class assignments regarding general substance use, and vaping is included as a topic.

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Measures

Measures are administered via REDCap during class time, using Chromebooks (Google LLC). The follow-up measure is give to both groups approximately 1 week after the VR group completes their final session of the game.

Primary Outcome Measures

Feasibility is assessed as the percent of students who assented, the percent who withdrew from playing the VR game, and the percent who withdrew from this study. Engagement is objectively assessed via the VR headset and includes the number of participants who complete the VR game, the amount of time that the game is played by each participant, and the number of game chapters completed (1-10). Satisfaction is assessed with several self-report measures: (1) an overall star rating of the VR program (1-5 stars); (2) 7-item scale of gameplay experience (eg, "I liked the way the game looked" and "I felt connected to my character in the game"), each item rated on a 4-point scale (1=strongly disagree to 4=strongly agree) [15]; and (3) after each VR game session, participants rate the degree to which they liked each play session and each minigame within that play session on a 4-point scale ("I liked it a lot," "I liked it," "meh," and "thumbs down"). An adapted measure of perceived program impact is used to assess how much participants agree (1=strongly disagree to 5=strongly agree) with a series of statements regarding the effects of the program on their vaping (awareness, knowledge, attitudes, behavior, intention to change, help-seeking, and ability to resist peer pressure), and ability to cope with stress, improve their mood, and avoid use of alcohol and other substances [23].

Secondary Outcome Measures

Vaping-related behaviors are assessed, including attempts to quit vaping since starting the VR program, use of quit vaping methods (behavioral, pharmacological, and digital), 7- and 30-day point-prevalence abstinence, and frequency of current vaping (not at all, some days, most days, and every day). Motivation to quit vaping (1-10 scale; 1=not at all to 10=very much) and intentions to quit vaping (eg, intention to stop in the next 30 days, 6 months, more than 6 months, and no intentions of stopping) are also assessed [24], as well as motivation to use evidence-based vaping cessation resources ("How much do you want to use at least one recommended treatment for stopping vaping [such as nicotine patches, nicotine gum, nicotine lozenges or counseling?"]) [19,25].

Vaping prevention is assessed with 2 items regarding the degree of motivation and confidence to avoid vaping (1-10 scales; 1=not at all to 10=very much), 1 item on intentions to try vaping (eg, I intend to vape within the next 30 days; 6 months; I may vape at some point in the future but not in the next 6 months) [26], 6 items on self-efficacy to resist vaping across a variety of high-risk situations (eg, "You feel agitated or tense. Are you confident you will not vape": definitely, maybe, neutral, maybe not, and definitely not") [27], and 7 items assessing refusal skills and perceived enjoyability of vaping ("If one of your friends were to offer you a vape, how easy would it be to say no to your friend?"; 4-point scale 1=very easy, 4=very hard) [26].

Determinants of vaping are also measured. Coping is measured with the 16-item Adolescent-Coping Orientation for Problem Experiences scale (eg, "When you face difficulties, how often do you...try to think of the good things in your life": never, hardly ever, sometimes, often, most of the time) [28,29]. Resilience is measured with 6 items regarding the frequency of different situations (eg, small problems got me very upset: never, a little, sometimes, or often) [30]. Positive affect is assessed with the 8-item PROMIS (Patient Reported Outcome Measurement Information System) Pediatric Positive Affect Scale [31], and negative affect is assessed with the 10-item negative affect scale from the Positive and Negative Affect Scale for Children [32].

Tolerability of the VR game is assessed with the 9-item Virtual Reality Sickness Questionnaire [33], which measures the degree to which participants are affected by a variety of symptoms (eg, eyestrain, headache, fatigue, or dizziness) while playing the VR game.

Data Management

Participants' data are kept confidential according to our institutional regulations. Participants are identified by ID numbers, with all data stored and managed in REDCap in a secure, HIPAA (Health Insurance Portability and Accountability Act)-compliant server. Unanticipated problems and adverse events are recorded on electronic case report forms and reported to our institutional review board per regulations. As the study is no more than minimal risk, a data safety and monitoring board was deemed unnecessary.

Sample Size

As this is a pilot feasibility study, a formal power calculation was not conducted. The sample size was determined based on the need to include a sufficient number of students exposed to the intervention, the availability of students in health classes at the participating public schools, and the timeframe allowed by school administrators. This approach allows us to assess our primary outcomes (eg, feasibility, acceptability, engagement, and satisfaction), as well as preliminary impact on relevant vaping-related constructs. We planned on including approximately 80 students in intervention classes and 40 students in control classes. This is based on an average of 25-35 students per class. We conservatively estimated that approximately 15%-20% of students will either not provide assent to be in this study or drop out post-assent. Therefore, we aimed to enroll approximately 150 participants.

Analytic Plan

Data will be inspected for outliers, and descriptive analyses of baseline differences in sociodemographic and vaping-related characteristics between the VR group and the control group will be conducted using *t*-tests or chi-square tests, as applicable. We will examine differences in key baseline characteristics (eg, gender distribution between groups) so that they may be covaried in analyses. Feasibility, acceptability, engagement, and satisfaction (primary outcomes) in the VR group will be summarized as means and SDs for continuous variables, or number and proportion of participants for categorical variables, as appropriate. We will then report the number and proportion

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of participants who progressed through each of the 3 play sessions (chapters 1-10) of the VR game. Lastly, game ratings obtained after each play session will be reported as number and proportion of participants rating each category ("I liked it a lot," "I liked it," "meh," or "thumbs down").

Data on secondary outcomes will be summarized as means and SDs for continuous variables, or number and proportion of participants for categorical variables as appropriate, and compared between the VR group and the control group (baseline and follow-up). If low cell sizes occur, data might be aggregated to support statistical stability in the models. Differences in secondary outcomes between the groups will be evaluated by computing effect sizes (eg, Cohen *d* or odds ratio) as appropriate.

We will conduct analyses on treatment completers (the subsample of participants who completed the entire VR game) as well as intention-to-treat (as randomized). Additionally, we will perform analyses on the entire sample (English learners and English proficient students) as well as conduct analyses separately by English proficiency status. This will allow us to gain invaluable knowledge to inform future research regarding the feasibility of gamified health interventions for students with different levels of English proficiency.

Ethical Considerations

The Boston University institutional review board approved the project on April 2, 2024 (IRB# 43102). Assent will be obtained from participants via REDCap, and parents will be sent an opt-out form, as per school protocol. Participants did not receive compensation for participation. All data will be deidentified, kept confidential, and stored in a secure location on an institutional server, which is backed up daily. Only certain members of this study's staff or others designated by the principal investigator will have access to this study's data. Protocol modifications will be reviewed and approved by our institutional review board and communicated to the American Heart Association.

Results

The project institutional review board approved on April 2, 2024, and data collection began in April 2024 and ended in June 2024, and 150 participants were recruited (98 intervention and 52 control). Although freshmen and sophomore classes were targeted in this study, there were several juniors and seniors (n=5) in these classes due to school transfers and the need for them to take the mandatory curriculum. Data cleaning and analysis are underway, and results are expected to be submitted for publication in August 2025.

Discussion

Both vaping and mental health issues are on the rise among teens. Given the relationship between vaping and mental health, both must be simultaneously addressed by vaping prevention and cessation interventions. We developed a VR intervention that focuses not only on the skills needed for the prevention and cessation of vaping but also on skills that are needed to cope with common teen mental health issues, such as stress, negative moods, and building resilience. Focusing only on vaping without attention to mental health is not in line with what teens want in a vaping intervention [19,20,34] and ignores critical determinants of vaping behavior [35,36]. Moreover, our VR app is transdiagnostic, in that vaping prevention and cessation skills can be transferred to other risky behaviors, and the general coping skills can be applied to several mental health issues, including depressed mood and anxiety.

The choice of using VR to deliver the intervention was driven by several factors. First, as VR technology has improved in both graphics and functionality, it is emerging as an engaging and effective method to treat a variety of mental health [37,38] and physical health issues [39,40]. Second, VR allows for visual and auditory intervention delivery, and interactivity with simulated objects and people. This multisensory delivery is ideal for practicing skills, supporting visual and tactile memory, and increasing the likelihood of transfer to the real world. In our study, we took the additional step of developing a companion mobile app that allowed for continued interaction with the characters from the game between VR sessions (while at home) to further reinforce the skills learned in the VR sessions. Third, data has shown that teens enjoy games and VR [15,16,41], making it an acceptable platform for intervention. Fourth, given the "cool" factor of many of the vaping device designs and functions, interventions are needed that are equally intriguing to teens. Finally, the immersive nature of VR allows teens to focus exclusively on the intervention, instead of checking their phones, scrolling social media, or engaging with other digital temptations.

Our study is innovative because it randomizes high schoolers at the class level, targets both prevention and cessation of vaping in teens, integrates mental health coping skills into a vaping prevention and cessation program, and tests VR in racially and ethnically diverse teens. The school-based setting and integration into the regular health curriculum allow for proactive reach to teens, with minimal burden on the school. As this is a pilot feasibility study, the conclusions will be limited given the small sample size and lack of power to detect effects. Additionally, our control group does not control for attention. Using an attention control in VR is costly, requiring additional development or an off-the-shelf product that would sufficiently match all of the user mechanics (eg, throwing, grabbing, etc) to ensure a true matched-control. For example, if effective, initial integration into schools would be a financial investment. However, the price of VR headsets continues to decline. Moreover, 10 years ago, there were no Chromebooks integrated into classrooms, and now every student has one. Another limitation to VR is that students with visual or auditory disabilities would not be able to fully experience VR, and, as with other learning platforms, accommodations would need to be made for these students. However, because VR has visual, auditory, and tactile learning components, it may be easier for English learners to learn concepts and skills through VR, rather than written material. Another advantage of VR is remote learning. If students need extra support for a particular lesson, they could take the VR headset home as homework, or if there is another pandemic, VR could be a platform for remote

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learning, particularly with a multiplayer platform (other teachers and students could interact in the same simulated environment).

Importantly, our VR program focuses on both prevention among teens who do not currently vape and quitting among teens who do vape. Therefore, it can be broadly applied in school settings to the general student population and not solely used among those who were "caught" vaping. Ideally, the VR program would be used in conjunction with other school-wide and community-wide policies that discourage vaping for maximum effect on reduction in teenage vaping and associated health outcomes.

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Data Availability

The datasets generated and analyzed during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

BB was the principal investigator responsible for the conception, overall design, and conduct of this trial; principally responsible for developing the intervention content; and cowrote the Introduction, Methods, Measures, and principally wrote the Discussion. BB reviewed and edited all sections of this paper. DW was project manager and cowrote the Methods section. RE was coinvestigator; cowrote the Measures section; and wrote the Data Management, Sample Size, and Analytic Plan, and reviewed and edited all sections of this paper. NL and K Konieczny were research assistants who assisted with the literature review and writing the Introduction. K Koval was a research assistant who assisted with writing the Methods section. LQ was coinvestigator and assisted with Discussion section. All authors contributed to this paper through review and editing and have approved the final paper.

Conflicts of Interest

None declared.

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Abbreviations

HIPAA: Health Insurance Portability and Accountability Act
PROMIS: Patient Reported Outcome Measurement Information System
REDCap: Research Electronic Data Capture
VR: virtual reality

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Protocol

Coronary Computed Tomographic Angiography to Optimize the Diagnostic Yield of Invasive Angiography for Low-Risk Patients Screened With Artificial Intelligence: Protocol for the CarDIA-AI Randomized Controlled Trial

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Abstract

Background: Invasive coronary angiography (ICA) is the gold standard in the diagnosis of coronary artery disease (CAD). Being invasive, it carries rare but serious risks including myocardial infarction, stroke, major bleeding, and death. A large proportion of elective outpatients undergoing ICA have nonobstructive CAD, highlighting the suboptimal use of this test. Coronary computed tomographic angiography (CCTA) is a noninvasive option that provides similar information with less risk and is recommended as a first-line test for patients with low-to-intermediate risk of CAD. Leveraging artificial intelligence (AI) to appropriately direct patients to ICA or CCTA based on the predicted probability of disease may improve the efficiency and safety of diagnostic pathways.

Objective: he CarDIA-AI (Coronary computed tomographic angiography to optimize the Diagnostic yield of Invasive Angiography for low-risk patients screened with Artificial Intelligence) study aims to evaluate whether AI-based risk assessment for obstructive CAD implemented within a centralized triage process can optimize the use of ICA in outpatients referred for nonurgent ICA.

Methods: CarDIA-AI is a pragmatic, open-label, superior randomized controlled trial involving 2 Canadian cardiac centers. A total of 252 adults referred for elective outpatient ICA will be randomized 1:1 to usual care (directly proceeding to ICA) or to triage using an AI-based decision support tool. The AI-based decision support tool was developed using referral information from

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over 37,000 patients and uses a light gradient boosting machine model to predict the probability of obstructive CAD based on 42 clinically relevant predictors, including patient referral information, demographic characteristics, risk factors, and medical history. Participants in the intervention arm will have their ICA referral forms and medical charts reviewed, and select details entered into the decision support tool, which recommends CCTA or ICA based on the patient's predicted probability of obstructive CAD. All patients will receive the selected imaging modality within 6 weeks of referral and will be subsequently followed for 90 days. The primary outcome is the proportion of normal or nonobstructive CAD diagnosed via ICA and will be assessed using a 2-sided *z* test to compare the patients referred for cardiac investigation with normal or nonobstructive CAD diagnosed through ICA between the intervention and control groups. Secondary outcomes include the number of angiograms avoided and the diagnostic yield of ICA.

Results: Recruitment began on January 9, 2025, and is expected to conclude in mid to late 2025. As of April 14, 2025, we have enrolled 81 participants. Data analysis will begin once data collection is completed. We expect to submit the results for publication in 2026.

Conclusions: CarDIA-AI will be the first randomized controlled trial using AI to optimize patient selection for CCTA versus ICA, potentially improving diagnostic efficiency, avoiding unnecessary complications of ICA, and improving health care resource usage.

Trial Registration: ClinicalTrials.gov NCT06648239; https://clinicaltrials.gov/study/NCT06648239/

International Registered Report Identifier (IRRID): DERR1-10.2196/71726

(JMIR Res Protoc 2025;14:e71726) doi:10.2196/71726

KEYWORDS

artificial intelligence; coronary artery disease; coronary computed tomographic angiography; clinical decision support; invasive coronary angiography

Introduction

Coronary artery disease (CAD) is a leading cause of death globally [1]. While invasive coronary angiography (ICA) remains the gold standard for CAD diagnosis, many patients undergoing elective ICA are found to have a nonobstructive disease or normal coronary anatomy, with variability between cardiac centers [2,3]. Despite lower population-based rates of ICA in Ontario, Canada, over 50% of elective ICA procedures find nonsignificant CAD (CorHealth Ontario, unpublished data, 2022). A low diagnostic yield of elective ICA is not only resource-intensive [4-6] but unnecessarily subjects patients not requiring invasive intervention to major procedural complications, including vascular injury, major bleeding, stroke, myocardial infarction, and death [7]. A noninvasive test able to provide similar information with less risk and cost is ideal in a lower-risk population.

Coronary computed tomographic angiography (CCTA) has emerged as one such noninvasive alternative to anatomically evaluate the coronary arteries. CCTA is highly sensitive for the detection of >50% coronary stenosis in patients with low to moderate pretest probability of obstructive CAD [8,9], is less expensive, and carries significantly less risk [10]. Appropriately, guidelines for the evaluation of chest pain from the American College of Cardiology/American Heart Association and the European Society of Cardiology both recommend first-line CCTA in this population [11,12]. However, limited access to CCTA in Canada due to limited diagnostic infrastructures has restricted its widespread use. Conversely, a CCTA-first approach can result in double-testing, since patients with abnormal CCTA frequently proceed to confirmatory or therapeutic ICA, which is wasteful and exposes patients to unnecessary radiation. Ultimately, appropriate test selection requires accurate prediction of the pretest probability of obstructive CAD.

Artificial intelligence (AI) has been leveraged to improve the prediction of significant CAD. Traditional risk assessment tools include a more limited number of variables and may not capture the full complexity of patient risk profiles. Conversely, machine learning algorithms can incorporate a greater number of predictors, including highly correlated predictors, and can account for complex, nonlinear relationships between predictors, including at the patient level [13]. We have developed an AI model to predict the probability of obstructive CAD using 12 years of referral data from 2 regional hospitals, comprising a cohort of over 29,000 patients, which significantly outperformed existing risk scores (area under the receiver operating characteristic curve of 0.81 vs 0.62) and achieved a net reclassification improvement of 44.7% over usual care (95% CI 42.4%-47.0%) [14]. The model has been updated using more recent referral data and has undergone external validation using 2008-2023 province-wide data to confirm generalizability (Petch et al, unpublished paper, April 2025). The integration of this model into clinical practice may enable a more accurate assessment of patient risk and improve diagnostic efficiencies.

A decision support tool that incorporates such an AI model within a centralized triage pathway may facilitate patient selection for first-line CCTA (Figure 1). We have established that a centralized triage model in which low-risk patients referred for ICA are considered for CCTA first can improve the diagnostic yield of elective ICA and that such a model is acceptable to both patients and referring physicians [15]. As such, we have deployed the AI model in our local cardiac center and conducted a pilot study using a silent trial design [16] to establish feasibility within the centralized triage pathway and address implementation issues (Schwalm et al, unpublished

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paper, April 2025). With the individual components of the intervention validated and piloted, the next appropriate step is to conduct a clinical trial of the intervention to measure its impact on clinical outcomes.

Figure 1. AI intervention in the context of the clinical pathway. The AI model is integrated into a centralized triage model for ICA and CCTA, where community cardiologists can refer to a single unit for an angiogram for suspected obstructive CAD, and the AI model provides a recommendation for which test is most appropriate for a given patient. Green boxes indicate the optimal test for a given patient, orange indicates suboptimal testing (patient received a "double-test" of both CCTA and ICA), and red indicates the least optimal (patient received an ICA but did not have obstructive disease). AI: artificial intelligence; CAD: coronary artery disease; CCTA: coronary computed tomographic angiography; ICA: invasive coronary angiography.

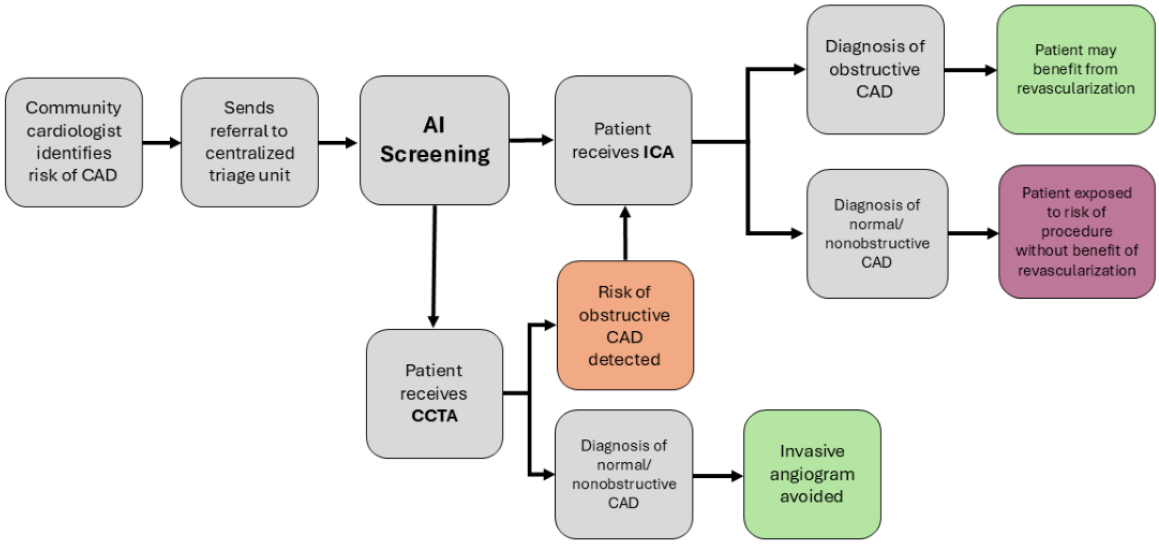

The CarDIA-AI (Coronary computed tomographic angiography to optimize the Diagnostic yield of Invasive Angiography for low-risk patients screened with Artificial Intelligence) trial will evaluate whether AI-based screening within a centralized triage pathway can optimize patient selection for CCTA versus ICA. The primary goal of this study is to reduce the proportion of unnecessary ICA procedures (showing normal or nonobstructive CAD) performed in patients referred for evaluation of CAD diagnosed in patients undergoing ICA. This trial will compare the AI intervention to usual care (ie, directly proceeding to ICA) to assess improvements beyond the current diagnostic pathway.

Methods

Objectives

The primary objective of the CarDIA-AI trial is to determine the effect of a centralized triage process incorporating AI-based risk assessment, compared to usual care, on the proportion of normal or nonobstructive CAD diagnosed via ICA, in adults referred for nonurgent (elective) outpatient ICA.

Study Design

The CarDIA-AI trial is a pragmatic, open-label, multicenter, superiority trial with two parallel groups and 1:1 allocation. The study was registered at ClinicalTrials.gov (NCT06648239). This protocol was prepared in accordance with the SPIRIT-AI (Standard Protocol Items: Recommendations for Interventional Trials—Artificial Intelligence) guidelines [17] (see Multimedia Appendix 1 for checklist).

Participants

Setting

Two cardiac centers located in Ontario, Canada, will participate in the CarDIA-AI trial: Hamilton Health Sciences' General Hospital (Hamilton site) and Niagara Health System's Marotta Family Hospital (Niagara site). These regional referral centers serve a large geographic area in southern Ontario with a population exceeding 1.8 million. ICA referral forms from the region are received at the Heart Investigation Unit located at the Hamilton site. Ordinarily, triage staff categorize the referrals according to urgency and site (Hamilton or Niagara; based on the patient's home address). For CarDIA-AI, outpatient ICA referrals will be reviewed daily to identify eligible participants.

The AI risk-assessment tool is deployed on a virtual machine housed at Hamilton Health Sciences' research data center. The virtual machine is allocated with 8 central processing unit cores and 16 GB of RAM. The virtual machine is accessed by the research team at the study sites using Citrix.

Informed Consent

Eligible patients are identified by a research assistant and reviewed by a board-certified cardiologist. The research assistant will then contact eligible patients by phone to discuss the study, review the consent form, and obtain verbal informed consent. At the time of the ICA or CCTA, research staff will also obtain written, paper-based consent from patients willing to participate (Multimedia Appendix 2).

Sample Size

The assumed proportion of normal or nonobstructive CAD on angiogram in the control arm is based on proportions at the two participating centers over the last decade, which have been stable at 44%. Our pilot work suggests that the proportion of

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normal or nonobstructive CAD diagnosed via ICA in the experimental arm is expected to be around 22%. We studied the power for various possible effect sizes (reduction in event proportions). A 1:1 sample of 200 people can detect an absolute reduction of 22% or higher in event proportion with 91.9% power, and a smaller 19% absolute reduction or higher with 81.3% power. To adjust for noncompliance of up to 5% in both arms, we increased the sample size from 200 patients by a factor of 1.23 to 246 patients [18]. Adjusting for up to 2% losses to follow-up, we require 252 patients (126 per arm).

An average of 115 eligible patients are seen at the participating centers each month. Given that recruitment is carried out by a centralized administration team (individual clinicians are not required to be involved), we do not anticipate significant recruitment barriers. Thus, we conservatively expect to recruit 100 patients per month. The recruitment will take place over 3 months to achieve our target sample size.

Eligibility Criteria

Patients are eligible if they (1) are 18 years of age or older; (2) are referred for nonurgent (elective) outpatient ICA; (3) have an indication for ICA that includes “Rule out CAD,” “Cardiomyopathy,” “Stable CAD,” or “Stable Angina”; and (4) are able to provide informed consent in English. Patients will be excluded if they (1) have received a prior high-quality CCTA within the last five years; (2) have atrial fibrillation or other arrhythmia precluding high-quality CCTA; (3) have known severe renal dysfunction (glomerular filtration rate of <35 mL/min/1.73 m^2); (4) have planned (coronary or noncoronary) cardiac surgery; (5) have any prior obstructive CAD, acute coronary syndrome, percutaneous coronary intervention, or coronary artery bypass graft; or (6) have known severe coronary artery calcification (calcium score >250) or not deemed to be “mild” on report if not quantified. Referral forms indicating “Stable CAD” will be reviewed to ensure the patient does not meet exclusion criteria (eg, known prior obstructive CAD), as many referring physicians check this indication without objective evidence of known CAD.

No exclusions will be made at the level of the input data after confirming patient-level eligibility. If data on the referral form are missing or of poor quality, research staff will review any additional documentation in the patient’s chart to attempt to obtain the missing data. Otherwise, the data will be imputed.

Randomization

Participants will be randomly assigned (1:1 allocation) to either usual care or centralized triage using AI-based CAD risk assessment. Block randomization using randomly varying block sizes (unknown to investigators and study personnel), stratified by site with a computer-generated random sequence, will be used. Research personnel will randomize participants via an interactive web response system, ensuring allocation concealment. The interactive web response system is a 24-hour computerized randomization internet system maintained by the coordinating center at Hamilton Health Sciences’ Population Health Research Institute.

Interventions

Centralized Triage

Participants randomized to the intervention arm will have their referral triaged using an AI-based decision support tool to determine the cardiac imaging test they will receive. The AI model uses participants’ medical history (as documented on their referral form) to predict the patient’s probability of significant CAD. Participants deemed high risk for obstructive CAD will receive ICA as recommended by the AI model, effectively receiving usual care. Those assessed to be low risk will receive CCTA, proceeding to confirmatory or therapeutic ICA if appropriate (Figure 2). For patients undergoing CCTA, recommendations for medical management versus referral for ICA will be made based on the CCTA results as per established clinical practice guidelines (Table S1 in Multimedia Appendix 3). Participants who withdraw consent or are admitted to the hospital with concern for acute coronary syndrome after randomization will receive usual care. As our pilot study suggests that the centralized triage process is acceptable and has high fidelity [15], no specific strategies to improve intervention adherence will be implemented.

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Figure 2. The flow of participants through the study. AI: artificial intelligence; CAD: coronary artery disease; CCTA: coronary computed tomographic angiography; HIU: Heart Investigation Unit; ICA: invasive coronary angiography.

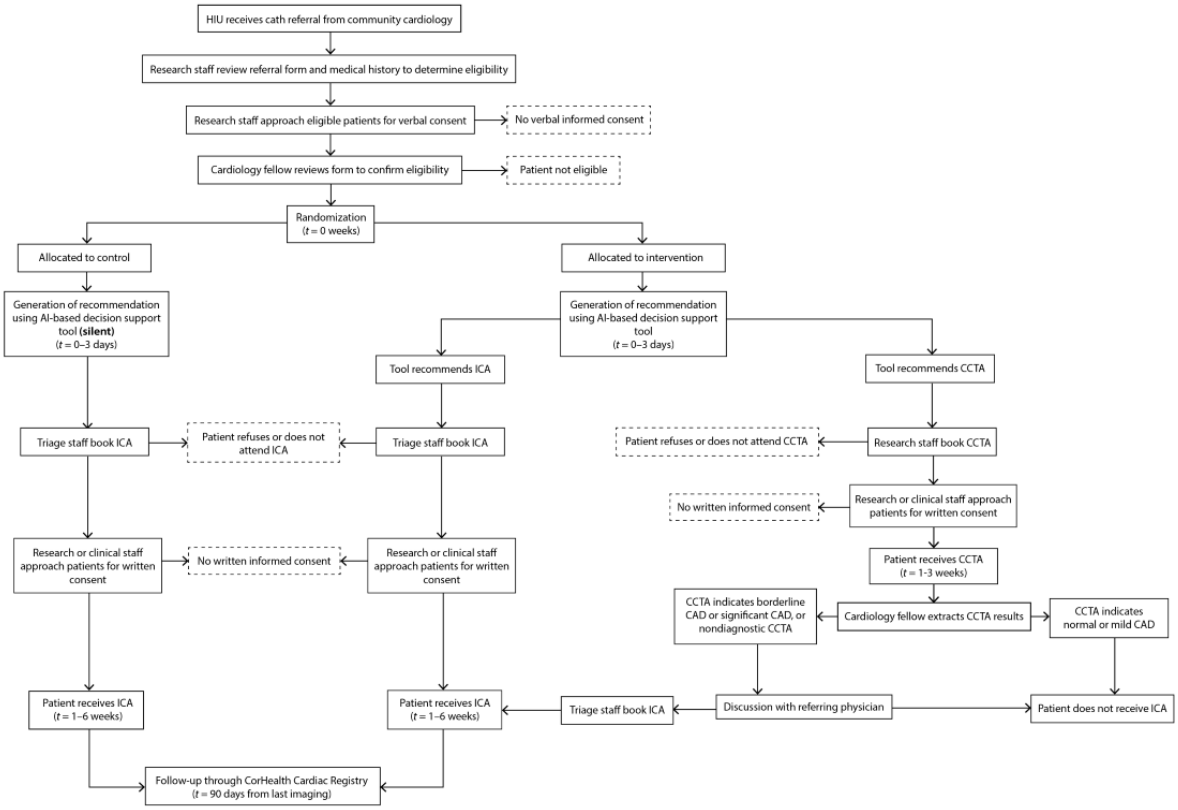

Only participants in the intervention arm will receive CCTA. Furthermore, interventional cardiologists require access to CCTA results to provide the best care and determine the appropriateness of subsequent ICA. As such, blinding of patients and providers is not possible.

AI-Based Risk Assessment for Significant CAD

As part of the centralized triage process, participants' allocation status will be entered into the risk assessment tool prior to generating the recommendation. For patients randomized to the intervention, the AI model outputs a predicted probability of significant CAD (not shared with clinical personnel), as well as an imaging modality recommendation (CCTA or ICA) informed by the predicted probability. Participants in the intervention arm will receive the imaging modality recommended by the tool.

The AI model uses a light gradient boosting machine algorithm to predict the probability of obstructive CAD based on 42 clinical predictors, including demographic characteristics, patient referral information, anthropometric measures, clinical symptoms, risk factors, medical history, and tobacco habits, as documented on the referral forms (Multimedia Appendix 4). Based on clinical input, we included variables related to the patient's medical history available at the time of referral, the unique physician number for each referring physician to capture patterns in referral practices, and socioeconomic variables. We selected the light gradient boosting machine algorithm based on our previous study, in which it showed the best discrimination performance among 8 machine learning models developed [14]. An analysis of variable importance and interactions between variables can be found in our previous publication [14]. The model was trained, validated, and evaluated on data from the CorHealth Ontario Cardiac Registry, a multicenter, prospectively collected registry of referral information from patients receiving ICA in the province of Ontario, Canada. The original model derivation cohort included 29,448 patients who received their ICA in the Hamilton or Niagara regions between 2008 and 2019 [14]. We subsequently externally validated the model using an additional sample of 7785 patients who underwent ICA between 2020 and 2023. This trial will use the most recent version of the model, based on 2008-2023 data from the two trial sites. The decision thresholds are 0.556 and 0.560 for the Hamilton and Niagara sites, respectively. The thresholds were optimized to maximize the difference between the true positive rate and the false positive rate (Youden index). An exhaustive description of the development, validation, and evaluation methods and results for this model will be available in a forthcoming paper (Petch et al, unpublished paper, April 2025). The AI model is not currently publicly available.

To obtain the input data for the tool, a research assistant will manually review the ICA referral forms of eligible patients and associated documentation in their chart (Figure S1 in Multimedia Appendix 3). If there are ambiguities or inconsistencies in the referral form or chart, these data will be managed based on predetermined standard operating procedures (Multimedia Appendix 5). Missing data will be imputed. Any ambiguities or inconsistencies requiring clinical interpretation will be treated as missing and imputed.

The user interface of the AI tool consists of various input fields that correspond to the model predictors (Figure S2 in Multimedia Appendix 3). Users either manually enter a value (eg, for Age)

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or select a value from the field drop-down menu (eg, for Referral Month). The input fields largely reflect nominal, structured data elements on the referral forms completed by referring physicians. While clinical expertise is not required to use the tool, study personnel using the tool have discussed the contents of the form at length with members of the Heart Investigation Unit in preparation for the trial.

Usual Care

Participants allocated to the control arm will receive usual care, meaning they proceed directly to ICA as referred. For control group participants, the AI-based decision support tool will always recommend ICA (ie, usual care) and provide the predicted probability of significant CAD, though this probability will not be shared with the clinical team.

Outcomes

Primary Outcome

The primary outcome is the proportion of normal or nonobstructive CAD diagnosed via ICA, calculated by dividing the number of patients diagnosed with normal or nonobstructive CAD through ICA by the total patients allocated to that arm. This was identified as the most policy-relevant outcome for Ontario Health.

Secondary Outcomes

Secondary outcomes include (1) the number of angiograms avoided, (2) deviation from management recommendations following CCTA (ie, angiograms performed when not recommended), (3) the diagnostic yield of ICA (ie, number of patients diagnosed with obstructive CAD out of all patients undergoing ICA), (4) the number of low-quality CCTAs, (5) the difference in the proportion of normal or nonobstructive CAD diagnosed through ICA between male and female patients; and (6) the difference in the proportion of normal or nonobstructive CAD diagnosed through ICA between sites. Furthermore, we will assess the budget impact of the AI intervention.

Data Collection

Overview

All patients will be followed for 90 days from the date of the final diagnostic procedure to capture any relevant outcomes in this stable, elective outpatient population. For patients receiving only ICA or CCTA, this would be the date of the diagnostic procedure; for patients receiving ICA after an initial CCTA, this would be the date of the ICA. All patients will have a CCTA or ICA within 6 weeks of their index referral as per provincial guidelines. Outcomes will be identified at the time one or both procedures (if indicated) are complete. We are allowing an additional 90 days from the final diagnostic procedure to capture any unplanned crossover from CCTA to ICA (see Safety). Follow-up will be done through the provincial CorHealth Ontario Cardiac Registry, housed at the Institute for Clinical Evaluative Sciences. All ICA findings in Ontario are transmitted to the provincial registry via its secure portal. We will extract ICA findings from the registry and derive our outcomes using the standard definition for normal or nonsignificant CAD: <70% stenosis on a major coronary vessel (>2 mm) or <50% stenosis on the left main. For patients who receive CCTA, a cardiologist will manually extract CCTA results from their charts as part of follow-up, as these results are not collected by CorHealth. CCTA findings will be collected in a format and structure that aligns with the CorHealth data collection standards used for ICA findings.

For each CCTA, we will assess the quality of the resulting image. The quality will be graded on a per-patient basis using a 3-class system: low quality, denoting an image in which the coronary anatomy cannot be clearly defined, requiring ICA within 90 days for clarification; suboptimal quality, denoting an image in which the coronary anatomy was equivocal for one or more nonprognostic vessels but not requiring ICA based on CCTA findings and clinical presentation; and high quality, denoting an image in which the coronary anatomy could be clearly defined.

To track participant retention, we will keep a log of all included participants to document any who are lost to follow-up, withdraw consent, or do not otherwise receive the recommended imaging intervention. Additionally, we will document all reasons for withdrawal, as well as ask whether the patient intends to proceed with usual care (if the patient is withdrawing prior to their imaging procedure). As the necessary outcome data is generated at the time of CCTA or ICA and direct participant involvement is not required for follow-up, the participant burden will be minimized.

Implementation Study

As part of a parallel implementation study, we will identify anticipated challenges to the implementation of the centralized triage process with AI-based risk assessment for CAD. Semistructured interviews and electronic surveys (via REDCap [Research Electronic Data Capture]; Vanderbilt University) will be conducted with key stakeholders—including the catheterization laboratory director, catheterization laboratory manager, catheterization laboratory triage staff, and representation from the CCTA program—at 3 cardiac centers not participating in CarDIA-AI. Survey and interview guides will explore a range of stakeholder perspectives including their awareness of the innovation and attitudes toward the change generally, as well as specific to the innovation, any skills and experiences they might have that could be required in the implementation of the innovation, any concerns about the proposed change, and their intentions to adopt or use the innovation. Development of the survey and interview questions will be informed by the updated Consolidated Framework for Implementation Research, a determinant framework to explain barriers and facilitators to implementation effectiveness [19]. At the participating centers, interviews will be conducted with triage staff to assess their perceptions of the AI model's success and identify what would be needed to integrate it completely into processes at their site. A list of potential interview and survey questions is available in Multimedia Appendix 6. Descriptive analysis of quantitative survey results (eg, Likert scale responses) will be conducted by the research team. Qualitative analysis of open-ended survey questions and interview transcripts will be carried out using thematic analysis

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approaches via NVivo software (Lumivero). Data will be coded and mapped to selected constructs of the Consolidated Framework for Implementation Research. Findings will be used to inform the development of strategies and interventions to mitigate identified barriers to the implementation of the centralized triage process if it is determined to be effective. Key barriers will be mapped to the most appropriate implementation strategies from an established compilation of potential strategies, the Expert Recommendations for Implementing Change [20].

Analyses

Statistical Analysis

The primary analysis will compare the proportion of patients referred for cardiac investigation with normal or nonobstructive CAD diagnosed through ICA between the intervention and control groups with a 2-sided *z* test comparing two proportions. All analyses will be carried out according to the intention-to-treat principle; that is, all participants with complete data will be analyzed according to the group to which they were randomized, including noncompliant participants. There are no planned interim analyses. A table of baseline characteristics will summarize patients overall and by randomization arm. Continuous variables will be summarized as mean (SD) or median (IQR), with comparisons between randomization arms made by a 2-sample *t* test (or Wilcoxon rank-sum test if data are not normally distributed). Categorical variables will be summarized as count and percentage, with comparison using the Pearson chi-square test. All statistical analyses will be performed using SAS software (version 9.4; SAS Institute Inc). We will report *P* values up to 3 decimal places and report *P* values less than .001 as <.001. We will use a type I error level of 5%.

We expect a small amount of missing data due to noncompliance and loss to follow-up. As noted above, participants who withdraw will be asked for a reason for withdrawal to determine whether the missing information is random. Participants withdrawing prior to the procedure will be asked whether they intend to proceed to ICA. Finally, we intend to conduct sensitivity analyses based on best- and worst-case scenarios to assess the impact of missing data on the results.

As part of our secondary outcome analysis, we plan to examine whether the intervention can address disparities in ICA findings and evaluate its effects across different sites and eligibility criteria. We will stratify by sex to evaluate whether the intervention reduces the discrepancy in the proportion of normal findings on ICA between male and female patients (female patients are currently 40% more likely to have a normal finding on ICA, meaning female patients are less likely than male patients to experience the therapeutic benefits associated with ICA). Similarly, we also plan to stratify by site to evaluate whether there are differences in the intervention effects between the Hamilton and Niagara sites. To simulate the impacts of using different criteria for CCTA-first eligibility, we will also evaluate the sensitivity of all outcomes to changes to the exclusion criteria, such as incorporating age- and sex-related exclusions. Formal statistical tests will not be used, as we do not anticipate that these hypothesis-generating secondary analyses will be adequately powered.

Given our relatively small sample size, there may be an imbalance at baseline for important covariates. We will therefore undertake an adjusted analysis as a secondary sensitivity analysis, adjusting for age and sex. These covariates were selected based on our external validation study (Petch et al, unpublished paper, April 2025), which found an association between these covariates and the outcome (event rate for male individuals was 71% vs 53% for female individuals, and 68% for those older than 65 years vs 59% for those 65 years and younger).

Economic Analysis

For the budget impact analysis, we will use the trial data and Ontario Health Insurance Program professional and technical fees to compare the procedural costs of screening with usual care (cost of ICA) and the AI model (weighted average of the cost of ICA and the cost of CCTA based on the AI model recommendation and CCTA output). A catheterization laboratory cost, which is not included in Ontario Health Insurance Program fees, will be added to the cost of ICA. In a secondary economic analysis, the 90-day health care expenditures post index investigation (eg, revascularization and hospitalization) will be derived using the Institute for Clinical Evaluative Science databases and compared between the 2 diagnostic strategies. Bootstrap techniques will be used to deal with sampling uncertainty and calculate 95% CIs around the costs [21]. The per-patient costs will be extrapolated to Ontario and Canada to document the health care cost savings at the population level.

Safety

Both CCTA and ICA are considered standard of care in the patient population for CarDIA-AI. A total of 50% (126/252) of patients (control arm) will automatically receive usual care. Patients randomized to the intervention who receive a recommendation to proceed directly to ICA will effectively also receive usual care. Patients who receive a recommendation to proceed to CCTA will not be at increased risk of missed diagnosis, as CCTA has been found to be as effective as ICA in both diagnosing and ruling out obstructive CAD in stable outpatients [9,22-24]. A potential harm in the intervention group is double testing, which would occur when the CCTA is of poor quality and the degree of obstructive CAD cannot be clearly quantified. Double testing may also occur when the AI model predicts a low probability of obstructive CAD, and in turn, recommends CCTA, but the CCTA is positive and the patient requires confirmatory or therapeutic ICA. Both of these potential harms are only expected to occur in a small number of patients, and the risk in the intervention group will be much lower as compared to usual care. We will also track ICA within 90 days of the last imaging procedure to ensure that there are no events in the intervention group representing unplanned crossover.

In terms of potential model performance errors, the data quality committee will periodically monitor the performance of the model, with particular attention to when the model appears to be performing outside its normal parameters. No formal auditing is planned.

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Ethical Considerations

This study was approved by the Hamilton Integrated Research Ethics Board (HiREB #17103, protocol version 1.8, February 21, 2025. The original study protocol was first approved on November 5, 2024). At the time of recruitment, participants will be provided with the informed consent form by email and will be given the opportunity to ask questions about the study. The email sent to participants contains the contact information of two members of the research team, as well as instructions for participants should they have further questions about the study or wish to opt out. Documented consent will be obtained either before or at the time of the index procedure (CCTA or ICA). Participants are made aware during the consent process that they will not be provided monetary compensation for participating in the study. The data obtained from the referral forms and medical histories that are entered into the decision support tool, along with the predicted probability of significant CAD, will be automatically stored in a secure, cloud-based database upon generation of the recommendation, with the exception of postal codes and referring physicians' College of Physicians and Surgeons of Ontario registration numbers. Participant data will be handled in compliance with all relevant privacy and security regulations. All personal information about potential and enrolled participants will be securely stored and accessible only to authorized research team members. To protect confidentiality, participants will be assigned unique identification numbers, which will link their personal data to study-related data. All study data will be deidentified before being stored in the study database, which is maintained on a secure institutional server with restricted access.

Results

CarDIA-AI received funding in 2023. Recruitment began on January 9, 2025, and is projected to conclude in mid to late 2025. As of April 14, 2025, we have enrolled 81 participants. Data analysis will begin after all follow-up data are obtained. We expect to submit the first results for publication in 2026.

Discussion

Contributions of the CarDIA-AI Trial

Appropriate test selection for evaluating the coronary anatomy of elective outpatients with suspected CAD is important for reducing unnecessary invasive procedures and optimizing health care resource usage. A recent statement from various radiology and cardiovascular imaging societies called attention to the need for research on the use of AI for personalized cardiac imaging test selection [25]. The CarDIA-AI trial aims to meet this need as the first to leverage AI to optimize patient selection for CCTA versus ICA. Building on strong pilot work demonstrating the feasibility and potential of the AI model and triage pathway, this trial will evaluate their effectiveness in clinical practice. Based on our previous work [14], we anticipate that patients triaged using the AI-based decision support tool will have a lower proportion of normal or nonobstructive CAD diagnosed via ICA compared to those proceeding directly to ICA. If successful, this intervention could streamline the triage of ICA referrals and enhance the use of CCTA, which could save health care systems millions of dollars each year while preventing procedural complications.

Comparison to Prior Work

In the assessment of stable CAD, various prediction models have been developed to estimate the probability of disease prior to diagnostic evaluation [26,27]. While most validated models rely on traditional statistical approaches, there is growing interest in the application of AI methods. In other areas of cardiology, AI has recently been successfully implemented to support the triage of chest pain in emergency care settings, reducing time to emergency cardiovascular procedures [28,29]. Another recent trial evaluated an AI model that predicts the probability of significant CAD from stress echocardiography images to guide referrals for ICA [30], highlighting the increasing focus on AI in cardiology decision-making. However, while AI models have been developed for numerous use cases in cardiology, their evaluation in clinical trials has been relatively limited thus far. Most models that have been prospectively assessed have demonstrated clinical or operational improvements relative to clinicians, particularly in applications related to imaging interpretation and CAD [31]. Despite these promising findings, there is still a need for prospective trials to determine the real-world effectiveness of AI interventions [32]. The CarDIA-AI trial will address this gap by evaluating an AI model in a pragmatic manner and inform future implementation strategies for similar interventions.

Strengths and Limitations

There are some limitations to our approach. Based on our pilot studies, we expect a certain amount of data to be missing from some patients' referral forms, which we have found to have a small effect on model performance compared to our original retrospective study. However, while our model may achieve slighter lower predictive performance than it would using retrospective data, the pragmatic nature of our trial design should ultimately yield a more realistic estimate of the effects this AI model would achieve in a real-world setting. Similarly, the immediate generalizability of the AI model remains uncertain, as its effectiveness may vary across different health care settings. However, the parallel implementation study will evaluate how effectively the intervention can be integrated into practice, identifying barriers and facilitators to clarify the contexts in which such an intervention may be most effective. Additionally, while the AI model is specific to the Ontario data on which it was developed and validated, similar datasets exist in other jurisdictions. While we are not assessing clinical efficacy and safety outcomes in this trial, these have been previously established in trials comparing CCTA-first strategies to direct ICA [33-36].

Future Directions

Further research is needed to more comprehensively understand the potential of the AI intervention and its sustainability. For example, prospective evaluations in other centers will provide insight into its generalizability and scalability. The implementation study will qualitatively explore barriers to using the intervention as perceived by triage staff. Future studies where the tool is actively used by triage staff should be

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conducted to further identify potential usability challenges and assess whether the intervention remains effective in routine practice. Similarly, future work may also explore the long-term effectiveness of the AI intervention, for example, by implementing methods to continually monitor model performance.

Conclusions

The CarDIA-AI trial is the first to leverage AI for the triage of patients referred for assessment of suspected CAD. If successful, the intervention could optimize the referral process, resulting in millions of dollars in cost savings to the health care system while improving the patient experience by reducing exposure to unnecessary procedural risks.

Acknowledgments

We would like to thank the cardiac catheterization laboratory triage staff, the members of the Hamilton and Niagara catheterization laboratories and diagnostic imaging teams, the Hamilton Health Sciences Innovation portfolio, CorHealth Ontario, and the Canadian Cardiovascular Society for their support of the CarDIA-AI (Coronary computed tomographic angiography to optimize the Diagnostic yield of Invasive Angiography for low-risk patients screened with Artificial Intelligence) trial. We would also like to thank the Hamilton Academic Health Sciences Organization and the Population Health Research Institute for their financial and logistical support. This trial will be funded by a Hamilton Academic Health Sciences Organization (HAHSO) AFP Innovation Grant (HAH-24-010), a Population Health Research Institute (PHRI) grant (PHRI-IGC-2023-Dr. Jeremy Petch-CarDIA-AI), and a grant from the Hamilton Health Sciences Foundation. The funding sources had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results. Information on trial oversight can be found in Multimedia Appendix 7.

Authors' Contributions

JP and JDS conceived of the project, obtained funding, and are the main administrators of the project. All authors contributed to the methodological design of the study. JPTB wrote the manuscript with support from JP, JDS, and MPB. All authors reviewed the final manuscript. The statistical analysis plan was conceived by SIB and will be implemented by SIB and SD.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT-AI (Standard Protocol Items: Recommendations for Interventional Trials—Artificial Intelligence) checklist.
[DOCX File , 64 KB - resprot_v14i1e71726_app1.docx]

Multimedia Appendix 2
Informed consent form.
[DOCX File , 62 KB - resprot_v14i1e71726_app2.docx]

Multimedia Appendix 3
Additional tables and figures.
[DOCX File , 649 KB - resprot_v14i1e71726_app3.docx]

Multimedia Appendix 4
Model input details.
[DOCX File , 13 KB - resprot_v14i1e71726_app4.docx]

Multimedia Appendix 5
Data entry standard operating procedure.
[DOCX File , 21 KB - resprot_v14i1e71726_app5.docx]

Multimedia Appendix 6
CarDIA-AI (CCTA [coronary computer tomographic angiography] to optimize the Diagnostic yield of Invasive Angiography for low-risk patients screened with AI [artificial intelligence]) implementation study interview and survey questions.
[DOCX File , 17 KB - resprot_v14i1e71726_app6.docx]

Multimedia Appendix 7

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Information on trial sponsor, steering committee, and data quality committee.
[DOCX File , 14 KB - resprot_v14i1e71726_app7.docx]

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Abbreviations

AI: artificial intelligence
CAD: coronary artery disease

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CarDIA-AI: CCTA to optimize the Diagnostic yield of Invasive Angiography for low-risk patients screened with AI
CCTA: coronary computed tomographic angiography
ICA: invasive coronary angiography
REDCap: Research Electronic Data Capture
SPIRIT-AI: Standard Protocol Items: Recommendations for Interventional Trials—Artificial Intelligence

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Protocol

Multimodal Web-Based Telerehabilitation for Patients With Post–COVID-19 Condition: Protocol for a Randomized Controlled Trial

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Abstract

Background: Patients with post–COVID-19 condition (PCC) experience persistent, long-term health consequences following SARS-CoV-2 infection, including fatigue, hyperventilation, cognitive impairment, and limitations in daily activities. There is emerging evidence suggesting that exercise and respiratory therapy–based telerehabilitation is safe and could potentially improve physical capacity while reducing health care costs.

Objective: This study aims to evaluate the superiority of a multimodal, symptom-titrated telerehabilitation program over standard care in patients with PCC who are severely affected, using the highest oxygen uptake rate (VO_{2peak} [mL/min/kg]) achieved during the cardiopulmonary exercise test (CPET) and minute ventilation/carbon dioxide production slope (VE/VCO_2 [full slope]) as primary outcomes. In addition, this study seeks to provide novel insights into the clinical and physiological adaptations associated with PCC, informing future rehabilitation strategies.

Methods: This prospective, randomized, waitlist-controlled trial was approved by the Rhineland-Palatinate Medical Association ethics committee. All procedures comply with the Declaration of Helsinki. This study comprises 3 examination time points, which include patient-reported outcomes, clinical assessments, and a CPET. It is structured into an 8-week intervention phase followed by an 8-week follow-up phase. Following baseline assessment, patients will be randomly assigned to either the intervention group (IG) or the control group (CG). During the intervention phase, IG participants will receive a web-based, multimodal, symptom-titrated telerehabilitation program consisting of sports medicine consultations, weekly teleconsultations, a structured pacing approach, and exercise and respiratory therapy. In contrast, CG participants will receive treatment as usual, which includes a single sports medicine consultation on healthy habits and a self-directed pacing approach for managing symptoms and daily activities. During the follow-up phase, IG participants will continue training independently without teleconsultations, whereas CG participants will undergo the same telerehabilitation intervention as the IG. A follow-up assessment will be conducted for both groups to evaluate long-term effects. This study adheres to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines and follows the Consensus on Exercise Reporting Template.

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Results: Recruitment began in August 2023 and was extended until March 2025. As of March 2025, 80 participants have been recruited, and data analysis is ongoing. Final results are expected by December 2025, with a cross-sectional analysis of baseline data anticipated by July 2025.

Conclusions: This study is the first randomized controlled trial investigating the effectiveness of multimodal and symptom-titrated telerehabilitation in patients with PCC who are severely affected. The integration of various objective diagnostic systems will provide valuable insights into emerging postviral fatigue syndromes, supporting the development of CPET-based diagnostics, personalized rehabilitation strategies, and future research on long-term telerehabilitation effectiveness. The findings will be disseminated through peer-reviewed publications, professional networks, and patient advocacy groups to ensure scientific, clinical, and public impact.

Trial Registration: German Clinical Trials Register (DRKS) DRKS00032394; https://drks.de/search/de/trial/DRKS00032394

International Registered Report Identifier (IRRID): DERR1-10.2196/65044

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KEYWORDS

myalgic encephalomyelitis; chronic fatigue syndrome; ME/CFS; postexertional malaise; PEM; exercise intolerance; return to work; physiotherapy

Introduction

Background

Many individuals with COVID-19 continue to experience symptoms well beyond the acute phase of the disease, which can last for months or even years [1,2]. This persistent condition, known as post–COVID-19 condition (PCC), affects an estimated 6% to 15% of patients with COVID-19, and conservative estimates suggest that approximately 65 to 75 million people worldwide are experiencing PCC [3,4]. Consequences go beyond individual health, impacting social systems and the economy. For instance, the financial strain on the German health care and pension system was projected to reach €1.7 billion (US $1.96 billion) in 2021, with additional production losses and gross value-added losses amounting to €3.4 billion (US $3.91 billion) and €5.7 billion (US $6.56 billion), respectively [5].

PCC manifests as a multisystemic disorder with diverse clinical symptoms and can be categorized into 3 clusters: physical and cognitive impairments and mental disorders [3,6]. The most common symptoms among all the clusters are fatigue, hyperventilation, limitations in daily activities, cognitive impairments, and mental disorders [7]. Overall, 8% to 16% of patients with PCC meet the diagnostic criteria for myalgic encephalomyelitis or chronic fatigue syndrome (ME/CFS) because they experience both chronic fatigue and postexertional malaise (PEM) [8-10]. Chronic fatigue, defined by fatigue persisting for at least 6 months, and PEM, characterized by physical, mental, or emotional stress intolerance with exacerbation of symptoms even during everyday activities, are the leading symptoms of ME/CFS [11]. In addition to physical, mental, or emotional stress, PEM in patients with PCC is often triggered by hypersensitivity to food, chemicals, noise, light, extreme temperatures, inadequate sleep, or illness [12].

Regardless of the severity of acute COVID-19, the symptoms listed can persist for months and lead to an impaired quality of life and ability to work [7,13]. Female sex, older age, overweight status, smoking habits, preexisting comorbidities, and previous hospitalization or intensive care unit admission are significantly associated with a higher risk of developing PCC [14]. The etiology of PCC is believed to involve a combination of organ damage caused by the pathogen; a misdirected immune response; and additional mechanisms such as viral persistence, autoimmunity, endothelial dysfunction, and dysautonomia [15]. However, the specific physiological and biochemical pathomechanisms remain elusive [15,16].

Consequently, the focus of PCC treatment is on symptom management via multidisciplinary therapeutic approaches [17,18]. A survey in German rehabilitation centers for PCC showed the effectiveness of such measures in alleviating symptoms and improving health-related quality of life and work capacity [19]. Notably, 96 (72%) of 134 rehabilitation facilities reported longer durations of follow-up care for individuals with PCC than for those with other diseases. The most important therapeutic areas include exercise and respiratory therapy, psychotherapy, and therapeutic relaxation. A recent review discussed the positive physiological effects of endurance and strength exercise programs, such as immunomodulatory optimization and anti-inflammatory effects, which could reduce the long-term and health-related effects of PCC [20]. Several systematic reviews have examined the effects of exercise and respiratory therapy, particularly on physical capacity, hyperventilation, and quality of life, in patients with PCC [21-24].

Hyperventilation has been identified as a potential contributor to dyspnea in patients with COVID-19 and ME/CFS [25] as it may result in reduced carbon dioxide levels, leading to respiratory alkalosis and related symptoms such as breathlessness, dizziness, and fatigue. This mechanism is particularly relevant for patients with PCC experiencing persistent dyspnea as dysfunctional breathing patterns, including hyperventilation, may exacerbate respiratory symptoms and negatively impact overall quality of life [26]. Consequently, addressing hyperventilation through targeted respiratory therapy could be an important approach to improving hyperventilation and enhancing rehabilitation outcomes. In general, exercise and respiratory therapy have been shown to be safe and effective; however, physical activity or structured exercise may also trigger PEM in some patients [12].

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Understanding PEM is important, especially for safe exercise therapy, and requires an analysis of the responses triggered by exercise. Objective pathological changes at the tissue level, particularly in blood and muscle tissue, can be observed following intense physical exertion in patients with PCC [27]. The cardiopulmonary exercise test (CPET), an objective assessment of cardiorespiratory fitness (CRF), oxygen uptake (VO_2), and ventilatory efficiency during exercise, is used to diagnose dysfunction at the pulmonary, cardiac, and muscle level [28]. Patients with PCC who are severely affected have decreased levels of CRF, lower VO_2 and ventilatory efficiency, and an impaired metabolic response during exercise and recovery [29-31]. Thus, the CPET serves as a valuable tool for the physiological characterization of patients with PCC, facilitating the prescription of personalized, symptom-titrated exercise programs.

Promising strategies for handling PEM in daily activities include pacing and the symptom-titrated approach to exercise therapy [32-34]. Both strategies focus on patient-centered care. Pacing therapy primarily aims to prevent the exacerbation of symptoms, especially fatigue and the onset of PEM, while promoting optimal activity levels for patients in their daily lives, whereas exercise therapy aims to improve their physical capacity. While pacing is widely used in the therapeutic treatment of patients with PCC and involves treatment as usual with a healthy lifestyle (eg, diet and sleep behavior) and drug treatment for accompanying symptoms, exercise therapy is controversially discussed, especially in patients with PCC who are severely affected, and is only used with reservations in standard care [35].

Given the widespread prevalence of PCC and its substantial impact on the health care system, telerehabilitation has emerged as a potentially cost-effective solution [36] for accessing a high number of patients irrespective of location and time [37,38]. Current systematic reviews on exercise and respiratory therapy–based telerehabilitation in patients with PCC [39,40] have reported improvements in quality of life and hyperventilation, as well as an increase in physical capacity.

Objectives

Therefore, we developed a multimodal, personalized, and symptom-titrated telerehabilitation program that includes weekly teleconsultations, a pacing approach, and exercise and respiratory therapy for patients with PCC who are severely affected and unable to work. The primary aim of this study is to investigate the superiority of our telerehabilitation program compared to treatment as usual in terms of CRF (highest VO_2 rate achieved during the CPET [VO_{2peak}; mL/min/kg]) and hyperventilation (minute ventilation [VE]/carbon dioxide production [VCO_2] slope [full slope]). In addition, the secondary aim is to explore the clinical and exercise physiology processes associated with PCC. A better understanding of postviral fatigue conditions can improve not only medical treatment but also the management of return to work for patients with PCC and ME/CFS.

Methods

This study was prospectively registered in the German Clinical Trials Register on July 28, 2023 (registration: DRKS00032394).

Ethical Considerations

This study was reviewed and approved by the ethics committee of the Rhineland-Palatinate Medical Association at the University Medical Center Mainz (registration: 2023-17082) in June 2023. The research was conducted in full compliance with institutional and ethical standards of the Declaration of Helsinki for research with human participants. All participants provided written informed consent before participation in the study. Participants were informed about the study purpose, procedures, potential risks and benefits, the voluntary nature of their participation, and their right to withdraw from the study at any time without consequences. Regarding any secondary analyses using existing data, the original consent and ethics approval explicitly covered the possibility of secondary analysis without requiring additional consent from participants. All collected data were fully anonymized before analysis. No personally identifiable information was stored or used in any publications or supplementary materials. Appropriate technical and organizational measures were implemented to protect participants' confidentiality and data security. Participants did not receive any monetary compensation for taking part in this study. Participation was entirely voluntary without financial incentive. No identifiable images of study participants are included in the manuscript or supplementary materials.

Study Design

Overview

This study is designed as a single-center prospective randomized controlled trial (RCT) with a waitlist control design (Figure 1) and is conducted by the Department of Sports Medicine, Prevention, and Rehabilitation at Johannes Gutenberg University Mainz in cooperation with the German social accident insurance provider for nongovernmental health and social care institutions (German: *Berufsgenossenschaft für Gesundheitsdienst und Wohlfahrtspflege* [BGW]). The total study duration is 16 weeks and consists of an 8-week intervention phase and an 8-week follow-up phase with 3 examination time points: baseline assessment (T0) before the intervention, primary assessment (T1) after the intervention, and follow-up assessment (T2) after the follow-up phase. Participants will be informed about the objectives and risks of the study 1 week before T0 in written form (information document and informed consent form via email) and verbally at T0. They are required to provide their written consent before the baseline examination and, therefore, are not blinded to the study intervention. Patients will then undergo a comprehensive baseline assessment at T0 (questionnaires, clinical assessment, CPET, and muscle strength testing). A summary of the study phases, examination time points, and assessments is provided in Table 1. After the baseline assessment, participants are stratified by sex, age, and peak power output (PO; W/kg of body weight) during the CPET and then randomly assigned to either the intervention group (IG) or the control group (CG) by a researcher (BH) using a self-written

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R script (R Foundation for Statistical Computing; Multimedia Appendix 1).

The CPET is used to allocate the participants from the IG to 1 of 3 training groups (TGs; TG 1-TG 3) based on the allocation criteria (Table 2). After the intervention phase, participants in both groups (IG and CG) will undergo the same comprehensive examination at T1 as at T0 to evaluate the effects of the intervention on the IG and assign CG participants to the intervention and allocate them to 1 of the 3 TGs. In the follow-up phase, the CG participants undergo the same intervention as the IG during the intervention phase, whereas the IG (reallocated if necessary) continues the exercise and respiratory therapy in a self-directed manner. To evaluate the long-term effects of the intervention on the IG and the short-term effects on the CG, both groups will undergo the same comprehensive examination at T2.

Figure 1. Study flowchart. The study consists of 3 assessment time points (T0-T2), including an 8-week intervention and an 8-week follow-up phase. Participants were allocated or reallocated to 3 training groups (TGs) based on baseline cardiorepiratory fitness parameters. The intervention included telerehabilitation (teleconsultation and web-based training), while the control group received usual care. CG: control group; Endurance: aerobic interval training; IG: intervention group; Pacing: pacing strategy for self-management of energy; POTS: postural orthostatic tachycardia syndrome training; Respiratory: respiratory training; Strength: strength training.

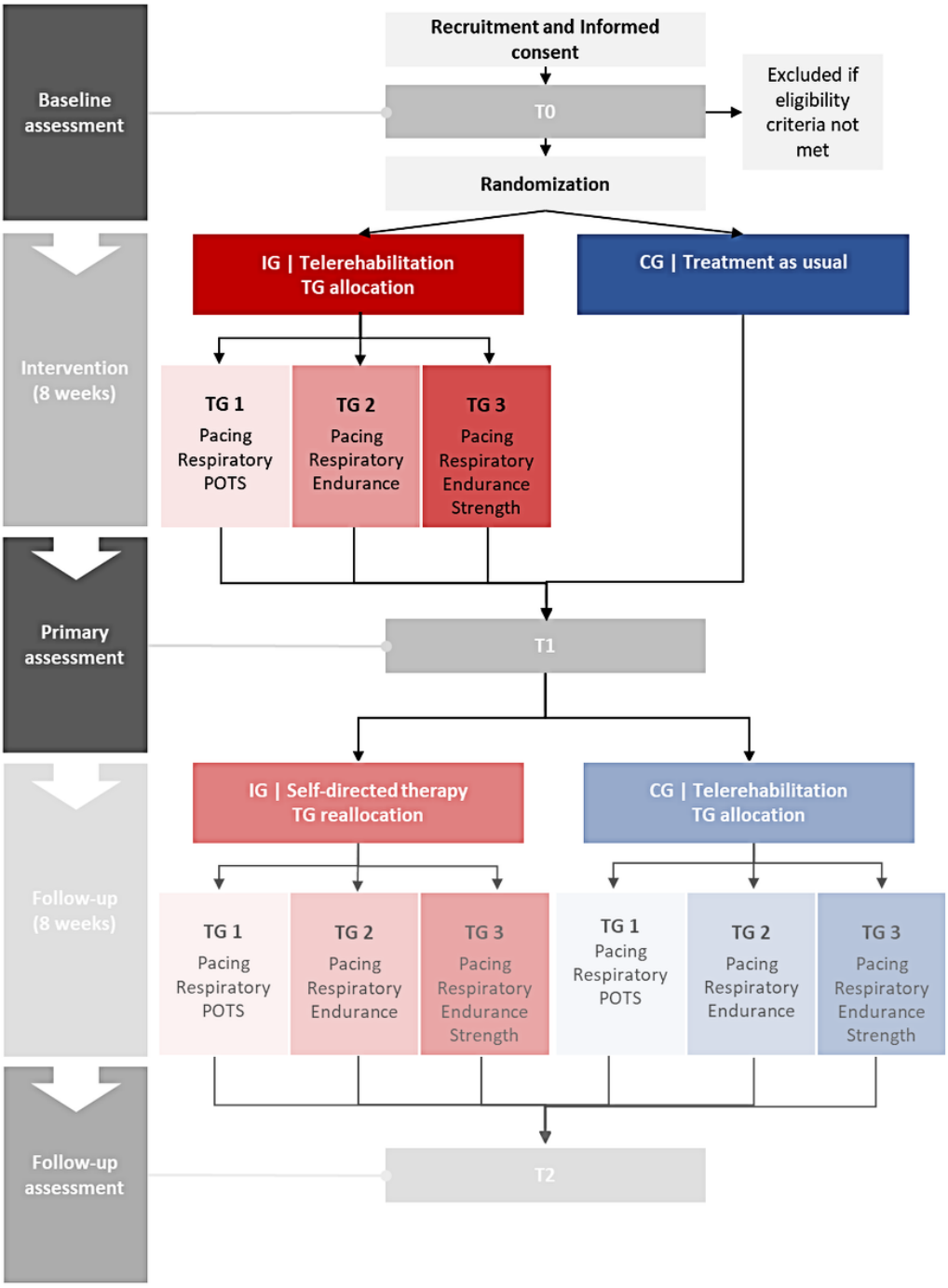

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Table 1. Overview of the study phases and groups, examination time points, and assessments.

	T0[a]	Intervention phase[b]		T1[c]	Follow-up phase[b]		T2[d]
		IG[e] (T0-T1)	CG[f] (T0-T1)		IG (T1-T2)	CG (T1-T2)	
Enrollment							
Informed consent	✓						
Eligibility criteria	✓						
Randomization (stratified)	✓						
Training group allocation	✓			✓			
Questionnaires							
Nijmegen questionnaire	✓			✓			✓
DSQ-SF-PEM[g] questionnaire	✓			✓			✓
Canadian Consensus Criteria	✓						✓
Bell scale	✓						✓
Brief Symptom Inventory–18	✓			✓			✓
Insomnia Severity Index	✓			✓			✓
Perceived Social Support Questionnaire	✓			✓			✓
Optimism-Pessimism Short Scale–2	✓			✓			✓
General Self-Efficacy Scale	✓			✓			✓
Satisfaction evaluation							✓
Clinical assessments							
Anamnesis[h]	✓						
Anthropometric data[i]	✓			✓			✓
ECG[j]	✓			✓			✓
Blood pressure	✓			✓			✓
Pulmonary function test	✓			✓			✓
Clinical examination[h]	✓						
Blood biomarkers[k]	✓			✓			✓
Hyperspectral imaging[l]							✓
Blood gas analysis							✓
Cardiopulmonary exercise testing							
Spiroergometry	✓			✓			✓
Lactate and cfDNA[m] diagnostics[n]	✓			✓			✓
Muscle strength testing							
Hand grip strength	✓			✓			✓
Intervention							
Telerehabilitation[o]		✓				✓	

[a]T0: baseline assessment.
[b]8 weeks.
[c]T1: primary assessment.
[d]T2: follow-up assessment.
[e]IG: intervention group.
[f]CG: control group.
[g]DSQ-SF-PEM: DePaul Symptom Questionnaire–Short Form for Postexertional Malaise.

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[h]Conducted by a study physician.

[i]Weight, height, and body composition.

[j]ECG: electrocardiography.

[k]The complete list of blood biomarkers can be found in Multimedia Appendix 2.

[l]Optical peripheral microcirculatory analysis.

[m]cfDNA: cell-free DNA.

[n]Capillary lactate (mmol/L) concentration and venous cfDNA concentration (ng/mL).

[o]Weekly teleconsultations and web-based exercise and respiratory therapy.

Table 2. Criteria for training group (TG) allocation based on the algorithm for prognostic and diagnostic stratification criteria for patients with chronic lung and heart disease described in the study by Guazzi et al [28][a].

Group	VO_{2peak}[b] (mL/min/kg)	PPO[c] (W/kg of body weight)	VE/VCO_2[d] slope (full slope)
TG 1	<16	<1	>45
TG 2	16-20	1-1.5	30-45
TG 3	>20	>1.5	<30

[a]If 2 out of 3 variables correspond to one of the TGs, the study participant is assigned to that group. If all 3 variables are aligned with different groups, the group allocation is discussed individually with the study physician.

[b]VO_{2peak}: highest oxygen uptake rate achieved during the cardiopulmonary exercise test.

[c]PPO: peak power output.

[d]VE/VCO_2: minute ventilation/carbon dioxide production.

Participants

A total of 80 participants will be recruited by the Department of Sports Medicine, Prevention, and Rehabilitation at Johannes Gutenberg University Mainz in cooperation with the BGW and selected according to the inclusion and exclusion criteria defined in Textbox 1 [41,42]. The study population will consist of employees in the German health care or social services sector who are unable to work full or part time due to PCC. All participants will have a documented SARS-CoV-2 infection acquired through their work and experience persistent PCC symptoms lasting >12 weeks [2], leading to substantial impairment in daily functioning and occupational disability.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Age of ≥18 years
- Signature of the consent form
- Proven SARS-CoV-2 polymerase chain reaction test provided by medical personnel
- Post–COVID-19 condition (PCC) diagnosis by the family or company physician (main diagnosis+ *International Classification of Diseases* diagnosis code U09.9)
- Occupational disability (full or part time) due to PCC
- Insured by the German social accident insurance provider for nongovernmental health and social care institutions

Exclusion criteria

- No internet access or inability or unwillingness to participate in the study
- Lack of capacity to consent or doubts about capacity to consent
- Participation in another rehabilitation program based on exercise and respiratory therapy (this means that individual passive physical therapy [eg, massage or thermotherapy], psychotherapeutic treatments, and visits to the physician are permitted)
- Red flags [41] and absolute contraindications for exercise training and physical activity [42]
- Participation in another study
- Inability to undergo performance diagnostics on the cycle ergometer
- Other unspecified factors discouraging study participation

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Outcomes

The primary objective of this study is to investigate the effects of the intervention on CRF and hyperventilation. Evaluation of changes from baseline to primary assessment with respect to the IG and CG will involve (1) changes in CRF (VO_{2peak} [mL/min/kg]) and (2) changes in hyperventilation (VE/VCO_2 slope [full slope]).

The secondary objective is to investigate the effects of exercise on other physiological, clinical, and psychosocial variables. Evaluation of changes from baseline to primary assessment with respect to the IG and CG will involve (1) changes in PO at maximal exertion (peak PO [W/kg of body weight]) and at the first and second ventilatory threshold (PO [W/kg of body weight]; if the ventilatory thresholds cannot be determined, the lactate thresholds will be used alternatively); (2) changes in VO_2 efficiency, measured using the VO_2 efficiency slope (OUES [VO_2/VElog]), oxygen pulse (O_2 pulse [mL/beat]), and oxygen cost of work ($\Delta VO_2/\Delta WR$ [mL/min/W]); (3) changes in ventilatory efficiency, evaluated using the cardiorespiratory optimal point (COP [VE/VO_2min]), ventilatory equivalent for carbon dioxide (ECO_2) and for oxygen (EO_2), end-tidal carbon dioxide tension ($PETCO_2$ [mmHg]) and end-tidal oxygen ($PETO_2$ [mmHg]) tension, and Nijmegen questionnaire score; (4) changes in handgrip strength (HGS; kg); (5) changes in blood biomarker levels, evaluated using venous cell-free DNA (cfDNA; ng/mL) and capillary lactate (mmol/L) concentrations; (6) adherence to the intervention protocol (percentage of the prescribed intervention days); (7) changes in clinical condition and functional disability (frequency and severity of PEM, measured using the rating scale for perceived symptom severity [RPSS; described in the *Monitoring of Clinical Condition and Control of Training Load* section], the score on the DePaul Symptom Questionnaire–Short Form for Postexertional Malaise, the Canadian Consensus Criteria for diagnosis of ME/CFS, and the Bell chronic fatigue and immune dysfunction syndrome disability scale); and (8) changes in selected psychosocial variables (somatization, depression, and anxiety [Brief Symptom Index–18]; severity of insomnia [Insomnia Severity Index]; social support [short form of the Perceived Social Support Questionnaire]; optimism and pessimism [Optimism-Pessimism Short Scale–2]; and self-efficacy [General Self-Efficacy Scale]).

It should be noted that, except for the VE/VCO_2 slope (full slope), which is calculated from the start of load to maximum exertion, and cardiorespiratory optimal point, which is the minimum ventilatory equivalent for oxygen during the CPET, all spiroergometric parameters are measured at rest, at the ventilatory (lactate) thresholds, and at maximal effort.

Outcome Measures

Questionnaires

Validated questionnaires are completed at each examination time point before the clinical assessment, and the CPET records various disease- and health-related aspects. The questionnaires are administered via the WordPress Gravity Forms Plugin (Rocketgenius Inc) and are accessible to participants from the day of consent until T0 or 7 days before for T1 and T2. To minimize response fatigue and bias, participants are explicitly instructed to distribute questionnaire completion over several days rather than completing them all at once, ensuring better energy management and more accurate responses. However, the completion period is limited to a maximum of 7 days to maintain the validity of the responses at each test time point. Any questionnaires not completed within this time frame are finalized on-site before the clinical assessment and CPET.

The Nijmegen questionnaire will be used to evaluate symptoms of breathing pattern disorders and hyperventilation syndrome [43]. The frequency, duration, and severity of PEM are determined using the DePaul Symptom Questionnaire–Short Form for Postexertional Malaise [44]. In addition, 2 already established questionnaires for ME/CFS will be used. These are the Canadian Consensus Criteria [45], which represent a definition scheme for the clinical diagnosis of ME/CFS, and the Bell chronic fatigue and immune dysfunction syndrome disability scale [46], which represents a determination of functional disability. Due to the strong similarity in symptoms between PCC and ME/CFS [12,47], both questionnaires are also suitable for patients with PCC. The Brief Symptom Index–18 will be used to quantify somatization, depression, and anxiety [48]. The Insomnia Severity Index will be used to quantify the severity of insomnia symptoms [49]. The General Self-Efficacy Scale will be used to assess general optimistic self-belief [50]. The short form of the Perceived Social Support Questionnaire will be used to assess social support [51]. The Optimism-Pessimism Short Scale–2 will be used to measure the psychological trait of optimism-pessimism [52]. To assess participant satisfaction with our multimodal telerehabilitation program, we created and applied a satisfaction questionnaire based on previous process evaluations of our last 4 clinical trials [53].

Clinical Assessment

All participants undergo a clinical assessment at all 3 examination time points before the CPET. The aim is to perform risk stratification, particularly to identify participants at high risk of PEM, and perform specific analyses to better understand PCC. Measurements of height, body composition (InBody 3.0; Biospace), blood pressure (digital sphygmomanometer; ERKA), 12-lead electrocardiography (CardioPart 12 PC; AMEDTEC Medizintechnik GmbH), and pulmonary function (Body Box 5500; Medisoft GmbH) will be conducted by medical assistants at rest. Anamnesis and clinical examinations will be conducted by a blinded study physician (EL [internist]) according to the inspection, percussion, palpation, auscultation, and functional check algorithm. The results of the clinical assessments will be discussed with the physician and sports scientist to decide whether the participant is physically able to perform the CPET or whether they will be excluded from the study. In addition, venous blood analysis (Multimedia Appendix 2), blood gas analysis (Stat Profile Prime Plus; Nova Biomedical GmbH), and optical peripheral microcirculatory analysis with hyperspectral imaging (TIVITA Tissue System; Diaspective Vision GmbH) will be conducted. For venous blood analysis, 4.9 mL of blood are collected from the antecubital vein into a K3-EDTA Monovette (Sarstedt) 5 minutes before the CPET. For blood gas analysis, 50 µL of capillary blood are collected

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from the earlobe 5 minutes before and immediately after the CPET.

CPET Component

Spiroergometry

To evaluate changes in CRF, hyperventilation, and other physiological exercise variables, spiroergometry will be conducted on an ER 900 PC cycling ergometer (Ergoline GmbH) using the Blue Cherry software (Geratherm Respiratory GmbH). The test protocols are designed to consist of 4 to 6 stages, each lasting 2 minutes, during which the exercise intensity (in W) is continuously increased at the end of each stage (Figure 2). In total, 2 test protocols with different exercise durations will be used. These protocols are tailored to the patient's physical capacity and ensure a test duration of 8 to 12 minutes, thus maximizing the reliability of the VO_{2peak} determination [54,55]. All CPETs is carried out by a blinded sports scientist (DTO).

A 12-lead electrocardiogram is continuously monitored during the tests. VE, VO_2, and VCO_2 will also be continuously measured and analyzed using the breath-by-breath method. The rating of perceived exertion (RPE) will be assessed using the Borg scale (6-20) in the last 30 seconds of each exercise stage [56]. Testing is stopped when absolute or relative termination criteria (Textbox 2) are met. Primary termination criteria or subjective symptoms (eg, fatigue, leg fatigue, angina, and dyspnea) are documented immediately after completion of the CPET.

To provide accurate information on the data processing strategy to determine the VO_{2peak}, we will follow the current guidelines for reporting of data processing strategies to determine maximum VO_2 (Multimedia Appendix 3) [58]. The raw, unmodified data are filtered using a third-order Butterworth forward-backward low-pass filter with a 0.04-Hz cutoff implemented in the *spiro* package for R (version 0.0.4) [59] to determine the $VO_{2peak.}$ The VE/VCO_2 slope (full slope) is calculated using linear regression analysis of VE and VCO_2 with unmodified raw data throughout the load phase of the exercise test protocol (Multimedia Appendix 4) [55]. For the analysis of submaximal CRF and energy metabolism, the ventilatory thresholds [60] are defined based on established criteria (Multimedia Appendix 5).

Figure 2. Illustration of the cardiopulmonary exercise test (CPET) protocols. The CPET protocol includes 2-minute stages starting at 25 W with load increments of 10 or 20 W per stage. Venous blood samples (filled drops), capillary blood samples (unfilled drops), blood pressure measurements, and rating of perceived exertion assessments are indicated.

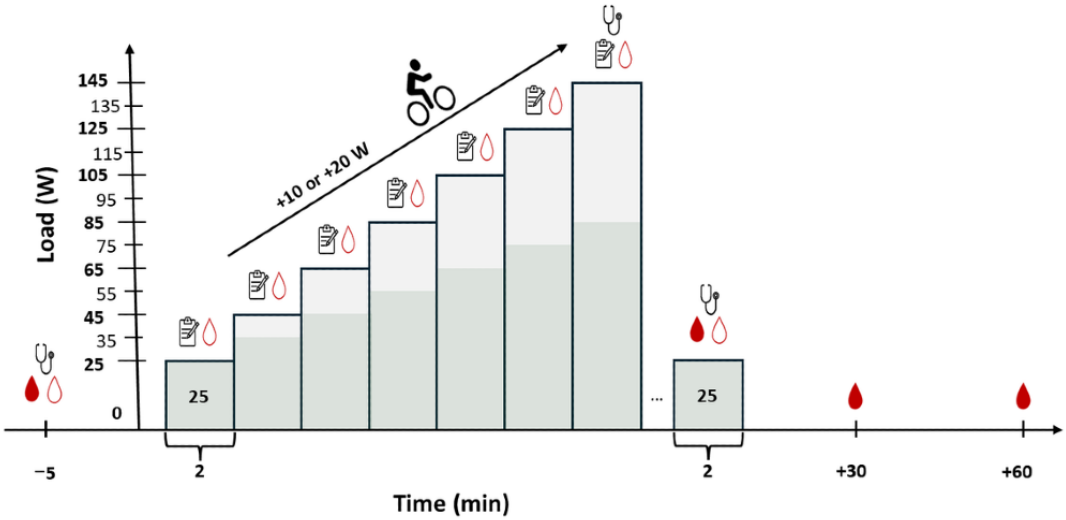

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Textbox 2. Absolute and relative termination criteria [54,57].

Absolute termination criteria

- Decrease in systolic blood pressure of >10 mm Hg compared to the initial blood pressure despite an increase in stress with other signs of ischemia
- Definite angina pectoris
- Increasing cerebral symptoms (eg, ataxia, confusion, or presyncope)
- Signs of reduced peripheral perfusion (cyanosis or pallor)
- Technical reasons that make it impossible to adequately analyze the electrocardiogram or systolic blood pressure
- The study participant's desire to terminate the exercise
- Persistent ventricular tachycardia
- ST segment elevation of at least 0.1 mV in leads without pathological Q waves (not augmented vector right or precordial lead V1)

Relative termination criteria

- Decrease in systolic blood pressure of >10 mm Hg compared to the initial blood pressure despite an increase in stress without other signs of ischemia
- Increasing angina pectoris
- Arrhythmias other than sustained ventricular tachycardia, including multifocal ventricular extrasystoles, triplets, supraventricular tachycardia, blockages, or atrial fibrillation
- Fatigue, breathlessness, wheezing, leg cramps, or claudication
- Development of a bundle branch block or intraventricular conduction delay that cannot be distinguished from ventricular tachycardia
- Reduced cadence of <40 revolutions per minute
- Arterial hypertension (250 mm Hg systolic or 115 mm Hg diastolic)
- ST segment or QRS complex changes, such as horizontal or descending ST segment depression (>0.2 mV) or pronounced change in position type

Lactate Diagnostics

For lactate diagnostics, capillary blood samples (20 µL) are taken from the earlobe 5 minutes before, during, and at the end of each exercise stage (last 30 seconds) and 3 minutes after completion of the CPET. Blood samples are measured immediately after the CPET through the polarographic determination method using an EKF Biosen S-Line measuring device (EKF Diagnostics GmbH) and analyzed using the winlactat 4.0 software (mesics GmbH). Lactate diagnostics include the measurement of the lactate concentration (mmol/L) and the determination of individual aerobic and anerobic thresholds for each participant using the *baseline +1.5 mmol/L method* according to Dickhuth et al [61].

cfDNA Diagnostics

At T0, venous blood samples are taken from the antecubital vein 5 minutes before, immediately after, 30 minutes after, and 60 minutes after the CPET using 4.9 mL of K3-EDTA Monovette (Sarstedt). In contrast to those at T0, the blood samples are only taken before and after the CPET at T1 and T2. The samples are centrifuged at 2500 × g for 15 minutes at room temperature. In total, 2 mL of plasma are taken and centrifuged a second time at 2500 × g for 15 minutes at room temperature. Plasma aliquots (150 and 550 µL) are collected in 1.5-mL tubes and stored at −20 °C according to established guidelines [62].

Concentrations of cfDNA will be measured using quantitative real-time polymerase chain reaction with unpurified plasma, as described previously [63]. The pipetting steps will be conducted using an automated pipetting system (ASSIST PLUS; INTEGRA Biosciences GmbH).

Muscle Strength Testing

HGS will be quantified during participants' clinical assessments (before and after the CPET) by medical assistants using a Jamar hydraulic hand dynamometer (SH5001; Saehan Industries GmbH) following an established protocol by Nacul et al [64]. Participants are instructed to sit in an upright position and squeeze the handgrip as hard as possible, lasting 3 seconds, in 3 consecutive trials with 30 seconds of rest between trials. The entire procedure takes approximately 3 minutes to complete, including instructions. To examine changes in HGS over the course of the study, HGS_{max} is defined as the highest value of the 3 consecutive trials. In addition, we calculate the HGS_{diff} to determine the decrease in HGS between the 3 consecutive trials by subtracting the mean value between the second and third trials from the value of the first HGS trial, as described elsewhere [64].

Intervention

Overview

Following the baseline examination (T0) and a 1-week washout period (recovery after the CPET), the IG will engage in therapist-led telerehabilitation for 8 weeks (intervention phase) followed by 8 weeks of self-directed therapy (follow-up phase). Concurrently, the CG will undergo treatment as usual for the initial 8 weeks, transitioning to the same therapist-led

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telerehabilitation as the IG in the follow-up phase. At each examination time point (T0-T2), after the clinical assessments and the CPET, all participants will undertake a sports medicine consultation with a sports scientist (DTO) to discuss the examination results, and they will be motivated toward a healthy lifestyle (eg, nutrition and stress control) and receive daily pacing recommendations. The results of the randomization (IG or CG) will be communicated to all participants within a few days after the baseline examination by a researcher (BH) via email.

Digital Infrastructure

The digital infrastructure that will be used during the intervention phase is divided into 2 different parts. The first part is a central website designed for mobile and desktop use (WordPress; WordPress Foundation). The second part is the software Mattermost (mobile app and desktop application; Mattermost Inc), which is used for digital communication between therapists and patients (Figure 3).

The website consists of three main areas: (1) a diary for monitoring and controlling clinical condition and training load in addition to the questionnaires already described in the *Questionnaires* section; (2) an education area with short educational videos about PCC and exercise and respiratory therapy, including a detailed explanation and the pacing approach; and (3) a therapy program area including written materials (eg, weekly therapy plans, instructions for each type of training, and control of training intensity depending on the clinical condition).

All important information on the use of the website and Mattermost is provided in the study manual and communicated to the participants via email. In the intervention phase, the IG participants can use both the website and Mattermost. In contrast, CG participants can use only a restricted version of the website (without the education or therapy program areas) for daily reporting via the clinical condition and training load diary (CCTD).

Figure 3. Digital infrastructure—(A) website for mobile and desktop use (WordPress; WordPress Foundation) and (B) mobile app and desktop application (Mattermost; Mattermost Inc). The author consents to the use of their image in this publication.

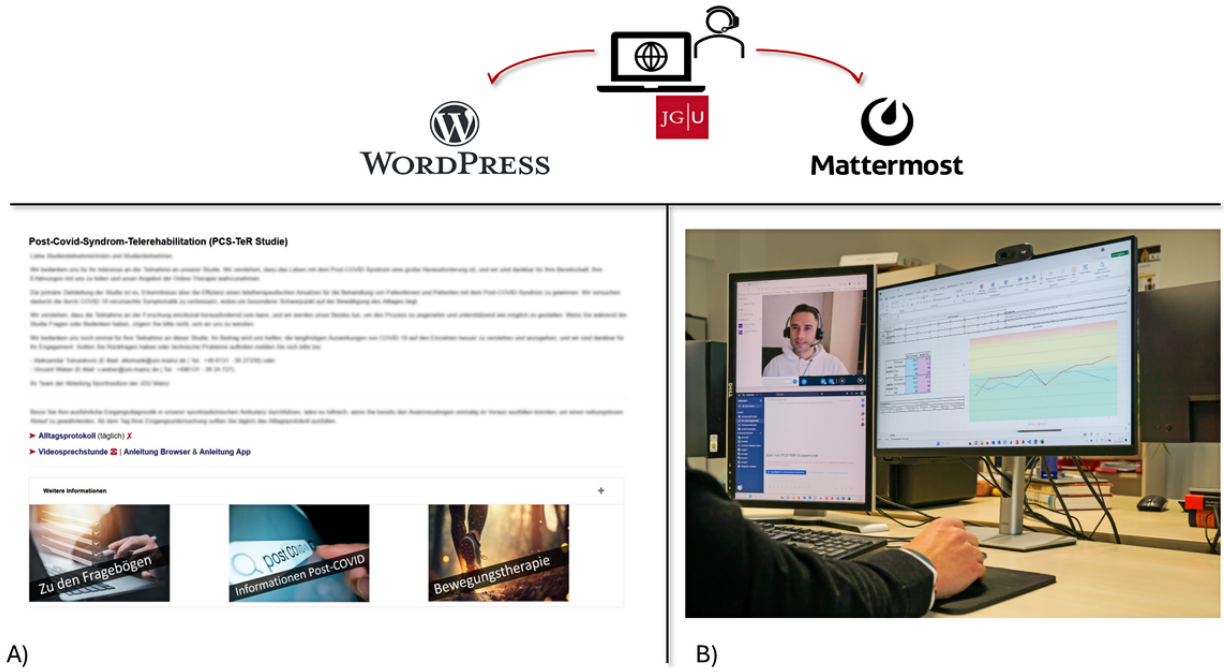

IG Setup

On the basis of the CPET results and the algorithm listed in Table 2, IG participants are assigned to 1 of 3 TGs (TGs 1-3). Before the start of the intervention, all participants will take part in 2 video-based introductory sessions in the first week to get to know their personal sports therapist, learn how to use the digital infrastructure, and understand the therapy program (eg, therapy plan and monitoring of clinical condition).

Therapy Program

Due to the short duration of the intervention (8 weeks), and to achieve an optimal balance between the disease condition and the workload, a therapy plan (Figure 4) was created consisting of a combination of exercise and respiratory training types and training and recovery days and following the principle of periodization and cyclization. The intervention and follow-up phases during the 16-week period are divided into 2 mesocycles (8 weeks) and 16 microcycles (1 week). A change in TGs (eg, from TG 1 to TG 2) is planned for the end of the mesocycle if an objective improvement (or deterioration), measured through the CPET and evaluated using the described TG allocation algorithm (Table 2), occurs. Depending on the clinical conditions and the RPE during the training (eg, no worsening of clinical symptoms, and the subjectively perceived training intensity is too low), an individual group change within the mesocycle can also take place in consultation with the head physician (PS). The therapy plan can be individually adapted after each microcycle in teleconsultations with the sports therapist.

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The cyclical alternation (Figure 4) between training and recovery days aims to consider the workload from the previous training session and provide the body with time to adapt. For example, if the intensity of the previous training session was too high, the study participants have time to reflect on this training stimulus and adapt, thus preventing the occurrence of PEM or not increasing its severity in a new training session. The training days include both exercise and respiratory training sessions held in the morning and afternoon. Because of the low exercise intensity, only TG 1 participants engage in daily training involving respiratory and postural orthostatic tachycardia syndrome (POTS) training, one in the morning and the other in the afternoon. The training sessions are conducted asynchronously for all participants (ie, without real-time therapist supervision).

Figure 4. Exemplary weekly therapy plan for training group 3. The intervention and follow-up phases during the 16-week period are divided into 2 mesocycles (8 weeks) and 16 microcycles (1 week). The therapy plan consists of a combination of exercise and respiratory training types, training days, and recovery days. Participants are required to keep a daily clinical condition and training load diary (CCTD).

Time	Monday	Tuesday	Wednesday	Thursday	Friday	Weekend
24/7	Master everyday life with PACING!					
8-8:30 AM	CCTD					
8:30-9 AM	Breakfast (anti-inflammatory; eg, fruit, vegetables, low-fat quark, and nuts)					
10-11 AM	Endurance training	Recovery day	Resistance training	Recovery day	Endurance training	Self-determined
12:30-1 PM	Lunch (anti-inflammatory; eg, porridge, rice noodles with vegetables, salad with goat´s cheese or mozzarella, and nuts)					
3:30-4 PM	Leisure time					
4:30-5:30 PM	Respiratory training	Recovery day	Respiratory training	Recovery day	Respiratory training	Self-determined
6-7 PM	Dinner (anti-inflammatory; eg, fish with salad)					
7-7:30 PM	CCTD					
8-9 PM	Reflect on the day: If something was clearly too much during the day, then this should be noted In particular, it is important to end the day with a positive reflection: what was good about the day? And if that does not work, what positive things can I do for the next day?					
10 PM	Sleep					

The 3 TGs (Figure 1) follow an individual therapy plan. For TG 1 participants, the therapy plan includes respiratory and POTS training every day for at least 5 times a week. Respiratory training is based on the apnea training method [65] for increasing hypoxemia and ischemia tolerance. One respiratory training session consists of 3 sets of 4 repetitions, with a 2- to 3-minute pause between sets. One repetition consists of a deep inspiration maneuver followed by 4 maximum expirations and 4 submaximal inspirations to the level of resting inspiration. A POTS training session involves position change exercises for the arms, legs, and total body (eg, an exercise for standing up). The structure of each exercise consists of 2 to 3 sets with 5 to 10 repetitions, with a 1-minute pause between sets and 2 to 3 minutes between each exercise. For TG 2 and TG 3 participants, the therapy plan includes exercise training every other day but at least 3 times a week. TG 2 engages in endurance training as a substitute for POTS training. Moreover, TG3 performs both endurance and strength training instead of POTS training. Endurance training, designed as aerobic interval training and patient-centered training (eg, walking and cycling), entails 1 to 2 sets for TG 2 and 2 to 3 sets for TG 3, with a set pause of 2 to 3 minutes. Each set involves 8 to 10 repetitions with a work-to-rest ratio of 30:30 seconds or 30:60 seconds, with intensity control based on the modified Borg scale (0-10) for the RPE. Work intervals aim for an intensity between 4 and 6 (less strenuous to moderately strenuous), whereas (active) rest intervals target an intensity between 1 and 3 (very light to light). The individual progression or regression of the training load (eg, number of sets, intensity, and active or passive rest) depends on the patient's exercise tolerance and can be carried out in consultation with a personal sports therapist.

All participants, both from the IG and CG, will be asked not only to practice additional pacing in their daily lives to be active but also to use their energy resources as efficiently as possible. To this end, based on the Royal College of Occupational Therapists pace, plan, and prioritize principle pacing approach [66] and the CPET, we developed a new objective pacing approach based on PO at the individual anaerobic threshold—ventilatory threshold 2/lactate threshold 2 (VT2/LT2)—as the threshold for continuous physical capacity and the metabolic equivalent of task (Figure 5 [67]) [67,68].

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Figure 5. Objective pacing approach based on metabolic equivalent of task (MET) data from the work by Jetté et al developed by the Department of Sports Medicine, Prevention, and Rehabilitation at Johannes Gutenberg University Mainz. Objective pacing approach using cardiopulmonary exercise testing (CPET)–derived thresholds, illustrated with a 30-year-old female pilot participant. A continuous physical capacity threshold of 55 W (approximately 3 METs) corresponds to the individual's ventilatory threshold 2/lactate threshold 2 (VT2/LT2). Household activities are categorized by intensity and color coded for pacing guidance (red: 30:30 seconds; yellow: individual pacing; green: continuous work). PPO: peak power output; VO_{2peak}: highest oxygen uptake rate achieved during the cardiopulmonary exercise test.

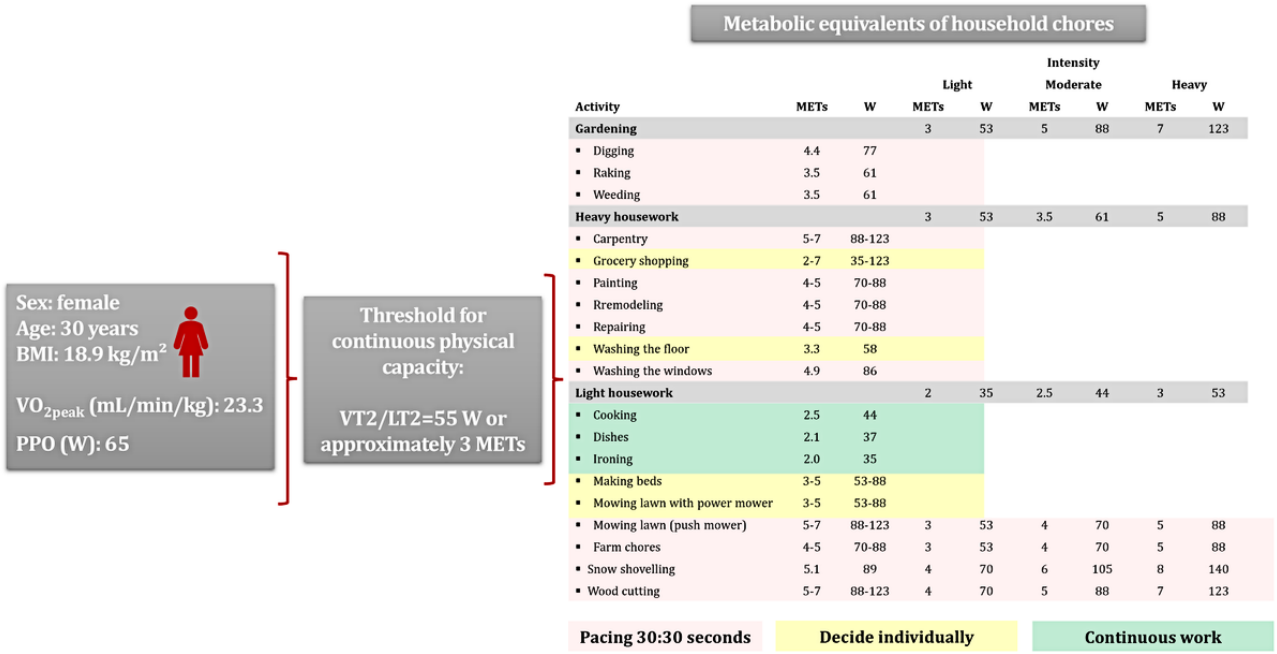

			Intensity					
			Light		Moderate		Heavy	
Activity	METs	W	METs	W	METs	W	METs	W
Gardening			3	53	5	88	7	123
▪ Digging	4.4	77						
▪ Raking	3.5	61						
▪ Weeding	3.5	61						
Heavy housework			3	53	3.5	61	5	88
▪ Carpentry	5-7	88-123						
▪ Grocery shopping	2-7	35-123						
▪ Painting	4-5	70-88						
▪ Rremodeling	4-5	70-88						
▪ Repairing	4-5	70-88						
▪ Washing the floor	3.3	58						
▪ Washing the windows	4.9	86						
Light housework			2	35	2.5	44	3	53
▪ Cooking	2.5	44						
▪ Dishes	2.1	37						
▪ Ironing	2.0	35						
▪ Making beds	3-5	53-88						
▪ Mowing lawn with power mower	3-5	53-88						
▪ Mowing lawn (push mower)	5-7	88-123	3	53	4	70	5	88
▪ Farm chores	4-5	70-88	3	53	4	70	5	88
▪ Snow shovelling	5.1	89	4	70	6	105	8	140
▪ Wood cutting	5-7	88-123	4	70	5	88	7	123

Our pacing strategy is based on the following six foundations:

1. Prevention of worsening of symptoms and occurrence of PEM: this requires the identification of extrinsic and intrinsic factors that trigger PEM, such as physical, cognitive, and emotional stressors.
2. Planning and prioritization of activities: this entails combinations of activity and rest phases and alternations among different activities (physical, cognitive, and emotional).
3. Pacing: all participants will receive a list of different physical activities sorted according to their metabolic equivalent of task.
4. Continuous physical activity is permitted only within the limits of dominant aerobic energy metabolism (<VT2/LT2) and must be subjectively well tolerated by the patient. If the desired physical activity is >VT2/LT2 in intensity, it should be performed only using the 30:30-second interval method (work-to-rest ratio of 1:1).
5. A cautious and gradual increase in activity can only occur if the clinical condition is good (refer to the *Monitoring of Clinical Condition and Control of Training Load section*).
6. The duration of work intervals and the work-to-rest ratio can be individually adjusted in consultation with a personal sports therapist depending on the patient's clinical condition, exercise tolerance, and regeneration capacity.

During the intervention phase, all participants will have weekly teleconsultations (30-minute video calls) via Mattermost with their personal sports therapist. The teleconsultation is designed as a motivational and problem-solving interview with the following structure: (1) review of the previous week, highlighting all the positive aspects; (2) discussion of the current clinical and training-related form; and (3) outlook or intervention modifications for the upcoming week. In addition to the clinical condition (clinical symptoms) and training-related variables, the participants are asked to record any problems that arise during training or throughout the day. During the intervention phase, participants have the opportunity to use a chat function to consult with their personalized sports therapist for immediate support. In addition to weekly teleconsultations between therapists and participants, the therapy team should meet once a week to discuss the progress of therapy and current challenges, among other things. The therapy team consists of 5 therapists and a head physician (PS), and they are not blinded.

Monitoring of Clinical Condition and Control of Training Load

The daily recording of the clinical condition and the interactive adjustment of the exercise therapy aim to reduce or stabilize symptoms and adjust the training load to achieve the best training effects.

The training load is regulated based on clinical condition using a clear algorithm (Figure 6), which includes the assessment of the clinical condition based on the RPSS and the recommendation of the training intensity based on the RPE. The RPSS was developed through our clinical experience with PCC at the sports medicine outpatient clinic, Mainz [69], and through insights from international literature on symptom occurrence in PCC [7,12]. The successful application of the RPSS in practice constitutes its inaugural use in a scientific context. Both the RPSS and RPE will be documented in the CCTD. The RPSS comprises the following items: fatigue (influenza-like symptoms or general fatigue), dyspnea (breathing

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difficulties, headache, visual disturbance, or chest pain), POTS (high pulse, inability to stand, and need to lie down), anxiety (anxiety, panic, or avoidance), and hypersensitivity (to noise, light, temperature, touch, and muscle or nerve pain). Each symptom group is accompanied by a free-text field for individual comments that is rated on a scale from 0 to 10 (0=no symptoms; 1-3=mild symptoms; 4-6=moderate symptoms; 7-10=severe to maximum symptoms).

Participants are asked to complete the RPSS every day in the morning to monitor their clinical condition. Every day starting with even 1 symptom cluster between 7 and 10 (PEM condition) is counted as a PEM episode. On training days, the RPSS should be completed by the start of training at the latest. To avoid exercise-induced overload and exacerbation of clinical symptoms, patients should only exercise when each symptom cluster has a value of ≤6 (Figure 6). Ideally, each symptom cluster should have a value between 0 and 3 (good clinical condition); then, patients can train with an RPE of 4 to 6 to maintain good clinical condition and provide an effective training stimulus. Even if only 1 symptom cluster has a value between 4 and 6 (pre-PEM condition), the RPE value must be set to 1 to 3 during training. However, if any of the RPSS symptom clusters have a value between 7 and 10 (PEM condition), the upcoming exercise training session should be canceled. In addition, if symptoms increase by ≥7 values during training, the current training session should be stopped. Finally, an increase in symptoms of ≥2 values in more than one symptom cluster should also be considered for training load management. The possible cause for this increase should be investigated via teleconsultation. After the training session or at the end of the day at the latest, participants are required to document their training (type; duration; intensity; and, if applicable, commentary) in the CCTD.

Figure 6. Clinical condition is assessed based on symptom severity (rating scale for perceived symptom severity), and training recommendations (rating of perceived exertion [RPE]) are derived accordingly. If any symptom cluster indicates a more severe condition (eg, pre–postexertional malaise [PEM] or PEM condition), the corresponding Borg value is applied. CCTD: clinical condition and training load diary; POTS: postural orthostatic tachycardia syndrome.

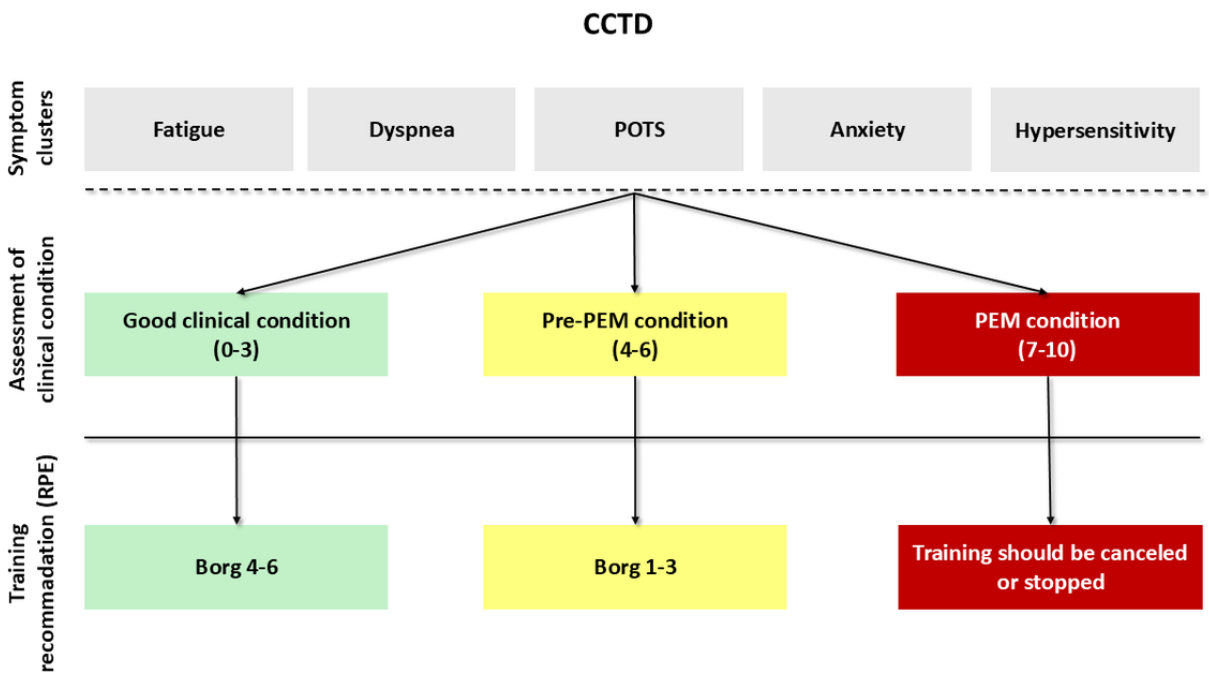

CG Setup

All the questionnaires, clinical assessments, and CPET scores at each examination time point correspond to the IG. After T0, the CG participants receive an email with written information explaining the importance of self-management of symptoms and activities through the pacing approach. CG participants will be motivated toward a healthy lifestyle (eg, nutrition and stress control) and receive pacing recommendations but will not receive web-based exercise or respiratory therapy or teleconsultations. The term *treatment as usual* refers to clinical assessment, the CPET, a sports medicine consultation on healthy habits, and the pacing approach. After T1, the CG will undergo the same intervention as the IG but in the follow-up phase.

Data Management

VW and AT are responsible for data management and analysis and are blinded. All analogue, digital, and biological study materials and data are pseudonymized. All the data entries and sensitive information about the participants are password protected and accessible only to the assigned researchers (VW and AT).

Statistical Analysis Plan

For data storage, transformation, and analysis, Microsoft Excel (version 2401; Microsoft Corp) and R (version 4.4.0) will be used. VW and AT do not know which IG receives which intervention (TG 1, TG 2, or TG 3). Standard statistical

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procedures will be performed according to the intention-to-treat principle.

Descriptive statistics will be used for all outcome variables at each test time point to obtain an overview of the changes in all relevant data. Descriptive statistics will include absolute and relative frequencies for categorically scaled data and means, 95% CIs, and SD or medians, 95% CIs, and IQRs for continuously scaled data. The normality of the distribution will be tested using the Shapiro-Wilk test and visual inspection of the data. The homogeneity of variance will be tested using the Levene test. In the case of a nonnormal distribution, the data will be log-transformed before statistical analysis to assess normality and variance homogeneity; alternatively, more robust statistical models such as mixed-effects models will be used.

A repeated-measure ANOVA or a linear mixed-effects model will be used to determine the differences between all groups and time points [70,71]. The primary analysis will focus on the comparison between the IG and CG at T0 and T1 to evaluate the superiority of telerehabilitation over usual care while minimizing potential waiting bias. Participants who transition from the CG to the IG (waiting group) will be analyzed separately to assess whether delayed intervention yields similar effects. In addition, the IG will be analyzed during the follow-up phase as these participants will continue training without therapeutic support, allowing for an exploration of long-term intervention sustainability.

The statistical significance will be set at $\alpha<.05$. The magnitude of the changes between time points, as well as the magnitude of the differences in changes between the groups, will be assessed using effect sizes. The threshold values for effect sizes will be 0.2 (small), 0.6 (moderate), 1.2 (large), and 2.0 (very large) [72,73]. In addition, 95% CIs for the between-group differences in changes will be estimated, and magnitude-based inferences will be made with reference to the smallest worthwhile change, which is calculated as 0.2 multiplied by the between-subject variation at T0 [73]. Correlations between variables will be assessed using parametric (Pearson) and nonparametric (Spearman rank) tests depending on the distribution of the variables. In the case of multiple comparisons, *P* values will be adjusted using appropriate procedures.

The sample size estimation is based on an a priori power analysis (repeated measures; interaction between group [intervention vs control] and time [before vs after the intervention]) performed using G*Power (version 3.1.9.7). Assuming a power of 0.8 and a medium to large effect (Cohen f=0.35) on the VO_{2peak} (in accordance with the work by Bacon et al [74]), 67 participants are needed. Considering the calculated required sample size and a dropout rate of 15% to 20% [53,75], the target number of study participants is set at a total of 80, or 40 participants per group.

Adherence to the intervention is defined as the percentage of training sessions completed of the prescribed training sessions [75]. Participants who drop out of the intervention or complete <60% (ie, <17 of the predefined 24 training sessions for TG 1) of the prescribed training are defined as dropouts. For those in the IG, adherence during the follow-up phase will also be tracked to assess sustained engagement without therapeutic supervision. Adherence to the training requirements will be assessed based on the information provided by the participants via the CCTD. Participants will continue to be monitored after their withdrawal from the study if they agree.

Publication Strategy

The analysis strategy and publication plan include a comprehensive cross-sectional analysis of baseline assessments (T0) aimed at thoroughly characterizing participants' clinical status (eg, symptoms, functional limitations, and comorbidities) and exercise physiology profiles (eg, CRF, ventilatory efficiency, and VO_2 efficiency). This analysis will encompass clinical history related to COVID-19 (eg, severity of COVID-19, duration of hospitalization, and previous rehabilitation) along with data from patient-reported outcome measures, clinical assessments, and exercise physiological measurements. These baseline data will be reported separately in a dedicated observational cross-sectional paper, providing a detailed clinical and exercise physiological characterization of patients with PCC who are severely affected.

The RCT analysis will primarily compare outcomes between the IG and CG. In addition, subgroup analyses will be conducted to assess differences in therapeutic efficacy across key patient categories, including hospitalized versus nonhospitalized patients and patients with PCC with versus without ME/CFS. The inclusion of these subgroup analyses aims to enhance comparability with other PCC rehabilitation trials and provide deeper insights into factors influencing rehabilitation outcomes.

Furthermore, the collected data will be used for various analyses in basic research aimed at gaining insights into critical aspects such as the molecular characterization of PCC pathogenesis, the pathophysiology of PCC, and the pathomechanisms of PEM. These investigations will contribute to a more comprehensive understanding of PCC and support the development of more targeted and effective rehabilitation interventions.

This study adheres to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [76] (Multimedia Appendix 6) and follows the Consensus on Exercise Reporting Template [77].

Results

Recruitment for the study began in August 2023 and was initially planned for 12 months. On December 27, 2024, a protocol amendment was approved, extending the recruitment period until March 2025. Updated study information is available in the German Clinical Trials Register [78]. No further modifications to the registered study are planned, and no results have been published yet.

As of March 2025, 80 participants have been successfully recruited, and data analysis is ongoing. Final results of the RCT are expected to be published by winter 2025. A comprehensive cross-sectional analysis of the baseline assessments (T0) is expected to be published by summer 2025.

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The study findings will be submitted to peer-reviewed journals and presented at scientific conferences, ensuring objective reporting regardless of the study outcome.

Discussion

Expected Findings

To our knowledge, the Mainz PCC telerehabilitation study is the first RCT to investigate the effects of a multimodal, personalized, symptom-titrated telerehabilitation program on CRF and hyperventilation in patients with PCC who are severely affected and have work disability. By integrating personalized teleconsultations, exercise therapy, and respiratory interventions, we expect improvements in VO_{2peak} (mL/min/kg) and the VE/VCO_2 slope, along with better management of PCC symptoms such as chronic fatigue and PEM. While previous studies have shown that telerehabilitation can enhance quality of life and symptom management in patients with PCC, its application in individuals who are severely affected remains largely unexplored. Moreover, previous interventions have relied primarily on self-reported outcomes and have been often conducted in mildly to moderately affected patients with PCC. Our study bridges this gap by integrating objective outcome measures, including CPETs and biomarker analysis, to provide a comprehensive evaluation of telerehabilitation effectiveness in this specific cohort. In contrast to standard telerehabilitation approaches, our intervention dynamically adapts the training load to the subjectively perceived symptom intensity, ensuring a symptom-titrated approach tailored to the current clinical condition of each patient. In addition to the expected improvements in VO_{2peak} and the VE/VCO_2 slope, this study will provide new insights into clinical and physiological adaptations associated with PCC and provide a structured framework for personalized telerehabilitation programs.

Comparison to Prior Work

Exercise and respiratory therapy–based rehabilitation programs have been shown to improve physical capacity, hyperventilation, and health-related quality of life in patients with PCC. However, their effects on fatigue remain inconclusive [23,24]. A critical gap in previous research is the lack of evidence regarding the interaction between exercise training and fatigue, particularly in minimizing the risk of exercise-induced symptom exacerbation. While exercise and respiratory training are essential for improving CRF and ventilatory efficiency, pacing strategies have gained attention as a promising approach for managing PEM in daily activities [32].

Despite the growing body of research supporting exercise-based rehabilitation for PCC, previous interventions have largely relied on self-reported outcomes and have primarily been conducted in patients with mild to moderate disease severity [23,24]. Furthermore, most existing studies lack objective outcome measures, such as CPETs, lactate diagnostics, and muscle strength assessments, which are critical for accurately quantifying physiological responses and intervention efficacy [79-91]. To date, only 4 studies have incorporated objective outcome measures of CRF and clinical condition in patients with PCC [92-95]. While telerehabilitation has been shown to be a safe alternative to conventional rehabilitation [39,40], its overall efficacy remains uncertain. A recent meta-analysis of 16 RCTs found no significant improvements in clinical symptoms, pulmonary function, psychological well-being, or quality of life [96].

Building on these previous findings, our study introduces a novel, symptom-titrated telerehabilitation program that is designed to dynamically adjust the training load based on individual clinical responses. By integrating objective diagnostic tools, weekly teleconsultations, and structured pacing strategies, our approach seeks to address the shortcomings of previous telerehabilitation interventions and establish a personalized telerehabilitation program for patients with PCC who are severely affected.

Strengths and Limitations

A key strength of this study is its comprehensive assessment strategy, which includes objective outcome measures rather than relying solely on self-reported outcomes. By incorporating CPETs and other objective physiological measures, we aim to quantify the physiological adaptations triggered by telerehabilitation and provide robust evidence on exercise tolerance in patients with PCC who are severely affected.

In addition, risk stratification and individualized exercise prescription are major methodological strengths. Our baseline assessment systematically classifies patients based on CRF, performance, and ventilatory efficiency, ensuring that telerehabilitation is personalized and adapted to each patient's specific condition [29,33,97]. This contrasts with previous studies that applied generic exercise protocols [79-91], which may not be appropriate for individuals with fluctuating symptoms and severe functional limitations.

Compared to traditional face-to-face rehabilitation, telerehabilitation presents several advantages. First, it allows for remote delivery of high-quality rehabilitation by health care professionals, including physicians, physiotherapists, and sports scientists [36-38]. This is particularly valuable for patients with PCC who are severely affected, who may face mobility restrictions and difficulties accessing in-person rehabilitation programs. Second, telerehabilitation provides a scalable and cost-effective solution, addressing health care system limitations and the growing demand for PCC rehabilitation services.

Our previous research has demonstrated that exercise-based telerehabilitation is safe, with both short-term [53,75,98,99] and long-term benefits [100] in various patient populations. Notably, no serious adverse events were reported, and the dropout rate remained relatively low (15%-20%). This evidence supports the feasibility and clinical applicability of a symptom-titrated telerehabilitation approach, particularly for patients with limited access to conventional rehabilitation.

Thus, our multimodal telerehabilitation program—which combines objective diagnostics, personalized symptom-titrated exercise therapy, and teleconsultations—represents a promising alternative to standard rehabilitation or a valuable adjunct to outpatient physiotherapy and self-directed therapy. By addressing critical gaps in prior work and implementing a robust methodological design, this study has the potential to advance

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telerehabilitation as a viable rehabilitation strategy for patients with PCC, particularly those with severe disease manifestations.

Despite the strengths of this study, certain limitations must be acknowledged. A key challenge in our approach is the introduction of asynchronous exercise training, where participants engage in rehabilitation without real-time supervision from therapists. Previous telerehabilitation interventions have predominantly relied on synchronous models, allowing for direct therapist interaction during exercise sessions [81,95,101]. While the asynchronous format enhances accessibility and flexibility, particularly for patients with PCC who are severely affected, it may also pose challenges in adherence and compliance as PCC symptoms can fluctuate daily. To mitigate this issue, we integrated weekly teleconsultations via Mattermost, providing participants with opportunities to seek guidance, discuss symptoms, and adjust their rehabilitation plans accordingly. However, the absence of real-time therapist feedback may still present risks, particularly in individuals considered vulnerable. Future studies should explore the potential integration of live internet-based supervision or automated biofeedback mechanisms to optimize adherence and safety. Another limitation of this study is the extensive number of questionnaires, which participants must complete at multiple test time points. Although we have implemented measures to minimize response fatigue—such as allowing participants to distribute questionnaire completion over several days—the risk of response depletion remains. In addition, an important limitation of this study is the reliance on self-reported adherence and symptom tracking through the CCTD. While the digital training diary and RPSS offer valuable insights into training loads and symptom fluctuations, they lack objective physiological monitoring, such as heart rate variability, oxygen saturation, or movement data. Without these objective markers, it is challenging to precisely quantify exercise intensity and patient responses. Previous research has highlighted the potential benefits of wearable technology, which could enhance exercise monitoring by providing real-time physiological feedback [102,103]. Although this study does not incorporate such technology, future research should explore the use of wearable sensors and mobile health apps to enable real-time tracking and personalized exercise adjustments, thereby improving intervention precision. However, using digital technologies such as the internet, PCs, smartphones, or smartwatches for monitoring clinical condition and training load control may present challenges [104], especially for populations considered vulnerable, such as patients with PCC. Finally, a further limitation is the potential confounding effects of concurrent medical treatments. Participants may receive additional interventions during the study period, including pharmacological therapy, relaxation treatments (eg, massage), or other symptom management strategies, which could influence outcomes. While we have minimized this risk by excluding individuals undergoing structured physiotherapy or other exercise-based interventions, this study cannot fully control for the impact of all external treatments. Future research should consider subgroup analyses to examine how concurrent treatments interact with telerehabilitation outcomes, enabling a more comprehensive understanding of multimodal rehabilitation strategies.

Dissemination Plan

The findings of the Mainz PCC telerehabilitation study will be disseminated through three channels:

1. Scientific community: the results will be published in peer-reviewed journals (eg, JMIR) and presented at national (eg, the German Long COVID Symposium) or international conferences on rehabilitation and digital health.
2. Clinical and professional outreach: the findings will be integrated into clinical guidelines (eg, the German Long/Post-COVID—Living Guideline), professional workshops, and webinars for health care providers (eg, BGW specialist meeting) in collaboration with rehabilitation specialists and patient organizations (eg, the German organization for patients with ME/CFS [*Bundesverband ME/CFS - Fatigatio*]).
3. Public and patient engagement: lay summaries, infographics, and media releases will be shared via our website, patient forums, and social media, ensuring accessibility for patients with PCC and ME/CFS.

Conclusions

The Mainz PCC telerehabilitation study aims to provide insights into the clinical and exercise physiological effects of an 8-week multimodal, personalized, and symptom-titrated telerehabilitation program for patients with PCC who are severely affected. The effectiveness of the intervention on CRF and ventilatory efficiency will be primarily assessed through VO_{2peak} and the VE/VCO_2 slope. Furthermore, this study aims to determine whether weekly teleconsultations can enhance treatment adherence compared to self-directed rehabilitation approaches.

While this study is not designed to establish causal relationships, its findings may support the further development of CPET-based diagnostic approaches, risk stratification models, and personalized exercise and respiratory therapy prescriptions. Moreover, the results may provide preliminary evidence for evaluating work ability and rehabilitation planning in patients with PCC and ME/CFS who are severely affected. Future research should build on these findings to validate the long-term effectiveness and safety of telerehabilitation and refine rehabilitation strategies for postviral fatigue conditions.

Acknowledgments

The authors would like to thank all the contributors for their help in planning and conducting the study. They also thank the participants who have already been included for giving their time, energy, and experience, which the authors hope will further improve the scientific knowledge and health care of all patients with COVID-19. This study is a cooperative project between the Department of Sports Medicine, Prevention, and Rehabilitation and the Institute of Sports Science at Johannes Gutenberg University

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Mainz (Germany) and the German social accident insurance provider for nongovernmental health and social care institutions (German: *Berufsgenossenschaft für Gesundheitsdienst und Wohlfahrtspflege*). This study receives funding from the German social accident insurance provider for nongovernmental health and social care institutions. The funding body has not peer reviewed the manuscript. This sponsor was not involved in the study design, the writing of the manuscript, or the decision to submit the manuscript for publication.

Data Availability

The datasets generated or analyzed during this study are not publicly available due to participant confidentiality and data protection regulations but are available from the corresponding author on reasonable medical or scientific request in anonymized form.

Authors' Contributions

PS, AT, and VW designed the study. AT, VW, BH, and NH planned the telerehabilitation program. EL conducted the clinical examination, and DTO conducted the cardiopulmonary exercise tests. VE and 4 other therapists carried out the telerehabilitation. PS conducted the weekly consultation with the therapists. EWIN, AB, and KE planned the blood analyses. PZ planned the psychological questionnaire assessments. LB and PS checked the medical plausibility of the study design and evaluations. AT and VW prepared the final manuscript. All the authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
R script for the stratified randomization.
[PDF File (Adobe PDF File), 165 KB - resprot_v14i1e65044_app1.pdf]

Multimedia Appendix 2
Venous blood parameters for the Mainz post–COVID-19 condition telerehabilitation study.
[PDF File (Adobe PDF File), 109 KB - resprot_v14i1e65044_app2.pdf]

Multimedia Appendix 3
Reporting on data processing strategies for determining the highest oxygen uptake rate achieved during the cardiopulmonary exercise test.
[PDF File (Adobe PDF File), 117 KB - resprot_v14i1e65044_app3.pdf]

Multimedia Appendix 4
Reporting on data processing strategies for determining the minute ventilation/carbon dioxide production slope (full slope).
[PDF File (Adobe PDF File), 135 KB - resprot_v14i1e65044_app4.pdf]

Multimedia Appendix 5
Standard method (V-slope method) and auxiliary criteria for determining the first and second ventilatory thresholds.
[PDF File (Adobe PDF File), 127 KB - resprot_v14i1e65044_app5.pdf]

Multimedia Appendix 6
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 307 KB - resprot_v14i1e65044_app6.pdf]

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Abbreviations

BGW: Berufsgenossenschaft für Gesundheitsdienst und Wohlfahrtspflege (German social accident insurance provider for nongovernmental health and social care institutions)
CCTD: clinical condition and training load diary
cfDNA: cell-free DNA
CG: control group
CPET: cardiopulmonary exercise test
CRF: cardiorespiratory fitness
HGS: handgrip strength
IG: intervention group
ME/CFS: myalgic encephalomyelitis or chronic fatigue syndrome
PCC: post–COVID-19 condition
PEM: postexertional malaise
PO: power output
POTS: postural orthostatic tachycardia syndrome
RCT: randomized controlled trial

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RPE: rating of perceived exertion
RPSS: rating scale for perceived symptom severity
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TG: training group
VCO_2: carbon dioxide production
VE: minute ventilation
VO_2: oxygen uptake
VO_{2peak}: highest oxygen uptake rate achieved during the cardiopulmonary exercise test
VT2/LT2: ventilatory threshold 2/lactate threshold 2

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Protocol

Intervention With WhatsApp Messaging to Compare the Effect of Self-Designed Messages and Standardized Messages in Adherence to Antiretroviral Treatment in Young People Living With HIV in a Hospital in Lima, Peru: Protocol for a Nonblinded Randomized Controlled Trial

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Abstract

Background: Young people living with HIV face challenges in consistently adhering to antiretroviral therapy (ART). Although mobile health interventions, particularly those using SMS text messaging, have been implemented to improve ART adherence, many lack a focus on specific behavioral mechanisms. Interventions incorporating behavioral change techniques (BCTs), especially those emphasizing customization, may enhance effectiveness. WhatsApp offers potential for delivering tailored, behaviorally grounded interventions with diverse communication features. We hypothesize that WhatsApp messages self-designed by participants, with spontaneous targeting of BCTs, could be more effective than standard WhatsApp messages designed by the researchers to improve ART adherence.

Objective: The objective of this study is to evaluate the effectiveness of WhatsApp messages created by participants (self-designed) compared to WhatsApp messages designed by the researchers (standardized) over adherence to ART at 16 weeks of intervention in young people living with HIV who receive HIV care under routine conditions at a public hospital in Lima, Peru.

Methods: A 2-arm randomized controlled trial with a parallel assignment of 1:1, with no blinding of study intervention, was performed. Eligible participants are consenting people living with HIV aged 18-29 years who receive HIV care at the study center and whose mobile phones support WhatsApp. Following informed consent and a baseline survey on clinical and personal preferences (eg, timing and frequency of messages), participants are randomized to the control group (messages designed by the research team) or to the experimental group (messages designed by participants), stratified by sex, educational level, current ART intake, and history of ART abandonment. Participants in both groups receive up to 3 WhatsApp messages per week for 16 weeks. ART adherence, the primary outcome, is measured using the Simplified Medication Adherence Questionnaire (SMAQ) at 4, 8, 12, and 16 weeks. Monthly feedback questionnaires on user experience are also administered. The WhatsApp chat format allows two-way communication between participants and the research team throughout the study. We will compare ART adherence between 2 groups at 16 weeks under the intention-to-treat principle, with no interim analysis planned. Based on an estimated 10% difference in adherence, 78.9% power, and a 2-sided α of .05, the target sample size was set at 120, later increased to 131 to include a 2-week pilot phase.

Results: In March 2024, we started enrolling and randomizing participants. The study follow-up will continue until the last participant completes 16 weeks of intervention (November 2024). As of February 2025, we are in the process of data curation.

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Conclusions: This trial will compare the effectiveness of standardized vs self-designed WhatsApp messages on ART adherence measured at 16 weeks among young people living with HIV receiving routine care in a low-resource setting in Lima.

Trial Registration: ClinicalTrials.gov NCT06500013; https://clinicaltrials.gov/ct2/show/NCT06500013

International Registered Report Identifier (IRRID): DERR1-10.2196/66941

(JMIR Res Protoc 2025;14:e66941) doi:10.2196/66941

KEYWORDS

mHealth; HIV; WhatsApp; adherence; ART; people living with HIV; young people; mobile phone messaging; digital app; messaging intervention; antiretroviral treatment; behavioral change technique; design; evaluation; self-design; randomized controlled trial; Peru

Introduction

HIV programs continue in search of effective interventions to increase adherence to antiretroviral therapy (ART), especially for young people living with HIV/AIDS. This group faces increasing rates of new HIV infections [1] and heightened vulnerability to drivers of antiretroviral resistance, such as suboptimal ART adherence [2], ART abandonment, and non-retention in care [3].

Mobile health (mHealth) interventions tailored to young people living with HIV/AIDS seem highly promising, considering that so-called Gen Z tend to be digital natives who routinely use apps. At first glance, messaging interventions to improve adherence seem practical, low-cost, and prone to tailoring to users' needs [4,5]. However, medication adherence involves complex behavioral aspects. Several behavioral change theories, notably the transtheoretical model, have been applied in interventions to improve medication adherence [6-8], often with contradictory findings [9,10]. The heterogeneity of findings may respond to messaging interventions operating simultaneously over different behavioral aspects, for instance, reminders and motivation. While a weekly frequency of delivery and a bidirectional platform have proven effective [11], the message's content seems crucial to achieving behavioral changes [12].

Due to difficulties in identifying the specific factors responsible for behavioral changes, Abraham and Michie [13] developed a standardized system to isolate the drivers of behavior change: behavioral change techniques (BCTs). Since then, several interventions have adopted the BCT taxonomy to more accurately target specific behavioral aspects, improve the rigor and replication of behavioral studies, and enhance their reliability [14,15].

Most messaging interventions to improve adherence to ART have involved SMS and worked with standardized messages created by researchers. Currently, young people in low- and middle-income countries, including people living with HIV/AIDS, extensively use WhatsApp [16-18]. This app's multiple content and delivery options facilitate integrating BCTs into message design. Moreover, WhatsApp allows documentation of intervention delivery processes, including records of scheduled, sent, read, and answered messages.

As self-designed products can convey more significance to users [19] based on an increased sensation of authenticity and usefulness [20], in this study, we implement an intervention to support ART adherence through WhatsApp messages with self-designed messages in one group and standardized messages in the second group under the hypothesis of more effectiveness for the group of self-design.

For the main analysis, we will compare the efficacy of both types of messages using the Simplified Medication Adherence Questionnaire (SMAQ), a validated ART adherence questionnaire measured at 16 weeks of intervention. As the use of mHealth is incipient in our setting, the study protocol includes secondary mixed-methods components aimed at understanding the acceptability of the intervention and the challenges participants face throughout its delivery.

Methods

Setting

In 2023, overall, 87.1%-90% of Peruvian people between 18 and 29 years of age had access to a mobile phone, with growing trends among lower socioeconomic groups [21]. The per capita country's GDP stood at US $7789.9 [22].

This study is conducted at Hospital Nacional Cayetano Heredia in Lima, Peru's largest city and home to over 60% of people living with HIV in Peru [23]. As part of the network of health services provided by the Peruvian Ministry of Health, this hospital serves primarily people from low-resource backgrounds and provides outpatient and inpatient HIV services to over 5000 people living with HIV. Conditioned on stocks, ART is usually dispensed monthly by HIV program nurses as walk-ins on a first-come, first-served basis at the offices of the HIV program. Pregnant people living with HIV have a much closer medical follow-up than the rest of the patient population (outside children), with monthly appointments with doctors, additional counseling services at their primary care clinics, greater priority for viral load and CD4 lymphocyte testing, and regular appointments with midwives in which adherence to ART is reinforced.

Through a longstanding alliance with Instituto de Medicina Tropical Alexander von Humboldt from Universidad Peruana Cayetano Heredia, this hospital's HIV Program continuously promotes clinical and operational research.

Study Design

A randomized controlled trial with 2 arms and a 1:1 assignment ratio will be conducted.

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Eligibility Criteria

We assessed the eligibility criteria at the first encounter with potential participants, as follows (Textbox 1).

We excluded pregnant people since their level of care differs significantly from the rest of our potential study population, which would introduce bias regarding the effects of receiving the intervention on ART adherence.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- People living with HIV receiving HIV care at the study center
- People living with HIV aged 18-29 years
- Ownership of a mobile phone that supports WhatsApp

Exclusion criteria

- Pregnancy
- Impossibility to read WhatsApp messages due to illiteracy or blindness

Study Procedures—Preimplementation Phase

First, during the study's design, we consulted with health staff to better respond to the study's population needs without disrupting routine HIV program operations. Once the study design was completed, the coordination was intended to communicate study standard procedures and facilitate the study's implementation. Our institutional review board (IRB) approved the full study protocol in July 2023. Then, we designed the web-based study platform with Infobox Latinoamérica, a Peruvian IT company. The web-based study platform is integrated with WhatsApp business and supports the delivery of personalized and standardized messages, a Chatbot for mass-sending questionnaires and continuous chat with participants. The Infobox provides technical support during the study as required.

The principal investigator (PI) completed the web-based training on BCT-Taxonomy to design the standardized messages. He created 44 standardized messages, each corresponding to one of 14 selected BCT categories, though the final format considered elements of other behavior change theories (health belief model, social support theory, and social cognitive theory). The number of standardized messages minimized the chance of participants receiving repeated messages during the study period. Table S1 in Multimedia Appendix 1 lists all standardized messages with their corresponding BCTs in the order those messages are sent to participants.

We created the randomization sequence using the REDCap (Research Electronic Data Capture) randomization module (REDCap Consortium); sex assigned at birth, educational level, current ART intake, and previous ART abandonment were the criteria for stratified randomization.

Study Procedures—Implementation Phase

To preserve confidentiality, nurses from the HIV Program are informed about the study's eligibility criteria and collaborate to identify potential participants. While they wait for infectious diseases outpatient consults or ART pick-ups, the nurses inform them about the study. For those interested, we reassess eligibility, explain the study in detail, and obtain informed consent privately (a model of our consent form is shown in Multimedia Appendix 2). Then, we fill out a REDCap baseline questionnaire, collect data to send messages through the study web-based platform, and, when applicable, explain and support the process of self-designing the messages. Figure 1 presents participant identification, recruitment, and allocation. After completing the baseline questionnaire, which provides information for stratification (sex assigned at birth, educational level, current ART intake, and previous ART abandonment), participants are randomized to one of 2 study arms allocated with a 1:1 proportion. Then, the research staff informs participants of their assigned group and provides details accordingly. Given the characteristics of the intervention, neither the researchers nor the participants are blinded.

Participants allocated to the self-designed messages group draft 10-15 messages that would help them take their ART; this number assures similitude in the number of messages received per participant in both study arms. Message creation is done during enrollment. Participants determine the final content of their messages. However, during their creation, the research staff ensures that the content excludes potentially harmful or offensive topics. If there are any doubts during the process, the staff provides support by offering examples based on characteristics identified during the baseline questionnaires and general conversation with participants (such as family, personal hobbies, goals, and other general topics). After the messages are created, the data manager reviews them and may slightly modify them to ensure clarity while keeping the original content. Once the messages are ready, the data manager enters them into the study messaging platform.

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Figure 1. Participant identification, recruitment, and allocation. ART: antiretroviral therapy; REDCap: Research Electronic Data Capture; SMAQ: Simplified Medication Adherence Questionnaire.

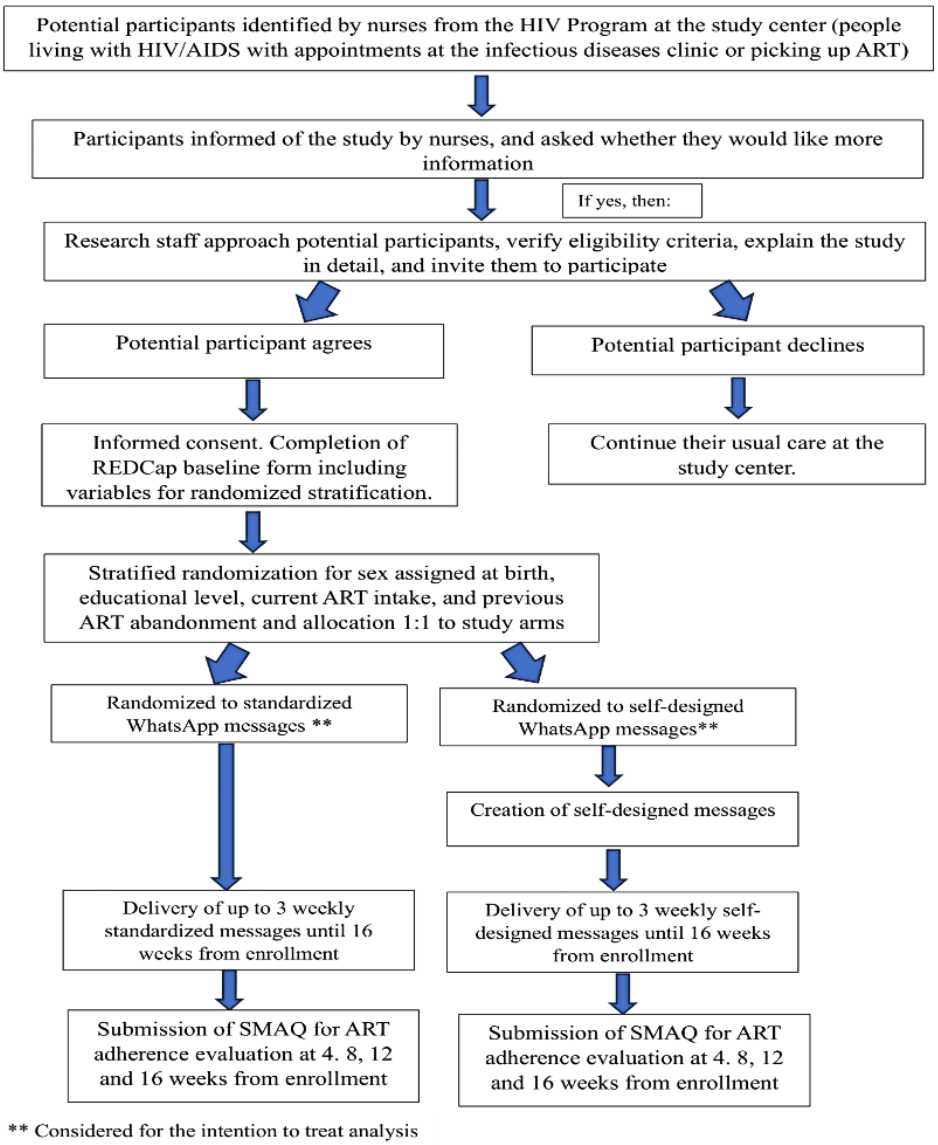

During 16 weeks from the date of enrollment, participants receive up to 3 intervention messages per week; they are requested to reply briefly once they read those messages. Weekly, the data manager schedules the delivery of messages according to participants' preferences, as recorded on REDCap, and monthly questionnaires. During the study, participants can chat with 2 medical doctors on the web-based study platform to ask about health issues, navigate the health system, and schedule infectious disease outpatient consultations (the standard of care requires in-person scheduling). If a participant requests modifications or additions to self-designed messages during the chat, the physician responsible for monitoring the chat will review the new messages initially. The PI will be notified if any content is deemed harmful or inappropriate. He will then contact the participant to explain the reasons for rejecting the message and will request an alternative message. This review process will continue with oversight from the data manager until the accepted messages are included in the platform's system. Additionally, if physicians responsible for monitoring the platform identify inappropriate content during chat conversations, they will address this with all parties involved non-punitively and constructively. They will explain why the content is inappropriate and direct the conversation to ensure it remains safe and respectful.

As a follow-up, participants receive WhatsApp questionnaires every 4 weeks after enrollment and 2 days apart to assess (1) adherence to ART and (2) user experience with the intervention delivery. After 16 weeks of intervention, participants receive a final message acknowledging their participation and reminding them that the messages will stop.

Participants may withdraw from the intervention at any time by sending a message through the chat platform, responding to messages sent as part of the intervention, or contacting research team members during a medication pick-up visit. The participant will be told that withdrawing from the study does not affect their usual care at the study center. The data manager will register that patient as "withdrawn" in REDCap, and no more messages will be sent.

No concomitant care or interventions are precluded for study participants.

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Sample Size Determination

The sample size calculus considered a 95% CI and the assumption of a 10% difference in optimal ART adherence between study groups (90% in the self-designed group versus 80% in the standardized group by the end of the study). Accounting for a power level of 78.9%, the obtained result was 120 (EPIDAT 4.0). To account for a 2-week pilot phase, we increased the sample size to 131 participants.

Outcomes

The primary outcome is ART adherence, measured by the SMAQ questionnaire at 16 weeks of intervention and adjusted for the effect of covariables. The SMAQ questionnaire evaluates medication adherence. It provides a dichotomic result of adherence (yes or no) and a semiquantitative estimate of adherence. >95% adherence is considered as “yes” and <95% as “no.”

The secondary outcomes are (1) ART adherence measured by the SMAQ Questionnaire at 4, 8, and 12 weeks of intervention; (2) loss to follow-up; (3) time of permanence in the study; and (4) metrics on the use of a bidirectional platform for intervention delivery.

Since the SMAQ provides a dichotomic result of adherence (yes or no), we will report the percentage of participants’ adherent to ART per study group at 4, 8, and 12 weeks of intervention.

To measure loss to follow-up, we defined it as either (1) participants not responding to messages for ≥30 continuous days since receiving the intervention and not responding to messages or questionnaires at the end of their intervention period (t=16), or (2) participants not responding to messages for ≥30 continuous days since receiving the intervention and not reading their messages until the end of their intervention period. We will measure it from the start of the delivery intervention until the completion of the study.

Time of permanence in the study will be measured from the first date of intervention delivery (baseline) until loss to follow-up or study completion (16 weeks). We will describe this result's median and interquartile range in both study arms.

To assess the use of the bidirectional platform, we will report frequencies, percentages, and means with an SD of messages and questionnaires programmed for sending, sent, received, read, and answered by participants. Also, the frequencies and percentages of different process indicators self-reported by participants.

Data Collection

For this study, data collection and management use REDCap electronic data capture tools hosted at Universidad Peruana Cayetano Heredia [24]. The enrollment form collects participants’ baseline sociodemographic data, history of ART, strategies for taking ART, assessment of their adherence with the SMAQ, depression screening, stigma, an evaluation of their satisfaction with the health services provided at the study center, and a measurement of their knowledge about ART and adherence. For participants allocated to the self-designed messages arm, we also register their created messages in REDCap. In total, 4 members of the research team are involved in data collection. The PI trained them with mock interviews and a web-based course on using REDCap.

We used an intermediate Excel file hosted in a secured drive to schedule messaging and questionnaire delivery per participant through the web-based study platform. This file contains the identification codes, a list of messages, and the date and time of sending.

The web-based study platform collects CSV file data on every message and questionnaire scheduled, sent, received, read, and answered per participant and chat sessions with providers. The records include anonymous hour-dated logs of all conversation contents with participants, including reasons for adding, modifying, or eliminating messages in the self-designed group and responses to study questionnaires.

To obtain the total number of eligible patients who meet eligibility criteria, independent of whether they are invited to participate, we collect routine data from the study center regarding the number of outpatient consults and patients in the age group of interest who pick up ART during the study period.

Data Management

All study data are stored in secure, password-protected platforms, with access restricted to the authors of this protocol. Members of the research staff review data collected at baseline to ensure accuracy and completeness. Weekly, we download CSV files and reports from the web-based study platform. To ensure the records' accuracy, we compare a subset with the corresponding intermediate Excel file containing messages and questionnaires scheduled for delivery. Data curation will be performed at the end of the trial to point out missing values, identify any measurement outside the expected range, and evaluate strategies for mitigating these occurrences.

Data Analysis Plan

The primary outcome variable is ART adherence, primarily measured as a binary variable defined by the SMAQ results at 4, 8, 12, and 16 weeks of intervention. For the analysis of the primary outcome, and with an intention-to-treat approach, we will compare between both study groups the proportion of participants adherent to ART at 16 weeks of intervention with bivariate (chi-square) and multivariate (logistic regression) analyses. We will build the multivariate logistic regression model with a stepwise approach (forward selection and backward deletion), adding 1 explanatory variable at a time and starting with the explanatory variables with the highest theoretical value and strength of association with the primary outcome in bivariate analyses. At each step of model building, we will check variations in the reported odds ratios and standard errors to define the retention or removal of explanatory variables. Irrespective of bivariate association, the study group variable and potential confounders, notably history of ART abandonment, ART pick-up visits during the study period, and time of permanence in the study, will be entered into the model. We will test the final model fit with Hosmer and Lemeshow goodness-of-fit test and report results with adjusted odds ratios and 95% CIs. Preliminary outcome analyses will not be

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performed since they require multiple measurements, and the intervention is relatively short. We will not perform multiplicity adjustments.

With mixed models for repeated measures, we will explore the changes in ART adherence, as determined by SMAQ, from baseline to 4, 8, 12, and 16 weeks on the intention-to-treat population, with no imputation of missing data. In this model, the change from baseline value will be the dependent variable, with participant random effect and baseline ART adherence, intervention group, and measurement time as the primary fixed factors. We will check linearity assumptions for time and use participants' unstructured covariance structure. Two-sided 95% CIs for the mean change within each study group will be calculated.

To compare the time of study permanence in both study groups, we will perform survival analysis and compare hazard ratios for study loss to follow-up between study groups, according to the study definitions. This definition lets us know how many participants are active each week of intervention.

Additionally, we will perform a descriptive analysis of participants' baseline characteristics overall and by study groups. We will also report the percentage of participants adherent to ART per study group at 4, 8, and 12 weeks of intervention. We will describe the characteristics of the intervention delivery, including the frequencies and percentages of messages received, read, and answered by participants. We will conduct all these analyses, blinding the study groups.

We will perform a thematic analysis of the most common themes in self-designed messages to evaluate relevant qualitative outcomes. In addition, we will report the median number of messages created by participants and the main reasons for adding, modifying, or eliminating messages.

We will report the results following the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) statement for randomized controlled trials [25].

Plan for Sharing Individual Participant Data

Deidentified individual participant data collected during the trial will be made available 6 months after study completion, up to 5 years after the trial end date. Individual participant data may be shared with qualified researchers for scientific purposes. Access will be provided after a formal request, including the research proposal and statistical analysis plan, has been reviewed and approved by the principal and senior investigators, with a signed data sharing agreement. We will publish the study protocol, informed consent, and statistical analysis plan in a peer-reviewed journal. Requested data and clinical study reports will be provided through a secure data-sharing platform (Vivli—Center for Global Clinical Research Data).

Ethical Considerations

This study protocol and all study forms, including the informed consent, have been approved by the IRBs of Universidad Peruana Cayetano Heredia (IRB00001014, Federalwide assurance number FWA00000525) and Hospital Nacional Cayetano Heredia. All amendments to this protocol are to be approved by both IRBs and amended on the trial registry's platform. Participants sign an informed consent form before enrollment. Trained research staff give participants a verbal explanation regarding the rationale, main procedures of the study, and the main risks and benefits. They are also told that participation is voluntary, and participating, remaining, or withdrawing from the study does not affect the care they receive at the study center. Nevertheless, patients were informed that data collected until withdrawal could be used in our analysis. Messages sent by the research team do not contain allusions to the hospital, HIV, or ART, and participants are encouraged to use secure passwords on their cell phones. Participants received a 1-time compensation of US $6 to account for potential expenses in mobile data. Only the researchers can access participants' personal data, and identifiable data are stored in secure platforms or locked cabinets. Findings will be published in peer-reviewed journals. This protocol adheres to SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (Multimedia Appendix 3).

Results

The study received funding from the School of Medicine of Universidad Peruana Cayetano Heredia in August 2022. The messaging platform was designed from December 2023 to March 2024. Enrollment began in March 2024, and as of July 2024, we have enrolled 131 participants. Data collection began with enrollment and intervention delivery for the first participant in March 2024. As of February 2025, we are in the process of data curation.

Discussion

Guided by the application of BCTs, we hypothesize that self-designed messages may be more effective in improving adherence to ART than standardized messages. Therefore, we aim to evaluate the effectiveness of a mobile phone messaging intervention with WhatsApp to improve adherence to antiretrovirals in young people living with HIV who receive routine HIV care at a public health facility in Lima and assess if there is a difference in effectiveness between the 2 types of messages tested. In a setting with still inceptive use of mHealth, our study protocol will provide valuable information on associations between several covariables, ART adherence, and participants' experience with our pilot mHealth intervention.

Self-designed messages offer customization features that may enhance participant engagement with the intervention and increase its efficacy [26,27]. Therefore, we expect participants in the self-designed messages arm to have improved adherence compared to the standardized messages arm. Some subgroups may benefit more from the intervention, although it is beyond the scope of this study to compare differences between study arms and potential effect size. Given the potential personal customization component, we hypothesize that the self-designed arm will have an increased median time of permanence in the study and lower loss to follow-up. We also anticipate that loss to follow-up may hinder the statistical significance of results for the primary outcome and ART adherence measured at 4, 8, and 12 weeks of intervention for both study arms.

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A recent meta-analysis showed that SMS interventions improved adherence to ART, although there was considerable heterogeneity among study results [28]. The studies with greater efficacy were interactive or used bidirectional SMS, which supports our approach and is consistent with previous studies [11]. Our study uses a bidirectional platform, and participants can constantly interact with the research team through chatting. However, evidence suggests that implementing a messaging intervention in low-resource settings may be challenging owing to technical limitations, and difficulties in delivering the intervention may result in suboptimal outcomes [29]. Therefore, we established a 2-week pilot period that allows us to assess intervention delivery using the messaging platform, and having real-time data on multiple delivery indicators (messages and questionnaires scheduled for delivery, sent, received, seen, and answered by participants) allows for constantly monitoring the fidelity of intervention delivery.

In addition to the rigor of a randomized controlled trial, our study protocol has other strengths. To our knowledge, it is the first study evaluating the effectiveness of an mHealth intervention with different types of BCT-guided messages to improve adherence to ART. Our trial is conducted in a resource-constrained setting where there is much need for similar interventions and a still limited body of evidence about effectiveness. The thorough data register of our web-based study platform allows us to measure the cascade of intervention delivery, including the differentiation of messages received but unread.

The study also has limitations. First, as in many other studies, we use a self-reported measurement of medication adherence; extensive use does not assure full accuracy for outcome measurement. We will compare SMAQ results to viral load and CD4 lymphocyte measurements when available to address this. Limitations inherent to the local health system might prevent participants from having up-to-date results of these objective indicators, which restricts the availability of more substantial outcomes related to HIV care. Second, the sample size corresponds to a 10% difference between study groups under the assumption that participants will respond to the final adherence questionnaire, which may not be the case. Third, despite the stratified randomization, it may not be possible to identify if a particular subgroup will benefit more from the intervention. By doing a subgroup analysis of adherence, we will be able to assess the difference in outcomes among subgroups.

To conclude, this study will generate valuable evidence on the use and implementation of mHealth services for young people living with HIV in Peru. If effective, it could inform public policies and improve the quality of care for young people living with HIV.

Acknowledgments

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Authors' Contributions

JF, RC, and EG were responsible for developing the concept of the study. JF and DE developed the questionnaires and aspects of intervention delivery. JF and EG designed the standardized messages with input from nurses from the National HIV Program at the study center. FM and EG contributed to adapting the intervention to the standard practices at the study center. JF and members of the research team are responsible for participant enrollment. DE and JF are involved in scheduling the messages and questionnaires. JF and medical doctors from the research team manage the chat with individual participants and schedule outpatient appointments as needed. DE and EG are responsible for managing data collected from the messaging platform. EG and FM supervise the implementation of the intervention at the study center. All authors contributed to writing and reviewing this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Standardized messages and their associated behavioral change technique.
[DOCX File , 24 KB - resprot_v14i1e66941_app1.docx]

Multimedia Appendix 2
Informed consent (original, Spanish).

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[DOCX File , 23 KB - resprot_v14i1e66941_app2.docx]

Multimedia Appendix 3
SPIRIT Checklist.
[PDF File (Adobe PDF File), 140 KB - resprot_v14i1e66941_app3.pdf]

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Abbreviations

ART: antiretroviral therapy
BCT: behavioral change technique
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
IRB: institutional review board
mHealth: mobile health
PI: principal investigator
REDCap: Research Electronic Data Capture
SMAQ: Simplified Medication Adherence Questionnaire
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

ENABLE—App-Based Digital Capture and Intervention of Patient-Reported Quality of Life, Adverse Events, and Treatment Satisfaction in Breast Cancer: Protocol for a Randomized Controlled Trial

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Related Article:

This is a corrected version. See correction statement: https://www.researchprotocols.org/2025/1/e78781

Abstract

Background: In recent years, breast cancer treatment has taken the path toward personalized medicine. Based on individual tumor biology, therapy tailored to the particular subtype of cancer is increasingly being used. The aim here is to find the most suitable therapy for the disease. However, the success of therapy depends to a large extent on the patient's adherence to treatment.

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This, in turn, depends on how the therapy is tolerated and how the treatment team cares for the patient. Patient-centered care seeks to identify and address the individual needs of each patient and to find the best form of care for that person.

Objective: In order to improve comprehensive oncological care of patients with breast cancer, the ENABLE trial digitally recorded the health-related quality of life (HRQoL), adverse events (AEs), and patient satisfaction using a mobile smartphone app. The trial provided individualized responses to reported AEs and offered assistance. Additionally, it assessed the impact of a patient-reported outcome–based intervention across various therapy settings.

Methods: Patients with breast cancer were eligible to participate in the study before neoadjuvant, adjuvant, postneoadjuvant, or palliative systemic therapy against breast cancer was initiated at the Heidelberg, Mannheim, and Tuebingen, Germany, university hospitals. After 1:1 randomization into an intervention and a control group, HRQoL assessments were performed at six fixed time points during the therapy using validated questionnaires. In the intervention group, HRQoL was also assessed briefly every week using a visual analog scale (EQ-VAS). In cases of significant deterioration, therapy-associated side effects were assessed in a graduated manner, recommendations were sent to the patient, and the treatment team was informed. Additionally, the app served as an "eHealth companion" for education, training, and organizational support during therapy.

Results: Recruitment started in March 2021; follow-up was completed in February 2024. In total, 606 patients were enrolled, and 592 patients participated in the study. Enrollment was completed in September 2023, and the last visit was in February 2024. The first results are expected to be published in Q2 2025.

Conclusions: Participation in the intervention group is expected to improve treatment satisfaction, adherence, detection, and timely treatment of critical AEs. The close-meshed, weekly, brief HRQoL assessment will also be tested as a screening tool to detect relevant side effects during therapy. The study offers a more objective HRQoL assessment across treatment strategies.

Trial Registration: Deutsches Register Klinischer Studien DRKS00025611; https://drks.de/search/en/trial/DRKS00025611

International Registered Report Identifier (IRRID): DERR1-10.2196/69855

(JMIR Res Protoc 2025;14:e69855) doi:10.2196/69855

KEYWORDS

breast cancer; electronic patient-reported outcomes; ePRO; health-related quality of life; HRQoL; eHealth apps

Introduction

Breast cancer is the most common cancer in women worldwide and the fifth leading cause of cancer-related deaths [1]. In recent years, oncological therapy, in general, and treatment of breast cancer, in particular, have taken the path toward personalized medicine [2]. Current treatment of both primary and advanced breast cancer is individualized and tailored to each patient's tumor subtype and needs. The aim here is to find the most suitable therapy. However, the success of therapy depends to a large extent on the patient's adherence to treatment [3,4]. This, in turn, depends on how the therapy is tolerated and how the medical team cares for the patient [5]. One approach is to personalize patient care overall. Therefore, a patient's individual needs must be identified and taken into account with the aim of finding the best form of care for each person. Patient-centered care "is respectful of and responsive to individual patient preferences, needs, and values, and ensuring that patient values guide all clinical decisions" and has been proven to be an important predictor for patient satisfaction and treatment outcomes [6].

One approach to assess these needs is to evaluate the patient's health-related quality of life (HRQoL) during therapy. They can be measured with the help of questionnaires. A distinction is made between disease-specific and generic (cross-disease) quality of life (QoL) questionnaires [7]. The gold standard for recording HRQoL is patient-reported outcomes (PROs) [8]. PROs describe the collection of health and health care data by the patients themselves, without interpretation by physicians or other health care providers [9]. This information can include symptoms, functional status, QoL, and quality of care. As patients directly transmit these data, side effects and losses in QoL that are not queried or underestimated by the medical staff are recorded in an unfiltered process.

PROs have proven to be a useful tool both for detecting adverse events (AEs) in the context of studies and for investigating HRQoL, treatment, and care. In particular, in drug trials, PRO-AEs represent the gold standard for measuring side effects [10]. Studies have shown that practitioners generally underestimate a large proportion of the relevant side effects or do not notice them at all [11,12]. By recording PROs, precision in monitoring therapy can thus be increased. This more relevant information on treatment, in turn, contributes to improving therapy quality and patient satisfaction [13].

PROs can be collected electronically, generating information about health status in real time both for the patients themselves and for the treatment team and offering the possibility to communicate in both directions, that is, information for the treatment team and feedback to the patients [12,14]. This provides immediate feedback, and interventions can be established if the results of the ePRO survey prove to be abnormal or critical. Studies have shown that this improves symptom control [15,16], offers improved doctor-patient communication [17,18], and increases patient well-being and satisfaction [19,20]. Basch et al [12,21] attracted particular attention with their work on ePROs in patients with cancer, as he was able to show that electronic patient-reported outcome measurement not only significantly improves HRQoL but also reduces emergency room visits and even improves overall survival in patients with metastatic cancer disease [12,21]. These

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results were confirmed in another study in patients with advanced lung cancer [22].

In the context of patient-centered care, PROs can represent an important component in clinical routine, comparable to laboratory values, in order to give the patients' HRQoL more weight in making decisions about treatment [7]. They can help stratify the side effects of the individual patient, make them more objective, and relate them to comparison groups.

Despite the positive outcomes of PRO-based interventions in patients undergoing metastatic (breast) cancer therapies, their impact in the neoadjuvant and adjuvant settings remains unclear. However, initial evidence suggests that PRO-supported monitoring may also have beneficial effects on HRQoL and in preventing AEs in these treatment contexts [23]. The available data, particularly regarding adjuvant therapy in patients with breast cancer, are still limited, and PRO-based interventions have not yet demonstrated a clinically significant effect [24].

The ENABLE study was designed to systematically evaluate HRQoL and AEs in patients with invasive breast cancer using digital questionnaires through the specially developed smartphone app "ENABLE." By implementing targeted interventions, the study aimed to improve treatment satisfaction and HRQoL across various therapy settings. Additionally, it sought to examine the impact of PRO-based monitoring on patients receiving neoadjuvant and adjuvant chemotherapy and to determine whether findings from metastatic settings could be applied to these treatment phases.

Methods

Study Design

Patients were included before starting systemic therapy for breast cancer in neoadjuvant, adjuvant, postneoadjuvant, and palliative treatment settings. Patients were recruited at the respective oncology centers. The study randomized patients 1:1 into an intervention and a control group. In both groups, QoL was assessed for at least six fixed time points during therapy using European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-C30, European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-BR45, and Patient-Reported Outcomes Measurement Information System-29 (PROMIS-29; Figure 1). Participating centers are the university hospitals of Heidelberg, Tuebingen, and Mannheim, Germany.

Figure 1. Timepoints of questionnaire assessments (visits) depending on the therapy and therapeutic strategy. Adj. CT: adjuvant chemotherapy; Adj. ET: adjuvant endocrine therapy; CT: chemotherapy; EoCT: end of chemotherapy; NACT: neoadjuvant chemotherapy; OP: operation; POST-NACT/pNACT: postneoadjuvant chemotherapy.

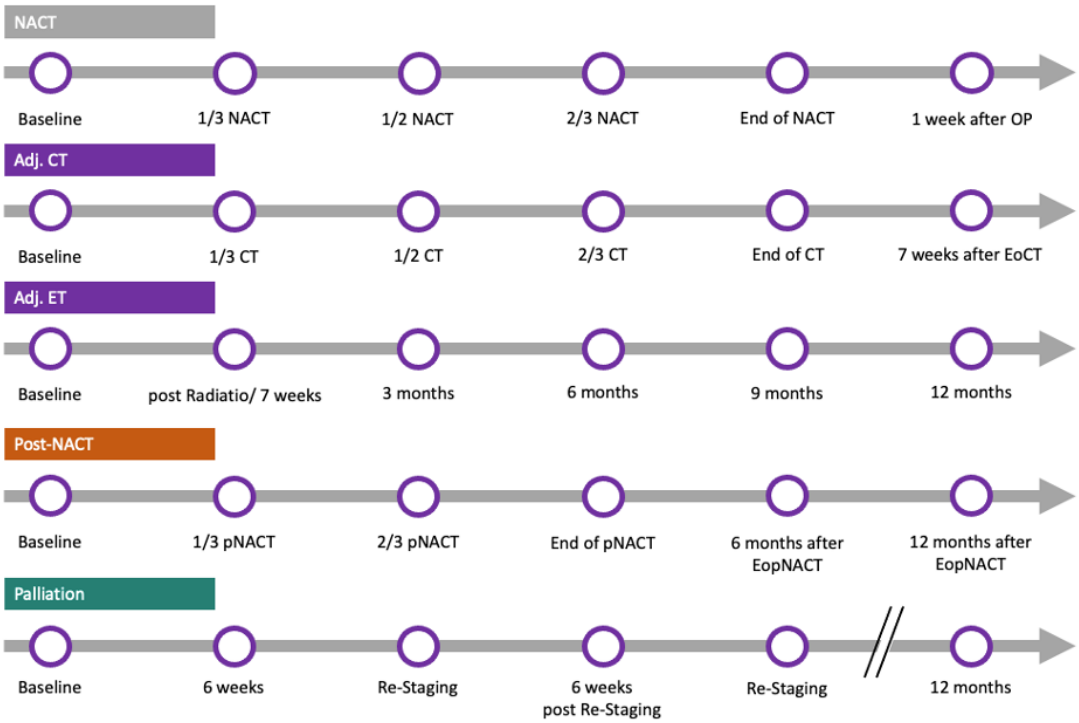

Intervention Group

In the intervention group, a brief weekly assessment of the current HRQoL was additionally carried out via the app using a visual analog scale (EQ-VAS). The EQ-VAS was used as a screening tool, as previous research has demonstrated its sensitivity in detecting deterioration of HRQoL at an early stage [25]. If significant deterioration (EQ-VAS value <50 or a decrease of 10% in comparison to the last EQ-VAS value) in the current HRQoL was discovered in the intervention group, a digital questionnaire was started, which asked about therapy-associated side effects in a graduated manner (ePRO symptom query based on the Common Terminology Criteria of Adverse Events stratification), that is, classified according to symptom severity, and the treatment team was informed; this so-called reactive PRO assessment (RPA) is depicted in Figure 2. Furthermore, a graduated psychological assessment was conducted using Patient Health Questionnaire-8, Generalized Anxiety Disorder 7, and the European Organization for Research

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and Treatment of Cancer Quality of Life Questionnaire for Cancer-related Fatigue. In addition, the patients were presented with evidence-based educational information via the app on how to deal with the side effects as learning content, and if the side effects were more severe, they were asked to contact the treatment team. In parallel, the treatment team was informed via a web app ("PIA"), and depending on the severity of the complaints, the patient was contacted directly. Figure 3 illustrates the RPA procedure.

Figure 2. Study design of the ENABLE trial: upon patient enrollment in the care portal, randomization is performed automatically using centralized block randomization. ePRO-CTCAE: electronic patient-reported outcome Common Terminology Criteria of Adverse Event; HRQoL: health-related quality of life; PRO: patient-reported outcome; PROMIS-29: Patient-Reported Outcomes Measurement Information System-29; QLQ-BR45: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-BR45; QLQ-C30: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-C30; R: 1:1 randomization; RPA: reactive patient-reported outcome assessment.

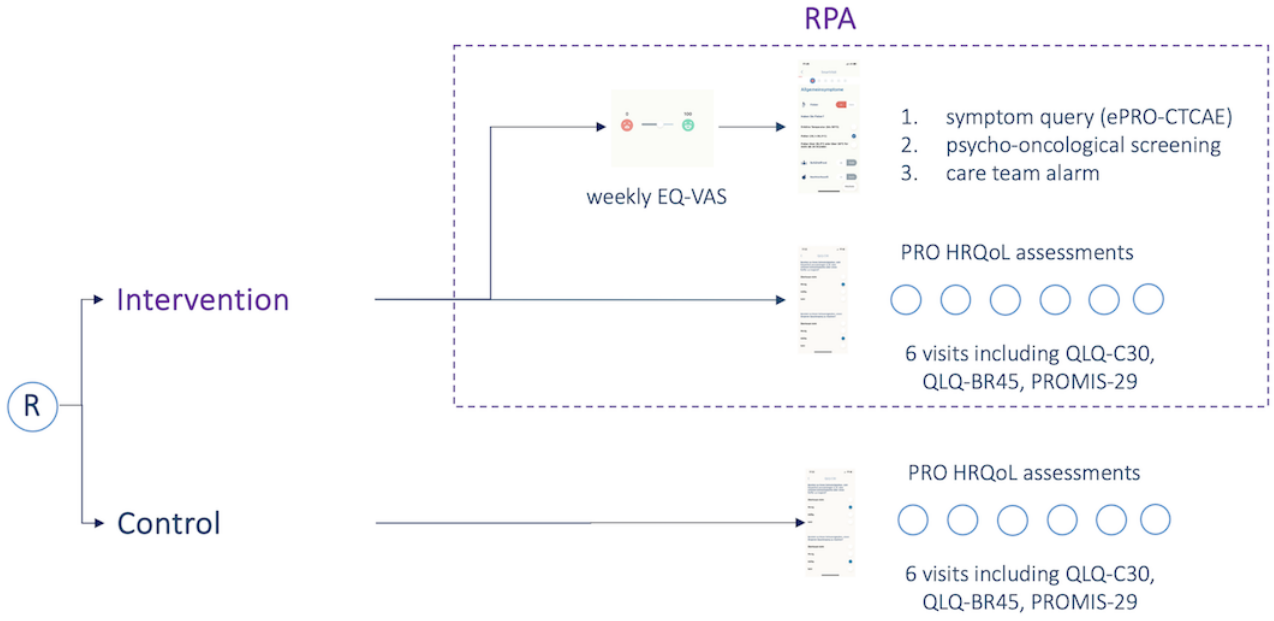

Figure 3. (A) RPA procedure with HRQoL screening via EQ-VAS, (B) symptom query, and psycho-oncological screening in case of a value <50 or a decrease of 10 % in comparison to the last EQ-VAS value. The symptom query is followed by (C) care advice, (D) an alarm for the care team via the "PIA" platform, and (E) educational content for the patient via the app. The images show the app representations for the patient. centralized block randomization. PRO-CTCAE: patient-reported outcome Common Terminology Criteria of Adverse Event; HRQoL: health-related quality of life; RPA: reactive patient-reported outcome assessment.

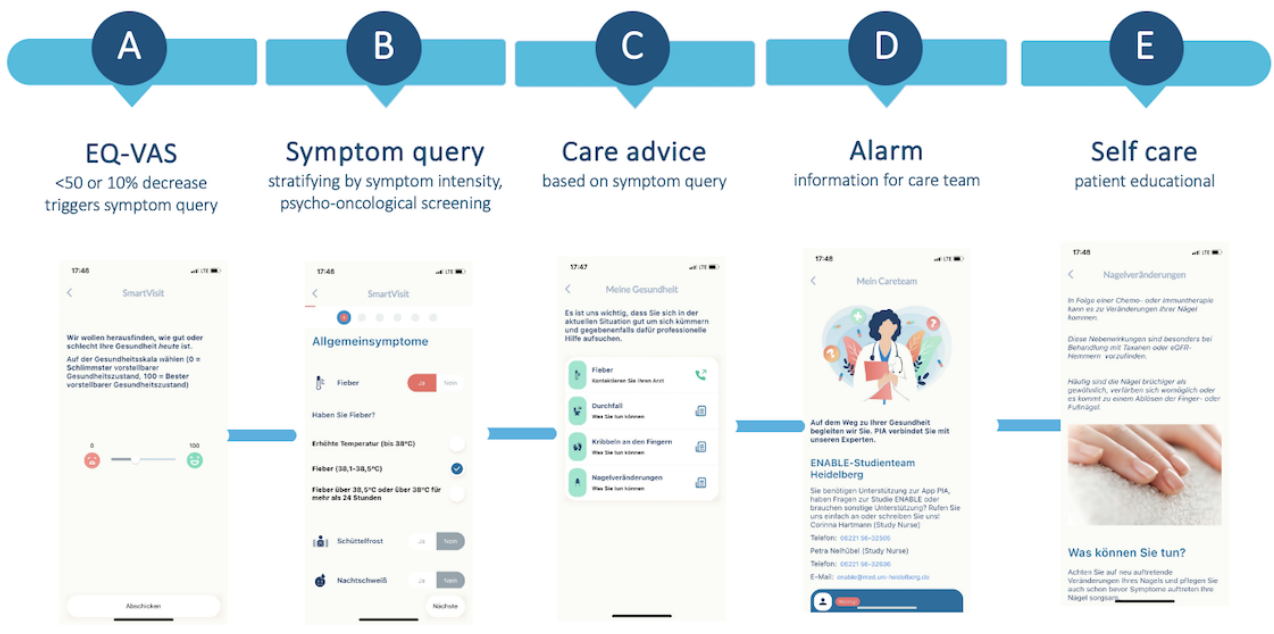

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Patient Empowerment

Each patient had an individual treatment and care plan that was mapped via the app. Via a content library in the app, all study participants were provided with information about care offers, such as self-care practices for managing side effects, nutritional counseling, social counseling, physiotherapy, and sport offers, and with patient-centered, evidence-based educational information. Depending on the respective therapy and the individual situation of the patients, this information was displayed as a feed on the app's home screen. In addition, the app provided an overview of the current status of the therapy and displayed the next appointments at the center via a calendar.

The smartphone app "ENABLE" was thus a bidirectional communication platform with an additional educational guide. This enabled patient education, and thus, patient empowerment on the one hand, and risk assessment, therapy control, and systematic QoL assessment on the other (Figure 4). The questionnaires and guides were individually adapted to the respective therapy situation and patient needs.

Figure 4. The home screen of the ENABLE app with representation of the different functions. ePROM: electronic patient-reported outcome measurement.

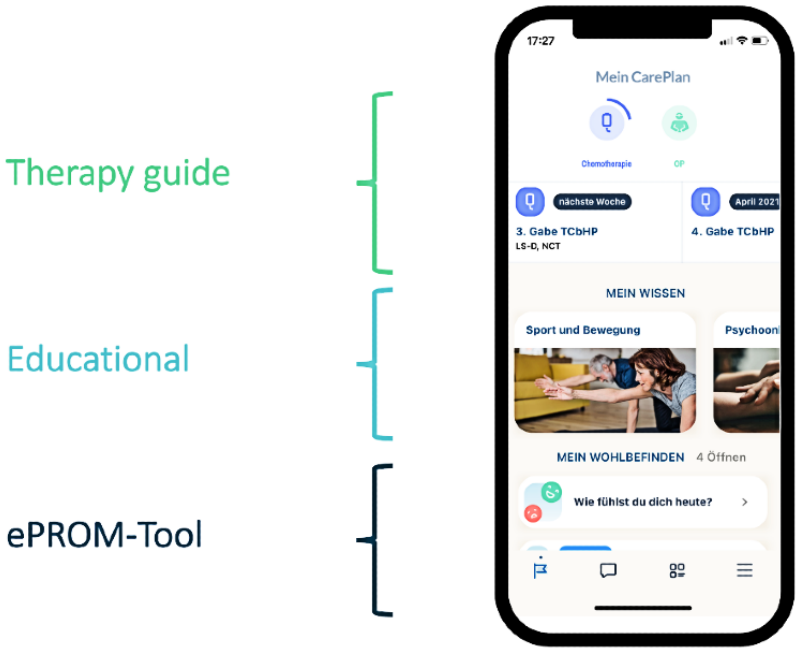

Care Team Web App

The treatment team of the respective study center had access to the web-based care team platform "PIA," developed and provided by the Center for Innovative Care and the Institute of Women's Health GmbH, via which the patients were included in the study and assigned to a treatment and care plan. The PRO data for each patient were visualized via the platform and alarms in the intervention group were displayed. In addition, the calendar could be set and the clinical data entered.

Aim

The study aims to improve therapy adherence, recognize and treat critical side effects in a timely manner, and make the HRQoL more objective in the context of different therapy strategies. The study is intended to test the overall benefit and added value of an electronic therapy companion and to increase patient satisfaction.

Primary Hypothesis and Outcome

The primary end point of the study is to compare HRQoL and treatment satisfaction (measured by the PROMIS-29) between the intervention and control groups.

Secondary Hypotheses and Outcomes

Participation in the intervention group is expected to improve treatment satisfaction, therapy adherence, and detection and timely treatment of critical AEs. The close-meshed, weekly, brief HRQoL assessment was tested as a screening tool to detect relevant side effects during therapy. The study provides HRQoL objectivity across treatment strategies. In addition, a usability and feasibility analysis of the app and the intervention concept was carried out.

Inclusion Criteria

The inclusion criteria are as follows: diagnosis of invasive breast cancer or metastasis of breast carcinoma; 18 years or older; fluency in German; access to a computer, tablet, or smartphone with internet connectivity; capacity to provide informed consent; and a signed informed consent form.

Data Acquisition and Management

The study is based on the principles of the Declaration of Helsinki. The study plan and all other study-relevant documents were approved by the ethics committees of the university medical faculties of Heidelberg, Mannheim, and Tuebingen, Germany. The current version of the study protocol is 4.2 from December 9, 2022. Protocol amendments were communicated to participating centers immediately. The study participants have the right to request information about the personal data collected from them. Participation in the study is voluntary after all study content and objectives have been declared and written

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consent has been given and can be terminated at any time without any disadvantages for the patient.

Patient data and clinical data are recorded pseudonymously and stored centrally in the electronic case report form (eCRF). The data were documented from the medical reports and tumor documentation of the treating center in a web-based eCRF via the study staff at the study centers. These eCRFs are stored and managed throughout the duration of the study in a secured cloud infrastructure, which was conceptualized and initiated by the Institute of Women's Health GmbH and the three partner sites of the Center for Innovative Care in Heidelberg, Mannheim, and Tuebingen. This high-availability infrastructure guarantees and verifies individual permission rights and user roles for all participating clinicians for strict compliance with data protection regulations. For future research, all accumulated data will be transferred into the individual clinic infrastructures after the study ends, and all externally hosted data will be permanently erased. An interim analysis of the secondary end points was conducted after 50% of the patients had been included and carried out by the Institute of Women's Health GmbH. The data monitoring committee is made up of the principal investigators from the Heidelberg and Tuebingen centers and is independent of the sponsor of the study.

The following clinical data are recorded: demographic data, Eastern Cooperative Oncology Group status, height, weight, stage of the disease, previous diseases, clinical tumor characteristics, tumor biology, staging results, therapy-associated side effects, and previous and current therapies.

Sample Size Calculation

The sample size was calculated according to the primary end point HRQoL (measured via the PROMIS-29). It was based on a minimal important difference of 5 points, an SD of 10 points, a power of 80%, a 2-sided significance level of 5%, and a dropout rate of 37.5%. PASS (NCSS, LLC) software was used to calculate the sample size.

Statistical Analysis

The primary outcomes will be examined in an intention-to-treat analysis for all randomized individuals with a mixed linear regression model. Primary analysis will be adjusted for age, therapy situation, type of systemic therapy, Eastern Cooperative Oncology Group status at enrollment, and other important confounders if necessary. The heterogeneity between the trial sites is considered through random effects (random intercept mixed model). The level of significance is set at α=5%.

All secondary outcomes will be analyzed analogously to the primary hypothesis and according to the respective outcome using further suitable statistical methods. As in the analysis of the primary outcome, the secondary hypotheses will be adjusted for relevant confounders. In addition, the heterogeneity between study centers will be considered. Secondary outcome analysis will be performed exploratively.

All statistical analyses will be planned in detail and documented in a statistical analysis plan that will be prepared before closing the database.

Ethical Considerations

The study was approved by the central ethics committee in Heidelberg (S-658/2020). All recruiting centers obtained approval from the local ethics committees (Ethics Committee at the Medical Faculty of the Eberhard Karls University of Tuebingen and the University Hospital of Tuebingen: 896/2020BO2; Ethics Committee II of the University of Heidelberg, Mannheim Medical Faculty: 2021-544) before study initiation. Written informed consent was obtained from all participants before study participation. The authors affirm that human research participants provided informed consent for publication. Patients signed informed consent regarding publishing their data. Participants received no financial or other compensation for their involvement in the study.

Results

Recruitment started on March 22, 2021, in Heidelberg; April 11, 2021, in Tuebingen; and November 4, 2021, in Mannheim. The last patient was enrolled on September 8, 2023, and the last visit was in February 2024. Due to the innovative specifications of the app, the protocol was only published after the recruitment phase was completed. The protocol was submitted before the end of data collection. A total of 606 patients were enrolled in the study; however, 14 patients did not complete the app's initial setup process and were therefore excluded from the trial. The remaining 592 patients included in the trial consisted of 380 (64.2%) patients who received neoadjuvant chemotherapy, 138 (23.3%) patients who underwent adjuvant chemotherapy, 38 (6.4%) patients who received adjuvant endocrine therapy, 12 (2%) patients who underwent postneoadjuvant therapy, and 4 (0.7%) patients who received palliative chemotherapy. The first results are expected to be published in Q2 2025.

Discussion

Principal Findings

Study results published in the last few years have already demonstrated the many possibilities for increasing the quality of care, treatment, and HRQoL in breast cancer treatment due to patient-reported outcome measurements (PROMs), and survival rates have improved, too [21,22]. These results fundamentally underscore the necessity of consistently integrating eHealth and telemedicine, particularly in the context of electronic patient-reported outcome measurement, into breast cancer therapy.

However, some barriers to implementing eHealth in mainstream care remain. Among the theoretical aspects is the fact that no standard has been established yet either for selecting questionnaires or for downstream interventions. One task for the coming years will be to develop basic items and a basic dataset in order to establish a system for quality control and to make it possible to compare the collected data.

For the purpose of standardizing the PROMs for a value-based PRO, the "International Consortium for Health Outcomes Measurement" has defined a minimal standard PRO Set [26]. In addition, the "Innovative Medicines Initiative—Health Outcomes Observatory" (H2O) consortium has developed core

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outcome sets to make HRQoL in patients with metastatic breast cancer more objective [27]. However, there is still no standard PROMs for PRO-based interventions in oncology.

In principle, we need to determine which intervals between assessments and for how long eHealth monitoring—in the sense of a PROM—are useful for patients with breast cancer. These questions need to be addressed in clinical studies, while simultaneously striving to integrate the findings from individual studies. Only then can PROMs be sensibly implemented in standard care. At the same time, different apps and providers must be able to access these interfaces, and we must also be able to transfer downstream interventions to a common system. Otherwise, implementation in everyday life could fail due to the abundance of additional documentation work required and the cost of developing additional software and apps.

The ongoing digitalization of all areas of life will ensure that there is no way back to less digitalized health care. However, despite all considerations of progress, the patient must never be left out of the focus of these efforts. Digitalization and the use of eHealth must always be based first and foremost on improving patient care and should never be an end in itself. The possibility to aggregate data through eHealth apps must also be weighed very critically in terms of scientific benefit and burden for the patient.

The ENABLE study aims to investigate the impact of a PRO-based intervention in different treatment settings for breast cancer. Recently, Karsten [28] presented findings at the San Antonio Breast Cancer Symposium demonstrating the beneficial effects of PRO-based interventions on fatigue, physical functioning HRQoL, and overall survival in the metastatic setting, too, underscoring the importance of bringing PRO monitoring into the standard of care for advanced breast cancer. These findings align with other positive PRO intervention studies in metastatic breast cancer that found improved therapy adherence, delayed onset of serious AEs, reduced toxicity, fewer unplanned hospitalizations, increased patient satisfaction, and enhanced HRQoL [29-31].

Conclusions

The impact of neoadjuvant and adjuvant chemotherapy on HRQoL has not yet been thoroughly investigated. It is particularly important to explore the extent to which a PRO-based intervention may also positively influence patients' HRQoL and symptoms in the adjuvant setting. Pappot et al [24] could not show a significant impact of a PRO-based intervention on treatment adjustments, unplanned hospitalization, or febrile neutropenia in a cohort of patients with breast cancer undergoing adjuvant therapy. Therefore, beyond its primary end point, the ENABLE study offers the opportunity to examine the effects of the intervention and the HRQoL on therapy outcomes, adherence, and AEs.

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed.

Authors' Contributions

TMD, AB, and MW developed the study concept. TMD, MF, and MW conducted the methodology. AB, OH, NP, SYB, and MW provided the funding for the study. TMD, AB, NP, PE, and MW developed the app and care portal and provided IT administration. TMD, CB, NP, ADH, and MW developed the electronic case report form. TMD, LB, KH, LT, and CB wrote the app content. TMD, LLV, SS, ADH, AB, AS, MM, and MW provided project administration. LB, LT, CA, and LW conducted usability and feasibility analyses. TMD, LLV, ADH, and MW served as the data management team. ADH, SYB, AS, and MW provided project supervision. The original draft was written by TMD and MW. TMD, MF, AB, and MW reviewed and edited the original draft. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AE: adverse event
eCRF: electronic case report form
HRQoL: health-related quality of life
PRO: patient-reported outcome
PROM: patient-reported outcome measurement
PROMIS-29: Patient-Reported Outcomes Measurement Information System-29
QoL: quality of life
RPA: reactive patient-reported outcome assessment

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Protocol

A Mobile Ecological Momentary Intervention for Reducing Experiential Avoidance in the Context of Rumination: Protocol for a Randomized Controlled Trial

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Abstract

Background: Rumination is a transdiagnostic process present in several psychological disorders, involving repetitive negative thinking that individuals may perceive as difficult to control. While the roles of numerous mechanisms underlying rumination have been supported, experiential avoidance (EA) still lacks empirical backing, despite a strong theoretical foundation, partly due to difficulties in examining EA in an ecologically valid context. One promising approach to addressing this challenge is through reducing EA using mobile health (mHealth) and ecological momentary intervention (EMI), and assessing any subsequent decrease in rumination's deleterious outcomes.

Objective: This paper outlines the protocol for a randomized controlled trial using a novel mHealth EMI to address EA in the context of rumination. The app was developed by a multidisciplinary team, incorporating feedback from potential end users.

Methods: Consenting individuals (target N=60) who meet the inclusion criteria (self-reporting problems with repetitive negative thinking) will be randomly assigned to 1 of 4 conditions: (1) intervention with therapist support and daily sampling, (2) intervention without support and with daily sampling, (3) partial intervention (emotion validation EMI only) with daily sampling, or (4) control (daily sampling only). The intervention consists of a series of modules delivered over 4 weeks, with assessments conducted before and after intervention, and again at 1-month follow-up (plus an additional 3-month follow-up for intervention participants). Data will be collected both through online self-report assessments and via the app itself. The potential of the EMI to modify the maladaptive feature of repetitive negative thinking will be assessed using mixed-design ANOVA, while the links between avoidance-mood and rumination-mood, in terms of the moderating effect of trial condition, will be evaluated using multilevel models. These will be assessed as primary outcomes. Secondary outcomes are the effects of a supporting therapist on postintervention outcomes in the intervention groups, and time spent using the app as a measure of engagement (analyzed using the mixed-design analysis of covariance). Compliance will be defined as completing both of the first 2 weeks of intervention content in full, and 5 out of the 6 exercises from weeks 3 and 4. Additionally, the study will control for both the amount of time spent in the app and the length of responses to open-ended questions.

Results: Recruitment and enrollment for the trial are expected to begin in May 2025 and be completed by July 2025. Data collection will conclude once the target sample size for each of the 4 conditions has been reached. The main results of the trial are expected to be submitted for publication in October 2025.

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Conclusions: The outcomes of this research trial will not only provide insights into the clinical capabilities of the app, including its usability and acceptability in real-world contexts (and its potential future viability as a scalable product), but will also offer valuable theoretical insights into the role of EA in maladaptive rumination.

Trial Registration: ClinicalTrials.gov NCT06570694; https://clinicaltrials.gov/ct2/show/NCT06570694

International Registered Report Identifier (IRRID): PRR1-10.2196/66067

(JMIR Res Protoc 2025;14:e66067) doi:10.2196/66067

KEYWORDS

rumination; experiential avoidance; mHealth; ecological momentary intervention; transdiagnostic processes; low-intensity intervention; repetitive-negative thinking; cognitive avoidance; psychoeducation

Introduction

Rumination and Psychopathological Outcomes

Epidemiological data suggest that comorbidity is the rule rather than the exception [1], with it frequently observed in at least half of the diagnosed population [2]. The experience of comorbidity has significant negative implications for clinical severity and prognosis [3,4]. Additionally, the persistently moderate outcomes of treatment programs and high levels of posttreatment relapse indicate a still limited understanding of the mechanisms that initiate, underpin, and maintain a number of psychiatric disorders [5].

Transdiagnostic models represent a shift away from disorder-centric approaches to the understanding and treatment of psychological disorders. Instead of focusing on a specific nosological diagnosis, they suggest focusing on processes that may serve as risk, maintenance, and relapse factors across multiple psychological disorders, thereby more effectively addressing the frequent comorbidity observed in mental disorders. Interventions based on transdiagnostic approaches have demonstrated positive outcomes in reducing symptom presentation across several disorders [3,6-10].

Rumination is a transdiagnostic process present in several psychological disorders [11]. Traditionally, rumination was explored in the context of mood disorders and defined as a mode of responding to distress that involves repetitively and passively focusing on symptoms of distress and the possible causes and consequences of these symptoms. Nevertheless, rumination is now recognized as being involved in numerous psychological disorders and adopts a broader definition—a form of repetitive thinking about 1 or more concerns perceived to be difficult to control [12]. While rumination may not necessarily be wholly maladaptive, it can become so when overgeneralized and used inflexibly [13], in which case it has been shown to impair emotional regulation and increase negative affect [14]. Thus, one can expect that addressing this maladaptive transdiagnostic process will result in a reduction of psychopathology symptoms (eg, [11]). Experimental studies that induce rumination in distressing contexts demonstrate elevated depressed and anxious mood [15]. Similarly, self-report studies find rumination to be a risk factor in numerous issues, including as a risk factor and consequence of depressive symptoms [16]; the onset, number, and duration of major depressive episodes [17-19]; and the development of generalized anxiety [19], social anxiety [19], eating disorders [19], posttraumatic stress [20], and borderline symptoms [21]. In addition to its symptomatological impact, rumination has also been shown to reduce the efficacy of psychological interventions [12].

Currently, several models explain the maladaptive nature of rumination—these involve abstract processing and dysregulation at the goal/action identification level (ie, adapting a specific processing mode to current requirements [22]); impairments in executive or attentional functioning [23,24]; or rumination as a learned, habitual response [13,23,24]. A recent H_Ex_A_Go_N model of rumination attempts to integrate the most prevalent theories with a relatively strong empirical background on the mechanisms maintaining maladaptive rumination, identifying rumination as a *h*abit, *e*xecutive function impairment, *a*bstract processing mode, *go*al discrepancies triggering rumination, and the *n*egative valence of rumination content [12]. Thus, the authors suggest that rumination becomes a maladaptive, transdiagnostic process when it is used as a habitual, overgeneralized response to negative affect [12,25].

Nevertheless, the literature suggests that another mechanism could be involved in making rumination maladaptive and in reinforcing it as a habitual response—namely, experiential avoidance (EA). Although this mechanism features prominently in the theory of repetitive negative thinking (RNT), it has received very limited empirical support. This is not necessarily due to a lack of supportive data (eg, [25]), but rather to the small number of studies testing this hypothesis, largely because of the challenges involved in evaluating EA in empirical research.

Mechanisms Underpinning Rumination: Examining the Role of Experiential Avoidance

EA refers to attempts to eschew emotional distress by engaging in maladaptive behaviors that temporarily allow escape from negative emotional experiences. Through the use of EA, individuals may disconnect from unpleasant emotions by altering the form or frequency of these experiences [26], even when such avoidance causes behavioral harm by interfering with goal pursuit and impairing learning through experience. This often leads to the adoption of additional maladaptive coping strategies, such as substance use [27].

Engagement in EA has adverse effects on the development, maintenance, and modification of chronic psychological disorders such as depression, due to its tendency to generate negative mood and initiate a maladaptive cycle of emotional distress and avoidance [28]. Consequently, EA may represent a core vulnerability for emotional distress [29]. To this end,

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randomized controlled trials delivering therapeutic interventions focused on reducing EA (such as acceptance and commitment therapy) have found that decreases in EA are associated with reductions in depressive and anxious symptoms [28,30,31].

As a mechanism underpinning rumination, however, despite some empirical evidence emerging to examine its role [12,32], EA continues to lag in terms of supporting data. This is despite the theoretical basis for the role of EA in rumination [22,33], where rumination serves as a means to avoid increased arousal and distress through an overgeneral, abstract style of thinking, despite its maladaptive implications for real-world problem-solving and long-term deleterious consequences for emotion regulation [22,24,25]. Of note, a study examining multiple indices of avoidance reported differential outcomes across the 3 modes of investigation (self-report, dichotic listening tasks, and psychophysiological measures), lending only partial support to the avoidance conceptualization of rumination [34].

Difficulties in examining the role of EA may, in part, be due to several methodological challenges associated with assessing EA in ecologically valid contexts. While experimental studies appear to lend support to an EA conceptualization of rumination [29,35], the tasks used to evaluate it in laboratory settings (eg, approach-avoidance task or dichotic listening task) do not reflect the real-world occurrences of EA. Similarly, while self-report evaluations connect EA with rumination [34,36], such data rely heavily on retrospective recollection, assuming that participants were aware of their use of (and the extent of their use of) avoidance. One alternative approach to examining the role of EA may involve adopting the experimental method, that is, reducing EA through ecological momentary intervention (EMI) [37], and examining any resulting reduction in the deleterious outcomes of rumination.

Mobile Health as a Vehicle for Ecological Momentary Intervention

The availability of mental health services has struggled to keep pace with the growing demand for treatment [38,39]. One means of addressing this imbalance has been through the use of digital interventions, which offer the potential to provide accessible, rapid, and scalable pathways to intervention [40].

Mobile health (mHealth) apps represent a dimension of digital health provision and allow for the delivery of validated psychological interventions on-demand via smartphones. Because of the ubiquity of smartphones [41] and the opportunities afforded for personalization of provision, mHealth apps offer the potential to deliver rapidly scalable interventions that can expand the reach of mental health services while overcoming a number of barriers faced by traditional forms of treatment [42].

EMI further represents an opportunity to utilize ubiquitous devices, such as smartphones, to integrate treatment protocols into people's everyday lives. Treatment can be delivered in natural environments as either a standalone intervention or as an addendum to existing treatment [43], and can be based on the outcomes of real-time daily sampling assessments also conducted in the real world (ecological momentary assessment [EMA]). The use of real-time assessment data allows for provision to be personalized and tailored to the general requirements of an individual client and, on a micro-level, as a form of opportune intervention within a specific environmental context [44]. As an assessment tool, EMA also helps overcome the limitations of global self-report measures, where retrospective recollections of emotions and events may be distorted by subsequent use of regulation strategies [45].

Literature has begun to explore the capabilities of mHealth EMIs as tools for mental health intervention, with promising results emerging across a range of conditions [46,47]. In addition to their potential therapeutic benefits, EMIs represent several methodological opportunities to improve ecological validity. First, the use of ubiquitous devices such as smartphones allows research to be conducted in real-world settings, reducing the reliance on laboratory-based experimental studies, where outcomes may, in part, be a product of the artificiality of the environment. Instead, the real-world nature of treatment delivery allows for the examination of intervention effects (eg, in the context of transdiagnostic processes) in real-world contexts. Second, while EMAs may not always be conducted in "real time" (eg, at the moment of symptom experience), data can be collected within a short period thereafter. The implementation of regular EMA also reduces the reliance of treatment efficacy studies on postintervention self-report data, which can be vulnerable to retrospective bias, particularly for individuals experiencing depressive disorders [48,49].

Uptake and engagement with mHealth, however, may be negatively associated with poor app design, technical issues, digital literacy, poor suitability of content, lack of professional support, and pathological factors (eg, low motivation), when content is delivered in a manner unsuited to user requirements, or when engagement is considered by users to be too labor intensive [50-55]. Numerous factors at both the individual and group levels have been identified that may affect the intention to use or uptake of digital interventions [56,57]. Effective multidisciplinary collaboration in app development, which acknowledges the intricate needs of target end users and incorporates these into the design of the intervention, is essential for improving acceptability, usability, and accessibility [58], particularly when interventions are deployed in unsupervised settings [59]. EMIs require unique considerations in their design, deployment, and evaluation [60], which help specify the procedures for collecting and examining user data and the circumstances under which the intervention may be delivered. Where EMIs actively respond to user data in real time, processes for determining appropriate intervention (while respecting user privacy) must also be considered.

Study Objectives

The scientific verification of processes that underpin several transdiagnostic maladaptive cognitive processes and psychopathological outcomes has several benefits. First, successfully identifying such processes advances the theoretical understanding of transdiagnostic processes themselves and their contributing roles in psychopathology. Second, it has the potential to improve several psychological treatment programs by identifying valuable targets for intervention [21], which is

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particularly valuable in treating cases of comorbidity. Using EMI and EMA in clinical trials offers a unique opportunity to evaluate the mechanisms underlying transdiagnostic processes that are difficult to assess through traditional self-report or laboratory methods (eg, avoidance). This study aims to examine whether the avoidance-focused EMI for rumination can modify the maladaptive feature of RNT, as understood through the link between daily RNT and well-being, depressive, and anxiety symptoms, compared with an active control group. We anticipate that the link between daily rumination and its maladaptive outcomes (lower well-being and higher depressive and anxiety symptoms) will be weaker in the intervention groups compared with the control group. Additionally, the study aims to confirm the role of avoidance in RNT.

Furthermore, by splitting the intervention condition into 2 groups (1 receiving concurrent therapist support and 1 not receiving concurrent therapist support), the study aims to evaluate whether intervention outcomes may be enhanced by the added availability of a supporting therapist [61].

Finally, the study aims to examine whether the impact of the avoidance-focused EMI for rumination on depressive and anxious symptoms can, compared with an active control group, be mediated by changes in beliefs about emotion (valuation of negative emotions) [62]. Similarly, the study aims to assess the EMI in terms of similar mediation effects of beliefs about rumination [63].

Methods

Study Design

The study takes the form of a 4-arm, parallel-group randomized controlled trial. Total study participation will last approximately 2 months, including preintervention eligibility screening, a 4-week intervention period using the app content and daily sampling, postintervention assessments at the end of the intervention, and a 1-month follow-up period (during which the app will remain available for self-directed use without daily sampling), concluding with follow-up assessments and measurement of any engagement with the app during this period. At this point, control participants will receive the app (minus daily sampling) and guidance on how to use the content. An initial follow-up period of 1 month has been chosen for ethical purposes to minimize the amount of time control participants will wait before receiving the app. For participants in the intervention groups, the study aims to conduct an additional evaluation of outcomes 3 months following the intervention. A graphical summary of the study design is presented in Figure 1.

Figure 1. Graphical representation of the randomized controlled trial protocol. CBT: cognitive behavioral therapy; RNT: repetitive negative thinking.

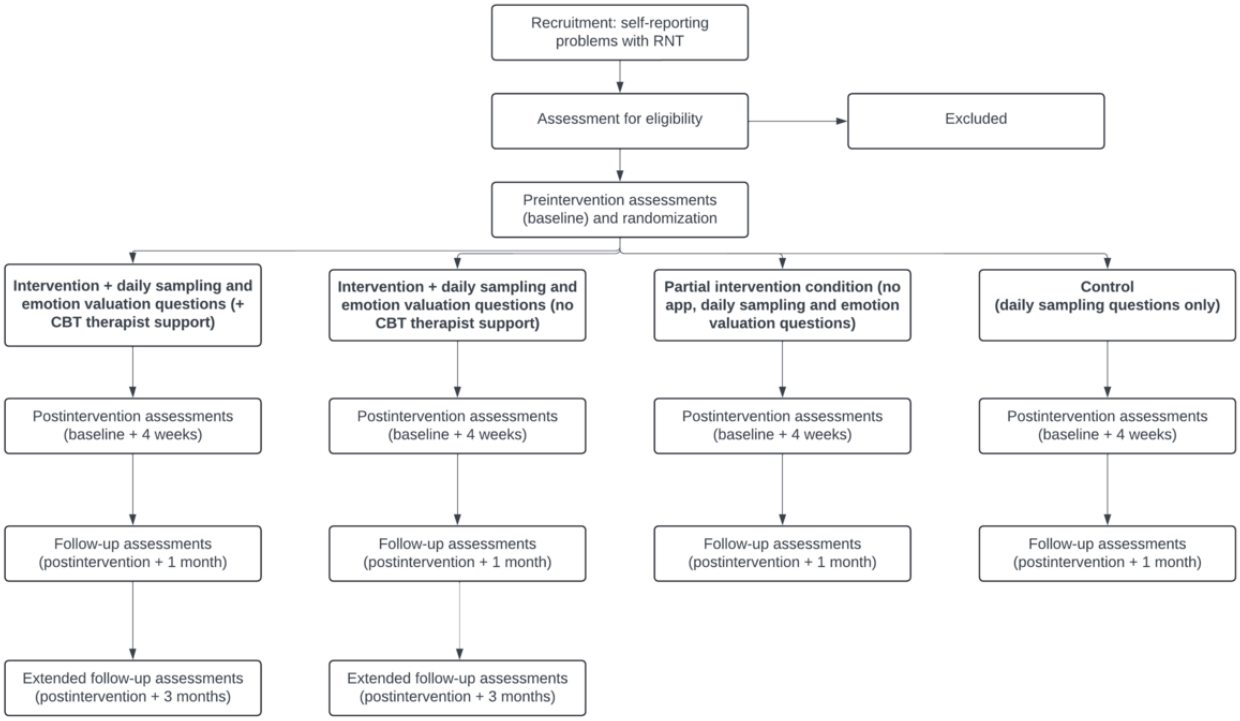

Participants will be randomly assigned, using a random-number generator, to 1 of 4 conditions: (1) intervention condition (therapist support); (2) intervention condition (no therapist support); (3) partial intervention (daily sampling and emotion valuation questions); or (4) control group (only daily sampling questions). Active control groups will be utilized to avoid artificially inflating comparisons with intervention condition outcomes [64]. The specific group allocations and the nature of other study conditions will be concealed from participants. Block/random stratification will not be used, as participants will be randomly allocated to 1 of the groups after agreeing to participate in the study. During analysis, demographic characteristics across groups will be compared, and any significant differences identified will be included as control variables.

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Therapist support has been shown to improve outcomes in studies of digital mental health interventions [61]. In this study, therapist support will take the form of asynchronous written communication with a cognitive behavioral therapy (CBT) practitioner—either fully qualified or in at least their second year of training—via WhatsApp (Meta Platforms, Inc). This support will be available 2 times a week to relevant participants at specific times predetermined by the therapist. Participants will have the option to utilize this support, but will not be directed to do so. Supporting therapists will be paid at their standard hourly rate for regular patients and will receive an introduction to the app and intervention—while remaining blinded to the full aims of the study—through an online workshop conducted by members of the research team experienced in delivering rumination-focused cognitive behavioral therapy (RFCBT), before the study.

Participants and Power Analysis

Participants who self-report problems with RNT will be sought. The first participation in the trial is planned to commence in May 2025. As the study will be conducted remotely and recruitment will continue beyond this date, participants are expected to begin their engagement asynchronously.

To be eligible for the trial, participants must self-report problems with RNT. Participants will be excluded if (1) they are under 18 years of age at the start of the trial; (2) they are currently receiving any form of psychotherapy; or (3) they are currently receiving any form of psychiatric medication. Participants with a psychiatric diagnosis will not be excluded, provided they meet the inclusion criterion and do not meet any of the exclusion criteria listed above.

Sample size was calculated using G*Power version 3.1 [65] for a repeated-measures design with 4 independent conditions measured at 3 time points and assuming a medium effect size. This indicated a required sample size of 60 with equal randomization of participants across groups, which aligns with previous intervention studies in the field [66-68]. As our initial feasibility study during the development of the app content experienced an attrition rate of approximately 60% [69], this study aims to recruit at least double that number to mitigate the risk of significant dropout throughout the trial.

Recruitment Strategy

Participants will be recruited through online advertising on social media platforms (Facebook/Instagram; Meta Platforms, Inc) and via the laboratory website, where a contact email address will be provided for interested individuals to express their interest in participating. Full study information will be sent by email to all interested participants, and informed consent will be obtained via email response before the delivery of the app and the commencement of participation. To minimize information sharing across groups, participants will not have access to one another's contact or identity details. Additionally, the current version of the app does not allow users to contact other participants or to determine how many others are using the app.

Recruitment is expected to begin in early May 2025 and will continue until the target number of participants in each condition has been reached. Participants may withdraw from the study at any time by contacting the research team via a designated email address provided in the study information form or through a link within the app. All data associated with participants who choose to withdraw will be fully removed from the study and destroyed. Participants will receive financial compensation of €50 (US $56) for taking part in the study.

Measures

Pre-Post and Follow-Up Measures

The following measures will be collected from all participants before/during the intervention, after the intervention, and at follow-up:

The Perseverative Thinking Questionnaire (PTQ) [70], a 15-item self-report measure that assesses the main characteristics of RNT: (1) core features (9 items); (2) unproductiveness (3 items); and (3) capturing mental capacity (3 items). Responses are recorded on a scale from 0 (never) to 4 (almost always). The PTQ has demonstrated good internal consistency and test-retest reliability [70], not only in clinical samples, but also in nonclinical populations and when administered online.

Emotions Beliefs Questionnaire (EBQ), a 16-item self-report questionnaire designed to measure the controllability of emotions and respondents' beliefs about the usefulness of emotions, which also demonstrates good internal consistency [71]. Respondents answer using a 7-point Likert scale, ranging from "1" (totally disagree) to "7" (totally agree), with higher scores indicating a belief that emotions are uncontrollable or useless.

The Positive and Negative Beliefs About Rumination Scales (PBRS and NBRS, respectively), which comprise 2 scales (positive beliefs: 9 items; negative beliefs: 13 items) that measure metacognitive beliefs related to depressive rumination. Respondents rate the extent to which they agree with each item using a 4-point Likert-type scale, ranging from "1" (do not agree) to "4" (agree very much), with higher scores on each subscale indicating greater positive or negative beliefs, respectively. Both the PBRS and NBRS demonstrate adequate to good internal consistency [72].

Hospital Anxiety and Depression Scale (HADS), a measure of the possible and probable presence of anxiety disorders and depression, comprising 7 items, developed by Zigmond and Snaith [73]. It has been shown to possess good internal consistency, with sensitivity and specificity comparable to the General Health Questionnaire [74]. Respondents rate each item on a scale of 0-3, with higher total scores for each subdomain (anxiety and depression) indicating a greater presence of the disorder. Thresholds for determining the clinical presence of the disorder are as follows: 0-7=normal, 8-10=borderline abnormal (borderline case), and 11-21=abnormal (case).

Cognitive Avoidance Questionnaire (CAQ), developed by Gosselin et al [75], is a 25-item measure of 5 worry-related cognitive avoidance strategies (thought suppression, thought substitution, distraction, avoidance of threatening stimuli, and transformation of images into thoughts), demonstrating good to excellent internal consistency and test-retest reliability [76].

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The scale comprises 5 subscales, each containing 5 items that represent individual cognitive avoidance strategies (avoidance of threatening stimuli, distraction, thought substitution, thought suppression, and transformation of images into thoughts). Respondents answer on a 5-point scale (1=not at all applicable to 5=very applicable), with higher scores indicating a greater presence of cognitive avoidance.

The Brief Experiential Avoidance Questionnaire (BEAQ) is a 15-item short version of the Multidimensional Experiential Avoidance Questionnaire, measuring EA content across 6 dimensions. Respondents provide answers to predetermined statements along a 6-point Likert scale (1=strongly disagree to 6=strongly agree), demonstrating good internal consistency and strong convergence with the original Multidimensional Experiential Avoidance Questionnaire dimensions [77].

Additionally, 2 attentional checks are included in the pre-, post-, and follow-up measures. Participants will be explicitly asked to choose a response option (eg, "This is an attentional check; please select the option 'sometimes' in response to this question").

Ecological Momentary Assessment

Users are provided with a daily notification (at a time in the evening of their choosing and for a total of 30 days) to respond to a series of items drawn from existing scales for depression [78], anxiety, well-being, daily goals (and the achievement thereof) [79], emotional experience during the day adapted from Pe et al [80], and RNT [81]. Upon first using the app, users are invited to personalize a time to receive the notification to complete the daily assessment. While a time in the evening is encouraged, flexibility is provided, for example, for individuals working nights. Assessment items can be found in English in Multimedia Appendix 1.

User Experience (Contextual, One-Item, Repeated, Timely, Open-Ended [CORTO])

To obtain data regarding the acceptability and usability of the app and to aid its future development, the CORTO (Contextual, One-Item, Repeated, Timely, Open-Ended) method was used, a novel qualitative EMA for obtaining user-experience data in real time [82]. Although originally designed to capture user experiences in relation to games, the method is also relevant in app design as a means of collecting real-time feedback. Data are obtained by presenting users, after each in-app exercise, with 2 closed-ended questions assessing their enjoyment of the app and any difficulties using it, plus 1 open-ended question allowing users to provide detailed, specific feedback on the exercise. Items were amended to replace original instances of "game" with "app" and can be found in English in Multimedia Appendix 2.

Additional Control Measures

In addition to the aforesaid measures, data regarding digital health literacy and intervention credibility/expectancy effects will be collected using the eHealth Literacy Scale (eHEALS) and CEQ, respectively [83,84]. The eHEALS assesses respondents' abilities and skills in sourcing, evaluating, and using electronic health information to address health-related concerns. The scale consists of 8 items measured on a 5-point Likert scale (1=strongly disagree, 7=strongly agree). Total scores range from 8 to 40, with higher scores indicating stronger perceptions of digital literacy in relation to electronic health. The eHEALS-PL demonstrates strong internal consistency (α=.94) [85].

The CEQ consists of 6 items measuring expectations of treatment and the credibility of its rationale in clinical outcome studies. The items are split into 2 sections ("think" and "feel"), with responses for 4 items measured on a Likert scale of 1-9 and for 2 items on an analogue scale from 0% to 100%. Credibility is derived from the first 3 "think" items, and expectancy is derived from the fourth "think" item and the 2 "feel" items. Test-retest reliability is high (expectancy: r=0.82; credibility: r=0.75; and composite: r=0.83) and demonstrates high internal consistency (expectancy: r=0.79-0.90; credibility: r=0.81-0.86; and composite: r=0.84-0.85).

Intervention

OverThinking

OverThinking version 0.3.1(4) is a mobile EMI for iOS and Android platforms, designed to reduce EA in the context of rumination. The app primarily consists of psychoeducation content and related exercises, intended to be delivered over a 4-week period. To examine the effectiveness of the app during the intervention and to assess user experiences with using the app for rumination intervention, several self-report tools are embedded.

Development, Content, and User Evaluations

The development of the app was undertaken by a multidisciplinary team of active RFCBT practitioners; research psychologists with experience in transdiagnostic processes, digital mental health interventions, and user experience; and experienced developers of digital tools from the Polish-Japanese Academy of Information Technology.

The intervention comprises psychoeducational content based on RFCBT, an effective intervention for maladaptive rumination [86]. The reduction of EA is targeted through (1) the provision of a functional analysis of rumination to identify the triggers and functions of this process (a classical component of RFCBT), and (2) the modification of beliefs concerning negative emotions and their experience [87,88]. Previous research on the use of RFCBT has also found it to be an effective rumination intervention when delivered in digital contexts [89].

Intervention content was initially developed by members of our team with expertise in RFCBT. The content is divided into 4 weeks, with the first 2 weeks containing several individual modules targeting specific learning outcomes (eg, learning about the function of emotion, learning about the avoidance of emotions). The delivery of informative content is interspersed with several small exercises in different formats (multiple choice or open-ended text entry). Weeks 3 and 4 provide users with a series of exercises designed to consolidate learning and offer an opportunity for users to apply the psychoeducational content to their personal lives. Individual modules are designed to take no longer than 10-15 minutes to complete. The app content is

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delivered linearly, with subsequent weeks unlocking only once previous ones are fully completed. On each day of the intervention, all users are required to complete an emotion valuation question. All user inputs when completing app content are stored remotely and securely via Firebase (Google LLC), accessible only to the research team and solely for analysis purposes. In addition to user inputs and assessment outcomes, the time taken to complete app content and assessments is also recorded to observe the time burden caused by app use. A summary of the app intervention content can be found in Table 1.

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Table 1. Overview of intervention content.

Week, module, and module name	Module objectives
Week 0	
Module 1	
Introduction	• To provide an introduction to the aims of the app. • To introduce the daily assessments and their purpose.
Week 1	
Module 1	
Introduction	• To introduce the aims of module 1 (eg, to inform the user about the nature and function of emotions and their potential negative consequences).
Module 2	
The nature of emotions	• To examine the nature of depression and anxiety through individual dimensions (thoughts, emotions/feelings, and behavior) in users' daily lives.
Module 3	
The function of emotions	• To examine the positive and negative functions of emotions.
Module 4	
The avoidance of emotions	• To examine the reasons for avoidance of emotions. • To identify how users avoid negative emotions. • To examine the consequences of avoidance.
Week 2	
Module 1	
Introduction	• To introduce the second week, which places greater focus on rumination.
Module 2	
Ruminating	• To identify and define rumination. • Via fictional case studies, to identify situations in which users engage in rumination.
Module 3	
Why do we ruminate?	• To examine motivations for engaging in rumination. • To identify some of the negative consequences of rumination.
Module 4	
Rumination and avoidance	• To examine rumination as a means of avoidance/as an emotional regulation strategy.
Week 3	
Module 1	
Introduction	• To introduce the aims of the third and fourth weeks of the intervention—consolidation exercises to apply the psychoeducational content.
Module 2	
Exercise 1	• Identifying the content and context of the users' ruminative thinking.
Module 3	
Exercise 2	• Identifying the triggers of the users' ruminative thinking.
Module 4	
Exercise 3	• Identifying the short-term consequences of the users' engagement in rumination.
Week 4	

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Week, module, and module name	Module objectives
Module 1	
Exercise 1	• Examining the use of rumination as a means of avoidance (and identifying what is being avoided).
Module 2	
Exercise 2	• Reducing/stopping the use of maladaptive rumination. • Identifying activities that help users reduce their use of rumination.
Module 3	
Exercise 3	• Summarizing learning: identifying the context, content, consequences of users' rumination, and how to reduce rumination and its maladaptive consequences.

During the development process, an initial feasibility study was conducted to consult with prospective end users. Participatory workshops were held to obtain feedback on the usability and acceptability of the app content and to discuss preliminary plans for the app structure, visual layout, and features [69]. Before these workshops, participants, selected based on their rumination levels, were asked to engage with a web-based version of the proposed app content (hosted via Qualtrics; SAP SE) for 4 weeks. Participants were asked to complete a series of pre- and posttests online, designed to mimic the randomized controlled trial protocol for this trial (see the "Methods" section, except for the BEAQ measure). A series of attentional tests was also included in the online assessment to control for response reliability. To be included in the analysis, participants were required to complete the first 2 weeks of content in full, followed by 5 of the 6 exercises from weeks 3 and 4.

Of the initial 687 participants who registered interest in participating, a sample of 55 was selected through prescreening using the PTQ. Participants were selected if their overall score was 1 SD above average. Of these, 21 participants completed all measures and were included in the quantitative analysis. Four participants volunteered to engage in participatory workshops and took part in semistructured interviews with members of the research team. The semistructured interviews focused on (1) factors determining compliance and strategies to overcome challenges in following the 4-week program; (2) strong and weak aspects identified in the program content; (3) accessibility of psychoeducational content in terms of language, clarity, and length; (4) strong and weak aspects of the user experience; (5) evaluation of different exercise types; and (6) evaluation of a mock-up for apps, with users having previous experience following the 4-week program.

Overall, data from the developmental feasibility study suggested that engagement with app content resulted in reductions in EA (comparison of pre- and postintervention measures; $P<.001$) and perseverative thinking ($P<.001$), including across all 3 subscales: mental load ($P=.001$), unproductiveness ($P=.003$), and core features ($P=.002$). While cognitive avoidance did not reduce significantly overall ($P=.07$), the descriptive reduction suggested an impact of the psychoeducational program on awareness. Thought substitution was significantly elevated after participation ($P=.06$), which may indicate increased awareness of this mechanism.

Because of the small sample size for participatory workshops, the data were not subjected to a formal analysis protocol and are unlikely to have reached saturation at this stage. However, feedback indicated that users found the intervention content and exercises interesting, with some participants reporting that they would have preferred more content to engage with. Additionally, participants requested that the app include an option to make personal notes invisible to the research team, provide links to additional information relevant to rumination and avoidance, and allow for text narration and audio recordings as alternatives to text entry.

Following user feedback, the app was updated to include a link providing further information about the research and the research team, along with relevant content details and additional external resources. Future versions of the app aim to incorporate further personalization options, such as voice narration, audio recording features, and a private notes function.

Remote Acquisition/Storage of Assessment Data

Data obtained through daily sampling are securely stored remotely via Firebase and are accessible only to authorized members of the research team, in compliance with General Data Protection Regulation (GDPR) requirements.

To capture user experiences during testing, the app also uses the CORTO method [82]. These data are likewise securely stored via Firebase and are accessible only to members of the research team.

Statistical Analysis

Data Exclusion

Compliance will be defined as the completion of both the first and second weeks of the intervention content in full, along with at least 5 out of 6 exercises from weeks 3 and 4. For EMA, a compliance threshold of 80% will be used, consistent with previous research using EMIs in adult populations [90]. Additionally, the study will control for time spent within the app and the length of responses to open-ended questions.

In addition to the aforementioned compliance measures, participants who fail both attentional checks embedded within the assessments will be excluded from analyses.

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Analysis of Trial Outcome Data

Primary Outcomes

Changes in outcomes across pre-, post-, and follow-up assessments (PTQ, EBQ, PBRS, NBRS, HADS, CAQ, and BEAQ) will be analyzed using mixed-design ANOVA across all 4 conditions. Additionally, multilevel models—treating daily observations as level 1 and participants as level 2—will be used to assess associations between avoidance and mood, as well as between rumination and mood, and to examine whether these associations are moderated by condition.

Secondary Outcomes

Mixed-design analysis of covariance will be conducted within the 2 intervention groups to examine whether time spent engaging with the app content serves as a covariate influencing intervention outcomes.

In-app user feedback collected through the CORTO method will be deductively coded following the process outlined by Saldana [91], using the 4 overarching categories proposed by Lukka et al [82]—(1) contextual use, (2) interaction-elicited emotional experience, (3) usability, and (4) technical issues—as a guiding framework. More detailed subdomains will be explored within each category.

Ethics Approval

Ethical approval for the trial was obtained from the Ethics Committee of SWPS University, Katowice Faculty (ethical approval number WKEB90/11/2023).

Results

Recruitment and enrollment for the trial are expected to begin in May 2025, with completion anticipated by July 2025. Data collection will conclude once the target sample size for each of the 4 conditions has been met. The main results of the trial are expected to be submitted for publication by October 2025. In addition to a formal publication in a peer-reviewed journal, the trial outcomes are anticipated to be presented in a summarized form at a relevant international conference.

Discussion

Study Strengths and Challenges

This paper outlines the protocol for a randomized controlled trial of an mHealth EMI aimed at reducing EA in the context of rumination. The primary objective of the trial is to investigate whether a reduction in EA through EMI intervention can lead to a decrease in RNT and its maladaptive consequences. Additionally, by implementing the CORTO method, the trial will gather user data on app usability and acceptability, identifying areas for continuous improvement and development.

While the primary objective of this study is to examine the role of EA, we are also collecting data on the use of the app itself. This information will inform its further development and potential efficacy testing in various settings. The app, as it currently stands, and its intervention content have been developed based on our formative user-experience research. While this approach is expected to enhance acceptability, usability, and user retention, and despite the app being thoroughly tested for issues, potential challenges during deployment to real-world users cannot be ruled out. For example, the app currently does not time-lock intervention modules and instead allows users to progress to the next week's content once the preceding week's material has been successfully completed. While this approach provides users with flexibility in how they complete the intervention, as recommended by prior studies [92,93], there is a possibility that some users may progress through the content more quickly than intended. This could potentially lead to poor information retention and a diminished impact of the intervention.

Definitions and reporting of compliance can vary significantly across studies of digital interventions [46]. The design of our app enables the remote collection of both daily assessment data and app usage metrics, allowing for precise measurement of engagement and, consequently, intervention compliance. For this study, we have adopted a compliance rate of 80%, consistent with a previous study using EMI and daily assessments with adult populations [89].

The incorporation of CORTO implementation enables the collection of real-time feedback from users regarding app usability and acceptability, addressing some of the limitations of retrospective interviews [82]. This approach acknowledges the central role of users as active participants in the treatment program and enhances the specificity of the feedback obtained [94]. As CORTO depends on sustained engagement with the digital tool under review, authors recommend considering survivorship bias when interpreting the data [82].

To address some of the limitations associated with using retrospective measures alone, the effectiveness of the intervention will also be assessed by analyzing daily sampling measures, as recommended by Heron and Smyth [43]. Additionally, we plan to compare the standalone version of the intervention with one that includes asynchronous support from CBT professionals. A recent meta-review of meta-analyses [95] suggested that guided interventions may be more effective and improve compliance; however, it notes that the quality of evidence is often low and that not all meta-analyses systematically compare the impact of guidance. Therefore, it is important to explore the effect of guidance. While including professional support can significantly enhance the intervention's effectiveness, it also increases the cost of large-scale implementation and limits its potential for widespread dissemination. For this reason, a compromise solution involving asynchronous support was chosen.

The outcomes of the trial will be reported in a peer-reviewed publication following the mHealth Evidence Reporting and Assessment guidelines, as outlined by the World Health Organization mHealth Technical Evidence Review Group [96]. These guidelines are designed to enhance the quality and clarity of mHealth evaluation reporting by specifying where detailed information should be provided regarding intervention content, implementation context, and relevant technical aspects.

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Conclusions

It is anticipated that the outcomes of this trial will not only provide insights into the clinical effectiveness of the app but also will primarily offer valuable theoretical understanding of the role of EA in maladaptive rumination. Additionally, the user feedback collected through the CORTO implementation will contribute to improving the app's usability and acceptability in future iterations and further enrich the growing body of literature in this field.

Acknowledgments

This project is funded by the SONATA Grant "Toward an Integrative Model of Maladaptive Spontaneous Task-Unrelated Thoughts (STUT): A Processual and Functional Approach" (2019/35/D/HS6/02364) from the National Science Centre, Poland, awarded to MK, and by the SWPS University Psychology Institute research grant 1305-11, also awarded to MK.

Data Availability

Once the outcomes of the trial have been published, data will be made publicly available via the Open Science Framework.

Use of Generative Artificial Intelligence

The authors confirm that generative artificial intelligence was not used at any point during the generation of the manuscript.

Authors' Contributions

SB was responsible for writing the original draft, project administration, methodology, and coordinating user experience aspects of the project. MS contributed to creating the content of the psychoeducational intervention, analyzing data from the initial feasibility study, and the methodology. MP was involved in creating the content of the psychoeducational intervention, collecting data in the initial feasibility study, analyzing the data, and the methodology. FM and WK contributed to software development, co-designing the app architecture and data model, and supervised the implementation and rollout of the app. MG worked on software development, as well as the implementation and rollout of the mobile app and backend infrastructure. PZ and AJ were involved in software development, verification, and testing of the app prototype. BK supervised the co-design processes, including the architecture and implementation of the mobile app and backend. MK contributed to conceptualization, analyzing data from the initial feasibility study, writing—review and editing, project administration, funding acquisition, and methodology.

Conflicts of Interest

Authors have no financial interests to disclose, but, in the spirit of full disclosure, wish to disclose a personal interest in the app, having been involved in its conceptualization and development. To this end, and following the principles of open science, all study data (in anonymized form) will be made available following publication of the results via the Open Science Framework.

Multimedia Appendix 1
Daily assessment items.
[DOCX File , 8 KB - resprot_v14i1e66067_app1.docx]

Multimedia Appendix 2
In-app CORTO (Contextual, One-Item, Repeated, Timely, Open-Ended) items.
[DOCX File , 7 KB - resprot_v14i1e66067_app2.docx]

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Abbreviations

BEAQ: Brief Experiential Avoidance Questionnaire
CAQ: Cognitive Avoidance Questionnaire
CBT: cognitive behavioral therapy
CORTO: Contextual, One-Item, Repeated, Timely, Open-Ended
EA: experiential avoidance
EBQ: Emotions Beliefs Questionnaire
eHEALS: eHealth Literacy Scale

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EMA: ecological momentary assessment
EMI: ecological momentary intervention
GDPR: General Data Protection Regulation
H_Ex_A_Go_N: habit, executive function impairment, abstract processing mode, goal discrepancies triggering rumination, and the negative valence of rumination content
HADS: Hospital Anxiety and Depression Scale
mHealth: mobile health
NBRS: Negative Beliefs About Rumination Scale
PBRS: Positive Beliefs About Rumination Scale
PTQ: Perseverative Thinking Questionnaire
RFCBT: rumination-focused cognitive behavioral therapy
RNT: repetitive negative thinking

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Protocol

Transforming Health and Reducing Perinatal Anxiety Through Virtual Engagement: Protocol for a Randomized Controlled Trial

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Abstract

Background: Prenatal anxiety affects between 20% and 30% of pregnant people and is associated with adverse prenatal health conditions, birth outcomes, and postpartum mental health challenges. Individuals from racial and ethnic minority groups, sexual and gender minority groups, and those with low income are all at heightened risk for prenatal anxiety due to disproportionate exposure to adverse social determinants of health. Digital cognitive behavioral therapy (dCBT) has been shown to reliably reduce anxiety in mostly White and middle- to higher-income samples, but its efficacy in low-income and marginalized pregnant people is understudied.

Objective: We propose a randomized controlled trial of a dCBT (Daylight app, Big Health, Ltd) in a sample of low-income pregnant people oversampled for racial, ethnic, sexual, and gender minority identity.

Methods: Participants (N=132) will be randomized to the intervention or waitlist control group using a 1:1 allocation ratio. The intervention will be a self-guided application that uses an online therapist to teach and encourage the practice of 4 key cognitive behavioral therapy skills (eg, identifying catastrophic thinking and increasing physical relaxation) that can reduce anxiety. The primary outcome will be generalized anxiety symptoms; secondary outcomes will include depressive symptoms, stress, pregnancy-specific anxiety, and insomnia symptoms. Focus groups with a subset of participants will provide qualitative data about the acceptability of dCBT.

Results: Recruitment began in June 2024. Data will be analyzed using linear mixed models, which will be fit with treatment condition (dCBT and waitlist control group) as the between-group factor, time (baseline, 3, 6, and 10 weeks post randomization) as a within-group factor, and a group-by-time interaction. Linear mixed models produce unbiased parameter estimates in situations where there are different numbers of observations per record and will accommodate intent-to-treat and sensitivity analyses.

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Conclusions: This clinical trial will evaluate the efficacy and acceptability of a self-guided dCBT for prenatal anxiety among low-income and marginalized pregnant people, a group that continues to experience substantial barriers to accessing in-person evidence-based psychotherapy.

Trial Registration: ClinicalTrials.gov NCT06404450; https://clinicaltrials.gov/study/NCT06404450

International Registered Report Identifier (IRRID): DERR1-10.2196/70627

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KEYWORDS

cognitive behavioral therapy; telemedicine; perinatal care; anxiety; ethnic and racial minorities

Introduction

Anxiety is common and consequential during pregnancy; globally, about 15% of pregnant people are diagnosed with an anxiety disorder, and 18%-25% of pregnant people self-report symptoms that surpass a clinical cutoff using a validated screener [1]. Symptoms of clinical anxiety include experiencing excessive worry, difficulty controlling worries, restlessness, irritability, and sometimes, physical symptoms, such as heart palpitations and dizziness [2]. Anxiety symptoms can be exacerbated by experiences common during pregnancy, which include poor sleep and managing uncertainties related to labor and delivery [3]. The COVID-19 pandemic had profound impacts on the prevalence rates of prenatal anxiety. Meta-analytic data showed that about 31% of pregnant people reported elevated anxiety symptoms during the COVID-19 pandemic compared to 22.4% before the pandemic, representing a 35% increase in prevalence [2,3]. Notably, increase in the rates of elevated prenatal anxiety and pandemic-related symptoms did not impact pregnant people equally. Elevations in symptoms of anxiety and comorbid symptoms like depression have persisted at higher rates in marginalized pregnant people, including those who are categorized as Black, Latinx, Indigenous, Asian and Pacific Islander, and lesbian, gay, bisexual, transgender, and queer (LGBTQ+), and in those with low income [4,5].

Elevated anxiety symptoms during pregnancy contribute to the risk of a host of adverse prenatal health conditions, birth outcomes, and postpartum mental health problems. For example, prenatal anxiety is prospectively associated with gestational hypertension, intrauterine growth restriction, and having a preterm birth [6,7]. Biological mechanisms, like dysregulation in the hypothalamic-pituitary axis leading to premature accelerations in placental corticotropin-releasing hormones and cortisol, and behavioral mechanisms, such as substance use and poor sleep help explain the relationship between prenatal anxiety and adverse birth outcomes [8]. Elevated anxiety is also associated with psychiatric comorbidities, including depression, insomnia, and suicidal ideation [9-11], which are more common in marginalized pregnant people and those with low income [4,5,12,13].

In addition to anxiety disorders and elevations in general anxiety symptoms, pregnant people also experience pregnancy-specific anxiety, an affective state of persistent worry surrounding a pregnant person's prenatal health, delivery, the well-being of the baby, and future parenting [14]. Pregnancy-specific anxiety is estimated to affect between 14% and 19% of pregnant people [14,15] and appears to be uniquely predictive of adverse birth outcomes like preterm birth. For example, pregnancy-specific anxiety is related to smaller gestational age and lower birth weight after accounting for generalized anxiety disorders [16]. Further, it is estimated that women with high levels of pregnancy-specific anxiety are 1.7-2.5 times more likely to experience a spontaneous preterm birth than women without pregnancy-specific anxiety [17]. Unsurprisingly, pregnant people reported high rates of pregnancy-specific anxiety during the COVID-19 pandemic [18]—a time when practices in labor and delivery units were in flux, and people worried about what a COVID-19 infection might mean for their developing fetus. With respect to sociodemographic risk, greater pregnancy-specific anxiety has been linked with lower income, non-White race, and Latina ethnicity [19-21]. These patterns suggest that rising rates of clinical and pregnancy-specific anxiety may be contributing to worsening racial and ethnic, LGBTQ+, and socioeconomic disparities in adverse pregnancy outcomes and postpartum mental health. Given the high need and lack of representation of racial and ethnic minoritized, marginalized, and low-income people in randomized trials for perinatal anxiety to date, testing the efficacy and acceptability of accessible interventions that address clinical anxiety among these groups is warranted [22,23].

Therapist-delivered cognitive behavioral therapy (CBT) has been shown to be effective in treating anxiety among White nonpregnant [24] and pregnant populations [25]. However, the effects of CBT on pregnancy-specific anxiety are largely unknown, as most studies testing interventions for anxiety in pregnancy do not measure this subtype of anxiety [26]. Notwithstanding, cognitive behavioral interventions can improve biological and behavioral variables that link pregnancy-specific anxiety to adverse birth and postpartum outcomes. For example, cognitive behavioral interventions can reduce cortisol [27] and improve sleep [28] in pregnant people.

Despite the promise of CBT for elevated anxiety symptoms experienced during pregnancy, racial and ethnic minoritized, marginalized, and low-income pregnant people often encounter several barriers to accessing evidence-based treatment (eg, long waitlists, childcare issues, and challenges with transportation) [29]. Recent innovations have focused on addressing barriers to CBT by adapting it for automated, digital delivery. Digital CBT (dCBT) is efficacious for treating clinical anxiety in mostly White, higher socioeconomic status, pregnant [30], and nonpregnant populations [31]. While marginalized pregnant people report high satisfaction with digital therapy, very few

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dCBT trials have enrolled meaningful numbers of racial and ethnic minoritized or low-income pregnant people [32,33]. This study addresses the critical need to evaluate whether dCBT can be used to address clinical anxiety among racial and ethnic minoritized, marginalized, and low-income pregnant people, subgroups disproportionately impacted by anxiety during pregnancy.

Building on a previous efficacy trial of the same dCBT in nonpregnant adult women that evidenced large improvements in anxiety symptoms, and high levels of engagement and safety [31], the Transforming Health and Reducing Perinatal Anxiety through Virtual Engagement (THRIVE) study tests whether the dCBT Daylight (Big Health), is an efficacious and acceptable treatment during pregnancy among racial and ethnic minoritized, marginalized, and low-income people. The hypothesis of this trial is that participants randomized to Daylight will demonstrate significantly greater reductions in anxiety symptoms compared to a waitlist control group. We also expect that participants randomized to Daylight will report reductions in associated mental health symptoms, including depression, stress, pregnancy-specific anxiety, and insomnia.

Methods

Objectives

Study objectives are to (1) measure the impact of dCBT (Daylight) on anxiety symptoms in racial and ethnic minoritized, marginalized, and low-income pregnant people with elevated anxiety; (2) assess the acceptability of dCBT for addressing elevated anxiety and related symptoms among pregnant participants; and (3) identify barriers and facilitators to the adoption of dCBT for use by racial and ethnic minoritized, marginalized, and low-income pregnant people enrolled in public insurance (MediCal).

Trial Design

Overview

This is a phase 1 randomized controlled trial (RCT) that tests the efficacy of dCBT (Daylight) for treating anxiety during pregnancy using a parallel group design. Study participants will be in the study from enrollment at 8-27 weeks gestation until 6-8 weeks after their expected date of delivery. All participants complete assessments of self-reported symptoms of generalized anxiety, depression, stress, pregnancy-specific anxiety, and insomnia at baseline, 3, 6, and 10 weeks following randomization, and at a follow-up time point between 6 and 8 weeks post partum. The study also includes focus groups with a subset of RCT participants following intervention receipt to evaluate the acceptability of dCBT.

Randomization and Blinding

As outlined in the study schema (Table 1), after completion of the study consent and enrollment survey, participants will receive an email informing them if they have been randomized to receive complimentary access to the Daylight app immediately (ie, intervention condition), or to receive access in 10 weeks (ie, waitlist control condition). If randomized to receive access immediately, they will receive instructions on how to download the app and start using it. If randomized to receive access to the Daylight app in 10 weeks, they will be sent instructions for downloading and starting to use the Daylight app 10 weeks later.

Table 1. Modules included in the Daylight digital cognitive behavioral therapy app.

Intervention module	Brief description	CBT[a] principle	Learning goals
Worry scheduling and worry time	Scheduling a specific time and pace to worry (Worry Scheduling), and then cycling through worrisome thoughts (Worry Time).	Stimulus control	• Learn to associate worry with a designated time and space. • Learn to delay worry until a designated time. • Learn to tolerate worry without avoidance.
Tense and release	Tensing and releasing muscles with relaxation cues.	Applied relaxation	• Increase awareness of tension. • Increase awareness of the difference between tensed and relaxed muscles. • Learn to reduce muscle tension.
Thought challenger	Identifying catastrophic or unhelpful thoughts and using challenge questions to develop new perspectives on these thoughts.	Cognitive restructuring (decatastrophizing)	• Increase awareness of catastrophic and unhelpful thoughts. • Learn to challenge catastrophic thoughts. • Increase cognitive flexibility.
Worry exposure	Imagining the “worst case scenario” or feared outcome of a specific worry.	Imaginal exposure	• Learn to tolerate emotions associated with feared outcomes. • Facilitate cognitive reappraisal of feared outcomes. • Facilitate habituation to fear response (ie, fear extinction).

[a]CBT: cognitive behavioral therapy.

This study is designed to enroll marginalized (Latinx; Black, Indigenous, and people of color; or LGBTQ+ individuals) individuals at a ratio of 2:1. To ensure that randomization is in keeping with our intention of equal representation across groups, we will use a 1:1 allocation ratio with blocked randomization of marginalized people and not. The randomization sequence

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will be generated by the study biostatistician. The randomization sequence and block sizes will be concealed from all other study team members and participants. Study team members will not be able to influence randomization. Once an eligible participant completes their consent and enrollment survey, unmasked study staff will reveal the allocation assignment and notify participants of their assigned condition. The principal investigator and any staff member involved in data analysis will be blinded to condition assignment. Although we cannot blind participants from condition assignment, allocation will occur after the participant has enrolled to avoid selection bias.

Participants

Enrollment and Eligibility

This is a remote RCT overseen at the University of California, San Francisco, and pregnant people residing in California are eligible to take part. In addition to California residence, participants must meet the following eligibility criteria: (1) enrollment in MediCal, a California health insurance plan for low-income people; (2) currently between 8 and 27 weeks pregnant; (3) age 18 years or older; (4) able to speak in English; (5) ninth-grade levels of education or greater; (6) daily access to a web-enabled computer, smartphone or tablet; and (7) elevated anxiety symptoms as measured by a score of 10 or greater on the Generalized Anxiety Disorder- 7 Scale (GAD-7; [34]). Consistent with the original Daylight efficacy trial [31], participants who have received CBT treatment for anxiety in the last 12 months, those with a new or changed dose of prescription medication for anxiety, depression, or insomnia in the last 4 weeks, and those with a self-reported diagnosis of schizophrenia, psychosis, bipolar disorder, seizure disorder, and substance use disorder will be excluded. A recent head trauma or brain damage, or a serious physical health concern necessitating surgery or hospitalization in the last 6 months will also lead to exclusion from the study.

Sample Size

In total, 110 pregnant people with elevated anxiety symptoms will be randomized to one of 2 study arms. Based on a previous study wherein the response to the Daylight tool (by the GAD-7; [34]) at 10 weeks post randomization was normally distributed with a mean of 12.15 (SD 4.73) in the waitlist control, and a mean of 7.90 (SD 4.85) in the dCBT group [31], we expect that a sample of 55 experimental and 55 control participants should detect a true difference in the mean symptoms of experimental and control participants of –2.696 or 2.696 with 80% power. An additional 22 participants will be recruited (ie, a total of 132 enrolled) to account for attrition rates of 17%, the average rate of attrition of marginalized pregnant people enrolled in psychological intervention studies [35]. While we are powered to detect intervention effects at 2 posttreatment time points (6 weeks and 10 weeks following randomization), we do not have pilot data to estimate power at our postpartum time point. Estimates of an effect size in this perinatal pilot are challenging to calculate, as gestational age may vary widely at enrollment (8-27 weeks) resulting in a postpartum assessment that will be up to 36 weeks post treatment for those enrolling at 8 weeks and as early as 15 weeks post treatment for those enrolling at 27 weeks. Thus, treatment effects at the 7-week postpartum time point are exploratory, and we will rely on effect sizes to describe effects as opposed to *P* values.

Recruitment

Recruitment methods include collaborations with the Postpartum Support International (PSI) and with the University of California, San Francisco (UCSF) Clinical & Translational Science Institute (CTSI). These partners will disseminate study information via emails to participants and partners in their programs, with affiliate organizations and community partners using a study-specific flyer, and by social media advertising.

Intervention and Comparator

Daylight

Participants who are randomly assigned to receive dCBT will be provided with complimentary access to Daylight [36]. The program uses an online therapist to guide individuals through interactive exercises and animations to facilitate the learning and implementation of 4 key CBT techniques. The four CBT techniques are cognitive (eg, identifying catastrophic thinking) and behavioral (eg, increasing physical relaxation and reducing avoidance) skills that can reduce anxiety with repeated use. At present, the Daylight app is only available in English. See Table 1 for a more detailed description of each intervention module.

Daylight is designed to be self-paced, with the app encouraging users to practice techniques both within the app and in real-life situations on a daily basis. Upon signing up, users automatically receive reminders and motivational messages via email and can choose to opt in for additional communication through text messages and push notifications to encourage daily use and intervention adherence, a prominent challenge in digital interventions [37]. Each of the 4 modules takes between 10 and 20 minutes to complete. In addition, shorter 5-minute exercises guide users through various skills (eg, progressive muscle relaxation) and are designed for repeated use over the intervention period. Weekly in-app assessments of anxiety, depressive symptoms, and sleep are also used, allowing for personalized feedback based on users' self-reported symptoms. For example, if a user reports difficulties with sleep, they may receive prompts to engage in relaxation techniques at bedtime. Daylight provides objective metrics for engagement, including the number of modules completed, the frequency with which the app is accessed, and the time spent to complete modules. All participants in THRIVE will receive access to Daylight for 12 months after delivery (ie, until their baby is a year old).

Waitlist Control

The waitlist control group participants will get complimentary access to the Daylight program after completing the 10-week follow-up survey. A waitlist control condition was chosen to ensure that the entire low-income sample, a group with documented health disparities during the perinatal period [38], would have access to the intervention. Allowing access to the intervention 10 weeks following randomization allows for access to treatment in pregnancy and reduces the risk of participant dropout, which tends to increase the longer participants are asked to wait to receive treatment [39]. All participants can also

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continue using other pharmacological or nonpharmacological interventions (excluding CBT) for anxiety or other symptoms.

Study Procedures and Timeline

Initial Screening and Orientation

Before enrolling, candidate participants will complete a 3-part screening and orientation process. First, participants will complete a screening consent form, followed by a screening questionnaire that will assess all inclusion and exclusion criteria. Second, candidate participants will verify key information submitted on the screening questionnaire via email (eg, expected due date and prenatal care provider) to minimize the risk of fraudulent screeners. Finally, candidate participants will attend a live online group orientation session where a staff member will provide an overview of the study and provide participants the opportunity to ask questions. This multistep process has maximized study engagement and retention in previous longitudinal RCTs [40].

Assessment Collection and Study Timeline

All participants, regardless of randomization grouping, will receive surveys that take approximately 20 minutes to complete at enrollment and at 3, 6, and 10 weeks after randomization that asks about health and well-being as well as about current experiences of anxiety, stress, depression, and sleep. As described in Table 2, demographic information collected at screening and enrollment includes information about race and ethnicity, insurance, housing stability, and food security. Pregnancy history and data about any previous preterm births, cesarean sections, or preeclampsia are collected only at enrollment. Information about pregnancy health and the diagnosis of conditions like gestational hypertension and gestational diabetes is collected across all time periods. Information about medical care and social support is also consistently collected across time periods.

Table 2. Overview of surveys and schedule of data collection for the Transforming Health and Reducing Perinatal Anxiety through Virtual Engagement (THRIVE) phase I randomized clinical trial

Instrumentation		Time point					
Measure	Validated for use in pregnancy	Screening	Enrollment	3 weeks+/- 1 week	6 weeks+/- 1 week	10 weeks+/- 1 week	7 weeks after delivery+/- 1 week
Demographics	—[a]	✓	✓				✓
Pregnancy outcome and history	—		✓				
Pregnancy health	—	✓	✓	✓	✓	✓	✓
Care and social support	—		✓	✓	✓	✓	✓
Labor and delivery experience	—						✓
Infant health and wellbeing	—						✓
GAD-7[b]	Yes	✓		✓	✓	✓	✓
PSS-4[c]	Yes		✓	✓	✓	✓	✓
PRAS[d]	Yes		✓	✓	✓	✓	
ISI[e]	Yes		✓	✓	✓	✓	✓
PHQ-9[f]	Yes		✓	✓	✓	✓	✓

[a]Not applicable.

[b]GAD-7: Generalized Anxiety Disorder 7 Scale.

[c]PSS-4: Perceived Stress Scale 4.

[d]PRAS: Pregnancy Related Anxiety Scale.

[e]ISI: Insomnia Severity Index.

[f]PHQ-9: Patient Health Questionnaire-9.

The final survey at 6-8 weeks after the expected date of delivery will ask participants to report on symptoms of anxiety, stress, depression, and insomnia as well as their experience of labor and delivery and the health of their baby. All surveys will alert participants to missing items to reduce missing data resulting from participant error. Participants will be contacted via email, phone, or text message, according to participant preference, with reminders to complete their surveys. Following the completion of each of the 4 surveys, participants will receive a US $50 electronic gift card sent via email. See Figure 1 for a schematic representation of the RCT and the optional focus group discussions.

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Figure 1. Study schema for randomized controlled trial and optional focus group discussion. dCBT: digital cognitive behavioral therapy.

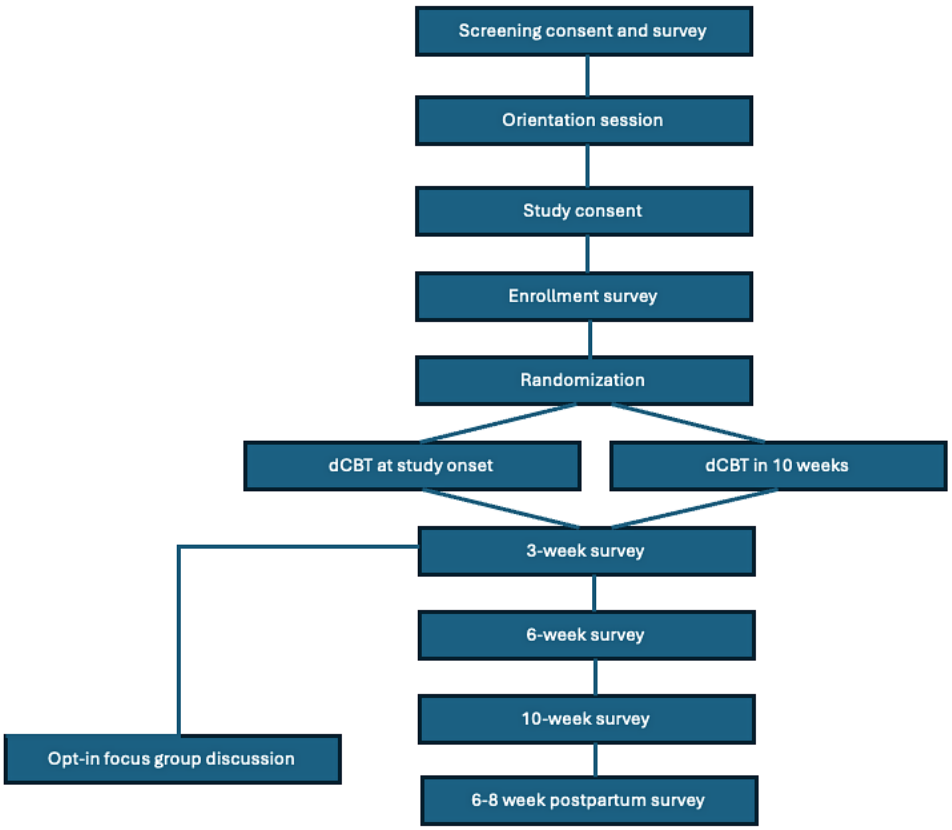

Ethical Considerations

Overview

This study has been approved by the Western Copernicus Group (WGC) institutional review board (IRB; approval number 1364733) and registered in the Clinical Trials Registry of the National Institutes of Health National Library of Medicine (protocol number NCT06404450). The clinical protocol for THRIVE (version 1.1) was IRB-approved and has not been changed since November 14, 2023. This study protocol was guided by the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials), 2013 statement [41]; the SPIRIT checklist is available in Multimedia Appendix 1. All roles and responsibilities of study personnel and study funders are described in Multimedia Appendix 2.

Informed Consent and Privacy Considerations and Data Monitoring

Informed consent will be obtained from pregnant women who qualify for the study after initial screening and following participation in a scheduled orientation session. Participants will complete consent forms (see Multimedia Appendix 3) online with the capture of electronic signatures. All potential participants will be offered the opportunity to complete consent forms with the help of study staff. Information in the consent form is also reviewed at the orientation session attended by eligible participants.

Personal identifying information (eg, first and last name, date of birth, phone number, email address, and postal address) will be collected at the time of enrollment and stored separately from all other study data with linkage only by a study ID, which is only available to a small set of study personnel. Participants will be instructed to complete all research activities in a private setting. In addition, participants will be assigned unique, coded, confidential identifiers that will be used to label all data forms, data entries, and questionnaires. The key linking participant identity to their unique coded identifier will be stored on REDCap (Research Electronic Data Capture; Vanderbilt University). REDCap is a secure, HIPAA (Health Insurance Portability and Accountability Act)-compliant web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture, (2) audit trails for tracking data manipulation, and (3) automated export procedures for seamless data downloads to common statistical packages [42]. Access to all data will be limited to the principal investigator and trained, authorized study staff. All data (recordings, transcripts, surveys, coded data) for the study are stored on encrypted servers kept behind UCSF firewalls, where access is by remote access with dual authenticated password protection. No study data is kept or accessible on local devices.

Results

Grant funding was received in July 2023. As of March 2025, a total of 24 participants were confirmed eligible and randomized. We expect that data analysis and results will be available in May 2026.

Primary Outcome: Anxiety Symptoms

Anxiety is self-reported using the GAD-7 [34]. The GAD-7 measures the frequency of generalized anxiety symptoms in the previous 2 weeks. Items are scored on a 4-point Likert scale

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(0=not at all to 3=nearly every day) and summed for a possible total score of 0-21, where higher scores indicate greater elevations in clinically significant anxiety. Cutoff points for the GAD-7 indicate that scores totaling 5-9 correspond to minimal anxiety; 10-14, to moderate anxiety; and 15-21, to severe anxiety. The GAD-7 shows strong psychometric properties, including sensitivity, specificity, and internal consistency in nonpregnant [34,43] and pregnant adults [44].

Secondary Outcomes

Depressive Symptoms

Depression is self-reported using the 9-item Patient Health Questionnaire-9 (PHQ-9 [45]). The PHQ-9 measures the frequency of depressive symptoms over the past 2 weeks. Items are scored on a 4-point Likert scale (0=not at all to 3=nearly every day) and summed for a possible total score of 0-27, with higher scores indicating greater depression severity. Cutoff points for the PHQ-9 indicate that scores totaling 5-9 correspond to minimal depression; 10-14, to moderate depression; 15-19, to moderately severe depression; and 20-27, to severe depression. The PHQ-9 is the most widely used depression screening measure globally and shows convergent and criterion validity as well as good sensitivity and specificity among pregnant and postpartum samples [46].

Perceived Stress

Perceived stress is self-reported using the 4-item Perceived Stress Scale (PSS-4) [47]). The PSS measures the frequency of stressful thoughts and feelings over the past month. Items are scored on a 5-point Likert scale (0=never, 4=very often) and summed for a possible total score of 0-16, with higher scores indicating higher perceived stress. The PSS shows internal consistency and construct validity among several adult samples [48] as well as convergent and concurrent validity and internal consistency in pregnant people [49].

Pregnancy-Specific Anxiety

Pregnancy-specific anxiety is measured using the 10-item Pregnancy-Related Anxiety Scale (PRAS-10) [50]). The PRAS measures the frequency and severity of pregnant people's present concern, worry, or fear about various aspects of their pregnancy and delivery. Items are scored on a 4-point Likert scale (1=never, 4=almost all the time), with a possible total score of 4-40, where higher scores indicate greater pregnancy-specific anxiety. The PRAS shows good reliability and internal consistency across diverse samples of pregnant people [21,50,51].

Insomnia Symptoms

Insomnia is self-reported using the 7-item Insomnia Severity Index (ISI-7 [52]). The ISI measures the nature, severity, and impact of insomnia symptoms over the last month. Items are scored on a 5-point Likert scale (0=no problem, 4=very severe problem), with a possible total score of 0-28, with higher scores indicating greater insomnia severity. The ISI shows excellent internal consistency and reliably distinguishes between clinical and nonclinical sleep problems [53]. It is also considered reliable, and structurally invariable in pregnant people [54].

Safety and Adverse Events

Per the UCSF Human Research Protection Program, an adverse event is defined as any untoward or unfavorable medical occurrence in a human participant, including any abnormal laboratory finding, symptom, or disease, temporally associated with the individual's participation in the research, whether or not considered related to the individual's participation in the research. All adverse events will have their relationship to study procedures, including the intervention, assessed by an appropriately trained clinician based on temporal relationship and clinical judgment. Adverse event reporting will be done in keeping with the WCG IRB Policy HRP-071. Specifically, adverse events will be reported within 5 calendar days of principal investigator awareness when the adverse event requires a change to the protocol or consent document. For additional information regarding documentation and definition of adverse events in the THRIVE trial, see Multimedia Appendix 4.

Analyses

To examine the efficacy of dCBT (Daylight) on generalized anxiety symptoms (primary outcome) and symptoms of depression, stress, pregnancy-specific anxiety, and insomnia (secondary outcomes) from baseline to 10 weeks post randomization, we will use LMMs. These LMMs will be fit with treatment condition (dCBT and waitlist control group) as the between-group factor, time (baseline, 3, 6, and 10 weeks post randomization) as a within-group factor, and a group-by-time interaction. LMMs maximize data use because they produce unbiased parameter estimates in situations where there are different numbers of observations per record, so long as data are missing at random. A model-based approach will be used to assess the potential impact of data missing not at random on our findings. Pattern mixture models will be used to identify missingness patterns (eg, differential attrition based on randomization group) and to stratify analysis by these patterns as needed [55]. All primary and secondary analyses will be conducted on all randomized participants using an intention-to-treat approach. Sensitivity analyses will also be conducted to test the effects of Daylight among participants who (1) download the app, (2) complete at least 2 modules, and (3) complete all 4 modules, mirroring planned analyses from the original Daylight efficacy trial [56]. Finally, dependent on sample size, exploratory moderation analyses will be conducted to test for differential intervention efficacy among subgroups of racial, ethnic, or sexual and gender minoritize. No interim analyses are planned.

Regarding the assessment of dCBT acceptability, focus groups will be transcribed for qualitative analysis. In line with implementation science frameworks, we will use rapid qualitative techniques for thematic network analysis [57] using NVivo (version 11.4.2; Lumivero) software. Following the identification of codes, the 4 raters will meet to discuss differences and similarities amongst codes to ensure consistency. Codes will be refined and discussed until consensus amongst raters is reached.

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Community Engagement and Dissemination

Study investigators engaged with community members who were part of a previous study focused on the biopsychosocial factors related to health in pregnancy [58] to identify treatments for anxiety as a community priority. Investigators will continue to engage with community members on outreach activities, including presentations to stakeholder groups. Investigators will also work with community partners on the next steps for disseminating dCBT to low-income communities if data from the trial support its efficacy and acceptability. Study results will be reported in one or more medical journals, presented to the funder, and interested stakeholders and community groups. Once published, we will also share a plain language summary of the results with study participants.

Discussion

Principal Findings

This randomized controlled trial assesses the impact of Daylight, a dCBT, among pregnant people with elevated anxiety symptoms who are minoritized based on race and ethnicity or sexual orientation and low income. This trial will also test whether there are salutary effects on symptoms often comorbid with anxiety in pregnancy, such as depression, stress, pregnancy-specific anxiety, and insomnia. This study is one of only 4 CBT trials to date [26,35] that examine effects on pregnancy-specific anxiety, a subtype of anxiety that remains understudied.

Given that all eligible participants in THRIVE will be part of California's Medicaid insurance program, data collected will speak to the generalizability of dCBT for prenatal anxiety for low-income people and can be used to test whether race or ethnicity may impact intervention engagement or efficacy, moderation effects which are often confounded by differences in income across racial and ethnic groups. However, results will require replication among participants on Medicaid insurance from other geographic regions where enrollment is less robust and covers fewer health benefits [59].

Conclusions

This dCBT adds to a very small literature on self-guided treatments for anxiety in pregnancy [60] and will provide valuable data surrounding adherence and engagement in the absence of regular clinical contact, which remains inaccessible for many low-income pregnant people.

Acknowledgments

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Authors' Contributions

CP contributed to writing-original draft, investigation and study administration. RB was responsible for investigation, study administration and, writing-reviewing and editing. KB, BB, JNF, and KMT handled study conceptualization and writing-reviewing and editing. SO managed investigation, study administration, and writing-reviewing and editing. LJP contributed to study conceptualization, funding acquisition, and supervision.

Conflicts of Interest

LJP is a co-founder, chief scientific advisor, and a stock-holder in a company called "EGG Healthy Pregnancy" which works to help pregnant women better understand and address their risk for preterm birth. All other authors declare no conflicts.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 117 KB - resprot_v14i1e70627_app1.pdf]

Multimedia Appendix 2
Study team roles and responsibilities.
[PDF File (Adobe PDF File), 101 KB - resprot_v14i1e70627_app2.pdf]

Multimedia Appendix 3
Consent form.
[PDF File (Adobe PDF File), 316 KB - resprot_v14i1e70627_app3.pdf]

Multimedia Appendix 4
Adverse event criteria.
[PDF File (Adobe PDF File), 74 KB - resprot_v14i1e70627_app4.pdf]

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Abbreviations

CBT: cognitive behavioral therapy
CTSI: Clinical & Translational Science Institute
dCBT: digital cognitive behavioral therapy
GAD-7: Generalized Anxiety Disorder- 7 Scale
HIPAA: Health Insurance Portability and Accountability Act
IRB: institutional review board
ISI-7: 7-item Insomnia Severity Index
LGBTQ+: lesbian, gay, bisexual, transgender, and queer
PHQ-9: Patient Health Questionnaire-9
PRAS-10: 10-item Pregnancy Related Anxiety Scale

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PSI: Postpartum Support International
PSS-4: 4-item Perceived Stress Scale
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
THRIVE: Transforming Health and Reducing Perinatal Anxiety through Virtual Engagement
UCSF: University of California, San Francisco
WGC: Western Copernicus Group

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Protocol

Smart Technology Facilitated Patient-Centered Venous Thromboembolism Management (the SmaVTE Study): Protocol for a Randomized Controlled Trial

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Abstract

Background: Venous thromboembolism (VTE) is a significant public health issue, with a rising global incidence despite extensive research efforts. Patient-centered care, which tailors treatment to individual needs, has shown potential in enhancing outcomes. The integration of smart technologies with psychological frameworks such as the health belief model and the knowledge-attitude-practice (KAP) model may further improve patient engagement and adherence. To address this, we have developed a smart technique–assisted patient-centered care mobile health app for managing VTE (mVTEA), which integrates psychological frameworks to improve patient outcomes in VTE management.

Objective: This study aims to investigate the impact of the mVTEA app on the knowledge, attitudes, and practices of VTE in patients with or at high risk of VTE.

Methods: The SmaVTE (smart technology facilitated patient-centered venous thromboembolism management) study is a 2-armed, single-center, parallel-group, randomized controlled trial. A total of 256 hospitalized patients with or at high risk of VTE will be recruited on the day of their discharge from August 2024 to June 2025. Participants will be randomly allocated to either the mVTEA management group or the routine management group in a 1:1 ratio. The mVTEA management group (n=128) will receive patient-centered VTE management facilitated by the mVTEA app after discharge. The routine management group (n=128) will be administered conventional postdischarge management according to local clinical practice. The KAP of patients will be assessed by a structured KAP questionnaire on VTE. The primary outcome is the difference in patients' KAP on VTE at 3-month follow-up between the 2 groups. Secondary outcomes include scores on each domain of the questionnaire, quality of life, VTE events, chronic thromboembolic pulmonary hypertension, chronic thromboembolic pulmonary disease, postpulmonary embolism syndrome, major bleeding events, VTE-related hospitalizations or rehospitalizations, deaths, and new-onset atrial fibrillation or atrial flutter at 3-month follow-up.

Results: Participants are currently being recruited. The first participant was enrolled in August 2024, which marked the official start of the study. The recruitment process is expected to be completed in June 2025. As of the submission of the paper, 185 patients had been enrolled in this clinical trial. At present, all included patients are being followed up according to the outlined schedule.

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Conclusions: The SmaVTE study offers a pioneering approach to VTE prevention and treatment by combining smart technology with patient-centered care and established theoretical frameworks. The findings could significantly impact clinical practice and inspire further research into the integration of smart technologies with behavioral science theories.

Trial Registration: ClinicalTrials.gov NCT06350331; https://clinicaltrials.gov/study/NCT06350331

International Registered Report Identifier (IRRID): DERR1-10.2196/67254

(JMIR Res Protoc 2025;14:e67254) doi:10.2196/67254

KEYWORDS

venous thromboembolism; deep vein thrombosis; pulmonary embolism; prophylaxis; mobile health; patient-centered care; patient education; thrombosis; thrombus; mHealth; mobile applications; mobile apps; apps

Introduction

Background

Venous thromboembolism (VTE), which encompasses deep vein thrombosis and pulmonary embolism (PE), affects more than 1 in 12 individuals over their lifetime and poses a substantial health and economic burden [1-4]. Despite decades of research on the prevention and treatment of VTE, the prevalence of VTE has substantially increased worldwide [5-7]. Up to 75% of VTE cases occur in the hospital or within 90 days after hospital discharge [2,8], highlighting the complexity and challenge of VTE management.

Studies suggest that many prescribed pharmacologic prophylaxes are not administered due to patient refusal or insufficient patient-nurse communication [9-12]. Even among patients who commence anticoagulant therapy, many discontinue treatment after bleeding or other setbacks. Clinicians also face the difficult task of balancing thrombosis and bleeding risks, which often share overlapping risk factors that can change over time [13,14]. Determining an optimal, individualized decision is therefore fundamental to improving VTE management.

Patient-centered care, recommended by cardiovascular guidelines [15,16], emphasizes meeting patients' unique needs and involving them in decision-making. Adoption of a patient-centered approach has demonstrated benefits in cardiovascular disease, improving patient knowledge, self-efficacy, and health outcomes [17,18]. A limited number of studies suggest similar benefits in VTE management [19-21], but further research is needed on the role of patient-centered care for patients with or at risk of VTE.

Smart technology, such as wearable devices, mobile health (mHealth) apps, artificial intelligence, and digital communication platforms, has shown potential in facilitating patient education, providing real-time feedback, and enhancing patient engagement [22-24]. The use of smart technology in patient-centered care supports personalized and proactive health care by empowering patients to manage their health, which is especially important for VTE, where patient behavior greatly affects outcomes [13,16,25]. A cohort study has shown that an mHealth-based web-based anticoagulation management system can effectively improve patient care and safety for warfarin-treated patients with VTE [26].

Although mHealth is effective, patient engagement tends to wane over time [27,28]. Furthermore, studies on health behavior suggest that simply emphasizing risk does not necessarily promote better adherence, due to psychological phenomena such as "optimistic bias" [29,30]. Various theoretical models have been advanced to explain health behaviors, with the health belief model (HBM) being one of the most common [31-34]. Studies demonstrate that HBM-based interventions can enhance self-management [33]; yet, their ability to predict health behaviors is limited [35]. The knowledge-attitudes-practices (KAP) model offers complementary insights, linking knowledge to behavioral attitudes, and thereby representing another potentially useful tool [32,34]. To the best of our knowledge, there is a lack of research in the field of VTE that integrates the theories of HBM and KAP, complemented by mHealth technology.

To address this research gap, we have recently developed a smart technology–assisted, patient-centered care mHealth app for managing VTE (mVTEA) [36]. Its goal is to improve patient-centered care for patients with or at risk of VTE by combining HBM and KAP frameworks.

Objective

The SmaVTE (smart technology facilitated patient-centered venous thromboembolism management) study aims to investigate the impact of the mVTEA app on the KAP of patients with or at high risk of VTE assessed by a VTE-KAP questionnaire in a 3-month randomized controlled trial. We hypothesized that this theory-based mHealth intervention can improve the KAP of these patients while ensuring their safety compared to traditional face-to-face medical visits.

Methods

Study Design and Setting

The SmaVTE study is a 2-armed, single-center, parallel-group, randomized controlled trial designed to evaluate the impact of the mVTEA app on the KAP of patients with or at high risk of VTE. The trial will be conducted at the Sixth Medical Center of the Chinese People's Liberation Army General Hospital, which is a tertiary hospital that integrates medical care, teaching, and research. A total of 256 hospitalized patients with or at high risk of VTE will be recruited on the day of their discharge. Participants will be randomly allocated in a 1:1 ratio to either the mVTEA management group or the routine management group. The mVTEA management group (n=128), also referred to as the experimental group, will receive patient-centered VTE management facilitated by the mVTEA app after discharge. In

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contrast, the routine management group (n=128), also known as the control group, will be administered with conventional postdischarge management according to local clinical practice. All of the above management will be performed for 3 months following discharge. Our study is scheduled to commence in August 2024 and conclude in November 2025. Recruitment began in August 2024 and is anticipated to conclude by June 2025. Data analysis is planned to commence in October 2025 after the follow-up data collection. The analysis is expected to be completed by November 2025. The protocol conforms to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 statement [37]. The latest protocol (version 1.0) was dated March 1, 2024. The trial was registered on Clinicaltrials.gov (NCT06350331).

Participants and Recruitment

Potentially suitable candidates for the study will initially be screened from the inpatients in departments at high risk of VTE through the clinical decision support system for VTE risk assessment and integrated care in our hospital [38]. Based on the initial screening list, a final identification of whether the patient meets the study recruitment needs will be made on the day the patient is discharged from the hospital. Patients who fulfill the recruitment criteria and are willing to participate will receive comprehensive information about the entire study protocol, including its benefits and potential risks. Once patients agree to participate, they will be directed to a web-based informed consent document or, depending on the subject's wishes, a paper version of the informed consent document will be given at the same time. This recruitment process will be carried out with the utmost respect for the individual preferences of each participant. In addition, we assure that the rights of participants to withdraw from the study will be upheld throughout all phases of the clinical trial. The inclusion and exclusion criteria of the study are shown in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Inpatients ≥18 years of age at admission.
- Previous or current definitive diagnosis of deep vein thrombosis (DVT), pulmonary embolism (PE), both by imaging, or high risk of venous thromboembolism (VTE) at discharge: Padua score ≥4 for medical patients and Caprini score ≥5 for surgical patients.
- Signed informed consent.

Exclusion criteria

- Mental disorder or a combination of other serious diseases leading to incapacity for independent living.
- Inability to use smartphones, computer tablets, and other smart devices.
- Being pregnant or breastfeeding.
- Have participated in similar trials or are undergoing other clinical trials.

Randomization

Stratified block randomization was used to allocate participants. Participants were divided into 4 strata based on 2 factors: age (≥60 years and <60 years) and their VTE diagnostic status at the time of recruitment. The strata consist of (1) patients aged ≥60 years diagnosed with VTE, (2) patients aged ≥60 years at high risk for VTE but not diagnosed, (3) patients aged <60 years diagnosed with VTE, and (4) patients aged <60 years at high risk for VTE but not diagnosed. Within each stratum, participants were assigned in a 1:1 ratio to either the mVTEA management group or the routine management group. This allocation was performed using a fixed block randomization method with a block size of 4. The random sequence was generated by a free, robust randomization app with a random seed number of 20240215 [39]. A web-based random allocation system was used to assign random numbers to each participant.

Blinding

Due to the limitations of the protocol and the specific nature of mHealth management, it is not feasible to blind participants, their primary care physicians, and clinic physicians. However, to enhance the quality and reliability of this study, the researchers will be blinded during the efficacy assessment, data collection, data management, and statistical analysis of the results. Therefore, those responsible for efficacy assessment, data collection and management, and analysis of results will not be informed of trial group assignments and will not be permitted to communicate with each other or with participants about the treatment. Furthermore, to minimize potential bias introduced by unblinded participants or researchers, the study will include only individuals who have no conflict of interest.

Intervention

Overview

The mVTEA management group will receive patient-centered VTE management facilitated by the mVTEA app based on the combination of HBM and KAP frameworks after discharge, while the routine management group will undergo conventional postdischarge management according to local clinical practice. In addition, VTE management using the mVTEA app is administered by certified thrombosis specialists and nurses with over 5 years of clinical experience and proficiency in operating the mVTEA app. Furthermore, regular training sessions and assessments on VTE prevention and treatment for health care professionals are conducted in our hospital, along with routine quality control meetings focused on VTE prevention and treatment. These measures ensure that all health care

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professionals in our hospital possess the necessary competencies to effectively implement VTE prevention and treatment.

Integrated VTE Management Pathway Within mVTEA

The long-term management of VTE is multifaceted, requiring individualized patient assessment and a nuanced approach to therapy. In this study, we have proposed the ABCDEF pathway for integrated management of VTE to complement mVTEA-assisted patient-centered management, thus minimizing the risk of VTE and its complications and ensuring patient safety and quality of life (QoL): (1) appropriate antithrombotic management; (2) bleeding risk management; (3) complication monitoring; (4) digital health management; (5) exercise and rehabilitation; and (6) facilitate the management of risk factors and comorbidities. Details of the integrated VTE management pathway are presented in Table 1.

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Table 1. The ABCDEF pathway for integrated management of venous thromboembolism.

Pathway and key point	Process
Appropriate antithrombotic management [13,40-46]	
Thrombosis risk management	Monitor patients' thrombotic risk after discharge to facilitate thrombosis prevention, improve treatment decisions, and enhance patient self-management.
Anticoagulant therapy selection	Choose the appropriate anticoagulant (eg, warfarin or DOACs[a]) based on individual patient risk factors, renal function, and potential drug interactions.
Dose adjustment and monitoring	Conduct regular blood tests (eg, INR[b] for warfarin and renal function tests for DOACs) and patient consultations to monitor therapeutic effects. Schedule follow-ups to reassess and adjust dosages based on test results and patient feedback.
Thromboprophylaxis	Assess patient risk factors to determine the need for prophylaxis, administer appropriate prophylactic measures, and monitor their effectiveness.
Bleeding risk management [13,14,40-47]	
Bleeding risk assessment	Conduct a thorough bleeding risk assessment using validated tools (eg, HAS-BLED[c] score) before initiating anticoagulant therapy and reassess periodically.
Personalized anticoagulant therapy	Tailor anticoagulant therapy to the individual's bleeding risk, opting for agents with lower bleeding risk profiles if necessary.
Bleeding precautions	Implement preventive measures such as avoiding unnecessary invasive procedures and managing concurrent medications that may increase bleeding risk.
Complication monitoring [13,44,48,49]	
Regular complication surveillance	Schedule regular check-ups and use diagnostic imaging (eg, Doppler ultrasound, CTPA[d]) to monitor for complications such as recurrent VTE[e], PTS[f], PPES[g], or CTEPH[h].
Patient self-monitoring	Encourage patients to report new or worsening symptoms promptly, and provide them with clear instructions on what to look out for.
Digital health management [22-24,50]	
Telemedicine	Implement telemedicine platforms for regular follow-ups, reducing the need for in-person visits and enabling remote monitoring of anticoagulation therapy.
mHealth[i] apps	Use mHealth apps that allow patients to track their medication adherence, report symptoms, and receive reminders for follow-up appointments.
Wearable devices	Encourage the use of wearable devices that monitor vital signs (eg, heart rate and oxygen saturation) to detect early signs of complications.
Exercise and rehabilitation [51,52]	
Personalized exercise programs	Develop individualized exercise programs that take into account the patient's overall health status, VTE history, and comorbid conditions.
Supervised rehabilitation	Initially, provide supervised rehabilitation to ensure safe exercise practice and adjust the intensity and type of exercise as needed.
Long-term physical activity	Encourage long-term adherence to physical activity guidelines to improve health outcomes.
Management of vascular risks and comorbidities [53-57]	
Comprehensive vascular risk assessment	Conduct a thorough assessment to identify and manage modifiable vascular risk factors such as obesity, smoking, hypertension, and diabetes. Monitor for cardiac arrhythmias such as atrial fibrillation and obstructive sleep apnea.
Lifestyle modifications	Provide education and support for lifestyle changes, including dietary modifications, smoking cessation programs, and weight management strategies.
Integrated care for cardiovascular risks and comorbidities	Coordinate care among specialists to manage comorbidities effectively, ensuring that treatments for VTE are compatible with other medical conditions and medications.

[a]DOACs: direct oral anticoagulants.

[b]INR: international normalized ratio.

[c]HAS-BLED: hypertension, abnormal renal or liver function, stroke, bleeding history or predisposition, labile INR, elderly (age ≥ 65 years), drugs or alcohol concomitantly.

[d]CTPA: computed tomography pulmonary angiography.

[e]VTE: venous thromboembolism.

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[f]PTS: postthrombotic syndrome.

[g]PPES: postpulmonary embolism syndrome.

[h]CTEPH: chronic thromboembolic pulmonary hypertension.

[i]mHealth: mobile health.

The HBM and KAP-Combining Framework

The HBM suggests that people's perceptions of the severity and susceptibility to a health issue, along with the perceived benefits and barriers to taking preventive action, influence their decisions to adopt health behaviors. The KAP highlights the sequential relationship among knowledge, attitudes, beliefs, practices, or behaviors. It posits that increased knowledge leads to changes in attitudes, which influence practices or behaviors. The key components of the HBM and the KAP are shown in Textbox 2. This study further extends the framework of the KAP by incorporating the HBM within the attitude domain. Through an in-depth analysis of the factors influencing the adoption of health behaviors, we believe that it will improve patients' health beliefs, increase self-efficacy in health behaviors, and promote patient-centered management. Furthermore, this study has taken an additional step by incorporating the ABCDEF pathway for integrated management of VTE into the practice domain of the KAP, thereby assessing patient health behaviors more comprehensively. Figure 1 shows the combined HBM and KAP framework.

Figure 1. Combined framework based on the health belief model and the knowledge, attitude, and practice approach. HBM: health belief model; VTE: venous thromboembolism.

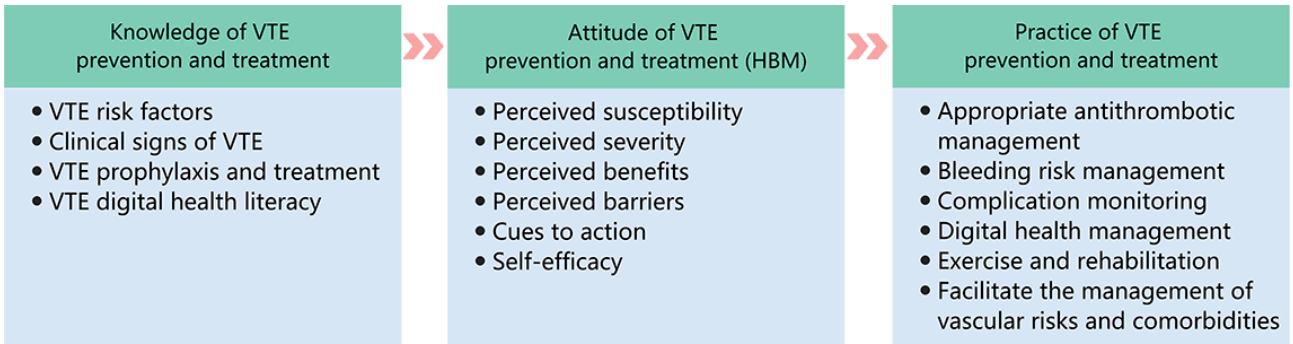

Textbox 2. The key components of the health belief model and the knowledge-attitude-practice frameworks.

Health belief model

- Perceived susceptibility: belief about the likelihood of getting a disease or condition.
- Perceived severity: belief about the seriousness of the disease or condition.
- Perceived benefits: belief in the effectiveness of taking action to reduce the risk or severity.
- Perceived barriers: beliefs about the obstacles to taking the recommended action.
- Cues to action: triggers that prompt individuals to take action, such as symptoms or media campaigns.
- Self-efficacy: confidence in one's ability to take the recommended action.

Knowledge-attitude-practice

- Knowledge: awareness or understanding of health-related information and facts.
- Attitude: beliefs, feelings, and values toward a particular health issue or behavior.
- Practice: the actual behaviors or actions taken in response to health knowledge and attitudes.

mVTEA-Facilitated Patient-Centered VTE Management

To achieve the goal of mVTEA-facilitated patient-centered VTE management, an mVTEA-assisted patient health education program has been structured around the joint HBM and KAP framework as shown in Figure 2. To begin with, in a pilot study, we have developed a structured VTE-KAP questionnaire (Multimedia Appendix 1), guided by this joint theory framework, via 2 rounds of Delphi surveys among the National VTE Prevention and Treatment Program Office Expert Group and the VTE Prevention and Treatment Nursing Expert Group of the Chinese People's Liberation Army General Hospital. This questionnaire demonstrated an overall Cronbach α coefficient of 0.959, with domain-specific coefficients of 0.885 for knowledge, 0.942 for attitudes, and 0.970 for practices. In addition, the overall split-half reliability coefficient was 0.834, with domain-specific coefficients of 0.879 for knowledge, 0.770 for attitudes, and 0.863 for practices.

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Figure 2. Specific intervention process of the mHealth app for patient-centered venous thromboembolism management. KAP: knowledge, attitude, and practice; mVTEA: smart technique-assisted patient-centered care mHealth app for managing venous thromboembolism; VTE: venous thromboembolism.

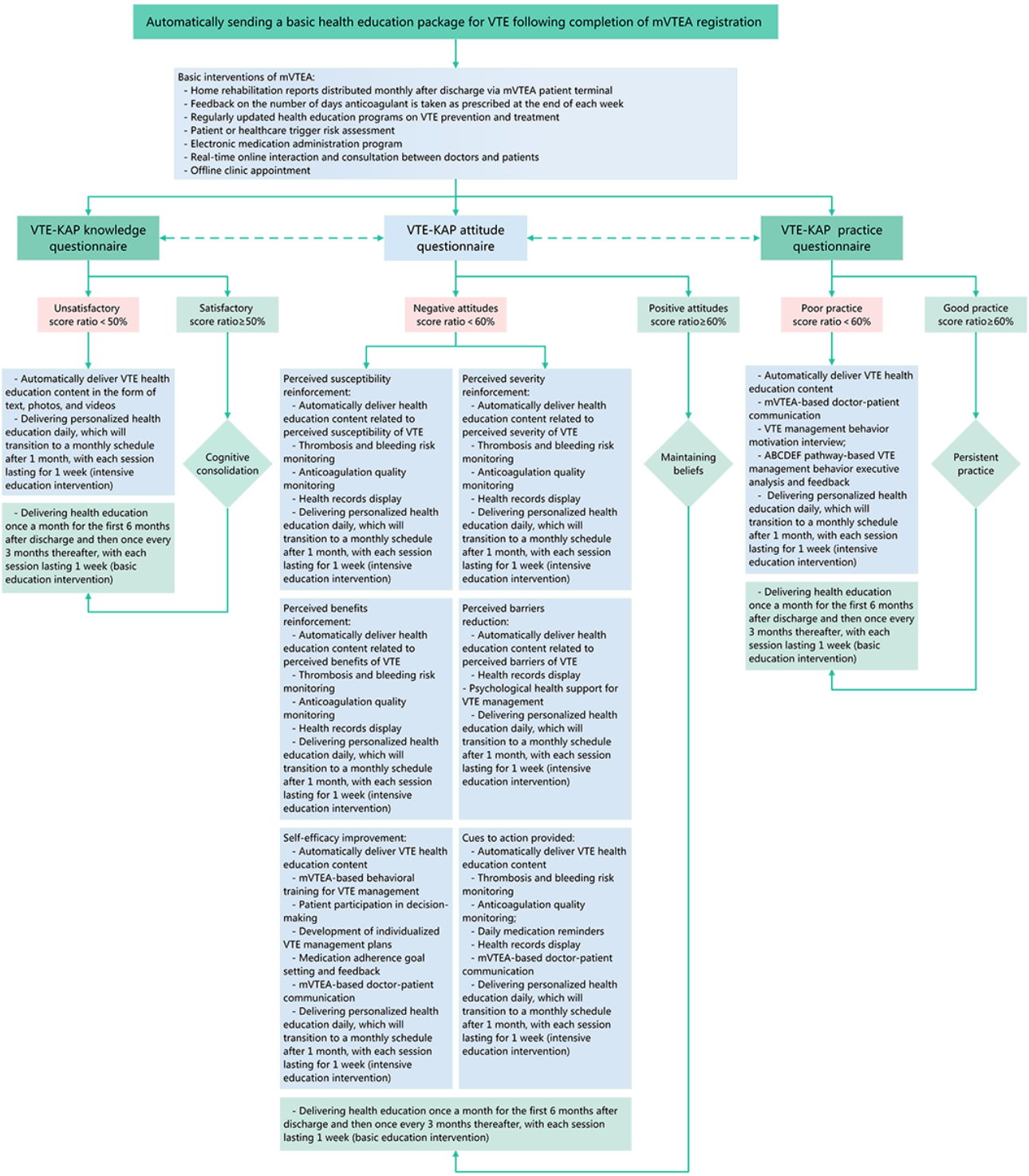

The VTE-KAP questionnaire is a self-administered questionnaire that includes demographic characteristics and KAP of patients toward VTE prevention and treatment. It is intended to evaluate the efficacy of health education programs and to inform the deployment of mVTEA-based health education strategies. This questionnaire consists of a total of 53 questions with an overall score range of 41-283. The knowledge domain contains seven questions to assess patients' levels of knowledge regarding VTE prevention and treatment. The total score of knowledge for each study participant ranged from 7 to 53. The attitude domain contains 20 questions to assess patients' attitudes toward VTE prevention and treatment. Each question was scored, and the final attitude score ranged between 20 and 100. The practice domain contained 26 questions with a score range of 21-130 for assessing the implementation of VTE prevention and treatment behaviors in the study patients. The higher the score, the higher the level of knowledge, attitude, and practice.

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To grade the KAP about VTE prophylaxis and treatment, the VTE-KAP questionnaire score is calculated according to the score ratio: score ratio=item score/total score of the item×100%. According to the previous study [58], a score ratio of ≥50% in the knowledge domain is classified as satisfactory and <50% as unsatisfactory; a score ratio of ≥60% in the attitude domain is classified as positive attitudes and <60% as negative attitudes; and a score ratio of ≥60% in the practice domain is classified as a good level of practice and <60% is classified as poor practice.

These VTE-KAP assessment outcomes determine the subsequent interventions delivered via the mVTEA app. Initially, upon registration, the mVTEA app delivers a standardized VTE education package containing 3 videos and 4 graphic resources covering VTE fundamentals, risk factors, symptoms, and prevention and treatment strategies. Following this initial phase, interventions are personalized based on the individual's VTE-KAP scores. Tailored components include specific education schedules (basic or intensive), medication reminders, adherence feedback, risk monitoring features, access to electronic health records, and specialist communication channels. In addition, the mVTEA patient terminal automatically dispatches all health education questionnaires and home-rehabilitation reports according to the schedule specified in Table 2. The detailed workflow of this mVTEA-facilitated patient-centered VTE management strategy is presented in Figure 2, and the core functional interface of the mVTEA app is shown in Figure 3.

Table 2. Distribution schedule of home rehabilitation reports and health education questionnaires for mHealth app-assisted, patient-centered venous thromboembolism management.

Timepoint	At discharge	1st month	2nd month	3rd month	6th month	9th month	12th month	>1 year
Home rehabilitation reports	None	✓	✓	✓	Once a month	Once a month	Once a month	Once a month
Knowledge questionnaire	✓	None	None	✓	✓	None	✓	Once every 6 months
Attitude questionnaire	✓	✓	✓	✓	✓	✓	✓	Once every 6 months
Practice questionnaire	✓	None	None	✓	✓	None	✓	Once every 6 months

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Figure 3. Core functional interface of the mHealth app for patient-centered venous thromboembolism management. (A) Health education program, (B) thrombosis risk assessment, (C) bleeding risk assessment, (D) anticoagulation management, and (E) home rehabilitation report.

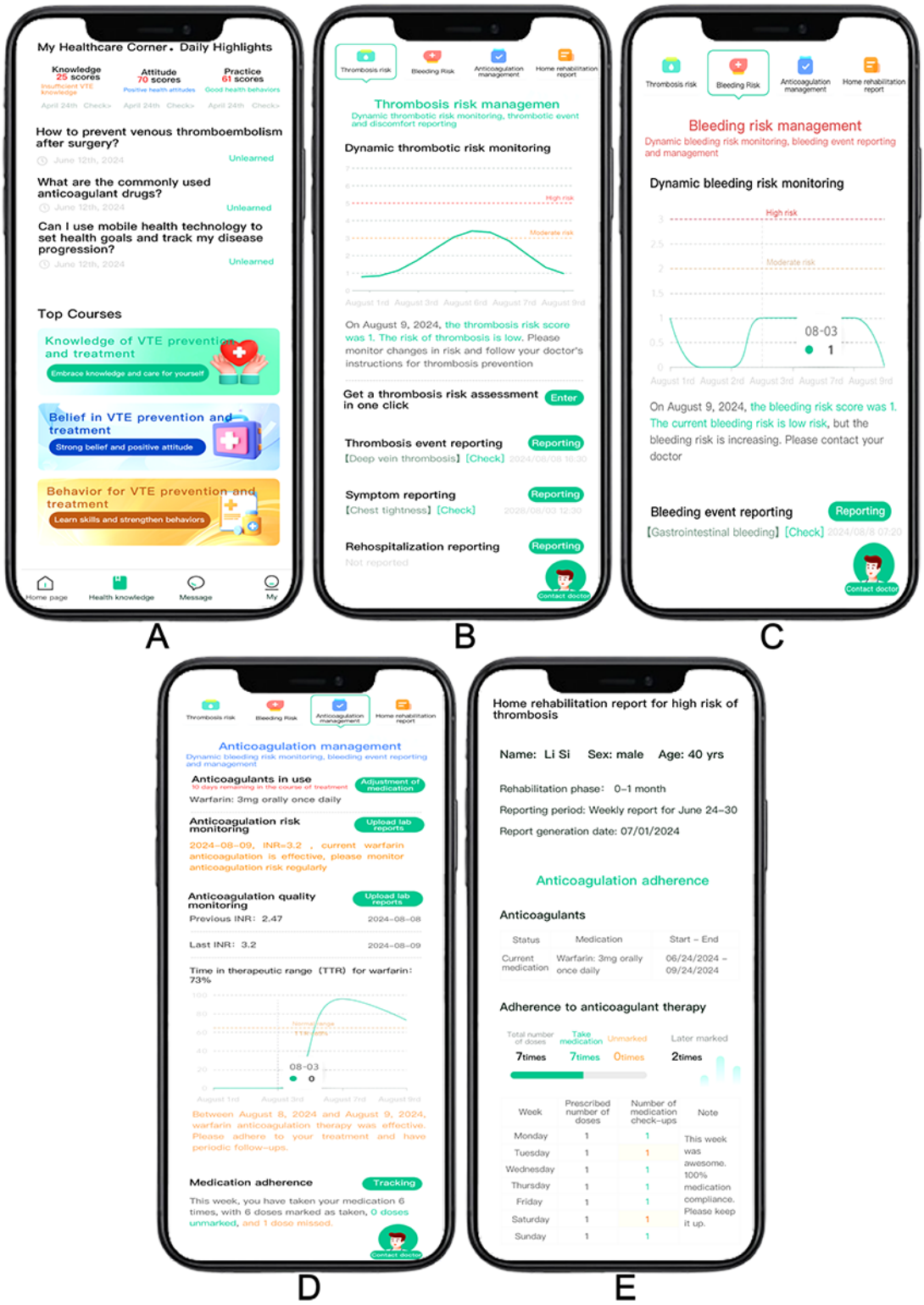

Routine VTE Management

The routine VTE management group will receive only conventional postdischarge management according to local clinical practice, including basic health advice appropriate for the prevention and treatment of VTE. The textual and graphical materials comprising the aforementioned basic package for VTE-related health education in the mVTEA app will be printed and distributed to patients within the routine management group on the day of discharge for home-based study. The video courses in the health education basic package can be accessed by scanning the QR code.

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Outcome Measures

Primary Outcome

The primary outcome of this study is the difference in patients' KAP on VTE at 3-month follow-up between the mVTEA management group and the routine management group.

Secondary Outcomes

Secondary outcomes include scores on each domain of the VTE-KAP questionnaire (knowledge domain, attitude domain, practice domain), QoL, VTE events, chronic thromboembolic pulmonary hypertension, chronic thromboembolic pulmonary disease, post-PE syndrome [13,48], International Society on Thrombosis and Hemostasis (ISTH) defined major bleeding events [59], VTE-related hospitalizations, VTE-related rehospitalizations, all-cause deaths, PE-related deaths, and new-onset of atrial fibrillation (AFI) or atrial flutter (AFL) at 3-month follow-up. For patients with more than 1 event, only the first event will be counted. A total of 3 investigators who are unaware of patients' group assignments will adjudicate all endpoints.

Generic, nondisease-specific health-related QoL is assessed using the EQ-5D-5L questionnaire and its corresponding visual analog scale [60]. Briefly, the EQ-5D-5L generates an overall index that ranges from 0 (lowest generic QoL) to 1 (highest generic QoL) and is calculated based on country-specific reference value sets. The EQ-5D-5L health index was calculated with the value set for China. The EuroQol visual analog scale ranges from 0 to 100, with higher scores indicating better health.

VTE events are categorized into 3 groups: new-onset VTE, hospital-acquired VTE (HA-VTE), and recurrent VTE. VTE that occurred for the first time during the study period is classified as new-onset VTE. HA-VTE is defined as any new-onset VTE that has occurred within 90 days of hospital discharge [4]. Recurrent VTE is defined as the appearance of new evidence of VTE after acute VTE has been treated in the acute phase (2 weeks) with significant clinical improvement in signs and symptoms. According to the time of VTE recurrence, it is further categorized into early VTE recurrence (within 3 months after the last VTE occurrence) and late VTE recurrence (more than 3 months after the last VTE occurrence) [61]. Hospitalization due to the new-onset VTE will be documented as VTE-related hospitalizations, while rehospitalization due to VTE recurrence, progression, or complications arising from VTE treatment will be classified as VTE-related rehospitalizations. All-cause death refers to any death occurring during the study period, regardless of the cause. PE-related death is defined as death explicitly caused by PE.

New-onset AFI or AFL is defined as an episode of AFI or AFL lasting at least 30 seconds, first detected by devices such as smart wearable devices or ambulatory electrocardiograms, or initially diagnosed during a medical visit and documented in outpatient charts or inpatient hospital records.

Data Collection and Management

Table 3 presents the detailed schedule for data collection and assessments. Baseline demographic and clinical data will be extracted from the hospital information system. Additional data—including mHealth use, electronic health literacy, EQ-5D-5L, and VTE-KAP—will be collected at discharge and follow-up via web-based questionnaires for the routine group and through the mVTEA platform for the intervention group. The Chinese version of the electronic health literacy scale (C-eHEALS) will be used to evaluate participants' eHealth literacy [62]. Follow-up at 3 months postdischarge will be conducted through outpatient visits, telephone interviews, or web-based interviews via the mVTEA platform (for the intervention group). All collected data will be deidentified and recorded in electronic case report forms. Data will be securely stored on password-protected servers with restricted access, and sharing with third parties will require authorization from the corresponding author. The quality control team will routinely verify data accuracy and reliability; upon confirmation, the data will be locked to prevent further modifications. The finalized database will be provided to statistical analysts as specified in the statistical analysis plan. All data collectors and managers will undergo standardized training and assessment before participating in the study.

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Table 3. Study protocol, schedule, and timing of data collection.

Activity or assessment	Screening (during hospitalization, t_1)	Enrollment (at discharge, 0)	Study visit (at discharge [intervention], t_1)	Follow-up (3rd month, t_2)
Prescreening consent	✓			
Eligibility screen	✓			
Informed consent		✓		
Randomization		✓		
Demographic information		✓		
Medical history		✓		
mHealth use		✓		
C-eHEALS[a]		✓		
VTE[b]-KAP[c] questionnaire		✓		✓
EQ-5D-5L		✓		✓
Interventions				
Basic health education			✓	
mVTEA[d]-assisted management			✓	✓
Routine management			✓	✓
VTE event				✓
CTEPH[e]				✓
CTEPD[f]				✓
PPES[g]				✓
Bleeding event				✓
VTE-related hospitalization				✓
VTE-related rehospitalization				✓
Death				✓
New-onset of AFI[h] or AFL[i]				✓
Adverse event				✓

[a]C-eHEALS: Chinese version of the electronic health literacy scale.
[b]VTE: venous thromboembolism.
[c]KAP: knowledge, attitude, and practice.
[d]mVTEA: smart technique-assisted patient-centered care mHealth app for managing venous thromboembolism.
[e]CTEPH: chronic thromboembolic pulmonary hypertension.
[f]CTEPD: chronic thromboembolic pulmonary disease.
[g]PPES: postpulmonary embolism syndrome.
[h]AFI: atrial fibrillation.
[i]AFL: atrial flutter.

Quality Control

To ensure the quality of the study, all researchers will undergo uniform and standardized training before the study's commencement. Researchers will be assessed, and only those who meet the qualifications will be allowed to participate. Structured follow-ups will be conducted by staff from the specialized follow-up office. In addition, the collected data will be regularly monitored monthly by the research supervisor to ensure the authenticity and reliability of the study results.

Statistics

Sample Size and Power Considerations

This study used a stratified block randomization method with 4 strata. Literature suggests an average of 50-100 patients per stratum for stratified randomization [63]. Previous studies in China have reported that the coefficient of variation for VTE-KAP questionnaire scores among patients at risk of VTE ranges from 0.1 to 0.12. In this study, a coefficient of variation of 0.1 was assumed, enrolling 50 patients per stratum, resulting in a total of 200 patients (100 per group). At a 2-sided

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significance level of .05, this design yields 94% statistical power to detect a 5% difference in VTE-KAP questionnaire scores between the two groups. Even with a 2-sided significance level of 0.025, the setup maintains 90% statistical power to detect the same 5% difference. Considering a 20% nonresponse rate, the final sample size was adjusted to 64 patients per stratum, leading to a total of 256 patients (128 in each group). The sample size was calculated by using Power Analysis and Sample Size software (version 19.4.1; NCSS, LLC).

Statistical Analyses

In this study, we define 2 analysis populations: full analysis set (FAS) and intention-to-treat (ITT). FAS is the set of all patients who have received VTE prevention and treatment intervention at least once after randomization. The ITT set will include all randomly assigned patients, regardless of whether they completed the study or followed the study protocol. FAS will be the primary analysis population, and ITT will provide supportive results. Missing data will be handled using the multiple imputation method. Since the study outcomes already include assessments of safety data, the safety analysis set is not performed. Sensitivity analysis will be conducted by comparing the results of the ITT and FAS analyses.

Continuous variables will be presented as mean and SD, or as median and IQR for variables not following a normal distribution. Categorical variables will be presented as counts and percentages. Differences in baseline demographic and clinical characteristics, as well as survey data between groups, will be assessed using the Student *t* test or the Mann-Whitney *U* test for continuous variables, depending on distributional assumptions. Categorical variables will be analyzed using the chi-square test or Fisher exact test, as applicable.

To account for the repeated measurements of EQ-5D-5L and KAP survey data collected at discharge and the 3-month follow-up, we will use a linear mixed-effects model for repeated measures. The model will include fixed effects for the treatment group (mVTEA management vs routine management), time point (discharge vs 3-month follow-up), the interaction between treatment group and time point, the baseline score of the respective survey (EQ-5D-5L or KAP), and the prestratification factors (VTE diagnosis status at discharge: Yes or No; age: ≥60 years vs <60 years). Patients and their hospitalization units will be included as random effects. The key parameter of interest for evaluating the intervention effect over time will be the group-by-time interaction term. The Cox proportional hazards model will be used to compare the hazard of the event (time to event) between groups during the follow-up period, taking into account the prestratification factors. The hazard ratio and its corresponding 95% CI will be calculated using this model. Statistical significance is set at $P<.05$ (2-sided). SPSS (version 22.0; IBM Corp) will be used for statistical analysis.

Ethical Considerations

This study will be conducted by the principles outlined in the Declaration of Helsinki, ensuring that no additional harm or risks are imposed upon the participants. The ethics committee of the Sixth Medical Center of the Chinese People's Liberation Army General Hospital has already provided ethics approval (HZKY-PJ-2024-8). Before the commencement of the clinical trial, all participants will receive comprehensive information about the trial's purpose, the procedures to be undertaken, the anticipated duration, and the potential risks and benefits. They will then voluntarily provide written informed consent. To maintain participant confidentiality, real names will not be used in case reports, and participants will retain the right to withdraw from any aspect of the study at any time. Research findings will be disseminated through publication in peer-reviewed journals and presentations at provincial, national, and international conferences or forums.

Results

Figure 4 describes the study flowchart. Participants are currently being recruited. The first participant was enrolled in August 2024, marking the official start of the study. The recruitment process is expected to be completed in June 2025. As of the submission of the paper, 185 patients were enrolled in this clinical trial. All included patients were followed up according to the outlined schedule.

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Figure 4. Flowchart of the trial. C-eHEALS: Chinese version of electronic health literacy scale; HBM: health belief model; KAP: knowledge, attitude, and practice; mHealth: mobile health; mVTEA: smart technique-assisted patient-centered care mHealth app for managing venous thromboembolism; VTE: venous thromboembolism.

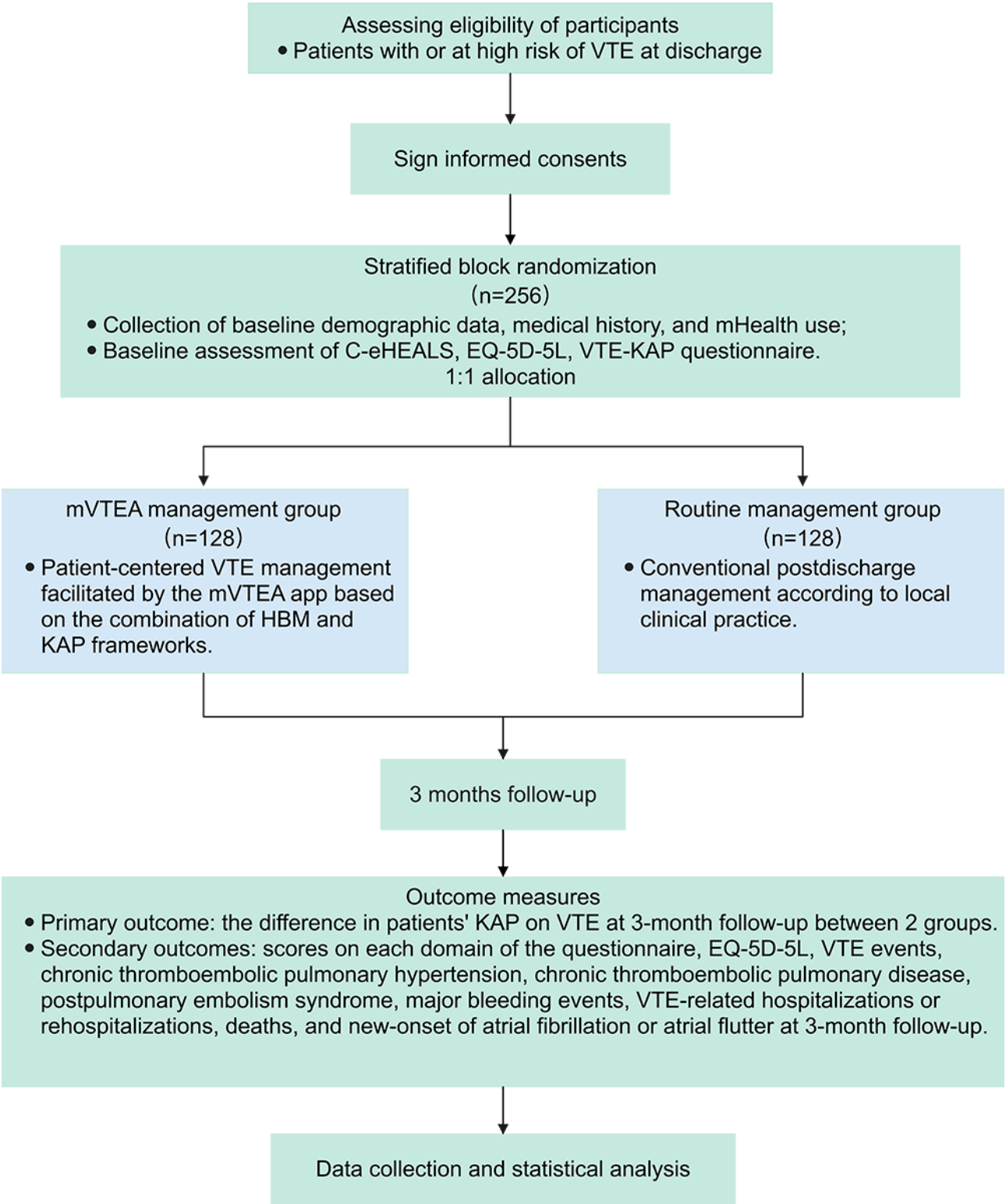

Discussion

Expected Outcomes

The SmaVTE study is an innovative study designed to address the multifaceted challenges of VTE management through the integration of smart technology. This trial aims to evaluate the effectiveness of the mVTEA app in VTE management, which is an mHealth app designed to enhance patient-centered care through the joint use of HBM and KAP theoretical frameworks. This study hypothesizes that such theory-based mHealth interventions can improve the KAP level for patients with or at risk of VTE while ensuring their safety compared to traditional face-to-face VTE management.

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Unlike previous mHealth studies that focused mainly on patients with warfarin therapy, targeting patients with AFI and heart valve disease [26,64-66], the SmaVTE study expands the target population to include both patients at risk for VTE and those already diagnosed, as well as patients using direct oral anticoagulants (DOACs). This comprehensive scope is designed to reflect real-world clinical practice and address emerging challenges associated with DOAC management, such as renal impairment, drug interactions, and the absence of specific reversal agents [45,67]. Integrating the ABCDEF pathway into the KAP framework further supports a comprehensive and dynamic approach to VTE care, encompassing not only anticoagulation management but modifiable risk factors, long-term complications, and comorbidities. If proven effective, findings from this trial may have significant implications for clinical practice, supporting more proactive and personalized approaches to VTE prevention and treatment.

The theoretical foundation of the mVTEA app is grounded in the principles of patient-centered care and behavioral science theories. Patient-centered care emphasizes tailoring medical care to individual patient needs, preferences, and values [15,16]. Behavioral science theories, such as the HBM and the KAP theories, suggest that empowering patients with information and involving them in their care can significantly enhance motivation and adherence to treatment protocols [31-34]. The mechanisms by which the mVTEA app may influence behavior change can be attributed to several factors, including goal setting, real-time feedback, personalized reminders, and tailored health education programs. These features are designed to facilitate continuous engagement and allow patients to monitor their progress, thereby enhancing motivation and adherence.

Limitations

There were some limitations to this study. First, the applicability of the results may be confined to the population studied and may not fully extrapolate to other patient groups, such as those with AFI or heart valve disease. Second, the study encompasses only those patients who can use smartphones or computer tablets, which introduces a potential bias related to the participants' digital literacy. To mitigate this effect, standardized training on the application's use will be provided following the patient's registration on the mVTEA app. Third, the experimental protocol could not implement double blinding, a limitation inherent to the specificity of mHealth interventions. To ensure the reliability of the data, blind statistical analysis will be conducted, and roles among interventionists, efficacy evaluators, and statisticians will be distinctly segregated. Finally, the clinical outcomes, designated as secondary endpoints in this study, require validation through subsequent research.

Conclusion

The SmaVTE study may contribute to advances in VTE prevention and treatment. By integrating smart technology with patient-centered care and applying well-established theoretical frameworks, the study aims to enhance the KAP of patients at risk for or diagnosed with VTE while improving clinical outcomes. In addition, this study provides a novel approach for the long-term management of VTE. The results from this trial could have significant implications for clinical practice and may encourage further research into the integration of smart technologies with theory-based behavior change techniques.

Acknowledgments

The authors thank all participants and staff at the Sixth Medical Center of the Chinese People's Liberation Army General Hospital for their support. This work was supported by the 14th Five-Year National Key Research and Development Program "Research on the Prevention and Treatment of Common and Frequently Occurring Diseases" Key Project (2023YFC2507201). We appreciate the team at Dr Breath Company, Ltd, and the technical assistance of computer expert Liu Chens with the mVTEA app.

Data Availability

The datasets generated and analyzed in this study are available upon request from the corresponding author. At present, data sharing is not applicable.

Authors' Contributions

ZGJ led the conceptualization, methodology, and supervision of the study and drafted the original manuscript. ZQZ and BBL contributed to the investigation and participated in reviewing and editing the manuscript. HW, YY, and HZ were involved in conceptualization and methodology and contributed to manuscript revision. LNR and WJ supported the investigation and assisted with reviewing and editing. ZGZ contributed to conceptualization, methodology, project administration, and funding acquisition and participated in reviewing and editing the manuscript. YG was responsible for conceptualization, methodology, project administration, and funding acquisition and drafted the original manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Additional material.

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[DOCX File , 101 KB - resprot_v14i1e67254_app1.docx]

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Abbreviations

AFI: atrial fibrillation
AFL: atrial flutter
C-eHEALS: Chinese version of the electronic health literacy scale
DOAC: direct oral anticoagulant
FAS: full analysis set
HBM: health belief model
ISTH: International Society on Thrombosis and Hemostasis
ITT: intention-to-treat
KAP: knowledge, attitudes, and practices
mHealth: mobile health
mVTEA: smart technique–assisted patient-centered care mHealth app for managing venous thromboembolism
PE: pulmonary embolism
QoL: quality of life
SmaVTE: smart technology facilitated patient-centered venous thromboembolism management
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
VTE: venous thromboembolism

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Protocol

Enhancement of Self-Management of Metabolic Syndrome Among Adults in Urban, Low-Income Settings of India Using Digital Health Interventions: Protocol for a Mixed Methods Study

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Abstract

Background: Metabolic syndrome (MetS) is a growing concern among adult populations in India, particularly among those living in urban, low-income settings. This group is challenged by a combination of risk factors, including an urbanized lifestyle, poor access to health care, and financial limitations, leading to high levels of obesity, diabetes, and hypertension.

Objective: This study aims to address this challenge by designing, developing, and piloting a tailored, mobile-enabled, interactive, digital health intervention to enhance self-management of MetS among individuals living in urban, low-income settings in New Delhi, India.

Methods: The study uses mixed methods, including both quantitative and qualitative data collection, to design and evaluate the effectiveness of the intervention built on a multifactorial model in improving the self-management of MetS. Data will be collected at baseline and 12 months from adults living in urban, low-income settings in New Delhi. The results will contribute to our understanding of the interplay of risk factors in MetS and the impact of tailored digital health interventions in addressing this challenge. The findings will be disseminated to both national and international audiences through peer-reviewed publications.

Results: This study was funded in March 2022 for 3 years. The project started in April 2022. Data collection began in June 2022. The results are expected to be published in 2025.

Conclusions: The study is expected to provide valuable insights into the role of digital health interventions in enhancing the self-management of MetS among urban, low-income populations.

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KEYWORDS

digital health intervention; metabolic syndrome; cardiometabolic risk factors; mixed methods; self-management; urban lifestyle; low-income setting; poverty; community health; India; health promotion

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Introduction

Background and Rationale

Metabolic syndrome (MetS), also known as "Syndrome X," poses a growing threat to public health. By 2020, cardiovascular diseases (CVDs) are projected to be the leading cause of death and disability in India, with 2.6 million deaths expected [1]. Meanwhile, stroke, a major contributor to CVD, is projected to increase to 894 per 100,000 people [2]. MetS is characterized by a cluster of metabolic factors including high blood pressure, impaired glucose tolerance or diabetes, and dyslipidemia (elevated levels of triglycerides and low concentration of high-density lipoproteins) marked by the presence of abdominal obesity [3]. The specific etiology of MetS remains unclear, but the interplay between genetic, behavioral, clinical, and environmental factors such as urbanization, mechanization, and rural-to-urban migration play an important role in its etiology [1,3-5].

Although there are numerous studies on the effects of health interventions for nutrition and physical activity on a single risk factor such as obesity, CVD, and diabetes [6,7], there have been no studies evaluating the impact of multifactorial interventions. The role of social determinants of health in reducing the burden of MetS has not been considered in these studies. As preventive measures, changes through intervention in dietary habits and physical activity are key lifestyle changes recommended by medical literature [8-10]. Despite increased public awareness about noncommunicable diseases (NCDs), the burden of NCDs has not decreased.

The individual behaviors of residents of urban, low-income settings in their environment are crucial in understanding the causes of NCDs and cannot be tackled through policy recommendations based on lumped quantitative data alone. Such methods ignore the interplay of culture, politics, poverty, economics, and actions in urban, low-income conditions and the role of the Sustainable Development Goals [11]. Given the concentration of health programs and policy resources in cities, it is assumed that city inhabitants have more access to services like rehabilitation and health care, and that people with low income living in cities are thus better off than their rural counterparts. This is where the vulnerability of individuals residing in urban, low-income settings arises; the issue of equality becomes critical for urban individuals with low income, who face complicated and debilitating issues such as the inability to pay for products and services, and a lack of social support structures. Urban individuals with low income also have economic hurdles when it comes to making healthier dietary decisions. The accessibility, availability, and affordability of ultraprocessed, high-sugar, high-fat foods in contrast to fresh fruits, vegetables, and meat lead to a high risk for MetS. A few barriers to telehealth interventions identified in the Indian context stand true for urban, low-income populations, such as the digital divide, language barriers, perceived usefulness or preference for face-to-face consultation, perceived ease of use, etc [12]. Food environments, food security, sanitation and hygiene, clean drinking water, etc, are contributing factors to MetS among those residing in urban, low-income settings [13,14].

Prior studies found that individuals treated for diabetes or hypertension only often received medications and do not adopt lifestyle changes such as consuming a healthier diet and increasing physical activity [15]. There is a dearth of effective intervention models that are feasible in Indian, rural, low-resource settings, which face significant challenges owing to poverty, low literacy, and gender norms [16]. Interventions to address social, behavioral, and environmental determinants of MetS and cardiometabolic disorders are less developed [17]. Hence, the creation of science-based, behavior-focused, context-specific, and culturally relevant interventions that take into account the social determinants of health is the solution to address the burden of MetS. Therefore, the proposed study aims to fill existing gaps in understanding how cardiometabolic and environmental factors interact and influence the self-management of MetS among urban, low-income populations.

Study Aim and Objectives

This study aims to design, develop, and pilot-test an interactive, tailored, internet- and mobile-enabled health intervention to enhance the self-management of MetS among individuals living in urban, low-income settings.

The study aims to fulfill the following 3 objectives:

1. To develop a model that examines cardiometabolic risk factors such as diet, physical activity, stress, and sleep and their interplay with the living environment in facilitating the self-management of MetS among adults living in urban, low-income settings in New Delhi;
2. To design and develop an interactive digital health intervention to enhance the self-management of MetS based on the findings of objective 1; and
3. To pilot-test the utility and feasibility of the proposed digital health intervention among adults living in urban, low-income settings to help them self-manage their MetS.

Methods

Study Design and Population

To achieve objective 1, a mixed method approach comprising qualitative and quantitative assessments will be used to develop a model that will describe the interplay between the living environment and other cardiometabolic risk factors such as diet, physical activity, stress, and sleep. In-depth interviews will be conducted among a sample population of 120 participants enrolled from urban, low-income settings across 4 zones of New Delhi (North, South, East, and West).

To achieve objective 2, a quasi-experimental study design will be used with a sample of 80 participants, using a human-centered approach to design and develop an interactive, tailored, mobile- and internet-enabled digital health intervention. The findings of objective 1 will help define the essential elements and features of the proposed digital health intervention.

Objective 3 of the study will be to pilot-test the utility and feasibility of the proposed digital health intervention and to

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measure usage, adherence, satisfaction, and acceptance regarding the proposed digital health intervention. For this, a sample size of 30 people will be enrolled from each of the 8 urban, low-income areas (240 participants) of New Delhi. The methodology is presented graphically in Figure 1.

Figure 1. Flowchart of study methodology. BP: blood pressure; MetS: metabolic syndrome.

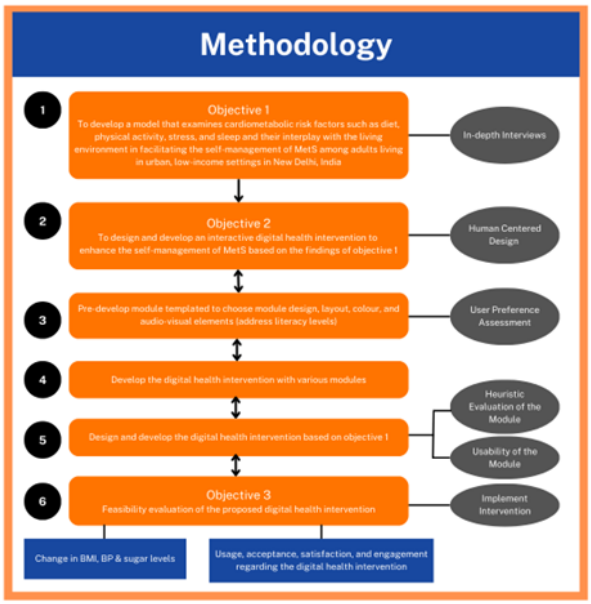

Inclusion and Exclusion Criteria

Eligible participants will include adults (aged 18 years and older) who provided informed consent, have an Android phone, are willing to use technology, are available for follow-up interviews, and have been diagnosed with MetS (presence of 3 of the 5 risk factors of MetS). Individuals who are aged <18 years; have a terminal illness, impaired cognition, presence of coexisting illness documented in the medical record (type 1 diabetes), or self-reported systemic inflammation (eg, rheumatoid arthritis or acute systemic infection); are pregnant or lactating; are involved in other clinical trials or protocols related to MetS; or fail to adhere to study procedures (eg, scheduled surgery, travel plans, or scheduling difficulties that do not permit full participation) will be excluded from the study.

Assessment Variables

The full text of the survey instrument is presented in Multimedia Appendix 1.

Sociodemographic Profile

Data regarding age, income level, employment status, education level, smoking, and alcohol use will be collected. Information about prior use of computers, their frequency of usage, prior use of the internet, and sources of health information will also be captured.

Medical History

The medical history of the participant will be gathered by taking in medical records of the participant, asking for the history of identified NCDs, and taking note of prescriptions and medications used.

Laboratory Assessment

Blood sugar, hemoglobin A_{1c}, and blood pressure levels will be assessed at baseline and after 12 months.

Anthropometric Status

Height, weight, and waist circumference will be collected using a standard technique. BMI will be computed from height and weight measurements.

24-Hour Dietary Recall

A standard protocol will be used to assess the dietary intake of the previous 24 hours. The methodology will include visual aids (photographs of servings) to assist them in accurately reporting food intake.

Dietary Diversity Questionnaire

The Food and Agriculture Organization's Individual Dietary Diversity Score tool [18] will be used to assess diversity in the diets of the individual participants; the tool comprises 16 food groups, of which 9 will be analyzed. Diets comprising foods from ≤3 groups will be categorized as having a low diversity, diets with 4-5 food groups will be categorized as moderate diversity, and those >6 groups will be categorized as diets of high diversity.

Perceived Stress Scale

The Perceived Stress Scale [19] is the most widely used psychological instrument for measuring the perception of stress. It is a measure of the degree to which situations are appraised as stressful.

Physical Activity Assessment

Participants' physical activity will be assessed using the Global Physical Activity Questionnaire [20]. The questionnaire will calculate the total time spent in physical activity for recreation,

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occupation, household work, and transportation in the last 7 days.

MEDFICTS Dietary Assessment Questionnaire

The MEDFICTS Dietary Assessment Questionnaire [21] consists of 8 food categories: meat, eggs, dairy, fried foods, fat in baked goods, convenience foods, fats added at the table, and snacks. It is an efficient tool to quickly assess the adherence of participants to the fat components of a diet and identify those consuming a diet higher in total fat, saturated fat, and cholesterol.

Satisfaction With the Digital Health Intervention

Satisfaction with the digital health intervention will be measured using the Client Satisfaction Questionnaire–8 Question [22]. This 8-item questionnaire is a self-report statement of satisfaction with the intervention.

Acceptance of the Digital Health Intervention

The Technology Acceptance Questionnaire will be used to measure acceptance of the digital health intervention. It comprises 25 questions based on the Technology Acceptance Model with six constructs: (1) perceived ease of use, (2) perceived usefulness, (3) attitude, (4) behavioral intention, (5) self-efficacy, and (6) subjective norm.

Engagement With the Digital Health Intervention

Engagement with the digital health intervention will be measured by the number of weekly log-ins, prompt completion of tasks, and submission of their day-to-day data.

The Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index [23] is a self-rated questionnaire that will be used to assess sleep quality and disturbances over a 1-month time interval. Together, 19 individual items generate 7 “component” scores: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The sum of the scores for these 7 components yields a single global score.

System Usability Scale

The System Usability Scale [24] assesses the appropriateness of the functionality and usability of the digital health intervention. It also assesses the extent to which users view the application as supporting their goals and tasks, as well as checks the interface’s usability.

Health Knowledge, Attitude, and Practice Assessment

The Health Knowledge, Attitude, and Practice Assessment measures the knowledge of MetS, risk factors of comorbidities, attitude to health-related choices, and practice patterns. It is an informative tool, and the measured items are bound to change with time. Deploying the assessment at different time points can help identify key changes and effects of the intervention.

Adherence to Medication

The Medication Adherence Report Scale [25] will be used as a self-reported tool to assess patient adherence to prescribed medication through 5 key questions about forgetfulness, dosage changes, interruption, skipping, and underuse.

Summary of Diabetes Self-Care Activities

Information regarding self-care activities among patients with diabetes will be collected using the revised version of the Summary Diabetes and Hypertension Self-Care Activities Questionnaire [26]. The core questionnaire components, along with a few more questions concerning each of the components and items on medication practices, will be assessed.

Data Analysis Plan

The gathered variable outcome data will be checked for inconsistencies or missing values and will be confidentially stored and retrieved for analysis. The qualitative (in-depth interviews) data will be analyzed by content analyses. Descriptive analyses will report the means and SDs of the data results. 2-tailed t tests will be used to compare the means between categorical and continuous variables. Chi-square analysis will be used to analyze categorical variables. Univariate and bivariate analyses of independent variables will be done. Reporting of results will be done at 95% CI, and $P<.05$ used.

Project Timelines

The detailed project timeline and schedule corresponding to the study objectives are presented in Table 1.

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Table 1. Study timeline.

Objectives, study phases, and tasks	Month							
	1	2-3	4-6	7-14	15-20	31-32	32-33	34-36
Preparatory phase								
1								
Stakeholder meeting	✓							
In-depth interviews		✓	✓					
Analysis of qualitative, in-depth interview data			✓					
Intervention development								
2								
Design and development of human-centered intervention				✓				
Heuristic evaluation				✓				
Usability evaluation of the proposed system				✓				
Refine the proposed, digital health, self-management intervention				✓				
3								
Final deployment of the proposed, digital health, self-management intervention					✓			
Data collection								
4								
Study recruitment					✓			
Baseline and follow-up data collection					✓	✓		
5								
Statistical analysis					✓	✓	✓	
Report writing and manuscript preparation							✓	✓

Quality Assurance

Data collection and entry will be done by trained field staff following standard techniques and protocols. Training sessions for the field workers will be held to acquaint the data collection team with the study aim, objectives, study area, and inclusion/exclusion criteria. Information will also be given for study instruments, anthropometric data collection, in-depth interviews (engagement with the respondent and probing), and informed consent (for data collection, audio recording, and pictures). To ensure efficiency and high-quality data collection and processing, weekly meetings with the field and research staff will be held. A log of all data collected will be maintained, and weekly data checks will be done.

Ethical Considerations

The study was approved by the Indian Council of Medical Research—National Institute of Pathology Institutional Human Ethics Committee in January 2022 (approval NIP-IEC/29-12-2021/05/01R1). The study will be conducted according to the Declaration of Helsinki, as it involves human participants [19]. Written informed consent to participate in the study will be obtained from each of the selected participants. Audio recording of consent will be done for individuals with limited education. Complete data confidentiality and anonymity of study participants will be ensured. Study consent will be available in English and a local Indian dialect. Data will be collected by trained data collectors electronically using tablet computers and saved on the servers.

Expected Outcomes

The study outcomes include the enhancement of self-management of MetS among individuals living in urban and low-income slum settings. The study will identify influencing risk factors on MetS and examine the role of digital interventions to address the risks. The authors also expect the study to increase self-efficacy and the knowledge, attitudes, and practices related to self-management of diabetes, hypertension, and other risk factors of MetS among individuals living in urban, low-income settings. The study results will be disseminated at various levels, including scientific journal publications, conference proceedings, etc.

Results

This study was funded in March 2022 for 3 years. The project started in April 2022. Data collection began in June 2022. The results are expected to be published in 2025.

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Discussion

The paper aims to address the growing threat of MetS in India, where despite numerous studies on the effects of health interventions, there have been no evaluations of multifactorial interventions, and the role of social determinants of health in reducing the burden of MetS has not been considered. The proposed digital health intervention model will use the principles of human-centered approach, involving users' input throughout the design and development of the intervention. The authors aim to fill the gap in understanding the interaction between cardiometabolic and environmental factors and self-management of MetS among urban, low-income populations. The study results are expected to increase the knowledge, attitudes, and practices related to self-management of MetS and other risk factors among urban, low-income populations. However, the study has limitations, such as being limited to urban, low-income populations only and facing challenges in implementing interventions, which may limit its generalizability. The findings from the study will contribute to understanding of the role of digital health interventions in enhancing the self-management of MetS, which will greatly impact public health at large.

Acknowledgments

The authors would like to acknowledge the funding and support of the Indian Council of Medical Research.

Data Availability

The data supporting this study's findings are available upon request from the corresponding author.

Authors' Contributions

All authors have contributed to this manuscript. All authors provide their consent to the publication of this protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Full text of the survey questionnaire.
[DOCX File , 155 KB - resprot_v14i1e40144_app1.docx]

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Abbreviations

CVD: cardiovascular disease
MetS: metabolic syndrome
NCD: noncommunicable disease

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Protocol

Efficacy of Solifenacin, Mirabegron, and Combination Therapy in Children With Daytime Urinary Incontinence (BeDry): Protocol for a Randomized Single-Blinded Controlled Trial

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Abstract

Background: According to International Children's Continence Society, the first-line treatment of children with daytime urinary incontinence is standard urotherapy, eventually followed by pharmacotherapy of anticholinergics. The effect of medical treatment is sparsely investigated and has been investigated primarily in nonrandomized trials.

Objective: The primary objective of this trial is to evaluate if (1) combination therapy of solifenacin and mirabegron in low doses is superior to monotherapy of solifenacin in high dose and if (2) combination therapy of mirabegron and solifenacin in low doses is superior to monotherapy of mirabegron in high dose in the treatment of daytime urinary incontinence among children aged 5-14 years who are noncomplete responders to monotherapy of solifenacin in low dose or monotherapy of mirabegron in low dose. The secondary objective is to evaluate the treatment response of combination therapy of solifenacin and mirabegron in low doses, monotherapy in high doses, and monotherapy in low doses as supplementary comparisons. Additionally, the secondary objective is to evaluate the side effects, safety, and tolerability of the medical treatment as well as the effect of the treatment on the well-being and quality of life.

Methods: Children aged 5-14 years diagnosed with daytime urinary incontinence refractory to standard urotherapy will be randomized 1:1:1:1 to 4 treatment groups. Initially, 2 groups will receive solifenacin 5 mg and 2 groups will receive mirabegron 25 mg. After 6 weeks, noncomplete responders will receive add-on treatments according to their primary randomization group. Group 1A will receive solifenacin 5 mg and add-on solifenacin 5 mg, group 1B will receive solifenacin 5 mg and add-on mirabegron 25 mg, group 2A will receive mirabegron 25 mg and add-on mirabegron 25 mg, and group 2B will receive mirabegron 25 mg and add-on solifenacin 5 mg. The total treatment period will be 18 weeks. The primary end point measure is treatment response assessed by change from visit 2 to the end of the study, according to the number of wet days per 7 days by DryPie.

Results: The BeDry study was approved by Clinical Trials in the European Union on June 12, 2024. Recruitment began on June 27, 2024, and will continue until 236 patients are included, which is expected to occur by September 2026. As of April 2025, 75 participants are included.

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Conclusions: This trial has the potential to optimize the medical treatment of children with daytime urinary incontinence, shorten the treatment period, diminish the side effects, and minimize unnecessary medical expenses.

Trial Registration: Clinical Trials in the European Union EUCT 2023-510187-13-00; https://tinyurl.com/2hva7ph8; ClinicalTrials.gov NCT06551246; https://clinicaltrials.gov/study/NCT06551246

International Registered Report Identifier (IRRID): PRR1-10.2196/63588

(JMIR Res Protoc 2025;14:e63588) doi:10.2196/63588

KEYWORDS

urinary incontinence; overactive bladder; solifenacin; mirabegron; children; teenager; pediatric; protocol; randomized controlled trial; pharmacotherapy; urotherapy; monotherapy; Denmark; outpatient clinics; multicenter

Introduction

Background and Rationale

Daytime urinary incontinence (DUI) is affecting up to 1 out of 5 children aged 5-7 years [1-4] and 4.5% of the children and adolescents aged 11-16 years [3,4]. Urinary incontinence is usually a physically benign condition [2]. Nevertheless, it is associated with a considerable psychological burden, as it leads to poor self-esteem and quality of life among the affected children, leading to psychological failure to thrive [5,6].

The most common cause of DUI is an overactive bladder (OAB) [2,7]. The International Children's Continence Society defines OAB as a condition with urinary urgency with or without DUI among children and adolescents without competitive pathology explaining the symptoms such as neurogenic detrusor overactivity or urinary tract infection [8].

Treatment often requires a multidisciplinary effort involving contributors in the health care system, home, and day care/school. The first-line treatment of urinary incontinence is urotherapy, aiming at improving the bladder reservoir function and the voluntary bladder control [2]. If urotherapy is insufficient for achieving continence, the second-line treatment in most clinical settings is addition of pharmacological treatment aiming at suppressing smooth bladder muscle contraction [2].

Solifenacin and mirabegron act on the bladder through different mechanisms. Solifenacin is an antimuscarinic agent that selectively inhibits M2/M3 muscarinic receptors in the bladder [2]. Mirabegron is a β3-adrenergic receptor agonist that stimulates β3 receptors in the detrusor muscle. While solifenacin decreases bladder contractions by inhibiting parasympathetic activity, mirabegron promotes bladder relaxation through sympathetic stimulation [9].

In Denmark, the current pharmacological therapy consists of an antimuscarinic, namely, solifenacin, or a β3-adrenoreceptor agonist, namely, mirabegron. If monotherapy of solifenacin or mirabegron is without sufficient effect, the child is treated with a combination of solifenacin and mirabegron. According to expert opinions, the current pharmacological treatment strategy in Denmark typically follows this sequence: initially, solifenacin is prescribed at 5 mg daily, with an increase to 10 mg depending on the therapeutic response. If monotherapy in high dose proves insufficient, add-on therapy with mirabegron at 25 mg daily is introduced and may be increased to 50 mg depending on the treatment effect. Occasionally, mirabegron monotherapy is used as an alternative second step before combination therapy. Solifenacin and mirabegron are widely used off-label in the pediatric population, and only a few studies have dealt with the efficacy and tolerability of these agents [10-14]. Only 1 study has evaluated combination therapy [14].

Since the pharmacological approach is widely used off-label in pediatric departments, an evidence-based treatment approach of pharmacological therapy is highly needed. This study aims to evaluate the efficacy, safety, and tolerability of solifenacin, mirabegron, and a combination of solifenacin and mirabegron in pediatric patients with DUI.

Objectives

We hypothesize that combination therapy with solifenacin 5 mg and mirabegron 25 mg is effective in the reduction of DUI episodes over an 18-week treatment period compared to baseline and that combination therapy in low dose is superior to high dose of either solifenacin 10 mg or mirabegron 50 mg.

The primary objective is to evaluate the effect of high dose anticholinergic monotherapy (solifenacin 10 mg) compared to that of low dose combination therapy of anticholinergic and β3-adrenoreceptor agonist (solifenacin 5 mg and mirabegron 25 mg) and the effect of high dose β3-adrenoreceptor agonist monotherapy (mirabegron 50 mg) compared to that of low dose combination therapy of anticholinergic and β3-adrenoreceptor agonist (solifenacin 5 mg and mirabegron 25 mg) for the treatment of DUI in children aged 5-14 years who are noncomplete responders to standard urotherapy and to low dose anticholinergic or β3-adrenoreceptor agonist monotherapy.

The secondary objective is to compare the treatment response to combination therapy of solifenacin and mirabegron in low doses, monotherapy with solifenacin or mirabegron in high doses, and monotherapy with solifenacin or mirabegron in low doses. Additionally, the secondary objective is to evaluate the side effects, safety, and tolerability of the medical treatment as well as the effect of the treatment on the well-being and quality of life.

Methods

Study Design

The BeDry study is designed as a multicenter, randomized, single-blind, controlled clinical trial. Included children will be randomized 1:1:1:1 to one of the 4 treatment groups. The study duration for each participant will be 18 weeks and encompasses

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3 visits to the outpatient clinic. See Figure 1 for an overview of the study design. Children aged 5-14 years who are diagnosed with OAB and DUI will be included if they meet the criteria for inclusion. This trial is in accordance with the CONSORT (Consolidated Standards of Reporting Trials) checklist (Multimedia Appendix 1). This study is registered at the research inventory of the Regions of Denmark (1-16-02-210-24) and at Aarhus University (ARG-2024-731-23829). Recruitment will take place from pediatric departments at 5 outpatient clinics in Denmark: Aarhus University Hospital, Aalborg University Hospital, Regional Hospital Kolding, Regional Hospital Esbjerg, and Gødstrup Hospital.

Figure 1. Study flowchart.

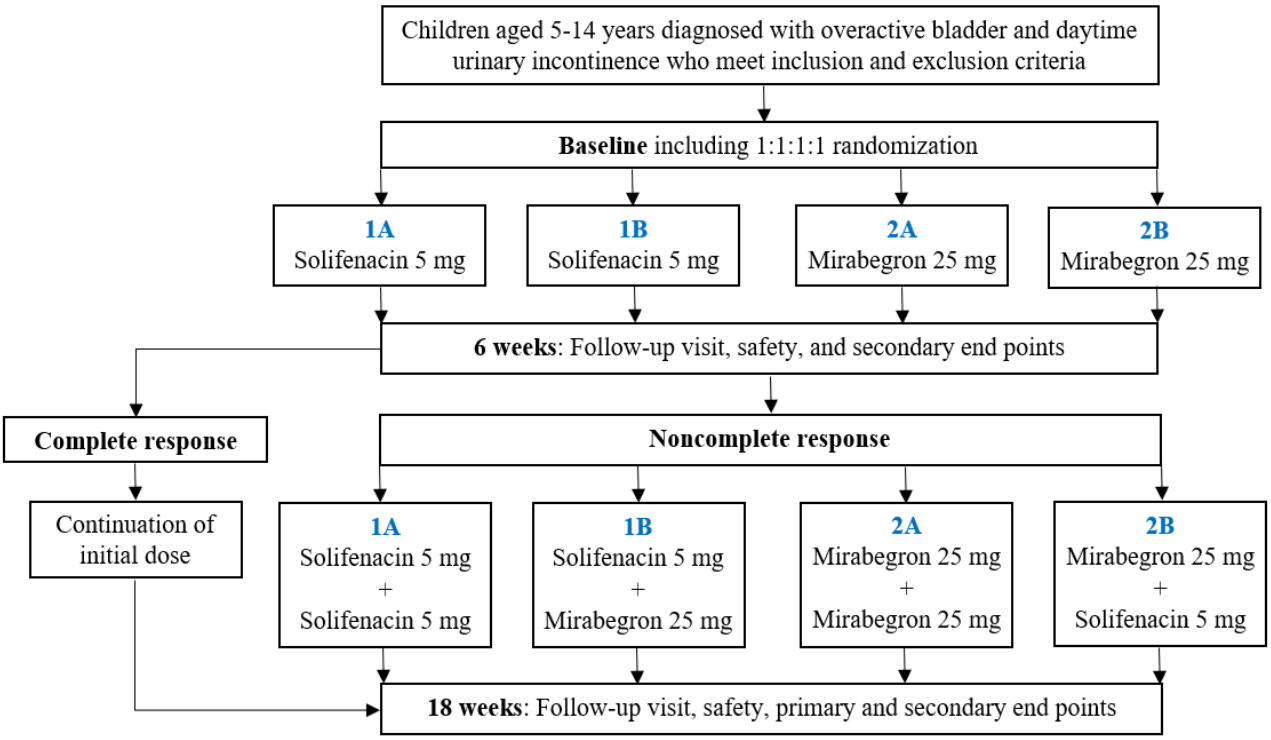

Eligibility Criteria

The inclusion and exclusion criteria for the participants in this study are provided in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- The participants' custody holders must voluntarily sign and date an informed consent prior to initiation of any study-specific procedures.
- Age 5-14 years (inclusive) at the time of inclusion.
- Overactive bladder as per International Children's Continence Society criteria.
- At least 2 daytime urinary incontinence episodes per week.
- Inadequate effect of at least 4 weeks of urotherapy (nonpharmacological treatment).
- No previous treatment with solifenacin, mirabegron, or bladder/sphincter botulinum toxin injections.
- No current constipation as per Rome IV criteria or fecal incontinence (laxative treatment is accepted).
- Per the investigator's judgment, the participant can swallow or can learn to swallow the study medication.

Exclusion criteria

- Inability of the patient or legal guardian to understand the Danish written and oral information.
- Known or suspected hypersensitivity to study medication.
- Any contraindication to the use of the study medication.
- Known urogenital anatomical abnormalities affecting lower urinary tract function.
- Known kidney or bladder stones.
- Known diabetes insipidus.
- Ongoing symptomatic urinary tract infection.
- Recurrent urinary tract infection or ongoing prophylactic antibiotic treatment.
- Known QTc prolongation, QTc >460 milliseconds, or risk of QTc prolongation (hypokalemia, exercise-induced syncope, or familial long QT syndrome).
- Other significant electrocardiogram abnormalities.
- Known hypertension.
- ≤3 daily voiding, evaluated by a 48-hour frequency-volume chart.
- Uroflowmetry is indicative of pathology other than overactive bladder (staccato-shaped, interrupted-shaped, or plateau-shaped curve).
- Postvoid residual urine >50 mL after double voiding.
- Dipstick hematuria (≥2+ erythrocytes) or macroscopic hematuria.
- Pregnancy or breastfeeding.
- Females of childbearing potential.
- Ongoing constipation according to Rome IV criteria, which is intractable to medication or fecal incontinence.
- Inability to swallow study medication.
- Use of any medication during the study period, except permitted medication.

Intervention

Eligible children will be randomized 1:1:1:1 to one of the following 4 treatment groups.

1. Treatment group 1A: Solifenacin 5 mg (and if noncomplete response after 6 weeks, add-on solifenacin 5 mg).
2. Treatment group 1B: Solifenacin 5 mg (and if noncomplete response after 6 weeks, add-on mirabegron 25 mg).
3. Treatment group 2A: Mirabegron 25 mg (and if noncomplete response after 6 weeks, add-on mirabegron 25 mg).
4. Treatment group 2B: Mirabegron 25 mg (and if noncomplete response after 6 weeks, add-on solifenacin 5 mg).

All participants will initially receive low dose monotherapy. Two groups will receive solifenacin 5 mg and 2 groups will receive mirabegron 25 mg. After 6 weeks, the treatment outcome will be evaluated based on the number of wet days per week assessed by DryPie [15] (see Figure 2). Noncomplete responders will receive add-on treatment according to their primary randomization group; group 1A will receive solifenacin 5 mg and add-on solifenacin 5 mg, group 1B will receive solifenacin 5 mg and add-on mirabegron 25 mg, group 2A will receive mirabegron 25 mg and add-on mirabegron 25 mg, and group 2B will receive mirabegron 25 mg and add-on solifenacin 5 mg. Participants who show complete response within 6 weeks of treatment will continue the initial low dose monotherapy for

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the rest of the study period. Total treatment period will be 18 weeks.

Figure 2. Danish translation of DryPie, developed by Bower et al [15]. Green: dry; yellow: wet underpants; red: wet trousers; blue: wet socks; Mandag: Monday; Tirsdag: Tuesday; Onsdag: Wednesday; Torsdag: Thursday; Fredag: Friday; Lørdag: Saturday; Søndag: Sunday.

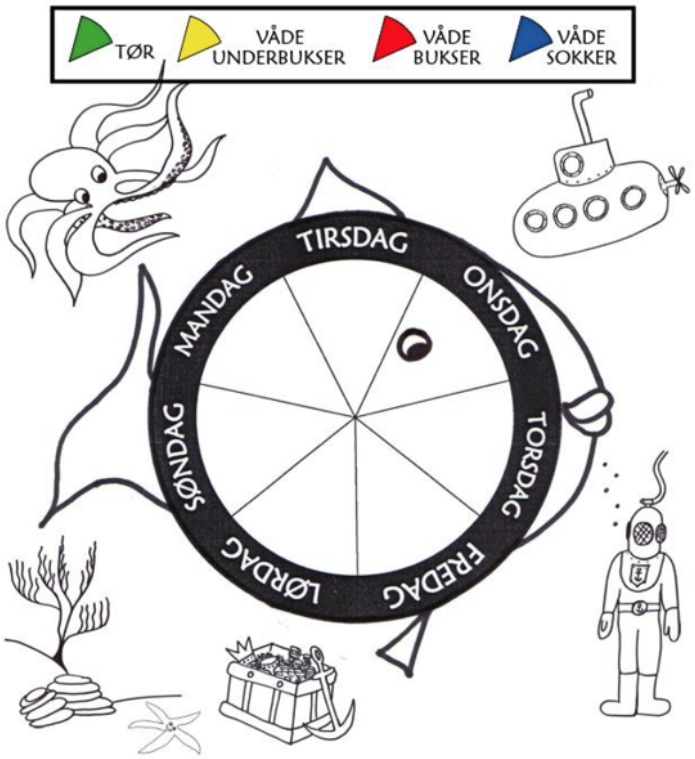

Withdrawal of Participants and Criteria for Discontinuation of Study

A study participant should be withdrawn from the study if at any time one of the following criteria is met:

1. It is the wish of the participant (or their parents/legally acceptable representative) for any reason (withdrawal of informed consent).
2. The discretion of the investigator for safety or behavioral reasons.
3. Severe noncompliance with protocol as judged by the investigator.
4. The investigator judges it necessary due to medical reasons.
5. Female participants who become pregnant should immediately discontinue study drug administration and will be discontinued from the study (female participants with childbearing potential are excluded from the study).
6. The participant experiences adverse reactions, which endanger the health of the participant, require emergency treatment, are incompatible with the continuation of the study, or are expected to influence the results of the study.
7. Participants with a condition or a situation that, in the investigator's opinion, may put the participant at significant risk or may interfere significantly with the participant's participation in the study will be discontinued from the study.
8. Participant with any other condition or situation that in the investigator's opinion may be valid for discontinuation from the study.

Primary End Point

The primary end point measure is treatment response assessed by change from visit 2 to end of study, according to the number of wet days per 7 days by DryPie.

Secondary End Points

Secondary outcome measures change from baseline across the 18-week treatment period in the following parameters.

1. Treatment response, according to the number of wet days per 7 days by DryPie.
2. Change in incontinence severity score per 7 days assessed by DryPie.
3. Change in urge severity quantified by Bower Visual Analog Scale (VAS) Urgency Scheme [15].
4. Change in volume of maximum voided volume.
5. Change in volume of age-standardized maximum voided volume.
6. Change in volume of average voided volume.
7. Change in micturition frequency.
8. Change in total score of pediatric incontinence questionnaire (PinQ).
9. Change in total score of World Health Organization-Five Well-Being Index (WHO-5).

Safety Outcomes

Safety outcome measures encompass the following.

1. Adverse event (AE), serious adverse event (SAE), and Suspected Unexpected Serious Adverse Reaction (SUSAR) monitoring.

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2. Identifications of electrocardiogram abnormalities before entering the study and after 6 weeks.
3. Increase in blood pressure and pulse beyond the 95th percentile.
4. Change in ultrasound-assessed postvoid residual (PVR) urine from baseline to 18 weeks.
5. Identification of urinary tract infection by urine dipstick and verified by routine urine culture.

Procedures During Pharmacotherapy

The participant timeline is illustrated in Table 1.

Table 1. Schedule of the assessments.

	Visit 1: baseline	Visit 2	Visit 3: end of study or premature discontinuation
Weeks (days)	0	6 (42)	18 (126)
Visit scheduling window (days)		(SD 5)	(SD 5)
Informed consent	✔		
Inclusion and exclusion criteria	✔		
Background information including demographics	✔		
Registration of concomitant medication	✔	✔	✔
Urotherapy	✔	✔	✔
Randomization	✔		
Dispensation of study medication	✔	✔	
Compliance		✔	✔
Drug accountability		✔	✔
Registration of side effects as reported in the product summary		✔	✔
Registration of adverse events/serious adverse events/suspected unexpected serious adverse reaction		✔	✔
Clinical examination	✔		
Weight and height	✔		
DryPie	✔	✔	✔
48-hour frequency-volume chart	✔	✔	✔
Bower Visual Analog Scale Urgency	✔	✔	✔
Uroflowmetry	✔		✔
Postvoid residual urine	✔	✔	✔
Blood pressure and pulse	✔	✔	✔
Electrocardiogram	✔	✔	
Urine dipstick test	✔	(✔)[a]	(✔)[a]
Pediatric Incontinence Questionnaire	✔		✔
World Health Organization-Five Well-Being Index	✔		✔

[a]Performed in case of symptoms of urinary tract infection.

Visit 1 (Day 0/Week 0)

Participants will enter the study after parents/parental custody holders have signed the informed consent. The participant and parents will be instructed in filling in a 48-hour frequency-volume chart (one filled out in the last 2 months prior to visit 1 is accepted) and DryPie for 1 week prior to visit 1. Background information (including age, gender, DUI history, urotherapy, any concomitant medication present and previously, any other diseases, or psychiatric diagnosis) will be obtained. A clinical examination, including anthropometric measurements, measurement of blood pressure and pulse, uroflowmetry (or one performed the last 6 months prior visit 1) with ultrasound-assessment of PVR urine (or one performed the last 2 months prior visit 1), a urine dipstick, and an electrocardiogram, will be performed. Moreover, Bower VAS Urgency will be filled out. The quality of life and well-being of the participating children will be assessed using PinQ and WHO-5. The questionnaires will be filled out electronically at the outpatient clinic or at home with help from the parents or parental custody holders. Participants will be instructed in continuing urotherapy during the study. The participant will be randomized 1:1:1:1 to one of the 4 treatment groups described above. The participants will be unblinded and receive study

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medications according to their unique participant number. An unblinded study nurse can guide if necessary.

Visit 2 (Day 42/Week 6)

The participant will be instructed to bring a 48-hour frequency-volume chart and the DryPie for 1 week, filled in prior to visit 2. Moreover, Bower VAS Urgency will be filled out during the visit. A clinical examination, including measurement of blood pressure and pulse, ultrasound-assessment of PVR urine, safety electrocardiogram, and a urine dipstick test (in case of symptoms of urinary tract infection), will be performed. Registration of side effects as reported in the product summaries will be performed. Any AE, SAE, or SUSAR will be registered and handled according to Good Clinical Practice.

The treatment outcome will be evaluated based on the number of wet days per week assessed by DryPie. Based on the International Children's Continence Society's definitions of treatment outcome, the participants in group 1 (solifenacin 5 mg) and group 2 (mirabegron 25 mg) will be treated as follows.

1. Level 1: If complete response (100% reduction in number of wet days), then maintain current treatment level.
2. Level 2: If not complete response (<100% reduction in number of wet days), then treatment 1A group receives solifenacin 5 mg + solifenacin 5 mg, treatment 1B group receives solifenacin 5 mg + mirabegron 25 mg, treatment 2A group receives mirabegron 25 mg + mirabegron 25 mg, and treatment 2B group receives mirabegron 25 mg + solifenacin 5 mg.

The dose titration will be notified in the electronic patient journal, and as the study is blinded by investigators, it will only be noted whether the participant is treated with study medication level 1 or level 2. An unblinded nurse will guide and answer questions to participants in case of dose titration. The compliance to the study medication will be evaluated by an unblinded project nurse at every site. Compliance will be evaluated by counting the remaining tablets in the container on every visit. Three categories will be used: ≥80%, 50%-79%, or <50%.

The participant should contact the outpatient clinic by phone between visit 2 and visit 3 in case of any AE, SAE, or SUSAR. In case dose titration to level 2 results in increased PVR urine, symptoms of urinary tract infections, positive urine dipstick, side effects, or development of hypertension, the investigator can adjust the dose to the initial dose (level 1).

Visit 3 (Day 126/Week 18)

The participant will be instructed to bring a 48-hour frequency-volume chart and the DryPie for 1 week, filled in prior to visit 3. Moreover, Bower VAS Urgency will be filled out during the visit. A clinical examination, including measurement of blood pressure and pulse and ultrasound-assessment of PVR urine, will be performed. In case of symptoms of urinary tract infection, a urine dipstick test will be performed. Side effects will be registered as reported reference documents of side effects, as reported in the product summaries. Any AE, SAE, or SUSAR will be registered and handled according to Good Clinical Practice. The quality of life at the end of the treatment will be evaluated using PinQ and WHO-5. The compliance to the study medication will be evaluated by an unblinded project nurse at every site by counting the remaining tablets in the container. At the end of the study or in case of premature discontinuation, the child continues at the outpatient clinic at the respective study site to determine the future treatment. An unblinded medical doctor at the study site will decide the future treatment.

Randomization Procedure

Randomization will be performed in the REDCap (research electronic data capture) portal and will occur centrally. An electronic case report form will be built for the study data to be entered. The randomization will be performed in a separate module, and the randomization list will be maintained by the unblinded nurse at the Department of Pediatric and Adolescent Medicine, Gødstrup Hospital, until the end of the study.

Following written informed consent, randomization is stratified by 1:1:1:1 allocation within each stratum by using predefined block sizes for sites. Block randomization is by a computer-generated random number list. The investigators and all other medical staff are kept blinded to the allocation, except for the unblinded study nurses. The unblinded study nurse at each study center will have a unique account for the electronic case report form that allows randomization and seeing which product needs to be prepared for the study participant. The blinded study team will not be able to see the allocation in the electronic case report form. The participants will be unblinded and receive study medication according to their unique participant number.

Blinding and Unblinding

This study is single-blinded, and the study participant will receive medications delivered from the study site. The investigator does not know which treatment the individual participant receives. Participants will be informed that they are not allowed to reveal the study medication to the blinded investigator, and an unblinded nurse will guide and answer questions to the participants in case of dose titration. The children and their parents will be asked for possible side effects at every visit and will always be able to contact a medical doctor or an investigator when a side effect is suspected. The participant should contact the outpatient clinic by phone between visit 2 and visit 3 in case of any AE, SAE, or SUSAR. All participating children will be provided with a trial card on which the investigational product, the trial number, investigator's name, and a 24-hour emergency contact number are stated. Unblinding is possible in case of an SAE or SUSAR. If an investigator needs to unblind a study participant due to a safety issue, the investigator will be able to do this in REDCap. Unblinding will be performed according to Good Clinical Practice guidelines. Any unblinding will be logged per user, with a timestamp. The investigator will keep the rest of the study team and study participant blinded, unless the nature of emergency requires that all parties should be informed. The sponsor will be notified of the unblinding.

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Statistical Analysis

The primary outcome will be analyzed as follows. First, the change from visit 2 across the 18-week pharmacological treatment period in the number of wet days per week assessed by DryPie will be assessed for all the groups. Second, treatment response (either nonresponse or response) will be assessed for all the groups. Third, to analyze and compare the treatment groups, the Pearson chi-square test will be used. The secondary outcomes of treatment response across 18 weeks will be analyzed as follows. First, change from baseline across the 18-week pharmacological treatment period in the number of wet days per week assessed by DryPie will be assessed for all the groups. Second, treatment response (either nonresponse or response) will be assessed for all the groups. Third, to analyze and compare the treatment groups, the Pearson chi-square test will be used. Additionally, secondary outcomes will be reported as follows. Continuous data will be reported as median with interquartile range for nonnormally distributed data and as mean (SD) for normally distributed data, and the assumption of normally distributed data will be checked by Q-Q plots. Categorical data will be presented as number (%). Safety parameters (treatment-emergent AEs, SAEs, vital signs, electrocardiogram, PVR urine volume, urinary dipstick) will be summarized using descriptive statistics.

Sample Size

The estimates for the sample size calculations are based on 1 placebo-controlled trial, prospective studies, and retrospective studies [10-12,14,16]. We expect 15% of the children to have a complete response to treatment with low dose solifenacin 5 mg and 15% of the children to have a complete response to treatment with low dose mirabegron 25 mg. Of the remaining children (100% – 15% = 85%) who are noncomplete responders to low dose monotherapy, we expect 20% to have complete response to solifenacin 10 mg, 20% to have complete response with mirabegron 50 mg, and 50% to have complete response to combination therapy (solifenacin and mirabegron).

With the abovementioned estimations, we assessed a proportion of 32% (15% with complete response to solifenacin 5 mg + 85% noncomplete responders to low dose monotherapy solifenacin 5 mg × 20% with complete response to solifenacin 10 mg) of the participants randomized to solifenacin 10 mg will have a complete response. In addition, we assessed a proportion of 57.5% of the participants randomized to solifenacin 5 mg and mirabegron 25 mg. The sample size calculation was based on solifenacin 10 mg versus combination therapy and mirabegron 50 mg versus combination therapy. The estimated sample sizes for a 2-sample proportions test were calculated by Pearson chi-square test. With a power of 80% and for obtaining a statistically significant (α=.05) difference between solifenacin 10 mg and combination therapy of solifenacin 5 mg and mirabegron 25 mg, the sample size was calculated by a 2-sample proportions test.

To obtain a power of 80% and with 2-sided statistical significance level of 5%, given the probability of complete response to solifenacin 10 mg is 32% (π_1=0.32) and the probability of complete response to combination therapy of solifenacin 5 mg and mirabegron 25 mg is 57.5% (π_2=0.575), the required sample size is 59 in each group (1A, 1B, 2A, 2B). The sample size included the expected children who will continue the initial dose. In total, the required sample size is 236 participants.

Ethics Approval

This study is authorized by The Danish Medicines Agency and The Danish Health Research Ethics Committee and registered at Clinical Trials in the European Union (EU CT 2023-510187-13-00).

Ethical Considerations

All pharmacological side effects will be handled in accordance with the Danish legislation. No risk or unknown side effects are expected from urotherapy, medical treatment, or withdrawal. No risks are expected by clinical examination and paraclinical measurements. The therapeutic potential for future patients justifies the project to be performed. Participation in this study will not lead to any disadvantages for the patient in their treatment. This study will be conducted in accordance with the protocol, applicable regulatory requirements according to Good Clinical Practice, and the ethical principles of the Declaration of Helsinki. Information regarding the participants is protected and anonymized according to the General Data Protection Regulation and the actual law. The study participants and their families will not be economically compensated for participating in this study; however, study medication costs will be covered throughout the entire study period.

Safety Evaluations

Safety evaluations include AE, SAE, and SUSAR monitoring, registration of side effects as reported in the product summary, blood pressure, pulse, ultrasound-assessed PVR, and identification of urinary tract infection by urine dipstick and verified by routine urine cultivation and electrocardiogram. The listed safety parameters, except electrocardiograms, will be monitored at every visit during the study treatment administration, and urine dipstick will be performed at visit 2 and 3 if a participant reports symptoms of a urinary tract infection. Electrocardiograms will be monitored at baseline and at visit 2. The children and their parents will be asked for possible side effects at every visit and will always be able to contact a medical doctor or an investigator when a side effect is suspected. All participating children will be provided with a trial card on which the investigational product, trial number, investigator's name, and a 24-hour emergency contact number are stated.

Results

The BeDry study was approved by Clinical Trials in the European Union on June 12, 2024. Recruitment began on June 27, 2024, and will continue until 236 patients are included, which is expected to occur by September 2026. As of April 2025, 75 participants are included. The results will be submitted to Clinical Trials in the European Union and ClinicalTrials.gov within 1 year after the end of the trial.

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Discussion

Anticipated Findings and Importance of This Research

Solifenacin is approved for the treatment of neurogenic detrusor overactivity in children and adolescents aged 2-18 years [17,18]. Though not approved for the treatment of idiopathic OAB in children, solifenacin is widely used off-label. The efficacy of solifenacin was found superior to placebo in terms of average voided volume per miction, daily maximum voided volume, and micturition frequency adjusted for total voided volume [11]. The efficacy of solifenacin by decreasing number of incontinence episodes per day was demonstrated by non–placebo-controlled prospective studies [19,20]. The safety and tolerability of solifenacin were found to be high, also by long-term use [12]. Predominantly, side effects such as xerostomia, constipation, blurred vision, headache, and fatigue were reported [11,19,20]. A few participants experienced more severe side effects, encompassing QT prolongation, severe constipation, fecal incontinence, and aggressive behavior, some of whom withdrew from the study due to the intolerable side effects and for safety reasons.

Mirabegron has been approved as an alternative to antimuscarinics in children with neurogenic detrusor overactivity [21]. In the pediatric population, mirabegron is used off-label in children with OAB, either as monotherapy or in combination with antimuscarinics [13,14]. The efficacy of mirabegron compared to that of placebo has been elucidated among children [10]. Furthermore, mirabegron has high safety and tolerability in the pediatric population [22]. Reported side effects [22] were blurred vision, constipation, abdominal cramps, and these were transient. No additional risk to the study participants is anticipated with the use of solifenacin and mirabegron.

A favorable safety profile was observed. In adult populations, the efficacy benefits of solifenacin and mirabegron outweigh the risks. This favorable benefit-risk ratio supports the further development of solifenacin and mirabegron in the treatment of pediatric populations with DUI.

With our protocol, we aim to investigate if treatment with a combination of solifenacin and mirabegron in low dose is effective in the reduction of DUI episodes over an 18-week treatment period compared to baseline and if combination therapy in low dose is superior to maximum dose of either solifenacin or mirabegron in children with noncomplete response to urotherapy and low dose monotherapy of solifenacin or mirabegron.

The results from our study will ensure evidence-based knowledge about the off-label treatment approach. By optimizing the stepwise medical treatment approach, the treatment can be shortened, side effects can be diminished, and unnecessary medical expenses can be minimized for individual families and the society both nationally and internationally.

Compared to experience from daily practice, randomized controlled trials allow for the systematic evaluation of both the safety and efficacy of treatments. This is crucial in pediatrics, where considerations such as appropriate dosing, potential side effects, and long-term outcomes need to be carefully assessed to ensure the well-being of children receiving treatment.

Strengths and Limitations

The strengths of our study are the randomized single-blinded and controlled design with multicenter inclusion at 5 pediatric departments in Denmark. The investigators are blinded, and the participants know the treatment. This could cause a possible risk of affecting the final outcome of the study. Hence, no placebo effect is introduced. With single blinding, the investigators are not biased while treating the patients nor when interpretating data.

This study is embedded into daily clinical practice and reflects standard practice in many aspects other than randomization and collection of data. Usually, mirabegron is add-on pharmacotherapy if anticholinergics are not fully effective in treating DUI. The pragmatic design ensures timely inclusion of patients and reflects daily clinical practice where pharmacotherapy is initiated after inadequate effects of urotherapy.

The main limitation is compliance to the study medication over 18 weeks. We aim to reduce this risk by early termination of children with severe compliance issues (as <50%) during the treatment period. Compliance to the study medication is determined by counting the remaining tablets in the containers at each visit. This is performed by an unblinded nurse.

The risk of unblinding the blinded investigators is present, but we expect to reduce the risk by introducing unblinded study staff as project nurses, as well as the participants and their parents are instructed to not inform the investigator about the medication. Another limitation is the fixed dose of the combination therapy, thereby introducing a potential risk of undertreating the children allocated to the intervention group.

Conclusion

If the low dose of combination therapy is superior to the high dose of monotherapy, children with DUI will benefit significantly from the new treatment in terms of shorter treatment periods, fewer side effects, and possibly a better quality of life. This trial has the potential to optimize the medical treatment approach, shorten the treatment period, diminish the side effects, and minimize unnecessary medical expenses. Due to predefined criteria for discontinuation of the allocated therapy, we expect the risk of treatment failure to be minimal. The results are expected to influence the treatment strategy of children with DUI worldwide.

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Acknowledgments

Generative artificial intelligence tools were not used for this study. This study is partly financed by grants from the Danish Regions (390,000 DKK), the Health Science Research Fund of Central Denmark Region (444,700 DKK), and the NIDO fund (175,000 DKK) and by economic support from the involved pediatric departments (777,099 DKK). None of the study personnel have any economic interests in this study.

Data Availability

The data sets generated during this study are planned to be available on reasonable request.

Authors' Contributions

Conceptualization: A-KMS, SH, KT, KK, AEO, LB
Data curation: A-KMS, LB
Formal analysis: A-KMS, LB
Funding acquisition: A-KMS, SH, LB
Investigation: A-KMS, SH, KK, LB
Methodology: A-KMS, SH, KK, AEO, LB
Project administration: A-KMS, LB
Resources: A-KMS
Supervision: SH, KK, JVB, AEO, LB
Validation: A-KMS, SH, KK, JVB, AEO, LB
Visualization: A-KMS
Writing – original draft: A-KMS, SH, KK, AEO, LB
Writing – review & editing: A-KMS, SH, KT, KK, JVB, AEO, LB

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT (Consolidated Standards of Reporting Trials) checklist.
[PDF File (Adobe PDF File), 164 KB - resprot_v14i1e63588_app1.pdf]

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Abbreviations

AE: adverse event
CONSORT: Consolidated Standards of Reporting Trials
DUI: daytime urinary incontinence
OAB: overactive bladder
PinQ: pediatric incontinence questionnaire
PVR: postvoid residual
REDCap: research electronic data capture
SAE: serious adverse event
SUSAR: suspected unexpected serious adverse reaction
VAS: Visual Analog Scale
WHO-5: World Health Organization-Five Well-Being Index

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Protocol

Corticospinal Intermittent Theta Burst Stimulation Propelling Sensorimotor Function Recovery in Complete Spinal Cord Injury: Protocol for a Randomized Controlled Trial

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Abstract

Background: Intermittent theta burst stimulation (iTBS) is a noninvasive stimulation technique to induce neuronal and synaptic plasticity. The induced cortical plasticity is imperative in the recovery of motor and sensory functions. Spinal cord injury (SCI) causes damage to neurons and results in sensorimotor dysfunction. The effect of iTBS on recovery of motor and sensory dysfunction in complete SCI (cSCI) is still elusive.

Objective: This study aims to assess the effect of iTBS on corticospinal tract integrity, plasticity, and regaining of motor and sensory function in patients with cSCI. The rationale behind using an iTBS protocol is to modify and augment the communication between spared neurons of the corticospinal tract and strengthen the synaptic transmission, which will improve motor function in underlying muscles.

Methods: A total of 40 patients with cSCI with American Spinal Injury Association (ASIA) grade A, aged 18-60 years, were randomly assigned to 5 groups. To evaluate the efficacy of iTBS versus traditional repetitive transcranial magnetic stimulation, patients were categorized into placebo, repetitive transcranial magnetic stimulation, and iTBS. In addition, to determine the optimal site for stimulation, groups were further subdivided into motor cortex, spinal cord, and combined. Each patient underwent 10 iTBS sessions twice daily for 5 consecutive days. Neurological outcomes and functional outcome parameters will be assessed. Electrophysiological evaluations included transcranial magnetic stimulation single-pulse and paired-pulse parameters. The effect of iTBS intervention on biomarkers will be quantified using the enzyme-linked immunosorbent assay, while neurotransmitters will be quantified by liquid chromatography and tandem mass spectrometry. Measurements will be done before and after the intervention, with follow-ups at 1, 2, and 3 months.

Results: The outcome of the study will be defined by electrophysiological parameters elicited by single- and paired-pulse stimulation, ASIA score, pain, activities of daily life, quality of life, anxiety, depression, and biomarkers related to SCI. The results of this study will uncover the effectiveness of iTBS stimulation on (1) recovery of motor and sensory function in cSCI, (2) excitability of the corticospinal tract, (3) neurological recovery and modulation of pain, and (4) cortical reorganization after injury.

Conclusions: iTBS in conjunction with an individualized rehabilitation program may serve as an integrated strategy to rejuvenate locomotor abilities and improve the overall quality of life for people with cSCI.

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Trial Registration: Clinical Trials Registry- India CTRI/2022/11/047038; https://ctri.nic.in/Clinicaltrials/main1.php?EncHid=13361.98443

International Registered Report Identifier (IRRID): DERR1-10.2196/66531

(JMIR Res Protoc 2025;14:e66531) doi:10.2196/66531

KEYWORDS

American Spinal Injury Association Impairment Scale; excitatory-inhibitory circuitry; intermittent theta burst stimulation; physical rehabilitation; protocol; randomized control trial; spinal cord injury; synaptic plasticity

Introduction

Background

Spinal cord injury (SCI) is a neurological condition that causes progressive neurodegeneration. The major symptoms of SCI are paralysis, paresthesia, pain, spasticity, bladder, bowel, and sexual dysfunction. It largely affects the young population (21-49 years); thus, the psychological impact on a healthy individual to adapt to a paraplegic or quadriplegic condition in their early life is devastating. SCI causes damage to neurons, nerves, and other surrounding cells that send and receive signals from different body parts to the brain via the spinal cord (SC) and vice versa [1]. SCI can be traumatic or nontraumatic. Traumatic SCI is a great challenge for therapeutic management considering its high morbidity. There is complete or incomplete loss of locomotor, sensory, and autonomic functions depending on the severity and level of the lesion [2]. The consequences of injury are not just a break in communication between neurons, but a cascade of events that sets up a vicious cycle and leads to widespread neuronal degeneration, cell death, and the formation of glial scars [3]. Cellular components such as proteins, phospholipids, neurotransmitters, and metabolites derived from SC neurons and glial cells diffuse from the injury site into the cerebrospinal fluid and blood [4]. These biomarkers could serve as good diagnostic markers to predict the severity of the injury. To regain functional connectivity, and attenuate gliosis and secondary injury, activity-dependent strategies have been proposed to be quite effective. The current treatment modalities for SCI include surgery, pain management, and rehabilitation. However, functional recovery by restoring connections of the corticospinal tract after a complete SCI is challenging.

High-frequency repetitive transcranial magnetic stimulation (rTMS) has decreased neuropathic pain and spasticity in incomplete SC–injured patients [5,6]. A newer form of patterned transcranial magnetic stimulation (TMS), intermittent theta burst stimulation (iTBS) is now being studied for the improvement of symptoms in incomplete SCI [7]. There is very limited literature available, showing the effect of either cortical iTBS or trans-spinal TMS in combination with a rehabilitation program to promote repair, regeneration, and recovery in patients with complete SCI (cSCI). This study aims to determine the functional outcomes of administering iTBS at the cortex as well as at SC along with intensive rehabilitation programs in patients with cSCI.

Study Objectives

This study aims to evaluate the comparative efficacy of iTBS and rTMS in promoting motor function recovery in individuals with cSCI. In addition, it seeks to identify the most effective stimulation site—motor cortex, SC, or a combined approach—for optimizing therapeutic outcomes. The study will further assess the impact of these TMS protocols along with customized rehabilitation programs on sensory and locomotor function, cortical excitability and neuroplasticity, SCI-related biomarkers, and self-reported outcomes, including pain, anxiety, depression, and overall quality of life.

Methods

Study Design

A double-blinded, prospective, randomized, placebo-controlled study will be conducted. The computer-generated sequence will be sealed in sequentially numbered envelopes, which will be opened after the patient is enrolled in the study. Both the patient and investigator will be blinded to the intervention. An experienced therapist will perform the intervention protocol. This protocol is based on the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (checklist provided in Multimedia Appendix 1).

Duration of the Study

The recruitment, intervention, and follow-up phase will be 2 years, followed by 6 months of data analysis. Patient recruitment will start in January 2023 and the trial will be completed by July 2025.

Inclusion and Exclusion Criteria

Adults aged 18 to 60 years with a thoracolumbar (T1-L5) SCI and complete motor loss below the lesion level (American Spinal Injury Association [ASIA] score A) will be screened and recruited within 1 month of injury.

Exclusion criteria include patients with osteoporotic fractures, a history of neurological or orthopedic diseases affecting the SC, head injuries, ferromagnetic metallic implants near the target stimulation area, pacemakers, cognitive impairment, pregnancy, a history of seizures, or acute eczema or bedsores.

Confidentiality

The personal privacy of patients will be protected. The results of this study will not disclose any identifying and personal information of the patient without his or her permission.

Sample Size

The sample size for this study is determined based on the methodology outlined by Roy et al [8], which assessed the reduction in motor evoked potential (MEP) amplitude following intervention. Using an α level of 0.05 and a power of 90%, these

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parameters are incorporated into the 2-tailed formula for sample size calculation.

For a 2-sample comparison of means, the null hypothesis (H0: m1=m2) will tested, where m1 and m2 represent the means of 2 distinct populations. The assumptions for the calculation are as follows:

> α=.05 (2-sided), Power=0.90, m1=12.85, m2=13.53, SD1=0.3, SD2=0.3, n2/n1=1.00

Based on these assumptions, the estimated required sample size is calculated to be 6 subjects per group. To account for potential dropouts, a 20% adjustment is applied, resulting in a revised sample size of 8 participants per group. Consequently, the total minimum sample size required for the study is 40 participants.

Experimental Groups

A total of 40 patients will be randomized into 5 groups using computer-generated random numbers. Patients will be categorized into placebo, rTMS, and iTBS to evaluate the efficacy of iTBS versus traditional rTMS on the primary motor cortex (MC). To determine the optimal site for iTBS application, stimulation was given at either MC or SC or combined MC+SC.

Mode of Stimulation

Group classification based on the mode of stimulation is listed as follows:

- Group 1: Placebo
- Group 2: High-frequency rTMS
- Group 3: iTBS

Site of Stimulation

Group classification based on the site of stimulation is listed as follows:

- Group 3: iTBS on motor cortex
- Group 4: iTBS on the SC
- Group 5: iTBS on the motor cortex and SC

This trial's conduct and report will follow the CONSORT (Consolidated Standards of Reporting Trials) statement for randomized trials (Figure 1).

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram. ASIA: American Spinal Injury Association; BDI: beck depression inventory; cSP: cortical silent period; ICF: intracortical facilitation; iTBS: intermittent theta burst stimulation; LICI: long-interval intracortical inhibition; MAS: ___; MC: motor cortex; MEP: motor evoked potential; QOL: quality of life; rTMS: repetitive transcranial magnetic stimulation; SC: spinal cord; SCIM: Spinal Cord Independence Measure; SICI: short-interval intracortical inhibition; STAI: State-Trait Anxiety Inventory; VAS: Visual Analog Scale.

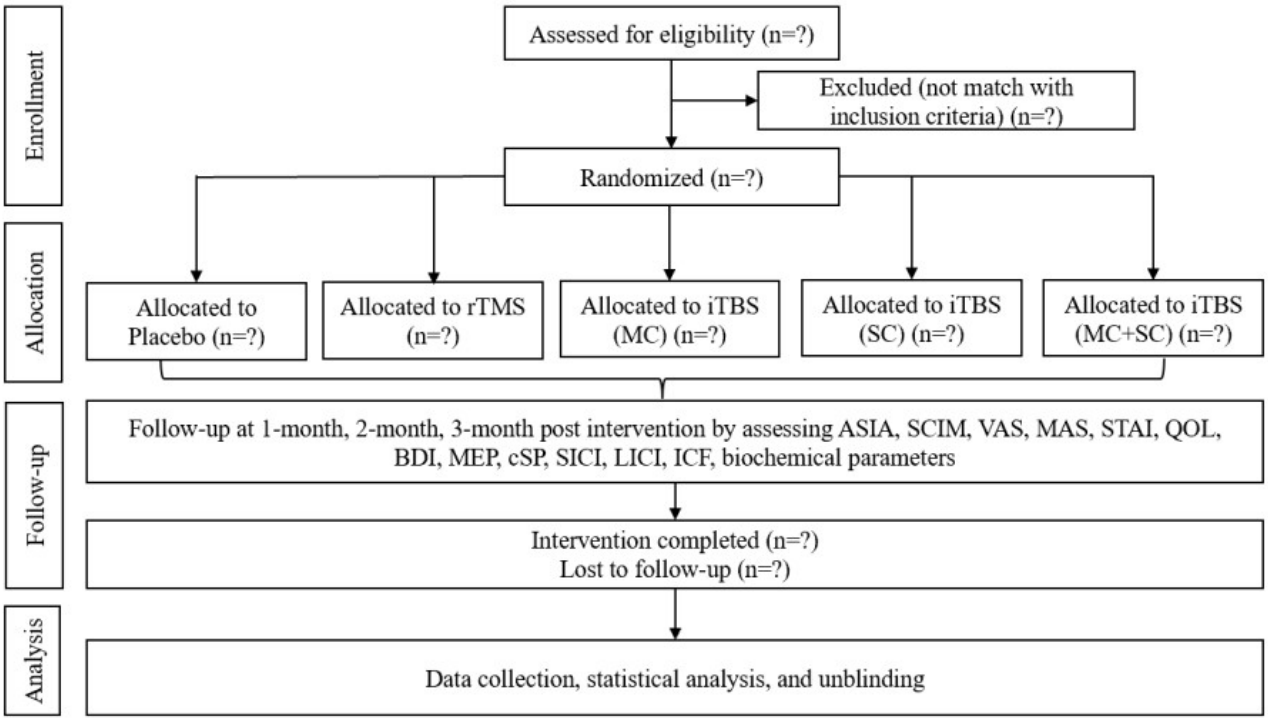

Patient Recruitment and Parameter Recording

Participants will be enrolled from the Jai Prakash Narayan Apex Trauma Centre at AIIMS (All India Institute Of Medical Sciences) Delhi. Following SCI surgery, a 15-day period will be designated for vertebral stabilization, after which sutures will be removed on the 15th day. Once the sutures are removed, baseline parameters will be measured. Patients will then be randomly assigned to one of the intervention groups. After completing the intervention, postintervention parameters will be recorded and follow-up assessments will be conducted at 1, 2, and 3 months (Figure 2). To ensure consistency during the intervention, all assessments will be recorded by the blinded primary investigator.

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Figure 2. Timeline: all the intervention and recording paradigms are organized as a timeline. iTBS: intermittent theta burst stimulation; rTMS: repetitive transcranial magnetic stimulation.

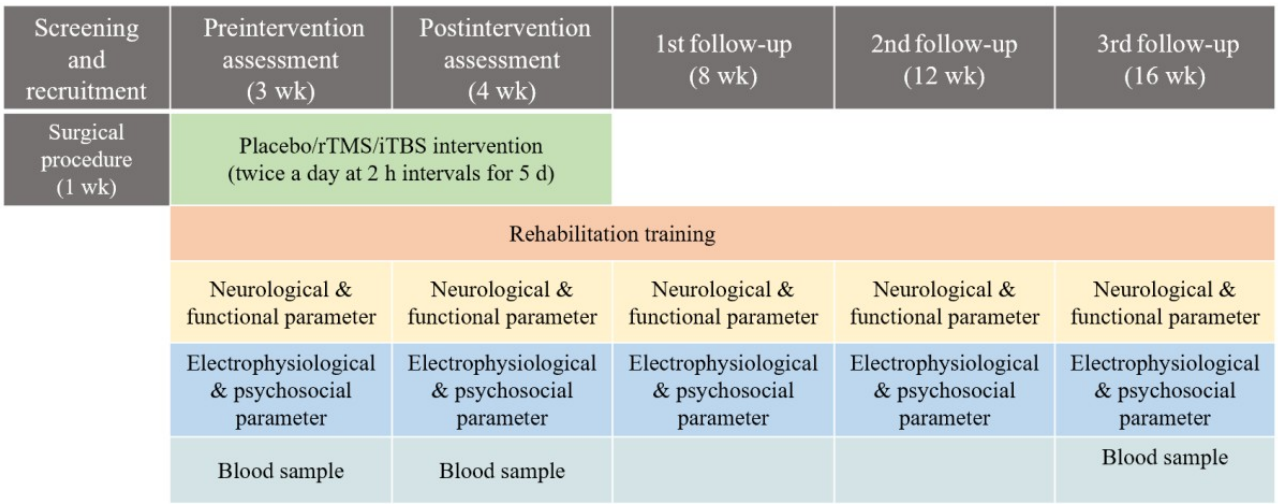

Intervention Protocol

During the intervention phase, patients will be randomly allocated to one of the interventional groups. The rTMS or iTBS will be administered using the Neurosoft - Neuro-MS 5 device (Neurosoft Ltd), a commercially available transcranial magnetic stimulator. The device will be equipped with both an angulated figure 8–shaped coil and a circular coil for stimulation. The intervention (rTMS or iTBS) will be applied to the lower-limb motor area located in M1 (to stimulate both lower limbs), with the handle of the coil aligned parallel to the interhemispheric midline (pointing occipitally) based on the vertex position according to the International 10-20 EEG system. For SC stimulation, the circular coil will be positioned over the injury site. In the placebo stimulation group, a sham coil (not generating a magnetic field but producing similar click sounds) will be used and the stimulation protocol remains akin to the iTBS group.

The standard protocol for iTBS will be used: 3-pulse bursts at 50 Hz, repeated at 5 Hz, with a 2-second train repeated every 10 seconds for 20 repetitions, amounting to a total of 600 pulses [7]. The rTMS protocol will consist of 1600 pulses at a frequency of 20 Hz, with a 2-second train repeated every 30 seconds for 20 minutes [9]. A resting motor threshold (RMT) of 90% will be used for both rTMS and iTBS stimulation intensity. RMT will be determined by recording MEP from the abductor pollicis brevis (APB). RMT will be recorded by placing figure-eight coils over the motor hotspots of the APB. The minimum stimulus intensity that causes an MEP with a peak-to-peak amplitude of at least 50 µV in at least 50% of consecutive stimuli will be considered as RMT. Interventions will be administered for 5 consecutive days, twice daily, with a total of 10 sessions [10].

Postintervention Care

All the participants will be required to fill out a TMS safety questionnaire both before and after the intervention. Briefly, the preintervention questionnaire takes care of any implants, past history of seizures, pregnancy, or head trauma, whereas the postintervention questionnaire reports any adverse effects observed by patients like headache, nausea, ear discomfort, or any seizure. Besides these, the participants will also undergo thorough screening for contraindications, continuous monitoring during and after stimulation, and adherence to standardized emergency protocols as approved by the institutional review board. If a patient experiences an adverse event during the trial, the principal investigator will provide treatment and corresponding financial compensation. Patients who are enrolled in the placebo group will also receive the conventional rehabilitation program during the study.

Outcomes

Primary Outcome (Neurological)

The primary outcome will measure the severity of injury with the ASIA Scoring System. The ASIA impairment score (AIS) ranges from complete loss of sensation and movement (AIS=A) to normal neurological function (AIS=E). The ASIA motor score uses a test of the strength of 10 key muscles on each side of the body (eg, elbow flexors, wrist extensors, hip flexors, quadriceps, and dorsi flexors). The score ranges from 0 (no contraction) to 5 (normal resistance) through a full range of motion. A total possible score of 50 for the upper extremities and 50 for the lower extremities may be obtained [11]. The ASIA sensory score involves pinprick and light touch sensation at key points representing each dermatome of the body, scored on a 3-point scale (0, 1, and 2). Scores are summed to give a total possible score of 224, where a higher score indicates better sensation than a lower score.

Secondary Outcomes

Functional Parameter Outcomes

Walking Index for Spinal Cord Injury II (WISCI-II) is a 0-20 level scale that evaluates the walking activity of a patient based on physical assistance, the need for braces and walker, and other adaptive devices. The levels on the scale are scored from 0 (patient unable to walk) to 20 (patient walking without braces and adaptive devices and without any physical assistance for at least 10 m) [12].

Spinal Cord Independence Measure-III (SCIM-III) includes 19 tasks organized in 3 subclasses based on the patient's general activity: self-care (score 0-20), respiration and sphincter

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management (score 0-40), and mobility (score 0-40). The overall scores range from 0 to 100, where a 0 score defines a total dependence of the patient on the caregiver and a score of 100 indicates complete independence [13].

Electrophysiological Parameter Outcomes

Single-Pulse TMS

A single pulse of TMS at minimum stimulus intensity will be delivered at the motor cortex that elicits an MEP of ≥ 50 µV at least 5 out of 10 trials in the target muscle (APB) and will be recorded as RMT [14]. For recording the inhibitory activity, a single TMS is delivered to produce an interruption in ongoing EMG activity during a tonic contraction followed by the reoccurring EMG activity. The duration of silencing of EMG in response to TMS will be measured as a cortical silent period (cSP) [15]. The recruitment curve plotted between the TMS intensity (%) and MEP sizes.

Paired-Pulse TMS

A total of 2 TMS pulses, conditioning stimulus, and test stimulus, delivered at specific interstimulus intervals result in either facilitation or inhibition. In short-interval intracortical inhibition, MEP elicited by test stimulus is inhibited when preceded by a conditioning stimulus at ~1- to 5-millisecond intervals. In long-interval intracortical inhibition, the interstimulus interval is kept between 50 and 200 milliseconds, whereas in intracortical facilitation, the interval is ~10-30 milliseconds [15].

Psychosocial Parameter Outcomes

Visual Analog Scale (VAS) measures the perceived intensity of pain on a self-explanatory scale of 0 to 10, where 0 (no pain) to 10 (severe pain) [16].

The Beck Depression Inventory-II (BDI-II) is a 21-question multiple-choice self-report inventory to measure the presence and severity of depression. The cut-off scores with 0-9 indicating normal, 10-19 indicating mild depression, 20-30 indicating moderate depression, and 31-63 indicating severe depression [17].

The State-Trait Anxiety Inventory (STAI) is a 40-item self-report scale, commonly used to measure anxiety [18].

The World Health Organization Quality of Life-BREF (WHOQOL-BREF) Scale was developed in the context of the 4 domains defining the QOL: physical, psychological, social, and environmental. The higher the QOL score, the higher the life satisfaction [19].

Biochemical Quantification

The disruption of the blood-spinal cord barrier and secondary damage following the injury releases several chemokines, growth factors, and neurotransmitters in cerebrospinal fluid and systemic circulation, which could help predict the severity of the injury. The released components, such as myelin basic protein (MBP), interleukins, phosphorylated neurofilaments, brain-derived neurotrophic factor, Fas-ligand, gamma-aminobutyric acid, and glutamate, may serve as potential biomarkers for remyelination, inflammation, neuronal survival, and excitatory or inhibitory neurotransmitters after SCI [20-23]. Liquid chromatography and tandem mass spectrometry and enzyme-linked immunosorbent assays will be performed to quantify these biomarkers in plasma and serum samples.

Physiotherapy

A trained physiotherapist will be assigned to provide individualized rehabilitation training for 5 days. After this period, patients will be instructed to perform the exercises independently at home, maintaining a logbook and submitting weekly videos of their performance for evaluation by the physiotherapist till the time of last follow-up (Figure 3).

Figure 3. Outline of physical rehabilitation regime for patients with spinal cord injury. Exercise prescription and progression will be based on the individual's performance and tolerance to baseline exercises. AROM: active range of motion; PROM: passive range of motion; RM: repetition maximum; SCI: spinal cord injury.

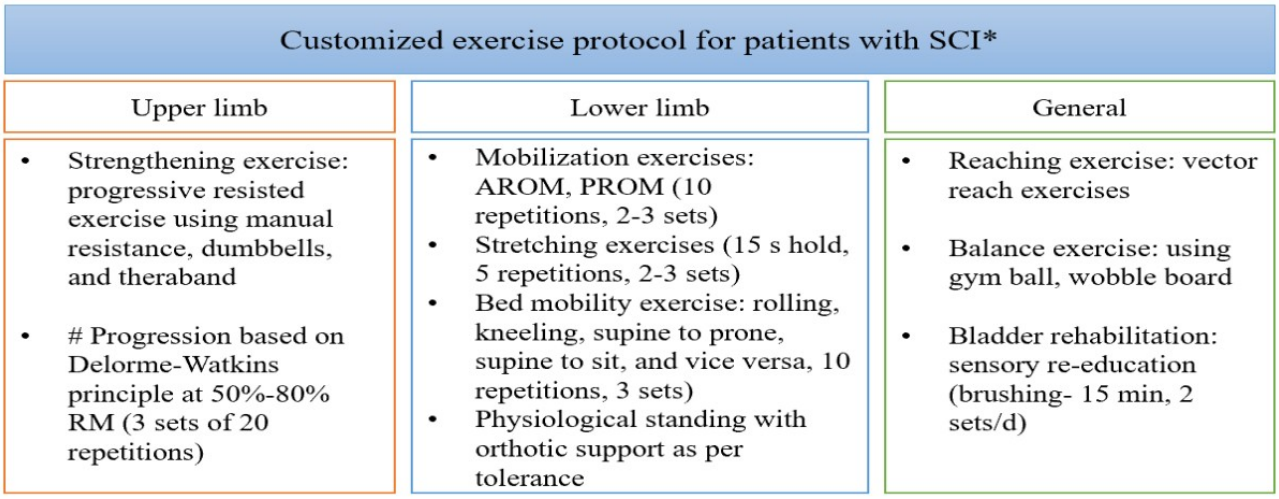

Statistical Analysis

Data will be analyzed using STATA 14.0 software (StataCorp). Continuous variables will be presented as mean and SD, and categorical variables as frequencies and percentages. The primary analysis will be the intention-to-treat analysis, where baseline values will be carried forward for subjects with missing data. Unless stated otherwise, intention-to-treat data will be

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presented throughout the study. In addition, a per-protocol analysis will be conducted, including only participants who comply with the protocol.

Normality will be evaluated using the Shapiro-Wilk test for each outcome, homogeneity of variance will be checked using the Levene test, and the Mauchly test will be used for sphericity. Depending on the data distribution, parametric or nonparametric tests will be applied.

If the data are found to be uniformly distributed, we will use repeated measures ANOVA to assess changes over time within and between groups. Bonferroni or Tukey correction will be done for post hoc pairwise comparisons. Nonparametric tests like the Friedman test followed by appropriate post hoc tests will be used for skewed data. Corrections for multiple comparisons will be applied as specified to reduce the risk of type I errors. To analyze categorical variables, the chi-square or Fisher exact test will be used to assess associations between groups.

A P value less than .05 with a 95% CI will be considered statistically significant.

Ethical Considerations

Ethical approval has been obtained from the Institutional Ethical Committee of All India Institute of Medical Sciences, Delhi (Project Ref. Id: IECPG/551/7/2022). The study is registered in the Clinical Trials Registry- India (CTRI; reference number CTRI/2022/11/047038). Informed, voluntary, and written consent will be taken, and the participants will be given a choice to withdraw from the study at any given point in time. They will be duly informed of the duration of the study along with any potential risks or side effects associated with TMS intervention. If a patient experiences an adverse event during the trial, the investigators will provide treatment and corresponding financial compensation. No names or any other forms of identification will be used in publications or reports resulting from the study without the permission of the participants.

All the experiments will be carried out in the Brain Stimulation and Neuromodulation Laboratory, Department of Physiology, and CARE, Department of Psychiatry, AIIMS, New Delhi.

Results

This randomized controlled trial will assess the impact of iTBS on motor and sensory functional recovery, alterations in corticospinal excitability, biomarkers, and quality of life in patients with cSCI. The project was funded by DBT in July 2019. The randomized controlled trial has been registered with the Clinical Trials Registry-India (CTRI/2022/11/047038) and ethical approval obtained from the Institutional Ethics Committee, AIIMS, Delhi (Project Ref. Id: IECPG/551/7/2022). The project was initiated in January 2023 and is likely to be completed by June 2025. The results of this study will be analyzed from January to July 2025 and will be submitted for publication in peer-reviewed scientific journals. We presume this study may support integrating iTBS into a rehabilitation program for motor and sensory recovery in patients with cSCI.

Discussion

Principal Findings

SCI significantly impairs the corticospinal integrity and afferent-efferent input-output circuitry. Theoretically, the pyramidal tract is the primary neural pathway that links the cortex and SC to facilitate the movement of distal extremities. The primary purpose of any treatment is to reconstruct the neural circuit immediately after SCI for functional sensory-motor recovery. To facilitate neural circuit reconstruction, it is required to stimulate nerve cell sprouting and regeneration as well as increase the strength of the existing neuronal connections. Previous research demonstrated that individuals with incomplete SCI can benefit from locomotor training to enhance their motor skills. Rehabilitation programs may use learning and relearning mechanisms, uncovering a previously inactive synapse, and forming a new synapse [24]. However, the reconstruction of the damaged neural circuit is quite difficult with locomotor training alone. Studies have shown that the functional effects of exercise along with transcranial magnetic stimulation, can activate spared neural pathways and enhance the possibility of neural reconstruction [25,26].

TMS induces electrical currents in underlying cortical areas, depolarizes neurons, and generates an action potential that modulates the activity of spinal motor neurons and target muscles via the corticospinal tract. Repetitive transcranial magnetic stimulation as well as iTBS is an intervention in various psychiatric and pain conditions. In SCI, few studies suggest improvement in locomotor function, spasticity, and pain in incomplete patients [6]. Although, the functional mechanism of rTMS or iTBS on sensorimotor recovery in patients with SCI is not fully understood, but thought to induce synaptic plasticity via LTP or LTD-like effects [27], thereby promoting functional recovery in patients with SCI.

In addition, SC stimulation can modulate the activity of the local central pattern motor generators, which promotes synaptic strengthening [28]. In rat models of complete and incomplete SCI, a significant attenuation of glial scaring, lesion volume, neurotransmitter imbalance, muscle atrophy, and facilitation of neuronal survival, axonal regeneration, and myogenesis has been shown following whole-body magnetic field exposure [29,30]. Therefore, we propose that SC stimulation along with motor cortical stimulation would attenuate secondary damage and promote regeneration even in patients with cSCI, leading to long-term functional recovery.

Various single- and paired-pulse paradigms of TMS have been used for the assessment of cortical excitability, plasticity, integrity of the corticospinal tract, and excitatory-inhibitory neural circuitry of the motor cortex. We shall use all paired-pulse paradigms (short-interval intracortical inhibition, intracortical facilitation, and long-interval intracortical inhibition) to objectively assess excitatory-inhibitory neural circuitry and single-pulse paradigms (RMT, MEP, recruitment curves, and contralateral silent period) for unraveling the excitability of corticospinal circuitry and motor units.

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Limitations

While this study offers valuable insights, several limitations must be acknowledged that may affect the interpretation and broader application of the findings. First, the sample size is relatively small, which could reduce the statistical power and may not fully represent the broader population of individuals with SCIs. Second, variability in the severity of SC injuries among participants may influence the outcomes, as responses to treatment could differ based on the level and completeness of the injury. Finally, the short duration of the follow-up period may not adequately capture the long-term effects of the interventions, suggesting the need for longer-term studies to assess the sustainability of the benefits observed.

Conclusion

An intensive individualized rehabilitation regime coupled with iTBS could be a holistic management strategy that can restore locomotor function and quality of life in patients with cSCI. TMS is also a promising tool to evaluate the cortical plasticity and excitability in SCI and thereby understand the mechanism of action of the proposed intervention and characterize the effective connectivity of neural circuits and mechanisms regulating the balance between inhibition and facilitation within the corticospinal pathway.

Acknowledgments

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

DP contributed to conceptualization, patient recruitment and screening, data curation, methodology, investigation, and writing—original draft. RB contributed to rehabilitation training, evaluation, scoring, and data curation. KF contributed to SCI surgery, recruitment, and screening. DG contributed to SCI surgery, recruitment, and screening. NK contributed to supervision and lab facility. KPK contributed to writing—review & editing, supervision. SJ contributed to lab facility, methodology, investigation, supervision, writing—review & editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendation for Interventional Trials) checklist.
[DOCX File , 21 KB - resprot_v14i1e66531_app1.docx]

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Abbreviations

AIIMS: All India Institute Of Medical Sciences
AIS: ASIA impairment score
APB: abductor pollicis brevis
ASIA: American Spinal Injury Association
BDI-II: Beck Depression Inventory-II
CONSORT: Consolidated Standards of Reporting Trials
cSCI: complete spinal cord injury
CTRI: Clinical Trials Registry- India
iTBS: intermittent theta burst stimulation
MBP: myelin basic protein
MC: motor cortex
MEP: motor evoked potential
RMT: resting motor threshold
rTMS: repetitive transcranial magnetic stimulation
SC: spinal cord
SCI: spinal cord injury
SCIM-III: Spinal Cord Independence Measure-III
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
STAI: state-Trait Anxiety Inventory
TMS: transcranial magnetic stimulation
VAS: Visual Analog Scale
WHOQOL-BREF: World Health Organization Quality of Life-BREF
WISCI-II: Walking Index for Spinal Cord Injury II

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Protocol

A Culturally Tailored mHealth Intervention (MobileMen App) to Promote Physical Activity in African American Men: Protocol for a Comparative Effectiveness Trial

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Abstract

Background: African American men are at a higher risk for serious health conditions such as cardiovascular disease, diabetes, and stroke compared to non-Hispanic White men. Physical activity (PA) is a modifiable health behavior that has been shown to decrease chronic disease risk; yet, PA engagement is alarmingly low in African American men. Interventions to improve PA engagement are effective in a number of populations; however, very few have been tailored to the unique needs of African American men. Even fewer have leveraged mobile health apps, despite African American men's interest in and willingness to use such technologies for health improvement.

Objective: This comparative effectiveness trial aims to evaluate MobileMen, a PA promotion app tailored to the needs and preferences of African American men. This trial will compare the MobileMen app to a commercially available PA promotion app with similar features but lacks culturally tailored components.

Methods: We will recruit a sample of "low active" (accumulating <7500 steps per day) African American men (n=100) aged >30 years from Baton Rouge, Louisiana, and the surrounding communities. All participants are given a Fitbit Charge 6 wearable activity tracker to assess daily PA and steps and are randomized to either the MobileMen intervention app or the comparator app, which is a commercially available PA tracking app called Stridekick. The Stridekick app has features similar to those in the MobileMen app but was not intentionally designed for African American men. The intervention period is 6 months during which participants will interact with their assigned mobile app. MobileMen includes features such as digital badges earned for PA; tangible prizes like exercise equipment; challenges among participants; goal setting; nutrition; PA; and behavior change educational information in text, audio, and video formats. Participants will complete assessments at baseline and at 6 months post randomization. Assessments include objective measurements of daily steps and minutes of moderate to vigorous PA, quality of life, dietary measures, self-efficacy for fruit and vegetable consumption and PA, and autonomous motivation for PA.

Results: This trial is in the start-up phase. The MobileMen app development and usability testing was completed in August 2024. Participant recruitment efforts began in October 2024. The trial and associated data analyses and interpretation are planned to be completed by fall 2025.

Conclusions: Mobile apps are a widely accessible means to disseminate culturally tailored PA promotion interventions to various populations, including African American men. MobileMen has the potential to impact PA engagement in African American men, which would dramatically improve the overall health and chronic disease risk in this underrepresented group.

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Trial Registration: ClinicalTrials.gov NCT05621044; https://clinicaltrials.gov/study/NCT05621044
International Registered Report Identifier (IRRID): PRR1-10.2196/67809

(JMIR Res Protoc 2025;14:e67809) doi:10.2196/67809

KEYWORDS
physical activity; motivation; mHealth; African American men; mobile app; digital intervention

Introduction

African American men experience disproportionately high rates of obesity, cardiovascular disease, hypertension, stroke, diabetes, and prostate cancer compared to their non-Hispanic White counterparts [1-4]. Increased levels of physical activity (PA) and fitness have been associated with the reduced risk of these chronic conditions [5-11]. However, there is a lack of regular PA in the African American community, and African American men's rates of PA are well below national guidelines [12-15].

Comparatively, research consistently shows that African American men engage in lower levels of PA than their non-Hispanic White counterparts. Although 48% of non-Hispanic White adults meet PA guidelines of 150 minutes of moderate to vigorous activity per week, only 39% of Black adults meet that guideline [16]. This disparity is due to a complex interplay of social, environmental, and cultural factors [13,14,17,18]. Black men are more likely to live in neighborhoods with limited access to safe recreational spaces and face greater exposure to crime, which discourages outdoor activity [19]. Socioeconomic constraints such as demanding work schedules and caregiving responsibilities further limit their leisure time for PA [20]. Cultural norms around family roles, along with a lack of culturally relevant health messaging, can reduce motivation or the perceived value of PA [21,22]. Additionally, experiences of racism and discrimination—both in everyday life and within health care—contribute to chronic stress, mistrust of health institutions, and lower engagement in preventive health behaviors, including PA [23]. These structural and psychosocial barriers collectively create significant obstacles to PA for Black men. Thus, novel interventions are needed to support PA initiation and persistence in this population.

Mobile health (mHealth), which is the use of mobile phones in providing medical care, has been increasingly used to change and maintain health behaviors such as PA across various populations [24-26]. Smartphones create enormous potential for intervention delivery because they are compact, portable, normally "on," readily available to individuals, affordable, user-friendly, offer advanced functionality, and allow online access on demand any day or time [27-32]. mHealth interventions have been used to successfully increase PA across several settings and health conditions, including in health care settings and among cancer survivors [33-36].

African American men appear to have a positive attitude toward mHealth interventions, and approximately 44% of African American men who received 5 months of PA training were willing to receive an mHealth maintenance intervention [32]. This was especially encouraging because the sample had a mean age of 53 years, and mobile app usage and acceptability is typically lower in men 50 years of age and older [32]. African American men also demonstrated a willingness to engage in mHealth interventions specifically targeting chronic disease risk reduction [32]. Moreover, evidence suggests that mHealth interventions are effective with African American men. A recent study of a comprehensive health app for African Americans indicated that users improved their minutes of moderate PA after 10 weeks of use [37]. Other studies have utilized text messaging to influence health behaviors in African Americans, also resulting in increased PA [38,39]. However, the samples in these studies were mostly females, and none of the outcome data were analyzed by sex, further elucidating the need for the development and testing of mHealth interventions specific to African American men [37-39].

To address the gap in mHealth apps developed specifically for African American men, we developed, to the best of our knowledge, a first of its kind smartphone app, MobileMen, to support PA engagement in this population. The process for developing this app and the further rationale for the selected components are described elsewhere [40]. MobileMen is grounded in 2 behavior change theories: social cognitive theory (SCT) and self-determination theory (SDT). SCT states that the environment and a person's behavior interact to shape behavior and that self-efficacy is the key component to behavior change [41]. SCT was the foundation of the PA adoption content focusing on self-monitoring, goal setting, and social support in the MobileMen app. We chose SCT because SCT-grounded interventions have been effective at increasing and maintaining PA in African Americans [42-47]. In addition, SDT posits that satisfying 3 fundamental needs contributes to behavior change: perceived competence, a feeling of relatedness (feeling connected to others), and autonomy (feeling that change is a choice and not coerced) [48-52]. When an activity fulfills these 3 needs, people can become more autonomously motivated, resulting in more PA initiation and persistence [53]. In African American men, specifically, intrinsic motivation associates PA engagement with personal values and overall health goals, increasing the likelihood that they will persist with the behavior [54]. In the MobileMen app, we included features such as reminders and goal setting to support the development of autonomy [55]. To support competence, we included activity history and feedback such as cumulative exercise statistics aggregated over weeks and months, logging of weight training workouts and health metrics, and tangible and digital rewards [55]. We also included the ability to participate in competitions with other users and a message function to support the basic need of relatedness [55].

Additionally, the MobileMen app was culturally tailored to African American men. The culturally tailored content was based on the model established by Kreuter et al [56] who

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describe 5 strategies to culturally tailor an intervention: (1) peripheral, (2) evidential, (3) linguistic, (4) constituent-involving, and (5) sociocultural. Peripheral strategies involve matching the materials and messaging to the observable characteristics of the target population (eg, utilization of images of African American men), analogous to face validity and like Resnicow et al's [57] surface structure. Evidential strategies seek to put into context the health impact for a target population (eg, notifications such as "African American men have higher rates of diabetes compared to men from other ethnic groups. Engaging in regular PA can reduce your risk of developing diabetes"). Linguistic strategies involve using language to make materials more accessible to the target audience (eg, Beast Mode badge). Constituent-involving strategies are informed by experiences or input from the population of interest (eg, utilizing focus groups with African American men). Sociocultural strategies reflect the underlying beliefs, values, and norms of a group, like Resnicow et al's [57] deep structure. Sociocultural strategies involve how cultural, social, psychological, environmental, and historical factors affect health behaviors specifically within the target population. It is concerned with the target population's conceptualization of the need for intervention and accurate incorporation of this information into the treatment model. Commonly noted facilitators of PA include the need for peer support and camaraderie specifically from men and competition [58,59]. African American men's gender role responsibility and commitment to family, friends, and community also play a role in the adoption and maintenance of PA. Although the men noted these factors during focus groups for the development of the app, they could not be incorporated into the prototype due to the limited scope. However, these factors largely contribute to the current app development. For example, educational content was included that explicitly acknowledges gender role expectations and provides practical strategies based on SCT (eg, cognitive restructuring, social support techniques) and SDT (eg, fostering relatedness through competition) to assist men with incorporating family and friends into PA as part of the adoption and maintenance strategies.

The purpose of this paper is to describe the study protocol for examining the effectiveness of MobileMen. This trial will test the hypothesis that the MobileMen app will increase PA in African American men in comparison with Stridekick, a popular fitness app.

Methods

Study Design

A comparative effectiveness trial (CET) is being conducted to compare the effectiveness of the MobileMen app at increasing PA in African American men compared to Stridekick, a similar fitness app. The participants are assigned to one of the 2 arms: intervention (MobileMen) or comparator (Stridekick). The participants will use the assigned app on their personal smartphones for the duration of the 6-month trial. This study was registered with ClinicalTrials.gov (NCT05621044).

Ethical Considerations

This protocol was approved by the Pennington Biomedical Research Center institutional review board on July 31, 2024 (approval 2021-052). All collected data will be deidentified before the analyses. All participants will complete an informed consent form and will receive US $200 compensation at the completion of their participation.

MobileMen App

MobileMen is a mobile app tailored to the needs of African American men who aspire to increase their PA engagement [60]. MobileMen was developed using an extensive and iterative process described elsewhere [40]. The development of the MobileMen app was completed in July 2024 and is available for use on both iOS and Android platforms. See Table 1 for features of the MobileMen app.

Table 1. Features of the MobileMen and Stridekick apps.

Feature	MobileMen app	Stridekick app
Syncs to Fitbit device	✔	✔
Display physical activity data	✔	✔
Message boards	✔[a]	✔
Goal setting	✔	✔
Challenges	✔	✔
Educational content (physical activity, nutrition, and behavior change articles)	✔	N/A[b]
Allows tracking of health metrics (blood pressure, blood glucose, body weight, and cholesterol)	✔	N/A
Incentives (virtual badges and tangible prizes)	✔	✔[c]
Designed with a behavior change theory framework	✔	N/A
Designed specifically for African American men	✔	N/A

[a]MobileMen is utilizing a private Facebook group for the message board feature during the comparative effectiveness trial.

[b]N/A: not applicable.

[c]Stridekick offers virtual badges but not tangible prizes.

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Comparator App

The Stridekick app is intended to increase PA in users through a variety of functions. Stridekick is a free app available on iOS and Android platforms. See Table 1 for Stridekick features.

Participants

Eligibility criteria include self-identification as an African American male, a resting systolic blood pressure ≤159 mm Hg and a diastolic blood pressure ≤99 mm Hg (to reduce risk of exercise-induced cardiovascular events), free of significant medical problems that would impact their ability to engage in aerobic and/or resistance training, smartphone ownership, age > 30 years, and "low active" at baseline (defined as having an average daily accelerometer-assessed step count of <7500 steps) [61].

Recruitment and Screening

Community-based efforts, including advertising at churches, health fairs, Young Men's Christian Association, fraternities, social media posts, and advertisements on paid, owned, and earned media, are being used to recruit study participants. Potential participants undergo a telephone screening to assess initial eligibility.

Study Visit 1

Men who meet the initial inclusion criteria are invited for an in-person or remote orientation visit with study staff. Study staff review the study protocol and facilitate an informed consent process. During this study visit, participants complete several baseline assessments, including a sociodemographic questionnaire and height, weight, pulse, and resting blood pressure measurements. We calculate BMI by using self-reported weight and height (kg/m^2). Health-related quality of life is assessed using the 36-item short-form health survey, a widely used validated measure with strong internal consistency (Cronbach $\alpha > 0.80$ across most domains) and robust evidence of construct and criterion validity and has been validated in African Americans [62,63]. To assess PA and dietary habits, participants complete the International Physical Activity Questionnaire and National Cancer Institute's Automated Self-Administered 24-hour Dietary Assessment Tool, respectively [64,65]. Self-efficacy for fruit and vegetable consumption is measured with 7 items that measure participants' confidence in their ability to consume fruits and vegetables in different contexts like when away from home or in a rush [66]. Self-efficacy for PA is measured using the Self-Efficacy for Exercise Scale [67]. SDT-based motivation for PA is measured using the Behavioral Regulations in Exercise Questionnaire v.3 [68,69]. This 24-item questionnaire assesses the 6 SDT subtypes of motivation, with each item scored on a 5-point Likert scale ranging from 0 (not true for me) to 4 (very true for me). The Behavioral Regulations in Exercise Questionnaire v.3 has strong internal consistency for each motivational subscale; it validly measures the different types of motivation and is predictive of exercise behavior [68,69]. Eligible participants receive a Fitbit to wear for 1 week to assess baseline PA levels.

Study Visit 2

At the start of this remote or in person visit, study staff evaluate the Fitbit wear compliance. Participants who did not wear the Fitbit for at least 3 weekdays and 1 weekend day are required to rewear the device. Participants who self-report <60 minutes of moderate to vigorous PA on the International Physical Activity Questionnaire are eligible. Eligible participants are randomized to one of the 2 conditions, the MobileMen intervention group or the Stridekick comparator group, as directed by the next assignment letter contained in a randomized sequence of sealed and numbered envelopes. Using a computerized pseudorandom number generator, the statistician determines the randomization order in advance. The study coordinator reveals the randomization after the participant is deemed eligible. Project staff assist each participant in downloading the designated (MobileMen or Stridekick) app onto their smartphone, provide an app orientation, and assist in app navigation.

Study Visit 3

At the conclusion of the 6-month intervention, participants complete all follow-up assessments (except for the Physical Activity Readiness Questionnaire for Everyone and demographic questionnaires) by using the same protocols as in study visit 1. Participants in both groups also complete additional measures such as a survey to assess their satisfaction with the mobile app and the System Usability Scale, a validated 10-item measure that provides a global view of the subjective usability for technology, to assess the app's usability [70]. Participants also complete a brief interview with the study staff to collect feedback regarding suggestions for app improvement and users' impressions of the app content.

Outcome Measures

Primary Outcomes

The primary outcome measure for this study is change in step counts derived from the Fitbit collected before the intervention (week 0) and after the intervention (week 24).

Secondary Outcomes

Time spent in moderate to vigorous PA, also derived from the Fitbit preintervention and postintervention data, is a secondary outcome measure. Other secondary outcomes include changes in body weight, blood pressure, quality of life, and healthy eating index score. Daily PA engagement assessed with Fitbit Charge 6 is another secondary outcome measure. Using the Fitbit application programming interface, study staff will access participant daily steps, time spent engaging in PA, number of PA bouts, and minutes spent in each Fitbit-defined heart rate zone. Although Fitbit's thresholds and algorithms are proprietary, research indicates that minutes categorized in Fitbit data as "active" (fairly active plus very active) generally correspond to what we consider moderate to vigorous PA [71-73]. Usability (using the System Usability Scale) and overall satisfaction with the MobileMen app are the additional secondary outcomes.

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Potential Mediators

We will measure autonomous motivation and self-efficacy for PA preintervention and postintervention as potential mediators [66-70].

Potential Covariates

Demographic variables, including age, marital status, education, family income, occupation, and employment status, will be tested as potential covariates in our statistical models. We will also examine BMI and the self-reported measured blood pressure (mm Hg) at baseline as covariates.

Sample Size and Power Calculation

A sample of 50 participants per trial arm was determined based on step count data from a recent meta-analysis [72]. The standard deviation in nondiseased populations on their step counts is 2000 to 3000 steps per day. When the sample size per group is 50, a 2-sided 95% CI for the difference of two means will extend to about 800 steps per day from the observed difference in means, assuming an SD of 2000 steps per day and the CI is based on the large sample *z* statistic. Doubling the sample reduces the half width of the CI to 560 steps per day, which reduces the half width by only 30% but disproportionately increases the recruitment time and difficulty. Within the 2 arms, we can estimate longer term adherence at 6 months with a width of a 2-sided 95% CI equal to 578 steps per day when the sample proportion adherent is 0.50, and the width shortens as the adherence increases.

Statistical Analyses

Response frequency, proportions, and means will be calculated. Means and standard deviations, medians and interquartile ranges, distributions, frequencies, and percentages will characterize the data. Comparisons on demographics (ie, age, marital status) will be done using chi-square tests, *t* tests, and correlations, with 2-tailed P=.05. The changes from baseline to all postbaseline visits until week 24 in steps per day will be assessed. The model includes response data from all postbaseline visits with no imputation for missing data, as the model assumes missingness at random. The step counts at baseline are included as a fixed factor in the model. An unstructured covariance structure is assumed, and the denominator degrees of freedom is computed using the Kenward-Roger method. In case the model will not converge with the unstructured covariance structure, the heterogeneous compound symmetry and the heterogeneous Toeplitz structure is used instead (in that order). The least-squares mean estimates for the mean change from baseline to week 24 as well as the difference in the estimates at 12 weeks is displayed with their corresponding standard errors, *P* values, and 95% CI. The characteristics of the dropouts and/or noncompliant individuals are intensively examined to shed light on the potential weaknesses of the MobileMen app (differential dropout overall or within certain subgroups) and assumptions about missingness in the estimates. The evaluation of the app will include its impact using the pre-post data. The examination of the correlation matrices along with the mean changes will inform whether the variables appear to move similarly in both arms and how the interventions are working.

To identify possible mediating constructs, we plan to assess preintervention and postintervention SDT motivation and self-efficacy for PA. The selected mediation variables will be assessed using PROC CAUSALMED, which provides estimates of direct, indirect, and total effects. We will be able to judge if mediation is occurring, and if so, the strength and direction of the mediation effect. Since this study may not have an adequate sample size to power mediation effectively, this analysis will be primarily used to estimate the potential effect in a larger sample for future trials.

App utilization data will be examined to understand the acceptability and intensity of the interactions with MobileMen via several criteria, including but not limited to logins, notifications sent and received, number of activities inputted, badges earned, tips read, number of health parameters inputted, competitions competed in, and incentives earned. Complier average causal effect models will be used to examine the intensity of the intervention app utilization [73].

Results

The development of the fully functional MobileMen app began in September 2022, and the app was completed in July 2024. The design and implementation of CET are led by the project principal investigator (RLNJ). Rolling recruitment and enrollment of participants began in October 2024 and is planned to be completed by June 2025. The trial will be completed in the first half of 2025, with analyses completed in September 2025.

Discussion

Potential Findings

There are no PA promotion apps designed specifically for African American men. The MobileMen app seeks to fill this gap by becoming the first smartphone app that aims to support PA adoption and maintenance in African American men. We anticipate that app usage will be high in African American men given that it contains content that was requested, including the ability to track activity, nutrition information, goal setting, competitions, communication with other men, and rewards. We also anticipate that MobileMen will result in increased PA compared to men utilizing the Stridekick app. Finally, it is expected that the men utilizing the MobileMen app will show increases in the theoretical components targeted, which may serve as mediators of effects. If these findings are shown, it will provide evidence that a tailored app can be effective in promoting health behavior change in African American men. The next step would be to find ways of disseminating and implementing the app broadly through health systems or community-based organizations during which it will have the potential to improve the health of African American men nationwide.

Comparison to Prior Work

To the best of our knowledge, MobileMen is a first of its kind intervention to promote PA in African American men. Existing literature demonstrates the importance of culturally tailored health interventions, particularly for populations that face unique

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structural and social barriers to health. Culturally tailored interventions have been shown to improve engagement, relevance, and outcomes in public health settings [56,57]. Despite the disproportionate burden of chronic disease among African American men, few health behavior change programs are specifically designed for this group [74]. African American men also face distinct barriers to PA related to gender role expectations and environmental constraints, making generalized PA programs less effective for this population [21]. The MobileMen app addresses this gap by providing a tailored solution grounded in the health behavior change theory and designed specifically for African American men. Additionally, African American people show high levels of engagement with mobile technology, supporting the use of mHealth tools as an accessible and culturally relevant strategy for promoting behavior change [75]. This focus on a high-engagement demographic with unique health needs sets MobileMen apart from existing health apps and underscores its potential value in fostering sustainable PA behavior change.

Strengths and Limitations

The CET, which is currently in progress, has several strengths, including a multidisciplinary research team with combined expertise in African American men's health, mHealth app development, PA assessment, wearable technology use in interventions, and psychological mediators of PA behavior change. The app was designed using a community-engaged approach [40]. The primary outcome of CET, that is, change in daily step count, will be assessed using objective activity monitoring rather than self-report, which is a study strength due to the reliability and validity of objectively measured step counts [76]. Further, this study not only aims to assess the primary PA outcome (steps) but also the hypothesized mediating construct (autonomous motivation), addressing the question of how MobileMen might support PA behavior change.

However, no study is without limitations. Even with a sample of 100 participants, we are underpowered to conduct statistical mediation tests, leaving us unable to assert if behavioral changes associated with MobileMen use can be attributed to changes in potential mediators. At present, the mechanisms of action for PA behavior change or most health behavior changes are not well understood, as they have not been closely examined [77]. Therefore, this is a critical next step for PA research in this population. Further, the location from which African American men are recruited, the Southern United States, presents a limitation in the generalizability of the results of the study. As such, a larger study with a more geographically diverse sample of African American men should be considered. Further, the mobile app is only available to men who have use of a mobile phone; nonmobile phone users will need other methods for accessing PA-tailored interventions. Finally, choosing a commercially available comparator app may introduce bias. Stridekick was not created by our team, and although we vetted the app, it is possible that components that were unaccounted for may influence our results. Further, differences in the content, degree of personalization, and theoretical foundation between Stridekick and MobileMen may introduce potential confounding. Therefore, any observed effects may partially reflect these differences rather than the cultural tailoring or theoretical elements of MobileMen alone. Further, the participants are aware of which app they are assigned to, which may introduce expectation bias. In summary, future studies of MobileMen might consider a comparator app that is more closely matched in content and theoretical underpinnings while also considering blinding or other strategies to reduce expectation bias.

Conclusions

To date, no mobile PA and health app exists that is specifically tailored to the needs of African American men. MobileMen seeks to fill this gap with culturally tailored content and foundations in the health behavior change theory. This CET will assess its efficacy compared to a popular mHealth app, providing the research team with important data for app modifications before testing the final version in a large-scale effectiveness trial.

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Authors' Contributions

Conceptualization: RLNJ (lead), DMG (supporting)
Funding acquisition: RLNJ (lead), DBB (supporting)
Methodology: RLNJ (equal), KN (equal), DMG (equal), DBB (equal), CH (supporting), PN (supporting), AB (supporting)
Project administration: AB (lead), CH (equal), PN (equal)
Supervision: KN (lead), RLNJ (equal), DBB (equal)
Writing – original draft: KN (lead), AB (supporting)
Writing – review and editing: AB (lead), RLNJ (equal), CH (supporting), DBB (supporting), AJS (supporting), DLS (supporting)

Conflicts of Interest

DBB, KN, and AB received salaries from Klein Buendel, the company that developed the MobileMen app.

Multimedia Appendix 1

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SPRINT 2025 Checklist.
[PDF File (Adobe PDF File), 128 KB - resprot_v14i1e67809_app1.pdf]

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Abbreviations

CET: comparative effectiveness trial
mHealth: mobile health
PA: physical activity
SCT: social cognitive theory
SDT: self-determination theory

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Protocol

Effects of a Digital Functional Exercise Program on the Disease Activities and Physical Capabilities of Patients With Ankylosing Spondylitis: Protocol for a Randomized Controlled Trial

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Abstract

Background: Ankylosing spondylitis (AS), a chronic inflammatory disease, causes spinal stiffness, functional impairment, and reduced quality of life. While exercise is critical for managing AS, traditional home-based programs lack real-time supervision to ensure movement quality and adherence. Emerging digital tools like inertial sensors may address this gap, but their clinical impact remains unproven.

Objective: This study aims to evaluate the feasibility and efficacy of a Digital Functional Exercise Program (DFEP) using wearable sensors and real-time feedback for patients with AS.

Methods: This single-blind randomized controlled trial (ChiCTR2300068327) enrolled 80 adults with AS from the Chinese People's Liberation Army (PLA) General Hospital. Participants were randomized 1:1 to: DFEP Group: 24-week sensor-guided exercises via the Healbone Mini Program (Jiakangzhongzhi, Co), with real-time feedback and remote physiotherapist oversight. Control Group: standard home-based exercises with written instructions. The primary outcome is the change in Ankylosing Spondylitis Disease Activity Score with C-reactive protein (ASDAS-CRP) at 24 weeks. Secondary outcomes include Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), Bath Ankylosing Spondylitis Functional Index (BASFI), Bath Ankylosing Spondylitis Metrology Index (BASMI), Assessment of Spondyloarthritis International Society Health Index (ASAS HI), 36-Item Short Form Survey (SF-36), pain visual analog scale, Five-Times-Sit-to-Stand, 4-meter walk test, Hamilton Anxiety Scale (HAMA), Hamilton Depression Scale (HAMD), and adherence. Analyses will follow an intention-to-treat approach with the Last Observation Carried Forward for missing data; continuous variables will be compared with *t* tests or ANOVA, and categorical variables with chi-square tests, using a 2-sided =.05.

Results: We have screened 216 outpatients who may be eligible subjects, among them 126 outpatients who initially met the inclusion criteria. After evaluating clinicians performed face-to-face assessments, 23 lacked a stable medication regimen, 5 presented with severe cervical vertebral bridges, 3 reported regular structured exercise, 2 could not be reached after prescreening, 10 had significant cardiovascular disease, and 3 declined participation due to time constraints. Ultimately, 80 eligible participants were enrolled, with 36 randomly allocated to the intervention group and 44 to the control group. Recruitment (February 2023-March 2024) and follow-up (concluding September 2024) are complete. Data analysis (November 2024) and result dissemination (April 2025) are pending.

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Conclusions: This trial is the first to test a fully digital, sensor-based exercise program for AS. If effective, DFEP could offer a scalable, cost-effective solution for home rehabilitation in AS and related conditions.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2300068327; https://www.chictr.org.cn/showproj.html?proj=190897

International Registered Report Identifier (IRRID): DERR1-10.2196/67556

(JMIR Res Protoc 2025;14:e67556) doi:10.2196/67556

KEYWORDS

ankylosing spondylitis; digital health; Digital Functional Exercise Program; physical capabilities; physical exercise; randomized controlled trial

Introduction

Ankylosing spondylitis (AS) is a chronic, systemic rheumatic disease that serves as the prototype of spondyloarthritis and is primarily characterized by inflammation of the spine [1]. The principal clinical features of AS include reduced physical activity, pain, stiffness, sleep disturbances, decreased spinal mobility, and psychological consequences such as depression [2]. Less frequently, AS affects peripheral joints and causes extra-articular manifestations, such as Achilles tendinitis, uveitis, psoriasis, and inflammatory bowel disease.

The main objectives of treatment are to alleviate symptoms, improve functioning, maintain the ability to work, decrease disease complications, and minimize skeletal damage. However, pharmacological therapy alone is often insufficient in managing AS, especially in patients with existing functional limitations. The importance of exercise in AS has been emphasized in the Assessment of SpondyloArthritis international Society/European League Against Rheumatism (ASAS/EULAR) recommendations for the management of AS [3]. Although there is no clear consensus on which specific exercise is the most effective, a comprehensive functional exercise program including stretching, mobilization, strengthening, and balance exercise is recommended.

A recent meta-analysis found that both supervised and home-based exercise programs are beneficial in reducing Bath Ankylosing Spondylitis Metrology Index (BASMI), Bath Ankylosing Spondylitis Disease Activity Index (BASDAI), and Bath Ankylosing Spondylitis Functional Index (BASFI) in patients with AS, with supervised exercise programs showing greater efficacy than home-based exercise programs in decreasing disease activity [4]. The main reason for this result is that supervised exercise could improve the compliance of patients with exercise, improve the accuracy of exercise, leading to better therapeutic outcomes. Fortunately, the development of electronic medicine is being driven by mobile technologies, including smartphones and other wireless communication devices [5]. In recent years, mobile devices have experienced dramatic innovations, enabling anytime, anywhere, and real-time connectivity and interactions. Unlike single physiological indicators such as heart rate, functional exercise involves complex multijoint movements, dynamic ranges of motion, and postural corrections. Traditional home-based exercise models lack real-time feedback, making it challenging to simultaneously evaluate movement accuracy, adherence, and clinical progress. While digital health technologies have advanced significantly, few studies have rigorously tested scalable solutions that merge the flexibility of home-based routines with the precision of supervised guidance—a critical gap hindering the development of accessible, long-term management strategies for AS. Building on our prior work with a WeChat mini-program to monitor home-based functional exercises in patients with AS [6], we have now integrated inertial sensors into an upgraded WeChat applet. This innovation enables real-time tracking of movement quality and adherence, addressing the limitations of traditional models by providing objective, quantifiable feedback akin to in-person supervision.

This randomized controlled trial aims to evaluate the feasibility and efficacy of a digital functional exercise program for patients with AS. We hypothesize that the intervention group using the digital platform (Healbone) will demonstrate superior improvements in disease activity, measured by the Ankylosing Spondylitis Disease Activity Score with C-reactive protein (ASDAS-CRP), compared to the control group receiving standard home-based exercises. Secondary hypotheses posit greater enhancements in physical function (BASFI), spinal mobility (BASMI), and quality of life (36-Item Short Form Survey [SF-36]) in the intervention group, attributable to improved exercise adherence and real-time feedback mechanisms.

Methods

Study Design

This randomized, prospective, controlled study was a single-blind trial, conducted at the Department of Rheumatology and Immunology, Chinese People's Liberation Army (PLA) General Hospital. After baseline assessments by an assessor who was blinded to the group assignments, eligible participants were randomly assigned to the trial group or the control group after providing informed consent. Assessors were blinded to group allocation, but participants were aware of their assigned intervention (digital platform or manual-based exercise) due to the inherent nature of the interventions. This pragmatic design reflects real-world conditions where patients would typically know their treatment modality. This protocol is in line with CONSORT (Consolidated Standards of Reporting Trials) guidelines (checklist in Multimedia Appendix 1).

Participants

Patients diagnosed with AS according to the 1984 modified New York criteria [7] at the Chinese PLA General Hospital, either as a first-time diagnosis or previously, were enrolled in

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the study and assigned to 2 groups. In addition to collecting their demographic characteristics (age, gender, weight, height, and BMI), the patients were also questioned about occupation, main symptoms, time of diagnosis, and drug usage (nonsteroidal anti-inflammatory drug, disease-modifying antirheumatic drugs, including biologics). Other inclusion criteria were aged ≥18 years, stable drug treatment in the preceding month, and ASDAS-CRP between 1.3 and 3.5 [8]. Exclusion criteria were cardiovascular disease or clinical status at high risk, screened with the American Heart Association/ACSM Health/Fitness Facility Preparticipation Screening Questionnaire [9], cervical vertebra bridges, surgery within the preceding 6 months, regular exercise in the preceding 3 months (eg, yoga, Tai Chi, Baduanjin 3 or more times per week, 20 minutes per time), and factors leading to the inability to receive regular exercise rehabilitation (such as language impairment, difficulty in understanding, and limited movements).

Procedures

All subjects in this study were patients diagnosed with AS in the outpatient Department of Rheumatology and Immunology, in the Chinese PLA General Hospital. First, the potentially eligible subjects were screened by a study physician, and the exclusion criteria of all screened patients were recorded. Then, the informed consent form was signed for eligible subjects, and the baseline data were collected in detail. The trial implemented evaluation physician blinding at both baseline and follow-up phases, with group allocation data concealed via an opaque envelope. Postassessment allocation to a physical therapist for exercise prescription occurred through a separate workflow managed by the trial coordinator. Finally, a personalized exercise rehabilitation scheme was given to all the subjects by the physical therapist according to the patient's function evaluation (Multimedia Appendix 2).

Interventions

A 24-week tailored functional exercise program, consisting of stretching, mobilization, and strengthening exercises, was designed based on the patients' basic functional abilities following randomization. All patients had a 1-hour training session at entry, providing information about AS and the purpose of physical exercises.

In addition to a face-to-face session, participants in the experimental group received a digital exercise program given by the physiotherapist. Participants in the intervention group were taught the usage of the digital exercise project that will be delivered via WeChat applets to individual exercise interfaces. In the first step, patients needed to wear a sensor on their chest, close to their armpits, and then connect to their mobile phones via Bluetooth. After a successful connection, they carried out the personalized workout program listed in Multimedia Appendix 2. During exercise, participants in the experimental group received real-time feedback on movement standardization and joint angles via the WeChat-based exercise applets. Postexercise feedback was systematically collected using the Borg Rating of Perceived Exertion scale (Figure 1), enabling adjustments to exercise regimens based on participants' subjective experiences of effort.

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Figure 1. Schematic representation of training feedback.

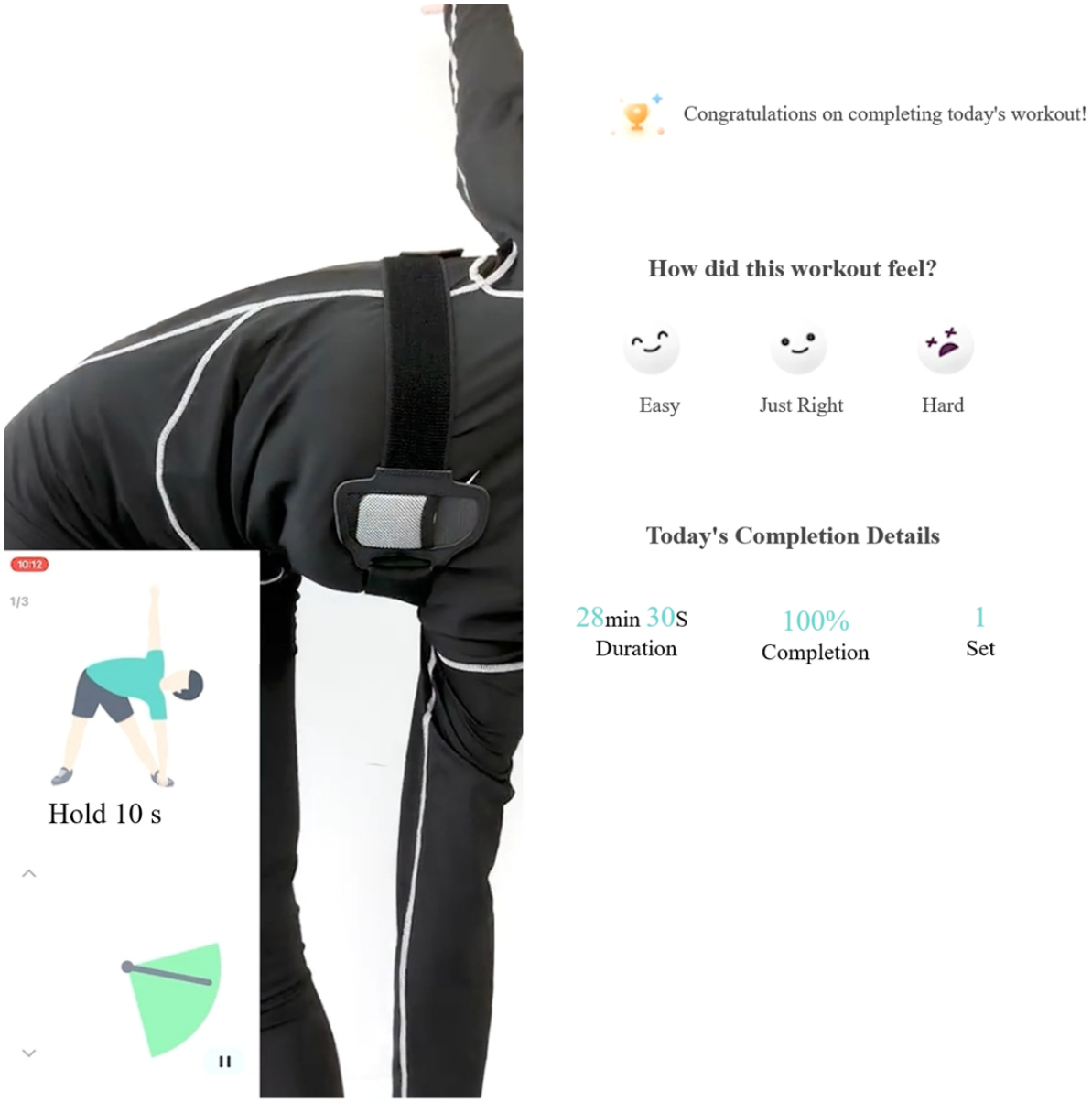

The physiotherapist's management platform enabled remote monitoring of participants' home exercise compliance through real-time data transmission from wearable sensors. Participants were instructed to complete exercises 3-4 times per week, with session frequency and duration tailored to their baseline functional assessments. To reinforce adherence, automated reminders were triggered via the platform if a participant missed exercise sessions for 7 consecutive days, prompting re-engagement through personalized notifications (eg, motivational messages and corrective feedback). Physiotherapists reviewed compliance metrics weekly to adjust exercise prescriptions or provide additional guidance as needed.

The participants in the control group received a home-based exercise program, and an exercise manual was given to each participant. The participants in the control group were also recommended to perform the exercise 3-4 times per week. Participants in the control group were provided with a paper logbook to record exercise frequency, duration, and perceived exertion. Research assistants conducted biweekly phone follow-ups to collect logbook data, reinforce adherence, and address participant questions. Adherence was calculated as the self-reported ratio of completed sessions to prescribed sessions (3-4 sessions/wk), mirroring the intervention group's digitally recorded adherence metric.

To minimize deviation risks, we established WeChat patient management groups for each participant (both control and intervention groups) comprising: the enrolled patient, a rheumatologist, a physical therapist, and a digital health assistant. The physical therapist provided targeted assistance in the intervention group under two predefined conditions: (1) when abnormal exercise difficulty was detected through our background monitoring system, and (2) if the intervention group participants failed to complete exercises consecutively for 1 week.

For participants in the control group, physical therapists solely addressed inquiries related to medical conditions and exercise clarification, without providing proactive rehabilitation guidance or progress monitoring. All communication occurred digitally

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via the WeChat platform except during scheduled in-person outpatient follow-up visit. No additional face-to-face meetings were conducted beyond these standard clinical appointments.

The Digital Platform

The digital exercise platform, Healbone, was developed through a participatory design process involving patients with AS and their relatives, rheumatology specialists, physical therapists, and a technical team. Healbone serves as a shared communication platform accessible to patients, their families, and associated health care professionals. Patients must provide written consent regarding data sharing. All information is uniformly available to all participants. Health care personnel and researchers have access to additional tools for managing care, obtaining overviews of patient conditions, and simultaneously monitoring multiple patients. The platform also functions as a coordination and communication tool among patients, relatives, and health care professionals.

All measurements are securely stored in a database. The web-based Healbone platform includes multiple features designed and developed through user-driven innovation. Facilities and input data specific to individual patients, such as symptom scores, are accessible and available to authorized personnel. The main features include:

1. Video consultation: Patients can conduct video calls with the health care team to receive professional advice and support.
2. Messaging: The platform facilitates message exchange between patients and doctors, enhancing communication and follow-up.
3. Personalized exercise plans: Tailored exercise plans are generated based on the patient's specific condition, with daily reminders.
4. Exercise tracking: Real-time monitoring and recording of patients' exercise activities.
5. Educational resources: The platform provides educational materials on AS management and exercise, aiding patients in better understanding and managing their condition.
6. Calendar: Patients can record appointments and other activities with the health care team for easy viewing.
7. Status tracking: Overview of questionnaire results completed by patients, available for viewing by patients and their authorized relatives and health care professionals.
8. To ensure the security of patient data, Healbone uses the following measures: (1) data encryption: all data are encrypted during transmission and storage; (2) user authentication: two-factor authentication ensures that only authorized users can access the platform; and (3) privacy policy: The platform complies with General Data Protection Regulation (GDPR) and other relevant data privacy regulations to protect user privacy.

In addition, Healbone can integrate with electronic health record systems and other medical devices, enabling comprehensive data management and analysis to provide holistic health management support for patients. Through these features, the platform not only improves patients' physical abilities and quality of life but also equips clinicians with effective tools for enhanced monitoring and treatment plan adjustments (Figure 2).

Figure 2. The overview diagram of the Healbone digital platform.

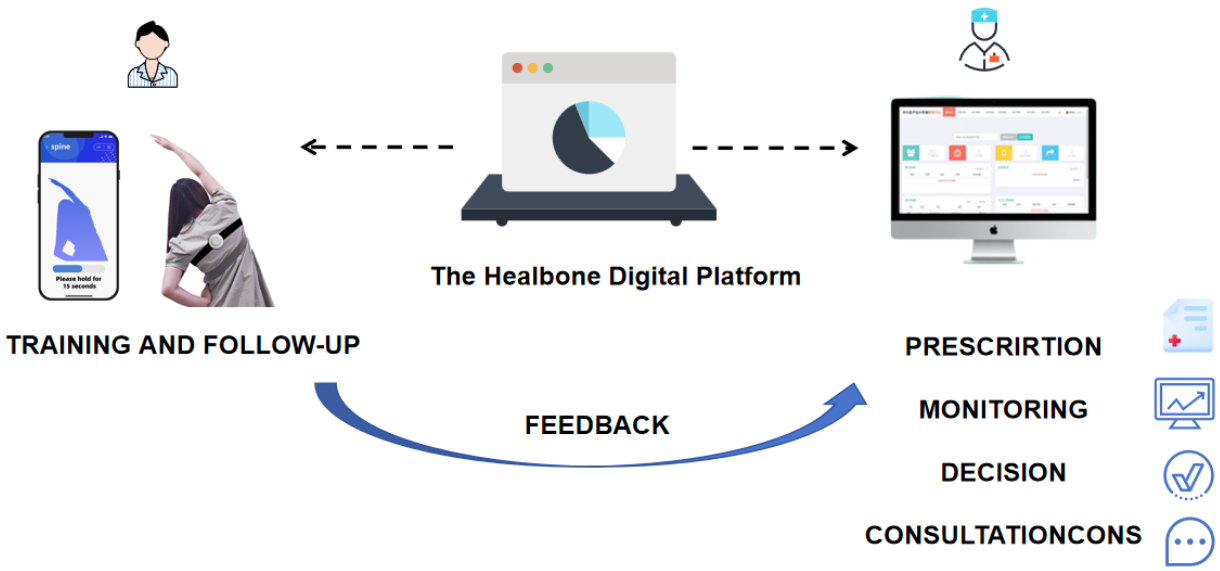

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Figure 3. Treatment assignments and withdrawal in the participants. ITT: intention-to-treat.

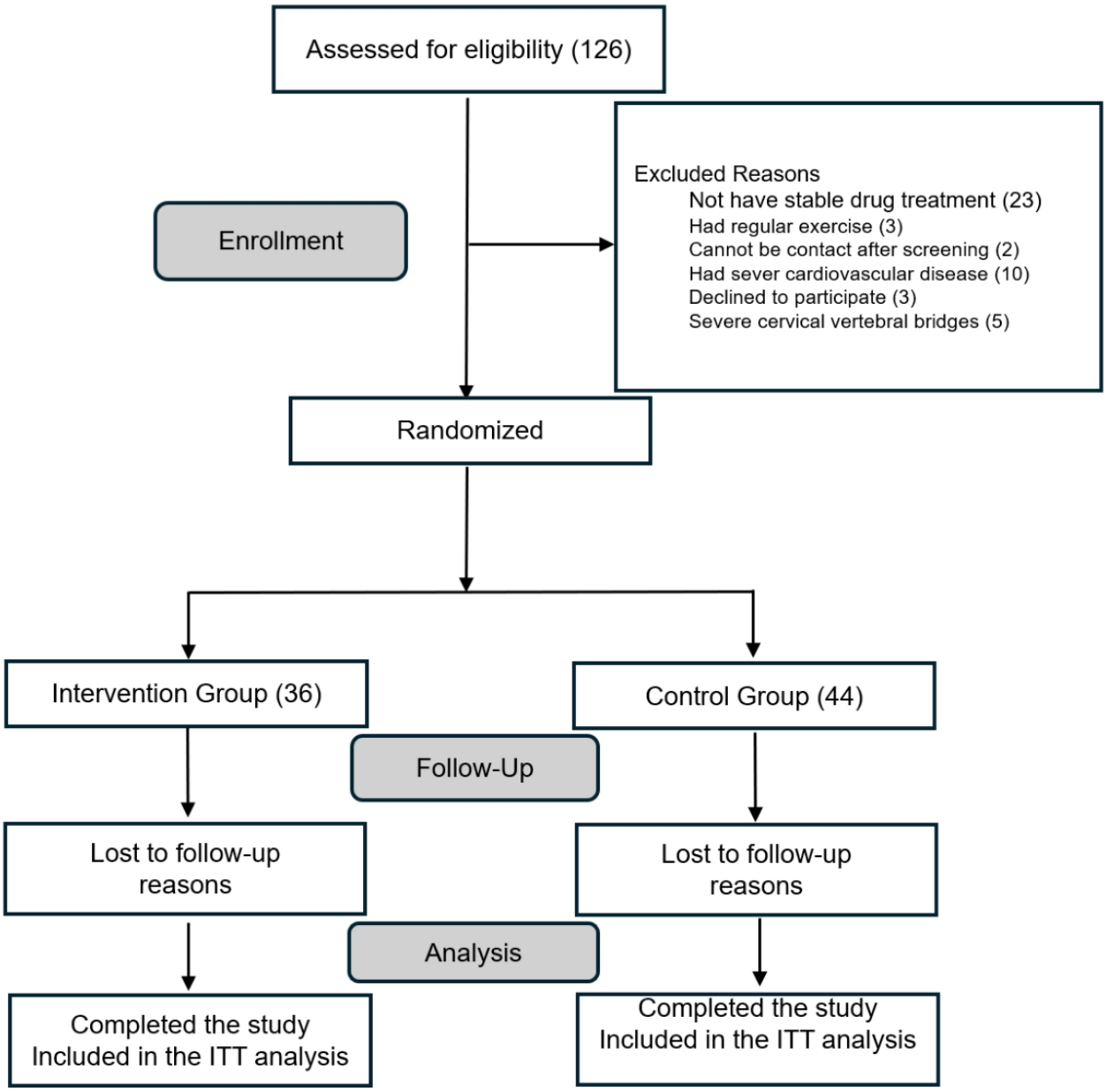

Randomization Scheme

All patients were recruited by a physician and randomly assigned to either the intervention or control group in a 1:1 ratio. To ensure allocation concealment, a computer-generated randomized table of numbers was prepared by an independent individual before the study's commencement. The numbered cards indicating the random assignment and group allocation details were sealed in opaque envelopes by the same independent person. The physical therapist then opened these envelopes and administered the exercise program based on the assigned group.

Assessments

For a schedule of data collection and measures list, refer to Table 1.

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Table 1. Measures and schedule for data collection.

Measure name	Screener	Baseline	24-week follow-up
Demographics information			
Age	✓		
Gender	✓		
Weight	✓		
Height	✓		
Marital status	✓		
Alcohol consumption	✓		
Duration of smoking (years)	✓		
Occupation	✓		
HLA-B27[a]	✓		
ESR[b]	✓		✓
Past history or symptoms at onset			
Psoriasis	✓		
IBD[c]	✓		
Uveitis	✓		
Hypertension	✓		
Hip pain	✓		
Low back pain	✓		
Neck pain	✓		
Upper back pain	✓		
Hip joint pain	✓		
Other joint pain	✓		
Disease duration (months)	✓		
Family history			
Hypertension	✓		
Diabetes	✓		
AS[d]	✓		
Physical examination			
Heel pain	✓	✓	✓
Joint pain	✓	✓	✓
Anterior chest pain	✓	✓	✓
Sacroiliac joint pain	✓	✓	✓
Hip pain	✓	✓	✓
Chest expansion		✓	✓
Finger-to-floor distance		✓	✓
Five Times Sit to Stand Test		✓	✓
4-meter walk test		✓	✓
ASDAS-CRP[e]		✓	✓
ASAS HI[f]		✓	✓
BASDAI[g]		✓	✓

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Measure name	Screener	Baseline	24-week follow-up
BASFI[h]		✓	✓
BASMI[i]		✓	✓
MASES[j]		✓	✓
HAMA-14[k]		✓	✓
HAMD-17[l]		✓	✓
VAS[m] night pain		✓	✓
VAS 24-h pain		✓	✓
PGA[n]		✓	✓
PhGA[o]		✓	✓
SF-36[p]			
Physical function		✓	✓
Physiological role		✓	✓
Bodily pain		✓	✓
General health		✓	✓
Vitality		✓	✓
Social functioning		✓	✓
Emotional role		✓	✓
Mental health		✓	✓
Overall health		✓	✓
Adherence			✓

[a]HLA-B27: human leukocyte antigen B27.
[b]CRP: C-reactive protein.
[c]IBD: inflammatory bowel disease.
[d]AS: ankylosing spondylitis.
[e]ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score with C-reactive protein.
[f]ASAS HI: Assessment of Spondyloarthritis International Society Health Index.
[g]BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.
[h]BASFI: Bath Ankylosing Spondylitis Functional Index.
[i]BASMI: Bath Ankylosing Spondylitis Metrology Index.
[j]MASES: Bath Ankylosing Spondylitis Functional Index.
[k]HAMD-17: 17-item Hamilton Depression Scale.
[l]HAMA-14: the 14-item Hamilton Anxiety Scale.
[m]VAS: visual analog scale.
[n]PGA: patient global assessment.
[o]PhGA: physician global assessment.
[p]SF-36: 36-Item Short Form Survey.

Primary Outcome

ASDAS, including total back pain, patient global assessment of disease activity, peripheral pain or swelling, duration of morning stiffness, and C-reactive protein level, is the primary outcome [10].

Secondary Outcomes

BASDAI, BASFI, and BASMI [11], which are used to reflect disease activity, will also be evaluated.

Assessment using the Spondyloarthritis International Society Health Index (ASAS HI) is performed to determine the common difficulties of patients with AS [12]. In addition, health-related quality of life is measured using the SF-36, including physical function; role of physical, bodily pain, general health, vitality, social functioning; and role of emotional, and mental health [13].

Hamilton Depression Scale (HAMD) is performed before and after the intervention. It is summarized into seven types of factor structures: (1) anxiety or somatization: mental anxiety, physical

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anxiety, gastrointestinal symptoms, hypochondriasis, and insight; (2) weight: weight loss; (3) cognitive disorders: guilt, suicide, agitation, depersonalization and derealization, paranoid symptoms, and obsessive - compulsive symptoms; (4) day and night changes; (5) block: depression, work and interest, block and sexual symptoms; (6) sleep disorder: difficulty falling asleep, lack of sleep and early awakening; and (7) feeling of despair: feeling of loss, hopelessness and low self - esteem. Scores of <8 points or less: no depression; 8 to <20 points: prone to depression; 20 to <35 points: depression; ≥35 points: severe depression.

Hamilton Anxiety Scale (HAMA) is performed before and after the intervention. Score interpretation is as follows: ≤7 points indicate no clinically significant anxiety; 8-14 points suggest possible (mild) anxiety; 15-21 points reflect moderate anxiety; and ≥ 22 points indicate severe anxiety.

Exercise adherence is defined as the ratio of the actual completed amount of exercise (recorded via the Healbone platform) to the recommended amount (3-4 sessions/wk), which will be quantified and compared between groups.

Statistical Analyses

Statistical tests will be performed with SPSS Statistics (version 29; IBM Corp). Significance is defined as $P<.05$. Quantitative data are reported as means and SD. Statistical significance for quantitative variables is assessed using Student *t* test or 1-way ANOVA. Categorical data are presented as percentages, and significant differences are determined using chi-square tests.

Power Calculations

The sample size was calculated using ASDAS-CRP as the primary outcome. Based on a previous randomized controlled trial comparing supervised versus home-based exercise in patients with AS, the study of the effect size was 0.714 [6]. Assuming a 2-tailed independent *t* test with $\alpha=.05$, power $1-\beta=.8$, and a 1:1 allocation ratio, G*Power 3.1 estimated a required sample size of 32 participants per group (total N=64). To account for a conservative 20% attrition rate-consistent with dropout rates reported in comparable AS exercise trial, we increased the total sample size to N=80 (40 per group).

Missing Data

Missing data due to participant dropout will be addressed using the Last Observation Carried Forward (LOCF) method for the primary analysis. Under this approach, missing values at the 24-week follow-up will be replaced with the last available measurement from earlier timepoints. This method assumes that unobserved outcomes remain stable after dropout, a rationale consistent with prior studies in chronic conditions like AS, where short-term interventions may yield sustained effects. All randomized and consented patients, constituting the full analysis set, are going to be included according to intention-to-treat principles for the efficacy analyses.

Ethical Considerations

This study was approved by the Ethics Committee of the Chinese PLA General Hospital (number S2022-738-02) in compliance with the Declaration of Helsinki. All participants provided written consent after being informed of the study's goals, procedures, risks, and benefits. They retained the right to withdraw at any time without affecting their care. Participant data were anonymized and securely stored on the Healbone platform using encryption, two-factor authentication, and restricted access. Personal details (eg, names) were stored separately. No financial payment was provided. Participants received standard clinical care and exercise programs for AS. No identifiable images or personal information appeared in this paper. Any future inclusion of such content will require explicit written consent.

Results

The recruitment of the first participant began on February 27, 2023. We have screened 216 outpatients who may be eligible subjects, among them 126 outpatients who initially met the inclusion criteria. After evaluating clinicians performed face-to-face assessments, 23 lacked a stable medication regimen, 5 presented with severe cervical vertebral bridges, 3 reported regular structured exercise, 2 could not be reached after prescreening, 10 had significant cardiovascular disease, and 3 declined participation due to time constraints. Ultimately, 80 eligible participants were enrolled, with 36 randomly allocated to the intervention group and 44 to the control group (Figure 1). Recruitment was completed on March 5, 2024, and the final participant was expected to complete the study in September 2024. Data analysis (November 2024) and result dissemination (April 2025) are pending.

Discussion

Principal Findings

This study anticipates that the digital functional exercise program (Healbone), which combines wearable sensors and real-time feedback, will lead to greater reductions in disease activity (ASDAS-CRP) and improvements in physical function (BASFI and BASMI) compared to standard home-based exercises. These benefits are expected to arise from higher adherence rates in the intervention group, driven by the platform's reminders and corrective guidance. Existing research consistently shows that supervised exercise programs outperform home-based regimens in managing AS but face practical challenges like cost and accessibility [14-16]. Healbone bridges this gap by using wearable sensors and real-time feedback to mimic supervised guidance, addressing key limitations of traditional home-based methods (eg, poor adherence monitoring). This aligns with evidence that digital tools (eg, apps and wearables) improve exercise accuracy and compliance in chronic diseases. Exercise is known to reduce disease activity, pain, and stiffness in AS while enhancing physical function and quality of life [17]. However, its effectiveness depends on adherence, which is often low in home-based settings. Healbone tackles this.

Digital-powered remote system enables real-time quantitative assessment and precision-guided rehabilitation for patients with AS through sensor-based tracking, which can promote improvements in health and physical function. Studies indicate that the intensity, frequency, and duration of exercise intervention are crucial for its effectiveness [18]. However,

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previous studies have shown that the optimal mechanical load range for patients with spondyloarthritis is significantly narrower than that for normal individuals, proposing the concept of the "Goldilocks zone" for exercise load [19]. Supervised exercise rehabilitation guidance is constrained by time and location, which may affect long-term patient participation. In contrast, online exercise guidance platforms offer greater convenience and flexibility but may lack the ability to provide effective feedback, movement correction, and timely verbal encouragement [20]. Our system establishes a standardized exercise training model and provides real-time feedback and correction during exercise rehabilitation, effectively ensuring that patients engage in safe and effective exercise within their capabilities. This approach is expected to further enhance the clinical treatment outcomes for patients with AS and, expected to be widely implemented in outpatient rehabilitation settings.

Limitations

This study has several limitations. One is that the patients are recruited for PLA General Hospital, which may limit the generalizability of the results to the rest of China and internationally. However, patients come from across the country, accordingly reducing some regional differences. Second, the differing monitoring strategies between groups-digital tracking for the intervention group versus self-reporting for the control group—may influence adherence comparisons. While this reflects real-world disparities between standard and technology-enhanced care, it introduces potential measurement bias. Future studies could use matched monitoring methods (eg, wearable devices for both groups) to isolate the effect of the digital platform itself, independent of adherence measurement tools. Finally, the exclusion of regularly active individuals may reduce the generalizability of our results. However, this approach aligns with prior trials aiming to evaluate novel interventions in controlled settings.

Conclusions

To our knowledge, this is the first randomized controlled trial to assess a digital functional exercise program, enhanced with real-time feedback and sensor-based monitoring, for improving disease activity and physical function in patients with AS. If effective, this program could offer a scalable, cost-efficient solution for home-based rehabilitation, addressing the critical need for precise, supervised exercise in AS management. By leveraging current technologies, this approach fills a significant gap in chronic disease care, with potential applicability to other musculoskeletal conditions.

Acknowledgments

This work is funded by the Youth Independent Innovation Fund of the Chinese PLA (People's Liberation Army) General Hospital.

Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

The inception of the study was facilitated through the collaborative efforts of AM, FH, CW, and ZZ. XL, the principal investigator of this study, is responsible for the study design. XJ and LH participated in the design of the study. LZ, YW, MZ, TJ, and JZ are responsible for the recruitment and follow-up. All authors contributed to the intellectual content of the manuscript and the development of the trial protocol, and all authors have read, revised, and approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT (Consolidated Standards of Reporting Trials) 2010 checklist.
[PDF File (Adobe PDF File), 108 KB - resprot_v14i1e67556_app1.pdf]

Multimedia Appendix 2
Example for a personalized workout program.
[XLSX File (Microsoft Excel File), 128 KB - resprot_v14i1e67556_app2.xlsx]

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Abbreviations

AS: ankylosing spondylitis
ASAS: Assessment of SpondyloArthritis international Society
ASAS HI: Assessment of Spondyloarthritis International Society Health Index
ASDAS-CRP: Ankylosing Spondylitis Disease Activity Score with C-reactive protein
BASDAI: Bath Ankylosing Spondylitis Disease Activity Index

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BASFI: Bath Ankylosing Spondylitis Functional Index
BASMI: Bath Ankylosing Spondylitis Metrology Index
CONSORT: Consolidated Standards of Reporting Trials
DFEP: Digital Functional Exercise Program
EULAR: European League Against Rheumatism
GDPR: General Data Protection Regulation
HAMA: Hamilton Anxiety Scale
HAMD: Hamilton Depression Scale
LOCF: Last Observation Carried Forward
PLA: People's Liberation Army
SF-36: 36-item Short Form Survey
VAS: visual analog scale

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Protocol

Strategy for Withdrawal of Pharmacological Treatment for Urinary Incontinence in Children (StayDry): Protocol for an Open-Label Prospective Randomized Trial

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Abstract

Background: To the best of our knowledge, no studies have investigated the withdrawal strategy of pharmacological treatment with solifenacin or mirabegron in children diagnosed with urinary incontinence who have achieved continence on pharmacotherapy.

Objective: The primary objective is to investigate if abrupt withdrawal versus gradual withdrawal of pharmacotherapy (solifenacin or mirabegron) influences the risk of recurrence of incontinence, assessed by a self-reported 14-day calendar of incontinence episodes.

Methods: Children aged 5-14 years diagnosed with urinary incontinence, treated with pharmacotherapy of solifenacin or mirabegron and ready for withdrawal, will be randomized 1:1 to either abrupt or gradual withdrawal, according to the medical treatment that the child is receiving. The primary outcome measure is the recurrence of incontinence after withdrawal, 1 month after initiation of withdrawal of the physician-prescribed medication, assessed by a self-reported 14-day calendar of incontinence episodes. In addition, recurrence of incontinence after 3, 6, and 12 months after initiation of withdrawal will be measured. The hypothesis that gradual withdrawal is superior to abrupt withdrawal regarding the risk of recurrence of incontinence will be analyzed by logistic regression.

Results: Recruitment began at the end of May 2024 and will continue until 216 patients are included, which is expected by December 2027. As of February 2025, a total of 25 participants are included.

Conclusions: The results are expected to influence the withdrawal strategy of pharmacological treatment with solifenacin or mirabegron in children with daytime urinary incontinence.

Trial Registration: ClinicalTrials.gov NCT06465576; https://clinicaltrials.gov/search?term=NCT06465576

International Registered Report Identifier (IRRID): DERR1-10.2196/63226

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(JMIR Res Protoc 2025;14:e63226) doi:10.2196/63226

KEYWORDS

urinary incontinence; withdrawal; children; solifenacin; mirabegron

Introduction

Background

Urinary incontinence is a common condition, affecting up to 21% of children aged 5 to 7 years [1-4], and 4.5% of children and adolescents aged 11-16 years [3,4]. The most common cause of urinary incontinence is an overactive bladder [2,5]. The International Children's Continence Society defines overactive bladder as a condition with urinary urgency with or without urinary incontinence among children and adolescents aged 5 years and older and without competitive pathology explaining the symptoms, such as neurogenic detrusor overactivity or urinary tract infection [6].

First-line treatment of urinary incontinence is urotherapy, aiming at improving the bladder reservoir function and voluntary bladder control [2]. If urotherapy is insufficient for achieving continence, second-line treatment in most clinical settings is the addition of pharmacological treatment aiming at suppressing bladder smooth muscle contraction [2].

In Denmark, the current stepwise pharmacological therapy consists of an antimuscarinic as solifenacin, or a beta3-adrenoreceptor agonist as mirabegron. If monotherapy of solifenacin or mirabegron is without effect, the child is treated with a combination of solifenacin and mirabegron. However, the pharmacological treatment with solifenacin and mirabegron of children with urinary incontinence is only sparsely investigated.

In children with daytime urinary incontinence, solifenacin and mirabegron have demonstrated efficacy in reducing daytime incontinence episodes [7-13]. Solifenacin and mirabegron are widely used off-label in the pediatric population, and only a few studies dealt with the efficacy and tolerability of the agents [7-10,14].

The pharmacological handling of pediatric incontinence is considered temporary, and withdrawal attempts are recommended after continence has been achieved [15]. There is no generally accepted withdrawal strategy for solifenacin or mirabegron in children. Currently, 2 different withdrawal strategies are being used in the clinical setting, namely abrupt withdrawal and gradual withdrawal, where the dosage prescribed is reduced or the interval between dosages given is increased.

Studies report on the differences in withdrawal strategies of antidiuretic therapy targeted at enuresis in pediatric populations, indicating that gradual withdrawal of desmopressin therapy results in prolonged intervals of continence without relapse [16-19]. One study has reported that gradual withdrawal of solifenacin is superior to abrupt withdrawal in adults [20]. However, to the best of our knowledge, no studies have investigated the strategy of withdrawal of pharmacological treatment with solifenacin or mirabegron in children diagnosed with urinary incontinence who have achieved continence on these pharmaceuticals.

Our study is proposed to ensure an evidence-based approach to a withdrawal strategy for pharmacological treatment with solifenacin or mirabegron in children with urinary incontinence.

Objectives

The primary objective is to investigate if abrupt withdrawal versus gradual withdrawal of pharmacotherapy (solifenacin or mirabegron) influences the risk of recurrence of incontinence, assessed by a self-reported 14-day calendar of incontinence episodes. We hypothesize that gradual withdrawal is superior to abrupt withdrawal regarding the risk of recurrence of incontinence.

Methods

Trial Design

This is an open-label, prospective randomized trial, allocating participants to each of the 3 pharmaceutical groups, according to the physician-prescribed medical treatment that the child is receiving (solifenacin, mirabegron, or solifenacin in combination with mirabegron; Textbox 1). Within each pharmaceutical group, the participant will be randomized 1:1 to the intervention being compared: either abrupt withdrawal or gradual withdrawal. The study duration for each participant will be 12 months and encompasses 1 virtual meeting and 4 follow-up phone consultations.

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Textbox 1. Overview of the pharmaceutical groups, according to the physician-prescribed medical treatment.

Solifenacin

- 1A: abrupt withdrawal.
- 1B: gradual withdrawal.

Mirabegron

- 2A: abrupt withdrawal.
- 2B: gradual withdrawal.

Solifenacin + mirabegron

- 3A: abrupt withdrawal.
- 3B: gradual withdrawal.

Eligibility Criteria

The inclusion and exclusion criteria for this study are provided in Textbox 2.

Textbox 2. Inclusion and exclusion criteria.

Inclusion criteria

- The participants' custody holders must voluntarily sign and date an informed consent before initiation of any study-specific procedures.
- Age 5 to 14 years old (inclusive) at the time of signing the consent and inclusion.
- Diagnosed with urinary incontinence as per The International Children's Continence Society criteria.
- Pharmacological treatment with solifenacin or mirabegron.
- Continence has been achieved in pharmacological therapy with solifenacin or mirabegron.
- Previously, withdrawal attempts were accepted.
- Continence remained on the same dosage of medication for a minimum of 3 months.
- Continence remained for a minimum of 3 months (defined as urinary incontinence maximum 1 time a month or less during the last 3 months), self-reported by the participant and the participant's custody holders.

Exclusion criteria

- The inability of the patents or parental custody holders to understand the Danish written and oral information.
- Neurogenic detrusor overactivity (neurogenic bladder).

Intervention

Eligible children will be randomized 1:1 to either abrupt or gradual withdrawal of the physician-prescribed medication (solifenacin or mirabegron), the children have been treated with before entering the study. Abrupt withdrawal indicates stopping the prescribed medication on the date of withdrawal initiation. Gradual withdrawal involves taking the prescribed applied dosage of the medication every other day over 14 days, with the complete cessation of the medication occurring 14 days after the gradual withdrawal process begins.

Withdrawal of Participants and Criteria of Discontinuation of Study

A study participant should be withdrawn from the study if at any time one of the following criteria applies:

1. Recurrence of incontinence during the course of the study (defined as >2 episodes of incontinence assessed by a 14-day calendar of incontinence episodes).
2. It is the wish of the participant (or their parents or parental custody holder[s]) for any reason (withdrawal of informed consent).
3. The discretion of the investigator is for safety reasons.
4. Severe compliance with study procedure as described in the protocol, as judged by the investigator.
5. The investigator judges it as necessary due to medical reasons.
6. Participants with a condition or a situation that, in the investigator's opinion, may put the participant at significant risk or may interfere significantly with the participant's participation in the study.
7. Participants with any other condition or situation that, in the investigator's opinion, may be valid for discontinuation from the study.

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Primary Outcome

The primary outcome measure is the recurrence of incontinence after 1 month after initiation of withdrawal of the physician-prescribed medication, assessed by a self-reported 14-day calendar of incontinence episodes. In addition, recurrence of incontinence after 3, 6, and 12 months after initiation of withdrawal will be measured.

Secondary Outcome

Secondary outcome measures are as follows. Development of symptoms occurring after abrupt withdrawal of the prescribed medication (solifenacin or mirabegron), assessed by self-reported questionnaires on listed symptoms, as a change from baseline up to 30 days after initiation of withdrawal. Development of symptoms occurring after gradual withdrawal of the prescribed medication (solifenacin or mirabegron), assessed by self-reported questionnaires on listed symptoms, as the change from baseline up to 44 days after initiation of withdrawal. Refer to the Multimedia Appendix 1 for the listed symptoms. The questionnaires are constructed by the authors and do not validate or apply CHERRIES (Checklist for Reporting Results of Internet E-Surveys) items.

Procedures During the Trial

The participant timeline is illustrated in Table 1.

Table 1. Schedule of assessment.

Visit	Visit 1 (baseline)	Visit 2	Visit 3	Visit 4	Visit 5 (end of study)
Day	0	30	91	182	365
Visit schedule window	__[a]	±5 days	±5 days	±5 days	±5 days
Type of consultation	Virtual	Phone call	Phone call	Phone call	Phone call
Informed consent	✓	—	—	—	—
Inclusion and exclusion criteria	✓	—	—	—	—
Background information incl. demographics	✓	—	—	—	—
Randomization	✓	—	—	—	—
14-day calendar with incontinence episodes	—	✓	✓	✓	✓

[a]Not applicable.

Recruitment

The participants will be included in outpatient incontinence clinics at the Department of Pediatrics at Aarhus University Hospital, Aalborg University Hospital, Regional Hospital Kolding, Regional Hospital Esbjerg, and Gødstrup Hospital.

Doctors and nurses specializing in urinary incontinence in the involved departments will be asked to screen patients. Possible eligible participants will be carefully informed orally and in writing about the objectives of the study, possible risks, and the study procedures, and answer questions regarding the study. Doctors and nurses employed at the involved outpatient clinics will call or send a direct note through the electronic patient journal to the coordinating investigator, site investigator, or his or her representative (a nurse with a specialty in childhood incontinence, affiliated with the involved pediatric departments and trained in the protocol).

Possible eligible participants and their parents or legal guardians will be contacted directly by the coordinating investigator, the site investigator, or his or her representative. The procedure for obtaining informed consent is elaborated in the Informed Consent subsection.

The site investigator or his or her representative must ensure eligibility. If a possible participant and their parents or legal guardians are willing to participate after the relevant time for consideration, they are invited to visit 1 in the outpatient clinic or by phone or via virtual contact. Here, informed oral and written consent from the parents or legal guardians will be obtained and signed and dated by the parents or legal guardians and an investigator.

Visit 1

Participants will enter the study after providing informed consent by parents or parental custody holders. Background information (including age, gender, height, weight, urinary incontinence history, any other medical diagnosis, including psychiatric diagnosis, any comedication, or any withdrawal of comedication) will be obtained.

The participant will be allocated to each of the 3 pharmaceutical groups, according to the physician-prescribed medical treatment that the child is receiving. Within each pharmaceutical group, the participant will be randomized 1:1 to the intervention being compared: abrupt withdrawal or gradual withdrawal. The date of initiation of withdrawal of pharmacotherapy will be decided.

Visits 2, 3, 4, and 5

Follow-up phone consultations with the coordinating investigator or the site investigator are planned 1, 3, 6, and 12 months following initiation of withdrawal. Data collected at the follow-up visits are the status of continence. The participant will fill out a 14-day calendar of incontinent episodes before each visit. Recurrence of incontinence (defined as >2 episodes of incontinence assessed by a self-reported 14-day calendar of incontinence episodes) or no recurrence of incontinence will be registered.

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Questionnaire on Withdrawal Symptoms

During the study period, participants will be instructed to complete electronic questionnaires regarding withdrawal symptoms associated with the withdrawal of medication. The number of times and when the participant must complete the questionnaire is dependent on the allocated withdrawal method (Figure 1). The questionnaires can be completed with assistance from the parents.

Figure 1. A detailed description and timeframe of how questionnaires on withdrawal symptoms should be answered regarding the applied withdrawal method.

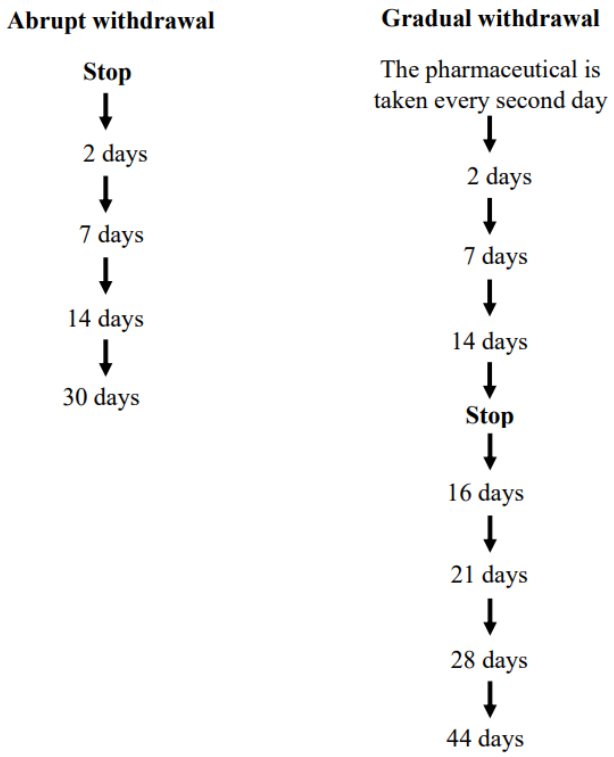

Randomization Procedure

Randomization will be performed in the REDCap (Research Electronic Data Capture, Vanderbilt University) portal and will occur centrally. An electronic case report form is built for the study data to be entered and for the randomization to be performed. Following written informed consent, randomization is stratified by a 1:1 allocation within each stratum using predefined block sizes for sites. Randomization is by a computer-generated random number list.

Statistical Analysis

Continuous variables will be presented as median with interquartile range for nonnormal distributed data, and as mean (SD) for normally distributed data. Categorical data will be presented as numbers and percentages. The distribution of data will be analyzed using histograms and QQ plots.

The hypothesis that gradual withdrawal is superior to abrupt withdrawal regarding the risk of recurrence of incontinence will be analyzed by logistic regression.

Two logistic regression models with different variations of adjustment. One logistic regression model with adjustment for each prescribed medication, as the randomization stratifies within the prescribed medication group. Another logistic regression model in which variables are adjusted due to suspicion of possible effect modification. The degree of adjustment will follow the event per the Variable rule. The logistic regression models will be analyzed at data of recurrence or not after 1 month, and hereafter 3, 6, and 12 months for a decreasing population who remain. Participants with recurrence of urinary incontinence will be described with descriptive statistics. The secondary outcome of side effects related to withdrawal will be presented with descriptive statistics.

Sample Size Calculation

To our knowledge, there is no available data regarding the efficacy of withdrawal strategies for pharmacological treatment with solifenacin or mirabegron in children diagnosed with urinary incontinence. Few studies have evaluated desmopressin withdrawal in children with enuresis. In the lack of alternatives, we have based our sample size calculation on these available desmopressin data, assuming a relapse rate of 40% with abrupt withdrawal of pharmacological treatment and 10% with gradual withdrawal of pharmacological treatment. With a significant level of .05 and a power of 80%, the minimal required sample size for adequate power is 64 participants in each group. We expect a maximum dropout rate of 10%. Therefore, 72 participants are included in the groups, for a total of 216 participants.

Ethical Considerations

Overview

The study is authorized by the authorities of the Danish Medicines Agency and the Danish Health Research Ethics Committee and registered at Clinical Trials in the European

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Union (EU CT 2023-510280-35-00). To our knowledge, no studies have been performed investigating the potential outcomes of abrupt versus gradual withdrawal of solifenacin or mirabegron used by children diagnosed with urinary incontinence. To our knowledge, no literature has assessed the connection between the abrupt withdrawal of antimuscarinic drugs and the development of withdrawal syndrome in children with urinary incontinence.

All pharmacological side effects will be handled in accordance with Danish legislation. No risk or unknown side effects are expected from medical treatment or withdrawal. The therapeutic potential for future patients justifies the project to be carried out. Participation in this study will not lead to any disadvantages for the patient in their treatment.

The study will be conducted in accordance with the protocol, applicable regulatory requirements according to Good Clinical Practice, and the ethical principles of the Declaration of Helsinki. Information regarding the participants is protected and anonymized according to the General Data Protection Regulation and the actual law. The study participants and their families will not be economically compensated for participating in the study.

Informed Consent

As a part of the process of obtaining informed consent, it is considered essential that face-to-face communication takes place. If the first visit is a virtual meeting, it will take place using Central Denmark Region's virtual meeting application. The virtual meeting application is encrypted to protect the confidential information that will be discussed.

The investigator will carefully explain orally the objectives of the study, possible risks, and the study procedures, and answer questions regarding the study. It must be ensured by the investigator that the possible participant or the parents have understood the information, and that informed consent is obtained. The possible participant should be informed within the limits of his or her understanding and with age-appropriate words.

If a possible participant and parents or parental custody holders are willing to participate, informed oral and written consent from the parent or parental custody holders will be obtained, signed, and dated by the parents or parental custody holders and the investigator. In case of a virtual visit, the informed consent is signed electronically.

Safety

Safety evaluation includes registration of adverse events and adverse reactions, as well as serious adverse events and reactions.

Registration

The trial is in accordance with the CONSORT (Consolidated Standards of Reporting Trials) checklist. The study is registered at the research inventory of the Regions of Denmark (1-16-02-211-24) and Aarhus University (ARG-2024-731-23833). The results will be submitted to Clinical Trials in the European Union within 1 year after the end of the trial. Furthermore, data will be published in the Clinical Trials Register.

Results

The StayDry study was approved by Clinical Trials in the European Union on May 22, 2024. Recruitment began on May 27, 2024, and will continue until 216 patients are included, which is expected by December 2027. As of February 2025, a total of 25 participants are included. The results will be submitted to Clinical Trials in the European Union and ClinicalTrials.gov within 1 year after the end of the trial.

Discussion

Anticipated Findings and Previous Work

This study is designed to provide valuable insights into the optimal withdrawal strategy for solifenacin and mirabegron in children with urinary incontinence, as this trial will fill a significant gap in the current literature.

The existing literature on pharmacological withdrawal in pediatric populations does not exist, particularly regarding antimuscarinics like solifenacin and mirabegron. More established literature exists on the withdrawal of desmopressin, a treatment used for enuresis. Studies examining the withdrawal of desmopressin therapy in children have found that gradual withdrawal is associated with a lower risk of relapse compared with abrupt cessation. Several studies have reported that gradual tapering of desmopressin results in longer periods of continence after discontinuation without relapse [17-19]. These findings have led to the widespread adoption of gradual withdrawal as the preferred approach for discontinuing desmopressin therapy.

Previous research in adult populations has focused on the effects of discontinuing antimuscarinics for overactive bladder [20], but findings may not be directly applicable to children. The trial has the potential to optimize the medical withdrawal and minimize the risk of recurrence of urinary incontinence after withdrawal of pharmacotherapy. The results are expected to influence the withdrawal strategy of children with urinary incontinence.

Strengths and Limitations

The strength of our study is the randomized multicenter design, encompassing 5 pediatric departments across Denmark. This ensures broad applicability and relevance in daily clinical practice. The study is embedded into and reflects daily clinical practice. The pragmatic design ensures the timely inclusion of patients and excludes participants with relapses of urinary incontinence.

The main limitation is the lack of blinding, which could introduce bias by influencing outcome assessment or potentially introducing placebo effects. Without blinding, investigators and participants are aware of withdrawal allocation, which can lead to biased behavior while answering the questionnaires and data interpretation. Another limitation is no background knowledge about socioeconomic factors.

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By conducting the study in real-life settings with medication that is familiar to patients and parents, the findings are more likely to apply to clinical practice, as they reflect the challenges and circumstances encountered in routine medical care. Furthermore, patients are more likely to adhere to treatment protocols involving medications they are familiar with or have easy access to through standard prescriptions, increasing the feasibility of recruitment and retention in the study.

Conclusion

If gradual withdrawal is superior to abrupt withdrawal, the children with urinary incontinence treated with solifenacin or mirabegron will benefit significantly from this knowledge once children with urinary incontinence can start withdrawal medical treatment.

Acknowledgments

The present study is partly financed by grants from the Health Science Research Fund of the Central Denmark Region and by economic support from the involved pediatric departments. Generative artificial intelligence tools were not used for this study.

Data Availability

The datasets generated during this study are planned to be available upon reasonable request.

Authors' Contributions

The investigation process and project administration are planned to be performed by SH, KK, LB, and AS.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Questionnaire on withdrawal symptoms.
[PDF File (Adobe PDF File), 116 KB - resprot_v14i1e63226_app1.pdf]

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Abbreviations

CHERRIES: Checklist for Reporting Results of Internet E-Surveys
CONSORT: Consolidated Standards of Reporting Trials
REDCap: Research Electronic Data Capture

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Protocol

Effectiveness and Cost-Effectiveness of a Mobile Psychoeducation Program (OkeyMind) for Social Anxiety Symptoms Among Youths: Protocol for a Randomized Controlled Trial

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Abstract

Background: Social anxiety is increasingly prevalent among youths, leading to social withdrawal, isolation, and heightened depression risk. Mobile health (mHealth) interventions offer anonymity, accessibility, and personalized support, but their effectiveness and cost-effectiveness for young individuals with social anxiety remain unclear.

Objective: This randomized controlled trial aims to evaluate the effectiveness and cost-effectiveness of a mobile-based psychoeducation program (OkeyMind) for mitigating social anxiety symptoms among youth.

Methods: Participants aged 15 years through 24 years with mild or more severe social phobia (Social Phobia Inventory [SPIN] ≥25) and access to WeChat will be recruited and screened onsite and then randomly assigned to the intervention or waiting list control group. The study will recruit 180 participants, with 90 in each group. The intervention group will receive a 1-month mobile psychoeducation program (OkeyMind), which includes both psychoeducation and meditation components, with all content fully automated. The waiting list control group will receive the same intervention after 3 months. The primary outcome is social anxiety symptoms measured using SPIN. Secondary outcomes include depression (Patient Health Questionnaire-9) and health-related quality of life (EuroQol-5). Assessments will be conducted at baseline, postintervention, and a 3-month follow-up.

Results: Recruitment began in September 2024. The study was funded in April 2024, and the first participant was enrolled in September 2024; as of the end of March 2025, 132 participants had been recruited. Recruitment is ongoing. Data collection will conclude in July 2025, after which data analysis will begin and be completed in August 2025, with primary findings targeted for publication in spring 2026.

Conclusions: This research evaluates the effectiveness and cost-effectiveness of OkeyMind, a mobile-based psychoeducation program, for reducing social anxiety symptoms among youth. OkeyMind might be a promising strategy for combating social anxiety, especially in low- and middle-income countries with limited medical resources. If effective, this intervention could provide an accessible, cost-effective approach to managing social anxiety, particularly in resource-limited settings.

Trial Registration: ClinicalTrials.gov NCT06490315; https://clinicaltrials.gov/study/NCT06490315

International Registered Report Identifier (IRRID): PRR1-10.2196/64518

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KEYWORDS

mHealth; digital health; Chinese; low cost; youth friendly

Introduction

Social Anxiety Among Youths

Social anxiety, also known as social phobia, is characterized by a marked fear of social situations where individuals may be scrutinized by others, often leading to avoidance behaviors and distress [1,2]. A core component of social anxiety is heightened sensitivity to negative evaluation, reinforcing self-doubt and anticipatory anxiety [1]. This persistent self-doubt and anticipatory anxiety can lead to social withdrawal, reducing social support and reinforcing feelings of isolation. Over time, these factors contribute to a negative self-concept and sense of helplessness, both of which are strongly associated with depression [3]. Numerous studies have demonstrated the link between social anxiety and depression [3-5]. A study tracking 2548 participants aged 14 years through 24 years from diverse communities found that social anxiety frequently coexists with major depression and, in most cases, social anxiety develops first, preceding the onset of depression [6].

Moreover, a frequently overlooked aspect in academic discussions is the distinction in depression between youths and the general adult population. This difference is significant due to various factors. First, youths experience rapid physical, emotional, and cognitive development, making them more vulnerable to depression during this period of intense change [7]. Additionally, young individuals are still developing effective coping strategies, making them more susceptible to negative influences, whereas adults, with more life experience, generally have better-established coping mechanisms [8]. Furthermore, youths often depend on guardians for access to mental health care, which can be hindered by stigma or a lack of awareness, while adults have more autonomy in seeking professional help [9]. Therefore, there is a growing demand for interventions specifically designed to address social anxiety in youths, tailored to the distinct characteristics unique to this age group.

mHealth Interventions as an Effective and Cost-Effective Method

Over the last decade, there has been a notable increase in the use of mobile health (mHealth) technologies to improve both access to and engagement with treatments for social anxiety [10]. Accumulated clinical evidence broadly supports this widespread promotion, especially in the young population. mHealth solutions in the delivery of interventions are widely accepted by youth users. Most young adults own a smartphone, have accessed mHealth apps, and report a stated preference for engaging with health services in this manner [11]. Moreover, mHealth interventions are capable of replicating, and even surpassing, the therapeutic gains achieved through traditional face-to-face treatments [12]. Studies indicate that these approaches are producing promising positive effects in reducing psychological distress, including symptoms of social anxiety [13-15]. The mobile intervention being evaluated in this study, OkeyMind, is designed to meet the specific needs of the target population and intended outcomes by leveraging WeChat's extensive global user base of 1.382 billion active users [16]. It provides a highly accessible and lightweight alternative to traditional mobile apps by eliminating the need for additional downloads and storage. Additionally, OkeyMind incorporates innovative features, including personalized feedback mechanisms for tracking progress and adaptive algorithms that tailor the intervention to individual needs. Given that young users tend to place a high value on privacy, convenience, and customization, this approach ensures greater usability and relevance for the target population [17,18].

Moreover, the delivery of mHealth services has demonstrated significant cost efficiency, a conclusion strongly supported by recent meta-analyses and synthesis studies [19,20]. This is especially evident in the realm of mental health, where mHealth solutions stand out for their ability to eliminate the need for physical infrastructure [21]. OkeyMind, a WeChat miniprogram, has a lower development complexity and shorter implementation cycle than a standalone mobile app, as it operates within the WeChat ecosystem, eliminating the need for separate app store approvals and extensive backend infrastructure [22,23]. Therefore, OkeyMind has the potential to be more easily accessible to a wider audience, including individuals who may face barriers to traditional in-person therapy, such as geographical limitations, scheduling conflicts, or stigma associated with seeking help [24].

Research Gaps

Despite the rising prevalence of social anxiety among youths, there is limited high-quality empirical evidence, particularly from randomized controlled trials, on effective interventions tailored to youth with social anxiety symptoms. mHealth interventions have shown promise, yet their efficacy remains underexplored [25]. Additionally, the scarcity of economic evaluations for psychological interventions becomes especially critical during global economic downturns, when funding for mental health support and research typically decreases [26]. The absence of economic evaluations further complicates the situation by not providing essential data on the interventions' cost-effectiveness and benefits. Without this information, policymakers struggle to allocate limited resources effectively, risking the sustainability of mental health services and potentially increasing the unmet need for psychological support in populations affected by economic hardship [27].

Research Objectives and Hypotheses

The primary objective is to assess the effectiveness of the OkeyMind mobile-based psychoeducation program on mitigating social anxiety symptoms among young adults aged 15 years through 24 years. The secondary objective is to evaluate the cost-effectiveness of the OkeyMind program as a mental health intervention tool, aiming to ascertain whether the financial investment in OkeyMind translates into significant economic and health-related advantages. The study tests 2 hypotheses: (1) OkeyMind is more effective than the control condition in reducing social anxiety symptoms among youths, and (2)

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OkeyMind is more cost-effective than the control condition for this population.

Methods

Trial Design

The design is a 2-arm, single-blind, parallel-group, randomized controlled trial to test whether the mHealth intervention program (OkeyMind), compared with the waiting list control, leads to reductions in social anxiety symptoms among youths. No additional interventions are provided beyond the OkeyMind program during the research period. Assessments will be carried out at baseline (T0), posttreatment (T1), and follow-up (T2). The choice of a 3-month follow-up assessment is primarily driven by its established feasibility in similar studies [24]. The protocol has been registered with ClinicalTrials.gov (NCT06490315). Figure 1 shows the CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

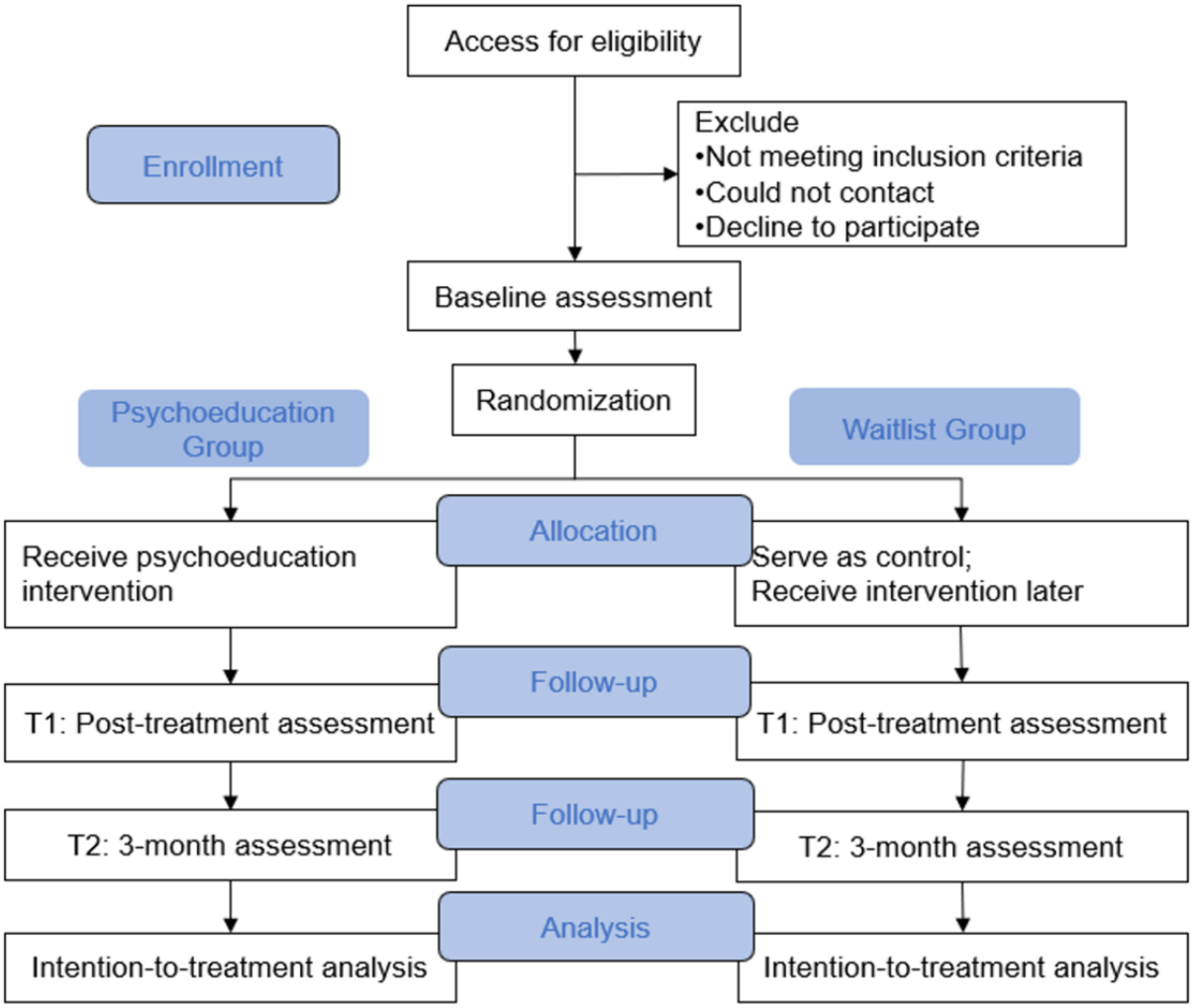

Ethical Considerations

The protocol and informed consent form received approval from the Hong Kong Shue Yan University of the Human Research Ethics Committee (HREC 24-06(6)). Eligible adult participants who are willing to join the study will provide consent by signing an online consent form. Eligible adolescent participants will be required to obtain parental consent before enrollment. To reduce the likelihood or detection of harm, various safety and security procedures will be implemented, such as excluding potentially psychologically ill participants during the screening stage.

To ensure the confidentiality and security of participant data, all collected information is securely encrypted during transmission and storage, preventing unauthorized access. Access to participant data is strictly limited to authorized research personnel. Additionally, personally identifiable information is anonymized or de-identified wherever possible to safeguard participant privacy. Each eligible participant will receive compensation of approximately HK$ 190 (US $25) for their participation in the study.

Randomization and Blinding

Participants will be randomized after the baseline assessment using computer-generated block randomization with a 1:1 allocation ratio within pre-established blocks of 90 participants. To ensure balance, a randomized blocking schema with block sizes of 2, 4, or 6 will be implemented. An independent research assistant, uninvolved in statistical analysis, will conduct the randomization. To minimize bias, participants will remain blinded to their group assignment.

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Recruitment

The study will be conducted in school settings, including middle schools and tertiary institutions, across China. The trial aims to enroll 180 participants, with 90 assigned to each group [28]. This sample size accounts for an anticipated attrition rate of 10% and is expected to offer 90% statistical power. This determination is based on using an independent group *t* test, a significance level of .05, and an effect size of 0.35 (Cohen *d*), which falls within the small-to-medium range [29]. To recruit enough participants, school faculty help with recruitment, and digital flyers and promotional videos are shared through WeChat and school online platforms.

The participant inclusion criteria include (1) youths aged between 15 years and 24 years old who are (2) exhibiting mild or more severe social phobia (ie, Social Phobia Inventory [SPIN] score ≥25) and (3) have a smartphone with WeChat installed and basic internet literacy. The exclusion criteria include (1) being unable to attempt a baseline assessment (eg, due to being unpermitted to leave a psychiatric ward), (2) currently receiving another intensive psychological intervention, (3) currently holding an active suicidal plan, and (4) having a current diagnosis of psychological disorders (eg, schizophrenia, bipolar disorder). These data will be collected through self-report questionnaires, including questions such as: "Have you been previously diagnosed with any psychological disorders (eg, schizophrenia, bipolar disorder)? If yes, please specify." Additionally, university tutors, who are familiar with students' mental health conditions, will assist with identifying ineligible participants. Participants will be recruited and screened offline but will complete all interventions and assessments online. Participants are briefed through online tutorial video clips in the OkeyMind miniprogram; these clips demonstrate the research flow regarding intervention timing, follow-up frequency, and usage intensity.

Protocol Development

Delivery Program

The intervention is delivered via a mobile phone using a WeChat miniprogram called OkeyMind. OkeyMind was initially tested during the COVID-19 pandemic in 2020. A pilot program was deployed to assess mental health conditions and promote mental health literacy among college students (n=254). Positive feedback from both students and staff emphasized the program's usability, accessibility, and relevance. Insights from this pilot informed the development of OkeyMind, improving its user interface, engagement strategies, and intervention content, with a focus on social anxiety, while maintaining high completion and satisfaction rates.

OkeyMind differentiates itself from other mobile mental health interventions through 3 main features [30]: (1) targeted focus on social phobia, (2) innovative content delivery methods, and (3) integration of evidence-based mindfulness. OkeyMind is specifically designed to address social phobia, providing tailored psychoeducation and interventions that directly target social anxiety symptoms. To enhance engagement, OkeyMind uses cartoon-based video clips, influencer interviews, real-life cases from internet celebrities, and engaging animations, making psychoeducation more interactive and appealing to youth. This approach helps maintain attention and improves information retention compared with traditional lecture-style content. OkeyMind incorporates mindfulness practices developed by the Jockey Club "Peace and Awareness" Mindfulness Culture in Schools Initiative, which have been empirically shown to reduce stress, regulate emotions, and enhance overall well-being [31]. This evidence-based component strengthens the intervention's effectiveness at supporting mental health.

OkeyMind features 3 main modules: self-learning module, psychological assessment tools, and meditation demonstrations. Participants can simply search "OkeyMind" on the WeChat miniprogram platform and access it free of charge. The mobile psychoeducation program (OkeyMind), based on the WeChat miniprogram, includes both psychoeducation and meditation components. Participants will complete the components as well as the psychological assessment tools at their own pace. For meditation practices, a tutorial video will be provided for guidance. All content is fully automated. No co-intervention will be provided alongside OkeyMind. To prevent delays in the intervention or follow-up assessments, an automated reminder function was developed. This feature ensures that participants receive pop-up reminders via WeChat if any delays occur. Trained research assistants will remind participants to engage in the activities (eg, intervention sessions, assessments) according to the study timeline and will be available to answer questions via social media platforms (eg, WeChat), phone calls, or messages.

Intervention Group—OkeyMind

This system features 3 main modules: self-learning modules, psychological assessment tools, and meditation demonstrations.

Self-Learning Modules

To design an appealing psychoeducation component for young adults, self-learning modules feature cartoon-based video clips, interviews with popular influencers, real-life cases from internet celebrities, and engaging animations. These entertaining and lively formats provide insights into social anxiety, educating users on the condition's characteristics, coping mechanisms, and guidance for seeking professional assistance. By rejecting dull content and incorporating elements that resonate with youth, these resources aim to effectively educate and support young adults.

Psychological Assessment Tools

The program incorporates interactive, user-friendly tools designed to evaluate and monitor the youth using the program. These tools might include questionnaires and scales that assess levels of social anxiety, depression, and other relevant psychological states. Tailored to provide immediate feedback, the assessments are structured to be engaging, ensuring users are motivated to complete them. By analyzing responses, the program can offer personalized insights and track progress over time, allowing users to understand their mental health patterns better. This feature aids with not only self-awareness but also identifying areas where intervention might be needed, enhancing the overall effectiveness of the psychoeducation provided.

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Meditation Demonstration

The program features guided meditation sessions led by calming, animated figures designed to appeal to young adults. These sessions aim to introduce users to various meditation techniques that can help manage symptoms of social anxiety. Each demonstration focuses on a specific meditation practice, such as mindfulness or breathing exercises, offering step-by-step guidance in a visually engaging and easy-to-follow manner. Through these demonstrations, users can learn and practice meditation in a way that is both informative and soothing, fostering skills that contribute to emotional and mental well-being.

Additionally, OkeyMind incorporates several strategies to improve adherence to intervention protocols and implements procedures for monitoring compliance, including (1) progress tracking, (2) reminders and notifications, and (3) optimal content length. Progress tracking includes features to monitor users' progress over time, such as module completion. This functionality not only encourage continued engagement but also helps users see tangible signs of their journey and growth. The reminders and notifications use automated prompts to encourage consistent use of the app's features and adherence to prescribed self-help activities. These reminders can play a critical role in fostering a routine and ensuring the beneficial use of the app. To ensure optimal content length, each video clip should be around 3 minutes to 5 minutes long, concise enough to maintain attention while providing substantial information or insights. Furthermore, complex concepts are broken down into digestible parts, with each video focusing on a single topic or coping strategy. This modular approach allows users to progress at their own pace.

Control Group—Waiting List

Participants in the waiting list control group will have access to the OkeyMind intervention withheld until after the 3-month follow-up assessment. To prevent confounding effects from relevant concomitant care and interventions, participants will be required to refrain from receiving any other treatments or interventions specifically targeting social phobia during the study period.

Outcomes

Basic demographic and clinical data, including age, gender, region, and socioeconomic status, will be collected. The primary outcome will be social anxiety symptoms, assessed using SPIN. Secondary outcomes include depressive symptoms, measured using the Patient Health Questionnaire-9 (PHQ-9), and quality of life, evaluated using the EQ-5D-5L, which will also be used for cost analysis. All outcomes will be self-assessed using online measurements at baseline, postintervention, and the 3-month follow-up (Figure 2).

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Figure 2. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist. PHQ-9: Patient Health Questionnaire-9; SPIN: Social Phobia Inventory.

	STUDY PERIOD				
	Enrolment	Allocation	Postallocation		Close-out
TIMEPOINT		Baseline	Postintervention	3-month follow-up	
ENROLLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:					
Intervention group (OkeyMind)			←	→	
Control group					X
ASSESSMENTS:					
SPIN	X		X	X	
PHQ-9	X		X	X	
EQ-5D-5L	X		X	X	
Usage metrics				X	
Qualitative evaluation				X	

The primary outcome is social anxiety symptoms measured using SPIN. Developed by Antony et al in 2006 [32], SPIN is a brief self-report tool consisting of 17 items that assess fear, avoidance, and physiological discomfort in social situations. It is specifically designed for use with social anxiety disorder [32]. The Chinese version of the SPIN has been examined with good internal consistency (Cronbach α=0.85) and test-retest reliability (r=0.73). A cutoff value of 25 or higher has demonstrated strong reliability and validity and is commonly used to screen for social anxiety in the Chinese population [33].

Secondary outcomes include depressive symptoms measured using the PHQ-9 and quality of life measured using the EQ-5D-5L. The PHQ-9 is widely used to screen for the presence and severity of depression, monitor the severity of depression over time, and assist with the diagnosis of depression. Each of the 9 items is scored from 0 (not at all) to 3 (nearly every day), with a total score ranging from 0 to 27. Higher scores indicate more severe depressive symptoms. PHQ-9 scores of 5, 10, 15, and 20 represent mild, moderate, moderately severe, and severe depression, respectively. The Chinese version of the PHQ-9 demonstrates high internal validity and consistency, evidenced by a Cronbach α of 0.86 and strong test-retest reliability with a correlation coefficient of 0.86, affirming its efficacy for use in Chinese-speaking populations [34].

EQ-5D-5L is an established tool for assessing the general health status of individuals across a wide array of health conditions and treatments [35]. It measures health outcomes in 5 dimensions: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. Each dimension is rated on a 5-level scale, from no problems (level 1) to extreme problems (level 5), facilitating a comprehensive evaluation of a patient's health-related quality of life. The total score is derived by converting the individual dimension scores into a single summary index value, reflecting overall health status, with higher scores indicating better health outcomes. Research supports the EQ-5D-5L's reliability and validity among Chinese-speaking populations, showing good internal consistency with a Cronbach α between 0.76 and 0.79 [36-38].

To assess participant adherence, usage metrics will be analyzed using log files. This includes the number of video views, instances of video interruptions, intervention completion dates, and assessment completion dates. Completion rates will be classified as follows: ≥81% indicates sufficient engagement, 61%-80% indicates moderate engagement, 41%-60% indicates partial engagement, and ≤40% indicates poor engagement. These engagement levels will be correlated with outcomes to assess intervention effectiveness. To evaluate external validity, a feedback scale will be used to collect qualitative data from

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participants. This scale will focus on how the intervention translates into their daily lives, covering aspects such as satisfaction with social functioning, academic or job performance, and other relevant real-world outcomes.

Analysis

Effectiveness Analyses

The primary hypothesis for the between-group difference in the primary outcome will be tested using a linear mixed-effects model. This model accounts for responses at postintervention and the 3-month follow-up, incorporating baseline outcome measures and intervention assignment as fixed effects, with a participant-specific random intercept. An interaction between time and the randomized group will also be fitted as a fixed effect to allow estimation of treatment effect at all time points. A similar approach will be used for the secondary outcome analysis. The imputation of missing values will be based on the assumption that data are missing at random. The primary analyses will follow the intention-to-treat principle, meaning participants will be analyzed based on their originally assigned groups, regardless of their adherence to entry criteria, the treatment received, or any withdrawal or deviation from the protocol [39]. The data will be automatically generated by the WeChat miniprogram once participants complete the process, eliminating the need for manual data entry. A P value <.05 will be used as the level of statistical significance. Data analysis will involve at least 2 statisticians or researchers and will be processed and verified using various statistical software, such as SAS and SPSS.

Cost-Effectiveness Analyses

Quality-adjusted life years (QALYs) will be used for economic evaluation to compare the relative costs and outcomes of different groups. Estimating quality of life weights involves quantifying the quality of life at different health states on a scale from 0, representing the worst imaginable health state or death, to 1, indicating perfect health. These weights are directly measured in this study population using standardized instruments (ie, EQ-5D-5L). To calculate QALYs, the quality of life weights are multiplied by the duration spent in each health state, with the results summed over the study period. Direct health care utilization, such as outpatient visits and prescribed medications, will be recorded, while indirect costs are excluded because most expected participants are secondary- or early tertiary-level students without a full-time income. Incremental cost-effectiveness ratios will then be calculated as the difference in mean cost divided by the difference in mean QALYs between the OkeyMind and waiting list groups.

Results

The study was funded in April 2024, and the first participant was enrolled in September 2024; as of the end of March 2025, 132 participants had been recruited. Recruitment is ongoing. Data collection will conclude in July 2025, after which data analysis will begin and be completed in August 2025, with primary findings targeted for publication in spring 2026. The study's design, management, analysis, and reporting are independent of the funder.

Demographic features, such as age, gender, and education level, will be reported to provide a comprehensive overview of the participant population. The primary analysis, focusing on social anxiety, will be conducted using an intention-to-treat approach, carefully accounting for missing values. Various visualizations, including trend graphs, charts, flow diagrams, and other illustrative tools, will be used to depict participants' changes over time. Additionally, subgroup analyses will be included to explore variations within specific segments of the participant population.

Metrics such as intensity and frequency of use will also be reported to offer insights into participants' engagement with the intervention. Last, any significant changes in the software or delivery of the intervention during the study period will be documented and reported to ensure transparency and to contextualize the findings.

Discussion

Expected Findings

The anticipated outcomes of this study aim to contribute to and expand upon the existing literature on mHealth interventions, particularly for youths with social anxiety. One expected finding is an improvement of access to mental health support. Prior studies have demonstrated that mHealth interventions improve accessibility for populations facing geographical, financial, or social barriers to traditional therapy [10]. This research builds on these findings by evaluating a WeChat-integrated intervention, which leverages a widely used platform to facilitate low-barrier engagement for youth with social anxiety. Another expected outcome is the provision of empirical evidence for effectively addressing social anxiety in youth. Early intervention of social anxiety is crucial to prevent long-term impairment. This study contributes to filling that gap by evaluating a mobile psychoeducation intervention designed to be culturally embedded, accessible, and engaging for young individuals. By leveraging mobile technology, this research advances empirical understanding of scalable, youth-centered mHealth interventions for social anxiety. Finally, the study anticipates economic and cost-effectiveness benefits. Previous research suggests that mHealth interventions can be cost-effective, particularly when reducing the demand for in-person services and optimizing health care resource allocation [19,20]. This study extends those findings by incorporating a cost-analysis component, providing concrete data on the economic impact of mobile-based psychoeducation for social anxiety, which remains underexplored in the current literature.

Limitations

Given that all intervention sessions and evaluations are conducted online and the research period extended over several months, there is potential for a relatively high attrition rate compared with on-site interventions. To address this issue, several measures are implemented. First, during the screening stage, interviews are scheduled to ensure each participant has the proper motivation and desire to participate, helping to select committed individuals more likely to complete the program. Second, support is provided during interventions and assessments, with manpower allocated to address any issues.

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Reminder systems, such as texts or calls, are implemented to prompt participants when delays occur, aiming to keep them engaged and on track. Third, the technology and software team continuously improves the user experience based on participant feedback, enhancing video quality and reducing buffering times to ensure a smoother and more enjoyable experience, thus reducing dropout rates due to technical frustrations.

Additionally, the technological nature of OkeyMind may limit the program's generalizability. Youths familiar with using social media and WeChat miniprograms are likely to benefit more from the intervention than older adults who may be less familiar and comfortable with these digital platforms. This discrepancy in technological proficiency could impact the overall effectiveness and reach of the program across different age groups, potentially introducing bias in the results and affecting the external validity of the study. Future research should consider addressing this limitation by exploring ways to make the program more accessible and user-friendly for older adults.

Last, achieving complete participant blinding could be challenging, particularly in behavioral interventions such as this study. Participants could infer their group assignment, introducing potential performance and self-report biases. However, using a waiting list rather than a no-treatment control ensured that control participants still anticipated full access to the intervention after follow-up, potentially softening, though not eliminating, these biases. Future studies should adopt more rigorous designs, such as concurrently running 2 active intervention arms, to mitigate performance and self-report biases.

Conclusions

In conclusion, this research aims to evaluate the effectiveness and cost-effectiveness of a mobile-based psychoeducation program, OkeyMind, designed to address social anxiety among youth. OkeyMind represents an innovative and promising strategy to combat social anxiety, especially in low- and middle-income countries where medical resources are limited. By leveraging mobile technology, this program has the potential to provide accessible and cost-effective mental health support to a population that might otherwise lack adequate resources, thereby improving mental health outcomes on a broader scale.

Acknowledgments

The study is supported by Hong Kong Shue Yan University (URG/23/17).

Data Availability

De-identified data are available upon reasonable request to the corresponding author.

Authors' Contributions

YZW, DHRZ, SMN, and XW participated in the study concept and design. YZW, XW, and BBW conducted the study. YZW drafted the manuscript. XW provided critical comments. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
mHealth: mobile health
PHQ-9: Patient Health Questionnaire-9
QALYs: quality-adjusted life years
SPIN: Social Phobia Inventory

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Protocol

Effects of Medical Ozone Injection via Intervertebral Foramen Epidural Space on Postherpetic Neuralgia: Protocol for a Randomized Controlled and Double-Blind Clinical Trial

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Abstract

Background: Previous studies have demonstrated that ozone injection into the dorsal root ganglion significantly reduces pain scores associated with herpes zoster, suggesting its therapeutic potential for managing postherpetic neuralgia (PHN) via the intervertebral foramen epidural space. However, there are no specific reports addressing the treatment of herpes zoster and PHN by involving the thoracic and lumbar nerves under computed tomography (CT) guidance. Our research focuses on the effect of medical ozone administered through the intervertebral foramen epidural space on PHN.

Objective: This is a protocol for a prospective, randomized, controlled, and double-blind trial to detect whether the injection of medical ozone via the intervertebral foramen epidural space can reduce the incidence of PHN.

Methods: After signing the written informed consent, patients meeting eligibility criteria will be allocated into the medical ozone group and the control group in a 1:1 ratio according to the randomized grouping information, with 35 patients in each group. Patients in both groups accepting the surgical procedure under CT guidance will be injected with 5 mL of therapeutic liquid. Subsequently, medical ozone (30 µg/mL, 5 mL in each segment) will be slowly administered in the medical ozone group versus a sham procedure in the control group. The primary outcome will be the incidence of PHN 3 months after the subsidence of rashes and vesicles. The secondary outcomes will be the times of injection treatment, complications during the surgical procedure, times of remedial analgesia with ultrasound-guided nerve block, numerical rating score and tactile sensation, Hospital Anxiety and Depression Scale score, and the use of lidocaine cataplasms and oral analgesics before and after the surgical procedure under CT guidance. Data analyses between the 2 groups will be compared using the 2-sided Student *t* test or Wilcoxon Mann-Whitney test based on the viability of the normality assumption, while chi-square or Fisher exact test will be used to compare the categorical data.

Results: This study was approved by the medical ethics committee of Deyang People's Hospital on February 27, 2024 (2024-03-002-K01). The first patient was enrolled on May 14, 2024. As of November 2024, 25 participants have been enrolled out of 70 who received screening. The analysis of the efficacy and safety data is expected to be performed in about May 2025 after all the patients have enrolled, with the approximate publication of results by September 2025.

Conclusions: If this exploratory trial proves effective, medical ozone administered via the intervertebral foramen epidural space may be utilized to aid in the recovery of the infected nerves and decrease the incidence of PHN in clinical settings. Positive outcomes will bolster the potential of employing medical ozone in the treatment of herpes zoster, thereby contributing to a reduction in the incidence of PHN.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2400084014; https://tinyurl.com/jk6p9hn2

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KEYWORDS

herpes zoster; postherpetic neuralgia; medical ozone; computed tomography; dorsal root ganglion; pain

Introduction

Herpes zoster (HZ) is a cutaneous disease caused by the reactivation of *Human herpesvirus 3* (varicella zoster virus) in humans [1]. The typical clinical characteristics of HZ include a cluster of rashes and vesicles on a red base, a unilateral dermatomal distribution, and intense neuralgia along the peripheral nerves near the skin lesions [2,3]. Approximately 1 out of 3 people in the United States will experience HZ within their lifetime [4]. The risk of developing postherpetic neuralgia (PHN) ranges from 5% to more than 30%, and over 30% of patients with PHN experience persistent pain for more than 1 year [5,6]. Moreover, patients with older age, immunosuppression, diabetes, systemic lupus erythematosus, rheumatoid arthritis, psychological stress, and organ transplant are more likely to experience HZ and PHN [4,6,7].

Currently, the treatment strategies for HZ include antiviral drugs, pain control, and prevention of PHN [1,7]. Studies have found that the earlier effective intervention of HZ can shorten the duration of illness, decrease the severity of HZ-related pain, and reduce the incidence of PHN [8-10]. Sufficient control of acute pain dampens the sensitization of peripheral nociceptors and the hyperexcitability of the central nervous system [11,12]. Although there are many methods to control HZ-related pain, including nerve block [13], pulsed radio frequency treatment [11,14], computed tomography (CT)-guided steroid injection [7], continuous epidural analgesia [15], and use of HZ vaccine and drugs [16,17], intractable PHN still remains [18]. More than 5% of the older patients experience PHN for more than 1 year after an acute herpes infection [19].

Ozone, consisting of triatomic oxygen atoms, is a highly reactive oxidant molecule, which is widely used in the clinic for pain management and several disease treatments [20,21]. Ozone can stimulate the body-repairing system, show anti-inflammatory effects, activate inhibitory interneurons, and generate analgesic effects via the release of enkephalin and endorphin, which also directly act on the inflammatory tissues around the nerves to alleviate pain [20]. Medical ozone therapy is also helpful for the treatment of zoster-associated acute pain [7]. Although the exact mechanism underlying ozone-related analgesia is still not understood completely, several studies have indicated that ozone therapy is able to treat PHN without tissue damage and complications [7,22,23]. Ozone autohemotherapy combined with pharmacological therapy has been reported to be superior to isolated pharmacological therapy in patients with PHN and is an effective and safe way to relieve PHN [23]. In a previous research, therapy under CT guidance combined with ozone injection–treated C3-C8 HZ neuralgia was safe and effective, and the numerical rating score (NRS) decreased significantly [7]. Ozone reaches the site of the involved intervertebral foramen epidural space segment under CT guidance, directly acting on the affected dorsal root ganglion (DRG) infected by the varicella zoster virus, where the virus establishes lifelong latency, and DRG is an essential site of generation of pain in HZ. Furthermore, DRGs lie at the entrance to the spinal cord receiving input from peripheral nerve terminals. Early effective treatment of HZ is beneficial for the prevention of PHN. However, the use of medical ozone injection–treated thoracic and lumbar nerves via the intervertebral foramen epidural space under CT guidance on PHN has not yet been investigated. Therefore, we speculate that medical ozone injected via the intervertebral foramen epidural space may reduce the incidence of PHN.

Here, we present the protocol for a prospective, randomized, controlled, and double-blind trial to evaluate whether the injection of medical ozone via the intervertebral foramen epidural space can show therapeutic effects for the infected nerve and reduce the incidence of PHN.

Methods

Study Design

This is a prospective, single-center, double-blind, randomized controlled study to detect whether medical ozone injection via the intervertebral foramina can effectively decrease the incidence of PHN. The patients will be recruited in Deyang People's Hospital, Deyang City, Sichuan Province, People's Republic of China. Table 1 shows the study schedule in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (Multimedia Appendix 1). Figure 1 shows the flowchart for this study. All researchers will be trained to conduct the study by using a standard and uniform protocol.

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Table 1. The study schedule of the enrollment, interventions, and assessments.

	Study period								
	Enrollment	Allocation	Postallocation						
Timepoint (T)	-T1	0	T1	T2	T3	T4	T5	T6	T7
Enrollment									
Eligibility screening	✓								
Informed consent	✓								
Allocation		✓							
Interventions									
With medical ozone injection			✓						
Without medical ozone injection			✓						
Assessments									
[List baseline variables]	✓	✓							
Times of treatment			✓						
Complications of surgery			✓						
Times of rescue nerve block				✓	✓	✓	✓	✓	✓
Use of lidocaine cataplasms		✓	✓	✓	✓	✓	✓	✓	✓
Use of oral analgesics		✓	✓	✓	✓	✓	✓	✓	✓
Numerical rating score		✓	✓	✓	✓	✓	✓	✓	✓
Tactile sensation		✓	✓	✓	✓	✓	✓	✓	✓
Hospital Anxiety and Depression Scale score		✓	✓	✓	✓	✓	✓	✓	✓

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Figure 1. The flowchart for this study. CT: computed tomography; HADS: Hospital Anxiety and Depression Scale; NRS: numerical rating scale; PHN: postherpetic neuralgia.

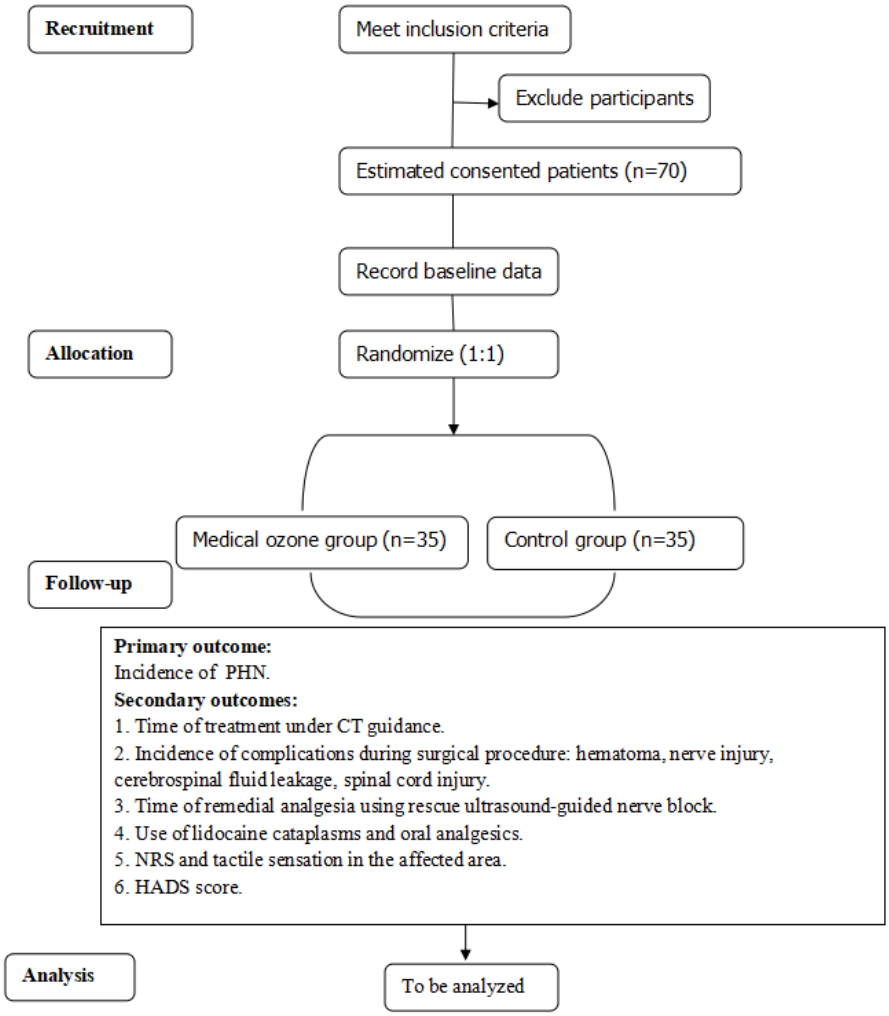

Inclusion and Exclusion Criteria

The inclusion criteria are as follows: (1) patients who are clinically diagnosed with HZ within 90 days, (2) patients who are older than 18 years, (3) the HZ region involves the unilateral thoracic 1-12 nerves and lumbar 1-5 nerves, and (4) the patients' NRS is higher than 4 when they come to the hospital.

The exclusion criteria are as follows: (1) patients who are unable to complete self-evaluation questionnaires; (2) patients who have contraindications to the use of medical ozone, steroids, and lidocaine, and to CT-guided puncture (puncture site infection, coagulation dysfunction, use of anticoagulants, or platelet count less than 70×10^9/L); (3) patients who have a history of glucose-6-phosphate dehydrogenase deficiency, hyperthyroidism, or sickle cell anemia; (4) pregnant or lactating women; (5) patients who have hemochromatosis or copper/iron therapy; and (6) critically ill patients.

Randomization and Blinding

Power Analysis and Sample Size (PASS 15) software (NCSS, LLC) will generate a random sequence. The allocation information is going to be concealed in opaque envelopes and maintained by a nurse who will not be involved in this study. Once a patient is recruited, according to the randomized grouping information, the patients will be allocated to the medical ozone injection group and the control group in a 1:1 ratio. This is a prospective and double-blind clinical trial where patients and observers do not know the grouping. To sustain blinding, an independent nurse will help prepare the medications in sterile syringes marked with research numbers, and the surgical operator will not participate in this study. Blindness can only be uncovered when severe adverse events occur.

Specifically, both patients and evaluators will be given questionnaires at the end of the study to investigate the grouping of patients, and the statistical results of the questionnaires will eventually be compared and analyzed with the true grouping. The blinding success rate will be evaluated to ensure that the blinding is conducted successfully.

Surgical Procedure and Interventions

In both groups, the surgical procedure will be performed under the guidance of a CT scan. The patients will lie in a prone position on the CT imaging bed. The vital signs will be monitored, and oxygen will be provided via a nasal oxygen tube at a rate of 3 L/min during the whole procedure. Only the surgical region will be exposed to the radiation, and other body regions will be covered by lead clothing to avoid extra exposure. The puncture segments will be based on the affected skin area.

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A slender metal needle will be placed parallel to the spine. The accurate puncture point will be determined by the following steps: Siemens Force CT scanning will be used to locate the upper edge level of the target intervertebral foramen, and the puncture target will be selected as the dorsal point of the target intervertebral foramen level. The point of the needle will be the intersection of the CT scanning level line and the extension. Subsequently, routine skin disinfection, drape, and local anesthesia of each puncture site with 1% lidocaine will be performed. After puncturing the skin, the operator will try to place the needle on the designed pathway, moving toward the target intervertebral foramen under CT guidance. When the tip of the needle enters the spinal canal, the resistance to the needle insertion will disappear and the negative pressure test will become positive. Once more, a CT scan will be performed to determine the precise position of the puncture needle tip. If more than one segment of DRGs is affected, puncture operations at all sites will be performed simultaneously. Then, 5 mL of the therapeutic liquid will be injected into each segment, which consists of 2 mL of 2% lidocaine, 0.5 mL of compound betamethasone (betamethasone sodium phosphate 0.2 mg/mL and betamethasone dipropionate 0.5 mg/mL), 0.5 mL of vitamin B12 (50 mg/mL), up to a total volume of 5 mL with saline. Patients in the medical ozone group will receive an additional slow injection of 5 mL of medical ozone (30 µg/mL) in each segment, while a sham procedure will be administered in the control group. A CT scan will be performed once again to confirm the satisfactory spread of the liquid and gas. Then, the needle will be pulled out, and the puncture point will be covered with sterile dressing. After an additional observation for 30 minutes, the patients will be safely escorted back to the ward in a supine position.

The treatment of the patient follows the relevant principles of HZ treatment at Deyang People's Hospital. Oral analgesics gabapentin and pregabalin can be used according to the patient's pain level from admission to discharge. When the patient's postoperative NRS is greater than or equal to 4 points within a week after the CT-guided treatment, rescue ultrasound-guided nerve block treatment of the affected range can be administered after excluding contraindications, and lidocaine cataplasms can be applied to the painful area of the skin after the subsidence of rashes and vesicles. After 1 week of observation and treatment after the first CT-guided treatment, if NRS is still greater than 4, the treatment under CT guidance can be repeated once, and all therapies ought to be carefully recorded in detail on case report forms on time. The treatment protocol will remain identical across both groups, with the sole distinction being the administration of medical ozone (30 µg/mL, 5 mL) in the medical ozone group versus a sham procedure in the control group, while maintaining consistency in all other therapeutic parameters, including injection technique, monitoring intervals, and adjunctive pharmacotherapy. The report of the security incidents of patients during their stay in the hospital will follow the relevant principles of Deyang People's Hospital.

Outcomes

Participants in both groups will be evaluated at time 0 (baseline), once after the operation procedure (time 1), 1 week (time 2), 2 weeks (time 3), 1 month (time 4), 2 months (time 5), 3 months (time 6), and 6 months (time 7) after the operative day.

Primary Outcomes

The primary outcome is the incidence of PHN at 3 months after the subsidence of rashes and vesicles.

Secondary Outcomes

The secondary outcomes are as follows.

1. Time of treatment under CT guidance.
2. Incidence of complications during the surgical procedure: the incidence of hematoma, nerve injury, cerebrospinal fluid leakage, and spinal cord injury.
3. Time of remedial analgesia using rescue ultrasound-guided nerve block.
4. Use of lidocaine cataplasms and oral analgesics at 1 week, 2 weeks, 1 month, 2 months, 3 months, and 6 months.
5. NRS and tactile sensation in the affected areas at once, 1 week, 2 weeks, 1 month, 2 months, 3 months, and 6 months after the operative day.
6. Hospital Anxiety and Depression Scale score before injection therapy under CT guidance and at once, 1 week, 2 weeks, 1 month, 2 months, 3 months, and 6 months after the operative day.

Data Collection and Management

Baseline demographic data, including age, gender, height, body weight, comorbidity, affected nerve segments, NRS, tactile sensation in the affected area, Hospital Anxiety and Depression Scale score, use of lidocaine cataplasms, oral analgesics, and the days from the onset of pain in the affected areas to CT-guided treatment, will be recorded before the intervention by the assessors of the research team. The primary outcome and secondary outcomes will be documented in case report forms by research observers who are independent of the grouping information. All data will be inputted and stored in the SPSS software (version 26.0; SPSS Inc) by an independent researcher. LD and XZ will be responsible for managing the data. All the researchers will be trained in skills such as eligibility evaluation, randomization, privacy protection, and interview skills before enrollment.

Data Reporting Guidelines

The SPIRIT reporting guidelines will be used for this paper.

Sample Size

The reported incidence of PHN ranged from 5% to 30% [5]. We aimed to detect a 25% difference in the incidence of PHN between the groups. The sample size was determined by the model of compare 2 proportions, that is, the 2-sample, 2-sided equality by using the PASS 15 software. We hypothesized an α level of 0.05 and a power level of 0.8. Therefore, we estimated that 33 participants were needed in each group. Considering a 5% dropout, we decided to include 70 patients, that is, 35 in each group.

Recruitment Plan

A recruitment advertisement will be posted on the WeChat Official Account of Deyang People's Hospital. Print advertising

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will be pasted on the doors of the department of pain treatment and the dermatology department. However, no persuasive advertising will be used to help with recruitment. Researchers will introduce this study to patients with HZ. To promote participant retention and completion of follow-up, we will inform them of the time points of phone calls during the recruitment period and reserve at least 2 records of contact numbers and their home address. A follow-up visit will occur at time 2 to time 7 after the treatment under CT guidance. All participants will be asked to return to the department of pain treatment and the dermatology department to accept regular fortnightly outpatient follow-up. The recruitment is planned to begin on May 14, 2024, and end on April 30, 2025.

Statistical Analysis

SPSS software will be used for all statistical analyses. The normality of the data distribution will be assessed using the Shapiro-Wilk test. Normally distributed data will be summarized as mean (SD), while nonnormally distributed data will be expressed as median (25th and 75th percentiles). Categorical data will be shown as frequency and percentages. Continuous data between the 2 groups will be compared using the 2-sided Student *t* test or Wilcoxon Mann-Whitney test based on the viability of the normality assumption, while chi-square or Fisher exact test will be used to compare the categorical data. Subgroup analyses will be conducted to analyze the primary and secondary outcomes based on the research findings. Sensitivity analysis for the findings will also be conducted. Significance is set as a 2-sided P value <.05.

Ethical Considerations

This study was approved by the medical ethics committee of Deyang People's Hospital on February 27, 2024 (ethics approval: 2024-03-002-K01). The ethics committee of Deyang People's Hospital will audit the ethic-related matters of this study once a year. This study will be performed in accordance with the Declaration of Helsinki. The research team will explain this study to the eligible participants and present them with informed consent forms. After signing the informed consent forms and relevant documents, candidates will be included into the procedure. They can withdraw from the study at any time. To ensure the privacy of the patients, all personally identifiable information will be rigorously deidentified prior to data analyses. Each participant will be assigned a random number upon participating in the study as his/her ID. The study protocol (version 3.0) was registered in the Chinese Clinical Trial Registry on May 9, 2024 (registration: ChiCTR2400084014). Patients who will complete the study will receive no compensation after completion. The results of this study will be published in a peer-reviewed journal with authorship eligibility according to the criteria of the International Committee of Medical Journal Editors.

Results

The first patient was enrolled on May 14, 2024. As of November 2024, a total of 25 participants have been enrolled out of the 70 who received screening. The analysis of the efficacy and safety data is expected to be performed in about May 2025 after all the patients have been enrolled, with an approximate publication of the results by September 2025.

Discussion

Anticipated Findings

The main finding of this study is the detection of the effects of medical ozone injection via the intervertebral foramen epidural space on PHN. This study aims to provide knowledge regarding the possibility of detecting medical ozone acting directly on DRGs affected by the varicella zoster virus. If the study proves that medical ozone can decrease NRS after the surgical procedure and the incidence of PHN, the results have the potential to improve the ability to prevent PHN in the future. Predicting the effects of medical ozone enables the possibility of initiating early HZ treatment, which is expected to reduce PHN and increase the quality of life among people with varicella zoster virus infection.

In the clinic, early effective treatment of HZ is beneficial for the prevention of PHN [24], because once the disease continues for more than 3 months after the onset of acute zoster, completely alleviating the pain becomes extremely difficult [25]. The transmission of peripheral pain signals to the upper signal center can be affected by the injection therapy of the epidural space, where the medicine acts directly on the spinal DRG [7,26]. This study is designed to assess whether the injection of medical ozone in combination with therapeutic liquid via the intervertebral epidural foramen space under CT guidance can reduce the incidence of PHN. PHN is very difficult to alleviate completely, despite several treatment methods reported [27]. According to Thompson et al [27], the proportion of individuals with HZ who developed PHN was higher from 2007 to 2018 than from 1994 to 2006, even though researchers and clinicians have made numerous attempts and efforts to reduce the incidence of PHN. Therefore, further research and exploration are urgently needed on the prevention and treatment of PHN.

Clinical evidence confirmed that escalating the ozone concentration from 25 µg/mL to 60 µg/mL in ozone autohemotherapy was clinically safe and effective, with no significant adverse events reported across multicenter trials [28]. A study [28] found that ozone autohemotherapy was an effective treatment for patients with acute HZ, where it rapidly and effectively alleviated pain symptoms and improved the cytokine levels [28]. However, the ozone autohemotherapy process often requires multiple sessions and may have a risk for bleeding. A previous retrospective study analyzed the clinical data of patients with zoster-associated pain treated under ultrasound-guided percutaneous ozone injection around the cervical DRG at the injured nerve level, supporting the effectiveness of percutaneous ozone injection [22]. However, that study only included 30 participants.

The combination of local anesthetics, steroids, and neurotrophic agents injected via the epidural space under CT guidance is also a common treatment method in clinical practice, usually performed once a week [7]. The early effective treatment can promote infected nervous tissue recovery, preventing the

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involved DRG scarring and fascial contracture in the innervated area [7]. In addition, therapy under CT guidance offers the unique capability to visualize and confirm real-time deposition of therapeutic liquid and ozone at targeted pathological sites through high-resolution anatomical imaging, thereby enhancing precision and minimizing off-target effects.

We attempt to explore whether injection of medical ozone combined with therapeutic liquid via the intervertebral foramen epidural space under CT guidance can heal the involved DRG scar and reduce the incidence of PHN since medical ozone is injected directly near the infected DRG. Thus, it is likely to help the nervous tissue recover early and completely, reducing the incidence of PHN.

Limitations

There are some limitations in this study. First, limited by the broad and variable incidence of PHN, it is difficult to calculate a perfect sample size. Second, no strict limitations will be placed on the regimen for adjunctive therapies such as gabapentin, pregabalin, and nerve blocks, which may introduce treatment heterogeneity across participants. However, the flexibility of adjuvant therapy allowed in this study was based on the context of ethical considerations and real-world applicability, and retaining adjuvant therapy flexibility would improve extrapolation of the results and reflect ozone therapy's incremental value in routine pain management. Based on the results of this study, we will further design multicenter and larger sample size clinical studies to detect the effects of medical ozone on PHN.

Conclusion

If this exploratory trial proves effective, medical ozone administered via the intervertebral foramen epidural space may be utilized to aid in the recovery of the infected nerves and decrease the incidence of PHN in clinical settings. Positive outcomes would bolster the potential of employing medical ozone in the treatment of HZ, thereby contributing to a reduction in the incidence of PHN.

Acknowledgments

This study is a clinical trial of Deyang People's Hospital. This work is supported by the Department of Pain, Department of Gastroenterology, and the Dermatology Department in Deyang People's Hospital. This work is not financially supported by any organization or individual.

Data Availability

The datasets of this study can be obtained from the corresponding author upon reasonable request at 6 months after the publication of the study results.

Authors' Contributions

Conceptualization: DX, LD, YZ, DZ, YP
Data curation: LD, DX
Formal analysis: LD, DX, YP
Investigation: XZ, YP
Methodology: DX, XZ, YP
Project administration: XZ, YP, LD
Supervision: RZ, YZ
Validation: YZ
Visualization: DX, LD, YZ, YP
Writing – original draft: DX, LD, XZ, RZ, YZ, DZ, YP
Writing – review & editing: YP, XD, LD, XZ, RZ, YZ, DZ

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT checklist.
[DOC File , 121 KB - resprot_v14i1e68847_app1.doc]

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Abbreviations

CT: computed tomography
DRG: dorsal root ganglion
HZ: herpes zoster
NRS: numerical rating score
PASS: Power Analysis and Sample Size
PHN: postherpetic neuralgia
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Online Peer Support for Long-Term Conditions: Protocol for a Feasibility Randomized Controlled Trial

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Abstract

Background: Over 30% of people in the United Kingdom are living with a long-term physical health condition. Early preventative peer support interventions could improve the lives and psychosocial well-being of people with long-term physical health conditions and reduce progression of any symptoms of low mood to more significant depression. In partnership with people with long-term conditions and industry stakeholders, we have co-designed an online peer support platform, CommonGround, to help people with long-term health conditions connect, support others, share experiences, and receive evidence-based information and advice on self-management.

Objective: This feasibility randomized controlled trial will investigate whether the CommonGround platform is usable and acceptable for people with long-term physical health conditions experiencing mild depressive symptoms and whether conducting a future, larger confirmatory randomized controlled trial is feasible.

Methods: A mixed methods, 2-arm, parallel-group, unblinded randomized controlled feasibility trial will be conducted nationally across the United Kingdom. Participants will include 150 adults (aged ≥18 years) who have access to the internet and are living with at least one long-term physical health condition and subthreshold depression (scoring 5-9 on the Patient Health Questionnaire–8). Following baseline assessments, eligible participants will be randomized to a coproduced online peer support and psychoeducation platform or a control condition where participants will receive fortnightly emails containing links to the National Health Service mental health web pages. Assessment measures will be collected at baseline and the midintervention (6 weeks) and postintervention (12 weeks) time points. A purposive sample of approximately 40 participants will be interviewed after the intervention to evaluate participant experiences and views on acceptability. The primary feasibility outcome is the number of participants recruited to the trial per week and in total via each recruitment route (as self-reported by participants).

Results: Recruitment for the feasibility trial began on February 12, 2024. Quantitative data collection was completed by October 23, 2024, and qualitative data collection was completed by December 3, 2024.

Conclusions: This trial will explore the acceptability and feasibility of our coproduced online peer support platform with embedded psychoeducational resources targeted for people living with long-term physical health conditions and subthreshold depression who are at risk of developing major depressive disorder. The findings will inform the future design of a larger randomized controlled trial exploring the platform's clinical efficacy and cost-effectiveness.

Trial Registration: ClinicalTrials.gov NCT06222346; https://clinicaltrials.gov/study/NCT06222346

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International Registered Report Identifier (IRRID): DERR1-10.2196/71513

(JMIR Res Protoc 2025;14:e71513) doi:10.2196/71513

KEYWORDS

chronic conditions; depression; long-term physical health conditions; mental well-being; online peer support; peer support; subthreshold depression

Introduction

Background

In the United Kingdom, approximately 30% of the population are living with a long-term physical health condition [1], with almost 15% of the population in England living with ≥2 long-term conditions [2,3]. Mental health conditions are common among people living with long-term physical health conditions [4]. Almost 20% of patients attending outpatient hospital appointments in the United Kingdom meet the criteria for major depressive disorder [5], and a further 20% experience symptoms of low mood, known as subthreshold depressive disorder [6]. Subthreshold depressive disorder, defined as experiencing between 2 and 5 depressive symptoms for at least 2 weeks [5,7] and scoring 5 to 9 on the Patient Health Questionnaire, adversely impacts patients' lives [8,9]. While psychological support may be offered to those reaching diagnostic thresholds for major depressive disorder (eg, National Health Service [NHS] talking therapies), there is little evidence of targeted psychological support for those living with long-term conditions who are experiencing subthreshold depressive disorder. This gap in mental health support for people with long-term conditions and subthreshold depressive disorder is a particularly pertinent issue given that the latter often precedes the development of major depressive disorder, which has downstream consequences for people with long-term conditions, their families, the NHS, and society [10,11]. Consultations with our patient and public involvement (PPI) group and the Mental Health Foundation's Living Better focus group study [12] both identified the need for greater research attention into supporting the mental health of people living with long-term conditions. Therefore, research into the development of low-cost and accessible early interventions for those with long-term conditions and subthreshold depressive disorder is warranted.

Online peer support interventions have the potential to offer inexpensive and scalable solutions where people with similar experiences interact and exchange emotional, informational, and appraisal support [13-15]. In particular, the online setting allows the support to be constantly available and overcomes practical barriers to physically accessing in-person support groups [16]. Following COVID-19, patients are also more comfortable with remote technologies in health care [17,18], with patients reporting that online peer support can also provide reciprocal social support [19-22] and access to the experiential knowledge [15,19,21] that face-to-face peer support provides. Numerous randomized controlled trials (RCTs) document the benefits of in-person peer support for decreasing depressive symptoms, increasing self-efficacy, and improving physical health outcomes [23,24]. In contrast, the number of high-quality RCTs exploring the safety and effectiveness of online peer support among people with long-term conditions is limited, and there are inconsistencies in the outcome measures administered. However, a recent scoping review found evidence of significant improvements in social participation, self-efficacy, and health-directed activity alongside reduced emotional distress due to engaging with online peer support [14]. Other studies on specific conditions such as cancer [25] have documented small to moderate reductions in depression, providing early evidence for the benefits of online peer support. Typically, online peer support communities are condition specific, overlooking the opportunity for people living with *any* long-term condition to reciprocate support based on *their shared experience of living with a long-term condition*. Furthermore, while it is suggested that patients may respond better to interventions addressing the mind-body link [26], to our knowledge, there are currently no online peer support communities specifically tailored to supporting patients' psychological well-being within the context of their physical health.

Participatory action research has been identified as a cornerstone in building successful online communities tailored to the wants and needs of people with long-term conditions [27]. Indeed, the United Kingdom's Five Year Forward View for Mental Health recommended expanding the provision of coproduced peer support interventions [28]. These views are echoed in what people with lived experience of long-term conditions have told us in our prior work: that online peer support interventions must be carefully co-designed, safe, and nonprescriptive and not feel commercialized or motivated by profit if they are to be liked and used by patients [29]. Therefore, our ultimate goal is to cocreate an online peer support platform that intervenes early to prevent comorbid major depressive disorder in people living with long-term conditions. Our collaboration with people with lived experience of mental-physical comorbidities is central to our work through our PPI groups and coapplicant with lived experience alongside clinicians, academics, and industry partners. We have collaborated for 18 months to iteratively co-design an online peer support platform with embedded psychoeducational resources called CommonGround. To inform the wider adoption of our intervention within health services, the next step is to conduct a feasibility RCT (fRCT) to evaluate the acceptability of the intervention and the feasibility of a future confirmatory trial to assess the platform's clinical effectiveness.

Objectives

The primary aim of this trial is to assess the feasibility and acceptability of our coproduced online peer support platform (CommonGround) for people living with long-term conditions and subthreshold depressive disorder and inform the design of and the feasibility of conducting a larger confirmatory trial to assess clinical efficacy and cost-effectiveness. Our specific objectives are to (1) estimate recruitment and retention rates;

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(2) determine participants' perspectives on the acceptability and usability of the platform and the acceptability of the trial procedures; and (3) determine the parameters needed to estimate the sample size for a future confirmatory RCT, including the incidence of major depressive disorder and SDs of the Patient Health Questionnaire–8 (PHQ-8) [30] and Warwick-Edinburgh Mental Well-Being Scale [31] in this population and preliminary estimates of treatment effects for clinical outcomes.

Methods

Design

A mixed methods, 2-arm, parallel-group, unblinded randomized controlled feasibility trial with a nested qualitative study will be conducted. We adopted a mixed methods approach to generate comprehensive and contextually grounded insights into the feasibility and acceptability of the intervention and trial design [32,33]. Quantitative data will support the assessment of key feasibility criteria for progression to a future efficacy trial. This includes evaluating recruitment, retention, and completion rates as well as responses to outcome measures.

Qualitative data will explore the acceptability and feasibility of both the intervention and trial procedures from the perspectives of participants and the moderation team. In particular, these data will identify views on the usability and acceptability of the CommonGround platform and opportunities for intervention optimization. Quantitative measures related to intervention acceptability, such as usability and sense of community, will be analyzed alongside interview data to provide a richer, integrated understanding of user experience. Data analysis will be collaborative, with qualitative and quantitative researchers collaborating to triangulate findings and inform future optimization and testing of the intervention and trial design.

Study Setting

This trial will be conducted remotely, with all assessments, interviews, and treatments delivered online. All participants will be recruited in the United Kingdom by King's College London (KCL).

PPI Aspect

This trial builds on prior work involving the coproduction of the online peer support platform rooted in PPI. The platform prototype was co-designed based on initial focus group insights on the psychosocial needs of people with long-term health conditions [29] and via a series of participatory design panel workshops. The participatory design panel workshops helped develop and translate a theory of change for the intervention's mechanisms into practical intervention components (eg, features that the peer support forum should have). The prototype then underwent subsequent content reviews by our research advisory group (RAG). The full details on the co-design and usability testing of the CommonGround platform will be published elsewhere.

For this trial, our RAG continued to provide input into the study procedures and documents and co-designed the adverse event (AE) schedule. From the initial development work, our RAG expanded to involve 10 members (n=6, 60% female and n=4, 40% male aged between 25 and 73 years) living with various long-term physical health conditions. In total, 60% (6/10) of the members were living with multiple long-term conditions, and 50% (5/10) had comorbid mental health diagnoses. During the trial, the RAG will continue to meet regularly to shape the development of the coding framework for the qualitative data analysis and provide feedback on the interpretation and dissemination of results. In addition, one of the coauthors (EA-F) has lived experience of multiple long-term conditions and expertise in health communications and has been a core member of our research team, helping ensure that the conduct of this study is firmly grounded in the experience of people living with long-term conditions.

Participants and Recruitment

Inclusion Criteria

Participants must be living with probable subthreshold depressive disorder (scoring 5-9 on the PHQ-8); be currently living with one or more long-term physical health conditions; be aged ≥18 years; have access to the internet (via phone, desktop, or laptop at any location, including at home, at the workplace, or free Wi-Fi in public spaces); have sufficient English proficiency to engage with the platform (self-assessed during screening); and have the ability to provide informed consent (ie, no known circumstances or conditions that may affect the capacity to consent).

Although there are no restrictions on the type of long-term condition (refer to Multimedia Appendix 1 for a list of common long-term condition options presented to interested participants), the long-term condition must be a diagnosed physical medical condition with a duration of ≥6 months that demonstrates recurrence or deterioration and is typically associated with a poor prognosis [34].

Exclusion Criteria

We will exclude participants who have ever received a diagnosis of dementia or a clinical diagnosis of severe mental illness of bipolar disorder, psychosis, posttraumatic stress disorder (PTSD), or schizophrenia. CommonGround has been specifically designed to prevent the onset of depressive episodes in those with subthreshold symptoms of depression and, therefore, may not be appropriate support for other groups of people. Individuals with established mental disorders and dementia will be excluded because CommonGround is not designed to support their mental health needs or able to support people with cognitive deficits who may find the platform problematic. All exclusion criteria are self-reported during screening.

Recruitment

Overview

In total, 5 potential recruitment routes are planned to minimize the time needed to recruit the required sample size.

Route 1 comprises consent to contact patient databases (eg, the BioResource database and Lambeth NHS Talking Therapies Service). The research team or gatekeepers from these organizations will contact individuals to share the online participant information sheet.

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Route 2 comprises outpatient clinics at King's College Hospital NHS Foundation Trust and Guy's and St Thomas' NHS Foundation Trust that have used the Integrating Mental and Physical Healthcare: Research Training and Services (IMPARTS) platform [35]. Clinicians in IMPARTS clinics will share information sheets with potentially suitable patients, and flyers will be displayed in waiting rooms to invite interested participants to contact the research team directly or access the online participant information sheet.

In route 3, outpatient clinics at King's College Hospital NHS Foundation Trust and Guy's and St Thomas' NHS Foundation Trust where IMPARTS has not been implemented will be approached to facilitate recruitment. Other primary or secondary care settings may also be approached (eg, general practices and other NHS Trusts with specialized clinics for long-term conditions). Clinicians will offer patients information sheets and display flyers in waiting rooms, inviting interested participants to contact the research team directly or access the online participant information sheet.

In route 4, public advertisements will be used throughout the social media accounts of KCL, King's Health Partners [36], and the research team (eg, X [formerly known as Twitter] and Facebook); through internal and external KCL communications and bulletins (eg, the disability team); and through flyers displayed around KCL campuses and other suitable public areas (where permission is granted). Flyers and advertisements will also be disseminated to the public through charity organizations.

Route 5 comprises word of mouth and snowballing. We will invite screened individuals or those who have already heard about the study to share the study information with their peers.

Sample Size

Sample sizes ranging between 24 and 50 are commonly recommended for feasibility studies, with Teare et al [37] recommending 70 participants for a 2-arm RCT (35 per arm). However, larger samples are typically required for online, group-based peer support interventions to gain traction as this form of peer support depends upon interactions among a large number of participants to maximize the volume of discussions and interactions that develop a sense of community. Therefore, to ensure an adequate group size for the platform, we aim to recruit 150 participants and randomize them 2:1 into intervention and control arms, respectively. Recruitment is expected to last 10 weeks. Recruiting 150 participants will allow us to estimate an expected recruitment rate (primary feasibility outcome: number recruited to the trial per week) of 15 participants per week (95% CI 12.7-17.6) based on an exact Poisson test. Given the aims of this feasibility trial, no power calculations for clinical outcomes were conducted.

Participant Timeline and Study Procedures

The flow of participants through the trial is summarized as follows (and illustrated in Figure 1): (1) recruitment (T_1); (2) consent to take part in eligibility screenings (T_1); (3) first eligibility screening (T_1); (4) wait period; (5) second eligibility screening, consent to trial, and baseline assessment (T_2); (6) randomization (T_3); (7) intervention period (T_4); (8) midintervention assessment (T_5); and (9) follow-up assessment and qualitative interviews (T_6).

All interested individuals will be directed to the trial URL or QR code on the recruitment materials to access the online participant information sheet hosted on Qualtrics (Qualtrics International Inc; T_1). Participants will have the opportunity to contact the research team with any questions. Those who read the study information and decline to consent will be asked to anonymously indicate their reasons for declining to identify potential recruitment barriers. Those interested will consent to the eligibility screenings and complete the first screening (T_1). Participants who are living outside the United Kingdom, are aged ≤17 years, do not have access to the internet, do not have a long-term physical health condition, do not have sufficient English proficiency, do not have the capacity to consent, or are living with a diagnosis of dementia or a severe mental health condition (bipolar disorder, psychosis, PTSD, or schizophrenia) will be informed that they are not eligible for the trial. All ineligible participants will be provided with information on available support and invited to contact the research team for further information.

Participants meeting all the inclusion criteria will be invited to enter the wait period. Participants ineligible at T_1*based solely on their PHQ-8 score* will also be invited to enter the wait period as PHQ-8 scores and, therefore, eligibility may change over time. The wait period is necessary so that all participants randomized to the peer support platform gain access simultaneously, maximizing the opportunity for discussion and the formation of a community. The wait period is a trial design feature and would not be necessary if CommonGround were implemented in the health care system as people with long-term health conditions could immediately enroll and gain access to the preexisting community. During the wait period, participants can opt in to receive recruitment updates via email and can access a live URL summarizing recruitment progress via the study website. The wait period will finish when the recruitment target is met (N=150). Participants will then be invited to complete the second, shorter screening via individually generated Qualtrics links to assess their eligibility on two time-varying inclusion and exclusion criteria (T_2): (1) meeting the criteria for probable subthreshold depressive disorder (scoring 5-9 on the PHQ-8) and (2) no new diagnosis received during the wait period of bipolar disorder, psychosis, PTSD, schizophrenia, or dementia.

All individuals found to be eligible at the second screening will be invited to consent to the fRCT and complete the baseline assessment (T_2). Participants have 2 weeks to complete consent and baseline assessments via their individually generated Qualtrics link. The research team will contact participants who do not respond to the rescreening invitation a maximum of 3 times via email, with a follow-up phone call if necessary. Those individuals who are found ineligible for the fRCT solely due to their PHQ-8 score (ie, they satisfy all other inclusion criteria) and have PHQ-8 scores of ≤4 or within the range of 10 to 14 will be offered the opportunity to consent to a community engagement observational cohort. Participants in the community engagement observational cohort will be onboarded onto

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CommonGround alongside trial participants and engage with the platform as they wish during the 3-month intervention period. The community engagement cohort will increase the size of the peer community, potentially facilitating the intervention to gain traction. The protocol for the engagement cohort is available in Multimedia Appendix 2 and is not described further in this paper.

Figure 1. Flowchart showing the participant timeline from recruitment (T1) to the end of data collection (T6). GP: general practitioner; HCP: health care professional; IAPT: Improving Access to Psychological Therapies; IMPARTS: Integrating Mental and Physical Healthcare: Research Training and Services; KCL: King's College London; KHP: King's Health Partners; LTC: long-term physical health condition; NHS: National Health Service; PHQ-8: Patient Health Questionnaire–8; PIS: participant information sheet; PTSD: posttraumatic stress disorder.

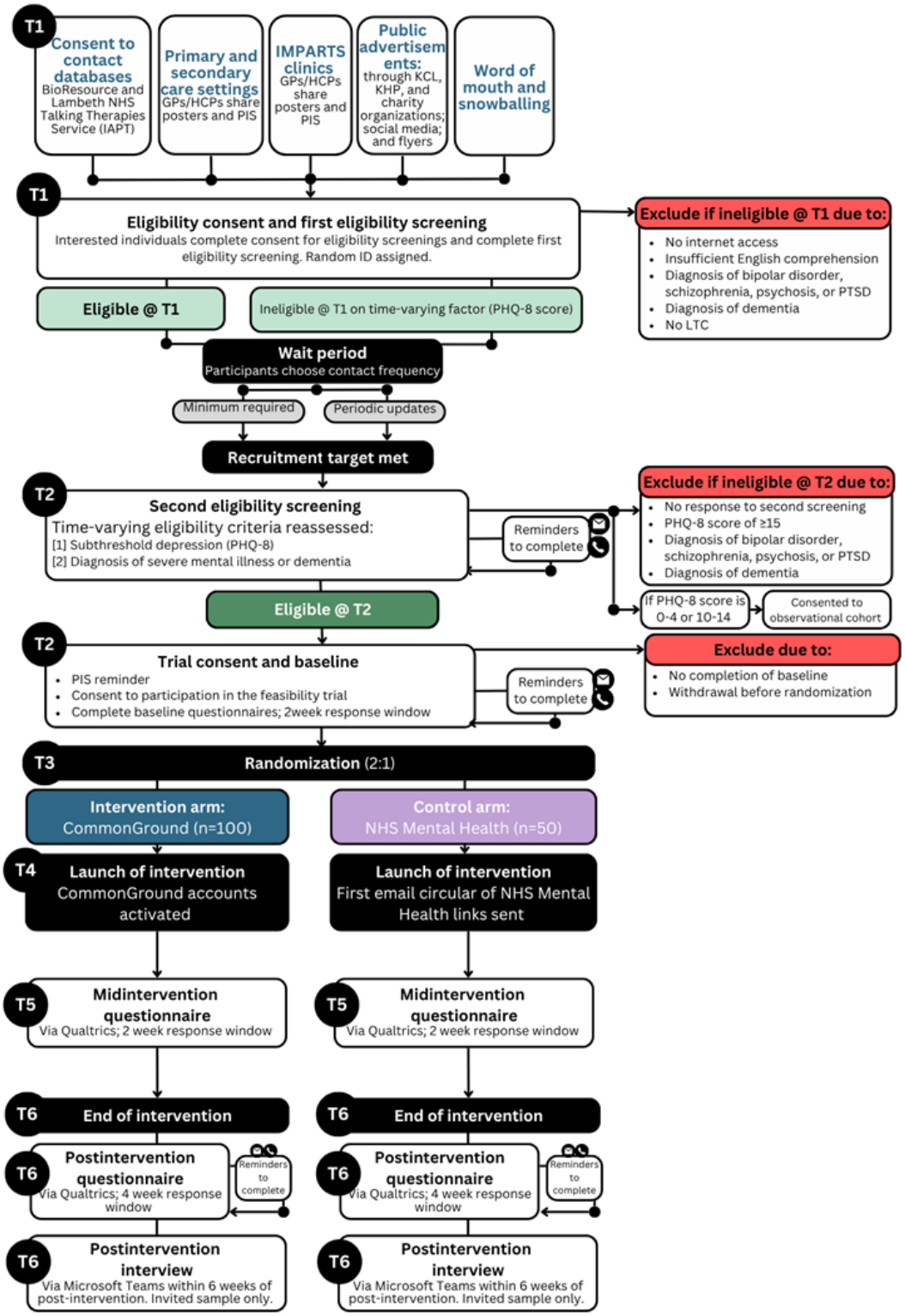

Following the baseline assessment (T_3), participants will be randomly assigned (2:1) to the CommonGround platform or the control group. The intervention period will begin on the trial launch date (T_4). At T_4, the control group will receive the first

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email sharing the NHS mental health web pages. For the intervention group, all accounts will be activated after the research team has verified their identity. Any accounts created after the launch date will be activated as soon as feasible. All participants will then have access to their treatment allocation for 3 months and can choose to engage as frequently as they wish. The control group will receive fortnightly emails resharing the links to the NHS mental health web pages throughout the intervention period.

At the midintervention time point (6 weeks; T_5), participants will be invited to complete a short online questionnaire via individually generated Qualtrics links. Symptoms of depression (via the PHQ-8) and experiences of AEs and serious AEs (SAEs) will be recorded. Participants will have 2 weeks to respond to the midintervention questionnaire. The research team will send up to 2 email reminders and follow up via telephone if required.

At the postintervention time point (12 weeks; T_6), accounts on the CommonGround platform will be closed, and the control group will no longer receive emails containing links to the NHS mental health web pages. Participants will be invited to complete the final questionnaire via individually generated Qualtrics links. Participants will have 4 weeks to respond to the postintervention questionnaire. The research team will send up to 2 email reminders and follow up via telephone if required with nonresponders. At any time, if there are any problems delivering the Qualtrics links via email (eg, email undelivered or detected as spam), the research team will attempt to call the participant to resolve the issue (eg, set up a new email address or resend from the study mailbox rather than via Qualtrics automation).

In the 6 weeks after the intervention period (T_6), a sample of participants (approximately 30 from the intervention arm and 10 from the control arm) will be invited to complete a one-to-one qualitative interview via Microsoft Teams. To explore a range of perspectives, those approached for interview will be purposively sampled based on long-term condition, age, gender, and ethnicity.

Randomization

Overview

Participants will be individually randomized (T_3) using the King's Clinical Trials Unit web-based randomization service upon completion of their baseline questionnaires (T_2) by a research assistant. Online peer support requires a sufficiently large community of active users to enable discussions and foster a community. Therefore, we will allocate participants using a 2:1 ratio (100 to the intervention arm and 50 to the control arm). Treatment allocations will be stratified based on baseline depressive symptom severity using minimization with randomly varying block sizes. Baseline depressive symptom severity will be measured using the PHQ-8 total score (low=PHQ-8 score of <7; high=PHQ-8 score of ≥7). Although the research team will be unblinded to treatment allocations, the web-based system will conceal subsequent allocations.

Blinding

Due to the nature of the interventions, it is not possible to blind participants. As the baseline and mid- and postintervention assessments will be self-reported by participants via web-based Qualtrics questionnaires, the outcome assessments will not be blinded. All research team members, including the trial statistician and qualitative interviewers, will be unblinded to treatment allocation.

Ethical Considerations

This feasibility study (and concurrent observational community cohort) has been approved by the South Central – Oxford C Research Ethics Committee (Integrated Research Application System ID328175). This study is sponsored by KCL. Approval for any amendments will be first sought from our sponsor (KCL) before submission and final approval from the South Central – Oxford C Research Ethics Committee. This trial has been registered on ClinicalTrials.gov (NCT06222346).

Informed consent will be collected on 2 occasions (Multimedia Appendix 3). Interested participants will first consent to the eligibility screenings (at T_1 and T_2, separated by the wait period). If found to be eligible at the second screening, participants will then provide informed consent for the feasibility trial. Participants who consent to the trial will be remunerated with vouchers upon completion of the baseline (£10 [US $13.74]) and postintervention (£10 [US $13.74]) assessments. Those who participate in online interviews will be remunerated with a £20 (US $27.48) voucher. Participants can choose to withdraw from the intervention, or the entire trial, at any time. Those who withdraw from their allocated treatment arm (ie, removal of access to CommonGround or ceasing of the receipt of control emails) but wish to continue with data collection will be contacted to complete the mid- and postintervention questionnaires. Participants will be invited to share their reasons for withdrawal.

All participants will have their right to privacy, communicated and protected at all times. A privacy policy will be drafted for CommonGround. No identifiable information will be published in any output from this fRCT. We will outline our procedures to maintain confidentiality via our participant information sheet with participants before seeking their consent to participate. All individuals who complete the eligibility screenings will be randomly assigned a unique ID. All research data will be pseudonymized, password-protected, and held on secure servers. Data from the one-to-one online interviews or focus groups will be audio recorded and stored in password-protected files on KCL secure servers. Personal data in the form of audio files will also be shared with our transcription service, "Way with Words," who will sign a nondisclosure agreement prior to listening to any recordings.

Interventions

Intervention Arm: CommonGround

The CommonGround platform has been co-designed through collaboration with people with lived experience of long-term conditions, clinicians, academics, and web design experts. The "all diagnoses welcome" approach, driven by the experiences of our PPI group, aims to be inclusive of all people living with long-term conditions. The online platform has a community feed for forum discussions (peer support component) and a resource section, including evidenced-based self-help

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information (psychoeducational component). Following usability testing and prototype refinement in collaboration with our RAG (pending publication), CommonGround includes the key features and functions outlined in Textbox 1 [38] (refer to Multimedia Appendix 4 for screenshots).

All participants will be required to provide personal details (name, email address, mobile number, and date of birth) upon creating their account to allow the research team to verify their identities. As participants will be anonymous to one another in the community, they will be asked to create an anonymous pseudonym username. Throughout the intervention period, the research team will be available to assist with any technical or accessibility issues. Participants can engage with CommonGround as often as they wish (ie, participation is voluntary).

Textbox 1. Key features and functions of the CommonGround platform.

- CommonGround is an online platform that is accessible via desktop and mobile devices. The platform has 2-factor authentication via SMS text message and automatic log-out after 10 minutes of inactivity.
- There is a discussion forum where users can create anonymous posts (eg, “How I am feeling”). Users can also react to (eg, “I hear you” or [laughter emoji]), comment on, and save forum posts.
- The platform includes an intuitive navigation bar that features a notification bell and a search tool to help users locate content of interest.
- Users have access to a private My Garden page, where they can store posts from other users and resources they have chosen to save.
- The Resources page gives access to evidence-based psychoeducational material on the mind-body link alongside self-help information and signposting to reputable resources and further support. The topics were selected for their relevance to people living with *any* long-term condition, such as advice on managing sleep, physical activity, and managing symptoms.
- Users have the ability to follow and mute other users, view other users’ profiles, and read their biography and view their recent activity.
- The platform includes an About Us page where users can read more about the research behind CommonGround, the platform itself, how to contact the research team, and technical troubleshooting (via “how-to” guides).
- There is a Crisis and Further Support page and web page banner where users can find organizations able to provide further support, particularly for crisis situations. This signposting is necessary because one-to-one and crisis support will not be offered on CommonGround.
- Dedicated administrative accounts will have access to an administrative panel and additional moderation functions that will allow our trained moderators to review, edit, and remove content from the community forum. The moderation team will be separate to the research team and solely dedicated to the safety of the platform. The moderators will mediate discussions between users and operate a “three-strike” policy whereby users repeatedly failing to adhere to the community principles (terms of use agreed to upon account creation) will be removed from the platform. Users can also flag posts to the attention of moderators. The moderation, safeguarding, and privacy policies that govern the operation of CommonGround will be clearly displayed on the platform. All policies have been coproduced with our coapplicant and based on guidance from King’s College London research and development and input from established organizations, including the online harms team from the Samaritans [38]. The community principles and moderation and safeguarding policies are available upon request from the corresponding author.
- There will be an engagement team (members of the research team) who will implement the engagement policy that has also been codeveloped with our patient and public involvement group and coapplicant. This policy includes weekly email circulars providing community updates and reminders to those who have not logged in recently. The engagement team will also have administrative accounts to encourage engagement via posts summarizing *trending* topics in the community feed and sharing relevant topics for people living with long-term conditions, which can be pinned to the top of the community feed. The engagement policy is available upon request from the corresponding author.

Control Group

From the launch date (T_4), participants in the control arm will be sent fortnightly emails directing them toward the NHS mental health web pages, a series of web-based resources provided by the NHS [39]. These web pages are not specifically targeted at people living with long-term conditions. The web pages include information sheets and mental health support, including topics such as managing different life situations and events. In addition, there is a self-help section that includes guides, tools, and activities to support mental health. Participants can engage with the NHS content as often as they wish (ie, participation is voluntary).

Criteria for Discontinuing or Modifying Allocated Interventions and Posttrial Care

The intervention is intended to complement the usual care participants receive for their long-term conditions. Participants can withdraw from the intervention (complete follow-up assessments) or the entire trial at any time. There are no criteria for discontinuing or modifying allocated interventions. However, for participants in the intervention group, platform access will be removed in the event of severe violations of the community principles and in accordance with the moderation policy. As this feasibility trial is not powered to assess the potential benefits or safety of the platform, there are no planned provisions for ancillary or posttrial care, and all CommonGround accounts will be closed after 3 months (at T_6). Upon study completion, all participants will be provided with PDFs containing links to the resources from the CommonGround resources page and further support and crisis information.

Measures and Outcomes

Overview

The measures and assessment time points for the CommonGround fRCT are illustrated in Table 1.

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Table 1. The schedule of enrollment, interventions, and assessments for the CommonGround feasibility randomized controlled trial.

	Study phase						
	Screening (T_1)	Enrollment (T_2)	Allocation (T_3)	After allocation			Closeout (T_6)
				T_4	T_5	T_6	
Enrollment							
Eligibility screening	✓	✓					
Informed consent	✓	✓					
Randomization			✓				
Interventions							
Intervention—CommonGround peer support platform				✓	✓	✓	
Control—NHS[a] mental health web pages				✓	✓	✓	
Assessments							
PHQ-8[b]	✓	✓			✓		✓
WEMWBS[c]		✓					✓
GAD-7[d]		✓					✓
SF-36[e]		✓					✓
SCS-R[f]		✓					✓
CDSES[g]		✓					✓
EQ-5D-5L		✓					✓
CSRI[h]		✓					✓
PAM-13[i]		✓					
SoVC[j]							✓[k]
3-item entitativity questionnaire							✓[k]
MAUQ[l]							✓[k]
AEs[m] and SAEs[n]					✓		✓

[a]NHS: National Health Service.
[b]PHQ-8: Patient Health Questionnaire–8.
[c]WEMWBS: Warwick-Edinburgh Mental Well-Being Scale.
[d]GAD-7: Generalized Anxiety Disorder scale.
[e]SF-36: 36-Item Short Form Health Survey.
[f]SCS-R: Social Connectedness Scale–Revised.
[g]CDSES: Chronic Disease Self-Efficacy Scales.
[h]CSRI: Client Service Receipt Inventory.
[i]PAM-13: Patient Activation Measure.
[j]SoVC: sense of virtual community questionnaire.
[k]Assessment delivered to the intervention group only.
[l]MAUQ: mHealth App Usability Questionnaire.
[m]AE: adverse event.
[n]SAE: serious adverse event.

Participant Characteristics

At baseline, we will use web-based Qualtrics questionnaires to collect age, date of birth, gender, sex assigned at birth, ethnicity, long-term physical health conditions, technology and internet use, history of using peer support, attitude toward peer support, and engagement in mental health treatment. The Patient Activation Measure (PAM-13) will also be administered [40]. The PAM-13 will measure the extent to which our sample are

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more passive care recipients versus more actively engaged in their health care. The PAM-13 is widely used within the NHS and for those living with long-term conditions [41] and has been validated among older adults with multimorbidity [42] and in mental health care settings [43].

Feasibility Outcomes

The primary feasibility outcome is the number of participants recruited to the trial per week and in total via each recruitment route (as self-reported by participants). The other feasibility outcomes are (1) number of participants who consent to the eligibility screenings of those contacted by the research team via the consent to contact route (eg, Bioresources and Lambeth NHS Talking Therapies Service), (2) number of participants found to be eligible at first screening (T_1) of those who consent to the eligibility screenings, (3) number of participants found to be eligible at T_2 of the number screened at T_1 and T_2, (4) number of participants who provide consent to take part in the feasibility trial of those eligible at T_2, (5) number of participants withdrawn from the trial of those randomized, and (6) number of participants who respond to the follow-up assessment at 3 months (postintervention time point; T_6) of those randomized.

Table 2 shows the criteria that have been selected to assess the feasibility of the trial. For each criterion, thresholds for *green* (the future definitive trial is likely feasible), *amber* (it may be feasible if appropriate changes are made), and *red* (it is likely not feasible) are presented.

Table 2. Feasibility criteria and associated thresholds to inform progression to a larger, future confirmatory randomized controlled trial.

Feasibility criteria	Green	Amber	Red
The number of participants randomized at T_2[a] (target: N=150 participants)	N≥120	N≥80	N≥40
Participants found to be eligible by T_2 of those who consent to the eligibility screenings at T_1[b]	≥30%	≥20%	≥10%
Participants responding to the follow-up assessment at 3 mo (postintervention time point) of those randomized (T_3[c])	≥80%	≥60%	≥40%

[a]Second eligibility screening, consent to trial, and baseline assessment.

[b]Recruitment, consent to take part in eligibility screenings, and first eligibility screening.

[c]Randomization.

Acceptability and Usability Outcomes

In the intervention arm only, the acceptability and usability of CommonGround will be measured via the following:

1. Perceived usability at the postintervention time point (T_6) using the mHealth App Usability Questionnaire (MAUQ). The MAUQ has demonstrated reliability and validity to measure mobile health app usability [44].
2. Qualitative data on the perceived acceptability and benefits of CommonGround to people living with long-term conditions who are experiencing subthreshold depressive disorder.

Platform adherence and use metrics will also be captured in the intervention arm only to provide insights into engagement. This will include the clicks and interactions of participants when accessing and using the CommonGround platform, specifically the (1) number of times logging into the platform (in total, per day, and per week), overall and by device type (eg, mobile and desktop); (2) time spent logged in (in total, per day, and per week), overall and by device type (eg, mobile and desktop); (3) number of original posts created in the community feed, comments on posts, reactions to posts, and searches; (4) number of user-to-user interactions, including follows and unfollows, muting, viewing other users' profiles, and posts flagged; (5) number of posts edited or deleted by moderators and time spent moderating; and (6) number of times participants download or open resources and save content to the My Garden private page.

Clinical and Health Economic Outcomes

Clinical outcomes will be measured for all participants at baseline (T_2) or the postintervention time point after the 3-month intervention period (T_6). All clinical outcomes will be treated as exploratory as this feasibility trial is not powered to evaluate clinical efficacy. These outcomes are (1) incidence of probable major depressive disorder at the postintervention time point only (T_6), measured using the PHQ-8 [30] (PHQ-8>9=1; PHQ-8≤9=0); (2) symptoms of depression at the midintervention (week 6; T_5) and postintervention (T_6) time points, measured using the PHQ-8 total score [30]; (3) well-being at the postintervention time point (T_6), measured using the Warwick-Edinburgh Mental Well-Being Scale [31]; (4) symptoms of anxiety at the postintervention time point (T_6), measured using the Generalized Anxiety Disorder scale total score [45]; (5) health-related quality of life at the postintervention time point (T_6), measured using the 36-Item Short Form Health Survey [46]; (6) social connectedness at the postintervention time point (T_6), measured using the Social Connectedness Scale–Revised [47]; (7) self-efficacy in managing their health at the postintervention time point (T_6), measured using the Chronic Disease Self-Efficacy Scales [48]; and (8) sense of virtual community at the postintervention time point (T_6), measured using the sense of virtual community questionnaire [49] and an adapted 3-item entitativity measure [50,51].

The following measures will be used for the health economic outcomes:

1. The EQ - 5D - 5L, a standardized measure of health status consisting of 5 dimensions [52]. Standard value sets are summarized using a single index value determining the valuation of health-related quality of life [53].

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2. The Client Service Receipt Inventory [54]. We will use an adapted version of the Client Service Receipt Inventory that measures services and supports that a participant may have used over the previous 3 months. Subsections include accommodation and living situation, employment history, health care service use, and informal support.

Qualitative Outcomes

A nested qualitative study will be conducted for this feasibility trial. Within 6 weeks after the intervention (T_6), a selection of participants will be invited to schedule a qualitative interview. For those who were in the intervention arm, the interviews will investigate their experiences and views on the peer support platform, examining the acceptability of the intervention and its perceived benefits and limitations in relation to the preconditions for change identified in the theory of change model. For all participants, the acceptability of trial procedures, including views on randomization and the relevance and burden of outcome measures, will also be explored. For those who were in the control arm, their perspectives on the acceptability of the control condition will be explored. Interview topic guides will be coproduced with our PPI group and coapplicant with lived experience. The online interviews will be audio recorded to enable transcriptions to be produced. The interviews will be conducted with approximately 40 individual participants (30 from the intervention arm and 10 from the control arm), which we estimate will afford sufficient information power [55].

The moderation team will also be invited to participate in an online focus group to explore their experiences moderating the CommonGround platform during the intervention period in accordance with the policies. Capturing moderators' experiences will provide a unique perspective on how users interact with the platform. It will also provide insight into any safeguarding issues or risks and their management to inform future iterations of the trial and the associated moderation policies and procedures.

AE Management

AEs and SAEs will be captured throughout the 3-month trial period. This includes the following:

1. Via a self-report questionnaire administered to participants in both arms at the midintervention (6 weeks; T_5) and postintervention (12 weeks; T_6) time points. This includes self-reporting of experiences of a list of expected AEs that we will coproduce with our PPI group.
2. Through monitoring and recording any other SAEs and AEs that occur throughout the intervention period.
3. As per recommended guidance on assessing the safety of digital health interventions [56] monitoring depressive symptom deterioration (as per the PHQ-8 score). The progression from mild depressive symptoms at baseline (score of 5-9) to either moderate (score of 10-14) or moderately severe (score of 15-19) depressive symptoms will also be classified as an expected AE. Progression to severe depressive symptoms (score of ≥20) will be classified as an expected SAE.

The AE protocol for this feasibility trial, including definitions, categorizations for expectedness and relatedness, and reporting procedures will be published elsewhere. Adequately capturing AEs and SAEs among a sample living with long-term conditions and subthreshold depressive disorder is important given that certain events (eg, hospitalization) are more likely to occur in our sample than in a healthy sample.

Nonadherence

In the intervention arm, nonadherence to the CommonGround intervention will be assessed based on those who (1) are randomized to the intervention arm but do not create an account, (2) create an account but do not log in, or (3) log in less than once a month. In the control arm, nonadherence will be assessed through self-report, where participants will be asked whether they accessed the NHS mental health web pages. In both arms, reasons for nonadherence will be explored in the qualitative interviews. Nonadherence to completion of the baseline, midintervention, and 3-month follow-up questionnaires will be considered if participants do not respond to or complete the questionnaires.

Data Management and Trial Monitoring

The procedures to maintain participant confidentiality will be outlined in the participant information sheet before consent. All individuals who complete the eligibility screenings will be randomly assigned a unique ID. Those randomized to CommonGround will be anonymous to other participants under their chosen pseudonym usernames. Such anonymity will be enforced by the moderation team, who will remove personally identifiable information from any forum posts or comments. Participants will be notified that anonymity may be broken by the research team under the circumstances required by the moderation and safeguarding policies (eg, disclosure of intent to commit terrorism offense or safeguarding concerns). Any use metrics or CommonGround account data shared between the software developer (Bitjam; data processor) and KCL (data controllers) external to the CommonGround platform will be pseudoanonymized (using the unique study IDs). Interview audio recordings will be shared securely with a transcription service and deleted thereafter. Platform data, data extracted from Qualtrics, and interview audio recordings or transcripts will be password protected and stored on secure servers.

A trial steering committee (TSC) will be formed, including an independent chair and independent members, the principal investigator, and the trial manager and statistician. The TSC will meet 3 times during the trial. For data monitoring purposes, we will also have an executive committee (with a single external member) who will review safety information (AEs and SAEs split by arm) and make recommendations to the blinded TSC chair, including recommendations regarding the continuation of the trial at the midintervention time point (T_5).

Statistical Analysis

We will follow the CONSORT (Consolidated Standards of Reporting Trials) 2010 statement extension for randomized feasibility and pilot trials [57] For this protocol, we have followed the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist

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(Multimedia Appendix 5). We will describe feasibility outcomes, use metrics, and clinical outcomes using appropriate summary statistics (eg, mean and SD, median and IQR for normally distributed continuous outcomes, and counts and proportions for categorical outcomes). As the clinical outcomes have been selected for their relevance for informing potential effect sizes for a future confirmatory trial, regression models will be used to estimate the effect of treatment allocation on outcomes measured at the postintervention time point (T_6). The analysis of clinical outcomes will follow a modified intention-to-treat principle. All eligible, randomized participants with a recorded outcome (ie, the outcome is not missing) will be included in the analysis and analyzed according to the treatment to which they were randomized. For binary outcomes (incidence of probable major depressive disorder at the postintervention time point), we will conduct a binary logistic regression where the model includes terms for treatment allocation (peer support platform=1; control arm=0), the baseline severity minimization factor (high=1; low=0), and the baseline value of the outcome. If the binary outcome of major depressive disorder is common (eg, >20%), we will consider robust Poisson models instead, following the work by Zou [58]. For linear outcomes (eg, symptoms of depression at the postintervention time point), we will use linear regression with the same covariates. Exploratory treatment effects will be estimated based on the coefficients for treatment allocation; 95% CIs will be estimated using bootstrapping. Given the sample size and purpose of this feasibility trial, all estimates of treatment efficacy will be treated as underpowered and not used as the basis for inferential statements. To inform sample size estimation for a future confirmatory trial, we will calculate the SD of the continuous clinical outcomes.

Qualitative Analysis

For the participant interviews, framework analysis [59] will be used to facilitate analysis within and between individual cases and groups of participants. Members of the research team will independently code the first 5 interview transcripts and discuss alternative viewpoints before agreeing to a provisional analytical framework to be applied to subsequent transcripts. The thematic framework will draw on a priori issues identified in the theory of change model as key factors related to acceptability and usability of the CommonGround platform and trial procedures while being responsive to any emergent themes. The wider research team will meet regularly to examine coding and preliminary interpretations to ensure that all themes are firmly rooted in the data. We will discuss theme names, descriptions, and illustrative quotes with the RAG to further enhance the trustworthiness of the findings. Once applied to individual transcripts, data will be charted to map the dataset as a whole, allowing the RAG and the wider research team to engage with and offer interpretations of the data. Quantitative measures related to the community (eg, sense of virtual community and entitativity) will be interpreted alongside participants' qualitative accounts of whether they felt connected with their peers and experienced a sense of community. In addition, use metrics (eg, number of log-ins, comments, and other interactions) will be examined in relation to participants' descriptions of the features that they engaged with the most and found most useful or enjoyable. For usability, scores on the MAUQ will be considered in conjunction with participants' interview accounts of their experiences navigating the platform, including any barriers to or facilitators of use.

Integration of these data will be carried out collaboratively by the qualitative and quantitative researchers, with discussion to explore patterns, contradictions, and complementary findings across data types. This triangulation will support a more nuanced understanding of participant engagement and user experience and will help identify priorities for refinement of the intervention and trial procedures.

Dissemination

We will hold workshops with our RAG to explore ways of sharing our results with patients and the public. We will also publish our results in peer-reviewed journals and present this work at key meetings or conferences.

Results

Recruitment for this feasibility trial began on February 12, 2024. We randomized 125 participants. Quantitative data collection was completed on October 23, 2024, and qualitative data collection was completed on December 3, 2024.

Discussion

Expected Findings

This trial will explore the acceptability and feasibility of CommonGround, a coproduced online peer support platform with embedded psychoeducational resources. The platform is purposefully targeted at people living with long-term physical health conditions and subthreshold depression who are at risk of developing major depressive disorder. Adopting a proactive, preventative approach to depression that intervenes earlier than the mainstream reactive approach currently used in the NHS could improve lives and reduce the burden of comorbid mental illness on patients, families, the health care system, and society.

As online peer support is accessible, inexpensive, and scalable, CommonGround might offer a way of bridging the gap in psychosocial care for people living with long-term conditions. Our intervention has been carefully coproduced through iterative prototype developments with our PPI and RAG groups, our coapplicant with lived experience, software developers, and clinicians and academics. This coproduction maximizes the potential for our intervention to address the unmet psychosocial needs of people living with long-term conditions explored in our previous work [29]. The "all diagnoses welcome" ethos of the CommonGround peer support platform contrasts with the traditional condition-specific siloed approach in the provision of peer support. While our prior work has highlighted how people with long-term conditions share common experiences that transcend diagnoses, it will be important to consider our findings in the context of a diverse patient sample and explore the acceptability of this ethos among a larger sample in the nested qualitative study.

The data derived from this feasibility trial will be essential to informing the completion of a larger multisite trial exploring

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the potential clinical efficacy and cost-effectiveness of CommonGround. We estimate that such a confirmatory trial would be completed within 42 months of the completion of this trial. If future confirmatory trials indicate the efficacy and safety of CommonGround, the intervention could be deployed in NHS services and benefit patients within 5 years. Such implementation would represent an efficient use of NHS health care resources, particularly as the "all diagnoses" inclusive approach will penetrate the NHS far more readily than a system that is distinct for each long-term condition. The platform's online, remote nature will likely ensure that rapid scale-up and wider implementation are easily achieved.

Limitations

Adoption of the intervention in routine care would require careful planning of referral strategies and a scaled-up moderation strategy, including recruitment, training, and support of a larger team of peer or clinical moderators. Large-scale adoption would also require long-term investment in hosting and maintaining platform software to support a larger community and volume of activity. It is possible that the software developer agency will cease to operate or that technical issues will occur. Therefore, we are ensuring that the platform is built using open-source software that can be maintained and adapted by any software developer with appropriate skills.

The online nature of the intervention and trial allows participants to become involved in peer support regardless of geographical location within the United Kingdom and proximity to physical services or support groups, offering a means of accessing evidence-based, reviewed self-management resources remotely. The online nature also allows participants to use CommonGround as they wish regarding the self-management of their condition and potentially fluctuating symptoms. However, this requires participants to have consistent access to both the devices and reliable internet connection required to successfully participate in the CommonGround community and research trial. While >96% of households in Great Britain have internet access [60], patients who live in households that do not have access to the internet might find this to be a barrier to enroll in the study or engage with the online intervention. The inclusion criteria of having access to the internet does not specify that this internet access must be in the home, and therefore, participants can engage from other spaces where they might be able to access the internet for free (eg, public libraries). Finding the time and space to engage with the research might be more difficult for those who do not have internet access within the home, and therefore, although it is not possible to explore methods of overcoming such barriers within the context of this feasibility trial, this could be the focus of future work to enhance access equity.

Anticipated challenges in running the intervention relate to forgotten passwords or issues logging in and technical bugs or glitches. To minimize the chance of these factors influencing engagement, there will be various "how-to" troubleshooting guides published on the platform, and both KCL and the software developers will have standardized procedures to diagnose and resolve technical issues in a timely manner. A final limitation of this feasibility trial is that, due to the nature of the intervention, it is impossible to blind participants or the study team. Due to the 2:1 design, it is not possible to blind the study statistician.

Conclusions

This trial will provide important feasibility and acceptability data on a coproduced "all diagnoses" welcome online peer support platform with embedded psychoeducation. It will inform the design of a future confirmatory trial, the essential next step in the potential for CommonGround to support the psychosocial well-being and self-management of people living with a variety of long-term physical health conditions who are at risk of developing major depressive disorder.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

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Authors' Contributions

All authors listed meet the International Committee of Medical Journal Editors criteria for authorship. MH, AS, VL, and GL conceived the study. All authors co-designed the study. GL will lead the running of the trial. GL, HGJ, and EC will lead the collection, management, and analysis of the quantitative data. VL and AS will lead the qualitative analysis. EC will lead the statistical analysis. All authors have read and approved the final manuscript.

Conflicts of Interest

MH declares funding from the Innovative Medicines Initiative for the Remote Assessment of Disease and Relapse–Central Nervous System program, a public-private precompetitive consortium on mobile health, which had partnership and funding to the university partners from Janssen, Biogen, UCB, MSD, and Lundbeck for research into depression, epilepsy, and multiple sclerosis. MH also declares research funding from the Medical Research Council, the Wellcome Trust, and the National Institute for Health and Care Research. EA-F declares voluntary and unpaid advice to Someone Who Knows, an early-stage technical initiative seeking to create an online platform that matches people with diagnosed long-term health conditions with peers for informal support and virtual conversations. Someone Who Knows is registered as a business in the Netherlands. EA-F has never received payment, shares, or any other form of exchange for this advice. All other authors have no conflicts of interest to declare.

Multimedia Appendix 1
List of long-term physical health conditions presented to interested individuals when completing the eligibility screenings.
[DOCX File , 30 KB - resprot_v14i1e71513_app1.docx]

Multimedia Appendix 2
Protocol for the community engagement cohort.
[DOCX File , 841 KB - resprot_v14i1e71513_app2.docx]

Multimedia Appendix 3
Consent forms for the eligibility screenings and trial enrollment for the CommonGround feasibility randomized controlled trial.
[DOCX File , 35 KB - resprot_v14i1e71513_app3.docx]

Multimedia Appendix 4
Screenshots of the CommonGround online peer support platform.
[DOCX File , 1113 KB - resprot_v14i1e71513_app4.docx]

Multimedia Appendix 5
SPIRIT checklist for the CommonGround feasibility randomized controlled trial.
[DOCX File , 56 KB - resprot_v14i1e71513_app5.docx]

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Abbreviations

AE: adverse event
CONSORT: Consolidated Standards of Reporting Trials
fRCT: feasibility randomized controlled trial
IMPARTS: Integrating Mental and Physical Healthcare: Research Training and Services
KCL: King's College London
MAUQ: mHealth App Usability Questionnaire
NHS: National Health Service
PAM-13: Patient Activation Measure
PHQ-8: Patient Health Questionnaire–8
PPI: patient and public involvement
PTSD: posttraumatic stress disorder
RAG: research advisory group
RCT: randomized controlled trial
SAE: serious adverse event
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TSC: trial steering committee

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Protocol

Examining the Dose-Response Effects of Mindfulness Meditation Interventions on Well-Being: Protocol for a Randomized Controlled Trial

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Abstract

Background: Mindfulness meditation has demonstrated modest benefits for mental health and well-being, although the relationship between practice dose and outcomes is unclear. Meta-analyses and randomized controlled trials have shown mixed results so far, although such results may stem from methodological issues rather than reflecting the absence of an underlying effect. Research outside structured programs suggests that long-term practice time is linked to positive outcomes, but bias due to self-selection over time may explain these results.

Objective: The proposed trial aims to test dose-response effects for an online mindfulness meditation course, examining outcomes and participant engagement across different practice doses. In this pragmatic randomized controlled trial, we hypothesize that larger doses of mindfulness training will yield significantly larger effects and different doses will be significantly associated with variation in participant engagement, with lower engagement evident for higher doses.

Methods: At least 688 healthy adults aged between 18 and 65 years will be randomized to join one of three 4-week online mindfulness courses with daily practices of varying lengths (ie, 10, 20, or 30 min) against a minimally active control condition (4 min). Psychological well-being will be measured using the Warwick-Edinburgh Mental Wellbeing Scale at the baseline, midintervention, and postintervention time points and at 1-month follow-up. Secondary outcomes are psychological distress, anxiety, depression, social anxiety, nonattachment, trait mindfulness, decentering, equanimity, repetitive negative thoughts, emotion regulation, attention control, and emotional reactivity. Other outcomes will be collected weekly and daily during the intervention period. The primary analysis will be undertaken following the intention-to-treat approach. We will also conduct per-protocol secondary analyses on all outcomes (ie, primary and secondary). In addition, we will systematically monitor for possible adverse experiences.

Results: This study began screening and recruitment in May 2024. Recruitment was paused approximately 6 weeks later after a substantial number of participants were identified as being fraudulent and not meeting the eligibility criteria. Recruitment reopened in October 2024, and by the end of 2024, a total of 70 eligible participants were enrolled. Recruitment recommenced in early 2025 and will continue until the end of March 2025 or until the target sample is reached. We estimate that the results will be published by March 2026.

Conclusions: This study will contribute to the evidence base for mindfulness meditation and the question of how much practice people need to engage in to improve well-being and other psychological outcomes.

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KEYWORDS

mindfulness; meditation; dose-response; well-being; internet- and mobile-based interventions

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Introduction

Background and Rationale

There is now reasonable evidence that mindfulness meditation can have modest beneficial effects on mental health and well-being [1-4]. For an individual starting to practice mindfulness meditation with the objective of improving their mental health and well-being, a natural question is how much practice is needed to achieve certain benefits. The empirical evidence that can be brought to bear on this question is still in its infancy. While benefits have been demonstrated at various practice intensities, there is little evidence of how different doses of daily practice relate to outcomes and whether and to what degree more practice is likely to deliver greater outcomes. Of the 4 empirical studies that have experimentally manipulated session duration to assess dose-response effects for mental health and well-being outcomes, most have failed to detect dose-response effects. However, the authors noted limited dose variation and program duration as limitations, with each of the studies including only 2 dose conditions ranging from 5 to 30 minutes in programs lasting up to 2 weeks of daily practice [5-8]. Meta-analyses investigating dose-response effects in which dose has been defined by the daily home practice component of mindfulness-based programs (MBPs) have so far shown mixed results. A meta-analysis by Parsons et al [9] found a small correlation between self-reported home practice and psychological conditions such as anxiety, depression, and stress (r=0.26, 95% CI 0.19-0.34), but a more recent meta-regression from Strohmaier [10] found no statistically significant dose-response effects for the same psychological conditions (where dose was defined as both recommended and self-reported home practice). However, as argued in the study by Bowles et al [11], the absence of evidence for daily practice dose-response effects may not constitute evidence of their absence and may, instead, be due to methodological issues. For instance, as daily practice dosages have not been experimentally manipulated in randomized designs [10], causation about the effects of different dosages cannot be inferred. In addition, as described in the study by Bowles et al [11], given that such meta-analyses were conducted on effect sizes that relate to overall program content, which features multiple active and mutually reinforcing elements [12], it is not known to what extent variation in daily practice time contributes to overall outcomes. Therefore, these dose-response meta-regression models may lack the sensitivity to detect the effects of marginal differences in daily home practice dose and, thus, may be ill-equipped to inform the question of the optimal amount of practice.

Outside the context of MBPs, regular mindfulness meditation dose-response investigations have focused primarily on the relationship between cumulative practice time over the course of an intervention and outcomes. In experimental conditions, such variation in practice time has arisen from natural differences across participants rather than systematic manipulations. While most [13-15], though not all [16], studies support a positive association between time spent practicing and outcomes, such findings may be subject to bias due to the nonrandom distribution of participants across different practice doses. In low-dose settings, while benefits have been demonstrated from single short sessions approximating 15 minutes [17], the measures used in such studies have tended to focus on transient or *state* effects that are more sensitive to change. Therefore, it is not clear what minimum dose is required for efficacious practice when measures focus on trait effects related to the psychological domains that most often motivate practice [18]. In addition, while it is likely that participants in high-dose settings such as meditation retreats represent individuals who derived enduring benefits from the practice, as evidenced by exceptional traits in several psychological and cognitive domains [19], such results may be biased by self-selection [20]. Therefore, there is a lack of empirical work in which practice doses are systematically varied in such a way as to enable differential effects to be causally linked to different practice doses. Moreover, because of this, there is a concomitant lack of empirical evidence of the merits of different practice doses given an individual's circumstances and disposition and knowledge of the trade-offs from recommending higher and lower doses.

Objectives

The proposed trial aims to (1) test for a dose-response effect on well-being across the active conditions (which feature different doses of mindfulness meditation instructions and practices; 10, 20, and 30 min) and a minimally active control condition (ie, minimal dose <10 min, <20 min, and <30 min) and (2) explore whether differential rates of program engagement and retention are evident across the 4 (active and control) conditions.

Our hypotheses are that (1) larger doses of mindfulness training will yield significantly larger effects on well-being and (2) different doses will be significantly associated with variation in participant engagement, with lower engagement evident for higher doses.

Methods

Trial Design

Overview

This study will compare the efficacy of receiving different "doses" of mindfulness training over a 28-day period in a prospective 4-arm, parallel-group randomized controlled trial. Participants will be randomized into 1 of the 4 groups: 10 minutes of meditation per day, 20 minutes of meditation per day, 30 minutes of meditation per day, or a minimal dose of 4 minutes of meditation per day (Figure 1). All participants will be encouraged not to complete any further mindfulness training or practice during the intervention period apart from informal practice during daily life. We chose these session lengths for our dose conditions to align with the range of dose variations that have been used in previous experimental research [5-8], as well as our own review of expert meditation teachers, as outlined by Bowles et al [11].

Self-reported biopsychosocial measures will be evaluated at 4 time points: before randomization (baseline; T0), 2 weeks after randomization (midintervention time point; T0.5), 4 weeks after randomization (postintervention time point; T1), and 8 weeks after randomization (follow-up; T2). In addition, weekly

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outcomes will be evaluated between T0 and T1. Individual adherence and meditation-related experiences (including adverse events) will be monitored and compared across treatments. The trial will consist of 3 main phases: the run-in period, the intervention period, and the follow-up period, as described in the following sections.

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

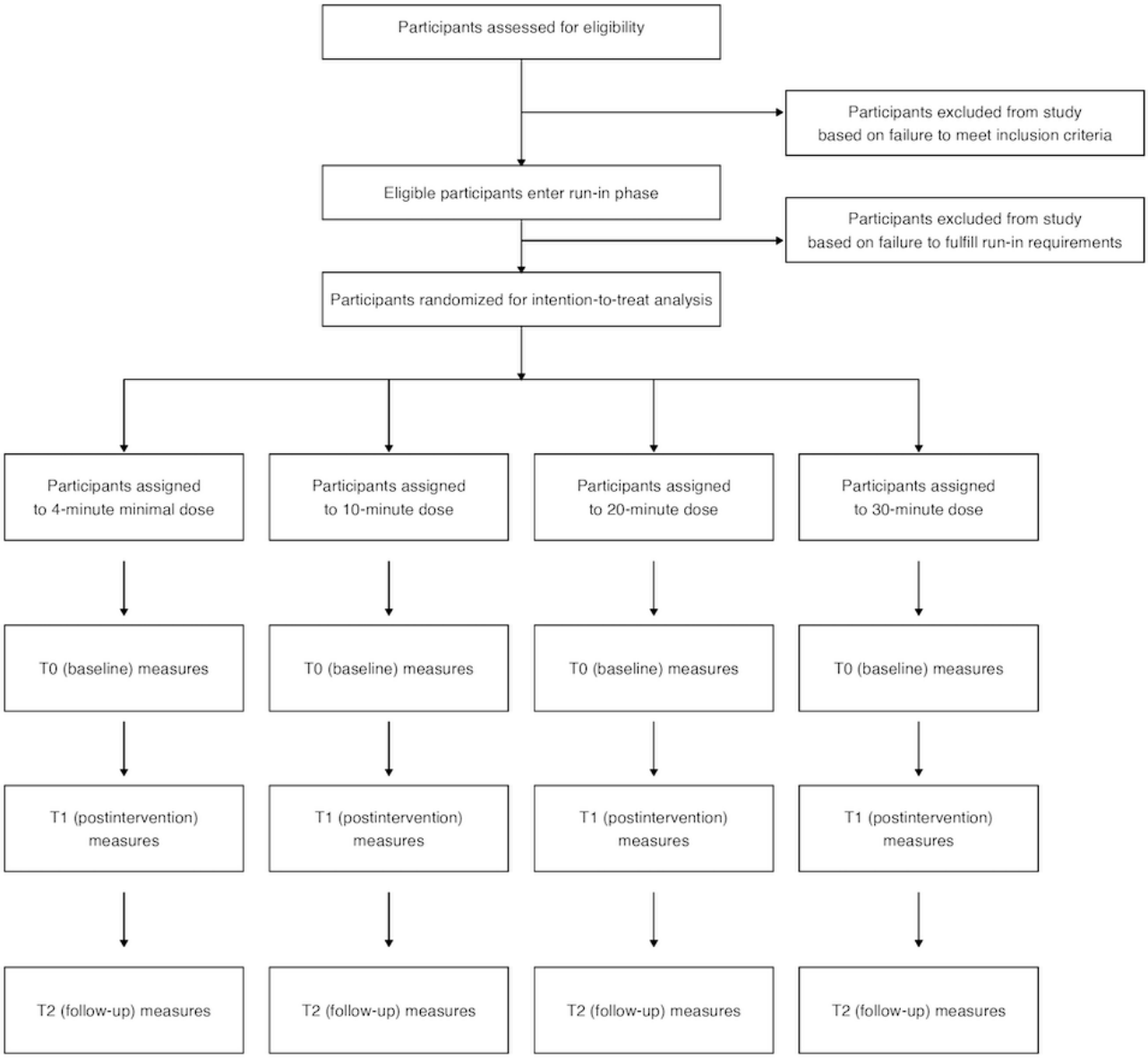

Run-In Period

We will randomize after the completion of a 7-day run-in period. Estimates of mindfulness and meditation app user retention over 28 days indicate that most attrition (approximately 90%) occurs within the first 7 days of app installation [21]. Therefore, the run-in period will be used to select the participants most likely to complete study measures. During the run-in period, we will ask participants to complete daily measures (refer to the Outcomes section) as well as listen to four short (5 min) “preparation for meditation” audios covering the following topics: (1) background of the teacher and mindfulness, (2) introduction to the concept of mindfulness, (3) introduction to mindfulness practice, and (4) results from practicing mindfulness. All this content will be accessed via a series of Qualtrics surveys (Qualtrics International Inc) that will be emailed to participants daily. Participants will also be asked to respond to measures that cover personality, sleep, and motivations and expectations. Participants will have successfully completed the run-in period if they engage with ≥57% (ie, at least 4 of the 7 days) of the run-in content.

We will monitor participant response patterns during the run-in period. If such monitoring raises suspicions about the accuracy of the information provided in the prescreening survey (ie, related to the eligibility criteria—most notably, participant identity and country of residence), additional verification procedures may be required. Participants flagged as suspicious who fail to complete or successfully pass additional verification procedures (refer to the Eligibility Criteria section) will be excluded from the study.

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Intervention Period

Participants who successfully complete the run-in period will be first asked to complete outcome measures at T0 (baseline) via Qualtrics. After completing outcome measures, participants will be randomized to 1 of the 4 study groups and provided with a unique participant identification code along with instructions on how to access the intervention materials. Participants will be asked to use only the specific mindfulness instructions provided for 28 days and complete all survey items when prompted. Throughout the 28-day period and at the conclusion of the intervention, participants will be prompted to complete outcome measures as specified in the Outcomes section.

Follow-Up Period

At the conclusion of the 28-day intervention period, participants will be offered full access to any of the 3 higher-dose courses that they choose. At the conclusion of the follow-up period (1 month after completion of the intervention), participants will again complete outcome measures as specified in the Outcomes section and Figure 1.

Study Setting

This study will be conducted entirely online; participants will complete the intervention (mindfulness program) in real-world (and, thus, ecologically valid) settings. Participants will be recruited and will communicate with the research team online. All data collection will be completed via their mobile phone, PC, or tablet.

Eligibility Criteria

Participants who provide written informed consent and meet the inclusion and exclusion criteria provided in Textbox 1 will be eligible for the study.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Age of 18 to 64 years (working-age adults as specified by the Australian Bureau of Statistics)
- Residence in Australia, with no overseas relocation or travel plans that would impact the ability to participate in the study (ie, engage with meditation practices or receive and respond to surveys)
- Sufficient comprehension of the English language to complete measures
- Registration for an account and agreement to the terms and conditions of Unforgettable.me, a web platform administered by Unforgettable Research Services Pty Ltd
- If experiencing anxious or depressive symptoms of moderate severity (defined by a score of >19 on the Patient-Reported Outcomes Measurement Information System [PROMIS] Anxiety Short Form or >22 on the PROMIS Depression Short Form), agreement to continue the recommended routine medical treatment for eligible underlying mental or physical health conditions for the duration of the study and to seek additional treatment if indicated by deterioration of symptoms
- Successful completion of the run-in period
- No or minimal experience with meditation, defined as <25 hours over the previous 6 months, and having never attended a multiday mindfulness course (eg, mindfulness-based stress reduction or Vipassana meditation). If we have not recruited 50% of our target sample size within the first 3 months of active recruitment, we will broaden the inclusion criteria to participants with up to 100 hours of mediation experience in the previous 6 months

Exclusion criteria

- Self-reported current or lifetime serious mental illness (eg, neurodevelopmental, schizophrenia spectrum, bipolar, obsessive-compulsive, trauma-related, dissociative, or personality disorder)
- Anxious and depressive symptoms in the severe range (defined by a score of >27 on the PROMIS Anxiety Short Form or >32 on the PROMIS Depression Short Form)
- Psychological distress symptoms in the severe range (Kessler Psychological Distress Scale ≥30)
- Threshold scores on prescreening and follow-up measures exceeded for mania, suicidal ideation, psychosis, repetitive thoughts and behaviors, and dissociation
- Moderate or higher alcohol, tobacco, or drug use
- Self-reported diagnosis of a neurological condition (eg, traumatic brain injury, amnesia, epilepsy, or stroke)
- Self-reported presence of any serious medical condition (eg, cancer, thyroid disorder, or multiple sclerosis)
- Recent bereavement or major loss
- History of unexplored, untreated traumatic experiences or adverse childhood events

The selection criteria will be self-assessed. Throughout the study, we will conduct various checks to verify the accuracy of the information provided in the prescreening survey to determine study eligibility. Participants whom we suspect provided inaccurate information may be required to verify specific details. If we cannot verify such information within 1 week, that participant will be deemed to have responded inaccurately and excluded from the study. Although we will make every effort to flag and remove inauthentic participants before randomization (ie, during the run-in period), in some cases, it may not be

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possible and, therefore, removal will take place after randomization. The Assignment of Interventions: Allocation and Blinding section provides details on how we will handle postrandomization exclusion.

Details on the procedure that we will use to flag and remove inauthentic participants were preregistered but are being kept confidential from study participants to avoid influencing behavior or actions that could compromise the procedure. Accordingly, the exact methodology has been embargoed [22] and will only be disclosed after data collection closes.

Prescreening Measures

Individuals will complete a prescreening survey to determine their eligibility.

Sociodemographic questions will consist of items related to age and gender. Supplementary sociodemographic questions will be asked on day 1 of the run-in period, comprising questions about ethnicity, household status, indigenous status, and education status.

English proficiency will be assessed by asking whether the primary language spoken is English. Participants for whom English is not their primary language will be asked whether they have sufficient proficiency to complete the study given that all study materials are in English.

Residency and location during the study will be assessed by asking whether the participant resides in Australia; whether they intend to travel outside Australia during the following 5 weeks; and, if so, whether such travel is likely to affect their participation.

Mental health status will be measured using the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, Self-Rated Level 1 Cross-Cutting Symptom Measure [23], a 23-item self-report measure designed to assess symptoms across 13 domains of mental health. We will measure 5 of the 13 domains: mania, suicidal ideation, psychosis, repetitive thoughts and behaviors, and dissociation. We will administer level 2 follow-up measures (Table 1) in cases in which scores for any level 1 domain exceed clinical cutoffs. For depression and anxiety, level 2 measures will be administered in lieu of the relevant level 1 items. Additional screening measures will include (1) the Kessler Psychological Distress Scale, for anxiety and depressive symptoms; (2) a single-item measure of substance use within the last year that, if any item is endorsed, will trigger a more detailed drug and alcohol screening questionnaire; and (3) a single-item measure of trauma that, if endorsed, will trigger a more detailed trauma screening questionnaire. Endorsement of any item on the more detailed screener will trigger a brief questionnaire to screen for posttraumatic stress disorder.

Meditation history will ask individuals whether they have practiced meditation in the past and, if so, to select the types of meditation they have practiced and total estimated practice time in the previous 6 months and since commencing.

The other selection criteria will be determined by asking participants directly (eg, a question about recent bereavement).

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Table 1. Follow-ups to prescreening measures if the threshold score is exceeded.

Domain of interest	Measure	Criteria	Description
Mania	ASRM[a]	Raw score>10[b], indicating high probability of manic or hypomanic condition	The ASRM is a 5-item measure that assesses mood, self-confidence, sleep disturbance, speech, and activity level [24].
Suicidal ideation	DSI-SS[c]	Total score>2	The DSI-SS is a 4-item measure that assesses the frequency and intensity of suicidal ideation, formulation of plans for suicide, the controllability of suicidal thoughts, and impulses related to suicide.
Psychosis	PQ-16[d]	Total score>5	The PQ-16 is a 16-item measure of psychosis with 9 items on perceptual abnormalities and hallucinations, 5 items on unusual thought content, and 2 items on negative symptoms.
Repetitive thoughts and behaviors	Repetitive Thoughts and Behavior	Average score of >2 (total raw score ≥11), indicating severe or extreme symptoms	Repetitive Thoughts and Behavior is a 5-item assessment of repetitive thoughts and behaviors that has been adapted from the FOCI[e] Severity Scale.
Dissociation	DES-B[f]-Modified	Average score of >2 (total raw score ≥17), indicating severe or extreme symptoms	The DES-B-Modified is an 8-item assessment of the severity of dissociative experiences [25].
Substance use	NIDA[g] Quick Screen (version 1.0), NIDA-Modified ASSIST[h], and AUDIT[i] alcohol screening tool	See the "Description" column	We will ask participants whether they have used alcohol (≥5 drinks for men and ≥4 drinks for women), tobacco, prescription drugs for nonmedical reasons, or other illegal drugs in the past year. If the participant endorses "once or twice" or more frequent use in the last year, we will ask which drugs and additionally ask about frequency of use in the past 3 months ("never," "once or twice," "monthly," "weekly," "daily," or "almost daily"). For alcohol, participants reporting daily use (of 5 drinks for men and 4 drinks for women) will be excluded. Participants reporting weekly or monthly use will be administered the alcohol screening tool, and a score of ≥14 will result in the participant being excluded. For tobacco, participants reporting daily use will be excluded. For drugs (prescription drugs for nonmedical reasons or illegal drugs), participants reporting weekly or daily use will be excluded. If participants report monthly use or use once or twice, we will ask additional questions as follows: (1) "In the past three months, how often have you had a strong desire or urge to use [drug]? How often has your use of [drug] led to health, social, legal, or financial problems? How often have you failed to do what was normally expected of you because of your use of [drug]?" (2) "Have you ever tried and failed to control, cut down, or stop using [drug]?" (response options: "no" and "yes"). For drugs other than cannabis, if monthly or more frequent use is reported for any of the 3 items from question 1 or the participant answers "yes" within the last 3 months for question 2, they will be excluded. For cannabis, if weekly or more frequent use is reported for any of the 3 items from question 1 or the participant answers "yes" within the last 3 months for question 2, they will be excluded.
Trauma	Single-item measure of trauma history and BTQ[j]	The BTQ is administered if the item is endorsed. Endorsement of any item on the BTQ will trigger assessment of PTSD[k] (see the following row)	We will ask participants to respond to the following item: "Sometimes things happen to people that are unusually or especially frightening, horrible, or traumatic. For example, a serious accident or fire; a physical or sexual assault or abuse; an earthquake or flood; seeing someone be killed or seriously injured; having a loved one die through homicide or suicide. Have you ever experienced this kind of event?" (response options: "yes" and "no"). If the participant answers "yes," the BTQ will be administered. The BTQ is a 10-item measure to ascertain whether the respondent has experienced a traumatic event, which includes experiences of potentially traumatic events such as crime and sexual and physical assault [26]. Endorsement of any item on the BTQ will trigger an assessment of PTSD (refer to the following row).
PTSD	PCL-5A[l]	Endorsement of any item indicates probable PTSD	The PCL-5A is a 5-item measure used to screen for the presence of PTSD.

[a]ASRM: Altman Self-Rating Mania Scale.

[b]The exclusion threshold for the ASRM was updated from >5 to >10 as of March 12, 2025, after it became apparent that the original threshold was too sensitive, excluding a higher-than-expected number of participants. A subsequent review of the literature confirmed that the ASRM has low specificity in nonclinical populations [27], supporting the decision to revise the threshold. The updated threshold was applied retrospectively, and individuals who had been excluded under the previous criterion but scored ≤10 were invited to recomplete the prescreening questionnaire.

[c]DSI-SS: Depressive Symptom Index–Suicidality Subscale.

[d]PQ-16: 16-item Prodromal Questionnaire.

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[e]FOCI: Florida Obsessive-Compulsive Inventory.
[f]DES-B: Brief Dissociative Experiences Scale.
[g]NIDA: National Institute on Drug Abuse.
[h]ASSIST: Alcohol, Smoking, and Substance Involvement Screening Test.
[i]AUDIT: Alcohol Use Disorders Identification Test.
[j]BTQ: Brief Trauma Questionnaire.
[k]PTSD: posttraumatic stress disorder.
[l]PCL-5A: abbreviated Posttraumatic Stress Disorder Checklist for the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

Interventions

Active Condition With Varied Doses

This study will include 3 active conditions that are dose variants of a newly developed 28-day mindfulness meditation program. The program is based on the *Satipatthana Sutta* (*The Discourse on the Establishing of Mindfulness* [28]—a foundational text within the Vipassana or insight tradition of Theravada Buddhism on which MBPs such as mindfulness-based stress reduction are largely based [29]). Most empirical work in the field of meditation has been conducted in the context of MBPs. The program generally aligns with the definition of an MBP developed by Crane et al [30]. The *Satipatthana Sutta* is structured into 4 progressive "contemplations": body, feelings, mind, and "dhammas" or mental qualities [28]. This program will feature daily instructions and guided practices that are based on the first 3 contemplations: the body, feelings, and the mind.

The program has been developed independently by Australian meditation teacher Patrick Kearney with support from Australian meditation teacher Jess Huon based on specifications (ie, number of sessions, session length and duration, and intended audience) but with limited additional input from the research team. Kearney has practiced meditation within the insight tradition since 1977 and has been teaching meditation full time for the past 20 years.

All 3 variants of the program will feature the same structure, progression, and content but will vary in length of daily teaching and practice: 10, 20, and 30 minutes. Each program consists of an introduction, practice, and conclusion. While the introduction and conclusion are consistent across the 3 programs, longer sessions include more practice points. Additional practice points in the longer sessions represent elaborations on content already introduced rather than new themes. In total, each 10-minute session includes 5 practice points, each 20-minute session includes 10 practice points, and each 30-minute session includes 15 practice points. The proportion of time allocated to spoken content varies across the 3 programs accordingly, from 62% for the 10-minute sessions to 47% for the 20-minute sessions and 40% for the 30-minute sessions.

Practices will be provided for 6 days each week (ie, a total of 24 guided practices), with participants given the option to practice without guidance on the seventh day. Each variant will teach the same core content; however, the longer variants will have more time to elaborate on this content through teaching and gain experience practicing the guided techniques.

Practice instructions will consist of a brief explanation of relevant theory as well as a set of instructions for the practice in the first few minutes, followed by intermittent guided instructions throughout the duration of the practice. The programs will consist entirely of prerecorded material and will be delivered asynchronously. Therefore, there will be no direct contact between teachers and participants for the duration of the program. While this element constitutes a point of departure from how most MBPs are delivered, Crane et al [30] note that the exact method of delivery is flexible and can vary across MBPs [31].

After the 28-day intervention period, participants will be offered full access to any of the 3 higher-dose courses that they choose. During this time, participants will be free to choose to engage as much or as little with the guided practices as they wish.

Minimal-Dose Control Condition

The minimal-dose condition will feature a short daily meditation approximating 4 minutes (akin to the breathing space practice in mindfulness-based cognitive therapy or short practices in popular meditation apps). This condition is intended to provide a brief introduction to the foundations of mindfulness in theory and practice and follows the same course structure as the 3 active conditions. However, due to time constraints, the content will be very superficial.

Outcomes

Overview

Personality will be measured on days 2 and 3 of the run-in period using the short form of the Big Five Inventory, a 30-item measure of personality across 5 domains: open-mindedness, conscientiousness, extraversion, agreeableness, and negative emotionality [32].

Sleep will be assessed on day 4 of the run-in period using a single item from the Sleep Quality Scale [33]: "During the past week, how would you rate your sleep quality overall?" (response options: *terrible*=1, *poor*=2-4, *fair*=5-7, *good*=7-9, and *excellent*=10).

Motivations and expectancy will be measured on day 4 of the run-in period using the following questions: (1) "How much benefit do you expect from this mindfulness meditation course?" (response options: not at all to very much), (2) "What is your main goal for completing this mindfulness meditation course?" (goal or motivation free-text field), (3) "How motivated are you by this goal?" (response options: not at all to very much), (4) "How much improvement or progress toward your goal do you expect from the course?" (response options: none at all to a great deal), and (5) "How confident are you that the amount of improvement or progress you indicated will occur?" (response options: not confident at all to extremely confident).

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The outcome measures in the following paragraphs will be obtained at baseline (T0) and the midintervention (T0.5) and postintervention (T1) time points and after a 1-month follow-up period (T2) unless otherwise indicated.

Psychological well-being (primary outcome) will be assessed at T0, T1, and T2 using the Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS) [34], which includes 14 positively worded items of mental well-being for the previous 2 weeks on a 5-point Likert scale from 1 (none of the time) to 5 (all of the time). The primary outcome measurement is at T1. Previous analyses of responsiveness to change analyses indicate that the WEMWBS detects individually meaningful improvement across a variety of mental health measures [35]. These analyses indicated an average SE of measurement over time of 2.69.

Psychological distress (secondary outcome) will be assessed at T0, T0.5, T1, and T2 using the Kessler Psychological Distress Scale [36], a 10-item self-report measure of psychological distress over the previous month, on a 5-point Likert scale from 1 (none of the time) to 5 (all of the time).

Anxiety (secondary outcome) will be assessed at T0, T0.5, T1, and T2 using the Patient-Reported Outcomes Measurement Information System (PROMIS) Anxiety Short Form [37], a 7-item measure of the pure domain of anxiety over the previous 7 days, on a 5-point Likert scale from 1 (never) to 5 (always) and the anxiety subscale of the Depression, Anxiety, and Stress Scale [38], a 7-item measure of anxiety over the previous 7 days that is assessed on a 4-point Likert scale from 0 (did not apply to me at all—never) to 3 (applied to me very much or most of the time).

Depression (secondary outcome) will be assessed at T0, T0.5, T1, and T2 using the PROMIS Depression Short Form [37], an 8-item measure of depression over the previous 7 days, on a 5-point Likert scale from 1 (never) to 5 (always).

Social anxiety (secondary outcome) will be assessed at T0 and T1 using the Social Anxiety Disorder Severity Scale [39], a 10-item measure of the severity of symptoms of social anxiety (phobia) in the previous 7 days, on a 5-point Likert scale from 0 (never) to 4 (all of the time).

Nonattachment (secondary outcome) will be assessed at T0, T0.5, T1, and T2 using the Nonattachment Scale [40], which measures the Buddhist concept of nonattachment on a 5-point Likert scale from 1 (disagree strongly) to 5 (agree strongly).

Trait mindfulness (secondary outcome) will be assessed at T0, T0.5, T1, and T2 using the Five Facet Mindfulness Questionnaire [41,42], a 15-item measure that includes 5 factors representing elements of mindfulness, on a 5-point Likert scale from 1 (never or very rarely true) to 5 (very often or always true).

Decentering (secondary outcome) will be assessed at T0, T0.5, T1, and T2 using the Experiences Questionnaire [43,44], an 11-item measure of decentering, on a 5-point Likert scale from 1 (never) to 5 (all the time).

Equanimity (secondary outcome) will be assessed at T0, T0.5, T1, and T2 using the Two-Factor Equanimity Scale [45], a 14-item measure of equanimity, on a 5-point Likert scale from 1 (never) to 5 (very often or always).

Repetitive negative thoughts (secondary outcome) will be assessed at T0, T0.5, T1, and T2 using the Repetitive Negative Thoughts Questionnaire [46], a 22-item measure of repetitive negative thinking, on a 6-point Likert scale from 1 (not at all typical of me) to 6 (extremely typical of me).

Emotion regulation (secondary outcome) will be assessed at T0, T0.5, T1, and T2 using the Difficulties in Emotion Regulation Scale–Short Form [47], an 18-item measure that includes 6 factors representing emotional regulation problems, on a 5-point Likert scale ranging from 1 (almost never) to 5 (almost always).

Attention control (secondary outcome) will be assessed at T0, T0.5, T1, and T2 using the Attention Control Scale–Short Form [48], a 10-item measure that includes 2 subscales of attention (shifting and focusing), on a 4-point Likert scale ranging from 1 (almost never) to 4 (always).

Emotional reactivity (secondary outcome) will be assessed at T0, T0.5, T1, and T2 using the Perth Emotional Reactivity Scale–Short Form [49], an 18-item measure of the activation, intensity, and duration of one's emotional responses, on a 5-point Likert scale from 1 (very unlike me) to 5 (very like me).

Weekly Measures

During the intervention period, additional measures will be obtained weekly (ie, 7, 14, 21, and 28 days after the baseline survey).

Mindfulness practice will be assessed using the following items: (1) "In the past week, how many daily sessions of this study's meditation program did you complete?" (response options: 0-7); (2) "In the past week, on the days you meditated with the study program, approximately how many minutes (on average) was each meditation session?"; (3) "In the past week, how many additional days did you practice meditation?" (response options: 0-7) and "In the past week, on the days you meditated in addition to the study program, approximately how many minutes (on average) was each meditation session?"; (4) "On the days you practised meditation, how many minutes per session did you practice? (this includes the guided sessions in the meditation program)" (response options: 0 to ≥60 min); and (5) "In the past week, how often did you engage in informal mindfulness practice? i.e. mindfully washing dishes, showering, walking etc." (response options: none of the time to all of the time).

Adverse events will be assessed using a modified short form of the Meditation-Related Adverse Effects Scale [50].

Sleep will be assessed using a single item from the Sleep Quality Scale [33]: "During the past week, how would you rate your sleep quality overall?" (response options: *terrible*=1, *poor*=2-4, *fair*=5-7, good=7-9, and *excellent*=10).

Expectancy will be assessed using the following item: "How effective do you think your training so far has been for your [goal or motivation free-text field from run-in survey]?" (response options: not at all effective to very effective).

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Momentary Measures

Participants will be assessed on study variables *daily*, before and after each meditation practice session. Meditators will respond to questionnaires assessing momentary mood before and after each meditation. Following the postmeditation mood items, meditators will complete 1 random questionnaire from a list of questionnaires assessing state mindfulness, decentering, mindful attitudes (including nonjudgment, nonattachment, and curiosity), and attention (attention regulation and self-regulation).

Participants who choose to skip a meditation session will be queried about their momentary mood and assessed on 1 random questionnaire from a list of questionnaires assessing disposition mindfulness, decentering, and attention control variables in the previous 24 hours.

Momentary mood will be assessed daily, before and after each meditation session, using a modified English version of the Multidimensional Mood Questionnaire [51]. The Multidimensional Mood Questionnaire assesses valence, arousal, and calmness dimensions of momentary mood using 6 items on a 7-point Likert scale (with the end points labeled as "very"). Participants will respond to the following statement—"At this moment I feel:"—with the following options: (1) tired-awake, (2) content-discontent, (3) agitated-calm, (4) energetic–lacking energy, (5) well-unwell, and (6) relaxed-tense.

State mindfulness will be assessed using a brief 6-item version of the State Mindfulness Scale [52]. The chosen items are among the highest-loading items on the original scale. Participants will respond to the following statement—"Please use the rating scale to indicate how well each statement describes your experience during the meditation:"—on a 5-point Likert scale with options ranging from 1 (not at all) to 5 (very well).

Attention will be assessed using the attention regulation and self-regulation subscales of the Multidimensional Assessment of Interoceptive Awareness [53] scale. A selection of 9 items based on the highest-loading items on the original subscales will be used to capture attention within the meditation session [53]. Participants will respond to the following statement—"Please indicate how often each statement applied to you during the meditation:"—on a 6-point Likert scale ranging from 1 (*never*) to 6 (*always*).

Decentering will be assessed using a brief 5-item version of the decentering subscale of the Toronto Mindfulness Scale [54]. The chosen items are among the highest-loading items on the original subscale. Participants will respond to the following statement—"Please indicate the extent to which each statement describes what you just experienced during the meditation:"—on a 6-point Likert scale ranging from 1 (not at all) to 6 (very much).

Mindful attitudes will be assessed using a face-valid selection of (1) Toronto Mindfulness Scale items to reflect attitudes of nonjudgment (acceptance or allowance) and curiosity [54], (2) Five Facet Mindfulness Questionnaire nonjudgment subscale items to reflect nonjudgment (nonevaluative aspect), and (3) Nonattachment Scale items to reflect nonattachment. Participants will respond to the following statement—"Please indicate the extent to which you agree each statement describes what you just experienced during the meditation:"—using a 5-point Likert scale ranging from 1 (not at all) to 5 (very much).

Participant Timeline

A timeline of all major study milestones is provided in Figure 2. For brevity, daily and weekly survey items have been excluded.

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Figure 2. Study timeline. Momentary measures collected daily between T0 and T1 are excluded. T0, T0.5, T1, and T2 represent time points before randomization, midintervention (2 weeks after randomization), postintervention (4 weeks after randomization), and follow-up (8 weeks after randomization). ATTC-SF: Attention Control Scale–Short Form; DASS-21: Depression, Anxiety, and Stress Scale; DERS-SF: Difficulties in Emotion Regulation Scale–Short Form; EQ: Experiences Questionnaire; EQUA-S: Two-Factor Equanimity Scale; FFMQ: Five Facet Mindfulness Questionnaire; K10: Kessler Psychological Distress Scale; MRAE: Meditation-Related Adverse Effects Scale; NAS-7: Nonattachment Scale; PERS-S: Perth Emotional Reactivity Scale–Short Form; PROMIS: Patient-Reported Outcomes Measurement Information System; RNTQ: Repetitive Negative Thoughts Questionnaire; SAD-D: Social Anxiety Disorder Severity Scale; SQS: Sleep Quality Scale; WEMWBS: Warwick-Edinburgh Mental Wellbeing Scale.

Study timepoint >			**T0**		**T0.5**		**T1**	**T2**
Days post enrolment >	**0**	**1-7**	**8**	**15**	**22**	**29**	**35**	**67**
Before the study								
Enrolment and informed consent	✓							
Determination of eligibility	✓							
Run-in tasks and surveys		✓✓✓✓						
Randomization		✓						
Interventions								
Group 1 – minimal dose			●	—	—	●		
Group 2 – 10-min dose			●	—	—	●		
Group 3 – 20-min dose			●	—	—	●		
Group 4 – 30-min dose			●	—	—	●		
Outcome measures								
Psychological well-being (primary, WEMWBS)			✓				✓	✓
Psychological distress (K10)			✓		✓		✓	✓
Anxiety (PROMIS-Anxiety + DASS-21 Anxiety subscale)			✓		✓		✓	✓
Depression (PROMIS-Depression)			✓		✓		✓	✓
Social Anxiety (SAD-D)			✓				✓	
Non-attachment (NAS-7)			✓		✓		✓	✓
Trait mindfulness (FFMQ)			✓		✓		✓	✓
Emotional regulation (DERS-SF)			✓		✓		✓	✓
Attention control (ATTC-SF)			✓		✓		✓	✓
Emotional reactivity (PERS-S)			✓		✓		✓	✓
Decentering (EQ)			✓		✓		✓	✓
Equanimity (EQUA-S)			✓		✓		✓	✓
Repetitive negative thoughts (RNTQ)			✓		✓		✓	✓
Weekly Measures								
Mindfulness practice				✓	✓	✓	✓	✓
Adverse effects (Single item MRAE)				✓	✓	✓	✓	✓
Sleep (Single item SQS)		✓		✓	✓	✓	✓	
Expectancy		✓		✓	✓	✓	✓	

Sample Size

A meta-analysis of meditation apps [1] indicates a standardized mean difference (SMD) effect size of 0.29 (95% CI 0.14-0.45) for psychological well-being when comparing apps to controls. A more recent study [6] randomized participants to approximately 10 or 30 minutes of sitting or movement practice for 2 weeks. They estimated a difference in the effects on the

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WEMWBS between the sitting groups of short and long duration of SMD=0.2 to 0.25. To be conservative, we determined a target sample size with an SMD of 0.2.

On the basis of an SD in WEMWBS scores of 9.84 [55] and a within-individual correlation of 0.83 in repeated assessments of the WEMWBS [34], we would need a final sample size of 688 participants to achieve 80% power (at the 2-sided P=.02 significance level to correct for multiple comparisons between conditions) to detect a difference of 1.97 points (SMD=0.2) for each active condition (10, 20, and 30 min) compared to one another and with the minimal-dose condition. This would translate to approximately 172 participants per arm. These calculations were conducted using the *sampsi* package in Stata (StataCorp).

Meditation app studies indicate overall retention rates of approximately 60% for active mindfulness meditation interventions [1]. Given our use of a run-in period, the aim of which is to allow participants who are most likely to disengage to do so before randomization, we anticipate postrandomization retention rates approximating 80%. In total, we will then recruit on a rolling basis until we achieve the required sample size at randomization of 860.

We will aim to recruit the full sample by March 31, 2025. We will conduct an interim analysis at this stage if the sample is at <90% of the target. If the sample is at ≥90% of the target by March 31, 2025, recruitment will be terminated. If continued recruitment is necessary (ie, we recruit <90% of the sample by March 31, 2025), recruitment will continue until the target sample is reached or 6 months (from March 31, 2025) have elapsed (whichever occurs first). If an interim analysis is required, the team member who undertakes this analysis will not implement the final analysis (as they will need to be unblinded). Other members of the team will undertake the final analysis and will alter the arm designation in the analytic code to further blind results relative to the interim analysis.

Recruitment

We will recruit participants to the study on a rolling basis via advertisements from the Contemplative Studies Centre using the following streams: trial website, relevant university websites (eg, “volunteer for research” pages), media releases (and media), online advertisements, social media, newsletters, and email lists. We will also promote “snowballing” by sending a flyer through our research, education, practice, media, and advisory networks (and asking them to forward it to their networks) and further asking participants interested or participating in the study to share it on social media and refer a friend. If recruitment is slow, we will additionally consider paid online advertising (eg, through Google or Facebook).

Interested individuals will be directed to the trial website for information about the study, including a plain-language statement about the trial and a link to register interest in participating. The link will take interested individuals to a staged prescreener survey (hosted via Qualtrics) that assesses broad eligibility before looking at specific eligibility to understand the individual’s sociodemographic profile, meditation history, smartphone access and use, and mental health (refer to the Prescreening Measures section). The research team will confirm eligibility before individuals are invited via email to enroll in the study. To accept the invitation, participants will acknowledge that they have read the plain-language summary and will complete an online informed consent form informing them of the aims and particulars of the study and their right to withdraw from it at any time. Once enrolled, participants will receive a welcome email with a link to the first run-in task.

Assignment of Interventions: Allocation and Blinding

After meeting the selection criteria and completing the run-in period and baseline measures, participants will be randomized to 1 of the 4 groups. Participants will be blinded to the dosing nature of the study and will only be told that they are participating in a trial to test the effects of a 28-day mindfulness meditation intervention. While participants will be informed of their group allocation (eg, group 1), they will not be informed of what the number refers to.

Randomization will be remote and computer based. The allocation process will be automatically concealed, so researchers will not be able to predict or influence who will be randomized to which group. Members of the research team will not be informed of participants’ allocation until after final analyses have been completed, and analyses will be conducted blind to group allocation.

Group allocation will be based on block randomization, with an equal number of participants allocated to each condition for every 24 participants. The randomization process consists of prepopulating a list of randomized allocated group orderings and putting this list in an Amazon Web Services Simple Queue Service First-In-First-Out queue (condition queue), from which group allocation occurs by polling an item from the queue. It is necessary to rebuild this condition queue regularly as queues have a maximum life span of 14 days. We decided to rebuild every night (as opposed to every 14 days), although the rebuilding process maintains the current allocated group orderings from the queue it replaces.

To generate the group ordering (condition list) that is placed on the condition queue, the following steps are taken using a Python script (Python Software Foundation) with the random seed set to 2023: (1) a list with 24 items constituting 1 block is created containing 6 occurrences for each group (ie, 1, 2, 3, 4, 1, 2, 3, 4...1, 2, 3, 4), (2) we randomize this list and then add it to the condition list, (3) this process is repeated 72 times to create a condition list of length 1728 (ie, 72 blocks of 24), and (4) this condition list is uploaded to the condition queue.

This method equates to block randomization as, for every 24 assignments to the condition list, an equal number of participants (ie, 6) will be randomly assigned to each group.

Participants flagged as suspicious and who fail to verify information used to determine their eligibility for the study within the designated time frame (ie, 1 week) will be removed from the study. If removal occurs after randomization, the group to which that participant was allocated will be added to a reassignment queue.

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The group assignment for new participants will be based on the next allocation in the reassignment queue. If the reassignment queue is empty, allocation will revert to the condition queue.

Data Management

Data management and analysis will take place at the Contemplative Studies Centre at the University of Melbourne. During the data collection phase, data from Qualtrics will be encrypted before being stored in their respective cloud-based storage databases. Access to these databases is gated so that entry is only permitted to users entering through the approved route. The research team will access the data via a secure site, which is accessed only using verified credentials, and the data will be stored on a longer-term basis on a password-protected University of Melbourne computer. Qualtrics will be responsible for data storage during the data collection phase. In addition, Unforgettable Research Services Pty Ltd will administer the storage of data on Amazon Web Services. Amazon uses a sophisticated identity management and permission infrastructure that includes rotating keys and encrypted communications. Deidentifiable data will be stored online in perpetuity in line with open science best practices. Storage of downloaded data will be the duty of the responsible researcher, NTVD. Deidentifiable data will be used by the research team for all analyses.

Statistical Methods

General Principles

The primary analysis will be undertaken on the primary outcome following the intention-to-treat approach [56]. The intention-to-treat analysis sample will consist of all randomized participants, assigning them to the arms they were randomized to independently of their subsequent behavior. An intention-to-treat approach was chosen for the primary analysis because the study's main purpose is to test whether larger *prescribed* doses of mindfulness practice yield larger effects on well-being. Intention-to-treat analyses will also be conducted for all secondary outcomes. Additional secondary analyses will be conducted following the per-protocol approach for all outcome measures (ie, primary and secondary). For data collected at weekly increments between T0 and T1, measurement occasions will be nested within individual participants.

The comparisons of interest will be each intervention (10, 20, and 30 min) compared to one another and with the minimal dose for each outcome (mean difference and 95% CI).

Baseline Characteristics

Demographic and baseline variables of participant characteristics will be summarized descriptively and presented by intervention group (4-min active control and 10-, 20-, and 30-min active group). No statistical comparisons between groups will be made at baseline. Characteristics will be summarized using frequencies and percentages (based on the observed sample) for categorical variables, means and SDs for continuous variables, or medians and IQRs for nonnormally distributed continuous variables.

Effectiveness Analyses

A constrained longitudinal data analysis method [57] will be used to build the linear mixed-effects model estimating the effect of the interventions on the primary outcome. The model will incorporate study visit (T0 and T1) as a categorical variable, intervention (10, 20, and 30 min each vs the minimal dose), and intervention by study visit interaction as main effects. The model will assume a common baseline mean of the outcome across the 4 intervention groups and an unstructured variance-covariance among the repeated measurements.

Models analyzing secondary outcomes will incorporate study visit (T0, T0.5, and T1) and intervention (10, 20, and 30 min each vs the minimal dose) as categorical variables. Secondary continuous outcomes will be analyzed similarly to the primary outcome (ie, the constrained longitudinal data analysis described previously). Additional analyses will include follow-up assessments (ie, T2) in the model.

Efficacy Analyses

Analyses of all outcomes will also be conducted on a per-protocol basis to test the efficacy of different doses under "ideal" conditions of high compliance. The model will incorporate study visit (T0, T0.5, and T1; additional analyses will include T2) and intervention (10, 20, and 30 min each vs the minimal dose) as categorical variables. The per-protocol analysis sample will consist only of those participants who were compliant with the allocated intervention dose, excluding those who did not comply as opposed to reallocating them to an arm representing their actual dose. A "complier" will be defined by having reported session completion for >66.67% and <117% of sessions (100%=6 weekly sessions=24 sessions).

Estimation of effects in randomized controlled trials is known to be biased when there are variable rates of nonadherence to treatment [58]. To control for prerandomization factors that may influence nonadherence to the 10-, 20-, and 30-minute conditions, we will adjust for prerandomization confounders for the per-protocol analysis, such as personality traits (conscientiousness [59,60]), openness to experience [59,61], depressive symptoms [59,61], and motivations and expectations [60]. The method of inverse probability weighting will be used to control for confounding bias due to prerandomization factors [62]. A causal diagram will be drawn to determine a priori potential pre- and postrandomization confounders associated with being a complier [58].

Additional Analyses

If any difference between any conditions is observed for any of the primary or secondary analyses, we will explore ways of quantifying that relationship as a means of representing dose-response effects. In particular, we will test for the presence of a linear and log-linear relationship across the treatment doses.

We will describe differential rates of attrition and adherence across the different treatment arms and explore whether any variables collected at baseline predict differential attrition and adherence.

Using estimated practice time per adherence measures, we will implement a receiver operating characteristic analysis to

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ascertain the practice amount at which individuals achieve a change of ≥7.45 points on the primary outcome of the WEMWBS (estimated temporal SE of measurement of 2.69 [35] using a multiplier of 2.77 [63]) to detect a statistically important change at the individual level.

Further exploratory analyses will be conducted using both the intention-to-treat and per-protocol approaches on outcomes collected at weekly and biweekly intervals.

Multiple Testing Adjustment

For the analysis of the primary outcome, we will use a Bonferroni adjustment to control the type I error rate for the primary outcome across all 3 pairwise comparisons by setting the 2-sided significance level at .02. For analyses of secondary outcomes, with nominal α set at $P<.05$, we will adjust for multiple comparisons at the variable level using the false discovery rate procedure [64], which is less conservative than the Bonferroni correction and, therefore, may provide a better balance than Bonferroni between the likelihood of type 1 and type 2 errors.

Missing Data Handling

As the primary strategy to handle missing data, the longitudinal constrained analysis assumes that the probability of missing outcome data is not related to the missing data but to some of the observed measured data in the model (missing at random). Our models will use a restricted maximum likelihood estimator to handle missing data. The use of the restricted maximum likelihood estimator will enable us to effectively handle the potential bias introduced by differential attrition as it allows for the estimation of unbiased fixed-effects coefficients and appropriately accounts for the variability introduced by random effects.

Sensitivity Analysis

The frequency and percentage of participants with missing data at T0, T0.5, T1, and T2 will be summarized for the primary and secondary outcomes. In addition, baseline and demographic characteristics will be summarized for those with and without missing data for the primary outcome measure (at T0, T0.5, T1, and T2) to explore the missing data assumption and identify and include in the relevant models any variables not included in the target primary analysis that are potentially associated with missingness.

Monitoring

Data Monitoring

In partnership with the trial sponsor, we have determined that the planned work is of low risk and, thus, a data monitoring committee is unneeded. Participant data will be monitored during the study for adverse events and managed by the responsible researcher. If adverse events are severe, an independent data monitoring committee will be formed in consultation with the trial sponsor to evaluate whether the trial needs to be discontinued.

Harms

To manage and minimize risks, potential participants will be informed (before consent) of the marginal risk of distress and emotional discomfort when responding to survey questions about symptoms of depression, anxiety, and suicidal ideation. Participants will be informed of their right to withdraw from the study at any point. To address potential distress, in the plain-language statement, we indicate that, should participants experience discomfort or distress because of their participation in the study, they can contact the study lead or one of the provided referral sources. In addition, we will provide details of a range of psychological service providers if they wish not to take up the aforementioned option, including one specifically related to meditation-related difficulties. In the prescreening questionnaire, for any participants who report experiencing mild to severe symptoms of depression or slight to severe symptoms of suicidal ideation, an automated message will appear at the end that refers the participant to psychological support services.

For meditation-related risks, participants will be asked each week whether they have experienced an adverse event during the previous week that they believe may have been caused by their meditation practice. If an adverse event is reported, further screening measures will be administered to assess the nature and severity of the event and whether more follow-up is needed. In such cases in which follow-up is needed, an automated email will be sent to the principal researcher (NTVD), who is a registered psychologist and, therefore, can personally assess what action is required. Adverse event and effect rates will be reported along with the study findings.

Auditing

Throughout the data collection phase, the research team will hold regular meetings to manage the project day to day and ensure that all procedures are being followed. The meetings will review recruitment progress, discuss any reported issues by participants, and anticipate and resolve any problems.

Ethical Considerations

Research Ethics Approval

Approval has been obtained from the Human Ethics Team at the University of Melbourne's Office of Research Ethics and Integrity (23299). The trial protocol has been developed consistent with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 statement [65]. Results will be reported using the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) clinical trial reporting tool [66].

Protocol Amendments

If needed, the study researchers will prepare protocol amendments and will seek approval from the Human Ethics Team at the University of Melbourne. Any updates to the protocol will be reflected in the trial registration on ClinicalTrials.gov, and an updated version will be posted on the Open Science Framework website [22].

Consent

The consent form will be embedded within the study landing page in Qualtrics. Participants can provide informed consent to participate in the trial by checking the box at the bottom of the

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form. Only once informed consent is provided will the participant be able to advance to the prescreening measures.

Confidentiality

Data that identify participants will be retained in a separate, password-protected database on an encrypted University of Melbourne computer to which only the responsible researcher will have access. All participants' data will be stored on a secure server by Unforgettable Research Services Pty Ltd (via Amazon Web Services). Amazon Web Services has extensive security measures, including rotating keys and a comprehensive identity management and permission system. All transmission of information across networks will occur in encrypted form. Only deidentifiable data will be stored online in perpetuity in line with open science best practices. All analyses will be conducted on deidentifiable data.

Participant Compensation

To promote study retention, participants will be reimbursed for the completion of surveys at each successive stage of the intervention: Aus $15 (US $9.75) for baseline measures (approximate completion time: 20 min), Aus $5 (US $3.25) for the surveys at the end of week 1 and week 3 (completion time: approximately 3 min each), Aus $15 (US $9.75) for the midintervention survey at the end of week 2 (completion time: approximately 15 min), Aus $1 (US $0.65) for each of the 24 daily surveys (completion time: approximately 24 min), Aus $25 (US $16.24) for postintervention measures (completion time: approximately 20 min), and Aus $20 (US $12.99) for follow-up measures (completion time: approximately 20 min). Total remuneration for participants who complete all surveys is Aus $109 (US $70.82), and they should take approximately 90 minutes to complete over the course of the study. In addition, participants who complete the prescreener will be entered into a draw for 1 of 10 Aus $100 (US $64.97) gift cards via GiftPay. Once eligible and enrolled, participants who successfully complete the run-in period will be entered into a further draw for 1 of 10 Aus $100 (US $64.97) gift cards via GiftPay. Participants will be invited to complete surveys regardless of whether they practice meditation or continue with the course, and no financial reward will be offered for completing meditation practice or listening to the guided practice audio instructions.

Access to Data

Only researchers listed as authors of this manuscript will have access to the final trial dataset.

Ancillary and Posttrial Care

The responsible researcher is a registered psychologist who will follow best clinical practices for follow-up and risk management. Given the low-risk nature of the intervention and the prescreening measures, it is not anticipated that additional posttrial care will be required.

Dissemination Policy

Results will be published in peer-reviewed journals and presented at conferences. A lay summary will be disseminated to a wider audience via the University of Melbourne's website and promoted via social media.

Results

This is protocol version 1.1. Version 1.0 was uploaded to the Open Science Framework website in early May 2024 to coincide with the start of recruitment. This study has been prospectively registered at ClinicalTrials.gov with the identifier NCT06378450. Recruitment was paused approximately 6 weeks later after a significant number of participants were identified as being fraudulent and not meeting the eligibility criteria. At this time, <5% of the sample had been recruited. Additional screening procedures have been introduced, and recruitment reopened in October 2024. Version 1.1 of the protocol incorporates these minor changes. We estimate that the results will be published by March 2026.

Discussion

Overview

This pragmatic randomized controlled trial aims to conduct a thorough evaluation of the dose-response effects of mindfulness meditation. This will contribute to understanding how much mindfulness practice people need to engage in to promote improved well-being and other psychological outcomes.

The evidence base for dose-response effects in mindfulness meditation practices remains inconclusive. Empirical studies exploring variations in session lengths and frequencies have not consistently demonstrated significant differences in outcomes across different doses [5,7,8]. These studies have had limitations such as small sample sizes and brief overall program durations. Meta-analyses and meta-regression models have also produced mixed findings, with some indicating minor benefits from larger doses over smaller doses and others showing no significant effects [10]. However, these studies lack random allocation of participants to different doses, and therefore, the results may be subject to bias. Overall, current industry practice (advocating for doses as low as 5 min/d) and current research underscore a need for more rigorous studies to establish clearer guidelines on effective mindfulness practice dosages.

Strengths and Limitations

When compared to previous empirical dose-response assessments, our study has several notable strengths and some limitations. These are described in the following paragraphs.

Our study has several characteristics that will improve our capacity to make inferences about dose-response effects for mindfulness practices compared to previous studies that have tested dose-response effects for mindfulness meditation. Our targeted sample size (N≥866) is powered to detect small effects (d=0.2 approximately) between active dose conditions. The program length is 28 days, which will allow us to test for changes in more stable "trait" effects. There is considerable variation in doses for daily sessions, ranging from 10 to 30 minutes. These doses are based on a nonsystematic search of the literature, MBPs, and mindfulness apps with dosage recommendations (for details, refer to the study by Bowles et al [11]). The random allocation of participants to different doses will allow us to make inferences about the effects of different doses, which are less subject to bias than those in previous

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assessments [3,10]. Finally, while our primary outcome is well-being, we have a range of outcome measures covering different aspects of well-being and mental health, as well as hypothesized mechanisms of change for mindfulness interventions, including decentering and emotional reactivity.

This study is being conducted entirely online. This has the advantage of allowing participants to practice in their homes and other familiar ecologically valid settings, although it also has the limitation of researchers having little control over the research environment. However, a common problem with internet-based interventions is high dropout rates and low adherence. Our primary analysis is to test the effectiveness of different doses, and therefore, our data will be analyzed on an intention-to-treat basis. As such, we are most concerned with the problem of high dropout rates. To minimize dropouts, we are offering financial inducements for participants to continue honestly reporting their practice amount and responding to questionnaires regardless of whether they are still completing the intervention. However, it is still in our interest to have high rates of adherence given that we will also analyze data on a per-protocol basis (ie, as secondary analyses only). To this end, we are using a run-in period to identify and exclude participants who are most likely to drop out and not complete the intervention before randomization. Given this use of the run-in period, we cannot make inferences about the likely adherence to similar mindfulness interventions in real-world settings. Therefore, while the use of a run-in period strengthens internal consistency, it introduces a selection bias. We will attempt to quantify this by reporting sociodemographic data and measures of mental health and well-being for people that complete the run-in period and compare them against those of people who do not. Despite the use of a run-in period, we still anticipate that adherence rates are likely to vary across dosage groups, with lower adherence at higher doses. This may limit our capacity to make inferences about the efficacy of different doses for the per-protocol analyses.

Given our focus on the question of dose-response effects, our analysis examines the effectiveness of different doses relative to each other (and to a minimally active control). Therefore, we cannot make inferences about the effectiveness of the intervention relative to other psychosocial interventions. However, the intervention shares several characteristics that align with the definition of MBPs by Crane et al [30]. Therefore, we are relying on this evidence base, which has demonstrated the effectiveness of similar MBPs, while focusing on one aspect of such programs that is less empirically validated, namely, whether and to what degree shorter or longer daily practices are more beneficial.

All outcome data are self-reported, introducing the potential for recall bias, social desirability bias, and inaccuracies. Despite these limitations, self-report measures were chosen for their practicality and suitability for collecting data online for well-being, the primary outcome, and various secondary outcomes.

Finally, we are tracking and will follow up on reports of adverse experiences throughout the intervention and follow-up periods. Britton [67] has hypothesized that meditation-related adverse experiences and problems with sleep may be more likely to occur at higher doses. While our dosage may still be relatively low compared to that of high-dose settings such as residential retreats, our study design will allow us to explore the question of whether and when higher doses of mindfulness may be riskier than lower doses.

Considering these strengths and limitations, our study will make a significant contribution to the growing literature on the dose-response effects of mindfulness meditation, providing much-needed empirical support to the question of whether and when larger doses are more beneficial than smaller ones. These findings may inform practical guidelines, helping beginner meditators and their advisors—whether in health, well-being, or spiritual contexts—estimate the amount of practice required to achieve particular outcomes.

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Data Availability

Data and other study materials will be openly available on the Open Science Framework website [22].

Authors' Contributions

NB and NTVD designed the study. NB and JND drafted the first version of the manuscript, which was modified by AB, JG, JAS, BS, and NTVD. NB and AB are involved in recruiting participants and obtaining participants' informed consent. AB, BS, and SJD are responsible for the logistics and data collection. All authors have read and approved the final manuscript.

Conflicts of Interest

SJD is the chief executive officer of Unforgettable Research Services Pty Ltd, a company engaged to store and validate participant data and administer participant reimbursements. BS is the chief technical officer of Unforgettable Research Services Pty Ltd. The remaining authors have no known conflicts of interest to disclose.

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Abbreviations

CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
MBP: mindfulness-based program
PROMIS: Patient-Reported Outcomes Measurement Information System
SMD: standardized mean difference
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
WEMWBS: Warwick-Edinburgh Mental Wellbeing Scale

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Protocol

Monitoring of Pregnant Women Using the “Risk Identification, Evaluation Counseling, Systematic Monitoring, Troubleshooting” (REST) Mobile App: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: The maternal mortality rate (MMR) in Indonesia is still quite high and has not reached the national target. The success of maternal health programs can be assessed through the main indicator of the MMR. Pregnancy monitoring is one of the efforts to reduce the increase in the MMR.

Objective: This study aims to improve maternal and child safety and health during pregnancy and childbirth through pregnancy monitoring using a mobile app called REST (Risk Identification, Evaluation Counseling, Systematic Monitoring, Troubleshooting).

Methods: The research used the cluster randomized controlled trial (RCT) design, involving pregnant women from 11 subdistricts in Purworejo Regency, who were randomized to 11 clusters in the intervention group and 11 clusters in the control group. The 22 ANC class clusters comprised 22 midwives and 220 pregnant women. The intervention group received monitoring using the REST mobile app, while the control group received standard pregnancy monitoring in the antenatal care (ANC) class. The mentoring program included the use of the REST mobile app, which consists of pregnancy checks according to the 10T pregnancy examination standard. The app was used by midwives and pregnant women, starting from the second trimester of pregnancy to childbirth.

Results: In July 2023, the REST mobile app was prepared and tested in small community groups, including midwives and pregnant women, through simulation, and in September 2023, the app was further refined based on feedback from these groups and introduced to study participants. The majority of participants were aged 20-35 years (n=168, 76.4%), consistent with national demographic trends. Approximately 185 (84.1%) had secondary education (junior and senior high school), and 57 (25.9%) had tertiary education (college graduates). The participants were evenly distributed across economic quintiles, reflecting diverse socioeconomic backgrounds, and most lived approximately 1 km from a health facility. Ethical approval was obtained in April 2024. Staff training was conducted from July to October 2023. Participants were recruited from November 2023 to January 2024, the intervention was implemented from February to July 2024, and data were collected from August 2024 to February 2025. Data were analyzed in April 2025, and dissemination of results is expected by the end of 2025.

Conclusions: Pregnancy monitoring using the REST mobile app is expected to have a significant influence on the number of ANC visits, reduce pregnancy complications, improve normal delivery methods, and ensure the birth weight of the baby stays within normal limits (≥2500 g).

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Trial Registration: ClinicalTrials.gov NCT05741931; https://clinicaltrials.gov/study/NCT05741931
International Registered Report Identifier (IRRID): DERR1-10.2196/66774

(JMIR Res Protoc 2025;14:e66774) doi:10.2196/66774

KEYWORDS
pregnant woman; midwife; antenatal screening; mobile health; mHealth; application; app; randomized controlled trial; RCT; antenatal class; risk identification; evaluation counseling; systematic monitoring

Introduction

The success of maternal health programs can be assessed through the main indicator of the maternal mortality rate (MMR). The gestation period is the focus of the main problem in preventing high MMRs, as it is during this time that the majority of risk factors for adverse maternal and fetal outcomes emerge. In particular, nutritional and metabolic issues, such as hypocalcemia, have been associated with complications in pregnancy, especially in resource-limited settings [1-3]. The gestation period is the focus of the main problem in preventing high MMRs. The World Health Organization (WHO) recommends that health workers improve consultation and care for pregnant women [4].

Antenatal care (ANC) services in normal pregnancy are provided at least 6 times: 2 times in the first trimester, 1 time in the second trimester, and 3 times in the third trimester. ANC examinations in normal pregnant women are carried out by a doctor at least 2 times in the first and third trimesters [5]. Failure in pregnancy care or ANC usually occurs due to social and economic factors, such as low education and family income, being too young or too old, living far from health facilities, unwanted pregnancy, and the consumption of illegal drugs [4].

The MMR in Central Java Province in 2021 was 199 per 100,000 live births (1011 cases), an increase compared to the MMR in 2020 of 98.6 per 100,000 live births (530 cases) and in 2019 of 76.93 per 100,000 live births (416 cases). Cases of maternal mortality increased from 2019 onward. The cause of disruption in maternal and child health services during the pandemic was due to major changes in health facility services and public health [6]. The still high mortality rate shows that the quality of maternal and neonatal services is not optimal. The issue of “3 late” is still the main problem in maternal health services, namely late decision-making, late arrival at the referral point, and late getting the services needed at health facilities. The low quality of pregnancy examination services is also reflected in the low compliance with ANC standards, which include 10 pregnancy examinations [7].

There are several studies on pregnancy using mobile apps, such as the m4Change app [8], which contains health promotion around maternal and child health, with the results of improving the quality of ANC. The PANDA (Pregnancy and Newborn Diagnosis Assessment) app is used to monitor during ANC, with the results of knowing the cause of pregnancy complications [9]. The Innovative Mobile Phone Technology for Community Health Operations (ImTeCHO) app for scheduling home visits, screening for complications, and counseling has effective results in areas that are difficult for health facilities to reach [10]. This mobile app can be used as a medium by pregnant women to monitor their pregnancy and by midwives who conduct pregnancy checks. Mobile apps should be used by considering their effectiveness and quality of use.

Pregnancy monitoring is a decision-making action for pregnant women and their fetuses in order to overcome previous adverse events in fetal development. Pregnancy monitoring facilitates early discovery of abnormal developments and complications and supports timely intervention so that early treatment can be administered and disorders and risks for pregnant women reduced. If pregnancy disorders are found in the mother and fetus, efforts are made to reduce the high risk in pregnancy [11].

Pregnancy monitoring is one of the efforts made by both health workers and health cadres in monitoring the condition of both mother and fetus during pregnancy, as it plays a critical role in early detection of complications and improving maternal outcomes. Monitoring by health care providers during the gestation period, such as to provide accurate real-time data on how many pregnant women are enrolled in ANC and what the ANC class characteristics, interventions, and outcome approaches are, will improve ANC information systems that can reduce maternal mortality cases [12].

An assessment of the implementation of health services for pregnant women can be carried out by looking at the K1, K4, and K6 coverage. K1 coverage is the number of pregnant women who have received ANC services for the first time by health workers compared to the target number of pregnant women in 1 work area within a period of 1 year. K4 coverage is the number of pregnant women who have received ANC services in accordance with the standard at least 4 examinations according to the recommended schedule in each trimester compared to the target number of pregnant women in 1 work area within 1 year. K6 coverage is the number of pregnant women who have received ANC services in accordance with the standard of at least 6 examinations and at least 2 doctor’s examinations according to the recommended schedule in each semester compared to the target number of pregnant women in 1 work area within a period of 1 year. This indicator shows access to health services for pregnant women and the level of compliance of pregnant women in checking their pregnancy with health workers [5]

The ANC class is an effort by the Government of Indonesia to promote health and prevent maternal and infant mortality. The Government of Indonesia began implementing the ANC class program in 2009. The program aims to increase the understanding of pregnancy, the use of ANC and postpartum family planning services, and awareness of infectious diseases.

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The target population of the ANC class is mothers with a gestational age of 22-36 weeks. Each class consists of a maximum of 10 pregnant women and is facilitated by midwives or health workers who have received training in ANC [13]. Mobile apps have been widely used by various groups, such as health cadres, health service users, and health service providers, to facilitate activities in the health sector [14].

Mobile apps for health are often used to improve the quality of health services. Mobile apps can continue to evolve through the correction of errors adjusted to needs [15]. There are many variations of mobile apps used for health purposes. They can contain patient medical records, health consultations, and health training, as well as health promotion [16,17]. Pregnant women make up a significant proportion of the world's population. With an average age of 30 years, pregnant women are a generation that wants to get to know new technologies and expand medical care in the digital sector. There are many types of mobile apps used in monitoring the health of pregnant women. These apps are often used in the field of midwifery because they are considered appropriate and easy to implement. They are used not only for pregnant women but also for several groups involved, including couples and families. Pregnancy-related mobile apps for postnatal care and parenting have also been developed. The success in modifying a pregnancy-related app and complying with its use make it a new lifestyle intervention for users [18].

Based on the aforementioned findings, it is important to conduct research on the use of mobile apps for pregnancy monitoring. The objectives of the study are to check for the presence of pregnancy complications, compare the intervention and control groups in the context of the number of pregnant women who give birth normally, ensure that the birth weight of babies reaches ≥2500 g, and improve the number of ANC visits to ≥6.

The benefits achieved from the results of the study are making it easier (1) for pregnant women monitor their pregnancy conditions and (2) for village midwives to be able to assist in monitoring maternal health during pregnancy, recognizing maternal problems, and helping make timely referrals. The benefits for related agencies are input for public health centers, the independent practice of midwives and doctors, the Health Office, and the regional general hospital in monitoring pregnant women to prevent maternal and infant mortality. The benefits for researchers include motivating and facilitating community leaders, cadres, and communities, as well as increasing cross-sector cooperation in monitoring the health of pregnant women. For science, conducting pregnancy monitoring can be a novelty.

Methods

Study Design

This research is an experimental study with a cluster randomized controlled trial (RCT) design. Cluster RCT is a research design that has multilevel characteristics. Generally, cluster RCT research uses 2 levels, the cluster or group level and the individual level. In this study, the class cluster will include pregnant women and participants of the ANC class. To minimize the risk of selection bias, we implemented the following strategies: (1) randomization at the cluster level was performed after cluster enrollment, and baseline characteristics of participants across the intervention and control groups will be carefully assessed and reported. The research design is described in Table 1.

Table 1. Research design.

Group	Activity sequence 1		Activity sequence 2		Activity sequence 3		Activity sequence 4
	Observation	Intervention	Observation	Intervention	Observation	Intervention	Observation
Control	O_0[a]	X_0[b]	O_1[c]	X_0	O_2[d]	X_0	O_3[e]
Intervention	O_0	X_1[f]	O_1	X_2[g]	O_2	X_3[h]	O_3

[a]O_0: early identification in pregnant women in the first class of pregnant women.

[b]X_0: standard intervention for routine antenatal classes without an app.

[c]O_1: observations in the second class of pregnant women (trimester 2).

[d]O_2: observations in the third class of pregnant women (trimester 3).

[e]O_3: observation of childbirth and the newborn.

[f]X_1: introduction of the REST (Risk Identification, Evaluation Counseling, Systematic Monitoring, Troubleshooting) mobile app for pregnancy monitoring for mothers and midwives using the 10Tpregnancy examination standard.

[g]X_2: monitoring pregnant women after using the mobile app.

[h]X_3: monitoring pregnant women using the mobile app and preparing for childbirth during the third trimester.

Assessment of the results of the research will begin from the implementation of the first class of pregnant women. The total number of meetings was 3. The final result (a comparison of the expected outcome) was at the time of delivery. The research was carried out after ethical approval was obtained. The research locations are in 11 subdistricts in Purworejo Regency (Central Java, Indonesia): Loano, Purwodadi, Bruno, Butuh, Purworejo, Bagelen, Kaligesing, Kemiri, Kutoarjo, Ngombol, and Pituruh. These 11 subdistricts were chosen because they have health centers with inpatient services that make it easier for pregnant women to give birth in their areas.

Each ANC class group consisted of 10 pregnant women and 1 midwife. In each of the 3 meetings, an examination based on

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the 10T pregnancy examination standard was conducted, which included measuring the weight and height (T1), blood pressure (T2), mid-upper arm circumference (T3), uterine fundal height (T4), tetanus immunization (T5), iron supplement tablets (T6), fetal presentation and fetal heart rate (T7), counseling (including childbirth and postpartum preparation; T8), hemoglobin levels (T9), and care as needed (T10), as per the policy of the Indonesian Ministry of Health [5]. The results of the examination at each meeting were entered into the REST (Risk Identification, Evaluation Counseling, Systematic Monitoring, Troubleshooting) mobile app, and the pregnant women could see these results. If they performed a self-examination outside the ANC class schedule, they could fill in the results of the examination according to what they knew. Midwives and pregnant women were provided with training and a guidebook module for using the app. The control group carried out the standard ANC class without the use of the app, and they were exempt from recording examination results.

Population

The target population in this study was all pregnant women in Purworejo Regency. The affordable population was all pregnant women in 11 subdistricts. In total, 14 inpatient health centers were included, which included 22 clusters of ANC classes. Each cluster or class group comprised 10 pregnant women who met the inclusion criteria.

The inclusion criteria were as follows: pregnant women with a gestational age of 20-22 weeks (trimester 2), pregnant women who had a pregnancy examination at a health facility, mothers who planned to stay in the research area for at least the next 2 years, and mothers who were willing to participate in the research by signing an informed consent form.

The exclusion criteria were as follows: chronic diseases that require special pregnancy care, inability to give birth normally, and inability to operate an Android cellphone. The applicant was dropped if she moved outside the research area, could not be contacted after agreeing to provide informed consent, or decided to stop participating in the research.

Sample Size

The sample size for this study was determined based on the following formula of Lemeshow [19]:

where n is the number of samples per group, $Z_{1-\alpha/2}$=1.96 (at the level of 95% trust), $Z_{1-\beta}$=0.842 (at 80% power), p_1 is the proportion of outcomes in the intervention group, p_2 is the proportion of outcomes in the control group, and $p_1 - p_2$ is the difference between the 2 proportions to be compared.

Based on the calculation of the sample size from previous studies [4,20-22], p_1=0.92 and p_1=0.72, so the minimum sample size for the intervention and control groups was 54 respondents each. In cluster RCT research, it is necessary to consider the *design effect* (DE) in determining the sample size. The formula used is DE = 1 + (m – 1), where m=10 (the average number of samples per cluster) and is the intraclass correlation coefficient, assumed to be 0.05.

Based on the calculation results, a DE of 1.45 was obtained. Furthermore, the sample size that was obtained was multiplied by the DE, resulting in a sample size of 78.3, which was rounded to 79 respondents per group. Therefore, the total number of participants needed was 158, although considering a loss to follow-up of ~35% (based on a preliminary study of the attendance of ANC classes in 2019 in Purworejo Regency). Therefore, it was necessary to take a total of 214 (107 participants in the intervention and the control group each) at the beginning of the study through cluster sampling. The number of clusters to be used was 22 groups of pregnant women, so each group needed 9.72 samples, rounded 10 pregnant women in each group.

Randomization, Allocation, and Blinding

Sample determination was carried out using a cluster sampling approach. The target population was all inpatient health centers spread across 11 subdistricts in Purworejo Regency. Based on data from the Health Office, 14 inpatient health centers met the inclusion criteria. Of these, 11 (78.6%) were randomly selected, each representing 1 subdistrict. These 11 subdistricts consisting of 22 pregnant class clusters (C1-C22) were randomized into an intervention group (n=11, 50%) and a control group (n=11, 50%) using the compute-generated random allocation method. A list of cluster codes was entered, and a random sequence was used to divide the groups in order. The results of randomization determined that the first 11 clusters in the list were allocated to the intervention group (C1-C11), while the remaining 11 clusters were allocated to the control group (C12-C22). Randomization was carried out by independent researchers to ensure unbiased random allocation.

The group allocation was kept secret until the intervention group received treatment. Blinding was not possible both for the treatment provider (researcher) and for the sample because the monitoring intervention allowed for active interaction between treatment provider and sample. To ensure the accuracy and completeness of the report, this study adheres to the standards set out in CONSORT (Consolidated Standards of Reporting Trials) EHEALTH V1.6 checklist (Multimedia Appendix 1), which includes a detailed description of the digital intervention and research methodology [23]. The timeline of participant participation was developed in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement (Table 2 and Multimedia Appendix 2) [24].

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Table 2. SPIRIT[a] checklist–recommended schedule for study participation.

Study period and activities	Enrollment time point	Allocation time point	Postallocation time points			Close-out time point
	Week 1	Week 0	Month 1	Month 2	Month 3	After month 3
Enrollment						
Informed consent	X[b]	—[c]	—	—	—	—
Eligibility screening	X	—	—	—	—	—
Random allocation (intervention vs control)	—	X	—	—	—	—
Interventions						
REST[d] app installation and training[e]	X	—	—	—	—	—
REST mobile app usage by pregnant women and midwives[e]	—	—	X	X	X	X
Routine ANC[f] class[g]	—	—	X	X	X	—
Assessments						
Baseline clinical measurements	—	—	X	—	—	—
ANC visit	—	—	X	X	X	—
Pregnancy complications	—	—	X	X	X	—
Mode of delivery	—	—	—	—	—	X
Birth weight	—	—	—	—	—	X

[a]SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials.
[b]Applicable.
[c]Not applicable.
[d]REST: Risk Identification, Evaluation Counseling, Systematic Monitoring, Troubleshooting.
[e]Intervention group.
[f]ANC: antenatal care.
[g]Intervention and control groups.

Intervention

The REST mobile app provides pregnant women with real-time access to test results during pregnancy, personalized health reminders, and interactive communication with midwives, empowering them to make informed health decisions immediately. To minimize delays in reaching care, the app includes a birthing site–planning feature, helps midwives direct when urgent referrals are needed, and facilitates mobilization in the case of an emergency. To address delays in receiving adequate care in health care facilities, REST supports midwives by enabling structured antenatal monitoring and facilitating prereferral communication with referral centers, ensuring that health care facilities are better prepared to receive and manage incoming patients. The REST mobile app, designed for pregnancy monitoring from early pregnancy to delivery, has been officially copyrighted by the Ministry of Law and Human Rights of the Republic of Indonesia (ID: 000655305).

Before starting the intervention, the midwives were first given face-to-face training on the use of apps and procedures for implementing the ANC class. This joint intervention was deemed necessary to ensure consistent use of the platform during the trial. Next, training was continued for the participants of the ANC class regarding how to use and fill in the app. A handbook for using the app was also provided to all participants in the intervention group. Participants in the control group received standard ANC class services, as outlined by Indonesia's national maternal health program. These services include providing health education, nutrition counseling, and pregnancy gymnastics activities in accordance with meeting materials in ANC classes conducted by midwives. No digital tools or mobile apps were introduced to this group. Educational materials were delivered in print format as per standard practices, and no structured training or technological support was provided. This approach ensured that any differences in outcomes observed between the control and intervention groups could be attributed to the use of the REST mobile app.

The intervention that was implemented was in the form of a Template for Intervention Description and Replication (TIDieR), as shown in Table 3 [25].

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Table 3. The TIDieR[a] format.

Item number	Item name	Description
1	Intervention	Use of the REST[b] mobile app
2	Reasons for the intervention	• Lack of discipline for pregnant women to participate in government program activities that support pregnancy health, such as ANCc classes. The ANC class is a monitoring effort to improve the welfare of mothers and babies. Monitoring using the REST mobile app is expected to make it easier for pregnant women and midwives to monitor the health condition of mothers.
3	Action	• Providing assistance to mothers during pregnancy using mobile apps. Assistance is provided to monitor the health condition of both mother and fetus. The mother takes part in a class for pregnant women and is examined (10 pregnancy examinations: height and weight, blood pressure, mid-upper arm circumference, uterine fundal height, tetanus immunization, iron supplement tablets, fetal presentation and fetal heart rate, counseling, laboratory tests, and case management).
4	Procedure	• Conducting initial identification of mothers at the first meeting of the ANC class. Mothers are examined by midwives at every class meeting of pregnant women, and the results of the pregnancy examination are entered into the REST mobile app. Each mother gets a different evaluation from the midwife according to the results of the mother's pregnancy examination. The ANC class is held 3 times, with a duration of approximately 90 minutes per meeting. In each implementation of the class for pregnant woman, the mother is given pretest and posttest questions.
5	Organizers	• Principal investigator: ensures the readiness of activities and the completeness of the equipment needed during the ANC class. • Midwife facilitator (trained in the use of mobile apps): carries out examinations of pregnant women, provides counseling, and documents examination results into mobile apps. • Cadres (trained in the measurement of height, weight, and blood pressure): assist midwives during the implementation of classes for pregnant women. • Enumerator (trained in the use of mobile apps): assists the principal investigator in monitoring the progress of ANC class activities.
6	Intervention delivery model	• The provision of interventions was carried out face to face in each group of pregnant women. Pregnant women were required to attend classes 3 times and were also advised to fill in the results of examinations outside of the class activities so that the midwives could still monitor.
7	Venue and facilities	• Pregnancy monitoring was carried out in the Purworejo Regency area. The infrastructure used was stationery, mobile phones (smartphones), weight scales and height-measuring instruments, tools to check hemoglobin levels, dopplers to check the fetal heart rate, mid-upper arm circumference tape, metline to measure the uterine fundal height, digital sphygmomanometers, and research questionnaires.
8	Changes or modifications during the process	• The time of the class for pregnant woman was adjusted for the mothers and midwives according to an agreement. Pregnancy monitoring using the REST mobile app was adjusted to local conditions and the ownership of mobile phones by pregnant women. Furthermore, pregnancy monitoring using an app in the ANC class was carried out by midwives at the workplace or their respective practices.
9	Planning	• On the REST mobile app, a reminder was created to remind midwives and mothers of the date of the ANC class. This reminder appeared in the form of a notification the day before the class for pregnant women was held.

[a]TIDieR: Template for Intervention Description and Replication.

[b]REST: Risk Identification, Evaluation Counseling, Systematic Monitoring, Troubleshooting.

[c]ANC: antenatal care.

The intervention given to the treatment group used the REST mobile app. The app was validated by 3 experts: an obstetrician and gynecologist, a health application expert, and a community midwifery expert. The app was piloted in a small group of pregnant woman communities who were not involved in the intervention study. Evaluation included the format, substance, presentation, and language. The results of the trial were measured by the distribution of simple questionnaires, interviews, and observations. After revision for refinement, the app was ready to use in research.

In a preimplementation survey involving 25 pregnant women and 10 midwives in Purworejo Regency, the REST app scored an average of 79.3 on the System Usability Scale (SUS), indicating above-average usability. Participants found the navigation intuitive, the language clear, and the visual design

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attractive. Of the 25 pregnant women, 23 (92%) successfully downloaded and used the REST mobile app independently within 3 days of onboarding. Midwives reported that training sessions only took an average of 60 minutes, and no major technical hurdles were encountered. In total, 30 (85.7%) pregnant women and midwives reported being very satisfied with the app and recommended it for use in pregnancy monitoring. To ensure cultural sensitivity and responsiveness to the needs of the target population, the study was developed in close collaboration with local stakeholders, including community health workers, midwives, and representatives of pregnant women in the study area. The content and language used in the REST mobile app were adapted to reflect local cultural norms, health beliefs, and communication styles, using Bahasa Indonesia and regionally appropriate terminology. Prior to implementation, the app and data collection instruments were pilot-tested with a sample of the target population to assess clarity, relevance, and acceptability.

Figures 1-3 show images of the validated and tested app [26]. The app display for midwives is different from that for participants; in the version for midwives, detailed data of pregnant women who are members of the ANC class group appear, monitored by each midwife.

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Figure 1. Image of the REST mobile app's welcome screen. REST: Risk Identification, Evaluation Counseling, Systematic Monitoring, Troubleshooting.

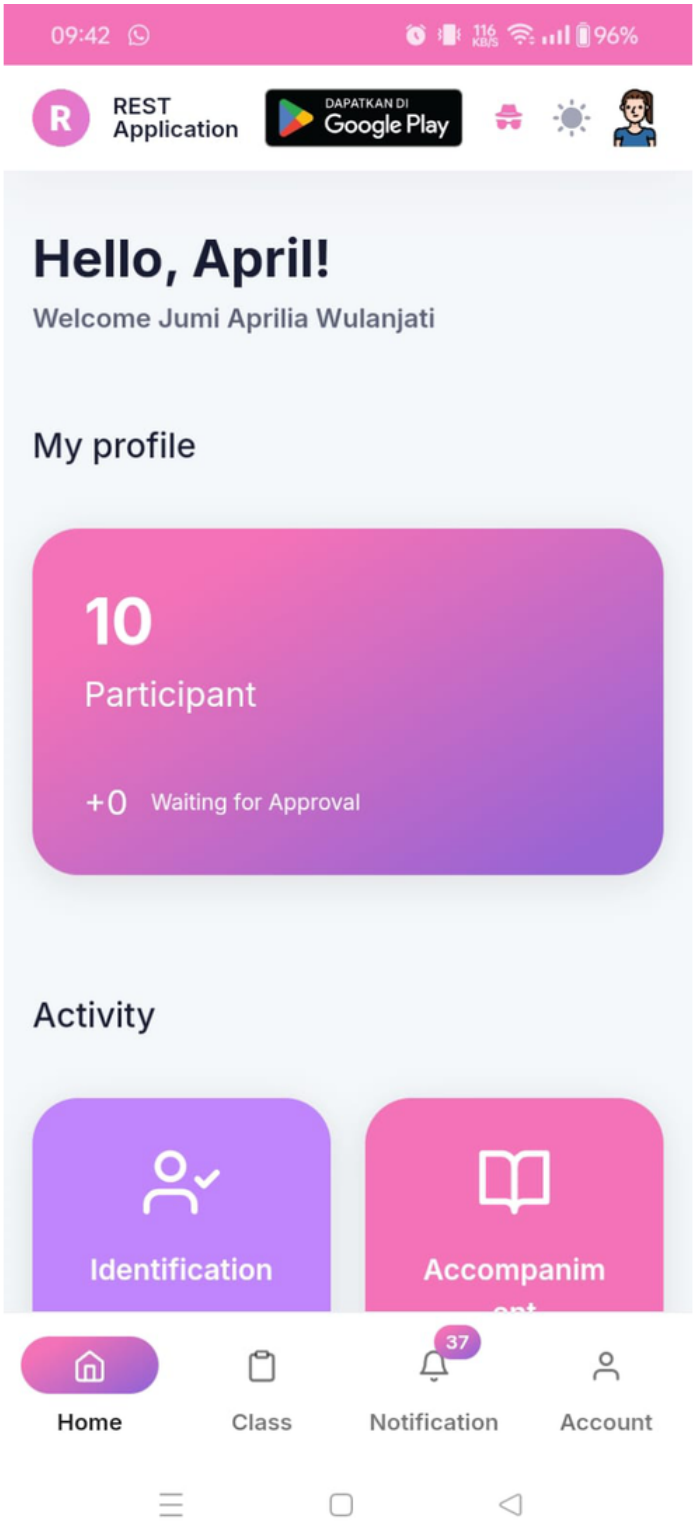

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Figure 2. Image of the REST mobile app's activity screen. The midwife can fill in the data of the results of the mother's examination during the implementation of the ANC class, and the mother can see it in pregnant women's app version. ANC: antenatal care; REST: Risk Identification, Evaluation Counseling, Systematic Monitoring, Troubleshooting.

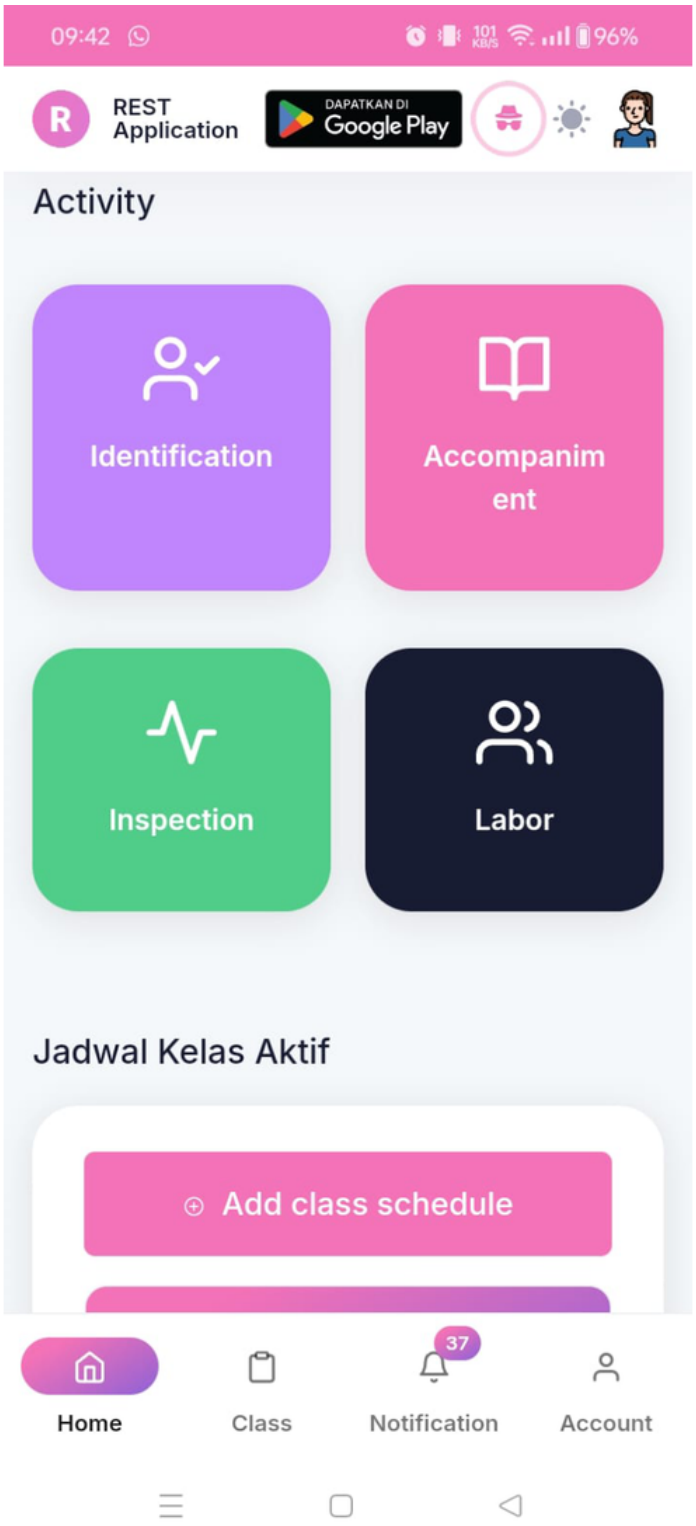

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Figure 3. Image of the REST mobile app's profile screen. Pregnant women (participants) can monitor their pregnancy based on the results of the examination that have been input by the facilitator midwife and can also fill in the results of the examination carried out outside the implementation of the ANC class. ANC: antenatal care; REST: Risk Identification, Evaluation Counseling, Systematic Monitoring, Troubleshooting.

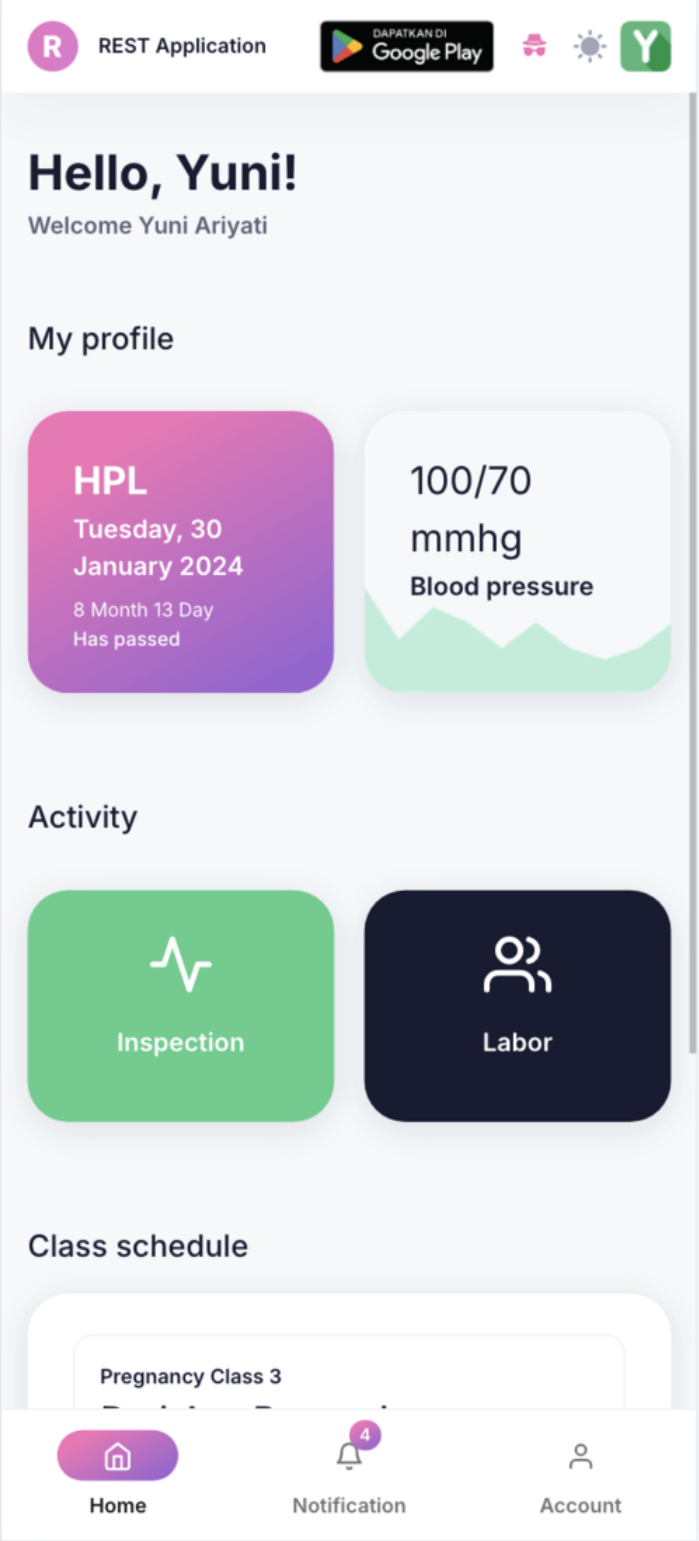

The fidelity of the intervention was assessed through a variety of strategies. First, the REST mobile app included an internal analytics system that automatically recorded user activities, such as examination results filled in by midwives and the completion of scheduled tasks by pregnant women (recording data on ANC visits). Second, the research assistant conducted periodic monitoring during ANC classes using a standard checklist to observe whether midwives and pregnant women were using the app according to protocol. Third, participants filled in the part of the delivery results they reported themselves. Any deviations from their intended use were documented and analyzed. This combined method allowed us to evaluate the compliance and quality of application usage across the cluster. The REST mobile app includes a built-in troubleshooting and

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decision support feature designed to assist midwives in early identification and management of maternal health issues. This feature operates on a rule-based algorithm that evaluates input data, such as blood pressure and hemoglobin levels against reference thresholds established by the Indonesian Ministry of Health and WHO guidelines. If an abnormal value is entered, the app automatically flags the entry and provides a visual alert. It then offers a set of recommended clinical actions, such as counseling, closer follow-up, or referral to a higher-level facility. Midwives retain clinical autonomy in making final decisions, but the app serves as a structured guide to enhance consistency and responsiveness in care. This feature was designed to strengthen early detection and ensure standardization in ANC service delivery, particularly in remote or resource-limited settings.

Study Outcomes

All results were measured at the end of the study after participants from both the control and the treatment group had undergone labor. The success of the intervention was determined from the examination data input in the REST mobile app. Results were compared between the 2 groups. In addition, the effectiveness of the app was assessed using a questionnaire.

Primary Outcomes

Pregnancy Complications

Pregnancy monitoring using the mobile REST mobile app can prevent complications during a mother's pregnancy compared to not using the app. Once the trial began, the definition of primary results was refined from "pregnancy complications" to "specific conditions of complications experienced by the mother during pregnancy, such as anemia, hypertension, and chronic energy deficiency." These changes were made before data analysis and have been documented in the protocol.

Methods of Delivery

Using the REST mobile app can identify conditions that further lead to pathological conditions from the beginning of pregnancy monitoring. Pathological conditions that are immediately resolved can facilitate a normal delivery.

Birth Weight of the Baby

In addition to monitoring the mother's condition, using the REST mobile app can help monitor the health of the fetus as well. The group that used the app paid more attention to the development of the fetus and could anticipate that the baby's birth weight can reach a normal value of ≥2500 g.

Antenatal Care Visits

The REST mobile app records how many maternal examination visit are made to health facilities. Mothers with the REST mobile app who did not undergo examinations in accordance with the minimum ANC visit standard of ≥6 received a notification from their midwives to immediately carry out the examination.

Secondary Outcomes

Monitoring using the REST mobile app makes pregnant women play an active role in their pregnancy conditions, including recording examination results independently, so that their knowledge of examination results increases. The pregnant women's perception of the current pregnancy by monitoring using the REST mobile app will be better. Because mothers will easily monitor their condition, they will understand every health development experienced. The app used by midwives and pregnant women for pregnancy monitoring was evaluated by assessing satisfaction with all aspects of use.

In addition to maternal and child health indicators, this study assessed secondary outcomes related to the impact of the REST mobile app on health systems. Specifically, we evaluated midwives' perceived workload, workflow changes, and time efficiency through qualitative methods, such as structured interviews and focus group discussions. These data will provide insights into how the app integrates into routine care, its acceptability among providers, and any unintended consequences on workload. Findings will inform future scale-up strategies and the refinement of app features to ensure that digital tools support rather than burden health care providers.

Ethical Considerations

This study received ethical approval from the Medical and Health Research Ethics Committee (MHREC), Faculty of Medicine, Public Health and Nursing, Gadjah Mada University – Dr Sardjito General Hospital (approval number KE-FK-0653-EC-2023). ClinicalTrials.gov reviewed this protocol (NCT05741931). Prior to enrollment, all eligible pregnant women were provided with detailed information regarding the study's objectives, procedures, potential risks, and benefits. The information was delivered in a clear and understandable manner by trained research staff. Written informed consent was obtained from all participants. For those with limited literacy, the information was read aloud, and a witness was present during the consent process to ensure comprehension and voluntary agreement.

To protect the confidentiality and privacy of participants, all data collected from pregnant women and midwives were handled in accordance with established ethical standards and data protection regulations. Personal identifiers were removed and replaced with unique codes to ensure anonymity.

Digital data collected through the REST mobile app were encrypted during both transmission and storage and securely stored on password-protected servers accessible only to authorized members of the research team. Any paper-based data were kept in locked storage within a secure research facility. Participants were informed about these measures during the informed consent process, and all procedures were approved by the Institutional Ethics Review Board.

Participation in this research was voluntary, without any coercion. All participants received comprehensive information about the research, especially about the intervention that would be administered and the possible benefits and risks. Participants were free to withdraw at any time without any impact on their access to health services or a penalty.

Data Analysis

Descriptive statistics were used to find out the basic characteristics of the entire study group. For bivariable analysis, the independent *t* test or Mann-Whitney U test, and the

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chi-square test or the Fisher precise test were applied for categorical results, adjusting for group design, if necessary.

Multivariable analysis was performed using mixed effects models to account for clustering at the level of the ANC class cluster. A mixed effects linear regression model was used for sustained outcomes, such as the number of ANC visits and birth weight. Mixed effects logistic regression models were used for binary outcomes, such as pregnancy complications and delivery methods. All models included random interception to account for variations between clusters and fixed effects for interventions, as well as potential confounding variables, including maternal age, education level, socioeconomic status, obstetric history, and nutritional status. Statistical significance was determined using a 2-headed *P* value of <.05.

For each primary and secondary outcome, we used an estimate of the effect size and its precision (95% CIs). Other analyses, including subgroup analysis and customized analysis, of study results were also carried out. Stata 14.0 was used to analyze the data.

Data Management

The data collected will be kept confidential for the duration of the study and disposed of after a period of 5 years. The data collection process from the beginning to the end of the study used 2 different methods. In the control group, data were collected using a form that was transcribed into electronic format, and in the intervention group, data were collected using an app and transcribed into electronic format that was stored on a desktop computer. These stored data will be used for further analysis. The individual appointed as the chair of the student project committee at the institute is responsible for overseeing data management.

To address missing or incomplete data, the researchers implemented proactive data validation and monitoring procedures within the REST mobile app. Real-time data entry validation rules were embedded in the app to minimize input errors and prevent incomplete submissions. In cases where data were missing or inconsistencies were detected, follow-up verification was conducted by the research team through direct contact with the respective participants or midwives, as appropriate. For statistical analysis, missing data will be assessed for patterns and mechanisms. Depending on the extent and nature of the missing data, appropriate methods, such as multiple imputation or complete-case analysis, will be used. To ensure overall data quality and accuracy, regular data audits will be performed, and all electronic data will be stored in secure, access-controlled databases with audit trails. These procedures have been designed to enhance data integrity and minimize bias due to incomplete or inaccurate information.

Results

In July 2023, the REST mobile app was prepared and tested in small community groups, including midwives and pregnant women, through simulation. In September 2023, the app was further developed and refined based on the feedback from these small group trials and then introduced to study participants. A total of 22 ANC class clusters were involved, comprising 22 midwives and 220 pregnant women in Purworejo Regency. These were divided into 2 groups: 11 (50%) intervention clusters using the REST mobile app and 11 (50%) control clusters. The majority of participating pregnant women were aged 20-35 years (n=168, 76.4%), consistent with national demographic trends. Approximately 185 (84.1%) had secondary education (junior and senior high school), and 57 (25.9%) had tertiary education (college graduates). The participants were evenly distributed across economic quintiles, reflecting diverse socioeconomic backgrounds, and most lived approximately 1 km from a health facility.

To provide a clearer overview of both completed and planned study phases, Table 4 presents the planned timeline for each phase of the RCT.

Table 4. Planned timeline[a] for study phases.

Phase	Start	End
Ethical approval	April 2023	April 2024
Staff training/preparation	July 2023	October 2023
Participant recruitment	November 2023	January 2024
Intervention implementation	February 2024	July 2024
Follow-up/data collection	August 2024	February 2025
Data analysis	March 2025	June 2025
Report writing/publication	July 2025	December 2025

[a]Dates are tentative and may be adjusted based on field conditions and recruitment outcomes.

Discussion

Summary

The advantages of using mobile apps for pregnancy monitoring vary from app to app as each app provides different features. The results of previous studies related to the use of mobile apps for pregnancy monitoring are considered effective and are grouped into 4 categories:

- Apps that provide information (eg, the Health Gestation app and CHAT). This app provides information that pregnant women need to monitor their pregnancy [4,27].

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- Apps used to conduct counseling between midwives and pregnant women through text messages and a voucher component [28].
- Apps that help pregnant women make decisions and provide them with mental support (eg, the Quantitative Innovation in Predicting Preterm Birth [QUiPP] app and SP+ [16,29].
- Apps that help pregnant women in managing during their pregnancy (eg, the ImTeCHO health assistant app). This app helps pregnant women perform self-monitoring and understand the condition of pregnancy well [10,30,31].

The REST mobile app is the first app designed to be used by midwives and pregnant women in which the data input by the midwives and pregnant women will be integrated. This app can also be used for comprehensive maternal health monitoring. This study used a cluster RCT design with the hope that the group comparison will be used as a benchmark for the effectiveness of using the REST mobile app.

Evidence from RCTs and systematic reviews indicates that mobile-based reminders and educational messaging can significantly increase ANC class attendance, facility-based deliveries, and maternal knowledge. For example, a cluster RCT in Zanzibar [28] demonstrated that mobile health (mHealth) interventions increased the proportion of women attending 4 or more ANC visits from 31% to 44%. Systematic reviews [32,33] further support these findings, confirming that mHealth tools enhance the uptake of maternal and newborn health services. However, although intermediate outcomes have improved, direct evidence showing a significant reduction in maternal mortality through mHealth interventions remains limited. This is largely due to the rarity of maternal deaths and the need for large sample sizes to detect such effects statistically. Despite this, by strengthening maternal health care behaviors and improving access to services, mobile apps like REST are likely to contribute indirectly to the reduction in maternal and neonatal mortality over time.

The risk identification component of the REST mobile app involves midwives identifying risks from the results of the ANC examination. Evaluation counseling involves app-based counseling from midwives for pregnant women, which makes it easier for pregnant women to make decisions. Systematic monitoring by midwives focusing on 10T includes measuring the weight and height (T1), blood pressure (T2), mid-upper arm circumference (T3), uterine fundal height (T4), tetanus immunization (T5), iron supplement tablets (T6), fetal presentation and fetal heart rate (T7), counseling (including childbirth and postpartum preparation; T8), hemoglobin levels (T9), and providing care as needed (T10) [5]. Troubleshooting involves midwives determining solutions to problems faced by pregnant women in their group.

Although the current version of the REST mobile app is limited to ANC, future development phases aim to expand its functionality to include postpartum and early childhood monitoring. Planned features include digital tools for recording postnatal visits, maternal well-being assessments, breastfeeding tracking, and early detection of postpartum complications. For child monitoring, key components will include vaccination tracking, child growth chart integration, and developmental milestone assessments based on national pediatric guidelines. This expanded scope will support a continuum-of-care approach and further strengthen maternal and child health outcomes through sustained digital engagement beyond pregnancy.

Strengths and Limitations

We hypothesize that the intervention will result in improvements in the number of ANC visits, a reduction in pregnancy complications, and improved delivery outcomes in the intervention group. However, this study has several limitations typical of eHealth trials. As this study used a cluster RCT design, potential biases, such as selection bias, limited comparability between clusters, and residual confounding despite adjustment, may have influenced the observed effects. Therefore, although the REST mobile app shows promise in supporting maternal health, causality cannot be definitively established, and further research may be needed to confirm these findings in other settings. Next, due to the nature of the intervention, participants could not be blinded, which may have introduced performance and reporting bias. Not all participants used the intervention as intended, revealing challenges related to usability and compliance in digital health trials. Additionally, varying internet access across regions posed a challenge in ensuring consistent results across health app trials. Although a mixed effects model was used to adjust for confounding, unmeasured factors may still contribute to residual confounding. Loss to follow-up could lead to attrition bias if it differs systematically between groups. Lastly, the findings may not be fully generalizable to all pregnant women in Indonesia or other low-resource settings due to the specific characteristics of the study sites and participants.

The REST mobile app installation process must be through a website [26], as the app is not yet available on App Store or Google Play Store. Its use is still limited to the research area, namely Purworejo Regency (Central Java, Indonesia). The output of the research is expected to have an effect on improving maternal and child health, and the app will be further developed more widely to reach national and global levels.

Conclusion

The cluster RCT study on the use of the REST mobile app aims to compare the welfare of pregnant women. The app used by midwives and pregnant women in the intervention group will help monitor the activities of ANC classes that are routinely carried out by the public health centers. The control group that did not use the app carried out class activities for pregnant women in accordance with implementation standards.

The study highlights the potential of the REST mobile app to enhance maternal health services in rural Indonesia by supporting early risk detection, improving service use, and empowering women through health education. Integration into national health programs is recommended. Findings will be disseminated to local stakeholders through presentations and simplified reports and to national policymakers, professional bodies, and the research community via publications, conferences, and open access platforms.

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Acknowledgments

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Data Availability

The datasets generated during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

RP contributed to the design of the REST mobile app, data curation, publication drafting, and investigations. AHS contributed to conceptualization, supervision, review, methodology, and supervision of research implementation. PDR contributed to conceptualization, supervision, data curation, review, and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 930 KB - resprot_v14i1e66774_app1.pdf]

Multimedia Appendix 2
Fillable SPIRIT Outcomes 2022 checklist, along with the SPIRIT 2013 checklist.
[PDF File (Adobe PDF File), 895 KB - resprot_v14i1e66774_app2.pdf]

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Abbreviations

ANC: antenatal care
CONSORT: Consolidated Standards of Reporting Trials
DE: design effect
ImTeCHO: Innovative Mobile Phone Technology for Community Health Operations
mHealth: mobile health
MMR: maternal mortality rate
RCT: randomized controlled trial
REST: Risk Identification, Evaluation Counseling, Systematic Monitoring, Troubleshooting
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TIDieR: Template for Intervention Description and Replication
WHO: World Health Organization

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Protocol

Developing a Behavioral Phenotyping Layer for Artificial Intelligence–Driven Predictive Analytics in a Digital Resiliency Course: Protocol for a Randomized Controlled Trial

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Abstract

Background: Digital interventions for mental health are pivotal for addressing barriers such as stigma, cost, and accessibility, particularly for underserved populations. While the effectiveness of digital interventions has been established, poor adherence and lack of engagement remain critical factors that undermine efficacy. Millions of individuals will never have access to a trained mental health care practitioner, underscoring the need for highly tailored and engaging self-guided resources. This study builds on a prior study that successfully leveraged behavioral economics (nudges and prompts) to enhance engagement. Expanding on that study, this research will focus on building a foundational dataset of behavioral phenotypes to support artificial intelligence (AI)–driven personalization in digital mental health.

Objective: This 6-arm randomized controlled trial aims to analyze user engagement with randomized tips and to-do lists within a resiliency course tailored for Ukrainian refugees affected by the ongoing humanitarian crisis (Спільна Сила), using the EvolutionHealth.care (V-CC Systems Inc) platform. Insights will inform the development of an AI-based personalization system to optimize engagement and address behavioral health challenges. Secondary objectives include identifying demographic and behavioral predictors of engagement and creating a scalable, culturally sensitive intervention model.

Methods: Participants will be recruited through digital outreach, enrolled anonymously, and randomized into 6 groups to compare combinations of tips, nudges, and to-do lists. Engagement metrics (eg, clicks, completion rates, and session duration) and demographic data (eg, age and gender) will be collected. Statistical analyses will include a comparison between arms and interaction testing to evaluate the effectiveness of each intervention component. Ethical safeguards include institutional review board approval, informed consent, and strict data privacy standards.

Results: This protocol was designed in January 2025. α and β testing of the intervention are scheduled to begin in July 2025, with a soft launch anticipated in August 2025. The experiment will remain active until the sample size requirements are met. Live monitoring and periodic data quality checks will be conducted throughout the study duration.

Conclusions: This trial represents a novel approach to behavioral health research by leveraging randomized experimentation to develop AI-ready behavioral datasets. By targeting an underserved and culturally sensitive population, it contributes critical insights toward scalable, personalized digital mental health interventions. Findings may help inform future digital health efforts that aim to improve engagement, accessibility, and long-term adherence.

Trial Registration: Open Science Framework 34rmg; https://osf.io/34rmg

International Registered Report Identifier (IRRID): PRR1-10.2196/73773

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(JMIR Res Protoc 2025;14:e73773) doi:10.2196/73773

KEYWORDS

digital mental health; behavioral economics; engagement; attrition; AI-driven personalization; machine learning; self-guided therapy; digital phenotyping; artificial intelligence

Introduction

Background

Self-guided digital mental health interventions play a crucial role in overcoming barriers such as stigma, cost, and accessibility, particularly for underserved populations [1-3]. While their efficacy is well documented in meta-studies [4-7], low adherence and lack of engagement limit their potential impact in publicly available interventions [8-14]. Improving user engagement is therefore essential to realizing the full public health value of these scalable tools.

Optimizing engagement is crucial, as research suggests dose-response relationships; higher engagement is associated with better outcomes such as improvements in mental health [15-17]. This mirrors the commercial world, where higher user engagement results in increased revenue [18,19], and research investigating ways to enhance participation is common.

For example, a 2015 study revealed that LinkedIn (Microsoft Corporation) conducted over 400 controlled engagement experiments per day [20]. The language app Duolingo (Duolingo, Inc) regularly conducts controlled experiments to assess the impact of features to make learning more engaging [21]. Meta (Facebook and Instagram) teaches and technically enables business customers to conduct randomized A-B experiments to optimize ad messaging and conversion [22].

Leveraging similar strategies that commercial platforms use to increase engagement holds the potential to both enhance the user experience in digital mental health and improve overall effectiveness. To that aim, this study builds on prior research on the EvolutionHealth.care (V-CC Systems Inc) platform, which leveraged behavioral economics to tailor user experiences to increase platform engagement [23,24].

For reasons described below, there is a need for further research in optimizing self-guided digital health [25-27], which falls far behind other large-scale commercial platforms that also rely on increasing engagement. Unlike large-scale commercial platforms that rigorously test user experience through ongoing experiments, most digital health platforms lack modern personalization methods. This study aims to address that gap by applying insights from behavioral economics and artificial intelligence (AI) to improve real-world adherence.

Mental Health Care Professional Deficits

Globally, the World Health Organization (WHO) estimates a deficit of 1.2 million mental health professionals [28]. In the United States, 50.6% of adults with any mental illness received treatment [29], and two-thirds of adults with serious mental health illness received treatment [30].

The Need to Reframe Digital Health Intervention Reach

Traditional digital health delivery models are primarily reaching the serviceable obtainable market (SOM)—individuals who are insured, tech-savvy, and already engaged with health care systems. This leaves a significant portion of the population unserved, including those without consistent health care access or digital literacy. Addressing this gap requires intentional design for broader accessibility and lower barriers to entry. The total addressable market (TAM) for mental health interventions is far broader, encompassing displaced individuals, the uninsured, and underserved populations around the world (Figure 1).

Figure 1. Estimated total addressable market, serviceable available market, and serviceable obtainable market for mental health and substance use in the United States, Canada, and Europe. B: billion; SAM: serviceable available market; SOM: serviceable obtainable market; TAM: total addressable market.

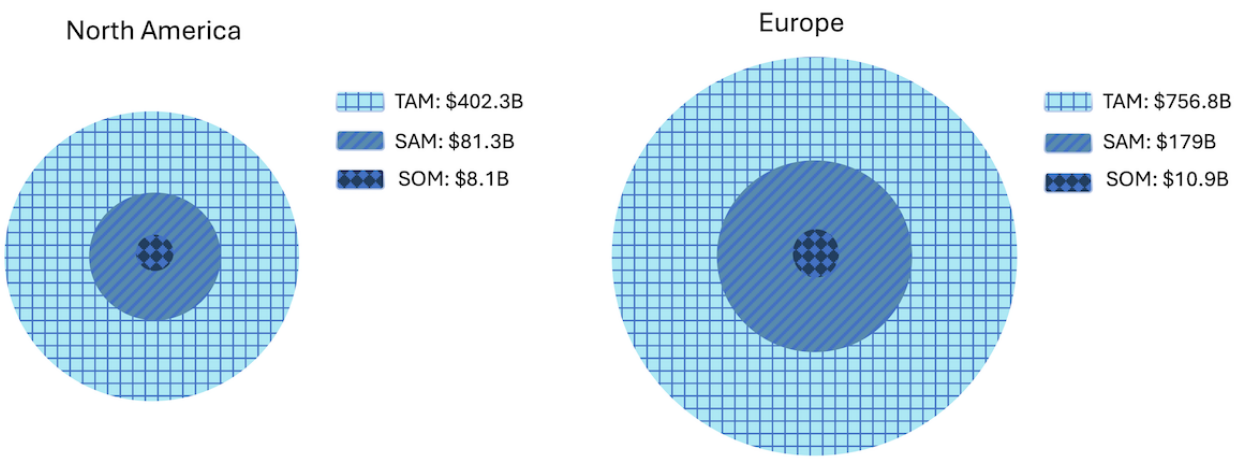

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The persistent engagement problem suggests that the field has not yet found scalable ways to reach or retain this wider audience. By focusing on open-access, low-barrier design, and tailoring through AI-driven nudges, this study represents an attempt to move beyond the SOM and explore pathways for digital health scale, first reaching the serviceable available market (SAM)—those who have digital devices but are not accessing interventions—and eventually the TAM, the full population of individuals worldwide, including those excluded by platform, policy, or economic barriers.

Issues With Telehealth Access

Intensified by the COVID-19 pandemic [31,32], digital health interventions have become increasingly common. Investment in mental health treatment, mainly telehealth, has seen significant growth [33,34]. The surge in interest reflects the urgent need to address access gaps identified during public health crises. However, while funding has increased, sustainable implementation remains a major challenge.

Despite billions in funding [35-37], the telehealth sector faces significant challenges. These include market saturation, intense competition, profitability, and workforce shortages. In addition, high costs related to patient acquisition and retention, coupled with regulatory demands and a projected shortage of trained professionals [28,38-40], continue to hinder long-term sustainability. These issues are estimated to extend into the next decade and affect access [41], so there is a need to mitigate these issues with alternative resources.

AI Models: Large Language Models Versus Predictive Analytics

In digital health, AI has primarily focused on large language models (LLMs). Predictive analytics has fallen behind the use of LLMs, as they require large amounts of AI training data. However, predictive models have the potential to enable personalized user journeys and improve long-term engagement, making them a vital area for future development.

LLMs

LLMs are advanced AI systems trained on vast amounts of text data to understand and generate human-like language. In digital health, LLMs power chatbots and virtual assistants that provide patient support, answer health-related queries, and assist health care professionals with information retrieval. These models can engage in natural language conversations, making them valuable tools for enhancing patient education.

Predictive Analytics

Predictive analytics involves analyzing current and historical health care data (including behavioral phenotypes) to forecast future outcomes. By leveraging statistical models and machine learning algorithms, health care providers can predict disease progression, patient admissions, and treatment responses. This proactive approach can enable personalized care and tailor user experiences, ultimately improving patient outcomes and operational efficiency.

Russia's Invasion of Ukraine and Resulting Displacement

In February 2022, Russia initiated a full-scale invasion of Ukraine, leading to widespread destruction and a significant humanitarian crisis. As a result, millions of Ukrainians have been displaced both internally and internationally, seeking refuge in various countries worldwide.

While exact figures are challenging to determine, Los Angeles has a significant Ukrainian community. The city has seen an influx of Ukrainian refugees since the onset of the war, with many individuals and families seeking to rebuild their lives in the area [42]. Before the 2022 invasion, approximately 60,000 Ukrainian immigrants resided in the state. Following the invasion, an estimated 20,000 or more Ukrainians have arrived, bringing the total to around 80,000 [43]. Major cities such as Los Angeles, San Francisco, and Sacramento have been primary destinations for these new arrivals.

Nationally, the Ukrainian diaspora includes more than 1.1 million individuals, encompassing both immigrants and those of Ukrainian ancestry. As of 2019, there were approximately 355,000 Ukrainian immigrants in the United States. In response to the 2022 invasion, the US government announced plans to accept up to 100,000 Ukrainian refugees. By late 2022, approximately 85,000 Ukrainians had used the "Uniting for Ukraine" program, which allows refugees with an American sponsor to remain in the country for 2 years [44]. By December 2022, President Joe Biden announced that the United States had accepted roughly 221,000 Ukrainian refugees through various programs [45].

Globally, the conflict in Ukraine has led to the displacement of approximately 6.8 million refugees, with nearly 4 million people internally displaced within the country as of November 2024 [46]. European nations have accepted the greatest number of refugees, hosting around 6 million Ukrainians, with Germany now hosting the largest number [47]. Canada has also received a significant number of Ukrainian refugees, with major cities such as Toronto, Montreal, and Winnipeg welcoming thousands of newcomers and implementing resettlement programs to support housing, employment, and cultural integration [48,49]. This mass displacement represents the largest population movement in Europe since World War II [50].

Behavioral Economics

Overview

Behavioral economics leverages psychological experimentation to develop theories about human decision-making. The field has identified a range of biases around how people think and feel. In this study, we will examine the engagement of users with nudges and behavioral prompts in an ad libitum, self-guided digital behavior change course.

Digital interventions can be customized using behavioral economics to correspond with the needs and behaviors associated with specific user types. Since interventions become more appealing and relevant to each user's unique needs and goals, this personalized approach may improve user engagement. Content and engagement techniques can be adjusted to better

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match specific goals and motivations by using data on user interactions and behavior trends. Through making digital interventions accessible [51] and culturally acceptable, personalization based on behavioral economics techniques can assist in fulfilling the various demands of different types of populations.

This study's engagement strategy aligns with the COM-B model of behavior, in which capability (C), opportunity (O), and motivation (M) interact to generate behavior (B) [52]. Directive tips enhance capability through actionable guidance, social proof, and present bias tips increase motivation, and checklists and gamification create opportunity by simplifying follow-through.

Nudge Theory

Nudge theory, popularized in the 2008 book *Nudge: Improving Decisions About Health, Wealth, and Happiness* [53], leverages indirect, positive suggestions to influence decision-making and behavior through designs or changes in the decision environment. The approach has been applied in various fields, including finance, education, and public health.

There is a lack of quality research analyzing the use of nudges in digital health. A 2019 scoping review examined the use of nudges in both web-based and real-world settings in physical activity interventions [54]. Of the 35 publications reviewed, 8 were web-based studies. The authors concluded that although nudging may be an effective approach to promote physical activity, there are large gaps in research, and further studies that are explicitly based on nudge insights are needed.

A 2020 editorial in *Personalized Medicine* addressed the meaningful adoption of nudges in digital health [55]. The authors acknowledged that using nudges in digital health interventions is rare and advocated for the use of nudges to promote positive behavior change. This reinforces the relevance of our trial, which aims to rigorously evaluate nudge-based strategies in a digital health setting.

Nudges must be culturally sensitive and adaptable to different cultural backgrounds [56]. This ensures that interventions work and are accepted in many kinds of cultural contexts. Addressing ethical issues, including consent, privacy, and potential biases in nudge design, is essential as nudges become more common in digital health. Reliability in digital health platforms can be strengthened by ensuring transparency and user control over the use of nudges, which we will use in this study [57].

Behavioral Prompts

Behavioral prompts are cues specifically designed to encourage a specific task [58]. In this study, we will use 2 types of behavioral prompts anchored in nudge theory: daily tips and a to-do checklist (Table 1). These prompts are intended to support self-guided action, reinforcing positive behavior without requiring direct human intervention.

An effective approach for boosting user involvement in digital health interventions may be offered by analyzing combinations of behavioral prompts that users engage with. Through machine learning techniques, the dataset emerging from this study may provide insight into which and what prompts work best with specific demographics and usage patterns [59]. By customizing interventions to meet the unique needs of every user, this integrated approach might increase the possibility of long-term behavior change and better health outcomes.

Table 1. Example nudges and prompts.

Delivery format	Content type	Example from our study
Tip	Directive content	Express yourself by uploading your image!
Tip	Social proof	Many members have similar goals to yours. Reviewing other members' goals can help you reach your goal.
Tip	Present bias	Feel better sooner by learning from others. Read what others have posted in the community.
Prompt	To-do checklist	Watch the getting started video.
Visual element	Gamification	A progress bar fills as users complete sections of the course.

Gamification

The use of game-like elements such as progress bars, badges, and rewards has been shown to increase user motivation and adherence in digital health interventions. These strategies leverage principles of intrinsic motivation, offering visual reinforcement and a sense of accomplishment as users complete tasks. When implemented thoughtfully, gamification can help sustain user engagement over time, especially in self-guided programs.

In our previous work, we explored the application of gamified tools to promote physical activity through a social, multiuser platform. This study highlighted the promise and limitations of these techniques in health behavior change [60]. In the current study, gamification is implemented through a dynamic progress bar that visually tracks user progress, reinforcing engagement through motivational feedback, and awarding badges for completing sessions and passing session quizzes.

Our Prior Work

We have experimented with nudges and prompts in the past. In our previous 3-arm randomized controlled trial (RCT) [24], arm 1 featured a member home page without nudges or prompts. Arm 2 featured a home page with a tip-of-the-day section. Arm 3 featured a home page with a tip-of-the-day section and a to-do checklist.

Control arm members (1788/13,224, 13.52%) completed an average of 1.5 course components. Arm 2 members (865/13,224, 6.54%) clicked on 5% of tips and completed an average of 1.8 course components. Arm 3 members (1914/13,224, 14.47%)

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clicked on 5% of tips, completed 2.7 of 8 to-do checklist items, and an average of 2.11 course components. Completion rates in arm 2 were greater than those in arm 1 (z score=3.37; P<.001), and completion rates in arm 3 were greater than those in arm 1 (z score=12.23; P<.001). Engagement in all 8 components in arm 3 was higher than that in arm 2 (z score=1.31; P<.001).

Further analysis confirmed that behavioral economics techniques, such as nudges and prompts, significantly enhance engagement in digital health interventions. Specifically, users in the nudge + prompt condition (arm 3) were 93% more likely to engage compared to those in the control group (arm 1), as indicated by an odds ratio of 1.93 (95% CI 1.71-2.17; P<.001). This increase in engagement was reflected across multiple platform activities, including self-assessments, goal setting, and content interaction.

However, while these findings validate the effectiveness of nudges and prompts, the study did not explore how individual-level factors shaped these outcomes. Specifically, we did not examine how the intersection of demographic characteristics and cognitive or behavioral phenotypes influenced engagement, if individual engagement followed properties of power laws [61], or if we could leverage economic tools such as the Gini coefficient to plot participation inequality [62].

Understanding these patterns is important for optimizing future interventions for full personalization and maximizing the effectiveness of digital health tools.

Objective

The primary objective is to analyze user engagement with randomized tips and to-do lists within a resiliency course tailored for Ukrainian refugees affected by the ongoing humanitarian crisis. Insights will inform the development of an AI-based personalization system to optimize engagement and address behavioral health challenges. This approach is designed to improve real-world adherence while maintaining cultural relevance. Secondary objectives include identifying demographic and behavioral predictors of engagement and creating scalable, culturally sensitive nudging [63,64] and intervention models. These insights will also inform future adaptations of the intervention across languages and cultural contexts.

Since there is a paucity of published research in this area [65-67], our unique dataset holds the potential to customize user experiences and transform digital engagement by leveraging behavioral phenotypes and machine learning. Few studies have explored the predictive potential of behavioral cues in real-world digital health environments. This trial is designed to fill that gap and generate data suitable for training scalable AI-driven models.

Methods

Digital Health Platform

The digital health platform used in this study is managed by Evolution Health. EvolutionHealth.care is an evidence-based digital health content provider that features courses based on behavior change techniques, including cognitive behavioral therapy (CBT), stages of change, structured relapse prevention, harm reduction, and quizzes based on brief intervention.

The platform offers interactive courses and quizzes for mental health issues, addiction issues, and obesity. It also contains a moderated community based on social cognitive theory.

Limited memberships are available to individuals who register through the organization's free-to-consumer program. Full memberships are available through white-label instances licensed to employers, insurance companies, employee assistance programs, educational institutions, nonprofit organizations, for-profit health care organizations, and individual therapists.

The Intervention

Shared Strength (Спільна Сила) is a self-guided interactive behavior change treatment course based on traditional evidence-based treatments (Table 2). It draws from multiple therapeutic frameworks, including CBT, motivational interviewing, and social cognitive theory. The goal is to provide users with a flexible, culturally sensitive, interactive course that supports emotional resilience and behavior change.

Other interactive courses in the Evolution Health platform have been extensively examined in the literature [10,23,24,61,62,68-90]. Shared Strength mirrors its structure and design (Table 3). This consistency enables us to leverage existing platform infrastructure and previous research insights while applying new engagement strategies.

Table 2. Theoretical constructs and evidence-based components.

Theoretical construct	Shared Strength (Спільна Сила)
Brief intervention	✓
Cognitive behavioral therapy	✓
Gamification	✓
Health belief model	✓
Motivational interviewing	✓
Social cognitive theory	✓
Targeting and tailoring	✓

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Table 3. Main course components.

Course component	Shared Strength (Спільна Сила)
Avatar upload	✓
Course completion certificate	✓
Course worksheets	✓
Gamified CBT[a] course	✓
Getting started video	✓
Goals exercise	✓
Moderated community	✓
Private messaging	✓
Statistics extranet (for corporate clients)	✓
Tailored depression and anxiety test	✓
Therapist extranet	✓

[a]CBT: cognitive behavioral therapy.

Course Content Overview

Shared Strength (Спільна Сила) contains nine interactive sessions. Each session is designed to foster emotional resiliency using evidence-based strategies drawn from CBT, behavior change theory, and supportive self-help principles. The structure allows participants to move at their own pace while reinforcing learning and self-efficacy. Key session themes include (1) understanding emotional responses to displacement, (2) managing anxiety and low mood, (3) setting personal goals and building hope, (4) practicing mindfulness and grounding techniques, and (5) strengthening connections and community.

Each session includes short readings and interactive tools, such as goal setting, a resiliency diary, to-do checklists, and a summary quiz to reinforce learning. Users progress at their own pace.

Cultural Adaptation Process, Participatory Design, and Interdisciplinary Collaboration

Following best practice [63,91-93], the Ukrainian version of the Shared Strength course is undergoing cultural adaptation. This process involves collaboration with a bilingual mental health professional and displaced Ukrainian software developers, each bringing insight into the lived experiences of displacement. The adaptation process includes (1) linguistic translation of all English course material, including prompts and tips; (2) contextual revision of examples, tips, and imagery to align with Ukrainian cultural norms and displacement-related stressors; (3) tone and voice refinement to reflect empathy, autonomy, and strength-based messaging in line with Ukrainian cultural communication preferences; (4) technical development and coding by displaced Ukrainian engineers, ensuring both usability and cultural sensitivity; and (5) clinical accuracy: a Ukrainian psychiatrist with experience in delivering CBT-based behavioral interventions and developing digital health tools will review the content.

In addition to linguistic and cultural adaptation, all content is written using plain-language principles to support accessibility for users with varying literacy levels. Usability testing is being conducted with displaced Ukrainian collaborators to ensure the platform is intuitive and accessible for individuals experiencing stress or trauma. This dual approach enhances both comprehension and user trust.

Recruitment and Participants

Participants will be recruited through partnerships with nonprofit organizations, digital outreach campaigns, and community organizations. Enrollment will occur via the EvolutionHealth.care platform, where participants will be randomized automatically upon sign-up using a computer-generated sequence, ensuring unbiased allocation.

As part of our ethical commitment to accessibility and user privacy, no personal or demographic data will be collected to identify users as displaced or Ukrainian. While this is a limitation, our dissemination model mitigates this concern by partnering with refugee-serving organizations and providing them with custom-branded course instances (eg, “https://YourOrg.EvolutionHealth.care”) or masking their instance with a full URL (eg, “https://YourChosenURL.extension”).

This strategy enables us to reach targeted communities through trusted channels, reducing the likelihood of sample contamination while maintaining an open-access structure that supports real-world scalability and humanitarian distribution. It allows refugee-serving organizations to promote the intervention under their trusted branding. This partnership model combines targeted outreach with the scalability of digital delivery.

Randomization

Participants will be randomly assigned to one of the following six arms, as presented in Figure 2:

1. Arm 1 (baseline control): directive tips only and no to-do checklist.
2. Arm 2: directive tips + social proof tips and no to-do checklist.

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3. Arm 3: directive tips + social proof tips + present bias tips and no to-do checklist.
4. Arm 4: directive tips + to-do checklist.
5. Arm 5: directive tips + social proof tips + to-do checklist.
6. Arm 6: gamification (progress bars) + to-do checklist.

Participants will be randomly assigned to one of the six experimental arms using computer-generated randomization in a 1:1:1:1:1:1 ratio. Randomization will be conducted at the point of user registration, ensuring equal probability of assignment to any condition. No stratification or blocking will be used, as randomization is expected to produce comparable groups given the planned sample size. Randomization will be logged automatically by the system to ensure reproducibility and allocation integrity.

Figure 2. Study flow diagram.

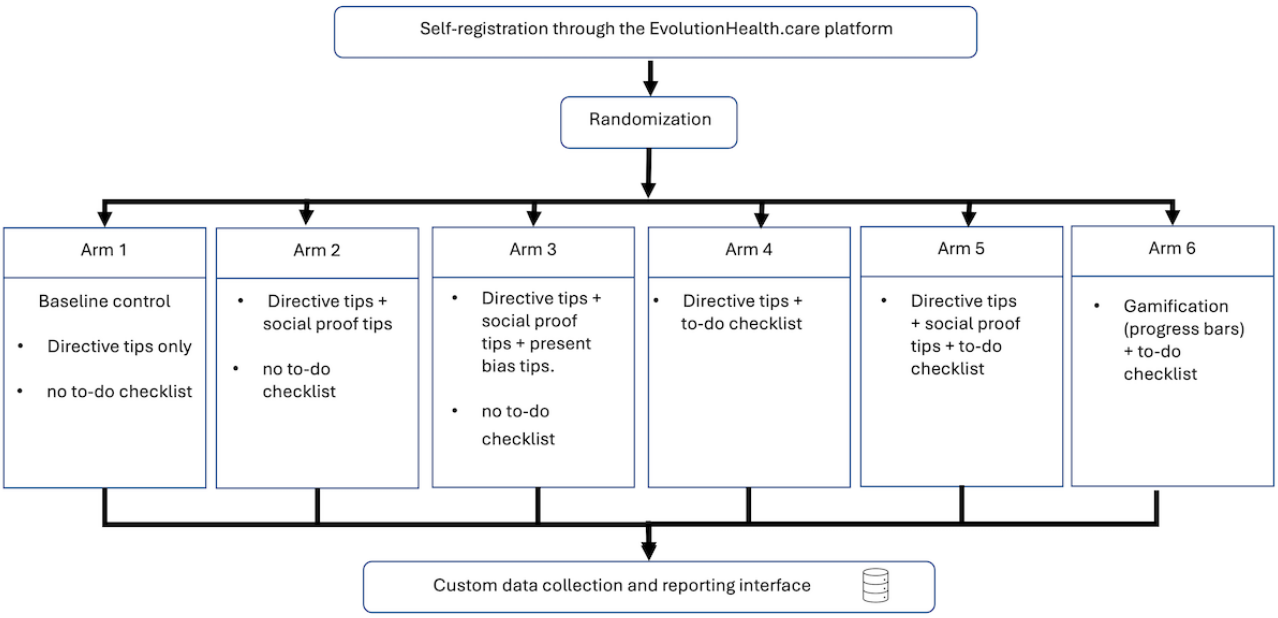

Multiarm Trial Rationale

The six study arms were developed to explore the individual and combined effects of behavioral prompts grounded in behavioral economics, to identify which strategies most effectively enhance engagement in a digital resiliency program. Each arm includes a specific configuration of tips, checklists, or gamification elements intended to test distinct motivational mechanisms. This design enables comparative analysis across different engagement strategies while remaining operationally feasible. These components tested include (1) directive tips, grounded in the theory of implementation intentions, which provide straightforward, actionable guidance; (2) social proof tips, which leverage peer effects by referencing the behavior of others to encourage participation; (3) present bias tips, designed to counteract temporal discounting by emphasizing short-term benefits of engagement; (4) to-do checklists, which introduce structured goals and progress-tracking to increase adherence; and (5) gamification, which builds intrinsic motivation through visual indicators of advancement and progress feedback.

While a full factorial design could have explored all possible combinations of these interventions, the current 6-arm structure is a deliberate balance between conceptual rigor and practical feasibility. This structure enables comparative analysis across a diverse set of nudge combinations without creating an unmanageable number of trial arms. It was also informed by operational constraints and the need for meaningful data distribution across arms.

Our study design is also a foundational step toward developing a predictive analytics dataset. The behavioral engagement data collected through the six arms will be used to build baseline models that inform AI-driven personalization strategies. Future iterations of the course will be updated with tailored nudges based on user profiles, and new user data will be used to validate and refine the models. We chose the current design to generate sufficient diversity and volume in behavioral data to create a baseline for our long-term, adaptive research agenda.

Primary and Secondary Outcomes

The primary outcome is engagement with behavioral prompts, defined as whether a user clicks on a specific tip, type of tip, or checklist item and is directed to the associated course component (refer to Table 3). This outcome reflects the initial behavioral response to a specific nudge. It serves as the basis for understanding which types of prompts are most effective at initiating action within the course. Secondary outcomes reflect broader patterns of use and progression through the course. These include (1) completion of main course components (eg, submitting a goal, completing the depression and anxiety test, completing course sessions, and engaging with other tools defined in Table 3); (2) click rate, defined as the proportion of tips and checklist items clicked; (3) session duration, or the total time spent on the platform; and (4) number of course sessions completed, including badge acquisitions and quiz completions.

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Power and Sample Size

The primary outcome of interest is engagement, measured through click-through rates, session duration, and to-do checklist completion rates across the 6 experimental arms. These metrics allow us to assess how different combinations of prompts and gamification elements affect user behavior. This will help us determine which strategies are most effective for sustaining participation in self-guided programs.

The study is designed to detect small to moderate effect sizes in engagement differences between intervention groups. Expected effect sizes range from Cohen f=0.1 (small) to f=0.25 (moderate). Our goal is to obtain a power of 80% (β=.20) and a significance level of .05 (α) to ensure adequate sensitivity in detecting meaningful differences between groups.

Sample Size Calculation for ANOVA

Given that engagement metrics will be compared across 6 arms, a one-way ANOVA test was used to estimate the required sample size. For a small effect size (f=0.1), approximately 86 participants per arm (a total of 516 participants) are required. For a moderate effect size (f=0.25), approximately 28 participants per arm (a total of 168 participants) are required. These calculations assume normality of residuals and homogeneity of variance for ANOVA-based analysis. Chosen effect sizes are based on prior research in digital health engagement studies [94-96]. In our prior RCT [23,24], engagement data were analyzed using mixed-effect logistic regression, which does not rely on these assumptions.

Sample Size Calculation for Regression Analysis

Regression analysis will be applied to assess the relationship between engagement and demographic factors (eg, age and gender). This will assist in the identification of predictors of engagement and potential subgroup effects [97]. These analyses are exploratory and may be underpowered. For linear regression, a common rule of thumb suggests 15-20 participants per predictor variable [98,99]. For logistic regression, a minimum of 10 outcome events per predictor variable is typically required [100].

A total of 600 participants will provide sufficient sample size power for multiple predictors while ensuring a balanced distribution across intervention arms. This sample size also accounts for expected variability in engagement behavior across arms and balances analytic rigor with the practical realities of digital recruitment.

Sample Size for Repeated Measures

Since engagement data will be collected across multiple time points, generalized estimating equations will be used to account for within-subject correlations. The generalized estimating equation is well-suited for analyzing longitudinal behavioral data in real-world digital environments, allowing more accurate estimation of SEs and robust modeling of repeated engagement behavior. A within-group correlation of ρ=0.3 was assumed, based on prior studies of engagement in digital health. This estimate aligns with findings from longitudinal analysis in behavioral health studies that report moderate within-person correlation of repeated engagement measures [101,102]. A 15% attrition rate was factored into the final sample size, suggesting an adjusted recruitment target of 100 participants per arm to maintain statistical power.

Sample Size Justification

To ensure the predictive model has sufficient training data, the study aims to recruit a minimum of 600 participants (100 per arm). This sample size balances feasibility with analytic rigor, ensuring adequate power to detect differences in engagement and to train AI-driven predictive models. Refer to Multimedia Appendix 1 for the study's CONSORT-SPI (Consolidated Standards of Reporting Trials-Social and Psychological Interventions) checklist [103].

Data Collection

The Evolution Health platform is equipped with a custom data collection interface and reporting mechanism. Data will be collected for each member who is randomly assigned to the experiment, and all data are self-reported. Information on age and self-identified gender will be collected at registration or during secure sign-on across various white-label instances.

The custom database will also track behavioral engagement with each tip and to-do item randomly presented to users, including whether a tip was displayed, whether it was clicked, and whether the user completed the corresponding course component.

Engagement Metrics: Operational Definitions

Engagement is defined as follows:

- Click rate is defined as tips or checklist items that users click on.
- Tip interaction is considered "complete" when a user clicks on a tip and completes an exercise.
- Gamification metrics (eg, progress bar status, quiz completion, badge acquisition) will be recorded as binary variables (earned vs not earned).
- Session duration is calculated as the elapsed time (in seconds) between a user logging in and logging out of the platform.

Ethical Considerations

All data collection policies and procedures adhere to international privacy guidelines, including the General Data Protection Regulation, the US Health Insurance Portability and Accountability Act, where applicable, and the Declaration of Helsinki [104-107]. At registration, all members endorse a checkbox confirming that they consent to have their data used for research purposes and approve the platform's privacy policy.

The platform does not collect personally identifiable information except a user's email address, which is required for registration confirmation, retrieval of lost passwords, and two-factor authentication. Email addresses are encrypted and stored in a separate database.

This study is conducted on a self-guided resiliency course for displaced Ukrainian refugees, but it does not measure clinical outcomes. While participants are randomized into 6 intervention arms, the study is classified as an RCT, but it is not an RCT under medical research standards [108]. To clarify, this study

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adheres to principles of an RCT, where participants are randomly assigned to conditions, but does not fall under medical trial classification as it does not measure health outcomes. The CONSORT-SPI guidelines for social and psychological intervention trials will be followed [103].

The primary outcome variable being tested is course engagement, not wellness or symptom reduction. The study does not evaluate whether participant engagement with course tools improves mental health or reduces emotional stress related to forced displacement. Any potential clinical effects of engagement strategies tested in this study will require investigation in future research.

Since this study does not measure clinical outcomes, it does not fall under ClinicalTrials.gov or the WHO International Clinical Trials Registry Platform requirements. However, to ensure transparency, the trial was registered with Open Science Framework, a widely recognized registry for social science and behavioral health research.

As the study was based on deidentified user data and did not collect medical or clinical measures, it was deemed exempt from further review by Evolution Health's Institutional Review Board. This exemption is per regulatory standards for minimal-risk research involving nonidentifiable behavioral data.

Results

This protocol was designed in January 2025. α and β testing of the intervention are scheduled to begin in July 2025, with a soft launch anticipated in August 2025. The experiment will remain active until the sample size requirements are met. Live monitoring and periodic data quality checks will be conducted throughout the study duration.

Discussion

Hypothesis

From our previous study, we anticipate higher engagement in arms that include the to-do checklist, particularly when combined with gamification (arm 6) or social proof tips (arm 5) (H1 and H2). Previously, these combinations demonstrated higher click-through and completion rates in earlier research. We expect similar trends in this trial, though results may vary based on population characteristics and platform context.

The study will also contribute to the development of AI models capable of predicting and optimizing user engagement, allowing for the customized delivery of to-do items and tips based on behavioral phenotypes (H2). These models will be trained using the behavioral data collected across study arms. Ultimately, this approach aims to enhance long-term adherence by tailoring interventions to individual patterns of use.

In our previous research on user engagement within the platform's social network, we observed that engagement patterns followed power law distributions [88]. A follow-up study found that demographic and condition-specific characteristics did not predict social network engagement [89]. However, this study will help determine whether course engagement follows similar power law properties or if age and gender are predictive of engagement outcomes, particularly given the inclusion of session duration and behavioral phenotypes as new analytical factors (H3).

Expected Results

This study builds on prior RCT findings, extending the use of behavioral economics to underserved, culturally sensitive populations. Unlike existing studies by platforms, our focus on mental health and refugees offers unique contributions to both research and practice. Findings may also advance AI-driven personalization in digital health.

Strengths and Limitations

A strength of this experiment is that it will be conducted in an ad libitum environment. Unlike most digital health studies, it will not be conducted with a small population in a controlled environment. Further, members will not be aware of the experiment, which will limit participant bias and the Hawthorne effect.

Based on stratified randomization, which will balance demographic factors, the dataset generated will enable predictive analytics for adaptive engagement strategies. Other indication-specific data, such as results and qualifying criteria from the mental health screener [81], have the potential to enrich tailoring. These layers of data will help evolve the platform from static guidance toward real-time personalization.

A limitation of this experiment is that, especially due to the anonymity of members, we have no way of confirming user identity. Registrants may be displaced Ukrainians, individuals reviewing the program based on general interest, researchers, practitioners reviewing the platform for professional use, Evolution Health competitors, industry analysts, or other users who may not be engaging with the platform to help achieve wellness. Sensitivity analyses will be conducted to filter and exclude anomalous user engagement data.

Although engagement correlates with improved intervention outcomes, this study does not measure wellness improvements. Follow-up research will be required to establish clinical efficacy.

Future Directions

By leveraging randomized experiments and AI, this study provides a blueprint for scalable, culturally sensitive digital health interventions based on demographic characteristics, indication-specific variables, and behavioral phenotypes. This methodology allows for the continuous refinement of engagement strategies over time. The framework can be adapted to support different populations and health indications across diverse settings.

Engagement data from this trial will serve as the foundation for training predictive analytics models that identify which behavioral prompts are most effective for specific user profiles. These models will help personalize the delivery of content in real time, increasing the likelihood of user interaction. Over time, this data-driven approach may significantly improve long-term platform engagement.

As data volume increases (training and validation data), models will be refined and validated using new user cohorts, allowing

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us to optimize recommendations and nudge strategies based on user behavior, language, and engagement patterns. This iterative refinement process will enhance model accuracy and reduce overfitting. It also enables better generalization across diverse user segments and use cases.

This adaptive approach will also support future deployment of the course in additional languages and for other displaced populations. The underlying platform is designed to be modular, making translation and cultural adaptation straightforward. This scalability is essential for addressing global mental health disparities across diverse regions.

Conclusions

This trial represents a novel approach to behavioral health research by leveraging randomized experimentation to develop AI-ready behavioral datasets. By targeting an underserved, international, and culturally sensitive population, it contributes critical insights toward scalable, personalized digital mental health interventions. Findings may help inform future digital health efforts that aim to improve engagement, accessibility, and long-term adherence.

Acknowledgments

This study is funded by the LARTA Institute and the Gilead Foundation. We thank our collaborators and advisors for their invaluable contributions to this project.

Data Availability

The datasets generated or analyzed during this study are not publicly available due to the platform's data privacy policy. Allowing the dataset in this study to be publicly available would violate the platform's data privacy policy, terms of use, and user agreement. The platform is designed to protect user anonymity, and releasing the full dataset could compromise these commitments. For these reasons, public access to raw data is restricted to protect participant privacy and system integrity. Furthermore, the data emerging from this experiment will be leveraged to train AI models to better understand how to increase and encourage healthy behavior change. Making this data publicly available may have the opposite effect and enable the development of models that can detect and target vulnerable populations. However, the dataset from this study, ongoing engagement data that is continually collected, or other platform datasets can be made available to researchers interested in conducting studies for noncommercial purposes. Researchers must agree to strict data use and privacy terms in line with the platform's ethical standards. This ensures that data-sharing efforts remain aligned with our core values of participant protection and responsible research. Interested researchers are encouraged to contact Evolution Health.

Authors' Contributions

TVM contributed to the conceptualization, methodology, funding acquisition, supervision, and original draft writing. SKY contributed to the methodology and review and editing of the manuscript. RF contributed to the original draft writing, as well as to the review and editing. SL contributed to the investigation and reviewed and edited the manuscript.

Conflicts of Interest

TVM is the founder of Evolution Health and the owner of the Evolution Health digital health platform. RF is a board member of Evolution Health.

Multimedia Appendix 1
CONSORT (Consolidated Standards of Reporting Trials)–Social and Psychological Interventions checklist.
[PDF File (Adobe PDF File), 101 KB - resprot_v14i1e73773_app1.pdf]

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Abbreviations

AI: artificial intelligence
CBT: cognitive behavioral therapy
LLM: large language model
NAMI: National Alliance on Mental Health
NIMH: National Institute of Mental Health
RCT: randomized controlled trial
SAM: serviceable available market
SOM: serviceable obtainable market
TAM: total addressable market
WHO: World Health Organization

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Protocol

Effectiveness of an mHealth Program on Reducing Blood Pressure Among Young Adults With Prehypertension: Protocol of a Pragmatic Cluster Randomized Controlled Trial

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Abstract

Background: The prevalence of prehypertension may be underreported because of its asymptomatic nature. This study will use a pragmatic mobile health (mHealth) app to deliver the intervention, which is expected to be well received by the young adult population.

Objective: This study aims to assess the prevalence of prehypertension among young adults and evaluate the effectiveness of an mHealth intervention in enhancing adherence to lifestyle practices, increasing knowledge on prehypertension and hypertension, and reducing blood pressure among participants in the experimental and control groups.

Methods: The study consists of 2 phases. Phase 1 used a cross-sectional survey design, and phase 2 included a pragmatic randomized controlled trial with cluster randomization. The protocol was prepared according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 checklist. The CONSORT (Consolidated Standards of Reporting Trials of Nonpharmacologic Interventions) 2017 guideline was followed for reporting the protocol. The estimated sample size for phase 1 was 762 participants, and the sample size for the phase 2 was 85 participants per group. Both the control and experimental groups will receive education on prehypertension and hypertension, with the experimental group additionally receiving an mHealth app. The experimental group's adherence to lifestyle practices will be monitored every 15 days, and reminder messages will be sent to nonresponders. Both groups will be followed up with on-site after 1, 3, and 6 months to assess their knowledge on prehypertension and hypertension, blood pressure, and lifestyle practices. The primary outcome of the study will be an improvement in blood pressure readings. The secondary outcomes will include adherence to lifestyle practices and knowledge on prehypertension and hypertension.

Results: This study was funded by the Indian Council of Medical Research (grant 2021-11792, received February 2023). The study is ongoing. Phase 1 was completed on March 29, 2024, with data collected from 762 samples from 8 randomly selected colleges from Udupi District. Currently, phase 2 is in progress. The data will be analyzed using jamovi software (version 2.3.21; The jamovi project). Phase 1 and 2 findings will be analyzed and the results will be published in a peer-reviewed journal. Ethical approval for the study was obtained in May 2022 (160/2022).

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Conclusions: Identifying high-risk groups of young adults with prehypertension enables early interventions to prevent future hypertension and combat the cardiovascular burden globally. The mHealth intervention is considered to be an effective strategy to impart knowledge and promote healthy behaviors among young adults. The study will contribute to achieving the United Nation's Sustainable Development Goal 3, which focuses on ensuring good health and well-being.

Trial Registration: Clinical Trial Registry of India CTRI/2023/04/051784; https://tinyurl.com/57y9enyd

International Registered Report Identifier (IRRID): DERR1-10.2196/67216

(JMIR Res Protoc 2025;14:e67216) doi:10.2196/67216

KEYWORDS

prehypertension; hypertension; blood pressure; cardiology; cardiac; young adult; randomized controlled trial; mobile-based program; global health; mHealth; mobile health; mobile app; smartphone; digital health; digital intervention

Introduction

Hypertension is the third most significant risk factor contributing to the burden of noncommunicable diseases (NCDs) and places a considerable public health burden on cardiovascular health in India [1]. According to the World Health Organization, hypertension is a leading cause of premature death, with prehypertension serving as a critical precursor to hypertension both nationally and globally [2]. The seventh report of the Joint National Committee classifies prehypertension as a systolic blood pressure of 120-139 mmHg or a diastolic blood pressure of 80-89 mmHg [3]. However, the eighth report of the Joint National Committee guidelines do not define prehypertension because their recommendations focus on individuals with diagnosed hypertension [4]. Despite the rising prevalence, increased awareness, and availability of treatments, hypertension remains poorly controlled, particularly in low-income and middle-income countries, leading to major cardiovascular events [2].

A study conducted in India revealed that the prevalence of hypertension and prehypertension among young adults is 11.2% and 33.3%, respectively [5]. Individuals with a family history of hypertension and those who are physically inactive have a higher risk of hypertension [6]. Identifying prehypertension during its asymptomatic stage allows for timely interventions to normalize blood pressure, thereby preventing or delaying the onset of hypertension [7].

Many young adults with increased blood pressure remain undiagnosed, and a substantial proportion of individuals are unaware of their existing prehypertension. Young people are one of India's most valuable resources. Studies in India reported the prevalence of prehypertension among young adults to be in the range 24.6%-65% [5,7-13].

Mobile devices have become integral to health care, providing easy access to health information both at home and on the go [14]. Early identification of prehypertension enables proactive blood pressure management through preventive strategies, thereby reducing cardiovascular morbidity and mortality.

Globally, hypertension is the leading cause of death, accounting for 10.4 million deaths annually [15]. Prehypertension, the initial stage of hypertension, represents a critical point for intervention where appropriate measures can delay or prevent the progression to hypertension. In addition, prehypertension is associated with an increased risk of both hypertension and cardiovascular diseases (CVDs) [16].

A study conducted in the coastal villages of Udupi District in Southern India found that the prevalence of prehypertension among young adults (aged 20-30 years) was 45.2%. Biological factors, such as being in the 25- to 30-year age group, having preobesity or obesity, and behavioral factors, including sedentary occupations and excessive salt intake, were found to be associated with prehypertension [7].

Globally, CVDs account for approximately 17.9 million deaths among middle-aged adults, with hypertension being the most common cardiovascular disorder, responsible for 20%-50% of all CVD-related deaths. Once considered a condition mainly affecting adults, hypertension is now increasingly prevalent among younger populations, with its onset reported even in childhood [6,17].

Studies have reported a high prevalence of hypertension among Indian adults, with nearly 1 in 3 individuals having this condition. With approximately 762 million adults aged 18 years and older in India, this equates to an estimated 234 million adults with hypertension, indicating a significant future increase in the CVD burden. This finding highlights the urgent need for early detection and treatment because effective blood pressure control can prevent nearly one third of all cardiovascular-related deaths [15]. In addition to blood pressure management, therapeutic strategies should include modifying lifestyle, managing weight, and addressing other risk factors to reduce residual cardiovascular risk [18,19].

Health education within the community is vital to increase awareness about hypertension and its risk factors among younger generations. Promoting physical activity and healthy eating is critical to counter the rapid rise of NCDs in many low-income and middle-income countries. Leveraging modern information and communication technologies to deliver interventions for physical activity and dietary changes is particularly promising, given the increasing availability of these technologies in such regions [17].

The prevalence of prehypertension among adolescents is rising, though it remains underreported. This condition often progresses to hypertension in adulthood, with young adults experiencing cardiovascular and cerebrovascular disorders before the age of 40 or 45 years. This leads to significant morbidity and mortality and a substantial socioeconomic burden on society [6,20].

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The conceptual framework adopted in this study is modified from the predisposing, reinforcing, and enabling constructs in educational/environmental diagnosis and evaluation (PRECEDE)-policy, regulatory, and organizational constructs in educational and environmental development (PROCEED) model [21,22] developed by Green and Kreuter [23] (Figure 1). Predisposing factors in the PRECEDE-PROCEED framework include antecedents to behavior, such as demographic and clinical factors, knowledge, and lifestyle behaviors. The enabling factors include existing knowledge on prehypertension and hypertension, lifestyle practices, and annual family income. The reinforcing factors include a family history of hypertension that encourages prompt health maintenance. The intervening variables are the on-site awareness program and the mobile health (mHealth) app aimed at enhancing knowledge on prehypertension and hypertension as well as adherence to healthy lifestyle practices. The outcome variables include blood pressure, knowledge on prehypertension and hypertension, and lifestyle practices.

Figure 1. Conceptual framework on mHealth interventions for prehypertension among young adults based on the PRECEDE-PROCEED model developed by Green and Kreuter [23]. mHealth: mobile health; PRECEDE: predisposing, reinforcing, and enabling constructs in educational/environmental diagnosis and evaluation; PROCEED: policy, regulatory, and organizational constructs in educational and environmental development.

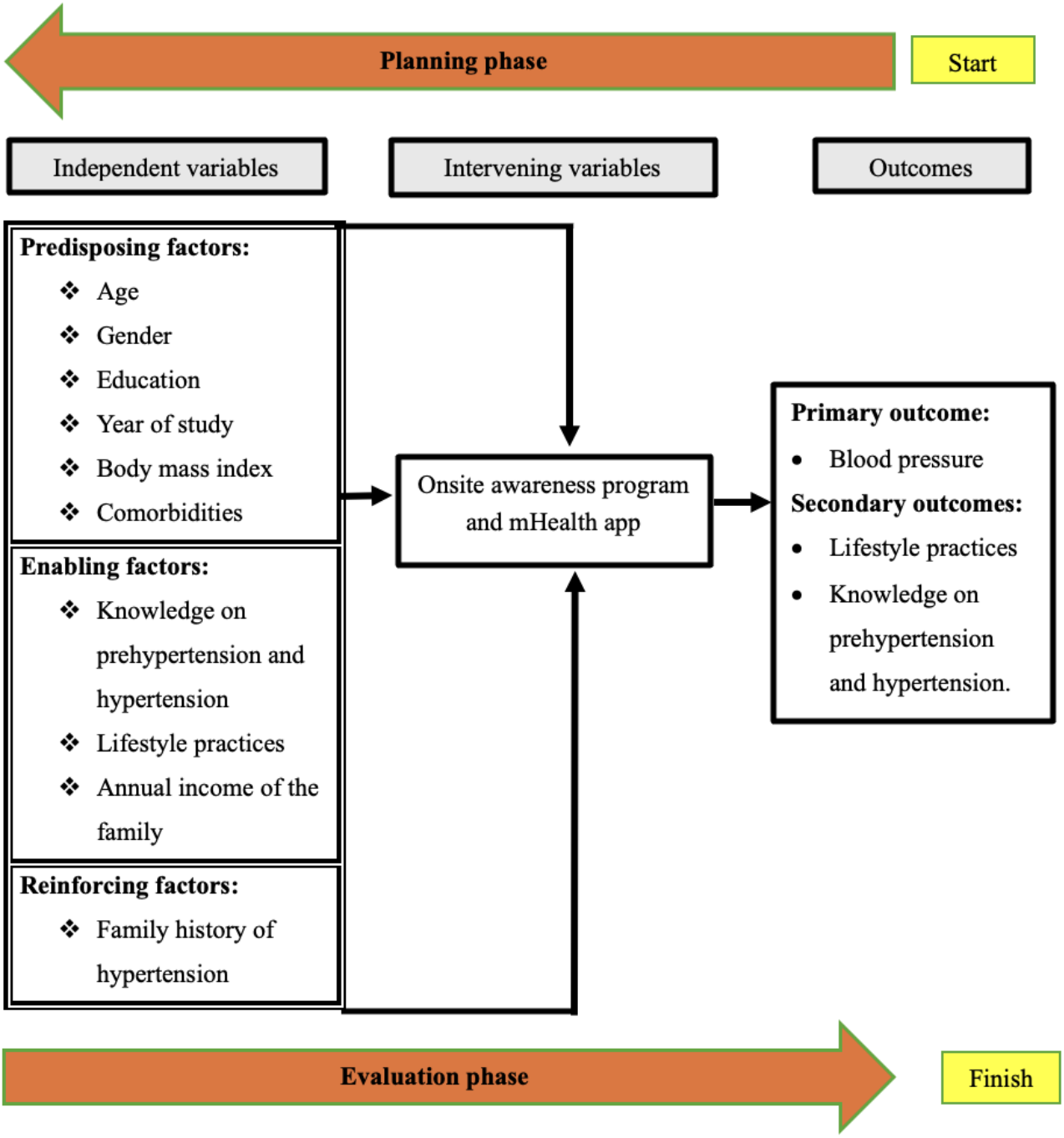

Given the severity of this problem, the present study aims to determine the prevalence of prehypertension and evaluate the effect of mHealth interventions on adherence to lifestyle practices, knowledge on prehypertension and hypertension, and

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blood pressure among young adults. The growing adolescent population in India and the increasing risk factors highlight the importance of primary prevention as a crucial strategy to combat this epidemic.

This study aims to contribute to the United Nation's Sustainable Development Goal 3 ensuring healthy lives and promoting well-being for all at all ages. The specific target is to reduce premature mortality from NCDs by one third through prevention and treatment and promote mental health and well-being by 2030.

Methods

Study Design

Overview

The study is designed to be carried out in 2 phases. A cross-sectional survey design was used in phase 1. Because the study aims to evaluate the effect of the mHealth program on adherence to lifestyle practices, knowledge of prehypertension, and blood pressure, a pragmatic randomized controlled trial with cluster randomization was implemented in phase 2. The protocol follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 checklist [24], which is provided in Multimedia Appendix 1. The CONSORT (Consolidated Standards of Reporting Trials of Nonpharmacologic Interventions) 2017 flowchart of the study is presented in Figure 2 [25-28].

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Figure 2. CONSORT (Consolidated Standards of Reporting Trials of Nonpharmacologic Interventions) 2017 flow diagram for the study. N denotes the number of colleges (ie, clusters) and n denotes the number of participants per cluster. DASH: dietary approach to stop hypertension.

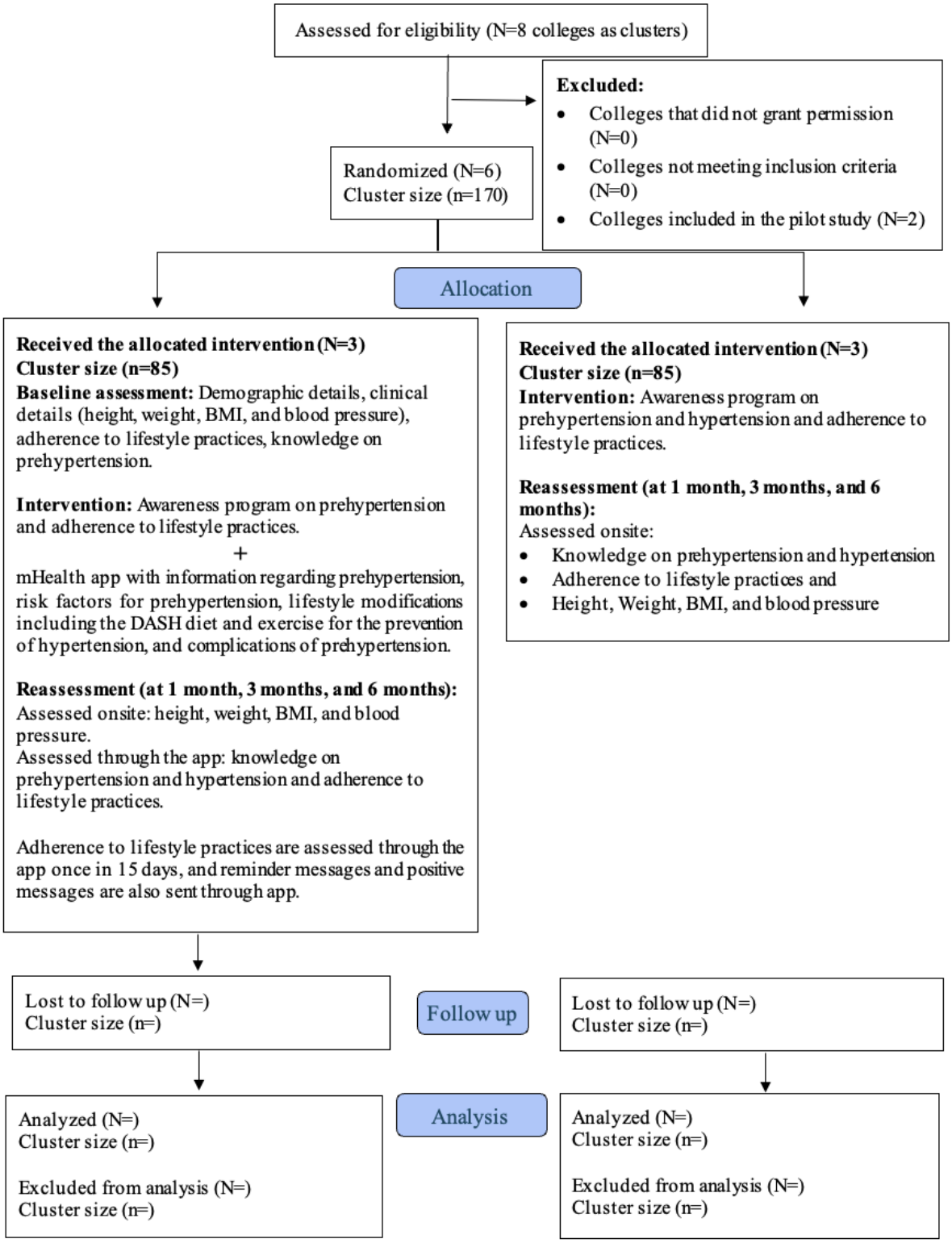

Phase 1

After obtaining administrative permission from the Institutional Research Committee, Institutional Ethical Committee, and Joint Director of Collegiate Education, Udupi District, taluks from Udupi District were randomly selected to collect data for assessing the prevalence of prehypertension in phase 1. The data were collected on-site from young adults of colleges from randomly selected taluks. Baseline information, clinical variables, lifestyle practices, knowledge on prehypertension and hypertension, and blood pressure were measured for all participants from the selected colleges. An automated, digital, oscillometric blood pressure machine (Omron) was used to measure blood pressure after device calibration. As of March 29, 2024, phase 1 was completed with data collected from 762 samples from 8 randomly selected colleges.

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Phase 2

Colleges with students having prehypertension identified during phase 1 were considered as clusters (N=6) and will be allocated to the intervention (N=3) and control groups (N=3) by simple randomization using the chit method. A random allocation sequence using the chit method was generated by research assistants who are not involved in the study. Currently, phase 2 is in progress.

Intervention

Overview

The intervention protocol includes an on-site awareness program on prehypertension and hypertension (Table 1) and an mHealth app. The information in the mHealth app is provided under the following headings in both English and Kannada: about blood pressure, prehypertension and hypertension, diet, exercises, yoga, smoking and alcohol consumption, and sleep. The information leaflet encompassing the details of teaching provided during the on-site awareness program will be given to the participants of all the clusters after the study at the end of sixth month.

Table 1. Plan for the mHealth intervention. The total duration of teaching is 45 minutes.

Areas of teaching in the teaching plan	Duration (min)
Introduction	2
Meaning of prehypertension	2
Risk factors for prehypertension	5
Lifestyle modifications for the control of blood pressure	10
Significance of adherence to lifestyle practices in controlling blood pressure	5
Role of diet in reducing blood pressure focusing on DASH[a] diet guidelines	5
Conclusion	1
Discussion	15

[a]DASH: dietary approach to stop hypertension.

mHealth App

The mHealth app designed for the study, INFOBP, was customized to the research topic and the population of interest. The app was designed with the support of the team from Information Technology. It provides information on prehypertension and its risk factors as well as lifestyle modifications, including the dietary approach to stop hypertension (DASH) diet and exercise, for preventing and managing the complications of prehypertension. The information provided in the app is available in both English and Kannada. When responding to questionnaires, the participants have the freedom to make changes to their responses until they submit the questionnaire. Once submitted, no changes can be made from the user's end. The information provided in the app can be viewed by the participants any number of times at their own pace. The app's user flow is depicted in Figure 3.

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Figure 3. User flow diagram for the mHealth app on prehypertension. HTN: hypertension.

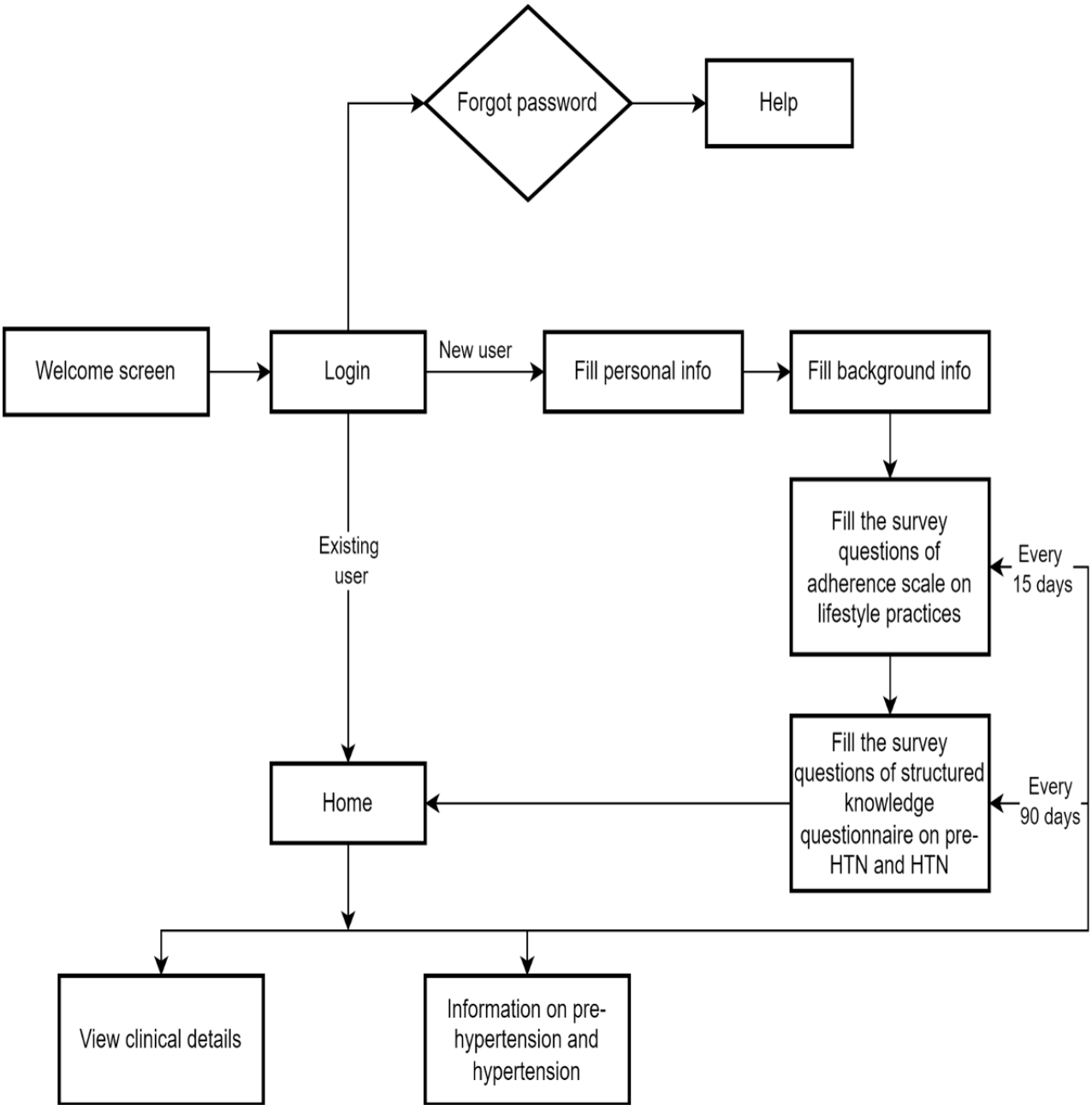

A screenshot of the mHealth app is presented in Multimedia Appendix 2. To evaluate the validity and applicability of eHealth trials, the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist [29] was used and is provided in Multimedia Appendix 3. To check the quality and usefulness of the mHealth app, the mobile application rating scale (Multimedia Appendix 4) [30,31] was used by 12 participants from the experimental group after a few days of app usage. The participants' responses are provided in Multimedia Appendix 5. Due permission was obtained from the original author for using the mobile application rating scale.

Both the control and intervention groups will receive education on prehypertension. The experimental group will also receive the mHealth app free of cost, provides information on prehypertension, risk factors for prehypertension, lifestyle modifications (including the DASH diet and exercise), and strategies for preventing hypertension and its complications. The mHealth app (INFOBP) will be installed on the mobile devices of all students in the intervention group, and they will receive orientation on its use. The experimental group will be monitored for adherence to lifestyle practices every 15 days through the mobile app, and reinforcement and reminder messages will be sent to nonresponders. All participants in the experimental group will receive a message of encouragement through the app every 15 days to continue practicing the recommended lifestyle changes. The participants will also be able to view the comparative report of their clinical parameters (BMI and blood pressure) and the result of the data entered by them (knowledge and lifestyle adherence scores) during every assessment as feedback. Both groups will be followed up after 1, 3, and 6 months to assess their knowledge on prehypertension and adherence to lifestyle practices and record their height, weight, BMI, and blood pressure on-site. At the end of the study,

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an information booklet on prehypertension will be provided to every college in Udupi District that was included in the study.

Study Participants and Sampling

The study will be conducted in the Udupi District of Karnataka, which is divided into 7 taluks (Udupi, Kundapur, Karkala, Hebri, Byndoor, Brahmavar, and Kapu). There are 33 private and 10 government-run colleges in the district. Young adults aged 18-25 years working toward a bachelor of science, bachelor of communication, or bachelor of arts in colleges in Udupi District who meet the inclusion and exclusion criteria (Textbox 1) will be considered for the study.

Textbox 1. Inclusion and exclusion criteria for the study.

Phase 1

- Inclusion criteria
  - Young adults aged between 18-25 years studying in selected degree colleges in Udupi District, Karnataka.
  - Young adults willing to participate in the study.
- Exclusion criteria
  - Young adults who have already been diagnosed with hypertension or other systemic disorders.
  - Young adults who are on medications for any other ailments.

Phase 2

- Inclusion criteria
  - Young adults identified to have prehypertension in phase 1.
  - Young adults with prehypertension willing to participate in the study.
  - Young adults with prehypertension having android mobile phones.
  - Colleges with students having prehypertension identified during phase 1 were considered.
- Exclusion criteria
  - Young adults identified to have hypertension in phase 1 and who were already diagnosed with other systemic disorders.
  - Young adults with prehypertension who are on medications for any other ailments.
  - Young adults with prehypertension who do not have android mobile phones.

The calculated sample size for phase 1 was determined to be 381 participants using the following formula for estimating a proportion, where n is the sample size required, $Z_{1-\alpha/2}$ is the desired confidence level (ie, for a 95% confidence level, $Z_{1-\alpha/2}$=1.96), P is the prevalence, and d is the margin of error:

This calculation assumes the prevalence of prehypertension among young adults to be 45% at a 95% confidence level with a 5% margin of error (absolute precision) based on a previous study by Kini et al [7]. After multiplying by a design effect of 2 due to cluster sampling, the sample size was determined to be 762 participants.

The sample size for phase 2 was 34 participants per group, considering a 38% anticipated population SD of the primary outcome variable (ie, the prevalence of prehypertension) obtained using the equation for repeated measures ANOVA given below. In the equation, n is the sample size required, $Z_{1-\alpha/2}$ is the desired confidence level (ie, for a 95% confidence level, $Z_{1-\alpha/2}$=1.96), $Z_{1-\beta}$ is the power of the test (ie, for a power of 80%, $Z_{1-\beta}$=0.84), σ^2 is the population variance (ie, square of the SD), m is the number of groups being compared, ρ is the correlation coefficient between groups, and d is the minimum detectable difference.

Accounting for a 20% dropout rate, the final sample size was 43 participants per group. After multiplying by a design effect of 2 due to cluster randomization, the sample size was determined to be 85 participants per group.

Outcomes

The primary outcome is blood pressure, and the secondary outcomes are adherence to lifestyle practices and knowledge on prehypertension and hypertension.

Data Collection Procedure and Instruments

The baseline data will be collected using a tool with 2 sections: demographic and clinical parameters. Adherence to lifestyle practices will be assessed using the adherence scale on lifestyle practices developed by the researchers, with a maximum score of 12. Adherence will be categorized as “adherent” for those achieving ≥80% (a score of ≥10) and “nonadherent” for those scoring <80% (a score of <10). A structured knowledge questionnaire on prehypertension and hypertension will be used to assess knowledge on the subject. The questionnaire consists

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of 30 items, with a maximum score of 30. The items are based on the Joint National Committee 7 recommendations for nonpharmacological interventions in the management of prehypertension. Knowledge levels will be classified as poor (a score of 0-9), average (a score of 10-20), or good (a score of 21-30). Blood pressure will be assessed using a digital blood pressure apparatus. The baseline blood pressure will be measured after a 5-minute to 10-minute rest period. Two readings will be taken 1-3 minutes apart, and the average will be calculated. In case of a difference of more than 5 mmHg between the 2 readings, an additional 2 readings will be obtained, and the average of these multiple readings will be used [32]. Prehypertension will be identified among young adults based on the average of 2 blood pressure readings. The same procedure will be followed during the follow-up sessions at 1, 3, and 6 months. A calibrated stadiometer and weighing machine will be used to assess the heights and weights of the participants.

The validated tools were tested for reliability on 20 students from the selected degree colleges in Udupi District. The reliability of the structured knowledge questionnaire was assessed using the split-half method (r=0.911). The tools were pretested with 10 students from a degree college in Udupi District. A pilot study was conducted with 20 students at a selected degree college.

Ethical Considerations

The study protocol received institutional ethical approval on May 11, 2022 (IEC1 160/2022) and is registered under the Clinical Trial Registry of India (CTRI/2023/04/051784). All the participants will receive a subject information sheet in both Kannada and English to help them understand the study. Written informed consent will be obtained from all participants prior to data collection. The study will adhere to the guidelines of the Declaration of Helsinki. The confidentiality and anonymity of the participants will be maintained.

Statistical Analysis

Data analysis will be conducted using jamovi (version 2.3.21; The jamovi project), using both descriptive and inferential statistics in line with the study objectives. For descriptive statistics, means and SDs will be used because all study outcomes are quantitative and continuous. Because the study involves assessing outcomes at 4 time points (baseline, 1 month, 3 months, and 6 months), repeated measures ANOVA will be used to evaluate the effectiveness of the intervention, and per protocol analysis will be used.

Results

Ethical approval was obtained on May 11, 2022 (IEC1 160/2022), and the Indian Council of Medical Research provided funding for this project on February 9, 2023 (Project ID:2021-11792). The project is still in progress. On March 29, 2024, phase 1 was completed, with data gathered from 762 samples from 8 randomly chosen colleges in the Udupi District. Phase 2 is now underway (Table 2). The outcomes of phase 1 and phase 2 will be published in reputable peer-reviewed journals.

Table 2. Progress of phase 2 detailing the timelines of sample assessment.

Time	Baseline	1 month	3 months	6 months
Intervention group	September 16 to November 19, 2024	October 16 to December 20, 2024	January 2 to February 28, 2025	Started on April 4, 2025, and is expected to be completed by June 30, 2025
Control group	September 19 to October 19, 2024	October 30 to November 29, 2024	January 2 to February 28, 2025	Started on April 4, 2025, and is expected to be completed by June 30, 2025

Discussion

Study Overview

The primary objective of the study is to enhance awareness on prehypertension and hypertension among young adults, the productive population of the country, thereby promoting positive health and preventing premature CVDs. Globally, hypertension is responsible for 10.4 million deaths annually [15]. Prehypertension, an early stage of hypertension, can be effectively managed with proactive measures, thereby delaying or preventing the future risk of hypertension and its complications [16].

Evidence from a study conducted in Southern India suggests a 45.2% prevalence of prehypertension among young adults (aged 20-30 years). The study also revealed that prehypertension risk is associated with obesity and several lifestyle factors, including unhealthy dietary habits and occupation-related physical inactivity [7]. Although hypertension was once considered a disease of adults, studies now show an alarming rise in cases among younger age groups [2].

CVD accounts for approximately 17.9 million deaths globally among middle-aged adults, with 20%-50% of these deaths attributed to hypertension-related cardiovascular conditions [2]. In India, hypertension is highly prevalent, affecting 1 in 3 adults. With an estimated 762 million people aged 18 years or older in India, this translates to 234 million adults living with hypertension. The rising prevalence of hypertension, particularly among young adults, poses a significant socioeconomic burden if not addressed promptly [9,18]. Globally, the number of adults with hypertension, estimated at 1 billion in 2000, is expected to double to 2 billion by 2025 [33]. Research strongly supports the role of lifestyle interventions as an essential measure in effective blood pressure control and the reduction of CVD-related morbidity and mortality [9,17,20].

Smartphones are becoming a part of almost everyone's lives, serving as essential tools for work, leisure, and communication. Smartphones are changing the way health education is delivered, promoting wellness activities and easing the management of diseases across a wide spectrum of populations [34]. The anticipated success of the mHealth app used in this study can

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be attributed to its customized approach. The app was developed as a blended approach to assess knowledge and lifestyle practices, track clinical parameters of participants with prehypertension, and disseminate information pertaining to health promotion. Any positive outcomes observed in this study would suggest that the mHealth app can be successfully used, supporting its extension to the population at large.

This protocol addresses a burning issue, and the methodology emphasizes assessing the real-world impact of the mHealth app. The effectiveness of digital health interventions in managing hypertension has led to successful blood pressure control. This approach could also be explored for its potential in weight management and obesity prevention. By supporting healthy weight maintenance and encouraging the development of healthy eating habits, particularly among students, these interventions may contribute to improved heart health and, more significantly, help prevent hypertension and CVDs [35-37]. Another study found that a youth-led digital intervention was effective in controlling blood pressure among adults with hypertension [38]. The growing population in India, coupled with increasing risk factors, supports the importance of primary prevention as a critical strategy to combat this epidemic. Based on the relevant research and existing data, this protocol underlines the importance of mobile health interventions in addressing prehypertension among young adults in this digital era.

Limitations

A limitation of this study is that it is confined to young adults studying at colleges in Udupi District, Karnataka, which restricts the generalizability of the findings. Additionally, the data collected to assess knowledge and lifestyle practices are self-reported by the participants.

Strengths

The cluster randomized controlled trial and customized app developed as part of the intervention are strengths of this study. Furthermore, research assistants are collecting the data and the researchers are not directly contacting the study participants, thus blinding the researchers.

Conclusions

Prehypertension is associated with a higher likelihood of developing hypertension and doubles the risk of cardiovascular events. Given the severity of this issue, this study is timely. In this study, mHealth interventions were designed to target individuals identified as having prehypertension. Further research is recommended to develop interventions that can detect early signs of CVDs in individuals with prehypertension. Because young adults represent the nation's most valuable resource and contribute significantly to its growth, prioritizing innovative interventions to combat prehypertension is essential for building a healthier nation.

Acknowledgments

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Data Availability

Supporting data cannot be made publicly available due to ethical issues and its proprietary nature. The data may be accessed upon reasonable request to the corresponding author and following the publication of the study results.

Authors' Contributions

MS, HMH, and JN conceived and developed the protocol. RC, NR, and AMJ contributed to the methodological design. All authors contributed to the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT 2013 checklist.
[DOCX File , 29 KB - resprot_v14i1e67216_app1.docx]

Multimedia Appendix 2
Screenshot of the mobile health app.
[PDF File (Adobe PDF File), 974 KB - resprot_v14i1e67216_app2.pdf]

Multimedia Appendix 3
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1024 KB - resprot_v14i1e67216_app3.pdf]

Multimedia Appendix 4

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Mobile application rating scale (MARS).
[PDF File (Adobe PDF File), 308 KB - resprot_v14i1e67216_app4.pdf]

Multimedia Appendix 5
Response of the participants on the INFOBP app obtained using the mobile application rating scale.
[DOCX File , 30 KB - resprot_v14i1e67216_app5.docx]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials of Nonpharmacologic Interventions
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
CVD: cardiovascular disease
DASH: dietary approach to stop hypertension

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mHealth: mobile health
NCD: noncommunicable disease
PRECEDE: predisposing, reinforcing, and enabling constructs in educational/environmental diagnosis and evaluation
PROCEED: policy, regulatory, and organizational constructs in educational and environmental development
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Exploring the Impact of the Caring Contacts Intervention on the Stress and Distress of Veterans and Service Members: Protocol for a Randomized Controlled Trial

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Abstract

Background: Suicide is a recognized global public health problem that continues to pose substantial challenges in the United States. Veterans and service members are particularly at risk. Caring Contacts is a simple, scalable intervention comprising brief, periodic messages sent over 1 to 2 years that express unconditional care and concern. It reduces suicide risk among individuals with recent suicidal ideation or attempts and has demonstrated acceptability in military and veteran samples, but little is known about the mechanisms of Caring Contacts or its applicability to populations who are not suicidal.

Objective: We aim to evaluate if receiving Caring Contacts reduces suicide risk among veterans and active service members recruited based on their stress or distress levels, using ecological momentary assessment (EMA) and survey measures of suicidal ideation and cognitions; to examine the experiences of diverse veterans and service members with Caring Contacts; to evaluate if receiving Caring Contacts reduces distress (depression, substance use consequences, hopelessness, defeat, and psychological pain); and to identify the potential mechanisms of action for Caring Contacts (mattering, connectedness, social responsibility, and entrapment). Using EMA, this study will be the first to investigate mechanisms of the Caring Contacts intervention both in real time, as the messages are received, and over the course of 1 year.

Methods: In this randomized controlled trial, veterans or service members (N=510) experiencing stress or distress recruited via social media advertisements will be offered best available resources and randomized into 1 of 3 study conditions: 12 months of Caring Contacts and monthly EMA, 12 months of Caring Contacts without monthly EMA, or 12 months of monthly EMA alone. The individuals in the Caring Contacts conditions will receive 13 messages. A subset of participants from each condition will be asked to complete a qualitative interview after the 12-month follow-up about their study experience.

Results: This trial was funded in October 2023; recruitment started in April 2024 and will conclude in May 2025. As of December 2024, we have enrolled 321 participants. Final quantitative data collection will be completed by July 2026, 2 months after the final 12-month follow-up date. Data from the qualitative interviews will be collected until September 2026. Data analysis will occur following data collection, and the results are expected to be published in winter 2027.

Conclusions: This study will be the first randomized controlled trial evaluating the impact of Caring Contacts among service members and veterans who were not recruited based on suicidality. If effective, our findings will demonstrate that Caring Contacts is beneficial for reducing multiple forms of psychological distress and suicide risk. In addition, we will evaluate potential

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mechanisms explaining the effects of Caring Contacts and assess the utility of EMA as a primary measure of outcome in suicide research trials.

Trial Registration: ClinicalTrials.gov NCT06136234; https://clinicaltrials.gov/study/NCT06136234

International Registered Report Identifier (IRRID): DERR1-10.2196/72140

(JMIR Res Protoc 2025;14:e72140) doi:10.2196/72140

KEYWORDS

suicide; intervention; stress; RCT; randomized controlled trial; EMA; ecological momentary assessment; Caring Contacts

Introduction

Background

According to the Centers for Disease Control and Prevention, 1 person in the United States died by suicide every 11 minutes in 2022, and suicide rates have substantially increased over the past decade [1]. However, mortality rates from heart disease, diabetes, and cancer have declined. Since 2011, new standards have led to improved screening and management of suicide risk [2-7].

However, treatment to reduce suicide risk has lagged because of the high cost of most evidence-based suicide care interventions, which require multiple sessions of psychotherapy [3,8-10]. Thus, the need for suicide prevention has skyrocketed without a corresponding increase in available resources. In addition, the COVID-19 pandemic substantially increased the demand for telehealth and technology-mediated interventions—a trend that has persisted, with both patients and health care providers continuing to favor remote treatment options [11-13]. Thus, there is a pressing need to quickly adopt scalable alternatives to office-based care for suicide prevention.

The Caring Contacts intervention consists of brief, periodic messages sent over 1 to 2 years that express unconditional care and concern. It has shown promise in reducing suicide, suicide attempts, and suicide ideation in at least one randomized trial [14-20]; is cost-effective [21]; is recommended by multiple clinical practice guidelines [4,5]; and has the potential to scale with a single individual messaging with hundreds of suicidal individuals simultaneously. A meta-analysis of Caring Contacts concluded that it has a protective effect against suicide attempts [22]. However, findings on the intervention's impact on suicidal ideation (SI), suicide deaths, and health care use— such as emergency department visits or hospitalizations—have been mixed [22,23]. While some fully powered recent studies have shown no substantial effects [24,25], others suggest that Caring Contacts decreases SI [18,20] and reduces the number of medical and psychiatric hospitalizations during follow-up [16,17]. These mixed findings underscore the importance of understanding the mechanisms through which Caring Contacts achieves its effects, as this knowledge could guide improvements to Caring Contacts as well as improve implementation by understanding why it works in some contexts but not in others. In previous research, our team has adapted Caring Contacts for SMS text messages and has culturally adapted and implemented Caring Contacts for military populations [20], Native communities [25], and through fully online trials in Idaho's rural and frontier health systems [26]. Colleagues have developed Caring Contacts models for veterans receiving Veterans Affairs services [27-31]. In addition, we have demonstrated that the intervention is both feasible and acceptable when delivered by community laypersons without clinical training [25]. Therefore, Caring Contacts is well-positioned for scale-up with veteran service organizations, with one significant limitation that it has only been evaluated with individuals who are seeking help due to suicidality, self-harm, or severe depression. It is unknown if Caring Contacts is helpful or suicide preventive for a broader population of veterans experiencing stress or distress. This is crucial because a large proportion of veterans who die by suicide do not disclose suicide risk and are served by veteran service organizations that do not screen for suicidality, so their risk is unknown [32]. As Caring Contacts do not discuss suicidality explicitly, there is no reason that the intervention should only apply to those experiencing suicidality. Further research is needed to determine whether Caring Contacts can reduce suicide risk in a broader population and how the intervention is experienced by individuals who are acutely suicidal compared to those who are not. In addition, it is possible and desirable to explore whether Caring Contacts can impact other forms of psychological distress. We aim to address these key gaps in Caring Contacts research.

While Caring Contacts has shown promise as a suicide prevention strategy, understanding its mechanisms of action is essential for refining and optimizing its effectiveness. Currently, these mechanisms remain unknown, as most research on Caring Contacts has focused on administrative records for assessment or contact only before and after the intervention [15,16,19,20,24,33,34]. It is often theorized that the Caring Contacts intervention reduces suicide risk by fostering a sense of connection, as individuals may feel cared for and less isolated after receiving messages of support [15,35]. However, this theory has not been formally tested. To evaluate whether the Caring Contacts intervention decreases SI by enhancing connectedness, we selected 4 mechanisms to examine in this study: perceived burdensomeness, mattering, personal and social responsibility, and entrapment. Perceived burdensomeness has consistently been identified as a robust predictor of SI, reflecting the damaging impact of feeling like a burden to others. Mattering reflects the perception of being valued and important, directly countering feelings of insignificance and isolation, which have been linked to suicide [36,37]. Although a sense of personal and social responsibility has not been explicitly examined as a predictor of suicide, it may encourage individuals to engage with broader social systems [38], thereby strengthening their sense of belonging [39] in their communities. Finally,

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entrapment captures the psychological state of feeling trapped with no escape, which is strongly associated with SI and intent within the integrated motivational-volitional model of suicidal behavior [40-42]. Together, these mechanisms encompass both interpersonal and intrapersonal dimensions of connectedness, offering a comprehensive framework for understanding how Caring Contacts may decrease suicide risk.

To understand the mechanisms and core processes driving the effectiveness of Caring Contacts, it is crucial to be able to capture the dynamic and evolving nature of outcomes over time. Traditional pre- and postintervention assessments often fail to account for the nuanced, day-to-day, or even rapid fluctuations in SI, stress, and distress [43]. This study will be the first to use periodic ecological momentary assessment (EMA) during a study of the Caring Contacts intervention to capture how the intervention decreases SI, stress, and distress. EMA is an intensive longitudinal data collection method that involves repeatedly sampling participants' current behaviors and experiences in real time in participants' natural environments, thereby reducing the chance of recall bias while also separating how much of the process is attributable to person- or sample-specific microprocesses that influence behavior in real time [29,30]. In addition, given the frequency of assessments, we are able to examine variability in constructs of interest over a discrete EMA period. EMAs are particularly important in suicide research given the dynamic, fluctuating nature of SI and its associated risk factors. In suicide research, EMA is particularly valuable for tracking the emergence of SI and tracking its dynamic nature along with its proximal warning signs, drivers, and risk factors [44,45]. Indeed, greater SI has more often been reported on EMAs than retrospective reports such as surveys.

Furthermore, EMA-based models have demonstrated strong predictive accuracy for near-term suicidal thoughts and posthospital suicide attempts [31,32], highlighting the utility of self-reported data and real-time monitoring in guiding risk assessment and intervention delivery. As such, using EMA to study time-varying changes in suicide risk and related proximal risk factors has been a priority for the advancement of suicide research [43,46]. However, EMA has been underused to study suicide risk in veterans and service members despite its feasibility [47] and potential for increasing understanding of mental health problems [48]. By using EMA as our primary outcome measure, we will explore how Caring Contacts influences proximal risk factors and mechanisms of change in veterans and active-duty service members, both when individual messages are received and across the year-long intervention period. To control for the potentially confounding impact of frequent EMA and the study intervention, 3 conditions are used to study Caring Contacts both with and without monthly EMA.

Aims

Our primary aim in this study is to evaluate whether stressed or distressed veterans and active-duty service members experience a greater reduction in suicide risk, suicide urges, the wish to live, and the wish to die when receiving Caring Contacts. We will measure these outcomes through EMA and survey measures of SI and cognitions. The second aim is to examine the experiences of diverse veterans and service members with Caring Contacts (ie, access, satisfaction, and preferences) via qualitative interviews. The third aim is to evaluate if veterans and service members receiving Caring Contacts will show reductions in measures of distress (ie, isolation, depression, substance misuse, loneliness, defeat, hopelessness, and psychological pain). Finally, the fourth aim is to examine potential mechanisms of action for Caring Contacts (ie, mattering, connectedness, social responsibility, and entrapment) measured via EMA.

Methods

Study Design

In this randomized controlled trial (RCT), we will examine the impact of the Caring Contacts intervention delivered through SMS text message across a large, diverse sample of veterans and service members who are stressed (external factors) or distressed (internal factors). This trial is conducted entirely online and will recruit veterans and service members (N=510). To ensure that all participants experiencing stress or distress have access to needed resources (enhanced usual care), each participant, regardless of condition, is provided a tailored set of resources to match their needs (eg, housing, finances, employment, food insecurity, and socialization). Participants are stratified based on whether they endorsed SI in the past year and randomly assigned to 1 of 3 study conditions, including receiving either Caring Contacts, EMA, or both, for the 12-month study period. Given that the frequency of messages and the self-monitoring process inherent to EMA may have its own effect on our outcome variables, we included a Caring Contacts–only condition to isolate the effects of Caring Contacts and EMA. The study design and methods were evaluated during an acceptability and feasibility pilot study, during which we also developed a web-based app platform custom-made for Caring Contacts (manuscript in preparation). The study staff worked with employees housed within a local veteran service organization and an outpatient psychiatry clinic to develop study procedures and the Caring Contacts intervention. From this feedback and use data, adjustments to the protocol, intervention, and EMA procedures were made before the launch of this RCT.

Setting

The study protocol is designed to operate entirely in an internet-based environment, using web-based recruitment and remote study staff. The study staff selection prioritized researchers with extensive experience overseeing large virtual clinical trials and implementing the Caring Contacts intervention. In addition, the research team is housed within a suicide specialty research center at the University of Washington (UW), where staff receive ongoing continuing education about suicide research.

Recruitment

Recruitment began in April 2024 and is anticipated to continue until May 2025. The data collection is ongoing and will continue until July 2026. Participants are primarily recruited using Nativve Health Research, a UK-based company that specializes in digital advertising for clinical research. Recruitment is

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primarily conducted through advertisements on Meta's platforms (including Facebook and Instagram), although advertisements on Google and X (previously known as Twitter) were used early in the study but were discontinued as they were less fruitful. Marketing of advertisements is segmented as needed to achieve demographic diversity of age, race or ethnicity, gender identity, education, regional representativeness, and rurality.

To mitigate the risk of fraud, the social media advertisement does not mention financial compensation. In addition, each participant is verified using a combination of fraud prevention strategies. To minimize the risk of fraudulent participation by automated bots, honeypots—hidden fields visible only to bots—were programmed into the study flow. Other fraud reduction techniques include outliers for the time it took for a participant to complete the survey, not sharing the participation link publicly, and attention check questions [49].

Ethical Considerations

Human Participant Ethics Review Approvals

The UW is the sponsor, and the UW Institutional Review Board (IRB) approved the study protocol and all modifications under the study identification number STUDY00019011 (approved October 2023). All items from the World Health Organization trial registration dataset [50] are described in in Multimedia Appendix 1. UW and its IRBs follow recommendations for participant safety given by the Belmont Report and the Declaration of Helsinki [51]. Furthermore, our study consultants from STRONG STAR Training Initiative at the University of Texas Health Science Center at San Antonio consulted on assuring military cultural competency in all study activities. The principal investigator, coinvestigators, and lead research scientists monitor data and safety. In addition to the UW IRB, a data safety monitoring board (DSMB) was established, consisting of 3 research scientists with relevant experience who were not affiliated with the study, the funder, or the sponsor. All adverse events are reported to the UW IRB and DSMB per approved protocols. When relevant, any necessary amendments will be submitted to the IRB and DSMB for their approval. This trial has been registered on ClinicalTrials.gov (NCT06136234).

Informed Consent

The informed consent process was designed to be interactive within the REDCap (Research Electronic Data Capture; Vanderbilt University) secure online environment. To facilitate the informed consent process, participants are presented with a video that walks them through the study procedures. REDCap prevents participants from advancing to the next page for the first 3 minutes to encourage participants to engage with the video (which is just over 7 minutes long). They then proceed to the next page, where they can review the consent document in its entirety (provided in Multimedia Appendix 2). To ensure complete understanding, participants are asked 10 true or false questions about the study procedures, payment structure, and safety measures that are in place. The REDCap page allows 2 chances to answer each question correctly, and only those participants who answered correctly are asked whether they want to participate in the study. Throughout this process, participants are reminded that study staff are available by request to clarify all informed consent documents and study procedures via telephone or videoconference. They are also reminded that at any time they can (1) refuse to complete any or all the surveys and EMAs, (2) decline the qualitative interview, (3) opt out of receiving the intervention messages, or (4) withdraw from the study entirely.

Privacy and Confidentiality

The study team makes every effort to protect participant privacy and confidentiality. Deidentified participant data are stored in Health Insurance Portability and Accountability Act–compliant, encrypted servers provided by UW Medicine. Identifiable information is only used for the purposes of contacting participants to complete the follow-up surveys and to send the Caring Contacts intervention messages when applicable. Access to participant data is limited to certain members of the study team and any individuals from the UW or other agencies that may need to review study records, all of whom are required to complete training in human participants research and Good Clinical Practice. Participants are made aware of these protections during the informed consent process, wherein it is also explained that if we have strong reason to believe that they are in danger of suicide, we will take steps to save their life. This may involve sharing information with clinicians or emergency services in their community. If they inform us that they are going to hurt a person they identified to us, we will connect them with someone who can help prevent the danger or alert the person. In addition, we disclose that we are legally required to report to local child protective services if participants inform us that a child is at risk of abuse or neglect.

Compensation Details

Depending on their assigned study group, each participant may earn up to US $290, which will be paid via Amazon gift cards. The payment structure is described in the Payment Structure section in detail.

Risk Management

Participant suicide risk is managed using the University of Washington Revised Risk Assessment Protocol (UWRRAP) [52-54]. Quantitative assessments (surveys and EMA) use the UWRRAP–online version, which is programmed to provide resources where appropriate throughout the REDCap flow that is activated if participants endorse elevated levels of SI, urges, or a recent suicide attempt for which they did not get treatment. The risk assessment or response is multitiered depending on the severity of a participant's score, including but not limited to the following:

- On-screen reminders about the National Suicide and Crisis Lifeline, the Crisis Textline, and instructions on how to reach the veteran-specific crisis line
- In-survey prompts for participants to report how they would respond to negative feelings or suicidal thoughts and whether they have any fun or distracting activities planned for the day
- Prompts to identify safety contacts
- Crisis line information (provided by email, text, or phone, depending on patient preference), along with study contact information and hours of availability

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EMA responses indicating elevated responses trigger alerts to the study staff, who review participant responses on a case-by-case basis, involving licensed psychologists on the team as needed. When appropriate, a member of the research study staff follows up with the participant and offers the needed resources, as well as crisis options. Qualitative interviews use the standard UWRRAP, which is designed for interview-based assessment.

Eligibility Criteria

To be eligible, participants must be aged at least 18 years, speak English, be a US service member or veteran, live in the United States, be willing to be contacted by SMS text message on their personal cell phone, and endorse at least one marker of either stress or distress. Inclusion criteria for stress, or external markers, include unemployment, financial strain, housing instability, recent separation from the military, or recent sudden loss. Inclusion criteria for distress, or internal markers, include depression, substance abuse, loneliness, defeat, hopelessness, psychological pain, suicide cognitions, or the presence of SI. Each criterion's definition and operationalization is described in the Measures section.

Randomization

A randomization module with participants stratified into 2 levels (recent suicidality vs no recent suicidality) and randomized into 3 conditions (Caring Contacts with EMA, Caring Contacts alone, and EMA alone) was built into REDCap. Recent suicidality is indicated by a participant endorsing that they have either wished they were dead or had thoughts of killing themself sometime in the past year. This module is programmed to randomize participants with no involvement of study staff to prevent potential bias, with intervention and control assignments distributed evenly across participants. Once participants have completed the online baseline survey, they are randomized into 1 of the 3 conditions (Table 1; Figures 1 and 2). Further details on the EMA procedures are provided in subsequent sections.

Table 1. Assessment and intervention message timeline[a].

Study procedure	Study condition		
	CC[b] and monthly EMA	CC only	Monthly EMA only
Consent and baseline survey	✓	✓	✓
Two weeks of baseline EMA[c]	✓	✓	✓
Randomization to study condition			
Month 1	EMA with CC	CC	EMA
Month 2	EMA without CC	CC	EMA
Month 3	EMA with CC	CC	EMA
Month 4	EMA with CC	CC	EMA
Month 5	EMA only	__[d]	EMA
Month 6	EMA without CC	CC	EMA
Month 7	EMA with CC	CC	EMA
Month 8	EMA only	—	EMA
Month 9	EMA without CC	CC	EMA
Month 10	EMA only	—	EMA
Month 11	EMA without CC	CC	EMA
Month 12	EMA with CC	EMA with CC	EMA
Follow-up survey	✓	✓	✓
Possible qualitative interview	✓	✓	✓

[a]Three other intervention messages are delivered at various times during the study year (birthday, New Year's holiday, and Veterans Day). Please refer to Figures 1 and 2 for examples of months that are labeled as "EMA with CC" and "EMA without CC."

[b]CC: Caring Contacts; indicates a Caring Contacts message is sent to participants in that condition.

[c]EMA: ecological momentary assessment; indicates that 3 EMAs per day are delivered for a week to participants in that condition during that month.

[d]Not applicable.

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Figure 1. Example of an ecological momentary assessment with Caring Contacts ("EMA with CC") month (ie, months 1, 3, 4, 7, and 12) wherein a CC message is delivered within the EMA period.

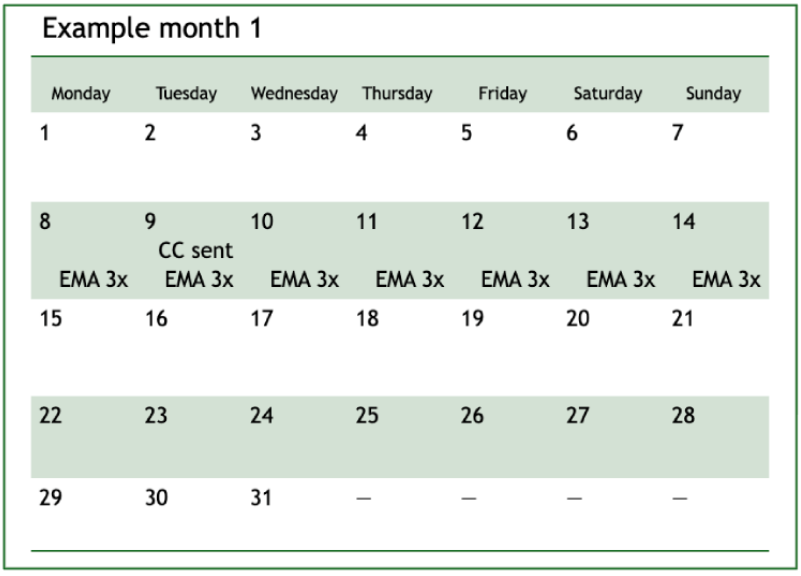

Figure 2. Example of an ecological momentary assessment without Caring Contacts ("EMA without CC") month (ie, months 2, 6, 9, and 11) wherein a CC message is delivered outside the EMA period.

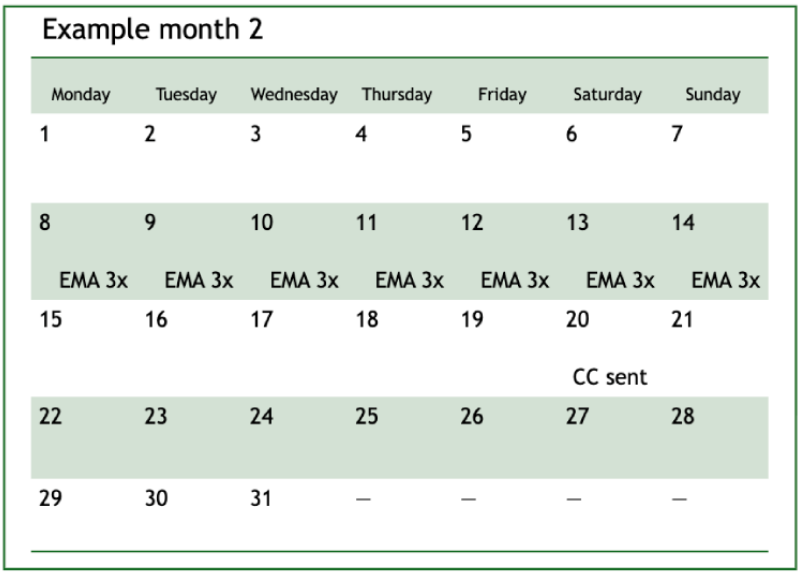

Payment Structure

Depending on whether they are assigned to a study group that includes EMAs throughout the year, participants may earn up to either US $180 or US $290. Reimbursement is provided via Amazon gift cards as presented in Textbox 1.

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Textbox 1. Payment structure for the participants.

- US $25 for the baseline survey and completing one ecological momentary assessment (EMA; ie, fully enrolling in the study) within 2 weeks
- US $2 to $10 per week of 3 EMAs each day (EMAs generally take between 30 s and 3 min to complete). For each week of surveys, payment will be as follows:
  - US $2 if any EMAs completed
  - US $4 if >5 but <50% of EMAs completed
  - US $6 if 50% to 89% of EMAs completed
  - US $10 if ≥90% of EMAs completed
- Each participant may earn a US $50 bonus if 80% of all assigned weeks of EMAs are completed (across the baseline and study year EMAs)
- US $25 for the follow-up survey (at the end of 12 and 1/2 months)
- US $50 for the qualitative interview (if they are selected)

Enhanced Usual Care

As the study is conducted entirely online and captures participants from across the United States, where access to behavioral health and other resources for stress and distress can vary widely and is sometimes extremely limited, usual care might be inadequate, and we want to assure some benefit for all study participants. Therefore, participants in all conditions receive enhanced usual care wherein they are provided resources tailored to the participant's needs and location. This approach is similar to the one conducted by the study team for a previous study (Hebert et al [33] and Comtois KA, unpublished data, July 2025) and as recommended by experts in treatment effectiveness studies [55,56]. Tailoring is based on each participant's selection of the needed resources, along with the inclusion of crisis and mental health resources if suicide risk items are endorsed. Participants are asked if they want resources in the following domains: online and community resources focused on crisis and mental health support; veteran and military-specific services; relationship support; and practical assistance with food, housing, medical care, employment, education, and financial needs.

Study staff maintain a library of resources in these areas to share with participants and conduct further research when participants request other resources (examples of requests include wellness, advocacy, hobbies, outdoor activities, and therapeutic adventures). In addition, participants whose responses indicate suicide risk are provided with crisis and mental health treatment resources. To further tailor the resources to individual preferences, participants are offered a one-on-one discussion with study staff about their resource needs via a phone or Zoom (Zoom Communications, Inc) if they would like that in addition to an emailed resource list.

Caring Contacts Intervention

Participants randomized to receive the Caring Contacts intervention will receive 13 nondemanding, caring messages over 12 months on the following schedule: a welcome message (following their baseline assessments), one message every 3 to 5 weeks for the first 21 weeks, and one message every 8 to 9 weeks for the last 31 weeks. In addition, participants will receive messages on New Year's Day, their birthday, and Veterans Day. The delivery day and time of each message vary throughout the year to follow a more naturalistic communication pattern and avoid appearing mechanistic or spam. Table 2 provides the examples of messages.

Table 2. Examples of Caring Contacts messages.

Message types	Examples
General	"Hey, this is Alex just checking in. I hope you are doing okay! Feel free to let me know how things are going if it helps."
Seasonal	"Sending you warm wishes for a bright year ahead! I am grateful to be in touch with you and hope this new year will be a good one, even as the seasons change – Alex"
Birthday	"Happy Birthday, Sam!! Here's to another year I hope you will enjoy the day!"
Veterans Day	"Happy Veteran's Day, Sam Thank you for volunteering for service. What you've done is greatly appreciated. I know that this time can be difficult, if you need someone please reach out, we're here for you if you need us. – Alex"

Caring Contacts is not designed as an automated intervention but explicitly presumes a human-in-the-loop who is choosing the messages and when they should be sent, as well as individually responding to replies from the recipients. Technology facilitates this process but does not replace it. For this study, the message schedule was determined by the lead staff, who have extensive experience with Caring Contacts, including a previous trial and our pilot work. All messages are signed with a nickname chosen by the study staff, and participants are invited (but not directly asked) to reply to the messages. The study staff respond during business hours and provide support and assistance in accessing resources as requested by the participants. The study team responds in a way that fits their personal communication style and accommodates

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the participant's communication preferences, including conversation initiated by the participant. All participants are reminded that the research study team does not monitor messages outside of regular business hours and is not able to provide crisis response services.

To facilitate our assessment of Caring Contacts mechanisms, the messages are scheduled to vary across the 7-day month 1 to 12 EMA blocks, with 5 messages falling within the EMA blocks, where the impact on subsequent EMAs that day can be measured, and 5 messages outside of the EMA blocks to minimize the likelihood of participants perceiving Caring Contacts and EMA as linked. (The remaining 3 messages are holiday messages—New Year's, Veterans Day, and their birthdays—that fall on set days and cannot easily be scheduled to fall either during or outside of the EMA periods.) Further details on the EMA procedures are found in subsequent sections.

If a participant's reply to a Caring Contacts message indicates distress or suicidality, study staff will reply with support and validation and, as appropriate, offer crisis or other resources. If the participant is in a suicidal crisis, a "warm handoff" to 988 or another crisis line is also offered. If there is a situation involving imminent suicide risk (ie, a participant indicates they are planning a suicide attempt or have a lethal weapon) and they refuse to speak with 988 or other crisis response, research staff and licensed clinical staff or faculty consult to determine the appropriate action.

Participants are free at any time to request that they stop receiving Caring Contact messages. In such cases, study staff will inquire if they are willing to continue with the other parts of the study (EMA, the follow-up survey, and the qualitative interview), and each participant is able to decide at what level they will proceed. Participants may also ask for the messages to be paused for a certain period (eg, if they are traveling or otherwise unable to be contacted), in which case the study team will simply remove any messages scheduled to be sent during the specified period. As described in subsequent sections, the web-based platform used to deliver the Caring Contacts intervention is able to track the number of messages to and from each participant, so it will be evident during data analysis how many intervention messages each participant received. Requests to temporarily pause the messages will not change the overall length of the intervention.

We do not anticipate any reasons to withdraw participants from the intervention. However, if withdrawal is considered, the principal investigator, coinvestigators, and lead research scientists will consult together (with the UW IRB and the study DSMB as appropriate) to determine why such a decision is in the best interest of the participant and only withdraw them for that reason. In the case of a withdrawal, the principal investigator will contact the participant via email to explain the withdrawal and reasons for doing so and include an offer of a meeting to discuss further should the participant desire it.

Caring Contacts via SMS Text Message Platform

To facilitate the scaling of Caring Contacts, our pilot work included biomedical informatics and software development methods, including human-centered design and agile prototyping, to design a web-based application to send, receive, and respond to messages with participants. Capabilities of the platform include the ability to preschedule messages and modify each message's content and delivery date and time as needed, a conversation history display, the ability to document notes and alerts within each participant's record for easy reference by study team members, notifications sent to specific study team members when a participant replies, and notifications to follow-up on unread messages. This platform allows oversight of all sent and received SMS text messages and the ability to export transcripts of SMS text message numbers and content with time stamps, which will be useful in analysis of the impact of Caring Contacts on participant stress and distress. Staff members had already established fidelity to Caring Contacts in our previous trial but they comonitor each other's messages to ensure consistency with the Caring Contacts protocol for all participants.

Study Procedures

Three different data collection procedures are used in this study.

Online Survey

After informed consent, participants are routed into an online REDCap survey flow to collect baseline data and route them through the steps of the study via links programmed to be sent by email or SMS text message, by the participant's preference. At 12 months, after completion of the Caring Contacts intervention for the applicable conditions, REDCap automatically prompts the participants to complete their follow-up assessment via an online survey. The follow-up window will remain open for 3 months for each participant, and the study team will provide periodic reminders to complete the survey within the window.

EMA Study

Participants will receive invite links to complete the EMAs at various time points across the study period, as shown in Table 1. Each EMA point has 10 or 11 items (described in the subsequent section), which usually take 30 seconds to 3 minutes to complete (based on participants enrolled thus far and the pilot testing of the EMAs). All participants will initially receive invitations for 3 daily assessments for 14 days before randomization (42 assessments) to establish baseline mean and variability metrics for the EMA outcomes and mechanisms, and an additional 7 days of EMA (21 assessments) at 12-month follow-up. Participants randomized to conditions that include EMA, following the baseline assessment period, complete 7 days of EMA per month at months 1 to 11 (231 assessments) to assess real-time mean and variability of risk and potential mechanisms (Table 1).

Qualitative Interviews

A purposive subset of participants will complete a qualitative interview about their satisfaction and experience with the Caring Contacts intervention. Participants will be selected to ensure representation of gender, ethnicity, study condition, whether they responded to the Caring Contacts message, and high and low stress and distress at baseline. The interviews will continue until saturation is reached. The qualitative interview guide can be found in Multimedia Appendix 2. The data obtained during

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the interviews will be coded following a thematic content analysis approach, wherein a combination of deductive and inductive codes will be applied to the data, which will then be reviewed for consensus with multiple members of the research team [57,58].

Retention Strategies

To increase retention rates, the study team uses multiple strategies. First, at the 6-month mark, the study staff reach out to participants via their preferred form of communication to confirm that their contact information is still correct and active. This check-in occurs only if (1) the participant has not responded to any Caring Contacts messages or other study-related communications, and (2) they have not completed any EMA since the end of their 2 weeks of baseline EMA.

Second, we collect a variety of contact information from each participant, including multiple phone numbers and email addresses, social media profiles, mailing addresses, and contact details of up to 2 friends or relatives who they would feel comfortable letting us reach out to if we are unable to contact them directly. This variety of contact information has been effective in keeping in touch with participants in our research, even over long stretches of time.

Measures

Study measures are organized by primary and secondary outcomes, potential mechanisms of Caring Contacts, measures of stress, and other background measures that characterize the sample. For measures used to determine eligibility, the inclusion criterion is specified.

Primary Outcomes (Aims 1.1 and 1.2)

The primary EMA outcomes are mean levels of 3 suicide risk indicators of motivation to live, desire to die, and urges for suicide rated on a Likert scale from 0 to 10 (aim 1.1). The specific items include “How much do you want to die right now?,” “How much do you want to live right now?,” and “How strong are your urges for killing yourself right now?” Higher scores indicate higher suicidal risk (the item regarding motivation to live is reverse-coded). They are assessed at every EMA point throughout the study follow-up period. In the pilot trial of this study, we used visual analog scale (VAS), consisting of a slider on a straight line with end points representing the extremes, to measure these items. Their convenience and ease of rapid administration make them highly compatible with EMA research designs, facilitating efficient real-time data collection in naturalistic settings [59]. VAS of suicide intent [60], suicide desire [61], suicide urges, and perceived burdensomeness [62] were pilot-tested. However, VAS was not found to be user-friendly due to the limitations of the REDCap survey interface when presented on a smartphone. As such, we changed the response options for these suicide risk items to buttons labeled 0 through 10 in place of a VAS from 0 to 100.

The primary survey outcomes of suicide risk are administered at baseline and follow-up (aim 1.2). Suicide ideation is measured with the 12-item Suicide Ideation subscale of the Harkavy-Asnis Suicide Scale (HASS) [63] on a 5-point Likert scale, from 0 (“never”) to 4 (“most or all of the time”). Higher scores indicate higher SI. While the original scale assesses for the past 2 weeks, this trial uses the measure to assess for the past month as recommended by the measure’s creators, and rather than 4 indicating “daily,” it indicates “most or all of the time.” An example question from this version of the measure is “Over the past month, how often have you...” with response options including the following: “Thought you would be better off dead?,” “Had ideas about killing yourself?,” and “Thought about killing yourself but did not try to do it?” This modified version of the HASS self-report measure has been validated by Asarnow et al [64]. The measure has also been demonstrated to have strong psychometric properties in youth samples, with good internal validity and high sensitivity to treatment changes [65]. The eligibility criterion for SI is a score of 3 or higher. The 6-item Brief Suicide Cognitions Scale [66], a shortened version of the Suicide Cognitions Scale-Revised [67], is also used to assess suicide cognitions without asking about SI or attempts and is administered before the Suicide Ideation subscale of the HASS. Items are scored on a 5-point Likert scale from 1 (“strongly disagree”) to 5 (“strongly agree”). Higher scores indicate more suicidal cognition. The Suicide Cognitions Scale-Revised has been validated with a sample of military adults by Fischer et al [68], and the Brief Suicide Cognitions Scale was used successfully with a sample of US military veterans [67]. The eligibility criterion for suicide cognitions is a score of at least 4 on any item.

Qualitative Interviews (Aim 2)

The qualitative interview—modeled on similar interviews in previous Caring Contacts research [33]—asks participants about their experience with the Caring Contacts intervention (including receiving and replying to the messages and responses they received from the author, and satisfaction with and preferences for the intervention messages), as well as their experience completing the EMAs. The interview content was refined during the pilot test of this trial with military veterans and clinical participants (manuscript currently in preparation). The qualitative interview guide is provided in Multimedia Appendix 3.

Distress: Secondary Outcomes (Aim 3)

Depression is assessed with the Patient Health Questionnaire-9 [69], a standard and widely used brief measure of depression severity. A total of 9 items are scored on a 4-point Likert scale from 0 (“not at all”) to 3 (“nearly every day”). Higher scores indicate a higher degree of depression severity. An example question from this version of the measure is “Over the last 2 weeks, how often have you been bothered by any of the following problems?” with response options including the following: “Little interest or pleasure in doing things” and “Feeling tired or having little energy.” The measure has been validated as a useful tool to assess depression in clinical and general populations [69,70]. The eligibility criterion for depression is a score of 10 or more.

Substance use issues are measured by the Short Inventory of Problems (SIP)-Alcohol and Drugs [71], a 15-item psychometrically sound measure [72] assessing the frequency over the past 2 weeks of adverse consequences of alcohol and drug use in 5 domains: interpersonal, intrapersonal, physical,

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impulse control, and social [73]. Items are scored on a 4-point Likert scale from 0 (“never”) to 3 (“daily or almost daily”), where higher scores indicate increased severity of drug and alcohol problems. An example question from this version of the measure is “During the past 2 weeks, about how often has this happened to you?” with response options including the following: “I have been unhappy because of my drinking/drug use,” and “When drinking/using drugs, I have done impulsive things that I regretted later.” The version of this measure, the SIP-2L, which is worded specifically to assess drinking problems, demonstrated strong internal consistency among items, and correlations with self-reported heavy drinking demonstrated convergent validity in a sample of adults with alcohol use disorder recruited for a harm-reduction trial [72,74]. A similar version of the SIP-Alcohol and Drugs, the SIP-Revised, has been shown to have excellent internal reliability and convergent validity in measuring substance use consequences in a sample of treatment-seeking drug users [73] The eligibility criterion for substance use issues is a total score of 3 or more, or any singular item rated at least 2.

Loneliness is assessed with the National Institutes of Health (NIH) Toolbox Loneliness Scale from the Adult Social Relationship Battery [75]. Participants are asked to rate how often in the past month they have, “felt alone and apart from others,” “felt left out,” “felt lonely,” etc on a 5-point Likert scale of 1 (“never”) to 5 (“always”). Higher scores indicate more loneliness. The scale was demonstrated to have convergent validity with 3 other validation instruments [75]. The eligibility criterion for loneliness is a total score of 15 or higher, or any 2 items scored at least 5.

A sense of defeat is measured using the 16-item Defeat Scale [76,77]. Items are scored on a 5-point Likert scale from 0 (“never”) to 4 (“always”) where higher scores indicate greater feelings of defeat. Items include, “I feel that I have not made it in life,” “I feel I have lost important battles in life,” and “I feel that there is no fight left in me.” Three of the items are reverse-coded and include, “I feel that I am a successful person” and “I feel able to deal with whatever life throws at me.” The scale was shown to have high levels of internal consistency and to be psychometrically sound by the authors [76]. The eligibility criterion for defeat is a score of 24 or more.

Feelings of hopelessness are measured using the Beck Hopelessness Scale (BHS) [78], which is composed of 20 true or false items (9 of which are reverse-coded). While the psychometric properties of the BHS have not been tested in US military samples, the scale has demonstrated good convergent validity across various populations. The scale has been shown [79-81] to be internally consistent with strong concurrent validity with other psychiatric measures, albeit in primarily clinical settings. It significantly correlates with measures of depression, anxiety, and SI [82-84] and has been validated in both clinical and nonclinical populations, including university students, general population samples, and caregivers of patients with psychiatric disorders. In addition, the BHS is sensitive to changes in depression over time [84-86]. The eligibility criterion for hopelessness is a score of 9 or more.

The extent to which an individual is experiencing psychological pain is measured using the 3-item Unbearable Psychache Scale [87]. Items are scored on a 5-point Likert scale from 1 (“strongly disagree”) to 5 (“strongly agree”). Higher scores indicate that one’s psychological pain is more unbearable. An example item is “The following statements refer to your psychological pain, not your physical pain. Please indicate the extent to which you disagree or agree with each” with response options including the following: “My pain is making me fall apart” and “Because of my pain, my situation is impossible.” This brief measure was demonstrated to be a valid and reliable measure of psychache [88]. The eligibility criterion for psychache is a score of 9 or more.

Potential Mechanisms of Caring Contacts (Aim 4)

To evaluate how Caring Contacts influence connectedness, we selected 4 mechanisms for testing based on prominent psychological suicide theories [40,89,90]: burdensomeness, entrapment, mattering, and personal and social responsibility. Measures of these possible mechanisms of action for the Caring Contacts intervention are administered through EMA and the baseline and follow-up surveys.

Two of the potential mechanisms, perceived burdensomeness and entrapment, are each assessed with a single question selected based on prior EMA studies studying suicide.

Perceived burdensomeness has consistently emerged as a robust predictor of SI, reflecting the harmful impact of feeling like a burden to others. During the EMA period, it is assessed using a slightly modified version of an item from the Interpersonal Needs Questionnaire [91] (“I felt that I was a burden to other people, or that they would be better off without me”), which has been used in previous EMA research [92].

Entrapment is a key construct in the integrated motivational-volitional model [40] of suicide and represents the psychological state of feeling trapped with no escape, which is strongly associated with suicidal intent. In this study, it is assessed at baseline and follow-up using the 16-item Entrapment Scale [76,77]. Items are scored on a 5-point Likert scale from 0 (“not at all like me”) to 4 (“extremely like me”) and include “I am in a situation I feel trapped in” and “I would like to get away from who I am and start again.” During the EMA period, it is assessed using a single item from the scale (“I feel trapped”). Higher scores indicate increased feelings of being trapped. The measure’s authors found it to be basically unidimensional and psychometrically valid [77].

A planned missingness design was implemented to reduce the length of each individual EMA, thereby lowering the effort needed by participants to complete it. Thus, 3 of the mechanisms that are measured with multiple items—mattering, personal responsibility, and social responsibility—are assessed in a random rotation at each of the 3 EMA points within a day.

Mattering is how an individual perceives their significance and importance to others, which directly counters feelings of insignificance and isolation. In this study, it is measured using the 5-item General Mattering Scale [93-96] at baseline, follow-up, and in the EMA. Items are scored on a 4-point Likert scale from 1 (“not at all”) to 4 (“a lot”) and include “How much

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do other people depend on you?" and "How important do you feel you are to other people?" Higher scores indicate increased feelings of mattering to others. In contrast to mattering, antimattering is the extent to which an individual feels insignificant or worthless. It is valuable to assess both mattering and antimattering as it has been postulated that these constructs are not opposites of each other but rather capture distinct protective and risk factors [97-99]. The 5-item Anti-Mattering Scale is administered with the General Mattering Scale at baseline and follow-up. Items are scored on a 4-point Likert scale from 1 ("not at all") to 4 ("a lot") and include "How much do you feel like you don't matter?" and "To what extent have you been made to feel like you are invisible?" Higher scores indicate greater feelings of antimattering.

In this trial, personal and social responsibility are defined as an individual's feeling of accountability toward their own well-being and the well-being of others. They speak to an individual's sense of belonging within broader social systems and reinforce protective roles within their network. In this study, they are measured by the two 4-item subscales of the 8-item Responsibility Scale [100] at baseline, follow-up, and during the EMA period. Items are scored on a 5-point Likert scale from 1 ("strongly disagree") to 5 ("strongly agree"). Items from the personal responsibility scale include "I discipline myself to make the best use of my time doing meaningful things" and "I am conscientious in whatever I do, big or small." Items from the social responsibility scale include "I am morally accountable for how I treat others" and "I am responsible to do my part to make the world a better place." Higher scores indicate a greater sense of personal and social responsibility [100].

Measures of Stress

Protocols from the NIH-funded PhenX Toolkit's Social Determinants of Health Core Collection [101] are used to assess external stress, including current employment status (unemployed, looking for work, or disabled); food insecurity; access to health services; and housing instability due to affordability. Recent military separation was assessed as separation within the past year. For consistency, we have adopted these protocols for our demographic and health disparities measures. However, many items do not have previous literature in the survey form and therefore had to be adapted for this study. The eligibility criteria for each of these stressors are provided in Textbox 2.

Textbox 2. The eligibility criteria for the measures of stress.

- Unemployment: participants indicate that they are looking for work, unemployed due to being temporarily laid off, on sick leave, or on parental leave, or temporarily or permanently disabled.
- Financial strain: participants indicate that they are unable to afford adequate food or health care service.
- Unstable housing: participants indicate that they are living in a temporary or unreliable housing situation, or that they have been worried about being able to afford a place to live for most of the last 12 months.
- Recent military separation: participants indicate that they left the military (including Reserves and National Guard) in the last 12 months.

A modified version of Cerel's Exposure to Loss measure [102,103] is used to assess the number of sudden losses, both suicide-related and nonsuicide-related, that participants have experienced, as well as he timing of the most recent loss, the extent to which the participant continues to feel impacted by the loss, and their relationship with the person who had died. Closeness is measured with a single item on a 5-point Likert scale from 1 ("not close") to 5 ("very close"). Impact of the loss is measured with a single item on a 5-point Likert scale from 1 ("The death had little effect on my life") to 5 ("The death had a significant or devastating effect on me that I still feel."). These items have been used successfully to capture participants' self-reported impact of their losses in other studies with both clinical [104] and military veteran samples [105] and are recommended to assess for psychological distress due to loss. The eligibility criterion for recent sudden loss includes experiencing either a suicide or nonsuicide death that occurred within the last year and had a moderate effect on their life, or occurred more than a year ago but had a significant or devastating impact that the participant still feels.

Other Measures That Characterize the Sample

The Columbia-Suicide Severity Rating Scale (C-SSRS) screener [106-113] assesses recent suicidal behavior, including preparatory behavior, and aborted, interrupted, and actual attempts. To maximize readability, the pediatric or cognitively impaired C-SSRS version [114] was selected for this study, and additional items were developed and added to gather additional details on suicidal behavior. The C-SSRS screener has strong psychometric properties demonstrated in general [113] and veteran [108] populations, is used in the Defense Health Agency's Behavioral Health Data Portal [115], and has shown predictive validity for suicidal behavior. The eligibility criterion for recent SI is having SI in the past month or making an aborted, interrupted, or actual suicide attempt in the last month.

Participants report their usual sleep and wake schedules at baseline, follow-up, and on the last day of each week of EMA. Items from the Consensus Sleep Diary [116] and the Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance Scale [117,118] ask about recent sleep quantity and quality. The Consensus Sleep Diary was shown to be a valid and reliable measure of sleep in multiple studies [119-121] while the PROMIS Sleep Disturbance scale was shown to have good face and construct validity, convergent validity, and internal consistency reliability [118].

Various protocols from the NIH-funded PhenX Toolkit's Social Determinants of Health Core Collection [101] are used to assess demographic characteristics, such as age, gender identity, sexual orientation, race, ethnicity, living situation, occupation, and highest education received. They are supplemented with military-specific questions, such as branch, rank achieved,

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military occupation, deployments, and services in Reserves or National Guard.

Data Analysis

Power and Sample Size

We plan to recruit 510 participants with the aim of holding type I (α=.05) and type II error rates (β=.05; power=0.95) at equal levels. For aim 1.1 with 3 conditions and 2 assessment time points, a sensitivity power analysis conducted using the *pwr* package in the R software (R Foundation for Statistical Computing) indicated that our proposed sample size will provide sufficient power to detect moderate effect sizes, with the smallest detectable effect size being f^2=0.17. For aim 1.2, our proposed sample size will provide sufficient power to detect small effect sizes, with the smallest detectable effect size being f^2=0.03. On the basis of the prevalence rate for SI in US military service members and veterans between 13.9% and 14.1% and between 1.9% and 2.4% for suicide attempts [122], we expect that 13.9% (71/510) of our proposed full sample will report current SI.

For aim 3, comparing the 2 primary conditions (n=340), with a 7-day assessment period and 3 assessments per day (total observations, n=21), power analysis using the *EMAtools* R package shows sufficient power (0.95) to detect moderate (Cohen *d*=0.5) to large (Cohen *d*=0.8) effects within a month at α=.05, even with a 50% response completion rate. For the full year of the monthly 7-day assessment period (total observations, n=252), the same analysis similarly indicates sufficient power to detect moderate to large effects across 12 months. For aim 4, the recommended sample size is for a 2-level mediation model based on Monte Carlo simulations [123] or detecting small effects with adequate power (0.8) while holding the type I error rate at α=.05, when there are at least 3 assessments per participant, are between 215 and 257 participants if within-participant correlations are moderate (intraclass correlation coefficient [ICC]=0.1),300 to 438 participants if within-participant correlations are moderate (ICC=0.4-0.6), and 495 to 544 participant if within-participant correlations are high (ICC=0.9). Notably, as within-participant observations increase, the required sample size to achieve adequate power decreases. With 12 within-participant observations, our required sample size would be smaller than the recommended sample size [123]. Altogether, 510 participants and 252 assessments per participant over the course of the study should provide sufficient power to detect the hypothesized between- and within-participant effects.

Analysis Plan

First, descriptive statistics will be calculated for all variables and group differences in baseline variables will be examined to ensure randomization success. All outcome variables will be examined for nonnormality, and given past suicide research, we anticipate a positive skew for suicidal thoughts and behaviors, and we will use an appropriate model for all analyses based on the distribution of the outcome variables. On the basis of a Directed Acyclic Graph model generated using DAGitty [124,125], demographic variables are conditionally independent of our outcome variables after accounting for the variables specified in our aims and thus do not confound the relationship between the Caring Contacts intervention and our outcome variables. However, to understand the nuanced effects of Caring Contacts on suicide risk across diverse subgroups, we will control for ethnicity, gender, and military status (veteran vs current US military service member) as covariates in our analysis. This stratification allows us to discern potentially differential impacts of the intervention and ensures that our findings are robust and applicable across the varying demographic profiles within the veteran population. Furthermore, all analyses will be conducted using an intent-to-treat framework, using all available data, and using robust maximum likelihood estimation to account for missing data.

For aim 1.1, individual participant means and SDs of each suicide indicator (motivation to live, passive ideation, active ideation, suicide intent, and urges to harm self) will be calculated from the baseline and 12-month EMA period (for all conditions). Then, to assess group differences in the outcome measures of interest, an analysis of covariance examining condition-specific differences at 12 months, controlling for baseline values of the outcome variable of interest, will be conducted. Preplanned post hoc comparisons will compare (1) any Caring Contacts (combined) to no Caring Contacts, (2) Caring Contacts with and without EMA, and (3) EMA with and without Caring Contacts.

For those participants who will complete EMA for all 12 months (n=340), we will conduct an *exploratory analysis* of changes over time in the mean and intraindividual SD of suicide outcomes. The unique and intensive sampling approach of EMA allows for fine-grained exploration of if and when outcomes change in a clinical trial. Specifically, we will first visually examine trajectories by condition to determine the shape of change *trajectories* over time. Then, following the determination of the shape, we will conduct a linear mixed effects growth model (eg, linear, nonlinear quadratic, and piecewise) [126-129], including a dummy-coded condition variable (with EMA only as the reference) as a predictor of both intercept and slope to determine how intervention condition impacts change in suicide outcomes over time.

For aims 1.2 and 3, to examine secondary suicide outcomes and measures of psychological distress, we will use analysis of covariance to examine condition-specific differences in continuous scores of suicide ideation and cognitions and examine group differences at 12 months, controlling for baseline values of the outcome variable of interest. Similarly, preplanned post hoc comparisons will compare (1) any Caring Contacts (combined) to no Caring Contacts, (2) Caring Contacts with and without EMA, and (3) EMA with and without Caring Contacts. For both aims 1.1 and 1.2, any baseline variables that were not successfully randomized will be included as covariates in the regression models.

For aim 2, thematic analysis will be used to systematically examine the qualitative data obtained from the interviews [57,58]. This process will begin with verbatim transcription of the interview audio recordings, ensuring a precise and comprehensive dataset. An inductive approach will be adopted,

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allowing themes to emerge organically from the data without preconceived categories. The research team will use open coding, assigning descriptive codes to individual text segments within each transcript. This initial coding will facilitate the identification of patterns and key themes related to participants' experiences and perceptions of the Caring Contacts intervention. To ensure accuracy and consistency, intercoder reliability will be established through regular team meetings where coding decisions are discussed and consensus is reached. This iterative process will continue as new codes emerge, with the team members actively refining and redefining codes to capture the nuances of the data accurately. Following open coding, the research team will engage in axial coding, grouping codes into broader categories to elucidate connections and relationships between them. This step lays the foundation for developing overarching themes that encapsulate the study's core insights. Finally, the coded data will be systematically reviewed and organized to refine these themes and develop a coherent narrative that accurately reflects the participants' experiences. Triangulation methods will be used throughout this process, comparing information from different participant groups and cross-referencing existing literature to validate the findings and ensure their robustness and reliability.

For aim 4, to examine potential mechanisms of Caring Contacts, we will use the within-EMA period data and examine within-participants mediation using dynamic structural equation modeling (with random intercepts and slopes) [130]. Dynamic structural equation modeling allows for the simultaneous estimation of within- and between-person effects that allow for idiographic mechanistic models over time, which can be ideal for answering questions about within-participant mechanisms of suicide outcomes. In line with recommendations for intensive longitudinal data analysis, all hypothesized mechanism variables (ie, mattering, personal and social responsibility, perceived burdensomeness, and entrapment) will be centered at both the between-person and within-person mean level. Then, within-person regression models will be run to examine the relationship between the hypothesized mechanisms and suicide outcome, using a lag-1 model and autoregressive covariance structure to account for assessments closer in time to be more highly correlated. Next, to examine the mediation effect of treatment condition on outcomes through the hypothesized mechanisms, we will estimate within-level indirect mediation effects, calculated as the product of the within-level effect of treatment condition on the mechanism (a path) and the effect of the mechanism on the suicide outcome. All mediation analyses will be examined at the within-person level (1-1-1), excluding cross-level mediation. Random starts will be used for all models to replicate the best log-likelihood. Finally, to examine the immediate versus delayed impact of the timing of Caring Contacts intervention, we will use autoregressive modeling to examine the direct impact on stress, distress, and suicide outcomes immediately following a Caring Contacts message compared to times without a message, using the EMA data. For all regressions, 95% CIs will be reported, and statistical significance will be set at $P<.05$.

Results

Recruitment for this RCT started in April 2024 and is projected to close in May 2025, or until the target sample size of 510 participants is reached. As of December 2024, we have enrolled 321 participants. Final quantitative data collection is projected to be completed by July 2026, when the final 12-month follow-up windows close. Data from qualitative interviews will be collected until September 2026. Data analysis will occur following the data collection, and the results are expected to be published in winter 2027.

Discussion

Significance

This innovative trial will be the first RCT to examine (1) the impact of the Caring Contacts intervention on a broad population experiencing stress or distress and (2) the mechanisms of Caring Contacts, both when each message is received and during the course of the 1-year intervention. By recruiting veterans and service members experiencing a wide variety of stressors and psychological distress, the sample is more generalizable to those served by veteran service organizations, primary care, and general behavioral health care. If Caring Contacts reduces the risk of suicide, improves psychological distress, or both, then the intervention could be scaled up to include individuals who do not endorse suicidality but have the potential to benefit. As veteran service organizations are not equipped to systematically assess suicidality or to provide an intervention specifically for this segment of their membership, positive results would support their implementation with any veteran experiencing stress or distress.

EMA provides a powerful tool for measuring the impact of Caring Contacts by enabling real-time data collection in participants' natural environments. This approach minimizes recall bias and allows a detailed exploration of how the intervention affects participants immediately after receiving Caring Contacts and over the course of 1 year. Thus, EMA allows researchers to gain valuable insights into the mechanisms of action of the Caring Contacts intervention. This can address critical gaps in understanding and pave the way for improved, scalable strategies to prevent suicide.

Limitations

For participants randomized to receive both Caring Contacts and EMA, the effect size of Caring Contacts may be diluted due to the increased contact associated with EMA. This is mitigated by including 2 other conditions—Caring Contacts without EMA and EMA without Caring Contacts—and by the EMA and Caring Contacts coming from different phone numbers, thus appearing as separate conversation threads on participants' cell phones. Another limitation is the risk of a smaller effect size across all study conditions from the enhancement of usual care with the provision of tailored resources to each participant. Given that all the veterans and service members were experiencing stress or distress and are at outsized risk of suicide, the risk that they did not have the resources they needed or the knowledge and access to find them

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meant that treatment as usual was ethically inadequate and offering what could be offered was important. Online research is inherently limited by the challenge of verifying the authenticity of participants. In this trial, we offset this risk with multiple automated and human-in-the-loop checks to prevent fraudulent participation. Finally, we are using EMA and survey assessments of suicidal thoughts and behaviors that are subject to the limitations inherent in self-report measures. However, EMA measures were selected based on previous research, standardized scales were used for survey assessments, and randomization will equate any self-report bias across the 3 conditions.

Conclusions

To conclude, this innovative RCT is designed to evaluate the Caring Contacts intervention for veterans and service members experiencing stress or distress while simultaneously evaluating potential mechanisms through which this evidence-based intervention is working. The EMAs right before and after Caring Contacts messages are received, as well as the monthly EMA tracking changes in mechanisms and outcomes during the course of the 1-year intervention, offer one view, while qualitative interviews with study participants offer another view into the impact of Caring Contacts. This is also one of the first trials for suicide prevention that focuses on EMA as the primary outcome. Results from this project will further inform optimal implementation of Caring Contacts and provide crucial insights to address the urgent need for practical, scalable mental health solutions.

Disclaimer

The views expressed herein are those of the authors and do not necessarily reflect the official policy of the sponsor or the funder.

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Data Availability

The datasets generated or analyzed during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization: BW (lead), AE (equal)
Funding acquisition: KAC
Methodology: AE (lead), BW (equal), KCL (supporting), AHR (supporting), KAC (supporting)
Project administration: AE (lead), BW (equal), CC (supporting)
Resources: KAC
Supervision: KAC (lead), KCL (equal)
Validation: KAC (lead), KCL (equal), AHR (equal)
Visualization: BW (lead), AE (equal)
Writing—original draft: BW (lead), AE (equal), CC (supporting), KCL (supporting), AHR (supporting), KAC (supporting)
Writing—review and editing: BW (lead), AE (equal), CC (supporting), KCL (supporting), AHR (supporting), KAC (supporting)

Conflicts of Interest

None declared.

Multimedia Appendix 1
World Health Organization trial registration dataset.
[DOCX File , 25 KB - resprot_v14i1e72140_app1.docx]

Multimedia Appendix 2
Example consent form.
[DOCX File , 57 KB - resprot_v14i1e72140_app2.docx]

Multimedia Appendix 3
Qualitative interview guide.

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[DOCX File , 30 KB - resprot_v14i1e72140_app3.docx]

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Abbreviations

BHS: Beck Hopelessness Scale
C-SSRS: Columbia-Suicide Severity Rating Scale
DSMB: data safety monitoring board
EMA: ecological momentary assessment
HASS: Harkavy-Asnis Suicide Scale
ICC: intraclass correlation coefficient
IRB: Institutional Review Board
NIH: National Institutes of Health
PROMIS: Patient-Reported Outcomes Measurement Information System
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture

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SI: suicidal ideation
SIP: Short Inventory of Problems
UW: University of Washington
UWRRAP: University of Washington Revised Risk Assessment Protocol
VAS: visual analog scale

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Protocol

An Interdisciplinary Ecosystem for the Prevention of Cardiotoxicity in Older Patients With Breast Cancer: Protocol for a Prospective and Multicentric Study

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Abstract

Background: Over 50% of newly diagnosed patients with breast cancer are aged ≥65 years. Due to age-related factors and the presence of comorbidities, these patients are particularly vulnerable to developing cardiac toxicity associated with cancer treatments, which may lead to suboptimal interventions and undertreatment, resulting in poorer health outcomes, quality of life (QoL) deterioration, and increased health care costs. Given the underrepresentation of older patients with breast cancer in clinical trials and the increasing recognition of the impact of psychosocial and behavioral factors on cardiovascular disease onset, broader and interdisciplinary studies are required to develop new and innovative best practices for this clinical population.

Objective: Using an innovative eHealth approach combining the CARDIOCARE (An Interdisciplinary Approach for the Management of the Elderly Multimorbid Patient with Breast Cancer Therapy Induced Cardiac Toxicity—grant agreement 945175) mobile app and technologically advanced wearable devices (ie, the Garmin Venu SQ watch and Polar H10 sensor), the CARDIOCARE prospective study pursues a twofold aim: (1) testing the effectiveness of the CARDIOCARE mobile app to

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monitor and assess the intrinsic capacity and QoL of older patients with breast cancer and evaluating the CARDIOCARE eHealth interventions' effectiveness on these parameters and (2) developing a holistic, patient-centered risk prediction model specific for the detection of cardiotoxicity before it clinically emerges.

Methods: This prospective and multicentric study involves 6 clinical and 5 technical partners across Europe. In total, 750 older patients with breast cancer (aged ≥60 years) are assigned to either the standard practice or enhanced monitoring group, with only patients in the latter receiving access to eHealth psychological, behavioral, and functional interventions implemented on the CARDIOCARE eHealtHeart app. Patients will be recruited in 6 clinical centers and will undergo clinical procedures to collect multimodal data, including clinical data, cardiac imaging, biochemical and psychological biomarkers and omics, intrinsic capacity, and QoL indicators measured at baseline (T0) and every 3 months up to 12 months (T5).

Results: CARDIOCARE is a project funded by Horizon 2020, and enrollment started in May 2023. As of October 17, 2024, a total of 50% (375/750) of the target number of patients had been recruited.

Conclusions: The CARDIOCARE prospective study will contribute to developing new best practice guidelines for managing older patients with breast cancer and multimorbidity while preserving their intrinsic capacity and improving their QoL. Furthermore, the CARDIOCARE mobile app and the wearable devices will allow clinicians to identify trajectories across the cardiotoxicity disease continuum and thus intervene in a preventative way among patients at higher risk. Such a health care approach will also benefit the health care system, which currently spends almost 40% of its resources on patients aged >60 years, with long-term care and hospital admissions being the primary cost drivers.

Trial Registration: ClinicalTrials.gov NCT06334445; https://clinicaltrials.gov/study/NCT06334445

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KEYWORDS

breast cancer; older adult; cardiotoxicity; prospective study; eHealth; mobile app; risk prediction model

Introduction

Background

Over 50% of newly diagnosed patients with breast cancer are aged >65 years and are particularly vulnerable to the cardiotoxic effects of cancer treatment due to multiple comorbidities and age-related risk factors [1]. The cumulative effect of risk factors in the older patient with breast cancer resembles a "snowball effect" in which baseline age-related risk factors and cancer-related changes are further exacerbated by cancer therapy–induced cardiotoxicity [2,3], resulting in severe multimorbid conditions and increased mortality. Underestimating the cardiotoxicity risk in this vulnerable population may lead to inappropriate interventions and undertreatment, contributing to poorer health outcomes, quality of life (QoL) deterioration, and increased health care costs. Considering that older patients with cancer are systematically underrepresented in clinical trials [1], there are currently limited means to effectively address the complex needs of these patients and their caregivers, often resulting in undertreatment and suboptimal health outcomes, with negative consequences to patients' QoL [1]. Therefore, in line with the World Health Organization's view that health is a state of complete physical, mental, and social well-being [4], broader, interdisciplinary, and patient-oriented clinical trials are urgently needed to provide new evidence-based best practices for managing older patients with breast cancer. To date, the most effective approach to minimize cardiotoxicity is baseline risk stratification and appropriate follow-up during treatment for the early detection of cardiotoxicity.

Moreover, psychological conditions such as depression, distress, and anxiety—often observed in patients with cancer after diagnosis [5]—can increase the risk of cardiovascular complications [6]. Similarly, people presenting negative affectivity and social inhibition are at higher risk of cardiovascular disease as such negative affectivity is significantly associated with higher systolic and diastolic blood pressure [7,8]. Similarly, prolonged exposure to stressful life circumstances may predict subsequent hypertension and cardiovascular disease [3]. Therefore, the Integrated Care for Older People guidelines recommend a comprehensive cardiological assessment as well as a detailed evaluation of patients' intrinsic capacity. Intrinsic capacity refers to the composite of all the physical and mental capacities that an individual can draw upon at any point in time. It encompasses a wide range of abilities, including cognitive, emotional, physical, and sensory functions, that together influence an individual's functional ability and QoL as they age [9]. This holistic and patient-oriented approach aims to establish new best practices for the management of older patients with cancer at risk of cardiotoxic effects associated with oncological treatments [10].

Novelty and Study Aim

Multimodal retrospective data have been retrieved from existing databases in 5 of the 6 clinical centers belonging to the CARDIOCARE consortium and involved in the observational prospective cohort study (hereafter referred to as the *prospective study*)—the Bank of Cyprus Oncology Centre (BOCOC) in Cyprus, the European Institute of Oncology (IEO) in Italy, Karolinska University Hospital (KSBC) in Sweden, National and Kapodistrian University of Athens (NKUA) in Greece, and University of Ioannina (UOI) in Greece—to develop a risk prediction model for cardiotoxicity in the older adult population with breast cancer to be refined and validated through the

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CARDIOCARE prospective study. In the prospective study, the cardiotoxicity risk prediction model will be enriched with novel biochemical, omics (metagenomics, micro-RNAs, and single-nucleotide polymorphisms), and psychological markers to better assess how patients' intrinsic capacity (physical and mental) and QoL are affected by cancer and anticancer treatments and how they influence the risk of developing cardiac toxicity. So far, no extensive studies have allowed for the collection of all the necessary data to conduct a meaningful assessment of the intrinsic capacity and QoL of older patients with breast cancer.

It has to be considered that patients recruited in the CARDIOCARE clinical study receive different types of systemic therapy, including chemotherapy, targeted therapy, immunotherapy, and hormonal therapy. They also receive different types of local treatment comprising surgical treatment (wide local excision vs mastectomy) as well as radiotherapy. The aim is indeed to explore the impact of each treatment separately (different categories) and present potential associations between therapies and QoL and intrinsic capacity parameters. In standard clinical practice, these are managed through a "one-size-fits-all" approach, but CARDIOCARE, focusing on personalization of care, may ultimately change that.

Indeed, different pharmacological interventions can cause different types of cardiotoxicity and side effects, hence varying the impact on QoL. Data on the individual impact of the different types of systemic cancer therapy on intrinsic capacity are scarce, and the CARDIOCARE platform provides a unique opportunity to explore this as aggregated data and separately.

Thus, the CARDIOCARE prospective study will adopt technologically advanced tools to collect a large amount of data on the physical, psychosocial, and behavioral parameters of older patients with breast cancer to better identify patients at risk of developing cardiotoxicity due to oncological treatments and improve their psychological and physical well-being during and after their oncological care pathway.

Monitoring technologies based on sensors, wearables, eHealth (ePsycHeart and eHealtHeart), and a mobile app are used to collect patient-reported data; engage patients in their ongoing health and behavior; and make an impact on the communications between patients and clinicians in a closer, more trusting environment.

The mobile app is structured in 2 different main sections: the ePsycHeart app and the eHealtHeart app. This app is used during the first 6 months of the study to collect psychological, social, and physical variables.

The ePsycHeart section has been developed with a patient-oriented approach aiming to easily monitor and inform patients and physicians on the patients' overall emotional, functional, and physical well-being by means of smart recommendations and on the most adequate intervention activity (eHealtHeart), tailored based on the output originated from ePsycHeart. In particular, ePsycHeart will contain different validated and standardized questionnaires to assess psychological, social, and physical variables.

The eHealtHeart section includes the main interventions, developed in modules to counteract dispositional, emotional, and behavioral risk factors for cardiotoxic effects and lower QoL after cancer therapy. Specifically, eHealtHeart will deliver effective interventions to prevent and delay progression of cardiotoxicity by targeting (1) the improvement of psychocognitive well-being, (2) the improvement of mobility and vitality, (3) the management of age-associated conditions (eg, urinary incontinence), (4) the prevention of falls, and (5) support for caregivers. The eHealtHeart main modules focus on several aspects.

One of the modules targets psychological well-being, with interventions on depression, emotional and dispositional states, and stressors based on a number of intervention tools. The first tool is biofeedback, which is a well-established method for collecting the user's physiological parameters to foster better outcomes in health care, understanding the disease and delivering treatment. More specifically, through noninvasive external sensors, biofeedback gives constant real-time feedback to the user about parameters such as heart rate (HR). This feedback allows the patient to gain awareness and learn how to self-regulate their own bodily reactions, which are usually unconscious and automatic, through individualized approaches that improve one's adaptability to physiological responses [11,12].

The second tool is the best possible self (BPS) activity, which was introduced by King [13] as a disclosure exercise in which participants write about their life goals and priorities imagining themselves in the future once everything has turned out for the best. Participants will be asked to carry out this task for 4 or 5 days every month for the first 6 months of the study. BPS is a writing paradigm developed to help participants set goals and priorities for a positive, imagined future [14], with strong evidence of improving mental and physical well-being.

The third tool is expressive writing, a cost-effective therapeutic intervention in which individuals are asked to write for approximately 15 to 20 minutes about a major life event or traumatic experience over 3 or 4 consecutive days. Research has reported reductions in biological indicators of stress and stress-related conditions affecting blood pressure, sleep, depression, immune function, and pain [15].

The fourth tool is ABCDE, a method in which each participant is asked to think about an adversity (A) that happened during the last period. The participant is then asked to return to the thoughts they had while facing the adversity and reflect on their own beliefs associated with that adversity (B). Successively, the participant is invited to focus on the consequences (C) of their beliefs in terms of experimented feelings and actions taken. After that, the participant needs to dispute (D) the beliefs, meaning that the person's beliefs will be attacked and questioned. Finally, the last step is called Energy I, and it helps the participant observe the connection between the thought (B) and the consequences (C). This last step should help the participant gain awareness about the fact that pessimistic thoughts lead to negative reactions and emotions, whereas positive beliefs lead to positive outcomes regarding one's own feelings as well as environmental consequences.

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Another eHealtHeart module focuses on cognitive stimulation and training via find the word, tic-tac-toe, color beans, and drawing exercises. Every 6 months, the cognitive effect of these exercises on patients will be assessed.

Improvement of mobility and vitality are addressed by another eHealtHeart module. The physical activity and exercise module offers a collection of different graphs, such as bar, line, and pie charts, that will represent data collected through a physical activity–tracking device. The monitoring of steps, duration of sleep, and daily summaries (exercise, type of activity, average HR, and stress level) will be presented to inform patients and physicians about the overall functional well-being of the patient.

Sensory screening is also conducted in the eHealtHeart main modules. A vision test that follows the Snellen test guidelines will be available. The patient must keep the mobile phone screen at a certain distance and, by closing each eye, must assess the letters that the mobile app shows. At the end, an overall score is provided based on the patient's answers. The Snellen test can be repeated as many times as the patient wants within a day. A hearing test that follows the whisper test guidelines will also be available. The procedure will play back certain sounds from the left to the right side of the smartphone speakers. On the basis of what the patient heard and did not hear, an overall score with scaling is provided. The whisper test can be repeated as many times as the patient wants within a day.

The eHealtHeart main modules also promote the management of geriatric syndromes. In the Incontinence Management module, a patient will be able to report urination incidents, follow instructions to exercise the pelvic muscles, and add reminders regarding pelvic floor exercises. The urination data will be stored on the CARDIOCARE server and will be available to the patient and the patient's assigned health care professional. Furthermore, the patient will be prompted to exercise their pelvic floor muscles with the help of instructions and visual aids. The pelvic floor exercises have different difficulty levels (regarding, eg, repetitions and time).

A fall detection and fall prevention module will be available on the app. The system, using sensors from the mobile device, will try to detect whether the patient had a fall incident and will inform the caregiver to communicate with the patient. Furthermore, educational material containing guidelines and videos for fall prevention will be available to the patients.

On the first day of recruitment, each patient receives a mobile phone (with the CARDIOCARE app), a smartwatch, and a belt from their clinical center to be used during the first 6 months of the study. Details on the frequency and duration of the interventions are provided in Table 1.

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Table 1. Frequency of the interventions of the eHealtHeart mobile app.

Module and interventions	Frequency
Psychological well-being measured until month 6	
• Biofeedback	If the patient reports a high anxiety and depression value in the ePsycHeart section (PHQ-4[a]), an alert will suggest to complete the module.
• BPS[b]	20 minutes each day for 4-5 consecutive days every 3 months starting 1 month after baseline
• EW[c]	20 minutes each day for 4-5 consecutive days every 3 months starting at baseline
• ABCDE[d]	Every 3 months starting 2 months after baseline
Cognitive stimulation and training	
• Find the word • Tic-tac-toe • Color beans • Drawing	5 consecutive days per month until month 6
Improvement of mobility and vitality	
• Physical activity and exercise	At least 48 continuous hours each week until month 6
Sensory screening	
• Vision test • Hearing test	At baseline and at month 6
Management of geriatric syndromes	
• Pelvic floor exercises	Daily for 3 months
• Fall detection and fall prevention	Twice a week for 6 weeks

[a]PHQ-4: 4-item Patient Health Questionnaire.

[b]BPS: best possible self.

[c]EW: expressive writing.

[d]ABCDE: activating event or situation, beliefs, consequences, disputation of beliefs, and effective new approach.

Objectives and Rationale

The objectives and rationale of this prospective clinical study are as follows:

1. To stratify patients aged ≥60 years with breast cancer based on their risk of developing cardiotoxicity. The rationale is that, so far, multiple studies have explored the effects of specific risk factors; however, these studies have yet to deal comprehensively with the impact of clinical, biological, psychological, and behavioral risk factors and their interactions.
2. To evaluate the effects of eHealth psychological and behavioral interventions on the intrinsic capacity and QoL of older patients with breast cancer and on their risk of developing cardiac toxicity. The rationale is that, although recent studies associate psychosocial and behavioral characteristics with the risk of developing cardiovascular diseases, these studies on older patients with breast cancer are still limited [16]. However, gaining such knowledge is necessary to generate hypotheses on using eHealth interventions to support this clinical population.

The primary study end point is to evaluate and monitor the onset of cardiotoxicity, where subclinical cardiotoxicity is defined as preserved left ventricular ejection fraction (LVEF; ie, LVEF≥50%) with >15% reduction in global longitudinal strain relative to the baseline or new rise in cardiac troponin I or natriuretic peptide levels in plasma and clinical cardiotoxicity is defined as the reduction in LVEF by ≥10% from baseline to a value of <50% at any time point during study follow-up [17,18].

Secondary end points include intrapatient assessment of major adverse cardiovascular events (MACEs) [19,20] (angina pectoris, acute myocardial infarction, major ventricular arrhythmias, pacemaker implantation, acute heart failure [New York Heart Association class 4], acute ischemic brain disease with neurological persistence evidence, and severe hypertension requiring treatment with angiotensin-converting enzyme or β-blockers), intrapatient assessment of plasma troponin I levels during the follow-up and their association or agreement with LVEF, intrapatient assessment of plasma brain natriuretic peptide elevation, hospital admissions due to cardiovascular causes or falls, cardiovascular death, noncardiovascular death, and health-related QoL (assessed using the European Organisation for Research and Treatment of Cancer Quality of

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Life Questionnaire–Breast Cancer, a validated breast cancer patient-reported outcome measure).

Secondary end points also include the cost-effectiveness of provided health care pathways, determined through costs combined with quality-adjusted life years (QALYs). Costs will consider health care provided, numbers of admissions and days spent in hospital, and patient costs for out-of-pocket expenses associated with their condition (ie, travel expenses [of both the patient and caregiver], over-the-counter medicines and supplements, complementary therapies not supported by the health care system, home help, and time away from work).

Psychological and behavioral variables will also be measured as secondary end points. Intrinsic (mental and physical) capacity will be evaluated through the comprehensive geriatric assessment using standardized patient-reported outcome measures where applicable, sensors and wearables, and performance tests. More specifically, the following variables will be measured—(1) mobility and locomotion (distance, balance, and gait speed), (2) sensory ability (Snellen test and whisper test), and (3) vitality status (exercise, electrocardiogram, HR variability, grip strength, nutritional or energy state, sleep, and fatigue)—together with a complementary frailty screening (using the Geriatric 8 frailty screening tool, declared as the preferred tool by the International Society of Geriatric Oncology for identifying frailty in older patients with cancer, including patients with breast cancer) and frailty assessment (comorbidity, mental health, cognition, functional status, polypharmacy, geriatric syndromes, and socioeconomic and nutritional status). Other psychological and behavioral variables measured are psychocognitive status (personal traits, cognitive factors, and emotional states), social and socioeconomic factors, and general QoL, measured using standardized validated questionnaires to make comparisons with the more specific psychological and behavioral measures listed previously.

The following continuous variables will also be measured to identify predictive factors of disease trajectories and cardiac toxicity related to the objective of developing, refining, and validating the risk stratification model. Imaging markers of cardiac structural and functional variables will be measured using echocardiography, including LVEF percentage (Simpson biplane method [left ventricle end-diastolic volume and left ventricle end-systolic volume]), left ventricular diastolic dysfunction+left ventricular systolic dysfunction, interventricular septal end diastole, left ventricular posterior wall end diastole, fractional shortening percentage, mass index+relative wall thickness, tricuspid annular plane systolic excursion+S′ tricuspid annulus, left ventricular outflow tract velocity time integral+left ventricular outflow tract maximum velocity+aortic velocity time integral+aortic maximum velocity+aortic dimension, early to late diastolic transmitral flow velocity+medial early diastolic mitral annulus velocity +systolic-to-diastolic duration ratio, maximal tricuspid regurgitation velocity, right atrial pressure, left atrial volume index+right atrial volume index, global longitudinal strain (of both ventricles if possible), and myocardial work (global work index, global constructive work, global wasted work, and global work efficiency if available)+systolic and diastolic pressure. In addition, 2D echocardiographic sequences (grayscale images or videos of at least one representative full cardiac cycle) will be extracted as Digital Imaging and Communications in Medicine (DICOM) files for 3 different views (4 chambers, 3 chambers, and 2 chambers); independent 2D grayscale static images at end-diastole and end-systole frames will be extracted as DICOM files for each view; and corresponding manual annotations of the left ventricle (or left endocardium), left epicardium, and left atrium will be extracted from a subset of the aforementioned provided images.

Mammography DICOM images corresponding to the left mediolateral oblique view, right mediolateral oblique view, left craniocaudal view, and right craniocaudal view (conventional or tomosynthesis) will be obtained if the patient did not undergo mastectomy.

Other continuous variables that will be measured are whole-blood and plasma biomarkers, including biochemical (troponin I and brain natriuretic peptide), inflammatory and psychological (eg, if available, interleukin-6, tumor necrosis factor, HR variability, C-reactive protein, fibrinogen, and ferritin), and omics (single-nucleotide polymorphisms and extracellular vesicle micro-RNAs) biomarkers, and microbiome biomarkers from metagenomic analysis of stool samples (species diversity indexes; relative abundance at the family, genus, and species levels; and presence of pathogenic species).

Methods

Partners

The CARDIOCARE prospective study is multicentric and involves 6 European clinical partners: the IEO—the study clinical coordinator—in Italy, the BOCOC in Cyprus, the KSBC in Sweden, the UOI and NKUA in Greece, and the Institute of Oncology Ljubljana (IOL) in Slovenia. The work of these clinical centers, and especially the technological aspects of eHealth tool implementation, is supported by 5 European technical partners: the Foundation for Research and Technology, the Hellenic Mediterranean University, and the UOI, all based in Greece; Stremble, a research and development company based in Cyprus offering a range of advanced analytics, bioinformatics, and software engineering expertise; the European Society of Cardiology based in France; and the Philips Electronics Nederland B.V. company in the Netherlands. The Institute of Health Management in Italy is also part of the CARDIOCARE consortium, ensuring the highest level of study conduct and management quality.

Study Design

This multicenter clinical study has been designed as a prospective observational study that examines whether integrated patient-oriented psychological, behavioral, and functional interventions can prevent, delay, or mitigate cardiotoxicity as an adverse effect of cancer therapy. It will include 750 older patients with breast cancer recruited across the participating clinical centers.

All recruited patients will be randomly assigned to either the standard practice or enhanced monitoring group. Patients in both arms, in addition to standard oncological care, will receive eHealth monitoring through the Garmin Venu SQ and Polar

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H10 technologically advanced wearable devices (described in detail in the Instruments and Measures section) and will have access to the ePsycHeart assessment tool on the CARDIOCARE mobile app (described in detail in the Instruments and Measures section). Furthermore, patients will be given a Motorola smartphone on which the CARDIOCARE mobile app is installed. These technological instruments will provide clinicians with the patients' physical and psychological intrinsic capacity and QoL indicators as foreseen in the study protocol. However, only patients in the intervention arm will have access to the behavioral, psychological, functional, and educational interventions in the eHealtHeart section of the CARDIOCARE mobile app, which will allow researchers to evaluate the effectiveness of such eHealth interventions on the intrinsic capacity and QoL of older patients with breast cancer, as well as these interventions' effectiveness in mitigating, delaying, or even preventing the onset of cardiac toxicity associated with breast cancer treatments.

As per the protocol, before undertaking any study procedure, the patients will receive a patient information sheet, in which the different study procedures are explained in lay language. The same document also sets out the study's risks, benefits, and aims. Once the patient has read the patient information sheet and has received answers to any questions or concerns, she can choose to provide informed consent to participate in the study by signing the written informed consent form, of which she will be left with a copy, whereas the CARDIOCARE researchers will keep the original document.

Patients will be assigned through the study electronic case report form (eCRF) at baseline to the standard practice or enhanced monitoring group in a 1:1 ratio. The study time points, follow-ups, and specific procedures are detailed in the Study Time Points and Procedures section (Figure 1).

Figure 1. Study design. BNP: brain natriuretic peptide; FU: follow-up; PREM: patient-reported experience measure; PROM: patient-reported outcome measure; QoL: quality of life; SNP: single-nucleotide polymorphism.

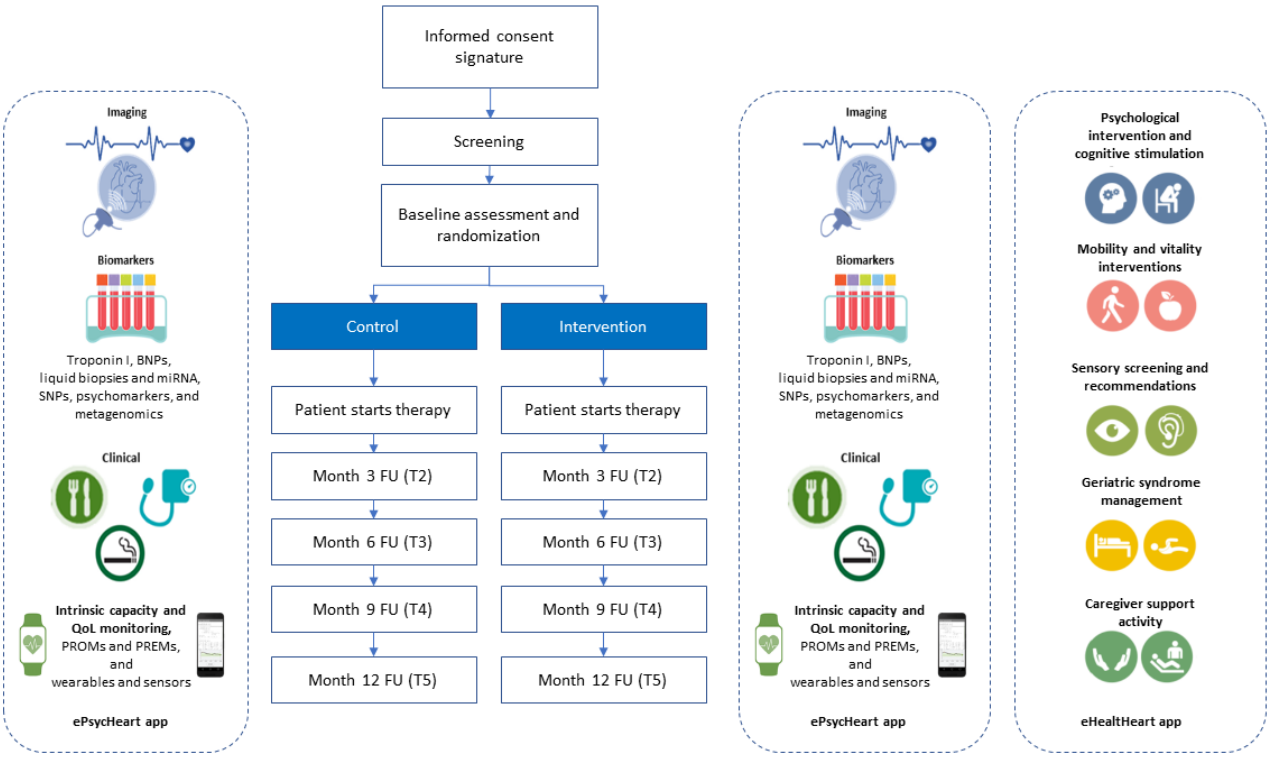

Great attention has been paid to the standardization of procedures among the clinical centers involved. Specifically, the inclusion criteria for the study are thoroughly detailed and are consistent across all 6 clinical centers involved in recruitment. This ensures that the same standards are followed at each site, allowing for a homogeneous participant selection process.

In addition, the technical partners involved in the study are responsible for continuously monitoring the data entered into the eCRF. They actively identify any values that may require further scrutiny or validation, ensuring the quality and integrity of the data.

Furthermore, the CARDIOCARE platform plays a crucial role in the standardization process. It provides real-time monitoring of whether patients are adhering to the prescribed activities according to the study protocol. If any discrepancies are detected, the clinical centers can contact their patients to address any issues, ensuring that all sites are aligned with the study protocol.

Therefore, while working across multiple centers presents certain challenges, the combination of detailed inclusion criteria, constant monitoring through eCRFs, and checks via the CARDIOCARE platform makes the process both feasible and practical. This multilayered approach allows for high levels of standardization and consistency across all sites.

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Potential sources of bias have been minimized as follows. Regarding recall bias, the same questions are asked in both groups, ensuring that the bias is homogeneous, and reminders are sent to patients to complete the questionnaire on time. Regarding selection bias, the inclusion criteria are stringent, and all suitable candidates are enrolled by the centers. Regarding confirmation bias, the primary end points and most secondary end points are quantitative, reducing the likelihood of interpretation errors. Regarding observation bias, some questions are repeated across questionnaires, and patients complete the same questionnaire 3 to 5 times during the study.

Study Participants

A total of 750 women aged ≥60 years with a diagnosis of breast cancer will be recruited across the 6 European clinical centers involved in the CARDIOCARE consortium in Italy, Greece, Cyprus, Sweden, and Slovenia (IEO: n=125, 16.7%; BOCOC: n=120, 16%; KSBC: n=125, 16.7%; UOI: n=60, 8%; NKUA: n=195, 26%; IOL: n=125, 16.7%). A subsample of 500 patients will be randomly selected (IEO: n=100, 20%; BOCOC: n=100, 20%; KSBC: n=80, 16%; NKUA: n=130, 26%; IOL: n=90, 18%) to allow Stremble to assess gut microbiome changes associated with oncological treatments. Details on the inclusion and exclusion criteria to recruit patients are provided in the Selection Criteria section.

Selection Criteria

Inclusion Criteria

The inclusion criteria are as follows: (1) women aged ≥60 years with a diagnosis of early or locoregional breast cancer who will undergo neoadjuvant or adjuvant treatment with regimens including anthracyclines or taxanes; (2) women aged ≥60 years with a diagnosis of human epidermal growth factor receptor 2 (HER2)–positive early or locoregional breast cancer who will undergo neoadjuvant or adjuvant treatment with anti-HER2 therapy (trastuzumab or trastuzumab and pertuzumab); (3) women aged ≥60 years with a diagnosis of early or locoregional breast cancer who will undergo neoadjuvant or adjuvant treatment with endocrine therapies with or without cyclin-dependent kinase 4 or 6 inhibitors; (4) women aged ≥60 years with HER2-positive metastatic breast cancer who will undergo first-line anti-HER2 therapy (trastuzumab or trastuzumab and pertuzumab with or without chemotherapy); (5) women aged ≥60 years before starting the aforementioned treatment for breast cancer; (6) eligible women aged ≥60 years who will undergo first-line therapy in the metastatic setting with any type of treatment (chemotherapy, immunotherapy, or biological agents); (7) willingness and ability to comply with scheduled visits, laboratory tests, and other trial procedures; (8) ability to understand the provided information and provide written informed consent; (9) affiliation to a social security system; and (10) life expectancy of at least 12 months.

Exclusion Criteria

The exclusion criteria are age of <60 years and a diagnosis of severe psychiatric or neurological disorders that might impair the ability to provide informed consent.

Study Time Points and Procedures

After the patient has signed the written informed consent form, she will follow the study procedures set for each time point, as shown in Table 2. Table 3 shows all self-administered scales that the patient has to complete for each study time point. These procedures are the same for both the standard practice and enhanced monitoring groups.

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Table 2. Summary of scheduled procedures.

Procedure	Day −15: T0 (screening)[a]	T1 (baseline)[a]	Day 0: treatment start	Month 3: T2	Month 6: T3	Month 9: T4	Month 12: T5	14-25 days after the end of treatment[b]
ICF[c] signature	✓							
Diagnosis	✓							
Personal and family medical history (including diagnosis of severe psychiatric disorders)	✓							
Smoking habits		✓						✓
Comorbidities	✓							
Oncological visit		✓			✓		✓	
Psychological visit[d] (if the center has a psychological support service)		✓		✓	✓	✓[e]	✓	
Cardiological visit (if needed)	✓	✓		✓	✓	✓[e]	✓	
BP[f] and HR[g] measurement		✓		✓	✓	✓[e]	✓	
Routine blood analysis (ie, hematology and biochemistry)[h]		✓		✓	✓	✓	✓	
Echocardiographic assessment[i]		✓		✓	✓	✓[e]	✓	
ECG[j] assessment		✓		✓	✓	✓[e]	✓	
Plasma troponin I level assessment	✓[k]	✓[k]		✓	✓	✓	✓	
Mammography (if the patient did not undergo mastectomy)		✓					✓	
Plasma BNP[l] assessment		✓		✓	✓	✓	✓	
Plasma myeloperoxidase and high-sensitivity CRP[m] assessment (if available)		✓		✓	✓	✓	✓	
Inclusion and exclusion criteria checklist	✓							
Blood sample for genetic analysis		✓						
Plasma sample for micro-RNA analysis		✓						✓
Stool sample		✓						✓
Oncological treatment (plan and changes) and cycle			✓	✓	✓	✓	✓	✓
Information on treatment status (ongoing or completed)				✓	✓	✓	✓	
Concomitant medications	✓	✓	✓	✓	✓	✓[e]	✓	✓
GSRS[n]		✓						✓
Patient lifestyle questionnaire		✓						✓
Verification of completion of self-administered scales and questionnaires (ePsycHeart section)[o]		✓	✓	✓	✓	✓	✓	
Cognitive effect assessment (if the center has specialized personnel)		✓			✓		✓	
Verification of collection of data from wearable devices				✓	✓			
Collection of information on patient's out-of-pocket expenses					✓		✓	

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Procedure	Day −15: T0 (screening)[a]	T1 (baseline)[a]	Day 0: treatment start	Month 3: T2	Month 6: T3	Month 9: T4	Month 12: T5	14-25 days after the end of treatment[b]
Hand grip test		✓			✓		✓	
AE[p] assessment		✓	✓	✓	✓	✓	✓	✓

[a]May be 1 or 2 visits.

[b]At the first visit after the end of each treatment, which should be within 14 to 25 days. The time of these sample collections will vary in relation to the therapeutic schedule of the patient.

[c]ICF: informed consent form.

[d]These visits can be conducted in person or remotely if the center can involve the required experts. The psychological visit consists of meeting the patient in person (if already at the clinical center) or remotely to touch base about the study—how they feel about it and whether they would like something to be different or modified. During the visit, a motivational intervention will also be carried out to minimize dropouts as much as possible.

[e]Only if possible.

[f]BP: blood pressure.

[g]HR: heart rate.

[h]Including cholesterols, glucose levels, and renal and liver function tests and interleukin-6, tumor necrosis factor, HR variability, C-reactive protein, fibrinogen, and ferritin if available.

[i]Including right and left ventricle dimensions and functions and diastolic function.

[j]ECG: electrocardiogram.

[k]Troponin can be analyzed either at screening or at baseline.

[l]BNP: brain natriuretic peptide.

[m]CRP: C-reactive protein.

[n]GSRS: Gastrointestinal Symptom Rating Scale.

[o]Table 3 provides a precise list of the questionnaires and scales administered at each time point.

[p]AE: adverse event.

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Table 3. Self-administered scales for each study time point.

Psychological or behavioral assessment	Day −15: T0[a]	T1 (baseline)[a]	Day 0: treatment start	Month 3: T2	Month 6: T3	Month 9: T4	Month 12: T5
Quality of life (EORTC[b] QLQ-30[c] and QLQ-BR23[d])		✓		✓	✓	✓	✓
Fatigue (FACIT[e]-Fatigue)		✓		✓	✓	✓	✓
Resilience (Brief Resilience Scale)		✓		✓			✓
Anxiety and depression (PHQ-4[f])		✓		✓	✓	✓	✓
Emotion regulation questionnaire (ERQ[g])		✓		✓			✓
LOT-R[h]		✓		✓			✓
Life satisfaction (single-item life satisfaction measure)		✓	✓	✓	✓	✓	✓
Perceived social support (MSPSS[i])		✓		✓			✓
Self-control and self-management (SCMS[j])		✓		✓			✓
Coping strategies (CBI-B[k])		✓		✓	✓	✓	✓
Post Traumatc Stress disorder (IES-R[l])		✓		✓			✓
Perceived Stress (PSS[m])		✓		✓	✓	✓	✓
Positive and negative affect (B-PANAS[n])		✓		✓			✓
Burden for family caregivers (BSFC-s[o])—optional		✓		✓	✓	✓	✓
Nutritional questionnaire		✓		✓			✓

[a]May be 1 or 2 visits.
[b]EORTC: European Organisation for Research and Treatment of Cancer.
[c]QLQ-30: Quality of Life Questionnaire.
[d]QLQ-BR23: Quality of Life Questionnaire–Breast Cancer.
[e]FACIT: Functional Assessment of Chronic Illness Therapy.
[f]PHQ-4: 4-item Patient Health Questionnaire.
[g]ERQ: Emotion Regulation Questionnaire.
[h]LOT-R: Life Orientation Test–Revised.
[i]MSPSS: Multidimensional Scale of Perceived Social Support.
[j]SCMS: Self-Control and Self-Management Scale.
[k]CBI-B: Cancer Behavior Inventory–Brief Version.
[l]IES-R: Impact of Event Scale–Revised.
[m]PSS: Perceived Stress Scale.
[n]B-PANAS: Brief Positive and Negative Affect Schedule,
[o]BSFC-s: short version of the Burden Scale for Family Caregivers.

Instruments and Measures

All recruited patients will receive additional supportive care in conjunction with standard care. Patients in the standard practice group and those in the enhanced behavioral and psychological monitoring group of the study will receive wearable devices and complete an initial evaluation on the CARDIOCARE mobile app.

The CARDIOCARE Mobile App

The CARDIOCARE mobile app is installed on the Motorola smartphone provided to patients, which they will have to return after use (end of month 6—T3). The CARDIOCARE app allows access to 2 different settings containing specific modules (described in this section) depending on the group—standard practice or enhanced behavioral and psychological monitoring—the patient is assigned to.

The Cognitive Stimulation, Education and Training, Vision and Hearing, and Psychology and Well-being (except for the Questionnaires submodule) modules will only be accessed by the intervention arm of the study.

The six modules are (1) Mobility and Vitality, (2) Cognitive Stimulation, (3) Education and Training, (4) Geriatric Syndrome Assessment, (5) Vision and Hearing, and (6) Psychology and Well-being.

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The Mobility and Vitality module contains 4 submodules, which are the nutrition questionnaire, physical activity, the cardio recording session, and the hand grip session. Together, these submodules will provide a collection of graphs—such as bar and pie charts—representing data on the patient's overall functional well-being, sleep duration, physical activities, and average HR, as well as proxies of the patient's stress levels.

The Cognitive Stimulation module includes 4 cognitive games, which are Find the Word, tic tac toe, Color Beans, and Drawing. If played consistently, such games can foster the patient's attention, concentration, and working memory capacities, thereby counteracting the cognitive impairment often found in patients undergoing oncological treatments [21].

The Education and Training module includes 2 submodules. The first one is Breast Cancer Material, which contains patient-oriented information related to breast cancer and cardiotoxicity and on the potential psychological and social implications that breast cancer and its treatment can have. This submodule provides a deeper awareness about the clinical implications of the disease and guidance for the patients to preserve their psychological well-being. The second submodule is named Training and contains a video tutorial for patients to improve their balance and reinforce their muscle strength.

The Geriatric Syndrome Assessment module includes 2 submodules. The first one is Incontinence Management, which will allow each patient to report urination incidents, perform guided exercises for pelvic floor strengthening, and set reminders for toilet use. The second one is the Fall Mitigation submodule, where the patient can access the Otago program, a set of exercises designed to help them enhance and restore their balance [22].

The Vision and Hearing module includes the Vision Test and Hearing Test submodules. The first is an assessment of the patient's vision capacity that was designed based on the Snellen test guidelines. The second one is an assessment of the patient's hearing capability designed based on the whisper test guidelines.

Finally, the Psychology and Well-being module includes behavioral and psychological interventions corresponding to 5 submodules: expressive writing, BPS, ABCDE (A=activating event or situation; B=beliefs; C=consequences; D=disputation of beliefs; E=effective new approach), Biofeedback Session, and Questionnaires. The interventions in the first 4 modules aim to mitigate the psychological risk factors associated with cardiotoxicity development and deterioration of the patient's QoL. The fifth submodule, Questionnaires, includes 15 self-reported measures that will provide critical information on the patient's levels of perceived stress, resilience, anxiety and depression, self-management and emotion regulation capacity, coping skills, perceived social support, satisfaction with life, QoL, and levels of optimism (see Table 3 for the list of questionnaires used).

Wearable Devices

The CARDIOCARE mobile app, described previously, will process data derived from 2 technologically advanced wearable devices: the Garmin Venu SQ watch and the Polar H10 sensor. The Garmin Venu SQ watch will collect data on the patient's HR (resting and high), body battery (percentage and charged or drained), stress (rest, low, medium, and high), intensity minutes (per week, for the current day, and goal), steps (for the current day and goal), calories (total for the current day, resting, and active), and respiration (breaths per minute, sleep average, and waking average). The Polar H10 sensor is a chest strap measuring highly detailed and accurate information about the patient's HR and electrocardiogram.

The patient is required to wear the Garmin Venu SQ watch for the first 6 months of the study and to wear the Polar H10 sensor for approximately 30 minutes every 2 weeks. At the end of month 6 of the study (T3), each patient must return the 2 wearable devices and the smartphone to their clinical center.

Patients will also be asked to use the hand grip dynamometer at T1 and T3 to assess their hand grip strength during their cardiological or oncological visit.

Statistical Procedure

Overview

The CARDIOCARE study proposes a comprehensive approach to measure the efficacy of the eHealth intervention by assessing its impact on 2 primary outcomes: intrinsic capacity and QoL in older patients with breast cancer. A prospective, multicentric study with 750 patients aged ≥60 years assigned to standard practice or enhanced behavioral and psychological monitoring groups will be conducted.

The enhanced behavioral and psychological monitoring group receives access to the eHealth psychological, behavioral, and functional modules on the CARDIOCARE mobile app. The primary measurements are intrinsic capacity, evaluated using physiological, physical, and cognitive parameters through wearable devices (Garmin Venu SQ watch and Polar H10 sensor) for the first 6 months, and QoL, measured through self-reported questionnaires integrated into the CARDIOCARE app covering aspects such as stress, resilience, and emotional regulation. Multimodal data, including clinical (cardiac imaging and biochemical markers), psychological (anxiety and depression scales), and behavioral data are analyzed to obtain a holistic understanding of the patient. The data are collected at baseline (T0) and every 3 months up to 12 months (T5).

This longitudinal approach captures changes over time. The intervention group undergoes targeted psychological, behavioral, and functional eHealth interventions. The comparison between the intervention and control groups will provide useful information on the interventions' impact on mitigating cardiotoxicity and improving QoL.

As of October 17, 2024, a total of 375 patients have been enrolled in the clinical study. For all these patients, data of different categories are collected and used in the training of the risk stratification model of cardiotoxicity and the prediction model of QoL. Once the model validation phase is complete, the results will be made available and presented in a subsequent publication.

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Statistical Considerations Regarding the Design

The primary statistical analysis will use an intention-to-treat approach. Therefore, all patients involved in the study will be included in the final analysis. Results will be presented using descriptive statistics (mean, SD, median, and range for continuous variables and proportions for nominal variables). Patient baseline characteristics will be compared using a 2-sample *t* test or a nonparametric test for continuous variables, and the Pearson chi-square test will be used for qualitative variables. All statistical analyses will be conducted using 2-tailed tests and adopting a 5% significance level. The effect of the interventions on the primary end point will be analyzed using the Cox proportional hazards model. Point estimates and 95% CIs will be calculated for the hazard ratio of the standard practice group versus the enhanced behavioral and psychological monitoring group. Any statistically significant difference between the 2 groups at baseline will be balanced by the multivariable adjustment. A logistic regression or Cox proportional hazards model will also be used to evaluate the effect of the interventions on the secondary end points in the 2 groups. Continuous variables such as those obtained from imaging and biochemical and molecular biomarkers will be summarized descriptively at baseline and follow-up visits. The differences between the 2 groups during the different follow-up visits will be evaluated using the analysis of covariance considering the corresponding baseline measurement as a covariant.

Finally, for the cost-effectiveness analysis, the health and QoL outcomes observed during the study will be used to calculate the QALYs. These QALYs will be combined with cost data in a cost-utility analysis to estimate the cost per QALYs associated with the implementation of the CARDIOCARE model and the eHealtHeart interventions. The incremental cost-effectiveness ratio will also be calculated to evaluate the CARDIOCARE model's effectiveness compared to current care practices. Therefore, the incremental cost-effectiveness ratio, which will be calculated using a threshold approach, will allow us to better understand how to distribute and allocate the different health care resources.

Sample Size Considerations

To identify the adequate sample size for the CARDIOCARE prospective study, a power analysis was conducted with 2-tailed α=.05 and 1 – β=.80. On the basis of this, and considering the 21% incidence of cardiotoxicity in our target population and the expected 10% dropout rate, it was estimated that a total of 736 patients (ie, 368 patients in the intervention arm and 368 patients in the control arm) would be large enough to detect a 40% relative risk reduction in the incidence of increased levels of troponin I (taken as a cardiotoxicity proxy) in this population. Such a sample size would also allow for the evaluation of the effectiveness of the behavioral and psychological interventions integrated into the study in mitigating, preventing, or delaying the onset of cardiotoxicity associated with oncological therapies for older patients with breast cancer.

The sample size calculation was followed by the Fisher exact test, conducted using the G*Power software (version 3.1.9.4). Considering our power analysis results and the number of patients affected by breast cancer each year, all clinical centers in the CARDIOCARE consortium agreed on the final recruitment goal of 750 patients (375 for the intervention arm and 375 for the control arm).

Data Collection, Storage, and Security

A well-defined data management plan has been submitted, providing detailed information on the procedures that will be implemented for data collection, storage, protection, retention, reuse, or destruction, complying with the General Data Protection Regulation.

By design, a robust data protection and security strategy will be implemented in all data collection and storage procedures in the CARDIOCARE platform. As part of the CARDIOCARE data management and high-performance computing, an eCRF—accessible by all clinical partners—has been developed to serve as the data entry tool for all patient data. eCRF data will be uploaded to and stored encrypted on the platform and systematically backed up in external redundant array of inexpensive disk drives. An audit log operation will be implemented to view the users' access history to the system, enabling the detection of any potential data security breaches. After final quality checks at the end of the prospective study, the eCRF will be frozen and exported to the technical partners for statistical analysis performance.

All members of the CARDIOCARE consortium will take appropriate organizational and technical measures to prevent any event of abuse, accidental loss, destruction, or damage of collected data, enabling the reinstatement of the system promptly if necessary.

Data quality, completeness, and integrity will be ensured through visits from the Independent Data Monitoring Committee members, who will certify, in each clinical center, the files' consistency, adherence to the study protocol and good clinical practice guidelines, the accuracy of the eCRF forms, and the compliance with safety reporting. Investigators of each clinical center will facilitate the Independent Data Monitoring Committee members' jobs by cooperating and enabling direct access to all data sources to be verified.

Strict confidentiality of all personal and study-related data is ensured. All recruiting centers will sign an agreement document detailing their commitment toward complying with the relevant laws, regulations, codes of practice, and obligations to publication.

Ethical Considerations

All involved clinical centers submitted the new version (1.2) of the CARDIOCARE prospective study protocol to their ethics committees and obtained official approval as follows: BOCOC on January 25, 2024 (approval EEBK/ETT/2022/58); KSBC on October 12, 2023 (approval 2023-0026201-413152); IEO on November 22, 2023 (approval R1754/22-IEO 1874); IOL on December 12, 2023 (approval ERIDEK-0038-2023); NKUA on November 24, 2023, for Aretaieion Hospital (approval 456/14-10-2022) and December 5, 2023, for Attikon Hospital (approval 683/22-11-2022); and UOI on November 23, 2023 (approval EBA683/22-11-2022).

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This multicentric prospective study has been designed to comply with national (ie, good clinical practice) and international (ie, the Declaration of Helsinki) regulations of proper ethical research involving human participants with written informed consent, which is obtained from all participating patients. Participants are clearly informed about the possibility to opt out of the study at any time. The collected data are anonymized and deidentified, ensuring the protection of privacy and confidentiality. No compensation is provided for participation in the study.

In particular, the study conduct is in line with the following regulations and norms: the Declaration of Helsinki ethical principles for medical research involving human participants, revised in October 2013; the Convention for the Protection of Human Rights and Dignity of the Human Being With Regard to the Application of Biology and Medicine: Convention on Human Rights and Biomedicine (Oviedo, 1997); the *International Ethical Guidelines for Biomedical Research Involving Human Subjects* by the Council for International Organizations of Medical Sciences in collaboration with the World Health Organization, revised in 2016; and the Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Biomedical and Behavioral Research (US Department of Health, Education, and Welfare publication [DHEW-05-78-0012], Washington, District of Columbia, 1978).

Results

The active phase of the recruitment process began in May 2023, and preliminary results will be published in a scientific journal and made available for consultation on the CARDIOCARE project website. Data analysis and dissemination of the study results will take place in 2025.

Patient recruitment started in May 2023, and by October 17, 2024, a total of 50% (375/750) of the target number of patients had been recruited (Table 4).

Table 4. Number of recruited patients in total and per clinical center.

Clinical center	Current number of patients in the study	Total target	Progress, %	Number of dropouts	Dropouts at each clinical center, %
BOCOC[a]	110	120	91.7	14	12.7
NKUA[b]	109	195	55.9	14	12.8
UOI[c]	42	60	70	6	14.3
IEO[d]	73	125	58.4	4	5.5
KSBC[e]	23	125	18.4	1	4.3
IOL[f]	19	125	15.2	4	21.1
Total	375	750	50	43	11.5

[a]BOCOC: Bank of Cyprus Oncology Centre.

[b]NKUA: National and Kapodistrian University of Athens.

[c]UOI: University of Ioannina.

[d]IEO: European Institute of Oncology.

[e]KSBC: Karolinska University Hospital.

[f]IOL: Institute of Oncology Ljubljana.

In October 2023, a new amended version of the protocol (version 1.2) was approved. In the face of emerging new evidence [23,24], an amendment was proposed regarding the definition of cardiotoxicity and inclusion criteria related to age and treatment. More specifically, the identification of cardiotoxicity also includes so-called MACEs, and the intrapatient assessment of MACEs, taxanes, and endocrine therapies with or without cyclin-dependent kinase 4 or 6 inhibitors were included among the inclusion criteria. In addition, the inclusion criterion of age decreased from ≥65 to ≥60 years.

Discussion

Expected Findings

The CARDIOCARE study is expected to demonstrate the feasibility and utility of a risk prediction model tailored to assess the likelihood of cardiotoxicity in older patients with breast cancer. It is hypothesized that this model, integrated with the CARDIOCARE mobile app and wearable technologies, will not only identify individuals at high risk more accurately but also provide actionable, personalized, and tailor-made interventions that help manage and mitigate risks associated with cardiotoxicity. In addition, the findings are anticipated to highlight the model's role in enhancing intrinsic capacity, QoL, and cost-effectiveness for both patients and health care systems.

The CARDIOCARE model is expected to bridge critical gaps in the early identification and management of cardiotoxicity, especially in older patients with breast cancer, a group at significant risk due to age-related factors, polypharmacy, and oncological treatments. The mobile app is designed to offer continuous, home-based care by promptly alerting patients and clinicians when health parameters are suboptimal. This facilitates timely interventions that can preserve intrinsic capacity, improve physical and psychological well-being, and enhance overall QoL. This study is also anticipated to underscore the potential for digital health tools to provide a

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more integrated and comprehensive picture of patient health compared to traditional electronic health records.

The CARDIOCARE risk prediction model for cardiac toxicity will allow health care providers to identify and monitor trajectories across the field of cardiotoxicity and, thus, advise and intervene promptly on patients at high risk while saving resources on those presenting a low risk of developing cardiotoxicity. The model will be particularly tailored to detect the risk of cardiotoxicity in older patients with breast cancer, whose risk of cardiovascular disease is almost the same as that of breast cancer relapse [23,25]. Furthermore, even when the cancer is not fatal, older women with breast cancer are especially prone to develop cardiac morbidity as a collateral effect of oncological treatments [26]. Indeed, in this clinical population, cancer treatment cardiotoxic effects are often added to baseline age-related factors and preexisting morbidity, leading to drug interaction complications resulting from polypharmacy [27,28], poorer health outcomes, and intrinsic capacity and QoL deterioration [29].

Considering the aforementioned factors, the CARDIOCARE mobile app, with its contents and health monitoring system, will provide older women with breast cancer with the opportunity to learn how to best manage their multimorbidity while preserving and enhancing their physical and psychological intrinsic capacity as well as their overall QoL, including their relationship with others. They will also benefit from the continuous and home-based care that the mobile app provides by notifying them promptly when one or more health parameters are suboptimal, and clinician-developed suggestions on how to intervene to improve such parameters will follow.

In addition, this study provides an opportunity to test the feasibility of digital tools (devices and mobile app) among this specific population of older patients (aged ≥60 years) and identify the possible areas that need improvement so that, in the future, these types of digital tools and interventions can be successfully applied to the specific segment of patients considered in this study.

Health care providers will also vastly benefit from the health monitoring and technologically advanced tools used in this prospective study. Such tools, including the mobile app, will provide clinicians with more integrated information on their patients' health than the information they can obtain through standard electronic health records. The CARDIOCARE mobile app and the wearable devices used in this study will, indeed, inform health care providers about several characteristics of their patients (psychological, behavioral, cognitive, and functional) that, based on the most updated scientific literature, are particularly relevant to determine the risk of older patients with breast cancer of developing cardiac toxicity when exposed to oncological therapy [6,30-32]. Furthermore, by being informed on their patients' intrinsic capacity (physical and psychological) and other QoL-related aspects, health care providers can more easily and quickly identify each patient's care gaps and specific needs and develop new and more integrated best practices, facilitating the implementation of personalized, patient-centered care.

The innovative CARDIOCARE model of care and its risk prediction model for cardiac toxicity hold promise from a socioeconomic perspective as well. It is to be underlined that almost 40% of public spending in the health care sector concerns people aged >60 years, with long-term care and hospital admissions being the primary cost drivers [33]. As health care systems that successfully provide effective community-based care and services are likely to significantly optimize their public spending [33], health care institutions and insurance companies are seeking new ways to decrease treatment costs for chronic diseases such as cancer.

Moreover, previous research has highlighted considerably higher mortality rates among patients with breast cancer of a low socioeconomic status (ie, education, employment, and income) compared to those whose socioeconomic status is higher [34,35]. This is a critical datum as socioeconomic disadvantage may result in later-stage diagnosis and poorer access to and quality of care. Using technologically advanced tools—provided to patients by the clinical centers—able to consistently monitor several health parameters beyond the time the patient stays at the clinical center, the CARDIOCARE health care model attempts to address the economic and societal challenges that afflict both our health care system finances and patients of a lower socioeconomic status. In addition, once the prospective study is concluded and the data are analyzed, a cost-effectiveness analysis will be conducted comparing the CARDIOCARE health care model to current practices.

Potential Limitations

This study's psychological and behavioral monitoring is based on the use of a mobile app and wearable sensors, which may be problematic for some older adult users who are not familiar with or proficient in the use of this type of technology. Assistance and training in the use of the technology are provided at the recruitment stage, but the continued engagement with the app over the study period and compliance with the use requirements could pose significant obstacles to data collection. To circumvent this problem, the implementation of the study protocol includes frequent interaction between clinical staff and participants, as well as encouraging the involvement of family members to assist in maintaining compliance with the study protocols. This may result in a bias introduced by the level of technological dexterity of the patient, support in this regard from family members, or willingness to initiate communication with and seek help from clinical staff.

In addition, as with all multicenter studies, the study protocol is strictly applied and monitored at each clinical center to maintain consistency between centers. All equipment (eg, mobile phones and wearables) is the same and is provided through the CARDIOCARE project. Assessments of cardiotoxicity and subclinical cardiotoxicity are performed by a consensus group of cardiologists from each clinical center using all the available blood tests, echocardiograms, and treatment and patient history data. However, differences between populations, cultures, and environmental factors will be considered in the analysis plan to minimize any inherent bias.

Finally, a potential limitation of this project concerns the fact that the study follow-up period is limited to 12 months from

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the enrollment date to encompass both acute and early (within the first year) cardiotoxicity, defined based on imaging and biological biomarkers. Late cardiotoxicity (occurring up to several years after treatment) is not considered in this study.

Conclusions

The CARDIOCARE prospective study will contribute to developing new best practice guidelines for managing older patients with breast cancer and multimorbidity while preserving their intrinsic capacity and improving their QoL. Furthermore, the CARDIOCARE mobile app and the wearable devices will enable clinicians to identify trajectories across the cardiotoxicity disease continuum, allowing for preventative interventions for patients at higher risk. This innovative health care approach will also benefit the health care system, which allocates nearly 40% of its resources to patients aged >60 years, with long-term care and hospital admissions being the primary cost drivers.

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Authors' Contributions

GGAS, KM, AC, AP, DM, MT, DR, DT, KK, AA, AB, EP, G Karanasiou, DC, CC, EM, DF, GC, and GP contributed to conceptualization. GGAS, KM, AC, AP, G Kalliatakis, MT, DT, KK, AA, G Karanasiou, and DF contributed to the design of the study. GGAS, KM, G Kalliatakis, MT, AA, FR, G Karanasiou, and DF contributed to the statistical and sample size considerations. GGAS, AC, AP, DM, DR, DT, VA, KK, OP, DC, CC, and EM contributed in conducting the investigation. AA, CB, GGAS, AC, AP, DM, DR, DT, VA, KK, OP, DC, and CC contributed in the provision of resources for the implementation of the study. G Karanasiou, DF, G Kalliatakis, MT, and FR contributed to data curation. GGAS, KM, AC, AP, DM, MT, DR, DT, KK, AA, G Karanasiou, DC, CC, EM, DF, GC, and GP contributed to the writing of the original draft. GGAS, KM, AC, AP, DT, KK, CB, FR, EP, G Karanasiou, DC, and CC contributed to the review and editing of the manuscript. GGAS, KM, G Karanasiou, and DF contributed to the supervision of the work. G Karanasiou, DF, KM, GP, and GC were in charge of project administration. Each author contributed to the manuscript in accordance with their listed roles. All coauthors have seen and agree with the contents of the manuscript.

Conflicts of Interest

GC is on the advisory board for Roche, Pfizer, AstraZeneca, Daichii Sankyo, Lilly, Novartis, Menarini, Gilead, and Exact Sciences. All other authors declare no conflicts of interest.

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Abbreviations

BOCOC: Bank of Cyprus Oncology Centre
BPS: best possible self
DICOM: Digital Imaging and Communications in Medicine
eCRF: electronic case report form
HER2: human epidermal growth factor receptor 2
HR: heart rate
IEO: European Institute of Oncology
IOL: Institute of Oncology Ljubljana
KSBC: Karolinska University Hospital
LVEF: left ventricular ejection fraction
MACE: major adverse cardiovascular event
NKUA: National and Kapodistrian University of Athens
QALY: quality-adjusted life year
QoL: quality of life
UOI: University of Ioannina

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Protocol

Patient-Centered Risk Prediction, Prevention, and Intervention Platform (TIMELY) to Support the Continuum of Care in Coronary Artery Disease Using eHealth and Artificial Intelligence: Protocol for a Randomized Controlled Trial

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Abstract

Background: Cardiac rehabilitation (CR) programs have shown promising results in tertiary prevention. However, achieving sustained behavioral changes remains a challenge.

Objective: The TIMELY project aims to develop and evaluate a personalized, artificial intelligence–driven eHealth platform and app to support sustainable behavior change during phase-3 CR, subsequently reducing cardiac risk scores.

Methods: An international, multicenter, randomized controlled trial will be conducted to evaluate the effectiveness of the TIMELY integrated platform and app. A total of 360 patients with cardiac conditions will be approached to participate in the study across Germany, Spain, and the Netherlands. Patients will be randomly assigned (1:1) to either the intervention group or the control group (care as usual). The intervention group will receive fully web-based, behavior change support through the TIMELY app, with personalized exercise prescription, chatbot assistance, and monitoring devices (eg, activity watch). Both groups will continue to receive care as usual, complete validated questionnaires, undergo physical tests, and provide blood samples. Assessments will be conducted at baseline and at 3, 6, and 12 months.

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Results: Trial recruitment has been finalized in July 2024. A total of 358 patients have been recruited and randomly assigned to the intervention (n=180, 50.1%) or care-as-usual (n=178, 49.7%) condition. As of January 2025, the 6-month follow-up has been completed for all participants. Follow-up data collection will be completed in May 2025. Results regarding the primary and secondary objectives are expected in September 2025.

Conclusions: This project will test a personalized platform and app, supported by artificial intelligence and designed to support health behavior change during phase-3 CR. It will target multiple health behaviors, with a primary focus on physical activity and fitness levels, using an integrated approach.

Trial Registration: ClinicalTrials.gov NCT05955625; https://clinicaltrials.gov/ct2/show/NCT05955625

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KEYWORDS

cardiovascular disease; cardiac rehabilitation; eHealth; lifestyle; physical activity; artificial intelligence; AI

Introduction

Background

Cardiovascular diseases are the leading cause of death worldwide, accounting for approximately 17 million deaths annually [1]. Improvements in cardiac treatment over the past decades have increased the number of people surviving cardiac events and living with cardiac disease. Consequently, cardiac disease management and tertiary prevention of adverse outcomes such as recurrent cardiac events or mortality have become increasingly important in clinical practice and patients' lives [2]. Cardiac rehabilitation (CR) programs play an important role in this risk factor management and have been demonstrated to improve patient outcomes effectively [3].

Cardiac Rehabilitation

The World Health Organization defines CR as "the sum of activities required to influence favorably the underlying cause of the disease, as well as to provide the best possible physical, mental, and social conditions, so that the patients may, by their own efforts, preserve or resume when lost as normal a place as possible in the community" [4]. CR is a guideline-recommended [5], multidisciplinary, multimodal tertiary prevention program consisting of modules that include exercise training, optimization of medical treatment and risk factor management, smoking cessation, heart-healthy dietary habits, risk factor education, and psychosocial counseling [6,7]. Phase 1 is the inpatient care that is characterized by the implementation of modern acute coronary revascularization techniques as well as the application of effective acute and long-term pharmacotherapy aiming at early mobilization of the patient after a cardiac event or surgery. This phase is followed by phase-2 CR, which typically addresses patient's personal risk factor modification by adopting a healthy lifestyle. This represents the most important challenge, often described as the intention-behavior gap. Changes achieved during phase 2 are aimed at being consolidated in phase-3 CR. Long-term maintenance of health behavior changes after CR (ie, during phase-3 CR) varies substantially in the level of support offered to patients [8]. In most countries, the availability of phase-3 CR support is limited because of reimbursement policies. When center-based support is offered, only a small subgroup of patients attends these sessions, often due to a lack of personalized guidance and logistical challenges such as time constraints and travel burden [9,10]. These patient- and health system–related barriers contribute to low adherence to and uptake of long-term rehabilitation and cardiovascular health maintenance programs despite their potential health benefits [11,12]. Therefore, it is of utmost importance to explore delivery modes for long-term CR maintenance that better align with the needs of both patients and healthcare providers, while addressing existing barriers.

eHealth in CR

Web-based care modalities for CR might be the way forward to address the challenges associated with "traditional" in-person CR. These modalities offer the opportunity to provide *personalized care* or support to patients at their convenience, while also being *scalable* and *cost-effective* [13-15]. Such an approach should include both a continuous risk analysis by monitoring multiple disease-related prognostic parameters as well as regular support and guidance for a cardiac healthy lifestyle. A recent meta-analysis by Heimer et al [16] demonstrated that eHealth-based, phase-3 CR is effective in increasing exercise capacity, improving quality of life, and decreasing blood pressure (BP). Another meta-analysis found that remote CR is associated with better behavioral, psychosocial, and health service use outcomes [13,17]. These findings suggest that technological innovations can help develop a continuum of care after initial center-based CR to sustain its benefits and improve health outcomes. Therefore, recent studies have focused on the development of behavioral interventions to support long-term CR maintenance [18-20].

Cardiac Healthy Behavior Change

Developing and maintaining a cardiac-healthy lifestyle is of utmost importance to improve prognosis and reduce mortality risk in people with cardiac disease. It has been demonstrated by multiple studies [21,22] and advocated by others [23,24] that health behaviors, and in particular physical activity, should be addressed to improve cardiac health. Changing health behavior is a challenging endeavor, and only few people succeed [25]. Particularly, patients who face complicated disease regimen or adjustment problems (psychological or psychosocial) due to their illness (such as coronary artery disease [CAD]) may experience health behavior change as burdensome. This is also reflected by the typically temporary nature of the changes in

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health behavior that do not persist in the long term [26]. To promote sustainable behavior change, the application of behavior change techniques (BCTs) has been advocated [27]. The current literature indicates that a variety of BCTs may be implemented in CR programs to enhance their effectiveness. The TIMELY consortium conducted 2 studies that guided the development of the TIMELY intervention, 1 focusing on the patient perspective (qualitative) [28] and 1 evaluating existing literature through a systematic review [29]. Triangulating the findings from the studies revealed that specific BCTs can be successfully implemented to improve health behavior and clinical outcomes when they align with patients' preferences and are optimally matched with target behaviors.

TIMELY

To overcome current barriers related to phase-3 CR programs, the TIMELY trial aims to evaluate the cost-effectiveness of a personalized eHealth platform and health behavior change app for patients with CAD. This platform and app will provide support for health behavior change (eg, artificial intelligence [AI]–supported personalized exercise prescription [EP]) and facilitate disease-related self-management based on current clinical guidelines and in accordance with patients' individual needs. The TIMELY intervention will integrate (through the TIMELY platform) demographic, clinical, and psychosocial data to assess cardiac risk and support patients in maintaining and improving health behaviors via app-based feedback and prompts. Therefore, the TIMELY intervention is designed to preserve the benefits of CR and reduce cardiac risk in patients with CAD. At the same time, this approach reduces the burden on health care providers and the health care system. The TIMELY intervention is the first intervention for patients with CAD to support its users with physical activity and stress management through a chatbot function, and to offer a personalized weekly EP that is adapted based on exercise parameters collected throughout the week [30]. Previous interventions using increasing exercise goals based the goals on single parameters such as baseline activity levels or heart rate reserve, whereas the EP in the TIMELY intervention is based on several medical, demographic, and behavioral parameters [31,32]. Figure 1 shows a graphic outline of the TIMELY approach. It is hypothesized that participants who follow the TIMELY intervention, as compared to care as usual, will have a lower 10-year cardiac risk mortality and improved physical fitness over time. In addition, they are expected to have better physical and mental well-being and quality of life.

Figure 1. The TIMELY approach. AI: artificial intelligence; BCT: behavior change technique; CR: cardiac rehabilitation.

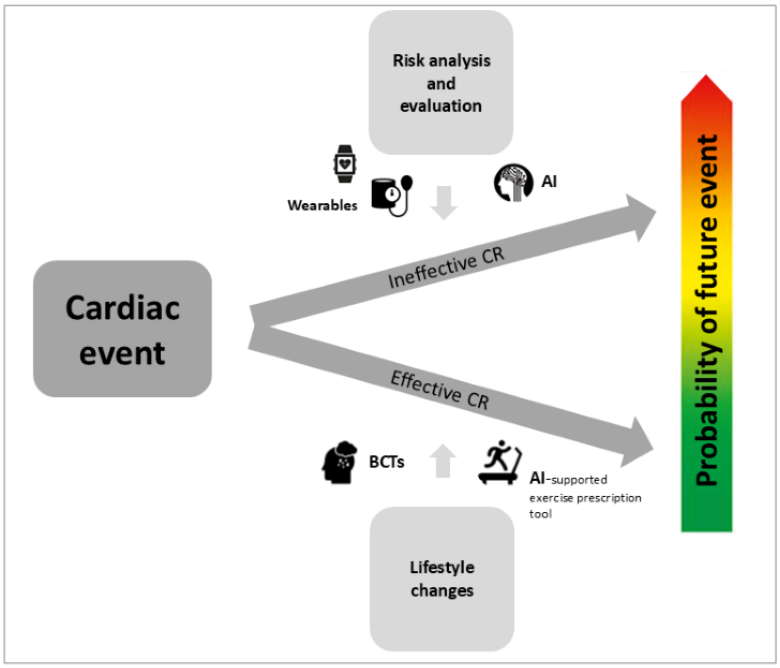

Methods

Design

The TIMELY study is an international (Germany, Spain, and the Netherlands), multicenter, randomized controlled trial. Patients randomly assigned to the intervention condition will receive a 6-month, app-based, personalized behavior change intervention. Assessments will be performed at baseline and at 3, 6, and 12 months.

Ethical Considerations

The TIMELY trial has been registered at ClinicalTrials.gov (NCT05955625) and has been approved by the Medical Ethics Committee (METC-Brabant NL82723.028.22/P2251 Tilburg, protocol V9 24-05-2023, the Netherlands). Local approvals from the participating centers (Germany: Z-125/2023; Spain: CEIm-G 2023/119) have been obtained. Data collection was initiated after receiving a signed informed consent from the participants. Participants have the option to opt out at any time—before, during, or after data collection—in which case their data will be deleted. Data will be pseudonymized, and only

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the research team from each center will have access to the key list for their center. A data sharing agreement between the participating centers has been signed for sharing pseudonymized data for data analysis purposes. Informed consent covers secondary analysis without additional consent. Participants were not reimbursed for participation except for study-related expenses (eg, parking costs).

Monitoring

Tilburg University has been appointed as the trial sponsor and will perform regular monitoring of the trial. This includes 2 visits (midterm and closing-out) to the clinical centers in Germany and Spain. During this visit, the investigator site file will be reviewed, and random checks of 20% of the participants regarding clinical data and questionnaires will be performed. Informed consent forms will be checked for all participants. In the Netherlands, the monitoring visits will be performed by an independent researcher from Tilburg University who is not affiliated with the TIMELY trial.

Throughout the study period, monitoring of serious adverse events will be performed per center. If serious adverse events are reported by patients or discovered in the patient record, this will be reported to the sponsor, who will register the events within 1 week at the Dutch Central Committee on Research Involving Human Subjects. The events will also be registered at the German Federal Institute for Drugs and Medical Devices.

Dissemination Policy

The results of the TIMELY trial will be disseminated in academic and health care settings through scientific publications, symposia, and conference visits. Study participants will be informed about the results via a newsletter containing the highlights of the study outcomes. To reach a broader audience, local newspapers will be contacted to disseminate the results among the general public.

Study Population

Women and men diagnosed with CAD will be included in the study. The following eligibility criteria have been defined:

- Inclusion criteria: (1) aged ≥18 years (there is no a priori upper age limit); (2) documented stable CAD and referred for CR (at >2 weeks but <10 weeks after percutaneous coronary intervention or >4 weeks but <12 weeks after coronary artery bypass grafting or myocardial infarction: with or without ST-segment elevation), or having documented CAD by coronary angiography (stenosis in a major coronary artery >50%); (3) access and ability to operate a smartphone; and (4) proficiency in the native language of the country (ie, German, Spanish, and Dutch).
- Exclusion criteria: (1) unable to fully understand the provided study information and consequences of participating in the study; (2) presence of an impairment interfering with the use of the app or devices (eg, blindness and wheelchair bound); (3) known diagnosis of an active malignant tumor (cancer) or any other medical condition associated with a life expectancy of <1 year; (4) cardiovascular, cerebrovascular, or other unstable medical condition; (5) having a pacemaker or life vest; and (6) refusal to provide informed consent. If any of the exclusion criteria emerge during the 1-year duration of the project, participants will be withdrawn from the study.

Sample Size

A total of 360 patients will be enrolled across 3 participating centers: Hospital Universitario de Santiago de Compostela, Spain (120/360, 33.3%); Clinic Königsfeld of the German Pension Fund at the University of Witten/Herdecke, Ennepetal, Germany (120/360, 33.3%); and Elisabeth-TweeSteden Hospital, Tilburg, the Netherlands (120/360, 33.3%). At each center, patients will be randomly assigned, with 60 (50%) out of 120 receiving the intervention in addition to care as usual, and 60 (50%) receiving care as usual. Of 360 patients, 180 (50%) will receive the intervention, and 180 (50%) patients will receive care as usual.

On the basis of participation rates in previous randomized controlled trials [33], it is expected that approximately 33% of patients will decline participation. It is expected that a total of 480 patients will have to be approached to include 360 participants across the 3 study sites. Sample size calculations were based on medium-large effect sizes and statistical power analyses were conducted using G*Power (version 3.1.9.4; Heinrich-Heine-Universität Düsseldorf) [34]. A sample of 120 patients per center will enable detection of a medium effect size. The f^2 for the between-within group interaction is 0.15 in a mixed model ANOVA, with a power of 0.80 and a two-sided α level of 0.025 (0.05/2, as two primary outcomes will be evaluated; details are provided in the *Study Objective* section). In brief, the set of variables for this analysis was based on a 2 (between-group: intervention vs control)×2 (repeated measures at baseline and 6 months) mixed model ANOVA, assuming sphericity and a correlation of 0.3 between the repeated measures.

Randomization and Blinding

Participants will be randomly assigned (1:1) to either the intervention group or the care-as-usual group. A computer-generated randomization sequence will be delivered, in an Excel (Microsoft Corp) file, to each recruitment site and will be concealed by one of the researchers by covering the allocation numbers with “black paint.” Randomization will be conducted and dated, per patient, by the researcher after the participant has signed the informed consent and baseline assessments have been performed.

Given the nature of the study, blinding of the researchers or participants during the behavioral intervention trial is not possible. However, the analysis of blood samples and all other outcome measures will be conducted by research team members who are blinded to the participants’ group assignment.

Study Procedure

Approximately 2 weeks before completing CR, patients who have started the program will be approached by a research assistant for participation after eligibility (inclusion and exclusion criteria) has been checked by the local primary researcher or clinician. Patients who are eligible for CR but decide not to take part in the program will be approached after

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the research assistant is notified of patients' participation status. If a patient expresses interest in participating, study information will be provided both verbally and in writing (patient information letter including the informed consent form).

For patients who consent to participate in the study, the baseline assessment includes physical exercise and functional tests, body composition analysis, blood draws (Multimedia Appendix 1), and completion of validated (web-based) questionnaires. Clinical data will be provided by the patient through an inquiry of selected data from the patient's medical record. At 3 months, all participants will receive an online link to fill in a set of validated questionnaires to evaluate potential early changes that occur during the intervention. At 6 months, participants will be invited to the hospital to return the study devices (refer to the *Study Procedure* section) and undergo the second physical exercise testing, blood sampling, and questionnaire assessment (online). At 12 months, patients will be invited for the final hospital visit during which the same assessments as obtained at the 6-month follow-up will be performed. For patients who do not fill in the questionnaires within a given period of 10 days, up to 3 reminder phone calls will be made by the researcher.

Study Objectives

Overview

The overall aim of the TIMELY study is to reduce the cardiac risk score through personalized health behavior change. The main focus is on the improvement of physical activity levels. All components of the TIMELY program should result in a reduction in the risk of recurrent cardiac events. All primary and secondary outcomes will be obtained at baseline; 6 months (the main outcome time point); and 12 months (long-term follow-up).

Primary Objectives

The primary objective of the TIMELY study is to investigate whether the TIMELY intervention is superior to usual care in terms of the following:

- Reducing the risk of 10-year mortality assessed by a validated biomarker risk score (CoroPredict, primary biomedical outcome) from baseline to 6 months. The Coropredict score assesses cardiovascular risk using a combination of laboratory-based parameters (including hemoglobin A_{1c}, N-terminal pro-B-type natriuretic peptide, high-sensitivity troponin I, cystatin C, and high-sensitivity C-reactive protein) and demographic information (age, sex, and smoking status) [35].
- Increasing the 6-minute walking test distance (primary behavioral outcome indicating functional fitness level) from baseline to 6 months.

Secondary Outcomes and Secondary Objectives

Improvements in the primary outcomes are expected to be associated with improvements in the following secondary outcomes:

- Increase in physical activity: physical activity levels during daily life will be assessed using the International Physical Activity Questionnaire [36].
- Increase in cardiovascular exercise tolerance: measures of cardiovascular responses to exercise will be based on graded symptom-limited exercise tests, using maximum watt (watt/kg body weight) as the outcome.
- Healthy dietary habits: dietary habits will be assessed using the dietary questions from the validated Health Promoting Lifestyle Profiles-II questionnaire [37].
- Decrease in body weight: body weight will be measured in kilograms.
- Smoking cessation: smoking cessation will be assessed by the validated Fagerström questionnaire [38].
- Better medication adherence: medication adherence will be assessed using the validated Medication Adherence Report Scale questionnaire [39].
- Decrease in psychological stress levels: changes in psychological stress levels will be assessed using the Perceived Stress Scale [40].

The secondary objectives of the TIMELY project will be assessed using questionnaire data obtained at baseline and at 3, 6, and 12 months:

- To investigate whether the TIMELY intervention is superior to care as usual in terms of improvement in physical and mental well-being and quality of life.
- To investigate the feasibility and usability of the TIMELY intervention.
- To investigate whether the TIMELY intervention is superior to care as usual in terms of cost-effectiveness.

TIMELY Intervention

Development

The TIMELY intervention, including all technical components (dashboard, app, and monitoring devices), was co-designed with input from patients and health care professionals (eg, cardiologists, cardiovascular nurses, and therapists). A living laboratory approach was followed to collect detailed insights into patients' needs and expectations on functionalities and app design. For a detailed description of the input provided by patients, refer to Douma et al [28] and Schmitz et al [41]. Furthermore, an extensive systematic review was conducted [29], which indicated that self-monitoring of behavior, prompts or cues, instructions on how to perform the behavior, goal setting, and social support were most likely to result in change in physical activity. In addition, the findings showed that providing prompts or cues as part of behavior change was unlikely to stimulate smoking cessation in patients with CAD and the intervention was adapted accordingly. The BCTs that were identified from focus groups and the systematic review were included in the TIMELY app throughout the functionalities of the app (chatbot, information provision, and monitoring).

Monitoring of Physical Activity, Hemodynamics, and Electrocardiogram During Daily Life Activities

All patients randomly assigned to the intervention group will be equipped with an activity tracker (Vivosmart 4, Garmin), an upper-arm BP monitor (Tel-O-Graph BT, IEM), and a 3-channel Holter monitor (netECG, livetec). Data from the activity tracker will be collected via Bluetooth on the patients' smartphone and transmitted directly to the TIMELY-Net server (Semdatex)

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using an application programming interface provided by FitRockr to comply with European data protection regulations. The BP monitor will be placed in the patient's home, together with a data transmission hub (eConnect, IEM), which allows secured mobile transmission of data (GSM standard) via the IEM gateway to the TIMELY-Net server. Collected data are then displayed in the TIMELY dashboard for case managers and made available to patients via the TIMELY app on their mobile phones, which can be downloaded from the app store for Android and iOS devices (see below for a detailed description of the TIMELY app).

Electrocardiogram (ECG) monitor data will be analyzed retrospectively after the trial. In brief, data will be downloaded from the ECG device at each participating center and uploaded to the TIMELY platform. The data will then be analyzed by ECG specialists at the participating partner institution, TU Dresden, using deep learning technology as described elsewhere [42]. Clinicians at the 3 centers will be involved to verify incidental findings of ECG abnormalities.

TIMELY Platform and Infrastructure

Data obtained from the monitoring devices and via the TIMELY app (patient-reported outcome measures [PROMs]) will be processed on the integrative TIMELY platform (Figure 2). The platform allows the assignment of devices to registered patients and provides insights into patients' functioning and progress to designated case managers. The platform was designed to ensure that no personally identifiable data are transmitted over the internet. Specifically, services are executed on the same server cluster to significantly reduce the number of off-site accessible application programming interface end points. These end points are protected by up-to-date authentication methods (OpenID-Connect) and are encrypted in transit using Transport Layer Security. Personal identifiable data are also encrypted in the database. The clinician dashboard is implemented as a separate plug-in in a certified medical office software (inSuite, Doc Cirrus) hosted on a private cloud (which is a type of cloud computing environment that is dedicated to a single organization that offers CR with TIMELY) in the same local network as the other services of the TIMELY-Net platform. The platform follows a microservice approach to implement different services and functionalities, including the following:

- Information from and to patients via the TIMELY mobile app (including messaging)
- Clinicians' dashboard enabling case managers to assess structured patient data, definition of thresholds, and connected tasks or alerts as well as decision support systems (DSSs)
- Service to analyze 24-hour ECG data and detect cardiac arrhythmias such as atrial fibrillation (atrial fibrillation–detection)
- A chatbot to guide behavioral change
- Ecological momentary assessment service for assessment of PROMs via the mobile app
- EP DSS
- Risk prediction service to predict 10-year mortality risk in cardiovascular diseases (described in detail elsewhere) [43]

Figure 2. TIMELY-Net infrastructure. AES: Advanced Encryption Standard; AF: atrial fibrillation; AI: artificial intelligence; DSS: decision support system; EMA: ecological momentary assessment; PROM: patient-reported outcome measure; SSL: Secure Sockets Layer; TLS: Transport Layer Security.

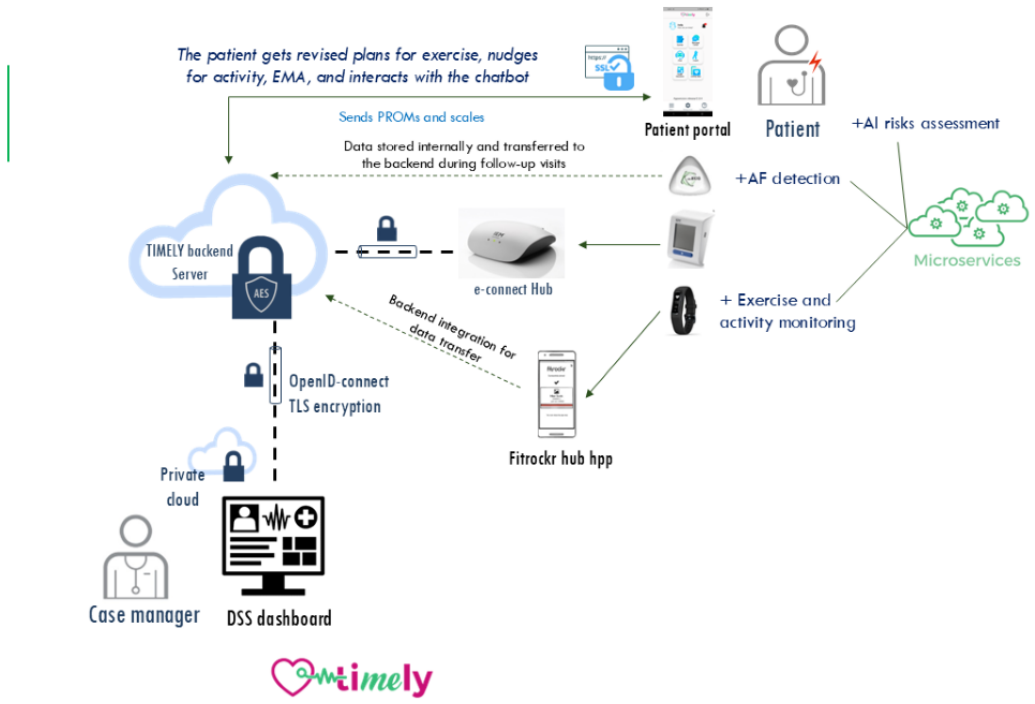

AI and Machine Learning

Demographic patient information and clinical data, including the ECG and exercise capacity results from the preceding clinic-based rehabilitation sessions, are entered into the risk profile database that is subsequently integrated and accessible to care providers and case managers via the TIMELY platform. Using machine learning–based algorithms, an optimal

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personalized exercise schedule is then developed and shared with the participants via the app (see below for details about the app). These exercise schedules are also adapted to the participant's (changes in) actual activity levels over the past week to personalize the patient's exercise levels during daily life activities.

AI is a key component of the TIMELY project as AI will support the modular, collaborative eHealth platform. AI is primarily directed toward the prediction of cardiac risk and complications. In addition, the targeted behavioral change interventions are designed to improve patients' self-care and empowerment. AI will be primarily used to optimize risk prediction based on patients' clinical and demographic background factors that will be integrated with the participants' responses to the TIMELY eHealth intervention. The chatbot-based patient prompts will use preset and validated phrases, but not directly involve AI-based text, as this would create unpredictability of conversation content, which might be undesirable in patients with CAD. Thus, TIMELY involves a combination of AI-based risk prediction with patient-tailored personalized behavioral prompts via the chatbot. This approach will optimize long-term clinical care and secondary CAD prevention.

Clinical Dashboard

Information provided in the dashboard includes systolic and diastolic BP, heart rate, step count, floors climbed, calories burned, physical activities (type of activity, duration, and activity calories), sleep duration, and stress levels. Data can be displayed per day or as an average per week, or month. By setting alert thresholds on critical values such as missing data (ie, no data transmitted within 7 days), reported symptoms, or detected BP deviations, tasks are automatically generated with an indication of severity: high, medium, and low. These tasks help guide case managers in informing patients about changes in their health status that may require attention.

TIMELY App

The TIMELY app (available for Android and IOS devices) was developed following a simplistic design approach and serves two central purposes: (1) collecting self-report data or PROMs and (2) providing personalized information (from wearable or monitoring data) and advice regarding health behavior change (Figure 3). To achieve these goals, the app provides seven functionalities: (1) messaging function for nudging and information; (2) ecological momentary assessment diary assessment of symptoms, perceived stress, sleep quality, affective states, social behavior, motivation, and goal setting; (3) lifestyle and health information; (4) chatbot interaction guided by specific counseling techniques and methods; (5) weekly EP; (6) documentation and visualization of physical activity and vital signs; and (7) documentation and visualization of BP. The app was freely available for study participants and could be used by participants at their own time and pace.

The functionalities provided by the app (in combination with the microservices run on TIMELY-Net) are detailed in Textbox 1.

Figure 3. TIMELY app functionalities (screenshot).

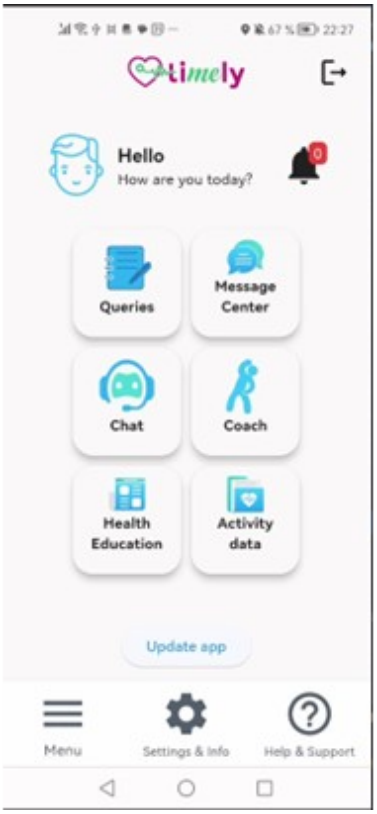

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Textbox 1. Functionalities of the TIMELY app.

- *Messaging function ("message center")*: Patients can receive messages (push notifications), which are either sent manually by the case managers (technical feedback on the system, available updates, and instructions) or automatically generated messages. Automatic messages include information on available queries, feedback on achieved goals, and activity nudges. The activity nudges have a reminder function combined with health information and are generated from a large list of different messages to avoid redundancies. Nudging is integrated with weather information to suggest activity options—for example, "It's warm and sunny today, perfect for exercising outside"—and to help overcome barriers, such as "It's rainy today, but you can still enjoy a healthy indoor workout." Moreover, geolocation nudging is used (based on GPS) to inform about the option to be physically active ("you are near a park, a good opportunity for a walk").
- *Self-report assessments ("queries") using ecological momentary assessment (EMA) diaries*: EMA (ie, brief diary-like questionnaires or "queries") will be used for daily assessments of psychological and physical functioning and goal setting. This feature includes behavior change techniques (BCTs) such as self-monitoring of symptoms, perceived stress, sleep quality, mood states, health-related behaviors, and prompts or cues to provide responses.
- *Lifestyle and health information ("health education")*: The app provides guideline-based information regarding cardiac health behaviors, benefits of regular physical exercise, and instructions on how to perform exercise (pictures and sample videos), medication, heart-healthy diet, stress management, smoking cessation, and risk factors selected by health care professionals (cardiologists, psychologists, and physical exercise specialists) using simple language. This section also provides web links to additional information provided by different societies and patient organizations. Several BCTs are part of this functionality, including *instructions on how to perform the behavior, information about health consequences, and demonstration of behaviors.*
- *Chatbot interaction ("chat")*: The TIMELY app includes a conversational agent that uses user context and artificial intelligence (AI)–based cardiovascular disease risk prediction information, referred to here as the "chatbot." Suggestions from the chatbot are based on domain knowledge of behavioral intervention theories and related BCTs [44]. The chatbot primarily focuses on improving physical activity levels and overcoming potential barriers such as fatigue, psychological stress, or the patient's environmental setting that interferes with or facilitates physical activity [45]. The chatbot also assists patients with planning health behaviors and identifying unhelpful behaviors and cognitions, including training modules to mitigate them based on cognitive behavioral interventions and motivational interviewing.
- *Exercise prescription (EP; "coach")*: During the intervention phase, patients will receive a personalized, guideline-based EP with weekly updates. The EP is generated automatically using a decision support system (DSS) for case managers developed as part of the TIMELY project. The design, functionality, and validation of the tool will be described in detail elsewhere. In brief, the rule-based tool was developed in accordance with the European Society of Cardiology Guidelines on EP [46] and follows the frequency, intensity, time, and type of exercise approach. It is composed of 2 integral functionalities: the permissibility report and EP. The patient's medical history and current exercise-related status inform the EP module, and information on sports to avoid or suitable sports disciplines and cautionary information to minimize the risk of injury or exercise-related cardiovascular problems are provided. The EP functionality suggests an initial exercise program and weekly progressions, relying on an algorithm crafted from best practices found in the clinical guidelines for exercise progression [47]. For initial exercise programs, the EP considers the fitness level of the patient after the phase-2 cardiac rehabilitation (CR), while for progressions, it factors success in achieving the caloric goals (metabolic equivalents, determined using the activity tracker based on heart rate) established in the previous week's program and any reported symptoms. This approach ensures that the exercise regimen remains tailored to the individual's needs and goals, promoting personalized exercise recommendations. Performed exercise sessions with duration and activity calories (as percent of the weekly goal) are provided. The EP incorporates the BCT of *action planning, instructions on how to perform the behavior, and biofeedback.*
- *Goal setting and physical activity monitoring ("activity data")*: Goal setting is a shared decision between the patient and case managers at the start. During the intervention, new goals are set by the case manager after receiving input from DSS. Patients are instructed to wear the activity tracker daily for 24 hours and wearing time (in percent) will be used (among other criteria) to define adherence to the program. Data on steps taken, physical exercise sessions performed (type, duration, activity calories, and percent of caloric goal), caloric expenditure, floors climbed, and heart rate are provided per day using simple, noncomplicated graphs. Data from previous weeks are provided for comparison and progress indication. For steps, a daily step goal is indicated in the graph. The step goal is discussed and defined with the patient during onboarding. Patients are informed about achievements via automated messaging weekly and can adjust the step goal if indicated using the diary function. This section of the app also provides feedback on set goals (eg, daily step goal) and goal achievement. The BCTs that are included in this feature are *biofeedback and feedback on outcomes of behavior.*
- *Blood pressure (BP)*: Patients can review their current and past BP data via the app and will be instructed to use the BP monitor at the same time every day. Similar to physical activity monitoring, feedback on BP data is incorporated into this feature.

The chatbot uses predefined scripts that have been previously validated [45] and translated into German, Dutch, and Spanish by native speakers.

In addition, a support function providing technical help and troubleshooting, including written instructions and videos, is available in the app.

The Role of the TIMELY Case Manager

In alignment with a realistic health care setting, case managers (rehabilitation nurses and health care assistants) will provide technological and app-specific support during the study. During the inclusion period, patients are onboarded by the case manager, which includes giving access to the app and related monitoring devices and ensuring that participants understand the study requirements and all provided functionalities. The case manager sets the first weekly step goal together with the patient, and the patient agrees to the first EP (shared decision-making). Within the first week after inclusion, the case manager will contact the participants to verify proper installation of the app and monitoring devices, ensuring data collection integrity. Participants will have the opportunity to ask questions about the device functionality. During the intervention period (6-month follow-up), patients will be contacted monthly to ensure intervention delivery and resolve any unforeseen technical difficulties. These follow-up calls are strictly for technical support and continued engagement, with no behavior change

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support provided. The case manager's actions are guided by a comprehensive handbook that includes protocols for missing data transitions and threshold violations.

For safety reasons, the case manager reviews new EPs generated by the EP DSS every Monday, before the EP is sent to the patient's phone. The DSS has been developed to assist case managers in their daily work, primarily focusing on the identification of patients with deviating variables who require further assistance. The EP tool was designed to prescribe exercise to patients based on the medical guidelines, individual clinical profile, and personal needs. The tool allows for weekly adjustments based on the patient's progress. EP additionally requires information on the previous (past week) exercise program, feedback on program execution (including metabolic equivalents achieved and reported symptoms), and patient preferences (if any) on which exercise parameters to increase or decrease (endurance or resistance, intensity, number of sets, and frequency). On the basis of these parameters, a prescription is produced. This DSS helps case managers in prescribing safe, well-informed, and patient-centered exercises. Depending on the task category, case managers can use various modes to contact patients. This includes sending (prewritten) messages via the app to guarantee data availability ("please wear your activity tracker regularly") or calling the patient for safety reasons in case of an incidental finding (eg, BP deviations less than or greater than preset limits). Patients can also request a phone call with the case manager if they experience any technical problems or have questions about the app or monitoring devices.

Care as Usual

Participants randomly assigned to the care-as-usual group will receive standard care without any restrictions and will be allowed to seek additional care or assistance for lifestyle changes if needed. Participants in the control group will be asked to fill in questionnaires and undergo the same assessments as the intervention group.

Statistical Analysis

For descriptive statistics, categorical variables will be compared with the χ^2 test (Fisher exact test when appropriate). Continuous variables will be compared using independent sample *t* test or a nonparametric test where appropriate.

To address the main hypothesis, repeated measures ANOVA using generalized linear mixed modeling analysis will be used to investigate the effect of the intervention on changes from baseline to 6 months for the 2 primary end points (Coropredict score and a 6-minute walk test) using a 2 (intervention vs control)×2 (baseline to 6 months) design, accounting for potential baseline differences and correlations between baseline and 6 months assessments. Data for the primary outcomes will be analyzed according to the intention-to-treat principle.

For the secondary outcome measures, a similar approach will be used. To explore long-term effects at 12 months, 2 (group)×3 (repeated measure) mixed models will be used. In addition, univariable and multivariable regression analyses (both linear and logistic regression) will be used to examine cross-sectional and longitudinal associations between variables, with the type of regression analysis depending on the distribution characteristics of the variables.

Exploratory analyses will also include completer analyses and evaluation of trial adherence as related to the outcome measures. As this study includes multiple secondary outcome measures without correction for statistical type 1 error, the obtained results will be interpreted with caution and will primarily provide estimates of effect sizes related to the TIMELY intervention. Data will be analyzed using SPSS statistics (IBM Corp) [48] or equivalent.

Results

A total of 809 patients were approached for participation. A subgroup (n=451) was excluded for not meeting the inclusion criteria or declined participation for various reasons (eg, travel burden to the hospital or perceiving the intervention as too demanding). Finally, a total of 358 patients were randomly assigned to either the intervention (n=180, 50.1%) or the care-as-usual (n=178, 49.7%) condition. In Figure 4, a schematic representation of the trial is provided, indicating the different stages of assessments. As of January 2025, all patients have completed the 6-month follow-up. The 12-month follow-up is currently underway and is expected to be completed by May 2025. Following data cleaning and analysis, results are anticipated by September 2025.

Figure 4. A schematic representation of the TIMELY trial.

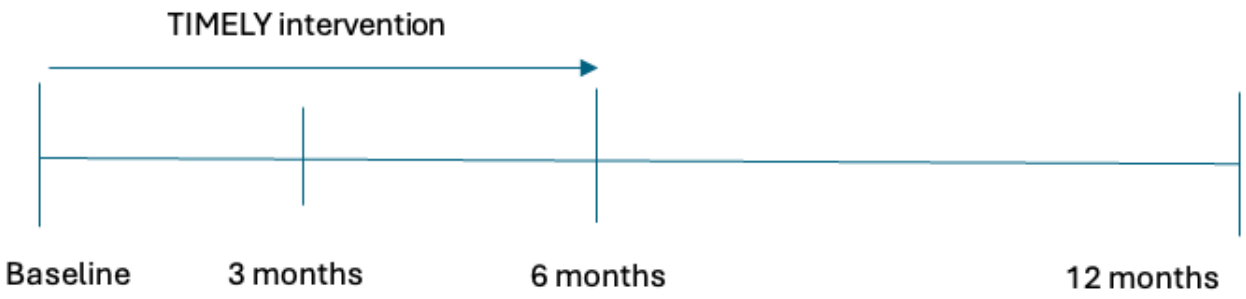

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Discussion

Anticipated Findings

Lifestyle behaviors are a recognized risk factor and account for a significant proportion of the disease burden among people with CAD [2,21-23]. Eliminating or attenuating of these behaviors is warranted, as up to 80% of cardiovascular events can be prevented by adopting a healthy lifestyle [49,50]. However, changing and maintaining healthy behaviors is challenging, and only a subgroup of people tends to adhere to the guideline recommendations and succeed in long-term behavior change [51]. CR programs (provided online or face-to-face) are successful in changing health behaviors; however, maintaining the gains accomplished during the initial phases of CR remains challenging and requires additional support [26]. To maintain the benefits of CR, eHealth has been identified as a potentially effective approach. However, there are still gaps in the evidence supporting its use [52]. This mode of delivery provides personalized yet scalable care to those who need it. Hence, the TIMELY project aims to evaluate the effectiveness of the described patient-centered eHealth-based maintenance program, composed of an integrative care platform and an app-based, long-term health behavior change program. It is expected that supporting patients with CAD using technological innovations and applying patient-tailored and behavior-specific change techniques or domain-specific BCTs may result in significant and relevant improvements compared to care as usual. The TIMELY project goes beyond the current state-of-the-art by (1) using a highly personalized approach supported by AI technology; (2) providing a fully eHealth supported program; (3) including effective BCTs per target behavior; (4) focusing on both mental and physical factors; and (5) including the perspectives of all relevant stakeholders. In addition, evaluating cost-effectiveness is crucial for determining the economic value of the TIMELY project's eHealth-based maintenance program. Integrating a cost-effectiveness analysis will measure not only the costs associated with implementing and using the integrative care platform and the app but also the economic benefits derived from improved health and reduced future events. This analysis will help justify the investment in these technologies by demonstrating that the proposed solutions are not only effective in terms of health outcomes but also economically efficient.

Limitations

Given the involvement of 3 different recruitment centers with varying phase-2 CR procedures (inpatient vs outpatient CR), patient enrollment procedures might be slightly different between centers. While these differences are not expected to affect the results of the study, it is important to note that patients may be approached at different time points during or following their center-based CR. Furthermore, participants will receive several monitoring devices and extensive instructions on navigating the TIMELY app. This could be perceived by some patients as overwhelming and perhaps result in refusal or early termination of participation. Finally, as the TIMELY intervention will provide personalized advice based on incoming patient data, the intervention may be more effective for those providing data frequently.

The results of the TIMELY intervention will provide insights into the effectiveness of a fully web-based, personalized program to support long-term cardiac healthy behavior and reduce cardiac risk. The results will also provide further understanding of relevant factors contributing to successful health behavior change over time and those that help sustain these behaviors. In addition, the TIMELY project can provide new insights into which BCTs are associated with successful behavior change, helping to enhance the effectiveness of future interventions.

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Data Availability

At the latest, by the end of the project, the data, associated metadata, documentation, and syntax codes will be deposited in a repository suitable for long-term storage or potential publishing. One of the repositories that the consortium is considering is Figshare, the repository that also serves as Universiteit van Amsterdam (timely coordinator) institutional repository. Figshare allows safely storing, controlled sharing, and publication of research data and complies with the Findable, Accessible, Interoperable, Reusable (FAIR) data principles.

Authors' Contributions

MH was involved in conceptualization, writing the original draft, reviewing, and editing. ED was involved in project administration, writing the original draft, reviewing, and editing. HS, MS-F, and TR were involved in project administration, reviewing, and editing. XS, DC-P, MK, JG-J, MS, and HM were involved in reviewing and editing. HS was involved in software analysis, reviewing, and editing. JW was involved in supervision, reviewing, and editing. FM was involved in supervision, visuals, reviewing, and editing. CP-G and DF were involved in supervision, reviewing, and editing. VT was involved in software analysis, reviewing, and editing. DG was involved in funding acquisition, visuals, software analysis, reviewing, and editing. JB was involved in

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funding acquisition, supervision, project administration, reviewing, and editing. WJK was involved in methodology, supervision, reviewing, and editing. BS was involved in funding acquisition, methodology, supervision, conceptualization, reviewing, and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Biological specimens.
[DOCX File , 14 KB - resprot_v14i1e66283_app1.docx]

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Abbreviations

AI: artificial intelligence
BCT: behavior change technique
BP: blood pressure
CAD: coronary artery disease
CR: cardiac rehabilitation
DSS: decision support system
ECG: electrocardiogram
EP: exercise prescription
PROM: patient-reported outcome measure

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Protocol

Clinical and Economic Evaluation of a Real-Time Chest X-Ray Computer-Aided Detection System for Misplaced Endotracheal and Nasogastric Tubes and Pneumothorax in Emergency and Critical Care Settings: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: Advancements in artificial intelligence (AI) have driven substantial breakthroughs in computer-aided detection (CAD) for chest x-ray (CXR) imaging. The National Taiwan University Hospital research team previously developed an AI-based emergency CXR system (Capstone project), which led to the creation of a CXR module. This CXR module has an established model supported by extensive research and is ready for application in clinical trials without requiring additional model training. This study will use 3 submodules of the system: detection of misplaced endotracheal tubes, detection of misplaced nasogastric tubes, and identification of pneumothorax.

Objective: This study aims to apply a real-time CXR CAD system in emergency and critical care settings to evaluate its clinical and economic benefits without requiring additional CXR examinations or altering standard care and procedures. The study will

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evaluate the impact of CAD system on mortality reduction, postintubation complications, hospital stay duration, workload, and interpretation time, as wells as conduct a cost-effectiveness comparison with standard care.

Methods: This study adopts a pilot trial and cluster randomized controlled trial design, with random assignment conducted at the ward level. In the intervention group, units are granted access to AI diagnostic results, while the control group continues standard care practices. Consent will be obtained from attending physicians, residents, and advanced practice nurses in each participating ward. Once consent is secured, these health care providers in the intervention group will be authorized to use the CAD system. Intervention units will have access to AI-generated interpretations, whereas control units will maintain routine medical procedures without access to the AI diagnostic outputs.

Results: The study was funded in September 2024. Data collection is expected to last from January 2026 to December 2027.

Conclusions: This study anticipates that the real-time CXR CAD system will automate the identification and detection of misplaced endotracheal and nasogastric tubes on CXRs, as well as assist clinicians in diagnosing pneumothorax. By reducing the workload of physicians, the system is expected to shorten the time required to detect tube misplacement and pneumothorax, decrease patient mortality and hospital stays, and ultimately lower health care costs.

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KEYWORDS

computer-aided detection system; artificial intelligence; pneumothorax diagnosis; endotracheal tube; nasogastric tube; clinical effectiveness; cost-effectiveness

Introduction

Background

Misplacement of medical tubes, such as endotracheal tube (ETT) and nasogastric tube (NGT), is a well-recognized clinical issue associated with serious complications, including pneumothorax, aspiration pneumonia, prolonged hospital stays, and even mortality [1-5]. Delayed management of pneumothorax could lead to tension pneumothorax, which is a life-threatening condition. In addition, misplacement of an ETT would cause hypoxia in critically ill patients. Misplacement of the NGT could lead to aspiration pneumonia. Taken together, these 3 conditions increase patient mortality, particularly related to respiratory causes. Portable chest radiography (chest x-ray [CXR]) is routinely performed in intensive care and emergency settings to confirm tube placement and detect complications. However, interpretation of portable CXR images can be challenging due to factors such as patient immobility and lower image quality, which may delay clinical decisions and increase the risk of adverse events. Therefore, with the rise of deep learning applications in the field of medical imaging, the development of artificial intelligence (AI) algorithms for CXRs has significantly enhanced the capabilities of image quality identification [6], and driving the development of computer-aided detection (CAD) systems for CXR imaging [7,8].

These systems support clinicians in diagnosing cardiopulmonary diseases, detecting pneumothorax, and preventing adverse events caused by improper tube placements. CXR imaging plays a vital role in assisting physicians with the diagnosis of cardiopulmonary conditions or pneumothorax and in identifying tube misplacements, as it is generally recommended to perform a CXR examination following the placement of ETT or NGT to confirm correct positioning [9,10]. Previous studies have demonstrated that deep learning models exhibit excellent performance in interpreting CXRs, particularly in detecting malpositioned tubes and thoracic abnormalities [11-15]. However, the development of these AI-CAD systems has typically relied on retrospective data and focused primarily on comparing their diagnostic accuracy with that of human clinicians. As a result, evidence remains limited regarding whether these AI-CAD systems can indeed deliver tangible clinical benefits when implemented in real-world clinical practice. Further validation through prospective studies, multicenter evaluations, and cost-effectiveness analyses is warranted to establish their real-world utility. Moreover, considering the increasing emphasis on health care sustainability and the need to allocate limited resources effectively, it is crucial to evaluate whether the adoption of AI-based CAD systems represents a worthwhile investment for health care systems.

In previous studies, we developed a real-time CAD system for emergency and critical care CXR imaging, incorporating deep learning technologies to detect mispositioned ETT and NGT as well as pneumothorax [16-18]. The system's modules have demonstrated its potential to improve diagnostic efficiency, reduce adverse events related to tube misplacement, and enhance patient outcomes. However, its clinical efficacy and cost-effectiveness have yet to be validated through rigorous randomized clinical trial and economic evaluations. To bridge this gap, this project aims to conduct comprehensive clinical trials (prospective studies and multicenter evaluations) and cost-effectiveness assessments, thereby enhancing the system's credibility and value for real-world clinical applications.

Objective

This study aims to apply the AI-based CAD system for automatic detection and assessment of catheter placement and pneumothorax in emergency and intensive care settings. We aim to evaluate the clinical and economic benefits of the CAD system via rigorous randomized trial without altering routine care and procedures.

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In terms of clinical benefits, the study will assess whether the use of the CAD system reduces mortality and will evaluate hospital stay duration, the time required to detect misplacement, and the time needed to reposition ETTs, NGTs, and chest drainage tubes. For the economic evaluation, the study will compare the cost-effectiveness of using the CAD system versus standard care without CAD.

Prior Work

Overview

Our team selected a CXR module developed through the Capstone project (MOST 111-2634-F-002-015-, Capstone project) in collaboration with the commercial product provided by EBM Technologies, which has been approved by the ethics committee of National Taiwan University Hospital (NTUH; reference number: 202003106RINC). The CAD system automatically retrieves CXR images from the hospital's Picture Archiving and Communication System, processes them within approximately 1 minute, and generates predictive results displayed on a centralized platform for clinical review. Alerts for abnormal findings are sent via text notifications to facilitate timely intervention. This system has been deployed in emergency and intensive care units (ICUs) to automate the identification and detection of mispositioned ETT and NGT on CXR images.

The Model of Localization and Detection of Malpositioned ETT

This model uses CXR images collected from NTUH, including both the Taipei main hospital and the Yunlin branch, which were divided into a training dataset and a testing dataset. The training dataset primarily consists of 5767 images collected from NTUH between 2015 and 2019. The testing dataset includes images from both chronological and geographical contexts: 955 images from NTUH during 2020 (NTUH-20 dataset) and 656 images from the NTUH Yunlin Branch (NTUH-YB dataset), representing different temporal and geographical backgrounds. During the image annotation process, the research team marked the position of the ETT and identified the instances of misplacement. The marking was done by nurse practitioners, emergency physicians, and radiologists with extensive clinical experience, and the images were classified according to whether the ETT was misplaced. The model uses a 2-stage model architecture for image processing.

The model uses a 2-stage architecture: DeepLabv3+ with ResNeSt50 as the backbone for segmenting the ETT, trachea, and main bronchi, followed by DenseNet121 for classifying ETT misplacement. Transfer learning was applied, using pretrained ImageNet weights fine-tuned on the dataset. The system demonstrated excellent performance. For segmentation, the Dice coefficients were 0.854 (NTUH-20 dataset) and 0.839 (NTUH-YB dataset), accurately delineating ETT contours. Mean tip localization errors were 1.107 cm (95% CI 0.807-1.513; NTUH-20) and 1.118 cm (95% CI 0.956-1.319; NTUH-YB). For classification, the system achieved area under the curve (AUC) scores of 1.000 (NTUH-20) and 0.994 (NTUH-YB) for ETT presence, and 0.847 (NTUH-20) and 0.734 (NTUH-YB) for ETT misplacement. It excelled in detecting one-lung intubation, with AUC of 0.991 (NTUH-20) and 0.966 (NTUH-YB), highlighting its robustness in critical scenarios. Results are summarized in Figure 1.

Figure 1. Summary of the model of localization and detection of malpositioned endotracheal tube (ETT). (A) original chest x-ray images. (B) Pixel-level annotations used by the labelers, including the ETT (brown) and the trachea and main bronchi (red), with dark brown dots indicating the ETT tip. (C) Segmentation masks generated by the segmentation model. (D) The gradient-weighted class activation mapping (Grad-CAM) results, highlighting that the classification model primarily relied on the region surrounding the ETT tip for its inferences.

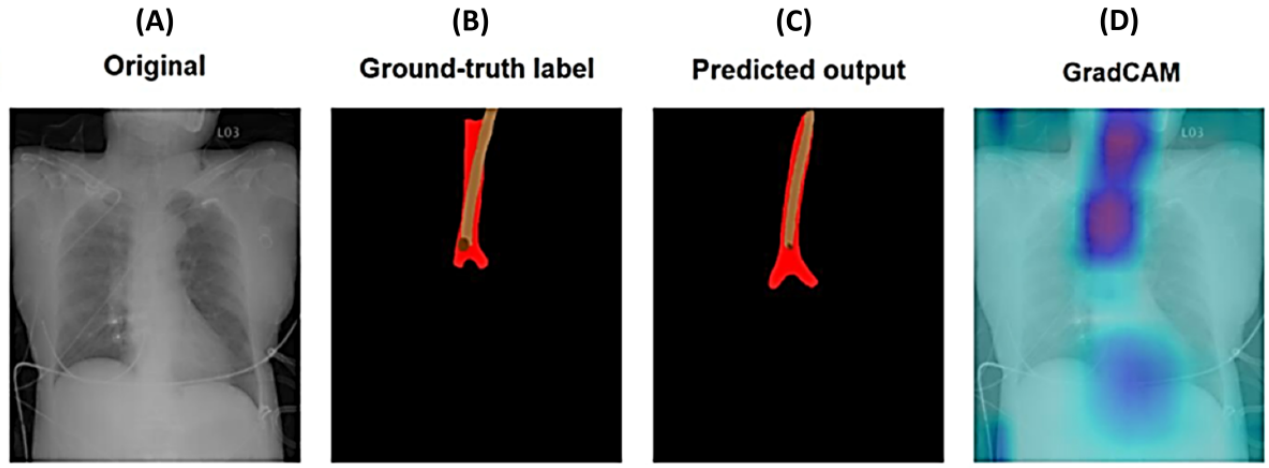

The Model for Misplacement Detection of NGTs

A total of 7378 portable CXRs were collected from NTUH Taipei main hospital and Yunlin branch (2015 to 2020) and annotated for NGT localization and malposition. The CAD system used DeepLabv3+ (ResNeSt50 backbone) for segmentation and DenseNet121 for classification. Testing on NTUH-20, NTUH-YB, and CLiP datasets demonstrated strong performance.

The segmentation model achieved Dice coefficients of 0.665 (NTUH-20) and 0.646 (NTUH-YB), with mean NGT tip localization errors of 1.64 cm and 2.83 cm, respectively. The classification model demonstrated strong performance, with an AUC of 0.998 for NGT detection and 0.964 (NTUH-20) and 0.991 (NTUH-YB) for malposition detection.

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In summary, this deep learning–based model for tube misplacement detection demonstrated excellent performance in detecting and localizing ETT and NGT. Its accuracy and reliability highlight its potential for broad applications in emergency and intensive care settings.

The Model for Pneumothorax Detection

A deep learning–based dual-model system was developed for diagnosing and localizing pneumothorax on portable supine CXRs in emergency and intensive care settings. Images from NTUH (Taipei main hospital and Yunlin branch), collected between 2015 and 2020, were divided into training (1571 images) and test (1071 images) datasets, with pixel-level annotations.

The detection system used EfficientNet-B2, DenseNet-121, and Inception-v3 for classification, and Deformable DETR, TOOD, and VFNet for localization. The segmentation system used UNet for both classification and localization. The detection system achieved an AUC of 0.940, and the segmentation system achieved an AUC of 0.979, both performing similarly to radiology reports. The detection system achieved a Dice coefficient of 0.758, and the segmentation system achieved a Dice coefficient of 0.681, showing high accuracy.

These systems demonstrate strong performance and generalizability, offering potential to assist health care facilities in prioritizing critical x-rays and notifying clinicians for timely interventions, improving patient outcomes. Results are summarized in Figure 2.

Figure 2. Summary of the model for pneumothorax detection. (A) Original image. (B) Boundary boxes (green rectangles) and segmentation masks (red regions) after preprocessing by the detection and segmentation model systems. (C) Boundary boxes (red rectangles) predicted by the detection model system. (D) Segmentation masks (purple regions) predicted by the segmentation model system.

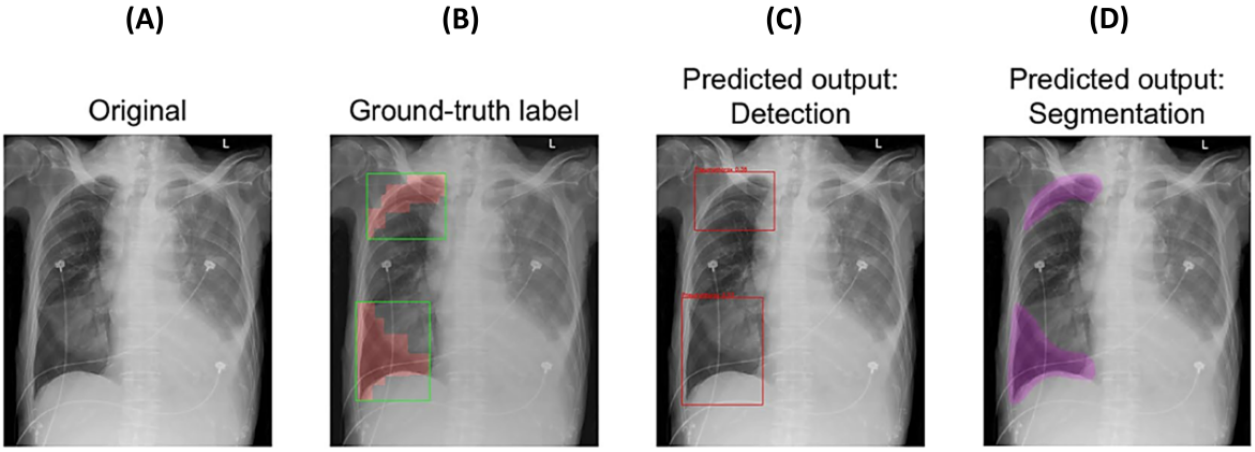

The AI-based computer-aided diagnostic system automatically detects and assesses catheter placement and pneumothorax, providing excellent prejudgment capabilities for potentially misplaced catheter images. It reduces delays between obtaining CXR images and clinical interpretation, thus improving clinician efficiency. This, in turn, helps to reduce adverse reactions from catheter misplacement and subsequent management of pneumothorax, thereby improving patient prognosis and reducing complications.

This study focuses on the clinical validation and deployment of this system rather than on algorithm development or segmentation metrics. Although several foundational studies involving segmentation performance and metrics such as the Dice coefficient were conducted within the NTUH health care system, this trial aims to extend the findings and tools developed in those earlier studies to a broader range of health care settings. To enhance the generalizability and applicability of the research across institutions with varying levels and organizational structures, we have included 3 participating sites: a medical center (NTUH), and 2 regional hospitals (Fu Jen Catholic University Hospital [FJCUH] and Min-Sheng General Hospital [MSGH]).

Methods

Research Design

This study adopts a 2-phase design, beginning with a pilot study followed by a multicenter cluster randomized clinical trial. The pilot phase focuses on integrating a CXR CAD system into the hospital's medical information systems, ensuring smooth functionality within the clinical workflow. The system will undergo testing and initial evaluations in the emergency intensive care and ICU at NTUH over a period of 6 to 12 months.

Building on the pilot phase, the multicenter clinical trial involves ICUs from NTUH, FJCUH, and MSGH. A total of 18 ICU units will participate, with NTUH contributing 14 units and the remaining hospitals contributing 2 units each. These units will be randomized into AI-assisted and control groups. Stratification is based on ventilator use, with randomization conducted within each stratum using uniform distribution. The AI-assisted group allows physicians to access real-time predictions from the CAD system during patient care. These predictions, generated within seconds, focus on identifying critical conditions, such as NGT misplacement, ETT misplacement, and pneumothorax. However, physicians in the control group will adhere to standard procedures without viewing AI-generated predictions, though the CAD system will still analyze images for internal validation.

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To minimize potential bias, both the outcome assessors and data analysts will remain blinded to group allocation throughout the data collection and statistical analysis phases.

The primary outcome is patient all-cause mortality rate: Assess whether the in-hospital mortality rate decreases after the intervention, reflecting the AI-assisted detection system's ability to identify life-threatening conditions in a timely manner and facilitate rapid clinical intervention.

The secondary outcomes are as follows:

1. Cause-specific mortality rate: a physician panel, blinded to group allocation, will adjudicate the cause of death among study participants. The focus will be placed on respiratory-related mortality, which is most relevant to the conditions targeted by the AI modules.
2. Length of hospital stay: evaluate whether the use of the AI-assisted system shortens hospitalization duration, particularly by enabling earlier detection of tube misplacement and pneumothorax, leading to timely treatment.
3. Time to misplacement detection: determine whether the AI system reduces the time required to identify misplaced tubes or pneumothorax, thereby enhancing the timeliness of clinical interventions.
4. Time to reposition ETT and NGT, and time to place a chest drain for pneumothorax.
5. Direct medical costs (eg, x-ray examinations, intubation fees, and hospitalization costs) and indirect medical costs (eg, CAD system costs and labor costs).

Determination of Sample Size

The primary outcome of the trial is to assess whether the CAD system can reduce in-hospital mortality. On the basis of data from the NTUH institutional database [19], the ICU mortality rate in 2023 to 2024 is estimated at 28%. A projected reduction to 25% was used for the sample size calculation. With an intraclass correlation coefficient of 0.01, a power of 80%, and a 1-sided α of 5%, each group requires 5450 patients, resulting in a total sample size of 10,900. This design is expected to provide sufficient power to detect clinically significant improvements in patient outcomes (Figure 3).

Figure 3. Illustration of study design. AI: artificial intelligence; FJCUH: Fu Jen Catholic University Hospital; ICU: intensive care unit; NTUH: National Taiwan University Hospital.

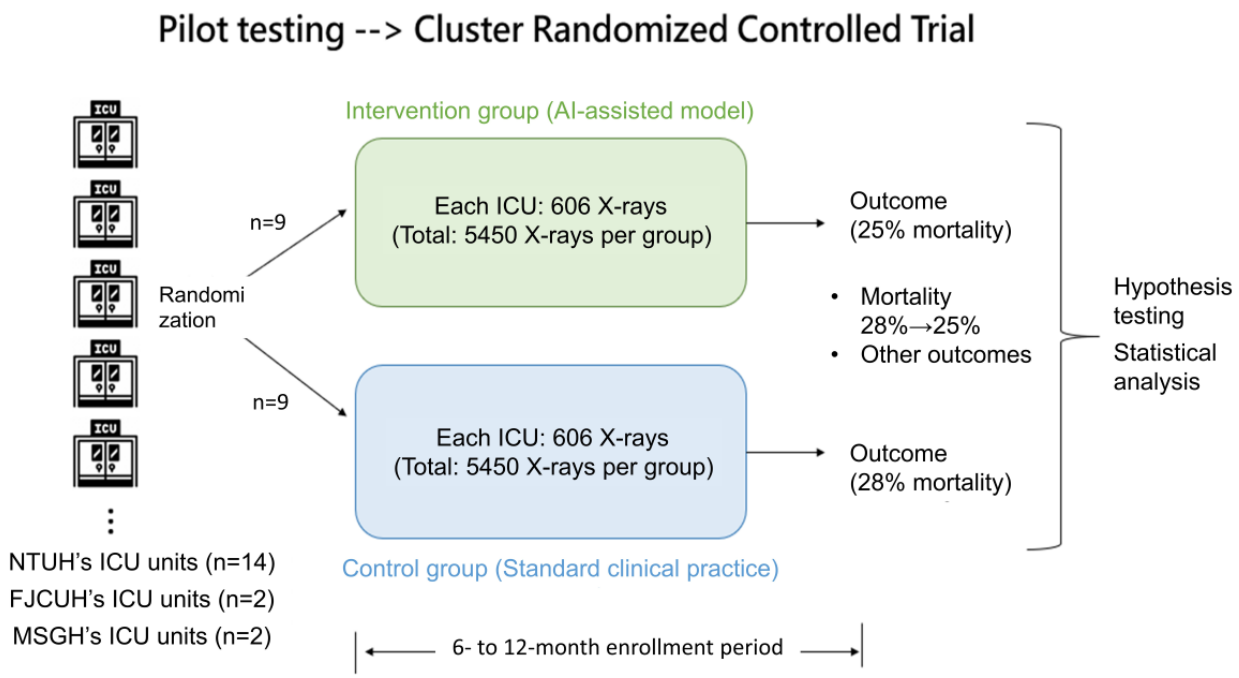

Because the causes of death in patients admitted in ICU may not necessarily be related to CXRs, adjustments to the primary outcome of the formal trial will be made following the pilot testing. This will involve evaluating and modifying the primary outcome (eg, time to detection of misplacement) to better align with the trial's objectives and needs.

The conduct and reporting of the trial follow the CONSORT (Consolidated Standards of Reporting Trials) 2010 statement with the extension to cluster randomized trials [20].

Recruitment and Enrollment

Phase 1: Pilot Study

During this phase, the emergency critical care (ECC) area and ICUs at NTUH will be selected as the pilot sites for system testing and preliminary evaluation. The implementation period will last approximately 6 months to 1 year from January 1 to December 31, 2025. Attending physicians, resident physicians, and advanced practice nurses from the ECC and ICUs will sign consent forms, enabling them to use the CAD system upon agreement.

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Simultaneously, an exemption from patient informed consent will be requested, as the study is classified as minimal risk. The potential risks to study participants do not exceed those encountered by nonparticipants, and the exemption will not adversely affect their rights or welfare.

The inclusion and exclusion criteria are shown in Textbox 1.

Textbox 1. The inclusion and exclusion criteria for the pilot study.

Units

- Inclusion criteria
- Emergency critical care or intensive care units at National Taiwan University Hospital
- The units included the patients requiring chest x-rays due to endotracheal intubation, nasogastric tube insertion, or ventilator use with a risk of pneumothorax.
- Exclusion criteria
- The unit supervisor does not agree to participate in the trial.
- The unit is unable to implement the artificial intelligence–assisted system (eg, no data connection or system support).

Patients

- Inclusion criteria
- Patients who are adults and require chest x-ray due to one of the following conditions: endotracheal intubation, nasogastric intubation, or the use of a ventilator with the potential to cause pneumothorax.
- Exclusion criteria for patients in isolation wards or pediatric wards
- Patients in isolation wards
- Patients in infant intensive care unit

The data collected includes the total number of patients in the ward, ventilator use, pneumothorax cases, CXR results, misplacement detection time, mortality rate, length of stay, ETT and NGT resetting times, pneumothorax drainage tube placement time, direct medical costs (eg, x-ray examinations, intubation fees, and hospitalization fees), and indirect costs (eg, CAD system and labor costs). System error messages will be recorded. Imaging data will not be collected, and the AI software will not undergo model training. A midterm evaluation at the end of phase 1 will determine the feasibility of phase 2.

Phase 2: Cluster Randomized Controlled Trial

Building on the results of phase 1, this phase will expand to include the ICUs of FJCUH and MSGH, conducting a cluster randomized controlled trial from January 1, 2026, to December 31, 2027, to evaluate the practical application of the CAD system in a multicenter setting, as well as to assess clinical and economic benefits. In addition, the attending physicians, residents, and specialized nurses in the ECC and ICUs will sign consent forms, which will allow them to use the CAD system. Patients will be exempted from providing informed consent, as the study poses minimal risk, and the potential risks for participants are no greater than those for nonparticipants. Exempting informed consent will not affect their rights. The inclusion and exclusion criteria are shown in Textbox 2.

The study will use cluster randomization, stratified by ventilator use frequency, to balance the risk of pneumothorax between the 2 groups and reduce potential confounding bias. Within each stratum, the ventilator use will be similar, while the difference in use between strata will be larger. A uniform distribution will be applied to assign each ward unit a random probability. On the basis of these probabilities, the units will be ranked and assigned to either the intervention or control group based on their odd or even rank.

In the control group, physicians will continue with the current diagnostic process and will not be able to view the model's predictions. In the intervention group, physicians will be authorized to access the AI model's predictions during patient care as an additional decision-making reference. These predictions will be generated in seconds and can help identify issues such as tube misplacement (eg, NGT and ETT) and pneumothorax through AI analysis of CXRs, which will alert the physician to review the images. Access to the model's prediction interface was restricted to physicians in the intervention group, with access for the control group technically disabled through role-based permissions within the hospital information system. This measure ensured that physicians in the control group were not exposed to any AI-generated outputs. In addition, to promote consistent use of the CAD system within the intervention group, log-in records will be monitored, and reminders will be issued in cases of noncompliance.

Data collection included the total number of patients in the ward, the number of patients using ventilators, the number of pneumothorax cases, CXR results, misplacement detection time, mortality rate, length of stay, ETT resetting time, NGT resetting time, pneumothorax drainage tube placement time, direct medical costs (eg, x-ray examinations, intubation fees, and hospitalization fees), and indirect medical costs (eg, CAD system costs and labor costs). The implementation costs are expected to differ between the intervention and control arms. The intervention arm includes additional expenditures related to AI system deployment, such as system infrastructure, routine maintenance, training, and IT support. These costs are captured as part of the economic evaluation to assess whether the clinical

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benefits of AI-assisted care justify the associated investment. Imaging data will not be collected, and the AI software will not undergo model training.

Textbox 2. The inclusion and exclusion criteria for cluster randomized controlled trial.

Units

- Inclusion criteria
- Emergency critical care or intensive care units at National Taiwan University Hospital, Fu Jen Catholic University Hospital, and Min-Sheng General Hospital.
- The units included the patients requiring chest x-rays due to endotracheal intubation, nasogastric tube insertion, or ventilator use with a risk of pneumothorax.
- Exclusion criteria
- The unit supervisor does not agree to participate in the trial.
- The unit is unable to implement the artificial intelligence–assisted system (eg, no data connection or system support).

Patients

- Inclusion criteria
- Patients who are adults and require chest x-ray due to one of the following conditions: endotracheal intubation, nasogastric intubation, or the use of a ventilator with the potential to cause pneumothorax.
- Exclusion criteria for patients in isolation wards or pediatric wards
- Patients in isolation wards
- Patients in infant intensive care unit

AI Detection Tool

The CXR real-time CAD system is an AI-assisted diagnostic software in medical devices. It uses AI algorithms to analyze bedside CXR images and detect conditions such as malpositioned NGTs, ETTs, and pneumothorax. The system provides immediate feedback on detection results and notifies the physician to review the images for confirmation. If a tube misplacement is identified, the physician can promptly adjust its position; if pneumothorax is detected, the physician can provide appropriate treatment, such as chest tube drainage.

This system is classified as a medical device software under Taiwan's Food and Drug Administration's "Artificial Intelligent/Machine Learning-Based Software as a Medical Device, AI/ML-Based SaMD" regulations. It uses clinical data, such as images and biochemical markers, to autonomously learn and adjust its performance through AI programming. The outputs from the analysis are not intended to manage clinical treatments but provide immediate feedback to clinicians for timely interventions or treatments. The system's data are sourced from patient examination files stored in the database and do not involve any invasive procedures.

Data Integration Workflow

The workflow (Figure 4) ensures seamless data exchange between the AI server and the hospital's medical information system, optimizing the use of AI in clinical decision-making. After CXR images are acquired, they are sent to the AI server via the QC workstation. To maintain data integrity, the system has a fail-safe mechanism: if transfer issues occur, the AI server queries or retrieves the images from the integrated information system or initiates a backup retrieval process directly. Once the AI server processes the images, critical findings are identified, and alerts are generated through the hospital's internal messaging system, improving response times for urgent cases.

Health care professionals can access images and AI-generated annotations through SoliPACS by activating the "tool" feature. In addition, physicians can provide feedback on the AI's diagnostic accuracy, facilitating model refinement. For research purposes, workflow configuration to enable AI access rights must be requested by ward physicians and specialist nurse practitioners in relevant departments.

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Figure 4. Data transmission flowchart for artificial intelligence (AI) server and medical information–system integration. BLE: Bluetooth low energy; CR: computed radiography; CT: computed tomography; DX: digital radiography; IP: internet protocol; PACS: picture archiving and communication system; TCP: transmission control protocol.

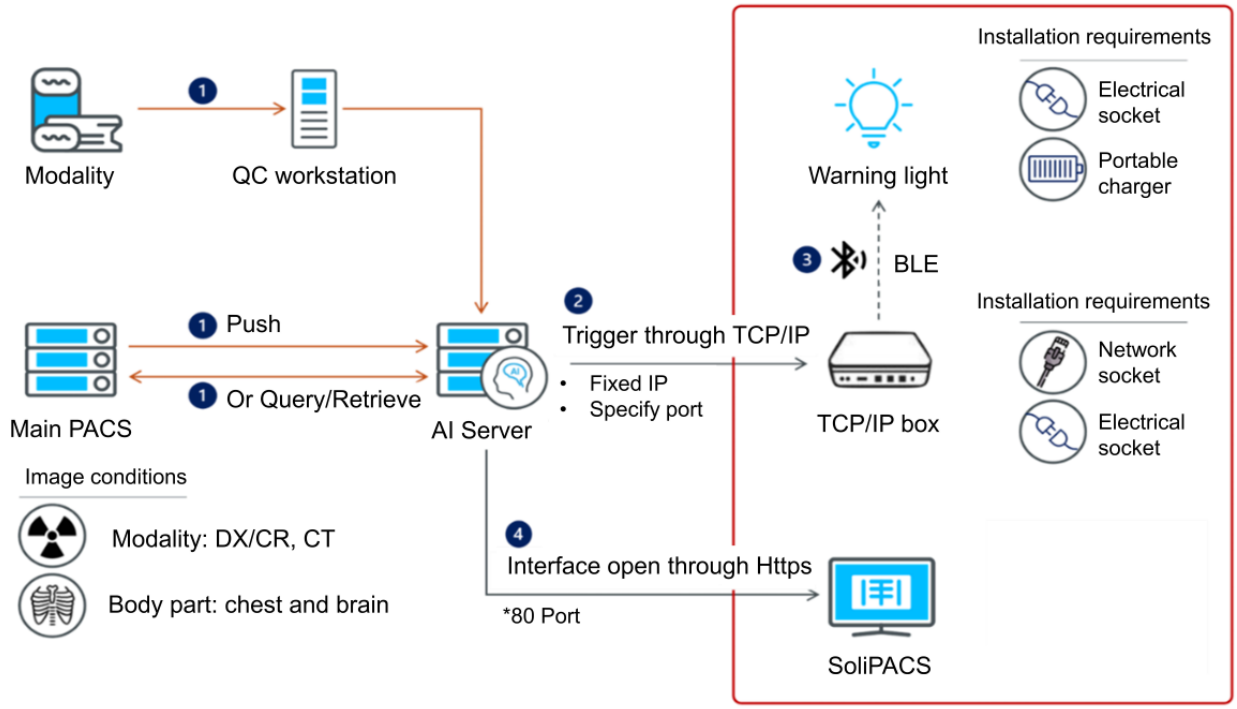

AI Computation Architecture

The system uses a file exchange method to handle the transfer of DICOM files and output data (Figure 5). Batch processing capabilities allow users to process multiple images simultaneously by placing them in the "Inputs" folder. Built on an Inference Server architecture, the system loads the AI models into memory at container activation, eliminating the need to reload models for each operation. This architecture enhances computational efficiency, particularly for high-throughput image analysis. Critical alerts and findings are displayed in real time within the hospital's information system, ensuring a streamlined workflow for health care providers.

Figure 5. Artificial intelligence (AI) computing architecture diagram. EPS: EBM PACS Server.

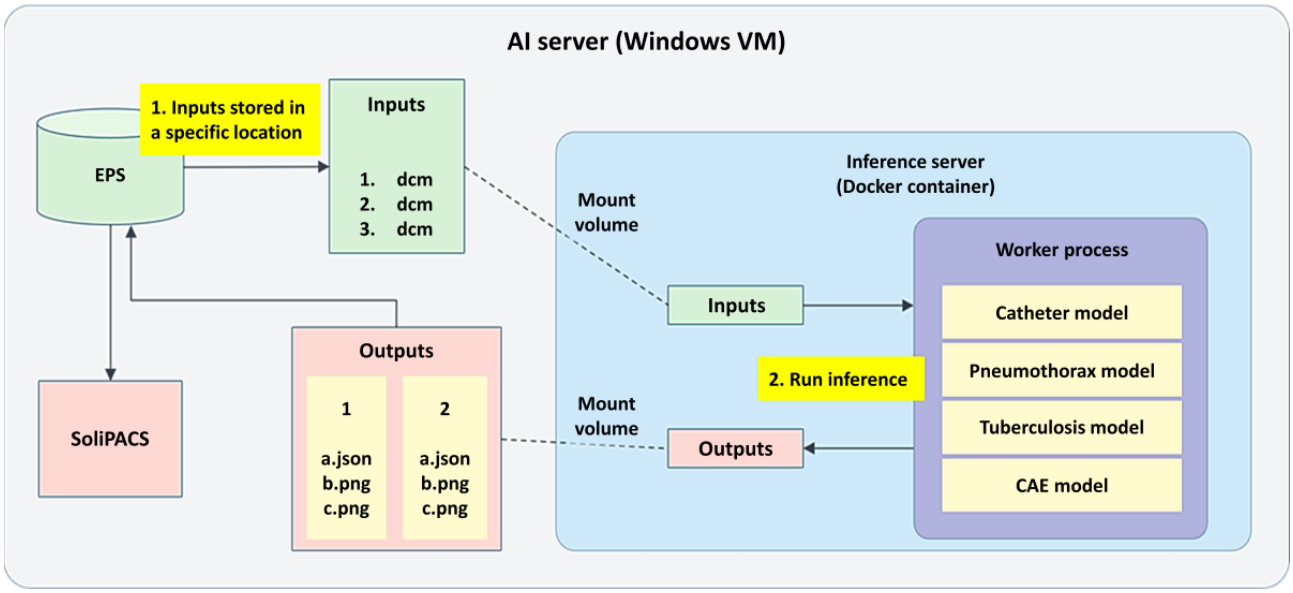

Statistical and Cost-Effectiveness Analysis

Statistical analysis will be conducted using SAS software (SAS Institute) to evaluate the outcomes of this study. Continuous variables, such as clinical outcomes and procedural times, will be summarized using descriptive statistics, including the number of observations, mean, median, SD, range, and 95% CIs. For categorical variables, frequency counts and percentages will be used to summarize the data.

In terms of clinical effectiveness, the primary outcome will be in-hospital mortality, and a proportional test will be used to

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compare the mortality rates between ICUs that have implemented the AI-assisted detection system and those that have not. The secondary clinical outcomes, which include the length of stay in the hospital, time to detect tube misplacements, and the time taken for medical interventions (such as repositioning of ETT and NGT and placement of pneumothorax drainage), will be analyzed using *t* tests for continuous variables. For categorical outcomes, including the rates of misplacement and other related interventions, chi-square test will be used. In addition, proportional tests will be conducted to examine the differences in the frequency of interventions across the 2 groups.

The study will also incorporate a health care technology and economic evaluation framework to assess the cost-effectiveness of the AI system alongside its clinical effectiveness. This evaluation will explore whether the clinical benefits derived from the AI system justify the associated resource consumption. Previous research by the team [21], such as the use of Markov models in gastric cancer screening and prevention, has demonstrated the utility of such economic evaluations, particularly in quantifying the cost-effectiveness of medical interventions and their impact on mortality reduction.

Cost-effectiveness analysis will be conducted using TreeAge software to compute the incremental cost-effectiveness ratio. This ratio will assess the additional cost required to achieve one unit of clinical benefit when using the AI system as compared to traditional methods. The incremental cost-effectiveness ratio will be calculated by dividing the cost of the intervention (which includes the medical, AI system, and maintenance costs) by the effectiveness, which will be measured through various clinical outcomes, such as reduced diagnostic time, decreased mortality rates, fewer misdiagnoses, and quality-adjusted life years (QALYs).

QALYs will serve as a composite measure of health outcomes by combining both the quantity and quality of life. The calculation of QALYs will involve multiplying the expected survival years after the intervention by a health state weight, which reflects the patient's quality of life during those years. This weight ranges from 0 (death) to 1 (perfect health), and negative values may be used to indicate health statuses worse than death.

$$\text{QALY} = \text{Years of Life} \times \text{Health State Weight}$$

To ensure the robustness of the findings, sensitivity analyses will be conducted, including both simple sensitivity analysis and probabilistic sensitivity analysis. These analyses will account for variability in model parameters and simulate different combinations of parameters to evaluate the stability of the cost-effectiveness conclusions. The results of these analyses will be assessed through acceptance curves and cost-effectiveness planes, which will allow a comparison of the cost-effectiveness of different treatment strategies under various assumptions.

Ethical Considerations

The study was approved by the Research Ethics Committee of National Taiwan University Hospital (reference number: 202412055DINA), Fu Jen Catholic University Hospital (reference number: FJUH114448), and Min-Sheng General Hospital (reference number: CIRB2025001). The trial was registered on February, 2025, with ClinicalTrials.gov (NCT06842043). During data transmission and system access, it is crucial to ensure the full protection of patients' medical information. To this end, physicians and advanced practice nurses from each ward involved in the study are required to request workflow permissions for AI system access. As AI systems typically rely on large volumes of medical imaging for training and optimization, any data breach or misuse could pose significant privacy risks.

The AI-assisted system may face potential challenges such as system malfunctions or delays, which could impact its reliability in real-time clinical decision-making. In critical care settings, detection delays or technical issues could result in treatment postponement. Furthermore, the AI system is integrated within the medical information infrastructure and must adhere to the institution's information security management standards.

All data will be stored on dedicated, password-protected computers equipped with antivirus software. These research data and related information will be securely retained for a period of 5 years.

Results

The implementation of the AI-assisted CXR CAD system is expected to yield substantial improvements in clinical outcomes and health care efficiency. By enabling timely identification of critical conditions such as misplaced ETT and NGT and pneumothorax, the system is anticipated to reduce in-hospital mortality rates from 28% to 25%. This improvement reflects the system's potential to facilitate faster recognition of life-threatening situations and prompt clinical interventions.

Moreover, the use of the CAD system is projected to shorten the length of hospital stays, particularly by accelerating the detection of misplaced tubes and pneumothorax, which allows for timely correction and treatment. The time required for specific interventions, such as repositioning ETTs and NGTs or placing drainage tubes for pneumothorax, is also expected to decrease, further enhancing patient care efficiency.

From an economic perspective, the adoption of the CAD system is anticipated to reduce overall health care costs. This includes direct medical costs, such as imaging fees and hospitalization expenses, as well as indirect costs, such as personnel and system maintenance. By improving diagnostic accuracy and reducing delays in treatment, the system is expected to contribute to long-term cost savings while ensuring better health outcomes for patients.

Discussion

Principal Findings

The integration of the CXR CAD system is expected to significantly transform clinical workflows in emergency and critical care settings. By leveraging automated diagnostic capabilities, the study aims to address persistent challenges in

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timely and accurate identification of misplaced ETTs and NGTs and pneumothorax. The findings are anticipated to highlight the potential of CAD systems to improve patient outcomes, reduce health care costs, and provide a foundation for broader adoption of AI-based diagnostic tools in critical care environments. These results could position the CAD system as an essential component in advancing precision medicine.

Limitations

Although this study is classified as low risk, the AI system used may present potential indirect risks. One concern is the possibility of false positives or negatives, where the system may inaccurately identify medical images, leading to missed diagnoses or misplacements, delaying treatment or causing unnecessary interventions.

Another risk is overreliance on the system by health care providers, particularly if they are unfamiliar with its use, which could affect decision-making accuracy. In addition, system errors or delays may occur, increasing clinicians' workload if the AI system fails to provide timely assistance. In addition, as the system analyzes patients' CXR images, there is a risk to patient privacy if proper data protection measures are not in place, potentially compromising confidentiality.

To address potential risks, a pilot study will validate the AI system's sensitivity and specificity, ensuring reliability. The AI system serves only as a supplementary diagnostic tool, with final decisions made by physicians based on its outputs and clinical information. Health care providers will receive training on the system's operation, limitations, and result interpretation to prevent overreliance. Regular feedback meetings will address issues as they arise. A monitoring protocol will log processing times and detect errors. In case of delays or malfunctions, standard diagnostic protocols will be followed. The AI software will also be approved by the NTUH Smart Medical Center to ensure data security and system integrity.

Conclusions

Despite its limitations, the real-time CXR CAD system represents an innovative and promising tool for automatically identifying and detecting misplacement of ETTs and NGTs on CXRs while also assisting clinicians in diagnosing pneumothorax. This system has the potential to reduce detection time for tube misplacement and pneumothorax, lower patient mortality and hospitalization duration, and ultimately decrease health care costs. Following the evaluation protocol of this CAD system, its clinical accuracy and feasibility can be determined. If proven effective, further clinical trials may be considered to assess its broader impact.

Acknowledgments

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during this study. The development processes of the 3 models supporting this protocol are detailed in the primary supporting research articles [16-18]. Additional data can be obtained from the corresponding author upon reasonable request.

Authors' Contributions

All authors contributed to the conceptualization and reviewing and editing the draft. CHH, JHK, YCL, and CLT performed supervision. TCCC, TAW, and SLC performed data curation. CLT, YCL, TAW, TCCC, and SLC performed methodology. CLT, YCL, JHK, TAW, and TCCC handled project administration. CHH, CHW, LCK, CJC, and WCW managed resource and software and conducted validation. CLT, TCCC, and TAW wrote the original draft. WTC, MST, SCK, YHL, HCT, SWK, KCW, AC, SCT, WLL, and MHT will contribute to research coordination, patient enrollment, inpatient research follow-ups, and data collection. All authors have read, refined, and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
AUC: area under the curve
CAD: computer-aided detection

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CONSORT: Consolidated Standards of Reporting Trials
CXR: chest x-ray
ECC: emergency critical care
ETT: endotracheal tube
FJCUH: Fu Jen Catholic University Hospital
ICU: intensive care unit
MSGH: Min-Sheng General Hospital
NGT: nasogastric tube
NTUH: National Taiwan University Hospital
NTUH-YB: National Taiwan University Hospital Yunlin Branch
QALY: quality-adjusted life year

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Protocol

An eHealth Delivery Alternative for Cancer Genetic Testing for Hereditary Predisposition in Patients With Metastatic Cancers: Protocol for a Randomized Trial

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Abstract

Background: Germline *BRCA1* and *BRCA2* testing is a standard evidence-based practice, with established risk reduction and cancer screening guidelines for genetic carriers. With Food and Drug Administration approval for poly (adenosine diphosphate ribose) polymerase (PARP) inhibitors in patients with metastatic breast, ovarian, pancreatic, and prostate cancer, there is an additional therapeutic rationale for testing all patients with these cancers for germline *BRCA1* and *BRCA2* mutations. However, many at-risk patients do not have access to genetic services, leaving many genetic carriers unidentified.

Objective: The eREACH (A Randomized Study of an eHealth Delivery Alternative for Cancer Genetic Testing for Hereditary Predisposition in Metastatic Breast, Ovarian, Prostate, and Pancreatic Cancer Patients) study evaluates the effectiveness of a theoretically and stakeholder-informed eHealth (eg, digital) delivery alternative to traditional genetic counseling for patients with metastatic breast or prostate cancer or advanced or metastatic ovarian or pancreatic cancer referred for genetic testing to determine whether they are candidates for a PARP inhibitor.

Methods: The eREACH study is a randomized noninferiority study using a 2 × 2 design to test a self-directed digital intervention to deliver clinical genetic testing for patients with metastatic cancers. The traditional standard-of-care pretest (visit 1) and posttest (visit 2—disclosure) counseling delivered by a genetic counselor is replaced with our patient-informed digital intervention. The four arms were as follows: arm A, genetic counselor for visits 1 and 2; arm B, genetic counselor for visit 1 and digital intervention for visit 2; arm C, digital intervention for visit 1 and genetic counselor for visit 2; and arm D, digital intervention for both visits. Participants were adults with advanced or metastatic breast, ovarian, pancreatic, and prostate cancer. The primary outcomes of this study were change in genetic knowledge and anxiety from baseline to postdisclosure assessment. We will test whether the digital intervention is noninferior to standard-of-care counseling with a genetic counselor using a modified noninferiority ANOVA

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of the posttest disclosure minus baseline change scores. In secondary analyses, we will test pairwise differences among the 4 groups.

Results: As of January 2025, we have completed enrollment of 229 participants. Data analysis is ongoing, and we expect the results to be published in 2025.

Conclusions: Increasing indications for *BRCA1* and *BRCA2* testing create a pressing need to evaluate alternative delivery models to increase access and uptake of these tests while maintaining adequate patient cognitive, affective, and behavioral outcomes. The eREACH study evaluates the effectiveness of an interactive, patient-centered digital intervention to deliver clinical genetic testing to patients with metastatic cancers. We expect that this work will inform evidence-based guidelines and the standard of care for delivery of genetic testing, and it is designed to be broadly applicable and easily adaptable for other populations and settings even beyond oncology.

Trial Registration: ClinicalTrials.gov NCT04353973; https://clinicaltrials.gov/study/NCT04353973

International Registered Report Identifier (IRRID): DERR1-10.2196/72515

(JMIR Res Protoc 2025;14:e72515) doi:10.2196/72515

KEYWORDS

genetic testing; genetic counseling; digital health; metastatic cancer, digital genetic education

Introduction

Metastatic Cancer and Genetic Testing

Increasing indications for *BRCA1* and *BRCA2* testing creates a pressing need to evaluate alternative delivery models for testing. Germline cancer genetic testing has become a standard evidence-based practice, with established risk reduction and cancer screening guidelines for genetic carriers [1-4]. With Food and Drug Administration approval for poly (adenosine diphosphate ribose) polymerase (PARP) inhibitors as treatment for patients with germline *BRCA1* and *BRCA2* mutations and metastatic breast, ovarian, pancreatic, and prostate cancer, there is an additional therapeutic rationale for testing patients with these cancers for germline *BRCA1* and *BRCA2* mutations [5-8]. However, many at-risk patients do not have access to genetic services, leaving many genetic carriers unidentified [9-13].

Traditional Model of Genetic Services

The traditional standard of care for genetic counseling services involves a patient having a pretest counseling session with a certified genetic counselor (GC). Genetic testing is then performed, following which there is a second visit with a certified GC where results are shared or disclosed. Thus, one test has traditionally required 2 visits with a GC. While this is the traditional model for services, many alternative models, including mainstreaming (oncologist provides all counseling) or replacing pretest counseling with videos, have been recently used, although many with limited comparison to the traditional model [14-21]. Furthermore, with the 21st Century Cures Act, results may become available in the medical record before the traditional disclosure with a GC. Access to genetic specialists is limited in many areas in the United States, and the traditional delivery model of pre- and posttest counseling with a genetic professional will not support the rising indications for *BRCA1* and *BRCA2* testing. With current policy movement toward testing all patients with breast, ovarian, pancreatic, and prostate cancer for germline mutations driven by advances in treatment with PARP inhibitors or other targeted therapies, there is a need to develop and evaluate innovative delivery models for genetic testing for *BRCA1* and *BRCA2* and other targeted mutations. This could become even more important if guidelines are modified to include additional tumor types for which PARP inhibitors could be effective based on *BRCA1* and *BRCA2* status [22].

eHealth-Based Genetic Services

eHealth (eg, digital) interventions are a novel and efficient delivery model with potential to increase access and throughput of genetic services. One alternative, efficient, and scalable model is to provide predisclosure education and return of genetic results through secure eHealth (eg, digital) interventions. Interactive health communication applications (eg, digital applications) have been implemented to support and enhance the delivery of patient-centered care and communication to optimize health outcomes [23,24]. Patients have high interest in communicating electronically with health care providers; 85% of patients report preferring electronic communication to phone [25-27]. Studies in a variety of disease settings have shown that digital interventions can improve knowledge, social support, self-efficacy, and some clinical outcomes [23-35]. A 2023 systematic review by Lee et al [36] identified 70 digital tools, of which 32 were designed to help with decision-making regarding genetic testing. Of these, only 11 were developed for posttest counseling, and approximately half were used in an oncology setting. However, these tools all had a neutral or favorable effect on knowledge and decision-making. Recently, Biesecker et al [16] reported that a web-based platform was noninferior to GC-mediated genetic counseling in a highly educated cohort undergoing carrier testing, and the Returning Genetic Research Panel Results for Breast Cancer Susceptibility (RESPECT) study [37] demonstrated that a web-based predisclosure education intervention in lieu of standard predisclosure counseling with a GC was acceptable to participants, with 88.5% opting for web disclosure. Thus, interactive digital interventions may be an efficient way to address the workforce shortage and other challenges in the delivery of genetic services while maintaining adequate patient outcomes [38-40].

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Conceptual Model

Our patient-reported outcomes of interest in the eREACH (A Randomized Study of an eHealth Delivery Alternative for Cancer Genetic Testing for Hereditary Predisposition in Metastatic Breast, Ovarian, Prostate, and Pancreatic Cancer Patients) study were informed by our conceptual model grounded in the self-regulation theory of health behavior to evaluate innovations in the delivery of genetic services [16,41-44]. This model proposes that an individual's understanding, knowledge, and perception of the disease threat and risk reduction behaviors (cognitive outcomes) drives the reaction to (affective outcomes) and use of health (genetic) information (behavioral outcomes) [42-44]. It focuses on lay representations instead of medical and scientific definitions. It further addresses the potential for individual variability in understanding by incorporating individual-level cognitive, emotional, familial, and cultural experiences. Thus, it has been proposed that the self-regulation theory of health behavior is an ideal framework for considering the outcomes of genetic testing when testing alternative delivery models [42,45-47].

This Study

This randomized study of an eHealth (eg, digital) delivery alternative for cancer genetic testing for hereditary predisposition in patients with metastatic breast, ovarian, prostate, and pancreatic cancers (eREACH) is a 4-arm noninferiority study with a 2 × 2 design in a population of patients with metastatic cancers to evaluate the effectiveness of digital delivery alternatives to increase access to genetic testing. Participants will be randomized to 1 of 4 arms. The control group will receive both pretest and posttest genetic counseling from a certified GC per the traditional standard of care. The intervention arms will receive pretest or posttest counseling via our interactive, patient-centered digital intervention.

Objectives

Overview

The goal of the eREACH study is to evaluate the effectiveness of replacing traditional pretest (visit 1—education and consent) and posttest (visit 2—disclosure) counseling delivered by a GC with an interactive patient-centered digital intervention for germline genetic testing in patients with advanced or metastatic cancers for which a PARP inhibitor could be considered for treatment. We hypothesize that offering digital alternatives for pretest or posttest (result disclosure) visits will result in equal or improved (noninferior) short-term and longitudinal cognitive, affective, and behavioral outcomes and reduce health care provider time, increasing throughput and access to genetic services. Furthermore, we will evaluate subgroups who benefit more or less from digital alternatives, which will provide critical information on how best to implement and increase access to germline genetic testing in the era of precision medicine.

Specific Aim 1

Our primary aim is to determine whether a patient-centered digital intervention delivery of pretest or posttest counseling can yield equal or improved short-term cognitive and affective outcomes as compared to a 2-visit telehealth delivery model with a GC. Our primary outcomes are change in knowledge and general anxiety from baseline to postdisclosure assessment. Secondary outcomes include uptake of testing, depression, cancer-specific distress, uncertainty, change in treatment plan, communication of results, and health care provider time.

Specific Aim 2

Our secondary aim is to evaluate patient and delivery factors that moderate the impact of digital delivery alternatives on short-term and longitudinal cognitive, affective, and behavioral outcomes and health care provider time.

Methods

We used the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist when writing this report [48].

Study Design

eREACH is a noninferiority study using a 2 × 2 design where traditional standard-of-care pretest (visit 1—education and consent) or posttest (visit 2—disclosure) counseling delivered by a GC are replaced with a patient-centered digital intervention (Figure 1). All patients randomized to the digital intervention can request to speak with a GC instead of completing the digital intervention or at any time during the process.

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Figure 1. Study schema. Genetic counseling was available for all eHealth (digital) visits upon request. V1: visit 1 (pretest education); V2: visit 2 (result disclosure).

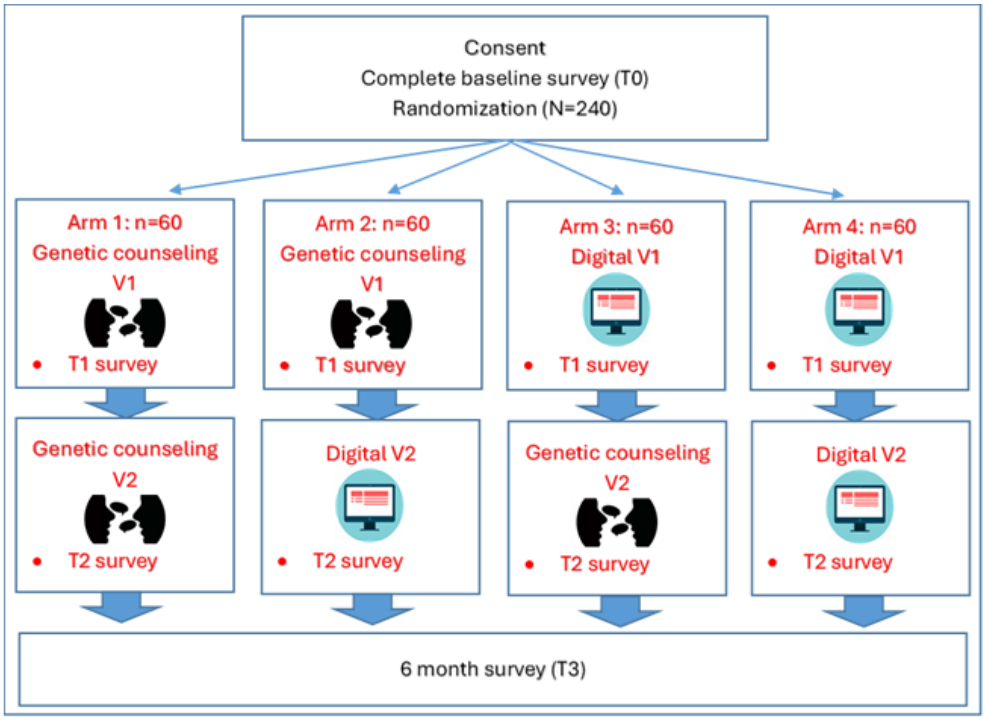

Ethical Considerations

This study has been approved by the University of Pennsylvania Institutional Review Board (protocol 833370). Any major protocol modifications will be reported in subsequent manuscripts describing study results. Recruitment emails to eligible participants include the study purpose and procedures as well as the direct REDCap (Research Electronic Data Capture; Vanderbilt University) web link to the electronic informed consent form, Health Insurance Portability and Accountability Act (HIPAA) document, and clinical consent to care (for patients new to Penn Medicine). Recruitment letter recipients can (1) immediately consent to the eREACH study directly using the provided electronic link, (2) request to speak with the research team for additional information, or (3) decline participation. Research staff follow up via email and telephone with individuals who do not respond. Individuals are given the option of signing a paper consent document if preferred. Reasons for declining are recorded, and all decliners are reminded that they can still receive counseling and testing services through usual resources. In addition, given the potential urgency for testing in patients with metastatic or advanced cancer, a verbal consent option is offered to interested participants not able to complete the electronic informed consent form and HIPAA document to reduce barriers to participation and testing. To ensure confidentiality, all responses and case characteristics will be deidentified. Participants will receive a US $10 gift card for each survey completed. With 4 surveys available, participants could receive up to US $40 in total for taking part in this study.

Patient-Centered eHealth Intervention

The patient-centered digital intervention is informed by the tiered-binned model and designed to replace a traditional counseling session for patients who find this to be sufficient information. The intervention includes tier 1 (indispensable information presented to all users) and optional tier 2 content (more in-depth information, examples, and videos). Completing tier 1 takes 11.5 to 14 minutes for the average user, and it takes 28 minutes to review all content and videos. Readability testing was completed for all content, and modifications were made to achieve a readability score of eighth grade or lower when possible. As shown in Table 1, the pretest intervention includes eight modules: (1) introduction, (2) purpose of testing, (3) genetics overview, (4) implications of results, (5) possible results and implications, (6) genetic testing options, (7) things to consider before genetic testing, and (8) testing decision. Example screenshots are shown in Figure 2.

After viewing the minimum tier 1 screens, participants are asked to record their decision to either proceed with testing and their testing choice (targeted test only, gene panel testing, or large or custom panel testing) *or* decline testing and their reason. Those who log a decision to move forward with testing have their selection, along with the details of their personal and family history, reviewed by a study GC. In the event that a study GC feels that an alternative decision for testing may be more appropriate based on family history, patients will receive a call and speak with the GC to confirm their decision.

The patient-centered digital result disclosure (visit 2) intervention includes four modules: (1) welcome page and instructions, (2) test result, (3) explanation of result, and (4) next steps (Table 2). Completing tier 1 once takes approximately 4 to 5 minutes for the average user, and it takes approximately 9 to 10 minutes to review all content and videos. Readability testing was completed for all content, and modifications were made to achieve a readability score of eighth grade or lower when possible. Example screenshots are shown in Figure 3.

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Table 1. eREACH (A Randomized Study of an eHealth Delivery Alternative for Cancer Genetic Testing for Hereditary Predisposition in Metastatic Breast, Ovarian, Prostate, and Pancreatic Cancer Patients) patient-centered eHealth pretest education (visit 1) intervention.

	Tier 1 content[a]	Tier 2 content	Tier 2 videos
Module 1—introduction	• Landing page and welcome (1 screen) • What is the eREACH study? (1 screen) • How to use this website (1 screen) • What to expect (overview of content and option to log testing decision at the end; 1 screen)	—[b]	—
Module 2—purpose of testing	• Role of genetic testing for patients with metastatic cancer (1 screen) • How testing might affect cancer treatment (1 screen)	• More information about PARPc inhibitors (1 screen) • More information about immunotherapy (1 screen)	—
Module 3—genetics overview	• Genes and mutations (4 brief sliding screens) • Difference between tumor (eg, somatic) and inherited genetic changes (1 screen) • How inherited mutations are passed down through families (1 screen) • Difference between sporadic and inherited cancers and examples and BRCA1 and BRCA2 example (2 screens) • Types of inherited cancer risk genes (high risk, moderate risk, and limited information; 1 screen)	• More information on inherited gene risks (4 screens), including high-risk genes (1 screen), moderate-risk genes (1 screen), and limited-information risk genes (1 screen) • Risks of cancer with each of the aforementioned genes (1)	• Basics of genetics (1 min, 19 s)
Module 4—implications of results	• How their results might impact their medical care (1 screen) • How their results might impact their family's medical care (1 screen)	• More information about PARP inhibitors (1 screen) • More information about immunotherapy (1 screen) • More information on cancer risks by gene and risk reduction options for relatives (1 screen)	—
Module 5—possible results and implications	• Types of results (positive, negative, and VUSd) and what they mean (1 screen)	• What is a VUS? (1 screen)	• What is a VUS? (3 min, 47 s)
Module 6—genetic testing options	• 3 testing options: targeted, panel, or customized panel (1 screen) • Benefits and limitations of each option (1 screen) • Choosing the test that is right for them (1 screen) • Things to consider before genetic testing (1 screen)	• How do patients decide on testing options (3 screens), including choosing option 1 (focused on treatment now; 1 screen), choosing option 2 (multigene panel; 1 screen), and choosing option 3 (customizing with a GCe)	• Genetic test panel options (2 min, 36 s) • Choosing a custom panel (1 min, 51 s)

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	Tier 1 content[a]	Tier 2 content	Tier 2 videos
Module 7—things to consider before genetic testing	• Risks and limitations of testing (2 screens) • Costs (billed to insurance; patients will be contacted if costs are of >US $100; 1 screen)	• What is a VUS? (1 screen) • Types of uncertainty (3 screens), including VUS (1 screen); uncertainties about risks or best medical management (1 screen); and uncertainty because family history does not match the gene mutation, with CDH1 example (1 screen) • More information on insurance coverage, financial assistance, and option to speak with a GC about potential costs (1 screen)	• What is a VUS? (3 min, 47 s)
Module 8—testing decision	• Next steps (GC review, sample collection, and average time for results; 1 screen) • Whether the patient has enough information and testing choice (2 screens) • Testing choice (1 screen)	—	—
Optional content	—	• Glossary of terms	—

[a]Completing tier 1 content takes 11.5-14 minutes to complete for the average user, and 28 minutes for all content and videos. Readability testing was completed for all content and modifications made to achieve a readability score of 8th grade or lower when possible.

[b]Not applicable.

[c]PARP: poly (adenosine diphosphate ribose) polymerase.

[d]VUS: variant of uncertain significance.

[e]GC: genetic counselor.

Figure 2. Examples of screens from the pretest counseling (visit 1) digital intervention.

Figure 3. Examples of screens from the post-test counseling (visit 2) digital intervention.

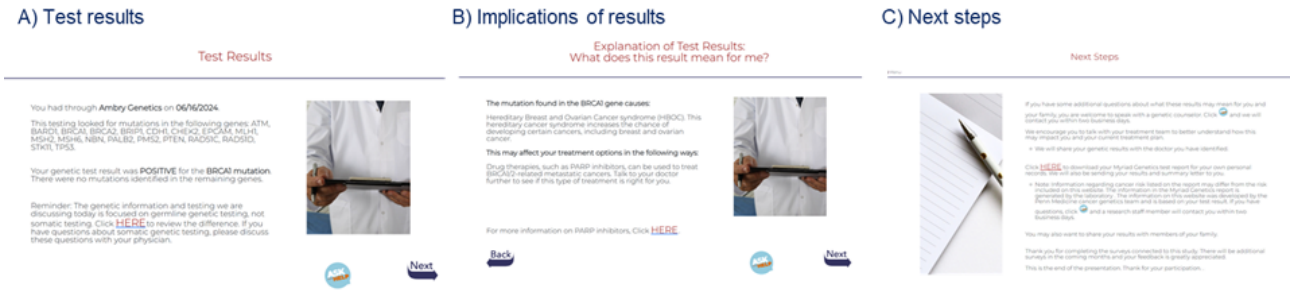

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Table 2. eREACH (A Randomized Study of an eHealth Delivery Alternative for Cancer Genetic Testing for Hereditary Predisposition in Metastatic Breast, Ovarian, Prostate, and Pancreatic Cancer Patients) patient-centered eHealth result disclosure (visit 2) intervention.

	Tier 1 content[a]	Tier 2 content	Tier 2 videos
Module 1—welcome page and instructions	• Overview and navigation instructions, including how to ask for help (1 screen)	• Reason for genetic testing (1 screen) • More information about PARPb inhibitors (1 screen) • More information about immunotherapy (1 screen) • Genetics overview (1 screen) • Types of results (positive, negative, and VUSc) and what they mean (1 screen) • What is a VUS?	• Genetic counselor explaining "a brief genetics lesson" (1 min, 19 s) • What is a VUS? (3 min, 47 s)
Module 2—test result	• Genetic test result and summary of genes tested (1 screen)	• Difference between tumor genetic changes (eg, somatic) and inherited genetic changes (1 screen)	—[d]
Module 3—explanation of result	• "What does this result mean for me?" (2 screens) • Follow-up recommendations (1 screen) • "What does this mean for my relatives?" (1 screen), including specific cancer risks for relatives if the patient tests positive (1 screen) and medical recommendations (1 screen)	• For positive results: what is a PARP inhibitor (1 screen) and more about cancer risk management for relatives (1 screen) • For VUS results: what is a VUS? (1 screen)	• What is a VUS? (3 min, 47 s)
Module 4—next steps	• Informing the patient that results have been shared with their health care provider and to talk with them about implications for treatment; recommendation to share the results with family members (1 screen)	• PDF of clinical test result available for download	—

[a]Completing Tier 1 content once takes approximately 4-5 minutes for the average user, and approximately 9-10 minutes for all content and videos. Readability testing was completed for all content and modifications made to achieve a readability score of 8th grade or lower when possible.

[b]PARP: poly (adenosine diphosphate ribose) polymerase.

[c]VUS: variant of uncertain significance.

[d]Not applicable.

Design and Development of the Web Intervention

The initial intervention content was reviewed with patients with cancer purposively selected to represent a range of ages, sexes, educational levels, and cancer types through individual user testing interviews (Table 3). We included both participants who had previously had and not had genetic counseling and testing to ensure a diverse range of perspectives in their feedback. Participants were asked to comment on the clarity, usefulness, and appearance of each screen. They were also asked to comment on proposed video topics, including usefulness, what they would expect to see covered in the video, and the likelihood of them watching the video. A total of 11 participants reviewed the pretesting education (visit 1) intervention content, and 8 reviewed the result disclosure (visit 2) intervention content. Interviews were reviewed to identify recommendations for changes or areas of confusion. Two research team members reviewed and selected key comments for consideration, and at least 2 research team members and a GC reviewed comments to consider changes to the content. All specific recommendations were considered, particularly cases in which more than one participant recommended a similar change. In scenarios in which user testing participants had conflicting recommendations, the team used best judgment to make changes. The most common recommendations to both the visit 1 and visit 2 interventions were to simplify content (eg, reduce words or details), address confusing content, change the order of the content, or move content to tier 2, as well as increase representativeness in photos, examples, and content.

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Table 3. Characteristics of the participants who completed the eREACH (A Randomized Study of an eHealth Delivery Alternative for Cancer Genetic Testing for Hereditary Predisposition in Metastatic Breast, Ovarian, Prostate, and Pancreatic Cancer Patients) user and usability testing.

Characteristic	User testing[a] (n=19)	Usability testing[b] (n=18)
Age (y), range	31-72	31-83
Sex, n (%)		
Female	13 (68)	8 (44)
Male	6 (32)	10 (56)
Race, n (%)		
Non-White	1 (5)	0 (0)
White	17 (89)	18 (100)
Declined to answer	1 (5)	0 (0)
Educational level, n (%)		
Some college or lower	3 (16)	2 (11)
College degree	4 (21)	5 (28)
Advanced degree	12 (63)	11 (61)
Personal history of cancer, n (%)		
Metastatic breast cancer	5 (26)	4 (22)
Advanced or metastatic ovarian cancer	3 (16)	1 (6)
Metastatic prostate cancer	5 (26)	7 (39)
Advanced or metastatic pancreatic cancer	6 (32)	6 (33)
Previous testing, n (%)		
Yes	13 (68)	15 (83)
No	3 (16)	3 (17)
In process[c]	3 (16)	0 (0)

[a]In total, 11 participants reviewed visit 1 content, and 8 participants reviewed visit 2 content.

[b]Nine participants reviewed visit 1 content, and 9 participants reviewed visit 2 content.

[c]Had had pretest counseling or blood drawn but no disclosure.

We completed usability testing with 18 participants, 9 (50%) who completed the visit 1 intervention and 9 (50%) who completed the visit 2 intervention (Table 3). These participants used the digital intervention and were asked to comment on things that were confusing, functions that were challenging, and other changes they suggested. A research assistant viewed their navigation through cobrowsing software. Several function challenges were identified, prompting revisions to the intervention. These included addressing clearer instructions and labeling for arrows, hyperlinks, and hover functions and addressing how to return to the main content after accessing tier 2 content. Some minor changes to content addressed participant comments regarding typos, confusing terms, and increasing representation in images and content. Representative user comments that resulted in key changes to the intervention are described in Table 4.

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Table 4. Summary of key changes made during development and design of the web intervention based on user comments during user and usability testing.

Key changes recommended	Representative user comments
User testing	
Simplify content	• "Don't like the small print. With 'chemobrain' this would be frustrating. Make it simple."
Address confusing content	• "...where it says 'unaffected family members have/will not have the option to pursue genetic testing.' According to what? Needs more clarification."
Change order of the content	• "Mention the glossary earlier on in the 'how to use this website' page so people know it is there from the get-go."
Move content to tier 2	• "Would like it to be shorter—what do people really need? Maybe make tiered 1 info as short as possible (10 slides) and everything else tier 2."
Usability testing	
Clearer instructions and labeling	• "Thought it would be nice to have text accompanying it [arrows] like the words 'next' and 'previous.'"
Hyperlinks and hover functions	• "Would like cursor to change when hovered over the menu—to indicate that you could click on it." • "On iphone—can't read instruction to hover over—too small."
Returning to main content from tier 2	• Some confusion about tier 2 loops—sometimes the forward arrow gets you back to where you started. Sometimes there is only a back arrow."
Correction of typos and confusing terms	• "'Targeted therapy' is not a phrase most people understand." • "Would expect more expanation or link to glossary for 'microsatilite instability.'"
Increase representativeness in photos	• "Noted throughout the images were of older folks and predominately white. Felt it should be more diverse to normalize genetic testing for a wider audience."

Setting

Remote genetic counseling services in this study are provided through the Penn Telegenetics Program and Penn Cancer Risk Evaluation Program. The Penn Telegenetics Program has developed procedures for individual patients and health care providers across the nation to access remote genetic counseling services. For patients outside Pennsylvania, the Penn Telegenetics GCs collaborate with local health care providers to provide genetic services in the home. This model includes a physician registration process to facilitate this collaborative care model and has been successfully used in related nationally recruiting studies (NCT04455698 and NCT05427240). The Penn Telegenetics GCs are licensed in all US states as required by state licensure laws [40].

Study Participants

Eligibility

Eligibility criteria include individuals diagnosed with metastatic breast or prostate cancer or advanced or metastatic ovarian or pancreatic cancer who are aged ≥18 years, able to understand and communicate in English, and residing in the United States. Exclusion criteria include uncorrected or uncompensated speech defects that would lead to the participant being unable to communicate effectively with a medical provider; uncontrolled psychiatric or mental conditions; or severe physical, neurological, or cognitive deficits rendering the individual unable to understand study goals or tasks. Participants who have already received cancer germline genetic testing are excluded.

Recruitment

Eligible patients can be referred by a health care provider or self-referred from a range of recruitment sources. First, at the University of Pennsylvania and affiliate oncology programs, members of the research team review treating physicians' schedules to identify potentially eligible patients and, with health care provider permission, contact them for enrollment. Health care providers in these programs can also directly refer patients to the research team. Second, the Penn Telegenetics Program provides remote clinical services at several regional centers without GCs on-site. Clinical coordinators and health care providers at these sites identify eligible patients in their practices and refer them to the research team. Third, cancer-specific support groups (eg, Facing Our Risk of Cancer Empowered and Cancer Support Community) advertise the eREACH study

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through study flyers and website banners. Patients can contact the eREACH team and enter the study as self-referrals. Finally, in collaboration with the University of Pennsylvania Office of Clinical Research, the team posts Facebook advertisements on ClinicalTrials@Penn. Interested patients can enter the study as self-referrals.

Health care providers who refer eligible patients can complete an online permission-to-contact registration form to provide contact information for the patient. Research staff then contact the patient via phone or email, which includes the study purpose and procedures and a REDCap link to the electronic informed consent form and HIPAA document. Potential participants receive up to 5 contacts, typically 3 emails and 2 phone calls. Recruitment invitations began in September 2020.

Enrollment Goals

As outlined in the following sections, we initially planned enrollment of 560 participants (120 participants per arm). Given the low initial recruitment (2020-2023), which was attributed to the COVID-19 pandemic, and an increase in mainstream testing in oncology practices (oncology health care providers ordering genetic testing without GCs), we re-evaluated our initial enrollment goals (see the Data Analysis Plan section). In December 2023, we adjusted our enrollment goal to 60 participants per arm with baseline (T0) and postdisclosure visit 2 (T2) data (at least 240 in total).

Study Arms

Overview

Once participants have completed informed consent, the baseline (T0) survey, and family history collection with research staff, they are randomized into 1 of the 4 study arms. Randomization is stratified by sex and cancer type using a permuted block design within strata for randomization. The allocation sequence was generated by the study biostatistician and made available to research staff.

Pretest Counseling (Visit 1)

Participants in the genetic counseling arms (A and B) complete their pretest counseling session via phone or videoconference (according to patient preference) in their home or their selected location. Penn Telegenetics GCs use communication protocols adapted from related studies [18,43]. The Penn Telegenetics team contacts participants up to 5 times to schedule their pretest counseling session. If a scheduled participant does not show up for their appointment, they are contacted 3 times to reschedule. If visit 1 is not completed, the corresponding health care provider is notified (if the participant was health care provider referred). Participants who select videoconference are provided links to download secure videoconferencing software on their home computer or device. The Penn Telegenetics team uses a HIPAA-compliant technology platform for videoconference visits. In our communication protocols, if videoconference technology fails, GCs convert the session to phone.

Participants randomized to the digital intervention arms (C and D) are provided with instructions for obtaining a private code to access the pretest counseling digital intervention. Participants are informed that they can choose to schedule a counseling session with a GC if they do not wish to access the digital intervention or do not have online access. They can also ask to speak with a GC at any point.

Participants are asked to complete a post–visit 1 survey (T1) after completing counseling or the visit 1 digital intervention. While participants will be asked to complete the survey within 72 hours (3 days), surveys that are completed up to 7 days after consent are still accepted.

Genetic Testing

In all study arms, there are 3 available options for testing (Figure 4). Option 1 is a targeted panel limited to genes that could immediately impact treatment for metastatic cancer (*BRCA1* and *BRCA2* and Lynch syndrome). Additional homologous recombination repair genes will be tested for patients with prostate cancer based on the Food and Drug Administration label for the use of PARP inhibitors in this tumor type. Option 2 is a larger gene panel including additional genes related to their cancer type that could have an impact on treatment in the future or additional impact for relatives. Option 3 is a customized panel based on other health concerns or a desire to exclude particular genes. For option 3, participants are asked to speak with a GC to review their concerns and options. Those who log a decision on the digital intervention (arms C and D) have their selection, along with the details of their personal and family history, reviewed by their assigned study GC. In the event that the GC feels that an alternative decision for testing may be more appropriate (ie, the participant selects the targeted panel when a large or custom panel may be indicated), the GC calls the participant to confirm their decision. Self-referred participants are asked to provide contact information for an oncologist (or other health care provider) to serve as the ordering health care provider with the GC as required by state licensure laws. The Penn Telegenetics clinical team contacts the health care provider's office to give them information about the program and procedures and confirm the health care provider's information to include in the testing order.

Consistent with current clinical care, all genetic testing will be sent to a commercial laboratory (eg, Invitae or Ambry Genetics) and covered by insurance. At the time, laboratories would notify patients if out-of-pocket expenses of >US $100 were expected. Patients are instructed to contact the GC for any questions regarding coverage and cost. Test kits are sent to the participants' home, and participants receive as many as 3 reminders to return their test kits. When requested, patients can have their samples collected at the University of Pennsylvania phlebotomy laboratory.

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Figure 4. Participant options for genetic testing. eREACH: A Randomized Study of an eHealth Delivery Alternative for Cancer Genetic Testing for Hereditary Predisposition in Metastatic Breast, Ovarian, Prostate, and Pancreatic Cancer Patients.

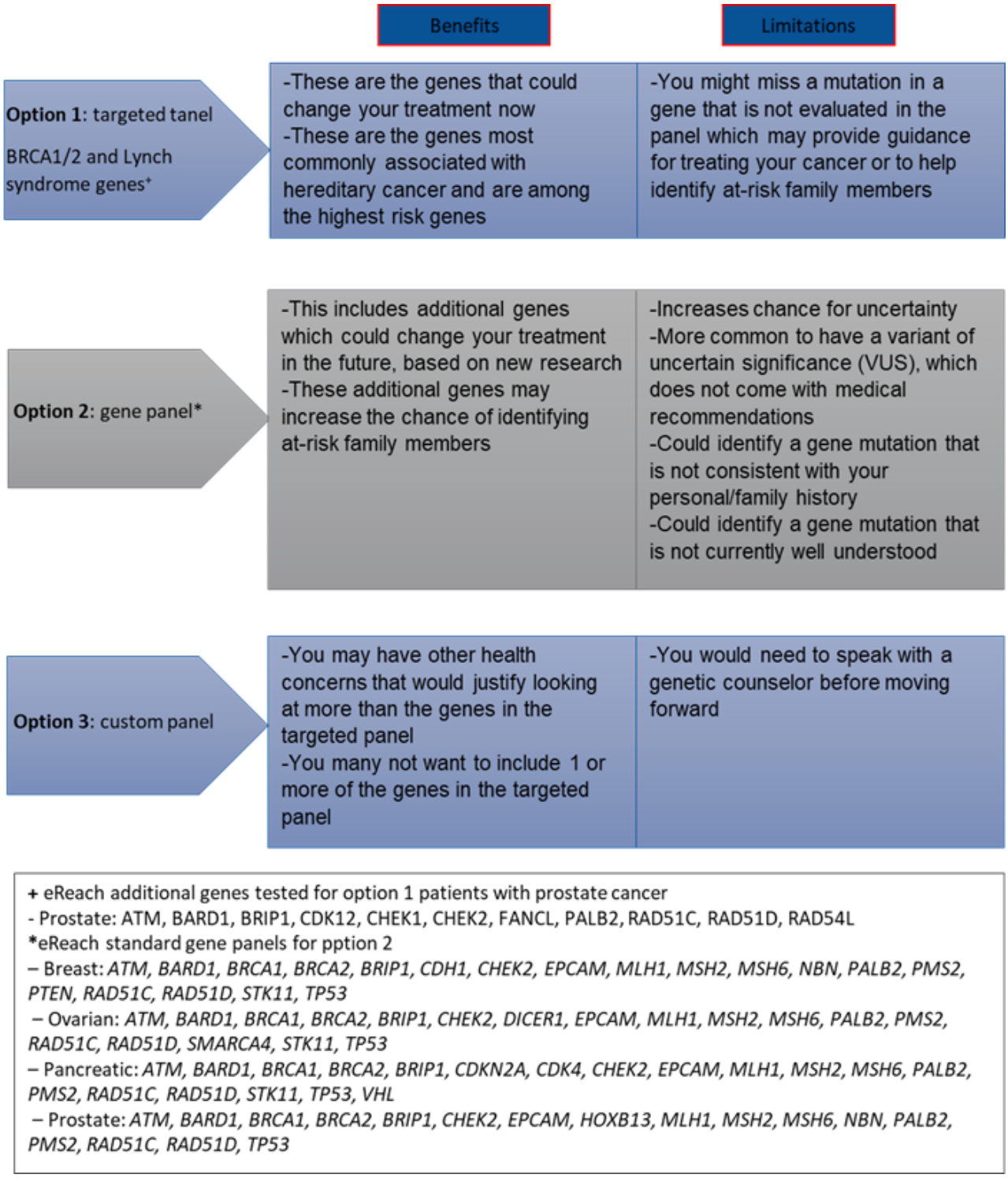

Disclosure of Results (Visit 2)

Those randomized to genetic counseling for visit 2 (arms A and C) are contacted via phone by their assigned GC to share their results. These are not scheduled calls, and GCs make up to 5 attempts over 10 days (routine cases) and up to 3 attempts over 3 days (urgent cases). For the disclosure sessions, a visual aid packet that is publicly available for clinical use, is provided to all participants, GCs complete disclosure checklists, and all sessions are recorded unless participants decline.

Those randomized to the digital intervention for visit 2 (arms B and D) are provided with their result and gene-specific screens (as appropriate), which are first reviewed by 2 study team members (a research team member and the GC) for accuracy and quality control. Results are uploaded into the digital intervention by a study team member. Participants are notified via email that results are available and can be accessed and that they can request to speak with a GC if they prefer before or after viewing their results. After return of results, the GC provides the referring or registered health care provider with

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the genetic test results and chart note. GCs are available to answer any patient or health care provider questions. Study team members contact patients via email or phone up to 5 times every 2 to 3 days for those who have not accessed the digital intervention after their results have been released. If results are not viewed after these reminders, the participants are contacted by their assigned GC to attempt to disclose results. If this is unsuccessful, a notification is sent to the treating physician to make them aware, and the results are provided to the treating physician. As of September 2023, all results have been also uploaded to the electronic medical record in accordance with Penn Medicine's policies to comply with the 21st Century Cures Act.

Outcomes

Uptake of Testing and Patient-Reported Outcomes (Aim 1)

Theoretically informed patient-reported cognitive, affective, and behavioral outcomes of genetic services will be collected at baseline (T0), after visit 1 (T1) and visit 2 (T2), and at 6 months (T3).

Uptake of counseling and testing is assessed through Penn Telegenetics service records for those assigned to (or who select) standard-of-care genetic counseling. Uptake for those assigned to the digital intervention will be recorded as completion of the digital intervention.

Understanding of genetic information is assessed at all time points (T0-T3). Knowledge of genetic disease will be evaluated using The KnowGene Scale, a 16-item scale administered to patients after genetic counseling and testing to measure their understanding of the health implications of genetic test results. It includes health implications to oneself as well as relatives and covers penetrance, actionability, limitations of current technology, and monogenic inheritance patterns [49].

Reactions to genetic information are assessed using multiple instruments that evaluate psychological distress, adjustment, and satisfaction:

- General anxiety and depression are assessed using the 4-item short Patient-Reported Outcomes Measurement Information System [50,51].
- Disease-specific distress is measured using the 8-item Impact of Event Scale [52-55], which has strong internal consistency (Cronbach α=0.82-0.90) in genetic delivery studies [56-58].
- Satisfaction with genetic services is assessed using 14 items evaluating satisfaction with genetic services (T1 and T2). These items have been used in our related studies evaluating alternative and traditional genetic testing delivery models (Cronbach α=0.73-0.85) and adapted for digital delivery [17,56,57,59-62].
- Multidimensional responses to genetic testing, including positive responses and uncertainty, will be assessed using the Multidimensional Impact of Cancer Risk Assessment questionnaire at T2 and T3. The Multidimensional Impact of Cancer Risk Assessment questionnaire has been used in many genetic studies to evaluate distress, uncertainty, and positive responses to receipt of genetic test results [63]. Four items were excluded as they were not relevant to patients with metastatic cancer.
- Decisional regret (T2 and T3 only) is assessed using the 5-item validated Decision Regret Scale used frequently in related genetic studies [64,65].

Use of genomic information includes change in treatment plan and communication of results (T3) to health care providers, family members, and others using items adapted from our related studies. For all actionable results (*BRCA1* and *BRCA2* and Lynch syndrome genes), we either confirm changes in the treatment plan in the medical record (Penn Medicine patient and health care provider participants) or by contacting the treating oncologist for confirmation of whether the patient received a PARP inhibitor or immunotherapy and, if not, why.

Health care provider time is recorded per patient for a subset of participants to estimate health care provider time by arm. This includes time for remote telehealth counseling. For patients in arms B to D, where services have the potential to be completed partially or entirely by the digital intervention, these patients will still have a GC review their history, decision, and support testing submission; review results and the disclosure information provided; and be available for questions upon request. Thus, in all arms, GC time for case review, genetic counseling, and conversations with patients and their health care providers will be recorded for a subset of patients.

Moderators of Uptake and Patient-Reported Outcomes (Aim 2)

Moderators are collected at baseline and include the following:

- Sociodemographic data, including race and ethnicity, educational level, marital status, sex, and age.
- Health literacy—assessed using 3 Brief Health Literacy Screen items that have been validated to detect inadequate health literacy in clinical medical populations [66].
- Comfort with technology—assessed using 8 selected Health Information National Trends Survey items [67].
- Psychological impacts due to the COVID-19 pandemic—assessed in a subset of patients (start of recruitment until May 2023) using the Social Psychological Measurements of COVID-19: Coronavirus Perceived Threat, Government response, Impacts, and Experiences Questionnaires, a 14-item measure previously published by the University of Montana in April 2020. While this protocol is independent of COVID-19, it was advised to use a measure that may help assess for psychological distress that is due to the COVID-19 pandemic separate or in addition to any psychological impacts from receiving genetic testing results [68].

In addition, individual use of the digital intervention is recorded throughout the study to evaluate the impact of intervention use (eg, dosage) on outcomes and who benefits more and less from the intervention. Intervention use includes actual use, adherence, and attrition [69,70]. For actual use, we record the time when each participant logs in and logs out. Actual use will be evaluated for the intervention in general and secondarily for specific intervention content (eg, videos and specific pages).

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Adherence will be defined as completing all of tier 1 at least once.

Data Analysis Plan

Primary Noninferiority Analysis

We hypothesize that the intervention arms incorporating the digital delivery intervention, with access to a GC upon request, can yield equal or improved short-term and longitudinal cognitive, affective, and behavioral outcomes and lower health care provider time. Our primary outcomes are change between T0 and T2 in knowledge and anxiety. We will test whether the digital intervention is noninferior to standard-of-care counseling with a GC. In noninferiority tests, the null and alternative hypotheses are the reverse of the usual; in this case, the null hypothesis is that the web intervention is worse than the standard of care. We will conclude that the web intervention is noninferior using a modified noninferiority ANOVA of the T2 minus T0 change scores. More details on the power and type I error are provided in the following section. We will use an intention-to-treat approach comparing randomization arms, but we will also confirm results in secondary per-protocol analyses; many recommend that both intention-to-treat and per-protocol analyses be consistent to declare noninferiority [71]. In secondary analyses, we will test pairwise differences among the 4 groups. For longitudinal analyses across the 3 survey times (T0-T3), we will examine time trajectories using regressions estimated through generalized estimating equations to account for within-subject correlation over time. We will include main and interaction terms of arm with time panel indicators.

Our noninferiority test will be based on an ANOVA F statistic test jointly comparing the 4 randomization arms, in which we declare noninferiority if the joint P value is of >.15 and all 3 experimental web arms have an observed standardized effect of −0.25 SD units or better (with the direction standardized such that higher values imply more beneficial change) when compared to the control standard of care–only arm. If the ANOVA F test P value is ≤.15, then we will declare noninferiority if the 3 standardized one-sided 85% confidence bounds for the 3 intervention arms relative to the controls are >−0.35 SDs. We define standardization as rescaling variables to have an SD of 1 relative to the pooled baseline SD (see more details in the following section).

Sample Size Justification for Aim 1

We originally anticipated 140 participants per arm (560 in total). We chose our 2 primary variables as they demonstrated possible differences between groups in preliminary data from a prior study in which genetic test results were returned to patients; in this study, we expect that harmful changes will not occur. We will use a noninferiority test and, to be conservative, will require noninferiority in both the intention-to-treat and per-protocol analyses, as recommended [71].

With 140 people per arm, we have <1% noninferiority type I error and >82% noninferiority power if we simply use the first criteria that the P value must be >.15 and all 3 intervention arm coefficients must be >−0.25 (ie, in the direction away from being harmful when compared to the standard-of-care group). If we further apply the decision rule that the 85% one-sided CIs are bounded away from −0.35 if P≤.15, the power increases to 94%, and the type I error rate remains at <1%.

In calculating the type I error rate, we assumed that the 4–change score standardized means (standardized to have an SD of 1) for the null hypothesis were 0 (arm A=control group), 0.3 (single web intervention arms), and −0.6 (double web intervention arm), with negative values indicating a harmful effect. Our alternative hypothesis was a null effect (4–change score means of 0). These were conservative estimates of changes based on standardized RESPECT web intervention findings of a change score movement of 0.3 in anxiety and a change score movement of 0.4 in knowledge. Hence, we have excellent noninferiority power. Calculations were made using PASS (version 11; NCSS Statistical Software) in conjunction with R simulations (R Foundation for Statistical Computing). In secondary analyses, we will examine pairwise comparisons among the 4 arms using 2-tailed t tests.

In Multimedia Appendix 1, we provide the probability of declaring noninferiority under a range of assumptions about the intervention effects relative to the standard-of-care control arm. We see that our probability of declaring noninferiority is appropriate under several assumptions about population-level mean differences among arms.

On the basis of low recruitment, we conducted an unplanned conditional power calculation (December 1, 2023) using data recorded until October 24, 2023, to determine whether it would be appropriate to end recruitment at 60 participants per arm. The statistician and the principal investigator were unblinded to the analysis, but the rest of the staff and coinvestigators were blinded. We used the same decision rules for declaring noninferiority as mentioned previously. We present the findings in Table 5. In the “Original assumptions” section, we replicated the findings of the original power calculations (Multimedia Appendix 1) but, instead, assumed a sample size of 60 participants per arm. In the “Genetic knowledge” and “PROMIS anxiety” sections, we conditioned on the probability of declaring the study noninferior on the observed data from the first participants enrolled through October 2023. Next, we simulated data for the future participants based on the assumptions in each row. We added the simulated data to the observed data and tested our noninferiority hypothesis. We iterated the simulations 50,000 times, creating simulated future participant data each time, and calculated the proportion of iterations in which we would conclude noninferiority. Conditioning on the data obtained until October 24, 2023, we have excellent power under assumptions of no effect or beneficial effects or an assumption that the future data will have the same average responses as the data collected until October 24, 2023. For anxiety, the noninferiority type I error rate (ie, the probability of declaring the study noninferior if the intervention is harmful) is still relatively low, which is appropriate.

Regarding standardization, we will standardize the change scores with respect to the baseline SD among the 4 groups (ie, before patients have received any component of the intervention). Hence, our power calculations assume change score SDs of 1, which would be the case if the within-person correlation of measurement between periods is 0.5 (SD of change score = 1

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$+ 1 - 2 \times 0.5 \times 1 = 1$). If the correlation is of >0.5, as may likely be the case, the power will be better.

Regarding the choice of −0.25 as a lower noninferiority bound, we chose −0.25 as an absolute 0.25 standardized effect is often considered a small effect. Hence, our noninferiority margin only tolerates small negative effects. If the *P* value is of ≤.15, we nonetheless ensure that the bound of the one-sided CI is >–0.35, which is still of modest magnitude.

Regarding the choice of our alternative hypothesis, it assumes that all average change scores are 0 (4 mean changes of 0). This is conservative as it does not assume any benefit of the interventions when compared to arm A (the control group). If the web intervention does have a beneficial effect, the power for the noninferiority design will be even better, as shown in Multimedia Appendix 1 and Table 5.

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Table 5. Probability of declaring the study noninferior under various assumptions about standardized change score means (N=60 per arm; SD 1 for all mean values).

General assumption	Arm A (control), mean (SD)	Arm B (web visit 2), mean (SD)	Arm C (web visit 1), mean (SD)	Arm D (web visits 1 and 2), mean (SD)	Probability of declaring the study noninferior (%)
Original assumptions (unconditional on observed data)					
No effect (power)	0	0	0	0	79
Arm B and arm C beneficial	0	0.2	0.2	0	86
Web intervention slightly beneficial	0	0.1	0.1	0.1	92
Heterogeneous effects	0	−0.1	0.1	0	71
Web intervention slightly harmful	0	−0.1	−0.1	−0.1	59
Web intervention harmful—small effect	0	−0.2	−0.2	−0.2	36
Web intervention harmful—relatively small effect	0	−0.25	−0.25	−0.25	25
Web intervention harmful—modest effect	0	−0.3	−0.3	−0.3	16
Only Arm B harmful	0	−0.35	0	0	23
Web intervention harmful—moderate effect	0	−0.35	−0.35	−0.35	9
Arm D very harmful (type I error)	0	−0.3	−0.3	−0.6	2
Genetic knowledge — conditional on observed data (higher scores are better)					
No effect	0	0	0	0	99
Arm B and arm C beneficial	0	0.2	0.2	0	100
Web intervention slightly beneficial	0	0.1	0.1	0.1	100
Heterogeneous effects	0	−0.1	0.1	0	99
Web intervention slightly harmful	0	−0.1	−0.1	−0.1	99
Web intervention harmful—small effect	0	−0.2	−0.2	−0.2	97
Web intervention harmful—relatively small effect	0	−0.25	−0.25	−0.25	96
Web intervention harmful—modest effect	0	−0.3	−0.3	−0.3	95
Only arm B harmful	0	−0.35	0	0	86
Web intervention harmful—moderate effect	0	−0.35	−0.35	−0.35	93
Arm D very harmful	0	−0.3	−0.3	−0.6	97
Observed effects until October 2023	0	Blinded	Blinded	Blinded	98
PROMIS [a] anxiety (conditional on observed data; direction of effect reversed so that higher scores are better)					
No effect	0	0	0	0	92

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General assumption	Arm A (control), mean (SD)	Arm B (web visit 2), mean (SD)	Arm C (web visit 1), mean (SD)	Arm D (web visits 1 and 2), mean (SD)	Probability of declaring the study noninferior (%)
Arm B and arm C beneficial	0	0.2	0.2	0	91
Web intervention slightly beneficial	0	0.1	0.1	0.1	96
Heterogeneous effects	0	−0.1	0.1	0	89
Web intervention slightly harmful	0	−0.1	−0.1	−0.1	84
Web intervention harmful—small effect	0	−0.2	−0.2	−0.2	72
Web intervention harmful—relatively small effect	0	−0.25	−0.25	−0.25	64
Web intervention harmful—modest effect	0	−0.3	−0.3	−0.3	56
Only arm B harmful	0	−0.35	0	0	73
Web intervention harmful—moderate effect	0	−0.35	−0.35	−0.35	47
Arm D very harmful	0	−0.3	−0.3	−0.6	17
Observed effects until October 2023	0	Blinded	Blinded	Blinded	98

[a]PROMIS: Patient-Reported Outcomes Measurement Information System.

Missing Data

We will conduct complete case analyses for the primary analyses. If there are substantial missing data, we will repeat analyses using the multiple imputation methods by Raghunathan et al [72]. The multiple imputation analyses will be considered secondary sensitivity analyses to investigate how missing data might be affecting inferences.

Additional Secondary Analyses for Aim 1 (Amendment Added in July 2023)

As treatment effects might differ with changes in procedures related to the 21st Century Cures Act period (before vs after the implementation of immediate genetic test result release to patients at the University of Pennsylvania), we will estimate interaction regression models of the primary and secondary end point in which we include dichotomized period (0 or 1; no or yes; before July 2023 vs after July 2023), randomization arm, and the interaction between period and randomization arm (randomization arm indicators × period) as covariates in the model. In addition, we will examine interaction models in which we compare outcomes of people who receive results before their study protocol disclosure method appointment with those who do not receive results before their study protocol disclosure method appointment. We will exclude those who do not receive results at all in this secondary analysis examining the potential moderation effect of preappointment disclosure.

Moderator Analysis

We will evaluate moderators of outcomes, identifying those who benefit more and less from the intervention in clinical practice. For moderation (ie, effect modifier analyses), we will include in the generalized estimating equations–estimated regressions indicators (0 or 1 variables) denoting randomization arms, the potential moderator variable, and interaction terms between the moderators and randomization indicators (ie, an interaction term will be created by multiplying 2 terms). We will further examine 3-way interaction models in which we include time interactions. To maintain power to detect moderation, we will examine nontime moderators separately. We will also examine adding potential confounders to models. For all analyses, we will examine effects after assigning participants to intention-to-treat, per-protocol, and as-treated groups.

Results

IRB approval was obtained in June 2019 and recruitment began in August 2020. We have completed the enrollment of 256 study participants and data collection was completed in September 2024. Data analysis is ongoing and we expect results to be published in Fall 2025.

Discussion

Expected Findings

We hypothesize that our digital delivery of pretest or posttest genetic counseling will yield equivalent or improved outcomes compared to the traditional 2-visit standard-of-care delivery model with a GC. This model has the potential to expand access to genetic services by leveraging digital technologies. For patients with metastatic cancers, access to genetic services is a necessary step to gain access to targeted therapeutic treatments,

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and our model may lead to improved access to targeted therapy reliant on germline genetic testing. We hypothesize that participants randomized to digital genetic counseling arms will experience noninferior changes in genetic knowledge and general anxiety compared to those randomized to the standard 2-visit genetic counseling model. We also predict that uptake of genetic testing, depression, cancer-specific distress, and health care provider time will be equivalent or improved in digital arms compared to the standard-of-care arm. Furthermore, we will explore demographic and clinical factors associated with uptake of the intervention and testing.

Several related studies looking at various alternative delivery models were ongoing at the time the eREACH study was designed and started recruiting [19-21,36,71,73]. Two studies among patients with prostate cancer (Technology-Enhanced Acceleration of Germline Evaluation for Therapy [TARGET] and ProGen) have been completed and found that digital pretest educational tools were noninferior to traditional genetic counseling [19,20]. TARGET used an educational web tool, and ProGen tested an educational video that was delivered to participants in person. Posttesting disclosure was performed by a GC in both studies [19,20]. The Making Genetic Testing Accessible (MAGENTA) study demonstrated that omitting pretest counseling for all participants and posttest counseling for participants without a pathogenic variant was noninferior to phone-based genetic counseling in terms of posttest distress [21]. MAGENTA included patients with breast cancer (3.3% of the total cohort) or a family history suggestive of a hereditary cancer syndrome but not patients with advanced or metastatic cancer. In addition, participants were highly educated (88.9% with some college education or higher) and mostly White individuals (95.3%) and likely represent an early adoption population; findings may be different in a diverse clinical population of patients with advanced cancer. While these studies support the premise that digital delivery alternatives may play a role in clinical genetics, there are no published randomized studies comparing the outcomes of using digital alternatives for returning genetic results to those of the traditional model of genetic counseling in metastatic cancer genetics (where testing is more complex and routinely now includes at least an option for multigene panels) and in diverse patient populations more reflective of real-world clinical practice. The eREACH study will address this gap in the literature by evaluating the efficacy of the proposed patient-centered digital delivery of pretest or posttest counseling for genetic testing among patients with metastatic breast or prostate cancer or advanced or metastatic ovarian or pancreatic cancer.

Another frequently endorsed model to increase uptake of testing is “mainstreaming,” wherein the traditional pretesting counseling session with a GC is replaced with educational materials and a conversation with a cancer care provider, such as an oncologist [15,74]. This provider orders the genetic test that they deem to be most appropriate, and results are disclosed by the medical provider with the option for a GC on patient request, when a positive result or a variant of uncertain significance is identified, or in the setting of a family history of cancer or a known familial mutation. A recent systematic review and meta-analysis identified 29 studies on mainstreaming, of which only 5 assessed patient-reported outcomes such as anxiety, depression, and decisional conflict [74]. Importantly, there are no published studies comparing mainstreaming to the traditional 2-visit genetic counseling model in which multigene panel genetic testing is offered. However, some of these studies include models that can be compared to arm C of the eREACH study (web intervention and GC), and we will be able to compare our patient-reported outcomes to those of studies that reported similar longitudinal measures.

The findings of this study will help determine whether the use of digital delivery of genetic counseling is an effective model for patients with metastatic cancers. If deemed noninferior, the eREACH study will provide an evidence base for a scalable digital model for genetic counseling for diverse and real-world patients with cancer in academic and community settings.

Strengths and Limitations

We may encounter potential challenges in this study. Loss to attrition for the surveys may result in missing data. We will monitor completion rates during our quality control checks and assess and address barriers to survey completion during the study period. Inability to contact treating health care providers could result in missing data regarding the use of genetic test results for participants outside of the Penn Medicine system. Some health care providers may not be willing to serve as the ordering health care provider for genetic testing services. Although we have not experienced significant challenges with local physicians being willing to register with the Penn Telegenetics program, identifying and understanding barriers to oncologist uptake would be important for future implementation of this model. The financial burden of genetic testing may limit patient access to these services. We do not anticipate that this will be a common issue, but understanding these barriers to testing would also be important for future iterations of our delivery model. The inclusion of self-referred participants has the potential to introduce a selection bias wherein patients with higher digital literacy may be more likely to participate in this study. Given that this is a randomized trial, such participants should be evenly distributed between study arms, thus only potentially posing a threat to generalizability. To address generalizability, we will compare the digital literacy of the study population to that of the general population using available normative data from the Health Information National Trends Survey. Finally, our delivery model includes the involvement of a GC (even if there is no direct contact with the patient), whereas mainstream testing, with no involvement of GC, has become increasingly common. While we will not be able to conduct direct comparisons to these different delivery models in this randomized trial, we expect to be able to compare our results to those of other studies that may evaluate the outcomes of mainstream testing, assuming that they assess similar patient-reported outcomes and use similar measures.

Future Directions

The eREACH study will provide critical empirical data on the effectiveness of an interactive patient-centered digital intervention to deliver clinical genetic testing to patients with metastatic cancers. We expect that this work will inform evidence-based guidelines and the standard of care for delivery

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of genetic testing, and it is designed to be broadly applicable and easily adaptable for other populations and settings even beyond oncology.

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Data Availability

The datasets generated or analyzed during this study are not publicly available as participants were not consented with knowledge of data sharing, but summary deidentified data are available from the corresponding author on reasonable request. The study principal investigator will have access to the final trial dataset.

Authors' Contributions

KTL contributed to visualization and writing—original draft.
BM contributed to writing—review and editing.
BE contributed to formal analysis, writing—original draft, and writing—review and editing.
SB contributed to investigation and writing—review and editing.
S Howe contributed to investigation and writing—review and editing.
D Fetzer contributed to writing—review and editing.
LG contributed to writing—review and editing.
CC contributed to writing—review and editing.
DC contributed to writing—review and editing.
SD contributed to investigation and writing—review and editing.
JE contributed to investigation and writing—review and editing.
D Falcone contributed to project administration, visualization, and writing—review and editing.
DO contributed to writing—review and editing.
HG contributed to writing—review and editing.
RM contributed to investigation and writing—review and editing.
S Hernandez contributed to investigation and writing—review and editing.
LF contributed to writing—review and editing.
KK contributed to project administration and writing—review and editing.
ES contributed to writing—review and editing.
AT contributed to writing—review and editing.
LW contributed to writing—review and editing.
MW contributed to writing—review and editing.
KY-W contributed to writing—review and editing.
EW contributed to writing—review and editing.
AB contributed to conceptualization, funding acquisition, investigation, supervision, and writing—review and editing.

Conflicts of Interest

ARB has received research funds from AstraZeneca for this study. All other authors declare no conflicts of interest.

Multimedia Appendix 1
Original power calculations: probability of declaring noninferior under various assumptions about standardized change score means. N=140/arm.
[DOCX File , 19 KB - resprot_v14i1e72515_app1.docx]

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Abbreviations

eREACH: A Randomized Study of an eHealth Delivery Alternative for Cancer Genetic Testing for Hereditary Predisposition in Metastatic Breast, Ovarian, Prostate, and Pancreatic Cancer Patients
GC: genetic counselor
HIPAA: Health Insurance Portability and Accountability Act
MAGENTA: Making Genetic Testing Accessible
PARP: poly (adenosine diphosphate ribose) polymerase
REDCap: Research Electronic Data Capture
RESPECT: Returning Genetic Research Panel Results for Breast Cancer Susceptibility
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TARGET: Technology-Enhanced Acceleration of Germline Evaluation for Therapy

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Protocol

Informing Facility Selection Through a Web-Based User Ratings System: Protocol for a Randomized Controlled Trial Among Mothers in Urban Lao People's Democratic Republic

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Abstract

Background: Despite the increasing options for public and private health care providers in the Lao People's Democratic Republic (Lao PDR), choosing a high-quality provider or facility is difficult because timely and reliable information about providers is not readily available. Additionally, only 28% described their most recent visit to a health care provider as high quality, suggesting that while options for care are expanding, people may need support in finding providers that meet their quality needs. To inform efforts to improve access to high-quality care, evidence is needed on mechanisms that empower people to identify and use such care. The rapid adoption of mobile phones in Lao PDR, particularly in urban areas, offers opportunities to enhance access to timely, reliable information about health care facilities.

Objective: This study aims to conduct an unblinded randomized controlled experiment using mobile phones to study whether routinely collected information on quality of care can improve access to high-quality care and patient satisfaction.

Methods: Mothers with at least one child under 2 years of age who are already enrolled in the Vientiane Multigenerational Birth Cohort (VITERBI) will be invited to participate during in-person visits by the research staff. Participants will be randomly assigned in equal numbers to the control and intervention groups. The intervention group will receive a URL with facility ratings for pediatric health care services every 2 weeks via WhatsApp; the control group will not receive any messages. WhatsApp will also be used to administer biweekly surveys to both groups to assess the quality of care received in the past 2 weeks. The web page shared with the intervention group will display results from these surveys and from the pilot study. Research staff will conduct baseline and endline surveys with all participants during in-person visits, 3 months apart.

Results: The trial is currently underway and scheduled for completion in 2025.

Conclusions: This study will use a demand-side intervention to increase demand for high-quality child health care among mothers in Vientiane Capital. We will assess whether information on the quality of health care facilities—generated by study participants during the study period—influences mothers to change their preferred providers for nonurgent conditions.

Trial Registration: ClinicalTrials.gov NCT06304831; https://www.clinicaltrials.gov/study/NCT06304831

International Registered Report Identifier (IRRID): DERR1-10.2196/66085

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KEYWORDS

randomized controlled trial; health care systems; quality of care; health care utilization; eHealth

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Introduction

While access to health care is expanding globally, there is appreciable variation in quality among providers, with low-quality care accounting for up to 5 million deaths each year [1]. These numbers are expected to grow as more people seek care and as the burden of disease shifts to complex conditions. Expanding access has also increased the options for public and private health care providers. Selecting a provider or facility, however, is difficult because timely and reliable information about providers is not readily available. In the Lao People's Democratic Republic (Lao PDR), only 28% of people describe their recent visit to a health care provider as high quality [2], suggesting that while options for care are increasing, people may need support to find providers that meet their quality needs.

In order to inform efforts to improve people's access to high-quality care, there is a need for evidence on mechanisms that empower people to identify and use such care. In low- and middle-income countries, the majority of efforts to date have focused on supply-side measures, such as enhancing the availability of medicines and equipment, introducing financing mechanisms that promote quality care, and strengthening the clinical competencies of health workers [1,3]. However, generating greater demand for health system quality is a key element of quality improvement strategies in low- and middle-income countries [4]. While there are new initiatives to study population perspectives and people's care experiences, measures to "ignite demand" for high-quality care remain poorly understood.

Patients often face significant information asymmetry due to their lack of medical expertise, which prevents them from accurately assessing the quality of care they receive. This asymmetry, coupled with a lack of information about the quality of health care providers, results in suboptimal health care decisions and forces patients to rely on word of mouth or the reputation of providers [5]. Empirical evidence suggests that quality metrics can influence patient choices [6,7]. Additionally, recent studies have shown that online reviews can affect the selection of health care providers [8,9]. Therefore, given the large variation in the quality of care in low-resource settings [10,11], providing quality information can empower patients to make better-informed decisions about their health care.

We plan to conduct a randomized controlled experiment using mobile phones to study whether routinely collected information on quality of care can improve access to high-quality care and patient satisfaction. Specifically, we will examine whether participants switched providers—as a measure of improved access to quality care—based on the information provided, and whether such information led women to be more satisfied with the health care services received for their child or children. The rationale for the study is that access to the intervention (user ratings of health care facilities) can influence where caregivers seek care for their children. By providing information to caregivers across multiple quality domains that matter to users (ie, provider skill, provider respectfulness, cost, waiting time, staff helpfulness, and cleanliness), the intervention is intended to increase caregivers' awareness of differences in quality and empower them to make more informed choices. We hypothesize that this increased awareness may lead to switching to better-rated facilities, particularly for nonurgent conditions—the study's primary outcome. Additionally, making a more informed choice may result in greater satisfaction with the care received, due either to actual improvements in service quality or to closer alignment between expectations and experiences.

To explore these pathways, we include secondary outcomes that capture reported use of the ratings website, its perceived influence on facility selection, caregiver confidence in decision-making, and perceived quality of care. These measures will help us interpret the mechanisms through which the intervention may affect the primary outcome.

Study participants will include mothers living in 2 urban districts in Vientiane, the capital city, who have children under 2 years of age and are already enrolled in an ongoing Vientiane Multigenerational Birth Cohort (VITERBI), which includes the entire population of children born in the past 2 years in the study districts.

Methods

Participants and Randomization

This study consists of a randomized controlled experiment involving 660 mothers with children under 2 years of age from an ongoing VITERBI study, which includes the local population of young mothers in 4 districts of Vientiane Capital. Mothers with at least one child under 2 years old, already enrolled in the VITERBI study and living in 1 of 2 urban districts (Sikhottabong or Chanthabouly), will be invited to participate in the study during in-person visits by the research staff. We will use rolling enrollment while ensuring that each participant is enrolled in the study for a maximum of 3 months. Participants will be randomly assigned to 1 of 2 groups: (1) a control group that will not receive any information about providers, and (2) an intervention group that will receive biweekly updates on quality ratings based on reviews collected from mothers of young children in the study areas. The unit of randomization will be the individual participant. A simple random number draw, generated by the Open Data Kit (ODK) package installed on the tablets, will be used to assign participants to treatment or control with equal probability.

Research staff will administer baseline (see Multimedia Appendix 1) and endline (see Multimedia Appendix 2) surveys to all participants during in-person visits held 3 months apart. Responses to these surveys will be used to measure the study's primary outcome: the proportion of mothers who changed their preferred health care facility for nonurgent child care services between the 2 surveys. This outcome assesses whether information about health care providers can influence users to seek alternative sources of care. For a completed CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist, see Multimedia Appendix 3.

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Selection of Participants

Inclusion Criteria

All women aged 18 years or older, enrolled in the VITERBI study with at least one child under 2 years of age, living in 1 of 2 urban districts (Sikhottabong or Chanthabouly), able to read, having exclusive access to a mobile phone, possessing a WhatsApp (Meta Platforms, Inc) account, and able to understand and sign the informed consent form will be eligible to participate in the study (see Multimedia Appendix 4). The eligibility criteria will be assessed using data collected from the VITERBI study. Ability to read will be tested using the Lao script: "I use my mobile phone every day." Before the study, we conducted interviews with 35 randomly selected women enrolled in the VITERBI study to gain insights into mobile phone ownership and usage. We found that 33 out of 35 (94%) owned a smartphone, and among these owners, all used the WhatsApp messaging app to send or receive messages and to make calls. Therefore, we limited the eligibility criteria in the main study to VITERBI participants with access to a smartphone and an existing WhatsApp account.

Exclusion Criteria

Women who are unwilling to sign informed consent, are under 18 years of age, do not have access to a smartphone, are unable to read the test script, or are unable to operate a smartphone will be excluded from the study.

Study Preparation Procedures

Overview

There were 3 preparatory phases leading up to the pilot. Phase 1 involved a preliminary survey of smartphone ownership and use among 36 randomly selected participants in the VITERBI study. In phase 2, we conducted cognitive interviews with 5 women to ensure the understandability of the baseline and endline questionnaires, and we tested both the understandability and usability of the website design prototypes. In phase 3, we conducted a pilot study with 68 participants to test the study procedures. The final phase involved conducting the main study.

Phase 1: Mobile Phone Ownership and Website Development

We conducted a preliminary survey to assess mobile phone ownership among VITERBI participants, usage frequency, and the types of software used for communication. This survey included 36 randomly selected mothers from the VITERBI study residing in 2 urban districts (Sikhottabong and Chanthabouly). Given that the sample resided in the urban core of Vientiane Capital, 33 out of 35 (94%) owned smartphones, and among these owners, all were regular WhatsApp users.

The website's design was informed by qualitative interviews with 13 randomly selected VITERBI participants, 23 exit interviews with women at 6 public hospitals, and additional study volunteers. We used a predefined interview guide to qualitatively assess, interpret, and analyze several prototypes consisting of facility rating summaries and detailed web pages of individual health facilities. To gather additional feedback, we conducted exit interviews with mothers at the same 6 major public hospitals. These hospitals were ideal locations to test the intuitiveness and interpretation of ratings, as they also serve women from remote or rural areas who may face literacy challenges, unlike the highly educated women in the VITERBI study. The qualitative interviews revealed that mothers were familiar with ratings or scores; 1 participant described it as "similar to a score for exams in school." Women were generally glad to receive information about health care providers for their children. There was a clear preference for using stars to represent the overall average score, and several women requested that phone numbers be displayed to help them contact health facilities. The prototypes selected for the study, shown in Figures 1 and 2, were the most favored and easily understood by the women.

The website was developed by Young Innovations, Private Limited, based in Lalitpur, Nepal, and procured by the study's sponsor. The website and the data generated by study participants through their ratings of health facilities are jointly owned by the study's sponsor and Lao Tropical and Public Health Institute.

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Figure 1. Home page of the website (intervention).

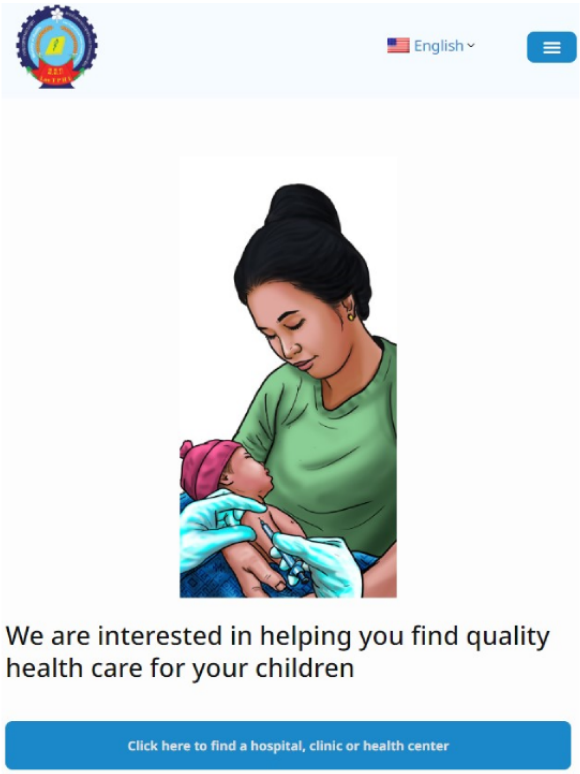

Figure 2. Second page of the website (intervention).

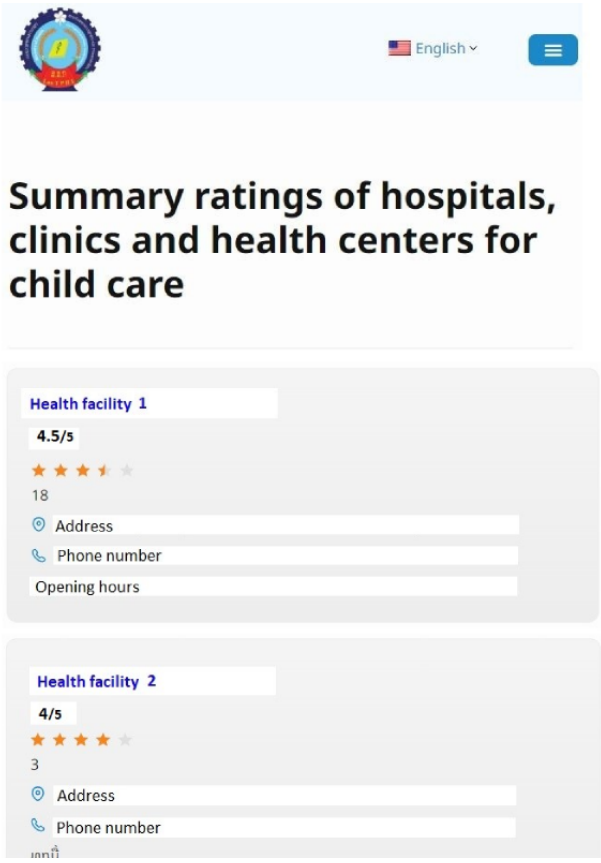

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Phase 2: Development of the Survey Questionnaire and Cognitive Interviews

Before the fieldwork in Laos, we developed baseline and endline survey questionnaires to measure primary and secondary outcomes, along with other relevant indicators. Measures of parental health literacy, parental confidence in navigating the health system, and parental confidence in interactions with health care providers were adapted from the Consumer Health Activation Index [12]. Measures related to sick children were adapted from the Integrated Management of Childhood Illnesses [13]. Additionally, measures on care utilization, care experience, expectations for health care quality, and quality of care were adapted from the People's Voice Survey [14], which had previously been implemented in Laos in 2022 [2]. Once finalized, cognitive interviews were conducted with 5 VITERBI participants in Lao-Tai, the official language, using a combination of the "think-aloud" and "scripted probing" techniques [15]. These interviews helped identify suitable terminology for concepts such as parental health literacy, health system navigation, and confidence in interactions with care providers.

The primary outcome of the study will be based on participants' responses to the following question, asked in both the baseline and endline surveys: "If your child is sick tomorrow with a mild fever of 38°C and cough, which hospital, clinic, or health center will you take your child to?" This question was developed in accordance with the Integrated Management of Childhood Illness guidelines [13], in which the described symptoms would be classified as nonsevere. We developed this measure specifically for this trial, guided by our theory of how the intervention might influence decision-making. We aimed to create a measure that captured intentions about where participants would seek care in a future scenario, as we anticipated that the information provided through the intervention could shape these intentions. We sought an outcome measure that could be collected from all participants without depending on recent health care utilization. For this reason, we chose this measure over alternatives such as "most recent facility visited" or "usual source of care." Cognitive interviews and pilot surveys indicated that the measure performed well in terms of participant comprehension.

Phase 3: Pilot Study

We conducted a pilot study to assess the study procedures and gather feedback on the intervention and questionnaire. For the pilot's endline survey, we added qualitative questions to capture participants' suggestions for improving the website. Based on pilot results, we made minor revisions to the baseline and endline survey questions to enhance clarity. We also refined the quality components to overall quality, skill and experience of the health care provider, equipment, respectfulness of the health care provider, cleanliness, waiting time, and cost.

Study Procedures

Research staff, with support from the respective village offices, will recruit participants during in-person visits. At the first meeting, before enrollment and the baseline survey, research staff will explain the study and obtain informed consent. The informed consent will cover key information, including the study's objectives, duration, level of participant involvement, and the assurance that participation is entirely voluntary. Tablets equipped with ODK will be used to record responses from enrolled participants during the baseline and endline surveys. All participants will receive a small gift in appreciation of their participation, in keeping with customary practice in Lao PDR.

After completing the baseline survey, research staff will assist all enrolled participants in connecting with the study's WhatsApp number and will demonstrate how to submit biweekly user ratings of facilities. In addition, staff will encourage participants in the intervention group to use the website, as needed, to access information on pediatric health care facilities and view user ratings submitted by their peers. Research staff will demonstrate the 3 main pages of the website, show participants how to navigate between them, and answer any questions they may have. The study coordinator will record enrolled participants weekly, along with their group assignment (intervention or control), and will schedule dates for each participant to receive biweekly surveys, the intervention URL (for those in the intervention group), and the endline interview.

Following enrollment, all participants will be asked to rate or review the most recently visited health care facility every 2 weeks; these ratings will generate user scores for the website (intervention). Participants will receive a WhatsApp message from the study coordinator: "Did you visit a health center, hospital, or clinic for your child in the last 2 weeks?" Those who respond "yes" will receive a URL to a web-based survey, along with their study ID and the last 4 digits of their phone number. Before completing the survey, participants will be required to enter their study ID and the last 4 digits of their phone number. This step will help track survey completions and identify duplicate entries. Once the 2 fields are entered, participants will be asked to complete the survey by identifying the name of the health facility visited, rating the quality of care received, and providing any additional comments about their visit. The questions in the web-based survey are adapted from the People's Voice Survey questionnaire [16], a mobile-based tool designed to capture patient experiences. All questions use multiple-choice response options and focus on participants' most recent visit to a health care facility within the past 2 weeks. Participants are asked to assess the quality of care their child received by responding to the following items:

- How would you rate the overall quality of care your child received?
- How would you rate the knowledge and skills of your provider?
- How would you rate the equipment and supplies available to the provider, such as medical equipment or access to laboratory tests?
- How would you rate the level of respect your provider showed you?
- How would you rate the amount of time you waited before being seen?
- How would you rate the courtesy and helpfulness of the health care facility staff, excluding your provider?
- How would you rate the cost of services?
- How would you rate the cleanliness of the facility?

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For each question, participants will select one of the following response options: excellent, very good, good, fair, poor, “I do not know,” or “I refuse to answer.”

The principal investigator will monitor survey entries weekly to ensure completeness and identify duplicate entries. In the case of duplicates, the most recent entry will be retained. If participants do not respond to the initial WhatsApp message or fail to complete the mobile survey, the study coordinator will make up to 5 attempts to contact them via WhatsApp and administer the survey over the call.

Average ratings for overall quality of care and for specific dimensions of care will be displayed on the web page, which is the main component of the intervention. The study coordinator will share the URL of the health facility ratings website with the intervention group biweekly via WhatsApp. The message will read: “Sabaidee, please click on the link to see ratings of hospitals, clinics, or health centers for health care for your children, and let us know if you have any questions or comments.” The control group will not receive any intervention. Given that all participants in the pilot study exchanged WhatsApp messages at least once per month, biweekly sharing of the intervention URL over 3 months is expected to provide sufficient exposure to the website for participants in the intervention group. Research staff will conduct endline surveys with all participants during in-person visits 3 months after the baseline survey.

Description of the Study Intervention

Every 2 weeks, the intervention group will receive a URL via WhatsApp linking to the website displaying user ratings of health care facilities that provide pediatric care. Although the survey is short, we were concerned about potential survey fatigue and, therefore, limited study participation to 12 weeks (6 survey rounds).

The website will consist of 3 unique pages, as shown in Figures 1-3, and will be accessible to anyone with an internet connection. All text will default to Lao, the official language of Lao PDR, while an English version will also be available for demonstration purposes. The logo of the Lao Tropical and Public Health Institute will be displayed at the top of the facility ratings website.

The website will consist of 3 unique pages: the home page, a listing of health care facilities (second page), and a detailed review of a single facility covering multiple quality components (third page). Figure 1 shows the home page. Figure 2 displays the list of health care facilities, with those having the highest average overall rating shown at the top. Only facilities with at least three reviews will be listed, while those with fewer reviews will be hidden. Clicking on any health facility will display reviews and average ratings for multiple quality components of that facility—provider skill, respectfulness of the provider, cost, cleanliness, equipment, and waiting time—along with comments left by recent users (Figure 3). The website’s design will remain fixed for the duration of the study; however, the ratings will be updated as participants submit new entries.

Health facility reviews will be generated based on biweekly reports of recent visits by all participants. Participants will receive a WhatsApp message asking whether they have visited a health care facility for their child in the past 2 weeks. Those who respond “yes” will receive a link to complete a short survey to review or rate their experience. The overall quality rating, which determines the order of facilities on the website’s second page (see Figure 2), is calculated based on participants’ responses to the question: “How would you rate the overall quality of the health facility?” Participants are asked to select 1 of the following response options: “excellent,” “very good,” “good,” “fair,” or “poor.” The average rating is calculated using numerical values assigned to these responses, with scores ranging from 5 (excellent) to 1 (poor). Golden stars visually represent the overall average quality rating. To further assist participants in exploring health facilities, hyperlinks to each facility’s address and phone number are provided, along with their opening hours.

Figure 3 shows the average ratings across multiple quality domains for a selected health facility, along with comments on participants’ experiences. Participants can access this information by selecting the facility’s name on the website’s second page (Figure 2).

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Figure 3. Third page of the website (intervention).

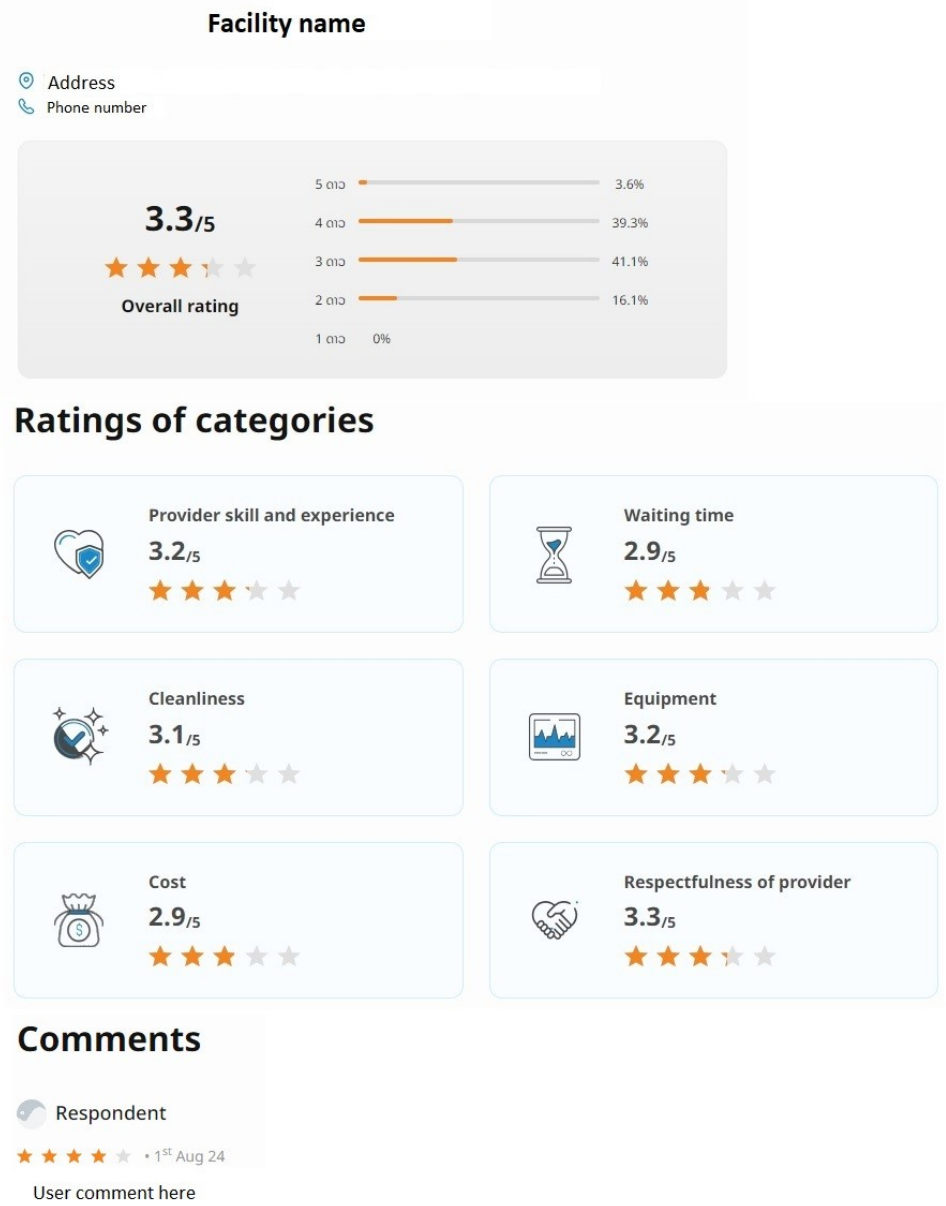

Auditing

No audits are planned. The principal investigator will be in Lao PDR during enrollment, baseline, and endline surveys. While in Lao PDR, he will monitor the progress of enrollment and survey responses daily and will remotely oversee the progress of mobile phone surveys every week. His review will include checking the progress and accuracy of enrollment logs, versions of enrollment logs, and the completeness of baseline and endline survey responses. Additionally, he will supervise the weekly web-based surveys that collect quality ratings of health facilities and ensure the functionality of the website.

Interim Analysis and Stopping Guidelines

Interim analyses are not planned for this study. Enrollment will stop once 660 participants have been recruited. Participants may withdraw from the study at any time. If the study team is uncertain whether a participant intends to withdraw, they may attempt to contact her up to 3 times at different times of the day. If she remains unreachable, the study team will conclude her participation.

The study team may discontinue a survey with an individual participant if she is not reachable after 3 attempts or if she has not responded to consecutive mobile survey questions. The project sponsor may terminate the study prematurely under certain circumstances, including ethical concerns, insufficient participant recruitment, or an inability to continue data collection due to public health emergencies.

Study Design

This study is an unblinded randomized controlled experiment with rolling enrollment. Participants' preferred facility for nonurgent care will be recorded during the baseline survey, immediately following enrollment. A detailed overview of the methodology and timing of the intervention is shown in Figure 4.

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Figure 4. CONSORT (Consolidated Standards of Reporting Trials) study flow diagram.

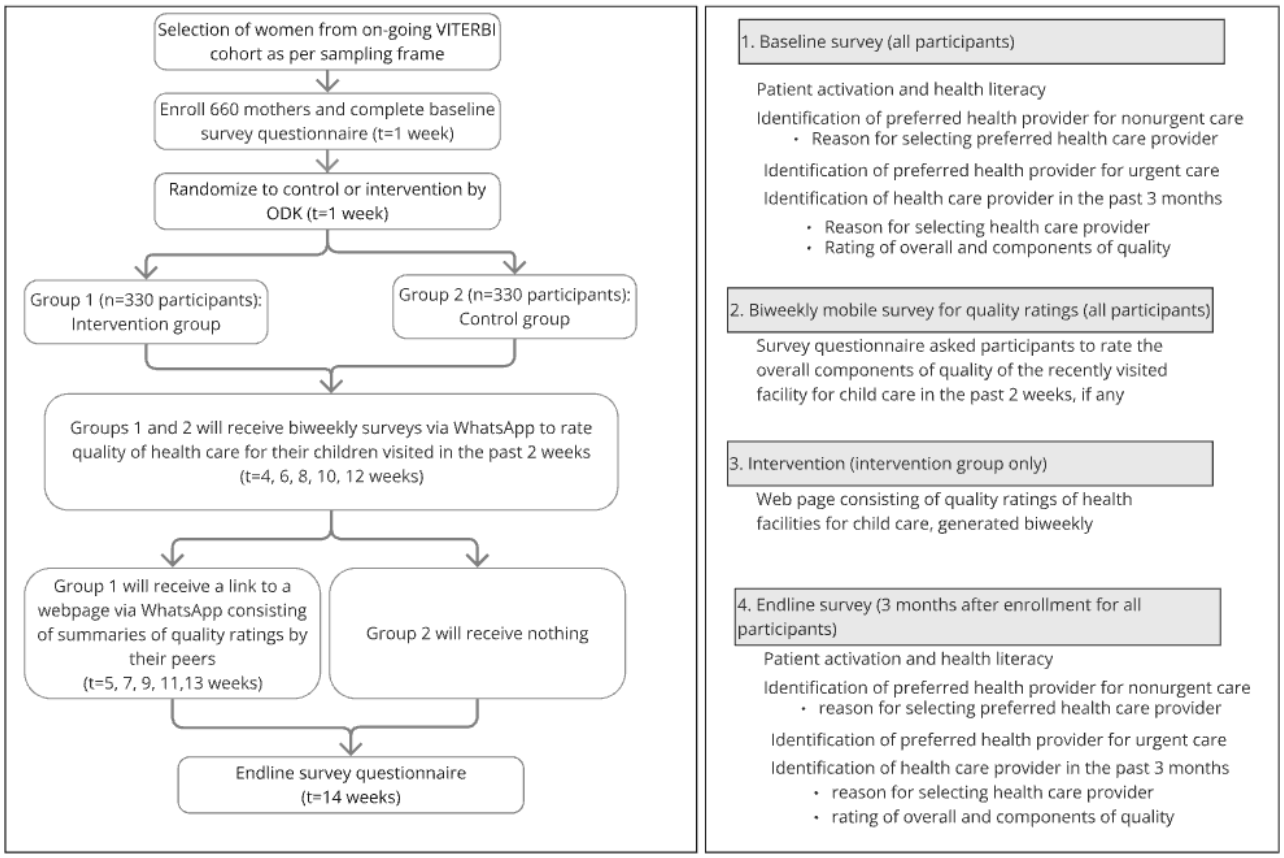

Sample Size Determination

The required sample size was calculated based on the proportion of mothers who changed providers for nonurgent care in a 6-week pilot study involving 58 participants. In the pilot, all participants received the intervention—a web page of facility ratings—once or twice, depending on when the endline survey was scheduled. A conservative sample size was calculated to detect a 12-percentage-point change in the outcome with 80% power and α=.05; 330 participants per group would be required. Assuming 10% attrition, the total required sample size was set at 660 participants.

Randomization

Participants will be randomized using the ODK package installed on tablets at enrollment. A simple random number generated by ODK will assign participants to the treatment or control group with equal probability.

Blinding

This will be an “open-label” trial; however, the analyst will be blinded during the endline assessments.

Adverse Events

We do not anticipate any adverse events resulting from this study. Participants will receive, via WhatsApp, a URL linking to the website containing quality ratings of health care facilities for children in Vientiane Capital.

Unexpected Events

We have developed study procedures and a detailed calendar to ensure a shared understanding of key activities and their timelines. These measures are also designed to minimize the impact of unexpected events, such as staff changes. A journal will be maintained to track critical events, including website downtime.

Equipment

We do not anticipate the need for additional equipment. Participants will use their own mobile phones to communicate with the research team.

Attrition

We attempted to minimize loss to follow-up by excluding participants who permanently or temporarily moved away from the 2 study districts and by monitoring participant engagement throughout the study period. The study coordinator called participants who did not respond to the biweekly surveys to encourage participation and resolve any issues they may have been experiencing with accessing the data.

Data Management

Survey data will be recorded using unique identifiers for each participant. An enrollment log will be maintained to link these codes with participants’ phone numbers and will be used solely for study administration. Responses to the baseline, endline, and mobile-based surveys will be stored electronically using only the individual codes, without any phone numbers.

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AA and a research coordinator will maintain the enrollment logs electronically on a password-protected, secure Swiss TPH server that will be regularly backed up. The enrollment log will be saved using the following format to ensure traceability of any changes: LaosMR_enrol_v1.0_DD.MM.YYYY. The research team (AA, GF, and ECD) will have access to password-protected survey responses from the baseline, endline, and mobile phone surveys.

Data collected during the biweekly surveys will be stored on a password-protected cloud server, accessible only to the research team (AA, GF, and ECD). Hard copies containing participant information will be kept in a locked filing cabinet in the project office at the Lao Tropical and Public Health Institute. These files will be accessible only to the local study coordinator and enumerators responsible for conducting the baseline and endline surveys.

We will use WhatsApp for 2 main purposes: (1) to ask all participants whether they have visited a health care facility for their children in the past 2 weeks and, if they respond affirmatively, to send them a link to an online survey to rate the quality of care they received; and (2) to provide the intervention group with a URL link to the website displaying user ratings of health facilities for pediatric care. The local study coordinator will communicate with participants using a dedicated tablet and a unique WhatsApp account, used exclusively for the study. The tablet will be password-protected and accessible only to the local study coordinator. Messages exchanged between participants and the study coordinator on WhatsApp are secured with end-to-end encryption [17]. At the conclusion of the study, all contacts will be deleted, and the WhatsApp account will be disabled.

Outcomes

Trial outcomes will be measured through the in-person endline survey. For the primary analysis, we will assess the proportion of mothers who changed their preferred health care facility for nonurgent child care services between the baseline and endline surveys. The null hypothesis is that there is no difference between the control and intervention groups. The alternative hypothesis is that there is a difference between the 2 groups. This hypothesis aligns with our study aims, as it examines whether the use of provider facility ratings influences caregivers to seek alternative sources of health care for their children. Our primary analysis is cross sectional; for the panel analysis using the care-seeking panel, observations will be clustered at the household level.

Nonurgent care is defined as a child presenting with a mild fever of 38°C accompanied by a cough. During the baseline and endline surveys, participants will be asked to specify their preferred location for child care using the following question: “If your child is sick tomorrow with a mild fever of 38°C Celsius and cough, which hospital, clinic, or health center would you take your child to?” The primary outcome will be a binary indicator reflecting whether participants changed their preferred location between baseline and endline.

We used the proportion of mothers who changed providers (n=26, 45%) for nonurgent care in a 6-week pilot study involving 58 participants. All participants in the pilot received the intervention—a web page of facility ratings. Eligible women will be randomly selected from the ongoing VITERBI study for enrollment, and recruitment will continue until we reach 660 participants, with 330 in each intervention arm, assuming 10% attrition. Enrolling 300 participants per intervention arm provides 90% power, with a 2-sided α of .05, to detect a 12-percentage-point change in health facility choice, assuming 80% follow-up. We will collect and analyze baseline and endline survey data from mothers enrolled in the study. We anticipate completing 600 endline surveys and analyzing this sample.

Additionally, we plan to measure 6 secondary outcomes to explore further effects of the intervention. These relate to caregivers’ actual health care use over the past 3 months, including satisfaction with care received, frequency of health care service use, and changes in the facility used for their most recent visit. Additionally, the secondary measures capture whether caregivers selected health facilities based on online or digital information, whether they changed their preferred provider for urgent care, and their confidence in identifying the best facility for their children’s care. The secondary measures are presented in Textbox 1.

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Textbox 1. Secondary measures.

1. Proportion of mothers satisfied with health care for their children during their most recent visit (time frame: 3 months)

This secondary outcome measure captures mothers' satisfaction with the health care facility visited most recently for care of their child under age 2 years. This measure will be available only for mothers who sought care for their child during the study period. It will be a binary variable, with satisfaction defined as responding "excellent" or "very good" (as opposed to "good," "fair," or "poor") to the question: "How would you rate the overall quality of care you received?" referring to the most recent visit for their child under age 2 years within the past 3 months.

2. Number and type of health care providers used in the past 3 months (time frame: 3 months)

This secondary outcome captures the number and types of providers (government health centers, government hospitals, private clinics, and private hospitals) visited by mothers for their children's health care during the study period. Every 2 weeks, all enrolled participants will be asked via a mobile app: "Did you visit a health center, hospital, or clinic for your child in the last 2 weeks?" Participants who respond "yes" will be asked to complete an online survey about the visit, specifying the health facility they visited.

3. Proportion of mothers who changed their most recently visited health care provider for children (time frame: 3 months)

This secondary outcome measures the proportion of mothers who changed the health care facility they most recently visited for child care services between the baseline and endline surveys. This will be a binary variable and will be available only for caregivers who sought care during the 3 months preceding both the baseline and endline surveys.

4. Proportion of mothers choosing the preferred facility for nonurgent care based on online or digital information sources (time frame: 3 months)

This secondary outcome measures the proportion of mothers who used online or digital information sources to inform their choice of providers for nonurgent care. During the baseline and endline surveys, participants will be asked to specify their preferred location for nonurgent child care using the question: "If your child is sick tomorrow with a mild fever of 38°C and cough, which hospital, clinic, or health center would you take your child to?" Immediately following this, participants will be asked: "Was this choice informed by online or digital information services?" This outcome will be recorded as a binary variable.

5. Proportion of mothers who changed their preferred health care provider for children for urgent care (time frame: 3 months)

This secondary outcome measures the proportion of mothers who changed their preferred health care facility for urgent child care services between the baseline and endline surveys. Urgent care is defined as a child presenting with a very high fever and a red rash covering the body. During the baseline and endline surveys, participants will be asked to specify their preferred location for urgent child care using the following question: "If your child is sick tomorrow with a very high fever of 39-40°C and a red rash covering their body, which hospital, clinic, or health center would you take your child to?"

This outcome will be a binary variable indicating whether participants changed their preferred location for urgent care between the baseline and endline surveys.

6. Proportion of mothers confident they can identify the best place for care for sick children (time frame: 3 months)

This secondary outcome measures the proportion of mothers who feel confident in identifying the best place to seek care for their sick children based on the child's health problems. During the baseline and endline surveys, participants will respond with "strongly agree," "agree," "unsure," "disagree," or "strongly disagree" to the following statement: "I am able to identify the best place to get care for my child when he/she is sick." This outcome will be recorded as a binary variable: participants responding "strongly agree" or "agree" will be classified as confident, while those responding "unsure," "disagree," or "strongly disagree" will be classified as not confident.

Statistical Analysis

We will use the STATA (StataCorp) statistical software package for all analyses. Descriptive statistics will first be used to assess differences between the intervention and control groups in terms of baseline characteristics and potential confounding variables. Missing covariates will be imputed as needed, and system use (including adherence to the intervention) will be measured through self-reports at endline. Differences between the intervention and control groups after the intervention will then be analyzed for both primary and secondary outcomes. Two-tailed *t* tests or ANOVA will be used for continuous variables, and chi-square tests will be used for binary outcome variables.

For our main analysis, differences between the 2 arms (participants who received provider information biweekly and those who received no information) will be assessed using regression models. Participants with missing outcome data will be excluded from the analysis, as we do not plan to impute outcomes. For missing baseline covariates, we will assume that the data are missing at random and conduct a complete-case analysis using only observations with complete data for the relevant variables. Additionally, we will perform multiple imputation to handle missing responses for baseline covariates.

Given that this is a randomized trial with individual-level randomization and a cross-sectional design, our primary analysis will compare outcomes between treatment arms using data measured at endline. Therefore, we do not anticipate issues related to clustering or intraindividual correlation in the analysis of primary outcome measures. Treatment effects for continuous outcomes will be estimated using linear regression with robust SEs to account for potential heteroskedasticity, using the following regression model:

$$Y_i = \beta_0 + \beta_1 T_i + e_i$$

where Y_i is the outcome for individual i; T_i is the indicator for the treatment group; β_0 is the value of the control group; β_1 is the estimated treatment effect; and e_i is the error term. For binary outcomes, we will use the following regression model:

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$$\text{logit}(Y_i) = \beta_0 + \beta_1 T_i + e_i$$

In secondary analyses, we will adjust for baseline covariates—including age, wealth status, educational level, ethnicity, and parental health literacy—to account for potential differences and address any imbalances between the treatment and control groups.

Ethics Considerations

This study was conducted in accordance with the Declaration of Helsinki and received ethics approval from the Ethikkommission Nordwest- und Zentralschweiz in Switzerland (approval ID AO_2023-00063) on September 8, 2023, and from the National Ethics Committee for Health Research (NECHR) in Lao PDR on February 6, 2024 (No. 16/NECHR). The research will adhere to the principles of the Helsinki Declaration, and any secondary use of the study data will undergo new ethical approvals.

All study participants provided informed written consent before taking part in any study procedures. They were informed that participation was voluntary, that they could withdraw at any time, and that withdrawal of consent would not affect their subsequent medical assistance or treatment. No financial compensation was provided for participation; however, a small gift of appreciation was offered upon successful completion of the endline survey.

The project included several steps to safeguard data privacy. First, deidentified survey responses (baseline, endline, and mobile) were stored on password-protected servers. Second, WhatsApp was used only as a communication channel with participants and not for any data collection purposes. Communication was managed by dedicated staff using a unique WhatsApp profile created specifically for the study. All exchanges via WhatsApp were protected by the platform's default end-to-end encryption. Finally, to further minimize risks, WhatsApp records were deleted once participants had completed the endline survey.

Results

The trial is currently in progress and is expected to be completed in 2025. From the results, we aim to determine whether web-based reviews of health care providers can influence mothers' care-seeking behavior for their children in Vientiane, an urban setting in Lao PDR. Additionally, we aim to validate a scalable model for generating demand for high-quality care in urban, low-resource settings with high mobile phone coverage. Findings will be disseminated through local seminars, international conferences, and peer-reviewed journals.

Discussion

Anticipated Findings

This protocol describes a randomized controlled trial designed to test whether a demand-side intervention influences health facility choices among mothers in Vientiane capital. We will assess whether information about the quality of health care facilities—generated by study participants during the pilot and study periods—encourages mothers to change their preferred providers for nonurgent conditions. Additionally, we will assess whether the intervention leads to higher satisfaction with care at the most recently used facility and test our theory of change that mothers in the treatment group are more confident in their ability to identify the best place to seek care for sick children.

This protocol has several key strengths. It will contribute to the literature on how to "ignite demand" for high-quality care, as called for by the Lancet Commission on High-Quality Health Systems. This study is among the first published efforts to generate demand for high-quality care, providing evidence on how users of the health system can influence its quality. The results will apply to health conditions beyond the focus of this study—health care for children. The study is particularly relevant in Lao PDR, where the number of health care providers is rapidly growing, ranging from small primary health centers to large tertiary hospitals. The absence of effective gatekeeping allows people to seek care at any facility, including tertiary hospitals. Despite the growing care options, Laotians remain unsatisfied with the quality of care, with only 28% rating their usual health care provider as high quality. It is critical to understand and address sources of low-quality care, as low perceptions of care quality can lead people to forgo care or not adhere to medical advice [18].

A recent study highlighted that facility selection is influenced by factors such as illness severity, distance, technical skills and respectfulness of health care providers, cost, availability of equipment and medicines, waiting times, and informal payments [19]. Many of these factors, however, are not readily accessible or comparable across facilities, despite persistent dissatisfaction with care quality and untapped options. This study seeks to change the status quo by empowering patients with comparable information on health care quality across multiple facilities.

Through online ratings of health care facilities for children, we aim to study whether access to information about providers influences caregivers' choice of facility—measured by switching behavior—as an indicator of improved access to quality health care. We will also assess whether this information affects caregivers' satisfaction with the health services received for their child or children. Drawing on findings from previous studies [2,19], the website presents user ratings across quality domains valued by residents of Vientiane, including provider skills, respectfulness, cost, availability of equipment, waiting time, cleanliness, and helpfulness of support staff.

As one of the first studies of its kind in a low-resource context, we aim to evaluate the online platform's perceived usefulness, gather participant feedback, and measure engagement metrics such as page views and reported use of the website. In addition, we will assess whether the website increased caregivers' confidence in selecting a health care provider for their children.

While empowering patients with information to make informed care choices, the intervention could also have unintended consequences. For example, demand for tertiary hospitals—already burdened with long waiting times—might increase, as they are generally perceived to provide the highest quality care. This effect may not apply to all types of illnesses, particularly those that can be easily diagnosed and treated at smaller facilities. Additionally, private care providers could

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attract patients by improving observable aspects of care without addressing underlying gaps in technical quality.

Despite potential unintended consequences, our study offers a demand-side approach to addressing low satisfaction with care quality by empowering patients with actionable quality metrics. We aim to validate a scalable model for "igniting" demand for high-quality care in low-resource settings by establishing an accountability mechanism that links provider performance with patient preferences.

Limitations

This protocol also has some limitations. First, the study may inadvertently encourage bypassing of lower-level public health facilities, directing mothers toward specialty hospitals or private providers. A recent study showed that a large majority (64%) of people used public hospitals as their preferred health care provider, while only 13% used health centers [20]. As a consequence of the study, government-managed specialty hospitals and private facilities may experience increased demand for services for minor health conditions that could be better managed at lower-level government facilities. This shift toward private and specialty providers could raise out-of-pocket expenditures for health care clients and increase costs for the health system as a whole. Second, the quality of care measures used in the study are based on participants' perceptions and may be influenced by social desirability bias. However, previous studies have shown that people in Lao PDR are highly critical of health system performance [2,21]. Third, nonadherence to the intervention due to unexpected events—such as technical issues with the website or not receiving the URL—may also bias study findings. To address this, we will assess participants' frequency of website use in the endline survey and document any website-related downtime. Fourth, because all participants reside in the same 2 districts and the study uses an open-label design, cross-arm exposure and spillover effects may bias the results. To minimize these risks, we have separated the roles of staff: the team member responsible for communicating with the intervention group (sending biweekly reminders and links to the ratings website) is not involved in scheduling or conducting endline surveys or other administrative assessment activities. Additionally, to assess aggregate exposure, we will track daily traffic to the website. To measure exposure at the individual level, all participants will be asked at endline about their knowledge of the intervention, whether they received the link, how they received it, and how frequently they accessed the website. Finally, the researcher responsible for data analysis will also be involved in data collection; therefore, complete blinding of the analyst is not possible. In practice, however, the analyst will remain blinded during the endline assessments.

Conclusions

In conclusion, if this demand-side intervention proves effective, it could offer a cost-effective approach for policy makers to ignite demand for high-quality care. To our knowledge, this is the first trial to examine how information about health care providers influences care-seeking decisions. Through this study, we aim to gain insights into patients' decision-making regarding treatment locations and to explore the factors that shape these choices. We hope to extend our research findings to other populations, including adults, older adults, and individuals living with noncommunicable diseases. We recognize that care-seeking behaviors in Lao PDR differ from other settings due to variations in facility availability, cost, and quality of care. While our study is tailored to the health care landscape in Lao PDR, the findings may offer insights relevant to understanding the experiences of individuals seeking care in other contexts.

Acknowledgments

The authors sincerely thank the Lao Tropical and Public Health Institute, local partner, for agreeing to host the study. The funding for data collection was supported by the Eckenstein-Geigy Professorship. ChatGPT (version 4o; OpenAI, Inc) was used to check grammar and suggest improvements to several sentences in the protocol.

Authors' Contributions

GF, AA, and ECD conceptualized the study. ECD and AA developed the study procedures. AA oversaw the pilot and drafted the initial version of the protocol. SS, ECD, and GF revised successive drafts. GF supervised the overall protocol development process. All authors reviewed and approved the final protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Baseline survey.
[PDF File (Adobe PDF File), 448 KB - resprot_v14i1e66085_app1.pdf]

Multimedia Appendix 2
Endline survey.
[PDF File (Adobe PDF File), 253 KB - resprot_v14i1e66085_app2.pdf]

Multimedia Appendix 3

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CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1027 KB - resprot_v14i1e66085_app3.pdf]

Multimedia Appendix 4
Informed consent form.
[PDF File (Adobe PDF File), 254 KB - resprot_v14i1e66085_app4.pdf]

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Abbreviations

Lao PDR: Lao People's Democratic Republic
NECHR: National Ethics Committee for Health Research
ODK: Open Data Kit
VITERBI: Vientiane Multigenerational Birth Cohort

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Protocol

Increasing Awareness and Early Detection of Common Skin Diseases in Indonesia Through an mHealth App: Protocol for an Awareness and Acceptability Study and Randomized Controlled Trial

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Abstract

Background: Various media are used to enhance public understanding about diseases. While mobile health apps are widely used, there is little proof for using such apps to raise awareness of skin diseases.

Objective: We intend to develop an app, called DEDIKASI-app, to raise awareness of skin diseases, including leprosy. The study will explore baseline awareness, assess the app's acceptance by community members and health care workers, and evaluate its effectiveness in enhancing awareness about skin diseases.

Methods: The study will be conducted in four phases: (1) development of DEDIKASI-app, (2) questionnaire development for an awareness study, (3) acceptability testing, and (4) effect measurement of DEDIKASI-app. We will adopt design thinking methodology to develop the app, involving systematic reviews, expert consultations, focus group discussions, and validation of the questionnaire on skin disease awareness. We will recruit 50 members of the community for the awareness and acceptability study and 1 health care worker per community health center to assess their perception of the app. A pilot study will assess the acceptability of DEDIKASI-app among community members and health care workers based on various constructs, with responses categorized as positive, negative, or undecided. The validity and reliability of a newly developed questionnaire on skin disease awareness will be tested, with validity results analyzed qualitatively and reliability measured using Cronbach α. The effectiveness of DEDIKASI-app in improving community awareness will be evaluated through a randomized controlled trial, using total scores, means, and SDs for control and intervention groups. Statistical significance of awareness level changes will be determined by delta change (P value), with $P<.01$ considered significant.

Results: This study received ethical approval from the Ethics Review Board of the Faculty of Public Health, Universitas Airlangga (160/EA/KEPK/2023) and was registered in the Indonesia Clinical Research Registry (INA-O8EX278). Funding for the field research was secured in the period of May 2022-December 2024 from NLR Indonesia and Erasmus University Medical Center. As of manuscript submission, phase 1 (app development) and phase 2 (questionnaire development) have been completed. Data collection for the randomized controlled trial has just finished and data analysis is ongoing, with publication of the study results expected in late 2025.

Conclusions: Innovative approaches are required to enhance awareness in the community. This study will introduce new tools and insights to address the limited knowledge about detecting skin problems.

Trial Registration: INA-CRR Indonesia Clinical Research Registry INA-O8EX278; https://tinyurl.com/ms3k5yvn

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International Registered Report Identifier (IRRID): DERR1-10.2196/64057

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KEYWORDS

community health awareness; digital health intervention; early detection education; health application usability; mHealth; skin diseases; leprosy; Indonesia

Introduction

Skin diseases are common all over the world. They can range from non–life-threatening conditions such as acne, contact dermatitis, benign tumors, atopic dermatitis (eczema), and psoriasis to more serious conditions such as autoimmune diseases and skin cancers. A particularly important group of skin diseases, categorized as neglected tropical diseases (NTDs), afflict disadvantaged communities in low- and middle-income countries [1,2]. These include Buruli ulcers, cutaneous and postkala azar dermal leishmaniasis, lymphatic filariasis, onchocerciasis, mycetoma, yaws, chromoblastomycosis and other deep mycoses, scabies and other ectoparasites, and leprosy [2]. Many of these conditions can cause lasting physical and mental complications and are associated with stigma. Leprosy is a typical example of such an NTD, with nearly 200,000 new cases reported worldwide in 2021 [3].

Detection delay is an important factor associated with disabilities in leprosy [4]. The stigma associated with leprosy, often exacerbated by a lack of understanding, challenges early detection considerably [5,6]. Stigmatization leads people to hide their condition, and this avoidance behavior results in delayed diagnosis and treatment [7-10]. The combined lack of knowledge and stigma creates barriers for prompt implementation of case finding and adherence to treatment protocols, undermining the overall effectiveness of leprosy control [7,11-13]. A pivotal element of timely detection is fostering self-awareness among populations at risk. Increasing public awareness on the relevance of early detection holds the potential to shift attitudes and behaviors toward increased health-seeking behavior [14]. This holistic approach should also target dispelling myths and misconceptions tied to leprosy. Furthermore, reinforcing health care systems is crucial to ensure streamlined diagnostic and treatment processes, while guaranteeing respectful and sensitive care for affected individuals [15-17].

National programs use information, education, and communication media to improve the knowledge and awareness of the community about health conditions and diseases. Both printed and electronic media are used widely for showcasing innovative approaches used to disseminate health-related messages [18]. The surge in mobile phone use has allowed health care support through mobile health (mHealth), a subset of eHealth. mHealth involves the application of mobile computing and communication technologies in health care and public health, commonly realized through mobile applications [10,18]. In 2018, the World Health Organization introduced an eHealth guidance book advocating mobile apps to enhance health services and achieve universal health coverage [19]. Aligning with this initiative, the Indonesian Ministry of Communication and Information initiated the Smart Health Initiative to digitize health services in the country [20]. The distribution of apps, however, varies across disease conditions and intended goals. Moreover, there is currently no evidence supporting the use of an app for raising awareness about early leprosy detection [21].

The proposed study entails the creation of a 2-way integrated mobile app known as DEDIKASI-app (“dedication” in English and would be application-based early skin detection translated from the Indonesia abbreviation), catering to both users and health care workers (HCWs). The application aims to raise awareness about early skin detection, encompassing possible leprosy cases and other prevalent skin conditions. Because of the stigma toward leprosy in the community, this study extends its scope to include common skin diseases within the app.

The study aims are as follows: (1) to develop a mobile app (DEDIKASI-app) as an awareness-raising strategy in the community for early signs of common skin diseases, (2) to develop a skin diseases awareness questionnaire, (3) to provide insight into the acceptability of DEDIKASI-app to the community and HCWs, and (4) to assess its effectiveness in improving community awareness of common skin symptoms.

Methods

Overview

The study will be conducted in four phases: (1) development of the DEDIKASI-app mobile app, (2) development of a questionnaire to measure the level of awareness in the community of common skin diseases, (3) an awareness study and acceptability test of DEDIKASI-app, and (4) a randomized controlled trial of DEDIKASI-app. The phases of this study are outlined in Figure 1.

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Figure 1. Flowchart of the 4 phases of the study.

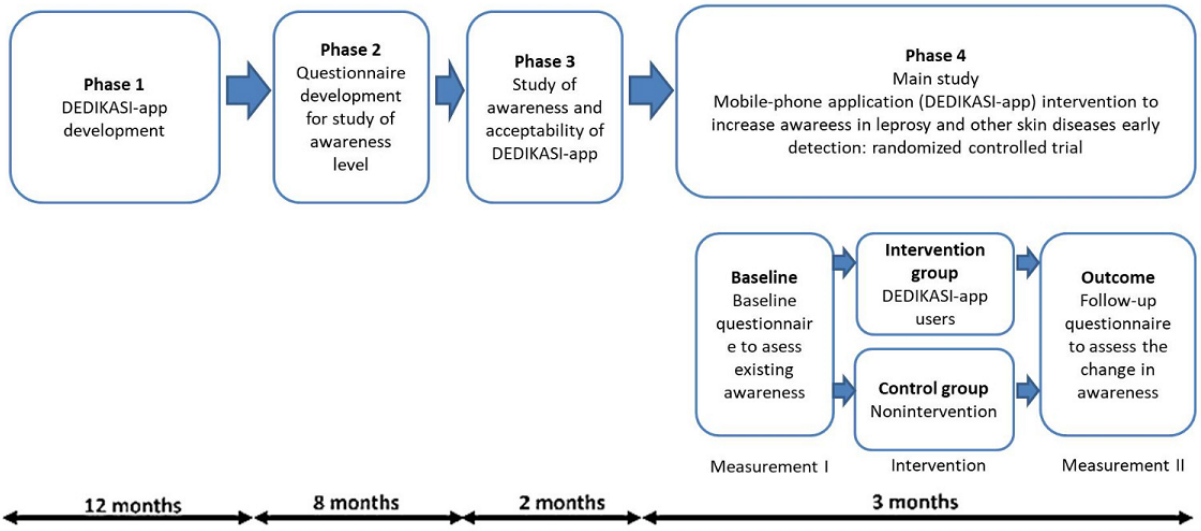

Phase 1: Development of DEDIKASI-app

We will apply a comprehensive approach to create an effective and user-friendly platform for common skin disease detection and awareness promotion. The platform is called DEDIKASI-app, an acronym of deteksi dini kusta berbasis aplikasi, which translates to application-based early skin detection. DEDIKASI literally means “dedication,” portraying the dedication to achieve leprosy elimination by increasing awareness and early diagnosis using this DEDIKASI-app.

DEDIKASI-app is a 2-way platform aimed at the general community (DEDIKASI-P) and HCWs (DEDIKASI-HCW) within community health centers (CHCs, puskesmas in Indonesia). The front end of the platform is openly accessible to the public while the back end is only accessible to HCWs functioning on Android devices with or without internet connectivity. While the front end allows offline reading of information, active tasks, such as skin self-detection and uploading, require internet access. Similarly, the back end can function offline for reading, but internet connectivity is essential for notifications and responses.

DEDIKASI-P will include an animated anatomy feature and a detailed catalogue of skin symptoms to assist users in self-assessment by offering valuable information. After completing the self-assessment, HCWs can review the results through DEDIKASI-HCWs, enabling internet-based consultations or scheduling in-person appointments.

Before developing the app, we conducted a systematic literature review of studies on mHealth apps and interventions to explore strategies and tools for promoting mHealth interventions aimed at promoting early detection and increasing awareness of chronic diseases [22]. This review helped identify various approaches to enhance early detection and awareness while also incorporating strategies to maintain user engagement. Additionally, expert consultations were carried out to design a user-friendly interface accessible to all community members, regardless of their educational background.

The mobile apps will be developed by identifying suitable design architecture and an interface aligned with its intended purpose. This step will entail outlining the overall requirements for app development, with content generated in the Indonesian language. DEDIKASI-app will be entirely self-developed, including its visual design and animations, ensuring that no copyrighted materials from other apps or owners are used in its development. Design thinking methodology [23], a human-centered approach, will be adopted to delineate the standardized process used in crafting the app. This methodology focuses on user needs and considers various stakeholders’ perspectives, involving HCWs closely in the development process [23].

We emphasize that DEDIKASI-app is not intended to replace the role of health care professionals in diagnosing common skin diseases. Instead, the app will serve as an interactive and communicative tool for raising awareness. The app aim to stimulate early common skin disease detection, particularly of leprosy, preventing severe physical and mental outcomes and stigma. Additionally, the users will be encouraged to seek help from HCWs by using DEDIKASI-app when they identify potential skin symptoms. Given the social isolation and stigmatization faced by individuals with leprosy, the app’s internet-based services offer empowerment and privacy, allowing for self-testing and reducing stigma-related fears [24-26]. However, the role of health care professionals remains crucial in case finding, diagnosis, and management of leprosy.

Based on prior studies, strategies will be selected to attract users, such as attractive animations, tailored messages, and rewards (eg, receiving a shopping voucher). Visual appeal, ease of use, social support, and trust are factors that encourage health app usage [27-29]. The app will feature an anatomy animation and a comprehensive list of skin symptoms aimed to aid the users in self-assessment by providing helpful information.

Although the main objective of DEDIKASI- app is to increase awareness about leprosy, given the stigma about leprosy, we decided to expand the context of the app to common skin diseases.

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DEDIKASI-app will be developed by a recognized digital health agency in Indonesia called Databiota. The Databiota team will use Android Studio to develop the app's software, with initial user evaluation during app prototyping. A navigating map (site map and screen flow diagram) will be applied for modeling graphs to describe the interface map. Version control and update tracking will be reported once the app is finalized and the trial begins.

App development will be funded by NLR Indonesia. The app will be owned by the research group on Tropical Diseases, Infectious Diseases and Herb in the Faculty of Public Health Universitas Airlangga in Surabaya, Indonesia.

Phase 2: Development of a Questionnaire for Measuring Awareness of Common Skin Diseases in the Community

The literature review showed the absence of specific instruments for measuring the level of awareness in the general community of early symptoms of common skin diseases. Thus, in this second phase of the study, we aim to develop a questionnaire for measuring awareness in the general community, which will assess common skin disease knowledge, common skin disease prevention, and the intention to seek health services.

The questionnaire will be developed in 2 steps. The first step involves conducting a literature review, consultation with professional experts, and focus group discussions with persons with and without knowledge or expertise in leprosy. Questions will initially be developed in English based on expert judgement and checks by English language experts. Because the study population is Indonesian, the second step will involve translating the questionnaire into the Indonesian language.

The validity and reliability study for the developed questionnaire will be conducted in the subdistrict of Batumarmar, Pamekasan District, East Java Province, ensuring the questionnaire accurately measures the awareness of the community regarding skin diseases and produces consistent results over time and different respondents. The Batumarmar area was chosen because of its variety of geographic and community characteristics, which include rice fields, mountains, and residential areas in both urban and rural settings. Study participants will include experts in leprosy and behavioral sciences (the study supervisor), local key informants, and members of the general community.

The eligibility criteria for the validity and reliability study are as follows: (1) residents living in Batumarmar subdistrict and Pamekasan District; (2) individuals aged 18-65 years; (3) individuals willing to participate and provide informed consent; and (4) individuals able to understand and communicate in Indonesian and Madurese languages. Aside from the results of the validity and reliability test, data on demographical characteristics, such as gender, age, educational level, and occupation, will be included for analysis.

Phase 3: Awareness Study and Acceptability Test of DEDIKASI-App

Awareness Study

Implementation of the awareness study in the general community will follow a cross-sectional mixed-method approach. The population being studied is the general community in Pamekasan District. Fifty respondents will be recruited from 4 CHCs that were randomly selected based on their representativeness of urban and rural areas in Pamekasan District. Two CHCs were chosen to represent urban areas (Teja and Proppo), while the other 2 represent rural areas (Sopa'ah and Galis). Recruitment of respondents will be conducted using a simple random sampling technique. The number of respondents is based on a minimum sample size proposed by Terwee et al [30] for the measurement properties of health status questionnaires.

The eligibility criteria for respondents are as follows: (1) residents living in the 4 CHCs in Pamekasan District, (2) individuals aged 18-65 years, (3) individuals willing to participate and provide informed consent, and (4) individuals able to understand and communicate in Indonesian and Madurese languages.

Acceptability Test

In parallel with the awareness study, acceptability testing for DEDIKASI-app will be conducted with the same 50 respondents selected for the awareness study. This study aims to measure the acceptability level of the community toward DEDIKASI-app and to assess their perception toward its use. In addition, 21 HCWs (1 from each of the 21 CHCs) will be included in an acceptability test of the DEDIKASI-HCW app to assess their perception of its use. We will include HCWs who actively coordinate with leprosy supervisors at the district health office level.

DEDIKASI-app will be shown to all participants. Community and HCWs' acceptability, defined as the degree to which users are willing to adopt and use a new technology influenced by key psychological and behavioral factors, will be conducted using a survey based on the technology acceptance model (TAM). The TAM is widely adopted to assess the acceptability of health technologies within the 4 constructs of perceived usefulness, perceived ease of use, attitude, and behavioral intention to use [31,32]. Based on previous studies [28,29], the following 4 constructs will be added: security and privacy, technology literacy, quality of information, and benefit. For the TAM questionnaire with these added constructs, we will not conduct a separate validation, as the reasons for including these constructs have already been established and validated in prior studies. However, in the current study, we will train the research assistants to carefully observe whether the respondents understand the questions during administration to ensure clarity and comprehension. A 5-point Likert scale will be used to quantify the responses.

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Phase 4: Randomized Controlled Trial of the Effectiveness of DEDIKASI-App to Increase Early Detection of Skin Diseases Including Leprosy

The fourth phase is an randomized controlled trial aimed to assess the effectiveness of DEDIKASI-app as a strategy to increase awareness and early detection of leprosy and other common skin diseases.

The sample size will be calculated using the following formula for hypothesis testing for 2 population means (2-sided test) [33]:

The following values will be used: level of significance (α)=5%; power of the test (1-β)=90%; population SD (σ)=5; and population variance (σ^2)=25. The population mean (μ_1) will be obtained after the awareness study in the second phase; as there was no previous study available, μ_2 represents the anticipated population mean of the intervention group. Sample size will be calculated afterward; however, we will expect to obtain 600 participants.

The study population is the general community located in 21 CHCs of Pamekasan District. The participating CHCs have already been randomly allocated to either the intervention or control group using a computer-generated sequence by an independent statistician. The intervention group comprises Tlanakan, Bandaran, Pademawu, Sopaah, Galis, Larangan Bedung Kadur, Batumarmar, Teja, and Kowel, and the control group comprises Larangan, Talang, Proppo, Panaguan, Palengaan, Pakong, Waru, Tampojung Pregi, Pasean, Pengantenan, and Bulangan Haji. Allocation concealment was ensured by using sequentially numbered, sealed, opaque envelopes, opened only after enrolment of each cluster. Research assistants will enroll participants through door-to-door recruitment. To reduce information contamination, we will ensure geographical separation of intervention and control CHCs where feasible. Pamekasan District, located on Madura Island in East Java Province, covers an area of approximately 792 square kilometers, with a population density of around 850 people per square kilometer. The district is divided into 13 subdistricts, with substantial distances between them; for example, the distance between Batumarmar (a northern subdistrict) and Proppo (a central subdistrict) is approximately 25 kilometers, often requiring over an hour's travel due to rural road conditions. Given this geographic spread and limited daily intervillage interactions, the risk of information spillover between intervention and control clusters is considered minimal. Baseline and postintervention surveys will be conducted within a short period of a fixed 4-week window across all clusters to minimize variation due to external influences such as health campaigns or seasonal trends. Data collectors will follow the arranged schedule based on the study procedure. For eligibility to participate in the study, participants must be a resident of Pamekasan District, especially in the working area of the 21 CHCs; aged 18-65 years; willing to participate in the study and provide informed consent; and an android or smartphone user. The final criterion might not apply to the control group.

Data regarding the effectiveness of DEDIKASI-app as a strategy to increase awareness and early detection of leprosy and other common skin diseases will be collected using the validated questionnaire that will be developed in phase 2.

Statistical Analysis

Results of validity and reliability testing of the community awareness questionnaire developed in phase 2 will be analyzed using both descriptive and analytical statistics. Demographic data will be analyzed descriptively, while the validation and reliability of the questionnaire will be assessed statistically using Pearson correlation and Cronbach α, respectively. Content and face validity will be qualitatively used to avoid question item ambiguity, ensure clarity and relevancy, and ensure that the questions are not judgmental, intrusive, or distressing to target participants [34]. The questionnaire will be administered through an interview setting, with all selected respondents interviewed at 2 points: a preintervention interview and a postintervention interview conducted approximately 4 weeks later (during the intervention study in phase 4).

During the third phase, the questionnaire developed in phase 2 will be used to collect the data on awareness in the general community. All responses to the questions will be given numerical scores based on correct or positive answers. The total score will be calculated, while the mean range will be used to illustrate the distribution and variation of scores. To measure the impact of the intervention, the change in scores (delta change) between preintervention and postintervention assessments will be calculated for each group. The Wilcoxon signed-rank test will be used to compare paired preintervention and postintervention scores within each group. A P value of <.01 will be considered statistically significant, indicating improvements in respondents' knowledge, prevention practices, and health-seeking behavior.

The acceptability test for DEDIKASI-app will be conducted during the third phase, using a survey based on the TAM. A Likert scale will be used as a scoring system. The results from both community members and HCWs will be descriptively analyzed and presented using a frequency table.

Data from the randomized controlled trial in the fourth phase will be analyzed using SPSS version 21 (IBM Corporation). We will conduct a descriptive analysis by calculating the either the mean or median values of the awareness scores and the count of reported common skin disease cases through DEDIKASI-app. The choice between mean or median will depend on the distribution of the scores. We will also use a box plot diagram to visually compare the measurements between the 2 groups.

For assessing the effectiveness of DEDIKASI-app as an intervention for enhancing awareness compared to the control group, we will apply an independent sample t test if the data exhibit a normal distribution. If the data distribution is not normal, we will use the Mann-Whitney test. All statistical analyses will be performed at a significance level of .05, with a 95% CI (or using the IQR if medians are used).

Missing data will be described and explored. We acknowledge that incomplete case analysis can introduce bias and will consider appropriate imputation techniques during final analysis

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depending on the extent and pattern of missingness. We will include the outcomes of all participants (intention-to-treat), regardless of the extent the intervention group used DEDIKASI-app.

Ethical Considerations

Ethical clearance for the study (all 4 phases) has been sought from the Ethical Review Board of the Faculty of Public Health Universitas Airlangga, Surabaya, with registration number 160/EA/KEPK/2023. The trial in phase 4 has been registered to the INA-CRR, the trial study registry of the Ministry of Health, Republic of Indonesia (INA-O8EX278). Paper-based informed consent will be asked from all participants. Participants will be informed during the consent process whether they will be allocated to the intervention or control group. As such, participants will be aware of whether or not they will be using DEDIKASI-app. This may have influenced their expectations.

All participant data collected via DEDIKASI-app will be stored securely with encryption and password protection. Only authorized HCWs will have access to identifiable information through the HCW interface. Study participants will be informed of data confidentiality, and in case of health concerns, they may be referred to their nearest CHC for follow-up. Research assistants and HCWs involved in the study will receive training on privacy, communication protocols, and referral procedures.

Results

Current Progress

This study received ethical clearance from the Ethics Review Board of the Faculty of Public Health, Universitas Airlangga (160/EA/KEPK/2023) and is registered in the Indonesia Clinical Research Registry (INA-O8EX278). Field research was funded by NLR Indonesia and Erasmus MC for the period of May 2022 to December 2024. At the time of manuscript submission, phase 1 (DEDIKASI-app development) and phase 2 (questionnaire validation) had been completed. Data collection for the randomized controlled trial has recently concluded, and data analysis is currently underway. Final study results are expected to be published by the end of 2025.

Phase 1: Development of DEDIKASI-App

The app will be developed following the design thinking methodology, incorporating literature reviews, expert consultations, and focus group discussions. The final version of the app will be validated by a panel of health care professionals and community members to ensure its usability and relevance.

Phase 2: Awareness Study and Questionnaire Development

A questionnaire will be developed and validated to measure awareness levels of common skin diseases. It is expected that initial results will show varying levels of awareness among different demographic groups, with the highest awareness likely among HCWs. Statistical validation will be conducted to confirm the reliability and accuracy of the questionnaire.

Phase 3: Acceptability Testing

The acceptability study will assess whether DEDIKASI-app is well-received by both community members and HCWs. Usability scores will be measured, and key concerns such as the need for localized content and ongoing updates will be identified.

Phase 4: Randomized Controlled Trial

The intervention study will evaluate whether there is a statistically significant increase in awareness and early detection behaviors among the intervention group compared to the control group. It is expected that participants using DEDIKASI-app will be more likely to seek professional health care assistance for skin conditions. Additionally, skin conditions reported by members of general public in the intervention group will be analyzed.

Although this is a low-risk, behavioral study, we will monitor for any unintended or unexpected events such as technical issues, privacy concerns, or participant distress resulting from the use of DEDIKASI-app. These events, if they occur, will be documented and reviewed.

Discussion

Anticipated Findings

Innovations are needed for improving awareness in the general community of symptoms of skin diseases, especially of those that are contagious or need timely treatment to prevent future complications. This is particularly the case for leprosy, in which disease elimination and disability prevention depend on early case detection and treatment. Aligned with World Health Organization guidance in applying digital health innovations, mobile phone apps are expected to improve health services in the community and place us on the road to achieving universal health coverage [35]. Through our proposed study, we will develop a mobile phone app aimed to increase awareness in the community of common skin diseases, including leprosy. DEDIKASI-app aims to address gaps in awareness and early detection of skin-related NTDs, including leprosy and other common skin diseases, by leveraging mHealth technology in a low-resource setting. We anticipate that it will be acceptable to both community members and HCWs and will lead to measurable improvements in awareness and early detection. The integrated approach of DEDIKASI-app broadens the scope of the app and simultaneously addresses the stigma attached to leprosy by not singling out just one disease, possibly discouraging its use by the general public.

Unlike previous mHealth interventions that focus on treatment adherence or symptom tracking, this app will integrate culturally tailored content and localized language support to target stigma and misinformation [25,26].This study will produce newly developed instruments and add insights into the level of knowledge regarding awareness of common skin diseases. The study will also provide insight into the acceptability and effectiveness of DEDIKASI-app for both the community and HCWs.

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The app could be adapted to other NTDs or used in other Indonesian provinces with future validation. Results will be disseminated via journal publication, stakeholder workshops, and presentations to health policymakers and nongovernmental organizations.

Strengths and Limitations

This study represents a pioneering effort in Indonesia as it is a novel study assessing awareness levels of skin diseases among the community and HCWs. As such, it is expected to fill a significant gap in existing knowledge. The study's strengths include a comprehensive design, which will use design thinking, the TAM, and a multiphase development and validation process. The integration of mobile technology in DEDIKASI-app serves as a key strength, enhancing accessibility and engagement in health education. The study uses a randomized controlled trial design, ensuring rigorous evaluation of the app's effectiveness. Additionally, the current study will monitor to which extent participants will actually reach out to CHCs with questions about their skin.

However, there are several limitations to consider. The first limitation includes potential challenges with digital literacy, limiting generalizability to similar rural populations across Indonesia with large characteristic variation. The study is conducted only in Pamekasan District, Madura Island, East Java, which has specific social and geographical characteristics, potentially limiting the generalizability of the findings. Although this study is limited to community members in Pamekasan District, the design of DEDIKASI-app allows for future use in other settings. The findings will be generalizable to similar rural or underserved populations in Indonesia or other low-resource areas. However, additional evaluation will be needed before applying this intervention in urban or higher-literacy populations or through fully web-based environments. Second, this study may face limitations common to eHealth interventions, including the inability to blind participants, which may introduce expectation bias. This limitation will be mitigated by ensuring anonymity, using validated questionnaires, and cross-referencing with objective measures where possible. Third, while mobile technology enhances accessibility, digital literacy and internet connectivity issues may affect the intervention's reach and effectiveness. Providing user training sessions and offering alternative offline materials will help ensure broader usability and impact. Additionally, participants' awareness of being observed or assessed may influence their behavior (the Hawthorne effect) [36]. Lastly, although multiple outcomes will be examined, this pilot study is not powered to control for multiplicity, so findings will be interpreted with caution.

Conclusion

This study is expected to contribute to new understandings on how communities recognize and perceive skin symptoms, with special reference to early-stage leprosy. It will also offer perspectives on how well DEDIKASI-app is received and how effective it is in enhancing awareness among both the community and health care professionals with regard to identifying leprosy and other common skin problems.

Acknowledgments

This study is part of the larger Post Exposure Prophylaxis (PEP++) project operating in the Pamekasan District that is funded by NLR Indonesia and Erasmus University Medical Center, Rotterdam.

Authors' Contributions

Conceptualization: UA, MAI, JHR, IJK
Project administration: UA, MAI
Methodology plan: UA, MAI, JHR, IJK
Supervision: MAI, JHR, IJK
Visualization: UA
Writing – original draft: UA
Writing – review & editing: UA, MAI, JHR, IJK

Conflicts of Interest

None declared.

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Abbreviations

CHC: community health center
HCW: health care worker
mHealth: mobile health
NTD: neglected tropical disease
TAM: technology acceptance model

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Protocol

A Self-Guided Digital Mental Health Promotion Service Targeting Young People: Protocol for a Randomized Controlled Trial

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Abstract

Background: The high and increasing rate of poor mental health among young people is a matter of global concern. Experiencing poor mental health during this formative stage of life can adversely impact interpersonal relationships, academic and professional performance, and future health and well-being if not addressed early. However, only a few of those in need seek help. Research indicates that young people perceive digital mental health support as having many benefits compared to traditional face-to-face services. However, the effectiveness of self-guided digital mental health services is not well documented, and research on their cost-effectiveness is lacking. Mindhelper is Denmark's largest open access, digital, self-guided mental health service for young people. While it does not provide direct psychological or therapeutic care, it offers practical strategies and tools to promote well-being and address a broad spectrum of mental health challenges, from everyday stress to more complex issues. Despite its widespread use, the effectiveness of Mindhelper has not been evaluated.

Objective: This trial aims to evaluate the effectiveness of building on the results of our feasibility study. We will assess Mindhelper's impact on mental health and well-being, psychological functioning, intentions of help seeking, and body appreciation among people aged between 15 and 25 years and provide insights into the service's cost-effectiveness.

Methods: We will recruit 4910 people aged between 15 and 25 years via social media and randomized and allocated to an intervention group (receiving information about Mindhelper) or a control group (no information about Mindhelper). Outcomes are self-assessed and collected at baseline and 2, 6, and 12 weeks after randomization through online surveys and analyzed using the intention-to-treat approach. Qualitative interviews with intervention group participants will provide complementary insights, and a cost-effectiveness analysis will also be conducted.

Results: This study was fully funded in November 2022, and the data collection started in January 2025. As of August 2025, we enrolled 2613 people. The data analysis will start after data collection concludes (by early 2026), and the results of the primary outcome are expected to be published in the second half of 2026.

Conclusions: This study will deliver crucial evidence on the effectiveness of self-guided digital mental health promotion targeting young people. If effective, this highly scalable service may contribute to combating the trend of rising mental health issues among young people and address key challenges in primary care by delivering timely, coordinated, and effective services to young individuals, potentially at a low cost.

Trial Registration: ClinicalTrials.gov NCT06385457; https://clinicaltrials.gov/ct2/show/NCT06385457

International Registered Report Identifier (IRRID): DERR1-10.2196/73736

(JMIR Res Protoc 2025;14:e73736) doi:10.2196/73736

KEYWORDS

mental health; adolescent; health promotion; randomized controlled trial; effectiveness study; qualitative research; cost-effectiveness

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Introduction

Background

The high and increasing rate of poor mental health in young people is a matter of global concern [1], and in Denmark, the proportion of people aged between 16 and 24 years reporting poor mental health increased from 12% in 2010 to 26% in 2023 [2,3]. If left unaddressed, poor mental health (even below the diagnostic threshold) during this formative stage of life can negatively affect interpersonal relationships, academic and professional performance, and long-term health and well-being [1,4]. Young people constitute the age group most affected by mental health problems, yet only a few of those in need seek help. Barriers to seeking help include concerns about stigma, confidentiality, difficulties navigating mental health services, and a preference for informal help [5-7].

Digital services, such as apps and websites, offer significant potential to enhance the scalability of mental health services. Research indicates that young people perceive digital mental health support as having many benefits compared to traditional face-to-face services, including greater accessibility, more interactivity, greater anonymity, and reduced stigma associated with help seeking [5,8-13]. Most digital mental health services focus on addressing symptoms after their onset, primarily targeting depression and anxiety, and digital services designed to reduce these conditions have shown small but promising effects [13-16]. However, evidence for symptoms beyond depression and anxiety remains limited, making the results more inconclusive [13].

Digital services incorporating an in-person element (eg, therapist or other health professional) are associated with greater effectiveness, better adherence, and lower dropout rates compared to fully self-guided services [13,15]. Nevertheless, self-guided services are highly scalable, as they can be delivered to a higher number of users with low additional costs. Although the effects remain mixed, self-guided smartphone apps have shown the potential for improving symptoms across various domains, particularly for depression [17].

Most studies assess the effects of an experimental service designed by researchers for testing in a controlled research setting, aimed at reducing one mental health issue, with little research on multicomponent services applied in real-world settings focusing on broader mental health problems. Samples are often drawn from narrowly defined populations, such as students from a single university or individuals with specific symptomatology, thereby reducing generalizability to real-world settings. Few large-scale randomized controlled trials (RCTs) have been conducted, as most involve fewer than 250 participants [14,17]. Furthermore, despite being widely considered as low cost, there is a lack of evidence on the cost-effectiveness of digital mental health services targeting young people [13].

Mindhelper is Denmark's largest open access, digital, self-guided mental health service for young people. While it does not provide direct psychological or therapeutic care, it offers practical strategies and tools to promote well-being and address a broad spectrum of mental health challenges, from everyday stress to more complex mental health issues. Despite its widespread use, the effectiveness of Mindhelper has not been evaluated.

Objectives

Building on the results of our feasibility study [18], this research will evaluate Mindhelper's impact on mental health and well-being, psychological functioning, intentions of help seeking, and body appreciation among people aged between 15 and 25 years. In addition, it will provide insights into the service's cost-effectiveness. We aim to recruit 4910 participants, making this the largest RCT to assess the effects of a self-guided digital mental health promotion service targeting young people.

Methods

Ethical Considerations

The study protocol follows the Standard Protocol Items: Recommendations for Interventional Trials checklist [19]. It was legally approved by the University of Southern Denmark (11.882) and ethically approved by the research ethics committee of the University of Southern Denmark (24-2933). Furthermore, the study was registered on ClinicalTrials.org before its initiation (NCT06385457). Before randomization, all participants are given additional information before they provide consent to participate. Participants who complete all follow-up surveys will be included in a lottery for cinema gift cards (DKK 299 [US $43]), with 200 gift cards being distributed.

Intervention: Mindhelper

Mindhelper is a service hosted at the Centre for Digital Psychiatry in Denmark. Mindhelper's primary service is a website [20] launched in 2016, which provides information, self-help tools, and evidence-based guidance on various mental health challenges that young people face today. This includes dealing with anxiety, loneliness, family difficulties, depression, romantic relations, eating disorders, and self-harm.

Mindhelper is different from other Danish digital mental health services in that it is the most comprehensive website containing unstructured information and tools across the whole spectrum of mental health problems and issues that young people may face in their everyday lives. Mindhelper is also unique in being integrated into the public mental health system and is free to use for everyone, self-administered, and self-guided.

Tools and information on Mindhelper are developed specifically for and with young people to enhance usability and encourage help seeking [21]. Most material is based on principles derived from cognitive behavioral theory, including mindfulness exercises and acceptance and commitment therapy–inspired self-instructions on beliefs, values, and general strategies for good mental health and well-being [22-24]. The website further serves as a national directory for local youth mental health services for further support and help.

The Mindhelper website also offers a supportive outreach service, where psychology students respond to digital letters sent by young people, supported by experienced psychologists when needed. The letters exchanged are published in an

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anonymized form so that other young people with similar concerns or worries may benefit from the supportive advice. Mindhelper was codeveloped between 2014 and 2016 by the Centre for Digital Psychiatry in partnership with young people and 4 Danish municipalities (Svendborg, Odense, Faaborg-Midtfyn, and Varde). The primary inspiration for Mindhelper is the Australian platform ReachOut [25].

Throughout its development and dissemination phase, Mindhelper has adopted a participatory approach, co-designing its resources with young people, parents, teachers, school counselors, youth workers, psychologists in community care, general practitioners, and youth mental health experts. More than 300 young people have participated in workshops, user panels, and content production teams. Iterative coproduction methods, based on the core principles of design thinking (understanding, defining, ideating, prototyping, and refining), have been crucial in ensuring the service remains relevant and useful to young people [26-28].

Since January 2019, Mindhelper has received permanent funding through a joint agreement between the 5 Danish regions and has been freely available and disseminated to young people and youth mental health professionals across the country. Mindhelper receives approximately 1 million visits a year [29]. Mindhelper's primary target group is people aged between 13 and 20 years; however, it also includes adults, parents, and youth mental health professionals [29].

In 2024, Mindhelper launched their first mobile app named Ro (Ro is Danish for calm), aiming to reduce stress and increase everyday calmness. The app is free to use and may be downloaded on Android smartphones and iPhones. In this paper, the Mindhelper website and the app Ro will be referred to commonly as "Mindhelper."

The research team was not involved in developing Mindhelper or its maintenance or promotion. Partnering with the Centre for Digital Psychiatry meant that the service tested builds on evidence-based information and is built by an expert team. Furthermore, the service is sustainable (independent of research funds) compared to most services tested, as Mindhelper was constructed and is funded and used independently of this study.

Study Design

The effects of Mindhelper will be evaluated in a 2-armed 1:1 RCT and complemented by qualitative insights from interviews with participants assigned to the intervention group. Figure 1 provides an overview of the study design.

Figure 1. Overview of the study design.

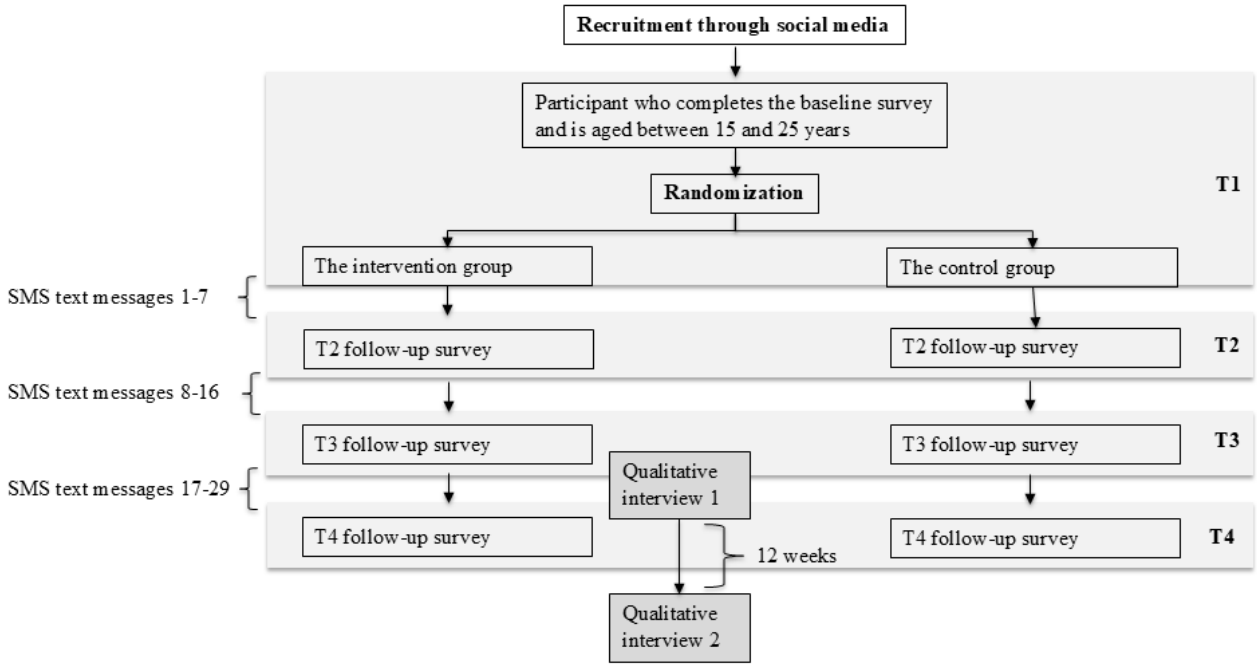

Participants are randomized upon responding to the baseline (T1) survey, and based on their group assignment, they will receive information about Mindhelper at the end of the survey (intervention group) or be informed that they have been placed in the control group. All data are collected online (in SurveyXact [Ramboll Management Consulting]). Randomization is conducted automatically in the survey setup and is done independently of the participants' responses at T1. There is no care provider or outcome assessor, as all measures are self-reported and collected through online questionnaires. Randomization, invitations for follow-ups, reminders to nonresponders, and distribution of information to the intervention group were all done automatically and independently of the research team.

By the end of the T1 survey, participants are asked to provide their mobile numbers, and invitations to follow-up surveys are sent by SMS text messages. Therefore, it is solely participants completing the T1 survey who can be invited to the follow-up surveys. In our feasibility study, participants preferred being contacted via SMS text messages as compared to emails, which is consistent with studies exploring how to engage young people in digital mental health interventions [18,30].

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All participants aged between 15 and 25 years who complete the T1 survey will be invited to respond to follow-up surveys 2 weeks after randomization (T2), 6 weeks after randomization (T3), and 12 weeks after randomization (T4). By the end of the survey at T4, the control group will be informed about Mindhelper and directed to the website.

Our feasibility study revealed very low engagement when participants were merely provided with a link to Mindhelper at the end of the T1 survey [18]. To increase use in the intervention group, we developed an SMS text message campaign. Participants will receive 29 SMS text messages throughout the study, each offering tips and guidance on using Mindhelper. Each SMS text message links to a restricted section of the website, where participants are introduced to a specific theme or feature through brief texts and videos before being guided to the unrestricted section of the website. Multimedia Appendix 1 provides a detailed overview of the campaign themes.

The recruitment material states that the study is evaluating a mental health promotion website for young people, but does not mention Mindhelper specifically, to avoid influencing the control group's use. Mindhelper remains publicly accessible during the study, and there is no way to ban access of participants from the control group. However, our feasibility study found that very few control group participants accessed the website, suggesting this is not a significant concern [18].

The intervention group participants may use the service as much as they like. Participants in the intervention group and control group may continue with any usual care they receive in addition to the trial. Nonresponse is minimized by sending up to 2 reminders.

At T3, participants in the intervention group will be invited to participate in 2 interviews (when responding to the survey): the 1st close to T3 and a follow-up interview approximately 12 weeks later. Further details of the qualitative part of the study are presented in the section "Qualitative Contributions."

At the end of each survey, it is emphasized that the research team does not provide counseling or treatment and will not contact anyone based on their survey responses. Participants (in the intervention and control group) are strongly encouraged to seek help and support if they experience distress or require assistance and are directed to counseling services, including Børnetelefonen and HØRT (Danish consulting services for young people). Furthermore, in cases of acute suicidal crises, they are encouraged to contact Livslinien (a Danish service for people with suicidal thoughts) or emergency services.

Recruitment

We aim to recruit approximately 4910 participants via Facebook [Meta Platforms, Inc], Instagram [Meta Platforms, Inc], and Reddit (the final number of participants depends on attrition at T2 as described in the Sample Size Calculation section).

The only inclusion criterion is age, with participants required to be aged between 15 and 25 years old at T1.

We aim to recruit participants in need of mental health promotion services, targeting a study population with below-average mental health and well-being status rather than a representative sample. However, as Mindhelper is a universal public health service, we have decided that all participants are eligible regardless of mental health status at T1, allowing us to assess the service's effectiveness in the broader target population.

Our feasibility study demonstrated that Facebook and Instagram were effective platforms for recruiting young people, and the self-selection based on the framing of advertisements resulted in a study population with below-average mental health and well-being status: 49.6% (275/554) of the sample had experienced a mental illness, and of those, 49.1% (135/275) reported daily impairment in the past 12 months [18]. In addition, 64.3% (356/554) of the respondents were identified as being at risk for depression or stress based on the World Health Organization–Five Well-Being Index (WHO-5) [18].

Before initiating data collection, we defined an optimal study population composition based on the parameters available for targeted advertisements: gender and age (from user profiles) and geographical location (from IP addresses). We aimed for a sample of 70% women, as young women generally report lower mental health and well-being than young men [3]. To ensure balanced representation, we aimed for an equal distribution across ages, as unpublished data from Danes' Health—the National Health Profile 2011 indicated no substantial age-related differences in mental health and well-being among people aged between 16 and 25 years. Similarly, because no substantial regional variation was observed in the same data for this age group, we sought to match the regional distribution of the general population in this age group.

The recruitment strategy will be monitored weekly throughout the study period and adjusted to target individuals underrepresented in the sample based on these characteristics. The ability to create multiple advertisements targeting different populations, closely monitor their real-time performance, and continuously adjust them makes online advertising a powerful tool for recruiting according to specific demographic requirements. However, as of November 6, 2023, Meta Platforms, Inc has prohibited direct advertisement to individuals aged <18 years due to European Union legislation. This regulatory change may challenge our goal of achieving equal representation across age groups, yet it remains our target.

In the feasibility study, we neither defined an optimal study population composition nor adjusted the recruitment strategy, resulting in a sample with 87.3% (488/559) women [18]. To increase male participation, we will include Reddit as a recruitment platform in this study. As of 2024, 63.6% of Reddit's global users were male individuals [31], compared to 52% on Instagram [32] and 57% on Facebook [33]. In Denmark, 41% of Instagram users and 46% of Facebook users are male individuals [34]. While Danish user demographics for Reddit are unavailable, we assume they align with global trends.

Figure 2 illustrates the recruitment process, from viewing an advertisement on one of the platforms to becoming a study participant. From the advertisements, young people will be directed to a landing page containing information about the study design, data protection, and other details, presented with graphics and a short explainer video [35]. If they choose to

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participate, they will be guided to the T1 survey and provided with additional information before they provide consent to participate. The participants are informed that the study is conducted in collaboration between the region of Southern Denmark and the National Institute of Public Health, University of Southern Denmark.

At the end of the T1 survey, the intervention group will receive information about Mindhelper and will be automatically directed to Mindhelper [20], while the control group will not receive any information about Mindhelper but instead receive instructions about the next steps in the study. website

Figure 2. Recruitment flow from advertisement to participant.

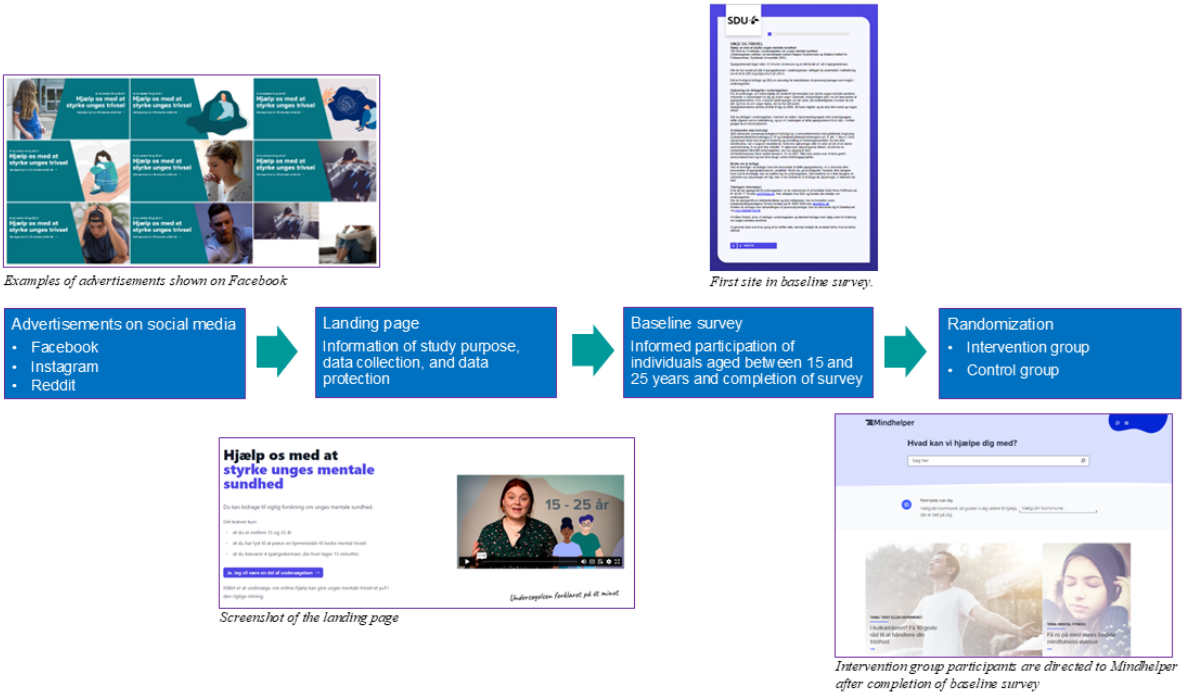

Measures and Outcomes

Overview

The data are self-reported and include demographic characteristics, use of Mindhelper, and validated scales for mental health and well-being (Table 1). Though we include some measures capturing negative aspects of mental health and well-being, the primary focus in the surveys is on positive aspects rather than symptomatology.

The primary outcome is mental well-being, measured using the WHO-5, while the secondary outcome is well-being and psychological functioning assessed with the Short Warwick-Edinburgh Mental Well-being Scale (SWEMWBS). In addition, the intention of and barriers to help seeking are explorative outcomes. The impact of Mindhelper will also be evaluated on body appreciation, and an economic effectiveness analysis will be conducted.

Where no suitable scale existed for specific measures, such as intentions to seek help, we developed our own. To maximize the response proportion, we aimed to balance comprehensiveness with brevity, ensuring that surveys are clear, easy to interpret, and completable within 5 to 15 minutes.

Objective data on use metrics from Mindhelper will not be collected at an individual level, as this is not possible without violating the core principle of anonymity of Mindhelper users. However, data on the intervention group's interactions with the SMS text message campaign will be collected at an aggregate level, and self-reported measures of use of Mindhelper will be collected in the surveys.

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Table 1. Overview of measures and outcomes.

Measures and outcomes	Surveys			
	T1[a]	T2[b]	T3[c]	T4[d]
Participant characteristics				
Age	✓			
Gender (male, female, other)	✓			
Primary occupation	✓			
Educational level	✓			
Parental educational level	✓			
Region of residence	✓			
Use of Mindhelper				
Digital behavior when feeling down	✓	✓	✓	✓
Use of Mindhelper (in the intervention group)		✓	✓	✓
Thoughts on the SMS text message campaign (in the intervention group)		✓	✓	✓
Familiarity with or use of Mindhelper and Ro (at T1 for all participants and at T4 for the control group)	✓			✓
Primary outcome				
World Health Organization–Five Well-Being Index	✓	✓	✓	✓
Secondary outcome				
The Short Warwick-Edinburgh Mental Well-Being Scale	✓	✓	✓	✓
Explorative outcome				
Intentions of help seeking	✓		✓	✓
Barriers to help seeking	✓		✓	✓
Other measures of mental health and well-being				
Patient Health Questionnaire-4	✓	✓	✓	✓
The Short Form Perceived Stress Scale-4	✓		✓	✓
Body Appreciation Scale-2 Short Form	✓	✓	✓	✓
Diagnosed with a mental health issue	✓		✓	✓
Affected by a diagnosis within the last month	✓		✓	✓
Treated for diagnosis within the last month	✓		✓	✓
Use of the health care system				
Absence from work or school	✓	✓	✓	✓
Contact with the health care system	✓	✓	✓	✓

[a]T1: baseline.
[b]T2: 2 weeks after randomization.
[c]T3: 6 weeks after randomization.
[d]T4: 12 weeks after randomization.

Primary Outcome: the WHO-5

The WHO-5 captures positive aspects of mental health and well-being, aligning well with the promotion-focused objectives of Mindhelper. Furthermore, the measure is brief (5 items) and has demonstrated high sensitivity to changes in mental well-being, which is crucial when applied to an evaluation [36].

It consists of 5 positively framed items asking respondents to rate how often they felt cheerful, calm, active, rested, and interested in life over the past 2 weeks, using a 6-point Likert scale from 0 (not at all) to 5 (all the time). Scores range from 0 to 25; to standardize, the raw score is multiplied by 4, producing a final score from 0 to 100, where higher scores indicate greater well-being.

The WHO-5 is a widely recognized measure of mental well-being with extensive validation across diverse populations, including young people, and has been translated into more than 30 languages, including Danish [36,37]. Given its widespread use in mental health research, using the WHO-5 allows for comparability with other studies.

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Secondary Outcome: The SWEMWBS

SWEMWBS, similar to WHO-5, is used to assess mental health and well-being by focusing on positive mental health aspects. It is a 7-item questionnaire, focusing on the past 2 weeks, covering aspects of both feeling good and functioning well, including optimism, relaxation, problem-solving, and interpersonal closeness. Each item is rated on a 5-point Likert scale from 1 (“none of the time”) to 5 (“all of the time”), with total scores indicating overall well-being; higher scores reflect greater well-being. Where the WHO-5 is an affective measure focusing on emotions and energy, the SWEMWBS is a hybrid measure that, in addition to measuring positive emotions, also includes aspects of functioning [38].

SWEMWBS is derived from the original 14-item version and is validated for screening mental well-being in both general and clinical populations, including young people, and has proven sensitive to changes [39].

Explorative Outcome: Intentions of Help Seeking

There is no standard approach for measuring intentions and barriers to help seeking, and existing studies have used a wide range of measures and definitions [5]. To retrieve a comprehensive measure of young people’s intentions of help seeking, we developed our own questions:

> *Imagine that you have been feeling very down over the past couple of months. Everything feels overwhelming, and you have started to feel that life is meaningless. How likely is it that you would seek help or support from the following if you found yourself in this situation? (1) Family, (2) Friends, (3) Partner, (4) A healthcare provider (e.g., doctor or psychologist), (5) Teacher, study counselor, manager, or HR., (6) Internet search (e.g. Google search or ChatGPT), (7) Social media (e.g., Instagram, TikTok and Reddit), (8) Telephone/chat counseling (e.g., Børnetelefonen or Headspace).*

Response categories included “very likely,” “likely,” “unlikely,” “very unlikely,” and “don’t know/don’t have.”

The intention was to present the responders with a scenario that we consider to be of severity demanding support and help. Furthermore, a scenario related to symptoms of depression was chosen, as this is one of the most common issues among young people.

If participants indicate that they are unlikely or very unlikely to seek help from the listed sources of support, they are prompted to select their reasons from the following categories: (1) “I don’t think they can help me”; (2) “I prefer to handle it by myself”; (3) “I am afraid of burdening them”; (4) “I find it embarrassing/shameful to feel this way”; (5) “I have sought help but did not receive it”; (6) “I don’t believe I can get better”; or (7) “Other, please describe.” In addition, all participants are asked which factors might encourage them to seek help for mental health issues through an app or website and what barriers prevent them from doing so, explored through 4 different phrasings in open-text questions.

Other Measures of Mental Health and Well-Being

The Patient Health Questionnaire-4 (PHQ-4) is an ultrabrief self-report validated questionnaire that consists of a 2-item depression scale (Patient Health Questionnaire-2) and a 2-item anxiety scale (Generalized Anxiety Disorder-2). A validation study showed that the scale consists of 2 discrete factors (depression and anxiety) that explain 84% of the total variance [40]. An elevated PHQ-4 score is not a diagnostic tool but rather gives an indication of the presence of depression or anxiety.

The Short Form Perceived Stress Scale is an instrument for measuring perceived stress [41]. The Perceived Stress Scale-4 is designed to assess how unpredictable, uncontrollable, and overloaded respondents find their lives and provides a measure of an individual’s perceived stress levels.

The Body Appreciation Scale-2 (BAS-2) focuses on positive body image and not just body appearance. Since its release in 2015, the BAS-2 has been translated into more than 20 languages and is well-validated. BAS-2 consists of 10 items; however, the work by Tylka et al [42] demonstrated that 2 items explain more than 95% of the variance captured by the full 10-item questionnaire, named the BAS-2 Short Form. To shorten the survey, we decided to only include 2 items: “I feel love for my body” and “I am comfortable in my body.” We are using a Danish translation of the BAS-2, previously tested among people aged between 12 and 19 years [43]. BAS-2 has not yet been validated in a Danish context nor among people aged between 15 and 25 years; however, we are currently conducting this validation and will consider these results when interpreting our findings.

Tests of Surveys and Setup

The initial survey was pilot-tested through cognitive interviews with 5 informants aged between 15 and 25 years. This process aimed to assess how the questions were interpreted and identify potential challenges in responding to the surveys [44]. Special attention was given to questions we had developed ourselves. On the basis of the informants’ feedback, the wording was adjusted for clarity, categories were refined to better capture expected answers, and some questions were omitted due to misinterpretations. In addition, as the preexisting scales for intentions of help seeking were found to be unfeasible, the researchers constructed a new scale for the study, inspired by preexisting scales and the informants’ comments. The constructed scale was tested among 4 new informants aged between 15 and 25 years and 2 from the initial test and adjusted accordingly.

Due to technical difficulties, an unplanned test phase of the survey setup was conducted. During this phase, 323 respondents, recruited via Facebook and Instagram, completed the T1 survey and were invited to participate in the follow-up surveys. The intervention group also received the SMS text message campaign invitation. However, technical errors led to some participants being invited for follow-up surveys at incorrect times, and most participants did not receive reminders for nonresponse. In addition, some participants in the intervention group received the SMS text message campaign invitation late or not at all. This phase allowed us to thoroughly assess the

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surveys. We reviewed all participants' comments and corrected or omitted questions that did not work as intended.

Sample Size Calculation

We performed a sample size calculation, considering an average effect size of 0.1 for mental well-being (on the WHO-5 scale) at T2 to be of public health relevance (it is equal to an improved WHO-5 score of 1.94 points on average in the intervention group compared to the control group). Even small effects on individual mental health outcomes can lead to a major impact at a population level, particularly when the service can be scaled widely and reach a large target audience.

We applied the conventional levels of statistical power (0.8) and level of significance (.05) and assumed an SD of 19.4 at T1 among the intervention and control groups combined (based on data from the feasibility study) [18]. On the basis of these assumptions, at least 3142 participants were required (n=1571, 50% in each group).

In the test phase, we retrieved a response proportion of 64.1% (323/504) at T2 (primary end point). Assuming a similar retention proportion, we aim to include 4910 participants. The proportion of participants responding to the follow-up surveys will be regularly reviewed to evaluate if the assumption regarding retention in the sample size calculation is correct or if the number of participants included should be increased or decreased.

Planned Statistical Analysis

Overview

We will evaluate the effect of Mindhelper on multiple outcomes, as illustrated in Figure 3. First, we will conduct a randomization check and a dropout analysis. The primary analyses will follow the intention-to-treat principle, including all participants according to their randomized allocation, regardless of intervention use, and will be based on imputed data in cases of missingness. Missing data will be handled by multiple imputations using information from all the time points [45]. To test the robustness of the findings, sensitivity analyses will be conducted among complete cases. In addition, we will assess the complier average causal effect using the "contamination-adjusted intention-to-treat" method, an instrumental variable approach that accounts for adherence while preserving the benefits of randomization [46]. In this analysis, self-reported Mindhelper use at T4 in both the intervention and control groups will serve as the measure of adherence.

Figure 3. Overview of the planned analysis.

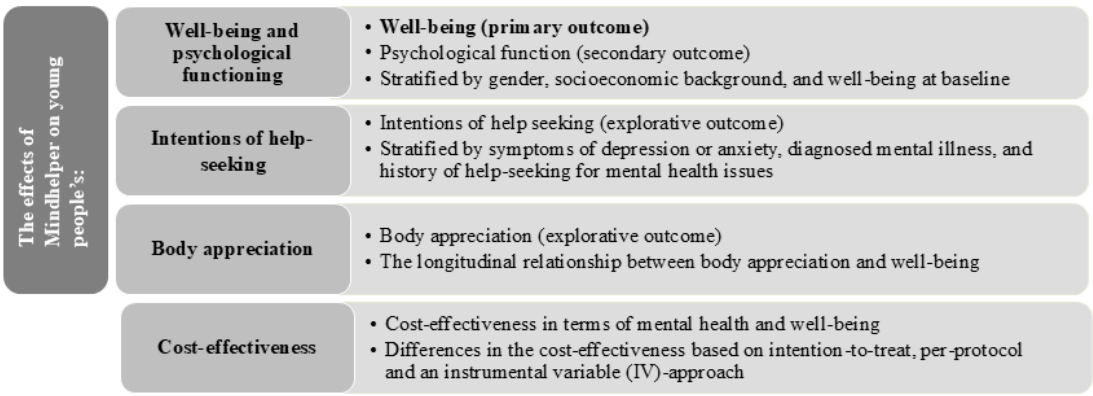

Analyses of data and interpretation of results will be done masked to the participant allocation. No interim analysis will be conducted during the trial. The subsequent section outlines the planned statistical analysis of each outcome and the cost-effectiveness analysis. A detailed statistical analysis plan has been published [47] before initiating any outcome analyses and unblinding the data.

The Effects of Mindhelper on Mental Well-Being and Psychological Functioning

The primary analysis will compare mean mental well-being, measured by WHO-5, between the intervention and control groups at T2, adjusted for WHO-5 scores at T1. If model assumptions are met, we will use a linear regression model. Psychological functioning, the secondary outcome measured by SWEMWBS, will be analyzed similarly as a continuous outcome, also adjusted for T1 values.

T2 was chosen for the primary assessment of effect because Mindhelper aims to provide immediate support and advice when problems arise. Most users visit thewebsite for a shorter period rather than regularly over multiple weeks. If the model assumptions are met, long-term effects will be evaluated at T3 and T4 using a repeated measures linear regression model.

To assess variation in effect by participants' gender (male, female, or other) and socioeconomic background (parents' highest educational attainment), analyses will be stratified accordingly. In addition, we will stratify by mental well-being at T1, expecting Mindhelper to be most effective for participants with moderate mental well-being (WHO-5 scores between 36 and 50) compared to those at high risk of depression or long-term stress (WHO-5 scores between 0 and 35) and those with mental well-being scores within the average range of the general population (WHO-5 scores >50). Furthermore, this stratified analysis will enable us to assess potential negative side effects of the intervention, assessing if the intervention group with WHO-5 scores >50 at T1 experienced a decline in mental well-being compared to the control group.

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The Effects of Mindhelper on Intentions of Help Seeking

To evaluate the impact of Mindhelper on help-seeking intentions, we will compare scores on the constructed scale between the intervention and control group at T3, adjusted for T1 values. Potential long-term effects will be assessed at T4 using a model accounting for repeated measures. We selected T3 for this evaluation because we hypothesize that changes in help-seeking intentions take longer to manifest compared to the primary and secondary outcomes.

The 8 categories of support will be assessed separately. Furthermore, we will categorize the sources into 3 groups: informal sources (categories 1, 2, and 3), formal sources (categories 4, 5, and 8), and self-guided sources (categories 6 and 7). Special attention will be given to category 6, which is the most common way to access Mindhelper.

The severity of mental health issues at T1, along with previous help-seeking behaviors, may influence both the use of Mindhelper and its effect on help-seeking intentions. To account for this, analyses will be stratified by symptoms of depression and anxiety (PHQ-4) and intentions of help seeking at T1. Among those with a mental health diagnosis, we will further stratify by T1 levels of impairment by mental health diagnosis within the last month (daily, weekly, more seldom than weekly, not affected, or do not know) and whether any treatment was received within the past month for the diagnosis (treatment received, on waitlist for treatment, or no treatment received).

The Effect of Mindhelper on Body Appreciation

The effect of Mindhelper on body appreciation will be assessed by comparing body appreciation scores (measured using the BAS-2 Short Form [42]) between the intervention and control groups at T2, using a linear regression model (if model assumptions are met) and adjusted for T1 scores. If model assumptions are met, potential long-term effects will be evaluated at T3 and T4 using a repeated measures linear regression model.

In addition, we will explore the mediating role of mental well-being and psychological function (WHO-5 and SWEMWBS) in the relationship between Mindhelper and body appreciation. The mediation analysis will estimate the natural direct and indirect effects [48], providing insights into how mental well-being and psychological function may explain any influence of Mindhelper on body appreciation.

Cost-Effectiveness Analysis

The cost-effectiveness analysis will be performed by constructing a standard incremental cost-effectiveness ratio (ICER) expressing the additional cost per mean mental well-being score, measured by WHO-5, obtained from the randomization to Mindhelper compared with standard care [49]. The analysis will apply standard techniques from economic evaluation aimed at estimating costs per quality-adjusted life years gained. The results from this analysis will contribute to the evidence-based economic evaluation of interventions aimed at increasing mental health and well-being.

Incremental estimates of costs and mental well-being scores obtained will be assessed in a regression model. To examine the second-order uncertainty of the estimated ICERs, a probabilistic sensitivity analysis using a 5000 bootstrap resample with a 95% CI will be conducted. Cost-effectiveness planes illustrating the resampled ICERs and cost-effectiveness acceptability curves at T2 to T4 will be constructed to show the probability that the intervention is cost-effective given varying threshold values for an additional change in the mean mental well-being score obtained. No standardized fixed threshold for the value of an additional mean mental well-being score obtained from a new health intervention exists. Therefore, the probability of cost-effectiveness will be investigated for several thresholds, for example, values ranging from 0 to DKK 500,000 (US $78,038.43).

Both potential health care savings and direct costs of delivering the intervention will be included in the analysis. Information on self-reported all-cause demand for acute health care services, general practitioner visits, use, and absence from employment in the project period will be gathered from surveys. To operationalize this in monetary terms, the average unit cost of acute health care use and average hourly wage earnings depending on gender and age in Denmark will be used in the economic evaluation. For the intervention group, operating costs related to Mindhelper will also be included based on the overall cost per user. These costs cover development, maintenance, and technical support for the service. Cost estimates will be calculated based on list prices from health care providers, and scenarios of changes in the number of users will be explored.

Transportability of Results

To assess how many young Danish people may benefit from Mindhelper, if it proves to be effective, we will compare the characteristics of our sample to a nationally representative sample of 31,420 young Danish people aged between 15 and 25 years. The national sample, drawn from the study “Young in 2023—Room for Everybody?” includes self-reported data on demographics, WHO-5, and PHQ-4 [50]. Furthermore, we will use the national sample to retrieve information on how our study population varies from a representative sample.

Qualitative Contributions

To gain a deeper understanding of how young people use and integrate self-help tools from Mindhelper in their everyday lives to promote mental health, a qualitative interview study will be conducted. In total, 20 young people will be interviewed twice, approximately 3 months apart. Participants for the interviews are recruited from the intervention group at T3. From the pool of participants who provide consent to be contacted to participate in interviews, 20 participants will be selected, considering gender, age, region of residence, and medical history of mental health disorders, to ensure a diverse group. This information will be based on responses to the T1 survey and solely used for selection purposes without influencing the themes of the interviews.

Selected respondents will be contacted via SMS text messages to arrange a time for the first interview. After the first interview, respondents will again be contacted via SMS text messages to schedule the second interview. Upon completing both interviews, participants will receive a cinema gift card via an

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SMS text message. Each interview will last up to 1 hour and follow a semistructured interview guide. The interviews will be conducted by AOK via phone or Microsoft Teams or Zoom (Zoom Communications, Inc), based on the participant's preference. The interviews will be audio recorded and transcribed verbatim. Conducting the first interview at T3 will allow for insights into how respondents experience receiving the intervention and how they have used it (eg, "What themes or tools on Mindhelper have you used?" "What did you gain from reading about these themes?" and "How has it been receiving the Mindhelper text messages?"). The second interview held after T4 will contribute to the knowledge of how respondents use Mindhelper following the SMS text message campaign's end (eg, "Have you been on Mindhelper since you stopped receiving text messages about the website," and "Has participating in this study changed your use of websites, apps, or social media to seek knowledge or advice about mental health?"). Themes for the first and second interviews are shown in Table 2. The qualitative data analysis software NVivo (Lumivero) will be used to process all data, with interviews analyzed according to the research questions, systematic text condensation, and template analysis [44,51].

Table 2. Themes for the first and second interviews.

Theme	First interview	Second interview
Background: gender, age, region of residence, and primary occupation	✓	
Knowledge of Mindhelper: How did they become aware of Mindhelper?	✓	
Use of Mindhelper: Have they used Mindhelper before or during the SMS text message campaign?	✓	
How they have used Mindhelper: What topics and features have they used on Mindhelper?	✓	✓
Use of Mindhelper after SMS text message campaign ended: Future use of Mindhelper?		✓
Impact of Mindhelper: What has the impact been? Are there any areas for improvement on Mindhelper?	✓	✓
Handling mental health struggles: What challenges does the young person face? What is their behavior in response to mental health struggles?	✓	
Handling mental health struggles: Are there any changes since last time?		✓
Digital behavior: How is the internet used in relation to mental health topics? Where do they get their information?	✓	
Help seeking—online versus network: When do they use the internet, and when do they turn to friends and family or professionals?	✓	

Results

This study was fully funded in November 2022, and the data collection started in January 2025. As of August 2025, we have enrolled 2613 people. The data analysis will start after data collection concludes, by early 2026, and the results of the primary outcome are expected to be published in the fall of 2026.

Discussion

Anticipated Findings

This is the first large-scale RCT to evaluate the effects of a digital, multicomponent, self-guided mental health promotion service among young people. If effective, this highly scalable service may contribute to combating the trend of rising mental health issues among young people and address key challenges in primary care by delivering timely, coordinated, and effective services to young individuals, potentially at a low cost [52].

Strengths and Limitations

This study has several strengths, including the large sample size, which enhances statistical power, enabling the detection of even small effect sizes that, while modest at the individual level, could generate substantial impact at the population level if the service is widely scalable and accessible. In addition, this study includes a more diverse participant sample than previous research, encompassing a broader population beyond specific university settings or patients with specific clinical symptom profiles [53,54]. This diversity may more accurately reflect the potential user base for the intervention. This is the first study to assess the cost-effectiveness of a digital, self-guided mental health promotion service targeting young people.

This study also has limitations, including that Mindhelper is publicly accessible and will continue to be so during the trial, raising the risk of exposure misclassification, which could dilute any observed differences between intervention and control groups. This misclassification would likely bias results toward the null, underestimating the intervention's effect. However, in the feasibility study, very few control group participants accessed thewebsite [18]; therefore, we do not consider this to be a major risk.

Conclusions

Individuals most commonly access Mindhelper via diagnostic and research-related search queries through search engines (eg, Google), where users are organically drawn to the content. In contrast, the Mindhelper study actively directs content to the intervention group. Therefore, our study deviates from the natural use patterns and evaluates the combined effects of the SMS text message campaign and Mindhelper. We create a situation that brings participants to Mindhelper, but Mindhelper and the use of Mindhelper are not designed for the intervention. Furthermore, conducting the study in Mindhelper's natural use

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context would preclude the establishment of a control group, thereby making it impossible to evaluate its effects within the framework of an RCT.

A key challenge is expected to be adherence in the intervention group, meaning the extent to which participants in the intervention group engage with Mindhelper. Our feasibility study indicated (very) low engagement when participants were solely provided with a link to Mindhelper by the end of the T1 survey [18]. Therefore, the SMS text message campaign was developed, aiming to boost adherence; however, we do not know yet whether this was sufficient.

Low adherence could lead to misclassification of exposure within the intervention group, potentially introducing bias into results. If nonadherence is unrelated to mental health outcomes (nondifferential misclassification), this misclassification could reduce observed intervention effects. However, if nonadherence is related to mental health outcomes (differential misclassification), this could either inflate or attenuate the observed effect, depending on adherence patterns. We will conduct sensitivity analyses based on the as-treated principle (complier average causal effect) to assess potential effects under full adherence. Adherence data will be collected in binary format (yes or no) at T2 to T4 for the intervention group. For the control group, adherence will be assessed at T1 and T4. In the feasibility study, participants' self-reports on specific Mindhelper features used did not align with their actual web history [18]. Therefore, we have revised our approach, asking the intervention group to describe how they have used Mindhelper and Ro apps in open-text questions, which will be coded with natural language processing models. Furthermore, qualitative information will provide insights into participant engagement and reasons for nonuse, and aggregated data on participants' interaction with the SMS text message campaign will provide information on adherence.

It must be noted that the self-guided nature of Mindhelper and the diversity of topics covered mean that adherent participants in the intervention group may engage with different content and receive varying "doses" of the intervention, which aligns with the real-world application but makes the evaluation more complex.

Low retention rates are a major challenge in digital mental health trials [55]. In particular, for self-guided services, the average level of dropout from treatment for depression has been found to be 26%, while for guided services, it has been found to be 72% [56]. Retention proportion will be regularly reviewed to evaluate whether the assumption regarding retention in the sample size calculation is correct or whether the number of participants included should be revised to secure the statistical power of the primary analysis. Missing data will further be addressed through multiple imputations. If we retain a response proportion of 64% at T2 (primary end point), as was the case in the test phase of this study, this may not be as critical as in other studies of self-guided digital services. However, nonrandom dropout could still introduce bias into the findings, potentially skewing the results and overestimating or underestimating the true impact of Mindhelper, depending on the characteristics of those who drop out compared to those who remain in the study.

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The evaluation will be conducted independently, although the authors collaborated with the team that developed and maintained Mindhelper. Furthermore, the team of Mindhelper has developed the SMS text message campaign and the landing page and has been vital for the practical setup of the evaluation. This collaboration did not influence the study's design or the planned data analysis.

Authors' Contributions

SHH, APF, LCT, and AOK conceptualized the study and its design. SHH is primarily responsible for the management of the study, coordination of recruitment, and conduction of the randomized controlled trial, with support and supervision from LCT and APF. AOK is primarily responsible for the qualitative contributions, and IPM is primarily responsible for the cost-effectiveness analysis. SHH drafted the initial manuscript, and all authors critically reviewed and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Themes and timing of the SMS campaign.
[DOCX File , 16 KB - resprot_v14i1e73736_app1.docx]

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Abbreviations

BAS-2: Body Appreciation Scale-2
ICER: incremental cost-effectiveness ratio
PHQ-4: Patient Health Questionnaire-4
RCT: randomized controlled trial
SWEMWBS: Short Warwick-Edinburgh Mental Well-Being Scale
T1: baseline
T2: 2 weeks after randomization
T3: 6 weeks after randomization
T4: 12 weeks after randomization
WHO-5: World Health Organization–Five Well-Being Index

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Protocol

Feasibility of the aktivplan Digital Health Intervention for Regular Physical Activity Following Phase II Rehabilitation: Protocol for a Mixed Method Randomized Controlled Pilot Study (ACTIVE-CaRe Pilot)

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Abstract

Background: Patients with cardiovascular disease (CVD) often encounter challenges in establishing and maintaining heart-healthy physical activity habits, even after successfully completing a cardiac rehabilitation program. Digital health technologies hold promise to support long-term habit formation in the secondary prevention of CVD. The aktivplan digital health intervention has been developed to support patients with CVD in establishing long-term heart-healthy physical activity habits.

Objective: The primary study aim is to pilot and assess the feasibility of a future randomized controlled trial design to investigate the effectiveness of the aktivplan intervention and to assess the usability, user experience, and acceptance of the aktivplan app. The secondary objective is to collect clinical and safety outcomes.

Methods: This multicenter, mixed method, randomized controlled pilot study aims to recruit 40 patients with an established diagnosis of CVD or with increased risk of CVD (physically inactive along with 1 further CVD risk factor) who are undergoing phase II rehabilitation at 2 rehabilitation centers in Austria. Participants will be allocated to the intervention or standard care control group by stratified randomization and will be monitored for 10 weeks after discharge from phase II rehabilitation. Participants, health care professionals, and outcome assessors are not masked (blinded) to group allocation. Data collection will include recruitment and drop-out rate; data completeness; adherence to the intervention; usability, user experience, and user acceptance questionnaires; technical reliability of the intervention; clinical assessments (exercise capacity, physical activity behavior, and CVD risk factors); adverse events; self-reported outcome measures (health-related quality of life, exercise self-efficacy, depression and anxiety, and kinesiophobia); patient interviews, and focus groups with health care professionals. Quantitative data will be analyzed descriptively, and 95% CIs will be calculated for recruitment and drop-out rates and for data completeness. No confirmatory inferential statistical analysis or hypothesis testing will be conducted. Qualitative data will be analyzed thematically by framework analysis.

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Results: A total of 34 participants were recruited between October 2023 and May 2024. Data collection was completed in August 2024. Currently, the data are being analyzed and prepared for publication. The first publication of feasibility results is expected by summer 2025.

Conclusions: This pilot study is expected to generate valuable and comprehensive insights to inform the study design of a future definitive effectiveness trial of the aktivplan intervention, guide the need for further iteration of the aktivplan app before entering a definitive trial, and inform future implementation strategies for the intervention.

Trial Registration: ClinicalTrials.gov NCT06025526; https://clinicaltrials.gov/study/NCT06025526

International Registered Report Identifier (IRRID): DERR1-10.2196/73704

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KEYWORDS

app; behavior change; cardiac rehabilitation; cardiovascular disease; digital technology; eHealth; exercise; habit formation; mHealth; mobile health; secondary prevention

Introduction

Background

Cardiovascular disease (CVD) remains the most common cause of death worldwide, with 18.6 million deaths attributed to CVD in 2019 [1]. In Austria, CVD was the most common cause of death in 2022 (34.3% of all deaths) and the most frequent discharge diagnosis for all acute hospital admissions (11.6%) [2]. Cardiac rehabilitation constitutes an important care pathway for the secondary prevention of CVD [3,4]. Cardiac rehabilitation programs aim to support patients in implementing a lifelong heart-healthy lifestyle, including regular physical activity, for example, through joining cardiac exercise groups or through self-directed training at home [3]. As a general recommendation, patients should carry out aerobic physical activity at a moderate or moderate-to-high intensity at least 3 times per week, and ideally 6 to 7 times per week. Aerobic physical activity should amount to at least 150 minutes per week at moderate intensity, or 75 minutes per week at vigorous intensity, or an equivalent combination thereof. In addition, patients should perform muscle-strengthening exercises for the large muscle groups twice per week with 8 to 15 repetitions per set. The overall training volume should amount to an energy expenditure of 1000 to 2000 kcal per week [5-7].

High-level scientific evidence demonstrates the effects of cardiac rehabilitation programs on reducing long-term morbidity and mortality. Cardiac rehabilitation has therefore received the highest class of recommendation in clinical guidelines for patients with chronic heart failure, chronic cardiovascular risk, after myocardial infarction with ST-elevation, after myocardial revascularization, and for CVD prevention in clinical practice [6]. The cardiac rehabilitation pathway is organized according to phases, whereby phase I describes the period of acute hospital admission. Phase II describes a structured and supervised program, delivered in an inpatient or outpatient setting and lasting several weeks. It aims to provide patients with the knowledge and awareness of the health-promoting effects of regular physical activity and other heart-healthy lifestyle choices, and to impart the skills to effectively plan and implement these CVD preventive behaviors [5,6].

However, it is a well-documented problem that many patients with CVD struggle to establish regular physical activity habits. In the EUROASPIRE V survey of 8261 patients with coronary artery disease in 27 European countries, only 34% of respondents reported performing regular physical activity (ie, ≥30 minutes on average 5 times a week) [8].

The same is true for people with an increased risk of CVD who have not yet developed the disease (ie, primary prevention of CVD) [9]. According to the Austrian Health Interview Survey, only 48.1% of men and 45.1% of women aged between 18 and 64 years meet the World Health Organization (WHO) recommendation to carry out at least 150 minutes per week of endurance-type physical activity at moderate intensity [10].

Moreover, successful completion of a phase II cardiac rehabilitation program does not necessarily lead to establishing long-term heart-healthy physical activity habits. The systematic review by ter Hoeve et al [11] included 26 randomized controlled trials and reported limited and conflicting evidence that cardiac rehabilitation programs improved long-term (≥6 months) maintenance of physical activity recommendations compared to groups who did not attend cardiac rehabilitation. These findings are corroborated in the systematic review by Dibben et al [12] who included 40 randomized controlled trials and found that ≤12 and >12 months after a cardiac rehabilitation program, only 26% of physical activity outcome comparisons showed statistically significant differences in favor of the cardiac rehabilitation groups.

This urgent and challenging problem has also been highlighted in statements and position papers from medical and scientific societies. For instance, the European Research Area Network for Cardiovascular Diseases has defined this problem as a priority topic for scientific research in 2019 [13]:

> *Maintaining a healthy lifestyle appears to be difficult for an increasing majority of the population, despite the general acknowledgment of the benefit of keeping risk factors for cardiovascular disease as low as possible. This not only applies to young people—for whom cardiovascular disease will often not develop for some time—but also to patients who, after a period of intensive rehabilitation, have difficulties maintaining the healthy lifestyle by themselves. So far, research has not delivered any effective strategy to improve healthy lifestyle maintenance. Research*

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in this area will have to explore whether optimal use of new technologies like intelligent wearables will offer personalized, innovative, and effective solutions to this problem.

The current European Society of Cardiology guideline on CVD prevention mirrors this statement, describing a specific evidence gap concerning physical activity "Implementation of strategies to achieve long-term adherence to PA [physical activity]" and a further evidence gap that suggests a possible solution through digital technologies: "Evaluation of the effects of eHealth tools in promoting PA [physical activity]" [14].

Digital technologies offer potential innovative solutions for long-term and sustainable habit formation for independent, regular, heart-healthy exercise. The systematic review of Wongvibulsin et al [15] included 31 studies to analyze the potential of digital health technologies in cardiac rehabilitation. The most used technologies were smartphones or mobile devices (20/31, 65%), websites or web-based portals (18/31, 58%), and email or SMS text message communications (11/31, 35%). The authors concluded that digital technologies have the potential to enhance care and broaden access to cardiac rehabilitation through tailored interactive interventions. Furthermore, the reviews by Meinhart et al [16] and Luijk et al [17] indicate that supporting physical activity through digital technologies following a cardiac rehabilitation program can achieve higher physical activity and physical performance outcomes compared to standard care (without digital technology support following a cardiac rehabilitation program).

Digital health interventions typically comprise of 2 interrelated components: the digital technology and the behavioral strategies implemented through and alongside the technology. These behavioral strategies are often based on established behavior change techniques (BCTs), such as goal setting, self-monitoring, feedback on performance, and education. However, disentangling the respective contributions of the digital technology and the underlying BCTs remains challenging. For example, in the review by Meinhart et al [16], 5 distinct BCTs were incorporated in almost all study interventions, making it difficult to distinguish their relative importance: goal setting (13/13, 100%), self-monitoring (13/13, 100%), feedback on exercise (13/13, 100%), physician or expert involvement (12/13, 92%), and tailored exercise prescription (11/13, 85%). The systematic review by Aguiar et al [18] described the most frequently implemented BCTs in 24 studies of mobile health interventions for patient adherence: feedback and monitoring (20/24, 83%), goals and planning (14/24, 58%), associations (14/24, 58%), shaping knowledge (12/24, 50%), and personalization (7/24, 29%). While there was mixed evidence of effectiveness, the BCTs that were most represented in positive studies were feedback and monitoring, goals and planning, associations, and personalization. Overall, this body of evidence illustrates the potential of digital interventions for improving patient outcomes, but it also highlights the heterogeneity and complexity of digital interventions, necessitating detailed and transparent descriptions of both their technological components and behavioral strategies [19].

This Study

This study aims to investigate the feasibility of a future randomized clinical trial on a novel digital health intervention, aktivplan [20]. aktivplan has been developed specifically to support patients in establishing regular heart-healthy physical activity habits following completion of a phase II rehabilitation program in the Austrian health care context. In addition to feasibility, this study will also evaluate the usability and acceptability of the aktivplan app.

Methods

Aim

The primary aim of this study is to pilot and assess the feasibility of a future randomized controlled trial design that will investigate the effectiveness of the aktivplan digital health intervention. In addition, the study will evaluate the usability, user experience, and acceptance of the aktivplan app, providing information on potential improvements.

The secondary aim of this study is to collect clinical outcomes to inform the sample size calculation for a future definitive effectiveness trial and to demonstrate the patient safety of the intervention.

Study Design

This is a multicenter, mixed method, randomized controlled pilot study. Forty patients undergoing phase II rehabilitation will be recruited from 2 study sites (20 patients per site). Study participants will be individually randomized to the intervention group (aktivplan digital health intervention) or control (standard care, ie, not including any routinely provided digital technologies) and will be followed up for 10 weeks after discharge from phase II rehabilitation.

The reporting of this study protocol adheres to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement [21], the CONSORT (Consolidated Standards of Reporting Trials) statement extension to randomized pilot and feasibility trials [22], and the TIDieR (Template for Intervention Description and Replication) checklist [23]. The SPIRIT, CONSORT, and TIDieR checklists are provided as Multimedia Appendices 1-3.

Ethical Considerations

This study protocol was reviewed and received favorable ethical opinion from the research ethics committees of the Austrian federal states of Salzburg (1065/2023) and Vorarlberg (EK-2-14/2023). Participation in this study is voluntary and all participants give written informed consent to take part in the study. Participants retain the right to withdraw from the study at any time and without giving a reason. In accordance with applicable medical device and product regulations in Austria, the study was registered with the Austrian Federal Office for Safety in Health Care (102214904). For general transparency and disclosure, the study was prospectively registered on ClinicalTrials.gov (NCT06025526). No person-identifying data or images will be published in the dissemination of this research.

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Regulatory Considerations

This study protocol is in accord with national and international ethical and regulatory standards, including the Declaration of Helsinki and the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use Guideline for Good Clinical Practice [24], the European Union Medical Device Regulation [25], and the European Union General Data Protection Regulation [26].

Indemnity Insurance and Monitoring Visits

Study participants, site principal investigators, and other clinical personnel at the study sites are covered by indemnity through a study insurance. Data monitoring is performed by the study steering committee in periodic meetings and by independent monitoring visits at the study sites.

Setting

The study is set in 2 rehabilitation centers in Austria, 1 outpatient rehabilitation center in the city of Salzburg (study site 1), and 1 inpatient rehabilitation clinic in the rural Montafon valley (study site 2). The outpatient rehabilitation center offers phase II rehabilitation of 4- to 6-week duration for adults with cardiac, pulmonary (including post–COVID-19 condition), metabolic, oncological, and orthopedic conditions. The inpatient rehabilitation center provides phase II rehabilitation stays of 3- to 4-week duration for adults with cardiac, neurological, orthopedic, and psychiatric conditions.

Participants

All patients admitted to phase II rehabilitation at study site 1 and all patients admitted to phase II cardiac rehabilitation at study site 2 will be screened against predefined eligibility criteria. The inclusion and exclusion criteria are presented in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Adult patients who are enrolled either in a phase II cardiac rehabilitation program or who are enrolled in phase II rehabilitation due to a noncardiac indication but who present with increased cardiovascular risk (ie, physical inactivity plus at least 1 of the following cardiovascular disease risk factors: smoking, hyperlipidemia, arterial hypertension, diabetes, or obesity).
- Possess and use a smartphone compatible with the aktivplan digital health intervention (Android [version 4.4; Google LLC] or Apple iOS [version 11.0; Apple Inc] or above and internet access).

Exclusion criteria

- Existent use of a digital intervention to support regular heart-healthy physical activity by the patient already established in standard care at the time of recruitment.
- Medical contraindications to: symptom-limited incremental cycle ergometry, regular heart-healthy physical activity, exercise and sports, or the use of a smartphone.
- Insufficient cardiovascular exercise capacity (eg, due to severe impairment of the musculoskeletal system).
- Participation of the patient in another clinical trial within the last 6 months.
- Lack of mental capacity to consent to study participation (addiction or other illnesses that do not allow the person to assess the nature, scope, and possible consequences of participation in the study).
- Pregnancy in the third trimester, or pregnancy in the first and second trimester with a medical contraindication to physical activity, exercise, and sports.
- Breastfeeding women with a medical contraindication to physical activity, exercise, and sports.
- Indications that the patient is unlikely to comply with the protocol (eg, unable to commit to attending follow-up appointments).

Sample Size

The sample size of 40 patients (20 patients per site) reflects the typical sample size for a clinical pilot study [27] and allows the detection of problems (eg, participant withdrawals) with a prevalence of 7.5% with 95% confidence [28]. This sample size is not powered for statistical hypothesis testing of intervention effectiveness because this is not the purpose of this study.

Recruitment

All patients admitted to phase II rehabilitation at study site 1 and all patients admitted to phase II cardiac rehabilitation at study site 2 will be screened against the inclusion and exclusion criteria by the site principal investigators. The eligibility of each individual patient will be documented in a screening log, including the reasons for exclusion.

All patients who meet the eligibility criteria will be invited to take part in the study by the site principal investigators. The site principal investigators explain the study, provide the study information sheet, and answer any questions about the study. Patients will be given at least 48 hours to consider participation in the study. Patients who express interest in participating in the study will be asked to provide written informed consent, which is required before study initiation.

Randomization

Participants will be individually randomized to the intervention or control group. Randomization will be stratified by study site, participant sex, and participant exercise capacity (peak power

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<1.3 Watts/kg, 1.3-1.8 Watts/kg, and >1.8 Watts/kg in incremental cycle ergometry). The randomization schedule will be prepared in advance by the study statistician who is not involved in participant recruitment. The *blockrand* package of the statistical program R (R Foundation for Statistical Computing) will be used [29]. The package enables the randomized allocation of participants for clinical and experimental studies in which participants are recruited individually and sequentially. The randomization schedule will be stored securely at the study sponsor's office (Ludwig Boltzmann Institute for Digital Health and Prevention), which is at a different location to the study sites. Random allocation is concealed, as personnel at the study sites have no access to the randomization schedule. After a new study participant has been recruited, the site principal investigator informs the study sponsor of the patient's sex and exercise capacity, and the randomization result is then returned to the site principal investigator.

Description of the Intervention

The aktivplan digital health intervention was developed at the Ludwig Boltzmann Institute for Digital Health and Prevention, Austria, in a human-centered process with both co-design and iterative participatory design elements, involving health care professionals and patients with cardiac problems between 2020 and 2022 [30]. The core feature of the aktivplan app is a digital calendar for planning regular heart-healthy physical activity. Health care professionals access this calendar via a website or web app (view for health care professionals), and patients access the calendar via an app on their smartphone, tablet, or—if required—via a website on a smartphone, tablet, or computer (view for patients). Before discharge from the phase II rehabilitation program, the aktivplan app is introduced to the patient in a 1:1 consultation with a health care professional experienced in exercise prescription (eg, physiotherapist, sports scientist, and exercise physiologist). This consultation is conducted according to the principles of shared decision-making [31]. A personalized heart-healthy physical activity plan is agreed upon, which the patient should carry out independently following discharge from the phase II rehabilitation program. The health care professional enters this training plan into the aktivplan calendar. Using the aktivplan app, the patient can view their planned physical activity sessions, mark sessions as completed, or enter additional unplanned physical activities (eg, spontaneous activities that are self-initiated by the patient). The health care professional can view the calendars and assess adherence with personal physical activity plans for all patients under their care.

In addition to this core functionality, the aktivplan digital health intervention includes further distinct features, such as automated messages to the patient with motivational content or reminders of planned physical activity sessions, personalized goal setting, and the option for the health care professional to give the patient feedback and contact them via an in-app message. Further details on the aktivplan digital health intervention are given in the TIDieR checklist in Multimedia Appendix 3. Details of the logic model and psychological and behavior change theory underpinning the aktivplan digital health intervention have been published previously [19].

Description of the Comparator

The control group will receive usual care according to Austrian national standards, which does not include any digital interventions or digital technology provision during or following phase II rehabilitation. No placebo or comparative treatment will be offered. In addition to standard care, patients in both study groups may take individual action to support their adherence to physical activity recommendations (eg, join an exercise class or gym, hire a personal trainer, and download a freely available physical activity app), and any such activities will be documented by self-report.

After completing their participation in the study, participants who are randomized to the control group will be offered the aktivplan physical activity planning session and use of the aktivplan app for a period of 2 weeks. This offer will be made following completion of study participation, and no study data collection will be conducted during this period. This offer is made for ethical reasons and to counteract possible premature withdrawal from the control group.

Procedure

The CONSORT flow diagram is presented in Figure 1. The SPIRIT checklist is presented in Figure 2. Study procedures are presented in Textbox 2.

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Figure 1. CONSORT flow diagram.

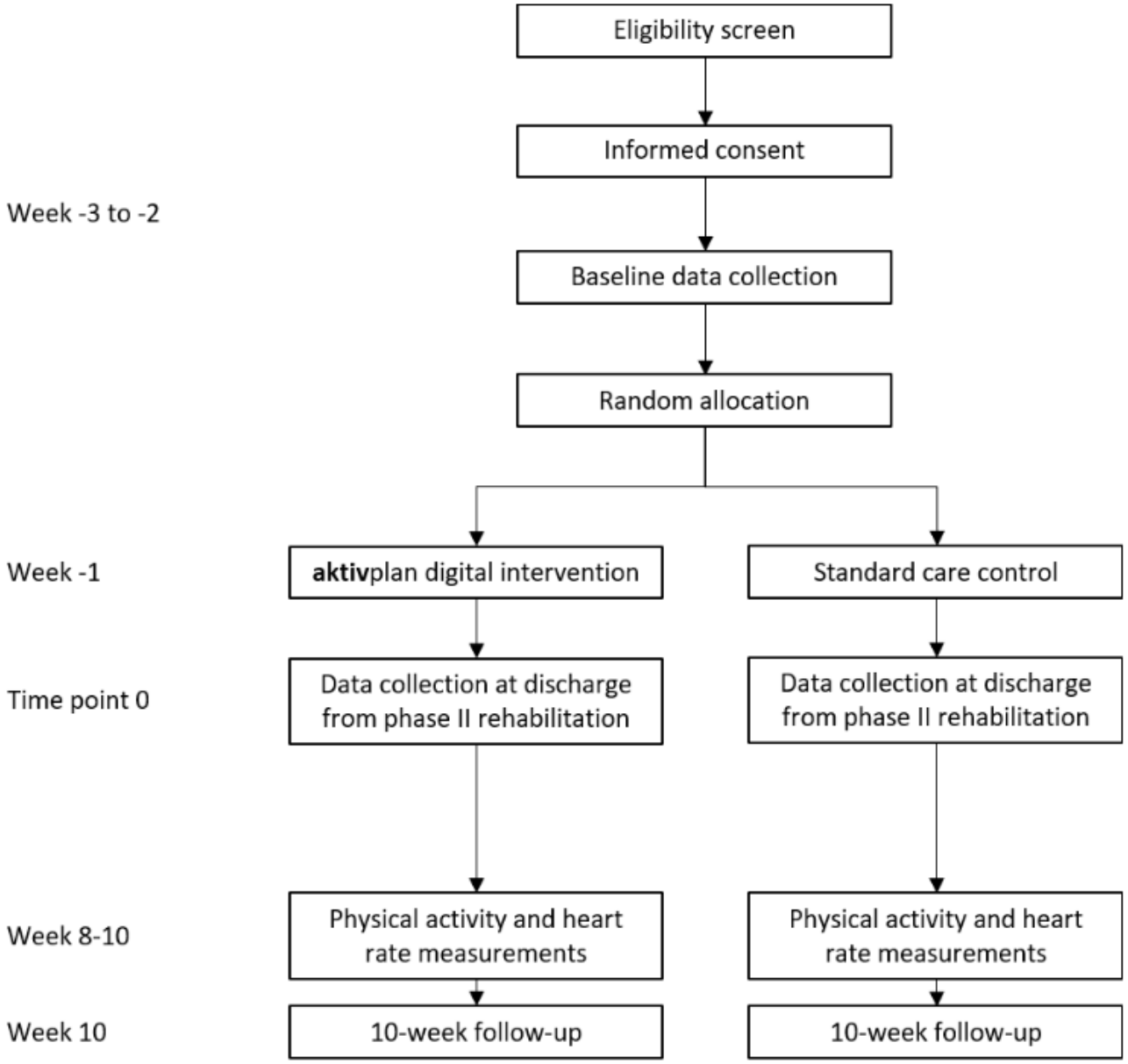

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Figure 2. Schedule of enrollment, interventions, and assessments according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement. *collected from routine clinical data, **for participants in the intervention group only. ATI: Affinity for Technology Interaction; BFI-10: Big Five Inventory; ESES: Exercise Self-Efficacy Scale; HbA1c: glycated hemoglobin; IPAQ: International Physical Activity Questionnaire; MARS-G: Mobile App Rating Scale; MAUQ: mHealth App Usability Questionnaire; PHQ-4: Patient Health Questionnaire 4; RAPA: Rapid Assessment of Physical Activity; UTAUT-2: Unified Theory of Acceptance and Use of Technology 2.

	Study period												
	Enrolment		Discharge from phase II rehabilitation	Follow-up period									Close-out
Time point	*Week -3 to -2*	*Week -1*	*Time point 0*	*Week 1*	*Week 2*	*Week 3*	*Week 4*	*Week 5*	*Week 6*	*Week 7*	*Week 8*	*Week 9*	*Week 10*
Enrollment:													
Eligibility screen	X												
Informed consent	X												
Baseline data collection	X												
Random allocation	X												
Intervention:													
aktivplan physical activity planning session		X											
aktivplan use for self-directed physical activity				←	—	—	—	—	—	—	—	—	→
Assessments:													
Demographic data	X												
Medical history	X												X
Medication	X		X										X
Height	X												
Weight	X		X										X
Vital parameters	X		X										X
Incremental cycle ergometry	X*		X*										X
Blood cholesterol and HbA1c	X*		X*										X
Physical activity and heart rate											←	—	→
Adverse event reporting													X
BFI-10, ATI	X												
RAPA	X												X
PHQ-4, EQ-5D-5L, kinesiophobia, ESES	X		X										X
IPAQ, wearable comfort rating													X
UTAUT-2, MAUQ, AttrakDiff mini, MARS													X**
Qualitative interview													X

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Textbox 2. Study procedures.

1. Screening for eligibility: all patients admitted to phase II rehabilitation programs at the study sites are screened against study eligibility criteria.
2. Recruitment: all eligible patients are invited to take part in the study. Consent is obtained from those who express interest to participate.
3. Baseline data collection (weeks −3 to −2): baseline data are collected. A detailed description of measures is provided subsequently and in Figure 2.
4. Randomization: patients are randomly allocated to the intervention or control group. Random allocation is concealed and stratified according to study site, patient sex, and patient exercise capacity.
5. aktivplan physical activity planning session (week −1): participants allocated to the intervention group receive the aktivplan physical activity planning session before discharge from the phase II rehabilitation program.
6. Data collection at discharge from phase II rehabilitation (time point 0): data are collected at discharge from phase II rehabilitation. A detailed description of measures is provided subsequently and in Figure 2.
7. Follow-up period: patients in both study groups are followed up for 10 weeks after discharge from phase II rehabilitation. Patients in the intervention group use the aktivplan digital health intervention.
8. Physical activity and heart rate measurements (week 8-10): patients in both study groups receive wearable sensor devices (accelerometer and heart rate sensor) for continuous measurement during waking hours for 3 weeks (weeks 8-10 of the follow-up period). A detailed description of measurements is provided subsequently.
9. 10-week follow-up (week 10): Data are collected in the concluding study visit. A detailed description of measures is provided subsequently and in Figure 2.
10. aktivplan digital intervention for patients in the control group: Following completion of the study, patients in the control group are offered to receive the aktivplan physical activity planning session and use the aktivplan app for 2 weeks. No study data collection will be conducted during this period.

Data Collection From Participants

Data From Routinely Conducted Assessments and Clinical Records

Demographic data and height will be recorded at week –3 to –2. Blood tests (cholesterol and glycated hemoglobin), medication, body mass, vital parameters, and incremental cycle ergometry will be recorded 3 times (at week –3 to –2, time point 0, and week 10). Adverse event reporting will take place at week 10.

Self-Reported Questionnaires

At week –3 to –2, time point 0, and week 10, study participants in the intervention and control groups will complete questionnaires on kinesiophobia (selected items from the Tampa Scale of Kinesiophobia [32]), exercise self-efficacy (Exercise Self-Efficacy Scale [33]), depression and anxiety (Patient Health Questionnaire-4 [34]), and health-related quality of life (EQ-5D-5L [35]). At week −3 to −2, they will complete a personality questionnaire (Big Five Inventory [36]) and the Affinity for Technology Interaction questionnaire [37]. At week −3 to −2 and at week 10, they will complete the Rapid Assessment of Physical Activity questionnaire [38]. At week 10, they will complete the International Physical Activity Questionnaire [39] and a questionnaire rating the comfort of the wearable sensor devices (Comfort Rating Scale [40]).

At week 10, study participants in the intervention group will complete questionnaires on the usability and user experience of the aktivplan app, including the mHealth App Usability Questionnaire [41], the Unified Theory of Acceptance and Use of Technology 2 questionnaire [42], the Mobile App Rating Scale [43], and the AttrakDiff mini questionnaire [44]. For some of these questionnaires, only selected relevant sections are used.

aktivplan Use Tracking

During the 10-week intervention period, use of the aktivplan app will be automatically tracked, including participants' log-in and duration, planned physical activity sessions that have been marked as completed by participants, and additional physical activity sessions that participants enter into the app. Adherence will be quantified as a percentage of planned physical activity sessions that have been marked as completed by participants. Engagement with the app will be quantified by the time spent interacting with the app. Notably, longer duration of interaction with the app does not necessarily equate to meaningful engagement in the sense of adherence to the personal physical activity plan.

Physical Activity and Heart Rate Measurements

Participants' physical activity and heart rate will be measured during the last 3 weeks of the study (weeks 8-10) in both study groups, using 2 wearable sensor devices (wearables). Study participants will be instructed to wear the devices daily for 3 weeks during waking hours, and to return the wearables at the final study visit (10-week follow-up). Physical activity will be measured with the ActiGraph GT9X Link accelerometer (ActiGraph LLC), worn on the nondominant wrist. Heart rate will be measured with the Polar Verity Sense device (Polar Electro Oy), worn on the nondominant upper arm or forearm. Study participants will receive both devices by post, together with written instructions and a link to an online instructional video on how to operate the wearables. Telephone support will be provided by the study team if needed.

Qualitative Interview

At week 10, audio-recorded semistructured interviews will be conducted in both study groups to inquire about participants' experiences of participating in the study and any self-initiated

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support for physical activity during the study period. Participants in the intervention groups will also be asked about their experiences of using the aktivplan app. The interview schedule is provided in Multimedia Appendix 4.

Study participants who discontinue or deviate from the intervention protocol will be encouraged to complete all outcome assessments regardless.

Data Collection From Health Care Professionals

Overview

To assess usability, user experience, and acceptance of the aktivplan app from the perspective of health care professionals, data will be collected from those members of staff at the study sites who implement the aktivplan digital health intervention with patients. These members of staff are physiotherapists or sports scientists who have provided written informed consent to have their data collected and who have received a full day of training on the aktivplan digital health intervention before the start of the study.

Self-Reported Questionnaires

At the beginning of the study, the health care professionals will complete the Affinity for Technology Interaction and Big Five Inventory questionnaires and rate their self-efficacy for implementing the aktivplan intervention. During the running of the study, the health care professionals will keep concurrent reflective notes on the use of the intervention, document any technical difficulties, and log their time requirements for implementing the intervention. After each aktivplan physical activity planning session, the 9-item Shared Decision Making Questionnaire [45] and items from the Nasa-Task Load Index [46] will be completed. At the end of the study, the health care professionals will again rate their self-efficacy for implementing the aktivplan intervention, and complete the mHealth App Usability Questionnaire, Mobile App Rating Scale, Unified Theory of Acceptance and Use of Technology 2, AttrakDiff mini, and the Normalization Measure Development [47] questionnaires.

Qualitative Focus Group

At the end of the study, a focus group discussion will elicit the health care professionals' views on implementing the aktivplan intervention in routine clinical practice at the study sites, facilitating and hindering factors for the implementation of aktivplan, any problems experienced with the app, suggestions for improvement and new desired features of the app, and any problems and other observations regarding the conduct of the study that would need to be considered in the design of a larger definitive trial. The focus group will be audio and videorecorded and moderated by 2 researchers. The topic guide is given in Multimedia Appendix 5.

Outcomes

The primary outcomes address the primary study aim, that is, to pilot and assess the feasibility of a future randomized controlled trial design to investigate the effectiveness of the aktivplan digital health intervention; and to assess the usability, user experience, and acceptance of the aktivplan app. The primary outcomes are presented in Textbox 3.

The secondary outcomes address the secondary study aim, that is, the collection of clinical outcomes to inform the sample size calculation for a future definitive effectiveness trial and to provide evidence toward demonstrating patient safety of the intervention. The secondary outcomes are presented in Textbox 4.

Textbox 3. Primary outcomes.

- Recruitment rate (number of recruits per week, percentage of screened patients who were recruited, and percentage of eligible patients who were recruited)
- Drop-out rate (number of drop-outs at the 10-week follow-up and percentage of recruited patients who dropped out)
- Data completeness (percentage of missing data fields in study database)
- Adherence to the aktivplan digital health intervention (automated use logging of the aktivplan app and video recording of the aktivplan physical activity planning session)
- Usability of the aktivplan app (mHealth App Usability Questionnaire)
- User experience of the aktivplan app (AttrakDiff mini questionnaire)
- User acceptance of the aktivplan app (Mobile App Rating Scale and Unified Theory of Acceptance and Use of Technology 2)
- Technical reliability of the aktivplan app (number and types of technical problems and qualitative data)
- Use of alternative and additional strategies for supporting physical activity (number and types of additional strategies and qualitative data)
- Experiences and perspectives of rehabilitation professionals regarding the intervention and study procedures (qualitative data from focus groups)

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Textbox 4. Secondary outcomes.

- Exercise capacity (highest mechanical power output achieved during incremental cycle ergometry, peak power)
- Physical activity behavior (accelerometry and daily minutes of moderate to vigorous physical activity)
- Body mass
- Arterial blood pressure
- Blood cholesterol levels
- Glycated hemoglobin levels
- Smoking (number and type of smoking products per week)
- Health-related quality of life (EQ-5D-5L questionnaire)
- Exercise self-efficacy (Exercise Self-Efficacy Scale)
- Depression and anxiety (Patient Health Questionnaire-4)
- Kinesiophobia (selected items from the Tampa Scale of Kinesiophobia)
- Patient safety (adverse events reporting according to regulatory standards: number, type, and severity of adverse events)

Data Management

At the study sites, data will be recorded on paper-based case report forms (CRFs). Following completion of data collection, the CRFs and electronic data collection devices (wearables, dictaphones, and video cameras) will be collated and securely stored at the study sponsor site. Data from CRFs will be entered onto a Microsoft Excel file. Quality of data entry will be assessed by independently cross-checking the accuracy of 10% of data cells. After completion of the analysis, study data will be securely archived by the sponsor for 10 years.

Analyses

The statistical data analysis will be carried out using statistical analysis software. The analytic code will be documented and stored to ensure that the statistical analyses can be reproduced at a later date. For descriptive data analysis, the appropriate summary measures will be calculated according to data type, including measures of central tendency and spread for continuous data (arithmetic mean, SD, median, IQR, minimum, maximum, and range) and frequency, proportions, or percentages for categorical data. 95% CIs will be calculated for recruitment and drop-out rates, for adherence data, and for data completeness. Because this is a pilot study, no confirmatory inferential statistical analysis or hypothesis testing will be conducted.

An exploratory group comparison (descriptive analysis and 95% CIs) will be described for the secondary (clinical) outcome measures for both intention-to-treat and per-protocol approaches. In intention-to-treat analysis, the pattern of missing data will be assessed, but due to the small sample size no imputation of missing data will be conducted. However, we will conduct sensitivity analyses based on the minima and maxima from complete cases for each missing variable, to evaluate the potential impact of missing data in the sense of a best and worst case scenario.

The qualitative data analysis will be conducted according to the framework analysis method [48] and using qualitative data analysis software. Recordings of the patient interviews and the focus groups with health care professionals will be transcribed verbatim by a professional transcription agency. The transcripts will be checked for accuracy against the original recordings. In the reporting of qualitative findings, care will be taken to preserve the anonymity of patients and health care professionals. Relevant themes and categories from qualitative analysis will be triangulated with corresponding quantitative data to describe a comprehensive picture. Questionnaire scores for usability and acceptability of the aktivplan app will be interpreted in relation to the possible score range for each questionnaire.

Results

Recruitment commenced on October 2, 2023. The study was completed with 34 participants recruited by May 2024, and all data were collected by August 2024. Currently, the data of the study are being analyzed and prepared for publication. The first publication of results is expected for summer 2025.

Discussion

Principal Findings

This feasibility study is expected to yield valuable insights to inform the design and methodology of a future definitive clinical trial evaluating the effectiveness of the aktivplan digital health intervention for regular physical activity following phase II rehabilitation. The initial implementation has already generated learnings to inform the study design. After 24 weeks, 34 (85%) participants were recruited, compared to the originally planned 40 participants, indicating that recruitment requires more time than initially anticipated. This observation supports the need for a broader, multicenter recruitment strategy in future clinical trials to ensure adequate sample size and generalizability. In addition, data on the usability, user experience, and acceptance of the aktivplan app will guide the need for further iteration before entering a definitive trial. Findings regarding the implementation in practice will inform future implementation strategies, including training for health care professionals, background technical support for health care professionals and

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patients, reimbursement strategies, and considerations to minimize barriers to implementation.

Dissemination Plan

The results of this study will be published in peer-reviewed scientific journals. Due to the large volume of data generated, 3 manuscripts will report on 3 distinct aspects of the study: feasibility of the study design; usability, user experience, and acceptance of the aktivplan app; and preliminary clinical outcomes. In addition, the results will be presented at scientific conferences relevant to cardiac rehabilitation and digital technologies. A plain language summary for the cardiac community will be available on the sponsor's website. Authorship will follow the International Committee of Medical Journal Editors authorship criteria. Professional medical writers will not be employed. It is not planned to make the participant-level dataset publicly available.

Comparison to Prior Work

As mentioned before, the Austrian Health Interview Survey shows that only 48.1% of men and 45.1% of women aged between 18 and 64 years meet the WHO recommendation of endurance-type physical activity at moderate intensity and only 26% of men and 21.1% of women meet the WHO recommendations for both endurance-type physical activity and muscle-strengthening exercises [10]. Even after completing a cardiac rehabilitation program, 75.3% of patients in Austria fail to sustain sufficient physical activity in the long run [49]. Furthermore, as mentioned in the review of Meinhart et al [16], digital technology offers possibilities to successfully support physical activity following a cardiac rehabilitation program. Nevertheless, a recent survey by Lunz et al [50] revealed a relatively high motivation for using digital technology, but still low actual use (52%) of digital technology by health care professionals in the secondary prevention of CVD in Austria. Digital technology is mainly used for monitoring heart rate, with no established evidence-based digital health interventions for supporting physical activity habit formation [50]. Internationally, the systematic review of Luijk et al [17] describes moderate outcomes and heterogeneous quality of studies investigating the effectiveness of digital health interventions for maintaining physical activity in patients with CVD after phase II cardiac rehabilitation. However, the authors still recommend using digital health interventions in clinical practice until further evidence becomes available. Importantly, the transferability of digital health interventions between countries is often limited due to local sociocultural aspects (eg, language and representativeness of imagery) and particularities of clinical pathways and health care systems [51]. An example of the latter in Austria is the definition of 4 phases of cardiac rehabilitation, in contrast to the 3-phase model commonly used in other countries. The Austrian rehabilitation pathway offers the choice between inpatient or outpatient settings for phase II rehabilitation, and the duration and intensity of cardiac rehabilitation programs can differ to current models in other countries [3].

The aktivplan digital health intervention is therefore specifically developed for the Austrian rehabilitation pathway, and this feasibility study is deliberately conducted within the Austrian health care system to avoid variability introduced by cross-national differences in health care structures and cardiac rehabilitation programs.

Strengths and Limitations

A strength of this study is the nature of the aktivplan intervention, which answers directly to an identified clinical need in the Austrian cardiac rehabilitation pathway, and which was developed specifically to match the cultural and systemic context in Austria using co-design methodology and patient involvement. This means that the aktivplan intervention has high clinical relevance and good sociocultural fit in the Austrian context. At the same time, this presents a limitation to the aktivplan intervention in terms of transferability to other international settings. A potential implementation of aktivplan in other countries would require an assessment of the intervention against national regulatory standards and requirements [52] and local clinical and sociocultural contexts. A further limitation to this study is the lack of blinding. Blinding of patients and health care professionals who are delivering the intervention is not possible in this case. Blinding of outcome assessors would be possible in principle; however, after early discussions with site principal investigators it was decided to conduct unblinded assessments. It was suggested that, because of the small number of available study staff and close working relationships at the study sites, blinding of assessors was not feasible, and the success of assessor blinding was unlikely. Finally, it is acknowledged that there are no prespecified criteria to judge whether, or how, to proceed with a future definitive trial [22]. Because no comparable previous studies are available for Austria, and prespecified criteria are not imposed by the funding organization, the decision whether, or how, to proceed with a future definitive trial will be made in discussion with relevant stakeholders and based on the data from this feasibility study and comparable international studies.

Conclusions

There is a need for evidence-based interventions to support regular physical activity after discharge from phase II rehabilitation for patients with CVD or at risk of CVD. This pilot study is expected to generate valuable and comprehensive insights to inform the study design of a future definitive effectiveness trial of the aktivplan digital health intervention, guide the need for further iteration of the aktivplan app before entering a definitive trial, and inform future implementation strategies for the intervention.

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Data Availability

Data sharing is not applicable to this paper as no datasets were generated or analyzed during this study.

Authors' Contributions

STK conceived and designed the study with contributions from BR, EC, RC, VG, DK, BM, JN, FP, EP, DW, MS, JDS, and GT. Particularly, DW and JDS contributed technical considerations and procedures for the aktivplan digital health intervention. MS drafted standard operating procedures for clinical assessments. DK and DL contributed considerations and drafted standard operating procedures for home-based physical activity assessment. DL, FP, EP, DW, and JDS contributed considerations and procedures for usability and acceptability assessment. FP developed the focus group topic guide. DL and EP developed training materials for therapists and patients. EC prepared the randomization schedule and advised on sample size requirements and statistical analyses. STK is the sponsor representative for this study. DL drafted this manuscript with contributions from STK. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT checklist.
[PDF File (Adobe PDF File), 244 KB - resprot_v14i1e73704_app1.pdf]

Multimedia Appendix 2
CONSORT (Consolidated Standards of Reporting Trials) checklist.
[PDF File (Adobe PDF File), 749 KB - resprot_v14i1e73704_app2.pdf]

Multimedia Appendix 3
TIDieR (Template for Intervention Description and Replication) checklist.
[PDF File (Adobe PDF File), 734 KB - resprot_v14i1e73704_app3.pdf]

Multimedia Appendix 4
Qualitative interview schedule.
[PDF File (Adobe PDF File), 708 KB - resprot_v14i1e73704_app4.pdf]

Multimedia Appendix 5
Focus group topic guide.
[PDF File (Adobe PDF File), 986 KB - resprot_v14i1e73704_app5.pdf]

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Abbreviations

BCT: behavior change technique
CONSORT: Consolidated Standards of Reporting Trials
CRF: case report form
CVD: cardiovascular disease
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TIDieR: Template for Intervention Description and Replication
WHO: World Health Organization

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Protocol

Effectiveness and Safety of Lumbar Erector Spinae Plane Block Versus No Locoregional Block in Hip Surgery: Protocol for a Randomized Controlled Trial

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Abstract

Background: Ultrasound-guided regional anesthesia in hip surgery has been shown to reduce the need for opioids and conventional analgesics, facilitate ambulation and early recovery, improve respiratory dynamics, and decrease the incidence of venous thrombosis and pneumonia. Lumbar erector spinae plane block (L-ESPB) has been proposed as a novel ultrasound-guided locoregional technique to relieve pain in hip surgery; however, the supporting evidence remains scarce.

Objective: This study aims to provide evidence on the role of L-ESPB in perioperative pain management during hip surgery. We hypothesize that patients receiving L-ESPB compared to those without block will have lower opioid consumption and less pain after hip surgery. The primary outcome is the difference in pain intensity, measured using the visual analog scale, at 2 hours postoperatively between the L-ESPB group and the control group. We will compare postoperative analgesic needs and opioid consumption in both groups, assess the technical ease of performing L-ESPB, and record any side effects in both treatment arms. Finally, we will evaluate the level of patient satisfaction.

Methods: This is a pragmatic, single-center, parallel-group randomized controlled trial. After patients provide informed consent, they will be randomly assigned in a 1:1 ratio to receive either ultrasound-guided L-ESPB or conventional intravenous analgesia. A total of 180 patients (n=90, 50% in each group) will be enrolled. Data analysis will be performed using SPSS software.

Results: This clinical trial was approved by the European Medicines Agency on May 27, 2024, following approval by the local ethics committee earlier that month. Patient recruitment took place between June 2024 and May 2025. Statistical analysis is currently ongoing, and final results are expected to be submitted for publication in early 2026.

Conclusions: This clinical trial will enable us to assess the analgesic effectiveness of L-ESPB in hip surgery. We will also evaluate its safety and potential adverse effects compared with conventional analgesia and opioid consumption.

Trial Registration: ClinicalTrials.gov NCT06567522; https://www.clinicaltrials.gov/study/NCT06567522

International Registered Report Identifier (IRRID): DERR1-10.2196/75854

(JMIR Res Protoc 2025;14:e75854) doi:10.2196/75854

KEYWORDS

hip fracture; hip osteoarthritis; lumbar erector spinae plane block; pain; morphine

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Introduction

Background

Hip surgery accounts for a high percentage of both emergency and elective surgical procedures in hospitals. Regardless of surgery being prescribed to treat a fracture or coxarthrosis, patients are usually older adults with multiple associated comorbidities [1]. In this patient population, there is a tendency to undertreat pain for fear of the side effects and pharmacological interactions of conventional analgesic drugs [2].

Ultrasound-guided regional anesthesia in orthopedic and trauma surgery has been shown to reduce the need for opioids and conventional analgesics, facilitate ambulation and early recovery, improve respiratory dynamics, and decrease the incidence of venous thrombosis and pneumonia [3,4].

Numerous ultrasound-guided peripheral nerve blocks have been evaluated in hip surgery, although no single analgesic technique has yet been established as the gold standard. Examples include the femoral nerve block [5], fascia iliaca block [6], and the more recently introduced pericapsular nerve group (PENG) block [7]. Although these blocks are considered safe, they are performed close to nerves and important vessels, such as the femoral artery, and are therefore not without risk. Furthermore, they do not provide complete analgesia of the hip because they do not cover, for example, the obturator nerve [8], or, in the case of the PENG block, cutaneous branches [9].

The lumbar erector spinae plane block (L-ESPB) remains a relatively novel technique, particularly in hip surgery. Several publications have reported its utility in this context; however, all are limited to case series and lack standardized clinical trials. Tulgar and Senturk [10] and Tulgar et al [11] have described extensive and long-lasting pain relief after L-ESPB in hip arthroplasty. Conversely, Chan et al [12] found that L-ESPB did not reduce pain or opioid consumption in patients undergoing hip surgery.

Objectives

Given the lack of high-quality clinical trials evaluating L-ESPB in hip surgery, this study is warranted. Our aim is to provide evidence that may help define the role of this technique in perioperative pain management, focusing on patients more vulnerable to opioid-related adverse effects.

We hypothesize that patients receiving L-ESPB, compared to those who do not, will experience lower opioid consumption and reduced postoperative pain after hip surgery. If L-ESPB demonstrates these benefits, it could represent a valuable addition to multimodal analgesia strategies, particularly for older adults or patients who are frail and thus more vulnerable to opioid-related side effects. Furthermore, the technical simplicity and safety profile of L-ESPB make it an attractive option for widespread clinical use, including in resource-limited settings.

Methods

Trial Design

This is a pragmatic, single-center, parallel-group, low-intervention randomized controlled trial comparing the analgesic efficacy of L-ESPB versus no block in the postoperative period of hip surgery. This protocol follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines. This trial has been registered on ClinicalTrials.gov (NCT06567522).

Study Setting

The study is conducted in a hospital setting, and we are recruiting patients scheduled for hip surgery due to either osteoarthritis or fracture.

Eligibility Criteria

Inclusion Criteria

This study will include adult patients (aged >18 y) of both sexes scheduled for hip surgery, classified as American Society of Anesthesiologists (ASA) I to III according to the ASA (where ASA I indicates low anesthetic risk and ASA IV indicates high anesthetic risk). Eligible patents must provide written informed consent and be able to understand and use the visual analog scale (VAS) for pain assessment.

Exclusion Criteria

Patients will be excluded if they have contraindications to the technique or drugs used, if the block cannot be technically performed, if they have severe cognitive impairment or documented mental disabilities, or if they are already enrolled in another clinical trial.

Randomization

Patients who consented to participate were randomly assigned to two groups: (1) experimental (L-ESPB will be performed at the L3-L4 level using 30 mL of 0.25% levobupivacaine) and (2) control. Randomization was performed using a computer-generated 1:1 balanced sequence, with both the sequence and group assignments concealed. This method is currently recommended as the standard for clinical trials.

The use of the locoregional technique makes blinding impossible for both patients and anesthetists. However, outcome assessment will be blinded: nurses collecting data in the immediate postoperative period and during subsequent ward care will be unaware of group assignments. To minimize blinding bias, we will use rigorous and uniform protocols to measure outcomes regardless of group assignment. In addition, a statistical analysis will be conducted with masked group labels (group A and group B) so that the analyst will remain unaware of treatment allocation. Blinded outcome assessment and independent statistical analysis are intended to minimize observational bias.

Intervention

This is a clinical trial designed and conducted by researchers without industry involvement. It follows a pragmatic, single-center, parallel-group, low-intervention, nonblinded randomized controlled design, with blinded assessment of the

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objectives. All patients scheduled to undergo emergency or elective hip surgery who meet the inclusion criteria and none of the exclusion criteria will be included. The main variable will be pain control (assessed using the VAS). There will be 2 groups of patients (one receiving ultrasound-guided L-ESPB at the L3-L4 level with 30 mL of 0.25% levobupivacaine and a control group receiving conventional intravenous analgesia).

L-ESPB will be performed using a portable ultrasound machine with a linear or convex transducer and a 22G Pajunk needle (Pajunk GmbH Medizintechnologie; 50 mm or 80 mm, depending on block depth). The patient will be placed in the lateral decubitus position, with the side to be blocked facing up. We will locate the transverse processes at the L3-L4 level with a parasagittal approach. The 22G needle (50 mm or 80 mm, depending on the target depth) will then be inserted from cranial to caudal in plane with the ultrasound probe. We will advance through the erector spinae muscles, subsequently performing hydrodissection, followed by injection of 30 mL of 0.25% levobupivacaine after negative aspiration is confirmed.

For patients receiving the locoregional technique, zero hour is defined as the earliest time within the first 2 postoperative hours when a VAS score greater than 1 is reported (Figure 1).

An analgesic postoperative protocol will be applied. For those receiving the locoregional technique, 1000 mg of paracetamol will be administered every 8 hours, along with either 50 mg of dexketoprofen or 400 mg of ibuprofen every 8 hours. For patients allergic to nonsteroidal anti-inflammatory drugs or paracetamol, or when rescue medication is needed, 1000 mg of metamizol every 8 hours will be prescribed. Tramadol is also available as rescue medication. If the VAS score is equal to or greater than 4, we will concurrently prescribe 2 mg of morphine, followed by reassessment after 15 minutes. If the VAS score remains equal to or greater than 4 after delivering the bolus, the same morphine dose will be repeated, with subsequent reassessment every 15 minutes, up to a maximum of 12 mg of morphine in 24 hours (Figure 2). This analgesic protocol will also be applied to patients in the control group.

Figure 1. Study timeline. OR: operating room; PACU: postanesthesia care unit.

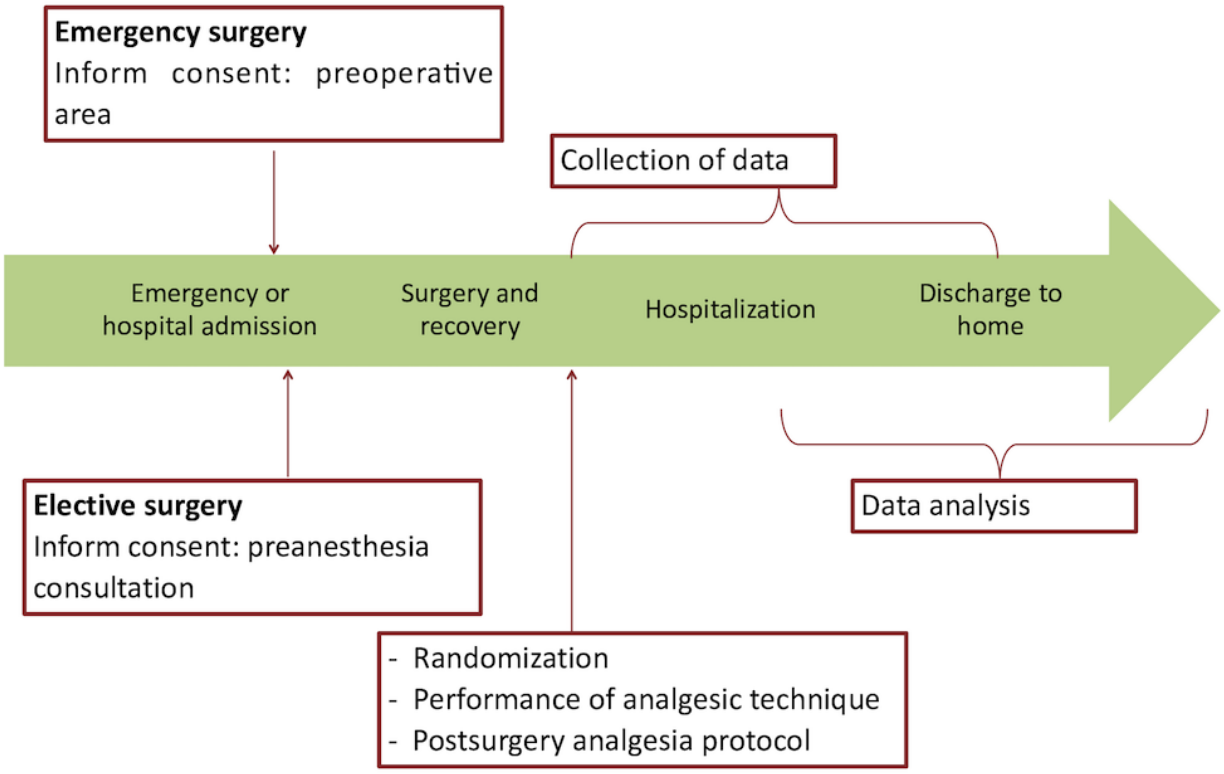

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Figure 2. Analgesic protocol. VAS: visual analog scale.

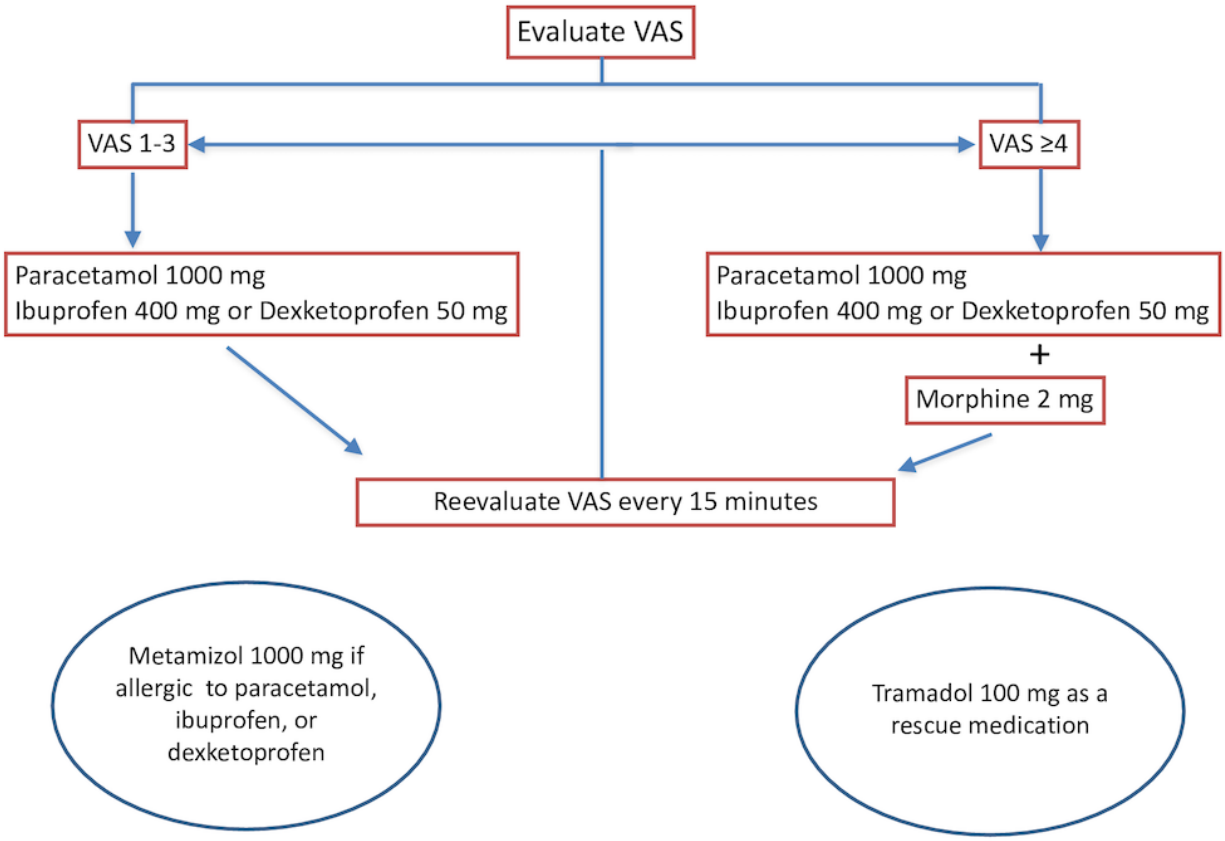

Variables Studied

The main variable is the VAS score, recorded at 30 minutes and at 2, 6, 12, 24, and 48 hours postoperatively. We will also assess adverse effects related to the locoregional block and opioid use, the level of patient satisfaction, and the technical ease of performing the block.

Sociodemographic variables will include age, sex, height, weight, ASA classification, date of admission, date of surgery, type of surgery (prosthesis or osteosynthesis), type of anesthesia, and preblock VAS score.

The technical ease of performing the block will be classified as “good” when we are able to clearly distinguish the anatomical structures necessary for locoregional analgesia; “fair” when the structures are intuited but not clearly defined; and “poor” when we are unable to distinguish any anatomical structure that would allow us to perform the block, which constitutes an exclusion criterion for participation in the study. Forty-eight hours after the procedure, the level of patient satisfaction with the quality of analgesic treatment will be recorded as “satisfied” if the patient considers pain management adequate or “dissatisfied” if pain management is considered inadequate.

Outcomes

Primary Outcome

The primary outcome is the difference in pain intensity between the L-ESPB group and the control group, measured using the VAS at 2 hours postoperatively.

Secondary Outcome

We will compare postoperative analgesic requirements and opioid consumption between the L-ESPB group and the control group. In the L-ESP block group, the technical ease of performing the block will be assessed and classified as good, fair, or poor. We will also compare the occurrence of side effects and the level of patient satisfaction between both groups.

Sample Size

Considering a reduction of at least 1 point on the VAS, with an expected SD of 2, a statistical power of 90%, and a type I error of 5%, we calculated a minimum sample size of 86 patients per group (total N=172). To account for potential losses, we increased the sample size by 5%. At the time this protocol was developed, no clinical trials had evaluated this type of block in hip surgery. Therefore, we chose a 1-point decrease on the VAS, aiming to be both conservative and pragmatic, which resulted in a larger sample size compared to similar studies of other locoregional blocks in hip surgery [8,13].

Recruitment is planned over 18 months.

Statistical Analysis

The analysis will be performed using SPSS software (IBM Corp). Descriptive statistics will be presented for all collected variables: frequencies and percentages for categorical variables; mean SD, and range for normally distributed quantitative variables; and median and IQR for nonnormally distributed variables. Normality will be assessed using the Kolmogorov-Smirnov test.

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Comparisons between the groups of both effectiveness and safety variables will be conducted using the chi-square test for categorical variables and the 2-tailed *t* test for numerical variables. For intragroup comparisons, the McNemar test will be used for qualitative variables and the *t* test for samples related to quantitative variables. For nondichotomous variables, we will use ANOVA for parametric distributions and the Kruskal-Wallis test for nonparametric distributions. If data from quantitative variables do not follow a normal distribution, the equivalent nonparametric Mann-Whitney *U* test will be used for independent groups and the Wilcoxon signed rank test for related samples.

In all hypothesis contrasts, differences will be considered statistically significant when $P<.05$.

We will perform a single interim analysis after 50% of the sample size is enrolled. The analysis will be performed by an independent statistician, using O'Brien-Fleming limits to control for overall type I error. The trial may be stopped in case of serious adverse events related to the technique. All intermediate analyses will be conducted blinded to the principal investigators.

Ethical Considerations

This study received clinical trials authorization from the MSCs-ES on May 27, 2024 (Clinical Trials Information System: 2024-511528-15-00), and ethics approval from the Ethics Committee for Drug Research in Galicia.

Patients scheduled for elective surgery will be provided with complete study information and will be required to sign informed consent forms during the preanesthetic consultation. Patients who are to undergo urgent surgery and therefore will not have a formal preoperative consultation will sign the informed consent form in the preoperative area.

Consent is obtained after sufficient time is given to patients to read and understand the information and to ask any questions. The informed consent form includes the option to withdraw from the study at any time. Patients who agree to participate will sign the informed consent form, which will be included in their medical record to inform postanesthesia care unit staff that the patient has been invited to participate and is enrolled in this study.

At any time during the study, patients may revoke their consent using a dedicated revocation document.

Results

This clinical trial was approved by the European Medicines Agency on May 27, 2024, following approval by the local ethics committee earlier that month. Patient recruitment took place between June 2024 and May 2025. Statistical analysis is currently ongoing, and final results are expected to be submitted for publication in early 2026.

Discussion

Summary

L-ESPB has emerged as a novel and technically accessible option for postoperative analgesia in hip surgery. Although its anatomical mechanism of action suggests the potential to provide effective somatic and visceral analgesia through spread to the lumbar plexus and adjacent structures, evidence supporting its use is currently limited to case reports and small observational studies. To date, no large-scale randomized controlled trials have definitively demonstrated its efficacy in this surgical context.

This randomized controlled trial aims to fill this gap by systematically evaluating the efficacy of L-ESPB in a well-defined patient population undergoing hip surgery. By comparing postoperative opioid requirements and pain scores between patients receiving L-ESPB and those receiving standard care, this trial seeks to generate high-quality data that may inform clinical practice and contribute to the development of standardized analgesic protocols for hip surgery.

If L-ESPB is shown to significantly reduce opioid consumption and improve pain control, it could represent a valuable addition to multimodal analgesia strategies, particularly for older adults or patients who are frail and thus more vulnerable to opioid-related side effects. Conversely, if no significant benefit is observed, the results will also be important to prevent unnecessary use of a block that may add procedural time and resources without clinical gain. This trial will thus contribute meaningfully to the evidence base on regional anesthesia in orthopedic surgery and help clarify the role of L-ESPB in modern perioperative care.

Hip surgeries have major health, social, and economic implications. Regardless of surgery being prescribed to treat a fracture or coxarthrosis, patients are usually older adults with multiple associated comorbidities [1]. In this patient population, there is a tendency to undertreat pain for fear of the side effects and pharmacological interactions of conventional analgesic drugs [14]. Poor analgesic control of pain in these patients results in a slower recovery with longer hospital stays, increased incidence of chronic pain, and increased cardiovascular risks, underscoring the importance of effective analgesic strategies [15]. In this context, regional anesthesia techniques offer a promising approach to optimize analgesia while minimizing opioid consumption [16,17].

Several peripheral nerve blocks have been validated in hip surgery, such as the fascia iliaca block, femoral nerve block, lateral femoral cutaneous nerve block, PENG block, and the quadratus lumborum block, among others [18]. The fascia iliaca block has been endorsed by multiple work groups, including Klukowski et al [19], who reported that patients receiving this block required fewer analgesic interventions (3 vs 11; $P<.01$) and showed a significantly lower need for analgesics than patients without block, with no associated complications. The blockade of the iliac fascia compartment has been found to be effective in hip surgery, but it has limitations because on many occasions it fails to provide adequate analgesia of the obturator nerve, which contributes to the innervation of the most anterior capsule of the hip [20].

The PENG block, introduced in 2018 by Girón-Arango et al [21], is currently one of the most widely used peripheral nerve blocks in patients with hip fracture. Lin et al [7], who conducted a single-center, double-blind randomized comparative trial,

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revealed that patients who received a PENG block for intraoperative and postoperative analgesia during hip fracture surgery experienced less postoperative pain in the recovery room, but no differences were observed on the first postoperative day. Locoregional analgesia of this type is useful not only for postoperative pain control but has also been successfully applied preoperatively. Uysal et al [22] confirmed the effectiveness of preoperative femoral nerve block in trochanteric femur fracture surgery and in preventing pain during the administration of regional anesthesia.

Furthermore, given the many therapeutic analgesic options available for hip surgery, it is possible to compare them to identify the most effective approach for each type of patient and surgical technique. There is an extensive comparative bibliography on this subject, such as the randomized clinical trial conducted by Mosaffa et al [23], who concluded that the PENG block is a good method for hip fracture analgesia and provides better analgesia than the fascia iliaca compartment block.

Another block with only limited application in hip surgery, although it is more commonly used in abdominal procedures, is the quadratus lumborum block. Parras and Blanco [24], who conducted a randomized clinical trial with 104 patients with hip fracture who underwent hip hemiarthroplasty in parallel groups, reported that this block provided satisfactory analgesia for this type of intervention. However, a recent systematic review and meta-analysis found inconsistent results for its use in hip surgery, largely attributed to the unclear mechanism of action and the different approach used for each patient, with overall nonsignificant outcomes [25].

L-ESPB involves identifying the transverse apophyses at the L3-L4 level and depositing local anesthetic at this level, advancing through the erector spinae muscles to reach the apophyses. Diffusion of the local anesthetic varies depending on whether the block is performed at the thoracic or lumbar level due to the differences in the anatomy of each area. It has been found that at least 5 mL of local anesthetic would be required at the lumbar level compared to 2.5 mL at the thoracic level [26]. Some studies support the notion that L-ESPB acts similarly to paravertebral blocks, as studies performed in cadavers have shown expansion of the local anesthetic at this level. The number of intercostal spaces it may cover ranges between 3 and 7 [27].

The classic approach is the lumbar parasagittal approach at the L4 level in the ultrasound-guided plane, and it may also be performed using anatomical landmarks [28]. Tulgar and Senturk [10] and Tulgar et al [11,29], among others, reported extensive and lasting pain relief after hip arthroscopy using a single-injection L-ESPB at the L4 transverse process with 0.25% bupivacaine without significant motor block. However, these publications are limited to case series rather than randomized clinical trials. This block has even been used by Ahiskalioglu et al [30] as an intraoperative anesthetic technique together with sedation in an observational study with 15 patients considered high risk. The authors performed L-ESPB with 40 mL of a local anesthetic mixture (20 mL of 0.5% bupivacaine, 10 mL of 2% lidocaine, and 10 mL of normal saline solution) together with propofol as a sedative. All surgeries were completed satisfactorily, without conversion to general or intradural anesthesia.

Combining this block with others is feasible and has proven effective, as described by Ince et al [31], who combined the PENG block and L-ESPB, providing postoperative analgesia for a boy aged 4 years who underwent surgery for congenital hip dysplasia, reducing the need for additional analgesics.

Application of this block also allows comparison with other techniques; for example, Tulgar et al [32] conducted a prospective study and concluded that both L-ESPB and the quadratus lumborum block provided similar effects, improving analgesia quality in patients who underwent hip and proximal femur surgery compared to those who received standard intravenous analgesia.

Although several peripheral nerve blocks have been proposed in recent years for pain management in hip surgery, L-ESPB remains a little-studied technique. Most existing literature consists of case series or small observational studies, and to date, no randomized controlled trials have specifically evaluated its efficacy in this setting. We believe that this study can provide relevant and necessary information, as it offers data collected using a robust methodological design, a relatively large sample size, and blinded outcome assessment. If L-ESPB proves to be effective and safe, it could represent a practical and accessible alternative within multimodal analgesia strategies, especially for older adults or patients who are frail in whom minimizing opioid use is a key concern.

This clinical trial has major limitations, including single-center, nonblinded randomized controlled design as well as the novel yet underresearched nature of L-ESPB. Furthermore, we do not evaluate sensory blockade, which could provide valuable information for understanding its exact mechanism of action. It is also noteworthy that we include patients receiving chronic home analgesic treatment that continues to be administered during the perioperative period.

Our study has several strengths. To date, it is the only randomized clinical trial evaluating L-ESPB in patients undergoing hip surgery under either general or intradural anesthesia. With a large sample size of 180 patients compared to similar studies [18], the risk of sampling error is reduced. We adopt rigorous methods, including adjustment by regression as well as standardized intervention and follow-up protocols, which help minimize selection, performance, and observer bias.

It is likely that, upon completion of this clinical trial, further research will be necessary to build on these findings.

The results of this clinical trial will be disseminated exclusively through *JMIR Research Protocols*, and the results (including negative or inconclusive outcomes) will be reported in accordance with CONSORT (Consolidated Standards of Reporting Trials) and International Committee of Medical Journal Editors guidelines.

Conclusions

Existing literature on the use of L-ESPB in hip surgery is scarce and inconsistent, largely relying on case reports and lacking

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well-designed clinical trials. If L-ESPB is shown to significantly reduce opioid consumption and improve pain control, it could represent a valuable addition to multimodal analgesia strategies.

Acknowledgments

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Data Availability

The datasets generated and analyzed during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

LGR conducted the investigation, wrote the original draft, and reviewed the manuscript. MAPL was responsible for conceptualization and project administration. JPL was responsible for data curation, software, and visualization. JJAP provided valuable comments on the study design. RPR facilitated the implementation of the study and reviewed the final version of this protocol. SR was responsible for the methodology, supervision, and validation of the clinical study.

Conflicts of Interest

None declared.

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Abbreviations

ASA: American Society of Anesthesiologists
CONSORT: Consolidated Standards of Reporting Trials
L-ESPB: lumbar erector spinae plane block
PENG: pericapsular nerve group
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
VAS: visual analog scale

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Protocol

Efficacy of a Web-Based Executive Function Training Program to Induce Healthier Food Choices and Increase Valuation of Fruits and Vegetables in Adults: Protocol for a Randomized Controlled Trial

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Abstract

Background: Executive function (EF) is a set of explicit (top-down) cognitive abilities theorized to assist in conscious control of eating behavior. However, it is unclear whether EF training can improve valuation and consumption of nutrient-dense foods while concurrently altering attitudes toward and perceptions of nutrient-poor foods and their consumption.

Objective: The primary objective is to determine the efficacy of a web-based EF training program designed to concurrently improve attitudes toward and perceptions and consumption of nutrient-dense foods (fruits and vegetables) while worsening those of nutrient-poor foods (ie, candy and fried snacks).

Methods: Participants include a nationally representative US sample (N=500) of men and women aged 18 to 70 years with a BMI between 18.5 and 38 kg/m^2. Potential participants are recruited through an open link to a prescreening questionnaire. Qualified participants are sent an electronic version of the informed consent form to sign. After consenting, they are invited to create an account on our semiautomated web-based platform and randomized to EF training via a suite of 4 web-based games that promote responding to fruits and vegetables, inhibit responses to nutrient-poor foods, and train attention toward the former and away from the latter or sham training that involves images of flowers and songbirds (control). Training occurs at least twice per week. EF is tested before and after 8 weeks of training. Dietary intake is measured before and after the 8-week intervention. Group and sex differences in frequency of participants violating inhibitory signals will be assessed using log-linear models. Linear mixed-effects models will test whether web-based EF training improves EF as measured via response inhibition and attention during computer-based gameplay. The independent and interactive associations between inhibitory and attentional learning and consumption of nutrient-poor foods will be tested using mixed model regression. If random assignment results in baseline imbalances across conditions on any variables, they will be used as covariates in the mixed models. We will use both an intention-to-treat analysis using (restricted) maximum likelihood estimation and a completer analysis to understand the results from those participants who completed the training at least twice per week.

Results: As of June 1, 2025, overall, 899 individuals have applied to participate in the study. Of 899 applicants, 763 (84.9%) qualified and 630 (70.1%) consented. There have been 386 withdrawals due to noncompliance with study requirements (n=342, 88.6%) or identification as a bot (n=35, 9.1%).

Conclusions: The association between improved EF and healthy eating behaviors may be key to improving diet quality. If effective, this web-based EF training program will provide a platform that can be made widely available to aid individuals in

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food-related decision-making. The platform could be modified to target other food choices and other health behaviors, such as reducing sedentariness and increasing physical activity.

Trial Registration: ClinicalTrials.gov NCT05938894; https://clinicaltrials.gov/study/NCT05938894

International Registered Report Identifier (IRRID): DERR1-10.2196/66394

(JMIR Res Protoc 2025;14:e66394) doi:10.2196/66394

KEYWORDS

executive function; vegetables; fruits; diet; food choices; energy-dense foods; nutrient-poor foods; nutrient-dense foods

Introduction

Background

There is a correlation between healthy behaviors and constructs of executive function (EF) [1]. Therefore, the purpose of this study is to determine whether a web-based EF training program can improve response inhibition and attention and concurrently improve attitudes toward and perceptions and consumption of nutrient-dense foods (ie, fruits and vegetables [FV]) while worsening those of nutrient-poor foods (ie, candy and fried snacks). In effect, the aim is to test whether a web-based EF training program can promote the substitution of nutrient-poor foods with FV. Greater FV consumption is associated with better weight control; reduced risk of all-cause mortality, cardiovascular disease, diabetes, and cancer; and better eye and skin health [2,3]. There is also an association with better mental and cognitive health [4-6]. Thus, EF training that effectively promotes increased FV intake will benefit both physical and mental health. It remains unclear whether EF training can be successfully implemented entirely remotely and independent of behavioral cognitive training.

EF Definition

EF is a set of explicit (top-down) cognitive abilities theorized to assist in conscious control of behavior, for instance, the ability to override impulsive (implicit) processes. Collectively, these processes exert influence on the decisions people make that drive appetitive behaviors; poorer EF is associated with unhealthy dietary choices [7,8]. Constructs of EF that are of particular interest and used in this project include (1) inhibitory motor control, or the ability to override impulsive responses; and (2) attentional control, or attention bias toward food cues in the environment.

Individuals who display personality traits associated with impulsiveness and inhibitory control deficits or those who show less recruitment of inhibitory regions of the brain are more sensitive to food cues and may be more vulnerable to the pervasive presence of food, particularly highly palatable nutrient-poor foods [9-11]. These individuals have a preference for immediate food reward [12,13] and poorer weight control [10,14,15]. Greater attention bias toward food cues predicts greater increases in body weight [16]. Food-related attention bias positively correlates with food craving, food intake, and hunger [17], and this may be more pronounced in individuals with overweight and obesity [11,18-21]. Furthermore, individuals who exhibit greater neural activation to energy-dense food images in reward and attention regions of the brain (eg, the orbitofrontal cortex and caudate nucleus) are more sensitive to food cues and more vulnerable to the pervasive temptation of appetizing foods in our environment [9] and have poorer weight management [18,19,22].

Encouragingly, there is evidence that using EF training tasks that target impulsivity and attentional bias can shift appetitive behaviors. Inhibitory control is predictive of FV consumption [23], and increased attentional bias toward healthy foods leads to increased consumption of “healthy” snacks (eg, mixed nuts) relative to “unhealthy” snacks (eg, chips) [24]. These findings suggest that an EF training intervention that simultaneously increases inhibitory control while reducing reward and attention responses to nutrient-poor food should improve dietary choices [25-27]. However, to date, there are no examinations of EF training on appetitive behaviors related to increasing FV consumption while concomitantly decreasing the valuation of energy-dense, nutrient-poor foods.

EF Training

EF training tasks that target attention bias (eg, dot probe) and support inhibitory control (eg, go/no-go) can shift eating behaviors. Training inhibitory control with weekly 30-minute go/no go training sessions for 4 weeks has successfully reduced body weight [28]. Shorter training periods (4 sessions in 1 week) have reduced energy intake and liking of energy-dense foods and promoted weight loss [29]. Overall, the current body of research indicates that EF training can be a key component in improving appetitive behaviors. However, it is unclear whether web-based EF training improves EF as measured via response inhibition and attention or whether EF training can alter attitudes and perceptions of nutrient-poor foods and consumption of those foods while concurrently improving attitudes toward and perceptions and consumption of FV. As such, we have designed a web-based EF training program—EFfect (Executive Function Forming Exercises for Cognitive Training) for food choices, or EFfect-food choices—that is, a suite of 4 games intended to target both attention bias and inhibitory control as they relate to FV consumption.

Moderators of EF Training

Consumption of complex carbohydrates, omega-3 fatty acids, and protein positively correlate with memory and working memory scores [30]. There is some evidence that greater-than-recommended protein intake is correlated with enhanced EF domains [30]. Conversely, consumption of simple carbohydrates and saturated fatty acids is associated with reduced global cognition and memory and learning scores [30]. This study will test whether habitual dietary intake at baseline

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moderates the effects of the intervention on baseline EF and with pretest-posttest changes in EF and dietary intake.

Greater time between trainings may contribute to greater reductions in "unhealthy" food intake, potentially because spaced training allows for consolidation of learning, suggesting that the interval between training sessions may be important [29,31]. This study will determine whether gameplay frequencies within weeks and across an 8-week intervention period predicts greater change in primary and secondary outcomes [31].

Chronic stress may also moderate EF training efficacy, although this hypothesis has not yet been tested. Chronic stress is associated with greater difficulties with concentration, memory, and decision-making and with poorer performance on tests of working memory, attention, response inhibition, and cognitive flexibility [32-34]—all constructs of EF. Mechanistically, chronic stress alters brain morphology in areas responsible for EF. Humans who have experienced chronic stress display altered connectivity within frontoparietal networks that mediate attention shifts [35] and atrophy of the medial prefrontal cortex and caudate nucleus [36]. Chronic stress also increases putamen volume and dendritic branching [36]. Thus, chronic stress produces central morphological changes that could reduce EF and increase impulsivity.

Self-reported baseline BMI will be tested as a moderator of the efficacy of the EF training in improving EF scores and reducing BMI. A meta-analysis found that people with obesity display impairment across inhibition, working memory, decision-making, and planning EF domains [37]. However, baseline BMI did not moderate the association between obesity and EF [37]. Excess adiposity may not be a function of overconsumption of energy but, rather, of population-level changes in composition of the gut microbiome, reduced diet-induced thermogenesis in response to consumption of processed foods, the magnitude of browning or beiging of adipocytes, the rate of mitochondrial respiration, and intergenerational transmission of epigenetic alterations that increase the risk of excess adiposity [38]. In addition, given that a period of overeating that results in weight gain is associated with increased reward region responsivity to energy-dense foods [39], it is possible that EF training will be more effective for participants with lower versus higher BMI values.

Objectives and Hypotheses

The primary objective of this project is to test the efficacy of the EFfect-food choices training program in improving EF and increasing consumption of targeted nutrient-rich FV. Secondary objectives include the effectiveness of the EFfect-food choices training program in (1) increasing an individual's awareness of dietary choices, (2) increasing positive attitudes toward FV, (3) increasing the valuation and consumption of FV, and (4) decreasing the valuation and consumption of nutrient-poor foods. We will also determine whether changes in self-consciousness of, attitudes toward, and valuation of FV predict change in dietary intake and whether baseline dietary intake, BMI, and psychological stress moderate the efficacy of EF training and food valuation.

The specific hypotheses are as follows: (1) EF training will increase behavioral response inhibition as measured through faster response time, performance accuracy, and delayed discounting; (2) EF training will reduce attentional bias toward nutrient-poor food cues as measured through faster response time and performance accuracy; (3) EF training will reduce intake of nutrient-poor foods in participants who demonstrate greatest inhibitory and attentional learning; (4) time spent playing EF games and number of EF game sessions completed will be positively associated with increases in EF in the EFfect-food choices group; (5) spaced EF training will facilitate greater increases in EF than massed EF training; (6) greater length of delay between the last training day and testing of EF game performance at 8 weeks will be associated with smaller improvements in EF; (7) usual consumption of complex carbohydrates, omega-3 fatty acids, and protein will correlate with baseline EF; (8) usual consumption of simple carbohydrates and saturated fatty acids will be associated with reduced EF; (9) greater baseline and pretest-posttest consumption of complex carbohydrates, omega-3 fatty acids, and protein will correlate with increased EF; and (10) lower usual and pretest-posttest consumption of simple carbohydrates and saturated fatty acids will be associated with increased EF.

Methods

Study Design

A single-blinded, parallel, 2-arm randomized controlled web-based clinical trial will be used to test the effectiveness of the EFfect-food choices training program in increasing FV consumption. Only designated study coordinators assigning the study intervention are unblinded. All study procedures are web based and by invitation only. All outcome measures are completed during baseline and at the end of the 8-week treatment period (Table 1). The baseline and posttraining testing periods are 1 week in duration to allow for obtaining 3 days of dietary recall and completion of study questionnaires and EF testing. The intervention consists of 8 weeks of EF training. Details of the EF training intervention are outlined in the following sections. SMS text message or email reminders are sent to participants throughout the study to ensure that all questionnaires and EF testing are completed within 1 week of starting and finishing the EF training intervention and remind participants to complete the EF training intervention each week.

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Table 1. Testing schedule.

Measurement	Week 0	Weeks 1-8	Week 9
3-d diet records	✓		✓
Questionnaires	✓		✓
EF[a] testing	✓		✓
EF intervention		✓	

[a]EF: executive function.

Ethical Considerations

This study has been approved by the University of North Dakota Institutional Review Board (IRB0005432) and is registered on ClinicalTrials.gov (NCT05938894; Train Your Brain—Executive Function; last updated April 7, 2025). Participants are provided with an electronic informed consent form before taking part. No data were collected from participants before obtaining informed consent in accordance with the Helsinki Declaration of 1975 as revised in 1983. After consenting, participants are assigned a study identifier that is used for the collection of all data and randomized to EF training via a suite of 4 web-based games that promote responding to FV, inhibit responses to nutrient-poor foods, and train attention toward the former and away from the latter or sham training that involves images of flowers and songbirds (control). Participants were compensated with US $340 for their time after all study procedures were completed. Any protocol changes will first be approved by the University of North Dakota Institutional Review Board before implementation.

Recruitment

Participants (N=500 completers) include men and women aged 18 to 70 years who are classified as having a healthy BMI but not greater than the upper end of class II obesity (BMI 18.5-38 kg/m^2) and are citizens of the United States. Recruitment media may include brochures, newsletters, television, radio, and internet or social media advertisements. Participants are recruited to estimate a nationally representative sample using a quota system based on US census data on sex, age, and race. A reasonable effort is made to achieve these sampling goals, although small deviations may be necessary to complete the study while still meeting the sample size of 500 total completers.

Inclusion criteria include US citizenship, not currently dieting to lose weight and no weight loss or gain of >4.5 kg (10 pounds) over the previous 3 months, no tobacco or e-cigarette use, and not being pregnant or lactating or planning to become pregnant while participating in the study. A history of bariatric surgery; diagnosis of a major medical or psychiatric condition that would interfere with participation, including not being physically able to complete the computer training; or a current eating disorder are additional exclusion criteria.

Potential participants complete an initial prescreen online survey to verify that they meet the study criteria. Eligible applicants are invited to participate in the full study and provided with a web-based informed consent form. After the participant submits the consent form, the information is verified, and a copy of the signed consent form is sent to the email address provided by the participant.

EF Testing and Training Intervention

Overview

EFfect-food choices consists of 4 games designed to test EF as associated with nutrient-rich food (NRF) choices and designed to train participants to search for and shift their attention toward FV, specifically by shifting attentional bias and increasing inhibitory control. The games are constructed to prompt responses to FV 100% of the time and prompt inhibition to nutrient-poor foods 100% of the time in the intervention group. All images are of the same background color (white) and size to allow for consistent alignment within a grid. Participants play each game once before and after the 8-week EFfect-food choices intervention at the same standardized game settings, and the game outcomes, namely, response time, percentage correct, and raw data on errors of omission and commission, will serve as EF outcomes.

For the 8-week EF training intervention, participants play all 4 of the EFfect-food choices games a minimum of twice per week on 2 separate days. A week is defined as beginning on a Wednesday and ending on a Tuesday. Participants who have not yet completed at least 1 of the 2 expected training sessions of each game by Friday at 11:59 PM receive a reminder email or SMS text message to complete the training. Participants are given 1 week to become current with their past-due training, after which they are removed from the study. If necessary, a second email or SMS text message reminder is sent on Monday. Participants can choose the days of the week on which they play the games. Participants have different schedules of daily living, and choice over scheduling of gameplay should help promote adherence. Participants must play the games at least twice per week but can play as many times as they wish. In addition, participants have control over the order in which the games are played. This structure allows for individual differences in gameplay order and frequencies within weeks and across the 8-week intervention period and allows for testing whether the pattern of training correlates with greater efficacy of the intervention on EF. In effect, this strategy allows for testing whether more widely spaced training facilitates greater consolidation of reward learning than massed (ie, consolidated) training.

The following sections provide detailed descriptions of the games for the intervention group.

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Go/No-Go

Participants are presented with a series of food images appearing on either the left or right side of a rectangular gameplay area that is centered on the screen (Figure 1). Participants are instructed to click on the images that appear in the solid boxes as quickly as possible and not click on the images framed in dashed boxes. For the intervention group, for 100% of the trials, FV images appear in a solid box, and images of nutrient-poor foods appear in a dashed box. If the participant fails to click on an image in a solid box within the allotted time, or if they click on an image in the dashed box, a red *X* is displayed to provide feedback of the error. This trains participants to focus on the FV images when playing the game. Neutral filler images (a water-filled glass) are presented and appear in the solid boxes 50% of the time and in the dashed boxes 50% of the time. The 50:50 ratio of box type for the filler images is to discourage a training effect for these images and permit calculation of inhibitory learning for nutrient-poor foods and FV. A description of the control group sham gameplay is provided in the Control Group section. It takes approximately 10 minutes to complete this game.

Figure 1. Screenshots of the Go/No-Go game.

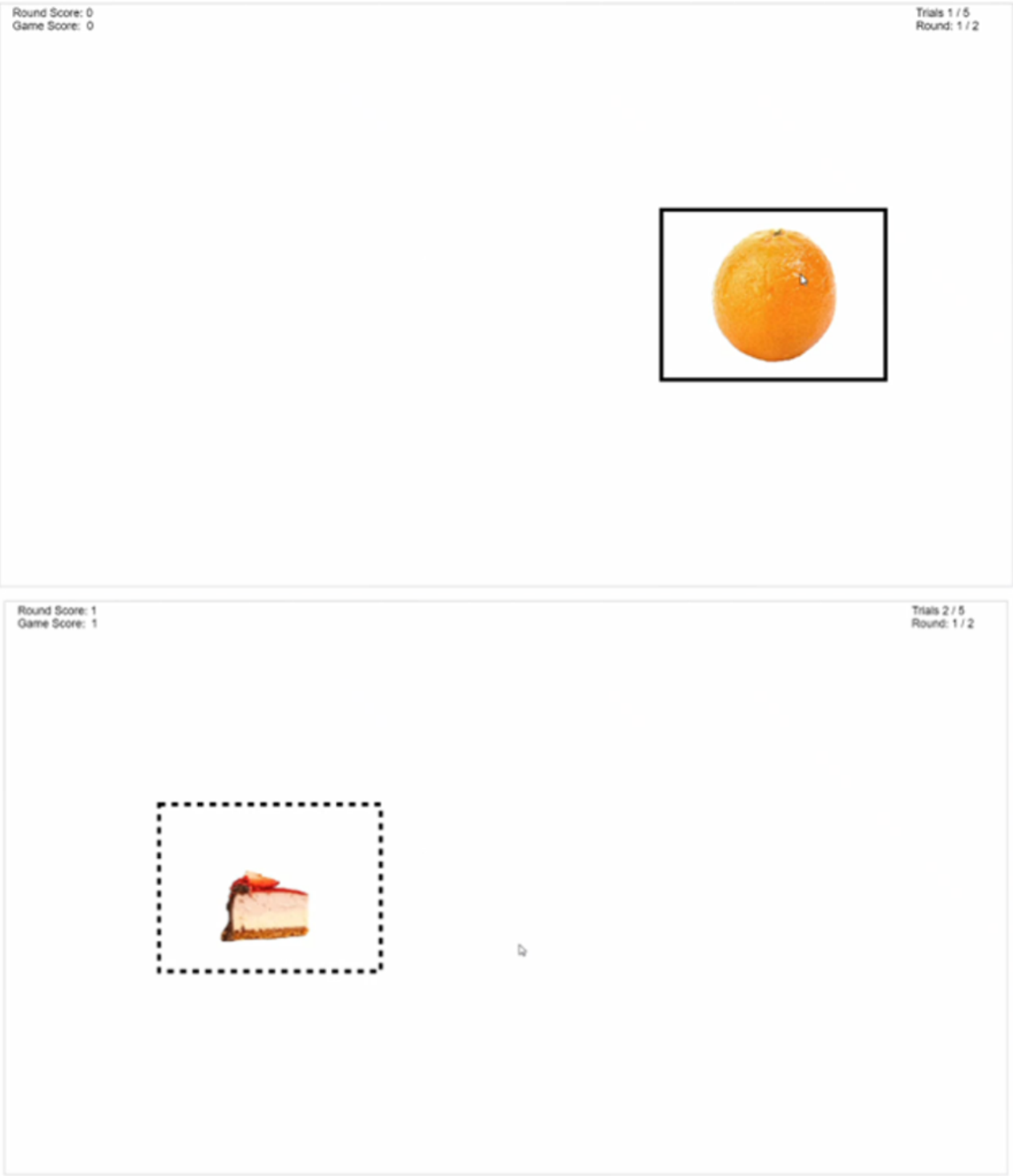

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Stop Signal

Participants are presented with FV, nutrient-poor foods, and filler images. These images are surrounded by either a red or green solid border that is delayed in appearance (Figure 2). Participants are instructed to click on the images surrounded by a green border as quickly as possible and not click on images with red borders. Images are presented for a short duration and then removed from the screen. Display duration of the images is discussed in the User Advancement section. When the participant fails to click on the image with a green border in the allotted time or clicks on the image that has a red border, a red *X* is shown on the screen. The FV images and nutrient-poor foods are framed with the solid green border 100% and 0% of the time, respectively. The filler water images are framed by the solid green border 50% of the time. It takes approximately 8 minutes to complete this game.

Figure 2. Screenshots of the Stop Signal game.

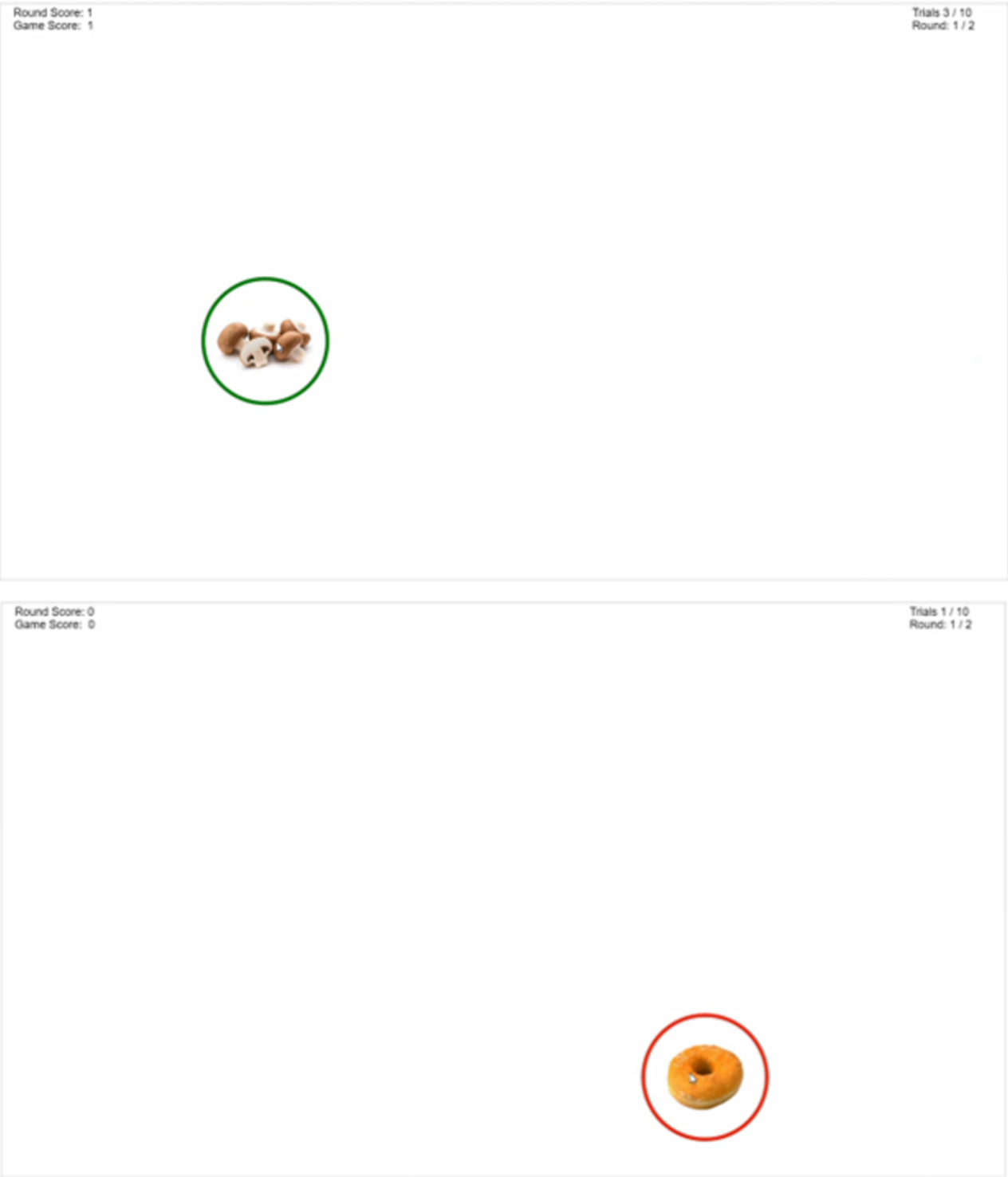

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Dot Probe

Pairs of a randomly selected FV image and a randomly selected nutrient-poor food image are shown on the screen (Figure 3). The images are shown side by side for a set duration (see the User Advancement section), and each individual image of the pair is shown on both sides of the rectangle gameplay area an equal number of times. Before the image pair is shown, a fixation cross appears in the center of the gameplay area for 500 ms. After the image pair disappears from the screen, a small black dot appears in the area that one of the images in the pair occupied and remains visible until a response in the form of a mouse click is registered in the gameplay area. Unlike the go/no-go game, a red *X* does not appear if the user does not click on the dot. Participants are instructed to click on the dot as fast as possible once it appears. In 100% of the trials, the dot appears within the space that the FV image occupied. The location of the dot changes for each image pair to prevent the participant from maintaining a single mouse position for the entire game. It takes approximately 14 minutes to complete this game.

Figure 3. Screenshots of the Dot Probe game.

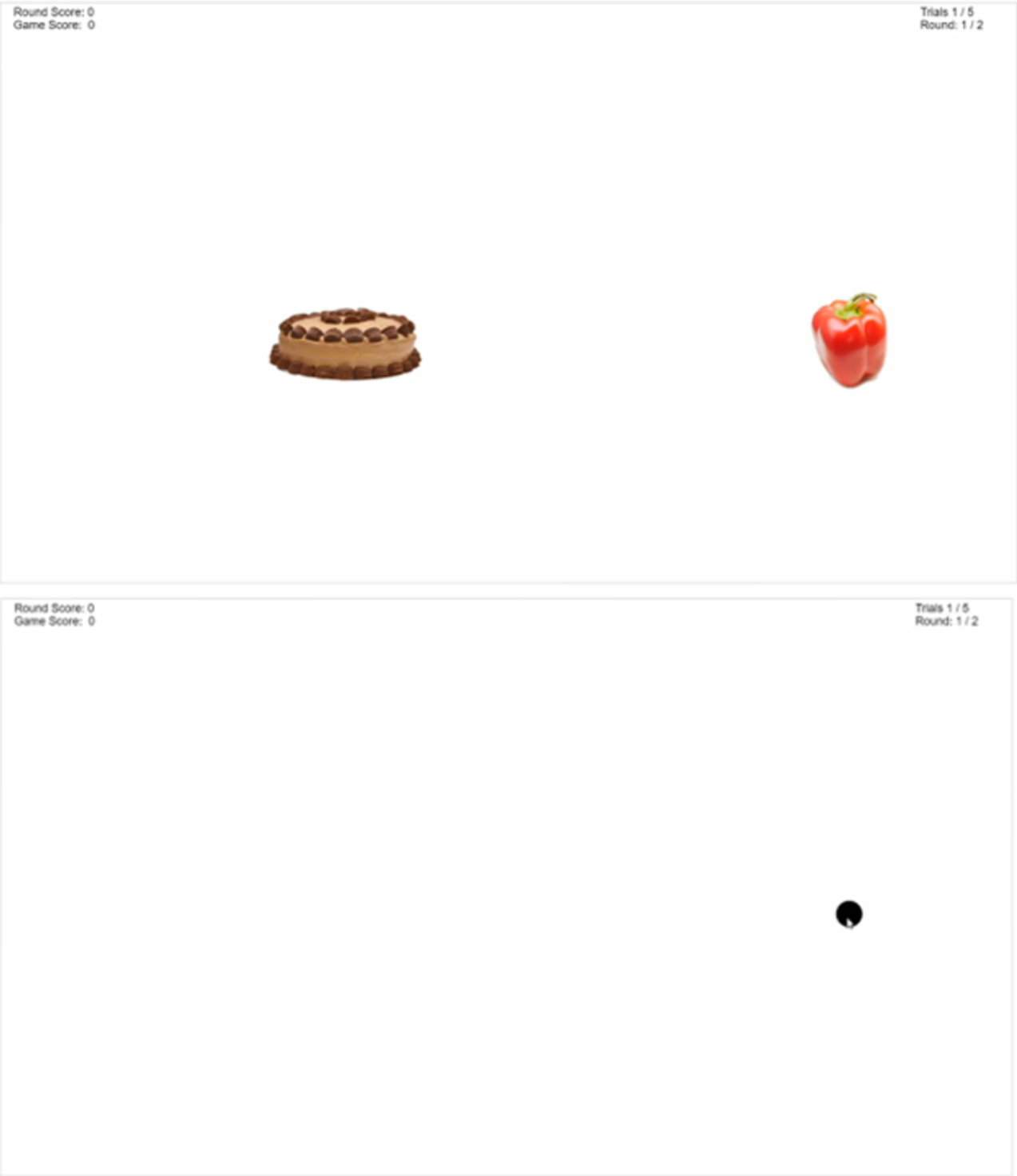

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Visual Search

Participants view a 4 × 4 array of randomly selected food images and then search and click on the FV image as quickly as possible within the allotted time (Figure 4). Each array consists of 1 randomly selected FV image and 15 randomly selected images of nutrient-poor foods (Figure 4). When the participant successfully clicks on the target FV image, the other 15 images disappear, and the target FV image is centered and framed with a green rectangle and becomes larger in size until the next set of images appears. If the participant fails to find the target FV image or clicks on one of the nutrient-poor images in the array, the images are removed from the screen, and a red *X* appears. It takes approximately 6 minutes to complete this game.

Figure 4. Screenshot of the Visual Search game.

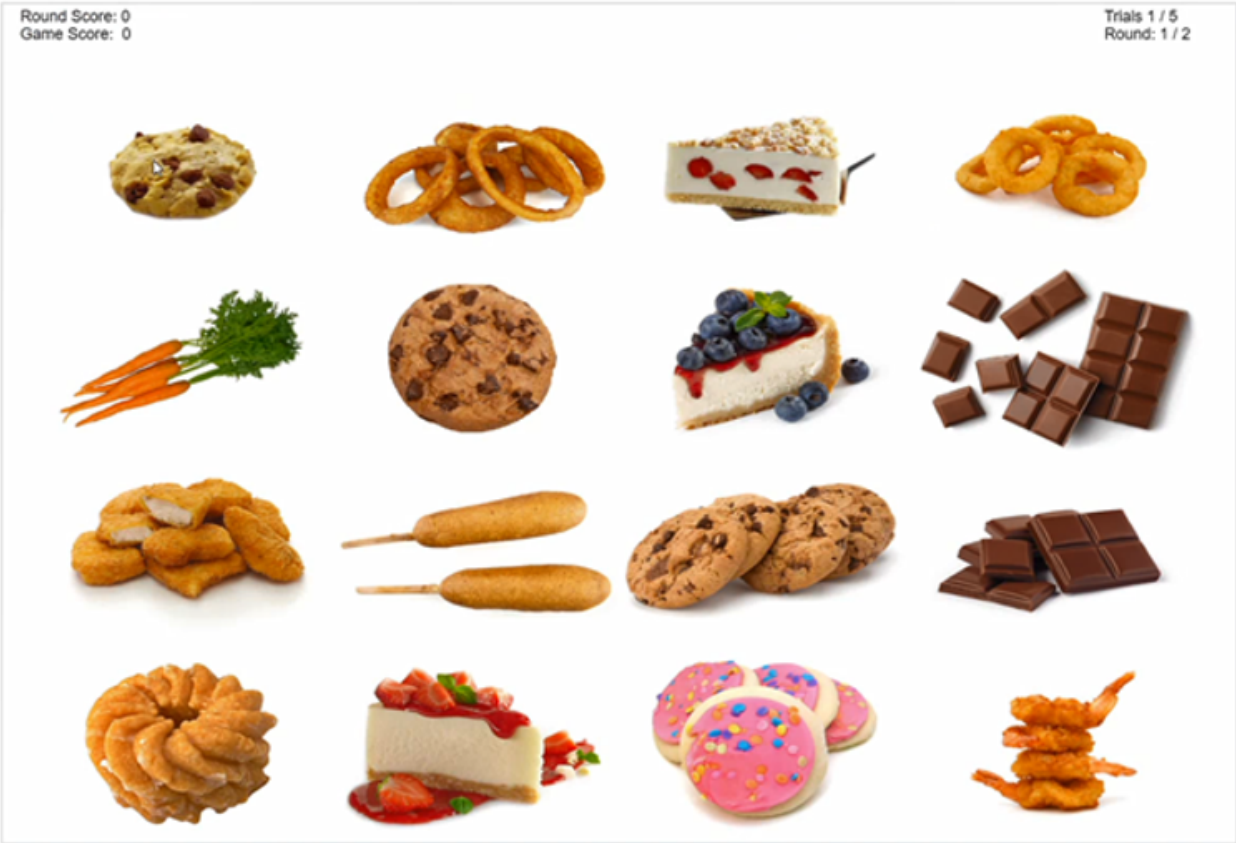

Image Selection

Image selection for the games was strategic and based on nutrient density as determined using the NRF Index (the Nutrient Rich Foods Index). The NRF Index is a method of quantifying nutrient density that has been validated against the Healthy Eating Index score [40]. The NRF 9.3, a scoring system within the NRF family of indexes, provides a numerical score for individual foods that is calculated by subtracting the sum of daily values of 3 nutrients to limit from the sum of daily values of 9 nutrients to encourage (thus, 9.3) per 100 kcal [41]. The 9 nutrients to encourage on the NRF 9.3 scale are protein, dietary fiber, vitamin A, vitamin C, vitamin E, calcium, iron, potassium, and magnesium, and the 3 nutrients to limit are added sugar, saturated fat, and sodium. For the purposes of calculating NRF Index values for this study, total sugar was used in place of added sugar due to data availability in the Food and Nutrient Database for Dietary Studies. The NRF Index score does not provide cutoffs for levels of nutrient density (ie, nutrient dense vs nutrient poor). For this study, nutrient-poor foods were defined as those foods with an NRF Index score of ≤15.

Images were purchased through Shutterstock (Shutterstock, Inc), and all images feature a single food item with a blank, white background. A total of 80 FV images (40 of fruits and 40 of vegetables) and 80 nutrient-poor food images, which include both sweet (ie, candy, cake, and ice cream) and savory (ie, fried chicken, onion rings, and pizza) foods were selected. The FV images include 9 fruits (pineapple, kiwi, peach, orange, berries, melon, grapes, banana, and apple) and 14 vegetables (asparagus, broccoli, Brussels sprouts, carrots, cauliflower, celery, corn, cucumber, lettuce, mushrooms, green peas, sweet peppers, radish, and tomato). The average NRF Index for all images is 83.7 (SD 132.4). The average NRF Index score for the FV depicted in the images is 169.2 (SD 142.8). A total of 13 types of nutrient-poor foods were selected, including cake, candy, cheesecake, chicken nuggets, cookies, corndogs, cupcakes, doughnuts, fried chicken, ice cream, onion rings, pizza, and milkshakes. The average NRF Index score for the nutrient-poor foods depicted in the images is −1.79 (SD 7.77). In addition to these images, 40 images of glasses of water were selected for use as neutral filler images. The filler images are paired with inhibition cues and attention probes on a 50:50 ratio and allow for calculating inhibition and attentional learning for nutrient-poor foods and FV images.

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Control Group

Participants randomized to the control group play nearly identical versions of the games except that, in place of foods, they are presented with images of flowers and songbirds. The control group is randomized at a ratio of 1:1 to have either flowers or songbirds as the images used in place of FV. For participants randomized to have flowers in place of the FV images, images of songbirds are used in place of nutrient-poor foods (Figure 5). For participants randomized to have songbirds in place of the FV images, images of flowers are used in place of nutrient-poor foods. Participants are informed through the study material that this training improves inhibitory and attentional control, which should reduce the risk of overeating. Similar to the intervention condition, images were selected and purchased from Shutterstock and have a plain, white background featuring only 1 songbird or flower. A total of 80 flower and 80 songbird images on a blank, white background were selected, and the images were evenly distributed to not overrepresent a given species. Participants in the control group are also required to play each game twice per week on separate days. All control participants complete the same series of measures and tests as those in the intervention group.

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Figure 5. Screenshots of the Willingness to Pay assessment.

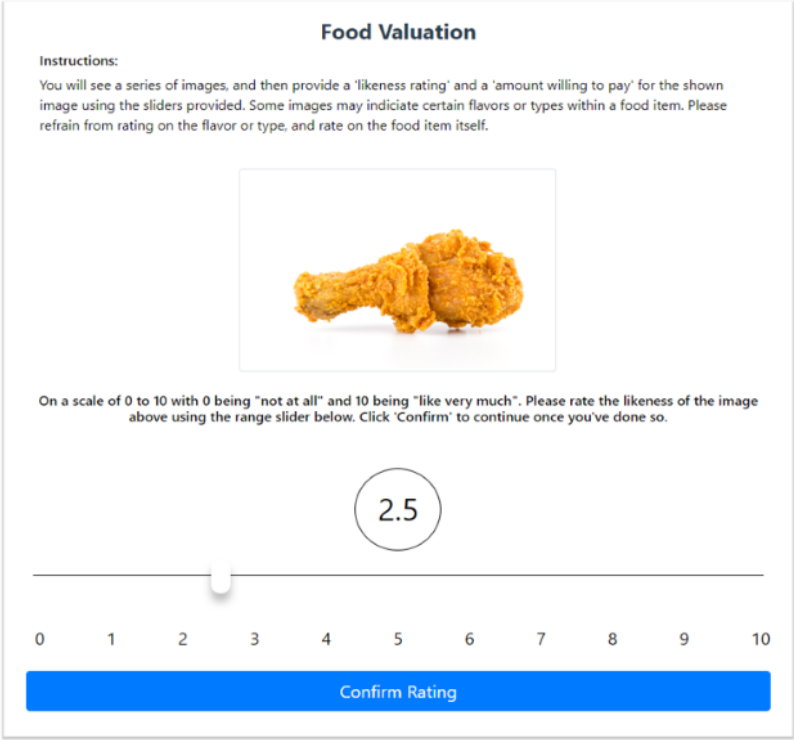

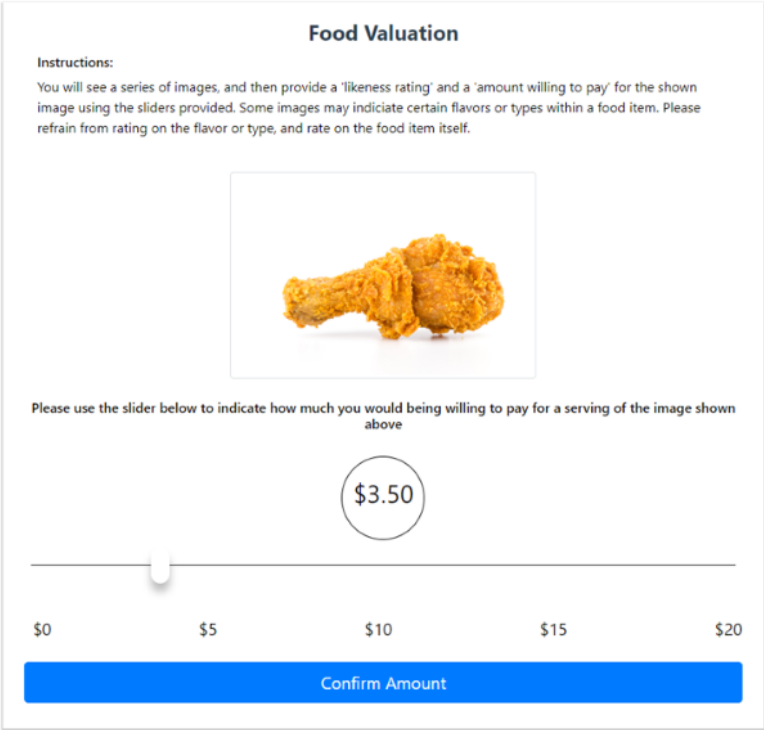

Treatment Fidelity and Training Volume

Treatment fidelity is encouraged through gamification strategies and reminder messages. Treatment fidelity and training time are measured using the web-based EFfect-food choices program as it provides a record of when and how often each of the games is played. This record provides real-time data regarding use of the EFfect-food choices program. Treatment fidelity and training volume measures include total time spent playing EFfect-food choices games, total number of sessions completing all 4 EFfect-food choices games, and total number of any of the EFfect-food choices games completed.

Gamification Strategies

To test whether EFfect-food choices with its fully online platform is more scalable and translatable than other EF training programs, participants complete all EF training outside a laboratory setting. To improve gameplay adherence,

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gamification theory [42-44] was applied to the development of EFfect-food choices. Gamification is commonly used in health-related apps, especially those targeting physical activity and weight loss [44]. Gamification includes features to increase engagement with nongame programs, such as badges, leaderboards, challenges, and adaptive features that are more effective (relative to games without adaptive features) in increasing EF [42]. A review of gamification suggests that, overall, gamification enhances engagement with health games; increases motivation, enjoyment, and understanding; reinforces the behavior; and increases adherence [45]. This strategy should increase participant motivation to continue playing the games and, thus, improve the efficacy of this trial as participants continue to engage with the treatment. If found to be effective, the impact of this research would be a low-cost, practical, easily accessible form of EF training that simultaneously increases FV intake while reducing consumption of nutrient-poor foods and that can be widely distributed to the general population via PC, tablet, or smartphone. Using the taxonomy of gamification approaches of Schmidt-Kraepelin et al [46], the gamification concepts of the EFfect-food choices training program are identified and classified (Textbox 1).

Textbox 1. EFfect-food choices training program gamification concepts.

1. Gamification messages are directly conveyed to users via text outputs.
2. User identity is determined from the user's first name and the first initial of their last name. The user's identity is displayed as a generic user icon on the user's account page.
3. Rewards or reinforcement are accessible only internally to the game. Badges are specific to each game to promote playing of all games. Earned badges are retained for all 8 weeks. Badges are unlocked when achieving a score within the top 10 on any game leaderboard for the current week or month or on the all-time leaderboard; achieving 100% correct answers in all trials on the easiest, normal, and hardest difficulty levels; the user plays the game for the first time; and the user plays the game for the 10th time. Positive messages are used to encourage gameplay. Participants receive 1 of 20 positive messages at the end of each round of a game and the end of each game. Participants also receive positive messages when achieving the milestones presented in Table 2.
4. Competition is in the form of comparison of gameplay to oneself and with all other users via point systems and leaderboards. Leaderboards are categorized as weekly, monthly, and for all time. Scores on the weekly leaderboard are reset at the start of the week, and scores on the monthly leaderboard are reset on the first day of each month to motivate continued gameplay across all 8 weeks.
5. The target group is individuals with a normal weight to obese but otherwise healthy who are seeking to eat healthier.
6. There is no collaboration or goal setting.
7. Regarding narrative, the gamification concept is reset to the starting difficulty at the beginning of each round of new play. Nothing persists from one gameplay to the next. The games adjust in difficulty between each round of the game session depending on performance.
8. Regarding level of integration, the gamification concepts are, for the most part, independent as gameplay could occur without the additional gamification elements. Gamification elements have been introduced to promote gameplay.
9. Regarding user advancement, an adaptive feature increases the difficulty of gameplay based on accuracy and speed of performance. The difficulty and speed level ranges from 0 to 10, with 0 being the easiest or slowest and 10 being the hardest or fastest, with the default difficulty level being 5. Scoring >90% accuracy prompts the game to increase in difficulty, and scoring <70% accuracy prompts the game to decrease in difficulty.

Table 2. Positive messages for attaining milestones.

Milestone	Message
Weekly high score badge	"That is your weekly high score! You're getting better every day."
Monthly high score badge	"Best score yet this month!"
All-time high score badge	"All-time high score! You did very well."
Easy ace (easily completes the low-difficulty level)	"You're learning fast."
Normal ace (easily completes the difficulty level 5)	"What an improvement! You've got it now."
Hard ace (easily completes the high-difficulty level)	"Great improvement! You just aced a hard difficulty level."
Playing the game for the first time	"Thanks for playing the game for the first time. Nice going!"
Playing the game 10 times	"That's the 10th time you've played the game. Keep up the great work!"

Gameplay Pattern

The massed-spaced training effect (playing all the games in a single session compared to playing the games across several days) measures include (1) the mean and SD of the number of days between training sessions; (2) the mode of the number of days between training sessions; and (3) the density index, which is calculated using the model established by Aulbach et al [47], where the number of trials completed on the most active day is divided by the total number of trials. For the first 2 indexes, a greater value indicates greater spacing of training. For the density index, a greater value indicates greater massing of training.

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Questionnaires

Two questionnaires are completed once at the beginning of the study. First, in the demographics questionnaire, participants are asked to report their age, sex, gender identity, ethnicity, weight, height, household income, educational level, marital status, employment status, income (individual and household), and food insecurity. Food insecurity is assessed using the Six-Item Short Form of the Food Security Survey Module [48].

Second, the Weight History Questionnaire assesses self-reported weight and was revised from the Weight History Questionnaire used for the National Health and Nutrition Examination Survey 2011 to 2012. The questionnaire also asks participants to report perceptions of their own weight, such as whether they believe they are over- or underweight or if they want to gain, lose, or maintain their weight. Participants also report their history with weight management, such as their highest past weight and whether they have attempted to lose weight and, if so, how.

There are also several questionnaires that are completed before and after the 8-week EF training intervention. The Automated Self-Administered 24-Hour Dietary Assessment Tool is used to measure food and drink consumption [49]. Participants complete three 24-hour dietary recalls before starting the intervention and 3 upon completion of the intervention. To lessen the day-of-the-week effect, 24-hour dietary recalls are randomly assigned so that 2 are collected on a weekday (Monday-Thursday) and 1 is collected on the weekend (Friday-Sunday). Participants report all meals, snacks, and drinks consumed from lists provided and may add anything they consumed that is not on the list. The number of FV cup equivalents consumed and Healthy Eating Index scores are calculated for each day that participants report their dietary intake to determine the efficacy of the EFfect-food choices training program in altering dietary intake patterns.

The Three-Factor Eating Questionnaire–Revised-18 is used as a measure of how people interact with food [50]. The 3 factors measured include cognitive restraint (eg, “I deliberately take small helpings as means of controlling my weight”), uncontrolled eating (eg, “Sometimes when I start eating, I just can’t seem to stop”), and emotional eating (eg, “When I feel anxious, I find myself eating”). All items are rated on a 4-point scale. Mean scores are calculated for each category.

The Power of Food Scale measures appetitive responsiveness to the rewarding properties of the food environment [51]. The Power of Food Scale is a 15-item questionnaire with a 5-point Likert-type scale ranging from 1 (do not agree at all) to 5 (strongly agree). Items are scored so that a greater score indicates greater responsiveness to the food environment.

The Food Attitudes and Behaviors survey is used to explore potential factors associated with the incorporation of FV into the diet [52]. The Food Attitudes and Behaviors survey measures domains of social support, perceived barriers, perceived benefits, motivation, and self-efficacy of FV consumption.

The transtheoretical model is a theory that posits that people’s behavior change can be classified into 1 of 6 stages, ranging from no intent to change to the change being made and maintained [53]. One scale that assesses this is the Health Behavior and Stages of Change Questionnaire [54]. This scale asks participants to select the stage that represents their stage of change for a variety of health practices, such as physical activity and seeing a nutritionist. For this study, we ask participants to complete the nutrition questions from this scale, which includes modified questions to reflect increasing consumption of FV and decreasing consumption of nutrient-poor foods.

Participants’ health consciousness is measured using a brief 11-item scale [55]. Participants rate the extent to which they agree with statements such as “I’m very self-conscious about my health” and “My health depends on how well I take care of myself.” This measure uses a 7-point Likert-type scale that ranges from 1 (strongly disagree) to 7 (strongly agree) [55].

Self-efficacy, or the belief in one’s own ability to perform a behavior successfully, is measured via the New General Self-Efficacy Scale [56]. This is an 8-item measure that uses a Likert-type scale ranging from 1 (strongly disagree) to 5 (strongly agree).

To ascertain whether “usual stress” impacts the efficacy of EFfect-food choices in increasing EF, participants are asked to complete the Perceived Stress Scale [57]. The Perceived Stress Scale is a brief, 10-item questionnaire that asks participants to indicate the frequency with which they have experienced a range of stress-related emotions during the previous month. This measure uses a 5-point Likert-type scale ranging from 0 (never) to 4 (very often).

Chronic stress is assessed via the English version of the Trier Inventory for Chronic Stress [58] that retains 9 factors derived from 57 items about situational experiences during the previous 3 months. The inventory’s response options are never, rarely, sometimes, frequently, or very often. The short form correlates (r=0.94) with the original Trier inventory [58].

Similar to the methods by Smith et al [59], at each EF testing session, participants’ level of hunger, fullness, thirst, and boredom are measured using a separate on-screen slider cross-modal visual analogue scale (VAS; range from 0 to 10 at 0.1-unit increments) and anchored by 0 (not at all) and 10 (extremely). Desire to eat is assessed using a VAS anchored by 0 (none) and 10 (maximum desire) [59].

Valuation of nutrient-rich and nutrient-poor foods was adapted from the methods by Stice et al [26]. A standard image for each of the 9 fruit types, 13 vegetable types, and 14 nutrient-poor foods was chosen by the investigators to establish a standard deck of 36 assessment images that most closely approximate a similar portion size. The deck of images is randomly sorted into a presentation order that becomes the standard order of presentation for all participants on each test date. Figure 5 shows an example of how liking and valuation are presented to the participants. Valuation of the 36 foods appearing in the images is conducted after at least 2 hours of not eating, in a single session, and one food at a time. With the image of the single food displayed on the screen, participants then use an on-screen slider cross-modal VAS to provide their liking (range from 0 to 10 at 0.1-unit increments) of each of the nutrient-rich and nutrient-poor foods. The VAS is anchored by 0 (not at all) and

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10 (like very much). After clicking on a submit button, the liking scale disappears. A second VAS appears, and participants assess how much they would be willing to pay (range from US $0 to US $20 at US $0.25 increments) for the displayed amount of each of the foods, which have been selected to correspond to commonly consumed serving sizes. Upon clicking on the submit button, the next food appears, and the process is repeated.

The 27-item monetary choice questionnaire by Kirby et al [60] asks the participants to make a choice between a smaller, immediate monetary amount (S) and a larger, delayed monetary amount (L). For example, participants are asked the following: "Would you prefer (a) $19 today or (b) $25 in 53 days?" The 27 items are grouped into 3 categories based on the value of the rewards: small (US $25-$35), medium (US $50-$60), and large (US $75-$85). Discount rates are calculated separately for each category using the syntax by Gray et al [61] to determine whether the size of the reward affects discount rates.

In addition, the System Usability Scale (SUS) is completed once at the end of the study. The SUS is used for online usability surveys and provides a global measure of system satisfaction [62]. The SUS uses a 5-point scale with anchors of 1 (strongly agree) and 5 (strongly disagree). Participants complete the SUS with minor revisions to the wording of several items to make them easier to comprehend [63]. A 1-item adjective scale is added to understand the usability associated with an individual's global SUS score [63].

Evaluation Outcomes

Improvements in response time and percentage correct are indicative of improved EF. EF testing is completed by playing the EFfect-food choices games at the initial (default) speed at both baseline and postintervention testing. Participants complete the EF testing on the same device type (ie, desktop, laptop, or tablet) at baseline and after completing the intervention. Study personnel remind the participants to complete the games on the same device type. The game records the type of device used to play. Records are checked to assess whether the games were played on the same device type at each testing session.

Data Validity

Following the recommendations of Jones et al [64], filtering methods to improve the validity of the data include low-probability (LP) screening questions presented near the beginning of the assessment questionnaire and trap questions placed immediately before the most critical sections of the questionnaire measures. At the beginning of the survey, LP screening questions are used to identify falsely answered screening questions to attempt to qualify for the study and the use of software to auto-complete surveys. In addition to purchasing fruits or vegetables in the previous year (study inclusion criterion), participants are asked to select specific fruits (fresh bananas, strawberries, grapes, apples, watermelon, oranges, blueberries, and peaches) and vegetables (fresh broccoli, cabbage, carrots, cucumbers, peas, peppers, potatoes, and tomatoes) that they have purchased in the previous year. Respondents could also select LP fresh options of fresh mangosteen, red currants, and romanesco broccoli. The very limited availability of these options makes it unlikely that a participant will have purchased 2 of the 3 LP fresh options in the previous year. Per Jones et al [64], "medium" and "high" gaming of the system occur when participants select 2 or all 3 LP options, respectively. A trap question is inserted just before the primary outcome sections of the questionnaire. The trap questions are modeled after the work by Jones et al [64]. The available response options for the trap questions are strongly disagree, disagree, agree, and strongly agree.

Data Quality

The quarantine strategy by Jones et al [64] is used to enhance data quality by flagging those responses for which there has been medium or high gaming via the LP questions and additional failure of a trap question immediately before each questionnaire section. If the aforementioned is true, the data for the sections that do not have a preceding trap question will also be evaluated for threats to validity with quarantining of those sections occurring due to either straight-lining (>40% of all questionnaire sections completed with response nondifferentiation) or "speeding" (mean response completion times for the section of <4 seconds per question). Descriptive statistics will then be determined, and the distribution of each variable will be examined to assess normality. Appropriate transformations based on the distribution will be considered before analysis, as will the assessment of outliers and conduct of sensitivity analyses in which they are omitted or winsorized. Winsorizing is a method of averaging that limits the effect of extreme values and reduces the effect of possibly spurious outliers [65].

Statistical Analysis

Power

On the basis of means and SDs from go/no-go and dot probe task reaction time results by Stice et al [26], the desired power of 0.9 is reached for the pairwise comparison of the control and intervention groups at week 8 for go/no-go and dot probe task response time with 448 participants and 532 participants, respectively. Multiple comparisons used for the power calculations were the Tukey honestly significant difference tests. On the basis of power calculations, data collection will continue up to the collection of complete data from 500 participants. On the basis of the work by Jones et al [64], we expect the data of approximately 15% of participants completing a single-setting online questionnaire to be quarantined. Attrition is also likely across an 8-week study, which we estimate will be another 5% of the participants.

Data Analysis

Analyses will be conducted using SAS (SAS Institute), SPSS (IBM Corp), and Systat (Grafiti LLC). The analytic plan to determine whether the EFfect-food choices training program improves EF as measured via response inhibition and attention bias is to use linear mixed-effects models to assess group changes in EF outcomes from each of the 4 EF games over time. Sex, race, and age will be tested as covariates in models of all primary and secondary outcomes. For each EF outcome variable, the mean scores from the first 3 to 5 sessions at baseline and the mean scores of the last 3 to 5 sessions completed at 8 weeks will be used as data.

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Group and sex differences in rates and proportions of participants violating measures of poor response behavior and of data being quarantined will be assessed using log-linear models. Per the CONSORT (Consolidated Standards of Reporting Trials) guidelines [66], testing of group baseline differences will be based on the "prognostic strength of the variables measured and the size of any chance imbalances that have occurred." Group baseline differences will be tested using statistics appropriate for the level of measurement of the data. Demographic differences between quarantined and nonquarantined participants will also be tested using linear regression or mixed models.

The analytic plan to test the independent and interactive associations between stronger inhibitory and attentional learning and greater reductions in intake of nutrient-poor foods is to use mixed model regression. Variables that are correlated to change in consumption of nutrient-poor foods will be tested as covariates in these mixed models. Establishing dose-response relationships is an important element of establishing the efficacy of an intervention. As such, training time as measured through total time spent playing EFfect-food choices games, total number of sessions completing all 4 EFfect-food choices games, and total number of any of the EFfect-food choices games completed will be tested as predictors of outcomes in the intervention condition.

The analytic plan to determine whether the EFfect-food choices training program improves awareness of dietary choices, positive attitudes toward FV, valuation of FV, and consumption of FV and lowers consumption of nutrient-poor foods and body weight is to use separate mixed models to test differences between groups (control and intervention) and across time (baseline and 8 weeks). EF treatment fidelity and any significant between-group differences in variables that are correlated with outcomes will be tested as covariates in these mixed models. Body weight response data will be tested in all participants and in the subset of participants with a BMI of >25 kg/m^2.

For all models, any significant between-group differences in variables that are correlated with outcomes will be included as covariates in the mixed models. Outcomes will be tested with an intention-to-treat approach using (restricted) maximum likelihood estimation [67] where all participants who are randomized will be included in the data analysis. This approach is associated with more accurate parameter estimates than listwise deletion or last observation carried forward approaches and is appropriate when missingness is correlated with study variables. We will also conduct a completer analysis that includes only those participants who completed the training at least twice per week and the pre- and posttesting.

Results

Participants

Recruitment began in September 2023 and is expected to continue until December 2027 or January 2028. As of June 1, 2025, a total of 899 individuals have applied to participate in the study. Of these 899 applicants, 763 (84.9%) qualified and 630 (70.1%) consented. There have been 386 withdrawals due to noncompliance with study requirements (n=342, 88.6%) or being identified as bots (n=35, 9.1%). A large proportion of those withdrawals (141/386, 36.5%) were due to not completing the preintervention questionnaires. To date, a total of 199 participants have completed all study requirements, with 17 (8.5%) in active gameplay and 27 (13.6%) in postintervention testing.

Study Outcomes

Due to blinding, all data analysis will begin after the last participant has completed all study requirements (anticipated start in January 2028 or February 2028). Results are expected to be published in 2028.

Discussion

Expected Findings

The Dietary Guidelines for Americans recommend regular consumption of FV as part of a healthy dietary pattern [68], yet consumption continues to be below the recommended amounts set forth by these guidelines across all age groups, with few exceptions [68,69]. Much research has been aimed at trying to increase FV consumption, with limited success. Intervention studies that provide participants with an allotment of FV demonstrate that FV consumption can be increased [70-72]. However, after the intervention is completed and FV are no longer provided, most return to habitual levels of consumption. This is likely because incentive sensitization does not readily occur with repeated vegetable consumption in adults [72]. Therefore, interventions that target the decision-making process may produce longer-lasting results.

A driver of healthy food choice is executive control in environments in which nutrient-poor foods are widely available and heavily advertised. Research suggests that EF training can help improve self-regulation, decision-making, and impulse control, potentially leading to healthier eating habits [28,29,73,74]. As such, EF training is emerging as a promising new method to change eating behaviors that provides a distinct advantage over other, more traditional interventions [75-78]. EF training may lead to more intrinsic motivation, strengthening the capacity to form and maintain healthy habits, resulting in more enduring behavior changes due to enhanced self-regulation capabilities.

To date, there are no examinations of longer-term cognitive training on eating behaviors. This project will fill this gap and be the first to use EF training targeting inhibitory control and attention bias as an intervention tool to increase valuation and consumption of FV. We expect that the EFfect-food choices training program will increase participants' ability to reduce their selection of nutrient-poor food options and redirect their attention to FV.

Potential Impact and Significance

The broader public health impact of the proposed EFfect-food choices program could be significant. By enhancing EF, individuals may become better equipped to make healthier food choices, especially in the context of FV consumption. This may lead to the development of healthier eating habits that persist

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over time, thereby creating a "culture of healthy dietary choices." As participants engage in healthier eating behaviors, they might experience improvements in mood, anxiety, and overall mental wellness. The online format of the program allows for widespread accessibility, possibly reaching underserved populations who may have limited access to traditional health interventions. This can help bridge health disparities among different demographic groups. The ability to change the images means that the platform can be implemented among populations with limited access to fresh produce by using images of the types of FV that are locally available.

Limitations

This study is entirely web based, which is a key strength but also the primary limitation. This study provides a unique opportunity to conduct a randomized controlled trial in a nationally representative group and decreases the potential of observer bias (Hawthorne effect) [79]. The key limitation to conducting this web-based study is ensuring compliance with study requirements. However, the EFfect-food choices program records gameplay and generates a weekly report that can be used to send reminder emails to stay on track with gameplay requirements. Another potential weakness is that the pre- and posttesting may not be conducted on the same device type (ie, desktop, laptop, or tablet), operating system, or browser, which could add variability to the response data. Bridges et al [80] found that, when removing the intertrial variability in response times due to a human user, reaction times varied across browsers but precision within a software package, operating system, and browser combination was small and within the range of 0.2 to 5.0 ms. This study was powered on a between-group reaction time difference during the go/no go task of 33 ms, much greater than the variability reported by Bridges et al [80]. Initial instruction and the reminders provided before each testing session should increase adherence to using the same device and browser, although this cannot be strictly enforced. The device type used by each participant for each testing session is recorded and will be tested as a covariate in statistical models. The reaction time data will be averaged across trials, which should minimize the effect of variability in response times due to the platform, operating system, browser, and device combinations on statistical results [80]. Another potential limitation is that the use of weight control medications is not considered as an exclusion criterion. Weight loss or gain of >4.5 kg over the previous 3 months is an inclusion criterion, and enrolled participants will complete a weight history questionnaire that gathers data on weight control attempts and how the participant tried to change their weight. In addition, response bias (ie, social desirability and demand characteristics) may limit the reliability of the findings. The large sample size and the anonymity that comes from conducting a study completely online will minimize participant bias and increase the accuracy of the results. It is also well known that self-reported dietary intake can be inaccurate, although the fact that we are using a placebo control condition should result in similar bias in both conditions. Finally, our training delivery, individual differences, engagement, contextual factors, and cognitive load may limit the impact of EF training on our outcome measures. The questionnaires that participants complete immediately before and after the EF training will provide an insight into limitations and allow us to determine how these moderate the effect of the EF training.

Conclusions

The relationship between EF and healthy behaviors may be key to improving diet quality given the obesogenic environments that many Americans are exposed to everyday. If shown to be effective, the EFfect-food choices program will provide a platform that can be used to increase FV consumption and, thus, improve diet quality. The capability of this EF training program to be broadly implemented via the internet will greatly expand the reach of interventional studies designed to aid individuals in food-related decision-making. The program allows for weekly planned training and timely training before anticipated exposures to environments that may require enhanced executive control to promote healthier food choices. This type of intervention can readily be made available to the public.

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Data Availability

The data, codebook, and analytic code will be made available from the corresponding author on reasonable request after the study has concluded and all manuscripts have been published.

Authors' Contributions

JNR, ES, and SLC developed the study. JNR led and ES, SLC, AMN, DGP, and JMH contributed to the development and writing of the study protocol. DGP will conduct the analyses. SLC wrote the first draft of this manuscript. JNR led the revisions and provided the additional writing necessary to meet the needs of the subsequent 2 manuscript drafts and of the submitted version

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of the manuscript. All authors contributed to and commented on all versions of the study protocol and this manuscript. All authors approved the final version of this manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
EF: executive function
FV: fruits and vegetables
LP: low-probability
NRF: nutrient-rich food
SUS: System Usability Scale
VAS: visual analogue scale

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Protocol

Potential of the World Health Organization's Skin NTDs App to Support and Improve the Detection of Skin-Related Neglected Tropical Diseases: Protocol for a Performance Evaluation and Feasibility Study in Senegal

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Abstract

Background: The World Health Organization (WHO) roadmap aims to control, eliminate, or eradicate neglected tropical diseases (NTDs) by promoting innovation in prevention, diagnosis, and treatment. In this context, mobile health (mHealth) tools could play an important role in improving health care across the globe, including for skin-related NTDs. One such tool is the WHO Skin NTDs App (currently available in its beta version), which utilizes artificial intelligence (AI) algorithms to classify skin lesion images and offers diagnostic suggestions and management information to bolster early detection at primary care levels. However, to harness the full potential of this and similar mHealth tools, additional insights into their diagnostic performance and potential implementation avenues in settings with limited access to trained dermatologists are essential.

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Objective: The objective of our mixed methods study is to test the functionality, operability, and potential of the AI-supported diagnostic component of the WHO Skin NTDs App (beta version) to support the detection of skin NTDs and common skin conditions in Senegal.

Methods: We are conducting a diagnostic accuracy study combined with a qualitative preimplementation usability exploration. For the quantitative component, we will collect and analyze approximately 800 skin lesion images from patients presenting to the dermatology unit at the Thiès regional hospital in Senegal. Each lesion will be independently assessed by the AI-based WHO Skin NTDs App and by a dermatologist who will provide a diagnosis serving as the reference standard. Performance metrics, including accuracy, sensitivity, specificity, precision, F_1-score, and area under the receiver operating characteristic curve, will be calculated for each diagnostic category to evaluate the app's ability to detect skin-related NTDs. In parallel, we will conduct semistructured in-depth interviews with a purposive sample of 70-80 stakeholders, including policymakers, health care workers, community leaders, dermatologists, and members of leprosy-affected communities. Interviews will explore perceptions of the app's usability, acceptability, and potential barriers and facilitators to its adoption within Senegal's health system. Thematic analysis will be used to interpret qualitative data. Findings will help inform the design of an app-based intervention to be piloted in future community-level studies.

Results: We expect the results to provide detailed insights into the feasibility and potential of the WHO Skin NTDs App to support and improve the detection of skin NTDs and common skin conditions at the community level in Senegal. We started data collection in August 2024, with the first results expected to be available in 2025.

Conclusions: Our study will assess the performance and potential use of the WHO Skin NTDs App to detect skin NTDs and common skin conditions in Senegal, outlining its potential role in supporting early diagnoses and enhancing public health responses.

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KEYWORDS

cutaneous; skin health; diagnostic; artificial intelligence; AI; image recognition; mobile health; mHealth; performance evaluation; community; capacity building; zero leprosy; qualitative research; quantitative research; West Africa

Introduction

Background

Neglected tropical diseases (NTDs) are estimated to affect more than 1 billion people worldwide, mostly in low- and middle-income countries [1]. With the NTD burden disproportionately high in disadvantaged communities, NTDs are rarely a priority in national and international health agendas or in the development of novel diagnostic tools or treatments [2]. To catalyze efforts, the World Health Organization (WHO) in 2020 set global targets to control and end the burden of NTDs by 2030 [1].

Skin NTDs are a subgroup of NTDs that manifest in lesions on the skin and can be detected by visual screening [3]. However, trained health care professionals who can reliably detect and diagnose such conditions are rare in many of the most affected settings [4]. Technological advancements are now promising to bridge this gap, especially in remote populations with limited access to resources [5-7].

In 2023, the WHO integrated 2 artificial intelligence (AI) algorithms into their existing WHO Skin NTDs App. Using a convolutional neural network approach, the algorithms classify images to identify skin conditions. Integrating AI into the app aims at further supporting frontline health workers in efforts to detect skin NTDs and other skin conditions at early stages of manifestation [8]. The app allows users to take images of a skin lesion on their smartphone and provides them with a list of potential diagnoses. The app uses 2 AI algorithms in a cascade. The first algorithm (Broad Skin Condition Screener) classifies images across 24 common skin conditions, included as individual diagnoses, and one group covering all 12 skin NTDs. If a skin NTD is flagged, the second algorithm (Skin NTD Classifier) identifies which of the 12 NTDs is most likely present (see Figure 1) [9]. Although the use of the AI component requires internet connection, images can be stored offline and uploaded at a later stage. Beyond the AI algorithm, the app also features an offline diagnostic decision tree with branching logic to assess symptoms, and app users can access a general learning section on skin conditions. Previous research has outlined the user-friendliness of these offline features, as well as their potential role in frontline health worker capacity building [10].

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Figure 1. Coverage of algorithms included in the World Health Organization (WHO) Skin NTDs App (beta version). *The Broad Skin Condition Screener algorithm does not differentiate between the 12 skin NTDs included in this category. Instead, if this category is flagged, users are recommended to use the Skin NTD Classifier for specific diagnosis suggestion. **During app development, Noma was not considered a skin NTD. In December 2023, the WHO changed their assessment and included Noma on their list of NTDs. NTD: neglected tropical disease.

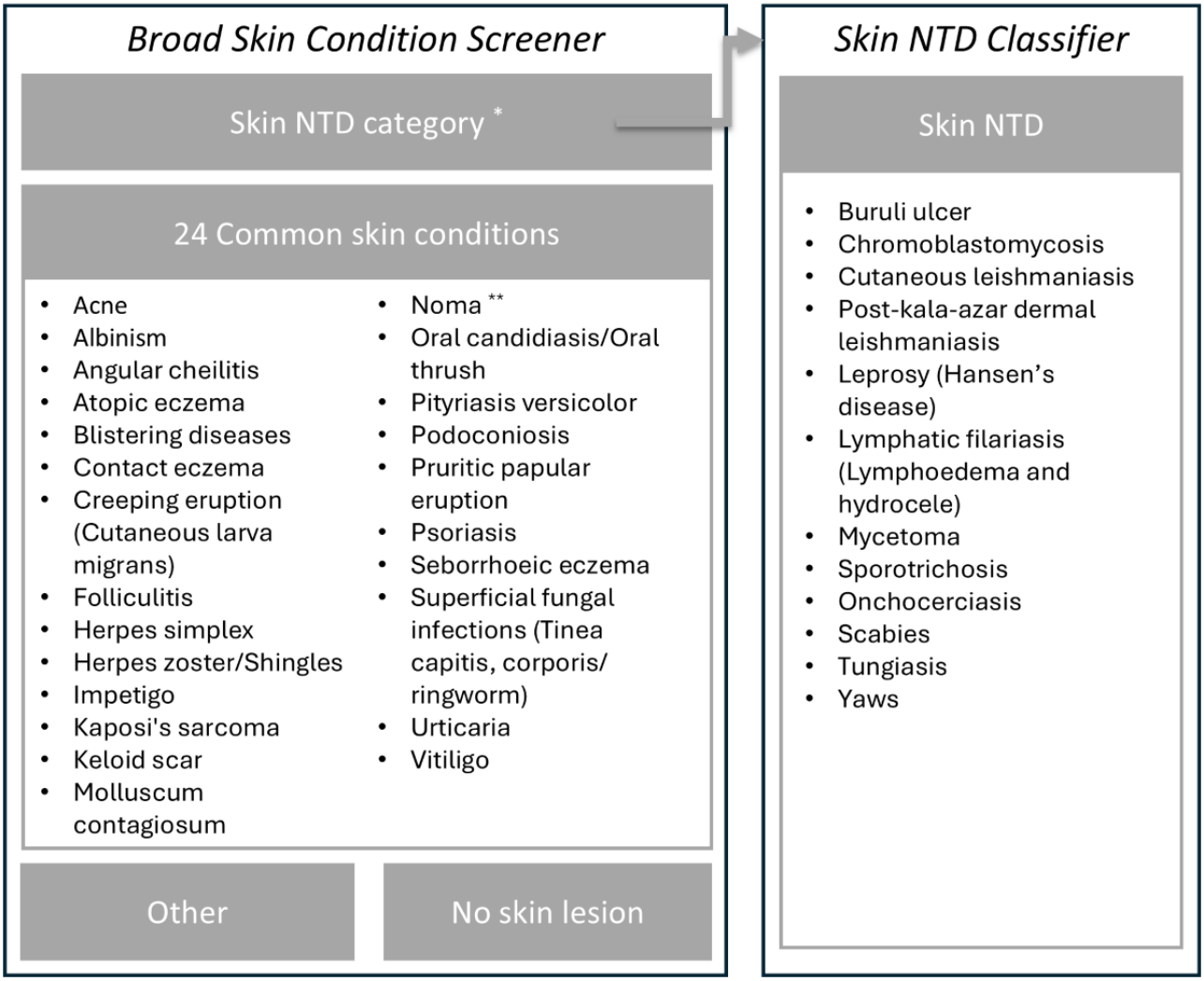

The free-of-charge availability of the overarching Skin NTDs App presents a promising opportunity for large-scale implementation in resource-poor settings. However, the AI algorithm component so far has not been tested extensively in real-world applications [8]. Parallel to this study, the AI component is undergoing a first assessment in Kenya, with results expected before the end of 2025. Evaluations of other AI algorithm-based image analysis models for diagnosis have highlighted how performance differs across screened populations [11]. In general, variations in demographic characteristics, skin tones, and both the severity and complexity of skin conditions are likely to influence the detection accuracy [12]. Insights into potential avenues for implementing such algorithms in real-world detection efforts and for their integration into national programs are lacking [8].

To address these gaps, we will evaluate the performance of the WHO Skin NTDs App in the Senegalese setting. To assess the feasibility and acceptability of the app's implementation, we are conducting qualitative interviews with stakeholders along the care cascade in Senegal. This is particularly critical for skin NTDs such as leprosy, where stigmatization of patients raises questions on the use of diagnostic tools at the community level [13,14]. Although early case detection might prevent disability and mitigate future stigma and psychological burden, maintaining diagnosis confidentiality is critical to protect patients.

Study Objectives

The objective of our study is to investigate the potential of the AI component of the WHO Skin NTDs App (beta version) to support and improve the detection of skin NTDs and common skin diseases in Senegal. We will (1) evaluate the performance of the WHO Skin NTDs App algorithm in the detection of skin NTDs and common skin diseases and (2) qualitatively explore the feasibility and potential avenues for integrating the app into NTD detection processes at the community level. Our results will provide recommendations for the integration of this and similar tools into broader public health strategies to enhance the diagnosis and management of skin NTDs in Senegal and beyond.

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Methods

Study Design

This study will combine quantitative and qualitative methods to evaluate the performance and potential of the novel AI diagnostic component of the WHO Skin NTDs App in the Senegalese context. This study protocol has been developed in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (Multimedia Appendix 1).

The quantitative component will evaluate the performance of the AI algorithms integrated into the current beta version of the WHO Skin NTDs App. We will compare the algorithms' suggested skin conditions with the diagnosis made by a dermatologist in the dermatology department of the Thiès regional hospital center.

The qualitative component aims at exploring the barriers, facilitators, and potential avenues for a larger scale implementation of the WHO Skin NTDs App. To this end, we will collect qualitative data from a range of key stakeholders, including policymakers, leaders and members of leprosy-affected communities, and medical professionals. Results are meant to inform the subsequent refinement of the app and the design and pilot testing of an intervention prototype.

Study Setting

Skin NTDs are a major public health issue in Senegal, particularly in rural and underserved areas. The key skin NTDs in the country include Buruli ulcer, leprosy, yaws, onchocerciasis, cutaneous leishmaniasis, and scabies, which can lead to long-term disabilities, social stigma, and mental health challenges [1]. In Senegal, the management of NTDs is overseen by the National NTD Control Program, which is under the Directorate of Disease Control within the General Directorate of Public Health of the Ministry of Health and Social Action. To address skin NTDs, a multi-stakeholder approach is employed, which includes nongovernmental actors (eg, Action Damien, Raoul Foundation, DAHW), universities (Thiès, Dakar, Ziguinchor), and various government bodies. The focus of these stakeholders includes disease prevention, medical treatment, research, disability prevention, and rehabilitation.

Compared to other skin NTDs in Senegal, leprosy stands out due to its association with a long-standing isolation policy in the country. Although effective treatment and cure has been available since the 1980s, a law mandating the establishment of 9 social reclassification villages to isolate patients with leprosy was not repealed until 2023 [8,15]. As such, the discriminating character of the previous isolation policy continues to shape leprosy perception and stigma in Senegal. Many former social reclassification villages continue to exhibit active transmission, making them focal points of leprosy prevention activities in Senegal [16-18].

The Thiès regional hospital center, the study site for the quantitative evaluation of the app, is located approximately 70 km from Dakar in the regional capital of Thiès. As of 2023, the health system in the region serves approximately 2,340,000 inhabitants via a network of 335 health huts, 243 health posts, 10 private clinics, and 9 health centers [19]. Of the region's 5 hospitals, 3 are public and 2 are private. Approximately 70% of the health posts are public [20]. The dermatology department of the Thiès regional hospital center, established in 2002, consists of a consultation room, a treatment room, a secretariat, and a hospitalization unit with a capacity of 9 beds. The department is staffed by 3 dermatologists, who consult with an average of 350 patients per week.

Quantitative Component: Performance Evaluation of the AI Algorithm

Eligibility Criteria

The target population of this component will include any patient seeking treatment for a skin condition at the dermatology department of the Thiès regional hospital center during the study period. This also includes patients referred to the dermatology department from other departments or health facilities. Further inclusion criteria are (1) aged 1 year or older and (2) visible skin lesion on an unidentifiable part of the body. To maintain anonymity of patients, we therefore exclude patients with lesions on the face, fingers, or on or near identifiable scars or tattoos.

Sample Size Calculation

Based on the sample size calculation for proportions, we determined that a sample size of 385 images is required to achieve a 95% confidence level with a margin of error of SE 5%, assuming an expected accuracy rate of 75%. In the absence of published performance metrics or internal validation results from the AI algorithm developers, we selected 75% as a conservative estimate of the algorithm's expected accuracy for the purpose of sample size determination. We conservatively increase our target sample size from 385 to 800 to account for potential exclusions of images due to quality or identifiability concerns and to improve statistical power and robustness.

Recruitment and Data Collection

We will collect the images of skin lesions within the dermatology department of the Thiès regional hospital. Using the mobile survey tool Kobo Collect, we will take a picture of the skin lesion from every eligible patient. We will further record the diagnosis made by the dermatologist. We will further collect images of healthy skin from patients, defined as skin being free from dermatological lesions. Data will be collected by a researcher with medical university training. Skin lesion images and dermatologists' diagnosis will then be linked to the suggested skin conditions from the WHO Skin NTDs App (see Figure 1). All images will be stored on a password-protected server, with access restricted to principal investigators and authorized researchers, ensuring participant data privacy and security.

Outcome Measures and Data Analysis

In our primary quantitative analysis, we will first evaluate the performance of the WHO Skin NTDs App's AI component in detecting whether a skin condition belongs to the broader category of skin NTDs. Specifically, we will assess the Broad Skin Condition Screener, the first of the 2 AI algorithms. We will use the dermatologist's diagnosis as the reference standard and calculate the following performance metrics:

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1. Accuracy: proportion of total cases correctly classified as skin NTDs or skin conditions not caused by NTDs.
2. Sensitivity (recall): proportion of actual skin NTD cases correctly identified by the algorithm (true positive rate).
3. Specificity: proportion of skin conditions not caused by NTDs correctly identified as such (true negative rate).
4. Precision: proportion of cases identified as skin NTDs that are truly skin NTD cases (positive predictive value).
5. F_1-score: harmonic mean of precision and sensitivity, providing a balanced measure of the algorithm's ability to detect skin NTDs while minimizing false positives.
6. Area under the curve: the algorithm's ability to distinguish between skin NTD and skin conditions not caused by NTDs, derived from the receiver operating characteristic curve.

We anticipate a degree of class imbalance in our dataset, with skin NTDs being less prevalent than common non-NTD conditions. To mitigate potential bias from this imbalance, we will emphasize the F_1-score. All performance metrics will be reported with 95% CIs, estimated using bootstrap resampling to reflect the uncertainty around our estimates. Our definition of correct prediction is as follows.

1. True positive: an image with any skin NTD is correctly classified as being a skin NTD.
2. True negative: an image without a skin NTD is correctly classified as not being a skin NTD.
3. False positive: an image without a skin NTD is incorrectly classified as being one.
4. False negative: an image with a skin NTD is incorrectly classified as not being one.

We will assess the performance across 3 levels of AI prediction output from the app.

1. Top 1: only the app's single most likely diagnosis is considered.
2. Top 3: the app presents its 3 most likely diagnoses.
3. Top 5: the app presents its 5 most likely diagnoses.

A prediction will be considered correct if the dermatologist's diagnosis appeared anywhere within the top 1, top 3, or top 5 predictions. Sensitivity will improve as more predictions are considered, but this comes at the cost of diagnostic precision, as it becomes less clear which suggestion should be acted upon. In our analysis, we will not assess the confidence score or rank the order of the predictions; we will focus solely on whether the correct diagnosis was present within the predicted set.

In cases where the dermatologist provides multiple diagnoses for a lesion (eg, cross-infections), all listed diagnoses will be considered valid labels during evaluation; for instance, if both acne and a skin NTD are noted, the image will be labeled as a skin NTD when assessing the algorithm's ability to detect skin NTDs.

We will apply the same approach to evaluate the performance of the second algorithm—the Skin NTD Classifier—which is intended to be used only when a skin NTD is suspected based on the output of the first algorithm or the clinician's judgment. For this analysis, we will include only images diagnosed by the dermatologist as one of the 12 skin NTDs covered by the app, excluding all images of conditions not caused by NTDs. This restriction is necessary because the Skin NTD Classifier algorithm does not offer a "no diagnosis" or "not a skin NTD" option; it always returns one of the 12 disease labels, even if none are appropriate. As a result, specificity cannot be meaningfully assessed unless the input is a confirmed case of one of the 12 target conditions.

In a secondary analysis, we will assess the Skin NTDs classifier algorithm's performance across the full sample, including both skin lesions and healthy skin. Healthy skin images will be treated as cases with no condition to evaluate the algorithm's ability to avoid false positives in the absence of disease. We will not include healthy skin images in the evaluation of the second algorithm, which assigns a diagnosis from a fixed list regardless of input. As it does not offer a "no condition" output, specificity cannot be meaningfully assessed in this context.

Qualitative Component: Feasibility and Acceptability of WHO Skin NTDs App Implementation

Eligibility Criteria

The intended populations for this work package are key stakeholders on community, national, and international levels who can provide insights into the feasibility and acceptability of the WHO Skin NTDs App in the Senegalese setting and who can ideate potential use cases of the app, including their respective chances and challenges. These stakeholders, who have to be at least aged 18 years or older and provide written informed consent, will belong to one of the following groups:

1. Policymakers: including representatives of the Ministry of Health, department administrators, and officials on national or local levels involved in decision-making processes for the implementation of health interventions or the treatment of skin diseases in their respective settings.
2. Community leaders: including local and religious leaders, as well as other key stakeholders on community level.
3. Health care providers: including community-level health workers, clinical staff, and doctors working with patients who have skin diseases in the study setting.
4. Patient representatives: including former patients as well as members of patient advocacy groups on local and national levels.
5. Community members: including individuals screened as part of large-scale skin NTD screening efforts.
6. Representatives of nongovernmental organizations and the civil society: including stakeholders involved in the design and deployment of mobile health (mHealth) interventions, in skin disease awareness, diagnosis, and treatment initiatives in Senegal.
7. Software developers: including individuals working on improving this and similar mHealth apps.

Sample Size Estimates

The total number of interviews will be based on the principles of saturation (when additional interviews cease to fundamentally provide new themes or new information) [21] and information power [22]. Based on previous experiences in this and similar contexts, at this point in time, we estimate up to 80 interviews across all respondent groups (approximately 40-50 interviews

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with community members, 10-15 interviews with frontline health workers involved in screening activities and care, and 20 interviews with other stakeholders).

Recruitment and Data Collection

Participants will purposively be sampled to ensure a broad range of perspectives and backgrounds and to maximize the depth of information collected [23]. Community members screened as part of larger skin NTD detection efforts will include individuals with and without a skin NTD diagnosis and will be purposively recruited during and after screening campaigns. Local trusted frontline health workers will establish contact to community members and facilitate rapport. Local decision-makers, frontline health workers, and community leaders will be contacted and recruited through their respective office's official communications channels or through channels established by study team members and partner organizations. If necessary, we will use snowball sampling to identify other potential participants [24].

If contacted individuals are interested in participating, we will provide them with detailed information about the study and schedule a date and time for the interview based on their preferences. Before the interview, we will obtain their informed consent, either in person by signature/fingerprint (if the interview takes place in person) or by digital signature (if the participant prefers the interview to take place via video call).

Qualitative data for this component will be collected via in-depth interviews by using a semistructured interview guide, which will be pilot tested at the start of data collection. Interviews with frontline health workers may also include think-aloud exercises (to further gain practical insights into app engagement) and shared walk components (in which respondents are invited to show locations featuring prominently in their accounts to the interviewer). All interviews will be conducted by trained research assistants in French or Wolof at a place and time of the participant's choosing and will be audio-recorded. Table 1 summarizes the quantitative and qualitative components of our study.

Table 1. Data collection tools to assess the feasibility and potential of the World Health Organization's (WHO's) Skin NTDs App to support the detection of cutaneous neglected tropical diseases at the community level in Senegal.

Data collection type	Data collection instrument	Population and recruitment	Sample size (n)	Estimated duration (min)	Timing of data collection
Quantitative	Survey	• Patients[a] • Individual[b] • Dermatology department of Thiès hospital[c] • Census[d] • Patient ≥1 year[e]	800	10	Q3 2024 to Q1 2025
Qualitative	In-depth interview guides	• Policymakers, community leaders, health care providers, community membersa • Individualb • Senegal, international (WHO)[c] • Purposived • Adult men and women aged ≥18 years who provide written informed consente	~70-80	45-60	Q3 2024 to Q3 2025

[a]Population.
[b]Observation unit.
[c]Sampling unit.
[d]Sampling method.
[e]Eligibility.

Data Analysis

Qualitative data analysis will start during data collection via systematic debriefings at regular intervals [25]. Audio recordings of interviews will be transcribed verbatim (potentially employing automated transcription using VINK [from voice to ink; an automated transcription tool] [26], followed by in-depth manual quality checks and corrections) and translated into English. Qualitative data will be analyzed thematically, for example, based on the tenets of the framework approach [25].

Epistemologically, our qualitative component is informed by a constructivist understanding, and we will draw on established guidance and best practices to ensure the quality and rigor of our work, including via the principles set forth by Lincoln and Guba [27], Tracy and Hinrichs [28], and Tracy [29]. We will also triangulate insights across (1) data collectors and analysts representing a range of both emic and etic perspectives (via systematic debriefings, regular team meetings, and collaborative analysis), (2) respondent groups (representing health system supply and demand sides, as well as various decision-making levels), and (3) interviewing techniques (including semistructured interviews, think-aloud exercises, and shared walk components).

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In line with this constructivist understanding and the explorative nature of our work, we did not design data collection tools based on specific implementation science frameworks such as the Consolidated Framework for Implementation Research [30] or the RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) framework [31]. Similarly, at this point, we do not aim for a purely deductive analytic approach based on predefined framework components. Instead, we will combine inductive and deductive facets: based on aspects that are inductively identified both during data collection and familiarization with the full dataset, as well as in the available literature, we plan to develop and iteratively apply a thematic codebook. The subsequent interpretation of insights from the coded data will then be supported by frameworks, theoretical concepts, and theories as applicable.

Subsequent Intervention Prototype Development and Pilot Testing

The results from both quantitative and qualitative components are meant to subsequently inform the refinement of the WHO Skin NTDs App and similar tools, as well as the development of an intervention prototype for utilizing the app in the Senegalese context. The exact format of the intervention, timelines, qualitative design data collected over the course of prototype development, as well as pilot testing approaches depend on the outcomes of the performance and feasibility evaluations and will be outlined in future publications.

Ethical Considerations

This study was approved by the National Ethics Committee for Health Research in Senegal (SEN24/22) and the Ethics Commission of the Medical Faculty Heidelberg (S-132/2024), Germany. No exemptions or waivers were granted. Prior to enrollment, participants will receive detailed verbal and written information about the study. Written informed consent will be obtained from all participants. Participation is voluntary, and participants may opt out of the study at any time without consequence. For secondary analyses, the original informed consent and ethics approvals cover the use of collected data without requiring additional consent. The data will be deidentified before analysis and securely stored in a password-protected file and on a password-protected computer. As the WHO Skin NTDs App itself will not be used to diagnose patients or in the dermatology department, we do not anticipate additional risks or burdens related to false positives or misdiagnoses associated with this study.

Results

Data collection started in August 2024 and is planned to be completed by September 2025. First quantitative and qualitative results are expected to be submitted for publication by the end of 2025.

Discussion

This mixed methods study aims to assess the performance of the novel AI component to be integrated in the WHO Skin NTDs App and to explore its potential to support skin disease detection at the community level in Senegal. The performance assessment will be performed in the dermatology department of the regional hospital of Thiès, where we will collect images of skin lesions and the corresponding gold standard diagnosis. We will use these data to assess the performance of the WHO Skin NTD App's algorithms in detecting skin NTDs and common skin diseases. In the study's qualitative component, we will conduct in-depth interviews with community, national, and international stakeholders to explore potential use cases of the app to support skin NTD detection in Senegal. The results from these 2 components will subsequently inform the refinement of the app and the development and pilot testing of a community-level intervention.

The availability of mHealth tools using AI image recognition in resource-limited settings is expected to bolster the early detection of skin diseases [8]. Nevertheless, variations in demographic characteristics, skin tones, and the severity and complexity of skin conditions are likely to affect the detection accuracy in real-world application [11,12], but real-world evaluation data remain limited. Our study contributes to filling this gap by providing a performance evaluation combined with the exploration of potential use cases for the WHO Skin NTDs App featuring an AI-based image recognition component.

Although our study, to the best of our knowledge, provides the first comprehensive evaluation of the WHO Skin NTDs App in a francophone context, our performance evaluation will be limited to skin conditions presented at the dermatology department in the regional hospital in Thiès, Senegal. Skin condition prevalence likely differs from that in other regions in Senegal or other countries. Further, the potentially low prevalence of certain skin-NTD conditions in our sample might limit our ability to evaluate the algorithms' performance on all skin conditions.

We expect our results to enable informed decision-making on the potential use of the WHO Skin NTDs App to support early skin NTD diagnosis in Senegal, particularly in regions with limited access to dermatologists. By providing insights into the potential benefits and risks associated with the app implementation, we aim to inform the development of context-sensitive use cases of the WHO Skin NTDs App and similar tools in Senegal and beyond.

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Data Availability

The final dataset used and analyzed for this study will be available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization: DS, DJ, PD, JW, LP, CK, TB, MD
Methodology: DJ (lead, quantitative), JW (lead, qualitative), PD, TB, JARP, CC
Ethics approval: MD (Senegal, lead), DJ (Germany, lead)
Formal analysis: DJ (lead, power calculations), TB (supporting)
Investigation: DS, DJ, JW, PD
Project administration: MN (Germany, lead), CR, MD (Senegal, lead)
Data curation: DJ, JW
Visualization: JW
Resources: PD, GB, MC
Supervision: MD, TB
Funding acquisition: DJ, JW, LP, CK, TB
Writing – original draft: DS (lead), DJ (lead)
Writing – review & editing: DJ (lead), JW (supporting), all authors (review)

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT checklist.
[PDF File (Adobe PDF File), 143 KB - resprot_v14i1e69420_app1.pdf]

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Abbreviations

AI: artificial intelligence
mHealth: mobile health
NTD: neglected tropical disease
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
VINK: from voice to ink
WHO: World Health Organization

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Protocol

Efficacy and Safety of Acupuncture at Sensitized Acupoints for Knee Osteoarthritis: Protocol for a Multicenter, Single-Blind Randomized Controlled Trial

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Abstract

Background: Knee osteoarthritis (KOA) is a prevalent osteoarthritic disorder. Although acupuncture is increasingly used in clinical practice for KOA management, its efficacy remains to be further optimized.

Objective: This trial aims to evaluate the efficacy and safety of acupuncture at sensitized acupoints for the treatment of KOA.

Methods: We will recruit 350 patients diagnosed with KOA from 3 clinical centers in this single-blind, sham-controlled, randomized controlled trial. Participants will be randomized to receive either acupuncture at 5 high-probability sensitized acupoints or sham acupuncture with nonpenetrative needling using Takakura acupuncture simulation devices. Both groups will receive 24 sessions over 8 weeks, followed by a 16-week posttreatment follow-up period. The primary outcome is the proportion of responders, defined as a reduction of 2 or more points in the Numeric Rating Scale score at week 8. Secondary outcomes include changes in scores on validated scales for KOA severity, walking distance, disability, depression, anxiety, insomnia, and pain self-efficacy. Adverse events will be documented for safety evaluation.

Results: The first participant was enrolled on February 15, 2025, and by June 28, 2025, we had enrolled 25 patients. Data analysis has not yet been initiated. The completion of data collection is anticipated by March 2026.

Conclusions: This trial aims to provide confirmatory and exploratory evidence regarding the efficacy and safety of sensitized acupoint-based acupuncture for treating KOA. If the hypothesized benefits are substantiated, sensitized acupoint-based acupuncture could emerge as a complementary and alternative therapy for KOA, potentially reducing reliance on medication and mitigating drug-related adverse effects.

Trial Registration: ClinicalTrials.gov NCT06805188; https://clinicaltrials.gov/study/NCT06805188

International Registered Report Identifier (IRRID): DERR1-10.2196/77336

(JMIR Res Protoc 2025;14:e77336) doi:10.2196/77336

KEYWORDS

randomized controlled trial; knee osteoarthritis; acupuncture; acupoint sensitization; efficacy; safety

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Introduction

Background

Knee osteoarthritis (KOA), which is a prevalent chronic degenerative joint disorder, severely impairs the functional capacity and quality of life of affected individuals. As a primary cause of disability among middle-aged and older adult populations, the incidence of KOA has risen significantly because of global demographic aging trends [1,2]. Epidemiological studies indicate that approximately 40% of individuals aged 50 years or older exhibit symptomatic KOA, with the prevalence increasing to 60% among those aged 65 years or older [3]. Notably, the increasing prevalence of obesity and sports-related injuries has contributed to a growing incidence of KOA in younger cohorts [4]. This trend is reflected in the rising use rate of total knee arthroplasty (TKA) among younger patients, whose proportion among all TKA procedures increased from 38.4% (2001-2005) to 42.7% (2006-2010) [5]. In addition to causing persistent pain and functional impairment, KOA imposes substantial socioeconomic burdens, with annual direct and indirect health care expenditures reaching US $136 billion in the United States [6] and US $12.1 billion in China [7]. Moreover, KOA is frequently associated with comorbidities, such as depression, anxiety, and cardiovascular diseases, further compromising patients' quality of life [8,9].

Current guideline-recommended management strategies for KOA primarily include pharmacological interventions, exercise therapy, and surgical options [10], all of which are associated with inherent limitations and adverse effects. Pharmacotherapy, as the most frequently used conservative approach, includes nonsteroidal anti-inflammatory drugs, analgesics, and corticosteroids. Although these agents provide short-term relief from pain and inflammation, their prolonged use elevates the risk of adverse reactions, such as gastrointestinal hemorrhage, renal impairment, and cardiovascular events [11,12]. A large-scale meta-analysis demonstrated that long-term nonsteroidal anti-inflammatory drug administration increases the risk of cardiovascular events by 20% to 50% [11]. Opioid use in KOA management remains restricted in international guidelines because of addiction potential and severe side effects [13,14]. With respect to exercise therapy, Cochrane systematic reviews indicate that while exercise interventions achieve short-term improvements in pain and functional capacity among patients with KOA, their long-term efficacy remains inconclusive [15,16]. Suboptimal adherence also substantially compromises therapeutic outcomes; studies report that 40% to 50% of patients with KOA discontinue long-term exercise regimens [17]. For advanced KOA, surgical interventions, such as TKA, may be indicated. However, perioperative risks and substantial postoperative care costs limit accessibility [18]. Approximately 20% of patients who have TKA experience persistent postoperative pain [19]. In addition, finite prosthesis longevity necessitates potential revision surgeries for younger patients, thereby increasing complication risks [20].

Given the limitations of routine therapies, identifying safe and effective alternative or adjunctive interventions for KOA has become imperative. Acupuncture, a core therapeutic modality within traditional Chinese medicine, has been used for centuries in pain management with broad clinical applications [21]. The proposed mechanisms underlying acupuncture analgesia include promoting local circulation, reducing inflammatory responses, modulating neuroendocrine function, and activating endogenous pain-inhibitory pathways [22,23]. Preclinical studies suggest that acupuncture may alleviate articular inflammation by downregulating proinflammatory cytokines, such as tumor necrosis factor-α and interleukin-1β [24]. Neurophysiological investigations have indicated that acupuncture mediates analgesia through central modulation of pain pathways, particularly by activating descending inhibitory systems [25]. Furthermore, emerging evidence suggests that acupuncture may influence KOA progression through regulation of gut microbiota, suggesting novel directions for mechanistic research [26].

Although several randomized controlled trials (RCTs) have explored the efficacy of acupuncture for KOA [25,27-29], their limitations preclude definitive conclusions. For instance, they used shallow needling as a sham acupuncture control, despite evidence that shallow needling may produce substantial therapeutic effects [30]. Additional limitations include predominantly single-center designs with insufficient sample sizes, unvalidated blinding results, and short follow-up periods that fail to capture sustained treatment benefits. To address these gaps, we propose a rigorously designed, large-scale, multicenter RCT to evaluate acupuncture's efficacy in KOA. This trial will use the validated nonpenetrating Takakura sham acupuncture device to minimize placebo effects and apply the James and Bang indices to assess blinding success. We will use validated assessment tools to systematically evaluate the multidimensional effects of acupuncture on pain, physical function, and quality of life in patients with KOA [31,32]. In addition, we will focus on the sustained effects after treatment cessation through a 24-week extended follow-up and document safety profiles to comprehensively determine the clinical utility of this sensitization-guided acupuncture approach.

Furthermore, previous RCTs exhibited heterogeneity and inadequate justification in acupoint selection. In clinical practice, we have found that there is potential for optimizing acupoint prescriptions in KOA management through the phenomenon of acupoint sensitization. Acupoint sensitization is defined as enhanced responsiveness of specific acupoints to mechanical stimuli (eg, acupuncture and acupressure) under pathological conditions. Applying acupuncture to sensitized acupoints facilitates the induction of "kuai ran" (translated as "comfortable sensation") and "de qi" responses (eg, soreness, numbness, distension, or heaviness). Theoretically, this approach enhances therapeutic efficacy by regulating qi blood flow in meridians, improving periarticular circulation, reducing inflammatory responses, and alleviating pain and swelling. Expert consensus [33] and cross-sectional evidence [34] further emphasize that sensitization status is a critical characteristic for acupoint selection in KOA. Therefore, to address heterogeneity in acupoint selection and optimize therapeutic outcomes, we propose targeting the most frequently sensitized acupoints. Through a multimodal approach combining pain threshold measurement, infrared thermography, and data mining analysis,

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we identified 5 acupoints exhibiting the highest mechanical sensitization frequency: Chize (LU5), Quchi (LI11), Dubi (ST35), Fengshi (GB31), and Xiyangguan (GB33) [33,35].

Objective

This RCT aims to generate confirmatory evidence for the efficacy of acupuncture based on sensitization-guided acupoint selection in KOA, implemented through standardized treatment protocols.

Methods

Ethical Considerations

This research protocol was approved by the ethics committee of the First Affiliated Hospital of Jiangxi University of Traditional Chinese Medicine (JZFYLL20250103002) and was prospectively registered on ClinicalTrials.gov (NCT06805188). The informed consent form will be explained by the investigator to participants in clear and understandable language, covering the interventions, associated risks, potential benefits, and the participant's rights within the trial. The form will be signed by the participant. If a participant wishes to withdraw from the trial, final analysis will be conducted using the available data, and their wishes will be accommodated accordingly. Participant confidentiality will be ensured, and all data will be deidentified in compliance with ethical standards.

Study Design

This study is a multicenter, single-blind, sham-controlled RCT. The study protocol was developed in compliance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (Multimedia Appendix 1) [36]. The study procedure is presented in Figure 1.

Figure 1. The study procedure. This schematic illustrates the structured flow of a randomized controlled trial designed to assess the therapeutic effects of acupuncture compared to sham acupuncture in patients diagnosed with knee osteoarthritis. 40mFPWT: 40 m Fast-Paced Walk Test; HAM-A: Hamilton Anxiety Rating Scale; HAMD-17: Hamilton Depression Rating Scale-17; ISI: Insomnia Severity Index; NRS: Numerical Rating Scale; PSEQ: Pain Self-Efficacy Questionnaire; RMDQ: Roland-Morris Disability Questionnaire; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

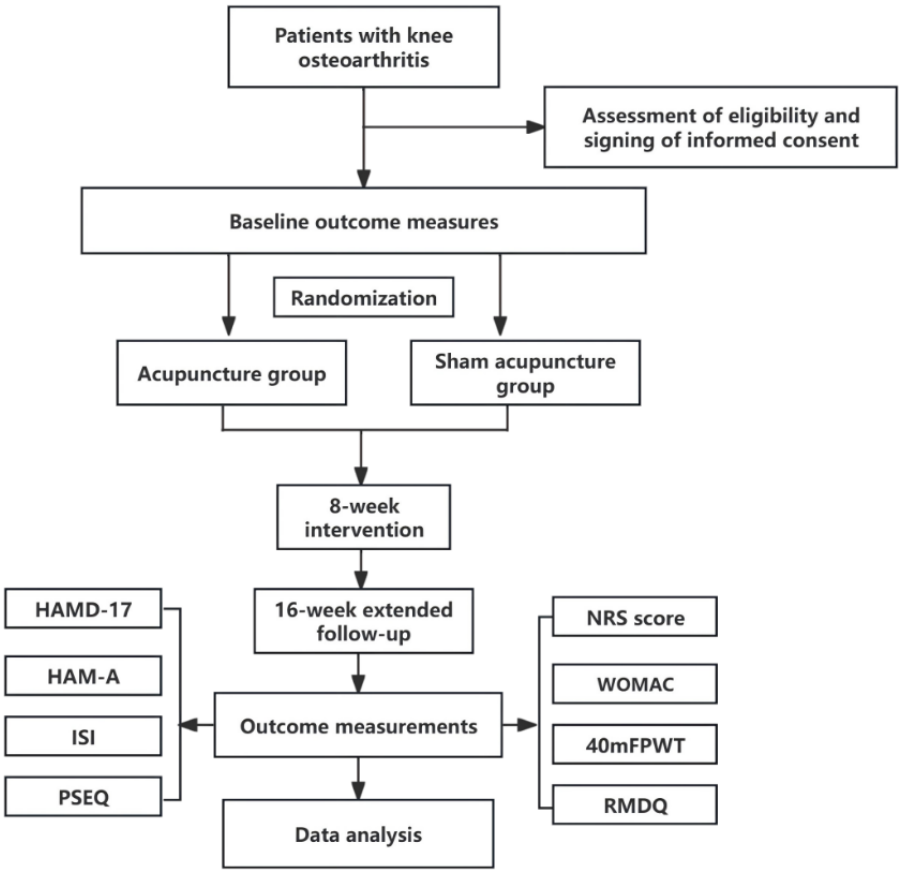

Study Sites and Recruitment

Participants will be recruited from the Affiliated Hospital of Jiangxi University of Traditional Chinese Medicine, the Second Affiliated Hospital of Jiangxi University of Traditional Chinese Medicine, and the Yuxi Hospital of Traditional Chinese Medicine. Recruitment notices will be posted on hospital bulletin boards, social media platforms, and official WeChat accounts of participating institutions. Potential participants expressing interest will receive an informed consent form outlining the study protocol, potential risks and benefits, and participant rights. Upon confirmation of voluntary participation, eligible individuals will undergo screening assessments to verify eligibility. Formal enrollment will commence only after written informed consent is obtained.

Eligibility Criteria

The inclusion and exclusion criteria for the patients are presented in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- A diagnosis of knee osteoarthritis (KOA) according to the American College of Rheumatology criteria [37], defined by at least 1 of the following combinations: knee pain on most days during the preceding month and radiographic osteophyte formation; knee pain and synovial fluid analysis consistent with osteoarthritis, morning stiffness for 30 minutes or less, and crepitus ; knee pain and being aged 40 years or older, morning stiffness for 30 minutes or less, and crepitus
- Aged between 18 and 70 years, accounting for the increasing prevalence of KOA in younger populations to enhance generalizability
- Persistent knee pain for 3 or more months with a pain intensity of 4 or more points on the Numerical Rating Scale at screening
- Provision of written informed consent

Exclusion criteria

- History of previous knee surgery
- Treatment with KOA-targeted therapies within the preceding 24 weeks, including intra-articular corticosteroid injections, acupuncture, or moxibustion (this criterion aims to minimize residual effects from previous therapies, as acupuncture efficacy may persist for 12-20 weeks after treatment [38])
- Comorbidities potentially confounding knee pain assessment, such as fractures, synovial cysts, or rheumatoid arthritis
- Severe degenerative disorders or neurological impairments (eg, stroke and Guillain-Barré syndrome) causing knee disability
- Documented history of severe psychiatric disorders, organ failure, or malignancy
- Scheduled knee surgery within the next 3 months
- Pregnancy or lactation
- Concurrent participation in other clinical trials

Randomization and Allocation Concealment

Eligible participants will be randomly assigned to either the acupuncture group or the sham acupuncture group. The randomization sequence will be created by an independent center not involved in study objectives, participant recruitment, and follow-up procedures, using the PLAN procedure (SAS Institute Inc) with variable block sizes of 4 and 6. The resulting allocation sequence will be concealed in sequentially numbered, sealed, and opaque envelopes. After eligibility confirmation, the assigned acupuncturist will sequentially access the corresponding envelope to receive the group assignment.

Blinding Procedures

Study participants, outcome assessors, and data analysts will remain blinded throughout the trial. The blinding of acupuncturists will not be maintained due to the inherent nature of the interventions. To minimize bias risks from unblinded acupuncturists, we will implement multiple measures. First, a rigorous standardized operating procedure has been established (Multimedia Appendix 2). All treatments administered by acupuncturists must adhere to predefined acupuncture parameters (including point location, needle retention time, stimulation techniques, etc), with compliance monitored on-site by clinical research coordinators. Second, nontherapeutic discussions between acupuncturists and participants will be limited; for example, conversations regarding treatment efficacy expectations or additional lifestyle advice are prohibited to reduce interference from the acupuncturists' unblinded status. Unblinding will be strictly limited to instances of serious adverse events (AEs) requiring immediate clinical management.

Interventions

Acupuncture Group

Participants assigned to the acupuncture group will receive 24 sessions administered three times per week over 8 weeks. Treatments will be performed by licensed acupuncturists who have more than 10 years of clinical experience and have also undergone a standardized 2-week protocol-specific training program before trial commencement. On the basis of previous measurements of tenderness thresholds and temperature sensitivity, 5 acupoints with the highest propensity for sensitization to acupuncture stimulation (mechanical pressure pain threshold of ≥2372 gf; thermal threshold of ≥32°C) will be selected for the acupuncture prescription [34,39,40]. These include Chize (LU5), Quchi (LI11), Dubi (ST35), Fengshi (GB31), and Xiyangguan (GB33) on the affected side. Acupoint localization will adhere to the *World Health Organization Standard Acupuncture Point Location in the Western Pacific Region* [41] (Figure 2 and Table 1 [42]). Sterile disposable acupuncture needles (Huatuo brand; 0.30 mm diameter×40 mm length) will be used. Needle insertion will be followed by manual stimulation to elicit "de qi" sensations (characterized by soreness, numbness, distension, or heaviness). Each acupoint will receive approximately 30 seconds of manipulation, with the intensity calibrated to individual tolerance thresholds. Needles will be retained for 30 minutes per session, supplemented by additional manual stimulation at 10-minute intervals.

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Figure 2. Anatomical location of selected acupoints. Diagram used with permission from www.3Dbody.com [42].

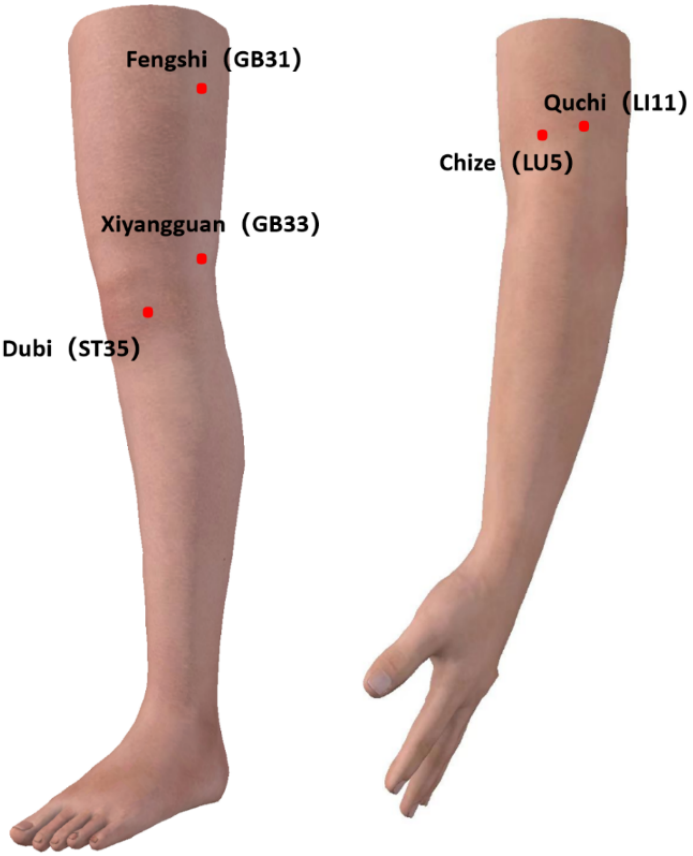

Table 1. Anatomical location of selected acupoints.

Acupoint	Location
LU5 (Chize)	On the anterior cubital crease, radial to the tendon of the biceps brachii muscle
LI11 (Quchi)	On the lateral aspect of the elbow, at the midpoint of the line connecting the lateral end of the cubital crease and the lateral epicondyle of the humerus, measured with the elbow in flexion
ST35 (Dubi)	On the anterolateral aspect of the knee, within the lateral depression of the patellar ligament
GB31 (Fengshi)	On the lateral midline of the thigh, 20 cm proximal to the popliteal crease, in the depression midway between the greater trochanter and the lateral femoral epicondyle, which lies between the vastus lateralis and the biceps femoris muscles
GB33 (Xiyangguan)	On the lateral aspect of the knee, in the depression immediately superior to the lateral epicondyle of the femur

Sham Acupuncture Group

The participants assigned to the sham acupuncture group will receive nonpenetrating stimulation at identical acupoint locations to those in the acupuncture group, which will be administered using validated Takakura nonpenetrating sham devices (Figure 3). The construction of this device includes a hollow needle handle, a retractable sleeve, a connecting ring, a stabilizing Park tube (telescope structure), a plastic adhesive ring, and double-sided tape. The device is affixed to the skin surface via double-sided tape, forming a stable platform. The retractable sleeve mechanism within the hollow needle handle creates tactile feedback, mimicking needle insertion while preventing actual skin penetration. The Park tube maintains structural integrity, preventing accidental dislodgement or penetration. Specifically designed blunted-tip needles, visually indistinguishable from verum acupuncture needles, are deployed. During application, the sham needle tip contacts the skin surface without penetration. A standardized 30-second simulated manipulation procedure, replicating the manual technique for the acupuncture group, is performed, ensuring equivalent sensory experience despite the absence of skin penetration. All treatment parameters, including acupoint selection (Figure 2 [42]), needle retention time (30 min), treatment frequency (thrice weekly), treatment course (8 k), and visit schedules, are identical to those of the acupuncture group to maintain procedural consistency.

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Figure 3. Sham acupuncture device.

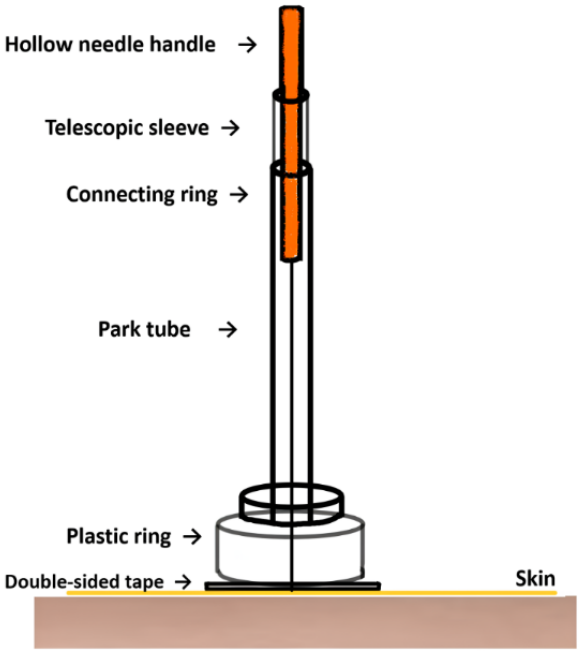

Cointerventions

All participants will be required to discontinue pharmacological interventions for KOA throughout the study duration, including both oral and topical agents. Paracetamol will be permitted as a rescue medication following physician-confirmed exacerbations of KOA symptoms, with mandatory documentation of dosage, frequency, and administration timing. Concomitant medications for non-KOA comorbidities may be continued without restrictions. Both groups will be prohibited from receiving adjunctive physical therapies or alternative treatments (eg, massage, moxibustion, or ultrasound therapy). Normal daily activities will be encouraged, while strenuous exercise is discouraged to minimize confounding therapeutic effects.

Extended Follow-Up

Following the 8-week treatment period, participants will enter a 24-week posttreatment follow-up phase without active interventions. Rescue medication will be permitted in cases of disease progression accompanied by intolerable pain, with paracetamol designated as the primary rescue agent. The daily dosage will be titrated based on symptom severity while ensuring adherence to the maximum daily limit specified in clinical guidelines. If pharmacological intervention fails to alleviate symptoms and surgical indications are met, patients will be referred for surgical evaluation. All rescue interventions, including timing, dosage, frequency, and rationale, will be systematically documented and incorporated into the per-protocol analysis.

Outcomes

Primary Efficacy Outcomes

The primary outcome will be the proportion of responders achieving a clinically meaningful reduction in knee pain at weeks 8 and 24. Response is defined as a 2-point reduction or more from baseline on the Numerical Rating Scale (NRS), where pain intensity ranges from 0 (no pain) to 10 (worst pain). This threshold represents the minimal clinically important difference for the NRS [32]. The NRS, endorsed as the gold standard for pain assessment by the American Pain Society, requires participants to select a single integer corresponding to their current pain intensity using a visual analog scale, where higher scores indicate greater pain severity.

Secondary Efficacy Outcomes

The validated instruments mentioned subsequently will assess secondary outcomes.

The first instrument is the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC). Aligned with the clinical practice guidelines for KOA assessment [43], the WOMAC assesses 5 domains: pain, stiffness, physical function, social participation, and quality of life. The 24-item scale generates a total score ranging from 0 to 240, with higher scores indicating greater disease severity.

The second instrument is the 40 m Fast-Paced Walk Test. This test quantifies knee joint function, lower-limb muscle strength, and ambulatory capacity [44]. Participants complete a 40 m walk at the maximum safe speed; the time (seconds) is recorded by a stopwatch. Shorter durations reflect better functional performance.

The third instrument is the Roland-Morris Disability Questionnaire (RMDQ). RMDQ scores (range 0-24) assess compensatory low back dysfunction secondary to chronic knee pain [45]. Its sensitivity to activity-related impairments captures biomechanical loading alterations and postural adaptations (eg, lumbar muscle overcompensation during gait). Higher scores indicate greater functional limitations.

Fourth, we will assess the depression status. Depressive symptoms will be assessed using the Hamilton Depression Rating Scale-17 [46]. The scale consists of 17 items, with a higher score indicating greater severity of depression.

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Fifth, we will assess the anxiety status. Anxiety symptoms will be assessed using the Hamilton Anxiety Rating Scale [47]. The scale comprises 14 items, with a higher score indicating greater severity of anxiety.

Sixth, we will assess the insomnia status. Sleep quality will be assessed using the Insomnia Severity Index (ISI) score [48]. ISI assesses self-reported insomnia symptoms experienced over the past 2 weeks. It consists of 7 items, yielding a total score ranging from 0 to 28, where higher scores indicate more severe insomnia. Notably, it may be challenging to distinguish between insomnia directly related to KOA pain and primary insomnia with items 1 to 3 of the ISI (difficulty falling asleep, difficulty maintaining sleep, and early morning awakenings). To increase the specificity of assessing KOA-related sleep disturbances, we will annotate these items with "caused by KOA."

We will also assess the pain self-efficacy. The impact of pain on daily functioning will be assessed using the Pain Self-Efficacy Questionnaire (PSEQ) score [49]. PSEQ measures an individual's confidence in performing activities while experiencing pain. It consists of 10 items, generating a total score ranging from 0 to 60, with higher scores indicating greater self-efficacy beliefs in managing pain-related challenges.

Safety Outcomes

Safety assessments will focus on monitoring the incidence of AEs, serious AEs, and acupuncture-related AEs throughout the trial. Acupuncturists are responsible for documenting all AEs, whether deemed treatment related or incidental. Reportable nonserious AEs encompass (1) acupuncture-related incidents, such as hematoma, needling syncope, needle breakage, or retained needles; (2) patient-reported symptoms impacting daily activities; and (3) any laboratory abnormalities exceeding twice the upper limit of normal or falling below half the lower limit of normal. The sham acupuncture group does not carry these specific risks. Standard management protocols for anticipated acupuncture-related AEs are detailed subsequently. First AE includes bruising and hematoma, in which small, localized hematomas will be disinfected and allowed to resolve spontaneously. Symptomatic treatment will be administered by a physician for larger hematomas or instances of significant bleeding. Second AE includes needling syncope, in which acupuncture treatment will be immediately discontinued. Symptomatic management will be provided. Third AE includes needle breakage and retention, in which acupuncture treatment will be discontinued. The affected needle fragment will be addressed (eg, removed, if feasible), and symptomatic management will be provided, as necessary.

In cases of serious AEs (defined as events resulting in hospitalization, persistent or significant disability, or immediate life-threatening conditions), trial participation will be immediately discontinued for the affected participant. The participants will receive comprehensive therapeutic interventions and nursing care at the study site until symptom resolution.

All costs associated with managing intervention-related AEs will be covered by research funding. Detailed documentation of all AEs, including onset time, severity, duration, outcome, and assessed causal relationship to the intervention, will be submitted to the medical ethics committee within 24 hours of occurrence.

Assessment Schedule

Outcome assessments will be performed at baseline and 4, 8, 16, and 24 weeks after randomization. At the baseline visit, data collection will include patient demographic information (eg, age and sex), anthropometric measurements (height and weight), lifestyle factors, educational attainment, and concomitant treatments. All primary and secondary outcomes and treatment adherence will be evaluated at every scheduled visit. The detailed visit procedures are outlined in Table 2. Any deviations from the study protocol will be recorded. While protocol deviations do not mandate trial withdrawal, they will be accounted for in the per-protocol analysis.

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Table 2. Study procedures and outcome measures by visit timeline.

Study procedures and outcome measures	Screening	Allocation	Active intervention		Postintervention follow-up	
	Week 0	Week 0	Week 4	Week 8	Week 16	Week 24
Procedures						
Eligibility screening	✓					
Informed consent from	✓					
Randomization		✓				
Acupuncture or sham acupuncture			✓	✓		
Outcome assessment						
Numerical Rating Scale	✓		✓	✓	✓	✓
Western Ontario and McMaster Universities Osteoarthritis Index	✓		✓	✓	✓	✓
40 m Fast-Paced Walk Test	✓		✓	✓	✓	✓
Roland-Morris Disability Questionnaire	✓		✓	✓	✓	✓
Hamilton Depression Rating Scale-17	✓		✓	✓	✓	✓
Hamilton Anxiety Rating Scale			✓	✓	✓	✓
Insomnia Severity Index	✓		✓	✓	✓	✓
Pain Self-Efficacy Questionnaire	✓		✓	✓	✓	✓
Analgesic use record	✓		✓	✓	✓	✓
Patient compliance			✓	✓	✓	✓
Blind evaluation			✓	✓		
Adverse event record			✓	✓	✓	✓

Quality Assurance

Case report forms for each participant will be archived in individual paper-based folders in secure, access-controlled storage to ensure confidentiality. Data from paper case report forms will undergo dual independent entry by 2 trained researchers into a designated electronic database. All discrepancies will be resolved through source data verification conducted by a third-party auditor, referencing original medical records. All personnel handling the study data will sign legally binding confidentiality agreements compliant with international regulations.

An independent data and safety monitoring board (DSMB), comprising multidisciplinary experts free of conflicts of interest, will be established to safeguard participant welfare and ensure trial integrity across implementation, monitoring, and data interpretation. The DSMB's responsibilities include overseeing interim analyses and determining trial continuation based on prespecified evaluations of safety profiles, efficacy signals, and protocol adherence rates. DSMB will conduct monthly reviews of safety data, including the frequency of all nonserious AEs and serious AEs, along with causal attribution assessments to the trial intervention. To address ethical considerations regarding the sham acupuncture group not receiving therapeutic acupuncture during the trial, all participants in this group will receive a complimentary equivalent course of acupuncture upon trial completion. This approach upholds the principle of distributive justice while maintaining enrollment retention and protocol compliance.

Data Management and Sharing

We will implement a rigorous data protection framework to ensure patient privacy and data security. During data collection, only participant IDs and anonymized aliases will be recorded, avoiding sensitive identifiers, such as national ID numbers. All physical documents will be stored in encrypted cabinets, while electronic data will be transmitted exclusively through secure channels. The database will enforce tiered access privileges with comprehensive activity logging. For multicenter collaboration, all research sites will transmit data via encrypted virtual private network tunnels and adhere to unified collection protocols. Upon trial completion, all datasets will undergo deidentification before storage on dedicated servers. Any future data sharing requires prior approval by an independent ethics committee. The entire data management process strictly complies with China's Personal Information Protection Law requirements. All researchers must sign confidentiality agreements and will be subject to continuous oversight by the DSMB.

Sample Size Calculation

We hypothesize that acupuncture is more effective than sham acupuncture in alleviating symptoms of KOA. On the basis of our pilot study data, we conservatively estimate response rates (the primary outcome) of 82% for the acupuncture group versus 65% for the sham acupuncture group. With a 2-sided α level of .05, a statistical power of 90%, and an allowable attrition rate of 20%, the sample size calculation resulted in a requirement of 343 participants per group. To enhance statistical robustness,

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we expanded the sample size to 350 cases, with 175 (50%) cases in both groups.

Statistical Analysis Plan

Data analysis will be conducted using SAS (version 9.4; SAS Institute Inc). In baseline analyses, continuous variables conforming to a normal distribution will be presented as means and SDs, whereas nonnormally distributed continuous variables will be summarized as medians with IQRs. Categorical variables will be expressed as frequencies and percentages. Normality will be assessed using the Kolmogorov-Smirnov test. For between-group comparisons of normally distributed outcome data with homogeneity of variance (verified by the Levene test), independent-sample 2-tailed *t* tests will be used. Nonnormally distributed outcome data will be analyzed using the Mann-Whitney *U* test. Differences in categorical variables between groups will be evaluated by the chi-square test.

For primary outcomes, generalized linear mixed models adjusted for prespecified covariates (sex, age, disease duration, baseline NRS score, BMI, occupation, study site, visit time, and group-time interaction) will be used to estimate treatment effects, with study sites modeled as random effects. To address multiplicity, significance testing for primary outcomes will follow a sequential testing approach: only if week 8 shows between-group significance can week 24 results be deemed significant. The tests for secondary outcomes will not be corrected for multiplicity because all secondary outcomes are for exploratory intentions. All analyses will follow the modified intention-to-treat principle, including all participants who received at least 1 session of the trial intervention and provided at least 1 postbaseline NRS score. To validate the missing at random assumption for missing data, we will implement a logistic regression model where the missingness indicator (binary status: missing vs observed) serves as the dependent variable, with treatment group allocation and baseline characteristics as covariates. The missing at random assumption is supported if the model demonstrates statistical significance (eg, treatment group affecting missing probability) without including the outcome variables themselves [50]. Missing data at random will be imputed using multiple imputation methods; categorical variables will be imputed via logistic regression models, and continuous variables will be imputed via linear regression models. The covariates included in the imputation model are identical to the confounding factors adjusted for in the primary analysis model, including sex, age, disease duration, baseline NRS score, BMI, occupation, study site, visit time, and group-time interaction. Data missing not at random will not be imputed. All the statistical tests will use a 2-sided α level of .05, with the results reported using 95% CIs.

To evaluate the robustness of effect estimates, two sensitivity analyses will be conducted: (1) a per-protocol analysis restricted to participants who completed both week 8 and week 24 visits, attended 80% or more acupuncture or sham acupuncture sessions, maintained blinding status, and refrained from all prohibited interventions (including rescue therapies) and (2) a complete-case analysis without missing data imputation.

Blinding success will be evaluated using the James and Bang indices [51]. The James index (range 0-1) measures overall blinding effectiveness based on “don’t know” responses, where higher values indicate better blinding. The Bang index (range –1 to 1) separately analyzes correct guessing rates for each group, where positive values suggest blinding failure, negative values represent successful blinding, and the absolute magnitude reveals intergroup differences.

Results

This study received funding in November 2024. Participant recruitment has been initiated. The first participant was enrolled on February 15, 2025. As of June 28, 2025, we have recruited 25 participants. Data analysis has not commenced. The final data collection is expected to be completed by March 2026, and the anticipated publication date for the study results is December 2027.

Discussion

Overview

KOA is recognized as one of the most prevalent chronic joint disorders in middle-aged and older adult populations. This condition imposes dual burdens through progressive functional disability that substantially compromises quality of life and escalates health care expenditures that strain medical systems. Although key pathological mechanisms, including articular cartilage degeneration, osteophyte formation, synovial inflammation, and altered synovial fluid composition, are well characterized [52], the therapeutic management of KOA remains suboptimal due to the persistent absence of clinically effective, mechanistically targeted disease-modifying therapies.

Although multiple studies have reported positive effects of acupuncture in KOA management, methodological limitations, such as small sample sizes, suboptimal study designs, and short-term follow-up durations, have precluded definitive conclusions [38,53]. A meta-analysis of acupuncture for KOA suggested superior efficacy over sham acupuncture or usual care in pain relief and functional improvement, yet it yielded low-certainty evidence due to the prevalent high risk of bias among the included trials [54]. Another meta-analysis incorporating 10 RCTs demonstrated significant acupuncture-induced improvements in pain and functional status among patients with KOA; however, considerable heterogeneity among these RCTs compromised the reliability of the results [55]. Furthermore, insufficient standardization of acupuncture protocols compromises comparability and reproducibility across the RCTs [56]. A methodological systematic review highlighted recurrent deficiencies in descriptions of acupuncture interventions, acupoint selection rationales, and acupuncturist qualifications, thereby undermining evidence credibility [57]. These limitations underscore the imperative of large-scale, multicenter RCTs with standardized protocols for the objective evaluation of acupuncture efficacy and safety profiles in patients with KOA. Notably, the clinical implications of acupoint sensitization phenomena, recently identified as potential therapeutic enhancers, warrant further validation through clinical trials.

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Innovations and Limitations

Given these considerations, we designed this multicenter RCT across 3 clinical sites to evaluate the efficacy and safety of sensitization-guided acupoint selection in acupuncture for treating KOA. This study incorporates 3 methodological advantages. First, the use of Takakura sham acupuncture devices enables simulated needle insertion, generating cutaneous perception of penetration without actual skin puncture, thereby achieving robust participant blinding. This rigorous blinding protocol ensures that observed intergroup differences arise from biological mechanisms rather than expectancy effects or procedural psychological influences, substantially enhancing scientific validity. Second, our sensitization-based acupoint selection strategy potentially enhances therapeutic responses. Third, the multicenter design with sufficient statistical power ensures the generalizability of the results while minimizing selection bias through centralized randomization and standardized protocols. Participants, outcome assessors, and data analysts maintain blinding throughout the trial to prevent performance, detection, and reporting bias. Therefore, we believe that this RCT will generate high-quality evidence to inform clinical practice.

This RCT has several potential limitations. First, blinding of acupuncturists is inherently unfeasible. Given their awareness of group allocation and responsibility for intervention delivery, acupuncturists may inadvertently or intentionally exert undue influence on participants, such as administering additional acupuncture sessions to the treatment group or reducing the proactive provision of lifestyle advice to the control group. These factors may introduce performance bias that could overestimate the therapeutic effects of acupuncture. To mitigate such bias, we implemented standardized operating procedures, restricted nontherapeutic clinician-participant communication, and established on-site monitoring protocols to ensure protocol adherence, as detailed in the Blinding Procedures section. Second, the selection of the NRS as the primary outcome may be susceptible to subjectivity. Although randomization balances subjective effects across groups, residual bias may persist. To address this, we established a multidimensional secondary outcome system to triangulate NRS results, including composite scale assessments (ie, WOMAC, RMDQ, Hamilton Depression Rating Scale-17, Hamilton Anxiety Rating Scale, ISI, and PSEQ) and objectively measurable end points (40 m Fast-Paced Walk Test). In addition, biological markers (eg, interleukin-1β and tumor necrosis factor-α) are excluded due to insufficient evidence correlating inflammatory factors with KOA pain severity or disease progression. Third, despite efforts to minimize placebo effects (eg, using nonpenetrating sham needle devices), residual placebo responses may introduce bias. Crucially, such bias would likely attenuate detectable differences between true and sham acupuncture groups. If statistically significant differences persist despite this conservative bias, they would provide stronger evidence for acupuncture's efficacy, aligning with the objective of this trial.

Communication Plan for Major Protocol Amendments

Any protocol amendments occurring after trial initiation, including adjustments to eligibility criteria, refinements in efficacy evaluation methods, or changes in outcome measures, will require formal approval by unanimous agreement among all relevant stakeholders (eg, the institutional review board and enrolled participants), complying with predefined communication procedures. Modifications directly impacting participants will be disseminated immediately through multichannel communication systems (eg, updated informed consent forms and specialized helplines), supplemented by structured interviews to actively solicit participant feedback. A standardized survey mechanism will be deployed continuously during the trial to quantitatively assess participant satisfaction with amendment processes, thereby guaranteeing auditable transparency practices and robust protection of participant rights through institutional grievance resolution frameworks.

Conclusions

In summary, this RCT aims to establish a protocol for applying acupuncture based on acupoint sensitization as a therapeutic approach to KOA management. If the anticipated therapeutic efficacy is demonstrated, this acupuncture approach may serve as a preferred therapeutic alternative for KOA management, aiming to reduce pharmacological dependency, mitigate adverse drug reactions, and ultimately enhance the quality of life for affected populations. Furthermore, the findings of this RCT can be expected to contribute to the development of clinical guidelines for KOA treatment and advance the evidence-based standardization of acupuncture protocols within KOA management.

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Authors' Contributions

ZW, ZH, and YF contributed to the study design and writing the paper. ZX, XZ, and QH contributed to the calculation of sample volume and the draft statistical plan. ZX and HZ contributed to preparing figures and graphs. ZW, ZH, and XZ contributed to revising and editing the manuscript.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
SPIRIT checklist.
[PDF File (Adobe PDF File), 153 KB - resprot_v14i1e77336_app1.pdf]

Multimedia Appendix 2
Standardized training records and consistency assessment protocol.
[PDF File (Adobe PDF File), 205 KB - resprot_v14i1e77336_app2.pdf]

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Abbreviations

AE: adverse event
DSMB: data and safety monitoring board
ISI: Insomnia Severity Index
KOA: knee osteoarthritis
NRS: Numerical Rating Scale
PSEQ: Pain Self-Efficacy Questionnaire
RCT: randomized controlled trial
RMDQ: Roland-Morris Disability Questionnaire
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TKA: total knee arthroplasty

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WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

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Protocol

Harnessing the Power of Technology to Transform Delirium Severity Measurement in the Intensive Care Unit: Protocol for a Prospective Cohort Study

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Abstract

Background: Delirium, an acute brain dysfunction, is a complication in up to 50% of patients in the intensive care unit (ICU). Measuring and mitigating delirium severity can reduce associated morbidity and improve long-term health outcomes post discharge. However, the perceived complexity of the available delirium detection tools and clinical workload limits the routine assessment of delirium severity. Developing a passive digital marker for delirium severity, combining routine electronic health record (EHR) and computer vision technology data, could be an implementable, scalable, and sustainable approach.

Objective: Our primary objective is to develop a passive digital marker for delirium severity (PDM-Del) and examine its performance in comparison to validated delirium severity tools. Our secondary objective is to evaluate the acceptability and usability of the PDM-Del by patients, families, and clinicians.

Methods: We will conduct a prospective, longitudinal cohort study to develop a PDM-Del using computer vision data and routinely collected EHR data. Following informed consent, the study team will collect image data through continuous digital video recordings of adult patients (>50 years) in their ICU room, routine EHR data (demographic and clinical variables), and administer delirium severity assessments (4 times daily) until ICU discharge or death. We will examine the usability and acceptability of the developed PDM-Del by patients, families, and direct care clinicians in a pilot randomized controlled clinical trial (aim 3). Descriptive statistics (means, SDs, medians, IQRs, and frequencies) and statistical differences between study instruments will be examined. We will use convolutional neural networks and machine learning to inform model development, testing, and validation. We will report model performance statistics, including accuracy, precision, recall, and the F_1-score.

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Results: We are currently in the recruitment and data collection phase. As of March 2025, we screened 3980 patients (32% eligible, n=1307), approached 665 (50%), and enrolled 150 participants (23% enrollment rate). Among the 150 patients, the median age was 67 (IQR 61-74) years, 62% (93/150) were male, and 91% (136/150) were White.

Conclusions: The PDM-Del could provide real-time, actionable feedback to direct care clinicians on the brain health of patients in the ICU. Early mitigation of delirium severity may decrease the risk of mortality, future Alzheimer disease and related dementia, and length of hospital stay.

Trial Registration: ClinicalTrials.gov NCT06172491; https://clinicaltrials.gov/study/NCT06172491

International Registered Report Identifier (IRRID): DERR1-10.2196/62912

(JMIR Res Protoc 2025;14:e62912) doi:10.2196/62912

KEYWORDS

ICU delirium; intensive care unit; computer vision technology; passive digital marker; delirium severity; artificial intelligence; Alzheimer's disease; other related dementias

Introduction

Background

Delirium, an acute brain dysfunction that manifests as a disturbance in attention (ie, reduced ability to direct, focus, sustain, and shift attention), accompanied by reduced awareness of the environment, is seen in up to 50% of mechanically ventilated patients in the intensive care unit (ICU) [1]. Delirium increases the ICU and hospital length of stay, leading to an estimated annual cost of US $152 billion [2-7]. Furthermore, delirium occurrence has been associated with an increased risk of future Alzheimer disease and related dementia (ADRD), with 26% of delirium survivors developing cognitive scores closer to mild ADRD at a 12-month evaluation [8]. Previous studies report that not only the occurrence of delirium (presence or absence) but also its severity increases the risk of mortality, institutionalization, and ADRD [3,9-13]. Delirium severity trajectories have been independently associated with increased 30-day mortality [9]. Increasing levels of delirium severity are also associated with decreased odds of discharge to home (multivariable; odds ratio [OR] 0.78, 95% CI 0.71-0.86) and a faster rate of global cognitive decline in a postoperative population [3,10]. Measuring delirium severity is a powerful prognostic tool associated with important health outcomes. In addition to prognostication, the longitudinal and sequential measurement of delirium severity tracks the patients' response to mitigation strategies over time.

Despite the existence of validated tools for measuring delirium severity, it is not regularly measured in clinical care, and up to 70% of cases of delirium are missed in routine ICU care [14-16]. These gaps in clinical care could be attributed to clinician workload, staff turnover, and the perceived complexity or lack of knowledge on using current delirium monitoring tools [16-20]. A recent study assessing nurses' perceptions of delirium assessment tools reported that nurses preferred scaled tools over binary instruments as a scaled score supports the monitoring of the patients' response to mitigation strategies [21]. Implementing frequent or continual documentation of minute-by-minute or hour-by-hour observations required for accurate delirium severity measurement is not feasible as it adds to the existing documentation burden faced by direct care clinicians [22,23]. One solution to address these limitations is to incorporate advanced artificial intelligence (AI) approaches, such as computer vision technology (CVT), in delirium care. CVT prospectively collects continuous observation (streaming) data that is collated and condensed for human decision-making [23-27]. Key features of delirium severity collected primarily through observation of the patient's behavior are prime candidates for continuous measurement by CVT, as outlined in Figure 1.

Figure 1. Mapping the outline of developing an artificial intelligence algorithm through computer vision technology and electronic health records data. BUN: blood urea nitrogen; Cr: creatinine; EMR: electronic medical record.

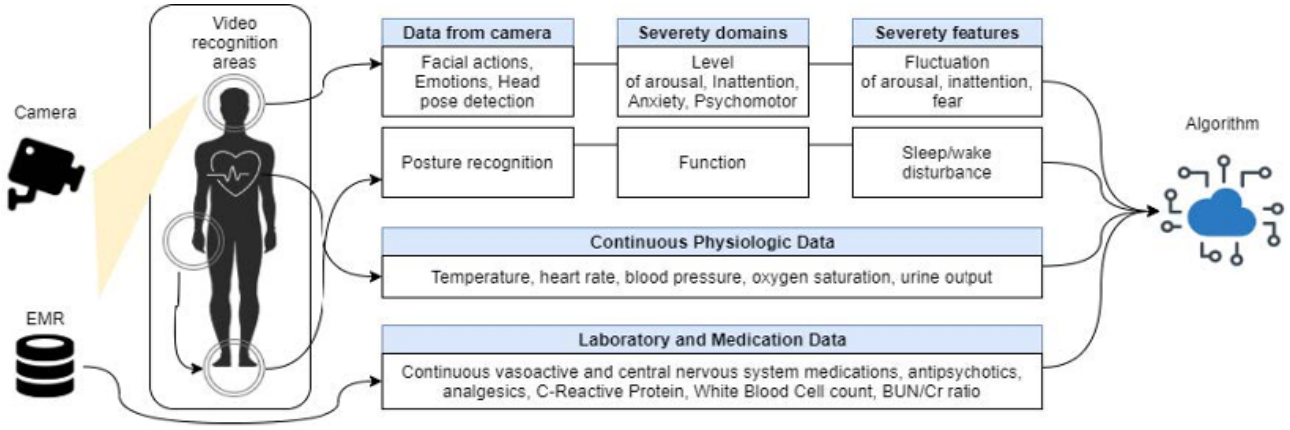

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Recent studies have demonstrated the feasibility of CVT use in the ICU, including delirium detection [23,24,27-29]. Compared to patients without delirium (n=8), those with delirium (n=4) demonstrated significantly different facial actions (eg, lip, cheek, and nose wrinkling), facial expressions (eg, sadness, pain, fear, and disgust), head pose and movement, and posture (eg, lying, sitting, and standing) [23]. This pilot study provided foundational work to investigate further how continuous, noncontact CVT data can measure delirium severity in the ICU. While CVT data may be sufficient to capture some features of delirium severity, the model performance may improve with the addition of routinely collected electronic health record (EHR) data such as medications and physiologic response (illness severity). Therefore, we seek to address this gap in research and clinical care by developing a passive digital marker for delirium severity (PDM-Del) that combines relevant CVT data with existing routine EHR data to produce a hybrid PDM that automatically and passively measures and monitors delirium severity.

Study Aims

The objective of the study had 3 aims:

1. To train convolutional neural networks (CNNs) to measure delirium severity using prospective observational computer vision data in older adults (age >50 years) in the intensive care unit.
2. To develop a PDM-Del using prospectively collected computer vision data and/or routine EHR data in a cohort of aging adult patients in the ICU.
3. To determine the usability and acceptability of the passive digital marker for delirium severity in a prospective pilot randomized controlled clinical trial in aging adult patients in the ICU.

Methods

Study Design

This prospective longitudinal study is recruiting critically ill, aging adults (age ≥50 years) admitted to ICUs at the designated study sites. We obtained institutional review board approval from Mayo Clinic (IRB), and the principal investigator (HL) registered the trial on ClinicalTrials.gov (NCT06172491). The study team uses Agile methodologies to conduct the day-to-day operations of the study. The study started recruiting on January 1, 2023.

Ethical Considerations

We submitted the study for human participant ethics review board during IRB submission and obtained approval prior to the start of the study (IRB#22-003098, Mayo Clinic). Study participants do not receive any compensation for participation in the study.

Informed Consent

The study team obtains informed consent for study participation from the patient or the identified proxy decision maker, with the option to opt out at any time. Participants provide specific permissions to share patient health information, including the use of video images in future presentations, for use in future research, and with external collaborators. IRB-approved study personnel approach eligible patients for inclusion into the study. Delirium status assessments are conducted before obtaining consent. If a potential patient is determined to have delirium, dementia, or a decreased level of arousal (RASS [Richmond Agitation and Sedation Scale] <–1 or >+1), proxy decision makers are approached for consent (ie, legally authorized representative). Once a consented participant regains capacity, the study team confirms the continued study participation with the participant.

Privacy and Confidentiality

Only IRB-approved study personnel can access study information and collected patient data. Following informed consent, participants are assigned a unique study ID to maintain confidentiality. The consent document and associated personal health information, such as name and medical record number, are stored in a separate folder from associated study data that are maintained in a password-protected folder on an encrypted computer behind institutional firewalls. The EHR and delirium assessments collected by the study team are de-identified. The collected videos rely on facial detection and therefore cannot be deidentified. These videos (ie, images) are maintained on a password-protected, encrypted computer that is only accessible by IRB-approved study personnel.

Inclusion and Exclusion Criteria

Inclusion Criteria

Eligibility criteria include older adults (age ≥50 years) with an estimated length of stay ≥24 hours in the ICU (including mechanically ventilated patients). To establish usability and acceptability, adult nurse clinicians (≥18 years), employed by the involved institutions, and assigned to care for a consented study patient for >4 hours, and adult proxy decision makers for patient participants (>18 years) who are willing to complete usability and acceptability surveys will be recruited for study participation.

Adult patients in the ICU ≥18 years of age are at an increased risk of delirium following an ICU admission. We chose the cutoff of 50 years of age or older to balance the increased risk from ICU admission along with the increased risk that accompanies aging adults. Each patient can function as their own case study with a unique set of observations; therefore, an ICU stay of 24 hours or greater was set as a temporal inclusion criterion.

Exclusion Criteria

Exclusion criteria include patients admitted for acute alcohol intoxication, drug (prescribed or illicit) overdose or withdrawal, acute neural injury, and unable to communicate with the research team due to sensory deficits (aphasic, blind, or deaf) or language issues (requires interpreter). Patients who were admitted for acute neurologic injury, alcohol withdrawal, or drug overdoses are excluded, as these injuries demonstrate similar behavioral observations to delirium. Patients with severe sensory impairments are excluded as delirium severity assessments currently require verbal and auditory-dependent patient participation.

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To assess for usability and acceptability, nurse clinicians not assigned to the study participants and proxy decision makers who did not visit the patient in the ICU during the study period are excluded.

Instruments and Data Collection

Longitudinal data collection (observational, n=400) includes continuous digital video images of the patient in their ICU room, routine EHR data, and delirium severity assessments collected by the study team to be used for the development of the convolutional neural network (aim 1) and the future passive digital marker for delirium severity.

For assessing sustainability and acceptability, we will collect data using the System Usability Scale (SUS), the Mayo Clinic Acceptability survey, and the Treatment Acceptability and Preferences (TAP) questionnaire. We will include data from enrollment until death or discharge from the ICU.

CVT Data

High-resolution and wide field-of-view computer vision data are collected 24/7 through video cameras for a minimum of 72 hours or until discharge or death, whichever occurs first. The cameras are positioned to capture the patient's face, their body (all 4 limbs), and the overall patient room. A touchscreen user-friendly interface allows clinical staff, families, or patients to stop and restart recording. The observational data collected through video images will be used to perform face detection, facial expression, head pose detection, posture recognition, vital sign waveform data, and disturbance in the sleep-wake cycle as outlined in Textbox 1. Examples of open-source algorithms are provided in Textbox 1. These are provided for reference; however, the study is not committed to using these specific open-source algorithms.

Textbox 1. Computer vision data (images) collected may be processed using the following open-source algorithms (provided as examples).

Description of proposed analysis of computer vision data

Face detection

FaceNet algorithm, Inception-ResNet V1 model. This is a publicly available open-source code developed by Google [30]. The model will detect the patient's face as a foundational step to completing other measurements, such as emotion detection.

Facial action unit

OpenFace deep neural network 2.2.0 toolbox to detect facial action units (n~action units) [31].

Includes eyebrows (upper, lower, and blink) and lip movement. Coded as present (yes/no) and graded in intensity (0-5). Open-source, publicly available code.

Facial expression

Facial Action Coding System with OpenFace deep neural network 2.2.0 toolbox [31]. Eight common facial emotions. Frequency and length calculated. Anger, contempt, disgust, fear, happiness, pain, sadness, and surprise.

Head pose detection

OpenFace deep neural network 2.2.0 toolbox [31]. Detects movement and position of head (rotation, up/down movements, and side-to-side).

Eye/Gaze Tracking

OpenFace deep neural network 2.2.0 toolbox [32].

Posture recognition

OpenPose multiperson estimation model [33]. Localizes anatomical key points of limbs/joints, length of limbs/angles, and informs recognition of movements and activity. Will calculate speed and absence of movement (including presence of chemical or physical restraints). Open-source, publicly available code.

Sleep-wake cycle

Posture recognition will measure patient posture, movement, and sleep poses.

Acute onset/fluctuation

Acute onset will be defined as an abrupt change in any of the computer vision technology features.

Fluctuation will be defined as the % variation in any of the computer vision technology features.

Cameras

Each intensive care unit room will begin with 1-3 video cameras to investigate which camera positions/angles are necessary to capture the outlined information. The necessity of >1 camera will be continually reviewed.

EHR Data

Patient demographic and clinical variables pertaining to the current ICU stay will be extracted from the EHR. Textbox 2 outlines these data. The variables selected for inclusion are informed by literature [34-36]. EHR data is automatically extracted every 15 minutes and stored in the ICU DataMart for all Mayo Clinic locations [37]. For the Delirium Severity feature, we will extract the RASS score and sedation administration to assess for the fluctuating course and medication administration to assess for psychomotor disturbance.

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Textbox 2. Routine electronic health record data to inform a passive digital marker for delirium severity.

Data collected

Illness severity

- Vital sign (minimum, maximum, and range)
- Vasopressor use
- Anti-infective use
- SOFA (Sequential Organ Failure Assessment Score) score [38]

Delirium severity

- RASS (Richmond Agitation and Sedation Scale) score (minimum, maximum, and range)
- Propofol use
- Dexmedetomidine use
- Benzodiazepine use
- Opioid use
- Paralytics use
- Benzodiazepine use
- Antidepressant use
- Sleep enhancement (eg, melatonin)
- Antiseizure use
- Neurological assessment scales

Covariates

- Age
- Sex
- Ethnicity
- Race
- Past medical history

Standardized Delirium Severity Measurement

The study team has been trained by the principal investigator (HL) to administer standardized, validated delirium severity assessments outlined in Textbox 3, four times daily between 5 AM and 10 PM until death or discharge from the ICU. An observational field study accompanies tool administration and uses a standardized data collection form to promote interrater reliability. Observations include behaviors, emotions, head, eye, and limb movement, or the absence of these items. The study team timestamps the CVT data images when assessments are performed to assist with labeling and annotation. Concurrent to delirium severity assessments, the study team asks the assigned direct care nurse about their concern for the patient's condition. Their concern is measured using the Worry Factor score, a 5-level scale with 0 being no concern and 4 being extreme concern [39]. The Worry Factor score was developed at the Mayo Clinic to improve early detection of acute deterioration.

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Textbox 3. Delirium and delirium severity assessment administered 4 times daily between 5:00 AM and 10:00 PM.

Delirium assessment tools and their definitions

CAM-ICU (Confusion Assessment Method for ICU [intensive care unit]) [40,41]

Gold standard. Scored as positive or negative. Sensitivity 85% and specificity 87%

ICDSC (Intensive Care Delirium Screening Checklist) [42,43]

Validated intensive care unit tool. Score (0-8) on symptom presence. Sensitivity 95% and specificity 91%

CAM-ICU-7 (Confusion Assessment Method for the Intensive Care Unit–7-point scale) [42,44]

Validated delirium severity tool scored directly from CAM-ICU, Cronbach α=0.85. Scoring (0-7): 0-2=no delirium, 3-5=mild/moderate delirium, 6-7=severe delirium.

DRS-R-98 (Delirium Rating Scale-R-99) [45,46] (nonintubated only)

Validated delirium severity tool for nonintubated patients. 16-item (0-44 score) symptom/feature measurement. Cronbach α=0.90

The PMD study (principal investigator: MB) and the Better Assessment of Illness study findings guided the selection of these tools [43,44,47,48]. Scales and subcomponents of each scale will be applied as a continuum of delirium severity to train the CVT neural networks.

To assess usability and acceptability (pilot randomized controlled trial, n=30), we will enroll one patient at a time across ICUs with similar patient populations and delirium rates to reduce the risk of contamination and randomize (1:1, computer-generated assignment) to usual care (nurse-administered Confusion Assessment Method for the Intensive Care Unit, standard care plan in place) or intervention (PDM-Del score, suggested interventions for level of severity; eg, mild=reorientation). The patient, proxy decision maker, and direct care clinicians assigned to care for the patient will complete acceptability and usability assessments: SUS, Mayo Clinic Acceptability survey, and the TAP questionnaire. To reduce learning effects by nurses, we will consider block randomization at the institutional level instead of randomization at the patient level. Table 1 outlines data collection for aim 3.

Table 1. Usability and acceptability of passive digital marker for delirium severity.

Tools and their description	Participant and time of completion
System Usability Scale [49]	
10 questions rate usability on a 1-5 scale, strongly disagree-strongly agree	Nurse clinician and end of shift with the study patient
Mayo Clinic Acceptance Survey [28]	
10 questions on the use of computer vision technology in ICU[a], Likert scale 1-5	Nurse clinician and end of shift with the study patient
Treatment Acceptability and Preferences Questionnaire [50]	
4 questions, Likert scale on effectiveness, believability, and acceptability of PDM-Del[b], high internal consistency (α>.80)	Patient and identified proxy and at ICU discharge
EHR[c] data	
Compliance with A2F[d] bundle [51], time to extubation, ICU mortality	Extracted from the EHR at ICU discharge and secondary outcomes

[a]ICU: intensive care unit.

[b]PDM-Del: passive digital marker for delirium severity.

[c]EHR: electronic health record.

[d]A2F: A: assess, prevent, and manage pain; B: both spontaneous awakening trials and spontaneous breathing trials; C: choice of analgesia and sedation; D: delirium (assess, prevent, and manage); E: early mobility and exercise; F: family engagement and empowerment.

Usual Care Group

In the usual care group, nurse administration of the Confusion Assessment Method for the Intensive Care Unit delirium assessment will be done once every 12 hours along with the administration of evidence-based strategies to mitigate delirium, such as the A2F bundle (ie, usual care).

Intervention Group

In the intervention group, the PDM-Del score will be displayed on a monitor in the patient's ICU room for the nurses' (formal caregiver) reference. Evidence-based strategies to mitigate delirium severity, such as the A2F bundle, will be suggested underneath the score for the nurse clinician to apply. Nurses will be asked to provide feedback on whether they felt the intervention suggested was appropriate. These are the initial steps to develop a decision support tool for nurses to mitigate delirium severity.

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Statistical Analysis

Power

The proposed sample size was calculated to develop the algorithms specified in aims 1 and 2. We assumed a delirium rate (prevalence and incidence) of 45% in enrolled patients as reported in recent literature [52,53]. HL recognizes the likelihood that this study may be underpowered. These findings will inform future grant applications to adequately power study aims. The minimum computer vision frames (n=2000) needed per class label (200 estimated labels; 80 CVT features and 120 delirium severity observations) were used to calculate the sample size [23]. Assuming an average of 2 frames per second and an average of 48 hours of video recording per patient, ~140 patients will be needed to train the CNN to measure delirium severity. An additional ~260 patients will be recruited to develop a PDM for a total sample of 400. This is powered for a confidence level of 0.95, an interval width of 0.10, and the ability to detect a 0.80 area under the curve. An additional 30 patients will be recruited for the pilot randomized controlled trial to determine the usability and acceptability of the PDM. Effect sizes will power future R01 or R-series grant applications designed to further test and refine the PDM-Del.

Data Analysis

Descriptive statistics (means, SDs, medians, IQRs, and frequencies) will be reported. Data among sites will be examined for statistical differences. Modeling assumptions (dependent on the types of models used) will be verified [23,27,29,54]. Missing data will be examined for level of missingness (missing completely at random, missing at random, etc) and procedures such as multiple imputation completed as needed. Figure 2 provides an overview of the planned statistical analysis.

Figure 2. Outline of specific aims, main outcomes, and suboutcomes (A, B, etc). A2F=ABCDEF Bundle: A: assess, prevent, and manage pain; B: both spontaneous awakening trials and spontaneous breathing trials; C: choice of analgesia and sedation; D: delirium (assess, prevent, and manage); E: early mobility and exercise; F: family engagement and empowerment; CNN: convolutional neural network; CVT: computer vision technology; EHR: electronic health records; ICU: intensive care unit; PDM: passive digital marker; RCT: randomized controlled trial.

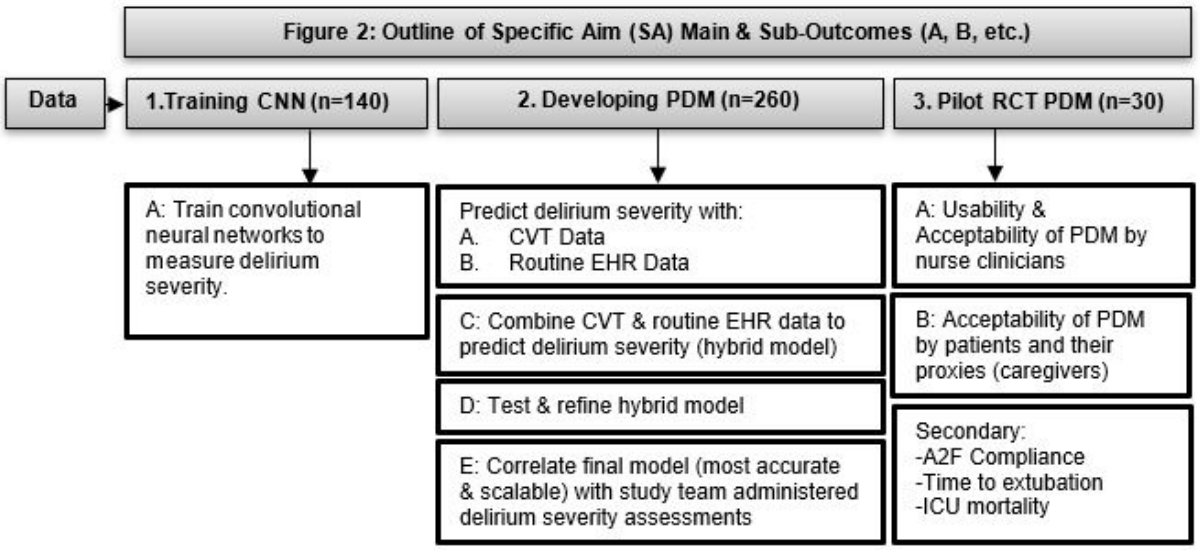

Data at the patient level will be split randomly 80/20 for training and testing purposes. Labeling and annotation of the CV images to train the CNNs will follow a stepwise process. Active learning is being used to minimize the number of manual annotations needed for modeling procedures. The annotation process will be iterative and focused on specific problems such as object recognition. When annotations are needed, a 2-step process that incorporates quality control checks and interrater reliability metrics will be implemented. Both supervised and unsupervised learning will be considered. Classification accuracy, model performance data including F_1-scores, correlations between the final CNN model, and administered delirium severity assessments (ordinal scale), will be evaluated and reported.

Exploratory analysis, factor association measurement, and multiclass machine learning models and ensembles (eg, random forests, gradient boosting, bagging methods, and support vector machines) will inform analysis. Depending on the number of delirium severity classes (ie, mild, moderate, and severe) identified, classification probabilities will be calculated. Classification into one of the severity classes will be based on the class with the highest predicted probability. Test error, variance, entropy, inference, Floating Point Operations Per Second, number of trees, and depth of forest statistics will inform model selection. Accuracy and precision of classification will evaluate model performance. Nested cross-validation will evaluate the final models, perform hyperparameter searches, and estimate the generalization error of the underlying models. Performance statistics (ie, sensitivity and specificity), including F_1-scores, will be reported. The Youden Index will determine optimal cut-off points for mild, moderate, and severe delirium [55]. ICU outcomes (admission and discharge time, mortality, discharge disposition, 30-day readmission) associated with the models will be reported for internal validation. We will select the model that balances accuracy with scalability for future testing and evaluation. A separate dataset of new patients will

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be used for external validation and performance evaluation of the model.

We will calculate means, SDs, and 90% confidence intervals for the SUS, the Mayo Clinic Acceptability survey, and the TAP questionnaire. We hypothesize that the PDM-Del will be acceptable and usable by frontline ICU nurse clinicians, patients, and identified proxies. The secondary outcomes of A2F bundle compliance, time to extubation, and ICU mortality will be collected and compared between groups [51]. Generated effect sizes will power future R01 grant applications.

Results

As of January 2023, data collection began and is ongoing across 3 health care institution sites. We have screened 3,980 patients, approached 665, and enrolled 150 participants as of March 2025. Among the 150 patients, the median age was 67 (IQR 61-74) years, 62% (93/150) were male, and 91% (136/150) were Caucasian. More than 34 million images were collected, and more than 1500 delirium severity assessments were completed.

The primary reason patients declined participation in the study to date was feeling uncomfortable with the continuous image collection and the video camera. Secondary reasons to decline study participation included patients not being interested in research while in the ICU, and finding the study team assessments (4 times daily delirium assessments) exhausting. To address these limitations in study recruitment, the principal investigator has presented to formal community groups and the study's data safety monitoring board to gain insight into how to improve the study. As a result, the study team is moving the camera to a different location in the room and has developed a frequently asked questions flyer for patients and families to reference.

The main inclusion criteria that were not met, leading to ineligible patients, was the length of stay of 24 hours or greater in the ICU (29.1%), followed by acute neurological injury (14.9%). Additional reasons for slower recruitment than expected are equipment malfunctions and availability, study team vacancies, and the length of the onboarding to study protocol.

Discussion

Overview

Delirium, while currently categorized as present or absent, lacks granularity in assessing severity [56]. While this is sufficient for detection and diagnosis, it may be better to obtain information on the level or trajectory of delirium severity. The passive digital marker for delirium severity (PDM-Del) aims to address this limitation and provide immediate and actionable information to healthcare clinicians on the patient's brain health, similar to other vital signs like heart rate. As clinicians work to mitigate delirium severity, the PDM-Del would provide actionable and nonjudgmental feedback on the interventions' effectiveness, providing the opportunity to individualize care based on the patient's response. The underlying hypothesis of this work is that clinicians will take more action to mitigate delirium severity if they receive prompt and actionable feedback on the performance of their interventions in real time. This study presents a novel approach to measuring delirium severity through the development of a scalable, feasible, and passive digital marker.

Early recognition and mitigation of severity play a crucial role in preventing adverse health outcomes and enhancing the lives of critically ill adults. The proposed PDM-Del may improve the lives of patients in the ICU by providing timely and actionable feedback to bedside clinicians about delirium severity, supporting the mitigation of delirium severity. In turn, the risk of future mortality and morbidities, including ADRD, associated with delirium severity may be reduced [8]. The close association between delirium and dementia has been studied exclusively, with a possible synergistic interrelationship between the two conditions [57-59]. Hospitalized patients with ADRD are at least twice as likely to develop delirium superimposed on dementia, and patients who develop in-hospital delirium are at a higher risk of subsequently developing dementia in the future. A prospective study on hospitalized patients with ADRD reported that 33% had delirium superimposed on dementia, and 25% of those patients with delirium superimposed on dementia had an increased mortality rate, functional decline, and increased hospital length of stay [60]. Delirium superimposed on dementia can be challenging to detect in the clinical setting due to the overlapping cognitive and behavioral features between dementia and delirium [61]. Yet, it is critical to detect delirium in this population as it likely signifies a medical emergency. We aim for our PDM-Del to be a valuable tool to improve the early recognition of delirium superimposed on dementia. Future studies may also examine how computer vision could aid in the recognition of symptoms such as pain and anxiety in patients with ADRD. Focusing on this vulnerable patient population may help reduce their inpatient and posthospitalization morbidity and mortality and improve their quality of life.

Clinical research to identify delirium subtypes and biological biomarkers could be accelerated with the use of a PDM-Del. Instead of relying on inconsistent clinical assessments or resource-intensive research assessments, the PDM-Del would provide continuous monitoring and real-time measurement across a large population of critically ill patients. The availability of such data could greatly expand and expedite the use of data science methods such as machine learning, elucidating biological and clinically relevant relationships that, in turn, could improve clinical trials aimed at identifying effective treatments for delirium. Furthermore, the PDM-Del can be used to study the trajectories of delirium severity and identify clinical interventions to modify the trajectory in real time, therefore potentially mitigating adverse outcomes such as post–intensive care syndrome [9].

The ICU of the future is poised to harness advanced AI technologies and ambient monitoring, specifically CVT, to augment patient monitoring, assessment, and support clinical decision-making. Recent studies show that CVT collected through ambient sensors in the ICU can perform autonomous patient monitoring, quantify progress in patients' mobility, monitor safety compliance, and detect differences between patients with and those without delirium [23-25,27,28,32,62]. This type of ambient CVT operates at a low variable cost, is

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passive, fatigue-free, and ceaseless, thus ideal for continuously measuring delirium severity. Depending on the performance of CVT to automatically measure delirium severity, additional ambient sensors may be considered in future studies to improve model performance and/or develop a more scalable and sustainable passive digital marker. These ambient sensors include passive infrared motion sensors, bed sensor devices that measure sleep quality, ambient vital sign monitors that measure continuous heart rate, respiratory rate, and thermography are a few examples that could be used to automatically measure delirium severity and provide feedback for delirium mitigation strategies [63].

Upon completion of the study aims, the machine learning methods used to integrate various data modalities, develop data pipelines, and model architectures will be reported. We will partner with direct care clinicians and use user-centered design principles to codesign the PDM-Del score structure, interface, and clinical integration. This work will be detailed in subsequent manuscripts. Future research is needed to explore how clinicians will interpret and integrate the PDM-Del score into daily practice. While we recognize that the scientific community may prefer the term "passive digital marker", we have opted to name the algorithm "BrainSaver" for use by clinicians." As we progress through usability and clinical deployment stages, we will work with the end user (clinicians, patients, families) to identify an appropriate name.

Limitations

The critical care setting presents unique challenges to autonomous delirium severity measurement, including paralyzed, mechanically ventilated, deeply sedated patients and the use of physical or chemical restraints. The impact of sedation levels on facial actions and expressions remains insufficiently documented. Therefore, the study team will closely document the level of sedation and the use of restraints in study participants to investigate this further.

It has been noted that privacy concerns play a significant role in limiting recruitment to our study. Since recruitment began, the most common reason for denied participation in the study is because the patients or families do not want to be recorded, followed by the discomfort in taking part in research while at the ICU. To address this issue, HL met with the Health Data and Technology Advisory Board, where the first author (RR) presented a mock consent and received feedback on the approach toward the consenting process. Study investigators (HL and VH) are also meeting with the ICU health care teams and patient partners to address these concerns and will continue to do so throughout the proposed project. In terms of analyzing computer vision data, we have identified that the collection of minimal amounts of information is needed to train and use the model so that patients' privacy and safety are protected. This includes blurring or removing unnecessary pieces of data that do not contribute to model development. To address staff concerns with the use of computer vision technology, the principal investigator and study team presented at unit meetings, held lunch and learn events, and recruited nurse champions from each participating unit to proactively learn and address privacy concerns. These efforts continue as the work is ongoing.

We have also encountered unforeseen challenges in the labeling and training of computer vision data that hinder progress. To optimize data collection through camera placement, the study team frequently uses the ICU simulation center to conduct experiments on camera placement, angle, aperture, and lighting.

This study is the first study to our knowledge that aims at creating a PDM-Del for continuous delirium severity measurement. Our study proposes a solution to the identification of missed delirium cases in critical care practice so that patients receive early interventions for delirium mitigation. As our assessments also encompass delirium severity, patients with severe or moderate delirium can be identified early, and specific behaviors related to these severities can be studied in detail. The results of the proposed study will be reported in full transparency, and data will be shared when applicable. The relevant biological variables of assigned sex and age will be used as covariates.

Conclusion

This study aims to develop a passive digital marker for delirium severity using CVT, a form of AI, combined with routine electronic health record data. By combining two different data modalities enhanced with AI, we anticipate a significant clinical impact. The continuous measurement of delirium severity, akin to a vital sign, is expected to prompt clinicians to take early and frequent actions for delirium mitigation. Through early recognition and mitigation of delirium severity, the proposed PDM-Del may decrease the risk of an extended hospital length of stay, ADRD, mortality, and improve the quality of life of ICU patient survivors and families.

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Conflicts of Interest

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Abbreviations

AI: artificial intelligence
ADRD: Alzheimer disease and other related dementia
CNN: convolutional neural network
CVT: computer vision technology
EHR: electronic health record
ICU: intensive care unit

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IRB: institutional review board
PDM-Del: passive digital marker for delirium severity
RASS: Richmond Agitation and Sedation Scale
TAP: Treatment Acceptability and Preferences Questionnaire
SUS: System Usability Scale

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Protocol

Caring Text Messages for Suicide Prevention in Urban American Indian Youth: Protocol for a Randomized Controlled Trial

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Abstract

Background: American Indian (AI) young adults in urban areas have many cultural strengths but also face unique challenges. Cultural norms within their communities strongly emphasize relationships. Previous research has found that receiving occasional positive and nondemanding messages—caring text messages—can be beneficial among people experiencing suicidality.

Objective: To ameliorate increasing rates of suicide and suicidality among AI young adults, we implemented a caring text message intervention designed to increase social connectedness.

Methods: This 2-arm, double-blinded, randomized controlled trial is being implemented at 2 clinical sites with large AI populations. Partnering with clinics in Albuquerque, New Mexico, and Rapid City, South Dakota, we are recruiting AI adults aged 18-34 years to participate in a caring text message study. During the baseline visit, participants complete several surveys and an interview with study staff to understand their history of suicidal behavior. After completion of the baseline visit, participants are randomized to receive the intervention—approximately 30 caring text messages—or treatment as usual. The text messaging platform selected for this study allows bidirectional messaging; while there is no expectation that participants respond, they can provide feedback or seek additional resources. Participants are followed up at 6 and 12 months postbaseline. At the final 12-month follow-up visit, they complete many of the same surveys and participate in an interview to ascertain suicidality since their initial visit. The primary outcomes of interest are suicide-related behaviors—suicidal ideation, suicide planning, suicide attempt, or thoughts and actions requiring hospitalization. Secondary outcomes include social connectedness and other measures of mental health. We will use an intention-to-treat analysis with logistic and linear regression to calculate odds ratios and risk differences (95% CIs) for binary and continuous outcomes.

Results: As of June 2025, the New Mexico site has finished recruitment and follow-up assessments. The South Dakota site is still enrolling participants and has conducted the first follow-up assessments. The project has been well-received by participants.

Conclusions: This randomized controlled trial will evaluate whether a caring text message intervention is effective in reducing suicidality among AI young adults in urban areas. Participants have received the culturally tailored caring text messages. This

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trial will help establish whether caring text messages are an effective strategy for reducing suicidal behaviors and promoting feelings of connectedness among AI young adults.

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KEYWORDS

suicide prevention; mental health; depression; American Indian; technology intervention

Introduction

Background

American Indian (AI) communities have a rich and diverse cultural heritage that is deeply rooted in their connection to the land, their families, and their communities [1-3]. These strengths, combined with their traditional values and beliefs, have enabled them to withstand centuries of colonization, oppression, forced assimilation, and the loss of land and resources [4]. Despite these strong cultural foundations, the rate of suicide among AI youth and young adults remains disproportionately high compared to other racial and ethnic groups in the United States [5]. It is a leading cause of mortality in many AI communities, particularly among individuals aged 10-34 years, making it a major public health concern for AI people [5]. This concern is especially pronounced among urban AI young adults, for whom risk and protective factors may differ from both non-AI peers living in urban areas and rural AI peers [6,7].

As concerns around mental health, depression, and suicidality continue to grow, the integration of behavioral health services into primary care has become increasingly common. One method of integration is through an evidence-based practice, screening, brief intervention, and referral to treatment (SBIRT) [8]. In a typical SBIRT model, patients seeking care from their primary care provider are routinely screened for substance use disorders and mental health conditions such as depression and anxiety. If they screen positive, a colocated behavioral health provider renders a brief intervention and refers the patient to further treatment [8].

The interpersonal theory of suicide is particularly relevant for young, urban AI populations, as it identifies thwarted belongingness as contributing to suicidal ideation [9,10]. Interventions that increase feelings of belonging and reduce feelings of loneliness can be effective in reducing suicide risk [11]. Previous work has found that while social support was not highly correlated with suicidality among rural AI and Alaska Native (AIAN) youth, it protects against depressive symptoms and suicidality among urban AIAN youth [6]. Community connectedness is a major cultural strength among AIAN people. Increasing people's sense of belonging and connection to their heritage and culture may be particularly effective for improving mental health outcomes and reducing the risk of suicide [12].

Given the importance of social connections in mitigating depressive symptoms and suicidal behaviors, previous studies have sought to supplement the SBIRT protocol with caring text messages [13-15]. This text message–based intervention sends participants messages of support and encouragement periodically throughout the year [11], a modern modification of earlier interventions that delivered similar styles of message through letter or postcard [16,17]. Due to the inequitable burden of suicide, unique risk factors, and limited availability of data regarding suicide prevention—including a dearth of culturally relevant interventions—we focused our efforts on AI young adults in urban areas. Community members and our academic team cocreated brief, powerful, site-specific text messages that highlight cultural strengths or impart wisdom of local adults, and combined them with an SBIRT protocol implemented at 2 clinical sites serving AIAN people. Our study assesses the program's effectiveness in reducing depressive symptoms, suicidal ideation, and suicidal behaviors among a group of at-risk young adults.

Objective

This study is part of a large AIAN-specific federal research program to address youth suicide, called the Collaborative Hubs to Reduce Burden of Suicide among American Indian and Alaska Native Youth, which has several aims [18]. Our double-blinded, 2-armed randomized controlled trial is designed to test the effectiveness of a 12-month intervention that combined caring text messages with SBIRT in reducing self-reported suicide ideation, attempts, and hospitalizations, and in increasing social connectedness and retention compared to treatment as usual among urban AI young adults. This paper describes the design and implementation of our randomized controlled trial, which seeks to increase resilience through social connectedness and engagement, thereby reducing suicidal ideation, attempts, and hospitalizations. We also detail the measures and procedures of the systematic economic evaluation of the SBIRT and caring text components of the intervention to determine their relative effects on the use of health care resources and quality of life.

Methods

Setting and Participants (Study Sites)

Participants are recruited from 2 partner sites: First Nations Community HealthSource (FNCH) in Albuquerque, New Mexico, and Oyate Health Center (OHC) in Rapid City, South Dakota, operated by the Great Plains Tribal Leaders' Health Board. Both health centers are funded in part by the Indian Health Service (IHS). As a federally qualified health center, FNCH serves all patients, while OHC primarily serves tribal members eligible to receive services through IHS. Both offer a variety of services, including primary care, behavioral health, women's health, and urgent care or same-day services.

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Eligibility

The population of interest for this study is young AI adults at mild, moderate, or severe risk for suicide. To participate, an individual must self-identify as AI, be between 18 and 34 years of age, and understand written and spoken English. They must complete the SBIRT process with clinic staff and screen positive for elevated risk of suicide or depression, but not be in danger of imminent self-harm. In addition, the participant must have a cell phone that can receive text messages and be willing to be contacted via text message. Participants who have contraindications (ie, are hospitalized) or are cognitively impaired are not eligible.

Recruitment and Retention (Recontact Protocols)

As part of the regular appointment process at FNCH, patients are asked to fill out the FNCH Healthy Lifestyle Questionnaire (HLQ), which includes the Columbia-Suicide Severity Rating Scale and the Patient Health Questionnaire screenings for suicide risk and depression. The HLQ is completed by newly enrolled patients at the first appointment of the calendar year and every 3 months thereafter. Trained clinic staff review and score the completed HLQ during the patient's visit, and this information is recorded in the electronic health record (EHR) and shared with the clinical provider. Depending on the score, the provider may offer treatment and/or referral for services. Study eligibility initially hinged on scoring positive for suicide risk (low, moderate, or severe) or depression. The clinic staff or provider informs the patient about the study. Alternatively, the patient could learn about the study from a flyer posted in the clinic. If interested, the patient was connected immediately to study staff through a warm hand-off. If a patient met eligibility criteria, the site coordinator proceeded with the informed consent procedures and the baseline interview. If the patient was unable to complete baseline procedures at that time due to time constraints, the site coordinator scheduled a time within a week that is convenient for the potential participant. In addition to screening patients referred to the study through SBIRT, site staff used medical records to identify potentially eligible patients. Patients who have not recently attended the clinic and have no HLQ assessment record in their EHR in the previous 3 months were contacted by study staff and screened for eligibility.

Patients—referred to as "relatives" by local staff, which underscores their shared heritage—receiving care at OHC complete routine depression screening as part of most health care encounters. Individuals who report moderate levels of depression or mild, moderate, or severe risk for suicide were referred to behavioral health. The behavioral health provider could offer treatment or referral for services. The relative was informed about the present study. If they were eligible and interested, their contact information was shared with research staff, who are not OHC employees. Study staff follow up with OHC referrals and invite relatives (patients) to participate in the study. Study staff scheduled a time to complete informed consent and the baseline interview.

While the text message intervention contacted participants in the treatment group, responses were unnecessary unless scheduled, requested, or activated by an immediate crisis. However, participants frequently respond to the scheduled messages, usually expressing gratitude or mild distress. To maintain contact and maximize retention, participants in the control group and the treatment group were contacted by the study team at 6 months postbaseline assessment to confirm their contact information. Ten months after enrollment, site staff were permitted to begin contacting participants to schedule or confirm the 12-month follow-up assessment. Participants received text messages (email or private messaging for those who can no longer use text messaging) asking them to confirm the follow-up assessment appointment. If site staff do not receive a response, they contact the alternate contact provided by all participants at the baseline assessment to try and ascertain updated contact information. If a participant does not respond to the reminders and misses their scheduled appointment, the site staff will continue to try and contact them for up to 6 months after their due date, unless they decline further contact. Eighteen months after enrollment, participants were considered lost to follow-up.

If a participant became ineligible during the study (eg, incarcerated), they were withdrawn, and all study procedures were halted. Withdrawn participants who subsequently become eligible and wish to rejoin the study were required to contact site staff and then be reconsented to be re-enrolled. If a withdrawn participant was incarcerated, the study coordinator made 3 attempts to contact them upon learning of their potential release from the participant or an emergency contact. Upon being re-enrolled, a participant restarted the study procedures. At the time that enrollment concluded, only 1 individual was lost to follow-up and subsequently requested to re-enroll in the study.

Assessment Procedures

After obtaining informed consent, the study staff conducted the baseline assessment interview. If the participant was unable to complete the interview on the same day, the interview was scheduled within 1 week and can be completed in person, through a secure video platform, or over the phone. The assessment consisted of a staff-administered interview and self-administered surveys and took approximately 1.5 hours to complete. Study data were collected and organized using Research Electronic Data Capture (REDCap) tools, which are hosted at Washington State University [19]. One exception was the Suicide Attempt Self-Injury (SASI), which was collected by interview, recorded on paper, reviewed, and then entered electronically after a study visit.

Randomization

Randomization to the intervention group or the treatment-as-usual (TAU) control group occurred after the baseline assessment had been completed. A biostatistician not involved with data collection programmed the randomization module in REDCap to enable site coordinators to access the assignment for each participant in real time. Randomization was stratified by site. To prevent bias that might arise when study coordinators intentionally or unintentionally anticipate an upcoming randomization assignment, assignments were blocked in randomly patterned groups of 2, 4, or 6, with assignments for each arm distributed evenly within each block.

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Follow-up interviews for the SASI were completed by staff blinded to the participants' treatment allocation.

Treatment Groups

Resources for All Participants

Study staff provided a "care card" to all participants at baseline, which detailed clinic contact information, business hours, and provided a list of local resources for mental health and traditional healing. This care card was developed in collaboration with behavioral and primary care staff at the clinics to ensure inclusion of appropriate resources. To protect patient privacy, the care cards did not mention the research study. Participants in both groups also received text messages to verify contact details at 6 months and to remind them of and confirm their 12-month follow-up interview.

Treatment as Usual

All participants in the study, regardless of their assigned treatment group, continued to receive the standard treatment normally provided by the clinic, including mental health services, medication management, substance abuse treatment, and case management. Data about the type and frequency of clinic visits by study participants during the study enrollment period were collected by the study team from the participants' EHR after their study completion.

Caring Texts Intervention

In addition to receiving TAU, participants assigned to the caring texts intervention group also received 28-30 supportive and nondemanding text messages; examples of these messages are available in Table 1, and the complete schedule of messages is available in Multimedia Appendix 1. The number of messages sent depended on the date of enrollment, the participant's birthday, anniversaries, holidays, and seasonal and local events. These messages were sent over 12 months, namely, daily for the first 3 days, then 6 weekly messages, 6 biweekly messages, and 6-monthly messages. Other messages include a birthday message, a holiday message (in December), a harvest message (in November), messages acknowledging an anniversary of loss and an anniversary of hope, and 4 messages for seasonal events. The study tailored messages to reflect locally appropriate holidays, events, and celebrations, and used the local language for greetings [20]. The messages were delivered through a secure online platform, LifeWIRE (LifeWIRE Group), which was compliant with HIPAA, HiTech, and FDA regulations for electronic interactions. This platform tracked all communication, preprogrammed messages, and offered the option for individualized responses to be typed and stored for record-keeping purposes.

Table 1. Sample messages for caring text messages sent to intervention participants by site.

Timing	FNCH[a] message (Albuquerque)	OHC[b] message (Rapid City)
First day after enrollment (#1)	It was nice meeting and talking with you yesterday, [displayname][c]. You showed great courage. Thanks for trusting me. -<staff name>[d]	Hello [displayname], It was nice meeting and talking with you yesterday. You showed great courage. Thanks for trusting me. -<staff name>
Weekly (#6)	Ya'at'eeh! Keshi! Guw'aadzi! No matter how you say "hello," everyone is welcome at the FNCH Traditional Wellness Program. Please call (XXX) XXX-XXXX for more information. - <staff name>	Aŋpétu wašté [displayname]! Sending you positive vibes. Creator has good things for you. Smudging is a good way to stay in touch with the Creator. - <staff name>
Biweekly (#11)	Diné Prayer: "In beauty I walk, with beauty before me, behind me, above me, around me. Today I will walk out, greet the sun and the stars, everything negative will leave me, nothing will hinder me" -<staff name>	"One of the things my parents taught me, and I'll always be grateful for the gift, is to not ever let anybody else define me." -Wilma Mankiller. I believe in you, [displayname]. -<staff name>
Monthly (#16)	[displayname], being alive is fighting: "Being Indian is a combination of things. It's your blood. It's your spirituality. And it's fighting for the Indian people" –Winona LaDuke -<staff name>	[displayname], I believe that the future holds many good things for you. Crazy Horse shared this vision: "I see a time of Seven Generations when all the colors of mankind will gather under the Sacred Tree of Life and the whole earth will become One Circle again."-<staff name>
Spring (#21)	Spring is a time for prayers to help corn grow. So much will come up to greet the sun daily. Today is a new day! -<staff name>	[displayname], the Thunder Beings return to the homeland. Spring is our time to welcome their return - we can pray and give thanks for the promise of rain. -<staff name>

[a]FNCH: First Nations Community Healthsource.

[b]OHC: Oyate Health Center.

[c][displayname] indicates that the participant's name was used here.

[d]<staff name> indicates that the site staff signed the message with their own name.

The intervention and study design were adapted to the cultural values and context of the participating communities (eg, type of messages and topics, number of messages, and schedule) [20]. To create messaging that appealed to young urban AIs, the study teams conducted focus groups and semistructured key informant interviews with AI individuals affected by suicide, and gathered input from staff in the clinic's behavioral health and traditional wellness departments, the project's youth representatives, and study staff. Participants were asked to brainstorm and review text messages for their cultural appropriateness and relevance to young urban AIs in their community. The messages were then carefully reviewed and

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adapted by staff from the clinic's behavioral health and traditional wellness departments, and research staff to ensure that they were consistent with the ideals of the caring texts intervention (ie, brief, supportive, and nondemanding). The messages used familiar language and were sent by research staff who had conducted the participants' baseline assessments to establish continuity and connection.

Data and Safety Monitoring

Site and coordinating center staff monitored participant safety. To determine and address potential suicide risk during assessments, study staff administered the University of Washington Risk Assessment Protocol to participants immediately before and after baseline and follow-up assessments [21]. If this assessment indicated moderate or severe suicidal intentions, or if the assessor has other reasons to be concerned about risk, a site-specific crisis protocol is implemented to ensure the participant receives appropriate care from a trained clinician who can more thoroughly assess their level of risk and initiate appropriate next steps.

All adverse events are identified through assessments or through care text messages, then recorded in the REDCap database, which automatically sends email alerts to the team overseeing participant safety. The site leads ensure high-risk participants receive appropriate management and follow the crisis protocol, including referral and a warm hand-off to clinic staff or a crisis line. The National Institutes of Health required a Data Safety and Monitoring Board to meet twice a year and oversee recruitment, adverse events, and protocol violations. After each meeting, the board prepares a brief report with recommendations for protocol modifications. All adverse events are reported to the universities' Institutional Review Boards and tribal review boards, in accordance with their policies.

Measures

A summary of all measures used in the study is available in Table 2. Unless otherwise noted, measures were administered as a survey in REDCap.

Table 2. Summary of outcome and measures used in the urban caring text study.

Type, topic, and domain	Scale or measure
Primary outcomes: suicidal behaviors	
Suicidal ideation	Suicidal Ideation Questionnaire (SIQ-Junior)
Recent suicide attempts	Suicide Attempt Self-Injury Count Recent
Suicide-related hospitalizations	Youth Health Services Measure
Secondary outcomes: social connectedness	
Thwarted belonging, burdensomeness	Interpersonal Needs Questionnaire
Loneliness	Loneliness Scale from NIH[a] Toolbox
Perceived rejection	Social Distress Scale
Objective frequency of socialization	Social Contact Questionnaire
Connection to community	Social Connection Venn Diagram Task
Potential covariates and relevant factors of interest	
Suicide risk	Acquired Capability for Suicide Scale and Exposure to Suicide Questionnaire
Stress and trauma	Breslau Post Traumatic Stress Disorder Screener, Ayers Coping Scale, and Historical Loss and Trauma Scale
Substance use	Addiction Severity Index, Native American Version
Indigenous identity	Oetting and Beauvais Orthogonal Ethnic Identification Scale
Overall psychological well-being	Kessler Psychological Distress Scale
Overall well-being	EQ-5D-5L[b]
Overall well-being and health care usage	Health Economics Analysis Questionnaire

[a]NIH: National Institutes of Health.

[b]EQ-5D-5L: EuroQol 5-Dimension 5-Level.

Primary Outcomes

Our primary outcome of interest was suicidal behavior. While suicidal ideation is more common than suicide attempts or attempts requiring hospitalization, ideation is not necessarily a concrete event and can be more difficult to measure. For this reason, ideation, attempts, and suicide-related hospitalization were all selected to measure the same underlying risk construct. The Suicidal Ideation Questionnaire-Junior, which has been validated with AIAN individuals, measured the study's primary outcome of suicidal ideation [22]. It consists of 15 items that evaluate thoughts of death, desire to be dead, and specific thoughts of self-harm. Scores range from 0 to 90, with scores above 32 indicating active suicidal ideation [23]. The "junior"

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version of the questionnaire was used to accommodate participants with lower reading levels.

The SASI count (lifetime and recent) assessed the primary outcome of suicide attempts [24]. It is a concise questionnaire that determines the first, most recent, and most severe suicide attempt or nonsuicidal self-injury. It assessed the date, method used, and intent to die (ie, clear intent to die, ambivalent intent, or no intent to die), the highest level of medical treatment received (ie, none, doctor or clinic visit, emergency room, or admission to a medical unit), and lethality of each event. The SASI also posed questions about the number of attempts for each of the 17 methods, specifying intent to die, medical treatment received, and lethality for each one. Intent to die and lethality were derived from the SASI interview [24]. A lifetime version of the instrument administered at the baseline assessment captured all historical suicide attempts or nonsuicidal self-injury. A recent version of the instrument assessed only those events that occurred in the past year, both at baseline and follow-up assessments. The adapted version of the SASI used in this study simplified the language, included methods commonly used in AIAN communities, and added an assessment of drug and alcohol use at the time of the self-injury. The SASI was administered via interview.

The primary outcome of suicide-related hospitalizations and health care encounters was measured via the Youth Health Services Measure [25]. The questionnaire collected information about the use of and satisfaction with inpatient and outpatient medical care, emergency room visits, and the use of traditional healing. It could be used to identify health care encounters related to suicidal ideation or behaviors.

Secondary Outcomes

We used several measures of social connectedness. The Interpersonal Needs Questionnaire describes the extent to which individuals feel connected to others (ie, belongingness) and the extent to which they perceive themselves to be a burden on other people (ie, burdensomeness) [23,26]. Previous psychometric analyses indicated that the latent variable “thwarted belongingness” significantly predicted suicidal ideation scores, supporting the measure’s construct validity [9]. The Loneliness Scale, which is part of the National Institutes of Health Toolbox Social Relationship Scales [27], assesses feelings of loneliness and exhibits both internal reliability and concurrent validity. The Social Distress Scale, also part of the National Institutes of Health Toolbox, measures perceived rejection and hostility and has good internal reliability and concurrent validity [27]. The Social Contact Questionnaire asks participants about their use of various forms of social contact, such as text messaging, email, and postal mail [28]. Finally, the Social Connection Measure asks participants to choose which of 7 Venn diagrams, each with a progressively greater proportion of overlap, best reflects their sense of closeness to their community [29]. This measure is intended to provide participants with a means of visualizing their integration within their community.

Covariates and Other Measures of Interest

Participants were also asked to complete surveys related to several other aspects of mental health so that they could later be assessed as possible mediators or effect measure modifiers. The Acquired Capability for Suicide Scale is a 20-item measure that quantifies one’s fearlessness about and capability to die by suicide [30-32]. It has adequate to good internal consistency (α=–.67 to .83), convergent and discriminant validity, and does not correlate with measures of depression or suicidal ideation. The Exposure to Suicide Questionnaire asks about participants’ exposure to suicide and suicide attempts made by family members, friends, or coworkers to assess possible contagion effects. This information allows a posthoc examination of the impact of exposure to suicide and suicide clusters on the intervention effects.

The Breslau Post Traumatic Stress Disorder Screening is a 7-item scale that assesses internalization of feelings following an upsetting or frightening event [33]. Questions about feelings in the past month are answered yes or no and summed to create a total score ranging from 0 to 7; higher scores indicate probable posttraumatic stress disorder. The Ayers Coping Scale is an 8-item scale that has been validated among AIAN populations to assess the frequency of using healthy coping strategies when faced with a problem [34]. The Kessler Psychological Distress Scale, also validated for administration to AIANs, is a 6-item scale that assesses the frequency of feelings of anxiety, hopelessness, depression, restlessness, and unworthiness in the past 30 days [35]. The scale is sensitive (0.36, 0.08) and specific (0.96, 0.02) with respect to predicting serious mental illness [35].

The Historical Loss and Trauma Scale is a 12-item self-report measure that assesses the frequency of thoughts regarding historical trauma (eg, “how often do you think about the loss of our traditional spiritual ways” and “how often do you think about the loss of our language”), which has high internal reliability [36-38]. The Oetting and Beauvais Orthogonal Ethnic Identification Scale poses 8 questions regarding the degree to which respondents follow the tribal and white way of life and the importance of keeping their tribal identity, values, and practices [39,40].

The EuroQol 5-Dimension 5-Level (EQ-5D-5L) is a 6-item measure that assesses respondents’ capacity to perform activities related to mobility, self-care, usual activities, and health dimensions, including pain, discomfort, anxiety, and depression, as well as overall self-reported health status [41,42]. The Health Economics Analysis Questionnaire estimates use of outpatient, inpatient, and emergency room visits; out-of-pocket costs of care; health insurance; employment and schooling benefits; income; publicly funded benefits; lifestyle behaviors (eg, substance use); and costs of participating in the study.

Self-reported drug use and drug use severity are assessed using the Addiction Severity Index, Native American Version [43]. This is a comprehensive measure of lifetime and current drug and alcohol use, as well as the impact of substance abuse on medical conditions, psychiatric well-being, employment status, and encounters with the legal system. The culturally adapted version of the measure also addresses the impact of substance

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use on the respondent's ability to participate in cultural or traditional activities and ceremonies.

Demographic information included gender, sexuality, relationship status, religion, number of children, living arrangement, employment, use of the native language, and education level. Demographic features that may change are reassessed at 12 months.

The COVID-19 Impact on Well-Being Survey, a brief 5-item survey, assesses the impact of COVID-19 infection, the pandemic, and related mitigation efforts on participants' economic, social, and overall health well-being.

We also queried intervention participants at follow-up about their experience of and satisfaction with caring texts.

Treatment Retention

Retention in the SBIRT program is assessed at 12 months. It is operationalized as a 3-category indicator (full, partial, and none) defining engagement for each participant in the appropriate level of care. The appropriate level of care is determined during the initial in-person session with the SBIRT behavioral therapist before enrollment in the study and is independent of study procedures. These variables will be included in sensitivity analyses if they appear unbalanced, although randomization and the large sample size should balance the severity of suicidality and intensity of appropriate intervention services across the study conditions.

Data Analysis

Analysis plan

We expect that individuals receiving the culturally tailored text messages will have better outcomes than those in the treatment-as-usual control arm. Chi-square and *t* tests will be used to compare the overall percentages (binary outcomes) and mean differences (continuous outcomes) between study arms. We will conduct a sensitivity analysis using logistic or linear regression to adjust for baseline factors that are imbalanced between the intervention and control arms. Results will be presented as risk ratios and risk differences for binary outcomes, extracted from logistic regression models using marginal standardization, with 95% CIs [44,45]. Primary analyses will use an intention-to-treat approach.

Missing Data

Our primary analysis will rely on complete case analysis. We will conduct sensitivity analyses with multiple imputation methods. Multiple imputation through chained equations will be applied when data are missing at random. We will also conduct sensitivity analyses to exclude individuals who were randomized to receive the intervention but did not receive it per the schedule outlined in Table 2 due to technological errors or temporary lapses in access to cell phone service. These additional sensitivity analyses will improve confidence in our findings.

Power and Sample Size

We plan to recruit 350 people across both sites. We assume the study will have 70% retention at 12 months, yielding an analytic sample of 240 people (120 per group). With this sample, we will have 80% power to detect a 16% difference (Risk Ratio=0.47) in suicidal ideation between intervention and TAU groups, assuming that 30% of the TAU group reports suicidal ideation at follow-up. We will also be able to detect an 11% difference (Risk Ratio=0.25) in suicide attempts if 15% of the TAU group participants attempt suicide within the 12-month follow-up. There is variability in the literature regarding what constitutes a clinically meaningful effect size for reductions in suicidality and the best means of measuring such an effect (eg, degree of suicidality, reported number of attempts, etc). Regardless, we are confident in our ability to recruit a sizeable analytic sample in a difficult-to-reach population.

Ethical Considerations

All study procedures—including consent protocol, data collection tools, and intervention materials—and subsequent modifications were reviewed and approved by the Institutional Review Boards of Washington State University (#17435), University of New Mexico (#19-401), and University of Colorado Denver (#18-0186), in addition to the Great Plains IRB (#23-R-09GP). The trial is registered on the United States National Institutes of Health Clinical Trials Registry (ClinicalTrials.gov NCT03136094). To ensure informed and voluntary participation, the study staff privately obtains consent from individuals, unless they request otherwise. The coordinator verbally explains the purpose, procedures, risks, benefits, compensation, withdrawal rights, and confidentiality of the study. While the consent form includes permission to be contacted by text message, the form does not make the nature of the intervention explicit. Potential participants are told that the clinic is testing a mobile phone program to support people who are having a difficult time, and that they will receive periodic text messages over the next 12 months. The consent process omits explanations of when and how often text messages will be sent. If participants ask for more details, they are informed that the text messages will be "periodic" and that their purpose is to check in. Keeping the participant blinded during the consent process is an important methodological feature of this study to minimize biased assessment of outcomes and maximize the validity of the results. Participants are informed that their participation is voluntary, and they can withdraw at any time without consequences. Participants at the FNCH site were compensated US $75 upon completion of the baseline visit and received an additional US $75 upon completion of the follow-up visit. Participants recruited from the OHC site were compensated US $100 upon completion of the baseline visit and received an additional US $75 upon completion of the follow-up interview.

Results

Overview

Participants are still being enrolled at the site in South Dakota; the site in New Mexico has concluded enrollment but is continuing with follow-up assessments. We expect to complete data collection by the Spring of 2025.

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Participant Reception

Thus far, participants have responded positively to the messages. While the messages are designed such that they do not demand anything of participants nor require a response, participants do occasionally respond. Most of these responses have been positive. Some responses are brief, with an expression of gratitude or the use of positive emojis. Other times, participants express that a particular message strongly resonated with them. Some of the messages received from participants in response to the caring texts intervention are included in Textbox 1. Names of site staff and site locations have been removed to preserve participant anonymity.

Textbox 1. Select participant responses to caring text messages.

- "It was also nice talking to you, having our short conversations about yoga. It's always great to spill information out to feel less worried than before. Thank you for working with <site>. :)"
- "Wow, love that quote makes so much sense, thanks for sharing."
- "Cool. I like that one."
- "Thank you for listening."
- "I hope all is well with you. Thank you for the great positive feedback throughout each day. Your time is much appreciated!"
- "Cool. Going through that right now. Thanks for the quote."
- "Thank you so much for putting in the time to relay the resources to me. I appreciate it so much, and thank you for sharing your light."
- "Thank you, <staff name>! Thank you for listening."
- "Hi! That's a great outlook. I'll use that today. Hope you have a good week too!"
- "Today is a new day indeed, hope you are having a good day!"
- "Happy New Year, <staff name>, thank you for all the positive words. I do appreciate it."
- "Good morning, thanks for the words of encouragement and wisdom."
- "I hope you have a great one as well. Thanks for keeping in contact."
- "Thank you, it made me very proud to give my answers, knowing people can know more about the struggles our people face. I hope I can help more one day."
- "Nothing that I can think of at the moment has been doing well, but it's good to know I have support and people to reach out to if need be. Thanks, you guys! Have a great rest of your day, <staff name>"
- "Thank you. It's hard to talk about that stuff. But I felt I could trust you."
- "I love that saying, and it helped put a smile on my face for the day."

Discussion

Principal Findings

This study represents an opportunity to prevent or reduce suicidality among AI young adults in urban areas across the country [9-11,15,28]. We anticipate finding that those individuals who received the caring text messages will show reduced indications of suicidality (primary outcome) and increased feelings of social connectedness (secondary outcomes) compared to those in the TAU cohort. This is because the caring texts intervention has strong theoretical foundations [9,10] and is supported by evidence-based practice guidelines [11,15,28].

In addition to being theoretically grounded and supported by other evidence-based practices, we have endeavored to develop an intervention that could be implemented at scale with limited need for involvement on the part of behavioral health specialists on a day-to-day basis. The intervention is structured and delivered in such a way that it can be integrated into primary care, emergency departments, or other services not explicitly designed to manage mental health care. There is mounting support for integrating behavioral health services into primary care, which can reduce stigma and improve access to limited behavioral health resources [46-51]. This is particularly pertinent for young adults who may be trying to access care from an already overburdened IHS.

Dissemination Plan

We believe that disseminating findings back to the community is a crucial component of community-based participatory research. To this end, we have planned several opportunities for dissemination within the scientific community and among urban AI communities more broadly. The findings from the study will be published in an academic journal following the conclusion of data collection and analysis. In addition, we have participated and will continue to participate in health fairs hosted near both study sites. Previous attendance has included sharing information regarding this trial and other behavioral health resources. Future presentations will include sharing the results of the completed trial back to the community. In addition to these health fairs, the staff at the South Dakota site routinely participates in local radio shows to share information on various health topics and ongoing research projects. They plan to dedicate one segment to discussing the findings of the urban caring text messages study.

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Conclusions

The intervention was culturally adapted by members of each participating urban native community. The inclusion of different constituents, such as patients at risk of suicide and behavioral health providers, in the cocreation of the intervention ensures the relevance and appropriateness of the intervention's content, including the text messages. The text messages are designed to be culturally appropriate and increase social support and connectedness without imposing demands on the recipient. By studying whether caring texts help to reduce suicidal ideation and behaviors, and improve social connectedness as well as connection to Indigenous identity, this trial will provide evidence to inform whether primary care clinics serving AIAN young adult should integrate caring texts into their services.

Acknowledgments

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Authors' Contributions

MO, LSS, TP, DB, and SM contributed to the conceptualization of the study. Data curation was performed by ERM, LH, and EP. Funding acquisition was led by DB and SM. Investigation was carried out by MB, EP, NT, NT, KG, RM, and GJ. Methodology was developed by ERM, LH, LSS, TP, DB, and SM. Project administration was managed by EP and SM. The original draft of the manuscript was written by ERM. Generative AI was not used in the production of this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Full schedule for caring text messages sent to intervention participants by site.
[DOCX File , 21 KB - resprot_v14i1e71344_app1.docx]

Multimedia Appendix 2
SPIRIT checklist.
[PDF File (Adobe PDF File), 141 KB - resprot_v14i1e71344_app2.pdf]

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Abbreviations

AI: American Indian
AIAN: American Indian and Alaska Native
EHR: electronic health record
EQ-5D-5L: EuroQol 5-Dimension 5-Level
FNCH: First Nations Community HealthSource
HLQ: Healthy Lifestyle Questionnaire

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IHS: Indian Health Service
OHC: Oyate Health Center
SASI: Suicide Attempt Self-Injury
SBIRT: screening, brief intervention, and referral to treatment
TAU: Treatment as Usual

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Protocol

Evaluation of the Comparative Efficacy of Navak Guggulu Versus Vachaharidradi Gana Vati in the Management of Sthaulya (Overweight) in Children: Protocol for a Randomized Controlled Trial

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Abstract

Background: Childhood obesity is a lifestyle-oriented disorder, which may lead to many comorbidities such as hypertension, coronary diseases, increased incidence of diabetes, and metabolic syndromes. Lack of diet control and increased screen time specifically after the COVID-19 pandemic among children and adolescents are the major reasons for this rising global concern. Despite various campaigns being carried out to lessen the rising rates of childhood obesity, the objectives have not yet been achieved. Ayurveda offers a multidimensional modality in managing children with overweight. The purpose of this study is to evaluate the combined efficacy of Ayurvedic medicine administration, diet restriction, and Sun Salutation. Navak Guggulu is a herbo-mineral compound already proven for its antiobesity action. Vachaharidradi Gana mentioned in Ayurvedic classics is a group of herbs, which are Kaphamedohara and Karshana. Ayurveda also emphasizes the importance of diet and physical activities for the treatment of obesity. The interventions together may help in promoting a healthy weight, improving metabolism, and reducing fat accumulation. So, in this study, the efficacy of Vachaharidradi Gana Vati will be compared with Navak Guggulu to treat children with overweight in addition to diet restrictions and Sun Salutation.

Objective: The aim of the study is to evaluate the efficacy of Navak Guggulu versus Vachaharidradi Gana Vati along with diet restriction and Sun Salutation in overweight (Sthaulya) children.

Methods: A double-blind randomized interventional study will be conducted on selected children with overweight in the age group of 10 to 16 years. They will be equally distributed into 2 groups. The control group will be given Navak Guggulu, and the trial group will be given Vachaharidradi Gana Vati for 90 days. Both groups will be advised of diet restrictions and the daily performance of the Sun Salutation. The study duration is 180 days, with assessment at baseline, followed by every 15 days up to 90 days, and at the end point, that is, after 180 days. Appropriate statistical techniques, such as analysis of covariance paired 2-tailed *t* test, Wilcoxon signed rank test, Mann-Whitney *U* test, and multivariate regression analysis, will be used to evaluate the efficacy of the interventions.

Results: The study got underway in April 2024. Since participants may begin at any time, our goal is for everyone to be finished by May 2025.

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Conclusions: This research will be useful to provide new insight into the effectiveness of the Ayurveda pharmacological approach in treating obesity in children. The results will guide evidence-based multimodality in treatments aimed at changing lifestyle behaviors in children with obesity, thus reducing social stigmatization in them.

Trial Registration: Clinical Trial Registry of India CTRI/2023/03/051135; https://ctri.nic.in/Clinicaltrials/pmaindet2.php?EncHid=NzgzNzE=&Enc=&userName=

International Registered Report Identifier (IRRID): DERR1-10.2196/58838

(JMIR Res Protoc 2025;14:e58838) doi:10.2196/58838

KEYWORDS

childhood obesity; Sthaulya; Vachaharidradi Gana Vati; Navak Guggulu; Sun Salutation

Introduction

Background

India is going through a socioeconomic, nutritional, cultural, and health transformation. In recent years, the country has been witnessing an increase in the overnutrition rates in children. It shows the emergence of the dual nutrition burden in India, namely, overnutrition and undernutrition. Overnutrition among children manifests in overweight or obesity. Children from affluent urban families are more prone to obesity; however, recent data indicate a significant rise in obesity rates among low-income groups in both rural and urban areas. Globalization has introduced multinational fast-food chains across India, leading to a shift from traditional to modern eating habits. This transition has resulted in increased consumption of processed, high-calorie, ready-made foods, particularly among children. Such foods, rich in sugars and salts, have significantly influenced dietary preferences [1-4].

According to the International Obesity Task Force categorization in 2013, the overall prevalence of overweight and obesity was 18.2% and 23.9%, respectively, as per World Health Organization (WHO) standards [5]. As per computation by Lobstein and Jackson-Leach [6], we expect the number of children with obesity in India to reach 17 million by the end of 2025. In a systematic review, the pooled data from the states of India after 2010, the combined prevalence of childhood overweight and obesity was predicted to be 19.3% [7]. The COVID-19 pandemic situation further added a load to it [8]. During the lockdown, web-based schooling forced children to stay indoors, which reduced their physical activity and increased their screen time, leading to prolonged sitting with increased screen time. Excessive screen time reduces physical activity, which results in fat deposition at an early age [9].

Overweight or obesity is characterized by increased weight, increased weight for height, and raised BMI [10]. Recently, new Indian standards have been notified, and new 5- to 17-year charts of BMI for boys and girls have been published by the Indian Academy of Pediatrics. According to that, the BMI cutoffs for overweight and obesity in children are defined at 23 and 27 kg/m^2, respectively (Indian Academy of Pediatrics 2015) [11]. Obesity is a risk factor for numerous noncommunicable diseases, including type 2 diabetes mellitus, asthma, joint pain, and multiple health conditions [12-16]. It frequently carries a high risk of early mortality and significant disability [17]. Children with overweight are more likely to experience cognitive developmental issues and are more likely to become adults with obesity. Obesity prevention should begin in childhood. According to the WHO expert constitution, on average, obesity reduces life expectancy by 6-7 years in adults [18-20].

Despite various campaigns being carried out to lessen the rising rates of childhood obesity, the objectives have not been achieved. The main causes include lack of awareness, poor adherence to balanced diet guidelines, and the absence of comprehensive policies to address this hidden epidemic [21]. It has become the need of the hour to recognize children with overweight and treat them as early as possible.

According to Ayurvedic classics, Sthaulya can be correlated with overweight or obesity. It is a Santarpanajanya Vyadhi [22], which means the disease caused due to excessive intake of food and decreased physical activities. In Ayurveda, the management of Santarpanajanya Vyadhi is a multidimensional modality. It includes medicine administration, Nidanaparivarjana [23] (avoidance of causative factors), diet control, and Vyayama (physical exercise). Ayurveda offers various medicines for the treatment of Sthaulya. Navak Guggulu is a well-known polyherbal compound containing guggulu (*Commiphora mukul* Linn) as the main ingredient. This compound is reported for its antiobesity action [24-27]. It has also been studied in the management of hyperlipidemia [28]. Though it is a proven drug, the availability of pure guggulu is a difficult task day by day. There is a scarcity of pure guggulu, and it is a tedious job to purify guggulu for oral administration, as the available guggulu contains many impurities.

Vachaharidradi Gana mentioned in Ayurvedic classics is a group of herbal medicines that have properties of Kaphamedohara (alleviating Kapha and reducing fats) and Karshana (therapeutic scraping). These are the characteristics of the medications that are recommended in the management of Santarpanajanya Vyadhi like overweight and obesity to improve fat metabolism. As a result, it should aid in maintaining weight and BMI. Further, the contents of Vachaharidradi Gana are easily available and cost-effective as well.

Diet control is as important as medicines in the management of Sthaulya. Bad eating habits are the main cause of obesity among children [29]. Eating in front of the television screen, drinking sugar-sweetened beverages, eating junk foods and packaged foods, and eating without hunger are the factors responsible for gaining excessive weight. Ayurveda has also emphasized the importance of diet in one's health by phrasing it as

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"Mahabheshaja," which means the most important medicine [30]. Therefore, strict diet control must be advocated for the management of children with overweight.

Physical activity is also important for preventing and managing obesity. Lack of exercise and obesity go hand in hand. Increasing physical activity in children is a nonrestrictive approach to obesity management, which is the discretionary component of energy expenditure [31,32]. Suryanamaskara (Sun Salutation) mentioned by Sayanacharya [33] is an ancient, Vedic, and sacred yogic technique that evolved in India for expressing gratitude to the Lord Sun. It is a series of asanas (postures). It helps in the activation of fat metabolism by rigorous movements and ultimately helps in the reduction of fat, thus beneficial in BMI reduction [34]. It also helps in psychological well-being [35], which will lead to a decrease in screen time.

If children with overweight are educated enough about diet restriction and performing Suryanamaskara along with Ayurvedic remedies, it will be beneficial to them to lead a healthy and happy life.

Objectives

The aim of the study is to evaluate the equivalent efficacy of Navak Guggulu versus Vachaharidradi Gana Vati along with diet restriction and Suryanamaskara in children with Sthaulya (Overweight).

Primary Objectives

The primary objectives are (1) to evaluate the clinical efficacy of Navak Guggulu along with diet restrictions and Suryanamaskara in children with Sthaulya (overweight) on BMI and other parameters, (2) to evaluate the clinical efficacy of Vachaharidradi Gana Vati along with diet restrictions and Suryanamaskara in children with Sthaulya (overweight) on BMI and other parameters, and (3) to compare the efficacy of Navak Guggulu and Vachaharidradi Gana Vati along with diet restrictions and Suryanamaskara as adjuvant therapies in children with Sthaulya (overweight) on BMI and other parameters.

Secondary Objectives

The secondary objectives are (1) to evaluate the residual efficacy of Navak Guggulu versus Vachaharidradi Gana Vati in children with Sthaulya (overweight) after discontinuation of treatment after 180 days as well; (2) to study the effect of desha, kala, and prakruti on the children with overweight; and (3) to study the adverse effects of Vachaharidradi Gana Vati if any.

Hypotheses

The hypotheses are as follows:

- H0 null hypothesis: Vachaharidradi Gana Vati and Navak Guggulu along with diet restrictions and Suryanamaskara are not equivalent in efficacy in reducing the BMI in children.
- H1 alternate hypothesis: The efficacy of Vachaharidradi Gana Vati is equal to Navak Guggulu along with diet restrictions and Suryanamaskara in reducing the BMI in children.

Methods

Study Design

A randomized, standard-controlled, double-blind equivalence clinical trial will be performed. The study flow is depicted in Figure 1. The study participants required for the trial include children with overweight aged between 10 and 16 years of age will be selected from the Outpatient Department and Inpatient Department of the Department of Kaumarbhritya, Mahatma Gandhi Ayurveda College Hospital and Research Centre, Salod (H), and Chhatrapati Shahu Maharaj Shikshan Sanstha's (CSMSS) Ayurved College and Hospital, Chhatrapati Sambhajinagar, based on the inclusion criteria.

Overweight (Sthaulya) children will be diagnosed as having a BMI greater than or equal to 23 and less than 27 kg/m^2 [11]. Screening will include hemoglobin percentage, thyroid-stimulating hormone, and random blood sugar. A total of 88 diagnosed children with overweight will be selected after obtaining written informed consent from their guardians. Participants will be randomly divided into 2 groups by block randomization using a computerized random number generator or statistical software. Group A (control group) will receive Navak Guggulu, while group B (trial group) will receive Vachaharidradi Gana Vati orally (Table 1). Medications will be dispensed in opaque containers following the sequentially numbered, opaque, sealed envelope (SNOSE) technique to maintain allocation concealment. Both groups will receive counseling to perform 12 Suryanamaskara (Sun Salutation) per day and adhere to the dietary restrictions. Guardians will be educated and advised to support their children's consistent participation in the interventions. All the baseline parameters will be recorded at the study's initiation. The treatment duration will be 90 days, with follow-up assessments on the 15th, 30th, 45th, 60th, 75th, and 90th day to monitor progress and ensure adherence. Lipid profile will be assessed before treatment and on the 90th day of intervention to evaluate the efficacy of the interventions. An additional follow-up will occur on the 180th day to determine whether the intervention's possible effects are lasting.

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Figure 1. The study design. SES: socioeconomic status.

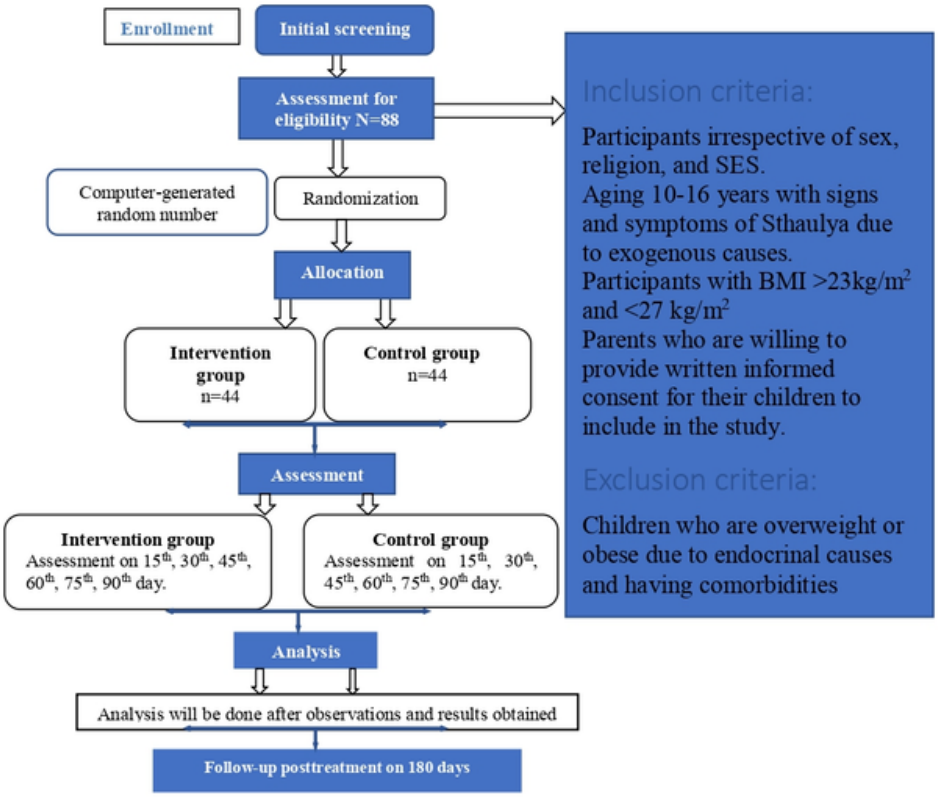

Table 1. Overview of intervention.

	A (control group)	B (intervention group)
Participants, n	44	44
Name of medication	Navak Guggulu	Vachaharidradi Gana Vati
Dosage	Young's formula	Young's formula
Frequency	Thrice a day before meals	Thrice a day before meals
Duration	90 days	90 days
Assessment	1st, 15th, 30th, 45th, 60th, 75th, and 90th day	1st, 15th, 30th, 45th, 60th, 75th, and 90th day
Follow-up	180th day	180th day
Route of administration	Oral	Oral
Anupana	Lukewarm water	Lukewarm water

The Suryanamaskara techniques following the Bihar School of Yoga Tradition will be advocated to the children [36,37]. Each participant will be provided with detailed written instructions, provided in local language, outlining the Ayurvedic diet restrictions as follows: avoid eating all sweet food items (chocolate, ice creams, etc), potatoes, dairy products (paneer, curd, cheese, Shrikhand, etc), fried foods (wafers, puri, and pakora), and bakery products (biscuits, pastries, cakes, bread, etc); refrain from consuming junk foods and fast-food items; avoid sweetened soft drinks and beverages; and avoid overeating and eating without hunger and ensure appropriate intervals between meals. Patients will be given regular reminders also through calls or SMS text messages to follow diet restrictions and perform Suryanamaskara. SPIRIT (Standard Protocol Items: Recommendation for Interventional Trials) guidelines will be used for the study.

Inclusion Criteria

The inclusion criteria are as follows: participants irrespective of gender, religion, and socioeconomic status, age group between 10 and 16 years with signs and symptoms of overweight (Sthaulya) due to exogenous causes, participants with BMI ≥23 and <27 kg/m^2, and parents who are willing to provide written informed consent for their children to be included in the study.

Exclusion Criteria

The exclusion criteria are as follows: children having BMI <23 and ≥27 kg/m^2, children aged <10 years and those aged >16 years, and children who are overweight due to endocrine causes.

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Children experiencing severe systemic illnesses like hypertension, asthma, diabetes mellitus, nephrotic syndrome, kwashiorkor, and congestive cardiac failure having anasarca condition are overviewed as overweight.

Drug Collection or Authentication

The raw material for the both the control and intervention drugs will be purchased from a reliable source and will be authenticated and identified by the department of Dravyaguna and Rasashastra of Mahatma Gandhi Ayurved College Hospital and Research Centre, Salod, Wardha.

Details of Drug Composition and Preparation Method

The control drug is Navak Guggulu, which is a polyherbal compound mentioned in Yogaratnakara [38]. It has been proven to have antiobesity effects in many randomized controlled trials (RCTs). The composition of Navak Guggulu is presented in Table 2.

Table 2. Latin name and family name of the herbs used in Navak Guggulu.

Serial No	Drug	Latin name	Family
1	Shunthi	*Zingiber officinale*, Roscoe	Zingiberaceae
2	Pippali	*Piper longum*, Linn	Piperaceae
3	Marich	*Piper nigrum*, Linn	Piperaceae
4	Haritaki	*Terminalia chebula*, Retz	Combretaceae
5	Bibhitaki	*Terminalia bellirica*, Roxb	Combretaceae
6	Amalaki	*Emblica officinalis*, *Phyllanthus emblica*, Linn	Euphorbiaceae
7	Musta	*Cyperus rotundus*	Cyperaceae
8	Chitrak	*Plumbago zeylanica*, Linn	Plumbaginaceae
9	Vidanga	*Embelia ribes*, Burm	Myrsinaceae
10	Guggulu	*Commiphora mukul* or *Balsamodendron mukul*, Hook	Burseraceae

Preparation Method of Navak Guggulu

In the Good Manufacturing Practice (GMP)–certified pharma company, guggulu will be first purified by dissolving in Triphala kwatha (decoction), and then, the decoction will be filtered and concentrated by heating it. In that concentration, the remaining herbs in the form of fine powder will be mixed well. Then, this mass will be dried in the drying machine. With the help of a punching machine, tablets of 300 mg will be made. Each tablet of Navak Guggulu approximately contains 150 mg of pure guggulu and 16.66 mg of remaining herbs each.

The intervention drug is Vachaharidradi Gana mentioned by Acharya Vagbhata in his classic Ashtanga Hridaya [39]. It has the opposite qualities to Kapha and Meda. Keeping this fact in mind, selected herbs from Vachaharidradi Gana were selected for oral use in children with overweight in the modified form of tablet (vati). The selected drugs are detailed in Table 3, and their preparation process is shown in Figure 2.

Table 3. Latin name and family name of the herbs used in Vachaharidradi Gana Vati.

Serial No	Drug	Latin name	Family
1	Vacha	*Acorus calamus*, Linn	Araceae
2	Musta	*Cyperus Rotundus*, Linn	Cyperaceae
3	Devdaru	*Cedrus deodara* or *Pinus deodara*, Roxb	Pinaceae
4	Shunthi	*Zingiber officinale*, Roscoe	Zingiberaceae
5	Haritaki	*Terminalia chebula*, Retz	Combretaceae
6	Haridra	*Curcuma longa*, Linn	Zingiberaceae
7	Daruharidra	*Berberis aristata*, DC	Berberidaceae

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Figure 2. Preparation method of Vachaharidradi Gana Vati. GMP: Good Manufacturing Practice.

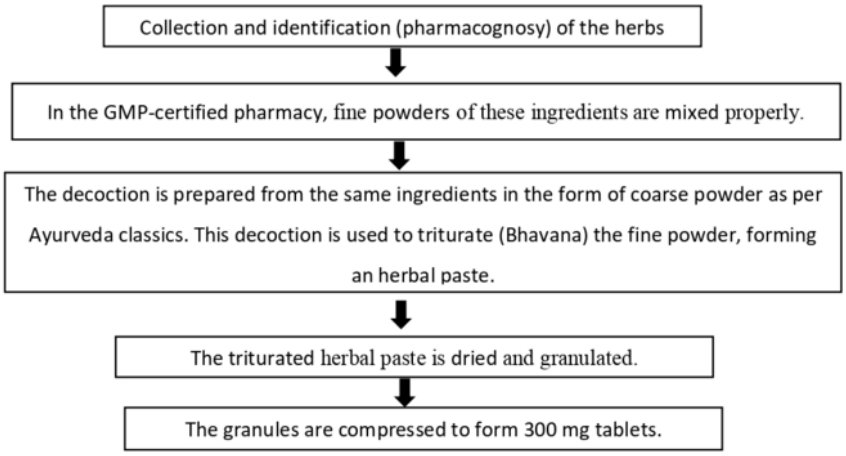

The process of trituration is a part of the Ayurvedic pharmaceutical concept known as Bhavana. It enhances the bioavailability of the active compounds. Each tablet of Vachaharidradi Gana Vati contains approximately 50 mg of each herb, along with 5 mg of decoction of each herb. The quality control of the final products will be assessed by analyzing both the raw materials and final products of both drugs in a GMP-certified pharmacy.

Criteria for Assessment

Objective Parameters

The anthropometrical parameters, weight, BMI, waist circumference, abdominal girth, mid-arm circumference, waist-hip ratio (WHR), and triceps skinfold thickness (TSFT), will be measured before and after treatment.

Instruments and Techniques Required for Anthropometric Data Collection

Children's weight will be measured with an electronic portable scale with high sensitivity and specificity and will be calibrated from time to time. Height will be measured by portable stadiometers, with the participants' feet placed together with heels, buttocks, and shoulder blades against the stick and head positioned in the Frankfurt horizontal plane. Waist and hip circumferences will be measured twice using inextensible anthropometric tape, with the children standing erect and relaxed with arms at the sides and feet positioned close together. Waist circumference will be measured midway between the lowest border of the rib cage and the upper border of the iliac crest, at the end of normal expiration [40].

Hip circumference will be measured at the widest part of the hip at the level of the greater trochanter. Mid-upper arm circumference will be taken at midpoint of the tip of the acromion process to the olecranon process, with the tape slung to the skin but not compressing the soft tissues. Both right and left sides will be measured, and the average will be taken [41].

For all measurements, the tape will be positioned at a level parallel to the floor. All measurements will be in centimeters to the nearest 0.1 cm, except TSFT. TSFT will be measured in millimeters at the midpoint between the tip of the acromion process and the olecranon process (back side of the middle upper arm) with the help of the calibrated skinfold caliper. BMI will be calculated as the ratio of body weight to the square of height (kg/m^2), and WHR will be calculated as the ratio of waist to hip circumference [42]. Proper training will be provided to the personnel for accurate measurements using these techniques.

Investigations Proposed

Hemoglobin percentage, thyroid-stimulating hormone, and random blood sugar are the screening tests to be done only before treatment, whereas lipid profile will be done to assess the efficacy of interventions before treatment as well as after treatment. These laboratory tests will be performed using standard equipment and gold standard methods to ensure accurate results.

Subjective Parameters

Signs and symptoms of obesity (Sthaulya) are mentioned in the Ayurvedic texts, and for assessing the severity of each symptom, they were graded following the book called WHO-Direct Financial Cooperation sponsored project on Developing Guidelines for Clinical Research Methodology in Ayurveda. It is illustrated in Table 4 [43].

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Table 4. Signs and symptoms of Sthaulya according to Ayurvedic classics.

Signs and symptoms or gradation	0	1	2	3	4
Pendulous hips, abdomen, breasts (chala sphika, udara, stana)	Absence of movements (in the areas) (Chalatva)	Little visible movement (in the areas) after rapid movement	Little visible movement (in the areas) after moderate movement	Movement (in the areas) after mild movement	Movement (in the areas) after changing posture
Bad odor (angagandha)	No odor	Bad odor but not offensive	Strong odor but can be lessened by the use of deodorants and perfumes	Very strong odor even after using fragrances (use of deodorants or perfumes)	—[a]
Perspiration (swedadhikya)	Sweating after heavy work and fast movement or in hot weather	Profuse sweating after moderate work and movement	Sweating after little work and movement (stepping ladder)	Profuse sweating after little work and movement	Sweating even at rest or in cold weather
Increased appetite (kshudha-adhikya)	As usual or routine	Slightly increased (1 meal extra with routine diet)	Moderately increased (2 meals extra with routine diet)	Markedly increased (3 meals extra with routine diet)	—
Increased thirst (pipasa-adhikya)	Feeling of thirst (7-9 times or 24 hours) and relieved by drinking water	Feeling of moderate thirst (>9-11 times or 24 hours) and relieved by drinking water	Feeling of excess thirst (>11 times or 24 hours) and not relieved by drinking water	Feeling of severe thirst (>13 times or 24 hours) and not relieved by drinking water	—
Exertional dyspnea (kshudra shwasa)	No dyspnea even after heavy work	Dyspnea after moderate work but relieved later and tolerable; dyspnea by climbing upstairs of 10 steps, and time taken will be more than 15 seconds	Dyspnea after little work but relieved later and tolerable; dyspnea by climbing upstairs of 10 steps, and time taken will be more than 25 seconds	Dyspnea after little work but relieved later and not tolerable; dyspnea by climbing upstairs of 10 steps, and time taken will be more than 35 seconds	Dyspnea in resting condition
Increased sleep (nidradhikya)	Normal and sound sleep for 6-8 hours or 24 hours with a feeling of lightness and relaxation in the body and mind	Sleep>8-9 hours with slight heaviness in the body	Sleep>9-10 hours or 24 hours with heaviness in the body associated with yawning (Jrimbha)	Sleep>10 or 24 hours with heaviness in the body associated with yawning (Jrimbha) and sleepiness (Tandra)	—

[a]Not applicable.

Participants

It is crucial to calculate the effect size according to the equivalence or superiority formula with the help of the SD and mean difference of the reference paper [44]. This approach enhances the RCT, making it superior to other types of research. In this study, an attempt is made to assess the equivalence effect of Vachaharidradi Gana Vati against the standard controlled drug, Navak Guggulu. The equivalence formula is applied, and the sample size is calculated to minimize any bias. So, the formula for equivalence (parallel design) has been used to calculate the sample size of this study. For that, the reference values of the control drug have been used [44].

The formula for equivalence (parallel design) is:

where Z_α=1.96, α=type I error at 5%, σ=SD, Z_β=0.84 (for equivalence 2-tailed), β=type II error at 20%, and δ=true differences in means.

Sample size (N) = $n1 = 2 \times (1.96 + 0.84)^2 \times (0.86)^2/(0.57)^2 = 39$ each

Total=78 samples. With 10% dropout=43 each=86 samples.

Justification on the Formula

The equivalence formula for parallel-group design is particularly suitable for this study, as it is specifically designed to determine the sample size needed to assess whether 2 interventions—Vachaharidradi Gana Vati and Navak Guggulu—are statistically equivalent within a defined margin of clinical acceptability. This approach is crucial for trials aimed at establishing equivalence rather than superiority or noninferiority. The formula accounts for the population variability in the population by incorporating the SD of the control drug and ensures a robust comparison by considering both type I and type II error rates, set at 5% and 20%, respectively. This balance between the risks of false-positive and false-negative results is critical in equivalence trials, where even small differences may have clinical significance.

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By including the true difference in means (δ), the formula ensures that the calculated sample size is adequate to detect equivalence within the predefined margin. The adjustment for a 2-tailed test reflects the bidirectional nature of equivalence testing, ensuring that the study is powered to detect differences in either direction. Given these attributes, this formula provides a scientifically robust framework for calculating the required sample size, ensuring that the study's conclusions about equivalence are statistically valid and clinically meaningful. The sample size ensures that each participant receives individualized care and monitoring.

For reference values, a clinical trial paper was used [44].

Randomization and Allocation Sequence Generation

The earlier estimated sample size of 86 is increased to 88 children with overweight to have an equal balance in each group of the treatment.

Randomization Procedure for 88 Participants (44 Each Group)

For a total sample size of 88 overweight patients (44 in each group: Navak Guggulu and Vachaharidradi Gana Vati), block randomization will be used to ensure balanced allocation throughout the study [45]. A block size of 4 will be used, dividing the sample size into 22 blocks. Each block will consist of predefined sequences, such as AABB, ABAB, BABA, or BBAA, where "A" represents group A (Navak Guggulu) and "B" represents group B (Vachaharidradi Gana Vati). These sequences ensure that within each block, participants are equally allocated to both groups. The randomization sequence will be generated using a computerized random number generator or statistical software, ensuring variability in block order. The randomization process will be managed by a trained, unblinded departmental faculty member who is not involved in the study. The block randomization procedure ensures that both groups maintain equal sample sizes while preventing predictability, preserving the study's internal validity and robust design.

Allocation Implementation

To maintain allocation concealment, the group assignments will be placed in SNOSE, with each envelope containing 1 allocation based on the pregenerated sequence. The SNOSE technique is widely used in clinical trials [46]. The process of assigning treatments to these envelopes will be conducted by personnel not involved in enrolling or assessing participants. To maintain blinding, treatments will be labeled with coded identifiers. Treatments A and B will be recoded by unblinded, trained faculty using either code III or code IIII. This unblinded faculty will not be involved in the trial's conduct and assessment. The blind code III or IIII will be labeled on the respective patient numbers on the opaque containers by the trained, unblinded faculty. These recoded opaque containers will then be handed over to the investigator for further administration to the patients. An unblinded, trained faculty will also provide 88 sealed envelopes to the investigator, containing unblinded information about the treatment administered to each patient. These sealed envelopes will be kept intact under the investigator's custody until the completion of the last visit of the last enrolled patient in the study and stored in a manner that prevents accidental disclosure. A master chart will be prepared as a data source for statistical analysis and will be handled with high security, ensuring confidentiality and limited access to authorized personnel only. When the data have been locked, the outcome assessor (statistician) will unblind the treatment codes for statistical analysis.

Data Collection Tools and Process

This study will use Ayurveda Samhitas (textbooks on Ayurveda), modern texts, and a web-based search of PubMed, Google Scholar, etc. Navak Guggulu (tablet) and Vachaharidradi Gana Vati (tablet) will be prepared in a GMP-certified pharmacy. The study will also use a case record form, patient information sheet, written dietary restriction, and written informed consent form. The observers will be trained properly to assess the subjective parameters and anthropometrical measurements to ensure proper data collection in the case record Form. The periodic follow-up of every fortnight for 90 days has been advocated, so the data of objective measurements and subjective criteria will be collected in case record forms every fortnight to ensure adherence. The data regarding lipid profile values will be collected before and after intervention. Quality checks will be performed manually.

Outcomes

Primary Outcome—BMI

BMI will be calculated as the ratio of body weight to the square of height (kg/m^2). Indian Academy of Pediatrics 2015 charts will be used to categorize weight as normal, overweight, and obese.

Secondary Outcome

The secondary outcomes are as follows: (1) anthropometric measurements including mid-upper arm circumference, abdominal girth, waist circumference, hip circumference, and WHR in children with overweight; (2) reduction in lipid profile values in children with overweight; and (3) reduction of signs and symptoms of obesity (Sthaulya) mentioned in Ayurvedic classics following the gradations in the book called WHO-Direct Financial Cooperation sponsored project on Developing Guidelines for Clinical Research Methodology in Ayurveda [43].

Statistical Analysis

The statistical analysis will be performed at the end of the study. It will involve various tests to evaluate both within-group and between-group efficacy of Navak Guggulu and Vachaharidradi Gana Vati in managing Sthaulya (overweight) among children. For normally distributed continuous variables like BMI, WHR, and skinfold thickness, paired 2-tailed *t* tests will be used to evaluate the efficacy of each intervention within the same group (pre- and posttreatment comparisons).

For nonnormally distributed data, the Wilcoxon signed rank test will be used. For normally distributed data, independent 2-tailed *t* tests will be used for between-group comparisons of mean changes; for nonnormal data, the Mann-Whitney *U* test will be used.

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To ensure valid comparisons, the analysis of covariance will be used to account for any potential baseline variations between groups. To evaluate residual efficacy after treatment discontinuation at 180 days, repeated measures ANOVA will analyze longitudinal changes in outcomes, while mixed-effects models will handle missing data or variability across time points. For stratified analysis based on Desha (geography), Kala (season), and Prakruti (body constitution), multivariate regression analysis will identify predictors of treatment efficacy, and interaction analysis will explore the influence of these factors. A statistician consultation will be considered for the selection of the proper statistical method.

Data Monitoring Committee

It consists of the researcher, under the guidance of the supervisor and cosupervisor, along with the statistician and departmental faculty members. The progress will be monitored by supervisors and statisticians by reviewing the group-wise case record forms and master charts.

Ethical Considerations

The Mahatma Gandhi Ayurved College Hospital and Research Centre's Institutional Ethics Committee approved this study (registration: MGACHRC/IEC/July-2022/521), and it was also registered with the Clinical Trial Registry of India (CTRI/2023/03/051135). The same ethical committee also approved the addition of the site at CSMSS Ayurved College, Chhatrapati Sambhajinagar. After receiving a No Objection Certificate from the institutional ethical committee of the CSMSS Ayurved College (AMCS/1407/2023), the participant recruitment at both sites will be initiated. The institutional ethical committee will decide on the end point and oversee the trial as it progresses. The researchers will assess any adverse events and will report to the ethics committee. Consent from parents and assent from patients (older than 12 years) will be obtained before conducting the trial in the local language while explaining every aspect of the study. Every participant will get information regarding the study's design and objectives, data confidentiality, and the freedom to withdraw from the study at any moment without giving a reason. The informed consent form includes a patient information sheet (part 1) and a certificate of consent (part 2). Secondary analysis will be covered without additional consent. Data will be anonymized, and the personal information of the participants will be kept confidential before, during, and after the trial. Physical data will be stored in a protected storage facility, with access available only to the researchers. Computerized data will be held in a password-protected computer. Data access will be restricted to members of the research team only. During data analysis, measures will be taken to protect participants' privacy. Participation in the study is completely voluntary; hence, no incentive will be provided to the participants. During the treatment period, if the patients' condition worsens, the case will be excluded and will receive conventional treatment and care until the symptoms subside, free of charge. The ethics committee will be informed of the patient's condition. The therapy will be discontinued, and the child will be withdrawn from the study if any other illness arises during the treatment period that could influence study outcomes. Similarly, if a participant experiences personal issues that prevent continuation of therapy and are likely to affect the study results, they will also be withdrawn. If the patient misses any of the periodic follow-ups during the intervention, they will be excluded from the study.

Results

In April 2024, the randomized controlled study got underway. Since participants may be in the study at any time, our goal is to complete the research by May 2025. Any significant changes to the protocol will be posted on ClinicalTrials.gov. The study's findings will be disseminated through publications.

Discussion

Principal Findings

Childhood obesity has been rising in the past 3 decades. Its prevalence is increasing both in the higher socioeconomic groups as well as lower socioeconomic groups [7]. The short- and long-term associations between overweight and a range of adverse health-related outcomes are well established and raise the level of importance for understanding overweight as a major public health concern for children and adolescents. Lack of physical activities and uncontrolled dietary habits are the root causes of higher incidence rates of overweight in children. Nowadays, increased screen time is also contributing to this problem. It increases motivated responses to food intake and snacking behavior among children and adolescents [47,48].

Vachaharidradi Gana is a herbal compound mentioned in Ayurvedic classics that is effective in the reduction of excessive fat by its Kaphamedohara property. In the case of Sthaulya [49], there is an abundance increase in Kapha and Medo Dhatu (fats). These Dhatu are predominant in Jala (water element) and Pruthvi (earth element) Mahabhuta. The contents of the Vachaharidradi Gana are opposite in characteristics to that of Kapha-Medodhatu. Thus, it is expected to break the etiopathogenesis of Sthaulya if administered to children with overweight.

Dietary changes are directly linked to weight loss. Fixed lunch and dinner times, low-fat meals, fiber-rich vegetables, and reduced frequency and amount of food are advocated in the management of Sthaulya [50]. However, it may be a matter of concern to maintain the reduced weight for a longer period. Hence, with the addition of diet control and medicine administration, it is essential to add some behavioral changes too. Behavioral modifications are found to be useful for good weight maintenance. In Ayurveda, it is aimed at exercises or yogic practice. Yogic practices involve stretching and relaxation of various muscles steadily, which breaks down triglycerides and mobilizes fatty acids. Yogic practices also act synergistically with diet restrictions in Sthaulya [51,52]. Yoga practices such as Suryanamaskara can be an enjoyable and engaging way to encourage physical activity among children, fostering self-discipline, which could extend to healthier eating habits and more structured activity levels with improved mental well-being. While specific studies on Suryanamaskara for childhood obesity are limited, studies on general yoga practices for children have shown promising results in reduced BMI and

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waist circumference and are equally effective as the standard weight management for BMI reduction in the pediatric and adolescent age group [53-55]. One-hour yoga session for 12 weeks comprising Suryanamaskara, asanas, pranayama, and meditation in adolescent girls having polycystic ovarian syndrome showed significant alterations in blood glucose, insulin, and lipid levels [56]. A review paper on Suryanamaskara concluded that if practicing Suryanamaskara is initiated in children at the age of 7-8 years, it helps them grow better not only physically but also with great mental health [36]. In this study, the daily performance of Suryanamaskara is advocated in the form of a yogic practice. Hence, it was hypothesized that the Vachaharidradi Gana Vati along with diet restriction and Suryanamaskara will help in the reduction of the weight and BMI of children with overweight.

Navak Guggulu, on the other hand, is a control drug, whose efficacy has been proven in obesity and hyperlipidemia. The addition of diet restriction and Suryanamaskara will add further to its proven efficacy. The effect of combined interventions in both groups is expected for a sustained period even after the stoppage of the medicines.

This is the first study in which Suryanamaskara is advocated as part of a multidimensional treatment modality for reducing weight and BMI in children. It will further elaborate on the benefits of Suryanamaskara in children. It is expected that this modality will also help to lower the raised values (if any) of lipid profiles and the signs and symptoms of Sthaulya.

Children do not tolerate dosage that is in powdered form; therefore, changing the powder form of a medication into a tablet makes dosage calculations simple and makes sure that the recommended quantity is administered. Further, the double blinding will help in controlling performance bias and ascertainment bias that might inadvertently sweep into the study.

Being overweight deteriorates cognitive functioning in children while it adversely affects them psychologically. Children with overweight show behavioral disorders, a high emotional nature, damaged self-awareness, and low self-evaluation and demonstrate unhappiness. It is a cause of social concern [57,58].

Considering all these factors, treating children with overweight and preventing them from becoming obese are of utmost importance. The available research on overweight in children is limited. Given the multifactorial etiopathogenesis of children with overweight, drug administration alone will not be sufficient for treatment. Therefore, a multidimensional approach to treating children with overweight will be practiced in this study. Positive study findings may implicate a feasible, promising, noninvasive, and affordable intervention for managing children with overweight, which also offers sustainable holistic lifestyle modifications and positive psychological changes. This study could enhance the scientific credibility of Ayurveda in managing childhood obesity and support its integration into modern health care guidelines. The use of locally available, affordable herbs like Vachaharidradi Gana Vati could make obesity management more accessible in low-income settings.

Limitations

The parents may resist accepting the fact that their children with overweight need treatment. It may be difficult to monitor whether the children follow diet restrictions and Suryanamaskara for a longer period. Additionally, as this is a PhD study without external funding, the sample size is relatively small.

Potential Avenues or Strengths of Study

Ayurveda herbal medicines have great potential or impact to cure the disease naturally without any side effects. The Ayurvedic diet and lifestyle recommendations can be added as multidimensional aspects of the conventional treatment modality.

This research trial is planned to know the Kaphamedohara effect of the classical formulation by administering it orally to children with overweight. The positive outcome of the study will facilitate the commercialization of the product, Vachaharidradi Gana Vati. Further, the medicines used in the study can be patented and made copyrighted later and publicized for the benefit of the population. Large-scale, multicentric RCTs can be conducted to test the effect of Vachaharidradi Gana Vati on children with overweight and also children with obesity. Such a trial can be conducted in adults and young children (aged 3-9 years) as well. Longitudinal studies could evaluate the long-term impact of Ayurvedic interventions on childhood obesity, focusing on not only weight and BMI management but also quality of life, psychological well-being, and prevention of obesity-related diseases in adulthood.

Conclusions

This research will be useful to provide new insight into the effectiveness of the Ayurveda pharmacological approach in treating obesity in children. The results will guide evidence-based multimodality in treatments aimed at changing lifestyle behaviors in children with obesity, thus reducing social stigmatization in them.

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of the study design, methodology, data collection procedures, data analysis plan, and ethical considerations. By disseminating this protocol, we hope to advance knowledge in the field and facilitate future research. Further, the original paper could be disseminated in a peer-reviewed journal. Oral poster and paper presentations of study findings could be done in national and international seminars and conferences. All authors declared that they had insufficient funding to support open access publication of this manuscript, including from affiliated organizations or institutions, funding agencies, or other organizations. JMIR Publications provided article processing fee support for the publication of this paper.

Data Availability

The study is ongoing, and the datasets that will be generated and analyzed will be available from the corresponding author upon reasonable request.

Authors' Contributions

KKF contributed to conceptualization, data collection, data curation, statistical analysis, writing the original draft, review, and editing. RBR managed conceptualization, methodology, data collection, writing the original draft, review, and editing. KSR managed conceptualization, methodology, and data collection. BJR managed writing original drafts in sections. PRD contributed to conceptualization, writing original drafts, and review.

Conflicts of Interest

None declared.

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Abbreviations

CSMSS: Chhatrapati Shahu Maharaj Shikshan Sanstha
GMP: Good Manufacturing Practice
RCT: randomized controlled trial
SNOSE: sequentially numbered, opaque, sealed envelope
SPIRIT: Standard Protocol Items: Recommendation for Interventional Trials
TSFT: triceps skinfold thickness
WHO: World Health Organization
WHR: waist-hip ratio

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Protocol

Effectiveness, Engagement, and Safety of a Digital Therapeutic (CT-155/BI 3972080) for Treating Negative Symptoms in People With Schizophrenia: Protocol for the Phase 3 CONVOKE Randomized Controlled Trial

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Abstract

Background: Negative symptoms of schizophrenia, such as lack of motivation, pleasure, social interest, and expression, are key contributors to functional impairments in people with schizophrenia. While psychosocial interventions have demonstrated efficacy, no Food and Drug Administration–approved pharmacotherapies exist specifically to target these symptoms. Evidence-based digital therapeutics (DTx) may offer novel, scalable treatment options to augment existing treatments.

Objective: This article describes the study design and methods of a phase 3, multicenter, double-blind, randomized controlled study (CONVOKE). It aims to evaluate the effectiveness and safety of CT-155/BI 3972080 (CT-155), a smartphone-based DTx, as an adjunct to standard-of-care antipsychotic medication in adults with experiential negative symptoms of schizophrenia.

Methods: Eligible participants were 18 years or older with a primary diagnosis of schizophrenia receiving stable antipsychotic medication for ≥12 weeks, scored ≥2 on average in at least 2 Clinical Assessment Interview for Negative Symptoms Motivation and Pleasure subscale (CAINS-MAP) domains, and were smartphone owners. Participants were randomized 1:1 to CT-155 (intervention arm) or a digital control app (control arm). CT-155 integrates aspects of multiple evidence-based psychosocial therapeutic techniques, incorporating principles of in-person psychotherapy aimed at targeting negative symptoms. Development of CT-155 was informed by patients during early clinical learning studies using earlier versions of the app. The digital control included elements of the disease educational components of CT-155 and daily digital check-ins. Participants were blinded to their assigned intervention. A blind-to-hypothesis was used so participants appropriately engaged with both apps. Accordingly, participants were informed that they would receive one of 2 interventions under investigation. Investigators, designated site personnel, and central raters were blinded throughout the study. The study comprised a 2-week screening period, 16-week active period, and a 4-week follow-up period. Change in experiential negative symptoms from baseline to Week 16 (primary end point) was assessed using CAINS-MAP (centrally rated). Other study end points included Clinical Assessment Interview for Negative Symptoms Expressivity, Positive and Negative Syndrome Scale, Personal and Social Performance Scale, Dysfunctional Attitudes

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Scale, Clinical Global Impressions-Severity, and Patient Global Impression of Improvement Scale. Frequency and severity of adverse events were also assessed, as well as engagement and adherence to either app.

Results: Study enrollment began in March 2023 and was completed in January 2025. Overall, 457 participants were enrolled across 66 clinical study sites in the United States.

Conclusions: We summarize an innovative trial design for CONVOKE, a phase 3 randomized controlled study aimed at assessing the effectiveness, engagement, and safety of CT-155 as an adjunct to standard-of-care for people with negative symptoms of schizophrenia. CONVOKE is the largest-to-date and most robust clinical trial evaluating the effectiveness and safety of a DTx in schizophrenia. The study protocol included a centrally rated primary end point (CAINS-MAP), blind-to-hypothesis, with an appropriately designed digital control.

Trial Registration: ClinicalTrials.gov NCT05838625; https://www.clinicaltrials.gov/study/NCT05838625

International Registered Report Identifier (IRRID): DERR1-10.2196/81293

(JMIR Res Protoc 2025;14:e81293) doi:10.2196/81293

KEYWORDS

digital control; digital therapeutics; negative symptoms; psychosocial intervention; randomized clinical trial; schizophrenia; smartphone; patient-centricity

Introduction

Schizophrenia is a complex psychiatric condition with a large disease burden and is one of the top causes of disability globally, presenting considerable challenges for patients, caregivers, and health care systems [1-4]. In the United States, people living with schizophrenia have a severely reduced life expectancy (losing ≈28.5 years of life) [5] and significantly higher mortality rate [6] than the general population. The economic burden of schizophrenia is also substantial, with estimated costs exceeding US $340 billion in 2019 [7]. Symptoms of schizophrenia are categorized into 3 primary domains: positive, negative, and cognitive [8,9]. Negative symptoms are a major contributor to poor quality of life, frequently occurring early in the prodromal phase and often persisting throughout all stages of the illness [10-14]. Despite several clinical trials, no pharmacological treatment has demonstrated efficacy for negative symptoms [15-23], and to date, no medication has been specifically approved by the Food and Drug Administration (FDA) to target negative symptoms [24,25].

Negative symptoms are conceptualized as being either expressive or experiential: expressive negative symptoms include affective flattening (reduced emotional expression) and alogia (reduced verbal expression), while experiential negative symptoms (ENS) consist of asociality (lack of social interest), avolition (lack of goal-directed behavior), and anhedonia (inability to experience joy or pleasure) [10,26]. People living with schizophrenia report a significant impact of negative symptoms on their daily functioning, through loss of interest in social activities, diminished pleasure, and reduced motivation [27]. These symptoms not only affect people with schizophrenia, but also place a substantial burden on their families and the wider health care system [28]. Furthermore, ENS have been associated with poorer outcomes than expressive negative symptoms [29,30]. Recent findings from a workshop conducted as part of the FDA's patient-focused drug development initiative [27,31], showed that patients and their caregivers have also expressed a need for new treatments to help meaningfully improve their quality of life (eg, by helping them enjoy daily activities, improving motivation, and making it easier to maintain relationships) [27].

Current schizophrenia treatment guidelines recommend a comprehensive and person-centered approach that includes pharmacological treatments (eg, antipsychotics) and evidence-based nonpharmacological treatments (eg, adjunctive psychosocial intervention) [32-34]. While many antipsychotics approved by the FDA for the treatment of schizophrenia help stabilize and manage positive symptoms, their effects on negative symptoms remain limited and inconsistent, with many individuals experiencing little to no meaningful improvement [10,33,35-37].

Research has demonstrated that psychosocial interventions may target negative symptoms by focusing on cognitive restructuring of dysfunctional beliefs [38-50]. These interventions aim to help revise internal motivation and pleasure seeking in people with schizophrenia, fostering a desire to pursue meaningful goals by reducing defeatist beliefs [42,51,52]. However, psychosocial interventions can be time-intensive, costly, and require specialized clinicians, who are not widely available [53-55]. Accordingly, there remains a critical need for innovative treatments that are not only effective and accessible, but also designed to navigate symptom-related challenges (eg, stigma and social isolation) and systemic health care barriers [53,56-63].

With many people living with schizophrenia having access to smartphones [64,65], evidence-based clinically evaluated digital therapeutics (DTx) can help expand the nonpharmacologic treatment options. Benefits of DTx include access to care anytime and anywhere, cost effectiveness, support during long wait times between referral and beginning in-person therapy, additional support between in-person therapy sessions, continuity of care, and anonymity, allowing people to avoid stigma or feelings of judgment [63,66-69]. Additionally, including patient perspectives during the development of a DTx may support the creation of treatments that can better assimilate into daily routines within the patient's own environment. However, DTx are often perceived to have limitations, including concerns about the lack of rigorous and inclusive clinical trials

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[70]. In the context of schizophrenia specifically, additional challenges include difficulties with patient engagement and adherence, and barriers related to access to technology and the requirement of digital literacy to use these interventions effectively [71].

Early research studies have shown the promise of DTx for the treatment of symptoms of schizophrenia [72-74]; however, these findings should be interpreted in the context of their limitations, such as small sample size and single-arm design, which are common in exploratory research [72-74]. More recent randomized controlled trials have produced mixed results. For example, a larger study evaluating PEAR-004 found no statistically significant difference in the reduction of positive symptoms compared with a digital control after 12 weeks [75], despite an early single-arm study showing clinical effectiveness [76]. Similarly, the Actissist study reported no significant differences between the DTx intervention and a remote symptom monitoring app used as an active control [77]. These findings illustrate the methodological complexity of evaluating DTx, particularly when control conditions may themselves carry therapeutic benefit. They also underscore the importance of adequately powered, controlled trials with well-characterized digital comparators to establish confirmatory evidence, in addition to early-phase clinical learning studies.

To establish DTx as a new treatment modality in mental health, it is especially important to consider study design elements such as appropriate blinding of both participants and investigators to treatment assignments and blinding of participants to the study hypothesis. Blinding minimizes bias and promotes comparable levels of engagement across both treatments [78,79]. Furthermore, the FDA recommends including a digital control when possible, to mimic the actual intervention without providing therapeutic benefit [80], while still maintaining blinding and face-validity [78].

Accordingly, there is a critical need for robust, well-designed randomized clinical studies to rigorously evaluate the effectiveness and safety of DTx to the standards of pharmaceuticals. This is not only to generate the evidence required for FDA regulatory approval but also to support establishing DTx as a new treatment modality delivering safe and effective treatment to patients. To this end, we are conducting a large phase 3 randomized, controlled, double-blind, 16-week study (CONVOKE; NCT05838625) to evaluate the effectiveness and safety of CT-155/BI 3972080 (CT-155) in reducing ENS compared with a digital control. Briefly, CT-155 was developed as a smartphone-based DTx that provides aspects of psychosocial intervention techniques adjunctive to standard-of-care antipsychotic medication to treat negative symptoms of schizophrenia [74,81]. CT-155 was granted Breakthrough Device designation in December 2023 [82]. Here, we discuss the rationale and study design for the CONVOKE study, which refers to study protocol version 5.0 (dated September 2024).

Methods

Study Design

Overview

CONVOKE is a phase 3, multicenter, randomized, double-blind, parallel-group, controlled, 16-week study to evaluate the effectiveness and safety of CT-155 as an adjunct to standard-of-care antipsychotic medication in participants 18 years or older with ENS of schizophrenia (NCT05838625). Participants were enrolled from 66 of 82 activated study sites in the United States. The study, conducted between March 2023 and July 2025, consisted of a 2-week screening period, a 16-week active period, and a 4-week follow-up period (Figure 1). The study is reported in accordance with the SPIRIT checklist.

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Figure 1. Study design. CAINS: Clinical Assessment Interview for Negative Symptoms; CT-155: CT-155/BI 3972080; EOS: end of study.

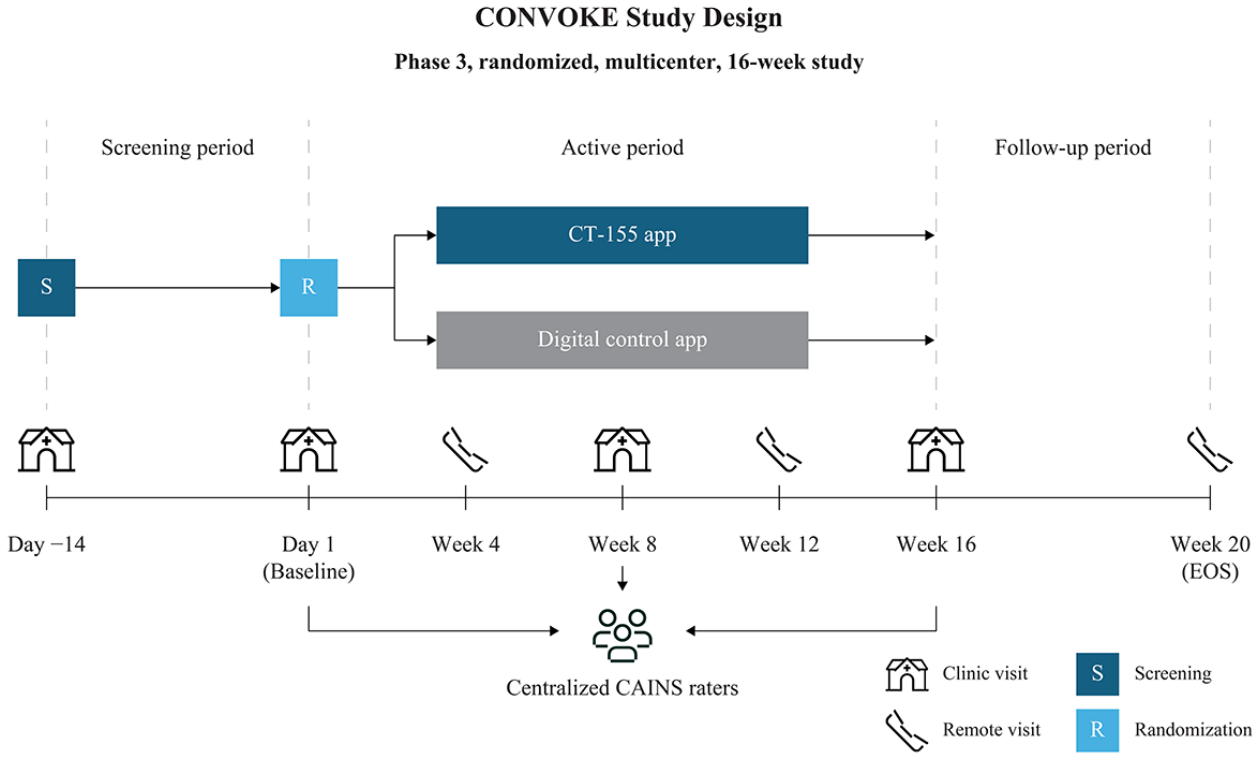

The study had 2 arms; CT-155 (active treatment) and digital control, which were masked as digital therapeutic A and digital therapeutic B, respectively, to maintain the blind-to-hypothesis (further details described below). Study interventions were activated following confirmation of eligibility during the baseline visit.

Eligible participants were randomized 1:1 on Day 1 using an interactive web response system to receive either CT-155 or the digital control app as the study intervention during the active period of the study.

Study Blinding

A blind-to-hypothesis design was used to help maintain face validity of the digital control app and adequate engagement with the study app in both arms [78]. Participants were blinded to the intervention assignment, as well as the study hypothesis. They were informed that they would receive one of the 2 digital interventions under investigation, both of which were called the "study app." Study participants were told that both interventions may or may not be effective and that the study was comparing the effectiveness of the 2 interventions.

Investigators, designated site personnel, and central raters were also blinded to participants' assigned study interventions throughout the course of the study. To maintain this blinding and mitigate the risk of blinded personnel being exposed to unblinded information, separate designated site personnel (ie, not investigator/rater) assisted with downloading, installing, and activating the study app and were responsible for conducting adherence checks. To further minimize potential bias, a blinded centralized rater team administered the primary outcome assessment, Clinical Assessment Interview for Negative Symptoms (CAINS).

Study App Procedures

During an in-person screening visit, designated site personnel assisted participants with downloading, installing, and activating their assigned study app, including account creation and account set-up. These site personnel were unaware of the individuals' assigned intervention. The same app was downloaded for all participants, but was configured based on an access code to either CT-155 or the digital control. After the completion of Week 16, the study app automatically became "inactive" and stopped proactively engaging the participant with therapeutic or control content. However, participants retained access to previously delivered content within the study app during the 4-week follow-up period. During Week 20 or upon discontinuation, designated unblinded site personnel instructed participants to log out of and uninstall the study app. The study procedures are presented in Figure 2. The study app automatically transferred data collected throughout the study. To reduce the risk of data transfer issues the study app displayed an error message if the participant had not connected to the internet for 2 days. Furthermore, consistent reminders were shared with the site to remind the participants to remain connected to Wi-Fi. Participants had access to human technical support throughout the study period. If participants experienced issues with the study app, they could contact support via email or telephone. Support staff were trained to troubleshoot common issues, guide participants through resolution steps, and, if needed, escalate more complex cases to designated escalation personnel who investigated the issue and provided updated instructions or workarounds. These cases were reviewed and resolved collaboratively, and participants were followed up with until the issue was addressed.

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Figure 2. Study design flow and study app procedures in CONVOKE. CT-155: CT-155/BI 3972080.

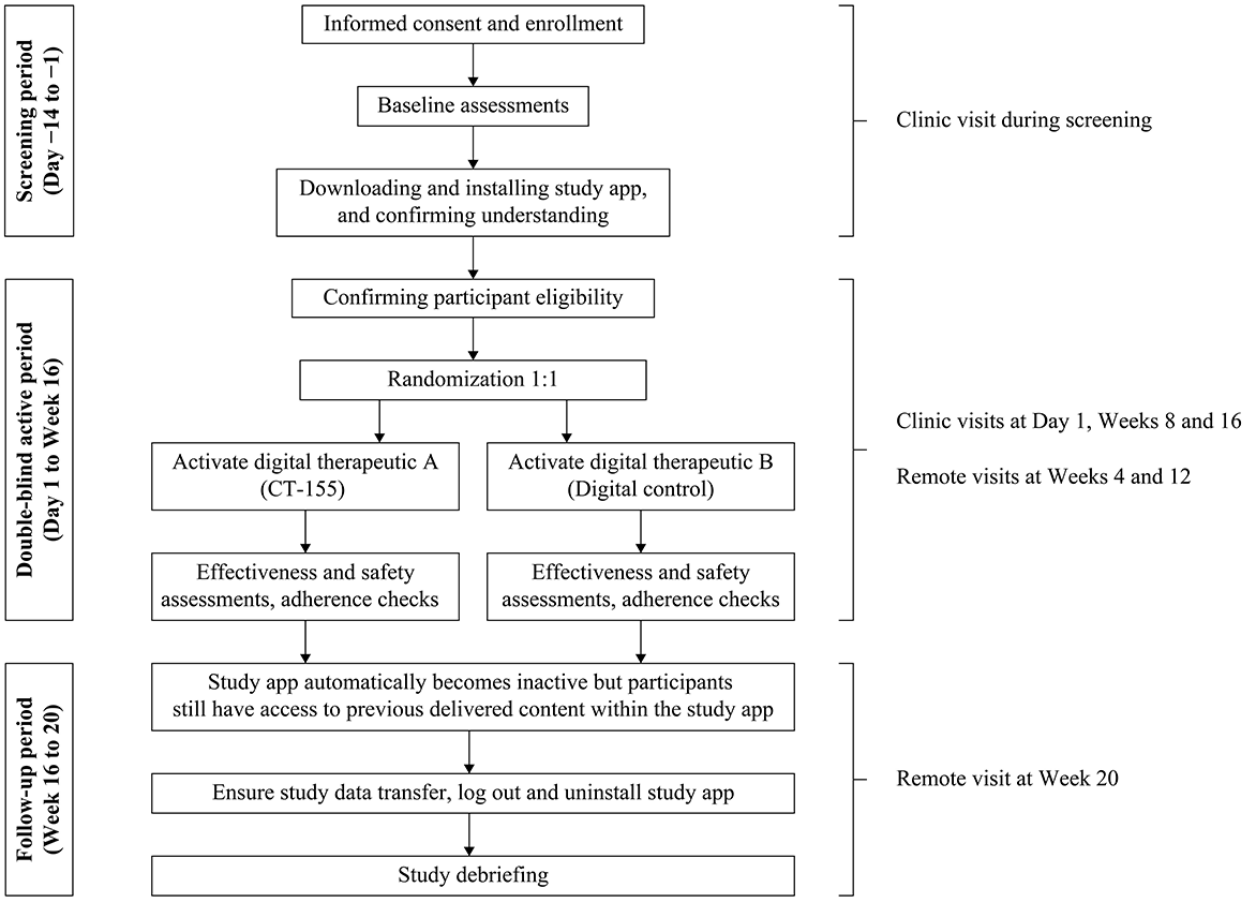

Study Participants

Eligible participants were 18 years or older, fluent in written and spoken English, and had a primary diagnosis of schizophrenia as defined in the *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) for ≥6 months prior to the screening visit. Participants were required to have been on a stable dose of antipsychotic medications for ≥12 weeks prior to randomization, to have obtained an average score of ≥2 (moderate to severe) in at least 2 of the 3 Clinical Assessment Interview for Negative Symptoms Motivation and Pleasure subscale (CAINS-MAP) domains (Social, Work or Recreational) at both the screening visit and at baseline, and to be the sole user of a smartphone. Individuals were excluded if they had a *DSM-5* diagnosis for schizophreniform or schizoaffective disorder, or were receiving or had received psychotherapy. Full eligibility criteria are presented in Multimedia Appendix 1.

Ethical Considerations

This study was conducted in accordance with the Declaration of Helsinki and the Good Clinical Practice Guidelines. The study protocol was approved by the Institutional Review Boards prior to study initiation. Institutional Review Board services were provided by Advarra (registration number Pro00065686). All participants were asked to provide written informed consent prior to starting the study and were informed that their participation was voluntary. All information collected during the study was considered confidential and was only used in accordance with the protocol, and participants were assigned a unique identifier by the sponsor at screening. Participants were offered up to US $45-US $200 and US $25-US $136 per in-person and remote visit, respectively, based on study center locality. While participants were compensated for their time attending site visits, they were not compensated for completing daily in-app activities. An independent Data Safety Monitoring Board reviewed safety events throughout the study period.

Intervention

CT-155 is an investigational smartphone-based DTx being developed for use as an adjunct to standard-of-care antipsychotic medications in adults with negative symptoms of schizophrenia. CT-155 was designed based on the underlying principles of face-to-face treatment to provide maximal support to people living with schizophrenia [83-86]. By integrating multiple components of evidence-based psychosocial therapeutic techniques in a patient-centered manner, CT-155 aims to address the dual challenge of accessibility and psychosocial therapy use for people with negative symptoms living with schizophrenia.

The components of CT-155 are designed to address defeatist beliefs and lack of motivation. Defeatist beliefs are a mediating variable between cognitive impairment, negative symptomatology, and poor functioning in schizophrenia [49], while a lack of motivation reduces an individual's ability to successfully overcome the challenges of daily living with

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schizophrenia [87,88]. CT-155 components included the setting of goals appropriate to the patients' current level of functioning (adaptive goal setting) [89,90] to promote real-world engagement (behavioral activation) [43,44], while targeting defeatist performance beliefs (cognitive restructuring) [47,49,72] and delivering therapeutic interventions to facilitate successful goal attainment (social skills training [33,41,48,50], positive affect training [45,46], distress tolerance skills [91]). These core components are intended to remediate dysfunctions in reward pathways, which contribute to reduced internal representations of behavioral goals and drive motivational impairments central to ENS [92-94]. In particular, targeted behavioral activation strategies followed by cognitive restructuring promote engagement in goal-directed behaviors, while also creating and maintaining associations between effort and positive affect in relation to those behaviors [42,95,96]. A selection of screenshots from the CT-155 study app are presented in Figures 3 and 4.

Figure 3. Example screenshots of the CT-155 study app and digital control app representing the login and onboarding experience. CT-155: CT-155/BI 3972080.

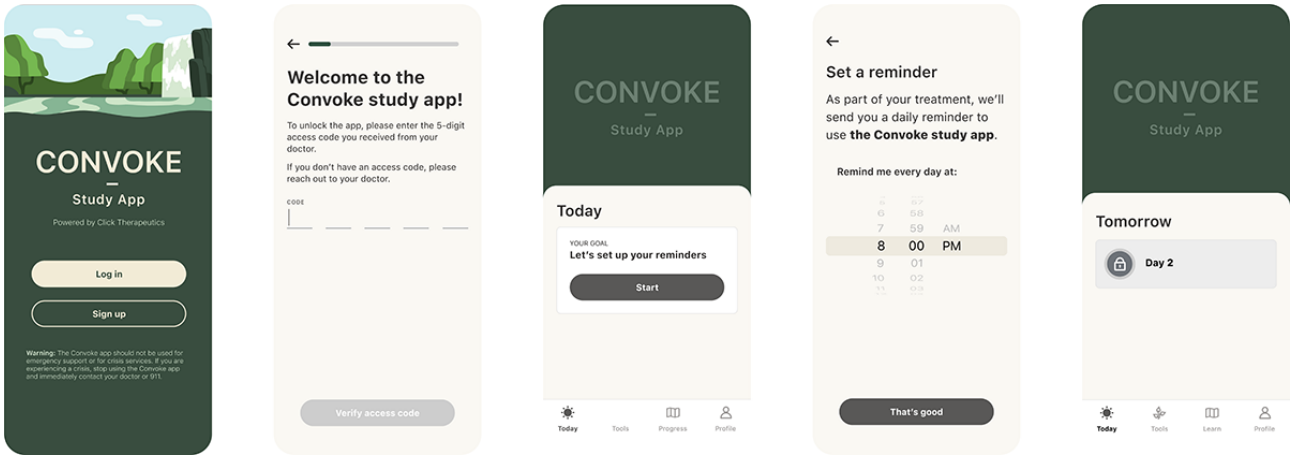

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Figure 4. Example screenshots of the CT-155 study app representing foundational therapeutic skill as delivered during the orientation phase, adaptive goal setting during the goal attainment phase, and reflection and celebration of treatment progress during the consolidation phase. CT-155: CT-155/BI 3972080.

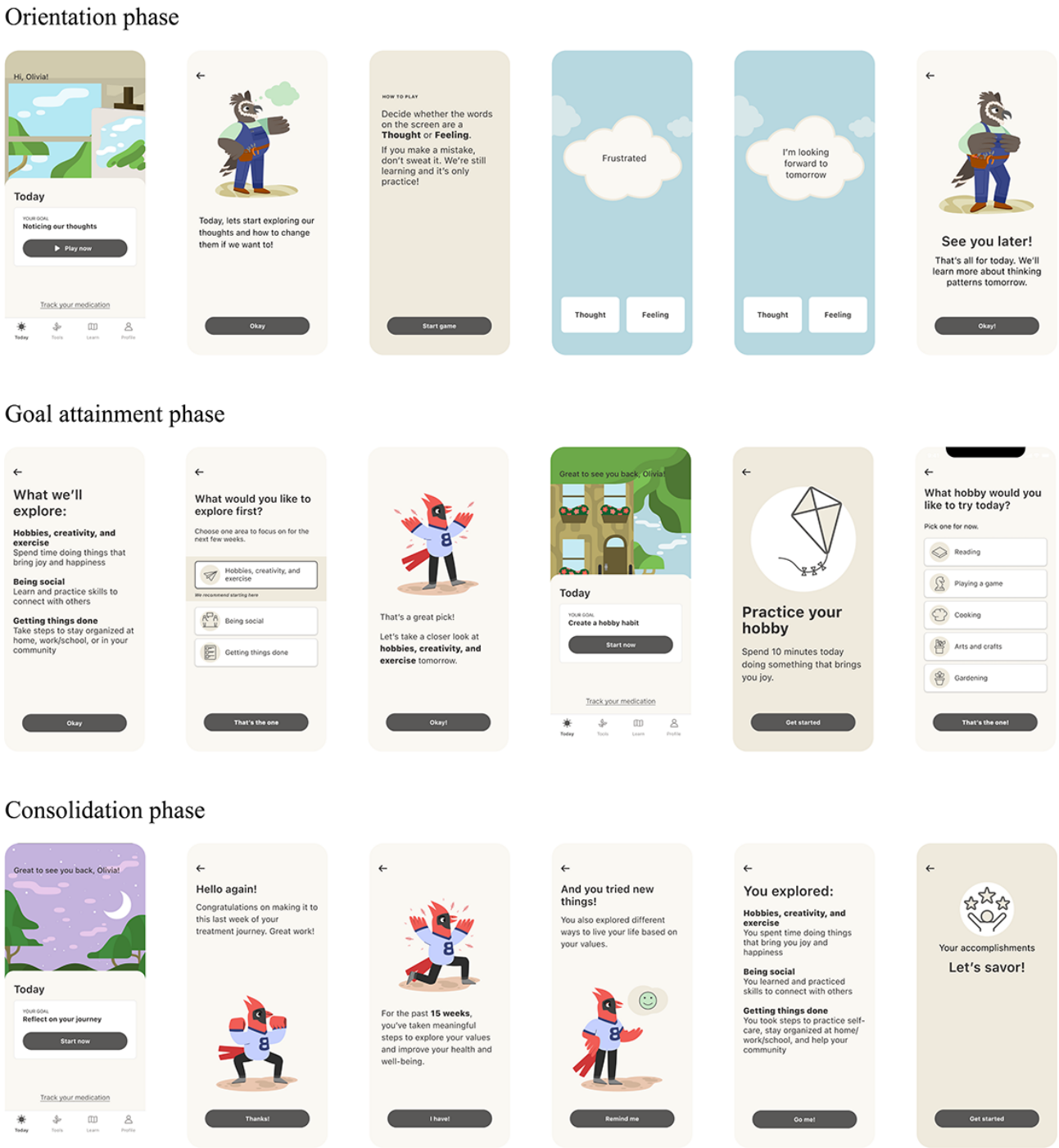

CT-155 design and development were informed by an iterative patient-centered approach from 156 people living with schizophrenia. For example, the mood check-in feature was refined based on feedback from individuals with lived experience. Initially designed as a simple, single-screen daily prompt, it evolved into a dynamic tool offering tailored feedback and coping strategies aligned with users' reported mood. Feedback also informed how therapeutic content was structured, the tone and pacing of the app's narrative, and improvements in usability and overall user flow. Further details are available in Figure S1 in Multimedia Appendix 1 and have been described by Snipes et al [81] and Goenjian et al [74].

The active period for CT-155 comprised 3 structured but personalized phases within the app: 3-week orientation phase, 12-week goal attainment phase, and 1-week consolidation phase. The orientation phase included lessons to set expectations and encourage daily adherence, provide schizophrenia-specific psychoeducation, and help build an effective therapeutic alliance (also referred to as a digital working alliance [81]), which is important for engagement with DTx. The goal attainment phase included adaptive goal setting, social skills training, and cognitive restructuring. The consolidation phase included guided reflection on, and celebration of progress, and establishment of a plan for continued application of skills learned over the course

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of the study in daily life. Lessons and activities were delivered through brief, daily interactive modules designed to be completed in under 10 minutes. These included a combination of text-based explanations, short exercises, and reflection prompts tailored to each phase. Participants also completed daily check-ins and were encouraged to access content regularly. The app included SMS and push notifications to prompt check-in completion and encourage daily lesson engagement. Two prior exploratory studies using earlier versions of CT-155 (CT-155 beta) demonstrated initial feasibility in engaging people living with schizophrenia and an associated reduction in ENS severity following 7 weeks of use [74,81].

Digital Control

The digital control app served as a comparator that controlled for common elements of a digital app (eg, receipt of notifications, on-demand access), daily engagement, and face validity [78,97]. It was designed to be reasonably equivalent to the active treatment in terms of daily engagement and face validity. For example, the user interface was similar (Figure 3 depicts the identical log-in screens of the CT-155 app and the digital control app), and the experience included SMS text messages, push reminders, daily check-ins, and daily activities. This design aimed to promote frequent use of the app and ensure that any differences in outcomes could be attributed to the therapeutic content, rather than to nonspecific effects of digital engagement. The digital control app also included elements of the disease-specific educational components of CT-155. The educational components were designed to increase knowledge about schizophrenia without encouraging behavior change or providing other therapeutic benefits.

Outcomes and Assessments

In line with FDA current best practices and terminology in medical device clinical research, improvement in clinical outcomes is herein referred to as effectiveness (rather than efficacy) [98].

End points included clinician-reported and patient-reported assessments. The primary effectiveness end point was change from baseline to Week 16 in ENS severity, as assessed by CAINS-MAP (Table 1). CAINS is a 13-item interview-based, clinician-administered assessment that consists of 2 subscales covering the 5 domains of negative symptoms: Motivation and Pleasure (referred to as “MAP”; ie, avolition, anhedonia, and asociality), and Expressivity (referred to as “EXP”; ie, blunted affect, alogia). CAINS items are scored on a 5-point scale, with lower scores indicating lower negative symptom severity [99]. CAINS is a second-generation negative symptoms scale that was developed to reflect updated conceptualizations of negative symptoms, as recommended by the National Institute of Mental Health and the Measurement and Treatment Research to Improve Cognition in Schizophrenia initiative [99,100]. CAINS offers a more detailed assessment of negative symptoms than older scales such as the Positive and Negative Syndrome Scale (PANSS) and assesses internal experiences (eg, joy, pleasure, interest, and intimacy) rather than just behavior to focus on experiential deficits important to the individual [101,102]. CAINS was administered by a centralized rater team. Raters were trained consistently with didactic training and posttests, and video scoring exercises; interrater reliability was measured every 6 months.

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Table 1. Study end points.

End point and measure	Description
Primary	
• Change from baseline to Week 16 in ENS[a], as assessed by CAINS-MAP[b] [99]	CAINS is a 13-item interview-based assessment comprised of 2 subscales that measure the 2 factors of negative symptoms: Motivation and Pleasure (MAP) and Expressivity (EXP). CAINS items are scored on a 5-point scale, with lower scores indicating lower negative symptom severity. The MAP scale consists of 9 items that measure interest and engagement in motivated behavior as well as the experience of pleasure across social, vocational, and recreational domains. Each item is scored based on patient-reported behavior and experience.
Secondary	
• Change from baseline in motivation and pleasure symptoms at Week 8, as assessed by CAINS-MAP [99]	See CAINS-MAP description above.
• Change from baseline in expressive negative symptoms at Weeks 8 and 16, as assessed by CAINS-EXP[c] [99]	See CAINS description above. The EXP scale consists of 4 items that measure verbal intonation (prosody), nonverbal expressivity (gestures, posture), facial expressivity, and speech output (alogia). Items are rated based on observation over the course of the interview.
• Change from baseline in positive symptoms at Weeks 8 and 16, as assessed by PANSS[d] [103]	Consists of 3 subscales containing a total of 30 symptom constructs. For each symptom construct, severity is rated on a 7-point scale, with a score of one indicating the absence of symptoms and a score of 7 indicating extremely severe symptoms.
• Change from baseline in social functioning at Weeks 8 and 16, as assessed by PSP[e] [104]	Validated clinician-rated scale that measures personal and social functioning in 4 domains: socially useful activities (eg, work and study), personal and social relationships, self-care, and disturbing and aggressive behaviors. Each area is scored on a 0-100 scale, with anchors for every 10-point interval.
• Change from baseline in self-reported defeatist beliefs at Weeks 8 and 16, as assessed by DAS[f] [105,106]	A 15-item subset of the DAS. Items are scored on a 1-7 scale, with higher scores indicating more severe defeatist thinking.
• Change from baseline to Week 8 and to Week 16 in PGI-I[g]	A patient-reported outcome measuring subjective improvement in ENS severity on a 7-point scale. A higher PGI-I score indicates a subjective report of disease worsening over time.
Exploratory	
• Engagement metrics	Measured passively as a result of participants' day-to-day app use and completion of in-app activities. These were the number of days the app was used, the number of days with at least one app session ≥60 seconds, and the number of days with at least one daily activity completed.
• Change from baseline in disease severity at Week 8 and 16, as assessed by CGI-S[h] [107]	A standardized, clinician-rated global rating scale that measures ENS severity in the past 7 days using a 7-point Likert scale (1 being not ill at all; 7 being among the most extremely ill participants). A higher score on the CGI-S represents a higher severity of disease.
• Change from baseline in disease severity at Week 8 and Week 16, as assessed by WHODAS 2.0[i] [108]	A 36-item self-assessment scale to measure a participant's function and disability across 6 domains of life: cognition (understanding and communicating), mobility (moving and getting around), self-care (hygiene, dressing, eating, staying alone), getting along (interacting with others), life activities (domestic responsibilities, leisure, work and school), and participation (community and society). Items are scored on a 5-point scale, with higher scores indicating greater disability.
• Change from baseline in disease severity at Week 8 and Week 16, as assessed by SQLS-R4[j] [109]	A 33-item self-assessment scale that assesses quality of life across domains of psychosocial feelings and vitality/cognition domains using a 5-point scale, with higher scores indicating comparatively lower quality of life.
• Change from baseline to Week 8 and to Week 16 in EQ-5D-5L [110]	A standardized, brief self-report instrument for measuring health status. It consists of 2 components: the EQ-5D descriptive system and the EQ visual analogue scale. The descriptive system comprises 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. The participant is asked to indicate his/her health status by selecting the box next to the most appropriate statement in each of the 5 dimensions. The EQ visual analog scale records the participant's overall self-rated health on a visual analogue scale, from "the best health you can imagine" to "the worst health you can imagine."

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End point and measure	Description
• Change from baseline to Week 8 and to Week 16 in SDS[k] [111]	A brief, 5-item self-report instrument that assesses functional impairment in 3 domains: work/school, social life, and family life. The first 3 items are rated from 0 (not at all) to 10 (extremely). There are 2 additional questions which measure the presenteeism and absenteeism over the preceding 7 days. The SDS total score is calculated as the sum of 3 items (range: 0-30), with higher scores indicating greater functional impairment.
Safety	
• Frequency and severity of AEs[l], serious AEs, and discontinuations from the study due to AEs • Frequency and severity of AEs related to the worsening of positive or negative schizophrenia symptoms	Every event recorded in the form as "Adverse event" will be counted as an adverse event. Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA).
• Incidence of suicidal ideation and behavior, as identified via the C-SSRS[m] [112]	A suicidal ideation and behavior rating scale that rates an individual's degree of suicidal ideation on a scale, ranging from "wish to be dead" to "active suicidal ideation with specific plan and intent and behaviors." Consists of a baseline evaluation that assesses the lifetime experience of the participant with suicide events and suicidal ideation, and a postbaseline evaluation that focuses on suicidality since the last study visit.

[a]ENS: experiential negative symptoms.

[b]CAINS-MAP: Clinical Assessment Interview for Negative Symptoms Motivation and Pleasure subscale.

[c]CAINS-EXP: Clinical Assessment Interview for Negative Symptoms Expressivity subscale.

[d]PANSS: Positive and Negative Syndrome Scale.

[e]PSP: Personal and Social Performance Scale.

[f]DAS: Dysfunctional Attitudes Scale.

[g]PGI-I: Patient Global Impression of Improvement Scale.

[h]CGI-S: Clinical Global Impressions-Severity.

[i]WHODAS 2.0: World Health Organization Disability Assessment Schedule.

[j]SQLS-R4: Schizophrenia Quality of Life Scale – Revision 4.

[k]SDS: Sheehan Disability Scale.

[l]AE: adverse event.

[m]C-SSRS: Columbia-Suicide Severity Rating Scale.

Other study end points included change from baseline to Week 8 in ENS severity (assessed by CAINS-MAP), and change from baseline to Weeks 8 and 16 in expressive negative symptoms (assessed by CAINS Expressivity subscale [CAINS-EXP]), positive symptoms (PANSS), social functioning (Personal and Social Performance Scale), self-reported defeatist beliefs (Dysfunctional Attitudes Scale), Patient Global Impression of Improvement Scale, Clinical Global Impressions-Severity, and quality of life (Schizophrenia Quality of Life Scale – Revision 4). PANSS consists of 3 subscales (positive, negative, and general psychopathology) containing a total of 30 symptom constructs. For each symptom construct, severity is rated on a 7-point scale, with a score of 1 indicating the absence of symptoms and a score of 7 indicating extremely severe symptoms [99]. Further assessment details are described in Table 1.

Participant engagement with CT-155 and digital control were measured passively by the smartphone as a result of participants' day-to-day app use and completion of in-app activities. These included the number of days the app was used, the number of days with at least 1 app session ≥60 seconds, and the number of days with at least 1 daily activity completed. Daily activities in CT-155 included completing lessons, completing check-ins, practicing skills, or completing steps to attain goals. Daily activities in the digital control included completing lessons or completing check-ins. Participants were considered adherent during the study if they completed at least 1 daily activity for at least 67 of the 112 days of the active period (≈60%). The schedule of assessments is presented in Table 2.

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Table 2. Schedule of activities and assessments.

Study day and visit window	Screening period	Active period					Follow-up period
	Screening[a] (days −14 to −1 [minimum of 7 days between screening and baseline CAINS[b]])	Baseline (day 1)	Week 4 (day 28 ± 3 days)	Week 8 (day 56 ± 3 days)	Week 12 (day 84 ± 3 days)	Week 16/early termination (day 112 ± 3 days)	Week 20 (day 140 ± 3 days)
Study visit number	1	2	3	4	5	6	7
Clinic visit	✓[c]	✓		✓		✓	
Remote visit[d]			✓		✓		✓
Informed consent	✓						
Demographics	✓						
Inclusion/exclusion criteria	✓	✓					
Medical history	✓						
Psychiatric history and *DSM-5*[e] diagnosis of schizophrenia	✓						
Urine drug screen[f]	✓	✓		✓		✓	
Urine pregnancy test[g]	✓	✓		✓		✓	
Randomization		✓					
Download app and confirm understanding[h]	✓	✓					
Complete enrollment in CT-155 study app to activate the assigned intervention		✓					
Concomitant therapy	✓	✓	✓	✓	✓	✓	✓
Adverse events	✓	✓	✓	✓	✓	✓	✓
Clinician-reported outcomes							
CAINS[i]	✓	✓		✓		✓	
PANSS[j]	✓	✓		✓		✓	
CGI-S[k]		✓		✓		✓	
PSP[l]		✓		✓		✓	
MINI[m]	✓						
C-SSRS[n]	✓	✓	✓	✓	✓	✓	
Patient-reported outcomes							
PGI-I[o]				✓		✓	
PGI-S[p]		✓		✓		✓	
DAS[q]		✓		✓		✓	
EQ-5D-5L		✓		✓		✓	
Sheehan Disability Scale (SDS)		✓		✓		✓	
WHODAS 2.0[r]		✓		✓		✓	
SQLS-R4[s]		✓		✓		✓	
Adherence check (use of study app)			✓	✓	✓		
Uninstall study app							✓

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[a]The screening period was a minimum of 7 days before the baseline visit to allow for proper CAINS assessments.

[b]CAINS: Clinical Assessment Interview for Negative Symptoms.

[c]Check marks show the activities and assessments that occurred at each study visit.

[d]All remote visits were conducted via telephone. The Week 20 visit could be in-person if enrolling in NCT06067984, an open label extension study, the purpose of which was to evaluate the maintenance of effect as well as the safety of a second consecutive course of CT-155 [113].

[e]DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition).

[f]The urine drug screen was conducted on-site.

[g]The urine pregnancy test was conducted on-site using the dipstick method.

[h]The study app could be installed at screening visit or baseline visit.

[i]CAINS was administered by a centralized blinded rater team, not the site clinician.

[j]PANSS: Positive and Negative Syndrome Scale.

[k]CGI-S: Clinical Global Impressions-Severity.

[l]PSP: Personal and Social Performance Scale.

[m]MINI: Mini International Neuropsychiatric Interview.

[n]C-SSRS: Columbia-Suicide Severity Rating Scale.

[o]PGI-I: Patient Global Impression of Improvement.

[p]PGI-S: Patient Global Impression of Severity.

[q]DAS: Dysfunctional Attitudes Scale.

[r]WHODAS 2.0: World Health Organization Disability Assessment Schedule.

[s]SQLS-R4: Schizophrenia Quality of Life Scale – Revision 4.

Safety end points included the frequency and severity of adverse events (AEs) and serious AEs, including those related to the worsening of positive or negative schizophrenia symptoms. The incidence of suicidality, as identified via the Columbia-Suicide Severity Rating Scale was also assessed.

Sample Size Determination

Using a 2-sample *t* test approach and assuming a type I error rate of 5% (2-sided), 173 participants per arm were required to achieve 90% power to detect an effect size of Cohen *d* of 0.35. Assuming 20% early termination, a total of 432 participants was calculated as being needed before being randomized to the study in a 1:1 ratio (approximately 216 in each arm). The assumed effect size (Cohen *d*=0.35) was informed by an earlier exploratory study of a related version of the digital therapeutic [74], early research studies with psychosocial interventions targeting negative symptoms [72,114,115], and moderate effect sizes seen in broader confirmatory trials in schizophrenia and major depressive disorder [116,117].

Statistical Analyses

Overview

All effectiveness, demographics, and baseline characteristics analyses will be performed using the intent-to-treat (ITT) set, unless otherwise specified. Baseline and demographic characteristics, including age, sex, race, and ethnicity, will be summarized using descriptive statistics.

Primary End Point

The primary effectiveness end point of change from baseline to Week 16 in ENS will be analyzed using both the ITT and per-protocol populations, with the ITT population serving as the primary analysis and the per-protocol analysis as a supportive analysis. The primary analysis will be conducted using a mixed models repeated measures (MMRM) approach. Missing data will be handled by the MMRM model and will not be imputed separately [118]. Sensitivity analyses will also be performed for the primary end point in the ITT set by imputing missing data using a multiple imputation method based on missing-at-random assumption and by the tipping point method [119]. An alpha value of ≤.05 will denote a significant difference in the change from baseline at Week 16 between the 2 interventions and determine study success.

The primary end point will be repeated in the ITT set by the following prespecified subgroups: length of time since diagnosis of schizophrenia, baseline CAINS-MAP negative symptom severity, sex, age group, race, ethnicity, education level, income level, living status, employment status, and geographical region. These subgroups were selected based on their relevance to clinical variability and social determinants of health in schizophrenia, which may impact symptom presentation and response to intervention [120-124]. Subgroup analyses are exploratory and are intended to assess the consistency of treatment effects across these distinct populations. No multiplicity adjustment will be applied to subgroup analyses for the primary effectiveness end point; nominal *P* values will be reported and interpreted descriptively, in line with their supportive role in the analytic framework.

Secondary End Points

All secondary end points will be analyzed in a similar manner to the primary end point. The analysis is the difference between the interventions using the MMRM and conducted in the ITT set. These analyses are considered nonhierarchical and will be interpreted in a supportive, exploratory framework. This analytical approach reflects health authority guidance for clinical studies, which consist of 2 treatment groups, use a single primary variable, and have a confirmatory statistical strategy that prespecifies just 1 single null hypothesis relating to the primary variable [125-127]. There is no formal multiplicity control for the secondary end points. The results are intended to provide additional context to the primary end point and to inform future research directions.

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Exploratory End Points

Key engagement metrics will be summarized descriptively by visit and by treatment group. All other exploratory end points will be analyzed using a similar MMRM method as for the primary end point by visit and treatment group.

Safety End Points

All safety end points will be analyzed in the safety analysis set, defined as all randomized participants who signed the informed consent form, activated the study app, and completed at least 1 available daily activity in the study app during the active period. Safety data will be summarized descriptively by treatment group. All AEs will be coded by system organ class and Medical Dictionary for Regulatory Activities preferred term. An independent Data Safety Monitoring Board reviewed safety events throughout the study period. Any technical issues reported by participants were assessed for potential AEs and forwarded to the Data Safety Monitoring Board for review.

Results

The study started enrolling in March 2023. As of January 2025, study recruitment was complete, enrolling 457 participants across 66 clinical study sites.

Discussion

Principal Findings

The treatment of negative symptoms is a critical unmet need for people living with schizophrenia. Evidence-based DTx have demonstrated the potential to provide a scalable new patient-centered treatment option to enhance existing care for individuals with schizophrenia [63,74,81]. However, well-designed randomized clinical trials are essential to rigorously evaluate the effectiveness and safety of DTx, and to generate the evidence required for FDA regulatory approval. We summarized the clinical trial protocol for the CONVOKE study, the largest phase 3, randomized, controlled, double-blind trial conducted to date to assess the effectiveness and safety of a DTx in schizophrenia. CT-155 is an investigational adjunctive treatment for negative symptoms in people living with schizophrenia who are on standard-of-care antipsychotic medication.

The CONVOKE protocol included study design elements that strengthen study rigor. First, CONVOKE will evaluate the potential of CT-155 to reduce participants' ENS of schizophrenia using the CAINS-MAP assessment. CAINS is a second-generation negative symptom scale recommended by experts as a more detailed measure of negative symptoms compared with the older PANSS assessment, capturing both experiential (CAINS-MAP) and expressive (CAINS-EXP) symptoms [99,100,128]. Compared with PANSS, CAINS demonstrates better construct validity and coverage of negative symptoms domains, better psychometric properties, and more sensitivity in detecting treatment-related changes [99,101,102,129]. Furthermore, CAINS-MAP was administered by central raters, an approach that has a significantly lower placebo affect than using site-based raters [130]. Second, the CONVOKE protocol was developed in the context of a conventional phase 3 registrational study, by including design aspects such as a blind-to-hypothesis and a digital control arm. The digital control app for CT-155 was designed to control for unintended therapeutic benefit that may arise from nonspecific factors (eg, self-monitoring, treatment expectations), referred to as a placebo response in pharmaceutical trials. To our knowledge, CONVOKE is the first DTx study in participants with negative symptoms of schizophrenia to include such a digital control. The blind-to-hypothesis approach requires the digital control app being masked as an active therapeutic by closely mirroring it in terms of design, delivery, participant engagement, and the duration of the intervention. Thus, the risk of unmasking and disengagement for those assigned to the digital control is expected to be reduced. However, it is important to examine whether the blind-to-hypothesis approach functioned as intended, and this could be investigated by comparing participant engagement between the 2 study arms.

Finally, in keeping with the FDA's patient-focused drug development initiative, CT-155 development was informed by a patient-centered design approach that considered the needs of those living with schizophrenia [31]. Feedback was captured from peer support specialists with lived experience of schizophrenia and patient panel participants with a diagnosis of schizophrenia, to iteratively improve CT-155. This patient-centric approach also supports establishing the digital working alliance and optimizes participant experience by creating an interactive, empathic, knowledgeable, and personally meaningful content within the CT-155 app that is critical for treatment outcome. These robust study design elements lay the groundwork for strengthening study rigor and ultimately improving confidence in the effectiveness of CT-155.

Safety

Safety analyses will determine whether CT-155 has a low safety risk and can be tolerated by participants, an important study design component for a prescription DTx to be made available under FDA regulation. CT-155 is expected to be well tolerated, as demonstrated in the 2 single-arm clinical learning studies [74,81]. In contrast to pharmacotherapy, DTx do not involve the administration of pharmaceutical compounds and are therefore not associated with side effects as frequently present for pharmaceuticals and may be considered minimal risk [131,132]. However, it is still important to assess the safety of a DTx throughout the study (eg, monitoring hospital admissions, referrals to crisis care, and suicidal ideation) [75,133-137]. The 4-week posttreatment follow-up was specifically designed to assess short-term safety and tolerability after treatment concluded, and was intended to monitor for adverse events, potential withdrawal effects, or other posttreatment concerns. To extend observation beyond the initial study and provide further insights into maintenance of effect and safety, there was an opportunity for some participants to enroll into an open-label extension study (NCT06067984) [113].

Limitations

Although the protocol had strengths by utilizing a conventional phase 3 clinical study design, there were potential limitations that may have introduced selection bias that could limit the

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external validity and generalizability of findings. First, participants were required to be on a stable dose of antipsychotic medication (≤2 antipsychotics) for at least 12 weeks. This was intended to ensure stability and reduce the likelihood of symptom fluctuations which could impact engagement with digital intervention. However, this may have also excluded individuals with recent diagnoses or those who had started antipsychotics within the last 12 weeks. These groups may have different treatment needs, and future studies will be important to assess the potential benefits of this intervention in more acutely unwell or treatment-initiating populations.

To address broader generalizability beyond a confirmatory phase 3 trial population, there is an ongoing prospective cohort study (ENSPIRUS) that aims to assess the effectiveness and safety of CT-155 in a broader population (eg, no exclusion criteria for those who recently engaged in psychotherapy; NCT06791122) [138].

Second, participants were required to own a smartphone, with consistent internet access, and have stable housing. While necessary for evaluating a digital intervention, these criteria may introduce some selection bias towards participants with greater digital literacy, greater socioeconomic stability, or higher overall functioning which could limit the external validity and generalizability of findings to the broader population of people with schizophrenia. The requirement for smartphone ownership aimed to reduce nonspecific effects related to unfamiliarity with digital devices and to avoid variability in engagement that could arise if participants were using loaned devices rather than their own. Although smartphone ownership is increasingly common across all socioeconomic groups, including among individuals with serious mental illness, disparities in digital literacy, data affordability, and reliable internet access may still limit broad generalizability across the target population [64,65,139]. Future studies should consider hybrid models that include loaning smartphones to further access the impact of accessibility and inclusiveness.

Finally, as no correction for multiple comparisons was applied across secondary end points or subgroup analyses, there is an increased risk of type I error; thus, these findings should be interpreted with caution and considered supportive of the study's primary objective.

Conclusion

This manuscript describes the methodological design for CONVOKE, the largest robust pivotal clinical trial evaluating the effectiveness and safety of a DTx as an adjunct to standard-of-care antipsychotic medication for negative symptoms in people living with schizophrenia. CT-155 development was informed by a patient-centered design approach. The CONVOKE study design included the centrally rated CAINS with its CAINS-MAP subdomain as the primary end point, blind-to-hypothesis, and used digital control arm. The treatment of negative symptoms has been a critical unmet need for people living with schizophrenia and the results of this study may shift the treatment paradigm for them. If the pivotal trial data show a significant difference between CT-155 and the digital control, CT-155 would offer an accessible, evidence-based psychosocial treatment delivered through smartphones in a patient-centered manner to augment standard-of-care for people with negative symptoms of schizophrenia.

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Data Availability

To ensure independent interpretation of clinical study results and enable authors to fulfill their role and obligations under the ICMJE (International Committee of Medical Journal Editors) criteria, Boehringer Ingelheim grants all external authors access to relevant clinical study data. In adherence with the Boehringer Ingelheim Policy on Transparency and Publication of Clinical Study Data, scientific and medical researchers can request access to clinical study data, typically, 1 year after the approval has been granted by major Regulatory Authorities or after termination of the development program. Researchers should contact Vivli [140] to request access to study data and visit MyStudyWindow [141] for further information.

Authors' Contributions

SEL, CDC, OB, CH, CS, AS, BW, CvdG, and AP contributed to the conceptualization of the study. Data curation was performed by SEL, OB, FD, CS, and WT. OB, WT, and AP carried out the formal analysis. Funding acquisition was undertaken by SEL, CDC, AS, CvdG, and AP. The investigation was conducted by SEL, OB, FD, RK, JPL, RM, CS, BW, JWF, CvdG, and AP. Methodology was developed by SEL, OB, CH, RI, RM, CS, WT, BW, JWF, CvdG, and AP. Project administration was managed

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by SEL, RM, AS, BW, JWF, and AP. Resources were provided by SEL, CDC, AS, and AP. CS and WT contributed to software development. Supervision was carried out by SEL, CDC, RK, JPL, RM, WT, BW, JWF, CvdG, and AP. Validation was performed by AS and WT. Visualization was provided by CDC, WT, and AP. The original draft was written by CDC and AP, and the review and editing were carried out by SEL, CDC, OB, FD, CH, RI, RK, JPL, RM, CS, AS, WT, BW, JWF, CvdG, and AP.

Conflicts of Interest

CT-155 was co-developed by Boehringer Ingelheim and Click Therapeutics Inc. SEL, OB, RM, CS, AS, and BW are employees of Click Therapeutics, Inc. CDC, CH, and CvdG are employees of Boehringer Ingelheim International GmbH. RI, WT, and AP are employees of Boehringer Ingelheim Pharmaceuticals, Inc. AP is also affiliated with King's College London, London, United Kingdom; Boston University, Boston, Massachusetts; and the University of Washington, Seattle, Washington. FD has received research grant funding from Boehringer Ingelheim and was a site investigator on the CONVOKE study. RSK is a consultant for Boehringer Ingelheim, BMS, and Alkermes. JPL is affiliated with the Department of Psychiatry, Grossman School of Medicine, New York, and receives research funding from Avanir, BMS, Alto, Neurocrine and Roche. JPL is a consultant to Newron and receives royalties for the Sci-PANSS. JWF is also affiliated with the Morsani College of Medicine, University of South Florida, Tampa, Florida. SEL is also affiliated with Western University of Health Sciences, Morehouse School of Medicine, A.T. Still University and Virginia Polytechnic Institute and State University.

Multimedia Appendix 1
Eligibility criteria and an overview of the patient-centered design process used to create the CT-155 study app.
[DOCX File , 169 KB - resprot_v14i1e81293_app1.docx]

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Abbreviations

AE: adverse event

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CAINS: Clinical Assessment Interview for Negative Symptoms
CAINS-MAP: Clinical Assessment Interview for Negative Symptoms Motivation and Pleasure subscale
CAINS-EXP: Clinical Assessment Interview for Negative Symptoms Expressivity subscale
CT-155: CT-155/BI 3972080
DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)
DTx: digital therapeutics
ENS: experiential negative symptoms
FDA: Food and Drug Administration
ITT: intent-to-treat
MMRM: mixed models repeated measures
PANSS: Positive and Negative Syndrome Scale

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Protocol

Evaluating the Efficacy of a Mobile Phone App in Enhancing Menopause Knowledge and Shared Decision-Making: Protocol for a Randomized Controlled Trial

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Abstract

Background: Menopause symptoms are common but often inadequately addressed by primary care clinicians due to limited time for discussions and resources. Mobile health apps can play a crucial role in symptom identification and management; yet, many existing menopause-focused apps lack evidence-based content and medical expertise.

Objective: The aim of this study is to describe the protocol study design and methodology of a randomized controlled trial to evaluate the effectiveness of the emmii mobile app for improving menopause-related knowledge and shared decision-making compared to a traditional menopause education pamphlet.

Methods: This randomized controlled trial will recruit women aged 45-55 years with upcoming primary care appointments at Mayo Clinic within 3 weeks of the date of initial outreach. Eligible patients must be English-speaking, able to provide informed consent, and report a Menopause Rating Scale score ≥5, which indicates that they are experiencing significant menopause-related symptoms. Patients will be randomized to have access to either the emmii app (intervention, n=200) or an evidence-based menopause education pamphlet (control, n=200). The emmii app is developed with direct input from primary care clinicians certified by The Menopause Society and offers symptom tracking, personalized treatment recommendations based on a protocol, and a discussion guide to support communication between patients and their primary care clinicians. Outcomes will include a postappointment survey sent to the patients and their primary care clinicians within 1-3 weeks of the appointment, and assessment of patient knowledge, clinical treatment plans, and both the patient and clinician experience. The study will also compare prescribing rates of hormonal and nonhormonal therapies for menopause symptoms between the emmii intervention and control groups to assess for influence on treatment patterns. Data will be analyzed using descriptive statistics, including chi-square tests, Wilcoxon rank sum tests, and multivariable modeling.

Results: Data collection is scheduled to begin in April 2025.

Conclusions: This protocol outlines the design and methodology of a randomized controlled trial that aims to assess the impact of the emmii app in facilitating menopause care through primary care clinician–patient communication and shared decision-making.

Trial Registration: ClinicalTrials.gov NCT06919887; https://clinicaltrials.gov/ct2/show/NCT06919887

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KEYWORDS

menopause; mobile health; mHealth; randomized controlled trial; RCT; digital health; mobile app

Introduction

Background

Menopause is defined as the absence of menses for 12 consecutive months or the surgical removal of both ovaries prior to natural menopause [1]. The average age of menopause is 52 years, with natural menopause occurring between the ages of 45 years and 56 years in 90% of the women [1,2]. However, menopause can also occur prematurely (<40 years) in approximately 3% of the women or early (40-44 years) in 6% of the women [3]. Perimenopause, occurring 2-7 years before the final menstrual period through the first year after menopause, is characterized by irregular menstrual cycles [4]. Common symptoms of perimenopause include vasomotor symptoms, mood changes, as well as genitourinary symptoms [5,6]. During perimenopause and menopause, 50%-75% of women experience vasomotor symptoms, 45%-68% experience psychological symptoms, and more than 50% develop genitourinary symptoms [7,8].

Menopause hormone therapy is the first-line treatment for bothersome vasomotor and genitourinary symptoms in symptomatic women without contraindications at and around the time of menopause and may also alleviate menopause-related sleep and psychological symptoms [7-9]. For women with contraindications to hormone therapy or a personal preference not to use it, nonhormonal treatments include selective serotonin reuptake inhibitors, serotonin-norepinephrine reuptake inhibitors, gabapentin, oxybutynin, and fezolinetant, which have shown efficacy for the treatment of vasomotor symptoms [10-13]. Lifestyle interventions such as cognitive behavioral therapy, yoga, and sleep hygiene are also recommended for symptom management [10]. However, these treatments may have limited effectiveness, potential side effects, and require access to trained professionals. As a result, substantial gaps remain in menopause care, leaving many symptomatic women without effective treatment [14]. Barriers also exist in clinical settings, and women may hesitate to report menopause symptoms due to prior negative experiences, discomfort discussing menopause, or the perception that primary care is not the appropriate setting to address such concerns [15,16]. Additionally, clinicians often lack the training or time to routinely screen for and manage menopause-related symptoms [17,18].

With the widespread use of smartphones, mobile health (mHealth) apps have emerged as useful tools for health care management. These apps offer a range of functions—from educational resources and symptom tracking to medical record access and therapeutic guidance. It is estimated that there is at least one app for every medical condition [19,20]. Research suggests that menstrual health and cognitive behavioral therapy apps can enhance physical and psychological well-being [21,22]. A small but growing number of mHealth apps focus specifically on menopause, addressing patient education, symptom tracking, and therapeutic guidance [20]. A longitudinal study of 1900 women using the “Health & Her” app found that those who engaged more frequently with the app’s features such as symptom tracking, period logging, and using in-app activities (eg, reminders to drink water, pelvic floor exercises) experienced significantly greater reductions in menopause symptoms over a 2-month period [23]. A recent randomized controlled trial evaluated the efficacy of Caria, an mHealth app for women experiencing menopause symptoms, which features an artificial intelligence chatbot-assisted symptom assessment and a 6-week self-guided program that includes daily cognitive behavioral therapy lessons, mindfulness-based exercises, physical activity video sessions, and community-based peer support [24]. After 6 weeks, patients randomized to the app had significantly reduced distress related to hot flashes compared to controls. However, the app did not directly facilitate engagement with clinicians or support shared decision-making about management.

Despite their potential benefits, most available menopause mHealth apps do not explicitly support shared decision-making or provide structured, evidence-based education tailored to women’s individual needs. A 2019 systematic review of 22 mHealth menopause apps found that only 27.3% of the apps involved medical professionals in their development, and only 22.7% used evidence-based information, raising concerns about the quality and reliability of these tools [20]. Key gaps include menopause knowledge deficits, lack of guidance on treatment options, limited shared decision-making support, and challenges in symptom self-management. As a result, many women remain underinformed about available therapies or uncertain about how to engage with clinicians regarding their symptoms and preferences.

To address these gaps, the Mayo Clinic Center for Women’s Health, in collaboration with a digital health company, BettrHealth, codeveloped a patient-centered mobile app called emmii for menopause symptom identification and management. The app was designed to provide evidence-based menopause education, individualized symptom assessment, treatment guidance, and a printable discussion guide to facilitate shared decision-making in the primary care setting.

Objectives

This paper describes the protocol, design, and methodology of a randomized controlled trial, which will evaluate the effectiveness of the emmii mHealth app (emmii) for improving menopause-related knowledge and shared decision-making compared to a traditional menopause education pamphlet.

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Methods

App Development

The emmii app was codeveloped through collaboration between the Mayo Clinic Center for Women's Health and BettrHealth, a digital health company, to offer comprehensive menopause education, evidence-based treatment options, and a personalized discussion guide for patients. It was developed with direct input from health care professionals who are certified by The Menopause Society. The initial app content was informed by clinical guidelines and menopause literature and a review of existing menopause-focused mobile apps, which often lack evidence-based content and do not provide individualized support. To address these limitations, the development process focused on accuracy, personalization, and usability. Content areas were identified and refined based on input from menopause experts and included symptom tracking, treatment education, and shared decision-making support. The app's educational and treatment content was developed using evidence-based guidelines on menopause symptom management from The Menopause Society, Endocrine Society, and American College of Obstetricians and Gynecologists [9,10,25,26]. The app presents treatment recommendations for both hormone and nonhormone options, including hormone therapy, serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors, gabapentin, oxybutynin, and fezolinetant, as well as lifestyle interventions [10-13]. These recommendations were created by menopause experts to ensure clinical accuracy. The personalized treatment guidance is based on user-reported symptoms and medical history to support individualized care and shared decision-making.

The app includes several key features designed to guide patients through their menopause journey. Features were selected based on their potential to educate users and improve clinical communication about bothersome menopause symptoms. Users initially enter basic health information, including height, weight, personal medical history, and current use of menopause treatments (Figure 1). Then, they rate their menopause-related symptoms by using the Menopause Rating Scale (MRS) [27] (Figure 2). Based on user input, the app generates personalized, evidence-based recommendations that include lifestyle modifications, hormone therapy, and nonhormone treatment options (Figure 3). A distinctive feature of emmii is its ability to also generate a personalized discussion guide (Figure 4), which users can share with their primary care clinicians to facilitate meaningful conversations about symptom management and treatment preferences.

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Figure 1. Screenshot of the basic health information and medical history in the emmii app.

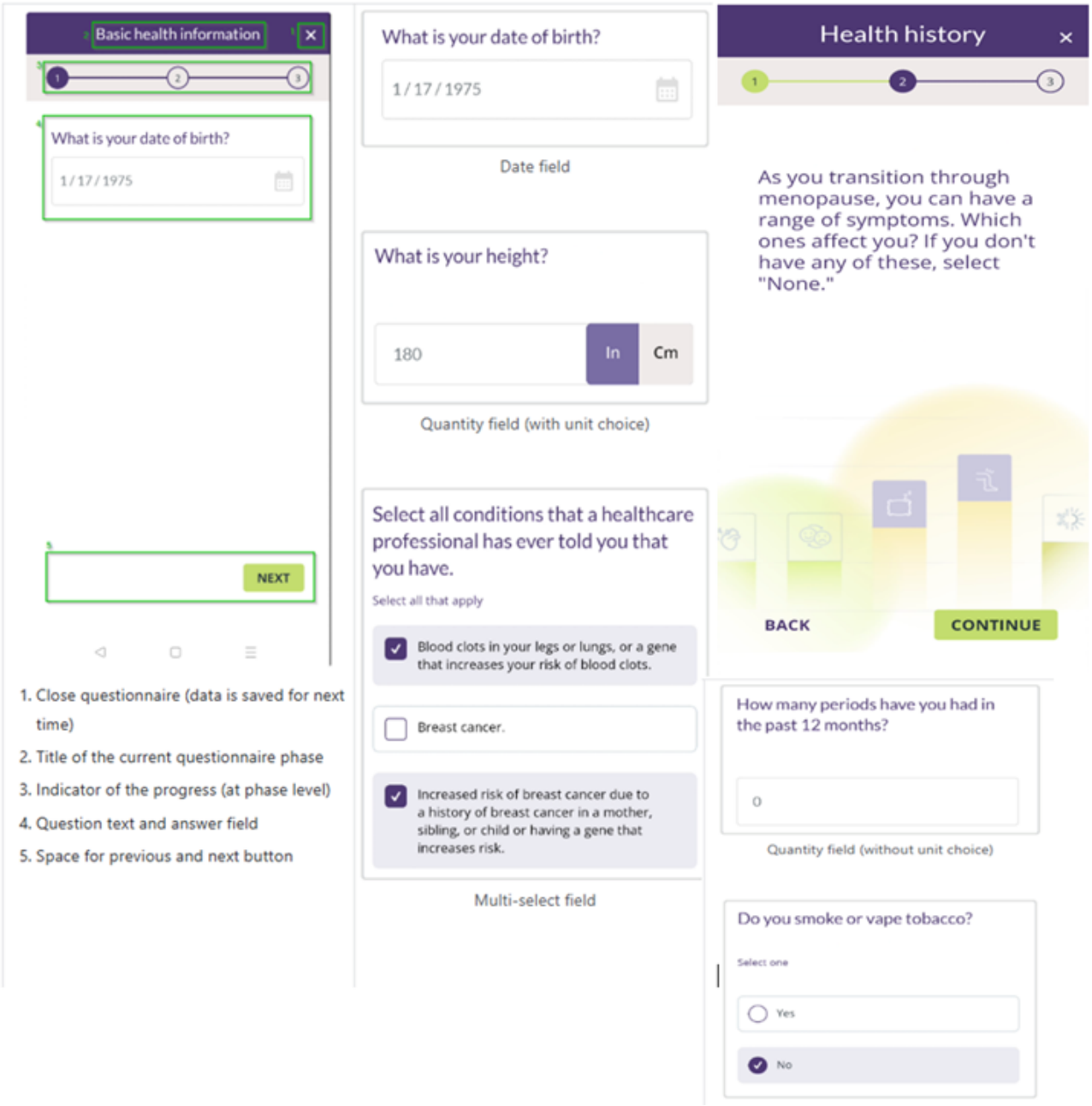

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Figure 2. Screenshot of the symptom checker in the emmii app.

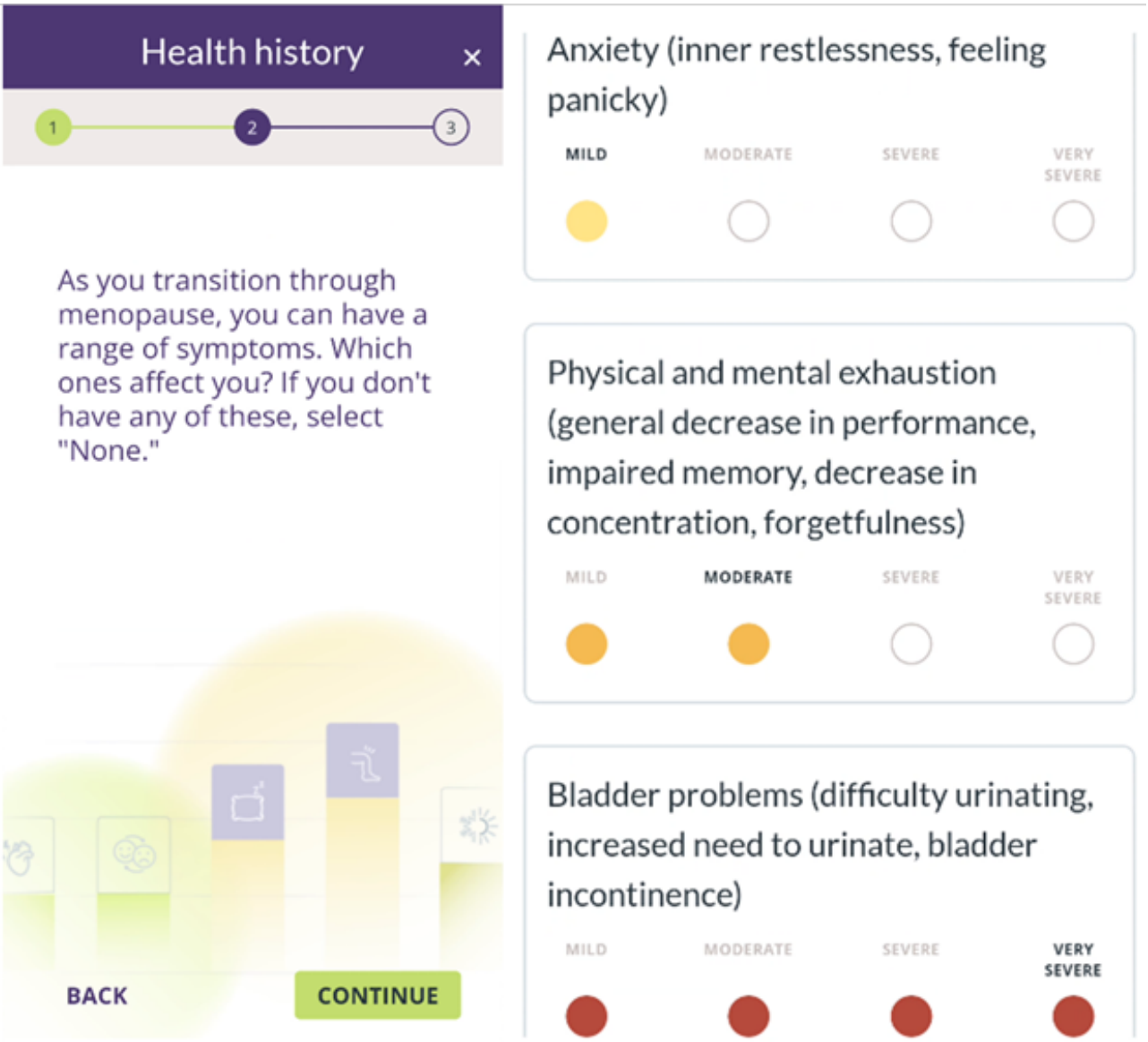

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Figure 3. Screenshot of the personalized recommendations generated based on user input in the emmii app.

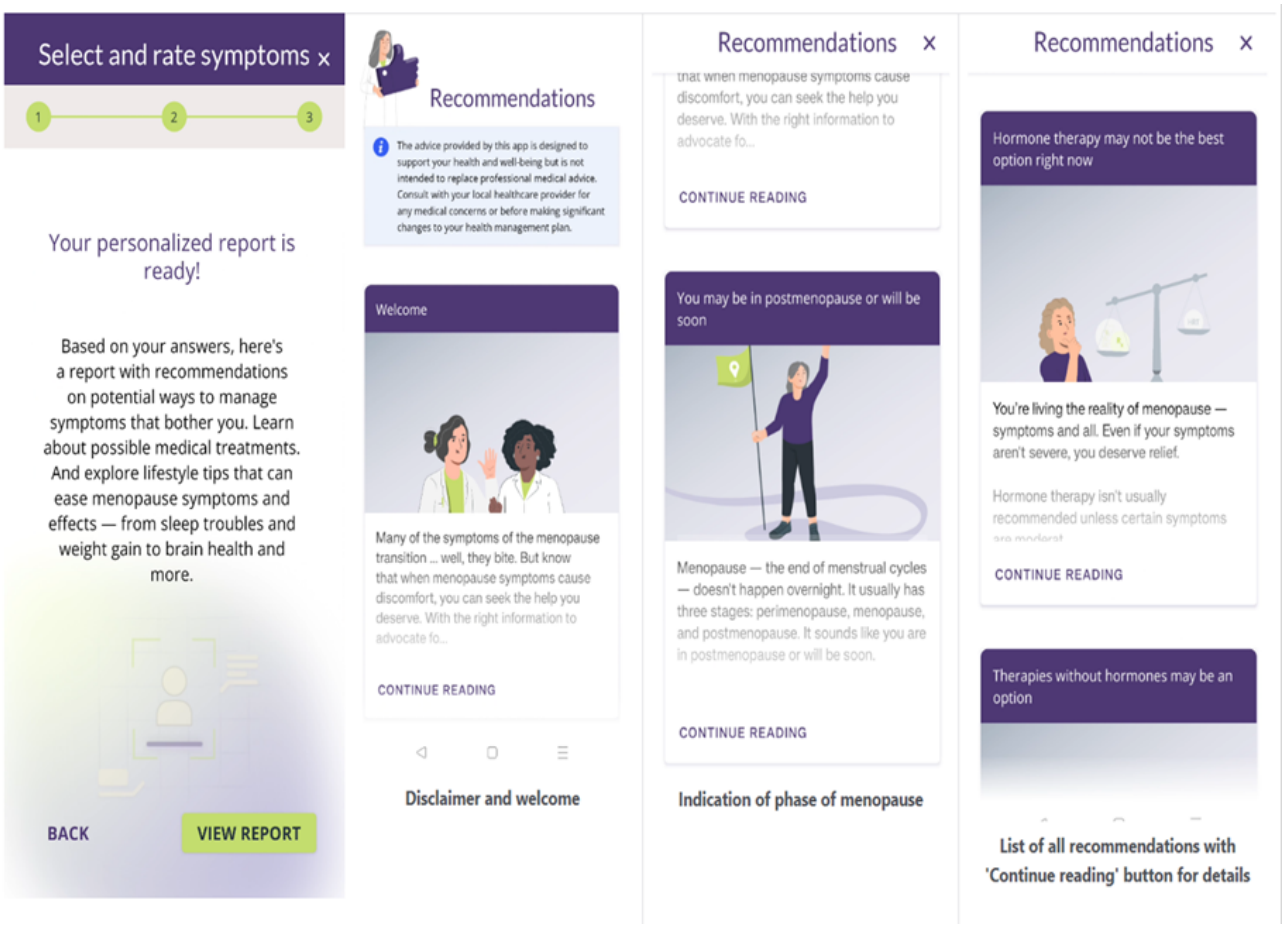

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Figure 4. Screenshot of the discussion guide generated based on user input in the emmii app.

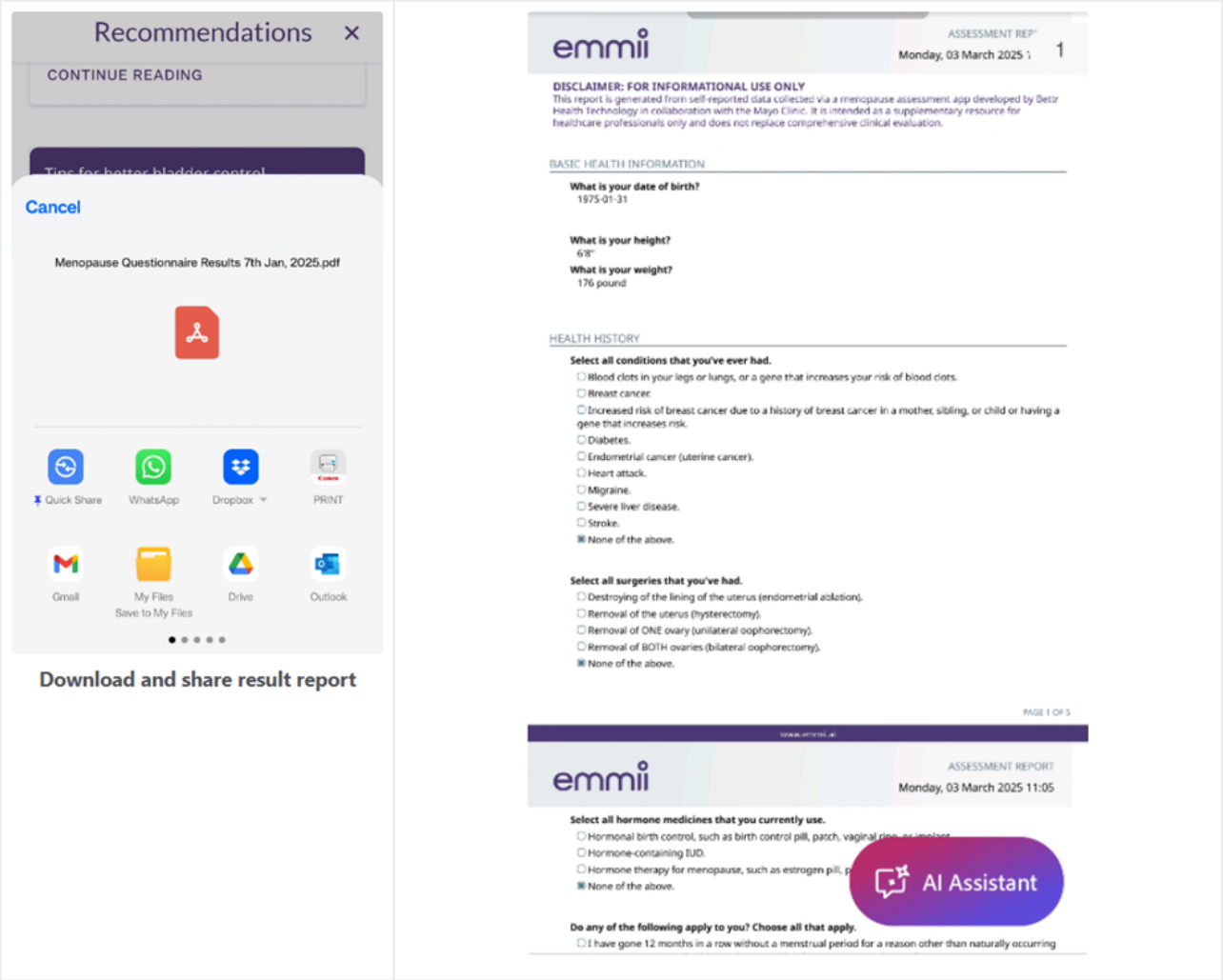

Beta Testing

The app underwent beta testing using Apple's proprietary TestFlight software (Apple Inc) and was tested on Android devices to ensure cross-platform functionality. A convenience sample of 24 women aged 40 years and older was recruited via email. Beta testers were asked to focus on app usability and therefore not required to meet a specific MRS threshold or have an upcoming primary care appointment. Individuals were recruited via email, and those who agreed to participate were provided with detailed instructions for downloading and accessing the app using a unique code. No incentives were offered for participation. After using the app, all beta testers completed a survey that included the System Usability Scale, a validated 10-question survey tool commonly used to assess perceived utility, design, and overall experience [28]. System Usability Scale scores above 50 are generally considered acceptable. The average System Usability Scale score among patients was 59, with a range from 35 to 88, indicating generally acceptable usability. A subset of 10 participants who completed the postappointment survey agreed to participate in follow-up interviews during which they provided more details about their experience with the app. These interviews lasted an average of 10 minutes and were conducted between 1 and 3 weeks following their engagement with the app.

The primary purpose of the beta testing period was to iteratively improve the interface based on feedback from beta testers, and several significant modifications were made to the app during this period. Key changes included improving data entry fields to better accommodate the input of height and weight, resolving display issues with the "Get My Results" button, improving onboarding with a new welcome page, adjusting font settings so that users could enlarge the fonts without sacrificing functionality, and modifying entry fields so that users could save and edit their information. These improvements were aimed at enhancing the app's accessibility and aligning it with the needs and expectations of midlife users.

Study Design and Participants

This prospective randomized trial will identify women aged 45-55 years with primary care appointments scheduled within 3 weeks of enrollment at one of the several geographic locations of Mayo Clinic. Eligible patients will be identified through the electronic health record (EHR) system and contacted via email with a link to complete the MRS and provide informed consent. Women with a total MRS score ≥5, indicating bothersome menopause symptoms, will be randomized to one of the 2 groups: the intervention group (n=200), which will receive access to the emmii app, or the control group (n=200), which will receive an educational pamphlet. The pamphlet includes

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educational content on perimenopause and menopause symptoms, hormone and nonhormone treatment options, and lifestyle strategies, based on clinical guidelines. Although it offers similar content to the app, it does not include emmii's interactive or personalized features. A copy of the full pamphlet is provided in Multimedia Appendix 1, and the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist is provided in Multimedia Appendix 2 for reference.

This is an unblinded trial; patients will be notified of their group assignment immediately after randomization. A formal sample size calculation was not conducted due to the absence of pilot data and the exploratory nature of the trial, which includes a range of primary and secondary outcomes of interest. The target sample size of 200 patients per group was based on anticipated recruitment feasibility within the study timeline.

Inclusion and Exclusion Criteria

Patients must be English-speaking, aged 45-55 years, have a qualifying primary care appointment, meet the MRS symptom threshold (≥5), and provide informed consent. Exclusion criteria include inability to provide consent or unwillingness to engage with the app.

Recruitment

Eligible patients will receive an email invitation with a secure link to complete the screening MRS and provide consent. Follow-up phone calls may be made to ensure that enrollment targets are met. Recruitment will continue on a rolling basis until the target sample size is reached.

Study Procedures

Patients randomized to the intervention group will be emailed instructions on how to download and use emmii. The app will guide users through symptom reporting and generate a personalized menopause discussion guide, which patients will be instructed to bring to their upcoming primary care appointments. Patients in the control group will be emailed a digital copy of the menopause education pamphlet.

Patients in both intervention and control groups will be asked to complete a postappointment survey within 1-3 weeks of the appointment date to identify whether they used the menopause discussion guide (from the app) or pamphlet. The surveys will also assess whether menopause symptoms were discussed during the visit, their priorities for menopause-related health care, their perceived access to menopause care, and preferences for receiving information on menopause symptoms and treatment options. App usage metrics, including frequency of use and features accessed, will also be collected for patients in the intervention group to explore potential associations between engagement and outcomes. Patients will receive up to 3 reminder messages and will have up to 3 weeks after their appointments to complete the survey.

After the appointment, the primary care clinician who provided care to the patient will also be asked to complete a brief postappointment survey to assess whether the app-generated guide or pamphlet was used during the encounter and evaluate their confidence in managing menopause-related symptoms in both scenarios.

Outcome Measures

Outcomes will be assessed from 3 main sources: patient surveys, clinician surveys, and EHR data. In the intervention group, adherence will be captured by BettrHealth, which will share information on whether individuals in the treatment group accessed the app and completed it to the point of receiving personalized recommendations. Adherence will be further assessed in more detail through patient-reported measures on the postappointment survey. App engagement metrics, including frequency of use and feature interaction, will be tracked through the app's built-in analytics platform. Outcome measures, including data sources, purpose, and timeline for measurement and data collection, are presented in Table 1.

Table 1. Outcome measures, data sources, and timeline for emmii app evaluation.

Data source	Outcome measures	Purpose	Timeline
Menopause Rating Scale	Symptom severity across somatic, psychological, and urogenital domains; includes 11 items scored 0 (absent) to 4 (very severe); total score range: 0-44.	Determines eligibility (≥5 threshold) and customizes participant information sheets after app engagement.	Pre-enrollment (intervention and control groups) and after app use (intervention group)
Patient survey	Patient use of the app-generated menopause discussion guide versus pamphlet, menopause-related health care priorities, perceived access to care, and information preferences.	Evaluates patient engagement with intervention materials, preferences for menopause care and information, and satisfaction with care.	After primary care appointment (intervention and control groups)
Clinician survey	Encounter use of the app-generated menopause discussion guide versus pamphlet, confidence in managing menopause-related symptoms.	Evaluates clinician perception of the intervention materials, satisfaction with the shared decision-making tools, and perspective regarding menopause treatment.	After primary care appointment (intervention and control groups)
Electronic health record	Prescription rates for hormone therapy and nonhormonal treatments (ie, serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors, gabapentin, oxybutynin, fezolinetant) for menopause symptoms, linked to survey data.	Assesses treatment patterns and correlates them with the use of the menopause app versus pamphlet alone.	Collected retrospectively 6 months after the appointment (intervention and control groups)

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MRS Questionnaire

MRS is a validated self-administered questionnaire used to assess the severity of menopause-related symptoms. Study participants will take this survey prior to enrollment to determine eligibility. MRS is composed of 11 distinct items across 3 symptom domains: somatic, psychological, and urogenital symptoms [27]. Each item is scored on a severity scale ranging from 0 (absent) to 4 (very severe), with increasing severity scores of 1 (mild), 2 (moderate), 3 (severe), and 4 (very severe). The overall score, which ranges from 0 to 44, is calculated by summing the individual item scores, with a higher total indicating a greater burden of menopause symptoms. For this study, a total MRS score of ≥5 will be used as the threshold to determine eligibility, indicating the presence of bothersome menopause symptoms warranting further evaluation. Patients will also take the survey again after accessing the app to enable the generation of personalized treatment recommendations tailored to their reported symptoms.

Patient-Reported Outcomes

A survey will be administered after the primary care appointment to assess how patients interacted with the app-generated discussion guide compared to the pamphlet. It will also capture their treatment preferences and perceptions of access to menopause care. This outcome will evaluate the effectiveness of the intervention in increasing patient engagement and shared decision-making.

Clinician-Reported Outcomes

A survey will be administered after the primary care appointment to assess how clinicians interacted with the app-generated discussion guide compared to the pamphlet. It will also inquire about the general confidence in treating menopause symptoms. This outcome will assess the clinician's perception of the intervention and satisfaction with the shared decision-making tool.

Clinical Outcomes (EHR-Based)

Clinical outcomes will be assessed by linking survey responses to EHR data to assess treatment outcomes that occur after appointments among those using the app and compare them to the control group. Specific outcomes include prescription rates of menopause-related pharmacologic treatments (hormone therapy and nonhormone treatments, including serotonin reuptake inhibitors/serotonin-norepinephrine reuptake inhibitors, gabapentin, oxybutynin, fezolinetant) among intervention and control groups. These data will allow the comparison of treatment patterns and explore whether app usage influences patient preferences and clinicians' prescribing patterns.

Data Collection

This study includes both existing data at the time of institutional review board submission and newly collected data. Existing appointment data will be used to determine eligibility, and demographic data will be incorporated into the analysis. Newly collected data will be gathered through participant surveys conducted after their appointments, as well as through the extraction of clinical outcome data from the EHR to evaluate treatment outcomes.

Data Analysis

Descriptive statistics will be used to analyze cross-sectional survey data and summarize participant characteristics. Statistical tests, including chi-square tests and Wilcoxon rank sum tests, will be used to compare treatment outcomes between intervention and control groups, where groups will be based on randomization (ie, intention to treat). Multivariable models will be applied to assess differences in the outcomes after adjusting for baseline differences in MRS scores and demographics (including age and self-reported race/ethnicity) between groups. Missing survey responses will not be imputed. All data analyses will be performed using SAS software (version 9.4; SAS Institute, Inc).

Ethical Considerations

This study was approved by the Mayo Clinic Institutional Review Board (approval ID: 24-013662). Informed consent will be obtained from all study participants. The consent process involves 2 main components: (1) the initial documentation of informed consent through Remote Electronic Consent technology, ensuring participant comprehension and agreement; and (2) for those who elected to participate, an oral consent script will be used to reinforce key study details, followed by the collection of a signed Health Insurance Portability and Accountability Act authorization. To protect participant privacy, all collected data will be deidentified prior to analysis and securely maintained on an encrypted server. No compensation will be offered to study participants. No identification of individual participants is included in the images, figures, or supplemental materials of this manuscript. All potential participants will receive explicit information regarding the voluntary nature of their involvement. It will be clearly communicated that participants have the right to withdraw their consent or cease participation at any point during the study, without incurring any penalty.

Results

The beta testing for emmii content and functionality was conducted from October through December 2024. Feedback collected during this phase led to several updates to the app, which were implemented in January and February 2025. Data collection for the randomized controlled trial is scheduled to begin in April 2025.

Discussion

Overview

By integrating symptom tracking, evidence-based educational content, and a personalized discussion guide, the emmii app has the potential to enhance patients' knowledge about treatment options for menopause symptoms. This may result in shared decision-making with their primary care clinicians regarding treatment options, including both hormonal and nonhormonal therapies. Many mHealth apps lack evidence-based content or medical expertise; however, emmii was developed by physicians at Mayo Clinic who are certified by The Menopause Society, ensuring that the app provides evidence-based, clinically relevant information. Given that many women may hesitate to

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discuss menopause symptoms in a health care setting, emmii offers a valuable tool for facilitating structured and informed conversations between patients and their primary care clinicians [29].

Although the strengths of the emmii app are clearly defined, evaluating its impact will be essential to understand its role in improving patient outcomes such as symptom management and treatment adherence. These results will help determine the app's broader applicability and its potential for widespread implementation in diverse health care settings. Because it is designed as a self-guided mHealth app, emmii has the potential to be scaled across various health care systems with minimal additional resource demands. Future integration of the app into EHR portals or patient intake workflows could optimize its use in primary care settings. Cost-effectiveness analyses will be essential to determine whether the app can reduce unnecessary clinical visits or improve adherence to effective treatments. Based on the study's findings, future adaptations may include culturally tailored content, language translation, or integration with telehealth platforms to further expand reach and clinical utility.

Limitations

Although this study will present an innovative approach by integrating evidence-based content, symptom tracking, and personalized discussion guides, there are several potential limitations. Despite its potential, successful implementation of the emmii app must consider barriers related to digital access and literacy. Disparities in smartphone ownership, internet access, and comfort with using technology may disproportionately affect older adults, those from lower socioeconomic backgrounds, and individuals from underrepresented racial and ethnic groups. These challenges could limit engagement and create inequities in app-based menopause care. To address these barriers, future efforts should explore providing digital literacy support, offering the app in multiple languages, and ensuring that accessibility features are embedded into the platform. Partnering with community health centers and integrating the app into existing patient education workflows may also facilitate access for underserved populations. Reliance on self-reported symptom data may introduce bias, as patients' engagement with the app may vary based on factors such as symptom severity, comfort with technology, and personal preferences. Additionally, the study's focus on patients with upcoming primary care appointments within a specific health care system may limit the generalizability of the findings, as the sample may not fully represent the broader population of women experiencing menopause. Moreover, the potential lack of cultural and racial diversity among the patients could limit the applicability of the results to all women.

Conclusion

This protocol paper outlines the use of emmii, an innovative mHealth app designed to improve the menopause experience for midlife women. The app offers a comprehensive approach to managing menopause symptoms by addressing knowledge gaps, tracking symptoms, and facilitating communication between patients and primary care clinicians. This tool has the potential to enhance clinical interactions, support shared decision-making, and ultimately improve patient experience and quality of life.

Acknowledgments

We thank Rob Scrimshaw for his assistance with beta testing.

Conflicts of Interest

CS has no conflicts of interest directly related to the subject of this manuscript. She is an advisor for Bayer Pharmaceuticals. JMK is consulting for Bayer and Elsevier, CME and non-CME honorarium for AiCME, City of Mesa, Paradise Valley Country Club, EPG Health, Vindico Medical Education, Arizona Public Services, WebMD, and Evolve Medical Education LLC. EK has no conflicts of interest directly related to the subject of this manuscript. However, over the past 36 months, she has had the following conflicts of interest. She has been a consultant for Astellas Pharmaceuticals, Estetra SRL, WellFound Inc, Fresenius Kabi USA Inc, and Exeltis. SSF is consulting for Era Women's Health Platform, Weight Watchers Scientific Advisory Board, CME lectures for PriMed, Medscape, MedAll, and AiCME. RC, EK, and SSF acknowledge that they and Mayo Clinic have a financial interest related to this research. This research has been reviewed by the Mayo Clinic conflict of interest review board and is being conducted in compliance with Mayo Clinic conflict of interest policies.

Multimedia Appendix 1
Educational menopause pamphlet provided to patients in the control group.
[PDF File (Adobe PDF File), 3735 KB - resprot_v14i1e76536_app1.pdf]

Multimedia Appendix 2
SPIRIT checklist.
[PDF File (Adobe PDF File), 365 KB - resprot_v14i1e76536_app2.pdf]

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Abbreviations

EHR: electronic health record
mHealth: mobile health
MRS: Menopause Rating Scale
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Comparative Evaluation of Autologous Sticky Bone, Platelet-Rich Fibrin, and Octacalcium Phosphate–Coated Deproteinized Bovine Bone Material for the Regeneration of Human Periodontal Infrabony Defects: Protocol for a Randomized Controlled Clinical Trial

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Abstract

Background: The term *periodontium* encompasses the supporting structures around a tooth, including gingival tissue, alveolar bone, cementum, and periodontal ligament. Periodontal disorders are highly prevalent, affecting approximately 95% of the Indian population. Restoring the missing attachment apparatus is the main goal of regenerative therapy in cases of periodontal disease. The reproduction or rebuilding of damaged or lost periodontal tissue to restore the structure and functionality of the periodontium is known as regeneration. This study investigates the effectiveness of autologous sticky bone (ASB), autologous platelet-rich fibrin (PRF), and octacalcium phosphate–coated deproteinized bovine bone material (OCP-DBBM). These materials are being evaluated for their potential to enhance bone regeneration in infrabony defects, which are a significant concern in periodontal therapy. Effective bone regeneration is critical for the successful treatment of periodontal defects, as it can lead to improved clinical outcomes, including better attachment levels and reduced probing depths. This study aims to provide insights into the most effective methods for achieving these goals.

Objective: We aim to assess the efficacy of ASB and autologous PRF in conjunction with OCP-DBBM in infrabony defects at 6 months after surgery with regard to radiographic bone fill, reduction in probing pocket depth, and increase in clinical attachment level.

Methods: This randomized controlled clinical trial will be performed on 20 defects in patients diagnosed with stage 2 and 3 grade B periodontitis. It will be a parallel-designed study where group 1 (n=10) will be treated with ASB and group 2 (n=10) will be treated with autologous PRF and OCP-DBBM. One sitting will be required to perform the treatment, and a follow-up checkup will be done at 6 months.

Results: Recruitment procedures started in June 2025. All data are anticipated to be collected by February 2026. Full trial results are anticipated to be analyzed and submitted for publication by March 2026. The study's anticipated end date is March 2026.

Conclusions: Both treatment approaches are expected to lead to notable gains in periodontal health and bone regeneration. The primary outcome, radiographic bone fill, and the secondary outcomes, clinical attachment level gain and probing pocket depth reduction, are critical indicators of treatment success.

Trial Registration: Clinical Trials Registry-India CTRI/2024/06/069603; https://www.ctri.nic.in/Clinicaltrials/pmaindet2.php?EncHid=MTAzODk0&Enc=&userName=

International Registered Report Identifier (IRRID): PRR1-10.2196/69666

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KEYWORDS

autologous sticky bone; ASB; autologous platelet-rich fibrin; autologous PRF; octacalcium phosphate–coated deproteinized bovine bone material; OCP-DBBM; infrabony defects

Introduction

Background

Disease problems affecting the periodontium are referred to by the word *periodontium*, which describes the supporting structure surrounding a tooth and is made up of the gingival tissue, alveolar bone, cementum, and periodontal ligament. The damaging, irreversible, chronic inflammatory disease that follows gingivitis is called periodontitis. As a result, the bacteria are more likely to enter the surrounding tissues and periodontium. This initiates the host defense system against the microbes that are invading the area [1].

Periodontal disorders, which impact 95% of the Indian population, are one of the most common oral ailments. Periodontitis frequently results in infrabony defects with periodontal pockets, which are the anatomical consequences of plaque spreading apically in the course of periodontitis. “Regeneration of periodontal attachment will become the major goal of regenerative therapy when periodontal disease results in the loss of the attachment apparatus” [2].

Regeneration has been defined as “the reproduction or reconstitution of a lost or injured part to restore the architecture and function of the periodontium. The aim of regenerative periodontal therapy is to restore the structure and function of the periodontium” [3].

Numerous regenerative periodontal therapies have been developed over the past 20 years with the goal of replacing lost tooth-supporting tissues, such as the cementum, alveolar bone, and periodontal ligament [4]. The various regenerative materials used are guided tissue regeneration, enamel matrix derivative, bone grafts like autografts, allografts, and xenografts, matrix-based scaffolds**,** and synthetic materials like demineralized freeze-dried bone allograft (DFDBA), anorganic bovine bone, hydroxyapatite, and tricalcium phosphate. These are osteoconductive in the repair of deformities, acting as a mechanical scaffold for the formation of new bone [5].

When it comes to periodontal graft materials, autograft is regarded as the best. However, patients often resort to alternative periodontal treatment approaches to avoid a surgical donor site and associated complications [6]. Hydroxyapatite, octacalcium phosphate, and DFDBA are a few of the several synthetic materials, xenografts, and allografts that are available and widely used as regeneration materials [7].

Both osteoconductive and osteoinductive qualities are present in the new gold standard for xenografts, macropore octacalcium phosphate–coated deproteinized bovine bone.

This is made from a 100% bovine cancellous bone substitute. Because graft bone materials have a high osteoconductivity, they aid in the proliferation of osteogenic cells and microvessels, which in turn stimulate the formation of new bone [8].

To facilitate the successful regeneration of damaged periodontal tissues, autologous sticky bone (ASB) was introduced as an alternative. ASB is defined as a physiologically solidified bone graft that is embedded in the fibrin network. Strong interconnection of particle bone powders by the fibrin network prevents scattering, even when shaken with a cotton plier. Sticky bone offers many benefits: (1) it can be shaped to suit virtually any kind of bony defects; (2) it prevents the grafted bone from moving; (3) no biochemical additives are needed to maintain the volume of augmentation during the healing period, thereby minimizing the need for block bone and titanium mesh; (4) fibrin accelerates bone and soft tissue regeneration by entrapping platelets and leukocytes that release growth factors; and (5) fibrin interconnection minimizes soft tissue ingrowth into the sticky bone graft [9].

One of the newest developments in regenerative surgery is the use of platelet concentrates for in vivo tissue engineering applications: the first two are platelet-rich fibrin (PRF) and platelet-rich plasma. Platelet concentrates, a concentrated solution of growth factors produced from platelets, are applied as a bioactive surgical adjuvant to facilitate the healing of wounds [10].

As radiographs can identify the quantity and type of damage to the alveolar bone, they play a significant role in periodontal diagnostics. Further research comparing radiographs to presurgical measures found that “bone loss can be underestimated by 1.5 mm, with considerable differences in examiners’ interpretations” [11].

Computed tomography scans have been explored for their potential in highly accurate 3D image alignment. However, they have limitations, including significant radiation exposure and the bulkiness and expense of the equipment [12]. Cone-beam computed tomography (CBCT) has recently emerged as a viable technique in dentistry, offering a lower-cost alternative to traditional computed tomography while still producing high-quality pictures and exposing patients to less radiation.

Therefore, this study will be carried out to evaluate the effectiveness of ASB and autologous PRF along with octacalcium phosphate–coated deproteinized bovine bone material (OCP-DBBM) in the treatment of human infrabony defects.

Rationale

Periodontitis can lead to the development of infrabony defects and periodontal pockets, resulting in the loss of the attachment apparatus. This can pose a significant problem.

Therefore, the main objective of regenerative therapy is to regenerate the periodontal attachment.

Two distinct approaches will be used: ASB and autologous PRF combined with OCP-DBBM. ASB is a bone graft that hardens

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physiologically and becomes integrated within the fibrin network. Autologous PRF with OCP-DBBM uses macroporous octacalcium phosphate–coated deproteinized bovine bone. This composite material offers both osteoconductive and osteoinductive properties, making it highly suitable for bone regeneration.

Objectives

The following are the objectives of this study:

- Objective 1: to assess the efficacy of ASB in infrabony defects at 6 months after surgery with regard to radiographic bone fill, reduction in probing pocket depth (PPD), and increase in clinical attachment level (CAL).
- Objective 2: to assess the efficacy of autologous PRF in conjunction with OCP-DBBM in infrabony defects at 6 months after surgery with regard to radiographic bone fill, reduction in PPD, and increase in CAL.
- Objective 3: to assess the efficacy of ASB and autologous PRF in conjunction with OCP-DBBM in infrabony defects at 6 months after surgery with regard to radiographic bone fill, reduction in PPD, and increase in CAL.

Methods

Recruitment

The selection of study participants was performed using well-defined inclusion and exclusion criteria to ensure uniformity and reliability of clinical outcomes. Only systemically healthy individuals diagnosed with chronic periodontitis and presenting with specific radiographic and clinical characteristics were enrolled. The inclusion criteria were designed to identify patients with distinct infrabony periodontal defects that could be assessed radiographically and managed surgically, thereby enabling accurate evaluation of regenerative outcomes. Each participant was selected after completion of initial nonsurgical periodontal therapy and demonstration of acceptable oral hygiene maintenance.

The inclusion parameters emphasized the presence of at least 1 or 2 well-defined infrabony defects with probing depth and clinical attachment loss of ≥5 mm, ensuring adequate disease severity for evaluating regenerative potential. Radiographic criteria, such as a defect depth ≥3 mm and a base positioned ≥3 mm coronal to the root apex, were essential to avoid endodontic involvement and to ensure sufficient bone support for defect containment. The requirement of a minimum of 3 mm of keratinized gingiva around the test tooth ensured soft-tissue stability and favorable surgical access.

The exclusion criteria were framed to eliminate potential confounding variables that could affect periodontal healing or regenerative outcomes. Patients with stage 4 grade C periodontitis, poor plaque control (plaque index >1), or smoking habits were excluded due to their known adverse effects on periodontal regeneration. Similarly, teeth exhibiting mobility greater than grade 2, advanced furcation involvement (class 3 or 4), or prior periodontal surgery in the same quadrant were omitted to maintain site comparability. Pregnant and lactating women were also excluded to prevent any ethical or physiological risks associated with surgical intervention and medication use.

These stringent criteria collectively will ensure that all participants meet the clinical and radiographic prerequisites for reliable assessment of treatment efficacy while minimizing biological and procedural variability (Textbox 1).

The sample size calculation was as follows:

where α=.05, β=.1, SD in group 1 (σ1) is 0.83, mean in group 1 (μ_1) is 0.522, SD in group 2 is (σ2) 0.044, mean in group 2 (μ_2) is 0.42, and ratio (group 2 to group 1)=1. The total sample size required was 10 participants per group, as indicated by the calculation [13].

Textbox 1. Inclusion and exclusion criteria for patient screening for infrabony defects.

Inclusion criteria

- Minimally 1 or 2 radiographically identifiable infrabony defects, with a clinical attachment loss and probing pocket depth of ≥5 mm after initial therapy
- Depth of intraosseous component of the defect ≥3 mm
- The radiological base should be ≥3 mm coronal to the tooth's apex
- The test teeth must have at least 3 mm of keratinized gingiva

Exclusion criteria

- Presence of stage 4 grade C periodontitis
- Patients with poor oral hygiene (plaque index>1)
- Habit of smoking
- Study tooth with mobility exceeding grade 2 and exhibiting a class 3 or class 4 furcation defect
- History of periodontal surgical therapy of the selected quadrant
- Women who are pregnant or lactating

Note: The inclusion and exclusion criteria are based on the American Academy of Periodontology 2017 classification [1].

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Intervention Description

Before the surgical procedure, patients will be instructed to rinse their mouths for 1 minute with 0.2% chlorhexidine gluconate solution. Only the oral cavity will be visible because of the patient's drapes. The patient will remain aseptic for the duration of the process. Using a local anesthetic solution of 2% lidocaine containing 1:100,000 epinephrine (Ligno-Ad local anesthetic, Proxim Remedies), the surgical site will be anesthetized by a nerve block or infiltration anesthesia.

Flap Design (Incisions)

A conventional approach consisting of a periodontal access flap will be initiated by intracrevicular (sulcular) incisions using Bard-Parker number 12 or 15 surgical blades on the buccal and lingual aspects. The incisions will be carried as far interproximally as possible to preserve the entire interdental papillae to achieve primary wound closure. A tooth mesial and distal to the defect-associated tooth will be included in the flap. If necessary, divergent vertical relieving incisions will be made one tooth away from the defect, where further access will be required.

Flap Reflection

A full-thickness mucoperiosteal flap will be reflected using a periosteal elevator (24G Hu-Friedy) to expose the alveolar bone in the area of the osseous defect. Extreme care will be taken to avoid flap perforation or loss of papillae during removal of granulomatous tissue from the inner aspect of the flap.

Debridement and Root Surface Management

The osseous defect will be debrided off the granulation tissue using hand instruments (Gracey curettes, Hu-Friedy) followed by ultrasonic instruments (EMS, Minipiezon), thus exposing the root surface, alveolar bone, and periodontal ligament. Any granulomatous tissue or epithelium adherent to the inner surface of the flap or papillae will be judiciously removed, taking care not to overthin the flap. The root surfaces will be planned to remove plaque and calculus by using ultrasonic instruments, followed by hand instrumentation. The root surfaces will be planed until a smooth and hard consistency is obtained.

At this stage, direct measurements of the vertical bone defects (BDs) and the number of bony walls present will be recorded with the UNC-15 probe. If the BD depth is ≥3 mm vertically, final participant eligibility will be confirmed.

Preparation of Autologous PRF

As part of the protocol, approximately 6 mL to 10 mL of venous blood will be collected from the patient's forearm using an 18G needle in a sterile plastic vacutainer for the preparation of autologous PRF by venipuncture of the median cubital vein and transferred to fresh sterile test tubes and without adding any anticoagulant, the original amount of blood will be divided equally in 2 tubes, which will be placed symmetrically around the rotor axis for proper balancing and centrifuged at 3000 rpm for 10 minutes to produce autologous PRF.

Preparation of ASB

Following complete debridement, an 18G needle will be used to draw about 30 mL of venous blood from the patient's forearm using 1 of 2 vacutainer types: (1) noncoated for autologous fibrin glue and (2) glass coated for concentrated growth factor (CGF) and alternated controlled centrifugation at 2400 rpm to 2700 rpm will be performed for 12 minutes. The autologous fibrin glue obtained will then be mixed with OCP-DBBM for polymerization, which produces a yellow, sticky bone. CGF will be mixed with the prepared sticky bone to produce the CGF–sticky bone mixture.

Procedure for Group 1

Complete isolation and hemostasis of the defect will be achieved. The flap will be presutured without tying the knot to allow rapid flap closure after placement of graft material. ASB will be placed into the osseous defect at the test site with light pressure until it is filled to the most coronal level of the osseous wall by raising the flap. The flap will then be coronally repositioned and sutured in such a way that the flap margin will be located 1 mm to 2 mm coronal to the cemento-enamel junction (CEJ), ensuring primary flap closure. A combination of vertical mattress and interproximal sutures (4-0 nonresorbable surgical sutures, braided black silk [Mersilk, Ethicon; Johnson & Johnson Ltd]) will be used to secure the flap in position. Slight pressure will be applied to the area with saline-soaked gauze for approximately 2 minutes to adapt the soft tissue well to the tooth surface and eliminate any space in which a clot might form and disrupt reattachment. The surgical site will be dressed with a periodontal dressing (Coe-Pak, GC Inc) on the buccal and lingual aspects.

Procedure for Group 2

The surgical procedure for the defect site will be identical to the procedure of the test site, except that osseous defects at group 2 sites will be packed with OCP-DBBM, and then a PRF membrane will be placed over the bone graft.

Maintenance Care

Patients will be recalled after 10 days for suture removal and subsequently for evaluation of both the plaque index (PI) and papillary bleeding index at 3 and 6 months postoperatively. All participants will be reinforced with oral care protocol and full-mouth ultrasonic supragingival scaling during the follow-up visits.

Statistical Analysis

Power

PI, papillary bleeding index, PPD, relative attachment level, and relative gingival marginal level will be calculated by mean and SD values. Statistical tests such as the paired 1-tailed *t* test or Wilcoxon signed-rank test for within-group comparison and the ANOVA or Kruskal-Wallis test for between-group comparison are typically used to assess clinical and radiographic outcomes. The choice of test depends on whether the data follow a normal distribution. The difference between radiographic bone fill, PPD, CAL and relative gingival margin level will be considered significant only if $P<.05$.

The study population will be divided into 2 groups: group 1 (ASB) and group 2 (autologous PRF with OCP-DBBM). There are no subgroups in the study.

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Evaluation Outcomes

Clinical measurements to be recorded on the day of surgery and 6 months after surgery are PI [14], papillary bleeding index [15], PPD, relative attachment level, and relative gingival marginal level. Periodontal charting on a specially designed form and CBCT will also be documented.

PI Assessment

Plaque will be assessed on the labial or buccal and lingual surfaces of all the teeth after using a disclosing agent (Table 1) [14].

Table 1. Score criteria for the plaque index.

Score	Criteria
0	No plaque
1	Separate flecks of plaque at the cervical margin of the tooth
2	A thin, continuous band of plaque (up to 1 mm) at the cervical margin
3	A band of plaque wider than 1 mm but covering less than one-third of the crown
4	Plaque covering at least one-third but less than two-thirds of the crown
5	Plaque covering two-thirds or more of the crown

Calculations of PI

The sum of the scores around each tooth was divided by 2 to obtain the PI score for the tooth. The PI score per person will be obtained by totaling all the plaque scores and dividing by the number of teeth examined.

Papillary Bleeding Index

A periodontal probe will be carefully inserted into the gingival sulcus at the base of the papilla on the mesial aspect and then moved coronally to the papilla tip [15]. This will be repeated on the distal aspect of the same papilla. The intensity of any bleeding thus provoked will be recorded on a 0 to 4 scale (Table 2).

Table 2. Score criteria papillary bleeding index.

Score	Criteria
0	No bleeding
1	A single discrete bleeding point appears
2	Several isolated bleeding points or a single fine line of blood appears
3	The interdental triangle fills with blood shortly after probing
4	Profuse bleeding occurs after probing; blood flows immediately into marginal sulcus

Calculations of Papillary Bleeding Index

Each papilla will be scored according to the aforementioned criteria. The sum of all scores will be divided by the number of papillae examined to obtain the papillary bleeding index score per person.

Probing Measurements

Both treatment groups will be subjected to recordings to measure PPD, relative CAL, and relative gingival margin level at 6 sites of the selected teeth. Measurements will be carried out using a UNC-15 calibrated periodontal probe (University of North Carolina) at the mesiobuccal, mesiolingual, distobuccal, distolingual, midbuccal, and midlingual points of the selected tooth. After measurement, only the deepest marking per defect will be considered for study purposes. After the fabrication of the acrylic stent, probing measurements will be recorded at baseline and 6 months postoperatively.

The UNC-15 probe will be positioned on the prepared groove of the acrylic stent. The probe will be placed with its tip at the gingival marginal level, and the distance between the gingival margin and the lower border of the stent will be measured as the relative gingival margin level. Then, the probe will be positioned at the bottom of the pocket, and the distance from the lower border of the stent to the bottom of the pocket will be noted as the relative CAL. PPD will be measured by subtracting the relative gingival margin level from the relative CAL. The width of keratinized gingiva will be calculated from the lowest point of the mucogingival junction to the crest of the gingival margin using the UNC-15 probe.

Radiographic Analysis

The infrabony defect sites will be investigated with CBCT at baseline and 6 months postoperatively. The CBCT analysis will include the measurement of BD height (CEJ–base of the defect), level of alveolar crest (AC; CEJ–AC), BD depth (AC-BD), and the mesiodistal (MD) and buccolingual BD width. The landmark of the base of the defect will be the lowest discontinuous point of the periodontal ligament. A line perpendicular from the AC to the root surface will be drawn, and the intersection point across the root surface will be termed as AC'.

Infrabony defect depth: The distance from the point AC' to the base of the defect (AC'-BD). MD width of the infrabony defect (AC-AC): The distance from the point AC' to the AC. The

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buccolingual width of the defect will be measured by selecting the innermost and most coronal points of the buccal and lingual AC on the axial plane, and calculating the horizontal distance between these two points. A 1.00-mm incremental slice thickness will be used in this study's investigation, as smaller slices decrease the image resolution. In the oblique view, the x-, y-, and z-axes will be sequentially analyzed to locate the most apical point of the BD or the most coronal aspect of the defect-associated AC [6].

Plans to Promote Participant Retention and Complete Follow-Up

Patients will be recalled after surgery at 1, 3, and 6 months. At every recall appointment, all participants will receive guidance on maintaining good oral hygiene as well as full-mouth professional prophylaxis, which involves ultrasonic scaling.

Ethical Considerations

This study received approval on January 30, 2024, from the Institutional Ethics Committee of Datta Meghe Institute of Higher Education and Research (DMIHER DU/IEC/2024/227) to ensure adherence to ethical guidelines, respect participant rights, and meet established standards. This study has been registered with the Clinical Trials Registry-India under registration CTRI/2024/06/069603. Participants will be provided with an informed consent form, clearly describing the study's aim, procedures, risks, benefits, and their right to opt out at any time. Consent for publication of data will be obtained and will be used for all analyses, including secondary analyses. We will confirm that the original consent and institutional review board approval explicitly cover the use of primary and secondary data. Collection of data and entering the data into the database for screening and randomization will be done by the primary investigator. The privacy of prospective and enrolled participants' personal information will be upheld to ensure confidentiality before, during, and after the trial.We ensure that the data collected will be fully anonymized, with no personally identifiable information retained or linked to any participant. As there are no interventions involved and as only a cross-sectional survey will be conducted in which the data will be collected via an interview and anthropometric measurements, participants will not be provided with any compensation in this study.

Results

It is anticipated that ASB will show better results. The study aims to evaluate the effectiveness of different materials in the regeneration of human periodontal infrabony defects. The principal outcomes are presented subsequently.

Primary Outcome: Radiographic Bone Fill

The primary outcome measured in the study is radiographic bone fill at 6 months after surgery. This outcome is crucial as it indicates the extent of bone regeneration achieved through the different treatment modalities being tested.

Secondary Outcomes

In addition to the primary outcome, the study also assesses secondary outcomes, which include the following:

- CAL gain, which measures the improvement in the attachment of the periodontal tissue to the tooth, indicating successful regeneration.
- PPD reduction, which is used to evaluate the decrease in the depth of periodontal pockets, which is a sign of improved periodontal health.
- Relative gingival marginal level, which has been documented to assess the health of the gingival tissue surrounding the teeth.

Discussion

Anticipated Findings

It is anticipated that the use of ASB will show a better outcome in treating infrabony defects because of its advantageous properties provided by the strong fibrin interconnection with particulate bone powder.

ASB, a composite graft derived from a mixture of bone particles and platelet-rich plasma, has been previously studied for its osteoinductive and osteoconductive properties, contributing to enhanced periodontal regeneration. This study aligns with previous reports demonstrating the ability of ASB to promote significant periodontal tissue regeneration and improved clinical outcomes, particularly in terms of bone fill and attachment gain [16]. The osteoconductive nature of ASB, combined with its growth factor–enriched environment, likely facilitates the recruitment of stem cells and fibroblasts, fostering tissue remodeling and bone regeneration [17].

PRF, obtained through centrifugation of autologous blood to isolate a fibrin matrix rich in platelets, has also been shown to enhance healing in periodontal defects through the release of growth factors and cytokines that promote cellular proliferation and angiogenesis [18]. Similar findings have been reported by Jee [19], who showed that PRF accelerates the healing process in periodontal tissue by facilitating the regeneration of the bone matrix and soft tissue. While both ASB and PRF have exhibited favorable outcomes, the superior regenerative capacity of ASB in terms of bone fill and attachment gain may be attributed to the additional presence of bone graft material, which enhances the scaffold effect and provides more robust osteoconductive support [20].

OCP-DBBM is a biomaterial composed of deproteinized bovine bone mineral coated with octacalcium phosphate, which has demonstrated promising potential for bone regeneration in periodontal defects because of its osteoconductive properties [21]. While OCP-DBBM contributed to moderate bone fill and clinical attachment gain, the lack of autologous growth factors may limit its regenerative potential compared with PRF and ASB, which both leverage endogenous healing factors.

It is also worth considering that the clinical success of biomaterials such as OCP-DBBM is often contingent on the patient's biological response, which may vary between individuals. The relatively lower efficacy of OCP-DBBM in comparison to the other two regenerative modalities may be attributed to the absence of a direct cellular component, limiting the healing potential to the osteoconductive properties of the material alone.

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Mechanisms of Regeneration

The regenerative success of both ASB and PRF can be attributed to the synergistic effects of their cellular and biochemical components. By combining platelet-rich plasma with autologous bone graft particles, sticky bone creates a scaffold that promotes osteogenic differentiation and tissue integration by releasing growth factors like platelet-derived growth factor, vascular endothelial growth factor, and transforming growth factor-β [22]. These growth factors play a critical role in enhancing osteoblastic differentiation and angiogenesis, key processes necessary for effective bone regeneration.

Similarly, PRF's effectiveness stems from its natural fibrin matrix, which facilitates the slow release of growth factors that contribute to soft tissue healing, as well as bone formation [19]. The combination of PRF with bone grafts has been found to produce a superior regenerative outcome compared with bone grafts alone, likely because of the enhanced cellular activity and tissue remodeling it promotes [23].

In contrast, OCP-DBBM primarily provides a physical scaffold that supports bone growth through osteoconductive mechanisms, relying on the native healing process of the host tissue. Although OCP-DBBM has shown efficacy in bone regeneration, it may not provide the same level of biological support as ASB and PRF, which actively participate in healing through growth-factor processes and cell-mediated processes.

Clinical Implications

The findings of this study underscore the importance of selecting appropriate regenerative materials based on defect characteristics and patient needs. For patients with complex periodontal defects, the combination of autologous biological materials like ASB and PRF may offer a more favorable outcome because of the incorporation of growth factors and cellular components that promote tissue regeneration. These treatments may be particularly beneficial in cases where rapid healing and significant bone regeneration are paramount.

However, for less complex defects or in cases where the use of autologous materials is not feasible, OCP-DBBM provides a viable alternative, offering satisfactory regeneration with a lower risk of complications and easier handling.

Limitations

This study has several potential limitations:

- A small sample size may not accurately reflect the larger population and may restrict how broadly the findings can be applied.
- Longer follow-up periods could provide more comprehensive insights into the long-term effectiveness and stability of the treatments used.
- The results may not apply to different kinds of bone graft materials or periodontal regeneration methods.
- No histomorphometric analysis will be performed.

Comparison With Prior Work

Singh and Kashyap [13] conducted a clinical study comparing ASB and a mixture of autologous PRF and bioactive glass (PRF-BG) for regenerating periodontal infrabony defects. They found that, unlike other platelet concentrates, PRF and CGF do not need external anticoagulants and release growth factors that aid healing. However, CGF and PRF alone cannot retain bone graft material long enough for proper healing. To improve bone graft stability, they tested 3 therapies (open flap debridement [OFD], PRF-BG, and ASB). The graft materials were well tolerated, and PRF-BG and ASB groups showed reduced postoperative inflammation compared with the OFD group.

Najeeb et al [8] conducted a clinical study comparing the resolution of infrabony defects and bone regeneration in three-walled defects treated with OFD using either OCP-DBBM (Ti-oss) or DFDBA. Based on CBCT analysis, they concluded that Ti-oss demonstrated superior regenerative outcomes.

Conclusions

The outcomes of this investigation may yield critical insights into the comparative efficacy of therapeutic modalities for periodontal regeneration, particularly in the management of infrabony defects. Such evidence could inform and refine clinical decision-making, contributing to enhanced patient-centered outcomes, including reductions in probing depth, gains in CAL, radiographic evidence of osseous fill, and the establishment of more efficacious and standardized treatment protocols within the field of periodontics.

Future Research Directions

The study may also highlight the need for further research to explore long-term outcomes and the effectiveness of these treatments in diverse patient populations. This could help with refining techniques and improving overall treatment strategies in periodontal therapy.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

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Authors' Contributions

All the authors contributed to the conceptualization of the study, implementation of the investigations, and project administration. Final review of the manuscript was done by all the authors.

Conflicts of Interest

None declared.

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Abbreviations

AC: alveolar crest
ASB: autologous sticky bone
BD: bone defect
CAL: clinical attachment level
CEJ: cemento-enamel junction
CBCT: cone-beam computed tomography
CGF: concentrated growth factor
DFDBA: demineralized freeze-dried bone allograft
MD: mesiodistal
OCP-DBBM: octacalcium phosphate–coated deproteinized bovine bone material
OFD: open flap debridement
PI: plaque index
PPD: probing pocket depth
PRF: platelet-rich fibrin
PRF-BG: platelet-rich fibrin and bioactive glass

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Protocol

Just-in-Time Adaptive Intervention to Improve HIV Prevention and Substance Use in Youth Experiencing Homelessness (MY-RIDE): Protocol for a Randomized Controlled Trial

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Abstract

Background: Youth who are experiencing homelessness face a higher risk of HIV infection compared to their housed peers, and suicide and overdose remain the leading causes of death among homeless youth. Just-in-Time Adaptive Interventions (JITAIs) are gaining momentum for HIV prevention and substance use research. Yet, most interventions for homeless youth have not addressed modifiable real-time factors.

Objective: This paper describes the development and implementation of a randomized attention-controlled trial to assess the efficacy of motivating youth to reduce infections, disconnections, and emotional dysregulation (MY-RIDE), a JITAI to improve HIV prevention and substance use in homeless youth.

Methods: This study will enroll 320 homeless youth aged 18-25 years. The intervention was co-designed with homeless youth using the Information-Motivation-Behavioral Skills Model and consists of an individual nurse-led session about HIV prevention and 3 months of a JITAI with personalized messaging delivered by phone in real time in response to one's current level of risk. Participants also had access to an on-demand nurse helpline through the app.

Results: Institutional review board approval was obtained in the summer of 2024. Recruitment began in the fall of 2024 at shelters, drop-in centers, and other organizations that serve homeless youth. Participants complete a baseline survey and HIV/sexually transmitted infection (STI) testing and are provided with a smartphone with the intervention app. Follow-up surveys and HIV/STI testing are conducted at immediate, 3-, 6-, and 12-month time points post intervention to assess uptake of HIV prevention strategies and substance use reduction. A total of 192 are enrolled to date.

Conclusions: The results of this study will determine whether MY-RIDE increases HIV prevention strategies and decreases substance use when compared to homeless youth in the attention control group. We will also evaluate if MY-RIDE impacts protective factors such as willingness to take pre-exposure prophylaxis medication and use of mental health and substance use services, and antecedents of risk such as stress, substance use urge, and substance use.

Trial Registration: Clinicaltrials.gov NCT06074354; https://clinicaltrials.gov/study/NCT06074354

International Registered Report Identifier (IRRID): DERR1-10.2196/78006

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(JMIR Res Protoc 2025;14:e78006) doi:10.2196/78006

KEYWORDS

youth; homelessness; HIV; prevention; just-in-time adaptive interventions; mHealth; ecological momentary assessments; drug use; intervention; risk; mobile phone; mobile health

Introduction

There are an estimated 2.4 million people aged 18 to 25 years who experience homelessness in the United States [1]. The highest HIV risk groups—young men who have sex with men, youth of color, heterosexual Black young women, young adults who inject drugs, youth who engage in trade sex or are sexually exploited, and transgender young women who have sex with men all disproportionately experience homelessness [1,2]. While surviving the dangers of the streets and meeting basic needs, youth experiencing homelessness face enormous difficulties in maintaining their health and well-being [3,4]. Questions remain related to how to best address the persistent HIV disparities among homeless youth. Interventions that address substance use, mental health, and housing while also addressing multiple nonmedical drivers of health that marginalize homeless youth are critically needed [5].

Homeless youth are 6-12 times more likely to become HIV positive than their housed peers [6], with prevalence rates as high as 16% [7]. Yet, homeless youth lack adequate access to HIV prevention, including highly effective pre- and postexposure prophylaxis medications (ie, pre-exposure prophylaxis medication [PrEP] and postexposure prophylaxis medication [nPEP]) [8]. Despite the high proportion of homeless youth found to be eligible for PrEP (84%) in 1 large study, only 29% knew what PrEP was, and very few (14%) reported that they were actively trying to prevent HIV [9].

Substance use and stress increase the risk for HIV [10,11]. High stress predicts condomless sex, inconsistent condom use, more sexual partners, and substance use [12-18], with substance use rates among homeless youth being twice that of housed youth [3,19]. Nearly one-third of homeless youth also meet the criteria for co-occurring substance use and mental disorder diagnoses [20-22], and homeless youth often fail to recognize when they need treatment [23]. Barriers such as where and how to access services, costs, wait times, discrimination, and stigma associated with being homeless, having a mental illness, or using substances perpetuate chronic undertreatment [24-27]. The most common barriers to accessing care include lack of transportation, lack of health insurance, and health care costs [28]. Therefore, HIV prevention efforts must simultaneously address substance use and mental health needs and be readily accessible to be effective [29-32].

Homeless youth are disconnected from health care [33], are highly transient, and geographically mobile, making it difficult to engage in traditional brick-and-mortar care models. Only about half of street-dwelling youth and one-third of sheltered youth use health care regularly [34]. Additionally, homeless youth who use substances or have mental health issues experience compounding barriers to accessing mental health care [16] and HIV prevention measures, such as PrEP [35], with only one-third who need care accessing it [24,36]. While homeless youth continue to be underserved and understudied, prevention interventions specifically targeting homeless youth have achieved improvements in substance and alcohol use [37] and sexual health outcomes when addressing substance-using youth [38]. Interventions that address substance use, mental health, and housing while also addressing multiple nonmedical drivers of health that marginalize homeless youth are critically needed [5].

Ecological momentary assessments' (EMAs) methodologies are also gaining momentum for HIV prevention and treatment research [39]. Using real-time, personalized motivational and prevention messages may provide more timely delivery of interventions. Yet, few HIV prevention mHealth (mobile health) interventions for homeless youth have been developed or rigorously tested [40]. Building on these mHealth efforts, this intervention uses EMA, Just-in-Time Adaptive Intervention (JITAIs) delivery, and on-demand nurse-led sessions that address substance use and stress management as an innovative, scalable, and accessible way to serve highly transient homeless youth [41].

Motivating youth to reduce infections, disconnections, and emotional dysregulation (MY-RIDE) is an mHealth intervention that uses EMAs to predict imminent risk behaviors and delivers personalized messaging at the time of heightened risk. MY-RIDE addresses HIV risk and its antecedents in real time using messages developed with the Information-Motivation-Behavioral Skills (IMB) model and homeless youth [42]. This nurse-led model offers on-demand education sessions that use motivational interviewing (MI) [43-47] and shared decision-making (SDM) [48,49] approaches to promote behavior change and uptake of coping strategies by facilitating goal setting and increasing motivation and skills (Figure 1). The methods are integrated by using the IMB-informed messages in the app while the nurse delivers the HIV prevention content using MI and SDM strategies. Finally, homeless youth receive personalized messages delivered to their phone that address their current HIV risk factors as well as substance use, stress, and housing needs. Pilot data found that MY-RIDE decreased drug use, sexual urges, and stress among homeless youth [50].

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Figure 1. Information, motivation, and behavior guided MY-RIDE. MY-RIDE: motivating youth to reduce infections, disconnections, and emotional dysregulation; nPEP: postexposure prophylaxis medication; PrEP: pre-exposure prophylaxis medication; STI: sexually transmitted infection.

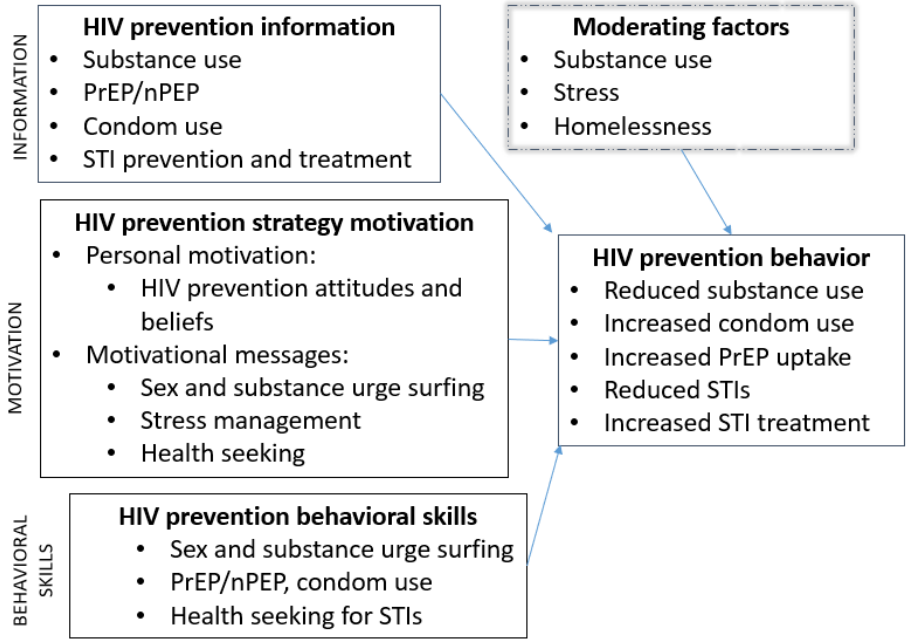

Overall, the current study is guided by the IMB model [42,51]. IMB model posits that 3 primary factors influence behavior changes: information and knowledge about the behavior, in this case HIV risk behaviors; the individual's motivation to perform the behavior; and the behavioral skills needed to modify the behavior [51]. Applying IMB, we hypothesize that homeless youth will reduce their risk for HIV when they (1) are provided with information on PrEP/nPEP, sexually transmitted infections (STIs), condom use, substance use, stress management, and health care services; (2) are motivated to change behavior by engaging in MI focused on HIV prevention and substance use reduction strategies with a nurse and receiving motivational messages in response to current stress symptoms; and (3) are provided with behavioral skills-building opportunities to reduce and manage stress, surf the urge to use substances or have sex, and increase health care seeking.

This randomized controlled trial will test the effects of MY-RIDE on HIV prevention in Harris County (Houston, Texas), 1 of the 48 Ending the HIV Epidemic counties that accounts for 50% of new HIV cases. The purpose of this trial is to determine whether MY-RIDE decreases substance use and increases HIV prevention strategies (condom use, PrEP uptake, and reduced STIs) compared to an attention control group of homeless youth (N=320; aged 18-25 years) immediately after the intervention and at 3-, 6-, and 12-months postintervention. An additional exploratory aim is to evaluate MY-RIDE effects on willingness to take PrEP, on stress levels, substance use urge, and use of mental health and substance use services when compared with attention control youth.

Methods

Study Design and Setting

This study uses a randomized 1:1 attention-controlled design to test the effects of MY-RIDE on substance use and HIV prevention among homeless youth. As there is some potential that EMAs or JITAIs can influence behavior, an attention-control design was chosen over a waitlist-control condition.

Participants

Participants are being recruited from locations frequented by homeless youth, including the largest homeless youth drop-in centers and the largest homeless youth shelter in Houston, Texas. Both approximate the real-world service organization that would have the capacity to disseminate the intervention if found to be efficacious.

Inclusion and Exclusion Criteria

The sample will include 320 homeless youth, aged 18-25 years, randomized 1:1 to either the intervention group or the control group. A random sequence generated in R (R Foundation) will be used for the simple randomization to ensure allocation concealment and minimize selection bias. Individuals at high risk for HIV will be included if they (1) have engaged in substance use (alcohol or illicit drugs) in the past 30 days, (2) are aged 18-25 years, (3) speak English, (4) are currently experiencing homelessness, (5) are engaged in sexual activity in the last 6 months or plan to in the next 30 days, and (6) are not planning to move out of the metro area during the 12-month study period. Current substance use is defined as having used any illicit drugs, drugs that are not prescribed, or alcohol in the past 30 days. Homelessness is defined as having slept on the streets, in a place not meant for habitation, a shelter, hotel or motel, or with someone where they cannot stay for more than 30 days (eg, couch surfing). This broader definition of homelessness aligns with the McKinney-Vento Homeless Assistance Act of 1987 and allows us to account for the transiency and instability of housing experienced by homeless youth, and increases the generalizability of this study's findings. Homeless youth who have low literacy, based on the Rapid Estimate of Adult Literacy in Medicine-Short Form (scores <4), will be excluded due to the need to read independently at a

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4th-grade level. We do not anticipate excluding many homeless youth based on this exclusion criterion. Only 1.2% of screened homeless youth from our prior study had low literacy [50].

Data Collection

Data are being collected at baseline, immediately post intervention, and at 3, 6, and 12 months post intervention using REDCap (Research Electronic Data Capture; Vanderbilt University) on tablets or delivered through a web-based link that is password-protected and sent via text message on the study-issued phone. In-person survey takers are provided a quiet, private room (eg, at the shelter, drop-in center, and library) and most need about 30 minutes for completion of the survey. EMAs are collected 3 times a day for 12 weeks using the Insight App [52] and take about 1 minute to complete. The app is downloaded on this study's issued smartphone to ensure all participants have functional devices on which to answer the EMAs and be contacted for study visits during the trial. To promote continuous engagement with the Insight app, EMA activity is monitored at 48-hour intervals, and participants are compensated based on percentage completion. Participants who do not complete an EMA in 48 hours are contacted on this study's issued phone to verify if they are experiencing problems that can be addressed and to encourage EMA completion.

The presence of HIV antibodies, syphilis antibodies, and detection of chlamydia or *Neisseria gonorrhoeae* are being collected at baseline, immediately postintervention, and at 3, 6, and 12 months post intervention. In a private setting, participants complete a finger prick for rapid testing of HIV and syphilis and provide a urine sample for detection of chlamydia and gonorrhea. Tests were not diagnostic; all positive results are referred for confirmatory testing and treatment. Additionally, participants could provide study staff permission to access HIV/STI results from the on-site clinic when tested in the last 2 weeks to reduce testing burden.

Instruments

We are using low-burden, empirically tested scales from our prior research with homeless youth [50,53]. The baseline survey includes demographics such as age, gender identity, race or ethnicity, sexual orientation, educational level, and employment. Historical factors are assessed to characterize the sample, such as foster care history, adverse childhood experiences [54], age at the first homelessness, and duration of current homelessness episode, all of which are mental health and substance use risk factors [55-58].

The primary outcome measure is substance use [59,60], measured with 2 items: "On many occasions (if any) have you used marijuana (weed/pot) in the last 30 days?" with responses ranging from 0 to 40+ and "select all drugs used in the past 30 days" with a range of drug options (not including marijuana). These items were separated based on feedback from the youth working group before the trial initiation. Due to the high use of marijuana in the population and the evolving laws around marijuana use, many youth did not consider it to be a drug. Descriptive statistics about the usage of marijuana and other types of drugs will enhance our understanding of trends in substance use in this population, while binary substance use (ie, use or nonuse of drugs, inclusive of marijuana) will be the primary outcome measure. One item in the daily EMAs "select drugs used yesterday" will be used to model changes in substance use over the intervention period compared to the intervention group.

Secondary outcomes are condom use, PrEP uptake, and STIs, and measurement was consistent with previous studies [50,53]. Condom use is assessed by two items: (1) "How often in the past 3 months did you use a condom during sexual intercourse?" with response options ranging from "never" to "every time" and (2) "The last time you had sexual intercourse, did you or your partner use a condom?" with response options of either "yes" or "no." PrEP uptake is assessed by a single item: "Are you taking PrEP for HIV prevention?" with options "Yes, I take a pill for PrEP daily, Yes, I take a pill for PrEP sometimes, Yes, I get injectable HIV PrEP (a shot), No, I don't take PrEP." Presence of STIs is collected using biological specimens (blood and urine) by research staff or shelter clinic staff.

Willingness to take PrEP is measured in the follow-up surveys using an item consistent with previous studies [53,61], "How likely would you be to take PrEP if it were available for free?" with response options ranging from "Definitely would not take PrEP" to "Definitely would take PrEP". The Perceived Stress Scale was also used, consisting of 10 items with response options from 0 (never) to 4 (very often), and can range from 0 to 40. Example item: "How often have you felt that you were unable to control the important things in your life?" Positively worded items are reverse-scored before scores are summed. This scale measures stress-related feelings over the last month, with higher scores indicating greater perceived stress [62,63]. Substance use urge is assessed in the EMAs with the item consistent with pilot study [50], "Right now, I am feeling a strong urge to: (Check all that apply): Steal, drink alcohol, use drugs, have sex, none of the above." Usage of mental health and substance use services is measured using 2 items in the follow-up surveys: "In the last 3 months, have you used mental health (or substance use) services?" Response options are: "yes," "no," and "not sure."

Measures from the PhenX Toolkit were used whenever possible to enhance data harmonization and data sharing efforts. EMA items measure real-time affect, stress, sexual risk behaviors, and urges (ie, right now), as well as real-time motivation measures. These Likert-type scale items have been successfully used with homeless youth and are based on our prior work and the work by Shiffman et al [50,64-67].

Intervention Arm

An individual-level intervention design was chosen due to the heterogeneity of homeless youth and variability in real-time risk factors that impact HIV risk and substance use. The intervention, MY-RIDE, has three main components: (1) one nurse-led face-to-face session, (2) three months of EMA with personalized messaging delivered by phone in real time in response to one's current risk, and (3) access to on-demand health care or PrEP navigation and referrals.

Nurses are ideal for leading the intervention sessions with homeless youth. Not only are nurses continuously ranked as the

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most trusted profession in the United States, an important consideration when working in a population with high levels of mistrust [68], but nurse-led interventions have the best potential for scalability and have been successful in improving HIV prevention strategies [69] among homeless youth, as they are trained to coordinate care across services through case management [53,70,71]. During the nurse-led face-to-face sessions, the nurse conducts an HIV risk assessment and assesses substance use, stress, and housing needs to guide the discussion about HIV prevention and goal attainment. The standard approach of the Screening, Brief Intervention, and Referral to Treatment tool is used for alcohol and drug use issues [72,73], with the nurse providing either a brief intervention or referral for substance use treatment. Sessions are held in a private setting such as a classroom, office space, library, or another empty room available at the community site.

The session allows for time to discuss HIV prevention strategies and establish a behavioral goal (ie, condom use, PrEP uptake, reduced substance use, sober sex, and reduced sexual partners). MY-RIDE builds on our previous prevention trial that supports the need for frequent, ongoing contact by providing ongoing prevention messages and booster sessions [50]. MY-RIDE participants are referred to local homeless youth-serving agencies to meet the complex, comorbid health or mental health, and social needs of homeless youth. MI and SDM strategies allow the nurse to tailor the discussion to the individual's needs based on their current risks, chosen goal, and HIV prevention motivation level. The nurses are trained to follow the manualized MY-RIDE intervention session and complete a checklist of core activities to document delivery of Screening, Brief Intervention, and Referral to Treatment, PrEP eligibility, selection of prevention strategy, and referrals made after each intervention participant. Following the session, participants receive a study-issued cell phone with the app installed and general resources programmed for food, housing, and other local services for homeless youth.

The second component consists of 3 EMAs every day for 3 months with personalized messaging after each EMA using the Insight app [52]. Youth receive a targeted prevention message that responds to real-time risk levels at the moment the risk is detected. Real-time risk factors for substance use and HIV risk are based on previous studies and include stress, urge to steal, and urge or indication of sex, drug use, or alcohol use [50,64]. Decision rules for message delivery assign the appropriate message dose and content based on each participant's current risk factors and relevant tailoring trait variables (eg, gender and sexual orientation) to deliver personalized, time-varying intervention content [65]. Over 900 intervention messages were co-developed with homeless youth and guided by the IMB model, and these were extensively beta tested and used successfully in the pilot [50]. In instances where multiple predictors are equally high, 1 message will be delivered with preference given to the strongest predictors (eg, real-time substance use). The justification for limiting to 1 message per EMA and the hierarchical ordering system based on prediction strength are grounded in the results from Projects Prevail and Smart-T [74,75], which indicated that receiving just 1 targeted message after each EMA reduced response fatigue. When low substance use and HIV risk are detected, a participant will receive more general messages reinforcing, for example, healthy stress management strategies, safety tips, or motivational quotes. Study staff reach out to youth weekly who have not responded to an EMA in 48 hours to assess for and address any challenges they may be experiencing (i.e., needing a phone charger). Additionally, the app automatically populates an interface that provides visual feedback about how one's current behaviors align with their health goals, which can be accessed on their study-issued password-protected phone during the 3-month intervention period. This serves as an ongoing motivation to align or maintain one's behavioral goals (Figure 2).

Figure 2. Insight app snapshots of the home screen, EMA item, intervention message, and behavioral feedback visual. EMA: ecological momentary assessment; MY-RIDE: motivating youth to reduce infections, disconnections, and emotional dysregulation; PrEP: pre-exposure prophylaxis medication.

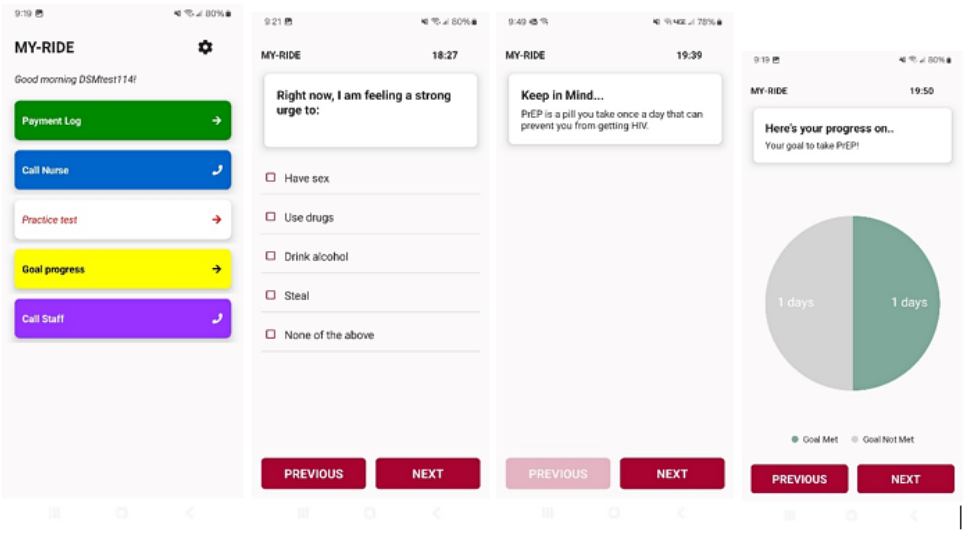

The third component of the intervention includes access to an on-demand nurse helpline. During the face-to-face session, the nurse demonstrates how the participant can reach this study's nurse using a single "contact nurse" button on the app home

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page. Participants are advised to use this feature when they have questions about substance use, sexual health, or anything discussed in the face-to-face sessions. A registered nurse who is a part of this study's team monitors this phone line and is prepared to answer questions and provide resources or local referrals regarding substance use, HIV/STI testing and treatment, PrEP or nPEP, and free condoms. Calls or texts are answered immediately or returned within 24 hours of a business day, and participants are directed to 911 if it is an emergency. Additionally, if a participant indicates that they need an STI test while completing a daily EMA, the nurse will automatically be notified via email and follow up with that participant to offer testing or navigate treatment seeking as needed.

Control Arm

Participants assigned to the attention control arm will receive a 1-hour general health promotion session from a nurse, research coordinator, or research assistant and be issued a phone that will deploy the EMA on the same schedule as the intervention arm, with general health messages delivered after the EMA. These messages are unrelated to HIV risk, substance use, or its antecedents and address topics such as fruit and vegetable consumption, physical activity, water intake, and sleep hygiene. They will also receive usual care from the clinics, drop-in centers, and shelter recruitment sites. Usual care includes accessing social workers and case managers for immediate housing, food, and clothing needs and assistance in navigating the local continuum of care system to access social services. Specifically, youth are assessed at intake at the drop-in centers and shelters for mental health, substance use, and housing needs. This standard of care does not currently include HIV prevention education, personalized HIV prevention behavioral goal setting, or personalized HIV prevention messaging. Usual care has some evidence of reducing substance use in homeless youth, aged 14-20 years [76]. Attention control youth will also have access to the homeless youth' resources programmed into the phone. While this is a low-risk study that will increase HIV prevention access and health care use, control youth will be monitored for adverse effects during this study and provided with the contact information for study staff, which will also be preprogrammed into this study's phone.

Sample and Power

The sample size (N=320) was determined from considerations of the MY-RIDE intervention effect on substance use (aim 1), STIs, PrEP use, and condom use (aims 2). For substance use, the effect size (odds ratio 0.61, 95% CI 0.39-0.97) was assumed from our previously published results that arose from a generalized linear mixed model framework [50]. Monte Carlo simulations implemented with the SIMR package [77] developed in the R programming language [78] yielded an estimated power of 0.96 for the intervention effect on substance use. Missing data were incorporated in the simulations by using a 50% response rate, from our pilot study, to EMA surveys over the 90-day intervention phase. Power for PrEP use was estimated similarly with a simulation that was based on the observed effect size in our ongoing National Institutes of Health–funded study that is testing a nurse case management intervention. The anticipated strong effect (odds ratio 10.59, 95% CI 2.44-50.90) was countered by the low prevalence of PrEP usage in youth, resulting in power=0.80 for the PrEP use outcome. The effect size (odds ratio 0.34, 95% CI 0.11-1.06) for STI was estimated from the aforementioned study, resulting in estimated power=0.81 for a 1-tailed test (and power=0.71 for a 2-tailed test). Lastly, the effect size (f=0.30) for condom use was estimated from a study involving youth of the same age group [79]. An estimated power=0.96 was determined using G*Power (version 3.1; Heinrich-Heine-Universität Düsseldorf) [80] for the intervention effect on condom use. In summary, estimated power for the primary and secondary outcomes ranged from 0.80 to 0.96 for a sample size of 320, randomized into 2 groups with 160 participants per group. All power calculations assumed α=.05 and included an allowance for 30% attrition, from our pilot study, from baseline to the first follow-up.

Data Analysis

Baseline demographic characteristics (eg, age, gender identity, race or ethnicity, and sexual orientation) will be summarized with descriptive statistics in each arm. Random group allocation will make distributional differences of baseline variables unlikely. However, if any differences are found, the models testing intervention effects will include adjustment via propensity scores.

For aim 1, we determine whether MY-RIDE decreases substance use in homeless youth randomized to an attention control group (N=320; aged 18-25 years) at 0-, 3-, 6-, and 12-months postintervention. Bayesian mixed effects models will be used to test intervention effects on binary substance use. We hypothesize that at 3-, 6-, and 12-months follow-up, substance use will be lower in the intervention group than the attention control group. Models will use a logit link, and time will be treated as a discrete variable to allow nonlinear time dependence. Flat priors will be used for population-level parameters and Student *t* distribution for the SDs and cluster-level distributions, or random effects, with posterior distribution estimated with Hamiltonian sampling carried out using Stan [81]. Inference will be based on the statistical significance ($P \leq .05$) of the interaction of time and intervention group. An adjustment term based on propensity scores will be included if demographic variables are unequally distributed in this study's arms. The need for a random intercept and random dependence on time will be explored in these partially pooled models to allow variable trajectories between participants. Analysis for this study will be based on the intent-to-treat principle [82]. Multiple imputation will be used to safeguard against potential bias arising from the inclusion of only complete-case data. The *jomo* package for joint modeling will be used to specify a multilevel imputation model that is identical to the analysis model [83]. A similar approach will be used for analysis of substance use in the EMA data, with focus on longitudinal changes in daily reports of substance use over the intervention period. Time will range from 0 to 90 days for the EMA data on and it will be transformed, if necessary, for validating the assumption of linearity. Sensitivity analysis may be conducted if we have reason to believe that missing data are not ignorable [82].

For aim 2, we determine whether MY-RIDE increases HIV prevention strategies—condom use, PrEP uptake, reduced

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STIs—when compared with an attention control group of homeless youth. Intervention effects on condom use, PrEP uptake, and STI test results will be analyzed with Bayesian mixed effects models [84], following the method described in aim 1 above. We hypothesize that at 3-, 6-, and 12-months follow-up, the use of HIV prevention strategies will be higher in the intervention group than the attention control group. Condom use will be modeled as an ordinal measure (never to every time) and as a binary measure of condom use at the last sexual encounter. PrEP uptake will be modeled as a binary measure that combines the irregular use of PrEP with regular use because both are expected to be found in a small proportion of the data. STIs may be combined if the frequencies of individual STIs (eg, gonorrhea, chlamydia, and syphilis) are low, which will result in an any or none binary measure for STIs. Time will be treated as a discrete variable, and random intercepts will be included per participant. Statistical significance (α=.05) of the fixed effect corresponding to the interaction of time and treatment group will be used for inference of the intervention effect at each follow-up. The primary follow-up of interest is the one immediately following the intervention, while longer-term effects of the intervention will be judged from the follow-ups at 3, 6, and 12 months.

Analysis of the exploratory aim (evaluate MY-RIDE effects on willingness to take PrEP, on stress levels, substance use urge, and use of mental health and substance use services when compared with an attention control group of homeless youth) will also be conducted. Changes in time and by group will be modeled with a Bayesian mixed effects model similar to those described for aims 1 and 2. However, the emphasis will be on descriptive statistics and effect sizes in the models rather than on the statistical significance of the treatment effect. Models for EMA outcomes (mental health symptoms and substance use urge) will treat time as a continuous measure, while the models for exploratory outcomes (willingness to use PrEP, use of mental health, and substance use services) measured at the 3-, 6-, and 12-month follow-ups will treat time as a discrete measure. A simplified analysis of the changes from baseline in each exploratory outcome will be conducted to provide estimates that could be used for estimating the power in future studies.

Ethical Considerations

Participant recruitment began after obtaining UTHealth institutional review board (IRB) approval (#HSC-SN-23-0360). Flyers describing this study are posted in the common areas of local shelters, drop-in centers, and clinics, as homeless youth often access services from multiple service providers and locations. Study information is disseminated during street outreach events hosted by partnering agencies. Local health care for the homeless providers, The Homeless Youth Network, and the Coalition for the Homeless were informed about this study, and flyers were posted at local clinics with permission, as well as housing first locations (where youth can access housing services). Project staff approach youth who receive services at drop-in centers and shelters such as Covenant House Texas to screen for eligibility. Additionally, participants can contact research staff after seeing flyers at other shelters, drop-in centers, or health care for the homeless clinics. The research staff is working with shelter staff to identify youth at the site each day who may be eligible. We are currently recruiting participants 3 days a week during regular business hours at the shelter and drop-in centers, and during street outreach. Research staff maintain a consistent presence at the agencies and approach young people who present to the agency. If the common room in the shelter or drop-in center is crowded, they will speak to the youth in a private office. The research staff explains this study and completes the informed consent process with interested youth. All prospective participants are assured that study participation will in no way affect their access to health and social services. Informed consent and contact information are obtained from participants.

Before this trial started, this study's team met with the youth working group to review this study's procedures, recruitment materials, survey questions, messages, and incentive amount and structure. Changes were made based on recommendations regarding the recruitment materials, wording, and response options for the survey questions, message wording, and incentive amount and timeline to enhance understanding, comfort, and fairness.

To ensure that potential participants do not feel coerced to enter or remain in this study, research staff recruiting participants will follow a standardized script to ensure that all ethical issues are reviewed and that this study's procedures are followed with fidelity. All protocols were reviewed and approved by the IRB before implementation. It is made explicit in the informed consent document that participation in this study is voluntary, that it is unrelated to their access to health and social services, and that they can drop out of the research at any time for any reason. Participants will be verbally reminded at each follow-up that participation is voluntary and will not affect their ability to access any resources at the recruitment sites or at any other agency. Due to the potential for mistrust among homeless youth, participants will be reminded at each session and follow-up visit that the data collected in this study and the information shared will be confidential unless they share that they are thinking of hurting themselves or someone else. Participants will be reminded that all study staff are mandatory reporters and are required to report if they suspect that a participant is at risk of hurting themselves or others. Additionally, research staff reviewing the consent will be trained to probe for comprehension of the consent form and study procedures. A step-wise process previously used with this population [85] is used to ensure participants wait a minimum of 1 week between signing the consent form and officially enrolling in this study to provide additional time to think about being in this study. Agreement to be in this study is confirmed verbally before study enrollment.

Through our experience with homeless youth, the IRB, and the homeless youth working group, we have also set the incentive levels at a modest amount that is commensurate with the amount of time youth will spend in the research study and not deemed to be coercive. Incentives are provided as gift cards for survey and STI testing at baseline (US $40) and all follow-ups (US $40-$60) to approximate the amount of money one could earn in a similar amount of time. Additionally, participants are paid every month for EMA completion during the intervention period (3 months), ranging from US $25 to US $100, depending on the percentage of EMAs completed.

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Results

Institutional review board approval was obtained (#HSC-SN-23-0360) in the summer of 2024. Recruitment began in the fall of 2024 at shelters, drop-in centers, and other organizations that serve homeless youth. To date, there are 163 youth enrolled in this study. A total of 192 are enrolled to date.

Discussion

Anticipated Findings

This study will determine if MY-RIDE reduces HIV risk and substance use among a high-risk, hard-to-reach, vulnerable population of youth. The goal of this intervention is to reduce HIV risk by addressing risk behaviors, substance use, and stress among homeless youth through an innovative, theory-driven, mHealth intervention. MY-RIDE responds to current symptoms and imminent risk assessed using EMAs and delivers targeted, personalized information, motivational messages, and skill-building using a JITAI to increase symptom management and prevent related risk behaviors before they occur. We hypothesize that MY-RIDE will be more effective than attention control in reducing substance use and increasing HIV prevention strategies among young adults (aged 18-25 years) experiencing homelessness at 3, 6, and 12 months. While few interventions use mobile delivery of a JITAI to prevent HIV or substance use, the tenets of pairing an IMB-informed mobile app with a nurse-led model using MI and SDM are well-informed and supported by the literature.

Prior Work

This intervention builds on our pilot study of MY-RIDE, which demonstrated reduced substance use, urge, and stress among homeless youth [50], though the current study was not powered to assess the intervention's impact on HIV prevention strategies. Therefore, this study will be used to determine its efficacy for reducing HIV risk among homeless youth.

Conclusions

MY-RIDE is grounded in a health equity lens that considers the social and structural determinants of success and nonmedical drivers of health, such as housing status and mental health, to find novel solutions to reach and engage youth who are transient and disconnected from services. By testing a novel and scalable mobile-based intervention, there is the potential to determine if MY-RIDE should be disseminated widely, offering health and social service providers a way to enhance HIV prevention among the youth that they serve.

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Data Availability

Data generated during this study will be available upon reasonable request to the corresponding author, following data sharing requirements per the National Institutes of Health and the University of Texas Health Science Center at Houston.

Conflicts of Interest

MB is the primary inventor of the Insight mHealth Platform, which was used to develop this study's smartphone app. MB receives royalties related to the Insight Platform. All other authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Abbreviations

EMA: ecological momentary assessment
IMB: Information-Motivation-Behavioral Skills
IRB: institutional review board
JITAI: Just-in-Time Adaptive Intervention
mHealth: mobile health
MI: motivational interviewing
MY-RIDE: motivating youth to reduce infections, disconnections, and emotional dysregulation
nPEP: postexposure prophylaxis medication
PrEP: pre-exposure prophylaxis medication
REDCap: Research Electronic Data Capture
SDM: shared decision-making
STI: sexually transmitted infection

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Protocol

Improving Palliative Care in Residential Aged Care Using Telehealth: Protocol for a Realist Process Evaluation Embedded in a Stepped-Wedge Cluster Randomized Controlled Trial

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Abstract

Background: This study describes the protocol for a realist process evaluation of IMPART (Improving Palliative Care in Residential Aged Care Using Telehealth), to be trialed through a pragmatic stepped-wedge cluster randomized controlled trial in Australia. IMPART consists of 2 key intervention activities: specialist palliative support provided through telehealth and tailored staff education.

Objective: The aims of the realist process evaluation are to (1) identify and explore the contexts and mechanisms that enable or hinder the implementation of the IMPART intervention, and (2) develop and refine a program theory to determine whether and how successful implementation of IMPART can be facilitated.

Methods: We will conduct this process evaluation in 3 phases, guided by a realist framework. First, to hypothesize an initial program theory, we will review trial documentation and literature to determine how IMPART is expected to work and identify the barriers and facilitators likely to influence implementation. To test this theory in the second phase, a case study methodology will draw on multiple data sources (qualitative and quantitative) from 10 participating residential aged care facilities. These include interviews with staff involved in implementation, data on staff engagement with training, program documentation, activity logs, action plans, and facility information. In the final phase, program theories developed from the case studies will be refined through consultation with the IMPART research team. This will inform the development of a refined program theory that provides key information about what works, for whom, how, and in what circumstances in the implementation of interventions aiming to improve palliative care in residential aged care.

Results: This study was reviewed and approved by the Royal Melbourne Hospital Human Research Ethics Committee. The randomized controlled trial commenced in May 2023, with completion anticipated in November 2025. Funding began in January 2022. Data for the realist process evaluation will be collected between May 2023 and February 2026. As of October 2025, a total of 61 interviews have been completed. Data analysis is ongoing, and a publication describing the results will be prepared in 2026.

Conclusions: Applying a realist framework to explore process outcomes allows for an in-depth inquiry into what works, for whom, how, and in what circumstances in the implementation of complex interventions aiming to improve palliative care in residential aged care. This realist process evaluation has the potential to provide transferable, context-specific findings that can support the development of meaningful policy and accelerate practice change.

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KEYWORDS
aged care; end of life care; implementation; palliative care; process evaluation; realist evaluation; residential aged care; telehealth

Introduction

Overview

In Australia, residential aged care facilities are the second most common place of death after hospitals [1]. Residential aged care, also known as nursing homes or long-term care, provides accommodation and 24-hour care for older people who can no longer live independently at home. In 2022-2023, 84% of exits from permanent residential aged care facilities were due to death, with an average length of stay of 21 months [2]. Yet, in Australian residential aged care facilities, a lack of clarity about residents' end-of-life care preferences is widely reported [3,4]. The quality of end-of-life care provided across the residential aged care sector also varies [5]. Studies suggest that insufficient staff capacity and resources [6], lack of staff confidence and knowledge [7-9], and residents' complex needs [10] contribute to this variation in quality of care. End-of-life care discussions are often avoided by residents, families, and staff in residential aged care, which can lead to suboptimal decision-making during medical crises [11,12]. Residents of residential aged care facilities are more likely to present to hospital emergency departments than older people living in the community [13,14]. These admissions, often considered avoidable, can result in the resident dying in hospital when appropriate care could have been provided at the residential aged care facility with the necessary supports in place [14,15]. More effective channels of communication and documentation of care preferences are needed.

Palliative care is an approach that focuses on improving the quality of life of patients and their families who are at the end of life through "the prevention and relief of suffering of any kind—physical, psychological, social, or spiritual" [16]. Palliative care should be considered the core business of aged care in Australia [17,18]. Accordingly, the Australian Royal Commission into Aged Care Quality and Safety recommended that palliative care be identified as a core competency to be included in the training and certification of residential aged care staff and that access to timely provision of specialist palliative care and other relevant specialists be expanded for residential aged care facilities [18]. In 2021-22, approximately 246,000 Australians lived in residential aged care facilities, with 2% appraised under the Aged Care Funding Instrument as needing palliative care services, which were often available only in the last days of life [1,17]. However, Palliative Care Australia argue that palliative care services in residential aged care are underfunded and underserviced [18]. The Comprehensive Palliative Care in Aged Care measure (2018-2024) introduced by the Australian Government, aimed to strengthen national efforts to improve access to quality palliative care in residential aged care. Projects supported by the measure found that improved communication channels with palliative care specialists were facilitated through telehealth use [19,20].

Telehealth, as described by the International Organization for Standardization, is the "use of telecommunication techniques for the purpose of providing telemedicine, medical education, and health education over a distance" [21]. This may occur through communication services such as a telephone, video, or messaging platforms [21]. Demand for telehealth has greatly increased due to the COVID-19 pandemic [22]. Telehealth has been reported to have the potential to improve access and clinical outcomes and reduce the cost of service delivery [18,23]. The Australian Government Digital Health Strategy 2023-2028 has consequently focused on widening access to telehealth services [24]. Individual-, interpersonal-, community-, and societal-level factors influence the successful uptake of health technologies such as telehealth [25]. A 2019 systematic review found that the benefits of using telehealth for palliative care, such as reduced need for emergency care, are often described without being adequately evaluated [26]. The review identified only one study that was set in residential aged care.

Since COVID-19 several studies have explored the use of telehealth to improve palliative care in residential aged care. Telehealth uptake has led to increased discussion and documentation of goals of care, improved symptom management, and decrease use of acute care use [27-29]. Participants were generally accepting of and willing to use telehealth to connect with palliative care specialists, particularly those living in rural areas [20,27,28,30,31]. Persistent barriers, however, included technical and connectivity issues, financial burden to the facility, concerns about privacy, logistics, and inflexibility of specialists [27,29,30]. The successful implementation and sustainability of telehealth-enabled palliative care interventions in residential aged care depend on policy commitment, clear practice recommendations, and financial support, with no "one size fits all" approach [20,29]. To support this, urgent attention is needed to evaluate intervention effectiveness and implementation outcomes [27,29,31].

The IMPART (Improving Palliative Care in Residential Aged Care Using Telehealth) Intervention

In 2020, the National Health and Medical Research Council, on the advice of the Australian Health Ministers' Advisory Council Working Committee, released a targeted call for research into end-of-life care, citing limited evidence to inform policy and practice [32]. In response to this call, and to support residential aged care facilities in improving palliative care, the IMPART (Improving Palliative Care in Residential Aged Care Using Telehealth) intervention was developed. IMPART aims to reduce avoidable hospitalization at the end of life by engaging

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specialist support provided through telehealth and tailored staff education. Its intended outcomes are to enable timely end-of-life discussions, improve documentation of care preferences and, therefore, enable preference-based care, reduce unplanned hospitalization, and improve residents' quality of end-of-life care. The program is being tested in a 2.5-year pragmatic, stepped-wedge, cluster randomized controlled trial (RCT), involving 10 residential aged care facilities located in metropolitan regions of Melbourne, Australia, along with 3 residential in-reach services accessed through telehealth. Residential in-reach services provide acute care within residential aged care facilities to reduce the need for hospitalization of residents [14]. This realist process evaluation is embedded within the IMPART trial. The trial consists of five 6-month waves, in which 2 new residential aged care facilities will start the active phase of the IMPART intervention during every wave in a randomized order. The trial schedule is displayed in Table 1. The full trial protocol was published in July 2025 [33].

Table 1. Overview of IMPART (Improving Palliative Care in Residential Aged Care Using Telehealth) intervention roll-out. Each block represents a 6-month period. ✓=Data collection point. Intervention=facilities actively receiving the IMPART intervention during that block. Control/waiting=facilities yet to receive the intervention.

Intervention roll-out (2 facilities per step)	Year 1		Year 2		Year 3	
	Block 0	Block 1	Block 2	Block 3	Block 4	Block 5
Roll-out 1		✓				
Roll-out 2			✓			
Roll-out 3				✓		
Roll-out 4					✓	
Roll-out 5						✓

Five Core Components of the IMPART Intervention

The IMPART intervention comprises 5 core components: component 1 involves forming a planning ahead team to guide implementation, component 2 focuses on conducting a local needs analysis; component 3 entails a facilitated workshop to co-design an action plan, component 4 provides targeted online training and goals-of-care education, and component 5 engages local specialists to provide telehealth support and monitor progress over 6 months.

Component 1

In month 1 of the intervention, a planning ahead team will be formed at each facility, made up of 2-3 staff (nurses, clinical care coordinators, managers, or anyone else with a passion for palliative care) who will champion the program, along with general practitioners who regularly attend the participating facilities. The planning ahead team will be provided with an intervention manual that will guide them through implementation for the 6-month period.

Component 2

Additionally, in month 1, the planning ahead team, with facilitation as required from the research team, will undertake a local needs analysis to identify areas for improvement in end-of-life care discussions, documentation, and provision. This involves a short survey assessing the planning ahead team's confidence in providing, discussing, and planning for end-of-life care, a postdeath file audit of end-of-life care documentation, and an audit of advance care planning documentation.

Component 3

In month 2, the research team will facilitate a workshop with the planning ahead team to present findings from the local needs analysis, highlighting strengths and challenges in current end-of-life care practice. The workshop allows the planning ahead teams to meet and establish communication channels between the residential aged care facility and in-reach teams. At the workshop, an action plan will be co-designed to tailor the intervention to meet their needs as identified during the session. The action plan will be implemented and monitored in months 3-6.

Component 4

Residential aged care facility staff will be given access to an online training package IMPETUS-D (Improving Palliative care Education and Training Using Simulation in Dementia) [6]. IMPETUS-D includes 11 modules containing video simulations, each taking approximately 15-30 minutes to complete. The IMPART intervention aims to tailor the application of the IMPETUS-D modules, allowing the planning ahead teams to incorporate the modules most relevant to them into their action plan. A 90-minute goals-of-care online training session, provided by aged care specialists, will also be arranged for each facility.

Component 5

Local palliative and aged care specialists will be engaged as facilitators to provide telehealth in-reach and participate in the planning ahead teams to support residential aged care facility staff in achieving the goals set out in their action plans. The aim is to foster rapid communication between the residential aged care facilities and in-reach teams through telehealth to promote sustainable collaborative working relationships beyond the completion of the study. The planning ahead teams will aim to meet fortnightly during months 3-6.

Realist Process Evaluation of Complex Interventions

According to the Medical Research Council, an intervention may be considered complex if it fits one or more of the following categories: contains multiple components, targets a range of behaviors, permits a level of flexibility, or requires a level of expertise and skills from those delivering and receiving

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the intervention [34]. As such, IMPART can be regarded as a complex intervention. Many complex interventions targeting residential aged care have demonstrated potential to reduce unplanned hospitalizations [35,36]. A systematic review found that more than one intervention is likely needed to impact hospitalization of residential aged care residents, with those targeting advance care planning or goals-of-care setting being the most effective [36]. Yet, if these interventions work and achieve their desired outcomes of reducing unplanned hospitalizations and inducing practice change in staff, how and in what circumstances is implementation successful? With limited evidence on how telehealth-enabled palliative care interventions function in residential aged care, there is a need to uncover causal linkages to reproduce the results and inform national strategies.

The Medical Research Council guidelines for evaluating complex interventions highlight the importance of investigating the interactions between the intervention and its context to identify mechanisms of change, "where mechanisms are the causal links between intervention components and outcomes" [34]. This is consistent with a realist evaluation framework which seeks to form context–mechanisms–outcomes configurations (CMOC), or context+mechanisms=outcomes, in order to understand for whom, how, and in what circumstances an intervention works [37,38]. Context is defined as the relational and dynamic factors not formally part of the intervention but having impact, for example, the physical and social environment, existing policy, cultural norms, and values [39]. This protocol describes a realist process evaluation of IMPART, conceptualized as a theory-informed approach that aims to strengthen the impact of evaluation on policy and practice [37]. A realist process evaluation thus answers questions relating to fidelity and quality of implementation, mechanisms of change, and context. Further, the realist understanding of fidelity investigates when and how adaptations are made to the RCT protocol and the reasoning behind such changes [40]. Successful implementation is more likely to be reproduced whereby these questions are answered.

The compatibility of realist evaluation and RCTs has been rigorously debated [41-43]. Highlighted in these discussions are the fundamental differences in ontological and epistemological perspectives, with realism distinguished by its understanding of causation [40]. The role of the realist evaluator is "to explain how and why programs or policies cause their various outcomes in different sets of circumstances" [40]. In contrast, post-positivist logic underpins RCTs, conflicting with the realist view that there are no "final" truths or knowledge [40]. This protocol takes guidance from the realist process evaluation undertaken by Rycroft-Malone et al [43]. We do not consider this to be a "realist" RCT, but an RCT involving a process evaluation that is realist-informed. Each residential aged care facility will be evaluated as a case study to uncover the different mechanisms operating in different contexts, generating various outcomes. By embedding a realist process evaluation within the IMPART RCT, we can go beyond describing barriers and enablers to implementation and uncover causal linkages that have not been identified in previous studies evaluating telehealth-enabled palliative care interventions.

Aims

The realist process evaluation has 2 aims. Aim 1 is to identify and explore the contexts and mechanisms that enable or hinder the implementation of the IMPART intervention, designed to improve palliative care in residential aged care using telehealth. This aim seeks to uncover the mechanisms inherent in successful implementation, understand how success is defined, and identify in what contexts and circumstances these mechanisms trigger success. Aim 2 is to develop and refine a program theory to optimize any future implementation of IMPART and similar interventions to improve palliative care in residential aged care. The primary research question seeks to answer what works, for whom, how, and in what circumstances in the implementation of the IMPART intervention. Subquestions address key implementation outcomes relating to intervention adoption, implementation fidelity, and protocol adaptations.

Methods

Ethical Considerations

This project was reviewed and approved by the Royal Melbourne Hospital Human Research Ethics Committee, protocol version 6 (HREC/84300/MH-2022). Original approval was granted on May 19, 2022. Participants will receive an invitation and consent form before the interview and may ask questions prior to providing written and verbal consent. Interviews will be audio-recorded (in-person, online, or by phone) based on participant preference. Each participant will receive an AUD $50 honorarium (approximately US $33), and all identifying details will be removed from transcripts to ensure anonymity. All data collected will be stored securely in a locked filing cabinet or under strict password protection in accordance with National Health and Medical Research Council requirements. Data will be deidentified by assigning participant codes. Only the research team will have access to the data. After analysis is completed, data will be retained for 7 years and then disposed of confidentially. Data will be used only for the current project.

Study Design

This realist process evaluation involves three key phases conducted iteratively: (1) theory elicitation and hypothesis generation, (2) theory testing and observation, and (3) theory refining [43,44]. Data collection and analysis will occur concurrently with the IMPART trial during the roll-out of the active intervention at participating residential aged care facilities, cycling through the hypothesizing and testing of causal pathways [44,45]. Figure 1 provides an overview of the realist process evaluation. To ensure the study adheres to the preferred quality and reporting standards for realist evaluations, guidance will be taken from the Realist and Meta-narrative Evidence Syntheses: Evolving Standards (RAMESES) [40].

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Figure 1. Overview of the IMPART (Improving Palliative Care in Residential Aged Care Using Telehealth) realist process evaluation.

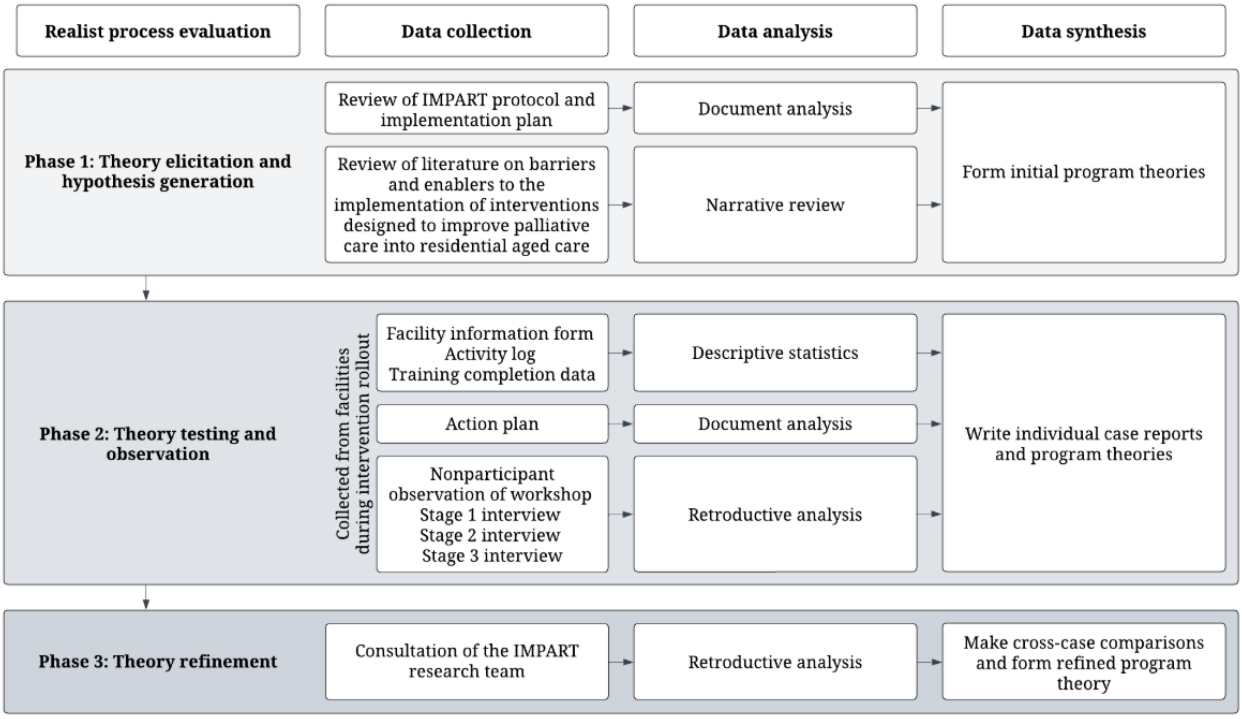

Data Collection and Analysis

Phase 1: Theory Elicitation and Hypothesis Generation

A realist approach first identifies the relevant intervention theories and asks, what is suspected to cause what to happen? RAMESES suggests that there are many ways to identify an initial "rough" program theory which presents a significant challenge to those new to the realist approach [40,46]. Flynn et al [46] recommend researchers "live within their means" to mitigate extensive use of time and resources, noting that generating an initial program theory is just the first phase of a larger funded project. To generate a hypothesis and understand how the researchers intend for IMPART to work and why, a document analysis of the IMPART protocol and implementation plan was conducted. The content of the protocol and implementation plan was coded inductively with the following categories: implementation strategies, intervention activities, mechanisms, implementation outcomes, service outcomes, and resident outcomes.

To identify barriers and enablers likely to impact the implementation of the IMPART intervention, a narrative review was undertaken. Peer-reviewed literature published in English after 2000 was included. MEDLINE was searched using key terms such as "residential aged care," "palliative care," and "implementation." Specialist journals (eg, Implementation science) and reference lists of identified studies were also hand searched. Articles were prioritized according to relevance and recency to increase significance of the findings to the current residential aged care setting. Literature was coded inductively using the Consolidated Framework for Implementation Research (CFIR) [47] categories: intervention characteristics, outer setting, inner setting, characteristics of individuals, and implementation process. Those determinants that reoccur most frequently were noted.

The results of the document analysis and narrative review supported the development of initial program theories and a coding framework to be used in the theory-testing phase. To ensure that the IMPART implementation strategies (how the intervention activities are being implemented) are clearly defined and distinguishable from the intervention activities (what is being implemented), guidance was taken from the Expert Recommendations for Implementing Change (ERIC) [48,49] and Proctor et al [50,51]. A total of 9 initial program theories were generated linking Context–Implementation Strategy–Mechanism–Implementation Outcome (Multimedia Appendix 1). The hypothesized mechanisms that will be tested draw on 3 established middle-range theories (Textbox 1). First, the Capability, Opportunity, and Motivation inform Behavior change (COM-B) model of behavior change is expected to influence training uptake [52-54]. Second, it is hypothesized that adoption of telehealth can be explained using the diffusion of innovation framework [55,56]. Finally, the 4 Normalization Process Theory constructs identified as mechanisms by May et al [57-59] are expected to inform how IMPART, as a complex intervention, is expected to work.

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Textbox 1. Theories informing hypothesized mechanisms.

Capability, Opportunity, and Motivation inform Behavior change (COM-B)

- If champions have capability and opportunity to engage with the IMPART (Improving Palliative Care in Residential Aged Care Using Telehealth) intervention, in addition to demonstrated motivation to improve palliative care practice, then uptake of the online training (IMPETUS-D [Improving Palliative care Education and Training Using Simulation in Dementia] and goals-of-care workshop) is more likely.

Diffusion of innovation

- If champions perceive specialist telehealth support to have potential benefits for residents, their families, and staff, then they will advocate for and act as early adopters.

Normalization process theory

- Coherence: If the planning ahead team is able to make sense of IMPART and its components through reflection and evaluation (needs analysis, IMPART workshop, and action planning), then they will differentiate the intervention from current ways of working and form collective agreement about the intervention purpose and actions required to achieve their goals.
- Cognitive participation: If IMPART is legitimized through the provision of additional funding and formal commitments from the research team, In-Reach service, and residential aged care facility, then there will be continued support to meet those commitments.
- Collective action: If formation of the planning ahead team and external facilitation allows champions to share the workload of implementation, then they will be able to mitigate staff changes and increase trust between services, which grants the In-Reach team membership to the residential aged care facility.
- Reflexive monitoring: If champions implement and monitor their action plans, then they will appraise the intervention through attainment of their tailored goals and the extent in which they meet the specific needs of the residential aged care facility.

Phase 2: Theory Testing and Observation

A case study methodology will test the 9 initial program theories during the trial of the IMPART intervention. Multiple qualitative and quantitative data sources will be triangulated [60,61]. This methodology is “an empirical inquiry that investigates a contemporary phenomenon in depth and within its real-life context, especially when the boundaries between phenomena and context are not clearly evident” [61]. The case study approach is appropriate for a realist evaluation and the evaluation of complex interventions, as it applies theories and methods in a similar tradition [62]. This methodology supports the analysis of the phenomenon (the IMPART intervention) in context to uncover the mechanisms that trigger specific outcomes [62] in the cases (the participating residential aged care facilities; n=10).

The researcher will have direct access to the case to ensure a cooperative working relationship and that the study is of interest to the participants [63]. This will increase the likelihood that the data gathered are informative and will answer the research questions. The RAMESES guidelines recommend that cases are examined to the point of saturation, “checking that the patterns of success and failure, intended and unintended outcomes are consistent with the theory” [64]. Any new theories that emerge will be tested in further cases. The timeline of IMPART components and how they correspond to the realist process evaluation is displayed in Figure 2. How the data to be collected align with the initial program theories is available in Multimedia Appendix 1.

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Figure 2. Timeline of IMPART (Improving Palliative Care in Residential Aged Care Using Telehealth) components. IMPETUS-D: Improving Palliative care Education and Training Using Simulation in Dementia.

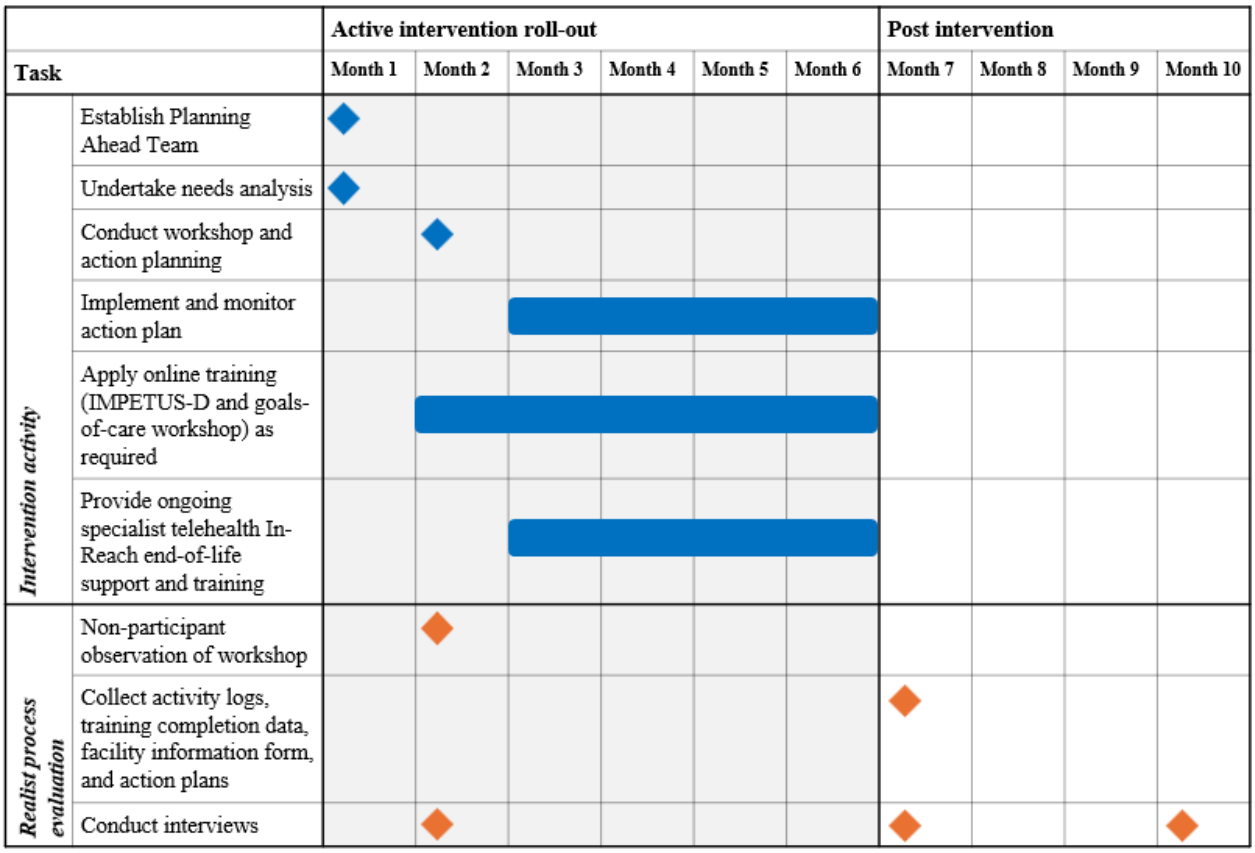

Data Collection

Qualitative Data

Nonparticipant observation will be conducted at the IMPART workshops in month 2 of the intervention. The workshops will be conducted online and recorded. Before the workshop the planning ahead team will be provided detailed information about their involvement through a preintervention meeting and manual. Their consent to participation in the planning ahead team will be implied by attendance at the workshop. Participants will be notified that the workshop is being recorded and observed. No identifiable information or direct quotes will be collected during the observation; therefore, informed consent will not be collected from participants. Up to 10 workshops will be observed. The data collected will be used to explore whether residential aged care facility and in-reach staff recruited to implement the intervention have been engaged as intended and the extent to which participants agree that the intervention is able to fulfil a need and is appropriate. To guide data collection, Spradley's [65] 9 dimensions of observation will be used. The dimensions cover the physical layout and objects present, the range of people involved, actions they undertake, the activities that take place and their sequencing, the goals that people are trying to achieve, and feelings expressed [65].

Upon completion of the intervention, action plans will be reviewed to assess whether the planning ahead teams were able to successfully implement the planned actions and whether the intervention addressed a need. Data from action plans will be used to assess implementation fidelity at participating facilities as well as to provide context. Data to be extracted and categorized will include the number of goals set and perceptions of attainment, the problem the goal is seeking to address, steps taken and by whom, resources required, any barriers identified to achieving the goals, and any adaptations made and documented to the plan during the intervention.

Semistructured interviews of approximately 30 minutes will be held at 3 intervals for each intervention wave with members of the planning ahead teams and the supporting in-reach teams. The interview guides will draw on realist interviewing, in which the intervention theory is the subject of the interview and presented to the interviewee for critique, refinement, or to propose alternate theories [66]. The IMPART research team aim to recruit 2-4 residential aged care facility staff to the planning ahead team at each participating site. As a result, using purposive sampling, the target number of interviews for each case is 6-10 interviews. In accordance with RAMESES, when sufficient evidence has been found across the cases such that it is reasonable to claim that a program theory is coherent and plausible, saturation will be considered reached for the interview sample [64].

Potential participants will be recruited by sending an interview invitation letter. Interested participants will be sent an information and consent form for review before meeting with the interviewer and given the opportunity to ask questions. Consent will be collected in written form and verbally confirmed by the interviewer before the interview commences. Interviews

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will be conducted and audio-recorded in-person, online, or by telephone, pending the participant's preference. An honorarium of AUD $50 (approximately USD $33) will be offered to acknowledge their time and expertise. During transcription, all identifiable information will be removed from interview transcripts to protect participant anonymity, and a participant ID number will be used instead.

The first stage of interviews will be conducted following the participant's attendance at the IMPART workshop. This interview will explore the participant's motivation for joining the planning ahead team, as well as investigate the contextual factors, barriers and enablers that they anticipate may affect the implementation of IMPART at the residential aged care facility. The second stage of interviews will take place upon completion of the intervention at the residential aged care facility. The interviews will explore perceptions of the intervention outcomes, conditions that supported or hindered the implementation, and how this corresponds to the initial program theories. The final interview stage will take place approximately 3 months following the completion of the intervention at the residential aged care facility to explore participants' views on the sustainability of the program.

Quantitative Data

Each site will complete a residential aged care facility information form, which will provide key demographic information about the facility, as well as their telehealth capacity and any concurrent projects or capacity-building taking place at the facility that may impact the implementation of IMPART. The residential aged care facility information will be used to describe the context in which the IMPART intervention is rolled out and to make cross-comparisons about how this may have influenced implementation at the varying sites similarly or differently.

Members of the planning ahead team and in-reach teams will complete an activity log to record telehealth consultations held during the intervention period, including consultations with the specialist palliative in-reach team for training purposes or discussions with residents or family. Other activities recorded in the activity log relating to intervention implementation include meetings, administration, and training (received or provided). At the conclusion of the intervention the activity logs will be assessed. For each site, the research team will collect data on how many and which of the IMPETUS-D online training modules were completed and by whom. Attendance at goals-of-care workshops will also be recorded.

Data Analysis

The preferred approach to data analysis in realist research is retroduction, which uses both inductive and deductive logic as well as insights or hunches [40]. To retroductively analyze the nonparticipant observations and interview transcripts, data will be imported into NVivo software (NVivo 14), and initial program theories from the coding framework created in the theory generation phase added as codes. A first reading of data will be undertaken to familiarize and extract demographic information. Data will be analyzed thematically using the coding framework and retroductive reasoning to form new CMOCs. Taking guidance from Gilmore et al [67] memos will be attached to coded content with the following fields: initial program theory, quote, source, context, implementation strategy, mechanism, outcome, CMOC, supports/refutes/refines, decision-making process, links to other initial program theories, and additional notes.

Findings will be organized according to case and compiled to build an evidence base whereby like CMOCs occur. The CMOCs will be reviewed for demi-regularities to form program theories for each case. The prevalence and strength of a CMOC will be indicated by how many participants expressed a similar experience [67]. Approximately 20% of the interview transcripts will be coded independently by the primary researcher and a second coder. The primary researcher will assign 1-2 transcripts at a time to the second coder, then arrange a meeting to cross-check codes and discuss for consistency. Where discrepancies occur, a senior member of the research team will be consulted. The primary researcher will then code the remaining transcripts using the same process.

The data collected from the action plans will undergo document analysis to validate findings from interviews and to support the development of individual case reports. Using inductive coding, the content of the action plan will be categorized, and causal inferences will be made about what has worked or not worked in enabling the planning ahead team to adopt its goals. These inferences will be tested against the hypotheses put forward in the initial program theories and later compared to make cross-case comparisons.

CMOCs will be linked to the quantitative data informing the evidence base for the descriptions of context and implementation outcomes. Results will assist in validating findings from interviews and support the development of individual case reports. The data collected from the residential aged care facility information form, activity logs, IMPETUS-D online training package, and goals-of-care training attendance will be analyzed with descriptive statistics. Responses from the residential aged care facility information form will be compared to identify any patterns between facilities that link context (eg, facility size, staffing, telehealth capacity) and implementation outcomes. Activity log statistics will be linked to fidelity and feasibility of the IMPART protocol (Did the planning ahead team and in-reach meet regularly as intended, and in what format?) and telehealth adoption (How frequently was telehealth used during the active intervention period?). Statistics extracted on online training engagement will provide a measurement of fidelity and adoption.

Phase 3: Theory Refinement

Following the theory testing phase, all CMOCs and program theories from the case studies will be reviewed for demi-regularities (frequently occurring themes or patterns) to make cross-case comparisons [40,64]. The prevalence and strength of a CMOC will be indicated by how many participants expressed a similar experience. Descriptive statistics will undergo comparative analysis to identify similarities and differences in context and implementation outcomes. Statistics will then be matched to qualitative data (context and implementation outcomes) to aid the explanation of patterns

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across the CMOCs. Cross-case theories will be arranged according to implementation outcomes to identify key causal mechanisms that either enable or hinder success.

The IMPART research team will be presented with the program theories and supporting evidence for discussion and will be asked to review the theories based on their own experience with implementing IMPART and to explain why they may support, refute, or refine certain theories. The key points from the discussion will be captured in field notes and checked and validated against available literature. Consent will be implied by participation in this theory refinement consultation. A refined cross-case program theory will then be finalized and reported back to the broader research team.

Results

The RCT commenced in May 2023, with completion anticipated in November 2025. Funding began in January 2022. Data for the realist process evaluation will be collected between May 2023 and February 2026. As of October 2025, 61 interviews have been conducted. Data analysis is ongoing. Results are expected to be disseminated through publications and conference presentations in 2026.

Discussion

Overview

This study describes a realist process evaluation protocol as part of a pragmatic stepped-wedge cluster RCT with the aim to identify and explore the contexts and mechanisms that enable or hinder the implementation of the IMPART intervention. Realist process evaluation is increasingly being used to evaluate RCTs as a way to engage a theory-informed approach to evaluation while preserving the design strengths of a RCT [43,44,68]. By sharing this protocol, we hope to contribute to discussion around the usefulness of combining these approaches and provide learnings to other interested researchers. The refined program theory developed will link implementation strategies to contextual factors specific to residential aged care that trigger mechanisms influencing the implementation of IMPART. There is a lack of understanding of the effects of different implementation strategies and the extent to which they can facilitate the uptake of interventions, particularly in residential aged care [53,54,69-76]. Implementation strategies are underreported and difficult to differentiate from the intervention. Applying a realist framework to explore process outcomes therefore allows for implementation to be analyzed and reported in detail. This realist process evaluation is novel in offering an explanatory account of what has worked or not worked in the implementation of a palliative care intervention in residential aged care.

This study also addresses key gaps in the evaluation and implementation of telehealth use for end-of-life care in residential aged care. The findings will be timely in their congruence with national strategic priorities around digital health [24]. As telehealth expands, it is important to monitor its use in complex settings such as residential aged care and ensure it is achieving the desired outcomes for residents, their caregivers, and the residential care workforce. This will be the first realist process evaluation to uncover causal mechanisms that influence the uptake of telehealth in residential aged care to support the provision of palliative care.

Residential aged care facilities are complex sites undergoing constant change. High staff turnover, lack of staff capacity at all levels, ongoing compliance and training obligations often impacts the ability of their workforce to engage meaningfully with research [54,70,74]. While it may be challenging to engage residential aged care staff into the study, the factors impacting engagement will be considered in analysis as part of the context influencing the implementation of the IMPART intervention. Similarly, any adaptations made by the participants or research team to the trial protocol to mitigate barriers to successful implementation will be documented and reported as part of the process evaluation but will not be informed by it. Effort has been taken in the selection of methods to minimize the burden of participation on residential aged care staff as their insights are crucial to progressing the translation of research evidence into practice.

Strengths and Limitations

Realist evaluation and synthesis is still considered a relatively new methodology, and using it comes with its own set of challenges [37]. Key to realist inquiry is flexibility to adapt the methodology to emerging theories [40,64]. Ethical approval for the trial protocol, selection of methods, and data collection materials such as interview guides is required before implementation of any intervention. This can make it difficult to undertake a truly realist-informed process evaluation within the parameters of the RCT rollout and budget timelines, whereby selection of methods and interview questions is informed by the initial program theories [40,64].

The methods for the IMPART realist process evaluation were selected before the development of the initial program theories and therefore are not truly realist-informed. It is intended that the semistructured interview format will allow for interview guides to be molded to test the initial program theories as they evolve and change with each facility. The initial program theories will be tested across up to 10 cases, allowing sufficient opportunity to present and discuss these theories using realist interviewing techniques. The coding framework applied to the interview transcripts is also informed by the initial program theories to ensure their interpretation explores the hypothesized mechanisms. While the overarching research questions are not specific to these hypothesized mechanisms, they are general enough to still reflect the evaluation aims of uncovering hidden causal linkages between context and mechanisms that lead to implementation outcomes. Nonetheless, this is an important consideration for researchers looking to integrate a realist process evaluation into an RCT.

A limitation of the realist approach is that the full extent of contexts and mechanisms influencing the implementation of the intervention is unlikely to be uncovered in one study, with findings from a realist evaluation not generalizable [37]. However, the findings from this study will provide rich insights that contribute to growing knowledge on what works, for whom, how, and under what circumstances in implementing

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interventions that seek to improve palliative care in residential aged care. The strength of this realist process evaluation lies in its potential to provide transferable, context-specific findings that can support the development of meaningful policy and accelerate practice change [37].

Another strength of the methodology is that it centers the voices of the residential aged care workers asked to undertake implementation activities. The findings will consequently go beyond quantitative measures of intervention adoption and implementation fidelity to integrate meaningful causal explanations with real-world implications.

Future Directions

Findings from the trial will be communicated back to participating residential aged care facilities and stakeholders through a written project summary prepared by the research team. Results will also be disseminated to the broader research community through conference presentations and publications. If IMPART is shown to be effective by trial outcome measurements, namely reducing unplanned hospitalizations at the end of life, the refined program theory from this realist process evaluation will inform the rollout of future iterations of IMPART to the residential aged care sector (including those in regional, rural, and remote areas), continuing the cycle of theory testing and refinement key to realist inquiry. The implementation plan for future rollout of IMPART will identify key causal pathways that have led to success during the trial, which can then inform decision-making around the level of support and resources a particular facility may need. In doing so, we can move closer to ensuring residential aged care staff have access to valuable professional development opportunities to develop their confidence and competence to provide quality palliative care, and that residents have access to high-quality end-of-life care they should expect.

Conclusions

Applying a realist framework to explore process outcomes allows for an in-depth inquiry into what works, for whom, how, and in what circumstances in the implementation of complex interventions that aim to improve palliative care in residential aged care. The refined program theory developed will help accelerate efforts to implement telehealth-enabled interventions to improve the provision of quality palliative care in residential aged care.

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Authors' Contributions

KL, AMYG, KG, JT, KM, and WKL wrote the manuscript, with KL drafting the first version and leading and coordinating the writing of this study. All authors read and approved the final manuscript. WKL, AMYG, KG, and KM are chief investigators of the IMPART randomized controlled trial. KL led the development of the realist process evaluation protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Initial Program Theories of the IMPART program.
[DOCX File , 26 KB - resprot_v14i1e68332_app1.docx]

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Abbreviations

CFIR: Consolidated Framework for Implementation Research
CMOC: context–mechanisms–outcomes configurations
COM-B: Capability, Opportunity, and Motivation inform Behavior change
ERIC: Expert Recommendations for Implementing Change
IMPART: Improving Palliative Care in Residential Aged Care Using Telehealth
IMPETUS-D: Improving Palliative care Education and Training Using Simulation in Dementia
RAMESES: Realist and Meta-narrative Evidence Syntheses: Evolving Standards
RCT: randomized controlled trial

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Protocol

The Effect of Electroacupuncture on Microcirculation in Patients With Hypertension and Cognitive Impairment: Protocol for a Multicenter Randomized Controlled Trial

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Abstract

Background: Hypertension is a significant risk factor for cardiovascular diseases and is associated with an increased risk of mild cognitive impairment (MCI). The lack of effective treatment for these conditions underscores the urgent need for novel therapeutic approaches. Previous studies have indicated that microcirculation serves as the pathological basis for the comorbidity of hypertension and cognitive dysfunction. Our initial clinical studies have indicated that acupuncture could be a safe and effective treatment for managing hypertension and MCI. Whether acupuncture can enhance hypertension and cognitive impairment by modulating microcirculation, and the precise mechanisms involved, warrants further exploration.

Objective: The objective of the trial is to evaluate the clinical efficacy of electroacupuncture on MCI of patients with hypertension and to explore whether it can improve hypertension and cognitive impairment by regulating microcirculation.

Methods: In this multicenter, large-scale, single-blind, randomized controlled trial, we will recruit 252 patients with hypertension and cognitive impairment from 3 hospitals and randomly assign them to 3 groups in a 1:1:1 ratio: the electroacupuncture group, the sham electroacupuncture (SEA) group, and the waiting list group. The electroacupuncture group and SEA group will receive either electroacupuncture or SEA for 12 weeks, while the waiting list group will not receive acupuncture treatment for the first 12 weeks. The primary outcome will be the changes in overall cognitive function, as measured by the Montreal Cognitive Assessment. The secondary outcomes include blood pressure status, subdomain cognitive function, mental status, sleep quality, hemodynamics, and microcirculation indicators.

Results: The study protocol has been approved by the institutional review board of the First Affiliated Hospital of Tianjin University of traditional Chinese medicine. This study was registered on April 26, 2024, with the Chinese Clinical Trial Registry. Data collection began in May 2024 and ended in April 2025. Currently, data from this trial are in the collection phase, and no data analysis has been performed. As of January 1, 2025, we have collected data from 65 patients. The results of this trial are expected to be submitted for publication in July 2026.

Conclusions: This clinical trial aims to compare the efficacy of electroacupuncture versus SEA or waiting list control in the treatment of hypertension with cognitive impairment and to explore its impact on microcirculation through hemodynamic and microcirculatory indices. The results of this trial will contribute to clarifying the microcirculatory mechanisms of electroacupuncture in the treatment of hypertension with cognitive impairment, providing a solid foundation for further research on electroacupuncture therapy.

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Trial Registration: Chinese Clinical Trial Registry ChiCTR2400083501; https://www.chictr.org.cn/showproj.html?proj=220722
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KEYWORDS
acupuncture; mild cognitive impairment; hypertension; microcirculation; randomized controlled trial

Introduction

Background

Mild cognitive impairment (MCI) represents a transitional stage between normal cognitive function and dementia. In China alone, the incidence rate of MCI ranges from 9.7% to 23.3% [1], and the annual conversion rate of MCI to dementia is estimated to be 5% to 20% [2]. Hypertension is an independent and significant contributor to cognitive impairment; it increases the risk of MCI by 1.62 times. From 2007 to 2011, the prevalence of hypertension with MCI (HTMCI) was 16.5% [3]; meanwhile, a meta-analysis published in 2023 showed that the overall prevalence of HTMCI in China was 37.6% [4]. Evidence suggests that hypertension can increase the risk of cognitive-related diseases, such as Alzheimer disease (AD) and vascular dementia [5]. A meta-analysis [4] published in 2021 revealed that the combination of high blood pressure and MCI is associated with a global prevalence of up to 30%. A *Lancet* study reported that over the past 30 years, the number of adults aged between 30 and 79 years with high blood pressure has risen from 650 million to 1.28 billion [6]. As the prevalence of hypertension continues to rise, the number of patients experiencing both hypertension and cognitive impairment is expected to increase.

There are established pathways from hypertension to cognitive impairment, which include atherosclerosis and arteriolar sclerosis [7]. Cerebral hypoperfusion and reduced neurovascular coupling can result in brain dysfunction by depriving energy-demanding areas of oxygen and glucose, essential for cognitive processes [8]. Hypertensive amyloid production and deposition might also contribute by promoting the pathogenesis of cognitive impairment [9]. Hypertension is widely recognized as an important risk factor for cognitive impairment. However, cognitive impairment can lead to limitations in daily behavior and activities [10], subsequently affecting the drug management and nursing routines of patients with hypertension, resulting in a vicious cycle [11]. Therefore, determining ways to prevent or delay the progression of hypertension accompanied by MCI represents an urgent clinical challenge.

Microcirculation is the comorbidity pathologic basis of hypertension and cognitive dysfunction. Microcirculatory dysfunction is closely related to the occurrence and development of cognitive impairment. Studies have shown that microvascular endothelial cell abnormalities and cerebral blood flow regulation disorders can lead to local tissue hypoxia, changes in blood-brain barrier permeability, and decreased metabolic waste removal efficiency, which in turn accelerates β-amyloid deposition and tau protein hyperphosphorylation through mechanisms such as neurovascular unit disorders, enhanced oxidative stress, and neuroinflammatory activation, eventually leading to neuronal damage and decreased synaptic plasticity. So, improving microcirculation (microcirculation disturbance [MD]) is a key link in the process of prevention and cure of HTMCI, mainly reflected in the occurrence and development of hypertension [12,13]. MD-based cerebral blood flow regulation disorder and cerebral hypoperfusion are closely related to cognitive function impairment [13]; MD is the common pathophysiological basis of hypertension and cognitive impairment: they interact and influence each other through microvascular thinning degree, hemodynamics, oxidative stress level, endothelial cell function, etc [14-16].

In recent years, numerous studies have demonstrated that acupuncture exhibits significant antihypertensive effects on mild to moderate essential hypertension [17-20] and is increasingly recognized as beneficial in improving cognitive function [21-24]. However, reports on the effect of acupuncture on patients with both hypertension and cognitive impairment are lacking. Our team conducted a randomized controlled clinical trial of large-sample, multicenter acupuncture treatment of essential hypertension in the early stage and found that after 6 weeks of electroacupuncture treatment, the 24-hour average systolic blood pressure in the treatment group was significantly decreased (mean 7.2, SD 11.0 mm Hg) compared with the sham acupuncture group and the waiting treatment group, and the antihypertensive effect lasted for 6 weeks [25]. Another experiment to observe the effect of acupuncture on cognitive function in patients with poststroke cognitive impairment found that acupuncture significantly reduced the overall cognitive function of patients with poststroke cognitive impairment compared with the sham acupuncture group and the waiting treatment group and had a certain lasting effect and also reduced the incidence of dementia [26].

Objectives

On the basis of the theory of MD and our previous research, this study will conduct randomized controlled experiments to explore the effect of electroacupuncture on improving cerebral microcirculation in improving cognitive function.

Methods

Trial Design

This is a multicenter, open-label, waiting list control randomized controlled trial. A total of 252 eligible participants will be randomly assigned in a 1:1:1 ratio to the electroacupuncture group, the sham electroacupuncture (SEA) group, and the waiting list group. The assessments of clinical outcomes will be performed at baseline, week 12, and week 24. Acupuncture treatment was administered once every other day, 3 times per

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week, for 12 weeks, followed by a 12-week follow-up. The flowchart and study design schedule are shown in Figures 1 and 2, respectively.

Figure 1. Flowchart. HTMCI: hypertension with mild cognitive impairment; SEA: sham electroacupuncture.

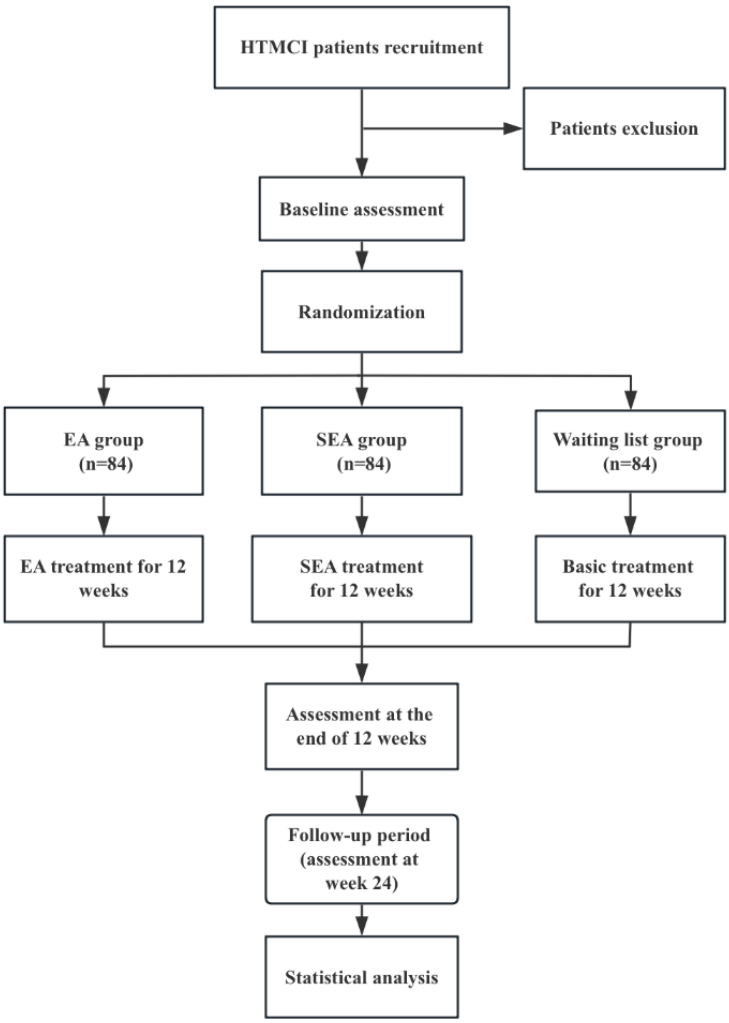

Figure 2. Location of acupoints and nonacupoints. Baihui: GV20; Fenglong: ST40; NA: nonacupoint; Neiguan: PC6; Shenting: GV24; Taichong: LR3; Zusanli: ST36.

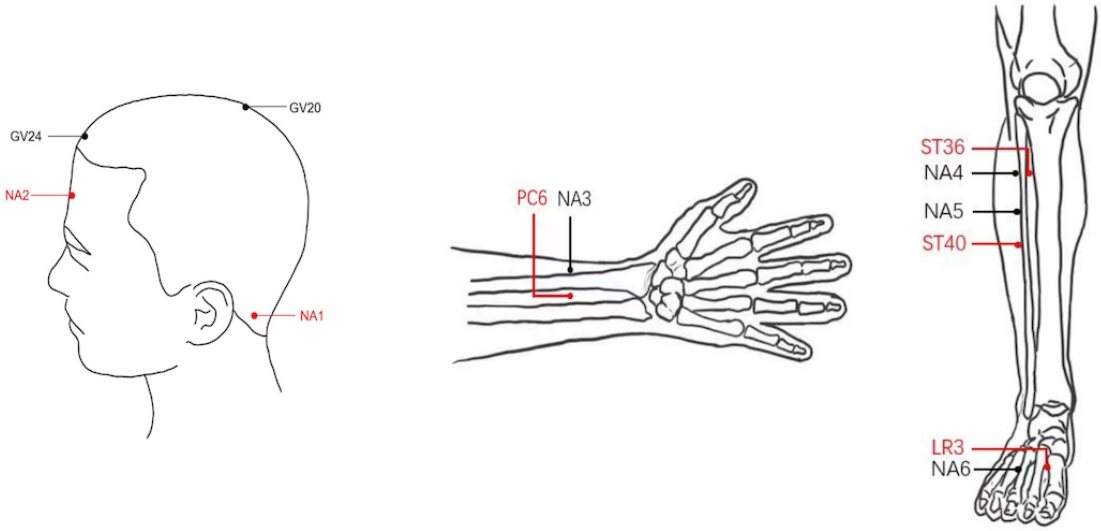

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Ethical Considerations

The protocol has been approved by the institutional review board of the First Affiliated Hospital of Tianjin University of traditional Chinese medicine (TCM; TYLL2023{6}051). All patients provided their written informed consent to participate in the study and authorized the publication of their data. This study was registered on April 26, 2024, with the Chinese Clinical Trial Registry (ChiCTR2400083501). Every participant will be informed of detailed information about the study before signing informed consent. The results of this trial will be published in a peer-reviewed journal. Patients and the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

Participants and Recruitment

We will recruit participants in the outpatient departments of 3 hospitals, including the First Teaching Hospital of Tianjin University of TCM, the TCM hospital of Sichuan Province and Hospital of Chengdu University of TCM, the Affiliated Sichuan Provincial Rehabilitation Hospital of Chengdu University of TCM, and Tianjin Medical University General Hospital. Patients with HTMCI and healthy participants who are interested and whose initial screening meets our recruitment needs will be fully informed of the entire study procedure, benefits, and risks. Clinical trial communicators will fully explain the trial to patients before the trial begins to ensure that all the patients participate voluntarily and sign an informed consent form.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria are presented in Textbox 1 [27-29].

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Meet the diagnostic criteria of primary hypertension [27]
- Meet the diagnostic criteria of mild cognitive impairment [28]
  - Mini-Mental State Examination ≥21 points and <27 points
  - Montreal Cognitive Assessment Scale ≥18 points and <26 points
  - Activity of daily living scale <22 points, and no more than 1 item in the single score may be ≥3 points
- Aged between 40 and 75 years
- Primary school education (6 years) or above and able to correctly understand and complete the scale
- No acupuncture treatment has been received within 3 months
- Voluntarily cooperate and sign informed consent

Exclusion criteria

- Undergone treatments potentially interfering with cognitive functions, such as the use of cognition-impacting medications (eg, donepezil, memantine, and rivastigmine) [29]
- With neurological or chronic conditions, including systemic diseases (eg, anemia, tumors, and metabolic disorders) that could impair cognitive functions
- Presence of infection or focal injury, as indicated by brain magnetic resonance imaging, multiple infarcts, or cerebral white matter lesions in critical memory areas (Fazekas Rating >3)
- With secondary hypertension, refractory hypertension, or hypertension accompanied by clinical syndromes and target organ damage
- With aphasia, hearing impairment, muscle strength functional impairment below grade 3, severe visual impairment, or myopia exceeding 300, rendering them unable to cooperate with the test
- With coexisting diabetes, hyperlipidemia, or a BMI <18.5 or ≥28
- Who is considered by the researcher to be unsuitable for this study

Randomization and Blinding

A total of 252 eligible patients will be randomly allocated to the acupuncture group, the sham acupuncture group, and the waiting list group at a 1:1:1 ratio. An independent professional statistician, uninvolved in the trial's implementation or subsequent statistical analysis, will generate the randomization sequence using SPSS (IBM Corp) software. Both the outcome assessor and the statistician will remain blinded to group assignments. Group assignments will be disclosed only after the completion of the statistical analysis.

Interventions

All the groups receive standard treatment, including controlling blood pressure, blood glucose, blood lipid, and symptomatic treatment.

In this trial, 0.25×40 mm needles manufactured by HUATO, Suzhou, China, and the SDZ-III electroacupuncture apparatus by Suzhou Medical Appliance, Jiangsu, China, will be used.

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Interventions in all groups will be practiced by registered practitioners of TCM with at least 5 years of clinical experience in acupuncture. Acupuncturists will be trained in the study protocol and standardized acupuncture manipulations before study initiation.

Electroacupuncture Group

Participants in the electroacupuncture group will receive electroacupuncture at Baihui (GV20), Shenting (GV24), Neiguan (PC6), Zusanli (ST36), Fenglong (ST40), and Taichong (LR3). Acupoints PC6, ST36, ST40, and LR3 will be applied bilaterally. All acupoints will be punctured to standardized needling depths and manipulated through lifting, thrusting, or twisting to induce the Deqi sensation. Three paired alligator clips from the electroacupuncture apparatus will be attached to GV20 and GV24, and to the homolateral ST36 and ST40, with a disperse-dense frequency (2/15 Hz) and a patient-tolerable current intensity. The precise locations and manipulations of these acupoints are depicted in Table 1 and Figure 2. This treatment will be administered over a period of 12 weeks, with sessions occurring once daily, 3 times per week.

Table 1. Locations and manipulations of acupoints in the electroacupuncture group.

Acupoints	Location	Manipulation
Baihui (GV20)	On the midline of the head, 5 cm directly above the midline of the head, approximately on the midpoint of the line connecting the apexes of both ears.	Horizontal insertion with a depth of 1 cm is applied with a small-amplitude, high-frequency twisting technique of the reinforcing method for 1 min.
Shenting (GV24)	On the midline of the head, 0.5 cm directly above the midline of the head.	Horizontal insertion with a depth of 0.5-0.8 cm is applied with a small-amplitude, high-frequency twisting technique of the reinforcing method for 1 min.
Neiguan (PC6)	On the forearm, 2 cm above the transverse crease of the wrist, between the tendons of musculus palmaris longus and musculus flexor radialis.	Vertical insertion with a depth of 1.0-1.5 cm is applied with the twisting, lifting, and thrusting technique of the reducing method for 1 min.
Zusanli (ST36)	On the outer side of the calf, 3 cm directly below Dubi, and 1 finger-breadth lateral to the anterior border of the tibia.	Vertical insertion with a depth of 0.7-1.0 cm is applied with the twisting of 360°, with a frequency of 120-160 revolutions per minute of the mild reinforcing-reducing method for 1 min.
Fenglong (ST40)	One finger-breadth lateral to Tiaokou and at the midpoint of the line joining Dubi and the tip of the external malleolus.	Vertical insertion with a depth of 1.0-1.5 cm is applied with the twisting, lifting, and thrusting technique of the reducing method for 1 min.
Taichong (LR3)	On the dorsum of the foot, in the depression distal to the junction of the first and second metatarsal bones.	Vertical insertion with a depth of 1.0-1.5 cm is applied with the twisting, lifting, and thrusting technique of the reducing method for 1 min.

The SEA Group

In the SEA group, 9 nonacupoints will be selected, with their locations detailed in Table 2 and Figure 2. The selection of nonacupoints in the SEA group involves choosing points situated on nonmeridians yet proximal to the acupoints selected in the electroacupuncture group, a common approach in sham acupuncture design [30]. A shallow needling technique (approximately 5 mm depth) will be used at these nonacupoints, eschewing both reinforcing-reducing techniques and the elicitation of the *Deqi* sensation. The SEA device will be connected, with its connecting wires internally disconnected. The number and frequency of treatments will mirror those of the electroacupuncture group.

Table 2. Location of nonacupoints in the sham electroacupuncture group.

Nonacupoint	Location
Nonacupoint 1	At the midpoint of the line connecting the Fengchi acupoint (GB20) and the Anmian acupoint (Extra).
Nonacupoint 2	At the midpoint of the line connecting the Shenting acupoint (GV24) and Yintang acupoint (EX-HN 3).
Nonacupoint 3	On the palmar side of the forearm, on a level with Neiguan (PC6) and 1 cm radialis to it (between the Pericardium Meridian of Hand-Jueyin and the Lung Meridian of Hand-Taiyin).
Nonacupoint 4	In the middle of the Yanglingquan acupoint (GB34) and Zusanli acupoint (ST36; between the gallbladder and bladder meridian).
Nonacupoint 5	In the middle of the Fenglong acupoint (ST40) and the Zusanli acupoint (ST36; between the gallbladder and bladder meridian).
Nonacupoint 6	At the midpoint of the dorsum of the foot; the 3rd and 4th metatarsal bones join the anterior depression.

Waiting List Group

No acupuncture treatment will be given in the waiting list group for the first 12 weeks. Participants will be required to complete the assessments at the corresponding time points. Considering the ethical requirements, compensatory treatment will be given after 12 weeks of following up.

The specific flowchart is shown in Figure 1.

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Outcomes

Baseline Comparability

We first confirmed the comparability of the baseline by independent 2-tailed *t* test for continuous variables and chi-square tests for categorical variables, all $P>.05$.

Outcome Measures

In this trial, both primary and secondary outcomes will be assessed at baseline, upon intervention completion (week 12), and during the 12-week follow-up period (week 24).

Primary Outcome: Montreal Cognitive Assessment

The Montreal Cognitive Assessment (MoCA) [31] tests key areas such as executive function, verbal fluency, orientation, calculation, abstract thinking, delayed recall, visual perception, naming, attention, and concentration. A systematic review [32] indicates that the MoCA effectively detects MCI. Furthermore, the MoCA is a straightforward, independent cognitive screening tool with superior sensitivity (100%). Its memory test encompasses more words, fewer learning trials, longer recall delays, and a shorter assessment duration, rendering it appropriate for clinical applications. It demonstrates excellent test-retest reliability and positive and negative predictive values for MCI and AD [31]. Therefore, we used the MoCA test as our primary outcome measure to ensure maximum diagnostic accuracy.

Secondary Outcomes

Mini-Mental State Examination

The Mini-Mental State Examination (MMSE) [33] is a comprehensive 30-question assessment tool evaluating cognitive functions, including attention and orientation, memory, registration, recall, computation, language abilities, and the capacity to draw complex polygons [34]. However, an increasing number of studies indicate that the MMSE's effectiveness in clinically detecting MCI is limited [34-36]. This implies that the MMSE is insufficient for identifying subtle cognitive changes in patients with MCI, particularly in cases of dementia without significant memory decline [34]. Consequently, in this study, the MMSE scale was used as a secondary outcome measure, complementing the MoCA scale to minimize the occurrence of false positives.

Blood Pressure Condition

Blood pressure measurements both in the clinic and through ambulatory monitoring were included. Clinic-based blood pressure measurement has primarily relied on the auscultatory method, using mercury, aneroid, or hybrid sphygmomanometers. Patients are advised to abstain from smoking, consuming caffeinated beverages, or exercising for 30 minutes before the measurement of their blood pressure [37]. In the clinic, at least 2 blood pressure readings will be obtained with an interval of 1 to 2 minutes, and the average of these readings will be considered. Should the difference between the first and second blood pressure readings exceed 10 mm Hg, a third measurement is advised, with the average of the latter 2 readings being taken.

The monitor should be fitted only after the patient has been in a relaxed state for at least 5 minutes. Blood pressure is subsequently measured in both arms, and an appropriately sized cuff is placed on the nondominant arm should the difference in systolic blood pressure be less than 10 mm Hg. In addition, an automatic noninvasive portable 24-hour dynamic blood pressure monitor will be attached to the nondominant arm for measuring brachial artery blood pressure. The monitoring frequency typically ranges from every 15 to 30 minutes during the day to every 30 minutes at night. The health care provider will instruct the patient to ensure that the monitor remains connected, to continue performing normal daily activities, and to keep the monitor arm stable and level with the heart throughout the 24 hours. A valid 24-hour ambulatory blood pressure monitoring session necessitates at least 14 readings during the day and at least 7 readings at night [38]. The computer will automatically calculate and record the following parameters: 24-hour mean systolic blood pressure, 24-hour mean diastolic blood pressure, daytime mean systolic blood pressure, daytime mean diastolic blood pressure, night mean systolic blood pressure, night mean diastolic blood pressure, along with the white coefficient of variance (defined as the ratio of the SD of blood pressure to the average systolic and diastolic blood pressure in the same time period) for daily and nocturnal systolic and diastolic blood pressures.

Verbal Fluency Test

Impaired executive function represents a principal manifestation of cognitive impairment related to hypertension. The Verbal Fluency Test demonstrates sensitivity in differentiating various cognitive impairments, with varying scores distinguishing between cognitively normal individuals and those exhibiting patterns of AD or MCI. Both in clinical and experimental contexts, the Verbal Fluency Test is extensively used for the diagnosis and assessment of a variety of neurological disorders [39].

The Shape Trail Test

The Shape Trail Test (STT) is a variant of the original Trail Making Test, known for its sensitivity in evaluating visual search and sequencing abilities, and is applied in cognitive function assessments. This study predominantly uses the STT, comprising 2 components, A and B. The STT-A assesses language and attention capabilities, whereas the STT-B focuses more extensively on executive function and memory [40].

Auditory Verbal Learning Test

The Verbal Learning Test is considered the most reliable predictor of the transition from MCI to AD. In this study, the primary tool used is the Auditory Verbal Learning Test–Huashan version. This version uses the principles and methods of the California Verbal Learning Test, a standardized Verbal Learning Test, and comprises both short-term and long-term delayed recall, making it apt for detecting cognitive impairment in patients with impaired memory [41].

Activity of Daily Living

Activities of Daily Living (ADL) are an effective instrument for dementia screening and are well-suited for assessing the daily functional abilities of patients with MCI [42]. This study predominantly uses ADL to diagnose hypertension-related cognitive impairment, encompassing both basic ADL and

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instrumental ADL. The former pertains to the fundamental skills necessary for independent living, while the latter involves capabilities for more complex daily and social activities [43].

Hamilton Anxiety Scale and Hamilton Depression Scale

This scale also serves to assess the anxiety or depression status of the participants over the past week, using a combination of conversation and observation. Research has indicated that cognitive impairment is bidirectionally associated with higher anxiety and depression scores. In this study, the Hamilton Anxiety Rating Scale and the Hamilton Depression Rating Scale will be used to assess hypertension combined with cognitive impairment [44].

Pittsburgh Sleep Quality Index

Sleep disorders are known to contribute to various metabolic disorders, including obesity, diabetes, and dyslipidemia, all of which are key factors in high blood pressure [45]. The Pittsburgh Sleep Quality Index evaluated sleep quality through 7 aspects: sleep quality, time to fall asleep, sleep duration, sleep efficiency, sleep disturbance, use of hypnotic drugs, and daytime dysfunction [46].

Transcranial Doppler

Transcranial Doppler (TCD) is a useful tool in the diagnosis and treatment of clinical cerebrovascular diseases. In particular, TCD can be used to assess the effects of cerebral artery stenosis and occlusion on cerebral hemodynamics [47]. Hypertension is the major vascular risk factor for cerebral small vessel disease. TCD is a noninvasive method that allows the monitoring of microvascular hemodynamic functional integrity to help guide therapies aimed at the cerebral microcirculation and neurovascular unit [48]. At the same time, studies have shown that cerebral hypoperfusion is associated with both cognitive decline and white matter lesions. Therefore, TCD can explore the cognitive impairment in the midbrain hemodynamic and small vessel disease caused by the relationship between the brain lesions [49]. Important parameters measured in this study include the mean velocity, resistance index, and pulse index within both cerebral arteries.

Microcirculation-Related Palliation

The microcirculation, often regarded as a hidden organ, consists of the smallest blood vessels, including resistance arterioles, capillaries, and venules [50]. The endothelium mediates the vasomotor tone of the microcirculation through the release of vasodilators (such as nitric oxide [NO]) and vasoconstrictors (such as endothelin-1 [ET-1]). Concurrently, impaired vasodilation, mediated by reduced NO production, is a characteristic feature of endothelial dysfunction [51]. Consequently, NO and ET-1 will be used as biomarkers to assess microcirculation indicators in patients.

Safety Evaluation

Adverse reactions, including needle-sickness, needle stagnation, needle bending, broken needle, and subcutaneous hematoma, will be closely monitored during the treatment process. Concurrently, a detailed analysis will be conducted on the correlation between all adverse events and acupuncture to rigorously evaluate the safety of acupuncture treatment. All adverse events will receive appropriate intervention, and serious adverse events will be reported to the ethics committee immediately.

Data Management and Quality Control

Quality control will be implemented for all records of clinical trials, including case reports, needling operation lists, blood pressure monitoring forms, cognitive assessment scales, among others, with strict control of the time window for follow-up collection to ensure that the data are accurate, complete, truthful, and timely. These records shall not be omitted or arbitrarily altered.

A specialized quality control team will be established to conduct regular on-site inspections. Simultaneously, a comprehensive quality control system will be established during the implementation of the project, and we will formulate a series of standard operating procedures, including standard operating procedures for the study process, the acupuncture treatment, and the follow-up assessment. Furthermore, the Data Inspection Committee has been commissioned to regularly review and assess the data accumulated from the clinical trials, thereby evaluating the quality, efficacy, and safety of the trials.

Sample Size

According to the literature [52], acupuncture treatment increased the mean MoCA score by 2.83 (SD 1.13); the mean change in MoCA in the sham acupuncture group was 1.97 (1.38), waiting group, the mean change in MoCA was 0.48 (SD 1.65); the test level was α=0.01; power was 95%; and it was calculated by the PASS (version 15.0; NCSS, LLC) software to obtain a sample size of 66, considering a 20% dropout rate, 84 cases were proposed to be included in each group, and 252 participants were finally included.

Statistical Analysis

Statistical analysis was performed using SPSS (version 27.0) software. All patients who completed the randomization and received the overall course of treatment were included in the efficacy analysis to ensure the integrity and comparability of the data. For different types of data, the following statistical methods will be used for analysis:

1. Data types and test methods: ×2 test is used for count data, and Shapiro-Wilk and Levene test are used for measurement data to analyze the independence, normality, and homogeneity of variance of data.
2. Comparison between groups: for normal distribution and homogeneity of variance, 1-way ANOVA with completely random design was used for comparison between groups. If the variance is not uniform, the Kruskal-Wallis rank sum test of the single-factor nonparametric method of completely random design is used for comparison between groups. For the measurement data conforming to the skewed distribution, the Kruskal-Wallis rank sum test of the single-factor nonparametric method of completely random design was used for comparison between groups.
3. Hypothesis testing and significance level: The count data are expressed as a ratio (%) using the chi-square test or Fisher exact test. The 2-sided test method was used

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uniformly, and the test statistics and corresponding *P* values were recorded. *P*<.05 was used as a criterion for judging significant statistical significance.

Results

The study protocol has been approved by the institutional review board of the First Affiliated Hospital of Tianjin University of TCM. This study was registered on April 26, 2024, with the Chinese Clinical Trial Registry. Data collection began in May 2024 and ended in April 2025. Currently, data from this trial are in the collection phase, and no data analysis has been performed. As of January 1, 2025, we have collected data from 65 patients. The results of this trial are expected to be submitted for publication in July 2026.

Discussion

Overview

Hypertension is the leading risk factor for the global disease burden, a major cause of cardiovascular and cerebrovascular morbidity and mortality in China, and one of the most prevalent chronic diseases [53]. Microcirculation plays an important role in maintaining peripheral vascular resistance and blood pressure stability. Abnormal microvascular blood perfusion is an early manifestation of hypertension [54]. At the same time, cerebral blood flow regulation disorder and cerebral hypoperfusion have direct influence on cognitive function [13]. Therefore, MD is the common pathophysiological basis of hypertension and MCI.

Clinical findings suggest that TCD markers of cerebral flow regulation in patients with hypertension are strongly associated with cognitive ability, with poorer cognitive function associated with enhanced dynamic brain autoregulation in the middle cerebral artery [55]; The content of NO is closely related to oxidative stress response, which can activate the nuclear factor kappa-light-chain-enhancer of Activated B Cells pathway, and then cause inflammation in vivo, promote the release of proinflammatory mediators in the blood vessel wall, and accelerate the occurrence and development of hypertension and vascular complications; ET-1, as an important substance regulating vasoconstriction, can promote vascular smooth muscle cell proliferation, fibrosis, and inflammation, and has important significance in the pathophysiology of vascular endothelium [56]. All the above can further affect the microcirculation index by affecting the vascular endothelium.

Acupuncture, as a special treatment method of TCM, can regulate blood pressure by regulating the neuroendocrine system, improving metabolic activities, changing gene expression related to blood pressure, and so on [57-59]. At the same time, it has been proved that acupuncture can restore the decreased cognitive function to some extent by regulating the hypothalamic oxidative stress pathway, proinflammatory cytokine [60] and improving the brain white matter injury [61].

According to previous studies, acupuncture stimulation of LR3 and ST36 with electroacupuncture and manual acupuncture can reduce the symptoms of hypertension and subsequent cognitive dysfunction in spontaneously hypertensive rats60. The acupuncture of DU20 and ST36 can reduce blood pressure, increase microvascular dilation, reduce nerve damage, and restore cognitive dysfunction to a certain extent [62]. In addition, electroacupuncture stimulation of bilateral PC6 can affect the inflammatory pathway mediated by the regulation of AngII-TGF-β and then achieve the effect of antihypertension and improvement of spontaneously hypertensive rat cardiac fibrosis [63]. On the basis of the research results mentioned earlier, we selected GV20, GV24, PC6, ST36, ST40, and LR3 for combination therapy.

In this study, the mechanism of microcirculation is combined with modern medicine to monitor cerebral microvascular hemodynamics by TCD. Endothelium dysfunction biomarkers ET-1 and NO were used to determine the contraction and dilation of cerebral microvessels. The relationship between microcirculation and hypertension and MCI was investigated by combining clinical and experimental methods. In summary, we propose a randomized controlled trial to verify whether the improvement of electrotherapy in HTMCI is related to the regulation of microcirculation indicators by acupuncture, and to provide more clinical evidence of the effectiveness of acupuncture in reducing blood pressure and improving cognitive impairment.

Limitations

This study aims to provide high-quality evidence on the efficacy and safety of electroacupuncture in patients with HTMCI. However, this protocol design also has limitations. First, it is impossible to accurately judge the causality between hypertension and cognitive impairment; thus, the reverse causality bias of MCI affecting blood pressure may occur. Second, the potential for spontaneous recovery early in cases of hypertension complicated with MCI may have confounding effects on this trial, though the waiting list group could mitigate these impacts.

Conclusions

This clinical trial aims to compare the efficacy of electroacupuncture versus SEA or waiting list control in the treatment of hypertension with cognitive impairment and to explore its impact on microcirculation through hemodynamic and microcirculatory indices. The results of this trial will contribute to clarifying the microcirculatory mechanisms of electroacupuncture in the treatment of hypertension with cognitive impairment, providing a solid foundation for further research on electroacupuncture therapy.

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Acknowledgments

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Authors' Contributions

LZ and JL are responsible for this study and conceived and designed the study. JW, XD, XC, XL, YW participated in drafting the trial protocol and preparing the manuscript. Acupuncture treatments were administered by LZ and JL. Participant recruitment and data entry were provided by JW, XL, YW, YG, QY, DZ, and KM. All authors have read and approved the submitted version of this manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AD: Alzheimer disease
ADL: Activity of Daily Living
ET-1: endothelin-1
HTMCI: hypertension with mild cognitive impairment
MCI: mild cognitive impairment
MD: microcirculation disturbance
MMSE: Mini-Mental State Examination
MoCA: Montreal Cognitive Assessment
NO: nitric oxide
SEA: sham electroacupuncture
STT: Shape Trail Test
TCD: Transcranial Doppler
TCM: traditional Chinese medicine

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Protocol

The Good Start Matters mHealth Parenting Program: Protocol for a Randomized Controlled Trial

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Abstract

Background: The family plays a critical role in shaping children's health behaviors during early childhood. Family-based interventions are a cornerstone of childhood obesity prevention but often yield modest effects and have several limitations, including a focus on a single caregiver and insufficient attention to coparenting dynamics. Mobile health (mHealth) interventions that include multiple caregivers and target coparenting practices are rare, but have the potential to amplify parenting intervention effects, leading to stronger child health outcomes.

Objective: This protocol aims to describe a randomized controlled trial designed to evaluate the efficacy of the Good Start Matters mHealth Parenting Program in improving parenting and coparenting practices (primary outcomes) and child health behaviors (secondary outcomes) among 2.5- to 6-year-olds.

Methods: This randomized controlled trial will recruit 118 two-parent families (ie, families with 2 caregivers participating in the trial) from childcare centers across British Columbia, Canada. To promote inclusivity, one-parent families (ie, only one parent participating) will also be eligible but will not count toward the target sample size for recruitment purposes. Eligibility criteria include at least one parent having primary custody of a child aged 2.5-6 years, both parents being fluent in English, and each caregiver owning a smartphone device. In addition, children must not have severe limitations that prevent adherence to general nutritional and 24-hour Movement Guidelines, nor can they be undergoing weight management treatment. After baseline data collection, families will be randomized into either the intervention group, which will receive immediate access to the app, or a waitlist control group, which will gain access to the app after the follow-up assessment, approximately 2 months later. Baseline and follow-up assessments will collect data on food, physical activity, and media parenting practices, coparenting agreement, and child eating, active play, and screen time behaviors. To analyze the data while accounting for its nested structure, multilevel mixed-effects models, integrating intention-to-treat principles and imputation techniques when deemed necessary, will be used. Sensitivity dose-response analyses will assess the extent to which differential adherence/exposure to the intervention influences the study's outcomes.

Results: The trial was registered in March 2023. Recruitment took place from November 2023 to January 2025, with 121 two-parent families and 62 one-parent families recruited. Data collection took place between November 2023 and April 2025. Data cleaning and analyses started in May 2025. Results are expected to be published in 2026.

Conclusions: This study will provide critical insights into the efficacy of mHealth interventions to improve parenting and coparenting practices while promoting healthier child behaviors during early childhood. The Good Start Matters mHealth Parenting Program has the potential to strengthen the foundation of family-centered interventions and set a new standard for systemic approaches to early childhood obesity prevention.

Trial Registration: ClinicalTrials.gov NCT05802160; https://clinicaltrials.gov/study/NCT05802160

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International Registered Report Identifier (IRRID): DERR1-10.2196/72642

(JMIR Res Protoc 2025;14:e72642) doi:10.2196/72642

KEYWORDS

parenting practices; coparenting; child health behaviors; mHealth; lifestyle intervention

Introduction

Background

Early childhood is a formative period for developing eating, activity, and screen-time habits, which significantly shape long-term health outcomes, including obesity risk [1,2]. Research [3-11] indicates that the family environment plays a critical role in shaping children's health behaviors through their parenting practices; the goal-oriented strategies parents use to guide their child's behaviors in a given context, such as nutrition or physical activity [7]. Parenting practices are typically categorized into 3 domains [7]: control (coercive and intrusive strategies to manipulate the child's behaviors and emotions); structure (noncoercive practices that organize the child's environment to support healthy habits); and autonomy promotion (strategies that encourage healthy habits while fostering independence and psychological autonomy). Structured and autonomy-promoting practices are associated with healthier diets, higher physical activity levels, and lower screen-time, whereas controlling practices are linked to unhealthy habits and increased obesity risk [3,5,6,8-10].

Despite the well-established influence of parenting practices, key limitations remain in our understanding of the family's role in childhood obesity. First, most studies have focused on a single caregiver (typically the mother) due to maternal predominance in child-rearing and difficulties in recruiting and engaging fathers [11-14]. However, emerging evidence underscores the distinct and complementary roles that mothers and fathers play in shaping child health behaviors. Studies examining feeding, physical activity, and media parenting suggest that mothers and fathers may interact with children in unique ways [3,6,15], potentially offering additive benefits when both caregivers are engaged in interventions.

Second, few studies have considered the coparenting subsystem [16]; that is, how caregivers collaborate in child-rearing and their agreement on parenting strategies, division of labor, and joint family management [17]. While underresearched, evidence suggests that low-quality coparenting (eg, undermining and inconsistent coparenting) can compromise parenting practices and is associated with negative child health outcomes, including increased picky eating, frequent snacking, and obesity [18-22]. Another study shows that children are more likely to meet physical activity guidelines when both parents support active behaviors [23].

Given the critical role of the family system, family-based lifestyle interventions are a cornerstone of childhood obesity prevention and treatment [24-26]. However, in-person programs have modest effects [24], likely due to the aforementioned limitations and practical barriers to participation, such as scheduling constraints and low caregiver engagement. Consequently, digital health interventions, particularly mobile health (mHealth) apps, are increasingly being used to support parenting and promote healthy behaviors in children. mHealth platforms offer advantages over traditional delivery formats, including accessibility, cost-effectiveness, scalability, and real-time feedback to support participant engagement [27,28]. These features could potentially help overcome persistent challenges in family-based interventions, such as reaching multiple caregivers. A 2023 integrative review [29] found that parents valued the flexibility and convenience of digital delivery, especially the ability to participate from home at times that suited their busy schedules.

Recent systematic reviews and meta-analyses [30-33] have shown promising, yet mixed, outcomes for mHealth interventions targeting childhood obesity. Programs grounded in behavioral theory, particularly social cognitive theory (SCT) and self-determination theory, and incorporating diverse behavior change techniques (BCTs), such as goal setting, feedback, monitoring, and social support, are more effective [32-34].

However, important gaps persist as most mHealth interventions focus on school-aged children and adolescents, with limited attention to the early years (2-5 years) [27,32,35]. When younger children are included in such interventions, weaker effects emerge among them, particularly for physical activity [32,33], possibly due to greater reliance on childcare providers. This highlights the need for early childhood interventions that explicitly target parenting practices. Surprisingly, parenting practices are rarely primary outcomes in these interventions, which often focus on more distant health outcomes such as child behaviors and weight [27,30-32,34-36], thereby overlooking the parenting strategies that influence them. Moreover, when parenting practices are targeted, the emphasis is on controlling practices, with less attention to positive parenting practices such as structure and autonomy promotion, and with effects that often diminish over time [31]. To address these shortcomings, Wang et al [31] have called for future trials to target a broader range of parenting practices. We further suggest that intervention effects may be strengthened by supporting a more unified caregiving approach. However, coparenting remains notably underrepresented in mHealth interventions aimed at preventing childhood obesity.

To address these limitations, we developed the Good Start Matters mHealth Parenting Program, a theory-informed mHealth intervention designed to promote both individual parenting practices and collaborative coparenting strategies in the context of child eating, physical activity, and screen-time routines during early childhood. This protocol describes the randomized controlled trial (RCT) testing the efficacy of the Good Start Matters Parenting Program.

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Purpose and Hypothesis

The RCT described in this protocol evaluates the efficacy of an mHealth intervention aimed at improving parenting and coparenting practices (primary outcomes) and child health behaviors (secondary outcomes) in families with children aged 2.5-6 years. We hypothesize that families participating in the intervention will show significant improvements in parenting practices (increased structure and autonomy promotion, reduced control), coparenting agreement/consistency, and children's health behaviors (eating, active and outdoor play, and screen-time) compared with control group families.

Methods

Study Design

With an experimental design, this article presents the protocol of a 2-arm RCT evaluating the efficacy of the Good Start Matters mHealth Parenting Program; an 8-week intervention targeting positive parenting and coparenting practices and healthy child behaviors among British Columbian families with young children. Participating families will complete baseline assessments and then be randomized into an intervention or a waitlist control condition, with the former giving families access to the mHealth app immediately after baseline, and the latter providing families with app access after the follow-up assessment, approximately 2 months later (Figure 1).

Figure 1. Flow diagram depicting the study's methodology.

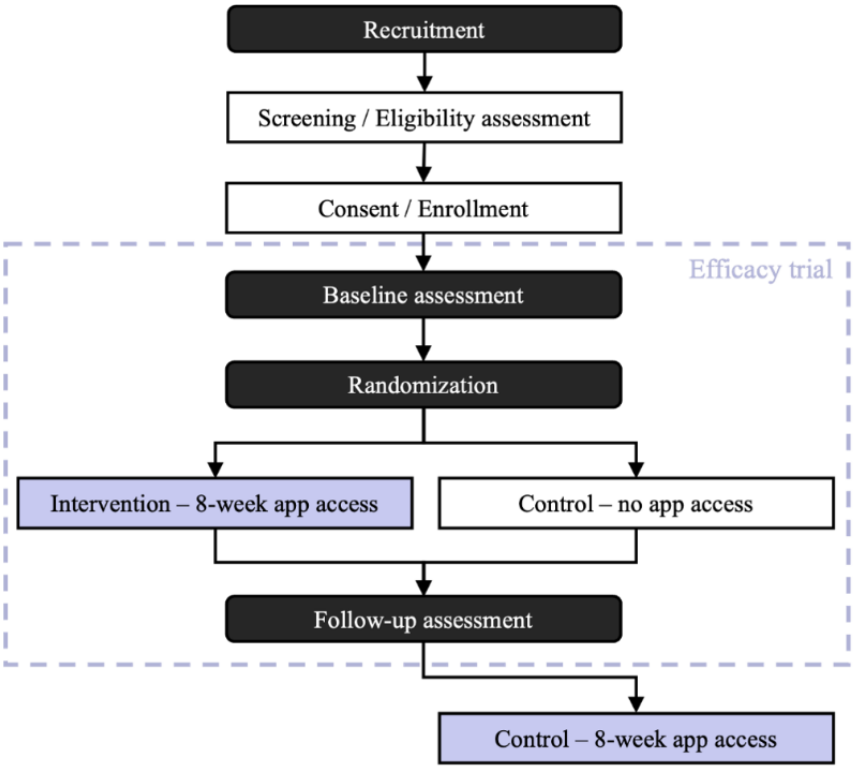

Ethical Considerations

This RCT was approved by the Research Ethics Board of the University of British Columbia (UBC, H18-01434), and all procedures were conducted in accordance with UBC's ethical standards, as well as the 1964 WMA Declaration of Helsinki and its later amendments. The trial was prospectively registered in ClinicalTrials.gov in March 2023 (NCT05802160). This protocol has been described in compliance with SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials [37]), and the trial will be conducted and reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials [38]) and the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist for reporting electronic and mHealth applications [39]. All participants will be requested to read and sign an informed consent, which will explain the nature and consequences of participating in this study, prior to enrolling in the study. Participants will be able to either sign a web-based consent in REDCap (Research Electronic Data Capture [40]) using the E-Consent framework or on paper. Participation in this trial will be entirely voluntary, and withdrawal will be permitted at any time without consequence. In such cases, participants will decide whether data collected up to that point will be retained or destroyed. While no known risks to families are anticipated, the use of the app may prompt parents to reflect on or discuss their parenting and coparenting practices, which could cause some discomfort for some individuals. Therefore, a list of support resources will be provided to all participants. All data will be kept strictly confidential and anonymous, deidentified using unique participant codes, stored securely on encrypted servers at the University of British Columbia/BC Children's Hospital Research Institute, and accessible only to the research team. Only deidentified findings will be disseminated through academic publications, conferences, and other media.

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Participants will receive a CAD $20 (US $15) gift card for each completed survey (baseline and follow-up). Those who complete both surveys will also be entered into a draw to win a CAD $100 (US $73) gift card, with 1 in 30 odds of winning.

Recruitment

This RCT will recruit families through their childcare centers, leveraging the recruitment infrastructure of a parallel RCT, the Good Start Matters Appetite to Play Plus (ATP+) study [41], which targets group-licensed childcare centers across the Greater Vancouver and Victoria areas in British Columbia. The ATP+ study evaluates an implementation support intervention in childcare settings and does not overlap or interfere with this parenting program. Managers of childcare centers invited to ATP+ will be asked to assist with recruitment by displaying advertisement posters for the parenting RCT at their facilities and distributing information packages to parents (printed and over email). Parents can enroll in the parenting RCT through various methods; scanning a QR code provided on the poster or in the printed invitation letters, accessing a URL link sent via email, or completing and signing a paper consent form which will be returned to the childcare facility, where the research team will collect and enter the information into REDCap, hosted at the BC Children's Hospital Research Institute.

Participant Eligibility

Eligibility will be assessed via screening questions included at the beginning of the consent process. Eligible families will then finalize the consent process and receive an automated email with a link to complete the baseline assessment. Participating caregivers must include at least one parent with full or partial custody of their child (families with more than one child can enroll, but data on parent-child interactions and child health behaviors will only be collected for one of their children aged 2.5-6 years). A second caregiver (eg, biological parent, adoptive parent, step-parent, grand-parent) residing with the child most of the time and engaged in child-rearing responsibilities during the study period will also be eligible to enroll. To participate in the program, families will have to meet the following criteria:

- At least one of the caregivers must have primary or shared custody of the child.
- Caregivers must be able to read and understand English.
- Caregivers must each own a smartphone device supporting the app.
- Children should not currently be participating in a pediatric weight management or nutritional program.
- Children should not have severe dietary or physical restrictions that would prevent them from adhering to Canadian dietary and 24-hour Movement Guidelines.
- Children must be aged 2.5-6 years. Note that this range was selected to target a critical window in early childhood, as the years from age 2 to 5 are pivotal for consolidating healthy behaviors and sustaining developmental gains [2]. Evidence indicates that multicomponent interventions combining diet and physical activity are effective for preventing and treating overweight and obesity in children up to the age of 6 years [42,43]. The upper limit also reflects the recruitment context in childcare settings, where some children are slightly older than 5 years but share similar routines, developmental characteristics, and caregiving environments with younger peers, thereby maintaining the intervention's ecological validity in this context.

Sample Size

The sample size calculation for this RCT is based on the primary outcome: parenting practices. The study is designed to achieve 80% power at an α level of 0.05 to detect a group difference of 0.5 points on a 5-point Likert scale (10% change), assuming a SD of 0.8. This 0.5-point difference corresponds to an effect size of Cohen *d* of 0.63, calculated as the mean difference divided by the anticipated SD (ie, 0.5÷0.8=0.63). According to Cohen conventional thresholds, where small effect >0.2, moderate effect >0.5, and large effect >0.8 [44], a *d* of 0.63 represents a moderate effect size. The assumed SD of 0.8 is drawn from secondary data analyses [4,45] of the measurement study that developed the PAPP and FPP item banks, which are the instruments used in this study. Based on this calculation, a minimum of 41 families per group (82 families in total) is required [46]. To account for an anticipated 30% attrition rate and missing data, informed by a previous Canadian study engaging one caregiver per family in an mHealth lifestyle intervention for pediatric obesity [47], we estimate that at least 118 families will be needed for this RCT. Given the additional challenges associated with recruiting a second caregiver and, in particular, fathers [13], the target sample size specifically refers to 2-parent families, defined, for the purpose of this study, as a family where there are 2 caregivers participating in the trial. However, to promote inclusivity and support diverse family structures, one-parent families (ie, families with only one caregiver participating in the trial) will also be eligible to participate and be included in the overall sample (provided that they meet the eligibility criteria) without counting them toward the target sample of 118 two-parent families. Therefore, recruitment will stop once 118 two-parent families have been randomized, which may result in a larger overall sample size.

Randomization

Families will be randomly assigned to intervention or waitlist control groups using a computer-generated randomization schedule created via Sealed Envelope [48]. Block randomization will be used with block sizes of 2, 4, and 6, and a 1:1 randomization ratio. The allocation schedule will be securely concealed within the randomization module of REDCap and will only be revealed after all participating caregivers in a family have completed the baseline assessments. To ensure integrity, research team members will not create, access, or modify the allocation schedule, as it will be fully computer-generated. Families will not be blinded to their group assignment because intervention group families will require immediate app access. Similarly, research team members will need to know the families' group assignments to register them on the mHealth platform and follow up with them if technical issues arise. However, the randomization group will remain concealed from researchers during the data cleaning and analysis stage to minimize bias.

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The Good Start Matters mHealth Parenting Program

Theoretical Underpinning

The Good Start Matters mHealth Parenting Program will be heavily grounded in SCT [49,50], while also integrating critical constructs from Systemic and Structural Family Theories (SSFTs) [16,51] to enhance parenting and coparenting practices in support of children's healthy behaviors. SCT highlights the interplay between personal, behavioral, and environmental influences that shape human behavior, recognizing the individual's abilities to alter environments to suit their purposes (a concept known as reciprocal determinism [49,50]). Similarly, SSFT views the family as a complex system; a deeply connected, changing collection of parts, subsystems, and family members, where each member has a known purpose or function [52]. SSFT recognizes that the behaviors of one member impact the entire system, and change requires addressing the behaviors of all individuals that are part of the system [52]. Therefore, this mHealth intervention will focus on supporting multiple caregivers within the family with strategies to create health-promoting home environments that enable parental use of best practices to promote children's health and well-being.

This intervention will leverage SCT's focus on outcome expectation [49,50] by linking specific parenting behaviors to measurable child health outcomes, helping parents visualize the long-term benefits of their efforts over short-term challenges. In addition, it will encourage parents to communicate with their child about the importance of adopting healthy lifestyle behaviors. To help parents navigate barriers, the program will incorporate strategies such as self-monitoring, goal-setting, feedback, and social support to build the practical self-regulatory skills necessary for changing and sustaining behavior change as described in the next section. Through this program, parents will also be encouraged to use autonomy-promoting parenting practices thought to facilitate self-regulatory skills in children [7] and support their development toward becoming adults capable of making healthy decisions.

Self-efficacy, another cornerstone of SCT [49,50], is thought to be essential for driving behavior change. This mHealth intervention will use diverse approaches (eg, verbal encouragement, peer-modeling) to enhance both parents' and children's confidence in their ability to adopt and sustain positive practices and healthy behaviors. Moreover, SCT also emphasizes collective efficacy, the shared belief in a group's ability to achieve desired outcomes [49,50]. Similarly, SSFT highlights the importance of parents' confidence in their leadership roles within the family hierarchy, while also promoting an appropriate family structure [16] (defined as an invisible set of functional demands that organize the ways in which family members interact, including the subsystems, boundaries, hierarchies, and coalitions [16,52,53]). A critical subsystem within the family is the coparenting subsystem. As such, this mHealth intervention will engage both parents in activities that promote collaborative teamwork, shared goal-setting, collective responsibility, and reinforcement of each other's efforts to strengthen the coparenting subsystem's capacity to create a cohesive home environment. Through topics such as environmental control, consistent parenting practices, rule-setting, and operating conditioning, this intervention aims to empower coparents to establish stable family hierarchies [16,53] where they can confidently guide their children while continuing to promote their psychological autonomy.

Observational learning is another SCT mechanism integrated into this intervention [49,50]. Coparents will model and learn from each other's parenting practices, observing the outcomes in their child and adapting their practices accordingly. This approach is expected to be effective because parents within the family likely face similar challenges, making peer-modeling relatable and actionable. Parental healthy lifestyle modeling will also be encouraged to help children engage in healthy behaviors [7].

Finally, recognizing that behavior change requires supportive environments [49,50], the program will provide facilitation strategies to remove potential barriers, as suggested in SCT. Program resources such as educational materials, step-by-step guides to implement positive practices, case scenarios, family-friendly recipes, suggestions for active play activities, and effective communication tips will help families address potential structural challenges (both physical and relational), make changes more accessible and sustainable, and facilitate children's healthy lifestyles as they grow by modifying their home environment.

Program Design and Behavior Change Techniques Included

Overview

The program was initially pilot-tested with 2 families with toddlers and preschoolers, providing early insights into its feasibility and acceptability. A follow-up qualitative study, approved by the Research Ethics Board at UBC, will further explore participants' perspectives on the intervention, including its perceived efficacy and feasibility.

To facilitate changes at both individual and family levels, this intervention will integrate a variety of evidence-based BCTs [54] across 9 modules delivered weekly over 8 weeks (see screenshots of the intervention in Figures 2 and 3). Each weekly module will be designed to take approximately 20 minutes to complete, including reviewing the core educational content and interactive elements. Additionally, caregivers will be encouraged to engage in independent activities such as goal setting, reflection exercises, and communication with their coparent, which are not counted toward the estimated 20-minute time commitment.

Reminders and notifications will be sent to participants every time a new module is released. Specifically, each week, participants will receive an automated email reminder informing them that a new module has been released. In addition, when participants set a goal within the app, they will be prompted to configure in-app notifications, which they may choose to enable to receive reminders related to their goal completion or review.

The text below provides a general description of each module, and illustrates examples of alignment between the program's goals and evidence-based BCTs based on the taxonomy of Michie et al [54].

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Figure 2. Screenshots of the Good Start Matters mHealth (mobile health) Parenting Program focused on feeding practices.

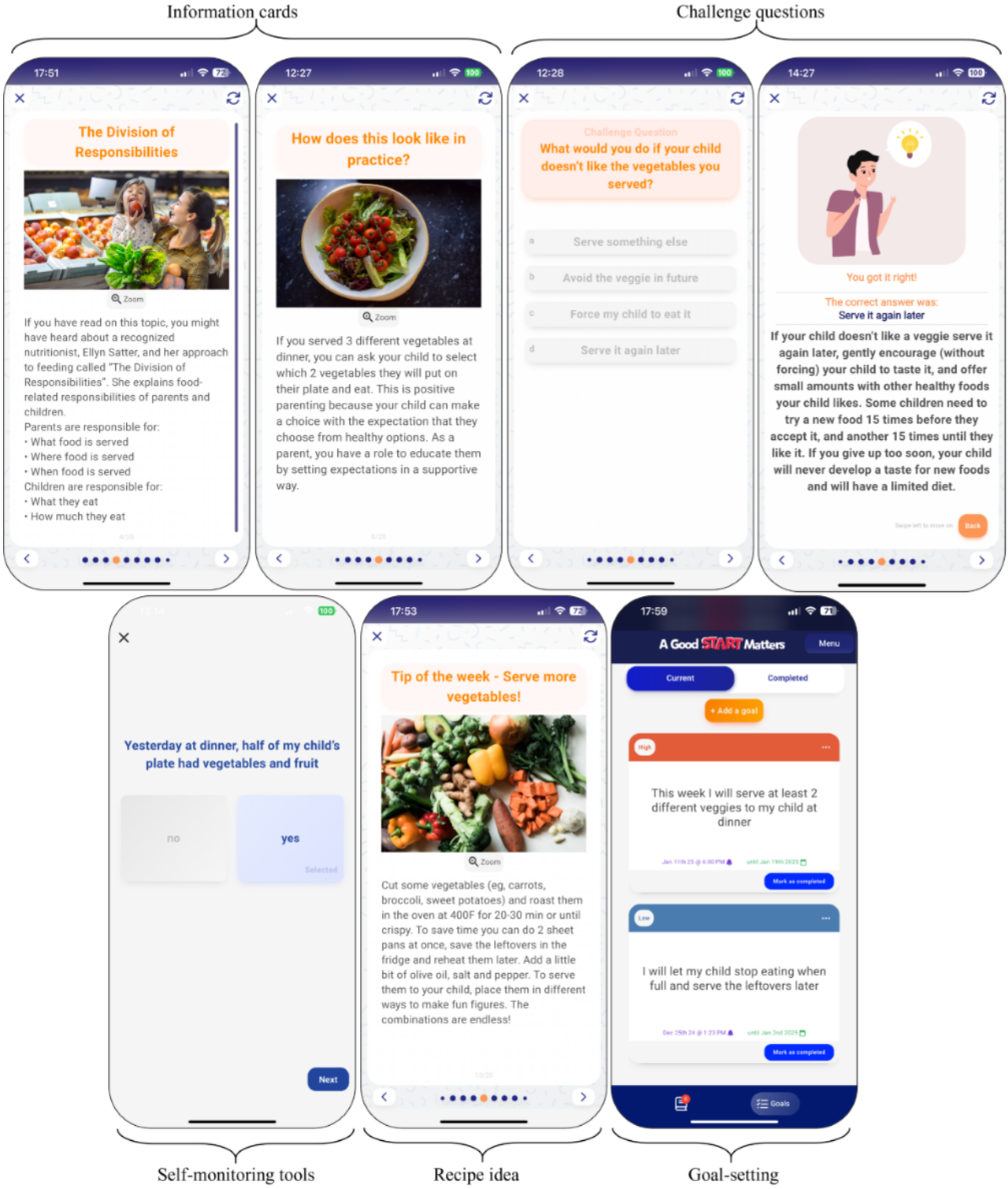

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Figure 3. Screenshots of the Good Start Matters mHealth (mobile health) Parenting Program focused on physical activity.

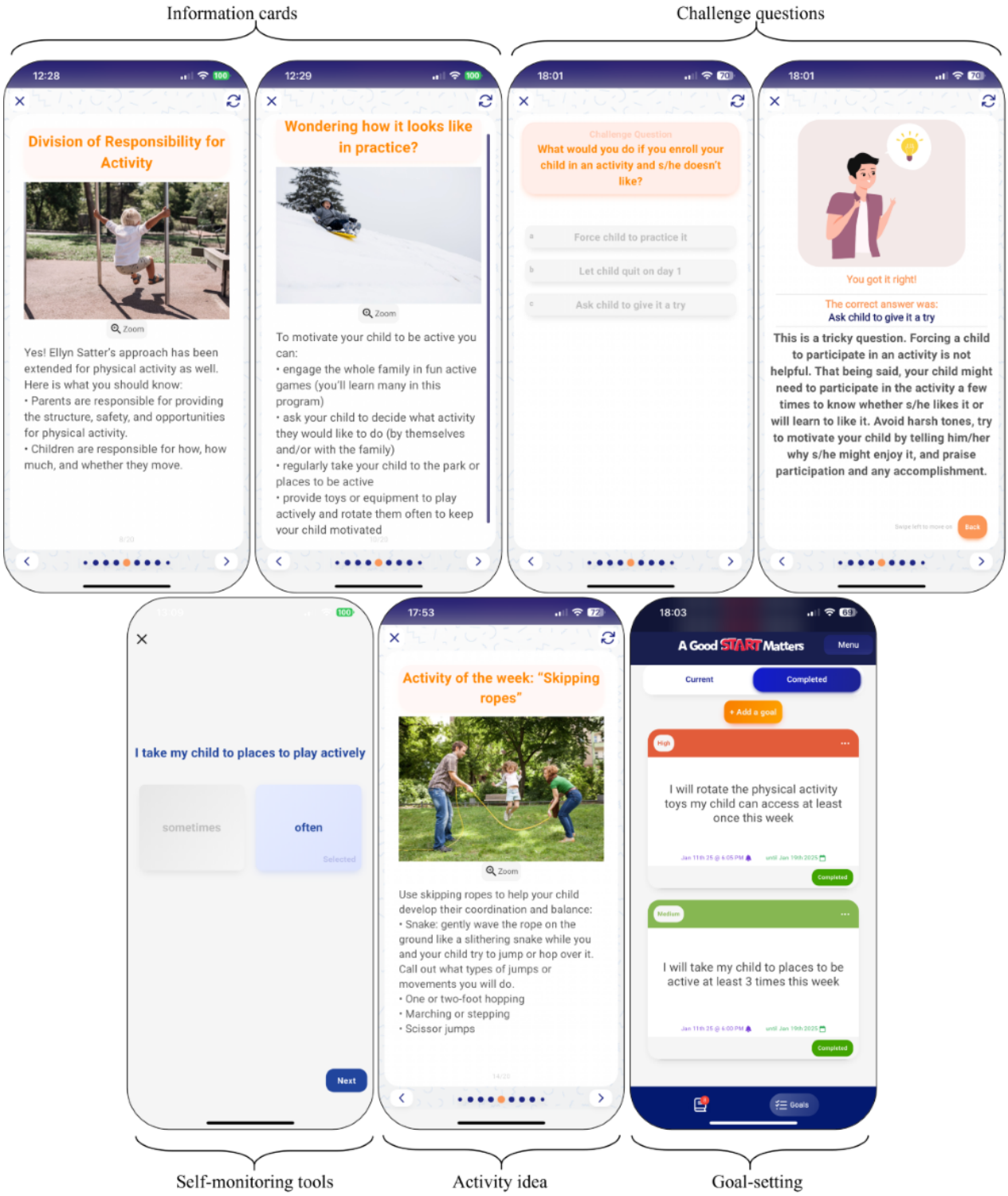

Module 0: Welcome

This introductory module will offer a general overview of the app's functionality and features, outline the content to be covered, and provide access to reliable information sources and external services for more specialized needs.

Module 1: Get Ready to Make Changes

This module will introduce parents to foundational concepts, goals, and expectations for young children. Recommendations will be related to healthy eating, active play, and screen time based on the Canadian Food Guide [55] and the Canadian 24-hour Movement Guidelines [56]. This module will also highlight the importance of developing fundamental movement skills such as balancing, locomotion, and coordination to support engagement in more complex physical activities later in life [57,58]. Using self-assessment tools integrated into the app, parents will evaluate their child's current health habits, identify areas for improvement, and set goals.

Examples of BCTs [54] included in this module are as follows:

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- Shaping knowledge: Structure of a healthy plate; screen time, and active play guidelines; what are fundamental movement skills (balancing, locomotion, and coordination).
- Natural consequences: Benefits of promoting healthy eating, active habits, and fundamental movement skills.
- Comparison of outcomes: Citing Canada's Food Guide [55], and 24-hour Movement Guidelines [56] as credible sources.
- Monitoring and feedback: Evaluation of the extent to which the child meets health behavior guidelines.
- Goals and planning: To serve a healthy plate and facilitate active play.
- Rewards and threats: Encouragement to use reward charts with the child.

Module 2: Divide Responsibilities

This module will focus on the division of responsibilities in dietary and activity contexts, drawing from Ellyn's approach [59,60]. Parents will learn to differentiate between their role in providing healthy options and their child's role in making decisions from the healthy options offered ("the parent provides, the child decides"). Practical examples will demonstrate how to implement this approach in real-life situations, while challenge questions will help parents anticipate and apply strategies in daily life. Self-assessment tools will encourage reflection on how well parents currently provide healthy opportunities for their child to make age-appropriate decisions, and recommended goals will emphasize both exposure to healthy options and child decision-making.

Examples of BCTs [54] included in this module are as follows:

- Shaping knowledge: Division of Responsibilities in eating and activity; exposure to healthy foods; facilitation and support for active play; reducing pressure and forceful practices.
- Natural consequences: Benefits of providing options within boundaries and encouraging age-appropriate decisions.
- Generalization of target behavior: Division of responsibility concept initially taught in the nutrition context and then extended to active play situations.
- Comparison of outcomes: Citing Ellyn's Division of Responsibility approach as a credible source [59,60].
- Monitoring and feedback: Evaluation of the extent to which the parent provides healthy opportunities and challenge scenarios on how to deal with a picky eater.
- Goals and planning: To serve 2+ veggies at dinner; engage in suggested fundamental movement skills activities; or take children to places to be active.
- Rewards and threats: Evaluative feedback to parents after completing self-monitoring tools and challenge questions.
- Self-belief: Encouragement of gentle parental persuasion to promote child engagement in healthy behaviors.

Module 3: Provide Opportunities

Centered on stimulus control [61,62], this module will emphasize the role of parents in modifying the home environment to promote healthy habits, such as managing food accessibility, removing screens from bedrooms, rotating active play equipment, and offering opportunities for both organized and unstructured physical activities. Parents will critically examine their home environment to identify and modify unhealthy stimuli, aiming to "make the healthy option the easy choice." Self-assessment tools will evaluate how well the home environment supports healthy behaviors, challenge questions will address common barriers, and recommended goals will focus on increasing the availability of healthy options at home.

Examples of BCTs [54] included in this module are as follows:

- Shaping knowledge: Controlling stimulus and environmental antecedents of unhealthy habits at home, exposure/availability of healthy foods, and facilitation of active play.
- Natural consequences: Benefits of exposure to healthy environments.
- Antecedents: Adding objects and modifying the home environment to facilitate adoption of healthier behaviors.
- Generalization of target behavior: Stimulus control and repeated exposure concepts initially taught in the nutrition context and then extended to active play.
- Monitoring and feedback: reflection on what the child's home environment stimulates and a scenario on how to deal with a child rejecting a specific sport class.
- Goals and planning: To cook healthy plate meals; plan healthy snacks ahead of time; rotate active play toys; or look for sport/dance classes.
- Rewards and threats: Evaluative feedback to parents after completing self-monitoring tools and challenge questions.
- Social support: Encouragement of parental practical, emotional, and unspecified support for children to engage in healthy behaviors.
- Associations: Prompts/cues in the environment to influence parent and child behaviors; remove rewarding stimulus at home.

Module 4: Engage Your Family

This module will highlight the role of family interactions in fostering healthy lifestyle behaviors. Parents will learn to model healthy habits, such as eating nutritious meals and staying active, and to establish family routines that support positive modeling. It will emphasize the importance of family meals and shared activities, providing practical tips for making these experiences enjoyable. Self-assessments will evaluate current family routines and modeling behaviors, while recommended goals will focus on family-centered activities like regular family meals and fun active games together.

Examples of BCTs [54] included in this module are as follows:

- Shaping knowledge: How to establish family-centered routines and create opportunities for modeling family-based interactions.
- Natural consequences: Benefits of family-based activities and positive/healthy role modeling.
- Antecedents: Advice to maximize quality family time, modeling, and positive experiences.
- Generalization of target behavior: Healthy plate concept initially focused on child meals, further extended to the whole family; focus on creating regular family meals and active time.

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- Monitoring and feedback: Evaluation of current family activities and the extent to which parents model healthy habits.
- Goals and planning: To coparticipate in active play; eat a healthy plate in front of the child; or have family meals.
- Rewards and threats: Evaluative feedback to parents after completing self-monitoring tools and challenge questions.
- Identity: Framing parents as key role models.
- Social support: Promotion of parental support (practical, emotional, and unspecified) to engage children in healthy behaviors.
- Self-belief: Encouragement of gentle parental persuasion to promote child engagement in healthy behaviors.
- Associations: Ensuring fun/enjoyable games are part of family physical activities and mealtimes.

Module 5: Create Routines

This module will emphasize the importance of structure and boundaries in fostering healthy routines. Parents will learn to establish consistent mealtimes, manage screen time, and create predictable schedules that support healthy habits. The module will highlight the need to place limits on less healthy behaviors, such as unhealthy food intake and excessive screen time, while encouraging active play without unnecessary restrictions to support the development of fundamental movement skills. Practical tips will include creating screen-free zones, setting rules around sugary treats, promoting outdoor exploration, and prioritizing family-centered activities. Self-assessments will help parents evaluate their current boundaries, and recommended goals will include pairing limits with education to encourage outdoor play and consistent meal routines.

Examples of BCTs [54] included in this module are as follows:

- Shaping knowledge: Creating routines, setting boundaries and limits in foods and screen time, and rethinking risky play boundaries.
- Natural consequences: Benefits of predictable environments; eating without distractions; consequences of highly processed foods intake, and risky play restrictions.
- Repetition and substitution: Focus on creating regular family meals and active time; replacing screen time during meals with fun-fact activities.
- Monitoring and feedback: Evaluation of the extent to which parents have boundaries and regular routines at home.
- Goals and planning: To eat meals and snacks at regular times; limit treats and sugary drinks or screen time; or let the child explore their limits at the playground.
- Rewards and threats: Evaluative feedback to parents after completing self-monitoring tools and challenge questions.

Module 6: Give Positive Feedback

Based on operant conditioning principles [63] ("behaviors depend on their consequences"), this module will teach parents how to respond to their child's actions. Practical tips and examples will demonstrate how to use differential attention to reinforce only healthy behaviors with effective feedback methods [61,62], including verbal praise, nonfood/nonscreen rewards, physical gestures, and second- or third-hand compliments engaging multiple caregivers. Self-assessments will help parents reflect on whether they are reinforcing healthy behaviors or unintentionally encouraging negative ones, challenge questions will provide practice scenarios (eg, managing food-related tantrums), and recommended goals will emphasize using some of the feedback techniques provided.

Examples of BCTs [54] included in this module are as follows:

- Shaping knowledge: How to respond to child health behaviors to increase/decrease the likelihood of occurrence; how to deal with tantrums.
- Natural consequences: Consequences of different types of parental immediate responses to child behaviors (ie, reinforcing, punishing, or ignoring).
- Monitoring and feedback: Evaluation of the extent to which parents reinforce healthy or unhealthy child behaviors.
- Goals and planning: To provide positive feedback after healthy eating or small rewards for active behaviors, or use second-hand praising techniques.
- Rewards and threats: Evaluative feedback to parents via self-monitoring tools and challenge questions; encouragement of incentives and reward systems for children based both on effort and outcomes.
- Social support: Encouragement of parental practical, emotional, and unspecified support for children to engage in healthy behaviors.
- Self-belief: Encouragement of gentle parental persuasion to promote the child's active role and engagement in healthy behaviors.
- Associations: Removing rewards for unhealthy behaviors.

Module 7: Involve Your Child

This module will focus on providing guidance and education on how to involve children in age-appropriate decision-making to promote psychological autonomy. Parents will learn strategies such as involving their child in simple meal preparation tasks (eg, washing vegetables, arranging ingredients) and teaching physical skills (eg, biking, kicking a ball) paired with gentle encouragement to help children understand the benefits of healthy choices, read their body signals, and feel motivated to participate in physical activities without pressure. Self-assessment tools will help parents reflect on how much autonomy their child currently has, and recommended goals will focus on empowering children to make simple decisions within a range of only healthy options.

Examples of BCTs [54] included in this module are as follows:

- Shaping knowledge: How to promote children's autonomy and skills to make healthy choices as they grow through age-appropriate decisions, education, and guidance.
- Natural consequences: Benefits of supporting the child's decision-making process within boundaries.
- Generalization of target behavior: Child involvement in simple tasks and decision-making was first presented in the nutrition context and then extended to the activity context.
- Monitoring and feedback: Evaluation of the extent to which the child can decide on their own activity and eating habits within boundaries.
- Goals and planning: To respect children's satiety cues; involve them in simple meal preparation; or ask about preferred physical activities to try.

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- Rewards and threats: Evaluative feedback to parents via self-monitoring tools and challenge questions.
- Social support: Encouragement of parental support (practical, emotional, and unspecified) to engage children in healthy behaviors.
- Self-belief: Encouragement of parental persuasion to promote the child's active role and engagement in healthy behaviors.

Module 8: Work as a Team

This module will address the importance of positive coparenting practices to strengthen the coparenting subsystem and create a consistent and supportive environment. Parents will be encouraged to collaborate with other key caregivers to agree on goals, expectations, and practices, facilitated by effective communication and cooperative decision-making tips. Self-assessment tools will evaluate alignment in coparenting practices, and recommended goals will emphasize partnership and collaboration in child-rearing tasks related to lifestyle habits.

Examples of BCTs [54] included in this module are as follows:

- Shaping knowledge: How to engage in positive coparenting practices; effective communication; cooperative and consistent practices around child lifestyle habits.
- Natural consequences: Consequences of disagreements and conflicts in front of the child; inconsistent approaches and lack of structure.
- Monitoring and feedback: Evaluation of the extent to which coparents' expectations, goals, and practices about the child's behaviors align.
- Goals and planning: To discuss goals and expectations for the child and approaches to meet these goals; praise the coparent for using practices they have agreed on; or provide structure at home.
- Rewards and threats: Evaluative feedback to parents via self-monitoring tools and challenge questions; promotion of social reward to coparent for engaging in an agreed-on parenting practice.
- Social support: Coparents are encouraged to seek help from and support each other to engage in positive parenting practices.

Module 9: Recap and Commit

The final module will summarize the program's content and key takeaways. It will encourage parents to reflect on the things they have accomplished, the resources and skills they can use, and commit to continue using health-promoting parenting and coparenting practices.

Examples of BCTs [54] included in this module the following:

- Shaping knowledge: Recap on health behavior guidelines regarding nutrition, active play, and screen time; recommended autonomy-promoting and structured practices; division of responsibility in nutrition and activity; importance of family-centered activities, and joint family management.
- Monitoring and feedback: Review of progress made; existing strengths, resources, and skills to continue using positive parenting and coparenting practices.
- Goals and planning: Parents asked to make statements and commitments to maintain existing or use new positive parenting and coparenting practices.
- Identity: Framing parents and caregivers as key role models.
- Social support: Encouragement of parental social support for children to engage in healthy behaviors.
- Self-belief: Focus on previous successes in using positive parenting and coparenting practices.

Measures

Overview

Data collection will occur at baseline and follow-up (approximately 2 months after randomization) for all variables listed below except for sociodemographic variables, which will be evaluated only at baseline. Participants will complete all surveys online using REDCap.

Primary Outcomes

Parenting practices related to nutrition and activity will be measured with items modeled after the validated food [64] and physical activity [65] parenting item banks designed for 5- to 12-year-olds, with some questions adapted for younger children (eg, the original item asks "how often do you have your child help prepare dinner meals"), while the adapted item will ask "how often do you involve your child in simple food tasks when preparing meals (eg, help wash vegetables, arrange the vegetables). Both item banks were informed by parenting and obesity experts and have been evaluated for construct validity (ie, designed to capture the 3 parenting domains of control, structure, and autonomy promotion) related to nutrition and active play. These item banks have shown strong psychometric properties, including measurement invariance by parent gender, making the comparisons valid between mothers and fathers, and Cronbach α ranging from 0.67 to 0.96 [64-67]. Additional items on food, physical activity, and media parenting practices were developed for this study to align with the intervention content. Accordingly, we will assess and report on the psychometric properties of the parenting measurement tools used in this RCT, focusing on construct validity (via factor analysis) and reliability (via Cronbach α). Reassessing these properties in the final sample will provide a more accurate evaluation of the validity and reliability of the measures applied in this trial.

Coparenting practices will be evaluated with items adapted from the Agreement subscale of the Coparenting Relationship Scale [17], designed for children aged 6 months to 3 years and further used with children up to 7 years old [18,68]. The scale shows adequate psychometric properties, including construct validity and reliability (Cronbach α ranging from 0.67 to 0.74). The questions will inquire about the level of agreement between key caregivers regarding their expectations, goals, approaches, and conceptions about their child's lifestyle behaviors. Additionally, coparenting practices will be examined in 2-parent families by comparing the parenting practice scores of both parents/caregivers within the family.

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Secondary Outcomes

Child eating behaviors will be evaluated with the Child Eating Behavior Questionnaire [69], examining child emotional overeating, food responsiveness, food fussiness, and satiety responsiveness. This instrument, designed for children aged 2-9 years, has been extensively used, showing adequate psychometric properties, including Cronbach α ranging from 0.72 to 0.91 [69]. In addition, parents will be asked to report on the number of days per week that their child consumes key food markers (ie, fruit and vegetables, fruit juice and sugary drinks, sweet and salty treats), with questions adapted from the Canadian Community Health Survey [70] and the Center for Diseases Control's Behavioral Risk Factor Surveillance System Questionnaire [71] and National Youth Physical Activity and Nutrition Study [72].

Child active and outdoor play will be measured with questions from the instrument designed by Burdette et al [73] for young children. The questions inquire about the number of minutes per day and the number of days per week that the child engages in active and outdoor play on a regular weekday and weekend day.

Children's screen time will be measured by inquiring about the number of days in the previous week that children spent more than 1 hour/day in front of screens, when counting all screen-media devices (eg, TV, computer, tablet, and smartphone).

Covariates

Covariates will include child-level, parent-level, and family-level variables that may have an influence on family dynamics, parenting practices, and child health behaviors. Sociodemographic questions (some created for this study and others adapted from the Canadian Community Health Survey [70] and General Social Survey [74]), will cover child and parent age and sex, parent gender, marital status, education, employment status, cultural/ethnic background, household income, number of households where the child lives in, number of children living at home and their age group, number and type of family members in the household, and familial relationship between participating coparents. In addition, we will evaluate the division of responsibilities between key caregivers regarding child-rearing tasks (eg, grocery shopping, cooking, cleaning, transport, and education) with questions adapted from Musick et al [75].

Intervention Group and Exposure/Adherence

The intervention group will be assessed based on randomization as a binary variable (intervention vs control). Exposure/adherence to the mHealth intervention will be measured with app-analytics data collected with the platform used to deliver the intervention (ie, Pathverse). Pathverse is a no-code app builder platform that supports mHealth research [76,77], making it easy for researchers to create engaging interventions with preprogrammed features (eg, goal setting, monitoring, feedback) that are known to support behavior change [54]. As Pathverse was developed for research, it collects extensive app analytics data, which can then be examined to assess how many and which components of the intervention the users engaged with. Using these data, adherence will be operationalized as the number of modules completed, self-monitoring tools completed, and goals set and completed.

Analyses

Descriptive statistics will be used to summarize the distribution of the data. Baseline comparisons between groups will be conducted using the Student *t* tests or chi-square tests, as appropriate, for continuous and categorical demographics, primary, and secondary outcomes. These comparisons will assess the extent to which differences remain between groups at baseline despite randomization. To evaluate the effect of the intervention, intention-to-treat multilevel mixed-effects models will be used. These models will be linear, ordered, or logistic, depending on the characteristics of the data and whether transformations are required. The models will examine the effects of the intervention on each key primary and secondary outcome, incorporating an interaction term between time point (baseline or follow-up) and randomization group (intervention or control). These multilevel analyses will account for the nested structure of the sample and the longitudinal nature of the data, with parents nested within families and repeated measures over time. Individual- and family-level covariates will be included in the models as appropriate. Secondary analyses will assess whether changes in parenting and coparenting practices, and the interaction between these two, predict changes in child health behaviors using multilevel and structural equation modeling. Additionally, dose-response sensitivity analyses with mixed-effect models will evaluate the relationship between the level of exposure/adherence to the intervention (measured via app analytics) and the magnitude of changes in parenting and coparenting practices and child health behaviors. If deemed necessary, imputation techniques will be applied to address missing data. In such a case, the specific imputation method (eg, multivariate multiple imputation, chained equations) will be selected based on variable types and patterns of missingness detected in the data.

Results

Recruitment was conducted between November 2023 and January 2025, and data collection occurred from November 2023 through April 2025. In total, 121 two-parent families and 62 one-parent families were enrolled. Since May 2025, and as of October 3, 2025, the study has been in the data cleaning and analysis phase, which is expected to be completed by December 2025. Study findings will be reported in 2026, with planned publication and updates to the ClinicalTrials.gov registry. Results will also be submitted to peer-reviewed journals and disseminated at academic conferences.

Discussion

Anticipated Principal Findings

This RCT is designed to assess the efficacy of the Good Start Matters mHealth Parenting Program in enhancing parenting and coparenting practices and promoting healthier child behaviors related to lifestyle habits. We anticipate that families receiving the intervention will demonstrate greater use of

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structured and autonomy-promoting parenting and lower use of controlling practices, stronger coparenting agreement/consistency, and healthier child behaviors, including eating habits, active and outdoor play, and screen time, compared with families in the control group.

Comparison to Prior Work

Family-based behavioral interventions remain the gold standard for preventing and addressing childhood obesity [25,26]. However, many in-person programs predominantly recruit a single caregiver (usually mothers), resulting in limited engagement from fathers or other key caregivers within the family system [13]. These interventions also tend to focus primarily on child outcomes [78], often overlooking important familial mediators such as parenting and coparenting practices, which play a central role in shaping children's health behaviors. In addition, in-person programs face well-documented barriers to adherence and attendance, including financial costs, scheduling conflicts, transportation issues, and other logistical and organizational challenges [78-81].

mHealth interventions offer a promising alternative to address some of these limitations [79], particularly by creating more opportunities for fathers to participate (a strategy recommended for family-based interventions in other child health domains [82]). Beyond their convenience, mHealth platforms can reduce structural barriers such as travel distance, scheduling conflicts, and limited childcare by enabling participation from home or other preferred locations; an aspect parents value for allowing them to integrate sessions into daily routines, choose times that work best for them, and avoid the stress associated with in-person attendance [27-29].

The Good Start Matters mHealth Parenting Program will build on these strengths, using a structured, theory-driven approach informed by SCT and SSFT, and incorporating evidence-based BCTs to equip parents with tools and skills to create a supportive environment for their children's health and development. This approach is consistent with mHealth research showing that programs grounded in these frameworks tend to be more effective [32-34].

However, despite their promise, existing mHealth interventions face challenges similar to those observed with in-person programs [30-33]. Notably, there is a substantial lack of mHealth studies targeting and measuring parenting practices [27,30-32,34-36] and, to our knowledge, none has explicitly focused on coparenting dynamics (despite the well-established influence of the family system and WHO's recommendations endorsing family-based approaches to childhood obesity prevention [25]). The Good Start Matters Parenting Program will address these gaps by targeting both individual parenting practices and coparenting dynamics, aiming to achieve sustainable improvements in both family- and child-level outcomes.

Another key distinction is the focus on early childhood. Most mHealth interventions in this field have focused on older children and adolescents [27,32,35,47], with limited attention to younger age groups. The decision to intervene early is supported by evidence showing that 34% of Canadian toddlers and preschoolers are at risk of overweight or obesity [83] and excess weight gain before puberty largely occurs by the age of 5 years [84], which makes the early years a critical intervention window. Taken together, this study will contribute to the growing mHealth literature by addressing critical gaps in caregiver engagement, coparenting, and early childhood prevention, offering a model that could inform the design of future family-based interventions.

Strengths and Limitations

This study will have some limitations, including a short intervention period and the absence of long-term follow-up assessments, which may affect observations of sustained changes. Future research could incorporate longitudinal designs to better assess longer-term effects. Strengths of this study should also be noted, including the involvement of multiple caregivers and the evaluation of intervention effects across the family system. Moreover, the program's concise, self-paced format, requiring less than 30 minutes per week, will provide flexibility for parents, potentially enhancing adherence.

Conclusions

Overall, this study will provide critical insights into the potential of mHealth interventions to improve parenting and coparenting practices and promote healthier child behaviors during early childhood. By addressing gaps in father engagement and coparenting dynamics, the Good Start Matters mHealth Parenting Program has the potential to strengthen the foundation of family-centered interventions and set a new standard for systemic approaches in childhood obesity prevention. Findings will inform the development of scalable, inclusive mHealth strategies practical for real-world implementation and tailored to diverse family needs, ultimately advancing the field of child health promotion.

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during this study.

Authors' Contributions

OD-JG and LCM contributed to the conceptualization of the study, the methodology, and funding acquisition. OD-JG, LCM, CNTL, and JWTM collaborated on the intervention design and on the reviewing and editing of the manuscript. OD-JG was responsible for visualization, project administration and implementation, and writing of the original draft of the manuscript. LCM provided resources.

Conflicts of Interest

None declared.

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Abbreviations

ATP+: Appetite to Play Plus
BCT: behavior change technique
CONSORT: Consolidated Standards of Reporting Trials
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
mHealth: mobile health
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SCT: social cognitive theory
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SSFT: Systemic and Structural Family Theory
UBC: University of British Columbia

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Protocol

Immersive Reality–Based Training Simulator for Dental Extraction: Protocol for a Randomized Pilot Trial

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Abstract

Background: Dental students' competencies are shaped by their training, yet traditional methods with mannequins often lack the depth necessary for comprehensive understanding, potentially impacting clinical proficiency. Immersive reality (IR) innovatively offers interactive and scenario-based environments that may enhance skill acquisition.

Objective: This study evaluates the effectiveness of IR-based training implementation in comparison with conventional training methods for dental extractions.

Methods: A prospective multicenter randomized clinical trial was conducted. Students were randomized to either IR-based training on open and closed extractions or conventional hands-on tutorials by oral surgeons. Post training, participants' satisfaction and understanding were assessed and analyzed.

Results: As of September 2025, 60 students from Hasanuddin University, Makassar, and Padjajaran University, Bandung, have been enrolled, and study enrollment will be expanded to Universitas Sumatera Utara, Medan. Data collection is ongoing and will conclude in November 2025, with expected dissemination in early 2026.

Conclusions: IR-based training offers a novel approach that may boost motivation, knowledge retention, and skill transfer in dental education. This pilot protocol explores IR's feasibility and potential to advance dental students' competencies.

Trial Registration: Indonesian Clinical Research Registry INA-QES4CC5; https://ina-crr.kemkes.go.id/en/studi/207

International Registered Report Identifier (IRRID): DERR1-10.2196/74978

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KEYWORDS

dental extraction; immersive reality; pilot trial; virtual training; study protocol

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Introduction

Dental extraction is among the most frequently performed procedures in dental practice [1]. Indications for extraction are diverse, including periodontitis, endodontic complications, orthodontic needs, ectopic eruption, prosthetic treatment planning, traumatic injury, and systemic conditions, with dental caries being the most common cause [2-4]. The high prevalence of extractions underscores the importance of equipping dental students with sufficient knowledge, technical proficiency, and clinical competence [5,6].

Conventional training methods and passive observation restrict students' ability to understand the complexity of treatments, particularly within the confined working environment of the oral cavity [7,8]. Moreover, novice dental students often lack familiarity with assisting tasks, reducing training efficiency and learning outcomes. Effective skill acquisition requires not only theoretical knowledge but also spatial imagination, active engagement, and repeated practice opportunities [9-11]. Consequently, extensive training and prolonged clinical exposure are often necessary before dental students achieve the level of competence required to provide safe and effective oral health care [12,13].

Immersive reality (IR), which integrates virtual reality and augmented reality, has emerged as a promising educational technology to overcome these challenges [14-17]. IR provides a safe, realistic, and hands-on platform for students to practice clinical procedures and refine their skills [18-25]. Evidence suggests that IR-based training improves practical competence, treatment planning, and standardized assessment while offering repeatable and engaging learning experiences [26-30]. Importantly, IR technology supports consistent training for complex procedures that demand precision and manual dexterity [31-33]. By addressing limitations of conventional learning—such as high costs, limited patient cases, and restricted opportunities for repeated practice—IR can bridge gaps in skill acquisition, foster collaboration, and enhance creativity in clinical training [34-38].

Despite these advantages, the application of IR as a simulator for dental extraction training remains insufficiently explored. To date, IR technology has been implemented in operative dentistry, periodontology, and dental radiography for practices such as tooth drilling, endodontic cavity access, crown placement, and periodontal procedures [39-43]. Furthermore, none of these applications involves students from multicenter institutions. This study seeks to highlight the use of IR training for dental extractions involving students from multicenter institutions while also generating feedback for further refinement of the simulator and its associated training protocol.

Methods

Apparatus

Unity 3D Engine software (Microsoft Corporation) was used as the platform for simulating dental extraction procedures in an IR environment. This platform enables users to engage from a first-person perspective. In the virtual environment, users can interact with 3D models by using either hand gestures or controllers.

In this study, the IR hardware setup consists of a personal computer featuring an Intel Core i7-11800H chipset and an NVIDIA GeForce RTX 3080 graphics card, which includes a GPU with 10 GB of GDDR6X memory. The configuration also incorporates a Meta Quest Pro 3 (Reality Labs) head-mounted display (HMD). The equipment enables Unity to run at a constant frame rate of over 60 frames per second using the "high quality" display settings of the HMD.

Trial Design and Study Population

Overview

This protocol is for a prospective multicenter randomized clinical trial, which began in March 2025 and is expected to end in November 2025. This protocol outlines our plan to assess the knowledge and skill enhancement of a pilot intervention across three centers: Hasanuddin University (Makassar, Indonesia), Padjajaran University (Bandung, Indonesia), and Universitas Sumatera Utara (Medan, Indonesia). A total of 90 dental students participated in the study (G*Power effect size 0.6, statistical power 85%). All participants enrolled in this study were randomly assigned to either an intervention group (n=15) or a control group (n=15) within each center. We used the block randomization method for the allocation of participants.

Blinding and Calibration of Reviewer

Two independent reviewers (an oral and maxillofacial surgeon) were assigned to evaluate and score each participant's pretest and posttest sheets (Multimedia Appendix 1). Before data collection, the assessors underwent a calibration session to standardize the answer key for the multiple-choice questions (MCQs) and ensure consistent scoring. During the study, the assessors were blinded to the participants' identities and allocation status, as they did not have access to names or group assignments. A final score for each participant was calculated.

Additionally, the reviewer will assess the participants' training videos, focusing on training time completion, in-app lag or confusion, and skipped steps, to evaluate participants' performance during training.

Informed Consent

Before participating in this study, the research assistant explained the trial flow and procedures for both the IR-based training and the conventional training. All participants will receive a brief introduction to the study and will have the opportunity to ask questions about the study procedures. After the participants provide their written informed consent (Multimedia Appendix 2), their basic health status will be recorded (Multimedia Appendix 3). Participants who are unable to give consent will be excluded from the study.

Inclusion Criteria

Participants will be enrolled from the Universitas Sumatera Utara, Hasanuddin University, and Padjajaran University. Eligible participants must be 20 years or older and be currently enrolled in their third year of dental school or have completed

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a minimum of seven semesters. They should have completed tutorials on both the open and closed methods of tooth extraction, possess knowledge of medical technology, and be capable of providing informed consent. Individuals who are unable to engage with virtual content for a minimum duration of 10 minutes while using an HMD will be excluded from participation.

Exclusion Criteria

Individuals who are unable to provide informed consent, possess health complications, display symptoms of cybersickness (eg, dizziness, disorientation, or vomiting) during training sessions, or are unable to complete the training session are excluded from participation. Additional exclusion criteria encompass a history of hallucinations, panic attacks, seizures, phobias (including claustrophobia and acrophobia), or active alcohol or substance abuse.

Intervention Group

Before the intervention, two oral and maxillofacial surgeons from each center will follow a comprehensive meeting held in Hasanuddin University, Makassar, to ensure consistent delivery of the interventions across centers and instructors. In addition, a facility assessment will be reported during the meeting to ensure that each center can deliver the intervention method using the same protocol.

Participants will be given a brief introduction and explanation of the study's purpose. A research assistant will present the informed consent both in writing and verbally. This study has adopted standardized procedures for tooth extraction, using both open and closed methods.

The IR training session will be conducted in a standing position, where participants role-play as dentists. The training session will focus on open and closed dental extraction for the first molar tooth (tooth 46), supervised by two oral and maxillofacial surgeons in each center. For all training sessions, the first 10 minutes will be conducted under direct supervision. Participants will then continue their sessions for the last 40 minutes using in-app assistance (sound, highlighted areas, and arrows) without additional support for the remaining session.

The IR HMD wirelessly streams to an external device and will be used during the first session to monitor the participants' training execution and provide guidance when necessary. Participants were required to complete a full round of training. This procedure included several steps: administering local anesthesia, making an incision and separating the tooth (in open method extraction mode), luxating and extracting the tooth, performing curettage, irrigating the wound, and suturing.

Following the completion of the procedure, participants are presented with the option to either restart the training sessions by selecting the reset button or terminate the session by choosing the exit button located in the menu area.

Control Group

Participants in the control group visited the Department of Oral and Maxillofacial Surgery at their origin center (Hasanuddin University, Padjajaran University, or Universitas Sumatera Utara) to receive a tutorial and hands-on laboratory instructions. Following a 10-minute lecture on the open and closed methods of dental extraction for the first molar tooth (tooth 46), participants will engage in hands-on training where they will extract artificial teeth from a phantom or mannequin, much like in the IR-based instructions. The hands-on training will have a duration of 40 minutes, starting from local anesthesia administration, gingival incision, tooth separation, tooth luxation, extraction, curettage, wound irrigation, and suturing. Tutorial and hands-on training will be guided by two oral and maxillofacial surgeons in each center. The trial flowchart is shown in Figure 1. To ensure a standardized methodology for conducting and reporting the trial, the SPIRIT (Standard Protocol Items for Intervention Trials) guidelines will be followed as shown in Table 1.

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Figure 1. Research flowchart. CVEQ: Clinical Virtual Evaluation Questionnaire; INRQ: Immersive Reality Neuroscience Questionnaire; IRTS: Immersive Reality Training System.

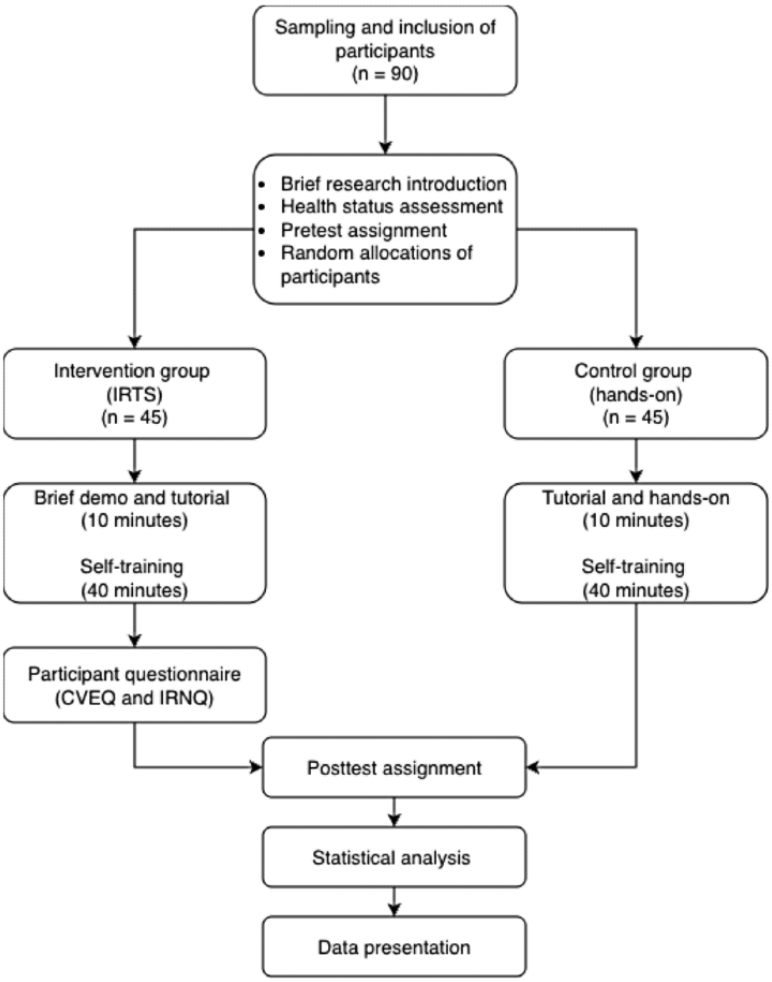

Table 1. SPIRIT (Standard Protocol Items for Intervention Trials) participant timeline.

Timepoint	Enrollment (t_{-1} to t_0)	t_0	Postrandomization (t_1; May 2025)	Closeout (t_x; Nov 2025)
Enrollment				
Eligibility screen	t_{-1}			
Informed consent	t_{-1}			
Baseline assessment (MCQs[a])	✓			
Randomization	✓			
Intervention/comparator				
IRTS[b] for tooth extraction		Tutorial of tooth extraction	✓	✓
Hands-on training		Tutorial of tooth extraction	✓	✓
Assessments				
MCQ questionnaires	✓			✓
Knowledge improvement, posttest scores				✓
Participants' satisfaction with IRTS				✓

[a]MCQ: multiple-choice question.
[b]IRTS: Immersive Reality Training System.

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Adverse Events

Participants who report feeling nauseated, dizzy, or disoriented, or having other health problems during a training session, will immediately be excluded from the activity. All such complaints will be recorded as cybersickness, and the occurrence of the condition will be noted for future evaluation.

Data Collection

Participants' Experience and Feedback

This study used two distinct questionnaires to assess the participants' perspectives toward the usability of the Immersive Reality Training System (IRTS) for dental extraction training, which were designed based on previous research [44]. The Clinical Virtual Evaluation Questionnaire is structured to gather participants' feedback on interactive education facilitated through simulator training (Multimedia Appendix 4). This questionnaire assesses three key parameters: experience and reliability (questions 1-9), knowledge (questions 10-14), and side effects (question 15). The questionnaire comprises 15 statements, which respondents assess using a Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree). Conversely, the Immersive Reality Neuroscience Questionnaire will assess the system's authenticity, the participants' experiences, and the occurrence of cybersickness (Multimedia Appendix 5). This assessment will concentrate on four principal parameters: user experience (questions 1-5), game mechanism (questions 6-10), in-app assistance (questions 11-15), and IR-induced symptoms and effects (questions 16-20). The questionnaire is composed of 20 questions, which participants will answer using a Likert scale ranging from 1 (extremely poor) to 7 (extremely good). To ensure that the system's quality is deemed suitable for use without causing significant cybersickness, each parameter must meet a minimum threshold (cutoff) score of 25 [45].

Participants' Performance and Knowledge Improvement

To assess the practical skills and knowledge acquired, participants from both the intervention and control groups will be required to complete a pretest prior to the training and a posttest following the training session. The MCQs were administered in accordance with the reference textbook used by the Faculty of Dentistry, as outlined in the dentistry curriculum [46]. The scores ranged from 0 to 100, and the test scores of both groups were subsequently compared. The MCQs are centered on the procedural steps, instrumentation, and guiding principles pertinent to dental extraction. This examination is an established component of the curricula at Hasanuddin University, Padjajaran University, and Universitas Sumatera Utara, aimed at assessing students' practical competencies and theoretical knowledge. Consequently, a comparative analysis test will be used to evaluate the scores obtained from the clinical skill training between these two groups.

Additionally, the performance of participants will be evaluated through recorded video training and will be assessed by an independent reviewer, focusing on training time completion, in-app lag or confusion, and skipped steps. The confidential paper-based data of participants will be securely stored in a locked storage unit at the study site, while electronic data will be maintained in a protected folder on a server at Hasanuddin University, Makassar, Indonesia.

Data Analysis Plan

The data were analyzed using SPSS v.22 (IBM Corp). Both descriptive statistics (frequency, percentage, mean, and SD) and inferential statistics (multivariate ANOVA) were used. A *P* value less than .05 was considered statistically significant.

Ethical Considerations

This study was approved by the Ethics Committee of the Faculty of Dentistry at Hasanuddin University in Makassar, Indonesia, in October 2024 (approval 001/KEPK FKG-RSGMP UH/EE/IX/2024). Written consent was obtained from all participants, and they were also assured that their information would be kept completely confidential. This manuscript is in accordance with the SPIRIT 2025 guidelines (Multimedia Appendix 6) [47].

Results

Study enrollment started in May 2025 and is expected to be completed in November 2025. As of October 2025, we have enrolled 60 participants from two centers (Hasanuddin University, Makassar, and Padjajaran University, Bandung) and will continue recruiting from a third center (Universitas Sumatera Utara, Medan).

The trial was registered in the Indonesian Clinical Research Registry (INA-QES4CC5) on November 18, 2024.

Discussion

Strengths and Limitations

This study uses IR technology to advance the training of dental students in dental extraction methods, allowing them to experience immersive, high-fidelity scenarios that closely resemble actual clinical situations. One of the primary strengths of the IR training program is its incorporation of essential procedures for both open and closed extraction. The adaptation and validation process involves a thorough selection procedure conducted in collaboration with engineering experts. Consequently, the findings will offer both quantitative and qualitative perspectives on the enhancement of participants' abilities. Moreover, the research included dental students from three distinct provinces (West Sumatra, West Java, and South Sulawesi) to provide an in-depth analysis of the potential influence of IR-based training on dental students' skills in performing tooth extractions.

The presence of a control group in this study enables the observation of improvements in dental students. The pre- and posttest MCQs allow not only comparisons within the same group but also evaluation of the IRTS against traditional methods regarding dental students' learning outcomes, thereby strengthening the validity of our findings.

In recognizing the strengths of this study, it is equally crucial to address its limitations. A notable concern is the potential for selection bias, as participants may inherently possess a favorable

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disposition toward technology or virtual reality environments. To mitigate this bias, we have meticulously documented the participants' prior interactions with virtual reality technology and incorporated this information into experience distribution tables.

Challenges

One of the primary challenges in this study is the adaptation of the IR environment to align with actual dental extraction procedures. The IR environment differs from conventional simulation in its representation of communication and interaction, as certain elements, such as natural communication with patients and their relatives, may be absent, while others, including nonverbal cues and nuanced interpersonal behaviors, are often not effectively captured within the IR environment. To address this concern, the IRTS has been developed, featuring interactive questions aimed at enhancing students' comprehension of patient diagnoses. Moreover, evaluators face the ongoing challenge of accurately observing and assessing participant behavior in an IR scenario. To consistently and objectively implement the IRTS, it is essential to have a clear and thorough understanding of participant behaviors, both as they occur in real time and through recorded observations. One significant challenge associated with the implementation of IR technologies in dental education is the cost of procurement [48]. However, recent publications indicate that while the initial investment in IR technology may be substantial, it offers the advantage of providing repeatable training without the need for physical materials. Consequently, it can be used in the long term to reduce the costs associated with practical models for tutorials and hands-on training [49]. As the technology becomes more affordable and user-friendly, its applicability in medical and dental training is expected to grow [49].

Future Implications

In addressing certain limitations of the study, future research could investigate the incorporation of more advanced haptic devices and natural language processing to enhance the realism of the IR environment and more comprehensively capture the full spectrum of participant behavior. As IR technology continues to progress, it is imperative to consistently refine the tools used to ensure they remain congruent with the evolving capabilities of the technology.

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The authors attest that there was no use of generative artificial intelligence technology in the generation of text, figures, or other informational content of this manuscript.

Data Availability

The datasets generated or analyzed during this study will be made publicly available after completion of the study and will be available from the corresponding author upon reasonable request.

Authors' Contributions

ES contributed to conceptualization, reviewing and editing, and data curation. MR contributed to data curation, formal analysis, software, and methodology. OAH contributed to project administration, supervision, and visualization. C Stevanie contributed to writing the original draft, reviewing and editing, and methodology. MA contributed to project administration and software. SHK and TF contributed to conceptualization and investigation. PB and C Sukotjo contributed to supervision and validation.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Pretest and posttest multiple-choice questions.
[DOCX File , 21 KB - resprot_v14i1e74978_app1.docx]

Multimedia Appendix 2
Informed consent form.
[PDF File (Adobe PDF File), 143 KB - resprot_v14i1e74978_app2.pdf]

Multimedia Appendix 3
Health status form.
[PDF File (Adobe PDF File), 39 KB - resprot_v14i1e74978_app3.pdf]

Multimedia Appendix 4
Clinical Virtual Evaluation Questionnaire.

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[PDF File (Adobe PDF File), 47 KB - resprot_v14i1e74978_app4.pdf]

Multimedia Appendix 5
Immersive Reality Neuroscience Questionnaire.
[PDF File (Adobe PDF File), 59 KB - resprot_v14i1e74978_app5.pdf]

Multimedia Appendix 6
SPIRIT 2025 checklist.
[PDF File (Adobe PDF File), 130 KB - resprot_v14i1e74978_app6.pdf]

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Abbreviations

HMD: head-mounted display
IR: immersive reality
IRTS: Immersive Reality Training System
MCQ: multiple-choice question
SPIRIT: Standard Protocol Items for Intervention Trials

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Protocol

A Freely Accessible, Anonymous Online Treatment for Social Anxiety: Protocol for a Partially Randomized Patient Preference Trial

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Abstract

Background: Many people with mental health problems do not receive the care they need. Digital mental health interventions have been shown to be effective in many trials and offer a promising way to reach more people in need. However, their uptake and use remain limited, in part due to concerns about data privacy. However, these concerns may not be equally significant for all users.

Objective: This trial aims to evaluate the efficacy of an anonymous online self-help tool for social anxiety that processes no personal data and has some disadvantages in terms of usability compared to an otherwise identical, nonanonymous evidence-based tool. Furthermore, the trial will investigate user preferences regarding the 2 program versions and evaluate the impact of these preferences on treatment outcomes.

Methods: In this partially randomized patient preference trial, 2 versions (anonymous vs nonanonymous) of the same previously researched program will be compared among 452 participants with increased levels of social anxiety. Half of the participants will be randomized to one of the program versions, whereas the other half will be assigned to their preferred version. The primary outcome is social anxiety symptoms. Secondary outcomes include depression, stigma of mental illness, and quality of life.

Results: Recruitment started in September 2024. As of the date of manuscript submission in May 2025, over 350 participants have been included in the study. Recruitment ended in September 2025, and results are expected to be available and published in 2026.

Conclusions: The results of this trial will determine whether anonymously accessible interventions, which could easily be made freely available, are less efficacious than their nonanonymous counterparts and will explore the impact of user preferences on treatment outcomes. The findings could contribute to making digital interventions more accessible and tailoring interventions to individual preferences.

Trial Registration: ClinicalTrials.gov NCT06465589; https://clinicaltrials.gov/study/NCT06465589

International Registered Report Identifier (IRRID): DERR1-10.2196/77573

(JMIR Res Protoc 2025;14:e77573) doi:10.2196/77573

KEYWORDS

internet-based cognitive behavioral therapy; social anxiety; anonymity; open access; digital mental health intervention; digital health; eHealth

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Introduction

As our lives become increasingly digitalized, one of the biggest challenges of our time is successfully transforming our health care system accordingly. The need for digitalization is especially great in the treatment of psychological issues, where access to care remains a significant issue that could be mitigated with digital solutions. A considerable proportion of individuals with psychological issues do not receive the necessary treatment, with reasons including shortages in personnel and limited awareness of treatment options [1]. Therefore, digitalization is crucial as it offers opportunities to reach more people than traditional methods such as face-to-face psychotherapy.

Digital mental health interventions (DMHIs) have been developed to address a wide range of psychological issues. These interventions can be either guided, involving therapist contact, or unguided, where individuals engage with the content independently. Although guided interventions have been shown to be more effective than unguided interventions [2], unguided interventions have also demonstrated effectiveness as low-threshold options for individuals who might not seek treatment otherwise [3]. Although many of these DMHIs are being evaluated in research and implemented in routine practice [4], the acceptance and use of such interventions remain relatively low among health care personnel and potential users [5-7]. Surveys with physicians, psychotherapists, and patients show that some of the greatest barriers to using online interventions are privacy and data security concerns [8,9]. Notably, the study by Batterham et al [8] is representative of the adult population in Australia, thereby highlighting that these concerns are prevalent among the public, including individuals who may not proactively seek DMHIs. In addition, the possibility to stay anonymous is reported as one of the chief factors influencing participation in DMHIs [8]. This underscores the importance of addressing privacy and data security in the development of such interventions, particularly in efforts to maximize accessibility and reach a broad audience.

These data privacy concerns are not unfounded as digital mental health applications have been found to be susceptible to data breaches and unauthorized access [10]. Beyond security vulnerabilities, there is also a risk that personal health data may be used for commercial purposes. For example, reports suggest that the online therapy provider BetterHelp shared user data with technology companies for targeted advertising [11]. Such practices not only compromise user trust but also raise ethical concerns about the commodification of sensitive health information, potentially deterring individuals from seeking digital mental health support [12].

Many DMHIs collect personal data such as names, email addresses, and symptom severity [8]. This is typically done to create a personalized user space through log-in access, allowing user inputs to be stored and later used—either by the users themselves to track progress or by the program to adapt the treatment based on individual information. However, evidence-based interventions can convey psychological knowledge, strategies for recovery, and practical exercises without requiring user data collection. While some mental health information is available on freely accessible websites where no user registration is required [13], the literature suggests that the quality and helpfulness of online mental health information vary considerably [14]. In addition, many of these websites typically provide general psychoeducational content rather than structured, interactive interventions. While such general resources can serve as initial support, comprehensive DMHIs with interactive elements—such as progress tracking, reminders, or tailored exercises—are often considered more effective [15].

Anonymity in DMHIs presents both advantages and limitations. Anonymous DMHIs, meaning programs that do not store user data, could lower barriers to access by alleviating privacy concerns, thereby increasing use among individuals hesitant to disclose personal information. In addition, such programs eliminate the need for secure data storage, reducing technical and regulatory burdens. However, anonymity restricts certain intervention features such as personalized feedback, progress tracking, and therapist interaction. From a research perspective, evaluating intervention efficacy becomes more challenging without user identifiers, limiting the ability to track long-term outcomes. Thus, the development of anonymous DMHIs requires balancing privacy protection with an effective intervention design. It is important to note that, while such anonymous DMHIs do not store user data in a personally identifiable manner, they may still use nonidentifiable technical data (eg, essential cookies) required for functionality. In contrast to conventional, nonanonymous programs, anonymous DMHIs are characterized by their inability to attribute data to specific individuals.

In summary, while anonymity in DMHIs may increase accessibility, it also introduces trade-offs that could impact intervention efficacy. This raises some key questions: are anonymous DMHIs less efficacious compared to conventional, nonanonymous programs? If presented with the choice between an anonymous and nonanonymous version of the same program, would users, given the privacy and data security concerns reported in previous research, prefer the anonymous version? This study aims to address these questions within the context of social anxiety (SA). While SA refers to heightened levels of anxiety in social situations and exists on a continuum within the general population, SA disorder (SAD) is a clinical condition characterized by an intense and persistent fear of social evaluation, often leading to significant distress and avoidance behaviors [16-18]. SAD is a condition for which DMHIs have been extensively researched [19-21]. SA and SAD are particularly relevant for DMHIs as individuals with SA and SAD often experience heightened fear of social evaluation, which can make seeking traditional health care services daunting [22]. By examining an anonymous version of the self-help intervention JOURNeY that is based on an evidence-based self-help intervention [23-27], this study will investigate the efficacy of an anonymous DMHI compared to a standard nonanonymous version. Furthermore, user preferences regarding anonymity and their potential impact on treatment outcomes will be explored. Understanding these aspects could inform future developments in digital mental health, particularly in optimizing accessibility while maintaining intervention effectiveness.

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Methods

Study Design

This study is part of the larger research project PRIVATE (Preference Research: Investigating Variations of Anonymity, Transparency, and Efficacy in Digital Health Applications) and is a single-center, partially randomized patient preference trial. There are 2 program versions: anonymous (a tool that does not allow user identification) versus nonanonymous (a tool that allows user identification). Participants are assigned to one of these versions either based on their preference or through randomization. Data are collected at 3 main time points: before the intervention, after the intervention, and at follow-up. This results in a 2 × 2 × 3 design with anonymity (anonymous vs nonanonymous) and allocation method (randomized vs preference) as between-subject factors and time (preintervention time point, postintervention time point, and follow-up) as a within-subject factor. Figure 1 shows the study design and participant flow.

Figure 1. Design of the study and expected participant flow.

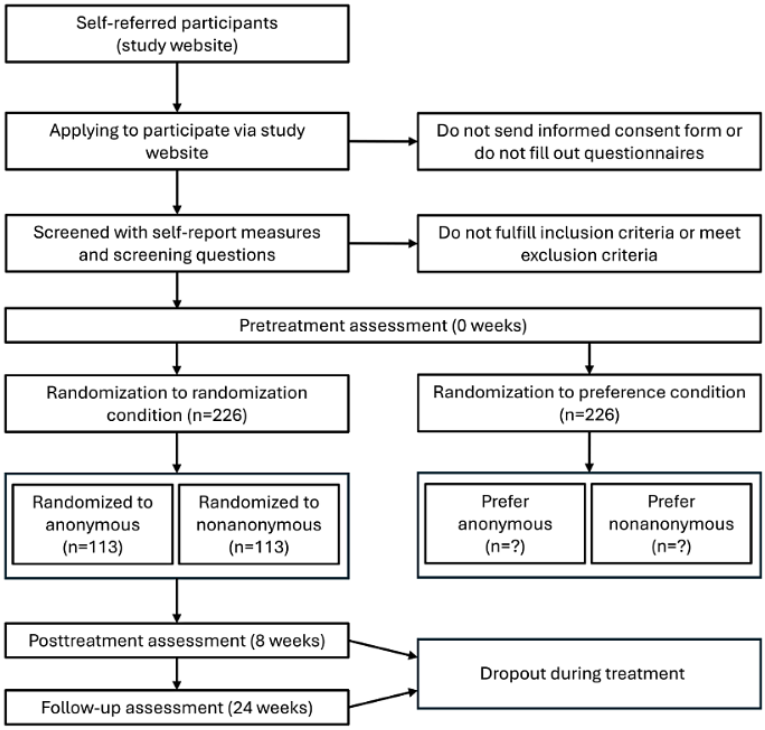

Ethical Considerations

The PRIVATE study has been approved by the Ethics Committee of the Canton of Bern, Switzerland (2024-00842). Interested people are provided with written study information, where potential risks and benefits are explained. No compensation is offered, and potential participants are informed that they can withdraw from the study at any time without negative consequences. Potential participants provide written consent, where they sign 1 or 2 consent forms. The first and mandatory one is the consent form to participate in the study, and the second optional form concerns consent to use of their encrypted data for future research. Once written consent is obtained, participants can be enrolled in the study. Participant data are collected and handled electronically in REDCap (Research Electronic Data Capture; Vanderbilt University) [28,29], where they can only be accessed by authorized personnel of the study team. Data are stored in encrypted form and are identifiable only by a code that is not linked to the participant's identity. Data are saved on a protected server of the University of Bern (the firewall-protected Network Attached Storage Unit server of the Institute of Psychology). At no time are the participants' names and unambiguous personal codes saved together. The code allocation form is saved in a safely encrypted file on an encrypted and protected server of the University of Bern. After the completion of the study, data will be completely anonymized.

Participants

We will recruit a total of 452 adults with increased SA symptoms, as indicated in the Power Analysis section. Therefore, in the randomization arm, there will be 113 participants per program version. The participant numbers in the preference arm will depend on the participants' indicated preferences. Candidates will be included if they (1) are aged ≥18 years; (2) return the informed consent form; (3) have access to the internet; (4) have a smartphone, PC, or tablet; and (5) exceed cutoff scores in at least one of the 2 SA measures (>22 points on the Social Phobia Scale [SPS] or >33 points on the Social Interaction Anxiety Scale [SIAS] [30,31]). A formal diagnosis of SAD is not required, and no clinical interviews will be conducted with potential participants. Conducting in-depth and personal interviews would be incongruent with the nature of anonymous DMHIs as such procedures are rarely part of routine practice, where users typically access these tools independently and without previous interaction.

Candidates will be excluded from the study if they (1) report acute suicidality at the beginning of the study (≥2 points on

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suicide item 9 of the Patient Health Questionnaire–9 [PHQ-9] [32,33]) or (2) report having previously been diagnosed with psychotic symptoms or bipolar disorder.

Recruitment

Participants will be recruited from the community through internet forums, newspaper articles, social media (eg, Facebook), and our study website in German-speaking countries. To accelerate the recruitment process, the link to the trial will also be publicized using online advertisements, such as Facebook ads, Instagram ads, and Google ads.

Treatment

Overview

The interactive self-help program JOURNeY is grounded in the established cognitive behavioral framework for treating SA as proposed by Clark and Wells [34] and Stangier et al [17]. Its efficacy has been supported by multiple studies [19,23-27,35]. JOURNeY comprises 4 primary therapeutic components: psychoeducation, cognitive restructuring, attention training, and exposure. The content of the 4 main modules and 2 supplementary modules will be explained further in the following subsections.

Participants are advised to use the program for approximately 50 to 60 minutes per week and work on 1 module per week for the first 6 weeks and repeat modules during the last 2 weeks of the intervention period. However, this is only a recommendation, and participants can use the program as they like.

Psychoeducation

This module provides comprehensive, evidence-based information on the mechanisms sustaining SA, such as the interplay of negative thoughts, self-focused attention, anxiety, and safety and avoidance behaviors. It encourages participants to build a personalized understanding of how these factors contribute to their own experiences and maintenance of SA. To deepen the participants' knowledge of SA, they are asked to answer questions about the module content. In addition, participants are instructed to systematically identify and document specific social situations and stimuli that they perceive as threatening or anxiety provoking.

Cognitive Restructuring

Participants are guided in recognizing and altering maladaptive beliefs through structured exercises, including keeping a thought diary to capture negative thought patterns and actively practicing techniques to generate more balanced and adaptive interpretations.

Attention Training

This component focuses on shifting self-focused attention. Through various video- and audio-guided tasks, participants practice strategies to redirect their focus outward. These include telling a story to a video of a person and focusing on them instead of themselves. This reduces the intense self-monitoring typical in SA and, thereby, interrupts some of the cognitive and emotional processes that maintain the disorder [36].

Exposure

Participants are encouraged to systematically engage in real-life exposure tasks. This module involves planning, executing, and reflecting on these exercises using an exposure diary, along with reducing safety behaviors (eg, avoiding eye contact or mentally rehearsing conversations), which typically maintain anxiety. Afterward, participants are asked to reflect on their experiences and what they learned from them.

Additional Modules

In addition, there is an introductory module discussing motivation and a conclusion module for relapse prophylaxis, which encourages participants to keep practicing and using techniques they learned in the program in their daily lives. The program will be delivered in an unguided format, which has been shown to be effective in various previous studies [19,24,35], to ensure anonymity and comparability across the 2 program versions, which are introduced in the following section.

Program Versions

Both versions of the program are accessible through a standard web browser and provide the same core content. The key difference lies in the presence or absence of account creation and how personal entries made by participants are handled. In the anonymous version (JOURNeY_A), no account or registration is required. To protect anonymity, the sections of the program that involve personal input are provided as a downloadable PDF. Participants can complete and save these entries locally on their own devices. In the nonanonymous version (JOURNeY_NonA), participants create an account, allowing them to enter personal reflections directly into the program and revisit them later. While both versions of the self-help program use cookies for essential functionalities, such as session management and ensuring smooth operation of the platform, these cookies do not track users' activities or collect personal data, meaning that they do not facilitate the tracking or identification of users in any way.

To account for the obstacle of collection of personal information that is met when assessing such an anonymous DMHI, JOURNeY_A itself will be usable without an account, but within the study, the participants will still regularly receive symptomatology questionnaires to fill out outside of the program facilitated through a data collection platform. This compromise allows us to monitor and assess outcomes to be able to draw conclusions about the efficacy of the program while still maintaining anonymity for users in the program itself.

Procedures

After receiving the study information and returning the signed informed consent form, the candidates will be screened for eligibility using the self-report measures described in the Instruments section. Participants will additionally be shown brief descriptions of both program versions during screening and asked to select their preferred option. If eligible, the participants will be assigned to a condition. The randomization will be performed in 2 steps to ensure correct condition allocation. In a first step, eligible candidates will be randomized with equal probability to either the randomization or preference

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condition. In a second step, the participants in the randomization condition will be randomized again with equal probability to one of the program versions (anonymous vs nonanonymous) regardless of previously expressed preference. The participants in the preference condition will be assigned to their preferred program version. Thus, the main effect of the treatment can be estimated, but it is also possible to explore preferences and their possible effects through the preference arm. The first randomization will be conducted using the built-in randomization tool in REDCap [28,29], where all the data will be collected, whereas the second randomization will be conducted by an external researcher with a randomization list created using randomly permutated blocks. An external researcher has to be involved in the randomization as REDCap can only perform one randomization per participant. The condition allocation will be unknown to investigators.

The intervention period, during which participants are asked to use the self-help program, will be 8 weeks. The duration of the study for 1 participant will be 24 weeks. There are 3 main measurement time points during this period: at the beginning (preassessment), after 8 weeks (postassessment), and after 24 weeks (follow-up assessment). In addition, there are 2 minor measurement points, after 3 and 6 weeks, where only preference and other measures unrelated to this part of the study will be assessed. The questionnaires will be sent out automatically through REDCap [28,29] via email at the corresponding time points.

Suicidality is monitored using item 9 of the PHQ-9 at baseline (week 0), the postintervention time point (week 8), and follow-up (week 24). If elevated suicidality is reported at any time point, the study team will reach out to the participant to provide appropriate crisis resources and encourage help seeking. Participants are informed that they may contact the study team at any time if they experience distress or wish to withdraw.

Instruments

Overview

A summary of the instruments and time points of assessment can be found in Table 1.

Table 1. Variables, instruments, and time points of assessment.

Dimension	Instrument	Authors (German version)	Time points
Primary outcome measure			
Social anxiety symptoms	SPS[a] and SIAS[b]	Stangier et al [31]	Before the intervention, after the intervention[c], and FU[d]
Secondary outcome measures			
Depressive symptoms	PHQ-9[e]	Gräfe et al [33]	Before the intervention, after the intervention, and FU
Quality of life	SF-12[f]	Gandek et al [37]	Before the intervention, after the intervention, and FU
Internalized stigma	ISMI[g]	Sibitz et al [38]	Before the intervention, after the intervention, and FU
Attitudes toward help seeking	IASMHS[h]	Kessler et al [39]	Before the intervention, after the intervention, and FU
Personality functioning	LPFS-BF[i]	Spitzer et al [40]	Before the intervention, after the intervention, and FU
Preference	Custom assessment	—[j]	Before the intervention, mid1[k], mid2[l], after the intervention, and FU

[a]SPS: Social Phobia Scale.
[b]SIAS: Social Interaction Anxiety Scale.
[c]8 weeks after baseline.
[d]FU: follow-up (24 weeks after baseline).
[e]PHQ-9: Patient Health Questionnaire–9.
[f]SF-12: 12-Item Short Form Health Survey.
[g]ISMI: Internalized Stigma of Mental Illness scale.
[h]IASMHS: Inventory of Attitudes Toward Seeking Mental Health Services.
[i]LPFS-BF: Level of Personality Functioning Scale–Brief Form.
[j]Not applicable.
[k]3 weeks after baseline.
[l]6 weeks after baseline.

Primary Outcome

The primary outcome measure is symptoms of SA at the posttreatment time point (ie, after 8 weeks). It will be measured using the companion scales SPS and SIAS [30,31]. Both self-report measures are frequently used in studies on SAD, and they assess fears of being judged by others during performance-related (SPS) and interaction-related (SIAS) social situations. They have been described as valid, reliable, and useful for clinical as well as research purposes. Good values of internal consistency have been found for the German versions of the scales (Cronbach α=0.94 for both scales [31]). Both scales consist of 40 items that are rated on a 5-point Likert scale (0=“not at all”; 4=“extremely”), with higher scores indicating

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higher levels of SA. For the analysis, the composite score will be used by simply averaging the *z* scores of the SIAS and the SPS sum score, which has been recommended for continuous variables and done in similar previous research [27,41,42].

Secondary Outcomes

Overview

Beyond primary treatment outcomes, this study investigates how measures of mental well-being, such as depression severity and quality of life, change during the study. It additionally assesses whether other outcomes, such as internalized stigma, attitudes toward help seeking, and personality functioning, may play a role in shaping preferences for anonymity. These secondary outcomes could help identify for whom and under which conditions anonymous digital interventions may be particularly beneficial.

PHQ-9 Instrument

This widely used self-report measure assesses symptoms of depression with 9 items that correspond to the symptoms of major depression described in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* [18], on a 4-point Likert scale [32,33]. Higher scores indicate more severe depressive symptoms. The PHQ-9 has shown good internal consistency as well as good sensitivity and specificity [33,43,44].

12-Item Short Form Health Survey

This self-report instrument measures quality of life. It has 2 subscales measuring physical and mental aspects of health-related quality of life with a total of 12 items. The 12-Item Short Form Health Survey has shown good psychometric properties, roughly equivalent to those of the 36-Item Short Form Health Survey, and is widely used as an estimate of general quality of life [37,45].

Internalized Stigma of Mental Illness Scale

This 29-item self-report scale [38,46] measures the internalized stigma of mental illness. It is widely used in various contexts and consists of 5 subscales: alienation, stereotype endorsement, discrimination experience, social withdrawal, and stigma resistance. It has shown good internal consistency and good test-retest reliability [38]. Often, the stigma resistance subscale is excluded in analyses as some researchers have suggested that another construct be measured using this subscale [47]. As suggested by these researchers, preliminary factor analysis will be conducted to decide whether to include this subscale in the total score.

Inventory of Attitudes Toward Seeking Mental Health Services

This 24-item self-report scale [39,48] measures the participants' attitudes toward seeking help for mental health issues. It is an adaptation of an older scale [49] and has 3 subscales. This scale is used in nonclinical as well as clinical samples. The German version has shown acceptable psychometric properties [39].

Level of Personality Functioning Scale–Brief Form 2.0

This 12-item self-report tool [40,50,51] measures the impairment in self-functioning regarding sense of self and interpersonal functioning based on the Alternative DSM-5 Model of Personality Disorders [18]. The questions are answered on a 4-point Likert scale (1="does not apply at all"; 4="applies exactly"). It consists of 2 subscales and is a fairly new tool. A thorough validation for clinical samples is still pending, but good internal consistency for the German scale has already been determined [40].

Preference

Preference will be assessed by presenting all participants with 2 approximately 150-word texts describing the 2 versions of the program. They will then be asked to indicate their preference and their preference strength by answering the question "How important is this choice to you?" on a 4-point Likert scale (1="not important at all"; 4="very important"), as done previously [52]. Participants are only forced to make a choice at preassessment to enable possible condition allocation for all participants that are randomized to the preference condition. At the remaining measurement points, participants can indicate that they have no preference.

Engagement

When it comes to engagement, "the more use the better" is not always true [53], especially for internet interventions such as this one, where the participants determine the dosage themselves. However, given that one version will be completely anonymous, it will not be possible to use complex measures of engagement for individual participants in this condition at a technological level. To find a compromise and gain insights into program use, the total number of clicks during the intervention period will be recorded for both program versions and then divided by the number of participants per version, providing an average that can be compared between groups. This has been done before for other internet interventions [54].

Power Analysis

This study is powered regarding the primary outcome (composite score of the SPS and SIAS) and first study aim (whether anonymous digital interventions are less efficacious than conventional, nonanonymous programs). This means the comparison of the 2 versions in terms of reduction in SA symptoms in the randomized condition. As we expect a superiority of the nonanonymous version, a Cohen *d* value of 0.35 was used as the target effect size between groups as we considered smaller effects clinically insignificant. We conducted a power analysis for Cohen d=0.35 with an α level of .05 and a power of 0.80 for the time × group interaction. The sample size was determined using the ANOVA power Shiny app [55], which is based on the R programming environment [56], and the *Superpower* package for R (R Foundation for Statistical Computing). This app performs Monte Carlo simulations tailored to factorial experimental designs, allowing for interaction effects and comparisons across both within- and between-subject factors [55]. For the power analysis, we defined the randomized condition as a mixed 2 × 3 design with 2 program versions (between) and 3 time points (within). For means and SDs of the nonanonymous version, values from another trial with the same basic online program were taken [26], and for the anonymous version, the means were calculated using the aforementioned effect size. The SDs used were the

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same as in the nonanonymous version, and the correlation of within-subject factors was set at r=0.5. For SPS values with 2000 simulations, a total of 113 participants per condition are needed, and for SIAS values, 112 participants are needed per condition to reach 0.80 power for the interaction effect. Therefore, for the 2 randomized arms, 113 participants per arm will be recruited. Although we do not know beforehand how many participants will be in each of the 2 preference arms, we doubled the participants from the randomized arm for the power analysis, resulting in a total of 452 participants across all 4 arms.

Statistical Analysis

We will evaluate the differences in SA symptom change between the anonymous version (JOURNeY_A) and the nonanonymous version (JOURNeY_NonA) using linear mixed models with the posttreatment assessment as the confirmatory primary end point. Time will be used as the within-subject factor, and condition will be used as the between-subject factor. Fixed effects will be time, condition (JOURNeY_A or JOURNeY_NonA), and the intervention term; the random effect will be the intercept of each participant as every participant is expected to have a different prescore. This analysis accounts for the correlation of residual errors within participants and includes a treatment-by-time interaction term to assess differential symptom change over time [57]. Estimates for each time point will be derived from this model. We will conduct the analysis based on the intention-to-treat principle. The intention-to-treat analysis set consists of all participants in the randomized group regardless of any protocol violations. The inferences about overall program efficacy will only be made based on the randomized arm. For the exploratory preference analysis, appropriate methods such as multiple logistic regression, t tests, and chi-square tests will be used depending on the type of data. Comparisons will focus, for example, on participants who received their preferred treatment (preference match) versus those who did not (preference not matched). The amount and pattern of missing data will be reported, and results will be interpreted accordingly in a cautious manner. To allow for comparison across trials, we will also report the standardized mean differences (effect sizes).

Results

This study was funded in 2023, approved by the Cantonal Ethics Committee of Bern, Switzerland in May, 2024 and recruitment and data collection started in September 2024 and are ongoing as of the submission of this manuscript. As of the submission in May 2025, over 350 participants have been included in the study. Recruitment of the study was finished in September 2025 and data collection is projected to be finished in March 2026. No data has been analyzed yet.

Discussion

Principal Implications

Internet interventions can present a low-threshold and effective way of providing evidence-based care. However, low acceptance and use rates highlight the need to design interventions that directly address potential users' concerns, particularly regarding data security and privacy. Freely accessible, evidence-based, and anonymous DMHIs could play a role in bridging the treatment gap for mental health care. This trial will assess whether an anonymous self-help tool for SA can be efficacious while addressing privacy concerns. In addition, the findings will provide insights into user preferences for anonymous versus nonanonymous versions.

Limitations

One limitation of this trial is that all measures rely solely on self-report questionnaires without incorporating observer-based measures such as assessments by a mental health professional to evaluate clinical outcomes. As the goal is to evaluate the tool in its intended real-world use, no in-depth diagnostic interviews will be conducted to avoid compromising participants' sense of anonymity. Second, the preference-based study arm may introduce confounding factors as user preferences might be linked to other characteristics that influence outcomes [58]. However, to still be able to make inferences about the overall efficacy, the randomization arm allows for direct comparison between the 2 program versions. Third, even in the anonymous conditions, participants provide intimate information through questionnaires, which may still affect their perception of anonymity. To mitigate this concern, we emphasize at various stages of participant interaction that only the program is anonymous, whereas the study itself does not guarantee complete anonymity. This approach strikes a balance between exploring the efficacy of an anonymous DMHI and monitoring changes in outcomes of interest. Fourth, it is plausible that individuals who place a particularly high value on anonymity may opt not to participate in the study due to the required disclosure of personal information during study procedures. As a result, this potentially relevant subgroup of the target population may be underrepresented in the sample, limiting the generalizability of the findings. Finally, the inability to accurately measure user engagement with the program is a problem. As there are no individual user data, the only indicator of adherence is the total amount of clicks registered on the website, which we will then divide by the total number of participants with access to the site during the trial to at least obtain some insights into user engagement.

Future Directions

Future research should examine whether similar anonymous DMHIs can be effective for other psychological conditions. In addition, further investigating user characteristics that influence preferences and engagement could provide valuable insights into optimizing intervention design. Our study data may also offer initial indications of which users benefit most from an anonymous format.

Conclusions

In conclusion, this trial will have important implications for future internet intervention development regarding degree of anonymity and possibilities of ensuring privacy. Freely and anonymously accessible DMHIs offer a low-threshold alternative to traditional approaches such as face-to-face psychotherapy. These interventions hold significant potential to extend evidence-based care to a wider audience, addressing

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unmet mental health needs and narrowing the mental health treatment gap.

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed. Following study completion, deidentified data and accompanying documentation will be made available in an open access data repository in accordance with the findability, accessibility, interoperability, and reusability data principles and ethics approvals.

Authors' Contributions

Conceptualization: TB (lead), ME (equal), SA (supporting), MFV (supporting)
Data curation: SA (lead), MFV (equal)
Funding acquisition: TB (lead), ME (equal)
Investigation: SA (lead), TB (lead), MFV (supporting), ME (supporting)
Methodology: SA (lead), TB (supporting), ME (supporting), MFV (supporting)
Project administration: SA (lead), MFV (supporting), TB (supporting), ME (supporting)
Resources: TB (lead), ME (equal), JB (supporting), FF (supporting)
Software: SA (lead), MFV (equal)
Supervision: TB (lead), ME (equal)
Visualization: SA (lead), MFV (equal)
Writing: SA (lead), TB (supporting)
Writing—review and editing: SA (lead), TB (supporting), MFV (supporting), ME (supporting), DS (supporting), JB (supporting), FF (supporting)

Conflicts of Interest

The self-help program JOURNeY was developed by the research team at the University of Bern under the supervision of TB based on previous programs developed by TB. There are no commercial interests behind the program.

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Abbreviations

DMHI: digital mental health intervention
IASMHS: Inventory of Attitudes Toward Seeking Mental Health Services
ISMI: Internalized Stigma of Mental Illness scale
LPFS-BF: Level of Personality Functioning Scale–Brief Form
PHQ-9: Patient Health Questionnaire–9
PRIVATE: Preference Research: Investigating Variations of Anonymity, Transparency, and Efficacy in Digital Health Applications
REDCap: Research Electronic Data Capture
SA: social anxiety
SAD: social anxiety disorder
SF-12: 12-Item Short Form Health Survey
SIAS: Social Interaction Anxiety Scale
SPS: Social Phobia Scale

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Protocol

Efficacy of Preventive Pressurized Intraperitoneal Aerosol Chemotherapy in Patients With Locally Advanced Gastric Cancer: Protocol for a Prospective Controlled Trial

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Abstract

Background: Gastric cancer is a serious health issue both globally and in Kazakhstan. Worldwide, gastric cancer ranks fifth in incidence, with the highest rates reported in East Asia, the Andes of South America, and Eastern Europe, while the lowest rates are reported in North America, Northern Europe, Africa, and Southeast Asia. Over 70% of the cases occur in resource-limited countries. In Kazakhstan, gastric cancer ranks third in morbidity and second in mortality, representing a serious clinical and social problem. Annually, 1600 deaths from malignant gastric neoplasms are registered. Peritoneal metastasis is considered one of the most severe complications of gastric cancer and has long been regarded as its terminal stage. The average life expectancy of patients with peritoneal metastasis is only 3-6 months, reflecting a high mortality rate and the limited efficacy of current treatments.

Objective: We hypothesize that the prophylactic use of pressurized intraperitoneal aerosol chemotherapy (PIPAC) may reduce the incidence of peritoneal metastasis. The aim of this study is to evaluate the incidence of peritoneal metastasis following prophylactic PIPAC in patients with gastric cancer. The primary goal of this research is to evaluate whether adding prophylactic PIPAC to standard treatment before neoadjuvant chemotherapy can reduce the incidence of peritoneal metastasis in patients with locally advanced gastric cancer.

Methods: This study is a single-center nonrandomized controlled trial with a planned enrollment of 160 patients. All participants will be included in one of the 2 groups: intervention group (PIPAC + perioperative chemotherapy + gastrectomy with D2 lymphadenectomy) or control group (perioperative chemotherapy + gastrectomy with D2 lymphadenectomy). The primary end point is the incidence of peritoneal metastasis, and the secondary end points are overall survival, recurrence-free survival, treatment-related adverse events, and personal satisfaction.

Results: As of September 2025, this study is funded and recruiting; 102 participants have already been enrolled. Recruitment is planned to be performed between January 2025 and December 2026. No interim analyses have been performed; primary results are planned for Q1 2027. The manuscript is expected to be published by Q4 2027.

Conclusions: Compared to standard chemotherapy, PIPAC has been reported to significantly improve survival rates in patients with peritoneal metastasis of gastric origin. We suggest that the neoadjuvant use of PIPAC may reduce the incidence of peritoneal metastasis and improve long-term survival outcomes. The results of our study will provide key information on the practicality and viability of PIPAC as a prophylactic technique for preventing the progression of gastric cancer.

Trial Registration: ClinicalTrials.gov NCT06784765; https://clinicaltrials.gov/study/NCT06784765

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International Registered Report Identifier (IRRID): PRR1-10.2196/78053

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KEYWORDS

gastric cancer; peritoneal metastasis; pressurized intraperitoneal aerosol chemotherapy; PIPAC; chemotherapy; HIPEC; hyperthermic intraperitoneal chemotherapy; oncology; intraperitoneal treatment

Introduction

Gastric cancer poses a serious health issue both globally and in Kazakhstan [1,2]. Worldwide, it ranks fifth in incidence, with the highest rates seen in East Asia, the Andes of South America, and Eastern Europe, while the lowest are reported in North America, Northern Europe, Africa, and Southeast Asia [1,3,4]. Over 70% of the cases occur in resource-limited countries. In Kazakhstan, gastric cancer ranks third in incidence and second in mortality among all malignancies, causing approximately 1600 deaths annually, highlighting its significant social and clinical burden [1,2,4]. One of the most serious complications of gastric cancer is peritoneal dissemination, which has long been considered a terminal stage of the disease, resistant to curative treatment [5,6]. Peritoneal metastasis (PM) develops in a considerable proportion of patients, even among those receiving multimodal therapy, and poses a major challenge in oncology. The median overall survival for patients with PM is only 3-6 months, underscoring the urgent need for more effective therapeutic approaches [5]. PM results from tumor cell detachment, survival in the peritoneal cavity via anoikis resistance, adhesion to mesothelial surfaces, and invasion into submesothelial tissues. Hypoxic environments such as milky spots and molecular pathways, including integrins and CXCR4, facilitate colonization [7]. Systemic chemotherapy remains the cornerstone of treatment for gastric cancer with PM. However, its efficacy is limited, particularly against peritoneal lesions, due to poor drug penetration into the peritoneal tissues [8,9].

In response to these limitations, new strategies such as the combination of cytoreductive surgery and hyperthermic intraperitoneal chemotherapy (HIPEC) have been developed [10]. Intraperitoneal drug administration allows for higher local drug concentrations while reducing systemic toxicity, potentially improving clinical outcomes [11,12]. Despite its promise, HIPEC has notable limitations in the context of gastric cancer. Its application is technically challenging, associated with significant morbidity, and its long-term benefits remain under debate. These drawbacks highlight the need for alternative, less invasive, and more effective intraperitoneal treatment modalities.

Pressurized intraperitoneal aerosol chemotherapy (PIPAC), proposed by Reymond et al [13] in 2011 represents an innovative alternative. PIPAC delivers chemotherapeutic agents in aerosol form under high pressure into the peritoneal cavity, enhancing drug penetration into the peritoneal tissues and improving drug distribution. This method combines the advantages of effective local delivery with reduced systemic toxicity [13,14]. According to Alyami et al [15], PIPAC improves drug penetration into the peritoneum and minimizes systemic exposure, offering a promising alternative to systemic chemotherapy [15]. Several studies have demonstrated the safety and efficacy of PIPAC for various types of PM [16]. Another study included 25 patients who were available for analysis of the primary end point [17]. Of these, 10 (40%) patients showed a radiological complete or partial response or stable disease. The median overall survival by intention to treat was 6.7 months, and the median time to progression was 2.7 months. Complete or major regression on histology was observed in 9 (36%) out of 25 patients (intention to treat) or in 6 out of 6 patients (100% per protocol) in the group with full protocol adherence. There were no unexpected serious adverse effects, no treatment-related deaths, no grade 4 toxicity by the common terminology criteria for adverse events, and only 3 (12%) patients experienced grade 3 toxicity. Changes in QLQ-C30 scores during PIPAC C/D therapy were minor and not statistically significant. Studies show that compared to HIPEC, PIPAC offers advantages such as minimal invasiveness, repeatability, reduced toxicity, and improved drug absorption.

According to Ramalho-Vasconcelos et al [18], patients with gastric cancer who had undergone 3 or more PIPAC procedures had a shorter hospitalization period (mean difference = –1.2) and significantly improved survival (mean difference = 6.0) [18]. Aksenov et al [19] performed 20 cytoreductive surgeries, wherein intraperitoneal aerosol chemotherapy was combined with limited PM, and they obtained the following results: 3 patients showed partial response, 17 showed stabilization of the tumor process at the primary site after preoperative treatment, and 50% of the patients had a complete response in the peritoneal tumor sites [19]. The median overall survival was 27 months, the median recurrence-free survival was 7 months, and the overall 1-year and 2-year survival rates were 95% and 60%, respectively. Luksta et al [20] reported that the postoperative complication rate was less than 5% with no complications threatening life.

By aerosolizing chemotherapy within the peritoneal cavity, PIPAC achieves more even distribution into anatomic recesses and enhances tissue penetration with sustained local exposure. It also limits systemic absorption, thereby reducing toxicity, and can be safely repeated, allowing consistent evaluation of treatment response [21]. Moreover, Solass et al [14] showed that with the treatment of doxorubicin, PIPAC showed no significant adhesions and was appropriate to be repeated 6x, 4x, and 2x [14]. Another study applied PIPAC in combination with cisplatin (7.5 mg/m^2) and doxorubicin (1.5 mg/m^2) every 6 weeks with no adverse reactions, no treatment-related deaths, and no grade 3 and grade 4 toxicities [17].

Nevertheless, the role of PIPAC in gastric cancer treatment, particularly in preventing peritoneal dissemination, requires further clinical evaluation. We hypothesize that the prophylactic use of PIPAC may reduce the incidence of PM. The aim of this

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study is to evaluate the incidence of PM following prophylactic PIPAC in patients with gastric cancer.

PIPAC is hypothesized to enhance chemotherapy penetration, improving local disease control, and potentially reduce the incidence of PM compared to standard treatment alone. The primary aim of this study is to assess the efficacy and safety of PIPAC in the preoperative management of patients with locally advanced gastric cancer without PM in combination with conventional treatment. A comparative analysis between the experimental and control groups will be conducted to identify the potential benefits and assess the effectiveness of this novel therapeutic approach.

Methods

Study Design

This study is designed as a single-center, nonrandomized controlled trial aimed at evaluating the efficacy and safety of PIPAC as a preventive strategy in the management of locally advanced gastric cancer. In line with IDEAL stage 2b (exploration), we use a prospective, nonrandomized controlled cohort to (1) standardize the procedure and perioperative workflow, (2) refine outcome definitions (especially peritoneal-metastasis ascertainment), and (3) estimate the effect sizes and variability to inform a later multicenter randomized controlled trial. The study will be conducted at the National Research Oncology Center, Kazakhstan, enrolling a total of 160 patients. Participants will be parallelly assigned to either the PIPAC intervention group or the control group in a 1:1 ratio. Patients receive PIPAC + standard care versus standard care when they consent to prophylactic laparoscopy-integrated PIPAC after shared decision-making. Personal information will not be available for the public and will be encrypted into special codes.

Since a single-centered nonrandomized approach can lead to several limitations, the adjustment for confounding will be done. First, we will minimize selection bias by consecutive screening, predefined allocation rules, and a log documenting the reasons for allocation. Second, we will adjust analytically by using propensity-score weighting to create comparable groups on pretreatment characteristics (age, sex, BMI, Eastern Cooperative Oncology Group score, clinical T/clinical N stage, tumor location/grade/Lauren type/linitis features, prior abdominal surgery, diabetes/Charlson comorbidity index, and perioperative timing). Outcomes will then be analyzed with robust standard errors, and PM will be adjudicated blinded to treatment. Baseline missing data will be handled with multiple imputation, and we will report preadjustment and postadjustment balance so that readers can verify that confounding was adequately controlled. This study is structured to ensure comprehensive data collection and analysis, enabling an in-depth understanding of PIPAC's impact on disease progression, survival outcomes, and overall patient well-being. Given its nonrandomized design, rigorous inclusion and exclusion criteria have been established to minimize bias and ensure homogeneous study groups.

This protocol adheres to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement (Multimedia Appendix 1). Intervention reporting follows TIDieR (Template for Intervention Description and Replication; Multimedia Appendix 2). Given the nonrandomized controlled design, the TREND (Transparent Reporting of Evaluations with Nonrandomized Designs) checklist is provided (Multimedia Appendix 3).

Study Population

To maintain a well-defined patient cohort, this study includes individuals who meet the inclusion and exclusion criteria. These eligibility criteria are designed to select a homogeneous study population that allows for a precise evaluation of PIPAC's preventive potential while minimizing the confounding variables (Textbox 1).

Textbox 1. Inclusion and exclusion criteria for the study population.

Inclusion criteria

- Age: 18-70 years in alliance with other studies in this area of research topic
- Diagnosis: Histologically confirmed locally advanced gastric adenocarcinoma (T3-4N0-3M0 gastric adenocarcinoma, according to TNM classification, confirmed by computed tomography, magnetic resonance imaging, or positron emission tomography-computed tomography)
- Performance status: Eastern Cooperative Oncology Group score of 0-2, indicating good to moderate functional status
- Peritoneal cytology: negative results for malignant cells from diagnostic laparoscopy, ensuring no evidence of peritoneal dissemination at baseline
- Staging laparoscopy

Exclusion criteria

- Distant metastases detected via imaging or cytological analysis
- Previous treatment with chemotherapy, radiotherapy, or surgical interventions for gastric cancer
- Severe comorbidities that contraindicate surgical procedures or systemic chemotherapy (eg, severe cardiovascular, hepatic, or renal dysfunctions; poorly controlled diabetes)
- Technical/anatomical issues: factors precluding safe laparoscopy/pressurized intraperitoneal chemotherapy (eg, dense adhesions after major abdominal surgery; clinically significant ascites not correctable)
- Hypersensitivity to cisplatin/doxorubicin
- Active infection: systemic infection or abdominal wall/intraperitoneal infection

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Allocation

At staging laparoscopy (time zero), all eligible patients are counseled using a standardized script and decision aid. Patients are allocated in the PIPAC + standard care if patient consents and (1) inclusion/exclusion remain met, (2) no day of contraindication, (3) a credentialed surgeon/device is available within 14 days. If any of the above conditions are not met or the patient declines, standard care is applied. We will keep a prospective allocation-reason log (refusal, clinical, capacity/scheduling, other). Crossovers remain in their intention-to-treat arm; a per-protocol analysis will be reported as sensitivity. All other care pathways are identical between the groups.

Interventions

Intervention Group

Patients in the intervention group will undergo preventive PIPAC with cisplatin (10 mg/m²) and doxorubicin (2.1 mg/m²) prior to the initiation of neoadjuvant chemotherapy. It was chosen based on the treatment protocol of the Republic of Kazakhstan as well as the existing justifications of efficiency in other studies performed [22]. Standard perioperative chemotherapy is administered according to international guidelines using the FLOT (5-fluorouracil, leucovorin, oxaliplatin, and docetaxel) regimen. Surgical intervention includes curative-intent gastrectomy with D2 lymphadenectomy, performed after the completion of neoadjuvant therapy and patient reassessment.

Control Group

Patients in the control group will receive standard perioperative chemotherapy with the FLOT regimen, followed by gastrectomy with D2 lymphadenectomy, according to the same protocol as in the experimental group.

Primary End Point

As a primary end point, we will control for the incidence of PM at 12 months and 24 months postsurgery. Computed tomography is scheduled for every 3 months for 2 years. Unless computed tomography data show clear signs of carcinomatosis, PM is confirmed via laparoscopy at month 12 and month 24 with histological assessment. Laparoscopy may be performed earlier if the imaging of the symptoms suggests PM. All PM events are centrally adjudicated, blinded to treatment (2 reviewers; third resolves discrepancies).

Secondary End Points

There are several secondary end points to measure: (1) overall survival (time from time-zero to death from any cause) at 1, 3, and 5 years postsurgery; and (2) recurrence-free survival (time from time zero to first recurrence [any site, including peritoneal] or death, whichever occurs first) assessed at multiple time points. To assess overall survival and recurrence-free survival, patients will undergo endoscopic and radiological assessment every 3 months for 2 years. To control for the safety of the trial, the frequency of chemotherapy-related adverse events is graded according to the common terminology criteria for adverse events (version 5.0) and by Clavien-Dindo classification system for surgical complications after each course of chemotherapy. Grading will occur 30 days post-PIPAC, 90 days after gastrectomy, and throughout chemotherapy. Another type of assessment is the quality of life (QoL) assessment, using the standardized EORTC QLQ-C30 questionnaire, designed to measure various functional and symptom domains affecting patients with cancer. QoL will be assessed after the PIPAC procedure and radical surgery: baseline, presurgery, end of adjuvant therapy, and months 12 and 24. These end points will provide insights into both the clinical efficacy and safety profile of PIPAC, allowing for an evidence-based assessment of its role in gastric cancer management. Figure 1 shows the study scheme: staging laparoscopy with cytology, prophylactic PIPAC for cytology-negative patients, neoadjuvant FLOT×4, restaging laparoscopy, D2 gastrectomy, and adjuvant FLOT×4. Cytology-positive or progressing patients exit to metastatic care pathways. The primary end point is PM incidence at 12 or 24 months.

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Figure 1. Study design. AdjCTx: adjuvant chemotherapy; cyt: cytology; FLOT: fluorocil, leucovorin, oxaliplatin, docetaxel; GC: gastric cancer; NeoAdjCTx: neoadjuvant chemotherapy; PC: peritoneal carcinomatosis; PIPAC: pressurized intraperitoneal aerosol chemotherapy.

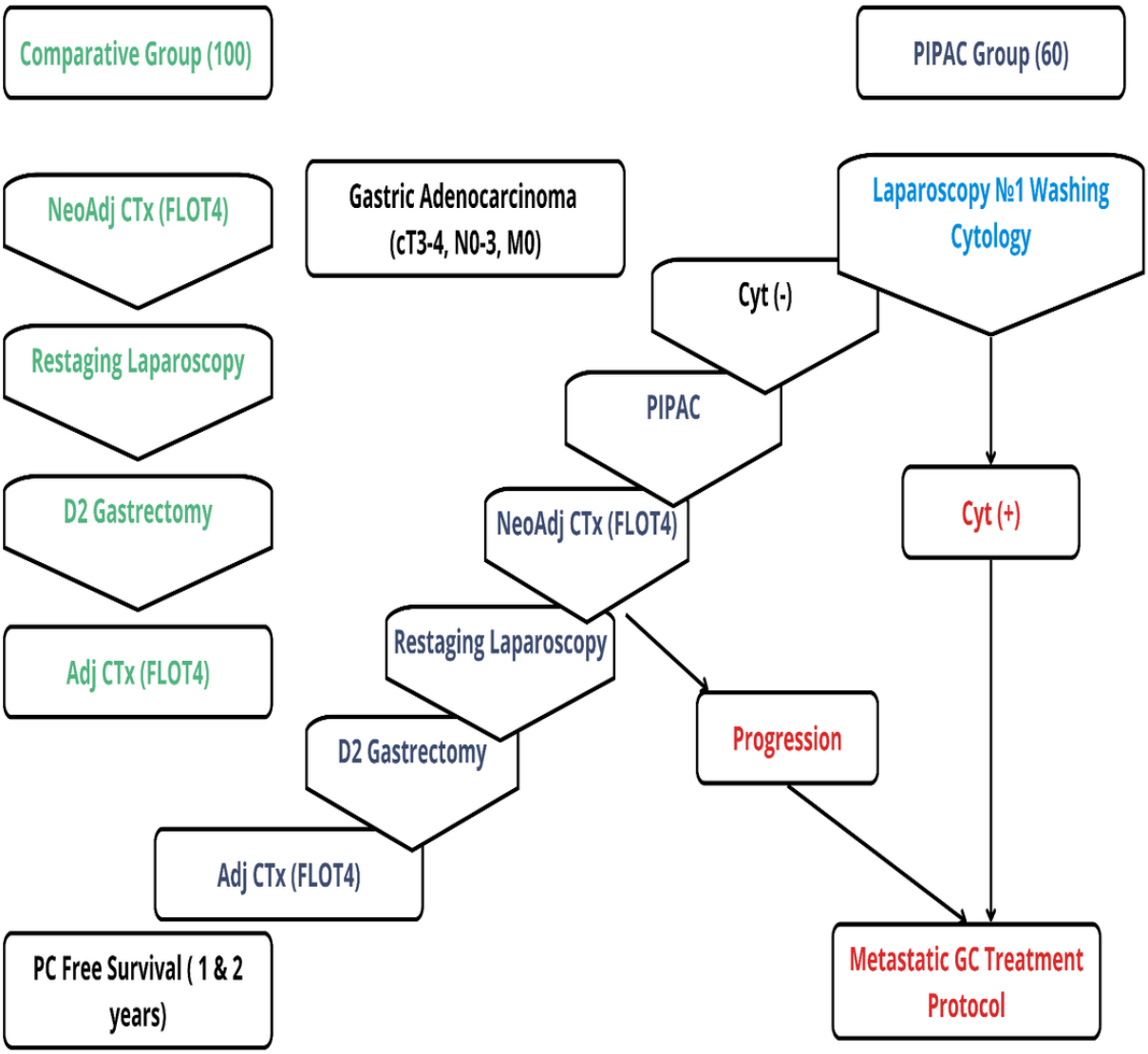

Statistical Analysis

To ensure the robustness of the study findings, the following statistical methods will be applied at the analysis stage.

For sample size calculation, powering was based on the primary end point (death as a competing risk; primary analysis via Fine-Gray), while secondary end points (overall survival, recurrence-free survival, QoL) are exploratory. The log-rank/Schoenfeld approximation in MedCalc with 2-sided α=.05, N=160 (1:1) provided ~79.7% power to detect a 25%-30% reduction in PM incidence. To mitigate low power, we will focus on the estimation analysis by calculating risk difference/ratio with 95% CI, avoiding dichotomous claims.

For the primary analysis (overall survival and recurrence-free survival), the Kaplan-Meier method with Inverse Probability of Treatment Weighting -adjusted Cox/Fine-Gray with robust SEs will be used. Once it is done, log-rank test will be applied for comparing the survival curves between the intervention and control groups. Fisher exact test and Pearson chi-square test will be employed for categorical data analysis, ensuring statistical rigor in comparing treatment outcomes. Multiplicity for QoL is controlled via a false discovery rate (q=0.10), while the global health status at month 12 is prespecified as the primary QoL end point. Shapiro-Wilk test will be used to assess the normality of the data distributions, and Student 2-sided *t* test will be applied to analyze continuous variables with normal distribution, while the Mann-Whitney *U* test will be used for nonnormally distributed data. Data will be censored at the last follow-up visit, with additional sensitivity analyses conducted if necessary for the better handling of missing data. These analytical methods will allow for an objective evaluation of PIPAC's effectiveness while ensuring statistical validity and the reproducibility of results.

Ethical Considerations

This study was approved by the National Research Oncology Center Board (approval 051; April 24, 2024). Written informed consent will be obtained from all the participants. Participants have the right not to participate in the study and be treated by standard therapy protocol. Participant data will be deidentified before analysis. Each participant will be assigned a unique study ID; the linkage file connecting IDs to personal identifiers will be stored separately on an encrypted, access-restricted server

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and will be accessible only to authorized study personnel. No personal identifiers will be visible during data processing or analysis. For this study, participants receive no monetary compensation.

Data and Safety Monitoring Board

An independent data and safety monitoring board (surgical oncologist, medical oncologist, biostatistician; with no study roles) oversees participant safety. The board works under a written charter (membership, conflicts, data access, decision rules). The board member receives unblinded safety reports from an independent statistician and meets quarterly/ad hoc to issue continue/pause/modify/stop recommendations to the sponsor/institutional review board. All additional information are available by request.

Results

As of September 2025, this study is funded and recruiting; 102 participants have already been enrolled. Recruitment is performed between January 2025 and December 2026. No interim analyses have been performed; primary results are planned for Q1 2027. Data collection is ongoing; database lock/analysis is expected to occur in Q1-Q2 2027; and the manuscript is expected to be published by Q4 2027.

Discussion

Principal Findings

The use of PIPAC as a preventive method represents a promising strategy to reduce the incidence of PM in patients with locally advanced gastric cancer and to improve overall survival [23,24]. This study aims to evaluate the effectiveness of PIPAC in combination with standard perioperative therapy and to determine its potential advantages over currently employed treatment modalities. Current data indicate a high incidence of PM in gastric cancer, which significantly worsens prognosis and often renders radical treatment unfeasible. Standard approaches, including systemic chemotherapy and HIPEC, demonstrate limited efficacy, particularly against microscopic peritoneal implants. Unlike HIPEC, which requires intraoperative administration and is associated with considerable toxicity, PIPAC is a minimally invasive procedure that enables repeated delivery of chemotherapeutic agents into the peritoneal cavity with high bioavailability [15,25].

The pathophysiology of peritoneal carcinomatosis underscores the need for early, localized intervention. Tumor cell adhesion, anoikis resistance, and colonization of hypoxic niches such as milky spots occur before macroscopic lesions develop. By targeting this early dissemination phase, PIPAC may interrupt key metastatic steps and reduce peritoneal spread in high-risk patients [7]. Although PIPAC has already demonstrated promising results in the treatment of PM from various solid tumors, its role as a preventive approach remains insufficiently studied. This research emphasizes the early application of PIPAC in patients at high risk of peritoneal dissemination, which may reduce the likelihood of PM development in the postoperative period. If the hypothesis is confirmed, the findings could support the integration of PIPAC into standard treatment protocols for locally advanced gastric cancer and potentially reshape existing clinical practice [15].

However, several questions require further investigation. First, it is essential to determine the optimal PIPAC regimen, including the number of cycles, choice of chemotherapeutic agents, and their dosages. Second, the potential complications associated with repeated aerosol chemotherapy administration remain unclear. Third, it is crucial to assess the impact of PIPAC on patients' QoL, particularly over the long term. Comparing the results of this study with data on HIPEC and systemic chemotherapy will enable a comprehensive evaluation of PIPAC's effectiveness and help define its role within the multimodal treatment paradigm for gastric cancer. Additionally, the development of a novel device for aerosol drug delivery may enhance dosing accuracy, improve drug distribution within the peritoneal cavity, and potentially increase therapeutic efficacy [15,26].

Thus, this study holds significant clinical importance, as its findings could contribute to refining current strategies for the treatment and prevention of PM. If successful, it will serve as a foundation for future multicenter trials aimed at validating the results and further optimizing the method. These aspects underscore the relevance of the proposed research and its potential to improve oncological care for patients with locally advanced gastric cancer.

Limitation and Potential Biases

Prophylactic PIPAC in cytology-negative potentially curable patients has an uncertain risk benefit: possible harms include laparoscopic complications, adhesions, port-site issues, and cumulative intraperitoneal chemotherapy toxicity. Any reduction in early peritoneal relapse may not translate into overall-survival benefit. As a single-center, nonrandomized study, selection/confounding, learning-curve effects, and PM ascertainment error remain possible despite standardized imaging and scheduled laparoscopy. We mitigate these via consecutive screening with a prospectively maintained allocation-reason log, standardized pathways and follow-up, propensity-score weighting with prespecified balance targets, blinded PM adjudication, and multiple imputation for baseline covariates. Analyses are estimation-focused (effect sizes with 95% CIs), and findings will inform a subsequent multicenter randomized controlled trial.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization: AK, TU
Funding acquisition: AG
Methodology: TS, MM, SS
Project administration: GY, A Rakhmankulov
Resources: TK, ZB
Writing – original draft: BU
Writing – review & editing: A Rakhmankulova, DK

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT checklist.
[DOCX File , 34 KB - resprot_v14i1e78053_app1.docx]

Multimedia Appendix 2
TIDieR checklist.
[PDF File (Adobe PDF File), 235 KB - resprot_v14i1e78053_app2.pdf]

Multimedia Appendix 3
TREND statement checklist.
[PDF File (Adobe PDF File), 218 KB - resprot_v14i1e78053_app3.pdf]

Multimedia Appendix 4
ChatGPT conversations.
[DOCX File , 23 KB - resprot_v14i1e78053_app4.docx]

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Abbreviations

FLOT: 5-fluorouracil, leucovorin, oxaliplatin, and docetaxel
HIPEC: hyperthermic intraperitoneal chemotherapy
PIPAC: pressurized intraperitoneal aerosol chemotherapy
PM: peritoneal metastasis
QoL: quality of life
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TIDieR: Template for Intervention Description and Replication
TREND: Transparent Reporting of Evaluations with Nonrandomized Designs

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Protocol

Culturally Tailored Tele–Mental Health Care Linkage for Indigenous Populations: Protocol for a Mixed Methods Pilot Study

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Abstract

Background: Urban Indigenous populations face disproportionate mental health challenges, including high rates of posttraumatic stress disorder, depression, and substance use disorders, yet they have limited access to health services, especially culturally relevant care. The mechanism for providing care to Indigenous people in the United States, the Indian Health Service, is significantly underfunded and only accessible to certain Indigenous people. With more than 70% of Indigenous individuals in the United States living in urban settings, there is a growing need for innovative health care solutions. A community-based, Indigenous-led health and mental health–focused nonprofit in the northeast United States developed ShockTalk, a tele–mental health linkage-to-care app tailored specifically for Indigenous communities, to fill this gap.

Objective: This study aims to assess (1) the feasibility, including accessibility, experience, and value, of ShockTalk for practitioners and clients interested in providing or receiving culturally responsive mental health treatment, and (2) changes in client attitudes related to tele–mental health treatment value and trust in ShockTalk technology.

Methods: This study outlines the development and pilot study of ShockTalk. The conceptual framework is based on the behavioral model of health care use. ShockTalk uses artificial intelligence to connect clients with Indigenous or culturally aligned therapists and facilitates access to care via Facebook Messenger. Using a prewaitlist or postwaitlist design, 5 client participants will be admitted to the study at first, and 5 additional participants at 3 months. Data collection includes presurveys and postsurveys on client attitudes toward mental health treatment and trust in the ShockTalk platform at baseline and a 3-month follow-up, followed by in-depth qualitative interviews at 3 months. A preliminary economic evaluation will track direct costs (ie, therapist time, platform fees, and administrative expenses) and compare relative costs across treatment doses. Analyses will assess the feasibility of data collection and inform a future full-scale trial.

Results: This study was funded in April 2022. Data collection occurred between May 2022 and October 2024. In total, 4 client participants and 2 therapist participants were enrolled. Data analysis is complete and results are expected to be published in February 2026.

Conclusions: This pilot study will offer insights into optimizing technology-based, culturally relevant mental health care. By examining varying levels of engagement and associated costs, this research seeks to identify the most effective and cost-efficient strategies for improving mental health outcomes in urban Indigenous populations in the United States. ShockTalk has the potential to shape future health care innovations in this field. Findings are expected to contribute significantly to Indigenous mental health care by offering insights into sustainable, accessible, and culturally appropriate telehealth interventions, guiding future policy and practice.

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(JMIR Res Protoc 2025;14:e67757) doi:10.2196/67757

KEYWORDS

Native American; Indigenous; tele–mental health; telehealth; linkage-to-care; culturally tailored; depression; anxiety; substance use disorder; mental health; posttraumatic stress disorder; PTSD; qualitative interviews; artificial intelligence; AI; conceptual posttraumatic framework; social media; public health

Introduction

Background

We use the term *Indigenous*, which does not center on arbitrary geopolitical lines, to describe American Indian, Native American, and Alaskan Native populations in what is now known as the United States. Urban-living Indigenous people experience disproportionately higher rates of mental health disorders [1,2], often as a result of forced isolation from their homelands of origin, communities, and a lack of adequate mental health care resources [3,4]. The most significant mental health concerns facing urban Indigenous communities include a high prevalence of substance use disorders [5], depression, suicide, anxiety [6], and posttraumatic stress disorder (PTSD) [2]. For example, estimates of rates of PTSD among Indigenous people range from 16% to 24% [7-9], which is 3 times the rate of lifetime PTSD among the general population [10], and rivals the lifetime rate (29%) among US veterans returning from Iraq and Afghanistan [11].

Access to Mental Health Services

Addressing the mental health disparities among Indigenous communities that reside in urban contexts presents unique challenges. The Indian Health Service (IHS), created in 1955 through Public Law 568, The Transfer Act of 1954, exists to fulfill the US government's treaty obligations and legal responsibilities to provide health care to Native American and Alaska Native tribes [12]. The IHS is currently funded at less than half of its required budget [13] and faces significant challenges, including barriers to service, staffing shortages, extended wait times, and diminished access to quality care [14]. Notably, the IHS dedicates only 1% to 2% of its line budget to urban Indian health programs, which are funded only through contracts, and many of these programs have limited capacity [15]. Due to colonial policies, such as the termination, boarding school, and relocation eras, many Indigenous community members have been displaced from their original homelands into urban areas [16]. As a result, more than 70% of Indigenous people, specifically those identified as American Indian or Alaska Native, in the United States today live in urban areas [17], of which only 25% live within an IHS service area [15]. The discrepancy between the location of Indigenous medical services and the areas in which most Indigenous individuals in the United States live poses a significant challenge, highlighting the need for health care innovation.

Furthermore, the rates of health insurance coverage are markedly lower for Indigenous people compared with those for non-Hispanic White individuals, compounding this health disparity. As of 2019, just over half (51.9%) of Indigenous individuals alone or in combination had private health insurance coverage [6]. The percentage of Indigenous people who were enrolled in Medicaid or other public health insurance coverage was 42.9%, and 14.9% of Indigenous individuals did not have health insurance coverage; the comparative rates for non-Hispanic White individuals were 74.7%, 34.3%, and 6.3%, respectively [6]. Therefore, there is a profound need to improve and expand systems of care to help urban Indigenous individuals access affordable mental health treatment.

Telehealth and Indigenous Populations

Telehealth, or telemedicine, uses two-way, real-time telecommunication audio and video technologies, such as computers, tablets, or smartphones, to deliver health care services and public health [18]. Telehealth interventions allow health care providers to meet with patients remotely to diagnose, consult, treat, educate, and manage care, and they also allow patients to manage their care [19]. Implementing care and interventions among underserved populations through telehealth has been shown to be feasible and cost-effective [20], with the ability to be culturally tailored to meet the needs of Indigenous populations [21]. In a recent scoping review regarding telehealth use by Indigenous populations from Australia, Canada, New Zealand, and the United States [21], 47% of the 321 studies identified used mobile health (mHealth), and 26% focused on mental health. Indigenous communities expressed concerns regarding privacy and confidentiality, limited broadband internet, uncertainty in their ability to use the technology, and lack of trust in the therapeutic relationship. However, collaboration with Indigenous communities to develop and implement the intervention and offer Indigenous health care providers or cultural liaisons (13%) in its delivery indicated an increase in cultural safety. Notably, none of the identified studies discussed interventions that served solely as a linkage to mental health care or facilitated a way for Indigenous clients to identify mental health support.

With these goals in mind, this manuscript provides a detailed protocol for the feasibility pilot of the first tele–mental health linkage-to-care app tailored specifically for Indigenous communities, named ShockTalk. The purpose of the telehealth app is to improve access to culturally relevant mental health care for Indigenous individuals. The following section outlines the conceptual framework, the process of development for the mobile app, and identifies the needs of community members.

Conceptual Framework

The proposed research is informed by the behavioral model of health care use [22], which aims to understand how health care use and health-related outcomes are influenced by predisposing, enabling or inhibiting, and need factors at both the individual and contextual (eg, community and policy level) characteristic levels. Individual and contextual factors also influence personal health practices and care processes. In an iterative cycle,

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outcomes affect subsequent predisposing and enabling factors, the perceived need for health services, and health behavior.

Figure 1 depicts the conceptual framework of this study. The variables shown in black font will be included in our preuse and postuse survey. Guided by these findings, primary data collection and analysis of in-depth interviews will seek to better understand the components of the conceptual model in gray font (eg, process of medical care). This study focuses on the relationship between *individual characteristics* and subsequent *health behaviors*.

Figure 1. Conceptual framework for the ShockTalk pilot study. PTSD: posttraumatic stress disorder.

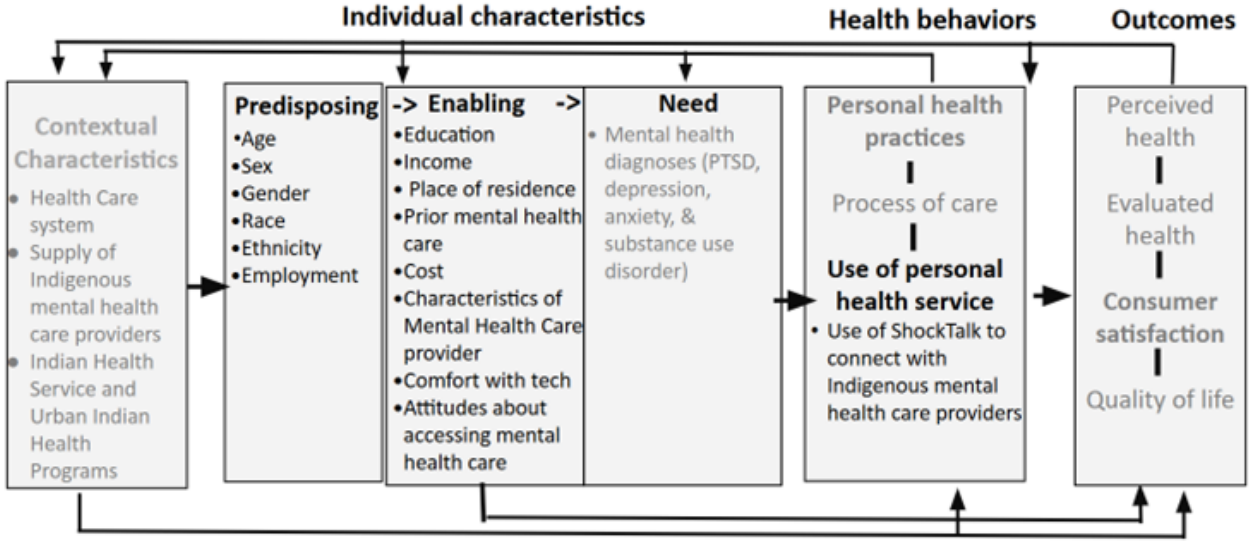

Preliminary ShockTalk App Development

ShockTalk was conceptualized by 3 New York City–based Indigenous individuals with experience in social work, public health, technology, and research. To better understand the barriers to and facilitators of culturally responsive mental health service access in urban areas for Indigenous individuals, 70 in-depth interviews with self-identified Indigenous individuals were conducted by the community-based partner team who originally conceptualized this app with community members and mental health clinicians in the urban area of Lenapehoking (specifically, in what is now known as New York City). The findings of this assessment are presented in Table 1. Finances, lack of insurance, and lack of systems to help Indigenous clients identify culturally appropriate service providers were identified as the most prominent barriers through qualitative analyses. Facilitators of care included sliding-scale service offerings and connections to Indigenous service providers or health care providers that match the client on other statuses or identities.

Table 1. Themes from the preliminary ShockTalk development.

Theme	Findings
Structural barriers to accessing therapy	• Perceived stigma of accessing therapy • Need for variety of therapeutic settings, online, in person, and “meet the client where they are” • Lack of availability of Indigenous therapists • Access to therapy, including telehealth • Limited scheduling and availability, and a cumbersome process
Interpersonal barriers to accessing therapy	• Lack of comfort with the therapist • Uncertainty about online therapy • Fear of not having a cultural connection • Cost • Lack of spiritual component in Western-dominant therapy
Characteristics of an ideal therapist	• Ability to connect deeply with someone “beyond the surface” who is “down to earth” • Relational (ie, compassionate and lets the person talk) vs advice giving • Can assure privacy and trust, especially in a small community • Shared characteristics and understanding of experience • Shared understanding of trauma and colonization • Understanding of Indigenous culture, experiences, and ways of knowing • Share Native or Indigenous identity who better understand the “everyday struggle” connected with Indigenous identity • History of working with Indigenous people “in a good way” • Feel connected • Can offer cultural or spiritual coping mechanisms and tools

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ShockTalk App: How It Works

ShockTalk (Figure 2) is a mobile app that uses Facebook Messenger as its entry point for clients. When a client first connects, they are greeted by ShockTalk's artificial intelligence (AI) assistant, which guides them through the initial process. The AI collects basic contact information, helps synchronize important dates directly to the client's calendar, and offers an option to schedule a 15-minute intake session with a licensed therapist from ShockTalk's vetted health care provider directory. Before the intake appointment, the AI sends reminder messages to help clients prepare. During the intake, the therapist and client discuss needs, goals, and preferences. Together, they decide whether the therapist is a good fit for ongoing care. If so, they begin a therapeutic relationship within the platform. If not, the therapist helps connect the client to other appropriate services or health care providers.

Figure 2. Preview of the ShockTalk tele–mental health linkage-to-care app.

Objective

The ShockTalk team has partnered with a researcher affiliated with the Columbia University School of Social Work to evaluate the pilot and feasibility of this app, which will involve interviews with 10 Indigenous mental health treatment seekers in Lenapehoking and 3 practitioners. The aims of this research are as follows: (1) assess changes in client attitudes related to tele–mental health treatment value and trust in ShockTalk technology; (2) assess the accessibility, experience, and value of ShockTalk for practitioners and clients interested in providing or receiving culturally responsive mental health treatment; and (3) estimate the potential benefit of the culturally responsive mental health treatment facilitated by ShockTalk. The ultimate evaluation of this pilot program will assess the prospective benefits of tele–mental health care linkage for Indigenous individuals living in urban settings.

Methods

Overview

To test the feasibility of ShockTalk among Indigenous clients, we will conduct a small pilot study with 10 Indigenous therapy-seeking clients and 3 Indigenous mental health practitioners in Lenapehoking. This study was designed as a preliminary feasibility pilot to inform a larger trial and, therefore, was not prospectively registered.

After informed consent and baseline assessment, clients will be randomly allocated 1:1 to immediate access to ShockTalk (treatment) or to a 3-month waitlist control (5 clients per arm). The allocation list will be generated by a study team member not involved in enrollment and uploaded to a centralized randomization module, which will reveal the assignment only after baseline data entry. Allocation events will be logged. In the absence of a centralized system, sequentially numbered, sealed opaque envelopes prepared from the same allocation list will be used.

All participants will complete baseline surveys and a 3-month follow-up survey (3 months postrandomization). Waitlist participants will be offered access to the linkage-to-care intervention 3 months after their initial baseline survey is completed. Qualitative data collection at 3 months from baseline will include 1-hour semistructured interviews (Multimedia Appendix 1) with a purposive subsample of 5 clients (selected to reflect a range of engagement and experiences across arms) and a single focus group with participating practitioners. Finally, a preliminary cost analysis will be conducted using data from

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both arms to assess the feasibility of cost data collection and to generate exploratory cost estimates across varying levels of engagement. Analyses will be descriptive and feasibility-focused (ie, recruitment, retention, acceptability, and data completeness); inferential effectiveness claims will not be made given the pilot sample size.

Study Sample Recruitment

Ten Indigenous clients and 3 Indigenous practitioners will be recruited to assess the feasibility and acceptability of ShockTalk on care linkage among therapists and clients. This proposed sample size aligns with other pilot and feasibility studies, which are not powered for hypothesis testing and are instead based on the pragmatics of recruitment [23]. Therapists will be contacted directly via email from a listserv that was previously compiled through the ShockTalk company website. Therapists who signed up with their names and email addresses and consented to being contacted later will be contacted by our team about their continued interest in ShockTalk and whether they would participate in the pilot program of the app. Indigenous therapy-seeking participants will be recruited via the ShockTalk internal listserv and social media posts on Facebook, Instagram, and X (formerly Twitter), which will include brief information about the study, compensation, and participant expectations.

Inclusion and Exclusion Criteria

Participants will be screened for the following eligibility criteria: (1) are aged at least 18 years, (2) self-identify as Indigenous to North, South, Central Americas, or the Caribbean, and (3) live in New York State. Individuals are not eligible if they live outside of New York State, do not self-identify as Indigenous, or are less than 18 years of age. Practitioners will be screened for the following eligibility criteria: (1) are a mental health professional licensed to practice in New York State and (2) self-identify as Indigenous to North, South, or Central America or the Caribbean.

Data Safety and Monitoring

The study facilitator, under the supervision of the principal investigator, will monitor data. Data will be securely stored on a password-protected computer, laptop, and on a password-protected Google Drive associated with the study facilitator's university-administered email address. Hard-copy data will be stored in a securely locked filing cabinet in the study coordinator's office, to which only the study facilitator will have access. All data collection will be entirely anonymous; no identifiers will be associated with the ID number labeled on the data.

Potential Risks

Despite best efforts to protect privacy and confidentiality, participants face a risk of potential loss of confidentiality. During the health care provider focus group, there is a potential for loss of confidentiality, although all participants are asked to keep their involvement in the study and what is shared during the focus group private. During an in-depth interview, there may be risks associated with discussing potentially stressful subjects. There is no more than a minimal risk of any harm to participants.

Potential Benefits

Participants may benefit from increased access to a culturally relevant mental health therapist. Some participants may find the in-depth interview process empowering and therapeutic in experience. Additionally, the information collected from this research may help others in the future.

Ethical Considerations

This study has been approved by the Columbia University Institutional Review Board (AAAU0850). The study coordinator will contact client and practitioner participants to determine their eligibility and to discuss the study purpose, risks, benefits, and compensation. During this meeting, the study coordinator will also obtain informed consent. Participants will be provided with an electronic version of the consent form and will be asked to sign and return the form at the end of the call.

Participants will be informed that they can opt out at any point during the study. Data will be anonymized, and no names or other identifiable features of research participants or users will be disclosed in any manuscript or supplementary material.

Participants (therapy seekers) will be compensated US $10 for completing each survey, one at baseline and one at 3 months follow-up. Participants (therapy seekers) will receive US $30 for completing an in-depth interview. In total, participants are eligible to receive a total of US $50 for completing both surveys and the in-depth interview. Additionally, as a part of participating in this study, participant clients will have the cost of their therapeutic sessions covered, up to 5 sessions and no more than US $600. Therapist participants will be compensated with US $40 for completing the focus group session.

Dissemination

Initial findings will be disseminated first to participants to obtain their feedback and to ensure that the themes that are developed from the qualitative interviews align with their experience and accurately represent their views. Additionally, results from this study will be disseminated in culturally relevant and accessible ways, such as community meetings, social media posts, and a community-facing report that will be developed with ShockTalk. Findings will be used to improve the current ShockTalk app and linkage-to-care process. The results will also be used to facilitate the search for additional sources of funding to implement broader assessments.

Measures

Quantitative Measures

The first survey instrument will examine changes in attitudes related to tele–mental health treatment value for clients before and after treatment facilitated by ShockTalk. One month before treatment and 3 months after treatment, clients will be given the Attitudes Toward Seeking Professional Psychological Help-Short Form survey [24]. This survey measures participants' openness to seeking professional help for emotional problems and the value and need for seeking professional help. Clients are asked whether they disagree, partly disagree, partly agree, or agree with an item, including questions such as, "The idea of talking about problems with a psychologist strikes me as a poor way to get rid of emotional conflicts" and "A person with

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an emotional problem is not likely to solve it alone; he or she is likely to solve it with professional help." Their attitudes toward seeking professional help are scored based on the sum of all responses. The short version of the scale demonstrates internal consistency ranging between 0.82 and 0.84, and high test-retest reliability (a=0.80) [24]. Once the presurveys and postsurveys are collected, the study team will examine the differences in openness to treatment before and after ShockTalk. A positive difference between the pretreatment and posttreatment Attitudes Toward Seeking Professional Psychological Help-Short Form score will indicate an increase in client valuation of mental health care treatment. *t* tests (1-tailed) will be used to evaluate whether the differences are statistically significant.

The second survey addresses trust and accessibility in tele–mental health care services and linkage services for clients. Clients will be asked 5 items each from the Trust in Technology and Trust in Telemedicine Service scales from the Patient Trust Assessment Tool (PATAT) [25]. The PATAT is a trust benchmarking survey and, currently, the only instrument that provides a comprehensive measurement of trust in an eHealth service and the underlying trust concepts. Clients will respond to questions related to their trust in technology and telemedicine surveys using responses on a Likert scale, which ranges from totally disagree (1) to totally agree (5). Questions from the Trust in Technology subset include items such as "Everything done on ShockTalk remains private" and "The personal information that is stored at ShockTalk will not get lost." Items from the Trust in Telemedicine Service include questions such as "I trust ShockTalk less than other online services." In conjunction, these 2 quantitative surveys will assess practitioner and client trust in the ShockTalk app and changes in client valuation of treatment resulting from culturally appropriate telehealth care linkage.

Qualitative Measures

To identify potential service gaps or accessibility concerns in the ShockTalk app, we will conduct in-depth interviews with the practitioners and clients 3 months after treatment participation. Practitioners will be interviewed in a talking circle, a technique consistent with Indigenous methodologies [26]. In the talking circle, practitioners will be asked a series of open-ended questions related to their past experiences with telehealth care linkage systems and how ShockTalk compares with other systems in terms of accessibility, organization, and usability. They will also be asked about their favorite elements of the app, any problems they experienced, and potential improvements that might benefit both the client and the practitioner. The qualitative interview consists of 6 base questions with several probing questions. The talking circle is expected to take 1 to 2 hours.

Clients will also engage in one-on-one in-depth interviews. Although talking circles may be preferable to facilitate discussions, the sensitive nature of the client interviews prevents the study team from conducting discussions of this type. Clients will be asked about their previous experiences in therapeutic contexts, how their experience in therapy resulting from ShockTalk is similar to or different from those experiences, and what could be done to make the app more accessible. Clients are asked to walk through the process of accessing ShockTalk and discuss points at which the app was not intuitive or was problematic. After discussing the process and experience of using the app, clients will be asked about their process in choosing and retaining a therapist—what therapist attributes were most important in deciding on a therapist, what factors influenced a therapeutic fit, and what influenced their likelihood of rescheduling with the therapist they saw. Finally, clients are asked about any potential changes or improvements they would make to improve their experience. Each client interview is expected to take 30 minutes to 1 hour.

Planned Analysis

Qualitative Analysis

To analyze the qualitative data, an exploratory approach within an applied thematic analysis framework will be used in this study. Following the 6 phases of thematic analysis of Braun and Clarke [27], the process will begin with familiarization through repeated readings of the interview transcripts and initial memo writing to capture early analytic impressions. In the next stage, initial codes will be generated inductively from the data. Codebooks will be developed separately for client and practitioner transcripts, allowing codes to reflect participant language and meaning while attending to the study's focus on the accessibility, experience, and value of ShockTalk.

After coding, the research team will search for themes by collating related codes into broader categories that capture patterned responses across the dataset. These candidate themes will then be reviewed for coherence and consistency within and across transcripts. To enhance rigor, 2 researchers will independently code transcripts, and coding decisions and candidate themes will be refined collaboratively during team meetings.

In the defining and naming stage, themes will be further refined to ensure clear boundaries and internal coherence, and concise names and definitions will be developed to represent their essence. Finally, the reporting phase will involve weaving together the analytic narrative with illustrative quotations from participants to demonstrate how themes capture client and practitioner perspectives on ShockTalk's accessibility, user experience, and value, and to link these findings back to the research objectives.

Cost Analysis

Given the pilot nature and limited sample size of this study (n=10), the economic evaluation is not designed to conduct a formal cost-effectiveness analysis. Instead, the cost analysis is focused on assessing the feasibility of cost data collection, identifying relevant cost components, and reporting preliminary, descriptive cost estimates across varying levels of engagement with the ShockTalk intervention.

We will adopt a health care provider perspective for this analysis, capturing the direct costs related to service delivery through the ShockTalk app. These costs will include (1) therapist compensation for up to 5 sessions per client, (2) platform use and administrative costs, and (3) personnel time involved in

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scheduling, coordination, and support. The time horizon for the analysis is 3 months, aligning with the study's follow-up period.

Clients' level of engagement will be characterized by treatment dose, defined as the number of therapy sessions completed during the 3-month period. Although we will descriptively report outcomes stratified by dose (eg, 1-2 sessions and 3-5 sessions), no inferential comparisons across groups will be made.

The primary outcome for exploratory effectiveness assessment in the cost analysis will be the change in client attitudes toward mental health treatment, as measured by the ATSPPH-SF. Secondary outcomes include trust in technology and telemedicine, measured via the PATAT, and client engagement, operationalized through session attendance and app interaction data.

This feasibility-focused cost analysis aims to determine the viability of collecting accurate and comprehensive cost and outcome data in a small-sample, community-engaged study context. Given the pilot nature of the study, these analyses are intended to test the feasibility of collecting cost data and to provide exploratory estimates to guide the design and analytic strategy for a future, fully powered economic evaluation.

Quantitative Analysis

Quantitative analysis will involve linear mixed-effects models to understand the impact of different treatment doses on mental health outcomes, accounting for repeated measures and potential intragroup correlations. ANOVA will be used to compare the mean outcomes across the dose groups. Because of sample size limitations, we acknowledge that *t* tests and ANOVA may be underpowered to detect the true impact of the intervention on changes in attitudes surrounding therapy. In tandem with the cost analysis, the ANOVA will provide insights into the optimal balance between treatment effectiveness and cost, guiding resource allocation and decision-making for culturally responsive mental health services delivered through the ShockTalk app.

Results

This study was funded in April 2022. Data collection occurred between May 2022 and October 2024. During this period, 4 client participants and 2 therapist participants were enrolled. Data analysis is complete and results are expected to be published in February 2026.

Discussion

Anticipated Findings

Given the limitations of the service provisions of IHS to service Indigenous communities in the United States, there exists a pressing need to connect urban-living Indigenous people to mental health services. The purpose of this work is to assess the potential of ShockTalk, the first tele–mental health care linkage app created for Indigenous treatment seekers, to improve the landscape of treatment. This research is novel as there is no current assessment of this kind and is salient given the significant mental health concerns of this population. Overall, the findings of this work are expected to facilitate improved mental health care provisions for a population of exceptional need.

Limitations and Future Research

Due to the nature of the pilot and feasibility aims and funding limitations, the outcomes of this work will be limited by the sample size. Specifically, it is not possible to establish statistically significant differences in outcomes before and after treatment with only 10 participants. However, this pilot study was intentionally sized to address feasibility objectives (recruitment yield, retention, acceptability, and protocol fidelity) and to produce actionable, community-driven improvements to the intervention and study procedures before a larger trial could be conducted. Practical constraints also informed the sample size: the project is community-partnered and prioritizes culturally appropriate engagement and data sovereignty, which limits rapid scale-up; the pilot grant resources were modest; and protecting participant confidentiality in a small, close-knit community was a priority. The findings from this pilot study will be used to refine measures, define progression criteria, and calculate sample sizes and power for a subsequent randomized trial. The results of this pilot program will be used to seek additional funding opportunities, which will be used to fund additional sites of research across the United States. Additional data collection will be performed to increase the statistical power for quantitative analysis and improve the generalizability of the results.

Conclusions

The disproportionate burden of mental health disorders among urban Indigenous community members highlights the critical need for innovative and culturally responsive health care delivery systems. ShockTalk, as the first tele–mental health care linkage app designed specifically for Indigenous individuals, represents a promising intervention to bridge this gap. This pilot study's comprehensive evaluation of ShockTalk will provide valuable insights into how culturally responsive, technology-mediated mental health treatments can be optimized and tailored to meet the unique needs of Indigenous clients in urban settings. By assessing different intensities of engagement and their associated costs, this research aims to identify the most effective and economically viable treatment strategies.

The findings from this study are poised to significantly contribute to the field of Indigenous tele–mental health care by demonstrating the potential benefits of integrating culturally relevant telehealth services into broader mental health support frameworks. By examining variations in treatment doses and their impact on client trust, engagement, and overall satisfaction, we aim to delineate the most effective approaches for delivering mental health care that is culturally appropriate and accessible to this population. The integration of a cost-effectiveness analysis further ensures that the proposed solutions are sustainable and scalable. Future expansions of this research, supported by additional funding, will extend these insights to a larger and more diverse subset of the urban Indigenous population, ultimately guiding policy and practice toward more equitable mental health care provisions.

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Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are not publicly available due to the small sample size and sensitive participant information but are available from the corresponding author upon reasonable request.

Authors' Contributions

Conceptualization: AMSR, SK, and AS
Funding acquisition: AMSR
Investigation: ALR
Methodology: AMSR and ALR
Project administration: AMSR
Writing—original draft: AMSR and ALR
Writing—review and editing: SK and AS

Conflicts of Interest

SK and AS are the founding members of ShockTalk and hold shares in the company.

Multimedia Appendix 1
Client and health care provider interview and focus group guide.
[DOCX File , 16 KB - resprot_v14i1e67757_app1.docx]

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Abbreviations

AI: artificial intelligence
IHS: Indian Health Service
PATAT: Patient Trust Assessment Tool
PTSD: posttraumatic stress disorder

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Protocol

Feasibility of mHealth Strategies to Promote Use of Wrist-Worn Alcohol Biosensors Among Young Adults With HIV: Protocol for the Engage Microrandomized Trial

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Abstract

Background: Alcohol use among young adults with HIV is disproportionately high compared to other age groups with HIV, despite its negative health-related consequences. However, alcohol use interventions tailored to the interests and needs of young adults with HIV are scarce. Self-management interventions that include self-monitoring components have the potential to improve chronic illness outcomes and mitigate alcohol misuse. Although wearable technologies promote self-monitoring behaviors and facilitate the delivery of personalized feedback, people rarely adhere to the long-term use of wearables.

Objective: The primary aim of this pilot study is to test the feasibility and acceptability of translating theoretically grounded reciprocity and personalized feedback strategies. These strategies will be delivered through app-based messages to promote engagement in wearing a wrist-worn alcohol biosensor among young adults with HIV.

Methods: A total of 40 young adults with HIV (aged 18-29 years) will be enrolled in a 30-day pilot microrandomized trial (MRT). The MRT is an experimental design that facilitates the development and optimization of mobile health just-in-time adaptive interventions. Participants will wear the BACtrack Skyn biosensor, a wrist-worn transdermal alcohol biosensor, and play a smartphone-based game geared toward earning points to care for virtual animals. Longer alcohol biosensor wear time will translate into earning more game points. Every morning and evening, participants will be randomized at equal probability to receive (1) a reciprocity message offering a no-strings-attached gift of either 100 game points or US $1, (2) a message with personalized feedback about their Skyn biosensor wear time, or (3) no message.

Results: Data collected during this 30-day MRT will be used to examine the feasibility and acceptability of translating theoretically grounded strategies into messages suitable for a mobile health alcohol intervention tailored to young adults with HIV. Recruitment for this study began in spring 2024, with data collection wrapping up in spring 2025.

Conclusions: This pilot MRT will provide valuable feasibility and acceptability data and set the stage for a full-scale MRT to optimize the integration of reciprocity and personalized feedback into a just-in-time adaptive intervention that increases engagement in biosensor-based alcohol self-management among young adults with HIV.

Trial Registration: Clinicaltrials.gov NCT05431855; https://clinicaltrials.gov/study/NCT05431855

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KEYWORDS

HIV; microrandomized trial; transdermal alcohol sensor; mobile health; wearable technology; self-monitoring; gamification; engagement

Introduction

Background

High-risk alcohol consumption, defined as drinking ≥4 standard drinks for women and ≥5 drinks for men in 1 sitting, is a major health concern among young adults aged between 18 and 29 years [1-3]. Alcohol consumption is especially common among young adults with HIV. Research shows that young adults with HIV exhibit disproportionately high rates of alcohol use disorder (AUD) compared to the general youth population, as well as other age groups of people with HIV [4]. High-risk alcohol consumption in this population can lead to detrimental health-related consequences, such as a higher likelihood of HIV transmission through risky sexual behaviors, increased risks for comorbidities such as declined liver and cognitive functioning, and lower adherence to antiretroviral medications that may lead to viral nonsuppression and disease progression [5-9].

Despite the clear need for interventions to address high-risk alcohol consumption among young adults with HIV, few interventions are tailored to meet their needs or interests. Existing alcohol interventions for young adults with HIV often fail to sustain behavior change beyond the intervention period, limiting their long-term effectiveness [10-17]. Furthermore, young adults with HIV may fear stigma [18] and often have limited access to intensive, in-person interventions; clinical resources [19-21]; and transportation [22,23]. Mobile health (mHealth) interventions delivered through smartphones and wearable technologies are promising for young adults with HIV because 98% of US young adults own smartphones [24]. However, there are a limited number of real-time mHealth alcohol use interventions for young adults with HIV. One promising approach to improving chronic illness outcomes and mitigating high-risk alcohol use and AUD is through the use of mHealth interventions to deliver self-management strategies such as self-monitoring.

Self-monitoring is a key strategy for supporting behavior modification across a number of health interventions, ranging from those focused on increasing weight loss and physical activity to reducing substance use, including unhealthy drinking habits [25-28]. Self-monitoring allows individuals to monitor their behaviors (eg, alcohol consumption); assess progress on their behavioral goals; and, through self-reflection and reinforcement, adjust their behaviors to achieve their goals [27-29]. Such self-monitoring behavior is a key component of many successful behavior change interventions [30].

Wearable technologies support systematic and continuous self-monitoring and the collection of individual data that can be used to generate personalized feedback and other information to support self-monitoring. However, the benefits of wearables for self-monitoring can only be achieved if used consistently [31]. This presents a challenge because many people abandon wearable technologies after only minimal use [32,33]. These findings suggest the need for research to identify different strategies for increasing consistent engagement with mobile-based, self-monitoring technologies [34,35].

Several theoretically grounded engagement strategies have been shown to help promote behaviors that improve self-monitoring [3,33]. Providing personalized feedback is a simple and effective way to motivate individuals to self-monitor their behaviors, including alcohol consumption [30]. For instance, in a meta-analytic review of randomized controlled trials testing alcohol interventions, Scott-Sheldon et al [36] found that personalized feedback was a significant predictor of a variety of alcohol-related outcomes, including quantity of alcohol consumed, frequency of heavy drinking, and alcohol-related problems. Reciprocity, another theoretically grounded strategy, can also promote engagement in behaviors that enhance self-monitoring. Reciprocity refers to an innate tendency of humans to want to return favors and acts of kindness [37-39]. For instance, if an individual receives a small amount of money as an incentive, regardless of whether or not they engage with (eg, use) an intervention, this may inspire them to reciprocate or give back by increasing their investment in the intervention, thus promoting greater self-monitoring of their drinking behaviors.

Self-monitoring can be further enhanced by incorporating those engagement strategies into a just-in-time adaptive intervention (JITAI). JITAIs aim to provide real-time mHealth support in a person's natural setting. They adapt over time to changes in an individual's internal states and surrounding contexts to deliver the right type of support at the right time [40-42]. For instance, a JITAI can be designed to deliver the right type of message (eg, either reciprocity or personalized feedback) at the right time (eg, first thing in the morning before a busy day when the person is more receptive and thus willing and able to use an intervention message) to engage participants in behaviors such as self-monitoring [41].

A microrandomized trial (MRT) is a novel experimental study design that helps optimize (ie, construct) a JITAI. During an MRT, participants are randomized repeatedly (eg, several times per day) over time (eg, several days or weeks) to different intervention options (eg, messages using reciprocity vs personalized feedback). The data collected from an MRT can be used to analyze which intervention option is more effective in increasing the target behavior (eg, self-monitoring) and at what time, under what contexts, or to whom it is more effective. This information can in turn be used to develop a JITAI that delivers the right type of support at the right time to promote engagement in self-monitoring behaviors [43,44].

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Objectives

This study is a first step toward building a JITAI to improve the engagement of young adults with HIV through increasing wear time of the BACtrack Skyn, a wrist-worn alcohol biosensor [45]. Over the past 5 years, wrist-worn transdermal alcohol biosensors have emerged as a promising new tool for continuous monitoring of alcohol use (for more detailed review on wrist alcohol biosensors, refer to the studies by Wang et al [46-48]). These alcohol biosensors can detect alcohol use passively by measuring the small fraction (<1%) of ingested alcohol that is excreted through the skin and producing continuous transdermal alcohol concentration [49] readings every 20 seconds that reflect near real-time alcohol consumption. Although the new-generation of wrist-worn alcohol biosensors are much more user-friendly compared to the previous generation of transdermal alcohol biosensors (eg, the SCRAM continuous alcohol monitor anklet; AMS Inc), adherence to wearing the sensor is still a challenge, especially for long-term use that is essential for sustaining self-monitoring and improving health outcomes [50].

The primary aim of the proposed pilot study is to test the feasibility and acceptability of integrating theoretically grounded reciprocity and personalized feedback engagement strategies into an mHealth intervention designed to increase engagement in Skyn biosensor wear time among young adults with HIV. A secondary aim is to explore for whom and under what conditions different strategies are best for promoting the engagement (Skyn biosensor wear time) of young adults with HIV.

Methods

Population

Up to 40 young adults with HIV (aged 18-29 years) will be enrolled to participate in this study. We expect an attrition rate of approximately 25%, yielding an anticipated final sample size of 30 participants. The HIV status of young adults with HIV will be verified in one of the following three ways: (1) viral load results obtained from a health care professional (eg, primary care physician) that is uploaded directly by participants, (2) viral load results uploaded by the provider upon request, or (3) completion of a dried blood spot test collection kit sent to the participant.

Recruitment and Screening

Participants will be recruited through social media platforms (eg, Instagram) via a recruitment service (ie, Build Clinical) and from HIV clinics across the state of Florida. Interested individuals will be screened based on the following eligibility criteria: participants must be aged between 18 years 0 months and 29 years 11 months; reside in the state of Florida for the duration of their study enrollment; have had at least 1 alcoholic beverage in the last 30 days; have been diagnosed with HIV; not be pregnant at the time of screening; have internet access via smartphone, tablet, or computer; and be able to read and understand English. Participants must also be willing and able to participate in the study for the entire 30-day study period. Participants will be informed that they can earn up to US $240 for completing all portions of the study. Participant recruitment began in spring 2024.

Data Collection Procedures

Eligible participants will be instructed to watch a web-based consent video and read an informed consent document outlining the details of the study, including its risks and benefits. Participants who consent to participate will complete a web-based survey to collect sociodemographic information (eg, race, ethnicity, gender, and socioeconomic status) and baseline data on individual characteristics. The individual characteristic items include measures of risk taking, depression, alcohol use, substance co-use (eg, tobacco, nicotine, prescription medications, and opioids), perceived stress, and personality. All study staff interacting with participants are trained in crisis mitigation and follow a comprehensive protocol to evaluate levels of distress risk and corresponding risk management. Any participant identified as high risk based on their responses to baseline questionnaires will be directly referred to a licensed clinical psychologist on the study team for further assistance. Once participants have completed the baseline survey, they will be scheduled for a videoconference-based onboarding session with research staff using Zoom (Zoom Video Communications, Inc).

Before the onboarding session, participants will be mailed a BACtrack Skyn biosensor to a preferred address, along with instructions for how to download and use each study-related app. All participants who do not own an iPhone will also be mailed a study iPhone that is compatible with the Skyn sensor (which is currently only compatible with an iOS system) to facilitate study inclusiveness and data collection. All study-related apps will be preinstalled on the study iPhone.

The onboarding session will take place virtually over Zoom. During this session, research staff will train participants on how to use the Skyn biosensor and guide them on how to download (if using their own iPhone) and use its associated app (Skyn app), an ecological momentary assessment (EMA) app for momentary and daily brief surveys on alcohol use, and an engagement wrapper (e-wrapper) app (described in the e-Wrapper App section). Participants will also receive instructions on how to sync or upload their Skyn sensor data using the Skyn app. Participants will be informed that they may reach out to study staff should they have questions or issues related to the study materials.

Study Design

Participants who complete all baseline measures will be enrolled in a 30-day pilot MRT study (refer to the MRT Design section). Participants will be instructed to wear the Skyn biosensor for as many hours a day as possible during the 30-day study period. The research staff will make it clear that the sensor should be worn continuously and can only be removed for the purpose of charging the battery or when it is likely to be submerged under water (eg, baths and swimming) to avoid potential damage to the sensor. The battery life of the Skyn sensor is approximately 10 to 14 days, and participants will be instructed to charge the device ideally when they will not be wearing it anyway (eg, while taking a bath).

Each morning, participants will receive a short EMA survey on their smartphone to self-report their drinking and other substance

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use behavior in the past 24 hours, as well as their adherence to antiretroviral therapy, sexual behaviors, quality of sleep, and any difficulties they encountered with the use of the Skyn biosensor.

In addition to the morning EMAs, participants will also receive random EMAs 3 times a day to assess their current mood, stress, urge to consume alcohol, confidence and self-efficacy to resist drinking, current location, and alcohol and other substance use behaviors since the time of the last EMA. Individuals who self-report drinking alcohol will initiate an additional event-contingent survey that gathers more details about the location where they consumed alcohol, the type of alcoholic beverage they consumed (eg, beer or liquor), and whether they were in the presence of other people.

e-Wrapper App

Wearing the Skyn sensor increases one's awareness of their drinking behaviors and will serve as a tool to promote the self-monitoring of alcohol use. Thus, it is critical that participants wear the sensor regularly throughout the intervention period. As participants in mHealth studies frequently abandon the use of wearable devices [31], it is necessary to identify strategies to enhance engagement [3,33,51], specifically time spent wearing the Skyn sensor. Principles of computer-human interaction suggest that incorporating gamification into an intervention can promote engagement [52,53]. Gamification [54,55] integrates game-like design components and principles into interventions to provide meaningful and sophisticated techniques to engage participants in mHealth behavior change interventions [56-58]. However, relying on incentives (eg, money and game points) alone for reward can undermine intrinsic motivation if an individual does not feel a personal connection to the activity [3,57,59,60], in this case, to the game.

To leverage the positive impacts of gamification strategies and promote greater intrinsic motivation through building a connection to the intervention, we developed an e-wrapper app. mHealth intervention apps tend to focus on the behavioral (eg, self-monitoring) tasks at hand, for instance, providing people with a platform for listing their goals or tracking when they drink alcohol. The e-wrapper app described here is novel because it can be paired with (eg, "wrap around") existing apps that aid in self-monitoring activities to offer additional incentives that can elicit interest and connection to the intervention, further enhancing intrinsic motivation to engage individuals in the self-monitoring activity. A variety of gamified apps, including those with virtual characters such as avatars and animals, have been shown to promote engagement in young adult populations [52,61-63], including young adults with HIV [64-69]. The gamified e-wrapper app is designed to sustain intrinsic motivation by providing an enjoyable interactive experience where the e-wrapper game challenges participants to make choices about caring for virtual pets. Upon starting the game, participants are initially given a virtual pet (eg, giraffe) living in a preselected "habitat" and 200 points to use toward care of the pet.

In addition to their first virtual pet, participants may also purchase additional pets from a list of options: a giraffe, an ostrich, or a salamander. Participants can also purchase a virtual baby pet (or in the case of the ostrich, an egg) with the goal of raising the pet into adulthood. Several reward-based engagement strategies are embedded within this gamified app (Figure 1) to further promote engagement, but these stay consistent across the study for all participants and are thus not part of the microrandomization. For instance, participants can personalize each pet (eg, giving names) to increase their connection with their virtual pets. As part of the game, participants must care for each of their pets by feeding them, providing water, and offering treats. They can use points to purchase 1-time quantities of food and water, meal packages that cover 5 feedings, individual treats or treat bundles, additional habitats (eg, forest), and various hats to dress up their pets (refer to Table 1 for full point allocations).

Participants can also earn additional points to care for their pet or pets by opening the app on consecutive days, by wearing their Skyn biosensor for a longer amount of time (Table 1), and through an additional engagement message strategy described in the MRT Design section. This metric for points based on wear time (engagement) provides the highest reward to those who wear their sensor at least 80% of the time and also allows participants to remove the Skyn biosensor when showering or charging the device.

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Figure 1. Gamified engagement wrapper (e-wrapper) app used to further promote engagement in the self-monitoring intervention.

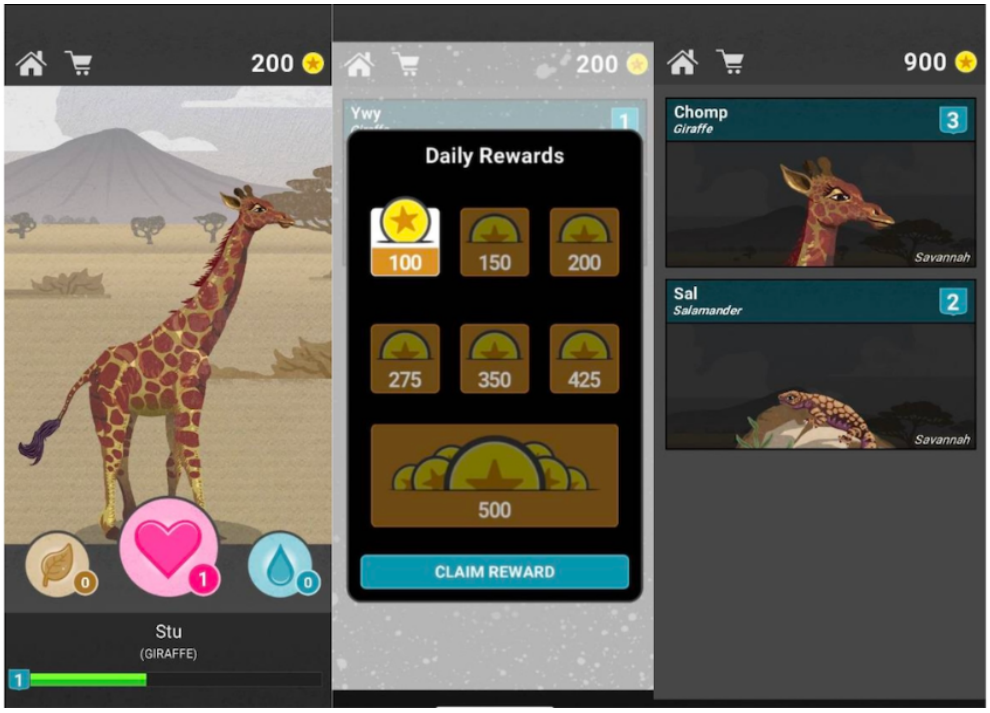

Table 1. e-Wrapper ranch game point allocation.

Game costs		Game points award schedule					
Items to purchase	Point totals	Consecutive day e-wrapper app opening (each week)	Point totals	Skyn biosensor wear time (h/d)	Point totals	Point-based reciprocity messages	Point totals
Food	50	Day 1	100	0	0	Each message	100
Water	50	Day 2	150	1-18	100	__[a]	—
Meal packages (food or water for 5 feedings)	200	Day 3	200	19-24	200	—	—
Individual treats	150	Day 4	275	—	—	—	—
Treat packages (5 treats)	600	Day 5	350	—	—	—	—
Accessories (eg, hats)	500-4000	Day 6	425	—	—	—	—
Habitats	2000	Day 7	500	—	—	—	—
Animals	1000	—	—	—	—	—	—

[a]Not available.

MRT Design

Overview

An MRT is an experimental design that provides empirical data to facilitate the development and optimization of mHealth JITAIs [40,43,44]. MRTs accomplish this by providing information on the proximal effects of specific interventions, changes in these effects over time, and the psychological and contextual factors that moderate these time-varying effects [43,44]. Here, participants are randomized repeatedly at equal probability to receive message prompts framed around reciprocity, personalized feedback, or to receive no message (refer to the Message Strategies section). Rerandomizing to different options throughout the study allows for the collection of data on under what internal states and external contexts, as well as at what time in the intervention [3], different intervention options may be more or less effective. Findings from an MRT allow researchers to better determine how and when an intervention component should be delivered to optimize the efficacy of that intervention. JITAIs have become increasingly common in recent years for preventing and treating substance use disorders [3,40], as JITAIs adapt to the changing internal and external contexts of individuals to provide support in the moments when an individual is most in need [40-42]. For example, a JITAI can promote engagement by intervening in those moments when an individual is likely to abandon use of the Skyn biosensor. This pilot MRT study will serve as the foundation for the development of a future JITAI.

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Message Strategies

To promote greater engagement with the BACtrack Skyn biosensor, we selected two theoretically grounded strategies that may be effectively translated into messages suitable for delivery through the e-wrapper mHealth app: (1) reciprocity and (2) personalized feedback.

Reciprocity

As described briefly in the Introduction section, reciprocity relies on the notion that giving a small, no-strings-attached reward will activate a human tendency to return favors and kind actions [37-39]. In other words, a small gift that is not contingent on the target behavior (Skyn biosensor wear time) will plausibly inspire the person to reciprocate by doing the desired behavior (wearing the Skyn biosensor). Prior research has shown that reciprocity can be translated into messages suitable for an mHealth intervention [33,40], making this strategy particularly appealing. The ideal form of the gift, however, remains unclear. Here, we operationalize reciprocity as either a gift of 100 points to use for care of the virtual pet in the e-wrapper app or as a US $1 gift. Points will be awarded in the e-wrapper app immediately for use in the game, while free money gifts will be paid to participants at the end of the study. We anticipate each participant may be awarded approximately 1000 points and US $10 total across the course of the study. Providing 2 different types of reward will help us determine if and when providing free game points or money is more effective for increasing the Skyn biosensor wear time.

Personalized Feedback

A second strategy that can promote Skyn biosensor engagement is personalized feedback about wear time. Personalized feedback entails directly showing an individual how much they are engaging in a specific behavior. This feedback enhances participants' awareness of their behavior and offers a foundation to guide future improvements [15]. By delivering encouraging messages that highlight how much time people are spending wearing the Skyn biosensor, it is possible to increase one's motivation to wear the biosensor for a greater duration of time.

Message Development

The study team translated the reciprocity and personalized feedback strategies into initial messages suitable for delivery in an mHealth intervention. To do this, we obtained feedback on these messages from community advisers in two phases. First, we collected feedback through a survey of Amazon Mechanical Turk workers consisting of members of the general population who were recruited using the CloudResearch Platform [70]. Next, we interviewed members of an expert advisory board consisting of individuals with a similar sociodemographic makeup (eg, young adults, majority from a racial and ethnic minority group) as the target population. Community advisers in these formative stages rated the messages in terms of how much they liked the messages and how likely they thought the messages would be able to promote the intended behavior (eg, wearing the Skyn sensor). They also provided suggestions for how to improve the messages. This feedback was used to iteratively refine the messages in preparation for the pilot MRT study. Messages were designed so that clicking on the message would automatically open the e-wrapper app. Table 2 includes examples of these messages.

Table 2. Sample engagement messages generated by the study team and revised by community advisers.

Message type	Message
Reciprocity (money)	"Got the blues today? How about some green! (app)'s added a $1 gift to your (cash account)."
Reciprocity (game points)	"Hey there! Your animal(s) miss you. Here are 100 free bonus credits from (app) to your Ranch account. Treat them today!"
Personalized feedback	"Look at you being productive! You wore your Skyn sensor for <<XX>> hours yesterday. Keep going!"

MRT Randomization

A key feature of the MRT design is that participants are randomized at various points in time (ie, decision points) across the study to answer scientific questions about if and when the delivery of specific types of messages (ie, reciprocity or personalized feedback) is likely to promote an outcome of interest [33,40,41,51], such as engagement. In this pilot study (Figure 2), during 2-hour time windows every morning (between 8 and 10 AM) and evening (between 6 and 8 PM) for 30 days, participants will be randomized at equal probability to receive (1) a reciprocity message, (2) a personalized feedback message about their Skyn biosensor wear time, or (3) no message. When the reciprocity messages are delivered, there is an equal probability they contain either a no-strings-attached gift of (1) 100 game points or (2) US $1. Participants will not receive any messages one-third of the time to explore whether, under some internal or external conditions, it may be best to not send a message. Messages will be sent as push notifications from the e-wrapper app to the study iPhones.

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Figure 2. Microrandomized trial design. Microrandomizations occur twice daily for 30 days.

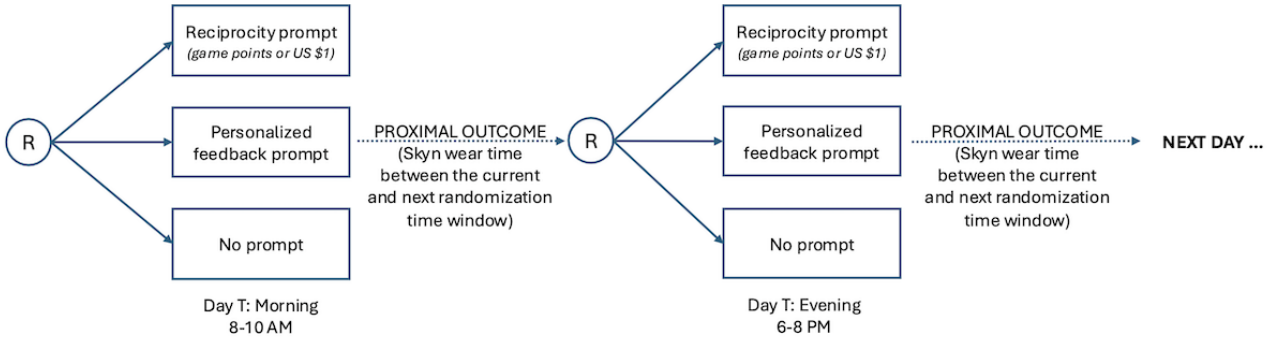

Poststudy Assessment

At the end of the 30-day MRT phase, participants will be asked to complete a poststudy assessment online. In this assessment, they will self-report on the feasibility and acceptability of integrating the theoretically grounded strategies into messages to promote engagement in Skyn biosensor wear time. Participants will also provide ratings of feasibility and acceptability (including liking and usability) regarding use of the Skyn biosensor and e-wrapper app.

Study Compensation

The total compensation that participants can earn for completion of all aspects of the study is US $240. Table 3 outlines the compensation schedule, including compensation type and amount earned for completing each component of the study. For the EMA bonus, if participants complete ≥80% of delivered EMAs, then they will receive a US $10, US $20, US $30, and US $40 bonus for each of the 4 weeks. Note that while recruitment began in spring 2024, the bonus was implemented after the first 4 participants were recruited to improve study retention. If participants fall below 80% compliance, then they will restart at the week 1 bonus rate of US $10. Including the base pay and bonuses, participants can receive up to US $160 for EMA completion. Finally, US $100 will be deducted from total earnings if the study iPhone and BACtrack Skyn biosensor are returned damaged or >2 weeks from the time of study completion, and no compensation will be provided if devices are never returned. Research staff will monitor data collection immediately following onboarding of each participant and contact them via phone (call or SMS text message) and email as soon as possible if data are missing on the EMAs, Skyn biosensor, or e-wrapper app within the first 2 days. We will similarly follow up with participants who are noncompliant with the study protocol, defined as missing data on the EMAs, Skyn biosensor, or e-wrapper app for more than a couple of days, or have not returned the equipment.

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Table 3. Study compensation.

Compensation type	Amount (US $)
Baseline survey	25
HIV viral load DBS[a] sample	10
DBS sample for phosphatidylethanol test	10
EMA[b] completion rate (%)	
≥80	60
60-79	50
50-59	40
40-49	30
20-39	20
0-20	10
EMA bonus schedule (for streaks of ≥80% completion)	
Week 1	10
Week 2	20
Week 3	30
Week 4	40
Poststudy follow-up survey	35
Maximum possible	240

[a]DBS: dried blood spot.
[b]EMA: ecological momentary assessment.

Statistical Considerations and Data Analysis

Study Outcomes

The primary purpose of this pilot MRT study is to assess the feasibility and acceptability of two key aspects of the intervention: (1) delivering messages to promote engagement in wearing the Skyn biosensor and (2) linking engagement (ie, Skyn wear time) to playing the e-wrapper game. In addition, we will evaluate whether delivering a message prompt versus no message prompt will increase Skyn biosensor wear time between the current and the next randomization time window (eg, the 8 h between the morning and evening randomization windows; Figure 2).

Feasibility and Acceptability Measures

As the main purpose of a pilot MRT is to assess the feasibility and acceptability of the study to refine the procedures and materials in preparation for a full-scale MRT, participants will be asked to complete a post-MRT assessment with questions related to how much they liked the messages and how much they thought the messages encouraged them to engage. For instance, participants will be asked to rate “How much did you like the messages you received?” on a scale ranging from 1 (*not at all)* to 5 (*very much*). Information will also be gathered on participant perceptions of the number and frequency of messages received. Participants will then rate the feasibility and acceptability of using the e-wrapper app and indicate how much they liked the app and its usability. Metrics of feasibility will also be assessed from paradata, including information on how often message notifications were clicked, how often the app was opened, how much time participants spent using the app, and how long participants wore the Skyn biosensor.

Analysis Plan

Feasibility and acceptability data will be analyzed using descriptive statistics (eg, frequencies, means, medians, and proportions). Results of this pilot MRT study will inform the development of a future full-scale MRT to test the optimal timing for delivering reciprocity and personalized feedback messages to promote proximal (time between the current and next randomization) sensor wear time (our proxy for self-monitoring). The pilot MRT data will be analyzed using a novel approach specifically developed to ensure unbiased estimates of causal effects of time-varying treatments for binary outcomes [71]. These analyses will pool time-varying, longitudinal data across all study participants and allow for marginal comparisons, that is, comparisons of intervention options without conditioning on participants’ full history of prior treatment [71]. Such marginal comparisons allow us to answer questions about the causal relationship between delivering a message and the outcome of interest (ie, Skyn biosensor wear time), as well as how such effects differ based on an individual’s internal states and external contexts. This analysis approach is preferred to other common methods for analyzing MRT data, such as random-effects models and generalized estimating equations, which may result in biased causal effect estimates for time-varying treatments and covariates [71]. This MRT will investigate whether providing any engagement strategy (either reciprocity or personalized feedback) will affect sensor wear time following

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microrandomization. Specifically, we will test whether there is an average proximal effect of the engagement strategies on the amount of sensor wear time in the window between the current and next randomization at each decision point during the study. Our proximal outcome is 75% engagement, which is a common average engagement goal for mHealth modalities, including those involving wearables [72-75]. For the pilot analysis, wear times of ≥75% of the total time between the current and next randomization (eg, ≥6 h when there are 8 h between prompt microrandomizations) will be coded as 1=engaged and wear times <75% (eg, <6 h when there are 8 h between prompt microrandomizations) will be coded as 0=not engaged. This will provide flexibility by considering instances when participants may not wear the sensor, for example, when they are bathing or charging the Skyn biosensor.

Power Analysis and Sample Size

Although the main purpose of this pilot study is to assess feasibility and acceptability, we conducted preliminary power analyses to begin exploring the comparison of receiving any prompt versus no prompt on Skyn biosensor wear time. Across the 30 days of the pilot MRT study, participants will be randomized twice daily with one-third probability to receive (1) reciprocity prompts (US $1 or 100 e-wrapper game points), (2) personalized feedback prompts (indication of the percentage of time they have worn the Skyn sensor either in the past day or over the course of the study), or (3) no prompts. For this exploratory study, a sample size of 40 participants will enable us to detect an average proximal treatment effect on a relative risk scale of at least 1.32 (ie, 16% improvement with any prompt, assuming participants will wear the sensor ≥75% of the time between prompt microrandomizations at least 50% of the total time) in favor of receiving any reciprocity or personalized feedback prompt (vs no prompt), with 80% power. These calculations are based on a 2-sided 0.05 type I error rate, 25% attrition, and 25% anticipated availability (ie, to receive a message; for instance, are not busy at work, commuting, or did not turn off SMS text message notifications on their phone) and were conducted using an established MRT power analysis calculator [76]. The conservative attrition and availability rates were identified based on existing work suggesting that populations with chronic diseases such as HIV have generally high attrition and low availability in mHealth-based research [41]. We aim to recruit 40 participants, anticipating that 30 will complete the trial, accounting for an expected 25% attrition rate.

Ethical Considerations

This pilot MRT is registered with Clinicaltrials.gov (NCT05431855) and approved by the Florida State University Institutional Review Board (STUDY00002534). Informed consent will be obtained from all individuals, and compensation disclosed, before enrollment in the study. Study IDs will be used to link data so no personal identifiers will be used in analyses. Once data linkage is completed, only deidentified datasets will be used for data analysis to protect participant privacy.

Results

Recruitment for the study began in spring 2024, with data collection wrapping up in spring 2025. Analyses of the feasibility data and exploratory analyses of the pilot MRT prompt data will begin in summer 2025. Initial manuscript submissions for the feasibility and exploratory MRT findings are expected in fall 2025. We expect these manuscripts to be published in 2026.

Discussion

Anticipated Findings

We anticipate the main findings of the pilot study to indicate that intervention components are acceptable and study procedures are both acceptable and feasible. This study makes a key contribution to the existing literature by laying the initial groundwork to develop a future JITAI that uniquely combines theoretically grounded strategies and a gamified app to promote Skyn alcohol biosensor wear time among young adults with HIV. The main limitation of this study is that because it is a pilot, results will focus on feasibility and acceptability, and the trial is not powered to test the effects of different prompt types on Skyn alcohol biosensor wear time.

Feasibility and acceptability results from this pilot MRT study will guide refinements to study procedures and to intervention components to set the stage for a full-scale MRT. These results will also allow us to determine the percentage of missing data across study measures (eg, EMAs), which will guide the development of future retention strategies. Although the primary purpose of this study is to assess the feasibility and acceptability of the proposed procedures, data collected during this 30-day pilot MRT will also be used to begin exploring when and for whom a prompt may promote engagement (wear time) with the BACtrack Skyn alcohol biosensor. We also seek to understand how feasible and acceptable it is to connect Skyn biosensor wear time to the e-wrapper app, including how appealing participants find the app and how highly they rate it on likeability and usability. We plan to disseminate findings from this pilot study through manuscript publications, conference presentations, and community outreach (eg, newsletters).

Conclusion

The future full-scale MRT will be appropriately powered to test the effects of different prompt types on Skyn biosensor wear time (engagement). Results of the full-scale MRT will optimize the integration of reciprocity and personalized feedback into a JITAI that provides the right support at the right time to increase engagement in biosensor-based alcohol self-management practices among young adults with HIV. By promoting greater Skyn biosensor wear time, this research has the potential to positively impact self-monitoring of alcohol use among young adults with HIV, which in turn may reduce high-intensity drinking behaviors and lower the risk of developing AUD.

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Acknowledgments

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Data Availability

The datasets generated or analyzed during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

SMC drafted the manuscript and contributed to the study design and creation of the engagement wrapper (e-wrapper) app. SC contributed to the study design, study coordination, creation of the e-wrapper app, and manuscript revisions. MLAL contributed to the study design, creation of the e-wrapper app, and manuscript revisions. LRM contributed to the study design, creation of the e-wrapper app, and manuscript revisions. QY contributed to the creation of the e-wrapper app and manuscript revisions. KM contributed to the study conception and manuscript revisions. SN contributed to the study conception and manuscript revisions. YW contributed to the study conception, design, creation of the e-wrapper app, and manuscript revisions.

Conflicts of Interest

None declared.

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Abbreviations

AUD: alcohol use disorder
EMA: ecological momentary assessment
e-wrapper: engagement wrapper
JITAI: just-in-time adaptive intervention
mHealth: mobile health
MRT: microrandomized trial

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Protocol

Evaluating the Impact of Telehealth Exercise Prehabilitation on Cardiometabolic Health in Bariatric Surgery Candidates: Protocol for the BARI-Prehab Randomized Controlled Trial

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Abstract

Background: Obesity affects over one billion people globally and is a leading contributor to chronic disease. For those with clinically severe obesity, metabolic and bariatric surgery (MBS) is the most effective intervention for long-term weight loss. However, surgery is often delayed due to systemic barriers, during which time patients may experience further health decline. Low cardiorespiratory fitness is a known risk factor for perioperative complications, prompting recommendations for prehabilitation to target readiness for surgery. Despite this, few patients meet physical activity guidelines, and supervised preoperative exercise programs are rarely offered in routine care. Telehealth-delivered exercise programs offer a promising solution, but evidence of their feasibility, acceptability, and impact in the MBS setting remains limited.

Objective: This study (BARI-Prehab) aims to assess the efficacy and acceptability of a telehealth-delivered prehabilitation exercise program in improving cardiometabolic health among patients awaiting MBS.

Methods: In this multicenter, open-label, randomized controlled trial, we will randomize 48 adult participants (1:1) to either usual care (control group) or a 4-week telehealth exercise intervention. The primary outcome is aerobic capacity (VO_2 in mL/kg/min at the anaerobic threshold), measured using cardiopulmonary exercise testing. Secondary outcomes include resting heart rate, heart rate variability, resting metabolic rate, body composition, grip strength, and 7-day physical activity. Intervention acceptability will also be evaluated.

Results: Data collection and analysis are ongoing. This trial, funded in September 2020, will evaluate the capacity of a telehealth exercise program to improve cardiometabolic health and determine its suitability for implementation in the MBS preoperative pathway. Following initial protocol development, ethics approval, and trial setup, the clinical phase formally commenced with registration on June 16, 2023. Enrollment is ongoing, with a projected end date of March 2026. As of May 2025, a total of 220

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patients have been screened for participation, of whom 30 have enrolled in the trial. The first results are expected to be submitted for publication by mid-2026.

Conclusions: The BARI-Prehab trial will provide evidence on the acceptability and impact of a remotely delivered exercise intervention in the context of MBS. These findings will have implications for the design of accessible, scalable preoperative care models. The significance of this research lies in its potential to guide clinical practice, inform policy, and improve health outcomes for patients undergoing MBS.

Trial Registration: ClinicalTrials.gov NCT05235945; https://clinicaltrials.gov/study/NCT05235945

International Registered Report Identifier (IRRID): DERR1-10.2196/77538

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KEYWORDS

bariatric surgery; cardiorespiratory fitness; digital healthcare; exercise; obesity; perioperative care; prehabilitation; telehealth

Introduction

Background

In 2022, over one billion people were classified as living with obesity, making it a well-recognized and critical global public health concern [1]. A multitude of individual [2], community [3], and countrywide [4,5] weight-management initiatives have been used; yet, the epidemic continues. For those living with clinically severe obesity (BMI ≥35 kg/m^2, or ≥30 kg/m^2 with comorbidities), metabolic bariatric surgery (MBS) has been shown to be the most effective treatment for weight loss compared to nonsurgical interventions [6,7]. However, eligible patients often face barriers to accessing surgery, such as extended wait-list times and costs [8]. Since obesity is a chronic progressive disease, it is likely that, without intervention, body mass and associated comorbidities may be negatively impacted by delays to surgery.

Surgical procedures, regardless of type, constitute a traumatic disruption to the body and are associated with a measurable stress response, which varies in intensity depending on the severity of the trauma [9]. Cardiorespiratory fitness (CRF) is considered a key indicator to predict the ability of a patient to withstand surgical injury in an adaptive manner [10]. For patients undergoing MBS, a lower CRF (<15.8 mL/kg/min) is associated with an increased risk of perioperative complications, including myocardial infarction, deep vein thrombosis, pulmonary embolism, renal failure, or death [11]. Current guidelines for Enhanced Recovery After Surgery recommend tailored preoperative physical activity (PA) interventions, or "prehabilitation," in the lead-up to MBS to assist with patients' functional recovery [12]. Improving PA levels has been reported to play an important role in postsurgical weight loss and its maintenance [13], in addition to well-established long-term physical and mental health benefits for people with obesity [14,15]. The timing of exercise programs before surgery is also important for establishing healthy behaviors, maintaining lean tissue, and mitigating potential decreases in metabolic rate [16]. Moreover, during this period, patients are yet to face challenges of recovering from surgery, including postoperative diet adaptation and loss of muscle strength.

The majority of MBS candidates do not meet PA recommendations, and consequently, often have associated reduced levels of CRF [17,18]. It has been established that exercise interventions in individuals with obesity should involve a combination of vigorous-intensity aerobic and high-load resistance training for the improvement of CRF [19]. In clinical populations, alternating short periods of vigorous-high intensity exercise with rest or low-intensity periods has been shown to be safe and effective for improving cardiometabolic risk factors and CRF in as little as 2 weeks [20-22].

Despite this, there is limited evidence supporting exercise services as a standard treatment in perioperative care for MBS patients. Supervised exercise programs are not commonly practiced in Australia or the United Kingdom, and unsupervised programs often have low participation rates [23,24]. Previous studies have identified several barriers reported by both clinicians and patients, including cost, limited access to exercise facilities, and time constraints [25]. Telehealth has emerged as a practical solution to address such barriers [26,27]. Evidence from recent studies supports the feasibility and acceptability of telehealth in MBS candidates [28-32]. However, these have typically focused on postsurgical populations, used group-based formats, or relied primarily on unsupervised digital resources. While these studies show promise for telehealth approaches, they also reveal a gap in evidence regarding the impact of supervised, individualized, preoperative exercise interventions for MBS candidates.

Several trials have been conducted to assess the effectiveness of a variety of exercise programs for patients with obesity, both before and after MBS. Overall, the evidence is limited by small sample sizes, insufficient long-term follow-up (<1 year), and differing methodologies and time frames for assessment [33,34]. Body mass change is often the primary outcome, while objective measures of fitness and PA, such as cardiopulmonary exercise testing (CPET) and accelerometry, have rarely been reported [33]. While the evidence in MBS is sparse, preoperative exercise and improved fitness in patients with obesity have been associated with reductions in cardiometabolic risk and early death [11]. Given the rising prevalence and detrimental impact of obesity, there is a need to explore strategies that can mitigate unfavorable outcomes in the perioperative period. Exercise prehabilitation may offer a scalable and impactful approach to improving patient readiness and resilience. Integration of such models into routine care pathways remains underexplored. This study therefore aims to evaluate the effect of a structured,

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telehealth-delivered prehabilitation exercise intervention on cardiopulmonary fitness in patients awaiting MBS.

Objectives

This randomized controlled trial, BARI-Prehab, aims to evaluate the efficacy of an exercise intervention in the preoperative MBS setting. Specifically, we will (1) objectively measure changes in cardiometabolic health–related parameters with an exercise intervention and (2) determine the acceptability of an online–delivered exercise program for patients preparing for MBS before surgery.

Methods

Ethical Considerations

Ethics approval has been granted by the Derby Research Ethics Committee (21/EM/0230) and the University of South Australia Human Research Ethics Committee (204474). The trial was registered on January 12, 2022, in ClinicalTrials.gov (NCT05235945). Each potential participant is given at least 24 hours to decide whether to participate after receiving the information sheet. Those who decide to participate will be invited to the laboratory to sign the consent form on the morning of their scheduled preassessment anesthetic clinic visit. They will receive a hard copy of both the information sheet and signed consent form and will have the opportunity to ask any study-related questions. Participants are free to withdraw at any time without providing a reason and without this affecting any benefits to which they are entitled. To ensure confidentiality, all identifiable data will be stored in a password-protected document or in a locked filing cabinet. The chief investigator is the custodian of personal data. Access to storage and premises will be limited to research team members only. All data will be anonymized and pseudonymized. A unique ID will be assigned to each participant once enrolled in the study. Access to participants' personal data will be restricted to research personnel only. Only anonymous data will be used in publications or presentations. The University College London (UCL) Data Protection Policy will be adhered to. Participant engagement strategies will be implemented, including compensation for travel expenses and provision of an exercise band (used during the intervention) to support adherence.

Trial Design

BARI-Prehab is a multicenter, open-label, randomized controlled trial designed to test the effect and acceptability of a novel preoperative exercise program in patients scheduled for MBS. The sponsor for this trial is University College London Hospitals (UCLH) National Health Service (NHS) Foundation Trust. Participants will be randomized to either a control group (usual care) or a 4-week supervised exercise intervention group, using a 1:1 allocation ratio. The study flow diagram is shown in Figure 1, and Table 1 outlines the exercise intervention. The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) reporting guidelines [35] have been used.

Figure 1. BARI-Prehab study design. Abbreviated assessment items include fat mass (FM), fat-free mass (FFM), resting metabolic rate (RMR), volume of oxygen consumption at anaerobic threshold (VO_{2AT}), and maximal oxygen consumption (VO_{2max}). Physical activity is monitored throughout the intervention period using 7-day (7d) accelerometry, and 4-week (4w) recall using an exercise diary.

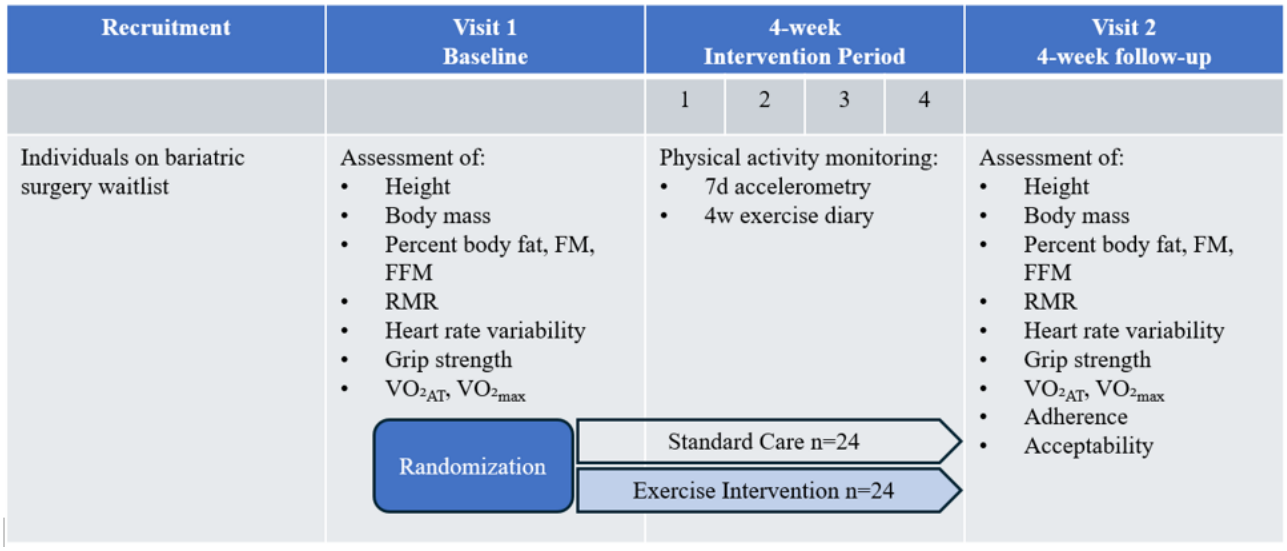

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Table 1. BARI-Prehab trial intervention session design. Exercises are tailored to match each participant's abilities, with the goal of reaching a perceived exertion (RPE) level of 5/10 (described as "hard"). Intensity is achieved by modifying factors such as range of motion (ROM), additional muscle groups engaged, or movement speed.

Phase	Exercise	Level 1	Level 2	Level 3
Warm-up (5 minutes)	Compound movements involving large muscle groups and dynamic stretches	__[a]	—	—
1	Sit-to-stand	Supported (wall)	Unsupported	Compound (+arms)
2	Wall push-up	Isometric	Full ROM	Plyometric
3	Lunge twist	Tap back	Supported (chair/wall)	Compound (+arms)
4	Standing oblique crunch	Supported (chair)	Unsupported	Increased ROM/speed
5	Deadlift + bent-over row	Without band	With band	Increased ROM
6	Walking squat	Isometric	Increased ROM	Compound (+arms)
7	Side reaches	Supported (chair)	Unsupported	Increased ROM/speed
8	Shoulder flexion + balance	Without band	With band	Increased ROM/speed
9	Arabesque/Standing hamstring curl	Supported (chair/wall)	—	Unsupported
10	Forward jabs (boxing)	Without band	With band	Compound (+legs)
Cool-down (5 minutes)	Dynamic and static stretches	—	—	—

[a]Not applicable.

Eligibility Criteria

Participants will consist of adults aged ≥18 years who are enrolled in the bariatric surgery programs at selected sites, with BMI ≥30 kg/m^2. Patients must have ≤5% variation in body weight over the preceding 3 months, be willing and able to comply with the trial protocol, and provide written informed consent.

A patient who meets any of the following criteria will be excluded from participation in this study: currently pregnant or lactating, body mass ≥180 kg (due to weight restrictions of equipment), currently using beta-blockers, participating in another clinical intervention trial, clinically significant medical comorbidities present (eg, uncontrolled hypertension, unstable cardiovascular disease) that could increase the risk of an adverse response to exercise [36], or a history of atrial fibrillation, unstable angina, acute coronary syndrome, or congestive heart failure (New York Heart Association class III–IV) within the preceding 12 months.

Sample Size

We will aim to enroll 48 participants. The sample size for this study was determined by detecting a clinically meaningful increase in anaerobic threshold (AT) in patients awaiting MBS. Previous research in a comparable patient cohort [37] reported a mean AT of 11.0 (SD 1.5) mL/kg/min among 95 patients. In this study, we aim to detect a 150 mL O_2 increase in AT, corresponding to a mean difference of 1.15 mL/kg/min between the two groups. This threshold was selected based on literature indicating that changes of approximately 0.75-1.25 SDs in AT are associated with improved perioperative risk profiles and functional capacity in surgical populations [37-39]. We calculated that a sample size of 21 participants per group would be sufficient to detect a 150 mL O_2 increase in AT, with a significance level of .05 and a power of 0.80. This calculation is based on having 2 repeated measurements per participant and an intracluster correlation of 0.5. Pilot research by Gilbertson et al [40] has informed our anticipated dropout rate of less than 10%, or 2 participants per treatment arm.

Recruitment

Eligible participants will be identified by the clinical team from the operating lists of recruiting hospitals, which are established at least 6 weeks before surgery. Identified patients will then be invited for enrollment by phone, where they are contacted by a research team member and provided with a participant information sheet. Patients will be offered opportunities to ask questions about the study and given time to consider enrolling. Recruitment will occur on a rolling basis at a rate of 5 patients per month. Recruitment rate assumptions will account for anticipated challenges, including those specific to the bariatric population. These may include mobility limitations, comorbid conditions, or logistical issues associated with travel for study assessments [25].

Allocation

Following enrollment, participants will attend a baseline testing visit (visit 1), where they will be allocated a unique subject number. Once baseline data collection has taken place, participants will be randomly assigned using an electronic third-party platform [41] to a treatment group—preoperative exercise intervention or usual care—on a 1:1 allocation basis. A member of the research team will generate the concealed allocation sequence, while a second researcher will assign participants to interventions. Members of the research team responsible for conducting preassessments and postassessments will be blinded to allocation. Participants and clinicians will not be blinded to allocation during the study, although all data will be analyzed blind to allocation.

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Interventions (Preoperative Exercise Group Only)

A 4-week structured exercise program will be delivered online using a cloud-based video conferencing service [42]. Participants in the exercise intervention group will individually undertake 7 instructor-led exercise sessions across the 4-week intervention period. In addition, participants will be provided with existing digital guidelines for presurgery exercise [43] and encouraged to participate in self-led PA on as many days as possible during the 4-week period. To guide this, participants will have access to prerecorded online exercises and are encouraged to replicate supervised sessions during each self-led session. The program is designed to meet the National Physical Activity Guidelines [44] of at least 150 minutes of low-to moderate-intensity or 75 minutes of vigorous PA per week, or a combination of the two [45]. Participants will be asked to record daily PA in an electronic diary, alongside a standardized exercise-related rating of perceived exertion [46] for each session and duration of exercise participation.

Sessions will be supervised by an accredited exercise physiologist, who is a university-qualified allied health professional with training in the design and delivery of safe and effective exercise interventions for people with chronic medical conditions, injuries, or disabilities [47]. Participants are offered a range of scheduling options to accommodate varying availability, including morning and afternoon time slots on both weekdays and weekends, with options within and outside standard business hours. If an appointment is canceled or missed, our protocol permits rescheduling within a 5-day window to maintain consistency with study timelines.

Each supervised session (Table 1) will consist of aerobic and resistance exercises, targeting all main muscle groups and tailored to participants based on their exercise history and limitations. Participants' baseline functional level will guide the targeted exercise prescription. Sessions will be prescribed at moderate- to vigorous-intensity (Table 2) for a 30-minute duration. A set of varying-resistance exercise bands will be provided for participants.

Intervention-group participants will receive weekly check-ins by text, emails, or phone call. The check-ins are designed to promote adherence to both the intervention program and their PA sessions. A summary of the content of participant communications is presented in Table S1 in Multimedia Appendix 1 [48-50], and is based on behavior change techniques such as goal setting, individualized feedback, and social incentive (ie, positive reinforcement), which have been shown to improve exercise participation in digital interventions [48-50].

Participants in the comparator group will receive the usual care provided at their respective treatment sites. This care varies across sites. It ranges from no formal intervention from the clinical team to inclusion of nutritional and psychological support but does not routinely involve structured or supervised exercise.

Table 2. Categories of exercise intensity and associated objective and subjective measures, such as percent of maximum heart rate (%HRmax), percent heart rate reserve (%HRR; heart rate reserve=HRmax−resting heart rate), and percent of maximal oxygen uptake (%VO_2max). Note: the relative intensity measures will not always correspond to the same rating of perceived exertion (RPE) among individuals, nor will the ability of participants to exercise for a specific duration at each intensity, since this varies depending on training status and other personal characteristics. Subjective measures are from Borg's [46] RPE scales, where C=category scale (6-20) and C-R=category-ratio scale (0-10). Adapted with permission from Norton et al [45].

Intensity	Objective measures	Subjective measures	Descriptive measures
Sedentary	• <1.6 METsa • <40%HRmax • <20% HRR • <20% V02max	• RPE (6-20): <8 • RPE (0-10): <1	Low energy requirement, such as sitting or lying activities
Light	• 1.6<3 METs • 40<55% HRmax • 20<40% HRR • 20<40% V02max	• RPE (6-20): 8-10 • RPE (0-10): 1-2	Aerobic activities that do not cause a noticeable change in breathing rate or can be sustained for ≥60 minutes
Moderate	• 3<6 METs • 55<70% HRmax • 40<60% HRR • 40<60% V02max	• RPE (6-20): 11-13 • RPE (0-10): 3-4	Aerobic activities that feel "light" to "somewhat hard" and can be conducted while maintaining a conversation; duration 30-60 minutes
Vigorous	• 6<9 METs • 70<90% HRmax • 60<85% HRR • 60<85% V02max	• RPE (6-20): 14-16 • RPE (0-10): 5-6	Aerobic activities during which a conversation cannot be maintained uninterrupted; duration up to 30 minutes
High	• >9 METs • >90% HRmax • >85% HRR • >85% V02max	• RPE (6-20): >17 • RPE (0-10): >7	Activities that feel "very hard" and generally cannot be sustained for longer than 10 minutes

[a]MET: metabolic equivalent of task.

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Outcomes

The primary outcome is oxygen consumption at the AT, expressed relative to body mass (mL/kg/min) or in absolute terms (mL/min), attained from maximal CPET. AT is a submaximal gas exchange threshold defined as "the VO_2 above which anaerobic metabolism supplements oxidative phosphorylation with additional carbon dioxide (CO_2) production" [51]. The gold standard method for determining AT is the V‑slope method [52], which identifies the first inflection point on the plot of CO_2 output versus O_2 uptake. Secondary outcomes, technical and data processing procedures, and equipment used are detailed in Table S2 in Multimedia Appendix 2.

At visit 1, all participants will undergo assessment of height, body weight and composition, resting heart rate and heart rate variability, resting metabolic rate, CRF, and grip strength. Participants will also be given an accelerometer to measure low-, moderate-, and vigorous-intensity PA patterns and sedentary behavior over a 7-day period. At the end of the 4-week intervention period, the baseline (visit 1) tests will be repeated for comparison (visit 2).

Following randomization, participants will receive an email containing allocation-specific instructions for the trial period and an electronic exercise diary. Participants in the intervention group will additionally receive a troubleshooting guide for online classes and a timetable of options for booking exercise sessions.

Acceptability

Intervention acceptability will be established by the Participant Satisfaction Survey responses on a 5-point Likert scale, where aspects of the intervention such as duration of sessions, equipment used, exercises included, supervision, and delivery mode are rated from "liked very much" to "disliked very much." This is measured only in the intervention group. Open-ended responses are requested for questions such as "What, if anything, would you change about the pre-surgery exercise program?"

Data Management

In accordance with UCL Data Protection Policy, study data will be collected and managed using the Research Electronic Data Capture tool [53] hosted at UCL. All data forms will be deidentified and paper copies will be double-entered and stored in the username- and password-protected electronic database. Electronic personal data will be stored separately from the study data in a password-protected document on encrypted UCL and NHS desktop computers. Pseudo-anonymized data will be stored on password-protected and encrypted UCL and NHS desktop computers.

Statistical Analysis Plan

Descriptive statistics will be used to summarize baseline characteristics and the primary outcome by treatment group, using mean (SD) and median (IQR) for continuous data and frequency (%) for categorical data. The distribution of the primary outcome will also be graphically investigated.

Treatment effect will be presented as the estimate and a 95% CI. This will be estimated from a linear mixed regression model with repeated measures of the outcomes at baseline and 4 weeks, with a random intercept for participants to account for correlations between repeated measures over time within participants. The model will include, as fixed effect a treatment arm indicator (during the follow-up phase only) and a time indicator (baseline or follow-up). All analyses will be performed on an intention-to-treat basis, and all modelling assumptions will be checked (eg, residuals).

A complier average causal effect estimate will be calculated to investigate potential effect of non-compliance. The number (%) of participants with missing outcomes will be summarized by treatment arm. A sensitivity analysis that includes predictors of missingness as covariates in the primary analysis model will be conducted. Multiple imputation will also be performed as an additional sensitivity analysis for missing data. A per-protocol analysis will also be carried out as a sensitivity analysis. The effect of the intervention on secondary outcomes will be assessed using methods analogous to those used for the primary outcome.

Satisfaction survey responses from the intervention group will be summarized descriptively. Where appropriate, exploratory analyses will examine variation in responses based on participant characteristics (eg, age, baseline fitness, engagement in sessions) to identify factors associated with higher acceptability or satisfaction.

Monitoring

The chief investigator will be responsible for the day-to-day monitoring and management of the study. The UCLH/UCL Joint Research Office, on behalf of UCL as Sponsor, will monitor and conduct random audits on a selection of studies in its clinical research portfolio. Monitoring and auditing will be conducted in accordance with the Department of Health Research Governance Framework for Health & Social Care [54] and in accordance with the sponsor's monitoring and audit policies and procedures.

Data Monitoring

In accordance with the UCL Records Retention Policy, at the end of the trial, all essential documentation will be archived securely by the chief investigator for a minimum of 20 years from the declaration of the end of trial. After 20 years, stored data will be securely destroyed.

Harms

In alignment with SPIRIT guidelines [35], adverse event monitoring and handling procedures have been established to ensure participant safety. Given the telehealth nature of the intervention, specific adaptations have been made to address challenges related to remote supervision, participant adherence, and emergency response. Participants are required to complete thorough pre-exercise screening, and real-time monitoring is conducted through online sessions by the supervising exercise physiologist. Additionally, clear protocols are in place for identifying and responding to adverse events, including escalation procedures for medical concerns and access to

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emergency services if needed. For research staff, there is a potential risk of sustaining an injury when assisting patients on and off the exercise equipment; however, this is part of the routine procedure in exercise testing, and only experienced staff will undertake this role. Manual handling and intermediate life support training have been completed by all involved staff.

Research Events and Incidents

In this trial, adverse events have been defined as any untoward medical occurrence in a trial participant, which does not necessarily have a causal relationship with the intervention. Serious adverse events are defined as any adverse event that results in death, is life-threatening (an event in which the participant was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe), requires hospitalization (inpatient admission), or results in persistent or significant disability or incapacity.

The number, nature, and severity of serious adverse events (if any) will be reported separately by study arm at each follow-up time point. The number of participants who experience adverse events will likewise be reported separately by study arm.

Results

This study was supported by a joint National Institute for Health Research UCLH Biomedical Research Centre grant (BRC789/OB/BD/110370) and Rosetrees Trust grant (UCL-Obesity-2020\101), funded in September 2020. Following initial protocol development, ethics approval, and trial setup, the clinical phase formally commenced with registration on June 16, 2023. Enrollment is ongoing, with a projected end date of March 2026. As of May 2025, a total number of 220 patients have been screened for participation, of whom 30 have enrolled in the trial. The first results are expected to be submitted for publication by mid-2026.

Discussion

Overview

This study is designed to evaluate the short-term physiological impact and acceptability of a telehealth-delivered prehabilitation program for patients preparing for MBS. We anticipate that the intervention will result in improvements in CRF over a 4-week period and will be acceptable to participants. These findings will inform refinements to the program and guide future implementation efforts.

The recruitment process for this study has been shaped by various logistical and contextual factors, including COVID-19–related surgical delays and considerations around participant engagement in exercise interventions. These factors highlight the need for flexible and accessible prehabilitation strategies for patients awaiting MBS. The use of telehealth for exercise delivery presents potential advantages in terms of accessibility and scalability, aligning with broader efforts to integrate remote interventions into routine clinical care. Although obesity-specific evidence on telehealth prehabilitation remains limited [55], insights from other clinical populations—such as those undergoing cancer treatment or orthopedic surgery—suggest that early investment in remote intervention models can yield long-term benefits in terms of program scalability and patient outcomes [56].

Strengths and Limitations

A key strength of this study is its pragmatic design, which reflects real-world clinical pathways and enhances accessibility using telehealth. The use of CPET for our primary outcome provides a gold-standard, objective measure of physiological change. However, several limitations must be acknowledged. The absence of postoperative or long-term follow-up limits our ability to assess sustained changes in outcomes. While the use of usual care as a comparator reflects current clinical practice, its variability across settings can introduce confounding and may not adequately control for study-induced behavioral changes.

Findings from this study will inform refinements to the BARI-Prehab program, helping to optimize its implementation and sustainability. Participant feedback will be used to identify which components of the program are most valued, which may require adjustment, and how delivery can be improved. Future phases of the research will examine the acceptability of telehealth-based prehabilitation in greater depth and evaluate its integration within standard MBS pathways. While this study focuses on short-term outcomes, future studies will be designed to include postsurgical and longer-term follow-up to assess whether early improvements translate into enhanced perioperative recovery and sustained cardiometabolic benefits. Ultimately, this study may contribute to the development of scalable, evidence-based, preoperative exercise interventions that better support patients preparing for MBS.

Dissemination Plan

Results from this study will be disseminated through peer-reviewed publications, conference presentations, and among clinical bariatric surgery providers. These efforts aim to support the translation of research into patient-centered prehabilitation practice.

Acknowledgments

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Authors' Contributions

BJD, DSM, and JM conceptualized the study and designed the methodology. NT, ALD, JC, ZL, CDP, KB, NFM, and BJD are responsible for participant recruitment and data collection. DSM secured funding and is responsible for overall project supervision, along with AMC, KD, and BT. BJD drafted the initial manuscript, and all authors contributed to the review, editing, and final approval of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Summary of Participant Communications and Behaviour Change Techniques.
[DOCX File , 15 KB - resprot_v14i1e77538_app1.docx]

Multimedia Appendix 2
Measured variables and timeline of outcomes.
[DOCX File , 20 KB - resprot_v14i1e77538_app2.docx]

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Abbreviations

AT: anaerobic threshold
CPET: cardiopulmonary exercise testing
CRF: cardiorespiratory fitness
MBS: metabolic and bariatric surgery
NHS: National Health Service
PA: physical activity
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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UCL: University College London
UCLH: University College London Hospitals

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Protocol

Effectiveness of Cognitive Rehabilitation on Cognition and Quality of Life in Chemotherapy-Induced Cognitive Impairment: Protocol for a Randomized Control Trial

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Abstract

Background: Abnormal cell growth that can multiply and transfer to other bodily parts is referred to as cancer. Chemotherapy is a standard treatment for cancer patients. During or after treatment, patients may have varying degrees of cognitive impairment caused by the drug, which can negatively impact their quality of life. Cognitive impairment brought on by chemotherapy is one of the most frequent side effects that occur both during and after chemotherapy. Cognitive effects after and during chemotherapy have not been addressed in patients.

Objective: To evaluate the effectiveness of cognitive rehabilitation on cognition and quality of life in chemotherapy-induced cognitive impairment.

Methods: In this Randomized Control Trial (RCT), 60 subjects with chemotherapy-induced cognitive impairments secondary to any cancer will be randomised into 2 groups by the sequentially numbered opaque sealed envelope approach. The cognitive functions will be measured as the outcome measures, which include all the recall strategies, executive function tasks, information processing speed, and attention. Both groups will receive intervention every day for 4 weeks. Wilcoxon signed the rank test for data analysis, and students paired the "t" test, which will be used to study within-group effects. Mann-Whitney U Test and students Unpaired "t" Test will be used to compare groups at pre-treatment and post-treatment.

Results: As of November 2024, we will enrol 60 participants, and the data collection process will start from November 2024-November 2025. The expected results of the effect of cognitive rehabilitation on cognition and quality of life in chemotherapy-induced cognitive impairment in cancer patients will be significant, and the expected results will be published at the end week of November 2025.

Conclusions: The study design is a framework to plan and test the feasibility of the intervention. The cognitive therapy will improve the cognition in chemotherapy-induced cognitive impairment patients.

Trial Registration: Clinical Trials Registry India CTRI/2024/04/065805; https://ctri.nic.in/Clinicaltrials/pmaindet2.php?EncHid=MTAyNTE1&Enc=&userName=

International Registered Report Identifier (IRRID): DERR1-10.2196/66011

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KEYWORDS

Cognitive Rehabilitation; Cancer; Chemotherapy; Physiotherapy; Cognitive Impairment; Chemotherapy-induced cognitive impairment; cognitive; cognition; cognitive impairments; cognitive decline; Effectiveness; Cognitive Rehabilitation; Quality of Life; QoL; patient; patients

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Introduction

Background

Cancer is the leading cause of death and a major limitation to increasing life expectancy in every nation across the globe. According to the World Health Organization (2019) [1], in 112 out of 183 countries, cancer was a primary cause of mortality before the age of 70, and it ranked third or fourth in 23 additional countries. While death rates from conditions such as stroke and coronary heart disease are declining, cancers have risen in prominence as a leading cause of mortality [2]. Patients with noncentral nervous system tumors often experience cognitive symptoms, commonly referred to as "cancer-related cognitive impairment" (CRCI). This condition, primarily studied following chemotherapy, involves deficits in working and short-term memory, attention, executive function, and processing speed. After chemotherapy, up to 75% of patients with cancer report cognitive problems, and approximately 35% continue to experience cognitive dysfunction for 5-10 years after completing treatment [3].

As a result of population growth and aging, as well as shifts in the distribution and prevalence of major cancer risk factors, the global burden of cancer incidence and mortality is continuously increasing. An estimated 58.3% of cancer deaths in both sexes and half of all cancer diagnoses are expected to occur in Asia, which is home to 59.5% of the world's population. According to GLOBOCAN 2020 estimates, India is projected to record 2 million new cancer cases by 2040, a 57.5% increase from 2020 [2]. Chemotherapeutic drugs have significantly improved cancer survival rates since their discovery and development over the past several decades. The 5-year survival rate across various cancers is around 60%, with skin melanoma, breast cancer (BC), and prostate cancer showing the highest rates. However, all treatments have side effects. Chemobrain, chemofog, or chemotherapy-induced cognitive impairment (CICI) is among the most common adverse effects of chemotherapy [4].

CICI is primarily investigated through neuroimaging studies of the brain, which reveal decreased gray matter density in the frontal, temporal, cerebellar, and right thalamic regions [5]. The prefrontal cortex and hippocampus are the primary centers of learning and memory; therefore, any damage to these areas results in cognitive dysfunction [6]. Consequently, altered behavior and memory are associated with impaired neuronal functioning in the hippocampus and frontal cortex [7]. Moreover, changes in cerebral white matter, mitochondrial dysfunction, and depletion of neural progenitor cells in the dentate gyrus contribute to cognitive impairments [8]. However, limited information is available regarding the precise mechanisms involved. Triple therapy with methotrexate, doxorubicin, and cyclophosphamide has been shown to increase peripheral and central levels of proinflammatory cytokines while reducing anti-inflammatory cytokine levels. This imbalance in the cytokine system disrupts neural plasticity and impairs cognitive function. Neuroimaging studies have shown reduced dendritic spine development in this model [9]. In summary, chemotherapy negatively affects cognition. Current reports on BC survivors highlight the occurrence of CICI. Variations in cytokine concentrations and the degree of cognitive impairment are associated with different chemotherapy regimens and dosages. However, the onset of cognitive disturbances remains unclear. The cellular targets, chemical composition of the drugs, dosing schedule, and numerous other confounding factors all play significant roles in determining the central nervous system's inflammatory or neurotoxic side effects. Peripheral inflammation may also contribute to cognitive problems. Therefore, it is essential to closely monitor the effects of each specific drug in both preclinical and clinical studies [10].

Methotrexate is one of the chemotherapeutic agents known to cause vascular damage through its antiangiogenic activity [11]. Overall, the complex nature of anticancer therapy and its multiple mechanisms of action may trigger multifaceted symptoms of cognitive disorders and behavioral toxicities. In both clinical and experimental settings, doxorubicin is commonly administered to patients with BC who subsequently exhibit cognitive impairment, structural abnormalities, and brain mitochondrial dysfunction [12]. Platinum-based agents (such as cisplatin, oxaliplatin, and carboplatin) disrupt protein synthesis by cross-linking mitochondrial DNA, which is more susceptible to irreversible mutation than nuclear DNA [13]. Studies in mouse models have shown that deep brain penetration and inhibition of neural stem cell proliferation underlie cisplatin-induced cognitive impairment [14].

Crucial regions of the cerebral cortex and peripheral neurons undergo structural degradation due to taxanes (paclitaxel or docetaxel). Studies in neuropathic rodent models have demonstrated that mitochondria are particularly susceptible to damage induced by taxanes [8]. Administration of the same drug combination for 4 weeks led to increased expression of interleukin-1β and tumor necrosis factor-alpha in the rat corpus callosum, while interleukin-10 levels were reduced, resulting in impaired working memory function [15].

In summary, chemotherapy adversely affects cognitive function. Current reports on BC survivors highlight the occurrence of CICI. Variations in drug dosage and cytokine concentration levels across different chemotherapy regimens are associated with differing degrees of cognitive impairment [16]. Research into the mechanisms underlying the development of these cognitive disorders is still ongoing. The deleterious effects of inflammation or neurotoxicity on the central nervous system largely depend on cellular targets, drug composition, dosage schedules, and other confounding factors. Cognitive disturbances may also arise from peripheral inflammation. Therefore, it is essential to closely monitor the effects of each specific drug in both preclinical and clinical studies [17].

Conventional treatment approaches include aerobic exercise and cognitive behavioral therapy. These involve activities such as brisk walking, jogging, cycling, and engaging in cognitive skill exercises or workbooks. Studies have shown that, in addition to medical treatment, combining cognitive and aerobic exercises helps reduce symptoms of cognitive impairment without causing complications. Therefore, such interventions should be recommended for all patients with cancer experiencing CICI.

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Objectives

- To determine the effect of cognitive rehabilitation on improving cognition in patients with CICI across all cancer types.
- To compare the effectiveness of cognitive rehabilitation with conventional therapy in patients with CICI.
- To determine the effect of cognitive rehabilitation on improving the quality of life in patients with CICI across all cancer types.

Methods

Trial Design

This is an equal allocation, parallel-group, 2-arm superiority study, with the sample size distributed equally between the 2 groups. Patients will be evaluated according to predetermined inclusion and exclusion criteria and will be recruited from Siddharth Gupta Memorial Cancer Hospital in Sawangi, which is affiliated with Acharya Vinoba Bhave Rural Hospital. After obtaining informed consent, eligible participants will be selected through simple random sampling using computer-generated random numbers. All patients will be informed about the study procedures and asked to provide written consent before participation. The trial will include patients with a medical diagnosis of cancer who are currently undergoing chemotherapy. Sequence generation will be performed using computer-generated random numbers.

The allocation concealment mechanism will involve simple random sampling. Study participants will be randomly assigned using computer-generated random numbers. Randomization will be conducted by a researcher not involved in participant recruitment. To ensure allocation concealment, opaque sealed envelopes will be used, which will be opened only after participants are deemed eligible for treatment by the research team. Data collection will be carried out after participants are assigned to their respective intervention groups, with outcomes assessed and recorded during the preintervention phase. Postintervention data collection will be conducted after 4 weeks of intervention.

In data management, information obtained will be summarized using frequency and percentage for qualitative data, and mean and SD for quantitative data. Figure 1 presents the CONSORT (Consolidated Standards of Reporting Trials) flow diagram outlining the study design. See Multimedia Appendix 1 for the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

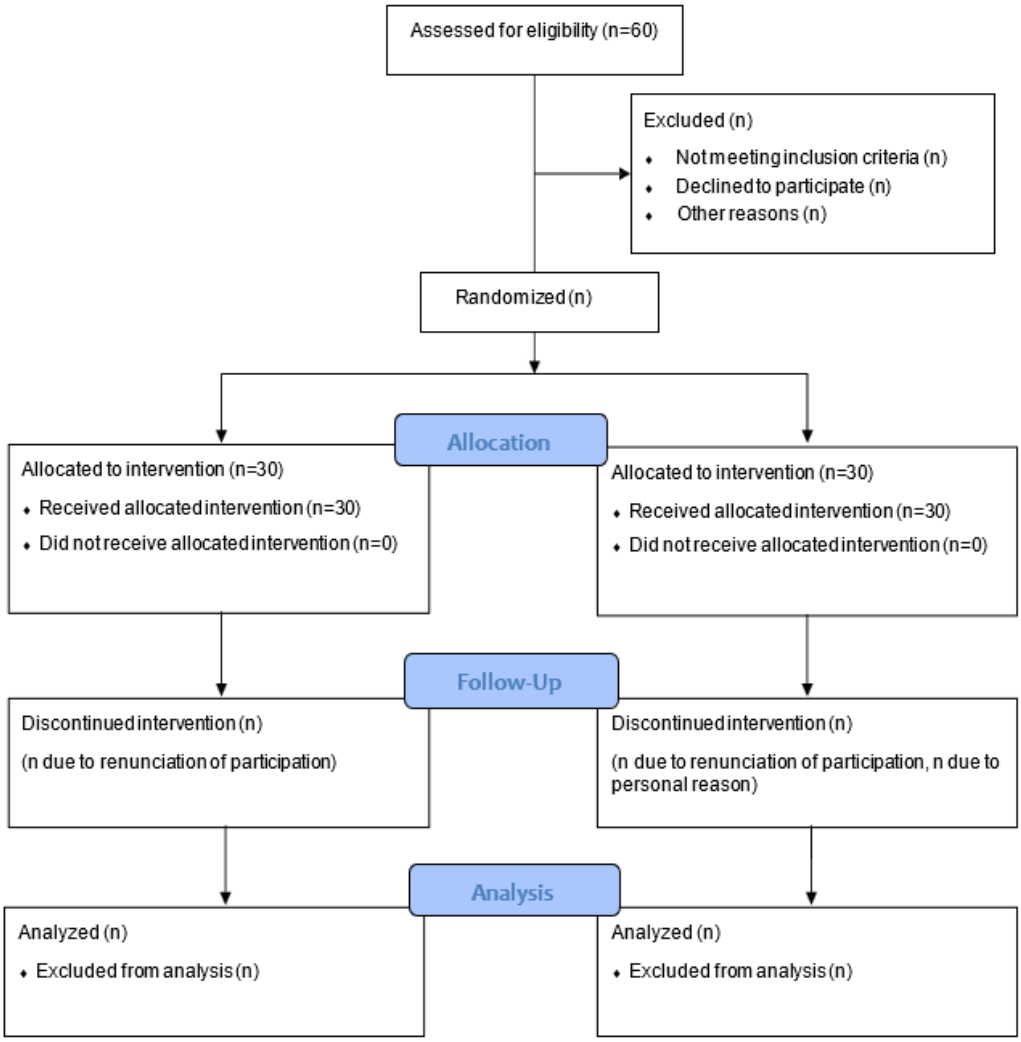

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Descriptive statistics will be used to analyze demographic variables such as age and gender. Measures including mean, SD, frequency (n, %), chi-square test, and independent *t* test will be applied to confirm the homogeneity of descriptive statistics. Inferential statistics between the 2 groups will be assessed using an unpaired (2-tailed) *t* test. All statistical analyses will be performed using SPSS software, version 21.0 (IBM Corp). For this study, a *P* value of less than .05 will be considered statistically significant.

Ethics Approval

The study was approved by the Datta Meghe Institute of Higher Education and Research Institutional Ethics Committee (approval number DMIHER [DU]/IEC/2024/169; approval date: January 31, 2024). All participants will be informed about the study and will provide written informed consent and assent before enrollment. All data on research participants will be kept strictly confidential. Patient information will be used only with the explicit permission of the individuals. There are no financial or conflicting interests to declare. The principal investigator will be responsible for preserving and maintaining all data collected during and after the study. The final trial dataset will be made available to the principal investigator upon formal request for research and publication purposes only, and access will be granted in a deidentified format.

In accordance with the policies of Ravi Nair Physiotherapy College and Datta Meghe Institute of Higher Education and Research, appropriate care will be provided to research participants if their involvement in the trial results in any harm. All information collected during or after the study will be used solely for academic and research purposes, with the ultimate aim of publication in a reputable journal. The key trial procedures, including enrollment, interventions, and assessments, are summarized in Table 1.

Table 1. Demographics and clinical characteristics of the patients.

Confounders	Enrollment	Completed the treatment	Dropout (lost to follow-up/death)
Age (years)			
14-21	✓	✓	✓
22-30	✓	✓	✓
31-38	✓	✓	✓
39-46	✓	✓	✓
47-55	✓	✓	✓
56-64	✓	✓	✓
65-70	✓	✓	✓
Sex			
Male	✓	✓	✓
Female	✓	✓	✓
Cancer type			
Skin	✓	✓	✓
Lungs	✓	✓	✓
Female breast	✓	✓	✓
Prostrate	✓	✓	✓
Colon and rectum	✓	✓	✓
Cervix and uterus	✓	✓	✓
Head and neck	✓	✓	✓
Chemotherapy type			
Cisplatin	✓	✓	✓
Paclitaxel	✓	✓	✓
5-Fluorouracil	✓	✓	✓
Carboplatin	✓	✓	✓
Dacarbazine	✓	✓	✓
Temozolomide	✓	✓	✓
Nab-paclitaxel	✓	✓	✓
Oxaliplatin	✓	✓	✓

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Eligibility Criteria

Inclusion Criteria

- Recently diagnosed patients with stage I to III cancers who are scheduled to receive a defined number of chemotherapy cycles involving platinum-based compounds.
- Patients currently undergoing chemotherapy treatment.
- Patients receiving taxane- or platinum-based compounds, including cisplatin, carboplatin, or oxaliplatin.
- Patients with grade I or II cognitive impairment as per the National Cancer Institute's standard toxicity criteria.
- Patients scheduled to receive a minimum of 4 cycles of chemotherapy with any of the aforementioned platinum-based agents.
- Male and female patients aged between 14 and 70 years.
- Patients receiving chemotherapy drugs approved by the National Cancer Board.

Exclusion Criteria

- Patients with preexisting cognitive impairment.
- Patients with a history of traumatic brain injury.
- Patients with any prior psychological disorder that could affect cognitive function.
- Patients who have not received any chemotherapy cycles following cancer diagnosis or treatment.
- Patients with a previous history of cancer or prior exposure to chemotherapeutic drugs.
- Patients with neurological conditions affecting the brain or spinal cord, including vascular dementia, multiple sclerosis, amyotrophic lateral sclerosis, Alzheimer disease, Lewy body disease, stroke (cerebrovascular accident), or Huntington disease; as well as those taking medications known to impair cognition, such as benzodiazepines.
- Patients using cholinesterase inhibitors or antipsychotics; those with current or recent (within the past 6 months) alcohol or drug use disorders; those exhibiting behavioral changes such as depression, anxiety, or stress; and individuals with systemic conditions that may interfere with cognition, such as hypothyroidism, folic acid or vitamin B12 deficiency, or viral infections (eg, syphilis, HIV). Patients with visual or speech impairments (eg, aphasia) will also be excluded.

Selection of Participants

After obtaining ethical clearance from the Institutional Ethics Committee, patients diagnosed with cancer and scheduled to undergo chemotherapy will be identified at Siddharth Gupta Memorial Cancer Hospital. Permission will be sought from the treating residents, and eligible patients who meet the inclusion criteria will be enrolled after obtaining informed consent. Treatment will commence within 1 week of initiating the chemotherapeutic agent, and baseline data will be recorded. Participants will receive cognitive rehabilitation focusing on memory, attention, information processing, and executive function, with the aim of enhancing cognitive performance and improving quality of life. The first outcome measure, the Mini-Mental State Examination (MMSE), will be administered before the initiation of chemotherapy along with baseline data to assess cognitive function. Subsequently, the Montreal Cognitive Assessment will be conducted over 4 chemotherapy cycles. Participants will undergo the intervention 5 days per week, and following the completion of the 4 chemotherapy cycles, postintervention baseline data will be recorded. The outcome measures will be used to assess the degree of cognitive impairment. Follow-up assessments will be conducted after each chemotherapy cycle and weekly after completion of the intervention. Baseline outcome measures will be recorded after 4 chemotherapy cycles, and follow-up evaluations will be carried out once a week for 4 consecutive weeks.

Participant Timeline

Pre- and postbaseline data will be collected, followed by a 4-week intervention period. After the completion of the 4 weeks, postintervention outcomes will be assessed. The study design is illustrated in the CONSORT flowchart presented in Figure 1.

Control Group

Participants will perform aerobic exercises and cognitive behavioral training daily. The program will include brisk walking, cycling, jogging, and cognitive skill activities for 45 minutes per day, 5 days a week, over 4 weeks. These activities will not require direct supervision.

Intervention Group

Domain-specific cognitive exercises to be administered to patients are outlined in Table 2.

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Table 2. Intervention group.

Problem identified	Physiotherapy intervention	Dosage
Memory recall		
Mnemonics (face-name recall)	Give a photograph of a relative. Generate a mnemonic after the discussion that will be used to assist recall. During the training phase, using the forward cueing method, increase the cues until the patient identifies the picture.	Run 1 training trial, then test immediately, and again after 30 seconds, 1 minute, 2 minutes, 5 minutes, and 10 minutes.
Cueing (number recall)	Generate mnemonics to remember phone numbers. During the training phase, prompt a line in increasing or decreasing order.	N/A[a]
Chunking (story recall)	Read a story in front of the patient. Break the story into parts and try to imagine the important key points, such as what, where, who, when, and why.	N/A
Method of loci (procedural memory and fluency training)	Prompting and fading, action-based encoding, chaining, and fluency training (names and numbers).	N/A
Spaced retrieval (semantic impairments)	Repeated rehearsal of word-picture pairing will improve the ability to name trained items for 4 people. For word association, the therapist will give a word and ask the patient to identify a related word with the same meaning.	N/A
Executive function		
Naming task	Ask the patient to say the name of any item. Show the item for 5 seconds, then repeat the task for 60 trials.	There were 60 trials in total, and the task lasted 5 minutes.
Calculation task	Ask the patient to add or subtract 2-digit numbers. The patient must respond within 5 seconds.	N/A
Stroop color-word task	The therapist shows words in different colored fonts. At times, the color matches the word itself, and at other times, it does not. The patient must name the color of the font.	N/A
Working memory task	Show the patient a series of numbers for 2 seconds. The patient should then repeat the series.	N/A
Attention		
Sustained and selective attention	Elemental training: focus on breathing and body-part awareness.	20 minutes of training
Alternating and divided attention	Functional training: make a grocery list to prepare meals, select the correct food pictures showing their expiry dates, and determine locations on the map.	N/A
Information processing	The perceive, recall, plan, and perform system [18]	N/A
Perceive	The patient decides which sensory information to attend to, then analyzes the characteristics of objects, surfaces, and body parts.	10 minutes of training
Recall	The patient will recall prior knowledge of the procedure and then apply the relevant knowledge required to perform the task.	N/A
Plan	The patient will think, prepare to perform, and make decisions to achieve the goal.	N/A
Perform	The therapist will analyze whether the patient is able to initiate and terminate the response, and to continue and persist as the task requires.	N/A
Physical fitness		
Aerobic exercises [18] (frequency, intensity, interval, and time principle)	Brisk walking, jogging, and static cycling	Frequency: 5-6 times per week; intensity: easy to moderate, approximately 60%-75% of maximum heart rate.

[a]N/A: not applicable.

Rationale

The rationale for including cognitive behavioral training in the control group intervention is based on its established effectiveness in addressing cognitive and behavioral disturbances, as demonstrated in several recent studies. Substantial evidence indicates that cognitive behavioral training significantly alleviates anxiety and depression among individuals diagnosed with cancer. Furthermore, a few studies have explored the role of cognitive behavioral training in reducing

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cancer-related fatigue. Consequently, cognitive behavioral training may serve as a promising approach to mitigating the adverse effects of chemotherapy [19]. A systematic review and meta-analysis further concluded that cognitive behavioral training, when combined with resistance and aerobic exercise, is more effective, as active exercise enhances physical capacity. In addition, cognitive behavioral training contributes to fatigue reduction by improving coping mechanisms for stress and promoting better activity management [20].

By targeting key domains such as attention, memory, processing speed, and executive function, neurocognitive exercises have been employed in an experimental study by Sundar et al [21] to aid cancer survivors in recovering from the cognitive effects of chemotherapy. Compared with aerobic exercises, neurocognitive training was found to produce significantly greater improvements in both cognitive function and overall quality of life. The study further demonstrated that enhancements in cognitive performance among postchemotherapy cancer survivors are strongly correlated with domain-specific cognitive training [21].

Outcome Measures

Primary Outcomes

Mini-Mental State Examination

The MMSE comprises 11 questions designed to assess cognitive performance across 5 domains: orientation, registration, attention and calculation, recall, and language. Developed in 1975, the MMSE has a maximum score of 30 points. A total score of 23 or below indicates cognitive impairment, whereas a score of 24 or above is considered within the normal range.

Montreal Cognitive Assessment

According to clinicians, the MMSE takes approximately 10 minutes to administer. It assesses various domains of cognition, including visuospatial skills, executive functions, attention, concentration, calculation, language, abstraction, memory, and orientation.

Functional Assessment of Cancer Therapy—Cognitive

The Functional Assessment of Cancer Therapy—Cognitive Function version 3 is a 27-item self-report questionnaire designed to assess cognitive concerns among patients with cancer. It comprises 4 subscales, including Physical well-being, Social/family well-being, emotional well-being, and Functional well-being.

Secondary Outcomes

European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30

The European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire (EORTC QLQ-C30, version 3) is a 30-item instrument specifically developed to assess health-related quality of life in patients with cancer.

Patient-Specific Functional Scale

The Patient-Specific Functional Scale is a self-reported, patient-centered tool used to evaluate functional changes over time. Developed by Stratford and colleagues [22], the scale serves as a versatile measure of function that can be applied to individuals with varying levels of independence.

Sample Size Calculation

Calculation of sample size by Cohen effect size by comparing 2 means:

$$\text{Effect size (d)} = (\mu_2 - \mu_1)/\sigma = 0.8 \text{ (estimated)}$$

Considering a large effect size difference of 0.8, the sample size is calculated as follows:

$$N=([1 + r]/r)([Z_{1-\alpha/2} + Z_{1-\beta}]^2/d^2) + (Z^2_{1-\alpha/2})/2(1 + r)$$

where $Z_{1-\alpha/2}$ at the 5% level of significance = 1.96; $Z_{1-\beta}$ at 80% power = 0.84; ratio allocation (group 2/group 1) = 1.

$$\text{Sample size (n)} = ([1 + 1]/1)([1.96 + 0.84]^2/0.8^2) + (1.96)^2/2(1 + 1) = 26 \text{ per group.}$$

Considering a 15% dropout (n=4), a total of 30 samples are required per group.

Sample Size

The sample size calculation used the Cohen *d* formula to compare 2 means. The effect size (*d*) was estimated using the following equation:

$$\text{Effect size} = d = (\mu_2 - \mu_1)/\sigma = 0.8$$

Given a large effect size (*d*=0.8), the required sample size per group was determined using the following formula:

$$N=([1 + r]/r)([Z_{1-\alpha/2} + Z_{1-\beta}]^2/d^2) + (Z^2_{1-\alpha/2})/2(1 + r)$$

where $Z_{1-\alpha/2}$ at the 5% level of significance = 1.96; $Z_{1-\beta}$ at 80% power = 0.84; ratio allocation (group 2/group 1) = 1.

Substituting these values:

$$n=([1 + 1]/1)([1.96 + 0.84]^2/0.8^2 + (1.96)^2/2(1 + 1)$$

$$n=2\times([2.8]^2/[0.64])+(3.84/4)$$

$$n=2 \times (7.84/0.64) + 0.96$$

$$n=2 \times 12.25 + 0.96$$

$$n=24.5 + 0.96= 25.46$$

Rounding up, 26 participants per group are required. Considering a 15% dropout rate (approximately 4 participants per group), the final sample size will be 30 participants per group, totaling 60 participants for the study.

Safety Outcomes

Adverse events will be reported as they occur. No negative effects are expected.

Statistical Analysis

For demographic factors, all data will be summarized using baseline characteristics, expressed as the mean and SD for continuous data and as frequency and percentage for categorical data.

The analysis of outcome variables will primarily focus on continuous variables. For parametric data, the minimum, maximum, mean, SD, SE, and 95% CI will be summarized. The normality of continuous outcome variables will first be tested

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using the Kolmogorov-Smirnov test at a 5% level of significance ($P \leq .05$). If the data are found to deviate from normality, a nonparametric test will be applied to determine significance. An independent *t* test will be conducted for group comparisons to assess significant differences at the 5% level ($P \leq .05$). The intervention groups will receive (1) cognitive training supplementing traditional physical treatment and (2) traditional physical treatment.

The effect size at different assessment visits between the 2 groups will be calculated for the variables MMSE and Montreal Cognitive Assessment. For nonnormal data, descriptive statistics will include the mean, median, and lower and upper quartiles. The Mann-Whitney test will be applied to determine statistical significance when nonparametric methods are required.

Categorical variables will be summarized using frequency (n) and percentage. Chi-square analysis will be performed to evaluate efficacy across categorical variables. An intention-to-treat analysis will be applied to minimize attrition bias among participants, including those lost to follow-up or deceased due to adverse effects of chemotherapeutic drugs.

Monitoring Methods

Data Monitoring

The Data Monitoring Committee of Ravi Nair Physiotherapy College will be responsible for overseeing and monitoring the study data.

Monitoring Harms

Every instance of an adverse event will be reported to the Ethics Committee and the clinician responsible for evaluating and managing both anticipated and unanticipated adverse events, as well as any other unforeseen consequences arising from the trial interventions or trial conduct.

Results

As of November 9, 2024, we enrolled 60 participants. Data collection will occur from November 14, 2024, to November 14, 2025. We expect the results on the effects of cognitive rehabilitation on cognition and quality of life in patients with CICI to be significant, with the findings scheduled for publication on November 25, 2025.

Discussion

Anticipated Findings

This study will evaluate and compare the effects of cognitive rehabilitation and conventional therapy on cognition in patients with CICI. It is anticipated that this framework will significantly enhance the cognitive functions of patients receiving cognitive therapy as an intervention alongside conventional management protocols.

We hypothesize that cognitive training will result in measurable changes in brain magnetic resonance imaging, including improved perfusion, enhanced white matter connectivity (particularly involving the hippocampus), and increased brain volume (including the hippocampus). We have designed a randomized controlled trial (RCT) to investigate the effects of cognitive training and physical exercise on cognitive functioning in patients with cancer who have undergone chemotherapy and reported cognitive difficulties confirmed by standardized and validated neuropsychological assessments. Several underlying mechanisms may explain the effectiveness of the therapies included in this study. Cognitive rehabilitation and active exercises (such as weight training, aerobic training, dance, and yoga) may enhance physical capacity by counteracting reduced activity levels during or after cancer treatment [23]. Furthermore, increased physical activity can positively influence mental health. Psychosocial therapies promote activity management and stress coping, thereby reducing fatigue. Cognitive rehabilitation enhances neuroplasticity, enabling the brain to reorganize and adapt in response to injury, and helps develop compensatory strategies that allow individuals to manage cognitive deficits more effectively. It also contributes to building cognitive reserve, thereby reducing the risk of cognitive decline and promoting resilience. Several RCTs have demonstrated the efficacy of cognitive rehabilitation in improving cognitive function and quality of life, as well as in reducing symptoms of anxiety and depression in individuals with CICI [24]. Meta-analyses have further shown that cognitive rehabilitation is associated with significant improvements in cognitive function, particularly in attention and memory [25].

A systematic review examined the effects of interventions aimed at enhancing cognitive function in patients experiencing CRCI. Studies involving patients with metastatic cancer or preexisting cognitive deficits were excluded. The review included studies published between January 2011 and September 2022. Various interventions were identified for managing CRCI, and the outcome measures were found to be consistent across studies [26]. An RCT focusing on patients with cancer with CICIs also highlighted cognitive rehabilitation as an effective approach to address the cognitive deficits commonly observed following chemotherapy [18]. According to research, the majority of BC survivors, particularly those who have undergone chemotherapy, experience long-term cognitive abnormalities that significantly diminish their quality of life [27]. Executive functions—including working memory, cognitive flexibility, multitasking, planning, and attention—are among the most severely affected cognitive domains. Previous studies across various populations have shown that cognitive training, a behavioral approach used to address cognitive deficits, can lead to notable improvements in specific cognitive abilities such as executive functions. Kiesl et al [24] conducted an RCT to evaluate the effectiveness of cognitive training through a 12-week program and concluded that it resulted in significant improvements in processing speed, planning, and task performance. A study by Ferguson et al [28] evaluated the efficacy of cognitive behavioral therapy and memory and attention adaptation training (MAAT), both designed to improve cognitive function in patients with cancer. Following treatment, they concluded that cognitive behavioral therapy was more effective than MAAT; however, patients reported higher satisfaction with MAAT [29]. A systematic review by Peng et al [30] suggested that exercise interventions improve cognitive function and quality of life, as assessed through self-reported outcomes, and emphasized the need for higher-quality research

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to further explore exercise strategies in CRCI. Similarly, a systematic review by Hilfiker et al [20] assessed physiotherapeutic interventions for CRCI following cancer treatment and concluded that physiotherapy, including cognitive rehabilitation, was effective and led to significant improvements in cognition and quality of life.

An RCT investigated the feasibility and preliminary effectiveness of a novel online executive function training program for long-term BC survivors. Forty-one BC survivors (21 active and 20 waitlist) completed the 48-session training program over 12 weeks. The cognitive training resulted in significant improvements in cognitive flexibility, verbal fluency, and processing speed, with marginally significant downstream improvements in verbal memory as assessed using standardized measures [31]. According to Pendergrass et al [32], cognitive rehabilitation and training methods incorporating adaptive challenge levels, awareness practice, and repetitive skills training had a positive effect on cognitive function and self-reported quality of life. Similarly, a study by Wongarsa et al [33] on integrated interventions for mild cognitive impairment in older adults demonstrated that brain training activities—such as word guessing and memorization, image classification, music-based responses, basic arithmetic computation, and step-by-step recipe writing and cooking—greatly enhanced processing speed, attention, and memory. A systematic review by Melillo et al [34] encompassing studies conducted worldwide illustrated various approaches to managing cognitive impairment. Bellens et al [7] investigated the effects of web-based cognitive training, while in Canada (2018 and 2022), Campbell et al [35] and Duval et al [36] examined the impact of aerobic exercise on cognitive functions. Another study focused on the use of mindfulness-based stress reduction as an intervention [25].

Strength

According to a consensus statement from the International Multidisciplinary Roundtable, cancer survivors can safely engage in sufficient exercise training to improve physical fitness, restore physical functioning, enhance quality of life, and reduce cancer-related fatigue. However, uncertainty remains regarding the effects of exercise on various outcomes, including peripheral neuropathy and cognitive functioning. The statement concluded that insufficient research exists on several aspects, such as anxiety, depressive symptoms, fatigue, health-related quality of life, cognitive decline, physical function, and the safety of exercise training for individuals who have or are at risk of developing BC-related lymphedema [35,37].

Limitations

The majority of the available literature currently focuses on the most prevalent early stages of BC. Further research is needed to address a broader range of tumor types and to enhance the specificity of findings within the exercise oncology field. The limited number of trials directly comparing 2 or more levels of exercise training restricts understanding of dose-response relationships. Additionally, the lack of sufficient evidence regarding cognitive impairment outcomes highlights a clear knowledge gap.

Literature is scarce on the application of strategies and techniques for cognitive rehabilitation in managing CICI symptoms. Only a few studies have investigated interventions targeting memory, attention, information processing, and executive function in individuals with CICI. Moreover, there is no evidence regarding the role of physical therapy interventions and their outcomes in enhancing cognitive function. However, substantial evidence supports the positive effects of exercise on cognitive function in various clinical populations, including older adults. In cancer populations, where cognitive function is a primary outcome, further research is warranted. Cognitive function is commonly assessed using both self-reported measures and neuropsychological tests.

Future Direction

The data on the prevalence rates of cognitive impairment in cancer survivors after chemotherapy accounted for variables such as age and time since therapy termination. Subgroup analyses and meta-regression were used to examine potential influences on prevalence estimates. The criteria for performing meta-regression were derived from Cochrane Guidance 35 [38]. A comprehensive meta-analysis was used to conduct the meta-regression. This review represents the first systematic comparison of prevalence rates of cognitive impairment in women with BC that has considered all methods used to ascertain impairment and evaluate long-term prevalence. Mean prevalence rates for CICI across all time points were 44% based on self-reports and 6% based on short cognitive screening [39]. The cognitive training intervention appears effective and may help reduce the deterioration of cognitive function in patients with CICIs.

Conclusion

This RCT aims to provide a comprehensive rehabilitation strategy that simultaneously addresses physical and cognitive issues. Outcome measures such as the MMSE, Montreal Cognitive Assessment, Functional Assessment of Cancer Therapy-Cognitive, EORTC QLQ-C36, and the Patient-Specific Functional Scale will be used to evaluate the efficacy of the protocol. It is crucial to consider several challenges and limitations, including variability in patient responses, adherence to guidelines, and the need for skilled health care professionals to deliver the treatments consistently. Furthermore, a robust RCT with an adequate sample size and an appropriate control group is essential to establish the protocol's effectiveness and generalizability in treating CICI.

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acknowledge that the article processing fee for this paper was waived by JMIR. The authors confirm that no generative artificial intelligence tools were used in writing or drafting the manuscript.

Authors' Contributions

GSK is the chief investigator who developed the study protocol with MIQ, RR, and the coinvestigator SH, and is responsible for the management and delivery of the trial. GSK, MIQ, RR, and SH have finalized the study protocol for utilization. All authors have commented on and approved the final version of the study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT checklist.
[PDF File (Adobe PDF File), 95 KB - resprot_v14i1e66011_app1.pdf]

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Abbreviations

BC: breast cancer
CICI: chemotherapy-induced cognitive impairment
CONSORT: Consolidated Standards of Reporting Trials
CRCI: cancer-related cognitive impairment
EORTC QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire
MAAT: memory and attention adaptation training
MMSE: Mini-Mental State Examination
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Layperson-Friendly AI Translation of Medical Documents to Improve Doctor–Patient Communication: Protocols for the AI-INFOCARE and AI-MEDTALK Randomized Controlled Trials

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Abstract

Background: Many patients struggle to understand referral letters and discharge summaries; low health literacy is prevalent, and short consultations limit explanations. Large language models (LLMs) can translate clinical jargon into layperson language, but their impact on doctor–patient communication in real care remains untested.

Objective: This study aims to determine whether providing an artificial intelligence (AI)–generated, medically validated layperson-language translation of key medical documents before a consultation improves the quality of doctor–patient communication.

Methods: We plan to conduct two single-center, parallel-group randomized controlled trials in neurosurgery: AI-INFOCARE (outpatients prior to treatment discussions) and AI-MEDTALK (inpatients at surgical discharge). Adults (aged 18 years or older, German-speaking, and able to consent) are randomized 1:1 to receive either (1) an AI-generated layperson-friendly summary of their referral or discharge document in addition to usual care or (2) usual care only. Summaries are produced with a Claude-based system (Simply Onno GmbH) and undergo human verification against the source document using a predefined checklist. The primary outcome is patient-rated interaction quality (Fragebogen zur Arzt-Patient-Interaktion/Questionnaire on the Quality of Physician–Patient Interaction) immediately postconsultation. Secondary outcomes are perceived autonomy support (brief Health Care Climate Questionnaire), self-rated understanding (5-point item), physician-rated encounter difficulty (Difficult Doctor–Patient Relationship Questionnaire, 10-item), and consultation length (minutes). Randomization uses a computer-generated allocation list with concealed, sequential assignment at the point of inclusion; recruiting clinicians have no access to the sequence, and analysts are blinded to group codes. Fidelity is assured by standard operating procedures, rater training, and periodic dual review with interrater agreement estimates. Safety monitoring defines information-related adverse events (eg, distress requiring unplanned clinical support or clinically relevant inaccuracies) and includes an independent safety overseer. Ethics approvals were obtained in February 2025 from the ethics committee of Technische Universität Dresden, and both trials are registered in the German Clinical Trials Register.

Results: Each trial targets 300 participants (150 per arm), providing greater than 80% power for an effect size $d \approx 0.4$ on the primary outcome ($\alpha=0.05$). Outcomes are assessed immediately after the index consultation, with no additional follow-up planned in this protocol. We hypothesize that providing layperson-friendly summaries will significantly improve patients' understanding and satisfaction with information, foster a more autonomy-supportive communication climate, and reduce physicians' perceived difficulty in the encounter without unduly prolonging consultation time. Neither study received external funding. Both trials are

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currently in the recruitment phase, with patient enrollment scheduled to begin in May 2025 and expected to conclude by February 2026. Results are anticipated to be published in summer 2026.

Conclusions: These pragmatic randomized controlled trials test a scalable AI intervention to strengthen understanding and interaction quality without adding clinician burden. If effective, AI-assisted layperson summaries could be integrated into routine workflows to advance health literacy and patient-centered care.

Trial Registration: Deutsches Register Klinischer Studien DRKS00036810; https://www.drks.de/search/de/trial/DRKS00036810 and Deutsches Register Klinischer Studien DRKS00036814; https://drks.de/search/de/trial/DRKS00036814

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KEYWORDS

artificial intelligence; autonomy support; doctor–patient communication; health literacy; patient education; randomized controlled trial

Introduction

Quality communication between physicians and patients is a cornerstone of effective health care. It is well documented that better doctor–patient communication improves patient understanding, satisfaction, adherence to treatment, and even clinical outcomes [1]. Conversely, communication breakdowns can undermine the therapeutic relationship and health results. Effective communication serves multiple purposes: building a good interpersonal relationship, exchanging information, and engaging patients in decision-making [2]. Achieving these goals requires that patients comprehend the information conveyed.

However, many patients struggle to understand complex medical terminology used in both verbal consultations and written documents such as specialist referral letters, procedure reports, or hospital discharge summaries. In Germany and internationally, limited health literacy is a pervasive challenge. A recent national survey found that 58.8% of German adults have inadequate health literacy, reporting difficulty understanding and using health information [3]. Such low health literacy is associated with poorer communication, lower patient engagement, and worse health outcomes [3]. Schaeffer et al [3] noted that improving the understandability of patient information is urgently needed to address this gap.

Doctor–patient communication can be conceptualized through the dual lenses of health literacy and shared decision-making (SDM). According to Leventhal's Common-Sense Model and SDM frameworks, understandable information is a prerequisite for autonomy support and meaningful participation in care. Our outcomes map onto these constructs: the Fragebogen zur Arzt-Patient-Interaktion (FAPI)/Questionnaire on the Quality of Physician–Patient Interaction (QQPPI) captures interaction quality, the brief Health Care Climate Questionnaire (HCCQ) reflects autonomy support, and self-rated understanding measures the informational pathway. By improving document comprehensibility before an encounter, the intervention directly targets these theoretical pathways expected to enhance both informational and relational aspects of communication.

Compounding the issue, physicians often face severe time constraints during appointments. Germany is among the countries with the shortest primary care visit lengths, historically averaging only about 7 to 10 minutes per patient [4]. This limited time makes it difficult to explain diagnoses and treatments in depth, especially if patients are encountering complex information for the first time. Studies indicate that physicians feel pressure to cover medical content quickly, which can lead to inadequate explanations and patients leaving with unanswered questions [4]. Time pressure has been linked to decreased patient recall and satisfaction [1]. Many patients turn to external sources, such as the internet, for clarification, which may yield unreliable information ("Dr Google"). In the worst cases, misunderstanding or lack of information can cause patient anxiety, unnecessary repeat consultations, or even nonadherence and premature therapy discontinuation [5,6].

Written medical documents are a key part of doctor–patient communication but are often written primarily for other health care professionals, not laypersons. For example, a hospital discharge letter typically contains medical jargon, abbreviations, and complex narrative that an average patient finds hard to decipher. This information gap represents a missed opportunity: if patients could better understand their medical records, they would be more empowered during follow-up visits with their doctors. Past efforts to improve this have included manually creating simplified, patient-friendly discharge letters. A preliminary trial in Austria demonstrated that providing patients (or proxies) with a simplified discharge summary significantly improved their acceptance of and satisfaction with the information compared to the standard technical letter [7]. Participants valued the clearer structure, avoidance of abbreviations, and layperson language, indicating that patient-friendly documents enhance communication.

Recent advances in artificial intelligence (AI) now enable automated translation of complex text into simpler language. Large language models (LLMs) such as GPT-4, Gemini, Llama, and Claude can parse medical text and generate explanations in more digestible terms. Early studies suggest that AI-generated summaries can dramatically improve readability. Zaretsky et al [8] showed that an LLM-transformed discharge summary achieved a mean reading level of sixth grade versus eleventh grade for the original and an understandability score of 81% versus 13%, without losing accuracy (although some errors occurred). Similarly, a Korean study found that ChatGPT could produce patient-friendly discharge notes that were easier to read, highlighting AI's potential in multilingual settings. These

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findings underscore that AI can serve as a powerful tool to bridge the language gap in medical communication, provided its outputs are properly validated for accuracy and completeness [8]. Compared with manual simplification approaches, which improve comprehension but are resource-intensive and difficult to scale, LLM-based systems offer immediate generation at low marginal cost. However, AI introduces distinct risks, such as hallucinations or omissions, which necessitate systematic human validation. Our protocol therefore emphasizes a fidelity process with predefined checklists, dual review of samples, and correction logging to balance scalability with safety.

To our knowledge, no completed randomized controlled trials (RCTs) have yet evaluated AI-generated, medically validated layperson translations of medical documents delivered before real-world consultations. However, related trials in digital health literacy and patient-oriented discharge summaries are ongoing or recently registered, underscoring the timeliness and originality of this study. For example, in Germany, study DRKS00035739 ("PALLADS") is currently recruiting and testing whether LLM-assisted simplification of discharge summaries improves patient activation; similarly, NCT06859216 examines AI-generated plain-language versions of ophthalmology notes. These confirm that although related trials are underway, none to date have completed RCTs of AI-generated, medically validated layperson translations of referral or discharge documents delivered before real-world consultations. The AI-INFOCARE and AI-MEDTALK trials have been conceived to fill this gap. These two parallel RCTs will test the central hypothesis that giving patients an easy-to-understand version of their medical documents before they speak with their doctor will lead to more effective and satisfying communication during the consultation. Specifically, we expect that patients with the AI-assisted information will feel more informed and autonomous, ask better questions, and overall experience a better-quality interaction with their physician, whereas doctors may perceive less difficulty in explaining and managing the visit.

Both trials are prospective, two-arm randomized controlled studies conducted at a large academic medical center in Germany (the Neurosurgery Clinic at Universitätsklinikum Carl Gustav Carus, Dresden). Importantly, they address two complementary patient populations and clinical contexts: AI-INFOCARE focuses on outpatients about to undergo treatment (improving understanding before a treatment discussion), whereas AI-MEDTALK focuses on inpatients at discharge after surgery (improving understanding of what happened and next steps). By covering both "front-end" and "back-end" clinical scenarios, the trials together aim to generate broadly applicable evidence on this AI intervention.

If successful, these studies will produce evidence for a scalable digital health intervention that could be implemented across various settings to improve patient comprehension and engagement. Enhancing communication in this way aligns with public health goals of improving health literacy and patient-centered care. Ultimately, clearer initial understanding can reduce follow-up questions, prevent misinformed decisions, and strengthen the therapeutic alliance [1]. We also acknowledge potential challenges: for instance, doctors must trust and verify AI outputs (to avoid any misinformation), and workflows must integrate generating and sharing summaries without causing delays. The Discussion section will address these considerations.

In summary, the trials will test an innovative strategy to achieve the age-old goal of "understanding instead of uncertainty" in health care communication. This manuscript presents the detailed protocol following SPIRIT guidelines, including rationale, methods, and planned analyses for AI-INFOCARE and AI-MEDTALK.

Methods

Ethical Considerations

This study was approved by the ethics committee of Technische Universität Dresden. The approval numbers are AI-INFOCARE: BOff(Mono)-EK-89022025 and AI-MEDTALK, BOff(Mono)-EK-91022025. The study protocol was prepared in accordance with SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines for clinical trial protocols and approved by the Technische Universität Dresden ethics committee in February 2025. Both trials are registered in the German Clinical Trials Register (DRKS00036810 and DRKS00036814). All participants will provide informed consent. We take care to ensure the intervention does not negatively impact care: the AI summaries are provided in addition to usual explanations, not replacing physician communication. Physicians are instructed to verify and correct any misunderstanding. We also ensure confidentiality of patient data; the AI processing is conducted on a General Data Protection Regulation/Datenschutz-Grundverordnung–compliant server, and no data are shared beyond the study team. Potential risks to participants are minimal—there is a slight risk that a patient might misinterpret an AI summary if it contained a minor error, but our human verification mitigates this. We also considered the psychological impact: for instance, reading one's medical details in plain language could be distressing if the news is bad (eg, diagnosis of a serious illness). In standard care, patients might not fully grasp the seriousness from the medical jargon, whereas the plain summary could make it clear. This is ethically complex, but we believe transparency is ultimately better for informed decision-making. Doctors will be available to discuss any concerns raised by reading the summary. Indeed, this may prompt important discussions that otherwise would not have occurred.

We define information-related adverse events (AEs) as (1) patient distress from the summary requiring unplanned clinical support during or after the visit, (2) clinically relevant inaccuracies identified in the summary, or (3) formal complaints linked to the intervention. All AEs are recorded on standardized forms and reviewed quarterly by an independent safety overseer; serious AEs are reported within 72 hours.

No monetary compensation is provided, but we find that patients are generally eager to participate in order to possibly receive a clearer explanation.

Lastly, we disclose that WHP is affiliated with Simply Onno GmbH, which developed the AI-based translation. This relationship is noted as a potential conflict of interest. To ensure

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unbiased conduct, outcome assessments rely on participant responses, and data analysis will be overseen by the academic investigators. There is no external funding for this study; it is supported by internal resources of the hospital and Simply Onno GmbH. The absence of external funding is declared to maintain transparency.

Study Design and Setting

Both AI-INFOCARE and AI-MEDTALK are designed as prospective, parallel-group RCTs. The trials share a common overall design, with nearly identical interventions and outcomes, but target different patient populations and phases of care (outpatient pretreatment vs inpatient discharge). The study setting is the Department of Neurosurgery at University Hospital Carl Gustav Carus, Technische Universität Dresden, Germany, which includes outpatient clinics and inpatient wards. The trials are investigator-initiated collaborations between the hospital and Simply Onno GmbH (Berlin; [9]), a health AI startup.

The overall structure of the trials is summarized in Figure 1. Each trial will enroll participants over a 6-month recruitment period and follow a simple two-arm randomized design (intervention vs control). There is no blinding (open-label) and no crossover between arms. Outcome assessments are conducted at a single postintervention time point (immediately after the index doctor–patient consultation during which the intervention could have an effect). There are no long-term follow-ups in this protocol, as the primary focus is on the immediate communication outcomes of the consultation.

Figure 1. Flow diagram of the trial design for AI-INFOCARE and AI-MEDTALK. Both trials follow the same procedure: eligible patients are approached and consented, then randomized 1:1 to receive either the artificial intelligence (AI)–generated layperson summary of their medical document (intervention) or standard care with no summary (control) before their doctor consultation. The consultation proceeds as usual, and afterward outcomes are assessed through questionnaires and data collection. Finally, data will be analyzed comparing the two groups.

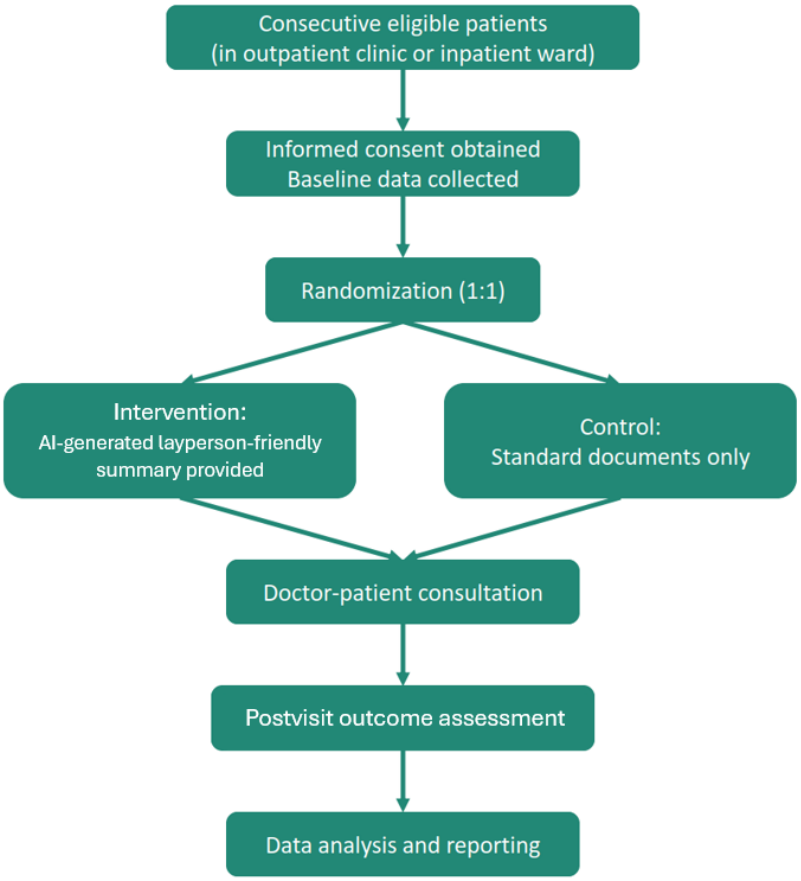

Participants and Recruitment

Each trial will recruit approximately 300 patients (150 per arm), for a total of 600 participants across both trials. Participants will be recruited consecutively from the patient population served by the neurosurgery clinic. AI-INFOCARE will enroll ambulatory patients before a planned treatment, and AI-MEDTALK will enroll hospitalized patients at discharge after surgery.

AI-INFOCARE (Outpatient Cohort)

Eligible patients are adults scheduled for a neurosurgery outpatient appointment in preparation for a procedure or treatment discussion. Examples include patients referred for elective neurosurgical procedures (e.g. tumor resection, spine surgery) who have prior medical reports (such as referral letters, imaging reports) that will be discussed during their consult. Enrollment will occur when the patient arrives for their pretreatment consultation or is identified shortly beforehand via appointment lists.

AI-MEDTALK (Inpatient Cohort)

Eligible patients are adults who have undergone a neurosurgical operation and are now being discharged from the hospital. Typically, such patients receive a discharge summary document

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and a briefing from the surgical team about the operation findings, postoperative care, and follow-up. Enrollment will occur on the day of discharge, prior to the discharge consultation.

Inclusion Criteria (Both Trials)

Eligible participants are adults aged 18 years or older and capable of providing informed consent, with sufficient German language proficiency to read the documents and complete questionnaires (the intervention and all outcome measures are in German). For AI-INFOCARE, the patient must have at least one relevant medical document available, such as a referral letter or diagnostic findings, that can be provided to them. For AI-MEDTALK, a written discharge summary or report must be prepared as per standard care, which can be used for the intervention. Participants must be willing to take part in the study and able to complete a brief survey after the consultation.

Exclusion Criteria (Both Trials)

Exclusion criteria include patients with severe cognitive impairment, altered mental status, or diagnosed dementia or delirium that would prevent comprehension of materials or completion of surveys. Patients who are unable to read (due to illiteracy or severe visual impairment that cannot be corrected) or unable to communicate in German are also excluded. Patients in emergency situations or acute distress where the study procedures could interfere with urgent care, such as an acute postoperative complication requiring intensive care, are not eligible. Inpatients who have had an extremely prolonged hospital stay with multiple prior discussions, which might dilute the effect of a one-time summary at discharge, are excluded. Any patient whom the treating physician deems inappropriate for the study—for example, due to extreme anxiety or other psychosocial factors, defined as inability to complete consent or questionnaires despite support or requiring acute intervention documented by staff—is also excluded. Finally, participation in another interventional study that could conflict with outcomes, or prior enrollment in the current trials (to avoid duplicate participation if a patient were first an outpatient and later an inpatient) renders a patient ineligible; in such cases, they would only be enrolled in one of the two trials.

Screening and Recruitment

A study team member (a trained research nurse or physician) will screen upcoming clinic appointments and inpatient lists daily to identify potential participants meeting the above criteria. Recruitment is consecutive, meaning every patient who meets criteria is approached without selection beyond eligibility, to minimize sampling bias. Patients will be provided written and oral information about the study, and written informed consent will be obtained by study personnel prior to randomization. The general nature of the intervention (receiving an AI-prepared explanation) will be explained, but participants will not be explicitly told whether their documents have been simplified by AI until after the consultation (to avoid expectation bias, although patients in the control arm will likely notice the absence of a simplified text). They are told that the study is comparing different ways of providing information.

At the time of consent, baseline data will be collected, including demographics (age, sex, education level) and clinical context (diagnosis, type of document available). No identifiable personal health data beyond what is needed for outcomes will be retained in the research dataset, and all AI processing of documents occurs on secure servers in adherence with privacy regulations (no patient-identifying information is input to the AI model). Participants are free to withdraw at any time. We anticipate high acceptability of the intervention; similar studies have reported that patients appreciate receiving additional explanations [7].

Randomization and Blinding

Randomization was performed using a computer-generated randomization list created prior to study start. The list was produced with a validated random number generator, fully covering the planned sample size for each trial (n=300). Assignments were generated in a 1:1 ratio (intervention vs control) and exported into a password-protected file with time-stamp documentation. The randomization list was stored on a secure hospital server, accessible only to the principal investigator and the designated study statistician. Allocation concealment was maintained because recruiting staff and treating physicians had no access to the sequence; group assignment for each newly enrolled participant was revealed sequentially through a locked module at the point of inclusion. This procedure prevents prediction of future allocations while ensuring reproducibility and auditability.

Due to the nature of the intervention, blinding is not possible for participants or treating physicians. Patients in the intervention arm will receive an additional written summary that is clearly different from standard documents, and physicians will likely recognize if a patient has an easy-summary or not (eg, patients might refer to it during the consult). We considered having a blinded outcome assessor, but our outcomes are primarily self-reported by patients and the treating physician immediately after their encounter, so blinding is not applicable. The study analysts will remain blind to group labels until after data analysis (groups will be coded as A and B during statistical analysis to prevent subconscious bias). While lack of blinding may introduce some risk of bias, outcomes such as questionnaire scores are less prone to observer bias and more a reflection of the participant's genuine experience. We will compare certain objective measures (like consultation length) to see if any Hawthorne effect (change in behavior due to being studied) is present similarly in both groups.

To mitigate expectancy and performance bias, we use several safeguards: (1) all participants receive a standardized neutral script at enrollment ("You will receive information materials that may vary in format"); (2) clinicians are instructed not to explicitly reference the AI summaries; (3) objective endpoints, such as consultation time, complement self-reported measures; (4) the analyst is blinded to group codes; and (5) sensitivity analyses adjusted for age, education, and clinician identifier will be conducted.

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Intervention: AI-Generated Layperson Summary

Intervention (AI-Based Translation)

Participants randomized to the intervention will receive a layperson-friendly summary of their medical documents, generated by an AI language model, in addition to the standard care documents. Specifically, for each patient, we will take the relevant medical text (eg, referral letter from the general practitioner detailing the condition and prior investigations, or the hospital discharge summary, which includes diagnosis, procedures, and follow-up recommendations) and process it through an AI system that produces an easy-to-understand version in German. The AI system, provided by Simply Onno GmbH, is built on the Claude 3.5 LLM (Anthropic), which has been configured through prompt engineering for patient-facing simplification. The model was instructed to rewrite the input document in clear, simple language targeting approximately a B1 reading level (roughly middle school reading ease). It replaces medical jargon with everyday terms (or explains them), expands abbreviations, and structures the information into a patient-oriented format (for example, using short bullet points or headings for diagnosis, treatment, and next steps).

Before being given to the patient, each AI-generated summary undergoes a quick verification by a member of the study team (typically a physician or medically trained researcher) to catch any obvious errors or unsafe omissions. This step is essential because LLMs can occasionally produce inaccuracies ("hallucinations"); any such instance will be corrected by the reviewer. In practice, the review has shown the summaries to be accurate, with occasional need to adjust a phrase. The final approved summary, typically 1-2 pages in length, is then provided to the patient before their consultation with the doctor.

To ensure fidelity, reviewers follow a 12-item checklist covering accuracy of diagnoses and procedures, completeness of follow-up instructions, preservation of risk or urgency language, and absence of contradictions or invented content. Ten percent of summaries undergo dual review, with interrater agreement reported (Cohen κ and intraclass correlation coefficient). A predefined correction log template (Multimedia Appendix 1) will be used to categorize and document any issues detected during validation. As the trial has not yet commenced, no entries are available at this stage.

For copyright and intellectual property reasons, the exact prompts cannot be disclosed. However, all prompts were version-controlled, and each version was archived with time-stamps in the study's secure documentation system. Any changes in prompt wording or model parameters were logged and linked to the summaries generated during that phase. This ensures transparency and reproducibility of the process without requiring disclosure of proprietary content.

For outpatients (AI-INFOCARE), the summary is handed to them at the clinic check-in, so they can read it while waiting. For inpatients (AI-MEDTALK), the summary is given on the morning of discharge, a few hours before the formal discharge meeting with the physician. Patients are encouraged to read the summary and note any questions they have. They are told that this is "an explanation of your medical letter in simple language that you can keep."

The physician conducting the consultation is aware that the patient has this summary (and in many cases, the physician will have seen it, since it mirrors the content of their own letter but in simpler form). However, physicians are instructed to conduct the consultation as they normally would, with no special training or script from the study. They will naturally address patient questions or clarify misunderstandings as needed. We will later examine whether having the summary changed the nature of questions patients ask or the flow of conversation (captured indirectly through outcomes such as consultation length and perception measures).

Control (Usual Care)

Participants randomized to the control arm go through usual care procedures without any additional intervention. For outpatients, this means they have whatever documents they normally would (often patients do bring their referral letter or test results, but these are in technical language, and we do not provide any translated version). They will have their consultation with the doctor using those standard materials. For inpatients, usual care means they receive the standard discharge summary at the end of the discharge discussion (or sometimes given to them to hand to their next doctor), but not ahead of time in simplified form. Essentially, the control group represents the status quo: the patient relies on the doctor's oral explanation during the consultation and on the standard medical documents, with no separate plain-language text.

All other aspects of care are identical between groups. Both groups' consultations take place with the same pool of physicians (neurosurgery attendings or senior residents), in the same settings. Physicians will have the original medical documents in both cases for reference. After the consultation, both groups complete the outcome questionnaires described below.

Notably, if a patient in the control group expresses strong confusion about their medical documents or requests an explanation in writing, the physician will handle it per usual care (which might involve some oral explanation or writing brief notes, but the prepared AI summary will not be provided at that point, to preserve the integrity of the comparison). However, at the end of the study, control patients will be offered the layperson-friendly summary if they desire, as an ethical consideration to avoid denying potentially helpful information.

Outcome Measures

Overview

We chose outcome measures that capture multiple dimensions of doctor–patient communication and the effects of improved information comprehension. The outcomes have been validated in prior research and will be assessed for each patient (and their physician, in one measure) immediately after the consultation. Figure 2 outlines and illustrates the relationship between the outcomes and instruments, categorized as patient-reported, physician-reported, and objective measures. The specific outcome measures are described in the following sections.

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Figure 2. Outcome structure for communication evaluation. The trials assess patient-reported outcomes (communication quality and autonomy support through the Fragebogen zur Arzt-Patient-Interaktion [FAPI] and brief Health Care Climate Questionnaire [HCCQ], and the patient's self-rated understanding), a physician-reported outcome (encounter difficulty through the Difficult Doctor–Patient Relationship Questionnaire [DDPRQ-10]), and an objective measure (consultation duration).

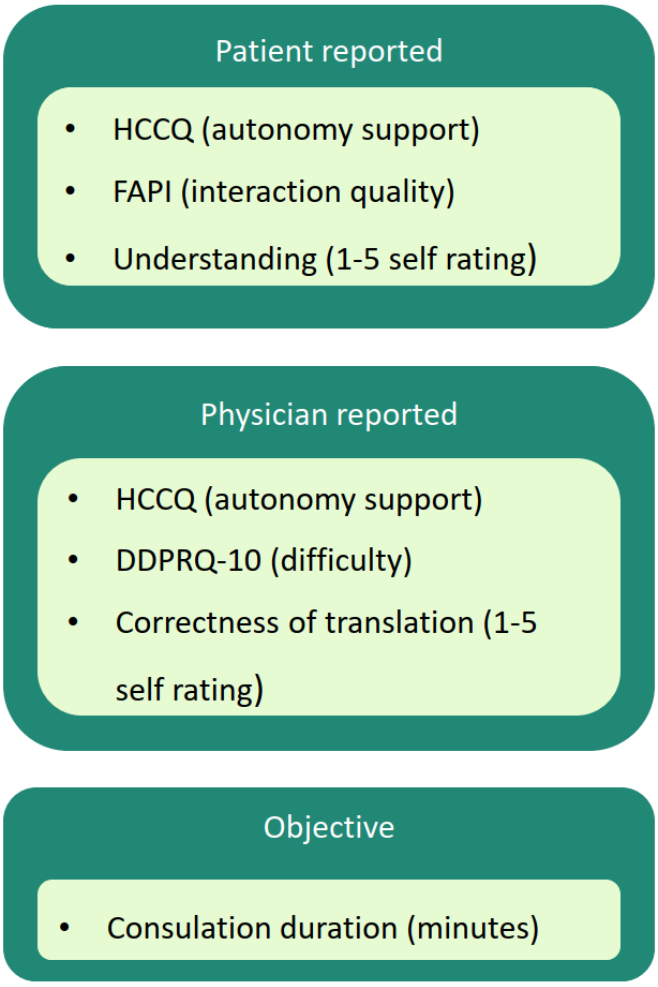

Primary Outcome

We designate the patient's perceived quality of the doctor–patient interaction as the primary outcome, measured by the FAPI (known in English as the Questionnaire on the Quality of Physician–Patient Interaction [QQPPI]). The FAPI is a 14-item self-report questionnaire developed and validated in Germany to gauge the quality of a specific medical consultation from the patient's perspective. It covers aspects such as the doctor's empathy, clarity of explanations, patient involvement in decisions, and time given. Each item is a statement (eg, "The doctor explained the treatment options in an understandable way" or "I felt the doctor took my concerns seriously") rated on a 5-point Likert scale ("not at all" to "very much"). An overall FAPI score is calculated as the mean of item scores (after appropriate reversal of any negatively worded items), with higher score indicating better interaction quality. The FAPI has demonstrated excellent psychometric properties in previous studies, with Cronbach α around 0.95-0.97, indicating high internal consistency. It has shown convergent validity by correlating strongly with patient satisfaction and decision comfort. In these trials, the FAPI is administered in German immediately after consultation. We hypothesize that FAPI scores will be higher in the intervention group, reflecting an improved communication experience when patients have had the opportunity to understand their medical information beforehand.

Secondary Outcome 1: Perceived Autonomy Support From the Physician

This outcome is measured by the HCCQ. The HCCQ is a widely used instrument rooted in self-determination theory, assessing the degree to which the patient feels their doctor was autonomy-supportive versus controlling [10]. We will use the 6-item brief HCCQ (German version), with items like "My doctor encouraged me to ask questions" and "I felt understood by my physician," rated on a 7-point Likert scale [10]. Scores are averaged, with higher scores indicating more autonomy support. The HCCQ has been validated in multiple contexts, showing strong reliability (Cronbach α approximately 0.90) [11]. This outcome captures an important facet of communication quality—whether having more knowledge through the summary makes patients feel more respected and involved in the conversation. We anticipate higher autonomy support in the intervention arm, as doctors may not need to adopt a directive stance and patients may participate more actively when they understand the information.

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Secondary Outcome 2: Patient's Self-Rated Understanding of the Information Discussed

This is a single-item outcome where, after the consultation, we ask the patient: "How well do you feel you understood the information and explanations given to you during this consultation?" on a 5-point Likert scale (1=not at all, 5=very well). This simple metric is commonly used in communication studies and correlates with knowledge retention. It serves as a direct subjective indicator of whether the intervention fulfilled its immediate purpose (improving understanding). We will compare the distribution of responses between groups, expecting a higher proportion of "well" or "very well" responses in the AI summary group. Even a one-point improvement on this scale would be meaningful in practice.

Secondary Outcome 3: Physician's Perception of the Encounter Difficulty

This outcome is measured by the Difficult Doctor–Patient Relationship Questionnaire, 10-item (DDPRQ-10) version [12]. The DDPRQ is a survey the doctor fills out after seeing a patient, reflecting how "difficult" or frustrating the physician found the encounter. It touches on feelings like "I found this patient difficult" or "This was a frustrating visit," rated typically on a 6-point scale [13]. We are using the 10-item short form (each item 1=not at all, 6=a lot), which has been shown to retain high reliability (Cronbach α approximately 0.93) [12]. A total score is averaged (higher score means the doctor perceived the patient as more difficult). We chose this outcome to capture the physician's side of the communication dynamic. Often, patients who are confused, anxious, or demanding due to lack of understanding can be perceived as "difficult" by doctors [13]. We hypothesize that doctors will rate encounters in the intervention arm as less difficult on average, since patients may be more at ease and focused on pertinent questions rather than expressing confusion or dissatisfaction. Each patient's consulting physician will complete the DDPRQ-10 immediately after the consultation, before seeing the next patient, to ensure responses reflect that specific encounter.

Secondary Outcome 4: Consultation Duration

We will record the length of the consultation (in minutes) from start to finish. In the outpatient setting, a research assistant will unobtrusively note the time the patient enters and leaves the doctor's office. In the inpatient discharge setting, the time of the conversation with the doctor (often in the patient's room or ward office) will be noted. This outcome addresses efficiency, as providing patients the summary could either increase time if patients ask more questions or discussion goes deeper, or decrease time if basic explanations need less repetition. Previous research offers mixed insights—sometimes better-informed patients make visits slightly longer due to more questions, but those questions may be more to the point, and satisfaction improves. We do not consider a modest change in time inherently negative; however, it is important to document if the intervention significantly alters physician time burdens. Our expectation is that consultation time might not differ greatly or could even decrease in the intervention group if clarification of basics is faster. This outcome is measured in a single-blind fashion, with the person timing is not influencing the interaction.

In addition to these main outcomes, we will collect exploratory data, for instance the number of questions patients ask during the consultation (not formally tallied, but physicians will provide a subjective rating of patient engagement) and any specific misunderstandings noted (physicians can report if they had to correct any wrong notions the patient had from reading the summary or otherwise). We will also debrief patients in the intervention group with a couple of questions about the summary itself (eg, "Did you find the AI-generated explanation helpful?" rated yes or no, and an open comment). These will be reported qualitatively to supplement interpretation, but they are not primary outcomes.

Sample Size and Power Calculation

We determined the target sample size of 300 patients per trial (150 per arm) through power analysis based on the primary outcome (FAPI score). From previous studies using the FAPI/QQPPI in similar settings, we estimate the mean (SD) FAPI score in usual care to be approximately 3.5 (SD 1.0) on the 5-point scale. We consider an increase of 0.3-0.5 in the mean score (with 0.5 being a medium effect, roughly half an SD) to be a clinically important improvement in communication quality. To detect a difference of 0.5 with 80% power at a 2-sided α of 0.05 using a 2-sample *t* test (2-tailed), approximately 63 patients per group are required. To be conservative and account for potential dropout or non-evaluable responses (eg, incomplete questionnaires), we inflated the sample. Our goal of 300 participants per trial (150 per arm) provides >90% power to detect an effect size of d=0.5 and approximately 80% power to detect a smaller effect of $d \approx 0.4$. This sample also provides ample power (>80%) for detecting differences in secondary outcomes, such as a 10-point difference in the 0-100 scaled DDPRQ-10 or approximately a 1-point difference in the understanding rating. We do not plan an interim efficacy analysis, but an internal check of assumptions, such as variance, will be conducted after approximately 50% enrollment to ensure the sample size remains adequate. Given the consecutive recruitment strategy, we anticipate reaching 300 patients in each trial within the planned 6-month recruitment window, as the neurosurgery service sees dozens of new patients weekly and discharges dozens monthly, with a good proportion expected to consent.

Data Collection and Management

Data are entered into a pseudonymized, access-controlled database on secure hospital servers with routine quality checks (double-entry for a 10% sample and discrepancy resolution from source forms). Each participant is assigned a study ID; no names or identifying information are entered in the analytic dataset. The patient questionnaires (FAPI, HCCQ, and self-rated understanding) are filled by the patient in a private area after their visit, with research staff available to assist if needed (for example, reading questions aloud if the patient has minor reading difficulties; severe impairment was an exclusion criterion). The physician questionnaire (DDPRQ-10) is filled separately by the physician immediately after the visit, without seeing the patient's responses. Consultation time is recorded in minutes by staff. Any technical issues (eg, the AI summary not being ready in time) are documented, and those patients are

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analyzed in their assigned group according to the intention-to-treat principle.

Data management will follow Good Clinical Practice guidelines. Regular data quality checks will be performed, and any discrepancies in entry will be corrected by checking against the source paper. The analysis will primarily be intention-to-treat, including all randomized patients in the groups to which they were assigned. If any patient does not receive the intervention (eg, technical failure to generate the summary) or does not complete outcomes, this will be noted; missing data will be handled through multiple imputation if less than 5% are missing, or through sensitivity analyses excluding those cases.

Statistical Analysis Plan

We will first describe the sample using summary statistics (means or medians for continuous variables, frequencies for categorical variables). The two trial populations (outpatient vs inpatient) will be described separately. Baseline characteristics will be compared between arms to ensure that randomization achieved balance; any significant differences will be noted and adjusted for in secondary analyses if needed.

For the primary outcome (FAPI score), we will compare the intervention and control group means using an independent-samples *t* test (or nonparametric Wilcoxon rank-sum test if the distribution is highly skewed, although previous studies suggest near-normal distribution). We will report the mean difference with 95% CI. The primary analysis will be carried out separately for each trial. However, since the interventions and outcomes are identical, we may also perform a pooled analysis across both trials to increase power, including an indicator for trial to account for any systematic differences in context. Our hypothesis test is 2-sided with α=0.05. We anticipate a positive difference (intervention > control).

Secondary Outcomes Analyses

HCCQ scores will be compared similarly using a *t* test. Understanding ratings, which are on a scale from 1 to 5, will be compared using a Mann-Whitney *U* test for ordinal data or by dichotomizing responses as “understood well” for ratings of 4 or 5 and “not well” for ratings of 1-3, followed by a chi-square test. DDPRQ-10 scores, which yield a numeric difficulty score, will be compared by *t* test; additionally, we may compare the proportion of encounters meeting a “difficult” threshold (there is no absolute cutoff in literature, but >30 on the original 0-100 scale is sometimes used). Consultation time (in minutes) is likely to be skewed; we will compare medians with a Wilcoxon test, and also compare proportion of consultations exceeding a certain length (eg, >15 minutes) using a chi-square test.

We will consider $P<.05$ as significant for the primary outcome. For secondary outcomes, P values <.01 or <.05 will be interpreted with caution due to multiple comparisons. We are not formally adjusting for multiplicity, given that outcomes are correlated; however, the pattern of results will be considered collectively. Effect sizes will be presented (Cohen *d* for continuous outcomes, odds ratios for categorical comparisons) to gauge practical significance.

Subgroup and Exploratory Analyses

We plan to explore whether the effect of the intervention differs by subgroups such as age, with older patients potentially benefitting more or less, education level, with those having lower education or health literacy possibly gaining more, and by doctor. To do this, we may run an ANOVA or regression with interaction terms. For example, we will use a linear regression with FAPI score as the outcome, the intervention as predictor, and an interaction term between intervention and health literacy level, if available from a brief screening question, to examine whether the effect varies. These analyses are exploratory and hypothesis-generating.

We will also analyze the results of the two trials side by side to see whether context, specifically outpatient versus inpatient, influences outcomes. If the direction and magnitude of effect are similar across trials, this strengthens generalizability. If one trial shows a different outcome, for instance if in one context the summary is more beneficial, that will be an interesting finding to explore qualitatively.

All analyses will be performed using SPSS (version 28; IBM Corp) and R software (R Foundation for Statistical Computing). Data analysis will commence after all follow-up is complete. No interim analysis for early stopping is planned, as the intervention is low-risk.

Results

As of May 2025, the trials are in the prerecruitment phase. All regulatory approvals and registrations are in place. Recruitment will commence on May 26, 2025, and is expected to continue until February 2026 or until the target sample sizes are reached. Statistical analysis plans have been finalized prior to trial initiation. Data analysis is expected to begin promptly after completion of data collection. Results are anticipated to be published in summer 2026. Neither study received external funding.

To date, no participants have been enrolled and no interim data are available; therefore, we cannot report any baseline characteristics or outcomes. Enrollment rates will be monitored closely. Based on clinic volumes, we anticipate enrolling approximately 50 outpatients and 25 to 30 inpatients per month, which should allow reaching 300 in each trial within 6 months. If necessary, recruitment may be extended or involve additional centers, but at this time the plan is to keep it single-center and within the 6-month window.

Each trial’s progress and any protocol deviations will be documented. An independent data safety officer will periodically review recruitment and any AEs. We do not expect any physical AEs from this type of intervention. Potential adverse outcomes could include a patient being very upset by understanding their diagnosis; ethically, such reactions are part of informed care. Physicians will manage these situations with appropriate counseling. No such cases have occurred to date, as the trials have not yet started.

We will publish the trial results in a peer-reviewed journal upon completion and also plan to share findings with stakeholders,

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including patient advocacy groups and the hospital administration for potential implementation. The trial registration details, DRKS00036810 for AI-INFOCARE and DRKS00036814 for AI-MEDTALK, are publicly accessible, and we will update those entries with a results summary after study completion as required by guidelines.

In summary, at this protocol publication stage, we confirm that everything is ready for execution of the trials. The key upcoming milestone will be the enrollment of the first patient, anticipated in late May 2025. We will treat the first few cases as a pilot to ensure logistics, such as timely generation of the AI summary while the patient is waiting, function smoothly, then proceed to full recruitment.

We will present the final analyzed results, including comparisons between the intervention and control group for all outcomes, after the trial is completed. These results will allow us to evaluate our hypotheses on whether AI-driven simplification of medical documents can measurably improve the doctor–patient communication experience.

In addition to peer-reviewed publication, results, whether positive or negative, will be posted on the Deutsches Register Klinischer Studien registry, summarized in patient-readable German on the hospital website, and shared with patient advocacy groups and professional societies. Appendices including standard operating procedures and fidelity metrics, will be made available where feasible.

Discussion

Overview

Effective communication is fundamental to patient-centered care, yet achieving it remains challenging in practice. Our protocol describes two novel RCTs addressing a simple but prevalent problem: patients often do not fully understand the written medical information that accompanies their care, which can hinder meaningful dialogue with their doctors. By leveraging AI to translate “doctor language” into “patient language,” we aim to enhance understanding and thereby improve various facets of communication.

The Discussion section examines the rationale for and potential implications of our intervention in light of existing literature, as well as the strengths and limitations of this study design.

Interpretation of the Intervention’s Potential Impact

If our hypothesis is correct, patients who receive an easy-to-read summary of their medical documents will feel more informed and engaged during consultations. Previous research strongly suggests that when patients comprehend their health information, several positive downstream effects occur. They are more likely to ask questions and participate in decision-making, which is a core aspect of patient-centered communication [2]. They may also experience reduced anxiety because uncertainty is diminished, as an informed patient is less likely to fear the unknown.

A classic review by Stewart [1] found that effective physician–patient communication positively influences outcomes ranging from emotional health to symptom resolution. Our intervention specifically targets the information exchange component of communication [2], aiming to make it more bidirectional and understandable. According to the model of Ong et al [2], better exchange of information, alongside a good interpersonal relationship, should improve patient satisfaction, recall, and adherence. We are measuring satisfaction with communication through FAPI and autonomy support through HCCQ, both of which we expect to improve. Autonomy support, in particular, could be enhanced because patients with preobtained knowledge might feel more control over the conversation and subsequent decisions [11]. This aligns with self-determination theory, which emphasizes that supporting a patient’s autonomy, for instance by providing choices or acknowledging their perspective, leads to better motivation and adherence to treatment plans. In our context, giving the patient information in advance is a way of respecting their role in the decision process, effectively saying, “we want you to understand and be an active partner.” We anticipate this will be reflected in higher HCCQ scores in the intervention group, indicating that patients feel their doctors were more autonomy-supportive. Notably, even without specific training for doctors, an intervention that educates patients can indirectly change the communication dynamic, as doctors might notice the patient is well-prepared and accordingly have a more nuanced discussion rather than spending most of the time explaining basics.

For physicians, one might worry that more informed patients could be more challenging, reflecting the stereotype of the patient arriving with a stack of internet printouts. However, research often contradicts this worry: physicians generally appreciate when patients have some baseline knowledge, provided it is accurate, because it can save time and lead to more focused questions [7]. Difficult physician–patient interactions often stem from misalignment of expectations or repeated explanation of basic issues [13]. We posit that our summaries will alleviate those factors, which is why we measure DDPRQ-10 to determine whether doctors find these conversations less frustrating or difficult. A reduction in “difficult” encounters is beneficial not only for patient care but also for physician well-being. Studies show that perceived difficult encounters correlate with physician burnout and suboptimal care [12]. If a simple intervention can reduce that strain, it represents a win–win. Of course, we must be cautious: it is possible that some doctors might feel the AI summary could undermine their role as information-giver or they might worry about inaccuracies. We have attempted to mitigate these concerns by involving physicians in validating the summaries and making clear that the tool is an aid, not a replacement for their explanations.

Comparison With Related Work

Our approach draws upon previous work in health literacy and patient education interventions. There have been efforts to rewrite medical documents in simpler language manually. For instance, Smolle et al [7] simplified discharge instructions, and found improved patient comprehension [7,8]. However, manual simplification is labor-intensive and not scalable in routine practice. The innovative aspect here is using AI (LLMs) to do this at scale and on-demand. Generative AI has only recently become capable enough to handle such tasks with reasonable

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accuracy. Zaretsky et al [8] provided evidence that an LLM (GPT-4 via Azure) can reliably simplify discharge summaries while maintaining content integrity. They did highlight safety concerns—in 18 of 100 reviews, physicians noted some missing or inaccurate information in AI outputs. This underscores the importance of having a human in the loop, as we have in our protocol. Our results will contribute real-world data on whether an AI-assisted workflow can be integrated feasibly without error-induced AEs.

Another related area is the use of patient question prompt lists or decision aids to improve communication. Those interventions provide patients with structured information and questions to consider, often leading to improved question-asking and involvement. Our AI summary could function similarly to a tailored information sheet; it might even prompt patients to ask about things they read. We will observe qualitatively if patients in the intervention ask more questions. If so, that could be an added benefit—engaged patients often lead to more accurate diagnoses and more concordant treatment plans [2].

In terms of health outcomes, our trials are not measuring long-term outcomes like adherence or health status. But literature ties improved communication to those outcomes. For example, a meta-analysis by Jahan and Siddiqui [14] found that good physician communication is associated with higher adherence to treatment (odds of adherence were 2.16 times higher when patients rated their physician's communication as excellent). While beyond our scope, it is conceivable that if patients understand their condition and instructions better (through the summary and ensuing discussion), they will be more likely to follow medication and follow-up plans. We plan future research to track such outcomes.

Public Health and System Implications

Health literacy has been called "the currency of health" in modern health care. Germany, like many countries, has recognized the need to improve health literacy at a population level [1]. Our intervention is one piece of that puzzle—a tool that health care providers can use to ensure each patient, regardless of background, receives information in an understandable form. If our trials show positive results, it would support wider implementation of AI-generated patient-friendly documents across hospitals and clinics. This could be particularly impactful in systems with high patient throughput and limited time, such as busy outpatient practices. By making written communications clearer, the onus on the doctor to cover everything orally in limited time might lessen, as patients come in with some pre-understanding.

From a system perspective, one might worry that providing these summaries is extra work or cost. However, thanks to AI automation, once set up, generating a summary takes only seconds and could be triggered as part of the electronic health record workflow. The physician's time to review the summary for accuracy is a few minutes—likely offset by time saved in repetitive explanations. And the cost of using the AI (computing cost) is minor per document—perhaps a few cents to a couple of euros depending on length and model pricing. There is also no external funding for this study, meaning this concept is being developed without pharmaceutical or large grant backing—a testament that it is a practical solution emerging from clinical need and tech opportunity, rather than a commercial product push. If effective, we imagine no difficulty in convincing hospital administrations to adopt it, given the relatively low cost and alignment with quality improvement goals (some countries might even incorporate it into guidelines for discharge processes to improve patient comprehension).

Another important aspect is generalizability. While this study is in a neurosurgery context with German-language documents, the principle is applicable to any specialty and any language where a robust translation model exists. Chronic illness management, for example, could benefit—patients with diabetes or cancer often receive complex written instructions, and simplifying those could empower them in self-care. Primary care referrals or interspecialist letters could also be translated so patients fully know what is being communicated about them. On a global level, organizations like the Organisation for Economic Co-operation and Development emphasize patient-centered care and health literacy; our approach directly operationalizes some of the Organisation for Economic Co-operation and Development's recommendations for using digital tools to improve communication and patient engagement. It exemplifies how digital health innovation can tackle the enduring issue of jargon-filled health care.

Potential Challenges and Limitations

It is important to consider potential limitations and how they will be addressed.

Accuracy of AI Output

While we have a verification step, there is a risk that an AI-generated summary omits a nuance or contains a subtle error. If not caught, this could mislead a patient. For instance, if a summary accidentally downplayed a serious finding, the patient might not realize its importance. We mitigate this with human review and by instructing doctors to double-check understanding. In our future results, we will audit how often corrections were needed. If too many corrections are needed, that could limit scalability. However, given the continuous improvement of LLMs, we expect accuracy to only improve over time. Our current safety plan appears robust for trial purposes.

Effects on Consultation Dynamics

We assume the effect is positive, but it is possible some doctors or patients might react unexpectedly. A doctor might feel that the patient's preknowledge encroaches on their explanatory routine, or a patient might feel overloaded if they read a lot before the talk. It is a delicate balance—one could liken it to giving patients laboratory results directly before talking to the doctor; some studies show patients prefer knowing results beforehand, while others caution that it can raise anxiety. Our trials will provide insight on this. Through the FAPI and qualitative feedback, we will see if any negative sentiments arise, for example, a patient could say "reading it alone made me worried." We believe the net effect is beneficial as long as the subsequent conversation addresses any anxiety the information caused. Indeed, knowing what to be worried about

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can lead to addressing it head-on with the physician, which is ultimately good.

Generalizability to Lower Literacy Populations

This study requires German proficiency. Those with very low literacy might still struggle, even with a simplified summary, although our summaries aim for fairly low reading level. If someone cannot read at all, our intervention does not help, and they would be excluded. In practice, family members could read to them, but we did not formalize that. Thus, the intervention mostly aids those who can read basic German but not medical German, which is a large group. Future solutions could include audio or video explanations, with AI generating spoken or visual content. This is beyond our current scope but is worth exploring.

Two Trials Versus One

We chose to run two separate trials for two scenarios. This is both a strength, covering more ground, and a complexity. It is possible the effect size differs between them. For instance, outpatients might benefit more because they have time to process information before making a decision, whereas inpatients at discharge may be still recovering and less able to absorb written information. Alternatively, inpatients might have a more immediate need to understand postoperative care. If one trial shows significant improvement and the other does not, interpretation will need to consider contextual differences such as pain, stress, and urgency. However, each trial on its own is powered and important. We will report them separately, as well as discuss combined lessons. We consider them as complementary pieces of evidence. Running two complementary RCTs allows us to capture distinct communication inflection points: preparing for treatment decisions in outpatients (AI-INFOCARE) and understanding postsurgical instructions at discharge (AI-MEDTALK). These contexts pose different informational and emotional demands. Analyzing both separately and in pooled form strengthens external validity and clarifies whether effects generalize across settings or are context-dependent.

No Blinding and Potential Bias

Because patients know if they got a summary, their responses could be influenced by a sort of placebo or novelty effect; they might rate the communication highly out of gratitude or perception that they got extra care. Similarly, physicians know which patients got summaries and might unconsciously treat them a bit differently, perhaps spending a bit less time explaining basics. These are real possibilities. However, they are part of the intervention's effect in a pragmatic sense—in real use, everyone would know the summary is given, and that itself could change behaviors; doctors in future might rely on these tools and adjust their approach accordingly. We opted for a pragmatic trial perspective: measure the outcome as it occurs with knowledge of the intervention. To gauge if bias is substantial, we will compare objective measure of time. If patients report much higher understanding but in reality asked many questions or time increased, we might consider that a bias in perception. We will triangulate data to judge this.

Single-Center, Single-Department Setting

Our sample comprises all neurosurgery patients, which may limit generalizability. Communication needs in neurosurgery might differ from, for example, internal medicine. Nonetheless, many issues, such as complex terms and short visits are universal. We deliberately included heterogeneity within neurosurgery, including spine issues, brain tumors, and other conditions across a broad adult age range, to obtain a diverse sample. Still, future multicenter trials in other fields would be valuable. For instance, applying this approach in primary care or oncology could be next steps. We anticipate our results will encourage such studies or implementations. Thus, while this study provides a proof-of-concept in neurosurgery, results may not directly extrapolate to other specialties. Future multicenter studies across diverse fields, such as oncology or primary care, are needed before broad implementation.

Risk of Workflow Disruption

Another important limitation is the risk of workflow disruption. Physicians may experience additional cognitive load from reviewing AI outputs, and patients may experience heightened anxiety if sensitive diagnoses are clearly stated. Furthermore, AI errors, even if rare, could undermine trust. These risks are integral to the evaluation and will be systematically monitored through the fidelity audit and AE reporting.

Expected Outcomes and Future Directions

We anticipate that the Discussion section in the results paper will highlight improvements in the intervention group across most measures. If, for example, we find that patients with AI summaries have significantly higher FAPI scores, indicating a better perceived interaction, and that their understanding ratings are substantially better, it will provide direct evidence that understanding written information translates to feeling of better communication. We also expect to see a small improvement in satisfaction, which the FAPI captures, and autonomy support, as measured by the HCCQ, possibly moderately higher. We are very curious about the consultation length outcome. A noninferiority result, showing no significant increase in time, would be encouraging because it means such summaries do not slow down clinics. Even if time increases by a minute or two, if outcomes are improved, many would argue it is worth it, as that time might be offset by fewer phone calls later.

One intriguing possibility is that improved understanding could reduce decisional conflict. Although we are not formally measuring decisional conflict in this protocol, some FAPI items indirectly relate to whether patients felt involved in decisions. If analysis of those items, such as "The doctor and I made treatment decisions together," shows higher agreement in the intervention group, that implies better SDM. This aligns with findings that information provision is a prerequisite for SDM.

After these trials, we foresee a need to evaluate longer-term outcomes. For example, do these better communication experiences lead to improved adherence to discharge instructions or follow-up attendance? Are there fewer calls to the clinic with questions, or less need for repeated explanations? We have heard anecdotal reports that patients often call days after discharge with questions indicating they did not grasp the

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discharge instructions. If our intervention works, those calls might be reduced; we may try to gather such data as an exploratory measure during the trial. Additionally, health outcomes such as blood pressure control, pain management, or recovery might indirectly benefit when patients truly understand their care plan. It would be worth examining specific cases, such as medication adherence after discharge; this could be a follow-up study. Some neurosurgery patients receive new medications, such as steroids or anticonvulsants, and comprehension of instructions for those is vital.

Another future direction is cost-effectiveness. Although this study is not an economic evaluation, if it shows improved outcomes, the next question is at what cost, or potentially savings? Given the minimal costs for AI text generation, the main cost is personnel time for review and implementation. If the approach reduces readmissions or unnecessary visits due to confusion, it could even be cost-saving. We will gather some data on postdischarge contacts that may feed into a later cost analysis.

Finally, our research contributes to the broader field of how digital tools can support health communication without replacing the human touch. We emphasize that this AI tool is not taking over the physician's role; rather, it augments the communication process. This distinction is important in discussions about AI in medicine. By focusing on translation of language, we are using AI in a targeted, low-risk way that potentially yields high impact. The trials' outcomes will inform not only this specific use case but also how acceptability of AI interventions is perceived by patients. If patient satisfaction remains high, or even improves, with an AI-assisted process, that bodes well for patient acceptance of other AI-supported health care tasks.

Conclusion

In conclusion, the AI-INFOCARE and AI-MEDTALK trials will shed light on a promising strategy to improve doctor–patient communication by addressing comprehension barriers. These studies are timely, given the dual trends of rising health information complexity and the emergence of AI solutions. A strength of our approach is that it aligns with fundamental ethical imperatives in medicine: respect for persons by informing them, beneficence by potentially improving outcomes, and justice by making information accessible to those who might otherwise not understand it. It operationalizes the recommendation that health information be made understandable as a means to improve health literacy on an individual level [1].

If successful, we envision that providing AI-generated layperson-friendly summaries could become a standard part of the workflow for many clinical encounters—patients routinely receiving two versions of every important document: one for clinicians and one for themselves. Our research will provide evidence on whether this indeed improves the patient experience and what pitfalls to watch for, such as ensuring accuracy of AI output. It may also encourage health systems to invest in patient education through technology, which historically sometimes lags behind clinician-facing technology investments. As health care increasingly adopts digital health records and patient portals, integrating an AI summarization feature is a logical next step; these trials will clarify the value of doing so.

The discussion around doctor–patient communication has often highlighted training doctors to speak more clearly and checking patient understanding using methods such as teach-back. Those remain crucial, but our intervention tackles the problem from another angle, modifying the written side of communication. In a sense, it relieves some burden from the spoken conversation by preinforming the patient. We believe these approaches—improving written information and improving oral communication skills—are complementary and both should be pursued to maximize understanding.

Ultimately, the goal is captured well by a simple idea: when patients truly understand their health situation, they are better equipped to care for themselves and engage with their providers. Our trials aim to provide rigorous evidence that a cutting-edge AI tool can help achieve that understanding in everyday clinical practice. The results, once available, will contribute to the evolving narrative of how technology can humanize medicine by fostering knowledge, trust, and partnership between patients and doctors, rather than detracting from it.

Our findings will add to a growing body of research on digital health literacy and AI-assisted patient communication. Recent JMIR publications have highlighted both the opportunities and risks of LLM-mediated patient materials, showing that readability can be improved substantially, but accuracy and safety remain critical [15,16]. Evidence from digital health literacy interventions demonstrates measurable benefits on comprehension and engagement [17]. Work on optimizing plain-language summaries further supports the importance of tailoring complexity to patient needs [18]. By embedding our protocol within this emerging literature, we extend previous findings into a pragmatic, RCT framework and provide real-world evidence of feasibility.

While this protocol focuses on German-speaking patients in a single neurosurgical center, the approach could be extended to other populations. Potential adaptations include tailoring summaries for patients with low literacy, generating multilingual versions, or providing information in alternative formats such as audio or video. These directions may broaden accessibility and scalability beyond the present setting and will be considered in subsequent studies.

Conflicts of Interest

The authors declare no external funding and no financial conflicts of interest. WHP is associated with Simply Onno GmbH, the developer of the artificial intelligence–based system used; this company is self-funded and not sponsored by outside entities. This affiliation is disclosed, and it did not influence the study design or outcome measures, which focus on patient-centered results. Given this, potential bias in design and reporting cannot be excluded. To mitigate this, we implement governance measures: the

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vendor has no role in randomization, allocation, or outcome assessment; analysis is conducted by independent investigators; and all correction logs and fidelity metrics will be transparently reported. All other authors have no conflicts to disclose. The trials are conducted as an academic-industry collaboration with the sole goal of improving patient care.

Multimedia Appendix 1
Correction log template.
[PDF File (Adobe PDF File), 55 KB - resprot_v14i1e77204_app1.pdf]

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Abbreviations

AE: adverse event
AI: artificial intelligence

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DDPRQ-10: Difficult Doctor–Patient Relationship Questionnaire, 10-item
FAPI: Fragebogen zur Arzt-Patient-Interaktion
HCCQ: Health Care Climate Questionnaire
LLM: large language model
QQPPI: Questionnaire on the Quality of Physician–Patient Interaction
RCT: randomized controlled trial
SDM: shared decision-making
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Gamified Optimized Diabetes Management With Artificial Intelligence–Powered Rural Telehealth Intervention (GODART): Protocol for an Optimization Pilot and Feasibility Trial

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is highly prevalent in the United States and represents a significant public health challenge. Telehealth interventions have shown promise for improving T2DM outcomes, but their effectiveness is often limited by disparities in digital literacy and access, especially in rural areas. To address this gap, we propose an innovative, individualized lifestyle modification intervention delivered via phone call to support glycemic control.

Objective: This paper outlines the protocol for a pilot study designed to assess the feasibility and preliminary effectiveness of an artificial intelligence–assisted intervention for T2DM self-management in rural settings.

Methods: The study uses the preparation phase of the MOST (Multiphase Optimization Strategy) framework to evaluate two components: (1) automated versus human health coaching and (2) fixed versus adapted gamified financial incentives, based on participants' daily engagement with automated monitoring calls. We aim to enroll 88 adults with T2DM and hemoglobin A_{1c} (HbA_{1c}) levels between 6.5% and 11.5%. Participants receive daily interactive voice response calls tracking diet, physical activity, medication adherence, and blood glucose, and weekly coaching based on randomization. In the fixed-reward arm, participants earn US $0.60 per day; in the adaptive arm, rewards start at US $0.20 and increase weekly, with penalties for missed days. Primary outcomes include feasibility metrics and preliminary changes in HbA_{1c}. Semistructured interviews will assess patient experience.

Results: This study was funded by the National Institute of Diabetes and Digestive and Kidney Diseases. As of October 2025, we have enrolled and completed data collection for 88 participants. We expect to complete the feasibility analysis by December 2025.

Conclusions: This pilot and feasibility study evaluates a low-tech, artificial intelligence–assisted T2DM intervention designed to reduce digital barriers and inform a future MOST optimization trial.

Trial Registration: ClinicalTrials.gov NCT05344859; https://clinicaltrials.gov/study/NCT05344859

International Registered Report Identifier (IRRID): DERR1-10.2196/70271

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KEYWORDS

telehealth; type 2 diabetes; lifestyle modification; digital health; artificial intelligence

Introduction

Type 2 diabetes mellitus (T2DM) is a major public health crisis exerting a considerable burden on individual health and the health care system across the United States. Its prevalence is especially high in the Deep South of the United States and in rural areas compared to urban settings [1-3]. Glycemic control through a combination of diet, physical activity (PA), glucose monitoring, and medication adherence has been shown to be effective in T2DM management (reduced hemoglobin A_{1c} [HbA_{1c}]) [4-8]. However, the majority of individuals with T2DM are unable to adhere to the diabetes management guidelines, and this problem is amplified in populations with low health literacy, higher poverty levels, or in remote rural settings [9-11].

T2DM significantly impacts clinical resource utilization because of its frequent comorbidity with cardiovascular and chronic kidney diseases [12-14]. Primary care providers serve as the initial point of contact for most patients with chronic conditions [15] and handle, on average, 4.6 problems per patient visit for patients with diabetes [14,16]. This significant workload and the shortage of primary care professionals lead to primary care access issues, highlighting the need to empower patients' behavior modification outside of the clinic. Increasing patients' knowledge and confidence to self-monitor and modify their health behavior is crucial to improving their health outcomes while conserving limited clinic resources.

Regular self-monitoring (tracking) helps informed decision-making [17-19]. For example, regular blood glucose monitoring provides objective feedback on glycemic control [20]. Similarly, tracking PA (steps) and dietary intake helps alter respective behaviors [21,22] and can influence medication adherence behaviors [23]. Therefore, self-monitoring (tracking) of behaviors has great potential to affect diabetes related health behaviors. However, maintaining diaries or apps for diabetes self-management activities has been shown to increase participant burden and reduce long-term engagement due to loss of interest, complexity, and digital literacy barriers [24,25]. While self-monitoring alone sees benefits, this intervention is often paired with health coaching to provide direct feedback on behaviors, plus provide goal setting and suggestions of dietary or PA alternatives where appropriate. Indeed, digital health coaching has been shown to be effective in improving T2DM outcomes, particularly lowering HbA_{1c}. A systematic review and meta-analysis of 28 studies, 82% of which were randomized trials, found that high-intensity digital coaching interventions are more effective in managing T2DM when compared to usual care [26].

Despite self-monitoring and health coaching's potential to aid in diabetes self-management, the effectiveness of their delivery is hindered by the digital divide [27]. The adoption of digital technologies like smartphones and tablets involved in such interventions is growing, but not uniformly, and sees disparities by age, gender, education, and income. For example, while 97% of adults aged 30-49 years have a smartphone, this rate drops to 91% for adults aged 50-64 years and to only 79% of adults aged 65 years and older [28,29]. Even when given access to a tablet or smart device, many adults are not sufficiently technically proficient to operate them or the software or apps loaded onto them [30]. To ensure broader accessibility and maintain digital equity, there is a need for a scalable, minimally digital intervention that can operate without a mobile app or high-speed internet connectivity. In response to this, the proposed study's intervention leverages the most pervasive and simplest technology—a telephone call, with no expectations of internet availability or smart device-based application proficiency. Use of telephone calls ensures inclusiveness and minimizes barriers for those who may lack or be unable to use smartphones or texting features for either self-monitoring or health coaching.

A telephone call-based self-monitoring and health coaching intervention would be responsive to the need for tech-agnostic self-monitoring for T2DM, but it is human resource-heavy. Hence, we are proposing artificial intelligence (AI)–assisted daily monitoring and automated health coaching as a scalable and low-cost alternative using the interactive voice response (IVR) system. The goal is to use accessible technology to optimize the reach and effectiveness of health coaching. To date, no study has reported using telephone calls for AI-assisted daily monitoring and health coaching focused on the four essential behaviors for glycemic control—PA, diet, medication adherence, and blood glucose monitoring. The daily nature of these automated calls for behavior monitoring presents a challenge for adherence. Rewards, especially monetary rewards, have been shown to provide significant extrinsic motivation toward behavior changes [31-33]. Gamification is also increasingly recognized as an effective method to stimulate adherence [34,35]. Very few studies have compared adaptive gamified financial incentives with fixed financial rewards. We incorporate gamification by implementing a gamified rewards scheme [31] based on participants' consistency of answering daily self-monitoring calls to improve self-monitoring (tracking) behavior. GODART's (Gamified Optimized Diabetes Management with Artificial Intelligence-Powered Rural Telehealth) theoretical framework is based on the social cognitive theory (SCT) for behavior change.

The proposed study aims to pilot GODART's core feature: an automated behavior monitoring program using natural language processing (NLP) and two intervention components. The first intervention component (technology optimization experiment) will assess the feasibility of automated coaching and human coaching, and estimate preliminary effects of automated coaching compared to human coaching. The second intervention component (resource optimization experiment) will assess the feasibility of fixed and adaptive gamified rewards and estimate the preliminary effects of adaptive rewards compared to

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gamified rewards. Overall, we will assess the feasibility of our GODART study protocol in terms of recruitment, retention, and adherence. We hypothesize that the proposed interventions will be feasible and acceptable, and show early promise for reducing HbA_{1c} in adults with T2DM.

Methods

Overview

For GODART, we developed an automated behavior monitoring system (ABMS) where participants receive phone calls to log their exercise, medication, and diet behavior each day for 24 weeks. Calls are delivered through IVR and transcribed using AI features available in Twilio software (Twilio Inc), removing the need for a human operator and allowing participants to report their daily behavior through natural speech. Rewards for completing calls are issued either at a flat rate or at an adaptive (gamified) rate. ABMS calls are supplemented by either human or automated IVR-delivered health coaching once per week. GODART's theoretical framework, based on the SCT for behavior change, is outlined in Textbox 1, and an overview of GODART's intervention structure is detailed in Figure 1.

Textbox 1. Social cognitive theory framework application in GODART (Gamified Optimized Diabetes Management with Artificial Intelligence-Powered Rural Telehealth).

Outcome expectations

- Definition: Anticipated outcomes to behavior change (diet, physical activity, medication adherence, and daily blood glucose monitoring)
- Change strategy: Coaching calls (both human and automated) will address any negative-outcome expectations. The educational content will have content focused on outcome expectations.

Social support

- Definition: Support from family and friends for participation in modified behaviors.
- Change strategy: All educational content and coaching calls will stress the importance of these behavior changes, irrespective of one's diabetes status. Thus, we will recommend including friends and family in this journey of transforming behaviors.

Self-efficacy

- Definition: Confidence in one's ability to exhibit positive behavior in specific situations.
- Change strategy: Our coaching call will, on a weekly basis, choose different specific situations and focus on positive behaviors during those situations. Our behavior-monitoring calls will set small incremental (adapted) goals, leading to increased self-efficacy. Coaching calls will include relevant content.

Self-regulation

- Definition: Exerting self-control over behavior.
- Change strategy: First, the core of our project is centered on behavior monitoring and providing feedback, which aids self-regulation. The fixed versus adapted rewards proposed are aimed at providing further extrinsic motivation toward self-regulation. Finally, the coaching calls will focus on stressing the importance of self-regulation.

Figure 1. Overview of the GODART intervention structure; all study participants receive the GODART core technology (ABMS), but are randomized to one of two optimization experimental conditions: the Technology Optimization Experimentation, comparing human versus automated health coaching, or the Resource Optimization Experimentation, comparing fixed versus adaptive gamified rewards. ABMS: automated behavior monitoring system; AI: artificial intelligence; GODART: Gamified Optimized Diabetes Management with Artificial Intelligence-Powered Rural Telehealth.

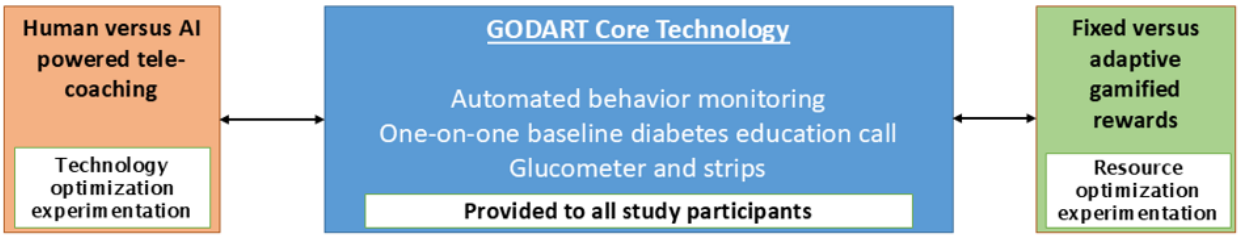

Ethical Considerations

This study was approved as expedited by the University of Alabama at Birmingham (UAB) Institutional Review Board under record IRB-300008752 and registered with ClinicalTrials.gov (NCT05344859). Informed consent was obtained for all participants either electronically using REDCap (Research Electronic Data Capture; Vanderbilt University) or, if needed, through telephone or a mailed physical copy. Participant data are deidentified to maintain privacy and confidentiality. Participants were compensated up to US $225.80 for their participation in study monitoring calls and attending study visits.

Study Design

The GODART study uses the MOST (Multiphase Optimization Strategy) design, grounded in resource management principles and continuous improvement [36-38]. This study aligns with

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the preparatory phase of MOST. We are applying factorial experimentation as part of this MOST preparatory phase to assess the feasibility of two different intervention components (experimentations), with two levels in each group, yielding four experimental conditions. The Technology Experimentation component (Figure 1) focuses on comparing automated coaching through IVR with traditional human-delivered coaching. The goal here is to assess the feasibility of optimizing health coaching by leveraging accessible technology and assessing the preliminary effect when compared to human coaching. The Resource Experimentation focuses on assessing the feasibility and preliminary effect of the adaptive (gamified) rewards when compared to the fixed rewards program. Upon completion of the intervention, all participants will be invited to complete an exit interview to gauge expectations and perceived benefits and to collect suggestions for protocol improvement. Study findings will help us assess the feasibility of the protocol, acceptability of the intervention components, and their preliminary effectiveness in reducing HbA_{1c}, leading to a confirmatory optimization trial. Figure 2 shows a schematic diagram of the study flow.

Figure 2. Flow diagram outlining screening, randomization (n=88), and intervention arms comparing fixed versus adaptive incentives and automated versus human coaching in the GODART study. EMR: electronic medical record; GODART: Gamified Optimized Diabetes Management with Artificial Intelligence-Powered Rural Telehealth; UAB: University of Alabama at Birmingham.

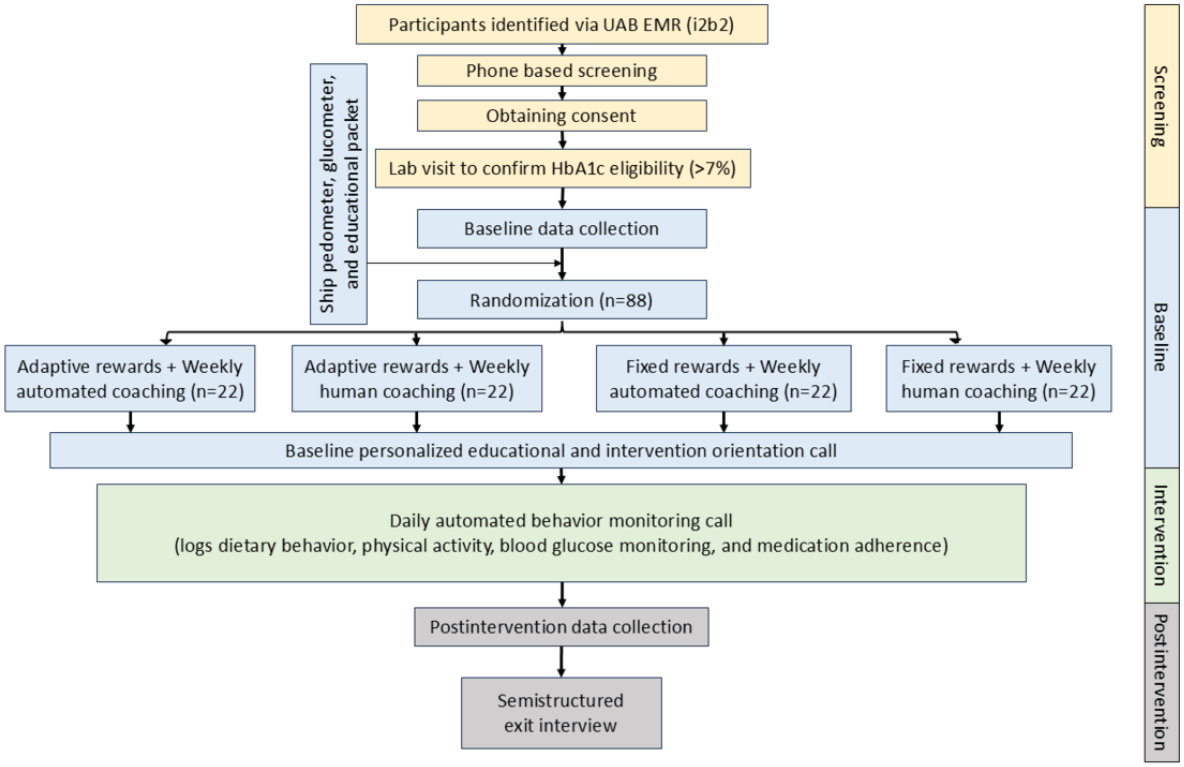

Participants and Eligibility Criteria

This study aimed to recruit a total of 88 patients diagnosed with T2DM [39]. Eligible participants must be individuals aged 18 years or older, can speak English, and have HbA_{1c} between 6.5% and 11.5%. English language proficiency was included as an eligibility criterion, as the telephone-based intervention is delivered in English and requires a level of comprehension sufficient for participants to understand the instructions and interact meaningfully with the system. Additionally, due to resource constraints and the pilot nature of this study, we limited recruitment to English-speaking individuals to ensure feasibility and optimize initial implementation. Participants with HbA_{1c} within the range of 6.5% to 11.5% were included in the study to ensure that we target individuals who will benefit from improved self-management and behavior modification.

Exclusion criteria include current enrollment in other diabetes and weight management interventions, speech or hearing impairments, a major cardiac event in the 6 months prior to screening, current or imminent pregnancy, and ongoing use of insulin. Additionally, participants are excluded if they are unwilling to accept random assignment, engage in regular intervention-related phone calls, or complete study procedures. Individuals currently enrolled in other diabetes or weight management interventions are excluded to prevent confounding effects and to isolate the impact of the study interventions. As the intervention relies on telephone-based communication, individuals with hearing or speech impairments are not included. Participants with major cardiac events, ongoing insulin therapy, or current or imminent pregnancy are also excluded due to safety concerns and the need for more intensive or specialized diabetes management.

Recruitment and Retention

Participants were identified and recruited using the National Institute of Health–funded Integrating Biology and the Bedside (i2b2) system implemented at the UAB Health System. This self-service tool allows users to build a cohort of patients by querying clinical data and developing a recruitment database

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for the study. Recruitment occurred from patients across the health system, which included community clinics that serve patients with Rural-Urban Commuting Area codes of ≥4, which includes all nonmetropolitan tracts, specifically micropolitan, small towns, and isolated rural areas (ie, large towns or clusters) [40]. Using the recruitment database, opt-out letters [41] were sent to all residences of potentially eligible patients either via mail or email. The opt-out letter informed individuals about the study and allowed them to decline contact regarding the study by calling or sending an SMS text message to the phone number provided. Only those who did not opt out within 2 weeks were contacted regarding their interest in participating in the study. Additional recruitment strategies included posting study flyers in high-traffic and clinical areas among UAB clinics and collaborating with clinical staff and providers to identify and refer eligible patients. We also sent the study referral to an application that is integrated within the electronic health record system. The application nudges primary care providers about the study eligibility when a potentially eligible patient visit is scheduled.

Our retention efforts include a combination of strategies to ensure participants remain engaged throughout the study. Participants receive regular reminders and check-in phone calls, and study visits are conducted at LabCorp locations close to their residences to reduce the travel burden. The interventions are delivered remotely, minimizing the need for on-site treatments, and participants receive monetary compensation as part of the participation rewards. Additionally, they provide alternative contact information to ensure consistent communication. All participants receive IVR calls throughout the study as part of the engagement strategy. If any participant stops responding, the research coordinator contacts them directly to address any issues. Participants are contacted per the approved Human Subject Protocol. Up to 3 attempts are made to reach out to each participant via phone call, voicemail, or text to verify whether missed calls were due to technical issues or an intention to withdraw from the study. If a participant fails to respond to three consecutive contact attempts, no further outreach is conducted, and the participant is classified as lost to follow-up and removed from the calling list.

Screening

All patients first undergo telephone-based screening to confirm eligibility. For electronic consent, participants receive a consent form via email using REDCap, a secure web app for managing research data. If the participant is unable to complete the consent form electronically, either a phone consent is obtained or a physical copy of the consent form is sent to the participant's mailing address. A completed, signed consent form is then uploaded to REDCap, and physical copies are stored in secure cabinets at the research site. Each participant is asked to visit a LabCorp location closest to the patients' home addresses to provide a fasting blood sample to be analyzed for HbA_{1c} and lipid profile (ie, low-density lipoprotein cholesterol, high density lipoprotein cholesterol, very low density lipoprotein, triglycerides, and total cholesterol) and biometrics (ie, blood pressure, height, weight, and waist circumference). Measurements are recorded to the nearest 0.1 inches (in) for height and waist circumference and to the nearest 0.1 pounds (lb) for weight.

Baseline Assessments

Once participant eligibility is confirmed from screening, the blood values used in the in-person screening visit described above are used as baseline values. In addition, a baseline survey packet consisting of sociodemographic questions and five validated survey instruments is sent electronically to the participants. The survey instruments are as follows: The Spoken Knowledge in Low Literacy in Diabetes Scale (SKILLD) assesses patients' understanding of diabetes management [42]; the Patient Health Questionnaire-4 screens for symptoms of anxiety and depression [43]; The Diabetes Distress Scale measures the emotional burden associated with diabetes management [44]; The Diabetes Empowerment Scale evaluates patients' self-efficacy in controlling diabetes [45], and the EQ-5D [46] survey assesses health-related quality of life. All study data are collected and securely stored in the REDCap database. If participants are unfamiliar or uncomfortable with completing the survey packet electronically or if they lack an email address, the survey packets are mailed to their preferred address. Included in the packet is a prepaid stamped envelope to return the survey packet. Upon receipt, survey responses are uploaded to REDCap, and the physical copies are stored in a secure cabinet at the research site.

Delivery of the Pedometer, Glucometer, and Educational Packet

Before the intervention began, participants across all arms of the study were shipped a pedometer, a glucometer with strips for 6 months, and a T2DM educational packet. The education content is highly pictorial and is based on the Diabetes Literacy and Numeracy Education Toolkit [47], a packet designed with low-literacy principles and visual aids, for T2DM education and management in patients with low literacy and numeracy skills. In addition, educational patient handouts from the Centers for Disease Control and Prevention (the National Diabetes Education Program and Diabetes Prevention Program) corresponding to all content areas measured by the SKILLD were included in the packet [48]. Topics covered in these materials included special considerations for exercise, understanding HbA_{1c}, eye health, foot exams for individuals with T2DM, and visual aids for making healthy food replacements to manage blood sugar. A guide for estimating portion sizes was also included to facilitate accuracy with daily diet tracking. Sending the educational packet ensures that all participants have access to the same basic principles of diabetes management before starting the intervention.

Randomization

Computer-generated randomization assignment was done for all consented participants. We implemented a permuted block randomization with varying block sizes, blinded to the assessment team. Participants were randomized to four experimental conditions based on a 2 by 2 factorial design with equal probability allocation. The randomization list is concealed within the REDCap randomization module. We have programmed this such that the participant can be randomized

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and allocated only to an experimental condition after it is confirmed that baseline data have been collected and entered. Once the primary outcome measures are entered in REDCap, the study staff members can assign the participants to their respective experimental conditions. The statistician and the Principal Investigators are blinded, but the participants and the health coach are not blinded. All participants enrolled in the study were randomized to one of the four arms:

- Arm 1: Adaptive reward+weekly automated coaching
- Arm 2: Adaptive reward+weekly human coaching
- Arm 3: Fixed reward+weekly automated coaching
- Arm 4: Fixed reward+weekly human coaching

Initial Personalized Orientation Session

All participants received an initial orientation session. Study team members served as health coaches, including a clinical registered dietitian and a certified health coach. During this session, the team reviewed the SKILLD survey completed as part of the baseline survey to identify gaps in the participants' knowledge of T2DM management. These gaps were then addressed, and an introduction to the intervention was provided. The Diabetes Literacy and Numeracy Education Toolkit educational packet was used by health coaches during the orientation process to ensure all participants have equivalent baseline knowledge regardless of their literacy level. For participants with limited literacy skills, the health coaches used this call to walk participants through the educational materials, focusing on the visual components and providing detailed verbal explanations of all key information. This individualized approach ensured that participants who cannot read are still able to access, understand, and engage with the educational content, thereby establishing a consistent foundation of T2DM management knowledge across the study population.

This call provided key information about the intervention, including expectations for the telephone-based ABMS and health coaching calls, participants' randomization to fixed or adaptive rewards, and recommended use of a glucometer and pedometer. Participants also listened to a sample ABMS call to learn best practices for voice recognition when reporting step counts, medication use, and blood glucose testing.

The call included instructions to improve the completeness and accuracy of diet records, with reminders about commonly forgotten items (eg, beverages, condiments, and sweeteners) and guidance to avoid brand names for better matching in Nutritionix. Participants also received introductory nutrition education focused on making healthy replacements to support glycemic control, specifically limiting added sugars, refined carbohydrates, and saturated fats. These behaviors are tracked through daily ABMS calls and discussed during weekly health coaching sessions to enhance both the accuracy and efficiency of self-monitoring.

Following the orientation call, all participants were activated in the ABMS and began receiving calls starting the following Monday.

Intervention Components

Automated Behavioral Monitoring System

All participants receive daily calls through the ABMS using IVR technology for a 24-week period. Each participant selects a preferred call time during their initial orientation session with a health coach. If a call is missed, the system automatically places a reminder call 30 minutes later. Participants who miss both calls can return the call at their convenience to record their data.

Unlike traditional self-monitoring approaches that rely on written logs or mobile apps, the ABMS enables participants to speak naturally during calls—for example, "For breakfast, I had a muffin, a banana, and a cup of coffee" or "Today I walked about 5000 steps." The system captures and processes this information seamlessly using AI-assisted NLP and nutrition databases. The ABMS is designed to collect daily data on four key self-management behaviors: dietary intake, PA, medication adherence, and fasting blood glucose monitoring (yes or no). Figure 3 outlines the 8-step structure of the ABMS used to support diabetes self-management in this study.

During the daily IVR calls, participants report their PA (eg, pedometer step count and engagement in moderate or vigorous activity), medication adherence (eg, whether medications were taken, taken as prescribed, and at the correct time), fasting blood glucose monitoring (yes or no), and dietary intake (meal-specific foods and beverages, including quantities). Textbox 2 lists the daily monitoring questions delivered by the IVR system, and the full branching logic is detailed in Multimedia Appendix 1.

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Figure 3. Overview of the automated behavior monitoring system: 8-step process used in the GODART study to support diabetes self-management. See our YouTube demo [49] for step 5. API: application programming interface; GODART: Gamified Optimized Diabetes Management with Artificial Intelligence-Powered Rural Telehealth; NLP: natural language processing; UAB: University of Alabama at Birmingham.

Step 1. Patient receives automated call or can call in anytime	All participants will receive a daily behavior monitoring call, typically after dinner time (user-selected time). The call will present the opportunity to the participant to log or track diabetes management behaviors over the day. Users can call any time, and if there is a pending monitoring call, that will be offered.
Step 2. Indicates monitoring choices through phone keypad	Simple choices such as "Press 1 to log your diet," "Press 2 to log your pedometer steps," etc will be available, and users can use the keypad or voice at this level.
Step 3. Verbally speaks into the phone using regular English	For complex tracking activities, that is, diet or free-form physical activity, users can log verbally using regular English.
Step 4. Audio is transcribed into text and sent to UAB servers by Twilio	Our automated call will be powered by America's largest programmable voice provider, Twilio. The Twilio API enables a seamless capture of either users' key presses or their voice. This voice is then immediately transcribed and sent to our secure servers at UAB, with Twilio not storing any copies of the data. More details about this technology can be read on Twilio website.
Step 5. UAB sends transcription to Nutritionix API NLP engine, receives food/ exercise Tracking Data	The text received by UAB servers will then be sent to the Nutritionix Food API, which features natural language processing capabilities for both diet and exercise. See our YouTube demo to see diet tracking text being understood by the API using its natural language capabilities.
Step 6. Simple objective data – step count, medication adherence, entered through keypad	Simple objective data such as pedometer steps (*using the study-provided pedometer*), medication intake, etc can be entered through the telephone keyboard or verbally.
Step 7. All tracking/ monitoring data stored in UAB servers	All daily tracking data are stored in a format ready for data analysis and for report generation.
Step 8. All data added to health coach dashboard for verification and call preparation	All behavior monitoring data will be loaded onto the health coach's dashboard. This is for two purposes. First, to ensure that the machine-based transcription and understanding (logging) was accurate. For this, we will implement a random checking policy, and health coaches will be required to verify before proceeding further. Second, if a participant is randomized to an arm involving manual (human) health coaching, the behavior-monitoring data in the dashboard will be used to prepare for the call.

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Textbox 2. ABMS (automated behavior monitoring system) daily monitoring call questions.

Category and sample questions

Daily PA (physical activity)

- Have you experienced any physical symptoms or complaints that could interfere with your PA?
- Did you wear your Fitbit or pedometer today? If yes, how many steps did you take today?
- Did you participate in any moderate intensity or greater PA today? If yes, approximately how many minutes did you spend participating in moderate intensity or greater PA today?

Daily medication adherence

- Did you take your diabetes medications today? If yes, did you take your diabetes medications in the amount prescribed by your doctor? If yes, did you take your diabetes medications at the appropriate time today?

Daily blood sugar monitoring

- Did you test your blood sugar in the morning today?

Daily food intake

- Did you have breakfast today? If yes, what did you eat or drink for breakfast? [Participant instructed to provide the amount of each food or drink]
- Did you have lunch today? If yes, what did you eat or drink for lunch?
- Did you have dinner today? What did you eat or drink for dinner?
- Was there anything else you had today? This could be a snack or a drink.

Our IVR-based ABMS is programmed to interact with both key presses and voice commands [50,51]. Keypresses are used for binary (yes or no) questions and numerical data, such as step counts, while dietary intake is captured exclusively through voice input. The system is built using a MySQL database and Laravel, a PHP-based framework. For telephony, the ABMS uses Twilio's application programming interface (API), which allows the system to immediately retrieve participant inputs, including keypress responses and transcribed voice recordings.

Yes or no and numerical responses are directly stored in the MySQL database. For dietary data, transcribed voice inputs are processed in real time using the Nutritionix API (Nutritionix, Bethesda, MD)—a commercial nutrition database that supports NLP. Nutritionix has been widely used as an NLP nutrition tracking system in prior research [52,53]. All calls are recorded, and the raw audio recordings, transcriptions, and nutrition outputs from the API are stored and made available to study staff for quality checks, such as identifying discrepancies or troubleshooting system limitations. All ABMS calls follow the same structure and are delivered uniformly to all study participants.

There are two experimental groups (two levels in each), which are explained below.

Experimentation Group 1: Automated Versus Human Health Coaching

Participants receive weekly human health coaching or automated health coaching for 24 weeks. Participants randomized to human health coaching receive a call from a human health coach, while those randomized to automated health coaching receive a rules-based automated health coaching call delivered via IVR. Topics include meal timing and spacing, monitoring nutrients for glycemic control, benefits of regular exercise, medication adherence, and consistent blood glucose monitoring.

Both coaching methods rely on data from the prior week's AI-assisted ABMS calls, which are populated into a coaching dashboard using Nutritionix and participant-reported data. In both coaching methods, the human health coach reviews participants' intake and performance against weekly goals. However, the scope and delivery of feedback differ. In the automated health coaching method, participants receive feedback via an IVR system using a rule-based AI engine. The human health coach provides weekly dietary suggestions specifically related to carbohydrate and saturated fat intake. The system flags whether the intake in these categories is within range or elevated, and highlights contributing food items. Based on this information, the coach inputs tailored suggestions that are aligned with participants' health goals, which are then delivered automatically via IVR. Feedback related to medication adherence, blood glucose monitoring, and PA is also delivered automatically via IVR, based on participant-reported data. In the human health coaching method, the same intake data are reviewed, but coaching occurs through direct human interaction, allowing for more nuanced discussion around dietary patterns, behavior change strategies, and personal barriers. The coach is able to engage participants in deeper conversation, explore the context behind food choices, and collaboratively problem-solve to support goal attainment.

Experimentation Group 2: Adapted Versus Fixed Gamified Reward Levels

Participants in this group are randomized into two arms: fixed-reward levels and adapted gamified reward levels; the total possible amount earned over the period of 24 weeks in each arm is US $100.80. The purpose of the rewards is to conduct daily self-monitoring, not as incentives per se to

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participate in the study. In the fixed-reward arm, participants receive 60 cents per day for answering daily monitoring calls for 24 weeks, earning up to US $100.80 if they answer daily. In the adapted gamified reward arm, participants' daily rewards increase weekly, starting at US $0.20 per day in the first week, US $0.25 per day in the second, US $0.30 per day in the third, and US $0.65 per day from the fourth week until the end of the study at 6 months. In this arm, missing one day of monitoring (in the past 7 days) drops the reward value by one level (eg, from US $0.65 to US $0.30), with additional missed days dropping the reward further. Participants can rebuild their reward levels by consistently answering daily calls. Like the fixed award arm, a participant answering the call daily for 24 weeks receives up to US $100.80. This resource management–driven study arm will inform us of the extent to which rewards can enable successful behavior change.

Postintervention Assessments at Month 6

At month 6, similar to the baseline visit, each participant is asked to visit their nearest LabCorp location to provide a blood sample for HbA_{1c}, lipid profile, and biometrics. Participants are also sent a 6-month survey packet either electronically via email using REDCap or via physical mail, depending on the participant's preference. This packet includes all of the surveys in the baseline packet in addition to: Speech User Interface Service Quality, which evaluates the quality, perceived ease of use, and user satisfaction of speech-based interfaces [54]; System Usability Scale, which measures system usability [55]; and the theoretical framework of acceptability survey [56] which assesses the acceptability of the intervention.

Semistructured Exit Interview

Upon completion of the intervention at month 6, participants are invited to complete a semistructured exit interview conducted over a phone call and recorded, to gauge expectations, perceived benefits, and suggestions for protocol improvement (see Multimedia Appendix 2 for interview guide).

Treatment Fidelity

Monitoring fidelity is essential to ensuring the intervention's internal and external validity. In that context, we have developed a fidelity-monitoring plan (Table 1) to address the five areas of intervention fidelity outlined by the National Institute of Health Behavior Change Consortium: design of study, provider training, delivery of treatment, receipt of treatment, and enactment of treatment. Monitoring fidelity is done by the study coordinator, along with the support of the programmer, who provides periodic reports.

Table 1. Overview of fidelity measures and areas addressed.

Data source	Monitoring frequency	Study design	Coach training	Intervention delivery	Intervention receipt	Intervention enactment
Coaching call checklist	Monthly	✓	✓	✓		
Coaching call logs	Monthly	✓		✓		
Content resource bank	Quarterly	✓				
Review of the dashboard and its event log	Weekly	✓		✓		
Review of participant food, physical activity, and medication	Weekly				✓	✓
Team meetings to discuss participant progress and protocol adherence	Biweekly	✓	✓	✓	✓	✓

Outcomes

We are collecting feasibility, process, clinical, and patient-reported outcomes (PROs) during the intervention, with feasibility outcomes serving as the primary end points. As outlined in Tables 2 and 3, our primary outcomes include key feasibility indicators: recruitment, retention, and adherence to the intervention. Secondary outcomes include other feasibility measures such as process measures (eg, time to recruit, percentage of missing data, and enrollment rate), and selected patient-centered and clinical outcomes. The choice of clinical and patient-reported assessments is based on guidelines from the American Diabetes Association [57]. Specifically, diabetes distress is a key PRO, while HbA_{1c} and weight are the key secondary clinical outcomes. Exploratory outcomes include additional PROs (eg, quality of life, depression, self-efficacy, and acceptability of the intervention) and clinical indicators such as blood pressure and lipid profile. PROs are collected using validated instruments such as the Diabetes Distress Scale, EQ-5D, Patient Health Questionnaire-4, and the Diabetes Empowerment Scale. Intervention acceptability is assessed using the Speech User Interface Service Quality, System Usability Scale, and theoretical framework of acceptability scales, in addition to qualitative exit interviews. PA is measured using step count data. Adherence data, including daily self-monitoring of blood glucose and medication adherence, are collected through the ABMS IVR system.

In addition to recruitment, retention, and adherence-related measures, other feasibility measures include process, resource, and management measures such as attrition rate, coach time, time to recruit participants, and technology delivery-related issues (Table 3).

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Table 2. GODART[a] outcome measures.

	Instrument	Mode of collection	Collection timepoint	Outcome type
Feasibility				
Recruitment, retention, completion, and adherence	See Table 3 for more details	Study logs	Ongoing	Primary
Clinical				
Blood sample				
HbA_{1c}[b]	Fasting blood draw	Laboratory visit	Baseline and month 6	Secondary
Lipid profile	Fasting blood draw	Laboratory visit	Baseline and month 6	Exploratory
Biometric				
Height (in)	Stadiometer	Laboratory visit	Baseline and month 6	Secondary
Weight (lb)	Weight scale	Laboratory visit	Baseline and month 6	Secondary
Waist circumference (in)	Measuring tape	Laboratory visit	Baseline and month 6	Secondary
Blood pressure (mm Hg).	Sphygmomanometer	Laboratory visit	Baseline and month 6	Secondary
Patient-reported				
Distress related to diabetes	Diabetes Distress Scale	Survey	Baseline and month 6	Secondary
Diabetes management self-efficacy	Diabetes Empowerment Scale	Survey	Baseline and month 6	Exploratory
Medication adherence	Amount or frequency as prescribed	IVR[c]	Daily	Exploratory
Self-monitoring of blood glucose	Measured or not	IVR	Daily	Exploratory
Anxiety and depression	Patient Health Questionnaire-4	Survey	Baseline and month 6	Exploratory
Health-related quality of life	EQ-5D-5L	Survey	Baseline and month 6	Exploratory
Step count	Pedometer	IVR	Daily	Exploratory
Quality, perceived ease of use, and user satisfaction of speech-based interfaces	Speech User Interface Service Quality	Survey	Month 6	Exploratory
System usability	System Usability Scale	Survey	Month 6	Exploratory
Acceptability of the intervention	Theoretical framework of acceptability	Survey	Month 6	Exploratory

[a]GODART: Gamified Optimized Diabetes Management with Artificial Intelligence-Powered Rural Telehealth.

[b]HbA_{1c}: hemoglobin A_{1c}.

[c]IVR: interactive voice response.

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Table 3. Feasibility outcomes.

Metric and outcome	Outcome variable computation method
Process	
Time taken to recruit	Time from study activation to enrollment of the last participant
Recruitment rate	Number of participants enrolled per recruitment time period
Retention rate	Percent of participants completing the trial
Enrollment rate	Enrolled of eligible or approached
Decline rate	Percent of eligible individuals who declined participation
Completion rate	Percent of enrolled participants who completed the study
Protocol adherence	Total number of sessions attended of the total 24 coaching sessions; number of monitoring calls answered
Challenges in collecting blood samples using LabCorp	Qualitative data from patients
Time to complete data collection	Time to complete pre- and postdata collection
Duration of human coaching	Time to schedule and conduct orientation and diabetes education
Data entry errors	Data entry errors
Percent missing data	Percent missing data
Resource	
Patients' technical difficulties with technology	Number of issues experienced by participants in technology, glucometer, and LabCorp visits
Number of replacement glucometers requested	Total cost and number of items purchased
Number of participant contacts by the team required to complete survey data	Number of contacts
Management	
Fidelity across conditions	Number of deviations from protocol per week of technical issues in interactive voice response
Fidelity across conditions	Frequency, duration, and nonbusiness hour times requested of contact or support

Data Management

Data are being collected and managed in a custom-designed REDCap database. Data will be exported to the statistical analysis software, using relational logic checks to identify internal inconsistencies and out-of-range values. Systematic cleaning and verification of all collected data will be conducted to examine ranges, provenance, and missing values. Any inaccurate data points, outliers, and influential cases will be identified and corrected within REDCap. Dashboards and reports will be created and periodically updated to assist the team with recruitment and retention efforts, and track and minimize missing data.

Sample Size Justification

The primary objective of this feasibility study is not to serve as a definitive, well-powered trial, but to conduct a pilot study that is sufficiently large to estimate design parameters, as well as assess feasibility parameters, such as attrition rate, adherence, and pre-post correlation [58-60]. Accounting for the bias and precision of the estimated pooled SD can help us conduct rigorous power and sample size calculations for a subsequent confirmatory study [61]. We are randomizing 88 participants across four conditions (22 per experimental condition). This is almost twice the number of participants per condition recommended when undertaking pilot studies, when there is no prior information on which to base a sample size [62]. The goal of our pilot study is also to estimate precise effect sizes and design parameter estimates, which requires sufficiently large pilot studies. Based on simulations published by Teare et al [61], an external pilot study should have at least 70 participants when estimating the pooled SD for a continuous outcome. Because we are using a factorial experiment, for each of the main effects, we will have 88 participants, with 44 participants in each of the two comparators. Hence, we have a sufficiently large pilot study to detect precise estimates of effect sizes for the two main effects and other design parameter estimates, such as pre-post correlation.

We also present power calculations of our experiment based on our sample size of 88. Assuming a type 1 error rate of 0.05, a conservative pre-post correlation of 0.5 in ANCOVA, and an attrition rate of 15%, we will have 80% power to detect an effect size (Cohen *d*) of 0.572 in our primary outcome. This would imply a main effect difference of 0.86% units of HbA_{1c}, assuming an SD of 1.5% [63]. Even if we assume the pre-post correlation is 0.3, which is very conservative, we will have 80% power to detect an effect size of 0.63 for the main effect. Assuming a more realistic pre-post correlation of 0.7, we can detect an effect size of 0.472. Missing outcomes data will be

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imputed using maximum likelihood estimation or a multiple imputation procedure, and primary analyses will not be restricted to only completers. Hence, our proposed study sample size of 88 participants is powered to detect an even smaller effect size than suggested here since the effective sample size, even assuming an attrition of 15%, would be between 74 and 88. Thus, our pilot study is well-powered to detect moderate to medium effect sizes. These power calculations were done using the MOST package in R (R Core Team), developed by Dziak et al [64].

Statistical Analyses

Feasibility-Related Analyses

Descriptive statistics of feasibility measures such as adherence, dropouts, and recruitment will be estimated and provided. Bias-corrected bootstrap CIs of the Spearman correlation between baseline and 6-month assessment will be reported. For participants identified through the i2b2 system at UAB Health System, we are tracking the following: (1) no response, (2) screened but failed, (3) screened as eligible but did not consent, (4) screened as eligible and consented, (5) enrolled but withdrew before the intervention started, (6) started the intervention but withdrew during the study, and (7) completed the intervention and final data collection. In addition to the descriptive measures of recruitment outcomes, we will run at least a binary logistic regression model to explore and predict factors associated with successful recruitment outcomes. Successful recruitment will be defined as participants screened as eligible, consented to participate, completed the intervention, and completed the final data collection. Age, gender, race, location status (urban vs nonurban), and health insurance status will be covariates.

Analytic Strategy for Preliminary Effectiveness Analyses

We will also estimate effect sizes as preliminary effectiveness estimates. All statistical analyses will follow an intent-to-treat approach. In line with a pilot study, we will also report 75% and 85% CI estimates in addition to the traditional 95% CIs to further aid in the statistical interpretation of the findings [65]. We will use linear mixed models to estimate effects by accounting for correlated data and benefit from the maximum likelihood estimation procedure that uses all information in the dataset in the presence of missing outcome data. Our overall approach will be similar to Pellegrini et al [38]. To evaluate the main effect of each component on pre-post differences in outcomes, we will use baseline as the reference cell to determine differences in change across time (ie, 6 months vs baseline) [38]. However, these effects will be statistically modeled as component-by-time interactions, with the 6-month outcome as the primary end point. We will also include two-way interactions between components (eg, Factor 1 by Factor 2 by time interaction). We will then identify all the active components or combinations of components, where active is operationalized as a mean reduction of 0.5 units (%) in HbA_{1c} between baseline and month 6 [66,67]. Similar analyses will be done for secondary outcomes. Where information related to minimally clinically important differences is available, we will use it to assess whether the combination is active. For example, an average 5% weight loss is considered to be active in the case of weight. We will leverage the generalized linear modeling framework and resampling-based approaches for nonnormal outcomes. We will conduct exploratory analyses to assess biases in the self-reported PROs. While we are not statistically powered to do mediation or moderation analyses, in line with the MOST Preparatory Phase, we will conduct exploratory mediation and moderator analyses using our tracking data as potential mediators or moderators.

Analysis of Qualitative Interviews

Collected interview data will be analyzed using a phenomenological approach. Two researchers will independently code the transcribed audio-recorded interviews. They will meet after coding every four transcripts to discuss and resolve any discrepancies in coding. A third researcher will be available to adjudicate unresolved discrepancies. Coding will follow an inductive, emergent approach grounded in the transcript data, using both descriptive and in vivo codes. The coding process will involve two levels: first-cycle coding, where initial codes are assigned using in vivo coding, and second-cycle coding, where these codes are refined and grouped into broader themes using pattern coding [68]. The codebook structure will include themes, codes, and text examples of quotes. Thematic saturation will guide the final sample size. We will enhance trustworthiness through triangulation, peer debriefing, and maintaining an audit trail. All qualitative analyses will be done using NVivo 12 Plus (Lumivero).

Results

We conducted 1938 phone contact attempts, resulting in 1192 participants completing phone screening. Of those, 162 were deemed potentially eligible and consented to screen for HbA_{1c}. As of October 2025, 88 participants who were randomized and enrolled in the study have completed the 6-month follow-up. We anticipate completing data analysis by December 2025. Table 4 outlines the study timeline and anticipated completion of key milestones.

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Table 4. Timeline of study progress and anticipated target completion.

	2022				2023				2024				2025			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Institutional Review Board approval				✓	✓											
Manual of Operating Procedures development and refinement	✓	✓	✓	✓	✓	✓	✓									
Recruitment period								✓	✓	✓	✓	✓				
Intervention period								✓	✓	✓	✓	✓	✓	✓		
Baseline assessment								✓	✓	✓	✓	✓				
6-month assessments								✓	✓	✓	✓	✓	✓	✓		
Data management and quality control								✓	✓	✓	✓	✓	✓	✓	✓	✓
Exit interview								✓	✓	✓	✓	✓	✓	✓		
Data analysis													✓	✓	✓	✓
Publications														✓		✓

Discussion

Principal Findings

This paper sought to outline the study protocol used in a pilot study grounded in SCT, aiming to assess the feasibility of an AI-assisted, low-cost, lifestyle modification intervention for glycemic control in the Deep South. The intervention is designed to be accessible through a standard telephone service and leverages MOST, an efficient and rigorous resource-management and continuous-improvement framework. The MOST design allows us to explore (1) a fixed versus adaptive (gamified) rewards program, and (2) automated versus human-delivered weekly health coaching for four total experimental conditions to see which is most effective for T2DM management. Findings from this pilot and feasibility study will inform the resources needed for a well-powered optimization trial. We will estimate key design parameters—such as effect sizes and pre-post correlations—to guide future sample size calculations. The study also helps identify protocol modifications to improve scalability, recruitment, and participant-centeredness.

The rationale for this study comes from the rising prevalence of T2DM in the Deep South and the lack of self-management in rural, underserved, or low digital literacy populations [69]. Given this escalating prevalence of T2DM, challenges in access to primary care and time available to assist patients in self-management of T2DM, coupled with disparities in its management, there is a need for an optimized, low-cost, scalable intervention that complements primary care for T2DM management to ensure health equity. Synchronous human coaching has been shown to be effective in glycemic control for patients with T2DM [70] and has been explored in rural-specific settings as well [71,72]. A nurse-led telecoaching study for rural patients was successful and cost-effective in T2DM management [73-80]. However, providing 10-15-minute live telephone calls to each patient at frequent intervals presents a significant barrier for scalability. This led to the development of automated health coaching delivered via an automated phone call by an IVR system. Participants use the keypad of any phone (landline, mobile, or smartphone) to interact with the IVR system, where the human coach is replaced by high-quality recorded interactive scripts [81]. IVR-delivered coaching is thus far more scalable than traditional delivery. IVR-based behavior monitoring has been shown to be effective in driving behavior changes [81]. Hence, the proposed intervention could contribute to an interprofessional primary care system, alleviating access issues. Our proposed resource optimization experimentation arms of fixed and adaptive gamified rewards are relevant in the context of existing wellness programs offered by employers and payors to incentivize behavior change. The intent is to promote behavior tracking that can facilitate behavior change where needed, leading to improved health outcomes and improved employee productivity, and less health care expenditure, such as emergency department visits or avoidable hospitalizations. The cost-effectiveness sustainability was not part of our pilot study; this is an important but different aspect of the Multiphase Optimization Strategy Preparatory phase and will be addressed in our future work using approaches such as microsimulations [82]. The GODART project aims to take a step toward building such a system. An overview of the innovative aspects and limitations is discussed below.

Strengths and Limitations

Our study has multiple strengths and innovative methodologies. From a technological standpoint, we combine NLP with standard telephone-delivered monitoring and coaching. By incorporating natural language understanding (AI) techniques, we aim to minimize the user burden in self-monitoring, which requires minimal time and low health literacy levels [83,84]. The study uses AI to allow participants to "speak" their daily updates into the phone for recording, significantly easing the data collection process. Additionally, we are implementing a gamified rewards scheme based on data collection done via phone to improve

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self-efficacy and self-monitoring behavior [31]. Gamification is widely recognized for its potential in managing chronic diseases, and our study leverages this approach through a simple reward system [85].

From the study design perspective, an additional strength is the adoption of the MOST framework, which emphasizes efficient resource management and continuous improvement [36]. Our study objectives align with MOST's preparatory phase, and it is also structured to serve as the preparatory phase for a future large-scale MOST optimization phase. MOST's preparatory and optimization phases are more efficient for intervention development than a traditional randomized controlled trial (RCT) since it would take substantially greater resources (time and sample size per RCT) to meet this goal [37]. These MOST phases in our study will provide more information than a typical feasibility and well-conducted pilot study using an RCT approach. Further, in MOST, intervention optimization could be an iterative and continuous process compared to a traditional RCT.

From the data collection and engagement perspective, our study leverages simple telehealth technology based on IVR to collect periodic data from participants and keep them engaged throughout the study period. Collecting these data as part of the diabetes self-management activities instead of apps or logs is meant to reduce the participant burden and keep the data collection process simple and accessible, regardless of patients' health literacy or technological access. Further, analyses of these data can help develop learning models that can enable further optimizations through the development of just-in-time adaptive interventions [86,87]. Finally, blood draws are collected at the LabCorp location nearest to each patient's home. This strategy minimizes potential delays by reducing the need for patients to travel to specific clinic locations.

There were several limitations to this study. First, the study design required participants to engage daily in a phone-based intervention, which may limit generalizability, as individuals who enrolled were likely more motivated at baseline than the broader population of adults with type 2 diabetes. As a result, the findings may be most applicable to patients already inclined to engage in self-management, highlighting the need for future research to develop strategies that also reach individuals with lower baseline motivation.

Second, although our system uses AI to process information collected through IVR calls, the coaching recommendations themselves are not generated by AI. Instead, they are developed by a human coach and then delivered asynchronously via IVR. Thus, the automated call arm still depends on human input and is not entirely independent of human resources. Since the design of this study, there has been a major shift in AI technology with the availability and mainstreaming of large language models. Future iterations of this project will be able to leverage LLM-based approaches to further enhance AI-based ABMS and AI-based health coaching.

We also asked participants to report whether they were checking their blood sugar, but did not collect actual glucose values. This was due to the lack of a clinical remote monitoring team available to respond to hypo or hyperglycemia alerts. Future studies may incorporate continuous glucose monitoring or partner with remote monitoring teams, such as registered nurses within a health care system, to respond to critical alerts and provide timely feedback and support.

Additional limitations include the exclusion of non-English speakers, which may reduce the generalizability of findings to linguistically diverse populations. All behavioral data was self-reported, which introduces the potential for recall bias—particularly underreporting—since more detailed entries (eg, food logs) led to longer IVR calls and may have discouraged full reporting. Additionally, the study does not include a scale to assess social desirability bias in the self-reported PROs, which we will incorporate in our future study. Coaching fidelity was not comprehensively evaluated: the automated coaching was still guided by a human coach, and the degree of standardization or comparability between the human and automated arms was not assessed. Given the applications of LLMs, we anticipate this issue to be addressed by the adoption of LLM in our GODART technology platform.

Conclusions

The rising prevalence of T2DM, specifically in the Deep South and rural areas, calls for interventions that can be delivered remotely yet with minimal digital complexity. These could serve as scalable digital care management plans offered in primary care settings to address the current primary care limitations due to limited access and time. This study seeks to test the feasibility of a telehealth and AI-driven intervention designed to be easily accessible, even for individuals with minimal digital literacy. By gathering data from this study, we intend to lay the groundwork for a future large-scale optimization trial as a step toward building an interdisciplinary primary care system that could integrate health technology effectively, ensuring that patients receive care at the right time and place.

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Data Availability

The datasets used or analyzed during the current study are available from the corresponding author upon reasonable request. The trial data will be publicly available for publication in international peer-reviewed journals, regardless of whether the results are positive or negative.

Conflicts of Interest

TM has received consulting fees from The Obesity Society, Novo Nordisk, Heart Rhythm Clinical Research Solutions, and the New Balance Foundation Obesity Prevention Center.

Multimedia Appendix 1
Branching logic for ABMS and coaching calls.
[PDF File (Adobe PDF File), 260 KB - resprot_v14i1e70271_app1.pdf]

Multimedia Appendix 2
Qualitative interview guide.
[DOCX File , 43 KB - resprot_v14i1e70271_app2.docx]

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Abbreviations

ABMS: automated behavior monitoring system
AI: artificial intelligence
API: application programming interface
GODART: Gamified Optimized Diabetes Management with Artificial Intelligence-Powered Rural Telehealth
HbA_{1c}: hemoglobin A_{1c}
IVR: interactive voice response
MOST: Multiphase Optimization Strategy
NLP: natural language processing
PA: physical activity
PRO: patient-reported outcome
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SCT: social cognitive theory
SKILLD: Spoken Knowledge in Low Literacy in Diabetes Scale
T2DM: type 2 diabetes mellitus
UAB: University of Alabama at Birmingham

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Protocol

The Scale-Up of a Digital Health Intervention (Healthy Beginnings for HNEKids) Targeting the First 2000 Days: Protocol for a Randomized Controlled Trial

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Abstract

Background: Digital health interventions, delivered directly to parents' mobile phones, could transform the delivery of health care during the first 2000 days of a child's life. Healthy Beginnings for Hunter New England Kids (HB4HNEKids) is an innovative SMS text message–based model of care that provides age-and-stage relevant preventative health information to parents during the first 2000 days. While HB4HNEKids demonstrates promise for population-wide scale-up, the optimal method for achieving universal, cost-efficient, and equitable scale-up remains unclear.

Objective: This protocol outlines a randomized controlled trial that evaluates 2 models for scaling up HB4HNEKids: an "opt-in" clinician-initiated model (intervention) and an "opt-out" system-initiated model (control). The trial will assess program reach (the number and proportion of eligible parents receiving HB4HNEKids) and participant representativeness to identify the most effective, equitable, and efficient approach to scaling up care for families during the first 2000 days.

Methods: A randomized controlled trial will be conducted in 6 Child and Family Health Service (CFHS) sectors (39 CFHS units) within the Hunter New England region of New South Wales, Australia. The 6 CFHS sectors will be randomized in a 1:1 ratio to one of 2 arms, stratified by sector location and average number of births per annum. The intervention arm (a clinician-initiated opt-in model of care) will involve a series of implementation support strategies delivered to CFHS staff (ie, training, audit, and feedback) to support clinicians in connecting eligible families to the HB4HNEKids program. The control arm (a system-initiated opt-out model of care) will use existing health service data to identify participants meeting the predefined eligibility criteria to automatically initiate the commencement of HB4HNEKids messages to families (ie, will not require input from CFHS staff). The primary outcome will assess the reach and representativeness of participants receiving HB4HNEKids. Secondary outcomes will include child health behaviors (breastfeeding rates; age of introduction to solids; child fruit, vegetable, and discretionary food intakes; as well as child immunization rates) captured via parent survey, as well as the cost-effectiveness.

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Results: This trial commenced in July 2024, and as of July 2025 enrolled 4212 participants. Data collection (via parent survey) commenced in January 2025 and is projected to end in July 2027.

Conclusions: Currently, little is known about the most effective model of scaling up digital health interventions. This trial will generate novel evidence for informing the effective scale-up of evidence-based health promotion programs that aim to provide universal care, which are needed to maximize the potential population health gains.

Trial Registration: Australian New Zealand Clinical Trials Register ACTRN12624000655549p; https://tinyurl.com/4krc9za5

International Registered Report Identifier (IRRID): DERR1-10.2196/81390

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KEYWORDS

digital health; scale-up; child health; infant feeding; first 2000 days

Introduction

The first 2000 days of a child's life (ie, conception to 5 y of age) represent a critical window for promoting child health and development, and lay the foundations for a child's lifelong physical, mental, social, and emotional health and well-being [1]. Early exposure to health-promoting behaviors, including breastfeeding, consumption of healthy diets, and adequate physical activity, can have powerful programming effects [2,3]. For example, longer breastfeeding duration is associated with better neurodevelopment outcomes, lower risk of childhood and adulthood obesity, as well as reduced risk of type 2 diabetes [4-7]. Reviews have also found that child physical activity and healthy dietary intakes before age 5 are associated with beneficial cognitive outcomes, motor skill development, and improved measures of adiposity [8].

As lifestyle exposures during the first 2000 days can have implications for children's academic, social, and health trajectories, there remains a need to support families to achieve optimal health behaviors during the first 2000 days [9]. Despite national infant feeding guidelines recommending that infants are exclusively breastfed until around 6 months of age and breastfeeding continued until 12 months and beyond [10], population data demonstrate that Australian exclusive breastfeeding rates decline from 74% at 2 months to 38% at 6 months, with only 43% of infants receiving any breast milk at 12 months [11,12]. In addition, while 97% of Australian children aged 2-3 years met the recommended intakes for fruit, only 20% of 2 to 3-year-olds met the recommendations for vegetables, with the proportion of children meeting fruit and vegetable recommendations drastically dropping by 4-8 years [13]. The report further identified that the proportion of children who did not usually eat fruit daily has doubled over the last decade (2011-2022), and the proportion of children who do not usually eat vegetables daily has tripled [13]. This reinforces the need to provide parents with direct and consistent support from birth to 5 years, to further limit the prevalence of suboptimal health behaviors during these crucial developmental stages.

For decades, the provision of universal health care during the first 2000 days has been recommended by national and international policies [14-16]. In Australia, this support has been traditionally offered by a range of health care providers via face-to-face models; however, this care can be fragmented and poorly attended by parents. For example, in New South Wales, Australia, Child and Family Health Services (CFHSs) provide access to routine universal care via face-to-face in-home or clinic visits. However, 2024-2025 data from the Hunter New England Local Health District (HNELHD) of New South Wales (internal data) indicates just 83% of parents accept the initial 1 to 4-week health check home visits, a trend that is consistent with wider New South Wales data [17], with engagement steadily declining to approximately 5% by 4 years. While ongoing CFHS usage is associated with reduced risk of hospitalization, emergency visits, and early identification of health and developmental concerns [18], barriers to parent engagement with face-to-face health care remain, including time, travel, and scheduling conflicts [19].

Digital models of health care delivery may address issues of reach and engagement by providing asynchronous care that parents can use at their convenience. Mobile health (mHealth) interventions (ie, SMS text messages), delivered directly to parents' or carers' mobile phones, could greatly enhance the delivery of health care during the first 2000 days [20]. This notion is supported by a meta-review including 25 systematic reviews that demonstrated parent-targeted mHealth interventions can improve literacy, antenatal service usage, child vaccination rates, preventive health behaviors, and maternal health outcomes [21]. As such, digital models of care that support families across the first 2000 days are recommended to improve child health outcomes [20].

Healthy Beginnings for Hunter New England Kids (HB4HNEKids) is an innovative SMS text message (mHealth) program designed to be delivered alongside the usual CFHS. It provides age-and-stage relevant preventative health information, child health check and immunization reminders, as well as information on health screening and support services, directly to parents during the first 2000 days (commencing within days after birth up until 5 years). HB4HNEKids was adapted from an original efficacy trial demonstrating improvements in infant feeding practices and screen time [22], and a pilot effectiveness trial which evaluated its feasibility, acceptability, and effectiveness when embedded into routine health service delivery within 5 diverse CFHS in the Hunter New England region of New South Wales. The pilot trial, implementing HB4HNEKids into routine health service delivery demonstrated that HB4HNEKids digital model of care program was feasibly delivered to families (delivered to over 6000 parents), reached approximately 70% (6243/8501) of eligible parents at a

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relatively low cost (approximately Aus $4.66/family per year, equivalent to US $3.03/family per year), had high parental engagement (73/96, 76% of parents or carers reported reading the messages) and acceptability (89/96, 93% of parents liked the program) [23]. The pilot also indicated that HB4HNEKids participants had improved child vegetable intakes (P=.006) and parental mental well-being (P<.001) at 12 months compared with families who had not received the program [24]. In addition, breastfeeding rates were 5% higher in the HB4HNEKids participants at 6 and 12 months compared with families who had not received the intervention. Thus, while the pilot of the HB4HNEKids program demonstrates promise for population-wide scale-up, the optimal method for achieving universal, cost-efficient, and equitable scale-up remains unclear.

The pilot implementation study of the HB4HNEKids SMS text message program required clinicians to offer the program to families during their first contact with the CFHS (clinician-initiated model). Clinicians provide child health and development assistance and advice, and, where needed, refer patients to secondary services. Clinician-initiated onboarding may increase the salience of the offer of the HB4HNEKids program, resulting in increased engagement and improved impact on behavioral outcomes, particularly as CFHS is considered a trustworthy source for infant and child health information and support [25]. However, engagement with CFHS is fragmented, with only 83% (8638/10393) of families in 2022-2023 attending their 1- to 4-week health check and a significant reduction in use of services thereafter. Additionally, there are barriers that impede a clinician's ability to enroll participants into digital health interventions (DHIs) like HB4HNEKids, such as a lack of training and education, a lack of time, and a concern for increased workload, competing priorities, as well as infrastructure and technological barriers [26]. A system-initiated model, relying upon an opt-out approach, whereby parents and families are automatically enrolled into digital health programs such as HB4HNEKids, via data and systems, may have the potential to facilitate the universal offering of DHIs to eligible parents, likely at much lower financial cost than developing implementation strategies that address clinician barriers to enrolling participants. Opt-out approaches have shown promise in increasing participation in DHIs internationally [27]. For instance, a study evaluating a maternal and child health SMS text message program in a study from New Zealand found that transitioning from an opt-in to an opt-out model resulted in an increase in enrollments but had no significant effect on withdrawal rates [27]. However, the retrospective study did not report on the acceptability of the opt-out model, nor its impact on behavioral outcomes or sustainability, highlighting the need for further research in understanding factors that influence opt-out approaches. While an opt-out approach may seem promising, offering a DHI that does not include clinician contact may result in less trustworthiness and salience of information, resulting in less engagement in the DHI [28,29]. The effects of such models may also differ by participant characteristics that have the potential to drive inequity [30]. Although opt-out approaches have demonstrated potential in enhancing the reach of DHIs, there is limited data comparing the effects of a clinician-initiated and system-initiated models of care on parent engagement, representativeness, retention, effectiveness, and cost-effectiveness in digital health programs. Therefore, it is necessary to understand the impact of both scale-up models on these outcomes to optimize the success of DHIs.

To address this gap, we aim to conduct a randomized controlled trial (RCT) to test the effects of a clinician-initiated (opt-in) model relative to a system-initiated (opt-out) model (control) of enrolling parents into the HB4HNEKids program. This RCT will explore the impact of the 2 scale-up models on (1) program reach (number and proportion of eligible parents that receive HB4HNEKids) and (2) representativeness (similarity of the characteristics of the parents receiving HB4HNEKids from all parents eligible to do so over the study period). Additionally, we will assess the effects on child health behaviors, costs, as well as implementation and process measures.

Methods

Study Design and Setting

An RCT will be conducted in 6 CFHS sectors (made up of 39 CFHS units) in the Hunter New England region of New South Wales, Australia. CFHS receives referrals to provide care to families with children aged 0-5 years and their families (parents or carers) from all public and private maternity services in HNELHD, following birth. In any given year in HNELHD, approximately 10,000 births occur, which is therefore indicative of the number of referrals received by CFHS. CFHS within HNELHD provides care to families from varying sociodemographic backgrounds, with 39% of services located in metro and 61% in regional or rural areas. Approximately 20.6% of babies born in the HNELHD are Aboriginal or Torres Strait Islander, and many families come from culturally and linguistically diverse backgrounds [31].

The research will be conducted and reported in accordance with the requirements of the CONSORT (Consolidated Standards of Reporting Trials) 2010 Statement and the Standards for Reporting Implementation Studies statement 2017 [32]. CFHS sectors will be randomized to one of 2 arms: the intervention arm, a clinician-initiated model, in which participants voluntarily "opt-in" to receive HB4HNEKids, or the control, a system-initiated model, where participants are automatically enrolled based on key eligibility criteria and must "opt-out" if they do not wish to receive the program. The protocol is reported according to the Standard Protocol Items: Recommendations for Interventional Trials (Multimedia Appendix 1) [33]. Any modifications or deviations from the methods outlined within this protocol will be documented by the research or project team, and updates will be logged in our online trial registration and disclosed within any relevant publications. The senior author (R Sutherland), together with the broader research and project team, will oversee the project dissemination plan, including all publications and reports to stakeholders. Authorship will conform to the International Committee of Medical Journal Editors guidelines.

Ethical Considerations

Approval to conduct this study has been obtained from Hunter New England Research Ethics Committee (2022/ETH00359

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and 2023/ETH02782) and the University of Newcastle (H-2022-0129 and R-2024-0095). This research study was granted a waiver to randomize participants and deliver the program as part of usual health service delivery. All participants were regularly sent a link to opt out of the program (n=6 in the first 12 months and n=4 from 1 to 2 years). The opt-out link remains open for participants to access at any stage. For the evaluation of child health behaviors, consent was expressed by the completion of a survey. Given that participant burden to complete surveys to evaluate child health behaviors was minimal (less than 10 min per survey) per data collection time-point, upon survey completion, participants could enter a draw to receive 1 of up to 3 gift cards to the value of Aus $30 (equivalent to approximately US $20) as an evidence-based strategy to encourage participant sustainment and engagement with evaluation activities. Health service and participant data were collected and securely stored using the Research Electronic Data capture (REDCap, version 14.1.2, 2025 Vanderbilt University) tool, hosted by HNELHD, which is a secure research electronic database commonly used in health service research, compliant with health service privacy and confidentiality policies. Data will be anonymized, deidentified, and stored so that only authorized individuals have access to the data.

Sample and Participants

Recruitment

CFHSs

In total, 6 of the 7 regions, which take in 39 CFHSs (ie, clinics) of HNELHD, will participate in the scale-up of HB4HNEKids. One region was involved in the HB4HNEKids pilot implementation study over the past 3 years and will therefore be excluded from this study analysis.

Parents

The mHealth SMS text message program, HB4HNEKids, will be delivered to eligible parents or carers (from herein named parents) alongside usual face-to-face CFHS care. Parent eligibility criteria for both the intervention and control arms were developed in partnership with CFHS clinical leads, and include: (1) must be eligible to access CFHS located in the HNELHD; (2) must own a mobile phone with SMS capability (96%) [34]; (3) must have a baby who has been discharged from a hospital in the last 8 weeks; (4) had a length of hospital stay less than 45 days; (5) absence of complex social issues resulting in the infant needing out of home care; and (6) baby was born ≥32 weeks of gestation. Furthermore, CFHS clinicians can use their clinical judgment to exclude families from the program at any time based on unforeseen personal circumstances. Over an 18-month intervention period, it is expected that approximately 15,000 parents (ie, 10,000 per year) who are referred to CFHS will be exposed to HB4HNEKids. All eligible parents who are referred to CFHS will be included in the sampling frame and analysis. While this RCT is planned to 24-month follow-up, there is scope to longitudinally follow this cohort across the first 2000 days (until their child is 5 years of age) to explore several outcomes of interest.

Randomization and Blinding

Given that CFHS clinicians may work across multiple CFHS within a region or sector, the randomization for this trial will be conducted at the CFHS sector level to minimize possible contamination across CFHS sites. The 6 CFHS sectors (including 39 CFHS) will be stratified by geographic location and number of births/year (based on whether the number of births is higher or lower than average), and randomized in a 1:1 ratio to one of the 2 trial arms (clinician-initiated or system-initiated). Randomization will occur by an independent statistician using Microsoft Excel. CFHS will not be blinded to group allocation; however, the primary trial outcome—reach and representativeness of HB4HNEKids—will be objectively assessed via electronic records of service enrollment.

HB4HNEKids SMS Text Message Program

HB4HNEKids is an SMS text message program delivered to parents who are accessing CFHS after having a baby. The program aims to provide evidence-based age and stage information to parents across the first 2000 days. The mHealth program is an adapted version of the Healthy Beginnings program evaluated via a 3-armed RCT [35] and demonstrated to have an impact on screen time and infant feeding practices. The optimization process for HB4HNEKids from the original Healthy Beginnings program aimed to enhance its effectiveness on breastfeeding duration and a delayed introduction to solids, as well as seeking to improve other health behaviors identified as a priority by health service executives, clinicians, and relevantly aligned policies and frameworks, such as the First 2000 Days framework [16], New South Wales Healthy Eating and Active Living Strategy [36], and National Digital Health Strategy [20]. Optimization of program format and content occurred via an extensive co-design process involving a multidisciplinary team of CFHS staff, Health Promotion practitioners and Dietitians, as well as partners from Aboriginal and Multicultural Health services, and end users. The process used the Behaviour Change Wheel (BCW) [37] and Theoretical Domains Framework (TDF) [38] to optimize the original program, adapting and developing new program content and materials, as well as maximizing recruitment pathways for participants, based on the local context and implementation infrastructure. To minimize resource costs and streamline the model used to provide regular health information to families, the adapted version also sought to use a digital-only format (via SMS text message), rather than providing brochures at key milestones, supplemented by digital care, as detailed in the original efficacy study [35].

The HB4HNEKids program aims to support improved health and developmental outcomes for families by targeting barriers and enablers to optimal preventative health behaviors including (1) breastfeeding and appropriate introduction of solids by providing guidelines and practical information and advice, as well as facilitating referral pathways, to support best-practice infant feeding; (2) child nutrition including guidelines and strategies to implement and address responsive feeding, family foods, reducing discretionary foods, and increasing healthy foods; (3) physical activity and small screen recreation by connecting families to evidence-based resources, credible

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content, and real-world strategies that facilitate daily activities; (4) child health and development according to age, stage-relevant child milestones, and pathways for more information and support; (5) parental well-being, targeting practical approaches to self-care, connections, and self-efficacy; and (6) immunization and primary health checks by prompting and reminding families about scheduled checks with CFHS or general practitioners.

SMS text message content was developed as part of a pilot project and optimized to be delivered across both experimental groups in this trial. SMS text messages are tailored to include the infant's name and infant feeding status (breast, formula, or mixed feeding status). The content includes up to 147 SMS text messages to be delivered over a 24-month period, with more frequent SMS text messages in the first 3 months (approximately twice per week), and every 1-2 weeks for the remainder of the first 2000-day period (Figure 1). The intervention messages included behavior change techniques that were designed to be primarily delivered via SMS text messages. Supplementary content was optional and available to access via embedded links, which require internet access. Almost all SMS text messages included embedded web links to related evidence-based online content, including websites, factsheets, podcasts, and videos (refer to Figure 2 for an example message).

The scheduling of messages was based on the baby's date of birth (or adjusted date of birth for the first 12 months for babies born prematurely), and daily message outputs were generated using SAS statistical software. A member of the research team generates and uploads daily message outputs to a cloud-based SMS provider, and messages are scheduled to be delivered at varied times between 9 AM and 12 PM, based on expert advice to encourage ongoing engagement with messages. The cloud-based SMS provider (DirectSMS) did not have the capability to track read receipts.

Figure 1. HB4HNEKids message topics by phase.

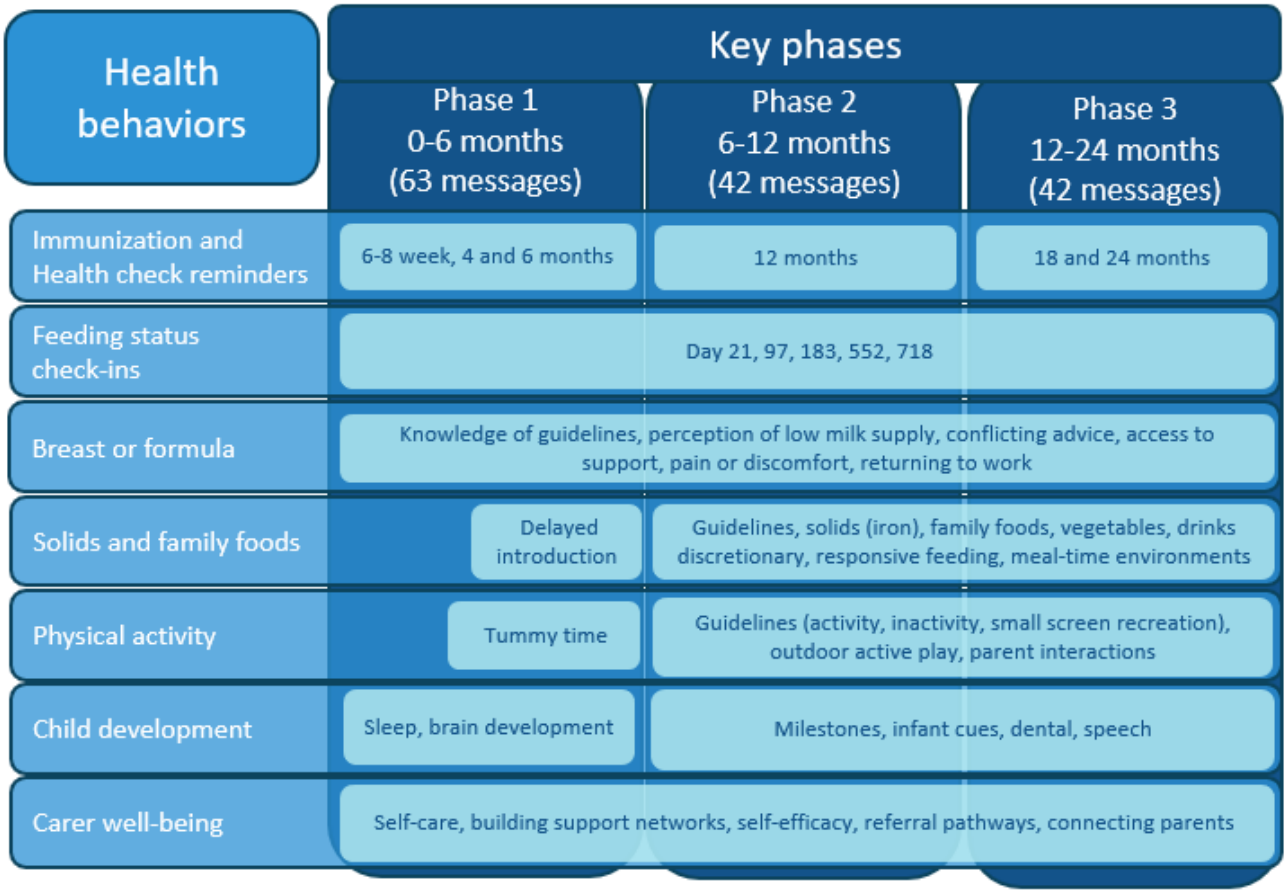

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Figure 2. Example SMS text message. HB4HNEKids: Healthy Beginnings for Hunter New England Kids.

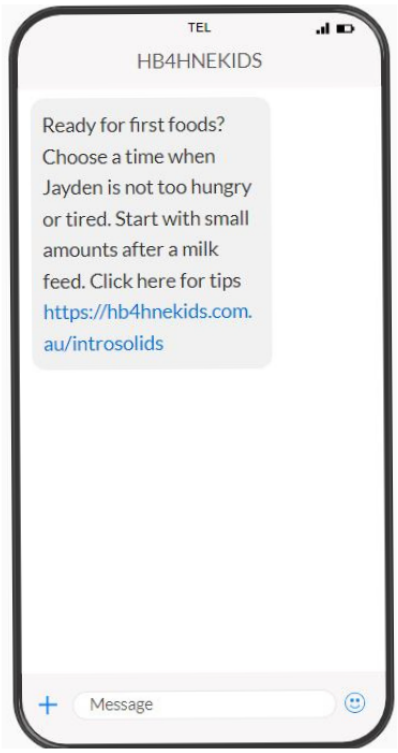

Intervention

Scale-Up Model Development

The intervention design for scale-up was based on findings from the pilot program and an expert task group, established to support the co-design process. A multidisciplinary team of public health practitioners, CFHS staff, service managers, and academics, with expertise in community health services, quality improvement initiatives, stakeholder engagement, behavior change, and implementation science, supported the review of evidence and provided local context to inform co-design of a scale-up model, resulting in a clinician-initiated model versus a system-initiated control model (usual care control).

To identify implementation strategies, barriers and facilitators to digital health care were identified via literature review [26] and findings from the pilot program, which were mapped to behavior change techniques [39] using the BCW and TDF [38]. The Expert Recommendations for Implementing Change (ERIC) [40] was used to define the implementation strategies, and objectives for each strategy were outlined using the Action, Actor, Context, Target, Time (AACTT) framework [41] (Multimedia Appendix 2 [26,38-41]).

Preimplementation Strategies

Preimplementation strategies for both the intervention and control arms were used before the trial commenced. These strategies provided CFHS staff members within the Hunter New England region with information on the HB4HNEKids program and provided scope and context for the scale-up of the program. Co-design with CFHS, service managers, and public health practitioners was undertaken to determine what strategies would be useful in preparing CFHS for the HB4HNEKids program throughout the local health district.

The preimplementation strategies, as illustrated in (Multimedia Appendix 2 [26,38-41]), were consistent across the intervention and control and included:

- Involve executive boards: executive endorsement or management support.
- Conduct educational outreach visits and assess for readiness and identify barriers and facilitators: sector-based information sessions, providing information on the pilot study and the proposed future of the program.
- Build a coalition: establishment of sector-based key contact.
- Make training dynamic: brief prerecorded (15 min) presentation for service staff, outlining the program and objectives of the scale-up trial and professional taster messages, which provided clinicians the opportunity to experience a sample of messages (n=13) that families receive during the first 6 months of the program.

Intervention: Clinician-Initiated (Opt-In) Model

The clinician-initiated (opt-in) model is based on the process used during the pilot program to support clinicians in connecting families to the program. As per existing health service procedures, CFHS receives a referral from public and private maternity services following the birth of a baby and discharge of the mother and child from the hospital [42]. Upon discharge, CFHS staff contact the parent (participants) via phone call or SMS text message to offer a 1 to 4-week health and development check. During this contact with parents, staff from one of the clinician-initiated CFHS offer HB4HNEKids as part of routine care. CFHS staff also confirm feeding status (ie, if the child was breastfeeding, mixed feeding, or formula feeding), child name, mother's mobile number, and “offer of service” (ie, yes, client refused, or unable to contact after multiple attempts). If a staff member is unable to determine the infant’s feeding status

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during the initial contact, they will locate the "infant feeding status" via the hospital discharge summary provided by maternity services.

Building on the pilot, a series of additional strategies to improve the process of enrolling parents to the HB4HNEKids program have been co-designed by an expert task group and are outlined in the logic model (Multimedia Appendix 2 [26,38-41]). Following the process used for the intervention design, the established task group used the literature and local expertise to identify and map barriers and enablers to implement a clinician-initiated model. The BCW and TDF were also used to develop implementation strategies [38]; strategies were mapped to the ERIC strategies [40] and defined using the AACTT framework [41].

Control: System-Initiated (Opt-Out) Model

The control was a system-initiated (opt-out) model. The selection of a system-initiated model was based on clinician feedback during the pilot phase and automates the connection of families to the program. This model requires minimal input from clinicians. As per existing health service procedures, health service data are generated when CFHS receives a discharge referral from public and private maternity services for a mother or baby following the birth of a baby to initiate usual care via CFHS. This health service data will be used to identify parents who meet the predefined eligibility criteria for the HB4HNEKids program and will also be used to initiate the commencement of program messages, resulting in families automatically receiving the program. Predefined eligibility criteria were developed with and approved by CFHS clinicians. Nonetheless, CFHS staff are encouraged to refer to the program content as a potential trigger for discussions when conducting usual care. As part of this model, clinicians may opt out families from the program if it is not considered appropriate. Families can also opt out themselves, using the established pathways that cease program delivery to a family (eg, via links provided in messages, via links on the program website, or directly through a request to CFHS staff).

Data Collection Procedures and Measures: Primary Outcome

The primary trial outcome will be the reach and representativeness of the HB4HNEKids program at 4, 6, 12, and 18 months from the commencement of the scale-up phase. The reach of the program by the scale-up model (clinician-initiated vs system-initiated) will be explored. Reach will be defined as: the number of eligible parents that are receiving HB4HNEKids (assessed via project records) and the proportion of parents receiving the program, calculated by the number of eligible parents receiving HB4HNEKids (numerator), divided by the total number of parents eligible for the program (denominator), identified via electronic health service records.

Representativeness will be assessed by comparing the characteristics of the parents receiving HB4HNEKids via each scale-up model to those of the total sample of eligible parents or carers referred to CFHS during the 18-month trial period. Characteristics of eligible parents (collected via electronic health service records and "The Good for Kids Parent Collective") include parental age, geographic location, highest level of education, employment status (before birth of child), first baby (yes or no), number of children, language spoken at home other than English, and Aboriginal and Torres Strait Islander status. Sample representativeness of parents receiving the HB4HNEKids program at baseline and those remaining engaged at 18 months from both scale-up models will be compared, as well as compared with characteristics representative of the wider Hunter New England population.

Secondary Outcomes

Child Health Behaviors

The effectiveness of HB4HNEKids on key preventative health behaviors including proportion of any breastfeeding at 4, 6, and 12 months old; age of introduction to solids; mean daily serves of vegetables, fruit, and discretionary foods at 12 and 24 months old; and child immunization rates will be assessed using validated items via computer assisted telephone surveys or online surveys (as part of the GFK Parent Collective or using service delivery data) sent out to program participants via a link. The data collected as part of the GFK Parent Collective will not be included within the individual child electronic medical records; however, the data will support the evaluation of this trial and support future health service planning through the ongoing development of the program and informing New South Wales Health services (eg, CFHS).

Cost-Effectiveness

The costs, cost-effectiveness, and potential cost savings of the scale-up models will be undertaken from the health service perspective. Resources used for the clinician-initiated and system-initiated models will be assessed via project records (infrastructure, staff, and consumables). Direct costs include digital infrastructure and text messaging platform, labor (health promotion team and CFHS), cost to develop additional material, clinician training, and implementation support. The cost-effectiveness of the scale-up models will be compared with the primary cost-effectiveness outcome, being incremental cost per unit change (%) in reach.

Process and Implementation Outcomes

Engagement (intervention adoption)

Project records obtained from project databases (REDCap) and the text message platform will be used to assess parental engagement with HB4HNEKids. Engagement data will include the proportion of eligible parents who click through on external hyperlinks embedded into SMS text messages at 4, 6, 12, and 24 months post baby's birth. Engagement will continue to be measured across the first 2000-day period and reported as part of a further phase of data collection.

Implementation

As per Proctor et al [43], the following digital health implementation outcomes will be measured: clinician acceptability, feasibility, and appropriateness using validated items sent to clinicians via a hyperlink to an online survey. Parent acceptability will be assessed using the same validated items embedded within the above-mentioned computer-assisted telephone interviewing or online survey.

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Maintenance

The parental opt-out rates from HB4HNEKids for intervention and control will be assessed via project and electronic health service records used to deliver the program as per the primary outcome – reach. Characteristics of parents opting out of receiving HB4HNEKids in both groups will also be assessed at 18 months post baby's birth.

Sample Size and Power Calculation

For the primary outcome, a sample of 1126 participants or families per trial arm will enable a detectable difference of 9.8%, assuming the opt-in model will achieve approximately 65% reach at 18 months (based on previous pilot data [awaiting publication]) with 80% power, α of .05, and an intraclass correlation coefficient of 0.05. Given the sectors involved in the trial are estimated to account for 55% of births within the Hunter New England area, achieving this sample should be possible.

Analysis

Analyses of trial outcomes will be undertaken under an intention-to-treat framework. For assessment of reach of HB4HNEKids—the primary trial outcome—between-group differences will be assessed using mixed logistic regression to account for any potential sector–level clustering effects. The regression model will include fixed effects for each arm of the trial and control for covariates prognostic of the outcome, including participant geographical location and ethnicity. To assess the impact of HB4HNEKids on child health behaviors, we will compare these outcomes between groups (clinician-initiated model vs system-initiated model) using mixed logistic and linear regression models. The model will include fixed effects for service and parent demographics that are found to be significantly different between scale-up models to account for potential consent bias. Subgroup analyses based on parent characteristics will also be conducted to examine differential effects on models of care against the outcome. We will use descriptive and comparative statistics to describe implementation and process outcomes, including engagement, acceptability, feasibility, appropriateness, and maintenance. All statistical tests will be 2-tailed with an α of .05.

Given that the trial is exploring the implications of the scale-up model (not the HB4HNEKids service), a data monitoring committee is not required for this trial. Data will be stored securely in accordance with the requirements of all ethics committees. Data will only be accessible to investigators listed on the ethics application and statisticians.

Results

This trial commenced in July 2024, and as of July 2025, enrolled 4212 participants. Data collection (via parent survey) commenced in January 2025 and is projected to end in July 2027 (Table 1). The CONSORT flow diagram of the included CFHS in Hunter New England is presented in Figure 3. Results are expected to be published in 2028 following the completion of data collection.

Table 1. Project timeline.

	2024		2025				2026				2027			
	Q3[a]	Q4[b]	Q1[c]	Q2[d]	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Preimplementation strategies – all services	✓													
Implementation strategies – clinician-initiated services only	✓													
Participant recruitment		✓	✓	✓	✓	✓								
Intervention delivery		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
6-month data collection[e]				✓	✓	✓								
12-month data collection[e]						✓	✓	✓						
18-month data collection[e]								✓	✓	✓				
24-month data collection[e]										✓	✓	✓		
Analysis							✓		✓		✓		✓	✓

[a]Q3 relates to July-September.

[b]Q4 relates to October-December.

[c]Q1 relates to January-March.

[d]Q2 relates to April-June.

[e]Primary outcomes assessed at 6 months (2025-Q2), 12 months (2025 Q4), 18 months (2026-Q2), 24 months (2026-Q4).

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Figure 3. CONSORT flow diagram. CFHS: Child and Family Health Service.

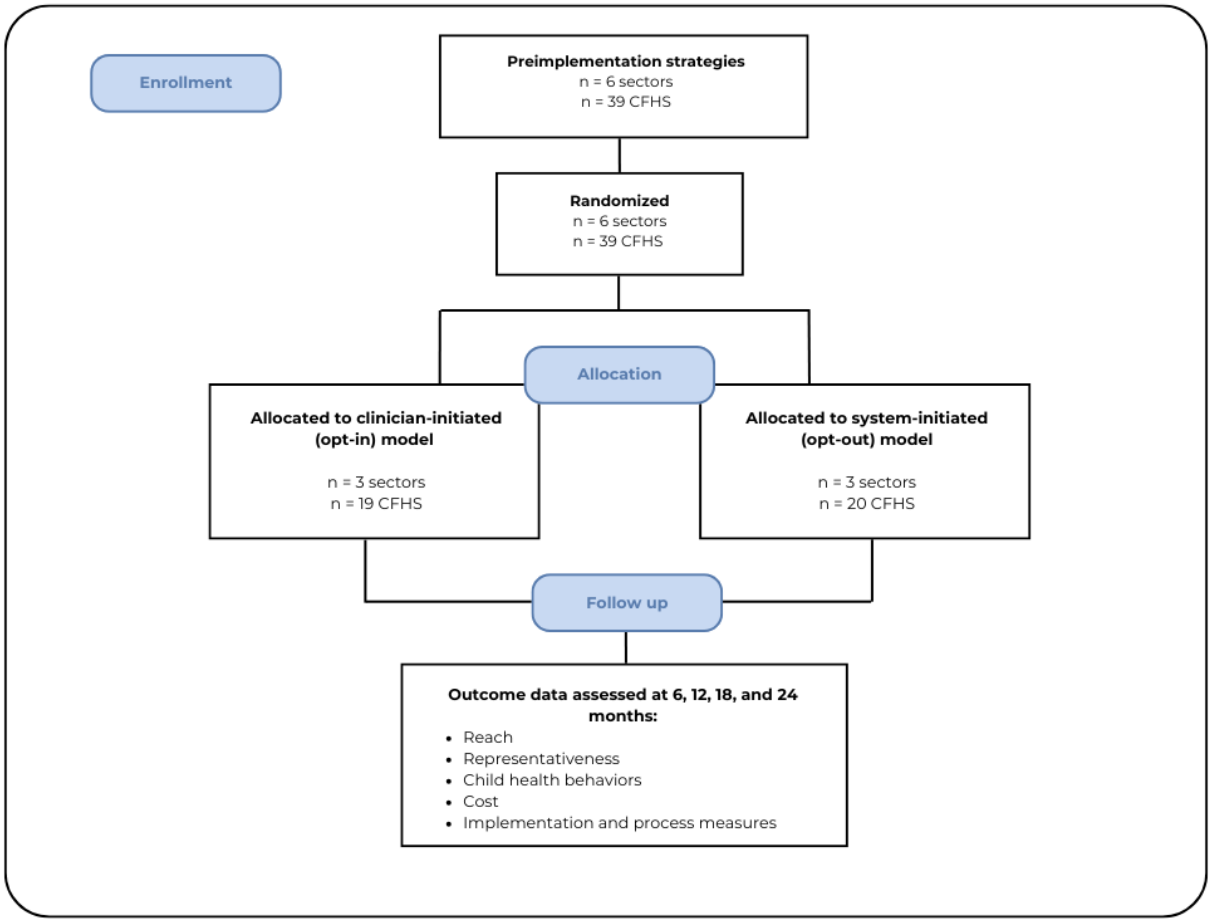

Discussion

Principal Findings

Effective models for scaling up digital care to maximize reach and impact at the population level remain elusive. This research trial will compare 2 models (clinician-initiated opt-in vs automated opt-out) of scaling up an evidence-based SMS text message program delivered directly to parents during the first 2000 days. While both scale-up models will offer families the same SMS text messaging program (HB4HNEKids), the "opt-in" arm focuses on providing CFHS clinicians with targeted implementation support strategies to onboard eligible families, and the "opt-out" arm represents an automated "hands-off" approach, whereby families are automatically connected to the program using health service data. Given that the opt-in model is expected to require greater clinician-parent interaction in relation to the program, we hypothesize that the opt-in model will be most effective for improving health behaviors, while the opt-out program is expected to achieve greater reach and representativeness of program participants and be more cost-effective.

mHealth interventions (eg, SMS text messages) delivered directly to parents' mobile phones present an opportunity to revolutionize the delivery of universal health care across the first 2000 days. Key international agencies recommend universal preventative health care across the first 2000 days as a critical initiative for improving population health outcomes, and scaling up such initiatives have been considered critical for attaining the United Nations Sustainable Development Goal [14,44,45]. However, a review of 14 obesity prevention interventions delivered to infants and young children indicated that only 1 study had been formally evaluated at scale [46], suggesting that methods of achieving effective scale-up are significantly lacking for this demographic, limiting potential population health gains. This research seeks to bridge this evidence-practice gap by testing 2 methods of scaling up HB4HNEKids that have been co-designed and assessed as suitable for scale-up according to the New South Wales Guide to scaling up [47].

Strengths and Limitations

A key strength of this research is the use of existing health service models, resources, and infrastructure to explore the most effective and efficient model of scaling up an evidence-based DHI that has huge potential to increase parental access and engagement with age-and-stage preventative health care. Despite this, research evaluating the reach and representativeness of program participants, a possible limitation of this research is the potential unintended widening of health inequalities. However, data suggest that people who are socially and economically disadvantaged, living in rural, regional, or remote areas, are Aboriginal or Torres Strait Islander, or are from culturally and linguistically diverse backgrounds, are among the highest users of digital technologies [48-50]. In addition, both scale-up models carry possible limitations in real-world implementation. For example, the impact of the clinician-initiated opt-in model relied heavily on clinician buy-in

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and engagement, and the automated opt-out model relies on having quality health system data; however, our evaluation is expected to highlight such problems. Furthermore, while efforts have been made to ensure a rigorous evaluation using multiple available streams of data sources, this evaluation will be limited to the quality of available data, with potential for significant missing data and reliance on self-reported data for secondary behavioral outcomes.

Dissemination Plan

This research will address a critical policy and practice gap and generate real-world novel evidence to inform the delivery of other key DHIs to be implemented at scale, and as such, disseminating these findings is of critical importance. The findings from this study will be presented at international conferences and published in academic journals following the conclusion of data collection and analysis. The findings of this study will be further disseminated to health service agencies to ensure the learnings of this research can be applied broadly to local and national health service plans as well as other emerging digital health initiatives.

Conclusions

Currently, there is limited evidence to guide the effective scale-up of mHealth interventions. Despite robust research evidence, effective mHealth interventions are rarely embedded within routine care, and no mHealth interventions have been implemented as usual care over the first 2000-day period. This research will be the first to compare the impact of “opt-in” versus “opt-out” approaches to better appraise their merits in scaling evidence-based programs and provide valuable insights into which model of care will facilitate the most equitable reach and uptake of digital health strategies.

Acknowledgments

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Data Availability

This study is a study protocol, and no data are generated as part of this manuscript. Data sharing is not applicable to this article as no datasets were generated or analyzed during this study.

Authors' Contributions

Conceptualization: R Sutherland, TD, LW, NH, JJ, ALB
Data curation: ALB, JJ, R Sutherland, LD
Formal analysis: CL
Investigation: NH, JP, LD, R Sewter, SS
Project administration: NH, JP, LD, R Sewter, SS
Writing – original draft: ALB, JJ, SK, NH
Writing – review and editing: all authors

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT checklist.
[PDF File (Adobe PDF File), 887 KB - resprot_v14i1e81390_app1.pdf]

Multimedia Appendix 2
Logic model for the scale-up of HB4HNEKids.
[DOCX File , 25 KB - resprot_v14i1e81390_app2.docx]

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Abbreviations

AACTT: Action, Actor, Context, Target, Time
BCW: Behaviour Change Wheel
CFHS: Child and Family Health Service
CONSORT: Consolidated Standards of Reporting Trials
DHI: digital health intervention
ERIC: Expert Recommendations for Implementing Change
HB4HNEKids: Healthy Beginnings for Hunter New England Kids
HNELHD: Hunter New England Local Health District
mHealth: mobile health
RCT: randomized controlled trial
REDCap: Research Electronic Data capture
TDF: Theoretical Domains Framework

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Protocol

Digital Training for Mental Health Promotion in Young People With Climate Change-Related Distress: Protocol for a Feasibility Randomized Controlled Trial

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Abstract

Background: Efforts in mental health research have long focused on the care and long-term outcomes of mental disorders. More recently, a shift in focus has occurred toward mental health promotion and prevention. One priority target population for promotion and prevention is youth with climate change–related distress. In light of the real-world threat of climate change, adaptive emotion regulation and engagement in meaningful action are 2 important strategies for promoting mental health. Ecological momentary interventions (EMIs) allow for the delivery of accessible interventions for young people with climate change–related distress, but evidence on their feasibility or beneficial effects is currently lacking.

Objective: We aimed to examine the feasibility and initial signals of efficacy of the Climate Mind and Act (CliMACT) training, a novel hybrid EMI for mental health promotion in youth with climate change–related distress.

Methods: A 2-arm, parallel-group, and assessor- and analyst-blinded feasibility randomized controlled trial (RCT) will be conducted in 50 young people aged 14-25 years with climate change–related distress, who will be allocated on a 1:1 ratio to the experimental condition (CliMACT training + care as usual [CAU]) or the control condition (CAU only). CliMACT involves 3 sessions with a mental health professional and 6-week access to a smartphone-based EMI to support the real-world transfer of training content based on compassion-focused interventions and acceptance and commitment therapy. The EMI delivery schemes involve enhancing (introducing new EMI components), consolidating (training of EMI components), and adaptive (triggered in

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moments of higher negative affect) components. CAU involves access to all standard health care and social services. Feasibility criteria of the trial methodology include recruitment, randomization, and retention. Feasibility outcomes of delivering the CliMACT training include participant satisfaction, participant adherence, and mental health professionals' fidelity to the training protocol. Initial signals of efficacy on mental health candidate outcomes and mechanisms will be explored. As feasibility criteria for a priori planned subgroup analyses, credibility criteria will be established and distributions of indicators for health inequities explored. Feasibility criteria for measuring costs of care and service use and health-related quality of life for an economic evaluation in a future definitive RCT will include exploring response distributions across groups. Candidate outcomes and mechanisms will be assessed at baseline, post training, and 4-week follow-up, using self-report and 6 days of ecological momentary assessment.

Results: The first enrollment took place in December 2024. Data collection was completed by August 25, 2025. Results are expected for publication in 2026.

Conclusions: To our knowledge, this is the first study to establish the feasibility and initial signals of efficacy of an EMI, targeted specifically at young people with climate change–related distress. If feasibility can be established, the trial will inform a future fully powered efficacy-effectiveness RCT, accompanied by an economic evaluation.

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KEYWORDS

climate change; climate change distress; ecological momentary intervention; ecological momentary assessment; mental health promotion; mHealth; youth; feasibility; randomized controlled trial; mobile phone

Introduction

Background

Climate change is one of the current societal challenges recognized to pose a threat to mental health. While it is commonly agreed that negative emotional reactions toward the real threat of climate change are natural and common [1], in a substantial proportion of individuals, climate change–related distress is related to impairment in daily life, including difficulties with sleeping, concentrating, or fulfilling daily roles [2-5]. For example, in a large survey among young people in Germany, 65% reported negative emotions in relation to climate change, and about 20% reported experiencing sleep problems and a limited sense of joy due to their concerns about climate change [2]. These findings indicate that youth with climate change–related distress may be one priority target population, but scalable strategies for mental health promotion and prevention remain very limited.

The recent rapid advances in digital technologies offer new avenues for ecological translation (ie, daily life application) of accessible and scalable mental health promotion [6,7], including for young people with climate change–related distress. Ecological momentary interventions (EMI) provide a unique opportunity for real-life and real-world transfer of therapeutic, preventive, or promotional principles, tailored to the person, moment, and context [8-12]. Due to their accessible and personalized nature, EMIs are a promising intervention method for ecological translation to the living environments of vulnerable groups. Thus, EMIs are a potential scalable digital intervention option for young people with climate change–related distress. While overall, there is evidence on acceptability, safety, and efficacy of EMIs for the prevention and early intervention in young people with early mental health problems [13-16], this remains to be established among young people with climate change–related distress in a target group-specific and vulnerability-sensitive approach.

While there is a lack of evidence with interventions among the target group, conceptual work on fostering resilience in young people with climate change–related distress indicates that interventions focused on the individual should consist of 2 strands: one enabling adaptation, which includes the successful regulation of stressful emotions, and one focusing on action, enabling youth to engage in meaningful transformation of their environments and living conditions [17-19]. In a recent feasibility randomized controlled trial (RCT), we found strong evidence for the safety and feasibility of trial methodology and intervention delivery for EMIcompass, a novel, transdiagnostic EMI intervention based on principles of compassion-focused interventions (CFI) for enhancing emotional resilience in youth with early mental health problems [16]. The feasibility RCT also revealed initial signals of efficacy for reduced momentary stress reactivity, and improved quality of life and momentary emotional resilience. These findings support using and adapting training components from EMIcompass for targeting emotion regulation in the target population of young people with climate change–related distress. Evidence has further shown that focusing on action and, more specifically, on meaning-focused coping in relation to climate change is related to more positive mental health outcomes [20]. This could support incorporating principles of acceptance and commitment therapy (ACT) into a training geared toward promoting mental health in youth with climate change–related distress. This includes encouraging distressed youth to choose and engage in actions that are aligned with their own values, as proposed by Niessen and Peter [18], and is further supported by ecological momentary assessment (EMA) research showing that value-based action is associated with better well-being [21]. Interventions based on ACT have shown promising results as a transdiagnostic approach for reducing stress in young people [22]. There is further evidence to suggest that digital interventions based on ACT principles

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for young people have stronger effects in targeted as compared to universal strategies for intervention [23]. Therefore, the current study adopts a targeted approach to bolster the mental health of young people who experience climate change–related distress. Taken together, CFI and ACT offer promising intervention principles and techniques amenable to being implemented in an EMI for reducing climate change–related distress in young people, but evidence on the feasibility of its delivery in this target population is lacking.

As underlying candidate mechanisms of change, transdiagnostic third-wave behavioral interventions such as CFI and ACT use techniques expected to foster mental health by enhancing self-compassion, mindfulness, psychological flexibility, and emotion regulation [24-26]. As a further candidate mechanism, in this particular target group and proposed intervention, value-based action may manifest in proenvironmental behavior (PEB) [27]. Acquiring both CFI- or ACT-based skills and strategies may moreover promote rather nonspecific candidate mechanisms such as emotional resilience and self-efficacy. As candidate outcomes, reduction of psychological distress or symptoms is often considered a secondary rather than primary aim of third-wave behavioral interventions [24,28]. In line with extensive literature that mental health is much more than the absence of psychopathology [29], candidate outcomes of a mental health promotion or prevention training for young people with climate change–related distress ought to include indicators of positive mental health, such as mental well-being, quality of life (including the emotional and social domain), and happiness. In a second vein, candidate outcomes include climate change distress and impairment itself, as well as general psychological distress often associated with the former [30].

Building on a marginalized population approach, population-based strategies for improving mental health may inadvertently augment the long-documented inequities in health among marginalized groups, who, for example, due to social position, limited resources, or problems with access, may benefit less from such strategies [31,32]. Developing novel intervention and training approaches, therefore, requires us to monitor and mitigate the potential of exacerbation of inequities, which may be caused by differential reach of and effectiveness for groups in marginalized or vulnerable positions. Urbanicity, low socioeconomic status (SES), lower education, female gender, and migrant and ethnic minority group status reflect indicators of socioenvironmental and ethnic mental health inequities also highlighted in the PROGRESS (Place of Residence; Race, Ethnicity, Culture, or Language; Occupation; Gender or Sex; Religion; Education; Socioeconomic Status; and Social Capital)–plus framework for equity in health [33,34]. Crucially, they have also been reported to play a direct or indirect role in accelerating the impact of climate change on mental health [5,35-37]. Despite evidence on initial signals of efficacy for the EMIcompass intervention [16], evidence in young people with climate change–related distress on target group- and training-specific candidate outcomes and mechanisms, taking relevant indicators of inequities in health into account, is pending.

This Study

This study aims to investigate the feasibility and initial signals of efficacy of the CliMACT (Climate Mind and Act) training, a novel hybrid EMI for mental health promotion in youth with climate change–related distress, in addition to access to all standard health care and social services (care as usual [CAU]), compared with CAU only in a feasibility RCT (ISRCTN33613914). Feasibility criteria are based on the principles of the CONSORT (Consolidated Standards of Reporting Trials) extension for pilot and feasibility trials [38] and adapted from the study by Reininghaus et al [16]. To achieve the overall aim, we will first, examine the feasibility of the trial methodology (based on recruitment, randomization, and retention). Second, we will examine the feasibility of delivering the CliMACT training (based on participant satisfaction, participant adherence, and fidelity to the training protocol) and explore its specific and nonspecific active ingredients (CliMACT training components; working alliance toward mental health professionals and toward the EMI). Third, we will explore signals of efficacy of the CliMACT training on candidate outcomes, that is, positive mental health (quality of life [psychological and social domain], happiness, and mental well-being), climate change distress and psychological distress, as well as on momentary affect and momentary climate change–related distress at posttraining and 4-week follow-up. Fourth, we explore signals of efficacy of the CliMACT training on candidate mechanisms of change, namely self-compassion, mindfulness, psychological inflexibility, self-efficacy, resilience, PEB, emotion regulation, internalized stigma, and experience of discrimination, self-stigma of help-seeking, as well as on momentary emotional resilience, momentary self-efficacy, momentary PEB, and momentary value-based living at posttraining and 4-week follow-up. Fifth, we examine the feasibility of establishing credibility criteria for an a priori planned subgroup analyses on social and ethnic inequities in health by exploring the distribution of indicators for health inequities relevant to climate change–related distress, and exploring the effects of the CliMACT training stratified by marginalized or vulnerable group status (defined as meeting any of the following criteria: gender not male, ethnic minority, migration history, low family SES, current urbanicity, or lower education level). Sixth, we examine the feasibility of measuring related costs of care and service use and health-related quality of life for the accompanying economic evaluation in a future definitive RCT, and explore the distribution of cost patterns across the experimental and control groups.

Methods

Cocreation

At the outset of this study, a society advisory group (SAG) including representatives from national mental health–related umbrella organizations, lived experience experts, policy makers, and mental health practitioners was set up in Mannheim, Germany. The SAG leads the research cocreation process in collaboration with the research team throughout the project. Throughout the project, the SAG will meet with the research team and be involved in decisions about this study's design, interpretation of findings, knowledge integration, dissemination,

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and development of a scaling strategy. Consultation meetings will be held at least annually and at key decision points (eg, after completing analyses on feasibility and initial efficacy signals). Representatives from the group with lived experience will receive financial compensation for contributing their personal time. Before the start of the feasibility RCT, a set of potential scenarios for intervention was cocreated with SAG members based on desk reviews and consultation meetings. The intervention scenarios specified different target groups, recruitment sites, and strategies, and the training delivery mode. The selection of a final intervention scenario was carried out by SAGs and other stakeholders in the mental health field using a set of methods (ie, a Delphi panel and scenario-based workshops) that are described in detail elsewhere [39]. The scenario selected will target a broader group of young people with climate change–related distress, with recruitment strategies focusing on Mannheim and the Rhine-Neckar region, including sites as outlined in the Recruitment section. Stakeholders favored a hybrid intervention, including access to a smartphone-based EMI combined with facilitating face-to-face sessions with a mental health professional.

Study Design

This feasibility study protocol follows the CONSORT 2010 statement extension to randomized pilot and feasibility trials (Multimedia Appendix 1). In a 2-arm, parallel-group, assessor- and analyst-blinded feasibility RCT, 50 individuals aged 14-25 years with climate change–related distress will be randomly allocated to (1) the CliMACT training in addition to CAU or (2) CAU only at a 1:1 ratio. Potentially eligible participants will be prescreened for eligibility in a phone call. Participants will then complete informed consent procedures with an authorized member of this study's team, followed by the completion of questionnaires to establish eligibility. Next, outcome data will be collected at baseline (t_0), at the end of the 6-week training period (t_1), and at a 4-week follow-up (t_2; Figure 1). Randomization takes place after baseline assessment. Hence, the full duration of this study's period for participants will be approximately 3.5 months (depending on the time between informed consent and completion of baseline assessment). Participants can withdraw consent from participation at any time. Participation will be terminated prematurely if participants are at risk for harm to themselves or others.

Figure 1. Study flowchart. CAU: care as usual; CliMACT+CAU: Climate - Mind and Act+Care as Usual; EMA: ecological momentary assessment; incl: including.

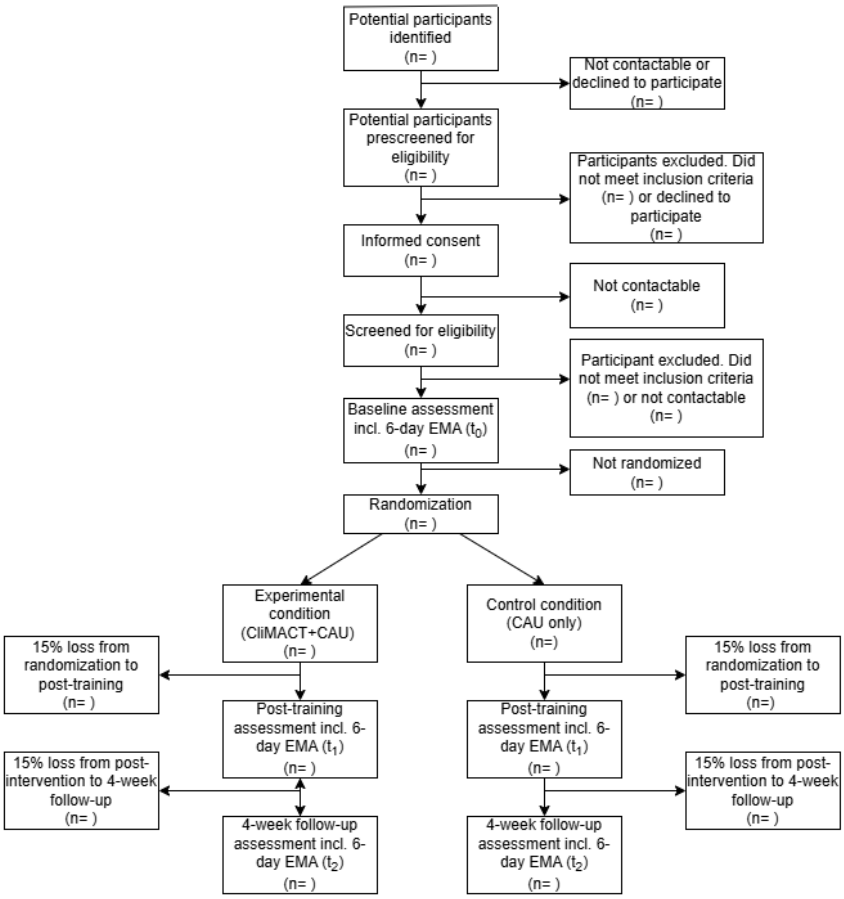

Participants

Recruitment

Participants will include young people aged 14-25 years with climate change–related distress, who will be recruited from the general population via social media, youth counseling and social services, youth centers, food banks, schools, universities, youth organizations, and climate change– and sustainability-related organizations, groups, and institutions in Mannheim and the Rhine-Neckar region. While recruitment efforts are focused on

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this region, participants from outside this region can be included. All potential participants will be contacted by the research team, receive full information about this study, participate in a prescreening phone call, and, if they pass the initial screen, complete a full screening for eligibility. Participant appointments can take place on-site or via a certified and encrypted videoconferencing system.

Inclusion Criteria

Inclusion criteria are (1) aged 14-25 years, (2) having a score of ≥3.5 on the distress subscale and ≥2.3 on the impairment subscale on the Climate Change Distress and Impairment Scale (CC-DIS) [3]. CC-DIS cutoffs for inclusion represent the average scale mean of the 4 samples used in the validation study by Hepp et al [3]. The age range of 14-25 years is based on what has been widely used in the international youth mental health reform, recognizing that most mental health problems have their onset before the age of 25 years [40], as well as youth developmental considerations regarding the appropriateness of the training.

Exclusion Criteria

Young people are excluded from participation if they (1) report current treatment for or a current diagnosis of a severe mental disorder which they received from a professional (*ICD-10* [*International Statistical Classification of Diseases, Tenth Revision*] codes: F32.2, F32.3, F20, F22-29, F30.x, F60.3) or (2) report a significant reduction in functioning in the past 30 days (World Health Organization Disability Assessment Schedule 2.0 ≥41) [41]. The World Health Organization Disability Assessment Schedule 2.0 cutoff for exclusion is based on population norms, representing the 90th percentile on the 36-item version [41]. Other exclusion criteria comprise (3) indications of acute risk to self or others, (4) the inability to provide informed consent, and, in case of minors, no consent by parents or legal guardians, and (5) insufficient German language abilities, per assessment of the investigator.

Intervention

Control Condition: CAU

Participants in the control condition will receive CAU, broadly defined, which includes access to all standard health care and social services. CAU broadly defined will include all public mental health services delivered according to local and national service guidelines and protocols by general practitioners, psychiatrists, clinical psychologists, school psychologists, social workers, psychological counselors, and other public mental health practitioners for mental health promotion, prevention, and treatment [42], available to participants in their living environment.

Experimental Condition: CliMACT+CAU

Overview

Participants allocated to the experimental condition receive the CliMACT training in addition to CAU. CliMACT will be delivered over a 6-week training period. It consists of an app-based, adaptive EMI and 3 sessions with a trained mental health professional, with a duration of 45-60 minutes, administered on-site or online using a certified and encrypted videoconferencing system. The EMI is geared toward real-time and real-world transfer of training content, principles, and techniques from face-to-face sessions to individuals' daily lives using an app- and web-based system (InteractionDesigner platform, movisens GmbH). The CliMACT training is based on principles of CFI as well as ACT. Multimedia Appendix 2 provides an overview of the key training components during the 6-week training period. The EMI consists of 3 different delivery schemes of EMI components and EMA-based monitoring.

Enhancing EMI Delivery Scheme

During the training phase, participants are successively introduced to new EMI components based on CFI and ACT according to a set schema (see Multimedia Appendix 2; for example, after session 1, participants learn how to conduct specific breathing exercises). Participants can receive reminders for enhancing EMI components at self-set times.

Consolidating EMI Delivery Scheme

Participants are asked to practice EMI components that have already been introduced via the enhancing EMI delivery scheme on the following days. When all new tasks have been introduced (week 4), participants are encouraged to practice tasks randomly presented. Consolidating EMI components can be completed in response to reminders at self-set times or on demand.

Adaptive EMI Delivery Scheme

Participants' responses to short, daily EMA questionnaires on momentary affect provide the basis for delivering CFI-based intervention via the adaptive EMI delivery scheme tailored to person, moment, and context. These are offered in moments of high negative affect, that is, when ratings exceed the threshold of an individual's moving average on any negative affect item by ≥0.5 SDs. A prerequisite for the use of the moving average is that respondents have responded to at least 7 EMA prompts within the past 7 days. If this is not the case, a value of ≥4 on any negative affect item serves as a threshold for the adaptive EMI delivery scheme.

EMA-Based Monitoring and Feedback

CliMACT allows young people and mental health professionals to monitor young people's well-being by delivering visual feedback in terms of reported climate change–related events, activities, affect, and completed training components, via the app and a web-based dashboard function.

The app further uses gamification elements to encourage practice and visualize progress throughout the 6 weeks. It provides FAQs (frequently asked questions) on training-relevant matters and web links to local and national climate change and sustainability-related topics and organizations to demonstrate network opportunities for collective action. The finalized CliMACT training manual, developed as part of the ADVANCE (Addressing Mental Health Vulnerabilities From Adolescence to Older Age: Innovating Prevention Science for Times of Change) project, will be published.

Adaptation

Theoretical and evidence-based considerations for interventions for young people with climate change–related distress informed

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adaptation from the original EMIcompass intervention to the CliMACT training (see Background section). Additionally, suggested adapted materials were reviewed with lived experience experts. Following recommendations from the World Health Organization's Psychological Interventions Implementation Manual [43], cognitive interviews with 9 individuals with lived experience of subjective climate change–related distress were conducted to assess the understandability, acceptability, and relevance of the study materials (eg, visual design and written content). Feedback indicated good acceptability and primarily led to minor adjustments in wording, which were subsequently incorporated into the materials.

Measures

Feasibility of Trial Methodology

The feasibility of trial methodology will be assessed based on the following criteria: feasibility of recruitment is assessed based on achieving the minimum monthly recruitment rate of 11 in (at least) the month with the highest recruitment rate of the feasibility RCT recruitment period. Feasibility of randomization is assessed based on achieving the minimum monthly rate of 10 participants successfully randomized after successful inclusion in at least 1 month. Retention is assessed using the percentage of retained participants at posttraining and 4-week follow-up.

Feasibility of Delivering the CliMACT Training

The feasibility of delivering the CliMACT training will be assessed at the posttraining assessment based on the criteria as delineated in the following. Satisfaction is measured through 3 scales. A 21-item participant debriefing questionnaire with a 7-point Likert scale ranging from 1-7, with higher values indicating higher satisfaction [16]. The 6-item perceived impact subscale of the Mobile App Rating Scale has a 6-point scale ranging from 0-5, with higher scores indicating higher perceived helpfulness. Lastly, there will be one item reflecting a global 5-star rating of the application, ranging from 1-5 [44].

Participant adherence is measured using the number of attended sessions and the number of completed consolidating and adaptive EMI components during training.

Fidelity to the training protocol is measured using a 19-item session component checklist adapted to CliMACT training components from the study by Reininghaus et al [16] with a yes-no format, and the 25-item Acceptance and Commitment Therapy Fidelity Measure with a 4-point scale ranging from 0-3 [45], with higher values indicating greater frequency of behavior aligned with ACT principles. Measures are completed by the mental health professional delivering the face-to-face session and by an independent rater. As active ingredients, CliMACT training components will be assessed as specific ingredients, and working alliance with the mental health professional and with the digital tool are measured as nonspecific ingredients, using the 12-item Working Alliance Inventory with a 5-point Likert scale ranging from 1-5 (Working Alliance Inventory-Self Report [WAI-SR]) [46,47] and 25-item Mobile Agnew Relationship Measure with a 7-point Likert scale ranging from 1-7 [48], with higher scores indicating a more positive working alliance for both measures.

Candidate Outcomes

As candidate outcomes, participants will complete the following self-report measures at baseline, post training, and 4-week follow-up: mental well-being is measured using the Warwick-Edinburgh Mental Well-Being Scale with 14 items using a 5-point Likert scale ranging from 1-5 [49,50]. The total score is a sum score, with higher scores indicating better mental well-being. Quality of life is measured using the World Health Organization Quality of Life measure with 26 items using a 5-point Likert scale ranging from 1-5 [51,52]. In the current study, the subscales for psychological health (6 items) and social relationships (3 items) will be considered as candidate outcomes. Domain scores are transformed to a scale from 0-100, with higher values indicating a higher quality of life. Subjective happiness is measured using the Subjective Happiness Scale with 4 items using a 7-point Likert scale ranging from 1-7 [53,54]. Reversing one negatively formulated item, a mean score is calculated, with higher scores indicating higher happiness. Climate change distress, used both as a screening and an outcome measure, is measured using the CC-DIS, with 15 items reflecting distress and 8 items reflecting impairment, using a 5-point Likert scale ranging from 1-5 [3]. After reversing items that indicate low levels of distress or impairment, a mean score is calculated, with higher scores indicating higher distress and impairment. General psychological distress is measured using the Core 10, a 10-item measure using a 5-point Likert scale ranging from 0-4 [55] and the Brief Symptom Inventory, a 53-item measure using a 5-point Likert scale ranging from 0-4 [56,57], with higher mean scores indicating higher psychological distress.

Using EMA (movisensXS app, movisens GmbH), 18 items are used to assess momentary affect on a Visual Analog Scale (VAS) ranging from 0-100. In this study, the mean of 4 unipolar positive affect facet items will be used as the total positive affect score. The mean of 9 unipolar negative affect items will be used as the total negative affect score. Based on the CC-DIS [3], 6 items are used to measure momentary climate change distress (3 items) and impairment (3 items), using a 7-point Likert scale ranging from 1-7. Mean scores will be used as scale scores. During the training phase, participants in the experimental condition complete an abbreviated EMA form in the InteractionDesigner platform, including 11 items assessing momentary affect on a 7-point Likert scale and a multi-select item to indicate which specific affects are currently related to climate change. All EMA items can be found in Multimedia Appendix 3.

Candidate Mechanisms

As candidate mechanisms, participants will complete the following measures at baseline, post training, and 4-week follow-up: self-efficacy is measured using the General Self-Efficacy Scale with 10 items using a 4-point scale ranging from 1-4 [58,59]. A sum score is calculated, with higher scores indicating higher levels of self-efficacy. Emotion regulation is measured using the Cognitive Emotion Regulation Questionnaire with 18 items using a 5-point Likert scale ranging from 1-5

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[60,61]. First, subscale items are summed. Next, a mean score of 5 subscales is calculated for the adaptive emotion regulation scale, and a mean score of 4 subscales is created for the maladaptive emotion regulation scale. Resilience is measured using the Connor-Davidson Resilience Scale with 25 items using a 5-point Likert scale ranging from 0-4 [62,63]. The total score is a sum score, with higher scores indicating higher resilience. Self-compassion is measured using the Self-Compassion Scale with 26 items using a 5-point Likert scale, ranging from 1-5 [64,65]. Negatively formulated items are reversed, means for subscales calculated, and then subscale scores summed for the total score, with higher scores indicating higher levels of self-compassion. Mindfulness is measured using the Five-Facet Mindfulness Questionnaire with 24 items using a 5-point Likert scale ranging from 1-5 [66,67]. Facet scores are computed as sum scores (observing: 4 items; describing: 5 items, acting with awareness: 5 items; nonjudging of inner experience: 5 items, and nonreactivity to inner experience: 5 items. Psychological inflexibility is measured using the Acceptance and Action Questionnaire II with 7 items using a 7-point Likert scale ranging from 1-7 [68,69]. The total score is a sum score, with higher scores indicating higher psychological inflexibility. Internalized stigma is measured using an adapted version of the Internalized Stigma of Mental Illness scale with 29 items using a 4-point scale ranging from 1-4 [70,71]. The measure covers alienation (6 items), stereotype endorsement (7 items), discrimination experience (5 items), social withdrawal (6 items), and stigma resistance (5 items). A mean score is calculated as the total score, excluding the stigma resistance subscale [72]. Experiences of discrimination are measured with the adapted version of the major experiences of discrimination measure [73], using a multi-select item asking about the experience of unfair treatments in different areas (police, judicial system, discouraging education, neighbors and family, service, medical attention, public transport, school, superiors, and other) due to the participants' climate change–related attitudes, views and actions. For areas in which unfair treatment is reported, participants can indicate the number of times this has occurred. The total number of experiences is used as the total score. Self-stigma of seeking help is measured using the Self-Stigma of Seeking Help Scale with 10 items using a 5-point Likert scale ranging from 1-5 [74]. Reversing positively phrased items, a sum score is used as the total score, with higher values indicating higher self-stigma. PEB is measured using an adapted and translated version of the PEB measure with 18 items using a VAS ranging from 0-100 [75]. Mean scores are calculated for personal behavior (10 items) and collective behavior (8 items), with higher scores indicating more opportunities at which the participant has engaged in PEBs.

Using EMA, momentary self-efficacy is measured with 2 items based on the measure per Majeed et al [76] on a VAS ranging from 0-100. Positive and negative event intensity are respectively measured on a 7-point Likert scale ranging from 1-7. For negative event intensity ≥2, momentary emotional resilience is assessed using 1 item [12] on a VAS ranging from 0-100. Current activity is reported using a multi-select item, and for each confirmed activity, 1 of 10 matching momentary PEBs is queried on a VAS ranging from 0-100. Momentary value-based living is measured using 3 adapted items from the Engaged Living Scale [77] on a VAS ranging from 0-100. During the training phase, activity and events, but not momentary self-efficacy, PEB, or value-based living, will be assessed in daily EMA.

Measures for the Economic Evaluation

Two measures for the economic evaluation will be administered to assess health-related quality of life, use of care services, and the associated costs of care and service use. Health-related quality of life is measured using the EQ-5D-Y-3L instrument with 5 items using a 3-point Likert scale, ranging from 1-3, with higher scores indicating lower health-related quality of life, and 1 VAS item ranging from 0-100, with higher scores indicating better health [78,79]. The information on use of care services, which is needed to calculate the associated costs of care service use, is captured using an adapted version of the Client Service Receipt Inventory (CSRI) [80,81]. Together with other self-report measures of the trial, both measures for the economic evaluation (EQ-5D-3L and CSRI) will be administered at the 3 time points: at baseline, post training, and 4-week follow-up.

Other Measures

At each assessment, it will be documented if any adverse events (AEs) related or unrelated to the training or study participation have occurred, including health-related events, technical problems with the smartphone, problems with the digital application, or other issues. Marginalized or vulnerable group status is reflected by equity-relevant sociodemographic indicators at baseline and coded present when at least one of the following is true: female gender, ethnic minority, migration history, low family SES, current urbanicity, and lower education level. At posttraining, adverse trial effects are measured with the measure by Hutton et al [82], using a 5-point Likert scale ranging from 1-5. An overview of all measures and time points can be found in Figure 2 (in line with the SPIRIT [Standard Protocol Items: Recommendations for Interventional Trials] statement [83]).

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Figure 2. SPIRIT figure. AAQ-II: Acceptance and Action Questionnaire; ACT-FM: Acceptance and Commitment Therapy Fidelity Measure; AE: adverse events; ATE: adverse trial effects; BSI-53: Brief Symptom Inventory 53; CAU: care as usual; CC-DIS: Climate Change Distress and Impairment Scale; CD-RISC: Connor-Davidson Resilience Scale; CERQ: Cognitive Emotion Regulation Questionnaire; CliMACT+CAU: Climate - Mind and Act+Care as Usual; CSRI: Client Service Receipt Inventory; FFMQ: Five Facet Mindfulness Questionnaire; GSES: General Self Efficacy Scale; ISMI: Internalized Stigma of Mental Illness-Scale; mARM: Mobile Agnew Relationship Measure; MARS-G: Mobile App Rating Scale - German Version; MED: major experiences of discrimination; PEB: proenvironmental behavior; SCS-D: Self-Compassion Scale - German Version; SHS: Subjective Happiness Scale; SPIRIT: Standard Protocol Items: Recommendations for International Trials; SSOSH-10: Self-Stigma of Seeking Help; WAI-SR: Working Alliance Inventory - Self Report; WEMWBS: Warwick-Edinburgh Mental Well-Being Scale; WHO-QoLBref: World Health Organization Quality of Life - Brief Version; WHODAS 2.0: World Health Organization Disability Assessment Schedule 2.0.

		Study period		
	Enrollment	Allocation	Post-allocation	
Time point	$-t_1$	0	t_1 post-training	t_2 4-week follow-up
Enrollment				
Eligibility prescreen	✓			
Informed consent	✓			
Randomization		✓		
Interventions				
6-week CliMACT+CAU		⟷	⟷	
6-week CAU		⟷	⟷	
Assessments				
Screening				
CC-DIS (and outcome)	✓		✓	✓
WHODAS 2.0	✓			
Candidate outcomes				
WHO-QoLBref		✓	✓	✓
SHS		✓	✓	✓
WEMWBS		✓	✓	✓
Core 10		✓	✓	✓
BSI-53		✓	✓	✓
Momentary candidate outcomes				
Momentary affect		✓	✓	✓
Momentary CC-DIS short		✓	✓	✓
Candidate mechanisms				
SCS-D		✓	✓	✓
FFMQ		✓	✓	✓
AAQ-II		✓	✓	✓
GSES		✓	✓	✓
CERQ		✓	✓	✓
CD-RISC		✓	✓	✓
PEB		✓	✓	✓
ISMI		✓	✓	✓
MED		✓	✓	✓
SSOSH-10		✓	✓	✓
Momentary candidate mechanisms				
Momentary self-efficacy		✓	✓	✓
Momentary emotional resilience		✓	✓	✓
Momentary PEB		✓	✓	✓
Momentary value-based living		✓	✓	✓
Nonspecific active ingredients				
WAI-SR			✓	
mARM			✓	
Other				
ACT-FM			✓	
Debriefing			✓	
MARS-G			✓	
ATE			✓	
AE	✓	✓	✓	✓
Other momentary				
Momentary activity		✓	✓	✓
Momentary event		✓	✓	✓
Momentary context		✓	✓	✓
Economic evaluation				
Demographics + CSRI		✓	✓	✓
EQ-5D-Y-3L		✓	✓	✓

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Randomization and Blinding

After completing baseline assessments, participants will be randomized at a 1:1 ratio to the experimental or control condition. Randomization will be performed by a nonblinded researcher training delivery team through a computer-generated sequence not accessible to blinded team members, applying block randomization with blocks of 5. Nonblinded researchers inform participants of their allocation. All outcomes will be assessed, and the statistical analysis will be performed, blind to random allocation. If unblinding occurs, this will be documented, and a different study team member will continue follow-up assessment for the respective participant.

In the experimental condition, a microrandomized trial (MRT) with repeated within-person randomization is implemented in the adaptive EMI components. Six CFI-based EMI components become available throughout weeks 1-3. If participants exceed the negative affect threshold (within-subject mean ±0.5 SDs) for triggering adaptive EMI components, participants will be randomized to receive a CFI-based EMI component they are already familiar with (ie, components that have been introduced as an enhancing EMI component) as experimental condition or no EMI component as control condition with a randomization ratio of 6:1. Repeated within-person randomization will be carried out via the InteractionDesigner platform.

Justification of Sample Size

Feasibility RCT

The sample size for this feasibility RCT is primarily determined to address the primary objective to provide the basis for successful recruitment in a fully powered efficacy-effectiveness RCT. Initial sample size planning points to ≈180 participants required for the full RCT. To this end, we set a feasibility limit of a minimum monthly recruitment rate of 11 participants in (at least) the month with the highest recruitment rate of the feasibility trial recruitment period. This lower bound reflects the minimum monthly recruitment rate required to recruit an expected ≈180 participants for a subsequent fully powered RCT within a designated period of 17 months. This study's population for the feasibility RCT will comprise a maximum of 50 youth aged 14-25 years (n=25 in the experimental and control conditions, respectively) with climate change–related distress. This upper limit of 50 is based on recommendations by Whitehead et al [84] for determining sample size for feasibility RCTs and would reflect a monthly recruitment rate of 17 if recruitment can be completed within 3 months. Thus, the feasibility trial will inform us about the feasibility of the aspired recruitment rate and the possibility of overrecruitment.

MRT Sample Size Calculation

To address the objective of exploring CliMACT training components as specific active ingredients, an MRT will be conducted. Based on the power approximation for MRTs [85,86], a sample size of 25 participants is sufficient to detect a small effect size of $d \geq 0.15$ on a proximal EMA outcome, with t=252 decision points (based on our EMIs with a training duration of 42 days with 6 random EMA prompts per day) and a power of 80% for a 2-sided test α=.05, with an availability rate η (ie, proportion of completed EMA observations at given decision point T) of 50% and a randomization probability of 0.85 (ie, a ratio of 6:1 for experimental vs control components).

Safety Considerations

All AEs or serious adverse events (SAEs) will be monitored and collected throughout this study's period. SAEs include any serious incidents resulting in death, persistent or significant disability or incapacity, requiring (extension of) hospitalization, or life-threatening situations. AEs include any nonserious incidents regarding the health and well-being of the participant, related or unrelated to trial participation, as well as technical problems with the hardware (ie, study smartphone), software (ie, smartphone app and assessments), and training used in this trial. SAEs are not expected to occur as a result of the intervention or study participation. If occurring, SAEs will be reported to this trial's steering committee (TSC) and ethics and data advisory board (EDAB), which can advise on ethical concerns and monitor evidence for intervention harm. At the end of this trial, SAE will be reported to the local ethics committee. AE and SAE will be reported in publications of this study's results. Insurance is in place for participants who endure harm through their participation in this study.

Statistical Analysis

Feasibility

All statistical analyses will be performed using Stata 17 (StataCorp LLC). To address the objectives of establishing the feasibility of this trial's methodology and delivery of the CliMACT training, descriptive statistics will be used (mean, SD, n, %). Evaluation of meeting important feasibility criteria will be based on a traffic light system with 3 categories, with green indicating that full feasibility is established, yellow indicating that feasibility is established, but study procedures need to be modified, and red indicating that feasibility is not established. Feasibility of trial methodology (objective 1) will be based on recruitment, randomization, and retention, and evaluated according to a priori determined cutoffs shown in Table 1, with the primary objective of establishing the feasibility of recruitment for a future efficacy-effectiveness RCT (that informed our justification of the sample size, see above). Feasibility of delivering the CliMACT training (objective 2) will be based on participant satisfaction, participant adherence, and mental health professional fidelity to the training protocol, and will also be evaluated according to predetermined cutoffs (Table 1).

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Table 1. Traffic light criteria for the feasibility of trial methodology and the feasibility of delivering the CliMACT[a] training.

	Green	Yellow	Red
Feasibility of trial methodology			
Recruitment	Monthly recruitment rate of n=11 to n=17 participants in (at least) the month with the highest recruitment rate during the feasibility RCT[b] recruitment period	Monthly recruitment rate of n=5 to n=10 participants in (at least) the month with the highest recruitment rate during the feasibility RCT recruitment period; recruitment area should be opened to places outside Mannheim and Rhine-Neckar	A monthly recruitment of n<5 participants for all months of the feasibility RCT recruitment period
Randomization	Successful randomization of n=10 to n=17 participants in (at least) the month with the highest randomization rate during the feasibility RCT recruitment period	Successful randomization of n=4 to n=9 participants in (at least) the month with the highest randomization rate of the feasibility RCT recruitment period	Successful randomization of <4 participants in all months of the feasibility RCT recruitment period
Retention	Retention rate of at least 85% of all randomized participants, for outcome assessment of at least one of the assessment time points at posttraining and 4-week follow-up	Retention rate of at least 75% for outcome assessment of at least one of the assessment time points at posttraining and 4-week follow-up	<75% retention at both posttraining and 4-week follow-up
Feasibility of delivering the CliMACT training			
Participants satisfaction with the training	Moderate to high satisfaction in general in a debriefing questionnaire (mean score of ≥4 on a 7-point scale) and the global star-rating of the Mobile Application Rating Scale (mean rating of ≥3 on a 5-point scale)	Fair satisfaction in general in a debriefing questionnaire (mean rating of >3 and <4) and the global star-rating of the Mobile Application Rating Scale (mean rating of >2 and ≤3). Adjustment and optimization of the training or app are required	Low satisfaction in general in the debriefing questionnaire (mean rating ≤3) and the global star-rating of the Mobile Application Rating Scale (mean rating ≤2)
Participant adherence to intervention protocol	Moderate to strong adherence to training sessions (at least 80% of participants attending at least 2 of the 3 face-to-face sessions) and EMI[c] components (mean of ≥1 consolidating or adaptive EMI components completed per week)	Fair adherence to training sessions (at least 60% of participants attending at least 2 of the 3 face-to-face sessions) and EMI components (mean of 0.8 consolidating or adaptive EMI components completed per week). Adjustment and optimization of sessions or the app are required	Poor adherence to training sessions (<60% of participants completing at least 2 of the 3 face-to-face sessions) and EMI components (mean of <0.8 consolidating or adaptive EMI components per week)
Mental health professional fidelity to training protocol	Moderate to high fidelity to intervention protocol (≥80% of core components delivered by trained psychologist) and use of ACT[d]-consistent skills (mean rating of ≥1.5 on a 4-point scale ranging from 0-3)	Fair fidelity to intervention protocol (≥60% of core components delivered by trained psychologist) and use of ACT-consistent skills (mean rating of >1 and <1.5 on a 4-point scale ranging from 0-3). Adjustment of sessions, EMI app, or training of psychologists is required	Poor fidelity to intervention protocol (<60% of core components delivered) and use of ACT-consistent skills (mean rating of <1 on a 4-point scale ranging from 0-3)

[a]CliMACT: Climate Mind and Act.

[b]RCT: randomized controlled trial.

[c]EMI: ecological momentary intervention.

[d]ACT: acceptance and commitment therapy.

As nonspecific active ingredients (objective 2 continued), we will explore the association of working alliance toward mental health professionals as well as working alliance with the app-based EMI with the 8 candidate outcomes in participants of the experimental condition, using linear mixed models. Separate models will be fitted for each alliance type and candidate outcome at both posttraining and 4-week follow-up; additionally, time (posttraining and 4-week follow-up), the respective outcome at baseline, and working alliance will be entered as independent variables (details set in preregistered statistical analysis plan, becoming public on OSF after publication of results) [87]. A level-2 random intercept for

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subject and a random effect for time will be added, and level-1 residuals will be allowed to be correlated to account for within-subject nesting of repeated measures. For the 2 momentary outcomes of nonspecific active ingredients, outcomes measured at baseline will be person-mean centered, and, in addition to the above specifications, random slopes for time and working alliance will be added, with an unstructured variance-covariance matrix. Within-subject residuals will be modeled with an autoregressive structure of the exponential type, allowing the models to account for unequally spaced time values. Restricted maximum likelihood estimation will be applied.

As specific active ingredients (objective 2 continued), we will explore proximal effects of CFI-based CliMACT training components on momentary negative affect in an MRT design in participants in the experimental condition using linear mixed modeling. MRT condition (experimental: any adaptive CFI-based training component vs control: no adaptive training component, randomized at a ratio of 6:1 in moments of higher negative affect), negative affect at t_n (person-mean centered), and time between assessment time points will be entered as independent variables. Negative affect at t_{n+1} will be entered as the dependent variable. A level-2 random intercept will be added, and level-1 residuals will be allowed to be correlated to account for within-subject nesting of repeated measures. Restricted maximum likelihood estimation will be applied.

Initial Signals of Efficacy on Candidate Outcomes and Mechanisms

Initial signals of efficacy of the CliMACT training will be explored according to the intention-to-treat principle (ie, data of all participants randomized to 1 of the 2 conditions will be entered into the analysis). Before data analysis, all data will be checked for quality and plausibility. For all analyses, we will inspect the 95% CI and obtain d-type effect sizes given their exploratory nature. Linear mixed modeling will be used to compare candidate outcomes (objective 3) and candidate mechanisms (objective 4) between the experimental and control conditions at posttraining and 4-week follow-up. Each candidate outcome and mechanism (applying joint analyses to posttraining and 4-week follow-up assessment) will be used as a dependent variable in separate analyses. Time (posttraining and 4-week follow-up), condition (experimental and control condition), and the respective outcome measured at baseline (grand-mean centered) will be entered as independent variables. A level-2 random intercept will be added, and level-1 residuals will be allowed to be correlated to account for within-subject nesting of repeated measures. Restricted maximum likelihood estimation will be applied. The coefficient for the condition reflects the difference between the intervention and control arm for the post- and 4-week follow-up assessments jointly. We will next extend the model by a condition × time interaction to determine the time-specific contrasts, reflecting differences between the 2 conditions at each time point, and an outcome or mechanism at baseline × time interaction.

Model specifications for momentary outcomes and mechanisms are as follows. The respective putative mechanism (momentary value-based living, momentary emotional resilience, momentary self-efficacy, and momentary PEB) or outcome (positive affect, negative affect, climate change distress, and climate change impairment) as measured 8 times per day on 6 consecutive days will be entered as dependent variables in separate models. As independent variables, the respective candidate EMA-based mechanism or outcome at baseline (person-mean-centered), time, condition, a mechanism or outcome at baseline × time interaction, and a condition × time interaction are entered. A 2-level model will be estimated with time points nested in participants. Random intercepts will be included for participant and time point. Random slopes will be included for time and the respective candidate mechanism or outcome, applying an unstructured variance-covariance matrix. For EMA observations at each time point (posttraining and 4-week follow-up), we assume within-subject residuals to be autocorrelated and apply an autoregressive structure of the exponential type. Hours since midnight of the first EMA day are used as a time indicator in our models. This approach, in contrast to using the beep number, accounts for unequally spaced delays between beeps. Again, restricted maximum likelihood estimation will be applied. Next, the respective model will, again, be extended by a condition × time interaction in order to determine the time-specific contrasts, reflecting differences between the 2 conditions at each time point.

Subgroup Analyses by Marginalized/Vulnerable Group Status

To address the objective of examining the feasibility of establishing credibility criteria for a priori planned subgroup analyses (objective 5), we will explore the feasibility of generating a marginalized/vulnerable group status score by, first, descriptively exploring the distribution of indicators for health inequities relevant to climate change–related distress as a basis for subgroup analyses (family SES, level of education, sex, migrant status, ethnic minority status, and current urbanicity) in the sample. Second, descriptively exploring the distribution of a combined marginalized/vulnerable group status variable (indicated by any of the following characteristics: family SES=low, level of education=lower, gender≠male, migrant status=yes, ethnic minority status=yes, and current urbanicity=yes) and a marginalized group status variable (indicated by any of the following characteristics: family SES=low, level of education=lower, migrant status=yes, ethnic minority status=yes; thus excluding gender and current urbanicity in comparison to the combined marginalized/vulnerable group status variable). Third, conducting subgroup analyses on candidate outcomes stratified by combined marginalized/vulnerable group status (yes or no) and by marginalized group status (yes or no), as defined in the second point above.

We will use a restricted set of established credibility criteria for subgroup analyses as appropriate for this feasibility RCT [88]: (1) measuring indicators for health inequities relevant to climate change–related distress at baseline, that is, before randomization, and (2) exploring differences in effect sizes and CIs stratified by subgroups with and without marginalized/vulnerable group status.

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Feasibility of Economic Evaluation

For the report of service use in the CSRI and the report of health-related quality of life in the EQ-5D-Y-3L, we will report missing rates and descriptive statistics (mean, SD, range, n, %). Response patterns will inform the handling of variables, possible adaptation of items or response categories, and statistical methodology of the economic evaluation in an efficacy-effectiveness RCT. Furthermore, we will explore the distribution of cost patterns across experimental and control groups to gain a first insight into differences between the 2 groups.

Research Governance

This study is part of the ADVANCE consortium, coordinated by the University of Copenhagen. The Central Institute of Mental Health is the lead of this feasibility RCT. Amendments to this study's protocol will be submitted to the local ethics committee for approval and communicated to relevant parties (eg, TSC, EDAB, funder, and collaborating institutions) and will be updated in this trial's registry. The principal investigator has overall responsibility for this trial. This trial coordinator and research team are responsible for the day-to-day management of this trial, monitoring trial progress (recruitment, assessment, and training delivery), and preparation of reports to the ethics committee, TSC, and EDAB. The TSC will consist of the trial's statistician and the SAG, and will be consulted biannually in a joint meeting with the research team, providing advice on cocreative practical, scientific, and target-group related matters. The project consortium holds monthly research meetings, as well as a quarterly management meeting, including EDAB as a standing agenda item. The EDAB will offer guidance, advice, and recommendations on four main aspects: (1) data management, protection, and privacy; (2) recruitment, inclusion, and exclusion criteria, and informed consent procedures; (3) improvement of the project data management and ethics plans; and (4) adherence to European Union regulations on ethical research trials. The EDAB will advise on any specific ethical question arising during the project, including any issues concerning the safety, rights, and well-being of study participants and research teams (including serious AEs in the clinical trials), as well as concerns regarding incidental study findings or tensions in reporting and dissemination of potentially contentious research findings. The Scientific Advisory Board (SAB) is an external advisory body of the ADVANCE consortium that aims to enhance the quality and impact of the project. The SAB will (1) serve as a resource for knowledge and expertise; (2) advise the consortium on political, social, environmental, technological, legal, and economic factors that may influence the project; and (3) give advice on the project's interaction with related research projects and initiatives. The SAB participates in project meetings, videoconferences, and workshops of the ADVANCE consortium as appropriate.

Ethical Considerations

This study has received ethical approval from the local ethics committee (Medical Faculty Mannheim, Heidelberg University, 2024-597). All participants (and in case of minors, their legal guardians) will sign written informed consent and receive financial compensation of up to € 110 Euro(US $145.60) for participation. Minors give written assent. Research data will be handled in compliance with the German and European Data Protection Regulation. Data will be stored securely and pseudonymized; that is, research data will be stored using a number code. Personal data will be kept separately from pseudonymized data. Participants who withdraw from this study can decide whether data collected up to that date can be processed or should be destroyed.

Results

Cocreation of this study design started in November 2023. Adaptation of the EMI to meet the needs of young people with climate change–related distress took place between February and September 2024. The trial was registered at ISRCTN (no. ISRCTN33613914) in November 2024. All study procedures were approved by the local ethics committee in September 2024 (Amendment I: November 2024). Recruitment started in November 2024, and the first enrollment was in December 2024. Data collection was completed by August 25, 2025. The results from the feasibility RCT are expected to be published in 2026. Its findings are going to inform the methodology of a fully powered efficacy-effectiveness RCT.

Discussion

As the main objective, this study will provide evidence on the feasibility of trial methodology (based on recruitment, randomization, and retention) as well as the feasibility of delivering the CliMACT training (based on satisfaction, compliance, and fidelity with the training manual). In addition, it will provide the first evidence on initial signals of efficacy of the CliMACT training on candidate outcomes and mechanisms. Climate change–related distress is common in youth [2,4]. To date, strategies for mental health promotion and prevention in this population are limited. Especially, evidence-based strategies to support this population using EMIs tailored to person, moment, and context are currently lacking. Therefore, the primary aim of this study will be to evaluate the feasibility of a hybrid adaptive EMI for mental health promotion in young people with climate change–related distress. The approach that we adopt here focuses on the ecological translation of CFI-based and ACT-based principles to the daily lives of young people with climate change–related distress.

Based on findings on feasibility of trial methodology from the current feasibility RCT, we will decide on necessary adaptations about recruitment sites and strategies (eg, moving from local to nationwide recruitment), the randomization procedure (eg, exposing errors), and strategies to maintain or improve retention (eg, optimize documentation, notification of participants, incentives, and reduction of number of measures). Based on findings on the feasibility of delivering the CliMACT training, we will improve intervention delivery based on quantitative and qualitative data on face-to-face sessions and EMI (eg, training components, frequency of EMAs, and visualizations), and optimize acceptability of the training in a future efficacy-effectiveness RCT. Initial signals of efficacy from the feasibility RCT will, based on effect size estimates, support the selection of a primary outcome for an efficacy-effectiveness

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RCT and will help us to formulate a more accurate theory of change model, which will be tested in the future.

Digital interventions for youth provide the benefit of being highly accessible and scalable. Recent evidence suggests that youth have generally positive attitudes toward mental health apps [89,90]. Meta-analytic evidence suggests that human support and guidance are central for digital mental health interventions to be effective [91]. Recent findings on the feasibility and efficacy of hybrid EMIs in youth [15,16] further support a guided approach. Based on this evidence, CliMACT was designed and developed adopting a hybrid, adaptive EMI. This was also informed by cocreation activities with lived experience experts and stakeholders at the outset of this study, opting for a hybrid rather than a stand-alone digital approach to ensure participants' understanding of training principles and foster adherence. In addition, prior research suggests young people prefer digital mental health interventions that contain videos, limited text, options for personalization, the ability to connect with others, and text message reminders [92]. Building on these findings, using a chat-based format, providing audio and video guides for EMI components, and the opportunity to implement personalized time windows for EMA prompts and reminders for EMI components, our cocreation and adaptation work has addressed several of these aspects in developing the CliMACT training. At the outset, SAG and scenario-based stakeholder workshops advised to primarily address a broader target group of young people with climate change–related distress, who would benefit from a generic training for mental health promotion, rather than prevention and early intervention for a smaller subgroup with clinically relevant symptoms. Hence, tailoring CliMACT to more specific target groups (eg, individuals affected by extreme weather events, climate activists, and individuals with pre-existing conditions) remains to be addressed by future research.

If the feasibility of the trial methodology and intervention delivery can be successfully established in the present feasibility RCT, this will provide the basis for a fully powered efficacy-effectiveness RCT. Findings from the feasibility RCT will be discussed with the SAG as a basis for cocreating adaptations before the efficacy-effectiveness RCT. As such, the feasibility RCT will directly inform the methodology of, and intervention delivery in, the fully-powered RCT.

EMI designs provide methodological advantages related to improving our understanding of the underlying mechanisms of mental health difficulties as well as the efficacy and effectiveness of interventions, building on an ecological interventionist causal model approach [11]. This approach allows us to establish criteria relevant to sole plausibility, such as association and temporal order. Sole plausibility can be addressed by examining whether an intervention component can modify a proposed mechanism in daily life, and whether changes in the proposed mechanism are, in turn, associated with changes in the outcome. This is what we set out to address in our future efficacy-effectiveness RCT.

In line with the broad scope of mental health promotion in public mental health provision, the comparator condition was selected to be CAU, broadly defined, as the systematic delivery of evidence-based strategies for mental health promotion in the broader public mental health care domain is still limited. Therefore, a key question from a public health (and service commissioner) perspective remains whether CliMACT confers superiority beyond that of broad CAU. Hence, design and comparator in this trial (ie, CAU, broadly defined) reflect an optimal choice for ensuring high external and ecological validity, as it mirrors the naturalistic service landscape and practice to which beneficial effects ought to generalize, including to newly emerging digital public mental health services.

This study will provide the first evidence of the feasibility and initial signals of efficacy of CliMACT, a hybrid, adaptive EMI targeted specifically at young people with climate change–related distress. While this study's design has considerable strengths (including cocreation, predefined feasibility criteria, randomization and blinding, an MRT, and assessment of equity-related participants' characteristics), several limitations need to be considered before interpreting findings from this feasibility RCT. While findings will support the selection of the primary outcome of CliMACT and develop the theory of change of the training further, uncertainty will remain in effect size estimates that will be minimized for the primary outcome by the fully powered RCT. Nevertheless, given the lack of prior empirical data on interventions in the target group, this feasibility RCT will lay important groundwork. Next, we are going to carefully evaluate the potential burden for participants due to the number and length of measures. Based on the feasibility RCT, we will identify and prioritize measures for which sensitivity to change is supported by efficacy signals and improve the selection of measures accordingly. Last, while individual-based interventions bear substantial potential and have their rightful place, it is important to note that climate change is a societal and global challenge rather than an individual challenge. Hence, developing strategies to support individuals' emotional resilience to climate change must be paralleled by, and not replace, collective and political action. The need for community-level strategies is currently endorsed by conceptual work on interventions addressing climate change–related distress at this level [17-19]. The CliMACT training, for now, addresses community building by means of suggestions for network opportunities. On a different note, it remains a challenge for digital mental health research to establish whether and how digital interventions actually offer effective support and increase accessibility for marginalized groups, with currently moderate evidence and further need for high-quality studies [93]. In the current study, we will establish whether the current trial and training methodology allows for reaching a sufficient proportion of young people in marginalized or vulnerable situations as a basis for evaluating the equity of CliMACT in our future work. Monitoring key sociodemographic indicators in intervention research with regard to reach and effectiveness is crucial to work toward interventions that mitigate, rather than augment, mental health disparities [33]. Overall, feasibility as established in the current study, coupled with efficacy and effectiveness that are to be fully established in a future efficacy-effectiveness RCT, lay the foundation for potential real-world implementation of accessible and equitable measures for mental health promotion, such as CliMACT as a relevant public mental health strategy. Trial results will be

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communicated to participants, lay audiences (traditional and social media coverage), stakeholders (SAG members and their networks), and researchers (national and international conferences and peer-reviewed journals).

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Data Availability

The datasets generated and analyzed during this study are available from the corresponding author upon reasonable request.

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Authors' Contributions

UR designed this study, is the principal investigator, and has managerial responsibility for the successful completion of this study. EK is the work package lead within the ADVANCE (Addressing Mental Health Vulnerabilities From Adolescence to Older Age: Innovating Prevention Science for Times of Change) consortium. WT is the coordinator of the ADVANCE consortium. UR and WT acquired funding for this study. UR, LF, FS, HW, and JRB were involved in the conceptualization and implementation of this study's design. UR, LF, FS, and HW were involved in the conceptualization and implementation of the Climate Mind and Act (CliMACT) training. FS provides supervision for the trained psychologists who deliver the training. CdF, RT, and LS supervise cocreation activities. AMdG supervised intervention adaptation work. MDA and HTN are responsible for economic evaluation planning. JRB provides supervision for planning and conducting statistical analyses. LF wrote the original draft of this paper. All authors were involved in critically reviewing, adapting, and approving this final paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT 2025 checklist of items to address in a randomized trial protocol.
[DOCX File , 33 KB - resprot_v14i1e77764_app1.docx]

Multimedia Appendix 2
Key components of the CliMACT ecological momentary intervention.
[DOCX File , 20 KB - resprot_v14i1e77764_app2.docx]

Multimedia Appendix 3
EMA items (English). EMA: ecological momentary assessment.
[DOCX File , 20 KB - resprot_v14i1e77764_app3.docx]

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Abbreviations

ACT: acceptance and commitment therapy
ADVANCE: Addressing Mental Health Vulnerabilities From Adolescence to Older Age: Innovating Prevention Science for Times of Change
AE: adverse event
CAU: care as usual
CC-DIS: Climate Change Distress and Impairment Scale
CFI: compassion-focused intervention
CliMACT: Climate Mind and Act
CONSORT: Consolidated Standards of Reporting Trials
CSRI: Client Service Receipt Inventory
EDAB: ethics and data advisory board
EMA: ecological momentary assessment
EMI: ecological momentary intervention
FAQ: Frequently Asked Question
ICD-10: International Statistical Classification of Diseases, Tenth Revision
MRT: microrandomized trial
PEB: proenvironmental behavior
PROGRESS: Place of Residence; Race, Ethnicity, Culture, or Language; Occupation; Gender or Sex; Religion; Education; Socioeconomic Status; and Social Capital
RCT: randomized controlled trial
SAB: Scientific Advisory Board
SAE: serious adverse event
SAG: society advisory group
SES: socioeconomic status
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TSC: trial steering committee
VAS: Visual Analog Scale
WAI-SR: Working Alliance Inventory-Self Report

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Protocol

Evaluation of the BALANCE Program as a Digital Therapeutic Solution for Type 2 Diabetes Management: Protocol for a Prospective Lifestyle Intervention Study

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Abstract

Background: Type 2 diabetes mellitus (T2DM) is a growing global health concern. In 2016, 9.7% of Bruneian adults aged 18 to 69 years had diabetes, making it the third leading cause of death. Effective self-management can mitigate complications that require health care interventions and lower health care costs. Brunei Darussalam has deployed BruHealth, a national mobile health platform synced with the Brunei Health Information Management System, allowing patients to access health records, schedule appointments, and explore medical articles. A digital therapeutics module for T2DM (diabetes mellitus digital therapeutics [DM DTx]) has been developed, consisting of a digital lifestyle intervention module within BruHealth and a separate health care professional portal for health coaches. The 16-week BALANCE program aims to support self-management. This study explores the efficacy of DM DTx in managing T2DM through digital lifestyle interventions.

Objective: The primary objective is to determine the proportion of participants who achieve at least a 0.6% reduction in glycated hemoglobin after 16 weeks. Secondary objectives include evaluating changes in glycated hemoglobin, fasting lipid profile, blood glucose, BMI, and waist circumference and analyzing participant feedback. Given the predominantly Muslim population, the study also aims to gain insight into fasting practices for Muslim participants with T2DM.

Methods: This single-arm, nonrandomized intervention study involves adults aged 18 to 70 years with T2DM. Participants complete a fully online 16-week program via BruHealth that includes diabetes self-management education, personalized diet and exercise plans, self-monitoring tools (eg, glucometer and smartwatch), and support from health coaches through video consultations and instant messaging. Anthropometric and biochemical measures are collected at baseline and after the intervention. Data sources include the Brunei Health Information Management System, BruHealth app logs, and the health care professional portal. Descriptive statistics will summarize participant characteristics and outcomes. Paired 2-tailed *t* tests or Wilcoxon signed-rank tests will compare the results before and after the intervention. Subgroup analyses will explore outcomes based on glycemic changes, BMI, medication type, and program engagement. Participant feedback will be qualitatively analyzed. Fasting risk in Muslim participants will be stratified using the International Diabetes Federation-Diabetes and Ramadan Alliance Risk score.

Results: Recruitment began on August 20, 2024, following project approval in July 2024, and continued until July 2025. By the end of data collection on November 12, 2025, a total of 459 participants had been enrolled, and 422 (91.9%) had completed the program. Data analysis is currently ongoing, with results expected in early 2026.

Conclusions: Self-management mobile health apps are promising tools for chronic disease management, including T2DM. The BALANCE program is Brunei's first national-scale study evaluating a fully online T2DM intervention. Localization to a region's population may support improved health outcomes.

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KEYWORDS

BALANCE program; type 2 diabetes mellitus; digital intervention; digital therapeutics; mobile health; mHealth; diabetes mellitus digital therapeutics; DM DTx; health coaching; chronic disease management

Introduction

Background

Type 2 diabetes mellitus (T2DM) has emerged as a significant global health concern, with a worldwide prevalence of 537 million adults in 2021, and it is projected to rise to 783 million by 2045 [1]. In 2016, 9.7% of Bruneians aged between 18 and 69 years were diagnosed with diabetes [2]. Diabetes is the third leading cause of death in Brunei Darussalam, accounting for 10.1% of total deaths in 2017 [3]. Therefore, there is a need for effective management strategies tailored for patients with T2DM to achieve target glycemic control and reduce the risks of developing complications. This will lead to more efficient use of health resources.

In Brunei Darussalam, diabetes-related health care costs strain the national budget and heighten demand for services necessary to manage complications related to diabetes. The global cost of diabetes was estimated at US $966 billion in 2021 and is projected to rise to US $1.03 trillion by 2045 [1]. This burden includes direct medical expenses and indirect costs from increased prescription use, costly hospital services, and complications that can reduce overall productivity and lead to unemployment [4,5].

T2DM is a chronic disease that can lead to severe complications if not managed appropriately [6]. This underscores the critical role of self-management. Effective lifestyle management, which incorporates regular physical activity, a healthy diet, and medication adherence, can reduce both disease complication risks and health care costs [7]. By using SMART (specific, measurable, achievable, relevant, and time-bound) goals and behavioral techniques, individuals can improve their diabetes control and disease outcomes [8]. Recent studies have demonstrated that digital health interventions favorably impact glycemic control, patient adherence, and engagement [9,10]. Additionally, mobile health (mHealth) apps have been shown to positively improve health self-management practices on chronic conditions [11-13].

The digitalization of health care can further benefit the management of chronic diseases, such as T2DM [14]. With mobile ownership reaching 78% globally [15], health care can access a broad audience, enhancing health equity by providing vital information and resources. This accessibility equips underserved populations with tools for effective self-management, such as tracking health metrics and connecting with health care providers for personalized guidance.

BruHealth is the national mHealth app and health care portal in Brunei Darussalam, initially developed to mitigate COVID-19 spread. It has since evolved into a comprehensive digital health solution, benefiting the general population. The app is synchronized with the Brunei Darussalam Health Care Information and Management System (BruHIMS), where 95% of the population has active health records, allowing real-time access to health care data. Users can view their health records through BruHealth, enabling them to monitor their health status and access their blood test results. Beyond pandemic-related features, BruHealth now offers online appointment scheduling, health assessments, and access to medical articles on topics such as nutrition and lifestyle. By providing an accessible, user-friendly platform, BruHealth promotes the adoption of digital health technologies while allowing users to manage their health effectively [16].

Most existing global digital therapeutics (DTx) apps function as stand-alone tools, often relying on self-reported data and offering limited integration with national health systems. These apps frequently incur additional costs to users and typically focus on a single behavioral domain, such as diet tracking or medication adherence, thereby limiting their impact. The BALANCE program, delivered through BruHealth, adopts a holistic and culturally contextualized approach to diabetes prevention and management. The program addresses multiple lifestyle domains and provides education that has been adapted to the lifestyle in Brunei. Through integration with reliable wearables and BruHIMS, data captured can be used to create an appropriate health plan, enabling users to monitor their condition more seamlessly. This centralized and personalized system overcomes the key limitations of conventional DTx tools, particularly by offering a tailored and accessible solution for Brunei's population [17]. The digitalization of this tool also increases accessibility to services and education that would otherwise be available only in person.

Rationale

DTx are software-based treatments that deliver interventions with the best available evidence to manage or prevent diseases. They supplement or replace traditional therapies and are prescribed for chronic conditions such as diabetes and mental health disorders. In Brunei Darussalam, a DTx module focused on the management of T2DM (diabetes mellitus DTx [DM DTx]) has been developed.

The benefits of the DM DTx include patient education on diabetes management through lifestyle adjustments for better glycemic control, and real-time advice that has been designed to seamlessly integrate into daily activities, thus enabling patients to self-manage their diabetes with greater confidence. DM DTx may improve self-management and the quality of life of individuals with T2DM while paving the way for a more efficient and effective health care model.

The DM DTx module consists of a digital lifestyle intervention (named the BALANCE program, which is integrated into the

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BruHealth app) and a health care professional (HCP) portal where health coaches can interact with their patients and help them manage their condition. The BALANCE program has evolved from a previous pilot study conducted to evaluate the efficacy and feasibility of a digital lifestyle intervention for T2DM [18]. The pilot intervention program was designed with the expertise of endocrinologists and dietitians based on national clinical guidelines and evidence-based practice in diabetes management. Following further refinement and complete digitalization of the initial program, our study aims to assess the potential impact of a T2DM digital intervention that uses a fully online management approach.

Separately, as Brunei Darussalam has a Muslim-majority community, there is an optional component within the DM DTx offered to Muslim participants as an opportunistic way of gaining more insights into their fasting practices during the last Ramadan. Studies have shown that a significant number of Muslim patients in Brunei Darussalam with diabetes fast during Ramadan. For instance, a study found that 93.4% of participants fasted during Ramadan, with an average of 24.1 days. This optional component in the DM DTx could provide valuable insights into how fasting impacts diabetes management and help tailor more effective treatment plans for Muslim patients [19].

Aims and Objectives

Our study aims to evaluate the efficacy of the DM DTx in managing patients with T2DM by delivering digital lifestyle interventions through an easily accessible platform (BruHealth), and to evaluate participants' feedback to improve the app's content and structure for better user experience.

The primary objective is to determine the proportion of participants who achieve at least a 0.6% reduction in glycated hemoglobin (HbA_{1c}) from baseline following a 16-week lifestyle intervention provided by the DM DTx module. Secondary objectives are (1) to evaluate overall changes in HbA_{1c}, fasting lipid profile, fasting blood glucose, BMI, and waist circumference over a 16-week period; (2) to analyze participants' feedback on the BALANCE program; and (3) to evaluate fasting experience among Muslims with T2DM during Ramadan and to calculate their fasting risk using the International Diabetes Federation-Diabetes and Ramadan Alliance Risk (IDF-DAR) score [20].

Methods

Study Design

This is a single-arm, nonrandomized intervention study that involves the use of BALANCE, a 16-week diabetes lifestyle management program (described in more detail subsequently under the "Intervention" section). Patients with T2DM are enrolled and taught diabetes self-management with structured educational courses, and their progress is monitored through the DM DTx with dedicated health coaches.

Anthropometric measurements are taken at baseline and at the end of the study. These include BMI (height and weight) and waist circumference. A fasting blood sample is also taken at baseline and at the end of the study. The blood tests include the following:

- Fasting blood glucose
- HbA_{1c}
- Fasting lipid profile (total cholesterol, triglycerides, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol)

Serum creatinine is also measured at baseline if there is no result available within 1 year of enrollment.

Participants

Sample Size

By using a paired 2-tailed *t* test, a sample of 439 participants will provide 90% power to detect a 0.14 effect size at a .05 significance level. Considering a potential attrition rate of 12% based on the previous pilot study, the target sample size has been set at 500 participants.

Inclusion Criteria

Individuals with T2DM, aged between 18 and 70 years, either on diet control, treatment with oral hypoglycemic agents, once or twice daily insulin injections, or at least 6 months of glucagon-like peptide-1 receptor agonists are included in the study.

Exclusion Criteria

The following individuals are excluded from the study: (1) those with T2DM requiring more than twice daily insulin injections; (2) those with type 1 diabetes; (3) those who are pregnant or breastfeeding; (4) individuals with a recent history of recent myocardial infarction or cerebrovascular accident in the past 6 months; (5) those with a history of heart failure, liver failure, or active cancer diagnosis; (6) those undergoing treatment for active foot disease or active diabetes-related eye disease; (7) those with chronic kidney disease stage 4 or 5 according to estimated glomerular filtration rate (based on chronic kidney disease-epidemiology collaboration); (8) those with a history of hospitalization in the past 6 months; (9) those with physician's advice not to participate in intense physical activity; (10) those with physical disability or who are unable to perform activities of daily living; and (11) those unable to use the BruHealth app or watch YouTube videos independently on their mobile devices.

Recruitment

This study uses a volunteer sampling strategy. Recruitment is undertaken through the BruHealth app, which can be accessed by residents with a mobile device in Brunei Darussalam. Upon completion of the screening questionnaire on BruHealth, eligible participants will be enrolled in the study.

Online promotions comprise several methods, such as digital banners on the BruHealth app, targeted nudges to BruHealth users diagnosed with T2DM, and digital marketing strategies on social media platforms. Offline strategies include health promotional events, radio promotions, and the distribution of printed promotional materials in hospitals and health centers.

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Intervention

Overview

Participants who have been enrolled in the study will undergo a briefing session on the BALANCE program. During the briefing session, Muslim participants who had fasted during Ramadan in 2024 and who intend to fast this year will be assessed using the IDF-DAR risk stratification tool to determine their risk score and their safety of fasting. Risk stratification is an important step in the process of providing guidance to individuals with diabetes who fast during Ramadan. Each participant is assigned a health coach for personalized care and provided with tailored lifestyle modification recommendations on the BALANCE program.

Participants are provided with the following equipment: a glucometer, lancing device, blood test strips, and lancets to measure blood glucose; a resistance band for exercise; a measuring tape to measure waist circumference; a Bluetooth-enabled weighing scale to measure weight; and a smart watch to track step count and aerobic exercise. The glucometer, weighing scale, and smart watch are synchronized to the app to enable automatic data logging.

Diabetes Self-Management Education

The structured diabetes self-management education course focuses on sharing health care knowledge and tips specifically for individuals with diabetes. The aim is to increase health literacy to enable participants to be more aware of how their lifestyle choices may affect their glycemic control.

The materials are presented in the form of videos and educational articles, split across 4 phases (Textbox 1) to build upon knowledge acquired in earlier phases. There are also practice and review components to test the participants' understanding of the materials.

Textbox 1. The 4 phases of diabetes self-management education across the 16-week intensive education program.

Phase 1 (weeks 1 to 2)

- Pathophysiology
- Diabetes self-management
- Goal setting, motivation, and coping skills
- Hypoglycemia and hyperglycemia management, healthy eating patterns, exercising with diabetes, and precautions

Phase 2 (weeks 3 to 6)

- Advance nutrition education on grocery shopping, tips for special occasions, etc.
- Monitoring skills and importance and medications
- Best exercise practices and planning tips

Phase 3 (weeks 7 to 10)

- Diabetes-related complications and prevention
- Incorporating nutrition into daily life and eating habits
- Problem-solving skills and tips to encourage diabetes self-management

Phase 4 (weeks 11 to 16)

- No new courses, focus on converting learning to behavior
- Recommend articles or animations targeting barriers

Lifestyle Modification Plans, Logging, and Reports

Overview

The BALANCE program administers lifestyle modification intervention in blood glucose monitoring, exercise, and diet through personalized recommendations and goals based on participants' current state of health and lifestyle habits. SMART goals, which are specific, measurable, achievable, relevant, and time-bound, are incorporated into the program through the design of logging functions and further reinforced through educational courses and active monitoring by the health coaches. Health coaches encourage participants to achieve lifestyle changes by ensuring that the set goals are clear, measurable, and time sensitive, which enhances motivation and accountability. This approach helps participants to clearly define and track their progress toward managing their condition more effectively through goal-setting and behavioral activation.

At the start of the program, personalized plans are generated for each participant, as described subsequently.

Blood Glucose Monitoring

Participants are taught to undergo structured capillary blood glucose monitoring with logging of their blood glucose readings (Figures 1 and 2). Management of hypoglycemia and significant hyperglycemia (defined by our study protocol) will be discussed in the Escalation Model section. For nonsevere hypoglycemia or hyperglycemia, participants will receive self-management guidance through the DM DTx.

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Figure 1. Blood glucose logging feature.

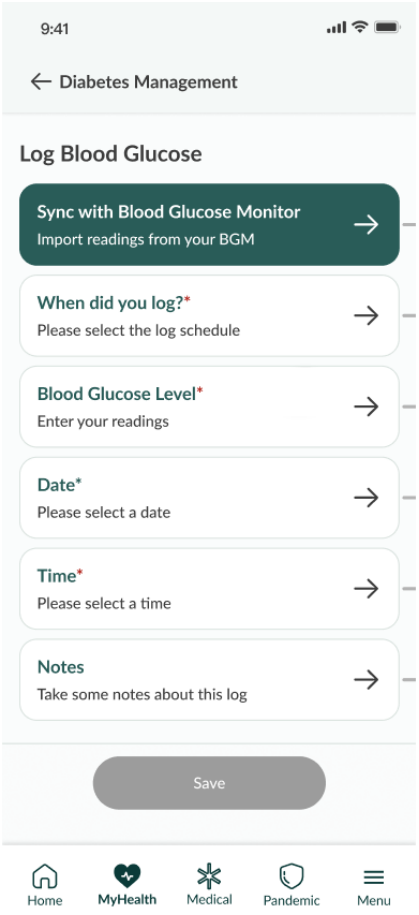

Figure 2. Instant feedback with blood glucose logging.

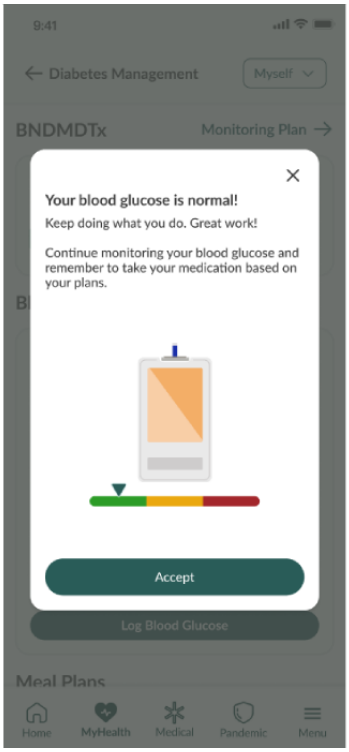

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Exercise

A weekly exercise plan is created based on each participant's current level of physical activity and mobility to recommend the duration and intensity of exercise most suited for them. Participants can record the type, duration, and intensity of their exercise for the day by synchronizing data from their smart watch or through manual entry (Figures 3 and 4).

Figure 3. Exercise plan.

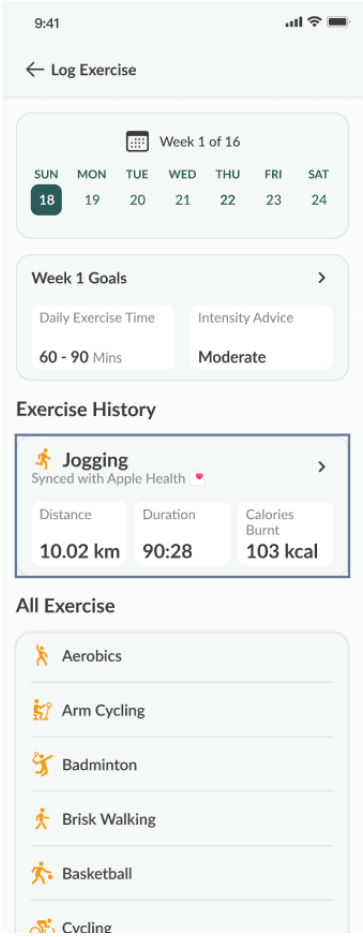

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Figure 4. Exercise logging feature.

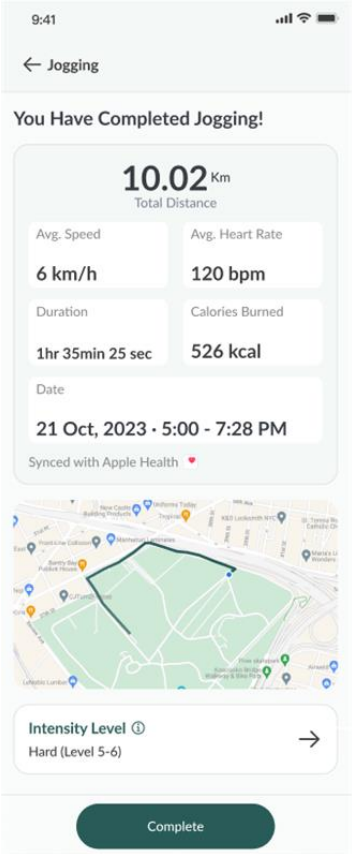

Diet

A daily nutritional plan, detailing recommended total calorie intake, including carbohydrate, fat, and protein intake across 3 meals (breakfast, lunch, and dinner), is created based on the participant's demographic data and physical activity level. Participants have access to a localized food database to help log their meals (Figures 5-7).

Figure 5. Meal plan.

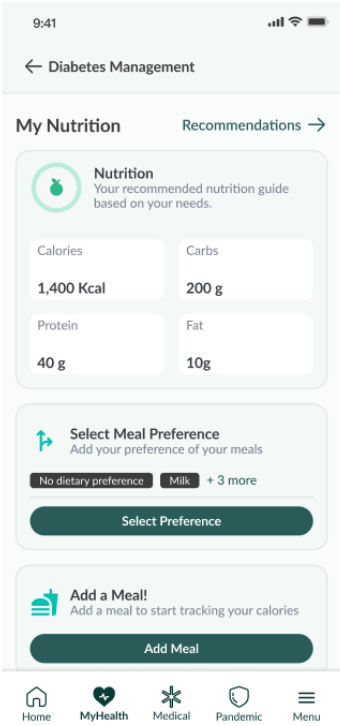

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Figure 6. Food logging feature (food database).

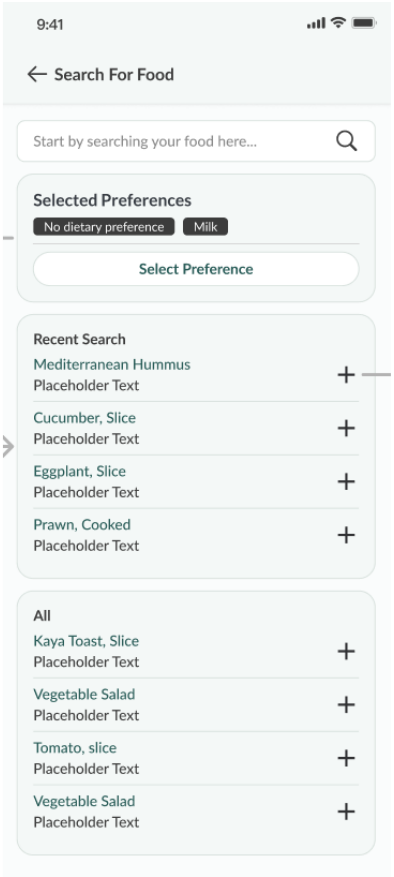

Figure 7. Food logging feature (meal information).

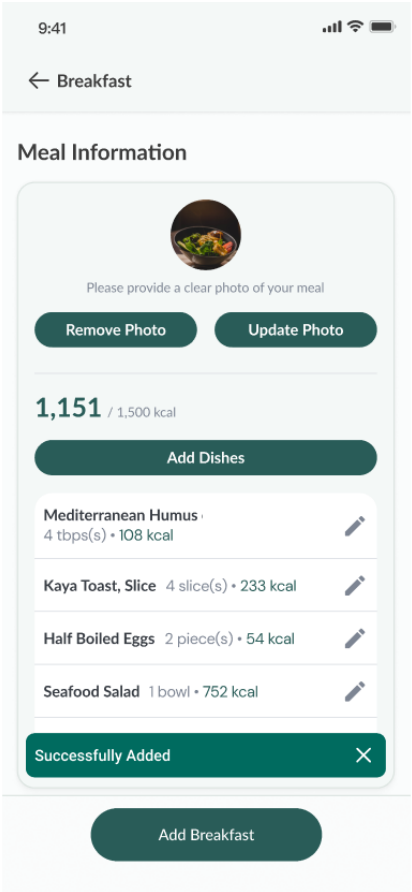

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Other Features

Other logging features, such as weight logging (Figure 8), sleep logging, and mood logging, are available for users to keep track of other parameters. Participants are also able to synchronize their medication list from the national electronic medical records, BruHIMS, into a medication logging function to remind them to take their medication in a timely manner (Figures 9 and 10).

Figure 8. Weight logging feature.

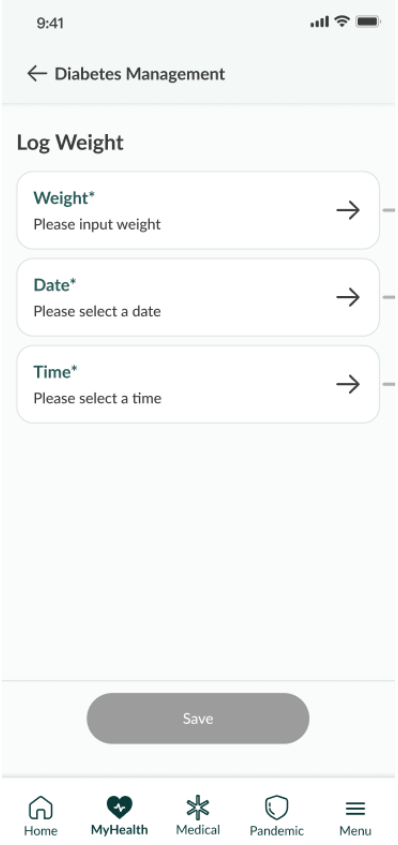

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Figure 9. Medication log.

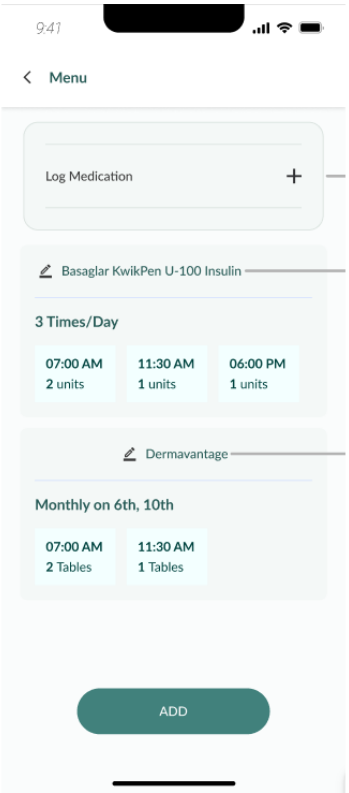

Figure 10. Reminders.

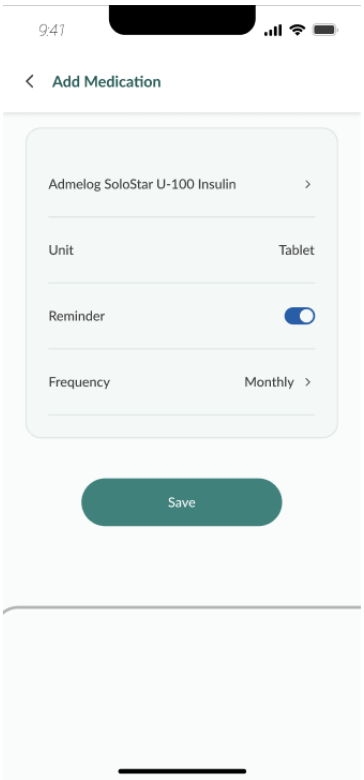

Participants receive daily nudges to remind them to log their daily progress. They also receive reports that outline their blood glucose monitoring, and dietary and exercise habits to monitor their changes throughout the program.

Health Coach Support

Overview

Health coaches manage and communicate with their participants through the HCP portal. The portal, designed for health coaches

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and relevant HCPs, enables access to the treatment plan for close monitoring and further action.

Each participant's assigned health coach conducts 5 scheduled video consultations with participants in the 16-week program. Health coaches review information logged by participants, track the changes in their anthropometric measures and habits, and provide additional guidance and advice to enable positive change in measured parameters. Sessions are aimed at reinforcing materials learned and emphasizing sustaining healthy habits for long-term management.

In addition to the regular video consultations, participants can engage with their health coaches through instant messaging. Health coaches also actively engage with participants to discuss their well-being, recent blood glucose readings, any symptoms, and adherence to prescribed medications. Health coaches also encourage participants to share details about their diet, exercise, and other factors that influence their blood glucose levels.

Additionally, health coaches respond to hypoglycemic events. During these times, if a hypoglycemic event alert is received, a health coach will initiate a video call to assess the situation based on the symptoms and signs presented by the participant.

Event Safety Monitoring

Health coaches are trained to identify and escalate cases of suspected diabetic emergencies, such as diabetic ketoacidosis, hyperosmolar hyperglycemic syndrome, and symptomatic hypoglycemia. Participants or their emergency contacts will be contacted to direct them to emergency services or to provide advice on blood glucose management based on the study protocol.

Escalation Model

The escalation pathway for managing participants in this study begins with a health coach assigned to the participant. Participants with hyperglycemia (defined per the study protocol) will be assigned to a dietitian or clinician in the research team for video consultation. Participants who experience (1) 2 or more episodes of hypoglycemia or (2) 3 or more episodes of hyperglycemia in a week despite dietetic interventions will be assigned to a clinical investigator for further evaluation.

Outcome

Primary Outcome

The primary outcome is to measure the proportion of participants with a reduction in HbA_{1c} of at least 0.6% at the end of the study.

Secondary Outcomes

The secondary outcomes include the following: (1) absolute change in HbA_{1c}; (2) changes in BMI, waist circumference, fasting blood glucose, and fasting lipid panel (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides) at the end of the study compared to baseline readings; (3) to describe the rate of fasting, rate of hypoglycemia, frequency of blood glucose monitoring, and fasting experience of Muslim participants in 2024; and (4) to calculate fasting risk using the IDF-DAR score

Data Collection, Management, and Analysis

Data Collection

Data for the study is collected from different channels as follows:

1. BruHIMS for blood test results (baseline and final), eligibility data, and medication data
2. BruHealth app for lifestyle data through logging and wearable data synchronized with the app
3. Health coach portal for eligibility and monitoring data

Data Security

Participant data will be captured within the HCP portal software app developed in conjunction with the DM DTx app. Data access is in compliance with the Ministry of Health regulatory requirements. The analysis will be conducted on password-protected computers.

Statistical Analysis

Descriptive statistics will be calculated to summarize the demographic profile of the research population and the primary and secondary outcomes outlined earlier. The mean, median, SD, and IQR will be reported for continuous variables, whereas frequencies and percentages will be used for categorical variables. Depending on the distribution of independent variables, appropriate paired statistical tests, such as the paired *t* test or the Wilcoxon signed-rank test, will be used to assess statistically significant differences between outcomes before and after treatment for both primary and secondary measures. Additionally, subgroup analyses will be conducted to assess for any significant differences in primary and secondary outcomes based on patient classifications, such as BMI categories, diabetic medication use profiles, or levels of engagement with the educational modules and health coaches in the BALANCE program.

Withdrawal

Participants are withdrawn from the study if it is deemed that continued participation in the study poses significant health risks to them. These considerations include the following: (1) participants who require hospitalization during the study period (which may or may not be related to the study), (2) those deemed by clinical investigators to require immediate adjustments to their diabetes medications as delay may cause harm, and (3) those who fail to provide 2 local emergency contacts.

Ethical Considerations

An online participant information sheet and consent form are available on the DM DTx module in the BruHealth app. Interested individuals are required to complete the online consent form before proceeding to complete the screening questionnaire. All participants are informed that their personal information will be kept confidential and securely stored within the Brunei Health Information Management System and BruHealth platforms, which follow national data protection and privacy standards. Identifying details will not be collected or published unless doing so is essential for scientific purposes, and no identifiable information (including names, initials, or images) will appear in any reports, publications, or

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supplementary materials. Participants have also been informed that they may withdraw from the study at any time without any effect on their access to routine health services. Ethics approval was granted by the Ministry of Health, Brunei Darussalam Medical and Health Research Ethics Committee (MHREC/MOH/2024/111).

Results

Recruitment began on August 20, 2024, following project approval in July 2024, and continued until July 2025. By the end of data collection on November 12, 2025, a total of 459 participants had been enrolled, and 422 (91.9%) had completed the program. Data analysis is currently ongoing, with results expected in early 2026 (Figure 11).

Figure 11. CONSORT (Consolidated Standards of Reporting Trials) flowchart: the recruitment process of the BALANCE program.

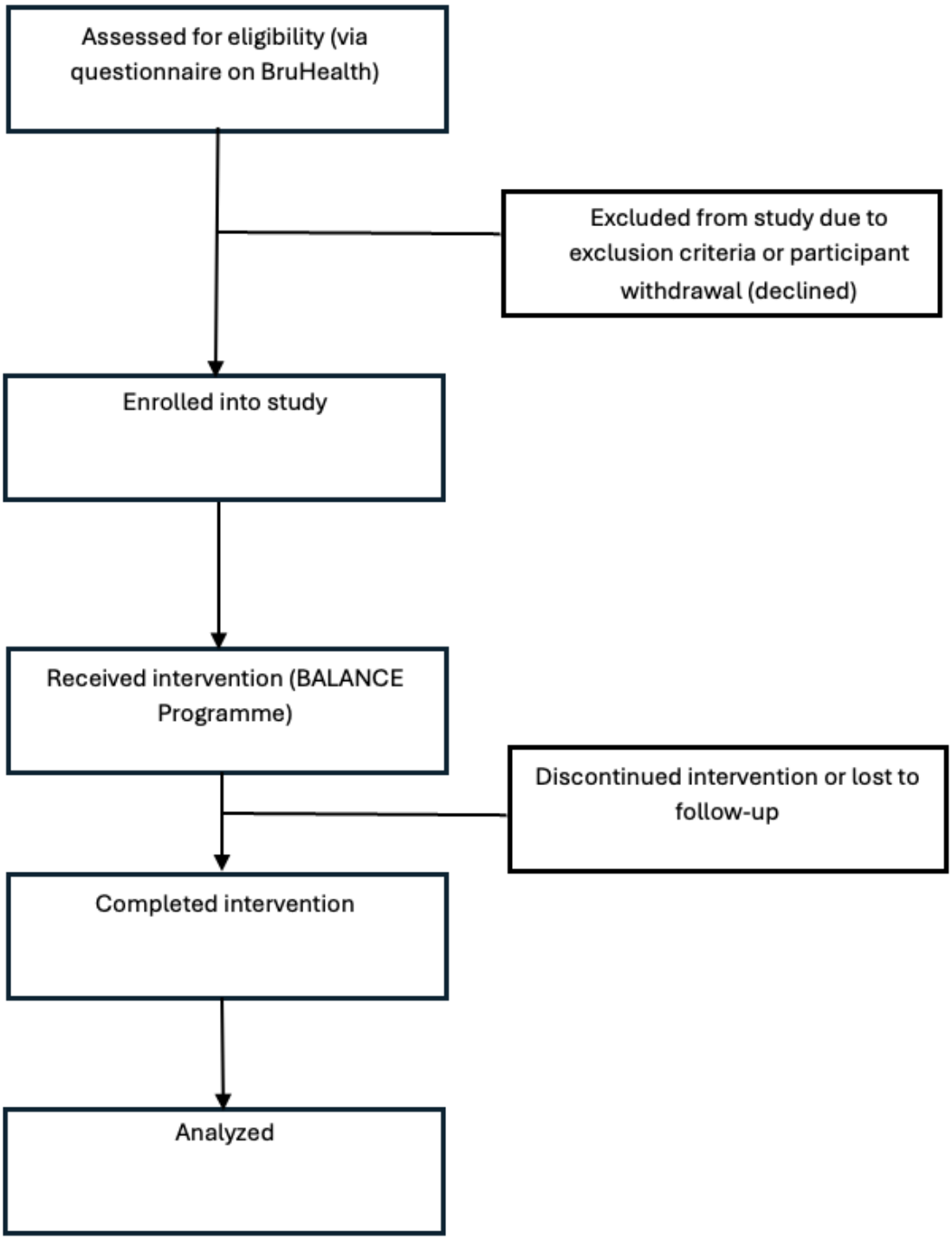

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Discussion

Anticipated Findings

With the rising prevalence of diabetes in Southeast Asia, organizations such as the International Diabetes Federation are increasing efforts in diabetes advocacy and exploring new ways to improve access to quality health care and affordable treatments. Patient empowerment by incorporating self-management represents an important component of diabetes care, which will improve health outcomes and reduce diabetes-related complications. Therefore, new interventions should be designed with a focus on incorporating the latest clinical guidelines with an all-encompassing program that includes monitoring, diabetes education, maintaining a healthy lifestyle through diet and physical activity, medication tracking, and motivational coaching. A reduction of 1% in HbA_{1c} levels over 3 months is associated with decreased mortality and a reduction in microvascular disease, while a reduction in weight has been shown to improve glycemic control and insulin sensitivity, and potentially reduce medication dosage [21,22]. Consequently, an effective program would focus on methods to improve key cardiovascular risk factors, such as a reduction in HbA_{1c} and weight.

The increasing digitalization in the health care landscape has led to the deployment of mHealth and digital interventions to guide self-management of chronic conditions, particularly in diabetes management. Diabetes management apps can supplement traditional face-to-face care. This will help reduce the time and resources required from the health care system. Patients who have better self-management practices tend to manage their condition better [9]. By allowing users to actively participate in their own health management, users can increase their health literacy and become more confident in navigating their condition. However, an issue faced by most diabetes management apps is low engagement, with many users lost to follow-up [23]. A study showed that users were less likely to engage due to the high effort and difficulty in using the apps [24]. Therefore, collecting feedback on participant experience is crucial to identify functions and protocols that need to be redesigned to create an app that enhances the patient experience and level of engagement.

Due to the global burden of diabetes, various apps for diabetes management are commercially available on the market [25]. The main functionalities offered include self-management tasks (medication, blood glucose monitoring, exercise, and food intake), weight and blood pressure tracking, and education [26]. Most apps cover at least 1 self-management task, with blood glucose monitoring being the most common function [26]. According to the research that has been conducted to assess the efficacy of these apps, diabetes self-management apps have demonstrated a significant reduction in HbA_{1c} and body weight after a 6-month follow-up [9,27]. Most of these apps are free to download, with premium functions that require additional fees. The average cost of diabetes management apps on the market is between US $4.57 and US $5.03, with a higher annual cost for apps with multiple functions, making mHealth a cost-effective solution focused on preventing disease progression [28].

DM DTx is the first digital intervention solution of its kind in Southeast Asia. Most diabetes mHealth solutions are targeted at the North American market as part of an annual subscription plan usually provided by employers. This is largely attributed to the increasing penetration of smart consumer devices and the higher acceptance of mHealth solutions in the region [28]. Additional research on the efficacy of diabetes self-management apps in Southeast Asia should be conducted, as recommendations from solutions on the market may not be suitable in Southeast Asia due to different cutoff ranges for clinical parameters and cultural differences. Lifestyle habits and user behavior may also differ vastly between different populations, solidifying the need for region-specific intervention designs. Most commercially available diabetes management apps showed only low-to-moderate success in terms of user adherence, proving that diabetes self-management solutions do not follow a one-size-fits-all approach.

This study possesses some limitations. First, the study is designed based on volunteer sampling. Ideally, the study should be designed as a randomized controlled trial to reduce selection bias and ensure that the results are generalizable to a broader population. Any observable effects cannot be conclusively attributed to the intervention due to the lack of a control group. Sampling is done within the Bruneian population, so the results may not apply to populations outside of the current demographic. As the participants are not followed long-term, there is a lack of understanding of the sustained effects and durability of the intervention over time. Participants' readiness to change their lifestyle habits was also not measured, as it was assumed that their participation translated to readiness. Finally, participants' digital literacy is not measured during recruitment, which may affect their participation in the digital intervention and lead to less optimal results due to external barriers.

Conclusions

Self-management mHealth apps remain a promising adjunct to chronic disease care, especially in T2DM. However, the impact of these apps in improving health is greatly dependent on localization to a region's clinical and cultural context. Through data-driven research, gaps in intervention and app design can be identified to bridge the gap between theorized and realized improvements in health outcomes.

Ultimately, this research aims to understand the efficacy of DM DTx to develop a solution that is fit for purpose, clinically sound, patient-centered, and sufficiently personalized.

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Conflicts of Interest

JL, JT, and YL are employed by EVYD Technology. EVYD Technology is the technology partner of this study and the developer of the BruHealth app and the health care professional portal. The other authors declare no conflicts of interest.

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Abbreviations

BruHIMS: Brunei Darussalam Health Care Information and Management System
DM DTx: diabetes mellitus digital therapeutics
DTx: digital therapeutics
HbA_{1c}: glycated hemoglobin
HCP: health care professional
IDF-DAR: International Diabetes Federation-Diabetes and Ramadan Alliance Risk
mHealth: mobile health
SMART: specific, measurable, achievable, relevant, and time-bound
T2DM: type 2 diabetes mellitus

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Protocol

Evaluating AI-Generated Podcasts Versus Traditional Reading for Learning From Medical Articles: Protocol for a Mixed-Design Study Among Resident Physicians

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Abstract

Background: Podcasts have emerged as a popular medium in medical education over the past decade. Audio learning allows flexibility and may help residents engage with content in new ways. Reading scientific literature is a core skill for residents, yet many residents struggle to comprehend complex research articles. Advances in artificial intelligence (AI) have enabled the automatic generation of podcast-style summaries of documents. It remains unclear whether listening to AI-generated podcast summaries can match the educational value of reading the full text of medical papers, and whether this depends on the complexity of the article.

Objective: This study aims to compare comprehension of medical research papers when learning via an AI-generated audio podcast versus traditional reading. We will examine whether article complexity (narrative vs technical) moderates any difference. We hypothesize an interaction: for a highly complex article, residents who read the full text should achieve a better understanding than those who listen to a summary, whereas for an easier article, the difference between modalities should be smaller.

Methods: We designed a 2×2 mixed factorial study with 60 resident physicians preparing for the board certification in internal medicine or cardiology. All participants will engage with 2 peer-reviewed cardiology articles differing in complexity: a narrative case report on eosinophilic myocarditis and a technical research article on quantifying the vena contracta area using 3-dimensional echocardiography. Each participant will read 1 article and listen to an AI-generated podcast summary of the other, with the order and assignment counterbalanced to control for order effects. The podcasts are created using Google NotebookLM's experimental *audio overview* feature. Participants will complete a multiple-choice knowledge test for each article. The primary outcomes are comprehension scores for each modality. The secondary outcomes include intrinsic motivation, perceived learning gains, and cognitive load for each condition. Data will be analyzed using a mixed ANOVA to test the main effects of modality and article complexity, as well as their interaction.

Results: Data collection is expected to be completed by early 2026. We will report the trial results according to the CONSORT (Consolidated Standards of Reporting Trials) guidelines, and any deviations from this protocol will be documented and justified. No results are available at the time of publication of this protocol.

Conclusions: This randomized trial will offer evidence on the effectiveness of AI-generated podcast summaries as a learning tool for medical literature. If listening to an AI-generated podcast yields comprehension comparable to or superior to reading the full article, it could validate an innovative, time-saving approach for busy medical trainees. Conversely, if significant deficits are observed in the podcast group (especially for complex content), the findings will highlight the limitations of AI summaries and the continued importance of traditional reading for thorough understanding.

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KEYWORDS

artificial intelligence; AI; podcasts; medical education; cardiology

Introduction

Medical education is increasingly embracing digital and asynchronous learning modalities. Podcasts, in particular, have seen a marked rise in their use as supplementary learning tools across many medical specialties. By 2021, an estimated 41% of Americans reported listening to a podcast in the past month [1], and medical education has mirrored this trend with numerous educational podcasts now available for both trainees and practitioners [2,3]. For medical residents, podcasts offer a convenient way to learn on the go and can introduce clinical topics in an engaging, conversational format [4]. The popularity of podcasts suggests that they may help sustain learners' interest and motivation [5]. However, it is important to evaluate whether learning medical content via podcasts is as effective as more traditional methods.

One traditional learning activity in medical school is reading and appraising journal articles. The ability to read and comprehend scientific papers is fundamental for evidence-based practice and lifelong learning [6]. However, medical residents often find it challenging to digest primary literature, especially when articles are dense or highly technical [7]. Journal club studies have documented that learners struggle to understand complex research papers, sometimes becoming lost in advanced methodologies or jargon [7]. Practical, case-based articles (eg, clinical case reports or case-based discussions) may be easier to follow, as they tend to have concrete patient narratives and applied lessons [8]. In contrast, theoretical or review articles (eg, a detailed review of endocrine pathophysiology) can be abstract, laden with data, and not immediately relatable to clinical practice. This disparity in content complexity could influence how well learners comprehend the material and stay engaged [9].

Beyond accessibility and learner motivation, self-regulation theory [10] predicts that podcasts may offer educational advantages related to repetition, self-pacing, and multitasking [11] if learners are able to use them appropriately. However, using podcasts to access medical journal articles may yield higher cognitive demands than reading the articles. The interplay between cognitive resources and learning outcomes is central to cognitive load theory, which posits that human working memory has a limited capacity crucial for learning [12]. According to cognitive load theory, learning activities typically demand a significant allocation of cognitive resources, and instructional design plays a pivotal role in either exacerbating or alleviating cognitive load. The theory delineates 3 types of cognitive load: extraneous, intrinsic, and germane, each influencing learning in distinct ways [13]. Listening to audio differs cognitively from reading: listeners process information sequentially, at a fixed pace, and may lack easy access to figures or references [14]. In addition, podcasts are inherently reductive; condensing full-text articles into short conversational scripts may reduce extraneous load [15] but risks omitting critical nuance or context [16,17]. This, in turn, may suppress the intrinsic load necessary for deeper understanding, ultimately resulting in shallow learning processes [15]. While learners may perceive these summaries as more enjoyable or efficient, it is unclear whether they support equivalent knowledge acquisition, especially for content of varying complexity.

Producing high-quality medical education podcasts typically requires expert knowledge, pedagogical insight, technical skills, and significant time for scripting, recording, and postproduction [18]. These constraints limit scalability and personalization, especially for institutions or learners aiming to integrate podcasts into dynamic, content-rich environments, such as medical curricula. Recent advances in generative artificial intelligence (AI) present an opportunity to overcome some of these barriers. AI-powered systems based on large language models can now generate podcast-style summaries of academic content by transforming articles into structured, conversational dialogues [16]. These AI-generated podcasts often simulate discussions between 2 virtual hosts, aiming to translate complex material into an engaging audio narrative. Early research indicates that such podcasts can enhance learner motivation and satisfaction, particularly when personalized according to user needs [19]. Some studies suggest comparable or even superior learning outcomes relative to traditional reading in specific contexts [17,19].

Nevertheless, the educational value of these AI-generated summaries remains largely untested in medical education [18]. AI-generated podcasts may lack the necessary accuracy or lose important contexts, which may cause either worse learning outcomes or potentially even misinform learners and endanger patients. Therefore, this study aims to address these questions through a randomized controlled trial comparing learning outcomes across 2 types of medical articles (practical vs theoretical) in the reading and listening modalities. By examining both knowledge acquisition and learners' motivational and cognitive responses, we aim to assess whether AI-generated podcasts can serve as a viable tool for engaging residents with scientific literature.

The primary objective of this randomized trial is to compare knowledge acquisition from medical journal articles between 2 learning modalities: listening to an AI-generated podcast versus reading the full text. We seek to determine if one modality leads to superior comprehension in medical residents. A secondary objective is to assess the influence of article complexity on learning outcomes and any interaction between complexity and modality.

In operational terms, the study will test two main hypotheses and one interaction hypothesis, as presented in Textbox 1.

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Textbox 1. Study hypothesis.

Main effect of modality (artificial intelligence [AI]–generated podcast vs reading the full text)

There may be a difference in knowledge scores between residents who listen to an AI-generated audio summary and those who read the article, regardless of complexity. We will explore the direction of this effect; we expect that reading the full article could confer an advantage for understanding, especially detailed content, but well-crafted audio summaries may yield comparable results for certain types of information.

Main effect of complexity (low vs high)

We anticipate that all residents, regardless of modality, will find the *complex* article more challenging, resulting in lower average test scores compared to the *easy* article, given the higher theoretical density of the former.

Modality × complexity interaction

We hypothesize an interaction such that the effectiveness of the podcast relative to reading will differ by article complexity. Specifically, the performance gap (if any) between listening and reading is expected to be larger for the complex article than for the easy article. In other words, for the easier, case-based article, listening to a summary might achieve nearly the same comprehension as reading, whereas for the complex article, listening to the summary might not capture enough detail, leading to lower comprehension compared to reading the full text.

Additional objectives include evaluating secondary outcomes related to the learning experience: we will compare residents' intrinsic motivation during the task, subjective cognitive load, and their subjective perception of learning between the 2 modalities. This will provide a more nuanced understanding of how engaging or difficult residents found the learning process in each condition, beyond the factual knowledge gains. Ultimately, the goal is not only to determine which method yields higher test scores, but also to consider which method residents prefer or find more motivating, because an engaging learning experience could encourage more frequent interaction with the scientific literature.

Methods

All study materials (articles, audio files, and questionnaires) and deidentified data will be made available in an open science repository [20] upon study completion, in line with open science practices.

Study Design and Setting

We will conduct a single-center, 2-factor mixed experimental study with a 2×2 design. The within-subjects factor is the learning modality (AI-generated podcast vs traditional reading), and the between-subjects factor is the presentation order (ie, which article-modality combination comes first). Each participant will engage with 2 cardiology articles—1 practical case report and 1 technical research paper—experiencing 1 via reading and the other via an AI-generated podcast. The assignment of modality to article and the sequence of presentation will be fully counterbalanced across participants to control for order effects and content bias.

The study will take place at LMU Munich. Each participant will attend a single study session, during which they will read 1 article and listen to the other in podcast form. After each learning task, participants will complete a multiple-choice knowledge test and questionnaires assessing motivation, cognitive load, and perceived learning.

All study sessions will be conducted in a controlled classroom environment at LMU Munich. A researcher will be present throughout the study to supervise the session and ensure adherence to the protocol. The physical setting will be quiet, with individual desks and study materials provided on desktop computers or tablets. Participants in the podcast condition will be provided with noise-canceling headphones to standardize audio delivery.

Participants and Recruitment

The study population will consist of resident physicians enrolled in specialty training programs at LMU Munich, specifically those preparing for the German board certification (Facharztprüfung) in internal medicine or cardiology. These physicians have completed medical school and are engaged in postgraduate training, making them an ideal population for studying learning strategies that support lifelong engagement with scientific literature.

Sample Size Calculation

We conducted an a priori power analysis using G*Power (version 3.1; Heinrich Heine University) [21] for a mixed ANOVA with 1 within-subjects factor (learning modality: podcast vs reading) and 1 between-subjects factor (article-modality order). To detect a moderate effect size ($f=0.25$) for the main effects or interactions, with $\alpha=0.05$ and power ($1-\beta=0.80$), the required total sample size is approximately N=44. To account for potential dropouts or missing data, we plan to recruit a total sample of N=60 resident physicians.

Inclusion Criteria

Participants must be currently enrolled in a medical residency program, specifically in a discipline such as internal medicine or cardiology. Additionally, they must be actively participating in a structured preparation course for the German specialist board certification (Facharztprüfung). Eligible participants should have completed their undergraduate medical education and be in the clinical phase of a postgraduate training.

Because the study materials, including the articles and AI-generated podcast summaries, are presented in English, participants must have sufficient English proficiency to understand both written and spoken academic medical content. While we expect most physicians in the preparation course to possess the necessary language skills, this will be confirmed informally during recruitment.

All participants must be willing and available to participate in a single research session lasting approximately 60 minutes and

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must provide written informed consent. Furthermore, they must have normal or corrected-to-normal hearing and vision to ensure that they can engage with both the reading and audio conditions, as required by the within-subjects design.

Exclusion Criteria

We will exclude individuals who have prior extensive familiarity with the specific articles used in the study. During recruitment and again at the start of the experimental session, we will present the titles and journal references of the 2 articles. If a participant confirms that they have previously read, studied, or discussed either article in detail (eg, in a journal club or as part of examination preparation), they will be thanked and excluded from participation to avoid a knowledge bias.

Additionally, individuals with uncorrected hearing impairment or severe visual impairment that would prevent them from effectively listening to the audio podcast or reading the article will be excluded. Because each participant will engage in both a reading and a listening task, we require all participants to have unimpaired or corrected functional access to both modalities.

We will recruit participants from a structured board examination preparation course organized by LMU Munich. This course attracts physicians actively preparing for their specialty certification and therefore reflects a highly motivated and relevant target group. Participants will be informed about the study through announcements made during the course sessions and follow-up emails. The study will be presented as a research project on learning from medical articles using different formats, without disclosing specific hypotheses. Participation is entirely voluntary and will not affect their standing in the course or the certification process.

Before participation, each physician will receive a full briefing on the study's goals, procedures, and data privacy protections. This study will generally be described as a comparison of different learning formats for medical content. Written informed consent will be obtained. We will emphasize that participation is voluntary, performance on the comprehension tests has no bearing on their training or certification, and all data will be anonymized and treated confidentially.

Study Materials

Articles (Learning Content)

Two published medical articles have been selected to represent different levels of complexity within the field of cardiology, both published in *BMC Cardiovascular Disorders*.

The *narrative* article is a case-based clinical report [22]. This report describes the diagnostic journey and clinical management of a patient with eosinophilic myocarditis who presented with cardiogenic shock and malignant arrhythmias. The article is structured in a narrative format and emphasizes clinical reasoning, interdisciplinary care, and escalation of treatment. It presents practical, concrete decision-making steps, making it highly accessible and relevant for clinical-phase medical students.

The *technical* article focuses on the validation of 3-dimensional echocardiographic measurements of the vena contracta area for quantifying mitral regurgitation severity [23]. It involves advanced imaging techniques, direct planimetry, multiplanar reconstruction, and statistical comparisons, including sensitivity and specificity analysis and Bland-Altman plots. The dense methodological content and reliance on imaging expertise and statistical interpretation make it cognitively demanding and better suited for advanced learners with prior knowledge of cardiac imaging and valvular pathology.

These articles were deliberately chosen to provide a clear contrast in complexity and content delivery within the same specialty and text length (8 pages), allowing for an effective assessment of learning outcomes across different formats and difficulty levels.

For the reading groups, the article text will be provided on a screen in PDF format. For the podcast groups, the content of these articles is used as input to generate the AI podcasts.

AI-Generated Podcasts

Using Google NotebookLM (an AI platform currently in experimental release) [24,25], we generated an audio summary for each of the 2 articles. The process involves uploading the article text into NotebookLM and then using the "audio overview" feature. The output is an audio file featuring 2 synthetic voices (the *AI hosts*) discussing the article. According to NotebookLM's design, the hosts begin by introducing the topic, then proceed to discuss key points, clarify terms, and make connections. This is similar to one host quizzing or interviewing the other about the article's content. The tone is meant to be conversational, which can help maintain listener interest.

Google NotebookLM was chosen for this study because, at the time of design, it was the only publicly accessible platform capable of generating conversational, dialogue-style audio summaries directly from full-text academic articles with no need for additional scripting. Its *audio overview* feature automatically organizes content into a simulated exchange between 2 hosts. This format aligns with well-established educational strategies, such as elaborative interrogation and peer explanation, which can foster learner engagement and retention. While alternative AI tools can produce summaries, they typically provide plain-text outputs or monologue-style narrations and require substantial manual adaptation to achieve a similar conversational format. Using NotebookLM enabled us to create standardized, pedagogically relevant podcasts with minimal human editing, thereby reducing the risk of inadvertent bias in the intervention materials while maintaining ecological validity for real-world use cases.

Each resulting podcast is approximately 15 minutes in length. The audio files are in English, matching the article's language. We reviewed the transcripts of these AI-generated discussions to ensure they cover the main sections of the articles (eg, the case presentation and outcome in the narrative article, and all major subtopics in the technical article). We also checked for any factual inaccuracies or misrepresentations.

During the session, participants in the podcast conditions will listen to the audio using over-ear headphones provided by the study team (to ensure good sound quality and noise isolation).

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The audio will be played on a tablet or computer via a simple media player interface. Participants will be instructed that they can pause, rewind, or replay the audio as needed (up to 1 full listening of the entire length again, if time allows), but they cannot fast-forward beyond sections they have not heard yet (to prevent skipping content). They will not have a transcript or any text of the article while listening to simulate a true audio-only learning experience.

English Proficiency

Participants will rate their level of English proficiency along the dimensions of *listening*, *reading*, *participating in conversations*, and *coherent speech* [26]. For each dimension, they will be given 6 levels (from A1 to C2) with short descriptions, such as "I can understand individual words and parts of sentences" (listening A1) or "I can write clear, fluent, stylistically appropriate reports, articles, and sophisticated letters" (coherent speech C2). English proficiency will be considered sufficient if no dimension is reported to be below B2.

Knowledge Tests

For each article, we developed a multiple-choice questionnaire to assess the comprehension and retention of key information. Each test consists of 10 questions in a single-best-answer format, and the sum of all correct answers represents the knowledge score. The questions cover important points from the article.

All questions were written specifically for this study. We ensured that each question could be answered based on the information in the article and that the AI podcast, if accurate, would also cover those points. We had 2 faculty members with a background in cardiology who were not involved in the study review the questions for content validity and clarity. Internal testing of the final items yielded no problems with comprehensibility.

Motivation

To gauge participants' motivation and engagement during the learning task, we will use items from the Intrinsic Motivation Inventory (IMI) [27], a well-established instrument for assessing subjective motivation in experimental tasks. We will focus on the interest and enjoyment as well as the effort and importance subscales of the IMI, as these are most relevant here. The interest and enjoyment scale serves as a measure of how enjoyable or engaging the student found the activity (considered a self-report proxy for intrinsic motivation), whereas effort and importance indicate how much effort they invested and how important they perceived doing well to be. Participants rate their agreement with the scales' 7 (interest/enjoyment) and 6 (effort/importance) statements (eg, "I enjoyed doing this activity very much"; "I put a lot of effort into this") on a 7-point Likert response from "strongly disagree" to "strongly agree." The IMI has been used in educational studies and has shown good psychometric properties in various contexts (Cronbach α >0.80 in similar studies) [28], allowing the use of mean scores across all items of a scale as the final score.

Cognitive Load

We will assess the cognitive load experienced by participants using the questionnaire developed by Klepsch et al [29]. This instrument allows for a separate evaluation of intrinsic load (the inherent difficulty of the content), extraneous load (the load imposed by the way information is presented), and germane load (the effort invested in meaningful learning). We will use the version with a total of 8 statements rated on a 7-point Likert response ("not at all true" to "completely true"). Examples of items include "The content was very complex" (intrinsic load), "The way the information was presented was confusing" (extraneous load), and "I invested a lot of effort into understanding the material" (germane load). All 3 scales showed good internal consistencies (Cronbach α >0.80 in similar studies), allowing the use of mean scores across all items of a scale as the final score.

Perceived Learning

We will ask participants to self-assess their perceived learning from the activity. This will be done with 3 custom questions adapted from prior studies on perceived learning [30]. Responses will indicate agreement on a 7-point Likert response from "strongly disagree" to "strongly agree." The 3 questions are "Overall, I was satisfied with my learning experience," "This type of learning met my needs as a learner," and "I could learn well with the material presented."

Procedure

Each participant will attend a single session, either individually or in small groups, depending on laboratory capacity. Even when in groups, each participant will complete the study independently at their own workstation (with individual screens and headphones).

Orientation (5 Min)

Participants are welcomed and seated at a computer or tablet station. Written informed consent is obtained if not already collected during recruitment. Participants then complete a short intake form to gather demographic information (age, gender, and specialty area), confirm their participation in the Facharztprüfung preparation course, and verify their English proficiency and lack of prior exposure to the study materials. They are also screened for any sensory impairments that might interfere with reading or listening tasks.

Participants are randomly assigned to one of the counterbalanced order conditions (ie, whether they first read the narrative article or listen to the technical podcast, or vice versa). The researcher then provides access to the appropriate learning material.

Learning Phase 1 (30 Min)

Participants begin with their first learning task: either reading 1 article or listening to the podcast version of the other. Each participant has up to 30 minutes for this phase, which accommodates the full podcast duration (approximately 12 min) or sufficient reading time (approximately 15 min) with sufficient buffer. Participants are instructed not to take notes or use external aids. The researcher monitors to ensure compliance (eg, that readers are not using mobile phones or writing and that listeners are not replaying segments excessively).

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Knowledge Test 1 (5 Min)

Immediately after the first learning task, the materials are removed. Participants complete a multiple-choice quiz assessing their comprehension of the content they just engaged with.

Posttask Questionnaire 1 (5 Min)

Participants complete a brief questionnaire assessing intrinsic motivation, cognitive load, and perceived learning for the first learning task.

Break (Optional, Approximately 2 Min)

A short, optional break (2-3 min) may be offered to reduce carryover fatigue between tasks.

Learning Phase 2 (30 Min)

Participants proceed to their second learning task, which is in the opposite modality and with the alternate article. Again, materials are provided for up to 30 minutes, and participants are instructed not to take notes or access external resources. The researcher continues to monitor the session.

Knowledge Test 2 (5 Min)

As before, the article or podcast is removed, and participants complete a second multiple-choice quiz focused on the second learning task.

Posttask Questionnaire 2 (5 Min)

Participants complete the same set of questions (motivation, cognitive load, and perceived learning) for the second task.

Debriefing (5 Min)

After all tasks are complete, the researcher provides a brief debriefing. Participants are informed about the study's purpose and hypotheses and may ask questions. If they are interested, they are offered access to the alternate format for each article (eg, if they read the case report, they may request the podcast version, and vice versa). Participants are politely asked not to discuss the study specifics with peers until the study has concluded to minimize bias for future participants.

Data Analysis Plan

Descriptive Statistics

Only cases with complete data will be used, with no imputations of missing values. We will summarize participant demographics (age, gender, specialty training area, and prior exposure to similar materials) for the entire sample and by order group (eg, whether the participant read first or listened first). We will report the mean and SD for all primary and secondary outcome measures (knowledge test scores, motivation, perceived learning, and cognitive load) by modality and article complexity.

Primary Analysis

To assess the effect of learning modality and article complexity on comprehension, we will conduct a 2×2 mixed ANOVA with the following factors:

- Within-subjects factor: modality (AI-generated podcast vs traditional reading)
- Within-subjects factor: article complexity (narrative case report vs technical research article)

Each participant completes both a reading task and a podcast task, 1 with the narrative article and the other with the technical article. The assignment of modality to article is counterbalanced. We will test for the main effects of modality and complexity, and their interaction, on knowledge test scores (range 0-10 per article). Effect sizes will be reported using eta squared (η^2). Assumptions of normality (Shapiro-Wilk test on residuals) and homogeneity of variance (Levene test) will be examined. If assumption violations are detected, we will consider using robust ANOVA procedures [31].

Secondary Analyses

We will perform similar 2×2 mixed ANOVAs for each of the following secondary outcomes:

- Intrinsic motivation, measured using the interest and enjoyment subscale of the IMI
- Cognitive load, using the scale developed by Klepsch et al [29], which includes subscales for intrinsic, extraneous, and germane load
- Perceived learning gain, rated on a single-item Likert scale

Each participant completes these measures after each learning task, allowing within-subjects comparisons across modalities and content types.

For all analyses, we will consider both the effect size and the *P* value when interpreting the results. To document test quality, we will report psychometric properties (eg, internal consistency and item characteristics) for both multiple-choice questionnaires. Differences in mean scores are expected due to content difficulty, but reliability (McDonald's Omega) will be used to ensure comparability across tests.

Ethical Considerations

This study was approved by the Ethics Committee of LMU Munich (23-0688). All procedures were reviewed for compliance with ethical standards in research with human participants.

Informed Consent

As noted, we obtain written informed consent from all participants. They are informed that the study is about learning from the medical literature and involves completing tests, but the full details of the interventions are somewhat masked until debriefing to preserve the blinding of the hypothesis. They are told that they can withdraw at any time without penalty.

Confidentiality

Each participant is assigned a code; no identifiable personal information is associated with their data. Any publications or reports will present only aggregated results. We do not foresee collecting sensitive personal information; the demographic data collected is minimal.

Compensation

As an incentive, all participants will be given the option to enter a lottery to win a €50 (US $58) gift voucher.

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Results

As of the submission of this protocol (August 2025), no participants have been recruited, and no data have been collected. Once data analysis is complete (by early 2026), we will report the trial results according to the CONSORT (Consolidated Standards of Reporting Trials) guidelines, and any deviations from this protocol will be documented and justified. No results are available at the time of publication of this protocol.

Discussion

Anticipated Findings

This study evaluates AI-generated audio summaries (*AI podcasts*) as a tool for learning from scientific literature in postgraduate medical education. By directly comparing podcast-based learning with the traditional method of reading full-text articles, we aim to generate evidence on comprehension outcomes, learner motivation, cognitive load, and perceived learning. Because each participant will experience both modalities—reading and listening—our within-subjects design allows for more precise comparisons while controlling for individual differences in prior knowledge, attention, and learning preferences.

The findings will have practical implications for adapting learning materials for resident physicians preparing for board certification. If we find that reading leads to significantly better comprehension than listening, particularly for complex or technical content, this suggests that caution is warranted in using audio summaries as a standalone resource. Resident physicians may miss subtle but clinically important nuances when relying solely on AI-generated podcasts for learning. In such a case, AI-generated audio could still be valuable as a supplementary tool—useful for introducing new material, reinforcing key ideas, or supporting review during time-constrained situations such as commuting or night shifts. The results could also inform developers and content curators about the limitations of current AI summarization models, especially for dense scientific material, and point to areas where greater fidelity and detail are needed.

On the other hand, if comprehension is equivalent across modalities, even for technical articles, this would support the integration of AI-generated audio into formal and informal learning routines. AI podcasts could then be leveraged to increase the flexibility with which physicians access and absorb scientific information, without compromising accuracy or depth. Medical educators and institutions might consider systematically producing and offering AI-generated audio summaries of core readings or recent guideline updates, especially for busy clinicians with limited time for traditional study methods.

Beyond comprehension, our secondary outcomes will help evaluate learner motivation and cognitive engagement. If AI podcasts are associated with higher intrinsic motivation or perceived enjoyment, this could be particularly relevant in postgraduate medical training, where learners face high workloads, cognitive fatigue, and declining study motivation. A more engaging modality could contribute to improved study adherence or knowledge retention over time. Even if comprehension is slightly lower in the podcast format, enhanced motivation might still justify its use—especially as a tool for sustained exposure or re-engagement with difficult topics. Conversely, if resident physicians report lower interest or higher cognitive load when listening, this will provide important feedback for educators and tool developers alike.

Limitations

We acknowledge several limitations of our study. First, our findings will be specific to the 2 articles chosen. While we intentionally selected examples of narrative and technical articles, they are only single instances of those categories. Thus, generalizing to all *narrative vs technical* content should be done cautiously. The results might differ with other topics or types of papers. Ideally, a follow-up study with more varied content would strengthen generalizability. Moreover, the expert screening of AI-generated podcasts may be influenced by confirmation bias during transcript editing, suggesting the need for additional studies replicating our findings based on different podcast outputs. Moreover, article identity is confounded with complexity, as only 1 narrative and 1 technical paper were used. This limits external validity and precludes treating article as a random factor. Future studies should include multiple articles per complexity level to strengthen generalizability and allow for modeling article-level variance.

Furthermore, our design does not fully disentangle the effects of learning modality (listening vs reading) from those of content completeness (summary vs full text). The AI-generated podcasts used in this study provide condensed, dialogue-style overviews and do not provide access to the original figures or data tables. In contrast, the reading condition involves the complete article. Consequently, any differences in comprehension could reflect the presentation modality and informational scope. We intentionally opted for this naturalistic comparison because AI-generated summaries are likely to be used as practical alternatives to reading full articles in real-world contexts. Nevertheless, future research should seek to match content more closely across modalities, for instance, by comparing narrated full-text versions with written full texts, or written summaries with audio summaries, and ensuring equitable access to visuals. Such studies would help clarify whether comprehension differences stem primarily from modality or from differences in content coverage and depth.

Finally, our sample of resident physicians preparing for board certification at a single academic medical center in Germany may not be representative of all medical learners. While many of these participants are accustomed to engaging with English-language scientific content and are relatively comfortable with digital tools, their exposure to audio-based learning formats, such as podcasts, varies. The results may differ in other training environments or cultural contexts, particularly where English proficiency is more variable or digital learning is less embedded. The major advantage of this sample lies in its ecological validity and the participants' strong background in internal medicine. This limits the potential variation due to differences in previous knowledge.

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Conclusions

In conclusion, the forthcoming results of our study will help determine whether AI-generated podcast summaries can serve as an effective study method for medical residents and how content complexity influences this. If successful, this could open the door to new learning strategies and tools in medical education, making the vast realm of medical literature more accessible through AI assistance. If challenges are identified, our work will highlight what needs to be addressed, whether improving AI summarization fidelity or guiding students on when to use such tools. Ultimately, this study aligns with the goal of leveraging technology to enhance learning while rigorously testing its efficacy and ensuring that educational innovations are evidence-based.

Data Availability

The datasets generated or analyzed during this study are available in the Open Science Framework repository [20].

Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
CONSORT: Consolidated Standards of Reporting Trials
IMI: Intrinsic Motivation Inventory

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Protocol

Efficacy of Artificial Intelligence–Assisted Appliances in the Selection of Tooth Shade: Protocol for an Observational Study

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Abstract

Background: Accurate shade matching in dentistry is crucial for achieving aesthetic outcomes, with increasing patient expectations driving advancements in shade selection technologies. Color perception is influenced by multiple factors such as incident light, reflection, absorption, observer variability, and environmental conditions. The evolution of shade-matching tools now includes digital and artificial intelligence (Al)-assisted appliances aimed at improving accuracy and ease of use.

Objective: This study aims to compare and evaluate the efficacy of AI-assisted appliances, namely, smartphone cameras, digital single-lens reflex (DSLR) cameras, and intraoral scanners in selecting tooth shades in clinical practice.

Methods: This observational study conducted at the Department of Prosthodontics and Crown & Bridge aims to evaluate shade selection methods in 221 participants recruited from the outpatient department based on specific inclusion and exclusion criteria, including age, oral health status, and informed consent. Three devices will be used for shade selection: a smartphone camera (iPhone 12, iOS 12.5.2) for quick, noninvasive, and accessible image capture; a DSLR camera (Canon EOS 200D) to obtain high-resolution images under standardized lighting for enhanced color accuracy; and an intraoral scanner (CEREC Primescan, Dentsply Sirona) offering precise 3D mapping and digital shade analysis. This multidevice approach allows for a comparative evaluation of conventional and advanced digital tools in clinical shade matching. The primary objective is to assess the effectiveness of commonly available digital teeth in accurately selecting tooth shades. Our study anticipates the following outcomes: validation of smartphone cameras as simple, economical, and efficient tools for basic shade matching; demonstration of DSLR cameras' superiority in resolution and lighting control for improved accuracy; and confirmation of intraoral scanners as precise, customizable devices that offer a high level of digital integration. Statistical analyses will include sensitivity, specificity, and subgroup evaluations to compare the performance of each device. The findings are expected to show that both DSLR and smartphone cameras can match the effectiveness of intraoral scanners, offering viable alternatives for clinical use.

Results: This study was intramurally funded in December 2024. Data collection is scheduled to commence following the publication of this study protocol. As of submission, no participants have been recruited, and data analysis is yet to begin. Results are expected to be completed and published in early January 2026.

Conclusions: This study aims to establish a standard protocol for the use of Al-assisted, easily accessible tools such as smartphones and DSLRs for dental shade selection. These devices, being user-friendly and nontechnical, could democratize the process of shade matching, benefiting both clinicians and patients by improving restoration outcomes while reducing costs and complexity. Our results will contribute to the growing body of digital dentistry literature and support the integration of practical Al tools in everyday clinical practice.

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KEYWORDS

intraoral scanner; vita classic; CEILAB coordinates; smartphone; DSLR camera

Introduction

Aesthetic dentistry has seen a vast demand to meet the requirements of the patients to achieve a perfect smile and is playing a vital role in contemporary dentistry. To ultimately meet the aesthetic requirements, dental restorations must precisely mimic the shade of the teeth [1]. The instruments used for shade matching are constantly evolving in dentistry due to the growing demand from patients for more aesthetic results. Numerous factors can affect the intricate process of color perception, including incident light, light reflection, light absorption, the observer's visual matching, and the object's surroundings [2].

Shade selection is broadly classified into 2 methods, namely, subjective and objective methods. Subjective methods rely on traditional tools such as the conventional Vita Shade Guide System and Vita Classic Shade Guide, while objective methods use advanced instruments, often powered by artificial intelligence (AI), including spectrophotometers, colorimeters, and intraoral scanners [3]. The accuracy of the subjective approaches used to choose shades for the vita shade guide and vita classical shade guide is influenced by the chromatic perception disability. Numerous factors such as the environment of the clinics and the reflection of light contribute to subjective techniques [4].

AI-based systems minimize human error in tooth shade selection, which is often affected by subjective factors such as lighting conditions, visual fatigue, and individual perception [5]. AI algorithms analyze digital images of teeth in real time, ensuring a more consistent and accurate shade selection by comparing them to vast databases of tooth shades. AI technology can be integrated with intraoral scanners, spectrophotometers, and colorimeters to automatically identify and suggest the most accurate shade. AI refines measurements by eliminating inconsistencies, compensating for lighting variations, and ensuring that the most accurate shade is selected based on the collected data [3].

A spectrophotometer is considered the gold standard for this purpose [6]. The spectrophotometer utilizes a 6500K light source to accurately match tooth color and displays the results by using a visual shade guide. Despite certain drawbacks such as the need for costly, nonintuitive, and technique-sensitive equipment, spectrophotometry remains a versatile and highly efficient method for shade matching [6]. However, given its limitations such as cost and limited accessibility in small dental practices, portable alternatives such as colorimeters were introduced to provide a more practical option for shade matching [6].

A colorimeter, which measures an object's spectrum reflectance or transmittance to determine its color attributes, is an alternative for choosing digital shades [7]. They usually use precise light sources and sensors to measure tooth color accurately. To determine how much light is reflected or transmitted onto the tooth, the colorimeter emits light onto it. Utilizing this measurement, the gadget provides numerical values in a given color space, like CIELAB coordinates [8]. However, this technique's drawback is that it may not be as exact at reproducing hues, especially for teeth with complex tones or translucency. Additionally, environmental factors such as illumination can affect colorimeter readings, requiring exact calibration and standardization [8].

Recent advancements in dentistry have led to an increase in the use of intraoral scanners, some of which can produce vivid images and distinguish between soft and hard tissues. Shade color information from intraoral scanners is also based on the visual shade criteria [9]. Additionally, scanners are able to identify tooth color and distinguish between the architecture of teeth and the oral cavity. The cost of the technology is one of the most significant challenges, and only some smaller or wealthier clinics may be able to afford it. The use of digital single-lens reflex (DSLR) and smartphone pictures as AI tools for choosing tooth shades is becoming more popular in modern dentistry as a solution to these problems because of their capacity to integrate sophisticated AI-driven analysis with excellent image capturing. Finding the ideal shade for dental restorations is made easier, more accessible, and more precise by these technologies. DSLR cameras provide high resolution and excellent image quality, making it possible to see the tooth's surface, texture, and translucency in great detail. AI software can subsequently process these photos to more precisely determine the shade. The number of dentists using their smartphones for photography is rapidly increasing due to the complex operation and manipulation of DSLR cameras [10].

However, the accuracy of evaluating the tooth shade by using smartphone cameras may vary based on a number of factors such as lighting and camera quality. The dentist can enhance the image for better shade-matching results by adjusting the camera angle or lighting conditions based on real-time feedback from AI algorithms on smartphones. Nonetheless, it remains a feasible and reachable substitute [11]. In this study, we will compare the efficacy of DSLR and smartphone cameras against that of intraoral scanners for selecting tooth shades. In order to accomplish this, factors such as color accuracy, image quality, and clinical user-friendliness will be assessed. This kind of comparison could help to determine the most effective method for accurately determining the tooth shade in dentistry. Posterior teeth will be included in this study, as they will be included as additional variables to assess the potential differences in shade selection accuracy across tooth types. This may influence the outcomes due to variations in morphology, translucency, and light reflection. Thus, the objective of this study is to evaluate the scope of readily accessible AI-assisted appliances for determining dental shades in aesthetic dentistry.

Methods

Study Design and Participants

This will be an observational study conducted in the Department of Prosthodontics and Crown & Bridge at Sharad Pawar Dental College and Hospital, Sawangi, Wardha, Maharashtra, India.

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The inclusion criteria and exclusion criteria are shown in Textbox 1. To reduce observer bias, the individuals responsible for analyzing and comparing the shade-matching outcomes (based on laboratory values) will be blinded to the device used for capturing the tooth shade (smartphone, DSLR, or intraoral scanner). Each image or scan will be coded and deidentified prior to analysis, ensuring that the evaluators are unaware of the imaging modality. All data will be stored securely and entered into a centralized, password-protected database. Double data entry will be employed for cross-verification, and all files will be time-stamped and logged for traceability.

Textbox 1. Inclusion and exclusion criteria for this study.

Inclusion criteria

- Co-operative patients who are not anxious and are not apprehensive
- Anterior maxillary central incisors will be used
- Patients willing to participate in the study

Exclusion criteria

- Teeth with any abrasion
- Teeth with enamel anomalies
- Adjacent teeth with crown prosthesis
- Teeth with calculus and stains (extrinsic and intrinsic)
- Root canal–treated teeth
- Teeth with restorations
- Fractured tooth (vertical and horizontal)

Data Collection Procedure

A total of 221 participants will be recruited from the outpatient department. To choose their shade, study participants will be exposed to an intraoral scanner, a smartphone, and a DSLR. The study participants will be informed about the study and asked to sign a consent form prior to the procedure. The participants will be instructed to clean their teeth and take off any makeup before the test. The treatment will be performed on the patients' maxillary central incisors by using 3 different technologies: an intraoral scanner, a DSLR, and a smartphone camera.

Shade selection using a smartphone (iPhone 12; software version iOS 12.5.2.) will be performed using natural daylight or daylight-mimicking LED lights that are ideal for accurate color reproduction. The smartphone camera will be positioned parallel to the patient's face at a distance of 30 cm and zoomed in to focus on the teeth of interest, that is, the maxillary central incisors. Photos will be then imported into the Adobe Photoshop software to obtain the L*a*b values.

Photographic color selection will be done using the DSLR camera (Canon EOS 200D) with a macro lens for close-up shots with high detail and resolution. The DSLR camera will be set to manual mode to grant full control over exposure, aperture, and white balance settings, allowing for optimal customization to capture high-quality images for shade selection. The tooth would be placed at a distance of about 22-28 centimeters from the DSLR camera. The L*a*b values will then be acquired by importing the photographs into the Adobe Photoshop software.

For color selection, the Cerec Primescan (Dentsply Sirona) intraoral scanner will be used. The vita classic color selection mode will be activated in the scanner's software. We will scan the maxillary central incisor and note the color that is detected. The L*a*b values will be determined.

Ethical Considerations

This study underwent ethical review and approval by the Datta Meghe Institute of Higher Education and Research institutional review board as per institutional guidelines (approval DMIHER[DU]IEC/2024/241). Informed consent will be obtained from all the participants involved in the study. The participants will be clearly informed about the study's purpose, procedures, potential risks, and benefits, specifically regarding the use of AI-assisted devices for tooth shade selection. Participant data will be anonymized to ensure privacy and confidentiality. Identifying information will not be included in any reports or publications. Strict data security measures, including encryption and secure storage, will be implemented to protect all participant information. Participants will be compensated for their time and involvement in the study with a modest stipend or gift card, the value of which will be specified in the informed consent form. Compensation will be fair and consistent for all participants. Details of the compensation will be clearly communicated prior to participation. No identifiable images of the participants will be included in the paper or supplementary materials. If such images are necessary, explicit consent will have been obtained from the individuals. Relevant consent forms and written communications will be uploaded during resubmission.

Sample Size

The sample size (N) was calculated using the standard formula:

$$N = ((Z_{\alpha/2} + Z_{\beta})^2 \times [P_1(1 - P_1) + P_2(1 - P_2)]) / (P_2 - P_1)^2$$

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$Z_{\alpha/2}$ = 1.96 for a 95% CI, representing the chosen level of statistical significance; Z_{β} = 0.84, which corresponds to 80% power; N represents the minimum number of samples required per group; and primary variable = reliability percentage.

Based on [12], the reliability of smartphone for classic shade determination = 7.7%, and the reliability of DSLR camera for classic shade determination = 15.4%.

Using a 5% level of significance and 80% power, the sample size calculation is as follows.

$$N = (1.96 + 0.84)^2 \times [0.077 (1 - 0.077) + 0.154 (1 - 0.154)] / (0.154 - 0.077)^2$$

This yields a minimum required sample size of 221 participants per group.

Expected Outcome

The primary outcome will be to evaluate if existing digital technologies, that is, DSLR camera and smartphone camera are equally efficient as the intraoral scanner for shade selection. The secondary outcome will be to establish a standardized protocol that ensures accuracy and efficiency of tooth shade selection by using readily available, economical digital devices.

Statistical Analysis

R software (version 4.3; R Foundation for Statistical Computing) will be used to calculate all the results. Descriptive statistics (mean, standard deviation) will be calculated for tooth shade measurements obtained from each method. Intermethod agreement will be evaluated using Bland-Altman plots or intraclass correlation coefficients. Subgroup analyses will be conducted to explore potential factors influencing intermethod agreement (eg, tooth condition, presence of restorations). Sensitivity and specificity analyses will be performed to evaluate the accuracy of smartphone and DSLR cameras compared to that of intraoral scanners by using the latter as the reference standard. Statistical significance will be set at $P<.05$. Additionally, a paired 2-sided *t* test or Wilcoxon signed-rank test will be used to compare the mean shade differences between each pair of methods (intraoral scanner vs smartphone camera, intraoral scanner vs DSLR camera, smartphone camera vs DSLR camera). The effectiveness of a smartphone and DSLR camera in various dental procedures such as examining the existence of restorations or enamel anomalies will be assessed in a subgroup analysis. In this study, we will test statistical assumptions (eg, normality, homoscedasticity) and apply multiple testing corrections (eg, Bonferroni or false discovery rate) to ensure valid inferences. The intraoral scanner will serve as the reference standard for sensitivity and specificity analyses, using $\Delta E \leq 2.0$ as the threshold for clinically acceptable shade matches.

Results

This study was intramurally funded in December 2024. Data collection is scheduled to commence following the publication of this study protocol. As of submission, no participants have been recruited, and data analysis is yet to begin. Results are expected to be completed and published in early January 2026.

Discussion

A smartphone, DSLR camera, and intraoral scanner will be used to capture and match the shade of a patient's teeth. The smartphone offers a simple portable tool for basic shade reference, while the DSLR camera provides high-quality, controlled images for accurate shade matching under standardized lighting. The intraoral scanner creates a detailed 3D map of the teeth, enabling precise, customized shade selection that can be compared with physical shade guides for optimal restoration outcomes. Advancements in digital dentistry, such as colorimeters, intraoral scanners, and computer-aided shade matching systems, have significantly transformed the shade selection process [13]. These technologies have greatly improved treatment outcomes and patient satisfaction by offering greater accuracy, efficacy, and consistency in shade matching. This study focuses on evaluating the efficiency of smartphone cameras and DSLR cameras in the field of tooth shade selection. Our research seeks to determine their utility as alternatives to subjective methods and cost-intensive objective method for shade selection in dentistry. A study conducted by Yung et al [14] compared the color consistency of digital images captured in a clinical setting by using smartphone cameras and single-lens reflex (SLR) cameras. They found that color accuracy is not considerably increased by using a polarizer. An effective substitute would be a smartphone camera that has an external light source attached to it.

Ziadeh et al [15] assessed the repeatability of the intraoral scanner for selecting dental shades in the anterior and posterior regions. They found that the intraoral scanner demonstrated better repeatability in the anterior region when compared to the visual method, and the difference between the two approaches is clinically acceptable. Faezeh et al [12] examined the validity of color selection techniques by using visual assessments, intraoral scanning, and photography (using an SLR camera and a smartphone). By evaluating and contrasting the dependability of the 3 most popular methods of color selection, that is, visual assessment, intraoral scanning, and photography, oral scanners showed more accurate results.

Abu-Hossin et al [16] compared the use of digital techniques for visual shade selection and evaluated the intraoral scanners' reproducibility. They found that while intraoral scanners are a useful addition for color determination, the visual approach should also be used for confirmation. Moussa et al [17] evaluated the measurements in photos taken with a DSLR, intraoral scanner, and smartphone camera at various distances. According to their study, the measurements of the maxillary right incisors using an intraoral scanner, DSLR, and smartphone (at a minimum distance of 24 cm) did not differ. Both the intraoral scanner and the visual method showed color differences in the central and canine regions that were below the perceptibility threshold—implying that the differences were so small that they could not be noticed by the human eye; these findings are consistent with the investigation performed by Mehl et al [18]. Ebeid et al [19] examined 3 intraoral scanners, namely, CEREC Omnicam (Dentsply Sirona), CEREC Primescan, and 3Shape Trio (Copenhagen, Denmark) by using the Vita Easyshade V spectrophotometer as the control. Ten

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distinct shades of Vita Mark II blocks were employed in the investigation. Each piece of equipment measured 10 colors per specimen by using the Vitapan Classical shading technique. The accuracy and repeatability data were obtained. According to their study, the accuracy and repeatability of all the intraoral scanners fell short of expectations. Therefore, the authors recommended using the color detection capability of the intraoral scanners with caution. Rutkunas et al [20] compared the accuracy of the intraoral digital 13 scanner, 3Shape Trios, with that of a spectrophotometer, SpectroShade, as a control, and they found that the Trios' mean accuracy for the Vitapan Classical shade tabs was just 27.5%, whereas that for the Vitapan 3D Master shade tabs was 53.3%. Fattouh et al [21], Gasparik et al [22], and Moussaoui et al [23] compared the accuracy, repeatability, and reproducibility of digital intraoral scanners for shade selection and verified whether intraoral optical scanning devices can be used to determine the color of restorations without requiring additional conventional color-measurement methods and concluded that the intraoral scanner Trios color could be an alternative to other methods for shade selection. Czigola et al [24] evaluated the shade measurement function of a digital scanning system (3Shape Trios 3) in relation to visual shade determination (Vita Classical and Vita Linearguide) and a digital spectrophotometry device (Vita Easyshade). Intraoral scanners proved to be as accurate as spectrophotometers; they could serve as objective and time-efficient tools for shade selection and could be seamlessly integrated into comprehensive patient case documentation, as reported by Vitai et al [25]. Although previous research has compared the accuracy of intraoral scanners and smartphone cameras, our study expands the scope by evaluating all 3 digital technologies together by comparing the smartphone camera, DSLR camera, and intraoral scanner to determine how each performs in tooth shade selection. This allows for a more comprehensive assessment of their relative accuracy and clinical usefulness. This study is an attempt to confirm the use of digital technologies for shade selection; if we obtain positive results, further research is warranted to ascertain its universal applicability.

When comparing the reliability of AI-assisted technologies such as intraoral scanners to that of DSLR and smartphone cameras, it is commonly anticipated that intraoral scanners will exhibit higher reliability. Intraoral scanners are specifically designed for dental applications, providing detailed and accurate images of intraoral structures, including teeth. Their direct intraoral capture minimizes the potential sources of error such as variations in lighting or camera positioning, which can affect the reliability of images obtained by DSLR and smartphone cameras. Additionally, intraoral scanners often incorporate advanced technology and software algorithms tailored for precise shade matching and analysis, further enhancing their reliability in dental practice. Therefore, in the context of tooth shade evaluation, it is expected that intraoral scanners will generally offer higher reliability compared to DSLR and smartphone cameras.

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Data Availability

Data sharing is not applicable to this study as no datasets were generated or analyzed during this study.

Authors' Contributions

NZ, SN, VB, and SG contributed to the concept and design of the study and drafting of the manuscript. All the authors critically revised the manuscript for important intellectual content.

Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
DSLR: digital single-lens reflex
SLR: single-lens reflex

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Efficacy of an Ayurvedic Intervention as an Adjunct to Standard Care in Preventing Acute Pain Crises in Sickle Cell Anemia: Protocol for a Randomized Controlled Trial

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Abstract

Background: Sickle cell anemia (SCA) represents a major health concern among the tribal population of India, with frequent acute pain crises significantly compromising the quality of life of the affected individuals. As an inherited disorder, there is no definitive cure for the condition. Hydroxyurea remains the primary therapeutic option and is typically used for lifelong management, although it may be associated with certain side effects. In light of the pressing need for a safe, accessible, and effective alternative for long-term care, this study is planned to explore the potential of Ayurveda in managing pain crises alongside conventional standard care.

Objective: This study aims to evaluate the efficacy of Ayurvedic intervention in preventing acute pain crises in individuals with SCA and improving their quality of life.

Methods: This study is designed as a randomized, active-controlled, open-label clinical trial. Participants diagnosed with SCA are enrolled in the study according to the selection criteria. The intervention group receives Ayurvedic interventions, namely *dadimadi ghrita* and Ayush-RP, along with standard care, whereas the control group receives standard care only. The intervention is administered over a period of 8 months. Participants are evaluated on the 30th, 60th, 105th, 150th, 195th, and 240th days to assess changes in the frequency of pain crises and quality of life.

Results: This study was initiated on September 5, 2023. Total enrollment of 1510 participants has been completed by screening 1644 participants. As of August 14, 2025, a total of 1137 participants have successfully completed the study, 280 (24.62%) are continuing, and 93 (8.18%) have dropped out.

Conclusions: This study aims to establish the efficacy and safety of Ayurvedic interventions as part of an integrated approach to managing SCA, with a focus on reducing the frequency of pain crises and improving patients' overall quality of life.

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International Registered Report Identifier (IRRID): DERR1-10.2196/76576

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KEYWORDS

hemoglobin; raktavaha srotas dushti; dadimadi ghrita; Ayush-RP; pandu

Introduction

Sickle cell anemia (SCA) is a hereditary condition within the broader group of sickle cell diseases (SCDs). It is one of the most prevalent monogenic disorders worldwide and is particularly common among the tribal populations in India [1,2]. SCA is a disease caused by a mutation in the β-globin gene, leading to the production of abnormal hemoglobin, which binds with other abnormal hemoglobin molecules within the red blood cells (RBCs) to cause rigid deformation of the cell. The

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abnormally shaped RBCs are unable to pass through the small vascular channels, resulting in sludging and congestion within the vascular beds, tissue ischemia, and infarction. The frequent occurrence of infarction in individuals with SCA is a principal cause of the early clinical manifestation, the acute pain crisis, often ascribed to bone marrow infarction [3]. The vaso-occlusive pain episodes frequently affect the limbs; abdomen; ribs; sternum; spine; and, occasionally, the skull, often elicited by illness and accompanied by clinical features such as fatigue, loss of appetite, anemia, jaundice, pneumonia, and recurrent infections. The life expectancy for those with SCA ranges from 42 to 48 years, with 50% of affected children dying before the age of 5 years, primarily due to recurring infections [4].

According to a survey by the Indian Council of Medical Research, the sickle cell gene is present in 5% to 34% of India's various tribal groups due to genetic predisposition [5]. Maharashtra is one of the states in India with a high prevalence of SCA, where the Vidarbha region exhibits a significantly higher prevalence, with 62% of the total cases concentrated in the Nagpur division [6].

While there is no cure for SCA, the quality of life of affected individuals can be improved through adequate management of the disease. Hydroxyurea, a ribonucleotide reductase inhibitor, is currently considered the standard treatment in the management of SCD. It has demonstrated a reduction in painful episodes, acute chest syndrome, and mortality [7]. Folic acid is given as a prophylactic drug in all patients [8]. Blood transfusion also plays a vital role in managing severe complications such as acute chest syndrome, heart failure, stroke, and aplastic crises [9]. In SCA, acute pain typically requires management with opioids and hydration. However, the conventional treatment also has certain side effects. Hydroxyurea is an extremely toxic drug [7] and requires intensive monitoring to prevent side effects such as neutropenia, bone marrow suppression, elevation of hepatic enzymes, anorexia, nausea, vomiting, and infertility [10]. Blood transfusion carries risks such as iron overload and viral transmission, necessitating careful and continuous monitoring [9]. Effective management of pain is also challenging due to difficulty in accurately identifying its underlying cause and concern about opioid addiction [11]. Furthermore, the disease requires lifelong therapy and imposes a significant macroeconomic burden due to severe complications. Hence, there is a need for evaluating newer alternatives for effective and safe long-term management of SCA.

In Ayurveda, hereditary diseases are classified as *adibalapravritta vyadhi*, which refers to disorders originating from the impairment of the sperm or ovum. These conditions are attributed to genetic imbalances inherited from both parents and are considered *asadhya* (incurable). However, integrating the principles of Ayurveda with modern medicine can help reduce the frequency of painful crises and improve the quality of life of the patients. Formulations that enhance the function of the hematopoietic system (*raktavaha srotasa*) and boost the body's vitality and strength may be beneficial in managing the condition [12]. Therefore, this study is planned with an aim to explore other alternatives for reducing pain crises associated with SCA, thereby enhancing the quality of life for affected patients. In a pilot study, Ayush-RP, a coded formulation developed for the management of SCA, demonstrated significant improvements in pain crises and quality of life for participants [13]. *Dadimadi ghrita* is a classical formulation used in the management of *pandu roga* (anemia) [14]. Furthermore, it mitigates the pain and increases the overall strength of the body [15,16]. Hence, both formulations were selected for this study. The primary objective of this study is to evaluate the efficacy of Ayurvedic interventions as an add-on to standard care for the prevention of acute pain crises in SCA. Secondary objectives include evaluating the safety of the Ayurvedic interventions, assessing their effects on various pathological and biochemical parameters, and measuring the quality of life of participants with SCA.

Methods

Study Design

This is a randomized, active-controlled, open-label clinical trial.

Study Setting

Participants are screened at 3 centers: Civil Hospital in the Gadchiroli district; Acharya Vinoba Bhave Rural Hospital, Datta Meghe Institute of Higher Education and Research (DMIHER), Sawangi (Meghe), Wardha district; and Shalinitai Meghe Hospital and Research Centre in Wanadongri, Nagpur, Maharashtra, India. However, enrollment and assessment are conducted only at the latter 2 centers.

Study Participants

Inclusion Criteria

Participants aged 18 to 50 years of any gender diagnosed with SCA confirmed via hemoglobin electrophoresis showing the HbSS pattern are eligible for this study. They must meet the following laboratory criteria: hemoglobin of >6%, platelets of >100,000 per cubic millimeter, serum creatinine of ≤1.5 mg/dL, international normalized ratio of ≤2.0, and partial thromboplastin time of ≤48 seconds. Additionally, participants should be willing to adhere to the study procedures and follow-up schedule and provide written informed consent.

Exclusion Criteria

Individuals are excluded from the study if they have a history of 5 or more hospitalizations for pain in the previous 12 months; require transfusions more frequently than once every 3 months; have a history of bleeding diathesis or a clinically overt stroke within the previous 2 years; are receiving chronic anticoagulation or antiplatelet therapy; have previously undergone a hematopoietic stem cell or solid organ transplant or recent RBC transfusion (within 60 days); have a history of cardiac arrhythmia, acute coronary syndrome, myocardial infarction, or stroke; or have symptomatic congestive heart failure. Individuals with chronic liver disease, alanine transaminase or aspartate transaminase levels exceeding 3 times the upper limit of normal, hypertension (blood pressure of ≥160/100 mm Hg), or clinically significant infections are also excluded. Furthermore, those unable to take oral medications or with malabsorption syndrome, active substance abuse, renal dysfunction (serum creatinine of >1.5 mg/dL for male individuals or >1.1 mg/dL for female individuals), uncontrolled

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pulmonary dysfunction (asthma or chronic obstructive pulmonary disease), or other severe comorbidities are excluded. Individuals with clinical manifestations such as hepatitis, glycated hemoglobin of ≥8%, AIDS or HIV, malignancy, or hyperthyroidism or currently participating in another clinical trial are also ineligible. Women who are planning conception, pregnant, or lactating are excluded, as well as individuals with conditions that the principal investigator deems may pose a risk to study safety or integrity. In addition, those with heterozygous sickle cell trait (AS pattern) or a history of severe sickle cell crises are excluded.

Rationale for Selection Criteria

The age group of 18 to 50 years was selected for this study as the incidence of SCA beyond the age of 50 years is low and the presence of age-related comorbidities in older individuals may introduce variability and potential confounding factors. Additionally, the previously reported maximum life expectancy for individuals with SCA is approximately 47 years [17]. Patients below the age of 18 years were not included in this study as they are considered a vulnerable population.

Withdrawal Criteria

Withdrawal from the study may occur if the participants choose to leave, if their condition deteriorates, or if they develop any health conditions listed in the exclusion criteria during the study. Participants who withdraw undergo a final examination if possible. In cases in which a participant leaves against medical advice, a final telephone interview is conducted to assess their health status. The reasons for withdrawal are documented in the case report forms (CRFs).

Study Intervention

Participants in both groups receive standard care, which includes folic acid tablets of 400 mcg once daily after meals and hydroxyurea tablets of 500 mg once daily after meals in accordance with operational guidelines for the management of SCA [18]. In addition to standard care, participants in the intervention group are administered *dadimadi ghrita* [19] at a dosage of 12 grams twice daily before meals with lukewarm water and a tablet of Ayush-RP at a dosage of 500 mg twice daily after meals with lukewarm water. In both groups, each medication is administered orally for a duration of 8 months.

The interventional drug *dadimadi ghrita* is procured from a good manufacturing practices–certified manufacturer—Indian Medicines Pharmaceutical Corporation Limited. The other interventional drug, Ayush-RP, is procured from the Ayurveda pharmacy of the Central Ayurveda Research Institute, Jhansi, Uttar Pradesh, India. Both interventional drugs are prepared in accordance with the standards outlined in the Ayurvedic Formulary of India. The quality and safety parameters of *dadimadi ghrita* have been validated as per Ayurvedic Pharmacopoeia of India standards.

Drug Compliance

Drug compliance forms are issued to the enrolled participants on each visit. Participants with a compliance of 80% or more continue in the study. Compliance is assessed at every visit by evaluating the approximate quantity of the interventional drugs consumed, confirmed with the quantity remaining in returned containers.

Outcome Measures

The primary outcome of the study is a change in the incidence or frequency of sickle cell–related pain crises.

Secondary outcomes include changes in complete blood count, hemoglobin levels, hemoglobin variants (HbS, HbF, and HbA), lactate dehydrogenase, indirect bilirubin, free haptoglobin, potassium, and the C-reactive protein inflammatory marker. Secondary outcomes will also assess changes in the intensity of pain (measured via the visual analog scale), frequency of bleeding episodes, frequency of blood transfusions, hospital admissions and duration of stay, the incidence and severity of adverse events (AEs), and analgesic or opioid use. Changes in fatigue, measured using the Modified Fatigue Impact Scale, and quality of life, assessed using the 12-Item Short Form Health Survey, will also be evaluated in this study.

Safety Outcomes

The safety of the study intervention is evaluated by recording the incidence of AEs, serious AEs, or adverse drug reactions on every scheduled visit. All AEs during the study timeline, if they occur, are recorded and monitored as per the good clinical practice guidelines. The safety assessment is conducted through hematological and biochemical tests, as mentioned previously.

Duration and Timeline of the Study: 36 Months

The preparatory period comprises 6 months for engagement of project staff, finalization of CRFs, procurement of interventional drugs and insurance, preparation of the investigators' brochure, and investigator training, among other aspects. The enrollment period comprises 16 months, and assessment of participants will be conducted on the 30th, 60th, 105th, 150th, 195th, and 240th days. The intervention will last for 8 months. Statistical analysis and preparation of the technical report and manuscript will last for 6 months.

Study Procedure

Overview

The participants diagnosed with SCA are enrolled based on the selection criteria from the respective outpatient departments of the centers. To ensure adequate participant enrollment and achieve the target sample size, patients visiting the outpatient departments of hospitals at each site will be screened. Additionally, data will be collected through nongovernmental organizations, government hospitals, and specially organized camps. Participants are evaluated for demographic details and medical history at baseline and are provided with the study drugs at each subsequent visit (30th, 60th, 105th, 150th, 195th, and 240th days). During the visits, participants are assessed for primary and secondary outcomes. The hematological tests, namely complete blood count, erythrocyte sedimentation rate, bleeding time, clotting time, prothrombin time or international normalized ratio, free haptoglobin, peripheral smear, and complete electrophoresis, along with the biochemical tests, namely fasting blood sugar levels, glycated hemoglobin, liver function test, renal function test, C-reactive protein, and routine urine examination, are conducted at baseline and on the 60th,

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150th, and 240th days. Radiological tests (electrocardiogram and ultrasonography) are conducted at baseline and the 240th day. For each visit, a window of 7 days from the scheduled date is allowed to minimize dropouts due to unavoidable circumstances. The participants are instructed to immediately inform if they encounter any adverse reaction or event throughout the study (Figure 1 and Table 1).

Figure 1. Study flow diagram.

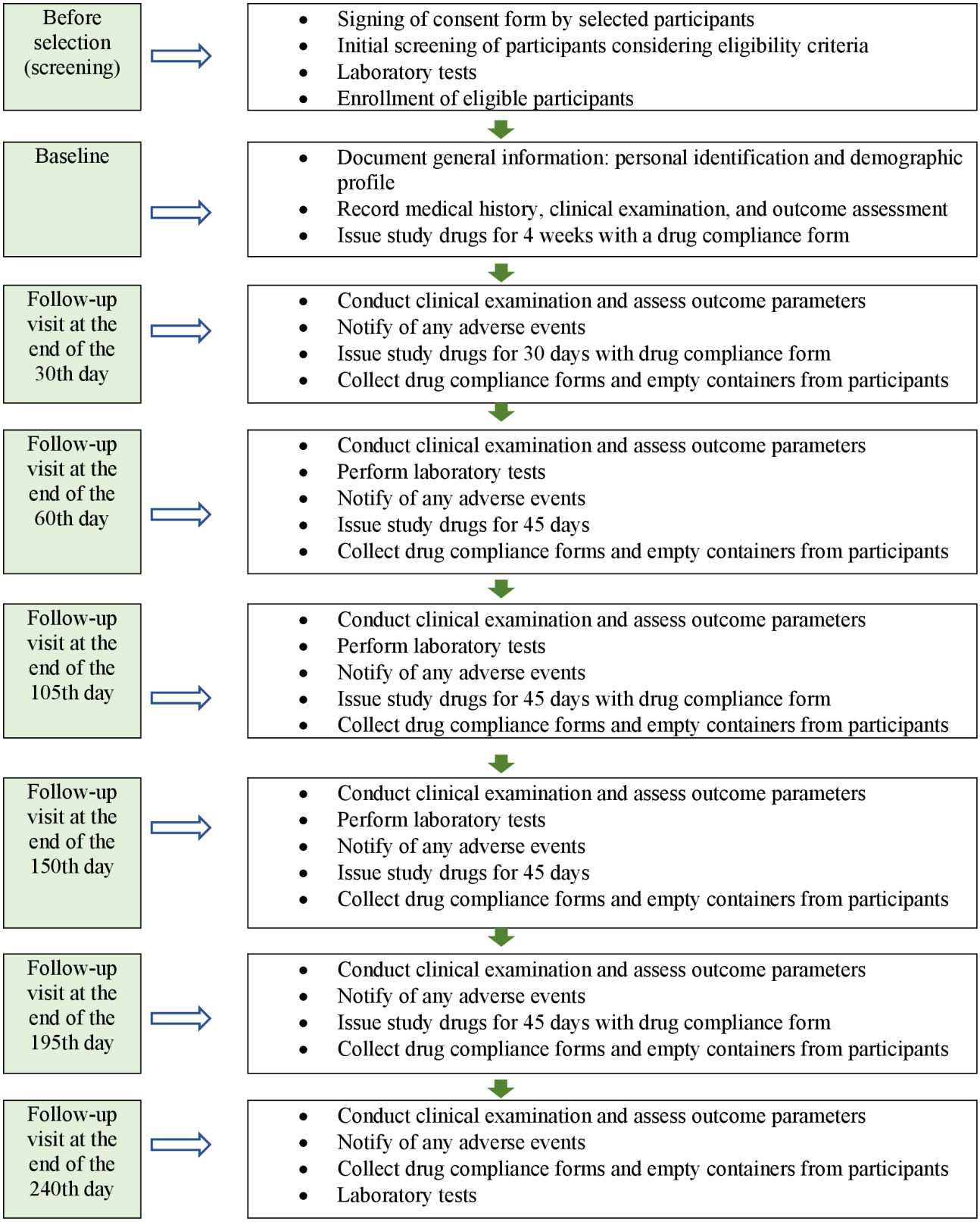

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Table . Study schedule.

	Screening	Baseline	End of the 30th day	End of the 60th day	End of the 105th day	End of the 150th day	End of the 195th day	End of the 240th day
Informed consent	✔							
Demographics and medical history	✔	✔	✔	✔	✔	✔	✔	✔
Laboratory tests	✔			✔		✔		✔
Clinical examination	✔	✔	✔	✔	✔	✔	✔	✔
Assessment of ADRs[a]			✔	✔	✔	✔	✔	✔
Assessment of drug compliance			✔	✔	✔	✔	✔	✔
Issue of trial drugs at every visit		✔	✔	✔	✔	✔	✔	

[a]ADR: adverse drug reaction.

Participant Selection and Blood Sample Collection

Blood samples will be collected by the participating centers as follows:

- For the Wardha division, samples will be obtained from the Sickle Cell Unit, Acharya Vinoba Bhave Rural Hospital, DMIHER, Wardha.
- For the Gadchiroli division, samples will be collected from patients identified in the list provided by the Gadchiroli district health office.
- Similarly, for the Nagpur division, patients listed by the Nagpur district health office will serve as the reference for sample collection.

All blood samples collected from these divisions will be transported to the Central Research Laboratory at DMIHER, Wardha, following the prescribed guidelines.

Blood Sampling Schedule

Participants' blood samples will be collected at 4 time points: during screening and subsequently on the 60th, 150th, and 240th days.

Sample Size

Considering the primary outcome of this study as change in the incidence of sickle cell–related pain crises, the sample size is 1510, with 755 (50%) participants in each group (Textbox 1).

Textbox 1. Justification for sample size calculation.

- Level of significance (α): .05
- Z1-α (type 1 error): 1.64
- Power of test (1 – β): 0.80
- Z1-β (type 2 error): 0.84
- P1 (Expected proportion in control group): 35.4% (0.354)
- True proportion difference between the 2 groups in the sickle cell population (ε): 5% (0.05)
- P2 (Expected proportion in experimental group): 40.4% (0.404; assumed)
- Clinically acceptable for superiority (δ) single tail: 11.5% (0.115; expected)
- Sample size: 1367
- Dropout rate: 10%
- Total sample size: approximately 1504 to 1510
- Final sample size for each group: sample size calculation for superiority (parallel design) using the proportion difference when the end point is qualitative via the formula, $n=2\times(Z1-\alpha+Z1-\beta)2(P1(1-P1)+P2(1-P2))(\varepsilon-\delta)2$

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Randomization and Allocation Concealment

Participants are randomly assigned to either the intervention or control group at a ratio of 1:1 according to a prespecified randomization scheme prepared using a computerized system. To prevent selection bias, the randomization sequence is concealed using the sequentially numbered opaque sealed envelope method. Following the baseline assessment, an envelope with the slip containing the details of the allocated group is opened by the participants in front of the principal co-investigator. The participants are then assigned to the designated groups.

Blinding

This study was conducted as an open-label trial, and no blinding was implemented. As preparing a placebo for one of the interventions, *dadimadi ghrita*, was not feasible, blinding was not planned.

Data Collection

All data related to this study are being properly documented in both the CRFs and electronic format. Investigators and project staff at the participating centers have undergone training to ensure standardized data collection procedures. All source documents supporting the entries in the CRFs are kept readily accessible. These documents are securely stored at the study centers. The records and data collected during the study are stored in password-protected folders on secure computers and external storage devices, with access restricted only to the investigator.

Concomitant and Rescue Medication

All participants are properly counseled not to take any medications other than the study drugs without prior consultation with the investigators. Concomitant therapy is continued for conditions such as diabetes mellitus, hypertension, or any other illnesses that are not listed in the exclusion criteria. Investigators may prescribe additional medications as needed to ensure reasonable supportive care during the study period. Details of all such interventions are recorded in each participant's CRF. Any administration of rescue medication in the event of a medical emergency is also documented in the CRF. Participants are advised to report any new symptoms, unusual occurrences, or health concerns to the investigator immediately.

Statistical Analysis Plan

The statistical analysis will be conducted after data collection, with a verification of their accuracy and limitations. Categorical variables will be presented as numbers and percentages, and pre- and posttrial comparisons will be analyzed using the McNemar chi-square test or Cochran *Q* test. Continuous variables such as scores and laboratory parameters will be assessed using the paired or unpaired 2-tailed *t* test if the data follow a normal distribution or the Wilcoxon test if the data are nonnormally distributed. For analysis of assessment parameters across multiple follow-ups, the repeated measures will be analyzed using ANOVA for normally distributed data or the Friedman test or Cochran *Q* test for nonnormally distributed or categorical data. Data with a normal distribution will be reported as means and SDs, and nonnormally distributed data will be presented as medians with IQRs. A 5% level of significance ($P<.05$) will be applied throughout the analysis, and the SPSS software (version 29.0; IBM Corp) will be used to conduct all statistical tests.

Data Monitoring

The committee responsible for monitoring the study systematically evaluates its progress through scheduled review meetings and site visits as necessary to ensure rigorous adherence to the study protocol, as well as the completeness, accuracy, and consistency of the data. Additionally, the committee ensures compliance with relevant local regulations pertaining to the conduct of clinical research. An interim analysis will be conducted upon completion of the intervention period for at least 25% of the participants.

Study Drug Management and Accountability

The study drugs are securely stored under the supervision of the investigators. Detailed records of the dispensed study drugs are maintained to prevent any discrepancies between the quantity dispensed and the amount remaining or returned.

Ethical Considerations

Overview

This study is being conducted in accordance with the ethical principles outlined in the Declaration of Helsinki for biomedical research and the Indian Council of Medical Research Ethical Guidelines for Biomedical Research on Human Participants (2006), which are consistent with the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use guideline for good clinical practice [20]. Recruitment started after obtaining approval from the institutional ethics committee and registration in the Clinical Trials Registry–India (Ctri/2023/04/052141).

Protocol Amendment

Any deviations from the study protocol will be implemented after obtaining prior approval from the institutional ethics committee.

Informed Consent

Written informed consent is obtained from all participants, with the benefits and limitations of the study clearly outlined in the consent forms and explained to participants by the investigators or senior research fellow before the commencement of the study.

Confidentiality

All participant information, including laboratory test results, is securely stored. Blood samples and study records are identified using a unique base ID. Documents containing personal identifying information are stored separately in a secure location. In addition to the study team, only authorized personnel have access to participant records for study monitoring purposes.

Results

This study was initiated on September 5, 2023. Total enrollment of 1510 participants (n=755, 50% in each group) has been completed by screening 1644 participants. As of August 14, 2025, a total of 1137 participants had successfully completed

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the study, 280 (24.62%) are continuing, and 93 (8.18%) have dropped out (n=48, 51.61% in the intervention group and n=45, 48.39% in the control group).

Discussion

Expected Findings

In Ayurveda, disease management focuses on understanding the pathogenesis of the condition. SCA can be explained in terms of *raktavaha srotas dushti*, which refers to the imbalance or dysfunction of the hematopoietic system. In some studies, it has been correlated with *sannipataja pandu roga* (advanced or multifactorial condition of anemia leading to complex blood disorders with systemic symptoms) [21,22]. The *yakrita* (liver), *pleeha* (spleen), and *amashaya* (stomach) are the sites involved in the transformation of the *rasa* (essence of the digestive food elements) into *rakta* (blood) with the help of *ranjaka pitta* [23] (intrinsic factor responsible for erythropoiesis), a predominant factor for the formation of *rakta* [24]. The *beejadushti* [25] (genetic mutation) may cause altered development and functioning of the *raktavaha srotas* as well as *ranjaka pitta*, thereby hampering the proper formation of *rakta dhatu* (vitiation of blood). The depletion is accompanied by imbalances in other *dhatus* (body tissues), aggravating *vata dosha* (body humor) [26]. The clinical features of *raktavha srotas dushti* comprise *jeerna jwara* (chronic fever), *yakritodara* (hepatomegaly), and *plihodara* (splenomegaly), among others [27]. The pathology in *raktavaha srotas* can lead to several diseases, including *raktapitta* [28] (bleeding disorder), which may be associated with SCD. It subsequently results in complications such as *raktakshaya* (deficiency of blood), identified through *sirashaithilya* (deformity of blood vessels) and manifestations in the appearance of the skin [29].

In SCA, the pathogenesis is caused by a hemoglobinopathy that leads to the sickling of RBCs. Due to increased oxidative stress and production of reactive oxygen species [30], it further leads to endothelial dysfunction, cell adhesion, vaso-occlusion, and hemolysis. The resultant tissue ischemia and infarction are responsible for the acute systemic painful vaso-occlusive crisis [31] and anemia as the extent of compensatory increased RBC production is insufficient to balance the increased rate of destruction [32]. Consequently, it affects systemic organs such as the liver, spleen, kidneys, and lungs and causes neurological, cardiovascular, renal, and urological complications [33].

There are various drugs in Ayurveda for the management of *raktadushti* (vitiation of blood), among which *dadimadi ghrita* was selected in this study due to its *rakta vardhana* (increases blood) and *balavardhaka* (increases strength) action [34]. The formulation is based on ghee, which itself has properties such as *brumhana* (nourishing or promoting growth) and *pushtikara* (providing strength or vitality), aiding in pacifying *vata dosha* [35]. It contains potent ingredients such as *chitraka* (*Plumbago zeylanica*), *dhanyaka* (*Coriandrum sativum*), *shunthi* (*Zingiber officinale*), and *pippali* (*Piper longum*), which are known for their *deepana* and *pachana* properties [36,37]. These ingredients support the elimination of *ama* (toxic metabolic waste), thereby aiding in detoxification through their *pachana* properties. By enhancing digestive efficiency, the formulation promotes better assimilation of nutrients and supports *dhatuposhana*—the nourishment of bodily tissues—while helping regulate imbalanced *doshas* and improve overall metabolic function [38]. Furthermore, the antioxidant properties of *dadima* (*Punica granatum*), *dhanyaka* (*C sativum*), and *shunthi* (*Z officinale*) may help mitigate oxidative stress, which is especially relevant in conditions such as SCA, potentially aiding in the prevention and management of related complications [39-41].

The other interventional drug, Ayush-RP, is a coded drug developed by the Central Council for Research in Ayurvedic Sciences. According to a pilot study conducted previously on different tribal populations residing in Maharashtra, Ayush-RP showed significant improvements in pain crisis episodes and quality of life for participants diagnosed with SCA [13]. The ingredients have *raktaprasadan karma* [42], an action that improves blood quality by restoring balance to the dysregulated *pitta dosha*, eliminating vitiated factors, and modulating the components of the blood. This may help alleviate *raktadushti* and further facilitate the free circulation of blood. The action of the constituents, such as *lekhana karma* (scrapping of unwanted tissues), helps in the elimination of *sanga-srotodushti* (obstruction in minute channels of the tissues). Consequently, it may reduce vaso-occlusion and further mitigate painful crises. Additionally, the *shonitasthapana* action may regulate hemolysis and enhance blood volume. *Ruksha*, *sheeta guna*, *tikta-kashaya rasa*, *madhura vipaka*, and *sheeta veerya* in the formulation pacify *tridosha* (all 3 body humors) and *raktadushti*, and its ingredients are specifically mentioned in Ayurveda texts for managing *rakta vikara* (blood disorders), particularly *raktapitta*. In addition, the components support *dhatuposhana*, which may improve the overall strength and vitality of the body. The formulation comprises nanoactive particles that increase the bioavailability of the compound, assisting in better absorption and assimilation. The ingredients of the formulation have antipyretic, analgesic, anti-inflammatory, immunomodulatory, antioxidant, and hepatoprotective properties and are considered to elevate hemoglobin levels as per pharmacognostical, preclinical, and clinical studies.

Hydroxyurea is the primary drug in the management of SCA and is currently the most effective disease-modifying therapy for individuals with SCA, reducing the production of rapidly dividing cells, including those involved in the inflammatory processes in SCD. It increases the production of fetal hemoglobin (HbF), which helps reduce sickling of RBCs and the frequency of painful episodes. It also increases overall hemoglobin levels, improving oxygen delivery and reducing the severity of symptoms [43]. In SCA, increased erythropoiesis often occurs as the body attempts to compensate for the rapid turnover of sickled RBCs. This heightened demand for new RBCs results in a greater need for folic acid, a crucial vitamin involved in DNA synthesis and cell division. For this reason, folic acid is prophylactically recommended in standard care [44].

Overall, these interventions, when applied in an integrated approach, are expected to mitigate vaso-occlusion, reduce oxidative stress and inflammation, limit the extent of hemolysis and organ damage, and decrease the frequency of pain crises and the need for blood transfusions. Collectively, these effects

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contribute to an improved quality of life in individuals living with SCD.

Strengths and Limitations of This Study

A key strength of this study is its rigorous design as a randomized active-controlled trial, which enhances the reliability of the findings. Additionally, the innovative integration of standard care with Ayurvedic interventions offers a holistic approach that may provide therapeutic benefits in the management of SCA. However, this integrated approach presents challenges in isolating the specific effects of the Ayurvedic component, making it difficult to determine its independent contribution to the overall outcome.

Future Scope

A future randomized controlled trial could be designed to compare the efficacy of Ayurvedic interventions versus the standard therapeutic care in the management of SCA, facilitating a precise evaluation of the effectiveness of each approach.

Conclusions

SCA, being a hereditary condition, is currently devoid of a definitive treatment through either conventional or traditional methods and is instead prevented and managed symptomatically.

This study may contribute to establishing the efficacy of Ayurvedic interventions as an integrated approach to managing SCA, aiming to reduce the frequency of pain crises and enhance patients' overall quality of life.

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Conflicts of Interest

None declared.

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Abbreviations

AE: adverse event
CRF: case report form
DMIHER: Datta Meghe Institute of Higher Education and Research
RBC: red blood cell
SCA: sickle cell anemia
SCD: sickle cell disease

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A Primary Care Program Based on Behavioral Reeducation and Abdominal Massage for Improving the Symptoms of Chronic Constipation: Protocol for a Randomized Controlled Trial

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Abstract

Background: Chronic constipation is a prevalent and often underestimated gastrointestinal disorder that significantly affects quality of life, particularly among women and older adults. In Spain, it is estimated to affect between 12% and 20% of the population, contributing to increased health care visits, economic costs, and medication dependency. Although pharmacological treatments such as laxatives are widely used, they often offer only temporary relief and may lead to adverse effects or dependency. There is growing interest in nonpharmacological interventions that address the root behavioral and functional causes of constipation, such as dietary habits, physical inactivity, and impaired defecation techniques. However, evidence regarding the effectiveness of such approaches, especially within a primary care setting, remains limited.

Objective: This study aims to evaluate the effectiveness of a primary care–based structured rehabilitation program that combines behavioral reeducation and abdominal massage therapy in reducing the severity of chronic constipation and use of laxatives. A secondary aim is to assess improvements in quality of life and sustainability of effects over time.

Methods: This is a randomized controlled trial involving adults aged 18 to 75 years from the counties of l'Anoia and Bages (Catalonia, Spain) who meet the Rome IV diagnostic criteria for chronic constipation. A total of 45 participants will be randomly assigned in a 1:1:1 ratio (approximately 22 - 23 per center, with 15 per group overall) into 3 groups: a control group, behavioral intervention (BI) group, and behavioral intervention and massage (BIM) group. All participants will complete baseline assessments that include the Rome IV criteria, the Bristol Stool Form Scale, the CVE-20 quality of life questionnaire, and the International Physical Activity Questionnaire. The BI group will receive 2 group education sessions, focused on healthy bowel habits, diet, hydration, physical activity, stress management, and medication use, delivered by a multidisciplinary team. The BIM group will receive the same intervention as the BI group, plus two 30-minute sessions with a physiotherapist to learn abdominal self-massage techniques. The control group will receive usual care. Follow-up assessments will occur at 3 and 6 months after the intervention using the same instruments and a self-recorded calendar of laxative use and massage application. Data will be analyzed using appropriate statistical tests, including the χ^2 test, a 2-tailed *t* test, and ANOVA/Kruskal-Wallis tests, depending on variable type.

Results: Participant enrollment concluded in August 2025, and data collection is ongoing and expected to continue until April 2026.

Conclusions: This trial will provide evidence on the efficacy of conservative, low-risk interventions for managing chronic constipation in primary care. The findings may support broader implementation of integrative approaches that reduce pharmacological dependence and enhance patient empowerment, with potential public health and economic benefits.

Trial Registration: ClinicalTrials.gov NCT06359249; https://clinicaltrials.gov/study/NCT06359249

International Registered Report Identifier (IRRID): DERR1-10.2196/72018

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(JMIR Res Protoc 2025;14:e72018) doi:10.2196/72018

KEYWORDS

primary health care; proctologic disease; pelvic floor disorders; physical therapy; health education

Introduction

Constipation is characterized by difficult or infrequent passage of stool, often accompanied by straining, pain, or a feeling of incomplete evacuation. It is one of the most common digestive problems in today's society and contributes significantly to decreased quality of life, increased medical visits, and high costs to the health care system [1].

Constipation may be acute, usually lasting less than 6 weeks, or chronic, lasting more than 3 months. Most often, chronic constipation is the result of a primary disorder, that is, one caused by dietary factors (such as insufficient fiber intake), lifestyle factors (lack of mobility or a sedentary lifestyle), or a disorder causing deficient colonic propulsion or rectal emptying [2].

The prevalence of constipation differs across countries due to varying lifestyles and diet. On a global scale, it is between 10% and 15% [3]. According to the American Gastroenterological Association, the prevalence in the United States is approximately 16% in adults and 33% in people older than 60 years [4]. In Europe, it varies between 8% and 26% [5]. In East Asia, it has been reported that in China the prevalence of this pathology is 8.5% [6]. In the African pediatric population, it is 31.4% [7], with no data for the adult population. There is a lack of prevalence studies in South America, West Asia, and Africa.

The Fundación Española del Aparato Digestivo (Spanish Foundation of the Digestive System) estimates that constipation affects between 12% and 20% of the Spanish population [8]. On the other hand, Navarro-Ruiz et al [9], in a study conducted in the primary care setting in 2015, stated that it varied between 16% and 33% of the population.

An analysis of prevalence based on factors such as gender, age, physical activity level, and medication use in the population shows that constipation tends to be more frequent in women (at a 2:1 ratio), older people, people with low physical activity levels, and people taking medications with digestive side effects (eg, opioids, anticholinergics, and calcium channel blockers) [2-5,8-10]. Therefore, this condition is expected to increase in the coming years due to the prevalence of sedentary lifestyles and aging populations, especially in developed countries.

The diagnostic criteria for chronic constipation are the Rome IV criteria, shown in Textbox 1 [11]. Criteria must have been met for at least the last 3 months and symptoms must have started at least 6 months prior to diagnosis.

Textbox 1. Rome IV criteria for constipation.

1. Two or more of the following criteria are met:
   - Excessive straining in at least 25% of bowel movements
   - Hard stools in at least 25% of the stools (Bristol type 1-2)
   - Sensation of incomplete evacuation in at least 25% of bowel movements
   - Sensation of anorectal obstruction or blockage in at least 25% of bowel movements
   - Less than 3 complete spontaneous bowel movements per week
2. The presence of liquid stool is rare without the use of laxatives.
3. Criteria are not met for the diagnosis of irritable bowel syndrome.

Acute constipation rarely causes complications or long-term health problems. Treatment is usually effective, especially if started promptly. However, long-term, chronic constipation is likely to pose a higher risk of complications [12] such as fecal incontinence [13], hemorrhoids (4%) [14], anal fissure (7.8%) [14], organ prolapse [15], fecal impaction [16] or stercoral perforation [17,18].

The current treatments available for this condition are limited: lifestyle modification, medication, and surgical intervention when the condition is severe [19-23]. Laxative treatment is effective, but there are often relapses after withdrawal, causing dependence in some patients. In addition, there are side effects such as electrolyte disorders, dehydration, and intestinal cramps [24]. Therefore, this condition calls for new multidisciplinary and conservative strategies, especially within primary care, that are accessible, low-risk, and empower patients in self-care.

There is growing evidence that abdominal massage can stimulate colonic motility, reduce transit time, and promote defecation through mechanical and neurophysiological mechanisms involving the enteric nervous system and visceral reflexes [25,26]. Behavioral reeducation, including guidance on bowel habits, posture, and toileting routines, has also been shown to improve constipation outcomes by targeting dysfunctional defecation behaviors and increasing patient awareness and adherence to lifestyle recommendations [27]. These approaches align with biopsychosocial models of gastrointestinal dysfunction, emphasizing nonpharmacological, patient-empowering strategies.

The primary objective of this study is to evaluate the effectiveness of a structured rehabilitation program based on behavioral reeducation and abdominal massage therapy in reducing the prevalence of chronic constipation and the use of

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laxatives at 3, 6, and 12 months after the intervention. The secondary objectives are to assess changes in quality of life among participants and to evaluate whether the observed effects are sustained over time.

Methods

This protocol has been developed and drafted in accordance with the recommendations of the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guide [28].

Design: Randomized Controlled Trial

This will be a randomized controlled trial with 3 groups: a control group, a behavioral intervention (BI) group, and a behavioral intervention and massage (BIM) group. The same number of people will be randomly distributed in each group with a 1:1:1 allocation ratio, so that the 3 groups are homogeneous for age, sex, and constipation characteristics. Data collection will be between 2024 and 2026.

Scope: Primary Care

The choice of primary care as the study setting reflects its central role in the early management and long-term monitoring of chronic constipation. This environment ensures high feasibility, as the intervention can be delivered using existing staff—nurses, physiotherapists, general practitioners, and nutritionists—and infrastructure, requiring minimal additional resources. Moreover, the intervention is designed to be easily integrated into routine care pathways, aligning with preventive care goals and enhancing patient self-management strategies within the primary care framework.

Population

This study will recruit patients aged 18 to 75 years assigned to the primary care centers of the counties of l'Anoia and Bages in Catalonia, Spain.

The inclusion criteria are having been diagnosed with primary constipation using the Rome IV criteria [11] lasting for more than 3 months and understanding Catalan, Spanish, or English.

The exclusion criteria are having constipation secondary to neurogenic, metabolic, endocrine, or postoperative diseases; having constipation secondary to medication for other pathologies, the medication list for which can be found in Multimedia Appendix 1; having any type of open abdominal and/or anal wound, such as a recent abdominal scar or anal fissure; meeting any absolute contraindication criteria for the use of abdominal massage therapy, such as an unstable fracture requiring absolute rest and immobilization, pregnancy, or active oncological procedures, and having a cognitive, psychiatric, or neurological condition that, in the clinical judgment of the health care professional, significantly limits the individual's capacity to provide informed consent or to participate meaningfully in the intervention and data collection procedures.

Sample and Randomization

Calculations were based on published evidence suggesting that approximately 90% of patients in the control group would remain constipated at 3 months. We hypothesized that this proportion would decrease to 40% in the intervention groups (BI and BIM), corresponding to a 50% absolute difference. To detect this difference with 80% power and a 2-sided significance level of 5%, while allowing for a 10% dropout rate, 15 participants per group are required. With 3 groups, the total sample size will therefore be 45 participants in total. Recruitment will take place across the 2 participating centers (Anoia and Bages), with approximately 7 to 8 participants per group expected to be recruited at each center.

The sample will be selected (1) by means of a medical history review by nursing or medical personnel; if the health professional considers that the patient meets the criteria, they will refer the patient to the research physiotherapist; and (2) indirectly, by putting up posters in *casals cívics* (civic facilities) and pharmacies in the city. Anyone learning about the study this way can make an appointment with their health professional of reference (ie, nursing or medical staff) and discuss their interest in participating in the study. If the health care professional confirms that the patient meets the criteria, they will refer the patient to the research physiotherapist.

The randomization and allocation of patients will be performed by simple randomization using the specialized software RStudio (version 4.2.1; R Foundation for Statistical Computing). The distribution is expected to be homogeneous between groups. Randomization will be conducted by an independent researcher, and allocation will be concealed using sequentially numbered, opaque, sealed envelopes prepared in advance. This procedure ensures allocation concealment and minimizes selection bias.

The chosen sample size is based on feasibility and resource availability and is sufficient to detect large effect sizes. This study aims to assess the feasibility and potential impact of the intervention and to provide effect size estimates to guide future large-scale trials.

The research physiotherapist will inform the participants of the whole process and ask for informed consent, so that they can be randomized into the 3 study groups and their data can be included in the study database for later analysis. Participants will be informed that if the expected results are obtained, they will be offered the same treatment as the intervention group that obtained the best results.

Intervention

BI Group

The behavioral education sessions are structured into two 60-minute workshops delivered in a progressive format. Session 1 focuses on understanding the physiology of defecation, the Rome IV diagnostic criteria, and bowel habits. Session 2 addresses lifestyle-related components, including dietary fiber and hydration guidelines, physical activity recommendations, stress management, optimal defecation posture, and the rational use of laxatives. The sessions are delivered by a multidisciplinary team (nurse, physician, physiotherapist, nutritionist, and psychologist) using multimedia presentations and printed handouts. Participants are encouraged to set personal bowel health goals. Questions and doubts raised during the first session will be discussed and resolved in the second session, ensuring continuity of learning and participant engagement.

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The Bristol scale, Rome IV criteria, CVE-20 quality of life questionnaire, and International Physical Activity Questionnaire (IPAQ) [11,29-31] will be explained, and a calendar will be given to the patients to mark when they take any laxatives. Once the information sessions are complete, follow-ups will be scheduled 3 and 6 months later.

BIM Group

The BIM group will receive the same intervention as the BI group, and the group will also participate in two 30-minute sessions with the physiotherapist to learn how to perform abdominal massage. In these sessions, the technique will be explained and an explanatory leaflet will be given to the participants so that they can do the massage independently at home.

The abdominal massage protocol follows a standardized clockwise technique that mirrors the path of the colon. The massage begins in the right lower quadrant (ascending colon), progresses to the upper abdomen (transverse colon), and concludes in the left lower quadrant (descending colon). Techniques include gentle effleurage, deep circular kneading, and vibration movements, applied in a slow, consistent rhythm. Each session lasts approximately 30 minutes. Participants are instructed to perform the massage once daily, preferably 20 to 30 minutes after a main meal, in a supine position with knees slightly flexed. The physiotherapist demonstrates the technique and provides a printed visual guide for home practice. The therapist will verify that participants have correctly learned the abdominal massage technique and are able to perform it independently.

To support adherence to the abdominal massage protocol, participants will be provided with a daily self-recording calendar to note each time they perform the massage at home. This calendar will be reviewed at follow-up visits. In addition, weekly SMS reminders will be sent to participants in the BIM group, encouraging them to maintain the daily routine and reinforcing key points of the technique.

Once these sessions are finished, follow-up sessions will be scheduled at 3 and 6 months. Participants will complete the questionnaires again and return the calendar, with marks showing when laxatives were used and massages performed.

Control Group

The control group will receive the usual care in their primary care center and will be asked to complete the Bristol scale, Rome IV criteria, CVE-20 quality of life questionnaire, and IPAQ [11,29,30] at the beginning of the study and after 3, 6, and 12 months. They will also be given the calendar to mark when they take laxatives. This calendar will be collected after 3 months.

Access to Usual Care

All participants in the study, including those in the BI and BIM groups, will continue to have access to usual care throughout the study period. Usual care refers to the standard clinical management offered by primary care physicians and nurses, which may include dietary advice, physical activity counseling, laxative prescriptions, or follow-up visits, depending on individual needs and clinical judgment. No restrictions are placed on access to routine health care.

Ethical Considerations

The study was designed in accordance with the principles of the World Medical Association Declaration of Helsinki, as amended in 2013, and applicable regulations. The protocol was approved by the ethics committee of Jordi Gol Primary Care Research Institute (Barcelona, January 22, 2024; code 23/253-P).

The data controller and processor will be the Catalan Institute of Health. The database will be stored for a period of 10 years. The data obtained will not be disclosed to third parties by the research team. International transfers are not provided for. Security mechanisms are sufficient to prevent breaches of confidentiality.

Participants will be informed of the objectives and general aspects of this study and will be asked for informed consent. The informed consent form will specifically include the voluntary nature of participation, security measures, and the confidentiality of the data and its exclusive use for research purposes.

The European Data Protection Regulation 2016/679 of the European Parliament and of the Council of 27 April 2016 on the protection of natural persons with regard to the processing of personal data and the free movement of such data and the Organic Law 3/2018 of 5 December on the Protection of Personal Data and guarantee of digital rights will be complied with at all times.

This protocol has been registered on ClinicalTrials.gov (NCT06359249). The final results will be submitted for publication in peer-reviewed journals and presented at relevant national and international conferences. In addition, findings will be shared with participating primary care centers and regional health authorities to support possible adoption into clinical practice. Participants will be informed of the study results through summary reports distributed via their primary care teams.

Results

Progress

Participant enrollment concluded in August 2025, and data collection is ongoing and expected to continue until April 2026. The primary and secondary outcomes will be assessed at 3, 6, and 12 months after the intervention. Results will be analyzed using RStudio and reported in accordance with the Consolidated Standards Of Reporting Trials (CONSORT) guidelines for randomized trials.

Dissemination Plans

The study's findings will be disseminated through peer-reviewed publications and presentations at national and international conferences.

Variables

We will evaluate a set of indicators on constipation and other patient characteristics, as shown in Table 1. Outcomes will be

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assessed individually and at 5 different time points: before starting the intervention, on the same day of the intervention, 3 months after the intervention, 6 months after the intervention, and 12 months after the intervention. Data will be collected through standardized questionnaires to be completed independently by the participants.

Table . Study variables.

Study area and instrument		Measurement time point
Constipation		
	Rome IV criteria—degree of constipation	Tpre[a], T0[b], T3[c], T6[d], T12[e]
	Bristol Stool Form Scale—stool type	T0, T3, T6, T12
Quality of life		
	CVE-20 questionnaire	T0, T3, T6, T12
Use of laxatives		
	Self-recorded calendar of laxative intake	T3, T6, T12
Patient characteristics		
	ECAP[f]—sex, age, previous conditions	Tpre
	IPAQ[g]—physical activity level	T0, T3, T6, T12
Habit change intention		
	Dichotomous question	T0

[a]Tpre: before the intervention.
[b]T0: start of the intervention.
[c]T3: 3 months after the intervention.
[d]T6: 6 months after the intervention.
[e]T12: 12 months after the intervention.
[f]ECAP: Electronic Primary Care Clinical Workstation.
[g]IPAQ: International Questionnaire of Physical Activity.

Statistical Analysis

The main variable will be the percentage of patients with constipation 3 and 6 months after the start of treatment for each group, a dichotomous qualitative variable. Prevalence will be estimated and analyzed using the χ^2 test.

The other variables will be reported as percentages and counts for categorical variables and through mean, median, deviation, and quartiles for continuous variables. In order to analyze relationships between the main variable and the sociodemographic or other explanatory variables, the χ^2 test will be used, and the relative risk will be estimated to compare the reduction between the two intervention groups with respect to the control group.

To evaluate the secondary variable, a continuous quantitative variable, ANOVA or the Kruskal-Wallis test will be used to determine differences between the 3 groups. To determine differences between pairs of groups, the Student *t* test or Mann-Whitney test will be used. Analyses will use 95% CIs, and the significance level will be set at 5%.

Due to the nature of the intervention, participant blinding is not feasible. However, to minimize potential bias in outcome assessment, data entry and statistical analysis will be performed by a researcher who is blinded to group allocation. This approach ensures objectivity in the interpretation of results, particularly for subjective outcome measures. All analyses will follow the intention-to-treat principle, including all randomized participants in the groups to which they were originally assigned. Missing data will be handled using multiple imputation under the assumption that data are missing at random. Statistical analysis will be performed with RStudio.

Discussion

Principal Anticipated Findings

We anticipate that the structured rehabilitation program combining behavioral reeducation and abdominal massage will lead to a reduction in chronic constipation symptoms and laxative use at 3 and 6 months after the intervention. We also expect improvements in quality of life, particularly among participants receiving both behavioral education and massage therapy. Furthermore, we expect that both intervention groups will show improvements compared to the control group, but that the BIM group will experience greater improvements.

Comparison to Prior Work

Constipation is often an underestimated condition, and the extent to which people experience hardship from it or its complications is not mentioned in primary care consultations. Reducing constipation will have a positive impact by reducing medicalization, alleviating complications, and decreasing the number of visits to primary care and specialized care. This will result in a better quality of life, reducing personal, physical, and

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social impacts. In addition, economic expenditures will be reduced due to the lowered use of the aforementioned resources. Therefore, the search for an effective therapy with fewer side effects, both to improve the quality of life of this part of the population and to reduce public health expenditure, should be a topic for research.

It is important to emphasize treating this condition in a logical, step-by-step manner. This includes the establishment of effective and simple conservative measures followed, if necessary, by pharmacological therapy, which is not always necessary. Concerningly, the general population often resorts to pharmacological therapy directly, often without having undergone conservative treatment [1].

The usual treatment for constipation is a reminder of healthy habits, including proper nutrition, hydration, physical activity, and use of laxatives, but these reminders are part of a very short consultation time, often not exceeding 5 to 7 minutes. There is little evidence on other possible conservative techniques, which include lifestyle changes, abdominal massage therapy, anal biofeedback, acupuncture, and dilators [32-39]. This research project guides new multidisciplinary treatments based on a change of habits and a more global approach to health, empowering the patient. In addition, there is the option of abdominal massage, a technique that is less harmful and invasive, less expensive, and self-performed by patient themselves to relieve the symptoms caused by constipation.

Strengths and Limitations

A key strength of this trial is its pragmatic design, making it well-suited for real-world implementation within the primary care system. The use of validated instruments (the Rome IV criteria, Bristol scale, CVE-20, and IPAQ) ensures reliable outcome measurement. Moreover, the multidisciplinary and participatory nature of the intervention promotes patient empowerment and supports long-term behavior change.

The selection of the counties of l'Anoia and Bages as recruitment areas is based on operational and organizational criteria, as the research team is embedded within the local primary care services, facilitating coordination and participant follow-up. L'Anoia represents a typical urban area in Catalonia (Igualada Urbà Primary Care Center), with demographic and health care characteristics comparable to similar regions, while the inclusion of the Bages region (Navàs Primary Care Center) provides representation of a rural setting. This dual approach ensures feasibility, consistency in intervention delivery, and participant retention, while also improving the external validity of the study by including both urban and rural populations.

One limitation of the study is that the intervention groups receive additional contact with physiotherapists and SMS reminders, while the control group only receives usual care. This greater interaction could introduce attention bias in patient-reported outcomes independently of the abdominal massage itself. Although a sham massage or a time-matched control condition would address this issue, we deliberately adopted a pragmatic design comparing the intervention with standard practice, as this better reflects real-world clinical conditions and enhances external validity.

Another limitation is the absence of a system to verify whether participants in the BIM group correctly perform the abdominal massages at home or whether they perform them at all. This lack of monitoring poses a threat to the internal validity of the study, as the actual exposure to the intervention may vary significantly between individuals. However, during the 2 in-person sessions, the physiotherapist will check that participants are performing the massages correctly. Future protocols should consider incorporating compliance tracking tools or remote follow-up to ensure adherence.

Additionally, the total sample size of 45 participants is relatively small for a 3-arm design with repeated follow-up, which may limit the generalizability of the findings. Moreover, recruitment is restricted to 2 geographic regions (Anoia, representing an urban area, and Bages, representing a rural area), which may affect the representativeness of the study population beyond these contexts.

Future Directions

Should the findings be favorable, future research should focus on scaling the intervention to other regions and health care systems, increasing the sample size, and assessing long-term outcomes, beyond 6 months. Moreover, future studies could include a sham massage group to control for attention bias and better isolate the effect of abdominal massage.

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Data Availability

Access to the full protocol, participant-level dataset, and statistical code can be granted upon reasonable request to the corresponding author.

Authors' Contributions

Conceptualization: CS-B
Methodology: CS-B, AR-C, JV-A, AR-M
Formal analysis: QM-C
Investigation: CS-B

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Writing—original draft: CS-B
Writing—review and editing: all authors: CS-B, AR-C, JV-A

Conflicts of Interest

None declared.

Multimedia Appendix 1
Medications for constipation.
[DOCX File, 13 KB - resprot_v14i1e72018_app1.docx]

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Abbreviations

BI: behavioral intervention
BIM: behavioral intervention and massage
CONSORT: Consolidated Standards Of Reporting Trials
IPAQ: International Questionnaire of Physical Activity
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Quality of Life and Metabolomics Analysis in Response to Meal Kit Intervention During Perioperative Chemotherapy in Patients with Early-Stage Breast Cancer: Protocol for a Single-Center Phase Randomized Crossover Trial

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Abstract

Background: Patients with breast cancer undergoing chemotherapy experience significant adverse effects, including fatigue, nausea, and taste alterations, leading to malnutrition in 40% of patients. Traditional nutritional counseling has shown limited effectiveness in addressing these challenges during treatment.

Objective: This study aimed to evaluate the impact of a structured meal kit intervention on quality of life and metabolomic profiles in patients with breast cancer during perioperative anthracycline and taxane-based chemotherapy.

Methods: This single-center phase 2 randomized crossover trial will enroll 20 patients with breast cancer scheduled for perioperative chemotherapy at Jikei University Hospital between October 2024 and October 2025. Patients will be randomized 1:1 to receive a meal kit intervention either during the first or second 3-month period of chemotherapy. The intervention consists of weekly deliveries of preportioned ingredients with dietitian-designed recipes (one 2-serving meal kit during chemotherapy weeks, two during nonchemotherapy weeks). The primary endpoint is the change in the EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30) “appetite loss” domain score. Secondary endpoints include changes in total EORTC QLQ-C30 score, plasma metabolome profiles, body composition, nutritional status, and chemotherapy completion rate. Data will be collected at baseline, crossover (12 wk), and study completion (24 wk).

Results: The study was funded in March 2024. Data collection began on March 26, 2025, and as of manuscript submission, 11 participants have been recruited out of the planned 20 participants. Data analysis has not yet commenced, and results are expected to be published in Spring 2026.

Conclusions: This trial will provide evidence for the effectiveness of a meal kit intervention in supporting patients with breast cancer during chemotherapy. The findings may help establish evidence-based standards for nutritional support in oncology care.

Trial Registration: Japan Registry of Clinical Trials jRCT1033240599; https://jrct.mhlw.go.jp/latest-detail/jRCT1033240599

International Registered Report Identifier (IRRID): DERR1-10.2196/72715

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KEYWORDS

nutritional intervention; perioperative treatment; patient-reported outcomes; metabolic profiling; supportive care

Introduction

Breast cancer is the leading cancer among Japanese women, with approximately 95,000 new cases diagnosed annually [1]. About 30% of early patients with breast cancer receive chemotherapy as part of their treatment [1]. While chemotherapy improves survival outcomes, treatment-related side effects significantly impact patients’ quality of life (QOL) and nutritional status. Studies have consistently shown that malnutrition is prevalent among patients with cancer undergoing chemotherapy, affecting 40% of patients [2,3]. Malnutrition is associated with poorer QOL outcomes, including reduced physical, emotional, and cognitive functioning. Common side effects impacting nutritional status include fatigue, nausea, vomiting, changes in taste and smell, and gastrointestinal disturbances [4,5]. These side effects can lead to inadequate nutrient intake and further deterioration of nutritional status [6].

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Poor nutritional status during chemotherapy is associated with decreased treatment adherence, increased adverse events, and higher health care consumption [7]. A systematic review of 71 studies found a significant association between poor nutritional status and increased mortality (hazard ratio 1.87, 95% CI 1.62 - 2.17), with malnourished patients being less likely to complete oncologic treatment according to plan [7]. Cross-sectional studies have shown that malnutrition during treatment correlates with lower QOL scores across all functional domains [3]. Despite this evidence, structured nutritional interventions during chemotherapy remain limited, with most support being generic dietary advice. Recently, Tang et al [8] reported a protocol for a multidisciplinary early intervention during chemotherapy in patients with breast cancer, highlighting the importance of structured support for dietary behavior and quality of life management from the early phase of treatment.

Meal kit interventions represent an innovative approach to addressing these challenges. Unlike traditional nutritional counseling, meal kits provide preportioned ingredients and recipes tailored to patients' needs, potentially improving dietary adherence and reducing the burden of meal preparation during treatment [6]. Recent studies have demonstrated promising results with nutritional interventions during chemotherapy, showing improvements in dietary intake, quality of life, and symptom management [9]. A randomized controlled trial of plant-based, high-protein meal kits showed significant improvements in fatigue scores and body composition measurements compared to standard nutritional counseling [10], while another study of Mediterranean Diet meal delivery found that home delivery services combined with nutritional education can facilitate better dietary adherence, though chemotherapy-induced side effects remain a significant barrier [11]. However, more comprehensive randomized trials are needed to fully evaluate the effectiveness of meal kit interventions specifically for patients with breast cancer during chemotherapy.

The present trial aims to fill these research gaps through three unique aspects. First, it used a randomized crossover design to evaluate the meal kit intervention during both anthracycline and taxane-based chemotherapy phases. Second, it combines patient-reported QOL outcomes with comprehensive metabolomics analysis to understand the biological impact of nutritional support. Third, it assesses the feasibility and effectiveness of a structured meal kit program that could be implemented in routine clinical practice.

This study will provide critical evidence for developing evidence-based nutritional support strategies during breast cancer chemotherapy. The findings may help establish standards for personalized dietary interventions and inform future large-scale implementation studies.

Methods

Ethical Considerations

The study protocol has been approved by the Institutional Review Board of Jikei University School of Medicine (approval number: 36-088[12191]). Written informed consent will be obtained from all participants. Results will be published in peer-reviewed journals and presented at scientific conferences. Patients were not involved in the development of the research question or study design. Study results will be disseminated to participants through a summary report.

Study Design and Setting

This is a single-center phase 2 randomized crossover trial at the Department of Breast and Endocrine Surgery, Jikei University Hospital, Tokyo, Japan. The study period is from October 2024 to December 2026, with patient registration from October 2024 to December 2025. This crossover design was selected based on established approaches for nutritional interventions in cancer patients, which maximize statistical efficiency by having each patient serve as their own control [12].

Participants

Eligible participants are women aged 20 years or older with histologically confirmed stage 0–III breast cancer who are scheduled to receive perioperative chemotherapy consisting of anthracycline- and taxane-based regimens. Participants must have an Eastern Cooperative Oncology Group (ECOG) Performance Status of 0 - 1 and be able to provide written informed consent. Patients with severe food allergies, serious comorbidities, or conditions preventing safe meal preparation will be excluded. Additional exclusion criteria include pregnancy or lactation and inability to understand or provide informed consent. These eligibility criteria are consistent with prior nutritional intervention and supportive care trials conducted in breast cancer patients undergoing chemotherapy [13-16].

Intervention

The meal kit intervention consists of weekly deliveries of nutritionally balanced, preportioned meal kits developed by registered dietitians in collaboration with oncology clinicians. These kits are part of the "Healthcare Oisix" program, a food support service specifically designed for cancer patients undergoing chemotherapy.

Each meal kit includes precut ingredients, seasonings, and recipe cards, and is designed to align with core principles of evidence-based nutritional support during chemotherapy. While current international guidelines do not recommend fixed per-meal nutritional targets, our kits are structured to reflect best practices derived from clinical trials and consensus recommendations, emphasizing key elements such as:

- High-quality protein content (~25 - 30 g/meal) to approximate 1.2 - 1.5 g/kg/day, supporting lean body mass preservation and mitigating cachexia during chemotherapy [13-15]
- Adequate energy density (400 - 500 kcal/meal) to help maintain energy balance, especially in patients experiencing appetite loss [17,18]
- Digestive tolerability, through soft-textured, low-fiber, easily digestible components (eg, tofu, simmered fish, soft vegetables), reduces mucosal irritation and improves intake in patients with gastrointestinal symptoms [19,20]
- Anti-inflammatory potential, incorporating Mediterranean-style elements such as olive oil, fish, and

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beans, which may modulate inflammatory markers and support overall resilience [21,22]
- Flavor optimization, through seasoning variety and familiar ingredients, to address taste alterations and promote appetite and food enjoyment during treatment [23-25]

In addition to the main dishes, supplementary items such as nutritional jelly, yogurt, soy milk, and protein-rich snacks (eg, cheese, tofu, chicken flakes) are included weekly to improve dietary adherence and intake consistency.

All meals are designed to require minimal preparation and cognitive demand, accommodating patients experiencing fatigue or chemotherapy-induced cognitive changes. Patients are instructed to log all consumed items weekly using a structured food diary to track adherence and enable dietary intake assessment.

During chemotherapy weeks and the following week, patients receive one 2-serving meal kit. During the subsequent week, they receive two 2-serving meal kits. Over 3 months, each patient receives 16 meal kits total.

Randomization and Blinding

Block randomization (block size=2) will be performed using a central registration system. The allocation sequence will be computer-generated by an independent statistician and concealed until interventions are assigned. Due to the nature of the intervention, blinding is not feasible. However, to minimize potential bias, several mitigation strategies will be implemented. Objective measures such as metabolomic profiles, anthropometric data, and laboratory values will serve as secondary validation of patient-reported outcomes. In addition, validated and structured questionnaires will be used to reduce reporting variability and enhance the reliability of self-reported data.

In this hospital, nearly all patients undergoing perioperative chemotherapy for breast cancer receive a standard regimen consisting of anthracycline-based treatment followed by taxane-based treatment. This reflects current clinical practice and minimizes heterogeneity in chemotherapy exposure. Therefore, the diversity of chemotherapy regimens is unlikely to introduce significant confounding. Nevertheless, randomization will be stratified by planned chemotherapy regimen (anthracycline-taxane sequence vs anthracycline-taxane with targeted therapy), and regimen type will be included as a covariate in the statistical models to account for any residual variability.

Outcomes

The primary outcome of this study is the change in the EORTC QLQ-C30 (European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30) “appetite loss” domain score between the meal-kit intervention and standard care periods. Key secondary outcomes include changes in the total EORTC QLQ-C30 global health and functional scores, body weight, body mass index, body composition, and chemotherapy completion rate, including relative dose intensity. Exploratory outcomes comprise changes in plasma metabolomic profiles, nutritional status evaluated by the Subjective Global Assessment, and laboratory parameters such as serum albumin, hemoglobin, zinc, and vitamin D levels. Additional exploratory analyses will assess adverse event rates, dietary intake, and nutrient composition, as well as patient-reported measures of meal satisfaction and adherence. Exploratory outcomes will be analyzed descriptively, with multiple comparisons adjusted using the Benjamini–Hochberg method.

Sample Size

As an exploratory phase 2 trial designed to generate preliminary data for future larger-scale randomized controlled trials, we plan to enroll 20 patients (10 per sequence group). This sample size was determined based on feasibility constraints for this single-center pilot study, similar to other exploratory nutritional intervention studies in oncology settings [16]. The crossover design maximizes statistical efficiency by having each patient serve as their own control, reducing interindividual variability in dietary habits, metabolic profiles, and treatment tolerance. These preliminary data will inform power calculations for future confirmatory phase 3 trials.

Chemotherapy Regimens

Anthracycline-based chemotherapy:

- Doxorubicin 60 mg/m2 Day1+Cyclophosphamide 600 mg/m2 Day1 q3w, 4 cycles, or
- Doxorubicin 60 mg/m2 Day1+Cyclophosphamide 600 mg/m2 Day1+Pembrolizumab 200 mg Day1 q3w, 4 cycles

Taxane-based chemotherapy:

Taxane-based chemotherapy:

- Paclitaxel 80 mg/m2 Day1,8,15 q3w, 4 cycles
- Docetaxel 75 mg/m2 Day1 q3w, 4 cycles
- With or without Trastuzumab, Pertuzumab, or Pertuzumab-Trastuzumab-Hyaluronidase-zzxf, or
- Carboplatin AUC1.5 Day1,8,15+Paclitaxel 80 mg/m2 Day1,8,15+Pembrolizumab 200 mg Day1 q3w, 4 cycles

Study Period

The registration period will be from October 2024 to December 2025; the study period will run from October 2024 to December 2026; and the follow-up period will continue until May 2026.

Data Sharing Statement

Deidentified participant data will be available upon reasonable request after study completion. Requests should be directed to the corresponding author. Data will be available for 5 years after publication.

Data Collection and Management

Clinical data will be collected from electronic medical records. Blood samples will be stored at −80°C until metabolomic analysis. QOL assessments will be conducted every 3 weeks during hospital visits. All data will be managed using a secure database with coded identifiers to protect patient privacy.

Dietary Adherence Assessment

Dietary adherence will be monitored through food consumption logs where participants record what they consumed from each meal kit. We will also conduct dietary habit change

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questionnaires to assess how the meal kit intervention influences participants' overall eating patterns compared to baseline. Meal satisfaction surveys will evaluate ease of preparation and palatability as indicators of adherence likelihood.

Adherence will be defined as consumption of meal kit components during at least 80% of delivered weeks. This approach allows evaluation of both direct meal kit consumption and broader dietary behavioral changes resulting from the intervention.

Carryover Effects Assessment

While a traditional washout period is not feasible due to the continuous nature of chemotherapy treatment, several strategies will be employed to assess and mitigate carryover effects.

1. Statistical analysis will include testing for period effects and treatment-by-period interactions using linear mixed-effects models
2. Sensitivity analyses will be conducted, excluding the first week of each period, to minimize immediate carryover effects
3. Baseline measurements will be monitored at each crossover point to detect persistent effects from the previous period
4. The analysis will specifically examine whether treatment effects differ between the first and second treatment periods

Metabolomics Analysis

Plasma metabolomic analysis will be performed using gas chromatography-mass spectrometry (GC-MS), a validated platform for detecting metabolic alterations in breast cancer patients undergoing chemotherapy or nutritional intervention. GC-MS has identified changes in amino acid (eg, glutamate, lysine, threonine), lipid, and energy metabolism (eg, lactate, hydroxybutyrate), reflecting tumor progression and treatment response [26,27]. Compared to other platforms, GC-MS offers superior resolution for volatile and small metabolites, complementing broader lipid and polar compound coverage by liquid chromatography-mass spectrometry and nuclear magnetic resonance [28].

Statistical Analysis

Primary analysis will use linear mixed-effects models for repeated measures, with treatment, period, sequence, and treatment-by-period interaction as fixed effects and subject as a random effect. The analysis will test for treatment effects comparing meal kit versus standard care, period effects between first and second treatment periods, and sequence effects with potential carryover effects assessed through treatment-by-period interactions. Missing data will be handled using multiple imputation. If significant carryover effects are detected, sensitivity analyses will be conducted using first-period data only. Metabolomic data will be analyzed using principal component analysis and partial least squares discriminant analysis. The Benjamini-Hochberg method will be used to control for multiple comparisons. Sensitivity analyses will include per-protocol analysis excluding participants with less than 80% adherence, analysis excluding the first week of each treatment period, first-period only analysis if carryover effects are detected, and subgroup analyses by chemotherapy regimen type if sample size permits.

This protocol was developed in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2025 statement for randomized trial protocols. The completed SPIRIT 2025 checklist is available as Checklist 1.

Results

This study was funded in March 2024 by Oisix ra daichi Co., Ltd. Enrollment began on March 26, 2025, following approval by the Institutional Review Board of The Jikei University School of Medicine. As of manuscript submission (July 31, 2025), 11 participants have been recruited and randomized out of the planned 20 participants. Data collection is ongoing with an expected completion date of March 2026. Data analysis will commence upon completion of data collection, with results expected to be published in Spring 2026.

Discussion

This trial represents a novel approach to assessing the impact of a meal kit intervention on the nutritional status and quality of life of breast cancer patients undergoing chemotherapy. Chemotherapy, while essential for improving survival outcomes, is often accompanied by adverse effects such as fatigue, nausea, and alterations in taste that contribute to malnutrition and diminished quality of life. Traditional nutritional counseling may be insufficient to address these challenges, particularly when patients struggle with the practical aspects of meal preparation during treatment. In contrast, our intervention, which provides preportioned ingredients and standardized recipes designed by registered dietitians, is designed to alleviate these burdens and promote better dietary adherence.

The randomized crossover design of this study allows each patient to serve as their own control, thereby reducing the confounding effects of individual variability in dietary habits, metabolic profiles, and treatment tolerance, similar to the approach used in other nutritional intervention studies [29]. This design allows us to compare the effects of meal kit intervention during both anthracycline and taxane phases within the same patient, which is particularly advantageous given the exploratory nature of this phase 2 trial and the relatively small sample size of 20 patients. By aligning the intervention with these distinct chemotherapy phases, we are able to evaluate the effects of the meal kit on appetite loss and other QOL domains, as previous research has shown that different chemotherapy regimens are associated with distinct side effect profiles affecting nutritional status [30].

A significant strength of this study lies in its comprehensive assessment of both patient-reported outcomes and objective biological measures. The integration of quality of life assessments using the EORTC QLQ-C30, which has been validated as an effective tool for measuring QOL in cancer patients [31], with metabolomic analyses via gas chromatography-mass spectrometry provides a multidimensional perspective on the intervention's impact. This integrated approach, combining patient-reported outcomes with

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metabolomic data, has shown promise in previous research for understanding treatment effects [32], and may yield valuable insights into the biological mechanisms underlying the relationship between nutritional intake and symptom management during chemotherapy, similar to previous metabolomic studies in breast cancer patients [33].

Despite these strengths, several limitations must be acknowledged. As an exploratory phase 2 trial conducted at a single center with 20 participants, the statistical power to detect subtle effects is limited, and the generalizability of the findings may be constrained. While the inability to blind participants and treatment providers to the intervention introduces the potential for reporting bias in the quality of life measures, we incorporate objective measures such as metabolomic analyses and standardized assessments to strengthen our findings. Furthermore, the six-month follow-up period, while sufficient for evaluating acute effects, does not allow for the assessment of long-term outcomes such as treatment adherence, survival rates, or sustained quality of life improvements.

Future research should build upon this phase 2 trial through larger, multicenter randomized controlled trials that can definitively establish the role of meal kit interventions in oncology care. Studies with extended follow-up periods would allow evaluation of not only immediate effects on quality of life and metabolic profiles, but also potential impacts on treatment adherence and long-term survival outcomes. While our statistical models will account for chemotherapy regimen type, future research could specifically explore whether the timing of meal kit intervention (during anthracycline vs taxane phase) differentially affects outcomes, as the impact of nutritional support may vary across different chemotherapy regimens. Additionally, investigating the integration of meal kits with other supportive care strategies could reveal synergistic benefits for symptom management and patient well-being. Such comprehensive research would help establish evidence-based standards for nutritional support during chemotherapy and potentially transform the approach to supportive care in oncology.

In conclusion, this study offers a systematic approach to evaluating a standardized meal kit intervention in breast cancer patients undergoing chemotherapy. By addressing both the practical and biological challenges of maintaining adequate nutrition during treatment through a structured program of preportioned ingredients and registered dietitian-designed recipes, our findings have the potential to inform the development of evidence-based nutritional support strategies that enhance quality of life and optimize clinical outcomes in oncology.

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The authors attest that no generative artificial intelligence tools were used in the generation of original content, data analysis planning, or interpretation. However, generative AI was used to assist with language editing and English grammar checking.

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Authors' Contributions

Conceptualization: A Fushimi
Data Curation: A Fuke
Formal Analysis: ET
Funding Acquisition: A Fushimi
Investigation: A Fushimi, ET, TK
Methodology: A Fushimi
Project Administration: A Fushimi, HN
Supervision: HN
Writing – Original Draft: A Fushimi
Writing – Review & Editing: ET, MK, TK, A Fuke, HN

Conflicts of Interest

A Fushimi reports receiving research funding from Oisix ra daichi Co., Ltd. for the conduct of this study. All other authors declare no conflicts of interest.

Checklist 1
SPIRIT 2025 editable checklist.
[DOCX File, 35 KB - resprot_v14i1e72715_app1.docx]

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Abbreviations

ECOG: Eastern Cooperative Oncology Group
EORTC-QLQ-C30: European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire Core 30
GC-MS: gas chromatography-mass spectrometry
QOL: quality of life
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Effectiveness of Different Methods of Interdental Hygiene in Daily Practice Among Young Adults: Protocol for a Randomized, Single-Blind Controlled Trial

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Abstract

Background: Interdental spaces are particularly susceptible to biofilm accumulation and gingival inflammation, which contribute to periodontal diseases and their systemic associations. While interdental brushes (IDBs) are recognized as the most effective method of interdental cleaning, their efficacy depends on proper adaptation to the interdental space. Calibration with a colorimetric probe may enhance their effectiveness and comfort. However, evidence directly comparing calibrated and noncalibrated IDBs, especially in young adults, a key target group for preventive strategies, remains limited. The Hygiene of Interdental Junctions in Adults (HIJA) trial was designed to address this gap.

Objective: This protocol aims to compare the clinical, microbiological, and acceptability outcomes associated with calibrated versus noncalibrated IDBs in young adults, focusing on interdental inflammation, periodontal indices, and microbiota composition.

Methods: The HIJA trial is a monocentric, randomized, controlled, single-blind, and parallel-arm study. Overall, 50 healthy, nonsmoking adults aged 18 - 30 years will be randomized (1:1) to receive either calibrated or noncalibrated IDBs. Participants will perform daily interdental cleaning in addition to conventional toothbrushing for 3 months. The primary outcome will be the reduction in interdental inflammation, expressed as the change in bleeding on probing at 3 months. Secondary outcomes will assess differences in interdental microbiota composition (16S ribosomal RNA sequencing), periodontal indices (plaque index, gingival index, probing depth, and clinical attachment loss), and user acceptability measured through the Theoretical Framework of Acceptability questionnaire at 1, 2, and 3 months.

Results: The HIJA trial will generate evidence on whether calibrated IDBs provide additional benefits over noncalibrated brushes in reducing interdental inflammation and improving oral health in young adults.

Conclusions: HIJA findings could contribute to the implementation of clinical guidelines and preventive strategies for interdental hygiene in daily practice.

Trial Registration: ClinicalTrials.gov NCT06848790; https://clinicaltrials.gov/study/NCT06848790

International Registered Report Identifier (IRRID): PRR1-10.2196/85154

(JMIR Res Protoc 2025;14:e85154) doi:10.2196/85154

KEYWORDS

prophylaxis; oral hygiene; periodontitis; gingival inflammation; microbiota; biofilm; toothbrush

Introduction

Oral health is a cornerstone of general well-being and systemic health [1-3]. Among the multiple ecological niches of the oral cavity, interdental spaces represent unique sites with minimal host defense mechanisms. Their anatomical configuration predisposes them to bacterial colonization and biofilm accumulation, which in turn promotes local inflammation and increases the risk of periodontal disease [4,5]. Periodontal diseases are strongly associated with systemic conditions,

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including cardiovascular disease, diabetes, adverse pregnancy outcomes, and certain cancers, making early prevention a public health priority [1-3].

The interdental microbiota plays a pivotal role in this process. A balanced microbiota contributes to oral homeostasis, while dysbiosis triggers gingival inflammation and subsequent periodontal destruction. Interdental cleaning, therefore, represents a key strategy to prevent dysbiosis [6,7]. Conventional toothbrushing cannot access interdental areas, which highlights the need for complementary interdental hygiene practices [8].

Current evidence indicates that interdental brushes (IDBs) are the most effective and widely recommended method of interdental cleaning, outperforming dental floss and wooden sticks in reducing gingival inflammation and plaque accumulation. Several meta-analyses and network analyses have confirmed their superiority, while observational studies have shown their acceptability in daily use [4,9]. However, substantial heterogeneity exists among IDBs, particularly regarding size, shape, and calibration. Calibration with a colorimetric probe ensures optimal adaptation of IDB to interdental space, thereby improving mechanical efficacy and user comfort [10].

Despite these insights, there is a paucity of clinical evidence comparing calibrated versus noncalibrated IDBs in young adults, a critical population in which preventive strategies should be implemented before the onset of irreversible periodontal damage [11]. To date, few randomized controlled trials have demonstrated that daily calibrated IDB use significantly reduces interdental inflammation and dysbiosis in young adults [6,7]. No study has yet addressed whether such calibration provides a measurable advantage in real-life daily practice compared to noncalibrated IDBs.

The Hygiene of Interdental Junctions in Adults (HIJA) trial is designed to address the following research question, formulated according to the Population, Intervention, Comparison, and Outcome framework: In healthy young adults aged 18 - 30 years (Population, P), does the daily use of calibrated IDBs (Intervention, I) lead to a greater reduction in interdental inflammation compared with the daily use of noncalibrated IDBs (Comparator, C), measured as bleeding on probing (BoP) at 3 months (Outcome, O)?

Methods

Trial Design

This clinical study named HIJA is designed as a monocentric, randomized, controlled, 2 parallel-arm, and single-blind clinical study (ratio 1:1; Figure 1). The protocol is presented in accordance with SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [12].

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Figure 1. Flowchart diagram of Hygiene of Interdental Junctions in Adults study. IDB: interdental brush.

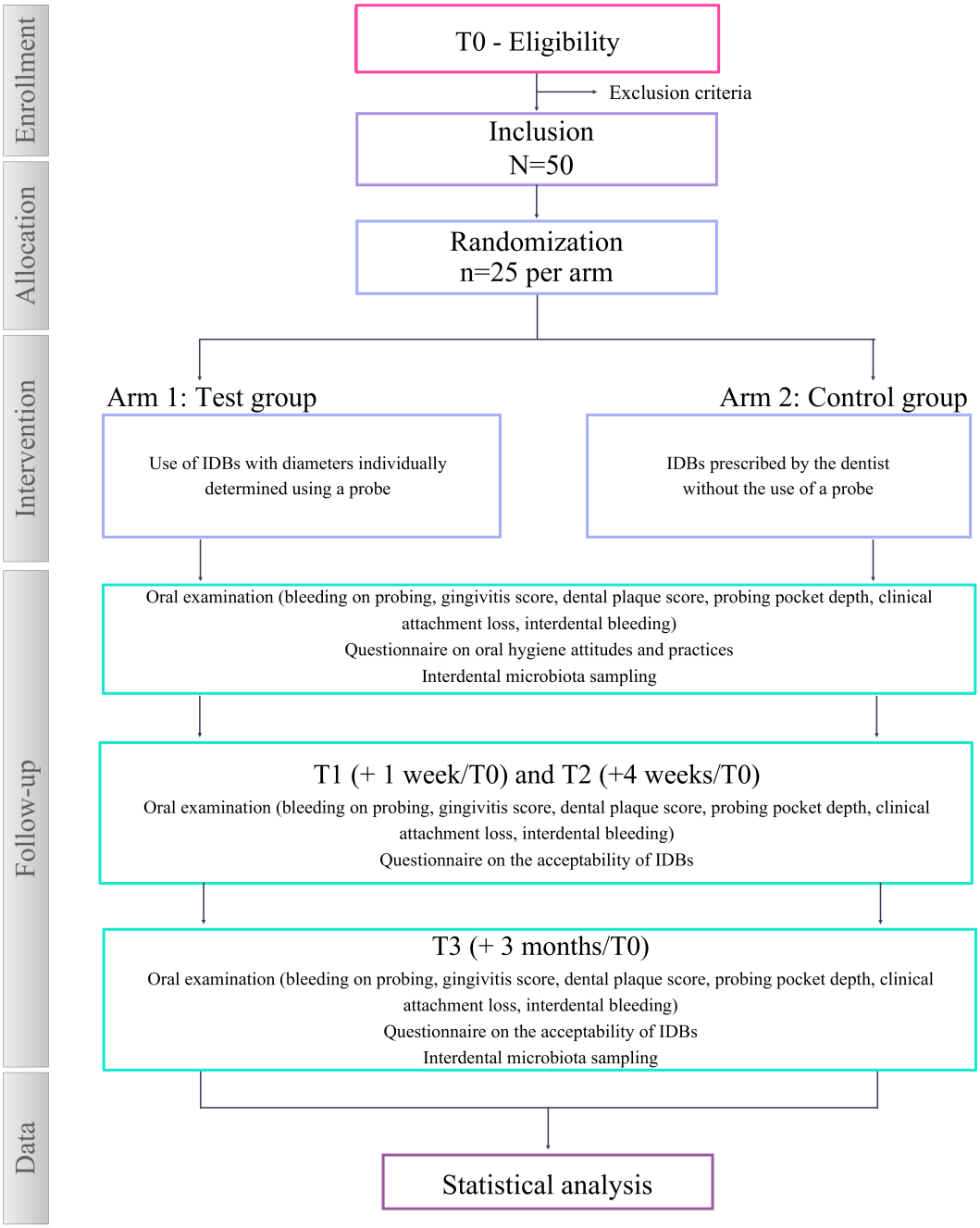

Study Setting

The HIJA study will be conducted within the Odontology Department of the Hospices Civils of Lyon, France.

Study Population

Eligibility Criteria

Inclusion Criteria

Eligibility criteria will be (1) participants between 18 and 30 years of age, (2) who have given their free, informed, and express written consent, (3) affiliated with a French social security scheme, and (4) living or working in Lyon or the Lyon metropolitan area.

Periodontal health will be required for inclusion, in accordance with the 2017 World Workshop classification [13], defined as the absence of gingival inflammation or active attachment loss. A reduced but stable periodontium, such as mild localized recession without probing depth ≥4 mm or generalized involvement, will be considered consistent with periodontal health and may include cases corresponding to Stage I

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periodontitis when such findings are localized, noninflammatory, and clinically stable.

Exclusion Criteria

Exclusion criteria will be (1) individuals with a tobacco addiction, (2) currently participating in another study related to oral hygiene, (3) at high risk of infective endocarditis, (4) with chronic medical conditions such as type 1 or 2 diabetes, (5) who have taken antibiotic treatment during the month preceding the start of the study, (6) pregnant or breastfeeding women, (7) deprived of their liberty by a judicial or administrative decision, (8) receiving psychiatric care, (9) admitted to a health or social care facility for purposes other than research, (10) subject to a legal protection measure (guardianship and curatorship), (11) not affiliated with a social security scheme or beneficiaries of a similar scheme, (12) with fewer than 20 natural teeth, (13) currently performing interdental hygiene and/or daily mouthwashes, (14) wearing orthodontic appliances, (15) with periodontal disease (stage II or higher according to the 2017 Chicago classification [ie, probing pocket depth, PPD ≥4 mm and/or clinical attachment loss, CAL ≥4 mm] and/or generalized, >30% of sites), active caries, or undergoing dental treatment, and (16) under judicial protection.

Materials Description

Colorimetric Probe

The IAP CURAPROX calibrating probe is a graduated conical instrument with a rounded tip (Figure 2A and B). The working part comprises colored bands from the point to the base corresponding to IDBs by increasing diameter. The largest section of each colored band corresponds to the cleaning efficiency diameter of the relevant brush. The nonworking part has a click-fastening joint for the attachment of a handle for easier use and access to the interproximal spaces at the back of the mouth.

Figure 2. Procedure for using the colorimetric probe to determine the appropriate interdental brush size. (**A**) Colorimetric probe, (**B**) color indication (yellow) corresponding to the measured interdental space, (**C**) available interdental brushes color-coded by size, and (**D**) use of the selected interdental brush in the interdental space.

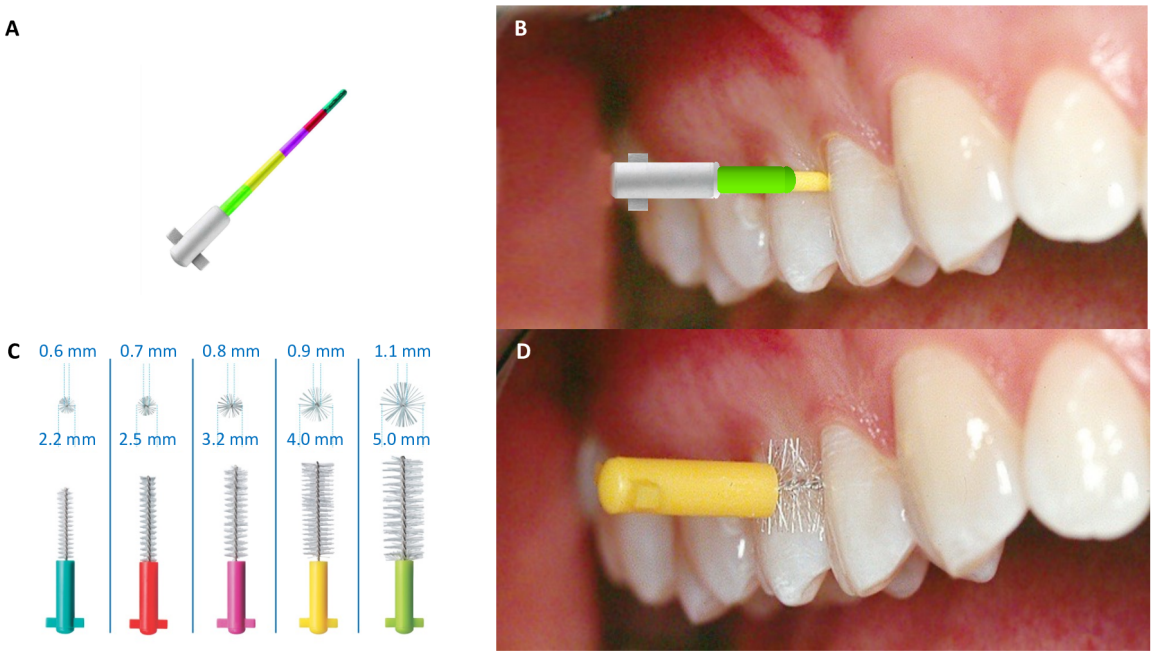

Interdental diameters were coded as 1=blue, 2=red, 3=pink, 4=yellow, and 5=green. The procedure consists of introducing the IAP CURAPROX probe into the vestibular interdental space, inserting it fully, then noting the color emerging from the interdental space on the vestibular side. This corresponds to the color code of the IDB most suitable for the interdental space in question. The pressure used to place the probe tip at the base of the interdental sites was approximately 50 N/cm^2 (0.20 gram force).

Interdental Brushes

The IDBs used in this study are from the CPS range of CURAPROX (Curaden; Figure 2C and 2D). These IDBs consist of cylindrical nylon fiber brushes mounted on a CURAL wire core coated with synthetic material to prevent galvanic or traumatic effects. The brushes are supplied with ergonomic plastic handles to facilitate grip and insertion in posterior sites. Each CPS pack comprises five IDBs with the following characteristics: (1) a specific color code corresponding to the brush size (Table 1); (2) an access diameter, defined by the gauge of the CURAL wire core, which determines the minimal interdental space into which the brush can be inserted; and (3) an effective cleaning diameter, defined by the length and elasticity of the synthetic bristles covering the working part of the device.

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Table . Characteristics of interdental brushes used in the Hygiene of Interdental Junctions in Adults study.

Color code	Access diameter (mm)	Cleaning diameter (mm)
Blue	0.6	2.2
Red	0.7	2.5
Pink	0.8	3.2
Yellow	0.9	4
Green	1.1	5

Interventions

In the intervention group, participants will receive IDBs with diameters individually determined by the dentist using a colorimetric probe to ensure optimal adaptation to each interdental space. In the control group, participants will receive IDBs prescribed by the dentist without calibration by a probe. In both groups, the dentist will visually assess the morphology of the interdental spaces, including the presence or partial loss of interdental papilla, to ensure that the prescribed brushes can be safely and comfortably inserted. This clinical evaluation will complement the calibration procedure in the intervention group and will guide professional judgment in the control group. All participants will be instructed to use IDBs once daily, in addition to their regular toothbrushing routine, for a duration of 3 months. They will not be allowed to use complementary techniques (dental floss, mouthwashes, etc) during the period of the study. All participants will be naive users of IDBs at baseline, as individuals already performing interdental hygiene will be excluded according to the study criteria.

Individual instructions on interdental brushing hygiene techniques will be provided by the dentist, who will first ensure that each participant is able to handle the IDBs correctly and safely, demonstrating sufficient manual dexterity and cognitive ability to perform the technique as instructed. Each participant will be provided with a logbook at the baseline visit to record daily IDB use by ticking the corresponding day for adherence monitoring. The logbook will be reviewed at every visit to assess compliance.

Procedures and Follow-Up Schedule

Participants will attend 4 visits: baseline (T0), week 1 (T1), month 1 (T2), and month 3 (T3).

Clinical Assessments (At All Visits)

The oral examination in accordance with clinical practices will be carried out by a dentist who will report the following clinical parameters:

1. BoP: dichotomous gingival index (GI) reporting the presence or absence of BoP after 30 seconds (0=absence of bleeding after 30 s and 1=presence of bleeding after 30 s). A total of 4 sites are recorded per tooth (mesiobuccal, distobuccal, mesiopalatine, and distopalatine) [14,15].
2. Gingivitis score (GI): measured by visual observation from 0 to 3 (0=no inflammation; 1=slight change, slight inflammation in color, and little change in texture; 2=moderate, moderate inflammation, redness, edema, and hypertrophy, tendency to bleed on probing; 3=severe, marked redness, inflammation, hypertrophy, and tendency to spontaneous bleeding). Gingivitis score=sum of GI scores divided by the number of total sites [16].
3. Dental plaque score (Rustogi Modified Navy Plaque Index): according to the Navy Plaque Index modified by Rustogi et al [17], the presence of plaque deposits is sought on the vestibular and lingual surfaces of the teeth. Each tooth face is divided into 9 areas to which a dichotomous score is assigned (0=absence of plaque and 1=presence of plaque). Thus, for each tooth, 18 measurements are carried out. This index makes it possible to detect minimal differences at the partial level of the marginal or interproximal zones, or at the total level of the oral cavity [17].
4. PPD score: a measure indicating the distance separating the top of the marginal gingiva from the bottom of the periodontal pocket. The measurement is expressed in millimeters. Overall, 4 sites are recorded per tooth (mesiobuccal, distobuccal, mesiopalatine, and distopalatine) [18].
5. CAL score: addition of PPD and recession height, which is the distance separating the enamel-cementum junction from the bottom of the pocket. In total, 4 sites are recorded per tooth (mesiobuccal, distobuccal, mesiopalatine, and distopalatine) [15].
6. Interdental bleeding: bleeding was assessed dichotomously following interdental brushing (0=absence of bleeding after insertion and removal of the brush and 1=presence of bleeding after insertion and removal). All interdental sites were recorded at each visit.

PPD and CAL will be assessed following the criteria defined by the consensus report of the 2017 World Workshop on the Classification of Periodontal and Peri-Implant Diseases and Conditions [13], using the US Williams PDT sensor probe (Zila-Pro-Dentec Inc) at a pressure of 20 g. Based on severity-defined stages of interdental CAL and tooth loss, complexity, extent, and distribution, they included a full oral examination of 6 sites on each permanent tooth. All measures will be performed on all teeth except for third molars. One calibrated dentist trained will perform the periodontal evaluations of all participants. Intraclass correlation coefficients for PPD and CAL will be determined at the level of the site. The intraexaminer coefficients for CAL will be, respectively, from 0.80 and 0.85, and from 0.75 and 0.85 for probing depth.

Interdental Microbiota Sampling (T0 and T3)

Interdental plaque will be collected from 4 sites (15-16, 25-26, 35-36, and 45-46). Each IDB used for sampling will be stored in RNase- and DNase-free tubes at –20°C within 4 hours and

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transferred later to the GenEPI platform (Hospices Civils of Lyon, Lyon, France) for long-term storage at −80°C. Analysis will be performed by 16S ribosomal RNA gene sequencing to determine microbiota composition in a single batch. Briefly, a 16S ribosomal RNA gene fragment comprising V3 and V4 hypervariable regions will be amplified using an optimized and standardized 16S amplicon library preparation. Sequencing will then be performed using a 250-base pair paired-end sequencing protocol on an Illumina MiSeq platform (Illumina). Bioinformatic analysis will then be performed using the QIIME2 software (Caporaso Lab, Northern Arizona University) in its latest version.

Questionnaires

Participants will complete 2 questionnaires: (1) First, the baseline oral hygiene questionnaire at T0 (Multimedia Appendix 1) that analyzes habits, frequency, and duration of daily hygiene; and (2) second, the Theoretical Framework of Acceptability (TFA) administered at T1, T2, and T3 (Multimedia Appendix 2). The TFA includes dimensions of perceived effort, intervention coherence, affective response, perceived effectiveness, and self-efficacy, allowing assessment of feasibility and long-term integration. The trial participation schedule is detailed in Table 2.

Table . Trial participation schedule.

Procedures and visits	Timeline			
	T0 (baseline)	T1 (1 week / T0)	T2 (1 month / T0)	T3 (+3 months / T0)
Prescreening	✓			
Eligibility screening	✓			
Informed consent	✓			
Questionnaires	✓	✓	✓	✓
Oral hygiene attitudes and practices[a]	✓			
Acceptability of IDB[b, c]		✓	✓	✓
Oral examination	✓	✓	✓	✓
BoP[d]	✓	✓	✓	✓
Interdental bleeding	✓	✓	✓	✓
GI[e]	✓	✓	✓	✓
Plaque index	✓	✓	✓	✓
PPD[f]	✓	✓	✓	✓
CAL[g]	✓	✓	✓	✓
Interdental microbiota sampling	✓			✓

[a]Multimedia Appendix 1 lists oral hygiene attitudes and practices.

[b]IDB: interdental brush.

[c]Multimedia Appendix 2 lists the acceptability of interdental brush.

[d]BoP: bleeding on probing.

[e]GI: gingival index.

[f]PPD: probing pocket depth.

[g]CAL: clinical attachment loss.

Outcomes

Primary Outcome Measures

Reduction in interdental inflammation, expressed as the proportion of sites with BoP at 3 months (T3), comparing calibrated versus noncalibrated IDBs.

Secondary Outcome Measures

Secondary outcome measures will be (1) biological outcomes: composition of interdental microbiota (16S ribosomal RNA sequencing, T0 and T3); (2) clinical outcomes: evolution of plaque index, GI, BoP, PPD, and CAL at T1, T2, and T3; and (3) patient-reported outcomes: acceptability and integration of daily interdental cleaning, assessed by the TFA questionnaire at T1, T2, and T3.

Sample Size

The reduction in gingival bleeding was considered the primary outcome variable, and an estimate of the mean difference in reduction was used to calculate the sample size. Based on a 2-sided α of .05, 80% power, an intraclass correlation of 0.8, and an expected 25% difference in BoP between groups, a total of 50 participants (200 sites) are required. Taking into account

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a dropout rate of 10%, in order to have 50 participants at the end, 56 participants (28 per group) will be included.

Recruitment

Participants will be recruited via an existing database of healthy volunteers previously enrolled in oral health studies at the P2S laboratory (Université Lyon 1) and public announcements on social media and digital platforms of the laboratory. All participants will receive free study materials (IDBs for 3 months) and reimbursement of travel costs (2 local transportation tickets per visit).

Randomization and Blinding

Randomization

Participants will be randomly assigned to one of 2 arms (arm 1: calibrated IDBs and arm 2: noncalibrated IDBs). Randomization will be performed using an interactive web response system integrated into the electronic case report form (v8.2.30 build 3, EnnovClinical Group). Allocation will be 1:1 without stratification, as the sample size is limited and the population is considered homogeneous. Participants will remain in the same arm during the study period. A total of 50 participants will be enrolled, with 25 assigned to each group.

Blinding

The study will be conducted under single-blind conditions. Participants will not know whether they are assigned to the calibrated or noncalibrated IDB group. To maintain blinding, both types of IDBs will be identical in packaging, color, and appearance. The investigator responsible for the allocation will not be blinded. Intervention implementation will be conducted by staff independent from data collection. To ensure impartiality, during the assessment and analysis phase, statisticians, clinical research associates, and clinicians will not know the group to which the participant belongs. The identification codes will be securely held by the study monitor and will remain sealed until the conclusion of the study to maintain confidentiality and prevent bias.

Data Collection, Management, and Analysis

Data Collection

A case report form, specific to the HIJA study, will be created in Lyon, France. Only data required for the protocol and scientific publication will be recorded in the case report form. Each participant will be assigned a unique identification code to label all documents, forms, and data files. Thus, data recorded by investigators for each participant will be anonymized according to the Data Protection Act. As data are collected, they must be completed by authorized persons (investigators) with their own identifiers, according to the Data Protection Act. During the entry, the data are immediately checked thanks to consistency checks. The person in charge of filing must validate and justify any value change in the electronic case report form. Entries and modifications are subject to an audit trail. The quality, exactitude, and relevance of all input data will be the responsibility of the investigator. Accordingly, each page of the patient's must be electronically dated and signed by the investigator to confirm agreement and responsibility for the collected data.

Data Management

Experimental and personal data will be analyzed using a unique identification code with no directly identifiable personal data. Participants can be reidentified through a subject identification file, which will be securely maintained solely at the clinical study site. The signed informed consent documents will also be kept exclusively at the clinical study site for confidentiality and privacy purposes.

Data Analysis

Statistical analyses will be conducted on both the intention-to-treat and per-protocol populations. All randomized participants will be included in the intention-to-treat analysis, while the per-protocol analysis will exclude those with major protocol deviations, such as nonuse of IDBs. Missing data will be addressed using multiple imputation by chained equations with Monte Carlo Markov Chain methods, assuming data are missing at random. Descriptive statistics, including means, SDs, medians, interquartile ranges, and frequencies, will be calculated. Between-group comparisons will be performed using Student 2-tailed *t* test or the Wilcoxon test for continuous variables and the Chi-square test for categorical variables. Changes over time will be assessed using mixed linear models, with log-transformed bleeding values when appropriate. Fixed effects will include independent variables such as age, socioeconomic status, and experimental group, while subjects will be included as a random effect to account for repeated clinical bleeding measurements. Estimated coefficients for each independent variable will be tested against the null hypothesis of zero, with significance set at $P<.05$. Analyses will be performed using SPSS (IBM Corp), SUDAAN (RTI International), and R software (R Development Core Team). Exploratory analyses will also be performed to assess potential correlations between CAL and participants' adaptation and compliance with IDB use, as evaluated through the TFA questionnaire and the compliance logbook.

Ethical Considerations

The HIJA protocol was approved by ethical and regulatory authorities and will be performed in conformity with the Declaration of Helsinki. The Committee for the Protection of Persons Sud-Méditerranée I (Marseille, France) approved the protocol on May 14, 2025 (2024-A02813-44 - 69HCL24_1272). This study will be conducted in accordance with the methodology of reference MR-001 of the National Commission for Information Technology and Liberties. This trial was registered with ClinicalTrials.gov (NCT06848790). Before taking part in the study, all participants must provide written informed consent. The following elements will be included in the consent form: (1) the name and affiliation of the principal investigator, (2) a clear description of the purpose of the study, (3) the procedure and duration of the study, (4) the right to stop at any time, (5) the approval of the ethics committee, and (6) a confidentiality guarantee. No compensation will be provided to participants

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Results

The HIJA trial is designed to address a critical gap in current oral health research, the comparative effectiveness of calibrated versus noncalibrated IDBs in daily practice among young adults. While IDBs are established as the most effective interdental cleaning method, clinical evidence is still lacking on whether calibration, a simple yet potentially impactful procedure, provides measurable additional benefits in reducing interdental inflammation and maintaining a balanced oral microbiota. Most available studies have assessed IDBs without clearly distinguishing calibrated from noncalibrated devices, which constitutes an important methodological weakness. This lack of differentiation limits the strength of current recommendations and contributes to heterogeneity in clinical practice. Calibration with a colorimetric probe theoretically optimizes the fit between the brush and the interdental space, thus enhancing mechanical efficacy while minimizing discomfort or trauma [10]. However, in real-life settings, calibration is often overlooked, mainly for reasons of simplicity, time, or cost, raising the question of whether its omission compromises clinical outcomes.

Discussion

Principal Findings

The HIJA trial is expected to generate high-quality evidence on whether calibration of IDBs offers a measurable clinical advantage. Because participants' comfort and adherence may influence interdental cleaning efficacy, compliance will be systematically assessed using the TFA questionnaire and the compliance logbook. These measures will allow the analysis of whether differences in adherence between groups could act as confounding factors in the interpretation of clinical outcomes. If calibration proves beneficial, it could support the systematic implementation of calibrated interdental cleaning in preventive dentistry, particularly in young adults at the onset of lifelong oral hygiene routines. Furthermore, integration of microbiological profiling will enhance the understanding of how interdental cleaning strategies shape the oral microbiome, which may contribute to broader preventive approaches against systemic diseases associated with periodontal inflammation. Ultimately, this research could provide an evidence base for updating oral hygiene guidelines and promoting personalized preventive strategies in dentistry. Another major strength of the HIJA trial is that it will be the first study to perform sequencing of the interdental microbiota in the context of a randomized clinical trial. This innovative approach will allow the exploration of whether calibrated versus noncalibrated IDBs differentially influence microbial composition and oral ecological balance, thereby providing novel mechanistic insights beyond conventional clinical indices. By combining clinical, microbiological, and acceptability outcomes, the HIJA trial will clarify whether calibration provides a meaningful advantage in reducing interdental inflammation and improving oral health. The results may ultimately inform preventive strategies and contribute to the refinement of oral hygiene recommendations in early adulthood.

Conclusions

By combining clinical, microbiological, and acceptability outcomes, the HIJA trial will clarify whether calibration provides a meaningful advantage in reducing interdental inflammation and improving oral health. The results may ultimately inform preventive strategies and contribute to the refinement of oral hygiene recommendations in early adulthood.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Oral hygiene questionnaire.
[DOCX File, 16 KB - resprot_v14i1e85154_app1.docx]

Multimedia Appendix 2
Theoretical framework of acceptability.
[DOCX File, 19 KB - resprot_v14i1e85154_app2.docx]

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Abbreviations

BoP: bleeding on probing
CAL: clinical attachment loss
GI: gingival index
HIJA: Hygiene of Interdental Junctions in Adults
IDB: interdental brush
PPD: probing pocket depth
SPIRIT: Standard Protocol Items Recommendations for Interventional Trials
TFA: Theoretical Framework of Acceptability

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Effects of Shallow Needling for Chronic Primary Insomnia: Protocol for a Randomized Controlled Trial

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Abstract

Background: Primary insomnia (PI), commonly identified by difficulties in initiating and maintaining sleep, negatively impacts both physical and mental health and increases the risk of occupational and vehicular accidents. Previous research has indicated that shallow needling, a form of acupuncture, may ameliorate the symptoms of PI. Nevertheless, the scientific evidence regarding its efficacy in enhancing sleep quality remains limited.

Objective: This trial aims to assess the therapeutic efficacy of shallow needling in the treatment of chronic PI in adults.

Methods: A single-center, prospective, assessor-blinded randomized controlled clinical trial retrospectively registered with the International Traditional Medicine Clinical Trial Registry (ITMCTR2024000409). With 2 parallel arms, the trial will be conducted at the Affiliated People's Hospital of Fujian University of Traditional Chinese Medicine. A total of 124 participants with PI will be randomly divided into the control group and the treatment group in a ratio of 1:1 (n=62 for each group). The control group will receive 1 mg eszopiclone orally, once a day for 4 weeks. In addition to taking eszopiclone, the treatment group will receive shallow needling therapy once daily, 5 times a week, for 4 weeks. Data will be collected at 3 time slots—before treatment, after treatment, and 4 weeks after treatment—and will be analyzed using SPSS (version 23.0). The primary outcome measure is the Pittsburgh Sleep Quality Index. The secondary outcome measures include the Hamilton Anxiety Scale, Insomnia Severity Index, serum neurotransmitter detection (including dopamine, norepinephrine, and melatonin), sleep parameters, and magnetic resonance spectroscopy of the thalamus.

Results: Participant recruitment for this study is currently in progress. The first participant was enrolled in August 2023, marking the official commencement of the trial. Following the completion of recruitment, data processing and statistical analysis will be initiated. The final results of this study are expected to be prepared and submitted for publication in January 2026.

Conclusions: This study will evaluate the therapeutic effectiveness and safety of shallow needling in the treatment of chronic insomnia to provide the necessary scientific basis for the clinical application and promotion of shallow needling. The findings of this study may provide a scientific and standardized treatment protocol for shallow needling in adults with chronic insomnia.

Trial Registration: International Traditional Medicine Clinical Trial Registry ITMCTR2024000409; https://itmctr.ccebtcm.org.cn/mgt/project/view/3352938396834771013

International Registered Report Identifier (IRRID): DERR1-10.2196/76501

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KEYWORDS

shallow needling; chronic insomnia; acupuncture; study protocol; randomized controlled trial

Introduction

Insomnia is one of the most common sleep disorders globally, characterized by difficulty in falling and staying asleep, early morning awakenings, and an inability to return to sleep [1]. It may occur secondary to psychiatric or organic disorders, the use of prescribed or illicit substances, alcohol consumption, or a combination of these factors. However, insomnia can also occur independently, known as primary insomnia (PI), which is driven by a psychophysiological hyperarousal process [2]. A

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recent large-scale study revealed that approximately 16.2% of adults worldwide experience insomnia [3], with PI accounting for an estimated 25% of the cases. Notably, many of these patients experience a chronic course of the disorder [4]. Chronic insomnia has been associated with a wide range of adverse health outcomes, including headaches, dizziness, hypertension, and various cardiovascular and cerebrovascular diseases, which collectively undermine physical health, reduce quality of life, and pose significant risks to public safety. These effects result in substantial harm to both individuals and society [5,6]. Therefore, chronic PI has become a critical public health issue in contemporary society.

Sedative drugs and cognitive behavioral therapy (CBT) are the primary interventions for insomnia [7]. Although sedative drugs have a fast onset of action, their adverse effects with long-term use are notable, including persistent sleep difficulties, performance issues, memory disorders, driving accidents, and withdrawal syndrome [8]. In contrast, CBT is widely recognized as the first-line treatment for chronic insomnia by recognized organizations, including the American College of Physicians [9], the American Academy of Sleep Medicine [10], and the European Sleep Research Society [7]. Despite its effectiveness for insomnia, CBT is not commonly used due to the intensive labor required and high costs, which may lead to low patient compliance [11]. Given these limitations, it is crucial to seek additional safe and effective nonpharmacological treatments to optimize existing therapies for chronic insomnia.

As an important component of traditional nondrug therapy, acupuncture has long been used for the treatment of insomnia in China [12] [1]. In recent years, a growing body of evidence-based research has reported the effectiveness and feasibility of acupuncture therapy in improving sleep quality [13-16]. However, in clinical practice, the discomfort and pain associated with traditional acupuncture often cause significant distress and fear among patients, which limits its widespread acceptance. Therefore, the development of noninvasive and painless acupuncture techniques has become a key focus of research in this field.

Shallow needling, a special type of acupuncture, is derived from the *hammer needle* in the ancient system of 9 needles. The nationally famous senior traditional Chinese medicine experts, Wu Binghuang and Liang Dongfu, have inherited and innovated this therapy, developing it into a characteristic acupuncture method of Fujian province [17]. In 2019, it was listed as part of the sixth batch of intangible cultural heritage projects in Fujian province and was selected as a characteristic traditional Chinese medicine technique by the National Administration of Traditional Chinese Medicine. Shallow needling is a noninvasive technique in which a rounded needle tip rests on the skin surface without penetrating it. Compared to conventional acupuncture needles, the needles used in shallow needling are designed with a thicker body, a longer handle to facilitate scraping with the fingernail, and a rounded tip that rests on the skin surface, avoiding penetration and minimizing discomfort (Figure 1). The technique involves applying a scraping motion with the fingernail on the needle handle at specific acupoints on the body surface to produce a needle sensation. This method promotes the flow of meridian Qi and blood, regulates the internal balance of the body, and treats various diseases.

Figure 1. Structure of the shallow needle used in this study, illustrating the key components, including the needle tip, body, root, handle, and tail.

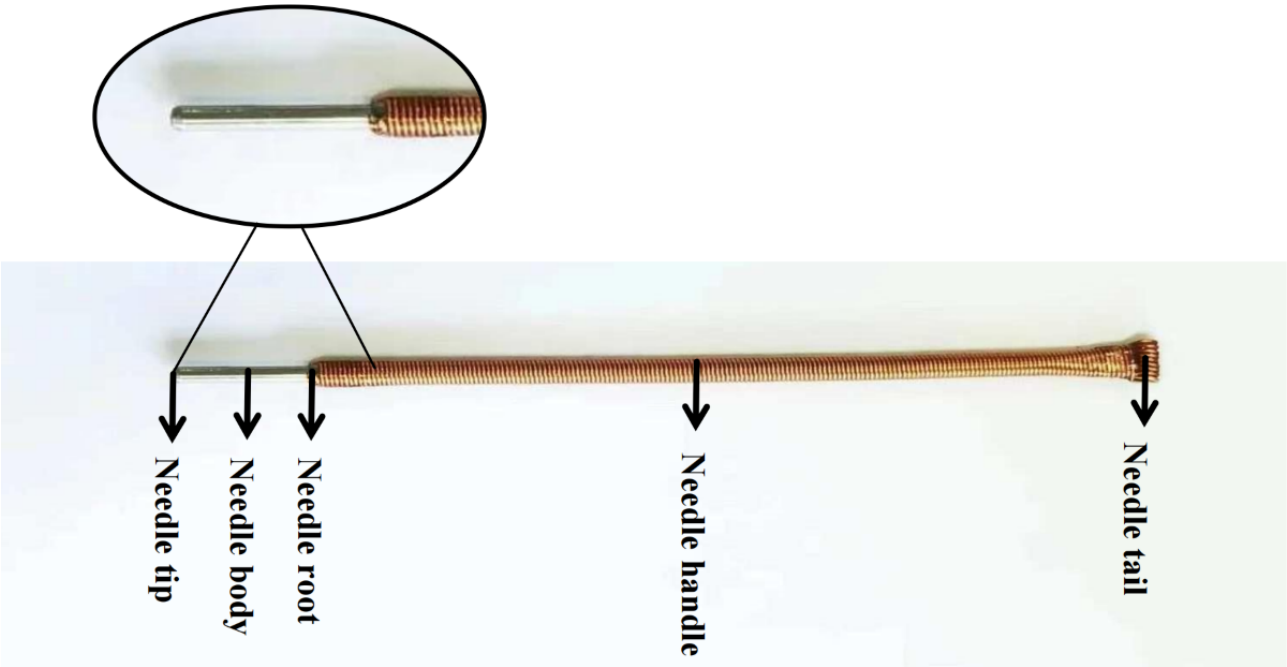

As a noninvasive and painless alternative, shallow needling is an attractive option for patients seeking less discomfort during treatment. Although shallow needling shows promising potential, its clinical efficacy in treating insomnia has not been thoroughly explored. A recent systematic review and meta-analysis [18] demonstrated that compared to nonshallow needling treatments, shallow needling demonstrates greater efficacy in reducing Pittsburgh Sleep Quality Index (PSQI) scores and improving clinical efficacy rates. However, most studies have small sample sizes, unclear reporting, and potential bias risks, and there is still insufficient high-quality clinical evidence to support its effectiveness.

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Furthermore, the specific mechanisms through which shallow needling ameliorates insomnia remain poorly understood, which has limited its broader clinical application. The current understanding of PI pathogenesis centers on hyperarousal as a core neurobiological pathology. Patients exhibit persistent whole-brain hyperexcitability, characterized by increased beta-band electroencephalographic activity. This abnormal cortical excitation interacts with the hypothalamic-pituitary-adrenal axis hyperactivity and autonomic nervous dysfunction, contributing to a vicious cycle of insomnia [19].

Existing evidence indicates that shallow needling restores autonomic balance [20] and mitigates the hypothalamic-pituitary-adrenal axis dysfunction, alleviating insomnia symptoms through correcting neuroendocrine abnormalities [21]. However, mechanistic research on the central nervous system effects of shallow needling remains inadequate, particularly regarding its impact on key brain regions regulating the sleep-wake cycle. Although preliminary studies have shown that shallow needling can regulate the functional connectivity of emotion-related brain circuits in patients with PI [22] and reduce the beta wave power in the frontal lobe and central regions of the brain [23], thereby creating neural conditions for sleep initiation, these findings still fail to systematically explain their core action targets.

The thalamus is a critical brain region involved in the regulation of sleep and wakefulness, and it plays a key role in sensory integration [24]. Neuroimaging studies have demonstrated that alterations in thalamic activity are associated with sleep disorders, including insomnia [25]. Recently, acupuncture has been shown to regulate the functional connections between the thalamus and the emotional network in patients with insomnia and improve the state of excessive arousal. Nevertheless, the underlying metabolic mechanisms remain unclear. Accumulating research has demonstrated that the occurrence of PI is closely linked to abnormal brain metabolites. Specifically, γ-aminobutyric acid (GABA) and glutamate/glutamine (Glx) maintain the balance between excitatory and inhibitory signals and are thought to be key players in sleep regulation. Notably, reduced GABA levels have been linked to hyperarousal in patients with insomnia, while abnormal Glx activity may contribute to disrupted sleep patterns [26]. Magnetic resonance spectroscopy (MRS) offers a noninvasive approach to quantify the concentrations of neurochemical substances within specific brain regions of living participants [27], providing a valuable tool for exploring the neurophysiological effects of acupuncture.

Therefore, we conducted a randomized controlled trial with a larger sample size and a rigorous design to generate high-quality clinical evidence regarding the efficacy of shallow needling for insomnia. We hypothesized that shallow needling acts as an effective external stimulus that modulates thalamic neurochemical activity through sensory nerve afferent pathways. To comprehensively evaluate its therapeutic effects, we incorporated peripheral serum neurotransmitter assays and objective polysomnographic sleep architecture measures, aiming to further elucidate the neural mechanism through which shallow needling ameliorates chronic PI.

Methods

Research Objectives

The purpose of this study is to evaluate the efficacy and safety of shallow needling in the treatment of chronic insomnia. The results of this study may provide a noninvasive and painless alternative therapy for patients with chronic insomnia.

Hypotheses

We hypothesize the following:

1. Compared with the control group, the symptoms of insomnia and anxiety in the treatment group were significantly relieved after treatment according to the scale evaluation. At the same time, according to the objective sleep outcome test results, the sleep treatment of the treatment group was further proved to be improved.
2. Compared with the control group, the levels of serum neurotransmitters, central neurotransmitters, and metabolites in the treatment group were significantly improved, reflecting the better regulatory effect of shallow needling.

Ethical Considerations

This study protocol has been approved by the ethics committee of the Affiliated People's Hospital of Fujian University of Traditional Chinese Medicine (IRB 2023-014-02). All patients and participants will provide written informed consent before their participation in this study. To protect participants' privacy and personal information in compliance with international ethical guidelines (eg, the World Medical Association Declaration of Helsinki), all identifiable data will undergo strict deidentification and anonymization processes immediately after data collection. This ensures that no individual participant can be traced or identified during data analysis, storage, or reporting stages. In recognition of participants' time and travel costs incurred during the study, each participant will receive a one-time transportation subsidy of 450 CNY (approximately US $63). The subsidy is provided to offset travel expenses related to study visits and will be distributed upon completion of all required study procedures.

Study Design

This study design is a prospective, randomized controlled trial with 2 parallel arms. The trial was retrospectively registered with the International Traditional Medicine Clinical Trial Registry under the number ITMCTR2024000409. The delay in registration occurred because the research team prioritized obtaining ethical approval and completing preliminary clinical preparations to ensure participant safety and study quality in the early stage; the registration process was initiated and completed immediately after the above preparatory work and subsequent administrative clearance were finalized. This protocol follows the guidelines of the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) (Checklist 1). We will compare the differences between shallow needling and pharmacotherapy for chronic PI in adults. The study procedure and details are presented in Figures 2 and 3.

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Figure 2. Flow diagram of the trial. DA: dopamine; MT: melatonin; NE: norepinephrine.

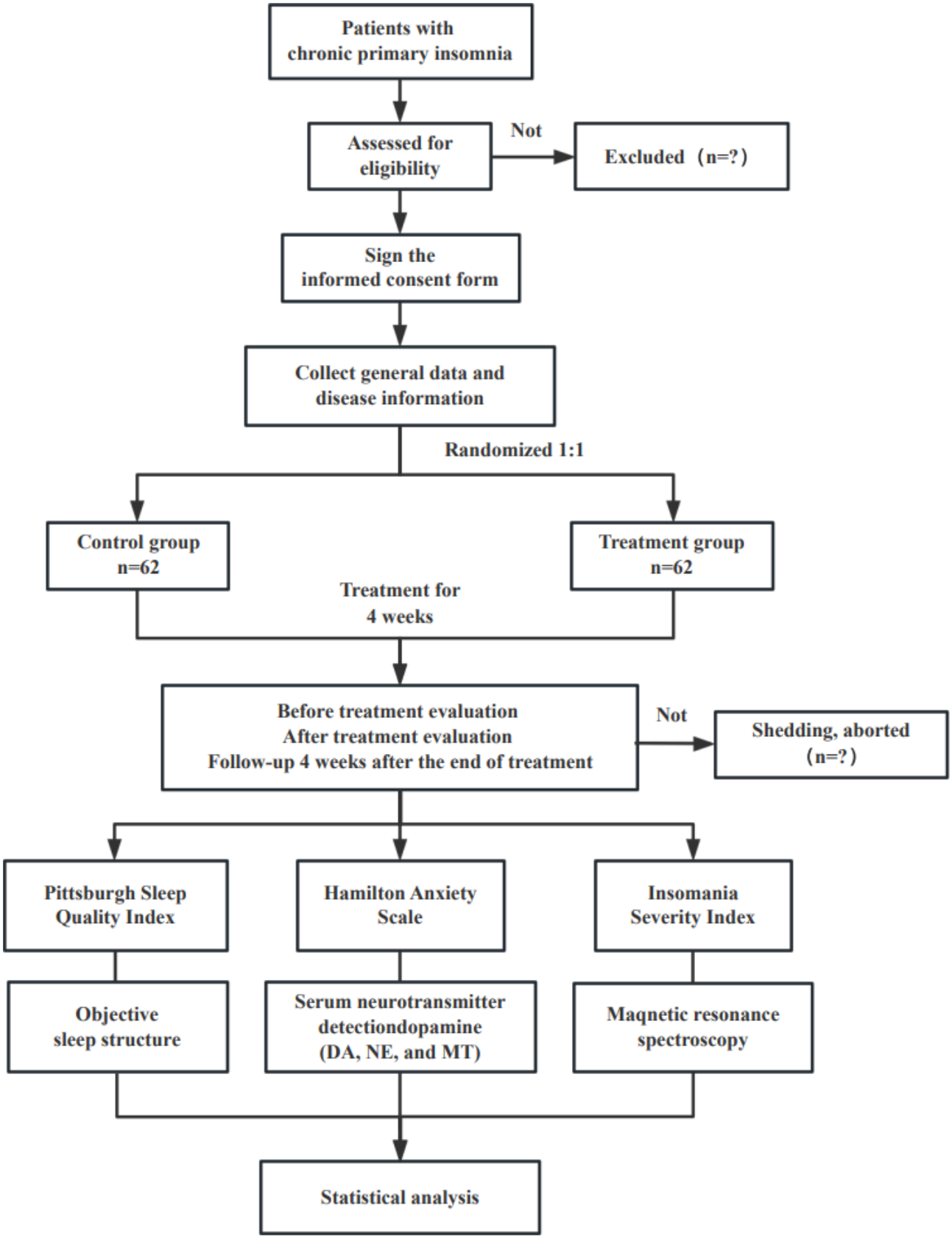

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Figure 3. Study schedule of enrollment, interventions, and assessments. HAMA: Hamilton Anxiety Scale; ISI: Insomnia Severity Index; MRS: magnetic resonance spectroscopy; PSQI: Pittsburgh Sleep Quality Index.

	Study period						
	Enrolment allocation		Intervention (wk)				Follow-up
Timepoint	-1 wk	0 wk	1 wk	2 wk	3 wk	4 wk	8 wk
Enrollment:							
Eligibility screen	X						
Informed consent		X					
Randomization		X					
Allocation		X					
Intervention:							
Taking eszopiclone orally			◆—	—	—	—◆	
Taking eszopiclone orally and required shallow needling			◆—	—	—	—◆	
Assessment:							
PSQI		X				X	X
HAMA		X				X	X
ISI		X				X	X
Serum neurotransmitter detection		X				X	X
Objective sleep structure		X				X	
MRS of the thalamus		X				X	
Safety evaluation:							
Adverse events			◆—	—	—	—	—◆

Participants

Sample Size

According to the relevant literature [28], the overall efficacy rate for the control group is reported to be 79.48%, whereas the treatment group is expected to have an efficacy rate of 98%. Assuming a significance level (α) of 0.05 and a power (1-β) of 0.9, the sample size was calculated using PASS 15.0 software. A minimum of 56 participants is initially required for each group. Considering a 10% dropout rate, we plan to recruit at least 62 participants per group. Therefore, a total of 124 participants are needed for this study.

Recruitment

We will recruit participants by posting advertisements on WeChat. Additionally, a series of educational lectures on shallow needling for chronic insomnia will be held at the Affiliated People's Hospital of the Fujian University of Traditional Chinese Medicine to attract potential participants. All participants who meet the selection criteria will sign an informed consent form after understanding the purpose of the study and the program implementation process. Individuals' personal information will be collected and securely stored in a separate cabinet to ensure confidentiality. The inclusion and exclusion criteria are detailed in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Patients who meet the diagnostic criteria
- Patients with insomnia aged 18 to 65 years
- Pittsburgh Sleep Quality Index score range from 7 to 15
- The duration of the disease ≥3 months
- No communication and cognitive impairment
- Voluntary enrollment and can sign informed consent form

Exclusion criteria

- Secondary insomnia
- Unwillingness to receive shallow needling therapy
- Pregnant or lactating women, or those who intend to become pregnant
- Patients with heart, liver, kidney, lung, brain, and other serious organic diseases
- Participants in other studies that may influence the results of this study

Randomization and Blinding

Randomization

The randomization sequence will be computer-generated by an independent statistician using SPSS Statistics (version 23.0; IBM Corp), using a block randomization method with a 1:1 allocation ratio. Sequentially numbered, opaque, sealed envelopes will be used to implement allocation concealment. Each envelope will contain a card specifying the random number, sequence number, and group assignment. After obtaining written informed consent, eligible participants will be assigned to either the treatment group or the control group by opening the next consecutively numbered envelope, and it is ensured that the random allocation sequence remains unknown to the researchers before enrollment to prevent selection bias.

Blinding

Due to the specific nature of the shallow needling procedure, we could not blind the investigators and participants, but outcome assessors and statisticians would be unaware of the trial-group assignments.

Interventions

The Control Group

Participants in the control group will receive oral eszopiclone (trade name: Itannin, manufactured by Chengdu Kanghong Pharmaceutical Group Co, Ltd, approval number: Sinopharm H20100074) at a dose of 1 mg before bedtime daily, for 4 weeks.

The Treatment Group

In addition to eszopiclone (same as the control group), participants will receive shallow needling therapy daily, 5 times a week, for 4 weeks.

The selected acupoints are Shangen (located at the intersection of the line connecting the inner canthi of both eyes and the midline of the nose), Zhenjing (located 0.3 cun above Yintang [GV29], with 1 cun being approximately the width of the patient's thumb at the knuckle), and Ezhong (located at the midpoint of the line connecting the hairline and Yintang). The locations of the acupoints are shown in Figure 4.

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Figure 4. Anatomical locations of the acupoints.

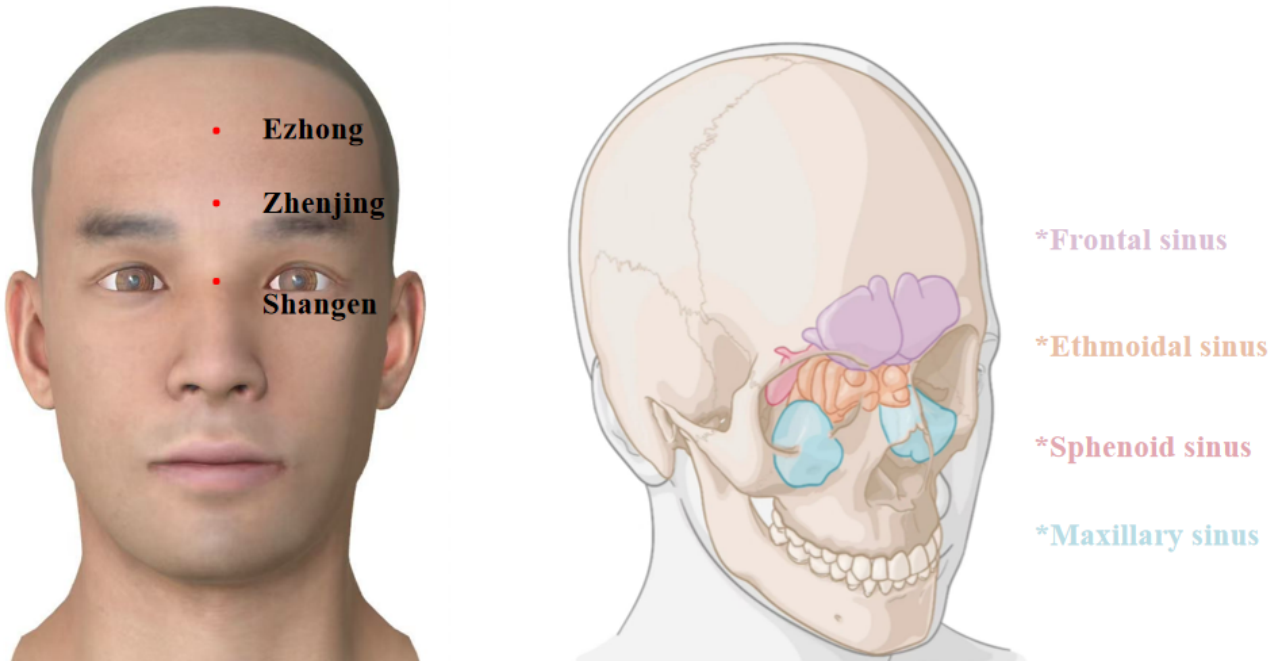

Before treatment, the participants are told to lie in a supine position in a quiet environment. The practitioner wraps a small piece of disinfected cotton around the tip of the needle and places it on the acupoint, applying light pressure without penetrating the skin of the patient. The practitioner uses the pad of the thumb to stabilize the needle handle, ensuring that the tip is perpendicular to the surface of the acupoint. The practitioner uses the edge of the middle fingernail to continuously scrape upward and downward along the needle handle, creating gentle and uniform vibrations. Each cycle of 81 scraping motions is 1 dose of stimulation, with 3 doses per acupoint.

The shallow needling will be performed by 3 licensed acupuncturists with at least 5 years of clinical experience in acupuncture. They will receive comprehensive training on the study procedures and shallow needling techniques before participating in this study.

In order to ensure the accuracy and reliability of the results of this trial, the use of other disease-related treatments was prohibited during the trial.

Follow-Up

The aim of the follow-up procedure is to assess the long-term effects of shallow needling for chronic PI. Follow-up assessments will be conducted after the 4-week intervention program. No further interventions will be provided during this period. Participants will obtain the same outcome measures as before the intervention. Regular reminders will be provided to ensure adherence, and any adverse events will be recorded and monitored by the researchers. This follow-up procedure is essential for understanding the long-term effects of shallow needling.

Outcome Measures

Primary Outcome Measures

PSQI [29] is a questionnaire used to assess an individual's sleep quality, with good reliability and validity, indicated by a Cronbach α coefficient of 0.83 and a test-retest reliability of 0.85 [30]. It consists of 7 components: subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The total score ranges from 0 to 21. A global PSQI score greater than 7 indicates the presence of sleep disorders, with higher scores reflecting poorer sleep quality. PSQI will be assessed before treatment, after treatment, and 4 weeks after treatment completion (follow-up).

Secondary Outcome Measures

Overview

Hamilton anxiety scale [31] consists of 14 items with a scale ranging from 0 to 4. Higher scores indicate more severe anxiety levels. This scale is usually used to measure the levels of anxiety. The evaluation time points are the same as those for the primary outcome indicator.

Insomnia Severity Index [32] is a self-assessment scale used to measure an individual's experience of insomnia. It consists of 7 items, each rated on a scale from 0 to 4. Higher scores indicate greater severity of insomnia. The total score ranges from 0 to 28, categorized as follows: 0 - 7 (no insomnia), 8 - 14 (mild insomnia), 15 - 21 (moderate insomnia), and 22 - 28 (severe insomnia). Assessment time points align with the primary outcome measure.

Objective Sleep Structure

Overnight sleep monitoring will be conducted using a polysomnography device (model: Alice 6 LDxN/LDxS, purchased from Respironics). The parameters, including total sleep time, sleep latency, wake after sleep onset, sleep

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efficiency, and the percentage of total sleep time spent in rapid eye movement (REM) and non-REM sleep stages 1, 2, and 3/4 (with stages 3 and 4 combined as deep sleep, reported as REM%, N1%, N2%, and N3%) were selected for outcome measurement. Participants will undergo sleep monitoring from 7 PM to 7 AM on the day before treatment and the day after the completion of the treatment course in the hospital.

Serum Neurotransmitter Detection

Fasting blood samples (5 mL) will be collected from participants between 8 AM and 10 AM. Blood samples will be centrifuged at 3000 rpm to separate the serum and subsequently stored in a laboratory freezer at −80°C. The concentrations of dopamine, norepinephrine, and melatonin will be measured using enzyme-linked immunosorbent assay kits, according to the manufacturer's instructions (Shanghai Enzyme-linked Biotechnology Co, Ltd). Measurements will be taken 1 day before treatment, 1 day after the completion of the treatment course, and at a 4-week follow-up.

Thalamic MRS

Scans will be performed with a 3.0T magnetic resonance scanner (Philips Ingenia CX 3.0T, Philips Healthcare). Participants will be required to keep their eyes closed, remain at rest, and stay awake during scanning. The bilateral thalamus will be selected as the region of interest, and all scans will be performed by the same experienced radiologist.

Imaging Parameters

The s2D_PRESS_144 sequence will be used for data acquisition, with a total scan duration of 5 minutes and 52 seconds. The field of view of the equipment will be anteroposterior, with a diameter of 230 mm. Right-left diameter will be 192 mm. The size of the acquisition voxel will be 10.0×10.1×15.0 mm. The echo time will be 144 milliseconds. The repetition time will be 2000 milliseconds. The acquisition matrix will be 23×19. The slice thickness will be 15 mm and the scan percentage will be 100%.

After the acquisition of MRS data, postprocessing will be executed using the Magnetic Resonance Spectro View software installed on the Intellispace Portal workstation. This postprocessing will mainly involve tasks such as noise reduction, frequency calibration, and baseline correction. Subsequently, the processed data will be analyzed to measure the levels of GABA, Glx, N-acetylaspartate, and choline-containing compounds in the thalamic region. The software will identify the characteristic peaks of these metabolites in the MRS spectra and calculate their relative concentrations based on the peak areas and predefined algorithms. MRS will be conducted before and 4 weeks after treatment to assess the changes in central neurotransmitter and thalamic metabolite levels.

Adverse Event Monitoring

Adverse events in this study will be closely monitored, with all details recorded in the case report forms (CRFs), to ensure that patients receive timely and appropriate management. Adverse events, including discomfort at the shallow needling site and drug-related reactions including nausea, vomiting, and dizziness, will be documented. Any serious adverse events will be promptly reported to the ethics committee to ensure participant safety.

Statistical Analysis

In this study, data will be analyzed with SPSS (version 23.0) software. Continuous variables will be reported as means and SDs, and categorical variables will be presented as frequencies or percentages. To compare continuous variables between the 2 groups, normality and homogeneity of variance will be initially evaluated. If these assumptions are satisfied, a 2-tailed *t* test will be used. Otherwise, a nonparametric rank-sum test will be used. Categorical variables will be analyzed using the chi-square test or Fisher exact test. *P* values of .05 or less will be considered statistically significant.

Data Collection and Management

Data will be collected by dedicated staff at the study center, and both the electronic medical record and CRF will be used to collect the data. In principle, missing values are not allowed in the report form. Particularly, important measures (the primary safety measure) must be clearly reported. If a test result is zero or if measurement fails, corresponding symbols (eg, "0" for zero values and "NM" for "not measured") will be used instead of leaving the field vacant. This ensures a clear distinction from missing values. If there are missing values, the original data should be searched first to determine whether the data are missing. If it is indeed missing, the data should be filled in. If the missing value is an important indicator related to safety, the participant should be informed to review it immediately to ensure their safety. If the missing values affect the outcome, the case will be excluded.

Quality Control

All participants, including acupuncturists, evaluators, and statisticians, will be required to undergo training to ensure the quality of the studies. By formulating detailed and operable clinical trial specifications, the intervention will be based on careful adherence to the standard operating procedures.

All participants, including acupuncturists, evaluators, and statisticians, need to be trained to ensure the consistency of relevant data collection and the quality of research through the development of detailed and operational clinical trial protocols. The intervention will be based on careful adherence to standard operating procedures, and the acupuncturists will perform standardized shallow needling procedures according to the standard acupoint positioning. After the training, the assessment effects of the scale by outcome evaluators need to be checked for consistency, mainly including the same case being scored by independent examination by several outcome evaluators and the same case being scored multiple times by one evaluator to ensure consistency of the scores.

The investigator will fill in all cases truthfully and carefully according to the design requirements of the CRF. Study medical records and CRFs are original records and cannot be altered.

Laboratory data in clinical trials should be documented, and the original report or photocopy needs to be glued to the CRF.

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In order to effectively improve the compliance of the participants, during the case screening and enrollment stage, it is necessary to maintain a patient and careful attitude; fully explain the purpose, process, and significance of the study to the participants; and ensure that the participants clearly understand the relevant content. At the same time, the participants will be clearly informed to strictly follow the established requirements to ensure the smooth progress of the study and the accuracy of the data.

Results

Participant recruitment is currently underway. The first participant was enrolled in August 2023, marking the official commencement of the experiment. As of April 2025, a total of 120 participants have been enrolled in this clinical trial. The final results of the study are expected to be prepared and submitted for publication in January 2026.

Discussion

This study is a randomized controlled clinical trial aimed at evaluating the clinical efficacy of shallow needling in the treatment of chronic PI and to further explore its underlying mechanism. The objectives include exploring a cost-effective, efficient, and safe standard therapy for chronic PI, as well as providing a scientific foundation for the clinical application and promotion of shallow needling therapy.

Through systematic data mining of extensive literature, we demonstrated that acupuncture points such as Shangen, Zhenjing, and Ezhong have been widely recognized for their efficacy in treating insomnia through shallow needling [33]. These acupoints correspond to the anatomical structures above the paranasal sinuses, where vibratory stimulation through shallow needling may induce resonance within the subcutaneous cavities. This resonant effect could further stimulate the Circle of Willis, thereby improving cerebral function and blood circulation [20]. A preliminary study indicates [34] that Professor Wu Binghuang frequently selected these acupoints in clinical practice, documenting significant improvement in over 80 patients with insomnia, many of whom experienced sleep onset during treatment. Furthermore, electroencephalography findings from the same study indicated that shallow needling can induce delta waves through regular and continuous vibratory stimulation. This mechanism shares similarities with the principle applied by hypnotists, who induce delta waves to treat insomnia specifically via the visual stimulation of a rhythmically swaying crystal ball. Our study will use these well-documented acupoints to improve therapeutic outcomes.

This trial will comprehensively assess the efficacy of shallow needling through both subjective and objective measures, including the PSQI, Hamilton Anxiety Scale, Insomnia Severity Index, and objective sleep monitoring via polysomnography. This multifaceted evaluation approach allows for a robust assessment of the treatment effects from various perspectives. Although previous studies have predominantly examined short-term outcomes, our study design incorporates a 4-week intervention period followed by a 4-week follow-up phase, enabling the investigation of both the immediate and sustained effects of shallow needling. This longitudinal design provides valuable insights into the therapeutic potential of the intervention. Additionally, to further elucidate the underlying neurophysiological mechanisms, we will analyze serum neurotransmitter levels and conduct thalamic MRS, exploring how shallow needling may modulate the neural pathways involved in sleep regulation. Moreover, this trial avoids the use of skin-penetrating interventions, ensuring participant safety and enhancing both participant compliance and the feasibility of the study.

Although our study comprehensively evaluates the efficacy of shallow needling for chronic PI, there are several limitations to consider. First, due to funding constraints, this study was designed as a single-center trial with a relatively limited sample size, which may, to some extent, affect the generalizability of the findings. Moreover, the assumed between-group difference used in the sample size calculation may have been overly optimistic, resulting in insufficient statistical power to detect more subtle yet clinically meaningful effects of shallow needling. Nevertheless, our study offers a valuable foundation for understanding the efficacy of shallow needling, and we hope that future large-scale, multicenter studies will further validate and extend these findings, thereby strengthening the evidence base for this intervention. Second, all participants received baseline pharmacotherapy with eszopiclone for ethical and adherence reasons, which may introduce confounding effects when interpreting the specific contribution of shallow needling. Therefore, we incorporated a follow-up period to reduce the residual pharmacological effects and more accurately assess the long-term efficacy attributable to shallow needling therapy. Finally, given the unique characteristics of shallow needling, developing a sham intervention that is both physiologically inert and indistinguishable from the actual treatment is difficult. Any form of simulated contact or scraping may inadvertently induce physiological reactions, thereby compromising its validity as a true placebo. Therefore, we adopted multidimensional objective outcome measures and blinded the evaluators and statisticians to reduce potential bias risks. At the same time, a 4-week follow-up was conducted to reduce the short-term placebo effect and enhance the validity of the research results. We hope that future research can develop and apply innovative sham-control methods tailored to shallow needling techniques to further reduce the possible placebo bias.

To the best of our knowledge, this is the first randomized controlled trial to objectively assess the efficacy of shallow needling for the treatment of insomnia and provide new insights into its neurophysiological mechanisms. The results of this study will establish a basis for the wider use of shallow needling in clinical practice and provide fresh evidence-based support for its application in treating insomnia.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

WL, CW, and BC conceived the experiment and participated in the study design. WL, CW, and MT were responsible for drafting the manuscript. JY and BC revised the original manuscript. BC and WL are the principal investigators of this study. YY and QH are the supervisors of this study. All authors have read and approved the publication of this protocol.

Conflicts of Interest

None declared.

Checklist 1
SPIRIT checklist.
[PDF File, 111 KB - resprot_v14i1e76501_app1.pdf]

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Abbreviations

CBT: cognitive behavioral therapy
CRF: case report form
GABA: γ-aminobutyric acid
Glx: glutamate/glutamine
MRS: magnetic resonance spectroscopy
PI: primary insomnia
PSQI: Pittsburgh Sleep Quality Index
REM: rapid eye movement
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Moderating Role of State and Trait Positive Affect in Virtual Reality Exposure for Public Speaking Anxiety: Protocol for a Multisite Experimental Study

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Abstract

Background: The identification of moderators of exposure-based cognitive behavioral therapy (EXCBT) outcomes has the potential to (1) guide the judicious application of the limited resource that is EXCBT and (2) identify additional treatment targets for ameliorating the deleterious effects of an identified moderator, thereby enhancing clinical response. Experimental and clinical

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studies have yielded intriguing findings for the moderating influence of positive affect on EXCBT outcomes. Mixed findings for state positive affect (at the time of extinction or exposure trials) as a predictor of EXCBT outcomes stand in contrast to evidence that baseline levels of trait positive affect may be a more effective predictor. As such, questions remain about the best way to assess positive affect as a potential treatment moderator.

Objective: This study was designed to investigate (1) the relative value of state and trait positive affect for predicting the outcome of a single-session virtual reality exposure intervention for public speaking anxiety in adults attending college and (2) the role of 3 related constructs—optimism, hopefulness, and mental health self-efficacy—that may explain the predictive significance of trait positive affect.

Methods: State affect will be manipulated at an experimental level using affect induction procedures; trait positive affect will be measured at baseline. Three dependent measures—a primary outcome of public speaking anxiety and secondary outcomes of social phobia and self-reported valence—will be examined. This study relies on a team science approach and is being conducted across 12 collaborating sites through the Exposure Therapy Consortium, allowing for replication of all findings across diverse study sites worldwide.

Results: Data collection for this study began in October 2024 and ended in August 2025. We expect to complete data analysis and submit results for publication in approximately November 2025.

Conclusions: This study will help clarify the relationship among positive affect (state and trait), exposure learning, and 3 related constructs (optimism, hopefulness, and mental health self-efficacy). These findings will illuminate strategies for future treatment improvement and enhanced efficacy.

Trial Registration: ClinicalTrials.gov NCT06593847; https://clinicaltrials.gov/study/NCT06593847

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KEYWORDS

team science; exposure therapy; moderators; state affect; trait positive affect; speech anxiety; virtual reality

Introduction

Background

Exposure-based cognitive behavioral therapy (EXCBT) is an efficacious first-line treatment for anxiety-related disorders (ie, anxiety, obsessive-compulsive, and trauma- and stressor-related disorders) [1-6]. However, despite its clear efficacy, a substantial minority of patients fail to respond adequately to EXCBT [7-9], continuing the distress and loss of productivity associated with these disorders [10-12]. These limitations on efficacy have motivated the study of extinction learning processes and potential moderators of these processes to better understand, strengthen, and target EXCBT efficacy [7,9].

One such moderator of interest is the affective context of the exposure. In a comprehensive review of the potential of positive affect for improving EXCBT outcomes, Zbozinek and Craske [13] considered the potential beneficial effects of positive affect on core processes linked to extinction learning and retention: attention, encoding, rehearsal, consolidation, retrieval, and stimulus valence. Empirical tests of these ideas have been ongoing. Initial significant findings have been observed for experimental paradigms where positive versus neutral affect were induced [14] or naturally occurring positive affect was examined [15] for predicting better fear conditioning outcomes. However, beneficial effects for positive versus negative affect induction before extinction learning trials were not replicated by Fitzgerald [16] using a fear conditioning paradigm or by van Veen et al [17] using 2-session virtual reality (VR) exposure for participants with high public speaking anxiety. Failures to observe a beneficial effect for preexposure positive affect have also been reported in studies examining extant levels of positive affect in individuals undergoing treatment [18,19].

One possible explanation for these inconsistent findings is that positive affect needs to be experienced across multiple phases of exposure learning, that is, before, during, and after exposure, when the therapeutic memory is consolidated or reconsolidated (eg, when reflecting on the exposure or during between-session exposure practices) [20]. If this explanation is accurate, trait positive affectivity should be a better predictor than state positive affectivity because it has the opportunity to exert its hypothesized effects at multiple phases of the exposure learning process. Results of predictor analyses from 2 clinical trials support this hypothesis [21]. These studies by Taylor et al [22,23] used a measure of trait positive emotionality drawn from the extraversion domain of the NEO Five-Factor Inventory (NEO-FFI) [24], and both studies predicted a significantly better response to cognitive behavioral therapy.

However, trait positive affect is arguably a broader assessment domain than state affect, as reflected by the nature of the assessments used by Taylor et al [22,23]. Specifically, in their first study, Taylor et al [22] used an 8-item positive emotion scale from the extraversion domain of the NEO-FFI, with items reflecting levels of happiness, joy, excitement, and optimism characteristic of one's personality. The second trial [23] used a shortened assessment: a 4-item positive emotion scale again derived from the extraversion domain of the NEO-FFI. Although Taylor et al [22,23] controlled for associations with the broader domain of extraversion and negative mood reflecting depression, potential elements or correlates of trait positive emotionality may help explain the ability of positive emotionality to predict treatment outcomes. For example, there are a number of

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variables that are correlated with both positive affect and treatment responsivity and outcomes and, hence, may account for the predictive significance of trait positive affect. Specifically, 3 additional variables—optimism, hopefulness, and self-efficacy—emerge as important assessment targets. Each was selected due to its potential to mediate effects of trait positive affectivity on EXCBT, as indicated by significant associations between each of these variables and positive affect in addition to significant associations with adaptive responses to stress, adaptive coping, positive expectancies, and positive treatment outcomes [25-35]. Accordingly, to hone prediction and better understand the nature of trait positive affect as a potential moderator of EXCBT outcomes, it is important to evaluate whether the prediction hypothesized for trait positive affect can be accounted for by related constructs such as state positive affect, optimism, hopefulness, and self-efficacy.

Study Objectives

This preregistered study is designed to enhance the understanding of positive affect as a potential predictor (moderator) of EXCBT outcomes by examining two related lines of inquiry: (1) Can we confirm that trait positive affect is a better predictor of treatment outcomes than state positive affect? (2) Can the prediction based on trait positive affect be better understood by considering 3 alternative assessment targets: optimism, hopefulness, and self-efficacy? Answering these questions has the potential to hone attention to a correct and specific mechanistic target (trait vs state positive affect) for understanding and prospectively intervening, with individual characteristics predicting nonresponse to EXCBT. Specifically, accurate specification of a marker of relative nonresponse to this treatment can have a public health impact by aiding (1) the judicious application of EXCBT (personalized medicine) and (2) pretreatment efforts to modify the moderator. Indeed, there is preliminary evidence that such affect-focused treatments can be successful [36]. Accordingly, the longer-term potential of this study is to provide additional strategies for the effective use of EXCBT for patients in need.

To assess the relative capacity of state and trait positive affect to predict responsivity to exposure therapy, we will examine both constructs as moderators of the degree of improvement from a single-session virtual reality exposure intervention for public speaking anxiety in college students. We selected public speaking anxiety as the therapeutic target because it is a prevalent concern among undergraduate students [37,38] and because the use of VR exposure has demonstrated efficacy for treating public speaking anxiety and other social anxiety symptoms [17,39,40]. Furthermore, a VR-delivered intervention is also a highly standardized procedure that can be reproduced exactly across participants and sites [40]. Finally, the use of a single-session VR exposure intervention to judge extinction learning approximates the intervention procedures used by van Veen et al [17] in their study of positive affect induction and exposure outcomes, as well as laboratory paradigms [14].

In this study, state affect just before exposure will be manipulated at an experimental level using affect induction procedures. Trait positive affect will be measured at baseline using procedures developed by Taylor et al [23]. Randomized affect induction will be used for two reasons: (1) to allow for comparison to previous studies that used similar methods [14,16,17] and (2) to ensure that state affect at the time of extinction will be distinct from the degree of trait positive affect. In addition, some studies that have found benefits of state positive affect for extinction learning and return-of-fear outcomes have used the Positive and Negative Affect Schedule [14,41] and, thus, may have been influenced by arousal given that the Positive and Negative Affect Schedule includes only high-arousal items [15]. Our inclusion of state arousal based on the Self-Assessment Manikin (see the Methods section) will help address this alternative explanation for conflicting state affect findings and the value of considering trait affect over state measures. Three dependent measures will be examined—a primary outcome of public speaking anxiety and secondary outcomes of social anxiety and self-reported valence to giving a speech—measured at the 1-week follow-up as the primary outcome window. Initial analyses will evaluate the capacity of both state and trait positive affect to predict VR exposure outcomes. Subsequent analyses will evaluate the degree to which the predictive value of trait positive affect can be accounted for or improved by considering measures of optimism, hopefulness, and self-efficacy.

Use of a Team Science Approach

Replication issues in psychological science have been well documented [42,43], motivating efforts to address them at the study design stage, including efforts to increase both the size and representativeness of the samples under study [44,45]. One strategy for achieving this goal is to conduct team science, defined as a "method involving a relatively large number of collaborators who may be dispersed across labs, institutions, disciplines, cultures, and continents" [46]. The goal is to facilitate replicable research by helping researchers pool their resources to reduce study burden while increasing the size and representativeness of the study sample.

In accordance with this recommendation, this study was designed and proposed and will be conducted by members of the Exposure Therapy Consortium (ETC [47]) [9]. This study responds to recommendations for team science [46] by using a consensus design (ie, examined and approved by the ETC Rigor and Reproducibility Committee and the research steering committee [9]); multiple measures for select constructs; strong documentation of materials and methods; a large and diverse sample; collaboration with colleagues from different settings, backgrounds, and cultures; registration of the trial and analytic plan; and a plan to share data and analytic codes through Open Science Framework registration. To this end, this team science approach will not only enhance the replicability of this study but also enable a more comprehensive investigation of the intricate interplay between positive affect and exposure therapy outcomes across diverse populations and settings.

Methods

Sites

This is a multicenter study with 12 participating sites. Boston University serves as the lead site (coordinating center), distributing study methods and materials to the collaborating

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investigators at Albright College, Curtin University, Erasmus University Rotterdam, Southern Illinois University, Tufts University, University of Arizona, University of Hong Kong, Marburg University, University of New South Wales, University of Texas at Austin, and Utrecht University. Adherence to study procedures is aided by videotaped procedures distributed to the sites. All data entry is conducted via self-report using a REDCap (Research Electronic Data Capture; Vanderbilt University) interface. Each site is asked to screen up to 150 participants, from whom up to 80 participants (the minimal target sample size per site is 40) are to be selected for the VR exposure intervention and posttreatment and follow-up assessments. If needed, each site is permitted to recruit beyond 150 participants for the screening phase to reach the target sample size in the intervention phase. This study is registered with ClinicalTrials.gov (NCT06593847).

Participants

Participants for this study will be undergraduate students reporting high levels of public speaking anxiety who are willing to engage in a single-session intervention. Inclusion criteria for the screening phase of this study (see the Procedures section) are self-reported age of between 18 and 70 years, current attendance to college, ability to read the dominant language used at the university, familiarity with a keyboard and mouse or touch screen device, and willingness to provide informed consent through the REDCap interface.

Assessments

Overview

Table 1 indicates the study phase in which each variable is assessed. Demographic information will be obtained using a brief questionnaire at screening, and an additional treatment history form will be used to obtain clinical information regarding mental health diagnoses and previous mental health treatment; this information will be used to characterize the sample. All outcomes are self-reported via REDCap.

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Table . Assessment schedule.

Measure	Screening and baseline assessment	In-person VREX[a] visit	1-week follow-up assessment
Selection and outcome variables			
Demographics	✓		
PRCA-PA[b]	✓	✓	✓
Valence	✓	✓	✓
SPIN[c]	✓		✓
Core predictor variables			
SAM[d]		✓	
Trait positive affect	✓		
AHS[e]	✓		
LOT-R[f]	✓		
MHSES[g]	✓		
Additional measures			
RRQ[h]	✓		
SCI[i]	✓		
CAMS-R[j]	✓		
SBI[k]	✓		
Treatment history	✓		

[a]VREX: virtual reality exposure.
[b]PRCA-PS: Personal Report of Communication Apprehension, Public Speaking Subscale.
[c]SPIN: Social Phobia Inventory.
[d]SAM: Self-Assessment Manikin.
[e]AHS: Adult Hope Scale.
[f]LOT-R: Life Orientation Test–Revised.
[g]MHSES: Mental Health Self-Efficacy Scale.
[h]RRQ: Ruminative Response Questionnaire.
[i]SCI: Sleep Condition Indicator.
[j]CAMS-R: Cognitive and Affective Mindfulness Scale–Revised.
[k]SBI: Savoring Beliefs Inventory.

Selection and Outcome Variables

The Personal Report of Communication Apprehension, Public Speaking Subscale (PRCA-PS), is a 6-item self-report measure for assessing level of public speaking anxiety; item responses range from 1 (“strongly disagree”) to 5 (“strongly agree”), providing total scores that can range from 6 to 30 [48]. Scores of 18 or higher indicate high- to moderate-severity public speaking anxiety and are used to select individuals for this study at the screening and baseline assessment. In a pilot study for this trial [49], 81.3% of the screened sample responding to advertisements for a public speaking anxiety study scored 18 or higher on the PRCA-PS, consistent with high rates of social anxiety reported for student populations [37,38]. The PRCA-PS serves as the primary outcome at the 1-week follow-up assessment.

The Social Phobia Inventory is a 17-item self-report scale to assess fear, avoidance, and physiological symptoms associated with social anxiety disorder over the previous week [50]. The total score (which can range from 0 to 68) will be used as a measure of social anxiety severity, a secondary outcome variable, and will be assessed at the screening and baseline assessment and 1-week follow-up assessments.

The valence of giving speeches is rated on a scale ranging from −3 (extremely unpleasant) to +3 (extremely pleasant). This measure will be administered at the screening and baseline assessment, immediately after treatment, and at the 1-week posttreatment assessment.

Core Predictor Variables

The Self-Assessment Manikin uses pictures of a humanlike form to have participants rate the degree of current pleasure, emotional arousal, and dominance by selecting the figure that most represents their current affective state on each of these dimensions [51]. The pleasure rating (ranging from 1 to 9) will be used as the measure of state positive affect, administered

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before and after the affect induction. In regression equations, prediction will also be examined for degree of state affective arousal.

Trait positive affect will be assessed at the screening and baseline assessment with the 4 items used by Taylor et al [23] drawn from the extraversion domain of the NEO-FFI (laughs easily, cheerful, and vivacious; reverse items: not cheerful or lighthearted and not a cheerful optimist) [24]. The total of these items rated on a 5-point Likert scale (with scores ranging from 0 to 16) will be used as a predictor of VR exposure outcome.

The Adult Hope Scale is a 12-item measure that assesses hope, a positive motivational resource consisting of agency, or goal-directed energy, and the capacity to identify pathways toward goals [52]. The total score (which can range from 8 to 64) will be used as a predictor of VR exposure outcomes.

The Life Orientation Test–Revised is a 6-item (with 4 additional filler items) measure of optimism: the dispositional tendency to expect positive outcomes of events [53]. The total score, which can range from 0 to 24, will be used as a predictor of VR exposure outcome.

The Mental Health Self-Efficacy Scale is a 7-item measure of self-efficacy for engaging in mental health–promoting behaviors, including the ability to accept uncomfortable mental events, emotions, or sensations; refrain from maladaptive coping or protective actions; and engage in health-promoting behaviors and valued activities (Tech, MJ, unpublished data, April 2025). The mean confidence rating for these items (expressed as between 0% and 100% confidence in the ability to engage in these behaviors) will serve as the self-efficacy measure for predicting VR exposure outcomes.

Additional Measures

The following measures, used to assess degree of rumination, sleep disruption, mindfulness, and savoring, will be assessed at baseline and used in independent, exploratory analyses of associations with VR exposure treatment outcomes given findings indicating such associations [54-57]: the Ruminative Response Questionnaire, a 22-item measure assessing an individual's tendency to ruminate when feeling sad, down, or depressed [58]; the Sleep Condition Indicator (SCI), an 8-item measure designed to assess an individual's sleep quality over the previous month [59]; the Cognitive and Affective Mindfulness Scale–Revised, a 10-item unidimensional scale that assesses mindfulness as it is experienced in general daily occurrences [60]; and the Savoring Beliefs Inventory, a 24-item scale that assesses the tendency to savor, or amplify, positive emotions [61].

Procedures

Select aspects of study procedures may vary from site to site (eg, follow-up session completed in person vs remotely); however, all core procedures (ie, affect induction, VR exposure, and self-report measures) remain consistent. To promote standardization of procedures across sites, study personnel were trained using an instructional video and followed a scripted protocol when implementing VR exposure; sites were also asked to track any deviations. This clinical trial is registered on both ClinicalTrials.gov (NCT06593847) and the Open Science Framework (4ucmj). No changes to the protocol, interim analyses, specific stopping rules, or external monitoring other than by the institutional review boards (IRBs) or health research ethics committees (HRECs) are planned for this study.

Ethical Considerations

All collaborating sites received IRB or HREC approval before data collection. IRB or ethics committee approval numbers were as follows: Boston University (7565E) for which Albright College, the University of Texas at Austin, and Southern Illinois University were reliant upon; Curtin University (HRE2025-0016); Erasmus University (ETH2425-0422); Tufts University (STUDY00005259); University of New South Wales (iRECS 7416); University of Hong Kong (EA240580); University of Marburg (2024-81k); University of Arizona (STUDY00004970); and Utrecht University (FETC 25-0150). All sites provided participants with compensation through either course credits, extra credit, and or monetary compensation.

Screening and Baseline Procedures

Interested participants responding to an advertisement for a "Virtual Reality Intervention for Speech Anxiety Study" will be given access to an online survey via REDCap [62]. Participants will be provided with an electronic consent form explaining all study procedures. If they agree to participate, they will click a button indicating their consent and will be told to continue to the screening and baseline survey. On the basis of responses to the survey (including fully completing core measures, responding correctly to quality assurance items, and completing the survey within 5 days of initiating it), eligible participants meeting the PRCA-PS selection score (>18) will be invited to the in-person session.

In-Person Study Session

The in-person study session lasts approximately 75 minutes and begins with an orientation to the VR device. Participants will put on the headset while sitting in a chair. Participants will be oriented to the VR environment by briefly viewing a 360-degree nature scene. Following VR orientation, participants will be asked to rate their current affect and will then watch 1 of 2 short film clips (totaling approximately 5 minutes) for either positive or negative affect induction, determined via random block assignment (1:1 allocation) using an online tool [63], with a block size of 6 and separate blocks for individuals whose sex assigned at birth was male versus female, as programmed into REDCap. Participants are blind to hypotheses. Film clips are shown on a separate laptop or tablet screen. Film clips for positive affect induction were sourced from the movie *Wall-E* and from the television show *Whose Line Is It Anyway?* The film clips for negative affect induction were sourced from the movies *Bambi* and *The Champ*. Studies have demonstrated that each of these film clips is effective in eliciting the targeted affect [64-67]. Before viewing the film clips, participants will be provided with the following instructions: "Let yourself experience whatever emotions you have, as fully as you can. Don't try to hold back or hold in your feelings." Participants rerate their state affect following their randomized affect induction procedures.

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Following affect induction and subsequent state affect ratings, participants will be shown a prerecorded exposure therapy instruction provided by a therapist from within the VR headset. Participants undergo 6 exposure trials wherein they give a speech to a virtual audience of 6 individuals sitting in chairs around a conference table or in a lecture hall in the 360-degree VR environments [68]. The topic for the speech is "something you're proud of." Following exposures, the VR therapist congratulates the participant and provides a short debriefing statement. Once they remove the headset, participants will be asked to rate their public speaking anxiety and current valence toward giving a speech.

Follow-Up Outcome Assessment

One week following the completion of the single-session VR exposure intervention, participants will be scheduled for the 1-week follow-up assessment. This survey is expected to take approximately 15 minutes to complete. Participants will receive course credit for the portion of the study in which they participate. Spontaneously reported adverse events will be reported to site IRBs or HRECs.

Data Sharing

Data will be analyzed and published by participating ETC investigators. Following publication of primary papers, deidentified data will be available to researchers who sign a data use agreement.

Data Analysis

The preregistered analysis plan on the Open Science Framework provides specifics on the tests to be conducted. In general, a linear mixed modeling approach will be used for data analysis, examining the overall and unique prediction afforded by predictor variables of interest while accounting for variance across sites. Preliminary analyses will evaluate the effects of the experimental manipulation (affect induction) on state affect. Preliminary analyses will also examine the relationships among predictors, particularly in relation to the degree to which trait positive affect shares variance with the hypothesized related constructs of interest: optimism, hopefulness, and self-efficacy. Core analyses will use linear mixed models to examine the hypothesis that trait positive affect is a stronger predictor of outcomes than state positive affect (also accounting for state affective arousal). Core tests of hypotheses will also examine the shared and unique prediction of outcomes, relative to trait positive affect, of measures of optimism, hopefulness, and self-efficacy. The goal of these analyses is to identify the strongest predictors of outcomes to provide greater clarity on the role of positive affect (and associated constructs) as a potential moderator of outcome of exposure-based interventions.

To address missing data and dropouts, we will implement a multipronged approach. The primary analysis will follow intention-to-treat principles using multiple imputation by chained equations, incorporating all available baseline predictors, affect condition assignment, and site indicators in the imputation model. For sensitivity analyses, we will conduct complete case analysis to compare with imputed results.

Power analyses were conducted using the following assumptions: α of .05, power of 80%, and a mixed-effects modeling approach accounting for clustering within sites. We examined detectable effect sizes across a range of intraclass correlation coefficients (ICCs=0.01 to 0.30) to account for variability in site-level clustering that is commonly observed in multisite studies. With our planned sample sizes (40-80 participants per site across 12 sites), this study is adequately powered to detect clinically meaningful moderation effects under realistic ICC assumptions. For example, with low clustering (ICC≤0.05), this study can detect moderation effects of Cohen d=0.36 to 0.48, representing medium effect sizes that are clinically meaningful.

Results

A pilot study of the efficacy of this VR exposure intervention for public speaking anxiety in a sample of 47 college students (who had undergone positive and negative affect induction procedures before exposure) indicated strong feasibility for the methods of this study. The results showed beneficial effects of the single-session VR exposure intervention as indicated by a small to moderate effect size for public speaking anxiety (d=0.32), a moderate effect size for social phobia symptoms (d=0.54), and a small to moderate effect size for self-reported speech valence (d=0.44) from baseline to the 1-week follow-up [49]. Data collection for this study began in October 2024 and is projected to ended in August 2025. We expect to complete data analysis and submit results for publication in approximately October 2025.

Discussion

The ETC was organized to *generate better data faster* by facilitating larger-scale studies that can be completed without substantial funding due to relatively low burden across multiple collaborating sites [9,47]. Furthermore, the use of a particularly large and diverse sample recruited at study sites reflecting different settings, backgrounds, and cultures addresses both issues of lower power and limited replication that have characterized the study of the influence of state and trait positive affect on extinction or EXCBT outcomes [13-19,21-23]. The findings being achieved across the various sites in this trial will provide a perspective on their robustness. In addition, although power to detect specific site differences is limited across a 12-site study, discussions of results will be summarized in relation to an ICC used to describe the amount of variability in prediction that can be attributed to cross-site differences.

A limitation of this study is the focus on the potentially homogeneous population of undergraduate students with high public speaking anxiety; the degree to which our results will fully generalize to a clinical population is not known. Accordingly, although this trial will provide a well-honed test of the role of positive affectivity in response to a well-defined exposure therapy intervention, replication of these methods will be needed for clinical samples. This study also relies on self-report instruments without the use of performance or physiological outcomes. This study is designed to address the influence of positive affectivity on acute (1 week) exposure

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outcomes; the influence of exposure on the maintenance of treatment gains awaits future study.

The accurate identification of markers of EXCBT's acute efficacy is important given that EXCBT is a limited resource, with evidence that only a minority of individuals receive EXCBT for anxiety-related disorders despite its status as a first-line treatment [69-71]. This study was designed to provide guidance on the role of positive affect in treatment response to aid personalized medicine decisions, including, perhaps, pretreatment efforts to modify the moderator [36,67,68].

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All authors are part of the "Exposure Therapy Consortium."

Data Availability

The datasets generated or analyzed during this study are not publicly available due to the complex data use agreements necessary for a worldwide collaboration, but are available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization: MWO (lead), LJL (supporting), TC (supporting), SP (supporting)
Methodology: MWO (lead), LJL (supporting), TC (supporting), SP (supporting), CTT (supporting), MR (supporting), HEF (supporting)
Writing – original draft: MWO (lead), LJL (supporting), TC (supporting), SP (supporting), HEF (supporting), JAJ (supporting)
Writing – review & editing: MWO (lead), LJL (supporting), TC (supporting), SP (supporting), CTT (supporting), MR (supporting), HEF (supporting), JAJ (supporting), QL (supporting), RAA (supporting), AA (supporting), CB (supporting), WRC (supporting), IME (supporting), SEF (supporting), RRG (supporting), BMG (supporting), BAH (supporting), HWH (supporting), JJ (supporting), HMJ (supporting), MAK (supporting), CLML (supporting), EBL (supporting), GVM (supporting), PMM (supporting), CAM (supporting), TMM (supporting), KM (supporting), SMN (supporting), JMN (supporting), PFRP (supporting), AR (supporting), WR (supporting), DR (supporting), LHS (supporting), SCS (supporting), MJW (supporting), AHKW (supporting), QJJW (supporting), NHZ (supporting), ZZ (supporting)

Conflicts of Interest

MWO receives compensation as an advisor to Big Health and receives grant support from the National Institute of Mental Health, the National Institute on Drug Abuse, and Big Health, United States, and royalties from book publications from various publishers. CTT declares that, in the past 3 years, he has been a paid consultant for Bionomics and Atai Life Sciences and has received payment for editorial work for UpToDate, Inc., and the Journal of Depression and Anxiety. JAJS has received grants from the National Institutes of Health, the Department of Defense, and the Trauma Research and Combat Casualty Care Collaborative, United States. He has received personal fees from Big Health, Boston University, and Brown University for consulting and from Elsevier and the American Psychological Association for editorial activities. JAJS also has equity interest in Earkick and has received royalty payments from various publishers. The terms of these arrangements have been reviewed and approved by the University of Texas at Austin in accordance with its conflicts of interest policies. BMG receives funding from the Australian National Health and Medical Research Council and the Australian Research Council. JJ receives royalties for book publications from the Springer Nature Group. PMM receives compensation from Guilford Press, Elsevier, Cambridge University Press, and McGraw Hill Education and grant funding from Perpetual, Healthway, the Future Health Research and Innovation Fund, Suicide Prevention Australia, Beyond Blue, the National Health and Medical Research Council, and the Medical Research Future Fund. JN receives funding from the Australian National Health and Medical Research Council; the Australian Medical Research Future Fund; the National Institute for Health and Care Research, United Kingdom; the Wellcome Trust; and the Australia-Indonesia Knowledge Partnership Platform. WR declares having received honoraria from Boehringer Ingelheim for workshops on post–COVID-19 and shares for book publications. SCS receives employment income from Duke-NUS Medical School; royalties from Oxford University Press; consultation fees from Clinical Psychology Associates; and research grants from the National Medical Research Council, SingHealth Duke-NUS Academic Medical Centre, and Duke University. NHZ receives employment income and research grants from the National University of Singapore. All other authors declare no other conflicts of interest.

Checklist 1

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SPIRIT checklist.
[PDF File, 307 KB - resprot_v14i1e80010_app1.pdf]

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Abbreviations

ETC: Exposure Therapy Consortium
EXCBT: exposure-based cognitive behavioral therapy

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HREC: health research ethics committee
ICC: intraclass correlation coefficient
IRB: institutional review board
NEO-FFI: NEO Five-Factor Inventory
PRCA-PS: Personal Report of Communication Apprehension, Public Speaking Subscale
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
VR: virtual reality

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Implementation Mapping to Identify Best Practices for Implementing Population-Wide Genomic Screening Programs: Protocol for the FOCUS (Facilitating the Implementation of Population-Wide Genomic Screening) Study

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Abstract

Background: Population-wide genomic screening (PGS) for genetic conditions such as hereditary breast and ovarian cancer syndrome, Lynch syndrome, and familial hypercholesterolemia presents opportunities to reduce morbidity and mortality among the 1% - 2% of the population at elevated risk for these serious, preventable diseases. With decreasing sequencing costs and growing support from national bodies, there are increasing numbers of PGS programs in the United States. However, guidelines and strategies to support implementation are limited, especially regarding equitable access to PGS. Contextual factors, such as organizational structures and processes, impact PGS implementation, often failing to benefit underrepresented populations. To address these challenges, we are completing the Facilitating the Implementation of Population-wide Genomic Screening (FOCUS) project, which will develop and test a freely available, web-based implementation toolkit to guide best practices for implementing PGS.

Objective: The FOCUS project aims to (1) examine barriers and facilitators of PGS implementation at diverse health systems, (2) develop implementation strategies with input from an advisory panel and package them into the FOCUS toolkit, and (3) evaluate the toolkit's impact on improving PGS reach, effectiveness, adoption, and maintenance using a hybrid stepped-wedge cluster randomized trial design.

Methods: We will complete implementation mapping, guided by the Consolidated Framework for Implementation Research integrated with health equity, and the Reach, Effectiveness, Adoption, Implementation, and Maintenance framework for Health Equity to develop and evaluate an equity-focused PGS implementation toolkit. The study will involve 10 design sites to identify implementation barriers and facilitators and 12 Test Sites to assess the toolkit's effectiveness. Both design and test sites will be representative of the following 4 stages of implementation: exploration or emerging, planning, implementation, and sustainment.

Results: The FOCUS project was funded in September 2024 and will conclude in June 2029. The project was funded through the Advancing Genomic Medicine Research Program at the National Human Genome Research Institute (R01HG013851-01). Data collection for aim 1 (qualitative interviews with implementation team members, patients, and laboratory vendors) began January 2024. At the time of reporting, 33 interviews have been completed with implementation team members, 8 with patients, and two with laboratory vendors. Qualitative analyses for aim 1 are underway at the time of reporting.

Conclusions: The FOCUS toolkit will establish a standardized approach to scaling PGS programs across diverse populations and settings, ensuring genomics benefits are accessible to all.

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KEYWORDS

protocol; learning health system; population genomic screening; health equity; implementation science

Introduction

Background

Population genomic screening (PGS) offers great promise in identifying the 1%‑2% of the population that carries a pathogenic variant that puts them at elevated risk for serious, yet manageable genetic conditions such as hereditary breast and ovarian cancer syndrome, Lynch syndrome, and familial hypercholesterolemia [1-5]. Rapidly decreasing sequencing costs, endorsement of PGS by national bodies, and attention to precision medicine applications have accelerated the spread of PGS programs [6,7].

Despite this growing momentum, no clear guidelines or strategies exist to support implementation of PGS. Contextual factors, including program-level procedures, organizational structure, patient population characteristics, stakeholder engagement, service delivery models, and access to genetic counseling influence implementation of these large-scale PGS initiatives [8-11]. Given the anticipated growth of PGS programs, practice-based research is needed to better understand these and other factors to inform implementation of PGS programs across diverse settings [11].

Previous genomic-implementation research studies have used systematic approaches grounded in implementation science to develop, evaluate, and user test implementation strategies. These implementation strategies were packaged into a toolkit for Universal Tumor Screening for Lynch Syndrome, and the toolkit components were found to be acceptable, appropriate, and meet the needs of stakeholders [12,13]. Yet, there remains a critical gap in translating such implementation strategies to broader PGS programs, especially those aiming to serve underrepresented populations and reduce disparities in access to genomic services [14-19].

To address this gap, our study aims to facilitate growth of PGS programs and enhance recruitment and retention of representative populations by developing and testing a freely available, online, multicomponent implementation guide (FOCUS [Facilitating the Implementation of Population-wide Genomic Screening] toolkit) to identify best practices for PGS implementation. Our project's specific aims are to (1) describe differences in processes, barriers, and facilitators to equitable implementation across sites at various stages of PGS implementation; (2) develop and package implementation strategies into the FOCUS toolkit to support the equitable implementation of PGS programs; (3) evaluate the impact of the FOCUS toolkit on improving implementation of PGS in diverse populations and settings using a hybrid stepped wedge cluster randomized trial. This project will establish a gold standard approach for equitably integrating PGS and offer the field generalizable methods and knowledge about PGS implementation. In this paper, we describe the planned approach for achieving these aims and highlight how this approach is intended to advance the goal of implementing equitable PGS programs that improve population health.

Contributions to the Literature

1. This study addresses a critical gap in implementation science by developing and testing an implementation toolkit to guide best practices for implementing PGS.
2. By examining barriers and facilitators across diverse settings, this work identifies key contextual factors, such as organizational structures and processes, that influence equitable PGS implementation.
3. Through its hybrid stepped-wedge cluster randomized trial, the study advances methods for evaluating the scalability and sustainability of PGS programs.
4. The findings contribute actionable insights to support the adoption and maintenance of PGS initiatives in healthcare settings across the United States.

Methods

Ethical Considerations

All components of this project involving human participants are approved through Wake Forest University School of Medicine institutional review board protocol (IRB00130700). We follow the Standards for Reporting Implementation Studies for all aims.

Overall Study Design and Conceptual Model

We will use an implementation mapping (IM) approach to complete the FOCUS project (Figure 1). Once an organization has made the decision to implement an evidence-based intervention (eg, PGS), use of IM supports the integration of this program in real-world settings [20]. IM is a structured framework involving five steps that incorporates theory, empirical evidence, and diverse perspectives with the target population to iteratively guide decision making at each step [20]. We incorporate a health equity (HE) focus in genomic medicine as described by the NHGRI in 2019 throughout all components of the IM process, the global applicability of genomic knowledge, fair and even access to genomic services such as testing and counseling, and unbiased implementation of genomic medicine. [17]

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Figure 1. Overview of Facilitating the Implementation of Population-wide Genomic Screening (FOCUS) study: aims and corresponding implementation mapping tasks.

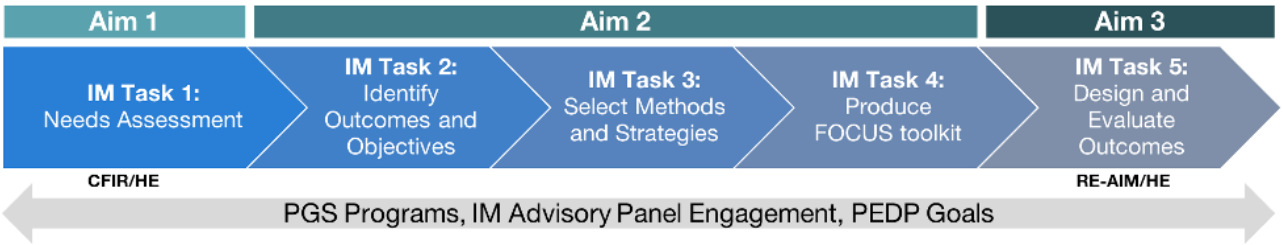

Consolidated Framework for Implementation Research Integrated With the Health Equity Implementation Framework

The Consolidated Framework for Implementation Research integrated with health equity (CFIR/HE) helps create a robust approach for advancing equitable implementation. Consolidated Framework for Implementation Research integrated with health equity includes multilevel determinants of implementation and factors that inform differences in individuals' access to health services, including key factors at the patient, provider, and system levels [21,22]. When combined with CFIR, the HE framework, which focuses on identifying and addressing structural and systemic barriers that perpetuate health disparities, supports a nuanced understanding of determinants of implementation. The CFIR/HE framework will be used to guide Task 1 of IM.

Reach, Effectiveness, Adoption, Implementation, Maintenance Framework for Health Equity

The Reach, Effectiveness, Adoption, Implementation, and Maintenance framework for Health Equity (RE-AIM/HE) framework emphasizes the five dimensions of reach, effectiveness, adoption, implementation, and maintenance to evaluate implementation across diverse settings. Integration of HE adds an explicit focus on identifying and addressing health disparities by incorporating structural, cultural, and systematic factors that influence equitable implementation, which can help inform the evaluation and impact of new programs such as PGS across diverse populations and settings [23,24]. The RE-AIM/HE framework will be used to guide task 5 of IM.

PGS Sites

We will work with 2 distinct sets of PGS sites: FOCUS design sites and FOCUS Test Sites. The FOCUS design sites will be part of Aim 1, which will involve identification and synthesis of evidence about the implementation processes, barriers, and facilitators for PGS implementation. We will include 10 diverse organizations that can speak to experiences across implementation stages: exploration, preparation, implementation, sustainment [25]. Exploration sites are defined as those sites that have not yet made a decision to adopt a PGS program and have not yet begun recruitment therein. Preparation sites are defined as those sites that have decided to implement a PGS program but have not yet begun actively recruiting participants. Implementation sites are defined as sites that have made the decision to adopt a PGS program and are actively recruiting participants but have not yet fully routinized and integrated PGS processes into clinical workflows. Finally, sustainment sites are defined as sites that are steadily recruiting participants and have routinized,integrated, or both types of PGS processes incorporated into their clinical workflows. We will also work with FOCUS Test Sites to rigorously evaluate the FOCUS toolkit for improving the implementation of PGS. These sites will also be at various stages of implementation. We plan to include 12 organizations as FOCUS test sites [25,26].

IM Advisory Panel

Stakeholder engagement is a critical part of IM to ensure an equity-focused approach to the project and support all aspects of this work. Thus, we have organized an advisory panel of 13 individuals consisting of public health agency members, community members, patient groups, a private population screening company, primary care, and clinical stakeholders that will be engaged throughout each aim. The group will meet virtually on a quarterly basis and support the study team in prioritizing, designing, and conducting research throughout the duration of the project. Details about how the IM advisory panel will be engaged are included in each study aim.

Study Aim 1: Describe Differences in Processes, Barriers, and Facilitators to Equitable Implementation Across Sites at Various Stages of PGS Implementation

The first Aim of the FOCUS study is aligned with IM Task 1. We will conduct a qualitative needs assessment among ten PGS programs (ie, FOCUS Design Sites) at various implementation stages (exploration, preparation, implementation, and sustainment). We will use the CFIR/HE framework to identify barriers and facilitators of implementing PGS [21,22]. These 10 sites will be enrolling either clinical or research PGS cohorts [24,27].

The needs assessment will be conducted via interviews of implementation team members (ITM), PGS patients, and laboratory sites. Participants will be assigned a study identification number and all identifying data elements such as names and dates will be removed. The questions asked during the interviews have been adapted from CFIR/HE and agreed upon by the FOCUS study team and the IM advisory panel. Interview questions will be specific to the type of participant, including implementation team members, patients, or laboratory site staff.

As interviews are completed, we will begin extracting qualitative data from the transcripts and audiovisual recordings, via Microsoft Teams for analysis. We will use rapid qualitative data analysis methods to code interviews for each site [28,29]. We

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will complete transcript summaries for each interview and match interview question responses to CFIR/HE domains and subdomains. These Transcript Summaries will be used in 2 subsequent qualitative data analysis steps—Process Mapping and Data Matrix Heat Mapping—that have been described by Salvati et al [30] Briefly, process maps will visually detail the PGS implementation process and workflow described by each team member during their interview. Upon completion of all interviews at the respective site, we will conduct member checking among these interviewees to reconcile discrepancies or omissions in the process maps. Member checking will include discussions with the original interviewees from each site to confirm our findings and process maps, allowing us to create a final aggregate process map for each site.

Site-level data matrix heat maps will be generated through an iterative process that involves mapping interview data to each of the CFIR/HE factors within a spreadsheet and then color coding each construct to represent the extent to which it serves as a facilitator or barrier for PGS implementation at that site. Site-level heat maps will then be consolidated and combined to allow for cross-site comparisons and the identification of patterns of factors that are similar and different across sites.

Study Aim 2: Develop and Package Implementation Strategies Into the FOCUS Toolkit to Support the Equitable Implementation of PGS Programs

The second aim of the FOCUS study is to develop the FOCUS toolkit consisting of implementation strategies, materials, and protocols for implementing and improving PGS programs. This aim will cover IM Tasks 2 - 4.

First, we will identify outcomes and objectives by working with the IM Advisory Panel to prioritize the facilitators, barriers, and inefficiencies identified in IM Task 1 by importance, relevance, and changeability. This will allow us to identify outcomes (ie, what needs to be added or changed to improve PGS implementation) and objectives (ie, how we will address the identified outcomes; IM Task 2).

We will work with the IM advisory panel during aim 2 to select evidence-based strategies to address the facilitators, barriers, and inefficiencies of PGS implementation (eg, information chunking and guided practice). Using the CFIR-Expert Recommendations for Implementing Change (ERIC) matching tool (IM Task 3) [29,31], which aligns ERIC strategies with CFIR factors identified in task 1. This will allow us to identify appropriate implementation strategies for each priority implementation need [32], including strategies that promote equity in access and quality of PGS. The study team will host a feedback session with the IM Advisory Panel on these potential methods and strategies at the conclusion of task 3 and integrate feedback from the panel based on this session.

Ultimately, we will draft implementation strategy protocols and develop materials to package our implementation strategies into the online FOCUS toolkit for PGS (IM task 4). Once the FOCUS toolkit draft has been developed, we will host a feedback session with the IM Advisory panel to capture and integrate recommendations. Finally, we will use a human-centered design approach to prototype and refine the FOCUS toolkit with our FOCUS design sites [33]. Engaging program champions and implementation team members from the 8 FOCUS design sites, we will conduct a live rapid prototyping and iterating session (nonstatistical approaches) to refine our proposed protocols and materials. Validated measures will be used to assess acceptability, appropriateness, and feasibility of using the FOCUS toolkit [34,35]. Through these live sessions, we will collect feedback until we have reached consensus among the IM advisory panel of the planned FOCUS toolkit materials. We will prioritize strategies that are common across PGS sites and that aim to achieve equity in PGS participation and implementation.

Study Aim 3: Evaluate the Impact of the FOCUS Toolkit on Improving Implementation of PGS in Diverse Populations and Settings Using a Hybrid Stepped Wedge Cluster Randomized Trial

The final aim of the FOCUS study is to evaluate the impact of the FOCUS toolkit on RE-AIM, for PGS in 12 FOCUS test sites with diverse populations and settings. The stepped-wedge cluster randomized trial design will evaluate the utility of the FOCUS toolkit for improving outcomes among the 12 FOCUS test sites [23]. This approach will allow us to assess improvements in RE-AIM/HE outcomes among sites at varying stages of implementation: exploration, preparation, implementation, and sustainment. Because sites in the exploration phase will not have begun implementing PGS before using the FOCUS toolkit (no baseline or pre-FOCUS toolkit data about the PGS program), they will be randomized 1:1 to either control (no FOCUS toolkit) or intervention (FOCUS toolkit) conditions using a parallel design. The 8 existing sites will be actively implementing or sustaining their PGS programs (have baseline or pre-FOCUS toolkit data) and will be randomized 1:1 to 1 of 4 possible time steps every 3 months for a 21-month implementation period (steps at 3, 6, 9, and 12 mo; Figure 2). This study is powered based on the effectiveness outcome measured by the proportion of individuals who have completed sample collection after being recruited for PGS. We will have 80% power with a type 1 error rate of 5% and an intracluster correlation coefficient of P=.01, to detect an increase in the proportion of participants submitting samples of at least 5.1% (10% before beginning to use FOCUS toolkit) to 6.0% (15% after beginning to use FOCUS toolkit). This hybrid stepped wedge cluster randomized trial design is a pragmatic approach that will allow us to simultaneously assess RE-AIM/HE outcomes across a representative and generalizable sample of PGS sites with varying amounts of baseline program implementation data and assessment of correlates of posttoolkit use outcomes [36-38].

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Figure 2. Hybrid stepped wedge cluster randomized trial with data collection summary.

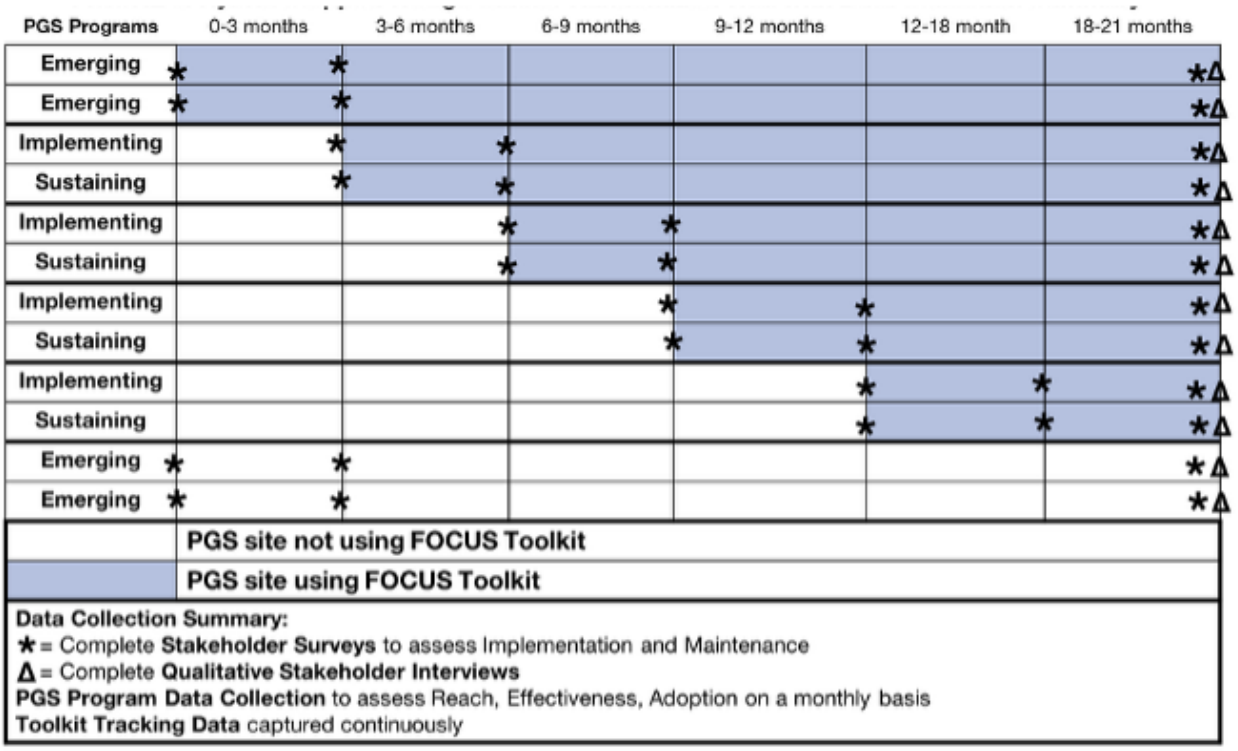

Quantitative data about RE-AIM/HE outcomes will be collected using three tools: (1) PGS program data collection form, (2) stakeholder surveys, and (3) toolkit tracking data (Table 1). The PGS program data collection form will be completed monthly by each site using a REDCap (Research Electronic Data Capture; Vanderbilt University) form designed by the study team. The form will assess metrics related to the implementation outcomes of Reach, Effectiveness, and Adoption. Reach, or how well the PGS site recruits the intended audience, will be measured by the total number of people recruited to participate in the PGS program [39]. Effectiveness will be assessed based on how well the PGS program is achieving its intended public health outcome of identifying individuals with pathogenic variants in genes associated with tier 1 conditions. Our primary measure of effectiveness is the proportion of eligible individuals tested. We will also evaluate the rate of positive findings (number of positive results returned/number tested). Adoption will be assessed based on the number of providers who participate in the PGS program at each site out of the total number of providers eligible to participate at the site.

Table . Aim 3 outcome metrics.

Outcome metric	Measure and description	Data source	Level
Reach	Number of participants	EHR[a] or site administrative records	Individual
Effectiveness	Positive findings: proportion of pathogenic variant and likely pathogenic variant results returned	EHR or site administrative records	Individual
Adoption	Number of providers participating in PGS[b] program versus number of providers that are available at the institution	Administrative records	Site
Implementation	Acceptability, appropriateness, and feasibility	REDCap[c] survey	Site
Maintenance	Intention to sustain PGS	REDCap survey [40]	Site

[a]electronic health record.

[b]PGS: population-wide genomic screening.

[c]REDCap: Research Electronic Data Capture.

The stakeholder surveys will be distributed to implementation stakeholders at each site before beginning to use the PGS toolkit, 3 months after starting to use the toolkit, and at the conclusion of using the toolkit. These will capture data to assess RE-AIM/HE outcomes of implementation and maintenance. Implementation assessment will include acceptability, appropriateness, and feasibility of PGS. These will be captured using the acceptability of intervention measure, intervention

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appropriateness measure, and feasibility of intervention measure, where the intervention is defined as PGS [35]. To assess maintenance, we will ask stakeholders to complete the program sustainability assessment tooprogram sustainability assessment tool to rate the PGS program on the presence of elements associated with long-term sustainability. We will also capture fidelity to the FOCUS toolkit through the toolkit tracking data, which will include website metrics of (1) FOCUS test sites' registered users and (2) the number of times the FOCUS toolkit is opened, along with the number of pages or components visited.

Our primary research question is: does the use of the FOCUS toolkit improve PGS implementation and effectiveness? RE-AIM/HE outcomes among the 8 existing sites (ie, implementation and sustainment sites) that are actively implementing or sustaining PGS using generalized linear mixed models [41]. The primary temporal variable for the analysis of RE-AIM/HE outcomes is the time step; all participants enrolled during a given time step will be retained in that step regardless of study completion date. Statistical analysis will be based on the principle of intention to treat.

The step at which a participant was enrolled in the PGS program will be used as the treatment indicator. At the participant level, a mixed effects logistic regression model will be used to estimate the impact of sites' use of the FOCUS toolkit strategies on the likelihood of participants returning for sample collection. Fixed effects of study time will be included in the model to adjust for secular temporal events throughout the study, and random site effects will be included to account for correlation of participants within sites over time. Participant-level baseline data will be assessed for association with study outcomes and when significant, included in adjusted models. Between-site sample size imbalance may impact the study power and estimation bias, thus initial models will be fit using Fay and Graubard bias-corrected sandwich variance estimator [42,43]. Period-specific recruitment totals will be assessed at the site level using a Gaussian distribution with an identity link. We will use generalized linear mixed models to assess the impact of the FOCUS toolkit among the 4 emerging sites that are part of the parallel design (FOCUS toolkit use vs no FOCUS toolkit use). In addition to addressing primary study outcomes, models including postintervention data from all sites will be assessed to determine if newly emerging PGS sites differ across outcomes as compared to existing sites. Generalized linear mixed effects regression will be assessed with an indicator of site implementation stage to assess postintervention RE-AIM/HE outcomes.

All RE-AIM/HE outcomes will also be assessed qualitatively through in-depth stakeholder interviews. At the conclusion of the implementation period, interviews will be conducted with 5 implementation stakeholders at each site (n=60): a program champion (n=1), a genetic counselor (n=1), an organizational leadership (n=1), and 2 members of the implementation team (n=2). Reach will include questions to understand whether all populations are equitably reached, who is not reached, and how the FOCUS toolkit supports better reach among diverse populations. Effectiveness will focus on whether program impact is equitable across groups, whether sample collection and findings are different across sociodemographics. Adoption will be assessed by asking about the uptake of PGS among clinicians and other key stakeholders within their setting. Implementation will be assessed by asking how PGS has been implemented, facilitators and barriers to implementation, and ways that the FOCUS toolkit helped the site overcome these barriers. To assess maintenance, we will ask stakeholders about the ways they plan to sustain the PGS program long-term and plans for institutionalization of the FOCUS toolkit [44].

A summary will be created immediately following each interview. These summaries will allow for high-level analysis during data collection, facilitate initial codebook development, and reduce the number of new codes requiring recoding during data analysis. Coding will be conducted using an a priori codebook guided by the RE-AIM/HE and CFIR (for contextual factors that are described as impacting RE-AIM/HE outcomes). After an initial review of this codebook, new codes will be added to the other relevant sections of the transcript text not fitting *a* priori codes. A team-based approach will be used to refine the codebook with discrepancies resolved by the study team. All coding will occur in MaxQDA and be completed by 2 coders. Qualitative and quantitative results will be reviewed together, and triangulation of data will occur using a rapid analytic coding matrix [45-47]. This will allow us to better understand how the PGS programs have changed over time and to what extent the FOCUS toolkit was adapted and used in accordance with the protocol.

Results

The FOCUS project was funded in September 2024 and will conclude in June 2029. The project was funded through the Advancing Genomic Medicine Research Program at the National Human Genome Research Institute (R01HG013851-01). Data collection for aim 1 (qualitative interviews with implementation team members, patients, and laboratory vendors) began January 2024. At the time of reporting, 33 interviews have been completed with implementation team members, 8 with patients, and 2 with laboratory vendors. Qualitative analyses for aim 1 are underway at the time of reporting.

Discussion

The FOCUS project will be the first to systematically identify facilitators and barriers to PGS implementation across a range of settings and stages of implementation. Further, the FOCUS toolkit will offer implementation strategies to address the identified barriers and leverage facilitators to support equitable PGS implementation. The diversity of PGS programs and comprehensive approach to data collection allows for findings to be broadly applicable and generalizable, recognizes contextual differences, collects data about strategies used in the real world, and is directly aligned with calls to develop a strategic PGS implementation agenda [48]. This approach can support widespread integration of PGS into routine practice by reducing evidence-based knowledge gaps about barriers and facilitators that impact PGS implementation.

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There are several limitations to consider, which include potential dropout of FOCUS Design Sites and difficulty in recruiting diverse stakeholders and participants from each site. We have identified a program champion at each FOCUS design site and offered incentives for qualitative interviews. We will continue outreach until we reach saturation of qualitative themes (eg, new themes or concepts do not emerge) among PGS programs or until all associated stakeholders from each program have been approached. In addition, testing the toolkit with FOCUS test sites could be challenging. We will include sites at various stages of implementation (emerging, implementing, and sustaining). Given the timing, we will need to identify emerging sites closer to the start of aim 3 to ensure they are still in the emerging phase. As such, we will not identify these sites a priori; however, the literature has demonstrated a steep annual increase in the number of PGS programs in the United States, with triple the number of programs since 2017 [2,6,49]. Thus, it will be feasible to identify at least four emerging sites to participate. We will use our professional and research networks to identify and invite these sites to participate.

The FOCUS project will be foundational for the field by capturing what has been collectively learned to date about implementation of PGS and providing a flexible multicomponent implementation guide (FOCUS toolkit) to support the success of these programs with a special focus on advancing health equity in PGS. We will fill an unmet need to understand the best practices associated with implementation of PGS, and the toolkit that we produce will help develop, implement, and optimize PGS programs in the face of an evolving landscape. Findings from this research are critical to enhance the rapid expansion of PGS programs in the United States by providing generalizable methods for effective implementation. Ultimately, this will improve health outcomes through more comprehensive and equitable identification of individuals with inherited cancer and cardiovascular conditions.

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Authors' Contributions

Conceptualization and Study Design: CA, MR, KF.
Methods: CA, MR, KF, CW, DC, AB, MH, NB, AE, MF, and CH.
Data Collection: CA, MR, JM, KF, and CW.
Formal Analysis: CA, MR, JM, KF, CW, and NB.
Writing Original Draft: CA, MR, and JM.
Writing Review and Editing: CA, MR, KF, CW, DC, AB, MH, NB, AE, MF, CH, and IW.
All authors have reviewed the manuscript and consent for publication.

Conflicts of Interest

None declared.

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Abbreviations

CFIR/HE: Consolidated Framework for Implementation Research integrated with Health Equity
ERIC: Expert Recommendations for Implementing Change
FOCUS: Facilitating the Implementation of Population-wide Genomic Screening
HE: health equity
IM: implementation mapping
ITM: implementation team members
PGS: population-wide genomic screening
RE-AIM/HE: Reach, Effectiveness, Adoption, Implementation, and Maintenance framework for Health Equity
REDCap: Research Electronic Data Capture

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Evaluation of the Comparative Efficacy of Honey Thermal Microcautery, Standard Physiotherapy, and Sida cordifolia Oil via Nasal Administration in the Management of Frozen Shoulder: Protocol for a Randomized Controlled Trial

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Abstract

Background: Frozen shoulder is an ailment that denotes dysfunction in the arm characterized by limited range of motion accompanied by pain. The prevalence of adhesive capsulitis is 3% to 5% in the general population and up to 20% in those with diabetes. Physiotherapy, analgesics, corticosteroids, and surgical capsulotomy are common forms of treatment. Administering oil through the nasal route (or *nasya karma*) is mentioned in the Ayurvedic scriptures for managing neck and clavicle disorders. Thermal microcautery (or *agni karma*) is a parasurgical procedure for treating related pathologies of bodily humors (*vata* and *kapha*). This study will aim to compare the efficacy of honey thermal microcautery, standard physiotherapy, and *Sida cordifolia* oil via nasal administration in the treatment of frozen shoulder to determine which provided the most relief.

Objective: The primary aim is to evaluate the efficacy of honey thermal microcautery, standard physiotherapy, and *S cordifolia* oil via nasal administration using the visual analogue scale, range of motion, the Shoulder Pain and Disability Index, and the McGill Pain Questionnaire and compare these interventions. The secondary objective is to assess sustained relief in all 3 groups.

Methods: We will enroll 60 patients, 20 in each group, for this single-blind assessor-controlled study. Group A will receive Ayurvedic treatment, that is, thermal microcautery using honey for 2 days (the first and seventh) and placebo capsules (twice per day) for 7 days, group B will receive standard physiotherapy and placebo capsules (twice per day) for 7 days, and group C will be given *S cordifolia* oil via nasal administration with 8 drops in each nostril and placebo capsules (twice per day) for 7 days. The evaluation parameters are pain (visual analogue scale), range of motion measured using a goniometer, the Shoulder Pain and Disability Index, and the McGill Pain Questionnaire. On September 18, 2023, approval was received from the Institutional Ethics Committee of Mahatma Gandhi Ayurved College Hospital and Research Centre (MGACHRC/IEC/Sep-2023/740).

Results: The results will be subjected to statistical analysis using appropriate methods such as ANOVA. If the ANOVA shows significance, post hoc tests (eg, the Tukey honestly significant difference test) will identify group differences, with $P<.05$ considered significant. As of January 2025, a total of 16 patients have been recruited, divided into 3 groups, and the final results are expected to be published in November 2025.

Conclusions: This comparative study seeks to establish the most effective treatment among honey thermal microcautery, standard physiotherapy, and *S cordifolia* oil *nasya* for managing frozen shoulder, potentially offering new integrative approaches to treating this condition.

Trial Registration: Clinical Trials Registry India CTRI/2023/11/059594; https://ctri.nic.in/Clinicaltrials/pmaindet2.php?EncHid=OTQyNjc=&Enc=&userName=

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KEYWORDS

frozen shoulder; range of motion; placebo; Sida cordifolia; physiotherapy; thermal microcautery

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Introduction

Background

Frozen shoulder (FS) is an ailment frequently seen in general practice. The prevalence of FS, also referred to as adhesive capsulitis and periarthritis, is between 3% and 5% in the general population and up to 20% in those with diabetes. It affects people aged between 40 and 60 years more frequently, including women and manual laborers [1,2]. In patients with diabetes, the incidence is 2 to 4 times higher than in the general population [3]. The prevalence of people who experience pain in the other shoulder after the first shoulder has healed is 6% to 17%, usually within 5 years. It is slightly more likely that the nondominant shoulder will be impacted [4]. The range of motion (ROM) in all directions is significantly reduced in FS (capsular pattern). It results from swelling, scarring, thickening, and shrinking of the capsule that typically encloses the shoulder joint [5]. Global fibroplasia results from a disruption in local collagen translation in FS, which is characterized by severe inflammatory changes in the capsule that point to the involvement of inflammatory mediators (interleukins, cytokines, B and T lymphocytes, growth factors, matrix metalloproteinases, tumor necrosis factors, and fibroblast activation markers) [6-9]. Synovitis-related inflammatory response in the capsule precedes the fibrotic rigidity of the capsule in cases of FS. Using nonsteroidal anti-inflammatory drugs, steroids, physiotherapy, and occasionally hydrodilatation and surgical procedures is the first line of treatment for FS. For most patients, conservative treatment, which includes corticosteroid infiltration and physiotherapy, is considered a suitable choice [1]. Still, despite conservative care, up to 50% of patients claim to have persistent pain, and up to 60% have noticeable motion restriction [10,11].

Steroid injections offer strong anti-inflammatory effects for FS, but potential complications such as pain and glucose changes may prevent patients from accepting this method. Patients endure lengthy rehabilitation times accompanied by a significant degree of pain and everyday disabilities [12,13]. Hence, an alternative Ayurvedic therapy is required in treating FS.

By using Ayurvedic principles, FS can be managed effectively [14] as several studies have investigated the efficacy of Ayurvedic treatments for FS [15]. There are few published clinical studies and case reports on the efficacy of Ayurveda interventions such as *laghumasha tail nasya* [16], *mahamasha taila nasya* [17], *agni karma* with *panchlohashalaka* [18], and *agni karma* with *tamra shalaka* [19].

One study was carried out at the Chaudhary Brahm Prakash Ayurved Charak Sansthan hospital on the efficacy of *mahamasha taila brihana nasya* and *agni karma* and found significant results [20].

Rationale of the Study

The 3 arms in our study were selected considering their unique mechanisms of action to adequately treat FS. Honey thermal microcautery is an Ayurvedic treatment with thermal effects. Standard physiotherapy is the classic gold standard, ensuring a robust comparator. *Sida cordifolia* oil via nasal route was selected considering its efficacy for *vata-kapha* disorders, particularly musculoskeletal diseases. These treatments were selected considering the evaluation and comparison of diverse approaches between modern medicine and traditional medicine toward optimal outcomes.

No study has been published comparing honey thermal microcautery, standard physiotherapy, and *S cordifolia* oil nasal administration. Additionally, no study has explored the use of honey thermal microcautery in FS. Considering these gaps, this study is essential to determine the most effective and safe therapeutic approach for FS, evaluating interventions such as honey thermal microcautery, standard physiotherapy, and *S cordifolia* oil nasal administration to identify treatments that optimize recovery time and minimize associated concerns.

Methods

Overview

This study is an interventional, randomized, single-blind (assessor), 3–parallel arm study to compare the efficacy of honey thermal microcautery versus standard physiotherapy versus *S cordifolia* oil via nasal administration in the management of FS. We will intervene using honey thermal microcautery 2 times (the first and seventh day) along with placebo capsules twice daily for 7 days. Standard physiotherapy will be administered once a day along with placebo capsules twice daily for 7 days. *S cordifolia* oil via nasal administration will be administered via 8 drops in each nostril along with placebo capsules twice daily for 7 days. Follow-up will be conducted on the 8th, 16th, and 32nd days. Placebo capsules will be administered to reduce the psychological effect that patients might feel from knowing that they are not receiving any oral medicine, especially in the honey thermal microcautery group, where the treatment is administered only 2 times a week.

Objectives

This study aims to determine the comparative effectiveness of honey thermal microcautery, standard physiotherapy, and *S cordifolia* oil nasal administration in managing FS. The primary objectives are to quantify pain reduction, measured via the visual analogue scale (VAS), and assess improvements in ROM, as well as administer the McGill Pain Questionnaire and Shoulder Pain and Disability Index (SPADI) for each treatment group at specific time points: 8 days, 16 days, and 32 days after the intervention.

Secondary Objective

The secondary objective is to evaluate and compare the sustained relief on the 32nd day in each group, defined as maintaining at least a 50% improvement in the VAS score, ROM, McGill Pain Questionnaire score, and SPADI score compared to baseline measurements.

Study Setting

The participants for this trial will be selected from specialized peripheral camps conducted in various urban and rural areas surrounding Wardha, Maharashtra, by the Datta Meghe Institute of Higher Education and Research, Mahatma Gandhi Ayurved College Hospital and Research Centre and the *panchakarma* (a prominent Ayurvedic tool) outpatient and inpatient department

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of Mahatma Gandhi Ayurved College Hospital and Research Centre.

Patients of either gender aged between 20 and 60 years clinically diagnosed as per the *International Statistical Classification of Diseases, 10th Revision* criteria code 75.00 regarding primary first- and second-grade FS will be selected.

The 2013 SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines will be followed for this study.

Simple randomization will be conducted using a computer-generated table. The participant enrollment process, allocation sequence creation, and intervention assignment will be handled by the researcher.

Inclusion and Exclusion Criteria

This study will include (1) patients who are willing to provide written informed consent; (2) patients who are fit for nasal oil administration as per classic Ayurvedic guidelines [21] (ie, those who are free of indigestion; have not consumed food or alcohol recently; or do not have severe thirst, hunger, or exhaustion); (3) patients of either gender aged 20 to 60 years [22]; (4) patients with controlled type 2 diabetes mellitus (fasting blood sugar ≤140 mg/dL and postprandial blood sugar ≤180 mg/dL); and (5) patients with primary FS at the inflammatory (first) and frozen (second) stages. This study will exclude patients who are unfit for thermal cauterization [23]; patients who are contraindicated for physiotherapy (eg, those with epilepsy or a pacemaker); patients with trauma or injury (eg, dislocation or fracture of the shoulder and clavicle); patients with uncontrolled hypertension (160/100 mm Hg); patients who have rheumatoid arthritis, spinal canal stenosis, all types of malignancies, and stroke; patients with infectious conditions or systemic disorders; patients who are indicated for FS surgery; postoperative patients with FS; and pregnant and lactating women.

Strategies to Improve Adherence to the Study Protocol

The participants will be assessed every day during the 7-day treatment period for procedure adherence and placebo capsule consumption. The participants will be asked to return the empty medicine container at the end of the study. Repeated phone reminders to regularly take the medicine from project staff will be given to participants or their family members.

Intervention Description

This study involves 3 groups, each with specific treatment protocols, shown in Table 1. All 60 eligible participants will be thoroughly informed about the study protocol, and their consent will be obtained. They will be randomly divided into 3 groups: group A, group B, and group C. In group A, participants will receive honey thermal microcautery 2 times (first and seventh days) and placebo capsules for 7 days. Group B will receive standard physiotherapy once a day along with placebo capsules for 7 days. Group C will receive *S cordifolia* oil via 8 drops in each nostril and placebo capsules for 7 days. All baseline parameters will be recorded at the beginning of the trial. This study conforms to the SPIRIT guidelines, ensuring standard execution and ethical handling of the clinical trial. Placebo capsules will be identical in appearance, taste, and administration schedule to mimic a real medication. These will be administered alongside the active intervention twice daily after food, ensuring blinding and consistency throughout the study.

Table . Grouping and posology.

Group	Intervention	Dose and frequency	Procedure time (min)	Duration (d)	Follow-up
A	Honey thermal micro-cautery+placebo	2 times a wk	20-30	2 (first and seventh)	On the 8th, 16th, and 32nd days
B	Standard physiothera-py+placebo	Once a day (in the morning)	30-60	7	On the 8th, 16th, and 32nd days
C	*Sida cordifolia* oil via nasal route+placebo	8 drops once a day	20-30	7	On the 8th, 16th, and 32nd days

Study drugs will be stored in a secure location and administered to the participants only under the direction of the investigator. Drug dispensing records will be kept. Any imbalance in the quantities dispensed and returned will be explained.

Properties of the Drugs Used in *S Cordifolia* Oil

The properties of the *S cordifolia* ingredients are shown in Table 2. The available *S cordifolia* oil of market preparation (*sahastra yoga*) [24] will be used. The treatment group medicine will be procured from good manufacturing practice–certified pharmacies to ensure the product's safety and quality standards.

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Table . The names of the drugs used to prepare *Sida cordifolia* oil with their Latin names and properties and the parts used.

No.	Ingredient	Botanical name	*Rasa* [a]	*Guna* [b]	*Virya* [c]	*Vipaka* [d]	*Doshaghnata* [e]	Part used
1	Bala[g]	*S cordifolia*	Madhura[j]	Guru[l], snigdha[m], and pichhila[n]	Sheeta[o]	Madhura[j]	Vatapit-tashamak[s]	Root
2	Tila taila[h]	*Sesamum indicum*	Madhura[j] and tikta[k]	Guru[l]	Ushna[r]	Ushna[r]	Vatakapha-hara[t]	—[f]
3	Godugdha[i]	—	Madhura[j]	Sheet[o], snigdha[m], Kinchidkled-karka[p], and kinchidgu-ru[q]	Sheet[o]	Madhura[j]	Vatpit-tashamak[s]	—

[a]Taste.
[b]Qualities.
[c]Potency.
[d]Postdigestive effect.
[e]Postdigestive action on doshas.
[f]Not used.
[g] Country mallow
[h] Sesame oil
[i] Cow milk
[j] Sweet
[k] Bitter
[l] Heavy
[m]Unctuous
[n]Slimy
[o]Cold
[p]Mildly unctuous
[q]Mildly heavy
[r]Hot
[s]Pacifies both Vata and Pitta (bodily humor)
[t]Removes aggravated Vata and Pitta

Procedure for Oil Administration Through the Nostrils

Oil administration through the nostrils is conducted in 3 phases [25]: preprocedure (*poorvakarma*), main procedure (*pradhanakarma*), and postprocedure (*aschatkarma*).

Preprocedure (Poorvakarma)

Collection of Material (*Sambar Sangraha*)

The procedure will be conducted in a room free of dust and direct flow of air; with appropriate lighting; and equipped with a table, a chair, medicine for nasal administration, an instrument for administering oil through the nasal route, a towel, cotton, a smoke-producing instrument, a spitting vessel, oil for massage, and material for sudation.

Examination of the Patient

Patients unfit for nasal oil administration will be excluded. Informed consent will be obtained, and the patients will be instructed to brush their teeth and clean their mouths.

Positioning

The patient will recline comfortably, either sitting with the neck slightly tilted backward or lying on a table with the head supported by a towel. A gentle massage with sesame oil will be applied to the face and head, followed by mild face heating.

Main Procedure (*Pradhana Karma*)

The patient's eyes will be covered with a cloth. Eight drops of *S cordifolia* oil will be gradually administered one by one into the distal portion of both nostrils using the index finger of that practitioner's hand and cotton.

A gentle massage will be administered to the forehead, cheeks, hands, and feet. The patient will be instructed to spit out any excess oil that reaches the mouth. The patient will be kept lying down while watching any symptoms that develop.

Postprocedure (*Paschatkarma*)

The patient will rinse their mouth with warm water and gargle. Mild medicated *Curcuma longa* smoke will be inhaled to clear

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the throat. The patient will rest in a warm, wind-free environment; follow a light diet; and drink warm water.

Thermal Microcauterization Procedure

Preprocedure (Poorva Karma)

The patient will be informed about the procedure, and written consent will be obtained. A pinpointed metallic rod will be made red hot by directly heating it on a fire and smeared with honey [26]. The affected shoulder will be cleaned using a povidone solution, and tender points will be marked.

Main Procedure (Pradhan Karma)

The heated rod will be applied to the marked tender points by keeping a 0.5- to 1-cm distance for approximately 1 second at each end. The number of burns will be determined based on the patient's tolerance and the number of tender points.

Postprocedure (Paschat Karma)

Aloe vera pulp will be applied to the treated areas, and *Glycyrrhiza glabra* powder will be sprinkled. The patient will be advised to avoid trauma, exertion, and water on the treated site for at least 12 hours.

Standard Physiotherapy Procedure

Preprocedure

The patient will be informed about the exercises, and written consent will be obtained. The patient will be instructed on proper technique and complete preparatory exercises (pendulum swing) [27].

Main Procedure

For the shoulder wheel, the patient will stand sideways, align their shoulders with the wheel's axis, and perform 10 anterior and 10 posterior rotations. Abduction and flexion exercises on a wall-mounted shoulder finger ladder will be conducted next. Patients will stand sideways facing the ladder and perform each movement for 10 repetitions.

Postprocedure

The patient will rest for 5 to 10 minutes.

Outcomes

This study aims to evaluate and compare the efficacy of honey thermal microcautery, standard physiotherapy, and *S cordifolia* oil vial nasal administration using criteria such as the VAS, ROM, the McGill Pain Questionnaire, and the SPADI in patients diagnosed with FS.

Ruja (Pain; VAS)

The patient will be asked to rate the intensity of the pain they are experiencing on a scale from 0 (no pain) to 10 (worst pain) [28].

There will be 5 pain subcategories: no pain, mild pain, moderate pain, severe pain, and intolerable pain. Numbers from the scale will be used to measure the intensity of the pain, as shown in Table 3. A score of 0 will be considered no pain, a score of 1 to 3 will be considered mild pain, a score of 4 to 6 will be considered moderate pain, a score of 7 to 8 will be considered severe pain, and a score of 9 to 10 will be considered intolerable pain. Identifying patients with FS using this VAS pain assessment will make it easier to include them in this study for treatment.

Table . The grading on the visual analogue scale (VAS) for frozen shoulder.

Pain level	Pain grade (VAS score)
No pain	0
Mild pain	1 (up to 3)
Moderate pain	2 (4-6)
Severe pain	3 (7-8)
Intolerable pain	4 (9-10)

Normal ROM of the Shoulder Joint

The goniometer measures the shoulder's ROM before and after treatment [29].

Flexion, extension, abduction, adduction, and internal and external rotation are possible shoulder movements, and the normal readings for these movements are shown in Table 4.

Table . The regular movements and readings for the shoulder joint.

Movement	Normal reading (degrees)
Flexion	180
Extension	50
Abduction	180
Adduction	50
Internal rotation	90
External rotation	90

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All the ROM measurements will be taken in a standing position, and the participant will be instructed to place the back of the head, back and buttocks, and heels against the wall to prevent the trunk from moving. Each movement will be measured 3 times on a goniometer at the glenohumeral joint to avoid human error, and the average of 3 readings will be calculated and recorded.

SPADI Measurement

The pain scale and disability score will be decided based on a questionnaire administered by the researcher to the participants [30], as shown in Multimedia Appendix 1. Verbal anchors for the pain dimension are “no pain at all” and “worst pain imaginable,” and those for the functional activities are “no difficulty” and “so difficult that it required help.” The scores from both dimensions are averaged to derive a total score.

Interpretation of Scores

The total pain score as a percentage is calculated using the following formula: total obtained score / 50 × 100. If a participant does not answer all questions, the score is divided by the total possible score (eg, if 1 question is missed, the score is divided by 40).

The total disability score as a percentage is calculated using the following formula: total obtained score /80 × 100. If a participant does not answer all questions, the score is divided by the total possible score (eg, if 1 question is missed, the score is divided by 70).

The total SPADI score as a percentage is calculated using the following formula: total obtained score /130 × 100. If a person does not answer all questions, the score is divided by the total possible score (eg, if 1 question is missed, the score is divided by 120) The means of the 2 subscales are averaged to produce a total score ranging from 0 (best) to 100 (worst).

McGill Pain Questionnaire

The McGill Pain Questionnaire assesses pain through 3 components: sensory, affective, and evaluation dimensions [31]. Patients select descriptors that match their pain experience, and pain is related to intensity using a present pain intensity scale. Results are interpreted by summing the pain rating index.

Participant Timeline With Deliverables

Table 5 outlines the study’s timeline, highlighting each phase’s duration and overlapping activities systematically. The total study period is 24 months, including preparatory work, recruitment, intervention, follow-up, and analysis and comprises 3 cycles (ie, 1-3.5 months for the drugs), including buying the drugs. Recruitment of the staff, procuring the equipment, and finalizing the case report form (CRF), among other related activities, were completed in the initial phase, not throughout the full 24 months. Participants will be recruited over 16 months, the treatment period will last 7 days, and the last follow-up will be on the 32nd day. Data compilation, analysis, report preparation, and publication will be conducted during the last 3 months.

Table . Gantt chart.

Step	Quarter							
	1	2	3	4	5	6	7	8
Approval from IEC[a]	✓							
Review of the literature		✓						
Drug preparation			✓					
Enrollment of patients				✓	✓			
Data collection				✓	✓			
Statistical analysis				✓	✓			
Thesis writing						✓		
Submission						✓		

[a]IEC: institutional ethics committee.

Sample Size

Formula Using Mean Difference

The sample size was calculated based on pilot study data due to the absence of larger studies on this topic as follows:

n1=n2=2·(Zα+Zβ)2σ2(δ)2 Zα=1.96at 5\% error \§amp; CI at 95\%Zβ=0.84Power at 80\%

Primary Variable: Abduction Improvement

The primary variable, shoulder abduction improvement, was used to calculate the minimum sample size required for the study, ensuring adequate power to detect a meaningful difference between groups. The primary variable in this study is shoulder abduction improvement, measured as the increase in the range of motion after the intervention. Based on expected differences, variability, significance level, and power, the minimum sample

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size required was calculated to ensure reliable detection of a meaningful improvement

Where the mean score for abduction in *shudhabala taila nasya* pre=2.23 (as per the study by Revathi et al [22]).

Mom score for abduction in *shudhabala taila nasya* post at follow-up=1.06.

Difference (pretest-posttest)=1.17

SD=0.58.

Considering 45% superiority in the thermal microcautery group=(1.17) × 45 = 0.526

Mean differen c e δ=0.526

Minimum Sample Size Required

Based on expected differences, variability, significance level, and power, the minimum sample size required was calculated to ensure reliable detection of a meaningful improvement:

$n=1=2=2 \times (1.96 + 0.84)^2 \times (0.58)^2/(0.526)^2=20$ per group

Total samples = 20 × 3 per group=60

Randomization and Allocation

Computer-generated random numbers will be used to create a randomization chart. The participants will be randomized at a ratio of 1:1:1. To guarantee that treatment assignments are balanced, allocation sequence creation will be conducted using permuted blocks and provided in a randomized table. The researcher will enroll and give the participants an intervention and allocation sequence.

Study Procedure

Overview

Before any activities related to the trial are initiated, participants or their guardians will be provided with verbal and printed information about the study. The investigator will ensure that they fully understand the study's objectives, procedures, possible discomforts, and expected benefits. Participation shall be voluntary, and participants shall retain their right to withdraw from the trial at any time without prejudice.

After screening, suitable patients will be included in the study after signing the consent form. A required examination will be conducted. If the patients fall within the inclusion criteria, they will be included in the study with that day written down as day 1 or the baseline visit. They will be administered the treatment after completing all the formalities according to the protocol. Participants will visit the study site on procedure days and follow-up days during the trial. The activity details during each visit are shown in Table 6 and Figure 1.

Table . Study schedule.

Component	Screening (day X)[a]	Baseline (day 0)	Day 1	Days 2-6	Day 7	Day 8	Day 16	Day 32
Informed consent	✓							
Demographic information and medical history		✓						
Assessment of *prakriti*[b]		✓						
Clinical examination	✓	✓	✓	✓	✓	✓	✓	✓
Honey thermal microcautery			✓		✓			
Standard physiotherapy			✓	✓	✓			
Sida cordifolia oil administration via nasal route			✓	✓	✓			
Placebo capsule issue			✓					
Assessment of adverse reactions			✓	✓	✓	✓		
Follow-up visit						✓	✓	✓

[a]Day X refers to the variable screening day when a participant is evaluated before the official baseline (day 0) of the study.

[b]Body constitution

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Figure 1. Study procedure.

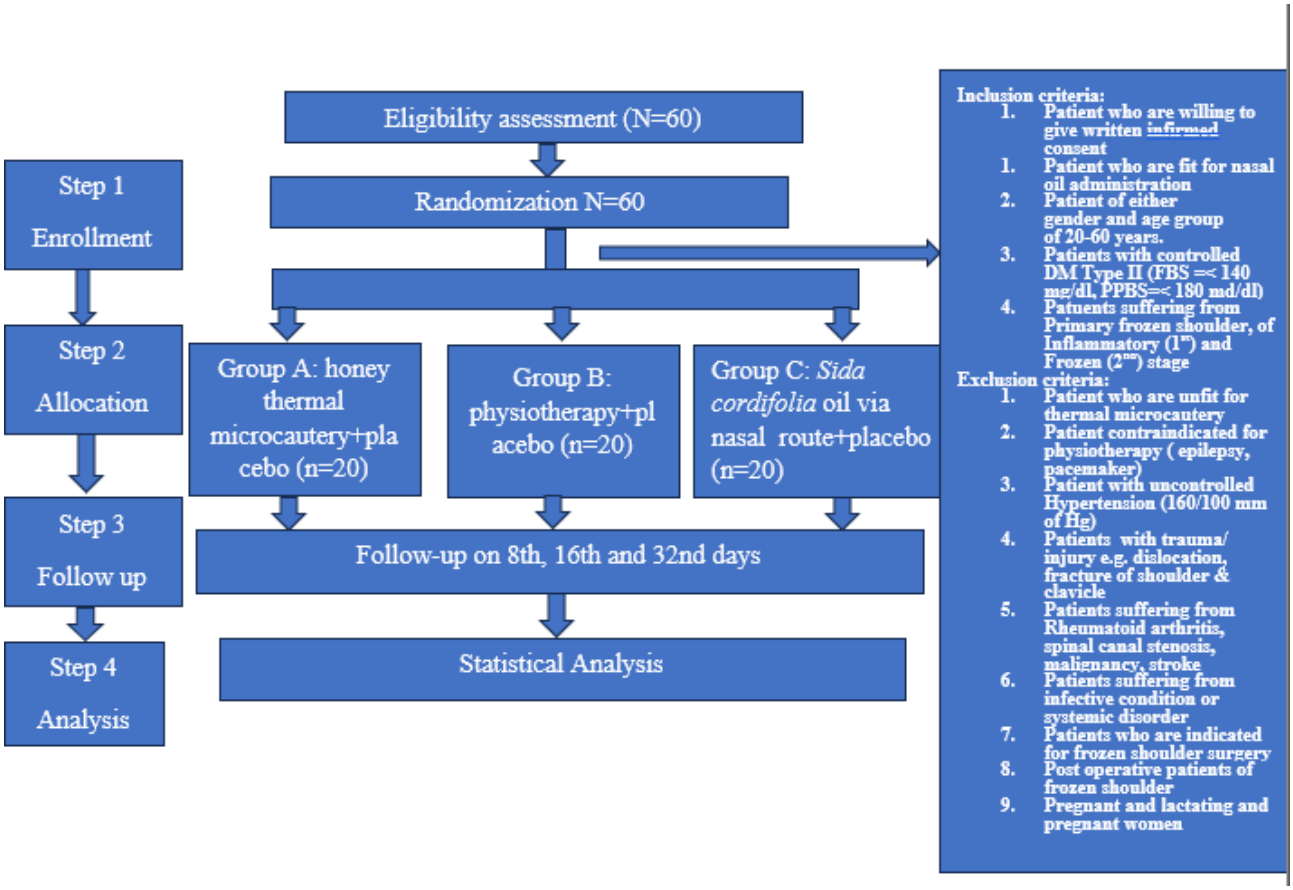

Withdrawal Criteria

The participants may be withdrawn from the trial under any of the following circumstances: (1) any adverse event or adverse reaction (AR), (2) voluntary withdrawal by the participant, (3) violation of inclusion or exclusion criteria, or (4) noncompliance with the treatment regimen (a minimum of 80% compliance is required to continue participating in the study).

Data Collection Plan and Management

All the details entered in CRFs will be collected, and each participant will be provided with a unique enrollment number. The signed consent forms, along with the CRFs, will be placed in locked cabinets, and all electronic data will be password protected. Data access will be limited to the principal investigator and coinvestigator during and after the study. For dropouts, 10% of the data will be imputed using proper techniques, and efforts will be made to collect data for at least 1 month after enrollment.

Emergency unblinding will be conducted only if necessary for the participant's safety or clinical management. If needed, the investigator will follow the emergency unblinding procedure. The allocation will not be revealed to the participant or study personnel unless necessary for patient care. All unblinding events will be recorded in the CRF.

Statistical Methods

One-way ANOVA will be applied to compare the means of the 3 groups. If ANOVA indicates a significant difference, post hoc tests will be further applied (eg, the Tukey honestly significant difference test) to identify which group differs. A P value of <.05 will be considered statistically significant. Covariates such as age and baseline severity will be considered, and adjustments will be made using analysis of covariance if needed. The analysis will be intention to treat, with missing data handled through multiple imputation. Statistical assistance will be provided by a statistician or someone skilled in statistics. We will use SPSS (version 26; IBM Corp) for statistical analysis.

Ethical Considerations

All study interventions and treatments will be provided completely free of cost, and participants will not be charged for any procedures, assessments, or related expenses.

Overview

Ethics approval from the Institutional Ethics Committee of Mahatma Gandhi Ayurved College Hospital and Research Centre was received (MGACHRC/1EC/Sep-2023/74) on September 18, 2023. The Clinical Trials Registry India registration number for this study is CTRI/2023/11/059594. The committee will oversee the trial's advancement and determine its conclusion. The researcher shall evaluate any unfavorable event and report it to the ethics committee. The participants will be provided with written research details in 2 languages (Marathi and English), and written consent will be obtained from the participants on an informed consent form. They will be informed about the confidentiality of their details. Safety will be monitored by recording any adverse events during the entire study. We will make sure that no photos include any identifiable participants.

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Consent

The patients will be fully informed about the study's purpose and provide signed consent before the study commences. The researcher will personally ensure that participants understand the information and voluntarily agree to participate in the trial.

Private information about the participants will be collected and kept confidential before, during, and after the trial. The consent form will include specific information about the study purpose, procedures, potential risks and benefits, confidentiality measures, and the voluntary nature of participation. Participant comprehension will be assessed through a follow-up discussion, allowing them to ask questions and clarify their understanding.

AR Management

In the event of ARs during the trial, the affected participants will receive treatment at the institute's attached hospital. The investigator will cover the costs associated with the treatment to ensure the participants' safety.

Intervention Modification

Any negative effects noted during the treatment will be recorded and immediately reported to the ethics committee. The patients will receive the necessary treatment for the negative effects. If participants opt out of the treatment, they will be asked why, and this will be carefully documented.

Previous and Concomitant Medication

Patients will be allowed to continue their allopathic medications for diabetes mellitus and hypertension, anticoagulant therapy, or hormonal medications as per their existing treatment regimen. Any analgesics will be discontinued during the study period to prevent bias or interference with the study outcome. The investigator will record any medication taken by the patients other than the protocol drugs via any route.

Results

Preliminary data collection is ongoing, and participant recruitment for the study commenced in October 2024. As of January 2025, a total of 16 participants have been recruited across all 3 study groups. Data analysis is currently in progress. The final results of the study are expected to be published in November 2025. The study's findings will be disseminated through peer-reviewed publications.

Discussion

Anticipated Findings

A group of 20 participants will receive honey thermal microcautery, another group of 20 participants will receive standard physiotherapy, and another group of 20 participants will receive *S cordifolia* oil through the nasal route. All 3 groups will receive the treatment for 7 days. On the 8th, 16th, and 32nd days, we will assess the patients using the VAS, the SPADI, the McGill Pain Questionnaire, and ROM. We will compare the changes before and after therapy. We expect that the interventional group, specifically the honey thermal microcautery group, will exhibit statistically significant outcomes.

The study evaluated the efficacy of *mahamasha taila brihana nasya*, administered as 8 drops in each nostril per session, over 2 sessions spaced 7 days apart, along with 3 sittings of *agni karma* performed once weekly on the same day. In contrast, the third group (group C), both *mahamasha tailabrihana nasya* and *agnikarma* were administered. The assessments were taken on days 0, 7, 14, 21, and 28 using the VAS, the SPADI, the McGill Pain Questionnaire, and ROM goniometric examination. Improvement was observed in all 3 groups, especially the group in which both treatment modalities were administered.

A systematic review [32] compiled different studies on FS and thermal microcautery.

Van't Hoff's principle states that, for every degree that the body temperature rises, the body's basal metabolism increases by a specific proportion. An increase in temperature causes muscles to relax, which reduces discomfort and inflammation associated with muscle spasms. This can be achieved via thermal microcautery [33]. Similar to infrared fomentation, the light waves cause inflammation to be reduced by penetrating deeper into the body; thermal microcautery similarly causes the local capillaries to dilate, improving the blood supply to the affected area and eliminating inflammatory compounds [34].

Physiotherapy, such as wheel and step ladder exercises, aids in FS by enhancing joint mobility and flexibility. Wheel exercise allows for gradual stretching, whereas step ladder exercise improves shoulder strength and ROM. Together, they facilitate functional recovery and improve ROM. Our hypothesis is that honey thermal microcautery will yield more effective results than standard physiotherapy and *S cordifolia* oil via the nasal route because of its instant and satisfactory benefits. This research may guide future studies, incorporating traditional and modern methods, thus providing a well-rounded treatment for FS. This study seeks to guide clinical decisions by systematically comparing these interventions, enabling the choice of a more effective and individualized treatment for FS. This study compares diverse interventions, uses multidimensional assessment tools, and integrates Ayurvedic principles with modern therapy. It provides a new perspective into honey thermal microcautery; thus, clinicians can fine-tune effective treatments for FS. The limitation of this study is the small sample size, which, while adequate for preliminary insights, may limit the generalizability of the findings. Future studies with larger cohorts and extended follow-up periods are recommended to validate and enhance the applicability of the results. The primary findings will establish that honey thermal microcautery, standard physiotherapy, and *S cordifolia* oil via nasal administration effectively manage FS, ultimately determining which provides the best outcome.

Conclusions

This study aims to evaluate the efficacy of *S cordifolia* oil administered through the nasal route, honey thermal microcautery, and standard physiotherapy for treating FS. We highlight that these are just preliminary theories based on available data, even though we anticipate that regular physiotherapy and honey thermal microcautery will show notable benefits. We will draw final conclusions about the

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efficacy of each treatment once data collection and analysis are finished.

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Data Availability

All data generated or analyzed during this study are included in this published paper. No additional data are associated with this paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The grading on the SPADI scale.
[DOCX File, 18 KB - resprot_v14i1e64066_app1.docx]

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Abbreviations

AR: adverse reaction
CRF: case report form
FS: frozen shoulder
ROM: range of motion
SPADI: Shoulder Pain and Disability Index
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
VAS: visual analogue scale

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The Effects of a Multidomain Lifestyle Intervention on Brain Function and Its Relation With Immunometabolic Markers and Intestinal Health in Older Adults at Risk of Cognitive Decline: Study Design and Baseline Characteristics of the HELI Randomized Controlled Trial

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Abstract

Background: Studies of multidomain lifestyle interventions show mixed results on preventing or delaying cognitive decline in aging. A better understanding of central and peripheral mechanisms underlying these interventions could help explain these mixed findings.

Objective: The HELI (Hersenfuncties na LeefstijlInterventie) study aims to investigate the brain and peripheral mechanisms of a multidomain lifestyle intervention in older adults at risk of cognitive decline.

Methods: The HELI study is a 6-month multicenter, randomized, controlled multidomain lifestyle intervention trial powered to include 104 Dutch older adults at risk of cognitive decline. Individuals were deemed at risk when scoring ≥2 points on a lifestyle-modifiable risk factor scale (eg, overweight, physical inactivity, hypertension, and hypercholesterolemia). The intervention consisted of 5 domains (diet, physical activity, stress management and mindfulness, cognitive training, and sleep) and participants were randomized to one of two groups: (1) a high-intensity coaching group with weekly supervised online and on-site group meetings, exercises, and lifestyle-specific course materials, and (2) a low-intensity coaching group receiving general lifestyle health information sent through email every 2 weeks. The primary study outcomes are changes between baseline and 6-month follow-up in (1) brain activation in dorsolateral prefrontal cortex (dlPFC) and hippocampus and task accuracy during a functional magnetic resonance imaging (fMRI) working memory task, (2) arterial spin labeling-quantified cerebral blood flow in dlPFC and hippocampus, (3) systemic inflammation from blood plasma (interleukin-6, tumor necrosis factor-α, high-sensitivity C-reactive protein) and (4) microbiota profile from feces (gut microbiome diversity [Shannon and phylogenetic diversity] and richness [Chao1]). In addition, we will investigate intervention-induced gut-immune-brain links by assessing relations between effects in primary brain and gut outcomes. Secondary study outcomes include (1) structural and neurochemical magnetic resonance imaging (MRI), (2) anthropometric measurements, (3) neuropsychological test battery scores, (4) lifestyle-related questionnaire and smartwatch measures, and peripheral measures from (5) fecal, (6) blood, and (7) breath analyses.

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Results: This work was supported by a Crossover grant (Maintaining Optimal Cognitive Functioning In Aging [MOCIA] 17611) of the Dutch Research Council (NWO), granted in December 2019. The MOCIA program is a public-private partnership. Between April 2022 and October 2023, we successfully included 102 older Dutch adults (mean age 66.6, SD 4.3 years; 67/102, 65.7% female) with ≥2 lifestyle-modifiable risk factors of cognitive aging (median risk 3, IQR 2-3). The most common self-reported lifestyle-modifiable risk factors at baseline were overweight or obesity (76/102, 74.5%), followed by hypertension (58/102, 56.9%), hypercholesterolemia (57/102, 55.9%), and physical inactivity (57/102, 55.9%).

Conclusions: The HELI study aims to enhance our understanding of the working mechanisms of multidomain lifestyle interventions through its comprehensive characterization of central and peripheral markers. We intend to achieve this aim by assessing lifestyle intervention-induced changes in functional and structural MRI brain measures, as well as peripheral measures of the gut-immune–brain axis involved in cognitive aging.

Trial Registration: ClinicalTrials.gov NCT05777863; https://clinicaltrials.gov/study/NCT05777863

International Registered Report Identifier (IRRID): DERR1-10.2196/69814

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KEYWORDS

lifestyle; cognitive ageing; risk factors; risk reduction; multidomain; intervention; randomized controlled trial; brain; gut-brain; magnetic resonance imaging

Introduction

Background

Multidomain lifestyle interventions have great potential to delay cognitive aging, but the effects of previous trials are small and mixed. Furthermore, previous studies mainly focused on cognitive functioning as the primary outcome. Consequently, underlying neurocognitive, central mechanisms, and involved peripheral pathways remain poorly understood. The HELI (Hersenfuncties na LeefstijlInterventie) study is a 6-month multidomain lifestyle intervention in older adults at risk of cognitive decline based on modifiable lifestyle factors, focusing on involved central and peripheral mechanisms by using a broad range of neuroimaging, blood- and gut-related outcome measures. Below, we explain the rationale of our objectives and hypotheses.

Lifestyle Interventions in Cognitive Aging

In our aging population, the incidence of cognitive decline and incurable neurodegenerative diseases like Alzheimer dementia (AD) and other types of dementia is increasing drastically [1]. A substantial part of the risk factors for dementia, such as obesity, hypertension, type II diabetes, and physical inactivity [2-6], is modifiable by changes in lifestyle. Indeed, observational research shows a relationship between a healthy lifestyle, such as a healthy diet, regular physical and cognitive exercise, not smoking, and maintaining social contacts, with a lower dementia risk [7,8]. As the signs of neurodegenerative diseases, such as amyloid beta pathophysiology and tauopathy in AD, begin decades before the first symptoms become apparent [9,10], paired with the fact that long-term healthy lifestyles show inverse relations with dementia risk, interventions addressing cognitive decline need to start at an early stage [11]. The World Health Organization (WHO) has therefore designated preventive multidomain lifestyle interventions as having the greatest potential to reduce the risk of cognitive decline and dementia within its 2019 guidelines [12].

Previous multidomain lifestyle intervention trials in aging individuals show small but significant effects on both cognitive functioning and dementia risk, as concluded by a meta-analysis from 2022 [13]. Especially when compared to single-domain interventions, multidomain lifestyle programs showed stronger effects [14,15]. However, previous studies are heterogeneous in population characteristics, intervention design, components, and duration and outcome measures. Moreover, when zooming in on individual studies and considering the latest published trials [16,17], the reported effects can be considered mixed. The 24-month Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability (FINGER) study [18] was the first large, longitudinal randomized controlled trial (RCT) in older adults at risk of cognitive decline (n=1260) and found subtle but robust positive effects of a multidomain lifestyle intervention on cognitive functioning. Other lifestyle interventions such as the Prevention of Dementia by Intensive Vascular Care (preDIVA) study (n=2994) [3], Multidomain Alzheimer Prevention Trial (MAPT; n=1680) [19], Japan-Multimodal Intervention Trial (J-MINT; n=531) [16], and AgeWell.de (n=1030) [17] did not find differences in cognition or dementia risk. However, specific subgroups within these trials with higher dementia risk based on modifiable cardiovascular lifestyle factors [3,19] did show improvements in cognitive functioning. Altogether, these findings point to specific at-risk older adults who are most likely to benefit from multidomain lifestyle interventions.

Crucially, these previous lifestyle intervention studies all had behavioral cognitive tests or dementia incidence as primary outcomes. We still have a limited understanding via which brain mechanisms and potential underlying peripheral pathways, the multidomain lifestyle interventions might exert their effects on cognition. To elucidate underlying brain mechanisms, different neuroimaging techniques are essential to analyze brain health and function in vivo in a longitudinal, intervention setting. Moreover, to understand involved peripheral pathways, we need extensive measures of inflammatory, metabolomic, and microbiome markers in blood and feces.

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Among the previous lifestyle intervention studies, only FINGER (n=132, 2 years) and MAPT (n=68, 6 months) used (structural) neuroimaging in a subsample of participants. Within FINGER, no structural (ie, anatomical) differences were found between intervention groups [20], whereas within MAPT, the lifestyle intervention group showed decreased deformation of periventricular areas and temporal lobes, and decreased whole-brain atrophy compared to placebo [19]. In addition, positron emission tomography (PET) scans within MAPT also demonstrated elevated levels of cerebral glucose metabolism within, for example, the hippocampus and the adjacent parahippocampal gyrus [21]. These limited and heterogeneous neuroimaging findings highlight the poor understanding we currently have of underlying neurocognitive mechanisms of lifestyle changes. In addition, some of the previous studies did assess blood, cardiovascular [3], inflammatory [19], or metabolomic markers [18,19], which confirmed that these pathways are influenced by lifestyle changes. However, none of the preceding lifestyle interventions have combined extensive blood and fecal measures to fully understand underlying peripheral(-central) mechanisms.

Therefore, within the HELI study, we will combine a broad neuroimaging protocol, including task-related functional magnetic resonance imaging (fMRI) and quantitative imaging of cerebral blood flow (CBF) as primary central outcomes, with peripheral measures in blood and feces, including blood inflammatory profile and fecal microbiota composition as primary peripheral outcomes. Below, we will explain the rationale of our chosen primary and secondary outcome measures.

Aging Brain and Lifestyle

The longitudinal process of aging impacts multiple facets of the brain, causing changes in both brain structure and function and, subsequently, in cognition. Age-related structural brain changes are characterized by changes in gray and white matter volume, leading to loss of overall brain volume [22]. Importantly, certain brain structures such as the hippocampus and dorsolateral prefrontal cortex (dlPFC) appear to shrink at a faster rate compared to other brain regions, possibly explained by their increased vulnerability to vascular risk factors such as hypertension and hypercholesterolemia [23-25]. These findings indicate a possible link between lifestyle-modifiable cardiovascular risk factors and aging-related cognitive decline. In addition, the large interindividual differences reported in age-related structural and functional brain deterioration have been proposed to be partially explained by differences in adherence to healthy lifestyle patterns [26].

Earlier studies in pathological aging, specifically in mild cognitive impairment (MCI) and AD, have broadly established key patterns of functional brain deterioration, even in prodromal stages of disease before structural deterioration becomes apparent [27]. These findings indicate that measures of brain function may be more sensitive to interventions targeting age-related cognitive decline and are more strongly modifiable by nature as opposed to brain structure. The most notable cognitive changes associated with normal and pathological aging can be found in the more complex cognitive domains, such as executive functioning and working memory [28]. Working memory is a fundamental cognitive process, supporting higher-order cognitive functions such as planning, problem-solving, and decision-making. Although the overall effects of age on working memory, which shows gradual decreases with advancing age, have been well-established, multiple studies have also identified increased activity in regions of the prefrontal cortex (PFC) in older adults who show comparable working memory performance to young adults [29,30]. These studies indicate that in aging, differences in functional activation patterns, measured with fMRI, may already show a—perhaps compensatory—reorganization before detriments in cognitive performance are observed [28,31]. However, as current literature remains scarce, it remains unclear how this potential functional reorganization is affected by a multidomain lifestyle intervention, especially in at-risk older adults. Another brain function measure, which is a potential cause underlying age-related decline in cognitive functioning, is decreased (local) CBF [32-35]. Multiple studies have reported the predictive value of quantified CBF on cognitive performance in both normal and pathological cognitive aging [32-35]. Moreover, increased local CBF in specific brain regions, such as the hippocampus and PFC, has been directly linked to increased cognitive performance [32]. Although previous studies have found short-term positive effects on CBF after lifestyle improvements such as improved diet or increased physical exercise, it remains unclear whether these effects retain after a multidomain lifestyle intervention and how the increase in regional CBF translates to cognitive functioning in aging [36].

Other promising brain measures in cognitive aging research are the quantification of local iron deposition and neuroinflammation. The accumulation of iron across the lifespan (especially in the deep gray matter), although conventionally found in healthy aging adults [37-39], has been directly linked with increased local oxidative stress leading to neurodegeneration [40-43] and decreased cognitive functioning in older adults with amyloid-β pathology [44]. Similarly, and in addition to intracranial iron deposition, neuroinflammation contributes to neurodegenerative processes in the normally aging brain [45], for example, by affecting the cerebrovascular endothelium leading to neurovascular dysfunction [46]. These impairments could eventually contribute to decreased brain functioning and cognitive decline [47]. We now know that increased regional neuroinflammation—for example, measured by quantifying intracranial myo-inositol concentrations with magnetic resonance spectroscopy (MRS)—is strongly associated with memory dysfunction in normal aging [48,49], in MCI and in AD [49,50]. These findings emphasize the effect of local neurodegenerative effects on specific cognitive domains associated with cognitive aging and dementia.

We currently know that age-related structural and functional brain changes consequently cause cognitive decline, and that brain perfusion, neuroinflammation, and iron accumulation are possible underlying mechanisms. A small number of lifestyle intervention studies, most of which target one specific domain, have reported positive associations between improved diet, exercise, and cognitive training, and neuroimaging measures of cerebral perfusion [51-53] and functional connectivity [54].

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However, it is currently unknown to what extent a multidomain lifestyle intervention influences the involved mechanisms of age-related changes in brain activation. Applying a broad neuroimaging protocol could provide important insights into the effects of multimodal lifestyle improvements on the underlying brain mechanisms of age-associated cognitive decline and provide direct mechanistic targets for future interventions.

Gut-Brain Axis and Peripheral Mechanisms

Growing evidence indicates an important role for intestinal health and other peripheral factors, like inflammation, metabolic, and vascular health, in the development of cognitive decline [55,56]. Furthermore, a substantial part of lifestyle effects on brain functioning is expected to arise via mechanisms in the periphery. An overview of these hypothesized pathways and the link with brain health can be found in Figure 1. These pathways are expected to be influenced by multidomain lifestyle interventions at different levels. Below, we will describe the rationale behind these pathways.

Figure 1. Hypothesized peripheral pathways from gut to brain affecting cognitive functioning, based on the existing evidence mentioned in the introduction. VAT/SAT ratio: ratio of visceral to subcutaneous adipose tissue.

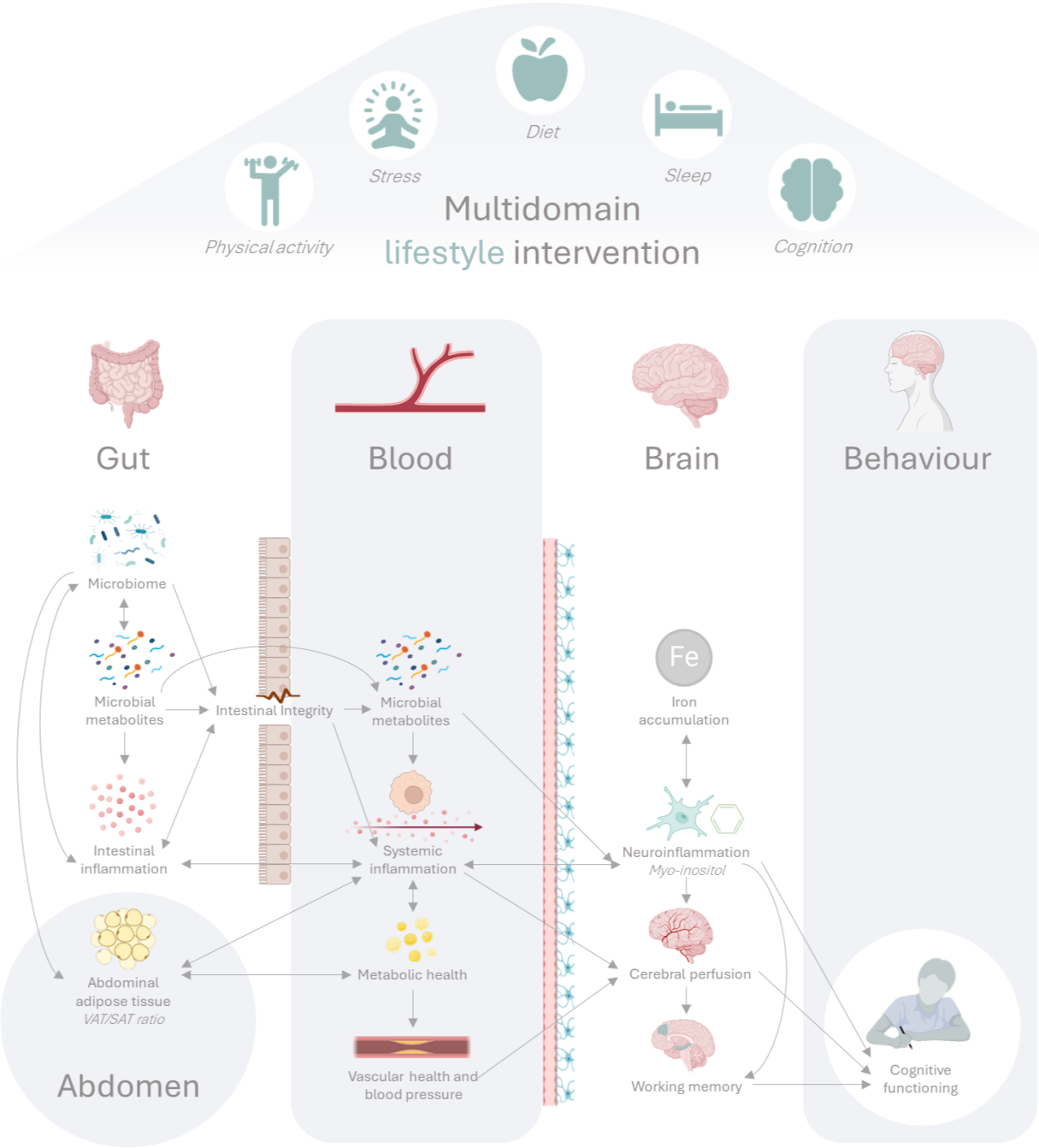

The gut microbiome, in particular, has an increasingly recognized impact on brain functioning and behavior via different routes captured in the gut-brain axis. These include the modulation of immune signaling to the brain, affecting the hypothalamic—pituitary—adrenal axis, and transmission via the vagus nerve [57]. Microbiota-derived bioactive metabolites,

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such as short-chain fatty acids (SCFAs), tryptophan metabolites, (endo)toxins, and secondary bile acids, could mediate the effects of the gut microbiome on brain health [58]. They reflect microbiome function [59] and have demonstrated health effects on the host (eg, [anti]inflammatory and metabolic processes) [60,61], also in aging [62].

We know that aging is associated with changes in microbial composition and diversity and gut health [63]. Older adults more frequently show gut microbiome dysbiosis (imbalance) compared to younger individuals, potentially due to prolonged exposure to an unhealthy lifestyle [64,65]. Particularly, microbial diversity and uniqueness seem to correlate with aging in Western societies [66]. A lower fecal microbial diversity predicted poorer cognitive function in healthy older adults [67]. Microbial metabolites are also affected by aging, as older adults show reduced fecal total SCFA levels [68]. SCFAs, especially butyrate, are known for their beneficial anti-inflammatory effects [69,70] and have been linked to improved cognition in mice [71,72]. Importantly, these microbial changes become more pronounced in the case of pathological cognitive aging like AD. Compared to healthy age-matched individuals, patients with AD show a decreased microbial diversity and stability over time [73], differences in abundance of individual taxa [56,74], and more often have small-intestinal bacterial overgrowth (SIBO) [75]. In addition, a further decrease in levels of fecal SCFAs and tryptophan metabolites was found, which correlated with cognitive decline [76]. However, as these findings mainly come from cross-sectional studies, causal evidence from intervention studies to provide a stronger link between these gut-brain mechanisms is still limited.

Among the proposed gut-brain pathways, inflammation is assumed to play a pivotal role in brain health. Dysbiosis of the gut microbiome can potentially impair the integrity of the intestinal barrier [77], thereby provoking a local inflammatory reaction that could eventually lead to systemic inflammation [78]. In addition, microbiota dysbiosis can also lead to the dysregulation of abdominal adipose tissue, affecting immune and insulin pathways, promoting systemic inflammation even more [79,80]. Low-grade, systemic inflammation is commonly seen in aging [81] and is characterized by a mild and sustained increase in immune mediators in the systemic circulation. For example, the acute-phase response marker C-reactive protein (CRP) and its major regulators interleukin (IL)-6 and tumor necrosis factor (TNF)-α are increased [81,82]. In turn, low-grade, systemic inflammation due to impaired intestinal health can lead to elevated levels of neuroinflammation [83] and is linked with neurodegenerative processes in the normally aging brain.

Importantly, a direct causal role for the gut-immune-brain axis in aging has been demonstrated in mice using fecal microbial transplantation (FMT) [84-87]. These findings emphasize that microbial modulation in humans might be of significant therapeutic benefit in preventing age-related inflammation and cognitive decline [88]. Altogether, the gut microbiome and its interaction with the host can be considered a crucial modulator of (un)healthy aging, determining the rate of physical and cognitive decline [89].

There are numerous studies showing that gut microbiome composition and immune-metabolic health effects on the host are modified by diet and nutritional components [90-92], including the Mediterranean-type diets [93,94]. In addition, other lifestyle components such as physical activity [95,96], stress [97], and sleep [98,99] are known to affect the microbiota composition and intestinal health, as well as immune, vascular, and metabolic health [100-107]. Importantly, we hypothesize that multiple lifestyle domains can synergistically affect peripheral markers and should therefore be targeted simultaneously. However, it is still largely unclear how gut microbiome, immune, and metabolic factors link to brain health in aging, and which mechanisms are involved. By investigating how lifestyle-induced changes in these peripheral factors relate to changes in brain health, we can make stronger conclusions about the role of these peripheral-brain links in cognitive aging. Moreover, elucidating peripheral-brain mechanisms might also explain individual differences seen in lifestyle interventions for healthy cognitive aging.

Study Objectives and Hypothesis

We designed the HELI study (derived from the Dutch "HErsenfuncties na LeefstijlInterventie," meaning "Brain function after lifestyle intervention") to better understand the neurocognitive effects of a multidomain lifestyle intervention and underlying peripheral (central) mechanisms. The HELI study is a 6-month multidomain lifestyle intervention in older adults at risk of cognitive decline (based on lifestyle-modifiable cardiovascular risk factors) with a high and low-intensity intervention arm. We focus on 5 different lifestyle domains within the intervention period: diet, physical activity, stress management and mindfulness, cognitive training, and sleep. We will assess effects on multiple neuroimaging brain measures (primary: working memory task-related fMRI responses and performance, and quantitative imaging of CBF), peripheral measures related to the gut-immune-brain axis (primary: blood inflammatory profile and fecal microbiota composition), as well as their connections. We propose that, compared to the low-intensity group, the high-intensity group will show greater improvement in central neuroimaging outcomes (eg, fMRI and CBF) as well as peripheral outcomes (eg, blood inflammatory profile and fecal microbiota composition). Moreover, we hypothesize that individual changes in central outcomes correlate with changes in peripheral outcomes, as summarized in Figure 1.

Methods

Trial Design

The HELI study is a multicenter randomized controlled trial, aiming to investigate the effects of a 6-month multidomain lifestyle intervention on brain functioning and its relation with immunometabolic markers in aging. Powered to include 104 total participants, HELI has two parallel-arm treatment groups: (1) a supervised "high-intensity" coaching intervention group with weekly group meetings, lifestyle-related information and exercises, and (2) a nonsupervised "low-intensity" coaching intervention group, receiving information leaflets every 2 weeks. Because the participants of the high-intensity intervention arm

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were supervised in a group context, we recruited and subsequently randomized participants in 4 different inclusion waves (between May 2022 and October 2023), consisting of 19 - 32 participants. Participants partook in outcome measure visits at baseline (T0) and at 6 months follow-up (T1) (see Figure 2).

The HELI study has been reviewed and accepted according to the Medical Research Involving Human Subjects Act ("Wet Medisch-wetenschappelijk Onderzoek met mensen" in Dutch) by an accredited Medical Research Ethics Committee (MREC), the MREC Oost-Nederland on December 2, 2021 (ToetsingOnline filenumber NL78263.091.21, ClinicalTrials.gov ID NCT05777863).

Figure 2. Overview of the study design. Schematic overview of study visits, assessments, and intervention groups. Before **T0** and after **T1,** the intervention period of 6 months, participants visited the Donders Center for Cognitive Neuroimaging (DCCN) and Wageningen University and Research (WUR) study centers with one week in between.

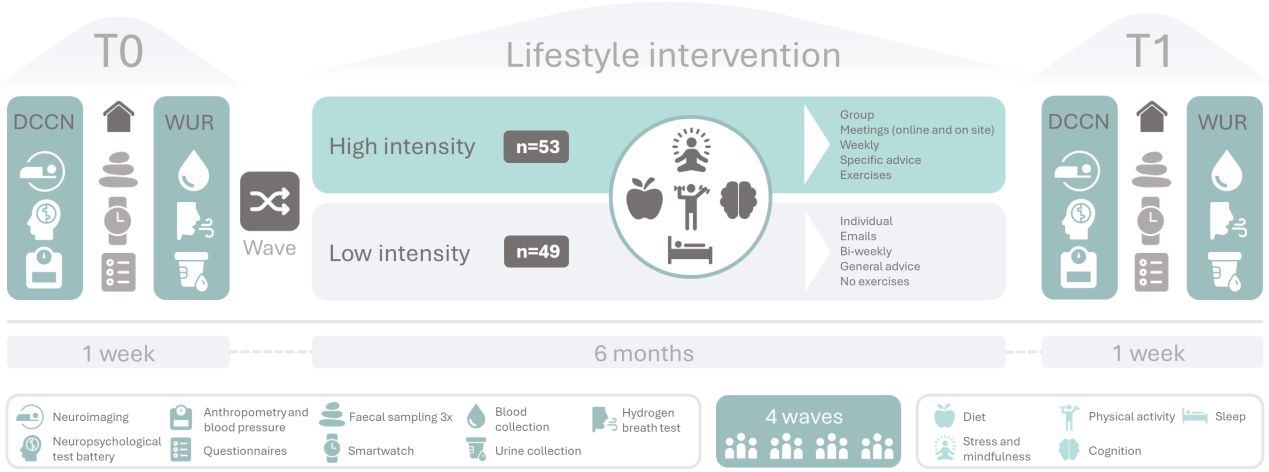

Methods: Participants, Interventions, and Outcomes

Study Setting

The HELI intervention is based on the FINGER-NL lifestyle intervention, a multicenter, randomized, controlled, multidomain lifestyle intervention effectiveness trial in the Netherlands. The rationale and study design of FINGER-NL have been published previously [108]. Both HELI and FINGER-NL are part of the overarching Maintaining Optimal Cognitive Functioning In Aging (MOCIA) research program [109], and follow an inclusion procedure with similar lifestyle modifiable risk factor inclusion criteria as the FINGER study [18,110]. The HELI study is conducted at two separate research centers in the Netherlands, namely the Donders Institute for Brain, Cognition and Behavior, Center for Cognitive Neuroimaging (DCCN; Radboud University, Nijmegen, the Netherlands), and the Division of Human Nutrition and Health at Wageningen University and Research (WUR, Wageningen, the Netherlands). Study visits were performed at both centers, but inclusion, screening, randomization, guidance of the intervention, and monitoring were performed by the DCCN.

Recruitment

To achieve adequate participant enrollment and reach the target sample size of 104 included participants, we have used an array of recruitment methods. Our primary sources of enrollments came from: (1) recruitment advertising on Facebook; (2) WUR and DCCN research center participant databases; (3) newsletters of Dutch brain research institutions and associations (eg, Netherlands Brain Foundation and Alzheimer Association Netherlands); (4) messages on WUR and DCCN research center websites and social media channels; (5) articles and recruitment dissemination via flyers, and in local newspapers, radio station, and television broadcast; and (6) word of mouth.

Eligibility Criteria

Inclusion Criteria

Individuals had to meet the following inclusion criteria to be eligible to participate in this study:

1. Aged between 60 - 75 years (at the moment of signing written informed consent);
2. Fluency in Dutch (speaking, reading, and writing);
3. Willing to travel to the partaking research centers in Nijmegen and Wageningen (to ensure study center visits are plausible without excessive travel burden);
4. Score ≥2 points on the self-reported "Modifiable cardiovascular risk factor scale" (see Table 1 below), indicating a presently increased risk for cognitive decline based on risk factors which are modifiable by lifestyle changes (adapted from Cardiovascular Risk Factors, Aging, and Incidence of Dementia [CAIDE] [111]).

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Table . Modifiable cardiovascular risk factor scale.

Risk factor	Points
BMI ≥25 kg/m^2 (overweight or obesity)	1
Physical inactivity (below the 2020 WHO guidelines [112]:<300 minutes of moderate intensity aerobic physical activity, or <150 minutes of vigorous intensity aerobic physical activity per week, spread out over several days)	1
Hypertension (systolic blood pressure ≥140 mmHg, and diastolic blood pressure ≥90 mm Hg)	1 (2 points are assigned if hypertension is not being actively treated with antihypertensive medication, given the increased cardiovascular burden)
Hypercholesterolemia (total cholesterol >5 mmol/L, or LDL-cholesterol >3 mmol/L)	1
Diabetes type II	1
Mild cardiovascular disease (eg, intermittent claudication, varicose veins; In contrast, moderate or severe cardiovascular disease such as stroke, angina pectoris, heart failure, myocardial infarction, or revascularization surgery in the last 12 months before pre-screening are exclusion criteria as described below under section "Exclusion criteria")	1

Exclusion Criteria

Individuals who met any of the following criteria were excluded from participation:

Practicalities and Participation

Practical and participation-related factors, of one (or more) of the following:

1. Concurrent participation in other intervention trials;
2. No access to technological infrastructure (ie, computers, smartphones, mobile applications, and internet access) because the intervention is primarily online (eg, online support groups and mobile apps);
3. Cognitive impairment, as determined by a score lower than 23 points on the Telephone Interview for Cognitive Status (TICS-M1) [113], performed during prescreening before inclusion.

Clinical Diagnoses and Medical History

Clinical diagnosis by a certified doctor or general practitioner of one (or more) of the following:

1. Cerebrovascular event (eg,transient ischemic attack, cerebral hemorrhage, and stroke);
2. Neurological disease (eg, mild cognitive impairment, multiple sclerosis, Parkinson disease, and epilepsy);
3. Current malignant disease, with or without current treatment;
4. Current psychiatric disorder (eg, depression, psychosis, and bipolar episodes);
5. Symptomatic, moderate to severe cardiovascular disease (eg, stroke, angina pectoris, heart failure, and myocardial infarction);
6. Revascularization surgery in the last 12 months at the moment of prescreening;
7. Inflammatory bowel disease (characterized by diarrhea);
8. Visual impairment, which is uncorrectable with visual aids (eg, total or partial blindness);
9. Hearing or communicative impairment, which is uncorrectable with hearing aids;

Magnetic Resonance Imaging Safety–Specific Criteria

Contraindications for magnetic resonance imaging (MRI), of one (or more) of the following:

1. Metal objects located in the upper body (exceptions: tooth fillings and dental crowns);
2. Metal splinters in the body, in particular within the eyes (eg, through labor work in the metal industry);
3. Jewelry items or piercings that cannot be taken off;
4. Undergone brain surgery in the past;
5. Active implants within the body (eg, pacemaker, neurostimulator, internal insulin pump, internal hearing aids that cannot be removed);
6. Medical plasters or patches which cannot or may not be taken off (eg, nicotine patch);
7. Self-reported claustrophobia.

Interventions: Description

In the HELI multidomain lifestyle intervention, five distinct lifestyle domains were combined, namely (1) diet, (2) physical activity, (3) stress management and mindfulness, (4) cognitive training, and (5) sleep. The intervention period was 6 months (26 weeks) in total, which was subsequently followed by the follow-up outcome measure visits (see Figure 3 for an overview).

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Figure 3. Intervention overview. HUBV (Houd uw Brein Vitaal; "Keep your brain fit") and iSLEEP are validated psychoeducational and cognitive behavioral therapy programs.

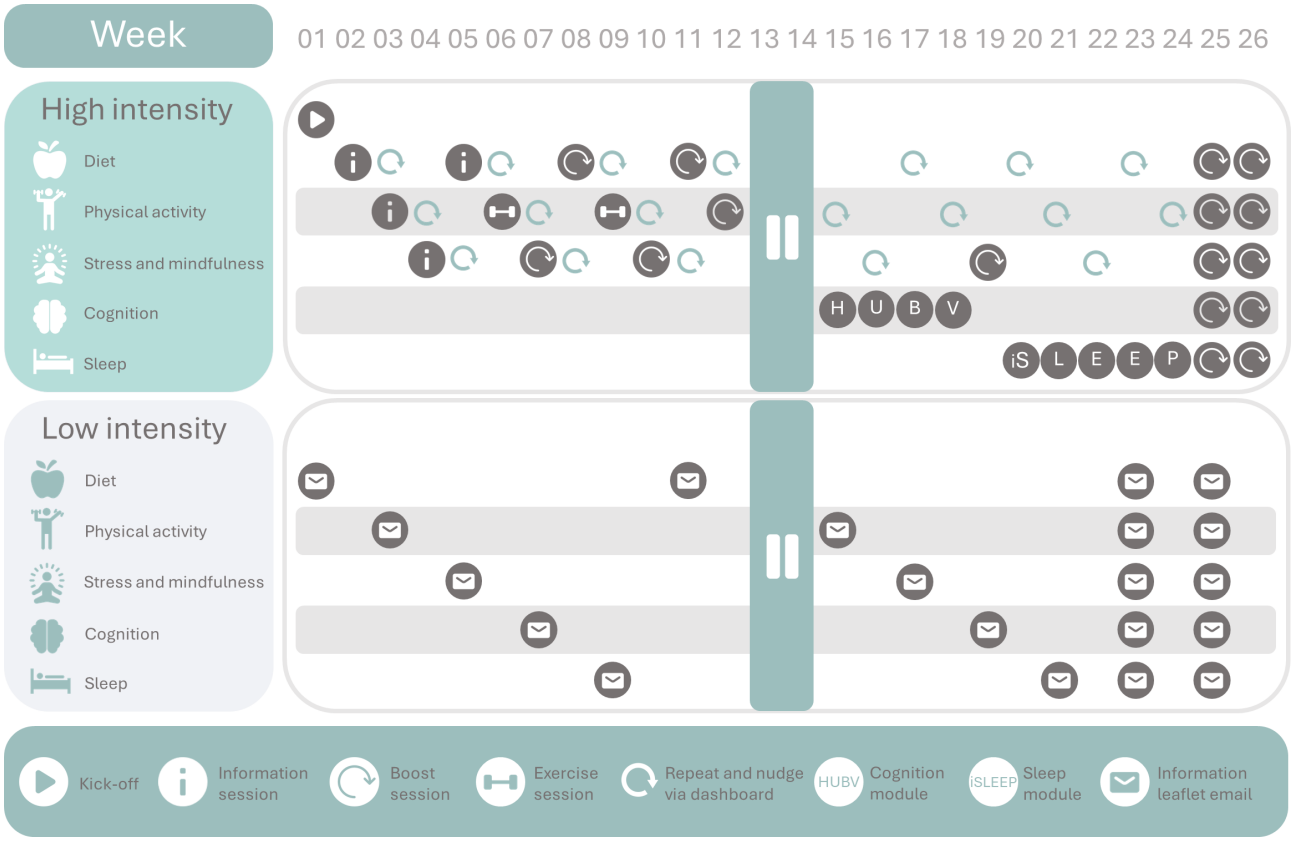

The high-intensity intervention group received a structured and personalized intervention program consisting of weekly group sessions, active guidance from an intervention supervisor, and lifestyle domain–related individual and group exercises. The low-intensity intervention group received access to general lifestyle-related health information in an individual context, provided through information leaflets sent by email once every 2 weeks. To promote intervention adherence and blinding, we adopted the FINGER-NL [108] and US POINTER approach [114] of framing both groups as lifestyle intervention recipients, instead of using the label "control group." The groups differ in intervention structure, engagement, and intensity rather than treatment versus control.

During communication with participants, we refrained from using the terms "high-intensity" and "low-intensity" to promote group blinding as much as possible. Instead, the intervention arms were called "weekly group sessions" for the high-intensity intervention group, and "independently working on your lifestyle" for the low-intensity intervention group. An extensive description and overview of the multidomain lifestyle intervention groups is provided below and depicted in Figure 3.

High-Intensity Group

Design

In order to achieve the domain-specific goals and ambitions, we provided participants within the high-intensity group with three key intervention elements: (1) weekly online or on-site group sessions to provide information, exercises, and personalized advice, (2) an extensive information folder containing supporting lifestyle-related information, exercises, and relevant practical information, and (3) access to an online dashboard with a personal intervention environment. Each weekly group session took approximately 90 minutes. We expected that participants required an average of 90 minutes to put additional work in the provided lifestyle advices, exercises, and other practical aspects (eg, reading online dashboard and intervention information folder; see S3.1 in Multimedia Appendix 1), resulting in a weekly expected intervention effort of 180 minutes.

Group Sessions

The weekly group sessions were offered throughout the 6-month (26 weeks) intervention period. For 20 out of 26 weekly sessions, a specific lifestyle domain acted as the central theme for a given week (Figure 3). At week 1, after the baseline measurements of all participants in a wave and subsequent randomization had been concluded (T0), the intervention started off with an on-site introductory session.

The weekly group sessions provided participants with detailed lifestyle-related information, guidelines, exercises, and advice, as well as the opportunity for discussion with other group members and with the intervention supervisor. Weekly group sessions were guided by the intervention supervisor and were composed of the following recurring elements: social interaction, introductory question round, reiteration of previous lifestyle domains, dissemination, exercises, and a final question round (see Table S1 in Multimedia Appendix 1 for further details).

Over the 6-month intervention period, each of the five lifestyle domains was addressed in separate weekly group sessions (see

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Figure 3). We provided three distinct types of weekly group sessions:

- "Information sessions" primarily focused on giving general instructions, advice, and exercises on a particular domain. During information sessions, participants were encouraged to ask questions and share experiences, problems, or advice with the group.
- "Boost sessions" primarily focused on recalling and reiterating domains which had been discussed in previous information or booster sessions, whilst also providing smaller amounts of new information. The main goal of boost sessions was to keep participants engaged in the multiple different lifestyle domains throughout the 6-month intervention period and remind them of instructions, advice, and exercises from previous sessions. During boost sessions, more time was reserved for repeating previously discussed material and information, group discussions, and sharing experiences, advice, or problems regarding one or more specific domains.
- "Exercise sessions" primarily focused on explaining and performing muscle-strengthening exercises (full-body work-out, ie, including all major muscle groups) in combination with balancing and stretching exercises in a group setting at an exercise center under the supervision of a physical exercise instructor specialized in instructing and guiding older adults. The exercise instructor provided instructions for conducting these exercises and for preventing strains or injuries.

Domains that were expected to require more instructions and guidance from the start (ie, diet and physical exercise) have two information sessions and 2 boost sessions or one information session and 2 exercise sessions, whilst domains that required less initial group and personal guidance and instruction (ie, stress management and mindfulness) had one information session and three boost sessions. The lifestyle domains of cognitive training and sleep differed from the information and boost session design, as these domains were composed of a psychoeducational program for the domain of cognition (spanning four consecutive weeks) and a sleep course module for the domain of sleep (spanning five consecutive weeks), further explained below. A more detailed explanation of the ambitions, goals, and content of the 5 lifestyle domains within the HELI lifestyle intervention is provided below and in S3.1 in Multimedia Appendix 1.

Ambition and Goals of Lifestyle Domains

Diet

Ambition and Goals

The goal of the diet domain was to support participants to adhere to the Mediterranean-DASH Intervention for Neurodegenerative Delay (MIND) diet, a diet specifically designed to slow down aging-related cognitive decline [115], and the Dutch guidelines for a healthy diet [116] which is associated with protective effects on multiple major (chronic) diseases (eg,coronary heart disease, stroke, diabetes, heart failure, and dementia). Specifically, we use the MIND-NL diet, which is adapted to the Dutch context and serving sizes [117]. Briefly, the MIND-NL diet-specific food recommendations comprise (1) green leafy vegetables, (2) other vegetables, (3) berries and strawberries, (4) whole-grain products, (5) unsalted nuts, (6) (unfried) fish, (7) (unfried) poultry, (8) beans and legumes, and (9) olive oil. MIND-NL diet-specific food restrictions comprise (1) full-fat cheese; (2) butter and stick margarine; (3) red and processed meat; (4) take-out, fried foods, and snacks; (5) cookies, pastries, and sweets; and (6) wine and alcoholic beverages [115]. The Dutch guidelines for a healthy diet consist of adhering to a healthy diet of the five major healthy food groups (in Dutch: "de Schijf van Vijf"): (1) fruit and vegetables; (2) (unsaturated) oil and spreads; (3) dairy, nuts, fish, legumes, meat, egg, or alternatives; (4) (whole-grain) bread, grain products and potatoes; and (5) hydration (water, tea, and coffee). As an additional component to this domain, to comply with Dutch national recommendations for older adults [118,119], participants are advised to take additional vitamin D_3 supplements throughout the intervention period (see S3.1 in Multimedia Appendix 1 for age and sex-specific advised doses). For more details on the exercises, information, and goals of the diet domain, see S3.1 in Multimedia Appendix 1.

Physical Activity

Ambition and Goals

The goal of the physical activity domain was to support participants to adhere to the official 2020 WHO Physical Activity guidelines [112]. These guidelines recommend engaging in physical activity of moderate intensity (eg, swimming, running, and cycling) for at least 300 minutes per week (spread out over several days), or 150 minutes of vigorous intensity aerobic physical activity (eg, cycling at a fast pace and playing singles tennis), or an equivalent combination of moderate- and vigorous-intensity physical activity (spread out over several days). Moreover, the guidelines recommend performing muscle-strengthening activities at moderate (or greater intensity) that involve all major muscle groups at least twice a week, combined with balance exercises. Finally, the amount of sedentary behavior (eg, sitting and lying down) must be limited according to these guidelines.

Stress Management & Mindfulness

Ambition and Goals

The goal of the stress management and mindfulness domain was to support participants in dealing with daily stress and becoming aware of their own thoughts and feelings, and to support participants in making brain-healthy choices regarding stress management. Participants received a selection of exercises from an evidence-based, self-guided online mindfulness training (provided through the VGZ Mindfulness Coach app [120]), as well as information regarding the potential negative effects of (chronic) stress on the body and brain, as well as practical advice on how to combat stress and improve relaxation.

Cognitive Training

Ambition and Goals

The goal of the cognitive training domain was to inform participants about functional and structural changes in the aging brain, to support participants in learning about strategies that

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could aid in coping with cognitive changes which are a part of normal aging (eg, informing participants about memory strategies and sharing tips to improve attention capabilities), and how to ultimately apply these strategies in daily life. The cognitive strategy training was based on the Dutch "Houd uw brein vitaal!" (HUBV; "Keep your brain fit!") psychoeducational program [121]. The HUBV program consists of 2 main parts: lifestyle and memory (complaints), and effective strategy training (see S3.1 in Multimedia Appendix 1 for a more extensive description).

Sleep

Ambition and Goals

The goal of the sleep domain was to support participants in improving sleep quality (and if applicable, reduce insomnia), and to inform participants about the possible health risks associated with poor sleep in aging. Participants received a 5-week sleep counseling module using a validated, guided, online Cognitive Behavioral Therapy for Insomnia (CBT-I), provided via i-Sleep (which was made available on paper to participants) [122,123]. During the program, participants received information about the different stages of sleep, a healthy sleep pattern, how this pattern might change as we get older, and practical advice on how to improve sleep quality. The course consisted of the following modules: psycho-education, sleep hygiene, behavioral interventions (eg, stimulus control and sleep restriction), relaxation, and dealing with worrying or sleep-obstructing thoughts. Specific recommendations and restrictions were also provided to improve sleep quality and quantity, such as a proper diet, physical exercise, and refraining from smoking or using alcohol before bedtime.

Low-Intensity Group

Participants randomized to the low-intensity intervention group received general lifestyle-related health information, addressing the aforementioned 5 lifestyle domains. Participants received this general information through information leaflets (1 - 2A4), through email, once every 2 weeks. The information leaflets discussed the lifestyle domains but exclusively offered general health information without providing participants any individual or personal guidance based on their personal circumstances. For example, participants were generally told that a healthy diet promotes a healthy brain, and which kind of food components are promoted by the guidelines for a healthy diet, but participants were not guided or advised how their own personal diet should therefore be adjusted to fit these diet recommendations and guidelines.

The information of these leaflets was also handed to the high-intensity intervention group to ensure both groups were provided with the same general health advice.

Outcomes

All outcome measures were measured at baseline (T0) and after participation in the 6-month multidomain lifestyle intervention (T1), during visits at both research centers. Blood drawing and breath tests were performed in a fasted state. Some outcome measures, such as lifestyle domain or adherence-related questionnaires, were also collected throughout the intervention period. For a detailed overview of all outcomes and the collection schedule, see S4 in Multimedia Appendix 1.

Primary Outcomes

The primary outcomes are the changes between baseline (T0) and follow-up after 6 months (T1) in:

1. Brain activity during working memory in dlPFC [124] and hippocampus (Harvard-Oxford atlas), using fMRI blood-oxygen-level-dependent (BOLD) activity and task accuracy during a numerical N-back task [125];
2. Cerebral perfusion levels, measured by MRI arterial spin labeling in dlPFC and hippocampus;
3. Peripheral immunometabolic biomarker levels in blood plasma (inflammation markers IL-6, TNF-α, hs-CRP) and feces microbiota diversity (Shannon- and phylogenetic diversity) and richness (Chao1).

In addition, we will investigate intervention-induced gut-immune-brain links by assessing the relation between the effects found in the abovementioned primary peripheral markers and brain outcome measures.

Secondary Outcomes

The secondary outcomes are the changes between baseline (T0) and follow-up after 6 months (T1) in:

1. Structural MRI (eg, gray and white matter volume, ventricular enlargement, abdominal adipose tissue T1 assessment), neurochemical assessment of neuroinflammation in dlPFC and hippocampus (using MRS) and whole brain analyses of primary neuroimaging outcomes (BOLD activity during working memory, cerebral perfusion);
2. Anthropometric measurements (eg, BMI, waist-to-hip ratio) and blood pressure;
3. Cognitive test performance scores of cognitive domains predominantly affected by cognitive aging (executive functioning, working memory, and processing speed) as measured by a neuropsychological test battery (NTB) containing: (1) Rey Auditory Verbal Learning Test (RAVLT) [126], (2) Verbal Fluency Test (VFT) [127], (3) Trail Making Test (TMT) part A&B [128], (4) Digit Symbol Substitution Test (DSST) [129], and (5) Digit Span Test (DST) [129];
4. Lifestyle domain-related questionnaire scores for (1) diet (MIND-adjusted Eetscore [130]), (2) physical activity (Short Questionnaire to Assess Health-enhancing Physical Activity (SQUASH) [131], LASA Sedentary Behavior Questionnaire (SBQ) [132] and SARC-F Sarcopenia Questionnaire [133]), (3) stress management & mindfulness (Perceived Stress Scale (PSS) [134], Hospital Anxiety and Depression Scale (HADS) [135], Five Facet Mindfulness Questionnaire (FFMQ) [136]), (4) cognitive training (Cognitive Failures Questionnaire (CFQ) [137] and Metamemory In Adulthood Questionnaire (MIA) [138]), (5) sleep (Pittsburgh Sleep Quality Index (PSQI) [139]).
5. Physiological parameters measured on the wrist using a smartwatch over a 7-day period (day and night), including galvanic skin response, skin temperature, and heart rate

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parameters (measured by photoplethysmography sensing), and contextual motion parameters (measured by an integrated 3-axis accelerometer and 3-axis gyroscope);

6. Fecal analysis, including intestinal transit time [140], stool water content, pH, microbiota composition (both relative- and absolute abundances), metabolite profiles, and inflammatory biomarkers;
7. Blood analysis, including intestinal integrity markers, inflammatory markers, cardio-metabolic and oxidative stress markers, nutritional status, (early) AD markers, and dietary- and microbiota-derived metabolites;
8. Breath analysis to measure SIBO [141,142].

Other Study Parameters

Other study outcomes include the following:

1. Baseline demographics (age, sex, education level, ethnicity, etc) and medication history;
2. Baseline intracranial myelin and iron deposition measured by quantitative susceptibility mapping (QSM) MRI, and by relaxation rates (R_1 and R_2*– longitudinal and apparent transverse relaxation rates respectively);
3. Baseline IQ based on the Dutch Adult Reading Test (DART) [143];
4. Intervention adherence (in the high-intensity group) during the intervention period: group meeting attendance and completion of provided exercises;
5. Changes between baseline (T0) and follow-up after 6 months (T1) of the Montreal Cognitive Assessment (MoCA) [144];
6. Urine analysis of microbiota-derived bioactive compounds (changes between baseline (T0) and follow-up after 6 months (T1);
7. Changes between baseline (T0) and follow-up after 6 months (T1) in other health or lifestyle-related questionnaire scores, including (1) (psychosocial) complaints in daily life (Dutch Four Dimensional Complaint Questionnaire [145]), (2) quality of life (EQ-5D-5L [146]), (3) modifiable dementia risk score (“Lifestyle for BRAin health (LIBRA) [147]), (4) social contact and perceived social support (Lubben Social Network Scale [148]), (5) cognitive coping strategies (Cognitive Emotions Regulation Questionnaire [149]), (6) apathetic symptoms (Starkstein Apathy Scale [150]), (7) gastrointestinal symptoms rating scale (GSRS) [151], and (8) stool consistency (Bristol Stool Scale [152]).

Sample Size

The expected effect size for this study was determined based on other, mostly single-domain, lifestyle intervention studies with similar outcomes as our primary outcomes in the brain (eg, cerebral perfusion, working memory assessments) and in the periphery (eg, immunometabolic biomarkers, gut microbiome diversity). These studies generally found medium-to-large effect sizes (see Table S4 in Multimedia Appendix 1 [52,53,95,106,107,153-161]). Therefore, we deemed a slightly above-medium effect size of 0.30 (Cohen f[V]) suitable for our primary outcomes from baseline (T0=week 0, before start intervention) to follow-up (T1=week 26, after end intervention). The sample size calculation was performed using G*Power (version 3.1.9.6; Universität Kiel [162]). Using a multivariate ANOVA (with repeated measures and within-between interaction) *F* test with a power of 80% and a 2-tailed α-error probability of .05, we calculated that a total of 90 study participants would be required. However, based on our experience with previous fMRI and intervention studies, we expect a potential loss of data of 15% due to poor fMRI data quality (eg, motion artifacts) and potential intervention drop-outs. Therefore, to reach sufficient power, we would require a total sample size of 104 (90 participants×15% potential data loss=103.5=104) participants in this study.

Methods: Randomization and Blinding

Participants were randomized per inclusion wave, using stratified (2,4) block-randomization to provide a 1:1 allocation between our two intervention arms. Randomization was stratified by the factors sex (male vs female), risk factor profile (medium risk 2 - 3 points vs high risk ≥4 points), and a combined factor of education level +age (70+ yearsor low education vs 60 - 69 years and high education, specified as university of applied science associate degree (Dutch: HBO associate degree or higher). As with our sample size, (2,4) block-randomization was only possible with up to 3 strata, age, and education were combined in one stratification factor as they are both important covariates of cognitive functioning and aging-related cognitive decline [163].

An independent researcher from the DCCN was authorized to manually perform the randomization. This authorized researcher had no affiliation with the project and therefore had no bias in the allocation procedure.

Given the nature of the intervention arms, the participants and intervention supervisor were unable to remain blinded to the assignment to the intervention arms. Researchers conducting the follow-up outcome measure visits remained blinded and unaware of the intervention arm allocation. Only in case of unforeseen circumstances would deviations be made (eg, an unblinded researcher conducting the MRI protocol). Neuropsychological tests and task trainings (ie, n-back task) were conducted by a blinded researcher in all cases. Participants were asked to refrain from speaking about the intervention contents and experience during the follow-up outcome measure visits to prevent accidental unblinding.

The requirement for emergency unblinding was not applicable to this study, as participants were unblinded to the group allocation and the nature of the study setting.

Methods: Statistics and Analysis

We will test for change between T0 and T1 in the primary and secondary outcome variables, both within-group and between-group, using linear mixed-effect models with random effects for intercept (individuals). The intervention group and time will be included as fixed effects, as well as the interaction term between intervention group and time, to model the difference in change between T0 and T1 as a function of group allocation.

In addition, we will test for correlations in change (T0 minus T1) between (primary) brain outcomes and (primary) peripheral outcomes. We will select an appropriate correlation test for our

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data, based on whether assumptions are met. We will include both the high- and low-intensity groups if there is enough variance in change across both groups; else, we will only include the high-intensity group.

The level of significance will be set at 0.05 (2-sided). FDR correction will be used to account for multiple comparisons of secondary and exploratory outcomes. FWE correction will be used for secondary whole-brain analyses.

As part of exploratory analyses to assess the domain-specific effects on our primary outcome measures, we will take the pre- and posteffects of the primary outcome measures and use domain-related questionnaire scores and smartwatch-derived physiological data as a measure of improvement for each respective domain as predictors in linear mixed-effect models.

We will perform an intention-to-treat analysis. Participants who withdrew from the study during the 6-month intervention period, but had not withdrawn consent, were invited to the T1 (after week 26) follow-up outcome assessments. This means that we will use all available collected data, including collected (follow-up) data of participants who dropped out of the intervention. Missing data or data with insufficient quality, however, will not be used in the analysis.

Ethical Considerations

The HELI study has been reviewed and approved by the MREC Oost-Nederland on December 2nd 2021 (ToetsingOnline filenumber NL78263.091.21, ClinicalTrials.gov ID NCT05777863). All participants provided written informed consent before study inclusion, and participants were free to opt out of participation at any stage of the study. Obtained study data were only accessible to the research team directly involved in the study, and personal privacy was protected by removing personal identifying information from the dataset. Participants received compensation for travel expenses and trial participation, which were evaluated and approved by the MREC to avoid financial motivation in study participation.

Results

This work was supported by a Crossover grant (MOCIA 17611) of the Dutch Research Council (NWO), granted in December 2019. Recruitment started in April 2022 and concluded in October 2023. Over this period, a total of 279 people showed interest in participating and enrolled, of which 269 participated in the first round of telephone screening and 235 participated in the second round of telephone screening (see Figure 4). We were able to initially include our goal sample size of 104 participants, but 2 last-minute cancellations resulted in a final included sample size of 102 older Dutch adults. This sample size was subsequently randomized in the two parallel intervention arms, with n=49 participants in the “low-intensity” intervention group and 53 participants in the “high-intensity” intervention group.

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Figure 4. CONSORT (Consolidated Standards of Reporting Trials) study flowchart of HELI (Hersenfuncties na LeefstijlInterventie) study participant enrollment, screening (inclusion and exclusion), randomization, and allocation.

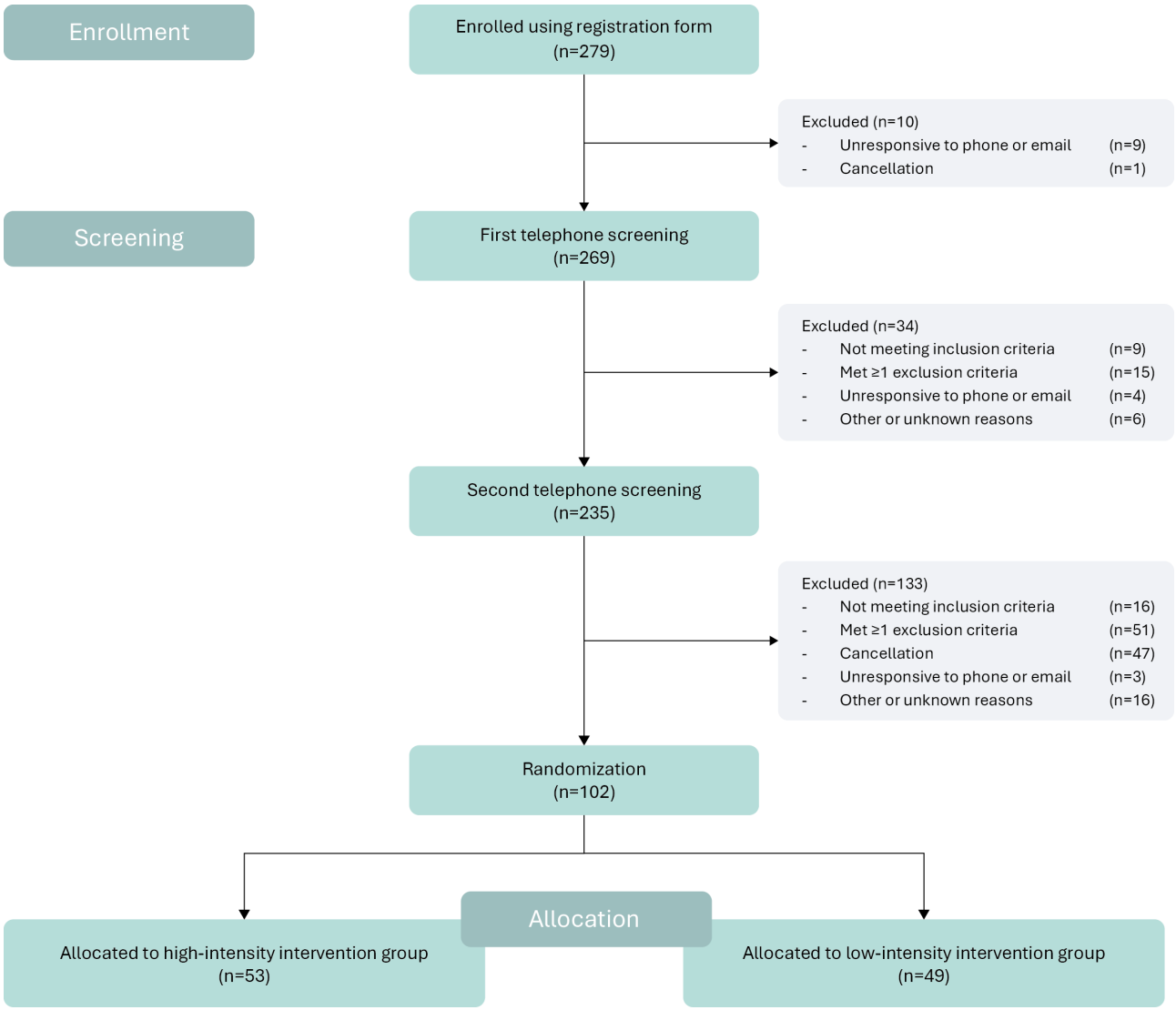

The baseline measurements at the DCCN and WUR centers were successfully completed by October 2023. The baseline mean age of our sample population was 66.6 (4.3) years, of which 65.7% (n=67) was female (see Table 2). The mean total years of education was 16.2 (SD 4.6) years. At baseline, 9.8% (n=10) of participants had a low level of education (International Standard Classification of Education [ISCED] 0‐2), 34.3% (n=35) had a medium level of education (ISCED 3‐4), and 55.9% (n=57) had a high level of education (ISCED 5‐8). The median risk, measured by points on the self-reported lifestyle-modifiable risk factor scale, was 3 (IQR 2‐3) points. The most common self-reported lifestyle-modifiable risk factors of cognitive aging at baseline were overweight or obesity (76/102, 74.5%), hypertension (58/102, 56.9%), hypercholesterolemia (57/102, 55.9%), and physical inactivity (57/102, 55.9%). See Table 2 for an overview of the HELI study baseline characteristics.

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Table . Baseline characteristics of the HELI (Hersenfuncties na LeefstijlInterventie) study (n=102).

Characteristic	Value
Participant demographics	
Age (years), mean (SD)	66.6 (4.3)
Sex (female), n (%)	67 (65.7)
Educational level, n (%)[a]	
Low	10 (9.8)
Medium	35 (34.3)
High	57 (55.9)
TICS-M1 score, mean (SD)	29.0 (3.6)
Self-reported inclusion factors	
Overweight and obese (BMI ≥25), n (%)	76 (74.5)
Obese (BMI ≥30), n (%)	35 (34.3)
Physically inactive, n (%)[b]	57 (55.9)
Hypertension, n (%)[c]	58 (56.9)
Hypertension medication usage, n (%)	84 (82.4)
Hypercholesterolemia, n (%)[d]	57 (55.9)
Diabetes type II, n (%)	20 (19.6)
Mild cardiovascular disease, n (%)[e]	11 (10.8)
Risk severity	
Risk factor score, median (IQR)	3 (2-3)

[a]Based on the International Standard Classification of Education (ISCED 2011) guidelines (low, medium, and high education categorization).

[b]Based on nonadherence to the WHO Guidelines on physical activity (300 or more min of moderate aerobic activity or 150 min of vigorous aerobic activity per wk).

[c]Based on systolic blood pressure of ≥140 mm Hg and diastolic blood pressure ≥90 mm Hg.

[d]Based on total cholesterol >5mmol/L or LDL-cholesterol of >3 mmol/L.

[e]Based on mild cardiovascular disease not mentioned in exclusion criteria (eg, varicose veins and atherosclerosis).

Discussion

Principal Findings

We described the design of the HELI study, an RCT focusing on the mechanisms of a 6-month multidomain lifestyle intervention in Dutch older adults at risk of cognitive decline, by assessing functional and structural MRI-related brain measures as well as peripheral measures related to the gut-immune-brain axis. The study design is based on the design of the FINGER-NL trial [108] and optimized for assessment of mechanisms instead of effectiveness.

The HELI study is characterized by its unique multimodal approach, which enables us to obtain mechanistic insights of a multidomain lifestyle intervention. We are using a broad range of neuroimaging techniques (see Table S3 in Multimedia Appendix 1 for the MRI sequence protocol) and neurocognitive tests to acquire a comprehensive profile of brain health. In addition, we also measure an extensive set of peripheral intestinal and immunometabolic markers, allowing us to investigate gut-immune-brain interactions and discover mediators of lifestyle effects on brain health. Combined with questionnaire data on lifestyle compliance, these brain, blood, and fecal markers have the potential to provide an elaborate overview of the pathways involved in lifestyle effects on cognitive aging and to explain individual differences in effectivity.

Compared to previous 24-month multidomain lifestyle interventions in cognitive aging [3,18,19,164] and the FINGER-NL trial [108], the HELI study intervention of 6 months is significantly shorter. However, our multidomain lifestyle intervention was carefully modified from the 2-year FINGER-NL intervention into a more condensed and intensified 6-month program. Especially, the high-intensity intervention group was characterized by more frequent meetings and group contact, requiring higher weekly effort. Within the field of functional neuroimaging, the duration of HELI (26 weeks) is relatively long compared to other (single-domain) lifestyle intervention studies (6 - 9 weeks), which reported significant central mechanistic intervention effects [52,54]. The main focus of our study is on the underlying mechanisms of lifestyle adaptations on cognitive aging, rather than on trial effectiveness. Therefore, we consciously chose to use multiple specific brain and peripheral parameters as primary outcomes, instead of

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cognitive functioning. We expect these parameters to be more sensitive to lifestyle changes, and therefore to be affected in an earlier stage than cognitive functioning.

We ultimately managed to include a total of 102 participants within our study. Our study population shares a similar baseline lifestyle modifiable risk factor profile (CAIDE) compared with the FINGER study, based on the total number of participants with hypertension, hypercholesterolemia, and diabetes (see Table S5 in Multimedia Appendix 1 [165-167]). Other previous multidomain lifestyle intervention studies in older adults, such as the pre-DIVA, MAPT, and J-MINT studies, used inclusion criteria different from the CAIDE-related lifestyle modifiable risk factors, or included participants solely based on age. Compared with previous studies, our study population is relatively highly educated, and we were unable to include a comparable number of participants with a lower education level. However, many of these earlier studies completed participant inclusion over a decade ago, and education levels have generally increased over time, which may reflect cohort effects. Because education level is often used as a covariate in task-related neuroimaging outcomes and neuropsychological test data, this is an important limitation to consider during data interpretation and comparison of results with other studies. For a more detailed description of the baseline characteristic comparison between the HELI study and previous multidomain lifestyle intervention studies, see Table S5 in Multimedia Appendix 1.

To summarize, the most important strength of the HELI study is its unique combination of multimodal neuroimaging and peripheral phenotyping with a multidomain lifestyle intervention. Moreover, the study has several additional strengths. First, the design has two active arms, which promote blinding and intervention adherence, while preserving between-group comparisons of lifestyle interventions. Second, the group approach within the high-intensity group is a strength, as it encourages peer support and intervention adherence. Finally, the online-onsite combination establishes a future-oriented intervention framework that ensures both quality and broad applicability. Limitations of the study comprise the limited number of objective domain-specific adherence measures and the selection bias toward more highly educated individuals, potentially due to the digital intervention format.

Conclusions

The HELI study offers a novel mechanistic approach by integrating multimodal neuroimaging and peripheral phenotyping with a multidomain lifestyle intervention in older adults at risk of cognitive decline. Results of the HELI study can help explain the previously observed small effect sizes of multidomain lifestyle interventions to prevent cognitive decline in aging, paving the way for personalized prevention strategies in the future.

Acknowledgments

Figure 1 was created with elements from BioRender [168], and adapted from BioRender, Remie L (2025) [169]. Figures 1-3 were created with elements from the Noun Project [170].

This work was supported by a Crossover grant (MOCIA 17611) of the Dutch Research Council (NWO), granted in December 2019. The MOCIA program is a public-private partnership [109].

Conflicts of Interest

None declared.

Multimedia Appendix 1
Detailed overview of study recruitment, intervention design, participant timeline, MRI-sequence protocol, sample size calculation, data management, and informed consents.
[DOC File, 457 KB - resprot_v14i1e69814_app1.doc]

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Abbreviations

AD: Alzheimer disease
BOLD: blood-oxygen-level-dependent
CAIDE: Cardiovascular Risk Factors, Aging, and Incidence of Dementia
CBF: cerebral blood flow
CBT-I: Cognitive Behavioral Therapy for Insomnia
CFQ: Cognitive Failures Questionnaire
CRP: C-reactive protein
DART: Dutch Adult Reading Test
DCCN: Donders Center for Cognitive Neuroimaging
dlPFC: dorsolateral prefrontal cortex
DSST: Digit Symbol Substitution Test

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DST: Digit Span Test
FFMQ: Five Facet Mindfulness Questionnaire
FINGER: Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability
fMRI: functional magnetic resonance imaging
FMT: fecal microbial transplantation
GSRS: Gastrointestinal Symptoms Rating Scale
HADS: Hospital Anxiety and Depression Scale
HELI: Hersenfuncties na Leefstijlinterventie
HUBV: Houd Uw Brein Vitaal
IL: interleukin
ISCED: International Standard Classification of Education
J-MINT: Japan-Multimodal Intervention Trial
LIBRA: Lifestyle for BRAin health
MAPT: Multidomain Alzheimer Prevention Trial
MCI: mild cognitive impairment
MIA: Metamemory In Adulthood
MIND: Mediterranean-DASH Intervention for Neurodegenerative Delay
MoCA: Montreal Cognitive Assessment
MOCIA: Maintaining Optimal Cognitive Functioning In Aging
MREC: Medical Research Ethics Committee
MRI: magnetic resonance imaging
MRS: magnetic resonance spectroscopy
NTB: neuropsychological test battery
PET: positron emission tomography
PFC: prefrontal cortex
preDIVA: Prevention of Dementia by Intensive Vascular Care
PSQI: Pittsburgh Sleep Quality Index
PSS: Perceived Stress Scale
QSM: quantitative susceptibility mapping
RAVLT: Rey Auditory Verbal Learning Test
RCT: randomized controlled trial
SBQ: Sedentary Behavior Questionnaire
SCFA: short-chain fatty acid
SIBO: small-intestinal bacterial overgrowth
SQUASH: Short Questionnaire to Assess Health-enhancing Physical Activity
TICS-M1: Telephone Interview for Cognitive Status
TMT: Trail Making Test
TNF: tumor necrosis factor
VFT: Verbal Fluency Test
WHO: World Health Organization
WUR: Wageningen University and Research

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Efficacy and Safety of Runzaozhiyang Lotion for Chronic Hand Eczema: Protocol for a Randomized Controlled Trial

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Abstract

Background: Chronic hand eczema (CHE) is a prevalent inflammatory skin disease in clinical practice. Guidelines recommend the use of topical medications, including corticosteroids and calcineurin inhibitors; however, prolonged use of these drugs may result in adverse effects, such as skin atrophy, drug tolerance, and rebound phenomena. Moreover, these medications exhibit limited efficacy in managing chronic hypertrophic hand eczema. Traditional Chinese medicine (TCM) has a long history of treating patients. The Runzaozhiyang lotion (RZZYL) is often used in the Department of Dermatology of Guang'anmen Hospital, China Academy of Chinese Medical Sciences, for these patients, with marked efficacy on symptoms, keratinization, hypertrophy, and pruritus improvements. Nonetheless, there is still no high-quality evidence from evidence-based medicine to prove the effectiveness and safety of CHE treatment.

Objective: This study aimed to examine the efficacy and safety of a classic Chinese herbal prescription, RZZYL, for CHE and to provide a different treatment option for patients with hand eczema who are resistant to conventional Western pharmaceutical treatments.

Methods: This study is a clinical trial characterized as randomized, double-blind, double-dummy, and positive drug-controlled. A total of 122 patients diagnosed with CHE have been randomized and allocated in a 1:1 ratio into 2 distinct groups, with one receiving the intervention and the other serving as the control. Participants in the intervention group will receive RZZYL granules along with a placebo cream of mometasone furoate, whereas the control group will get mometasone furoate cream in combination with a placebo for RZZYL granule. Both groups will be treated with either the active drug or a placebo for 4 weeks. The primary outcome metrics are the Hand Eczema Severity Index (HECSI) and the Numerical Rating Scales (NRS). Secondary outcome metrics consist of the target lesion area score, the Patient-Oriented Eczema Measure (POEM), the Dermatology Life Quality Index (DLQI), and the Investigator Global Assessment (IGA). The outcomes will be assessed at the start of the study and again at 2 and 4 weeks after the treatment period.

Results: The study will be conducted according to the guidelines and regulations approved by the participating institutions. Recruitment is expected to commence in March 2025 and conclude in March 2026. Data collection is anticipated to be completed by June 2026, with the study expected to conclude in August 2026.

Conclusions: This protocol addresses the limitations of previous research and aims to explore the efficacy and safety of RZZYL in treating CHE through a higher-quality clinical study. It seeks to provide additional treatment options for patients with CHE who are resistant to or have poor responses to current therapies.

Trial Registration: International Traditional Medicine Clinical Trial Registry ITMCTR2025000287; https://itmctr.ccebtcm.org.cn/mgt/project/view/698241578753484879

International Registered Report Identifier (IRRID): PRR1-10.2196/76555

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KEYWORDS

runzaozhiyang lotion; chronic hand eczema; clinical trial; traditional Chinese medicine; topical medication

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Introduction

Eczema is a type of inflammatory disorder that affects the dermis and epidermis. It is caused by both internal and environmental factors. This prevalent clinical condition is categorized into acute, subacute, and chronic eczema according to its progression and clinical features. The hands are a common site for the onset of this condition. Chronic hand eczema is characterized by episodes that occur at least twice a year or persist for more than 3 months during each occurrence. Clinically, chronic hand eczema (CHE) is distinguished by dermal thickening, lichenification, hyperkeratosis, and pruritus [1]. CHE is highly prevalent in the general population, with studies worldwide reporting an incidence rate of 4.0% in the general population and up to 14.5% of individuals experiencing the condition throughout their lifetime [2]. This disorder has become a significant global public health issue in recent years.

At present, there are no medications sanctioned by the US Food and Drug Administration (FDA), specifically for CHE, and a significant unmet demand persists for effective treatments to attain long-term management of CHE [1]. Topical treatment is the conventional method for CHE, and topical corticosteroids (TCS) are the primary suggested therapy. Nevertheless, up to 65% of cases encounter recurrence, skin shrinkage, and other adverse outcomes post treatment, and no evidence indicates that TCS can achieve long-term management of CHE [3]. Calcineurin inhibitors, as an alternative to TCS, can be used for long-term maintenance therapy. These agents help regulate the immune system and reduce inflammation. However, their clinical efficacy in treating skin thickening and lesion-like changes remains suboptimal [4,5]. While some studies have demonstrated that crisaborole (a phosphodiesterase four inhibitor), delgocitinib [6], and ruxolitinib effectively treat hand eczema, large-scale clinical trials are still needed to confirm their efficacy and safety. Furthermore, the high costs associated with these medications impose a significant financial burden on patients [7]. Consequently, current treatment options for CHE in Western medicine remain limited, highlighting an urgent clinical need to identify alternative medications that specifically target the keratotic hyperplasia symptoms associated with CHE.

Traditional Chinese medicine (TCM), as a form of complementary and alternative medicine, has a longstanding history of usage in China for the treatment of hand eczema and remains widely practiced both domestically and internationally [8]. As a unique part of TCM diagnostic and therapeutic techniques, the external treatments of TCM have a long history of success in treating dermatological disorders. Over-the-counter TCM topical preparations, such as Qingpeng Ointment and Longzhu Ointment, are commonly used in China for the treatment of hand eczema. These preparations are adequate for anti-inflammatory and anti-itch therapies. However, Qingpeng Ointment is suitable for acute and subacute eczema, demonstrating limited efficacy for chronic eczema [9,10]. In contrast, Longzhu Ointment is primarily used for treating acne, with no clinical trial evidence supporting its use in treating eczema [11].

Runzaozhiyang lotion (RZZYL) is derived from the *Galla chinensis* ointment developed by Mr Zhu Renkang, the founder of the Department of Dermatology at the China Academy of Chinese Medical Sciences, Guang'anmen Hospital. It combines the traditional *Galla chinensis* ointment formula with the clinical experience of the esteemed Beijing physician, Professor Xu Xian. This formula has established itself as one of the standard prescriptions in the Department of Dermatology at Guang'anmen Hospital, demonstrating apparent clinical efficacy. The primary ingredients of RZZYL comprise *Galla chinensis*, *Tribulus terrestris*, *Cannabis fructus*, *Bletilla striata*, *Cnidium monnieri* (L) Spreng, and *Sophora flavescens* Aiton. Pharmacological research has underscored the diverse therapeutic properties associated with these components (given in Table 1). Our preliminary investigation suggests that this formula exhibits a markedly superior efficacy rate relative to placebo in the treatment of CHE. However, there is a lack of high-quality randomized controlled trials, and the current evidence is insufficient to validate the effectiveness and safety of RZZYL for CHE. Therefore, our study aims to thoroughly evaluate the efficacy and safety of RZZYL for treating CHE through a carefully designed randomized controlled trial.

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Table . Overview of Runzaozhiyang lotion.

Chinese name	Common name	Latin name	Species and family	Proportion (%)	Efficacy
Wubeizi	Chinese Nutgall	*Galla chinensis*	The female aphids of *Aphis gossypii* or *Aphis craccivora* from the Aphididae family of the Hemiptera order, after piercing the tender leaves or petioles of *Rhus chinensis* (or its related species), parasitize them to form galls. These galls can be obtained by baking and drying them.	22.2	Antibacterial and anti-inflammatory effects [12]
Baijili	Caltrop	*Tribulus terrestris*	The mature dried fruits of *Tribulus terrestris*.	22.2	Antibacterial and anti-inflammatory effects [13]
Huomaren	Hemp Fruit	Cannabis fructus	The dried mature fruits of the Moraceae family plant *Cannabis sativa* L.	22.2	Antibacterial, anti-inflammatory, lipoid-regulating, and immunomodulatory properties effects [14]
Baiji	*Bletilla striata*	*Bletilla striata*	The tubers (or bulbs) and underground corms, after being washed, soaked, or blanched, are sliced thinly and then dried in the sun.	11.1	Wound healing, antibacterial, and anti-inflammatory effects [15,16]
Shechuangzi	Common Cnidium Fruit	*Cnidium monnieri* (L) Spreng	The dried mature fruits of the Apiaceae plant *Cnidium monnieri* (L) Cuss.	11.1	Antipruritic, antibacterial, and anti-inflammatory effects [17,18]
Kushen	Light yellow Sophora Root	*Sophora flavescens* Aiton	The dried roots of the leguminous plant *Sophora flavescens* Ait.	11.1	Antipruritic, antioxidant, and anti-inflammatory effects [19,20]

Methods

Trial Design

The trial is randomized, double-blind, double-dummy, and positive drug-controlled. The research will be carried out at Guang'anmen Hospital of the China Academy of Chinese Medical Sciences. Before therapy, patients with CHE have standardized baseline examinations, including medical history, physical examination, specialist assessments, and laboratory tests. Dermatologists will conduct the evaluation scales. The hospital's laboratory and electrocardiogram departments will test blood, urine, and electrocardiogram. All enrolled patients will be randomly assigned to 2 groups: RZZYL (granules) plus mometasone furoate cream placebo and RZZYL (granules) placebo plus mometasone furoate cream. The treatment method for each patient will be the same within their respective groups. The trial will comply with the World Medical Association Declaration of Helsinki and China's legislation and recommendations on Good Clinical Practice. Informed consent will be acquired from all participants after a comprehensive explanation by the doctors prior to the intervention. The study design is illustrated in Figure 1.

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Figure 1. Flow diagram of the randomized double-blind study on the treatment of chronic hand eczema with the Runzaozhiyang Lotion. ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; CHE: chronic hand eczema; Cr: creatinine; DBIL: direct bilirubin; DLQI: dermatology life quality index; γ-GGT: gamma-glutamyl transferase; HECSI: Hand Eczema Severity Index; IGA: Investigator Global Assessment; MFC: mometasone furoate cream; NRS: numerical rating scale; POEM: Patient-Oriented Eczema Measure; RZZYL: Runzaozhiyang lotion; TBIL: total bilirubin.

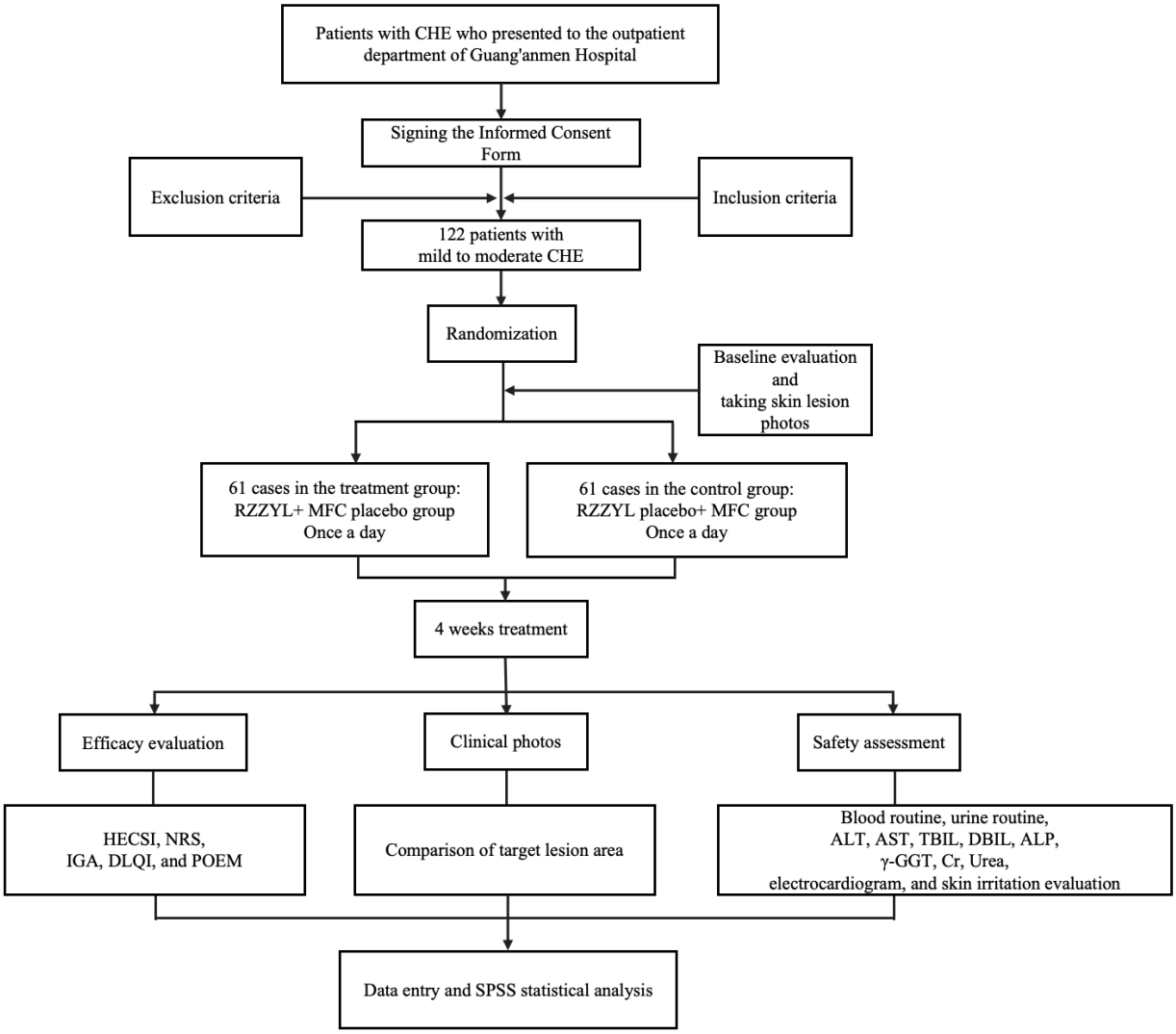

Sample Size

This trial aims to objectively assess the efficacy and safety of RZZYL for CHE through a high-quality clinical study design, thereby providing substantial data support for medication development and translation. The trial uses mometasone furoate cream as the positive drug control, categorizing it as a noninferiority trial. According to pertinent literature, the efficacy rate of mometasone furoate cream for treating HE, as assessed by the symptom improvement index using the Nimodipine method, is 53% [21]. Based on previous clinical observations, the efficacy rate for the RZZYL (granules) group is 73.47% [22]. Using the noninferiority study formula (equation 1) [23], with a statistical power (1-β) set at .9, an alpha level (α) of .025, and a noninferiority margin (δ) of 0.095 [24], the values for z_α and z_β are 1.95996 and 1.28155, respectively, with k (prespecified noninferiority margin) set to 1. The symbol "z" typically represents the critical value in a standard normal distribution, used to calculate the critical region in hypothesis testing. The sample size calculation indicates that the control group requires approximately 53 participants (n_c). Consequently, the sample size for the experimental group (n_t) is calculated as $k \times n_c$=53 participants, leading to a total sample size of 106 participants. Considering an anticipated attrition rate of 15.0% [25], the necessary sample size is adjusted to 61 participants for both the control and experimental groups, resulting in a total required sample size of 122 participants.

(1)nc=(Z1-α+Z1-β)2·[PC(1-PC)+PT(1-PT)](PC-PT-δ)2

Participants and Recruitment

The inclusion, exclusion, and exit criteria are listed in Textbox 1.

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Textbox 1. Inclusion, exclusion, and exit criteria.

Inclusion criteria

Individuals who satisfy the subsequent criteria will be incorporated into the trial:

- Diagnosis of mild to moderate CHE by the diagnostic criteria established in the Chinese Expert Consensus on the Diagnosis and Treatment of Hand Eczema (2021 Edition) [26] (HECSI score ≤27).
- Diagnosis of chronic eczema classified as blood deficiency and wind-dry type according to the Expert Consensus on the Diagnosis and Treatment of Eczema in Traditional Chinese Medicine (2021 Edition) [27].
- Patients aged 18-70 years (inclusive), both male and female.
- The primary affected region is the hands.
- Signed clinical informed consent and ability to adhere to the treatment protocol.

Exclusion criteria

Individuals meeting any of the following criteria will be excluded from participation

- Presence of any systemic or active skin disorders (eg, psoriasis) or conditions that could affect the evaluation of skin lesions, such as scars, tattoos, birthmarks, or other pigmentary skin conditions.
- Existence of specific bacterial, viral, or fungal infections at the site of application that require antibiotic therapy.
- The presence of serious concomitant primary diseases impacting the heart, cerebrovascular system, liver, kidneys, or hematological system, along with individuals experiencing mental health issues.
- Use of systemic corticosteroids or immunosuppressants within the 30 days leading up to treatment; administration of biologics or small molecule medications within the preceding 90 days; or application of topical corticosteroids or retinoids within a week prior to treatment.
- Confirmed allergies to any component of the investigational drug.
- Pregnant or breastfeeding individuals, as well as those planning to conceive in the next 3 months.
- Participation in other clinical trials for pharmaceuticals in the last 3 months.

Exit criteria

Patients will be withdrawn from the trial under the following conditions:

- Protocol noncompliance: Missing one or more scheduled follow-up visits without prior notification or valid justification; failure to complete at least 80% of the required clinical assessments (eg, symptom diaries and laboratory tests).
- Safety or medical reasons: Development of a new condition (eg, severe infection and pregnancy) requiring intervention that conflicts with the trial; concurrent use of medications outside the prescribed protocol, particularly those affecting the evaluation of the investigational drug's efficacy or safety.
- Participant-initiated withdrawal: Voluntary withdrawal via written or verbal request; loss to follow-up (no contact for 14 days or more despite 3 attempted reach-outs via phone or email).
- Other: Death or investigator-determined necessity to terminate the trial (eg, Grade 3 or higher adverse event).

Concomitant Treatments and Forbidden Drugs

All systemic and topical medications administered to participants during the clinical trial, excluding routine study drugs, will be documented. The reporting period commences from the date of informed consent signing or the randomization date and extends to the final follow-up visit (the date, month, and year of signing will be specified when the informed consent form is signed). Participants must submit their medical history and medication records from the past 3 months to verify medication usage and the date of discontinuation. To eliminate the potential interference from other therapeutic agents, participants are restricted from using systemic corticosteroids, immunosuppressants, biologics, small molecules, or any additional treatments, aside from the standard study medication, from 30 days prior to the informed consent signing or randomization until the final follow-up. Applying topical Chinese patent medicines, corticosteroids, retinoids, calcineurin inhibitors, or other medications is prohibited within 1 week before the final follow-up.

Recruitment

This research mainly focuses on outpatient individuals from Guang'anmen Hospital, which is connected to the China Academy of Chinese Medical Sciences. This trial is scheduled to conduct a pilot recruitment from March to April 2025 to achieve 5% of the target enrollment. Full patient recruitment is anticipated from May 2025 to March 2026, using advertisements, posters, and physician referrals. The advertisements and posters will provide a brief overview of the trial, outline the inclusion criteria and compensation details, and include the contact information for the researchers. Prior to enrollment, all participants will receive a thorough explanation of the trial procedures, the objectives of the research, possible adverse effects, and expected benefits. During the screening phase, each individual's eligibility for participation

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will be evaluated, and they will be informed of their right to withdraw from the study. Those who decide to participate in the trial will be required to complete 2 informed consent documents: one for their records and one to be kept by the research team.

To enhance patient retention, the following measures will be implemented:

1. Follow-up reminders: SMS text messaging and WeChat (Tencent) reminders will be dispatched 48 hours and 24 hours prior to the appointment.
2. Incentive system: A participant subsidy of 200 RMB (approximately US $27.64) will be provided upon the completion of all follow-up visits.
3. Convenience optimization: Weekend follow-up slots will be made available.

Randomization, Concealment, and Blinding

This study will use the SAS (SAS Institute) PROC PLAN process statement to generate random numbers to determine the seed number and fragment length. The treatment tasks corresponding to run numbers 001 - 120 will be documented. To ensure allocation concealment, the randomization process will be overseen by an independent statistician who is not involved in the study [28]. Eligible participants will be randomly assigned to either the treatment or control groups in a 1:1 ratio. The random numbers will be placed in a closed, opaque envelope, secured in our center. To ensure objectivity, operators will not be aware of any evaluations by efficacy evaluators and vice versa. Only the operators will have access to the random numbers prior to the commencement of the treatment. Further, they are not going to take part in the evaluation. To maintain strict allocation concealment, the system shall log metadata, such as time of randomization, operator's identity, and IP address. The quality control will regularly check these logs for any violations or deviations. In order to blind the participants, both groups will receive the same package of drug and placebo, with a similar treatment protocol. The placebo will add artificial coloring to ensure size, color, shape, taste, odor, and packaging are all identical to the active drug. Unblinding will occur only after the completion of case collection. However, an emergency unblinding procedure may be initiated if a serious adverse event or urgent medical treatment is necessary during the study.

Furthermore, the quality control team will conduct anonymous surveys at 3 critical stages, including when the trial reaches (1) 50% completion, (2) just before its conclusion, and (3) before unblinding. These surveys will evaluate whether participants, clinical researchers, and efficacy evaluators are aware of the group allocations. The data collected from these surveys will be subjected to statistical analysis to mitigate the risks of performance and detection biases, thereby enhancing the study's credibility.

Intervention

Patients will initially dilute the granules (either the moisturizing and anti-itch wash or the placebo wash) in 1500 - 2000 mL of hot water during the treatment period. When the medication cools to around 37°C, instruct the patient to fully immerse both hands in the solution for 15 minutes. After this, the medication will be rinsed off. Following the wash, an external cream (either mometasone furoate cream or placebo cream) will be applied to the affected area using the fingertip unit method, where 1 fingertip unit is sufficient to cover the entire hand of an adult (both front and back). The cream will be applied evenly in a thin layer to cover the lesions fully, followed by gentle circular massaging to enhance absorption. This application will occur once daily. Daily care will be administered throughout the day using Xiehe Vitamin E Cream (Product Standard number SuG Cosmetics Network Backup 2019002615). Clinical researchers will distribute medications biweekly to mitigate the risk of early dropout associated with a single 4-week supply. During the week 4 follow-up, both used and unused wash and cream will be collected, and panoramic photographs of the medication bags and tubes (including the participant ID label) will be taken and archived. A follow-up phone check will be conducted for medications that are not returned within 48 hours to confirm usage frequency and document the reasons for nonreturn. The sensitivity analysis will include participants with adherence rates below 80% or exceeding 120%. Furthermore, all medications used in the study will only be distributed after passing quality control testing.

Outcome Measures

Figure 2 shows the study timeline. As detailed below, all outcome measurements, along with drug administration and collection, will be documented from baseline to the conclusion of treatment.

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Figure 2. Timeline for trial enrollment, intervention, and assessments. ALP: alkaline phosphatase; ALT: alanine aminotransferase; AST: aspartate aminotransferase; Cr: creatinine; DBIL: direct bilirubin; DLQI: Dermatology Life Quality Index; HECSI: Hand Eczema Severity Index; IGA: investigator global assessment; NRS: numerical rating scale; POEM: Patient-Oriented Eczema Measure; TBIL: total bilirubin; γ-GGT: gamma-Glutamyl transferase.

Study period					
		Enrollment	**Allocation**	**Treatment (weeks)**	
Time point		-1	0	2	4
Enrollment					
	Eligibility screen	×			
	Informed consent	×			
	Demographic information	×			
	Disease Information	×			
Observations of effectiveness					
	Photographs of skin lesions		×	×	×
	HECSI		×	×	×
	NRS		×	×	×
	The target lesion area score		×	×	×
	POEM		×	×	×
	DLQI		×	×	×
	IGA		×	×	×
Safety assessments					
	Blood routine, urine routine, ALT, AST, TBIL, DBIL, ALP, γ-GGT, Cr, Urea, electrocardiogram		×		×
	Skin irritation evaluation		×	×	×
	Adverse Events		◄	———	►
Others					
	Trial drug distribution		×	×	
	Trial drug retrieval and documentation				×
	Summary of tests				×

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Primary Outcomes

Hand Eczema Severity Index

Hand Eczema Severity Index (HECSI) serves as a global standard for assessing the severity of skin lesions, facilitating a quantitative description of the clinical manifestations of hand eczema and enabling the monitoring of treatment outcomes [29]. The HECSI scoring system categorizes each hand into 5 distinct regions, such as fingertip, fingers (excluding the fingertips), palm, back of the hand, and wrist. Skin lesions are categorized as erythema (E), papules (I), scales (S), and fissures (F). Areas are assessed based on the intensity of skin lesions, with points allocated for no lesions (0), mild alterations (1), moderate alterations (2), and severe alterations (3). The total lesion area of both hands is assessed as follows: no involvement is assigned a score of 0. For involvement between 1% and 25%, the score is 1. Involvement between 26% and 50% is scored as 2, while involvement between 51% and 75% corresponds to a score of 3, and 76% to 100% corresponds to a score of 4. The total HECSI score is derived from the aggregate of scores for each site, specifically the sum of the lesion scores, which is then multiplied by the lesion area score. The score categorizes hand eczema into 3 classifications, including mild (0 - 11 points), moderate (12 - 27 points), and severe (≥28 points).

The Numerical Rating Scale

The numerical rating scale (NRS) is a horizontal line segment akin to the Visual Analog Scale, generally anchored at one end as “no itching” and at the other as “extremely itchy” or “the worst itching ever experienced,” with the end points marked as “0” and “10,” respectively. A score of 0 indicates the absence of itching while a score of 10 signifies the highest level of itching possible. A higher score indicates increased severity of itching. Patients report a numerical value reflecting the average intensity of itching experienced over the preceding 24 hours or the past week. Itching severity is categorized as no itching (score 0), mild itching (0<score <4), moderate itching (4≤ score <7), severe itching (7≤ score <9), and very severe itching (score ≥9).

Secondary Outcomes

The Target Lesion Area Score

This experiment focuses exclusively on hand lesions; thus, a single representative lesion is chosen as the target lesion. The lesion area will be assessed prior to treatment and after the trial. The percentage reduction in area will be determined from the measurements and used for comparative analysis.

Patient-Oriented Eczema Measure

The Patient-Oriented Eczema Measure (POEM) scoring scale has 7 questions that assess the severity of hand eczema symptoms experienced last week. Each question is scored on the basis of frequency or severity in the range of 0 to 4 points. The total score is the sum of all individual scores. Scores can range from 0 to 28 points. A more severe score denotes a greater severity of eczema symptoms and a more substantial impact on the patient’s quality of life.

Dermatology Life Quality Index

The Dermatology Life Quality Index (DLQI) measures the quality of life of patients with skin diseases. It measures both the symptoms and the impact of the skin disease on the patient’s everyday activities. This scale has a total of 10 questions regarding the patient’s life in the last week. These are emotional, professional, and social experiences. The scoring for each question is done on a scale of 0-3; the higher the score, the greater the impact of the condition on the quality of life of the person. The total score is the total of all individual responses. For this score, the higher the score, the worse the patient’s quality of life.

Investigator Global Assessment

Researchers and clinicians use the Investigator Global Assessment (IGA) score to gauge a patient’s skin condition. The score is often used in clinical trials for eczema and other skin diseases. Rating the severity of a disease depends on the characteristics of skin lesions, such as redness, exudation, and thickness. The dermatological revised scoring system works on a 5-point scale, ranging from 0 to 4, where higher scores indicate more severe skin conditions.

Safety Assessment

Safety indicators will be evaluated through the subsequent assessments:

1. General physical examination: The patient’s general condition and basic vital signs (body temperature, blood pressure, pulse, and heart rate) will be monitored and recorded both prior to and following enrollment. The participants’ health status will be assessed to determine eligibility for the trial and monitor health changes throughout the trial.
2. Laboratory assessments: At allocation and after 4 weeks of treatment, the assessments that will be conducted are blood routine, urine routine, alanine aminotransferase, aspartate aminotransferase, gamma-glutamyl transferase, total bilirubin, direct bilirubin, alkaline phosphatase, creatinine, urea, and electrocardiogram.
3. Evaluation of skin irritation: Skin erythema, blisters, dryness, scaling, pigmentation changes, tightness, and itching will be assessed and documented at allocation and after a 4-week treatment period.

During each visit to the trial, adverse events were recorded in the participant’s pathological report form. If required, all serious adverse events and unanticipated events should be immediately reported to the Guang’anmen Hospital Ethics Committee and relevant authorities. If the injury assessment confirms that the injury caused by the research is related to the trial, the treatment and compensation costs will be borne by Guang’anmen Hospital of the China Academy of Chinese Medical Sciences. If there is a significant change in the research protocol related to the participant or a substantial increase in the related, it will be essential to resecure his informed consent. In addition, a committee will track participant safety and integrity of the study, called the Data and Safety Monitoring Committee (DSMC). The principal investigator will regularly assess all reported adverse events. Based on necessity, the principal investigator

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may call for a meeting with the research team to evaluate the risks and benefits. Scheduled interim analyses will be performed to monitor the study's ongoing safety and amend the study protocol if necessary.

Oversight and Monitoring

Data Collection and Management

Original documents will be prepared for each participant randomly assigned to the study by the researchers. All pertinent information will be documented in the case report forms and archived in Microsoft Excel spreadsheets. Under the direction of the principal investigator, an internal data monitoring team will oversee and audit the clinical data to maintain data integrity and quality. The case report forms will be reviewed regularly or intermittently, and timely feedback will be provided to the researchers if any issues are identified. All participant data will be maintained strictly confidential and not accessible to the public.

Data Analyses

The results of this trial will be analyzed from three perspectives:

1. Full Analysis Set (Intention-to-Treat Analysis): This set includes all randomized participants, with data analyzed according to the principle of "randomization equals analysis." Missing data will be addressed using multiple imputation methods. Predictive mean matching will be used for continuous variables while logistic regression imputation will be used for categorical variables.
2. Per Protocol Set: This set comprises participants who meet specific criteria; that is, they must have completed at least 80% of the treatment regimen (ie, a minimum of 22 days of medication within 4 weeks), have not used prohibited study drugs, and possess complete data for the primary end point (HECSI score).
3. Safety Set: This set includes all participants who received at least 1 dose of the study medication.

The variable processing and statistical methods for this trial are outlined as follows: (1) continuous variable data that adhere to a normal distribution will be presented as mean (SD). Independent sample *t* tests (2-tailed approach) will facilitate between-group comparisons while repeated measures ANOVA will be applied for comparisons across multiple time points (eg, baseline, during treatment, and post treatment); (2) data that do not conform to a normal distribution will be expressed as median (IQR), with between-group comparisons executed using the Mann-Whitney *U* test; (3) categorical data will be described in terms of proportions or percentages, with between-group comparisons conducted using chi-square tests or Fisher exact test, depending on the final sample size. (4) All data processing and chart generation will be performed using R 4.0 software (R Project for Statistical Computing). Statistical tests will be 2-sided, with a significance level at $P<.05$.

Quality Control

Prior to the commencement of the trial, all participating researchers will receive standardized training on diagnostic interviews to ensure familiarity with the management process and to clarify the implementation procedures. During the trial, 2 clinical physicians will evaluate CHE. The allocation will be fixed, and migration between groups will not be permitted. The reason for a participant's withdrawal from the study will be documented if they discontinue treatment.

Ethical Considerations

Ethics Approval

Ethics committee, Guang'anmen Hospital China Academy Of Chinese Medical Sciences, China.

Ethics and Dissemination

The trial will be carried out in line with the World Medical Association's Declaration of Helsinki and the legislation and guidelines on Good Clinical Practice established in China. This protocol has been approved by the Ethics Committee of Guang'anmen Hospital, China Academy of Chinese Medical Sciences (2024 - 262-KY), and registered on the International Traditional Medicine Clinical Trial Registry Platform (ITMCTR2025000287). Researchers must thoroughly inform participants regarding the study's purpose, procedures, potential risks, and compensation. Participants will complete 2 informed consent forms: one for their records and the other for the researchers, to be included in the clinical research documentation for future reference.

To express gratitude to participants for their investment of time and transportation costs, and by the ethical committee's guidance on reasonable compensation (based on local standards for volunteer participation in research and minimum wage rates), participants will receive a subsidy of 200 RMB (approximately US $27.64) upon the completion of the entire treatment and follow-up. This compensation adheres to ethical guidelines for reimbursement, aiming to avoid undue inducement while ensuring fairness. Participants' privacy and confidentiality will be rigorously protected throughout the study. When the study results are published, participants' names will be replaced with a unique serial number and the initials of their names to ensure that personal information is not disclosed. Data handling will comply with applicable data protection regulations, and access to personal information will be restricted to authorized researchers.

Results

Recruitment is scheduled to commence on March 1, 2025. The initial month will be a pilot phase, targeting an enrollment of 4-7 patients. Subsequently, it is projected that 8-12 participants will be recruited each month. The recruitment process is anticipated to conclude by March 2026, with the results published in the winter of 2026. By July 1, 2025, a total of 40 patients have been recruited. Data analysis and report writing are expected to be finalized by August 2026.

Discussion

Strengths and limitations

One limitation is that participants may exaggerate the severity of CHE due to the subjectivity involved in completing self-assessment questionnaires. In addition, the study is carried

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out in a single hospital, which may limit the applicability of its results. Despite these constraints, the outcomes of this research will contribute new evidence for RZZYL from a meticulously designed trial. These results will promote the advancement of complementary and alternative therapies within TCM for chronic health issues while improving patients' quality of life.

Future Directions

RZZYL can potentially reduce inflammation, combat bacterial infections, and facilitate the recovery of skin lesions, thus providing an alternative treatment option for patients with clinically resistant or recurrent chronic hand eczema and enhancing their quality of life. Following the publication of our research findings, we will further promote the RZZYL treatment regimen through formulation development, academic conferences, and training sessions. In addition, we will disseminate the academic results of this project nationwide through academic exchanges, paper publications, and participant reports, thereby facilitating the development, national promotion, and application of the research outcomes.

Conclusion

This study protocol describes a randomized, double-blind, double-dummy, positive drug-controlled trial to evaluate RZZYL for treating chronic hand eczema (CHE). The trial will assess the efficacy and safety of RZZYL, using rigorous quality control and precise methodologies to ensure high validity and reliability. Detailed methods for allocation concealment, recruitment, randomization, and data collection have been thoroughly outlined. Objective measures such as scale scoring, lesion area, and laboratory tests will be used to evaluate the treatment's effectiveness and safety. The results may provide insights into RZZYL's potential as an alternative treatment to the current TCS for clinically resistant or recurrent CHE.

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Authors' Contributions

JY and CX conceptualized the study. JY is the chief investigator who led the protocol development and secured funding. RZ, BC, JB, AS, and FW are the investigators who enrolled most of the participants in this study. CX and BC planned the statistical analyses. RZ and JY proofread the manuscript, oversaw protocol publication, and will conduct data interpretation and result publication.

Conflicts of Interest

None declared.

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Abbreviations

CHE: chronic hand eczema
DLQI: Dermatology Life Quality Index
DSMC: Data and Safety Monitoring Committee
FDA: US Food and Drug Administration
HECSI: Hand Eczema Severity Index
IGA: Investigator Global Assessment
NRS: numerical rating scale
PDE-4: phosphodiesterase four inhibitor

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POEM: Patient-Oriented Eczema Measure
RZZYL: Runzaozhiyang lotion
TCM: traditional Chinese medicine
TCS: topical corticosteroids

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Protocol

Evaluating the Effectiveness of a Multimodal Psychotherapy Training Program for Medical Students in China: Protocol for a Randomized Controlled Trial

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This is a corrected version. See correction statement: https://www.researchprotocols.org/2025/1/e71220

Abstract

Background: Psychotherapy is central to the treatment of mental disorders, highlighting the importance of medical students and residents developing competencies in this area. Chinese medical residents have expressed a strong need for psychotherapy training, yet they are generally dissatisfied with the current offerings. This paper presents the protocol for an evidence-based, well-structured psychotherapy teaching program aimed at medical students and residents.

Objective: This study involves a randomized controlled trial of a 2-day multimodal intensive educational intervention designed to evaluate the effectiveness of a new psychotherapy teaching program for medical students and residents in China. The primary outcomes include participants' knowledge and utilization of psychotherapy, training program acceptability, self-reported self-efficacy, and motivation to apply psychotherapy.

Methods: This 2-arm randomized controlled trial was conducted at Sir Run Run Shaw Hospital. The study aimed to recruit approximately 160 medical students and residents, with about 80 participants in the intervention group and 80 in the control group. Both groups completed a baseline survey before participation, reporting their psychotherapy knowledge, utilization of psychotherapy, self-efficacy, and self-motivation. The intervention group received a 2-day multimodal intensive educational intervention (supervision-based online teaching), while the waitlist control group did not receive any intervention during this period. Both groups were followed up for 8 weeks, completing the same survey administered at baseline. At the end of the study, the control group received the intervention. The primary outcome measure was the change in trainees' psychotherapy knowledge before and after the intervention training. Secondary outcome measures included changes in the trainees' utilization of psychotherapy, self-reported self-efficacy, and self-reported motivation for psychotherapy. Additionally, training program acceptability was assessed. Analysis of covariance was used to analyze the primary outcomes. Pearson correlations and regression analysis explored factors associated with the knowledge score at baseline. The secondary outcomes, including participants' psychotherapy utilization, confidence, and motivation, were analyzed using the same methods as for knowledge. All tests were 2-tailed, with a significance level set at $P<.05$.

Results: A total of 160 participants were recruited and randomized between January 4 and 12, 2024. Baseline assessments were conducted from January 28 to February 1, 2024. The psychotherapy training program for the intervention group took place on February 3 and 4, 2024. Posttraining assessments were conducted starting April 1, 2024. Due to withdrawals, incomplete surveys,

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and data loss, we had a total of 113 participants: 57 in the intervention group and 56 in the control group. The amount of data varied across measures. The data analysis was finished in August 2024.

Conclusions: This study aims to evaluate the effectiveness of the multimodal psychotherapy training program for medical students in China. If this brief, cognitive behavioral therapy–based psychotherapy skill training proves effective, the potential mental health impact of its nationwide expansion could be significant.

Trial Registration: ClinicalTrials.gov NCT06258460; https://clinicaltrials.gov/ct2/show/NCT06258460

International Registered Report Identifier (IRRID): DERR1-10.2196/58037

(JMIR Res Protoc 2025;14:e58037) doi:10.2196/58037

KEYWORDS

multimodal teaching; psychotherapy training; Chinese medical students; randomized controlled trial

Introduction

Background

The delivery of psychosocial and psychotherapeutic interventions remains central to the treatment of many patients with psychiatric disorders (eg, obsessive-compulsive disorder, panic disorder, major depression, eating disorders, and addictive behaviors) and psychosomatic disorders (eg, hypertension, bronchial asthma, and rheumatoid arthritis) [1,2]. Cuijpers et al [3] conducted a large-scale network meta-analysis to examine the effects of various types of psychotherapies for adult depression, including cognitive behavioral therapy (CBT), interpersonal therapy, psychodynamic therapy, problem-solving therapy, behavioral activation, life-review therapy, and "third-wave" therapies, as well as nondirective supportive counseling. They found that all types of these therapies were more effective than care-as-usual and waiting list control conditions and that most therapies were more efficacious than placebo. Additionally, most therapies maintained significant effects at the 12-month follow-up compared with care-as-usual. A strong evidence base indicated that several psychotherapy modalities were effective for most mental disorders, whether used alone or in combination, primarily including behavior therapy, CBT, and interpersonal psychotherapy [4,5]. According to a systematic review and meta-analysis, the emotional change processes and mechanisms of psychotherapy were most strongly associated with specific CBT methods, such as fear habituation, emotion regulation and experience, and the habitual reorganization of maladaptive emotional perceptions [6]. Today, CBT is recommended as a first-line intervention for both the acute treatment and relapse prevention of various mental illnesses, including major depressive disorder, and most patients prefer psychological treatment over pharmacologic options [5]. Therefore, medical students in clinical rotations and residents working in psychiatric and psychosomatic departments should be required to develop competencies in psychotherapy, particularly in CBT [7]. However, there remains a significant treatment gap for mental disorders in China [8]. Despite the high prevalence of mental disorders in the country, medical professionals in psychiatric or mental health departments often have a comparatively low capacity to provide adequate care and lack qualified training in psychotherapy. Learning basic psychotherapy skills would benefit medical students, residents, and other health care providers (HCPs), including doctors and nurses, across all departments. These skills can be applied in clinical practice to enhance doctor-patient relationships [9]. A study conducted in Beijing found that after participating in a 2-year psychotherapy training program, medical doctors reported improvements in diagnosing and treating mental illness, as well as in doctor-patient communication and the development of strong doctor-patient relationships. Patients also demonstrated significant improvements in levels of depression and anxiety, the severity of physical symptoms, quality of life, and the patient-rated therapeutic relationship [9]. Therefore, psychotherapy training for medical students, residents, and other HCPs requires greater emphasis.

A narrative review indicated that medical residents in psychiatry have a strong need for psychotherapy training to enhance their competence, yet they generally express dissatisfaction with the current training programs [10]. Therefore, providing evidence-based and well-designed psychotherapy training programs is essential for equipping medical students and residents with a foundational understanding of psychotherapy and the necessary skills for clinical practice [11]. Compared with traditional methods, psychotherapy teaching that emphasizes skill practice and role experience is more popular and effective. For instance, a single-day simulation training program has proven effective in psychiatry for medical students, enhancing their knowledge, communication and interview skills with patients, and confidence in treatment [12]. Despite the critical importance of learning psychotherapy skills during medical school and residency, there is a notable lack of formal evaluation of psychotherapy teaching methods and their efficacy. Given the lack of access to psychotherapy, medical and psychological educators, along with program directors, should design high-quality curricula to teach medical students, residents, and other HCPs the essential knowledge and skills in psychotherapy. These curricula should be evaluated through well-conducted, methodologically robust randomized controlled trials (RCTs) [13].

Aim and Hypotheses

To evaluate the effectiveness of the multimodal psychotherapy training program for medical students in China, well-designed RCTs of psychotherapy teaching programs are urgently needed. The primary aim of this proposed project is to assess the effectiveness of a new multimodal psychotherapy teaching program for medical students and residents in China, which is designed to enhance their psychotherapeutic skills and improve their performance in entry-level clinical settings. The primary

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hypothesis was that, compared with a control intervention, the intervention group receiving the psychotherapy teaching program would acquire significantly more knowledge about psychotherapy after training. We also hypothesized that the program would lead to an increase in the utilization of psychotherapy and be associated with improved knowledge in this area. The third hypothesis posited that trainees' self-reported self-efficacy and motivation to apply psychotherapy in clinical practice would increase significantly.

Methods

Patient and Public Involvement

Neither participants nor the public were involved in the trial's design, recruitment, or conduct of this study.

Study Design and Participants

This study was an RCT of a 2-day multimodal intensive educational intervention aimed at enhancing the clinical skills in psychotherapy of Chinese medical students and residents. The trial included a waitlist control group, with 8 weeks of follow-up for all participants. A detailed schedule of the study procedures is summarized in Figure 1.

Figure 1. Flowchart study design.

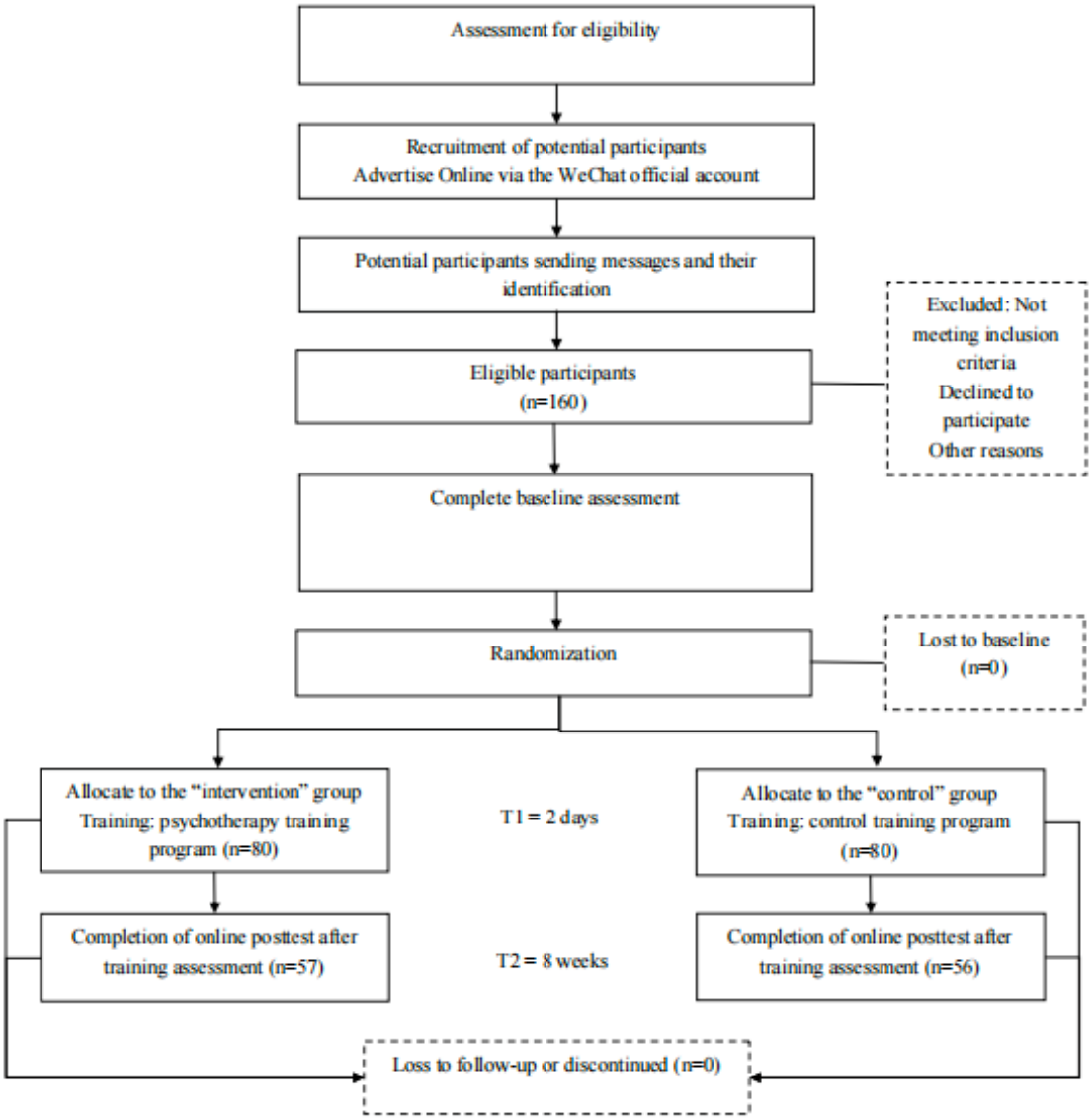

Study participants (n=160) primarily included medical students, residents, and a few other HCPs, such as doctors and nurses, in China. There were no specific restrictions for participants, although most were from Zhejiang University School of Medicine. An overview of participant eligibility criteria is provided in Textbox 1.

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Textbox 1. Study inclusion criteria (participants who did not qualify for the criteria were not recruited to participate in this study).

- Medical students, residents, and other health care providers
- Aged 18 years or older
- Expressing an interest in psychotherapy
- Willing to receive randomization
- Willing to provide informed consent to participate in the study

Sample Size and Power Calculation

The sample size was calculated based on the primary outcome using G*Power [14] (version 3; Universität Düsseldorf). As the data were continuous variables and analysis of covariance (ANCOVA) would be used to compare differences between the 2 groups, an a priori analysis selecting ANCOVA as the statistical test was conducted to determine the required sample size. As only a few studies have examined the effectiveness of psychotherapy training for medical students, we were unable to reference effect size or other data as criteria. Therefore, a medium effect size for the primary outcome was estimated preliminarily. It was determined that 128 participants (64 in each group) would be required to achieve 80% power (effect size f=0.25; $1 - \beta$=0.80; α=.05). To account for potential attrition, we aimed to recruit approximately 160 participants (80 in each group), ensuring that the proposed analysis would be sufficiently powered even if 25% of participants in each group were lost to attrition.

Randomization and Group Allocation

This study aimed to recruit approximately 160 participants, with about 80 in each group. The study coordinator randomized participants into the intervention and control groups using a random number generator in R software, maintaining a 1:1 ratio for allocation to the experimental and control conditions. Participants in the intervention group first received the experimental condition, which included the psychotherapy training program after the baseline assessment. The waitlist control group received the control condition, meaning they participated in the psychotherapy training program only at the end of the study. The timeline of the study was as follows: all participants underwent a baseline assessment, the intervention group received the training program, and the control group received a control training program. After 8 weeks, all participants were followed up, and finally, the control group received the intervention training program (Figure 1).

Recruitment

The researchers advertised the program online through the WeChat (Tencent Holdings Limited) official account of the Department of Psychiatry at Sir Run Run Shaw Hospital, Zhejiang University School of Medicine, to recruit potential participants. They encouraged sharing the program details with medical schools and hospitals. Interested individuals could register by sending messages and their identification to the research assistants (Zitang Zhou and Luyao Zou). Research assistants then contacted the respondents to assess their eligibility, explain the study to each participant, and inform them about the allocation to either the control or intervention groups, where they would receive the psychotherapy training program.

Baseline and Posttraining Data Collection

Before randomization, demographic information and self-reported questionnaires were collected from all participants at baseline. This information included participants' sex, age, identity (student, resident, or HCP), education level (undergraduate or graduate degree), department affiliation (psychiatric or nonpsychiatric), and years of psychotherapy-related work. Additionally, outcome measurements were gathered, including trainees' knowledge of psychotherapy, utilization of psychotherapy, self-reported self-efficacy, and self-reported motivation, among others. The questionnaires on psychotherapy knowledge, utilization, and self-efficacy and motivation to engage in psychotherapy were specifically designed based on our training program. Outcome measurements were assessed again 8 weeks after training (Table 1). Data were collected online using WenJuanXing (Questionnaire Star), a Chinese platform that provides professional online questionnaire surveys and data collection for RCTs [15]. The hospital's data monitoring committee oversaw the data collection process, and personal information was deidentified to ensure confidentiality.

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Table 1. Schedule of enrollment and posttraining assessments.[a]

Schedule	Baseline	8 weeks after training
Initial approach	✓	N/A[b]
Informed consent	✓	N/A
Eligibility screen	✓	N/A
Randomization	✓	N/A
Intervention/control initiation	✓	N/A
Demographic characteristics	✓	N/A
Knowledge	✓	✓
Self-reported self-efficacy	✓	✓
Self-reported motivation	✓	✓
Utilization	✓	✓

[a]This table illustrates the schedule of enrollment and posttraining assessments. Initial approach, informed consent, eligibility screen, randomization, intervention/control initiation, and demographic characteristics were evaluated and collected only at the baseline timeline. Psychotherapy knowledge, self-reported self-efficacy, self-reported motivation, and utilization were both collected at the baseline and 8 weeks after the training.

[b]N/A: not applicable.

Development of the Psychotherapy Training Program

The psychotherapy training program was primarily developed by an experienced psychotherapist (Tao Pei) and an MD-level psychiatrist (Yanhui Liao), both of whom have approximately 20 years of relevant experience. The details of the 2-day psychotherapy training program are outlined in Multimedia Appendix 1. The program included 2 days of intensive training followed by 8 weeks of follow-up, with guidance on applying psychotherapy in clinical settings.

Intervention

Control Group

After providing consent, participants allocated to the waitlist control group received a message encouraging them to complete all questionnaires from baseline through to the final follow-up at 8 weeks. They were sent messages via WeChat to thank them for their participation and to remind them of the timeline for completing the study. Once they finished the posttraining measurement, a digital booklet of the psychotherapy training program was provided to them via WeChat or as a hard copy upon request. After the trial concluded, participants in the control group were offered the opportunity to receive the psychotherapy training program free of charge.

Intervention Group

All participants in the intervention group received the 2-day psychotherapy training program and were given a hard copy of the program booklet at recruitment. Additionally, supervision-based group meetings were held during the follow-ups at weeks 1, 2, 4, and 8, with each meeting lasting approximately 2 hours. During these follow-up meetings, instructors—including psychotherapists and psychiatrists—were available to answer any psychotherapy-related questions, encourage participants to practice psychological interventions, and provide further information to support the clinical application of psychotherapy.

Outcomes and Outcome Measures

Primary Outcome

Trainees' psychotherapy knowledge was assessed by participants using an 11-point scale (ranging from 0 to 10) before and after the 8-week period (Table 2). At baseline, 160 participants completed the self-reported psychotherapy knowledge questionnaire, and the results indicated a high internal consistency coefficient (Cronbach α) of 0.980 for the scores across the 17 items.

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Table 2. Knowledge about psychotherapy.[a]

Variables	Measures (0-10)
Overview of psychotherapy	
Supportive psychotherapy techniques	
Overview of cognitive behavioral therapy	
Beck's cognitive therapy	
Identify automatic thinking and do cognitive conceptualization	
Cognitive conceptualization	
Evaluation of automatic thinking	
Reconstruction techniques for automated thinking1: Socratic questioning	
Reconstruction techniques for automated thinking2: pie charts, continuous spectrum, cost-benefit analysis, behavioral experiments	
Challenge automatic thinking	
Social skill training	
Problem-solving	
Behavioral therapy theory and behavioral conceptualization	
Behavioral activation	
Relaxation training	
Exposure therapy	
Competency structure of psychotherapists and the growth path of cognitive behavioral therapy therapists	

[a]This is the assessment of participants' knowledge about psychotherapy. Each item was rated on a 0-10 scale, where 10 means "knowing very well."

Secondary Outcomes

Training Program Acceptability

Program acceptability in the intervention group was measured using questions designed to assess acceptability, as detailed in Table 3.

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Table 3. Questions for assessing the psychotherapy training program acceptability.[a]

Category and questions	Rating
General	
• Overall rating of the program	5=like very much; 4=like somewhat; 3=neutral; 2=dislike somewhat; 1=very dislike; 5=very likely
Appraisal	
• Appraisal of the program—the likelihood of applying the program for patients • Appraisal of the program—the likelihood of recommending the program to other medical students or other health care providers	5=very likely; 4=somewhat likely; 3=neutral; 2=unlikely; 1=not at all likely
Acceptability	
• I would have been able to help patients to deal with mental problems with the program • The program made it easier to communicate and help patients during clinical work • The program disrupted my daily schedule • The program is easy to understand	5=strongly agree; 4=agree; 3=neutral; 2=disagree; 1=strongly disagree
Frequency	
• Frequency of using psychotherapy	1=almost never; 2=sometimes; 3=always

[a]This is the rating of the training acceptability assessment. The last item, "Frequency of using psychotherapy," was rated on a 1-3 Likert scale, where 3 indicates "always."

Utilization of Psychotherapy

The utilization rate of psychotherapy interventions for patients during the 8 weeks of follow-up was assessed using items from Table 4.

Table 4. The utilization rate of psychotherapy.[a]

Variables	Measures (0-10)
Supportive psychotherapy techniques	
Social skill	
Problem-solving skill	
Behavioral activation	
Relaxation training	
Exposure therapy	

[a]This is the assessment of participants' utilization rate of psychotherapy. Each item was rated on a 0-10 scale, where 10 means maximum utilization and 0 means minimum utilization.

Self-Reported Self-Efficacy and Self-Reported Motivation

Self-efficacy and motivation were measured using a visual analog scale on a 10-cm line, representing a continuum from "no self-efficacy or motivation" to "the strongest self-efficacy or motivation" (Table 5).

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Table 5. Self-reported self-efficacy and motivation of psychotherapy.[a]

Variables	Visual analog scale
Self-reported self-efficacy	
Confidence in practicing psychotherapy	
Confidence in practicing supportive psychotherapy	
Confidence in practicing cognitive behavioral therapy	
Self-reported m otivation	
Willingness or motivation to practice psychotherapy	
Willingness or motivation to practice supportive psychotherapy	
Willingness or motivation to practice cognitive behavioral therapy	

[a]This is the assessment of participants' self-reported self-efficacy and self-reported motivation. Each item was measured by the visual analog scale on a 10-cm line that represents a continuum between "no self-efficacy or motivation" and "the strongest self-efficacy or motivation.

All secondary outcomes were reported as mean values. According to the baseline measurements of our study, 160 participants evaluated their psychotherapy utilization, confidence, and motivation using self-reported questionnaires. The internal consistency coefficients (Cronbach α) for these 3 questionnaires were 0.950, 0.961, and 0.936, respectively.

Procedures

Figure 1 and Table 1 summarize the schedule for enrollment and posttraining assessments. Participants were evaluated at baseline (0 weeks), before and after receiving the intervention training, and at 8 weeks after training. They were also asked to maintain a daily log of their utilization of the psychotherapy training program, which included activities such as providing emotional support and teaching patients breathing techniques for stress relief. Reminders were sent to participants who did not complete the 8-week posttraining questionnaires.

Withdrawal From the Program

All participants were free to withdraw from the trial at any time without needing to provide a reason. Following the intention-to-treat principle [15], participants who did not respond to the 8-week posttraining assessment were retained in the analysis according to the group to which they were randomized, regardless of whether they received the intervention. Participants who withdrew were excluded from the analysis, and their reasons for withdrawal were recorded. A complete case analysis was conducted, excluding any participants who withdrew at the posttraining assessment point.

Data Analysis

All data were automatically collected via WenJuanXing through a WeChat-based link. The data were downloaded from the WenJuanXing database into a user-specific Excel file. This study did not include interim analyses; data were analyzed only after all had been collected. The trial statistician blinded the intervention assignment in the data using R software (R Foundation for Statistical Computing) and SPSS (2013 release; IBM Corp.).

The primary hypothesis was that, compared with the control intervention, the intervention group receiving the psychotherapy teaching program would significantly gain more knowledge about psychotherapy after training. We also hypothesized that the program would lead to increased utilization of psychotherapy and be associated with improvements in knowledge. The third hypothesis posited that trainees' self-reported self-efficacy and motivation to apply psychotherapy in clinical practice would increase significantly.

Descriptive statistics were used to assess demographic and psychotherapy-related characteristics at baseline. Following normality and homogeneity of variance tests, ANCOVA was used to analyze the primary outcomes. In the ANCOVA model, the dependent variable was the change in the knowledge score. The fixed factor was the group (intervention group or control group), while the covariates included the mean score of psychotherapy knowledge at baseline and years of psychotherapy experience. Pearson correlations and regression analysis (both linear and binary regression models) were used to explore factors associated with the knowledge score at baseline and to assess the increase in psychotherapy utilization in both the intervention and control groups. The secondary outcomes—participants' psychotherapy utilization, confidence, and motivation—will also be analyzed in the same manner as knowledge.

A complete case analysis was performed, excluding any participants with missing information on the posttraining assessment. Additionally, a sensitivity analysis of the missing data was conducted to determine whether the missingness is random. Demographic information and scores for psychotherapy knowledge, utilization, confidence, and motivation at baseline were compared between the complete data group and the missing data group. All tests were 2-tailed, with a significance level set at $P<.05$.

Safety and Adverse Events

Throughout the psychotherapy training program, adverse events were closely monitored. Participants were encouraged to communicate any psychotherapy-related issues or adverse events encountered during their clinical work. We prompted each participant to report any adverse events experienced at each group meeting, and they could also report them at any time. If participants experienced severe adverse events, they were encouraged to seek support from a psychologist or psychiatrist.

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We did not anticipate any training-related serious adverse events (SAEs), such as life-threatening incidents, during this trial. However, if any adverse events occur, we will document the SAE, record it on the SAE form, and submit it to the ethics committee of Sir Run Run Shaw Hospital (the principal investigator's affiliation) within 24 hours.

Ethics Approval and Consent to Participate

This study was approved by the ethics committee of Sir Run Run Shaw Hospital, an affiliate of Zhejiang University School of Medicine (2024 Ethics Approval File No. 2024-0066). The trial was conducted in accordance with the Declaration of Helsinki. Participants were provided with informed consent before the baseline assessment. After thoroughly reading and understanding the content of the consent, they received a link to electronically sign their name at the end of the informed consent form and submit it via WeChat. Each participant was informed about the study's purpose, procedures, measurements, potential risks, and benefits before recruitment. Informed consent was then obtained from each participant. Participation was entirely voluntary, and participants could withdraw from the study at any time. Coordinating researchers' contact information was provided to all participants for any inquiries or concerns.

Data Security

The authors utilized the professional version of WenJuanXing, which features high-level security management, alongside an applet on WeChat that ensures the secure and confidential protection of participants' data.

Results

This study recruited 160 participants from January 4 to January 12, 2024. The 2-day training program took place on February 3 and February 4, 2024, and the posttraining assessment was completed on April 1, 2024. Due to withdrawals, incomplete surveys, and data loss, we had a total of 113 participants: 57 in the intervention group and 56 in the control group. The amount of data varies for each measure. Data analysis was completed in August 2024. The results will be published in peer-reviewed journals. If found to be effective, the psychotherapy training program and the accompanying program booklet will be made freely available to the public by the end of the trial.

Discussion

To our knowledge, this will be the first RCT to evaluate the efficacy of a multimodal psychotherapy training program for medical students in China.

The strength of this study lies in its theoretical framework, primarily guided by cognitive behavioral theory. With a large sample size, this RCT evaluates the efficacy of the psychotherapy training program using multimodal teaching methods in China. If effective, this multimodal psychotherapy training program could be applied nationwide, significantly enhancing its potential impact on public health. Its expansion could help HCPs acquire the necessary psychotherapy skills to effectively manage patients' psychological issues.

There are several limitations to this study. First, the effectiveness of teaching and the quality of learning can be influenced by various factors, such as opportunities to implement psychotherapy practice, the intensity of clinical work during the follow-up period (including the impact of holidays), and the availability of continuing education resources. These factors cannot be adequately controlled in this study. Second, the 2-day training will take place at Sir Run Run Shaw Hospital, which may deter participants from other regions of China from attending the program. Third, there are only 2 main instructors (Psychiatrist YL and Psychologist TP) involved in this training program. While both have nearly 20 years of teaching and clinical experience, their individual teaching styles and characteristics may still influence the overall effectiveness of the program. Fourth, although this 8-week training program aims to enhance the acquisition of therapeutic skills, developing proficiency in psychotherapy is likely to be a more prolonged process. Fifth, all measures rely on participants' subjective assessments, which may be influenced by personal biases and expectations of improvement following the intervention training. Lastly, we submitted this protocol to the journal during the recruitment process.

In conclusion, this is the first RCT to evaluate the efficacy of a multimodal psychotherapy training program for medical students in China. If this educational program, which offers brief and short-term psychotherapy skills training, proves effective, its nationwide expansion could have a significant health impact. It provides evidence-based psychotherapy training—primarily in CBT—for medical students, and its dissemination will equip HCPs to better manage mental health issues, such as stress and depression. Therefore, it is crucial to develop effective psychotherapy training that emphasizes basic psychotherapy skills. The results of this training's effectiveness can offer valuable insights for the future development of training programs, enabling them to better meet the learning needs of medical professionals and enhance doctor-patient relationships.

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Availability of Data and Materials

Data sets from this study and the corresponding analysis code will be made publicly available at the conclusion of the study's analyses.

Declaration of Artificial Intelligence Use

Generative artificial intelligence was not used in any portion of the manuscript writing.

Authors' Contributions

YL designed the study, while YL and TP developed the program. YD verified the analytical methods. JT supervised the design of the work and revised the manuscript. All authors discussed and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The details of the 2-day psychotherapy training program.
[DOCX File , 26 KB - resprot_v14i1e58037_app1.docx]

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Abbreviations

ANCOVA: analysis of covariance
CBT: cognitive behavioral therapy
HCP: health care provider
RCT: randomized controlled trial
SAE: serious adverse event

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Protocol

Impact of the Mediterranean Diet on Patients With Psoriasis: Protocol for a Randomized Controlled Trial

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Abstract

Background: Psoriasis is an inflammatory disease primarily treated through molecular-targeted therapies. However, emerging evidence suggests that dietary interventions may also play a role in managing inflammation associated with this condition. The Mediterranean diet (MedDiet), prevalent in southern European countries, has been widely recognized for its ability to reduce cardiovascular mortality, largely due to its anti-inflammatory properties. This anti-inflammatory potential has prompted interest in exploring the MedDiet's role in immune-mediated diseases, including psoriasis. Observational studies have indicated potential benefits, such as reductions in the Psoriasis Area and Severity Index. However, there is a need for well-designed clinical trials to address the methodological limitations of these studies and to establish specific dietary recommendations for psoriasis.

Objective: This study aims to evaluate the impact of an intensive dietary intervention based on the MedDiet in patients with psoriasis. The study will assess the effects of this intervention on skin involvement, metabolic parameters, and inflammatory cytokines. In addition, the emotional well-being and quality of life of participants will be evaluated using validated questionnaires. A methodological analysis will also be conducted to enhance the design of future large-scale clinical trials.

Methods: An open-label, single-blinded (evaluator) randomized controlled trial was designed to assess the impact of a high-intensity MedDiet intervention in patients with mild-to-moderate psoriasis. A total of 38 patients will be randomly assigned into 2 groups—an intervention group receiving the MedDiet intervention and a control group receiving standard care. The intervention group will participate in dietary education sessions aimed at adopting the MedDiet over 4 months, with monthly monitoring by experienced nutritionists. Participants will receive 500 mL of extra virgin olive oil per week, along with informative materials, recipes, and weekly menus. In contrast, the control group will receive standard low-fat diet recommendations without nutritionist monitoring. All participants will undergo a baseline visit, a 2-month follow-up visit, and a final visit at 4 months.

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Blood tests will be conducted at the beginning and end of the study. This study protocol was approved by the Institutional Review Board of the Hospital Ramón y Cajal (Madrid) in July 2023.

Results: Enrollment concluded in October 2024, with data collection set to finish by February 2025. The findings will be presented at national and international conferences and published in peer-reviewed journals.

Conclusions: This protocol outlines the design of a clinical trial that implements the MedDiet in patients with psoriasis to evaluate its benefits on skin involvement, systemic inflammation, and quality of life.

Trial Registration: ClinicalTrials.gov NCT06257641; https://clinicaltrials.gov/study/NCT06257641

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KEYWORDS

psoriasis; Mediterranean diet; MedDiet; nutritional intervention; olive oil; inflammatory disease; Impact of the Mediterranean Diet on Patients with Psoriasis; MEDIPSO; dietary intervention; methodological analysis; randomized controlled trial; RCT; clinical trial; nutrition; diet; Europe

Introduction

Psoriasis is a common skin disease, affecting between 2% and 4% of the population [1,2]. Its pathogenesis involves a complex interplay between innate and adaptive immunity, with the interleukin (IL)-17/IL-23 axis playing a crucial role. While not all underlying molecular mechanisms have been fully elucidated, current medical treatments primarily target proinflammatory cytokines [3]. In today's era of media, nutrition has become a significant topic of interest among patients with psoriasis. A survey conducted by the National Psoriasis Foundation involving 1206 patients revealed that 89% (n=1073) believed it was important to discuss the role of diet in their disease with their physician, and 86% (n=1037) had attempted dietary modifications. Despite this, only 31% (374/1206) of patients had actually discussed dietary changes with a health care provider [4]. In fact, nutritional approaches play a very important role in the prevention and treatment process of chronic diseases such as inflammatory diseases, autoimmune diseases, cardiovascular diseases, and even mental diseases [5,6].

There is well-established evidence supporting the beneficial effect of weight loss in patients with psoriasis [7]. Dietary interventions that promote weight loss are recognized as valuable therapeutic strategies for reducing inflammation, particularly in obese patients with psoriasis [8]. In addition, the nutrigenomic effects of certain food components have been documented [9]. However, the only firm dietary recommendations currently reflected in most psoriasis guidelines and expert consensus are weight loss for patients who are overweight and obese and a gluten-free diet for those with positive celiac disease serology [10]. Therefore, there remains a need for dietary guidance that offers benefits beyond weight loss, applicable to patients of any body weight.

The Mediterranean diet (MedDiet) refers to the eating patterns typical of the olive-growing regions around the Mediterranean Sea. This dietary approach emphasizes the consumption of fruits, whole grains, vegetables, nuts, seeds, legumes, and olive oil—the hallmark of the MedDiet. It also includes a moderate intake of red wine with meals, seafood, poultry, and fermented dairy products, while limiting red and processed meats, sweets, and other ultraprocessed foods [11]. Growing evidence suggests that the MedDiet may influence the progression and severity of psoriasis [12,13]. In a 2018 cross-sectional study by Phan et al [14], which included 35,735 participants from the NutriNet-Santé cohort, 3557 participants had psoriasis, with 878 classified as severe cases. The multivariate analysis, adjusted for factors such as age, sex, weight, and cardiovascular risk, showed a significantly lower percentage of severe psoriasis cases among those with greater adherence to the MedDiet [14].

Several research groups have designed large-scale dietary interventions to implement the MedDiet in large patient cohorts. The PREDIMED (Prevention with Mediterranean Diet) study [15], which included 7447 patients at high risk of cardiovascular disease, randomly assigned participants into 3 groups—2 groups received Mediterranean dietary advice supplemented with extra virgin olive oil (EVOO) or a mixture of nuts, while the third group followed low-fat dietary recommendations. All groups were closely monitored by nutritionists. The PREDIMED study demonstrated the positive role of the MedDiet in preventing cardiovascular events. Subsequent satellite studies, such as the PREDIMAR (Prevention of Recurrent Arrhythmias with Mediterranean Diet) study [16], which used an entirely online dietary intervention, further underscored the MedDiet's benefits and the feasibility of achieving high adherence to this dietary pattern through a dietary intervention.

The MEDIPSO (Impact of the Mediterranean Diet on Patients with Psoriasis) study, detailed in this paper, was conceived to address the need for more evidence on the relationship between psoriasis and the MedDiet. This proof-of-concept randomized controlled trial, inspired by the PREDIMED study, involves a high-intensity MedDiet intervention in patients with psoriasis. The primary objective is to evaluate the impact of this dietary pattern on psoriasis skin involvement, inflammatory cytokines, and quality of life.

Methods

Study Design

The MEDIPSO study is an open-label, single-blinded (evaluator) randomized controlled trial. This experimental study involves patients with mild-to-moderate psoriasis who are on stable topical treatment, which will be randomly assigned to either a

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control group or an intervention group. Patients in the intervention group will receive dietary education focused on adopting the MedDiet, with monthly monitoring by nutritionists experienced in the PREDIMED clinical trial. In contrast, the control group will not receive any active dietary modification interventions.

Both groups will undergo blood tests to assess metabolic parameters before and after the study period, and data on anthropometric characteristics and quality of life will be collected. The study aims to evaluate the effects of the MedDiet on skin involvement, metabolic parameters, and inflammatory cytokines, as well as its impact on emotional well-being and quality of life. In addition, a methodological analysis will be conducted to refine the design for future large-scale clinical trials.

Participants

In total, 38 patients with mild-to-moderate plaque psoriasis and no systemic treatment will be included. Participants for this study will be recruited from among patients who regularly attend dermatology consultations at Hospital Universitario Ramón y Cajal. The inclusion criteria and exclusion criteria are stated in Textbox 1.

Textbox 1. Inclusion and exclusion criteria for the participation in the Impact of the Mediterranean Diet on Patients with Psoriasis study.

Inclusion criteria:

- Psoriasis clinically diagnosed by an experienced dermatologist
- Predominantly psoriasis vulgaris
- Psoriasis Area and Severity Index ≥2 and ≤10 at the time of recruitment
- Stable weight (<5% weight loss or gain) in the last 3 months
- Treated exclusively with topical treatment for psoriasis at enrollment and throughout the study
- Willing and able to follow the study procedure, attend all scheduled visits during the study period, and provide blood samples as indicated in the procedure
- Able to give informed consent
- Willing to implement pregnancy prevention measures throughout the study period

Exclusion criteria:

- Type 1 or 2 diabetes mellitus
- Good adherence to the Mediterranean diet at the time of screening (energy-restricted Mediterranean Diet Adherence Screener score ≥8)
- Language barrier (patients not fluent in Spanish or English) or conditions that make telephone communication difficult (eg, severe hearing loss)
- History of cardiac disease
- Comorbidities that may compromise the implementation of the intervention (eg, cancer, digestive diseases, and so on) or limit survival to less than 6 months
- History or current eating disorder (anorexia, bulimia, etc; screening will be carried out using the Diagnostic and Statistical Manual of Mental Disorders, fifth edition, if indicated)
- Malnourished patients (screening using the Malnutrition Universal Screening Tool, if indicated)
- BMI greater than 40 kg/m^2
- Presenting gout
- Pregnant, planning pregnancy, or breastfeeding
- Use of diuretics at the time of sampling
- Difficulty or inconvenience in changing dietary habits and following the Mediterranean diet (allergies, food intolerances, and special diets)
- Participation in a clinical trial with drugs or dietary intervention in the year prior to inclusion in this study

Sample Size

There are no previous studies specifically evaluating the impact of MedDiet on skin involvement in patients with psoriasis. The only dietary intervention study in psoriasis to date is by Castaldo et al [8], which reported a decrease in Psoriasis Area and Severity Index (PASI) of 7.2 (95% CI –8.7 to –5.6) in a sample of 37 patients. However, this study differs significantly from MEDIPSO in design; it involved a single group without a control group, used a highly aggressive intervention including prolonged fasting periods, targeted only patients with obesity who have severe psoriasis, and excluded other adjuvant treatments, with a longer follow-up period.

In contrast, our study includes a control group, applies a less aggressive dietary intervention, and focuses on patients with mild-to-moderate psoriasis who are allowed to continue their stable topical treatments. Consequently, we anticipate the SD in PASI reduction at week 16 to be much lower, around 1. To

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detect a difference of 1 unit on the PASI scale, with an α risk of 0.05 and a β risk of less than 0.2 in a bilateral contrast, we estimate that 19 participants per group (intervention and control) are needed. We assume a common SD of 1 and estimate a loss-to-follow-up rate of 15%.

Randomization

After signing the informed consent, all participants will be enrolled and randomly assigned into either the MedDiet intervention group or the standard-of-care group using closed envelopes. Randomization will be conducted using a computer-generated list created by an independent statistician, who is blinded to the trial and not involved in participant recruitment. The allocation will follow a 1:1 ratio. The recruiter will only open the envelope and learn of each patient's group assignment after the informed consent form has been signed by the patient.

Blinding

The study is single-blinded, as only the investigator evaluating the PASI is blinded. Both the patient, the nutritionists responsible for carrying out the intervention, and the person in charge of follow-up and nonsubjective data collection are aware of the group to which the patient has been assigned.

Roles

The entire dermatology department will be involved in patient recruitment. The principal investigator will oversee initial screening, follow-up, data collection, and the evaluation of side effects. Randomization will be conducted using a sealed-envelope system, with the principal investigator opening the envelopes only after the patient has been enrolled in the study and the informed consent has been signed. This investigator will not be blinded.

The nutritional intervention was fully designed by nutritionists from the University of Navarra, who will implement the intervention with the support of the principal investigator. The nutritionists will also not be blinded.

Evaluation of nonobjective parameters, such as PASI, and data analysis will be conducted by coinvestigators who are blinded to the group assignments.

The Nutritional Intervention

The objective of the nutritional intervention in the MEDIPSO study is to enhance adherence to the MedDiet. A hybrid approach combining remote and face-to-face interactions will be implemented. During the initial visit, when the first blood sample is taken and the patient's data are collected, initial dietary recommendations will be provided along with supportive materials, including instructions on the MedDiet, infographics, sample menus, and recipes. Following this, dietitian-nutritionists with experience from previous MedDiet intervention studies, such as PREDIMED, will conduct monthly telephone consultations with each participant.

During these consultations, the dietitian-nutritionists will assess adherence to the MedDiet and set individualized goals for improvement based on the participant's needs. In addition to the printed materials provided at the first visit, participants will have the opportunity to discuss any questions or concerns with the research team.

Participants in the intervention group will receive 500 mL of EVOO each week, distributed during clinic visits. The goal is to encourage participants to consume at least 4 tablespoons of EVOO daily, using it as the primary culinary fat in their homes as part of the MedDiet.

The dietary recommendations for the intervention will align with the habits defined in the MedDiet according to the Energy-Restricted Mediterranean Diet Adherence Screener (er-MEDAS) scale (Table 1) [17]. Participants will be instructed to follow specific guidelines, including consuming 4 or more tablespoons of EVOO daily for cooking and seasoning; 2 or more servings (200 g per serving) of vegetables per day (with at least 1 serving being raw); 3 or more servings (125 g per serving) of fruits per day (including natural juices); 3 or more servings (60-80 g per serving) of legumes per week; 3 or more servings (150 g per serving) of fish or seafood per week (including at least 1 serving of oily fish); and 3 or more servings (30 g per serving) of nuts per week. Participants will be advised to choose white meats (eg, skinless poultry and rabbit) over red meat (eg, beef and pork) or processed meats (eg, sausages and hamburgers). Regular use of sofrito (a sauce made with chopped tomato, garlic, and onion simmered in olive oil) for cooking, at least twice per week, will also be encouraged. In addition, whole grains (eg, bread, pasta, and rice) should be chosen over refined cereals. The dietary plan will recommend eliminating or limiting the consumption of cream, butter, margarine, carbonated and sugary drinks, baked goods (eg, sweet desserts, cakes, pastries, and cookies), and ultraprocessed foods. The nutritional intervention will not prescribe a specific caloric intake or macronutrient distribution.

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Table 1. Energy-Restricted Mediterranean Diet Adherence Screener scale score (the maximum possible score is 17; this was the scale used to assess the adherence to the Mediterranean diet during the study; a score ≤7 was considered to be poor adherence to Mediterranean diet).

Question to be asked to the patient	Criterion to score 1 point; otherwise, 0 is recorded
Do you use extra virgin olive oil as the principal source of fat for cooking?	Yes
How many servings of vegetables do you consume per day? Count garnish and side servings as half a serving; a full serving is 200 g.	≥2
How many pieces of fruit (including fresh-squeezed juice) do you consume per day?	≥3
How many servings of red meat, hamburger, or sausages do you consume per week? A full serving is 100-150 g.	≤1
How many servings (12 g) of butter, margarine, or cream do you consume per week?	<1
How many carbonated and sugar-sweetened beverages do you consume per week?	<1
How many servings (150 g) of pulses do you consume per week?	≥3
How many servings of fish and seafood do you consume per week? (100-150 g of fish, 4-5 pieces, or 200 g of seafood)	≥3
How many times do you consume pastry such as cookies, cake, or sweets per week?	<3
How many times do you consume nuts per week? (1 serving=30 g) per week?	≥3
Do you prefer to eat chicken, turkey, or rabbit instead of beef, pork, hamburgers, or sausages?	Yes
How many times a week do you eat cooked vegetables, pasta, rice, or other dishes dressed with sofrito (a tomato, garlic, onion, or leek sauce simmered with olive oil)?	≥2
Do you add sugar to your beverages (coffee, tea)?	No
How many servings of white bread do you consume per day (1 serving=75 g)?	<1
How many servings of whole-grain bread, pasta, or rice do you consume per week?	≥5
How many servings of refined bread, rice, and pasta do you consume per week?	<3
Do you drink wine? How much do you consume per week? (1 cup=100 mL)	Male 14-21 cups; female 7-14 cups

Study Protocol

The intervention period will last 16 weeks, comprising 3 face-to-face visits for all participants and 2 additional telephone visits for those in the intervention group.

During the baseline visit (visit 1), patients will sign the informed consent, undergo randomization, and have clinical information collected. A complete physical examination will be conducted, and blood samples will be obtained. For patients randomized to the intervention group, this visit will also include the provision of informational materials, the distribution of EVOO, and the initiation of the nutritional intervention.

At week 8, a face-to-face visit (visit 2) will be conducted. The primary objective of this visit is to perform a clinical evaluation to determine if the patient has experienced any clinical worsening that would necessitate the initiation of systemic treatment. If systemic treatment is deemed necessary, the corresponding analytical tests and vaccination protocol will be initiated. This visit at week 8 ensures that participation in the study does not delay the start of systemic treatment if required.

During the final visit (visit 3), clinical information will once again be collected, a complete physical examination will be performed, and final blood samples will be drawn. In addition, feedback will be gathered from the patient regarding their experience in the study, any challenges encountered, and suggestions for improvement. This feedback will be collected through an anonymous, free-response online survey, as well as a brief interview in which the patient can discuss any issues identified during the study with the investigator.

The study protocol is summarized in Figure 1.

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Figure 1. Comprehensive overview of the study protocol. As shown, patients in the control group will attend 3 on-site study visits. In contrast, patients in the Mediterranean diet intervention group will attend 3 on-site visits as well as 2 additional remote visits. Participants in the intervention group will receive 4 L of EVOO at weeks 0 and 8 (500 mL per week). Blood tests will be conducted at week 0 and week 16 in both groups. EVOO: extra virgin olive oil; PASI: Psoriasis Area and Severity Index.

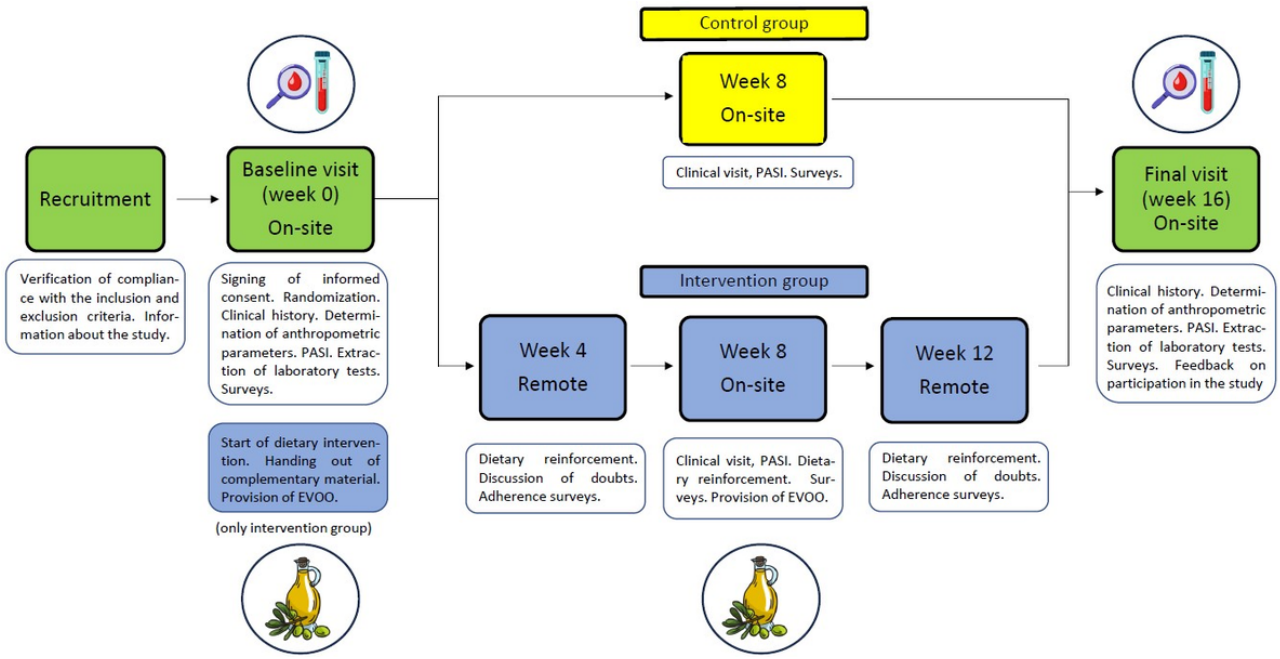

Outcomes

The primary outcome is the change from baseline in the PASI at week 16. PASI is the most widely used scale for assessing psoriasis severity and informing therapeutic decisions, with scores ranging from 0 (no lesions) to 72 (severe lesions across the entire body surface) [18].

The secondary outcomes include:

1. Change from baseline in adherence to the MedDiet at week 16: Adherence will be assessed using the validated er-MEDAS questionnaire, which scores from 0 to 17, with higher scores indicating better adherence [17].
2. Change from baseline in anthropometric parameters at week 16: This includes weight, BMI, and abdominal circumference, measured before and after the intervention.
3. Change from baseline in serum inflammatory interleukins at week 16: Levels of various ILs and cytokines will be assessed, including granulocyte-macrophage colony-stimulating factor, interferon gamma (IFNγ), IL-1β, IL 2, IL 4, IL 5, IL 6, IL 9, IL 10, IL 12 (p70), IL 13, IL 15, IL 17A/CTLA8, IL-17E/ IL-25, IL 17F, IL 21, IL 22, IL 23, IL 27, IL 28A/IFNλ2, IL 31, IL 33/NF HEV (mature), MIP-3α/CCL20, tumoral necrosis factor alpha (TNFα), and TNFβ/Lymphotoxin-α (LTA).
4. Change from baseline in metabolic blood parameters at week 16: changes in serum cholesterol, low-density lipoproteins, high-density lipoproteins, lipoprotein A, apolipoprotein A1, apolipoprotein B, fasting serum insulin, hemoglobin, A_{1c} and C-reactive protein (CRP) will be measured.
5. Change from baseline in the impact of the disease on patient's life at week 16: quality of life will be assessed using the validated questionnaire Dermatology Life Quality Index [18]. Change in sleep quality will be evaluated using the Insomnia Severity Index [19] and emotional state changes will be measured using the Hospital Anxiety and Depression Scale [20].

Data Analysis

Once data collection is complete, statistical analysis will be performed using StataIC 17 (Stata Corp). A descriptive analysis of the baseline demographic and clinical characteristics of the patients included in the trial will be conducted. Normality will be assessed using skewness, kurtosis, and histogram plots. Parametric variables will be reported as mean (SD), nonparametric variables as median (IQR), and categorical variables as n (%).

To evaluate differences between the intervention groups, statistical significance will be assessed using the Student *t* test for comparing 2 groups and the ANOVA test for comparisons involving multiple groups, for parametric variables. For nonparametric variables, the Wilcoxon rank-sum test and Kruskal-Wallis test will be applied. Pearson chi-square test will be used for categorical variables. An intention-to-treat analysis will be performed.

Linear mixed-effects models will be used to assess changes in nutritional variables from baseline to follow-up visits. Statistical significance will be determined using a 2-tailed level of significance, with *P* values less than .05 considered significant.

Ethical Considerations

The study protocol (version 2.0; July 10, 2023) was approved by the Institutional Review Board of the Hospital Ramón y Cajal (Madrid) in July 2023 (170/23).

All personal and clinical information of potential and enrolled participants will be coded and used exclusively for clinical trial

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purposes. This information will be securely stored in the BioeBank 3.01.0.R26 storage system. Access to this data will be restricted to the investigators involved in this study. No monetary compensation was provided to the participants.

Results

Enrollment concluded in October 2024, with data collection set to finish by February 2025. The findings will be presented at national and international conferences and published in peer-reviewed journals. The estimated study timeline is illustrated in Figure 2.

Figure 2. Estimated study timeline. MEDIPSO: Impact of the Mediterranean Diet on Patients with Psoriasis.

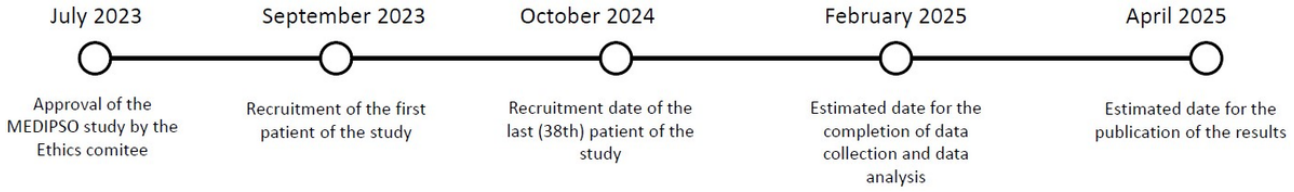

Discussion

Expected Findings

The relationship between psoriasis and the MedDiet has been explored in several cross-sectional studies. Barrea et al [21] conducted a case-control study involving 62 patients with untreated moderate-to-severe psoriasis and 62 healthy controls matched for age, sex, and BMI. This study found that patients with psoriasis were less adherent to the MedDiet than healthy controls. In addition, the consumption of EVOO and fish were identified as predictors of a lower PASI [21]. Similarly, Korovesi et al [22], in a study with a comparable design, reached analogous conclusions and also highlighted the beneficial effect of legume consumption on PASI reduction. Furthermore, Molina-Leyva et al [23] observed a lower severity of psoriasis in patients with greater adherence to the MedDiet, along with a reduction in CRP, a marker of systemic inflammation.

Despite the growing evidence suggesting the potential benefits of the MedDiet in psoriasis, the current evidence remains weak, primarily limited to nonexperimental studies [10]. In an attempt to provide more robust data, Castaldo et al [8] designed an experimental study where an aggressive weight loss was induced through a ketogenic diet followed by a hypocaloric Mediterranean-type diet. Significant reductions in skin involvement were observed, as measured by PASI. Interestingly, no linear correlation was found between weight loss and PASI, suggesting that ketone bodies and other dietary components from both dietary patterns may contribute to the observed anti-inflammatory effects [8]. However, the study's design lacked a control group, making it difficult to attribute the anti-inflammatory effects solely to the dietary intervention. In addition, the study only included obese patients, leaving unanswered the critical question of whether these potential benefits of the MedDiet could also be observed in patients with normal weight.

The molecular mechanisms underlying the potential benefits of the MedDiet on psoriasis severity are not yet well characterized. Beyond psoriasis, greater adherence to the MedDiet has been shown to reduce the severity of other immune-mediated diseases, such as rheumatoid arthritis [24] and inflammatory bowel disease [25]. This observation has shifted attention toward the MedDiet's potential systemic anti-inflammatory effects. Olive oil, a key component of the MedDiet, is rich in monounsaturated fatty acids. Virgin olive oil, in particular, retains all the lipophilic components of the olive, as well as α-tocopherol and phenolic compounds—molecules with strong antioxidant properties—whereas refined olive oil loses most of its antioxidants during the refining process [26]. Supporting this hypothesis, Mena et al [27] conducted a clinical trial demonstrating that patients who followed a MedDiet supplemented with EVOO exhibited a down-regulation of proinflammatory biomarkers associated with atherogenesis, including serum IL-6, soluble intercellular adhesion molecule-1, and CRP [27].

Our study's prospective and longitudinal design offers a valuable opportunity to assess how different inflammatory molecules vary following a dietary intervention specifically in psoriasis, potentially illuminating the molecular mechanisms by which the MedDiet exerts its effects in immune-mediated diseases. A key strength and distinguishing factor of this study compared with previous research is the inclusion of a control group, which enhances the ability to attribute observed changes directly to the dietary intervention. This is particularly important given the frequent use of topical treatments in psoriasis patients, regardless of systemic therapy, and the episodic nature of psoriasis, where spontaneous improvements in severity can occur. In addition, maintaining close contact with a small cohort of patients will enable a thorough evaluation of logistical challenges, which will be crucial for planning future larger-scale multicenter trials.

Several limitations of the study design should be noted. First, this is a unicentric clinical trial, which may limit the external validity of the results. In addition, the interventional nature of the study—characterized by close follow-up and the free provision of EVOO—may mean that the findings are not generalizable to all patients with psoriasis. Furthermore, the MedDiet intervention and follow-up period is limited to 4 months, and the sample size is relatively small, potentially resulting in insufficient statistical power for some analyses. However, these limitations should be viewed in the context of the study's proof-of-concept nature.

Strengths and Limitations of This Study

First, there are no firm dietary recommendations that can be provided to patients with psoriasis. This study is a pioneering effort in implementing the MedDiet in this patient population,

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drawing on the expertise of epidemiologists and nutritionists who have specialized in MedDiet interventions, particularly in prestigious studies like the PREDIMED clinical trial.

Second, multiple outcomes resulting from the intervention such as psoriasis severity, cardiometabolic parameters, inflammatory cytokines, and quality of life will be evaluated. In addition, this clinical trial is designed to pave the way for a larger study, involving more patients, multiple centers, and extended follow-up periods.

Third, a possible limitation of this study is the relatively small sample size and the intervention duration of only 4 months, which reflects the proof-of-concept nature of the study.

Finally, the results of the nutritional intervention may not be generalizable to all patients with psoriasis for 2 reasons. First, the study population consists of patients with mild-to-moderate psoriasis who attend dermatology clinics, potentially indicating a higher level of health engagement than the general population. Second, while the provision of EVOO is a strength of the study, it may present a barrier in real-world situations due to the high cost of this product.

In conclusion, the MEDIPSO study was designed to generate high-quality evidence on the relationship between the MedDiet and psoriasis. Through this clinical trial, we aim to explore the anti-inflammatory effects of the MedDiet and their manifestation at both the clinical and molecular levels. In addition, this study is intended to lay the groundwork for future research in this area.

Acknowledgments

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Data Availability

Access to the full protocol, participant-level dataset, and statistical code can be granted upon reasonable request to the investigative team.

Authors' Contributions

JP-B, AG-C, and MAM-G conceived and designed the study. JP-B, LG, EB-R, and CA-JdA will perform the study. JP-B and EB-R will collect and analyze all experimental data. JP-B provided the first version of the manuscript. EB-R, CA-JdA, RC-M, AB-M, and PJ-O provided critical comments on the original manuscript. JP-B and AG-C revised and finalized the manuscript. All authors read and approved the final version of the manuscript.

Conflicts of Interest

NM is a full-time US government employee. All the authors have no conflicts of interest to declare that are relevant to the content of this paper.

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Abbreviations

CRP: C-reactive protein
er-MEDAS: Energy-Restricted Mediterranean Diet Adherence Screener
EVOO: extra virgin olive oil
IFNγ: interferon gamma

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IL: interleukin
MedDiet: Mediterranean diet
MEDIPSO: Impact of the Mediterranean Diet on Patients with Psoriasis
PASI: Psoriasis Area and Severity Index
PREDIMAR: Prevention of Recurrent Arrhythmias with Mediterranean Diet
PREDIMED: Prevention with Mediterranean Diet

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Protocol

Efficacy and Safety of Murivenna Anal Infiltration Compared to Diltiazem Topical Application in Chronic Anal Fissure: Protocol for a Prospective, Randomized, Open-Label Clinical Trial

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Abstract

Background: Anal fissure is a common proctologic condition that causes significant pain and anguish to patients, significantly impacting their quality of life and well-being. There are various treatment options for anal fissure, ranging from pharmacological agents that reduce anal sphincter tone to surgical interventions for cases resistant to medical management. Ayurvedic treatments have shown potential for the therapeutic management of anal fissure.

Objective: This clinical study aims to analyze the efficacy and safety of murivenna anal infiltration compared to diltiazem topical application in chronic anal fissure.

Methods: This is an open-labeled, randomized, controlled parallel group clinical trial with a sample size of 66 participants to be randomized and allocated in a 1:1 ratio to 2 groups. The intervention group will be treated with murivenna anal infiltration, and the control group will be treated with topical application of diltiazem for a period of 4 weeks. The primary outcome will be the proportion of participants demonstrating complete healing after 4 weeks of treatment. The secondary outcomes will be the proportion of participants demonstrating complete healing after 7 days and 14 days of treatment, change in pain at or after defecation, cessation of bleeding, and any recurrence during the study period. Any adverse events will also be recorded during the trial period.

Results: The project was funded in July 2023, and the study period is 24 months. Participant recruitment started in December 2023. As of August 2024, we have enrolled 50 participants. The data analysis will be complete by June 2025, and the results are expected to be published by August 2025.

Conclusions: High recurrence rates, adverse effects, incomplete healing, and the negative impact on patients' daily activities and quality of life underscore the need for alternative therapeutic options. Ayurveda offers potential for more sustainable relief with fewer adverse effects. Murivenna oil is a time-tested medicated oil effectively used by Ayurvedic physicians for various ulcers of traumatic and pathological origin. This study will provide scientific evidence on the efficacy and safety of murivenna anal infiltration; further, it can be incorporated into the cost-effective management of chronic anal fissure.

Trial Registration: Clinical Trials Registry India CTRI/2023/09/057330; https://tinyurl.com/y4ut9e8p

International Registered Report Identifier (IRRID): DERR1-10.2196/63063

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KEYWORDS

chronic anal fissure; murivenna anal infiltration; Ayurveda; efficacy; anal infiltration; murivenna; diltiazem; app; chronic; study protocol; randomized clinical trial; proctologic condition; proctologic; pain; quality of life; well-being; surgical intervention; defecation; cessation of bleeding; treatment

Introduction

Anal fissure is a painful tear or split in the distal anal canal. It is a common proctologic condition characterized by intense, prolonged anal pain after defecation, bleeding, and a significant deterioration in the patient's quality of life. The symptoms of anal fissure are a cause of considerable morbidity to the patient. The condition presents with symptoms including severe pain on defecation, which lasts from a few minutes to several hours, bleeding from the rectum, anal discharge, and swelling. If acute, there may be severe pain; the intensity will be comparatively less in the chronic phase. Spontaneous healing of anal fissures is rare due to the reactive spastic contraction of the internal anal sphincter, which diminishes blood flow to the affected area. This constriction impedes the natural healing process, prolonging the duration of symptoms such as pain and bleeding. Therapeutic intervention is often required to alleviate discomfort and promote healing. Various treatment modalities aim to relax the anal sphincter, increase blood flow, and facilitate tissue repair, thereby addressing the underlying cause and promoting resolution of the fissure. Conservative management includes, among other approaches, bulk agents, stool softeners, warm sitz baths, botulinum toxin injections, or topical application of ointments like diltiazem and glyceryl nitrate [1]. New treatment options, such as hyperbaric oxygen therapy to increase tissue oxygenation and induce wound healing, are now being studied [2]. Considerable drawbacks are reported, such as recurrences, toxicity, headaches, and giddiness, while using these external ointments [3]. Surgical treatment is adopted for those cases in which nonsurgical treatment for more than 6 to 8 weeks does not produce desirable results or when there is a recurrence of anal fissure. Surgical treatments include Lord dilatation, lateral internal sphincterotomy, advancement flaps, and fissurectomy [4,5]. Complications of surgical treatments include incontinence to flatus and feces, nonhealing external wounds, abscess, and fistula formation [6]. Miscellaneous novel therapies such as sacral nerve stimulation, autologous adipose tissue transplantation, and posterior tibial nerve stimulation are now being examined as alternatives to lateral sphincterotomy and reliable procedures to avoid fecal incontinence [7]. However, pharmacological modalities are more preferred for treatment of anal fissure, as they are well tolerated, with minimal to no side effects. *Susrutha Samhitha*, a comprehensive Ayurvedic textbook on surgical and parasurgical practices of ancient India, mentions anal fissures as being iatrogenic, and mentions a condition called *parikartika* ("cutting pain in the anus") in the context of *vaidya nimitha bastivyapat* ("indiscretion of the clinician while administering a medicated enema") and *gudakshata* ("ulceration/injury in the anus") in *bastinetravyapat* ("complications due to the enema pipe"). The book further says that this condition should be treated in the same way as traumatic wounds [8]. The *Susrutha* advocates oil irrigation or infiltration to pacify *pitta dosa* (metabolic and biochemical processes that generate heat), which is considered pivotal in the pathology of inflammation and wound formation. [8] *Murivenna* oil is a time-tested medicated oil that treats various exogenous and endogenous ulcers. The drugs used for the preparation of murivenna oil, namely *Aloe vera*, *Pongamia glabra*, *Borreria hispida*, *Asparagus racemosus*, and *Moringa oleifera* are *pittasamaka* (pacifying *pitta*) and *vranavasadana* (ie, they reduce the hypergranulation of wounds). Further, they have been proven to have analgesic and anti-inflammatory properties [9]. Murivenna can potentially help to lessen pain and spasm and promote healing of anal fissures. Further, the anal infiltration process enables the medicine to be retained in the anal canal for an extended period, which can help in reducing increased sphincter tone and associated symptoms.

Hence, this clinical study will compare the effect of murivenna anal infiltration against diltiazem topical application in the treatment of chronic anal fissures. The primary objective of the study is to determine the efficacy of murivenna anal infiltration for healing of anal fissures in comparison with a topical application of 2% diltiazem. The secondary objectives are to determine the safety and efficacy of murivenna anal infiltration for the reduction of pain and bleeding and the prevention of recurrences of anal fissure in comparison with the topical application of 2% diltiazem.

Methods

Study Design and Setting

The study is an open-label, randomized, controlled, parallel group clinical trial conducted at the National Ayurveda Research Institute for Panchakarma (NARIP), Cheruthuruthy, Thrissur District, Kerala, India. The schedule of enrollment, intervention, assessments, and follow-up visits for the study participants is given in Table 1.

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Table 1. Schedule of screening, enrollment, intervention assessments, and follow-up in the clinical trial.

Content	Screening	Intervention period					Follow-up period				
		Day 1 (baseline)	Day 8	Day 15	Day 22	Day 30 (treatment end)	Day 60	Day 90	Telephonic follow-up		
									Month 1	Month 2	Month 3
Eligibility evaluation	✓										
Provision of participant information sheet	✓										
Informed consent	✓										
Medical history and demographic profile		✓									
Clinical examination		✓	✓	✓	✓	✓	✓	✓			
Assessment of subjective parameters		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Laboratory test	✓					✓					
Drug compliance assessment			✓	✓	✓	✓					
Rescue medication assessment			✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse events assessment			✓	✓	✓	✓					
Recurrence of disease							✓	✓	✓	✓	✓

Study Participants

Inclusion Criteria

Participants of either sex will be included if they are in the age group of 16-65 years, have a chronic anal fissure persisting for more than 6 weeks, are capable of and freely willing to provide written informed consent prior to participation in the study, and comply with the study protocol requirements.

Exclusion Criteria

Individuals with comorbidities, including uncontrolled diabetes mellitus, hypertension, anemia, malnourishment caused by systemic disease, fistula in ano, hemorrhoids, perianal abscess, clinically evident fecal incontinence and anal stenosis/fibrosis, inflammatory bowel disease, tuberculous ulcer, malignancies, HIV, clinically significant renal disease, hepatic disease and cardiovascular disease, psychological disease (eg, anxiety and depression), and active substance abuse will be excluded; participants using medications hampering wound healing will also be excluded. Patients with fissures associated with abscess, drug-induced fissures, fissures resulting from external trauma, fissures located at lateral locations, and multiple fissures will be excluded. Participants using oral calcium channel blockers, having sensitivity to the intervention drugs or calcium channel blockers, with frequent history of headaches, or using drugs such as steroids or nonsteroidal anti-inflammatory drugs, either for fissure or any other unrelated disease or condition, will be excluded from the study. Pregnant and lactating women and participants who have used either of the trial interventions within 30 days prior to the trial's randomization will be excluded from the trial.

Study Intervention

Participants in the intervention group will be treated with anal infiltration of murivenna oil for 4 weeks. The medical team will administer the oil through the anal canal using sterilized rubber tubes attached to syringes at baseline. Either the participant or the attendee will receive education on the procedure and will be asked to perform the procedure on subsequent days until the next visit. The participant should lie down for 15 minutes after completing the procedure. In the first week, the patients will receive anal infiltration of 30 ml of murivenna oil once daily, and for the remaining 3 weeks, they will receive anal infiltration of 20 ml of murivenna oil once daily. During the trial period, participants in the intervention group will receive *triphala choornam* (another Ayurvedic medicine; 10 g) at bedtime as a mild laxative, and the participants will be further advised to perform a sitz bath with triphala kashayam once a day. Participants in the control group will be treated with 2% diltiazem gel for 4 weeks. They will be instructed to apply the gel at least 1.5 cm to 2 cm into the anus in the morning and at night after the sitz bath. During the trial period, participants in the control group will receive lactulose syrup (15 ml) at bedtime as a laxative. Participants in both groups will be advised to consume foods rich in dietary fiber and avoid activities that could cause microtrauma to the anus, such as prolonged sitting or traveling on a bicycle or motorcycle.

The murivenna oil was manufactured at the Good Manufacturing Practices (GMP)–certified pharmacy at NARIP, and the triphala choornam was manufactured by a GMP-certified pharmacy at the Central Ayurveda Research Institute, Jhansi, India, as per the respective standards available in the Ayurvedic

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Pharmacopoeia of India [10]. Table 2 lists the ingredients of murivenna oil.

Table 2. Ingredients of murivenna oil.

Serial number	Ingredient	Sanskrit name	Quantity	Part used
1	*Pongamia glabra* Vent	Karanja	384 g	Bark
2	*Piper betle* L	Tambuli	384 g	Leaf
3	*Aloe vera* L	Ghritakumar	384 g	Leaf
4	*Erythrina indica* Lam	Mura	384 g	Leaf
5	*Allium cepa* L	Palandu	384 g	Bulb
6	*Moringa oleifera* Lam	Sobhanjana	384 g	Leaf
7	*Borreria hispida* (L) Schum	Madanaghanti	384 g	Whole Plant
8	*Asparagus racemosus* Wild	Shatavari	192 g	Rhizome
9	Coconut oil	__[a]	768 ml	Oil

[a]Not applicable.

Outcome Measures

The primary outcome will be the proportion of participants who undergo complete healing after 4 weeks of treatment. The secondary outcome measures will include the proportion of participants with complete healing after 7 days and 14 days of treatment, respectively. In the present context, we define healing of the fissures as the disappearance of symptoms and the evidence of fissure re-epithelization, which the investigators will record based on an examination. The investigators will categorize the healing as follows at each follow-up visit: none, partial, or complete.

Another secondary outcome measure will be the mean change in pain intensity during or after defecation. The investigators will ask the participants to record their pain intensity during or after defecation over the last 24 hours using a 100-mm visual analog scale at each follow-up. The investigators will also record how long it takes for participants to experience an improvement in pain intensity and cessation of bleeding, as well as how many participants require analgesics for pain relief. The investigators will advise the participants to log their pain intensity, bleeding status, and any need for analgesics in diary log sheets. The team will issue these sheets on the baseline day, as well as on the 8th, 15th, and 22nd days. Investigators will educate the participants on how to fill out the sheets. The participants will be followed up for 5 months after the intervention period to record any recurrence of anal fissure.

Safety Outcomes

Participant-reported adverse events (AEs) during the trial period will be recorded on every scheduled follow-up visit in a structured format. All AEs during the study will be monitored and appropriate care will be provided. There have been no past reported AEs for murivenna anal infiltration [11]. The predictable AEs for triphala choornam include loose stools, obstipation, change in the sense of taste, nausea, skin lesions, and tiredness [12]. Dizziness, headache, weakness, nausea, or swelling of the hands or feet may rarely occur with the use of diltiazem ointment [13]. Diarrhea, bloating, nausea, vomiting, and stomach pain are reported side effects of lactulose syrup. Rarely reported serious AEs include weakness and irregular heartbeat [14].

Withdrawal Criteria

Participants not willing to continue or who are noncompliant with the study procedures (a minimum 80% compliance is essential to continue in the study) will be withdrawn from the study. Participants developing life-threatening complications or any other severe illness because of another pathology that requires urgent treatment will also be withdrawn from the study. Participants developing serious AEs or treatment-induced AEs requiring hospitalization will be withdrawn from the study. It will be ensured that these participants receive appropriate incidental care or are referred to a higher medical facility if required. The reasons for withdrawal will be recorded in the participant's case record form (CRF). The sponsor and the ethics committee will be informed within 2 working days, and will be provided with proper justification.

Sample Size

The sample size was calculated based on the previous differences in the proportion of participants having complete healing of anal fissures between study groups. In a previously published study, 25% of participants had complete healing of anal fissure by the fourth week of treatment with 2% diltiazem gel, and based on the results of another previously published observational study, we assumed that fissures would heal in nearly 60% of participants treated with the trial intervention [11,15]. A sample size of 30 per group is needed to achieve 80% power with a 95% CI. Adding an attrition rate of 10% results in a sample size per group of 33. Therefore, a total of 66 participants will be enrolled in the trial.

Recruitment

Participants from the outpatient department of NARIP diagnosed with chronic anal fissure will be screened for their eligibility to participate in the clinical trial. Informed consent will be obtained from the participants before screening. Participants eligible as per the inclusion and exclusion criteria will be allocated to one of the study groups based on the randomization schedule.

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Randomization and Allocation Concealment

A computer-generated randomization number sequence with block randomization will be created by the study statistician independently of the investigators undertaking recruitment and subsequent visits. The statistician will use Stata (version 16; StataCorp) to generate a random sequence, ensuring that each participant is randomly assigned to one of the study arms in a 1:1 ratio. The assignments will be enclosed in sequentially numbered, opaque, sealed envelopes, which will be opened by the participants at the time of enrollment.

Compliance

Compliance with the prescribed medicines will be monitored through a compliance assessment form issued to the participants on each visit. The participants will be instructed to complete the assessment form after each medicine intake or administration. In addition, compliance will be evaluated by counting the number of containers and tubes returned and the approximate quantity of medications used by each participant. A minimum of 80% compliance is essential for the participant to continue the study.

Concomitant and Rescue Medication

The participants will be instructed to inform the investigators before taking any type of medication apart from the trial drugs. The investigators will record the details of the medications and the reason for taking them in the CRF. If there is any medical emergency, the use of any rescue medication will be permitted, and this medication will be recorded in the relevant section of the CRF.

Data Collection and Documentation

Before conducting this clinical study, the investigators and research team will be uniformly trained on Good Clinical Practice (GCP) protocols, trial-specific processes, and documentation. The research team will collect the information and fill in the details in the CRF (Table 1 provides details) for each visit. All documented data will be checked regularly by the principal investigator (PI) to avoid mistakes and omissions. Any modifications made will be clearly visible, and the corrections will be signed and dated by the PI. The data will subsequently be recorded in an e-format and verified as required; the original CRFs will be archived in order with a search catalog.

Statistical Analysis

All statistical data analyses will be performed using SPSS (version 26.0; IBM Corp). Categorical data will be presented as numbers (percentages) and will be compared using the χ^2 test or Fisher exact test. Continuous variables will be described with either means and SDs for data with a normal distribution or median and IQR for nonnormally distributed data. The within-group analysis will be done using a 2-tailed paired sample *t* test for normal data, whereas the Wilcoxon signed-rank test will be used to compare nonnormal data. Comparisons between the experimental and control groups at each time point will be done using an independent sample 2-tailed unpaired *t* test or Mann-Whitney test for normal and nonnormal data, respectively. $P \leq .05$ will be considered statistically significant.

Monitoring

The monitoring committee set up by the sponsor will conduct on-site or virtual monitoring to ensure adherence to the trial protocol and compliance to GCP and the Central Council for Research in Ayurvedic Sciences Research Policy.

Trial Audit

The regulatory authorities, the institutional ethics committee (IEC), or the funding agency will audit the trial, and the investigators will ensure access to all the documents related to the study for the on-site audit.

Ethical Considerations

The study has been approved by the IEC of NARIP (8/16/23/NARIP/Tech meeting/2511; March 31, 2023) and has been registered prospectively at Clinical Trials Registry - India (CTRI) (CTRI/2023/09/057330). The study will be conducted in accordance with the Indian Council for Medical Research National Ethical Guidelines for Biomedical and Health Research on Human Participants (2017). Written informed consent (in English and Malayalam) will be obtained from the eligible participants before screening. All protocol modifications will be communicated to the IEC and funding agency and corrected accordingly in the CTRI. The CRFs will be stored in a secure area, and the participants' data will be coded to ensure confidentiality. The study participants will be given routine medical care, if required, after the completion of the study period. The study participants will be compensated for any financial losses (eg, loss of wages) with an incidental support of Rs 300 (US $3.49) for each visit.

Results

The project was funded in July 2023, and the study period is 24 months. The participant recruitment was started on December 2023. As of August 2024, we have enrolled 50 participants. The data analysis will be complete by June 2025, and the results are expected to be published by August 2025. The study outcomes will be disseminated through research articles in peer-reviewed scientific journals and presentations at national conferences.

Discussion

This randomized, open-label clinical trial is expected to assess the effect of murivenna anal infiltration compared to topical application of diltiazem in the treatment of chronic anal fissure.

Strength

This is the first randomized clinical trial to evaluate the efficacy of murivenna anal infiltration for chronic anal fissure. The quantitative outcome measures included in this trial will yield valid data for clinical use of murivenna for the treatment of anal fissure.

Limitations

The study is being conducted at a single center, and hence participants from only a single area are included in the trial. The study will apply to countries where Ayurveda is practiced. However, the procedure can be performed by trained persons of other countries provided they have regulatory permission to

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use murivenna and triphala choornam. Further, single-pack administrations with a fixed dose of murivenna may be considered for better patient adherence.

Conclusion

If this clinical trial proves effective, medical professionals can consider murivenna anal infiltration as a potential alternative therapeutic option, which may further be incorporated into cost-effective management for chronic anal fissure.

Acknowledgments

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Authors' Contributions

Conceptualization and writing (original draft): PSKM
Methodological support: IPP, PB, AKR, AA
Writing (review and editing): SJ
Protocol review and administrative support: BCSR, NS, RA

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOCX File , 24 KB - resprot_v14i1e63063_app1.docx]

Multimedia Appendix 2
Consent form and patient information sheet.
[DOCX File , 28 KB - resprot_v14i1e63063_app2.docx]

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Abbreviations

AE: adverse event
CRF: case record form
CTRI: Clinical Trial Registry - India
GCP: Good Clinical Practice
GMP: Good Manufacturing Practices
IEC: institutional ethics committee
NARIP: National Ayurveda Research Institute for Panchakarma
PI: principal investigator

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Protocol

ChatGPT-4 Performance on German Continuing Medical Education—Friend or Foe (Trick or Treat)? Protocol for a Randomized Controlled Trial

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Abstract

Background: The increasing development and spread of artificial and assistive intelligence is opening up new areas of application not only in applied medicine but also in related fields such as continuing medical education (CME), which is part of the mandatory training program for medical doctors in Germany. This study aimed to determine whether medical laypersons can successfully conduct training courses specifically for physicians with the help of a large language model (LLM) such as ChatGPT-4. This study aims to qualitatively and quantitatively investigate the impact of using artificial intelligence (AI; specifically ChatGPT) on the acquisition of credit points in German postgraduate medical education.

Objective: Using this approach, we wanted to test further possible applications of AI in the postgraduate medical education setting and obtain results for practical use. Depending on the results, the potential influence of LLMs such as ChatGPT-4 on CME will be discussed, for example, as part of a SWOT (strengths, weaknesses, opportunities, threats) analysis.

Methods: We designed a randomized controlled trial, in which adult high school students attempt to solve CME tests across six medical specialties in three study arms in total with 18 CME training courses per study arm under different interventional conditions with varying amounts of permitted use of ChatGPT-4. Sample size calculation was performed including guess probability (20% correct answers, SD=40%; confidence level of $1-\alpha=.95/\alpha=.05$; test power of $1-\beta=.95$; $P<.05$). The study was registered at open scientific framework.

Results: As of October 2024, the acquisition of data and students to participate in the trial is ongoing. Upon analysis of our acquired data, we predict our findings to be ready for publication as soon as early 2025.

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Conclusions: We aim to prove that the advances in AI, especially LLMs such as ChatGPT-4 have considerable effects on medical laypersons' ability to successfully pass CME tests. The implications that this holds on how the concept of continuous medical education requires reevaluation are yet to be contemplated.

Trial Registration: OSF Registries 10.17605/OSF.IO/MZNUF; https://osf.io/mznuf

International Registered Report Identifier (IRRID): PRR1-10.2196/63887

(JMIR Res Protoc 2025;14:e63887) doi:10.2196/63887

KEYWORDS

ChatGPT; artificial intelligence; large language model; postgraduate education; continuing medical education; self-assessment program

Introduction

ChatGPT-4 is the latest development in the large language model (LLM) family from ChatGPT. It is said to be trained on more than one trillion parameters, making it one of the most advanced LLMs currently available for generating conversation-style responses to user input. The parameters are the numerical values that determine how a neural network processes input data and produces output data. They are learned from data during the training process, encoding the model's knowledge and skills [1].

Since its launch by OpenAI, the ChatGPT family has stimulated widespread conversation and momentum across different specialties in medicine, as demonstrated by more than 3300 publications related to ChatGPT (or Chat-GPT) indexed in PubMed as of mid-May 2024. Generally, LLMs enable humans to interact and discuss a broad range of topics with artificial intelligence (AI) chatbots. New features of ChatGPT-4 include the acceptance of images as input and the generation of captions, classifications, and analyses, which were not available in earlier versions. Compared to its predecessors, ChatGPT-4 is 82% less likely to respond to inappropriate content requests and 40% more likely to provide factual answers than GPT-3 in internal evaluations [2].

After its success in passing the United States Medical Licensing Examination, performing at a level comparable to that of a third-year medical student [3], these results have been largely confirmed across various medical specialties. Comparisons with different ChatGPT versions and other LLM providers, such as Google, support these findings [3-13]. There are currently two reviews on this topic [14,15], and recent data specific to Germany have been published [16].

In conclusion, there is now a range of data on the use of LLMs in undergraduate education and teaching but less on postgraduate education, such as continuing medical education (CME) [17] or self-assessment programs [4]. Table 1 shows a selection of studies on this topic.

In Germany, CME, which is mandatory for medical specialists, requires earning 250 training points over five years. These CME points can be acquired through further specialization, attending congresses and conferences, and studying medical literature with consecutive answers to specific questions in the text. This approach essentially "credits" the self-study time spent attentively reading a text and then answering questions.

For this study, we decided to use ChatGPT-4 because of its extensive database and ability to enter texts directly. Additionally, the input and operation of ChatGPT are carried out by adult high school students without any prior medical training. This was to differentiate as clearly as possible whether and to what extent LLMs can offer support today. This study aims to provide further insight into whether AI, in the form of LLMs, can support various levels of medical education by correctly answering CME-relevant questions, allowing participants to generate CME credits independently of existing medical knowledge.

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Table 1. Data on ChatGPT and postgraduate medical education (continuing medical education or self-assessment programs).

First author	Year	Study	Comparator	Major findings	Conclusions
Sherazi and Canes [4]	2023	Comparative trial	ChatGPT-3.5 versus ChatGPT-4	GPT-4 scored significantly higher than GPT-3.5 on the AUA[a] SASP[b] examinations in overall performance, across all test years, and in various urology topic areas.	Results suggest improvement in evolving AI[c] LLM[d] in answering clinical urology questions. Certain aspects of medical knowledge and clinical reasoning remain challenging for LLM.
Riedel et al [16]	2023	Comparative trial	Performance of ChatGPT on OB/GYN[e] course examinations versus questions from the German medical state licensing examinations	ChatGPT demonstrated consistent and comparable performance across both datasets, providing correct responses at a rate comparable with that of medical students.	ChatGPT has promise as a supplementary tool in medical education and clinical practice, providing efficient and personalized learning experiences and assistance for health care providers.
Noda et al [18]	2024	Comparative trial	ChatGPT-3.5 versus ChatGPT-4 versus Bard (Gemini)	GPT-3.5 and Bard performed similarly while being significantly surpassed by GPT-4. GPT-4's performance was between third- and fourth-year nephrology residents.	GPT-4 outperformed GPT-3.5 and Bard, meeting the Nephrology Board renewal standards in specific years, albeit marginally. The results highlight LLMs potential and limitations.
Ali et al [6]	2023	Comparative trial	ChatGPT-3.5 versus ChatGPT-4 versus user average	GPT-4 significantly outperformed question bank users and GPT-3.5. Increased word count and higher-order problem-solving were associated with lower accuracy for GPT-3.5 not however for GPT-4.	LLMs achieved passing scores on a mock 500-question neurosurgical written board examination, with GPT-4 significantly outperforming ChatGPT.
Watari et al [13]	2023	Comparison study	Chat GPT-4 versus Japanese Residents' performance on GM-ITE[f]	Of 137 GM-ITE questions in Japanese, GPT-4 scores were significantly higher than the mean scores of residents.	GPT-4 demonstrated a tendency to score higher on difficult questions. However, GPT-4 scored comparatively lower on questions testing attitudes toward patients and professionalism requiring an understanding of context and communication.
Guerra et al [5]	2023	Comparative trial	ChatGPT-4 versus ChatGPT, SANS[g] users, medical students, and neurosurgery residents	GPT-4 outperformed ChatGPT exceeding the performances of medical students, neurosurgery residents, and the national average of SANS users across all categories.	GPT-4 significantly outperformed medical students, neurosurgery residents, and the national average of SANS users.

[a]AUA: American Urological Association.

[b]SASP: self-assessment study program.

[c]AI: artificial intelligence.

[d]LLM: large language model.

[e]OB/GYN: obstetrics and gynecology.

[f]GM-ITE: General Medicine In-Training Examination.

[g]SANS: self-assessment in neurosurgery examination.

Methods

Study Design

This is a randomized controlled trial that will be undertaken following the Declaration of Helsinki principles and after approval by the local Ethics Committee of Witten/Herdecke University (S-108/2024, date of approval May 15, 2024) and after registration in a study register (open scientific framework). To obtain representative, comprehensive, and meaningful data, three large German publishing houses (Deutscher Ärzteverlag GmbH, Cologne; Georg Thieme Verlag KG, Stuttgart; and Springer Medizin Verlag, Heidelberg) that offer journals with CME will be evaluated for one volume each of already expired journals (ie, without the possibility of earning credit points) from the fields of internal medicine, surgery, gynecology, pediatrics, neurology, and anesthesiology. The CME tests provided by the publishing houses needed no further adaptation for utilization in the study.

Ethical Considerations

The study protocol which was submitted to and accepted by the Ethics Committee of University Witten/Herdecke (S-108/2024, date of approval May 15, 2024) stated decisively that no monetary or other compensation was to occur. The participant's information was depersonalized by means of not collecting any personal information to begin with, as they were deemed insignificant to the study's results leading to participants enrolling entirely voluntarily. Furthermore, to participate in the study, the students were required to provide a signed informed consent form which all students were given the opportunity to voice concerns and questions and were informed about their ability to revoke their consent without having to provide a reason, while not having to expect any repercussions.

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Study Participants

To minimize any influence from prior medical knowledge on the results, adult high school students from North Rhine-Westphalia who are willing to participate will be randomized into three study arms. As high school students can be assumed to be void of relevant medical prior education, the choice to include this group as participants is based on its ability to represent the approximate level of medical knowledge of the general population. The inclusion and exclusion criteria are shown in Textbox 1. It should be emphasized that it is not the high school students who are the participants of the study but the CME course tests to which the methods of the three study arms are applied. Careful considerations were put into the selection of the CME tests screening for images of diseases that students may have deemed disturbing. Such CMEs were excluded. The students were encouraged to voice concerns if the contents of the CME tests resulted in uneasiness. Furthermore, ample opportunity was provided for discussing the students' experiences if deemed necessary by the participants. All these measures aided in minimizing the potential psychological impact of participation in the study. The experience of the participants while attempting to solve the CME tests is not represented in the study's results as they were deemed to exceed the scope of the study. The student's proficiency in the German language was required in the hope of avoiding skewed results based on linguistic incomprehension of the provided literature. The students act purely as "tools," preferably without any medical knowledge of their own.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Aged 18 years or older
- Voluntary participation
- No financial compensation
- German as a native language or at a native speaker level
- Ability to operate ChatGPT or other required software

Exclusion criteria

- Being underage
- Refusal to participate
- Insufficient German language skills
- Inability to operate ChatGPT or other required software

Interventions

This trial is designed as a three-armed randomized controlled trial, including one control arm.

Intervention Group 1: "All-In"

In this group, CME-subject-specific text is entered into ChatGPT-4 first, and then, the questions are answered by ChatGPT based on that input.

Intervention Group 2: "Just Answers"

In this group, questions are answered using only the knowledge available in the ChatGPT-4 database at that time, without entering any subject-specific text first.

Control Group 3: "Search and Find"

Participants in this group were asked to answer the questions using only keywords and common sense without any AI support. As the CME were viewed as digital files, the use of "find in text" of the respective document viewing software was permitted.

The approach to having the CME test questions answered in three study arms aims to uncover significant differences in ChatGPT-4's ability to solve the CME tests, as well as assess the varying time required in the individual study arms.

Data Analysis

Sample size calculation was performed for the hypothesis that CME test results will improve from guess probability (20% correct answers, SD= 40%) to pass level (70% correct answers) with a confidence level of $1–\alpha=.95$, that is, $\alpha=.05$, and a test power of $1–\beta=.95$. Therefore, for an independent-samples, two-sided study, a sample size of at least 18 CME training courses per study arm is needed. Nonetheless, since the CME courses, as our study subjects, can be processed repeatedly using different methods without altering them or the methods, a paired-sample study is possible and preferable. This allows the same CME courses to be used in the three study arms. Although a sample size of 9 for a single-sided paired-sample study would be sufficient (only an improvement in CME test results is expected and desired by applying the study arm methods), we decided to take a conservative route and will work with 18 CME tests that will be run through all three study arms. The CME tests treated were randomly chosen from a large number of available tests. Care was taken to ensure that every high school student completed the same number of tests in each arm of the study so that confounding variables in the students were evenly distributed across the three groups. In addition, none of them would work on a single CME test twice using different methods to avoid learning effects. Together with the reuse of the CME tests in the three study arms (paired study, see above), these measures prevent any bias arising from the high school students

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as performing tools or the CME tests themselves as study participants. The AI-supported arms would run through within the shortest possible time and in the correct order so that unwanted training of the AI or the students during the process could be ruled out as much as possible. Statistical data analysis will be performed using the open-source software "R" (R Core Team; 2023). The data is presented as mean ± SD. Since the aim of the study is to identify differences in the percentage test results due to the different approaches in the three study arms, the Student *t* test (1-tailed) or the Mann-Whitney *U* test will be used for the pairwise comparison of means between groups, depending on the normality of the datasets. The Shapiro-Wilk test will be used to check normality. Fisher's exact test was used to assess the independence of categorical variables. Benjamini-Hochberg adjustments of *P* values will be applied in multiple comparisons. Values of $P<.05$ were considered statistically significant.

Results

As of October 2024, we have tested five out of the six students we deemed necessary to examine the 18 CME tests across the three study arms. We are set to terminate the data acquisition by November 2024. The ensuing data analysis is predicted to end in December 2024, enabling us to present our results as early as early 2025.

Discussion

Principal Findings

To present the influence of AI as objectively as possible, we deliberately refrained from using medically trained test participants. This allowed us to identify the pure influence of AI. Depending on the degree of success, it was necessary to determine to what extent AI can be permissible in CME training courses and what conditions or protective measures were to be imposed.

Since its launch in 2023, not only the development of ChatGPT but also its integration into the medical context increased rapidly, as shown by the ever more extensive database versions and the steadily growing number of medical publications [3-6,19-23]. However, as the capabilities of AI increase, so does the responsibility of actual intelligence to use it in the best possible way for the benefit of all without causing harm ("primum nihil nocere"). Even if the use of AI to solve examinations, whether student or specialist examinations, has already been investigated several times, there is still a knowledge gap in postgraduate teaching and its effects. Ethical, social, and above all, legal aspects, also need to be clarified.

AI has the potential to revolutionize various aspects of our lives. In medicine, its strength lies in its wide range of possible applications. However, the use of AI in education, training, and specialization must be clearly labeled, as it presents not only opportunities but also weaknesses and threats, particularly with the use of LLMs such as ChatGPT and related programs [1]. The correct use of AI in postgraduate medical education, especially LLMs, still needs to be explored and discussed.

This study aims to show that medical training tests can be successfully completed by medical laypersons using AI, which raises questions about the continued usefulness of current training programs, potential regulations to prevent misuse, and opportunities to harness AI capabilities in this context. Currently, self-study to obtain CME credits is an integral part of German postgraduate medical education. This study's results may have the potential to influence this practice significantly.

The decision to examine ChatGPT's results in three study arms was based on the hope of being able to compare the results obtained while gaining insight into whether the literature backgrounds of the CME were required to generate significantly superior results.

The rationale behind the choice of medical specialties whose CME tests were analyzed in the study results from ChatGPT-4's ability to merely process text. All the medical specialties we chose to include do not predominantly diagnose based on visual symptoms. However, a new investigation on newer ChatGPT versions, which possess the ability to obtain information from images is underway.

Limitations

This study has several limitations. First, only German CMEs are evaluated. Second, only a minority of specialties were chosen. Finally, we completely dispensed CME with image content, as is usual in radiology, dermatology, or pathology, for example, to avoid changing the selectivity.

How potential biases that result from the data that was used in training the AI tools impacted the results of the study is not derivable, as ChatGPT does not possess knowledge in the classical sense. It is rather the case that lexical data is produced based on prior training.

If knowledge acquired through AI-generated literature is retained differently than medically conventionally attained knowledge is yet to be assessed in future research.

Conclusions

The impact on current on future CME programs should be considered as the certified means of personalizing one's medical education remains scarce. AI could play a role in tailoring continuous education to personalized needs and, for example, adapting the modules based on prior results to target potential individual shortcomings. The role AI could play in medical education provided by university faculties, as well as personalized learning programs surely merits further investigation [24-26].

Acknowledgments

This research received no external funding.

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Data Availability

The datasets generated during or analyzed during this study are not yet publicly available as they are yet to be analyzed but can be made available from the corresponding author upon reasonable request.

Authors' Contributions

The conceptualization was a result of cooperation by TS, DG, AB, and CB; the formal analysis was performed by CB, AB, DG, and TS; funding acquisition was accomplished by DG; our methodology was developed by TS, FB, and JE; project administration was supervised by TS and DG; the original draft was written by CB and AB, and it was then rewritten, edited, and reviewed by TS, JE CB, AB, FB, SCT, and DG. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
CME: continuing medical education
LLM: large language model

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Protocol

Proposal and Strategy for Nursing-Led Research: Protocol for an Unfunded Clinical Trial

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Abstract

Background: Clinical trials are known to provide cause-and-effect results and data with low levels of bias. However, a lack of funding for clinical trials, which are considered expensive, means that academic sponsors are rarely able to conduct them. Academic trials are considered highly relevant for the valuable results they provide for clinical questions. This is why initiatives to conduct unfunded clinical trials have been identified as an important issue to pay attention to in future studies. Therefore, we present our initiative through Rogers' theory, which is highlighted in the literature for diffusing innovative change across organizations.

Objective: The purpose of this paper was to describe our case regarding management for conducting a nonfunded nurse-led clinical trial based on our previous low-interventional clinical trial across a specific health organization and with nurses.

Methods: We conducted a low-intervention, nonexternally funded clinical trial using the human and material resources available on site. We managed our trial in a clinical trial unit where there were staff, sources, and ongoing commercial clinical trials. We conducted our trial based on an ongoing commercial trial, and, to do so, we needed behavioral changes. We relied on Rogers' theory, and we identified strengths and barriers to change by analyzing actors' characteristics, perceptions of the situation, motivation, and information. Afterward, we divided the staff according to their characteristics related to innovation and change into permanent staff (research staff with a culture of change) and nonpermanent staff (nursing staff with occasional attendance and resistance to change). First, we preselected only those nurses who were more aware of change (innovators and pioneers) to participate in our trial to avoid a massive rejection, and later, we asked others to join (late adopters). We followed Rogers' phases. For research staff who were aware of the funding, we focused on the "persuasion phase," while for nursing staff, we mixed the "knowledge and persuasion phases" and used pioneers and early adopters as a positive example for other nurses as well as nonfinancial incentives (persuasion). Our trial consisted of different methods of vein cannulation, which was performed in the ongoing commercial trial. Thus, the entire development of our low-interventional clinical trial was conducted without interfering at any point with the parallel commercial clinical trial.

Results: Our management allowed effective conduct of our study, and we met our aims without external funding and without ethical impact during the commercial clinical trial. Costs remained low, primarily because the major expenses were covered by the commercial clinical trial as an inherent part of its design.

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Conclusions: Our initiative to conduct a low-intervention clinical trial with no or limited funding was cost-effective. This initiative can be used by researchers with valuable academic research questions who do not have the external funding to conduct studies.

Trial Registration: ClinicalTrials.gov NCT04027218; https://clinicaltrials.gov/study/NCT04027218

International Registered Report Identifier (IRRID): RR1-10.2196/56062

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KEYWORDS

clinical trial; academic trial; nonfunded; commercial; nurse-led; low intervention; health product; peripheral venous cannulation; PVC; protocol; randomized controlled trial; RCT; adults; healthy adults; funding; academic sponsors; cause-effect results; insurance

Introduction

Background

Clinical trials are known to provide cause-and-effect results and usually yield high-quality data due to low levels of bias [1]. In addition, clinical trials not only provide the best context for advancing clinical research and health care but also create opportunities to reduce health care costs [2]. Moreover, clinical trials involve key personnel, such as nurses, who can be recruited and trained to carry out a protocol [3]. In the case of clinical research nurses, their ability to work independently has been recognized, but they face practical, ethical, and resource challenges [4]. In particular, the lack of funding for clinical trials, which are considered expensive and involve additional effort (especially investigator-led clinical trials), leads to voluntary activities [5]. It should also be noted that academic sponsors are rarely able to conduct trials without external funding [6]. Therefore, it has become clear that there is a need for increased coordination to ensure that robust research is conducted and to adopt adaptive trial design strategies to respond to the rapidly evolving evidence landscape [7].

Nevertheless, academic trials (ie, trials in which the comparator is usually standard clinical practice [1]) are considered highly relevant due to the valuable results they provide when investigating clinical questions [8]. Academic trials enable comparative data and may lead to changes in practice [5], but researchers in such trials face multilevel challenges, most notably applying for grants and managing funds to pay for participation or study-related injuries [9].

In Europe, between 10% and 30% of clinical trials are conducted by academic or noncommercial sponsors [8], and only a limited number of nurses receive support through funding mechanisms [10] despite evidence showing that trials led by a nurse or physician have noninferior results [11].

Therefore, although our trial is registered at ClinicalTrials.gov (NCT04027218) and our results are published [12], initiatives to conduct nonfunded clinical trials, such as low-interventional clinical trials, have been identified as a major issue to be targeted in future studies [8]. However, implementing initiatives, new ideas, or innovative processes across an organization is challenging. The literature suggests the use of Rogers' curve or Rogers' diffusion of innovation theory to introduce innovation because it applies within and across organizations [13], such as in schools and for teachers [14,15] as well as in health care organizations [16].

Objective

The purpose of this paper was to describe our case of managing the conduct of a nonfunded, nurse-led clinical trial across a specific health organization and with nurses.

Methods

The Field and Study Context

The aim of our initiative was to conduct a phase 4 low-interventional clinical trial without external funding that resulted in low bias, was of high quality, and used available onsite human and material resources.

Thus, we managed our trial in a clinical trial unit where staff and sources were already available. However, up until our trial, almost all clinical trials in this unit evaluated drugs, were financed by the pharmaceutical industry, and involved procedures, particularly venipuncture by nurses, that were performed in the same way.

In other words, the nurses and other research staff in the unit did not participate in a culture of conducting different clinical trials, such as our clinical trial involving medical devices and that proposed changing "the assembly line." In our case, a clinical trial was conducted with different forms of venipuncture, which had previously always been performed using the same technique. This involved changing certain positioning and behavioral barriers.

In the clinical trials unit, there were fixed staff (researchers) and variable staff (nurses). The variable staff consisted of a pool of 20 to 25 nurses who came on occasional days to support the clinical trials but whose main activity was in other hospital departments.

Management and Sampling Access

Rogers' 5 stages of innovation decision-making consist of knowledge, persuasion, decision, implementation, and confirmation information [16]. There are different roles to implementing change. His theory shows that the following roles exist in certain proportions: innovators (2.5%), early adopters (13.5%), adopters (34%), late adopters (34%), and nonadopters (16%). He also considered the minimum threshold for change to be the sum of innovators and early adopters.

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Thus, we contemplated the "knowledge phase" for the fixed and variable staff. In the case of workers in the fixed staff component, they were already aware of the problem of obtaining funding to pay employees, so we only focused on the "persuasion phase" as we aimed on getting approval from the director of the unit, who introduced our clinical trial to the fixed and variable staff members.

Another exception had to be made at this stage regarding the expert in blood sample analysis (research staff), as we needed him to analyze our indicators in addition to those that were requested for the unit's trials. Persuasion consisted of suggesting authorship in publications given his interest in his scientific career and the potential for indirect income.

For the variable staff (nurses), we mixed the "knowledge and persuasion phases." We chose to invite only nurses who had the most knowledge or awareness of the change (knowledge) to participate in our clinical trial. In other words, we preselected the nurses (innovators and early adopters) to avoid mass rejection of the trial and to try to allow other nurses to see that a few nurses (innovators and early adopters) had seen this change as a positive step (persuasion). We did not conduct a survey to classify the nurses according to Rogers' roles because we knew the pool of our nurses well and we already knew their positions.

Specifically, to carry out the research, the nurse in charge of this study could not offer any direct payment. We offered to thank the staff in publications, and if anyone wanted to play a more active role in writing manuscripts about this study, they would be positively considered for authorship of articles resulting from the study. The publications are considered professional merit in our country and serve to increase the salary in one's professional career.

Nurse innovators and early adopters agreed to appear in acknowledgements (they did not want to have a more active role) and contribute to the culture and advancement of innovation and research in the nursing profession for colleagues who did not have this insight (late adopters mainly).

In the implementation phase, some nurses (adopters) asked the nurse in charge of the study about the new technique being performed by some collaborating nurses in this study. Therefore, we took advantage of this interest to invite more than one-half of the pool of nurses (adopters and late adopters) to participate in our study. We had a small group of nurses who we knew would not be interested in participating (nonadopters), and they were the last to be invited to participate and declined.

In relation to the fixed staff (research staff), we only focused on the "getting to know" and "confirmation" phases, as they already had knowledge of the project. They were observers, and we only gave them a 20- to 30-minute training on how the study was going to be developed in the unit at the same time a phase 1 clinical trial was being conducted (which was the routine work of the unit) and sought their confirmation to be aligned with the project.

Trial Design

Although our clinical trial protocol was already registered at ClinicalTrials.gov and is freely accessible, we deemed it necessary to provide a brief summary of our trial design so that our management of the field and study context were fully understood.

Study Sample and Eligibility Criteria

Our participants were recruited from the population of individuals who provided written informed consent for the primary clinical trial at the unit (phase 1 bioequivalence study). As shown in Table 1, on the night of first admission (visit 2 in phase 1), participants in the phase 1 bioequivalence study were invited to enroll in our phase 4 clinical trial. They signed the informed consent at that time. Participation in our phase 4 clinical trial was voluntary. We informed participants that this study was a nonfunded study and that no incentive would be provided beyond the payment they received from the phase 1 trial. We also communicated that the potential benefit for them was the expected effective interventions hypothesized in our phase 4 trial (Table 2).

The inclusion and exclusion criteria were the same as those for the bioequivalence trial. In addition, we added 3 criteria for our phase 4 clinical trial that were also compatible with the criteria for the phase 1 trial. These 3 criteria were 6 hours to 8 hours of fasting before vein cannulation, fluid intake limited to ≤500 mL 6 hours to 8 hours before venous cannulation [17], and having been a former participant in a bioequivalence clinical trial at our hospital.

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Table 1. Procedures of the phase 1 clinical trial.

Procedures	Visits												
	0	1. Screening[a]	2. Day 1 of first entry[b]	3. Day 2 of first entry[c]	4. Day 3 of first entry[d]	5. Day 4 of first entry[e]	6. Day 4 of first entry[f]	Washout[g]	7. Day 1 of second entry[h]	8. Day 2 of second entry[i]	9. Day 3 of second entry[j]	10. Day 4 of first entry[k]	11. Day 4 of first entry[l]
Informed consent	✓	__[m]	For the phase 4 trial	—	—	—	—	—	—	—	—	—	—
Inclusion and exclusion	✓	✓	✓	✓	—	—	—	—	—	—	✓	✓	—
Concomitant medications	—	✓	✓	✓	✓	✓	✓	—	✓	✓	✓	✓	✓
Blood and urine analysis	—	✓	—	—	—	—	—	—	—	—	—	—	—
Medical history	—	✓	—	—	—	—	—	—	—	—	—	—	—
Physical examination	—	✓	—	✓	—	—	—	—	—	✓	—	—	—
Height	—	✓	—	—	—	—	—	—	—	—	—	—	—
Weight	—	✓	—	✓	—	—	—	—	—	✓	—	—	—
Electrocardiogram	—	✓	—	✓	—	—	—	—	—	✓	—	—	—
Vital signs (HR[n], BP[o])	—	✓	—	✓	—	—	—	—	—	✓	—	—	—
Tympanic temperature	—	✓	—	✓	—	—	—	—	—	✓	—	—	—
Peripheral vein catheterization	—	—	—	✓	—	—	—	—	—	✓	—	—	—
Pharmacokinetic blood basal sample	—	—	—	✓	—	—	—	—	—	✓	—	—	—
Drug administration	—	—	—	✓	—	—	—	—	—	✓	—	—	—
Pharmacokinetic blood samples	—	—	—	✓	✓	✓	✓	—	—	✓	✓	✓	✓
Venepuncture	—	—	—	—	✓	✓	✓	—	—	—	✓	✓	✓
Adverse events record	—	—	✓	✓	✓	✓	✓	—	✓	✓	✓	✓	✓

[a]Up to 3 days after visit 0.
[b]1 week after screening.
[c]10 hours after visit 2.
[d]24 hours after visit 3.
[e]48 hours after visit 4.
[f]72 hours after visit 5.
[g]1 week after visit 6.
[h]Up to 24 hours after washout.
[i]10 hours after visit 7.
[j]24 hours after visit 8.
[k]48 hours after visit 9.
[l]72 hours after visit 10.
[m]Not applicable.
[n]HR: heart rate.
[o]BP: blood pressure.

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Table 2. Procedures of the phase 4 clinical trial.

Procedures	Visits										
	0	1	2	3	4	Washout	5	6	7	8	9
Informed consent	✓	—[a]	—	—	—	—	—	—	—	—	—
Inclusion and exclusion	—	✓	—	—	—	—	—	✓	—	—	—
Vein perception	—	✓	—	—	—	—	—	✓	—	—	—
Sequence allocation	✓	—	—	—	—	—	—	—	—	—	—
Intervention or comparator	—	✓	—	—	—	—	—	✓	—	—	—
Pain assessment	—	✓	—	—	—	—	—	✓	—	—	—
Hemolysis	—	✓	—	—	—	—	—	✓	—	—	—
Skin type assessment	—	✓	—	—	—	—	—	—	—	—	—

[a]Not applicable.

Randomization, Allocation, and Sample Size

Participants were randomized to 1 of 3 interventions and one of the sequences of applying those interventions within 2 periods. Thus, we allocated sequences of 1 intervention and a comparator (1 sequence for each participant).

As Figure 1 shows, randomization was performed at visit 0 of the phase 1 clinical trial after informed consent form was obtained and before participants were screened for inclusion and exclusion criteria for both the phase 4 and 1 trials. As shown in Table 3, we designed 6 sequences.

The study was carried out in the clinical trial unit at our hospital, where bioequivalence clinical trials (phase 1) were performed with groups of 12 participants. Accordingly, we duplicated the 6 sequences used for each group of participants.

Figure 1. Combined fieldwork of the phase 1 and 4 clinical trials. Pk: pharmacokinetics; v: visit.

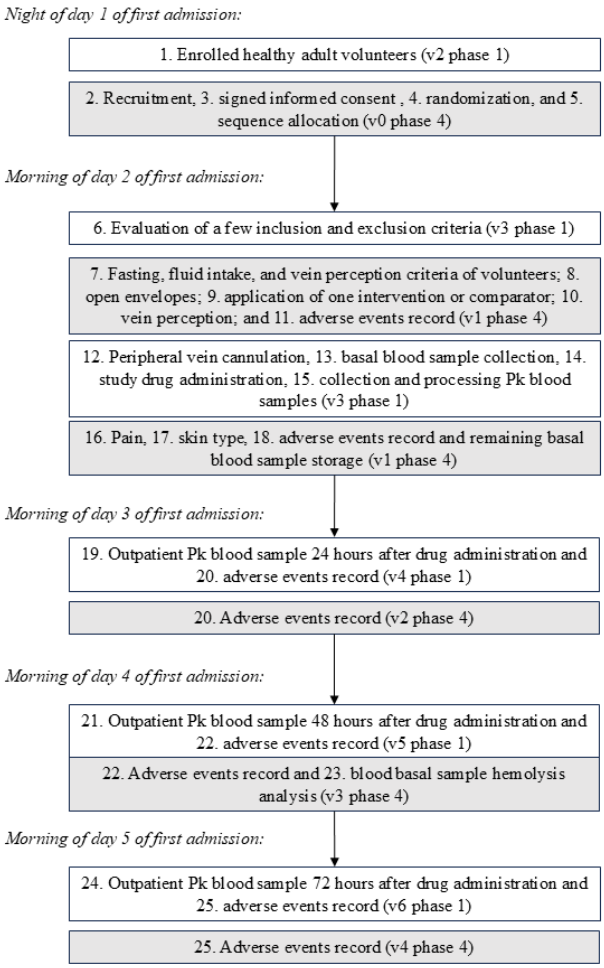

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Table 3. Description of the sequences.

No	Sequence	First period	Second period
1	Dry topical heat, comparator	Dry topical heat	Comparator
2	High pressure, comparator	High pressure	Comparator
3	Dry topical heat and high pressure, comparator	Dry topical heat and high pressure	Comparator
4	Comparator, dry topical heat	Comparator	Dry topical heat
5	Comparator, high pressure	Comparator	High pressure
6	Comparator, dry topical heat and high pressure	Comparator	Dry topical heat and high pressure

Interventions and the Comparator

Our interventions, given that we designed the additional eligibility criteria, were compatible with the interventions planned in the bioequivalence clinical trial. In the bioequivalence clinical trial, venous cannulation is always performed to obtain blood samples, and we established the following interventions and comparator to avoid interfering with those in the phase 1 trial. First, to apply dry topical heat, 2 bags were heated and placed on each participant's forearm for 7 minutes while an elastic compressor was applied [18]. Second, high pressure was applied via a sphygmomanometer cuff set at 100 mm Hg [19]. Third, for the combined intervention, dry heat was applied followed by pressure per interventions 1 and 2. The 3 interventions had a common comparator (ie, the elastic compressor), which was provided by the hospital and used according to CLSI GP41-A6 guidelines [20], as was performed in the phase 1 clinical trial.

Measures

Vein perception was assessed using the Venous International Assessment scale, which is a validated scale [21]. Vein cannulation was performed using a 20-gauge diameter catheter, and an EDTA K2 blood sample was collected using a Vacutainer blood collection tube (Becton, Dickinson and Company). Pain was assessed using the visual analogue scale, which is validated for acute pain [22]. Skin type was assessed using the Fitzpatrick scale, which has been previously validated [23]. Adverse events were assessed with a severe causality algorithm from the World Health Organization (WHO) [24].

The aforementioned materials are routinely used by nurses in the clinical trial unit and in clinical practice at our hospital. The nurses were familiar with the scales except for the Venous International Assessment scale, Fitzpatrick scale, and WHO algorithm. Therefore, collaborative nurses were trained to administer these tools. We also measured hemolysis in our blood samples, which was performed by an expert who routinely used a NanoDrop 2000 Spectrophotometer (ThermoFisher Scientific) at the unit. Again, we used human and material resources already available in the unit.

Adherence and Monitoring

Our phase 4 clinical trial involved the use of nonharmful interventions. Our interventions delayed vein cannulation by only 7 minutes (heat application), and the data collection did not require extra visits or blood draws. Because our phase 4 clinical trial was a nonfunded study, economic incentives for participants came only from the phase 1 commercial clinical trial. Therefore, the phase 1 trial guaranteed a low dropout rate and adherence to our clinical trial.

According to the low-interventional clinical trial regulations [25], an external monitor was not provided, and the nurse principal investigator conducted the study.

Ethical and Financial Considerations

The research protocol and methodology were approved by the Ethics Committee of the Hospital de La Princesa (Madrid, Spain) under code ECYPVEN-H/17 and registration number 3113.

This was considered a low-interventional clinical trial because "the intervention poses only very limited additional risk to the subject compared to normal clinical practice." We performed our clinical trial based on a phase 1 clinical trial that involved a vein cannulation procedure to ensure participant safety in relation to the same procedure in other clinical trials. Thus, we did not require specific insurance for any potential injury to participants; they were covered by the phase 1 insurance or health system insurance. Data from participants in the phase 1 clinical trial were coded for our study to ensure privacy [25].

Both clinical trial protocols and informed consent forms were in accordance with the Declaration of Helsinki [26]. Specifically, as our clinical trial was concerned with nursing, announcements and information about this trial were made by the nurse who was the principal investigator.

The participants did not receive any remuneration for participation in the low-intervention trial or any other type of compensation.

Furthermore, none of the information appearing in this article allows the identification of data or images of the participants.

We calculated that less than €200 (US $209.50) would be sufficient to cover the overall costs of our phase 4 study, including materials required for our interventions and comparators: 6 pairs of carob seed bags for heat application (4 pairs for use and 2 pairs for backup), 5 sphygmomanometers for pressure application (4 for use and 1 for backup), and 4 timers.

The aforementioned cost overrun was mainly for materials, as the rest of the costs were covered because we used resources from the clinical trials unit where the phase 1 study was conducted.

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Blinding

This open study was justified by the complexity of masking interventions (heat or pressure) and operators, as proposed by the CONSORT (Consolidated Standards of Reporting Trials) Statement for Randomized Trials of Nonpharmacologic Treatments [27]. Only the biologist who analyzed plasma sample absorbance was blinded [27].

Results

Our management was effective for conducting a low-intervention study, and we met our objectives without external funding. We conducted a clinical trial in the clinical trial unit of Hospital Universitario de La Princesa (Madrid) during the months of June 2017 and July 2017 with 59 healthy adults who were randomly allocated to 1 of 3 interventions: (1) using dry topical heat for 7 minutes produced by 2 hot seed bags (n=21), (2) applying controlled pressure from a sphygmomanometer inflated to 100 mm Hg (n=18), and (3) combining heat and pressure (n=20). We found that the pressure intervention (n=18) was the most effective for relieving pain, followed by heat (n=21) and the combined intervention (n=20). Furthermore, hemolysis was not significantly affected by any of our interventions, and no serious adverse events occurred [12]. None of the participants dropped out of the study, and a total of 10 nurses who had at least 1 year of experience in the clinical trial unit contributed to the fieldwork of the trial.

Discussion

Main Findings

Our strategy was effective for carrying out a low-intervention, academic clinical trial, as claimed by previous studies. Therefore, we were able to provide an answer to a problem detected in the scientific literature [8].

Our results [12] were consistent with those of previous parallel clinical trials that were funded by (1) a foundation and involved a specific device provided by a manufacturer [18] and (2) a grant [28].

Comparison With Prior Work

Similar to our study sample of 59 participants [8], additional studies have been conducted using 68 participants per group [18] and 36 and 34 participants in 2 groups [28]. In contrast, our study was a crossover, nonfunded study [12]. Although a previous study stated that noncommercial clinical trials recruit fewer participants than commercial trials [1], presumably due to the lack of financial compensation, we could not confirm that statement based on our results.

In addition to the clinical benefits, our results supported our strategy and showed how nurses, who receive relatively little funding (39.4% of total National Institutes of Health funding), can benefit from research funding [29] and lead a high-quality clinical trial without funding. Nurses in a variety of positions are involved in clinical trials, including clinical research nurses (69.7%), research nurse coordinators (17.9%), nurse practitioners (4.4%), and clinical and administrative or program support staff (8%) [30], even if they are not principal investigators [3]. Many are involved in oncology clinical trials [30]. In contrast, our study was conducted with a nurse as the principal investigator [12].

Our trial management was in accordance with the standard framework of Core Competency Domains by the Joint Task Force for Clinical Trial Competency, which consists of 8 domains [31]. Specifically, our study met domains 1 (research design) and 5 (study and site management), which describe a cost-effective, low-interventional clinical trial design and a commercial clinical trial design, respectively. Additionally, domain 7 (leadership and professionalism) [31] was met because our principal investigator was a nurse scientist with a PhD, which the literature highly recommends for research management [3,32].

According to the Rogers' management curve or theory, contextual factors are crucial and, although we were in a suitable environment (clinical trial unit), both the variable and fixed staff had standardized working procedures to reduce variables. Therefore, paradoxically, we agree with other studies [16] that negotiations (persuasion) for the diffusion of innovation are the biggest complication in those environments where there is no routine development of innovative concepts. However, the fixed staff members were easier to persuade due to their professional profile and career and the possibility of authorship in publications or other merits. Furthermore, unlike the aforementioned study, we did not apply the 5 stages of this theory to all variable and fixed professionals, as the latter had a more advanced research and innovation culture.

We also agree with Lundblad [13], as we were able to establish this theory across the health care organization and in a field where work is dedicated to improving research but the traditional theoretical basis does not include diffusion innovation, as in the variable nursing staff. For this reason, we consider our work to be groundbreaking in a collective that is resistant to change [33]; therefore, we could be introducing an innovative initiative according to Rogers' curve.

We also agree with the previous study that less complex innovations (such as our research procedure of vein cannulation) are adopted more quickly than those where the adopter must develop new skills and understanding [16].

Unlike the previous study, we did not conduct an interview to categorize staff profiles according to Rogers' theory, because we believed we knew our pool of nurses (variable staff) and research staff (fixed staff) well and did not need to obtain more information for profile categorization.

We consider that we used the theory adequately, as we were able to conduct our clinical trial and conclude with published results. Furthermore, we agree that this theory is very social, and it depends mainly on two important factors: interpersonal communication relationships and similar actors [13,16]. These were nurse to nurse in our study, rather than doctor or employer to nurse. In our study, the nurses in the pool had very strong rapport and even had a WhatsApp group. Because they asked each other questions through the chat group, they were able to diffuse this innovation. As recommended by Afraz et al [16],

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we used the innovators as a factor for promoting diffusion, and we demonstrated that it was effective.

A total of 36.5% of registered clinical trial protocols are sponsored by universities, hospitals, and other academic and nonprofit agencies worldwide [34], although the rate is lower in Spain (ie, 10%-30%) [8]. Noncommercial registered protocols are mainly for phase 4 studies and unmasked, controlled clinical trials. Additionally, only 39.4% of noncommercial protocols registered in ClinicalTrials.gov were published in peer-reviewed scientific journals [8]. However, our nonfunded study was an open phase 4 clinical trial registered in a database and published in a peer-reviewed scientific journal [12].

Additionally, we believe that our nonfunded management benefited from industry-sponsored clinical trials in study design, site selection, quality recruitment support, clinical coordinator centers, and access to study databanks, as Laterre and François [35] proposed that academic and industry trials should be constructive and not opposed.

Controversial statements declare that, compared with commercial studies, academic clinical trials are less restrictive with regards to inclusion and exclusion criteria, have less complex protocols, and have higher external validity than internal validity [1]. Others have reported that methodology clinical trials are as valid as commercial and noncommercial clinical trials; however, blinded and multicontinental trials that are usually conducted by major pharmaceutical companies are still considered superior [34]. Conversely, we believe that academic trials could be as restrictive as commercial trials if they are designed like commercial trials, given that our results were in line with such funded studies [18,28].

Our findings also agree with those of Fuentes Camps et al [8], who highlighted the scarcity of economic resources and suggested that initiatives such as low-interventional clinical trials could fill the void. Our low-interventional management optimizes scientific research by conducting a clinical trial at a cost of approximately €153 (US $186) and without ethical concerns or injury to the participants of the commercial clinical trial.

Clinical trials require specific insurance to cover the potential risks; thus, funding is required [36]. However, clinical trials funded by grants, public institutions [5], or associations [36] usually do not have all their costs met [36]. Therefore, our strategy for a low-interventional trial could be a solution when little or no funding is available. Commercial clinical trials could assume 15% to 22% and 11% to 29% of total costs for clinical procedures and administrative concerns, respectively [5].

Additionally, project management was identified as having a high impact on the total costs of a clinical trial [5] and is usually performed by a coordinator [26]. We agree with the proposal by Bevans et al [30] that a principal investigator who coordinates a single-center clinical trial reduces costs without assuming extra effort.

Contrary to our management, a previous study proposed that a better choice to decrease research costs would be to add a hospital employee to the research team instead of modifying the study design [37]. Although the research question guides the study design [37], we consider that, sometimes, a modified study design could contribute superior benefits from a nonfunded clinical trial for the original or similar research purposes compared with foregoing the study altogether.

As a reflection, if the proposed low-intervention study were to be developed in tandem with a nonfunded study, we consider that, obviously, the benefits of funding and use of resources would be lost. Therefore, when considering the possibility of such studies, one of the main criteria is likely to be that the context or the study on which it is based is funded or standard practice, as is the example of the study proposed here.

It may not be so much a question of whether to obtain funding but rather of making existing funding more efficient and taking advantage of the sometimes scarce resources available for research. We believe that rigorous, relevant, pertinent, and original research can be carried out, even without funding, if creative solutions are devised, such as the one that this article aimed to provide: taking advantage of existing resources to carry out low-intervention but rigorous studies from an experimental point of view. In this sense, would higher quality research be possible if funding was available? It seems obvious that the answer is yes but not in the sense of being rigorous or methodologically robust (which is mandatory when it comes to research). Rather, the answer is related to the sense of opportunity, of deciding what I want to investigate, and when and where I am going to do it. For the rest, we believe that it is even an obligation in the use of resources.

Most of the literature consists of partnership sponsors [10], budgeting [1,5], qualifications of research staff [31], or data contributions from registries [34]. However, a description of a nonfunded, low-interventional clinical trial and its corresponding results was identified for analysis in future research [8]; thus, no comparison is possible in the current article. Therefore, we suggest that our management description can be used for other researchers to conduct a clinical trial without funding or with limited funding.

Strengths and Barriers of the Field and Study Context

According to Rogers' theory, the adoption process depends on the characteristics of actors (such as values, skills, status), situational perception (such as norms, economical aspects), motivation, and information [16]. Thus, adoption depends not only on the individual position, which is conditioned by the collective one, but also on other environmental factors. In our specific noneconomic health care environment, we found strengths and barriers to change.

Regarding strengths, of all the nurses in the hospital, the nurses (variable staff) working in the unit were the most aware of research and innovation. However, the fixed research staff were aware and accepted that additional things were conducted, but they did not collaborate actively; they were only observers.

Regarding barriers, we cannot forget that the nursing profession is one of the least sensitive to innovation and only collaborates with economic incentives. Moreover, the fact that it is a variable component makes constancy difficult, both in the introduction of a new procedure and in the acceptance of changes. Although

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they were offered recognition in publications or similar, the big barrier was the lack of a direct financial incentive.

Limitations

Our case is not applicable to all commercial trial designs, but it enables the creation of an option of management that can be adjusted according to the study field and commercial trial. Although our strategy could not guarantee the optimum design for ambitious aims, the proposed strategy could make it possible to conduct a nearly optimal study design and, therefore, provide results for research progress.

This article provides a strategy for conducting noncommercial or nonfunded clinical trials by including similar procedures in a funded study in order to reduce budget, personnel, and the cost of providing participants with extra conveniences.

Consequently, another limitation could be that knowledge about research methodology along with change theories or strategies is required. In this study, there was a research nurse with knowledge about change theories for innovation; therefore, we suggest this innovative management to help anyone who has to face a similar challenge.

Conclusion

Our strategy is a cost-effective means of conducting a low-interventional clinical trial with no funding or with limited funding. Furthermore, this strategy can be used by nurse researchers or other researchers to facilitate clinical trial design and site management to provide high-quality results without ethical concerns. Ideally, nurses engaged in care themselves should be able to pose research questions like research nurses, develop them as such, and not be figures with necessarily distinct roles.

Data Availability

The data sets generated and analyzed during this study are not publicly available but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
WHO: World Health Organization

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Protocol

Effectiveness of Adaptation of a Resilience-Building Intervention Among Individuals With Adverse Childhood Experience: Protocol for a Randomized Controlled Trial

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Abstract

Background: The impact of adverse childhood experiences (ACEs) has been the focus of most studies for the past decade. There is an indication that developing resilience can help youth overcome these ACEs.

Objective: This article presents a study protocol for a randomized controlled trial (RCT) to investigate the effects of a resilience-building intervention on psychological well-being, coping strategies, stress, quality of life, resilience, resource finding, and resilience among individuals affected with ACEs in Malaysia.

Methods: The is a 2-armed, single-blind, RCT, whereby 50 participants (25 in each group) with ACEs will be randomly assigned to intervention and control groups. The former will be exposed to a resilience-building program (R2), which entails a multisystemic approach to resilience and recognizes the importance of rugged qualities and access to resources among individuals affected with ACEs. The intervention will be delivered via internet-based by a facilitator and broadly divided into 5 sessions, focusing on self-exploration and social support, coping techniques and coping skills, resource finding, spirituality, and resilience building. Meanwhile, the control group participants will not receive any form of intervention. Saliva samples will also be collected from both groups and assessed for salivary cortisol levels. Outcome measures will be assessed during baseline and postintervention using validated instruments. Another follow-up measurement will be conducted 4 weeks later.

Results: The clinical trial has been registered with the Australia New Zealand Clinical Trials Registry. Ethical approval was obtained from the Research Ethics Board at the National University of Malaysia (UKM PPI/111/8/JEP-2021-894). A total of 28 participants have been recruited to the RCT Participant recruitment will be completed by January 2025. The final analysis will be conducted by March 2025.

Conclusions: This is among the first studies to provide evidence in the context of RCTs for resilience-building intervention that combines self-report and physiological measures (ie, saliva and heart blood pressure) among individuals with ACEs. The findings will assist relevant authorities in the health and policy sectors to develop effective strategies for addressing the negative impacts of ACEs on the vulnerable population in Malaysia.

Trial Registration: ACTRN12622000604707; https://www.anzctr.org.au/Trial/Result/DataSharingStatement.aspx?id=383614

International Registered Report Identifier (IRRID): DERR1-10.2196/56826

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(JMIR Res Protoc 2025;14:e56826) doi:10.2196/56826

KEYWORDS

adverse childhood experience; resilience; resilience-building intervention; young adults; stress; psychological well-being

Introduction

Background

Adverse childhood experiences (ACEs) are stressful or traumatic events faced by individuals that could have a pervasive impact throughout the developmental stages of their lives through psychological and physiological mechanisms, particularly when the consequences are neglected [1]. ACE can have profound effects on individuals of all ages [2,3]. These experiences may culminate in disrupted development of brain areas that are stress-sensitive [4,5], which are reflected in behavioral alterations.

For example, individuals with ACEs may face challenges with emotion regulation, thereby leading to diverse negative consequences such as difficulties with interpersonal relationships, alcohol, and smoking habits [6,7]. Overall, these events are associated with obesity, depression, suicide, anxiety, heart attack, chronic health problems, chronic obstructive pulmonary disease, asthma, stroke, cancer, and unemployment [8,9]. Apart from emotion regulation, ACE survivors' experience deficits in several domains of executive functions [10], which impact their well-being and psychological health [11]. Evidence suggests that individuals with ACEs, particularly children and young adults, are disadvantaged in terms of coping with increased stress relative to their peers without such bad experiences [12]. Since young adults are still experiencing biological and psychosocial development, the consequential impacts of ACE can be profound during adolescence and young adulthood [12].

Mental health problems are common among children and adults, which are predominantly presented as depression or anxiety and are characterized by frequent comorbidities [13]. Studies have demonstrated that ACEs represent an important predictor of emotional problems [14]. Previous research has documented several underlying events for the association between emotional problems and early ACEs among young children and adults [13,14]. For instance, individuals with a history of early ACEs were more accurate in recognizing threatening stimuli [15], constituting an adaptive response in harmful conditions. Nevertheless, it can heighten the risk of mental health disorders over time [16]. While individuals with ACEs are more likely to adopt maladaptive emotional regulation skills such as disengagement, expressive suppression, and rumination, they are less likely to perform successful activities such as cognitive appraisal [15], thereby leading to early emotional anomalies [16].

Specifically, ACEs also constitute a significant barrier to an individual's capacity for resilience. Resilience depicts the resources, capability, and processes available to a system or an individual to adapt successfully in the face of challenges or adversities [17-19]. Resilience encompasses the factors that facilitate positive adaptation and navigation toward resources to sustain well-being in the context of adversity [16]. Therefore, researchers have developed an interest in resilience intervention as a potential approach to addressing the negative impacts of ACEs [19]. For instance, cognitive behavioral therapy (CBT) has been used in resilience interventions in ameliorating health problems, particularly among adults with a history of ACEs [19-21]. Hence, building resilience in individuals with adversity in the context of psychological intervention offers a new approach to managing individuals with ACEs.

Adverse Childhood Experiences and Negative Consequences Among Children and Adults in Malaysia

ACEs refer to neglect, abuse, and dysfunctional households that may be deleterious to a person's health and well-being. Research conducted in Malaysia has depicted an increasing frequency of child abuse and neglect cases, which are typical examples of ACEs that may impact negatively on physical and mental health [22]. ACEs also contribute to the growing health care expenditure, as the health consequences of ACEs reportedly accounted for 2% of the gross domestic product [23].

Nevertheless, information on the prevalence and negative impacts of ACEs among children and adults in Asia, specifically Malaysia, is scarce due to limited research. A recent study revealed a high prevalence of various ACEs among university students in northeast Malaysia, with a report of emotional abuse, emotional neglect, physical abuse, and sexual abuse occurring in 30.2%, 29.2%, 28.7% and 9.1% of the studied population [22]. High-risk behaviors (HRBs), particularly physical inactivity and community violence were recorded among 39.3% and 54.5% of the students, respectively [22].

Apart from HRBs, depression has been identified as a consistent outcome of ACEs among young adults in Malaysia [24,25]. Young individuals from Shah Alam, Malaysia, exhibited a high level of depression and ostracism, which was associated with ACEs. Early psychological mistreatment such as parental neglect of a child's needs can lead to poor mental well-being [25], externalizing and internalizing problems, as well as anxious and avoidant attachment styles, making it challenging for children to develop a sense of belonging and feeling ostracized [26,27]. Therefore, early life traumatic events and ignorance appear to have strong influences on psychological well-being among this vulnerable population.

Besides the younger population, older adults in Malaysia have also been shown to be affected by ACEs, which may ultimately transit into elder abuse [28]. Furthermore, the risk of elder abuse increased with the cumulative number of ACEs. The results depict how early life adversities play an important role in older adults' victimization. Recognizing the possibility that vulnerability to maltreatment can persist throughout the life course of elderly individuals is critical when attempting to address the problem through emotional and social support.

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Resilience-Building Interventions for Individuals With Adverse Childhood Experiences

Resilience is considered to be pertinent in the association between emotional problems and ACEs. Studies have depicted that resilience is a protective factor that can propel an individual to successfully address adverse experiences [29]. Thus, resilience is regarded as playing a protective role in the relationship between emotional disorders and ACE [29-31].

ACEs constitute a public health crisis that requires a wide range of interventions due to their high prevalence and impact on health disparities [31,32]. Resilience interventions are typical examples of CBT that are effective in ameliorating mental health disorders faced by individuals with ACEs [15]. According to Iniguez and Stankowski [33], ACE research has yielded strong evidence to support claims that "resilience resources and well-timed interventions to promote resilience can ameliorate the negative effects of ACEs" [33].

Chandler et al [21] demonstrated the feasibility and efficacy of an empower resilience intervention to enhance resilience and health behaviors among young adults with a history of ACEs. By using a 2-arm pre-post repeated measures design, young adults in the intervention group recorded significantly higher scores for building strengths, creating support connections, and reframing resilience. Meanwhile, a face self-help app designed by Brodbeck et al [34] and based on cognitive-behavioral principles, is currently being tested for its efficacy in promoting resilience and well-being in emerging adults with a history of ACE. MacIsaac et al [35] also evaluated the effects of an innovative, smartphone app-based resilience intervention on first-year university students' self-regulatory skills (ie, emotion regulation and executive functioning), and the mediating role of emotion regulation. After 4 weeks of using the app, students' emotion regulation and depressive symptoms improved significantly, with a faster rate of change in emotion regulation among those with more ACEs. Thus, evidence suggests that app-based resilience intervention can assist young adults with ACE by improving their emotion regulation skills and mitigating depression.

Systematic review findings depict that most interventions for addressing ACEs focused on psychological interventions and mental health outcomes, and cognitive-behavioral therapy has been consistently found to be effective in mitigating the negative impacts of abuse [36]. On the other hand, findings from interventions involving psychological therapies, specific support such as parent training, and broad support interventions are generally inconclusive despite some promising results [36]. In summary, significant gaps exist in the available evidence on interventions for ACEs, with most research focusing on individual psychological effects while neglecting the social pathways which may indirectly influence the negative impacts of ACEs. Several areas such as social relationships, life circumstances and health behaviors are examples of several negative impacts of ACEs that are still under investigation in most intervention research [34-36].

Building upon the global view on ACE research and resilience-building interventions, the Malaysian context must be taken into account in order to develop an effective intervention to address the problem of ACEs among children and young adults. Literature findings from the studies conducted in Malaysia have shown that ACE is a multifactorial problem that requires a multidimensional approach, rather than focusing on one individual aspect [22,23]. Such an approach is well-described in the multisystemic model of resilience developed by Ungar [8], highlighting the capacity of biopsychosocial and social-ecological systems to support external and internal conditions for well-being, as well as improving diverse populations' quality of life. Thus, resilience encompasses the process whereby individuals harness the resources that are necessary for them to function optimally and seek resources to be provided using meaningful approaches, either contextually or culturally [8].

Interventions that emphasize individual change without considering the environmental domain may yield short-term benefits [37]. Hence, intervention should have a dual focus, encompassing personal and environmental change. For instance, a child's resilience is a product of both their capacity to cope effectively under stress and the capacity of their physical and social environments to facilitate positive development. Under conditions of normal stress, individual ruggedness may be sufficient to support well-being; nevertheless, resources become more important and required as the individual experiences greater barriers to functioning. These 2 broad aspects form the foundation of the multisystemic perspective of resilience "R2," which was coined to affirm the need to mitigate both the rugged qualities of individuals and their access to resources) [38].

Research has shown that individuals with more internal capacities such as problem-solving, self-regulation, and positive future orientation are more likely to harness opportunities for relationships and exploit such opportunities for academic or financial success [39,40]. Likewise, higher levels of motivation to execute life tasks and being more optimistic were observed among individuals with better access to external resources [41,42]. These findings reflect the dynamicity of resilience, whereby individuals interact with the world around them to make the best use of available resources despite exposure to adversity or atypical stress.

As highlighted in the reviewed resilience-building interventions for ACEs, while some target the public and common adversities like job burnout [43] and stress [44], others are aimed at specific groups, such as chronically diseased individuals [45], employees returning to work [46], and health care workers [47]. These interventions are delivered using diverse methods, ranging from phone apps to web-based tools or printed manuals, and duration may be as short as single-day workshops to weekly or monthly sessions. However, a recent meta-analysis revealed that such interventions have a small to moderate effect on improving resilience [44,47]. Existing resilience interventions also differ in terms of the targeted protective factors, such as self-efficacy, problem-solving skills, and cognitive flexibility, with most focusing on rugged factors. Only a few interventions consider resources that are external to individuals with ACEs [48]. Accumulated evidence suggests little to no data on interventions that explicitly target both coping strategies and ways of creating better-resourced environments around individuals with ACEs.

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Hence, this study will modify and implement an R2 resilience program based on a resilience-building intervention designed with the principles of implementation science [38]. The multisystem aspect of the intervention allows it to focus on multiple systems for the individual's change process and adaptation process around life circumstances. It is a curriculum-based approach that integrates all the well-researched factors and presents equal emphasis on the surrounding environments to the individual [8,38]. Thereafter, the factors and aspects can be modified and implemented into the resilience-building intervention accordingly. This study aims to explore the effects of the resilience-building intervention on mental health, stress, resilience, and resource finding among individuals affected with ACEs in Malaysia.

Methods

Study Design and Setting

This is a 2-armed, single-blinded, randomized controlled trial (RCT) that will be conducted among Malaysian youths with ACEs at the Department of Clinical and Health Psychology, National University of Malaysia. Briefly, the intervention group includes an evidence-based curriculum and components such as emotion regulation, active coping and goal setting, cognitive flexibility, mindfulness-based stress reduction, social support, self-exploration, resources and navigation, and finally, spirituality and religion. Participants in the control group will not receive any form of intervention. The main outcome of this study is resilience among youths with ACE while the secondary outcomes include coping, psychological well-being, quality of life, subjective stress, perceived stress, personal resources, and adult resilience. These variables will be evaluated at baseline and postintervention. Intention-to-treat analysis will also be performed. This clinical trial has been registered with the Australia New Zealand Clinical Trials Registry (trial Id: ACTRN12622000604707).

Sample Size

Sample size calculation was performed using G*power 3.1 software (Heinrich-Heine-Universität Düsseldorf). By assuming a study power of 0.8, 95% CI (α=0.05), and a moderate effect size of 0.25 as recommended by Ferguson (2009), the *F*-test was selected alongside repeated measures ANOVA with in-between interaction, with 2 groups and the number of measurements. Thus, a total sample size of 36 was obtained, reflecting 18 participants per group. We considered a high drop-out rate of 50% as several individuals may be unwilling to participate given the adverse effects of ACEs and confidentiality in sharing experiences with the researchers. Therefore, the sample size was increased to 50, amounting to 25 participants per group.

Eligibility Criteria

The inclusion criteria entail participants aged 18 to 30 years old and an individual who scores more than 4 or higher levels of ACE. This age group spans the young adulthood phase of an individual, and it is considered a significant developmental stage characterized by exposure to unique challenges and opportunities [21]. Meanwhile, the exclusion criteria are individuals receiving any type of intervention, demonstrating any severe psychopathology or psychiatric illness that requires a psychopharmacological approach, and those who had received intervention or therapy consistently in the past. Individuals need to fulfil the criteria to be recruited as mentioned above. Individuals will be recruited through multiple centers and social media platforms

Participant Recruitment and Randomization

The participants for this study are Malaysian youths with ACE, particularly those visiting the Psychological Department at the National University of Malaysia Medical Centre. During the selection stage, participants will be approached by the researcher and seek their consent to participate in the study. Those providing affirmative responses will then be instructed to fill up the self-administered ACE questionnaire.

This assessment period is the screening stage to identify those that fulfil the inclusion criteria. Participants who score four or more of ACE will then be included in a pool of participants and assigned randomly to either the control group or intervention group. Random assignment procedure will be implemented by random allocation software, Research Randomiser [31], to generate numbers and assign participants to an intervention group or control group. Allocation concealment will be performed by a single blinding procedure, whereby the assessors of the outcome measures will be unaware of the specific group the participants belong to. In other words, only the investigator allocating participants to either the control or intervention group will be aware of this information while other assessors are blinded. Table 1 depicts the participant enrolment schedule, time points and assessments to be performed during the study period.

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Table 1. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) schedule of enrolment, interventions, and assessments.

	Study period			Close-up
	Enrolment	Allocation	Postintervention	Four-week follow-up
Timepoint	t_1	0	t_2	t3+4weeks
Enrolment	✓			
Screening	✓			
Eligibility screen	✓			
Informed consent	✓			
Allocation		✓		
Interventions				
Intervention A				
Control				
Assessments				
Brief Coping Orientation to Problem Experienced Scale - English and Malay version	✓		✓	✓
Ryff's Scale of Psychological Well-being (SPWB) - English and Malay version	✓		✓	✓
Quality of Life –WHOQL-BREF - English and Malay Version	✓		✓	✓
Subjective stress – Perceived Stress scale - English & Malay version	✓		✓	✓
Personal Resources Questionnaire 2000 - English and Malay version	✓		✓	✓
Adult Resilience Measure-Revised - English and Malay version	✓		✓	✓
Biomarker - measure changes in salivary cortisol	✓		✓	
Blood pressure (blood pressure measured with a sphygmomanometer	✓		✓	

Participants in the control group will receive no intervention, while those in the intervention group will receive five sessions of resilience-building intervention conducted by a trained facilitator. Hotlines, post session, and appropriate resources will be provided for those reporting distress after the intervention. Investigators will be blinded throughout the whole process of randomization and data collection as the whole process is handled by a research assistant (randomization), counsellor, and clinical psychologist (data collection). Under no circumstances will unbundling occur as a research assistant, counsellor, and clinical psychologist are briefed with the standard operating procedure to follow when an incident occurs. The flow diagram is presented in Figure 1.

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Figure 1. Consolidated Standards of Reporting Trails 2010 flow diagram.

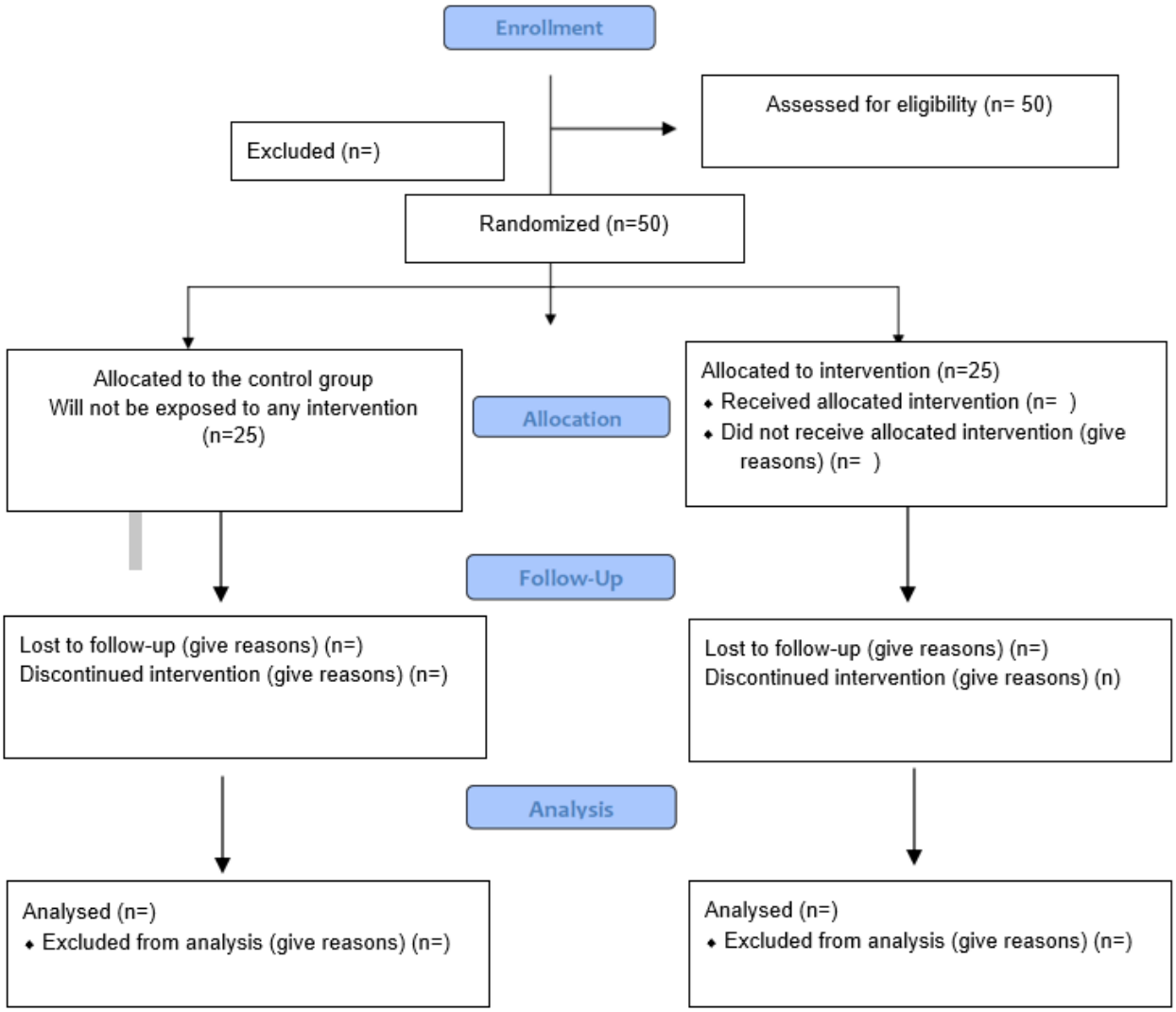

Contents and Delivery Method of the Intervention

The intervention will be adapted and modified according to the R2 Resilience building program designed by Ungar [20], which comprises 7 principles; help people to navigate, help people to negotiate, think about systems, coordinate services and supports, provide continuous support, be relevant to place and culture, and share responsibility for solutions. These principles will guide the process of modifying the intervention and the principles will be reflected in each session. The intervention will be delivered in 5 sessions.

Session 1 is divided into subsessions entitled “Self-exploration” and “Social support.” The first subsession focuses mainly on building rapport with the participants and helping them explore their coping skills, strengths, weaknesses, and talents. The second subsession emphasizes the importance of social support to enhance a sense of belonging and connection, as well as explore resources relating to social support. Both sessions will be delivered via internet-based with each lasting for 60 minutes.

The second session is also divided into 2 parts, coping technique including cognitive flexibility and grounding technique, and coping skills. The coping technique focuses on participants’ coping strategies and a deeper insight compared with the first session. This section also aims to provide cognitive exercise for preventing catastrophic thinking. As for coping skills, the strategies will be discussed in depth and practiced together with the facilitators. Participants will also be directed to work in pairs and assisted to identify their best coping strategies, either emotion-focused or solution-focused.

The third session comprises 2 parts to familiarize the participant with resource findings and explore their understanding of resilience. First, the facilitator will recap what the participant has learnt in the previous sessions and help identify where they can get help and access the available resources. Such assistance will be tailored for each participant to learn about resilience resources and harnessing them accordingly. In the second part, in-depth discussion will be held with each participant by focusing on past ACEs and how they were able to overcome the experiences, as well as their past resilience resources. Both

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sessions will be delivered via internet-based with each lasting for 60 minutes.

The fourth session is also divided into 2 subsessions; (1) what is resilience to you (part II), and (2) spirituality. The first subsession is the continuation of the second part of the third session with the same components as shown in Table 2. Meanwhile, the second subsession entails learning from each other regarding the role of religion and spirituality in addressing past adversities. The last session is the "Resilience-building (wrap-up)," whereby all the intervention components will be reviewed and visualized in the form of a diagram. Each session of the intervention will last for 2 hours (60 minutes for each session, with 15-minute breaks between sessions). Each session will be conducted weekly, week 1 for the first session and week 5 for the fifth session respectively. All sessions of the intervention will be administered via internet-based to each participant by the facilitators.

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Table 2. Components of the intervention.

Week	Session	Session	Duration	Mode of delivery	Focus
Week 1	1st session (1A)	Session 1A: Self-exploration	60 minutes	Internet-based	1. Build rapport among students with an ice-breaking activity 2. To help participants explore their coping skills, strengths, weaknesses, and talents
Week 1	1st session (1B)	Session 1B: social support	60 minutes	Internet-based	1. To talk about the importance of social support 2. To foster a sense of belonging and connection. 3. To explore resources regarding social support
Week 2	2nd session (2A)	Session 2A: coping techniques: cognitive flexibility and grounding technique	60 minutes	Internet-based	1. Explore participants' coping strategies (be mindful of labelling participants' strategies). Go deeper from session 1A 2. Cognitive exercise to prevent catastrophic thinking 3. How do you practice cognitive exercise? 4. What is fallacy thinking? 5. Introduce A-B-C and how to practice them
Week 2	2nd session (2B)	Session 2B: coping skills	60 minutes	Internet-based	1. Discuss the strategies in depth and practice them together. (Follow up from Session 2A) 2. Finding allies (participants form a pair and check in with each other) 3. Emotion-focused coping vs. solution-focused coping 4. During a crisis, how do these routines help? 5. Helping the body to feel safe
Week 3	3rd session (3A)	Session 3A: resource finding	60 minutes	Internet-based	1. Review and monitor from the previous session to recap what has been learned 2. To help participants know where to get help and the resources available 3. To help participants learn about their resilience resources and how to tap into them
Week 3	3rd session (3B)	Session 3B: what is resilience to you?	60 minutes	Internet-based	1. How do you survive? 2. What is the meaning of your stories? 3. What are your resilience resources in the past?
Week 4	4th session (4A)	Session 4A: what is resilience to you? part II	60 minutes	Internet-based	1. How do you survive? 2. What is the meaning of your stories? 3. What are your resilience resources in the past?
Week 4	4th session (4B)	Session 4B: spirituality	60 minutes	Internet-based	1. Review and monitor from the previous session to recap what has been learned 2. To learn from each other about the role of religion and spirituality
Week 5	5th session (5A)	Session 5B: eesilience-building (wrap-up)	120 minutes	Internet-based	1. To review and discuss all of the components 2. To draw a diagram with all of the components involved

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Intervention Protocol and Fidelity

The intervention will be conducted in Malay or English. It aims to encompass both languages and will be provided according to the participant's native language. Therapists will be trained to follow the protocol and the manual. A recap will be conducted at the end of the session. Dynamic assessment will be used to track the learning progress. Participants will use journaling as a method to practice their skills. In addition, progress and practice will be discussed at the beginning of each session. As for intervention fidelity, journals and progress of group sessions will be collected from mental health professionals after each session to ensure they continue a similar structure for the intervention. The checklist will be prepared for the mental health professional.

Data Collection Instruments and Outcome Measures

Adverse Childhood Experience Questionnaire

The Adverse Childhood Experience Questionnaire (ACE-Q) is a 10-item measure to assess events of traumatic or adverse experiences that an individual experienced before the age of 18 years. The instrument evaluates the individual's exposure to childhood physical, psychological, or sexual abuse, as well as household dysfunction such as substance use, domestic violence, and incarceration. The ACE-10 has been validated among the Malaysian population with an acceptable internal consistency of 0.86 and internal validity ranging from 0.28-0.70 [49].

Patient Health Questionnaire-9

The English and Malay versions of the Patient Health Questionnaire-9 (PHQ-9) will be used in this study to assess depression among youths with ACEs. The instrument has been validated among the Malaysian population by Sherina et al [50] with a sensitivity of 87% (95% CI 71%-95%) and specificity of 82% (95% CI 74%-88%). It was also reportedly suitable as a case-finding instrument in Malaysian primary care clinics.

Brief Coping Orientation to Problem Experienced Scale

The brief coping orientation to problems experienced (COPE) instrument comprises 28 items with 14 broad coping strategies. The Malay version of the instrument was validated by Saiful [51] among secondary school adolescents and was found to be valid and reliable in identifying coping strategies. Specifically, the overall Cronbach α value was 0.83 with the majority of the coping strategies reflecting acceptable internal consistency.

Ryff's Scale of Psychological Well-Being and Quality of Life

The Ryff's Scale of Psychological Well-being (SPWB) and World Health Organization Quality of Life Assessment (WHOQL-BREF) will be used in this study to assess the psychological well-being and quality of life among adolescents with ACEs. These instruments have been validated among the Malaysian population with acceptable discriminant validity, construct validity, and test-retest reliability greater than the threshold value of 0.5 [52-54].

Personal Resources Questionnaire 2000

The personal resources and workability of the participants will be assessed using the Work Ability-Personal Radar (WA-PR) instrument, which has been previously translated into Malay and validated by Hamdan et al [55]. The instrument has adequate psychometric properties and has been validated with acceptable discriminant validity, construct validity, and test-retest reliability greater than the threshold value of 0.5, making it suitable to be used in investigating personal resources and workability levels in the Malaysian population [55].

The Perceived Stress Scale-10

The Perceived Stress Scale-10 (PSS-10) is generally used in assessing stress perception. The Malay version of the PSS-10 has been validated among diverse populations in Malaysia, with the latest being nurses from government hospitals [39]. The instrument revealed acceptable internal consistency with a Cronbach α value of 0.63 and intraclass correlation coefficient of 0.81 (95% CI 0.62-0.91) following a 7-day test-retest reliability analysis. Furthermore, previous studies found significant correlations between the stress component of Depression Anxiety and Stress Scale 21 and the total score and negative component of the PSS-10 (r=0.56-0.61). Therefore, the PSS-10 is considered valid and suitable for investigating stress perception among Malaysian youths, including adolescents [56].

Saliva Cortisol and Blood Pressure Assessment

Each participant will be instructed to provide approximately 2 mL of whole saliva by passive drool, which will be then split into multiple 100 uL aliquots and frozen immediately. One aliquot of each of the 50 participants' saliva will be transported overnight on dry ice to the institutional laboratory. Cortisol analysis will be performed using commercially available immunoassay according to the manufacturer's guidelines (Salimetrics). Meanwhile, participants' blood pressure will be measured objectively with a sphygmomanometer.

Time Points for the Primary Outcomes and Retention

Premeasurements will be conducted at baseline, whereas postmeasurements will be collected after the fifth session as shown in Figure 1. Participants will be given Ringgit Malaysia 50 after the third and fifth sessions of the intervention to ensure they do not drop out of the study. Another follow-up will be conducted 4 weeks after the Intervention.

Data Analysis

All data management and statistical analysis will be conducted using SPSS (version 26; IBM Corp). Data management will be performed by screening for missing data and checking for potential outliers. Descriptive statistics will be used to assess the data normality and to summarize the pre and postintervention scores for each group at different periods. Mean and SDs will be provided for normally distributed data, followed by mixed ANOVA with repeated measures to compare the pre and postintervention mean scores between and within the groups.

The assumptions of ANOVA include randomly collected and normally distributed data, sufficient sample size, homogeneity of variances, and absence of violation and outliers. Levene's test will be applied to test the homogeneity of variance. Mixed ANOVA benefits RCT design as it allows testing for 2 groups across 2-time points. Mixed ANOVA analysis aims to handle

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response outcomes conducted on the same experimental unit at a different time or under different conditions [57]. The differential effects of the intervention components will be tested with interactions between the component and time. These analyses will model random slopes and intercepts for participants, explore the fixed effects of the condition, and test the repeated measures over time. This type of analysis is advantageous by accounting for missing values through the maximum likelihood estimation method [57]. Effect sizes will be computed based on Cohen *d*.

In addition, the intention-to-treat analysis will be applied to analyze the participants according to their assigned groups. This analysis includes all participants and ignores noncompliance, protocol deviation, and withdrawal. The intention-to-treat analysis is a complete trial strategy for the design, execution, and analysis of RCT, focusing on the consolidated standard of reporting trial guidelines. Thus, the number of participants in each assigned group will be analyzed by the intention-to-treat principle.

As for missing data, drop-out in this study refers to participants who withdraw actively from the intervention post randomization. All cases of dropouts will be considered in the intent-to-treat samples since they have been randomized and included in the analysis. The extent and pattern of missing data will be assessed, and depending on the results, missing values will be replaced by using multiple imputations. The impact of the imputation of missing values will be further explored by conducting sensitivity analyses.

Criteria for Discontinuing or Modifying Intervention

All the intervention modules were well understood by the participants enrolled in the pilot test; hence, no attempt has been made to review the intervention. Participants have the right to withdraw from the research at any given time if they do not feel comfortable continuing with the study. If the counselor or clinical psychologist reviews and discusses the harm of the participants continuing to participate in the research project, they will advise the participants to drop out of the study based on their professional judgment. A panel comprising counselors, and clinical psychologists will jointly review the case and make a consensus decision.

Data Auditing and Management

The team is required to submit first and second progressive reports to the Research Ethics committee, at the National University of Malaysia as part of the auditing process. Only group data will be reported. Data will be reported collectively; individual data will not be disclosed. Journal and progress of group sessions will be collected from mental health professionals after each session to ensure they continue a similar structure for the intervention. The checklist will be prepared for the mental health professionals.

As for data storage and management, the data will be entered digitally and stored in a Microsoft Excel sheet and Microsoft Word document by the investigator after being collected from mental health professionals. Each dataset will be assigned a code to protect the participants' identity. The encryption of the firewall will help secure and protect the data. A passcode will be generated to protect these documents. The data will be stored in the institution for 5 years, kept confidential and used only for educational purposes.

Standard Operating Procedure to Manage Harm

Counsellors and clinical psychologists will evaluate if any of the participants feel discomfort or express interest in withdrawing from the studies. This assessment will be carried out during the break intervals between each session of the intervention and the follow-up periods post intervention. Participants will be asked verbally if they still feel comfortable and willing to proceed with the intervention. Follow-up and proper redirecting to resources will be practiced with individuals who dropped out of the study.

Protocol Amendments

Any modification to the protocol, an update will be submitted to the Australia New Zealand Clinical Trials Registry and Research Ethics Board, The National University of Malaysia, and related journal publications.

Recordkeeping and Specimen

Consent will be obtained from participants to collect saliva. Data obtained through this study will only be published under group data. No individual data will be identified. The saliva samples obtained will not be kept and discarded right after the cortisol level measurement and analysis. All participants' data and information will be stored for this research as group data.

Ethical Considerations

Ethical approval was obtained from the Research Ethics Board at the National University of Malaysia (UKM PPI/111/8/JEP-2021-894; January 28, 2021). Detailed information on the intervention and recruitment process is provided in the next sections.

Results

This protocol, the informed consent and other relevant documents were reviewed and approved before the conduct of the research. Letters of extension and ethics approval were obtained from the Research Ethics Board at the National University of Malaysia. Amendments will be communicated to investigators, ethics review boards and publishing journals.

By January 2025, a total of 28 participants have been recruited into the study, comprising 14 in the intervention and 14 in the control group. Only 2 participants withdrew from the intervention group mainly due to a change in location and issues relating to data privacy and security. It is expected that participant recruitment will be completed by 30 January 2025. Preliminary analysis is ongoing, and the results suggest improvement in the investigated outcomes among participants in the intervention group across time. Final analysis will be conducted by March 2025, upon completing the data collection.

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Discussion

Principal Findings

ACEs are relatively common, trigger substantial suffering and are well-documented as a risk factor for diverse physical and mental health conditions throughout life. While primary prevention is pertinent in reducing ACE, the deleterious short and long-term consequences of ACE can be mitigated by selective prevention.

This study adopted the multisystemic approach to resilience "R2," which recognizes the importance of rugged qualities and access to resources among individuals affected by ACEs. As discussed earlier, the multisystemic model of resilience emphasizes 2 broad aspects, encompassing personal and environmental change [37]. We considered these 2 aspects as pertinent in addressing the consequences of ACEs among young adults in Malaysia, aligning with recommendations from previous studies to approach the problem in a multidimensional manner [8,38]. This study will be the first attempt to adopt an evidence-informed intervention for resilience-building among Malaysians with ACEs. In addition, this research is among the few interventions that explicitly entail both coping strategies and creating better-resourced environments around individuals affected by ACEs.

It is anticipated that the resilience-building intervention will have moderate to strong effects by ameliorating mental health, and stress, and improving participants' resilience and resource finding compared with those in the control group. These expected findings are consistent with the report by Chandler et al [21], whereby a resilience intervention centered around 4 main components (ie, active coping, building strength, cognitive flexibility, and social support) was effective in mitigating the adverse effects of ACEs.

Our intervention is structured into 5 sessions, focusing on self-exploration and social support, coping techniques and coping skills, resource finding, spirituality, and resilience-building. These components are expected to enhance participants' internal capacities such as self-regulation and problem-solving, thereby harnessing opportunities to achieve success in life [39]. By educating them on how to identify and gain better access to external resources, they will be motivated to accomplish life tasks and be more optimistic [42]. These events will assist in building resilience, facilitating participants' interaction with the world around them, and using available resources effectively regardless of being exposed to adversities.

This intervention aims to focus on vital resilience components which are emotion regulation, active coping and goal setting, cognitive flexibility, physical health, mindfulness-based stress reduction, social support, self-exploration, resources and navigation, financial planning, and spirituality and religion. One of the weaknesses of this intervention is that these components will be monitored by informal assessment such as observation, tracking, and recap to ensure participants have learned and acquired the tools and knowledge. It is also difficult to ensure participants from the control group will not receive any form of therapy during the whole duration of the intervention. Hence, the therapist has to check in with the group from time to time to ensure their well-being is taken care of. If needed, the therapist will conduct a post-group counselling session with an individual who is distressed by the intervention. Given that the participants were selected from a pool of individuals obtaining a specific level of ACEs, the findings might not be generalized to the entire population of people with ACEs in the country.

Conclusion

This is the first full clinical trial study investigating resilience-building intervention for youths with ACEs in Malaysia. There are limited studies evaluating the effectiveness of resilience-building interventions combining mental health and physiological responses as outcome measures in Malaysia. Thus, this study conceptualizes resilience from a biopsychosocial-ecological perspective and adapts resilience-building intervention in the Malaysian context. This study aims to develop resilience-building intervention modules specifically for Malaysia, focusing on the process of adapting the modules and modifications according to the Malaysian culture. This will be one of the first studies to provide evidence in the context of RCTs for resilience-building intervention combining self-report and physiological measures (ie, saliva and heart blood pressure) among individuals with ACEs. The findings will assist relevant authorities in the health and policy sectors to develop effective strategies for addressing the negative impacts of ACEs on the vulnerable population in Malaysia.

Acknowledgments

The study has received financial grant support from grant research National University of Malaysia (GUP-2022-054). The grant sponsor is only required to submit a progressive report at the end of the project. It will not involve any of the research activities.

Data Availability and Dissemination Policy

Group data will be available on the Australia New Zealand Clinical Trials Registry. The public will have access to full protocol and group-level datasets. The investigator will publish trial results to participants and health care professionals through publication and data-sharing arrangements on the Australia New Zealand Clinical Trials Registry. The public will have access to the full protocol. Data will be available upon the study's completion.

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Authors' Contributions

NJK, MA, CMHC, SZ, and MU contributed to conceptualization and methodology. NJK and MA handled project administration. NJK, MA, CMHC, SZ, MU, and PA/LS managed module refinement, data analysis, and supervision. NJK wrote the original draft. NJK, MA, CMHC, SZ, MU, PA/LS contributed to review and editing.

Conflicts of Interest

None declared.

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Abbreviations

ACE: adverse childhood experience
ACE-Q: Adverse Childhood Experience Questionnaire
CBT: cognitive behavioral therapy
COPE: Brief Coping Orientation to Problems Experienced Scale
HRB: high-risk behavior
PHQ-9: Patient Health Questionnaire-9
PSS-10: Perceived Stress Scale-10
RCT: randomized controlled trial
SPWB: Ryff's Scale of Psychological Well-being
WA-PR: Work Ability-Personal Radar
WHOQL-BREF: World Health Organization Quality of Life Assessment

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Protocol

Neural Mechanism of Cognitive Reserve in Acupuncture Stimulation: Protocol for a Randomized, Placebo-Controlled Functional Near-Infrared Spectroscopy Trial

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Abstract

Background: Dementia is a clinical syndrome characterized by a progressive decline in various cognitive domains. Since there is still no treatment for dementia, early diagnosis and prevention are the best approaches. In this context, the cognitive reserve (CR) concept has received considerable attention in dementia research with regard to prognosis. It originates from discrepancies between the degree of brain pathology and clinical manifestations. Acupuncture, as a complementary intervention, has long been widely applied in neurological diseases in East Asia. At the macroscale level, how acupuncture stimulation affects neural activity concerning CR in normal aging and dementia is largely unknown.

Objective: The aim of this study is to investigate the acute neural mechanisms of acupuncture stimulation concerning CR in the normal aging group and the group with cognitive impairment using neuroimaging methods.

Methods: This study is a randomized, placebo-controlled trial. Participants without (n=30) and with cognitive impairment (n=30) will be randomly assigned to the verum or sham acupuncture groups. The verum acupuncture group will receive acupuncture stimulation at acupoints related to cognitive function and gain deqi sensation. The sham acupuncture group will receive superficial needling at nonacupoints not related to cognitive function. Each group will undergo cognitive function tests, functional near-infrared spectroscopy imaging before and after acupuncture stimulation, and an assessment of CR. The primary outcomes will be differences in resting brain activities according to disease status, differences in resting brain connectivity before and after acupuncture stimulation between the 2 groups, and changes in brain activity in relation to the CR index. The secondary outcomes will be brain connectivity or network metrics associated with CR and differences in neural activity between the cognitive task and resting states.

Results: The recruitment began in August 2023; to date, there have been 50 participants, divided into 20 in the group with cognitive impairment and 30 in the unimpaired group. The recruitment process will continue until February 2025.

Conclusions: CR refers to the individual susceptibility to age-related brain changes and pathologies in cognitive impairment, and it is a factor affecting the trajectories of the disease. Although acupuncture is a widely used intervention for various neurological diseases, including dementia, its mechanism associated with CR at the macroscale has not been clearly identified. This study

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could contribute to identifying the neural mechanisms of acupuncture stimulation associated with CR using neuroimaging methods and provide a basis for future longitudinal research.

Trial Registration: Clinical Research Information Service of the Republic of Korea KCT0008719; https://tinyurl.com/ydv5537n

International Registered Report Identifier (IRRID): DERR1-10.2196/66838

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KEYWORDS

cognitive reserve; acupuncture; dementia; mild cognitive impairment; neuroimaging; fNIRS; brain connectivity; neural mechanism; RCT; randomized controlled trial

Introduction

Cognitive impairment refers to a generic term in which various cognitive functions, such as memory and executive function, are impaired, and the symptom severity ranges from mild to severe enough to interfere with daily life. Among them, dementia is a clinical syndrome preventing patients from leading a daily life due to the severe decline in several cognitive domains. Alzheimer disease (AD) is by far the most frequent cause of dementia and accounts for up to 80% of all dementia diagnoses [1]. AD symptoms typically begin with mild memory difficulties and gradually progress to severe memory impairment, inducing dysfunctions in daily life [2]. The prevalence and incidence of AD are increasing with an increase in life expectancy, leading to a socioeconomic burden worldwide [3,4].

The concept of cognitive reserve (CR) has received consistent attention in dementia-related research. CR refers to the adaptability of cognitive processes, which helps explain the individual vulnerability of cognitive abilities. It has also been suggested as an active model of the reserve, indicating that dynamic cognitive and functional processes counteract aging-related brain changes or damage [5]. This concept suggests that the brain actively attempts to cope with brain damage, allowing an individual with high CR to better deal with brain pathology. Many studies have shown that CR works differently depending on disease status. In the group without cognitive impairment, participants with high CR showed a slower decline in cognitive function; however, in the AD group, individuals with high CR showed more rapid cognitive deterioration than those with low CR [6,7]. Therefore, CR is considered a factor that modulates the relationship between the neuropathological burden of dementia and clinical symptoms [8,9]. Generally, CR has been measured through proxies, such as years of education, occupational complexity, and questionnaires covering various lifelong experiences.

Various neuroimaging techniques such as magnetic resonance imaging, functional magnetic resonance imaging (fMRI), positron emission tomography, and electroencephalography have been used for the early detection of AD [10]. Although fMRI is noninvasive and has good temporal and excellent spatial resolutions among functional neuroimaging methods, it has inherent limitations such as high cost, immobility due to heavy equipment, and vulnerability to head motion artifacts. In contrast, functional near-infrared spectroscopy (fNIRS) has been suggested as an alternative tool for functional neuroimaging. fNIRS is an optical neuroimaging technique that allows the measurement of changes in brain tissue concentrations of oxyhemoglobin (HbO_2), deoxyhemoglobin (HbR), and total hemoglobin (HbT) within the brain, achieved by irradiating the head with near-infrared (NIR) light [11,12]. This equipment has several practical advantages over conventional techniques represented by fMRI: It has a relatively higher temporal resolution, is noninvasive, cost-effective, lightweight, and easy to handle. It is applicable to cases difficult to fMRI scanning, such as agitated patients, individuals with claustrophobia, and those with pacemakers [13,14]. Moreover, it can be used on patients without moving from the hospital or laboratory, which can be critical for dementia patients with mobility difficulties. With these advantages, it allows us to monitor the alterations in brain function in patients with cognitive impairment in real time and explore neural responses induced by long-term or short-term interventions.

In a recent systematic review of dementia research using fNIRS, its diagnostic and investigative usefulness was evaluated while reviewing 88 studies in the field of dementia [15]. In summary, fNIRS could capture the aberrant hemodynamic responses and a lack of task-appropriate lateralization, often focused on frontal regions, in dementia. On the other hand, inconsistent results were found in prodromal stages. Cognitive decline accompanied by either reduced functional responses or hyperactivity was identified, the latter implying a compensatory response not represented at the dementia stage. However, there have been few fNIRS studies dealing with CR, one of the important factors in cognitive impairment.

Acupuncture has been practiced for thousands of years as an important treatment for a variety of diseases in East Asian medicine [16,17]. It is also being explored in AD research as a complementary and alternative therapy. In a meta-analysis, acupuncture treatment alone showed acceptable efficacy compared to conventional medicine for the management of AD. In addition, in a randomized controlled trial in patients with mild to moderate AD, acupuncture was found to be safe, well tolerated, and effective in improving cognitive function and global clinical status [18]. Specifically, acupuncture has been shown to regulate the release of central neurotransmitters, including acetylcholine and monoamine neurotransmitters [19]. Current neuroimaging studies of acupuncture cover a variety of diseases ranging from pain-related diseases such as chronic low back pain to peripheral and central nervous system disorders including carpal tunnel syndrome, stroke, Parkinson's disease, and dementia [20-24]. Through these, the analgesic mechanism and neuroprotective effect of acupuncture, which are distinct

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from sham needling, are consistently elucidated. Among them, a systematic review dealing with 13 AD-related neuroimaging studies found that acupuncture may modulate the default mode network, the central executive, and the frontoparietal networks in the brains of AD patients [24]. However, on the macroscale, the acute neural mechanisms of acupuncture stimulation in relation to CR according to disease status are largely unknown. To identify the neural mechanisms of acupuncture stimulation associated with CR in healthy aging and cognitive impairment patients, rigorous clinical trials such as randomized, placebo-controlled trials with neuroimaging techniques are required.

In this study, our main hypothesis would be that brain networks and brain activations focused on frontal regions would be altered according to the disease status and CR level, and that brain connectivity in the frontal regions would change before and after acupuncture stimulation. Next, we aim to investigate the neural substrates of CR and cognitive function using network metrics. Herein, we present a protocol for a randomized, placebo-controlled, parallel-group clinical trial to explore the acute neural changes after acupuncture stimulation according to CR and elucidate the neural substrates of CR according to disease status by applying fNIRS.

Methods

Trial Design, Setting, and Aim

This study will be a single-center, block-randomized, placebo-controlled, parallel-group clinical trial. The study will be conducted at the College of Korean Medicine at Sangji University. This protocol complies with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [25]. The aim of this study is to investigate the acute neural mechanisms of acupuncture stimulation concerning CR and to identify the neural substrates of CR in the group without cognitive impairment and the group with cognitive impairment using fNIRS.

The participants will be divided into 2 equal groups: the verum acupuncture group (study group) and the sham acupuncture group (control group). After each group is confirmed to participate in the study through screening (visit 0), fNIRS scanning and acupuncture manipulation will be conducted at visit 1. Cognitive function assessments, including the Korean version of the Mini-Mental State Examination (MMSE-K) and Montreal Cognitive Assessment (K-MoCA), will be conducted during screening. At visit 1, each participant will be measured twice using fNIRS (first and second scan) before and after acupuncture stimulation. Finally, CR marker assessment, such as the Cognitive Reserve Index Questionnaire (CRIq), will be conducted through interviews in visit 1. The period between visit 0 and visit 1 will not exceed 1 week. Participant recruitment was initiated on August 22, 2023, and the study is scheduled to continue until February 2025. The flow chart is illustrated in Figure 1, and the overall procedure is presented in Table 1.

Figure 1. Flowchart of this study. K-MoCA: Montreal Cognitive Assessment (Korean version); MMSE-K: Mini-Mental State Examination (Korean version).

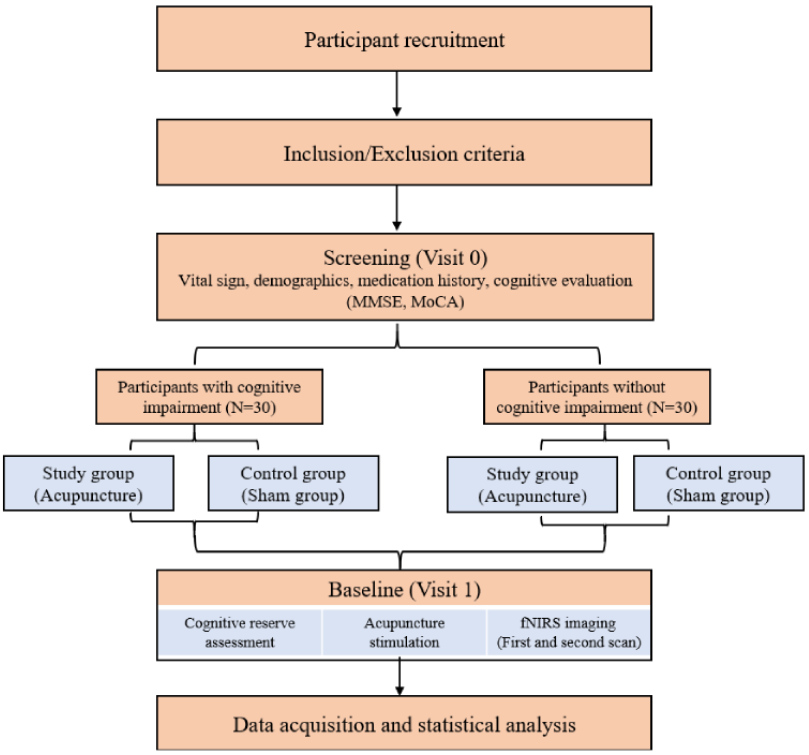

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Table 1. Overall procedure of this study.

Time point	Study period Visit 0 (screening)	Visit 1
Enrollment		
Eligibility screen	✓	
Informed consent	✓	
Randomization and allocation	✓	
Intervention		
Verum acupuncture group		✓
Sham acupuncture group		✓
Assessment		
Demographics	✓	
Medical history	✓	✓
MMSE-K[a]	✓	
K-MoCA[b]	✓	
CRIq[c]		✓
fNIRS scan[d]		✓
Safety		
Vital sign	✓	✓
Adverse events		✓

[a]MMSE-K: Mini-Mental State Examination (Korean version).

[b]K-MoCA: Montreal Cognitive Assessment (Korean version).

[c]CRIq: Cognitive Reserve Index Questionnaire.

[d]fNIRS: functional near-infrared spectroscopy.

Participants and Recruitment Strategy

Eligibility Criteria

The inclusion criteria for healthy controls (the group without cognitive impairment) are as follows: (1) males and females aged ≥19 years without cognitive impairment (MMSE-K≥24, K-MoCA≥23); (2) participants without severe neurological, organic dysfunction; and (3) participants or authorized surrogates who voluntarily sign the informed consent.

The inclusion criteria for the group with cognitive impairment are as follows: (1) males and females aged ≥60 years showing cognitive impairment (MMSE-K<24, K-MoCA<23) or diagnosed with mild cognitive impairment (MCI) or dementia with a clinical dementia rating<3; (2) participants or authorized surrogates who voluntarily sign the informed consent; and (3) participants who can complete this study.

The exclusion criteria for healthy controls (the group without cognitive impairment) are as follows: (1) participants with other brain disorders, alcoholism or drug abuse, neuropsychiatric disease, or taking psychiatric medicines, and severe organic dysfunctions inducing cognitive impairment; and (2) participants with any other reasons that may be considered inappropriate by the researcher.

The exclusion criteria for the group with cognitive impairment are as follows: (1) severe dementia patients with a clinical dementia rating of 3; (2) patients with other brain disorders such as cerebrovascular disease and epilepsy; (3) patients with cognitive impairment induced by another primary disease; (4) patients with severe organic dysfunctions; (5) patients presenting alcoholism or drug abuse, with neuropsychiatric disease or taking psychiatric medicines; and (6) patients with any other reasons that may be considered inappropriate by the researcher.

Enrollment, Randomization, and Blinding

Recruitment will be conducted through advertisements on websites and public announcements. Promotion through local communities is also under consideration. The recruitment of participants with cognitive impairment will be promoted through cooperation with community dementia care centers. In this study, in accordance with the recruitment of the participants, the effect of age on brain function will also be investigated; therefore, recruitment in the group without cognitive impairment will not be restricted to older adult participants.

Stratified block randomization will be performed according to sex. Both groups will be assigned in a 1:1 ratio to the study and control groups by applying a block size of 4. Randomization will be conducted using a computer-generated allocation list by an assigned researcher not involved in the assessment or intervention. Participants will be blinded to the type of

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intervention used. The practitioner will not provide clues regarding allocating information to the participants during the study. Blinding will be maintained until the end of the study. Participants will be asked about their experience of blinding after the end of the study.

Sample Size

In this study, the number of participants has been determined statistically. In our hypothesis, the significance level (α) and power (1–β) will be set to 5% and 80%, respectively. Then, an effect size will be calculated using an estimated value of the variability in the MMSE-K and K-MoCA scores based on the literature [26]. As a result, the number of samples came out to be about 10-15 for each group (study or control group) to satisfy the criteria of the normal deviates of significance level and power in the healthy controls and patient groups. The anticipated dropout rate was set to 10%. A similar number of subjects (i.e., 10–15 subjects in each group) can be found in the previous neuroimaging studies [27-29].

Study Procedures

All participants will be subjected to measurement of vital signs (blood pressure, pulse rate, and temperature), demographic information, and medical history (past, present, and family). Cognitive function assessments (MMSE-K and K-MoCA) will also be performed during visit 0 (screening). Eligible participants who meet the inclusion and exclusion criteria will receive the schedule for visit 1.

At visit 1, the investigator will check the participant's vital signs and changes in medication, perform 2 fNIRS scans before and after acupuncture stimulation, and assess the level of CR using CRIq. For medications, the investigator will check for changes but will not specifically allow or restrict certain drugs. According to stratified randomization, the participants will be assigned to 2 acupuncture stimulation groups. Acupuncture stimulation will be performed by a Korean medicine doctor with >3 years of clinical experience. fNIRS scans consist largely of 2 main parts: a 5-minute resting state scan and a task scan of working memory.

Cognitive Function Assessment

The investigator will assess 2 cognitive function tests: the MMSE-K and K-MoCA. The MMSE-K is a 30-point questionnaire consisting of 12 questions that are widely used in clinical and research settings to measure cognitive impairment [30]. The K-MoCA is an extensively used 30-point cognitive assessment tool that effectively differentiates MCI [31]. The evaluation of each assessment will be conducted by an investigator blinded to the assigned group.

Measurement of Cognitive Reserve

CR assessment will be conducted using the CRIq questionnaire [32]. It includes demographic data and items categorized into 3 sections: education, working activities, and leisure time; each item returns a subscore. It evaluates the CR of an individual by compiling the information associated with the individual's entire adult life. The quantification of CR will be calculated as the sum of all domains, and the subscore of each domain will also be applied in further correlation analysis. Depending on the mean value of CRIq, it will be dichotomized into the high CR and low CR groups. The investigator will also assess the participants' bilingualism. The evaluation of each assessment will be conducted by an investigator blinded to the assigned group.

fNIRS Imaging

For this experiment, fNIRS equipment (NIRSIT, OBELAB) will be used. fNIRS is a portable near-infrared neuroimaging device that measures hemodynamic variations in cerebral blood by irradiating the cerebral cortex with a near-infrared laser. The equipment irradiates the wavelengths of 780 and 850 nm of laser, which is harmless to humans. It contains 48 channels that can cover the frontal regions of the brain, allowing the quantification of ΔHbO_2, ΔHbR, and ΔHbT in that area. Based on this, the analysis applied in fMRI, such as graph theory analysis and general linear model analysis, can be used.

The fNIRS scans will be conducted before and after acupuncture. The scan consists of 2 parts: a resting state and working memory task scan. The resting-state fNIRS scan lasts for 5 minutes, during which the participant is asked to look at the monitor screen and remain comfortable. The task fNIRS scan is performed while conducting a Corsi block tapping task, a cognitive task related to working memory [33]. This experiment requires participants to tap a spatially separated sequence of up to 9 identical blocks in the same order in which they are presented. The sequences start simple, using 4 blocks, and become more complicated using a maximum of 6 blocks (Figure 2).

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Figure 2. Presentation of Corsi block task.

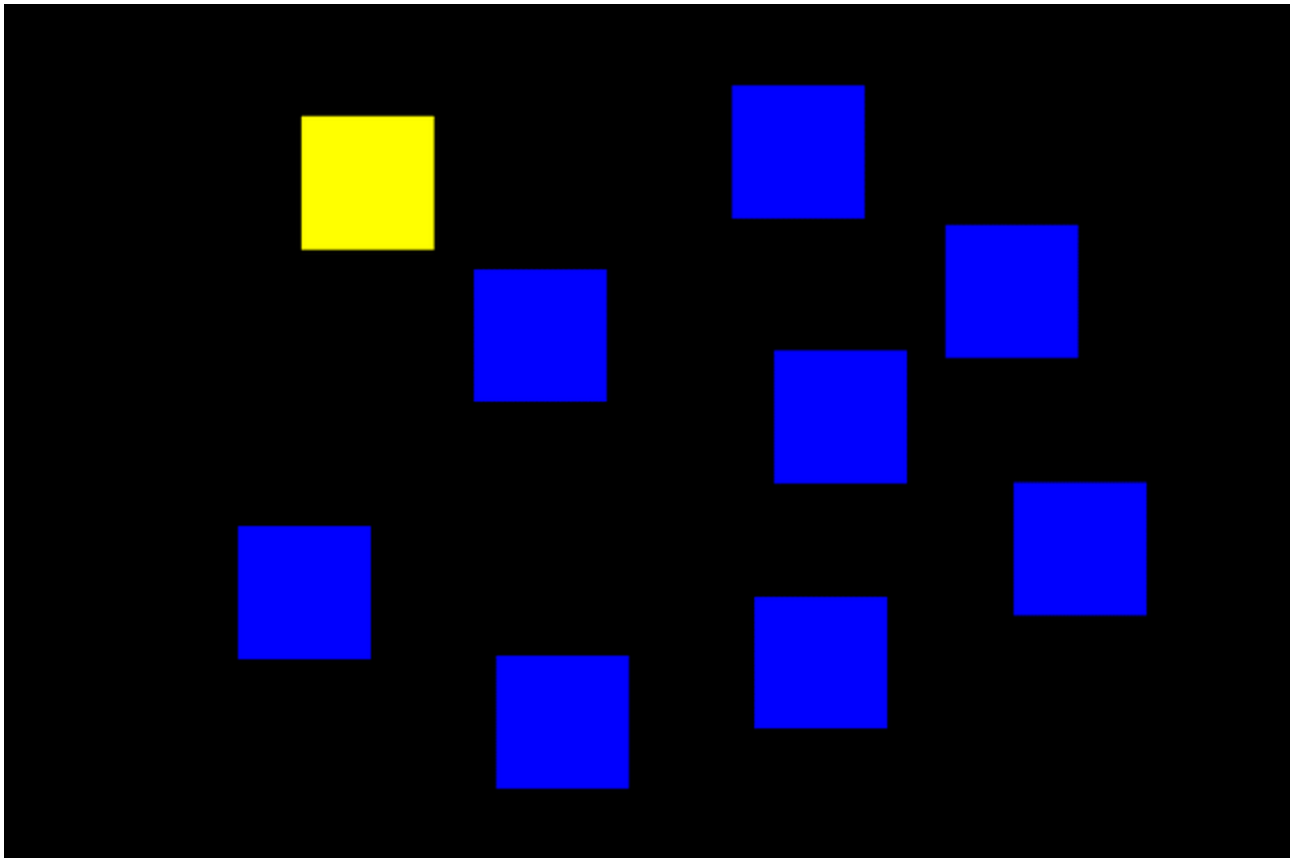

Interventions

In the study group, verum acupuncture stimulation will be conducted for 15 minutes by stainless steel acupuncture (0.25 mm×40 mm, Dongbang acupuncture) on acupoints, which are known to be associated with cognitive functions in previous studies (Baihui [GV20], Sishencong [EX-HN1], Taixi [KI3], Zusanli [ST36], Hegu [LI4], and Taichong [LR3]), and deqi sensation will be induced [24,34,35]. The needle will be lifted and thrust approximately 30-50 mm and twisted and rotated at approximately a 90°-180° angle 60 times/minute (60 Hz). The manipulation will then be performed at 1-minute intervals to maintain the amount of stimulation and achieve deqi sensation. A questionnaire on deqi sensations will be implemented.

For the control group, superficial needling acupuncture (depth of needling: 1-2 mm per nonacupoint) will be performed for 15 minutes using stainless steel acupuncture (0.25 mm×40 mm, Dongbang acupuncture) on nonacupoints. Nonacupoints, which are not related to cognitive function, would be approximately 1 cm away from the acupoints of the study group. The needles for sham acupuncture will remain in place. In the case of superficial needling, manipulation techniques and induction of deqi sensation will not be achieved.

Superficial needling can be a subtype of minimal acupuncture [36]. We thought that the characteristics of acupoints, depth of acupuncture stimulation, intensity of the stimulation, and deqi sensation would all be determinants of acupuncture stimulation. Therefore, we selected minimal acupuncture that lacks these features as a sham control. This type of sham acupuncture has been applied in various studies, including Bell's palsy, migraine, and chronic musculoskeletal pain syndrome, for a long time [37-40].

Outcome Measures

This study aims to explore the immediate neural mechanisms of the acute response to acupuncture stimulation associated with CR in normal aging and disease status and identify the neural substrates of CR.

The primary outcomes will be as follows: (1) differences in brain activation and resting-state brain connectivity according to disease status (the groups with vs without cognitive impairment); (2) differences in brain activation before and after acupuncture between study and control groups (verum acupuncture vs sham acupuncture); and (3) differences in brain activation according to CR (high CR group vs low CR group).

Secondary outcomes are brain connectivity or network metrics (graph theoretic metrics) associated with the CRIq index, differences in brain activity between working memory tasks and resting states, and network metrics associated with cognitive function scores (MMSE-K, K-MoCA).

The brain connectivity matrix will be obtained as Pearson correlation between 48 channels using time-series data during the scan period (Figure 3). Network metrics, including the index of efficiency, clustering coefficient, and centrality, can be calculated using the connectivity matrix by the Brain Connectivity toolbox in MATLAB 2023b (The Mathworks).

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Figure 3. Resting-state brain connectivity matrix before acupuncture stimulation (A) and after acupuncture stimulation (B).

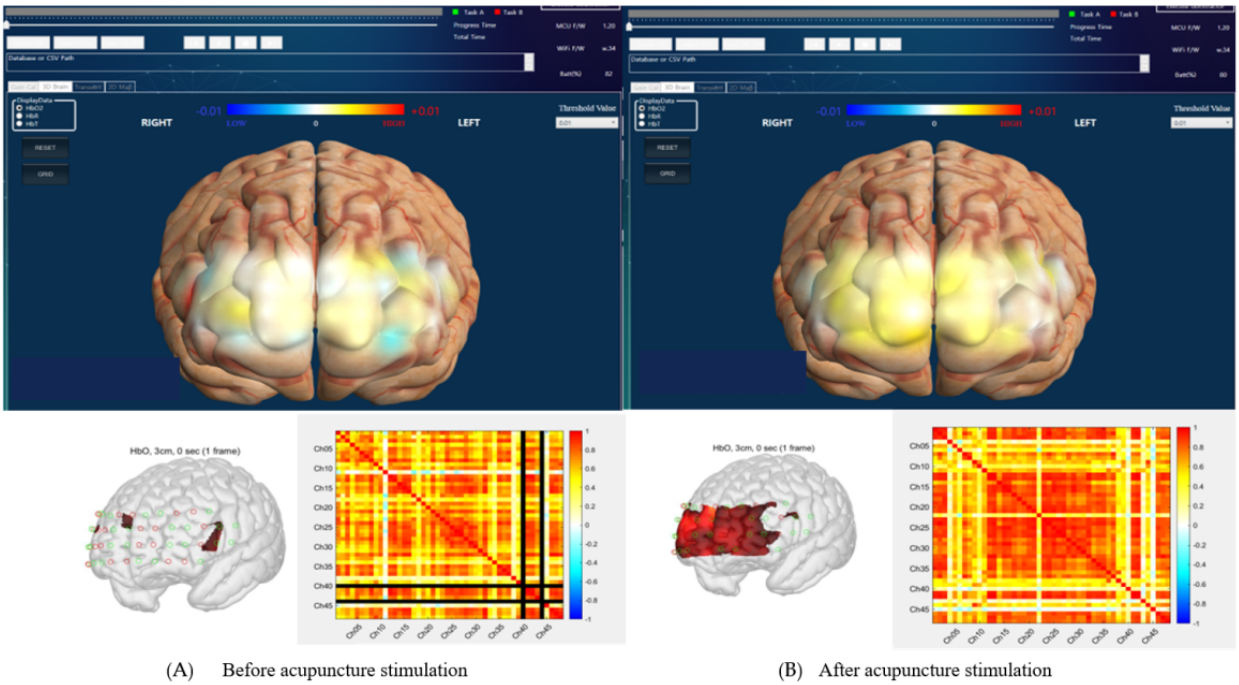

(A) Before acupuncture stimulation (B) After acupuncture stimulation

Data Collection, Monitoring, and Dropout Criteria

Data Collection and Adverse Events Monitoring

Demographic information (age, sex, height, and weight), medical history, and concomitant medication will be collected for each participant at the start of the study. Researchers will record blood pressure, body temperature, respiratory rate, and pulse rate in visits 0 and 1. All adverse events will be fully reported in case report forms, and the association between the adverse events and intervention will be evaluated as not related, possibly related, or related. Severity will be evaluated as mild, moderate, or severe. When severe adverse events, including death, life-threatening events, and the need for hospital admission, occur, the investigator will suspend all or part of the clinical trial and notify other investigators and the Institutional Review Board within 24 hours.

Dropout Criteria

The participants will be excluded in the following cases: severe adverse events occur; difficulty proceeding with the trial due to adverse events; the participant or a legal representative wants to stop the trial; the participant withdraws consent to join the trial; the participant fails to finish the interview or the fNIRS scan; and progression of the trial is considered inappropriate by the principal investigator.

Statistical Analysis

Only data from participants who completed the fNIRS scan, cognitive function test, and measurement of CR will be contained in the statistical analysis. All categorical data are presented as frequencies or percentiles and will be analyzed using the chi-square or Fisher's exact test. All numerical data will be presented as the mean and standard deviation and analyzed using an independent *t* test or Wilcoxon rank-sum test. Preprocessing and analyses of fNIRS data will be performed using MATLAB and the NIRSIT analysis tool.

A two-sample *t* test will be performed to compare the brain activations and connectivity between the groups with and without cognitive impairment. A paired *t* test will be conducted to compare the brain activations and connectivity before and after acupuncture stimulation. The CR values from CRIq will be applied for correlation analysis in the form of continuous variables or divided into binary groups (high and low CR) by mean values for subgroup analysis. Since the expression of CR may appear differently depending on the disease status, a subgroup analysis will be conducted by dividing the healthy control and the patient group. Mixed model analysis will be adjusted to determine the interaction effect of intervention and CR in both groups. Pearson correlation will determine the CR-related brain connectivity or clinical score–related metrics. If there is a significant age difference between 2 groups, the age factor will be added as a covariate in the analysis to adjust the effect of age as much as possible.

Statistical significance in fNIRS imaging would be explored using uncorrected and corrected levels (false discovery rate and family-wise error). At the uncorrected level, uncorrected $P<.001$ will be used, and at the corrected level, $P<.05$ will be applied.

Data Management

The investigators will collect and record the medical information in each participant's case report form. All study data, including all patient confirmations, all original signed informed consent forms, and detailed original records, will be retained by the study institution for 3 years after the end of the trial.

Quality Control

Important protocol modifications must be reported to the IRB. The approval period of the trial is 1 year, and after 1 year,

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regular reports must be submitted to the IRB, and re-approval should be obtained. Before the beginning of the trial, all investigators involved in the intervention will be trained in the process of the trial. In total, 2 independent research assistants will check the data and case report forms to avoid mistyping or errors during the trial. There is no plan for early termination of the study before February 2025. If the target number of participants is complete, additional recruitment may proceed depending on the research funding status.

Ethical Considerations

The trial will be performed in accordance with the Declaration of Helsinki. This trial has been approved by the Institutional Review Board of Sangji University (1040782-230426-HR-04-112). The protocol has been registered with the Clinical Research Information Service of the Republic of Korea (number KCT0008719), one of the WHO ICTRP Primary Registries. Written informed consent will be obtained from each participant or their legal representative. All data will be anonymized, and the identification information of all documents will be recorded according to the identification code. The information will be kept confidential in a locked place. Participants in this study will be paid a small compensation fee, approximately 50,000 won (equivalent to approximately US $30), for participation in the study.

Results

The recruitment and enrollment of the study began in August 2023, and to date, there have been 50 participants, divided into 20 in the group with cognitive impairment and 30 in the unimpaired group. Within the group with cognitive impairment, 16 participants (80%) had dementia and 4 subjects had MCI. The percentages of female participants in the group with cognitive impairment and the group without cognitive impairment were 70% and 57%, respectively. Ongoing recruitment is in progress. The protocol version used in this study is V.1.0 (2023.06.12). This study will continue until February 2025, after which the communication of final results will be made in accordance with the CONSORT checklist.

Discussion

Overview

Dementia affects an estimated 57 million people worldwide, and AD is the most common dementia-inducing disease [41]. The neuropathologic hallmark of AD is extracellular amyloid beta deposition and neurofibrillary tangles consisting of phosphorylated tau protein [42]. Although various therapeutic drugs are being developed with the advancement of medical technology, there is no definitive treatment for AD. Therefore, early diagnosis and prevention are important for cognitive impairment disorder.

At first, CR originated from the observations of the mismatch between the pathological degree of brain damage and clinical symptoms. In a postmortem study, there were neuropathological alterations comparable to dementia; however, the participants had no symptoms of dementia in their lives [43]. In this context, CR is considered a factor mediating the relationship between the neuropathology of the disease and clinical manifestation and has clinical importance as a prognostic factor of the disease trajectory [44]. There are several CR surrogate markers, including years of education, occupation, leisure activities, composite scores, questionnaires, and residual methods using imaging markers. This study applies a CRIq, which consists of subscores of lifelong education, occupation, and leisure activity as the main CR proxy.

Acupuncture has been used to treat several neurological diseases in East Asian countries. Several studies have revealed the effects and mechanisms of acupuncture in MCI or AD using neuroimaging methods. Moreover, studies applying fNIRS have reported the neural mechanisms of acupuncture manipulation in patients with MCI and healthy participants [45,46]. However, there have been no studies on the neural mechanisms of acupuncture stimulation in relation to CR.

This randomized, placebo-controlled clinical trial aims to investigate the neural substrates of CR in both the normal group and the group with cognitive impairment and explore the neural mechanisms of acupuncture stimulation in relation to CR using fNIRS. The potential significance of this research lies in elucidating the connection between acupuncture and CR, thus providing insights into the therapeutic possibilities for cognitive impairments. We expect to contribute to identifying neural mechanisms of acupuncture stimulation in cognitive impairment in relation to CR. This study could provide a basis for further study about the long-term effects and mechanisms of acupuncture treatment in cognitive impairment.

Innovations and Limitations

This is the first study to identify the association between CR, an important factor related to the prognosis of dementia, and acupuncture stimulation. The application of the neuroimaging method (fNIRS) can provide new insights into the neural mechanisms of complementary medicine in the field of convergence research. This randomized, controlled trial can contribute to elucidating the genuine neural response to the acupuncture stimulation. However, as a cross-sectional study, it is not possible to identify the long-term effect of acupuncture treatment on cognitive impairments and explore the longitudinal neural mechanism of acupuncture treatment. Additionally, to ensure the reliability of the data, we still further expand the sample size.

Conclusions

This study will provide data on the neural substrates of acupuncture stimulation associated with CR as well as brain network alterations depending on disease status. More importantly, if the acute neural mechanisms of acupuncture stimulation are identified, the results could serve as a basis for the long-term effects of acupuncture treatment on cognitive impairments. This study could provide a scientific foundation for further clinical application of acupuncture as a complementary medicine for cognitive impairments, which induce a high socioeconomic burden.

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Acknowledgments

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Data Availability

All study data will be retained by the study institution for 3 years after the end of the trial. All investigators participating in this trial will have access to the final dataset after recruitment is completed. The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

AD: Alzheimer disease
CR: cognitive reserve
CRIq: Cognitive Reserve Index Questionnaire
fMRI: functional magnetic resonance imaging
fNIRS: functional near-infrared spectroscopy
HbO2: oxyhemoglobin
HbR: deoxyhemoglobin
HbT: total hemoglobin
MCI: mild cognitive impairment
MMSE: Mini Mental Status Examination
MoCA: Montreal Cognitive Assessment
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Auricular Acupressure Versus an Intermittent Low-Carbohydrate Diet in Children With Overweight or Obesity With Gastric-Heat and Dampness-Obstruction Syndrome: Protocol for a Randomized Controlled Trial

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Abstract

Background: Childhood obesity frequently persists into adulthood and is associated with an increased risk and earlier onset of cardiovascular disease in later life. Behavioral change strategies have been proposed as the first-line weight management approach for children and adolescents with obesity. Nonpharmacological interventions, such as traditional Chinese medicine (TCM) auricular acupressure treatment and intermittent low-carbohydrate diet (ILCD), are increasingly being investigated in the young obese population. However, there is limited high-quality evidence about effectiveness and safety in weight control and reducing cardiometabolic risk in the pediatric population.

Objective: This study aimed to compare the effect of cardiometabolic risk reduction between TCM auricular acupressure treatment (TAAT) and ILCD in children with overweight or obesity with gastric-heat and dampness-obstruction syndrome.

Methods: This is a randomized controlled trial. Eligible participants are children with overweight or obesity and enrolled at the obesity clinic of the department of TCM at a tertiary children's hospital. Eligible participants must meet the following criteria: (1) be aged between 6 and 18 years, (2) be overweight, and (3) have gastric-heat and dampness-obstruction syndrome. Recruited children will be randomized 3:1 to receive either TAAT or a self-administered ILCD for 1 month: 150 in the TAAT group and 50 in the ILCD group. The primary outcome is the change in body weight from the beginning of treatment to the end of 1 month. Secondary outcomes included body weight, waist circumference, waist-to-height ratio, BMI, blood pressure, body fat content, indexes of liver and renal function, indexes of glucose metabolism, gut microbiota, and TCM syndrome scores at the end of 1 month and 3 months, respectively. Primary statistical analyses were conducted using the intention-to-treat strategy. A generalized linear model was used to compare the difference in weight change between the groups, with the baseline body weight as the covariate, to obtain the estimate of the mean difference in body weight change and its 95% CI, using Gaussian for family function and identity for link function.

Results: The study protocol was approved by the institutional ethical committee and registered on ClinicalTrials.gov on May 5, 2023, before recruitment. Recruitment began in June 2023 and is expected to be completed by December 2025. As of November 2024, we have enrolled 112 participants.

Conclusions: This randomized controlled trial will provide evidence on the treatment effects and safety of TAAT versus ILCD among children with overweight or obesity with gastric-heat and dampness-obstruction syndrome, in reducing body weight and

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improving cardiometabolic risks. Exploratory aims include potential underlying mechanisms of the 2 kinds of interventions, based on biosamples.

Trial Registration: ClinicalTrials.gov NCT05847478. https://clinicaltrials.gov/study/NCT05847478

International Registered Report Identifier (IRRID): DERR1-10.2196/59856

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KEYWORDS

children with obesity; traditional Chinese medicine; TCM auricular acupressure treatment; intermittent low carbohydrate diet; study protocol

Introduction

The Report on Cardiovascular Health and Disease in China (2022) [1] shows that cardiovascular disease is the leading cause of death among urban and rural residents in China, which is mainly caused by hypertension, dyslipidemia, diabetes, overweight or obesity, physical inactivity, inappropriate diet, and metabolic syndrome. It is important to note that obesity, especially abdominal obesity, is a direct risk factor for cardiovascular disease. Unfortunately, obesity can persist from childhood and adolescence into adulthood [2,3]. Obesity in children and adolescents is a global health issue [4], with China, India, the United States, Indonesia, and Brazil being the top-ranked countries, each estimated to have more than one million children with obesity in 2030 [5].

First-line treatments for obesity should be supported by behavioral change strategies [4]. Family-based interventions that address diet, physical activity, sedentary behavior, and sleep quality are recommended. However, the weight loss effect is not ideal and is difficult to maintain. Although evidence for pharmacotherapy and bariatric surgery as supplemental therapies is emerging, they are not recommended for weight loss in children [6]. In fact, safer and more acceptable nonpharmacological interventions, such as traditional Chinese medicine (TCM) and TCM auricular acupressure treatment (TAAT), are increasingly used.

The earliest known mention of TAAT dates back to Huang Di Nei Jing (circa 100 BC) [7,8]. Currently, auricular therapy is widely used in clinical settings for pain relief, epilepsy treatment, improving sleep quality, and obesity [9-11]. This approach offers the advantage of individualized treatment based on the dialectical theory of governance. TAAT has been found effective on children, adolescents, and adult obesity [12-14]. The study found that auricular acupuncture stimulation clearly modulates the feeding-related hypothalamic neuronal activity of experimental (both hypothalamic and dietary) obese rats. The results suggest that auricular acupuncture stimulation may not reduce appetite but is more likely concerned with satiation formation and preservation [15]. However, high-quality clinical evidence is lacking. According to TCM, obesity is located on the spleen and stomach, followed by the liver and kidney. TCM identifies several syndrome types of obesity, including gastric-heat and dampness-obstruction syndrome, spleen-deficiency and dampness-stagnation syndrome, liver-qi stagnation syndrome, and spleen-kidney deficiency syndrome [16,17]. Among these, gastric-heat and dampness-obstruction syndrome is the most common type [18]. In order to ensure the sample size is attained, the gastric-heat and dampness-obstruction syndrome has been selected for inclusion in the study. In addition, the choice of a single syndrome in preference to multiple options ensures comparability in the evaluation of efficacy between groups.

Numerous studies have demonstrated the effectiveness of low carbohydrate diets (<50 g per day or <10% energy from carbohydrates) in combating obesity [19], deemed feasible and acceptable [20,21]. Our previous research has shown that the intermittent low carbohydrate diet (ILCD) was effective in improving weight-related outcomes in children and adolescents [22]. However, the efficacy needs to be further investigated, and long-term effects are uncertain. So far, there are currently no randomized controlled trials comparing the effectiveness between ILCD and TAAT. At the same time, our secondary aim is to explore the mechanistic differences between the 2 nondrug interventions. Therefore, this study aims to assess whether TAAT as the experimental arm is more effective than ILCD as the control arm in improving the cardiometabolic risk in children with overweight or obesity with gastric-heat and dampness-obstruction syndrome.

Methods

Objective and Trial Design

This is a randomized controlled superiority trial that aims to compare the effects of TAAT versus ILCD in reducing the cardiometabolic risk in children with overweight or obesity with gastric-heat and dampness-obstruction syndrome. Participants were allocated in a 3:1 ratio to either an auricular acupressure treatment group or a control group. The TCM clinicians were aware of the allocation but did not participate in the following research. Conversely, the outcome observers were blinded about the allocation.

Recruitment and Study Setting

Eligible participants were recruited by a pediatrician at the obesity clinic of the Department of TCM in Children's Hospital of Fudan University. All participants were required to provide written consent before intervention.

Participants Eligibility Criteria

Eligible participants must meet the following criteria: (1) be aged between 6 and 18 years, (2) be overweight [23], and (3) have gastric-heat and dampness-obstruction syndrome [16].

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Overweight or obesity with gastric-heat and dampness-obstruction syndrome was defined as follows:

(1) The "Expert Consensus on Diagnosis, Assessment, and Management of Obesity in Chinese Children" states that BMIs between 85% and 95% were classified as overweight, while those above 95% were classified as obese for children of the same gender and age [23].

(2) The "Pediatrics of Traditional Chinese Medicine" framework [16] outlined the conditions that must be met for the gastric-heat and dampness-obstruction syndrome, which include (1) dizziness and heaviness in the head, (2) thirst, (3) rapid digestion of food and polyorexia, (4) heaviness of limbs, (5) fatigue body and lack of strength, (6) a red tongue, (7) greasy fur, and (8) a slippery pulse. It is important to note that conditions (7) and (8) must be satisfied, while conditions (1) to (6) must be satisfied at least 3 conditions.

Participants who met any of the following exclusion criteria were excluded: (1) having hereditary obesity or obesity caused by endocrine disorders, such as Cushing syndrome, primary hypothyroidism, and hypothalamic obesity; (2) currently being enrolled in other clinical trials or having participated in another clinical trial in the past 3 months; (3) self-administration of oral weight-loss medications or other forms of meal replacements; and (4) having serious organic diseases of the heart, liver, kidneys, or brain, or infectious diseases or psychiatric disorders.

Interventions

Experimental Group (TAAT Group)

Specialized TCM clinicians conducted TAAT following a standardized procedure. The location and operation of the ear acupoints followed the guidelines outlined in the "National Standard of the Peoples Republic of China for Nomenclature and Location of Auricular Points (GB/*t* 13734-2008)." In addition, all TCM clinicians had received specialized training to ensure a comprehensive understanding of the auricular acupressure intervention program and to standardize the procedures performed by different clinicians.

The study selected the following ear acupoints for acupressure treatment: Shenmen (TF4), Xiaoping (TG2), Endocrine (CO18), Stomach (CO4), Mouth (CO1), and Subcortex (AT4) (refer to Figures 1 and 2) [24]. The acupressure was administered using an opaque patch with Vaccaria seed. Participants were instructed to apply pressure for 1 minute before and after meals each day, for a total of 2 to 3 days per week. They were followed weekly and received a 3-course treatment, with 1 course per month.

Figure 1. Location of the subcortex (AT4).

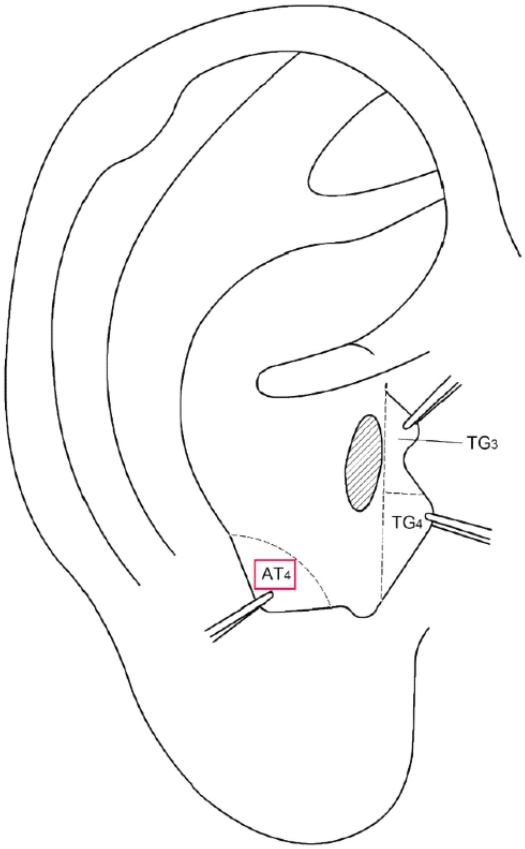

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Figure 2. Location of the shenmen (TF4), Xiaoping (TG2), endocrine (CO18), stomach (CO4), mouth (CO1).

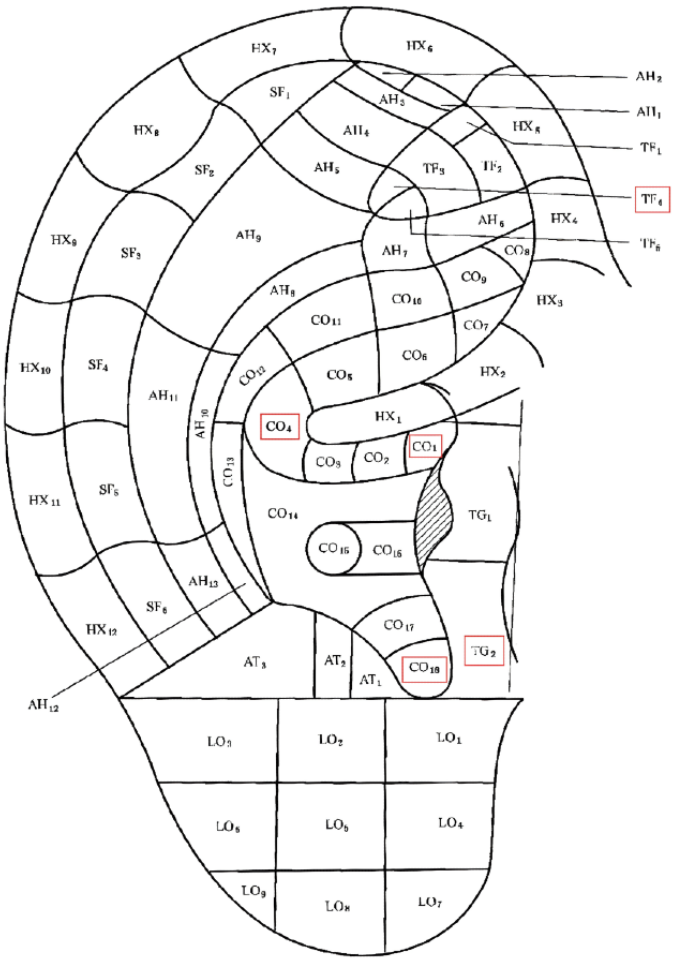

Control Group (ILCD Group)

Participants were required to limit their daily carbohydrate intake to 50 g or less, while their dietary calorie intake was not restricted for nonconsecutive 7 days of 2 weeks, corresponding to 14 days in a month. On the remaining days, participants should maintain their normal diet. The intervention period lasted for 1 month, followed by a 2-month follow-up period [20].

Follow-Up Period

First, a WeChat group was created for parents of participants to facilitate communication and monitoring about diet and exercise recording, as well as scheduling follow-up appointments. Second, adherence to the study interventions were uniformly assessed in both groups at each visit. Third, if participants missed any visits, investigators would contact them directly by telephone to encourage continued participation and evaluate barriers.

The research assistant attempted to establish contact with the missed participants. A dropout participant was defined as someone who had not been reached for 3 months. If participants decided to withdraw before completion, all collected data would be remained for analysis.

Outcomes

Primary Outcome

Change in body weight from the beginning of the treatment to 1 month.

Secondary Outcomes

Secondary outcomes included body weight, waist circumference, waist-to-height ratio, BMI, blood pressure (BP), body fat content, glucose metabolism, blood lipid levels, liver and kidney function, composition of gut microbiota, and TCM syndrome score, and were assessed at the end of 1 month and 3 months, respectively.

Measurement

Anthropometry

Including the measurements of weight, height, waist circumference (WC), and BP. These measurements should be taken by the same person, using the same instruments, at the same time of day. Each measurement should be taken 3 times in a row, and the average of the 3 values should be used.

(1) **Weight measurement:** The participant should be weighed in light clothing and preferably with an empty bladder. They should also remove shoes, heavy jewelry, and watches. The electronic weight scale should display 0.0 before the participant stands on it. The participants should stand with their feet

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together in the center and their heels against the back edge of the scales. The participant's arms should be hanging loosely at their sides and their head should be facing forward. The weight measurements were recorded in kilograms and were accurate to 0.1.

(2) **Height measurement:** Height should be measured using a stadiometer with the participant standing barefoot and with feet together. The head should be positioned level with a horizontal Frankfurt plane, which is an imaginary line from the lower border of the eye orbit to the auditory meatus. Any hair knots or braids that may interfere with the measurement should be untangled. The press plate should be in contact with the head with moderate tightness. The height measurements were recorded in centimeters with an accuracy of 0.1.

BMI was a widely used tool for assessing the risk of overweight and obesity in individuals. It was calculated using the following equation:

(3) **Waist circumference measurement:** The measurement should be taken while the participant exhales. WC was measured by placing a tape measure around the waist, 1 cm below the navel, with the participant standing and arms naturally at their sides. Record the data in centimeters with an accuracy of 0.1.

Waist-to-height ratio had emerged as a surrogate for abdominal obesity that also takes into account body size and allows the same cut of across age and gender [25]. It was calculated using the following equation:

(4) **Blood pressure measurement:** BP was measured on the right arm using the CONTEC08A electronic sphygmomanometer (CONTEC Medical Systems Co). The participant should be seated in a quiet room for 3-5 minutes before measurement, with the back supported and feet uncrossed on the floor. The right arm should be at heart level, supported, and uncovered above the cuff. The correct cuff size should be used. The bladder length should be 80%-100% of the circumference of the arm, and the width should be at least 40%.

Body Fat Content

Body composition was measured by determining the body fat percentage using the LUNAR dual photon X-ray dual-energy X-ray absorptiometry equipment (General Electric Company). Dual-energy X-ray absorptiometry was a medical imaging technology that used low dose radiation for a whole-body scan to provide accurate measurements of fat percentage. The equipment was operated by qualified professionals.

Venous Blood Tests

The tests were conducted after a 10-hour overnight fast to avoid any influence of diet on the test results. The tests included glucose metabolism, blood lipid levels, and liver and kidney function. The remaining blood samples were stored in a –80°C refrigerator for further testing. The operators conducting the tests possessed professional qualifications.

TCM Syndrome Score

"Pediatrics of Traditional Chinese Medicine" listed a number of TCM symptoms in obesity with gastric-heat and dampness-obstruction syndrome: (1) dizziness and heaviness in the head, (2) thirst, (3) rapid digestion of food and polyorexia, (4) heaviness of limbs, (5) fatigue body and lack of strength, (6) a red tongue, (7) greasy fur, and (8) a slippery pulse. Each item was scored on a scale of 0-2, with 2 points for obvious symptoms, 0 points for nonsymptomatic, and 1 point for symptoms that are between obvious and nonsymptomatic. The total syndrome score was obtained by adding up the scores for each item. A qualified clinician performed the score evaluation.

Gut Microbiota Test

Stool samples were collected using Boyou nucleic acid storage tubes (Shanghai Biotechnology Corporation) and stored in a laboratory refrigerator at –80°C. To study intestinal flora diversity, the 16S rDNA target region would be amplified, and information on intestinal microbial diversity and community composition will be obtained by detecting sequence variation and abundance of the target region. The operators possessed professional qualifications.

Dietary and Exercise Data

Diet and exercise data were recorded by the children and their families, but they were educated by qualified clinicians before recording [26,27].

(1) **From the baseline to the first month:** The weight of the food was measured using an electronic scale before and after each meal, and photographs were taken as well. Participants were required to wear sports watches every day, including during sleep, but not while bathing, swimming, or in other special cases. Dietary data included the type and weight of the foods consumed, while exercise data included step count, calorie consumption, resting heart rate, sleep duration, and exercise type. All data was meticulously recorded daily in the "Diet and Exercise Handbook."

(2) **From the second month to the third month:** The method and content remained unchanged. Dietary and exercise data were recorded on Thursdays, Fridays, and Saturdays during 1 week, and distributed at the beginning, middle, and end of the month, rather than every day.

Participant Timeline

The participant timeline was shown in Table 1, following the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) diagram [28].

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Table 1. Schedule of enrollment, interventions, and assessments for the trial. t1, preinclusion assessment; t0, baseline; t1, intervention for one 1 month; t2, intervention for 3 months.

Time point	Enrolment ($-t_1$)	Allocation (t0; Day 0)	Post allocation		Closed out
			t_1 1 month	*t_2 3 months*	
Enrolment					
Eligibility screen	✔	N/A[a]	N/A	N/A	N/A
Informed consent	✔	N/A	N/A	N/A	N/A
Allocation	N/A	✔	N/A	N/A	N/A
Interventions					
Auricular acupressure	N/A	N/A	✔	✔	N/A
Intermittent carbohydrate restriction diet	N/A	N/A	✔	N/A	N/A
Assessments					
General investigation	N/A	✔	✔	✔	N/A
Anthropometry (Height, Weight, WC[b], and BP[c])	N/A	✔	✔	✔	N/A
Body fat content	N/A	✔	✔	✔	N/A
Indexes of liver and renal functions	N/A	✔	✔	✔	N/A
Indexes of glucose metabolism	N/A	✔	✔	✔	N/A
Levels of serum lipid	N/A	✔	✔	✔	N/A
TCM[d] syndrome score	N/A	✔	✔	✔	N/A
Gut microbiota	N/A	✔	✔	N/A	N/A
Dietary data	N/A	✔	✔	✔	N/A
Exercise data	N/A	✔	✔	✔	N/A
Adverse events	N/A	N/A	✔	✔	N/A

[a]N/A: not applicable.

[b]WC: waist circumference.

[c]BP: blood pressure.

[d]TCM: Traditional Chinese Medicine.

Sample Size

The primary outcome was the change in body weight from baseline to 1 month. The sample size calculation was based on the difference in weight change between the 2 groups: the TAAT group and the ILCD group.

Our pilot data from 12 patients revealed a weight loss of 1.9 kg after 4 weeks of TAAT and a weight reduction of 1.4 kg after 4 weeks of ILCD, with an SD of 1.1 kg. We assumed a 0.5 kg difference in weight reduction between the 2 arms, power of 0.80, a 2-sided α of .05, and a sample size ratio of 3:1, a minimum sample size of 150 for the TAAT group and 50 for the ILCD group were required, respectively. Assuming a dropout rate of 15%, the trial enrolled at least 240 participants. The “test for 2 means module” of the PASS 16.0 software was used.

Recruitment

The estimated period for recruitment, intervention, and data collection would take probably 30 months to complete. Eligible clients attending the obesity clinic at the Children’s Hospital of Fudan University were invited to participate in the study through collaboration with TCM clinicians. The time required for participant recruitment and baseline assessment was approximately 30 to 45 minutes.

Randomization and Blinding

Participants were randomly assigned to either the experimental or control group through a simple randomization process generated by the R Language (version 4.2.2; R core team). This process was designed by the clinical trial unit of the Children’s Hospital of Fudan University and follows a 3:1 allocation ratio.

The study coordinator, who was not involved in data collection, performed the allocation. The randomization list was kept strictly confidential. Allocation was done by the study coordinator in a sequentially numbered fashion using identical, opaque, sealed envelopes. The recruiting clinicians were blinded to study group allocation and did not have access to the allocation sequence.

Eligible participants were enrolled by trained clinicians. The study coordinator independently assigned participants to either the intervention or control groups. Outcome observers were blinded. The analysis team received aggregated data obtained for the control and experimental groups. Study participants

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could be blinded, but they were scheduled for separate follow-up dates.

Adverse Events and Assessment of Safety

After participants provided informed consent and enrolled in the study, any adverse events were collected and recorded until the end of the study period. Adverse events that occurred after consent was signed, but before receiving the study intervention was reported as not related to our intervention. Any serious adverse event that occurred would be reported to the principal investigator and documented.

Data Management and Monitoring

Trained clinicians were input data onto a paper-based clinical research form designed by the research team. Once data collection was complete for each participant, it would be entered into an electronic database with built-in checks to ensure completeness. Data monitoring has occurred periodically throughout the study. We used access to create a database, and 2 investigators independently performed dual data entry twice. Once verified, the database was saved appropriately. After confirming the accuracy of the database, it was locked and submitted to an independent statistical team for analysis.

Statistical Analysis

Primary statistical analyses were conducted using the intention-to-treat strategy. Sensitivity analyses were performed using per-protocol set analysis.

Analysis of Primary Outcome

The primary outcome in this study was the change in body weight from baseline to 1 month. A generalized linear model (GLM) was used to compare the difference in weight change between the groups, with the baseline body weight as the covariate, to obtain the estimate of the mean difference in body weight change and its 95% CI, using Gaussian for family function and identity for link function.

Analysis of Secondary Outcomes

GLM was used to obtain differences in effect sizes and their 95% CI for continuous variables between groups. Categorical variables were described in absolute numbers (percentages) and GLM was used to obtain differences in effect values and their 95% CI, using logistic for family function and logit for link function.

Statistical analyses were conducted using Stata 16.0 software (StataCrop). All statistical tests were 2-sided with a significance level of α=.05. Differences were considered statistically significant at P<.05.

Ethical Considerations

This study has been approved by the Medical Ethics Committee of the Children's Hospital of Fudan University and will be conducted in accordance with the approved guidelines and regulations of the participating institution (approval number 2021 [.350]). This trial was conducted in accordance with the current version (AP_IDR_2.0) of the protocol, which has been registered at ClinicalTrials.gov. Informed written consent was obtained from all patients before inclusion in the study. As the involvement of the patients were voluntary, the study could be stopped at any time. All records that contain names or other personal identifiers were stored separately from study records identified by code number. The identification of participants in any images of the manuscript or supplementary material was impossible. For example, the researchers provided the necessary recording materials and sample collectors. The intervention method did not entail additional costs for the participants; thus, no compensation was required.

Results

The protocol was registered on ClinicalTrials.gov (NCT05847478) on May 5, 2023. The current protocol is version 2.0, dated February 28, 2023, which is the final version as approved by the institutional ethical committee. Recruitment started in June 2023 and is expected to be completed in December 2025. By November 2024, we had enrolled 112 participants (Figure 3).

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Figure 3. Flowchart of the study. TCM: traditional Chinese medicine; T0: baseline; T1: intervention for 1 month; T2: intervention for 3 months.

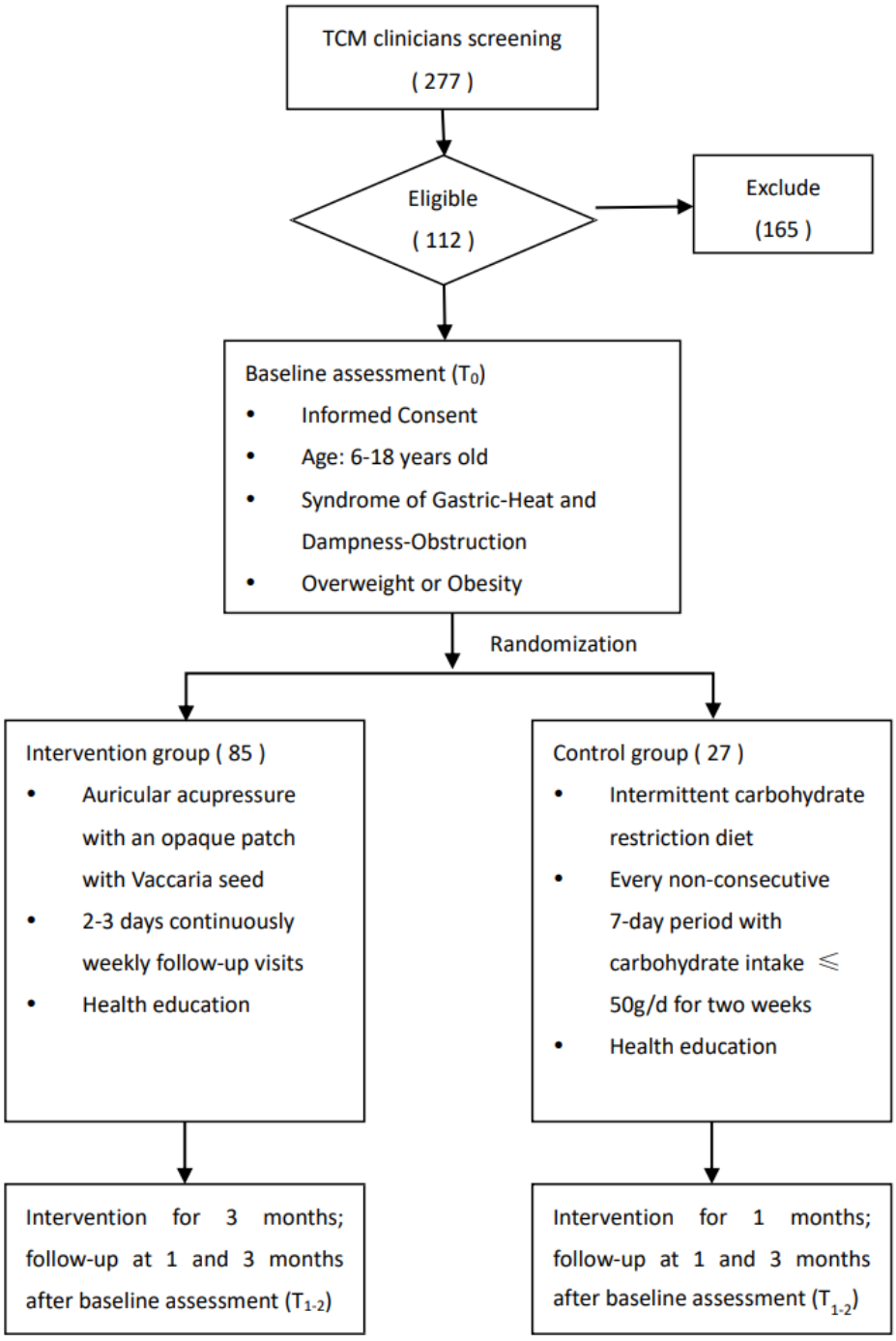

Discussion

Anticipated Findings

It is hypothesized that TAAT will prove superior to ILCD in controlling body weight through this clinical trial. In addition, it is anticipated that the mechanistic differences between the 2 nondrug intervention methods will be elucidated. This study will be the first randomized controlled trial to investigate the effect and safety of TAAT compared with ILCD for overweight or obesity and other cardiometabolic risk factors. Previous studies on the effects of auricular treatment have mainly focused on adolescents and adults [12,14]. A study was conducted as a randomized controlled trial to examine the effects of auricular acupressure on obesity improvement in children. However, this trial had a small sample size and did not take into account the impact of diet, exercise, and lifestyle on body weight [15]. Consequently, there is a lack of high-quality clinical trials on the effects of TAAT in children with obesity, although we found some clinical evidence of this approach in children. Furthermore, the participants' gut microbiota will be studied in order to explore the underlying mechanisms of the 2 different interventions.

All participants in this study are patients from the Department of TCM and seeking TCM intervention. As one of the treatment methods in TCM, previous studies have shown that TAAT is effective in reducing body weight, WC, and body fat mass

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[14,29]; therefore, we did not consider a blank control group, instead, using an ILCD, according to its effect indicated in recent randomized trials [30,31].

TAAT appears minimal side effects, including the pain caused by local noninvasive stimulation that can be tolerated by most children [32]. As participants are recruited from the obesity clinic of the Department of TCM, randomization is set in a 3:1 ratio, allowing that needs of more participants are satisfied.

Maintaining compliance remains challenging to the young population. To ensure better compliance, we use methods such as regular reminders and random checks. To avoid bias, the outcome observer is unaware of the grouping of the participants.

In conclusion, we will evaluate the efficacy and safety of the TAAT in losing weight and improving the cardiometabolic risk of overweight or obese children with gastric-heat and dampness-obstruction syndrome. The results of this study will lead to an update of the consensus on TCM intervention for obesity. However, given the limitations of the intervention time in the experimental design, it is hoped that in future clinical trials, the intervention and follow-up time will be extended in order to obtain a long-term evaluation of the intervention effect.

Conclusion

We conducted a pragmatic randomized controlled trial to investigate the effect and safety of TAAT compared with ILCD for overweight or obese children comorbid with at least one cardiometabolic risk factor. Furthermore, our study will investigate the participants' differential responses of gut microbiota and serum biomarkers to examine underlying mechanisms. The protocol of our study will provide methodologic information and obtain interesting evidence from children for the 2 kinds of nonpharmacological interventions.

Acknowledgments

We thank all the patients and doctors who participated in this study. The funding agency had no role in the study design, data collection, data analysis, data interpretation, writing of the report, or the decision to submit the report for publication.

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Data Availability

The datasets analyzed in this study are available from the corresponding author upon reasonable request.

Authors' Contributions

WS and JWH designed and wrote the manuscript. WLY and JY designed and revised the manuscript. WQW and CL prepared the figure. YLD prepared the table. YTL searched the literature.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOC File , 114 KB - resprot_v14i1e59856_app1.doc]

Multimedia Appendix 2
CONSORT (Consolidated Standards of Reporting Trials) checklist.
[PDF File (Adobe PDF File), 83 KB - resprot_v14i1e59856_app2.pdf]

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Abbreviations

BP: blood pressure
GLM: generalized linear model
ILCD: intermittent low carbohydrate diet
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TAAT: TCM auricular acupressure treatment
TCM: traditional Chinese medicine
WC: waist circumference

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Protocol

Evaluation of the Efficacy of the Traditional Chinese Medicine Formulation Ru-Yi-Jin-Huang-Saan on Colles Fracture After Surgery: Protocol for a Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract

Background: Colles fracture, a common wrist injury, often requires surgical intervention. After surgery, patients may experience persistent pain and reduced wrist function, potentially resulting in long-term disability. In clinical practice, traditional Chinese medicine practitioners frequently use Ru-Yi-Jin-Huang-Saan (RYJHS) to treat such patients in Taiwan. RYJHS is a traditional Chinese herbal formula with a history spanning centuries, primarily used topically for the treatment of bone fractures and the promotion of healing. However, there is currently a lack of substantial clinical evidence supporting its efficacy in the management of postsurgical Colles fractures. To the best of our knowledge, there are no studies evaluating the clinical effectiveness of RYJHS.

Objective: This study aims to investigate the therapeutic potential of RYJHS in postsurgical Colles fracture cases. An additional objective is to provide an alternative treatment option for postoperative patients unable to take anti-inflammatory and pain relief medications.

Methods: This is a protocol for a randomized, double-blind, placebo-controlled trial. A total of 100 postoperative patients with Colles fracture, aged 20-80 years, will be recruited for this study. They will be randomly assigned to either the experimental or control group in a 1:1 allocation ratio. Both groups will receive standard postoperative Colles fracture treatment. The primary outcome measure will assess wrist functional recovery using the Patient-Rated Wrist Evaluation score. Secondary outcomes will include C-reactive protein levels and ultrasound measurements of wrist swelling. All of these examinations will be assessed at baseline, 3 days after surgery, and 6 days after surgery. In addition, the Dyshidrotic Eczema Area and Severity Index will be used to monitor for adverse skin reactions.

Results: This protocol was registered at ClinicalTrials.gov on December 6, 2022. It was performed in accordance with the approved guidelines and regulations of the participating institutions. Recruitment began in May 2023, with data collection expected to conclude in May 2025. Study completion is expected in December 2025.

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Conclusions: This is the first protocol discussing the assessment of the therapeutic efficacy and safety of topical traditional Chinese medicine in patients after fracture surgery. The protocol will establish an integrated care model combining both traditional Chinese medicine and Western medicine for postsurgical fracture cases.

Trial Registration: ClinicalTrials.gov NCT05638360; https://clinicaltrials.gov/ct2/show/NCT05638360

International Registered Report Identifier (IRRID): DERR1-10.2196/56849

(JMIR Res Protoc 2025;14:e56849) doi:10.2196/56849

KEYWORDS

traditional Chinese medicine; Ru-Yi-Jin-Huang-Saan; external application; Colles fracture; Patient-Rated Wrist Evaluation; PRWE; PRWE score; surgeries; fracture; randomized controlled trial; RCT; alternative treatment; postoperative; protocol; Western medicine; wrist evaluation; pain relief medication

Introduction

Distal radial fracture is the most common fracture clinically and is approximately one-sixth of cases in emergency departments in the United States [1]. Studies on the Taiwanese population have shown that the prevalence of Colles fracture was 10.2-14.5 per 10,000 people [2]. This situation causes huge losses to the social economy, as well as decreased school attendance, lost work hours, care needs, and permanent disability [3]. In the Western world, closed reduction and cast immobilization are the first choices of treatments in most cases of distal radius fracture [4]. However, surgery intervention is the first choice in Taiwan. Unfortunately, pain and swelling after surgery may hinder rehabilitation and the regaining of hand function, such as postponed recovery of range of motion, daily function, and muscle power [5]. To control pain and swelling, physicians often use ice packing [6], opioids, nonsteroidal anti-inflammatory drugs (NSAIDs), and steroids [7-9]. Some studies reported that these drugs can have the risk of addiction, lead to respiratory restriction, delay fracture wound healing, raise the risk of osteoporosis, and raise glucose levels [10-13]. Since internal medicine has side effects, external medicine should be used to reduce swelling and relieve pain after the operation.

Traditional Chinese medicine (TCM) has been used to treat fractures for thousands of years. In animal studies, TCM extracts have been shown to accelerate bone healing and prevent delayed fracture healing and nonunion [14]. Other studies have also shown that TCM inhibits the inflammatory response in osteoarthritis rat models [15,16]. Until now, there has been no published study on the application of TCM in the treatment of postoperative fractures. However, TCM for external application has been widely used to treat swelling and pain after fracture. Therefore, we have designed an experiment to verify the curative effect of the external application of TCM in fracture surgery.

Ru-Yi-Jin-Huang-Saan (RYJHS) is a TCM herbal patch composed of a fixed blend of TCM ingredients combined with water. It is traditionally applied to relieve swelling and pain in the early stages of musculoskeletal injuries, attributed in TCM theory to its heat-clearing and swelling-reducing properties. Modern pharmacological studies also confirm its antibacterial, anti-inflammatory, wound-healing, and hemostatic effects [17,18]. As recorded in the classic TCM text, *The Golden Mirror of Medicine*, RYJHS is prescribed for conditions such as furuncles, carbuncles, traumatic wounds, mumps, contact dermatitis, lower limb edema, mastitis, and cellulitis. An animal study also demonstrated that RYJHS significantly accelerated fracture healing, notably enhancing collagen formation and bone cell metabolism [19].

The primary components of RYJHS include *Trichosanthis radix, Rhei radix et Rhizoma, Phellodendri cortex, Curcumae longae rhizoma, Angelicae dahuricae radix, Magnoliae cortex, Glycyrrhizae radix et Rhizoma, Citri reticulatae pericarpium vetum, Atractylodis rhizoma*, and *Arisaematis rhizoma*. Pharmacological research highlights the various therapeutic properties of these components (given in Table 1). For example, *Trichosanthes kirilowii* extract has been shown to accelerate wound healing and possesses antibacterial and anti-inflammatory effects [20-22]. *Rhei radix et rhizoma* inhibits inflammation via NF-κB inactivation [23], and *Phellodendri cortex* has both anti-inflammatory and antibacterial properties [24,25]. Curcumin, the active component in *Curcumae longae rhizoma*, exhibits antioxidant, antimicrobial, and wound-healing effects through growth factor induction [26]. Studies on *Angelicae dahuricae radix* highlight its antinociceptive and anti-inflammatory activities [27]. *Magnoliae cortex*, rich in magnolol, is noted for its anti-inflammatory and antimicrobial activities [28-38]. *Glycyrrhizae radix et rhizoma* has shown anti-inflammatory effects through inhibition of PGE2, TXB2, and LTB4 [39], along with antimicrobial properties [40-42]. *Citri reticulatae pericarpium vetum* offers significant antioxidant and anti-inflammatory benefits [43-46]. *Atractylodis rhizoma* demonstrates antifungal, antibacterial, antioxidant, and anti-inflammatory activities [47-50], while *Arisaematis rhizoma* has been found to have anti-inflammatory and analgesic effects [51,52].

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Table 1. The proportion of Ru-Yi-Jin-Huang-Saan (RYJHS) and the efficacy of its ingredients.

Latin crude drug name (English name)	Plant part	Proportion	Efficacy
Trichosanthis radix (Trichosanthes root)	Root	25%	Wound healing, antibacterial, and anti-inflammatory effects
Rhei radix et rhizoma (Rhubarb)	Root and rhizome	12.5%	Anti-inflammatory effect
Phellodendri cortex (Phellodendron bark)	Bark	12.5%	Antibacterial and anti-inflammatory effects
Curcumae longae rhizoma (Turmeric rhizome)	Rhizome	12.5%	Wound healing, antioxidant, radical scavenging, antimicrobial, and anti-inflammatory effects
Angelicae dahuricae radix (Dahurian Angelica root)	Root	12.5%	Antinociceptive and anti-inflammatory effects
Magnoliae cortex (Magnolia bark)	Bark	5%	Anti-inflammatory and antimicrobial effects
Glycyrrhizae radix et rhizoma (Liquorice root and rhizome)	Root and rhizome	5%	Anti-inflammatory and antimicrobial effects
Citri reticulatae pericarpium vetum (Aged tangerine peel)	Peel	5%	Antioxidant and anti-inflammatory effects
Atractylodis rhizoma (Atractylodes rhizome)	Rhizome	5%	Antifungal, antibacterial, antioxidant, and anti-inflammatory effects
Arisaematis rhizoma (Jackinthepulpit tuber)	Rhizome	5%	Anti-inflammatory and analgesic effects

Further research indicates that RYJHS can alleviate inflammatory pain without causing sensitization [53]. Clinically, it is used to manage conditions such as phlebitis [54], osteoarthritis of the knee [55], gout, diabetic foot ulcers [56], and herpes zoster.

However, despite the numerous studies mentioned above, there is still a lack of clinical research on RYJHS. This study aims to evaluate the efficacy and adverse effects of using RYJHS on Colles fracture after surgery.

Methods

Study Design

The study is a randomized, double-blind, placebo-controlled trial design based on SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) reporting guidelines (Multimedia Appendix 1) [57], and the results will follow the CONSORT (Consolidated Standards of Reporting Trials) guidelines [58]. Our research project is scheduled to recruit patients from May 1, 2023, to April 30, 2025. All postoperative patients with Colles fracture will be recruited through referrals from orthopedic physicians at Changhua Christian Hospital. Researchers will screen and select participants based on specific inclusion and exclusion criteria. In this study, all participants are randomly assigned using a computerized block randomization schedule. We randomly generate a pool of 100 patients, who are assigned to sequentially numbered opaque envelopes. The treatment allocations are balanced within each group, with each group containing 50 patients. Researchers and patients are both blinded to the treatment allocation, with the exception of the statistician responsible for the randomization process. The two groups in the study consisted of the experimental group receiving RYJHS treatment and the control group receiving a placebo.

Study Settings and Participants

All participants undergo standard medical treatment after surgery and are involved in the efficacy assessment of RYJHS external application. Figure 1 shows the study's flowchart. Both groups apply a patch plaster on the back of the wrist without wounds (avoiding the suture of the fracture operation). Figure 2 shows the site of the medication application. The experiment group apply the RYJHS plaster, while the control group apply a placebo plaster. The patch is applied twice a day, for 6 hours each time, with a 6-hour break in between, repeated for 3 days, completing one course of treatment. Patients undergo two courses of treatment, with the first course completed during hospitalization, and the second course completed 3 days after discharge.

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Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram of enrollment, randomization, treatment, and evaluation. CRP: C-reactive protein; DASI: Dyshidrotic Eczema Area and Severity Index; ORIF: open reduction and internal fixation; PRWE: Patient-Rated Wrist Evaluation; RYJHS: Ru-Yi-Jin-Huang-Saan.

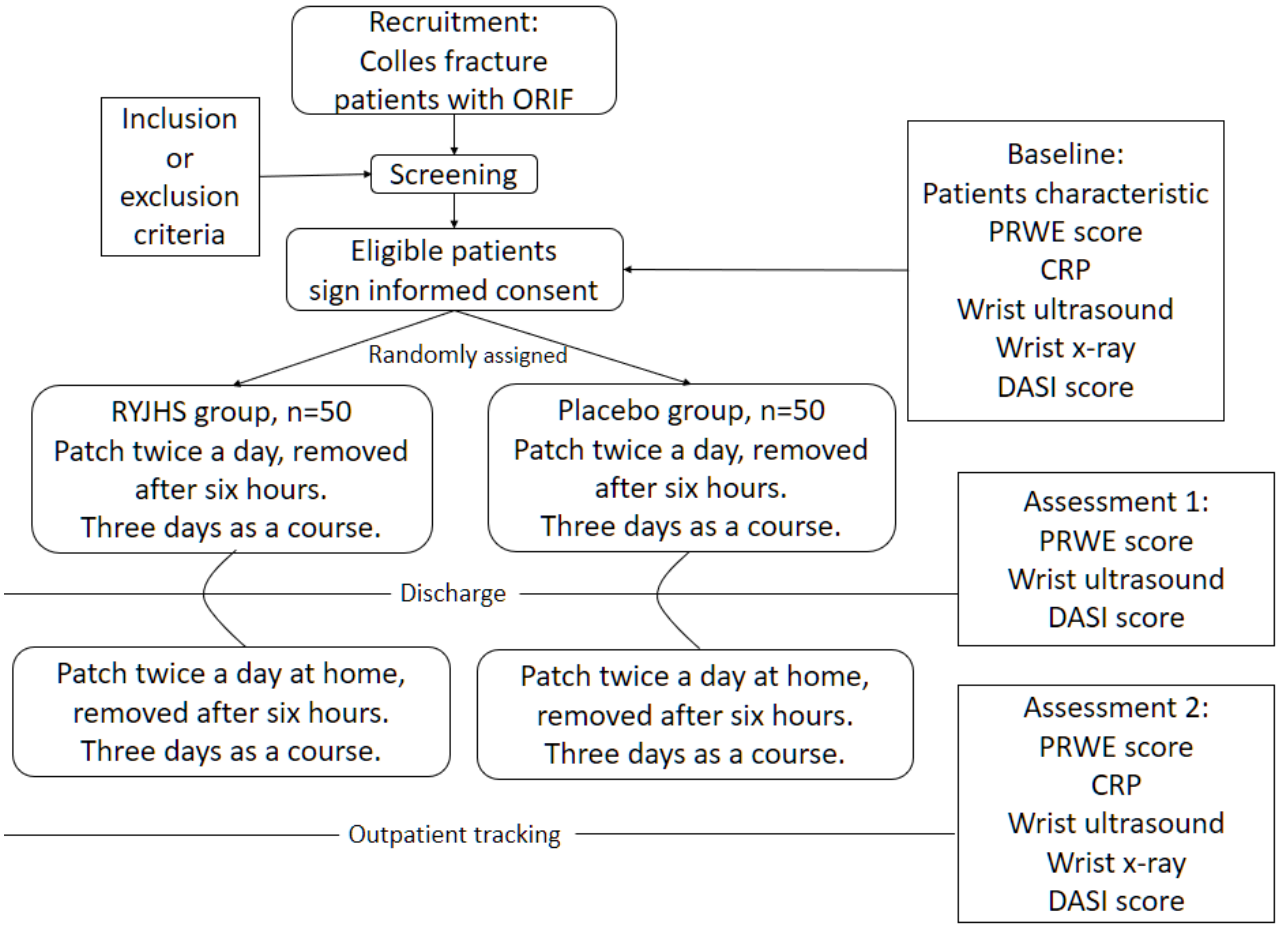

Figure 2. Applying Ru-Yi-Jin-Huang-Saan (RYJHS) plaster on Colles fracture after surgery. (A) The surgical incision site. (B) The site of the RYJHS plaster on a Colles fracture after surgery.

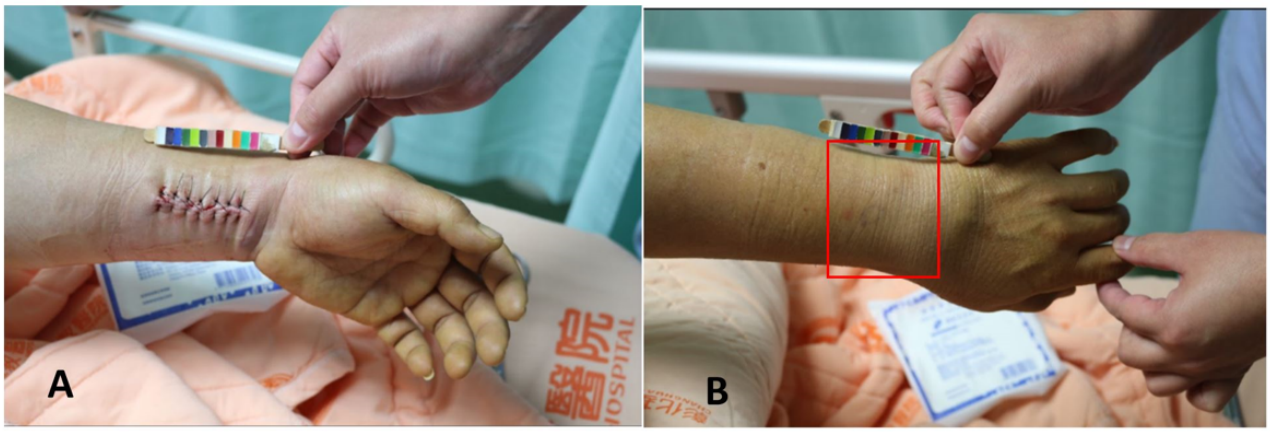

Inclusion Criteria

To be eligible for our study, patients must meet the following criteria: be 20-80 years of age, have a Colles fracture (Frykman classification type I-VI) [59] diagnosis that has been treated with open reduction and internal fixation (ORIF) surgery, and provide informed consent either personally or through their family members.

Exclusion Criteria

The following exclusion criteria will be applied: age older than 80 years or younger than 20 years; inability to comply with experimental procedures or complete questionnaires; presence of wounds on the back of the wrist; allergy to the herbal patch before; use of other Chinese herbal topical medicine after fracture; pregnancy; cancer; stroke; and systemic diseases such

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as severe anemia, thyroid disease, and poorly controlled diabetes.

Sample Size Calculation

Our study closely resembles the design of phase-2 studies in clinical trials, which aim to assess the effectiveness of drugs in participants with specific conditions or diseases. We used G*Power (Heinrich-Heine-Universität Düsseldorf) to estimate the necessary sample size for our study, taking into account repeated-measures ANOVA within-between interactions with a medium effect size of f=0.25 and α level=.05. To achieve a statistical power of 0.95, we calculated a total sample size of 86 [60]. To account for potential dropouts and satisfy our inclusion criteria, we will enroll 100 individuals who have been admitted to our orthopedic care ward and diagnosed with Colles fracture after surgery.

Study Medication

RYJHS is a common TCM plaster that has been used for more than 500 years. RYJHS is composed of 10 herbs: *Trichosanthis radix*, *Rhei radix et rhizoma*, *Phellodendri cortex*, *Curcumae longae rhizoma*, *Angelicae dahuricae radix*, *Magnolite cortex*, *Glycyrrhizae radix et rhizoma*, *Citri reticulatae pericarpium vetum*, *Atractylodis rhizoma*, and *Arisaematis rhizoma* (given in Table 1). This herbal formula is a fixed prescription announced by the Department of Chinese Medicine and Pharmacy. The RYJHS used in our study is manufactured by Kaiser Pharmaceutical Co and meets the requirements of Good Manufacturing Practice. It has also been issued a drug certificate. The placebo powder, which uses computer color-matching technology in the color simulation of RYJHS [61], is also produced by Kaiser Pharmaceutical Co. Both RYJHS and the placebo are prepared by mixing 13 grams of powder with 23 mL of water, which is then evenly spread onto a cotton cloth and covered with gauze for later use. The aforementioned procedures are all carried out by the same experienced technician, as given in Figure 3.

Figure 3. Preparation of Ru-Yi-Jin-Huang-Saan (RYJHS) plaster. (A) Spread the paste onto a cotton cloth and (B) cover with gauze.

Outcome Measurements

In this study, we will gather data from each participant including their gender, age, affected hand and dominant hand, Patient-Rated Wrist Evaluation (PRWE) score, C-reactive protein (CRP) levels, wrist ultrasound results, wrist x-ray images, and Dyshidrotic Eczema Area and Severity Index (DASI) score. Patients who have undergone Colles fracture surgery are required to be evaluated, and data will be collected before the trial, as well as 3 days and 6 days after topical medication application. The participant timetable of enrollment, assessments, and treatments is given in Table 2. The primary outcome is the PRWE score, which is used to assess wrist function recovery. The PRWE score, collected via a questionnaire, was developed in Canada for patients with wrist problems to express their pain and level of function [62]. The secondary outcomes are CRP level and wrist imaging records, which are used to demonstrate the degree of inflammation and swelling reduction. In addition, the DASI score is used to monitor any allergic or adverse events that may occur at the application site [63].

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Table 2. Timetable of enrollment and assessments.

Time	Screening	Baseline	Treatment 1 at hospital	Treatment 2 at home
	D_0[a]	D_1	D_3	D_6
Enrollment				
Inclusion or exclusion	✓	__[b]	—	—
Informed consent	✓	—	—	—
Demographic data	✓	—	—	—
Dominant and affected hand	—	✓	—	—
Medical history	✓	—	—	—
Randomization	—	✓	—	—
Assessment				
PRWE[c] score	—	✓	✓	✓
CRP[d]	—	✓	—	✓
Ultrasound	—	✓	✓	✓
X-ray	—	✓	—	✓
DASI[e] score	—	✓	✓	✓
Adverse events	—	Record at any time[f]	Record at any time	Record at any time

[a]D_x: number of days into the experiment.

[b]Not available.

[c]PRWE: Patient-Rated Wrist Evaluation.

[d]CRP: C-reactive protein.

[e]DASI: Dyshidrotic Eczema Area and Severity Index.

[f]If a patient has any side effects during the experiment, they must be recorded immediately.

Statistical Analysis

We will conduct statistical analyses using the SPSS software (version 22; IBM Corporation). Descriptive analyses will be performed on demographic data using frequencies and percentages to characterize the sample. Categorical variables will be compared using chi-square tests, while continuous variables will be compared using 2-tailed *t* tests. We will use repeated-measures ANOVA to determine if changes in wrist function (the dependent variable) are due to the interaction between the "type of treatment" (RYJHS) and "time" (measurement time). Multiple regression will be used to assess the impact of latent factors on primary outcomes (wrist function) and secondary outcomes (swelling and inflammation), adjusting for all possible covariates. Regression models will be performed in different outcome groups to compare the effects of different treatments (RYJHS intervention vs placebo).

Ethical Considerations

Approval for this trial (protocol ID 221006) was granted by the Institutional Review Board of Changhua Christian Hospital (CCH) on November 25, 2022, following the principles outlined in the Declaration of Helsinki. The study protocol has also been registered on ClinicalTrials.gov (NCT05638360). Individuals interested in participating will be required to provide written informed consent before the study's initiation. They will receive comprehensive information about the study, including procedures, potential benefits, and risks, excluding specific details regarding the RYJHS medication. Participants are free to withdraw at any time without any impact on their future medical care.

Data collected will be anonymized to protect participants' privacy, and all information will be kept confidential according to institutional data protection policies. No direct compensation will be provided to participants. The results of this research will be disseminated through publication in a peer-reviewed journal and presented at scientific conferences.

Results

The protocol was registered on ClinicalTrials.gov (NCT05638360) on December 6, 2022. Patient recruitment commenced in May 2023, with the first patient enrolled on June 15, 2023, and is projected to continue until April 30, 2025. As of December 2023, a total of 32 patients have been enrolled. Data analysis and report preparation are expected to be completed by the end of 2025.

Discussion

Expected Findings

The primary clinical treatments for Colles fractures, such as closed reduction, casting, percutaneous fixation, external fixation, and ORIF, generally yield positive functional outcomes.

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However, both percutaneous and external fixation have reported a higher risk of infection, while percutaneous fixation has been shown to have a higher rate of soft tissue injuries [64,65]. Besides, the ORIF procedure including local dissection, reduction, and the insertion of plates or screws results in a higher incidence of tendonitis, tendon irritation, or tendon rupture [66,67]. In Taiwan, the routine conventional treatment for Colles fracture is ORIF surgery. However, operations often result in soft-tissue and lymphatic vessel damage. As a result, patients may experience heat, pain, redness, and swelling after the operation. The discomfort disrupts their willingness to undergo rehabilitation. Prolonged swelling can also affect the range of motion, hand function, muscle strength, and outward appearance of these patients [68]. Therefore, resolving pain and swelling is a significant problem for patients with Colles fracture after ORIF surgery.

The most common method of relieving swelling is ice packing. Ice packing can reduce swelling, capillary permeability, and delivery of inflammatory substances [69]. Besides, ice packing can decrease nerve conduction velocity, increase pain threshold, and provide analgesia [70]. However, many studies have reported that ice packing not only delays wound healing but also has a higher risk of cold injury [71,72]. Besides, pain management is also a concern for patients who undergo ORIF surgery. Physicians often prescribe opioids; NSAIDs; or a combination of opioids, NSAIDs, and steroids for pain management [73]. However, due to the potential side effects, these medications raise concerns for patients with diabetes, hypertension, gastrointestinal disorders, impaired liver function, or impaired kidney function.

There are several limitations in this study design. First, during the patients' hospitalization, patients were assisted by nurses who ensured regular medication application. However, it may be challenging to confirm whether the patients continued to apply the medication on schedule after discharge. Therefore, it might be necessary to use phone reminders to engage caregivers in assisting with regular medication application. Second, theoretically, the closer the topical medication is applied to the lesion, the more effective it is likely to be. However, due to concerns about postsurgical wound infections, the application of topical medication needs to be avoided on the site of surgical incision. Therefore, for the purpose of this experiment, only the uninjured area on the back of the wrist can be selected for topical medication application. Finally, the inclusion criteria for the trial of Colles fracture did not encompass comminuted fractures; thus, the efficacy of RYJHS may not be evaluated in patients with severe Colles fractures.

This study represents the first randomized, double-blind, placebo-controlled trial to investigate the efficacy of RYJHS for postoperative Colles fractures. RYJHS, with its natural ingredients known for anti-inflammatory and antibacterial properties, could serve as a noninvasive adjunctive therapy to reduce postoperative complications and enhance functional recovery. Its application aligns with patients' increasing interest in integrative medicine options that minimize reliance on pharmaceuticals. Future directions include exploring RYJHS's active ingredients, assessing formulation efficiency, and developing a more accessible application method, which may strengthen RYJHS's role as an adjunctive treatment for Colles fractures.

Conclusion

This randomized, double-blind, placebo-controlled trial aims to provide robust evidence of the efficacy and safety of RYJHS as a topical adjunctive treatment for postsurgical Colles fractures. With the potential to reduce inflammation and aid functional recovery, RYJHS could offer an alternative, nonpharmaceutical option for managing postoperative complications in patients with Colles fractures.

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Data Availability

Since this protocol does not contain any data, it will be provided after analysis and published in a journal upon trial completion. Data can be made available upon the author's request.

Authors' Contributions

Lien-Cheng Lin contributed to conceptualization, validation, visualization, writing-original draft and steering the primary author. WHW handled resources and writing–review and editing. WKC performed methodology and formal analysis. JLG assisted with data curation and project administration. RCY handled investigation and software. PCH and Lun-Chien Lo contributed to funding acquisition, supervision, and writing–review and editing.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 169 KB - resprot_v14i1e56849_app1.pdf]

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Abbreviations

CRP: C-reactive protein
CONSORT: Consolidated Standards of Reporting Trials
DASI: Dyshidrotic Eczema Area and Severity Index
NSAID: nonsteroidal anti-inflammatory drug
ORIF: open reduction and internal fixation
PRWE: Patient-Rated Wrist Evaluation
RYJHS: Ru-Yi-Jin-Huang-Saan
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TCM: traditional Chinese medicine

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Protocol

Novel Versus Conventional Sequencing of β-Blockers, Sodium/Glucose Cotransportor 2 Inhibitors, Angiotensin Receptor-Neprilysin Inhibitors, and Mineralocorticoid Receptor Antagonists in Stable Patients With Heart Failure With Reduced Ejection Fraction (NovCon Sequencing Study): Protocol for a Randomized Controlled Trial

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Abstract

Background: Chronic heart failure has high morbidity and mortality, with approximately half of the patients dying within 5 years of diagnosis. Recent additions to the armamentarium of anti–heart failure therapies include angiotensin receptor-neprilysin inhibitors (ARNIs) and sodium/glucose cotransporter 2 inhibitors (SGLT2is). Both classes have demonstrated mortality and morbidity benefits. Although these new therapies have morbidity and mortality benefits, it is not known whether rapid initiation is beneficial when compared with the conventional, slower-stepped approach. Many clinicians have been taught that starting with low-dose therapies and gradually increasing the dose is a safe way of intensifying treatment regimens. Pharmacologically, it is rational to use a combination of drugs that target multiple pathological mechanisms, as there is potential synergism and better therapeutic outcomes. Theoretically, the quicker the right combinations are used, the more likely the beneficial effects will be experienced. However, rapid up-titration must be balanced with patient safety and tolerability.

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Objective: This study aims to determine if early addition of ARNIs, SGLT2is, β-blockers, and mineralocorticoid receptor antagonists (within 4 weeks), when compared with the same therapies initiated slower (within 6 months), will reduce all-cause mortality and hospitalizations for heart failure in patients with stable heart failure with reduced ejection fraction.

Methods: This is a single-center, randomized controlled, double-arm, assessor-blinded, active control, and pragmatic clinical trial. Adults with stable heart failure with reduced ejection fraction and idiopathic dilated cardiomyopathy will be randomized to conventional sequencing (the control arm; over 6 months) of anti–heart failure therapies, and a second arm will receive rapid sequencing (over 4 weeks). Study participants will be followed for 5 years to assess the safety, efficacy, and tolerability of the 2 types of sequencing. Posttrial access and care will be provided to all study participants throughout their lifespan.

Results: We are currently in the process of obtaining ethical clearance and funding.

Conclusions: We envisage that this study will help support evidence-based medicine and inform clinical practice guidelines on the optimal rate of sequencing of anti–heart failure therapies. A third placebo arm was considered, but costs would be too much and not providing study participants with therapies with known morbidity and mortality benefits may be unethical, in our opinion. Given the post–COVID-19 economic downturn and posttrial access to interventions, a major challenge will be acquiring funding for this study.

International Registered Report Identifier (IRRID): PRR1-10.2196/44027

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KEYWORDS

heart failure; SGLT2i; sodium/glucose cotransporter 2 inhibitors; ARNi; angiotensin receptor-neprilysin inhibitors; HFrEF; heart failure with reduced ejection fraction; idiopathic dilated cardiomyopathy; heart; chronic heart failure; patient; control; clinical; adult; cardiomyopathy; therapy

Introduction

Background

The current management of heart failure with reduced ejection fraction (HFrEF) has been revolutionized by the emergence of novel classes of drugs, namely, angiotensin receptor-neprilysin inhibitors (ARNIs) and sodium/glucose cotransporter 2 inhibitors (SGLT2is) [1,2]. With landmark clinical trials [3-6] demonstrating the efficacy of the latter drugs, there has been a paradigm shift in initiating and sequencing optimal anti–heart failure therapy and a concomitant reevaluation of the evidence base that guides conventional heart failure management. The American Heart Association heart failure guideline supports the rapid titration of guideline-based therapies every 1-2 weeks, with the goal of achieving target doses [7]. However, the European Society of Cardiology does not contain a timeline for the initiation of guideline-based heart failure therapy [8]. Pharmacologically, it is rational to use a combination of drugs that target multiple pathological mechanisms, as there is potential synergism and better therapeutic outcomes. Theoretically, the quicker the right combinations are used, the more likely the beneficial effects will be experienced. However, rapid up-titration must be balanced with patient safety and tolerability.

Sacubitril and valsartan, β-blockers, mineralocorticoid receptor antagonists (MRAs), and SGLT2is are disease-modifying agents that are used as combination therapy and are now regarded as a foundational therapy for HFrEF [1,2]. The conventional approach to initiating and optimizing HFrEF therapy reflects the sequence in which drugs were developed and trialed over the past 40 years [1]. Clinicians initiate therapy with an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, followed by a β-blocker, then an MRA, then a neprilysin inhibitor, and, finally, an SGLT2i. Each drug required up-titration to the target dose, or the maximally tolerated dose, before initiating another class of drug, with a treatment period usually spanning >6 months [1].

This approach is limited by several clinical misconceptions and assumptions: first, the most efficacious anti–heart failure therapies were developed first. The counterargument is exemplified by the fact that digitalis has been used in clinical practice for 200 years, yet it is no longer considered a key therapeutic agent. Second, drug efficacy is only achieved at maximum target doses [1]. However, studies have demonstrated morbidity and mortality reduction with the use of low-dose anti–heart failure therapy in HFrEF, with maximum target doses adding only a smaller clinical benefit. Third, the efficacy and safety of individual anti–heart failure drug class were assessed in clinical trials that required patients to be receiving all background therapy at target doses. However, most trials were conducted with patients receiving subtarget doses of anti–heart failure therapy [2].

Initiating drugs over a 6-month period is undesirable for several reasons. Practically, target doses of anti–heart failure therapy are infrequently achieved due to patient factors (nonadherence, perceived adverse effects, and costs), drug factors (adverse effects and frequency of dosing), physician factors (clinical inertia and limited time), inadequate patient follow-up, and a lack of perceived benefit of higher drug doses. Furthermore, there is a strong evidence base suggesting that the use of each of the foundation drugs has demonstrated morbidity and mortality reduction within 30 days of therapy initiation [1,2,9].

The aim of this study is to determine if early addition of ARNIs, SGLT2is, β-blockers, and MRAs (within 4 weeks), when compared with the same therapies initiated slower (within 6 months), will reduce all-cause mortality and hospitalizations for heart failure in patients with stable HFrEF.

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Rationale

The use of ARNIs and SGLT2is in low- to middle-income country settings is limited by high cost and accessibility. Despite the strong body of evidence supporting the safety and efficacy of ARNIs and SGLT2is, these agents are not yet included in the South African Essential Drug List. ARNIs and SGLT2is are available to private funders, yet access is limited as costs are only partially reimbursed by medical insurance schemes. Furthermore, SGLT2is have not yet been approved for heart failure by the South African Health Products Regulatory Authority, and use within clinical practice is predominantly off-label. Donations by the pharmaceutical industry have enabled limited access to ARNIs and SGLT2is in the public sector.

The challenge in this regard is maximizing access and rationalizing the use of ARNIs and SGLT2is while canvassing for widespread cost-effective rollout in the public sector.

The data on ARNIs and SGLT2is from high-income country settings suggest that morbidity and mortality reduction is achieved early in the clinical presentation of heart failure [1,2]. There, however, remains a paucity of data on the safety and efficacy of these drugs in sub-Saharan Africa.

Within sub-Saharan Africa, the main driver of heart failure remains hypertension, with ischemic heart disease emerging as a key etiology. There, however, is a growing cohort of young patients with idiopathic dilated cardiomyopathy with HFrEF who are often suboptimally medically treated with minimum prospects of receiving heart transplants. In our opinion, such a group of patients would ideally benefit from ARNIs and SGLT2is. Data from key clinical trials have demonstrated the use of ARNIs as de novo therapy in patients presenting with heart failure [3,10,11]. The latter trials have argued against the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers upfront with a transition phase to ARNI therapy, as there would be merely a delay in using the most effective therapy with a concomitant risk of sudden cardiac death.

The rapid initiation of anti–heart failure therapy described above seems rational in a high-income country setting where drug monitoring and assessment of adverse reactions are facilitated by the ease and rapidity of access to health care facilities [1,2]. However, in low- to middle-income country settings, the infrequent and irregular access to health care facilities limits instituting the rapid initiation algorithm for heart failure therapy. Furthermore, there is a lack of robust data and randomized controlled trials comparing rapid initiation versus a slower, phased initiation of heart failure therapy [1].

Study Objectives

Primary Objective

The primary efficacy end point is the composite end point of all-cause mortality and hospitalization for heart failure.

Secondary Objectives

Secondary end points include death from cardiovascular causes (eg, cardiogenic shock, myocardial infarction, tachycardia, or brady-arrythmia), improvement in the 6-minute walk test, improvement in the New York Heart Association functional class, improvement in symptoms as per the Kansas City Cardiomyopathy Questionnaire, trans-esophageal echo-determined ejection fraction (chamber dilatation, left ventricular systolic function, global longitudinal strain, and speckle tracking), and N-terminal prohormone of brain natriuretic peptide levels. Adverse drug reactions will also be collected and analyzed.

Definitions

Heart Failure

Heart failure is defined as a “clinical syndrome consisting of cardinal symptoms (eg, breathlessness, ankle swelling, and fatigue) that may be accompanied by signs (eg, elevated jugular venous pressure, pulmonary crackles, and peripheral edema). It is due to a structural and/or functional abnormality of the heart that results in elevated intracardiac pressures and/or inadequate cardiac output at rest and/or during exercise” [7].

Reduced Left Ventricular Ejection Fraction

Reduced left ventricular ejection fraction is defined as an ejection fraction ≤40%, that is, those with a significant reduction in left ventricular systolic function [8].

Methods

Proposed Novel and Rapid Sequencing

The proposed algorithm for initiation of anti–heart failure therapy comprises of 3 steps once clinical euvolemia has been achieved with diuresis [2].

Step 1 is the concurrent initiation of treatment with a β-blocker and an SGLT2i. β-Blockers are pertinent in the treatment of HFrEF, especially in the context of reducing sudden cardiac death. Evidence has demonstrated reduced hospitalization for heart failure with the use of SGLT2is. The early diuretic effect of SGLT2is may attenuate the early risk of worsening heart failure when β-blockers are initiated [2].

Step 2 comprises of the addition of an ARNI (sacubitril and valsartan) within 1-2 weeks of step 1. The presence of hypotension (systolic blood pressure <100 mm Hg) warrants evaluation of blood response with an angiotensin receptor blocker before switching to an ARNI [2].

Step 3 is the addition of an MRA, within 1-2 weeks of step 2, depending on the serum potassium and the presence and degree of renal impairment. ARNIs and SGLT2i may improve renal function and potassium homeostasis, thereby permitting the use of MRAs. In patients with hypotension, MRAs may be used as step 2 [2].

The above algorithm represents a generic approach and may be individualized to specific scenarios. Patients with decompensated heart failure are a subgroup that require greater caution when initiating anti–heart failure therapy. β-Blocker therapy should only be initiated in the hospital after discontinuation of intravenous therapy for several days and the patient is clinically euvolemic, defined as the absence of rales and ascites and the presence of minimal peripheral edema [2].

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In the appropriate patient, treatment with all 4 foundational treatments may be achieved within 4 weeks, with subsequent dose up-titration. This strategy increases the probability that highly effective therapies will be implemented in a manner that reduces mortality and hospitalizations and enhances the tolerability of subsequently administered treatments [1]. Figure 1 shows the proposed study flow diagram, which contains the novel and conventional sequencing approaches. A key difference is the rate at which therapies are added, with the novel sequence arm having patients on all the efficacious therapies initiated within 4 weeks.

Figure 1. Study flow diagram. ACE: angiotensin-converting enzyme; ARB: angiotensin receptor blockers; ARNI: angiotensin receptor-neprilysin inhibitors; HCP: health care professional; MRA: mineralocorticoid receptor antagonists; SGLT2i: sodium/glucose cotransporter 2 inhibitors.

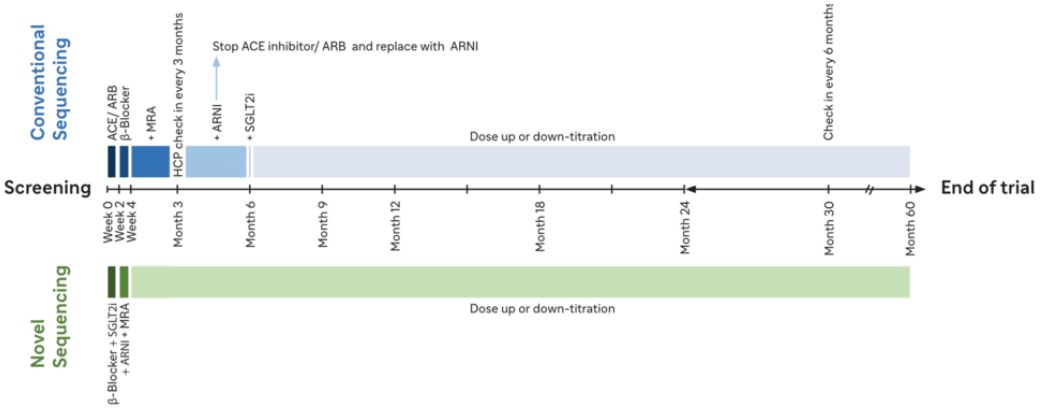

Study Design

This is a prospective, double-arm, randomized, assessor-blinded, and pragmatic clinical trial. The study will take place at a single site, that is, Tygerberg Hospital, Western Cape, South Africa.

Selection of Patients

Study participants will be adults with idiopathic dilated cardiomyopathy who consent to participate in the study. Patients will be free to withdraw at any time. The recruitment period will be 1 year.

Study participants will be randomized to the study arms by using a computer-generated randomization sequence.

Inclusion, exclusion, and withdrawal criteria are listed in Textbox 1.

Textbox 1. Selection criteria (inclusion, exclusion, and withdrawal criteria).

Inclusion criteria

- All patients aged <18 or >50 years who fulfill the clinical criteria for idiopathic dilated cardiomyopathy with reduced ejection fraction
- New York Heart Association Functional class II-IV

Exclusion criteria

- Aged >18 years or <50 years
- Unable or unwilling to provide informed consent to undergo any of the recommended investigations or to participate in the study
- Acute coronary syndrome, bypass graft surgery or other major cardiac surgery, stroke, or transient ischemic attack ≤90 days from visit 1
- Acute decompensated heart failure
- Systolic blood pressure ≥180 mm Hg or <100 mm Hg
- Estimated glomerular filtration rate <30 mL/min/1.73 m^2
- Serum potassium level >5.4 mmol/L
- History of angioedema

Withdrawal criteria

- Patient decision to leave the study
- Adverse drug reactions

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Selection of Investigators

This study will be conducted at a tertiary-level public hospital's department of cardiology. Investigators will be the authors of this publication and other staff based at Tygerberg Hospital.

Statistical Considerations

Sample Size

We determined that a target number of 248 primary outcome events would provide a power of 80% to detect a 30% lower relative risk of the primary outcome in the novel sequencing arm than in the conventional sequencing arm at a 2-sided α level of .05. Assuming an incidence of the primary outcome of at least 50% over 5 years in the conventional sequencing arm and a dropout of 10% per arm, we established a planned enrolment of 584 patients (292 per study arm).

Analysis Population

The analysis population will include all study participants included in the study. This is an intention-to-treat analysis and even participants who have withdrawn, or dropped out, from the study after randomization will have their data analyzed.

Statistical Methods

Patient demographic and clinical profiles will be described using the statistical software SAS (version 9.4; SAS Institute). Continuous variables will be expressed as an absolute number, with associated percentage, mean, SD, median, and range where applicable. Clinical assessment of response to heart failure therapy will be performed using the Kansas City Cardiomyopathy Questionnaire, New York Heart Association functional classification, 6-minute walk distance, and hospital admission for heart failure. Objective measures of therapy response will be ascertained by serial N-terminal prohormone of brain natriuretic peptide levels and 2D echocardiography. Echocardiographic features of response to therapy will be characterized according to left ventricular ejection fraction as determined by the Simpson biplane method, global longitudinal strain, and speckle tracking.

Associations between outcomes and indicator variables will be explored through logistic regression. Where appropriate, indicator variables and specific outcomes will be investigated individually through a univariate analysis. Where significant, variables will be entered into and controlled for in a Cox-proportional hazards regression model. Adjustment for confounding will be performed by a competing risks analysis and propensity score matching (Table 1).

Table 1. Statistical methods.

Outcome measures	Hypothesis	Measure	Time points	Analysis methods
Primary end points	The intervention will reduce the outcome from baseline to 5 years.	—[a]	—	—
All-cause mortality	Rapid sequencing of anti–heart failure therapy will reduce all-cause mortality.	All-cause mortality (binary)	End of trial	Cox proportional hazards regression
Hospitalization	Rapid sequencing of anti–heart failure therapy will reduce all-cause mortality.	Hospitalized for heart failure (binary)	End of trial	Cox proportional hazards regression
Secondary end points				
Deaths (from cardiovascular causes)	Intervention will reduce cardiovascular-related deaths	Cardiovascular mortality (binary)	End of trial	Chi-square test
6-minute walk test	Improvement in distance walked in 6-minutes	Distance in meters (continuous)	Baseline and end of trial	✓
NYHA[b] functional class	Improvement in dyspnea	Functional class 1, 2, 3, and 4 (ordinal)	Baseline and end of trial	✓
KCCQ[c]	Improvement in symptoms of heart failure	Questionnaire (ordinal)	Baseline and end of trial	✓
Trans-esophageal echo	Improvement in ejection fraction	Ejection fraction measured in percentage (%; continuous)	Baseline and end of trial	✓
NT-pro[d] and BNP[e] levels	Reduction in levels	Concentration units (pg/mL; continuous)	Baseline and end of trial	✓

[a]Not applicable.

[b]NYHA: New York Heart Association.

[c]KCCQ: Kansas City Cardiomyopathy Questionnaire.

[d]NT-pro: N-terminal prohormone.

[e]BNP: brain natriuretic peptide.

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Ethical Considerations

This study will be conducted in accordance with the principles laid down by the 18th World Medical Assembly [12]. Study participants' data will be deidentified of names and surnames and identifying information. An application for ethical approval will be submitted to the Stellenbosch University Research and Ethics Committee. The study will be performed in accordance with local regulations, including local data protection regulations and requisite hospital and Provincial Department of Health Approval. Posttrial access and care will be provided to all study participants, throughout their lifespan.

Results

We are currently in the process of generating funding. If funding is obtained, we will apply for ethical clearance and requisite permissions.

Discussion

Principal Findings

This study aims to determine if rapid sequencing of anti–heart failure drugs with proven morbidity and mortality benefits would be superior to slower titration of these therapies.

We chose a composite end point to reduce the sample size, as a larger sample size would result in greater costs and reduce the feasibility of the study. Given the high mortality and frequent hospitalizations for heart failure, we included both events in the combined primary efficacy endpoint.

Intuitively, it makes sense to ensure that the most efficacious heart failure therapies are initiated as soon as possible. Given that the therapies have varied modes of action, we hypothesize that if they are started together as soon as possible, they would have greater benefits than starting them later. Combination therapies are likely to target different pathophysiological aspects of heart failure and thus improve clinical outcomes. Issues with rapid initiation may potentially include hypotension and other adverse effects. We will guard against hypotensive events by starting with the lowest possible dose and stopping the drug if the patient becomes hemodynamically unstable. Furthermore, study participants are required to be euvolemic before rapid sequencing so that we do not worsen patients' heart failure and thus limit hemodynamic instability and decompensated heart failure. It is a standard clinical practice to ensure euvolemia before titration of anti–heart failure therapies. Euvolemia is usually achieved by loop diuretics [8].

We chose a relatively young group of patients so that underlying issues such as ischemic heart disease are less probable and would not serve as confounders. Furthermore, this group of patients may benefit from the increased life expectancy as compared with the older group.

The public health sector in South Africa has resource constraints. Often, there are not enough clinicians to adequately manage the patients. Thus, doing trials in this setting is challenging. However, given the proven safety and efficacy of ARNIs, SGLT2is, and MRAs, and their widespread use in high-income countries, we envisage limited problems. Furthermore, making these novel therapies available to a vulnerable population would serve as a motivation for clinicians who work in this setting. The setting is a teaching and training facility, and having exposure to these novel therapies will grow the expertise and skills of health care practitioners. Furthermore, we envisage reducing the complexity of the study by using a pragmatic study design so that we can integrate the trial into routine clinical practice in the department of cardiology. This will reduce the administration burden while also resulting in the collection of safety, efficacy, and tolerability data. We feel that the trial would not add to the administrative burden of the clinicians, as we will not ask them to do any work beyond what they usually do in the clinic. Furthermore, a separate designated individual will collect and analyze the data, so that clinicians will not be burdened with this task and not impinge on their demanding clinical work.

Posttrial access and posttrial care are contentious issues [13]. In this study, we plan to provide both posttrial access and posttrial care because it is, in our opinion, ethically justified. Given that the newer therapies are efficacious, safe, and tolerable, it would be unkind to stop the therapies after the trial is completed, as the study participants would not be able to procure the therapy privately because of their limited financial resources. The provision of posttrial care would also increase the cost of the study, but we will continue to provide posttrial care in our cardiology clinic at no cost to the study participants.

We hope to acquire funding from the manufacturers of ARNIs, SGLT2is, β-blockers, and MRAs, as the data generated from this study have the potential to inform clinical practice guidelines. Given the high costs of doing such trials, we hope companies will assist if they are only providing the drug and not covering the other clinical trial costs like investigator fees, protocol development, manuscript writing, and statistical analysis, and so on. The study has dual objectives of generating of evidence while also providing patients with access to highly efficacious and premium therapies for heart failure.

Given that both study groups will receive the same therapies, we do not pitch drugs head-to-head, as we feel that the combination of drugs with proven mortality and morbidity data would be most likely to have synergistic effects and further reduce morbidity and mortality. This approach is also more likely to generate funding as all companies can contribute to financing the study, not with the risk of their products being negatively affected by head-to-head trials that show one drug being superior to another drug.

We have tried to create a "win-win" situation by generating data to inform clinical practice guidelines and providing access to novel therapies in resource-limited settings. The research can help with master's and PhD degrees, given the rich dataset generated.

Limitations

The study is proposed to use one study site in the Western Cape of South Africa, which may not be reflective of the demographics of the South African population. Due to the nature of the study and means of intervention, implementation of a

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placebo-controlled arm will not be possible but is nonetheless cited as a limitation.

Conclusions

Recent additions to the armamentarium of anti–heart failure therapies such as ARNIs and SGLT2is have demonstrated morbidity and mortality benefits. Earlier use of such therapy within patients with stable HFrEF may impact patient outcomes. This study will provide important data to support evidence-based medicine and will help inform clinical practice guidelines on the optimal rate of sequencing of anti–heart failure therapies.

Acknowledgments

We are grateful to Novartis for paying the article processing fee.

Data Availability

The dataset will be made available upon written request.

Conflicts of Interest

PN was sponsored by Novartis for online attendance at European Society of Cardiology (ESC) Congress 2022 and received drug sponsor for a phase IV clinical trial from Sandoz, a subsidiary of Novartis. PN was previously employed as a Medical Manager by Boehringer and was responsible for preregistration medical activities related to empagliflozin. KH was previously employed as Medical Director by Boehringer and was responsible for preregistration medical activities related to empagliflozin.

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Abbreviations

ARNI: angiotensin receptor-neprilysin inhibitor
HFrEF: heart failure with reduced ejection fraction
MRA: mineralocorticoid receptor antagonist
SGLT2i: sodium/glucose cotransporter 2 inhibitor

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Protocol

Comparative Evaluation of Effectiveness of Standard of Care Alone and in Combination With Homoeopathic Treatment in COVID-19–Related Rhino-Orbito-Cerebral Mucormycosis (ROCM): Protocol for a Single Blind, Randomized Controlled Trial

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Abstract

Background: Rhino-orbital-cerebral mucormycosis (ROCM) is the most common (45%-74%) mucormycosis in India. With contemporary medical care, ROCM has a mortality rate of 40%-50% and 70% of survivors are left with residual defects. Recently, several cases of mucormycosis in people with COVID-19 have been increasingly reported worldwide, from India, due to immune dysregulation caused by SARS-CoV-2. To reduce the high mortality rate and residual defect in most survivors under the guidelines of the Ministry of AYUSH, the Government of India recommended homoeopathy as an add-on therapy to maximize the effectiveness of standard treatment in conventional therapy.

Objective: This study aimed to evaluate the role of existing homoeopathic treatment as an adjuvant therapy in patients with COVID-19–related ROCM and enhancing the survival of the patients hospitalized due to COVID-19 infection and to access the initial treatment response and duration required for significant or complete recovery in patients receiving adjuvant treatment.

Methods: This superiority, randomized controlled clinical trial would include two parallel comparator groups A and B. Group A would be the experimental group and would receive homoeopathic treatment along with the standard line of treatment as per investigational medicinal product (IMP) and group B would be the control arm and would receive standard line of treatment as per IMP along with identical placebo. Allocation would be 1:1 through randomization. Based on the inclusion and exclusion criteria, 36 participants per arm would be screened. Participants would be assessed clinically twice a day and magnetic resonance imagery or endoscopy cum-biopsy would be assessed on days 1, 14, and 28. Laboratory investigations may vary as per demand of disease conditions.

Results: In India, the COVID-19 pandemic, particularly during the second wave, resulted in a surge of mucormycosis cases among patients with COVID-19. At the time this protocol was being developed, there was a significant spike in mucormycosis cases in India, particularly in Mumbai (June 2021). However, by the time the Central Council for Research in Homoeopathy obtained the necessary approvals and ethical clearance for the study, the incidence of mucormycosis had drastically declined (September 2021). As a result, the study was not initiated and registered. The authors feel it is their ethical responsibility to share the reviewed protocol with the medical community as a reference for future work.

Conclusions: This study aims to evaluate the role of existing homoeopathic medicines as an adjuvant therapy in managing COVID-19–related ROCM, potentially contributing to the use of homoeopathy as an evidence-based medical approach. The protocol can also serve as a valuable resource for clinicians and researchers addressing mucormycosis cases unrelated to COVID-19,

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particularly in immunocompromised patients. It would help ensure preparedness, whether or not sufficient evidence is available, in the event of a future health emergency.

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KEYWORDS

Rhino-orbital-cerebral mucormycosis, randomized controlled trial, homoeopathy, fungus, CE-MRI PNS mucormycosis; India; medical care; mortality rate; conventional therapy; ethical; mortality; survival; recovery; homoeopathic medicines; management

Introduction

Immune dysregulation induced by SARS-CoV-2, along with the extensive use of glucocorticoids and immunomodulatory drugs like tocilizumab, has heightened the risk of secondary bacterial and fungal infections in patients with COVID-19 [1-3]. Recently in past, India experienced a significant surge in mucormycosis cases, caused by a group of molds known as mucoromycetes, commonly found in the environment. These molds release spores that are easily aerosolized and dispersed [4]. The most frequent genera causing infections in humans include *Rhizopus* and *Mucor* species, along with others like *Apophysomyces*, *Rhizomucor*, *Cunninghamella*, *Lichtheimia*, *Cokeromyces*, and *Saksenaea* [5]. *Rhizopus oryzae* is the most prevalent species, responsible for nearly 60% of human mucormycosis cases and about 90% of the rhino-orbital-cerebral mucormycosis (ROCM) form [6]. The primary mode of infection is through the inhalation of fungal spores.

Both *Aspergillus* and *Candida* have been identified as the primary fungal pathogens involved in co-infections among patients with COVID-19 [7]. Prolonged hospitalization, with or without mechanical ventilation, is also a contributing factor to these types of fungal infections [8]. Studies suggested that COVID-19 infection is associated with the destruction of β-cell of the pancreas [9,10]. A history of corticosteroid use for treating COVID-19 was found in 76.3% of mucormycosis cases, with remdesivir use in 20.6%, and tocilizumab in 4.1%. The most commonly affected organs were the nose and sinuses (88.9%), followed by rhino-orbital involvement (56.7%), and the ROCM type (22.2%) [8]. Uncontrolled hyperglycemia and the onset of diabetic ketoacidosis are often linked to corticosteroid use. COVID-19 infection can lead to endotheliitis, endothelial damage, thrombosis, lymphopenia, and reduced CD4+ and CD8+ lymphocyte counts, which increase susceptibility to secondary or opportunistic fungal infections [8]. Mucormycetes can invade blood vessels and spread to the brain and other organs through the bloodstream, leading to disseminated infections [11]. Diagnosis of ROCM should include early radiological imaging with a magnetic resonance imaging (MRI) of the paranasal sinuses (PNSs) and the brain with contrast, and confirmation can be made through fungal staining or culture from properly collected specimens [12].

ROCM is the most common form of mucormycosis in India, accounting for 45%-74% of cases. Complications of ROCM include blindness [13] cerebral infarction, cerebral abscess, cavernous sinus thrombosis, and intracranial hemorrhages [14]. The disease progresses rapidly and has a poor prognosis if not diagnosed early. Early detection, aggressive management of the underlying condition, surgical debridement, systemic and local antifungal treatments, and hyperbaric oxygen therapy significantly improve prognosis and survival rate [15]. The standard treatment for mucormycosis involves correcting diabetic ketoacidosis or other metabolic disturbances, daily irrigation and packing of the affected orbital and paranasal areas with amphotericin B, along with intravenous amphotericin B therapy [16].

Staging of ROCM

Stage 1 of ROCM has involvement of the nasal mucosa and subdivision 1a is limited to the middle turbinate, 1b involves inferior turbinate and ostium of the nasolacrimal duct, 1c involves nasal septum, and 1d involves bilateral nasal mucosal involvement.

Stage 2 of ROCM has involvement of paranasal sinuses and subdivision 2a involves only 1 sinus, 2b involves 2 ipsilateral sinuses, 2c involves more than 2 ipsilateral sinuses and palate or oral cavity and 2d has involvement of bilateral paranasal sinuses, the zygoma and mandible [17].

Despite all efforts in the conventional line of treatment, ROCM has a mortality rate of 40%-50% and 70% of survivors are left with residual defects [18]. To reduce the high mortality rate and residual defect in most of the survivors, Ministry of AYUSH, Government of India [19] has recommended homoeopathy as an add-on therapy to maximize the effectiveness of the standard line of treatment in conventional therapy. It is a well-established fact that homoeopathy is helpful as an adjuvant therapy along with the standard line of treatment for treating various disease conditions where conventional medicine has its own limitations [20].

In various research studies undertaken on various fungi, in vitro models showed that homoeopathy medicine could prevent the growth of the fungus. Prajapati et al [21] showed that showed that homoeopathic drugs, namely *Zingiber officinale*, *Holarrhena antidysenterica*, *Terminalia chebula*, *Allium cepa*, *Caesalpinia bonducella*, *Eucalyptus globulus*, *Ruta graveolens*, and *Thuja occidentalis* have significant antifungal activity against human pathogenic fungi *Aspergillus niger* whereas Gupta and Garg [22] revealed that homoeopathic medicines Mezereum 1000 potency showed maximum inhibition of growth of Candida albicans.

Hence, this study is intended to evaluate the role of homoeopathy as an adjuvant therapy in COVID-19–related mucormycosis and to enhance the survival of the hospitalized patients with ROCM. Due to the decline in COVID-19 cases in September 2021, the period when approvals could be sought,

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the study was deemed unfeasible and had to be canceled. The authors consider it their ethical responsibility to share this reviewed protocol with the professional community as a resource for further research applicable to mucormycosis cases not specifically linked to COVID-19 infection. This initiative aims to ensure preparedness with evidence, regardless of its availability if similar emergencies arise in the future. Thus, we present this protocol to the community in hopes it would be used for immunocompromised or diabetes-related mucormycosis in individuals.

Objectives

Primary Objective

The primary objective is to evaluate the role of adjuvant homoeopathy in addition to the standard treatment of patients with COVID-19–related ROCM through standard parameters in respective conditions.

Secondary Objective

This study also aims to enhance the survival of the patients hospitalized due to COVID-19–related mucormycosis.

Methods

Study Design

The study is a superiority, single-blind, randomized controlled trial (RCT) with 2 groups: group A (experimental) and group B (control). Group A would receive homeopathic treatment in addition to the standard treatment for COVID-19–associated mucormycosis, as recommended by the Investigational Medicinal Product or Fungal Infections Study Forum (IMP or FISF; Multimedia Appendix 1) [23]. Group B would receive conventional treatment per the same guidelines, along with an identical placebo. Participants would be randomly assigned to either group in a 1:1 ratio using a computerized random number generator.

The trial would be planned to be conducted in a hospital setting, with informed consent obtained from patients admitted for the treatment of COVID-19–related mucormycosis. The study duration is 3 months, with an extension if needed to complete the required sample size. Patients with stage 1 or 2 COVID-19–related ROCM would be enrolled and randomized based on the trial's inclusion criteria. Both groups would receive the same auxiliary care, with dose repetition following the same pattern in both groups.

Participants would be assessed clinically twice a day, and MRI or endoscopy with biopsy would be performed on days 1, 14, and 28, with variations depending on the disease progression. The study protocol adheres to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 guidelines, as illustrated in Figure 1.

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Figure 1. Flow diagram of study design. CEMRI PNS: Contrast-Enhanced Magnetic Resonance Imaging of Para Nasal sinus; CBC: complete blood count; CT: computed tomography; ESR: erythrocyte sedimentation rate; HbA1c: hemoglobin A1c; IMP: investigational medicinal product; KFT: kidney function test; KOH: potassium hydroxide; LFT: liver function test; PPBS: postprandial blood sugar; ROCM: rhino-orbital-cerebral mucormycosis.

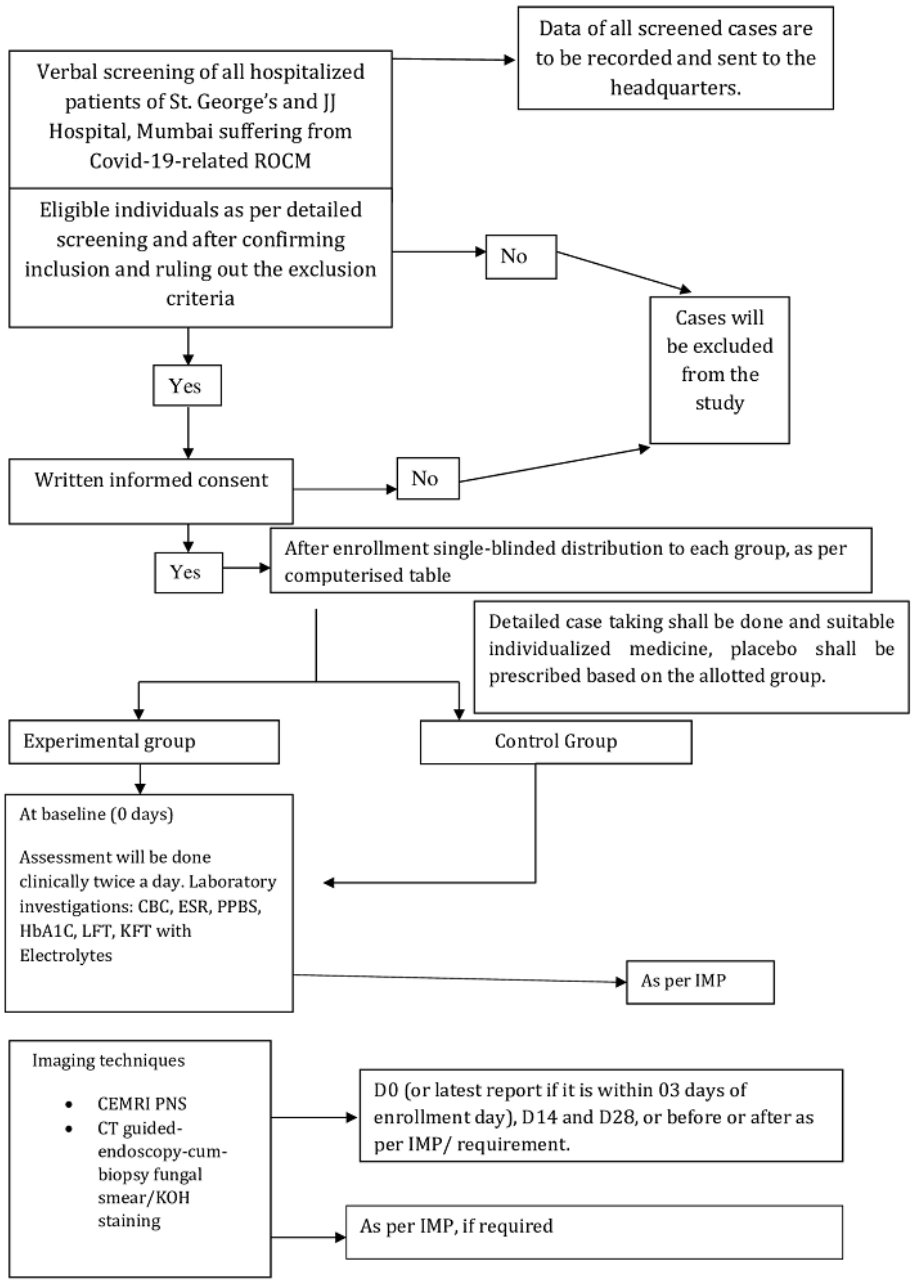

Study Setting and Duration

This RCT was planned for the St. George's and JJ Hospital, Mumbai, which was the hospitals of Sir JJ Group of hospitals, and had a common Institutional Ethics Committee. An informed consent of the patients admitted in the inpatient department for treatment of COVID-19–related mucormycosis planned to be taken before inclusion. Duration of the study would be 3 months and maybe extended if the desired sample size is not achieved.

Eligibility Criteria

The eligibility criteria are shown in Textbox 1.

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Textbox 1. Eligibility criteria.

Inclusion criteria

- Both male and female participants aged 18 years or older and confirmed cases of COVID-19–related rhino-orbital-cerebral mucormycosis (ROCM) diagnosed as stage 1 and stage 2 (Multimedia Appendix 2) by potassium hydroxide staining (KOH staining) or magnetic resonance imaging (MRI) or biopsy would be included in the study. MRI would show Mucosal thickening with T2 hypointense components at T2W images, nonenhancement of involved mucosa or soft tissue at postcontrast T1W images, Marrow edema and enhancement of adjacent bones and skull base at fat-saturated T2W and postcontrast T1W image [24]. A hyperintense lesion extending from paranasal sinus along orbital apex into intracranial structures and narrowing or slow flow in the ipsilateral internal carotid artery in the vicinity of mucor invasion seen in T2W [25]. KOH staining or microscopy and biopsy of affected area would show nonseptate or pauci-septate, ribbon-like hyphae (at least 6-16 µm wide), and vessel occlusion [26].

Exclusion criteria

- ROCM at stage 3 and 4 (Multimedia Appendix 2) presenting with bony erosion, cerebral vascular invasion, invasion into the cranium, orbital apex or cribriform plate of the ethmoid bone, cavernous sinus (II-VI cranial nerve palsies) and diagnosed cases of pulmonary, cutaneous, gastrointestinal, advanced disseminated mucormycosis, pregnant and lactating women, cases where progression to death is inevitable and imminent within the next 24 hours according to the clinical team irrespective of the provision of treatments would be excluded from the study.

Intervention

Preparation of Study Intervention and Placebo Materials

Homoeopathic medicines to be used in the trial are known pharmacopeial preparations. As no new remedy is proposed to be investigated, there is no potential risk due to intervention. Intervention medicines would be administered orally. The medicine would be repeated depending on the potency and complaints of the patient in accordance with the principles of homoeopathy. Once the improvement sets in, placebo would be continued till the main medicine continues to act. The placebo (30 CH) would be identically prepared using only purified water, and pharmaceutical-grade ethanol, without glycerin or any medicinal active component.

Details of Intervention

The intervention would be a homoeopathic medicine which would be given as pills medicated with an ultradiluted homeopathic remedy. As a basic rule, increased dilution is proportionate to increased therapeutic power and no side effects. Owing to the nanoparticle nature of the drugs particles in serial dilutions above the Avogadro constant [27], homoeopathic intervention does not have any safety issue since inception. As the medicines used for this trial are already in use for decades and therefore, practical safety of medicines is well-established, this trial would be phase 3 trial and further validate the efficacy of these medicines, specifically in ROCM.

Through patient information sheet, patient would be duly informed about equal chances of receiving placebo or homoeopathic medicine, depending on the group she or he's allotted, and then consent would be taken. Furthermore, patients would be getting standard care of conventional medicine in both groups, and, therefore, would not be at risk. A detailed history and examination would be gathered from the already available information of the patient in the admission records at hospital. The patients randomized into experimental group would be interrogated by the homoeopathic physician only for the additional information required from homoeopathy perspective. Daily recording of the administered dose would be recorded and also captured in the case record form developed by the homoeopathy team, which would be having content other than, and in addition to the standard form, which would be filled at the hospital. If there is any change in dosage or prescription of medications during the study period, that would be mentioned with reason in the prescription chart. If these medicines are stopped, that too would be recorded with reason.

The patients assigned to the placebo group would be given placebo in the form of similar looking homoeopathic pills of size 30, dispensed with the 30% V/V dispensing alcohol. The prescribed medicine would be changed if no change in the next scheduled laboratory investigations or patient reports to be clinically unwell, even after at least 3 doses of the prescribed medicine.

In either arm, no patient would be devoid of conventional management as per IMP at any given point of time. Till the end point of the study in hospitalized patients, if required to enquire about well-being of the patient, phone call may be done in both groups and it would be considered as a phone follow-up.

FISF recommendations on Treatment of COVID-19–associated mucormycosis [23] (Multimedia Appendix 1) would be followed for regime of medication under standard care of intervention, which includes 3-6 weeks of amphotericin B therapy, followed by consolidation therapy for 3-6 months, strict control of hyperglycemia, steroids for lifesaving purposes in patients with COVID-19; abuse or misuse or untimely use to be avoided, judicious immunomodulating drugs, surgical debridement of the infected tissues, and regular monitoring through clinical, radio-imaging, and microbiological assessment.

For Homeopathic Intervention

As the condition is immunocompromised, very acute and progressive in nature, the homoeopathic medicines would be recommended in low potency and in frequent repetition. Medicine will be repeated in the following instances (Textbox 2).

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Textbox 2. Condition where medicine would be repeated.

Repetition of medicine:

- If improvement stops, repeat the same medicine in the same potency.
- If no further amelioration occurs even after repeating the medicine in the same potency or improvement lasts for a very short period, give higher potency of the same medicine.
- If there is too short relief of symptoms (lasting for a few hours and diminishing further on subsequent repetition of the doses), reassess the case and observe.
- If the medicine remains appropriate after reassessment, it should be administered in a next higher potency.
- If no further amelioration occurs, reassess the case and prescribe the indicated remedy.
- If aggravation is quick, short, and strong with rapid improvement of the patient, discontinue the medicine and prescribe placebo.
- If the appearance of new symptoms is observed, and if the symptoms are not of a serious nature, wait till the new symptoms pass off. Then select another indicated remedy after reassessing the case.
- In case of serious symptoms, change the medicine and check for safety end point.

Withdrawal of a trial participant:

- If the patient worsens, and mucormycosis expands beyond the range of inclusion criteria.
- If the patient is in need of ventilator support.
- If the participant is unwilling to continue or turns noncompliant.

Outcome Measures

Primary Outcome

The following changes would be observed in MRI contrast:

1. Mucosal thickening with reduction in Transverse Relaxation time T2 hypointense components at T2-weighted (T2W) images.
2. Infiltration of mucosa/soft tissue at postcontrast T1-weighted (T1W) images.
3. Marrow edema and enhancement of adjacent bones and skull base at fat-saturated T2W and postcontrast T1W image.
4. Hyperintense lesion extending from paranasal sinus along orbital apex into intracranial structures and narrowing or slow flow in the ipsilateral internal carotid artery in the vicinity of mucor invasion seen in T2W.
5. Staging of Code Mucor as per Guidelines for the Diagnosis, Staging and Management of ROCM in the setting of COVID-19 pandemic [17]. The absence of stage 1 would be considered as cured and progression from stage 1 to stage 2 or stage 2 to stage 3 or 4 would be considered as worse outcome.

Secondary Outcomes

The median survival rate of the patients would be assessed in both the groups during hospitalization.

Participant Timeline

Each patient would be followed up for 28 days. Participant would be followed up every 4 hours, or sooner, as per the case and would be asked a few questions as per case recording form, before commencing the treatment. Participants would be requested to be available on phone for follow up by the doctor on day 14 and day 28, in case they are discharged from the hospital before day 14 of the illness.

The following variables would be clinically assessed in every follow up:

1. Nasal stuffiness
2. Nasal discharge
3. Foul smell
4. Epistaxis
5. Facial pain
6. Facial edema
7. Dental pain
8. Malaise
9. Fever

Sample Size

Based on the computation of sample size, literature, and expert opinions and assuming a type 1 error of 5% and type 2 error of 20% with a power of 80%, it was estimated that there would be 36 participants each in the intervention and control group, with a total of 72 participants. This could be escalated based on attrition due to loss in follow-up. If this loss to follow-up is considered at 25%, a total of 45 participants have to be enrolled in each group, with a total sample of 90 for the study.

Randomization and Blinding

The study participants were planned to be recruited from St. George's and JJ Hospital, Mumbai. The recruitment would be based on the inclusion criteria. The participants would be allocated to either intervention or placebo groups as per the randomization sequence generated by using GraphPad (GraphPad Software) by Dotmatics (Insightful Science) software. Coded or prenumbered identical containers would be used for allocation concealment. The principal investigator (PI) at Central Council for Research in Homoeopathy (CCRH) headquarters would be involved in the sequence generation process and allocation concealment procedure. The PI would label the interventions as per the randomization codes, which would be handed over to the site PIs. The site PIs would enroll

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participants and randomly assign participants to interventions. The only trial participants interventions would be blinded. To ensure the quality of blinding the packaging for both the interventions and placebo would be identical in odor, color, size, and taste. The unblinding would be done by the PI at CCRH headquarters at the end of the study. If severe adverse events would be reported by the participants during the trial, unblinding may be performed per Data and Safety Monitoring Board (DSMB) or ethical committee recommendations. The reason for urgent unblinding should be well-documented.

Screening and Enrollment

All the participants would be voluntarily invited to the study and then required to sign an informed consent form containing information on the regulatory authorities and the related procedures, including laboratory investigations and subsequent randomization after enrollment. Enrollment of the participants would be based on inclusion criteria. The hospital must maintain a log register that records all the details of the screened participants and the reasons for exclusion. After enrollment the participants would be randomized and allocated to the intervention or the placebo arm as per the generated randomization sequence using GraphPad by Dotmatics software.

Data Collection Methods

Considering the critical importance of COVID-19–related ROCM, data from the trial participants would be collected extensively. The following documents below would be developed and retained.

1. Case record form of COVID-19–related ROCM.
2. A database that stores the above information for each patient with the subsequent observations by the physician at every visit.
3. Reports of all laboratory investigations to help physicians understand efficacy of diagnostic tools or interventions.
4. All data pertaining to homoeopathy, like case taking, repertorization chart, and prescription decisions would be maintained.

Assessment and Data Analysis

Potassium hydroxide staining and Contrast-Enhanced Magnetic Resonance Imaging (CEMRI PNS) would be used for diagnosis and staging of ROCM. However, for assessment of the progress of the condition, following parameters would be evaluated on days 14 and 28:

1. CEMRI PNS impression
2. Code Mucor staging
3. Clinical assessment
4. Laboratory parameters

The participants would be assessed clinically twice a day and the laboratory parameters complete blood count, erythrocyte sedimentation rate, fasting blood sugar, postprandial blood sugar, hemoglobin A_{1c} levels, liver function test, and kidney function test with electrolytes would be assessed on days 0, 14, and 28. These tests would be repeated as many times as required as per Institutional Management Protocol, which is essentially based on FISF guidelines. However, the assessments would be done only on the fixed days, as mentioned above.

CEMRI PNS would also be done on day 1 (or latest report if it is within 03 days of enrolment day), day 14, and day 28, or before or after as per IMP or FISF requirement Multimedia Appendix 3.

Follow-Ups

Each patient would be followed up for 28 days. Participants would be followed up daily as long as they are hospitalized; in case of discharge before this follow up period, they would be followed up telephonically on day 14 and day 28.

The following variables would be clinically assessed in every follow-up:

1. Nasal stuffiness
2. Nasal discharge
3. Foul smell
4. Epistaxis
5. Facial pain
6. Facial edema
7. Dental pain
8. Malaise
9. Fever

The case would be said to be completed when there is either recovery of the participant as per the outcome parameters, followed by discharge from the hospital, or has advanced in the form of advanced disseminated mucormycosis or death of the patient.

Data Analysis

The study center would send a weekly report as per weekly report proforma on case recruitment to headquarters either by fax or email every week. The DSMB would assess the research data regularly. The conclusion report on completion of the study (after 3 months) is to be submitted to Headquarters as per concluding report proforma.

Withdrawal Criteria

The participant would be withdrawn from the study if the condition of the participants worsens and the mucormycosis expands beyond the inclusion criteria (safety end point), participants require ventilator support, it suggests a severe respiratory condition, possibly due to complications from mucormycosis or other underlying health issues, or participants become unwilling to continue or become noncompliant in the RCT and request the site PI to withdraw them for the RCT would be withdrawn from the study. Every participant can withdraw from the trial anytime for any reason and without prejudice.

End Point

A case would be considered complete when the participant either recovers based on the defined outcome parameters and is discharged from the hospital within or before 28 days. Safety end points include advanced disseminated mucormycosis and patient death.

Statistical Analysis

Data collected would be compiled on to a Microsoft Excel worksheet and would be subjected to statistical analysis using

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an appropriate package like SPSS (IBM Corp) software. Descriptive statistics like frequency and percentage of categorical data, mean (SD) of numerical data in each group or subgroup would be depicted. Frequency and percentage of various categories in each group or subgroup would be compared using chi-square test. Normality of numerical data would be checked using Shapiro-Wilk test or Kolmogorov-Smirnov test. Depending on the normality of data, statistical tests would be determined. For a numerical continuous data following a normal distribution, inter group comparison (2 groups) would be done using *t* test, else a nonparametric substitute like the Mann-Whitney *U* test would be used. Intra group comparisons for a numerical continuous data following a normal distribution would be carried out using paired *t* test (for 2 observations) or repeated measures ANOVA for >2 observations, else a nonparametric substitute like Wilcoxon signed-rank test (for 2 observations) or the Friedman test for >2 observations would be used. Frequency and percentage of various responses in each time interval would be compared using the chi-square test or McNemar test. Having set the α error at 5%, β error at 20%, and power at 80%, $P<.05$ would be considered statistically significant (Multimedia Appendices 4, 5, and 6).

Data Monitoring and Management

Project Monitoring and Reviews

Record of each enrolled case is also to be electronically maintained and this electronically maintained record is to be sent to headquarters through email to the study coordinator at CCRH headquarters as soon the case is enrolled for verification of the case record with annexures. Concerned authority shall do on-site monitoring at 1-month interval till completion of the study.

Quality Control

A centralized workshop would be organized for the investigators (to be involved in specific study) to ensure standardization and quality control. A periodical review would be conducted at all the sites for quality assurance. A random subset of records from each site would be evaluated for quality control. Investigators would be asked to bring all medical records for selected subjects to the data analysis workshop. Information in the medical records would be compared with the data on the case report form to assess completeness and accuracy of reported data.

Harms

Homoeopathic medicines which shall be used in the trial are known pharmacopeial preparations. As no new remedy is proposed to be investigated, there is no potential risk due to intervention.

Auditing and Inspecting

The study center would send a weekly report as per weekly report proforma on case recruitment to headquarters either by fax or email every week of the month. The DSMB would assess the research data regularly. The conclusion report on completion of the study (after 3 months) is to be submitted to hqrs. as per concluding report proforma.

Ethical Considerations

Protocol Development

This is carried out in consultation with experts of St. George's and JJ Hospital, Mumbai and then subsequently reviewed by Dr V Shankar Kumar, Consultant ENT Surgeon Apollo Spectra Hospitals, Chennai and Dr Sushil Kabra, Department of Pediatrics, AIIMS New Delhi before it was submitted to ethics committee.

Human Subject Ethics Review Approvals or Exemptions

The study protocol shall be in accordance with the latest revision of the Helsinki Declaration on human experimentation and Good Clinical Practices India. Although medicines proposed to be used during the study are known homoeopathic pharmacopeial preparations, necessary clearance of the Ethical Committee shall be obtained before undertaking the study. The Scientific Advisory Board and the Central Ethics Committee of the CCRH have approved the study protocol and the amendments (1-29/2021-22/CCRH/Tech/Post-covid Mucormycosis/887; July 15, 2021). The investigator must meet the study requirements as specified in the protocol. Protocol amendments are possible only in exceptional cases (eg, where the health or well-being of the participant is affected) and only after authorization by the Scientific Advisory Committee (SAC) of the Council. If there is any modification in the protocol, an addendum of the same shall be circulated to all the investigators after due approval of SAC and EC. The investigator shall update the protocol by attaching the addendum of the amendment to the already circulated protocol. In case of any administrative or technical amendments, which do not affect the health of the participant, agreement of all the concerned shall be made. These changes shall also be justified in writing and all those concerned are to be informed.

Informed Consent

Individuals aged 18 years or older would be considered eligible for consent. The site PI would obtain voluntary consent from the participants before the screening test after explaining the study. The participants would be provided with the participant information sheet describing the study details and would voluntarily sign the consent form if they agree to take the intervention.

Privacy and Confidentiality

The investigator would inform the participants that all trials results recorded would be treated in strict confidence. During documentation and analysis, the participants would only be identified by their subject code and unique identifier number. The confidentiality of the participants' personal data would be maintained as per data protection regulations.

Compensation Details

CCRH would provide insurance cover in the trial for the said study duration, according to the terms finalized under clinical trial cover with the identified insurance firm.

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Protocol Violation

If the patient stops taking the intervention medication on their own, this would be considered as protocol violation. So, these participants would not be considered for per protocol analysis.

Declaration of Interest

No conflict of competing interest of the PI or site PI, or any other member of the investigation team.

Access to Data

The access to data would be restricted for analysis and interpretation only by CCRH and other collaborating organization, as and when involved. For all purposes, the data would remain strictly confidential, and anonymity would be assured through the best possible means.

Ancillary and Posttrial Care

The participant would be provided with all ancillary care during the study and other ancillary techniques. Besides, she/he would be provided with regular outpatient department care, even after the study is over.

Dissemination Policy

The investigators would communicate trial results to participants, health care professionals, the public, and other relevant groups (through publication, reporting in results databases, or other data sharing arrangements) after completion of the study. However, no information based on unjustified claims, or the findings of interim analysis would be communicated in any form.

Results

India faced a significant impact from the COVID-19 pandemic, with 44,587,307 confirmed cases and 528,629 deaths reported as of January 17, 2023, according to the World Health Organization [28]. The second wave placed tremendous strain on the nation's health care system, resulting in severe shortages of drugs, vaccines, ventilators, and oxygen. During this period, there was a notable increase in mucormycosis cases among patients with COVID-19, leading the government to classify it as a notifiable disease under the Epidemic Diseases Act of 1897 on May 20, 2021 [29]. To address the high mortality rate and long-term complications experienced by many survivors, the Ministry of AYUSH, Government of India, recommended homoeopathy as an adjunct therapy to enhance the effectiveness of standard conventional treatments. The CCRH developed a protocol to incorporate homoeopathy as an additional therapy for treating COVID-19–associated mucormycosis. However, when this protocol was created, there was a significant number of mucormycosis cases in India, particularly in Mumbai (June 2021). By the time CCRH obtained all necessary approvals and ethical clearance for the study, the incidence had decreased dramatically (September 2021), resulting in the study not being initiated or registered. The authors believe it is their ethical duty to share this reviewed protocol with the medical community as a reference for future research.

Discussion

Principal Findings

This study was conceived during the exponential increase in Mucormycosis cases in India since March 2021. This opportunistic infection was being observed in patients with severe COVID-19. Globally, the prevalence of mucormycosis varied from 0.005 to 1.7 per million population in 2019-2020. Its prevalence in India was 0.14 per 1000 population. In May 2021, the cases peaked to 11,717 cases of mucormycosis across 18 states of India [24]. ROCM is extremely fatal with mortality rates ranging from 85%-93%, despite the best treatment in immunocompromised patients [30]. Patients with poorly controlled diabetes mellitus are the primary group at risk for developing ROCM. Other recognized risk factors worldwide include diabetes-associated ketoacidosis, hematological malignancies, solid organ or bone marrow transplants, surgeries, trauma, neutropenia, protein-calorie malnutrition, autoimmune diseases, chronic kidney disease or renal failure, HIV infection, deferoxamine therapy, and corticosteroid therapy [31]. ROCM typically starts in the paranasal sinuses and then spreads to adjacent structures, such as the orbit and neurocranium. Most reported cases are from Iran (26%), India (22%), China (17%), and the United States (15%), regions where diabetes prevalence is significantly increasing [32]. Chavda et al [33] state that mucormycosis affects the nose, eyes, and brain and is a potentially fatal intrusive fungal infection that frequently affects immunodeficient individuals.

In conventional treatment, surgical and pharmaceutical interventions are key to treat mucormycosis, thus necessitating a multidisciplinary approach team of otolaryngology, ophthalmology, neurosurgery, and infectious disease specialists in a facility setting. Intravenous antifungal pharmacotherapy is the first line of treatment, amphotericin B deoxycholate and posaconazole or isavuconazole being the 2 antifungal agents recommended for the primary therapy of mucormycosis [34]. However, the scope of treatment in limited in this condition, and resulting side effects are known. Chakraborty et al [34] have reported side effects from liposomal amphotericin B, which include fever, chills, nausea, vomiting, loss of appetite, headache, and some serious side effects which include swelling or pain at injection site, muscle or joint pain, unusual tiredness, weakness, muscle cramping and signs of kidney problems (such as a change in the amount of urine or painful urination) and so on after infusion of the drug, which, in turn, causes hindrance to continue the required conventional treatment [17]. Sachdeva et al [35] states that hepatotoxicity and nephrotoxicity are well-known serious side effects of intravenous Amphotericin B and posaconazole treatment. Pal et al [36] reports palatal, facial soft tissue necrosis, loss of vision, and invasion of soft tissues of the infratemporal fossa, orbit or palate through neurovascular structures as complications of ROCM.

Due to limited scope of conventional medicine, side effects that are serious or interfere in the treatment, advance complications and poor prognosis with high mortality rate, the authors felt a need of exploring the usefulness of alternative system of medicine to complement the standard line of treatment for

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COVID-19–related ROCM. The authors have had a successful experience of providing adjunct homoeopathic treatment in severe cases of COVID-19 before planning this RCT, which, is now reported [37]. Planning this RCT, thus, seemed to be a step in the right direction.

The evidence for similar studies in the past in homoeopathy sector is limited. The literature was, therefore, looked up for role of homoeopathy in fungal studies, instead. A study on dermatophytosis and its management by homoeopathic medicines reports successful reduction in the NRS and DLQI scores, thus suggesting it as a feasible integrative treatment option for tinea infections [38]. An in vitro study on antifungal activity of homoeopathic medicines against plant fungus *Aspergillus niger* observed that homoeopathic medicines with various potencies (6C to CM) had a significant antifungal activity, compared with the controls, which is bavistin (Carbendazim) and ethanol (Dispensing alcohol 90%) [39]. A case series by Roy et al [40] reports positive effect of homoeopathic medicines against dermatophytosis. Furthermore, a pilot study by Sherr et al [41] reported that homoeopathic medicine Bacillinum had a potential to improve long term tinea status and reduces the chances to relapse as compared with the standard treatment for tinea and homoeopathy can be used as an alternative to standard treatment care. Other in-vitro studies have also reported homoeopathy medicines to have worked effectively against the growth of different forms of fungus [21,22].

There was, however, no study reported so far to assess the role of homoeopathic medicines in mucormycosis. Hence, to the authors' knowledge, this protocol was a first with the aim to evaluate the efficacy of homoeopathic medicines as an adjuvant in the treatment of COVID-19–related ROCM. However, with the decline in COVID-19 cases in September 2021, which was the time when the approvals could be sought, the study had to be called off due to nonfeasibility reasons. The authors feel this as their ethical duty to share this reviewed protocol with the profession as a reckoner or source of further work for the clinicians or scientists alike, in a more generalized manner, which is to say, in the cases of mucormycosis not particularly resulting from COVID-19 infection. This would help in being prepared with the evidence, or the lack of it, should such an emergency situation arise in future. We, thus, share this protocol with the community with the hope that it may be adopted for mucormycosis cases that are generally seen in immunocompromised individuals.

Conclusion

This study aimed to evaluate the role of existing homoeopathic medicines as an adjuvant therapy in managing COVID-19–related ROCM, potentially contributing to the use of homoeopathy as an evidence-based medical approach. The protocol can also serve as a valuable resource for clinicians and researchers addressing mucormycosis cases unrelated to COVID-19 infection, particularly in immunocompromised patients. It would help ensure preparedness, whether or not sufficient evidence is available, in the event of a future health emergency. The authors have tried to adopt universally acceptable, standardized parameters for determining the improvement, with secondary parameters intended for evaluating the survival rate of the hospitalized patients besides other parameters that have been selected for assessing initial treatment response through laboratory and imaging techniques. A planned outcome of the study includes comparing the time required for significant or complete recovery between patients receiving adjuvant treatment and those in the control group. The authors welcome future studies based on this protocol and would be pleased to see their work advanced by fellow professionals.

Acknowledgments

Dr VK Gupta, Chairman of the Scientific Advisory Board of the Central Council for Research in Homoeopathy (CCRH), and Dr LK Nanda, Chairman of the Special Committee on Clinical Research at CCRH, along with their respective committees, are acknowledged for granting technical approvals. Additionally, reviewers Dr V Shankar Kumar, Consultant ENT Surgeon at Apollo Spectra Hospitals, Chennai, and Dr Sushil Kabra, Department of Pediatrics at the All India Institute of Medical Sciences, New Delhi, are thanked for their valuable comments that enhanced the protocol during its development. The funding authority was the Central Council for Research in Homoeopathy under the Ministry of AYUSH.

Data Availability

No data are associated with the protocol as the study could not be initiated because mucormycosis cases started declining.

Authors' Contributions

RB and HK conceptualized the study. JS planned its conduct and methodology under the guidance of HK. JS and TG developed the protocol and contributed in final manuscript writing. All authors agreed with the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Treatment for COVID-19-associated mucormycosis recommended by the FISF.
[PNG File , 314 KB - resprot_v14i1e57905_app1.png]

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Multimedia Appendix 2
Staging of rhino-orbital-cerebral mucormycosis.
[DOCX File , 15 KB - resprot_v14i1e57905_app2.docx]

Multimedia Appendix 3
SPIRIT flow diagram.
[DOC File , 52 KB - resprot_v14i1e57905_app3.doc]

Multimedia Appendix 4
Dummy table for Baseline.
[DOCX File , 15 KB - resprot_v14i1e57905_app4.docx]

Multimedia Appendix 5
Dummy table for follow ups.
[DOCX File , 14 KB - resprot_v14i1e57905_app5.docx]

Multimedia Appendix 6
Dummy table for Survival time.
[DOCX File , 13 KB - resprot_v14i1e57905_app6.docx]

Multimedia Appendix 7
Original Protocol.
[DOCX File , 71 KB - resprot_v14i1e57905_app7.docx]

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Abbreviations

CCRH: Central Council for Research in Homoeopathy
CEMRI PNS: Contrast-Enhanced Magnetic Resonance Imaging of Para Nasal sinus
DSMB: Data and Safety Monitoring Board
FISF: Fungal Infection Study Forum
IMP: investigational medicinal product
MRI: magnetic resonance imaging
PI: principal investigator
PNS: paranasal sinus
RCT: randomized controlled trial
ROCM: rhino-orbital-cerebral mucormycosis
SAC: Scientific Advisory Committee
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
T1W: T1-weighted
T2W: T2-weighted

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Protocol

Evaluation of the Clinical Nursing Effects of a Traditional Chinese Medicine Nursing Program Based on Care Pathways for Patients With Type 2 Diabetes: Protocol for a Randomized Controlled Clinical Trial

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Abstract

Background: To improve the performance of health care institutions, reduce overmedication, and minimize the waste of medical resources, China is committed to implementing a clinical pathway management model. This study aims to standardize nursing practices, foster clinical thinking in nurses, and promote patient recovery.

Objective: The purpose of this study is to evaluate the clinical effects of a traditional Chinese medicine (TCM) nursing program based on nursing pathways for patients with type 2 diabetes mellitus (T2DM).

Methods: This study uses a prospective, randomized, single-blind, parallel-controlled design. Based on sample size calculations, the study will include 594 patients with diabetes, with 2 groups of 297 patients: an observation group will receive a TCM nursing program based on clinical pathways, while a control group will receive routine care. Both groups will be evaluated before and after the intervention using assessment indicators. The primary outcome is the quality of life score, measured by a diabetes-specific quality of life questionnaire. Secondary outcomes include hospital stay duration, medical expenses, health knowledge, blood glucose control, symptom scores, and patient satisfaction.

Results: This study was funded in August 2021 and has received approval from the Ethics Committee of Guang'anmen Hospital, China Academy of Chinese Medical Sciences (2022-022-KY-01). The trial is ongoing, with the first patient enrolled in September 2022. The study is expected to conclude in April 2025. To date, 380 patients have been recruited, with 202 randomized into the study, though no statistical analysis of the data has yet been conducted. A single-blind method is used; nurses are aware of group assignments and intervention plans, while patients remain blinded. Final results are planned for release in the first quarter of 2025.

Conclusions: This study seeks to integrate existing national standardized nursing protocols with clinical pathways to implement more efficient and higher-quality nursing practices. The goal is to standardize nursing procedures, enhance patients' quality of life, and improve self-care and medication adherence after discharge.

Trial Registration: International Traditional Medicine Clinical Trial Registry ITMCTR2022000048; https://tinyurl.com/y4jd68h4

International Registered Report Identifier (IRRID): DERR1-10.2196/58951

(JMIR Res Protoc 2025;14:e58951) doi:10.2196/58951

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KEYWORDS

type 2 diabetes; traditional Chinese medicine; TCM nursing program; clinical pathway; application research; diabetes; diabetes mellitus; research protocol; nursing; nursing program; nursing care; chronic disease; disease monitoring; prevalence; China; adult; patient recovery; psychological care; health education; quality of life; blood glucose; self-care; medication; control group; patient satisfaction

Introduction

According to the Guideline for the Prevention and Treatment of Type 2 Diabetes Mellitus in China (2020 Edition) [1], the prevalence of diabetes in China has surged from 0.67% in 1980 to 11.2% in 2015-2017 [2,3]. Diabetes management in China faces significant challenges, particularly in rural areas where awareness, treatment, and control rates remain low. Large-scale epidemiological surveys conducted in 2010 and 2013 reported diabetes awareness rates of 30.1% and 36.5%, treatment rates of 25.8% and 32.2%, and control rates of 39.7% and 49.2%, respectively [3-5].

Most existing studies have focused on evaluating clinical nursing pathways or nursing programs. For instance, a study by Li [6] analyzed the effectiveness of clinical nursing pathways in type 2 diabetes mellitus (T2DM) care, demonstrating that a research group using clinical nursing pathways achieved better control of fasting blood glucose and postprandial 2-hour glucose levels compared to a control group ($P<.05$). The research group also had significantly fewer instances of improper hypoglycemia treatment, insulin injection errors, dietary mistakes, inadequate exercise, and nonadherence to medical advice ($P<.05$). Additionally, compared to the control group, the research group had shorter hospital stays, lower hospitalization costs, and higher overall nursing satisfaction ($P<.05$), indicating that the application of clinical nursing pathways can effectively control blood glucose levels, improve nursing quality, and enhance patient satisfaction.

Similarly, a study by Ren et al [7] showed that implementing traditional Chinese medicine (TCM) nursing programs in general hospitals resulted in higher quality-of-life scores for patients in an observation group 1 month after discharge compared to a control group. At discharge, the observation group had a significantly higher nursing satisfaction rate (93%) than the control group (77%; $P<.05$). This suggests that the TCM nursing program model can improve both quality of life and nursing satisfaction. These studies demonstrate that clinical nursing pathways or TCM nursing programs can effectively control blood glucose levels and reduce medical costs while enhancing patients' quality of life. However, no studies to date have explored the combined clinical application of these two nursing methods, which is the focus of our study.

The evolution of national standards and their integration with nursing practices have increasingly shifted the focus toward nursing pathways aligned with these standards. This development combines nationally standardized nursing protocols with nursing pathways to create a coherent, interconnected, and progressive nursing model. Pathway-based TCM nursing interventions built on TCM clinical pathways standardize the care of single diseases, promote systematic intervention processes, highlight the efficacy and unique features of TCM, and make nursing operations more standardized. This enables nurses to provide planned and anticipatory care based on structured procedures. A preliminary retrospective analysis of clinical data from 4196 patients with diabetes revealed that integrating traditional Chinese nursing techniques with clinical treatments effectively alleviated patients' discomfort. Nurses found this approach more practical and valuable in standardizing care, reducing variability, lowering costs, and improving care quality for patients with T2DM [8,9]. Nevertheless, no research has yet examined the simultaneous clinical application of these two nursing methods, which is the aim of our study.

Thus, we conducted a prospective, randomized, single-blind, parallel-controlled trial to further investigate the impact on patient outcomes of integrating nationally standardized nursing protocols with TCM nursing programs based on clinical pathways. These outcomes include hospitalization indicators (eg, length of stay and medical costs), self-management (health knowledge), clinical efficacy (blood glucose control, clinical symptoms, and quality of life), and patient satisfaction. We expect that the findings of this study will provide robust evidence for delivering personalized care, standardizing procedures, improving patients' quality of life, and enhancing self-care and medication adherence after discharge.

Methods

Study Design

The intervention protocol for this study is titled "TCM Nursing Protocol for Type 2 Diabetes Based on Care Pathway." The study uses a prospective, randomized, single-blind, parallel-controlled clinical design and aims to assess and demonstrate differences, supported by high-quality evidence, in outcomes between an intervention group and a control group that received standard care. The research team comprises nurses from the Department of Endocrinology at Guang'anmen Hospital, China Academy of Chinese Medical Sciences. The study participants are patients with T2DM admitted to our department between September 2022 and December 2024. The study is registered with the International Traditional Medicine Clinical Trial Registry (ITMCTR2022000048). Inclusion, exclusion, and elimination criteria are shown in Textbox 1.

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Textbox 1. Inclusion, exclusion, and elimination criteria.

Inclusion criteria

- The primary diagnosis must align with *International Classification of Diseases, Tenth Revision* codes for type 2 diabetes mellitus, specifically in the range of E11.2 to E11.9.
- Admission criteria must be met for inpatient treatment, as determined by the clinical physician.
- In cases where patients have concurrent diagnoses of other diseases, if these conditions do not require special treatment during the hospital stay and do not hinder the implementation of the clinical nursing pathway for the primary diagnosis, the patient can be included in that nursing pathway.
- Informed consent must be obtained from the patient and documented, indicating their understanding and agreement with the proposed care plan.

Exclusion criteria

- Patients who meet the diagnostic criteria for type 2 diabetes mellitus but are unable to comply with the treatment regimen.
- Patients with cognitive impairments or cognitive dysfunction.
- Patients with concurrent diagnoses of other diseases that require treatment during the hospitalization period.

Elimination criteria

- Patients whose condition worsens, resulting in a hospitalization duration exceeding 14 days and increased hospitalization costs.
- Patients with concomitant systemic diseases that require special treatment, leading to a hospitalization duration exceeding 14 days and increased costs.
- Patients with serious complications that arise during the course of treatment and necessitate discontinuation of the nursing pathway.
- Patient and family preferences and wishes that affect the implementation of this nursing pathway.

Interventions

Intervention Plan

Upon admission, nurses provide admission education and assign eligible patients to the study group or the control group based on the time of admission (Figure 1). The intervention plans for both groups are outlined in a pathway form and include 3 components: executing medical orders, nursing tasks, and health education, along with TCM-specific treatments (Multimedia Appendix 1). For the control group, nurses subjectively implement the nursing plan according to the pathway form. The study group strictly follows the TCM nursing pathway for T2DM.

Figure 1. Study design and flow.

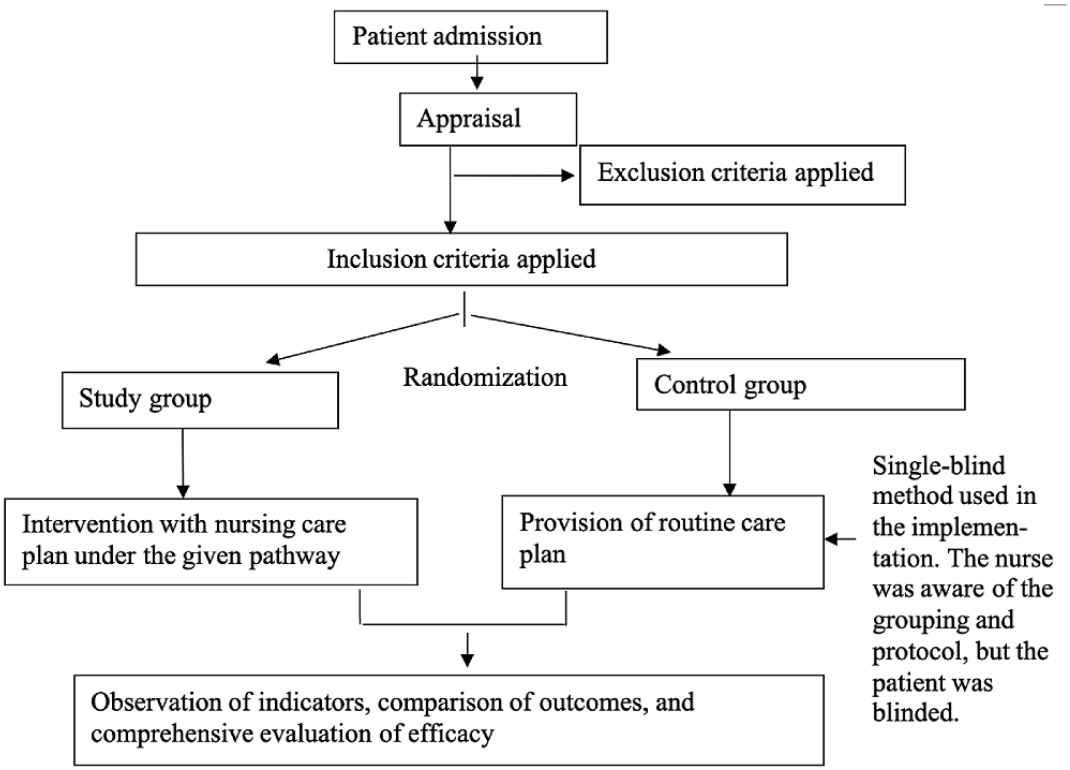

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Implementation of the TCM Nursing Pathway for T2DM

Upon admission, nurses provide admission education and assess the patient's condition using an evaluation form for the TCM nursing pathway for T2DM. This assessment determines whether the patient qualifies for inclusion in the study. Eligible patients receive the TCM nursing pathway for T2DM. For patients included in the study, nurses ensure that physicians perform a thorough examination upon admission. The TCM nursing pathway form for T2DM is distributed, and patients are informed about their treatment and the nursing plan during hospitalization. This ensures patients understand the medical and nursing measures to be implemented.

During hospitalization, the responsible nurse uses the evaluation form of the TCM nursing pathway for T2DM to develop an appropriate care plan. This plan may include TCM techniques, syndrome differentiation–based dietary therapy, exercise and health practices, herbal prescriptions, and emotional regulation. The study group strictly adheres to the schedule outlined in the TCM nursing pathway for T2DM. Nurses coordinate with relevant departments promptly to complete necessary examinations. The control group receives routine care.

If there are any changes in the patient's condition, the responsible nurse promptly analyzes and addresses the changes, adjusting the sequence of items in the TCM nursing pathway as necessary. The head nurse checks the implementation of the TCM nursing pathway for T2DM and the routine care plan daily. The head nurse ensures compliance with the nursing pathway protocol and evaluates the quality of care promptly. Relevant data are collected and evaluated at the time of the patient's discharge.

Sample Size Calculation

A literature-based approach was used to compare the preset effect, with α=.05 and β=.10, against the known efficacy of general nursing from previous studies. Based on methods found in the literature [10] and conclusions from earlier research, the historical effective rate (very satisfied + satisfied) was determined to be approximately 74.5% [9]. The effective rate for this pathway nursing program is projected to be 85%. Using *Z* values from standard tables ($Z1 - \alpha / 2 = 1.96$; $Z1 - \beta = 1.28$), the sample size for each group was estimated as follows:

$N1 = N2 = (Z1 - \alpha / 2 + Z1 - \beta)\ 2\ [P1(1 - P1) + P2(1 - P2)] / \delta 2 = (1.96 + 1.28)\ 2\ [0.745 \times (1 - 0.745) + 0.85 \times (1 - 0.85)] / (0.85 - 0.745)\ 2 = 296$. Thus, 242,272 indicated 297 cases, and the sample size of this study was 297 × 2 = 594 cases.

Randomization Method

The randomization method used in this study involves selecting an appropriate block size and assigning participants into 2 groups (the study group and the control group) in a 1:1 ratio. Using the *PROC PLAN* procedure statement in SAS (version 9.2; SAS Institute) and specifying a seed number, a randomized allocation was generated for 594 participants. This process produced a complete randomization table, listing the treatment assignments corresponding to sequential serial numbers from 001 to 594.

Blinding Method

This is a single-blind study, and patients with diabetes are unaware of their group assignment.

Outcomes

Researchers use standardized questionnaires to collect baseline data. The primary efficacy indicator is a quality of life scale (the Diabetes-Specific Quality of Life Scale) [11]. Secondary efficacy indicators include the length of hospital stay, medical costs, blood glucose control, patient symptom scores, patient satisfaction, and the level of health knowledge acquired at admission. Data are collected 1 day before discharge and at 4 weeks, 12 weeks, and 24 weeks after discharge.

Harm

Apart from the risk of data violations, there is no anticipated harm to the study participants. The investigator will be identified by experimenter number to reduce the risk. Although greater adherence to treatment is expected in the intervention group, no systematic differences in diabetes management are expected.

Ethical Considerations

The ethical principles guiding this study include the Measures for Ethical Review of Biomedical Research Involving Humans, Good Clinical Practice for Drug Trials, Regulations on Clinical Trials of Medical Devices, Ethical Review Guidance for Drug Clinical Trials, Clinical Ethical Review Management Guidelines for Traditional Chinese Medicine Hospitals, the Declaration of Helsinki, and the International Ethical Guidelines for Biomedical Research Involving Human Subjects.

The trial has been approved by the Ethics Committee of Guang'anmen Hospital, China Academy of Chinese Medical Sciences (2022-022-KY-01). Prior to the implementation of the study, informed consent must be obtained from patients. Participation in this study is entirely voluntary. Patients may choose not to participate or withdraw from the study at any time without providing a reason, and participation requires signing an informed consent form.

All patient data collected during the trial will remain confidential. Medical records will be identified using research ID numbers instead of names. Identifiable information will not be disclosed to anyone outside the research team unless the patient provides explicit permission.

In accordance with relevant national regulations, in the event of research-related injuries, the study institution, Guang'anmen Hospital of the China Academy of Chinese Medical Sciences, will bear the corresponding medical costs and provide appropriate financial compensation.

For any questions regarding participant rights in this study, individuals can contact the Ethics Committee of Guang'anmen Hospital, China Academy of Chinese Medical Sciences.

The study form will be kept by the data collector in a folder in the study office. Study data will be processed without participants being recognizable. Only the researcher responsible for the analysis can access the final data set; after the trial study is published, we will provide research references and the scientific basis for relevant clinical practice, formulate the

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implementation specifications of the nursing program under the chosen pathway, and promote the research results in the industry.

Statistical Analysis

We will use SPSS (version 26.0; IBM Corp) to perform the statistical analysis. Descriptive statistics for quantitative variables will include at least the mean and SD or the median and IQR. Descriptive statistics for qualitative variables will include at least the frequency and percentage for each category. Comparisons between the 2 groups will be conducted using an independent-sample *t* test (for normally distributed data with equal variances) or the nonparametric rank-sum test. For unordered categorical data, comparisons between the 2 groups will be made using the χ^2 test or Fisher exact test, while ordinal categorical data will be analyzed using nonparametric tests. All statistical tests will be 2-sided, with a $P<.05$ considered statistically significant.

Results

This trial received funding in August 2021 and is currently ongoing. The first patient was enrolled in September 2022, and the study is expected to conclude in December 2024. The trial uses a single-blind design where nurses are aware of group assignments and intervention details, but the patients remain blinded. Final results are planned for publication in the first quarter of 2025.

To date, 380 patients have been recruited, with 172 excluded, resulting in 202 randomized participants (101 in the study group and 101 in the control group). Details on the screening process are provided as a Consolidated Standards of Reporting Trials (CONSORT) flowchart in Multimedia Appendix 2.

This study primarily aims to compare health knowledge, comprehension, and scores between the 2 groups, with the goal of optimizing an innovative model for the TCM nursing pathway for T2DM. The findings are expected to enhance the standardization and precision of clinical nursing practices. The pathway will be validated clinically, combining theory with practice through prospective research to provide high-level clinical evidence. This will contribute to the development of a high-quality TCM nursing pathway, expand the global influence of TCM, and support national economic growth and public health.

Discussion

Overview

Data show a significant increase in China in the incidence of diabetes over 30 years, leading to a high prevalence of acute and chronic complications. Simultaneously, deficiencies in patient awareness, understanding, treatment rates, and control rates have become evident in diabetes care. This underscores the urgent need to explore and improve diabetes care methods.

In recent years, China's economic growth has created opportunities for more targeted and standardized care, providing promising prospects for development. Under the framework of National Standards + Nursing Pathways, TCM-based nursing models have become prominent in diabetes clinical care. However, despite positive outcomes with existing standards, a comprehensive clinical pathway management model has yet to be established, resulting in inconsistencies and nonstandardized practices.

Thus, it is crucial to conduct in-depth research to integrate these methods and improve the effectiveness of nursing practices. Exploring and developing nursing plans that combine clinical pathways with TCM principles is essential. High-quality prospective clinical research is needed to meet patients' increasing demand for improved health care quality and to refine standardized nursing protocols.

Since the Ministry of Health launched the clinical pathway pilot project in 2009, the effectiveness of clinical pathway management in improving health care quality and controlling medical costs has become increasingly evident. Against the backdrop of advocating "high quality, high efficiency, and low cost," studying the application of clinical nursing pathways in China's health care quality management is of significant importance. This emphasizes the need for further development and research into the implementation of a TCM nursing model for T2DM based on National Standards + Nursing Pathways.

Principal Findings

This study focuses on comparing health knowledge and scores in the 2 groups, aiming to optimize an innovative model for the TCM nursing pathway for T2DM. This approach should help enhance the standardization and precision of clinical nursing practices. Its application in the clinic will combine theory with practice, providing high-level clinical evidence through prospective research. The goal is to establish a high-quality TCM nursing pathway that will expand the international influence of TCM and support economic and public health development.

Strengths and Limitations

Building on prospective findings from previous studies, this study will use a prospective design to enhance the level and reliability of evidence. The study's significance also lies in providing a foundation for high-quality clinical evaluation that will enable selecting targeted and distinctive TCM clinical nursing pathways. The aim is to improve the clinical application and quality of standard nursing procedures within nursing projects based on a T2DM nursing pathway.

However, this study uses a single-center design and does not include additional hospitals, which is a limitation. Nevertheless, the focus is on optimizing the TCM nursing pathway at this center and obtaining high-quality evidence of its effectiveness to facilitate broader future applications and clinical use.

Future Directions

The TCM nursing pathway explored in this study has a solid foundation, demonstrating its potential for effective care. We anticipate that as the study progresses, high-quality evidence will confirm its efficacy. Subsequently, this TCM nursing pathway will be promoted in more hospitals, benefiting a larger population of patients with diabetes.

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Conclusions

This study aims to integrate existing national standardized nursing protocols with clinical nursing pathways to implement more efficient and higher-quality clinical nursing practices. It seeks to standardize nursing procedures, improve patients' quality of life, and promote self-care and medication adherence after discharge.

Acknowledgments

The study was funded by the Science and Technology Innovation Program of the Chinese Academy of Chinese Medical Sciences (CI2021A03212).

Authors' Contributions

NS contributed to conceptualization, critical revision of the study design, data collection and analysis, manuscript writing, and final approval of the manuscript. YZ and SL contributed to data collection and analysis, critical revision, and final approval of the manuscript. TH contributed to data collection and manuscript writing. JZ, XH, and YC made contributions to the implementation of the planned intervention.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Clinical pathway form.
[DOC File , 96 KB - resprot_v14i1e58951_app1.doc]

Multimedia Appendix 2
Consolidated Standards of Reporting Trials (CONSORT) flowchart of participant recruitment and allocation to date.
[PDF File (Adobe PDF File), 38 KB - resprot_v14i1e58951_app2.pdf]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials

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TCM: traditional Chinese medicine
T2DM: type 2 diabetes mellitus

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Protocol

Effects and Safety of Press-Needle Therapy for Improving Visual Function and Eye Blood Circulation in Patients With Glaucoma With Controlled Intraocular Pressure: Study Protocol for a Multicenter Randomized Controlled Trial

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Abstract

Background: Glaucoma is the leading cause of irreversible blindness worldwide, causing continuous and progressively worsening damage to visual function, which leads to vision loss. Optic nerve protection is an important treatment for glaucoma with controlled intraocular pressure (GPCI), but to date, there is no universally accepted effective optic nerve protection agent. Acupuncture can protect the optic nerve by increasing blood flow to the eye. However, fear of pain or the limitations of treatment place and time lead to poor patient compliance. Press-needle therapy is a characteristic of traditional Chinese medicine (TCM) external treatment methods; its safety is high, the effect is fast and lasting, it is easy to conduct, and it has high patient compliance.

Objective: The objective of the trial is to evaluate the safety and clinical efficacy of press-needle therapy and investigate whether it can improve visual function by regulating eye blood circulation in patients with GPCI.

Methods: In total, 192 participants aged 18-75 years with GPCI from the Mianyang Central Hospital, the Mianyang Hospital of Traditional Chinese Medicine, and the Mianyang Wanjiang Eye Hospital will participate in this study. Participants will be allocated to 2 treatment groups (experimental and control groups) in a ratio of 1:1 and will undergo press-needle therapy and sham press-needle therapy, respectively, for the same 4-week period. Primary outcomes will include the best-corrected visual acuity (BCVA), optical coherence tomography angiography (OCTA), color Doppler flow imaging (CDFI), and visual field assessment results. Secondary outcomes will include the intraocular pressure (IOP) and traditional Chinese medicine (TCM) clinical symptom scales. The primary outcomes and safety assessments will be measured at baseline and 4 weeks thereafter, while the secondary outcomes will be measured at baseline and 1, 2, 3, and 4 weeks thereafter.

Results: Recruitment and data collection began in February 2023. The final outcomes are expected in September 2025. As of October 2024, the project had recruited 220 eligible participants, of whom 192 (87.3%) will complete the study, exceeding initial projections for the study time frame. The remainder of the participants will provide the ability to explore cross-level interactions

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that could not be statistically powered at the outset. The strengths of the project include rigorous data collection, good retention rates, and high compliance rates.

Conclusions: This study will provide data on the effects of press-needle therapy on visual function and ocular circulation in patients with GPCI, and these results will help demonstrate whether acupuncture can improve patients' visual function by regulating ocular circulation, thus providing a clinical and theoretical basis for the wider application of acupuncture therapy in GPCI.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2300067862; https://tinyurl.com/mrxd58x9

International Registered Report Identifier (IRRID): DERR1-10.2196/67737

(JMIR Res Protoc 2025;14:e67737) doi:10.2196/67737

KEYWORDS

press needle; press-needle therapy; needling technique; glaucoma; acupuncture; visual function; eye blood circulation; randomized controlled trial; traditional Chinese medecine

Introduction

Glaucoma is a leading cause of irreversible blindness worldwide [1]. Progressive degeneration of retinal ganglion cells (RGCs) and the optic nerve is the basic pathological characteristic of glaucoma [2]. Optic nerve protection is the focus of glaucoma treatment based on intraocular pressure (IOP) control. Neuroprotective targets include glutamate-induced neurotoxicity, nitric oxidase synthetase, neurotropins, calcium channel receptors, free radicals, vascular insufficiency, and the rho-kinase pathway [3]. Nevertheless, at present, there is no satisfactory neuroprotective agent for glaucoma.

Ocular blood flow disorder is a potential cause of visual field deterioration in patients with glaucoma [4]. Therefore, therapeutic options to protect the optic nerve in glaucoma by improving ocular blood flow have attracted increasing attention [3]. Acupuncture therapy has been used to treat glaucoma for thousands of years and has demonstrated favorable safety and convenience [5]. Acupuncture can modify glaucoma blood flow parameters to protect the optic nerve, such as increasing the flow of blood in the eye [6] and reducing anomalies of blood flow in the central artery of the retina [7]. Acupuncture treatments relay electrical signals via the dorsal root ganglion (DRG) and spinal cord, finally regulating ocular blood flow [8].

However, the fear of acupuncture pain or the limitations of the treatment place and time lead to poor patient compliance. Press-needle acupuncture is one kind of acupuncture that has a longer treatment duration and simpler operation with less pain [9]. The theoretical basis of press-needle therapy is the combination of acupuncture theory and skin meridian and acupoint theory. *Suwen: Treatise on the Dermis* states that "all twelve meridians are also part of the skin" and that "the skin is closely related to the veins. The skin is also part of the pulse." The dermis is connected with the 12 meridians by qi and blood. Through the 12 meridians, the 12 dermises are in close contact with the 5 viscera, 6 internal organs, and the eye orifices, forming a coordinated and unified organic whole. Press-needle therapy has been widely used to treat glaucoma with controlled intraocular pressure (GPCI), but useful empirical research is insufficient for its popularization and application. The disadvantages of less rigorous designs, small sample sizes, and low quality have led to many traditional Chinese medicine (TCM) studies being insufficient to convince people of its value. Hence, a randomized, sham-controlled trial will be conducted to assess the potential of press-needle therapy in improving visual function and eye blood circulation in patients with GPCI.

Methods

Research Objectives

The main objectives of this study are twofold: (1) to observe the clinical efficacy of press-needle therapy in patients with GPCI and provide feasible and affordable press-needle treatment for them and (2) to investigate whether press-needle therapy improves the visual function of patients with GPCI by regulating eye blood circulation.

Trial Design and Setting

This multicenter, sham-controlled, blinded, randomized trial of press-needle therapy (Seilini Ltd) for GPCI will be executed in the Mianyang Central Hospital (Sichuan, China), the Mianyang Hospital of Traditional Chinese Medicine (Sichuan, China), and the Mianyang Wanjiang Eye Hospital (Sichuan, China). The study time schedule is presented in Table S1 in Multimedia Appendix 1.

Ethical Considerations

The trial protocol was approved by the Science and Technology Department of Sichuan Province (approval no: 2021YJ0443), the National Natural Science Foundation of China for the Youth (approval no: 82305324), Mianyang Central Hospital Incubation Subjects (approval no: 2020FH07), and the Medical Ethics Committee of the Mianyang Central Hospital (approval no: S2021046 (02)). It has been registered with an identifier (ChiCTR2300067862) with ClinicalTrials. The study will be strictly conducted according to the principles of the Declaration of Helsinki, as well as Good Clinical Practice (GCP) guidelines. The trial will be performed in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist [10]. Signed informed consent will be obtained from all patients or their legal guardians by specific researchers prior to beginning the trial. If there are changes to the eligibility criteria, outcomes, or analyses, a new version of the protocol will be submitted to the Medical Ethics Committee of the Mianyang Central Hospital for approval.

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Participants and Recruitment Strategy

In total, 192 patients with GPCI recruited from the Mianyang Central Hospital, (Sichuan, China), the Mianyang Hospital of Traditional Chinese Medicine (Sichuan, China), and the Mianyang Wanjiang Eye Hospital (Sichuan, China) will participate in this study. All patients will be screened by specialists and acupuncturists according to the diagnostic criteria in the *European Glaucoma Society Terminology and Guidelines for Glaucoma* [11]. The TCM syndrome of kidney deficiency and blood stasis will be diagnosed based on guidelines delineated in the *Clinical Research Guideline of New Investigational Drugs in Traditional Chinese Medicine* [12].

Inclusion and Exclusion Criteria

Participants who meet the following inclusion criteria will be eligible for the study:

- Diagnosed with primary open-angle glaucoma (POAG) [13]: open anterior chamber angle, pathologically high intraocular pressure (HIOP), with a peak IOP exceeding 21 mmHg (1 mmHg=0.133 kPa) within a 24-hour period, indicative of glaucomatous neuropathy (retinal nerve fiber layer defect [RNFLD] or optic disc changes) or visual field loss or both. Other causes resulting in HIOP were excluded for this diagnosis. Note that only 1 eye from each patient will be selected for examination.
- Having a visual field defect that can be assessed through standard automated perimetry with a reliability factor of less than 15%, as well as an IOP below 18 mmHg, at least 3 months after undergoing antiglaucoma surgery.
- Exhibiting a Chinese syndrome pattern associated with kidney deficiency and blood stasis.
- Refraining from the use of any other optic nerve protective agents, except for methylcobalamin, for a minimum of 2 months.
- Having a spherical refractive error ranging between +3.00 and –6.00 diopters, a fundus clearly visible without the need for pupil dilation, and a BCVA equal to or greater than 0.3.
- Within the age bracket of 18-75 years.
- In a conscious state and capable of cooperating with the examination and treatment process.
- Displaying a willingness to actively participate in the study and provide informed consent.

Participants who have any of the following conditions will not be eligible to participate:

- Poorly controlled IOP (≤7 mmHg or >18 mmHg), accompanied by a thin filtering cystic bleb or bleb leakage.
- Glaucoma that is not open-angle glaucoma.
- A Chinese syndrome pattern that does not meet the criteria of kidney deficiency and blood stasis.
- Other conditions, such as macular degeneration, cataract, proliferative diabetic retinopathy, retinal vascular occlusion, or any other diseases that may cause visual field loss.
- Pregnancy or lactation.
- Abnormal primary liver or kidney function or serious systemic conditions, such as heart disease, primary hypertension, diabetes mellitus, or peptic ulcer disease.
- A history of allergic reactions to the ingredients of press-needle therapy or mecobalamin tablets.

TCM Syndrome Differentiation

The TCM syndrome of kidney deficiency and blood stasis will be based on guidelines delineated in the *Clinical Research Guideline of New Investigational Drugs in Traditional Chinese Medicine* [12]: primary signs and symptoms include blurry visual acuity, narrow visual field, and eye distension, while secondary signs and symptoms include dry eye, limp aching lumbus, and knees.

The conditions for a diagnosis of kidney deficiency and blood stasis are the presence of at least 2 or more primary signs/symptoms and at least 2 or more secondary signs/symptoms. The necessary condition is a dark-purple tongue and a thready deep, stringy, or unsmooth pulse. The investigators must receive training in standard operating procedures (SOPs) for examining TCM symptoms. They will then conduct a symptom assessment survey using the TCM Symptom Score Scale (Figure 1) for each participant.

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Figure 1. TCM Symptom Score Scale. TCM: traditional Chinese medicine.

Blurry visual acuity	□ 0: None □ 2: Mild blurred visual acuity □ 4: Unable to read □ 6: Difficult to see anything
Narrow visual field	□ 0: None □ 2: As if something obscures visual acuity □ 4: Inconvenient to walk □ 6: Difficult to walk
Eye distension	□ 0: None □ 2: Mild eye distension □ 4: Endurable eye distension □ 6: Intolerable eye distension
Dry eye	□ 0: None □ 2: Mild dry eye □ 4: Obvious dry eye, as if there is a foreign body in it □ 6: Intolerable dry eye, frequent blinking
Limp aching lumbus and knees	□ 0: None □ 2: Early morning aching lumbus, which can be alleviated by beating; mild limp knees □ 4: Continuous aching lumbus, which is aggravated when working knees are too limp to carry a heavy weight □ 6: Severe aching lumbus, which is not relieved by rest; knees are too limp to desire to walk
Dark-purple tongue	□ 0: None □ 2: Exist
Thready deep, stringy, or unsmooth pulse	□ 0: None □ 2: Exist

Recruitment Procedure

Potential participants with GPCI were recruited from the Mianyang Central Hospital (Sichuan, China), the Mianyang Hospital of Traditional Chinese Medicine (Sichuan, China), and the Mianyang Wanjiang Eye Hospital (Sichuan, China). We used the internet, hospital announcements, and posters to provide a hotline calling for potential volunteers. If patients were interested in our study, researchers informed them in detail of the purpose and content of the research and the benefits and risks of participating.

After screening, participants meeting the inclusion criteria will be enrolled. Frequent follow-up phone calls are an important aspect of adherence monitoring. Every participant will have the right to withdraw from the trial at any time. Furthermore, it will be obligatory for all subjects to sign an informed consent document prior to commencement of the trial.

Randomization and Allocation

Baseline evaluation will be conducted for eligible subjects. All eligible patients will be stratified according to early, moderate, and advanced stages of glaucoma [14]. Patients with early glaucoma exhibit early glaucomatous visual field impairment, as characterized by a mean deviation (MD) of >–6 dB. Conversely, patients with moderate glaucoma present a moderate glaucomatous visual field loss, defined as MD≤–6 to ≥–12 dB. Patients with advanced glaucoma experience advanced glaucomatous visual field loss, defined as MD<–12 dB. SAS software will be used to automatically generate a set of random numbers ranging from 001 to 192. These numbers will be further classified into 3 ranges based on the disease stage. The early stage will incorporate random numbers from 001 to 064, the moderate stage will encompass numbers from 065 to 128, and the advanced stage will comprise numbers from 129 to 192. Following stratification, the participants will be assigned randomly to either an experimental group or a control group in a 1:1 ratio. Random numbers will be inserted into identical envelopes of equal dimensions, which will then be sealed to ensure concealment of group allocation and minimize the risk of selection bias. The random sequence allocation will be preserved and withheld from the investigators, statisticians, and outcome assessors to avoid detection bias.

Blinding

The researcher assistants, outcome assessors, statisticians, and subjects will be blinded to the group assignment. All participants will undergo press-needle therapy while lying on a bed in a tranquil clinic setting. For the control group, a nonpenetrating sham apparatus, similar in appearance to acupuncture needles, will be used to achieve blinding. Moreover, every participant will be asked about their experience subsequent to the acupuncture session to evaluate the efficacy of blinding. Unblinding of researchers is permitted only in exceptional circumstances, such as when there is a strong need to know about the actual treatment in order to manage the subject appropriately.

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Interventions

Experimental Group

Acupoints will be selected based on acupuncture combined with clinical experience [15]: main acupuncture points (BL2 Cuanzhu, TE23 Sizhukong, EX-HN5 Taiyang, and ST2 Sibai) and matching points (PC6 Neiguan, SP10 Xuehai, BL17 Geshu, BL18 Ganshu, BL23 Shenshu, SP6 Sanyinjiao, and K13 Taixi) (Figure 1). These points can exert a concerted effect to nourish the liver and kidneys, promote blood circulation, and dredge collaterals. Press-needle treatment will be performed by acupuncturists with more than 3 years of clinical experience. The acupuncturist will disinfect the skin around the acupoints (on the same side of the affected eye) with povidone iodine when the subject lies down on the treatment bed in a supine position. Disposable sterile press needles (0.2 mm in diameter and 0.6 mm in length; Seirin Corporation) will then be inserted into the right acupoints (Figure 1). The needles will be pressed so that they can adhere and be tied, the peelable paper will be removed, and the adhesive tape will be pressed down to ensure a secure fit. The needles will be left in place for 2 days, and participants will be asked to press the needles themselves 3-4 times/day, every 4 hours, for 1 minute each time to achieve deqi sensations, including soreness, numbness, heaviness, fullness, and aching.

Control Group

Sham press needles are the same as press needles but lack the needle element [9]. The procedures and manipulations carried out in the control group will be indistinguishable from those implemented in the experimental group. Subjects will be treated individually in a secluded room to prevent any disruptions from family members or other individuals.

Criteria for Discontinuing or Modifying Allocated Interventions

Participants will have the freedom to withdraw from the clinical study and opt for alternative treatments (eg, citicoline sodium tablets) if they believe their condition will not improve. Reasons for discontinuing treatment may include, but are not limited to, the following: (1) the pregnancy, (2) severe side effects or complications, (3) taking other medications during the study, (4) failure to comply with the study protocol, and (5) request for withdrawal for other reasons.

Outcome Measures

Primary Outcome Measures

The primary outcomes will enable us to evaluate improvements in visual function, retinal blood circulation, and retrobulbar blood vessel circulation due to press-needle therapy. The outcomes will be as follows:

- The mean change in the BCVA will be measured at baseline and 4 weeks thereafter.
- The mean change in the values of the pattern standard deviation (PSD), mean defect, and square root of loss variance (sLV) will be determined using an Octopus 900 perimeter at baseline and 4 weeks thereafter.
- The whole-image vessel density (wiVD), radial peripapillary capillary vessel density (RPCVD), superficial macula vascular density (smVD), parafoveal vessel density (paraVD), perifoveal vessel density (periVD), macular ganglion cell complex (mGCC), and peripapillary retinal nerve fiber layer (pRNFL) will be determined using optical coherence tomography angiography (OCTA) at baseline and 4 weeks thereafter.
- The ophthalmic artery (OA), central retinal artery (CRA), short posterior ciliary artery (SPCA), peak systolic velocity (PSV), end diastolic velocity (EDV), and resistance index (RI) will be determined using CDFI at baseline and 4 weeks thereafter.

Secondary Outcome Measures

The following secondary outcomes will help us determine whether press-needle therapy improves TCM clinical symptoms and changes in the IOP:

- The mean change in the IOP in the study eye will be determined uisng a TX-20P full autotonometer at baseline and at 1, 2, 3, and 4 weeks thereafter.
- Changes in TCM symptoms will be assessed by the investigators trained in SOPs according to the TCM Symptom Score Scale (Table S1 in Multimedia Appendix 1) at baseline and at 1, 2, 3, and 4 weeks thereafter.

Safety Evaluation and Adverse Events

Safety assessments using 3 routine tests (blood, urine, and stool), electrocardiography, liver function tests (alanine aminotransferase [ALT], aspartate aminotransferase [AST], alkaline phosphatase [ALP], gamma-glutamyl transferase [GGT], and serum total bilirubin [TBIL]) and kidney function tests (blood urea nitrogen [BUN], serum creatinine [SCr], uric acid [UA], and β 2-microglobulin) will be measured at baseline and 4 weeks thereafter.

A research assistant will monitor and record data regarding adverse events (AEs) associated with interventions, which may include infection, hematoma, severe pain, needle breakage, bleeding, heart palpitations, fainting, and headaches, in case report forms (CRFs). Severe AEs will be managed by emergency medicine physicians or acupuncturists. Additionally, any significant AEs will be reported to the Ethics Committee of the Mianyang Central Hospital.

Data Collection and Quality Control

Thorough recording of all data will be performed on CRFs subsequent to in-person visits or telephonic communications with participants. The same examiner will assume responsibility for conducting the examination of every patient during each assessment. Baseline measurements, demographics, medical history, and prior medications will only be gathered during the initial visit. Primary outcomes, secondary outcomes, and safety indicators will be gathered at baseline and 4 weeks thereafter. Following adequate training and successful completion of a test, 2 data entry clerks will thoroughly review the CRFs and subsequently enter the collected data independently. Participants' personal information will be kept confidential the same way as their medical histories in the hospitals before,

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during, and after the trial. The absence of a data monitoring committee in this study is justified by the anticipated low incidence of AEs and the limited participant numbers at each center. The Epidata 3.1 statistical application will be used for data entry. Subsequently, the collected data will be transferred to IBM SPSS 22.0 statistical software for the purpose of analysis.

Sample Size Calculation

The sample size calculation was based on previous studies. The basis of optic nerve protection effectiveness is 70% [16,17]. We hypothesized an 80% effective rate of the basis of optic nerve protection + press needles for GPCI in a larger sample size. According to the sample size of the estimation formula [18], α=.05 and β=0.10 in a 2-sided test, P_1=.67 and P_2=.87, 2-sided $u_{\alpha/2}=u_{0.05/2}=1.96$, and 1-tailed $u_\beta=u_{0.1}=1.282$. We substituted these values into the following formula:

This resulted in $n^1=n^2=79.02$, that is, approximately 80 cases each in the experimental and the control group, or 160 cases in both groups. To account for a 20% dropout rate, the calculation 160 + (160 × 20%) = 192 suggested that 192 patients be recruited.

Quality Control

To guarantee the quality of the proposed experiment, a unified and standardized training program will be conducted for the researchers in each role prior to commencement of the study. Subsequently, the researchers will be subjected to a proficiency assessment, and only those deemed competent will be permitted to participate in the study. Furthermore, to enhance participant compliance, regular health education activities will be conducted, humane care will be enhanced, and a long-term follow-up plan will be developed. Finally, in accordance with the requirements set forth in the Specifications for Quality Control and Quality Assurance of Clinical Research in Chinese Medicine [19], a 4-level quality monitoring system will be established to monitor the clinically collected data on a regular monthly basis, thereby ensuring the authenticity and reliability of the study results.

Statistical Analysis

Statistical analysis will be conducted independently by statisticians. The data will be presented as means (SDs). IBM SPSS 22.0 statistical software will be used. All statistical tests will be 2-sided tests, and the limit for statistical significance will be set at $P<.05$. The chi-square test will be performed for categorical variables, the independent Student *t* test will be used for measurement data, and the rank-sum test will be used for grade data. To evaluate the covariate balance, baseline characteristics will be summarized and compared between the experimental group and the control group using simple descriptive statistics.

Due to the expected low number of missing data, we will deal with missing data by transferring the last data item to the final dataset. This participant's data will be invalidated in the full analysis set (FAS), and this case will not be included in the per protocol set (PPS). Finally, the statistical significance of the FAS and PPS will be analyzed. A consistent statistical significance will indicate a significant difference.

Results

The study flowchart is shown in Figure 2. The figure also presents an outline of the case distribution across each center, as well as comprehensive outline of precise measurements and designated data collection time points. Recruitment was conducted from February 2023 to March 2024. The first participant was enrolled in February 2023. As of October 2024, the project had recruited 220 eligible participants. At the time of submission, there were 192 (87.3%) participants, who will complete the study. The recruitment process is expected to continue until September 2025. The data will be further processed and analyzed in October 2025.

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Figure 2. Flowchart of the clinical trial on patients with GPCI. GPCI: glaucoma with controlled intraocular pressure.

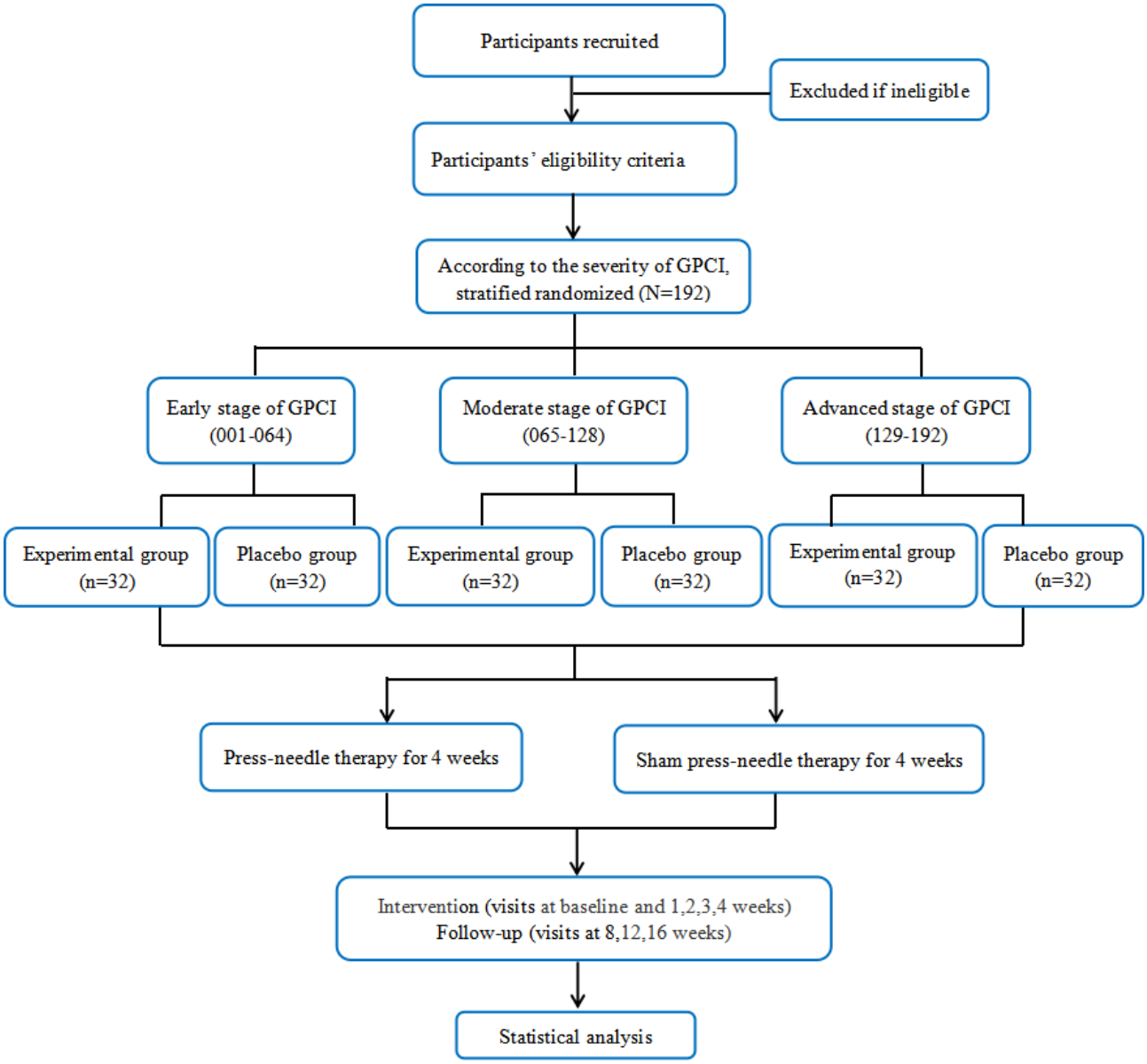

Discussion

Overview

Acupuncture is a major treatment in TCM, and studies have shown that acupuncture can protect the optic nerve in patients with glaucoma [20]. The press needle is a new kind of acupuncture device that can create a more lasting stimulus and simpler operation, while resulting in less pain, with the therapeutic effect of cumulative treatment characteristics. At present, press-needle therapy is widely used in various clinical diseases and has achieved satisfactory therapeutic effects [9,21]. Acupuncture is effective in protecting visual function in glaucoma [22]. Press-needle embedding can improve the deteriorating vision and shrinking visual field of patients with optic nerve atrophy and increase clinical efficacy [23]. Abnormal blood flow is an important factor in optic nerve damage in glaucoma [24], and acupuncture can modify the blood flow parameters in glaucoma [7]. Clinically, we have widely used press-needle therapy for glaucoma visual function protection and achieved good clinical efficacy, and we have further found that press-needle therapy can improve ocular circulation in patients with glaucoma. However, the quality of evidence supporting the use of press-needle therapy for GPCI is limited due to methodological limitations. Therefore, it is necessary to explore the effect of press-needle therapy on visual function and eye blood circulation in patients with GPCI. The double-blind method reduces the differential assessment of outcome events and improves subject adherence. Previous studies have shown that press needles and sham press needles (lacking the needle element) enable effective double-blind settings for acupuncture clinical studies [25]. Therefore, sham press needles were chosen as the control intervention for this study.

Due to the unique nature of glaucoma, patients experience progressive optic nerve damage as the disease progresses. To avoid violating medical ethics and reduce the rate of patient detachment, methylcobalamin has been chosen as the basic optic neuroprotective drug for the experimental and control groups in this study. In addition, to observe the effect of

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press-needle therapy on GPCI of different disease severities, participants will be classified as early, moderate, and advanced based on their visual field defects.

This study is designed as a double-blind, placebo-controlled trial. To guarantee the quality of the study, its design and execution will be strictly performed with proper quality control. A training session for each center will be held to explain the detailed study protocol, the diagnosis of the TCM syndrome pattern, and the SOPs. The same investigator will be responsible for the examination of each patient at different times. All indicators will be assessed by independent assessors. The principal investigators, statisticians, and outcome assessors will be blinded to the treatment assignments until the database is locked.

Innovations and Limitations

This is the inaugural clinical trial protocol devised by our team to investigate the potential mechanisms of acupuncture for patients diagnosed with GPCI. We have selected eye blood circulation as the entry point for this study. The trial will be conducted in accordance with rigorous methodology. For example, patients with GPCI will be randomly assigned to 2 groups. For the control group, a nonpenetrating sham apparatus, similar in appearance to acupuncture needles, will be used to achieve blinding. Furthermore, each participant will be requested to provide feedback on their experience following the acupuncture session, with a view to evaluating the efficacy of the blinding process. The data will be subjected to statistical analysis in a blinded trial, with the intervener, efficacy assessor, and statistician all acting independently. However, it is not possible to eliminate gender bias in the randomization process. Consequently, to guarantee the reliability of the data, it is necessary to expand the sample size further.

Conclusion

In conclusion, the purpose of this research is to verify that press-needle therapy can effectively improve visual function and eye blood circulation in patients with GPCI. The outcome of this study will provide evidence-based data for the use of press-needle therapy to treat GPCI accompanied by liver-kidney deficiency, blood stasis, and fluid retention syndrome, thereby providing a new avenue for the treatment of GPCI.

Acknowledgments

We are grateful to all the researchers who participated in this trial. Upon completion of the study, the findings will be disseminated to relevant stakeholders, including health care professionals, the general public, and pertinent organizations, through the publication of academic papers and presentations at academic conferences.

This trial is supported by the Science and Technology Department of Sichuan Province (approval no: 2021YJ0443), the National Natural Science Foundation of China for the Youth (approval no. 82305324), and Mianyang Central Hospital Incubation Subjects (approval no: 2020FH07). The results of the research will be presented in the form of publication or conference reports. All the study funders have no role to play in the study design, data collection and management, or manuscript writing and publication.

Authors' Contributions

HJL designed the trial and drafted the manuscript. HJL, CW, and ST are the principal investigators at each hospital. XY (Xuemeng Yu) is responsible for assisting with patient recruitment. XY (Xing Yan) will perform press-needle treatment for patients with glaucoma with controlled intraocular pressure (GPCI). YD and MY will conduct the quality control of this trial. MX, FL, and RZ will be responsible for data collection. MS is responsible for the revision of this manuscript. All the authors have read and approved the final version of this manuscript. Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of our research.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Measurement items and points of data capture.
[DOCX File , 23 KB - resprot_v14i1e67737_app1.docx]

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Abbreviations

AE: adverse event
BCVA: best-corrected visual acuity

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CDFI: color Doppler flow imaging
CRF: case report form
FAS: full analysis set
GPCI: glaucoma with controlled intraocular pressure
HIOP: high intraocular pressure
IOP: intraocular pressure
MD: mean deviation
OCTA: optical coherence tomography angiography
PPS: per protocol set
RGC: retinal ganglion cell
SOP: standard operating procedure
TCM: traditional Chinese medicine

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Protocol

Effectiveness of Stromal Vascular Fraction (SVF) and Platelet-Rich Plasma (PRP) in Patients With Knee Osteoarthritis: Protocol for a Phase 3, Prospective, Randomized, Controlled, Multicenter Study (SPOST Study)

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Abstract

Background: Available evidence on the conservative treatment of knee osteoarthritis still leaves questions about the efficacy of platelet-rich plasma (PRP) and whether stromal vascular fraction (SVF) offers a superior therapeutic tool.

Objective: This study aims to assess the clinical efficacy of SVF as adjuvant therapy to PRP on functionality and tissue regeneration for knee osteoarthritis.

Methods: In a multicenter, randomized, triple-blind, controlled trial, 108 individuals with knee osteoarthritis will be block-randomized in a 1:1 ratio. Patients will receive an initial single PRP or PRP + SVF injection followed by PRP doses at 1 month and 2 months. The primary endpoint is functional improvement measured with the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) at the 6-month follow-up. Secondary endpoints, collected at the 1-month, 2-month, 3-month, 6-month, and 12-month follow-ups, will include the pain visual analogue scale during maximal physical activity, WOMAC score, length of time to return to work and sports in days, magnetic resonance imaging (MRI)–based Whole-Organ Magnetic Resonance Imaging Score (WORMS), Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) score, MRI Area Measurement and Depth and Underlying Structures (AMADEUS) score at 6 months and at 12 months, adverse events, and serious adverse events.

Results: Participant recruitment and data collection are expected to begin in July 2025 and finish in July 2027. Final end points will be gathered in August 2027, and the results are expected to be published in late 2027.

Conclusions: The study results will provide insight into the clinical efficacy of SVF as adjuvant therapy to PRP on functionality and tissue regeneration in patients with knee osteoarthritis.

Trial Registration: ClinicalTrials.gov (NCT05660824); https://clinicaltrials.gov/study/NCT05660824

International Registered Report Identifier (IRRID): PRR1-10.2196/62659

(JMIR Res Protoc 2025;14:e62659) doi:10.2196/62659

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KEYWORDS

stromal vascular fraction; platelet-rich plasma; osteoarthritis; adjuvant therapy; tissue regeneration; clinical efficacy

Introduction

Osteoarthritis, the most common joint disease [1], has a high social and individual impact, and the development of therapeutic options is a public health priority. Its multifactorial etiology is still a source of active research [2,3]. The most common conservative treatments for osteoarthritis include painkillers, active physical therapies, orthotics, corticosteroid infiltrations, hyaluronic acid, and platelet-rich plasma (PRP) [1,4].

PRP may be beneficial in osteoarthritis by interfering with catabolic and inflammatory events and by subsequently promoting anabolic responses. Activation of PRP releases biologically active components, including platelet-derived growth factor, transforming growth factor-β, type I insulin-like growth factor, and vascular endothelial growth factor. These proteins are responsible for a range of critical tissue healing roles, such as chondrocyte and mesenchymal stem cell (MSC) proliferation, bone and vessel remodeling, inflammatory modulation, and collagen synthesis [5].

Several clinical trials have found improvement in clinical outcomes for osteoarthritis [6,7], presumably associated with the chondroprotective effect of PRP. Nevertheless, despite the numerous studies on the subject, the evidence is inconsistent, there is a lack of uniform improvement in functional outcomes, and an in vivo effect on human cartilage regeneration has not yet been demonstrated [8,9].

Stem cell therapy has arisen as a new therapeutic option for knee osteoarthritis. Preclinical models have elucidated how injected adipose-derived mesenchymal stem cells (AD-MSCs) coordinate the cartilage regeneration process [10-12] through paracrine mechanisms [13], producing cytokines and trophic bioactive factors that stimulate cellular proliferation and reduce inflammation, fibrosis, oxidative stress, and chondrocyte senescence [1].

AD-MSCs seem to have a better hypoxic tolerance, fewer immunologic and inflammatory responses [14], better chondrogenic induction and gene expression [15], and less variable and more reliable clinical result [14] than bone marrow–derived mesenchymal stem cells (B-MSC).

Stromal vascular fraction (SVF), a product from processed adipose tissue, contains MSCs, endothelial precursor cells, T regulatory cells, macrophages, smooth muscle cells, pericytes, and preadipocytes. SVF extraction and injection techniques have recently been used as an alternative to harvest AD-MSCs due to their logistical simplicity and feasibility in clinical practice. The superiority or inferiority of SVF compared with AD-MSC has not yet been established.

Randomized trials indicate that intra-articular SVF injections can provide clinical benefits in knee osteoarthritis [16], with some studies noting cartilage quality improvements [16-19]. Despite their potential, SVF treatments are invasive, costly, and supported by a limited number of studies, many of which lack the homogeneity needed for clinical guideline endorsement, even though research in this area is steadily increasing and yielding promising results. Although PRP is often recommended in sports medicine for knee osteoarthritis, it is unclear whether combining it with SVF offers greater benefits for patients unresponsive to conservative treatment. This randomized controlled trial (RCT) will be the first to provide comparative data on the efficacy of SVF as an adjunct to PRP, addressing a critical gap in osteoarthritis treatment research.

The objectives of this study are to assess the clinical efficacy of SVF as adjuvant therapy to PRP on (1) functionality for knee osteoarthritis and (2) tissue regeneration for knee osteoarthritis.

Methods

Study Design

This multicenter, parallel-group, triple-blind study will enroll 108 patients who will be randomly assigned in a 1:1 ratio to either the intervention (SVF+PRP injection at baseline) or control group (PRP-only injection at baseline) using stratified randomization. The study will use a superiority framework.

The follow-up will last 12 months, with endpoints at 1 month, 2 months, 3 months, 6 months, and 12 months.

Study Setting

In this multicenter study, we aim to recruit all patients between July 2025 and August 2027 in the Sports Medicine Division of La Providence Hospital and in the Rehabilitation division, Hôpital Fribourgeois, both in Switzerland. The lead center is the Sports Medicine Division of La Providence Hospital where author AS is the sponsor-investigator. All the interventions will be performed in the lead center.

Eligibility Criteria

Patients will be recruited if they have knee osteoarthritis with persistent symptoms despite appropriate first-line treatment (ie, active physical therapies, sport and daily activity adaptations, orthotics use, medication) and for whom a surgical procedure is not indicated nor recommended.

The following main inclusion criteria will be used: (1) age older than 16 years; (2) symptomatic knee osteoarthritis confirmed by magnetic resonance imaging (MRI); (3) absence of free or displaced meniscal or cartilage fragments on the MRI of the affected knee; and (4) failure of first-line conservative management, including medical or infiltrative treatment, orthotics use, active rehabilitation plan, and adaptation of sports and work habits, in the last 3 months.

The following main exclusion criteria will be used: (1) patients familiar with the lipoaspiration process; (2) significant disease of the contralateral member with a disability, as evaluated with a Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score >80%; (3) co-existence of microcrystalline disease (ie, gout, pseudogout); (4) active inflammatory rheumatic disorders; (5) a need for regular anti-inflammatory treatment (either nonsteroidal

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anti-inflammatory drugs [NSAIDs] or corticosteroids) or anticoagulants; (6) patients with decompensated renal failure, hepatic dysfunction, or severe pulmonary or cardiovascular disease; (7) patients with an immunocompromised status; and (8) women who are pregnant or intend to become pregnant during the study.

If bilateral disease is present and both sides require either the experimental or control intervention, only the most symptomatic side will be studied.

Informed consent will be obtained by the local site investigator. Other physicians in associated structures (ie, orthopedists, general practitioners, physiotherapists) are informed of the study and will be asked to refer patients to the referent sports medicine departments.

Interventions

In both study groups, the intervention will be performed in the operating room under aseptic conditions and following the Arthrex protocols to prepare the autologous conditioned plasma [20], which is our PRP, and autologous conditioned adipose [21], which is our SVF, as described in the following paragraphs.

The patient is placed with a surgical drape hiding the interventional zone from the patient's sight. The blinded investigator performs a 1.5 mm incision under local anesthesia on each abdomen side in order to introduce the microcannula used to extract the SVF. Tumescent solution is prepared by mixing 500 mL NACL with 30 cc 2% lidocaine + adrenaline 1:200000 and 3 cc 8.4% sodium bicarbonate, then 60 mL of this preparation are injected into each side and left in place. An interval of 20 minutes is allowed, which is necessary to let the tumescent solution act on the abdominal adipose tissue. At this point, the blinded investigator leaves the room. In the experimental arm, the unblinded investigator uses a double syringe system to extract 30 mL adipose tissue from the abdominal incisions. This is then centrifugated at 2500 rpm for 4 minutes. The oil and water are discarded. The lipoaspirate is then filtered using two 20 mL syringes and a 1.4-mm diameter transfer hub. One last centrifugation is performed at 2500 rpm for 4 minutes obtaining 2 mL to 6 mL SVF and the remaining oil. This last mixture is then discarded. In the control arm, the unblinded investigator performs a sham adipose tissue extraction by introducing the extraction cannula and moving it for 2 minutes on each side. In both study arms, the venipuncture is then performed, and 15 mL blood are extracted for the PRP preparation using the Arthrex double syringe system [20]. The blood is then centrifuged at 1500 rpm for 5 minutes, resulting in 4 mL to 7 mL of PRP. No anticoagulant, calcium chloride, nor other PRP activator is added. Following the aseptic technique, the unblinded investigator prepares the SVF-PRP mixture or PRP alone in an opaque 10-mL syringe. In parallel, the patient is prepared for the ultrasound-guided injection procedure. With an 18-gauge needle, the SVF-PRP mixture or PRP alone is then injected by the blinded investigator.

Postintervention care includes (1) partial weight-bearing for 1 month; (2) active strengthening of the muscles without overloading the knee using, if possible, the blood-flow restriction technique and gentle nonweight-bearing muscle activation, including core stability exercises; (3) mobility; and (4) modification of daily activities, work, and sports habits.

A total of 5 follow-up visits are planned for the study, during which principal and secondary outcomes will be gathered by a blinded investigator. At the 1-month and 2-month follow-up visits, patients in both study arms will receive 2 additional ultrasound-guided PRP injections performed by the blinded investigator and following the same Arthrex autologous conditioned plasma technique. The same postintervention care will be provided after these 2 PRP injections. Figure 1 shows the study flow chart.

Anticoagulants (eg, aspirin) and anti-inflammatory drugs (eg, ibuprofen, naproxen, meloxicam) should not be used 2 weeks before and 2 weeks after each injection as it can potentially interrupt the therapeutic acute inflammatory response and cytokine production.

Active physical therapies regimens, orthotics use, sports, and daily activities are adapted to the patient, on a day-by-day basis, during the postintervention care.

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Figure 1. Study flow chart. MRI: magnetic resonance imaging. PRP: platelet-rich plasma.

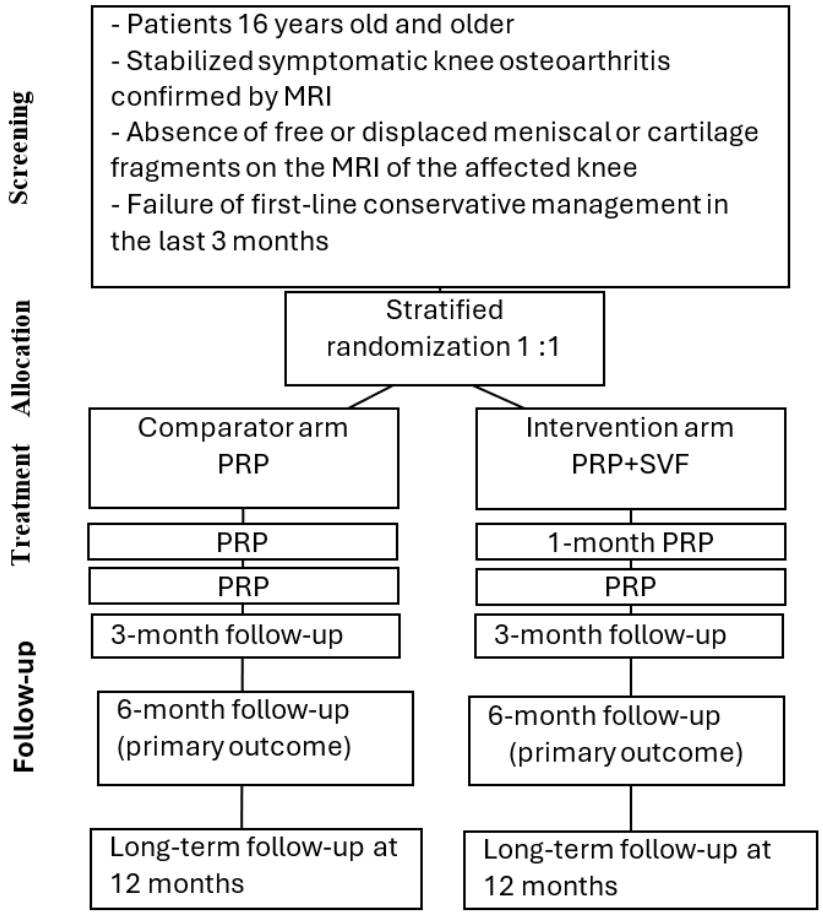

Outcome Measurements and Assessments

The primary outcome is functional improvement measured with the 0%-100% normalized WOMAC at the 6-month follow-up, where 0% indicates complete absence of symptoms and 100% indicates maximal possible symptom severity. A clinically relevant functional improvement is a difference of 9.1 points out of 100 points.

The secondary outcomes will be clinical and radiological parameters gathered at the 1-month, 2-month, 3-month, 6-month, and 12-month follow-ups. These include a 10-point pain visual analogue scale (VAS) during maximal physical activity performed by the patient according to manageable pain and clinical recommendations, the 0%-100% normalized WOMAC [2], length of time to return to work and sports in days, adverse events (AEs), and serious adverse events (SAEs). Pain will be assessed as an AE of interest, during the intervention and 48 hours following the intervention.

The improvement in cartilage quality will be assessed at the 6-month and 12-month follow-ups (previous MRI should not be dated more than 3 months before the intervention) using 3 key MRI-based scoring systems: Area Measurement and Depth and Underlying Structures (AMADEUS) [13], Whole-Organ Magnetic Resonance Imaging Score (WORMS) [22], and Magnetic Resonance Observation of Cartilage Repair Tissue (MOCART) [23].

We initially planned to statistically assess these outcomes at 6 months and 12 months. However, assessment of these parameters at other time points might be subject to exploratory analysis.

The participant timeline is presented in Table 1. The following information will be collected at baseline: age, gender, height, weight, BMI, smoking status, comorbidities, baseline Kellgren–Lawrence grade, current and previous treatments, and posttraumatic etiology. The set of clinical and radiological scores include the VAS, WOMAC, return to work and sports in days, AMADEUS, WORMS, and MOCART.

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Table 1. Study assessments and procedures at the study visits.

Procedures	Screening[a]	Baseline	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5
Timing (visit window)	–3 weeks (+3 weeks)	0	1 month (±7 days)	2 months (±7 days)	3 months (±7 days)	6 months (±7 days)	12 months (±7 days)
Informed consent	X	—[b]	—	—	—	—	—
Inclusion/exclusion criteria	X	—	—	—	—	—	—
Baseline characteristics	—	X	—	—	—	—	—
Clinical scores	—	X	X	X	X	X	X
MRI[c]	—	X	—	—	—	X	X
Randomization	—	X	—	—	—	—	—
Lipoharvesting or sham lipoharvesting	—	X	—	—	—	—	—
Intervention[d]	—	X	—	—	—	—	—
PRP[e] injection	—	—	X	X	—	—	—
Concomitant medication	—	X	X	X	X	X	X
AEs[f] and SAEs[g]	—	X	X	X	X	X	X

[a]Screening and baseline visits can be performed on the same day if the patient has been given reasonable time to make a consented decision about participation in the study.

[b]—: not applicable.

[c]MRI: magnetic resonance imaging.

[d]Stromal vascular fraction+platelet-rich plasma (PRP) or PRP-only injection depending on the group.

[e]PRP: platelet-rich plasma.

[f]AEs: adverse events.

[g]SAEs: serious adverse events.

Sample Size

The sample size for this study was calculated using PS software (Vanderbilt University) [24]. We aimed to detect a clinically meaningful difference of 9.1% in the absolute change in the WOMAC function score between the experimental and control groups. The calculation assumed an SD of 13.9%, based on findings from the study conducted by Tubach et al [25].

In their study, Tubach et al [25] evaluated changes in the WOMAC function score in patients with knee osteoarthritis treated with NSAIDs over a 4-week period. They reported an average baseline WOMAC function score of 42.8 (SD 16.1) and an absolute improvement of –11.6 (SD 13.9). These values were used to estimate the variability in absolute changes for our calculation.

With these parameters, a sample size of 108 patients (54 per group) was determined to provide 90% power to detect the specified difference at a 5% significance level using a 2-tailed test. This calculation ensures that our study is adequately powered to detect a meaningful treatment effect based on absolute improvements in functional outcomes. The study will collaborate with health care providers in both study centers to achieve the target sample size. Additionally, potential participants will be contacted through patient registries and referrals. All recruitment efforts will comply with ethical guidelines and prioritize informed consent. Figure 2 shows the CONSORT (Consolidated Standards of Reporting Trials) diagram [26].

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Figure 2. CONSORT (Consolidated Standards of Reporting Trials) diagram showing the flow of participants through each stage of the randomized trial. PRP: platelet-rich plasma; SVF: stromal vascular fraction.

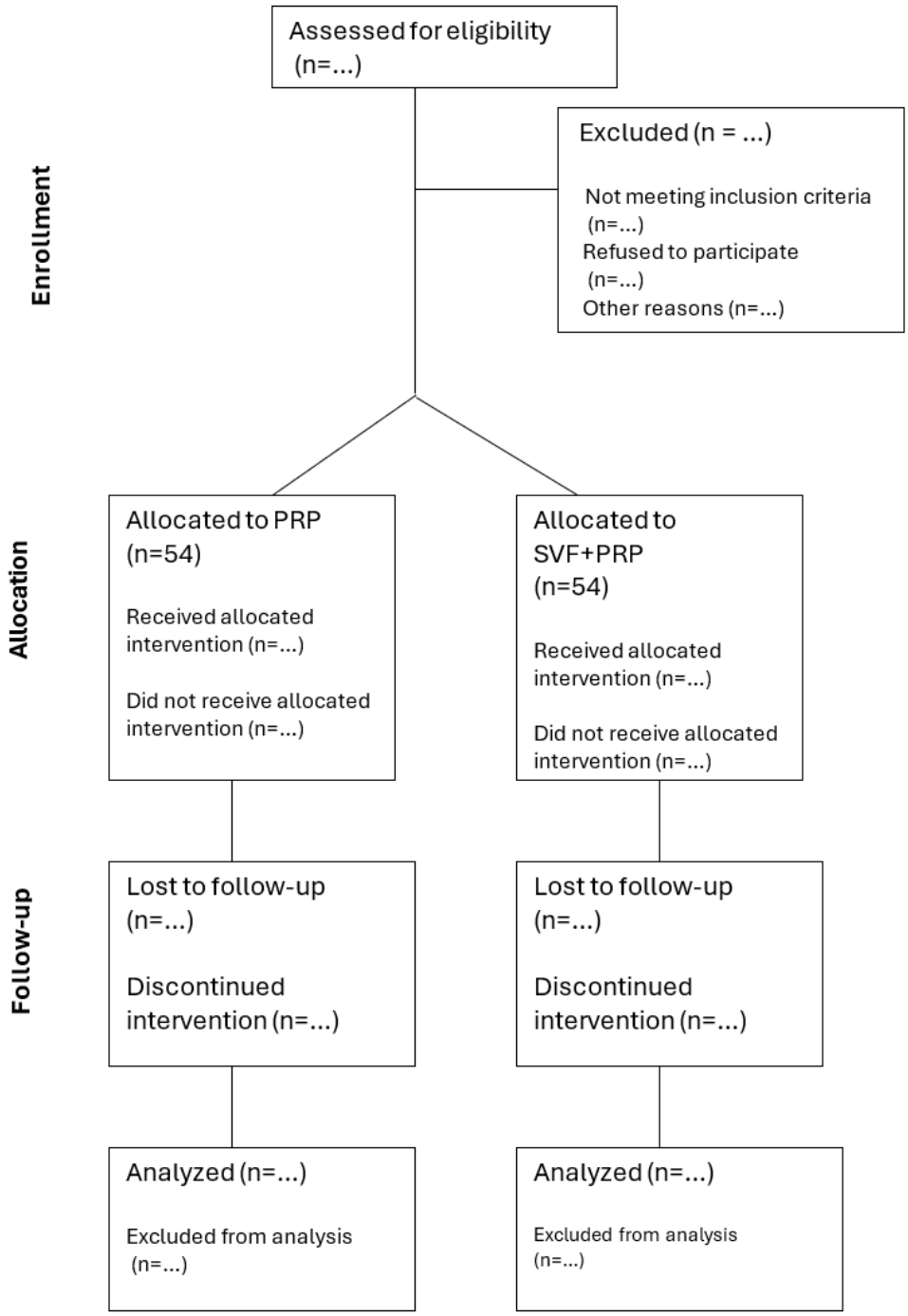

Randomization and Blinding

Study participants will be randomized at a 1:1 ratio to either the intervention arm or the active comparator arm using a randomization table and blocked randomization with blocks of 4 patients. Participants will be assigned to specific strata based on age (older or younger than 40 years) and the presence of cartilage defects (partial, full, or full with bone deformation).

The unblinded investigator responsible for the study interventions will perform the randomization shortly before administering the interventions. This study is triple-blinded: (1) Participants will be unaware of their group assignment throughout the intervention and study duration, (2) the investigator performing the intraarticular injection and the outcome assessor will remain blinded, and (3) the statistician will also be blinded. The investigator responsible for preparing the PRP+SVF or PRP-only preparation will be unblinded and will not participate in outcome assessments.

All patients will undergo a venipuncture, either a lipoaspirate or a sham lipoaspirate, followed by an ultrasonographically guided PRP or PRP+SVF injection. It is anticipated that unblinding will not be required to ensure patient safety, as no known adverse effects of the SVF (such as local pain, tenderness, hematoma on donor site, or infection) require

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unblinding for clinical management. However, if unblinding becomes necessary due to unexpected circumstances, the unblinded investigator will disclose the allocated intervention for the affected patients.

Data Collection and Management

All data collected in this study will be recorded in standardized electronic case report forms (CRFs; see Multimedia Appendices 1-4). We plan to use Hermes software. Hermes is a tool developed by sponsor-investigator AS, used for a patient registry, and validated by the local ethics committee board (authorization # CERVD AO_2020-00006). Only data with logical numeric variables within the correct ranges or predefined categorical variables can be entered into the electronic CRFs. Data entry for variables of interest is mandatory.

CRFs will be kept current to reflect participant status at each phase during the course of the study. Study-related data will be collected in a coded manner (participants will not be identified in the CRF by name or initials). Identification of patients must be guaranteed at the study site. Patients' identifications will be recorded in a sequential list stored in the local investigator's secured server. At the end of the study, when the database has been checked for completeness and validated by the sponsor-investigator, it will be locked and used for statistical analyses. All "study essential documents" (eg, informed consent form, CRFs) will be archived for at least 10 years after completion of the clinical trial.

Data sharing is not applicable to this article, as, to date, no data sets have been generated nor analyzed.

Statistical Analysis

The WOMAC score will be normalized to a 0%-100% scale, where 0% indicates no symptoms and 100% represents the highest severity of symptoms. This normalization involves converting the raw scores into percentages, facilitating the interpretation and comparison of results across participants and study groups. The absolute difference at 6 months will serve as the primary outcome and will be compared using either the paired Student *t* test or the Wilcoxon signed-rank test, depending on the distribution of the variable, with intention-to-treat analysis. The absolute differences in secondary outcomes (changes from baseline to other time points) between the treatment and control groups will be evaluated with the appropriate statistical test (categorical variables: chi-square or Fisher exact tests; continuous variables: Student *t* or Wilcoxon rank tests). All analyses will include both intention-to-treat and per-protocol analyses. Effect estimates, 95% CIs, and descriptive *P* values will be reported whenever possible, along with corresponding graphs.

A post hoc analysis will attempt to identify variables of interest using the appropriate global linear model.

Since the intervention is considered low risk, no interim analysis is planned. In case of missing primary outcome data, patients will be withdrawn from the analysis. Patients missing secondary outcome data will remain in the study but be excluded from those specific analyses.

Oversight and Monitoring

For quality control of the study conduct and data retrieval, all study sites will have regular monitoring activities performed by appropriately trained and qualified monitors, who are outsourced by the sponsor-investigator. Monitoring activities will consist of on-site monitoring as well as remote and centralized monitoring.

The objectives of a monitoring visit are to (1) verify the informed consent form process for each monitored participant, (2) verify the prompt and accurate recording of all monitored data points and prompt reporting of all safety events, (3) compare collected data with participants' source documents, and (4) ensure investigators comply with the protocol.

The monitors may also inspect the clinical site regulatory files to ensure that regulatory requirements and applicable guidelines (International Council for Harmonisation [ICH] Good Clinical Practice [10]) are being followed.

SAEs will be defined as any untoward medical occurrence that results in death, is life-threatening, requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or in a congenital anomaly or birth defect. SAEs should be followed until resolution or stabilization. Assessment of causality will be based on the criteria listed in the ICH E2A guidelines [10], and severity will be graded based on the Common Terminology Criteria for Adverse Events Version 5 [27]. All SAEs will be reported immediately and within a maximum of 24 hours to the sponsor-investigator of the study. The sponsor-investigator will re-evaluate the SAE and return the form to the co-investigator. SAEs resulting in death will be reported via the sponsor-investigator to the Swiss Business Administration System for Ethics Committees and to the other ethics committees involved in the trial within 7 days.

Regular audits are not planned. For the purpose of on-site inspection or audit, the competent authorities or ethics committee may require access to all source documents and other study-related records. The sponsor-investigator and local investigators must ensure the availability of these documents at any time.

Ethical Considerations

Ethics Review Approvals

To comply with local regulations in Switzerland regarding clinical trials involving human subjects, this study design is classified as risk category C [28-30].

Therefore, both Swissmedic (the Swiss authority responsible for the authorization and supervision of therapeutic products) and the local ethics committee must review and approve the research protocol. Since both applications require a significant investment, a grant request will be submitted prior to applying to these two institutions. The principal investigator will obtain approval from the competent authority (Swissmedic) before the start of the study. Once the protocol is approved, no changes will be made without prior approval from the ethics committee, except when necessary to eliminate immediate hazards to participants.

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Informed Consent

The recruiting investigator will explain the study's nature, purpose, procedures, duration, risks, benefits, and discomforts. Participation will be voluntary, and participants can withdraw at any time without affecting their medical care. Each participant will receive an information sheet and consent form to make an informed decision, with time to consult others and ask questions. Consent will be obtained before any procedures, and the signed form will be kept as part of the records. Participants will be informed that authorized individuals may examine their medical records. The informed consent is available in Multimedia Appendix 5.

Privacy and Confidentiality

The investigator upholds the participant's right to privacy and complies with privacy laws, ensuring anonymity in scientific presentations and publications. Medical information from the study is confidential, and third-party disclosure is prohibited. Participant confidentiality will be maintained using identification code numbers. Authorized representatives, such as those from Swissmedic or the ethics committee, may access relevant medical records for data verification.

Compensation Details

There is no compensation provided for participants in this human subjects research.

Identifiable Features

Identifiable features of research participants in any image or supplementary material will not be visible.

Results

This version of the study protocol presented in this article is ready to be presented to the Switzerland regulatory authorities. A request for funding was submitted to the Swiss Medical Foundation in December 2024, and the study was registered in the portal for clinical trials in Switzerland (number pending).

Enrollment to the study is expected to begin in July 2025 and finish in July 2027. Final end points will be gathered in August 2027, and the results are expected to be published in late 2027. The findings will be shared through conference presentations targeting rehabilitation and sports medicine specialists. The Swiss Medical Network and Switzerland's Physical Medicine and Rehabilitation Network will be engaged through presentations at their yearly research events to help implement findings in clinical settings.

Given the open-access nature of the target journal, all results will be publicly available. To gather feedback, we will use postpublication surveys, interactive webinars, and follow-up interviews with patients and practitioners to discuss the applicability and impact of SVF therapy in practice.

Discussion

This study design intends to assess the potential benefits of SVF injection, an easy-to-use, simple, and noninvasive cellular therapy, on the most frequent joint disease. With this high-quality RCT, SVF will be compared with one of the most commonly used noninvasive therapies in the field of sports medicine, PRP.

Based on available clinical trials, we hypothesize that SVF treatment in addition to PRP may lead to significant clinical and radiological improvement in patients with knee osteoarthritis. The WOMAC and VAS scores are among the most commonly used clinical outcomes in RCTs and meta-analyses for knee osteoarthritis research. For radiological assessment, 3 MRI-based scoring systems—AMADEUS, MOCART, and WORMS—are frequently cited in RCTs. Including these scores as primary and secondary outcomes will facilitate future meta-analyses and allow direct comparison of our trial's results with those of previous studies

Compared with PRP, cellular therapy with SVF requires more physician training, takes more time, and ultimately incurs higher costs. In other words, it demands greater resources. From the authors' perspective, patients and caregivers should only invest in these additional resources if clear benefits are demonstrated, which this study aims to establish.

Different techniques have been used to inject or implant cellular therapy with MSCs to the required site, but consensus about the best approach does not exist. However, biologically, some elements support the use of AD-MSCs for nonbone tissue. AD-MSCs would theoretically be more resilient than B-MSCs to the hypoxic articular cavity because they are less dependent on mitochondrial respiration for energy production. From an immunological perspective, AD-MSCs should be preferable to B-MSCs since B-MSCs could induce a higher immunological response due to their higher cell-surface human leukocyte antigen class I expression. AD-MSC highly expresses interleukin-33, which promotes regulatory T cell phenotype proliferation, which would theoretically mean a beneficial effect on anti-inflammatory responses [14].

Han et al [11] compared AD-MSC with B-MSC for knee osteoarthritis and found a superior therapeutic effect of AD-MSC compared with B-MSC on VAS and WOMAC scores. Zhou et al [31] performed a meta-analysis comparing AD-MSC and B-MSC therapies, and they found no statistical differences in clinical scores between the two therapies but did find a higher variability in B-MSC results, suggesting AD-MSCs might be a more reliable therapeutic option. Ude et al [32] found better chondrogenic inductions and gene expressions with AD-MSCs than with B-MSCs.

The therapeutic potential of MSCs is of great interest due to their possible long-term chondroprotective and even chondroregenerative effects. A meta-analysis by Lee et al [19] demonstrated significant improvements in imaging outcomes measured using the WORMS and MOCART scores. WORMS scores improved significantly with SVF therapy compared with controls at both 6 months and 12 months posttreatment (6 months: mean difference [MD]=–18.29, 95% CI – 21.75 to –14.84; 12 months: MD=–26.78, 95% CI –29.95 to –23.61). Similarly, MOCART scores showed notable improvements with AD-MSC therapy at 6 months (MD=24.7, 95% CI 5.92 to 43.48) and 24 months (MD=25.8, 95% CI 5.52 to 46.08), while SVF therapy resulted in significant gains at 6 months, 12 months,

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and 24 months (6 months: MD=30.11, 95% CI 26.08 to 34.13; 12 months: MD=36.82, 95% CI 23.95 to 49.68; 24 months: MD=10.60, 95% CI 1.37 to 19.83).

The comparative superiority of SVF over AD-MSCs, or vice versa, remains uncertain, as no RCT has yet directly addressed this question. An observational study [33] suggested the superiority of AD-MSCs, but further evidence is needed.

The meta-analysis by Lee et al [19] showed some differences between both therapies on clinical outcomes. A significant improvement in the VAS score was found at 6 months and 12 months with AD-MSCs (6 months: MD=–1.62, 95% CI –2.46 to –0.79; 12 months: MD=–1.97, 95% CI –3.22 to –0.72), whereas SVF showed significant results only at 12 months (6 months: MD=–2.32, 95% CI –5.15 to 0.52; 12 months: MD=–2.13, 95% CI –3.06 to –1.21). In contrast, functionality measured with WOMAC scores improved significantly 6 months after SVF treatment (MD=–6.12, 95% CI –10.71 to 1.52), while AD-MSC therapy yielded significant improvements only after 12 months (6 months: MD=–1.96, 95% CI –5.36 to 1.45). At 12 months and 24 months, both SVF and AD-MSC therapies produced significant improvements in the WOMAC score (12 months SVF: MD=–9.09, 95% CI –12.67 to –5.51; 12 months AD-MSC: MD=–9.19, 95% CI –12.48 to –5.90; 24 months SVF: MD=–10.71, 95% CI –18.49 to –2.93; 24 months AD-MSC: MD=–6.88, 95% CI –10.24 to –3.52).

The first main strength of our study design is the large sample size. Second, our study population is well-designed and reproducible, with standardized diagnostic criteria and failure of a first-line standardized rehabilitation plan. Third, the multicenter design allows for better reproducibility of patient selection and management, even if interventions are performed at the main study center by a single investigator. This is, however, a study strength, as it will avoid bias related to the intervention techniques.

A sham lipoaspiration procedure with the patient awake is performed to maintain blinding in the control group. Despite all precautions taken to uphold allocation concealment, breaches may occur if the patient diligently questions the procedure. For ethical reasons, if at 6 months, the progression is unsatisfactory, the intervention's nature may be disclosed if deemed clinically relevant, allowing the patient to benefit from SVF infiltration. Consequently, the study may be limited, as the initial 12-month secondary outcomes will not be considered in the final analysis. Finally, the patient selection, clinical follow-up, and rehabilitation plan might differ across the various recruitment centers (multicenter design).

The minimal clinically important difference was chosen as the limit to detect a clinically relevant difference for sample size calculation. From the authors' point of view, even in the case of statistically significant positive effects of the treatment, the generalization of the procedure should be balanced by a complementary cost-effectiveness analysis. Indeed, in case of mild benefits, other procedures such as strengthening, biomechanics adaptation, medication, annual PRP infiltrations, shockwave therapies, or even slight daily activity adaptations might be options of choice. One should be aware that cellular therapies should not be presented to patients as a "magic potion" or "youth elixir." Especially, the authors warn about the recognized risk of financial benefits based on overemphasized clinical promises.

This study will contribute data to establish the clinical relevance of SVF treatment for the most relevant disease of the musculoskeletal system.

Acknowledgments

A request for funding has been presented to the Swiss Medical Foundation.

Data Availability

All data requests should be directed to the corresponding author.

Authors' Contributions

DARC, AS, and TDS established the study design and wrote the draft of the manuscript. CB contributed to the protocol conception and statistical analysis. PD participated in the manuscript writing. All authors read and approved the final manuscript. Data management activities will be conducted by AS and DARC. DARC and AS contributed equally.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Participant Screening Case Report Form (CRF).
[PDF File (Adobe PDF File), 429 KB - resprot_v14i1e62659_app1.pdf]

Multimedia Appendix 2
Participants Enrollment Case Report Form (CRF).
[PDF File (Adobe PDF File), 211 KB - resprot_v14i1e62659_app2.pdf]

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Multimedia Appendix 3
Participants Follow-up Case Report Form (CRF).
[PDF File (Adobe PDF File), 354 KB - resprot_v14i1e62659_app3.pdf]

Multimedia Appendix 4
Averse Events and Serious Adverse Events Case Report Form (CRF).
[PDF File (Adobe PDF File), 134 KB - resprot_v14i1e62659_app4.pdf]

Multimedia Appendix 5
Patients informed consent.
[PDF File (Adobe PDF File), 190 KB - resprot_v14i1e62659_app5.pdf]

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Abbreviations

AD-MSC: adipose-derived mesenchymal stem cells
AE: adverse event
AMADEUS: Area Measurement and Depth and Underlying Structures
B-MSC: bone marrow–derived mesenchymal stem cells
CONSORT: Consolidated Standards of Reporting Trials
CRF: case report form
ICH: International Council for Harmonisation
MD: mean difference
MOCART: Magnetic Resonance Observation of Cartilage Repair Tissue
MRI: magnetic resonance imaging

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MSC: mesenchymal stem cell
NSAID: nonsteroidal anti-inflammatory drug
PRP: platelet-rich plasma
RCT: randomized controlled trial
SAE: serious adverse events
SVF: stromal vascular fraction
VAS: visual analog scale
WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index
WORMS: Whole-Organ Magnetic Resonance Imaging Score

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Protocol

Effect of Continuous Positive Airway Pressure or Positional Therapy Compared to Control for Treatment of Obstructive Sleep Apnea on the Development of Gestational Diabetes Mellitus in Pregnancy: Protocol for Feasibility Randomized Controlled Trial

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Abstract

Background: Obstructive sleep apnea (OSA) is a common sleep disorder, and in pregnancy, it is associated with an increased risk of complications, including gestational diabetes mellitus and preeclampsia. Supine sleep may worsen OSA, and in pregnancy, it is associated with an increased risk of stillbirth due to effects on fetomaternal blood flow. Continuous positive airway pressure (CPAP) therapy is considered the gold-standard treatment for moderate to severe OSA, although compliance is frequently poor; positional therapy (PT) is generally less effective than CPAP in nonpregnant patients but may be better tolerated and more accessible during pregnancy. There is limited data on whether widespread, early screening for sleep disorders in pregnant women with symptoms of sleep-disordered breathing or at high risk of metabolic complications and subsequent early intervention with CPAP or PT attenuates fetomaternal risks.

Objective: This study aims to determine the feasibility of conducting a randomized controlled trial to assess improved fetomaternal outcomes in a high-risk pregnant population with OSA, using CPAP or PT, initiated by the 16th week of gestation.

Methods: This study is a randomized, controlled, open-label feasibility study in which pregnant women with an apnea-hypopnea index (AHI) or respiratory disturbance index (RDI) ≥5 are treated with CPAP (auto-titrating and fixed pressure) or positional therapy from early gestation (by 16 weeks) until delivery. The primary outcome is the feasibility of the study protocol and the development of gestational diabetes mellitus by the 28-week gestation period. Secondary outcomes include the development of hypertensive disorders of pregnancy (HDP), maternal weight gain, uterine artery blood flow, glycemic control during pregnancy (in participants who develop gestational diabetes), changes in maternal circulating biomarkers, and neonatal birthweight

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complications. Polysomnography at 28- to 32-week gestation period, postpartum polysomnography, therapy compliance, and patient acceptability are also assessed.

Results: The trial commenced on September 30, 2019. The trial is ongoing as of August 6, 2024.

Conclusions: The trial intends to contribute to the growing evidence base to support the need for the identification and treatment of OSA occurring during pregnancy and to assess the feasibility of the study protocol. This will be the first trial to compare the early initiation of CPAP (auto-titrating and fixed pressure) and positional therapy in pregnant women from early gestation, providing alternative therapies for the treatment of OSA in this important population.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12619001530112; https://tinyurl.com/yctdzs4u

International Registered Report Identifier (IRRID): DERR1-10.2196/51434

(JMIR Res Protoc 2025;14:e51434) doi:10.2196/51434

KEYWORDS

obstructive sleep apnoea; OSA; sleep disordered breathing; pregnancy; CPAP; positional therapy; gestational diabetes; GDM; preeclampsia; fetomaternal; maternal; pregnant; fetus; fetal; breathing; apnoea; sleep; respiratory; eclampsia; pregnant women; pregnancy complications; hypertension

Introduction

During pregnancy, physiological changes, including upper airway edema and hormone-related upper airway pressure changes, predispose women to sleep-disordered breathing (SDB) [1]. The prevalence of obstructive sleep apnea (OSA) in pregnancy increases from 3.6% in early pregnancy to 8.3% in midpregnancy and is associated with an independent risk of gestational diabetes mellitus (GDM), preeclampsia, and hypertensive disorders of pregnancy (HDP) [2]. In addition, emerging evidence suggests that the presence of SDB before pregnancy may place women at an increased risk of developing GDM [3]. Supine sleeping in late pregnancy is associated with an increased risk of stillbirth [4], and supine sleep avoidance is recommended from the 28-week gestation period [5].

Treatment options for OSA in non-pregnant adults include continuous positive airway pressure (CPAP), weight loss, positional therapy, mandibular advancement splints, surgery (both upper airway and bariatric), and pharmacological therapies, though not all are suitable for use in pregnant populations. CPAP and positional therapies reduce the occurrence of OSA by reducing the occlusion of the upper airway through pneumatic splinting [6] and repositioning the sleeping persons to reduce collapsibility of the airway [7,8], respectively. Within nonpregnant populations, longer duration CPAP compliance (more than 7 hours) was associated with a reduction in hemoglobin A_{1c} by 1% when CPAP was used for more than 85% of the rapid eye movement stage of sleep during the night [9]. Improvements in blood pressure control have been demonstrated in nonpregnant patients with OSA [10,11], and a small benefit in 24-hour diastolic blood pressure in patients using fixed pressure CPAP compared with auto-titrating CPAP has been reported [12].

In pregnancy, CPAP is recommended as the first line of treatment for OSA [13,14], although alternatives to CPAP may be beneficial but require clinical trials to investigate their utility [14]. In pregnant populations, many studies investigating CPAP treatment have used small sample sizes [15] or initiated therapy in later gestation periods. An early study of 12 pregnant women with OSA at risk of preeclampsia demonstrated no improvement in clinical maternal outcomes [16]; likewise, CPAP failed to demonstrate improvements in glucose levels in obese pregnant women with 2 weeks of CPAP use between 24- and 34-week gestation periods, although compliant use of CPAP in this study demonstrated an improvement in insulin secretion and sensitivity [17]. There are, however, some benefits reported in the literature; a single night of CPAP in a study of 10 pregnant women with preeclampsia and coexisting obesity demonstrated improvements in fetal movements [18], and an improvement in blood pressure control both during sleep and wake was reported in a small study of 7 women, resulting in down titration of antihypertensive medication [19].

Compliant use of CPAP remains a challenge, and in some patients, it may be dependent on clinical support mechanisms, with pre- and postacclimatization phase support improving therapy compliance [20]. Gender-based differences in CPAP compliance have been demonstrated in a large study of nearly 800,000 CPAP users, where women aged 18-30 had the lowest CPAP compliance (51.3%) and were most likely to cease therapy [21]. Barriers to compliant CPAP therapy in pregnant women with OSA are relatively unknown though targeted supports, which have demonstrated improvements in maternal medication compliance, may be beneficial [22]. A recent randomized controlled trial assessed blood pressure outcomes in 340 high-risk pregnant women recruited predominantly during the first trimester, allocated to CPAP or no treatment (control). Despite a mean CPAP compliance of 2.5 hours nightly, and an overall compliance (≥ 4 hours nightly) of 32.7% of participants randomized to CPAP, this reported reductions in diastolic blood pressure and preeclampsia rates [23]. This study additionally presents data on CPAP side effects, and despite rhinitis, mask difficulties, and pressure intolerance reported, there was no significant difference in the reporting of these symptoms between compliant and noncompliant participants, indicating the possibility that these side effects are not barriers to treatment in this special population.

CPAP devices are available in fixed and auto-titrating options and in nonpregnant OSA patients, patient preference has demonstrated mixed results [24,25], although data are lacking in pregnant populations. Furthermore, evidence of the efficacy

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of auto-titrating devices through gestation advancement is limited, and despite the availability of auto-titrating devices that attempt to target flow-limited breathing using reduced air pressure in premenopausal women [26], their utility in pregnancy is unknown.

Positional therapy is less effective at reducing apnea-hypopnea index (AHI) and nocturnal oxygen desaturation [7,27] but is effective at reducing supine sleep time [7], which is associated with the worsening of OSA [8]. Positional therapy (PT) in pregnancy is hypothesized to impact outcomes by two potentially independent pathways: first, by addressing SDB, which is typically worse in the supine position, and second, by minimizing compression of the vena cava by the gravid uterus, which may reduce fatal blood flow. A feasibility study using a back-worn positional therapy band for a single night in healthy pregnant women at 32- to 38-week gestation periods showed improvement in maternal oxygenation and reduced fetal heart rate decelerations compared with the controlled night [28].

Given placentation completes around 16-week gestation period, the timing of OSA treatment intervention may be particularly important, as data demonstrates significant benefits of time-specific interventions in pregnancy, for example, aspirin is generally beneficial in preventing preeclampsia if commenced before 16-week gestation period [29]. We thus outline a protocol to determine the feasibility of a parallel group, individually randomized, controlled, open-label trial comparing CPAP or PT to usual care (control). Commencement of therapy by the 16th week of gestation has been chosen to reduce exposure to intermittent hypoxia on the developing placental function during early pregnancy and to establish early compliance to treatment. The use of fixed pressure CPAP after auto-titration of pressure in this trial was determined by factors including access to trial equipment, cost, and absence of evidence of the superiority of auto-titrating over fixed pressure CPAP in pregnancy. This trial aims to determine the feasibility of conducting a larger trial and to obtain preliminary recruitment and efficacy data that may be used to design and power a larger trial. This study may be of interest to others conducting sleep therapy intervention studies in pregnant women.

Clinical Trial Objectives

This study aimed to determine whether CPAP or PT initiated by the 16th week of gestation in pregnant women with a respiratory disturbance index (RDI) or AHI ≥5 results in improved clinical outcomes, particularly in relation to the development of gestational diabetes.

Trial Feasibility Objectives

This study aims to assess the feasibility and acceptability of trial interventions and schedule of visits and determine limitations of trial design, including patient and hospital staff participation.

Methods

All trial primary and secondary outcomes are described in the Australian New Zealand Clinical Trials Registry Trial Registry.

Ethics Approval and Consent to Participate

Overview

Participant recruitment commenced on September 10, 2019. The final patient was recruited in December 2022 and is expected to complete participation in June 2024. The participants affected by product recalls in this trial will be followed up annually for 5 years, if agreeable as per the protocol. Data from participants who choose to withdraw from study participation will be included in the final analysis unless requested by the participant. The trial was registered on November 6, 2019 (ACTRN12619001530112), 7 weeks after the first participant was recruited for the study. The study protocol was not amended during this time.

Human Subject Ethics Review Approvals or Exemptions

The South Western Sydney Local Health District Human Research and Ethics Committee (SWSLHD HREC) approved this study (June 12, 2019, project identifier 2019/ETH00283). The current protocol version 3.1 was approved on November 11, 2022.

Informed Consent

The participants with scheduled antenatal bookings at Liverpool and Campbelltown hospitals will be invited to undertake a screening eligibility preconsent questionnaire, which is presented in Multimedia Appendix 1 by research study staff to determine participation eligibility as described in the eligibility criteria above. Women will be sequentially approached.

Following the screening, study staff will invite eligible participants to provide written informed consent. Multimedia Appendix 2 presents the postconsent baseline information questionnaire, which will be collected at the next trial consent.

The participants will undertake attended polysomnography to determine eligibility in the RCT. Additionally, the participants will be invited to undertake Apnealink Air and Somte at both the baseline and 28- to 32-week gestation periods, in addition to the attended polysomnography as part of a substudy assessing agreement in AHI or RDI scores in the early to mid-gestation period. Sleep studies will be undertaken within a 7-day window, where practicable. Completion of Apnealink and Somte are not required for RCT participation but will be used to determine the validity of these tests for future use in this population. Eligibility for participation in RCT will be determined by polysomnography outcome.

Women who undergo polysomnography by 14-week gestation period and demonstrate OSA as evidenced by an RDI or AHI ≥5 on polysomnography will be invited to participate in the RCT provided exclusion criteria are not met as described above. A second written informed consent will be collected by study staff, and the participants will be randomized to CPAP, PT, or control as described in the randomization section below.

Validation of home sleep testing in this population will be undertaken via a separate substudy. After validation of the home testing method, further recruitment and screening measurements will continue with screening questionnaires and home Apnealink Air only.

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Privacy and Confidentiality

Unattended polysomnography, Apnealink Air, and biomarker data will be deidentified, as described in the relevant methods sections below. Patient data are deidentified for the purpose of randomization, as described below.

Participant consent forms, printed results, and other identifying information on hard copy will be stored in a locked cabinet in a security-access area of the Respiratory and Sleep Medicine Research Department at Liverpool or Campbelltown Hospitals. Where possible, study data will be stored separately to participant identifiers. A master list of study ID numbers and participant identifiers will be stored electronically in a password-protected file within a designated electronic folder on the Respiratory Research drive on the secure Liverpool Hospital server. A separate password-protected folder will be designated for any electronic records with results and identifying information.

Compensation

If the participants suffer any harm, they will be compensated as per health authority regulations.

Trial Design

Pregnancy-associated obstructive sleep apnea (POSA) is a 2-center randomized controlled feasibility trial. The participants will be recruited following participation in an observational study by our group that assesses diagnostic validation of Apnealink air and Somte devices and long-term fetomaternal outcomes. The participants will also be approached at antenatal visits or called by telephone to assess eligibility. Recruitment at both study sites will be concurrent, and the participants who meet the eligibility criteria based on AHI or RDI results in the observational study will be approached for participation in the RCT.

The RCT will use a parallel group, individually randomized, open-label design with two interventions and one control group (1:1:1), with minimization allocation among the 3 arms stratified for BMI, previous history of preeclampsia, or gestational diabetes mellitus. A total of 48 participants (16 in each arm) will be recruited. Study visits will occur monthly after randomization until 32-week gestation period and fortnightly thereafter until delivery, as is local routine clinical practice for antenatal visits. Data collection will include demographic, clinical and physical details, sleep questionnaire responses, sleep study data, maternal pathology, fetal scans, birth details, maternal and fetal clinical outcomes, sleep therapy compliance, and therapy acceptance questionnaires.

We used the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist when writing our protocol [30], which can be found in Multimedia Appendix 3.

Trial Setting

POSA will be conducted at Liverpool Hospital (LPH) and Campbelltown Hospital (CTN) public hospitals within the South Western Sydney Local Health District in metropolitan Sydney, New South Wales, Australia. LPH is a tertiary referral center offering comprehensive antenatal services, delivering approximately 4000 women annually, and includes a level 6 neonatal intensive care unit for neonates from a 24-week gestation period in the district and a comprehensive sleep and respiratory service, including a 5-bed sleep laboratory, ambulatory testing, and a comprehensive outpatient service, including clinics for CPAP therapy. CTN delivers approximately 4200 women annually, with a level 4 nursery that cares for neonates from a 32-week gestation period and a general respiratory and sleep clinic, without the capacity to undertake polysomnography. POSA participants recruited from CTN will be referred to LPH for laboratory polysomnography.

Eligibility Criteria

Eligible participants are defined as women aged 18 years of age and older; in early pregnancy (up to 14-week gestation period); at increased risk of metabolic complications defined as one or more of (1) BMI greater than or equal to 35 kg/m^2, (2) previous GDM, (3) previous personal history of preeclampsia (or in mother or sister), (4) underlying renal disease, (5) maternal type 2 diabetes (pregestational), and (6) symptoms of SDB including snoring, witnessed apnea, mild excessive daytime sleepiness (EDS; which does not meet the criteria for severe EDS defined by Epworth Sleepiness Scale (ESS>15), or a fall asleep accident, or near-miss accident in the previous 12 months), or tiredness; and obstructive sleep apnea diagnosed by polysomnography defined as RDI or AHI ≥ 5.

The participants will be excluded if they have (1) a previous diagnosis of OSA on active treatment, (2) confirmed GDM or preeclampsia, (3) maternal type 1 diabetes, (4) multifetal gestation, (5) known fetal chromosomal abnormality, (6) inability to provide informed consent, and (7) severe EDS based on clinical assessment (eg, including a fall asleep motor vehicle accident or near miss, transient sleepiness while driving or at lights or needing to pull over due to sleepiness while driving, or transient sleepiness in any other dangerous situation, ie, cooking, carrying a baby) or ESS of greater than 15.

Interventions

All groups will have antenatal care as usual without restriction during the trial. The participants will be randomized to CPAP, PT, or control, and the participants randomized to intervention (CPAP or PT) will undertake therapy device education at the randomization visit and commence therapy on the day of randomization or as soon as is practicable. The participants will also be encouraged to use their therapy device for all sleep periods (including naps) from randomization until delivery. CPAP and PT devices will be returned following delivery or withdrawal or discontinuation from the study. The CPAP masks used by the study participants may be retained at the end of the study.

All participants will undertake polysomnography at the 28- to 32-week gestation period. CPAP or PT intervention participants will complete polysomnography at a 28- to 32-week gestation period with the device in situ to confirm treatment efficacy. CPAP will be titrated, if required, as described above. In addition, participants will be invited to complete Somte and Apnealink at 28- to 32-week gestation period, as part of the device validation substudies.

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CPAP Intervention

The participants in the CPAP intervention group will use a close-fitting facial mask worn overnight during sleep to ensure that the collapsible upper airway is kept patent with a column of air and they will commence on auto-titrating pressure 6-20 cm H_2O (Philips Dreamstation Auto with heated humidification) per clinical practice at the study site. The participants will also be offered a range of CPAP masks to trial with an option to take home multiple masks or sizes if needed. CPAP participants will be educated in device use and troubleshooting by an experienced sleep therapist before commencing therapy. The trial sleep therapist will telephone CPAP group participants on day 3 to gain access to CPAP efficacy data via remote monitoring software (Care Orchestrator, Philips). Pressure will be changed to the 90th percentile pressure in fixed pressure mode, provided compliance data show average usage of CPAP across a period of more than 4 hours (All Days≥4 hours), and treatment efficacy is achieved as determined by residual AHI≤5. The participants with poor compliance or efficacy will be given additional acclimatization time on CPAP, up to 7 days (or as clinically necessary), and changed to the 90th percentile when clinically appropriate. CPAP data will be downloaded via Secure Digital card (SD) data card and reviewed at each study visit and at the return of the device as per the study schedule and interrogated for CPAP compliance, efficacy, and mask leak.

CPAP pressure will be adjusted empirically at scheduled study visits to maintain treatment efficacy (AHI≤5). Polysomnography will be conducted at 28 weeks on the current CPAP pressure. Titration of CPAP pressure will be undertaken if criteria for pressure increase is met per AASM (American Academy of Sleep Medicine) manual titration guidelines, that is, up to 1 increase by 1 cm H_2O per 5-minute period for any of the following: 2 of obstructive apneas, 3 of hypopneas, 5 of the respiratory event–related arousals, or 3 minutes of loud or unambiguous snoring [31]. CPAP pressure changes will be reported in published study findings at the conclusion of the trial.

Compliance and efficacy of treatment feedback will be provided to study participants at each visit to encourage compliance. Additional phone or video support will be available, at participants' request, for participants who encounter difficulty with CPAP compliance. To ensure equal therapy support for CPAP and PT treatment arms, remote monitoring of CPAP compliance will not be conducted beyond the acclimatization period. CPAP devices used in this trial have been replaced by the manufacturer in accordance with the Therapeutics Goods Administration device repair or replacement program following product defect correction order RC-2021-RN-01373-1.

Positional Therapy Intervention

The participants in the PT intervention group will use a noninvasive vibratory device (Night Shift Device: Advanced Brain Monitoring, Inc) that is worn around the neck and promotes sleep in the nonsupine position (Figure 1 [source: Frances Clements, Liverpool Hospital, November 10, 2022]). The device provides a vibratory alert to the wearer when the supine position is detected and is secured at the anterior neck with a magnetic closure (Figure 2 [source: Frances Clements, Liverpool Hospital November 10, 2022]).

Figure 1. Nightshift positional therapy device posterior view.

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Figure 2. Nightshift positional therapy anterior view.

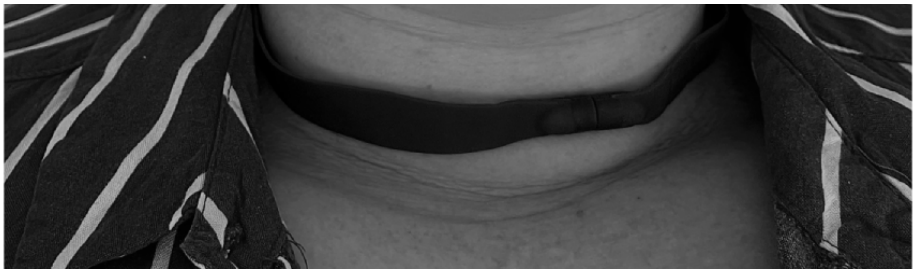

The participants randomized to PT will be provided education by an experienced sleep therapist before commencing therapy. The device will be fitted by measuring the neck circumference and adjusted to ensure that the device does not slide down the neck. The device will be set with a 15-minute feedback delay, with vibration feedback mode on and the device location at the posterior neck. Downloads of therapy data will be obtained by an experienced sleep therapist at each study visit, where possible, as per the protocol schedule, and at the return of the device, compliance and efficacy data will be interrogated. Recording time, position, patient alert frequency, and snore data will be recorded. Feedback will be provided to study participants at each visit. Additional phone or video support will be available for participants with therapy as requested.

Control Group

Control group participants with significant SDB at polysomnography at the 28- to 32-week gestation period and symptoms of severe EDS (ESS>15) will be identified, withdrawn from the study, and managed according to standard clinical practice under the direction of a sleep physician.

Participant Timeline

The participants will be reviewed monthly until the 32-week gestation period and then fortnightly until delivery, coinciding with scheduled antenatal visits where possible. The trial flow chart is depicted in Multimedia Appendix 4. The flowchart describes the participant's progression through the trial protocol and depicts the timing of the interventions.

Sample Size

There are limited data on this topic, particularly on the estimated risk reduction in event rates. We intend to pilot the RCT with an initial 48 patients. This data will be used to refine the protocol and optimize logistics and will be used to inform a larger RCT.

Randomization, Allocation, Concealment, and Blinding

The participants will be individually randomized via a telephone call to the National Health and Medical Research Council's Clinical Trials Centre at Sydney University, who are independent of the trial, by the study coordinator. Randomization will be based on a minimization method with stratification for previous preeclampsia, personal history of gestational diabetes, and BMI≥35, to either CPAP, PT, or control groups. A maximum imbalance value of 1 between any of the 3 arms will be used in determining whether a forced allocation (ie, to achieve minimization of difference of stratification factor totals) or random allocation is used in a specific subject randomization. Treatment allocation will be unblinded for both study staff and participants.

Data Collection, Management, and Analysis

The complete schedule of study visits, procedures and data collection points is presented in Multimedia Appendix 5, which depicts the trial participant study visits and intervention schedule.

Data Management

Data from Apnealink screening tests, CPAP, and PT will be stored in a deidentified format. Polysomnography data will be stored on the secure hospital network. The system is secured via the Information Management and Technology Division's corporate backup software. Research Electronic Data Capture (REDCap; Vanderbilt University) database [32] will be used for data collection and management. Questionnaires will be completed electronically by participants via an email link where possible or by paper questionnaire where needed. In the event of participant discontinuation from the RCT, long-term fetomaternal outcomes of interest will be collected, where agreed to by participants during consent, in writing.

Data Collection Methods

Blood and Urine Collection

With consent, blood will be collected at 12-16, 16-20, 28 gestation weeks, and 6-12 months post partum by study staff or using hospital pathology collection services in EDTA tubes. The blood will be centrifuged (3000 rpm, 10 min), and plasma will be aliquoted (250 µL). The buffy coat will be collected and stored in approximately 250 µL RNA. Later, all specimens will be snap frozen in liquid nitrogen and stored at –80C at the Ingham Institute of Medical Research (Liverpool, New South Wales, Australia). Biomarkers (sFlt-1 [soluble fms-like tyrosine kinase 1], PlGF [placental growth factor], IL-6 [interleukin-6], TNFα [tumor necrosis factor alpha], and HIF1α [hypoxia-inducible factor 1-alpha]) will be assayed at the conclusion of the study blinded to outcomes.

Urinalysis will be conducted at each study visit using SIEMENS Multistix 10SG Test strips. A score of negative, trace, 30 mg/dL (++), 100 mg/dL (++), 300 mg/dL (++), or >2000 mg/dL (+++) will be recorded. If greater than 1+ protein is detected, a random spot urine sample will be sent to hospital pathology services for measurement of urinary protein adjusted for creatinine excretion.

Fetal Monitoring

Fetal ultrasound will be undertaken at the study site fetomaternal units (FMUs). Uterine artery blood flow (pulsatility index measurements) will be recorded at the randomization visit (12-16-week gestation period), 2-6 weeks later (average 4 weeks

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to 16-20-week gestation period), and at 36-week gestation period. Morphology scan (16 weeks) (may be combined with uterine artery blood flow) and growth scan (36 weeks) will be performed. Fetomaternal scans performed at study sites will be performed using ViewPoint 6 (General Electric Healthcare) by experienced sonographers supervised by physician consultants within the FMU.

Questionnaires

ESS [33] and STOP-BANG (snoring, tiredness, observed apnea, high BP [STOP] and snoring, tiredness, observed apnea, high BP-BMI, age, neck circumference, and gender) [34] questionnaires will be used in baseline screening and scored according to standing scoring recommendations (sum of 8 item-scores [ESS] and score 0-8 [STOP BANG]). Functional outcomes of sleep will be assessed using the Functional Outcomes of Sleep Questionnaire (FOSQ-10) [35], which has been validated in pregnancy and scored according to FOSQ-10 marking guidelines [36]. Questionnaires assessing sleep study acceptability, sleep study preference, and therapy acceptability will be undertaken and are presented in Multimedia Appendices 6-13. Questionnaires will be emailed to participants using REDCap or completed in paper hardcopy where the patient is unable to complete electronically. The acceptability questionnaires used in this trial were evaluated on hospital staff unaffiliated with the trial. Feedback was implemented, and questionnaires were redesigned before SWSLHD HREC approval and implementation.

Sleep Study Data Collection

The participants will undergo attended polysomnography (with therapy device in situ for CPAP and PT arms) using Grael v2 (Acquisition System, Compumedics), unattended polysomnography using SOMTE v2 (Acquisition system, Compumedics) and Apnealink Air (Resmed) at 28- to 32-week gestation period at LPH. Laboratory-based polysomnography will be repeated 6-12 months post partum.

Attended and unattended polysomnography will be scored using Profusion PSG 4 auto analysis software (Compumedics) by a single experienced sleep scientist using the 2020 AASM Manual for the scoring of sleep and associated events (Version 2.6 guidelines). Apnealink Air will be automatically scored using Airview (Resmed; AASM 2012, Automatic Scoring) and manually scored by a single experienced sleep scientist using 2020 AASM guidelines (events Version 2.6). All sleep study sets will be reported by the same sleep physician for consistency. Unattended polysomnography and Apnealink Air studies will be scored and reported blindly by sleep scientists and reporting sleep physicians.

Apnealink Air data collection includes airflow (pressure transducer), respiratory effort (abdomen) and oximetry (SpO_2), snoring, and pulse. The participants will complete a self-setup in the home, will be provided with an instruction sheet, and will also manually start study recording as close to anticipated sleep onset as possible and manually stop recording at sleep offset.

Unattended polysomnography data collection included electroencephalography (F3 and F4, M1 and M2), electrooculography (E1 and E2), electromyography (EMG chin [submentalis]), electrocardiogram (modified lead II), airflow (pressure transducer), snoring, airflow (thermistor), respiratory effort (abdomen and thoracic), anterior tibialis EMG (left and right leg), oximeter (SpO_2), and position sensor. The participants will complete a self-setup at home. A comprehensive instruction booklet will be provided, and the participant will be encouraged to watch an instructional video [37]. The participants will have access to phone or video support from experienced sleep staff. Study recording will commence as close to the anticipated sleep onset as possible and manually stop recording at sleep offset.

Attended polysomnography collection includes those in unattended polysomnography as described above, with the addition of electroencephalography (C1 and C2 and O1 and O2), EMG Chin (Chin 1 and Chin 2 and Chin 3), EMG diaphragm, snore (microphone), sound level (dB meter), and digital video (audio and visual). Competent sleep technicians will conduct participant setup.

Outcome Assessment

An oral glucose tolerance test will be undertaken for the assessment of gestational diabetes at 28 weeks (in addition to earlier testing if clinically requested). Collection of fasting blood will be followed by administration of 75 g oral glucose load, with 1 and 2 hours of blood collection. Interpretation will follow the Australasian Diabetes in Pregnancy Society (ADIPS) 2020 guidelines [38].

Blood pressure (BP) will be recorded at each study visit. Diagnosis of HDP will be defined as per the Society of Obstetric Medicine of Australia and New Zealand (SOMANZ) guidelines [39].

Anthropometric measurements (height, weight, and BMI) will be recorded during the randomization visit, and weight will be checked at subsequent study visits by study staff using hospital clinic scales.

Postpartum Follow-Up

RCT participants will be followed up in the clinic at 6-12 months post partum. At this time point, women will be offered repeat polysomnography, an oral glucose tolerance test (if they developed diabetes and have not already undertaken this in the postpartum period), biomarker blood, and urine collection.

Statistical Methods

This trial is a feasibility trial, and as such, no power calculations for the RCT were derived. We prespecified to assess the diagnostic accuracy of the home sleep tests as well as the screening questionnaires following the STARD (Standards for Reporting of Diagnostic Accuracy) guidelines. The accuracy will be assessed at various cutoff points using a receiver operating characteristic curve. The area under the receiver operating characteristic curve and positive and negative predictive values in the patient population will be derived. The first recruitment target will be 50 participants, which provides at least 80% power (α=.05) to detect a C-statistic of 0.7 when the allocation ratio is 1 (ie, 50% prevalence) and 0.75 when the allocation ratio is 2 (ie, 20% prevalence). We will be comparing Apnealink Air and SOMTE unattended PSG to attended PSG. Further exploratory analysis will be undertaken to assess

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whether any factors at booking, including the results of the sleep questionnaire, biomarkers, clinical factors, and history in combination with findings of unattended PSG, Apnealink, or attended PSG, are predictive of poor outcomes (either maternal or fetal, as discussed above). A composite of the combined adverse maternal outcomes and combined adverse fetal outcomes will also be assessed as an outcome. Data will be displayed as mean (SD), 95% CIs, and median (IQR) as appropriate based on data distribution. An intention-to-treat analysis will be undertaken for the primary outcome as well as the secondary outcomes. A per-protocol analysis (for primary and secondary outcomes) will also be undertaken, and both data will be presented. A P value of <.05 will be considered statistically significant. Where multiple analyses are undertaken, adjustments will be made for multiple comparisons. Longitudinal analysis of repeated measures will be undertaken where measurements are undertaken several times. Where differences at baseline exist between the groups, adjustments will be made statistically. Where less than 10% of any data point is missing, data will be imputed. We have preplanned an exploratory analysis of flow characteristics of all sleep tests to investigate sub-criterion flow changes related to long-term fetomaternal outcomes.

Patient and Public Involvement

The participants were not involved in the design of this study protocol. Participant feedback will be obtained via a series of questionnaires as described above. Members of the public (hospital staff) participated in providing feedback on acceptability questionnaires as described above, and feedback was implemented in the development of the questionnaires.

Data Monitoring

No data monitoring committee has been appointed.

Risk Assessment and Termination of Study

An interim analysis will be performed halfway through enrollment by the safety committee. If there is a convincing signal that either CPAP or PT therapy is associated with adverse outcomes, the study will be terminated immediately, and the SWSLHD HREC will be notified. Significant safety issues and patient complaints will be reported immediately via email to SWSLHD HREC.

Safety Considerations

A safety committee will be established to monitor the safety of participants and to review any potential adverse outcomes. The safety committee will review the outcomes after each of the 4 subjects for the first 16 subjects or if any severe adverse events occur.

Posttrial Care

The participants affected by product recalls in this trial will be followed up annually for 5 years if agreeable as per the protocol.

Results

The trial commenced on September 30, 2019. The trial is ongoing as of August 6, 2024.

Discussion

Principal Findings

Despite the growing interest in the potential for improved fetomaternal outcomes in pregnant women with OSA occurring during pregnancy through the use of CPAP, few large RCTs have been undertaken. In addition, no RCT has compared CPAP and positional therapy for the treatment of OSA occurring during pregnancy. This RCT feasibility study will assess the feasibility of conducting a large RCT to initiate CPAP or positional therapy in pregnant women by the 16th week of gestation.

To date, the largest RCT to investigate the treatment of OSA in pregnant women studied 310 pregnant women with OSA from the first trimester. The primary outcome of the study was BP control during pregnancy and the secondary outcome was the incidence of preeclampsia. The overall CPAP compliance was 2.5 (SD 2.5) hours per night and median use was 1.7 (IQR 0.2-4.5) hours per night, and the authors concluded CPAP therapy reduced the incidence of preeclampsia and demonstrated a reduction in DBP throughout the pregnancy, in high-risk pregnant women with mild to moderate OSA [23]. A recent systematic review assessed the use of CPAP therapy for the prevention of hypertensive-related adverse outcomes in pregnant women with OSA. The authors report risk reduction of gestational hypertension and preeclampsia in the CPAP groups (relative risk [RR] 0.65, 95% CI 0.47-0.89; P=.008) and preeclampsia (RR 0.70, 95% CI 0.50-0.98; P=.04), which were not correlated with age or BMI. The authors concluded that while the results suggest CPAP therapy as a potential mediator to adverse gestational hypertensive outcomes in pregnant women with OSA, the association remains inconclusive [40].

This feasibility RCT will assist in the understanding of the maternal and health care system challenges in undertaking a CPAP intervention during pregnancy. The therapies in this study will commence by the 16th week of gestation and will be overseen by an experienced sleep therapist to improve CPAP and PT compliance. This is important as many clinical trials involving CPAP are limited by poor compliance of the participants. We will encourage compliance to interventions through an initial education session at randomization by the trial sleep therapist and at each study visit. At these visits, the participants will be provided feedback regarding their therapy compliance and efficacy, and through a series of questionnaires, we will assess barriers to therapy. We anticipate an improvement in fetomaternal outcomes such as improved blood pressure control, reduced incidence of GDM, and preeclampsia in the interventional groups with good adherence to therapy. The learnings from undertaking this work will be important for consideration when expanding to a larger trial. The results of the study will be published in peer-reviewed journals and presented at national and international conferences.

Limitations

Limitations to the trial will be poor acceptability of the trial protocol by the participants and the potential for pregnancy complications to participants in the trial, given the risk of adverse events occurring during pregnancy, particularly in high-risk populations with comorbidities such as obesity and a

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history of hypertension and diabetes [41]. Additional limitations to the trial will be the potential for poor CPAP and PT compliance of the participants randomized to these interventions. The use of an experienced sleep therapist in the trial to educate the participants and provide ongoing therapy support during the trial is anticipated to minimize poor therapy compliance but may limit the generalizability of findings.

Conclusions

If this trial protocol demonstrates good overall feasibility, a larger multicenter RCT will be conducted. The results of this feasibility trial will inform a redesign of the protocol for the larger RCT, if required. The use of positional therapy in this trial may provide evidence of the utility of OSA treatment options other than CPAP in pregnant women with OSA. Furthermore, it is anticipated that the follow-up schedule in this trial may inform other study designs involving pregnant women with OSA, ultimately leading to changes to clinical policy in the care of pregnant women.

Data Availability

Data generated during this trial will be available following the completion and publication of the trial from the first and last authors upon reasonable request and approval by the local ethics committee.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Screening eligibility preconsent questionnaire. Participants are invited to complete a Screening eligibility preconsent questionnaire to determine trial eligibility.
[PDF File (Adobe PDF File), 252 KB - resprot_v14i1e51434_app1.pdf]

Multimedia Appendix 2
Baseline information. Participants complete the baseline information questionnaire following trial consent.
[PDF File (Adobe PDF File), 321 KB - resprot_v14i1e51434_app2.pdf]

Multimedia Appendix 3
The checklist presents the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 checklist.
[PDF File (Adobe PDF File), 210 KB - resprot_v14i1e51434_app3.pdf]

Multimedia Appendix 4
POSA (pregnancy-associated obstructive sleep apnea) trial flow chart. The flow chart describes the participant progression through the trial protocol and depicts the timing of the interventions.
[PDF File (Adobe PDF File), 338 KB - resprot_v14i1e51434_app4.pdf]

Multimedia Appendix 5
Schedule of study visits. The image depicts the trial participant study visits and intervention schedule.
[PDF File (Adobe PDF File), 232 KB - resprot_v14i1e51434_app5.pdf]

Multimedia Appendix 6
Polysomnography (PSG) 28-32 weeks gestation questionnaire. Participants are invited to complete the questionnaire at 28-32 weeks' gestation to assess participant experience following completion of the sleep test.
[PDF File (Adobe PDF File), 89 KB - resprot_v14i1e51434_app6.pdf]

Multimedia Appendix 7
Somte 28-32 weeks gestation questionnaire. Participants are invited to complete the questionnaire at 28-32 weeks' gestation to assess participant experience following completion of the sleep test.
[PDF File (Adobe PDF File), 128 KB - resprot_v14i1e51434_app7.pdf]

Multimedia Appendix 8
Apnealink 28-32 weeks gestation questionnaire. Participants are invited to complete the questionnaire at 28-32 weeks' gestation to assess participant experience following completion of the sleep test.
[PDF File (Adobe PDF File), 126 KB - resprot_v14i1e51434_app8.pdf]

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Multimedia Appendix 9
Preferred test questionnaire. Participants are invited to complete the questionnaire to assess participant preference of sleep diagnostic tests.
[PDF File (Adobe PDF File), 44 KB - resprot_v14i1e51434_app9.pdf]

Multimedia Appendix 10
CPAP (continuous positive airway pressure) therapy Questionnaire 16-20 weeks' gestation. Participants randomised to CPAP intervention are invited to complete the questionnaire to assess participant experience of CPAP therapy to 16-20 weeks' gestation.
[PDF File (Adobe PDF File), 163 KB - resprot_v14i1e51434_app10.pdf]

Multimedia Appendix 11
CPAP (continuous positive airway pressure) therapy questionnaire 36 weeks' gestation. Participants randomised to CPAP intervention are invited to complete the questionnaire to assess participant experience of CPAP therapy to 36 weeks' gestation.
[PDF File (Adobe PDF File), 163 KB - resprot_v14i1e51434_app11.pdf]

Multimedia Appendix 12
Position therapy questionnaire 36 weeks' gestation. Participants randomised to positional therapy (PT) intervention are invited to complete the questionnaire to assess participant experience of PT therapy to 36 weeks' gestation.
[PDF File (Adobe PDF File), 163 KB - resprot_v14i1e51434_app12.pdf]

Multimedia Appendix 13
Position therapy questionnaire 16-20 weeks' gestation. Participants randomised to positional therapy (PT) intervention are invited to complete the questionnaire to assess participant experience of PT therapy by 16-20 weeks' gestation.
[PDF File (Adobe PDF File), 163 KB - resprot_v14i1e51434_app13.pdf]

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Abbreviations

AASM: American Academy of Sleep Medicine
ADIPS: Australasian Diabetes in Pregnancy Society
AHI: apnea-hypopnea index
BP: blood pressure
CPAP: continuous positive airway pressure
CTN: Campbelltown Hospital
EMG: electromyography
ESS: Epworth Sleepiness Scale
FMU: fetomaternal unit
FOSQ-10: Functional Outcomes of Sleep Questionnaire
GDM: gestational diabetes mellitus
HDP: hypertensive disorders of pregnancy
HDP: hypertensive disorders of pregnancy
HIF1α: hypoxia-inducible factor 1-alpha
IL-6: interleukin-6
LPH: Liverpool Hospital
OSA: obstructive sleep apnea
PlGF: placental growth factor
POSA: pregnancy-associated obstructive sleep apnea
PT: positional therapy
RDI: respiratory disturbance index
REDCap: Research Electronic Data Capture
RR: relative risk
SDB: sleep-disordered breathing
sFlt-1: soluble fms-like tyrosine Kinase 1
SOMANZ: Society of Obstetric Medicine of Australia and New Zealand
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
STARD: Standards for Reporting of Diagnostic Accuracy

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STOP-BANG: snoring, tiredness, observed apnea, high BP (STOP) and snoring, tiredness, observed apnea, high BP-BMI, age, neck circumference, and gender
SWSLHD HREC: South Western Sydney Local Health District Human Research and Ethics Committee
TNFα: tumor necrosis factor alpha

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Protocol

Interventions to Reduce Serum Per- and Poly-Fluoroalkyl Substances Levels, Improve Cardiovascular Risk Profiles, and Improve Epigenetic Age Acceleration in US Firefighters: Protocol for Randomized Controlled Trial

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Abstract

Background: Occupational cancer and acute cardiac events are the leading causes of death among firefighters. Increased exposure to toxicants on the fire ground, such as polycyclic aromatic hydrocarbons, benzene, and per- and poly-fluoroalkyl substances (PFAS), has been linked to certain cancers, cardiovascular disease, accelerated epigenetic aging, and other adverse health effects. PFAS are a major concern because they are persistent, can bioaccumulate, and are present in several firefighting tools. Compared to the general population, firefighters have elevated serum levels of some types of PFAS. A randomized clinical trial in Australian firefighters found that routine blood and plasma donation for 1 year led to decreased serum PFAS levels, although health outcomes were not directly measured in that study.

Objective: In collaboration with fire service leadership in Arizona, the Firefighter Collaborative Research Project (FCRP) was established to evaluate the effectiveness of 3 interventions in a randomized controlled trial design to reduce serum PFAS levels, reduce cancer and cardiovascular risk, and improve overall health and wellness in US firefighters.

Methods: This study aimed to recruit and enroll up to 1500 active firefighters between August 2023 and October 2024. Between August 2023 and October 2024, active firefighters were recruited and randomized into a study arm based on their eligibility, including serum PFOS levels, for the specific arms. The trial arms include (1) blood and plasma donation, (2) zone 2 physical activity, and (3) intermittent fasting. FCRP outcomes include serum PFAS reduction (arm 1), epigenetic age acceleration (all arms), cardiovascular conditioning (arm 2) and cognitive outcomes (all arms), mental health (all arms), and overall disease risk (all arms). Each study arm includes an intervention and a control group. At enrollment and end of the study, participants provide blood and urine samples and complete a comprehensive questionnaire on their occupational and health history, exposures, and lifestyle behaviors. At the end of the study, participants also participated in a cognitive evaluation. Depending on the study arm,

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participants may additionally complete a cardiopulmonary exercise test at baseline and follow-up, a mid-study survey, and a mid-study blood and urine collection.

Results: Participant activities and data collection will conclude by December 2025.

Conclusions: The FCRP is a randomized controlled trial that aims to test the effectiveness of fire service–selected interventions in reducing serum PFAS levels. Study results will contribute to potential interventions that could be used to reduce serum PFAS levels in firefighters.

Trial Registration: ClinicalTrials.gov NCT05869747; https://clinicaltrials.gov/study/NCT05869747

International Registered Report Identifier (IRRID): DERR1-10.2196/67120

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KEYWORDS

firefighters; PFAS; epigenetics; phenotype; heart disease; cardiovascular disease; CVD; atherosclerosis; occupational health; RCT; cardiovascular; fasting; exercise

Introduction

Occupational cancer and acute cardiac events are the leading causes of death among firefighters [1,2]. The firefighting occupation is classified by the International Agency for Research on Cancer as a group 1 carcinogen due to the direct and indirect exposures to hazards on the job [3]. Firefighters have a significantly higher risk of cancer and cancer mortality when compared to the general population, including skin melanoma, other skin cancers, and prostate cancer, with higher mortality for rectal, testicular, brain and nervous system cancers, and non-Hodgkin lymphoma [4,5]. Increased exposure to toxicants on the fire ground, such as polycyclic aromatic hydrocarbons, benzene, and per- and poly-fluoroalkyl substances (PFAS), have been linked to certain cancers, cardiovascular disease, accelerated epigenetic aging, and other adverse health effects [4,6,7].

PFAS are primary toxicants of concern due to their persistence, ability to bioaccumulate, and associated adverse health effects [8]. Firefighters have additional exposure to these chemicals beyond the general population, with significant sources of PFAS exposure on the fire ground including fluorinated class B aqueous film-forming foam and smoke from burning household materials [6]. A study involving 4 municipal US fire departments located in different states and regions of the country found that firefighters had higher levels of several PFAS chemicals in their blood than the general population [9].

In the human body, PFAS accumulates primarily in the liver, kidneys, and blood. Long-chain PFAS, such as perfluoro octane sulfonate (PFOS) and perfluorooctanoic acid (PFOA), have reported half-lives of several years (3.1-7.4 and 2.1-8.5, respectively) [8]. These chemicals bind strongly to albumin, the most abundant protein in plasma [8,10]. Therefore, these chemicals may be removed from the body through blood or plasma donation. An Australian study among firefighters previously demonstrated the effectiveness of blood or plasma donation to lower serum PFAS levels over 12 months, although no health effects were investigated. Findings from the study revealed that plasma donation was more effective than blood donation at reducing the mean serum level of PFOS at 12 months, while serum PFOS did not significantly change in the control group [11]. Plasma donation reduced PFOS levels by approximately 24% (–2.9 ng/mL, 95% CI –3.6 to –2.3 ng/mL), while blood donation reduced PFOS levels by approximately 11% (–1.1 ng/mL, 95% CI –1.5 to –0.7 ng/mL) [11]. Based on the findings from that study and concern for PFAS exposure, Arizona firefighters requested research to replicate the study and additionally investigate health outcomes such as cardiovascular health and epigenetic age acceleration.

Lifestyle and environmental exposures are associated with DNA methylation patterns, a type of epigenetic alteration. DNA methylation affects gene expression by adding a methyl group to 5'—C—phosphate—G—3' dinucleotides. These DNA methylation patterns can be analyzed to determine epigenetic age or "biological age" through epigenetic clocks. Previous research has found that accelerated epigenetic age can be a risk factor for cancer, cardiovascular and neurological diseases, as well as death from all causes combined [12]. In addition to the physical health impacts, accelerated epigenetic age has been linked to negative mental health impacts [13]. Studies on firefighters have found differential DNA methylation patterns, or accelerated epigenetic age, potentially as a result of fire ground exposure and increased serum PFAS levels [7,14].

Lifestyle interventions, such as physical activity and dietary restriction or intermittent fasting, may be associated with slowed epigenetic aging [12,15,16]. Findings from the Comprehensive Assessment of the Long-term Effects of Reducing Intake of Energy trial revealed that caloric restriction slowed epigenetic aging [17]. Similar findings have been observed in mice [18]. A recent randomized controlled trial tested the effectiveness of a fasting-mimicking diet (low calorie, low protein, plant-based diet) in improving biological age. After 3 cycles, a cycle being a consecutive 5-day period in a month, biological age was reduced by a median of 2.5 years [19].

Zone 2 physical activity, or continuous, moderate aerobic physical activity corresponding to the near lactate threshold (4 mM blood lactate), shows greater benefits than other types of aerobic physical activity for improving cardiovascular risk factors [20,21]. Common examples of this type of activity include brisk walks, light jogs, and cycling for a continuous interval of time. Occupational health clinicians working with the firefighter community also anecdotally noted that zone 2 physical activity confers the greatest benefits for cardiovascular fitness, although this claim has not been formally tested. Both

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types of lifestyle interventions, intermittent fasting, and zone 2 physical activity, have received interest from the firefighter community.

The Firefighter Collaborative Research Project (FCRP) aims to assess the effectiveness of fire service–selected interventions for improving firefighter health. The target population for recruitment is participants enrolled in the Fire Fighter Cancer Cohort Study (FFCCS), a national framework study that collects information on firefighter exposures and works to improve the health of the fire service [22]. Through this randomized controlled trial, we seek to engage our existing cohort of firefighters to evaluate 3 firefighter-identified lifestyle interventions: blood or plasma donation, zone 2 physical activity, and intermittent fasting. The primary outcomes of the study include epigenetic age acceleration, serum PFAS reduction (blood or plasma arm only), and cardiovascular risk reduction (zone 2 arm only). Based on the previously mentioned associations with accelerated epigenetic age and therefore aging and aging-related diseases, secondary outcomes of this study include mental health, sleep quality, and cognitive functioning [12,13].

Methods

Overall Study Design

The FCRP is a community-engaged, randomized controlled trial with the goal of screening 1500 firefighters. The study enrollment period is planned for August 2023-October 2024. Based on eligibility criteria, participants are randomly assigned to regularly donate blood or plasma for 1 year, engage in zone 2 physical activity for 4 months, intermittent fast for 4 months, or serve as a control for the duration of the respective study arm.

We have chosen a community-based approach working with fire service leaders in participating states that are willing to educate firefighters on the importance of the study and encourage participation. Departments designate a liaison who completes training for institutional review board (IRB) approval to distribute study information, coordinate events, and serve as an additional point of contact between researchers and participants. The study team also hosts online informational sessions upon request and actively maintains a study website. Individuals interested in participating in the study are directed to complete a screening survey and to schedule an appointment for an in-person event near them. Both surveys may be accessed through informational materials dispersed by liaisons. Events are hosted regionally, and locations are prioritized based on interest numbers and resources for study activities.

Initially, the state of Arizona was designated as the only state for enrollment for all 3 study arms (blood and plasma donation, intermittent fasting, and zone 2). However, upon interest from other US fire departments, the blood and plasma donation arm of the trial has been expanded to Idaho, California, Washington, Oregon, and Massachusetts. The intermittent fasting and zone 2 arms of the trial will not include non-Arizona fire departments. Given that there are a limited number of volunteer departments with who we have established contacts within these areas, enrollment is focused on career departments. Firefighters of all demographic backgrounds were encouraged to enroll.

Participants

Eligibility Criteria

Individuals interested in participating in the study are directed to complete an online screening survey to assess eligibility. Overall study eligibility criteria include active firefighters enrolled in the FFCCS, with full criteria described in Textbox 1. If participants are not already enrolled in the FFCCS at recruitment, they are given the opportunity to enroll. Individuals currently doing study arm activities at the time of screening are deemed ineligible for participation in the respective study arm. Subjects with conditions that may affect their ability to complete study activities (eg, they do not meet national standard criteria for blood or plasma donation, or have an injury preventing physical activity) are also deemed ineligible for participation in the respective study arm. Individuals who are deemed ineligible for all study arms are thereby ineligible for participation in the overall study. Specific inclusion criteria are detailed in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria for the Firefighter Collaborative Research Study (FCRP).

Inclusion Criteria

- Active firefighter (including emergency medical responder and all firefighter subgroups) with either a volunteer or career status
- Individual plans to remain in active service with their current agency for the next 2 years (not planning to retire or resign)
- 18 years of age and older
- Fluently speak and write in English
- All genders, races, and ethnicities
- Enrolled in the Fire Fighter Cancer Cohort Study before enrolling in the FCRP
- Complete a signed and dated informed consent document that indicates the participant has been informed of all aspects of the study before enrollment.
- Agree to avoid participating in FCRP intervention activities outside of their assigned intervention group for the duration of the study.
- Able to comply with scheduled visits, laboratory tests, and other study procedures
- BMI ≥17.5 kg/m^2 and weighing more than 115 pounds

Exclusion Criteria

- Overall
  - Not able to fluently speak or write in English
  - Younger than 18 years
  - Currently a tobacco smoker or vaping (eg, >2 cigarettes or cigars, or incidents of vaping in the past month)
  - Those with planned travel or extended leave (eg, >6 weeks) that would prevent their ability to participate in other interventions
  - Those who are pregnant or become pregnant during study, breastfeeding, or have given birth within the past year
  - Those with a history or diagnosis of any significant metabolic, hematologic, pulmonary, cardiovascular, gastrointestinal, neurological, immune, hepatic, renal, urological disorders, severe injury, or cancer that, in the opinion of the investigator, would potentially put the candidate at risk.
- Blood or plasma
  - Those with any medical contraindication (medical condition or medication) to blood donation, according to Red Cross Guidelines
  - Those who donated blood or plasma in the past 3 months
  - Those knowing they have a condition indicative of levels of hemoglobin, hematocrit, red blood cells, or iron below the lower limit of normal levels
- Zone 2
  - Currently participating in zone 2 physical activity
  - Currently participating in more than 120 minutes per week of aerobic, and cardiovascular training (eg, jogging, cycling, walking, swimming, high-intensity interval training) at >60% of their max heart rate.
- Intermittent fasting
  - Those with a history or diagnosis of diabetes, hypoglycemia thyroid disease, or an eating disorder
  - Those who recently participated in intermittent fasting or Time Restricted Eating
  - Those who recently used antidiabetic medication such as Semaglutide (sold as Ozempic, Wegovy, and Rybelsus) or Tirzepatide (sold as Mounjaro) for the treatment of type 2 diabetes or weight loss will also be excluded from this group.
  - Use of drugs that might affect intermittent fasting or eating behaviors

Interventions

Randomization groups are created at regular monthly intervals and clustered by recruitment region. Participants who have consented to participate in the study are randomized into 1 of the 4 study arms as either an intervention or control, accounting for their eligibility determined during the screening process and baseline serum PFOS concentrations. Upon enrollment into their specific group, participants are provided with instructional materials for assigned activities, activity timelines, and frequently asked questions.

Participants randomized in the blood donation or plasma donation arm include all participants with serum PFOS ≥5

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ng/mL, following the previous Australian study [11], while also meeting additional study criteria outlined in Textbox 1. We also included a smaller intervention group of participants with PFOS <5 ng/mL in the plasma arm, to evaluate whether improvements in epigenetic age are independent of baseline PFOS. Participants in the blood intervention arm are expected to donate whole blood every 12 weeks for 12 months, while those in the plasma intervention are expected to donate plasma every 6 weeks for 12 months. Participants are provided with a list of donation centers in their region and acceptable types of donations (eg, whole blood donation is acceptable, but not "Power Red" or platelets). Participants go to donation centers on their own. Controls are asked to refrain from donating plasma or blood throughout the trial period.

Participants randomized into the zone 2 physical activity arm complete a Cardiopulmonary Exercise Test (CPET) before starting their intervention. The CPET uses a mouthpiece and external sensors to measure the heart rate and other cardiovascular health indicators of the individual while they engage in mild exercise on a stationary bicycle. The initial CPET provides a baseline evaluation of cardiovascular fitness, as well as the zone 2 heart rate zone used for the intervention. The calculated range from this exam is provided to participants in their results and they are asked to self-report these results to the study team. The zone 2 heart rate range was based on current American College of Sports Medicine guidelines and corresponded to a lower limit of 40% and an upper limit of 60% of achieved peak VO2 to indicate the anaerobic threshold [23]. Functionally, engaging in zone 2 translates to moderate physical activity, with examples of zone 2 physical activity including hiking up a hill, a light jog, or a moderate cycling session. Participants in the intervention are asked to complete a minimum of 45 minutes of physical activity in their zone 2 range for at least 4 days a week, tracked by a study-provided heart rate monitor watch. Controls are permitted to continue their regular physical activity regimen but are asked to not intentionally engage in zone 2 activity. All participants randomized to the zone 2 physical activity arm are provided with a wrist-worn accelerometer (Garmin Forerunner 45) to passively record their physical activity and sleep data. They are reminded to always wear the device except when it is charging and receive regular compliance checkups from study staff. Participants are also reminded to open the application on their phones at least once a week to allow data to be uploaded to their Garmin account. This data is synced with Fitabase to allow the study team to monitor adherence. Participants in the zone 2 physical activity arm are monitored for compliance through Fitabase and can manually report exercises if they do not wear their wrist-worn heart tracker [24]. At the end of the 4-month period, participants complete a final CPET exam and share their results with the study team to evaluate changes over time.

Participants randomized into the intermittent fasting arm are asked to fast for 14 to 16 hours per day, for at least 4 days a week for the 4-month period. Participants select their own time windows to accommodate firefighter shift schedules. During fasting windows, participants are allowed to consume medications and zero-calorie beverages (eg, black coffee, sparkling water, unsweetened tea). They are not asked to alter their diet in any other manner. Controls are asked to not engage in intermittent fasting throughout the trial period and continue their current dietary regimen. Additional details are provided in Textbox 2.

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Textbox 2. Description of study interventions within the firefighter collaborative research project.

Arm 1: Blood or plasma donation

- Blood or plasma donation
  - Participants with perfluorooctane sulfonate >5 ng/mL were prioritized for this arm
  - Blood: 12-month commitment to donating blood every 12 weeks. Each blood donation will take approximately an hour to an hour and 15 minutes each time.
  - Plasma: 12-month commitment to donating plasma every 6 weeks. Each plasma donation will take approximately an hour and 30 minutes to 2 hours each time.
  - Additional surveys administered will involve a time commitment between 30 to 45 minutes.
- Blood or plasma control group
  - 12-month commitment into the control group
  - Additional surveys administered will involve a time commitment between 30 to 45 minutes.

Arm 2: Zone 2 physical activity

- Zone 2 physical activity intervention
  - 4-month commitment to completing a minimum of 45 minutes of physical activity in zone 2 for a minimum of 4 days per week.
  - Cardiopulmonary Exercise Test (CPET) testing before beginning and after completing the zone 2 arm for 4 months.
  - 4-month commitment to wear a wrist-worn heart and health tracker at all times unless it is charging.
  - Additional surveys administered will involve a time commitment between 30 to 45 minutes.
- Zone 2 control group
  - 4-month commitment to wear a wrist-worn heart and health tracker at all times unless it is charging
  - CPET testing before beginning and after completing the participation in zone 2 control group arm for 4 months.
  - Additional surveys administered will involve a time commitment between 30 to 45 minutes.

Arm 3: Intermittent fasting

- Intermittent fasting intervention
  - 4-month commitment. The participant will limit intake of food and calorie-containing beverages to an 8-10 hour window a day and fast for the remaining 14-16 hours on 4 days per week.
  - Additional surveys administered will involve a time commitment between 30 to 45 minutes.
- Intermittent fasting control group
  - 4 month-commitment into the control group
  - Additional surveys administered will involve a time commitment between 30 to 45 minutes.

Data Management

Research activities primarily occur through electronic communications such as email, text, and internet-based surveys, telephone contacts, or postal or express mail. Surveys are self-administered by participants on a computer or smartphone. Should participants be unable or unwilling to access them online, they may be administered by study staff by telephone. Participant information given to study staff via phone or email conversation is entered and stored in the REDCap database [25].

The database for this study is maintained through REDCap, which securely keeps participant identifiers and contact information according to the University of Arizona's standard operating procedures. These procedures operate with respect to cybersecurity, privacy, patient confidentiality, and compliance with applicable patient privacy regulations. All study-related documents and specimens contain a unique identifier for each participant, with any study-related documents with personal identifiers stored in a locked cabinet in lockable offices on campus. Laboratory results are entered directly into the REDCap study database from the study reference laboratory.

Twilio is a cloud-based communications platform that allows for automated text messaging chains to be sent to study participants. It is used to send study survey links to their phones that will take them directly to secure REDCap surveys.

At enrollment and their end-of-study visit, all participants provide biological specimens (blood and urine), and a survey is administered to collect information on occupational history

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and exposures, relevant medical history, sleep quality, physical activity information, a food frequency questionnaire, the Center for Epidemiological Studies Depression scale (short form), and environmental exposures (Table 1, and described further in the Outcomes section). Throughout their enrollment period, all participants also receive regular study adherence questionnaires (described below). At end-of-study only, all participants additionally take a cognitive assessment (MindCrowd, described below). Participants assigned to the zone 2 physical activity arm complete a CPET before the beginning of the 4-month intervention and again after the conclusion of the intervention. Once participants in the zone 2 physical activity arm report the results of their first CPET, they are sent a wrist-worn accelerometer (Garmin Forerunner 45) that they are instructed to wear throughout the 4-month period and to return upon completion.

Zone 2 wears their accelerometer every day for the duration of the trial.

Table 1. Participant data collection time points for participants enrolled in the firefighter collaborative research project.

	Baseline	Mid-intervention	End of study[a]
Blood	All	BP[b]	All
Urine	All	BP	All
Questionnaires[c]	All	BP	All
Adherence[d]	N/A[e]	All[f]	N/A
Cardiopulmonary Exercise Test	Z2[g]	N/A	Z2
MindCrowd cognitive assessment (verbal cognition, processing speed)	N/A	N/A	All
Accelerometer	Z2	Z2	Z2
Epigenetics (Infinium MethylationEPIC v2.0 BeadChip)	All	N/A	All
VO2max, resting heart rate, HRV[h], HR[i] recovery	Z2	Z2	Z2
Sleep quality (accelerometer): deep, REM[j], light	Z2	Z2	Z2
Sleep quality (National Health Interview Survey Questionnaire): hours, rested, interruptions	All	N/A	All
Depression (CES-D[k] Short form)	All	N/A	All
Firefighter gear and occupational exposures	All	N/A	All
Dietary quality	All	N/A	All
Self-reported weight	All	All	All

[a]End of the study is approximately 4 months after randomization for zone 2 and intermittent fasting and approximately one year for blood or plasma.
[b]BP: blood/plasma arm.
[c]Questionnaires include diet, depression or mood, physical activity, occupational characteristics, and lifestyle.
[d]Intervention adherence questionnaires are evaluated weekly for IF and Z2, and monthly for blood or plasma.
[e]N/A: not applicable.
[f]All: all arms.
[g]Z2: Zone 2 physical activity.
[h]HRV: heart rate variability.
[i]HR: heart rate.
[j]REM: rapid eye movement.
[k]CES-D: Center for Epidemiologic Studies Depression Scale.

Biological Specimens

All participants provide up to 50 mL of blood via venipuncture at baseline as part of the study screening process and at the completion of assigned study arm activities. Participants in the blood and plasma arm complete an additional collection at mid-study, between 4 and 8 months. Each venipuncture is performed by qualified study staff, phlebotomists, nurses, or paramedic-EMTs at organized study events hosted at participating fire stations or facilities. Upon collection, blood specimens are stored locally in coolers with ice packs for transportation to the University of Arizona, where they are processed within 24 hours, with aliquots stored at –80 °C before testing. Baseline blood specimens for all participants are analyzed for PFAS as the final step in the study screening process and for markers of epigenetic age, such as DNA methylation patterns. At the end of assigned activities, only participants in the blood and plasma arm will have their blood specimens analyzed for PFAS. All blood specimens collected at the end of assigned activities for all study arms will be analyzed for markers of epigenetic age.

Participants are asked to self-collect approximately 80 mL of urine at baseline as part of the study screening process and at

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the completion of assigned study arm activities per FFCCS protocol and to be stored for future analyses. Participants in the blood and plasma arms complete an additional collection at mid-study, between 4 and 8 months. Collections take place at organized study events hosted at participating fire stations or facilities. Upon collection, urine specimens are locally stored on dry ice for transportation to the University of Arizona, where specific gravity is measured using the Atago Refractometer (Model PAL-10S, Cat# 4410, Fisher Scientific). The sample is aliquoted and prepared for long-term storage at –80 °C for potential future analyses associated with these interventions.

Adherence to Study Activities and Retention

To determine activity adherence, participants are contacted at regular intervals determined by their intervention via email or secure SMS test messages using Twilio. Each survey asks if the participant has completed their required study activities. Participants randomized to an intervention are asked detailed questions about completing their activities, and participants randomized to control are asked if they engaged in the intervention activities since the last study survey. During the check-in surveys, participants are able to report any adverse events. They will then be contacted by study coordinators, and the events will be reported to the IRB for review to determine any necessary actions to take.

Study coordinators call and email noncompliant participants each week to improve adherence. Participants are contacted if they are due to start study activities but have not completed their baseline survey, have at least 1 week past due for a blood or plasma donation, have not completed a weekly survey for zone 2 physical activity or intermittent fasting in 2 weeks, or have not scheduled an appointment for a follow-up biological collection. Participants may also be contacted if they do not sync their wrist-worn accelerometer (Garmin Forerunner 45) with their mobile application, or if they do not share the results of their CPET with the study team. If the participant does not respond and continues to fall behind on study activities, then the IRB-approved liaison for their department is contacted to engage with the participant and ensure they complete their activities.

Laboratory Methods

Per- and Poly-Fluoroalkyl Substances Concentrations

Serum samples are tested for PFAS by the New Jersey Department of Health Centers for Disease Control method #6304.09 as a reference using Chronos online SPE – uHPLC by Spark Holland coupled with a Sciex 7500 MS/MS. A total of 20 analytes are tested, including perfluorobutanesulfonic acid, perfluorodecanoic acid, perfluoroheptanesulfonic acid, perfluoroheptanoic acid, perfluorohexanesulfonic acid, perfluorohexanoic acid, perfluorononanoic acid, perfluorooctanesulfonamide, perfluoroundecanoic acid, PFOA (perfluorooctanoic acid), PFOS, branched and linear isomers of PFOA and PFOS, 9-Chlorohexadecafluoro-3-oxanonane-1-sulfonic acid, 4,8-Dioxa-3H-perfluorononanoic acid, 2-(N-Ethyl-perfluorooctane sulfonamido) acetic acid, 2-(N-Methyl-perfluorooctane sulfonamido acetic acid), and Hexafluoropropylene oxide dimer acid. Note that total PFOA and total PFOS are calculated as the sum of the branched and linear isomers [26].

DNA Methylation Analysis

DNA methylation analysis of serum samples is conducted at the University of Arizona Genetics Core. After sample accessioning and preparation, genomic DNA is extracted using a Qiagen DNeasy Blood and Tissue Kit (REF: 69581) or similar following the manufacturer's recommendations for whole blood. The extracted DNA is then quantified using promega quantiflor fluorometric dsDNA assay (PN: E2671) and dsDNA quantities are detected using a SynergyHT plate reader (Agilent or Biotek). Samples are then normalized or diluted robotically with HPLC water to the range of 200-500ng in a total volume of 45uL. Following normalization, a bisulfite conversion using the Zymo EZ-96 DNA Methylation Kit (PN: D5004) is performed with the specified thermocycler conditions (95 °C for 30 sec, 50 °C for 60 min for 16 cycles, and Hold" at 4 °C) with 15uL as the final elution volume.

The bisulfite-converted DNA is then input into the illumina infinium methylation EPIC Kit (PM 20087706-8) following the manufacturer's recommendations. Whole genome amplification is then performed on the bisulfite-converted DNA. The amplified DNA is then fragmented and precipitated before being resuspended and hybridized onto the bead chip (v2.0) during an overnight incubation. Unhybridized DNA is washed off before the bead chip undergoes single base extension and staining. Before scanning, the bead chip undergoes a final round of washing and coating to prepare the chip for imaging. Once prepped for imaging, the bead chip is then scanned on an Illumina NextSeq 550 following the manufacturer's recommendations.

Outcomes

The primary outcomes of the study include epigenetic age acceleration, serum PFAS reduction, and cardiovascular risk reduction, with secondary outcomes including mental health, sleep quality, and cognitive functioning. Intervention-specific outcomes include PFAS concentrations (plasma or blood arm), and cardiovascular fitness (zone 2 arm). Urine and blood samples are stored at –80 °C for future biomarker-based outcomes. In total, 20 PFAS types are measured for all participants at baseline and again at end-of-study for participants in the blood and plasma study arm. Participants are provided with a report back of their PFAS concentrations at baseline and again at follow-up if measured. Epigenetic age acceleration will be calculated for baseline and end-of-study samples for all participants using several different clock-based methods, including the Horvath clock, GrimAge, Hannum, SkinBlood, PhenoAge, and Dunedin PACE [26-28]. Epigenetic age acceleration will be calculated using residuals after regressing each clock on chronological age [29,30]. Participants who complete activities required by the study protocol will have their epigenetic age acceleration reported back to them.

Cognitive functioning is measured with the MindCrowd web-based platform created by TGen. MindCrowd measures verbal memory performance using paired associates learning, and processing speed via simple visual reaction time. Both tests

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are strongly predictive of age and functional ability across the lifespan, and MindCrowd has been validated in hundreds of thousands of participants across the world [31-33]. To minimize the time burden on enrollment and possible learning effects, MindCrowd is only assessed at follow-up.

Cardiovascular fitness is evaluated with baseline and end-of-study CPETs, and additionally on an ongoing basis with wrist-worn accelerometers. The CPETs produce validated measures of resting VO2 (maximal aerobic capacity), peak VO2, VO2 reserve, and heart rate. The accelerometers from the wrist-worn watch also generate an estimate for peak VO2, and we will assess the progression of this over time as a function of intervention status.

Depression and mood are evaluated at baseline and follow-up using the revised version of the Center for Epidemiologic Studies Depression Scale. Diet quality is measured from a food frequency questionnaire at baseline and follow-up. Sleep quality is measured via the wrist-worn accelerometers for those in the zone 2 arm, and through a modified version of the Centers for Disease Control's National Health Interview Survey's Sleep Surveillance questionnaire for all participants. The National Health Interview Survey sleep survey is slightly modified to account for firefighter's shift work.

Statistical Considerations

Power Analysis

We conducted a power analysis based on the outcomes of changes in PFAS concentrations, as well as changes in epigenetic ages. Following the initial Australian study, to see a change in concentration of 20% PFOS from before and after, we calculated an N of approximately 100 participants per group or 300 total for the blood, plasma, or control groups. However, to observe a change of one year of epigenetic age acceleration, with a standard deviation of 3, we required an N of 141 per group. To account for missingness, we are targeting an N of 150 per group.

Therefore, the targeted sample size for PFOS ≥5 ng/mL is 150 plasma test participants, 150 blood test participants, and 150 shared controls for blood or plasma; and for PFOS <5 ng/mL we are targeting 75 intervention participants; for zone 2 is 150 controls and 150 test participants; for intermittent fasting, sample size is 150 controls and 150 test participants. Thus, the total number of participants that complete the study is targeted at 1120. Randomization of the intervention groups is conducted using R v4.2.0 [34].

Data Analysis

All models will evaluate intent to treat effects, as well as the average treatment effect of the treatment. We will first evaluate characteristics by treatment group to ensure randomization is effective.

To estimate the effect of blood and plasma donation on the reduction of PFAS concentration, mixed effects models with random effects by department or region will be fit to compare changes in PFAS concentration before and after the study among intervention groups. We will report mean differences in the change from baseline to end-of-study measurements by group and adjust for residual confounders. We will also evaluate whether the volume of plasma and blood donated is a significant predictor of PFAS change, and account for adherence in these models. The results of these models will evaluate if there is a statistically significant difference in the change of PFAS concentration from baseline to follow-up, in cases compared to controls, and if there is a dose-response relationship between volume donated and PFAS concentration change.

Linear mixed-effect models will also be used to examine differences between groups in epigenetic age acceleration, cardiovascular fitness, cognitive functioning (measured only at follow-up), mental health, sleep quality, and other measured outcomes. Similar models will be used for zone 2 physical activity and intermittent fasting interventions. Missing data will be assessed and if substantial missing data is identified (greater than 10%), a sensitivity analysis will be conducted using multiple imputations by chained equations.

Ethical Considerations

This study was reviewed and approved by the University of Arizona IRB (STUDY00002462). All participants complete informed consent electronically through the REDCap database system and all collected identifiable data is stored within the database (Multimedia Appendix 1). The research staff verifies that participants fully understand all risks and the necessary study activities that are required of them. Once participants agree to be active participants in the study, the study staff sign the informed consent. All participants receive the results of their PFAS concentrations, measured from the baseline blood collection during the screening process. No monetary compensation is provided to any participant in the study. At the end of study activities, only participants in the blood and plasma donation arm will receive a second set of PFAS results, measured from the blood collection at the end of the study. In addition, following the completion of all study activities, all participants receive the results of their epigenetic clocks.

Any participant information provided in this manuscript is de-identified. Any identifiable information is stored within the REDCap database, which securely keeps participant identifiers and contact information according to the University of Arizona's standard operation procedures. These procedures operate with respect to cybersecurity, privacy, patient confidentiality, and compliance with applicable patient privacy regulations. All study-related documents and specimens contain a unique identifier for each participant, with any study-related documents with personal identifiers stored in a locked cabinet in lockable offices on campus.

Results

This study was funded by the Arizona Board of Regents. Enrollment began in August 2023 and concluded in November 2024. As of January 2025, a total of 916 participants were enrolled in the study and 1893 participants were screened. The conclusion of the blood and plasma interventions is set for December 2025, contingent upon funding. Data analysis will begin once sufficient data has been collected.

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Discussion

Overview

All study interventions were selected based on interest from a community-engaged participatory framework with the fire service. Testing the effectiveness of blood and plasma donation in reducing serum PFAS levels in firefighters is a high priority among firefighters, given that this population has been found to have higher serum levels of these chemicals compared to the general population [6,9]. Evaluating all interventions as potential ways to improve epigenetic age acceleration and reduce disease risk is a priority in improving the health of the fire service. A primary strategy for promoting participant adherence to study activities is by reporting the results of their serum PFAS concentrations and epigenetic clock measurements back to them. Newsletters and website updates are also to provide study updates and promote participant engagement.

Strengths

One strength of the study includes measuring the baseline serum PFAS concentrations of approximately 2000 firefighters, leading to a better understanding of the impact of occupational activity history on PFAS. In addition, given that all interventions were requested by fire service leaders, there is more interest and determination to complete study activities. This study will also contribute to research into epigenetic age acceleration and potential interventions to improve it.

Limitations

Our study has some limitations; first, there are significant barriers to plasma donation, including time commitment and distance, which can impede participant adherence. The Australian study being replicated identified an adherence rate of 93.7% to their interventions [11]. All the intervention arms require a time commitment; therefore, compliance is a concern [35]. Finally, not meeting enrollment targets will reduce our study's power to evaluate relationships between the intervention and PFAS levels and epigenetic age acceleration.

Conclusions

The design, enrollment, and research activities of this randomized controlled trial provide an opportunity to observe PFAS interventions in real time and assess their feasibility and benefit.

Acknowledgments

Members of the University of Arizona study team assist with screening and enrollment events, participant contacts, daily operations, and laboratory processing. The University of Arizona team includes Hailey Freeman, Elizabeth Valdivia, Nina Wittmer, Samantha Castro, Danielle Stea, Erin Woods, Joe Mirabito, Elisabeth Hoornaert, Jessica Hlomatchi, Nagateja Yeddulla, Jordan Baker, Dylan Rogers, Alissa Coleman, Mia Huerta, Kylie Lew, and Natalya Mayhew. The Arizona State University team assists with screening and enrollment events in Phoenix and surrounding areas. The Arizona State University team includes Brendan Thomas, Kinta Schott, Avaani Bhalla, Theresa Jorgensen, Alexandra Levendi, Debra Baldauff, Margarita Stirk, Theresa Crain, Hanna Lybbert, Olivia Tilley, and Kyle Reid. Jackie Goodrich of the University of Michigan provided expertise in epigenetics and analyses. A special thanks to our fire service liaisons who assist in recruitment and coordination of events. Our fire service liaisons include Jason Miller, Kane Nixon, Jake Rhoades, McKenzie Hess, Rayne Gray, Dan Jarrett, Jeff McMenemy, Bryon Mabery, Ed Pahl, Orion Godfrey, Brad Pitassi, Jay Evans, Rob Brewster, Stephen Gunn, Blas Minor, Val Gale, David Switzer, Jodi Spargo, Joe Fioresi, Scott Figgins, Clint Steeves, Eric Valliere, Shauna O’Dell, Colt Weddell, Dave Endres, Kevin Montgomery, Kyle Carman, Mark Manor, Rick Olson, Scott Freitag, Adrianne O’Brien, Greg McLaughlin, Chris Sanchez, Elliot Riggs, Jeremy North, Joe Kosiorowski, Robert Corbell, Holger Durre, Jason Heartisan, Dennis Gasrow, Steve Legros, Craig Artrip, Jason Schnase, Rob Mathis, Karyn Barr, Jay Lee, David Hunt, Michael Warmuth, Mark Niemeyer, Heather Fleek, Kirk Carpenter, Derek Biering, Jeff Hughes, Jonathan Hernandez, Doug Menard, Kyle Taylor, Pat McKenna, Paul Lombard, Conor Flaherty, Nick Querzoli, Aaron Guggenheim. The certified testing locations for participant Cardiopulmonary Exercise Tests are 1582 (Rick Hutton) and HeartFit for Duty (Kepra Jack).

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Data Availability

The datasets generated or analyzed during this study are not publicly available due to participant confidentially, and final datasets are accessible by approved study staff.

Authors' Contributions

JLB, MF, SCB, and KL handled the concept and design. RC and CP managed the drafting of the manuscript. All authors contributed to the critical revision of the manuscript for important intellectual content. JLB, MF, and FW managed funding. KJK, JH, CP, and OH performed data management. MindCrowd Implementation was handled by MH, MF, and CP. JJG and KJ managed Firefighter Research Liaisons. Granting final approval of the version for publication was managed by all authors.

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Conflicts of Interest

FW received grants from external partners that were not related to this project, including Arizona Parks and Trails, Pac-12 Health and Wellbeing Initiative, the Collegiate and Professional Sports Dietetic Organization, FrieslandCampina, Standard Process Inc, Kraft Heinz Company, Unilever Corporation, and FEMA. The other authors have no conflicts of interest to report.

Multimedia Appendix 1
Study consent form.
[DOCX File , 123 KB - resprot_v14i1e67120_app1.docx]

Multimedia Appendix 2
SPIRIT Checklist.
[PDF File (Adobe PDF File), 6578 KB - resprot_v14i1e67120_app2.pdf]

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Abbreviations

CPET: Cardiopulmonary Exercise Test
FCRP: Firefighter Collaborative Research Project
FFCCS: Fire Fighter Cancer Cohort Study
IRB: institutional review board
PFAS: per- and poly-fluoroalkyl substances
PFOA: perfluorooctanoic acid
PFOS: perfluoro octane sulfonate

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Protocol

Comparison of Efficiency of Closed Kinetic Chain Exercises Versus Proprioceptive Exercises in Improving Balance and Gait in People With Hemophilia: Protocol for a Randomized Controlled Trial

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Abstract

Background: Inherited bleeding disorders involve prolonged bleeding due to clotting protein deficiencies, with hemophilia A and B being the most common types. The severity of bleeding in people with hemophilia depends on the deficient factor level. Treatment includes coagulation factor concentrates, nonreplacement preparations, gene therapies, and physiotherapy, whereby bleeding is prevented, symptoms are reduced, and the quality of life is improved. Closed kinetic chain exercises improve joint stability and neuromuscular control by stabilizing the proximal base, making them favored in musculoskeletal rehabilitation. Proprioceptive exercise training improves the sensorimotor system's adaptability and injury prevention through tailored programs involving progressively complex movements and surfaces.

Objective: The aim of this study is to investigate the effects of closed kinetic chain exercises and proprioceptive exercise training on improving balance and walking in people with hemophilia.

Methods: This study is a 3-arm, parallel-group randomized controlled trial with 63 people with hemophilia aged 13-25 years who meet the inclusion criteria. The primary outcome measures are medio-lateral swing, anterior-posterior swing, walking speed, and Hemophilia Joint Health Score. Secondary outcome measures are kinematic assessment of gait, one-leg stand test, 6-minute walk distance (6MWD) test, proprioception assessment, and the Functional Independence Score in Hemophilia. Participants will be evaluated with the Biodex balance system for postural sway, 10-meters walking test for gait speed, Hemophilia Joint Health Score for joint health, Kinovea 2D motion analysis for kinematic evaluation of gait, one-leg stand test for balance measurement, 6MWD for functional capacity, digital goniometer for proprioception, and Functional Independence Score in Hemophilia for functional independence. Participants will be randomly assigned to a closed kinetic chain exercise group, a proprioceptive exercise group, or a control group. All participants in exercise training groups will receive a 30-minute education session on joint protection techniques and energy conservation prior to the first exercise session. Closed kinetic chain exercises will include progressive lower limb exercises of approximately 45 minutes each session. Proprioceptive exercise training will focus on vibration training; reposition exercises and proprioception exercises will be administered to increase proprioceptive input for the same duration as the other group. The control group will receive no intervention. All participants will undergo 24 exercise sessions (2 days a week for 12 weeks). After the treatment, the initial measurements will be repeated.

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Results: This study began in September 2023 and is scheduled to be completed in May 2025. A total of 34 participants have completed the study to date.

Conclusions: This study will investigate the effects of 2 different exercises on functional parameters in people with hemophilia. The effects of different exercise protocols on parameters such as postural sway, walking speed, and joint health will be evaluated. It is predicted that both exercise methods may have positive effects on balance and gait.

Trial Registration: Clinical Trials.gov NCT05879549; https://clinicaltrials.gov/study/NCT05879549

International Registered Report Identifier (IRRID): DERR1-10.2196/66770

(JMIR Res Protoc 2025;14:e66770) doi:10.2196/66770

KEYWORDS

hemophilia A; hemophilia B; exercise; gait; postural balance; efficiency; hemophilia; proprioceptive exercises; balance; protocol; randomized controlled trial (RCT); bleeding disorder; protein deficiencies; blood clotting; quality of life; young adult; teenager

Introduction

Inherited bleeding disorders are rare diseases characterized by prolonged bleeding time due to deficiencies in protein cofactors and enzymes involved in blood clotting [1]. Among coagulopathies, hemophilia A, caused by a deficiency of factor VIII, and hemophilia B, resulting from a deficiency of factor IX, are the most common [2]. The severity of hemophilia is determined by the levels of the clotting factors in the blood, and is classified as mild, moderate, or severe hemophilia [3]. In mild hemophilia, bleeding occurs due to trauma, surgical procedures, and dental intervention. In moderate hemophilia, recurrent musculoskeletal bleeding is observed. In severe cases, spontaneous bleeding is also common [1].

In people with hemophilia, the location, timing, and severity of the clinical symptoms and findings vary depending on the level of the deficient factor. Bleeding in the musculoskeletal system is the most common type of bleeding, with 70%-80% occurring in the joints and about 15% occurring in the muscles [4]. The most frequently affected joints are the knee, ankle, and elbow [2]. Recurrent hemarthroses in people with hemophilia cause hypertrophy of the synovial membrane, making the joint more susceptible to further bleeding and increasing the risk of hemophilic arthropathy [5].

Current pharmacological treatments for hemophilia include standard or extended half-life factor preparations, therapies balancing the nonfactor coagulation system, intravenous or subcutaneous applications, and gene therapies that have been licensed in recent years [5,6]. In addition to pharmacological treatment, various physiotherapy methods are applied to prevent new bleeds and alleviate existing symptoms. The goals of physiotherapy and rehabilitation are to relieve pain, increase joint range of motion, prevent muscle atrophy, improve functional ability, reduce the frequency of joint bleeds, and enhance the quality of life [7].

According to the closed kinetic chain exercise model, consecutive rigid segments are connected by intermediary segments [8]. The terminal segment is fixed in this exercise model, and body weight resistance is provided. The advantage of closed kinetic chain activities is that they create stability in the proximal segment, providing a more solid base for distal mobility or ambulation, resulting in increased joint stability and neuromuscular control [9]. Closed kinetic chain exercises have been preferred in the rehabilitation of many musculoskeletal problems over the past 20 years [8,10].

Proprioception is a neural process that includes the body's ability to respond to sensory inputs from the environment [11]. Proprioceptive exercise training can enhance the sensorimotor system's ability to adapt to changing environments, thereby protecting the body from injuries [12]. Proprioceptive exercise training includes various exercises tailored to the patient's condition, focusing on transitioning from hard to softer surfaces, stable to unstable surfaces, simple to more complex movements, supported to unsupported movements, and different joint angles [13]. Sensorimotor training programs for lower extremity proprioception exercises include active joint repositioning exercises, coordination exercises, muscle performance, balance or unstable surface training, plyometric training, and vibration training [14].

Due to the frequent occurrence of hemarthroses in the lower extremity joints, changes in balance and walking parameters can be observed in people with hemophilia. A previous study has shown that the restricted rolling behavior of the foot in individuals with hemophilia, which may be caused by movement limitations and pain, can alter the balance between different foot areas [15]. Another study reported that changes in gait patterns in boys with hemophilia are associated with altered physical function performance [16].

Research [17,18] has demonstrated that both proprioceptive and closed kinetic chain exercises have beneficial effects on functional abilities in patients with lower extremity impairments. However, comparative studies evaluating the efficacy of these 2 exercise modalities specifically in people with hemophilia are yet to be conducted. This study aims to investigate the effects of closed kinetic chain exercises and proprioceptive exercise training approaches on improving balance and walking in people with hemophilia.

Methods

Participant Selection

The sample size was calculated as 18 individuals for each group using the G*Power program (version 3.1.9.4; Heinrich Heine University) with 90% power and .05 type 1 error using the medio-lateral swing effect size value as reference in the balance assessment in the study by Tat et al [19]. Considering that there

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might be individuals who would not complete the study, a total of 63 participants, that is, 21 individuals for each group, will be included.

The inclusion criteria of the participants in this study were as follows: (1) diagnosed with hemophilia A and hemophilia B, (2) have a blood factor level below 5%, (3) is 13-25 years of age, (4) have a history of bleeding in the lower extremities, (5) have a target joint, (6) have a total lower extremity Hemophilia Joint Health Score ≥3, and (7) is receiving prophylaxis (factor support to prevent bleeding). The exclusion criteria were as follows: (1) individuals having undergone lower extremity surgery in the last 6 months, (2) having BMI>30 kg/m^2, (3) having an inhibitor, (4) using a walking aid, and (5) being involved in any physiotherapy or exercise program in the last 6 months.

Ethics Approval

This study was approved by Istanbul University-Cerrahpaşa ethics committee (E-74555795-050.01.04-689576; May 3, 2023). The Declaration of Helsinki will guide this study. After eligibility is confirmed, written and verbal information about the study will be provided to all the participants. Then, the participants will sign a written informed consent form stating that they agree to participate in the research. The informed consent form also states that participation in the study is free and voluntary. No additional fees will be charged to the participants, and no payment will be made. The personal data and identity information of the participants will be kept confidential. Participants have the right to withdraw from the study at any time. The data will be used purely to contribute to science without any profit motive (Multimedia Appendix 1). At the same time, the data can be statistically analyzed without secondary approval when necessary. The trial intervention is similar to other clinical practices; therefore, we consider that risks from the trial are minimal. Additionally, exercise training approaches in the intervention group will be applied with the same protocol and duration to the participants in the control group at the end of the study.

Study Design

This study has been registered with Clinical Trials.gov (NCT05879549). It is a 3-arm, parallel-group, single-blinded randomized controlled trial. This trial has been reported according to CONSORT (Consolidated Standards of Reporting Trials) guidelines (Multimedia Appendix 2) and the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist (Multimedia Appendix 3). This study will be performed in Istanbul University-Cerrahpaşa Laboratory. A permit has been obtained from the institution. The demographic characteristics of the participants (age, height, weight, diseases, etc) will be recorded. Participants will be divided into 3 groups using a simple randomization method according to the order of arrival (1:1:1) with a web-based randomizer. Participants do not know the exercise group that they will be included in nor will they know the differences between the exercises. The flowchart of this study is shown in Figure 1.

Figure 1. Flowchart in this study.

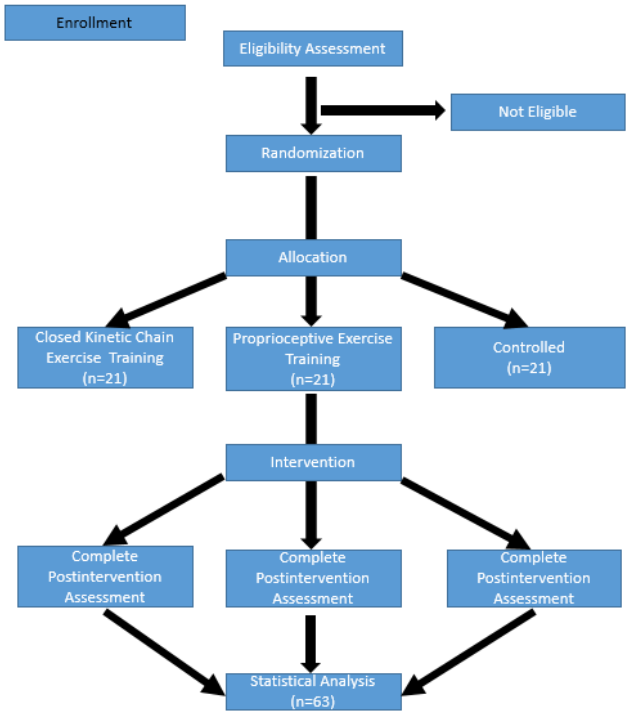

Outcome Measures

The primary outcome measures are medio-lateral swing, anterior-posterior swing, walking speed, and Hemophilia Joint Health Score. Secondary outcome measures are kinematic assessment of gait, one-leg stand test, 6-minute walk distance (6MWD), proprioception assessment, and Functional Independence Score in Hemophilia. All patients will have completed their factor replacement 1 hour before the assessment section.

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Postural Sway

Postural sway will be evaluated using the Biodex balance system, which is a reliable method (Figure 2) [20]. Postural sway, center of pressure, center of gravity, anterior-posterior, and lateral sway will be evaluated with eyes closed and open. Patients will be informed about the purpose and performance of the tests before the assessment. Each test will be repeated 3 times. A lower sway index in all tests indicates a better postural stability, while an increase in the sway index indicates a decrease in postural stability (Figure 3).

Figure 2. Biodex balance system.

Figure 3. Example of postural sway. (A) Postural sway with eyes open. (B) Postural sway with eyes closed.

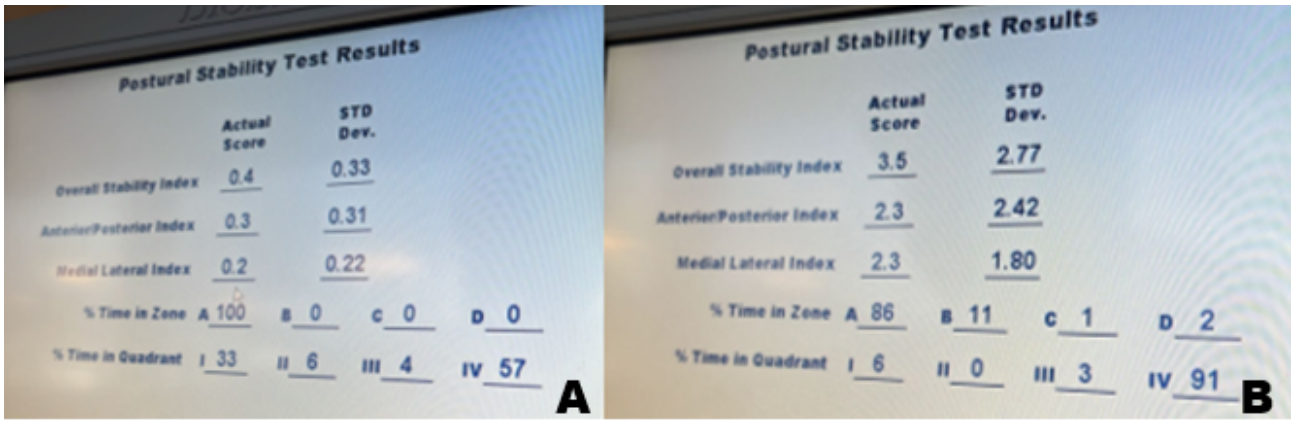

Joint Health

The Hemophilia Joint Health Score is a hemophilia-specific score, including measurements of muscle strength; edema; crepitation; range of motion of bilateral elbow, knee, and ankle joints; and assessments related to walking [21]. The maximum score to be obtained from each joint is 20, and the maximum score to be obtained from the global gait score is 4. The maximum score to be obtained from the assessment tool is calculated as 124, and a high score indicates poor joint health. The parameters to be evaluated within the scope of the score are as follows: swelling, swelling duration, muscle atrophy, flexion and extension loss, joint pain, muscle strength, and global gait score.

Kinematic Evaluation of Gait

The spatiotemporal parameters of hip, knee, and ankle joints and walking speed will be analyzed during walking using Kinovea 2D motion analysis software (Figure 4). In order to evaluate the lower extremity joint angles during walking, video footages will be taken with 2 cameras fixed with a tripod placed laterally and anteriorly [22]. The fifth metatarsophalangeal joint, lateral malleolus, lateral femoral condyle, and trochanter major will be marked using the reflector tape (adhesive circular tapes that contrast with the background).

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Figure 4. Screenshot of Kinovea 2D motion analysis software.

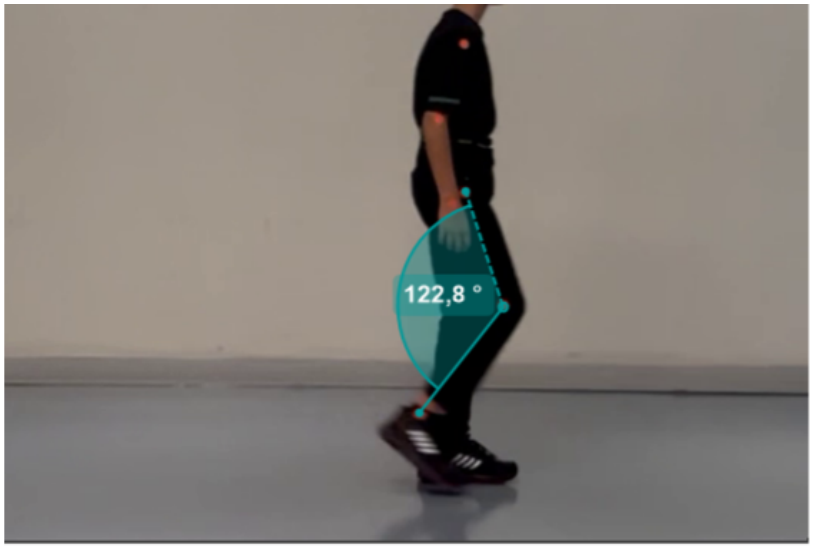

Balance

The one-leg standing balance test will be evaluated with eyes open and closed [23]. The participant lifts one foot with eyes open so that it does not touch the support leg and tries to maintain this position. The individual is expected to maintain this position for a maximum test duration of 30 seconds. The time he remains on one leg will be recorded.

Functional Capacity

The 6MWD test will be applied for the evaluation of functional capacity. The patient is asked to walk as far as possible at their own walking pace for 6 minutes in a 30-meter straight corridor. Before starting the test, the patient rests in a sitting position for 10 minutes in the corridor where the test will be performed. At the end of the test, 6MWD is recorded in meters [24].

Proprioception

A digital goniometer will be used to assess proprioception. Proprioception assessment will be performed for knee and ankle joints. During the knee joint assessment, the patient will be positioned from the bed with feet hanging down and knees in 90° flexion. The pivot of the digital goniometer will be placed on the lateral condyle of the femur, and the knee will be brought to the previously determined 15° and 30° extension angles. The patient will be asked to perceive the position of this angle by waiting for 10 seconds with eyes open. Then, the patient will be asked to actively repeat these angles 3 times for both knees with eyes closed. For ankle proprioception measurement, the patient will be placed in a long sitting position on the bed. A neutral position will be provided for the ankle; the lateral malleolus of the fibula will be taken as the pivot point and the goniometer will be placed on the pivot point. The fixed arm of the goniometer will be kept parallel to the lateral midline of the fibula, and the movable arm will be placed to follow the lateral midline of the 5th metatarsal bone. The goniometer will be brought to an angle of 20°, and the patient will be asked to make a plantar flexion movement of the ankle and hold it at this angle for 5 seconds with the eyes open. Then, the patient will be asked to return to the starting point and find the target angle, that is, the range of motion of 20°, with the eyes closed. The measurement will be repeated 3 times for both ankles with the same method [25].

Functional Independence

The Functional Independence Score in Hemophilia has been developed as an assessment tool used to measure the functional ability of the patient with hemophilia. The patient is asked to score their level of independence in 8 activities under 3 main headings related to activities of daily living. These activities are eating or self-care, bathing, dressing, transfers, squatting, walking, climbing stairs, and running. The patient will be asked questions and asked to score between 1 and 4. The total score will be recorded [26].

Intervention

All participants will be divided into 3 groups. Group 1 is the closed kinetic exercise group, group 2 is the proprioceptive exercise group, and group 3 is the control group. Participants in group 1 and group 2 will receive exercise training twice a week for 12 weeks for a total of 24 sessions of 45 minutes each. The control group will not receive any intervention. Exercise training will continue under the supervision of the physiotherapist. Patients will have completed their factor replacement on the day of exercise. If any signs of bleeding are observed, the exercise session will be terminated. Following randomization, all participants in exercise training groups will receive a 30-minute education session on joint protection techniques and energy conservation prior to the first exercise session. This training will cover the goals and basic principles of joint and energy education; correct and incorrect posture characteristics; proper standing, sitting, and lifting techniques; the benefits of correct posture; posture recommendations for different activities; hand protection methods; factors contributing to fatigue; and basic principles of energy management.

Closed Kinetic Chain Exercise Training

Group 1 exercises will start with a 5-minute warm-up. The warm-up exercises include marching in place, shoulder circles, elbow stretching, seated knee flexion and extension, as well as stretching exercises targeting the hamstring and gastrocnemius muscles. Thereafter, 6-8 different closed kinetic chain exercises

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will be planned as 2-3 sets and 8-10 repetitions (Figure 5). Subsequently, the session will be finished by cooling down for 5 minutes and applying ice to the lower extremity joints for 15 minutes. Each session is expected to last approximately 40-45 minutes. Exercises will be progressively made more difficult once every 2 weeks. Exercise training will continue under the supervision of a physiotherapist 2 days a week for 12 weeks. The details of the closed kinetic chain exercise training and progression are given in Table 1.

Figure 5. Examples of closed kinetic chain exercises. (A) Terminal knee exercise with resistance band. (B) Single leg bridge exercise.

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Table 1. Closed kinetic chain exercises protocol.

	Repetitions (n)	Sets (n)
Weeks 1-3		
Terminal knee extension (both sides)	10	2
Bridge	10	2
Bridge with hip adduction	10	2
Lunge (both sides)	10	2
Side lunge (both sides)	10	2
Mini squat	10	2
Step up (both sides)	10	2
Weeks 4-6		
Terminal knee extension (both sides)	10	3
Bridge	10	3
Bridge with hip adduction	10	3
Lunge (both sides)	10	3
Side lunge (both sides)	10	3
Mini squat	10	3
Step up (both sides)	10	3
Weeks 7-9		
Terminal knee extension with mild resistance band (both sides)	10	2
Bridge with mild resistance band	10	2
Single leg bridge	10	2
Lunge (both sides)	10	2
Side lunge (both sides)	10	2
Mini squat on unstable surface	10	2
Mini squat with hip adduction (both sides)	10	2
Weeks 10-12		
Terminal knee extension with mild resistance band (both sides)	10	3
Bridge with mild resistance band	10	3
Single leg bridge	10	3
Lunge (both sides)	10	3
Side lunge (both sides)	10	3
Mini squat on unstable surface	10	3
Mini squat with hip adduction(both sides)	10	3

Proprioceptive Exercise Training

Proprioceptive exercise training will focus on sensorimotor training. In this training model, vibration training, reposition exercises, and proprioception exercises will be given to increase proprioceptive input (Figure 6).

Exercise training will start with the same 5-minute warm-up as in the closed kinetic chain exercise group and will continue with vibration application to the knee and ankle joints. Since damage or loss of mechanoreceptors due to degenerative events in the joint in people with hemophilia may adversely affect the balance and proprioception required in activities, there may be a decrease in lower extremity vibration sensation [27].

Vibration training will be applied to 4 points, that is, patellar tendon, medial knee joint, lateral knee joint (medial collateral ligament and lateral collateral ligament), and the upper part of the patella bone. The application to each point will start with 30 seconds, and the application time will be increased by adding 15 seconds every 2 weeks.

Then reposition exercises will be started. Kinetic reposition exercises will be performed on 3-way lines drawn on a white cardboard paper. One of the lines drawn on the white cardboard

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is straight, and the other 2 are lines drawn at 30° angles to the straight line, considering that the internal and external (axial) rotation of the tibia on the femur is 45° when the knee is at 90°. Numbers in centimeters will be written on the lines. The patient will be seated on the chair with 90° knee flexion and will be asked to put his or her foot on these lines and hold it for 10 seconds to take his or her foot to the point 10 cm away and learn that point. Afterwards, the patient will return to the starting point and will be asked to find the point he or she learnt with his or her eyes closed.

The program will be planned as 6-8 different proprioceptive exercises performed in 2-3 sets and 8-10 repetitions. Finally, the session will be finished by cooling down for 5 minutes and applying ice to the lower extremity joints for 15 minutes. Each session is expected to last approximately 40-45 minutes. Exercises will be progressively made more difficult once every 2 weeks. The details of proprioceptive exercise training and progression are given in Table 2.

Figure 6. Examples of proprioceptive exercises. (A) Standing on a Bosu ball. (B) One-leg stand on a foam surface.

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Table 2. Proprioceptive exercises protocol.

	Duration or repetition (min or s)	Sets (n)
Weeks 1-3		
Warm-up	5 min	N/A[a]
Application of vibration (patellar tendon, medial, and lateral sides of the knee joint; both sides)	30 s	N/A
Kinetic repositioning exercises (both sides)	All directions	5
Standing on a balance board	10 s	2
Standing on a Bosu ball	10 s	2
One-leg stand	10 s	2
Semitandem walking	10 s	3
Cool down	5 min	N/A
Weeks 4-6		
Warm-up	5 min	N/A
Application of vibration (patellar tendon, medial, and lateral sides of the knee joint; both sides)	45 s	N/A
Kinetic repositioning exercises	All directions	5
Standing on a balance board	10 s	3
Standing on a Bosu ball	10 s	3
One-leg stand	10 s	3
Semitandem walking	30 s	2
Cool down	5 min	N/A
Weeks 7-9		
Warm-up	5 min	N/A
Application of vibration (patellar tendon, medial, and lateral sides of the knee joint; both sides)	60 s	
Kinetic repositioning exercises (both sides)	All directions	10
Eyes open and close standing on a balance board	15 s	2
Eyes open and close standing on a Bosu ball	15 s	2
Eyes closed one-leg stand	15 s	2
One-leg stand on foam surface	15 s	2
Tandem standing	15 s	2
Weeks 10-12		
Warm-up	5 min	N/A
Application of vibration (patellar tendon, medial, and lateral sides of the knee joint; both sides)	60 s	N/A
Kinetic repositioning exercises (both sides)	All directions	10
Eyes open and close standing on a balance board	20 s	3
Eyes open and close standing on a Bosu ball	20 s	3
Eyes closed one-leg stand	20 s	3
One-leg stand on foam surface	20 s	3
Tandem standing	20 s	3

[a]N/A: not applicable.

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Statistical Analysis

Data will be statically analyzed using SPSS (version 25.0; IBM Corp). Normality tests (visual and analytical) will be applied. Descriptive statistics will be presented as mean (SD) or frequency (percentage). The Shapiro-Wilk test will be used to assess the normality of data distribution. For normally distributed data, a one-way analysis of variance test will be applied for between-group comparisons, and a 2-sided paired sample *t* test will be used for within-group changes. For nonnormally distributed data, the Kruskal-Wallis test will be used for between-group comparisons, and the Wilcoxon test will be applied for within-group changes. In cases where between-group comparisons of normally distributed data show significant results, Tukey or Bonferroni corrections will be used as post hoc analyses to identify the source of the differences. For nonnormalized distributed data, Mann-Whitney *U* tests will be conducted for between-group comparisons. A *P* value <.05 will be considered statistically significant for all analyses.

Results

This research received funding from the Turkish Scientific and Technological Research Institution as of September 1, 2023. From this date, cases began to be incorporated into the study. By April 2025, a total of 34 participants had completed the treatment phase. Once all enrolled participants have finished their treatment, data analysis will commence. The anticipated completion date for this study is May 2025.

Discussion

This study will investigate the effects of 2 different exercise approaches on functional parameters in people with hemophilia. In this study, the effects of exercise protocols on parameters such as postural sway, walking speed, and joint health will be evaluated. The predicted main findings of this study suggest that both exercise approaches may positively affect functional parameters such as postural sway, walking speed, and joint health in individuals with hemophilia, with anticipated improvements in balance and gait.

Recurrent bleeding in the lower extremities of people with hemophilia may cause changes in gait. Fouasson-Chailloux et al [28] observed that patients with moderate hemophilia may have impairments in gait parameters if their joint health scores are poor [28]. Joint movement limitations in people with hemophilia may occur due to movement restrictions and pain sensation, and this may lead to decreased pressure in the forefoot center and shorter step length [28]. Fukuchi et al [29] reported that people with hemophilia walked with less range of motion in the hips and ankles compared to their healthy peers. In addition, a decrease in gait speed and step length and an increase in double support and swing phase duration were observed in patients with moderate or severe hemophilia [30]. Changes in the walking patterns of boys with hemophilia are associated with changes in physical function performance [15]. Deniz et al [31] reported that an 8-week structured exercise program can improve the kinematic parameters of walking. For these reasons, the effect of exercise programs on walking will be investigated in our study, and for this purpose, changes in walking speed and kinematic parameters will be evaluated using the Kinovea software (Joan Charmant, open source).

Recurrent bleeding is the major factor leading to hemophiliac arthropathy. Lower extremity arthropathies may cause balance problems. A previous study [19] where static posture was evaluated using Biodex similar to our study showed that medio-lateral oscillations increased in people with hemophilia. These changes were found to be associated with the clinical scores of the lower extremity joints. That study emphasized the importance of balance assessment and suggested that exercises to enhance medio-lateral stability should be incorporated into rehabilitation programs. Although lower extremity arthropathies may affect balance scores, worse balance scores have been reported in patients with and without hemophilic arthropathy compared to healthy individuals. For this reason, we incorporated methods from the literature known to positively impact balance parameters into our study.

Exercise training is one of the most commonly recommended methods to prevent and treat musculoskeletal problems that may develop in patients with hereditary bleeding disorders [15]. Traditionally, the most commonly used exercise types are aerobic exercises, strengthening exercises, aquatic exercises, and combined training. In our study, the effectiveness of customized exercise programs will be compared differently from that in existing literature. Chronic synovitis, cartilage damage, and subchondral bone damage due to recurrent joint bleeding in people with hemophilia may decrease proprioceptive information [32]. For this reason, one of the exercise groups that we planned was based on proprioception. The effect of progressively developed sensorimotor exercises on balance and gait parameters will be revealed.

Gönen et al [33] performed different exercise trainings for 21 patients for 12 weeks in people with hemophilia: 7 patients were included in the closed kinetic chain exercise training group, 7 in the conventional exercise group, and 7 in the control group. They concluded that closed kinetic chain exercise training was superior in proprioception and physical activity compared to conventional exercises for people with hemophilia A [33]. In our study, we aim to investigate the effects of closed kinetic chain exercises on balance and gait parameters. Additionally, by the end of the study, we will compare the outcomes of proprioceptive exercise training and those of closed kinetic chain exercises. This comparison will contribute to developing optimal exercise training programs for people with hemophilia.

Bleeding episodes induced by exercise in people with hemophilia have been reported as rare adverse events [15]. In our study, to prevent any bleeding during exercises, the exercises were scheduled on the days when patients received their factor replacement therapy.

A limitation of this study is the lack of long-term follow-up, which is particularly relevant, given that hemophilia is a chronic condition that predisposes individuals to ongoing musculoskeletal system challenges. The absence of extended outcome assessments limits the ability to evaluate the sustained effects of the exercise interventions on balance, gait, and joint health over time.

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Our study will contribute to the literature as the first study comparing the protocols of closed kinetic chain exercises and proprioceptive exercises in people with hemophilia. We expect our study to be a pioneer in the future, especially in protocols that contribute to the improvement of daily life activities such as balance and walking, which are affected by bleeding.

Acknowledgments

This study is entitled to be supported for 12 months with a project decision letter dated September 1, 2023 (223S216), within the scope of the Tübitak 1002-A Rapid Support Module.

Data Availability

The data sets generated during and analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-reviewer report from the Turkish Scientific and Technological Research Institution.
[PDF File (Adobe PDF File), 273 KB - resprot_v14i1e66770_app1.pdf]

Multimedia Appendix 2
CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist (version 1.6.1).
[PDF File (Adobe PDF File), 426 KB - resprot_v14i1e66770_app2.pdf]

Multimedia Appendix 3
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 226 KB - resprot_v14i1e66770_app3.pdf]

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Abbreviations

6MWD: 6-minute walk distance
CONSORT: Consolidated Standards of Reporting Trials
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

A Rent Subsidy and Identity Capital Intervention for Youth Exiting Homelessness: Protocol for the Transitioning Youth Out of Homelessness 2.0 Pilot Randomized Controlled Trial

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Abstract

Background: For young people who have experienced homelessness, relative housing stability alone is insufficient to achieve socioeconomic inclusion. There is little peer-reviewed research investigating interventions targeting socioeconomic inclusion outcomes for youth who have experienced homelessness. Our previous community-engaged work signaled that identity capital (purpose, control, self-efficacy, and self-esteem) may mediate socioeconomic inclusion outcomes for youth exiting homelessness. This 12-month pilot randomized controlled trial (RCT) explores whether portable rent subsidies and an intervention targeting

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identity capital hold promise as a way to facilitate socioeconomic inclusion for youth exiting homelessness and living in market rent housing in Ontario, Canada.

Objective: The objectives of this study were (1) to examine the feasibility and acceptability of an RCT of targeted economic and identity-based supports to foster socioeconomic inclusion (primary objective), (2) to estimate the effect of adding identity-based supports to economic supports (intervention group) compared with economic supports alone (control group) at the 12-month end point with respect to self-reported proxy indicators of socioeconomic inclusion (secondary objective), and (3) to explore, among the intervention group, whether the estimated effect of the intervention differs by baseline variables or level of engagement with the intervention (exploratory objective).

Methods: This study is a convergent mixed methods, 2-arm parallel RCT, open-label design with 1:1 allocation. All youth participants (n=40) received rent subsidies; half were randomly assigned an identity capital intervention (co-designed leadership guide+coach). The overall study was guided by community-based participatory action research axiology. The qualitative component used a qualitative descriptive design underpinned by critical social theory. The measures used were (1) recruitment, enrolment, and dropout metrics; self-report composite checklists regarding intervention engagement; coaching session attendance; and qualitative focus groups (primary measures); (2) education, employment, and training; housing security; and identity capital (secondary measures); and (3) impact of baseline variables (eg, participant demographics such as gender or mental health symptoms as measured by the Global Appraisal of Individual Needs–Short Screener) or level of engagement with intervention (coaching session attendance) on secondary measures (exploratory measures).

Results: Recruitment and enrolment began March 1, 2023, and ended June 19, 2023. Data collection began March 7, 2023, and ended June 17, 2024. Qualitative and quantitative data analyses concluded on August 20, 2024.

Conclusions: Findings from this RCT will help inform the way we conceptualize the types of supports that are necessary to sustain successful exits from homelessness. The intervention was co-designed with youth who have experienced homelessness, and their voices will continue to inform the next iteration of this work.

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KEYWORDS

youth homelessness; socioeconomic inclusion; transition; critical qualitative methodology; community-based research; identity capital; youth; homeless; rent; community; feasibility; acceptability; novel intervention; socioeconomic; participatory action research; pilot study; protocol; RCT; randomized controlled trial

Introduction

There is a vast literature describing youths' pathways into homelessness; much less is known about transitions out of homelessness. A common belief is that youth who have experienced homelessness will achieve socioeconomic inclusion—equity in health and well-being [1]—through housing stability. The provision of relatively stable accommodation is seen as a sort of springboard toward socioeconomic inclusion. Longitudinal studies conducted in high-income countries suggest this is often not the case. Despite the attainment of relative housing stability, many young people continue to struggle with day-to-day survival, a lack of purpose, hopelessness, and a sense of being stuck [2-5].

In contrast, there is a dearth of peer-reviewed literature on interventions targeting socioeconomic inclusion outcomes for youth who have experienced homelessness [6]. A 2020 systematic review synthesizing evidence from 53 unique interventions conducted in high-income countries with youth (age 13-25 years) who were experiencing or had experienced homelessness highlights the urgent need for robust evidence on this issue [7]. Most of the reviewed studies focused on interventions related to counseling or treatment (eg, substance use) and many were described as low-rigor designs. Only 42% of the studies involved some form of randomized evaluation; of those, 64% reported mixed, negative, or null findings.

There was only one published study of a randomized intervention offering rent subsidies in the systematic review. This was a secondary analysis of youth (age 18-24 years) in the Canadian study of Housing First in adults (At Home/Chez Soi); there was no systematic adaptation of the intervention for youth. The youth-focused analysis found that Housing First (subsidized housing+intensive mental health supports) was effective for housing stability; however, there were no significant improvements in health and well-being outcomes in the intervention group relative to the control group [8]. The authors of the systematic review concluded, "The field lacks rigorous evaluative evidence of many of the program models on which communities and governments rely to address youth homelessness" [7].

Many of the community collaborators and researchers involved in this study have been working together for several years to try and support successful exits from homelessness and improve socioeconomic inclusion outcomes for youth who have experienced homelessness. In March 2019 (after several months of prestudy collaboration), we began the Transitioning Youth Out of Homelessness (TYOH) study, a 2.5-year pilot community-based mixed method randomized controlled trial (RCT) with youth (mean age 22 years) from 3 cities in the

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province of Ontario [9]. All participants (n=24) received portable rent subsidies (ie, subsidies not tied to a specific location) for 2 years; 13 were randomly assigned an adult mentor. The overall aim of TYOH (now referred to as TYOH 1.0) was to understand whether youth who received rent subsidies and mentorship achieved better socioeconomic inclusion outcomes relative to the group that only received rent subsidies. We believe TYOH 1.0 was the first published RCT in this population to identify socioeconomic inclusion as the primary outcome (proxy indicators of socioeconomic inclusion encompassed measures such as community integration, self-esteem, and engagement in education, employment, and training).

Quantitative data from TYOH 1.0 revealed that, as a cohort, study participants had stable or nonsignificant improvements in all study outcomes at the primary end point of 18 months compared to baseline (potentially attributable to rent subsidies); however, there were no statistically significant improvements in proxy indicators of socioeconomic inclusion in the mentorship group relative to the nonmentorship group 18 months post randomization [10]. While we were unable to prove that youth receiving rent subsidies and mentorship had significantly better socioeconomic inclusion outcomes compared to the group who received rent subsidies only, there were signals from our quantitative and qualitative data that connecting with informal mentors—people outside the study who played “coach-like” roles (eg, asking powerful and future-oriented questions vs simply providing advice)—was key to fostering socioeconomic inclusion [10].

Drawing on 71 in-depth interviews over the 2.5-year study period, TYOH 1.0 also highlighted the crucial role of identity capital (a sense of purpose, control, self-efficacy, and self-esteem) as an important mediator of socioeconomic inclusion [11]. When people with limited identity capital encounter challenges, they are more likely to give up and take the path of least resistance [12]. Youth in TYOH 1.0 who seemed to more easily navigate their transitions out of homelessness drew on this internal resource of identity capital to push forward despite external challenges [11]. Taking these 2 ideas together (coaching+identity capital) we decided to design a study similar to TYOH 1.0, but with certified coaches (instead of mentors) and a more deliberate targeting of identity capital.

Interventions designed to mediate socioeconomic inclusion by bolstering some or all components of identity capital is an undeveloped area of research but there are some promising transferrable findings from interventions with youth from low socioeconomic backgrounds and with youth who have experienced homelessness [13-18]. In 2018, the principal investigator of TYOH 1.0 and this current study led The Identity Project – a pilot nonrandomized identity capital intervention with youth (n=19) who had experienced homelessness [19]. The results were promising: 9 months after the 6-week 6-session intervention (leadership guide+group coaching) concluded, there were statistically significant improvements and moderate effect sizes in hopelessness and self-esteem compared to baseline [19].

Building on what we learned from our previous work, our team of community and academic partners, including youth with lived expertise, developed TYOH 2.0—a 1-year mixed methods RCT with youth exiting homelessness. The overarching aim was to determine the feasibility and acceptability of a trial focused on identity capital and intended to facilitate socioeconomic inclusion for youth (aged 16-24 years) exiting homelessness and living in market rent housing (refer to Multimedia Appendices 1 and 2 for SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) and CONSORT (Consolidated Standards of Reporting Trials) checklists). Specifically, the objectives were to (1) examine the feasibility and acceptability of an RCT of targeted economic and identity-based supports to foster socioeconomic inclusion (primary objective), (2) estimate the effect of adding identity-based supports to economic supports (intervention group) compared with economic supports alone (control group) at the 12-month end point with respect to self-reported proxy indicators of socioeconomic inclusion (education, employment and training; housing security; identity capital; secondary objective), and (3) explore, among the intervention group, whether the estimated effect of the intervention differs by baseline variables or level of engagement with the intervention (exploratory objective).

Methods

Philosophical Underpinning

This work was grounded in the commitment to centering the voices of youth with lived expertise as well as responding to priorities defined by community partners. The overall study drew on key principles of community-based participatory action research (CBPAR) axiology, and the qualitative component was framed with a critical social theoretical lens [20-23] (Textbox 1).

Textbox 1. Transitioning Youth Out of Homelessness 2.0 philosophical underpinning.

- Research participants are viewed as experts in their own lives.
- Focus on highlighting how inequitable social structures of power (including the intersection of factors such as race, class, and gender) play out in the lives of participants.
- Search for examples of resilience and agency despite sociostructural inequities.
- A concerted effort to acknowledge and reduce power imbalances between researchers and the community.
- Equal value is placed on academic knowledge and experiential knowledge.
- Commitment to coproducing practical, actionable data to build community capacity and improve the lives of research participants.
- Duty to remain invested in the community beyond the life of the research project.

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Trial Design

This pilot study used a convergent mixed methods (quantitative and qualitative data collected concurrently and the findings combined), 2-arm parallel RCT (participants randomly assigned to either the intervention or control group), open-label (participants and research team aware of random assignment) design with 1:1 allocation (equal number of participants in each study arm) embedded within a CBPAR framework. The study was conducted collaboratively with 4 community partners who work with youth who are experiencing or have experienced homelessness: (1) Covenant House Toronto (Toronto, Ontario), (2) Living Rock (Hamilton, Ontario), (3) The RAFT (St. Catharines, Ontario), and (4) StepStones for Youth (Toronto, Ontario).

The study was prospectively registered on ClinicalTrials.gov (NCT05781503) and received Unity Health Toronto Research Ethics Board approval (#22-230). All protocol amendments were reported to both these organizations. The only protocol deviation was submitted in October 2023, which allowed community partners to send the rent subsidies directly to youth for those at risk of losing their housing due to refusal of third-party payments from landlords, or fear losing their housing due to disclosing a history of homelessness.

Sample Size

This pilot feasibility and acceptability study was designed with the intention of generating data and hypotheses to inform a full-scale study; therefore, no formal sample size calculation was performed. Instead, we chose a pragmatic sample size of 40 participants, based on the financial resources available to provide rent subsidies and coaching over a 12-month period.

Participants

Eligible youth ages 16-24 years who had left homelessness (defined by the Canadian Observatory on Homelessness [24] as unsheltered, emergency sheltered, provisionally accommodated, and at risk of homelessness) within the past 12 months and living or planning to live in market rent housing were identified by our community partners. This age mandate was chosen because this is the age group served by our community partners. We chose to target the first year of exiting homelessness because our collective experience has shown that this is a particularly precarious time for youth in terms of mental health challenges and the risk of returning to homelessness. Foster care was included in our definition of homelessness given the time-limited and provisionally accommodated nature of these living arrangements, which put youth at high risk of homelessness.

In addition to the above conditions, recruited and enrolled participants were required to meet the following criteria (Textbox 2).

Textbox 2. Inclusion and exclusion criteria.

Inclusion criteria

- Were able to provide free and informed consent.
- Were able to understand English (intervention and data collection conducted in English).
- Were willing to actively participate in the intervention (co-designed leadership guide+coach) if randomized to this arm.

Exclusion criteria

- In imminent danger of losing their housing and not being able to use the rent subsidy to sustain market rent housing (eg, facing jail time).
- Already receiving rent subsidies (eg, Canada-Ontario Housing Benefit).
- Enrolled in a program or study with similar features to the Transitioning Youth Out of Homelessness 2.0 intervention (eg, individual coaching or program targeting identity capital).

Identification and Consent

Study participants were recruited from the cities in which our community partners are located: Toronto, Ontario (Greater Toronto Area population 6.7 million), Hamilton, Ontario (population 785,000), and St. Catharines, Ontario (St. Catharines-Niagara population 416,000). The initial introduction to the study was facilitated by our community partners. Frontline staff (eg, case workers, housing workers) working with youth who have experienced homelessness were responsible for identifying youth who may be interested in the study and met the inclusion and exclusion criteria. Staff provided potential participants with information about the study and the study consent form to review. Potential participants were directed to contact the study lead research coordinator by email or phone, who then conducted eligibility screening over the phone. Once participants were deemed eligible for the study, they were connected to a member of the research team. To build rapport with community partners and study participants, one dedicated research team member was assigned to each partner site.

Each research team member reached out to eligible youth for an initial Zoom call. Free and informed verbal consent was first obtained after carefully reviewing the information and consent form with the participant. During the same Zoom call, electronic consent was also obtained once the research team member emailed participants the secure baseline data collection web link and a unique login and password. The baseline data collection questionnaire was programmed so that participants were unable to proceed until they selected “Yes” for consent. The research team member stayed on the call while the participants completed the baseline questionnaire.

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Randomization and Allocation

Once participants completed the baseline questionnaire the research team member opened a sequentially ordered randomization file from a sequentially ordered electronic randomization folder to obtain the participant's group assignment. The participant's group allocation was noted, and participants were informed immediately if they had been allocated to the intervention (rent subsidies and co-designed leadership guide+coach) or control (rent subsidies alone) group (Figure 1 [25]). Randomization was stratified by site using block randomization (random block sizes of 2 and 4). In keeping with typical community-based RCTs with psychosocial interventions, blinding of participants, community partners, and research staff to allocation group was not pragmatic due to the nature of the intervention [26].

Further to Figure 1, the participant excluded post randomization was found to be ineligible before the intervention was initiated. We will not be using data from the ineligible participant. A new youth was then enrolled and randomized. In addition, the participant who withdrew during follow-up did so in order to meet the criteria for a different (longer-term) rent subsidy program.

Figure 1. CONSORT diagram for pilot and feasibility studies of the anticipated flow of participants through the study.

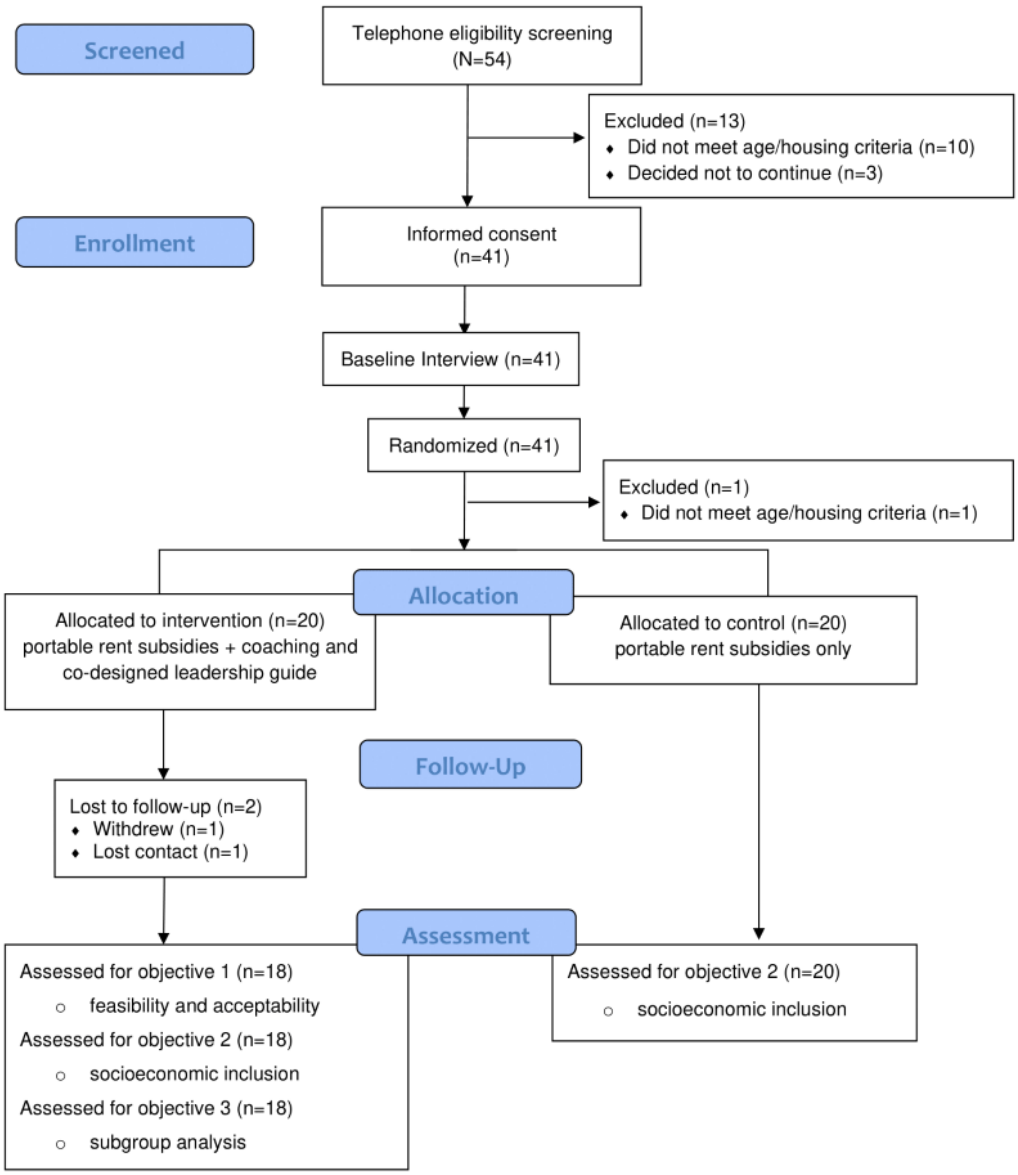

Intervention

Youth in both arms (n=40) were provided monthly rent subsidies (CAD $700/month Hamilton and St. Catharines; CAD $800/month Toronto) for 12 months, which was generally paid directly to landlords and facilitated by our community partners (refer to Trial Design re: protocol deviation; at the time of recruitment, the conversion rate was CAD $1=US $0.7357). Youth who participated in TYOH 1.0 suggested the TYOH 2.0 research team should encourage participants to delegate a portion of the money they would have spent on rent toward a savings account, which they would be able to access at the end of the study. This idea received unanimous support from our community partners and was suggested to all participants at enrolment and suggested periodically during the study. Youth randomized to the intervention group (n=20) were also provided

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a co-designed leadership guide and assigned a study coach. The control group (n=20) was offered the co-designed leadership guide at the end of the study.

Co-Designed Leadership Guide

The strengths-based leadership guide (Finding Home: A Guide for Youth in Transition) was co-designed with 12 youth who had experienced homelessness, including youth who participated in TYOH 1.0. NST drafted the original version of the guide and cofacilitated a full-day co-design workshop with research team member MD. MD is an experienced peer engagement specialist who draws on her lived expertise of homelessness to collaborate with researchers and youth who have experienced homelessness. Significant enhancements were made to the guide based on feedback from workshop participants.

The Leadership Guide contained 12 chapters with the overarching aim of enhancing identity capital along with providing strategies to achieve participant-identified goals (Table 1). Each chapter contained 4 activities (eg, a self-reflection exercise or listening to a podcast). It was suggested youth complete one chapter every month; however, they were also encouraged to go at their own pace. Copies were provided in print and electronic formats. While the guide was designed for individual study, it was also meant to serve as a reference point for individual and group discussions with the study coaches.

Table 1. Co-designed leadership guide.

Chapter	Key learning
1. The “Mind Hack”	Learning how to regulate the brain through mindfulness training
2. Living Core Values	Exploring the link between core values and a sense of mastery
3. Leading with Your Mind	Understanding the connection between core values, activities, and mood
4. Check-In	Assessing progress and considering what strategies need refinement
5. Building A Good System	Developing successful strategies to live out core values
6. Identity-Based Habits	Examining the link between identity and habits
7. Simple Strategies to Get Stuff Done	Exploring simple techniques to boost efficiency
8. Check-In	Assessing progress and considering what strategies need refinement
9. The Role of Grit	Examining the relationship between mindset and grit (passion and perseverance)
10. Wholehearted Living	Learning to connect with and belong to oneself
11. Leading with Courage and Purpose	Overcoming shame and cultivating self-worth
12. Check-In	Assessing progress and considering what strategies need refinement

Study Coaches

The role of the coach was to speak with youth about how to draw on internal resources to help orient them toward their preferred future. This role was different from case management or mentorship in that a specific coaching methodology (Brief Solution-Focused Coaching) [27] was used to walk alongside youth as they developed strategies to reach self-defined goals (Table 2). Each coach was instructed to devote 2.5 days/week to the intervention and was given a caseload of 9-11 youth. The coaches were instructed to meet individually with each youth on their caseload every two weeks and collectively with the rest of the youth in their group every month.

Table 2. Coach training[a].

Training	Focus	Method
Foundations of Brief Coaching	• Solution-Focused theory and Brief Coaching framework (solution-building vs. problem-solving)	• Asynchronous online modules (approximately 24 hours in length)
Applications of Brief Coaching	• Strategies to co-construct a preferred future with clients	• Asynchronous customized virtual training (approximately 24 hours in length)
Coaching masterclass case conferences	• Coaching dialogue analysis • Providing and receiving peer feedback	• 90-minute live virtual sessions (every two – four weeks for 12 months)
Supervision and mentorship	• Opportunity for coaches to connect with coach mentor, Dr. Haesun Moon	• Available throughout the 12-month study • Designated check-ins at 6 and 9 months

[a]Coach training conducted by the Canadian Centre for Brief Coaching [27].

The 2 study coaches were selected by a panel that included 2 leaders from our community partner organizations, 2 research team members, and 3 youth from TYOH 1.0 who work as paid experts on the TYOH 2.0 Community Partner and Researcher

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Advisory Board. Each of the coaches had their own coaching practices outside the homelessness sector, which they maintained during the study. The coaches met monthly with our youth advisors and team members to provide updates as to how the coaching sessions were progressing.

Study Outcomes

The primary outcomes of this pilot study were feasibility and acceptability (Table 3). Secondary outcomes included proxy indicators of socioeconomic inclusion based on our clinical expertise and research with this population: (1) education, employment, and training; (2) housing security; and (3) identity capital (Table 3). The relative timing of interventions and assessments is described in Figure 2.

Table 3. Key outcome variables, domains, and instruments

Key outcome variables and domains	Instruments
Primary outcomes	
Feasibility and acceptability	• Recruitment and enrollment metrics • Coaching session attendance (recorded by coaches) • Intervention engagement questionnaire (includes items on engaging with leadership guide and frequency of contact with coach) • Dropout metrics • Focus groups
Secondary outcomes and domains (proxy indicators of socioeconomic inclusion)	
Education, employment, and training	Composite education, employment, and training checklist (includes items on current school, work, and training or trades programs)
Housing security	Housing Security Scale–V.3 [29] (subscales: housing need, subjective stability, safety net, threats to stability)
Identity capital	Multi-Measure Agentic Personal Scale [12] (subscales: self-esteem, purpose in life, internal locus of control, self-efficacy)
Exploratory domains	
Demographics	Baseline demographics questionnaire (includes age, gender, race or ethnicity, sexual orientation, immigration, child welfare, homelessness history, and formal and informal supports)
Baseline mental health	Global Assessment of Individual Needs-Short Screener V.3.0.2 [30,31] (subscales: internalizing disorder, externalizing disorder, substance disorder, crime, and violence)

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Figure 2. SPIRIT schedule of enrolment, interventions, and assessments [31].

	STUDY PERIOD				
	Enrolment	Allocation	Post-allocation		
TIMEPOINT	t_0 (pre-randomization)	t_1 (baseline)	t_2 (month 4)	t_3 (month 8)	t_4 (month 12)
ENROLMENT:					
Eligibility screen	✓				
Informed consent	✓				
Allocation		✓			
INTERVENTIONS:					
Rent subsidies (control)		♦—	—	—	—♦
Rent subsidies + coaching/leadership guide (intervention)		♦—	—	—	—♦
ASSESSMENTS:					
Baseline Demographic Questionnaire	✓				
Mental Health (GAIN-SS) [29-30]	✓				
Education, Employment, and Training (EET)	✓				✓
Housing Security (HSS) [28]	✓		✓	✓	✓
Identity Capital (MAPS20) [12]	✓		✓	✓	✓
Intervention Engagement Questionnaire (intervention)			✓	✓	✓
Coaching Session Attendance (intervention)			✓	✓	✓
Focus Groups (intervention)			✓	✓	✓

Decision to Scale

The decision to proceed to an adequately powered definitive trial will be based on feasibility and acceptability (Table 3). The research team is particularly interested in quantitative metrics pertaining to coaching session attendance (eg, number attended out of a possible 24 sessions), leadership guide engagement, and intervention dropout rates, as well as qualitative data from the focus groups. We predetermined that we would not proceed to a definitive trial if we found intervention attendance or engagement was less than 50% (ie, average coaching attendance of less than 12 sessions over one year), more than 30% of participants (n=6) dropped out of the intervention, or qualitative feedback from intervention participants during focus group sessions was overwhelmingly negative.

Quantitative Methods

Questionnaires were completed via a secure weblink, which was emailed to participants along with a unique login and password, at baseline and 4-, 8-, and 12-months post randomization. Those unable to access the weblink were offered the option of using computers at MAP Centre for Urban Health Solutions or at their respective community partner agency.

Quantitative Analysis

Quantitative analysis was performed using the intention-to-treat principle; that is, all participants were included and analyzed in the groups they were originally randomized. Baseline characteristics of the intervention and control groups were summarized using descriptive statistics (ie, mean, SD, median, and IQR for continuous variables, and frequencies and proportions for categorical variables).

Primary Outcomes

Primary outcomes were analyzed by estimating the recruitment rate as the proportion of contacted individuals who expressed interest in participating in the study. The enrollment rate was calculated as the proportion of recruited individuals who were eligible and consented to participate in the study. Dropout rates were separately calculated for intervention and control groups at the end of the study as 1 – proportion of randomized participants who completed the study at 12 months. Exact (Clopper-Pearson) 95% confidence limits were also calculated. Among those in the intervention group, acceptability was measured as the percentage of coaching sessions attended over the 12-month period, out of a maximum of 24.

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Secondary Outcomes

Secondary outcomes were analyzed by calculating descriptive statistics at each study time point and exploring differences in trajectories from baseline to 12 months follow-up between intervention and control groups using scatterplots and box plots. Adjusted mean group differences with 95% CI in continuous outcomes at 12 months (housing security and identity capital) between participants who received the intervention and control participants were estimated using analysis of covariance (ie, linear regression models), including an indicator of the intervention group and the baseline value of the outcome, adjusting for the site. We performed regression diagnostics and repeated analyses using the nonparametric Wilcoxon rank-sum test if there were extreme outliers or influential observations.

The education, employment, and training (EET) indicator was a composite binary outcome for education employment or training based on the EET questionnaire. EET was 1 if "Attending secondary (eg, high school) or postsecondary (eg, college or university) classes," "Employed in the past month," or "Participating in a paid or unpaid training or trades program." Otherwise, EET was 0. We compared groups with respect to the housing need indicator and EET at 12 months by estimating differences in proportions. A logistic regression model estimated odds ratios with 95% CI, adjusted for site.

Exploratory Subgroup Analysis

Exploratory subgroup analysis was conducted considering only the intervention group and stratifying the primary outcomes by selected baseline demographics (for example, gender) or severity levels of components of the Global Assessment Individual Needs-Short Screener [30,31]. Severity levels are: 0 problems=low (unlikely to have a diagnosis or need services); 1-2 problems=moderate (a possible diagnosis; the client is likely to benefit from a brief assessment); 3 or more problems=high (high probabilities of a diagnosis; the client is likely to need more formal assessment and intervention, either directly or through referral). We also calculated the correlation between secondary outcomes and the level of engagement with the intervention measured as the percentage of class sessions attended out of a maximum of 24 over the 12-month period. Spearman correlation and Spearman partial correlation coefficients were calculated.

Interim Analysis

There was no interim quantitative analysis planned to guide a decision to stop the study early for this pilot study [25]. We decided before the study began to either stop the intervention early or make adjustments to the intervention if feedback from participants during the focus group sessions was overwhelmingly negative and/or the majority of youth stopped participating in the intervention.

Qualitative Methods

Focus groups with those in the intervention group were conducted by NST and MD in Toronto, Hamilton, and St. Catharines at 4, 8, and 12 months post randomization. Focus group questions primarily centered around intervention acceptability but also explored the impact of the intervention on identity capital and socioeconomic inclusion (eg, connection to broader social networks). Analysis began during and after the first data generation session, meaning the questions asked evolved over time based on our preliminary interpretations of the data [32-34]. Keeping in mind that data generation context impacts participant responses [34-36], focus groups were held in a community setting to help minimize researcher-participant power imbalance and increase participant comfort. Participants unable to attend in-person focus groups were offered the option of virtual attendance.

All focus groups were audio recorded using a password-protected device. Audio recordings were transcribed verbatim by a member of the research team, and the transcripts were uploaded to the web-based application Dedoose [37] for storage and retrieval. One member of the research team served as an observer and note taker at each focus group session to document nonverbal communication (eg, eagerness or disinterest) as well as preliminary analytic insights based on listening to the discussion. In addition, each focus group facilitator documented field notes as soon as possible after the meeting to capture their own observations and reflections on the sessions [33-35]. Food was also provided at the focus groups.

Qualitative Analysis

The team used reflexive thematic analysis to help make sense of the data [38]. Reflexive thematic analysis is comprised of 6 iterative phases (data familiarization, coding, initial theme generation [patterns anchored by a shared idea or concept], theme development and review, theme refining, and writing up). Crucially, this form of analysis also requires engagement with theory (eg, critical social theory), reflexivity (awareness of social location on analysis), and interpretation (findings not seen as self-evident) [38]. Before each monthly qualitative data analysis session, 2 team members read the most recent focus group transcript multiple times, coded ("tagged") data relevant to intervention acceptability and our assumption that identity capital was a mediating factor in socioeconomic inclusion (and looked for data that might disprove that assumption), and compared codes to previous transcripts [32,33,38].

At the monthly analysis sessions led by NST, codes were discussed (and revised or deleted as needed) and organized in a code book, clustered into initial themes, and eventually refined and synthesized into key themes. Analysis was primarily inductive (moving from data to conceptualizing); however, deductive reasoning (moving from conceptualizing to data) was used when we wanted to understand new data through the lens of our emerging conceptual framework. The analysis team also formulated new focus group questions based on our preliminary analytic insights. Focus group participants were asked for their perspectives on the emerging interpretations during subsequent focus groups, and these perspectives played a key role in helping shape the data analysis.

As in TYOH 1.0, the aim of our analysis was to go beyond superficial understandings of intervention acceptability. Instead, we engaged in "value-adding" qualitative analysis—interpreting, contextualizing, and adopting a critical posture (eg, attention to power)—with the intention of operationalizing key conceptual insights in a conceptual framework [39]. As we did this, our team embraced the "creative presence of the researcher,"

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drawing on our own knowledge, insights, and experiences (including the experience of homelessness) to help make sense of the data [39].

Participant and Public Involvement

A genuine partnership with the community—including youth with lived expertise—has been woven into this study from inception to dissemination. As noted previously, we have been working with most of the community partners on this study for several years, and the leadership guide being used in the intervention was co-designed with youth who have experienced homelessness. Three participants from TYOH 1.0 worked as paid advisors on the TYOH 2.0 Community Partner and Researcher Advisory Board. The Board met approximately every 3 months from June 2022 to October 2024. Our community partners and youth advisors were actively involved in planning TYOH 2.0, including discussions around research questions, outcome measures, recruitment, the burden of the intervention, and the time required to participate.

Ethical Considerations

We endeavored to weave ethical considerations into all aspects of the study design, including our decision to use a CBPAR methodology, ensure all participants received portable rent subsidies (not just the intervention group), and offer the co-designed leadership guide to those in the control group after the study was over. The consent form highlighted that participants could withdraw from the entire study or just the identity capital intervention at any time, and this would not impact their monthly rent subsidy. Participants received honoraria via e-transfer within 24 hours of each data collection session (CAD $20 [US $14.28] for completing quantitative questionnaires and CAD $40 [US $28.57] for attending focus groups). Efforts were made to mitigate potential privacy and confidentiality concerns at all stages of the study (Table 4).

Table 4. Privacy and confidentiality.

Potential concerns	Mitigation strategies
Recruitment	• Interested participants reached out to the study lead research coordinator rather than community partners sharing contact information with the team.
Eligibility screening	• No personal health information or personal identifying information was collected.
Enrollment	• There were no signed paper consent forms; instead, electronic consent (after verbal consent) was required before baseline data collection. The consent form indicated that limits to confidentiality applied if a participant disclosed that they intended to hurt themselves or others, or if they informed a member of the research team that someone under the age of 16 years was experiencing abuse or neglect.
Quantitative data collection	• The MAP SRU[a] programmed the questionnaires into Snap Professional software [40] and provided a secure weblink along with unique logins and passwords for data collection. The electronic data was kept on the Snap server that is owned and operated by the SRU and is located inside Unity Health Toronto's secure network at SMH[b]. Deidentified data was downloaded directly to the SMH secure server.
Qualitative data collection	• Focus groups were audio recorded on a password-protected application on a password-protected device. The audio-recorded files were securely sent to a research team member via Unity Health email with a link that expired in 24 hours. After the team members had transcribed the audio file, they deleted the file. • We had a contingency plan that if focus groups had to pivot to virtual because of pandemic-related concerns, we would use a Zoom platform, enable end-to-end encryption, and only record the audio (not video). All transcripts were stored on an SMH secure server and uploaded to Dedoose [37]. • Pseudonyms (chosen by participants) were used in focus group transcripts. All notes pertaining to the focus groups (eg, participant observation and field notes) were stored on an encrypted USB key and the files were transferred to the SMH secure server as soon as possible after each focus group.
Linking log	• A key that linked each participant's name with their participant identification number and pseudonym was created by the lead research coordinator and stored as a separate electronic file on the SMH secure server.
Data access	• Only authorized members of the research team have access to quantitative and qualitative study data, and an access log was maintained by the lead research coordinator. Deidentified raw data will be made available upon reasonable request (eg, request comes from a researcher affiliated with an academic institution).
Data retention	• All data will be destroyed after 10 years. NST will be responsible for ensuring the data is destroyed.

[a]SRU: Survey Research Unit.

[b]SMH: St. Michael's Hospital.

We intentionally did not choose deficit-focused questions or scales for the T2-T4 quantitative data collection sessions, and questionnaires were programmed to allow participants to skip questions if they chose. The focus group questions also targeted participant strengths, and participants were reminded at the start of each session that they did not have to answer any questions that made them uncomfortable. NST and members of the research team met monthly with the study coaches. These

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meetings provided an opportunity to assess or discuss any unintentional harms or risks to intervention participants, which were followed up immediately.

The study was approved by the Unity Health Toronto Research Ethics Board (REB# 22-230). Any protocol amendments were approved by the research ethics board. Free and informed verbal and electronic consent was obtained from all participants before the initiation of intervention and research activities.

Results

Recruitment and enrolment began March 1, 2023, and ended June 19, 2023. Data collection began March 7, 2023, and ended June 17, 2024. Qualitative and quantitative data analyses concluded on August 20, 2024.

Discussion

Anticipated Outcomes

We anticipate that this pilot study will provide important new insights regarding the feasibility and acceptability of an intervention using coaching and a co-designed leadership guide to target identity capital for youth transitioning out of homelessness. Although the study is not powered to detect statistically significant differences in the proxy indicators of socioeconomic inclusion outcomes, we hope to see signals in this data—especially in the Multi-Measure Agentic Personal Scale [12]—that the intervention holds promise. As we have found with our previous research [10,11], we anticipate the rigorous qualitative component will strongly influence our decision-making as to the next steps.

Homelessness in Canada is increasing, with 44% of those experiencing homelessness reporting they were first homeless before the age of 25 (with a spike between the ages of 15-19 years of age) [41]. This represents a crucial missed opportunity for homelessness prevention. Interventions like TYOH 2.0 offer promise as a way to prevent young people from returning to homelessness and potentially becoming chronically homeless adults. To be clear: we are not suggesting with this intervention that young people should “bootstrap” themselves out of homelessness. Rather, our aim is to provide young people with some of the tangible (eg, money toward rent) and intangible (eg, fostering identity capital) resources typically provided or nurtured—at least in part—through living at home.

Over 60% of Canadian youth (20-24 years of age) live with at least one parent [42]. This is important to consider when thinking about what to expect from young people attempting to transition out of homelessness. At a minimum, we need to adopt a holistic response to youth homelessness and think beyond housing when considering what supports might foster socioeconomic inclusion. We anticipate using the findings from this study to develop a multicomponent intervention that incorporates aspects of this current intervention (potentially revised) along with components that may need to be added to better facilitate socioeconomic inclusion for youth exiting homelessness.

Dissemination Plan

Working alongside community partners to disseminate findings with the aim of highlighting sociostructural inequities, building community capacity, and improving the lives of the youth we work alongside is fundamental to this work. We anticipate disseminating our findings broadly in a variety of formats such as oral presentations, open-access plain language summaries or reports, and scientific journal papers. We are committed to dissemination beyond academic audiences. For example, for TYOH 1.0, we produced an animation of our study findings along with a documentary film [43]. Whenever possible, we intend to discuss our study findings alongside a lived expert involved in this research.

Limitations

This study has limitations. All youth were connected to urban-based social service agencies in the province of Ontario; youth living in rural locations and outside of Ontario may not take up the intervention the same way. In addition, all of the quantitative instruments were based on self-reports and thus subject to social desirability bias. We also chose quantitative measures that we believe signal socioeconomic inclusion; it is plausible that these measures do not adequately capture this complex concept. Finally, this pilot study was not powered to detect statistical significance; findings beyond feasibility and acceptability must be interpreted with caution.

Conclusions

Findings from this RCT will help inform the way we conceptualize the types of support that are necessary to sustain successful exits from homelessness. This is important given the limited peer-reviewed evidence base on interventions designed to foster socioeconomic inclusion for youth exiting homelessness. The intervention was co-designed with youth who have experienced homelessness, and their voices will continue to inform the next iteration of this work.

Acknowledgments

We would like to acknowledge the scholarly contributions of Dr James Côté, who developed the Identity Capital Model being used in this research project. We are grateful for our collaboration with RAFT, Living Rock, StepStones for Youth, and Covenant House Toronto. Thank you for your ongoing partnership.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

NST, AA, MD, BD, TF, SWH, NK, AN, CP, MR, RR, and RN contributed to the study conceptualization. AC and CP were responsible for quantitative data curation. A formal quantitative analysis was done by RN. Formal qualitative analysis was done by NST, RKS, AA, AA, MD, and TT. NST and SWH were responsible for funding acquisition. The investigation was done by NST, RKS, AA, AA, OF, MD, and TT. NST, AA, MD, BD, TF, SWH, NK, AN, CP, MR, RR, and RN helped develop the study methodology. RKS and AA were responsible for project administration. NST provided supervision. NST wrote the original draft. NST, RKS, AA, AA, TF, SWH, NK, AN, MR, RR, and RN participated in writing reviews and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Completed SPIRIT 2013 checklist: Recommended items to address in a clinical trial protocol and related documents.
[PDF File (Adobe PDF File), 119 KB - resprot_v14i1e66210_app1.pdf]

Multimedia Appendix 2
Completed CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial.
[PDF File (Adobe PDF File), 91 KB - resprot_v14i1e66210_app2.pdf]

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Abbreviations

CBPAR: community-based participatory action research
CONSORT: Consolidated Standards of Reporting Trials
EET: education, employment, and training
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TYOH: Transitioning Youth Out of Homelessness

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Protocol

Impact of Tai Chi Therapy on Fatigue and Cognitive Function in Individuals With Chronic Fatigue Syndrome: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Chronic fatigue syndrome (CFS) is a psychosomatic disorder characterized by persistent fatigue, primarily involving physical and mental exhaustion, with greater emphasis on the latter. This leads to a deterioration in concentration and memory. These symptoms affect cognitive functions, including attention and memory, to varying degrees. Previous research has shown that Tai Chi can help reduce fatigue in individuals with CFS. However, the relationship between alleviating CFS-related fatigue through Tai Chi and its impact on cognitive functions remains unclear. The effects of Tai Chi on cognitive functions in individuals with CFS have not been clinically validated, and its efficacy and safety have yet to be examined through large-scale randomized controlled trials. Therefore, this protocol outlines a pilot randomized, parallel, single-blind clinical trial designed to evaluate the impact of Tai Chi therapy on fatigue and cognitive functions in individuals with CFS, using both subjective and objective assessments.

Objective: This pilot study aims to explore the preliminary efficacy and safety of Tai Chi in reducing fatigue and improving cognitive function in patients with CFS, and to generate data to inform future large-scale trials.

Methods: We will conduct a randomized, analyst-blinded, parallel-controlled trial with a 12-week intervention period and a 4-week follow-up. Enrolled patients will be randomly assigned to either the Tai Chi group (30 patients) or the health education group (30 patients). The Tai Chi group will receive the 24-style simplified Tai Chi intervention, while the control group will receive a health education intervention. Following the 12-week intervention, a 4-week follow-up will be conducted. The Tai Chi group will train 3 times per week, consisting of 2 in-person sessions at the Physical Education Center of Shanghai University of Traditional Chinese Medicine and 1 self-directed session guided online by an instructor. The primary outcome measure is the 20-item Multi-Dimensional Fatigue Inventory (MFI-20). The secondary outcome measures include the Montreal Cognitive Assessment (MoCA), Pittsburgh Sleep Quality Index (PSQI), Attention Network Test (ANT), working memory performance (N-Back task), and magnetic resonance imaging.

Results: The research protocol and informed consent form were approved by the Shanghai Clinical Research Ethics Committee on March 18, 2024 (approval number SECCR2024-22-01). Participant recruitment began in April 2024. All interventions and concurrent data collection will be completed by October 2025, and the 4-week postintervention follow-up assessments will be finalized by the end of October 2025. Data management is still ongoing; therefore, data analysis has not yet been performed.

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Conclusions: As a pilot trial, the findings of this study will provide preliminary clinical evidence on the role of Tai Chi in improving cognitive function in patients with CFS and will serve as a foundation for designing future large-scale trials.

Trial Registration: China Clinical Trials Registry ChiCTR2400082268; https://tinyurl.com/2tkr7j7x

International Registered Report Identifier (IRRID): DERR1-10.2196/65958

(JMIR Res Protoc 2025;14:e65958) doi:10.2196/65958

KEYWORDS

Tai Chi; chronic fatigue syndrome; cognitive impairment; ANT; N-Back; fatigue; cognitive function; cognitive; protocol; protocols; randomized controlled trial; RCT; controlled trial; controlled trials; psychosomatic disorder; cognition; therapy; efficacy; safety; CFS; intervention; data analysis

Introduction

Chronic fatigue syndrome (CFS), also known as myalgic encephalomyelitis, is a complex chronic disease characterized by pathological fatigue, generalized weakness, immune dysfunction, poor sleep, pain, and cognitive impairments [1]. Its defining feature is persistent or recurrent debilitating fatigue that is not alleviated by rest and occurs despite the absence of significant abnormalities on physical examination or laboratory tests. This condition can severely affect the work and daily life of affected individuals. The etiology and pathogenesis of CFS remain unclear; however, it is generally associated with viral infections, stress, and immune, psychological, social, and genetic factors. Furthermore, it is considered part of a group of systemic diseases caused by multisystem dysregulation [2]. In recent years, with rapid societal development, the accelerating pace of life, and increasing life pressures, many people have been in a prolonged state of excessive physical and mental fatigue. Therefore, CFS is a disease with distinct contemporary characteristics. It is prevalent among individuals in a subhealthy state across various sectors, particularly those with higher education levels, those primarily engaged in mental work, and those under high psychological stress—such as office, technology, and medical professionals. The global prevalence rate of CFS is 0.8%-3.3% [3], with a rising trend annually [4], especially among middle-aged and young populations [5]. The incidence of chronic fatigue and cognitive symptoms is substantial. Long-term, recurrent fatigue can significantly reduce quality of life and may even lead to functional disability. Patients with CFS are often forced to reduce their daily activities by as much as 50%. Furthermore, 87%-95% of patients experience nonrestorative sleep and related daytime dysfunctions [6]. Thus, CFS is considered one of the most serious public health challenges globally.

CFS can be categorized as a psychosomatic disease, primarily characterized by physical and mental fatigue, with the latter being more pronounced. It often manifests as difficulties in concentration and memory. These symptoms affect cognitive functions—such as attention and memory—to varying degrees. Cognitive impairment is the most common symptom among patients with CFS and has the greatest impact on daily functioning and learning abilities [7]. In 2021, the UK's National Institute for Health and Clinical Excellence (NICE) included cognitive impairment (brain fog) as 1 of the 4 core symptoms of CFS. Several meta-analyses conducted in other countries have shown that patients with CFS commonly experience cognitive impairment, including dysfunctions in attention, memory, and information processing [8-10]. Approximately 89% of patients with CFS present with cognitive impairments, such as memory decline and difficulty concentrating [11]. Yongjie and colleagues [12] found that among the comorbidities of CFS, memory decline and attention deficits were the most prominent, affecting over 90% of cases. Patients with CFS exhibit impairments in immediate memory, delayed memory, and attention, with attention impairment being the most severe [13]. Some scholars believe that cognitive impairment is the most severe symptom in patients with CFS. Therefore, clinicians should remain vigilant for the development of cognitive symptoms and intervene promptly. The mechanism underlying cognitive functional impairments in patients with CFS is extremely complex and not yet fully understood. Increasing evidence suggests that disruptions to normal brain function may underlie the core symptoms of CFS, including fatigue, pain, sleep disturbances, and cognitive issues [14,15].

Currently, the etiology and mechanisms of CFS remain unclear. Diagnostic criteria are still not standardized, and highly reliable treatment methods are lacking. There are no specific diagnostic or therapeutic approaches for CFS worldwide, and most treatments remain symptomatic. Modern medicine primarily focuses on symptom management through approaches such as antianxiety therapy, immune regulation, and nutritional supplementation—aimed at alleviation rather than cure. However, the efficacy of these treatments remains controversial [16]. Moreover, they are often costly and may lead to adverse reactions such as gastrointestinal dysfunction, as well as liver and kidney damage. Patients undergoing these therapies are also at risk of relapse after discontinuing treatment. Therefore, there is an urgent need for safe and effective treatment options for CFS. In recent years, exercise therapy has emerged as a research hot spot in CFS treatment, showing notable benefits in symptom improvement. Traditional Qigong, in particular, offers several advantages, including the regulation of the body, breath, and mind. Previous studies [17,18] have shown that Qigong can relieve both overall fatigue and psychological fatigue, making it an effective treatment for CFS. As a mind-body exercise with traditional Chinese cultural roots, Tai Chi holds a unique position in alternative and traditional medicine. It engages a wide range of muscle groups, including those in the legs, trunk, and arms, and requires high levels of attention and memory. Clinical studies have shown that, compared with general aerobic exercises, Tai Chi can improve or delay the decline of overall cognitive functions, including

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memory, attention, and executive functions, in healthy older individuals [19,20]. It has also shown benefits in those with mild cognitive impairment [19,20], as well as in individuals with Parkinson disease [21], Alzheimer disease [22], multiple sclerosis [23], and cardiovascular diseases [24]. However, the impact of Tai Chi on cognitive functions in CFS has not yet been clinically validated, and its efficacy and safety have not been assessed in large-scale randomized controlled trials.

Regular Tai Chi practice is beneficial for relieving fatigue and improving cognition in CFS, and it is more effective than general aerobic exercise. To assess the clinical effects of Tai Chi on fatigue relief and cognitive function improvement, this study aims to design a randomized, parallel, single-blind clinical trial. The purpose of this study is to examine the effects of Tai Chi therapy on fatigue and cognitive function in CFS through both subjective and objective assessments, thereby exploring the potential links between fatigue, cognitive function, and the treatment process in CFS. This trial is currently underway, and the data will be shared through scientific publications.

Methods

Research Design

We designed a randomized, evaluator- and statistician-blinded, parallel-controlled trial to be conducted at Shanghai University of Traditional Chinese Medicine and The Affiliated Yueyang Hospital of Integrated Traditional Chinese and Western Medicine. Participants will be randomly allocated to either the Tai Chi group or the health education group. The Tai Chi group will receive Tai Chi intervention, while the health education group will receive cognitive behavioral therapy (CBT) intervention. The total study duration is 17 weeks: a 1-week screening period, a 12-week treatment period, and a 4-week follow-up period. The protocol version issue date is March 13, 2024. Figure 1 shows the study flowchart (see Multimedia Appendix 1 for the SPIRIT [Standard Protocol Items: Recommendations for Interventional Trials] checklist).

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Figure 1. Flow diagram of the study design. ANT: Attention Network Test; CBT: cognitive behavioral therapy; MFI-20: 20-item Multi-Dimensional Fatigue Inventory; MoCA: Montreal Cognitive Assessment; TJQ: Tai Ji Quan (Tai Chi).

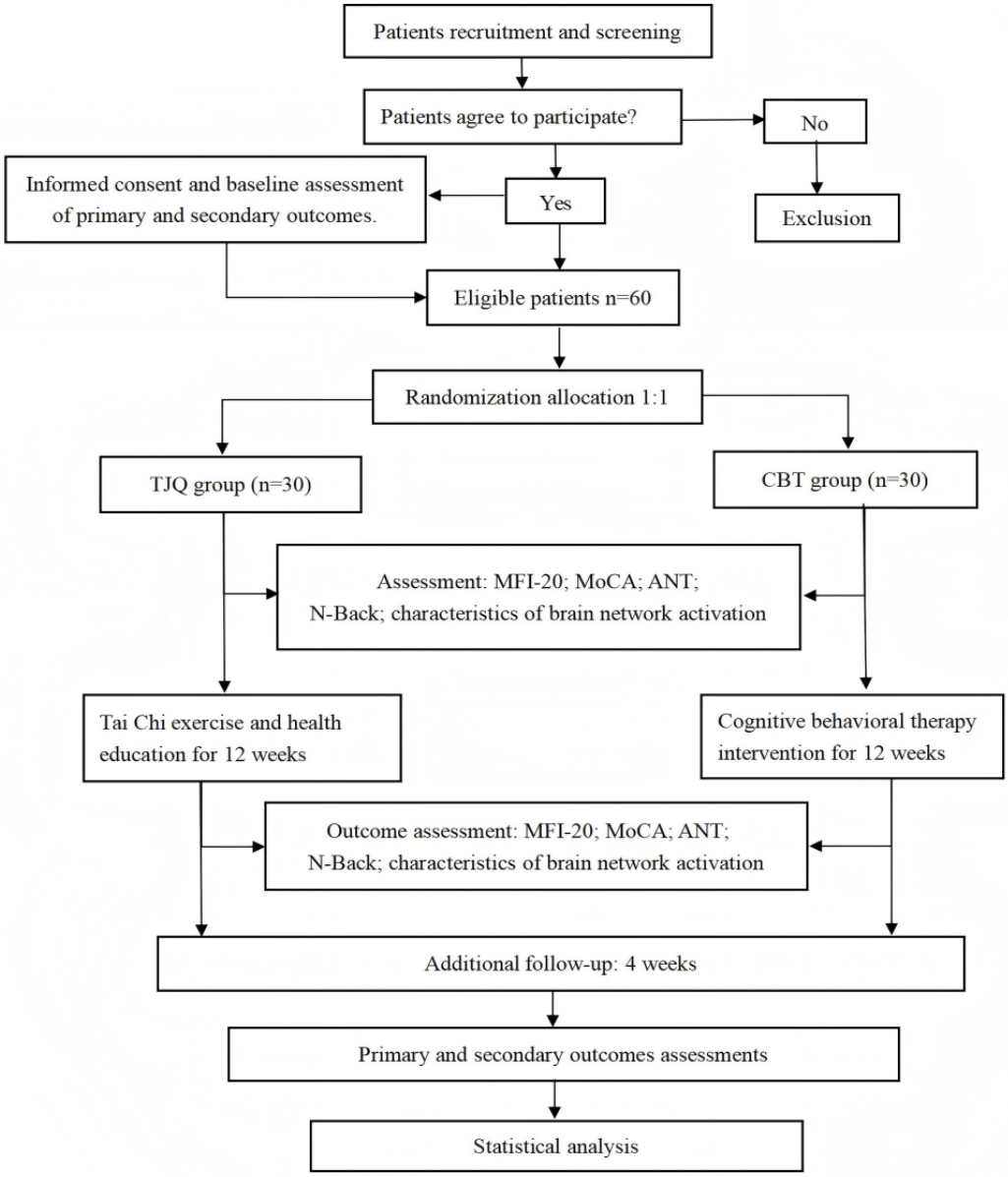

Sample Size Calculation

According to Cohen [25], the ideal statistical test power and effect size should be greater than 0.8. The GPower 3.1 software (Heinrich-Heine-University) was used to conduct a 2-tailed, independent samples *t* test (paired) to calculate the sample size. Based on a previous study on CFS, the mean 20-item Multi-Dimensional Fatigue Inventory (MFI-20) score of the experimental group was 4.80 (SD 2.11), and the mean MFI-20 score of the control group was 7.13 (SD 3.29) [26]. These values were input into the GPower software to calculate the effect size (d=0.843, α=.05, and $1-\beta$=0.80), which determined the sample size for each group to be 24, accounting for a 20% dropout rate. The research group ultimately determined that the sample size for each group would be 30 participants, with a total of 60 participants. They were then divided into the Tai Chi and control groups. The sample size for this experiment provides sufficient statistical power for testing.

Participants and Recruitment Strategy

Patients with CFS will be recruited from Shanghai University of Traditional Chinese Medicine, Yueyang Hospital of Integrated Traditional Chinese and Western Medicine, and other medical institutions. Recruitment will primarily be conducted through advertisements in the outpatient lobby, WeChat (Tencent Holdings Ltd.), and posters both inside and outside the university. All eligible participants will undergo testing at Yueyang Hospital of Integrated Traditional Chinese and Western Medicine and receive a clinical diagnosis from the physicians responsible for recruitment. Patients who meet the inclusion criteria will be selected. Before recruitment, they will be informed of the potential benefits and risks associated with participating in the exercise component of the study. Participants will then be asked to fill out an informed consent form and will be free to withdraw from the study at any time without consequence. After the intervention, patients will be informed

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of the study results. The results will be disseminated through peer-reviewed publications and academic conferences.

CFS Diagnostic Criteria

The clinical diagnosis is based on the CFS diagnostic criteria published by the UK's NICE in 2021 [27]. The criteria are as follows: (1) debilitating fatigue exacerbated by activity, not by excessive cognitive, physical, emotional, or social exertion, and not significantly alleviated by rest; (2) cognitive impairments (brain fog), including slow responsiveness, short-term memory issues, and difficulties with concentration or multitasking; (3) Postexertional malaise, with symptoms typically delayed for hours or days after activity and disproportionate to the activity, with extended recovery time, lasting for hours, days, weeks, or longer; and (4) unrefreshing sleep or sleep disturbances (or both), characterized by exhaustion upon waking, feelings of stiffness and flu-like symptoms, interrupted or shallow sleep, altered sleep patterns, or hypersomnia. All 4 symptoms must be present simultaneously and persist for at least 3 months, with other possible medical causes of fatigue ruled out. The inclusion, exclusion, and withdrawal, drop-out, and termination criteria are listed in Textbox 1.

Textbox 1. The inclusion, exclusion, withdrawal, drop-out, and termination criteria.

1. Inclusion criteria

- Patients who meet the diagnostic criteria.
- Male or female patients aged 18-60 years and right handed.
- Patients with normal results from routine blood and urine tests, and normal liver and kidney function.
- Patients who have not received other treatments in the past month.
- Patients who agreed to participate in the study and provided informed consent.

2. Exclusion criteria

- Individuals who do not meet the diagnostic and inclusion criteria.
- Individuals with serious cardiovascular or psychiatric conditions.
- Individuals taking medications that may affect the outcome assessment.
- Individuals unwilling to participate in the study.
- Individuals without a primary complaint of fatigue.
- Individuals whose fatigue symptoms can be alleviated by rest.
- Individuals whose fatigue symptoms do not cause a substantial decrease in their ability to work, receive education, engage in social or recreational activities, or manage personal life responsibilities.
- Individuals with a clear diagnosis of gastrointestinal organic lesions, abnormal liver or kidney function, tumors, or other diseases.
- Pregnant or lactating women.

3. Withdrawal, drop-out, and termination criteria

- Individuals who do not meet the inclusion criteria and were mistakenly included.
- Participants who do not adhere to the protocol for safety evaluations.
- Participants who experience severe adverse events or complications, making it inappropriate for them to continue with the trial.

Randomization and Allocation Concealment

Patients diagnosed with CFS who have signed the informed consent forms will be randomly assigned to either the Tai Chi group or the health education group at a 1:1 ratio. The random number table will be generated by researchers who are not involved in recruitment or intervention, using a computer. Each random number will be sealed in a pre-prepared opaque envelope with the patient's sequence number. After providing written informed consent, participants will open an envelope labeled with their sequence number to learn which group they have been assigned to.

Blinding

Given the nature of the interventions, the Tai Chi and health education groups cannot be blinded. However, statisticians, managers, data collectors, and outcome assessors will remain blinded during the study. Blinding will be lifted after statistical analysis is completed.

Intervention

Tai Chi Group

The Tai Chi group will practice the 24-form Tai Chi, led by an instructor from Shanghai University of Traditional Chinese Medicine with at least 5 years of teaching experience. Throughout the intervention period, there will be 3 sessions per week: 2 offline classes at the Shanghai University of Traditional Chinese Medicine Sports Center and 1 self-practice session, guided online by the instructor. Each practice session lasts 60 minutes, beginning with 5 minutes of Tai Chi preexercise stretching, followed by 10 minutes of Tai Chi standing postures.

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The instructor will then introduce and demonstrate each movement, explain precautions, answer participants' questions, and provide individual guidance, correcting their movements for the next 30 minutes. The session ends with 5 minutes of relaxation. For home self-practice sessions, the duration is 60 minutes, supervised via video in a WeChat group. After each practice session, a practice log will be provided, and participants will be required to fill it out. The entire treatment process lasts for 12 weeks.

Health Education Group

Before treatment, participants will receive information related to CFS and CBT to help them understand the principles and role of cognitive therapy in CFS treatment. The health education group will receive daily health education via a WeChat group or WeChat public account. Experts in the field will be invited to give a weekly 1-hour lecture or psychological counseling session on CFS prevention and treatment. If participants are unable to attend, lecture videos will be distributed to those who missed the session. After each learning session, a practice log will be provided, and participants will be required to fill it out. The entire treatment process lasts for 12 weeks. CBT is a psychological treatment method that combines behavioral therapy and cognitive therapy.

Comparator Justification

CBT was chosen as the control condition in this study based on its established role as a standard evidence-based treatment for CFS. According to the NICE guideline NG206 [27], CBT is recommended as one of the management approaches for individuals with myalgic encephalomyelitis/CFS, particularly to help them cope with the impact of symptoms and improve function. Moreover, CBT has been widely used as a comparator intervention in previous randomized controlled trials evaluating alternative or complementary treatments for CFS. Notable examples include the PACE trial, which compared CBT, graded exercise therapy, and adaptive pacing therapy, as well as other randomized controlled trials that assessed the relative effectiveness of novel interventions against CBT [28,29]. Therefore, selecting CBT as the control group in this study is methodologically appropriate and allows for a direct comparison with an established therapeutic modality.

Accompanying Interventions

During the study period, other CFS treatments, including both pharmacological and nonpharmacological interventions, will be prohibited. However, participants may receive treatments unrelated to CFS. Any changes in concurrent treatments will be recorded.

Follow-Up Period

Follow-up will be conducted 4 weeks after the end of the trial, during which all participants will return to their original lifestyle. However, participants will be required to log their daily exercise or study activities. They will use WeChat to take weekly photos, providing researchers with evidence of their daily exercises or studies. At the end of the follow-up period, participants' fatigue, attention, and working memory will be reevaluated. The follow-up assessment aims to assess the long-term effects of Tai Chi on patients with CFS. Additionally, at the end of the follow-up assessment, participants will receive a special Tai Chi souvenir to encourage their enthusiasm for the follow-up.

Functional Magnetic Resonance Imaging Examination Procedure

Resting-state functional magnetic resonance imaging (fMRI) data will be collected using a 3.0-T Siemens magnetic resonance scanner at Yueyang Hospital of Integrated Traditional Chinese and Western Medicine and the Affiliated Shanghai University of Traditional Chinese Medicine, utilizing a 32-channel head and neck coil. The MRI sequence parameters are as follows: blood oxygen level–dependent fMRI, repetition time=2000 ms, echo time=30 ms, matrix=64 × 64, field of view=230 × 230 mm^2, slice thickness=4 mm, gap=0.8 mm, and voxel size=3 × 3 × 3 mm^3. Participants will arrive 30 minutes before the MRI examination and will be instructed to close their eyes and rest for 10 minutes before the scan. Throughout the experiment, participants will lie in the supine position on the examination bed and will be instructed not to move their heads during data collection. To prevent head movement, the head will be comfortably fixed with sponge pads and a head holder. Cotton ball earplugs will be provided to reduce machine noise and prevent adverse emotions. A skilled MRI technician will be assigned to complete the magnetic resonance data sampling for the participants.

Preliminary Processing of fMRI Data

Imaging data will be processed and analyzed using MATLAB 2015a (MathWorks), SPM12 (Wellcome Department of Cognitive Neurology, UK, University College London), and VBM 8 (Voxel-Based Morphometry 8; Structural Brain Mapping Group). The raw data will be converted from DICOM to the NIFTI format, excluding the first 10 abnormal time points. MRICON will be used to convert the original scans from DICOM to the NIFTI format. The first 10 time points and images will be removed to eliminate differences in fMRI signal slice timing, adjusting the scanning time to a consistent moment. Head motion correction will be applied to remove artifacts caused by minor movements, and participants with head motion >2.5 mm (framewise displacement standard) will be excluded. The position of the anterior commissure will be manually corrected. DPABI (Data Processing & Analysis for [Resting-State] Brain Imaging) software will be used to segment 3D high-resolution structural images into gray matter, white matter, and cerebrospinal fluid, and these will be matched with the corresponding regions in the standard brain. After head motion correction, the functional images will be matched with the segmented structural images to align individual images with the standard brain template space. These images will then be further normalized to the Montreal Neurological Institute space and resampled to a voxel size of 3 × 3 × 3 mm^3. The normalized functional images will undergo spatial smoothing with a Gaussian kernel of 4 × 4 × 4 mm^3 full-width at half-maximum and linear detrending. High-frequency physiological noise and low-frequency drifts will be removed using a filter bandwidth of 0.01-0.1 Hz.

The amplitude of low-frequency fluctuation (ALFF) uses the amplitude of BOLD signals and the fast Fourier transform

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algorithm to convert the smoothed signal of each voxel from the time domain to the frequency domain. This transformation allows for the observation of changes in brain activity within the power spectrum. ALFF primarily calculates the squared values in the power spectrum within the 0.01-0.08 Hz range, reflecting the intensity of neuronal activity in various brain regions.

Functional connectivity (FC) refers to the degree of correlation between BOLD signal time series in different brain areas over time. Each voxel in a brain region contains a time series that represents the level of signal change associated with that region over time. Brain areas with significant differences in ALFF are selected as regions of interest for whole-brain FC analysis to assess changes in brain network connectivity. Changes in the time series can identify brain areas that are functionally coordinated and positively correlated with the BOLD signal, while areas negatively correlated are considered antagonistic. The most common form of FC is voxel based (seed-based FC). This process involves selecting a seed point and calculating the correlation between the BOLD signal of the seed point and that of all other voxels throughout the brain.

Outcome Measure Assessment

The outcome measures assessed include mental and physical fatigue, overall cognitive condition, attention, working memory, sleep quality, and resting-state MRI scans. Primary and secondary outcomes, along with related self-assessment scale measurements such as the MFI-20, Montreal Cognitive Assessment (MoCA), Attention Network Test (ANT), and Working Memory Test (N-Back), will be assessed at baseline (week 1), at the end of the intervention (week 13), and at follow-up (week 18). Table 1 presents the detailed outcome assessment time points.

Table 1. Outline and timelines of the assessments.

Time points	Baseline (week 1)	Intervention period (weeks 2-13)	Postintervention (week 14)	Follow-up (week 18)
Inclusion criteria	✓	N/A[a]	N/A	N/A
Exclusion criteria	✓	N/A	N/A	N/A
Informed consent	✓	N/A	N/A	N/A
Randomization and allocation	✓	N/A	N/A	N/A
Intervention	N/A	✓	✓	N/A
20-item Multi-Dimensional Fatigue Inventory	✓	N/A	✓	✓
Montreal Cognitive Assessment	✓	N/A	✓	✓
Attention Network Test	✓	N/A	✓	✓
Working Memory Test (N-Back)	✓	N/A	✓	✓
Pittsburgh Sleep Quality Index	✓	N/A	✓	✓
Amplitude of low-frequency fluctuation	✓	N/A	✓	N/A
Functional connectivity	✓	N/A	✓	N/A
Adverse events	N/A	✓	✓	✓

[a]N/A: not applicable.

Demographic and Clinical Characteristics of the Participants

The researchers will collect data on the demographic characteristics of the participants (such as age, sex, education level, marital status, living arrangements, occupation, and socioeconomic status), as well as their medical and medication history using a self-designed questionnaire. Baseline assessments will be completed before randomization.

Primary Outcome Measure

MFI-20

The MFI-20 scale was developed by Smets et al [30] in 1995, after validation with patients undergoing cancer radiotherapy, individuals with CFS, psychology students, medical students, doctors, and recruits. The scale consists of 20 items, which are grouped into 5 dimensions: general fatigue, physical fatigue, reduced activity, reduced motivation, and mental fatigue. To minimize bias toward a particular direction, each dimension includes 2 statements about fatigue and 2 about the opposite (ie, not fatigued), making up a total of 4 items. Each item is scored using a 5-point Likert scale, where 1 point indicates “completely disagree” and 5 points indicate “completely agree,” resulting in a total score range of 20-100. Among these, items 2, 5, 9, 10, 13, 14, 16, 17, 18, and 19 are positively scored to reflect fatigue. Items 1, 3, 4, 6, 7, 8, 11, 12, 15, and 20 are scored inversely, reflecting the absence of fatigue. A higher score indicates more severe fatigue symptoms [31].

Secondary Outcome Measures

MoCA

The MoCA scale is used to assess general cognitive status and overcomes the low sensitivity of other cognitive assessment tools to cognitive impairment. It is one of the most widely used

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cognitive assessment tools in clinical practice and effectively screens for cognitive dysfunction caused by various diseases, especially with high sensitivity in the early stages. It covers a wide range of cognitive domains, including orientation, attention, language, visuospatial function, memory, and executive functions. The total score is 30, with a score of 26 or higher considered normal. Scores are slightly adjusted based on educational level; for example, participants with less than 12 years of education receive an additional point added to their final MoCA score.

ANT

The behavioral measurement of attention is conducted using the ANT protocol proposed by Fan et al [32]. This test is administered on a computer using the E-Prime 3.0 software (Psychology Software Tools, Inc.), where stimuli are presented, and the participants' keypress responses and reaction times for all trials are recorded. ANT measures 3 distinct attention networks: alerting, orienting, and executive control. It includes 2 main operational variables: cue type and target stimulus type. Cue types are divided into no cue, neutral cue, and spatial cue. The target stimulus types are categorized into congruent and incongruent stimuli.

The experimental stimuli consist of 3 types of original materials: the cue stimulus ("*"), the target stimulus arrow (either "→" or "←"), and the fixation point ("+"). Each trial begins with a phase where the "+" fixation point appears at the center of the screen for approximately 400-1600 ms. This is followed by the cue stimulus ("*"), which appears in 1 of 4 forms for approximately 100 ms. After the cue signal disappears, the fixation point ("+") reappears alone for approximately 400 ms. Following this, the target stimulus is displayed either above or below the fixation point and remains on the screen until the participant responds. The participant's reaction time must be less than 1700 ms. After the participant presses a key within the allotted time, the target stimulus disappears, and the fixation point ("+") reappears in the center of the screen, signaling the start of the next trial. Each trial lasts less than 4000 ms. The cue stimulus (the asterisk "*") can be in 1 of 4 states based on its presence and location: no cue, double cue, spatial cue, and center cue. No cue indicates that only the fixation point is displayed. The double cue indicates that asterisks appear simultaneously above and below the fixation point. The spatial cue indicates that an asterisk appears just below or above the fixation point. The center cue indicates that the asterisk is positioned in the center of the screen, replacing the fixation point. The target stimulus is a gray arrow displayed on the screen, flanked by 2 arrows on each side. These arrows may point in the same direction as the target arrow (congruent condition), in the opposite direction (incongruent condition), or be replaced by short lines (neutral condition).

In the experimental condition, participants are required to place their hands on the keyboard and focus their eyes on the fixation point in the center of the computer monitor. They must make a fast and accurate autonomous response based on the direction of the target stimulus. Specifically, if the central arrow of the target stimulus points left, participants are instructed to press the "F" key. If the central arrow points right, they should press the "J" key. The software automatically records the participant's accuracy and reaction time. The task begins with 24 practice trials, followed by the formal experiment, which is divided into 3 blocks, each containing 96 trials. Participants are allowed to rest appropriately between blocks and can start the next block by pressing the space bar on the keyboard. The distribution of cue stimuli and target stimuli is balanced to ensure equal representation across trial types. The total duration of the task is approximately 30 minutes. The behavioral metrics include accuracy rate (higher is better), reaction time (faster is better), alerting score (no-cue reaction time [RT] to neutral-cue RT), orienting score (neutral-cue RT to spatial-cue RT), and conflict score (incongruent RT to congruent RT).

N-Back Test

This study uses the N-Back task paradigm to assess working memory, one of the classic experimental approaches for evaluating this cognitive function. The task is implemented using E-Prime 3.0 software and is performed on a computer with a keyboard. It presents stimuli and records participants' reaction times and accuracy rates across all trials. During the test, participants are required to sit in front of the computer screen, maintaining a horizontal distance of 60 cm. The index fingers of the participant's left and right hands should lightly touch the F and J keys on the keyboard, ready to respond by pressing a key when a letter appears. The N-Back paradigm includes 3 levels of memory load (0=back, 1=back, and 2=back tasks), with stimuli consisting of the letters A, B, C, D, E, and F against a black screen background with white letters. At the start of the experiment, a "+" is first displayed for 500 ms, followed by the random presentation of English letters. Each stimulus is presented for 500 ms, with an interstimulus interval of 2000 ms (blank screen). If no response is made within 2000 ms, the next stimulus is automatically presented. After each block, a prompt message saying, "Please rest for a moment; press the space bar to continue" appears. In the 0=back task, participants are instructed to compare the current letter with "X" and press the F key if they are the same or the J key if they are different. In the 1=back task, starting from the second letter, participants are instructed to determine whether the current letter is the same as the previous letter, pressing the F key if they are the same or the J key if they are different. In the 2=back task, starting from the third letter, participants are instructed to determine whether the current letter is the same as the letter 2 positions back, pressing the F key if they are the same or the J key if they are different. Participants are required to respond both quickly and accurately. The task includes 60 practice trials, followed by the formal experiment, which consists of 9 blocks, each with 30 trials (15 targets and 15 nontargets). Each memory load level includes 3 blocks, with the 0=back, 1=back, and 2=back tasks completed in sequence. Each task type involves a total of 90 stimuli (30 × 3), with a target-to-nontarget ratio of 1:1, presented in a pseudorandom order. The behavioral metrics include reaction time and accuracy rate.

In the sequence of conducting the ANT and N-Back tests, the ANT test lasts for 30 minutes, followed by the N-Back test, which lasts 15 minutes. The tests are administered consecutively, with a structured break in between. Specifically, after completing the N-Back test, participants are given a 5-minute

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rest period before proceeding with the ANT test. This design ensures a smooth transition while allowing participants to briefly recuperate, minimizing cognitive fatigue and maintaining optimal performance throughout the testing process. By balancing test durations and incorporating rest intervals, this approach facilitates a more reliable assessment of cognitive abilities.

Pittsburgh Sleep Quality Index

The Pittsburgh Sleep Quality Index (PSQI) was developed in 1989 by Buysse and colleagues [33] at the Sleep and Chronobiology Center of the Department of Psychiatry at the University of Pittsburgh Medical Center. The reliability and validity of the scale have been evaluated in China, with results showing that the index has good empirical validity. The PSQI comprises 19 items, covering 7 dimensions: subjective sleep quality, sleep duration, sleep latency (the time it takes to fall asleep), sleep disturbances, sleep efficiency, use of sleeping medication, and daytime dysfunction. The scale uses a scoring method of 0, 1, 2, and 3, with scores accumulated across dimensions, yielding a range of 0-21 points. A higher score indicates poorer sleep quality. A PSQI score of 7 is used as the cutoff point, with a score of less than 7 indicating acceptable sleep quality and more than 7 indicating poor sleep quality.

Adverse Events and Safety

Adverse events are any unfavorable and unintended signs (including abnormal laboratory findings), symptoms, or diseases associated with the study, regardless of whether they are related to the medication used. Several studies have shown that Tai Chi is a relatively safe method for treating various diseases, including hypertension, with no reports of serious adverse reactions. If unexpected adverse events occur, defined as any functional impairments caused by the intervention, such as headaches, dizziness or vertigo, head fullness, tinnitus, chest tightness, worsening shortness of breath, increased heartbeat or palpitations, muscle soreness or pain, excessive sweating, irritability, neurasthenia, hallucinations, paranoia, or psychological stress—whether or not related to the treatment—the nearest doctor will be promptly notified for assessment and initiation of treatment.

If a serious adverse reaction occurs, the researcher will report it to the principal investigator and the ethics committee to determine whether the participant should be withdrawn from the study and treatment. The researchers will make every effort to prevent and treat any harm that may arise from this study. If the expert committee believes that the adverse event is related to the Tai Chi treatment, the research team will cover the treatment costs and provide appropriate financial compensation for damages related to the trial.

Quality Control

The project leader will be responsible for the design, coordination, and quality control of the entire study. All researchers will undergo uniform training before the data collection period. Before data collection, patients are required to maintain a healthy lifestyle, such as avoiding staying up late and abstaining from alcohol, to prevent the influence of unstable factors. During the study, all data will be statistically analyzed by trained independent assessors. We will collect outcome data from all participants, regardless of whether they complete the study. The Data and Safety Monitoring Board will consist of an internal medicine physician, a Tai Chi instructor, a medical statistician, an ethicist, and a radiologist, and will conduct assessments throughout the study.

To ensure that the patients in the Tai Chi group can practice correctly at home, we will provide them with a video of Tai Chi practice methods recorded by a national Tai Chi champion, along with a booklet containing specific practice details. The Tai Chi group will also receive a practice record that will be filled out after each practice session.

Data Collection and Management

Data entry and database creation will be handled by 2 data managers who are not part of the research team and are unaware of the group assignments. Everyone participating in the trial will have access to the full data set. All original data will be retained for clinical data analysis and safety evaluation. All research-related original data will be stored at Shanghai University of Traditional Chinese Medicine.

Informed Consent

Before the trial begins, participants will be informed about the research process, their responsibilities, and the physical examinations and precautions involved. Most importantly, they will be informed that their participation is entirely voluntary and that they can refuse or withdraw at any time without affecting their medical care or other benefits. If a participant withdraws, the collected data will not be deleted and will be included in the final analysis. A written informed consent form will be obtained from each participant before starting any treatment related to the study. The research assistants will be responsible for obtaining informed consent from all participants.

Statistical Analysis

All statistical analyses and processing will be independently performed by a researcher who did not participate in the treatment or scale assessments during the process. The Statistical Package for the Social Sciences version 20.0 (IBM Corporation) will be used for statistical analysis. Quantitative data with a normal distribution will be described as mean (SD). For quantitative data with a nonnormal distribution and outcome indicators, the rank-sum test will be used. A P value of <.05 indicates a statistically significant difference.

For the neuropsychological test outcome indicators, ANT, and N-Back test behavioral metrics, a 2 (group: Tai Chi group, education group) × 2 (time: pretest, posttest) repeated measures ANOVA will be used. For cases not meeting the sphericity test, the Greenhouse-Geisser method will be applied to correct the statistical data (degrees of freedom and P value), and Bonferroni correction will be applied for post hoc comparisons. All statistical inferences will be 2-tailed, with the level of significance set at α=.05. A P value of <.05 indicates statistically significant differences.

Statistical Analysis of Neuroimaging Results

The ALFF values and FC between the Tai Chi group and the health education group will be compared using independent

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samples *t* tests. A 2-sample *t* test will be used to compare the ALFF values between the 2 groups. Pre- and postintervention data within groups will be compared using paired *t* tests. After the ALFF analysis, the maximum peak coordinates of different brain regions will be selected, and the cluster at the peak coordinates will be considered the region of interest. Differences in FC of the region of interest with the whole brain will be calculated. Correlation analyses will be conducted using Pearson correlation coefficients based on clinical and fMRI imaging data. Missing data will be processed using the multiple imputation method.

Ethical Considerations

This study follows the Declaration of Helsinki (as revised in 2013) and the International Ethical Guidelines for Biomedical Research Involving Human Subjects (Articles 37 and 38). The study protocol and consent forms have been approved by the Shanghai Clinical Research Ethics Committee (approval number SECCR2024-22-01). They were registered on March 26, 2024, in the Clinical Trial Registry (a World Health Organization International Clinical Trials Registry Platform [WHO ICTRP] member) under registration number ChiCTR2400082268.

All participants will be fully informed of the inclusion and exclusion criteria for this study before the trial begins. They will sign informed consent forms before the trial and be informed that they have the right to withdraw from the trial at any time. Recruitment and randomization will be conducted transparently. If changes occur in our research protocol, a written application will be submitted to the research ethics committee. The committee members will decide whether it is necessary to modify the protocol. After the clinical study is completed, a study completion report will be submitted and published in academic journals.

Results

Participant recruitment commenced in April 2024. All interventions and concurrent data collection will be completed by October 2025. The 4-week postintervention follow-up assessments will be finalized by the end of October 2025. Data management is currently ongoing, and statistical analysis has not yet been performed.

Discussion

To the best of our knowledge, this study is the first to explore the effects of Tai Chi on CFS from a cognitive functional perspective. To validate the specific role of Tai Chi in CFS treatment, this study aims to evaluate the impact of Tai Chi on fatigue, cognitive functions, and changes in brain function using different clinical scales, psychological experimental paradigms, and neuroimaging scans. Currently, it is widely accepted in the academic community that CFS can cause cognitive impairments. However, some reports occasionally yield inconsistent results [34,35], possibly because early mild cognitive impairments may not be fully detected by conventional neuropsychological scales and can easily be overshadowed by other clinical symptoms. In most studies, subitems measuring cognitive functions, such as attention and memory, are typically included in the composite scores of scales for other cognitive domains or in overall cognitive assessment paradigms. Moreover, due to the strong subjectivity of scale assessments and the low sensitivity of indicators, there are certain limitations. With the use of various cognitive tasks and different methods of assessing cognitive functions, direct comparisons are not feasible, leaving a lack of more direct evidence for assessing cognitive functions in patients with CFS. Therefore, there is an urgent need to apply more precise and scientific neuropsychological experimental paradigms to assess specific cognitive domains, providing objective and accurate data to support the assessment of cognitive impairments in CFS.

Togo [36] showed that the ANT has clinical value for assessing the cognitive functions of patients with CFS. Some scholars have proposed using continuous attention assessment as a reliable biomarker for diagnosing CFS [37]. Nevertheless, there is still a lack of comprehensive ANT paradigm evaluations and analyses of attention network functions in patients with CFS. The N-Back test is a commonly used paradigm in cognitive psychology for assessing working memory capacity [38], and the N-Back task paradigm, a continuous processing operation task, is one of the most widely used experimental paradigms in working memory brain imaging studies.

This study uses more precise and scientific neuropsychological experimental paradigms, such as the ANT and N-Back, to assess specific domains of cognitive impairments in CFS. It provides objective and accurate data to support the assessment of cognitive impairments in CFS. This approach offers a theoretical basis for the early clinical diagnosis and intervention of cognitive function impairments in patients with CFS, offering significant guidance.

Resting-state fMRI studies are essential for elucidating the intrinsic functional organization of the brain and can enhance our understanding of brain functional changes in CFS and its treatment. Neuroimaging scans can reveal changes in brain activation and FC in patients with CFS after Tai Chi interventions, providing clear, effective, and direct evidence. Previous fMRI studies have found brain functional changes or metabolic abnormalities in areas such as the prefrontal cortex, posterior cingulate cortex, parieto-occipital cortex, hippocampus, parahippocampal gyrus, and precuneus in patients with CFS. These changes in the central nervous system may serve as a pathological basis for the physical fatigue and cognitive impairments observed in patients with CFS [39,40].

The academic community has conducted clinical research on mind-body exercise interventions for CFS from various perspectives, yielding a wealth of effective research outcomes. Tai Chi emphasizes the unity of form and spirit, practiced with the guidance of mind over energy. It stresses the coordination of body and mind, advocating stillness and emphasizing nourishment. It can improve insomnia and fatigue symptoms in patients with CFS without toxic side effects. A meta-analysis showed that Tai Chi can improve fatigue more effectively than traditional therapies and has a positive effect on cancer-related fatigue [41]. Kuangshi et al [42] recruited 21 patients with CFS, with 19 in the control group, implementing a 4-week 24-form Tai Chi training and conducting functional brain MRI. Results

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showed that, before practicing Tai Chi, the experimental group exhibited significantly weakened FC in the default mode network, compared with the control group, in regions including the left superior temporal gyrus and the left dorsolateral prefrontal cortex. Meanwhile, significantly enhanced FC was observed in the right lateral temporal lobe. Therefore, Tai Chi has a characteristic modulatory effect on abnormal activity in the default mode network of patients with CFS .

Kuangshi et al [43] showed that, after practicing Tai Chi, the experimental group exhibited significantly reduced functional ALFF values in brain regions including the left orbitofrontal/cortical pole, right anterior cingulate gyrus, and right lateral temporal lobe. However, significantly increased functional ALFF values were observed in the left sensorimotor cortex and the right visual cortex. Therefore, Tai Chi exercise can improve fatigue and sleep in patients with CFS, enhancing their quality of life, possibly due to its specific effect on the brain's sensorimotor cortex, left frontal lobe, right lateral temporal lobe, anterior cingulate gyrus, and visual cortex. This research provides biomarkers for subsequent studies and imaging support for the central mechanism of Tai Chi. However, as an exploratory study with a small sample size, it does not include groups practicing aerobic exercise or other interventions, which would help determine the specificity of the Tai Chi intervention.

Wu et al [44] designed a longitudinal trial with Tai Chi as the intervention therapy, using the FCs of the whole brain as exploratory variables to detect abnormalities in the brain's connectivity structure in patients with CFS and explore changes during Tai Chi exercise. Our study explored the impact of Tai Chi on brain FC in CFS. Results showed that Tai Chi could improve fatigue, sleep quality, and physical health status in patients with CFS by enhancing the FCs within the left frontoparietal network and default mode network [42].

The results of this trial can evaluate the efficacy of Tai Chi in treating fatigue symptoms and cognitive impairments in patients with CFS by assessing changes in brain activation, ANT and N-Back results, and related clinical scale outcomes.

Despite the promising hypothesis of this study, it also has some notable limitations. First, the screening for inclusion criteria is solely based on self-assessment scales without the use of specialized psychometric testing equipment, which may lead to less stringent inclusion of patients with CFS. However, by limiting participants' ages to 18-60 years, the likelihood of chronic fatigue caused by medical and psychiatric conditions is reduced. Thus, the study results cannot be generalized to other populations. Second, in this study, the intervention is a nonpharmacological treatment, which cannot be ideally implemented according to double-blind standards. Ideally, each participant should be blinded to the trial; however, this is challenging to achieve in nonpharmacological trials. Hence, bias may be inevitable. However, to ensure the authenticity of the experimental data and reduce biases during the experiment, we will rigorously randomize participants and ensure that the interveners, assessors, and statisticians remain blind to each other. Additionally, the neuroimaging study in this trial is only at an exploratory stage with a limited sample size. In future research, increasing the sample size could provide more persuasive evidence. Finally, this trial only conducted a 4-week follow-up. Therefore, the follow-up period should be extended to validate the long-term clinical outcomes and potential effects of Tai Chi.

Furthermore, this study was designed as a pilot randomized controlled trial, with the primary aim of assessing the feasibility and preliminary efficacy of Tai Chi therapy in patients with CFS. The relatively small sample size limits the statistical power and generalizability of the results; therefore, all findings should be interpreted with caution. The outcomes of this pilot study will help inform the design and methodology of future large-scale, multicenter trials.

Despite the limitations mentioned, this study still possesses several advantages. Compared with other treatment methods, such as medication and psychological counseling, Tai Chi offers significant benefits for patients with CFS. It is easy to learn, not restricted by time or space, and can be practiced independently for therapeutic purposes. Moreover, this is the first study to investigate Tai Chi intervention for cognitive impairments in CFS. More importantly, it will objectively demonstrate the efficacy of Tai Chi in addressing cognitive impairments in CFS using precise, sensitive computerized neuropsychological experimental paradigms and high-spatial-resolution fMRI technology. Finally, the use of posters and social platforms for recruitment aims to include individuals from various social strata, thereby enhancing the representativeness of the sample.

In conclusion, this protocol outlines a rigorous, well-structured pilot randomized controlled trial designed to evaluate the preliminary efficacy and safety of Tai Chi for cognitive impairments in CFS.

While the findings may not be definitive, they will provide important initial evidence and contribute to the foundation for future larger-scale studies.

Acknowledgments

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Authors' Contributions

BW and XZ are the first authors. BW conceived and designed the study protocol and participated in drafting the manuscript. XZ wrote the paper and contributed to the coordination and implementation of the research. PL and PS revised the study protocol and wrote several sections of the manuscript. TH assisted in developing research measures and collecting data. All authors participated in drafting the manuscript and have read and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT checklist.
[DOCX File , 28 KB - resprot_v14i1e65958_app1.docx]

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Abbreviations

ALFF: amplitude of low-frequency fluctuation
ANT: Attention Network Test
CBT: cognitive behavioral therapy
CFS: chronic fatigue syndrome
DPABI: Data Processing & Analysis for (Resting-State) Brain Imaging
FC: functional connectivity
fMRI: functional magnetic resonance imaging
MFI-20: 20-item Multi-Dimensional Fatigue Inventory
MoCA: Montreal Cognitive Assessment
MRI: magnetic resonance imaging
NICE: National Institute for Health and Clinical Excellence
PSQI: Pittsburgh Sleep Quality Index
RT: reaction time
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
WHO ICTRP: World Health Organization International Clinical Trials Registry Platform

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Protocol

Efficacy of DaXianXiong Decoction in Preventing the Progression of Acute Pancreatitis Severity: Protocol for a Randomized Controlled Trial

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Abstract

Background: Low- and middle-income countries are facing an increase in the incidence of acute pancreatitis (AP)—characterized by rapid onset, fast progression, high rate of severity, and high mortality. Progression of AP into severe AP (SAP) results in a series of complications such as organ dysfunction, local abscesses, pseudocysts, and necrosis. Although the treatment of AP is primarily supportive, including fluid resuscitation and organ support, there is still a lack of consensus on the optimal management regimen for fluid therapy, and strategies to promote gastrointestinal recovery remain limited. As no effective intervention measure has yet been developed, supportive therapy remains the primary approach for the early treatment of AP. DaXianXiong decoction is a widely used traditional Chinese medicine formulation; however, limited research has been conducted on its clinical efficacy.

Objective: This study aims to evaluate the efficacy and safety of DaXianXiong decoction in preventing AP from progressing to SAP, assessing its impact on SAP incidence, clinical severity scores, inflammation markers, and gastrointestinal function, and providing evidence for AP management.

Methods: This study is a randomized, double-blind, placebo-controlled, single-center clinical trial. The primary outcomes will include the incidence of SAP, modified computed tomography severity index score, APACHE II (Acute Physiology and Chronic Health Evaluation II) score, modified Marshall score, and levels of the inflammation factor. The secondary outcomes will include the effect of the gastrointestinal dysfunction treatment. Evaluations will be conducted at baseline; 24 hours after the intervention; and on days 3, 7, and 28 after the intervention in both groups. A total of 60 eligible patients will be randomly allocated in a 1:1 ratio to the intervention group and the control group. Both groups will receive standard Western medical treatment for pancreatitis. The intervention group will additionally receive DaXianXiong decoction, while the control group will receive a placebo similar to the decoction.

Results: This study has been funded by the Performance Incentive Project of Scientific Research Institutions in Chongqing. The trial was registered in April 2024, and data analysis is expected to be completed by April 2025. The study results will be presented at both national and international conferences and published in peer-reviewed journals.

Conclusions: This trial will help us assess the effectiveness and safety of DaXianXiong decoction in patients with AP and provide clinical evidence on the efficacy and safety of DaXianXiong decoction in preventing the progression of AP to SAP. By evaluating its impact, the findings will contribute to the understanding of DaXianXiong decoction as an adjunct therapy in AP management and may offer a novel complementary treatment strategy for AP, potentially improving patient outcomes and reducing complications.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2300076885; https://www.chictr.org.cn/showproj.html?proj=207084

International Registered Report Identifier (IRRID): DERR1-10.2196/67392

(JMIR Res Protoc 2025;14:e67392) doi:10.2196/67392

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KEYWORDS

acute pancreatitis; traditional Chinese medicine; protocol; severe acute pancreatitis; prevent

Introduction

Acute pancreatitis (AP) is a common yet potentially fatal inflammatory disorder of the pancreas, characterized by severe abdominal pain, multi-organ dysfunction, and pancreatic necrosis. The global incidence of AP is approximately 30-40 cases per 100,000 people, with over 2000 fatalities annually [1]. Severe AP (SAP), which involves persistent organ failure lasting ≥48 hours, is the most life-threatening form of AP, with a mortality rate of 20%-40% despite significant advancements in treatment [2-4]. Approximately 20% of patients with AP progress to SAP, which is associated with severe complications such as organ failure, infections, and increased health care costs [1,5].

The pathophysiology of AP is characterized by premature activation of trypsin within the pancreatic acinar cells, triggering pancreatic autodigestion and leading to a systemic inflammatory response. This response results in systemic inflammatory response syndrome, which can progress to multi-organ dysfunction syndrome [6,7]. Although the treatment of AP is mainly supportive, including fluid resuscitation and organ support, there remains a lack of consensus on the optimal management protocols for fluid therapy [8,9], and strategies to promote gastrointestinal recovery remain limited [10].

In addition to conventional Western treatments, Chinese herbal medicines have gained attention for their potential in managing AP. Chinese herbal medicines are known for their ability to target multiple biological pathways involved in inflammation, immune response, and organ protection, offering a broader approach compared to single-target Western therapies [11,12]. DaXianXiong decoction, a traditional herbal formula used in China for over 30 years, has been reported to improve gastrointestinal symptoms and modulate inflammation. However, its clinical efficacy in preventing the progression of AP to SAP has not been conclusively demonstrated due to the lack of robust randomized controlled trials [12-14].

In light of these challenges, there is an urgent need for high-quality studies to evaluate the efficacy and safety of DaXianXiong decoction in the treatment of AP. This study aims to assess the potential of DaXianXiong decoction in preventing the progression of AP to SAP, reducing inflammatory markers, improving gastrointestinal function, and assessing safety and complications.

Methods

Trial Design

This is a single-center, randomized, double-blind, placebo-controlled study. It adheres to the guidelines mentioned in the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement (Multimedia Appendix 1).

During the trial, all eligible patients will be randomly assigned to either the intervention group or the placebo group. Both groups will receive the standard treatment for AP. A detailed workflow depicting the study process is presented in Figure 1.

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Figure 1. Workflow.

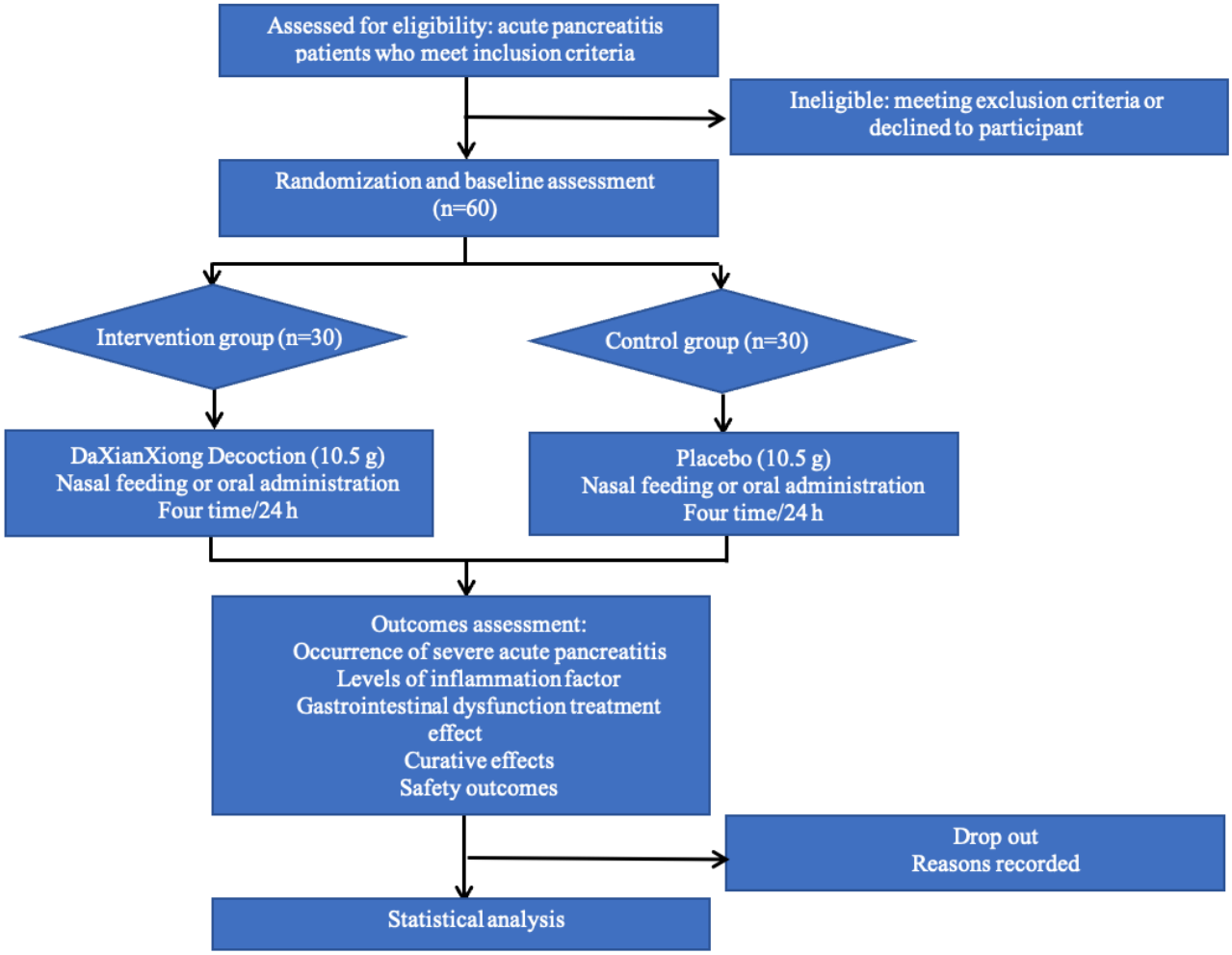

Study Population

Patients will be enrolled from the intensive care unit in Chongqing Traditional Chinese Medicine Hospital, a grade III level A hospital in China.

Recruitment of Patients

The study group will be recruiting and allocating the patients. Eligible patients who are willing to participate in the trial will be provided with an informed consent form with details of the study objectives, procedures, and potential risks (Multimedia Appendix 2).

Patient and Public Involvement

Our research will not include any design, implementation, or reporting from patients or the public.

Inclusion Criteria

We will select patients based on the following inclusion criteria:

- Presence of AP as confirmed using the revised Atlanta classification [15]
- Aged 18-75 years
- Time of illness onset under 24 hours

Exclusion Criteria

We will use the following exclusion criteria:

- Patients with severe diseases affecting vital organs, such as liver dysfunction, heart failure, and malignant tumors
- Patients participating in another study within 3 months of enrollment
- Those with known allergies to any of the prescribed medicines
- Pregnant or lactating women

Withdrawal Cases

Patients can withdraw from the study at any point without any repercussions. If a patient discontinues the intervention or decides to participate in another study, they will no longer be included in the present study. However, even when a patient withdraws from the study, the data collected up to that point will be retained and included in the analysis, unless specifically requested otherwise. The withdrawal and noncompliance of patients will also be documented. Incomplete data will be addressed based on the withdrawal rate. If the rate is <5%-10%, we will perform data cleaning. If the withdrawal rate exceeds 10%, the missing data will be managed through imputation, intention-to-treat analysis, and sensitivity analysis.

Management of Dropout Cases

All patients who provide informed consent and meet the eligibility criteria for enrollment in this randomized controlled trial, irrespective of the timing or reasons for their withdrawal later, will be categorized as dropouts if they are lost to

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follow-up. However, patients who discontinued the treatment regimen because of complete symptom remission will not be considered dropouts. The investigators will comprehensively document the reasons for each dropout in the case report form. Real-world circumstances, including adverse events (AEs), will be accounted for during the statistical analysis. In addition, we will carefully record and preserve the data about all enrolled patients who will receive the assigned investigational medications, regardless of their withdrawal status, for observation purposes and to be used as a data archive and for the intention-to-treat analysis.

Interventions

All patients will be provided with detailed information about the study. Once informed consent is obtained and baseline assessments are completed, eligible patients will be randomly allocated to the intervention or placebo group. Notably, the investigational drug in this study was Chinese medicine, so patients were required not to take other Chinese medicine or Chinese patent medicine throughout the study. Both groups will receive standard treatments. In addition to the standard treatment, the intervention group will receive DaXianXiong decoction (Figure 2). The constituent botanical drugs of the DaXianXiong decoction are listed in Table 1. DaXianXiong decoction includes three herbs, namely, 30 g of Rhei Radix et Rhizoma (Shengdahuang), 30 g of Natrii Sulfas (Mangxiao), and 3 g of Kansui Radix (Gansui). The dosage of each herb was determined based on the guidelines outlined in *The Chinese Pharmacopoeia*, 2020 edition [16].

Figure 2. Components of DaXianXiong decoction.

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Table 1. Components of DaXianXiong decoction.

Drug name	Part this formula uses	Location of manufacture	Dose (g)	Use	Medicine form, dosage, frequency	Registration status (yes/no)	Quality control report (yes/no)	Storage condition
Da Huang (Rhei Radix et Rhizoma)	Roots	Sichuan Neautus Co, Ltd, Sichuan, China	7.5	Nasal feeding or oral administration	Powder, dissolved in 50 mL of warm water, every 6 h, lasts 48 h	Yes	Yes	• Powder: stored in the pharmacy department; 18-20 °C and 45%-75% humidity • Decoction: kept in the ward; 26-28 °C and 50%-60% humidity
Mang Xiao (Natrii Sulfas)	Mineral	Sichuan Neautus Co, Ltd, Sichuan, China	7.5	Nasal feeding or oral administration	Powder, dissolved in 50 mL of warm water, every 6 h, lasts 48 h	Yes	Yes	• Powder: stored in the pharmacy department; 18-20 °C and 45%-75% humidity • Decoction: kept in the ward; 26-28 °C and 50%-60% humidity
Gan Sui (Kansui Radix)	Roots	Sichuan Neautus Co, Ltd, Sichuan, China	0.5	Nasal feeding or oral administration	Powder, dissolved in 50 mL of warm water, every 6 h, lasts 48 h	Yes	Yes	• Powder: stored in the pharmacy department; 18-20 °C and 45%-75% humidity • Decoction: kept in the ward; 26-28 °C and 50%-60% humidity

The Department of Pharmacy of the Chongqing Traditional Chinese Medicine Hospital will perform the following processing steps on DaXianXiong decoction: water extraction, separation, concentration, drying, and granulation. Each sachet will contain 10.5 g of powdered decoction. The production and processing procedures will be conducted as per the guidelines specified in *The Chinese Pharmacopoeia*. The powder will be processed and filled in standardized clean production workshops. The treatment method will involve nasal feeding or oral administration of DaXianXiong decoction four times a day, once every 6 hours, and dissolved in 50 mL of warm boiled water. The course of the treatment will be 48 hours.

We will design placebos similar to the intervention drugs in terms of shape, color, smell, and solubility so that patients have a similar sensory experience. Placebos have no efficacy or side effects. They will also be produced by the Department of Pharmacy of the Chongqing Traditional Chinese Medicine Hospital.

In the event of a serious AE or allergic reaction caused by the research medication, the principal investigator will open the emergency envelope and discontinue the trial for that patient. Details of the event and unblinding will be recorded in the case report form, and the patient will receive appropriate treatment. The relevant departments and ethics committees will be promptly notified within 24 hours.

Randomization

Randomization will be conducted by an independent statistician using SPSS Statistics 26.0 (IBM Corp) software. A predetermined random number table will be generated, and 60 patients will be randomly assigned to either the intervention group or the standard-of-care group in a 1:1 ratio. To ensure accuracy and reliability, a random distribution table will be created in triplicate, with copies provided to the project leader, pharmacist, and statistician. The statistician, who remains blind to the trial and is not involved in patient recruitment, will generate the allocation sequence and securely store the master randomization list. Randomization will be implemented using a sealed envelope method to maintain allocation concealment. Each patient will receive a unique study identification number upon enrollment. The randomization table will be used to sequentially assign these numbers to either the intervention or control group. Each assignment will be enclosed in an opaque, sequentially numbered, and sealed envelope. After obtaining informed consent, the recruiter will open the envelope corresponding to the patient's study ID and determine the group assignment.

Blinding

This study will be conducted as a double-blind trial to ensure that both patients and researchers remain unaware of group assignments. Each patient will be provided with a package containing medication numbers and labels. Random numbers will be securely sealed in double opaque envelopes and managed by a specialist (ZL). Each patient will be provided with their designated emergency letter, which will be carefully kept in secure storage until the study is completed. Discontinuation of the intervention and unblinding will only occur under specific circumstances: the patient experiences a drug-related serious

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AE, the patient fails to comply with the protocol regarding the administration of the investigational drug, or the investigator determines that continuing the trial may pose potential harm to the patient.

Outcome Measures

The outcome measures will be determined at various time points throughout the study, including baseline (T0, before treatment), 24 hours after the final treatment (T1, end point 1), 3 days after the final treatment (T2, end point 2), 7 days after the final treatment (T3, end point 3), and 28 days after the final treatment (T4, final end point). The data collection and assessment schedule are listed in Table 2.

Table 2. The data collection and assessment schedule.

Assessments	Study period			Follow-up		
	Enrollment and allocation (T0)	Intervention (48 hours)	Primary end point (T1)	T2	T3	T4
Enrollment						
Eligibility screen	✓					
Informed consent	✓					
Medical history	✓					
Allocation	✓					
Randomization	✓					
Intervention						
Intervention group		✓				
Placebo group		✓				
Assessments						
Incidence of SAP[a]			✓	✓	✓	✓
Modified Marshall score	✓		✓	✓	✓	✓
Modified CTSI[b]	✓		✓	✓	✓	✓
APACHE II[c] score	✓		✓	✓	✓	✓
C-reactive protein	✓		✓	✓	✓	✓
IL[d]-1	✓		✓	✓	✓	✓
IL-4	✓		✓	✓	✓	✓
IL-6	✓		✓	✓	✓	✓
IL-8	✓		✓	✓	✓	✓
IL-10	✓		✓	✓	✓	✓
TNF[e]-α	✓		✓	✓	✓	✓
Safety outcomes	✓		✓			
Hospitalization						✓
Survival						✓

[a]SAP: severe acute pancreatitis.
[b]CTSI: computed tomography severity index.
[c]APACHE II: Acute Physiology and Chronic Health Evaluation II.
[d]IL: interleukin.
[e]TNF: tumor necrosis factor.

Primary Outcomes

The primary outcome of this study is the incidence of SAP, which will be calculated using the following formula:

SAP incidence (%) = (number of SAP cases/total number of patients) × 100%

Secondary Outcomes

Modified Computed Tomography Severity Index

According to the analysis of the area under the curve, the modified computed tomography severity index demonstrates the highest accuracy in predicting SAP. It is a simpler and more

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accurate scoring tool, showing a stronger statistical correlation with factors such as length of hospital stay, development of infection, organ failure, and mortality [17,18]. It will be determined using the following formula:

Computed tomography severity index = (original score – current score)/original score × 100%

APACHE II Score

The APACHE II (Acute Physiology and Chronic Health Evaluation II) scoring system has high sensitivity and exhibits a negative predictive value in predicting pancreatic necrosis and organ failure. This makes it an ideal prognostic tool for assessing the severity of AP and in guiding clinical decision-making, particularly in resource-limited countries [19]. It is determined using the following formula:

APACHE II = (original score – current score)/original score × 100%

Modified Marshall Score

Organ failure plays a significant role in the severity of AP. The revised Atlanta classification recommends the use of the modified Marshall scoring system as the primary tool for assessing organ failure. The modified Marshall scoring system encompasses scoring systems for respiratory, cardiovascular, and renal systems to evaluate organ dysfunction in AP [6].

Levels of Inflammation Factor

The level of an inflammation factor is a surrogate marker for important clinical end point variables in AP. Multiple studies have shown that C-reactive protein is a good surrogate marker for SAP [20,21]. Additionally, interleukin (IL)–6 is superior in predicting SAP compared to other commonly used markers such as erythrocyte sedimentation rate. The level of an inflammation factor can be determined using the following formula [22]:

Inflammation factor = (original figure – current figure)/original figure × 100%

We will also use IL-1, IL-4, IL-8, and IL-10 to investigate the potential targets of DaXianXiong decoction. In pancreatitis, cytokines such as tumor necrosis factor–α secreted by acinar cells and damage-associated molecular patterns play a major role in activating immune cells such as neutrophils and macrophages. This process leads to increased pancreatic damage, systemic inflammation, and the development of SAP [8,23].

Gastrointestinal Dysfunction Treatment Effect

A comprehensive assessment of the gastrointestinal function is essential for the early detection of SAP. This assessment involves evaluating symptoms such as abdominal pain, distention, hematemesis, hematochezia, number of independent defecations, and digestive function. Signs such as tenderness, rebound tenderness, muscle tension, and the number of bowel sounds are also considered. Additionally, scores such as the gastrointestinal function score used in multi-organ dysfunction syndrome diagnostic criteria can provide a standardized measurement of gastrointestinal function.

Other Measures

Given the constraints of ethics and experimental techniques, certain indicators are valuable for assessing the improvements and prognosis of patients with AP. These include the time to bowel sound recovery, time to first defecation, and the gastrointestinal function score. These measures provide predictive information regarding gastrointestinal function and can be useful in evaluating the prognosis of patients with AP. We will also record hospitalization costs and duration.

Safety Outcomes

The safety outcomes of the investigational medication were assessed at T0, T1, T2, T3, and T4 by considering the following:

- Measurement of vital signs: heart rate, blood pressure, temperature, and respiration
- Laboratory tests: blood routine, stool routine, and urine routine
- Liver function tests: alanine aminotransferase, aspartate aminotransferase, and bilirubin
- Renal function tests: urea nitrogen and creatinine
- Electrocardiogram

Adverse Events

All AEs will be carefully documented, including the start and end dates, severity, relationship to the study drug, and patients' continued involvement in the study. Any serious AE will be promptly reported to the research ethics committee within 24 hours. If an AE occurs, the patient will be advised to discontinue the use of the decoction, and the researchers will evaluate whether it is related to the formulation. Emergency safety measures will be implemented, if necessary, to ensure the well-being of patients. Persistence of AEs will be monitored until their resolution. Please note that AEs are not the complications clearly related to AP, such as acute respiratory distress syndrome, abdominal compartment syndrome, and acute kidney injury.

Sample Size

We will use preset sample sizes (n) determined using the following formula:

Where μ_1 and μ_2 are the means of the intervention and placebo groups, respectively, and σ is the SD. The study aims to maintain the type I error probability (α) to <5% and the type II error probability (β) to <10%, with the α at .05 and the β at .1. To determine the sample size, we referred to literature reports in Chinese [24] on the use of DaXianXiong decoction for the treatment of AP. We used the time blood amylase took to return to normal levels to determine the clinical efficacy of the decoction. We fixed the total sample size for the study at 60. We allocated 30 patients to the intervention group and the remaining 30 to the placebo group.

Data and Sample Collection

To minimize selection bias, three study members will receive comprehensive training on the criteria and methods used for case collection. Detailed records of patient medication will be

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collected, and any interfering or contaminating factors will be excluded from the statistical analysis.

Data Management and Monitoring

An independent data and safety monitoring board will be established to monitor the conduct and safety of the study. Two of our research team members will be responsible for updating our clinical trial–related information on the Chinese Clinical Trial Registry website and for making sure that no data are missed. However, if this becomes inevitable, we will use various processing methods to handle the issue. We will also perform a sensitivity analysis of the test results simultaneously.

Adherence to Study Interventions

Throughout the study, patients will be given clear oral and written instructions to ensure proper adherence to the intervention. We will closely monitor their progress and provide personalized guidance when necessary. Any unused medication will be collected, documented, and returned as part of the study protocol.

Data Analysis

Data analyses will be performed using SPSS 24.0 software. Continuous variables with a normal distribution will be analyzed using Student *t* test, while nonnormally distributed variables will be analyzed using the Wilcoxon rank sum test. Categorical variables will be analyzed using Pearson χ^2 test. Continuous variables will be presented as mean (SD), while categorical variables will be presented as percentages. Values with *P* values ≤.05 will be considered statistically significant, and all tests will be 2-sided.

Frequency and Plans for Auditing Trial Conduct

The trial conduct will be audited at specified frequencies by an independent team that does not include the investigators and sponsor. The details of the auditing frequency and plans are provided in Table 2.

Ethical Considerations

This study protocol involving human patients was reviewed and approved by the Chongqing Traditional Chinese Medicine Hospital on September 6, 2022 (2023-KY-52).

Patients will be provided with a consent form with a clear outline of the use of their data, allowing them to choose whether to continue participating or withdraw from the trial. Biological specimens collected for storage will be handled according to ethical guidelines, and they will be destroyed after their intended use. Patient privacy will be strictly maintained. Physical documents related to the study will be secured in a locked office.

Modification of the Protocol

Any modifications to the program will require the consent of both the project leader and the supervisor. After obtaining approval from the ethics committee, the sponsor and all members of the research team will be notified of the changes.

Results

This study has been funded by the Performance Incentive Project of Scientific Research Institutions in Chongqing. The trial was registered in April 2024, and data analysis is expected to be completed by April 2025. The recruitment for the trial commenced in December 2023. The data has been collected and is being analyzed. The study results will be presented at both national and international conferences and published in peer-reviewed journals.

Discussion

Expected Findings

This study aims to evaluate the efficacy and safety of DaXianXiong decoction in preventing the progression of AP to SAP by conducting a randomized, double-blind, placebo-controlled, single-center trial. The treatment of SAP continues to be a challenge, and preventing the progression of AP to SAP has been a hot spot of research in critical care medicine and gastrointestinal diseases. Inflammatory cascade-driven response is considered to be an important cause of progression to SAP in patients with AP combined with organ failure [25]. Inflammatory response to AP triggers visceral edema and gastrointestinal dysfunction, leading to increased abdominal pressure and possible abdominal septal compartment syndrome and organ failure [26]. Among the studies on blocking the progression of AP to SAP, Huang et al [27] observed that cyclooxygenase 2 (COX-2) inhibitors (parecoxib and celecoxib) reduced serum tumor necrosis factor–α and IL-6 levels in patients with AP, reducing the incidence of SAP by approximately half. He et al [28] observed that neostigmine reduced AP and abdominal pressures and facilitated defecation, thereby reducing the incidence of organ dysfunction in patients with AP. However, these drugs have a single therapeutic target and have potential risks, such as COX-2 inhibitors that may lead to gastrointestinal mucosal damage or even gastrointestinal bleeding, and neostigmine that may cause bradycardia and increase airway resistance.

DaXianXiong decoction has been commonly used in Asia for the treatment of AP for more than 30 years [29,30]. In our study, we used DaXianXiong decoction in addition to conventional treatment to observe its efficacy in preventing the progression of AP to SAP. The key advantage of this study compared with previous studies is that DaXianXiong decoction has the advantage of being multi-targeted to simultaneously act to improve gastrointestinal function and reduce the inflammatory response, which has the potential to block the progression of AP. In addition, this study may pave the way for larger multicenter trials to further investigate the potency and cost-effectiveness of complementary treatment strategies in larger populations.

Limitations

The study has limitations because of the small sample size. Additionally, the mechanism path of DaXianXiong decoction remains unclear and requires further investigation. However,

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these limitations provide further opportunities for expanding the findings and gaining a deeper understanding of the treatment.

Acknowledgments

This study was funded by the Performance Incentive Project of Scientific Research Institutions in Chongqing (project jxyn2021-2-15). The study sponsor does not have any role in study-related activities or the final publication of the study.

Data Availability

The datasets generated or analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

DR and JT served as the primary investigators for this study, contributing to its conceptualization, design, and drafting of the manuscript. YZ and ZL were involved in the conception and critical revision of significant intellectual content. DR contributed to the study's design and provided statistical guidance. JT, YZ, and ZL were involved in the conception and design. All authors revised the protocol for intellectual content and approved the final manuscript, adhering to trial authorship guidelines.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT checklist.
[PDF File (Adobe PDF File), 110 KB - resprot_v14i1e67392_app1.pdf]

Multimedia Appendix 2
Informed consent.
[DOC File , 27 KB - resprot_v14i1e67392_app2.doc]

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Abbreviations

AE: adverse event

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AP: acute pancreatitis
APACHE II: Acute Physiology and Chronic Health Evaluation II
COX-2: cyclooxygenase 2
IL: interleukin
SAP: severe acute pancreatitis
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Short- and Long-Term Effectiveness of Brief Intensive Trauma Treatment for Adolescents With Posttraumatic Stress Disorder and Their Caregivers: Protocol for a Multicenter Randomized Controlled Trial

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Abstract

Background: Childhood trauma is pervasive, with approximately 50% of adolescents experiencing at least one potentially traumatic event before adulthood. Eight percent to 33% of potentially traumatic event–exposed adolescents develop posttraumatic stress disorder (PTSD), which can cause extreme suffering and coincides with numerous comorbid illnesses and high-risk behaviors. PTSD can be effectively treated in adolescents through weekly sessions of eye movement desensitization and reprocessing or trauma-focused cognitive behavioral therapy. Despite the availability of these treatments, numerous severely traumatized adolescents do not receive available treatment options due to high treatment avoidance. In adolescents who receive care, a large group of youth does not experience a sufficient symptom decrease after regular treatment. In addition, dropout rates during prolonged treatment are substantial, varying between 10% and 30%. This underscores the need for innovative and brief trauma treatment. Pilot studies indicate that Brief Intensive Trauma Treatment (BITT) can be a safe and effective treatment for adolescents with PTSD. However, randomized controlled trials on its effectiveness are crucial and urgently needed.

Objective: This is the first study to test the effectiveness of a 1-week BITT in adolescents with PTSD and comorbid symptoms and their caregivers.

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Methods: This multicenter, single-blinded randomized controlled trial will be conducted in 4 youth care centers in the European and Caribbean Netherlands: Levvel, Karakter, Fornhese-GGz Centraal, and Mental Health Caribbean (Bonaire). We will randomize adolescents (12-18 years old) with PTSD to a BITT (n=50) or waitlist control group (WLCG; n=50). BITT comprises 1-week (ie, 5 consecutive workdays) intensive trauma treatment, encompassing daily 90-minute manualized sessions of trauma-focused cognitive behavioral therapy and eye movement desensitization and reprocessing. The day begins and ends with psychomotor therapy. Caregivers receive daily parental counseling sessions consisting of psychoeducation and social support skill training. We will conduct measurements at similar intervals for both groups: at baseline; directly after BITT or WLCG; and at 3, 6, and 9 months' follow-up. The WLCG will receive BITT after the 3-month follow-up assessment. We will assess all study parameters using digital or face-to-face questionnaires and semistructured interviews. We will assess the primary outcome PTSD symptoms using the Child and Adolescent Trauma Screen 2 (CATS-2) and the Clinician-Administered PTSD Scale for *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition])-Child/Adolescent Version (CAPS-CA-5).

Results: As of September 2022, we enrolled 104 participants. Data will be collected until December 2025. Results are expected to be published in the summer of 2026.

Conclusions: This first, innovative study on BITT's effectiveness may enhance treatment outcomes for PTSD by preventing dropout, reducing avoidance, shortening therapy duration, and empowering therapists by working together intensively. This research will provide valuable insights across cultures for treating severely traumatized adolescents who do not benefit sufficiently from regular treatment.

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KEYWORDS

brief intensive trauma treatment; adolescents; stress disorder; post-traumatic; adverse childhood experiences; eye movement desensitization reprocessing; trauma-focused cognitive behavioral therapy; Caribbean; randomized controlled trials; multicenter studies

Introduction

Childhood trauma is pervasive, with around 50% of adolescents experiencing at least one potentially traumatic event (PTE) before adulthood [1-3]. Posttraumatic stress disorder (PTSD) is the most common disorder that can develop after experiencing PTE and occurs in around 16% of PTE-exposed adolescents, with a range of 8%-33%. Importantly, the variability within this range is influenced by the type of trauma and gender. In particular, PTSD is less prevalent in boys exposed to noninterpersonal trauma, while girls exposed to interpersonal trauma are at a greater risk of developing PTSD [4]. PTSD manifests through symptoms such as re-experiencing (ie, flashbacks, nightmares, dissociation, repetitive distressing images or sensations, and physical sensations such as pain, sweating, nausea, or trembling), avoidance and emotional numbing, negative alterations in cognitions and mood, and hyperarousal (ie, irritability, angry outbursts, sleep disturbances, and difficulty concentrating) [5].

Furthermore, PTSD significantly affects an individual's quality of life [6,7]. Adolescents with PTSD have been found to show high rates of psychopathology at the age of 18 years, including 48.8% engaging in self-harm, 20.1% attempting suicide, 54.7% diagnosed with major depressive disorder, 23.8% with generalized anxiety disorder, and 27% with conduct disorder [8]. In addition, subclinical PTSD (sPTSD) in adolescents is often neglected. However, adolescents with sPTSD can experience similar distress as adolescents with full-blown PTSD [9]. These findings emphasize the critical importance of early treatment for both clinical and sPTSD.

The internationally recommended treatment guidelines for PTSD are weekly sessions of eye movement desensitization and reprocessing (EMDR) or trauma-focused cognitive behavior therapy (TF-CBT) [10-13]. However, 30% of individuals do not benefit enough from evidence-based PTSD treatments. This might be explained by PTSD symptom severity and high rates of psychiatric comorbidity within this group of patients. Notably, greater symptom severity and high rates of comorbidity are associated with reduced treatment success [14]. In addition, dropout rates during prolonged treatment are substantial, varying between 10% and 30% [15-18]. The duration of therapy and treatment avoidance potentially cause these dropout rates. Current treatment strategies are prolonged (at least 3-4 months) and, therefore, subject to engagement and compliance barriers. For example, adolescents can be reluctant to engage in therapy due to fear of re-experiencing their trauma over a long period of time [19]. Due to frequent appointments over a longer period, adolescents miss school time and the opportunities to engage in hobbies, social activities, and peer contact, hampering healthy development and resulting in therapy disengagement. Notably, a greater number of therapy sessions is found to be an important predictor of dropout in adolescents with trauma [20]. These findings underline that innovative trauma treatments are crucial and that treatments in a novel, brief, and intensive format are urgent.

Brief Intensive Trauma Treatments (BITT) entail multiple trauma-focused sessions, often integrating various treatment modalities simultaneously. Recent studies have indicated that BITT for adults can serve as a safe and effective strategy for reducing PTSD [21-24]. These studies have yielded promising outcomes in adults, characterized by notably low dropout rates

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and minimal adverse events. Unfortunately, evidence of the effectiveness of brief trauma treatments in children and adolescents is limited. To date, only 9 studies have shown promising results [25-33]. However, 8 of the 9 studies were conducted without control groups and all studies had relatively small sample sizes (ie, N=10, N=27, N=22, N=15, N=15, N=33, N=44, N=27, and N=36). Hence, from the perspective of clinical relevance and optimizing treatment and healthy development of children with trauma, randomized controlled trials (RCTs) investigating the effectiveness of BITT in adolescents are urgently needed. This was the rationale for the present innovative multicenter RCT. This RCT follows up on a pilot study (N=22) of the same BITT program, which previously demonstrated promising results, including a reduction in PTSD symptoms up to 3 months post treatment [34].

Methods

Aims

Primary Objective

The primary objective of this RCT is to assess the effectiveness of a BITT compared to a waitlist control group (WLCG) in reducing symptoms of PTSD among adolescents aged 12-18 years.

Secondary Objectives

The secondary objectives of the study are to investigate whether BITT for adolescents with PTSD:

1. in comparison to a WLCG, demonstrates effectiveness in reducing comorbid psychiatric symptoms (ie, anxiety, depression, and anger) and improving the quality of life;
2. is safe (ie, does not increase suicide attempts or self-harm)
3. reduces dropout rates;
4. is affected by moderators (ie, age, gender, socioeconomic status [SES], type of trauma, number of traumatic events, comorbidity, caregivers PTSD, and treatment center) in its effect on PTSD symptoms and BITT dropout (moderators: residency [ie, urban and rural area] and ethnicity).

Study Design

In this multicenter, single-blinded RCT, we will examine the effectiveness of BITT compared to a WLCG. Participants will be recruited over 27 months (October 2022-December 2024). To determine the effectiveness of BITT, we will compare the outcomes of the BITT intervention group (n=50) with the outcomes of a WLCG (n=50). We will conduct assessments at similar time points for both groups: at baseline (T0), directly after BITT or WLCG (T1), and at 3 (T2), 6 (T3), and 9 (T4) months follow-up after the baseline measurement. The WLCG will receive BITT after the 3-month follow-up assessment. Figure 1 provides an overview of the study design.

Figure 1. Flowchart of the randomized controlled trial design. BITT: Brief Intensive Trauma Treatment.

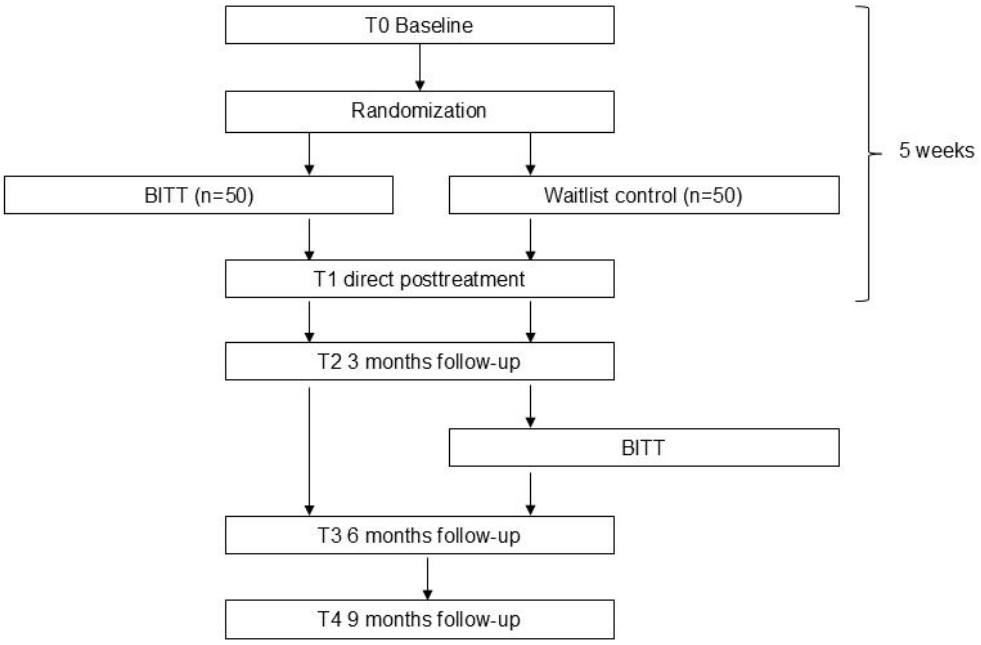

The treatment phase of BITT lasts only 1 week (ie, 5 consecutive workdays). The WLCG will not receive psychological care (ie, EMDR and TF-CBT) during this week. After this week, participants from the BITT group will follow regular follow-up care, which usually consists of EMDR and TF-CBT. Apart from BITT, the WLCG can receive any treatment including EMDR and TF-CBT, during this period. We will monitor and register all provided care in the research database (inclusion and exclusion criteria listed in Textbox 1).

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

Participants must meet all of the following criteria:

- 12-18 years of age;
- A history of psychological trauma (as measured by the Life Events Checklist of the Clinician-Administered Posttraumatic Stress Disorder Scale for Children and Adolescents in the *DSM-5 [Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition)]) [35,36];
- At least subthreshold posttraumatic stress disorder criteria, conform to the Clinician-Administered PTSD Scale for Children and Adolescents *DSM-5*, that is:
  - fully meets criteria A, F, and G, and at least one symptom of criteria B, C, D, and E;
  - fully meets criteria A, F, G, and at least one of the B, C, D, or E symptom clusters;
- The adolescent must provide written informed consent. For adolescents aged 12-15 years, all legal guardians must also provide consent.

Exclusion criteria

Adolescents who meet any of the following criteria will be excluded from participation in this study:

- inability to speak and write Dutch;
- estimated or determined intellectual disability (IQ <70);
- having ongoing trauma by a parent who is part of the adolescent's current primary care system.

Power Analyses

A power analysis in R (R Core Team) [37] (script available on request) showed that a sample size of n=66 (33 in the direct group and 33 in the WLCG) is sufficient to reach a required power of at least 80% when assuming Cohen *d*=0.5. Regarding trauma-focused therapies, we expected a dropout rate of around 25% [15-17], implying that we would need at least 88 (ie, 66 divided by 0.75) participants. To ensure sufficient statistical power, we aimed for a total sample size of 100. This sample size will also be sufficient when adding the covariates to the model.

Participant Recruitment and Procedure

We will conduct this study in four youth care centers in the European and Caribbean Netherlands: Levvel, Karakter, Fornhese-GGz Centraal, and Mental Health Caribbean (Bonaire). Centers were eligible to participate if they had extensive experience in treating chronically traumatized children and adolescents, were trained in EMDR and TF-CBT, had experienced systemic therapists and psychomotor therapists, and had the capacity to implement the study. The therapist from the participating center will verbally inform eligible adolescents about the study and provide them with an information letter. In addition, the adolescent and their caregivers will be offered the opportunity to discuss the study with the researcher to receive more information about the study and ask questions. The researcher will discuss all referrals with an experienced child and adolescent psychiatrist with expertise in PTSD. All adolescents will provide written informed consent, and legal caregivers of adolescents aged 12-15 years will also provide consent.

Randomization

After obtaining written informed consent from participants, an independent researcher will randomize them to either the BITT group or WLCG using computerized block-wise randomization in Castor Electronic Data Capture [38]. We will use random block sizes to avoid predictability for the researchers and we will stratify by center. The researcher completing the assessments will be blinded to the group allocation (ie, BITT vs WLC). We will explicitly instruct participants not to communicate their group allocation to the researcher.

Treatment

Pretreatment

A personalized "crisis prevention plan" will be developed individually with all participants and, if applicable, their caregivers before the treatment phase. The crisis prevention plan will include the following:

1. Possible risk factors to consider (eg, self-harm, suicidality, alcohol and drug abuse, and aggression);
2. Signs and tools for maintaining stability and preventing deterioration;
3. Clear arrangements regarding whom to contact in case of emergency (eg, the main responsible clinician during working hours and local crisis service outside regular working hours) with up-to-date contact information.

Furthermore, before starting BITT, a personalized treatment plan will be developed with specific trauma targets in close collaboration with the adolescent, caregivers, and BITT therapist. The therapist will also be assigned as a personal case manager for individual adolescents throughout the BITT week. The BITT therapist will provide psychoeducation concerning PTSD symptoms and intensive treatment to adolescents and caregivers before the start of BITT.

The BITT

BITT consists of a 1-week (ie, 5 consecutive workdays) intensive trauma treatment with 2 daily manualized therapy sessions comprising TF-CBT (90 min) in the morning followed by EMDR (90 min) in the afternoon (ie, 10 sessions in total; 5

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TF-CBT and 5 EMDR). The 90-minute session duration is based on the results of a previous pilot study into BITT for adolescents, which indicated that the burden of 90-minute sessions was evaluated as acceptable [25]. Both TF-CBT and EMDR therapy are effective and well-established treatments for children and adolescents suffering from trauma [15,39]. In both TF-CBT and EMDR, the primary objective is to address and reprocess traumatic memories and diminish the distressing emotions associated with traumatic life events. In TF-CBT, therapists apply gradual exposure from the beginning by having adolescents create a trauma narrative. Gradual exposure is applied by first telling the trauma narrative aloud, then writing it, and then reading it aloud. This also helps adolescents modify dysfunctional trauma-associated cognitions. On the last day of the BITT, the adolescent shares the trauma narrative with the caregivers during a so-called social sharing, which is a module of TF-CBT. Often this is the first time caregivers and adolescents engage in a conversation about the traumatic experience. The caregiver or caregivers are then provided with the opportunity to acknowledge the harm experienced by the adolescent, reflect on their role as a parent, and consider how they could have acted differently. This interaction is seen as an important step in trauma processing. In EMDR, the adolescent recalls the traumatic memories while simultaneously making horizontal eye movements and performing tasks with a high working memory load [40]. Therapists will use the Dutch EMDR protocol for children and adolescents [41,42].

The sequence of TF-CBT first and EMDR second is related to a proven better treatment outcome compared to the reversed sequence [43]. Experienced therapists trained in EMDR and TF-CBT will conduct all treatment sessions. Different therapists will provide sessions that conform to a so-called “therapist rotation” scheme with a maximum of 3-4 therapists per adolescent per week. Therapist rotation is applied since it seems to decrease avoidance in adolescents to engage in trauma therapy [44]. Treatment will take place in an outpatient setting.

Between therapy sessions, adolescents will participate in psychomotor therapy (PMT). PMT is a therapeutic approach in which physical movement and bodily awareness play a central role. In the morning of every BITT day, the focus during PMT will be on bodily awareness (eg, observing body signals related to PTSD) and in the afternoon, the focus will be on relaxation. Existing evidence shows that body- and movement-oriented interventions have a positive effect on diminishing PTSD symptoms [45,46].

During parental counseling, primary caregivers will receive psychoeducation, social support skill training, and social sharing (a total of 5 sessions of 90 min). Research has shown that involving caregivers is a crucial element in the treatment of children and adolescents, which contributes to fewer dropouts and increased treatment effects [39].

Adolescents will start and end the day together. PMT sessions are provided in a group setting. The TF-CBT and EMDR sessions are provided individually. Table 1 provides an overview of the therapy program.

Table 1. Therapy program.

Time	BITT week				
	Monday	Tuesday	Wednesday	Thursday	Friday
9-9:15 AM	• Start (8:45 AM)	• Start	• Start	• Start	• Start
9:15-10:15 AM	• PMT[a]	• PMT	• PMT	• PMT	• PMT
10:30 AM-12 PM	• TF-CBT[b] • Parental counseling[c]	• TF-CBT	• TF-CBT • Parental counseling	• TF-CBT	• EMDR
12-1 PM	• Break	• Break	• Break	• Break	• Break
1:15-2:45 PM	• EMDR[d]	• EMDR • Parental counseling	• EMDR	• EMDR • Parental counseling	• Social sharing
3-3:45 PM	• PMT	• PMT	• PMT	• PMT	• Closing (3-3:30 PM)
4-4:15 PM	• Closing	• Closing	• Closing	• Closing	N/A[e]

[a] PMT: psychomotor therapy.

[b]TF-CBT: trauma-focused cognitive behavioral therapy.

[c]Caregivers receive parental counselling at the same time that the adolescent receives trauma therapy.

[d]EMDR: eye movement desensitization and reprocessing.

[e]N/A: not applicable.

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Training and Implementation

All health care professionals involved in BITT are trained by expert therapists before providing treatment, ensuring the quality of care. During this 1-day training, all modules of the BITT will be taught. In addition, the TF-CBT therapists will follow a 1-day training about the BITT-specific TF-CBT elements. Furthermore, BITT therapists from all participating centers without a TF-CBT or EMDR license will be trained by expert and licensed senior TF-CBT and EMDR supervisors from Levvel. These expert therapists were also involved in the development of the BITT program and have nationally renowned expertise. The researcher determining the PTSD symptoms during the study will be trained in the Clinician-Administered PTSD Scale for *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition])-Child/Adolescent Version (CAPS-CA-5). During the BITT, the supervisors from Levvel will provide daily supervision to all therapists at the participating centers during a daily multidisciplinary consultation. During this consultation, all BITT therapists work closely together enhancing a clear focus on the treatment plan.

Treatment Integrity

During the BITT, 2 supervisors from Levvel will provide daily supervision to all therapists of the participating centers in close collaboration with dedicated experts from those centers. In this way, the consistency and quality of the BITT are monitored across sites. Furthermore, therapists will complete detailed therapy checklists that will be assessed by a researcher to ensure that the treatments are delivered as intended by the protocol. In addition, therapists will record the therapy sessions with audiotapes if the participant provides permission. A total of 2 trained psychologists will independently code a random 15% of these therapy sessions to assess the treatment integrity.

Assessment Instruments

The assessments of the primary and secondary outcomes and demographic predictor variables consist of digital questionnaires and digital or face-to-face semistructured interviews administered to both the adolescents and one of their caregivers. The measurement instrument we selected for assessing the primary outcome, namely the CAPS-CA-5, is considered the golden standard for measuring PTSD. In selecting the questionnaires, we aimed to select short surveys with adequate psychometric properties. If the participant provides permission, we will audiotape the semistructured interviews. A total of 2 trained psychologists will independently code a random 15% of these sessions to measure the interrater reliability. All questionnaires will be completed in Castor Electronic Data Capture [38]. The completion time of the assessments for adolescents varies from 75 to 120 minutes per assessment moment and for the caregiver from 30 to 65 minutes per assessment moment. The overall time for therapists to complete the assessments is 20 minutes. Table 2 provides an overview of the study parameters.

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Table 2. Study parameters.

Outcomes	Assessment instrument	T0[a]	BITT[b]	T1[c]	T2[d]	T3[e]	T4[f]
Demographics	—[g]	A[h], C[i]	—	—	—	—	—
Primary							
PTSD[j] symptoms	CATS-2[k]	A, C	A	A, C	A, C	A, C	A, C
Clinical diagnosis of PTSD	CAPS-CA-5[l]	A	—	A	A	A	A
Secondary							
Depression symptoms	PROMIS[m] depression	A	A	A	A	A	A
Anxiety symptoms	PROMIS anxiety	A	A	A	A	A	A
Anger symptoms	PROMIS anger	A	A	A	A	A	A
Quality of life	EQ-5D-Y-3L	A, C	A	A, C	A, C	A, C	A, C
Risk-behavior and safety	Risk behavior and safety	A	—	A	A	A	A
Parental PTSD	PCL-5[n] including LEC-5[o]	C	—	C	C	C	C
Rating of sessions and therapy	ORS[p] and SRS[q]	—	A	—	—	—	—
Qualitative							
BITT[r] experience	Qualitative interview	—	—	A, C, T[s]	A, C	—	—

[a]T0: baseline.
[b]During the BITT questionnaires are assessed daily.
[c]T1: directly after BITT or WLCG.
[d]T2: 3 months follow-up.
[e]T3: 6 months follow-up.
[f]T4: 9 months follow-up.
[g]Not applicable.
[h]A: adolescent.
[i]C: caregiver.
[j]PTSD: posttraumatic stress disorder.
[k]CATS-2: Child and Adolescent Trauma Screen.
[l]CAPS-CA-5: Clinician-Administered PTSD Scale for *DSM-5 (Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition])-Child/Adolescent Version.
[m]PROMIS: Patient-Reported Outcomes Measurement Information System.
[n]PCL-5: PTSD Checklist for *DSM-5*.
[o]LEC-5: Life Events Checklist for *DSM-5*.
[p]ORS: Child Outcome Rating Scale.
[q]SRS: Session Rating Scale.
[r]BITT: Brief Intensive Trauma Treatment.
[s]T: therapist.

Primary Outcomes

Child and Adolescent Trauma Screen

The Dutch version of the Child and Adolescent Trauma Screen 2 (CATS-2) [47,48] is a self-report and proxy-report measure for children (aged 7-18 years) and their caregivers. The questionnaire contains a list of potentially traumatic life events (16 items) and questions about PTSD symptoms (25 items; ie, re-experiencing, avoidance, emotional numbing, negative alterations in cognitions and mood, and hyperarousal). Respondents can answer each potentially traumatic life event with yes (scored as 1) or no (scored as 0). The questions about PTSD symptoms are rated on a 4-point Likert scale (range 0-3). A score of ≥2 indicates positive screening for PTSD symptoms. The highest possible total score is 60, with higher scores reflecting a higher severity of symptoms. The CATS-2 also asks informants to indicate whether the symptoms cause difficulties in daily life (yes or no). The CATS-2 has adequate psychometric properties [48].

The CAPS-CA-5

The CAPS-CA-5 [35,36,49] is used to determine the presence of PTSD based on the *DSM-5* criteria. In addition, with the CAPS-CA-5, we will collect information about the number of traumatic events and the type of experienced trauma. The CAPS-CA-5 is a 30-item structured clinical interview suitable for children aged 8-18 years. In addition, the CAPS-CA includes

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a Life Events Checklist consisting of 26 items related to stressful life events. The interviewer assesses per event if the adolescent has "experienced it," "witnessed it," "heard about it," "is not sure about it," or "never experienced it."

Afterward, the interviewer assesses the frequency and intensity of PTSD symptoms experienced in the past month using a 5-point Likert scale (range 0-4). A score of ≥2 indicates the presence of a symptom. PTSD is present when an A criterion event has occurred, when symptoms are present for more than 1 month (criterion F), when the symptoms affect the adolescent's daily life (criterion G), and when there is at least one symptom of re-experiencing (criterion B) and avoidance (criterion C) and 2 symptoms of emotional numbing, negative alterations in cognitions and mood (criterion D), and hyperarousal (criterion E). Subthreshold PTSD is present when the adolescent fully meets criteria A, F, and G and has at least one symptom of criteria B, C, D, and E, or has at least one of the B, C, D, or E symptom clusters. The highest possible total score is 80, with higher scores reflecting a greater severity of symptoms. The Dutch version of CAPS-CA-5 has adequate psychometric properties [35,49].

Secondary Outcomes

Patient-Reported Outcomes Measurement Information System

The Patient-Reported Outcomes Measurement Information System (PROMIS) [50] is a questionnaire for children aged 8-17 years and will be used to measure anxiety (8 items), depression (8 items), and anger symptoms (9 items). The questions are rated on a 5-point Likert scale (range 0-4). The highest possible total score for anxiety and depression is 32 and 36 for anger, with higher scores reflecting a higher severity of symptoms. Raw scores will be converted to *t* scores. The PROMIS anger, anxiety, and depression scales displayed sufficient psychometric properties within the Dutch population [51,52].

The EQ-5D-Y-3L

The EQ-5D-Y-3L [53] assesses the perceived quality of life in children aged 8-15 years. This questionnaire maps the quality of life based on 5 dimensions: mobility, self-care, usual activities, pain, and anxiety or depression. Both self-report and caregiver proxy versions will be used. All 5 items of the EQ-5D-Y-3L are rated on a 3-point scale, indicating levels of difficulty as "no problems," "some problems," or "a lot of problems." The highest possible total score is 15, with higher scores reflecting a higher severity of symptoms. The EQ-5D-Y-3L has adequate psychometric properties [54].

Risk-Behavior and Safety Questionnaire

We will assess risk behaviors by administering a self-report questionnaire based on previous work by Hendriks et al [25], who administered this questionnaire to children aged 12-18 years. This questionnaire assesses suicidal ideation, self-harm, and aggressive behavior with 8 items using an 11-point Likert scale, ranging from "no, not at all" (=0) to "yes, very much" (=10) [25]. Higher scores reflect a higher severity of symptoms. Alcohol use, drug use, inclination to medication, crisis contacts with mental health care professionals, and psychiatric hospitalization will be measured with 7 items on a dichotomous scale (yes or no). The psychometric properties of this instrument have not yet been examined.

PTSD Checklist for DSM-5

We will evaluate the presence and severity of the caregivers' posttraumatic stress symptoms with the Dutch version of the PTSD Checklist for *DSM-5* (PCL-5) [55] The PCL-5 is a 20-item self-report questionnaire gauging the 4 cluster symptoms of PTSD. The caregiver indicates the degree of burden caused by each symptom on a 5-point Likert scale ranging from 0 ("not at all") to 4 ("extremely"). The severity of symptoms can be determined either by adding the scores of the items within each of the four clusters or by summing all 20 items. The highest possible total score is 80, with higher scores reflecting a higher severity of symptoms. The PCL-5 has adequate psychometric properties [56].

Life Events Checklist for DSM-5

We will administer the Dutch version of the Life Events Checklist for *DSM-5* (LEC-5) [57] to assess the caregivers' exposure to trauma. This is a self-report questionnaire that consists of 17 items related to stressful life events. The caregiver will specify their experience of each event by selecting from the options "happened to me," "witnessed it," "learned about it through an affected friend or family member," "exposed through work," or "unsure or not applicable." The LEC-5 has adequate psychometric properties [58].

Outcome Rating Scale and Session Rating Scale

We will assess the adolescents' well-being after each BITT day through the Dutch version of the Child Outcome Rating Scale (ORS) [59]. Adolescents will mark their well-being on 4 visual analog scales that range from 0 to 10, providing information on their well-being ("How am I doing?"), well-being at home ("How are things at home?"), school ("How are things at school?"), and their overall sense of well-being ("How is everything going?").

We will use the Child Session Rating Scale (SRS) [60] to assess how the child experienced the BITT sessions. Respondents will be asked to rate on a visual analog scale ranging from 0 to 10 the extent to which they felt that "they were listened to," "what was done and talked about was important to them," "they liked what was done," and "hoped they would do something similar next time."

Both the ORS and SRS have adequate psychometric properties in an adult population [61].

Demographics

We will collect demographic information by asking the adolescents and one of the caregivers at baseline about: age, gender, educational level, SES, ethnicity, residency (ie, urban and rural area), and previous and current psychological or psychiatric treatment (eg, psychotherapy, trauma therapy, and medication).

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Qualitative Secondary Study Parameters: Qualitative Interview About BITT Experiences

We will conduct interviews with adolescents, caregivers, and therapists about their experience with BITT in collaboration with 2 of our experts by experience (bachelor education level). Together with the 2 experts by experience, we will develop a broad topic list about experienced benefits and possible improvements of BITT. Topics will be related to adolescents', caregivers', and therapists' preparation for and expectations of BITT, the effects of BITT, the added value of BITT compared to regular trauma therapy, and follow-up treatment. These interviews will be conducted individually with around 15 adolescents, caregivers, and therapists. In addition, we will hold focus groups with the therapists to collect their perspectives regarding BITT. We will conduct interviews 1 month after BITT. The 2 experts by experience will be closely involved in the preparation, conduction, assessment, and analyses of the qualitative interviews.

Statistical Analysis

We will conduct the analyses in consultation with a statistical expert. Data analyses will include the following:

1. We will define the effects of BITT in terms of group differences between the BITT and WLCG. These differences will be tested according to both the intention-to-treat-principle and completers' analyses. That is, the pre, post, and follow-up changes (BITT vs WLCG) on the continuous outcomes (ie, trauma symptoms, anxiety symptoms, depression symptoms, anger symptoms, quality of life, and self-harm) will be tested with mixed models; dichotomous outcomes (ie, suicide attempts and dropout) with generalized estimating equation (GEE).
2. Mixed models will also be used to investigate possible moderation effects, which concern effects of (1) age, gender, SES, type of trauma, number of traumatic events, comorbidity, caregivers' PTSD, and treatment center on PTSD; and (2) residency (ie, urban and rural) and ethnicity on BITT dropout.
3. The qualitative interviews about the experiences of adolescents, caregivers, and therapists with regard to BITT will be verbatim transcribed and analyzed to conform to qualitative research standards.

Ethics Approval

This study will be conducted in accordance with the Declaration of Helsinki. The ethics review board of the Amsterdam University Medical Center in the Netherlands approved this study (2022.0347, September 12, 2022). We will handle participant data in compliance with the General Data Protection Regulation (GDPR). All adolescents will give written informed consent, and legal guardians of adolescents aged 12-15 years will also provide consent before conducting any study procedures. All serious adverse events will be monitored and reported to the Medical Ethical Committee of the Amsterdam University Medical Center until the end of the study. In addition, during the measurements (directly, 3, 6, and 9 months after the BITT) we assess PTSD symptoms, comorbid symptoms, and risk behavior. In case of safety concerns, we contact the referring professional of the adolescent. Participants will receive a voucher of 10 euros (US $11.36) upon completing the final measurement.

Results

This project was funded in June 2021 and approved by the institutional review board in September 2022. As of September 2022, we enrolled 104 participants. Data will be collected until December 2025. Results are expected to be published in the summer of 2026.

Discussion

Anticipated Findings

This study protocol describes the design of a multicenter, single-blinded RCT with the aim of examining the effectiveness of BITT compared to a WLCG in treating PTSD among adolescents. We hypothesize that the results will demonstrate a superior effect of BITT compared to WLCG and we expect a change in PTSD and comorbid symptoms among adolescents in the BITT group, while symptoms in adolescents in the WLCG will remain unchanged. We hypothesize that BITT can be a suitable treatment option for traumatized adolescents who do not receive the available treatment options due to high treatment avoidance, those who do not experience sufficient symptom decrease after regular trauma treatment or adolescents who drop out of treatment. For this group of severely traumatized adolescents, BITT could potentially be effective. Research in the adult population already has shown positive effects of BITT on PTSD symptoms [21]. However, not much research has been conducted among children and adolescents. Pilot studies show that BITT can be a safe (ie, no increased risk of suicidality) and effective treatment for adolescents with PTSD [25,26,30,31] but RCTs into its effectiveness are lacking and urgently needed.

There are several strengths to the proposed study. First, the implementation of a single-blinded RCT with a waitlist control group provides an opportunity to assess the effectiveness of the BITT and allow each participant to engage in the BITT. This is an important benefit since adolescents who participate in the BITT experience severe PTSD symptoms and comorbid symptoms and do not benefit sufficiently from regular treatment. Engaging in the BITT might offer an effective treatment for this severely traumatized group of adolescents. An RCT is considered the golden standard in clinical research, because, unlike other research models, it controls for selection bias, time effects, effects of administering questionnaires, and chance occurrences in potential treatment effects [62]. This enables us to research the true effects of a BITT on PTSD symptoms Notably, to the best of our knowledge, this RCT represents the first of its kind conducted across multiple (cross-cultural) sites, thereby broadening the scope and generalizability of the findings [63]. In addition, applying this study in multiple centers in the world might increase the quality of care worldwide because of the trainings and supervisions by the licensed TF-CBT and EMDR supervisors at the different sites and gives us the opportunity to treat traumatized adolescents across cultures [64].

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Another strength of this study lies in the use of multiple variants of trauma-focused treatments combined with psychoeducation, psychomotor therapy, social sharing, and parental counseling. In this way, BITT incorporates several common elements from trauma-focused treatments for adolescents that are presumed to be effective [65]. Another novel element of the BITT is the therapist rotation, which seems to reduce the therapists' fear of applying trauma treatment in adolescents with PTSD and therefore contributes to a better implementation of the treatment [44]. Notably, this study is innovative since there is no research yet about a BITT for adolescents that incorporates all these important elements.

In addition, in determining the effectiveness of the treatment program, we will use multiple sources of information which improve the reliability of the results [66]. We ask adolescents to report their symptoms over time, semistructured interviews are used which also incorporate clinical judgment, and caregivers are actively engaged as informants in monitoring treatment outcomes. In addition, we conduct measurements including a 3-, 6-, and 9-month follow-up, which enables us to detect an effect of BITT over time.

Despite these strengths, possible limitations need to be acknowledged. First, although an RCT design remains the golden standard in clinical research, it comes with challenges. RCTs often operate in controlled environments with strict eligibility criteria, which may limit the external validity or applicability to diverse populations. Furthermore, participants who volunteer for the study may differ systematically from those who do not, thus affecting the generalizability of the findings. However, by conducting the study across multiple (cross-cultural) sites, each with distinct teams serving diverse target populations, we aim to achieve a diverse and representative study sample, thereby minimizing the limitations to the fullest extent possible.

Conclusions

This first, innovative study on the effectiveness of BITT may enhance treatment outcomes for PTSD in adolescents, by preventing dropout, reducing avoidance, shortening therapy duration, and empowering therapists by working together intensively. This research provides valuable insights across cultures for effective treatment of severely traumatized adolescents who do not benefit sufficiently from regular treatment.

Acknowledgments

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Data Availability

Data sharing is not applicable to this article due to the sensitivity of the data.

Authors' Contributions

MMW contributed to conceptualization, investigation, project administration, and writing—original draft preparation. MvdM was responsible for conceptualization, supervision, and writing—review and editing. RK, MdKA, MJEH, ATJ, RZ, and AAK were involved in conceptualization, project administration, and writing—review and editing. KM handled conceptualization, funding acquisition, and writing—review and editing. NA and CH managed conceptualization and writing—review and editing. FJA and KJK were responsible for conceptualization, funding acquisition, methodology, and writing—review and editing. WGS participated in conceptualization, funding acquisition, and writing—review and editing. EMWJU and RJLL contributed to conceptualization, funding acquisition, supervision, and writing—review and editing.

Conflicts of Interest

None declared.

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Abbreviations

BITT: Brief Intensive Trauma Treatment
CAPS-CA-5: Clinician-Administered PTSD Scale for *DSM-5*-Child/Adolescent Version
CATS-2: Child and Adolescent Trauma Screen 2
***DSM-5*:** *Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)*
EMDR: eye movement desensitization and reprocessing

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GDPR: General Data Protection Regulation
GEE: generalized estimating equation
LEC-5: Life Events Checklist for *DSM-5*
ORS: Outcome Rating Scale
PCL-5: PTSD Checklist for *DSM-5*
PMT: psychomotor therapy
PROMIS: Patient Reported Outcomes Measurement Information System
PTE: potentially traumatic event
PTSD: posttraumatic stress disorder
RCT: randomized controlled trial
SES: socioeconomic status
sPTSD: subclinical posttraumatic stress disorder
SRS: Session Rating Scale
TF-CBT: trauma-focused cognitive behavioral therapy
WLCG: waitlist control group

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Protocol

Effects of Traditional Chinese Exercise Yijinjing on Disability and Muscle Strength Among Patients With Chronic Low Back Pain: Protocol for a Randomized Controlled Trial

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Abstract

Background: Chronic low back pain (CLBP) is a common public health problem. Progressive loss of muscle strength leads to long-term chronic pain and disability. Yijinjing exercises, an ancient therapy dating back thousands of years, are widely used in China to treat low back pain. However, little is known about its benefits and scientific evidence for back extensor strength. This trial aimed to assess the efficacy of Yijinjing on disability and dorsal extensor strength in patients with CLBP.

Objective: We present a randomized controlled study to evaluate the efficacy of the traditional Chinese exercise Yijinjing on disability and back extensor strength in patients with CLBP.

Methods: This is a 2-arm, parallel-design, assessor-blinded, and analyst-blinded randomized controlled trial. The 106 participants with CLBP who were recruited will first receive basic traditional Chinese manual therapy to help relieve their physical discomfort. Second, they will be randomly divided into a Yijinjing group (n=53) and a control group with functional exercises (n=53) at a ratio of 1:1. The interventions for both groups will be carried out twice a week for 4 weeks. Patients in both groups will be followed up at 1 and 3 months after the intervention. The primary outcome is disability (measured by the Oswestry Disability Index). The secondary outcomes included pain intensity (assessed by the Numerical Rating Scale), data from isokinetic dynamometry, flexibility (assessed by the fingertip-to-floor test), mood (evaluated by the Pain Catastrophizing Scale and Fear Avoidance Beliefs Questionnaire), and quality of life (measured by the EQ-5D-5L). All adverse effects will be assessed using the Treatment Emerging Symptoms Scale, and data will be analyzed using an intention-to-treat analysis.

Results: The trial was funded in December 2023. The Institutional Ethics Committee of Yueyang Hospital of Integrative Medicine, Shanghai University of Traditional Chinese Medicine, approved this study. The first patient was enrolled in February 2024, and as of August 2024, a total of 106 participants have been recruited. Data analysis has not yet begun and is expected to be published in January 2025. The protocol has been registered with the Chinese Clinical Trial Registry (ChiCTR2400081105).

Conclusions: If this trial proves effective, it will guide the setup of a randomized controlled trial to demonstrate whether traditional Chinese exercise Yijinjing improves disability in patients with CLBP and is more effective than usual stretching exercises.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2400081105; https://www.chictr.org.cn/showprojEN.html?proj=214425

International Registered Report Identifier (IRRID): DERR1-10.2196/67557

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KEYWORDS

chronic low back pain; traditional Chinese exercise; Yijinjing; muscle strength; randomized controlled trial

Introduction

Chronic low back pain (CLBP, Multimedia Appendix 1) is the second most common reason for medical consultations worldwide. It leads to disability and loss of muscle strength and affects quality of life and work [1,2]. This results in a high health care burden and indirect social costs [3]. Although most patients with CLBP recover quickly with a variety of medications, including nonsteroidal anti-inflammatory drugs, muscle relaxants, and opioids, 20%-30% still fail to improve function sufficiently, endure diminished lower back muscle strength, and even experience pain recurrence or worsening [4,5]. Therefore, active research into complementary therapies for CLBP to improve function, increase muscle strength, and reduce recurrence is important.

In China, many people with CLBP voluntarily seek traditional Chinese manual therapy (TCMT). It provides short-term pain relief. However, the recurrence rate is high. This is likely because TCMT is a passive therapy with limited effects on muscle strength recovery [6]. As popular sports become more influential in society, increasing attention is being given to the impact of physical activity on mental health [7,8]. Physical activity plays an important role in CLBP [9-11]. Nonpharmacological treatments recommended for CLBP include exercise therapy, yoga, and back school [5]. Among these treatments, yoga is widely recommended for patients with CLBP, but there are many types [12,13]. It is too difficult to choose for patients with CLBP. In China, many patients with CLBP voluntarily seek Yijinjing, which has a long history as an ancient traditional Chinese exercise therapy that originated in 221 BC. It combines positive thinking with deep contemplation, fluid movement, deep breathing, and relaxation techniques to promote the circulation of vital energy (or Qi) throughout the body [14]. It is considered a multifaceted intervention that includes physical, mental, social, emotional, spiritual, and cognitive-behavioral aspects. Our previous studies demonstrated that Yijinjing can significantly reduce the disability and pain associated with osteoarthritis and increase the effects on mood and muscle strength [15,16]. However, its potential benefits for CLBP remain less well studied [17]. Therefore, if proven beneficial for CLBP, Yijinjing could provide another exercise therapy option for the large number of Chinese residents enduring CLBP.

This RCT compared Yijinjing with self-stretching exercises (SSE), such as yoga. We hypothesized that patients randomized to Yijinjing would have greater short- and long-term improvements in functional disability, back muscle strength, and other outcomes associated with CLBP compared to those randomized to stretching training. We will explore the correlation between these outcomes.

Methods

Study Design

This study is a single-center, assessor-blinded and analyst-blinded prospective randomized controlled trial with 2 parallel arms. This study was conducted in Shanghai, China, at Yueyang Hospital of Integrated Traditional Chinese and Western Medicine affiliated with Shanghai University of Traditional Chinese Medicine. All eligible participants will be recruited. First, they receive basic TCMT to help relieve their physical discomfort. Second, they will be randomly assigned to the Yijinjing and SSE groups at a 1:1 ratio after receiving TCMT. This trial protocol was approved by the Ethics Committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine affiliated with the Shanghai University of Traditional Chinese Medicine (project number 2023-203). It is registered with the Chinese Clinical Trial Registry (ChiCTR2400081105). All patients signed a written informed consent form. The intervention will be administered twice per week for 1 month. The outcome assignment and statistical analyses will be completed blindly. The trial flowchart and research design are shown in Figure 1. The protocol for this study will adhere to rigorous standards as outlined by the Declaration of Helsinki, the CONSORT (Consolidated Standards of Reporting Trials) [18], and the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) [19] guidelines. This commitment ensures the ethical and transparent conduct of our trial.

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Figure 1. Flowchart of the study procedure.

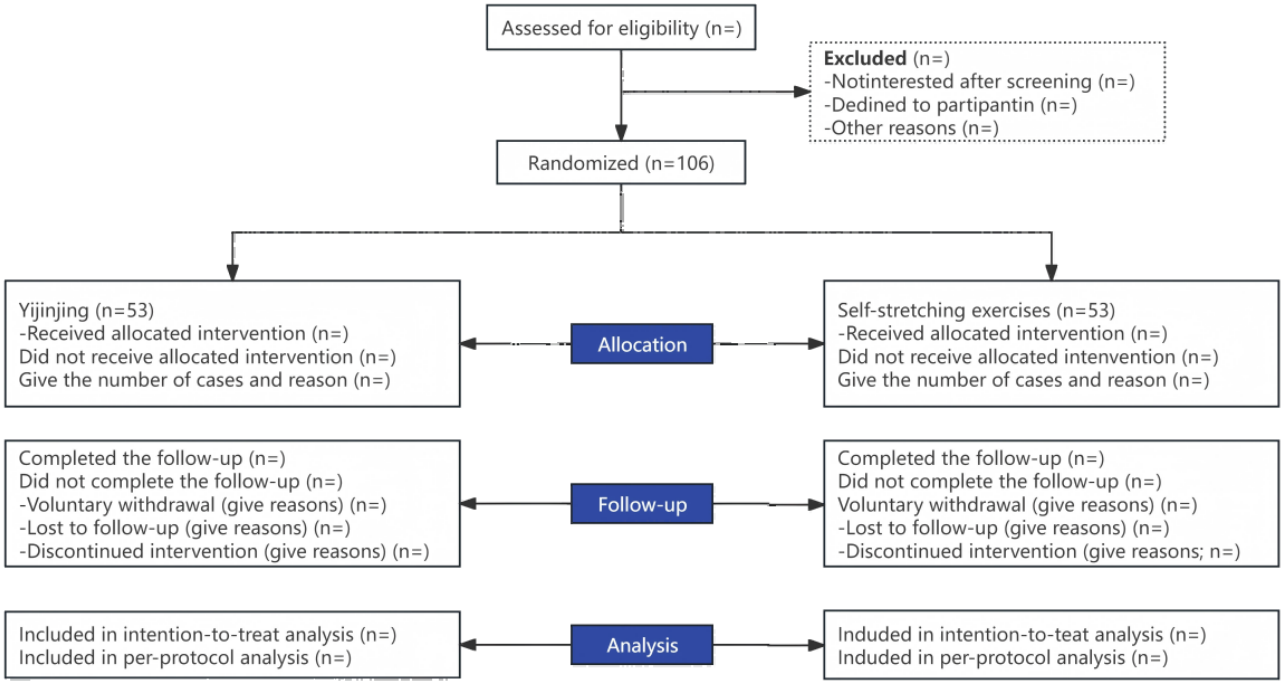

Outcome

This study will evaluate the Oswestry Disability Index (ODI), Numerical Rating Scale (NRS), Pain Catastrophizing Scale (PCS), Fear Avoidance Beliefs Questionnaire (FABQ), EQ-5D-5L, the Flexibility Test, and the muscle strength test in the fourth week of the experiment. Furthermore, the results of the ODI, NRS, PCS, FABQ, and EQ-5D-5L will be followed up at the 8th and 16th weeks. The schedule of evaluations is outlined in Table 1 (Multimedia Appendix 2).

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Table 1. Schedule of enrollment, intervention, and outcome measures.

Enrollment	Screening and allocation	Treatment period		Follow-up period	
	Week 0	Week 1-3	Week 4	Week 8	Week 16
Inclusion or exclusion criteria	✓	__[a]	—	—	—
Informed consent form	✓	—	—	—	—
Medical history	✓	—	—	—	—
Physical examination	✓	—	—	—	—
Eligibility for study	✓	—	—	—	—
Baseline characteristics	✓	—	—	—	—
C-spine x-ray	✓	—	—	—	—
Allocation	✓	—	—	—	—
Intervention	—	—	—	—	—
Yijinjing[b]	—	—	—	—	—
SSE[b,c]	—	—	—	—	—
Outcomes	—	—	—	—	—
ODI[d]	✓	—	✓	✓	✓
NRS[e]	✓	—	✓	✓	✓
PCS[f]	✓	—	✓	✓	✓
FABQ[g]	✓	—	✓	✓	✓
EQ-5D-5L	✓	—	✓	✓	✓
Flexibility test	✓	—	✓	—	—
Muscle strength test	✓	—	✓	—	—

[a]Not applicable.
[b]Two times a week from weeks 1-4.
[c]SSE: self-stretching exercises.
[d]ODI: Oswestry Disability Index.
[e]NRS: Numeric Rating Scale.
[f]PCS: Pain Catastrophizing Scale.
[g]FABQ: Fear Avoidance Beliefs Questionnaire.

Participant Recruitment

Recruitment advertisements for this trial will be posted in the outpatient clinics of Yueyang Hospital and the Traditional Chinese Manipulative Therapy Department. Additionally, we will advertise through WeChat, which is the most widely used social media platform in China, to ensure easy access to interested participants. Potential participants will contact this study's team by phone or WeChat. One of the researchers will verbally explain this study's protocol and eligibility criteria to the potential participants and assess their eligibility over the phone after they provide verbal consent. Eligible potential participants will receive participant instructions and informed consent via WeChat or email, which will allow them at least 24 hours to review the documents. If the potential participant still expressed interest in participating and met the eligibility requirements, then they were invited to attend a baseline meeting. At baseline, one of our researchers will review this study's protocol, reconfirm participant eligibility, and obtain written informed consent. Additionally, a baseline assessment will be conducted during the meeting, which will include all primary and secondary outcomes and demographic information. Thereafter, patients will be randomized.

Sample Size Calculation

The calculations are based on hypothetical changes in the ODI at week 6. We use the results of a randomized controlled trial to formulate the intended effect. We hypothesize a 3.57-point improvement on the ODI scale in the Yijinjing group compared to the control group [20]. The sample size for each group provided 90% power, and these differences were detected using PASS software (version 15.0.5; NCSS, LLC) at a 2-sided significance level of .05. Considering an expected dropout rate of 20%, a total of 106 patients are required for this study.

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Eligibility Criteria

Inclusion Criteria

The inclusion criteria are (1) the duration of CLBP is at least 3 months [21], and CLBP can be accompanied by numbness and weakness in the lower limbs; (2) computed tomography or magnetic resonance imaging showing lumbar disc herniation; (3) age between 20 and 60 years, regardless of gender; (4) NRS≥3 points and persistent low back pain (LBP) for more than 12 weeks; (5) those who have not received any other treatment regimen regarding lumbar disc herniation within the last 1 month; (6) no long-term exercise training in the last 3 months, including swimming, jogging, and yoga; and (7) voluntarily participate in this trial and sign an informed consent form.

Exclusion Criteria

The exclusion criteria are (1) combined with other major lumbar diseases, such as tumors and tuberculosis; (2) history of spinal surgery within 1 year; (3) those who are scheduled to undergo lumbar surgery in the next 3 months or who have plans to go out for a long period; (4) patients with severe mental system disorders (eg, schizophrenia, bipolar disorder, and major depression); and (5) pregnant or lactating women.

Randomization

This trial used computer-generated block randomization with a fixed block size of 6 to ensure balanced group allocation. The intervention is unified after the block is full. Randomization sequences were securely stored in sequentially numbered, opaque, sealed envelopes to maintain allocation concealment. These envelopes were managed by an independent staff member not involved in trial procedures or participant assessments. Envelopes were opened sequentially after participant enrollment was formally confirmed, strictly following the order of study identification numbers assigned at recruitment. Each enrolled participant received a unique study identifier linked to their randomization group, ensuring traceability while preserving blinding integrity throughout this trial.

Blinding

Participants and therapists will not be blinded due to differences in treatment methods. Assessors, data managers, and analysts will not be aware of the group assignments in the outcome evaluation process and data analysis to reduce the risk of bias.

Interventions

In Chinese hospitals, manipulative therapy interventions are the first choice for patients with CLBP; therefore, manipulative therapy was chosen as the basic treatment protocol before randomization. It is administered by licensed doctors who have a minimum of 5 years of clinical experience in treating LBP. They have extensive experience in practicing manipulative therapy. In a previous study [22-24], we provided a detailed description of the manipulative therapy technique applied to CLBP. A similar technique will be used in this trial. A complete manipulative therapy intervention will have a duration of 15 minutes. Specifically, kneading and rolling techniques will be used to relax the muscles in the patient's lower back. Palm root pressure was applied to the lower back muscles of patients with LBP, and pressure was applied along the erector spinae muscle from top to bottom. The pressure was applied for 10 minutes, 80-100 times per minute.

Once all patients were enrolled, baseline data were collected, and baseline information such as disease and age was recorded on the envelope to eliminate baseline imbalance and other factors in the randomization of blocks. After the manipulative therapy, all the patients will be randomly divided into 2 groups. Participants will receive 2 treatments every week for a total of 4 weeks. The teacher must pass clinical tests to ensure consistency in every treatment for all patients. At the same time, the participants may continue to take their usual pain relief medication, such as nonsteroidal anti-inflammatory drugs. Changes in dosage should be recorded on the case report form (CRF).

Yijinjing Group

The participants in the Yijinjing exercise group will receive 4 weeks of Yijinjing exercise intervention. The course includes the instruction of a 5-step program, involving details such as the breathing rate, meditation method, extension rotation angle, and how to use your back muscles. Each session consisted of a warm-up for 5 minutes, 20 minutes of Yijinjing exercises, and 5 minutes of calming activities. The specific action characteristics are shown in Figure 2 and Table 2 (Multimedia Appendix 3) [25]. During the first week, the instructor guided the participants throughout the entire process, introducing the details and confusion to ensure that the correct exercise routine was followed. The teacher will provide ongoing support and supervision by videoconferencing. Participants were asked to record the time spent practicing in a punch card booklet, which was to be shown to the tutor. At the end of this trial, the participants were asked to return the booklet to the tutor so that the number of exercises could be counted.

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Figure 2. All movements of the 5-step program.

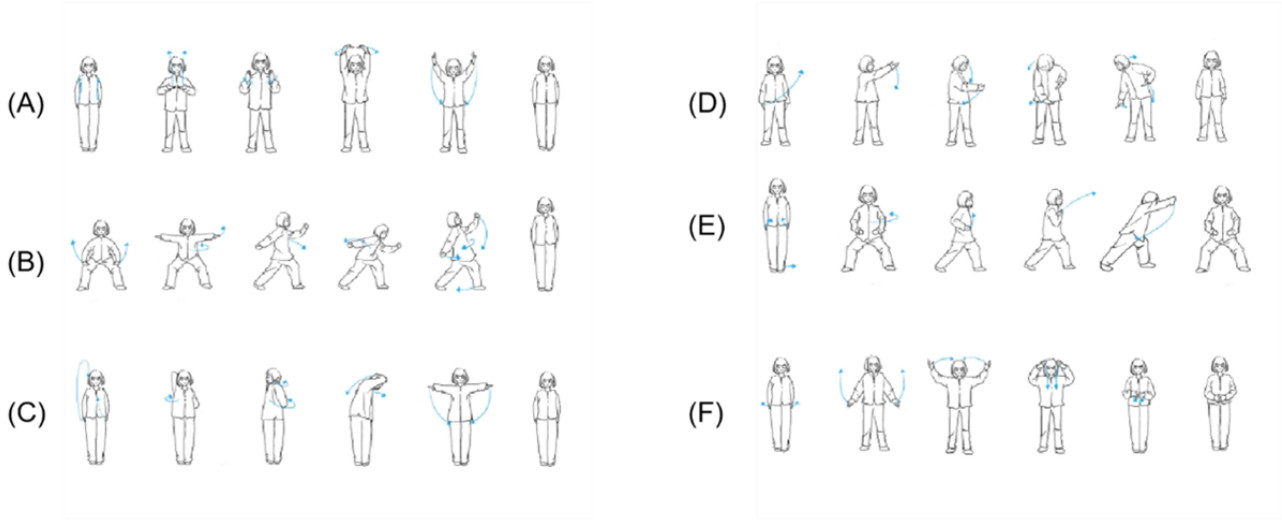

Table 2. Details of the operation of the Yijinjing exercise. Specific information can be viewed on the Web [25].

Sequence of actions	Action details
Step 1: Resting the palm over the head	Take a step to the left. Raise your hands before your chest with palms up and fingertips facing. Rotate your wrists and raise your palms above your head. Slightly bend your elbow and look upward toward the dorsum of your palm. Lift your heels and stand on your toes. Hold for 5 s. Then, make fists, rotate your wrists, and slowly lower your fists to waist level. Place your whole feet on the ground. Repeat the entire procedure 3 times.
Step 2: Dragging the tail of a 9-cow ox backward	Begin by stepping sideways to the left with your left foot, while internally rotating both feet and slightly bending your knees and hips into a squatting position. Clench your fists and gradually lift them toward your chest. Extend your arms outward until they form a straight line on each side of your body. Rotate your torso to the left while lowering into a lunge position with your left leg bent and your right leg straight. Externally rotate your left forearm and flex your elbow to create a semicircular shape in front of your chest. Simultaneously, internally rotate your right forearm and extend it behind you. Keep your right elbow naturally extended and slightly backward at approximately 30°. Lastly, relax and repeat the sequence on the right side. This exercise should be performed symmetrically on both sides.
Step 3: Nine demons drawing their swords	Step to the left while crossing your hands over your chest and lifting them upward. Separate your hands above your head. With your left hand placed on your neck and your right hand on your back, tilt your head to the left at a 45° angle and twist your waist. Exhale while tightening your hands. Maintain this position for 5 s. Next, lower your hands to both sides of your body and relax as you exhale. Repeat the exercise on the right side.
Step 4: The green dragon probing the claws	Step your left foot sideways to the left while ensuring your feet are shoulder-width apart. Raise both palms upward to waist level while keeping your gaze forward. Extend your left palm diagonally forward and upward and reach above your head while simultaneously rotating your body to the right. Keep your right palm positioned by your waist on the right side to maintain stability. Internally rotate your left arm while turning your palm downward, and bend your torso from the right side while leaning toward the outer edge of your right foot. As you rotate your body to the left, trace a semicircle with your arm in front of your body. Inhale deeply as you gradually straighten your torso while lifting your hands from the right side and retracting them toward your body.
Step 5: A hungry tiger pouncing on its food	Start by positioning your feet shoulder-width apart. Rotate both feet to the left while turning your body in the same direction. Keep your palms facing upward as you lift both hands together until they reach chest level. Rotate your hands outward and lean your body forward while extending your hands forward with force. Arch your back forcefully and bend the front leg while straightening the back leg. Relax your arms, then turn your hands back into fists and slowly bring them down to the sides of your waist. Repeat this movement.
Step 6: Finishing moves	Open your feet as wide as your shoulders. Inhale and open your hands and raise them slowly above your head. Flip your palms. Exhale and press your hands downward and stop at your abdomen. Drop your hands down. Return to the initial preparation position.

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About SSE

Through graphic media, videos, and personal dialogue, participants received detailed explanations of biopsychosocial knowledge related to LBP. The educational content will aim to better understand pain, promote healthy work and lifestyle habits, and encourage moderate physical activity. These educational initiatives will continue throughout the intervention. This study will reference the previously validated SSE program used in published research for its effectiveness in treating a specific population with CLBP [26]. The therapist provided verbal cues and instructions for the stretching postures. Participants were instructed to engage in a warm-up for 5 minutes before the session, 20 minutes of SSE exercises, and a cool-down for 5 minutes afterward. Throughout the sustained stretching phase, participants were encouraged to advance each posture at their own pace. The primary goal was to achieve full back extension and maximum ankle dorsiflexion in each posture. Some postures targeted maximal back muscle abduction, while others focused on back muscle adduction. Participants were also advised to reduce the arching of their lower back (maintaining contact with the surface). Proper breathing techniques were emphasized during all postures, with participants instructed to inhale deeply through the nose, expanding the lower ribcage during inhalation. Exhalation involved lowering the chest and allowing the abdomen to expand. The specific action characteristics are shown in Figure 3 (Multimedia Appendix 4).

Figure 3. SSE protocol. SSE: self-stretching exercises.

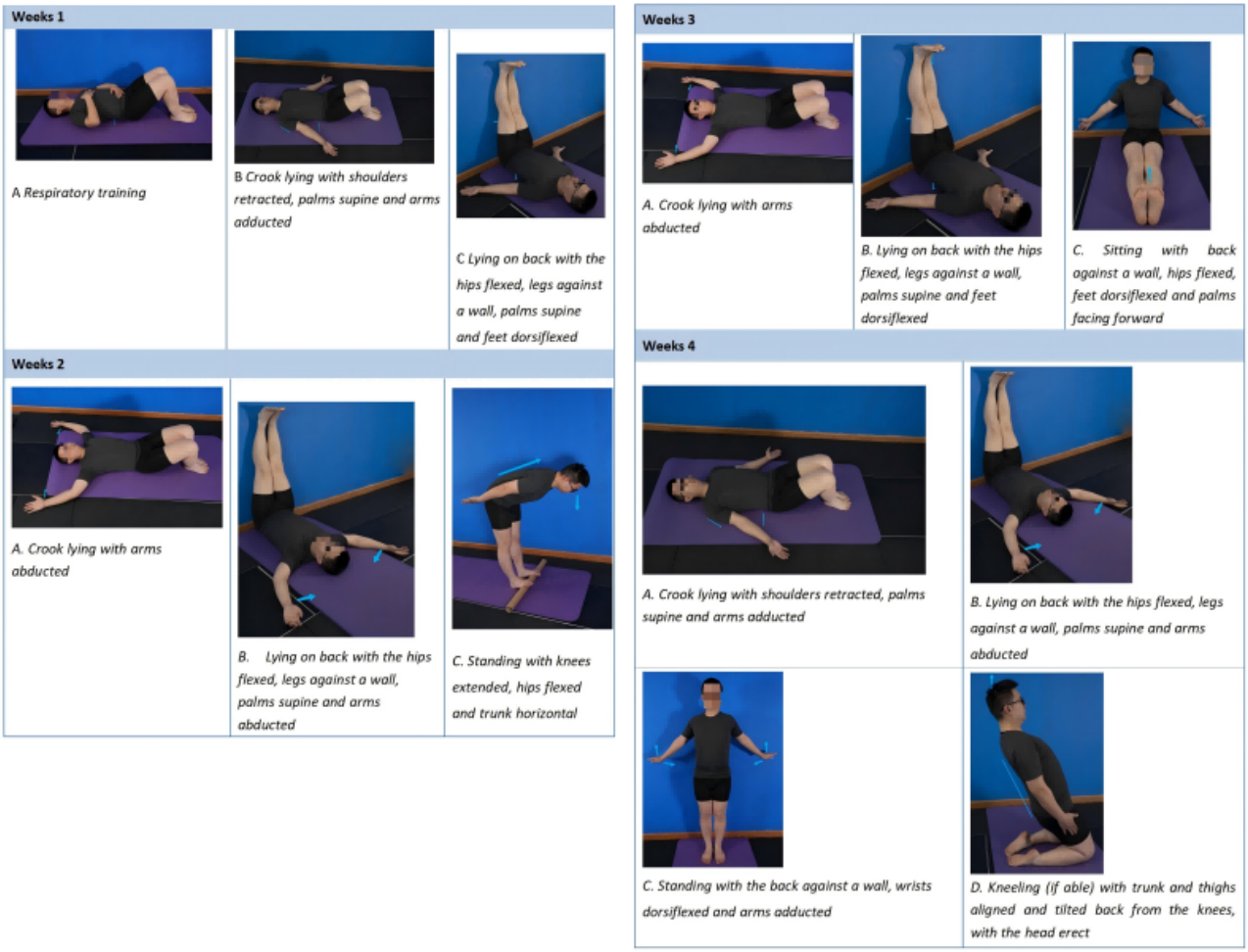

Primary Outcome

The ODI is a disability questionnaire specific to the disease that consists of 10 items (scoring between 0 and 100) [27]. It is among the most frequently used in populations with LBP and is a fundamental measure of outcomes suggested for assessing disability related to pain in this group of patients. The validity, reliability, and responsiveness of the ODI have been demonstrated for individuals with LBP [28].

Secondary Outcome

About NRS

The outcome was pain intensity, which was measured on an 11-point NRS (a score of 0 indicates no pain; 10 indicates the worst pain imaginable) 4, 8, and 16 weeks after the intervention [29,30].

Measures of Muscle Strength

The maximal voluntary muscle strength of the extensor and flexor muscles will be measured by isokinetic dynamometry at angular velocities of 90 and 120 deg/s (Biodex System 4 Pro, Biodex Medical System) at baseline and during week 4. Subjects

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were advised to wear comfortable, loose-fitting clothing on the day of testing. Both the thighs and the backs of the subjects were fixed to the testing chair using straps. The axis of the dynamometer was located on the anterior superior iliac spine of the pelvis of the patient. During the formal test, each patient will be required to fold their arms across their chest and be given verbal encouragement in an attempt to achieve a maximum level of effort. Angular velocities of 90 and 120 deg/s will be applied to 2 sets of 5 maximal waist extensions and flexions with a rest interval of 30 seconds between sets [31]. The Biodex isokinetic muscle strength test method is shown in Figure 4.

Figure 4. Biodex isokinetic muscle strength schematic diagram of the test method.

About PCS

The PCS will be used for the assessment of catastrophizing thinking associated with chronic pain. It comprises 13 self-report items, and individual perception determines the total score, which ranges from 0 (indicating no catastrophizing) to 52 (indicating extremely severe catastrophizing). The PCS has demonstrated significant clinical acceptance, good construct validity, excellent internal consistency, and test-retest reliability [32,33].

About FABQ

The FABQ consists of 16 items, with items 1-5 measuring how fear avoidance beliefs about physical activity affect LBP and items 6-16 measuring how fear avoidance beliefs about work affect LBP, with each item rated on a scale of 0-6 (from “strongly disagree” to “strongly agree”) [34]. The FABQ has demonstrated robust psychometric properties, and its cross-cultural validity has been confirmed [35].

About EQ-5D-5L

The 5-level EQ-5D-5L Questionnaire will be used to evaluate health-related quality of life [36]. It encompasses 5 dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each dimension consists of 5 levels, which correspond to different points. Additionally, the EQ-5D-5L includes a visual analogue scale ranging from 0 (representing the worst imaginable health) to 100 (representing the best imaginable health) [37].

Flexibility

The fingertip-to-floor test is a global stretching assessment that was described and validated by Perret et al [38]. The participant stood barefoot on a 20 cm-high platform with their feet together, and the torso was bent forward as much as possible while the knees, arms, and fingers were extended for the test. The vertical distance between the tip of the middle finger and the platform should be measured with a flexible measuring tape, and the measurement is expressed in centimeters. A test was considered positive when the tip of the middle finger did not reach the platform and negative when it passed through the platform. This test has good psychometric properties [39]. The minimum clinically important difference has not been established, but the minimum detectable change for this test was 4.5 cm.

Dosage of Pain-Relieving Medication

The participants may continue to take their usual pain relief medication, such as nonsteroidal anti-inflammatory drugs. Changes in dosage should be recorded on the CRF. Dose diaries are notebooks in which participants record their daily dose of pain medication as well as the duration of the dose. The researcher does not recommend any changes in the medical regimen.

Data Collection and Monitoring

The data collectors, who are blinded to the subgroups and not involved in other aspects of this study, will accurately record all the data collected into the CRF. Upon completion of this trial, the CRF will be handed over to 2 professional data workers who are also blinded to allocation and who are not involved in other parts of this study. The 2 data workers independently extract the data from the CRF into Excel (Microsoft Corp) and verify the accuracy of the data. All electronic data will be stored on a password-protected server, while all paper data will be kept in a locked filing cabinet. Additionally, deidentified data will be stored separately from the files and filing cabinets containing participant details and trial identification numbers. An electronic data capture system will also be used throughout this study to record any traces of data entry or modification. The Department of Information Science and the Clinical Research Centre of Yueyang Hospital, Shanghai University of Traditional Chinese Medicine, will provide the electronic data

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capture platform and will oversee the entire process of study data collection and management. They will review this study's data every 6 months to ensure the quality of this study and the reliability of the data.

Statistical Analysis

In this study, the principle of intentionality analysis will be used to analyze the data. The safety analysis set will be used to analyze the safety of this study. A statistician who is unaware of the group assignments will use SPSS statistical software (version 26.0; IBM Corp) to analyze the data. All effects will be estimated using 95% CIs, and all the statistical tests will be 2-sided. A *P* value less than .05 indicated statistical significance.

Continuous variables are presented as the mean (SD) if they follow a normal distribution; otherwise, they are presented as medians and quartiles. Categorical variables are presented as percentages. Primary outcomes will be assessed using analysis of covariance adjusted for baseline. For other secondary outcomes, *t*-tests or Wilcoxon rank-sum tests will be used.

Repeated outcomes over time will be compared using linear mixed-effects models with the following fixed effects: (1) time points (categorical), (2) intervention group, (3) time-by-group interaction, and (4) baseline measurement as a covariate. Random intercepts for participant ID will be included to account for within-subject correlations. Additional adjustments will be made for prespecified covariates, including age, gender, and study site (if multicenter). Bonferroni correction was used for multiple comparisons across time points.

Missing data will be replaced according to the principle of carry-over of last observations. Missing values for dropout cases will be imputed using either the last observation carried forward method if the dropout rate is below 5% or the multiple imputation method for a dropout rate of 5% or higher. If the attrition rate exceeds 10%, we use per-protocol analysis to ensure the reliability of this study.

Research Security and Quality Control

Quality control will be conducted during this trial under the management of the steering committee. Before researchers participate in this trial, professional trial methods and regular monitoring techniques should be used to ensure the consistency of the methods. If this study protocol is modified or corrected, then the steering committee and ethics committee should be informed. Quality control will be performed during this trial under the management of the steering committee. Researchers should be trained in specialized test methods and routine monitoring techniques before participating in this trial to ensure consistency of the approach. The Steering Committee and Ethics Committee were informed of any modifications or corrections to this study's protocol. During this study, a booklet was given to each patient, and patients were asked to record the time and number of exercises per day.

The Ethics Committee of Yueyang Hospital of Integrative Medicine, Shanghai University of Traditional Chinese Medicine, will be responsible for the safety and quality control of this study. They may suggest changes in this study's design to protect the participants, and the principal investigator will make the final decision. All the participants must sign the informed consent form before enrollment.

The following adverse events may occur in this trial. If participants report severe pain during treatment and follow-up and have a visual analog scale score greater than 8, they will be allowed to return to the hospital for another visit. This visit will be recorded in the CRF. If anything out of the expected range occurs, the therapist must report it to the investigator within 24 hours of the event, and the investigator will report it to the Safety and Treatment Monitoring Committee for recording.

Ethical Considerations

This study has been approved by the Medical Ethics Committee of Yueyang Hospital of Integrated Traditional Chinese and Western Medicine affiliated with Shanghai University of Traditional Chinese Medicine (2023-203), and will be conducted per the guidelines and regulations approved by the participating institution. This trial is being conducted based on a protocol registered with the China National Clinical Trial Registry. Informed consent forms were obtained from all patients before enrollment in this study. Participation is voluntary, based on the patients' wishes, and therefore, this study can be stopped at any time. All records containing names or other personal identifiers are stored separately from the research records identified by code numbers. Participants cannot be identified from any images in this paper or supplementary materials. The intervention method does not incur additional costs for participants; therefore, no compensation is required.

Results

Our protocol has been successfully approved by the institutional review board of Yueyang Integrated Traditional Chinese and Western Medicine Hospital affiliated with Shanghai University of Traditional Chinese Medicine, obtaining ethical approval in December 2023, and registered with the Chinese Clinical Trial Registry (ChiCTR2400081105). As of August 2024, we have recruited 106 participants. Data analysis has not yet begun and is expected to be published in January 2025. At the time of submission, recruitment for this trial started. The first participant was included on February 20, 2024.

Discussion

Principal Findings

This study aims to provide critical evidence to support the therapeutic efficacy of Yijinjing intervention for CLBP. There is a lack of high-quality clinical trials on the effects of Yijinjing in CLBP, although we found some clinical evidence of this approach in patients, we hypothesize that a 12-week Yijinjing regimen will yield clinically meaningful improvements in functional disability, lumbar muscle strength, and pain intensity, with durable therapeutic effects persisting through a 3-month follow-up period. Crucially, concurrent improvements in emotional distress measures and lumbar flexibility would suggest that Yijinjing confers multidimensional benefits extending beyond biomechanical adaptations—a finding that could redefine its role as a holistic intervention addressing both

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somatic and psychosocial dimensions of CLBP. While existing literature substantiates the moderate efficacy of exercise therapies in CLBP management [40], Yijinjing's distinctive focus on graded neuromuscular control and dynamic muscular equilibrium [41] differentiates it from conventional strength training paradigms, potentially offering unique mechanistic advantages.

This study's strengths include multidimensional outcome assessment (functional, physiological, and psychological domains) and longitudinal follow-up. However, 3 limitations warrant acknowledgment: first, inherent challenges in participant blinding for behavioral interventions may introduce expectation bias in self-reported outcomes, though objective biomechanical measurements partially mitigate this concern. Second, the single-center recruitment strategy may constrain population generalizability. Third, while the pragmatic 30-minute intervention protocol enhances clinical translatability, it precludes exploration of dose-response relationships relative to extended regimens.

In conclusion, this trial will systematically evaluate Yijinjing's efficacy and safety profile in CLBP management. Its findings may inform clinical guidelines for integrating traditional mind-body exercises into contemporary pain rehabilitation frameworks. Nevertheless, given the constrained intervention duration inherent to this design, subsequent investigations should prioritize extended treatment phases and prolonged follow-up windows to elucidate long-term outcomes and potential decay patterns of therapeutic benefits.

Acknowledgments

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Authors' Contributions

LG collects and manages data and writing, and has made major contributions. CW, MF, and JXL designed, studied, and revised the main paper. XB, YT, and MS analyzed and interpreted the data. All the authors approved this paper. As guarantors, JL and QZ are responsible for the overall content.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Abbreviations.
[DOCX File , 13 KB - resprot_v14i1e67557_app1.docx]

Multimedia Appendix 2
Schedule of enrollment, intervention, and outcome measures.
[DOCX File , 16 KB - resprot_v14i1e67557_app2.docx]

Multimedia Appendix 3
Details of the operation of Yijinjing exercise.
[DOCX File , 15 KB - resprot_v14i1e67557_app3.docx]

Multimedia Appendix 4
Self-stretching exercises (SSE) protocol.
[DOCX File , 2089 KB - resprot_v14i1e67557_app4.docx]

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Abbreviations

CLBP: chronic low back pain
CONSORT: Consolidated Standards of Reporting Trials
CRF: case report form

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FABQ: Fear Avoidance Beliefs Questionnaire
LBP: low back pain
NRS: Numerical Rating Scale
ODI: Oswestry Disability Index
PCS: Pain Catastrophizing Scale
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SSE: self-stretching exercise
TCMT: traditional Chinese manual therapy

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Protocol

Metabolic Flexibility to Predict Lifestyle Interventions Outcomes (MEPHISTO): Protocol for Predictive Validation Study and Randomized Controlled Trial

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Abstract

Background: Weight loss is a cornerstone of obesity treatment and diabetes mellitus type 2 (T2D) prevention, but its implementation in clinical practice is limited by its perceived burden and variability in response. Personalizing interventions to increase their success rate is an unmet clinical need.

Objective: Identification of predictive factors associated with successful weight loss after sequential exercise in women with obesity.

Methods: The study will consist of a 2-stage analytical approach, including a predictive validation study and a 2:1 randomized cross-over controlled trial. Women aged 25-45 years with obesity (BMI>30) will be included in the study. The intervention will consist of a progressive protocol of aerobic exercise on a treadmill and a bicycle ergometer. We will measure weight loss in terms of fat mass (FM) and fat-free mass (FFM), metabolic flexibility (MetFlex) as ΔRQ (change in respiratory quotient (VCO2/VO2) between basal and insulin-stimulated state during glucose clamp), insulin sensitivity, glucose tolerance, hemoglobin A_{1c}, microbiome composition, and metabolomic signatures.

Results: Recruitment for the trial began in January 2024. A total of 12 participants were enrolled and randomized. Among them 6 participants have completed the first phase of the A-arm and 6 participants have completed the control period of the B-arm and their intervention is ongoing. Recruitment is ongoing. We expect the preliminary data from this study to be completed in 2026.

Conclusions: This intervention will investigate whether whole body and gut MetFlex can be further explored and used as ex ante predictors of successful weight loss following exercise intervention, providing proof of concept and paving the way for personalized lifestyle interventions.

Trial Registration: ClinicalTrials.gov NCT06329349; https://clinicaltrials.gov/study/NCT06329349

International Registered Report Identifier (IRRID): DERR1-10.2196/67570

(JMIR Res Protoc 2025;14:e67570) doi:10.2196/67570

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KEYWORDS

obesity; overweight; weight loss; physical activity; exercise; gut microbiota; metabolic flexibility; diabetes; endocrinology; validation study; randomized control trial; protocol

Introduction

Obesity has reached pandemic proportions and is a major risk factor for type 2 diabetes (T2D), cardiovascular disease, and other metabolic disorders. Prevention progression to T2D in individuals with obesity through effective lifestyle interventions is a public health priority Substantial and sustained weight loss achieved through lifestyle modifications is a key strategy to reduce the risk of T2D and improve metabolic health [1,2]. The most effective lifestyle interventions aim to achieve a negative net energy balance through two key principles: increasing physical activity and reducing caloric intake. The health benefits associated with regular physical activity are closely linked to the systemic adaptive responses elicited by each training session [3]. Similarly, the beneficial effects of weight loss induced by hypocaloric diets depend on complex adipose tissue remodeling [4]. However, detailed analysis of clinical trial data reveals substantial interindividual variability in responses to these interventions, leading to differences in their effectiveness and health benefits [5,6].

This highlights the need for more personalized lifestyle interventions tailored to individual phenotypes. Recent studies have emphasized phenotype-based interventions as a promising strategy [7,8], particularly focusing on behavioral phenotypes and maladaptive eating patterns in patients with obesity. However, the physiological determinants that may influence weight loss success remain underexplored.

Among the influential determinants that affect the effectiveness and health outcomes of an intervention is an individual's level of metabolic flexibility (MetFlex). MetFlex refers to the body's ability to adapt in response to changes in metabolic demands and nutrient availability [9]. Impaired MetFlex is a hallmark of obesity and T2D but can be improved by lifestyle interventions such as exercise training or caloric restriction [9-11], similar to improvements in insulin sensitivity. Despite this, MetFlex has not been systematically investigated as a potential mechanism underlying successful weight loss. Impaired MetFlex, that is the limited ability of cells or tissues to cope with excess or deficiency of energy substrates, leads to impaired mitochondrial function and excessive lipid accumulation in ectopic tissues, resulting in metabolic disorders such as T2D or metabolic syndrome.

Another potential predictor of an individual's ability to respond to lifestyle interventions is the gut microbiota (gut microbiome and metabolome [MIME]). It has repeatedly been shown to be one of the most important sources of interindividual variability in the development of obesity [12] and also responsiveness to weight loss interventions [13]. The microbiome not only influences host physiology directly, for example through contact with immune cells, but also through the large number of metabolites produced, that is, the microbiota-derived metabolome [14]. The composition of the gut microbiota and the microbiota-derived metabolome is largely determined by the host's diet, which is the main source of nutrients and energy for the microbiota [15]. It is therefore striking that published studies to date have yielded rather inconsistent results regarding dietary interventions to alter gut microbiota composition [16]. This discrepancy can be explained by the large variability of individual microbiomes at the start of the intervention, and also by the fact that the baseline MIME signature is a significant determinant of weight loss success.

Here we propose a comprehensive project MEPHISTO (MEtabolic flexibility to Predict Health lIfeSTyle intervention Outcomes) to investigate whether whole-body and gut MetFlex can be further explored and used as ex ante predictors of successful weight loss following exercise intervention. By identifying key physiological and microbial signatures, this research aims to provide a basis for personalized obesity treatment strategies, ultimately improving diabetes prevention efforts.

Methods

Design

A randomized, cross-over, controlled clinical trial will be conducted at Charles University in Prague, Czech Republic. The study will consist of a two-stage analytical approach that will be used to obtain specific results:

1. The first stage is a predictive validation study where we will compare changes in fat mass (FM)/ fat-free mass (FFM) weight loss (after an intervention - predictor variable) with baseline characteristics (independent variable) in the whole sample (n=40). The expected results are the identification of baseline characteristics associated with total and FM/FFM weight loss after the intervention.

2. The second phase is a 2:1 randomized cross-over control trial where we will investigate the effects of the progressive aerobic exercise intervention protocol on MetFlex, metabolic adaptation, and insulin sensitivity. As an exploratory outcome, the fecal metabolomic response will be analyzed.

Participants

Women aged 25-45 years with obesity (BMI>30) are included in the study. Only female participants were selected to reduce heterogeneity, as MetFlex and energy metabolism are sex-dependent and to improve statistical power in a small sample. This selection aligns with previous studies at our research center and will allow for future data pooling. Practical considerations, including shared facilities and standardized protocols, also supported this decision.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria are mentioned in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

Participants who meet the following criteria will be eligible for the study:

- BMI>30
- Age 25-45 years

Exclusion criteria

- Active cancer
- Diabetes (medical history, fasting glycemia >7.6, and glycemia of >11.1 on the 2-hour oral glucose tolerance test)
- Uncontrolled endocrine diseases
- Corticosteroid therapy
- Immune-suppressive therapy
- Pregnancy
- Breastfeeding

Recruitment Process

Potential volunteers will be recruited from outpatients and previous research participants at the Department of Internal Medicine, University Hospital Kralovské Vinohrady, Prague, or through social media advertising via the university and hospital platforms. Our research participant network is only used to advertise studies, and individuals who have previously participated in interventional trials will not be included. In addition, patients from the Obesitology Centre will be considered only before their enrollment in clinical interventional programs to prevent previous interventions from influencing study outcomes.

Allocation

After screening for eligibility, a baseline clinical examination will be performed to assess the inclusion and exclusion criteria and to ensure weight stability for 12 weeks before enrollment. Participants will then be randomized by an independent investigator to either exercise intervention arm A or exercise intervention and control arm B using a computer-generated random number table.

After the baseline visit 1 examination, the A-arm will undergo 12 weeks of a progressive aerobic exercise intervention protocol, after which the clinical examination will be repeated. Participants in the B-arm will be assessed after 12 weeks of no intervention and then crossed over to the exercise intervention, after which the final clinical assessment will be carried out (Figure 1).

Figure 1. Enrollment, intervention, and evaluation project schedule.

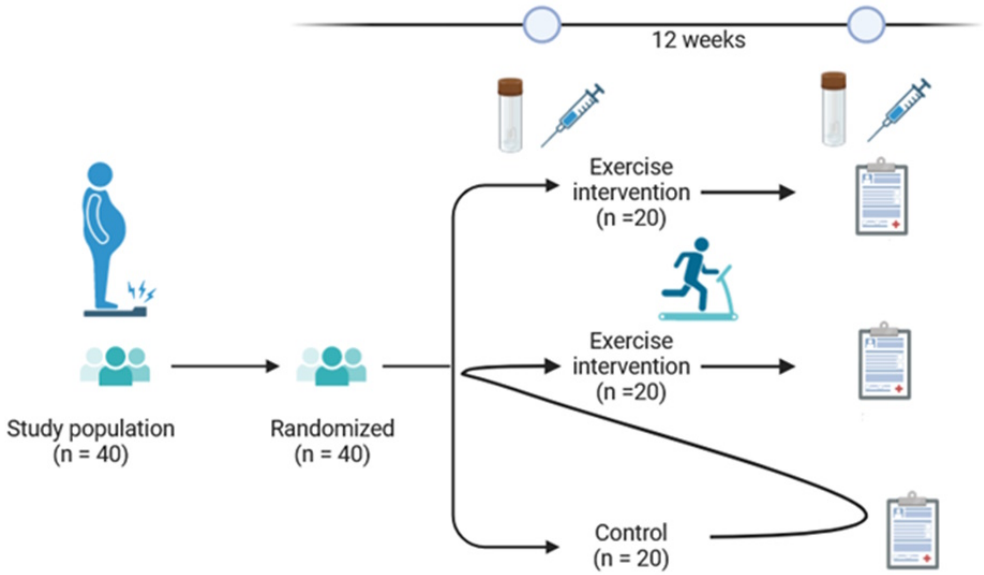

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Intervention

The exercise intervention is designed according to the 2021 European Association for the Study of Obesity (EASO) guidelines to maximize the effect of reducing body weight and adipose tissue [17]. These guidelines recommend 150 to 200 minutes of at least moderate-intensity aerobic exercise (Grade A). The exercise intervention will last 12 weeks, during which the study participants will perform aerobic endurance exercise 3 times a week in groups of 6 people under supervision.

The exercise will be performed as fast walking on a treadmill. The duration and intensity of the exercise will be controlled so that the energy expenditure per unit of exercise is 150 kcal in the first week, increasing by 50 kcal each week thereafter until week 6 when it reaches 400 kcal, a level that will be maintained until the end of the intervention [18]. The walking pace will be adjusted individually, based on input of indirect calorimetry, to correspond to moderate intensity physical activity (metabolic equivalent of task 3 to 6) and to achieve the required energy expenditure in the given time. A progressive increase in energy expenditure during the intervention will be therefore ensured by an appropriate combination of increasing intensity and duration of exercise. For this reason, the duration of each session will be individual, for example, 30 minutes of walking at a speed of 5 km/hour corresponds to approximately 180 kcal for a person weighing 95 kg [19].

During the intervention, participants' compliance will be strictly monitored: if a session is missed, it will be made up as soon as possible. If more than one session is missed (eg, due to illness), the intervention will be extended to make up for the missed sessions, but not more than 2 weeks. Only participants who complete at least 90% of the training sessions will be included in the analysis (so they can skip a maximum of 3 sessions).

Primary Outcome Measures

Stage 1: the relationship between FM/FFM weight loss and baseline characteristics of MetFlex, calculated as the change in respiratory quotient (ΔRQ).

Stage 2: change in MetFlex, defined as the ΔRQ between basal and insulin-stimulated state during glucose clamp examination, and change in insulin sensitivity (glucose infusion rate).

Secondary Outcome Measures

Changes in glucose tolerance (glucose level on the 2-hour oral glucose tolerance test), hemoglobin A_{1c}, and insulin sensitivity (glucose infusion rate) following the intervention will be evaluated following the intervention.

Exploratory Outcome Measures

Changes in microbiome composition and metabolomic signatures will also be assessed following the intervention.

Data Collection

Anthropometry

The anthropometric measures used were weight, height, bioimpedance analysis (TANITA MC-980U Plus Multi-Frequency Segmental Body Composition Analyzer, manufacturer, state), DXA (Hologic's Horizon DXA Platform), and plethysmography (BOD POD's Air Displacement Plethysmography Cosmed).

Indirect Calorimetry

The resting gas exchange will be measured using a canopy hood ventilated system with a metabolic cart (Quark RMR, Cosmed). Standard air, gas, and flow calibrations will be performed before each measurement. Important deviations may limit the reliability of measurements, to correct for this postcalorimetric simulation with high-precision mass flow regulators (EL-Flow Prestige, Bronkhorst high-tech B.V., NL) will be done after each measurement with a defined gas mixture. VO_2, VCO_2, and nitrogen loss per 24 hours will be used to calculate basal substrate utilization of carbohydrates, fat, and protein.

Oral Glucose Tolerance Test

A standard 75 g oral glucose tolerance test will be performed with blood sampling at 0, 30, 60, 90, and 120 minutes. The test will assess dynamic changes in substrate metabolism, including ΔRQ shifts over time (120–60–0 min) and changes in circulating free fatty acids (ΔFFA), glucose, and insulin levels in response to the glucose load.

Hyperinsulinemic-Euglycemic Clamp

A 2-step hyperinsulinemic-euglycemic clamp will be conducted over 200 minutes, with insulin infusion rates of 10 and 40 mIU/m², each maintained for 100 minutes. This will be followed by a 100-minute tapering period of glucose infusion after insulin discontinuation. The primary outcomes will include ΔRQ (at 300–250–200–100–0 min), free fatty acid suppression (ΔFFA), and glucose infusion rate (ΔGIR) as markers of insulin sensitivity and MetFlex.

Maximal Oxygen Uptake Test

A graded maximal exercise test will be performed on a bicycle ergometer (Ergoline GmbH) using a ramp protocol with an incremental workload increase of 15 W/min. Gas exchange parameters will be measured continuously via spiroergometry (Quark RMR), and electrocardiogram monitoring will be conducted throughout the test. The primary outcomes (maximal oxygen uptake [VO_2 max], heart rate, and peak power output), will be used to individualize the exercise intervention protocol.

Diet Record

Each participant will provide a 3-day diet record before the intervention or control period, once during the period, and then after the completion of the intervention or control. Nutrixo (Arcai Health) software with validated food composition databases will be used to calculate dietary intakes.

Metagenomics Analysis of Gut Microbiota

The microorganism populations present in the stool samples will be assessed by shallow shotgun sequencing using NovaSeq ox NextSeq Illumina platform targeting sequencing depth of approximately 1 million reads or samples. Demultiplexing, BAM and FASTQ file generation will be performed using the Picard suite (Broad Institute). Quality-filtered metagenomes will be taxonomically profiled using MetaPhlAn3 (Metagenomic Phylogenetic Analysis) with default parameters.

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Untargeted Analysis of Serum Metabolome

Serum metabolite spectrum will be determined using NMR-based methods. Serum samples will be analyzed on Bruker AVANCE III 600 MHz and 700 MHz spectrometers according to the standard protocols. Metabolites will be identified by comparison with spectral databases (BBIOREFCODE, Chenomx, HMDB [Human Metabolome Database]) and published assignments. Liquid chromatography–mass spectrometry analysis in serum extracts will be performed using previously optimized procedures including extraction, separation by liquid chromatography (Agilent 1200), and detection by Bruker MS spectrometer micrOTOF-Q III. Suitable conditions will allow identification per exact mass, retention time, isotopic pattern, and fragmentations. For this purpose, Bruker software and MZmine 2.17 will be used.

Data Analysis and Statistical Considerations

To assess the effectiveness of the weight loss intervention and identify key predictors of response, such as microbiome, metabolomic profiles, and demographics, we will use generalized mixed effects models. These models account for both fixed effects (the intervention and relevant covariates) and individual variability, providing a robust analysis of the impact of the intervention. In addition, we will develop elastic net-based predictive models, complemented by machine learning algorithms, to stratify individuals into intervention groups, with the secondary aim of identifying responders. These models will be subjected to rigorous validation, including cross-validation or bootstrapping, to ensure their accuracy and generalizability. This approach aims not only to determine the efficacy of the intervention but also to improve personalized treatment by accurately classifying individuals based on their unique profiles, thereby advancing the field of personalized medicine. The analyses will be performed using IBM SPSS Statistics and R statistical packages.

Sample Size

Sample size considerations will be based on the power to address the primary hypothesis. The main predictor variables for the sample are ΔRQ (200-0) and glucose disposal (mg/kg/min). In recent observations from our TRIEMA (Treatment of Insulin Resistance: a Personalized Approach) study (NCT03710850), glucose disposal was 6.6 (SD 2.1), while ΔRQ was 0.05 (SD 0.04). The dependent variable, the expected weight loss after the intervention, is 4 (SD 5) kg [20]. The 30-subject study will have 80% power to detect a difference in weight loss of 4 kg (which is a clinically significant 5% weight loss for a woman weighing 80 kg at a difference of ΔRQ=0.07 (calculated using the PWRSS library in the R environment), at a probability level of α=.05. We plan to enroll 40 women to allow for attrition to the end of the intervention without risk of losing statistical power.

Major Confounders

It is known from the literature that people who start a structured exercise program may experience behavioral compensation in the form of increased food intake [21] and reduced habitual physical activity in everyday life [22,23]. Therefore, in our study, we will monitor participants' caloric intake using repeated 24-hour recalls and physical activity using an accelerometer. Caloric intake and habitual physical activity will always be assessed (1) in the week before the exercise intervention, (2) in the 6th week of the intervention, that is, after reaching the target energy expenditure, and (3) in the last 12th week of the intervention. In each of these weeks, caloric intake is assessed using 24-hour menu records from 3 specific days (the day of exercise, a weekday without exercise, and the weekend), using an application that works with validated food composition tables [24]. The caloric intake for each of the 3 weeks will be calculated from these 3 days.

Physical activity will be assessed in each of the specified weeks using the Axivity AX3 accelerometer. The accelerometer will be attached to the participant's wrist and worn within 24 hours for 7 full days. The data from the accelerometer will be processed using the GGIR library in R and the volume (average acceleration) and intensity (intensity gradient) of physical activity [25] will be calculated for each of the 3 weeks.

Compensation will be calculated as the difference between caloric intake or physical activity during the intervention (average of weeks 6 and 12) and before the intervention.

Feasibility Consideration

The team has extensive experience in conducting clinical trials and all methods are routinely available in the team members' facilities. Therefore, we do not anticipate any feasibility issues. We anticipate difficulties in recruitment and enrollment due to the challenging protocol and strict inclusion and exclusion criteria and anticipate a buffer time in the timetable for up to double the recruitment of participants. In case of an emergency situation that would make it impossible to carry out the clinical trial (such as the experience during the COVID-19 pandemic), we plan to work within work package 2 with databases and biobank material from previous studies that would allow the project outputs.

Ethical Considerations

The institutional review board of the University Hospital (EK-VP/28/1/2022) and the Faculty of Physical Education and Sport of Charles University (218/2023) reviewed the protocol before recruitment, and all participants will sign an informed consent form before enrollment. The study will be conducted in accordance with the Declaration of Helsinki and GCP.

The study will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP). The protocol was reviewed by the institutional ethics committee of University Hospital Kralovske Vinohrady and the Faculty of Physical Education and Sport Charles University.

Results

Recruitment for the trial began in January 2024. A total of 12 participants were enrolled and randomized. Among them, 6 participants have completed the first phase of the A-arm and 6 participants have completed the control period of the B-arm and their intervention is ongoing. Recruitment is ongoing. We expect the preliminary data from this study to be completed in

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2026. This clinical trial protocol was developed based on the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 Statement [26] (Multimedia Appendix 1).

Discussion

This randomized trial will assess the strength of predictive factors associated with successful weight loss after an exercise intervention in women with obesity. By focusing on both whole-body and gut MetFlex, the study aims to elucidate key mechanisms that contribute to individual variability in weight loss outcomes. The findings have the potential to lead to the development of more personalized and effective weight loss treatments, filling a critical gap in current obesity and diabetes management.

Several key decisions were made in the design of this clinical trial to overcome limitations in existing literature and reduce potential bias. One such decision is the use of a cross-over trial design, which enhances the robustness of the study by allowing participants to serve as their own controls. This approach helps reduce interindividual variability and provides stronger evidence of the causal relationship between the interventions and the observed outcomes.

Lifestyle interventions, particularly those combining dietary and exercise components, are as essential for managing and potentially reversing diabetes progression [27,28]. Substantial evidence supports the role of sustained weight loss in improving insulin sensitivity, glycemic control, and other metabolic outcomes. However, the heterogeneity in response to such interventions highlights a critical need for personalization [29,30]. Individuals vary widely in their ability to lose weight and maintain that loss, which is often attributed to differences in MetFlex, the gut microbiome, and behavioral adaptations [31]. An additional strength of this study is the comprehensive monitoring of participants' dietary intake and physical activity throughout the intervention. By accounting for compensatory behaviors, such as changes in caloric intake or reduced physical activity outside of exercise sessions, we aim to provide a clearer understanding of how these factors contribute to weight loss variability.

However, some limitations need to be considered. The strict eligibility criteria may make recruitment challenging, potentially limiting generalizability to the broader population of women with obesity. Furthermore, while compensatory behaviors are monitored, other factors such as psychological and social influences could still impact outcomes.

In conclusion, this trial will provide important insights into the role of MetFlex and the gut microbiome in predicting successful weight loss. These findings could lead to more personalized interventions in clinical practice, ultimately improving adherence and outcomes in obesity and diabetes management.

Acknowledgments

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During the preparation of this work, the authors used ChatGPT in order to improve readability and language. After using this tool or service, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

ML, JP, and BK performed investigation. ML and MS contributed to writing the original draft. KK, MC, and JG contributed to conceptualization. MS and JG contributed to funding acquisition. TV contributed to methodology. MS and JG performed supervision. MS, KK, and JG contributed to writing, review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT checklist.
[PDF File (Adobe PDF File), 233 KB - resprot_v14i1e67570_app1.pdf]

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Abbreviations

EASO: European Association for the Study of Obesity
FFM: fat-free mass
FM: fat mass
HMDB: Human Metabolome Database
MEPHISTO: Metabolic flexibility to Predict Health Lifestyle Intervention Outcomes
MetaPhlAn3: Metagenomic Phylogenetic Analysis
MetFlex: metabolic flexibility
MIME: gut microbiome and metabolome
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
T2D: type 2 diabetes
VO_2 max: maximal oxygen uptake
ΔFFA: changes in circulating free fatty acids
ΔGIR: change in glucose infusion rate
ΔRQ: change in respiratory quotient

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Protocol

Effect of Early Treatment of Spasticity After Stroke on Motor Recovery: Protocol for the Baclotox Multicenter, Double-Blind, Double-Dummy Randomized Controlled Trial

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Abstract

Background: Individuals with poststroke hemiplegia often develop spasticity, which increases disability. Antispastic treatments such as baclofen and botulinum toxin are commonly prescribed in poststroke recovery. However, their impact on motor recovery, especially when administered within the first 2 months after stroke, remains unclear.

Objective: This study aims to compare the motor recovery effects of botulinum toxin versus oral baclofen. The hypothesis is that botulinum toxin is more supportive of motor recovery than baclofen and enhances functional recovery.

Methods: The study is a multicenter, controlled phase IV, comparative, prospective, randomized, double-blind, double-dummy, superiority trial to compare the toxin and baclofen, and a noninferiority trial to compare the toxin and the placebo. It focuses on the time course of the Fugl-Meyer Motor Assessment (FMA) as the primary outcome. The main inclusion criterion is patients with a single stroke in the past 2 months. Treatment comprises 1 intramuscular injection at treatment initiation and oral tablets for 4 months. Randomized patients are allocated to 3 arms: botulinum toxin with placebo baclofen, baclofen with placebo botulinum toxin, and placebo baclofen with placebo botulinum toxin. FMA scores are assessed at pretreatment, 1 month, and 3 months later. Spasticity, functional abilities, activities of daily living, pain, and quality of life are also evaluated. Adverse effects are monitored. A positive difference of 13 points in the FMA time course between the botulinum toxin and baclofen groups is considered a relevant effect. The data analysis plan involves linear regression models to compare primary and secondary outcomes, with adjustments for covariates such as age, center, and associated treatments. Subgroup analyses will examine proportional recovery profiles, and missing data in Fugl-Meyer scores will be addressed using imputation methods.

Results: A total of 179 participants were randomized across 18 centers, with inclusions delayed due to the COVID-19 pandemic. As of December 2024, the data manager currently has all the data, and a review of data quality is in progress. No statistical analysis has been conducted so far, and the blind will be lifted after the analysis.

Conclusions: This study identifies the most suitable spasticity treatment, considering the specificities of the stroke and constraints during the recovery phase. It will provide recommendations for the primary treatment of early spasticity post stroke.

Trial Registration: ClinicalTrials.gov NCT02462317; https://clinicaltrials.gov/study/NCT02462317; European clinical trials (EudraCT) 2010-022881-28; https://www.clinicaltrialsregister.eu/ctr-search/trial/2010-022881-28/FR

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International Registered Report Identifier (IRRID): DERR1-10.2196/62951

(JMIR Res Protoc 2025;14:e62951) doi:10.2196/62951

KEYWORDS

stroke; rehabilitation; muscle spasticity; botulinum toxin A; baclofen; hemiplegia; motor recovery

Introduction

Background

Stroke is the leading cause of acquired motor disability in adults, with 80% of patients experiencing corticospinal tract damage that results in hemiparesis [1,2]. A significant proportion of people who have had a stroke face long-term disability, with many requiring assistance with daily activities, walking, or occupational activities [3]. Early subacute poststroke rehabilitation, which occurs during the period between 7 and 90 days post stroke, focuses on promoting motor recovery and reducing activity limitations, often through intensive rehabilitation and, where appropriate, pharmacological intervention. This phase is considered a critical window for neuroplasticity and motor recovery [4]. While there is substantial evidence from animal models suggesting that certain drugs impact motor recovery, human studies are limited, especially in the context of spasticity management during the subacute phase post stroke [5].

Spastic motor syndrome involves spasticity, dystonia, co-contraction, and clonus due to diminished tonic stretch reflexes and increased muscle tone due to upper motor neuron damage [6]. Although spasticity is typically treated in the chronic phase, there is an increasing trend toward early intervention during the subacute phase [7]. Early management may potentially mitigate long-term functional limitations; however, it remains uncertain whether early pharmacological treatment of spasticity positively or negatively influences motor recovery [8].

Two primary pharmacological treatments for spasticity in France are baclofen and botulinum toxin A, each with distinct mechanisms and evidence of efficacy [9].

Baclofen is a GABA (γ-aminobutyric acid)-B agonist that reduces spasticity by enhancing presynaptic inhibition, thereby decreasing the excitability of afferents in spinal reflexes. Despite its widespread use and endorsement by the French National Health Authority, Haute Autorité de Santé, as a first-line treatment, studies in animal models have raised concerns about the impact of GABAergic drugs on motor recovery. Research indicates that GABAergic agents, such as diazepam, can impair motor recovery and brain plasticity postinjury [10,11]. Baclofen has shown similar detrimental effects on visuomotor learning in healthy human participants, suggesting a potential risk for individuals undergoing motor recovery post stroke [12]. However, the absence of direct studies on baclofen's effects during the recovery phase post stroke leaves a critical gap in understanding its impact on motor outcomes.

Botulinum toxin A, meanwhile, acts by blocking acetylcholine release at the neuromuscular junction, thereby temporarily paralyzing targeted muscle fibers and reducing spasticity [13]. Its effects generally become noticeable within days and persist for approximately 4 months [14]. Randomized controlled trials demonstrate botulinum toxin's effectiveness in reducing spasticity in patients with chronic stroke; yet, its effects on motor function are less clear [9,13,15,16]. Most studies have focused on its use in the chronic phase over 6 months post stroke, a period when plasticity decreases and muscular changes may be irreversible. Notably, research using transcranial magnetic stimulation and functional magnetic resonance imaging indicates that botulinum toxin injections may have modulatory effects on the central nervous system, potentially enhancing brain plasticity and supporting recovery [17-21]. This evidence suggests that early use of botulinum toxin in the subacute phase could offer motor recovery benefits by influencing neuroplastic processes.

Given the limited understanding of how these treatments affect motor recovery in the subacute phase, this study aims to investigate the comparative efficacy of baclofen and botulinum toxin A on motor recovery post stroke. Our hypothesis is that botulinum toxin will demonstrate a superior effect on motor recovery compared to baclofen, as it may mitigate spasticity without the potential negative effects on plasticity observed with GABAergic drugs.

Objectives

Main Objective

This study aims to demonstrate the superiority of botulinum toxin A over baclofen on motor recovery in the subacute phase after stroke. The primary end point is the change in the Fugl-Meyer Assessment (FMA) motor score from the start of treatment to 3 months later.

Secondary Objectives

Our secondary objectives are as follows:

- To compare the effects of botulinum toxin A and placebo on motor recovery (FMA) over 3 months and establish clinical equivalence.
- To evaluate the impact of treatment on motor recovery (main objective and placebo comparison) based on initial FMA-upper extremity (FMA-UE) scores.
- To assess changes in motor recovery (FMA) during the first month of treatment.
- To compare the effectiveness of the treatments in reducing spasticity symptoms over 1 and 3 months using the Tardieu Scale and Modified Ashworth Scale (MAS).
- To evaluate functional improvement 3 months after treatment using the Rivermead Motor Assessment (RMA), Rankin score, and Barthel score.

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Exploratory Objectives

- To assess the impact of treatments on pain using a visual analog scale (VAS) at 1 and 3 months.
- To evaluate the quality of life over 3 months using the Reintegration to Normal Life Index (RNLI), a scale validated for patients with vascular hemiplegia.
- To compare reaction times at baseline, 1 month, and 3 months to investigate cognitive effects of treatment.
- To measure patient satisfaction with treatment at 1 and 3 months.

Methods

Study Design

This is a multicenter, controlled phase IV, comparative, prospective, randomized, double-blind, double-dummy, superiority trial to compare the toxin and baclofen, and a noninferiority trial to compare the toxin and the placebo. Because of the different modes of administration of these treatments, each group receives both an injection and oral tablets. The study therefore comprises three arms: (1) a "toxin" group treated with an injection of botulinum toxin and placebo oral baclofen; (2) a "baclofen" group treated with oral baclofen and an injection of placebo botulinum toxin; and (3) a double "placebo" group treated with placebo oral baclofen and an injection of placebo botulinum toxin. The CONSORT (Consolidated Standards of Reporting Trials) flowchart in Figure 1 summarizes the enrollment and allocation of the participants.

All patients, regardless of their assigned group, benefit from daily neurorehabilitation care. This care starts simultaneously with the initiation of treatment. For each patient, the protocol duration spans 4 months: 3 months of the controlled protocol and 1 month of gradual discontinuation of the tablets. This gradual discontinuation reflects the standard procedure for stopping baclofen. Participants are recruited from the 18 French physical medicine and neurorehabilitation hospital wards participating in this protocol. The list of study sites can be found in Multimedia Appendix 1.

The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines resume the intervention and assessments of the study (Figure 2).

This study is registered in the European EudraCT database (2010-022881-28) and is also registered in ClinicalTrials.gov (NCT02462317).

Figure 1. CONSORT (Consolidated Standards of Reporting Trial) flow diagram. mITT: modified intention-to-treat; PP: per-protocol; V1: visit 1; V2: visit 2; V3: visit 3.

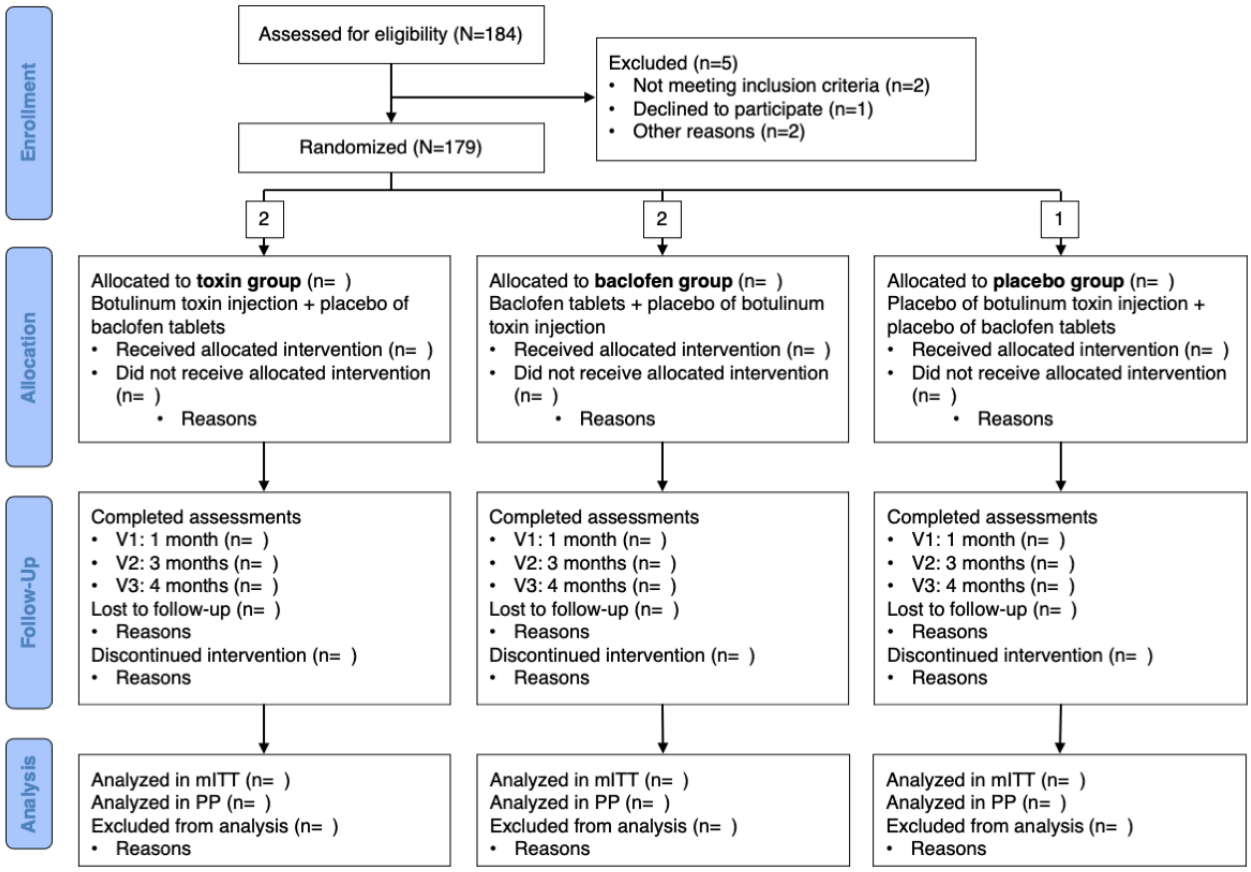

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Figure 2. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) schedule of enrollment, interventions, and assessments. FMA: Fugl-Meyer Assessment; RMA: Rivermead Motor Assessment; RNLI: Reintegration to normal life; V0: allocation visit; V1: visit 1; V2: visit 2; V3: visit 3; VAS: visual analog scale.

	Enrollment	Allocation	Postallocation		Close-out
TIMEPOINT	*5 to 15 days before allocation*	V0	*V1 1 month*	*V2 3 months*	*V3 4 months*
ENROLLMENT:					
Eligibility screen	X				
Informed consent	X				
Allocation		X			
INTERVENTIONS:					
Toxin or placebo intramuscular injection		X			
Oral baclofen or placebo intake period		·····	———	———	·····
Collection of blister packs			X	X	X
ASSESSMENTS:					
Clinical examination		X			X
Blood count	X		X		
FMA		X	X	X	
Tardieu & Ashworth	X	X	X	X	
RMA		X		X	
Barthel		X		X	
Rankin		X		X	
Satisfaction VAS			X	X	
Reaction time		X	X	X	
Pain VAS		X	X	X	
RNLI		X		X	
Adverse events		X	X	X	X

Ethical Considerations

This study received Ethics Committee approval (CPP Sud-Ouest et Outre-Mer II) on March 23, 2015 (review number 2-14-33) and authorization from the Agence Nationale de Sécurité du Médicament (ANSM) on December 29, 2014. Conducted in accordance with the Declaration of Helsinki, the study requires both oral and written informed consent from participants. During the preinclusion visit, the investigating physician explains the study's objectives, procedures, potential risks, benefits, and patient rights. Each participant receives an information sheet and consent form, followed by a minimum 48-hour reflection period to decide on participation. An ancillary study is carried out in the main investigating center. The patient is given a different consent form for this ancillary study and is provided with comprehensive information. In line with the French Public Health Code (articles L.1121-3 and R.5121-13), confidentiality is strictly maintained. Collected data are anonymized, with patient codes generated from initials and inclusion numbers, which are linked only to the center and enrollment order. The sponsor ensures that all participants consented to data access solely for quality assurance. No financial or material compensation was provided; participation was voluntary without incentives.

Participants

Eligibility Criteria

Inclusion Criteria

The inclusion criteria are as follows:

- Man or woman between the ages of 18 and 80 years.
- First ischemic or hemorrhagic stroke resulting in hemiplegia.
- Sufficient understanding to participate in the study: Boston Diagnostic Aphasia Examination>3.
- The stroke occurred less than 2 months ago.

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- Presence of spasticity warranting treatment: Tardieu score>1(≥2) in one of the following muscle groups: triceps sural, wrist flexors, finger flexors, and elbow flexors.
- The patient's consent was obtained.
- Affiliated with a social security scheme or equivalent.

The inclusion criteria ensure that participants represent the target population most likely to benefit from the intervention, including adults with recent first strokes and spasticity warranting treatment. These criteria also confirm their capacity to engage meaningfully in the study through sufficient cognitive understanding and access to standard rehabilitation care.

Exclusion Criteria

The exclusion criteria are as follows:

- Renal failure at the time of inclusion.
- Currently on antispastic therapy: baclofen, dantrolene, and tizanidine.
- A history of botulinum toxin injection.
- A history of traumatic or vascular brain injury, myasthenia gravis, Lambert Eaton syndrome, or neuromuscular disease.
- Pregnancy
- Surgery with curare within the last month
- Treatment with aminoglycosides, aminoquinolines, or cyclosporine.
- Progressive disease at the time of inclusion.
- A history of convulsive seizure or taking antiseizure medication.
- A history of psychosis or neuroleptic treatment.
- Liver function test abnormalities, at the investigator's discretion.
- Blood count abnormalities, at the investigator's discretion.
- A history of intolerance or allergic reaction to lactose.
- Glucose or galactose malabsorption syndrome and lactase deficiency.
- A history of anaphylactic reaction.
- Inability to undergo daily rehabilitation for 2 hours.
- Under guardianship, curatorship, safeguard of justice.
- Receiving anticoagulant treatment: heparin with an electric syringe or antivitamin K at an effective dose.

The exclusion criteria are designed to ensure participant safety and the validity of the study by excluding individuals with medical conditions, treatments, or histories that could compromise the intervention's safety or effectiveness. Participants unable to follow the study protocol are also excluded. These criteria include the standard exclusions for Botulinum toxin treatment and oral baclofen therapy.

Study Center Inclusion Criteria

Study centers must have experience in spasticity assessment and conducting botulinum toxin A injections. They must admit an adequate number of patients post stroke in the subacute phase for hospitalization every year.

Participants are recruited from among the outpatients and inpatients of the physical and neurorehabilitation medicine ward. Two or more experts determine eligibility according to the inclusion and exclusion criteria.

Intervention

At the allocation visit (V0), the investigator administered the intramuscular injections and prescribed the tablets. The tablets were taken daily for 3 months until the second postallocation visit (V2). The dosage of tablets was then gradually decreased over 1 month and the effects were monitored during the close-out visit. All participants also received at least 2 hours of neurorehabilitation daily, 5 days per week, led by specialized therapists. This regimen included both physiotherapy and occupational therapy to support comprehensive motor recovery in accordance with the routine practices of the neurorehabilitation centers.

Botulinum Toxin Injection Protocol

The choice of muscle groups to be injected depended on the investigator's clinical examination. The muscle group that validated the patient's inclusion (Tardieu>1) was systematically injected. Other muscle groups that met the specific criteria (Tardieu score1) were also systematically injected: the triceps surae, flexor digitorum superficialis, flexor digitorum profondus, flexor carpi radialis, flexor carpi ulnaris, and the brachialis (Multimedia Appendix 2). The maximum total dose permitted is 500 units. Additional muscle groups were injected based on the remaining dose of toxin [22].

Injection site localization was tracked using electrostimulation sometimes combined with muscle ultrasound. Depending on the muscles injected, 1 or 2 injection points would be considered at sites with the highest density of motor endplates. The total number of injection points could range between 15 and 20. If requested by the patient, an analgesia protocol with class II analgesics (paracetamol, codeine, and hydroxyzine) was administered 2 hours prior to the procedure, along with inhalation of an equimolar mixture of oxygen and nitrous oxide (Meopa). This was the standard procedure for toxin injections in the participating centers.

Baclofen Intake Protocol

Baclofen was provided in a 10 mg capsule and the chosen dose was 60 mg per day in 3 doses commonly used with success in baclofen studies [9]. Treatment was initiated at a dosage of 10 mg in the evening (1 capsule). The dosage was then increased by 1 tablet (10 mg) every 4 days until a dosage of 60 mg per day was reached. If excess sedation occurred during dosage escalation, the clinician reverted to the previous level for an additional 3 days. After 2 unsuccessful attempts to increase the dosage, the last tolerated dosage was maintained throughout the study. Abrupt discontinuation of treatment was not recommended. On completion of the protocol, the baclofen dosage was gradually reduced by 10 mg (1 capsule) every 3 days.

Exiting the protocol occurred either by the patient's deliberate choice or by necessity, according to the investigator's decision, in the following circumstances.

- Nonadherence to study conditions: poor compliance with the treatment, unauthorized use of other medications.
- Uncontrolled painful spasticity despite the use of class I and II analgesics.

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- Occurrence of a serious adverse effect or event.

Premature discharge may be warranted in the event of a clinically significant adverse effect, such as mental confusion, severe sedation, swallowing difficulties necessitating discontinuation of oral feeding and insertion of a nasogastric tube, leuconeutropenia, or drug-induced hepatitis revealed by the laboratory tests (1-month visit). On study discharge, the patient was promptly referred to the investigator for follow-up consultations and ongoing management.

To ensure compliance, drug blister packs were collected, and the remaining capsules were counted.

Permitted Care During the Trial

Certain medications could impact motor recovery, particularly GABAergic treatments, which were closely monitored. Patients already on a long-term prescription (over 1 month) of sleeping or anxiolytic treatment might continue this treatment. Discontinuing these patients' medications had more drawbacks than benefits. Zolpidem and zopiclone, commonly prescribed to patients with poststroke sleep disorders, were permitted during this trial.

Considering the prevalence of poststroke depression and its influence on functional recovery, specific antidepressants are authorized. Antidepressants in the serotonin reuptake inhibitor class were permitted. These medications could potentially facilitate motor recovery irrespective of their antidepressant properties [23]. However, randomization aimed to evenly distribute these treatments across all groups, which minimized the risk of bias.

For secondary stroke prevention, patients were administered treatment according to current recommendations (antiplatelet agents, antihypertensive agents, and cholesterol-lowering agents). Effective-dose anticoagulants (heparin and anti–vitamin-K) were grounds for noninclusion due to the risk of muscle hematoma during injections. However, if necessary, during the protocol postinjection, effective-dose anticoagulants were prescribed without necessitating withdrawal from the study.

It is important to note that all patients received standardized functional neurorehabilitation for 2 hours daily, which included physiotherapy and occupational therapy sessions in line with current practices.

Prohibited Care During the Trial

Anxiolytics and other benzodiazepines were prohibited, except zolpidem or zopiclone, which may have been prescribed for the duration of the protocol. Similarly, neuroleptics and tricyclic antidepressants were contraindicated due to their deleterious effects on recovery. Effective-dose anticoagulants at the time of inclusion were a criterion for noninclusion.

Outcomes

Primary Outcome: FMA

The primary end point is the progression of the FMA score from allocation (V0) to the visit three months after allocation (V2) [24].

This is a tool for assessing the motor function of participants with hemiplegia after a stroke. It is also recommended by the European Stroke Organization as a poststroke evaluation outcome [25]. Sensitivity to change is moderate for the overall scale and better for the upper limb subscale after a recovery period. This scale has excellent test-retest reliability and interrater reliability [26]. The floor effect and the ceiling effect are good [27]. This scale is widely used in current practice in France and the study investigators are accustomed to performing it.

Secondary outcomes

Fugl-Meyer Motor Assessment

Subscores of FMA, specifically FMA-UE and FMA-lower extremity (FMA-LE), from allocation (V0) to the visit 3 months after allocation (V2) are secondary end points.

The progression of the FMA score from allocation (V0) to the visit 1 month after allocation (V1) is a secondary end point.

Tardieu Scale

Spasticity is assessed using the Tardieu Scale [28]. This scale is of better metrological quality than the Ashworth scale usually used in this type of study [29]. It allows the analysis of the resistance to stretching at several different speeds. Two speeds are used: XV1 is the slowest possible stretching speed and XV3 is the fastest possible stretching speed. Two results are noted: first, the Tardieu angle, which is the difference between the angle of passive joint amplitude obtained at XV1 and the angle of the first resistance to stretching at XV3, and second, the Tardieu intensity score of the resistance to stretching measured by an ordinal score from 0 to 4.

The end point was the progression from the allocation to 1 month later (V0 to V1) and from the allocation to 3 months later (V0 to V2), focusing on muscle groups such as the triceps surae (knee flexed and extended), carpal flexors, and elbow flexors. This score can be applied to muscles that have not been injected, but given the global action of baclofen, measurement of all these muscle groups was essential.

Modified Ashworth Scale

The MAS evaluates muscle tone of the same muscles evaluated with the Tardieu Scale. However, it primarily assesses the intensity of resistance to stretching without considering stretching speed [30]. It is therefore much less precise than the Tardieu Scale in terms of the increase in the myotatic reflex, but it allows a very global consideration of the modifications of the intrinsic biomechanical properties of the muscle fibers and the dystonia of the muscles examined. The end point was the progression from the allocation to 1 month later (V0 to V1) and from the allocation to 3 months later (V0 to V2) on the same muscle groups.

RMA

The RMA, validated in individuals with vascular hemiplegia [31], appraises motor performance across various functional aspects, including balance, walking, trunk and lower limb motor skills, and upper limb activities. The end point was the progression from the allocation to 3 months later (V0 to V2).

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Rankin Score

The Rankin score is a widely accepted scale for the global assessment of poststroke disability [32]. It features 6 degrees and is an evaluation tool recommended by the Haute Autorité de Santé. The end point was the progression from the allocation to 3 months later (V0 to V2).

Barthel Score

This scale measures autonomy in the activities of daily living and has been validated in individuals with vascular hemiplegia [33]. It comprised 10 items and demonstrated excellent reproducibility. The end point was the progression from the allocation to 3 months later (V0 to V2).

Pain via VAS

Changes in pain were evaluated using a VAS from the allocation to 1 month later (V0 to V1) and from the allocation to 3 months later (V0 to V2).

Quality of Life Measurement Via the RNLI Questionnaire

The RNLI questionnaire assessed the quality of life specifically for individuals with vascular hemiplegia [34] and was measured from the allocation to 3 months later (V0 to V2).

Reaction Time Measurement

Sound and visual reaction time assessments via laptop aimed to quantify the overall impact of spasticity treatments on cognitive functions. The change in measurements was assessed from the allocation to 1 month later (V0 to V1) and from the allocation to 3 months later (V0 to V2).

Treatment Satisfaction Via VAS

Patient satisfaction with spasticity treatment was compared using a VAS at both postallocation visits (V1 and V2).

Safety

Adverse events (AE) were systematically monitored at the allocation visit (V0), both postallocation visits (V1 and V2), and the close-out visit (V3). Monitoring covered sedation, somnolence, fatigue, muscular weakness, swallowing difficulties, epileptic seizures, liver function, and blood count.

Sample Size

The study includes three arms as follows: (1) the “toxin” group, which receives an injection of botulinum toxin and placebo oral baclofen; (2) the “baclofen” group, which receives oral baclofen and an injection of placebo botulinum toxin; and (3) the “placebo” group, which receives placebo oral baclofen and an injection of placebo botulinum toxin. All groups receive standard neurorehabilitation care.

This study is a randomized parallel 2-2-1 type design, which corresponds to the “toxin,” “baclofen,” and “placebo” groups, respectively. The main objective, which is to demonstrate the superiority of “toxin” over “baclofen” on motor function, corresponds to a 2-2 comparison. The secondary objective, which is to demonstrate the noninferiority of “toxin” to “placebo” on motor function, corresponds to a 2-1 comparison. The “placebo” arm is limited due to ethical considerations.

The sample size for the “toxin” and “baclofen” arms was calculated with the 2-sided test at a 5% significance level. This analysis compared the superiority of the toxin over baclofen indicated by the FMA gain, between the allocation visit (V0) and the second postallocation visit (V2). The expected variation in FMA was estimated at 30 points between V0 and V2. [35]. For an 85% power and an FMA difference of 12 points between the “toxin” and “baclofen” groups, 120 patients per group were initially required, accounting for missing data and protocol deviations. This 12-point difference was based on the minimal clinically important difference of FMA, which was approximately 6 points for both the upper [36] and lower extremities [37]. Doubling the minimal clinically important difference for a total FMA score ensured a clinically significant change.

To demonstrate equivalence between the “toxin” and “placebo” groups, a 12-point unilateral zone of equivalence was defined. With an SD of 30 points, 60 patients in the “placebo” arm yielded a power of approximately 80% (77.6%), accounting for 10% missing data.

The original target was 300 patients, but by September 30, 2018, only 140 had been included. Given the time and funding constraints, an amendment increased the target FMA difference to 13 points between V0 and V2. This adjustment, while slightly higher, remains within a clinically meaningful range and is achievable under the study’s operational constraints. Accordingly, 85 participants were required in both the “toxin” and “baclofen” groups, factoring in a 10% data loss. The “placebo” group was reduced to 44 patients to maintain the 2-2-1 randomization ratio. A total of 214 patients were therefore needed for trial inclusion.

Allocation

Randomization follows a 3-arm, type 2-2-1 (“toxin,” “baclofen,” and “placebo”) design. This process is conducted by Creapharm, the manufacturer and packager of the protocol’s therapeutic batches. Creapharm is an independent company approved by the French drug agency (ANSM). Each center receives therapeutic batches containing 5 treatment packages (2-2-1). Randomization is therefore stratified by center.

A copy of the randomization list is kept by Creapharm and the sponsor’s pharmacy. Randomization is performed before the study starts by assigning an inclusion number in the protocol that aligns with a specific therapeutic batch number. The pharmacy in each center is responsible for accurately assigning the therapeutic batch number associated with the inclusion number. This detail is routinely verified by the principal investigator at each center.

Blinding

Participants, care providers, investigators, outcome assessors, the data manager, and the biostatistician are blinded to the assignment of the intervention. The blind will be lifted after the statistical analyses.

During the research, the investigator and the sponsor can request unblinding if necessary, with the agreement of the coordinating investigator. Unblinding might be necessary in case of a serious,

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life-threatening AE. Otherwise, unblinding only occurs after the database has been finalized at the end of the research.

In this study, a 2-2-1 randomization scheme is used, resulting in 2 treatment groups and 1 placebo group with differing sample sizes. While blinding is strictly maintained for the 2 treatment groups, the smaller size of the placebo group could potentially reveal its identity during data analysis. To minimize bias and preserve blinding integrity, all data analyses will be conducted on coded datasets, with each group labeled as "group 1," "group 2," or "group 3," without specifying treatment identities. This approach ensures that data handling and interpretation are unbiased until the final analysis is complete. Additionally, the randomization and allocation processes are managed independently by a third-party data manager who has no role in data collection or analysis. These measures aim to uphold objectivity and reduce any influence of group size on the interpretation of results.

Data Collection and Management

All personnel involved in data collection undergo training before the study begins. The data are routinely collected in the management of patients post stroke.

Participants are informed that there will be additional tests during the close-out visit (V3) following the treatment. Moreover, there is a sincere desire among participants to receive the treatment for an adequate duration. Any discontinuation or deviation from the study protocol is documented along with the reasons for discontinuation.

All the information mandated by the protocol is documented in observation logbooks, with explanations provided for any missing data. Data should be recorded promptly and transcribed neatly into the logbooks. If any erroneous data are identified, it should be clearly crossed out and the correct information entered along with the initials, date, and justification by the investigator or the authorized person who made the correction. These records are maintained in paper observation logbooks with 2 copies generated. One copy is kept by the center investigator, while the second is kept by the research monitor after monitoring. Laboratory and clinical examination results are clearly entered in the clinical records, and scales, which are considered source data, are entered directly in the observation logbooks.

Data are entered on paper by the research technician at each center and electronically at the coordinating center. One copy of the observation logbook triplicate is sent to the coordinating center. The clinical research technician at the coordinating center verifies the accuracy of data and validates the computerized data. Data validation aligns with the data management plan developed by the coordinating investigator and the Methodology and Data Management Centre, which comprises a methodologist, a data manager, and a statistician.

The process of freezing or unfreezing data follows the established procedure at the Methodology and Data Management Centre where raw data are frozen in XML format and as an SAS (version 9.4; SAS Institute) table. Daily backups of the dataset are kept for 4 weeks, followed by monthly tape-recorded archiving.

MéDatAS-CIC is a methodology, data management, and biostatistics center to which the sponsor is affiliated, and which acts as a research support team. The Clinical Investigation Centre is responsible for coordinating the conduct of the study. This service is funded by the Programme Hospitalier de Recherche Clinique (PHRC) grant.

AE Reporting

The investigator was required to promptly notify the sponsor of any serious AEs (SAEs) or significant developments, occurring at any time from the date of informed consent signing, throughout the patient's scheduled follow-up, and up to 30 days after follow-up completion if the event was likely related to the research. SAEs are defined as events resulting in death, life-threatening situations, hospitalization or prolongation of existing hospitalization, significant or permanent disability, or interventions to prevent such outcomes. Minor AEs are defined as medical occurrences not meeting SAE criteria but which may still relate to study procedures. The sponsor is then responsible for timely reporting of unexpected SAEs and other new occurrences to the ANSM and the relevant ethics committee.

In cases where participants may have been affected, the ethics committee will ensure that the participants are informed of relevant AEs and confirm their ongoing consent.

Statistical Methods

Statistical Methods for Primary and Secondary Outcomes

The baseline characteristics of the participants are described for the 3 treatment groups and the pairwise standardized differences are used to compare the distribution of baseline covariates between treatment groups.

The variation in the Fugl-Meyer score between the "toxin" and "baclofen" groups is compared using linear regression models. First, the model contains the treatment group as the explanatory variable and the Fugl-Meyer delta score as the response variable. The adjusted model then incorporates the patient's age, the center, and any associated treatment as explanatory variables, in addition to treatment. The associated treatment is represented by a binary variable indicating the use of at least 1 serotonin reuptake-inhibiting antidepressant (yes or no) or at least 1 benzodiazepine (yes or no). This list is validated during the descriptive analysis of concomitant treatment.

The primary objective tests the superiority of the "toxin" versus "baclofen" in motor recovery at 3 months using 2-sided tests at a 5% α level. The secondary objective aims to demonstrate the clinical equivalence of the "toxin" versus the "placebo" in motor recovery after 3 months, using a 1-sided noninferiority test at a 5% α level and a margin of 13 FMA points to assess noninferiority.

To assess the efficacy of these treatments on spastic symptoms (MAS, Tardieu angle, and Tardieu Scale), 2-tailed *t* tests at a significance level of 5% are conducted for pairwise comparisons. The first analysis is carried out on all muscle groups, and a second analysis is carried out on the muscle groups that have been injected.

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For the FMA at 1 month and the variation score between allocation and the second postallocation visit which consists of the RMA the Barthel Index, the Rankin score, the reaction time, satisfaction, pain, and the RNLI, the analyses will be descriptive using the usual statistical measures in each group with a 95% CI.

The modified intention-to-treat population consists of all randomized participants who meet the inclusion criteria, having taken at least 1 dose of the study treatment, and with at least 1 postrandomization evaluation. The per-protocol population includes all patients who complete the study as specified in the protocol, excluding those who do not meet the inclusion criteria, for whom there are major protocol deviations during follow-up, or who do not adhere to the treatment regimen as per protocol. The safety analysis population includes all randomized participants who received at least 1 dose of the study treatment. The modified intention-to-treat population is used to analyze all study objectives. Only the secondary objective, which assesses the noninferiority between the "toxin" and the "placebo is analyzed in the per-protocol population, while AEs are analyzed in the safety population. All statistical analyses are conducted in SAS.

Methods for Additional Analyses (eg, Subgroup Analyses)

The proportional recovery rule serves as a predictive model for understanding poststroke recovery. It examines the correlation between initial impairment and subsequent recovery by analyzing FMA-UE both at baseline and in follow-up sessions and defines recovery as the change over time [38]. This research suggests that, on average, a significant subset of patients typically regains approximately 70% of their maximum potential recovery from impairment, while a smaller subgroup experiences notably less recovery. For recovery to be considered proportional, patients must recover roughly 70% of their maximum possible potential at the 3-month mark [38]. Patients who initially show mild to moderate deficits according to the FMA-UE (>10) at baseline often follow a pattern known as "recoverers" [39,40]. Those who display a proportional recovery profile tend to have corticospinal tracts that are less affected throughout the entire course [40,41].

Identifying participants with a proportional recovery profile based on the initial FMA-UE seems to be a promising method for participants with stroke, allowing for a more accurate assessment of treatment effectiveness [42]. This subgroup analysis helps to avoid missing treatment effects within the larger group by focusing on those with a "recoverers" profile.

These groups are determined based on whether the FMA-UE is greater than or equal to 11 or strictly less than 11 during the allocation visit [40].

Within the "recoverers" and "nonrecoverers" groups, linear regression models are used in a comparative analysis between the "toxin" and "baclofen" groups regarding the variation in the FMA-UE score. Initially, an unadjusted analysis uses treatment as the sole explanatory variable and the FMA-UE delta score as the response variable. The adjusted model incorporates the patient's age, the center, and the presence of associated treatment as explanatory variables, in addition to treatment.

The same unadjusted and adjusted models are also computed using the FMA-LE as the response variable in both the "recoverers and the nonrecoverers" groups.

Methods to Handle Missing Data

The primary and secondary outcomes involve examining the difference in a quantitative variable measured at 2 distinct time points. Since the measurements are based on quantitative longitudinal scores, we use the CopyMean approach in the R software (R Foundation for Statistical Computing) [43]. The specific methodology details are determined after assessing the structure of the missing data (such as monotone patterns). Consequently, with this method, scores at the 3 targeted times will be imputed, and subsequently, differences from the initial measurement will be computed. This methodology is only applied to the FMA, the FMA-UE, and the FMA-LE. Other missing data are not imputed.

Details regarding oversight, monitoring, auditing, and protocol amendments are provided in Multimedia Appendix 3.

Results

The first participant was included on April 20, 2015, and the last on July 9, 2020. A total of 184 poststroke participants were included, with 179 randomized across 18 centers. Regarding the ancillary study, 28 poststroke participants agreed to participate, and 20 healthy participants were included between March 10, 2021, and May 27, 2021.

In December 2024, all data are currently kept by the data manager. The data quality review is underway. It should be completed in January 2025. After this date, the database will be frozen and statistical analyses can begin. The blind will be lifted after statistical analyses.

In December 2024, investigators had no data, no conclusions could be drawn, and no result trends could be identified.

Discussion

Principal Findings

This study uses a dual analysis framework: a superiority analysis comparing botulinum toxin with baclofen and a noninferiority analysis comparing botulinum toxin with placebo. This approach provides a comprehensive evaluation of the efficacy of botulinum toxin relative to both an active treatment of spasticity (baclofen) and an inactive comparator (placebo). If mixed outcomes are observed—for instance, if botulinum toxin is found to be superior to baclofen but not to placebo—we will interpret these results separately within the context of each hypothesis. This distinction ensures clarity and rigor in the interpretation of findings and supports transparent discussion of implications for spasticity management.

Comparison With Prior Work

Previous studies on spasticity treatments after stroke have primarily focused on their effects on muscle tone rather than

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motor recovery. Botulinum toxin and baclofen are well-established treatments for spasticity, but their impacts on motor recovery remain unclear [9,13,15]. Most randomized controlled trials have investigated botulinum toxin in the chronic phase of stroke recovery (more than 6 months post stroke), where brain plasticity is reduced and muscle changes are often irreversible. Conversely, evidence of baclofen's effects on motor recovery is largely absent, despite animal studies and small human trials suggesting that activation of GABA receptors may hinder motor learning [10,44,45]. This study uniquely investigates these treatments during the subacute phase, a critical window for neuroplasticity and motor recovery. Spastic symptoms usually begin around 4 weeks post stroke [46,47]. The inclusion criteria of 2 months after stroke provide a balance between including a sufficient number of patients with spasticity and ensuring a sufficient period before the end of the early subacute poststroke phase (more than 3 months) when most of the recovery occurs. By incorporating a placebo group, the study addresses a significant gap in the literature by evaluating the efficacy of these treatments against an untreated baseline. A placebo group was necessary because there is no evidence demonstrating that botulinum toxin or baclofen is superior to placebo for motor recovery during the subacute phase after stroke [48]. Botulinum toxin's effect on motor recovery compared to placebo is unlikely to show significant differences due to the small sample size and limited study power, though previous literature suggests potential central effects [21]. An ancillary magnetic resonance imaging study aims to investigate the toxin's impact on brain connectivity, tractography, and activation, making it the first to include both placebo and healthy comparative groups to explore its role in neuroplasticity. The "placebo" group was intentionally kept smaller due to ethical concerns among investigators, who believe it is unethical to withhold spasticity treatment despite the lack of evidence supporting its efficacy for motor recovery. Additionally, a larger placebo group would likely hinder patient recruitment and limit participation from many centers.

Strengths and Limitations

A major strength of this study is its design, which integrates both placebo and active comparator groups to rigorously assess the effects of botulinum toxin and baclofen on motor recovery. The inclusion of a placebo group—despite ethical and logistical challenges—is crucial for disentangling treatment effects from natural recovery processes. Additionally, the ancillary imaging study offers a unique opportunity to explore the central effects of these treatments on brain plasticity.

However, the study has limitations. While the adjusted sample size is sufficient to detect clinically meaningful differences, it may reduce sensitivity to smaller effects on motor recovery outcomes. Furthermore, the follow-up period of 4 months, though valuable for assessing short-term outcomes, does not capture long-term effects or delayed AEs. Extending follow-up durations in future studies could provide more comprehensive insights into sustained efficacy and safety profiles. Nevertheless, the 3-month follow-up in this study offers valuable early insights into the immediate posttreatment phase, which is a critical period for poststroke motor recovery.

Practical or operational issues arose during the course of the study, reflecting the complexity of its implementation. Securing funding from the PHRC in 2010 marked the first step, but the subsequent year-long process to obtain administrative approvals and transfer funds delayed the study's initiation. Ensuring blindness between baclofen tablets and their placebo required encapsulating baclofen tablets after a request to affix the manufacturer's logo was denied. This additional step, involving patient safety measures like verifying expiry dates, added another 2 years. Consequently, the first patient inclusion occurred in 2015. The inclusion rate was slower than anticipated, necessitating a protocol extension and recalculating the required sample size to maintain sufficient statistical power. The COVID-19 pandemic further disrupted the recruitment process in 2020, causing additional delays. Despite these challenges, the study progressed without major technical or procedural issues. Importantly, the question of whether early spasticity treatment affects motor recovery remains unresolved, underscoring the relevance of this research.

Future Directions

The results of this study will inform recommendations for the timing and selection of spasticity treatments after stroke. Future research should build on these findings by examining the long-term impact of these treatments on functional recovery and quality of life. Larger, multicenter trials with extended follow-up periods are needed to confirm the findings and explore delayed effects. Additionally, further investigation into the neurobiological mechanisms underlying the effects of botulinum toxin and baclofen, particularly through advanced imaging techniques, could deepen our understanding of their roles in poststroke recovery. If botulinum toxin demonstrates its potential to boost natural poststroke recovery in clinical or ancillary studies, it may be possible in a larger protocol to focus on these properties independently of spastic symptoms by including patients earlier after stroke (eg, within 2 weeks).

Conclusions

This study addresses critical gaps in the understanding of the effects of early spasticity treatments on motor recovery during the subacute phase of stroke. Comparing botulinum toxin to both baclofen and placebo provides robust insights into the efficacy and safety of these treatments. The ancillary magnetic resonance imaging study further deepens our knowledge of the neurobiological mechanisms underlying recovery, offering the potential to guide future therapeutic strategies. Despite challenges in implementation, the study is well-positioned to advance clinical guidelines and improve outcomes for people who have had a stroke.

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Authors' Contributions

PM and CT conceptualized the study. PM is the chief investigator who led the development of the protocol and secured funding. NB, PM, ECL, XDB, and CC are the investigators who enrolled most of the participants in this study. VR and GT planned the statistical analyses. EM proofread the manuscript, oversaw protocol publication, and will conduct data interpretation and result publication. All the authors have reviewed and approved the final manuscript.

The Baclotox group includes the following collaborators, who contributed to the study and are listed here by their full names: Philippe Marque, Evelyne Castel-Lacanal, Camille Cormier, Nabila Brihmat, Emmeline Montané, Antoine Faurie-Grepon, Claire Lebely, Claire Thalamas, Vanessa Rousseau, Christophe Morin, Philippe Gallien, Stéphane Idée, Huei-Yune Bonnin, Xavier De Boissezon, Bernard Parratte, Etienne Alenton, Pierre Decavel, Patrick Dehail, Claire Delleci, Helene Cassoudessale, Adrien Petit, Michel Begue, Dominic Perennou, Patrick Davoine, Alexis Schnitzler, Gilberte Robain, He´le` ne Le Liepvre, Etienne Allart, Jean-Christophe Daviet, Romain Joste, Isabelle Laffont, Ve´ronique Carre, Fre´de´ric Pellas, Claire Jourdan, Jérôme Froger, Marion Delorme, Alain Yelnik, Maryle` ne Jousse, Dominique Mazevet, Kosta Vassilev, Hélène Robert, Blaise Bignami, Franc¸ois Boyer, Tiphaine Berthier, Claire Le Meur, Anne-Laure Roy, Sabine Petrilli, Emilie Leblong, Isabelle Thiery-Escudie, and Myriam Thiebaut.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Study sites and investigators.
[DOCX File , 24 KB - resprot_v14i1e62951_app1.docx]

Multimedia Appendix 2
Injection sites and recommended dosage.
[DOCX File , 15 KB - resprot_v14i1e62951_app2.docx]

Multimedia Appendix 3
Oversight and monitoring.
[DOCX File , 15 KB - resprot_v14i1e62951_app3.docx]

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Abbreviations

AE: adverse event
ANSM: Agence Nationale de Sécurité du Médicament
CONSORT: Consolidated Standards of Reporting Trials
FMA: Fugl-Meyer Assessment
FMA-LE: Fugl-Meyer Assessment-lower extremity
FMA-UE: Fugl-Meyer Assessment-upper extremity
GABA: γ-aminobutyric acid
MAS: modified Ashworth Scale
PHRC: Programme Hospitalier de Recherche Clinique
RMA: Rivermead Motor Assessment
RNLI: Reintegration to Normal Life
SAE: serious adverse event
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
V0: allocation visit
V1: visit 1
V2: visit 2
V3: visit 3

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VAS: visual analog scale

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Protocol

Evaluating the Efficacy and Safety of 48-Week Low-Dose Dienogest Administration in Patients With Dysmenorrhea Caused by Endometriosis: Protocol for a Randomized, Open-Label, Parallel-Group Trial

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Abstract

Background: The treatment of endometriosis includes analgesics, hormone therapy, and surgery. Even after surgical removal of endometriotic lesions, the risk of recurrence remains high once the normal menstrual cycle resumes. Therefore, long-term hormone therapy is essential to prevent recurrence. Among hormonal treatments, low-dose estrogen progestin preparations are not recommended for patients older than 40 years due to the increased risk of thrombotic side effects. In contrast, dienogest does not carry a thrombotic risk, making it a suitable option for older patients. Although dienogest requires long-term administration until menopause in patients with endometriosis, data on its long-term efficacy and potential adverse effects remain limited. In particular, comparative studies assessing the safety and effectiveness of long-term use of dienogest at different doses (1 mg/day vs 2 mg/day) have not been conducted, highlighting the need for further investigation.

Objective: The purpose of this study is to investigate the efficacy and the incidence of adverse events of dienogest 1 mg/day after 48 weeks in patients with dysmenorrhea due to endometriosis, compared with dienogest 2 mg/day.

Methods: This randomized, open-label, parallel-group, dose-comparison, multicenter trial follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 guidelines and is conducted at 6 centers in Japan. Participants are randomly assigned in a 1:1 ratio to receive either dienogest 1 mg/day or 2 mg/day. The drug is administered for 48 weeks, and its therapeutic effects and side effects are evaluated. Hospital visits include the use of questionnaires, vital sign measurements, imaging studies (magnetic resonance imaging and ultrasound), blood tests, and bone density assessments. The primary endpoint is the change in the pain visual analog scale (VAS) score from baseline to 48 weeks. The VAS is a 10 cm horizontal scale where 0 cm represents no pain and 10 cm represents the maximum imaginable pain; participants indicate their pain level on the scale, and the change is analyzed over time. The target sample size is 88, determined with a noninferiority margin based on existing literature. The protocol was approved by the Nagoya City University Hospital Clinical Research Review Board. Findings will be presented at academic conferences and published in peer-reviewed journals.

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Results: Currently, data collection is ongoing. The first participant was enrolled in August 2021. As of March 22, 2025, a total of 88 participants had been enrolled in this clinical trial.

Conclusions: This is the first trial to compare efficacy and safety between 1 mg/day and 2 mg/day of long-term dienogest use in patients with dysmenorrhea caused by endometriosis. Combining diagnostic imaging with patient questionnaires and blood tests allows the determination of efficacy against endometriosis itself.

Trial Registration: Japan Registry of Clinical Trials jRCTs041210016; https://jrct.mhlw.go.jp/en-latest-detail/jRCTs041210016

International Registered Report Identifier (IRRID): DERR1-10.2196/66246

(JMIR Res Protoc 2025;14:e66246) doi:10.2196/66246

KEYWORDS

endometriosis; dysmenorrhea; dienogest; clinical trial; open-label

Introduction

Background

Endometriosis and Dysmenorrhea

Dysmenorrhea is characterized by menstrual pain, nausea, headaches, and related symptoms. One of its primary causes, endometriosis, is an estrogen-dependent disease affecting sexually mature women. This condition significantly reduces quality of life and imposes a substantial socioeconomic burden [1,2].

The incidence of endometriosis has increased due to delayed childbirth and declining birth rates. Hormonal and anatomical changes associated with menstruation and pregnancy significantly influence the risk of endometriosis. Research indicates that nulliparous women with an earlier age at menarche and shorter menstrual cycles are at the greatest risk due to increased lifetime menstrual exposure. Conversely, among parous women, both higher parity and longer lifetime duration of lactation are associated with a decreased risk of endometriosis. Given the current societal trends of delayed marriage and declining birth rates, it is anticipated that the prevalence of endometriosis will continue to rise in the coming years [3,4].

Although the exact etiology and pathogenesis of endometriosis remain unclear, no effective preventive measures exist. Endometriosis can begin at menarche and persist until menopause [5-7], often requiring long-term treatment. Surgical intervention may be necessary, but estrogen exposure in premenopausal patients increases recurrence risk, necessitating prolonged postoperative hormone therapy.

Hormonal Treatments for Endometriosis

Hormonal treatments include gonadotropin-releasing hormone agonists, low-dose estrogen progestin therapy, dienogest, and the levonorgestrel-releasing intrauterine system.

Gonadotropin-releasing hormone agonists suppress ovulation, inducing a hypoestrogenic state and alleviating symptoms. However, their use is limited to 6 months due to secondary hypoestrogenic side effects [8]. A low estrogen state, also referred to as hypoestrogenic symptoms, is characterized by significantly reduced circulating estrogen levels. This hormonal reduction can affect various bodily functions, including menstrual regulation, bone metabolism, and cardiovascular health. Common hypoestrogenic symptoms include hot flashes, night sweats, vaginal dryness, mood changes, and decreased bone density.

Levonorgestrel-releasing intrauterine system provides sustained annual efficacy without discontinuation risks but may be more difficult to use in patients with uterine fibroids, adenomyosis, or uterine deformities due to expulsion risks [9].

Low-dose estrogen progestin therapy is associated with an increased risk of thromboembolism, making it less favorable for patients aged 40 years or older [10].

Role of Dienogest in Endometriosis Management

Dienogest is a progestin with a lower risk of thromboembolism, making it suitable for patients older than 40 years [11]. It was first approved in Japan in 2007 for the treatment of endometriosis at a dose of 2 mg/day (administered as 1-mg tablets taken twice daily). In 2020, a lower dose of 1 mg/day (administered as 0.5-mg tablets taken twice daily) received approval for the treatment of dysmenorrhea.

However, dienogest 0.5-mg tablets are available only in Japan, and comprehensive knowledge regarding their pharmacological characteristics and potential side effects remains insufficient. In addition, data on the long-term efficacy of dienogest and the side effects associated with low estrogen symptoms are limited [12-14].

Consideration of Pharmacological Mechanisms

The therapeutic effects of dienogest on endometriosis are believed to result from multiple mechanisms. Harada et al [15] reported that dienogest reduces estrogen levels, thereby alleviating symptoms of estrogen-dependent endometriosis. In addition to estrogen suppression, dienogest demonstrates high selectivity for progesterone receptors [16] and exhibits antiproliferative activity in isolated human endometrial cells [17]. Furthermore, it has been shown to reduce the proliferative activity of the endometrium in a dose-dependent manner at doses of 0.5 mg or higher [18]. These findings suggest that dienogest's efficacy may stem not only from lowering serum estradiol levels but also from directly inhibiting endometrial cell proliferation [15].

It has been reported that the use of 0.5 mg tablets results in serum estrogen levels comparable to those of a placebo [19]. However, their efficacy in treating dysmenorrhea has already been demonstrated. If this study shows that 0.5-mg tablets are

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as effective as 1-mg tablets in treating endometriosis, it may provide new insights suggesting that mechanisms beyond estrogen suppression contribute to the improvement of endometriosis.

The objective of this study is to evaluate the long-term efficacy and safety of low-dose dienogest (0.5 mg/day) compared to the standard 1 mg/day regimen in patients with endometriosis. In particular, we focus on the incidence of adverse effects related to estrogen suppression and the potential for improved treatment adherence with lower doses. Clarifying the dose-dependent relationship between pain relief and adverse effects may help to individualize hormonal therapy strategies for endometriosis.

Study Objectives

The objective of this study is to compare the efficacy and safety profiles of dienogest 1 mg/day and 2 mg/day in patients with endometriosis-associated dysmenorrhea over a 48-week treatment period. We hypothesize that dienogest can effectively alleviate menstrual pain in these patients without significant adverse effects. Furthermore, by comparing pain improvement, the incidence of adverse effects over the 48-week period, and the occurrence of menopausal symptoms, this study aims to provide insights into optimal treatment selection for individual patients.

Methods

Study Design and Participants

This study is a randomized, open-label, parallel-group, dose-comparison, multicenter trial conducted at 6 centers in Japan, in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 guidelines (Multimedia Appendix 1). To ensure that participants have endometriosis, only patients diagnosed with ovarian endometriosis were enrolled in the study.

Eligible patients who meet the inclusion and exclusion criteria will be invited to participate in the study by the site investigators (Textbox 1).

Textbox 1. Eligibility criteria.

Inclusion criteria

- Patients who have been diagnosed as having endometriosis (ovarian endometriotic cyst) and have not planned surgery.
- Patients with dysmenorrhea.
- Patients who plan to use dienogest for 48 weeks.
- Patients with a regular menstrual cycle and aged 20 years or older at the time of obtaining consent.
- Patients who have provided written consent to participate in this study.

Exclusion criteria

- Patients who have difficulty verbalizing subjective symptoms related to menstruation, etc.
- Patients currently under treatment for malignant diseases.
- Patients who have taken dienogest, low-dose estrogen progestin preparations, or other hormonal drugs within 4 weeks of obtaining consent.
- Patients in whom it has been difficult to diagnose endometriosis.
- Patients were deemed inappropriate for the study by the study investigator.

Data Collection and Study Procedures

The study data will be collected through a combination of patient questionnaires (Multimedia Appendices 2 and 3), laboratory tests, bone density measurements, and imaging studies, including preregistration magnetic resonance imaging scans and ultrasound examinations.

Once eligibility is confirmed, study personnel will input patient information into the electronic data capture system to facilitate enrollment and randomization. Randomization using the permuted block method with a block size of 2 or 4 will be stratified based on allocation factors, such as patient age and the presence or absence of uterine adenomyosis.

Treatment will commence on the second to fifth day of the first menstrual cycle following enrollment. Patients will be randomly assigned to receive either dienogest 0.5 mg (1 mg/day group) or dienogest 1 mg (2 mg/day group), administered orally twice daily for up to 48 weeks. Follow-up visits will be scheduled at 4 weeks post enrollment and every 12 weeks thereafter.

At each follow-up visit, comprehensive assessments will be conducted, including patient questionnaires, vital sign measurements, blood tests, and ultrasound examinations to evaluate the size of ovarian endometriotic cysts. A magnetic resonance imaging scan will be performed before study enrollment to establish baseline imaging data. Pain symptoms and estrogen-deficiency symptoms will be assessed through standardized questionnaires. Dysmenorrhea-related pain will be evaluated using the visual analog scale (VAS) and a modified dysmenorrhea score based on Harada et al [20] (Table 1).

The dysmenorrhea score (total score: 0 to 6) is the sum of the subscores on the severity of pain and the use of analgesics.

Estrogen-deficiency symptoms will be assessed using the Kupperman score (Table 2).

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Table 1. Dysmenorrhea score.

Degree	Definition	Score
Pain		
None	No pain.	0
Slight	Some difficulty with work, household chores, and schoolwork.	1
Moderate	Interference with work, housework, or schoolwork to the point of needing to lie down and take a break.	2
Severe	Sleeping for more than 1 day and unable to work, do housework, or study.	3
Painkiller usage		
None	None.	0
Slight	Used painkillers for 1 day during menstrual period.	1
Moderate	Used painkillers for 2 days during menstrual period.	2
Severe	Used painkillers for 3 days during menstrual period.	3

Table 2. Kupperman score.

Symptom	Degree	Evaluation
Hot and sweaty face	3,2,1,0	4
Numbness in the limbs and loss of sensation	3,2,1,0	2
Difficulty falling asleep and waking easily	3,2,1,0	2
Easily agitated and nervous	3,2,1,0	2
Worried and depressed	3,2,1,0	2
Feeling dizzy or nauseous	3,2,1,0	1
Tire easily	3,2,1,0	1
Pain in the shoulders, knees, and knots in the hands and feet	3,2,1,0	1
Headache	3,2,1,0	1
Palpitations	3,2,1,0	1
Feels like ants crawling on the skin	3,2,1,0	1

To determine the score, multiply the “Degree of Symptomatology” (Degree) number by the “Rating Scale” number (Evaluation).

Scoring is classified as follows: mild disease: 16-20, moderate: 21-34, and severe: 35 and above. Degree is defined as strong: 3, moderate: 2, weak: 1, and none: 0.

Patients will be allowed to use analgesics for the management of dysmenorrhea-related pain as needed. Bone density assessments will be conducted twice, at the beginning and end of the study period, using dual-energy x-ray absorptiometry.

Study Endpoints

The primary efficacy endpoint is the change in VAS from baseline to 48 weeks after administration. The secondary endpoint of effectiveness evaluation is the amount of change in the dysmenorrhea score from baseline to 48 weeks after administration. Another secondary endpoint is the rate of reduction in the size of ovarian endometriotic cysts from the baseline to 48 weeks after administration.

For safety evaluation, an important safety endpoint is the incidence of symptoms related to low estrogen (symptoms other than those listed in the Kupperman score) during the study treatment phase. Symptoms are listed in question number 5 of the questionnaire (Multimedia Appendix 3).

Other safety endpoints include the amount of change in the Kupperman score, the rate of change in bone density, and the amount of change in blood estradiol concentration from baseline to 48 weeks after administration.

Statistical Analysis

The primary analysis involves comparing the change in VAS from baseline to 48 weeks between the dienogest 1 mg/day group and 2 mg/day group using the mean difference and its 95% CI. When the lower limit of confidence exceeds –15 (noninferiority margin), the noninferiority of the effect of the 1-mg group to the 2-mg group will be recognized.

For the secondary efficacy endpoint, each of the dienogest 1 mg/day group and the 2 mg/day group will be compared to estimate the difference and its 95% CI for the mean value of dysmenorrhea score and change in endometriotic cyst size from baseline to 48 weeks.

In the safety evaluation, the frequency of low estrogen symptoms during the study treatment period is aggregated, and a 95% CI is calculated that is based on a normal approximation

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of the binomial distribution. In addition, a chi-square test will be used to compare groups. The 2-sided significance level is 5%.

The frequencies of the occurrence of adverse events and side effects are calculated for the safety analysis target population. As a secondary safety analysis, each of the dienogest 1 mg/day group and 2 mg/day group will be compared to estimate the difference and its 95% CI for the mean value of bone density, Kupperman score, and estrogen concentration. Statistical analyses are performed by R (version 4.1.0; R Foundation for Statistical Computing).

Sample Size

Based on a Japanese study [21], the mean change in VAS after 52 weeks with 1 mg dienogest was –52.1 (SD 24.13) for secondary dysmenorrhea. In the Japanese phase II dose-finding study, [19] the average change in VAS was –35.74 at 0.25 mg×2, –44.31 at 0.5 mg×2, and –50.78 at 1 mg×2 at 12 weeks. Therefore, it is assumed that at least an effect of 0.25 mg×2 or more can be expected by this test administration, and the noninferiority margin is set to 15. It is assumed that the effects of the 1 mg group and the 2 mg group are similar, and SD is assumed to be 24.13 with reference to the Japanese phase III study. [22] In the above setting, 41 cases in each group (82 cases in total) are required to achieve a power of 80% at a one-sided significance level of 2.5%. When 5% of dropout cases are added to each group, the required sample size becomes 44 cases in each group (88 cases in total).

We evaluated the incidence of low estrogen symptoms during the study treatment period as an important secondary endpoint. On the basis of the long-term use of dienogest [23], we assumed the incidence proportion for dienogest 1 mg/day and 2 mg/day to be 20% and 50%, respectively, with the chi-squared test providing more than 80% power at a 2-sided significance level of 5%. Therefore, the sample size in this study (88 cases in total) is also sufficient to assess the incidence of low estrogen symptoms.

Ethical Considerations

The study protocol was approved by the accredited clinical research review committee of the Naoya City University Hospital Clinical Research Review Board (approval number 2021A001-23b001). Informed consent was obtained from all participants before their enrollment. Researchers must ensure that all patients who have provided written informed consent meet the inclusion criteria and do not meet any of the exclusion criteria. The study adheres to the ethical principles of the Declaration of Helsinki. All data are anonymized to protect participant privacy. No personally identifiable information is included in the dataset. In addition, stringent protective measures such as encrypted data storage and restricted access protocols have been implemented to ensure data confidentiality.

Results

Participant enrollment for the trial has been completed. The first participant was enrolled in August 2021, and a total of 88 participants have been enrolled, with 44 participants allocated to each group (Figure 1). As of March 22, 2025, data collection has been finalized and is currently being fixed for analysis. Study flowchart showing the allocation of participants, in accordance with the CONSORT (Consolidated Standards of Reporting Trials) checklist (Multimedia Appendix 4).

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flowchart. DNG: dienogest.

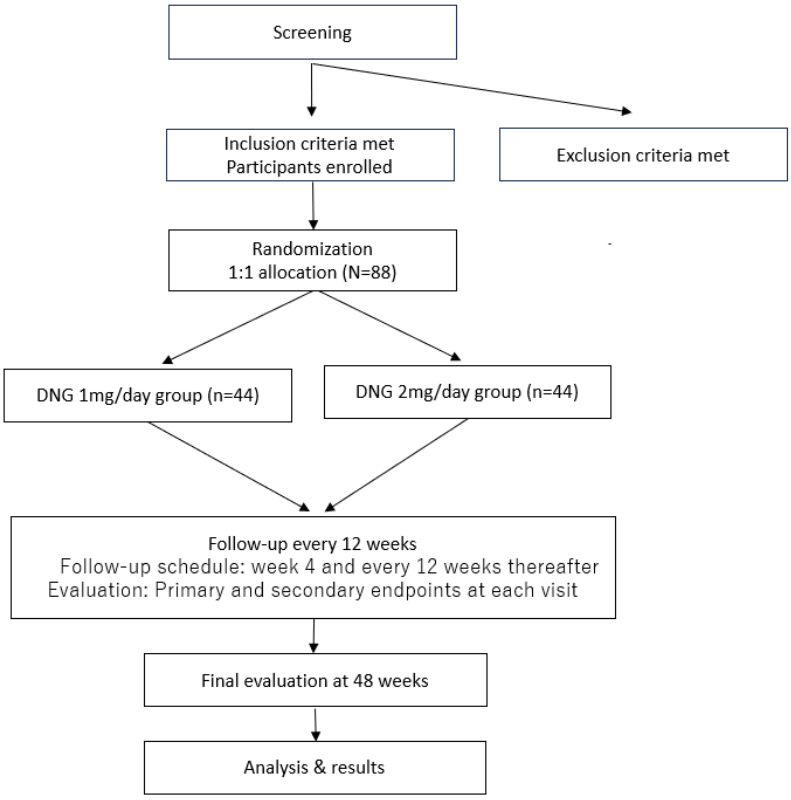

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Discussion

Principal Findings

This study aims to demonstrate that dienogest 0.5 mg tablets are as effective and safe as dienogest 1-mg tablets in the treatment of endometriosis. Furthermore, based on the evaluation results from this study, recommendations for the optimal use of dienogest 0.5-mg and 1-mg tablets could be proposed.

Currently, 0.5 mg dienogest tablets are approved for dysmenorrhea, but their effectiveness in improving endometriosis symptoms and lesions remains unclear.

Osuga et al [19] conducted a study comparing dienogest 1 mg/day and 2 mg/day in patients with primary dysmenorrhea and reported equivalent improvements in VAS scores between the 2 groups. However, this study did not include patients with endometriosis-related dysmenorrhea, making it insufficient to evaluate the efficacy of dienogest for endometriosis.

Another study by Osuga et al [22] compared dienogest 1 mg/day with placebo and demonstrated its efficacy in treating dysmenorrhea. However, only approximately 23% of the study population had endometriosis, which is insufficient to fully assess its effectiveness for this condition. Currently, there are no other studies comparing dienogest 0.5-mg tablets with 1-mg tablets for endometriosis, and thus, the findings of this study are expected to provide novel insights into the efficacy and safety of dienogest 0.5-mg tablets for endometriosis.

With respect to serum estrogen levels during dienogest administration, it was observed that estrogen levels did not decrease significantly with a 1 mg/day dosage compared with the placebo group. However, a dose-dependent reduction in estrogen levels was observed [19,24].

Prolonged hypoestrogenic states induced by dienogest therapy may increase the risk of adverse effects such as bone mineral density loss. Estrogen plays a crucial role in maintaining bone homeostasis by promoting osteoblast activity and inhibiting bone resorption by osteoclasts [25].

In a study by Momoeda et al [12], bone density changes were measured at 24 and 52 weeks following the administration of 2 mg/day of dienogest. There was a significant reduction in bone mass at both time points (mean –1.6%, SD 2.4%; $P<.001$; mean –1.7%, SD 2.2%; $P<.001$), though the decrease was concluded to be mild. According to Seo et al [13], after one year of administering dienogest 2 mg/day, lumbar spine bone mineral density decreased by 2.2% at 6 months and by 2.7% after 1 year compared to baseline. Furthermore, 75% (45/60) of women experienced significant bone mineral density reduction after one year. Given the high likelihood that dienogest-induced bone density reduction is correlated with estrogen levels [15], it is anticipated that the 1 mg/day group in this study will exhibit less bone loss.

While bone density reduction has been the primary focus of existing studies, other low estrogen symptoms, such as vasomotor symptoms, mood changes, and cardiovascular risks, also warrant evaluation in the context of long-term dienogest administration. Although the frequency of these symptoms is expected to be low with dienogest therapy, this study will assess the incidence and severity between the 1 mg/day and 2 mg/day groups. By analyzing these differences, this study aims to clarify whether dosage variations influence adverse effects beyond bone density reduction and provide insights into dose selection for the treatment of endometriosis-associated dysmenorrhea.

Limitations

This study has several limitations. First, only patients with ovarian endometriotic cysts were included, excluding cases of endometriosis without ovarian involvement. This selection criterion was implemented to ensure diagnostic accuracy and maintain a homogeneous study population. However, future studies may be needed to evaluate the effects of long-term dienogest therapy in patients with other forms of endometriosis.

Second, as it was not conducted as a double-blind trial, there is a potential risk of bias in VAS and dysmenorrhea score evaluations.

This study was conducted within the framework of Japan's health insurance system, which required specifying the prescribed drug formulation (0.5-mg or 1-mg tablet). Consequently, blinding was not feasible, and an open-label design was adopted. To minimize bias, we implemented 3 key measures. First, objective assessments, including ultrasound imaging, hormone levels, and bone density, were incorporated as primary endpoints to reduce reliance on subjective pain evaluations. Second, centralized randomization via an electronic data capture system was used to eliminate selection bias. Third, covariate adjustment for age and adenomyosis presence ensured balanced group allocation. These strategies enhance the study's validity and reliability.

Given that endometriosis often requires long-term treatment until menopause, evaluating the efficacy and safety of extended dienogest administration is crucial. Although the observation period of this study is limited to 48 weeks, it provides valuable data, as no previous study has examined the effects of 1 mg/day beyond 12 weeks. Further research with extended observation periods is necessary to assess long-term efficacy and safety.

Conclusions

This study will enable us to evaluate the efficacy and safety of the dienogest dosage over 48 weeks and provide a more precise and safer treatment for patients with endometriosis.

After the completion of the study, the treatment of endometriosis and assessment of side effects in enrolled patients will continue. The findings from this study will be disseminated through conference presentations and academic publications to contribute to the ongoing refinement of treatment strategies for endometriosis.

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Acknowledgments

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Data Availability

As this study is still ongoing, the data are not currently available for public use. However, the datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

KK, RA, and K-IM contributed to conceptualization and methodology. TI provided formal analysis and data curation. KK, RA, MI, and K-IM were responsible for writing —original draft and writing—review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 175 KB - resprot_v14i1e66246_app1.pdf]

Multimedia Appendix 2
This figure shows the medical questionnaire for the first visit.
[PNG File , 49 KB - resprot_v14i1e66246_app2.png]

Multimedia Appendix 3
This figure shows the medical questionnaire for the 2nd and subsequent visits.
[PNG File , 51 KB - resprot_v14i1e66246_app3.png]

Multimedia Appendix 4
CONSORT (Consolidated Standards of Reporting Trials) checklist.
[PDF File (Adobe PDF File), 2560 KB - resprot_v14i1e66246_app4.pdf]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
VAS: visual analog scale

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Protocol

Clinical Efficacy and Safety of the Herbal Prescription, HH333, in Preventing Recurrent Stroke in Patients With Ischemic Stroke Induced by Small-Vessel Disease: Protocol for Multicenter, Double-Blind, Randomized, Prospective, Pilot Clinical Trial

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Abstract

Background: Patients with ischemic stroke are at high risk of recurrence, making preventive care an important factor. Current antiplatelet therapy for recurrence prevention treatment has several limitations. Recent retrospective observational studies suggested that HH333, an herbal prescription, has an inhibitory effect on stroke recurrence in small-vessel diseases.

Objective: This study aims to propose a protocol for evaluating the efficacy and safety of HH333 in patients with ischemic stroke induced by small-vessel disease.

Methods: In this multicenter, double-blind, randomized, prospective, pilot clinical trial, 236 patients from 3 university Korean medicine hospitals in South Korea with ischemic stroke caused by small-vessel disease will be recruited and randomly assigned to either the HH333 or the placebo group. Both patients and investigators will be blinded to prevent access to the allocation results. The HH333 group will take 2 capsules of HH333 once daily for 720 days, whereas the placebo group will take HH333 placebo capsules in the same manner. Efficacy will be assessed using the recurrence rate of ischemic stroke, which will be assessed on days 30, 90, 180, 270, 360, 450, 540, 630, 720, and 750 after starting the medication. The effects on quality of life and fatigue with the Fatigue Severity Scale (FSS), Fatigue Assessment Scale (FAS), and Korean Patient Health Questionnaire (K-PHQ-9), functional improvement with Korean National Institutes of Health Stroke Scale (K-NIHSS), modified Rankin Scale (mRS), Korean modified Barthel Index (K-mBI), and Korean Montreal Cognitive Assessment (K-MoCA) and Pattern Identification also will be evaluated on days 0, 90, 180, 270, 360, 450, 540, 630, and 720 after starting the medication. Safety will be evaluated by performing blood and urine tests and electrocardiography on days 30, 90, 180, 270, 360, 450, 540, 630, and 720 after starting the medication.

Results: Recruitment for the study started on May 22, 2024, and is scheduled to end on November 30, 2026. As of November 13, 2024, a total of 12 participants have been randomized.

Conclusions: The protocol will provide a detailed process for a clinical trial evaluating the efficacy of preventing recurrent ischemic stroke caused by small-vessel disease and improving neurologic symptoms and the safety of HH333 in ischemic stroke. The results of this study provide a basis for alternative treatments to prevent and treat ischemic stroke.

Trial Registration: Clinical Research Information Service KCT0009431; https://tinyurl.com/y2ctvje8

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International Registered Report Identifier (IRRID): DERR1-10.2196/70953

(JMIR Res Protoc 2025;14:e70953) doi:10.2196/70953

KEYWORDS

HH333; ischemic stroke; herbal medicine; randomized controlled trial; protocol

Introduction

Patients with ischemic stroke are at high risk for recurrence [1]. Generally, ischemic stroke recurrence rates over 5 years range from 10% to 53% [2]. Recurrent stroke is associated with twice the risk of death and worse functional outcomes compared to patients with first-time stroke [3]. It also costs twice as much as hospitalization for a first-time stroke [4].

Antiplatelet or anticoagulant therapy is currently recommended as the first-line treatment for the prevention of recurrent ischemic stroke [5]. However, there are differences in the pathogenesis of ischemic stroke between Western and Asian populations, with Northeast Asians such as Koreans, Chinese, and Japanese having a higher proportion of strokes caused by small-vessel disease than Westerners [6,7]. Ischemic stroke induced by small-vessel disease usually results from the gradual thickening of the vessel wall caused by hypertension and is more likely to be accompanied by intracerebral microbleeds [8]. This may limit the use of antiplatelet or anticoagulant medications that may increase the bleeding propensity. HH333 is a complex herbal medicine that has inhibitory effects on coenzyme A reductase and pancreatic lipase [9], antioxidant and anti-inflammatory effects through suppression of nitric oxide biosynthesis and prostaglandin E2 [10], antihyperlipidemic and anti-inflammatory effects through activation of nitric oxide production [11], and endothelial cell proliferation through activation of MAP kinase [12]. Previous clinical studies have reported antihypertensive effects in stroke patients with hypertension [13], antilipidemic effects in patients with hypercholesterolemia [14], immediately improving cerebral blood flow in normal subjects [15], and improvement in arterial stiffness in patients with increased pulse wave velocity [16]. Based on these effects, HH333 is a promising medication for cerebrovascular and cardiovascular disease [17].

Specifically, HH333 inhibits the progression of microangiopathy, a key factor in small-vessel disease, and thus prevents the recurrence of ischemic stroke induced by small-vessel disease with a 2-year recurrence rate was 1.12%-2.02% [18-20], which is less than conventional antiplatelet agents [21-24]. Regarding safety, a previous retrospective study showed that the incidence of adverse events with HH333 was 2.0%, with no serious adverse events (SAEs) [25]. However, since these studies were all single-arm retrospective observational studies, there is no comparative analysis with a control group, and the data rely on medical records, which can be inaccurate. Therefore, there is a need for prospective clinical studies with a control group to rationalize and better understand these findings.

We present a protocol for a randomized controlled clinical trial to validate the clinical efficacy and safety of HH333 in patients with ischemic stroke induced by small-vessel disease. This study aimed to provide a high level of evidence for the efficacy of HH333 in ischemic stroke and ultimately propose a novel alternative for stroke treatment.

Methods

Study Design

This multicenter, double-blind, randomized controlled trial (RCT) aimed to assess the prevention of recurrent ischemic stroke and the safety of HH333 in patients with ischemic stroke induced by small-vessel disease. It was conducted at 3 university Korean medicine hospitals in South Korea: Kyung Hee University Korean Medicine Hospital, Dongguk University Ilsan Korean Medicine Hospital, Wonkwang University Gwangju Korean Medicine Hospital. Within 90 days of onset at baseline, patients will receive HH333 or a placebo, 2 capsules (800 mg) at a time, once a day for 720 days. The clinical effect of HH333 will be evaluated by ischemic stroke recurrence, which is the primary efficacy endpoint, at baseline and on days 30, 90, 180, 270, 360, 450, 540, 630, 720, and 750 after starting the medication. Total scores on the Fatigue Severity Scale (FSS), Fatigue Assessment Scale (FAS), Korean Patient Health Questionnaire (K-PHQ-9), and the probability of each type of Pattern Identification (fire heat, dampness-phlegm, qi deficiency or yin deficiency) will be evaluated as secondary efficacy endpoints at baseline and 90, 180, 270, 360, 450, 540, 630, and 720 days after starting medication. The total scores on the Korean National Institutes of Health Stroke Scale (K-NIHSS), modified Rankin Scale (mRS), Korean Modified Barthel Index (K-mBI), and Korean Montreal Cognitive Assessment (K-MoCA) will also be measured as exploratory endpoints at the same time as the secondary efficacy endpoints. The safety of HH333 will be assessed based on the presence of adverse events at the same time as the primary efficacy endpoints. The enrollment, interventions, and assessments of the study are summarized in Table 1. A schematic of the study process is shown in Figure 1.

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Table 1. Schedule of enrollment, interventions, and assessments.

Visit	0	1	2	3	4	5	6	7	8	9	10	11[a]	UV[b]
Day	–14[c]	0	25-35	80-100	165-195	255-285	345-375	435-465	525-555	615-645	705-735	745-755	
Informed consent	✓												
Demographic information[d]	✓												
Medical history[e]	✓												
History of ischemic stroke[f]	✓												
Medications[g]	✓												
Physical examination	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		If needed
Vital sign	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		If needed
Physical measurements	✓												
Laboratory tests[h]	✓												
Electrocardiogram	✓		✓	✓	✓	✓	✓	✓	✓	✓	✓		If needed
Evaluating inclusion and exclusion criteria	✓												
Randomized allocation		✓											
Experiment medication administration		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Medication adherence[i]			✓	✓	✓	✓	✓	✓	✓	✓	✓		If needed
Concomitant treatment		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	If needed
Primary efficacy endpoint: recurrence of ischemic stroke			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	If needed
Secondary efficacy endpoints[j]		✓		✓	✓	✓	✓	✓	✓	✓	✓		If needed
Exploratory endpoints[k]		✓		✓	✓	✓	✓	✓	✓	✓	✓		If needed
Safety assessments[l]			✓	✓	✓	✓	✓	✓	✓	✓	✓		If needed
Adverse events[m]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	

[a]Telephone investigation.

[b]UV: Unscheduled visit. Visiting on a day other than the original visit schedule due to an adverse event, etc.

[c]Screening performed within 14 days of informed consent.

[d]Age, sex, smoking, and alcohol history.

[e]Within 1 year prior to visit 0.

[f]Time of first onset and diagnosis (including year, month, and day if possible), date of computed tomography or magnetic resonance imaging, ischemic stroke territory, Trial of Org 10172 in Acute Stroke Treatment classification, history of stroke-related surgery, stroke risk factors, and stroke-related symptoms.

[g]Within 4 weeks prior to visit 0.

[h]Complete blood count (red blood cell, hemoglobin, hematocrit, platelet, white blood cell); biochemistry (fasting blood glucose, blood urea nitrogen, creatinine, natrium, potassium, chloride, aspartate aminotransferase, alanine aminotransferase, C-reactive protein, calcium, uric acid); urine human chorionic gonadotropin for women of childbearing age, excluding sterilization and menopause (more than 12 months since last menstrual period); premature menopause before the age of 40 years, follicle-stimulating hormone test for differential diagnosis.

[i]Drop out if <80%.

[j]Total scores of Fatigue Severity Scale (FSS), Fatigue Assessment Scale (FAS), Korean Patient Health Questionnaire (K-PHQ-9), and probability of each type of Pattern Identification (fire heat, dampness-phlegm, Qi deficiency, and Yin deficiency).

[k]Total scores of the Korean National Institutes of Health Stroke Scale (K-NIHSS), Korean modified Rankin Scale (K-mRS), Korean modified Barthel Index (K-mBI), Korean Montreal Cognitive Assessment (K-MoCA).

[l]Complete blood count (red blood cell, hemoglobin, hematocrit, platelet, white blood cell); biochemistry (fasting blood glucose, blood urea nitrogen, creatinine, natrium, potassium, chloride, aspartate aminotransferase, alanine aminotransferase, C-reactive protein, calcium, uric acid); urine tests (specific gravity, pH, albumin or protein, glucose, ketone, bilirubin, occult blood, urobilinogen, nitrite, leukocyte, human chorionic gonadotropin for women of childbearing age); electrocardiogram; hemorrhage events (cerebral hemorrhage, gastrointestinal bleeding, etc) related to antiplatelet or anticoagulant;

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vital sign; physical examination.

[m]Self-reported by the participant or judged by the investigator.

Figure 1. Flowchart of the study process FSS, Fatigue Severity Scale; FAS, Fatigue Assessment Scale; K-mBI, Korean modified Barthel Index; K-MoCA, Korean Montreal Cognitive Assessment; K-NIHSS, Korean National Institutes of Health Stroke Scale; K-PHQ-9, Korean Patient Health Questionnaire; mRS, modified Rankin Scale.

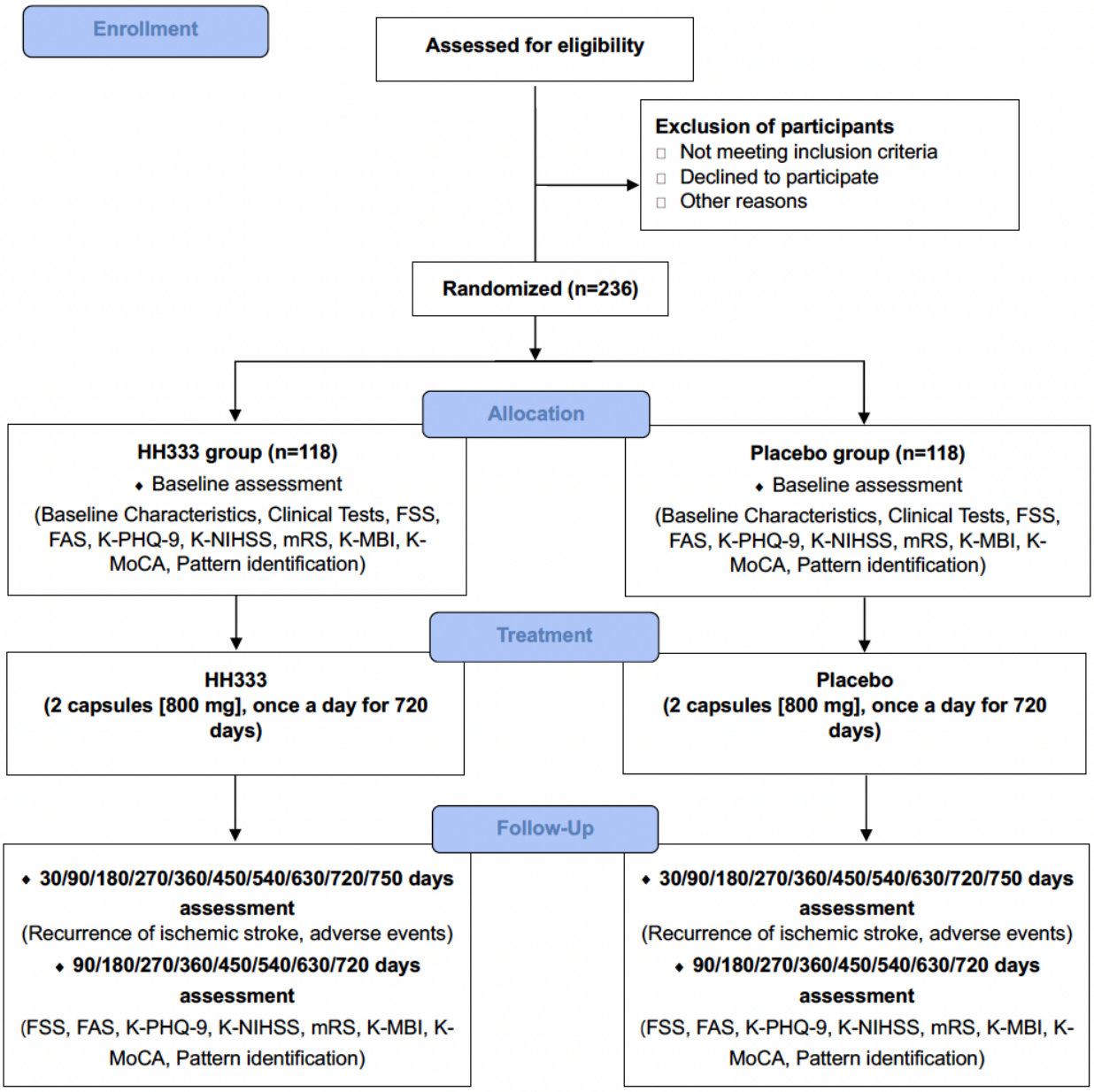

Eligibility

Eligibility criteria and other details are listed in Textbox 1.

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Textbox 1. Inclusion criteria, exclusion criteria, and dropout criteria.

Inclusion criteria

- Men and women aged 19 to 80 years.
- Diagnosed with ischemic stroke induced by small-vessel disease in the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification within 90 days of screening based on new neurologic and brain imaging (computed tomography or magnetic resonance) findings to support them.
- Participants had no communication problems and voluntarily agreed to participate.

Exclusion criteria

- Diagnosis of degenerative brain diseases (eg, Parkinson's disease, Alzheimer disease, etc).
- Have a brain condition other than ischemic stroke (eg, brain tumor, traumatic brain injury, arteriovenous malformation, Moyamoya disease, and stroke due to these conditions).
- Unstable vital signs at screening (eg, systolic blood pressure greater than 160 mm Hg despite taking blood pressure medications).
- Serious medical condition (eg, liver cirrhosis, chronic kidney disease stage V, or severe heart failure of New York Heart Association (NYHA) grade III or greater).
- History of malignancy, including leukemia and lymphoma, within the past 5 years.
- Hepatic and renal dysfunctions.
  - Aspartate aminotransferase, alanine aminotransferase ≥2 times the upper limit of normal at screening.
  - An estimated glomerular filtration rate < 60 mL/min/1.73 m2 at screening.
- Within 24 hours of onset.
- Patients with Korean National Institutes of Health Stroke Scale (K-NIHSS) score 21 to 42.
- Pregnant, nurses, or women of childbearing potential who have negative pregnancy test results and have not agreed to use contraception during the study.
- Previously experienced hypersensitivity after taking HH333's constituent medicines *Scutellariae radix*, *Coptidis rhizoma*, *Phellodendri cortex*, *Gardeniae fructus*, and *Rhei rhizoma*.
- Any other study medications administered within 30 days prior to screening.
- Patients who have not been administered the study medication or who have participated in a simple observational clinical trial are eligible.
- Difficulty taking the doses required in this study.
- Judged by the investigator as nonconformity for participation in the trial for any reason.
- Plans to use anticoagulants during the study or have difficulty discontinuing them.

Dropout criteria

If the researcher determines that it is not appropriate for the study to continue according to the dropout criteria, the researcher may stop the treatment and evaluation and drop the participant. Participants may also drop out of the study at any time of their free will. The dropout criteria were as follows:

- Found not to meet inclusion or exclusion criteria after screening.
- Patients or caregivers withdraw consent during the study period.
- Patients or caregivers request to discontinue the study or refuse treatment during the study.
- Participants cannot be traced.
- According to the judgment of the investigator, the patient is no longer able to participate in the study because of adverse events or comorbidities.
- Study medication compliance <80%.
- Participation in another clinical trial.
- Judged by the investigator as unfit to continue the study for any other reason.

Recruitment

A total of 236 patients with ischemic stroke induced by small-vessel disease will be recruited through walk-in or hospital and school bulletin boards, public transportation billboards, newsletters, and other online advertisements. Participants who wish to participate will receive the consent form and provide written consent of their own free will. Multimedia Appendix 1 presents the research consent form. Participating in the study will be decided if the researcher determines that they are suitable through the screening process. The screening items were as follows: demographic information, medical history, history of ischemic stroke, medications, physical examination, vital signs, physical measurements, laboratory findings, electrocardiogram,

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and evaluation of the inclusion and exclusion criteria. All data were simultaneously recorded in a case report form.

Randomization, Blinding, and Allocation Concealment

A total of 236 participants who met the criteria were assigned to the HH333 or control group at a ratio of 1:1 by a statistician independent of this clinical study, using the block randomization method with R 4.4.0 (Comprehensive R Archive Network). Patients and investigators will be blinded to prevent access to the allocation results. Patients will be blinded to the study medication they are administered because they are taking either the treatment medication or a placebo. The treatment medication and placebo will be identical in size, shape, and appearance and packaged in the same type of packaging.

For allocation concealment, an independent statistician who generates the random numbers delivers a randomization code to each clinical trial site in a sealed, impermeable envelope. The investigators at each site will open the randomization envelopes in sequence in front of the patients to assign participants, and the open envelopes will be kept separate.

Interventions

HH333 or placebo capsules (one dose: 2 capsules, 800 mg) will be orally administered with water once a day on an empty stomach after waking for 720 days. HH333 is an herbal medicine manufactured by Kyungjin Pharmaceutical Co, Ltd. (Icheon, Republic of Korea). It is a capsule formulation derived from 80% ethanol extracts of *Scutellariae radix*, *Coptidis rhizoma*, *Phellodendri cortex*, *Gardeniae fructus*, and *Rhei rhizoma* (Table 2). The placebo was a capsule manufactured by Kyungjin Pharmaceutical Co., Ltd. (Icheon, Republic of Korea) with the same appearance as HH333.

Table 2. Composition of HH333.

Constituent herbs	Scientific names	Weight (g)
Scutellariae radix	*Scutellaria baicalensis* Georgi (from Republic of Korea)	0.28
Coptidis rhizoma	*Coptis japonica* Makino (from Republic of Korea)	0.28
Phellodendri cortex	*Phellodendron amurense* Ruprecht (from Republic of Korea)	0.28
Gardenia fructus	*Gardenia jasminodes* Ellis (from Republic of Korea)	0.28
Rhei rhizoma	*Rheum palmatum* L. (from Republic of Korea)	0.07
Total		1.2

Medication compliance will be recorded in patients taking either HH333 or placebo. The participants will be instructed to return the empty containers of study medications taken and the remaining medications at each visit to count the actual number of doses of study medications. Compliance was calculated as follows:

If compliance was less than 80% at any point during the study, the participant was excluded from the study

Outcome Measurements

The clinical efficacy of HH333 in patients with ischemic stroke induced by small-vessel disease will be evaluated based on whether ischemic stroke recurrence occurs after administration of HH333. Furthermore, the effects on quality of life and fatigue will be evaluated by measuring FSS, FAS, and K-PHQ-9 scores, and changes in pattern identification probability will be investigated to provide basic data for the Korean medicine treatment of stroke. The K-NIHSS, mRS, K-mBI, and K-MoCA will be used to assess functional improvements related to ischemic stroke. All outcome measurements will be conducted through face-to-face visits.

Primary Endpoint: Recurrent Ischemic Stroke

Recurrent ischemic stroke within 750 days while taking the study medication was investigated. Recurrent ischemic stroke is defined as a new neurological finding supported by new imaging findings. New neurological findings corresponded to the sudden onset of neurological symptoms identified on neurological examinations that did not occur prior to study participation. New radiological findings are abnormal findings on brain imaging (computed tomography or magnetic resonance), which can explain new neurological findings that did not exist before study participation. The investigation will be conducted on days 30, 90, 180, 270, 360, 450, 540, 630, 720, and day 750, which is 30 days after the end of administration.

Secondary Endpoints: FSS, FAS, K-PHQ-9, Pattern Identification

The FSS is a 9-item, self-reported screening tool developed by Krupp et al [26] that assesses fatigue over the past week on a scale of 1 to 7 per item, with higher total scores indicating higher levels of fatigue. The FAS is a 10-item, self-reported screening tool developed by Michielsen et al [27] that examines the psychometric qualities due to fatigue on a scale from 1="Never" to 5="Always" per item, with a higher total score indicating higher levels of the psychological impact of fatigue. The PHQ-9, developed by Kroenke et al [28] was validated in the Korean version [29]. It comprises 9 items in total. Respondents rate the frequency of symptoms on a scale of 0-3 per item, with a total score of 10 or higher indicating major depression. These secondary endpoints will assess the clinical effectiveness of HH333 on poststroke fatigue and depression. Pattern identification is a unique diagnostic system in Korean medicine, and the diagnosis of stroke is based on 4 patterns which are fire heat, Dampness-phlegm, Qi deficiency, and Yin deficiency [30]. Jung et al [31] developed an equation model that predicts the probability of each pattern identification diagnosis given variables for stroke pattern identification and is being used for Korean medicine's standardized diagnosis of patients with stroke. Using a stroke pattern identification prediction model,

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the change in each pattern identified after HH333 administration was collected to obtain data for stroke treatment in Korean medicine. Investigations were conducted during the administration period on days 0 (baseline), 90, 180, 270, 360, 450, 540, 630, and 720.

Exploratory Endpoints: K-NIHSS, mRS, K-mBI, and K-MoCA

The NIHSS is a tool for assessing neurological deficits resulting from stroke developed by the National Institutes of Health [32] and is currently the most widely used tool for stroke severity assessment, with a Korean version validated and used [33]. It comprises 15 questions in 11 checkpoints, each of which is scored on a scale of 0 to 4, with a total score calculated, with higher scores indicating higher severity. The mRS is a tool developed by van Swieten et al to assess the degree of disability in patients with stroke [34] and is currently the most widely used stroke functional assessment scale [35]. It is rated on a scale of 0 to 6, with higher scores indicating more severe impairment. The mBI is a tool to assess independence in activities of daily living after stroke developed by Shah et al [36], and translated with validation in Korean [37]. It contains 10 questions, each rated on a scale of 0 to 5, 0 to 10, or 0 to 15, with a higher total score indicating a lower dependency. The MoCA is a tool that examines cognitive function and was originally developed to identify mild cognitive impairment [38] but is now widely used for cognitive impairment caused by stroke, and the Korean version has been validated and used [39]. It consists of visuospatial and executive (5 points), naming (2 points), attention (6 points), language (3 points), abstraction (2 points), delayed recall (5 points) and orientation (6 points). The perfect score is 30, with a higher total score indicating higher cognitive function. Investigations were conducted during the administration period on days 0 (baseline), 90, 180, 270, 360, 450, 540, 630, and 720.

Safety Assessments and Monitoring

At each visit, participants will be screened for adverse events, laboratory tests, urine findings, electrocardiograms, hemorrhagic events such as cerebral hemorrhage or gastrointestinal bleeding related to antiplatelet or anticoagulant use, vital signs, and physical examinations. Laboratory findings included complete blood count (red blood cells, hemoglobin, hematocrit, platelets, and white blood cells) and biochemistry (fasting blood sugar, blood urea nitrogen, creatinine, natrium, potassium, chloride, aspartate aminotransferase, alanine aminotransferase, C-reactive protein, calcium, and uric acid). Urine findings included specific gravity, pH, albumin or protein, glucose, ketone, bilirubin, occult blood, urobilinogen, nitrite, leukocytes, and human chorionic gonadotropin in women of childbearing age. Adverse events included both self-reported symptoms and those judged by the investigator and were collected until 30 days after the end of administration.

After collecting all adverse events that appeared as test findings and symptoms in each group, we compared the frequency and severity of adverse events between the groups and their relationship with the study medications. Adverse events that are not related to the study medications do not meet the criteria for dropout but allow the patient to receive the best possible care regardless of the study. If SAEs occur, the study will be stopped immediately, in part or in whole, and the study researcher will report it to the principal investigator and the institutional review board for appropriate action.

Concomitant Medication

All concomitant medications except conventional treatments for ischemic stroke are prohibited. Medications that have been used for the participants' underlying medical condition for 12 weeks prior to screening that are considered stable and unlikely to affect the interpretation of the results of this study with no change in dosage or dose will be allowed with a note of the reason, as determined by the investigator. Transient symptoms unrelated to stroke, such as cold, flu, dyspepsia, constipation, and concomitant use, will be allowed on a one-time basis at the discretion of the investigator. The use of supplements such as vitamins is not permitted. The use of vitamin K antagonists, direct thrombin inhibitors, factor X inhibitors, and heparin (except for temporary use during percutaneous coronary intervention) that may affect bleeding propensity will be strictly prohibited.

Sample Size

In previous studies, ischemic stroke recurrence rates of 12.5%-12.8% over 24 months with conventional antiplatelet therapy (aspirin or dipyridamole) [22] and 1.7% over the same period with HH333 [19] were reported. Therefore, the sample size was 106 patients per group and 212 patients in total at 2 years with a control group (P_2=0.125-0.128), HH333 group (P_1=0.017), a significance level (α) of 5% and a target power of 80%. Finally, a dropout rate of 10% was considered, resulting in a sample size of 118 patients per group for a total of 236 patients.

Statistical Analysis

All statistical analyses were two-sided with a 5% significance level. The statistical program SAS (version 9.4 or more, SAS Institute) was used for the analysis. If at any point there are missing values or participants are dropped before the end of the study, the data will be treated as missing data. All data obtained from the participants were analyzed in 3 forms: full analysis set, per-protocol set, and safety set. Efficacy analysis will be conducted using the results of the full analysis set as the main analysis, and a per-protocol set analysis will be conducted separately to evaluate whether there are differences from the full analysis set results. Safety analysis was performed on the safety set and the safety of the study medications was evaluated. The full analysis set includes all data from participants with at least one efficacy assessment at the primary outcome after taking the study medication. The per-protocol set included participants who were eligible for full analysis and successfully completed the study. The safety set included all data from participants who received at least one dose of the study medication.

Demographic Information Analysis

For each group, continuous data yielded the mean, SD, median, minimum, maximum, and 95% CIs, whereas categorical data yielded frequencies and percentages. To compare groups, we used a two-sample *t* test or Wilcoxon rank-sum test for

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continuous data, and a chi-square test or Fisher's exact test for categorical data. Baseline information that was recognized as significantly different between the 2 groups was considered a covariate in the efficacy analysis to correct for heterogeneity between the treatment groups.

Efficacy Analysis

Analysis of Primary Efficacy Endpoints

The number of events will be presented for ischemic stroke recurrence during the 2-year study medication treatment period, the odds ratio of stroke recurrence will be calculated, and logistic regression analysis will be performed with ischemic stroke recurrence as the dependent variable and other factors such as HH333 treatment, risk factors, and neurological deficits as independent variables.

Analysis of Secondary Efficacy and Exploratory Endpoints

Secondary efficacy endpoints that FSS, FAS, K-PHQ-9 total score change, each pattern identification probability change, and exploratory endpoints K-NIHSS, mRS, K-mBI, K-MoCA total score change are continuous variables, and the average for each measurement, SD, median, minimum value, maximum value will be presented and the difference between the HH333 group and the control group will be tested using repeated measures ANOVA.

Safety Analysis

An adverse event is a new occurrence of a symptom after study medication administration that was not observed before administration and includes unintended consequences such as abnormal laboratory findings, symptoms, and temporary events related to the study medications. The severity of adverse events, both self-reported and non–self-reported, will be assessed by the investigator by applying Spilker's classification as follows: mild, not requiring additional intervention, nor significantly inhibiting the normal lifestyle (function) of the participant; moderate, significantly inhibiting the normal lifestyle (function) of the participant and may need additional intervention, recovering afterward; severe, severe adverse events requiring intensive intervention; and leaving sequelae. The causal relationship between adverse events and the study medication will be assessed by the investigator using the following six-level grading scale: (1) definitely related, (2) possibly related, (3) probably related, (4) not related, (5) definitely not related, and (6) unknown.

For all adverse events and abnormal findings on examination, the symptoms, frequency, and degree of relationship with the study medication were recorded in detail for each group. The number and proportion of participants in whom adverse events occurred at least once, 95% CI, and number of occurrences within each group will be presented. Differences in proportions between groups will be tested using the chi-square test or Fisher exact test.

Ethical Considerations

This study protocol was approved by the Kyung Hee University Korean Medicine Hospital institutional review board (KOMCIRB 2023-05-010-007; approved on April 19, 2024), and conducted in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist. Multimedia Appendix 2 presents the SPIRIT checklist of the study protocol [40]. Participants who wish to participate receive an explanation of the consent form and give written consent of their own free will. All participants receive cash compensation of ₩50,000 per visit. In addition, all costs related to the clinical trial medications and examinations are covered by the research team. All data from participants will be simultaneously recorded in an electronic case report form with an identification code rather than the participant's name to protect personal information.

Results

The study was funded by the Ministry of Health and Welfare, Republic of Korea (RS-2022-KH127675 and RS-2021-KH111831) on April 1, 2022. Recruitment for the registry commenced on May 22, 2024, and is scheduled to end on November 30, 2026. As of November 13, 2024, a total of 12 participants have been randomized: 4 participants from Kyung Hee University Korean Medicine Hospital, 1 participant from Dongguk University Ilsan Korean Medicine Hospital, and 7 participants from Wonkwang University Gwangju Korean Medicine Hospital. To date, no data analysis has been conducted.

Discussion

The potential application of HH333 in ischemic stroke caused by small-vessel disease has been consistently raised. HH333 is Hwangryunhaedoktang (HHT, Orengedokuto, in Japanese; Huanglian Jiedu Tang, in Chinese) combined with *Rhei rhizoma*, with HHT being the main component of HH333. Network pharmacology analysis of HHT to explore its potential applications in brain diseases predicted that it could be used for ischemic and degenerative brain diseases such as ischemic stroke, vascular dementia, and Alzheimer disease [41]. A review of the efficacy and safety of herbal medicine treatments for patients with acute ischemic stroke reported that the combination of HHT and conventional therapies was shown to significantly improve neurological deficits [42]. *Rhei rhizoma*, another component of HH333, also significantly improved neurological deficits and activities of daily living in a review study of herbal medicine containing *Rhei rhizoma* for acute ischemic stroke [43]. Furthermore, previous experimental and clinical studies have demonstrated HH333's antihyperlipidemic [14], antihypertensive [13], vascular endothelial cell-enhancing [11,12], anti-atherosclerotic [16], cerebral blood flow-enhancing [15], and neuroprotective effects in models of ischemic stroke [44,45], hypoxia [46], and neurodegenerative neurological diseases [47], suggesting that HH333 has the potential to modulate risk factors for ischemic stroke.

Previous retrospective studies of HH333's effectiveness in inhibiting ischemic stroke recurrence reported that the combination of HH333 and conventional ischemic stroke recurrence prevention therapy was superior to conventional therapy alone [18-20]. Specifically, the effect was the best in

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small-vessel disease among the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification of ischemic stroke [20], and the mechanism was proposed to be due to the biochemical effect of HH333 on microangiopathy by acting as an antiapoptotic and cell migration–inducing agent [12].

Most patients with stroke have a multimorbidity status due to various risk factors such as high blood pressure, diabetes, and hyperlipidemia, and controlling risk factors is crucial, making them susceptible to polypharmacy [48]. In a study of the Scottish general population, patients with stroke were more than twice as likely to have multimorbidity compared to patients without stroke, with 12.6% of patients with stroke taking 11 or more medications compared to only 1.5% of patients without stroke [49]. Patients with stroke taking more than 5 or 6 medications are at increased risk for adverse events and falls [50,51], which can severely impact rehabilitation outcomes [48]. Since HH333 has effects on improving stroke risk factors [17], it is expected to complement or replace stroke risk factor therapies, thereby reducing medication use.

Although most herbal medicines are safe and rarely cause liver and kidney injury, some herbal medicines occasionally cause liver injury, and *Scutellariae radix*, a component herbal medicine of HH333, is the main causal herbal medicine responsible for herb-induced liver injury with about 1% of incidence [52]. However, there have been no studies on the dose-dependent toxicity of *Scutellariae radix*, but previous *in vivo* studies have reported no toxicity at a dose of 2000 mg/kg [53,54], which is a much higher dose than the *Scutellariae radix* dose of HH333. In addition, in a 656-patient safety study, no liver or kidney injury was reported with HH333, and mild adverse events of gastrointestinal symptoms, headache, insomnia, chest discomfort, fatigue, and thirst occurred in 2% of patients, with no SAEs [25]. No adverse events were reported in 771 patients in a retrospective cohort study of HH333 published to date [18-20,55]. Therefore, HH333 is expected to be safe with no adverse events, including liver or kidney injury.

Based on this evidence, the Korean Medicine Clinical Practice Guideline for Stroke, compiled by the Korean Ministry of Health and Welfare, recommends that HHT, the main component of HH333, may be considered for the treatment of ischemic stroke to improve neurological disability and prevent recurrence [56]. However, the recommendation is graded as C/Low because clinical studies of HH333 have only been conducted on hypertension and hyperlipidemia, which are risk factors for ischemic stroke, and experimental studies, literature reviews, or retrospective cohort studies on ischemic stroke, which are not sufficient for high quality. In modern clinical research, RCTs represent the highest level of evidence in evidence-based medicine, and significant results from RCTs are more conclusive than other types of clinical research information [57]. Therefore, in order to realize the possibility of HH333 as a therapeutic and recurrent prevention agent for ischemic stroke by improving the quality of evidence, we present a double-blind RCT compared with a placebo to evaluate the clinical effectiveness and safety of HH333 for ischemic stroke in patients with ischemia induced by small-vessel disease.

A limitation of this protocol is that it excluded patients at high risk of bleeding, such as those taking anticoagulants. This exclusion was made because it was important to exclude any factors that could influence bleeding propensity in this study, but it may limit the generalizability of the results.

We hypothesized that HH333 would be effective and safe in preventing recurrent ischemic stroke and improving neurological symptoms in patients with small-vessel disease induced by ischemic stroke. This clinical study will generate data on the therapeutic efficacy and safety of HH333 in ischemic stroke. If the results of this study prove the efficacy and safety of HH333, they will serve as a basis for further use of HH333 with ischemic stroke and will also contribute to the development of novel alternatives for the treatment and prevention of ischemic stroke.

Acknowledgments

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Data Availability

Data sharing does not apply to this protocol, as datasets have neither been collected nor analyzed.

Authors' Contributions

HGL contributed data curation, formal analysis, investigation, methodology, and writing—original draft. SK assisted with conceptualization, funding acquisition, methodology, project administration, supervision, writing—review & editing. WSJ handled resources and writing-review & editing. SKM contributed to validation, writing—review & editing. CHK assisted with visualization, writing—review & editing. DJC handled project administration and writing—review & editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1

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Research consent form.
[DOCX File , 28 KB - resprot_v14i1e70953_app1.docx]

Multimedia Appendix 2
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOCX File , 50 KB - resprot_v14i1e70953_app2.docx]

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Abbreviations

FAS: Fatigue Assessment Scale
FSS: Fatigue Severity Scale
HHT: Hwangryunhaedoktang
K-mBI: Korean Modified Barthel Index
K-MoCA: Korean Montreal Cognitive Assessment
K-NIHSS: Korean National Institutes of Health Stroke Scale
K-PHQ-9: Korean Patient Health Questionnaire
mRS: modified Rankin Scale
RCT: randomized controlled trial
SAE: serious adverse event
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TOAST: Trial of Org 10172 in Acute Stroke Treatment

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Protocol

Water, Sanitation, and Hygiene for Everyone Intervention Study: Protocol for a Controlled Before-and-After Trial

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Abstract

Background: Community-based behavior change interventions are a common approach to Water, Sanitation, and Hygiene (WASH). Yet, published evaluations of how these interventions work in district-wide approaches are rare.

Objective: This study reports the baseline characteristics and study design for a trial assessing the effectiveness of a district-level Community-led Total Sanitation (CLTS) intervention compared to the additional integration of local care groups (CG) on sanitation coverage and use and hygiene behaviors in Chiradzulu District, Malawi.

Methods: This study is a controlled before-and-after trial with 2 treatment arms and a control group. Clusters are rural villages in 3 traditional authorities (TAs). One arm will receive CLTS and the CG model (CLTS+CG group), one arm CLTS only (CLTS group), and one group will serve as the control. The trial is part of the wider WASH for Everyone (W4E) project, led by World Vision Malawi that aims to expand access to WASH services across the entire district by 2025. Study participants were selected from the 3 TAs. Systematic sampling procedures were used to select 20 households per cluster with a total of 1400 households at both baseline and end line. The primary outcome is sanitation coverage. Secondary outcome measures include sanitation use, safe disposal of child feces, observed handwashing facility, and Sanitation-related Quality of Life Index (SanQoL-5).

Results: The baseline observations indicate a balanced distribution of potential demographic confounders in the trial arms with a slight variation on some WASH proxy measures. We noted the low coverage of handwashing facilities with soap and water in all 3 arms: 8% in the CLTS group, 4% in the CLTS+CG group, and 4% in the control group. There was a marginal variation in handwashing practices among the study arms with 3% of individuals handwashing with soap and water in the CLTS group, 5% in the CLTS+CG group, and 2% in the control group. Sanitation coverage also varied among the study arms at baseline as 83% of households had access to unimproved sanitation in the CLTS group, 70% in the CLTS+CG group, and 81% in the control group.

Conclusions: Results from this trial will provide evidence on whether the CLTS+CG approach is effective at improving sanitation and hygiene practices in the W4E program area compared to CLTS alone and no intervention, as well as inform implementing partners on future interventions in Chiradzulu District, Malawi. The results are expected to be published in 2025.

Trial Registration: ClinicalTrials.gov NCT05808218; https://clinicaltrials.gov/study/NCT05808218

International Registered Report Identifier (IRRID): RR1-10.2196/68280

(JMIR Res Protoc 2025;14:e68280) doi:10.2196/68280

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KEYWORDS

community-led total sanitation; care group model; WASH for everyone; Malawi; sanitation intervention trial

Introduction

Globally, it is estimated that 3.6 billion people lack access to basic sanitation services and 494 million people practice open defecation (OD), with the highest rates of OD in Sub-Saharan Africa [1]. Consequences of OD include fecal contamination of drinking water sources and food, which contributes to a high burden of diarrheal diseases and child stunting, adversely impacting health and socioeconomic development [2,3]. Further, OD and inadequate sanitation disproportionately affect the safety and dignity of women, girls, and marginalized groups [3-6], as well as other aspects of quality of life [7]. Efforts by governments and other sanitation stakeholders to eliminate OD, such as the provision of subsidized latrines to households combined with hygiene and health education programs, have failed to make adequate sustained progress [8,9]. Behavior-centered interventions have been associated with improved uptake of sanitation interventions, but more evidence is needed to assess their impact on behavioral outcomes when implemented in combination with one another.

Our study focuses on 2 specific community-led interventions widely used in the Water, Sanitation, and Hygiene (WASH) sector. The first is Community-Led Total Sanitation (CLTS), an approach to sanitation behavior- change centered on community-wide behavior change and community self-enforcement in rural settings [9]. Introduced in Bangladesh in 2009 and now adopted globally, the major goal of CLTS is to mobilize communities to construct and use latrines to end OD [9]. CLTS uses 3 phases to leverage social and emotional drivers to “trigger” a change in people’s mindsets towards OD [10]. Evidence on the efficacy of CLTS is mixed. Certain studies highlight that CLTS only generates significant short-term impact for reducing OD through increased latrine coverage and use [9,11-14]. CLTS implementation factors, such as triggering session attendance, the number of supportive community leaders, participants’ anticipation to receive an incentive, and the number of follow-up visits, have been reported to significantly influence latrine coverage [15]. The second is the care group (CG) model which relies on a multiplier effect to reach a high number of households in a community at a low cost through the development of a supportive network of peer-to-peer counseling [16]. The CG model is a well-tested program for the delivery of health interventions in rural communities, historically focusing on maternal and child health [16-19]. A total of 23 nongovernmental organizations (NGOs) have implemented the CG model across 27 countries, including Malawi [17,19]. Studies have documented the effectiveness of the CG model in increasing coverage of child survival interventions and reducing under-five mortality [18-20]. However, despite their clear alignment, studies of the effectiveness of CGs as they relate to WASH interventions are limited.

In Malawi, communities struggle to sustain 100% latrine coverage after attainment of Open Defecation Free (ODF) status [21]. This has been attributed to a number of factors, including the lack of involvement of marginalized and disadvantaged people, the use of low-quality building materials, lack of technical support, and improper program implementation [14,22]. To achieve high and sustained latrine coverage and behavior change, it is essential to address all physical and contextual factors that directly relate to long-term CLTS success. The Government of Malawi adopted CLTS as one of its official approaches to sanitation in 2008 [23]. The Government formally adopted the CG model in 2011 as an operational framework for the Scaling Up Nutrition (SUN) Strategy [24]. However, little is known about how effective the CG model can be in promoting wider community health benefits, such as improved sanitation. Models to promote sustained reductions in open defecation and improved sanitation outcomes through a combination of behavior-centered intervention need to be tested and adopted to support long-term positive health outcomes.

This study aims to assess the effectiveness of CLTS combined with the CG model on sanitation coverage and use and hygiene behaviors in Chiradzulu District, in rural Malawi, compared to CLTS alone or with no intervention. The study objectives are to assess: (1) how the 2 interventions compare with one another for improving sanitation coverage and use, and (2) whether the 2 interventions are individually more effective than no intervention at all.

Methods

Study Setting and Population

The study is implemented in Chiradzulu District, Malawi (Figure 1). Chiradzulu District is situated in the southern region of Malawi and is subdivided into 10 administrative regions, or traditional authorities (TA). The Malawi 2015-2016 Demographic and Health Survey (DHS) indicated that 52% of the population has access to improved sanitation. According to the National Statistical Office, in 2019, 93% and 10% of the households in Chiradzulu District had access to safe water and improved sanitation facilities, respectively. OD rates in Malawi and Chiradzulu District are 6% and 7%, respectively [25]. Given this low level of coverage, Chiradzulu District is the target of a 3-year (2021-2024) district-wide water, sanitation, and hygiene program, known as WASH for Everyone (W4E), implemented by World Vision and Water for People, alongside which this trial is embedded.

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Figure 1. (A) Map of Malawi with Chiradzulu District in red, and (B) Map of Chiradzulu District with W4E study areas with TA Chitera (CLTS+CG group) in red, TA Ntchema (CLTS only) in yellow, and TA Nkalo (control) in green. CG: care group; CLTS: community-led total sanitation.

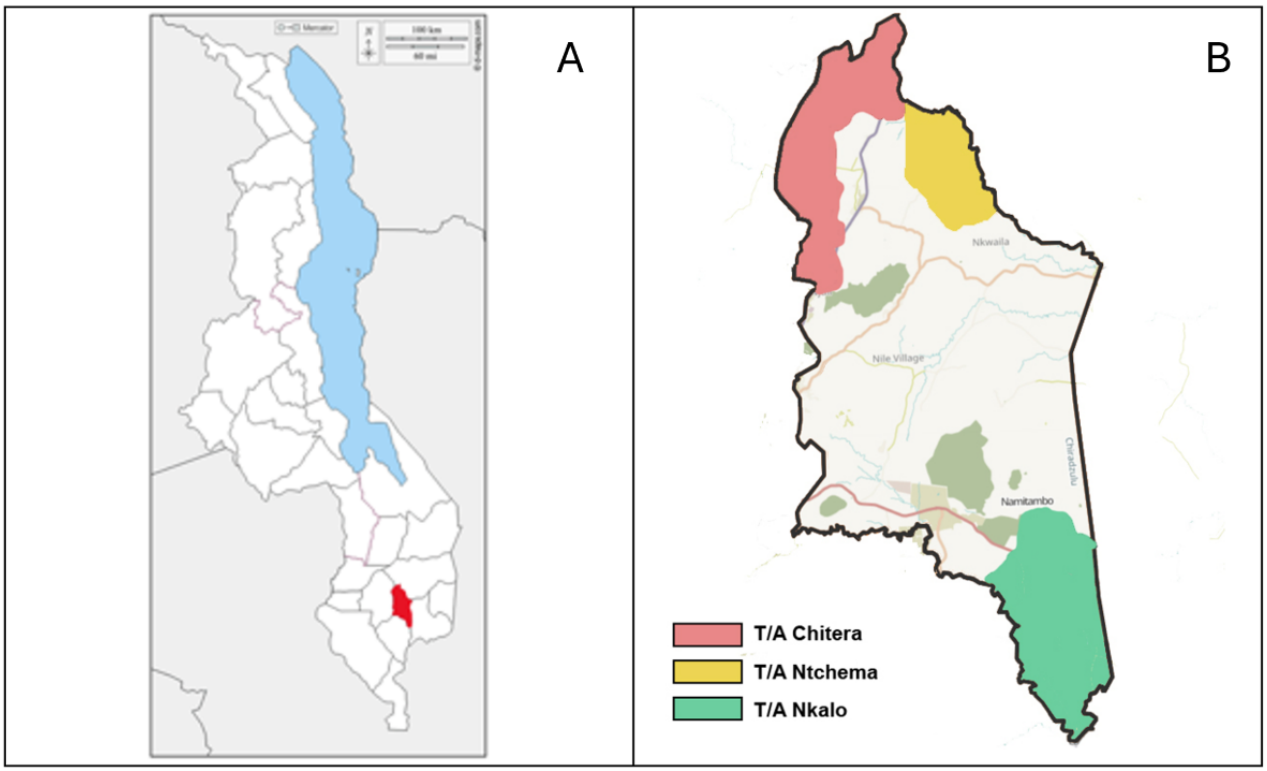

Study Design

The study design is a controlled before-and-after (CBA) trial with 2 treatment arms (each with 20 villages or clusters) and a control group (30 villages; Figure 2; Multimedia Appendix 1). CBA intervention designs are a nonrandomized approach used to evaluate the impact of interventions [26]. The advantages and disadvantages of the CBA study designs, also known as nonrandomized cluster-controlled trials, have been discussed elsewhere [27]. In this study, TAs are the unit of intervention assignment and villages (clusters) are the unit of analysis. [28] In our study, we selected 3 TAs (Figure 1) in Chiradzulu District, Malawi. TAs are 4th-level administrative units, with an average population of 34,000 in Chiradzulu [29]. Details on the program intervention are described below. For our trial, we selected 2 out of the 5 TAs scheduled to receive the full W4E intervention during the second year of program implementation to align with our implementation. We selected the 2 TAs with the closest match in population and estimated sanitation coverage from previous surveys. In discussion with program partners, one TA was assigned to receive the CLTS intervention, and one TA was assigned to receive the CLTS+Care Group intervention. We selected a third TA from the 3 TAs scheduled to receive the WASH for Everyone intervention in the third year of program activities as a control group for our study (Figure 2). The control TA was selected based on generally similar population and sanitation coverage measures and lack of contiguous borders with the 2 intervention TAs. TAs are the unit of intervention assignment for our study. Within each TA, villages serve as the specific study clusters which are the primary sampling units for data collection.

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Figure 2. Study CONSORT (Consolidated Standards of Reporting Trials) diagram for a controlled before-and-after trial to assess the effectiveness of two interventions (CLTS only and CLTS+CG) on rural sanitation coverage and use in Chiradzulu District, Malawi. CG: care group; CLTS: community-led total sanitation.

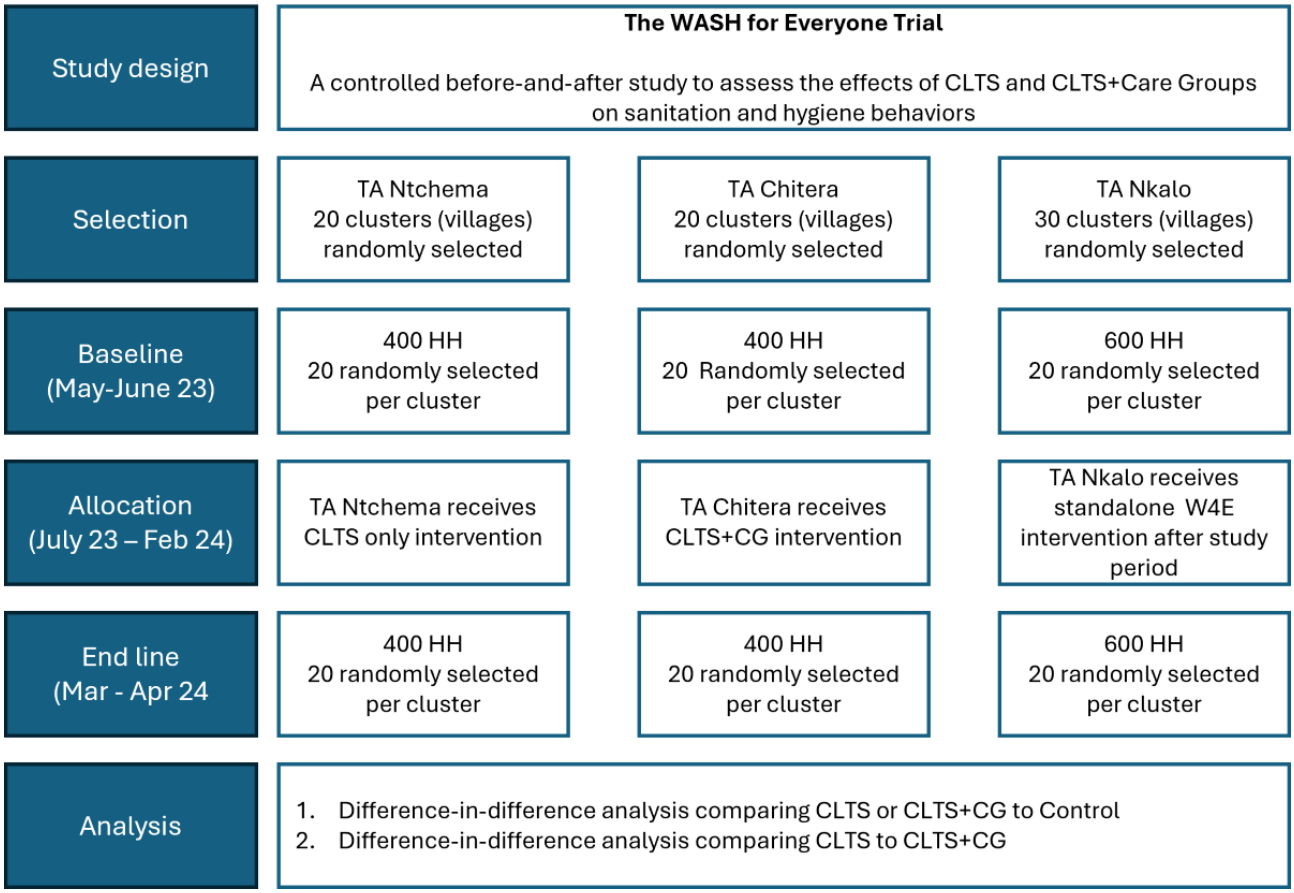

Sample Size

Sample size calculations were based on the minimum detectable effect (MDE) to assess changes in sanitation coverage, the primary outcome measure, at the project end line. Data for all parameters used in sample size calculations were drawn from the baseline survey conducted by World Vision before the implementation of the W4E project between January and April 2021. For the MDE calculation, we assumed a 2-tailed test with a significance level of 0.05 and a power of 0.8. We assumed a conservative intracluster coefficient of 0.1 [30]. As baseline data indicates that the average percentage of households with at least unimproved sanitation coverage across Chiradzulu District was 67%, power calculations assumed a total enrollment of 20 intervention clusters in each TA receiving interventions and 30 clusters selected from the control arm of the study. Assuming an average of 20 households surveyed per selected cluster results in an MDE of 0.136 or an average difference of 13.6 percentage points in sanitation coverage (relative change in coverage of 19%) between either arm of intervention clusters and the control cluster. Therefore, the study aims to recruit a total of 1400 households (CLTS+CG: n=400; CLTS only: n=400; Control: n=600; Figure 2) at each data collection round.

Description of the Intervention

Households in TA Ntchema (CLTS only) will receive standard CLTS intervention plus government-delivered hygiene promotion. We refer to this arm as the CLTS group. Households in TA Chitera (CLTS+CG group) will receive the same combination of interventions as the CLTS group in addition to community-based CGs. We refer to this as the CLTS+CG group.

CLTS is the main sanitation intervention component for W4E and is implemented in line with the Malawi National Sanitation and Hygiene Strategy [29]. As part of W4E, relevant district technical officers and community leaders (also known as Natural Leaders) are responsible for implementing CLTS. Trained CLTS facilitators will conduct the triggering sessions that include participatory activities, such as the walk of shame, shit calculation, and community sanitation mapping. The purpose of these activities is to trigger behavioral emotions, such as shame and disgust so that community members understand the consequences of open defecation. If successfully implemented, triggering sessions have the potential to stimulate community members to stop open defecation and adopt improved sanitation practices, including the construction and effective use of latrine facilities. In addition to sanitation promotion, the project partners delivered hygiene promotion campaigns using pre-established sanitation and hygiene messages from the Ministry of Health in marketplaces and villages. This was achieved through 4 separate campaigns, each lasting 5 days, using a mobile van for message dissemination and distributing information leaflets.

In TA Chitera, in addition to the activities outlined above, households will receive visits from local CGs. CG leaders and cluster leaders support intervention delivery and local triggering sessions, specifically by facilitating CG meetings with CG

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households and conducting household follow-up visits. CGs are intended to extend the reach of CLTS behavior change messaging, providing additional points of contact with program households. CGs also participate in posttriggering follow-up visits to households to assess sanitation coverage and use.

In line with CLTS values, the W4E project does not intend to provide any latrine construction or hygiene facility materials or financial subsidies to households. It is the responsibility of the household owners to support themselves throughout the latrine and hygiene facility construction process.

Selection of Clusters and Households

The primary sampling units (clusters) for the study are clusters (also called villages) and represent the units of W4E delivery for CLTS. Communities from the 3 participating TAs were randomly selected from a list of communities obtained from the Chiradzulu District Health Office. Inclusion criteria for the selected communities include that the community is in one of the 3 selected TAs that are part of the study area and have not yet received any exposure to the W4E project. Communities that were exposed to CLTS-related activities in the past 12 months and are outside the area of the 3 selected TAs are excluded from the study.

In early 2023, a list of all clusters in each study TA and their associated number of households was provided by the District Health Office. TA-specific median village size was calculated, and villages were categorized as either above or below the TA-specific median. Villages in each TA-specific above and below median list were ranked ordered according to a random number generated in Microsoft Excel and villages were enrolled sequentially until the necessary number of villages were enrolled. If a cluster could not be located or if the village chief did not provide permission for data collection, the next cluster on the rank order list was enrolled.

Households are the secondary sampling unit and individuals living in households in the study area are the primary study population. Twenty communities will be selected from TA Chitera (CLTS+CG), 20 from TA Ntchema (CLTS), and 30 from TA Nkalo (control). Among selected communities, a systematic sampling procedure (selecting every kth household) was used to select 20 households from each cluster included in the study. For each cluster, the population of households obtained from the District Health Office was divided by 20 (cluster sample size) to find the sampling interval (kth number). Then, the kth household was selected and included in the survey from any starting household chosen by an enumerator within the cluster.

Data Collection

A baseline survey was conducted in all 3 TAs between May and June 2023 before intervention implementation in TA Chitera (CLTS+CG group) and TA Ntchema (CLTS group). An end-line survey was conducted in all 3 TAs between March and April 2024. TA Nkalo (control group) received the CLTS intervention after the end-line survey. A structured questionnaire with closed-ended questions with precoded responses on mobile devices on the KOBO collect platform (KoboToolbox) was used to collect data on household membership, wealth index, sanitation and hygiene facilities, and child health (Multimedia Appendix 2). Further, the enumerators conducted spot checks and recorded hygiene proxy measures, such as the presence and state of a latrine, presence, location, and type of handwashing facility (including the availability of soap and water). The interviews were conducted in Chichewa, the local language of Chiradzulu District. Chichewa-speaking enumerators with extensive training and expertise administered the structured questionnaire.

To confirm the availability of WASH infrastructure and hygiene practices, we conducted structured observations in 350 selected households (ie, 100 households from each intervention arm and 150 households from the control group) among the recruited 1400 households. A line listing of the 1400 households was created and a Microsoft Excel random generation number was run to identify the 350 households for observations. Specifically, the observations were intended to capture practices pertaining to the presence of latrine and handwashing facility with soap, handwashing practice at critical times (ie, before eating, before food preparation, after changing the child's nappy, and after latrine use), and child feces disposal. One observer was placed at each selected household. As behaviors of interest mostly occur in the morning hours to noon [31], observations lasted 4 hours from 8 AM to noon. The observer first conducted the structured observations after which he or she proceeded to administer the structured questionnaire.

Data Management

Data collected using mobile devices was uploaded directly on the web to KOBO daily. Only the PI, coinvestigators, and study personnel with authorized access have access to web-based data. At the end of the data collection, the full dataset was uploaded into STATA (version 18; StataCorp) for analysis. Although no identifiable information was recorded during the surveys, study personnel will review the final database and permanently delete any identifiable information inadvertently collected during surveys. All data is stored on encrypted, password-protected servers.

Study Outcomes

The primary outcome is sanitation coverage. Secondary outcomes include basic sanitation coverage, sanitation use, sanitation-related quality of life, latrine quality, presence of a handwashing facility, handwashing behavior, and safe disposal of child feces (Multimedia Appendix 3).

Analysis

Statistical analysis will be carried out at the individual or household levels with appropriate adjustments for clustering within villages (and within households for individual-level outcomes). Data will be analyzed according to the TA and intervention assignment irrespective of whether the intervention was taken up fully, partly, or not at all. Since this is an effective study, only an intention-to-treat dataset will be maintained.

The primary estimates of the effectiveness of the intervention on primary and secondary outcomes will be based on a difference-in-difference analysis and models adjusted for design variables alone (TA, village population above or below

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TA-specific median); a fixed effect for village size (above or below the median) will be included in the model. All models will include a dummy variable for the treatment arm (ie, CLTS, CLTS+CG, or control) and data collection round (baseline and end line) as well as the interaction term of those 2 variables.

To account for the clustering of observations, hierarchical mixed-effects models will be used for all analyses. For household-level outcomes or outcomes where there is only one respondent per household, mixed effects models will account for clustering by including a random effect at the village level. For outcomes with multiple respondents or data points per household (specifically sanitation use, and hand washing behavior), an additional random effect will be added at the household level.

All analysis of primary and secondary outcomes will be based on the difference-in-difference approach. The regression coefficient of the interaction term between the treatment arm and the data collection round will be used as the primary effect measure. For binary outcomes measure, we will use melogit with robust SEs and regression coefficients exponentiated to estimate an odds ratio (OR). For continuous outcomes, we will use meglm, with identity link and Gaussian family.

The results will be presented with 95% CIs. Analyses will report on ORs and 95% CIs of each treatment arm compared to the control as well as the CLTS alone compared to CLTS+CG. Secondary outcomes include the following:

1. Sanitation use: measured as an individual-level binary indicator based on the reported location last time each member of the household used a latrine.
2. Safe disposal of child feces: will be analyzed as a mixed effect model (household, village, and cluster) of observed household disposal sites of last defecation for all children under the age of 5 years.
3. Basic sanitation coverage: this is a household-level indicator based on the presence of an observed sanitation facility that meets Joint Monitoring Programme (JMP) criteria for basic sanitation facilities, specifically an improved sanitation type.
4. Sanitation-related Quality of Life (SanQoL-5): SanQoL-5 index is an individual-level variable reported by only one participant per household. It is a continuous variable (0-1) based on the weighted score of responses to 5 questions on a 3-level frequency scale [32].
5. Latrine quality: latrine quality is a composite index based on observed and reported characteristics of household latrines [8]. Specific binary indicators will be combined using principal components analysis (PCA) and iteratively refined using standard approaches to index development. Outcomes will be analyzed as a continuous variable based on the PCA score.
6. Basic handwashing facility: the presence of handwashing where both soap and water are available is a household-level binary variable. This will be analyzed in two ways: (1) both observed and reported handwashing facility (HWF) with both soap and water available at the time of data collection and (2) observed HWF with soap and water.
7. Handwashing behavior: A binary outcome measure based on structured observation data. Structured observation data will be used to identify all predefined hand hygiene opportunities (eg, before food preparation, before eating, before feeding a child, after using a latrine, after cleaning a child, and after being in contact with an animal) and associated hand hygiene (0=no hand hygiene or hand hygiene with water only; 1=hands washed with soap). The analysis will be conducted at the event level with adjustment for repeated observations within the same household.

Adjustment for Covariates

Results will present 2 sets of outcome measures. First, we will report on all outcome measures adjusted for design variables (village above or below TA-specific median) and models also adjusted for a priori-defined covariates and design variables. We will explore differences between the design-adjusted and covariate-adjusted models but will consider the covariate-adjusted models as the primary effect estimates.

Covariates have been selected based on hypothesized relationships that could confound the relationship between intervention exposure and primary and secondary outcome measures.

At the respondent level, gender and primary education (less than vs completed primary) will be included. The following covariates will be included at household-level: household size, household economic status based on PCA of household assets, any member of the household experiencing a disability as defined by the Washington Group (any functional disability for a member of the household greater than 2 on the functional disability assessment) and household reports a water source that is located on site or on plot [33]. At the community level, we will look at the village having an improved road as reported by the Village Chief at the time of baseline enrollment. The improved road is used as a proxy measure of village accessibility to both the intervention and markets.

Missing Data

It is likely that some missing outcome data will be encountered, especially for individual-level self-reported outcomes. The patterns of missingness of variables will be tabulated to describe and compare the extent of missingness of any affected variable between study arms. No adjustment will be made for missing data.

Outliers

Unusual values and potential outliers will be flagged and queried. Unlikely values will be dropped and treated as missing data in the main analysis. A sensitivity analysis will be conducted which includes potential outliers (but not unlikely values).

Multiple Comparisons

The number of primary outcomes that will be tested for significant differences between arms is small; thus, no formal adjustment for multiple comparisons will be made.

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Ethical Considerations

The study protocol, which includes data collection tools, participant information sheets, and consent forms, has been approved by the National Commission for Science and Technology (P01/23/718) in Malawi and the London School of Hygiene and Tropical Medicine (28249). Further, consent was obtained from the Chiradzulu District Council and community leaders. Informed written consent was obtained from all study participants recruited into the study before data collection. The trial was registered in ClinicalTrials.gov (NCT05808218).

Results

Most baseline characteristics, such as gender, education, marital status, presence of children under 5, and wealth quintile, were balanced across the 3 study groups (Table 1). A total of 400 respondents were sampled from TA Chitera (CLTS+CG group), 400 from TA Ntchema (CLTS group), and 600 from TA Nkalo (control group). Across the 3 TAs, most survey respondents were female (83%), had at least some primary education (67%), and were married (68%). The median household size was 4 members. Approximately half (49%) of households had a child under the age of 5 years. Around 6% of households had at least one member living with a disability. The baseline results indicate some imbalance between trial arms on self-reported water treatment practices.

At baseline, 1094 out of 1400 (78%) households had an unimproved sanitation facility as defined by JMP (eg, a pit latrine without a slab). Specifically, most households (76%) had a pit or twin pit latrine without a slab and in a yard or plot (68%). The median number of households among those sharing one latrine was 3. A total of 5183 out of 5386 (96%) individuals reported using a sanitation facility for their last defecation event. The mean SanQoL is 0.62. Around 980 out of 1395 (70%) households used an improved water source as defined by JMP (98%; Table 2), with 1317 out of 1400 (94%) households using a borehole as their main water source. Around 25 minutes was the median round-trip time to collect water. A total of 787 out of 1400 (56%) households had access to a handwashing station, either observed or reported (Table 2). However, only 104 out of 1400 (7%) households had a handwashing facility with reported or observed soap and water available at the handwashing facility.

Table 1. Description of baseline respondent characteristics.

Variable	All participants (N=1400)	Control (TA Nkalo) (n=600)	CLTS+CG (TA Chitera) (n=400)	CLTS (TA Ntchema) (n=400)
Sex (female), n (%)	1167 (83)	510 (85)	317 (79)	340 (85)
Median age	40	39	39	40
Education, n (%)				
None	107 (9)	44 (7)	30 (8)	33 (9)
Less than primary	43 (3)	25 (4)	9 (2)	9 (2)
Completed primary	940 (67)	405 (68)	246 (61)	289 (72)
Secondary	296 (21)	119 (20)	110 (27)	67 (17)
Vocational	6 (0)	2 (1)	3 (1)	1 (0)
University	8 (0)	5 (0)	2 (1)	1 (0)
Marital status, n (%)				
Single	85 (6)	33 (6)	33 (8)	19 (5)
Married	958 (68)	37 (67)	20 (71)	15 (69)
Separated or divorced	208 (15)	103 (17)	48 (12)	57 (13)
Widow	149 (11)	62 (10)	37 (9)	50 (13)
Median household size, n	4	5	4	5
Presence of children under 5 years of age, n (%)	171/350 (49)	68/150 (45)	53/100 (53)	50/100 (50)
Wealth quintile, n (%)				
1	281 (20)	115 (19)	80 (20)	86 (22)
2	279 (20)	114 (19)	71 (18)	94 (24)
3	280 (20)	135 (23)	72 (18)	73 (18)
4	280 (20)	123 (21)	81 (20)	76 (19)
5	280 (20)	113 (19)	96 (25)	71 (18)
At least one household member living with a disability, n (%)	72 (6)	31 (6)	18 (5)	23 (6)

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Table 2. Description of outcomes at baseline.

Characteristics	All participants	Control (TA Nkalo)	CLTS+CG (TA Chitera)	CLTS (TA Ntchema)
Improved water source (JMP[a]), n/n (%)	1364/1395 (98)	587/598 (98)	384/397 (97)	393/400 (98)
At least basic drinking water (JMP), n/n (%)	980/1395 (70)	466/598 (78)	253/397 (63)	261/400 (65)
Report treated water at least once a day, n/n (%)	876/1400 (63)	342/600 (57)	255/400 (64)	279/400 (70)
Sanitation (MP), n/n (%)				
At least basic	97/1400 (7)	26/600 (4)	43/400 (11)	28/400 (7)
Limited	149/1400 (11)	55/600 (9)	64/400 (16)	30/400 (8)
Unimproved	1094/1400 (78)	483/600 (81)	278/400 (70)	333/400 (83)
No facility	60/1400 (4)	36/600 (6)	15/400 (4)	9/400 (2)
Number of households sharing one latrine (among those sharing), median (IQR)	2 (2-3)	2 (2-3)	3 (2-3)	2 (2-3)
All members of the household (aged ≥5) reported using the latrine for last defecation, n/n (%)	5183/5386 (96)	2201/2338 (94)	1480/1520 (97)	1502/1528 (98)
SanQoL-5 index, mean (SD)	0.62 (0.25)	0.59 (0.26)	0.64 (0.26)	0.64 (0.24)
Reported safe child feces disposal, n/n (%)	641/715 (90)	263/291 (90)	184/209 (88)	194/215 (90)
Handwashing facility available (reported or observed), n/n (%)				
Basic[b]	104/1400 (7)	59/600 (10)	15/400 (4)	30/400 (8)
Limited[c]	683/1400 (49)	309/600 (52)	168/400 (42)	206/400 (52)
No handwashing facility	613/1400 (44)	232/600 (39)	217/400 (54)	164/400 (41)

[a]Joint Monitoring Programme.

[b]Basic handwashing facility: handwashing facility with soap and water.

[c]Limited handwashing facility: handwashing facility with no soap or water.

A total of 1099 hand hygiene structured observations were conducted across the 3 TAs (Table 3). Specifically, 330 structured observations were conducted in TA Chitera (CLTS+CG), 295 in TA Ntchema (CLTS), and 474 in TA Nkalo (control). The median number of observed hand hygiene opportunities per household was 3. Most households did not practice hand hygiene or wash hands with water at specific hand hygiene junctures (eg, after using the toilet, before food preparation, before eating, before feeding a child, and after being in contact with an animal; Table 3). A total of 73 child feces disposal structured observations were conducted across the 3 TAs, with 26 in the CLTS+CG group, 18 in the CLTS, and 29 in the control. Overall, approximately half of the households safely disposed of child feces (Table 3).

Table 3. Hand hygiene and child feces disposal structured observations.

Characteristics	All participants (N=1099)	Control (TA Nkalo) (n=474)	CLTS+CG (TA Chitera) (n=330)	CLTS (TA Ntchema) (n=295)
Hand hygiene, n (%)				
Handwashing with soap and water	36 (3)	12 (2)	17 (5)	7 (2)
Handwashing with water only	505 (46)	231 (49)	128 (39)	146 (50)
Handwashing with other materials (ie, ash)	2 (0)	0 (0)	1 (0)	1 (0)
No handwashing	556 (51)	231 (49)	184 (56)	141 (48)
Safe child feces disposal[a], n/n (%)	36/73 (49)	13/29 (45)	14/26 (54)	9/18 (50)

[a]Safe child feces disposal is defined as child latrine use or caregiver disposal of child feces into the latrine.

Discussion

Anticipated Findings

Given that CLTS alone is reportedly not effective at ensuring sustained uptake of sanitation and hygiene behaviors, we test the hypothesis that the CLTS+CG intervention will be more effective at improving sanitation coverage in a rural area of Malawi than the CLTS intervention alone, and also relative to the no intervention arm. Studies have shown the effectiveness of using the CG model in promoting community health interventions, mainly nutrition programs [19,34-37]. However, there is limited evidence on the impact of interventions integrating CLTS and the CG model to address this gap, we

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tested an intervention that integrates the CG model into the standard CLTS approach. The CG model is a community-level government-recognized approach that can potentially support the already existing informal natural leaders in the delivery of CLTS, both pre- and post-ODF status attainment. This could strengthen the sustainability of CLTS as CG members are trained to continuously monitor groups of households post-ODF attainment, whereas Natural Leaders only follow up with households until the community has achieved ODF status [9,11,38,39]. Results from this trial will provide evidence on the extent to which the CLTS+CG approach is effective at improving sanitation and hygiene practices in the W4E program area compared to CLTS alone and no intervention, as well as inform implementing partners on future interventions in Chiradzulu District, Malawi.

Our baseline results indicate that the study is conducted in a rural area where the literacy level is moderate and the quality of housing relatively poor. Some households had no latrines, while traditional unimproved latrines (eg, pit latrines without slab), which are prone to collapse during the rainy season, are common. Relatively high sanitation coverage in the communities indicates the short-term success of CLTS, however, other TAs in Chiradzulu District have reverted to OD after achieving ODF status. Thus, the district provided a suitable environment for this study to assess alternative approaches for promoting sustainable sanitation interventions.

Handwashing with soap is low in low- and middle-income countries, including Malawi [40-44]. Similar findings were observed in our baseline results. Access to easy-to-use and effective handwashing facilities was limited among the study population as most households did not have a dedicated handwashing facility. Observations at critical times indicated a challenge with soap availability for hand washing. As such, nearly half of the study participants did not use soap during handwashing.

The baseline results indicate some imbalance between trial arms on self-reported water treatment practices. Treatment of household water was more frequently reported among the control group compared to the treatment groups. A possible explanation for this imbalance could be that immediately before baseline data collection, other NGOs promoted the use of safe water through the drilling of boreholes and installation of chlorine dispensers in all the water points in the control communities. This included the installation of chlorine dispensers in both treatment groups, although a similar trend was not observed in responses. In terms of sanitation, we observed that the control arm had the highest coverage of latrines without a slab, while more latrines with a slab were observed in the CLTS group. We could not find an explanation for this difference and expect it to be by chance.

This study has several limitations. Structured observations were used to collect the data. This approach has limitations as the presence of the observer can influence the behavior of the person under observation [45]. To minimize bias, study participants were not informed about the observed hygiene behaviors, though they were generally informed about the purpose of the study. Nonetheless, structured observations remain the gold standard for measuring hygiene behaviors [46,47]. Treatment arms and the control were purposively selected based on the presence of care groups and the CLTS program for the treatment arms rather than random assignment. The control arm was selected based on the absence of care groups and CLTS. Systematic random sampling was used to select study households in each arm.

Conclusion

We highlight the study design and baseline results from an ongoing BCA trial implemented in rural households in Chiradzulu District, Malawi. The study, implemented within a district-wide WASH program, assesses the effectiveness of CLTS alone against CLTS combined with the CG model for improving sanitation coverage and sustained uptake. The baseline observations indicate a balanced distribution of potential demographic confounders in the trial arms with a slight variation on some WASH proxy measures. We expect to publish the trial findings in peer-reviewed journals in 2025 and share findings at local and national events in Malawi, as well as at international conferences.

Acknowledgments

This work was supported by World Vision US (grant number WVSOW34730).

Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

RD, KC, and TM contributed to conceptualization. CM and JW assisted with data curation. MC and JW handled formal analysis. RD contributed to funding acquisition. KC, RD, MV, and TM assisted with methodology. RD and IR contributed to resources. RD, KC, IR, TM, and MP assisted with project administration. KC, MP, and BW handled supervision. MP and BW assisted with investigation. JW contributed to validation. KC, CM, RD, IR, and JW handled visualization. KC and RD contributed to writing—original draft. MP, CM, TM, MV, IR, BW, TM and JW handled writing—review and editing.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
CONSORT (Consolidated Standards of Reporting Trials) 2010 checklist.
[DOC File , 220 KB - resprot_v14i1e68280_app1.doc]

Multimedia Appendix 2
Survey tool.
[DOCX File , 38 KB - resprot_v14i1e68280_app2.docx]

Multimedia Appendix 3
Description of study outcomes.
[DOCX File , 17 KB - resprot_v14i1e68280_app3.docx]

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Abbreviations

CBA: controlled before-and-after
CG: care group
CLTS: community-led total sanitation
DHS: Demographic and Health Survey
HWF: handwashing facility
JMP: Joint Monitoring Programme
MDE: minimum detectable effect
NGO: nongovernmental organization
OD: open defecation
ODF: open defecation free
OR: odds ratio
PCA: principal component analysis
SanQoL-5: Sanitation-related Quality of Life Index
SUN: Scaling Up Nutrition strategy
TA: traditional authorities
W4E: WASH for Everyone
WASH: Water, Sanitation, and Hygiene

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Protocol

The Communities Organizing for Power Through Empathy (COPE) Community-Based Intervention to Improve Adult Mental Health During Disasters and Crises: Protocol for a Stepped-Wedge Cluster Randomized Trial

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Abstract

Background: Severe weather events, exacerbated by climate change, can lead to hardships such as displacement, resource scarcity, and social network disruptions. Such disasters impact mental health, triggering conditions such as anxiety, depression, and posttraumatic stress disorder. For communities in the Gulf South, the increasing frequency of disasters often further exacerbates already disastrous levels of inequality. In this context, there is an urgent need for evidence-based, multilevel, community-based interventions to support individual and community mental health and resilience.

Objective: This protocol describes the design of a community-based participatory research (CBPR) study to improve individual and community mental health in Gulf South communities by examining the implementation and effects of the multilevel, community-based intervention, Communities Organizing for Power through Empathy (COPE). Specifically, this study aims to (1) examine factors affecting the implementation, effectiveness, and adoption of the COPE intervention and (2) test its effects on mental health and community resilience. We hypothesize that participants in the COPE intervention will experience greater reductions in psychological distress (eg, perceived stress, anxiety, and depression); improvements in protective factors (eg, social support and coping self-efficacy); and community participation as compared with an attention control group.

Methods: The Consolidated Framework for Implementation Research guides our analysis of data collected from surveys, fidelity and field notes, interviews, and focus groups to examine aim 1. We examine aim 2 primarily via a 2-arm pragmatic stepped-wedge cluster randomized trial (SW-CRT) with individuals (approximately n=300) in clusters (faith-based and secular community-based organizations; approximately n=15) in a disaster-prone community in the US Gulf Coast. The cluster-based design implemented in steps supports the community-based nature of the study where timelines differ by organization. A total of 5 self-assessments will be conducted both in person and via email at later time points. We will integrate mixed methods in our analyses for aim 1 by combining themes from interviews and focus groups with implementation measures, and for aim 2 by constructing a data matrix to combine findings from the SW-CRT with thematic analyses of field notes and interviews.

Results: The SW-CRT is being conducted from June 2022 to June 2025. Recruitment began in April 2023, to conclude in spring 2025, to assess mental health, social support, and community resilience at 5 time points. Data analysis and dissemination of results are expected by spring of 2026.

Conclusions: This protocol is among the first to use a CBPR approach to examine the implementation and effectiveness of a multilevel intervention on psychological distress and resilience. This study provides new insights into how CBPR can enhance intervention implementation research and expand the evidence on community-based mental health interventions during disasters. Policy makers should consider integrating CBPR approaches into disaster response frameworks to ensure culturally relevant and sustainable outcomes.

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KEYWORDS

mental health; community-based group mental health intervention; disaster; community-based participatory research; stepped wedge cluster randomized trial; Gulf Coast

Introduction

Background

Exposure to severe weather events can have far reaching consequences as affected individuals and communities confront hardships such as displacement, property damage, and resource scarcity [1]. These catastrophic events also often disrupt social networks and community structures, further complicating recovery [2,3]. Climate change, linked to greater frequency of these severe weather events and environmental disasters, such as hurricanes and tropical storms, has increased the threat to communities across the globe [4]. For many communities, these events exacerbate already precarious living situations and accompanying high levels of psychological distress [5-7], often persistent across generations, as evidenced by higher levels of posttraumatic stress symptoms (PTSS) found among children [8]. In addition, individuals and communities have become so disconnected that the US surgeon general advisory in 2023 stated that the country was facing an “epidemic” of social isolation [9]. In this context of increasing risk, there is an urgent need for evidence-based multilevel interventions that support individual and community mental health. This protocol describes a study that aims to add to that evidence base, detailing a community-based participatory research (CBPR) approach to examining the implementation and effectiveness of the multilevel, community-based intervention, Communities Organizing for Power through Empathy (COPE) [10].

Designed to address the compounded psychological stresses that communities face during crises, COPE expands resources available to support communities during crises and disasters by integrating interventive and community-building components with training on providing support using elements of psychological first aid (PFA) and mental health first aid (MHFA) [11-13]. The COPE intervention is particularly important for the Gulf Coast region, where the enduring legacies of slavery and systemic racism have contributed to disastrous levels of inequality [14] and the impacts of climate change and frequency of disasters further exacerbate disparities [15,16]. CBPR is a collaborative approach to research that establishes structures to meaningfully engage affected communities in partnership with researchers in all aspects of the process [17-20]. The CBPR project that developed the COPE intervention is now in the implementation phase and aims to address this heightened need for mental health support in a context of limited access to services. Adapted from an intervention that has shown sustained reductions in PTSS for participant survivors of hurricanes Harvey and Maria [21], the COPE intervention uses group process, psychoeducation, and dynamic activities to strengthen individual and collective coping strategies, as well as individual and community relationships.

Mental Health and Disasters

The mental health impact of environmental disasters is both profound and multifaceted [22,23]. Trauma and loss associated with disaster exposure can trigger a range of conditions, including anxiety, depression, and posttraumatic stress disorder (PTSD) [5,6]. Rates as high as 59% for clinical depression have been found among survivors after severe flooding in China, and as 70.5% for PTSD among survivors after Hurricane Sandy in New York [5]. Furthermore, the psychological effects experienced from a disaster can persist, seen in higher rates of mental health disorders observed years following the disaster [24]. A study conducted 3 years after Hurricane Katrina devastated the Gulf Coast and the city of New Orleans in the United States found that 33% of survivors reported probable PTSD symptoms [25]. Another conducted 12 years after Katrina found that 1 in 6 low-income survivors still reported symptoms of PTSD, and the rates of psychological distress remained higher than before the hurricane [26].

The adverse effects of a disaster are shown to be further exacerbated when individuals and communities already face deficits or inequalities in resources or supportive services, and particularly when those inequities have spanned generations [14,27-30]. Low-income families, older adults, people with disability, immigrants, children, those who are imprisoned [31,32], and women [33] are disproportionately impacted, often due to limited resources and infrastructure with which to effectively prepare for, respond to, and recover from disasters [28,34]. Limited financial or social resources, coupled with reduced access to basic health and mental health services, can impede capacity to rebound from such events [35]. This can lead to enduring psychological distress, deepening socioeconomic disparities, and a prolonged disruption of community cohesion and recovery [31,34,36].

The development of the COPE intervention and this study were motivated by our awareness that many of the factors associated with increased risk of experiencing adverse psychological outcomes after a disaster, such as prior trauma [37], limited income [27], and low levels of social and community support [38], are omnipresent in our community and the Gulf South. In addition, uncertainty and chronic stress associated with disaster exposure, frequent in the region, have been shown to exacerbate existing mental health conditions [39,40]. Studies have shown, however, that protective factors, including individual adaptive coping strategies [41-43], self-efficacy [44-46], and spirituality [47-50] interpersonal social support and relationships, and community or neighborhood cohesion [33,51], can reduce the

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likelihood of experiencing adverse mental health outcomes after a disaster. This study aims to examine whether the COPE multilevel intervention, designed to enhance individual protective factors (eg, adaptive coping), and delivered in a format designed to strengthen social capital (ie, interpersonal and community protective factors such as social support, relationships, and community cohesion), could improve individual mental health outcomes in communities with persistent high levels of inequity and disaster-related stress.

Disaster-Related Mental Health Support Interventions

Mental health support services are important in all phases of a disaster (preparedness, response, and recovery) to help individuals and communities cope with trauma, prevent long-term psychological consequences, and support healthy recovery. In the preparedness phase, disaster mental health programs are designed to psychologically prepare individuals and communities for potentially traumatic events. Education and training interventions in this phase enhance the community's capacity to respond to mental health needs if a disaster occurs [52].

One widely disseminated preparedness training, PFA, is designed to increase the capacity of non–mental health specialists to provide basic safety and stability to survivors during the response phase [11,53]. Core elements of PFA include addressing basic needs, mitigating harm, providing reassurance and safety, and connecting survivors to supports and services [11,54]. A similar training intervention, MHFA, is designed to equip nonspecialists with the knowledge and skills to identify and respond to individuals experiencing psychological distress [55]. Specifically, MHFA focuses on identifying signs of mental illness and substance abuse, providing basic psychological support, and connecting distressed individuals to professional support services [55]. Both PFA and MHFA primarily use didactic lectures and instruction focused on disseminating information instead of delivery methods that engage participants in group processing, interactive learning through hands-on activities, and reflection. Although MHFA and PFA have been shown to increase participant knowledge on providing mental health support to disaster survivors, research on how the knowledge and skills gained is deployed during disasters is limited [13,54].

During the disaster response phase, mental health services focus on the immediate needs of survivors [34,56]. Disaster mental health response efforts generally involve identifying and triaging individuals to crisis counseling services or providing immediate stabilization to distressed survivors [56]. However, crisis counseling varies widely in approach and method, making it difficult to standardize care and measure outcomes [56]. Psychological debriefing (PD), a brief intervention delivered by a mental health professional as a single individual or group session within 72 hours of a traumatic event, includes discussing, validating, and normalizing survivors' trauma response [56]. There is mixed evidence on the effectiveness of PD: some studies suggest debriefing can reduce PTSS [57] and others have indicated PD may cause further distress [58].

The recovery phase focuses on the long-term mental health and well-being of survivors. It also contributes to preparedness and mitigation. Formal mental health treatment is one category of intervention provided to support survivors exhibiting clinical manifestations of distress [59]. Cognitive behavioral therapy, narrative exposure therapy, and other forms of psychotherapy have all been found to reduce clinical rates of PTSD, depression, and anxiety in disaster survivors [60,61]. Other mental health supports provided during the recovery phase include community-based wellness and resilience-building psychosocial interventions, generally designed for specific groups (eg, teachers, social service, or health care providers). One brief intervention, Caregivers Journey of Hope (CJoH), is designed to increase coping and reduce stress among disaster-affected social service providers [62]. It has been found to significantly reduce perceived stress and improve social support and knowledge of community resources [62]. Another intervention, Resilience and Coping for the Healthcare Community (RCHC), incorporates psychoeducation, action learning, and solution-focused strategies to reduce distress and increase social and peer support among health care providers [21,62,63]. A study assessing the effects of the RCHC among health care employees after hurricanes Harvey and Maria in 2017 found a significant likelihood of experiencing reductions in PTSS, anxiety, and secondary traumatic stress at the $P<.01$, $P<.05$, and $P<.05$ levels, respectively, at week 12 for those who received the RCHC as compared with a control condition [21]. Targeting both the recovery and preparedness phases, the COPE intervention being examined with this protocol adapted the RCHC for delivery to laypersons, incorporating illustrated materials to deepen conceptual understanding and foster dialogue across diverse literacy levels, content on historical trauma to acknowledge systemic factors, and sessions on supporting people in distress and identifying neighborhood resources to improve community response capacity [10].

Research examining the efficacy of disaster mental health interventions has primarily focused on the effectiveness of interventions designed to treat clinical diagnoses such as PTSD, anxiety, and depression [34,64], or on trainings that prepare individuals to provide basic psychological support [34,65]. Emerging evidence suggests community-based interventions, such as the CJoH and RCHC, improve individual mental health after the disaster [21,62]; however, more research is needed on their applicability across contexts and with diverse populations, as well as on how they affect individual mental health and community resilience [34,52]. In addition, as highlighted by Gil-Rivas and Kilmer [18], scholars have recommended "a CBPR approach to disaster preparedness and response that involves community-level organizing" as an effective strategy to strengthen community resilience in a culturally relevant and contextually appropriate fashion [66-68]. Better understanding the effectiveness and implementation of multilevel interventions designed for broad audiences that address mental health and well-being at the individual, interpersonal, and community levels is key to improving access during recovery [69].

Rationale for the Study

The compounding psychological effects of successive disasters on the Louisiana Gulf Coast, including 5 named storms in the 2020 hurricane season followed by the catastrophic Hurricane Ida in 2021, in the context of the long-term stress of the global

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COVID-19 pandemic, brought to the foreground the need to consider mental health as a component of community resilience. Community resilience refers to a community's capacity to prepare for, respond to, and recover from crises and disasters [70]. Important aspects of community resilience include strong community networks, local knowledge and response capabilities, and access to physical and mental health care [70].

Often, and particularly in the Gulf Coast region, it is neighbors and local community members who are the first to respond to a disaster [71]. This role that neighbors and local community members play in disaster response underscores the need for multilevel interventions to increase individual and community capacity to prepare for and cope in the aftermath of disasters. It also underscores the value of engaging community members in a CBPR approach to adapting and implementing those interventions. In response, the COPE curriculum [10] was developed via a CBPR project undertaken by the community organization Together Baton Rouge (TBR) and academic researchers. TBR is a 501(c)3 nonprofit and a broad-based organization [72,73], meaning that it is comprised of, and financially sustained by, other faith-based and secular organizations (community-based organizations [CBOs]) in the community that pay membership dues to support its work. This partnership structure thus provides a unique opportunity to test a distinct implementation design by delivering COPE at a variety of CBOs that are interconnected as members of the single committed partner organization, TBR.

This study responds to 2 primary questions about the COPE intervention model: (1) How do contextual factors affect intervention implementation? and (2) How does COPE affect individual, interpersonal, and community level well-being? We examined these questions using a pragmatic, stepped-wedge cluster randomized trial (SW-CRT) design with rolling enrollment. This design permits study of intervention effects in a context where individual randomization was not feasible given the group-based intervention and its delivery to individuals associated with the cluster (community institution) where they participate. In addition, the stepped roll out better supported the community-based nature of the study in which all clusters were not ready to deliver at the same time, and all expected to participate in the intervention.

Aims and Hypotheses

In this paper, we describe the design of our mixed methods study that includes a pragmatic 2-arm SW-CRT [74] that examines the effectiveness and implementation of COPE, a group psychoeducational intervention designed to support individual and community mental health. The SW-CRT research design randomly assigns clusters (eg, communities and organizations) to transition from control to intervention in phases, until each eventually receives the intervention [74]. This research design supports phased community engagement and recruitment by sequentially introducing interventions, helping to reduce staff and organization burden. The aims of this SW-CRT are 2-fold. First, we aim to examine contextual factors, such as organization type and timing of delivery, to understand how they affect implementation, efficacy, and adoption of the COPE intervention. We hypothesize that cluster-level factors—such as organizational support, participant engagement, and facilitator training—and individual-level factors—such as age and education level—will influence feasibility, implementation, and acceptability of the COPE intervention. In addition, we hypothesize that the interrelationship between clusters as part of a larger organization will improve recruitment both at the cluster and individual level. Second, we aim to test the effectiveness of the COPE intervention [10], compared with an attention control arm (house meetings), in reducing mental health distress and strengthening coping, social support, and community engagement across 5 time points (Figure 1). We hypothesize that individuals who participate in the COPE intervention will report greater reductions in psychological distress symptoms (perceived stress, depression, and anxiety) than the attention control group, alongside significant increases in protective factors (coping self-efficacy, social support, and community resilience).

Figure 1. Timeline for Communities Organizing for Power through Empathy (COPE) stepped-wedge cluster randomized trial design and assessment. C1-3: COPE sessions 1-3; H1-2: house meetings 1-2; T1: baseline measurement period; T2-5: time points 2-5. *Steps 4 and 5 follow the same sequence as steps 1-3.

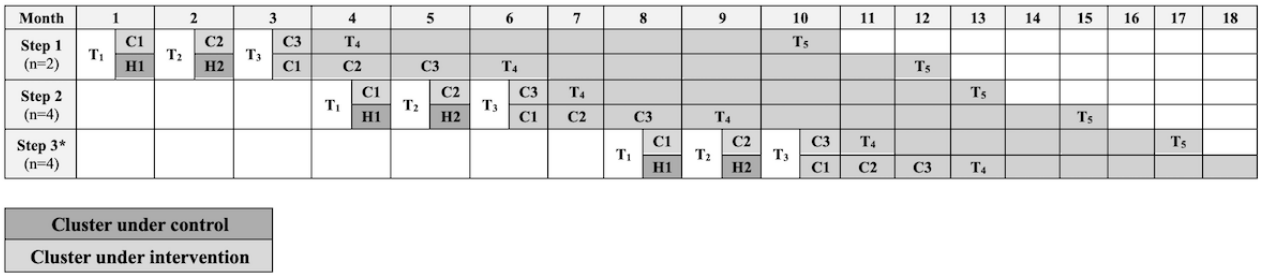

Methods

Overview and Study Design

This study uses a pragmatic mixed methods approach to examining the effectiveness and practical relevance of COPE in a real-world context [75]. We will collect and examine qualitative data to address aim 1, capturing contextual information about cluster-level and individual-level factors that influence the feasibility, implementation, and acceptability of COPE. We will approach aim 2, the test of intervention effectiveness, using a SW-CRT with a rolling enrollment design. As a pragmatic 2-arm SW-CRT, the study has two conditions or arms: (1) the intervention arm, in which clusters of participants begin by engaging in the COPE intervention, and

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(2) the attention control arm, in which clusters of participants begin by attending "house meetings" (listening sessions) before switching to the COPE intervention. A cluster is defined as a single CBO (or in a rare case, a pair of related CBOs). Clusters are eligible to participate if they are CBO members of TBR. Steps are clusters grouped by availability (ie, feasible start date as provided by CBO leadership). At the initiation of a step and before participant enrollment, clusters are randomized into study arms.

As a SW-CRT, every cluster will provide before and after observations, and will switch from control to intervention, but not at the same point in time (Figure 1) [74]. At study outset, clusters are assigned by the first author to 1 of 5 sequential steps: 2 in step 1, 4 in steps 2 and 3, and 6 in steps 4 and 5 (Figure 1). At the initiation of a step, clusters will be randomized by the first author into the intervention and control arms using a random number generator. Allocation into intervention or control arms will not be concealed at either the cluster or individual level, nor will clusters or participants be blinded, as doing so is not feasible given the group-based nature of the intervention and community-based nature of the study implementation. We will include controls to account for temporal and enrollment differences. Presurvey data collection will occur immediately before the start of the intervention within each cluster. After the third data collection time point, the clusters in the attention control arm will switch to receive the COPE intervention (see Figure 1 for the design timeline).

To accomplish aim 1, we are using the Consolidated Framework for Implementation Research [76] to examine factors that affect intervention implementation and program efficacy, as well as standardized measures of perceptions of feasibility, acceptability, and cultural appropriateness. We will conduct quantitative assessments, interviews, and focus groups with community facilitators (CFs), institutional leaders, and participants (see Multimedia Appendix 1 for facilitator interview guide). In addition, to align with our CBPR approach, our research team includes a group of community members we refer to as the "CBPR strategy team" who guided the adaptation process that developed COPE and will guide the study design, implementation, and analysis of findings. For example, we presented them with options for measures of mental health and discussed the overall survey design. The team chose measures and approved the final survey instrument. We also worked with the team to discuss options for implementation of the COPE sessions and recruitment. As we analyze data, we will review findings and papers developed with the team, along with other community members. In our analyses for aim 1, we will integrate the methods by combining themes from interviews and focus groups with analyses of implementation measures.

To accomplish aim 2, we are collecting cohort data from participants in clusters in both arms assessed along measures of mental health, coping, social support, and community resilience at 5 time points (see Figure 1 for study design and data collection time points). Participants will complete assessments at each time point before content delivery using Qualtrics survey software loaded on a tablet. In cases where participants are unable to use a tablet (eg, discomfort with technology or visual impairment), they will complete the assessment on paper and research staff will enter the data into the software. Participants will be given a US $10 gift card at the completion of each questionnaire.

Ethical Considerations

The current SW-CRT is approved by the institutional review board of Louisiana State University (IRBAM-21-1391) and funded by the Gulf Research Program of the National Academies of Sciences, Engineering and Medicine. All enrollees will provide informed consent. The trial has been registered on ClinicalTrials.gov (NCT06093737) and is following the SW-CRT extension for the CONSORT-SPI (Consolidated Standards of Reporting Trials–Social and Psychological Intervention) guidelines for reporting (see Figure 2 for the flow diagram) [77-79].

Research staff and coinvestigators will undergo human subjects training by completing the Collaborative Institute Training Initiative social and behavioral health training module. Individual data are confidential; however, as a community group-based intervention, cluster- and individual-level participation itself is not. To account for differential exposure times between clusters inherent to a SW-CRT design, we will clearly communicate timelines to manage expectations and provide adequate referrals to mental health resources.

To ensure data confidentiality, participants' responses will be self-reported, and a unique identifier will be assigned to link surveys from the same participant across time. With regard to the qualitative data, at the start of each session of the COPE intervention, participants will discuss confidentiality guidelines, emphasizing respect for privacy to minimize risks of unintentional disclosures. Similarly, at the start of each focus group and interview, confidentiality will be discussed as part of the informed consent process. After transcription of qualitative data, names will be replaced with pseudonyms.

Only the researchers listed on the institutional review board approval will explain, collect, and manage informed consent. Before initial data collection, researchers will explain the study's purpose, procedures, potential risks, benefits, and right to refuse, as well as the limits of confidentiality, using a plain language script developed by the authors with feedback from the strategy team. In addition, we will allow time for question and answer to ensure participants understand the information before consenting. Researchers will collect signed consent forms that are stored in a locked filing cabinet separate from the data. A reminder of their rights as research participants will be provided before each subsequent assessment, even though signatures are only collected at the initial assessment. Enrollees of both trial arms will be compensated for participation with a US $10 gift card provided for each survey, to a potential total of US $50, and food provided at each in-person or data collection session. CFs will also sign their informed consent to participate in their initial training, be compensated for their time in training and facilitation at a rate of US $600 per series plus US $400 for training (1-time payment, approximately US $50 per hour), and be provided all materials required for facilitation.

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Figure 2. Communities Organizing for Power through Empathy (COPE) stepped-wedge cluster randomized trial enrollment flow diagram.

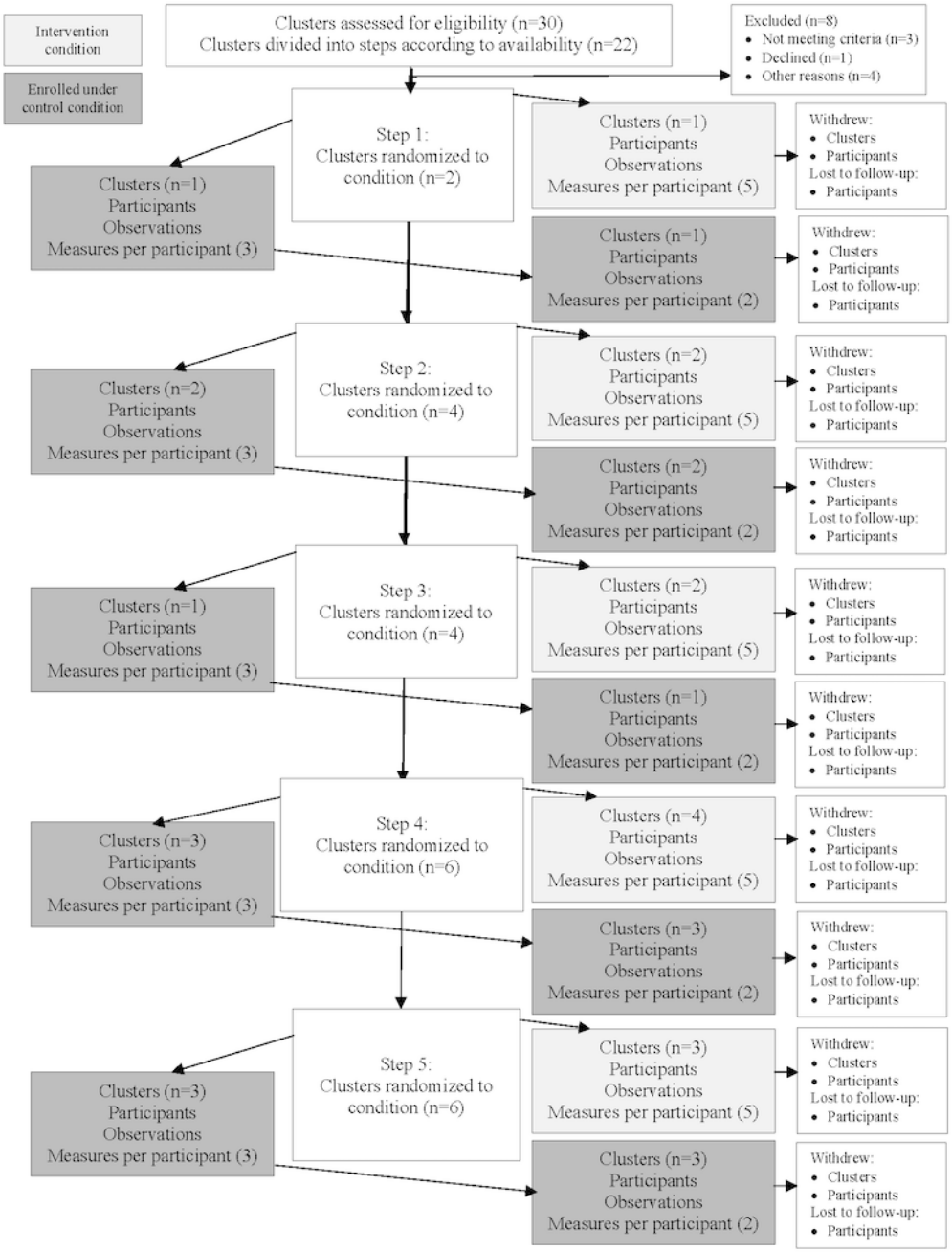

Sampling Strategies and Sample Size

Multilevel mixed methods, with convenience, purposive, and probability sampling techniques at different levels of analysis, in this case clusters and individuals, will be used as different strategies are required for each aim. Convenience sampling will be applied in the initial phases of the study during the adaptation process to pilot-test the COPE intervention's components with accessible participants from across the clusters to ensure broad acceptability and commitment to participation in the SW-CRT. For aim 1, maximum variation sampling will be used to gain perspectives from a heterogenous pool of participants and facilitators [80]. This will include purposive sampling of participants from different institutions to gain a diverse set of perspectives on barriers or facilitators that impact implementation of COPE.

For the SW-CRT component of aim 2, we did a power analysis to estimate the required sample size for a target power of 80%. We assumed a standardized moderate effect size of 0.3, 5 time points, a conservative intraclass correlation coefficient (ICC) of 10% (10% site-level and 90% person-level variation), and a within-person correlation of 0.3. The power analysis results indicated that 300 participants at 15 sites with 20 participants per site achieves the target power. We also did sensitivity analyses varying the effect size, ICC, within-person correlation, and number of sites, and with very conservative estimates the target power can be achieved.

After clusters are randomized into groups, participants will be recruited by CFs and project staff using convenience sampling techniques. As one cluster includes a large Spanish-speaking population among its membership, COPE will be delivered to

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participants in that cluster in Spanish by native Spanish-speaking bilingual facilitators and participants will be provided materials in Spanish.

Study Setting, Participants, and Eligibility Setting

Louisiana, overall, is estimated to be affected with higher rates of mental health conditions than the national population. As of February 2021, about 715,000 adults in Louisiana had a mental health condition [81]. Nearly half (47.5%) had reported symptoms of anxiety or depression and, that same year, 720 lives were lost to suicide [81]. Despite this need, approximately 3.4 million people in Louisiana lived in a community without sufficient mental health providers [81]. In 2022, about 16% of adults in East Baton Rouge Parish reported experiencing frequent mental health distress [82].

The trial is being conducted at TBR and the cluster CBO locations. The inclusion and exclusion criteria for trial participants are listed in Textbox 1.

Textbox 1. Eligibility criteria.

Inclusion criteria

- Currently aged ≥18 years
- Staff, members, or affiliates of a community-based organization (CBO) affiliated with Together Baton Rouge (TBR)
- Willing to participate in the intervention

Exclusion criteria

- Not aged ≥18 years
- Not staff, members, or affiliates of a CBO affiliated with TBR
- Unwilling to participate in the intervention

Recruitment and Enrollment

CBO clusters are members of TBR selected to account for geographic and socioeconomic diversity. Clusters are enrolled by program staff who work with the CBO leadership to identify qualified CFs and enroll eligible participants. Engagement efforts emphasize building relationships with trusted local leaders and inclusive outreach that uses culturally relevant materials and ensures transparency. CFs deliver the intervention and recruit participants. Licensed mental health professionals (eg, licensed master or clinical social worker, licensed professional counselor, or licensed marriage and family therapist) or individuals with experience in group or community facilitation, who are affiliated with a TBR institution, and who are willing to commit to the training and delivery of all components of the intervention are eligible to be a CF. To every extent possible, CFs are members or strongly affiliated with the cluster where they are delivering the COPE intervention. In some cases, however, trained CFs may facilitate for a cluster with which they are not strongly affiliated.

Potentially eligible participants will be recruited by the CFs and leaders at each participating cluster CBO. This will be accomplished by a combination of posting fliers, announcements at critical meetings, word of mouth, phone, and social media, as appropriate to each cluster. Enrolled participants will be those who signed the informed consent and completed the baseline (T1) assessment.

Intervention Arm: COPE

COPE is a 3-session group psychoeducational workshop series we developed that combines psychoeducation and peer support strategies to effect individual, interpersonal, community, and ultimately, societal change. The primary COPE session (C1) is adapted from the RCHC [63] curriculum developed by the second author (TP) and colleagues to provide psychosocial support to professional caregivers, specifically health care and social service providers. During the COPE adaptation, we engaged a team of mental health professionals from diverse backgrounds (in terms of race and ethnicity, gender, national origin, age, and primary language) in a collaborative process to tailor the RCHC to fit the unique needs of Gulf Coast communities at risk of or having survived disasters. Key elements of the adaptation include illustrated materials to engage varied literacy levels and language backgrounds, addition of content on historical and systemic trauma, and incorporation of activities on how to support individuals in distress and build community support.

As illustrated in the COPE conceptual model in Figure 3, the 3 sessions are designed to increase well-being at the individual (coping capacity), interpersonal (social support), and community (engagement) level and decrease adverse individual-level mental health outcomes (perceived stress, anxiety, and depression). Designed to normalize common reactions to stress after traumatic events, the psychoeducational component includes information on stress reactions and their biophysical components (eg, neurological trauma response), reactions common to caregivers, and adaptive coping strategies. The curriculum is grounded in active learning principles, engaging participants in Socratic dialogues about concepts and practical activities. In addition, COPE delivery integrates a group practice model that allows for within-group dialogue, social learning, and cooperation to support group reinforcement of positive change [83]. Through group process incorporated with the discussion of psychoeducational components, COPE helps to reduce isolation by creating an environment in which participants share their experiences and support each other, thus strengthening relationships and social networks.

As shown in Figure 4, the COPE series consists of the primary session 1 (C1, 4 h), focused on recognizing stress in oneself

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and developing healthy coping strategies while simultaneously building relationships to increase social and community support, and 2 additional follow-up sessions (C2 and C3, 90 min each). Each workshop session engages participants in group exercises that provide information in stress and trauma, skills training on recognizing and supporting individuals exhibiting distress, identifying and developing healthy coping strategies, and identifying and building community-based support.

The second session (C2) focuses on supporting individuals in distress and the third (C3) focuses on building community support. More specifically, session 2 (C2) centers skill building for nonspecialists to increase their capacity to provide basic psychological support to individuals in distress, and it incorporates an interactive role play to provide an opportunity to practice skills learned. Session 3 (C3) centers community resilience, engaging participants in an interactive discussion to name community assets and then map those available within the geographic area of their institution. COPE has been standardized in a single manualized curriculum with accompanying large-format illustrated posters laminated for interactive use and participant workbook [10]. The COPE participant workbook has been translated into Spanish and validated using back translation. For the SW-CRT, assessments will be conducted before each session.

Figure 3. Communities Organizing for Power through Empathy (COPE) conceptual model. S2: COPE session 2; S3: COPE session 3.

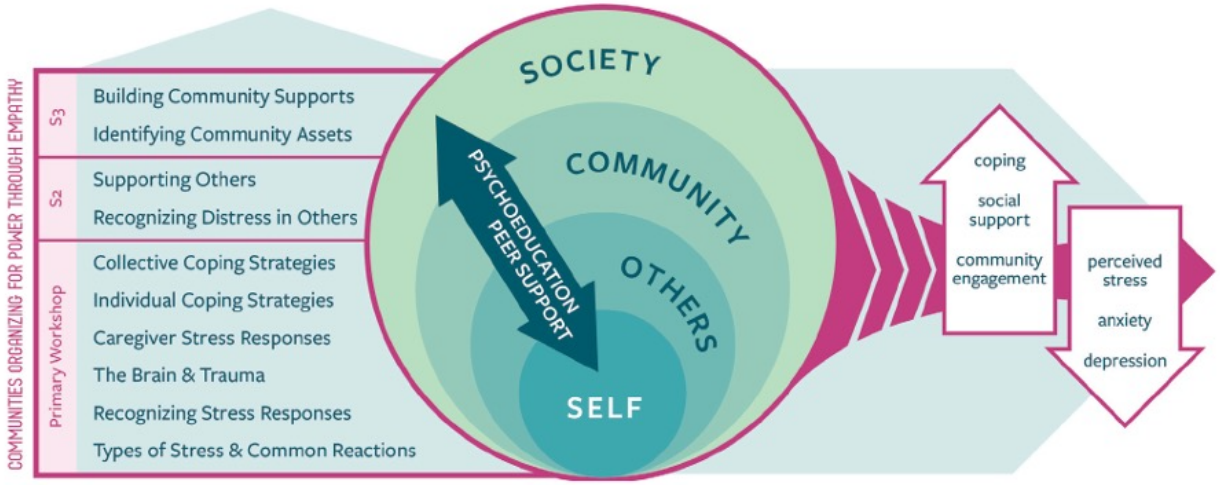

Figure 4. Communities Organizing for Power through Empathy (COPE) session topics.

Attention Control Arm: House Meetings

Parallel to the intervention arm, participants in clusters randomized to the control arm will complete assessments before content delivery at the first 3 time points. After the first 2 assessments, they will participate in house meetings—group deliberative conversations, sometimes referred to as listening sessions—following a model regularly practiced by TBR [84,85] before participating in the COPE intervention at their third meeting and just after completing their third assessment. The house meeting is a group session that lasts approximately 1.5 hours and engages participants in a discussion about a specific question posed by the facilitators. At the first house meeting, and after administering the first assessment, participants are prompted to discuss "How are you a caregiver in your everyday life? What does it mean to you to be a caregiver?" or a similar question. Each participant is encouraged to share at least once. The facilitator is not necessarily a mental health professional, and no therapy is provided. At the end of the house meeting, participants are reminded of the date for the next meeting. The second house meeting follows the same protocol with a modified prompt question. After completing the third assessment, participants engage in the COPE intervention.

Study Outcome Measures

We will examine measures of implementation to respond to aim 1 and respond to aim 2 by assessing 3 levels of outcomes (primary, secondary, and tertiary) from the SW-CRT (see Table 1 for a detailed list of outcomes and measures). To address aim 1, we will use the Consolidated Framework of Implementation Research [76] to examine factors that affect intervention implementation and program effectiveness, as well as perceptions of feasibility, acceptability, and cultural appropriateness. We will use standardized measures of acceptability (Acceptability of Intervention Measure [AIM]), appropriateness (Intervention Appropriateness Measure [IAM]), and feasibility (Feasibility of Intervention Measure [FIM]), as well as items related to facilitator preparation and logistics and intervention acceptability developed by the research team. The AIM measures degree of satisfaction with intervention, the IAM its relevance and fit, and the FIM perception of potential for success within an organization. Each construct consists of 5 items rated on a 5-point Likert scale ranging from 1 (completely

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disagree) to 5 (completely agree). The measures have demonstrated acceptable fit and structural validity and reliability (Cronbach α=0.73-0.88) [86]. We are collecting these data via a survey, interviews, and focus groups conducted with CFs. In addition, we will analyze data from field notes, fidelity observations, interviews, and focus groups with institutional leaders and participants.

Table 1. Study outcomes and measures

Measure	Time frame	Type	Source
Psychological well-being			
Depression Anxiety Stress Scale Short Form	In the past week	Primary outcome	Lovibond and Lovibond [87], 1995
Perceived Stress Scale	In the last month	Primary outcome	Cohen et al [88], 1983
Social support			
Coping Self-Efficacy Scale	__[a]	Secondary outcome	Chesney et al [89], 2006
Multidimensional Scale of Perceived Social Support	—	Secondary outcome	Zimet, et. al.[90], 1988
Community connectedness			
Communities Advancing Resilience Toolkit	—	Tertiary outcome	Pfefferbaum et al [68], 2020
Process evaluation			
Acceptability of Intervention	—	Acceptability	Weiner et al [86], 2017
Intervention Appropriateness	—	Appropriateness	Weiner et al [86], 2017
Feasibility of Intervention	—	Feasibility	Weiner et al [86], 2017

[a]Not applicable.

To address aim 2, we will collect cohort data on the outcome measures at the 5 assessment time points of the SW-CRT: baseline (T1), before session 2 (T2; 1 m after baseline), before session 3 (T3; 2 m after baseline), after the series (T4; 1 month after session 3), and 6 months after the series (T5). Figure 1 provides a visual of the design and timeline of survey measures. As the control arm switches to the COPE intervention after the T3 assessment, assessments pause until 1 month after session 3 so that T4 assessments align (Figure 1). Both arms complete the T5 assessment 6 months after session 3. As part of the CBPR process, the CBPR strategy team deliberated on the outcomes and measurements, coming to consensus on the final survey.

The primary outcomes and their measures assess individual mental health. Perceived stress is assessed with the Perceived Stress Scale (PSS), a 10-item scale that measures the degree to which a person rates situations as stressful [88], for example, how often respondents find their lives “unpredictable,” “uncontrollable,” or feel “overloaded.” Responses are scored on a 5-point Likert scale ranging from 0 (never) to 4 (very often). Total PSS scores range from 0 to 40, with higher scores reflecting higher perceived stress [91]. The 10-item Perceived Stress Scale has high internal reliability (Cronbach α=0.78-0.90) and has been translated and tested in >25 languages [88,91]. Depression, anxiety, and stress are measured with the Depression, Anxiety, and Stress Scale (DASS-21), a set of 3 self-report scales [87]. The 21 DASS-21 items ask about the presence of symptoms over the past week on a scale from 0 (did not apply to me at all) to 3 (applied to me very much or most of the time) [92,93]. Depression scores range from 0 to 4 (normal), 5 to 6 (mild), 7 to 10 (moderate), 11 to 13 (severe), and >14 (extremely severe). Anxiety scores range from 0 to 3 (normal), 4 to 5 (mild), 6 to 7 (moderate), 8 to 9 (severe), and >10 (extremely severe). Stress scores range from 0 to 14 (normal), 15 to 18 (mild), 19 to 25 (moderate), 26 to 33 (severe) and >34 (extremely severe). The DASS-21 has shown high internal reliability (Cronbach α=0.72-0.91) [92-94].

Secondary outcomes and their measures assess coping and social support. Coping self-efficacy is assessed with the Coping Self-Efficacy Scale (CSES), a 12-item measure of confidence in managing stress [89]. The CSES combines 3 subscales measuring distinct dimensions: problem solving, thought stopping, and obtaining social support. Each item is scored on an 11-point scale ranging from 0 (cannot do at all) to 10 (certainly can do). The CSES has high reliability and validity across diverse contexts (Cronbach α=0.76-0.93) [89]. Social support is measured with the Multidimensional Scale of Perceived Social Support (MSPSS), a 12-item measure combining 3 subscales examining perceived support from family, friends, and significant others [90,95]. Each MSPSS item asks at to what degree the respondent agrees that they felt supported by each group and is scored on a 7-point scale ranging from 1 (very strongly disagree) to 7 (very strongly agree). The MSPSS consistently demonstrates internal consistency across diverse populations in the United States and internationally (Cronbach α typically >0.90) [96-98].

The tertiary outcomes measure community resilience and use the Communities Advancing Resilience Toolkit (CART), a 21-item tool that assesses four domains, including (1) connection and caring, (2) community resources, (3) transformative potential, and (4) disaster management [68,99,100]. Each item asks participants to rate their agreement on a 5-point Likert scale from 0 (strongly disagree) to 4 (strongly agree). The 5

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domains of the CART have demonstrated validity (connection and caring: Cronbach α=0.83; resources: Cronbach α=0.75; transformative potential: Cronbach α=0.90; and disaster management: Cronbach α=0.91) [101]. Data on relevant covariates, including demographic information (age, race, ethnicity, sex, household income, education, etc), will also be collected at baseline and, in cases where the item may vary over time (eg, self-rated health), repeated at each time point.

Planned Analyses

Aim 1: Evaluate Factors That Affect Intervention Implementation, Efficacy, and Adoption

A mixed methods approach will be used to assess acceptability and feasibility of the COPE intervention. We will survey CFs, using the AIM, IAM, and FIM, to assess acceptability, appropriateness, and feasibility, along with items to assess preparation and satisfaction with the COPE intervention. In addition, intervention fidelity will be monitored in person by research team staff using a standard tool developed for the COPE intervention series. Qualitative assessments will also be conducted throughout the study, especially during the implementation and after the conclusion of every COPE series, and field notes will be taken at workshops. CFs, key leaders, and participants will be interviewed or participate in focus groups using semistructured interview guides.

We will conduct reflexive thematic analysis using the steps outlined and refined by Braun and Clarke [102,103] as a guide to analyze verbatim transcripts or field notes using the MAXQDA qualitative data analysis software. Each of the 6 steps of thematic analysis involves an iterative examination and reexamination of the data to ensure thematic coherence, generating themes from codes and refining the purpose and meaning of themes to clarify their interpretive story [102-104]. This approach permits reflexive discernment of differences across clusters and steps, accounting for nuance given variations in procedures, adjustment to delivery, and development of interpretative stories that convey deeper meaning around collective coping and community resilience [103].

Aim 2: Testing of Intervention Effects

Aim 2 will test the effectiveness of the COPE intervention on improvements in mental health symptoms (perceived stress, depression, anxiety, and stress), coping self-efficacy, perceived social support, and community resilience (see Table 1 for measures). The SW-CRT design involves clusters sequentially transitioning from control to intervention, allowing for within-cluster comparisons and accounting for time-dependent effects. The primary analysis for aim 2 will follow an intent-to-treat approach using a linear mixed model to examine within- and between-group differences across time. Missing data will be handled under the assumption that they are missing at random, using restricted maximum likelihood estimation, and we will assess the benefit of multiple imputation across missing values and conduct sensitivity analyses. The linear mixed model will account for the hierarchical structure of the data (eg, individuals, clusters, and time), and include fixed effects for the intervention arm, time, and covariates, such as age, ethnicity, and education. We will also include a random intercept for the clusters to assess between cluster variability and random slopes for time given the variability in time points between the clusters.

At time points 4 and 5, participants in the control arm will have transitioned to the intervention arm. To account for this transition, participants will be categorized based on their current condition (control or intervention) at each time point. This approach ensures that the analysis reflects the condition under which participants were exposed during each survey period. We will also conduct a sensitivity analysis to compare outcomes across time points 1 to 3 (before the switch) to time points 4 to 5 (after the switch). This will allow us to examine intervention effects during the period that the control group is unexposed to the COPE intervention. Results will be presented as regression coefficients with 95% CIs and *P* values, ICCs, and variance estimates for random effects.

Reflexivity, Transferability, and Generalizability

As a study that uses a CBPR approach, local knowledge is central to optimizing the COPE intervention and study implementation. Our core research team consists of 3 academic researchers, each of whom also have lived experience in Louisiana during a climate disaster, and a CBPR strategy team that brings together individuals with a range of professional and personal backgrounds, including a church pastor and licensed therapist, a retired chemistry professor and civil rights activist, a community organizer, a retired English professor, an executive director of an environmental justice nonprofit, and 2 clinical social workers. The team includes members of different racial or ethnic, gender, and faith backgrounds, each of whom bring lived experience to our collective understanding of mental health challenges in the face of climate disasters and social inequities. Our research team members share identities, experiences, or community ties with our participants, furthering a sense of empathy and responsibility in our approach as our personal experiences are echoed in the stories we hear from friends, family, and neighbors, informing and additionally driving our commitment to this research.

We are approaching our research collaboration from a perspective that recognizes knowledge as accumulated through observation and relationships, reflections, and adaption, which allows us to construct the COPE study and implementation together. Our team believes that community-based mental health support must be integrative, proactive, sustainable, and culturally appropriate. Although we hypothesize that we will find evidence that the COPE intervention effectively improves individual and community mental health outcomes, the trustworthiness of our analyses and interpretation is enhanced by our greater aim, which is to catalyze change that improves mental health and fosters resilience within our community and beyond.

We will ensure confirmability and dependability through extensive intervention monitoring with data collection following structured formats, including fidelity assessment checklist tools and field note guides, as well as interview and focus group guides and transcripts. In addition, we will keep detailed documentation of decisions made throughout the research process and conduct periodic team debriefings. The credibility of our data will be strengthened through our periodic member

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checking done with monthly meetings of the CBPR team to review the research process and validate findings. Finally, our inclusion of contextual variables and rich description will enhance transferability to allow for application, adaption, or replication.

Results

The trial testing the COPE intervention funded by the Gulf Research Program of the National Academies of Sciences, Engineering, and Medicine is being conducted from June 2022 to June 2025. The first 9 months of the funding period were dedicated to adapting the RCHC curriculum to develop the COPE intervention model and the pilot. Recruitment was launched with the first cluster of participants in April 2023 and is scheduled to end in spring 2025, with data analysis and peer review submission of results to follow. Our principal focus will be on outcomes related to aim 2, for which we will prioritize individual-level changes on mental health outcomes including depression, anxiety, and perceived stress. Secondarily, we will examine changes in coping, social support, and community resilience. For aim 1, we will examine cluster-level variations and questions regarding COPE implementation.

Discussion

Anticipated Findings and Implications

This study aims to evaluate the implementation and effectiveness of COPE, a multilevel, community-based intervention developed to support individuals and communities in mitigating adverse psychological outcomes by enhancing individual coping capacity, social support, and community engagement. There is increasing recognition of the value of multilevel, community-based interventions to address mental health in communities facing compounded effects of inequality and disasters; however, methodologically sound research documenting their implementation and substantiating their effectiveness is limited [69,105]. The study implementing this protocol is among the first to examine the effectiveness and implementation of a multilevel intervention such as COPE in a community that has both experienced prior disasters and is at high risk for future extreme weather events.

Testing the implementation and effectiveness of the COPE intervention holds theoretical and practical significance, contributing to the existing literature on disaster interventions. Multilevel, community-based interventions have become increasingly recognized for addressing the complex interplay between individual, social, and environmental factors that influence disaster resilience and recovery [106-109]. However, few studies examine multilevel interventions, which address the dynamic interplay between individual and systemic factors influencing psychological well-being [110].

At the individual level, COPE focuses on equipping participants with evidence-based skills, such as stress management, emotional regulation, and resilience-building, which can be customized to incorporate local variations on coping practices such as mindfulness or storytelling [111,112]. At the interpersonal level, COPE aims to foster social support through structured group sessions that promote sharing and mutual aid [113]. At the community level, COPE seeks to enhance social capital and engagement by mobilizing local resources and networks, such as partnering with faith-based organizations [114,115]. This approach acknowledges that psychological recovery depends not only on individual factors but also on their concomitant social determinants [69]. At the policy level, COPE aims to inform improvement of existing public health infrastructures to better address community mental health, both in general and after a disaster. In addition, our findings may inform the development of a replicable intervention framework for incorporating facilitator training within local institutions, guiding community health planning; shaping services at the city or state levels; and supporting sustainable, community-driven initiatives throughout the Gulf South region.

Practically, this study will assess how the COPE intervention materials permit tailoring to improve their relevance to discrete groups. Exploring how COPE is adapted at the group-level to include culturally specific symbols, narratives, and traditions, or adjusting focus areas to specific disasters, may further contribute to understanding of the contextualization of disaster mental health intervention approaches [115]. This could provide rich opportunities for future research to not only expand its evidence base and applicability, but also to better understand the interrelationship of cultural processes. Specifically, examining processes of modifying COPE in different contexts to align with diverse cultural norms, values, and beliefs, while maintaining its core principles, could provide insight into how other group-based interventions might better use similar flexible frameworks to expand their cultural relevance [115,116]. Comparative studies examining how COPE is implemented across different cultural and socioeconomic contexts (eg, rural vs urban and collectivist vs individualist communities) could identify best practices for additional contextual tailoring.

Studies are also needed to examine the long-term effects of COPE on individual coping and social capital, including support networks and community resilience. Such studies could also evaluate COPE's role in enhancing preparedness for future disasters and mitigating long-term mental health challenges. Finally, implementation science studies could explore COPE's feasibility and scalability in low-resource settings in terms of cost-effectiveness, training requirements, availability of facilitators, and integration with existing community structures [115].

Potential Limitations

Although this study design presents a rigorous approach to evaluating the effectiveness and implementation of the COPE intervention, limitations should be considered. First, the SW-CRT design may introduce potential biases related to the sequential rollout of the intervention across clusters [74]. Clustering can occur because randomization happens on the group level, potentially generating high intracluster correlation, as participants within the same cluster may respond to COPE more similarly to each other than to those in other clusters. In addition, the clusters are grouped for randomization based on when they could reasonably begin the intervention, then randomized at different time points. This might impact the

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outcomes due to temporal context particularly as the intervention is introduced sequentially which requires a longer time to completion than would a parallel-group randomized controlled trial [117]. This prolonged duration can increase the risk of external factors, such as in environmental conditions (eg, hurricane season and winter), that may influence the implementation and effectiveness of the intervention [117,118]. We will implement several mechanisms for ensuring fidelity across clusters, including detailed fidelity checklists and monitoring of each facilitator's initial delivery of the COPE intervention. In addition, to improve generalizability of our findings, we will control for cluster, as well as for step and important seasonal variations.

The prolonged duration of the enrollment and study period can also contribute to attrition and missing data, potentially threatening the robustness and long-term applicability of findings. We will estimate the treatment's average causal effect to manage missing data effectively [119]. In addition, as is common with intervention studies, long-term impacts may be difficult to assess despite positive short- and medium-term impacts [119,120]. The duration of the study may restrict the ability to assess long-term sustainability and effectiveness of the COPE intervention beyond 6 months. Despite these limitations, the study provides significant insight into the effects of COPE and similar community-based psychoeducational group interventions on mental health in communities at high risk for a disaster, as well as insights into using CBPR in real-world settings to enhance intervention implementation. Together, these findings and insights lay the groundwork for future research on community-based interventions and disaster mental health programs.

Conclusions

First, this study will provide an understanding of how the multidimensional COPE intervention can address various biopsychosocial (individual, interpersonal, and community) factors that influence well-being, expanding our understanding of the effects of disaster interventions beyond the current focus on individual mental health outcomes [34,121]. Second, the study's CBPR approach, engaging community members and professionals from the region in close collaboration on all aspects of the study from design to dissemination, increases the cultural relevance, acceptability, and long-term adoption of the COPE intervention, as well as the rigor of the interpretation of its findings. This points to replicable methods for using CBPR to improve upon both the limited tailoring of disaster mental health interventions to specific cultures and contexts, as well as the implementation of intervention research studies. Finally, through its robust examination of the factors that influence implementation of the COPE intervention and its effectiveness in a disaster-prone community in the Gulf Coast, the study will add rich insights into effective delivery strategies for future dissemination or adaptations of COPE and similar multilevel, community-based interventions.

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Data Availability

This paper presents the study protocol of a stepped-wedge cluster randomized trial testing the Communities Organizing for Power through Empathy intervention in communities at high risk of experiencing a disaster and does not generate nor analyze an associated dataset, making data sharing nonapplicable. Once the protocol is implemented and data have been collected, the authors will provide access to the detailed protocol and general findings on ClinicalTrials.gov (NCT06093737). Finally, after processing derived data following rigorous procedures to ensure it is deidentified and privacy, rights, and confidentiality of human research participants are protected, deidentified data may be made available upon request.

Authors' Contributions

JS was responsible for conceptualization, funding acquisition, methods development, project administration, supervision, and writing. TP handled conceptualization, funding acquisition, methods, and writing. NML-J completed data collection and management, analyses, and writing

Conflicts of Interest

None declared.

Multimedia Appendix 1
Example facilitator interview guide.
[DOCX File , 19 KB - resprot_v14i1e63723_app1.docx]

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Abbreviations

AIM: Acceptability of Intervention Measure
CART: Communities Advancing Resilience Toolkit
CBO: community-based organization
CBPR: community-based participatory research
CF: community facilitator
CJoH: Cargivers Journey of Hope
CONSORT-SPI: Consolidated Standards of Reporting Trials–Social and Psychological Intervention
COPE: Communities Organizing for Power through Empathy
CSES: Coping Self-Efficacy Scale
DASS-21: Depression, Anxiety, and Stress Scale
FIM: Feasibility of Intervention Measure
IAM: Intervention Appropriateness Measure
ICC: intraclass correlation coefficient
MHFA: mental health first aid
MSPSS: Multidimensional Scale of Perceived Social Support
PD: psychological debriefing
PFA: psychological first aid
PSS: Perceived Stress Scale
PTSD: posttraumatic stress disorder
PTSS: posttraumatic stress symptoms
RCHC: Resilience and Coping for the Healthcare Community
SW-CRT: stepped-wedge cluster randomized trial
TBR: Together Baton Rouge

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Protocol

Testing an Innovative Gait Training Program in Immersive Virtual Reality for Healthy Older Adults: Protocol for a Randomized Controlled Trial

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Abstract

Background: Impaired gait adaptability is one of the major causes of falls among older adults owing to inappropriate gait adjustments in cluttered environments. Training programs designed to improve gait adaptability behavior in a systemic approach may prevent falls in older adults. Recently, virtual reality (VR) technology has been prominent as a relevant gait training tool because of its training implementation potential.

Objective: This study was designed to compare the effectiveness of a VR-based gait training program (VR group) for improving gait adaptability behavior and, thus, reducing the risk of falls relative to a conventional training program such as Nordic walking (NW; NW group). We hypothesized that the VR-based gait training program will lead to greater gait adaptability improvements.

Methods: We will be conducting a randomized controlled trial with pretests, posttests, retention tests, and follow-up. In total, 40 healthy independent-living community dwellers (aged between 65 and 80 years) will be allocated, after a general medical examination, to the VR or the NW group for a training program of 6 weeks. Primary outcomes related to gait adaptability capacities (ie, analysis of adjustments made in different locomotor tasks) and acceptance of the VR device (ie, analysis of acceptance) will be assessed before and after the intervention and 1 month after the completion of the training program (retention). A follow-up will be done during the 12 months after the completion of the gait training program.

Results: Data collection will begin in September 2025, and the first results are expected in December 2025.

Conclusions: The findings of this study may demonstrate the relative relevance of a gait training program in VR versus a conventional one for improving gait adaptability behavior in healthy older adults and, thus, prevent the chances of a fall.

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KEYWORDS

virtual reality; VR; exercise; locomotion; adaptive behavior; aging; accident prevention; falls

Introduction

Fall Prevention in Older Adults

Falls are a significant health issue because they lead to severe injuries, hospitalizations, and death [1,2]. They also lead to serious physical and psychological restrictions after the fall, with a decline in social activities and a reduced quality of life [3]. Repeated falls often occur after a first fall [4]. Given that fall history is the strongest predictor of future falls [5], gait training programs must also be offered to healthy older adults with no fall history. Therefore, these fall prevention programs must be developed to avoid (or at least delay) the first fall occurrence leading to potential, future repeated falls.

Impaired gait adaptability, which is the ability to adjust locomotion parameters to move safely in cluttered environments, is one of the major causes of falls among older adults [6,7]. In

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cluttered environments, inappropriate gait adjustments can cause older people to hit obstacles or distribute stride length adjustments less than optimally and thus cause falls [2,8,9]. Some studies have shown that impaired gait adaptability is associated with a high risk of falls in older adults [10-12]. To prevent falls in older adults, training programs, including physical activity, designed to improve gait adaptability are thus particularly relevant [13,14].

In fall prevention, several studies have shown the beneficial effects of physical activity, focusing either on one specific (analytic approach) or multiple (systemic approach) physical components [15-18]. In this study, we decided to focus on training programs with a systemic approach, which have been shown to lead to greater improvement of both functional capability and quality of life compared with those based on an analytic approach [19,20].

Gait Training Programs Adopting a Systemic Approach to Prevent Falls

Training programs adopting a systemic approach can be provided by conventional gait training (without the use of dedicated technologies) or by gait training using new technologies.

Conventional Gait Training

In conventional gait training, Nordic walking (NW), defined as "Scandinavian walking with poles," appears, for instance, as a relevant physical activity in the fall prevention context. This type of walking training promotes an easily accessible physical activity that can be performed by many people to improve their gait capacities [21]. Recent systematic reviews showed that NW training leads to beneficial effects on many biomechanical parameters and motor skills development [22] and appears as a promising and effective way to improve motor capacities in older adults [23], such as increases in arm-leg coordination [24], gait speed and step length [25], and postural control and gait parameters [26-28]. Gait improvements obtained by NW training also reduce the risk of falls [29]. However, in recent years, the use of new technologies has given new impetus to the development of gait training programs based on a systemic approach [30].

Extended Reality at the Service of Gait Training

Among these new technologies, extended reality (XR) is an emerging technology that involves virtual reality (VR), augmented reality (AR), and mixed reality [31]. VR is defined as a computer-simulated environment that includes real-time simulation and interaction through multiple sensory channels and a sense of being physically and psychologically present in another place by completely occluding the real world [31]. Contrary to VR, the real world is not occluded in AR: virtual objects are overlaid in the real-world environment. In the same way as in AR, in mixed reality, virtual objects are overlaid in the real-world environment; however, users can physically interact with these virtual objects.

Several studies have demonstrated the effectiveness of XR gait training on balance and gait ability in older adults [32-37]. Shema et al [36] conducted a 5-week VR gait training program for older adults with a fall history. Participants walked on a treadmill and performed obstacle negotiations during a virtual course, while their displacement was displayed in a virtual environment (VE) represented on a screen located in front of them. In their study, Mirelman et al [35] provided a 6-week VR gait training program for older adults with a high risk of falls. During the training sessions, participants walked on a treadmill and performed several goal-directed locomotion tasks (ie, multiple obstacles and paths either with or without distractors), while their displacement was displayed in a VE represented on a screen located in front of them. For their part, van Ooijen et al [37] provided a 6-week AR gait training program for older adults with fall-related hip fractures. Participants walked on an instrumented treadmill on which a visual context was directly displayed on the belt, proposing various goal-directed locomotion tasks (eg, stepping and obstacle avoidance).

These XR gait training programs led to greater improvements in gait ability and thus a reduction in the risk of falls compared with conventional ones [35-37]. However, the implementation of these programs may have some limitations in terms of gait training relevance. Consequently, some precautions need to be considered to identify areas for improvement of XR gait training programs.

Four Precautions for XR Gait Training Program Implementation

Precaution 1: Preserving the Ecological Validity of the XR Setup

The actual use of these XR devices may be examined to ensure the ecological validity during gait adaptability training programs [38] in terms of the level of immersion and locomotion.

First, the level of immersion is an important characteristic of XR devices in training implementation [39] because a high level of immersion leads to high engagement and enjoyment [40]. The XR setups used in previous studies did not make it possible to provide a high level of immersion. Shema et al [36] and Mirelman et al [35] used the same VR setup, which provided a third-person view of the foot avatar in the VE presented on a small screen in front of the participants, leading to a low level of immersion. An immersive experience with a first-person view (ie, the transposition of the usual user's viewpoint into the VE) seems primordial in a gait training program intended to improve gait adaptability capacities. In their review, Liu et al [38] demonstrated that the use of fully immersive XR devices with older adults induced greater gait improvements compared with nonimmersive ones. Future XR gait training program implementation with older adults should be based on the use of a fully immersive XR device (as a VR head-mounted display [VR-HMD]).

Second, in the 3 previous studies, older adults walked on a treadmill. This constitutes a second limitation in gait training implementation, given that the use of a treadmill gives rise to partly different gait kinematics compared with natural locomotion (eg, sagittal plane kinematic differences at foot strike [41]). Conversely, overground locomotion preserves natural locomotion, allowing a high level of ecological validity and natural interaction with virtual objects [42,43].

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A recent study underlined the high ecological validity of a VR setup that combines a fully immersive experience and overground locomotion. Delbes et al [44] aimed to compare the gait behavior of older adults during a similar goal-directed locomotion task (ie, a simple locomotor pointing task) performed in the real world and in VR. In the 2 conditions, participants walked and performed the task with overground locomotion. In the VR condition, participants wore a VR-HMD displaying 2 VEs: a replica of the real one and a new environment. The authors demonstrated the similarity of the gait adaptability behavior produced in the real world and in VR. The use of a VR-HMD coupled with overground locomotion appears particularly relevant for future XR gait training program implementation by (1) ensuring a first-person view with a high level of immersion, (2) ensuring nonconstraint locomotion, and (3) proposing enjoyable scenarios that mimic real-life tasks.

Precaution 2: Following Motor Learning Principles

According to Hendry et al [45], gait adaptability training program implementation should be based on 4 motor learning principles.

The first principle is related to the variability of practice, which is necessary to optimize the improvement of gait adaptability behavior in older adults. Task variability is crucial for learning optimization by confronting older adults with a large range of potential gait adjustments based on their own gait capacities. In previous studies, older adults were confronted with various environmental lighting conditions [36]; changes in the number, size, and shape of obstacles [35]; and configurations of obstacles [37] with a training progression. Future XR gait training implementation should include the manipulation of variability based, for example, on the modulation of VE spatial constraints (obstacle characteristics and configurations).

The second principle is related to the amount of practice and, more precisely, to task repetitions. Performing any repetitions is a *sine qua non* for optimizing any learning [45]. In previous studies, experimenters provide a very global estimation of the amount of practice, for example, 15 sessions of 60 minutes [36], 18 sessions of 45 minutes [35], and 30 sessions of 40 minutes [37]. However, there is no precise information about the number of repetitions for each task performed. The combination of these first 2 principles underlines the importance of the concept of “repetition without repetition” [46,47]. Future XR gait training implementation should be based on a large amount of practice (task repetition) coupled with a large variability of practice.

The third principle is related to the individualization of the training content based on individual characteristics (eg, foot size and leg length) to lead to greater effects of the gait training program [20,48]. In previous studies, task manipulation cannot be regarded as task individualization of the training content because task configurations were manipulated without considering individual characteristics. Mirelman et al [35] manipulated the treadmill speed and the duration of training. However, this kind of task configuration was only based on the modulation of global parameters. Task individualization should also provide a gradual increase in task difficulty based on individual capacities and performance to induce an appropriate level of challenge to optimize motor learning and engagement [45,48]. In summary, future XR gait training implementation should include individualized training content based both on considering the anthropometric characteristics of the participants and on their rate of progress.

The fourth principle is feedback supplementation during the training sessions, which improves motivation, engagement, and adherence and enhances motor learning [45,49]. Various types of visual and auditory feedback, informing about performance and results, were provided during training sessions in previous studies [35-37] and at the end of the sessions in the study by Mirelman et al [35]. Future gait training program implementation should provide feedback (ie, knowledge of performance and result) with a gradual decrease in the frequency of feedback over the training program. Finally, to optimize motor learning, feedback may be requested by the participant to avoid a guidance effect [50].

Precaution 3: Choosing the Right Level of Analysis to Characterize the Effect of Training

In previous studies [35-37], the examination of gait behavior was limited to gait parameters reflecting only the participant behavior (eg, gait speed, step width, step length, and cadence). As mentioned previously, an analytic approach (based on the measure of global gait behavior parameters) only allows an overall understanding of the gait behavior of older adults. However, a precise characterization of participant behavior in relation to the environment (ie, the state of the agent environment system) is needed to provide a better understanding of the improvements induced by gait training.

Additional levels of analysis are consequently required to study gait adaptability behavior appropriately during goal-directed locomotion tasks. During obstacle negotiation, the evolution of the state of the agent environment system can be investigated through intertrial and trial-by-trial analyses, which allow gait adjustment strategies to be characterized in relation to obstacles (eg, the modulation of each footfall target distance [and its variability] over the obstacle approach). Gait adjustments are indeed based on a continuous coupling between information and movement [51]. These additional levels of analysis allow us to investigate the agent environment system as a whole and not the agent alone. Finally, the study of global gait behavior (as done in previous studies) coupled with the study of gait adaptability behavior (ie, based on gait adjustment indicators of the state of the agent environment system) constitutes complementary levels of analysis to characterize gait behavior in older adults more precisely.

Precaution 4: Studying the Acceptance of the XR Device Used

Merely examining the effectiveness of a training program is not sufficient. Acceptance of the XR device should also be investigated because attitudes of older adults toward the technology used in the training program may influence its effectiveness [52,53]. The fact that the use of an XR device is objectively effective does not mean that it is necessarily accepted, and, conversely, an XR device that is accepted is not necessarily effective. However, in the studies by Mirelman et al [35], Shema et al [36], and van Ooijen et al [37], only the

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effectiveness of XR gait training programs was proven without considering the acceptance of the XR device by older adults.

Some studies have investigated the acceptance of XR devices in older adults, for instance, acceptance before the first use of a VR-HMD intended to prevent falls [53]. This study revealed that older adults' intention to use the VR-HMD was positively predicted by perceived usefulness, perceived ease of use, and perceived enjoyment and that no initial blockages appeared among older adults before the first use. Moreover, Delbes et al [44] compared acceptance before and after the use of a VR-HMD specifically intended to prevent falls among older adults. They highlighted that older adults did not intend to use the VR-HMD before the first use, but they did not refuse it either (ie, neutral attitudes toward VR-HMD before the first exposure). Finally, they intended to use it after the first effective use during a single session in VR.

To date, no study has shown the potential evolution of acceptance of the VR-HMD by older adults throughout a gait training program intended to prevent falls. As the study of the effectiveness of an XR gait training program cannot be done without ensuring that the XR device is accepted [52], the effectiveness of the program and the acceptance of the device will be conjointly investigated, in contrast to previous studies.

Objectives of the Study and Hypotheses

The ambition of our study is to investigate both the effectiveness of a VR gait training program (using a VR-HMD) and the acceptance of the VR device among healthy older adults. The effectiveness of the VR gait training program will be compared with that of a conventional training program of NW. The choice to compare a VR gait training program method to NW reflects the ambition of this work. From our point of view, NW offers the ecological context that is most conducive to the maintenance and even improvement of the functional relationships between perception and action. The walker must constantly adjust locomotion parameters in reference to obstacles to produce adaptive behavior in cluttered environments. Our VR gait training program aims to be the counterpart of NW in a perfectly controlled context thanks to VR technologies. Demonstrating the potential of our protocol would seem more convincing to us if it were established that the improvements induced by using a VR device were equivalent or even superior to those induced *via* NW. The comparison of the gait training programs' effectiveness will be based on a pre- and postintervention comparison of gait adaptability capacity improvements based on further levels of analyses (as presented earlier). The 2 gait training programs will be offered to healthy older adults (with no fall history) with a systemic approach to fall prevention intended to avoid or at least delay the first fall occurrence. The study of VR-HMD acceptance will be based on the Technology Acceptance Model (TAM) [54-56].

The VR gait training program will be implemented following the different guidelines presented earlier. On the basis of all the previous precautions, our future gait training program in fully immersive VR may potentially improve both functional and psychological outcomes. We hypothesize that both gait training programs will lead to improvements in gait adaptability behavior capacities (hypothesis 1) but that the VR gait training program will induce greater improvements in gait adaptability capacities in comparison with the NW training (hypothesis 2). Finally, we hypothesize that older adults will accept the VR-HMD before the VR gait training program (hypothesis 3) but that acceptance will increase throughout the gait training program (hypothesis 4).

Study of Secondary Variables

In addition, the study of secondary variables will allow us to compare our results with those of previous studies and provide additional knowledge in the specific population of healthy older adults with no fall history. As done in previous studies [35-37], some specific tests will be carried out before and after the intervention. First, in terms of functional capacities, we will evaluate mobility and balance capacities, which are linked to the risk of falls in older adults [57-59]. Second, in terms of psychological states, we will study motivation toward health-oriented physical activity [60], intrinsic motivation [61], and self-reported fear of falling [62,63], which may impact the risk of falls in older adults. The secondary variables will allow us to investigate the training program's potential effects on some specific health components, given that interactions exist among gait behavior, functional capacities, and psychological states [64]. Recently, Dermody et al [43] reviewed the high potential of VR-HMD to improve both functional and psychological outcomes in older adults. Finally, in addition to the study of gait adaptability behavior and the acceptance of the XR device, the study of secondary variables will allow us to demonstrate potential general health changes after the gait training program.

Methods

Participant Recruitment

The initial recruitment will be carried out from an existing cohort of healthy older adults recruited by the Active Aging Chair.

Inclusion Criteria and Informed Consent

Participants are independent-living community dwellers aged between 65 and 80 years. They are active older adults with weekly moderate to vigorous physical activity. This study is a part of a broader research program aimed at determining the extent to which new technologies (eg, exergames and XR) can be used to promote healthy aging among active older adults [23,24,65]. Of course, populations of more fragile older adults (eg, older adults who fall) could benefit from an appropriate intervention approach; however, our objective in this study consists, rather, within the framework of a preventive approach of creating the conditions allowing the delay or even avoidance of the occurrence of a first fall.

The exclusion criteria are inability to practice activity at a moderate or vigorous intensity (checked by medical examination supervised by cardiologists), moderate or severe cognitive impairments (ie, a Mini-Mental State Examination score <26 [66]), severe noncorrected visual impairments, and uncontrolled psychiatric disorders.

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Every 5 minutes of VR use, the Fast Motion Sickness scale [67], designed to measure cybersickness, will be completed orally by the participant. According to the protocol set up by Keshavarz and Hecht [67], if a participant reaches a score of 15 or more, they will immediately be asked if they wish to stop participating and be told that this will have no harmful consequences for them.

Information about the organization of the gait training programs will be presented to the eligible participants by the principal investigator. Those who are willing to participate will be asked to give informed consent.

Ethical Considerations

Importantly, this protocol will be submitted during April 2025 to a national ethics committee (ethics committee for research in science and technology of physical and sporting activities) for approval. The approved protocol will be implemented from September 2025 in accordance with the Helsinki Convention. Before the study, participants will give their written informed consent to participate for free in the experiment. For their part, the researchers who carry out the experiment undertake to respect the rules of data confidentiality and the privacy of the participants.

Study Design

This study is based on a comparison of a gait training program in VR (ie, the VR group) with sessions of NW (ie, the NW group). Participants who meet the inclusion criteria will be randomly allocated to the gait training program (in the VR or NW group) using a computer-generated block randomization with a block size of 30 participants (1:1 rate). The data for participants in both groups will be obtained at 3 different times: 1 week before the beginning of the training program (T0), 1 week after completion of the training program (T1), and 1 month after completion of the training program (retention assessments; T2). Moreover, a follow-up (T3) with the incidence of trips and falls will be done during the 12 months after completion of the gait training program. Participants' flow is presented in Figure 1.

Figure 1. Flowchart of the study design. MMSE: mini-mental state examination; NW: Nordic walking; VR: virtual reality.

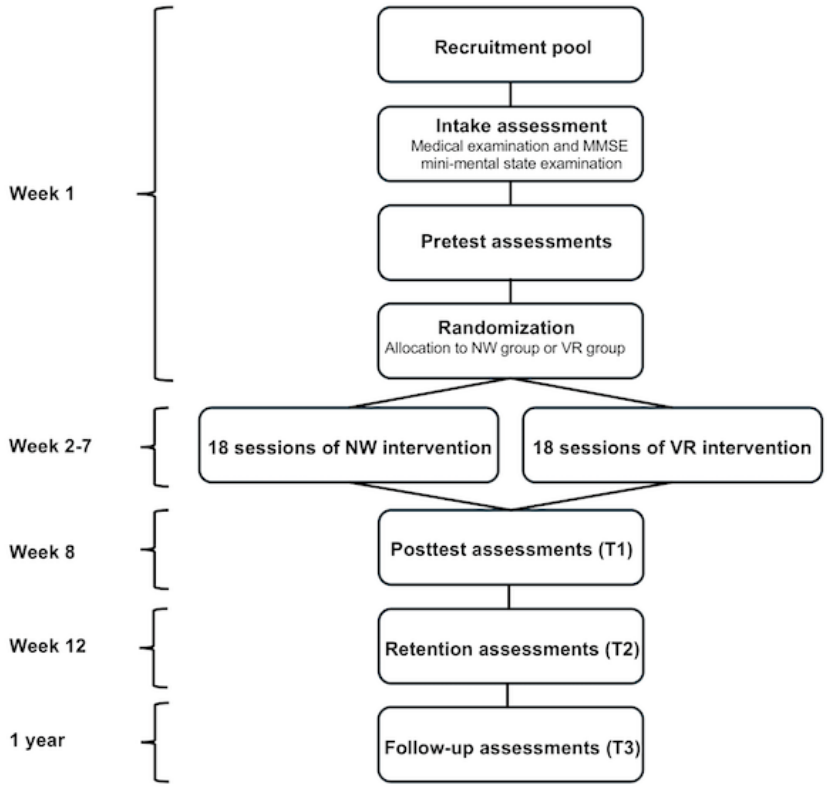

Gait Training Programs: NW Versus VR

Overview

The 2 gait training programs will be dose-matched in terms of duration (ie, 45 min per session) and frequency (ie, 3 sessions per week) of training over a 6-week program (ie, 18 training sessions) following the methodology used in previous gait training studies [35-37]. Previous studies have shown that extensive practice is important for the consolidation and retention of motor memory [68]. Therefore, in line with our ambition to develop long-term improvements in gait adaptability behavior, a large amount of practice in our gait training programs is necessary.

NW Group

In the NW group, participants will practice the training sessions in a nature park. They will be instructed to walk with poles continuously around the park. Each training session will consist of a warm-up period (10 min), main exercise (45 min), and cool-down period (5 min). Participants will adapt their locomotion to uneven terrain. They will negotiate natural obstacles such as avoiding a rock or crossing over a tree root, thus improving their gait adaptability capacities. Sessions will

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be provided by a coach from a multisport club proposing programs of physical activity adapted to older adults. Participants will follow the coach, who will progressively increase the level of difficulty over the 6 weeks, show the way, and adapt to the gait speed.

VR Group

In the VR group, participants will practice the training sessions in an experimental room. In 1 training session, participants will negotiate 60 trials. Sessions will be provided by the principal investigator. Participants will practice gait training sessions in a fully immersive VR. A wireless HTC Vive Pro VR-HMD will be used to display VE (Figure 2A). Participants will wear HTC Vive Pro foot trackers on their feet, which will record their feet positions (in relation to obstacles) and display 2 virtual foot avatars in the VE. A security system consisting of a safety harness (Figure 2C) connected to an in-ceiling rail by a lanyard (Figure 2B) will provide training sessions in a safe context. This setup has been validated in a previous study [44] in which gait adaptability behavior was similar in the real world and in VR.

Figure 2. Test equipment. (A) A wireless HTC Vive Pro will be used to display the virtual environment. Two HTC Vive Pro 2.0 trackers will be used to record the positions of the feet and display virtual 3D shoes in the virtual environment; (B) in-ceiling rail; (C) safety harness.

VR training sessions were created with homemade software developed with Unreal Engine (version 5.1; Epic Games) and OpenXR (Khronos Group). It will be used with a wide panel of AR and VR technologies (Oculus, HTC Vive, HP, etc). The software contains 2 operation modes: design and simulation.

The design mode is used to create the content of the different training sessions (ie, 60 trials in different configurations per training session) with a user interface. Each kind of task can be modulated *ad infinitum* by changing the position, number, and size of the obstacles. Moreover, configurations will be modulated by the number of different tasks displayed: participants can negotiate one or several kinds of tasks in 1 trial. The 3 tasks mainly used in the training protocols are illustrated in Figure 3. The pointing task consists of positioning the foot as close as possible to the line without exceeding it. The crossing-over task consists of crossing over a horizontal obstacle without meeting it. The stepping-over task consists of stepping over a vertical obstacle without touching it. The technology used (tracker positioned on the feet) makes it possible to locate the feet at any time with reference to virtual obstacles and to determine the performance produced depending on whether the task is carried out in accordance with the success criteria or, conversely, if collisions with obstacles occurred. This method is based on the exclusive use of virtual obstacles. Examples of different trial configurations are provided in Figure 3. In this mode, different criteria of success will be determined at different scales (ie, obstacle, trial, and training session). The criterion of success for each obstacle negotiation is fixed according to the

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kind of task: pointing accuracy (in cm) for simple locomotor pointing; recovery (in cm) for successive locomotor pointing; and clearance (in cm) for stepping-over, crossing-over, and obstacle avoidance. The criterion of success for each obstacle is set as a certain percentage of successful obstacle negotiation. Finally, the criterion of success for each training session is set as a certain percentage of successful tasks.

The simulation mode is used to display the training sessions created in the design mode and to record participants' foot positions in relation to obstacles. In this mode, the participant's anthropometric data are considered to propose individualized session content based on a certain percentage of each participant's leg length. In real time, the participants' performance is calculated in terms of obstacle negotiation and completion time. On the basis of these real-time data, the success or failure of the obstacle negotiation will be measured depending on the determined criterion of success. Different types of feedback can be provided to inform the participant about their obstacle negotiation performance. Moreover, at the end of the trial and the training session, additional feedback can be given to inform the participant about their trial and session success, respectively. This feedback can be provided on the screen as text ("success" or "fail") or coloration of the virtual scene (in green for success or in red for fail).

Given that the software allows the modulation of the content of the training sessions by setting specific criteria, several goal-directed tasks in various VEs will be provided to propose relevant gait adaptability exercises. Six different VEs have been created (Figure 4): subway, shopping center, forest, beach, office, and street.

Figure 3. Schematic of the 4 different goal-directed tasks performed on the walkway GaitRite (in gray). (A) simple locomotor pointing task; (B) crossing-over task; (C) stepping-over task; and (D) "mixed condition" with 2 locomotor pointing (in purple), 1 crossing-over (in green), and 1 stepping-over (in orange) tasks.

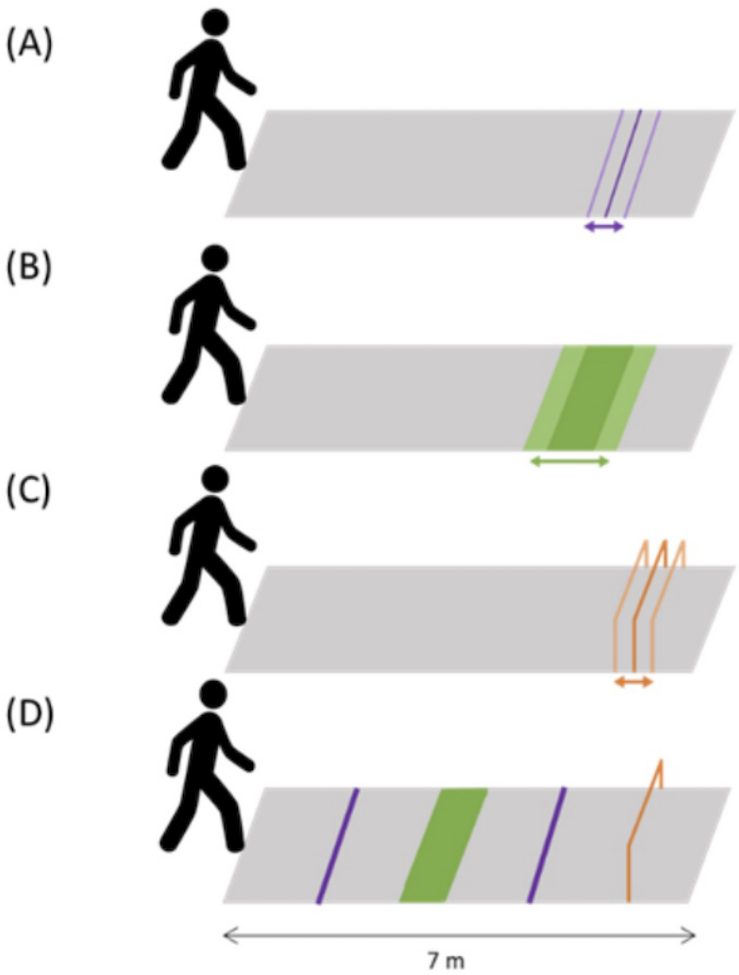

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Figure 4. Examples of first-person views of locomotor goal-directed tasks in the different virtual environments (A) cross over road tar in a street, (B) step over a pipe and stepping on successive flyers in a subway, (C) avoid cardboard boxes in a shopping center, (D) step over successive seashells on the beach, and (E) step over successive leaves in a forest, (F) avoid chairs in an office. Green areas represent the start and the finish lines.

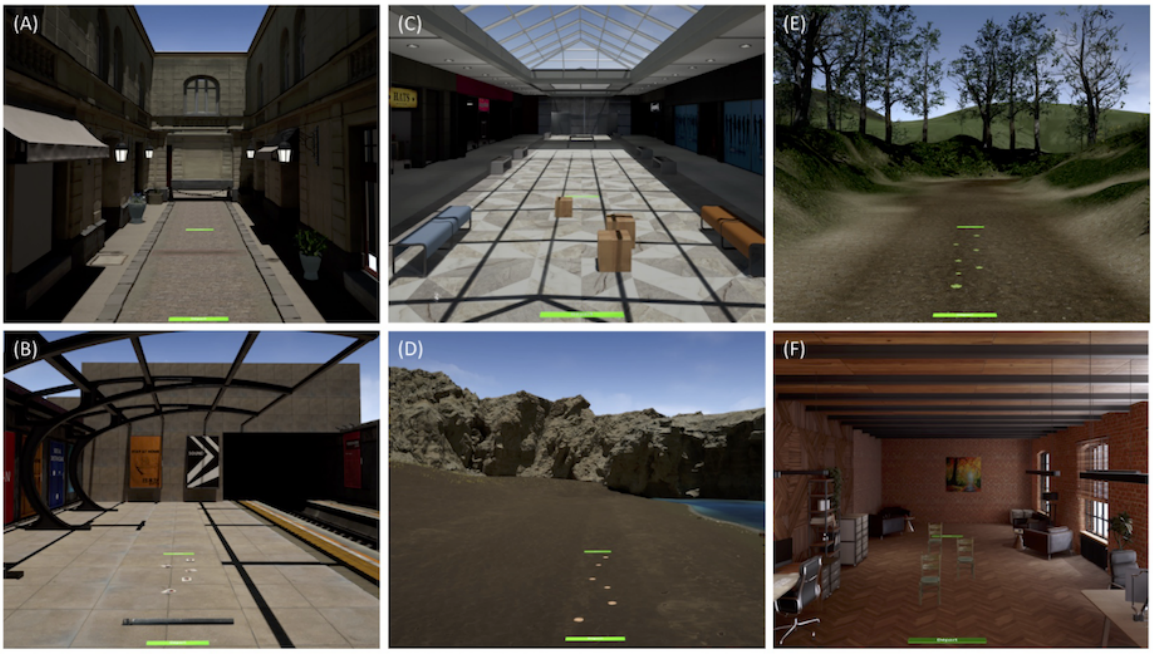

Our gait training sessions will be developed with an increasing level of difficulty over the 6 weeks. In terms of progress, 18 levels of difficulty have been created (to be able to provide a new level per new training session). In the first training sessions, only one kind of task will be displayed in a single trial in the presence of a limited number of mainly small obstacles. Progressively, the number and size of the obstacles will increase. Afterward, 2 kinds of tasks will be displayed in a trial. In the last training sessions, participants will negotiate various obstacles with 2 kinds of tasks in a trial. On the basis of the criteria of success previously presented, when a participant succeeds in the training session, they advance to the next level of difficulty for the next training session. Conversely, if they fail, they remain at the same level for the next training session. In addition, the session content has been created with a high level of individualization. As presented earlier, the participant's anthropometric data will be considered to propose training according to individual capabilities. The obstacle sizes will be proportional to each participant's leg length. The surface area, the height, and the depth of the obstacle will be modulated, respectively, for the successive locomotor pointing, stepping-over, and crossing-over tasks. Obstacle modulation will lead to equivalent levels of difficulty for all the participants over the training program.

In summary, our software will allow us to implement the main principles of Hendry et al [45] presented in the introduction. The VR training program was designed in particular to optimize the variability of the practice conditions and to allow the learner to have qualitative feedback on the success of the task. The variability of the practice conditions was obtained essentially by manipulating the location of the obstacles, their dimensions, and the nature of the task. The speed of locomotion was not manipulated as such, given that participants were asked for each trial to complete the route as quickly as possible while giving priority to precision. Concerning feedback, at the end of each trial, the participant will have the possibility of requesting feedback related to the knowledge of result (self-controlled feedback). It has been shown that this type of feedback makes it possible to enhance learning by placing the participant at the heart of the learning experience and developing their autonomy [69-71]. One of the main advantages of the self-controlled feedback procedure is that it allows participants to use feedback to optimize control processes without inducing a dependency effect. Indeed, the literature indicates that participants spontaneously implement a fading procedure [71] by requesting feedback massively at the start of the training period and then less often, which protects them from any dependence on feedback [50].

A stratified randomization (with the sex factor) will be conducted, using a computer software program to generate a random sequence. Two strata (male and female) will be identified, and randomization will be applied to each stratum. For instance, when a male older adult participates in the study, he will be the first to be allocated to the male strata, and the group (VR group and NW group) will be determined through randomization applied to the male stratum.

Outcome Measures and Data Collection

Primary Outcome Variables

Two major variables will be computed to investigate the effect of these two gait training programs intended to develop gait adaptability behavior in older adults. In terms of gait adaptability behavior, gait parameters will be computed from an innovative gait adaptability test. In the context of fall prevention, this specific test will allow us to investigate gait adaptability behavior with several levels of analysis. In terms of VR-HMD acceptance, we will examine acceptance before and after the use of the VR device designed to prevent falls in older adults. We will determine attitudes and representations toward the

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technology device used in this training program to ensure that older adults accept the VR-HMD.

Gait Adaptability Test

Gait adaptability capacities will be assessed by a specific gait test created to assess gait parameters during goal-directed tasks. Feet positions will be measured by a 7-m-long portable pressure-sensitive walkway, GaitRite (CIR Systems, Inc), in the real world. The security system (safety harness connected to an in-ceiling rail by a lanyard) will also be used to carry out the tests. First, participants will be instructed to walk at a normal pace on the walkway. The average preferred gait speed, step length, and step duration (with their variabilities) will be calculated over 6 trials. Afterward, physical obstacles will be placed on the walkway. Participants will perform 3 different locomotor tasks: simple locomotor pointing, crossing-over, and stepping-over tasks (Figure 3). They will perform 10 trials of each goal-directed task. Participants will be instructed to negotiate obstacles as quickly as possible without colliding with them. The size of the obstacles will be proportional to the anthropometric data of the participants (ie, based on individual leg length).

For the locomotor pointing task, participants will be instructed to place the right foot tip as close as possible to the lower extremity of the target. The pointing performance (ie, the horizontal distance between the tip and the lower extremity of the target) will be measured. For the crossing-over task, participants will be instructed to cross an obstacle with a depth of 60% of their leg length. The crossing performance (ie, the horizontal distance between the tip and the lower and upper extremities of the target) will be measured. For the stepping-over task, participants will be instructed to step over an obstacle with a height of 20% of their leg length. The stepping performance (ie, the vertical distance between the tip and the target) will be measured using Kinovea Video analysis software (version 0.8.15; 2006-2011 Joan Charmant and Contrib). The position of obstacles will be manipulated (3 different positions each separated by 30 cm intervals) and presented in a randomized order (2 trials for each position condition) to avoid locomotor regularities and prevent any calibration of the distance being covered. Finally, participants will perform 10 trials of a mixed condition: a combination of 2 previous goal-directed tasks (Figure 3).

By recording successive feet positions in relation to the obstacles, gait adaptability behavior will be analyzed through intertrials and trial-by-trial analyses [44,51,72].

In the intertrial analyses, the SD of the toe-obstacle distances and the SD of the step lengths will be measured. If the locomotion behavior produced is functional, the intertrial analysis should reveal inverted patterns of variability [44,51]. This result reveals that step length adjustments are produced to minimize toe-obstacle distance at the last footfall and thus perform optimal foot positioning. We hypothesize that the training carried out should accentuate the presence of compensatory variability (pre- vs posttest comparison) but also that the compensatory variability produced following the training should be more pronounced for the VR group than for the NW group.

The trial-by-trial analysis makes it possible to identify precisely for each trial the presence of adjustments of the step lengths and their distribution throughout the trial by comparing each step length with the average pattern of step length (see the study by Montagne et al [72] for a similar procedure). The second part of the analysis consists in computing for each step the number of adjustments needed to place the foot on the target and the number of adjustments actually implemented [44,72]. Here again, we hypothesized that the training carried out should enable participants to improve their ability to produce adaptive behavior. More precisely, not only should step length adjustments be initiated sooner after training (ie, after the test) so that they can be spread over a larger number of steps but also the adjustments produced should more accurately reflect the adjustments required to succeed in the task. These improvements in adaptive locomotor skills should be more pronounced for the VR group.

To sum up, from this gait adaptability test, we will characterize the gait adaptability behavior with different levels of analysis. In addition to a traditional analysis of locomotion (ie, performance, mean step length and associated variability, and mean walking speed and associated variability), further levels of analyses (ie, intertrial and trial-by-trial analyses) will investigate the onset of the regulation, the regulation strategy, the relationship between needed and produced regulations over the obstacle approach, and the strength of the perceptual motor coupling. Our hypothesis was that the combination of traditional measures and these new measures should provide a more integrated understanding of the improvements caused by the implementation of VR training protocols. While traditional measurements are focused on the behavior of the older adult, the new measurements make it possible to analyze their behavior in relation to the environment. We believe that the joint use of these levels of analysis allows a finer characterization of product behavior and its evolution.

Finally, in the mixed condition, a gait adaptability score will be calculated based on gait performance and speed. The gait adaptability score is calculated from the pointing, crossing, and stepping performances modulated by the gait speed. The score is the product of gait performance and velocity so that it accounts for the capacity of older adults to manage the speed-accuracy conflict in the context of producing a goal-directed locomotor displacement. The performance obtained is the sum of the performance achieved in the two tasks. In the pointing task, performance is higher the closer the foot is to the mark (a score of 10 when the tip of the foot is <10 cm from the edge of the target, 8 between 10 and 15 cm, etc). In stepping-over tasks, performance is maximum (a score of 10) when the task is carried out in accordance with the instructions (ie, without meeting the obstacle), while imperfect completion of the task gives rise to a score of 5. The same methodology is applied during the crossing task. The sum of the performances achieved gives rise to an overall performance for each trial (maximum 20) that will be weighted by the average walking speed to complete the route (eg, 20×0.90=18).

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VR-HMD Acceptance

For the VR group only, VR-HMD acceptance before and after use will be assessed using the TAM. According to this model, intention to use a technology is positively predicted by its perceived usefulness and its perceived ease of use. VR-HMD acceptance will be assessed through 4 variables: perceived usefulness, perceived ease of use, perceived enjoyment, and intention to use [54,73,74]. Participants will answer the 3 items per variable on a Likert scale from 1 (strongly disagree) to 10 (strongly agree): perceived usefulness (eg, "I believe using VR hardware would help me be more effective in my locomotion"), perceived ease of use (eg, "I believe using VR hardware would be easy for me"), perceived enjoyment (eg, "I believe I would find using VR hardware enjoyable"), and intention to use (eg, "I intend to use VR hardware within the foreseeable future"). In older adults, the TAM has been recently used to study VR-HMD acceptance before [44,53] and after the use [44] of a device intended to prevent falls among older adults.

Secondary Outcome Variables

As mentioned in the Introduction section, interactions exist among gait behavior, functional capacities, and psychological states. In addition to the study of gait adaptability behavior and VR-HMD acceptance, several secondary variables will be investigated to characterize potential functional capacities and psychological state changes over the gait training programs.

Functional Capacities

Mobility evaluation will be assessed with the Timed Up and Go test [75]. Participants must sit down on a chair with their feet on the floor and their hands on their legs. At the "go" signal, they will stand up, walk 3 m, turn around the cone, walk back, and sit down again. The performance time (in seconds) will start when the participant starts moving, and it will end when the participant sits down again. Two trials at a self-paced velocity and 2 as fast as possible will be performed. For analysis, the mean value of the 2 trials in each condition will be considered.

Balance evaluation will be assessed with the Unipedal stance test [76]. Participants must lift one of their legs (while looking at a mark placed in front of them at eye height) and keep a stable equilibrium. The performance time (in seconds) will end when participants lose equilibrium (with a maximum trial duration of 60 seconds). Three trials with eyes open and 3 with eyes closed will be performed. For analysis, the best value of the trials in each condition will be considered as recommended in the study by Springer et al [76].

Psychological Assessment

Motivation for physical activity will be assessed using the motivation scale for physical activity for health purposes questionnaire recently validated in French [60]. This provides a measure of motivation to engage in physical activities from a health perspective through different behavioral regulations: intrinsic motivation, integrated regulation, identified, introjected, and extrinsic motivation, and amotivation. Intrinsic motivation will be assessed using the Inventory Motivation inventory questionnaire [61]. This provides a multidimensional measure of subjective experience while performing a given activity through interest, perceived competence, effort, and tension. Fear of falling will be assessed using the French version of the Modified-Falls Efficacy Scale [77]. This provides the level of concern about falling during activities inside and outside the home.

To sum up, primary outcome variables related to gait adaptability behavior and VR-HMD acceptance (for the VR group only) will be assessed at T1, T2, and T3 in the same way. Secondary outcome variables related to functional capacities and psychological states assessment will be assessed at T0, T1, and T2 in the same way. Adherence to programs will be measured at each training session. Occurrence of falls and near falls will be assessed during the follow-up period (ie, T3 at 12 months after completion of the training program) *via* a smartphone app (eg, the iFall app [78]). Table 1 provides an overview of the outcome measurements.

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Table 1. Outcome measurements schedule.

	T0 (pretests)	Training sessions	T1 (posttests)	T2 (retention)	T3 (follow-up)
Primary outcome variable related to gait adaptability behavior					
Gait adaptability test	✓		✓	✓	
Primary outcome variable related to VR-HMD[a] acceptance					
Acceptance	✓		✓	✓	
Secondary outcome variables related to functional capacities					
Timed Up and Go test	✓		✓	✓	
Unipedal balance test	✓		✓	✓	
Secondary outcome variables related to psychological assessment					
Motivation for health-related physical activity (EMAPS[b])	✓		✓	✓	
Inventory Motivation inventory	✓		✓	✓	
French version of the Modified-Falls Efficacy Scale	✓		✓	✓	
Adherence to programs		✓			
Incidence of trips and falls					✓

[a]VR-HMD: virtual reality head-mounted display.

[b]EMAPS: Echelle de Motivation pour l'Activité Physique à des fins de Santé.

Sample Size

The sample size calculation was performed using G*Power (version 3.1.9.7). To detect relevant within-between-group differences, we calculated a sample size sufficient to detect small effect sizes. On the basis of values generally observed in studies conducted in the field of acceptability and acceptance of technologies in general (because no study similar to ours has yet been conducted), f=0.2, α=.05, and *P*=.80 were chosen to favor clinically significant effect sizes [79]. To test the main hypotheses of this study, 50 participants are required. To compensate for possible dropouts, 5 more participants will be included in each group. The 2 groups will be composed of 30 participants each.

Statistical Analysis

The statistical software JASP (version 0.17.1; 2023) will be used to run statistical analyses. The statistical level of significance was set at α=.05. Nonparametric tests were used when the distribution of the data was nonnormal. The statistical analysis will allow us to determine the effects of the two different training programs on the primary and secondary variables. The analysis will include participants who completed all the pretests and the posttests. Adherence to programs will be measured by the absence rate (in terms of %). Comparisons within and between groups before and after the intervention will be done using repeated measures ANOVA and Tukey tests as post hoc analyses. Effect sizes will be calculated using partial η^2.

Results

Data collection will begin in September 2025, and the first results are expected in December 2025.

Discussion

This study aims to compare the effectiveness of 2 gait training programs intended to improve older adults' gait adaptability behavior. More precisely, the aim is to evidence that VR is the more relevant tool to propose gait training programs for healthy older adults compared with a conventional training program such as NW training.

Why Should the VR Gait Training Program Be More Effective?

It is expected that the 2 gait training programs will make it possible to improve adaptive locomotor skills. However, we expect that VR training will show larger benefits.

The expected superior outcome of VR gait training in comparison with NW training is supported by many studies. Levin [48] showed that VR can enhance gait adaptability training benefits by proposing motivational training content. Recently, Delgado and Der Ananian [80] reviewed the great potential of using VR in fall prevention. In an encouraging study, Lima Rebêlo et al [34] found a greater effectiveness of a gait training program using an immersive VR device (ie, VR-HMD) in comparison with conventional ones with regard to balance improvements and fall reduction in older adults with balance disorders.

Even if the results discussed in the previous section reveal the potential of VR tools, the use of VR in the context of training

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protocols for older adults is in no way a guarantee of success, and a certain number of preliminary steps have been carried out before being able to propose this research protocol. First, it seemed necessary to us to assess the validity of the VR device that we plan to use in the context of this study. The demonstration of the similarity of the regulation behavior produced in an equivalent locomotion task performed both in VR and real reality was a *sine qua non* for the proposal of a training program in this type of VR [44]. We also believe that the choices made as part of our VR training program, in particular basing the training sessions on the main principles of learning, could potentiate the effects usually associated with the use of VR.

As already mentioned in the first part of this paper, we hypothesize here that by adopting a systemic approach consisting of exposing older adults to accident-prone situations systematically requiring the production of adaptive behavior, we endow them with the perceptual motor mechanisms best able to allow them to move in complete safety. The idea is to allow the older adults to mobilize their resources (perceptual, decisional, and motor) in an appropriate way to produce a behavior appropriate to the constraints encountered or even to develop a form of adaptive flexibility.

Finally, with greater individualization compared with the NW training and the possibility of offering feedback during training, the VR training should maximize the behavioral and psychological benefits of the training program in older adults.

VR-HMD Acceptance

In accordance with previous studies, we expect that older adults will accept the VR-HMD before its first use [53] and also after use [44,81]. Moreover, we expect that acceptance will increase at the beginning of the gait training with an augmentation of both perceived usefulness, perceived enjoyment, and perceived ease of use. On the basis of the previous literature review focusing on the TAM, we know that intention to use a VR-HMD is positively predicted by 3 variables: perceived usefulness, perceived enjoyment, and perceived ease of use. Due to motivating training content leading to high adherence, perceived ease of use and perceived enjoyment should be superior to the mean of the scale during the VR gait training and remain constant until the end. In addition, perceived usefulness should also be superior to the mean of the scale because the training program is designed to develop gait adaptability behavior. By confronting older adults with several goal-directed tasks, they should have a positive perception of device utility during the VR gait training.

Differences in Effectiveness on Secondary Variables

In terms of functional capacities and psychological variables, both gait training programs should lead to improvements. Physical activity adopting a systemic approach provides beneficial effects on physical and psychological components, which are linked to gait behavior and thus to fall prevention [20,64]. However, due to VR's large potentiality in gait training program implementation, improvements after the VR training (and long-term effects) should be greater on these general health components.

Limitations of This Study

This research protocol was designed to overcome some conceptual and methodological limitations identified in previous studies. However, this protocol also has a certain number of limits linked, for example, to the choice of the population studied or to the possibilities of deploying VR training protocols in the clinical sector. Even if the choice of the population (healthy older adults) as part of the implementation of a preventive approach is totally committed, it is possible to question the possibility in the future of adapting the protocol to target other populations (older adults who fall or those with specific pathologies) within the framework of the implementation of a curative approach. On the material level, the device developed to carry out this study (Delbes et al [44] give a complete description) includes, among other elements, an aluminum structure permanently fixed and therefore not transportable, which limits for the moment the implementation of training protocols in other locations, which constitutes a limiting factor. Finally, although this measurement is not initially included in our protocol, a measurement of the VR device's usability could also be considered later.

Conclusions

The validation of the hypothesis concerning the greater effectiveness of the VR gait training program compared with the training program of NW should confirm that VR is the more promising tool in fall prevention. In addition, the study of VR-HMD acceptance in a longitudinal way (over a training program) should allow a better understanding of the psychological determinants of the behavioral intention to use technology among older adults to prevent falls. Increasing the effectiveness and acceptance of older adults' training programs based on XR devices to prevent fall occurrence is a challenge to be met in the face of such a significant health issue.

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Authors' Contributions

NM, LD, CG, and GM were responsible for the conceptualization.

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Conflicts of Interest

None declared.

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Abbreviations

AR: augmented reality
NW: Nordic walking
TAM: Technology Acceptance Model
VE: virtual environment
VR: virtual reality
VR-HMD: virtual reality head-mounted display

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Protocol

Impact of M nuka Honey on Symptoms and Quality of Life in Individuals With Functional Dyspepsia: Protocol for a Feasibility Randomized Controlled Trial

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Abstract

Background: Functional dyspepsia is a common gastrointestinal condition that reduces the quality of life and increases health care costs. The lack of well-defined causes limits effective treatments. Consumers report using mānuka honey to treat gastrointestinal symptoms, although clinical evidence supporting such use is limited. Preclinical studies suggest its unique bioactive compounds may reduce gastrointestinal inflammation. Recently, 3,6,7-trimethyllumazine (Lepteridine), a natural pteridine in mānuka honey, was shown to inhibit enzymes involved in gastrointestinal inflammation in in vitro studies. Therefore, Lepteridine-standardized mānuka honey may deliver digestive health benefits.

Objective: The aim of this feasibility study is to gather the data required to estimate sample size and support study logistics to design future trials. The primary objective will be preliminary assessments of the impact of Lepteridine-standardized mānuka honey on symptom severity and the quality of life in participants with mild-to-moderate functional dyspepsia. Other feasibility objectives include assessing the biological responses to mānuka honey standardized to medium and high levels of Lepteridine and measuring mānuka honey–derived metabolites in blood and urine.

Methods: This is a 3-arm, parallel, controlled, double-blind, randomized feasibility study. A total of 75 healthy adults with symptoms of functional dyspepsia (Rome IV criteria) and mild-to-moderate dyspepsia severity (Short Form Leeds Dyspepsia Questionnaire) were recruited between October 2022 and September 2023. Participants were randomized into one of three groups: (1) mānuka honey standardized to contain 10 mg/kg Lepteridine, (2) mānuka honey standardized to contain 40 mg/kg Lepteridine, or (3) honey maple flavored syrup control. After a 2-week lead-in period, participants consumed 10 g of allocated intervention twice daily for 6 weeks. Throughout the study, participants completed daily bowel movement diaries and validated weekly questionnaires about their gastrointestinal symptoms and quality of life. Stool samples and 3-day diet records were collected at

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baseline and the end of the intervention. Blood samples were collected at baseline, weeks 2 and 4, and at the end of the intervention. In addition, 6 healthy participants without symptoms of functional dyspepsia were recruited to undergo an acute 5-hour assessment for the appearance of Lepteridine and related metabolites in plasma and urine following consumption of Lepteridine-standardized mānuka honey. The study was approved by the Northern B Health and Disability Ethics Committee.

Results: Initial analysis includes 68 participants, with laboratory and data analyses being undertaken as of March 2024. The results of the primary and secondary outcomes will be published in peer-reviewed journals.

Conclusions: This study will provide essential information on the potential efficacy and suitability of Lepteridine-standardized mānuka honey for designing future clinical trials investigating its effect in treating symptoms of functional dyspepsia.

Trial Registration: Australian New Zealand Clinical Trials Registry (ANZCTR) ACTRN12622001140741p; https://anzctr.org.au/Trial/Registration/TrialReview.aspx?id=384094

International Registered Report Identifier (IRRID): DERR1-10.2196/66417

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KEYWORDS

functional dyspepsia; quality of life; mānuka honey; Lepteridine; randomised controlled trial; feasibility protocol

Introduction

Background

Functional dyspepsia (FD) is a common gastrointestinal disorder characterized by epigastric pain, early satiety, postprandial fullness, and epigastric burning sensations that occur without explanation of the symptoms at upper gastrointestinal endoscopy [1]. The prevalence of FD ranges from 10% to 40% and varies depending on the country or criteria used to define its presence [2]. FD is more common in women than in men, which could be attributed to sex-specific differences in gastrointestinal motility caused by sex hormones, responses to pain signaling, or health-seeking behavior [3]. Currently, the pathophysiology of FD is only partially elucidated, with growing evidence implicating multifactorial causes [4]. Several pathophysiologic mechanisms have been proposed to cause FD [1,4] which include altered gastric motility [5,6], visceral hypersensitivity [7,8], altered gut microbiota composition [9-11], and gastroduodenal inflammation characterized by lymphocyte infiltration and increased eosinophils [12-14]. Psychological factors also play a crucial role in FD, as the gut and brain communicate through the enteric nervous system and hypothalamic pituitary adrenal axis [15].

FD is not life-threatening but can negatively impact health-related quality of life [16], work productivity [17], and increase health care expenses [18]. This disorder is complex and challenging to treat, primarily because of its heterogeneous nature and absence of well-defined underlying causes [19,20]. Current treatment options for FD include the eradication of *Helicobacter pylori*, use of proton pump inhibitors, H_2 receptor antagonists, antidepressants, or prokinetic agents [19]. These existing treatments often fail to provide consistent relief, and side effects can limit their use [21]. Individuals often seek alternative therapies because of the severe impact of FD on health-related quality of life and suboptimal treatment options; however, these alternative therapies lack clinical evidence.

Honey has been an essential component of ancient medicine, with uses including preventing and treating digestive diseases [22]. Honey contains many nutrients, such as sugar, proteins, enzymes, vitamins, amino acids, and many phytochemicals [23]. The composition of honey varies depending on the flora from which nectar is collected, the type of bee that produces it, and environmental conditions. The variation in the composition of honey contributes to its diverse potential health benefits, making it useful in therapeutic therapies [24]. Studies suggest that honey could have gastroprotective properties due to its anti-inflammatory, antimicrobial, and antioxidant properties [25,26]. In addition, honey could help promote beneficial gut microbiota [27-29]. Few studies have examined the effect of honey on FD. For example, when combined with standard treatment, the adjuvant supplementation of a honey-based formulation of *Nigella sativa* significantly improved the symptoms of FD [30]. A clinical trial that examined the effects of honey and diet education on FD reported improvements in symptoms, although honey alone did not have significant gastrointestinal effects [31]. A significant improvement in symptoms was observed when honey was combined with proton pump inhibitors in children with FD [32]. However, these studies use honey as an adjuvant intervention to standard therapy, making it difficult to attribute any observed effects to honey.

Mānuka honey is a monofloral honey produced from the nectar of the *Leptospermum scoparium* tree. Mānuka honey has unique bioactive compounds, including phenolic acids, flavonoids, 1,2-dicarbonyl compounds, and pteridines [33]. Studies suggest these unique compounds [34] elicit anti-inflammatory, antioxidant, or antibacterial effects [35-37]. In vivo studies indicate mānuka honey may have gastroprotective properties by inhibiting gastric lesions and preserving gastric mucosal glycoproteins [35,36,38]. Mānuka honey also decreased the production of inflammatory cytokines such as tumor necrosis factor-alpha (TNF-α), interleukin (IL)-1β, and IL-6 [35,37]. These proinflammatory cytokines may play a key role in gastric lesions, as TNF-α is a key modulator in gastric mucosal cell death [39]. Different doses of mānuka honey provided protection against trinitrobenzene sulfonic acid–induced colitis in Wistar rats [36] and acetic acid-induced gastric lesions in Sprague-Dawley rats [35]. Furthermore, 4 weeks of oral application of mānuka honey led to changes in gut microbiota composition in mice with colorectal cancer [27]. While these studies suggest a plausible link between mānuka honey and

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digestive health, no clinical trials have investigated its effect on FD.

3,6,7 Trimethyl lumazine (Lepteridine) is a recently discovered pteridine derivative unique to mānuka honey [40]. Pteridines are aromatic compounds that are produced naturally by living organisms. They play essential metabolic roles, including enzymatic cofactors and immune system activation molecules. They may also have activity in the treatment of chronic inflammatory diseases [41], with methotrexate, a pteridine-derivative medicine, being used in the treatment of inflammatory bowel disease, rheumatoid arthritis, and psoriasis. Recent in vitro studies have shown that Lepteridine may contribute to the anti-inflammatory properties of mānuka honey by inhibiting the proteolytic activity of matrix metalloproteinase-9 (MMP-9) [42], which is key in maintaining the integrity of the gastric mucosa and promoting wound healing [43,44]. Lepteridine might work synergistically with other bioactive properties in mānuka honey to amplify its anti-inflammatory properties. However, the natural variation in Lepteridine concentration in mānuka honey necessitates the need for standardized formulations to ensure consistent therapeutic efficacy [42]. Currently, no clinical trials have been conducted to evaluate the potential therapeutic effects of mānuka honey standardized to Lepteridine concentration in treating FD.

Objectives

The SOOTHE (Study of Mānuka Honey for Digestive Health) feasibility study aims to gather information required to design and undertake future clinical trials investigating the effect of Lepteridine-standardized mānuka honey on FD. The primary objective is to assess the effect of 6-week consumption of Lepteridine-standardized mānuka honey on symptom severity and quality of life in FD. This will be measured by changes in global Nepean Dyspepsia Index (NDI) scores from baseline to the end of the intervention. Data on recruitment time frame, strategies to improve recruitment, potential issues with adherence and attrition, and strategies to optimize adherence shall also be collected.

Secondary objectives include examining changes in Patient-Reported Outcome Measurement Information System (PROMIS gastrointestinal, anxiety, and depression) scores, immune parameters, and the gut microbiota composition between the Lepteridine-standardized mānuka honey and control groups. The study will also explore the pharmacokinetic profile of Lepteridine and other mānuka honey–derived metabolites in plasma and urine following acute consumption of Lepteridine-standardized mānuka honey.

Methods

Study Design

The protocol was developed in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Intervention Trials) guidelines for clinical trial protocols [45]. Multimedia Appendix 1 provides a complete checklist of SPIRIT Outcomes 2022.

Study Overview

This was a 3-arm, parallel, controlled, double-blind, randomized feasibility study in participants with FD with mild-to-moderate symptoms. The study duration was 10 weeks, consisting of a 2-week lead-in phase, a 6-week intervention phase, and a final 2-week follow-up phase (Figure 1). During the intervention phase, participants in 2 arms consumed 10 g of mānuka honey, standardized to contain either 10 mg or 40 mg/kg of Lepteridine twice daily. The third arm received 10 g of honey maple–flavored syrup twice daily as a placebo control.

Figure 1. Study flowchart. BID: bis in die (10 g of allocated intervention twice daily, before breakfast and dinner).

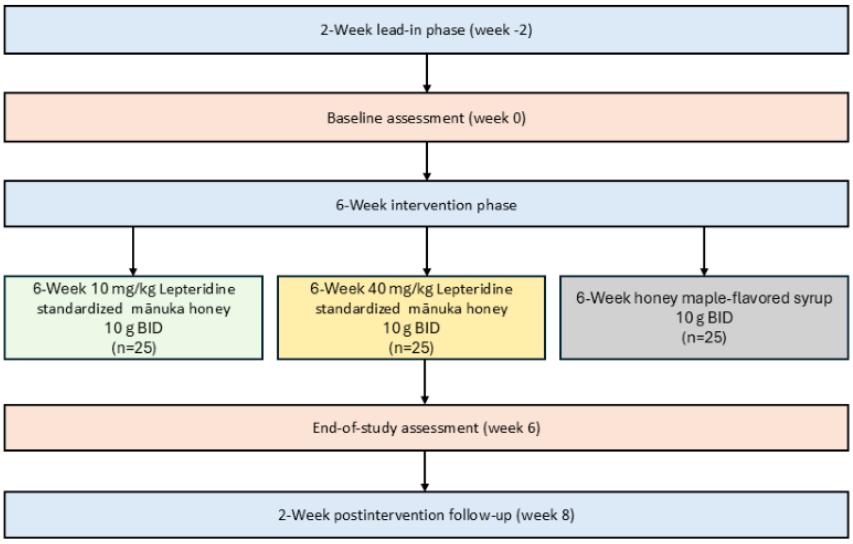

Before the study commenced, a mutually agreed schedule was discussed and set with each participant to ensure they understood all expected clinic visits and the study timeline. However, participants' needs were accommodated if they could not come on a scheduled clinic day by allowing them to attend the clinic up to 1 week later. This approach aimed to reduce the risk of participants running short of the intervention product and dropping out due to scheduling issues.

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Recruitment

Recruitment was conducted between October 2022 and December 2023. Adults from the community who self-identified as having mild-to-moderate symptoms of FD contacted the study team (through email, phone, or text) in response to study posters, radio, newspaper, or social media (Facebook and Instagram [Meta]) advertisements, word-of-mouth referrals, or from community outreach activities undertaken by the study team and a specialist clinical trial recruitment company (Trialfacts). Potential participants were then given a unique identifier link to the internet-based study information sheet and consent form. All eligible respondents were allowed sufficient time to consider participation in the study. Once informed consent was given, they completed a screening questionnaire to ascertain their eligibility for participation in the study. The screening questionnaire included the Rome IV Diagnostic Questionnaire for Functional Gastrointestinal Disorders in Adults (R4DQ) [46], the Short-Form Leeds questionnaires (SF-LDQ) [47], and general health questionnaires. Research staff reviewed the completed questionnaires, and eligible respondents were invited to a screening visit at research clinics in Dunedin or Christchurch, New Zealand.

Eligibility Criteria

All interested respondents were assessed for eligibility based on the following inclusion and exclusion criteria (Textbox 1).

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Aged between 18 and 70 years.
- BMI between 18.5 and 40 kg/m^2
- Met the Rome IV criteria for diagnosing functional dyspepsia.
- Had Short-Form Leeds questionnaires score <23 (to exclude people with very severe dyspepsia symptoms).
- Willing to consume 10 g of intervention twice daily, provided during the intervention period.

Exclusion criteria

- Unwilling to give informed consent.
- Taken antibiotics within the month before starting the study.
- Use of certain prescribed medication or recreational drugs: proton pump inhibitors, H^2 receptor antagonists, antacids, mucosal protectants, prokinetics, antidepressant drugs if they were prescribed solely for controlling dyspepsia symptoms, anticholinergic agents, cholinergic agents, and over-the-counter herbal remedies used to treat dyspepsia symptoms (participants were asked to stop taking these for 2 weeks before the start of the study if they were to be eligible for recruitment).
- Helicobacter pylori–positive (physician-diagnosed or identified during screening) or undertaking treatment for the infection.
- Alarm features associated with significant gastrointestinal or other disorders, such as abdominal pain that wakes the participant from sleep, frequent vomiting, family history of gastrointestinal malignancies suggestive of a significant hereditary cancer syndrome, lower gastrointestinal bleeding, odynophagia, and dysphagia.
- Medical history of upper gastrointestinal surgery or other significant disorders (eg, inflammatory bowel disease and celiac disease), significant cardiorespiratory disease, diabetes mellitus, significant bleeding disorders, sleep disorders, and active psychiatric conditions (major depressive disorder and schizophrenia).
- Significant weight loss (>5% of total body weight) during the 6 months before starting the study.
- Significant dietary changes within the month before starting the study (ie, being on a controlled diet or dietary weight loss regimen).
- Intolerance or allergy to honey and bee products.
- Pregnancy or breastfeeding.
- Smokers.
- Excessive alcohol intake: >20 g of pure alcohol (2 drinks)/day on average (>21 standard drinks a week).
- Inability or unwillingness to comply with the study procedures.

Screening

During the screening visit, research staff provided further information on the study and collected fasting blood samples for standard blood chemistry analyses (eg, glycated hemoglobin [HbA_{1c}], liver and kidney function, acute inflammation, and complete blood count). Participants also provided stool samples within 24 hours after attending the clinic for an *H pylori*-antigen test. Basic blood chemistry analyses and *H pylori* antigen testing were conducted by local health clinics. Participants were excluded if either the HbA_{1c} level was above 40 mmol/mol, basic blood chemistry results were twice the upper limit, or the hemoglobin level was below 120 g/L. To reduce the risk of a false-negative *H pylori* test result, they were asked to stop taking proton pump inhibitors or bismuth preparations 2 weeks before the screening visit. Height and weight measurements were also taken to calculate BMI.

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Enrollment

Upon enrollment, participants received unique links to study questionnaires. They were also instructed to download an app to monitor daily bowel movements and compliance. The *Measurements and Outcomes* section provides more details about this.

Study Intervention

The active intervention for this feasibility study was monofloral mānuka honey standardized to contain either 10 or 40 mg/kg of natural Lepteridine. The concentration of naturally occurring compounds does not correlate with other known compounds found in mānuka honey, such as methylglyoxal. Lepteridine in mānuka honey is derived from the nectar of the mānuka. Naturally, it varies; therefore, to produce a mānuka honey product with standardized Lepteridine concentration, testing for the presence and quantity of Lepteridine in raw honey drums was undertaken, and the resulting drums were blended to achieve the desired concentration of Lepteridine in the final mānuka honey product [40]. The composition of the intervention products is shown in Table 1. Participants received the study products in unidentifiable sachets containing 10 g of Lepteridine-standardized mānuka honey or honey maple–flavored syrup solution. Participants took the assigned intervention before breakfast and dinner for 6 weeks. They were asked to avoid consuming any other honey during the study.

Table 1. Composition of intervention product.

Nutrient	Mānuka honey[a] per 100 g	Honey maple–flavored syrup[b] per 100 g
Energy (kJ)	1370	1290
Carbohydrate (g)	80	76
Sugars (g)	78	76
Protein (g)	<1	<1
Fat (g)	<1	<1
Sodium (mg)	12	18

[a]Sourced from Comvita New Zealand.

[b]Sourced from New Zealand Sugar Company.

Randomization, Blinding, and Allocation

A week before the baseline visit, participants were randomly assigned to a 1:1:1 allocation using randomized permuted blocks (block size 4) to either the Lepteridine mānuka honey or control groups. An independent researcher allocated participants to their intervention group using a computer-generated randomization list.

Participants and the research team were blinded to the intervention allocation. The manufacturer of the honey was responsible for labeling the intervention products to maintain the blinding of research team members. A specified research team member was responsible for enrolling participants, giving the intervention, and managing the stock. Unblinding will only be permissible once the statistical analyses of the primary outcomes are completed.

Measurements and Their Timing

After enrollment, study clinic visits were undertaken at baseline, weeks 2, 4, and 6 (end of intervention). Currently, there is no information on the potential time course for which a treatment effect might be observed. Therefore, the multiple assessment time points enabled monitoring of potential symptom trends and identified optimal time points when any treatment effect can be observed. Table 2 shows when the study measurements were done. The information from this feasibility study will be used to determine the appropriate timing and selection of sensitive measurements for future trials.

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Table 2. Timing of study measurements.

Measurement	Lead-in week –2	Lead-in week –1	Baseline	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6	Week 7	Follow-up week 8
Nepean Dyspepsia Index	✓		✓		✓		✓		✓		✓
Anthropometry[a]			✓		✓		✓		✓		
3-Day diet record		✓							✓		
Patient-Reported Outcomes Measurement Information System	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Daily bowel diary	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Blood samples			✓		✓		✓		✓		
Stool samples			✓						✓		

[a]Measured height, weight, and waist circumference at baseline and week 6; measured weight only at weeks 2 and 4.

Outcome Measurements

Primary Feasibility Measurement

The primary feasibility outcomes are changes from baseline to week 6 in FD symptoms and FD health-related quality of life, which were assessed using the NDI questionnaire. This is a validated instrument with a 2-week recall that evaluates the severity of symptoms and its impact on quality of life [48].

The symptom instrument of the NDI consists of 15 common dyspeptic symptoms that are rated using a Likert scale that evaluates the frequency, intensity, and bothersomeness of each symptom. The scores for frequency, intensity, and bothersomeness are summed to give a score for each symptom with a possible score range of 0 to 13. Higher scores represent greater symptom severity. The total symptom score is calculated as the sum of scores for all 15 individual symptoms and can range from 0 to 195. The total symptom scores are not scaled to 100, and no minimum clinically important difference (MCID) has been established [49].

The quality-of-life component of the NDI includes 25 questions that are summed to form a global score and scores for 4 subscales (or domains) measuring the impact of the condition on enjoyment of life and emotional well-being, lack of knowledge and control over the illness, disturbance to eating or drinking, and disturbance to sleep. The scores are scaled to 100 and are sometimes reversed so that high scores indicate better quality of life [50]. The quality-of-life scales can also be weighed to rank the importance of the domain to the respondent. An MCID of 10 points has been established for the NDI-weighted quality-of-life instrument [48].

In addition to changes in mean scores, responder analyses will be conducted based on the percentage of participants who demonstrated improvement in NDI scores from baseline to follow-up of 10%, 20%, 30%, and 40% for symptom severity, and 10, 20, and 30 points for quality of life. Furthermore, the percentage of participants reporting an improvement equal to or exceeding the MCID for quality of life will be compared between the groups. Effect sizes and SDs in symptom changes and quality of life between and within groups will help identify key outcome measures and sample sizes required for future studies.

Additional feasibility information was collected to inform the design of future trials. This information included response and enrollment rates and strategies, data on participant adherence to protocol, perceptions of protocol, and attrition rates. Upon exiting the study, a research team member interviewed the participants on their experiences participating in the study, using open-ended questions.

Secondary Measurements

The Patient-Reported Outcomes Measurement Information System (gastrointestinal, anxiety, and depression) was collected weekly. This validated system with multiple domains evaluates patient-reported outcomes that significantly impact the quality of life [51]. Measures from the gastrointestinal, anxiety, and depression domains were used as gastrointestinal disorders can impair health-related quality of life, leading to physical and mental distress [52]. The measures used evaluate gastrointestinal symptoms (bowel movements, difficulty in swallowing, belly pain, bloating, and reflux), anxiety, and depression by severity rating from “not at all” to “very much” and from “never” to “always” [51]. The data collected will provide additional information on possible beneficial or adverse effects of Lepteridine mānuka honey or placebo in individuals with FD.

A daily bowel habit diary was collected upon enrollment and throughout the study through a mobile app or paper version. The diary provided a comprehensive record of the participants’ bowel habits. It had variables on the frequency of bowel movements, which included questions on spontaneity and completeness of bowel movement, ease of defecation or level of straining, and stool form based on the Bristol Stool Scale [53].

A 3-day weighed food record was collected a week before baseline and during week 6. Participants were given an electronic dietary scale (Model 1023 WHDR 14, Salter Electronic, Salter House Wares) to weigh the food items they consumed. They also received verbal and written instructions on completing the food record, which covered 2 nonconsecutive weekdays and one weekend. The food record included written

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prompts for detailed information about time, place, type of food or drink, brand details, preparation or cooking methods, quantity, and a section for details on recipes. Participants were asked to record details that could have affected their usual food intake. Participants completed a paper-based version of the 3-day weighed food record during the week before their baseline and week 6 visits and returned the records during their respective visits. The food records were reviewed by a member of the research team at the time of collection, and queries were clarified with the participant. Data from the food records will be entered into a dietary analysis software, FoodWorks 10 (version 10.0, Xyris Brisbane, 2019). The New Zealand Food Composition Database (FOODfiles 2018, version 1.0, The New Zealand Institute for Plant and Food Research Limited and the New Zealand Ministry of Health) will be used to estimate energy and nutrient intakes. These data will be used to determine habitual food intake and identify dietary patterns and symptom-triggering foods. The findings will then be linked to symptom severity and gut microbiota.

Biological Measurements

Blood Samples

A trained phlebotomist collected fasting peripheral blood at each visit (baseline, week 2, week 4, and week 6). Blood was collected into 10-mL EDTA tubes (Becton, Dickinson and Company) for peripheral blood mononuclear cells (PBMCs) extraction, 2 EDTA tubes (4 mL each) to measure insulin, glucose, and alpha-1 acid glycoproteins levels, and 1 serum tube without clot activators (4 mL) to measure cytokine, MMP-9, lipid, and high-sensitivity C-reactive proteins concentrations. Blood samples collected in the EDTA tubes were kept in a chilled box with ice packs until processing. Blood samples collected in the serum tubes were kept at room temperature for 45 minutes to allow coagulation before processing. Vacutainers (excluding those for PBMC extraction) were centrifuged at 2200 *g* for 10 minutes at 4 ˚C, and aliquots were stored at –80 ˚C until analysis.

The PBMCs were extracted using standard procedures (Multimedia Appendix 2) at the Department of Microbiology and Immunology, University of Otago, Dunedin, New Zealand, and Mātai Hāora-Centre for Redox Biology and Medicine laboratory at the University of Otago, Christchurch, New Zealand. The extracted cells were stored in liquid nitrogen until analyses at the Malaghan Institute of Medical Research (Wellington, New Zealand). Immuno-profiling of the PBMCs, including phenotypic and functional markers, will be performed using spectral flow cytometry.

Plasma cytokines including IL-1β, IL-6, IL-8, IL-10, IL-12p70, IL-17A, IL-18, IL-23, IL-33, interferon-α2, interferon-γ, TNF-α, and monocyte chemoattractant protein-1 will be measured using a cytokine bead assay (MILLIPLEX MAP Kit Human Cytokine Chemokine Magnetic Bead Panel Immunology Assay, Millipore) as per the manufacturer's instructions at the Malaghan Institute of Medical Research (Wellington, New Zealand).

Plasma lipids, high-sensitivity C-reactive proteins, and insulin concentrations will be measured using enzymatic assays (Abbott C series analyzer, Abbott Diagnostics), immunoturbidimetric assay (Cobas c311 analyzer, Roche Diagnostics), and Cobas e411 analyzer (Roche Diagnostics) respectively, at the Canterbury Health Laboratories. The remaining plasma and serum samples will be analyzed at the Department of Human Nutrition, University of Otago, Dunedin Campus. For this, serum MMP-9 concentration will be measured using enzyme-linked immunosorbent assay (Human ELISA Kit, Invitrogen, Thermo Fisher Scientific), plasma glucose will be measured by enzymatic assays (Abbott C Series analyzer, Abbott Diagnostics), and alpha-1 acid glycoproteins will be measured using immunoturbidimetric assay (Cobas c311 analyzer, Roche Diagnostics).

Stool Samples

Once enrolled, participants submitted a stool sample using the provided OMNIgene.GUT|OM-200 (DNA Genotek) stool kit 24 hours before the clinic day at baseline and week 6. The samples were stored at room temperature until processing was done within a week. A total of 2 aliquots (2 g each) of stool samples were stored at –80°C until analysis.

DNA was extracted from the stool samples using the Macherey-Nagel NucleoSpin DNA stool kit per the manufacturer's instructions. Only data relevant to analyzing the gut microbiome composition were extracted. Long-read Oxford Nanopore sequencing will be used for full-length 16S rRNA gene sequencing (~1500 bp) [54] to capture information from all 9 hypervariable 16S regions. Nanopore-generated sequence reads, which are re-base-called using "Super high accuracy base-calling" post run, will be passed through FastQC and then the standard EPI2ME amplicon workflow using the SILVA-138 database for taxonomic assignment.

Lepteridine Metabolites Acute Study

As a preliminary investigation into the postprandial absorption and excretion of selected mānuka honey-derived compounds, a randomized, crossover, acute study involving 6 healthy participants without symptoms of FD was conducted. Each participant attended 2 clinic visits, where they consumed 20 g of either of the Lepteridine-standardized mānuka honey formulations (containing 10 mg or 40 mg Lepteridine). After a 1-week washout, participants consumed the other formulation. The sequence in which they received the honey was randomly selected.

Blood and urine samples were collected before and after the participants consumed the assigned honey. To ensure they were hydrated, participants were asked to drink 250 mL of water every hour. Participants could not eat or drink any other food during the clinic except for the allocated study honey and water. Blood and urine samples were collected over 5 hours. A cannula was fixed by medically trained personnel to allow multiple blood sample collection at baseline (fasting samples) and at 0.5, 1, 2, and 5 hours after consuming the assigned honey. At each time point, 4 mL of blood was collected in a heparin and EDTA vacutainer. The blood was centrifuged at 3000 *g* for 10 minutes at 4 ˚C, and aliquots were stored at –80 ˚C. All urine voided during the 5-hour clinic was collected into sterile containers and stored at –80 ˚C.

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The analytical methods for measuring mānuka honey–derived compounds and metabolites will be based on a previous study that investigated the in vivo absorption and metabolism of Leptosperin over 3 hours [55], with amendments as required. Briefly, acidified urine will be extracted using solid-phase extraction (Strata-C18E cartridge, 3 mL, 500 mg, Phenomenex), which will be preconditioned with methanol and 0.1% acetic acid in water. After washing with 2 mL 0.1% acetic acid in water, metabolites will be eluted with 2 mL methanol and then analyzed by liquid chromatography with tandem mass spectrometry. For plasma, 20 µL of the sample will be extracted with 300 µL methanol, and the extract will be evaporated and reconstituted in 0.05% formic acid for liquid chromatography with tandem mass spectrometry. The analyses will be performed on an EXION high-performance liquid chromatography system fitted with a C18 column (Waters 1.7 µm ACQUITY UPLC BEH C18, 100 × 2.1 mm ID) attached to a SCIEX 6500+ Q-TRAP (AB SCIEX). Urine samples will be analyzed in precursor ion mode for m/z 211 (methyl syringate ion) while the plasma will be analyzed in multiple reaction monitoring modes. Biotransformer 3.0 [56] will be used to predict possible metabolites to extend the list of metabolites provided in Ishisaka et al [55]. The metabolites will be quantified using commercial standards where available.

Data Analysis

Sample Size

The determinant of the sample size for this study was to enable the estimation of the SD and the potential effect size for the primary outcome. This estimation is crucial as it allows for sample size calculation in future trials, ensuring the study's findings are robust and applicable. A sample size of 75 gives an estimated degree of freedom to calculate SDs, allowing reasonable precision.

Data Management

The study will generate quantitative and qualitative data, including questionnaires, laboratory data, clinically relevant information regarding symptoms, and face-to-face interviews on participants' perceptions of the study protocol. Only data relevant to answering the research question will be collected. There was no anticipated harm during data collection beyond standard care and everyday life risks.

The data collected were in the form of electronic files, Microsoft Word documents, and a small number of paper-based questionnaires. Study data were collected and managed using the REDCap (Research Electronic Data Capture, Vanderbilt University) tool hosted at the University of Otago, Dunedin Campus. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for data integration and interoperability with external sources [57,58]. It was only accessible to the researchers to contact participants for planned data collection. All participants were assigned a unique study identification number at the time of providing consent, which was recorded in REDCap and used instead of personal identifying information in all other data files. A formal data monitoring committee was not required as the intervention and control treatments in the study were considered sufficiently minimal risk. No harm was anticipated beyond the risks of standard care and everyday life. Data monitoring occurred through weekly meetings of the research team.

Data Collection and Storage

The researchers collecting data were trained in data collection and maintaining security and health-related confidentiality. Most of the data were collected electronically through the REDCap data capture system using unique identification. Participants who preferred paper-based data collection were accommodated. Paper-based and telephone-collected data were entered directly into the REDCap.

The data files were stored in Microsoft Excel for raw data and as data analysis files in R (version 4.3.2, R Foundation for Statistical Computing), Stata (version 18.0, StataCorp), or SPSS (version 29, IBM Corp). These data were only identified by the unique identification of the participant. Participants were identified by researchers only by their unique identification.

Raw data collected in hard copy were stored after electronic data entry as part of the case report form in a locked filing cabinet in the principal investigator's (JM's) office. Electronic data files generated in the study were stored on a password-secured University of Otago server or Otago OneDrive cloud storage. These files will be accessed as needed on password-protected computers of named investigators.

Statistical Analyses

All statistical analyses will be done using either R (version 4.3.2), Stata/SE version 18.0, or IBM SPSS version 29. The primary outcome analyses will use the intention-to-treat population (ITT) and per-protocol population. Secondary and exploratory analyses will be conducted with the ITT population. The ITT population will include all randomized participants who took at least 1 dose of the intervention. The per-protocol population will include those in ITT who had no major protocol violations, had all the study assessments required to analyze any outcome, and consumed at least 80% of their intervention product. Participants with missing data for a relevant outcome assessment will be imputed using the last observation carried forward.

The primary analysis will compare the overall NDI score changes for symptom severity and quality of life from baseline to week 6. Quality of life scores weighted by the participants' perception of importance and unweighted scores will be examined. A general linear model that includes the randomized group as a fixed factor will be used (unadjusted results), and models adjusting for baseline values will also be presented. The residual plots from these analyses will be visually inspected, and if reasonable normality is not apparent, alternative generalized linear models will be undertaken.

For the secondary outcomes, changes in scores from baseline to the end of the intervention will be analyzed using appropriate statistical tests, depending on the data distribution. Descriptive

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statistics will be presented as frequencies, percentages, and mean (SD) for normally distributed parameters or medians (IQRs) for non-normally distributed parameters with a 95% CI and $P \leq .05$ value to show statistical significance. Appropriate statistical techniques shall be used to mitigate any potential confounders and shall be reported in subsequent publications of this study. No formal hypothesis testing will be conducted on these variables.

Stool microbiome data will be analyzed using principal coordinate analysis and permutational multivariate ANOVA. Alpha-diversity and beta-diversity indices will be calculated. Differential abundance analysis of the microbiome abundance data (Analysis of Composition of Microbiomes with Bias Correction) [59] will be used to explore relationships between diet, metadata, diversity indices, and microbiome taxonomic traits. All analyses will be done in R with probability values adjusted for multiple comparisons using the Benjamini-Hochberg method [60] and data will be reported according to the reporting guidelines for human microbiome research (STORMS [Strengthening The Organizing and Reporting of Microbiome Studies]) [61].

Ethical Considerations

The study was conducted in accordance with the International Conference of Harmonisation guidelines, national and local requirements, and the ethical principles originating in the Declaration of Helsinki. Ethical approval was granted by the Northern B Health and Disability Ethics Committee (reference 20222 FULL 12734). Before commencement, the study was registered on the Australian New Zealand Clinical Trials Registry (ACTRN12622001140741p). All participants were required to date and sign an informed consent before participating in the study.

Results

Enrollment into the study began in December 2022 and was completed in September 2023. The intervention phase and data collection for the main study were completed in December 2023. A total of 75 participants were enrolled in the study. Out of 75, 7 participants withdrew before receiving the allocated intervention and were not included in the analysis, resulting in a final population of 68 participants (52/68, 76% female and 16/68, 24% male). As of March 2024, data analysis of the PROs and laboratory analyses is being undertaken, with full results expected to be published in 2025. The study's results will be disseminated in scientific manuscripts published in peer-reviewed journals and through abstracts, posters, and presentations at national and international conferences.

Discussion

Anticipated Findings

FD is a common chronic gastrointestinal condition that can significantly affect the quality of life [16]. However, despite high prevalence rates, its pathophysiology is poorly understood [1,4], limiting the development of effective treatment options [21]. These factors may lead people to seek alternative therapies, although the evidence supporting the effectiveness of such therapies is limited and inconclusive [19]. Honey has been used to treat digestive diseases, based primarily on anecdotal or preclinical research [22,30,38]. Emerging evidence suggests honey might promote healthy gut microbiota composition [27,28,62]. Mānuka honey has many unique bioactive compounds that might lend it to be an alternative treatment for FD. Although preclinical studies have shown potential gastroprotective properties of mānuka honey, and recent in vitro evidence suggests the naturally occurring mānuka compound Lepteridine may modulate digestive inflammatory pathways, clinical studies are needed to explore and validate these findings. Recently, a pilot study reported a potential benefit of mānuka honey on symptoms of gastroesophageal reflux disease [63]. However, well-designed clinical studies have yet to test these postulated benefits.

The SOOTHE study is a randomized, controlled, feasibility study designed to gather crucial information to inform the design and implementation of clinical trials to test the effects of Lepteridine-standardized mānuka honey on FD symptoms and the quality of life. The study involves a well-defined population group, identified using a validated diagnostic tool (Rome IV), and provides information on symptom severity using the validated SF-LDQ. In addition, using an intervention with a standardized formulation allows for consistent dosing.

Given the lack of previous clinical studies to inform this study design, we were unable to power this study to detect a significant treatment effect; however, this study will provide information as to whether further investigation into mānuka honey for FD treatment is warranted. If a treatment effect is indicated, the information gathered will allow future studies to be well-designed and adequately powered. Frequent assessments during the study period will allow for the investigation of the time course of any potential treatment effects and will help refine future study duration and study measurements.

The inclusion of 2 different formulations of Lepteridine will provide an initial indication of a potential causal effect of Lepteridine on gastrointestinal health. The inclusion of biological assessments along with patient-reported outcomes will contribute to the emerging knowledge about this poorly understood condition and can be used to support the interpretation of patient-reported results.

Disclaimer

Consent for Publication

Data derived from this study will be the exclusive property of the principal investigators. No use or transmission to a third party will be made possible without their consent. The principal investigators will approve any publication or presentation related to the study. In addition, biological samples and participant data collected during this study may not be used by site investigators for research unrelated to this protocol without the previous approval of the principal investigators. Other legal aspects, including intellectual property, are covered by contracts between the High-Value Nutrition National Science Challenge-Ko Ngā Kai Whai Painga, University of Otago, Comvita New Zealand, Massey University, and Malaghan Institute of Medical Research.

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Protocol Amendment

Any protocol changes that may affect the conduct of the study and the safety of participants, including changes in study objectives, study design, study population, and sample size, require a formal amendment to the protocol. There were amendments to the cut-off criteria for BMI from 18.5-35 kg/m^2 to 18.5-40 kg/m^2, allowing a wider scope of persons to be recruited into the study. In addition, adjustments were made to the design of the Lepteridine acute study. Initially, the acute study was to be done during the baseline visit in a subgroup of 5 participants in each honey group. However, the design was adjusted to a crossover design with a 1-week washout period as there is no information on the absorption and metabolism of Lepteridine honey in healthy people. However, these changes were not considered significant, although the ethics committee was informed of the changes.

Acknowledgments

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Authors' Contributions

JM contributed to conceptualization, funding acquisition, investigation, methodology, supervision, and writing-review and editing. LO managed data curation, formal analysis, investigation, project administration, writing—original draft, and writing—review and editing. LW handled investigation, writing—review and editing. HH and SB conducted investigation, writing—review and editing. JT managed methodology, investigation, formal analysis, and writing—review and editing. OL handled methodology, investigation, formal analysis, writing—review and editing. KF managed methodology, writing—review and editing. RC conducted investigation, data curation, and writing—review and editing. AH managed investigation, data curation, and writing—review and editing. RK conducted investigation, data curation, and writing—review and editing. JE handled methodology, resources, and writing—review and editing. TM managed methodology, resources, and writing—review and editing. MS managed methodology and writing—review and editing. CF conducted formal analysis and writing—review and editing. RG contributed to conceptualization, funding acquisition, investigation, methodology, supervision, and writing—review and editing. WM handled conceptualization, funding acquisition, investigation, methodology, supervision, and writing—review and editing. NR contributed to conceptualization, funding acquisition, investigation, methodology, supervision, and writing—review and editing.

Conflicts of Interest

TLM and JCE are employees of Comvita NZ, the industry partner. They had input on the study design and will have input on interpreting the results. The University of Otago researchers were involved in data collection, they will lead data analysis and will be responsible for final interpretation and decision to publish the results. The remaining authors declare that the research was conducted without any financial or commercial relationship that could be a conflict of interest.

Multimedia Appendix 1
Revised SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 121 KB - resprot_v14i1e66417_app1.pdf]

Multimedia Appendix 2
Isolation of peripheral blood mononuclear cells.
[DOCX File , 16 KB - resprot_v14i1e66417_app2.docx]

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Abbreviations

FD: functional dyspepsia
IL: interleukin
ITT: intention-to-treat
MCID: minimum clinically important difference
MMP-9: matrix metalloproteinase-9
NDI: Nepean Dyspepsia Index
PBMC: peripheral blood mononuclear cell
PROMIS: Patient-Reported Outcome Measurement Information System
R4DQ: Rome IV Diagnostic Questionnaire for Functional Gastrointestinal Disorders in Adults
REDCap: Research Electronic Data Capture
rRNA: ribosomal RNA
SF-LDQ: Short Form Leeds Dyspepsia Questionnaire
SOOTHE: Study of Mānuka Honey for Digestive Health
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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STORMS: Strengthening The Organizing and Reporting of Microbiome Studies
TNF-α: tumor necrosis factor-alpha

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Protocol

A Clinical Study on the Efficacy of Acupuncture Treatment in Essential Hypertension: Protocol for Randomized Controlled Trial

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Abstract

Background: Primary hypertension represents a significant global public health issue and is a major risk factor for severe cardiovascular disease complications. Previous research has indicated that acupuncture, as a relatively safe therapeutic approach, effectively reduces blood pressure and alleviates clinical symptoms.

Objective: This study aims to assess the clinical efficacy and safety of the “HuoXueSanFeng” acupuncture technique in patients with essential hypertension.

Methods: This investigation is designed as a multicenter, randomized, single-blind, sham-controlled clinical trial. A total of 228 participants with essential hypertension will be recruited from 5 tertiary hospitals in China. Participants will be randomly allocated to either the acupuncture group or the sham acupuncture group in a 1:1 ratio. Each participant will undergo treatment 3 times per week over a 6-week period, amounting to 18 sessions in total. Follow-up assessments will be conducted at 1, 2, and 4 weeks post treatment. The primary outcome measures include 24-hour ambulatory blood pressure and immediate in-office blood pressure readings. Secondary outcome measures included the Dizziness Handicap Inventory, the Headache Impact Test-6, and the Pittsburgh Sleep Quality Index. In addition, any adverse events will be documented throughout the study to assess safety.

Results: This study was registered with the China Clinical Trial Registration Center on May 23, 2024. Data collection commenced in July 2024 and is anticipated to conclude in June 2025. Currently, the study is in the data collection phase, with 27 participants recruited, and data analysis has yet to be conducted. The findings of this study are expected to be submitted for publication in November 2025.

Conclusions: The outcomes of this study are anticipated to further elucidate the benefits of acupuncture in reducing blood pressure and to provide more robust evidence for the treatment of essential hypertension using the “HuoXueSanFeng” acupuncture method.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2400084696; https://www.chictr.org.cn/showprojEN.html?proj=229194

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KEYWORDS

acupuncture; sham acupuncture; hypertension; randomized controlled trial; study protocol

Introduction

Hypertension is one of the major risk factors for fatal complications of cardiovascular disease [1-4] and represents a significant public health concern worldwide. Annually, hypertension is responsible for approximately 10.4 million deaths [5]. Therefore, the primary goals of hypertension management are to regulate blood pressure and prevent damage to target organs [6-8]. In 2015, the global prevalence of adults with elevated blood pressure reached 1.13 billion [9], with projections indicating an increase to 1.56 billion by 2025 [10], thereby posing a considerable global health and socioeconomic challenge [11]. The pathophysiology of essential hypertension is intricate, and its etiology is not yet fully elucidated [12]. Although antihypertensive medications have traditionally been the cornerstone of hypertension management, many patients experience inadequate blood pressure control [13]. Approximately 50% of patients discontinue antihypertensive medications within the first year [14], and adherence rates are generally low [15]. Approximately 9% of patients with hypertension discontinue their medication due to adverse side effects [16]. Furthermore, a significant proportion of patients with hypertension continue to experience severe symptoms associated with hypertension, such as headache, dizziness, and insomnia [17-19]. Consequently, the search for effective and low-harm alternative or complementary therapies has become a critical goal in the management of hypertension [20].

Acupuncture, a traditional Chinese medicine intervention, has been practiced for over 2000 years. Currently, several studies have confirmed that acupuncture is effective in lowering blood pressure and relieving symptoms of hypertension [21-24] with little or only minor side effects [25], making it a relatively safe treatment option [26]. It can serve as an alternative or complementary therapy to lower blood pressure in patients who prefer not to use medication [25], thereby improving adherence to treatment. Acupuncture offers advantages such as multitarget, multipathway, and holistic regulation in the management of hypertension [27]. Nonetheless, the current scientific basis for the modulation of primary hypertension by acupuncture is insufficient [28,29]. There are limited intervention trials comparing acupuncture with sham acupuncture in the regulation of hypertension [24]. Previous clinical investigations have predominantly concentrated on examining circadian rhythm alterations in blood pressure, 24-hour ambulatory blood pressure [25,30-32], as well as the combined use of acupuncture and antihypertensive medications [32-36]. These studies indicate that acupuncture may effectively reduce blood pressure in patients with hypertension. In addition, numerous animal studies have demonstrated that acupuncture significantly reduces blood pressure levels in spontaneously hypertensive rats [37,38]. The underlying mechanisms are complex [27,38,39], and it is noteworthy that studies on the relevant aspects of the onset time, effect duration, and dominant effect of acupuncture in lowering blood pressure remain unclear. Therefore, there is an urgent need for large-scale, well-designed multicenter randomized controlled clinical trials to further investigate the efficacy of acupuncture in treating essential hypertension [36].

Academician Xuemin Shi, a distinguished member of the Chinese Academy of Engineering, is recognized as a pivotal figure in the development of modern acupuncture in China. He pioneered the “HuoXueSanFeng” acupuncture technique, specifically designed for the treatment of hypertension, which is grounded in the “Qihai” theoretical framework. This method involves meticulously defined parameters regarding the direction, intensity, duration, and frequency of the twisting force applied during acupuncture, thereby establishing a standardized and replicable antihypertensive protocol to ensure both the operability and consistency of the treatment.

This study aims to conduct a multicenter randomized controlled trial to evaluate the efficacy and safety of the “HuoXueSanFeng” acupuncture technique in managing essential hypertension. The primary objective is to assess the onset and duration of the blood pressure–lowering effects of acupuncture.

Methods

Study Design

This ongoing study is a multicenter, randomized, participant-analyst, single-blind, sham-needle-controlled clinical trial of acupuncture for essential hypertension, conducted in 5 tertiary care hospitals in China. Enrollment will begin in June 2024 and will continue through November 2025. The study will enroll 228 participants with essential hypertension, all of whom will be required to voluntarily sign an informed consent form after rigorous screening. Eligible participants will be randomized in a 1:1 ratio into two groups: the treatment group will be treated with the “HuoXueSanFeng” acupuncture method, and the control group will be treated with sham acupuncture. In this trial, all participants will receive acupuncture 3 times a week for 6 weeks, totaling 18 times. Follow-up visits will be made at weeks 1, 2, and 4 after the treatment.

Participant Recruitment

This study will be conducted at 5 tertiary hospitals in China: Dongzhimen Hospital of Beijing University of Traditional Chinese Medicine, the First Affiliated Hospital of Tianjin University of Traditional Chinese Medicine, the Beijing Hospital of Traditional Chinese Medicine of Capital Medical University, the Third Affiliated Hospital of Beijing University of Traditional Chinese Medicine, and the Dongfang Hospital of Beijing University of Traditional Chinese Medicine. Participants who meet the inclusion criteria will be enrolled in this study, and we

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will use 3 ways to recruit participants with essential hypertension. First, we will recruit on site by pasting recruitment posters in the outpatient departments of the hospitals. Second, we will disseminate information about this study via WeChat Moments and the hospital's WeChat Official Account; at the same time, we will distribute posters and hold academic lectures at regular intervals at the 5 hospitals and nearby communities. It is important to note that participants will be excluded from the study design, implementation, and outcome assessment throughout the study. The inclusion and exclusion criteria are detailed in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- 18 years old ≤ age ≤75 years old, both male and female individuals.
- Those who meet the diagnostic criteria for primary hypertension in the International Society for Hypertension's 2020 Practice Guidelines, with a hypertension classification of grade 1 and a risk stratification of low to moderate risk; and those who receive acupuncture treatment while their original treatment is not changed;
- Those who had not taken medication in the past, with an office systolic blood pressure of 140-159 mm Hg and/or a diastolic blood pressure of 90-99 mm Hg; and those who had not changed medication for at least 1 month in the past, with an office systolic blood pressure of 120-159 mm Hg and/or a diastolic blood pressure of 80-99 mm Hg. The types of antihypertensive drugs used are calcium channel blocker+angiotensin converting enzyme inhibitor/angiotensin II receptor antagonist, but no more than two types;
- Correct understanding of the significance of this clinical study, good compliance with the observations and evaluations of the investigators, and voluntary signing of an informed consent form by the participant himself/herself.

Exclusion criteria

- Secondary hypertension such as aldosteronism, pheochromocytoma, Cushing's syndrome, and pregnancy hypertension;
- Patients with other serious cardiovascular, cerebrovascular, renal, retinal, peripheral vascular complications and diabetes mellitus, blood disorders that are not suitable for acupuncture treatment, combined with diagnosed epilepsy, obstructive sleep apnea, hypoventilation syndrome, and so on;
- People with mental disorders such as severe anxiety and depression;
- Pregnant and lactating women;
- Patients who have received acupuncture treatment since the last 1 month or are participating in other clinical trials.

Randomization and Assignment Hiding

Randomization

Randomization will be performed using stratified block randomization. Randomization will be performed by a statistician not involved in trial implementation or statistical analysis, and random sequences will be generated using the Proc plan program in SAS 9.3 software (SAS Institute). Eligible participants will be randomized in a 1:1 ratio into a needling group and a sham needling group. Stratification by center factor will be applied, with block sizes of 4 or 6.

Allocation Concealment

The randomization sequence will be kept by a designated person who is not involved in the screening, recruitment, treatment, or evaluation of participants. The randomized grouping scheme is concealed using sequentially numbered, opaque, sealed envelopes, all prepared by staff independent of the study, and after participants sign informed consent and meet inclusion criteria, the envelopes are opened sequentially by the coordinator in the order of enrollment, and the acupuncturist is informed of the grouping in accordance with the allocation scheme inside the envelope.

Blinding Setup

The grouping results were kept confidential to the participants, outcome assessors, and data statisticians. Participants received acupuncture treatments in separate compartments of the clinic to avoid interactions and ensure confidentiality. The steps of each acupuncture operation and the method of administration were kept as consistently as possible to minimize bias. Due to the specificity of acupuncture therapy, it was not possible to blind the physician who performed the needling operation. Similarly, outcome assessors and data statisticians were not involved in the experiment throughout, thus controlling for bias that might be introduced to the trial due to knowledge of the allocation scheme. In addition, patients were asked relevant questions at the end of the last acupuncture session to assess the success of the blinding.

Acupuncture Group

In the acupuncture group, the original individualized treatment plan will remain unchanged, and the "HuoXueSanFeng" acupuncture method will be used. All therapists have many years of clinical experience in acupuncture.

Disposable sterile acupuncture needles with a diameter of 0.25 mm and a length of 40 mm (Beijing Zhongyan Taihe Medical Equipment Co, Ltd) will be used. Participants will be placed in a supine position, and the local skin will be routinely sterilized. The acupoints chosen here were bilateral Renying (ST9), Baihui (BL7), Hegu (LI4), ZuSanli (ST36), Taichong (LR3), and Quchi (LI11, right side). The specific localization and operation are shown in Figure 1 and Table 1. The frequency of acupuncture was 120-160 times/minutes, and the twisting amplitude was <90°. Foam pads were fixed on each acupoint, and each acupoint

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will be administered for 1 minute, after which the needle will be left in place for 30 minutes. The treatment was performed 3 times per week. The measurement time was kept consistent every day, between 9 AM and 11 AM.

Figure 1. Location of acupuncture points.

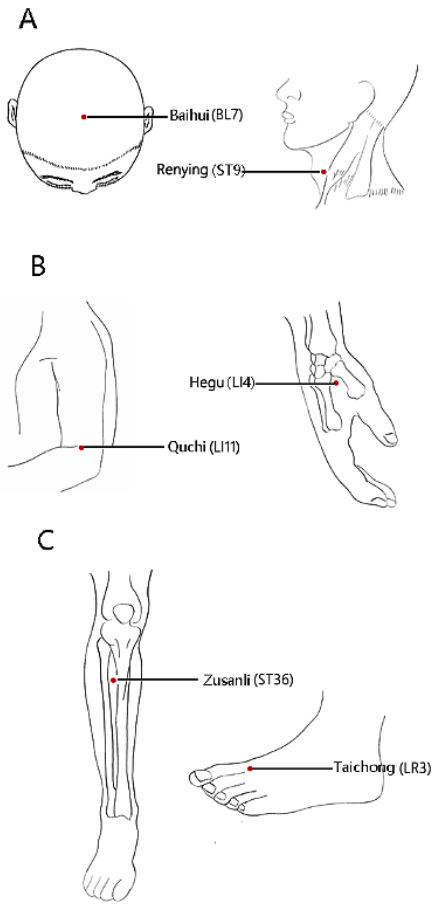

Table 1. Location of acupoints for the acupuncture group.

Acupoints	Locations	Needling methods
Baihui acupoint (GV20)	On the head, the middle of the front hairline is straight up 5 cun[a].	Baihui stabbed 10-20 mm along the governor vessel, and then twirled and laxated for 1 min.
Renying acupoint (ST9)	In the anterior part of the neck, the upper edge of the thyroid cartilage (approximately at the level of the laryngeal prominence), the anterior border of the sternocleidomastoid muscle, and the pulsation of the common carotid artery are aligned horizontally.	The needle was inserted vertically for 25~40 mm, and the twirling method was applied for 1 min (both sides of the neck).
Quchi acupoint (LI11)	On the lateral side of the elbow, at the midpoint of the line between the Chize point (LU5) and the lateral epicondyle of the humerus. Quchi point was only punctured on the left side, while the right side was used to measure the immediate blood pressure.	The needle was vertically inserted for 25~40 mm, and then twirled and laxated for 1 min (one side of the left arm).
Hegu acupoint (LI4)	On the back of the hand, between the first and second metacarpals, about the midpoint of the radial side of the second metacarpal.	The needle was vertically inserted for 20 ~25 mm, and the twisting and laxation method was applied for 1 min (both sides of the back of the hand).
Zusanli acupoint (ST36)	On the outside of the lower leg, 3 cun below the Du Bi acupoint (ST35), and on the line between Du Bi acupoint (ST35) and JieXi acupoint (ST41).	The needle was inserted vertically for 25~40 mm, and the twirling method was applied for 1 min (both sides of the lower limbs).
Taichong acupoint (LR3)	In the dorsum of the foot, between the first and second metatarsals, in the depression in front of the metatarsal base junction, or touching the arterial pulse.	The needle was inserted vertically for 20~25 mm, and the twisting and laxation method was applied for 1 min (both sides of lower limbs).

[a]1 cun (≈20 mm) is defined as the width of the interphalangeal joint of the patient's thumb.

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The total observation period was 11 weeks, with a baseline period of 1 week, a clinical treatment period of 6 weeks, and follow-up visits of 15 minutes each at weeks 1, 2, and 4 after the end of treatment.

Sham Acupuncture Group

Participants in the sham needling group will receive the same duration and frequency of treatment as the needling group, while keeping the original treatment unchanged. Participants will be placed in the supine position and nonmeridian and nonacupuncture points will be selected as the needling location. The specific location and operation method can be found in Figure 2 and Table 2, along with routine sterilization. Foam pads will be fixed on each nonmeridian nonacupuncture point and a disposable sterile comfort needle (customized by Beijing Zhongyan Taihe Medical Instrument Co, Ltd) will be used to pierce through the foam pads to the surface of the skin, simulating needling without actually penetrating the skin, simulating needling without actually penetrating the skin. Participants will be informed that they are receiving a treatment comparing the effects of 2 types of acupuncture to increase their compliance with the treatment while avoiding any deceptive behavior.

Figure 2. Location of non-acupoints.

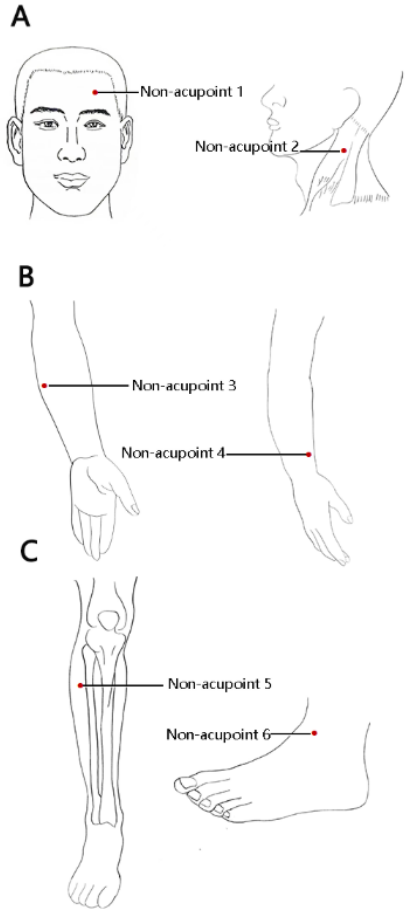

Table 2. Location of non-acupoints for sham acupuncture group.

Non-acupoints	Locations
Non-acupoint 1	In the middle of Touwei (ST8) and Yuyao (EX-HN4)
Non-acupoint 2	In the neck, between the anterior and posterior edges of the sternocleidomastoid muscle, 1 cun above the Futu point[a] (bilateral neck)
Non-acupoint 3	On the radial side, the midpoint between the medial epicondyle of the humerus and the first process of the ulna (unilateral on the left arm)
Non-acupoint 4	3 cun above the dorsal stria of the wrist, the midpoint of the line between Pianli (LI6) and Zhigou (SJ6); both sides of the forearm
Non-acupoint 5	Three inches below Yanglingquan (GB34), between the gallbladder and stomach meridians (bilateral lower limbs)
Non-acupoint 6	On the dorsum of the foot, the middle of the connecting line between Qiuxu (GB40) and JieXi (ST41); both sides of the lower limbs

[a]1 cun (≈20 mm) is defined as the width of the interphalangeal joint of the patient's thumb. All non-acupoints were directly punctured with a 1 cun blunt head needle through the fixed pad to reach the skin surface, and evenly lifted, inserted and twisted 3 times each, but the skin was not punctured.

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Adjustment of Antihypertensive Drug Therapy

In this study, participants are required to maintain their current treatment, including antihypertensive medication, after participating in the trial. This will be documented in detail. Discontinuation of medication, adjustment of medication, and use of over-the-counter or herbal medications will not be permitted during the treatment period.

Outcome Measurements

Primary Outcome Measurement

In this study, the assessor will be blinded to the specific subgroups. The primary outcome will include 24-hour ambulatory blood pressure and in-office immediate blood pressure. We plan to measure 24-hour ambulatory blood pressure once at baseline, once a week 6 of treatment, and once a week 4 after the end of treatment. In-office blood pressure will be measured when the patient first arrives at the office, 5 minutes after lying down, and at 5, 15, and 30 minutes after completing the acupuncture operation and 10 minutes after finishing the needle.

Secondary Outcomes

Some of the symptoms associated with essential hypertension, such as vertigo, headache, and insomnia, will be assessed using scales such as the Dizziness Handicap Inventory (DHI), Headache Impact Test-6 (HIT-6), and the Pittsburgh Sleep Quality Index (PSQI). The DHI is a classic tool for assessing vestibular or dizziness-related dysfunction and contains 25 entries covering functional, affective, and somatic dimensions [40]. In hypertensive patients, dizziness is a common symptom that may be associated with blood pressure fluctuations or medication side effects. The HIT-6 is a 6-item questionnaire that assesses the impact of headache on daily functioning in patients with hypertension associated with headache (eg, migraines or medication-induced headache) [41]. The PSQI is a 19-item tool that assesses sleep disorders, which are often comorbid in patients with hypertension (eg, insomnia and sleep apnea) [42,43].

The above assessments will be performed at baseline, at week 6 of starting treatment, and at weeks 1, 2, and 4 after the end of treatment. In addition, other safety indicators will be assessed, including general physical examination, liver and renal function and electrocardiogram at baseline. These tests will be performed at baseline and at week 6 of treatment.

Follow-Up

Telephone follow-ups will be conducted at weeks 1, 2, and 4 after the completion of acupuncture treatment. Patients will record their home self-measured blood pressure values, medication intake, and related scale contents accurately and completely in the case report form (CRF). The researcher will provide professional guidance to the patients according to their blood pressure level and related accompanying symptoms.

Sample Size and Statistical Analysis

The sample size of this study was estimated using the 2-sample *t* test in PASS (Power Analysis and Sample Size Software; NCSS LLC) 11 efficacy. According to existing literature [44], the mean improvement in systolic blood pressure within 24 hours for patients with essential hypertension treated with acupuncture was 8.9 mm Hg, while the mean improvement for those treated with sham acupuncture was 5.4 mm Hg, resulting in a clinical effect difference of 3.5 mm Hg. The SD for each group was 9.9 mm Hg. The sample size calculation assumed a 2-tailed significance level (α) of 0.05 and a statistical power (1-β) of 80%, the total sample size required for acupuncture treatment of mild-to-moderate essential hypertension was calculated to be 102 cases. Accounting for a 10% dropout rate, a total of 228 hypertensive participants needed to be recruited, with 114 participants in each group.

Statistical analyses we will leave to a statistician who is unaware of the groups. Data will be analyzed using the SAS 9.3 and SPSS 29.0 (IBM Corp) packages, and a 2-sided $P<.05$ will be considered statistically significant. We will use the intention-to-treat analysis set for outcome analysis and also validate it using per-protocol analysis to determine if the two results are consistent and inconsistency will require further analysis and discussion. For patients who withdrew from the study midway through the study, baseline data and follow-up data that had been collected before withdrawal were included in the intention-to-treat analysis. Missing values will be interpolated by the last observation carried forward method.

Baseline data on participants' demographic information and general state characteristics such as age, gender, and disease duration will be represented by descriptive statistics for both groups. We will measure in-office immediate blood pressure values at different time points of the needle prick and 24-hour ambulatory blood pressure values at baseline, week 6 of treatment and week 4 after the end of treatment, and comparisons between groups will be assessed using repeated measures ANOVA.

For continuous variables, expressed as mean (SD), grouped *t* tests will be used if they conform to normal distribution and vice versa, that is, they will be assessed by Wilcoxon rank-sum test; categorical variables will be compared using chi-square test or Fisher exact test (Fisher), and the results of the data will be documented in the form of percentage.

Patient Safety

During acupuncture treatment, participants may experience adverse events such as bleeding, subcutaneous hematomas, persistent feeling of getting gas, increased pain, infection, needle fainting, stress elevation of blood pressure, and allergic reactions to alcohol. As investigators, we will carefully observe changes in the participant's vital signs and record them in the CRF at all times.

Data Management and Quality Control

A thorough assessment will be performed during the screening and preparation phase of the trial and periodically throughout the trial. The screening phase will last for 1 week and will include assessment of basic information such as gender, age, temperature, heart rate, respiration, BMI, etc, as well as detailed information about the participant's chief complaint, current medical history, past history, family history, routine checkups,

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blood pressure, and medication use. The timing and process of data collection are detailed in Table 3.

Before the formal commencement of the study, all researchers will undergo a uniform and rigorous training to ensure that they are familiar with and equipped with the diagnostic and therapeutic measures and basic assessment skills to improve the consistency of internal observations. According to the study protocol, we will collect complete and authentic raw data from the participants and keep detailed records. Any data that deviate significantly from the clinically acceptable range must be examined and interpreted. The completed and validated CRF will be given to the relevant personnel for data entry, management and statistics, and the data on the CRF will not be modified. Professionals will be assigned to provide regular supervision and quality control throughout the study.

Table 3. Clinical research flowchart.

Phase project	Baseline period	On-treatment		Follow-up period		
	Week 0	Week 1	Week 6	Week 7	Week 8	Week 10
Signed informed consent	✓[a]					
Filling in demographic information	✓					
Previous diseases and medication	✓					
Prestudy medication and other treatments	✓					
General physical examination items	✓					
Physical examination	✓					
Acceptance and discharge standard	✓					
24-hour ambulatory blood pressure monitoring	✓		✓			✓
Immediate blood pressure in the consulting room[b]		✓	✓			
Biochemical function test[c]	✓		✓			
Electrocardiogram	✓		✓			
Scale evaluation[d]	✓		✓	✓	✓	✓
Blinded evaluation			✓			
Adverse reactions/adverse events (ADR/AE)	✓[e]	✓[e]	✓[e]	✓[e]	✓[e]	✓[e]
New drug combinations	✓[e]	✓[e]	✓[e]	✓[e]	✓[e]	✓[e]

[a]"✓" in this table represents the items that must be completed; The participants made corresponding records after treatment.

[b]Immediate blood pressure in the consulting room: it needs to be measured in the first to sixth weeks.

[c]Biochemical function test: liver function, kidney function, blood lipid, etc.

[d]Scale evaluation: Traditional Chinese medicine symptom scale, Dizziness Handicap Inventory (DHI), Headache Impact Test-6 (HIT-6), Pittsburgh Sleep Quality Index (PSQI), 36-Item Short Form Health Survey.

[e]Recorded at any time.

Dissemination

At the end of the trial, we will endeavor to share the results with other experts from the Chinese medical field, with the aim of benefiting them by exploring the immediate antihypertensive effects of the "HuoXueSanFeng" acupuncture method and its effects on the central nervous system.

Biological Specimens

Routine blood tests will be performed and analyzed to collect the necessary data.

Ethics Approval

This trial was conducted in strict accordance with the Declaration of Helsinki and relevant Chinese clinical trial research norms and regulations. The study protocol has been approved by the Ethics Committee of the Clinical Research Unit (number: 2024DZMEC-153-03) and was successfully registered on May 23, 2024, at ChiCTR2400084696 (Chinese Clinical Trial Registry). Before each participant is enrolled in this study, the investigator will provide a complete and comprehensive written introduction to the purpose, procedures, and potential risks of the study. Participants will be informed of their right to withdraw from the study at any time. If a participant withdraws during the course of the trial, we reserve the right to retain the data obtained for statistical analysis. All data will be anonymized. All participants are entitled to 18 free acupuncture treatments, as this study does not include compensation for transportation and lost wages.

Results

This study was registered in China Clinical Trial Registration Center on May 23, 2024. Data collection began in July 2024 and is expected to end in June 2025. At present, the data of this experiment is in the collection stage, 27 participants have been

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recruited, and the data has not been analyzed. The experimental results are expected to be submitted and published in November 2025.

Discussion

Anticipated Findings

This study is a multicenter, randomized, single-blind, sham acupuncture-controlled clinical trial designed to assess the efficacy and safety of the "HuoXueSanFeng" acupuncture method in the management of hypertension.

Hypertension is intricately linked with a range of comorbidities, including cardiovascular disease, chronic kidney disease, and diabetes mellitus [45,46]. The primary focus of hypertension management is the regulation of blood pressure and the protection of target organs. Nonetheless, the global burden, health care costs, and societal impact of hypertension are escalating, particularly in low- and middle-income countries [3,47]. Although oral pharmacotherapy remains the cornerstone of hypertension, many patients experience suboptimal blood pressure control, attributable to factors such as the single-target action of medications and their associated adverse effects [48]. In recent years, nonpharmacological therapies have gained recognition for their efficacy in blood pressure reduction, largely due to their minimal or absent side effects, in both developed and developing nations [49]. As a nonpharmacological intervention, acupuncture offers distinct advantages in the treatment of hypertension, owing to its multitarget, multipathway, and holistic regulatory effects [50,51]. Acupuncture can not only regulate hypertensive conditions caused by the imbalance of sympathetic and parasympathetic nervous systems by activating different brain regions, but also regulate neurotransmitters in related brain regions and alleviate autonomic responses, thus exerting antihypertensive effects [27]. However, there are fewer high-quality clinical studies on the treatment of hypertension with acupuncture, and the following three problems exist. First, there are no detailed studies to assess when acupuncture is effective in lowering blood pressure and its duration. Second, there is a lack of effective integration of symptoms accompanying the disease (eg, headache, vertigo, and insomnia). Consequently, the current scientific basis for the regulation of hypertension by acupuncture is insufficient, and the mechanism of antihypertensive by acupuncture needs to be further elucidation.

The "HuoXueSanFeng" acupuncture method, founded by Academician Xuemin Shi based on the "Qihai" theory, is used for the treatment of hypertension. In this method, Renying (ST9) is selected as the main point, supplemented by Baihui (BL7), Quchi (LI11), Hegu (LI4), ZuSanli (ST36) and Taichong (LR3), to treat hypertension. In this study, the Renying (ST9) acupoint is selected as the primary focus, with supplementary points including Baihui (BL7), Quchi (LI11), Hegu (LI4), Zusanli (ST36), and Taichong (LR3), to address hypertension. This methodology integrates the specificity of meridian points with anatomical insights from Western medicine. Furthermore, the approach adheres to academic standards for acupuncture techniques and specifies the precise amount of needling required. This acupuncture therapy is regarded as an environmentally friendly, safe, and effective treatment for hypertension. Consequently, the objective of this research was to thoroughly assess both the immediate and short-term antihypertensive effects of "HuoXueSanFeng" acupuncture, employing sham acupuncture as a control group and using office blood pressure and 24-hour ambulatory blood pressure monitoring. In addition, we evaluated the beneficial effects of the acupuncture method using various assessment tools, such as the DHI, HIT-6, and PSQI, to provide robust, evidence-based support for its application in the treatment of essential hypertension.

It is noteworthy that our trial assessed the immediate effect of acupuncture in lowering blood pressure and the persistence of short-term effects, but the long-term efficacy of acupuncture-such as sustained blood pressure control over months or years remains unproven. Hypertension is a chronic disease that requires long-term management, and the durability of nonpharmacologic interventions such as acupuncture must be rigorously evaluated through long-term follow-up studies. Future studies should prioritize longitudinal designs with 6- or 12-month follow-ups to determine whether repeated acupuncture or intensive treatment is necessary to maintain treatment efficacy.

In addition, there are some noteworthy limitations of our trial. The inclusion of patients with essential hypertension was relatively difficult for us because hypertension, if left untreated, increases the risk of cardiovascular and renal complications [12]. To ensure the safety and reliability of the study, we excluded individuals with severe complications in strict accordance with the inclusion criteria. However, as a double-blind design could not be realized in this experiment, we used sham acupuncture as a control and tried to maintain the consistency of the operation between the 2 groups as much as possible. At the same time, we assessed the effectiveness of blinding in time to achieve a single-blind design. Blinding could not be applied to the acupuncturists because they could perceive the sensation under the needle and visually recognize the needling device during the procedure.

Conclusions

This study is a multicenter, randomized, single-blind, sham-acupuncture controlled clinical trial. We will apply the "HuoXueSanFeng" acupuncture method proposed by Academician Xuemin Shi, aiming to provide more reliable evidence to support the treatment of essential hypertension. In addition, we seek to explore the advantages of acupuncture in lowering blood pressure and grasp the best opportunity for acupuncture to lower blood pressure.

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Acknowledgments

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Authors' Contributions

XMH, LLZ, and YG contributed to the design and writing of the study. QGL received research funding. XDZ and MX have contributed to the calculation of sample volume and the draft statistical plan. TTL and YL participated in the drawing of pictures and graphs. YG, WLQ, and JPL participated in the revision and editing of the manuscript. JW, QLG, and BNY participated in the study design.

Conflicts of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Abbreviations

CRF: case report form
DHI: Dizziness Handicap Inventory
HIT-6: Headache Impact Test-6
PASS: Power Analysis and Sample Size Software
PSQI: Pittsburgh Sleep Quality Index

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Protocol

The Effects of Acupoint Stimulation Combined With Transcutaneous Electrical Nerve Stimulation on Labor Pain: Protocol for a Stepped Wedge Cluster Randomized Controlled Trial

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Abstract

Background: Pain experienced during childbirth can significantly impact the progress of labor and the well-being of both the mother and the fetus. Effective management of labor pain is a crucial component of childbirth care. Nonpharmacological methods of pain relief offer notable advantages over pharmacological approaches, including enhanced maternal and fetal safety, equitable access to health care, and greater availability. Among the nonpharmacological options, transcutaneous electrical nerve stimulation (TENS) and acupoint stimulation are two commonly used methods for alleviating pain during labor. However, the clinical efficacy of these methods remains inconsistent, which hinders the generation of high-quality evidence for clinical practice.

Objective: This study aims to assess the effects of acupoint stimulation combined with TENS on labor pain, delivery outcomes, and childbirth experience for women undergoing a trial of labor.

Methods: This is a 12-month stepped wedge cluster randomized trial to be conducted in 4 labor and delivery units (LDUs) at the Obstetrics and Gynecology Hospital of Fudan University. Each unit will implement 4 types of interventions: TENS, acupoint stimulation, TENS combined with acupoint stimulation, and a control group. We aim to recruit approximately 588 pregnant women. The project will be evaluated using both quantitative and qualitative data. Quantitative data will include visual analog scale (VAS) scores, the nonpharmacological to pharmacological pain management interval (NPI), the rate of epidural analgesia, and childbirth outcomes. Qualitative data will include interviews with the women and midwives.

Results: The study commenced on April 1, 2023, and as of March 29, 2024, a total of 600 eligible participants have been enrolled, surpassing the initial target of 588. Data collection has been completed, including quantitative assessments of labor pain intensity, analgesic use, and childbirth outcomes, alongside qualitative interviews with participating women. Currently, data analysis is in progress, with preliminary findings anticipated to be available by March 2025. We hypothesize that TENS combined with acupoint stimulation will demonstrate greater efficacy in managing labor pain compared with standard care. This effect may be observed in key outcome measures, including the VAS score and enhanced maternal childbirth experience.

Conclusions: This study protocol details the interventions of acupoint stimulation and TENS for women undergoing a trial of labor. We introduce a novel outcome indicator termed NPI, which monitors whether the application of nonpharmacological pain relief measures can delay or prevent the use of epidural analgesia. The integration of qualitative and quantitative methods will enrich the research on TENS and acupoint stimulation technology within the realm of nonpharmacological labor pain relief, providing high-quality evidence for the future establishment of industry standards and guidelines.

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KEYWORDS
labor pain; transcutaneous electric nerve stimulation; acupressure; complementary therapies; pain management; acupuncture points; medicine, Chinese traditional; pulsed electrotherapy; electrotherapy; nerve; pain; acupuncture; women; protocol; randomized controlled trial; childbirth; pregnancy; pregnant women; quantitative data; qualitative data

Introduction

Childbirth pain is widely regarded as one of the most intense forms of pain, often cited by women as the most severe pain they have ever experienced [1]. Approximately 60% of primiparous women report experiencing severe or extremely severe labor pain [2], with 74.2% scoring 8 or higher on the pain perception scale [3]. The intensity of labor pain can lead to anxiety, fear, and tension, which in turn diminishes pain tolerance and exacerbates the cycle of pain. This can negatively affect the childbirth experience, potentially leading to prolonged labor, higher cesarean section rates, and increased risks for both mother and infant [4]. Therefore, effective pain relief strategies are essential for improving maternal health outcomes and the overall childbirth experience.

Pain relief during labor is typically categorized into two approaches: pharmacological and nonpharmacological [5]. Pharmacological methods, including epidural analgesia, nitrous oxide, and intravenous opioids, are generally more effective in managing pain [6]. However, they may have potential drawbacks, such as prolonged labor, dietary restrictions, the risk of intrapartum fever, higher cesarean section rates, and challenges with breastfeeding [7,8]. In contrast, nonpharmacological methods offer a range of alternatives that can reduce pain and anxiety with minimal risk to both the mother and fetus [9]. These approaches, which include transcutaneous electrical nerve stimulation (TENS), aromatherapy, water immersion, and massage, are recommended in clinical guidelines for enhancing the childbirth experience and reducing discomfort [10,11].

TENS and acupoint stimulation have both been extensively explored as nonpharmacological interventions for labor pain relief, each exhibiting distinct mechanisms of action. TENS involves the application of low-frequency electrical currents to stimulate the body's pain-relief systems, primarily targeting the central nervous system to inhibit pain transmission [12]. Specifically, TENS at frequencies ranging from 2Hz to 100 Hz activates large-diameter Aβ fibers, which, at the dorsal horn level, inhibit incoming nociceptive signals transmitted through small-diameter, slow-conducting Aδ and C fibers that innervate spatially adjacent skin areas. This mechanism produces a pronounced analgesic effect in response to homotopic nociceptive stimulation [13]. TENS has been widely used for relieving chronic pain [14], postoperative pain [15], and cancer-related pain [16]. In the context of labor, several randomized controlled trials (RCTs) have found that TENS can reduce labor pain [17-19], shorten the active labor phase [19], and delay the need for pharmacological analgesia [18]. However, other studies have reported no significant effects on pain relief or labor satisfaction. Consequently, the efficacy of TENS remains inconclusive, with some studies indicating minimal effects on labor satisfaction and pain relief [1,20]. These conflicting results imply that TENS alone may not be adequate for consistent pain management during labor.

Acupoint stimulation, a traditional nonpharmacological method for pain relief rooted in traditional Chinese medicine (TCM), encompasses techniques such as auricular seed acupressure and acupoint massage. This practice is founded on the principle of promoting Qi and blood circulation to alleviate pain [21]. From a contemporary medical standpoint, acupoint stimulation is believed to function through the gate control theory, wherein massage or pressure inhibits nociceptive transmission [22]. In addition, it has been suggested that acupoint stimulation activates Mu opioid receptors, increases serum endorphin levels, and stimulates the release of adrenocorticotropic hormone, all of which contribute to pain relief [23]. Several studies have explored its application during labor, with findings indicating that acupressure can reduce pain during the first stage of labor [21] and that auriculotherapy can alleviate labor pain in primiparous women [24]. However, these studies frequently exhibit methodological limitations, such as small sample sizes and insufficient randomization, which hinder the ability to draw definitive conclusions regarding their effectiveness.

Although both TENS and acupoint stimulation have demonstrated analgesic effects, the existing evidence for nonpharmacological labor pain relief remains limited in strength and lacks standardized implementation protocols, which restricts its clinical applicability [25-27]. The combination of TENS and acupoint stimulation was selected for this study due to the complementary nature of their pain-relieving mechanisms. TENS primarily functions by modulating the nervous system to block pain signals, while acupoint stimulation enhances pain relief by promoting the body's natural pain modulation processes, such as increasing endorphin release. Together, these approaches may provide synergistic benefits in alleviating labor pain and enhancing the overall childbirth experience. Furthermore, the combination of these two methods may optimize pain relief without increasing risks to the mother or fetus, thus offering a promising alternative to pharmacological interventions.

Based on these considerations, this study aims to evaluate the effects of acupoint stimulation combined with TENS on labor pain, delivery outcomes, and the overall childbirth experience for women undergoing a trial of labor. The primary hypothesis posits that this combination will lead to reduced labor pain,

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improved delivery outcomes, and a more positive childbirth experience for women. A stepped wedge cluster randomized controlled trial (SWCRCT) design is selected to ensure that all groups will ultimately receive the intervention, thereby promoting equity and adherence to ethical standards. This design also minimizes individual differences by using data from each group's own participants as a control, while facilitating phased implementation, which effectively addresses resource and personnel feasibility [28].

Methods

Trial Design

This 12-month exploratory SWCRCT will be conducted at the Obstetrics and Gynecology Hospital of Fudan University in Shanghai, China—a specialized tertiary hospital that manages approximately 10,000 births annually across its 2 campuses. The study involves 4 parallel groups, assigned in a 1:1 ratio, each receiving 1 of 4 interventions: TENS, acupoint stimulation, a combination of TENS and acupoint stimulation, or control measures. Randomization is performed at the cluster level using computer-generated sequences to determine the staggered initiation order of interventions across 4 labor and delivery units (LDUs; LDU1, LDU2, LDU3, and LDU4). Each LDU will be assigned to deliver a single intervention for a 3-month period, followed by a transition to the next phase according to the predetermined sequence. This design ensures that each 3-month cohort will comprise unique participants, eliminating crossover exposure to multiple interventions. Participants will be selected based on predefined criteria and confirmed for inclusion before the initiation of the interventions. Figure 1 shows the overall study flow. Recruitment began on April 1, 2023, and all interventions were completed by March 29, 2024, aligning with the 12-month study window. This protocol adheres to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 checklist [29].

Figure 1. Study flowchart.

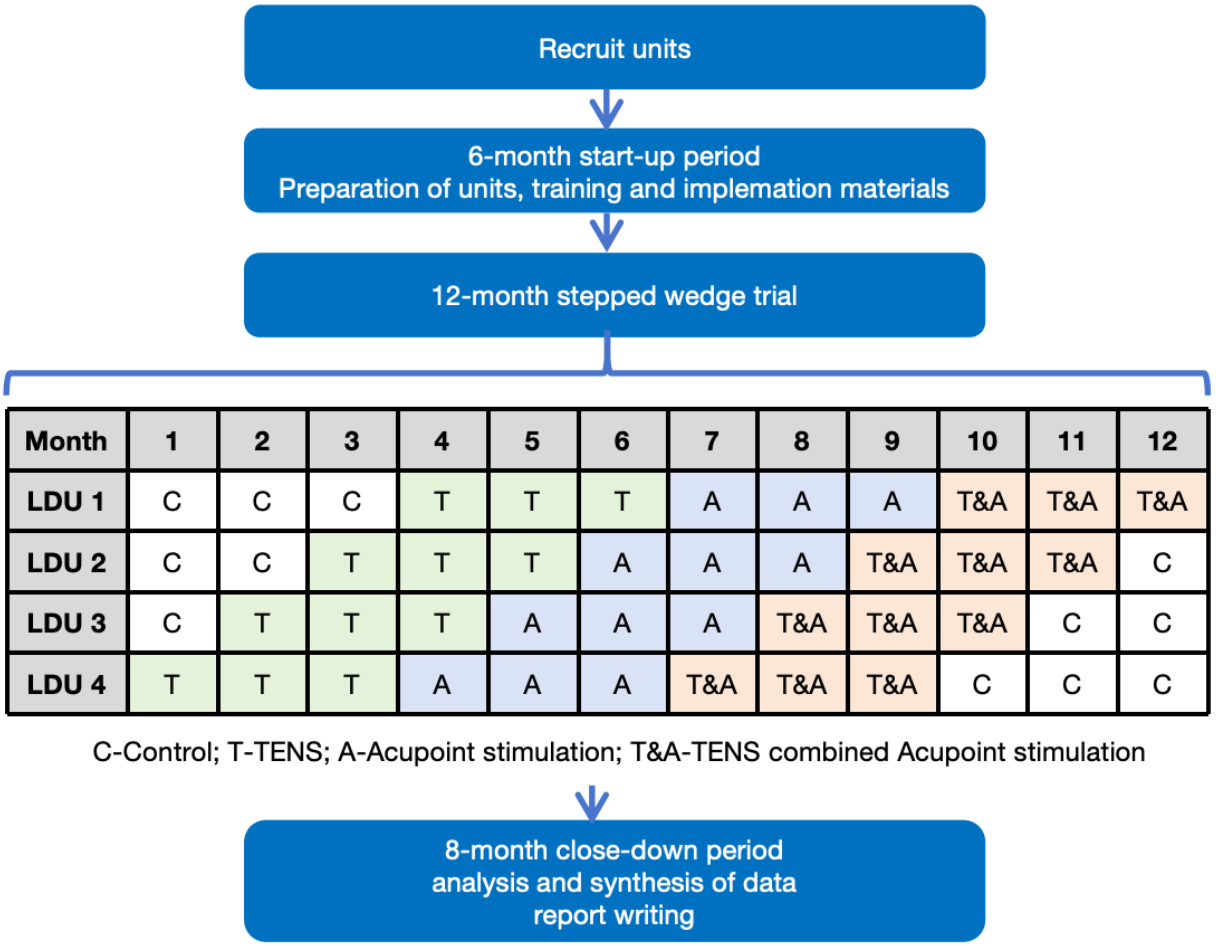

Eligibility and Recruitment

Participants will be recruited from the Obstetrics and Gynecology Hospital of Fudan University, where they will receive routine antenatal care and plan to give birth. Upon admission to the LDU, trained research staff will identify eligible women through a screening process that includes reviewing medical records and conducting brief assessments. Inclusion criteria require participants to have a singleton pregnancy with cephalic presentation, to be in good maternal and fetal health at admission, to plan to undergo a trial of labor, and to have no cognitive dysfunction or communication difficulties. Women with preexisting or pregnancy-related

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complications, as well as those with medical indications necessitating a cesarean section, are excluded from the study.

Eligible participants will be approached by trained research staff, who provide detailed information about the study's purpose, procedures, and potential risks and benefits. Written informed consent will be obtained from all participants before enrollment, and they will be informed of their right to withdraw from the study at any time without consequences.

Sample Size

The sample size calculation is conducted using the formula for SWCRCTs as outlined by Hemming and Taljaard [30]. The design effect (DE) was calculated based on the meta-analysis by Johnson et al [14], which suggests that a reduction exceeding 0.7 in VAS pain scores indicates a clinically significant effect of TENS. Assuming an expected effect size of 0.7, an intraclass correlation coefficient (ICC) of 0.01, and an estimated sample size of 117 participants in each intervention group, the DE is determined to be 2.16. The total sample size is then estimated using a significance level of 0.05 and a power of 0.8, resulting in 132 participants per group. After accounting for a 10% dropout rate, the required sample size is adjusted to 147 participants per group, culminating in a total of 588 participants. This calculation is verified using PASS 15.0 software (NCSS), which confirms a power of 0.89, thus ensuring the study's adequacy.

Randomization and Allocation

This study uses a SWCRCT design, wherein the interventions are allocated at the cluster level, specifically based on the LDUs, rather than at the individual participant level. The randomization process is conducted by a researcher not involved in the intervention using a computer-generated random number list to determine the sequence of interventions across the 4 LDUs. The random allocation sequence is subsequently sealed in opaque envelopes, each corresponding to a specific LDU. This allocation sequence will be disclosed to the midwives in each cluster at the appropriate time. The midwives, trained to implement the intervention, will execute it according to the allocated sequence. This approach ensures allocation concealment and mitigates the risk of selection bias.

Intervention

A literature analysis method is used to systematically search for relevant studies across multiple databases, including the Cochrane Library, JBI Evidence-Based Nursing Database, Medline, Embase, WanFang Data, SinoMed, CNKI, and VIP. This search uses keywords related to TENS, auricular seed acupressure, and acupressure specifically for women undergoing a trial of labor. A total of 27 studies on TENS, 30 studies on auricular seed acupressure, and 41 studies on acupressure were retrieved. Content analysis is subsequently applied to extract key information from the selected literature. The research team will conduct content extraction, analysis, and synthesis on relevant topics to draft an initial intervention plan for labor pain relief using TENS combined with acupoint stimulation for women in the trial of labor. Based on this draft, expert consultations will be organized to revise the plan, ultimately resulting in the final version of the intervention protocol.

Before the implementation of the project, the midwives at the 4 LDUs will participate in a 1-week training course led by researchers qualified in TCM nursing. The course will cover the operational procedures and assessment of the 3 nonpharmacological pain relief techniques. Competency will be evaluated using a percentage-based scoring system that assesses key aspects such as knowledge of protocols, practical skills, and communication effectiveness. Midwives who achieve a score of 80 or higher will pass the assessment and receive a TCM-based labor pain relief technique certification from the study institution. This certification ensures that all relevant personnel are proficient in the standardized implementation of these techniques before the intervention.

Table 1 shows detailed descriptions of the 3 intervention techniques. These interventions will be administered to participants during labor progression, spanning from the initial onset of contractions to final delivery. All interventions will be individualized according to each participant's unique labor progression and birthing context while being strictly confined to a single care episode to ensure protocol consistency. To mitigate cross-contamination risks among study groups, designated cluster units (LDU wards) will maintain geographic separation and administrative independence.

Participant adherence to the interventions will be rigorously monitored throughout the study. The intervention protocol will initiate upon the onset of regular contractions and be suspended during intercontraction intervals. During these pauses, midwives will assess maternal comfort levels and dynamically adjust interventions in real time based on participant feedback. For the acupoint stimulation group, adherence will be ensured through direct observation by trained midwives, who will administer massage techniques and maintain continuous stimulation at predefined acupoints. Adherence metrics, including duration, frequency, and intensity of each intervention session, will be recorded using a standardized log sheet. Maternal willingness and comfort will serve as primary adherence indicators, ensuring that interventions remain tolerable and beneficial throughout labor. Participants retain the autonomy to modify or discontinue the intervention at any time, with all adjustments documented for analysis. Regular feedback will be collected through brief interviews and comfort assessments, with findings integrated to refine intervention delivery while safeguarding maternal well-being.

To ensure data accuracy and protocol fidelity, a comprehensive quality assurance framework will be implemented, including (1) regular oversight by the research team, involving scheduled audits to assess adherence to intervention protocols; (2) mandatory use of standardized checklists by midwives to systematically verify and document each procedural step; and (3) prompt documentation and analysis of protocol deviations, with root-cause investigations conducted to address discrepancies. In case of identified nonadherence, targeted retraining sessions will be provided to reinforce proper procedures and ensure understanding of the protocol. These measures are designed to maximize intervention fidelity, ensure methodological rigor, and uphold the integrity of the study.

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Table 1. Description of intervention protocols.

Intervention types	Detailed descriptions
Low-frequency pulsed electrotherapy or TENS[a] (T)	• Preprocedure preparation: The midwife will prepare the TENS device, electrodes, and connecting wires. The laboring woman will be positioned comfortably, and the skin will be cleansed with warm water. • Procedure: Electrodes will be placed on the Hegu (LI4) point, Neiguan (PC6) point, T10-L1, and S2-S4 (Figure 2). The device will be set to alternate between frequencies of 2 Hz and 100 Hz every 6 seconds, with pulse widths of 0.6 ms for 2 Hz and 0.2 ms for 100 Hz. The intensity will be gradually increased from low to high based on the laboring woman's feedback until the optimal stimulation level is achieved. Typically, the intensity for channel 1 (Hegu and Neiguan points) will be set between 6 and 15 mA, while for channel 2 (T10-L1 and S2-S4), it will range from 6 to 40 mA. The midwife will instruct the laboring woman on how to adjust the intensity, empowering her to modify the settings according to her comfort level. • Timing of application: TENS therapy will commence at the onset of contractions, with intensity increased during contractions and decreased during periods of relief. This therapy will continue as tolerated until the delivery of the placental. • Postprocedure care: Upon completion of the treatment, the device will be turned off, electrodes will be removed, and the skin will be inspected for any signs of irritation. The area will be cleansed to ensure hygiene is maintained.
Acupoint stimulation (A)	
Auricular seed acupressure	• Preprocedure preparation: The midwife will prepare a treatment tray containing a kidney dish, 75% alcohol swabs, and vaccaria seeds (Wang-Bu-Liu-Xing) with adhesive tape, tweezers, and a probe. The laboring woman will be positioned comfortably in a sitting, supine, or lateral position to ensure full exposure of the ear. • Procedure: The midwife will stabilize the auricle and use a probe to identify the positive reaction points at the bilateral Uterus (TF2), ShenMen (TF4), Endocrine (CO18), Sympathesis (AH6a), and Subcortex (AT4) points (Figure 3). After disinfecting the ear with an alcohol swab, the midwife will apply vaccaria seeds with adhesive tape onto the selected acupoints and press them for 1-2 min per side to enhance stimulation. • Timing of application: The procedure will be performed at the onset of contractions. The seeds should be pressed for 1-2 min per contraction or as tolerated until placental delivery. • Postprocedure care: The seeds can remain in place for up to 1-2 days post delivery to alleviate uterine contraction pain. If the laboring woman experiences discomfort or requests removal, the procedure should be terminated immediately. After removal, the midwife should clean the auricle, ensure patient comfort, and adjust clothing and bedding.
Acupressure	• Preprocedure preparation: The midwife should encourage the woman in labor to empty her bladder and bowels, ensure a comfortable position, and maintain warmth. • Procedure: During the latent phase of labor, due to the slow cervical dilation, abdominal pain tends to concentrate around the GuanYuan (CV4) point. The midwife can provide a massage using the palm of her right hand in a clockwise direction. Simultaneously, the left thumb can be used to apply pressure to the HeGu (LI4), NeiGuan (PC6), and KunLun (BL60) points (Figure 4). In the active phase of labor, the woman will be advised to adopt a left lateral position with the ZhongJi (RN3) point as the center. Pillows and cushions can be used to support the woman's head and upper thigh. The midwife will use clockwise abdominal massage and apply pressure to the HeGu (LI4), SanYinJiao (SP6), TaiChong (LR3), and ZuSanLi (ST36) points. For back pain, focusing on the CiLiao (BL32) points, the woman should lean forward against a wall or support herself on the edge of the bed to minimize fetal weight on the spine. The midwife will provide a massage to the lumbar and sacral regions, as well as the back, including the ShenYu (BL23) points, and perform a circular massage around the buttocks with the HuanTiao (GB30) point as the center (Figure 5). • Timing of application: Acupoint massage should begin at the onset of contractions and be paused during periods of relief. It may continue as tolerated until placental delivery. • Postprocedure care: If the laboring woman experiences discomfort or requests termination, the procedure should be stopped immediately. The midwife should cleanse the skin, adjust the woman's clothing, and ensure her comfort.
Combination of TENS and acupoint stimulation (T&A)	• Preprocedure preparation: The midwife will prepare all necessary tools, including TENS equipment, Vaccaria seeds, alcohol swabs, tweezers, and a probe. The laboring woman will be positioned comfortably to ensure relaxation. • Procedure: Initially, the midwife will apply auricular acupressure and place the TENS electrodes. During contractions, the laboring woman will be encouraged to massage the auricular acupoints, adjust the TENS intensity, and receive an acupoint massage. When experiencing contraction relief, the acupoint massage should be paused, allowing the laboring woman to adjust the TENS settings as needed. This intervention may continue as tolerated until placental delivery. • Timing of application: This combined approach may be sustained as tolerated until placental delivery. • Postprocedure care: If discomfort occurs, adjustments to the technique should be made, or it should be discontinued. The midwife should turn off and remove the TENS device, inspect the skin, and cleanse the area. Auricular acupressure may be continued for 1-2 days post delivery unless discomfort arises.

[a]TENS: transcutaneous electrical nerve stimulation.

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Figure 2. Points for transcutaneous electrical nerve stimulation (TENS) electrodes placed on.

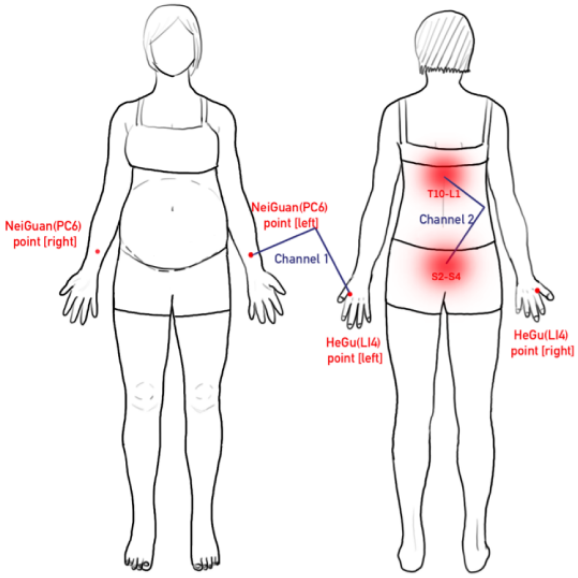

Figure 3. Points for auricular seed acupressure.

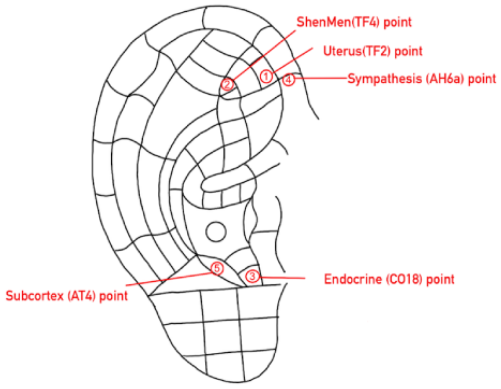

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Figure 4. Points for acupressure during the latent phase of labor.

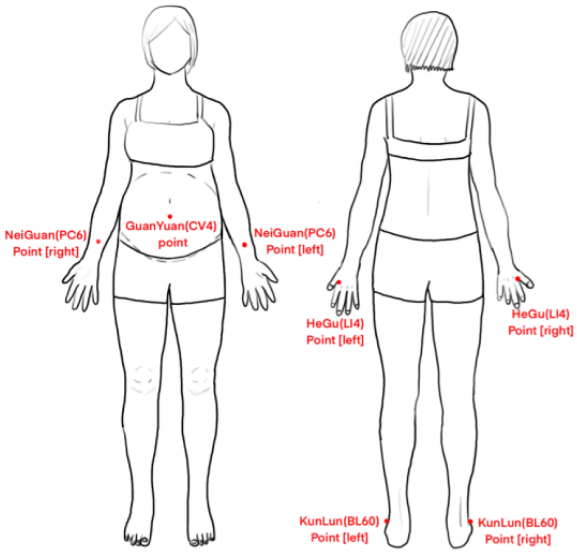

Figure 5. Points for acupressure during the active phase of labor.

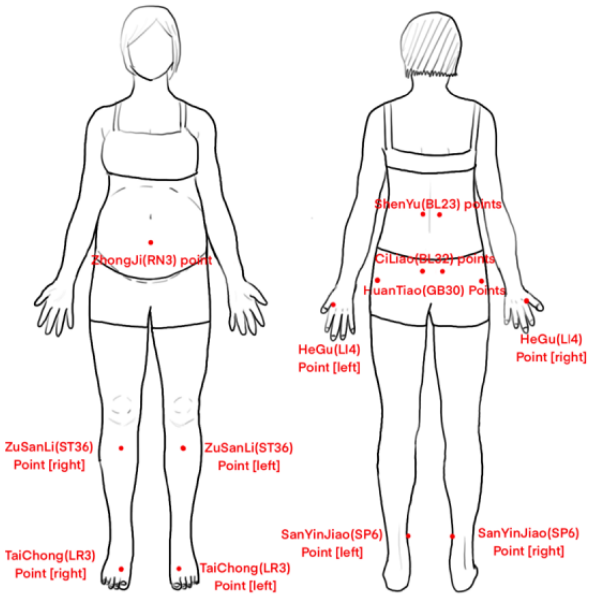

Ethical Considerations

This study has been approved by the Ethics Committee of the Obstetrics and Gynecology Hospital of Fudan University (OGHEC2023-21). The Data Safety Monitoring Committee will conduct continuous safety monitoring of the project implementation and perform annual ethical reviews to ensure procedural coherence. The Data Management and Quality Control Committee will execute quality control evaluations at the initial, intermediate, and preconclusion phases of the project, with a preliminary analysis performed at the midterm stage to guarantee the high-quality execution of the study.

The trial was prospectively registered in the Chinese Clinical Trial Registry on March 23, 2023 (ChiCTR2300069705). All data will be kept confidential, with access restricted to the researchers. Before enrollment, all participants will provide informed consent and will be fully informed of their right to withdraw from the study at any time. Participating women are explicitly assured that their personal data will be managed under strict confidentiality protocols within the research group. All collected study materials will undergo deidentified processing to ensure complete anonymization.

Blinding

A double-blind design is not feasible in this study due to the necessity for participants to provide informed consent regarding the pain relief methods administered. However, several measures are implemented to minimize potential bias. Midwives

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delivering the interventions will not be involved in outcome assessment or data analysis, thereby reducing both performance and detection bias. A standardized protocol will be established to ensure consistent delivery of interventions and uniformity in data collection. To minimize measurement bias, outcome assessors will be blinded to the group allocation, and participants will be instructed not to disclose which treatment intervention they receive. Data collectors, who will be independent of the intervention process, do not have access to any information regarding the intervention groups. In addition, statisticians conducting the data analysis will be blinded to group allocation and will not have access to the intervention details. Analyses will be performed according to a prespecified plan to prevent selective reporting. Regular monitoring of adherence to the protocol across the LDUs will be conducted to ensure consistency and reduce the risk of bias. To further enhance the validity and objectivity of the findings, data analysis will be independently verified by a third party to minimize any potential bias.

Outcome Measures

The primary outcome of this trial is pain perception, measured using the visual analog scale (VAS). Pain perception was assessed from the onset of labor pain, with evaluations recorded every 30 minutes until pharmacological pain relief was administered or delivery occurred. VAS scores ranged from 0 (no pain) to 10 (extreme pain). Secondary outcomes included the interval from the NPI, the rate of epidural analgesia, mode of delivery, the amount of postpartum bleeding within 2 hours, neonatal Apgar scores at 1 and 5 min, labor duration, perineal tear rates, and the overall childbirth experience. The Chinese version of the Childbirth Experience Questionnaire (CEQ) [31] was used to evaluate women's overall childbirth experience. All secondary outcomes, with the exception of the childbirth experience, assessed post delivery using the CEQ, will be extracted from electronic medical records by the research team, who will not be involved in providing care.

In addition, a purposive sampling method will be used to recruit women from each group for semistructured interviews. The interviews will primarily focus on women's perceptions and experiences of nonpharmacological pain relief methods during childbirth. The number of women to be interviewed will not be predetermined. Interviews will continue until data saturation is reached, which is the point at which no new information or themes are detected in additional data [32].

Statistical Analysis

Data will be entered into the database after verification by 2 independent researchers. Quantitative data will be analyzed using SPSS 26.0 statistical software (IBM Corp), following an intention-to-treat (ITT) approach. Normally distributed continuous variables are presented as mean (SD), while non-normally distributed continuous variables are expressed as median (25th percentile-75th percentile). Categorical data are described using frequencies and percentages. Comparisons of normally distributed continuous variables were conducted using ANOVA or the Kruskal-Wallis test, while *t* tests were used for intergroup comparisons. A significance level of $P<.05$ is deemed statistically significant. Missing data will be addressed using multiple imputations.

Qualitative data will be analyzed using NVivo 14 software (Lumivero) through content analysis. Interview materials will be coded and categorized based on key themes derived from the interview guide. Perspectives on similar topics will be grouped and synthesized. Following coding, the software's classification extraction function will be used to retrieve relevant content from all files under specific codes, allowing for comparison and linkage of different coded content, and identification of primary and secondary viewpoints based on frequency of occurrence for further analysis.

Results

The study commenced on April 1, 2023, and as of March 29, 2024, a total of 600 eligible participants have been enrolled, surpassing the initial target of 588. Data collection has been completed, including quantitative assessments of labor pain intensity, analgesic use, and childbirth outcomes, alongside qualitative interviews with participating women. Currently, data analysis is in progress, with preliminary findings anticipated to be available by March 2025. We hypothesize that TENS combined with acupoint stimulation will demonstrate greater efficacy in managing labor pain compared with standard care. This effect may be observed in key outcome measures, including the VAS score and enhanced maternal childbirth experience.

Discussion

Principal Findings

This study protocol outlines a SWCRCT designed to evaluate the effectiveness of TCM-based TENS and acupoint stimulation for labor pain management. By addressing the limitations of previous research, such as inconsistent implementation techniques and a lack of high-quality evidence [9,33], this study aims to generate robust and clinically relevant findings. We anticipate that the results will provide valuable insights into the potential of nonpharmacological methods to delay the use of pharmacological pain relief, particularly epidural analgesia, while also reducing associated risks such as intrapartum fever [34,35]. Furthermore, the introduction of the NPI as a novel outcome indicator is expected to offer a new perspective on evaluating the efficacy of nonpharmacological interventions. The mixed methods approach, incorporating both quantitative and qualitative data, will provide a comprehensive understanding of the interventions' impact on labor pain management and women's childbirth experiences.

Comparison With Previous Work

This study builds on previous work by conducting a meta-analysis of 32 RCTs evaluating the use of TENS for labor pain relief [33]. The findings indicate that TENS can effectively reduce labor pain; however, the overall quality of the evidence was low, with significant heterogeneity across studies. This variability likely arises from individual differences among laboring women and inconsistencies in the implementation of TENS techniques.

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Furthermore, previous studies have predominantly explored comparisons between nonpharmacological pain relief methods and pharmacological pain relief methods [1,36]. However, there is limited evidence on the sequential use of nonpharmacological interventions followed by pharmacological approaches, particularly in the context of delaying the administration of epidural analgesia.

Furthermore, several studies have demonstrated that nonpharmacological pain management can reduce the necessity for epidural analgesia [37] and that epidural analgesia is directly associated with an increased risk of intrapartum fever [34,35]. In light of this, we introduce a novel outcome indicator in this study: the NPI. Compared with the VAS, a subjective evaluation metric for assessing analgesic efficacy, the NPI provides an objective measure to evaluate how nonpharmacological pain management affects the use of epidural analgesia and the incidence of intrapartum fever. This study seeks to evaluate the effectiveness of TCM-based nonpharmacological pain relief methods in delaying and reducing the duration of epidural analgesia, thereby potentially lowering maternal fever rates and improving the quality of labor management.

We have also found that previous studies primarily focused on the effects of nonpharmacological pain relief measures during labor on quantitative health outcomes [19]. In contrast, the perceptions and experiences of women receiving labor pain management have been less thoroughly explored. This study aims to incorporate a mixed methods approach, supplementing the quantitative findings with experiential feedback from various stakeholders. This approach allows for a more comprehensive understanding of the effectiveness of TENS and acupoint stimulation in women undergoing a trial of labor.

Limitations

However, the study has certain design limitations. First, participants are recruited from a single midwifery institution in Shanghai, which is a tertiary, university-affiliated women's hospital. Consequently, factors such as geographical location and the level of medical and nursing care may limit the generalizability of our findings to the broader population. Future large-scale multicenter clinical studies will be necessary to further validate the effectiveness of acupoint stimulation and TENS technology for labor pain management in pregnant women from diverse regions and cultural backgrounds. In addition, labor pain intensity in this study was quantified using the VAS score, which carries inherent subjectivity. Finally, participants included in this study are low-risk pregnant women; thus, the applicability of TCM-based nonpharmacological pain relief methods for high-risk women undergoing a trial of labor remains to be further explored and validated.

Future Directions

This study aims to provide robust evidence supporting the integration of TCM-based nonpharmacological pain relief techniques into routine maternity care. Future research should explore the feasibility of implementing these methods across various health care settings, including community hospitals and primary care centers. Furthermore, additional studies should assess the long-term effects of these pain relief techniques on maternal and neonatal outcomes, as well as their cost-effectiveness. It will also be essential to explore their applicability in high-risk pregnancies and diverse cultural contexts to inform the development of universal guidelines.

Conclusion

This study protocol details the interventions of acupoint stimulation and TENS for women undergoing a trial of labor. The main objective of this SWCRCT is to determine the effects of acupoint stimulation combined with TENS in reducing labor pain, enhancing women's childbirth experiences, and improving maternal-fetal health outcomes. In this study, we introduce a novel outcome indicator termed the nonpharmacological to pharmacological pain management interval (NPI), which monitors whether the application of nonpharmacological pain relief measures can delay or prevent the use of epidural analgesia. In addition, the integration of qualitative and quantitative methods will enrich the research on TENS and acupoint stimulation technology within the realm of nonpharmacological labor pain relief, providing high-quality evidence for the future establishment of industry standards and guidelines.

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Data Availability

The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

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Authors' Contributions

YG, CG, and XW contributed to the study design and literature search. CZ, HM, JZ, LM, HG, and HS implemented the plan. YG and XW wrote the first draft of the manuscript. CG and XZ revised this manuscript. All authors have read and approved the final draft.

Conflicts of Interest

None declared.

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Abbreviations

CEQ: childbirth experience questionnaire
DE: design effect
ICC: intraclass correlation coefficient
ITT: intention-to-treat
LDU: labor and delivery unit
NPI: nonpharmacological to pharmacological pain management interval
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SWCRCT: stepped wedge cluster randomized controlled trial

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TCM: traditional Chinese medicine
TENS: transcutaneous electrical nerve stimulation
VAS: visual analog scale

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Protocol

Impact of Virtual Care With Remote Automated Monitoring on the Rate of Acute Hospital Care Post Discharge and Index Length of Hospital Stay: Protocol for the Post Discharge After Surgery Virtual Care With Remote Automated Monitoring Technology 3 (PVC-RAM-3) Trial

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Abstract

Background: A substantial proportion of patients require acute hospital care after hospital discharge post surgery, and many regions and countries have surgical backlogs.

Objective: The Post Discharge After Surgery Virtual Care with Remote Automated Monitoring Technology-3 (PCV-RAM-3) trial tests the hypothesis that informing surgeons and patients of virtual care with remote automated monitoring (VC-RAM) assignment will promote earlier discharge, thereby reducing the index length of hospital stay, and that postdischarge VC-RAM will reduce acute hospital care.

Methods: The PVC-RAM-3 trial is a randomized controlled trial that compares VC-RAM to standard postdischarge care among 2500 adults undergoing elective noncardiac surgery in 3 Canadian hospitals. Following the randomization of patients prior to surgery, surgeons and patients are immediately notified whether the patient has been allocated to the VC-RAM or control group. Outcome adjudicators remain blinded to each participant's group assignment. Patients in the intervention arm learn to use a Health Canada–approved cellular modem–enabled tablet computer and Bluetooth-enabled remote automated monitoring technology from Cloud DX to take daily wound photos for 7 days and measure daily vital signs (ie, blood pressure, heart rate, oxygen saturation, temperature, and weight) three times daily on days 1-7 and twice daily on days 8-14 post discharge, along with completing a brief recovery survey. Nurses review these data and conduct scheduled virtual visits (days 1, 3, 7, and 14). Nurses

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will escalate care to a preassigned and available perioperative care physician if predetermined vital sign thresholds are exceeded, concerning symptoms arise, or a medication error is detected. These physicians manage the issues and add or modify treatments as needed. The standard care group will receive postdischarge care as per the standard of care at the hospital where they undergo surgery. The coprimary outcomes are acute hospital care and the index hospital length of stay within the first 30 days after randomization.

Results: Study recruitment and follow-up are completed, and analysis of the study results is underway.

Conclusions: This trial will offer insights into the role of VC-RAM in reducing acute hospital care and index length of hospital stay among adults undergoing elective surgery.

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KEYWORDS

elective surgery; virtual care; remote automated monitoring; index length of stay; acute hospital care; randomized controlled trial

Introduction

Each year, more than 100 million adults (including >500,000 Canadians) aged 45 years and older undergo major surgery; of these, 29% develop prognostically important complications, 7.5% require hospital readmission, and >1.5% die within 30 days [1,2]. A Canadian Institutes of Health Information study analyzing 2.1 million acute hospitalizations found that surgical patients (both inpatient and same-day procedures) accounted for 31% of cases. Among the surgical cases, 7% had an unplanned 30-day readmission (costing CAD $9700 [US $6985.70] per readmission), and 19% returned to the emergency department within 30 days [3]. Overall, 20%-25% of adults discharged after elective surgery require acute hospital care within 30 days. With rising surgical volumes outpacing the growth of hospital bed capacity, surgical backlogs continue to grow [4,5]. Addressing these challenges requires innovative strategies to both shorten hospital length of stay (LOS) and reduce readmissions after surgery.

Virtual care with remote automated monitoring (VC-RAM) has emerged as a promising approach to improve postsurgical transitions to the home [6,7]. Virtual care encompasses all the ways that health care providers remotely interact (eg, telephone and tablet computer) with their patients. Remote automated monitoring (RAM) refers to the use of technology to remotely obtain data regarding patients' biophysical parameters (eg, blood pressure) [6].

In our previous Post Discharge After Surgery Virtual Care with Remote Automated Monitoring Technology-1 (PVC-RAM-1) trial, 905 patients who had undergone nonelective surgery were randomized to VC-RAM for 30 days or standard care [8]. Patients in the experimental group used a cellular-enabled tablet and RAM technology that collected biophysical data, took wound photographs, and engaged in scheduled, and when needed, unscheduled virtual visits with nurses and physicians. There were threshold-based alerts that immediately triggered nurse-physician interventions to ensure the timely detection and management of abnormalities. We found a signal for the reduction in acute-hospital care (22% in the virtual care group vs 27.3% in the standard-care group; relative risk 0.80, 95% CI 0.64-1.01), brief acute hospital care (13.7% vs 18.1%; relative risk 0.75, 95% CI 0.56-1.02), hospital readmission (9.5% vs 12.8%; relative risk 0.77, 95% CI 0.53-1.11), and emergency department visits (19.7% vs 24.4%; relative risk 0.81, 95% CI 0.64-1.04) [8].

It is only credible to expect VC-RAM to impact outcomes if identified problems lead to a change in management. In PVC-RAM-1, centers could adjust the threshold parameters for care escalation. Post hoc analyses demonstrated that in the centers with the highest escalations of care (ie, centers where nurses identified, and physicians rapidly addressed abnormalities based on adherence to the predetermined vital sign thresholds), substantial absolute reductions in these outcomes were realized: acute-hospital care 14.1% (95% CI 5.2-23.0); brief acute-hospital care 11% (95% CI 3.6-18.4); and emergency department visits 14.2% (95% CI 5.4-23.0). However, these findings were post hoc and hypothesis-generating, requiring confirmation through an adequately powered trial. Additionally, the impact of advanced knowledge that a patient will receive VC-RAM on discharge timing and subsequent outcomes remains unclear.

The use of VC-RAM for patients discharged home after surgery can help identify and manage early postoperative complications. We hypothesize that this approach will reduce the need for acute hospital care, which includes hospital readmissions or emergency department visits after discharge. Additionally, we believe that if surgeons and patients know that postdischarge virtual care and RAM are available, they may be more inclined to opt for earlier discharges, potentially decreasing the length of the index hospital stay. To test these hypotheses, we are evaluating the impact of our VC-RAM intervention compared to standard postdischarge care on two coprimary outcomes: the rate of acute hospital care postdischarge and the index length of hospital stay.

By evaluating both acute hospital care and index LOS, this trial aims to build on lessons from PVC-RAM-1, extending to elective surgeries and providing evidence on integrating VC-RAM into routine postsurgical care. The goal is to optimize safe discharge and patient outcomes while addressing significant systemic challenges like bed capacity and surgical backlogs.

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Methods

Design and Setting

The Post Discharge After Surgery Virtual Care with Remote Automated Monitoring Technology-3 (PVC-RAM-3) trial is a multicenter, parallel-group superiority randomized controlled trial involving 2500 patients undergoing elective noncardiac surgery at 3 Canadian hospitals: Hamilton General Hospital, Juravinski Hospital and Cancer Center, and St. Joseph's Healthcare Hamilton. The trial evaluates the effects of VC-RAM compared to standard care post discharge. A study flow diagram is provided in Figure 1, and the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist is provided in Multimedia Appendix 1.

Figure 1. Trial flow diagram. RAM: remote automated monitoring.

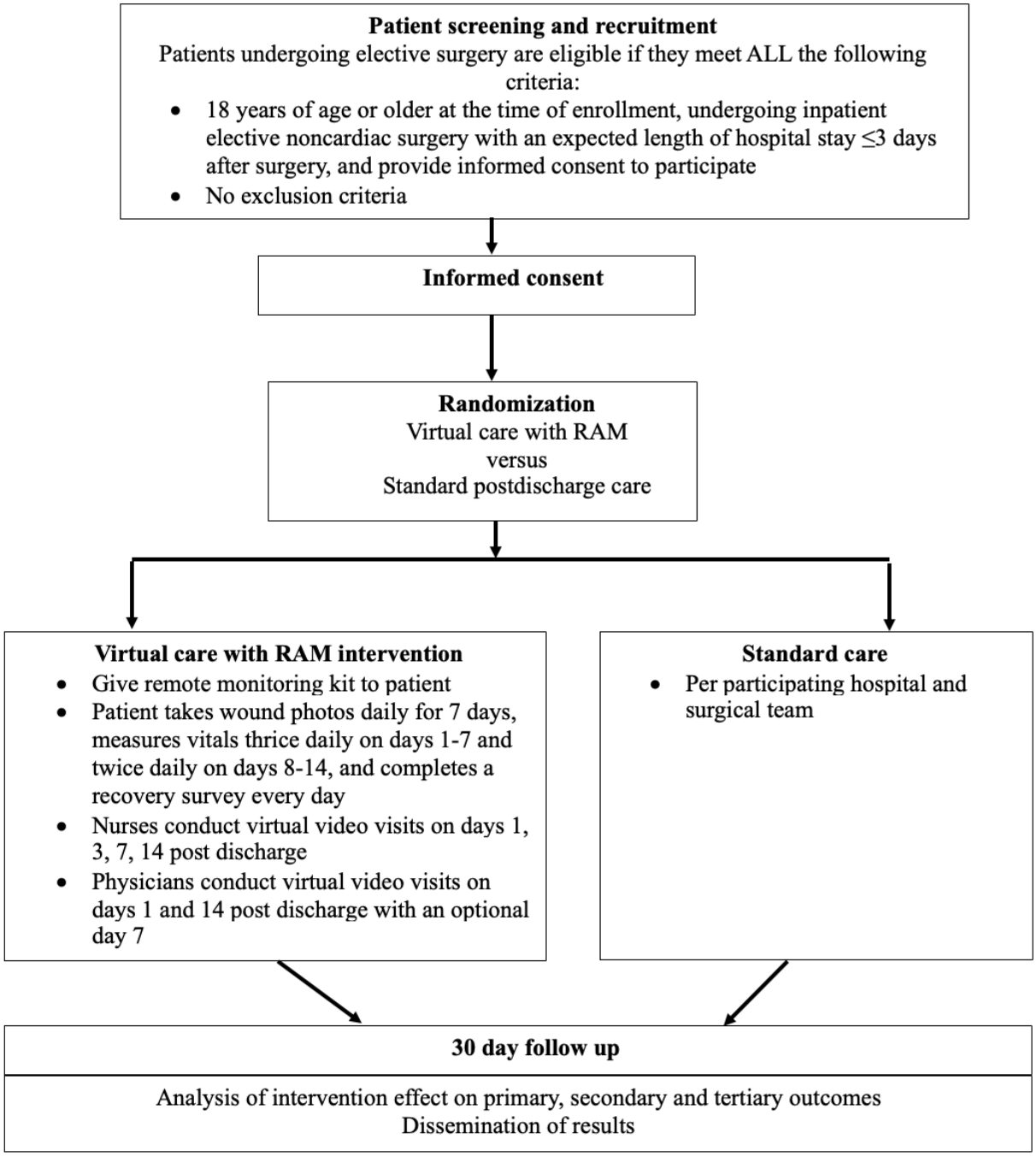

Trial Population

Patients included in the trial are 18 years of age or older, undergoing inpatient elective noncardiac surgery with an expected hospital stay of ≤3 days after surgery, and provide informed consent. Exclusion criteria include the inability to communicate with research staff, complete study surveys, or undertake an interview using a tablet computer due to a language barrier or a cognitive, visual, or hearing impairment. Patients residing in areas without cellular network coverage are also excluded.

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Patient Recruitment

Study personnel use efficient recruitment strategies we previously developed in our perioperative trials, including identifying eligible patients through daily screening of surgical lists [8-10]. Surgeons with appropriate surgical populations (ie, surgeries with an anticipated LOS of 3 or fewer days) are contacted prior to any recruitment of their patients and asked to confirm their willingness to have their patients participate. Research personnel approach eligible patients during the preoperative period to obtain written informed consent (Multimedia Appendix 2).

Randomization

Randomization occurs before surgery, after eligibility is confirmed, and informed consent is obtained. We randomize as close to the time of surgery as possible to minimize the risk of surgery postponement. Patients are randomized using an Interactive Web Randomization System, a 24-hour computerized system maintained by the coordinating center at the Population Health Research Institute, a joint institute of Hamilton Health Sciences and McMaster University in Hamilton, Ontario, Canada.

The randomization process uses block randomization with varying block sizes stratified by site, ensuring that study personnel and investigators remain unaware of block sizes. Patients are randomized in a 1:1 ratio to receive VC-RAM or standard care. Following randomization, research personnel notify the patient's surgeon and the patient of the treatment allocation. Patients, health care providers, and data collectors are aware of treatment assignments, while outcome adjudicators remain blinded to treatment allocation.

Trial Interventions

Patients are randomized to receive VC-RAM or standard care. Participating surgeons receive information on the trial protocol, objectives, and intervention model through rounds, in-service education, and discussions with trial researchers. This ensures that early discharge decisions for their patients are guided by their clinical judgment and understanding of the intervention care model (ie, when patients are assigned to the VC-RAM group, the patient will go home with VC-RAM to facilitate virtual care and vital sign monitoring).

The Cloud DX tablet is equipped with a camera and Bluetooth-enabled, Health Canada–licensed RAM technology (Figure 2). The Cloud DX Connected Health mobile app, hosted on the tablet, serves as the primary interface for the virtual care intervention and complies with the Personal Information Protection and Electronic Documents Act and the Personal Health Information Protection Act. This system has undergone extensive validation and user testing and was used in our previous PVC-RAM-1 trial [8,11]. The intervention begins the day after discharge and lasts 14 days or until 30 days post randomization, whichever comes first. The 14-day time frame is based on a period where major perioperative complications occur, and from our previous PVC-RAM-1 trial findings, where we determined that 30 days of monitoring often exceeds the needs of most patients [1,2,8]. Nurses establish contact and set up the system with patients as soon as possible after discharge, ensuring patients know how to seek help if they experience symptoms or issues arise.

Figure 2. Cloud DX Connected Health kit. Cloud DX Connected Health kit, including Bluetooth-enabled Pulsewave wrist cuff blood pressure monitor, body weight scale, wireless oximeter, and temperature probe, paired with an Android health tablet. Reproduced with permission from Cloud DX.

Research staff teach patients (with family members participating where possible) in the VC-RAM group to use the automated Bluetooth-enabled monitoring devices paired with a preprogrammed, cellular modem–enabled tablet computer to measure their biophysical parameters, including blood pressure, heart rate, oxygen saturation, and temperature, three times daily on days 1-7 and twice daily on days 8-14. They measure their weight daily. They also complete a recovery survey developed for the trial, consisting of questions related to infection, bleeding, pain, dehydration, and cardiovascular and respiratory complications, daily. Patients photograph their wounds daily for the first 7 days unless otherwise directed. The biophysical

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parameters automatically upload via Bluetooth to the tablet, except for temperature, which is entered manually. These results are immediately wirelessly forwarded to the VC nursing team, and nurses actively review these results daily. If nurses do not receive a patient's measurements, they will contact the patient at the earliest opportunity to understand the reasons behind the missing data. These vital signs, recovery surveys, and wound photos are parameters typically monitored in the hospital or during clinic visits, which we are now extending into the home setting.

Nurses conduct scheduled video visits on days 1, 3, 7, and 14 to assess symptoms, review wound photographs, reinforce recovery principles, and assess pain. They perform medication reconciliation on days 1, 7, and 14. Unscheduled video visits are arranged if biophysical measurements or survey responses exceed thresholds or if other health concerns are identified. Nurses escalate care to a preassigned physician when necessary, such as when RAM measurements exceed predetermined thresholds (examples in Multimedia Appendix 3), patients report specific symptoms (eg, shortness of breath), drug errors are identified, or concerns arise that require physician intervention. Physicians adjust treatments, order outpatient laboratory and diagnostic testing, liaise with surgeons, patients' family physicians, or other health care providers, and arrange in-person clinic care when required.

Perioperative physicians hold scheduled video visits with patients on days 1 and 14 to assess patients, ensure proper medication use (by reviewing medication indications and proper dosing), and address medical needs. For patients who have a history of atherosclerotic disease, or are current smokers, an additional video call occurs on day 7 to optimize cardiovascular secondary prevention and smoking cessation therapy by ensuring that where indicated, patients were receiving secondary prevention medications (aspirin, statin, angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers) and smoking cessation medications, respectively. These mechanisms ensure patients have 24/7 access to virtual nurses or physicians for urgent issues via secure video (Multimedia Appendix 4).

In both groups, discharge occurs when the most responsible surgeon deems it fit to discharge the patient. In the standard care group, patients receive postdischarge management according to the standard of care at the hospital where they underwent surgery. No changes to surgeons' standard of care regarding postdischarge management occur for patients randomized to either group as a result of the trial. In Canada, standard postsurgery care typically involves follow-up with a health care provider within 30 days of discharge. Before this appointment, patients are responsible for contacting their surgeon or family physician with any concerns.

Trial Outcomes

The PVC-RAM-1 trial provided encouraging data that virtual care with RAM may reduce acute hospital care [8]. In PVC-RAM-3, we wanted to inform the impact on acute hospital care and the index length of hospital stay. Initial sample size calculation assumptions suggested index length of hospital stay would require a larger sample size than acute hospital care. To avoid being underpowered by these outcomes, we made the index length of hospital stay the primary outcome. At the time of the final interim analysis, blinded overall data on the LOS and acute hospital care indicated there was adequate power to split the α and evaluate two coprimary outcomes (ie, acute hospital care and length of hospital stay). Consequently, we revised the primary outcome to include both index LOS and postdischarge acute hospital care as coprimary outcomes, making this change without any knowledge of the trial results.

The primary objective of this trial is to determine whether VC-RAM, compared with standard care after elective surgery, and informing surgeons and patients of VC-RAM allocation, reduces the occurrence of the coprimary outcomes within 30 days of randomization. The first coprimary outcome is postdischarge acute hospital care (defined as hospital readmission or emergency department visit) within 30 days after randomization. The second coprimary outcome is index hospital LOS (ie, time from the end of surgery to index hospital discharge).

Secondary outcomes during the first 30 days after randomization include (1) hospital readmission; (2) emergency department visit; (3) medication error detection; (4) medication error correction; (5) surgical site infection; (6) days in hospital; (7) pain of any severity, and moderate to severe pain assessed at 15 and 30 days after randomization; (8) proportion of patients with the atherosclerotic disease taking classes of efficacious medications at 30 days, (ie, an antiplatelet or anticoagulant drug, an angiotensin-converting enzyme inhibitor or angiotensin-receptor blocker, and a statin); and (9) the proportion of active smokers before surgery receiving pharmacological smoking cessation interventions at 30 days after randomization. Outcome definitions are presented in Multimedia Appendix 5.

Tertiary outcomes include (1) infection; (2) reoperation; (3) composite of myocardial infarction, acute heart failure, and arrhythmia that results in acute hospital care; (4) death; (5) health-related quality of life; and (6) health services usage–related costs.

We hypothesize that VC-RAM will reduce all primary, secondary, and tertiary outcomes, except for identifying more medication errors in the intervention group compared to the standard care group, which would reflect improved care through increased detection.

Follow-Up

The day of randomization is day 1 of the trial, and all patients undergo 30 days of follow-up. Study personnel contact patients on day 30 to collect data on acute hospital care, secondary and tertiary outcomes, medication error detection and corrections, and current medications. The EQ-5D-5L is administered at baseline and day 30, and the Brief Pain Inventory-Short Form is administered on days 15 and 30. In the virtual care group, virtual nurses collect data on medication error detection and corrections throughout the intervention period.

If a patient reports an event, study personnel obtain source documentation from hospital or family physician records. If patients cannot be contacted directly, study personnel reach out to a designated relative, friend, or primary care physician. Study

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personnel and virtual nurses record all data in case report forms that are then entered into an electronic data capture system (Trial Master).

Sample Size Calculations

Postdischarge acute hospital care and index hospital LOS are coprimary outcomes with a shared α. We allocate α=.04 for acute hospital care and α=.01 for index hospital LOS (details in Multimedia Appendix 6).

Table 1 presents the trial power for acute hospital care based on a log-rank test with a 2-sided α of .04 using SAS software (version 9.4; SAS Institute Inc). Assuming a 14% event rate in the control group, with an overall sample of size 2500 participants (1250 in the control group and 1250 in the treatment group), we will achieve 88.7% power to detect a relative risk reduction of at least 0.70 (30% relative risk reduction). Table 2 presents the trial power for index LOS based on a 2-sample Wilcoxon test assuming equal variance with a 2-sided α of .01. We expect patients in the standard care group to have a mean index hospital LOS of 2.5 days. If the knowledge that patients in the intervention group will receive virtual care with RAM after hospital discharge results in 35% of patients having their index hospital LOS reduced by 1 day, we will require a sample size of 2500 to have more than 80% power to detect this difference, with a 2-sided α of .01.

Table 1. Power to detect an RR[a] (0.65, or 0.70, or 0.75) based on log-rank test with a 2-sided α of .04 assuming control group event rates 12%, 14%, 16%, and 18% for a given total sample of size 2500, 2800, 3000, or 3200.

Sample size per group	RR 0.65 (35% reduction)			RR 0.70 (30% reduction)			RR 0.75 (25% reduction)		
	Assumed control event rate (%)	Treatment P (%)	Power (%)	Assumed control event rate (%)	Treatment P (%)	Power (%)	Assumed control event rate (%)	Treatment P (%)	Power (%)
2500	12	7.8	__[b]	12	8.4	—	12	9	—
1250	—	—	93.3	—	—	82.5	—	—	65.5
1400	—	—	95.6	—	—	86.7	—	—	70.6
1500	—	—	96.7	—	—	89.0	—	—	73.7
1600	—	—	97.6	—	—	90.1	—	—	76.5
2800	14	9.1	—	14	9.8	—	14	10.5	—
1250	—	—	96.6	—	—	88.7	—	—	73.4
1400	—	—	98	—	—	92	—	—	78.3
1500	—	—	98.6	—	—	93.6	—	—	81.1
1600	—	—	99	—	—	95	—	—	83.6
3000	16	10.4	—	16	11.2	—	16	12	—
1250	—	—	98.4	—	—	93	—	—	80
1400	—	—	99.1	—	—	95.4	—	—	84.4
1500	—	—	99.4	—	—	96.5	—	—	86.8
1600	—	—	99.6	—	—	97.4	—	—	88.9
3200	18	11.7	—	18	12.6	—	18	13.5	—
1250	—	—	99.3	—	—	95.8	—	—	85.3
1400	—	—	99.7	—	—	97.4	—	—	89.1
1500	—	—	99.8	—	—	98.2	—	—	91.1
1600	—	—	99.9	—	—	98.7	—	—	92.8

[a]RR: relative risk.

[b]Not applicable.

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Table 2. Power calculation based on 2-sample Wilcoxon tests assuming equal variance in LOSa with a 2-sided α of .01.

Standard care group expected index hospital LOS (days)	Intervention group expected impact on index hospital LOS	Sample size, n		
		80% power	85% power	90% power
3	40% of patients have their LOS reduced by 1.5 days	1078	1216	1400
3	35% of patients have their LOS reduced by 1.5 days	1450	1634	1882
3	30% of patients have their LOS reduced by 1.5 days	2030	2288	2634
3	40% of patients have their LOS reduced by 1.0 days	2618	2950	3396
3	35% of patients have their LOS reduced by 1.0 days	3482	3924	4518
3	30% of patients have their LOS reduced by 1.0 days	4826	5438	6260
2.5	40% of patients have their LOS reduced by 1.5 days	714	806	928
2.5	35% of patients have their LOS reduced by 1.5 days	968	1090	1256
2.5	30% of patients have their LOS reduced by 1.5 days	1362	1536	1768
2.5	40% of patients have their LOS reduced by 1.0 days	1764	1988	2290
2.5	35% of patients have their LOS reduced by 1.0 days	2356	2656	3058
2.5	30% of patients have their LOS reduced by 1.0 days	3280	3696	4254
2	40% of patients have their LOS reduced by 1.5 days	424	478	552
2	35% of patients have their LOS reduced by 1.5 days	582	656	754
2	30% of patients have their LOS reduced by 1.5 days	828	932	1074
2	40% of patients have their LOS reduced by 1.0 days	1078	1216	1400
2	35% of patients have their LOS reduced by 1.0 days	1450	1634	1882
2	30% of patients have their LOS reduced by 1.0 days	2030	2288	2634

[a]LOS: length of stay.

Statistical Analyses

We will analyze all data according to a prespecified statistical analysis plan developed and finalized before any investigator is unblinded.

Following the intention-to-treat principle, we will analyze patients in the treatment groups to which they were randomized. For both coprimary outcomes, we will compare all patients allocated to the PVC-RAM-3 intervention to all patients allocated to standard care.

For coprimary 1 (composite of hospital readmission or emergency department visit), we will compute the time to event from the discharge date and plot the cumulative incidence curves between the two treatment groups. We will use a Cox regression model to obtain hazard ratios and 95% CIs. Any acute hospital care event that occurs before patients undergo their index surgery, in cases where surgery is postponed, will not be included in this outcome.

For coprimary 2 (index hospital LOS), we will calculate the hospital LOS for both groups and compare them with a 2-sample Wilcoxon rank sum test. Given the large sample size, the 2-sample Wilcoxon rank sum test will produce results that will be similar to the 2-sample *t* test.

For the coprimary outcome analyses, we will censor patients whose surgeries were canceled and not rescheduled within 30 days of randomization.

VC-RAM will be considered effective if either of the 2 coprimary efficacy analyses is significant. We will use a gatekeeping with a fallback procedure to analyze their statistical significance [12]. We will start with an overall α of .05, split between the two outcomes with a computed 2-sided *P* value less than an α of .04 for postdischarge acute hospital care and less than an α of .01 for index length of hospital stay. If the first coprimary outcome achieves significance at an α level of <.04, the α from this test will be added to the second coprimary outcome's α (ie, the α will be .05). However, if the first coprimary outcome is not significant, the second coprimary outcome will be tested at an α level of <.01.

For secondary and tertiary outcomes, we will use the chi-square test for binary or categorical variables and the 2-sample *t* test for continuous variables. We will assess the effect of VC-RAM using log-binomial regression models and report the corresponding relative risks and 95% CIs. For continuous outcomes, we will evaluate the intervention effect using analysis of covariance regression models to obtain effect estimates and their 95% CIs. Depending on the frequency of time-to-event outcomes, we may use the log-rank test to assess differences between groups. The α level for all secondary and tertiary outcomes will be set at .05. For the secondary and tertiary outcomes, we will not adjust for multiple testing as we will be evaluating the consistency of effect, number of outcomes, and size of the effect to offer insights into the reliability of any statistically positive secondary or tertiary outcomes. Economic

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analysis (Multimedia Appendix 7) will be done in a separate protocol and publication.

Subgroup Analyses

We will analyze subgroups based on weekdays of randomization: Mondays and Tuesdays versus Wednesdays, Thursdays, and Fridays. We hypothesize that the treatment effect will be less among patients randomized mid to late week as they may have longer stay because their postsurgical recovery is more likely to overlap with weekends where there may be operational delays in discharge, such as the absence of physiotherapists, that cannot be influenced by knowledge of VC-RAM allocation. To examine this, we will include interaction terms between group assignment and weekday randomization into the Cox regression model, with significant interaction inferred at a P value of <.05.

Interim Analyses

Two interim efficacy analyses based on the primary outcome occurred when 50% and 75% of the patients had been followed for 30 days. The data monitoring committee (DMC) used the modified Haybittle-Peto rule of 4 SDs (α=.0000633) for analyses in the first half of the trial (including the first planned interim analysis) and 3.5 SDs (α=.0004653) for all analyses in the second half. For a finding of the treatment to be considered significant, these predefined boundaries had to have been exceeded in at least two consecutive analyses, 2 or more weeks apart. The interim analyses were conducted under protocol version 1.0 dated December 22, 2021, and therefore, did not take into consideration the changes made to the primary outcome in protocol version 2.0 dated January 25, 2025.

Ethical Considerations

This trial is conducted in compliance with the protocol, the principles outlined in the Declaration of Helsinki, and Good Clinical Practice. The Hamilton Integrated Research Ethics Board provided its approval for the protocol and consent form (project ID 14365) before initiating the study. Research personnel obtain informed consent for each patient before randomization. All patient information is stored in a high-security computer system and kept strictly confidential. Participant confidentiality is further ensured by using identification code numbers to correspond with treatment data in computerized files. Medical information obtained during the trial is considered confidential and is not disclosed to third parties. However, this information may be shared with the patient's personal physician or other appropriate medical personnel responsible for the patient's care.

Trial Organization

The Population Health Research Institute is the sponsor and coordinating center for this trial, overseeing trial organization, randomization scheme development, study database creation, data consistency checks, data analysis, and study center coordination. The trial structure includes a project office, operations committee, steering committee, DMC, site principal investigators, coinvestigators, and adjudication committee. The coprincipal investigators, project officers, program manager, and research coordinator are responsible for the activities of the Project Office. If safety concerns arise during the trial, the DMC Chair convenes a formal committee meeting. The DMC reviews all available data and relevant external studies before making recommendations to the Project Office Operations Committee. If termination is considered, the committee explores all alternatives before a decision is made. A detailed charter governs the DMC's activities. Details about trial groups and investigators are provided in Multimedia Appendix 8.

Results

The first patient was randomized on December 29, 2021, and recruitment of the target 2500 patients was completed on October 25, 2024. The DMC conducted the first and second scheduled interim analyses and recommended continuing the trial. The final version of the study protocol was submitted prior to the unblinding of the trial investigators. Some protocol amendments were implemented during the trial, with the most recent version finalized near the end of the study period. This paper is based on the most recent version of the study protocol (version 2.0, January 1, 2025). The data will be analyzed, and the study results will be published in a separate paper.

Discussion

Overview

Reducing postdischarge acute hospital care and index length of hospital stay remains a critical unmet need for surgical patients. We hypothesize that VC-RAM holds significant potential to address these challenges by lowering the incidence of these key outcomes. Building on the lessons learned from the PVC-RAM-1 trial, which established a scalable and effective model for VC-RAM, the PVC-RAM-3 trial adapts the intervention for elective surgical populations and examines how presurgical knowledge of VC-RAM allocation influences discharge decisions.

Throughout the last decade, there have been substantial changes in the duration of hospital admission for some surgical interventions. The relationship between the length of hospital stays and readmission rates is unclear, as some research indicates that shorter hospital stays are associated with higher readmission rates, while other studies suggest that longer stays may lead to more readmissions [2,13]. To the extent that shorter hospital stays may result in the need for more acute hospital care post discharge, this identifies a greater need for interventions to decrease acute hospital care post discharge, an objective that our VC-RAM intervention seeks to address. Our inclusion of patients undergoing elective surgery with an expected LOS of ≤3 days in this trial focus on a lower-risk population, where hospital discharge is less likely to be delayed by competing comorbidities. This targeted approach allows for a meaningful evaluation of VC-RAM's ability to safely shorten hospital stays and optimize postdischarge care. Previous evidence has not identified significant safety risks associated with VC-RAM [8], supporting its feasibility for broader implementation.

With our VC-RAM intervention, when escalation triggers are met, nurses promptly escalate care to the perioperative physicians. These physicians can then take several actions depending on the patient's needs, including continuing remote

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monitoring, conducting a video visit, referring the patient to an outpatient diagnostic facility, initiating or altering medications, or arranging follow-ups with themselves or nonstudy doctors, such as the surgeon or family physician. These measures are designed to manage complications within the community or through virtual care, thereby reducing the necessity for acute hospital visits.

PVC-RAM-3 trial is powered to detect a 30% relative risk reduction in acute hospital care and a 1-day reduction in index LOS in at least 35% of patients. With estimated baseline rates of 20%-25% for acute hospital care and an average hospital stay of 2.5 days [7], a 30% reduction could prevent 6-7.5 acute care visits per 100 patients. Postpandemic elective surgery volumes for those meeting PVC-RAM-3 inclusion criteria is approximately 4500 surgeries per year. If we reduce the LOS by a day for 30% of these elective surgeries, we could free up hospital beds and increase surgical volume by an additional 1350 cases per year to address surgical backlogs. This has the potential to generate substantial cost savings for the health care system.

Our previous trial demonstrated the potential of VC-RAM to improve other patient-important outcomes, such as the identification and correction of drug errors, pain management, and the medical optimization of patients, including those with atherosclerotic disease, for whom proven secondary prevention therapies exist, and those who smoke tobacco [8]. However, significant opportunities remain to further optimize pharmacological therapy to enhance long-term health outcomes, and these are evaluated in PVC-RAM-3.

Strengths and Limitations

This is a large randomized controlled trial that evaluates the impact of knowledge of assignment to receive VC-RAM on index LOS and VC-RAM on postdischarge acute hospital care. The intervention builds on our prior VC-RAM studies and is optimized for efficiency by shortening the intervention period from 30 to 14 days, reducing wound photo duration to 7 days, and strictly enforcing vital signs' escalation thresholds across all centers. A potential limitation of this study is the burden of frequent monitoring and patient contacts, as well as the possibility that the resources required to deliver the intervention may offset in-hospital cost savings in settings outside our health system, thereby limiting generalizability. However, a separate economic evaluation is planned to address this issue.

Dissemination

We will disseminate findings through presentations at national and international conferences, publications in high-impact peer-reviewed journals, and posts on the “Reducing Global Perioperative Risk” Resource Center, a global multimedia platform linked to Elsevier’s online readership.

Conclusions

The results of the PVC-RAM-3 trial will provide critical insights into the role of VC-RAM in addressing current health system pressures and enhancing perioperative care globally.

Acknowledgments

This trial was funded by the VIrtual Care and remote auTomated monitoring TechnOlogy Research (VICTOR) Program at the Population Health Research Institute and Hamilton Health Sciences. The funder had no role in the collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

Data Availability

The Population Health Research Institute (PHRI) believes the dissemination of clinical research results is vital, and the sharing of data is important. The datasets generated during this study are not publicly available because PHRI prioritizes access to data analyses to researchers who have worked on the trial for a significant duration, have played substantial roles, and have participated in raising the funds to conduct the trial. PHRI balances the length of the research study and the intellectual and financial investments that made it possible with the need to allow wider access to the data collected. Data will be disclosed only upon request and approval of the proposed use of the data by a review committee. Data requests from other non–PVC-RAM-3 (Post Discharge After Surgery Virtual Care with Remote Automated Monitoring Technology-3) investigators will not be considered until 5 years after the close of the trial. All data requests should be made to the corresponding author.

Authors' Contributions

All authors planned the conceptualization and design of the study and the protocol. All authors contributed to critical revisions of the manuscript and approved the final version to be published. All authors agreed to be accountable for all aspects of this work.

Conflicts of Interest

MHM undertook training sessions for study nurses with CloudDX regarding how to use their technology. Outside of this work, he has received patient monitors from Philips Healthcare. MKW is supported by the CIHR Canada Graduate Scholarships Doctoral Research Award. DC reports grants from CIHR, speaker fees from Servier, and consulting fees from Trimedics, all outside of this work. DMT is a Stryker consultant but is not relevant to this study. All the other authors declare no competing interests. No investigator has a financial relationship with CloudDX. The devices in the Connected Health kit used in the PVC-RAM-3 trial are licensed and approved for use by Health Canada, independent of any involvement from the investigators or Population Health

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Research Institute. Based on the fee for service, participating sites engaged Cloud Diagnostics Canada for trial devices, patient management software, data plans, participant onboarding to the system, and technical support. In addition, Cloud Diagnostics Canada provided training sessions for virtual nurses, perioperative physicians, and surgeons on how to use their technology. Cloud Diagnostics Canada did not fund the trial and was not directly involved in protocol development, trial management, or data analyses.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 88 KB - resprot_v14i1e72672_app1.pdf]

Multimedia Appendix 2
Consent form.
[DOCX File , 30 KB - resprot_v14i1e72672_app2.docx]

Multimedia Appendix 3
Example of vital sign thresholds and recommend nurse and physician actions.
[DOCX File , 23 KB - resprot_v14i1e72672_app3.docx]

Multimedia Appendix 4
Additional details on nurse and physician actions.
[DOCX File , 14 KB - resprot_v14i1e72672_app4.docx]

Multimedia Appendix 5
Outcome Definitions.
[DOCX File , 22 KB - resprot_v14i1e72672_app5.docx]

Multimedia Appendix 6
Sample size.
[DOCX File , 15 KB - resprot_v14i1e72672_app6.docx]

Multimedia Appendix 7
Economic Analysis.
[DOCX File , 14 KB - resprot_v14i1e72672_app7.docx]

Multimedia Appendix 8
Trial Groups and Investigators.
[DOCX File , 15 KB - resprot_v14i1e72672_app8.docx]

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Abbreviations

DMC: data monitoring committee
LOS: length of stay
PVC-RAM-1: Post Discharge After Surgery Virtual Care with Remote Automated Monitoring Technology-1
PVC-RAM-3: Post Discharge After Surgery Virtual Care with Remote Automated Monitoring Technology-3
RAM: remote automated monitoring
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
VC-RAM: virtual care with remote automated monitoring

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Protocol

Effectiveness of a Person-Centered and Culturally Sensitive Course of Treatment in Arabic-, Turkish-, and Urdu-Speaking Individuals With Type 2 Diabetes (the ACCT2 Study): Protocol for a Pragmatic Randomized Controlled Trial

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Abstract

Background: Individuals with non-Western backgrounds consistently exhibit a higher risk of type 2 diabetes (T2D) than ethnic Danes. Factors such as health behaviors, limited health care access, and social determinants of health often contribute to this disparity. Culturally sensitive interventions are crucial; however, effective interventions for managing T2D in non-Western populations remain limited.

Objective: This study aims to examine the effect of a 1-year person-centered and culturally sensitive intervention on improving glycemic control (hemoglobin A_{1c} [HbA_{1c}]) in Arabic-, Turkish-, or Urdu-speaking individuals with T2D. The secondary objectives are to improve diabetes management and overall well-being.

Methods: This study is designed as a 2-arm randomized controlled trial. A total of 96 women and men with T2D (HbA_{1c}≥53 mmol/mol) speaking either Arabic, Turkish, or Urdu as their native language will be randomized for 1 year to a health care professional–assisted intervention group (person-centered and culturally sensitive course of treatment) or a control group (usual care) in a 1:1 ratio in Denmark. Assessments are scheduled at baseline and 1 year. The primary outcome is HbA_{1c}, while lipids, blood pressure, and patient-reported outcomes, including well-being, diabetes management, health literacy, and use of and adherence to diabetes medication, are secondary outcomes. Feasibility and satisfaction are evaluated through interviews. The study is approved by the Ethics Committee of the Capital Region of Denmark (H-23042245).

Results: A 5.0-mmol/mol change in HbA_{1c} is the minimally important difference, requiring 88 participants. To allow for uncertainties and dropouts, the total was increased to 96. As of January 2025, a total of 88 participants have been recruited. Recruitment was completed in March 2025. Data collection will continue until December 2025, with the first results expected by March 2026.

Conclusions: This study will contribute to the limited knowledge regarding the effects of person-centered and culturally sensitive treatment approaches for T2D in Arabic-, Turkish-, or Urdu-speaking individuals. The study uses a robust methodological design and will present an alternative avenue for managing T2D and improving overall well-being. The study offers valuable insights

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into the experiences of participants and health care professionals, including potential obstacles and strategies for implementation in outpatient clinics.

Trial Registration: ClinicalTrials.gov NCT06147245; https://clinicaltrials.gov/study/NCT06147245

International Registered Report Identifier (IRRID): DERR1-10.2196/67319

(JMIR Res Protoc 2025;14:e67319) doi:10.2196/67319

KEYWORDS

immigrants; migrants; diabetes management; ethnic minorities; trial; well-being; public health; type 2 diabetes; culturally-sensitive; randomized controlled trial

Introduction

European studies have steadily indicated that immigrant groups born in non-Western countries are at a significantly higher risk of developing type 2 diabetes (T2D) than the majority population [1-3]. In Denmark, immigrants from the Middle East exhibit a T2D incidence rate 2.5 times higher than native Danes [4,5] and face increased risks of complications [2,3,6]. Individuals with non-Danish ethnic backgrounds have poorer glycemic control [7,8], and a lower proportion receive diabetes monitoring and care within recommended intervals outlined in the Danish Diabetes guidelines [7].

Individuals with non-Western backgrounds experience difficulties in managing their diabetes effectively. This is due to factors such as health behavior, access to health care, and social determinants, as well as low health literacy, cultural norms, and language barriers that hinder access to and comprehension of information and treatment of diabetes [4,9-13]. Other factors include misconceptions about diabetes, inadequate adherence to medication regimens, lifestyle factors, limited social support, and lack of cultural competencies among health care professionals (HCPs) [1,13-16]. This emphasizes a need for culturally appropriate interventions to improve access to health care and support, but existing interventions often overlook these cultural considerations [17,18].

Resnicow et al [17] define cultural sensitivity as incorporating cultural characteristics, experiences, norms, values, behavioral patterns, beliefs, and environmental and social forces of a target population to design, deliver, and evaluate interventions. Despite some interventions tailored for cultural minority groups that have shown positive effects on hemoglobin A_{1c} (HbA_{1c}) [19,20], recent research highlights a significant gap in person-centered and culturally sensitive interventions for individuals with T2D. Despite guidelines recommending a person-centered approach, there is a disconnect between theory and practice [21], and current diabetes self-management education and support programs often lack cultural competence and literacy-sensitive recommendations [22-24]. These findings underscore the need for more research on culturally sensitive, person-centered interventions to improve diabetes management and reduce health disparities, particularly in outpatient clinics [25-27]. This study aims to explore the effectiveness of a person-centered, culturally sensitive intervention for individuals with T2D speaking Urdu, Arabic, or Turkish to improve glycemic control, as well as diabetes management, health literacy, and overall well-being by using a pragmatic randomized controlled trial (RCT) design [28,29].

Methods

Objectives

The overall objective of this study is to examine the effect of a 1-year, person-centered and culturally sensitive intervention on alterations in glycemic control (HbA_{1c}) in Arabic-, Turkish-, or Urdu-speaking individuals. Secondary objectives describe changes in cardiometabolic risk factors and patient-reported outcomes, including well-being, diabetes management, health literacy, and adherence to diabetes medication.

Hypotheses

We hypothesize that a 1-year, person-centered and culturally sensitive intervention added to standard care will be superior for reducing HbA_{1c} in Arabic-, Turkish-, or Urdu-speaking individuals with T2D. Superiority will be claimed if the baseline-corrected difference between the 2 groups is equal to or surpasses the minimal important difference (5 mmol/mol) in favor of the intervention group and if the $P<.05$.

Participants

Women and men aged 75 years or younger with T2D whose native language is Urdu, Arabic, or Turkish will be considered eligible based on the specified inclusion and exclusion criteria.

Eligibility Criteria

The inclusion and exclusion criteria are listed in Textbox 1. The eligibility criteria, including the age limit, were carefully selected based on several considerations. The language criteria were chosen to focus on the largest language groups at Steno Diabetes Center Copenhagen (SDCC), as individuals who speak fluent Danish generally face fewer challenges in managing their treatment and T2D compared with those with limited Danish proficiency. Regarding the age limit, participants older than 75 years were excluded as they are typically offered a different, combined approach to care. However, we recognize that older individuals need support, and it is believed that those younger than 75 years have the potential to become more self-sufficient with the right intervention. Therefore, the age limit was set to target those who could most benefit from this specific approach.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Men and women whose native language is Arabic, Turkish, or Urdu with limited to moderate proficiency in Danish.
- Already in treatment at the outpatient type 2 diabetes clinic at Steno Diabetes Center Copenhagen, Denmark.
- Having suboptimal glycemic control (hemoglobin A_{1c} [HbA_{1c}] ≥53 mmol/mol).
- Individual treatment goal for HbA_{1c} has not been achieved (in 2 consecutive measurements).

Exclusion criteria

- Being older than 75 years at inclusion.
- Residing part-time in Denmark.
- Having disabilities that inhibit physical attendance.
- Having severe mental disorders.
- Having an estimated glomerular filtration rate below 30 mL/min/1.73 m^2.
- General condition contraindicates continuing the study, judged by the investigator or medical expert.
- Withdrawal of the informed consent.
- Other reasons determined by the investigator.

Recruitment, Screening, and Consent

We plan to recruit 96 Arabic-, Turkish-, or Urdu-speaking individuals with T2D from the outpatient T2D clinic at SDCC. During the latest visit to the usual course of treatment at SDCC, potential participants will receive a brief introduction to the person-centered and culturally sensitive course of treatment in the type 2 diabetes (ACCT2) study. If interested, potential participants will be met by a project worker who will provide an oral introduction and, if interested, play an audio recording containing study information in Urdu, Arabic, or Turkish, depending on the participant's preference. All study participants will receive written study information in their native language. The information will be given in quiet surroundings at SDCC. The ability to bring one companion is allowed.

The project worker will have a written informed consent ready to sign and be available to address any questions. Participants may have at least 24 hours to consider participation. A participant folder containing the written study information and the written informed consent will be handed to the potential participant, and a project worker will follow up with a phone call within a week. If the participant wishes to take part in the study, the written informed consent must be signed and forwarded to the project worker. By January 16, 2025, a total of 88 out of 96 participants were recruited. The recruitment process will continue until March 2025.

To ensure accessibility, all written information is translated into Urdu, Arabic, or Turkish by international standards [30]. Study participants are informed that they can always withdraw their commitment to participate. The individual participant's right not to know their data will be respected.

Randomization

After obtaining written informed consent, participants will be randomized to either the intervention or control group in a 1:1 ratio using block randomization (Figure 1). Block randomization is used to secure an equal distribution of participants in the 2 groups if the study, for unexpected reasons, should be terminated before inclusion of all participants, and further to account for potential seasonal confounding.

Figure 1. Randomization.

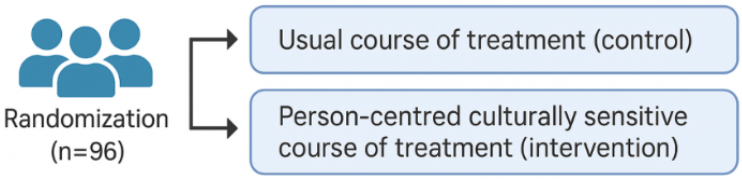

Randomization will be performed by the investigator before the first visit using the randomization module in the software REDCap (Research Electronic Data Capture; Vanderbilt University). The randomization list is created by a researcher not involved in the trial, who will be the sole person to access it throughout the trial. Should this person be unable to continue this function, a new person not involved in the trial will be appointed to store and access the sequence. Participants are recruited continuously.

Patient and Public Involvement

The intervention was developed in collaboration with the target group and HCPs from the outpatient T2D clinic at SDCC. Overall, the ACCT2 study consists of three phases: (1) needs assessment, (2) intervention development and element testing, and (3) RCT.

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Phase 1 (needs assessment) included interviews and workshops with Arabic-, Turkish-, or Urdu-speaking individuals with T2D (n=18) and 2 workshops and individual interviews with HCPs (nurses, physicians, and dieticians) from the SDCC outpatient clinic (n=33). The findings from the needs assessment suggested adjustments in the standard course of treatment by focusing on (1) extended time in consultations, (2) use of technology for diabetes monitoring, (3) awareness of language barriers, (4) meeting the same HCP, (5) use of accurate communication and dialogue tools, and (6) a need for increased levels of health literacy. A culturally sensitive approach of HCPs was also considered vital to increase understanding and engagement in diabetes management among the target group while emphasizing a whole-person approach rooted in individual everyday life.

Based on the results from the needs assessment (unpublished), a 1-year intervention was designed to target the target group's needs. Visits in the intervention design were tested on 3 individuals speaking Urdu, Arabic, and Turkish as their native languages to test if the flow, content, and overall design match their needs. Tools and methods included in the intervention are partly inspired by the research-based diabetes self-management education, Culturally Sensitive Tools and Methods (CUSTOM) for individuals with non-Western backgrounds [31,32]. The RCT design is described in this study (phase 3). The CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) reporting guidelines were applied (Multimedia Appendix 1) [33].

RCT Study Design

The ACCT2 study is a 1-year pragmatic randomized controlled parallel group open-label effectiveness trial including 96 Arabic-, Turkish-, or Urdu-speaking individuals with T2D (Figure 2). The intervention consists of 6 visits to SDCC. All visits are based on specific values and competencies of HCPs, which are important in the organization, implementation, and completion of the intervention.

Figure 2. Visit flow.

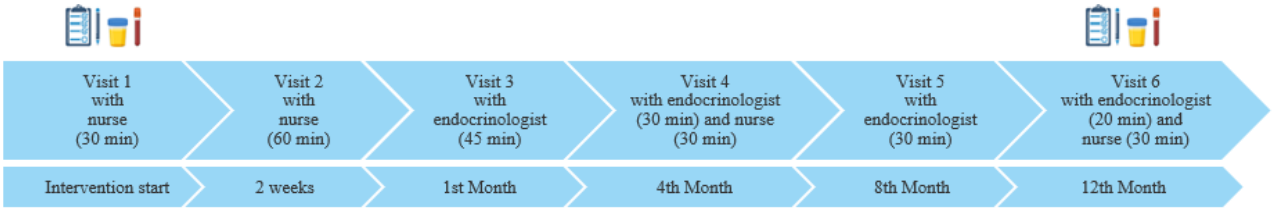

Values of the Intervention

The intervention is based on a person-centered approach [34,35]. A person-centered approach is characterized as a collaborative process between the participant and the HCP, wherein the participant's priorities, preferences, and needs are incorporated into decisions regarding their diabetes treatment. It focuses on understanding the patient's capacity and pace for change [34,35], where cultural competence among HCPs is crucial. This includes adapting attitudes to individual needs and recognizing the implications of emotional, cultural, social, and psychological consequences [17]. Striking a balance, HCPs must acknowledge potential cultural differences without letting them dominate encounters. The intervention's visits consider individual circumstances, resources, expectations, and prerequisites for changes. In addition, it aligns with the empowerment treatment philosophy, where well-informed participants actively engage in diabetes management. The HCP's role is to support the participant in making decisions, achieving goals, and overcoming obstacles [36].

Study Visits

The visits will be run by the same diabetes nurse and endocrinologist under the responsibility of the investigator. Visits with dieticians will be arranged if requested by participants (up to 60 min per visit). For logistical reasons, windows are allowed for the visits (±30 days). The intervention staff includes the same diabetes nurse and endocrinologist, each overseeing the 48 participants in the intervention group. The 48 control participants will continue their care with their usual HCPs. A detailed visit flow is presented in Figure 2.

Visit 1

The first visit, lasting 60 minutes, will involve meeting with a diabetes nurse. During this visit, the focus will be on introducing the participant to the course of treatment and to a continuous glucose monitor (CGM; FreeStyle Libre 2 sensor), which the participant will use for the following 2 weeks. This will enable the participant to gain insight into personal glucose levels. In addition, the nurse will provide information about T2D and its treatment and discuss everyday challenges and topics relevant to the participant.

Visit 2

The second visit, lasting 60 minutes, will involve the same diabetes nurse. The main aim is to talk about pattern identification obtained from the CGM sensor for the past 2 weeks to enhance knowledge of lifestyle factors contributing to stable or fluctuating glucose levels. The nurse will engage in a dialogue about the challenges participants face in everyday life. A new sensor will be applied to the participant for the upcoming 2-week period.

Visit 3

During the third visit, lasting 45 minutes, the participant will meet with an endocrinologist. Patterns derived from the CGM sensor will be discussed to enhance participants' comprehension of unique glucose levels and determine if any changes or solutions discussed during the second visit have been implemented and proven effective in promoting more stable glucose levels. The endocrinologist will evaluate patterns of variation, for example, focus on hypoglycemia, and make necessary adjustments in pharmacological treatment. The

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treatment plan will be negotiated with the participant, providing information on the rationale for the change in treatment regimen and potential benefits and risks. The participant will also be guided to continue self-monitoring of blood glucose according to individual plans.

Visit 4

During the fourth visit (2x30 mins), the participant will meet with the same endocrinologist and diabetes nurse. The main purpose is to evaluate and follow up on the participant's everyday life with diabetes, medication use, and individual needs. The aim is to support the participant's positive experience with the treatment and lifestyle changes, address misperceptions, and reinforce the information provided. If necessary, the endocrinologist will adjust the medication regimen.

Visit 5

During the fifth visit, lasting 30 minutes, the participant will meet with the same endocrinologist. The main purpose is to evaluate and follow up on the participant's medication usage and individual needs. The aim is again to support the participant's positive experience with the treatment and lifestyle changes, address misperceptions, and reinforce the information provided. If necessary, the endocrinologist will adjust the medication regimen.

Visit 6

During the sixth visit (20+30 min), the participant will again meet the same endocrinologist and diabetes nurse. The primary aim is to provide a comprehensive overview of the treatment progress and patterns obtained from the CGM sensor for the past 2 weeks. The participant will be instructed to apply the sensor at home 2 weeks before the last visit. If the participant prefers, they can be booked for a short visit at SDCC with the diabetes nurse to apply the sensor. The last visit will serve as an opportunity to ask any questions, clarify doubts, or express any specific needs the participants may have.

Besides the 6 visits, the participant will receive links to 4 short videos about T2D developed by the Danish Diabetes Knowledge Center at SDCC. The videos are translated into Urdu, Arabic, or Turkish and include knowledge on (1) T2D, (2) complications associated with T2D, (3) exercise and diabetes, and (4) carbohydrates and diabetes (for details on content, refer to [37]). Participants in the intervention group may also have visits, for example with a psychologist and a podiatrist, as part of their usual course of treatment.

To minimize the risk of intervention contamination, HCPs in the study will not interact with participants in the control group. The control group does not have access to any materials, technology, or other components provided to the intervention group. This will ensure that the 2 groups remain distinct, preventing cross-contamination and preserving the integrity of the intervention's evaluation.

Control Group

Participants in the control group will follow the standard course of treatment, which includes regular visits with a physician, often an endocrinologist, and a nurse at the T2D outpatient clinic at SDCC 3-4 times per year (Figure 3). These visits can be in-person or computer-based, depending on the preferences of the participant and HCPs. The standard course of treatment also often includes visits with a podiatrist and eye screening, and it may also include visits with a dietician and psychologist.

Figure 3. Standard course of treatment over 1 year.

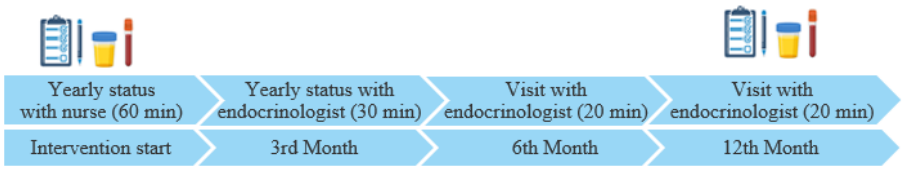

Outcomes

Primary Outcome

The primary outcome is changes in HbA_{1c} (mmol/mol) from baseline to the end of the 1-year intervention.

Secondary Outcomes

The secondary exploratory outcomes encompass a range of metabolic and behavioral factors that may be linked to the intervention. These involve changes from baseline to the end of the intervention (1 year), including plasma lipids, markers of kidney function, hormones involved in glucose metabolism, blood pressure, resting heart rate, CGM (time-in-range, time-above-range, and time-below-range), body weight, and use of diabetes medication (Table 1).

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Table 1. Data collection.

Visit sequence number	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Clinical assessments						
HbA_{1c}[a]	✓			✓	✓	✓
Plasma lipids	✓					✓
Blood pressure and resting heart rate	✓		✓	✓	✓	✓
Hormones involved in glucose metabolism	✓					✓
CGM[b]		✓	✓			✓
Markers of kidney function	✓					✓
Albumin-creatinine ratio	✓					✓
Body weight	✓					✓
Use of diabetes medication	✓					✓
Questionnaires						
Sociodemographic characteristics	✓					
Diabetes distress (PAID-5[c] scale) [38]	✓					✓
Well-being (WHO-5[d]) [39]	✓					✓
HLQ[e] (3 items) [40]	✓					✓
Diabetes management (PRO[f] scheme diabetes) [41]	✓					✓
MARS-5[g] [42]	✓					✓
Acceptability, retention, and satisfaction [43]						✓
Interviews						
Individual interviews (subgroup of participants)				✓		✓
Interviews with HCPs[h] delivering the intervention				✓		✓

[a]HbA_{1c}: hemoglobin A_{1c}.
[b]CGM: continuous glucose monitoring.
[c]PAID-5: Problem Areas in Diabetes Scale–5.
[d]WHO-5: World Health Organization–Five Well-Being Index.
[e]HLQ: Health Literacy Questionnaire.
[f]PRO: patient-reported outcome.
[g]MARS: Medication Adherence Rating Scale.
[h]HCP: health care professional.

Clinical Assessments

Blood Samples

Blood samples are, as part of the regular treatment protocol at the outpatient clinic in SDCC, routinely taken before visits. The participant must arrive at the SDCC laboratory at least 70 minutes before visit 1 and visit 6 for nonfasting blood sampling from the antecubital vein and urine analysis.

CGM Use

CGM is initiated using the authorized FreeStyle Libre 2 device. Participants will be provided with detailed information about the device during visit 1. It will be applied for 2 weeks. The monitoring will be repeated at visit 2 and again 2 weeks before visit 6. FreeStyle Libre 2 allows individuals to monitor glucose levels without routine fingerstick blood glucose testing. It is a small sensor worn on the skin that measures glucose levels in the interstitial fluid to display real-time glucose readings. With features such as trend arrows and built-in memory for data storage, FreeStyle Libre 2 supports diabetes management and provides insights into glucose patterns to inform decisions about medication, diet, and lifestyle.

Blood Pressure and Resting Heart Rate

Blood pressure and resting heart rate are measured using approved and calibrated equipment (Microlife BP A3 Plus) and taken with the participant after a minimum of 10 minutes of rest, without talking during the measurement. Measurements are repeated 3 times, separated by 2-minute breaks to prevent artificially elevated blood pressure resulting from an unfamiliar and potentially stressful environment. The mean value is calculated.

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Height and Body Weight

Height is measured with the participant's heels, buttocks, and upper back remaining in contact with the wall. Results are noted to the nearest 0.1 cm. Body weight is measured to the nearest 0.1 kg, with the participant wearing indoor clothes and no shoes.

Questionnaires

Participants will fill in a baseline questionnaire and a questionnaire at the end of the intervention (refer to Table 1). Questionnaires will be answered during the 70-minute waiting time between blood samples before visit 1 and visit 6. A project worker will be present to address technical questions. Questionnaires are translated into Urdu, Arabic, or Turkish following international standards [30]. The following measures will be assessed at baseline alone: marital status, cohabitation status, social network, educational level, and occupation. Participants' acceptance of the intervention is only explored in the questionnaire at the end of the intervention.

Interviews

Interviews will be conducted by a qualitative researcher with a subgroup of participants in the intervention group after the last visit. Participants' experiences during the intervention will be explored to examine experiences with the 1-year intervention, possible improvements, and important factors for successful implementation into the clinical setting. HCPs delivering the intervention will also be interviewed about acceptability and experiences with intervention delivery in the clinical context.

Measurement of Adherence

Adherence to the intervention is determined by calculating the number or percentage of visits during the intervention in which participants actively engage in all 6 scheduled visits. Per protocol is defined as ≥80% adherence.

Statistical Considerations

Sample Size Calculation

A 5.0-mmol/mol change is the minimal difference for the primary outcome, HbA_{1c}. This resulted in the total number of participants required to enter and complete this 2-arm, parallel-design trial of 88 participants. The sample size was estimated using a general linear model equivalent to a repeated measures mixed model with 2 time points (PROC GLMPOWER, SAS 9.4; SAS Institute). The estimation was based on the following conditions: an allocation ratio of 1:1, α=.05, β=.1, a mean HbA_{1c} level of 70 (SD 14) mmol/mol at each timepoint [44,45], and a correlation between repeated measures of 0.8 [46]. The total number of participants was multiplied by 1.1 to account for potential uncertainties in the conditions used in the power calculation and to account for potential dropouts, resulting in 96 participants.

Data Management

Data will be entered directly into electronic case report forms using REDCap, licensed by the Capital Region of Denmark, or saved electronically. All forms are filled out during (or immediately after) each visit. Errors and corrections are logged as provided by the REDCap interface. For CGM, source data will be registered in web-based software (LibreView, Abbott).

Statistical Analysis

An intention-to-treat analysis, encompassing all randomized participants, will be conducted upon completion of the last participant's final visit. A per-protocol analysis will be carried out, including participants who demonstrate compliance throughout the intervention. Data will be presented using standard descriptive statistics, with means and SDs for normally distributed data and medians with IQRs for data not conforming to normal distribution. Changes from baseline and distinctions in delta values between groups will be assessed using linear mixed-effects models, considering the outcome as a function of group, time, and the interaction between group and time, and accounting for a participant-specific random intercept. The adequacy of assumptions regarding normality and homogeneity of variances will be verified through graphical methods, and data will be log-transformed for analysis and subsequently back-transformed for presentation. In cases where model assumptions are not met even after logarithmic transformation, nonparametric statistical tests will be used. Statistically significant findings will be determined with $P<.05$ (2-tailed). To assess the potential impact of missing data on the primary outcome, a sensitivity analysis will be conducted, involving multiple imputations with missing data at follow-up, which will be included in the imputation process with the control group. Results will be presented as estimated mean changes, accompanied by 95% CIs, degrees of freedom, and, if appropriate, the test value.

Covariables such as age, sex, diabetes duration, and so on, will be included in analyses to assess their potential influence on the outcomes. This approach will allow us to adjust for confounding factors and provide an accurate estimation of the intervention's impact. In addition, if the intervention proves effective, a health economic evaluation will be conducted to estimate the cost per person. This evaluation will consider direct costs, for example, staff time and technology, alongside potential cost savings from improved health outcomes, reduced complications, and fewer health care visits.

Risk of Harm

All equipment used in the study meets the requirements for patient safety and has previously been used in research projects. Participants will have blood samples taken before visits (maximum 18 mL). The total amount of blood collected during the entire study period is at the same level as during the standard course of treatment and is considered safe.

Participants will not have any study-specific clinical measurements taken besides three 2-week periods of CGM measurement. During the sensor placement, participants may experience minor and brief discomfort. The sensor is generally well-tolerated, and only a few potential discomforts are associated with its use. Some participants may experience mild skin irritation or redness where the sensor is inserted. There may be a slight discomfort during the insertion process, although it is generally brief. In rare cases, an allergic reaction to the sensor adhesive or materials may occur, leading to more significant skin irritation. It is also worth noting that the sensor needs to be replaced twice, which involves removing the old sensor and applying a new one, which can cause minor

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discomfort. However, these discomforts are small and temporary. A rare complication is a superficial skin infection obtained in connection with penetration of the skin. The risk of superficial phlebitis is minimized by following hygiene standards, including double cleansing of the skin with an alcohol swab and using sterile materials. Superficial phlebitis is not dangerous. Medication will be reviewed and adjusted according to current clinical guidelines. Participants can contact the physician and diabetes nurse or use the hotline at SDCC about medical issues, for example, concerns related to medication use.

Dissemination

Appointed researchers affiliated with SDCC will be granted access to data. The principal investigator will facilitate direct access to source data and documents for regulatory inspection. Since we anticipate no adverse effects associated with the intervention, recording of harm or side effects will be conducted. Positive and negative study results and inconclusive findings will be presented at conferences and published in international peer-reviewed journals. All coauthors are expected to adhere to the guidelines of the International Committee of Medical Journal Editors, and no professional writers will be involved in the writing process.

Ethics Approval

The study has been approved by the Ethics Committee of the Capital Region of Denmark (H-23042245) and the Research Legal Affairs of the Capital Region of Denmark (P-2023-14503). The study will be conducted following the Declaration of Helsinki and will comply with the Danish Data Protection Agency and the General Data Protection Regulation. Adequate blinding of all personal data during data processing and publication will be ensured. The participants are covered by the Patient Compensation Association according to the Danish Act on the Right to Complain and Receive Compensation within the Health Service.

Results

Study funded in June 2023. By March 2025, all participants were successfully enrolled in the study. Data collection will proceed until December 2025, allowing for comprehensive data gathering. Once data are collected, the research team will begin the analysis process, with the first results anticipated to be available by March 2026.

Discussion

Comparison With Prior Results

Despite the existing gaps in the literature, it is well-established that the target group faces an elevated risk of T2D [1-3], often attributed to factors such as health behavior, limited health care access, social determinants of health, low health literacy, cultural norms, and language barriers [4,9-16]. Our study aims to build on this understanding by using several robust methodologies. The use of a scientifically rigorous design, power calculation for sample size estimation, and a replicable intervention are among the strategies used. A control group allows for a meaningful comparison to “usual care,” enhancing the reliability of our findings. In addition, administering the intervention through the same HCPs ensures continuity in care and familiarity for participants, which may reduce dropout rates. A distinctive feature of our approach is the systematic involvement of the target group and HCPs in the intervention’s design. By incorporating their insights into their needs, barriers, and potential solutions, we aim to create an intervention that better addresses their challenges than previous research. This tailored approach could lead to improved diabetes management, enhanced well-being, and reduced obstacles that typically hinder care within this high-risk population.

Strengths and Limitations

The interdisciplinary nature of our study, coupled with feasibility assessments, offers valuable insights into the experiences of both participants and HCPs, shedding light on potential barriers and effective strategies for implementing the intervention in outpatient clinics. However, it is important to acknowledge certain limitations. The 1-year duration of the trial restricts the exploration of long-term effects. In addition, the broad inclusion criterion, while facilitating a more representative study population, may introduce heterogeneity in some secondary outcomes. Also, the inherent challenge of blinding participants poses a potential for performance bias, which we cannot eliminate from the study design.

Moreover, we compare the intervention group to the usual care group, which, by definition, represents the standard treatment available. The intervention group, however, received additional resources and structured support, which may have led to greater improvements. This is a common approach in intervention studies, where the objective is to assess the added value of the intervention. While the observed benefits in the intervention group may be partly attributed to the enhanced support provided, it is essential to evaluate whether these improvements can be directly linked to the intervention itself. Therefore, intervention scalability, if it proves effective, includes further evaluations. Key considerations for scalability include assessing cost-effectiveness, resource allocation, and how the intervention can be integrated into routine clinical practice. We also plan a comprehensive realist evaluation, which will provide additional insights into the implementation and feasibility of the intervention. This evaluation will explore the perspectives of participants, their relatives, and HCPs with a focus on understanding what works for whom, why, and under what circumstances. By examining the mechanisms driving the intervention’s success or failure, we aim to identify the conditions and contexts necessary for effective implementation.

Conclusions

The intervention design, tailored to address the needs of both the target group and HCPs, is poised to maximize its potential for acceptability within the target group, particularly should the outcomes prove positive. This study is expected to provide knowledge translatable to clinical settings, with the anticipated clinical impact extending to the future development and implementation of interventions adapted to preferences, needs, and satisfaction.

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Acknowledgments

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Data Availability

Data sharing does not apply to this article, as no datasets were generated or analyzed during this study.

Authors' Contributions

NB, LC, SMJ, CH, UBC, and KA conceptualized the study and designed the intervention. NB drafted and registered the study protocol with the Ethics Committee of the Capital Region of Denmark. CO and NB registered the study at ClinicalTrials.gov and elaborated the first draft of the paper. NB led a content validation of the study materials, involving both the project and steering groups.

Conflicts of Interest

SDCC is a hospital providing health services for the public health care system. The Novo Nordisk Foundation partly funds the research project and SDCC through unrestricted grants, but does not have economic interests in the study. The Novo Nordisk Foundation does not influence (1) study design; (2) collection, analysis, and interpretation of data; (3) writing of the study report or any publication; and (4) the decision to submit the paper for publication. The investigators employed at SDCC will not benefit economically from conducting the study.

Multimedia Appendix 1
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1151 KB - resprot_v14i1e67319_app1.pdf]

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Abbreviations

ACCT2: a person-centered and culturally sensitive course of treatment in type 2 diabetes
CGM: continuous glucose monitor
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
CUSTOM: Culturally Sensitive Tools and Methods
HbA_{1c}: hemoglobin A_{1c}
HCP: health care professional
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SDCC: Steno Diabetes Center Copenhagen
T2D: type 2 diabetes

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Protocol

Integrated Psychosocial Care in Intensive Care (IPS-Pilot): Protocol for the Systematic, Multimethod Development of a Complex Intervention (Phase A)

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Abstract

Background: There is a high, co-dependent strain on health care professionals (HCPs), patients, and their relatives in intensive care units (ICUs), leading to long-term mental, physical, and occupational consequences. To date, there is no systematic intervention to address this growing problem.

Objective: The aim of the IPS-Pilot (German: Integrierte Psychosoziale Versorgung; English: “Integrated Psychosocial Care”) project is the development (phase A) and pilot testing (phase B) of an integrated and complex psychosocial care intervention for HCPs, patients, and their relatives in ICUs. This study protocol focuses on phase A. A separate protocol for phase B will be published later.

Methods: A structured, multimethod approach was used to gather evidence from the target groups mentioned above on the needs, expected benefits, and necessary conditions for implementation. These methods included (1) a scoping umbrella review conducted by 2 researchers, who independently screened and selected reviews and meta-analyses in the field of needs and demands in the ICU setting, following the Levac framework; (2) web-based and face-to-face interviews and focus group discussions, which were coded independently by 2 researchers and analyzed using qualitative content analysis; the identified categories and codes were then quantified by (3) an online survey conducted with former ICU patients, their relatives, HCPs working in ICUs, and members of the general population. Synthesized results—complemented by the theories of Psychosocial Safety Climate and Conservation of Resources, as well as online and face-to-face stakeholder workshops—were used for intervention development, which was guided by the Intervention Mapping framework.

Results: Through the 4 substudies, we aim to gain insights into the psychosocial needs of the aforementioned target groups. Intermediate analyses were conducted to develop both a model of the problem and a model illustrating how these needs can be effectively addressed through a psychosocial intervention that involves integrating a clinically trained psychologist into the HCP team. Data collection and analysis for the intervention development were completed by June 2024, including substudy 1 (n=104 included articles), substudy 2 (n=22 interviews and n=18 participants in focus groups), substudy 3 (n=237 survey participants),

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and substudy 4 (n=11, n=15, and n=20 participants in 3 consecutive workshops), with further analyses still ongoing beyond the scope of intervention development. The results of the substudies, as well as the final needs-based intervention design, will be published separately. These findings form the basis for the feasibility study (phase B), conducted from July 2024 to July 2025, during which the intervention will be implemented in randomly selected ICU wards and evaluated in terms of feasibility.

Conclusions: Phase B will assess the feasibility of the IPS intervention. The findings will be incorporated into the intervention design and serve as the basis for a future randomized controlled trial to evaluate its efficacy.

Trial Registration: OSF Registries 10.17605/OSF.IO/VFXJK; https://osf.io/vfxjk

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KEYWORDS

health services research; psychosocial intervention; health personnel; intensive care units; critical care; complex intervention; feasibility study

Introduction

Background

The German health care system is well equipped in terms of the number of intensive care unit (ICU) beds. Compared with other European countries, Germany had the highest average rate, with 29.9 ICU beds per 100,000 population during the COVID-19 pandemic [1]. However, on a global scale, there is a considerable shortage of ICU-qualified nurses and doctors. In accordance with the legal requirements for minimum care staffing in care-sensitive settings in Germany (Pflegepersonaluntergrenzenverordnung), and the recommendations of the German Interdisciplinary Association for Intensive Care and Emergency Medicine (Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin; DIVI), ICU nurse understaffing affects 45% and 74% of all units, respectively. In addition, in Germany, more than half of intensive care nurses work part-time, and many are considering leaving the profession [2]. The reasons are diverse but certainly include the unique circumstances in ICUs, which place high demands on health care professionals (HCPs), patients, and relatives—demands that worsen with increasing short-staffing. Exposure to adverse events, such as critical incidents in intensive care, can lead to secondary traumatization [3]. In a nonrepresentative survey conducted in 2013 among emergency nurses in Scotland, 75% of the sample reported experiencing 1 or more secondary traumatic stress symptoms in the previous week [4]. Additionally, potentially traumatizing events in the workplace are linked to depression, addiction, and suicidality, as stated in an annual report by the DIVI [5]. A significant number of HCPs in intensive care exhibit psychosomatic symptoms or signs of burnout [6].

Despite the negative impact on HCPs themselves, high stress also harms the health care system: nurses in poor physical and mental health report significantly more medical errors than those in better health [7]. As the connection between practitioners' mental health and the quality of care is increasingly acknowledged [8], these circumstances raise important concerns about patient safety.

For patients and their relatives, the ICU is associated with significant stress and pressure. A systematic review of 42 prospective cross-sectional studies [9] identified stressors related to disease and treatment (eg, pain), mental health (eg, fear of death), communication (eg, inability to speak, lack of information about one's condition), and the ICU environment (eg, noise, seeing, or hearing other patients). Patients are exposed to multiple potentially traumatic experiences during their treatment [10]. The observation that many patients experience new or worsening cognitive (eg, memory impairments), physical (eg, difficulties with activities of daily living), or psychological symptoms (eg, depression) after an ICU stay has led to the classification of postintensive care syndrome (PICS) [11,12]. In a prospective study conducted across 16 ICUs in Japan, 63.5% of participating survivors experienced at least one PICS-related impairment 6 months after their ICU stay [13]. Psychological symptoms related to the ICU stay can also be observed in relatives, such as anxiety, posttraumatic stress disorder, or depression, a condition referred to as postintensive care syndrome—family [11], which in some cases may be even more pronounced than in patients [13]. The German Association for Neurorehabilitation [14] has recommended implementing additional measures alongside standard ICU treatment to prevent PICS and to address existing PICS-related impairments. These measures target physical (eg, early mobilization), cognitive (eg, delirium prophylaxis), and psychological symptoms (eg, ICU diaries, improved communication, and family support). The stress experienced by ICU patients and their relatives may further intensify the emotional demands placed on HCPs, potentially exacerbating the issues described above and creating a downward spiral.

From a theoretical perspective, this phenomenon of accumulating stressors and problems can be explained by the Conservation of Resources (COR) theory [15]. The COR theory is an integrated, motivational theory of resources that focuses on coping and resource gain. It is based on the fundamental assumption that people tend to protect their existing resources and abilities while striving to acquire new ones [16]. According to this theory, stress is defined as a response to environmental conditions in which resource loss is threatened, has occurred, or cannot be offset by a gain in resources. The COR model particularly suggests that (threatened) resource losses can lead to further losses, reinforcing the downward spiral described above.

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By contrast, also embedded in COR theory, positive circular processes—referred to as "positive gain spirals"—describe a salutogenetic process involving positive development and growth. The availability of key resources fosters the development and acquisition of additional resources: "resources cotravel in resource caravans" [17]. According to COR theory, the provision of additional resources, such as integrated psychosocial care, could therefore initiate a positive developmental spiral. COR theory has already been applied to perceived stress among nurses [18], the etiology of nurse burnout [19,20], and the development of posttraumatic stress disorder in survivors of COVID-19 [20]. While COR theory primarily focuses on resource losses and gains at the individual level, one study also highlights that resource loss in nurses, leading to burnout, should be addressed at the institutional level [19].

A broader perspective on organizational resources, demands, and their relationship to psychological and occupational health is offered by the concept of the Psychosocial Safety Climate (PSC) [21]. PSC refers to employees' perceptions of the extent to which their organization considers their mental health in decision-making, particularly in the design of working conditions. In line with this, nurses who perceived their workplace as highly supportive of their well-being were twice as likely to report better physical health [7]. Interventions based on this concept target the root causes of stressful working conditions, rather than just addressing the stress symptoms of the employees themselves. One of its goals is to establish standards for best practices in stress prevention within organizations and to develop a solid evidence base for effective prevention and intervention strategies [22]. An increasing number of studies show that PSC is positively correlated with factors such as motivation, productivity, and self-reported health status, as well as a reduced number of workdays lost due to absence [23,24]. At the same time, PSC is negatively correlated with job and career change intentions [25].

Based on both evidence and theory, the need for psychosocial care as an intervention during and after intensive care is undisputed; however, it is being addressed only slowly [26,27]. Barriers remain significant: factors such as time constraints and lack of experience hinder the widespread use of such support [4]. Moreover, not only patients and their relatives, but also ICU HCPs, require access to psychosocial care, as has been advocated [28]. Recently, the Federal Joint Committee in Germany published a decision to amend the regulations for intensive care centers. It mandates "psychological support and crisis intervention for patients and staff to be available every working day" [29]. However, in the current care landscape of the German health care system, there are no integrative structures for the psychosocial care of ICU teams, patients, and their relatives. To our knowledge, corresponding interventions have never been systematically developed based on theory and evidence, nor with the involvement of all relevant stakeholder groups.

Initial experiences with an integrated psychosocial care concept have been gained in 2 project partner institutions, Charité Berlin and Ulm University Medical Center, where psychosocial care in ICUs was implemented during the COVID-19 pandemic [30] in response to the increased pressure on ICU HCPs, patients, and their relatives. Through an iterative and needs-focused approach, various psychosocial treatment tools, such as individual counseling, team supervision, health circles, and efficacy monitoring surveys, were selected, developed, and implemented for HCPs, patients, and their relatives. Specifically at Charité Berlin, up to 15 psychologists from the Psychosocial Emergency Care department worked as part of the ICU team (team-integrated), providing care for patients, relatives, and HCPs. Over 500 end-of-life care sessions were conducted. To date, 3 similar interventions have been carried out at the University of Ulm. While this makeshift intervention appears to have a positive effect, its design is based solely on clinical experience, and its feasibility and efficacy have yet to be empirically evaluated.

Effectively addressing patients, their relatives, and ICU HCPs with a single intervention would require the development of a complex intervention [31]. Complex interventions are characterized by several factors: they consist of multiple interacting components, target different groups and organizational levels simultaneously, expect a range of different outcomes, and involve a high degree of flexibility in design. The Medical Research Council (MRC) proposes a framework for developing and evaluating complex interventions, which prioritizes understanding both the contextual factors and the mechanisms of change, as they illustrate the connection between the intervention components and the outcome [32]. The development of a complex intervention is grounded in available evidence and theory, supplemented by participatory measures to incorporate the target group's perspective.

Objectives

This study aims to address the stress-related symptoms and consequences previously mentioned, primarily in ICU HCPs, as well as in patients and their relatives. The objective of the IPS-Pilot project (German: *Integrierte Psychosoziale Versorgung*; English: "Integrated Psychosocial Care") is to (1) develop an integrated psychosocial care intervention (phase A), and then (2) assess the feasibility of its implementation and evaluation in a randomized controlled pilot trial in the ICU setting (phase B).

This protocol reports on phase A.

Our primary research question in this phase is "How should an integrated psychosocial care concept be designed to address the specific psychosocial needs of ICU HCPs, as well as those of intensive care patients and their relatives?"

The secondary research questions are (1) What are the psychosocial needs of ICU HCPs, ICU patients, and their relatives? and (2) What are the potential benefits and challenges of an integrated psychosocial intervention in the ICU?

Our focus is on identifying which needs (psychosocial and otherwise) must be addressed by the intervention to be developed, as well as the hurdles and resources important for its implementation. This will ensure the best possible practicability in the development of interventions, maximizing both effectiveness and acceptance by those affected.

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Methods

Responsibilities

The IPS-Pilot project is coordinated by the Ulm University Medical Center (Department of Psychosomatic Medicine and Psychotherapy) in collaboration with the Otto von Guericke University Magdeburg (Institute of Social Medicine and Health Systems Research), the University Medical Centre Magdeburg A.ö.R. (Department of Psychosomatic Medicine and Psychotherapy), and Charité University Medicine Berlin (Department of Psychosomatic Medicine).

Study Design

The following protocol is based on the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [32] (see Multimedia Appendix 1) and the CONSORT (Consolidated Standards of Reporting Trials) statement [33]. IPS-Pilot is a mixed-methods study that will be conducted in 2 phases according to the MRC's framework [31] for the development and evaluation of complex interventions; for reference, see Figure 1. The project runs from January 2023 to December 2025. This protocol focuses on the first study phase (phase A: needs assessment, intervention development, and optimization; January 2023 to June 2024), as the specific implementation and evaluation concept for feasibility in the second phase (phase B) will depend on the intervention developed in phase A. As shown in Figure 1, data collection for phase A and partial analyses for the intervention development were completed by June 2024, while the final analyses are still pending.

Figure 1. Overview on the study timeline. Timeline on the right side ranging from start to finish of the IPS-Pilot project and covering phase A and B. Rounded rectangles indicate sample origin. Blue boxes indicate substudies of the needs assessment and intervention development (phase A); green boxes indicate steps of the Pilot RCT on intervention feasibility in phase B which is to be covered in a separate study protocol.

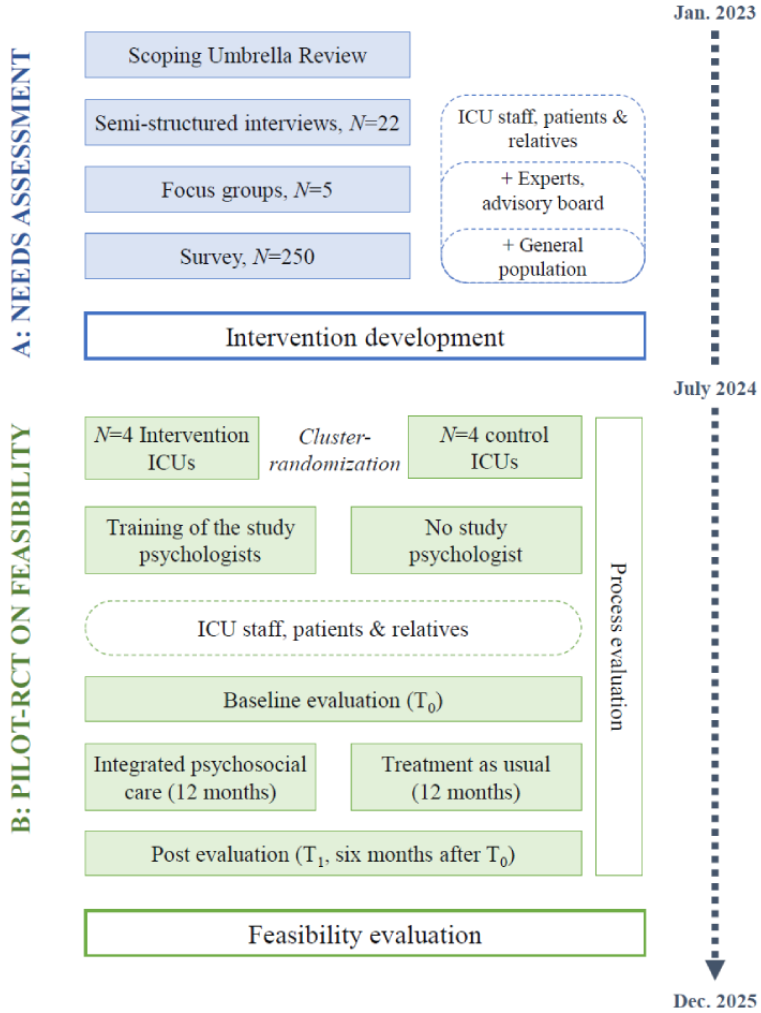

Phase A: Gathering Evidence and Development of Intervention

Overview

In phase A, we assess the psychosocial needs of ICU patients, their relatives, and ICU HCPs through the evaluation of existing research (substudy 1: scoping umbrella review) and original data collection using qualitative (substudy 2) and quantitative (substudy 3) methods. The data from these studies will be used for intervention development in the fourth substudy.

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Substudy 1: Scoping Umbrella Review

Methodological Overview

This substudy is registered online [34]. Numerous studies and reviews have examined the relevant needs, typically focusing on 1 of the 3 perspectives mentioned above. There are reviews addressing patient needs [35], the needs of relatives of ICU patients [36], and those of ICU HCPs [37]. However, to our knowledge, there is no comprehensive overview that encompasses all 3 perspectives. With the planned scoping umbrella review, we aim to systematically compile and compare studies on the needs and requirements of the various groups involved in ICU care. The findings can then be incorporated into the subsequent development of the intervention. This scoping umbrella review aims to provide an overview of systematically collected and evaluated reviews and meta-analyses addressing needs and demands in the ICU setting. The identified needs will be categorized, with a particular focus on the psychological and psychosocial needs of all those involved in the treatment process. This review will offer a comprehensive overview of the current state of research, and the insights gained can serve as a foundation for conceptualizing targeted psychosocial interventions in ICUs.

Inclusion and Exclusion Criteria

All systematic reviews or meta-analyses that summarize primary studies assessing the needs of individuals directly involved in ICU care, including patients, their physicians and nurses, and relatives, will be included. We will also consider reported factors that indicate a problem or suggest an underlying cause related to a specific need.

Studies focusing solely on pharmacological outcomes in neonatal or pediatric ICUs, as well as studies conducted exclusively in rehabilitation or palliative care settings, will be excluded.

Data Collection and Analysis

The search strategy includes both medical databases (MEDLINE via PubMed, Embase via Ovid, and Scopus) and social science databases (PsycINFO via EBSCOhost). In addition, we conducted searches in the Cochrane Database of Systematic Reviews and PROSPERO (International Prospective Register of Systematic Reviews), which are specifically dedicated to reviews. We are also performing a hand search of the reference lists of the included reviews. Titles and abstracts are being screened based on the research question, developed using the Person-Content-Context-Method framework of the Joanna Briggs Institute [38]. The review process follows the framework outlined by Levac et al [39]. Two researchers (WS and SP) independently screened and selected titles and abstracts. Full-text versions of potentially relevant articles were obtained, and inclusion and exclusion criteria were applied. Disagreements were resolved through discussion within the review team. A standardized data extraction form, developed by researchers and professionals with a focus on the usability of findings for intervention development, was used. The software ASReview (ASReview Team) was used for title and abstract screening, and EndNote (Clarivate Plc) was used to manage the literature database. Findings will be synthesized narratively and, if possible, quantitatively assessed and categorized. Categories will focus on study design, perspectives, and identified needs. Reporting will follow the guidelines outlined in PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) [40]. The PRISMA-ScR checklist and the search string are provided in Multimedia Appendix 2.

Substudy 2: Interviews and Focus Group Discussions

Methodological Overview

This substudy is registered online [41]. To evaluate ICU-related stress factors and needs regarding the intervention across all 3 target groups, individual interviews were conducted with former ICU patients, relatives of former ICU patients, and ICU HCPs in Germany. These insights were then explored further in focus groups, where HCPs, former patients, relatives, psychologists, and experts discussed the content requirements and implementation conditions for an integrated psychosocial intervention in ICUs. The research questions in this substudy were exploratory and therefore nondirectional. The primary research question aimed to identify psychosocial needs in intensive care from the perspectives of patients, relatives, and HCPs. Secondary research questions focused on exploring support factors and barriers to the use of an integrated psychosocial intervention, as well as design requirements to make such an intervention accessible and acceptable to those affected. The goal was not to identify converging perspectives, but rather to gather diverse viewpoints to develop a vivid and comprehensive understanding of the phenomenon of interest.

Sample and Eligibility Criteria

We conducted interviews with ICU HCPs, former ICU patients, and relatives of former ICU patients, as well as focus group discussions, each involving up to 6 participants. Participants either belonged to 1 of the 3 aforementioned groups or had relevant professional experience, such as working as an ICU-integrated psychologist or holding administrative roles (eg, controlling, clinic directors). We aimed to include patients, relatives, and HCPs with and without prior experience of interacting with an ICU-integrated ward psychologist. Study participants had to be at least 18 years old and provide informed written consent to the scientific staff conducting the interviews. Only patients and relatives who had received treatment in the participating ICUs (Berlin, Magdeburg, and Ulm) within the last 6 months were included. ICU HCPs with varying levels of work experience and professional backgrounds (nurses and doctors from different hierarchies) were also included. Participants were recruited by directly approaching them in the context of their treatment or occupation in the ICUs of the participating hospitals.

Data Collection

Before data collection, a test interview was conducted. The interviews and focus group discussions were carried out either face-to-face or online via data protection–compliant videoconferencing systems at the 3 study sites in Germany. These sessions were conducted by project staff trained in qualitative data collection. All interviews and discussions were audio-recorded using a recording device and transcribed by a

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qualified external contractor. Semistructured questions were developed for conducting the interviews and focus group discussions. The guiding questions were adapted during data collection as needed. For both the interviews and the focus group discussions, sociodemographic data (eg, age, gender, work position, and experience in ICU) were collected to better categorize the results after each session. These data were gathered using a standardized questionnaire filled out under a pseudonym. The interview and focus group guides can be found in Multimedia Appendix 3.

Data Analysis

Depending on the research questions, the data material is analyzed using qualitative content analysis [42] with the aid of MAXQDA (VERBI GmbH). For the interviews, an initial code system was developed deductively, based on relevant literature [42] and previously identified topics. This code system was then expanded inductively during the analysis of the first few interviews (5/22, 23%). The remaining material was coded by pairs of independent researchers (KS, HH, GK, and RKN) and validated through consensus. If any differences could not be resolved through discussion, the results were presented to a third team member to reach a consensus. The same procedure will be applied to the focus group discussions, with the category system based on the final code system used for the interviews. We aim to ensure a methodologically controlled analysis process and high-quality data analysis through communicative, interdisciplinary validation within the research team.

Substudy 3: Survey

Quantifying Psychosocial Needs and Assessing Care Model Implementation

This study is registered online [43]. In substudy 3, an online questionnaire survey was conducted to complement the data on needs collected in substudies 1 and 2. The goal was to quantify the aforementioned needs. Additionally, the survey gathered information on known and utilized care models, including their frequency and nature of use, as well as obstacles encountered in implementing a potential intervention.

Sample and Eligibility Criteria

The target sample size was 250 participants. Participants had to be of legal age, able to complete the questionnaire, and provide informed consent. The substudy aimed to quantify and compare psychosocial needs across 4 groups: former ICU patients, relatives of former ICU patients, ICU HCPs, and the general population. We planned to recruit at least 50 participants in each of the 4 groups. Participation in the survey was anonymous and voluntary.

Data Collection

Four different sets of partially overlapping questionnaires were developed, each tailored to 1 of the 4 target groups. Participants were presented with a combination of individually developed questions and items from validated questionnaires, depending on the group to which they belonged. Participants were allocated to 1 of the 4 groups described above through consecutive filter questions, which determined whether they were an ICU patient within the last 3 years, a relative of a former ICU patient, an HCP currently working in the ICU, or none of the above. Figure 2 illustrates the allocation procedure and the questionnaires administered to each group (also see [44-54]).

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Figure 2. Overview on the administered scales [44-54] in the questionnaire depending on group allocation by filter questions.

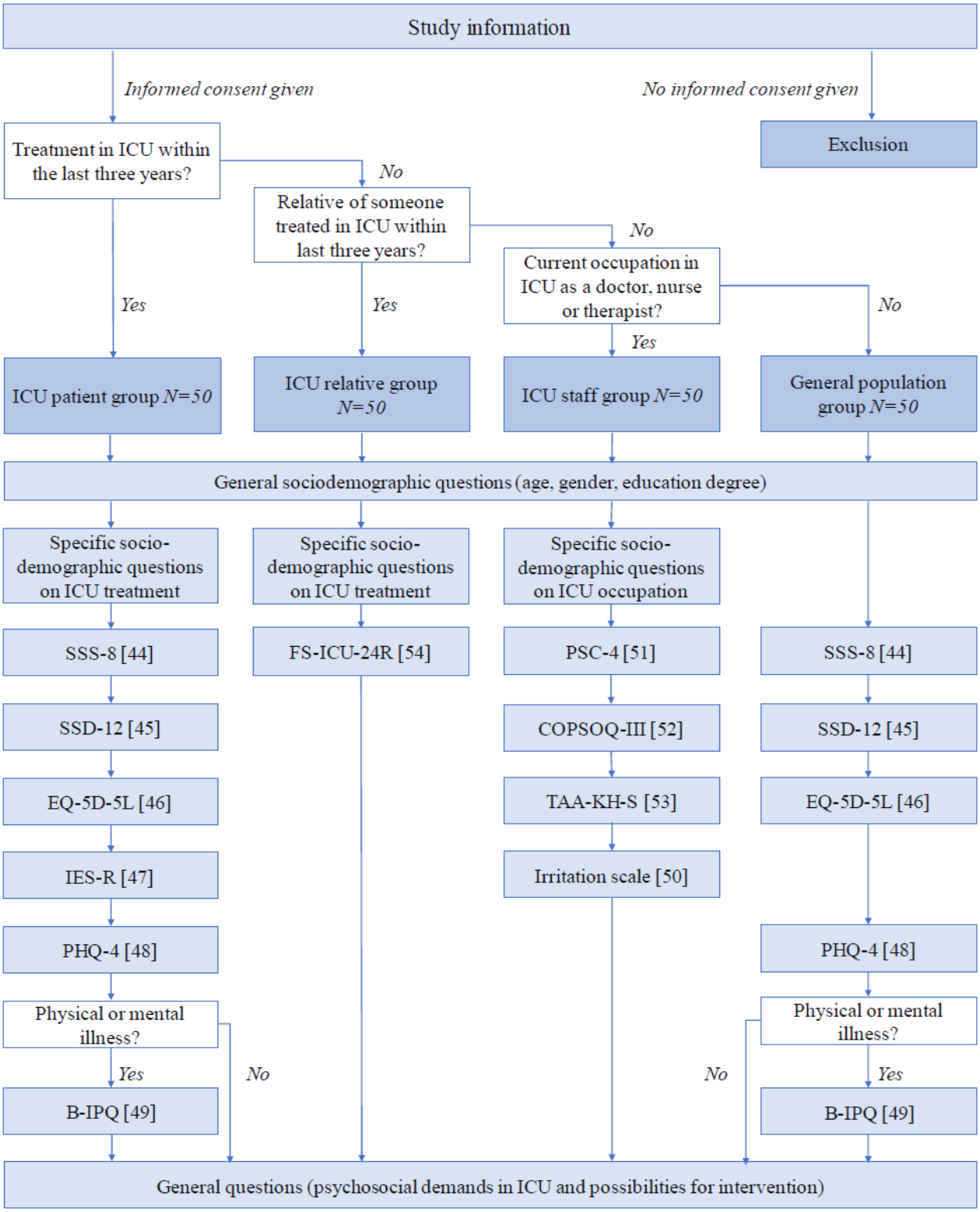

The survey was conducted and evaluated digitally and anonymously using LimeSurvey (LimeSurvey GmbH) online [55], with recruitment through German professional societies, interest groups, and other relevant channels. A pretest with 20 participants was conducted to assess the comprehensibility and feasibility of the survey.

Data Analysis

We will use descriptive statistics to analyze and report the findings, focusing on differences in psychosocial needs and support across participant groups. As all analyses are exploratory, no hypotheses were specified. Exploratory analyses may involve examining patterns of psychosocial needs and support across demographic variables. Missing data will be addressed by reporting the available data without imputation.

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Substudy 4: Intervention Development and Optimization Process

For the intervention development, we planned an extensive multistep participatory process, structured according to the MRC framework [31,56]. The specific steps follow the Intervention Mapping (IM) framework [56]. To ensure a comprehensive understanding of the needs of our target groups, the evidence obtained from substudies 1, 2, and 3 was summarized and integrated. Figure 3 provides an overview of the synthesis process. For example, in step 3 of the IM framework, effective interventions in ICUs identified in the scoping umbrella review (Substudy 1) were listed, organized, discussed, and selected by the research team based on their potential feasibility in German ICUs. In the context of 1 of 3 workshops, this selection of intervention tools was compared and supplemented with findings from the interviews and focus groups regarding desired interventions (substudy 2). The evidence was then aligned with and incorporated into our model of change, synthesizing it with our theoretical approach—the resource-oriented perspective of the PSC [21] and COR [16] theory. Following this, a first draft of the intervention was developed according to the IM concept [56], within the scientific study team and in close collaboration with experts. During this process, 3 online and face-to-face workshops were held, involving members of the study team and stakeholders (former ICU patients, relatives, and various representatives of HCPs, such as physicians, nurses, and therapists). Stakeholders were selected for participation and approached personally by the study team, for example, as members of the IPS-Pilot advisory board. The goals of these workshops were to (1) develop the logic model of change, mapping the interrelationships and corresponding intervention components (IM step 2); (2) select intervention components that had already been evaluated in previous studies (substudy 1) or suggested by target groups (substudy 2; IM step 3); and (3) review and refine the intervention draft, as well as the planned implementation process, with the stakeholders (IM step 4). For this substep, methods from the design thinking approach [57] were used, specifically the Disney Strategy [58], which has been applied in various program and intervention design processes, including those involving stakeholder participation [59,60]. Discussion topics included the description, timing, scope, and other framework conditions of the intervention components. The final draft of the intervention tools was then refined through the survey (substudy 3), in which the needs were quantified. The resulting psychosocial care intervention is primarily designed to be delivered by a clinically experienced psychologist (in psychotherapeutic training; hereinafter referred to as the IPS therapist) with a 50% deputization. This IPS therapist will be an integral part of the permanent ICU HCP team for the duration of the intervention. Individual components of the complex intervention may be delivered by other HCPs, depending on local availability. The final concept (hereinafter referred to as the IPS intervention) will be documented in the form of an intervention protocol and an intervention manual, which will provide instructions for the interventions to be administered by the IPS therapist.

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Figure 3. Synthesis and integration process of the sub-studies (left column) and their respective outcomes as well as theoretical and empirical input (middle column) into the steps of the IM process (right column).

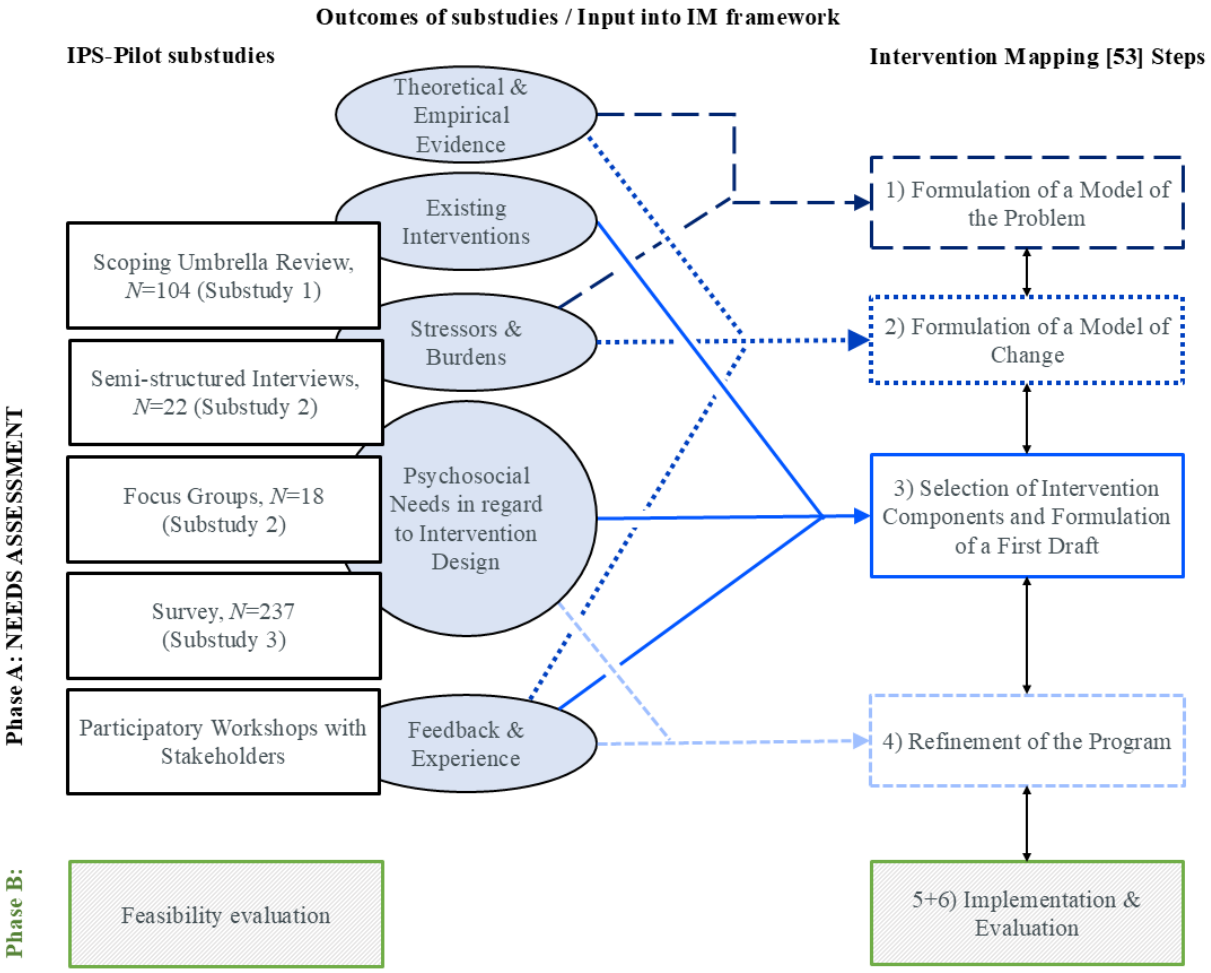

Patient and Public Involvement

In all substudies, the perspectives of our target groups—ICU HCPs, patients, and their relatives—are collected and incorporated. In substudy 1, their needs are included indirectly through research on existing studies. In substudies 2 and 3, they are directly involved as participants in the interviews, focus groups, and survey. In our fourth and final substudy, we invited all target groups to participate in workshops where the concrete intervention design was discussed. Throughout the project, we will continue to engage our target groups in our advisory board.

Outlook on Phase B: Pilot Study

The feasibility of a pilot RCT on the IPS intervention developed in phase A will be evaluated in a multicenter study involving the 3 sites in Germany. Eight nonspecialized ICUs for adults will be selected from the university hospitals in Berlin, Magdeburg, and Ulm. Using a randomized cluster design, 4 ICUs will be assigned to the intervention group, and 4 to the control group. Over the course of 12 months, psychologists in psychotherapeutic training will be assigned to each of the 4 intervention ICUs as IPS therapists from mid-2024 to mid-2025. Meanwhile, a survey with 2 measurement points will be conducted across all participating wards, involving HCPs, patients, and relatives, to evaluate feasibility criteria such as participation rate and practicability. A separate study protocol for phase B will be submitted and preregistered. Further descriptions of the methods and end points can be found in this study protocol.

Ethics and Dissemination

With regard to scientific quality, the guidelines for ensuring good scientific practice from the German Research Foundation, as well as Good Epidemiological Practice [31], were followed.

Research ethics approval was obtained from the Ethics Committee of the University of Ulm (approval number 108/23-FSt/Sta) and the University Medical Centre Magdeburg (approval number 34/23), both of which were recognized as valid by Charité-Universitätsmedizin Berlin in accordance with §15 Section 2 of the Professional Code of Conduct of the Berlin Medical Association [61]. Any modifications to the study plan, as described above, were communicated to the ethics committees and the funder, and permission for the modifications was obtained where necessary.

The EU General Data Protection Regulation and the Federal Data Protection Act apply to data protection. A data protection concept has been developed in accordance with these guidelines,

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specifically addressing the planned methods of data collection, storage, and analysis. This concept has been approved by the data protection officers at Ulm University Medical Centre. Guidance on the procedure was obtained from the Center for Clinical Trials Ulm, and processing activities have been registered at all sites. A trustee office has been established to ensure the secure transfer of data. Personally identifiable data were only collected when necessary (eg, for data withdrawal after participation). These data were transferred solely between the involved parties using secure messaging systems. Pseudonyms or personal data were never transmitted via an unencrypted internet connection or any other medium.

The trial was conducted in accordance with the Declaration of Helsinki. Informed written consent was obtained from all participants (see Multimedia Appendix 4). Participants were informed that their participation was voluntary and could be discontinued or canceled at any time, before, during, or after participation. No payment was provided for participation.

Results

The development of the IPS intervention was completed by the beginning of June 2024. Because of the time frame, analyses of the substudies were only partially completed at this stage, with a focus on psychosocial stressors and needs to be included in the intervention design. Through the 4 substudies, we aimed to establish both a logical model of the problem and a logical model of change. Together, these models describe the psychosocial needs of ICU patients, their relatives, and ICU HCPs, and explain how the stress caused by these needs in ICUs could be addressed and effectively reduced through a complex psychosocial intervention. To formulate these models, we collected, compared, classified, and quantified the demands and needs from the 3 different perspectives, and will continue to analyze them. The final results of the individual substudies will be reported separately in 2025.

Data collection and analysis for the scoping umbrella review (substudy 1) are yet to be completed, due to the breadth of the included studies. A total of 109 studies on psychosocial needs, as well as existing psychosocial interventions, were included in the synthesis for intervention development. In the next step, the included studies will be analyzed in more detail with regard to psychosocial needs and requirements. The final analysis of the scoping umbrella review will be completed in 2025.

Interviews and focus groups (substudy 2) were completed in November 2023 and March 2024, respectively. We conducted interviews with 10 ICU HCPs, 6 former ICU patients, and 6 relatives of former ICU patients, as well as 5 focus group discussions with a total of 18 participants. Analysis of the interview data was completed in August 2024; analysis of the focus groups is expected to be completed by April 2025. The survey (substudy 3) was conducted from April to June 2024 and collected data from 51 ICU patients, 52 relatives, 73 ICU HCPs, and 61 participants from the general population. Analysis of the data was completed in October 2024. The workshops in substudy 4 were conducted in March (n=11 participants), April (n=15 participants), and May 2024 (n=20 participants). The intervention manual was completed at the beginning of June 2024.

Discussion

This study protocol provides an overview of a structured, theory-guided, multimethod, participatory approach for designing an integrated psychosocial intervention in ICUs within the framework of the IPS-Pilot project. The methods described in the protocol are expected to lead to a deeper understanding of the psychosocial needs of our target groups and, therefore, ensure the best possible fit of the resulting IPS intervention.

During the COVID-19 pandemic, public awareness of the psychosocial burdens and needs of HCPs, patients, and relatives in the ICU context increased. To address the growing pressure on these groups, a makeshift intervention—in the form of a psychologist integrated into the ICU team—was implemented at Berlin Charité and Ulm University Medical Center. Our experiences during the pandemic indicated that all groups benefited from this complex psychosocial treatment. However, there is still a lack of scientifically grounded evidence regarding the psychosocial needs that should be addressed through a complex intervention in the ICU context—along with its optimal design, feasibility, and, ultimately, its effectiveness.

This study protocol aims to make the development process of the IPS intervention transparent and accessible. A key limitation arises from the complexity of the development process itself. As all steps outlined in the IM framework [56] required a synthesis of theory alongside existing and newly generated evidence, the procedures and analyses of our interdependent substudies were constrained by a tight time frame. This time frame may seem at odds with intervention development frameworks, which emphasize a dynamic rather than linear development process [31,56]. Therefore, to avoid delays and ensure sufficient knowledge synthesis, intermediate or partial data analyses and repeated feedback loops between substudies were necessary. This required adequate time resources and close collaboration within the scientific team.

It is well established that HCPs experience a high stress burden, which also affects patients and their relatives—albeit in different ways. Based on interacting theoretical concepts of individual [15,16] and structural stress [17,21], the stress perceived by these 3 groups appears to be interconnected. In addition to the possible interdependence of the 3 groups, there are differences in their perception of various stressors, such as the perceived importance of post-ICU outcomes (eg, survival rate). This highlights the need for an intervention that includes the perspectives of patients, relatives, and HCPs, and mediates between them [62]. There is empirical evidence on the efficacy of intra-ICU psychological care, such as for reducing post-ICU depression, posttraumatic stress disorder, and anxiety [63,64]. However, all controlled trials on stress-reduction interventions in ICUs known to us have focused solely on parts of these groups, such as patients [65], relatives [66], or HCPs [67]. To our knowledge, the IPS-Pilot is the first project to systematically assess psychosocial needs in ICUs and to develop and evaluate a complex intervention that addresses these needs for all

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involved groups at once, using a participatory process grounded in theory and evidence.

It remains to be examined whether integrated and simultaneous psychosocial care for these groups is beneficial or may lead to difficulties or even adverse effects. Based on prior experiences in Berlin and Ulm, the integration of a psychologist into ICU teams appears to be accepted, perceived as helpful, and frequently utilized by HCPs, patients, and their relatives. The integration of psychological care for both patients and professionals in the ICU context has also been advocated by professional associations, legal committees, and, based on our experience, by the involved groups themselves (eg, staff members).

A nonexperimental evaluation of patient and relative surveys conducted in Brazil [68] highlighted the different roles of psychologists working in ICUs. ICU psychologists can help patients and their relatives manage stress and negative emotions experienced during ICU treatment. In addition, psychosocial care may support HCPs in managing both individual and work-induced stress. The authors conclude that psychologists integrated into ICU teams can help improve team relationships and communication among HCPs, patients, and their relatives. A review on the role of psychologists in pediatric ICUs in Britain suggested that team integration and the mere presence of a psychologist may lead to greater consideration of psychological factors by the ICU team. Additionally, the ICU psychologist's easy approachability allows HCPs to seek advice on personally demanding cases or request short debriefing sessions [69].

By contrast, one could argue that consulting the ICU team or individual team members while treating patients and their families as part of the interdisciplinary team could lead to role conflict and affect the professional independence of the psychologist. Team members may be hesitant to seek advice from a team-integrated psychologist due to an unclear understanding of the psychologist's role or concerns about confidentiality or stigmatization, as research on the acceptability of workplace-integrated psychotherapeutic consultation suggests [70]. Similar difficulties may arise if supervision is needed due to a team conflict. Additionally, HCPs might fear being seen seeking the psychologist's advice, a limiting factor previously identified in studies on the use of psychological consultation in the workplace [71]. By involving stakeholders at multiple points throughout our intervention development process, we aimed to identify these and other potential issues in the intervention's implementation and explore possible solutions, such as outsourcing conflict-laden, multiperson interventions to external supporters. Based on the experiences of the research team and insights gained from former ICU ward psychologists in the focus groups, we will also include measures to support IPS therapists during the evaluation phase, such as supervision and intervision. The evidence described above clearly highlights the importance of a careful, trusting approach with a high level of confidentiality, as well as the need to consider possible role conflicts and the psychologist's role itself. These factors, which may limit the feasibility of the IPS intervention, were considered during the development process and will also be surveyed and evaluated in the feasibility study, which will be described in detail in the study protocol for phase B of the IPS-Pilot project.

In conclusion, there is a lack of systematically gathered evidence on how a complex, team-integrated psychosocial intervention in ICUs should be ideally designed, and whether the outcome of such an intervention design process proves to be feasible and effective. Through a multimethod approach, we aim to gain a broader insight into the needs of our target groups. Difficulties encountered in phase A, resulting from our choice of methods and targeted samples, will be monitored and included in the feasibility analysis during phase B.

Through a feasibility trial, the conditions that contribute to the successful implementation of the intervention and enable the execution of its mechanisms of change can be explored. Based on the results of phase B, it will then be determined whether a randomized controlled trial on the efficacy of the IPS intervention is feasible and should be conducted. Although our study is conducted solely in Germany to assess feasibility in this specific health care context, the IPS intervention may also be applicable in other health care settings. The similarity of the IPS intervention to examples from countries such as Brazil [68] and the United Kingdom [69] highlights the international interest and relevance of psychosocial support in ICUs. Furthermore, because the development of the IPS intervention is based not only on a needs assessment of German samples but also on international evidence gathered in the scoping umbrella review and internationally applied stress theories [17-24], there is reason to believe in its generalizability and potential for international feasibility.

Acknowledgments

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Data Availability

The data sets generated or analyzed during this study are available from the corresponding author (SFN) or principal investigators (HG, CA, FJ, and MR) upon reasonable request. Participants can assign themselves to a mailing list if they are interested in updates on and results of the study. The results of the substudies will be made public via scientific publications and presentations at conferences for ICU HCPs and in the field of health care research in general. Deidentified individual clinical trial participant-level data cannot be shared due to strict ethics committee and staff council regulations.

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Authors' Contributions

The coordinating center of IPS-Pilot is the Ulm University Medical Center (Department of Psychosomatic Medicine and Psychotherapy). HG is the principal investigator of the trial consortium. CA, FJ, and MR are the principal investigators of the collaborating study centers. Authors' contributions according to CRediT (Contributor Roles Taxonomy) [72] are as follows: KPD, SFN, HG, CA, FJ, and MR were responsible for conceptualization and funding acquisition. SFN, SK, GK, KS, LE, JK, LS, HH, WS, MB, SP, RKN, and JG were responsible for the investigation. HG, CA, FJ, MR, and WS were responsible for the methodology. SFN, SK, and CH were responsible for project administration. HG, CA, FJ, MR, and KH were responsible for supervision. SFN and SK were responsible for writing the original draft. SFN, SK, GK, LS, JG, WS, HH, KPD, CA, and HG were responsible for review and editing. All authors approved the final version. The funder, the Innovation Fund of the Federal Joint Committee (G-BA), has contributed to the study design. However, they have no role in data collection, management, analysis, interpretation, or reporting.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT checklist.
[PDF File (Adobe PDF File), 94 KB - resprot_v14i1e65682_app1.pdf]

Multimedia Appendix 2
PRISMA-ScR checklist and search string of the Scoping Umbrella Review.
[PDF File (Adobe PDF File), 262 KB - resprot_v14i1e65682_app2.pdf]

Multimedia Appendix 3
Interview and Focus Group guides.
[PDF File (Adobe PDF File), 547 KB - resprot_v14i1e65682_app3.pdf]

Multimedia Appendix 4
Sample Participant Information and Consent form.
[PDF File (Adobe PDF File), 252 KB - resprot_v14i1e65682_app4.pdf]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
COR: Conservation of Resources
DIVI: German Interdisciplinary Association for Intensive Care and Emergency Medicine (German: Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin)
HCP: health care professional
ICU: intensive care unit
IM: Intervention Mapping
IPS: Integrated Psychosocial Care (German: Integrierte Psychosoziale Versorgung)
MRC: Medical Research Council
PICS: postintensive care syndrome
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
PROSPERO: International Prospective Register of Systematic Reviews

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PSC: Psychosocial Safety Climate
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Efficacy and Safety of Haidebao Body Lotion in Patients With Mild Atopic Dermatitis: Protocol for a Multicenter, Double-Blind, Randomized, Placebo-Controlled Trial

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Abstract

Background: Atopic dermatitis (AD) is a chronic, relapsing skin condition that significantly impacts patients' quality of life. In clinical practice, AD is commonly managed through the use of emollients and topical corticosteroids. Haidebao Body Lotion (HBL) incorporated with calcium-based antimicrobial peptide compounds (CAPCS) has demonstrated clinical benefits for patients with mild AD, but there is a lack of high-quality clinical trial evidence.

Objective: In this study, we will implement a multicenter, double-blind, randomized, placebo-controlled trial to evaluate the efficacy and safety of HBL incorporated with CAPCS as an adjunctive therapy in ameliorating mild AD.

Methods: This multicenter, double blind, randomized, placebo-controlled trial will recruit 200 eligible participants from 10 hospitals in China from October 2023 to October 2025. In this study, AD will be confirmed in accordance with Williams diagnostic criteria, and patients with mild AD, aged 18-55 years, who provide signed informed consent will be enrolled. However, patients who are pregnant, have serious underlying diseases, have communication barriers, and violate medication regulations will be excluded. The 200 patients will be randomly assigned (1:1) to a treatment group (HBL with CAPCS; n=100, 50%) and a control group (HBL without CAPCS, placebo; n=100, 50%), and each participant will receive 3 sessions of treatments per day for 4 weeks. The primary outcome is the proportion of patients who achieve at least 60% improvement in the Eczema Area and Severity Index (EASI) score from baseline to week 2. The secondary outcomes include the Numeric Rating Scale (NRS), EASI50, EASI60, and Dermatology Life Quality Index (DLQI) scores at weeks 2 and 4, as well as adherence and adverse events. The full analysis set (FAS) and the per protocol set (PPS) will be analyzed using SAS 9.3 software, and missing data will be processed using the multiple imputation method. In this study, $P<.05$ is considered statistically significant.

Results: Participant recruitment began in January 2024. As of May 2025, we enrolled 180 patients, with 160 (88.9%) completing the 2-week follow-up. Data collection and management are still ongoing, and data analysis has not yet been performed.

Conclusions: This study will evaluate the clinical efficacy and safety of HBL incorporated with CAPCS in the treatment of patients with mild AD. If treatment efficacy is proven, HBL incorporated with CAPCS could be clinically used as an adjunctive therapy in ameliorating mild AD.

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KEYWORDS

atopic dermatitis; emollient; randomized controlled trial; study protocol; double blind; double-blind

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Introduction

Atopic dermatitis (AD) is a chronic, recurrent, inflammatory skin condition that affects approximately 11%-20% of children and 5%-8% of adults [1,2]. AD often begins in infancy, with approximately 50% of cases occurring before the age of 1 year [3]. AD usually exhibits a chronic course, occasionally protracts into adulthood, and is distinctly characterized by acute erythema featuring vague borders, accompanied by edema, blisters, and oozing blood [4]. In the chronic phase of AD, there is thickening of the skin, particularly in areas such as the cheeks, arms, and flexor surfaces of the trunk, which can result in sleep disturbances, severe life quality interference and daily activity deprivation, and the loss of psychological well-being [5,6]. AD is often associated with other allergic conditions, such as asthma and food allergies, and it may also increase the risk of nonallergic comorbidities, including various autoimmune or immune-mediated disorders, and psychiatric illnesses [7]. The persistent relapsing trajectory, elevated comorbidity rate, substantial economic burden, and involvement of the entire family in the treatment process have significantly reduced the quality of life of patients with AD and their family members [8,9].

The pathogenesis of AD is complex, involving genetic susceptibility, microbiome effects, environmental factors, and immune dysregulation [10]. Anti-inflammatory agents, phototherapy, wet-wrap therapy, systemic immunosuppressants, and short-term systemic steroid treatment are used to manage persistent or severe cases of AD [11]. However, use of the aforementioned local and systematic AD treatments often fails to provide long-term disease control due to safety concerns. Previous studies indicate that oral corticosteroids can ameliorate AD lesions, but the disease may flare up again if these medications are discontinued [12]. Moreover, topical steroids may cause side effects, involving skin thinning, lines, acne, cataracts, glaucoma, and delayed growth in children [13]. The use of antihistamines may lead to an increase in attention deficit hyperactivity disorder (ADHD) in children [14]. These side effects induced by local or systematic treatments restrict prolonged application of antihistamines in patients with AD.

The external application of moisturizing emollients is the basis for AD treatment, which can not only improve cuticle hydration and reduce inflammation [15] but also repair the damaged skin barrier, decrease the stimulation of external factors, and, thus, reduce the attack frequency and disease severity [16]. In patients with mild AD, continuous, frequent, and heavy use of emollients is recommended to maintain skin barrier function, even in the absence of lesions [17]. In recent years, the development of new active ingredients has led to the widespread clinical application of emollients to improve the skin barrier, with reparative, anti-inflammatory, and moisturizing effects, especially in patients with mild AD [18,19].

Calcium-based antimicrobial peptide compounds (CAPCS) consist of naturally occurring active calcium and a variety of antibacterial peptides (AMPs) derived from farmed marine shellfish. Previous studies indicate that active calcium can enhance capillary wall density, reduce capillary permeability and exudation, and safeguard the integrity of cell membranes. Simultaneously, active calcium can inhibit the release of inflammatory mediators and exhibit anti-inflammatory and anti-allergic properties. Previous studies indicate that calcium exists in the human body in the form of calcium ions. Calcium ions and their concentration gradients in the epidermis play a crucial role in regulating various skin functions, including keratinocyte differentiation, skin barrier formation, and permeability barrier homeostasis [20]. G protein–coupled receptors (GPCRs), which are widely expressed in mammals, are associated with skin pruritus through their signaling pathways. So, calcium ions can bind to G proteins, thereby inhibiting their activity and alleviating pruritus [21]. Moreover, the AMPs in CAPCS can alter bacterial cell membrane permeability, creating openings that allow calcium ions to rapidly enter the cells. This influx of calcium ions raises intracellular calcium levels, causing metabolic disruption and organelle leakage, ultimately leading to the death of pathogenic bacteria [22]. Additionally, AMPs can prevent bacterial infections, alleviate skin inflammatory responses, and thereby further improve patient symptoms [23]. Previous experimental studies indicate that CAPCS have therapeutic effects on AD, with similar efficacy as desonide cream (a weak corticosteroid) in controlling scratching and relieving itching in mice [24]. Haidebao Body Lotion (HBL) incorporated with CAPCS has also demonstrated clinical benefits for patients with mild AD, but there is a lack of high-quality clinical trial evidence. Therefore, this study aims to evaluate the treatment efficacy and safety of HBL incorporated with CAPCS in patients with mild AD.

Methods

Study Design

This study is a multicenter, double-blind, randomized, placebo-controlled clinical trial that will be conducted in 10 tertiary hospitals in China from October 2023 to October 2025. The 10 hospitals are the Shanghai Skin Diseases Hospital, the Third Hospital affiliated to Chongqing Medical University, the First Hospital of Hangzhou, the Third Hospital affiliated to Peking University, the First Hospital of Fujian Medical University, the Skin Diseases Hospital affiliated to South Medical University, the First Hospital of Wuhan, the First Hospital affiliated to Kunming Medical University, the Skin Diseases Hospital of Jiangxi, and the First Hospital affiliated to Anhui University of traditional Chinese medicine. In this study, patients with mild AD who provide signed informed consent will be randomly assigned (1:1) to a treatment group (HBL with CAPCS) and a control group (HBL without CAPCS, or placebo). This study is registered with the Chinese Clinical Trial Registry (ChiCTR2400087274).

Sample Size

In this study, the sample size was calculated based on the proportion of patients achieving at least 60% improvement (defined as the effective rate) in the Eczema Area and Severity Index (EASI) score from baseline to week 2 ($EASI_{60}$) in both the treatment group and the control group. A previous pilot study (data not published) indicated that the proportion of

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$EASI_{60}$ achievement at week 2 was 50% in the CAPCS group and 20% in the placebo group. In addition, a previous open-label clinical trial involving 60 pediatric patients with AD demonstrated comparable efficacy outcomes, with CAPCS combination therapy showing a 42.86% response rate versus 7.14% for the control group at week 2, with statistically significant differences (P<.05) [25]. In this study, we used the following formula to calculate the sample size:

We set the proportion of $EASI_{60}$ achievement at week 2 in the treatment group to p1=45%, the proportion of $EASI_{60}$ achievement at week 2 in the control group to p2=20%, the type I error to α=0.05, the type II error to β=0.1. The sample size calculation indicated that at least 70 patients be recruited in each group. Considering a 20% dropout rate and a 10% multicenter effect, we plan to enroll 100 patients with mild AD in each group, for a total of 200 patients with mild AD.

Participants

In this study, AD will be confirmed in accordance with Williams diagnostic criteria [26], and patients with AD will be recruited and screened from 10 tertiary hospitals in China from October 2023 to October 2025 by publishing recruitment announcements in newspapers or on information platforms of the hospital official websites, display boards outside the clinics, and information counters. All patients are required to sign informed consent forms before the study begins.

In this study, patients will be included if they meet the inclusion criteria as follows: (1) diagnosis of AD according to Williams diagnostic criteria, (2) age 18-55 years for both males and females, (3) a target lesion with a diameter of 2-10 cm located on the limbs or the trunk, (4) EASI score<6, and (5) skin area<5% body surface area before treatment. The exclusion criteria are as follows: (1) pregnant or lactating women; (2) patients who have undergone AD system treatment within 3 months or local treatment or phototherapy within the past 2 weeks at the time of recruitment; (3) patients with serious systemic diseases or disorders of the heart, lungs, liver, or kidneys or mental illness; (4) patients who are allergic to calcium supplements; (5) patients with systemic disease or an active skin condition (eg, psoriasis) that affects the evaluation; (6) patients with scars, birthmarks, tattoos, freckles, etc; (7) patients with bacterial, viral, or fungal infections requiring anti-infective therapy; (8) patients who have participated or are currently participating in clinical trials of other drugs within the past month; and (9) patients with communication barriers, unable to complete the questionnaire.

Randomization and Allocation Concealment

In this study, the block randomization method with a random combination of block lengths 4 and 6 will be used to assign the 200 patients with mild AD (1:1) to the treatment group (HBL with CAPCS; n=100, 50%) and the control group (HBL without CAPCS, placebo; n=100, 50%). Independent statisticians will use the entire randomization feature of SAS (SAS Institute) to construct 200 unique computer-generated random sequences for subsequent block randomization. The random numbers printed for participants will be placed in a light-resistant envelope and managed by a third party (not the investigators). If a patient is eligible after the baseline assessment and has provided informed consent, the clinical research coordinator will call the third party to obtain the patient's random number and finish the group assignment. Next, a dermatologist will administer the corresponding intervention to the patient.

Blinding

In this study, both patients with mild AD and dermatologists (investigators) will be blinded to the treatment allocation. Furthermore, the outcome assessors, data collectors, and statistician responsible for data analysis will also be unaware of the group assignment during the trial period to prevent bias.

Intervention and Control

Treatment Group

Patients with mild AD in the treatment group will undergo 3 treatment sessions with HBL incorporated with CAPCS every day for 4 weeks. To ensure the correct application of HBL, we will provide individual guidance to each patient, instructing them that 1 knuckle length of HBL should be used to cover no more than 2% of the body surface area and to apply a 3-5-minute finger massage to promote its absorption. In this study, patients will also be instructed not to use any additional treatment for AD. If a patient uses additional treatment for an emergency, detailed information will be recorded and the patient will be asked to withdraw from the trial.

Control Group (Placebo)

Patients with mild AD in the control group will undergo 3 treatment sessions with the placebo (HBL without CAPCS) every day for 4 weeks. The HBL placebo is produced and provided by Shell Party Innovations Technology (Shenzhen) Co, Ltd, which maintains complete consistency in HBL in terms of appearance, weight, color, odor, and package, except for the incorporation of CAPCS (Figure 1). The application, individual guidance, and instruction regarding HBL placebo use in the control group will be completely in line with that in the treatment group. Patients in the control group will also be instructed not to use any additional treatment for AD. Like before, if a patient uses additional treatment for an emergency condition, detailed information will be recorded and the patient will be asked to withdraw from the trial.

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Figure 1. Images of HBL used for the 2 study groups. CAPCS: calcium-based antimicrobial peptide compounds; HBL: Haidebao Body Lotion.

Follow-Up

In this study, all patients will undergo a physical examination and skin lesion evaluation at baseline (day 0) following enrollment and then will be followed up for 4 weeks subsequently and undergo treatment efficacy evaluation at weeks 2 and 4. Detailed information about data collection, physical examination, and skin lesion evaluation is shown in Table 1.

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Table 1. Detailed information about the timeline for data collection, physical examination, and skin lesion evaluation.

Study period	Enrollment (day 1)	Baseline (week 0)	Follow-up (week 2)	Follow-up (week 4)
Informed consent	Yes	N/A[a]	N/A	N/A
Screening	Yes	N/A	N/A	N/A
Clinical assessment	Yes	N/A	Yes	Yes
Medical history	Yes	N/A	Yes	Yes
Laboratory examination	Yes	N/A	N/A	Yes
Taking photos of lesions	N/A	Yes	Yes	Yes
NRS[b] for itching	N/A	Yes	Yes	Yes
EASI[c]	N/A	Yes	Yes	Yes
DLQI[d]	N/A	Yes	Yes	Yes
Drug use	N/A	N/A	Yes	Yes
Adverse effects	N/A	N/A	Yes	Yes

[a]N/A: not applicable.

[b]NRS: Numeric Rating Scale.

[c]EASI: Eczema Area and Severity Index.

[d]DLQI: Dermatology Life Quality Index.

Outcomes

Primary Outcome

In this study, the primary outcome is set as the proportion of patients who achieve $EASI_{60}$ at week 2. The $EASI_{60}$ is defined at least 60% improvement in the EASI score from baseline to week 2, which is calculated as (EASI at baseline – EASI at week t)/(EASI at baseline) × 100%.

Secondary Outcomes

EASI Score

The EASI score is commonly used to evaluate the condition of AD that is based on the severity of erythema (E), edema/papules/infiltration (I), desquamation (D), and lichenification (L) of the patient's skin lesions and the affected area of involvement of the skin lesions in the head and neck (H), upper limbs (U), trunk (T), and lower limbs (L). The EASI score is calculated as H(E + I + D + L) × 0.1 + U(E + I + D + L) × 0.2 + T(E + I + D + L) × 0.3 + L(E + I + D + L) × 0.4, in which the affected area of involvement of the skin lesion (H, U, T, L) is evaluated through a 7-point Likert scale, with 0=0%, 1≤10%, 2=10%-29%, 3=30%-49%, 4=50%-69%, 5=70%-89%, and 6=90%-100%. The severity of erythema (E), edema/papules/infiltration (I), desquamation (D), and lichenification (L) is assessed through a 4-point Likert scale, with 0=none, 1=mild, 2=moderate, and 3=severe [27]. The EASI score ranges from 0 to 72, with a higher score suggesting that the patient is more ill. In this study, EASI scores will be assessed at baseline (week 0), week 2, and week 4 after treatment, and EASI50 and EASI75 scores will be assessed at weeks 2 and 4.

NRS Score

In this study, we will use the Numeric Rating Scale (NRS, score 0-10) to evaluate the degree of pruritus in patients with mild AD. The NRS is an 11-point Likert scale scored from 0=no pruritus to 10=extreme pruritus. The degree of pruritus will be categorized as no pruritus (NRS=0), mild pruritus (NRS=1-3), moderate pruritus (NRS=4-6), severe pruritus (NRS=7-8), and extremely severe pruritus (NRS=9-10) based on the NRS score [28,29]. In this study, we will assess the degree of pruritus in patients with mild AD before HBL application and at 1, 5, 10, 15, and 30 minutes following HBL application at baseline. We will also assess the degree of pruritus based on the NRS score once at weeks 2 and 4 after treatment.

IGA Score

The investigator's global assessment (IGA) score will be used to estimate the overall condition of patients with mild AD. The IGA is a 6-point Likert scale, with 0=no erythema or inflammatory signs of AD, 1=minimal erythema and barely perceptible edema/papules/infiltration, 2=mild erythema and edema/papules/infiltration, 3=moderate erythema and edema/papules/infiltration, 4=severe erythema and edema/papules/infiltration, and 5=extreme skin lesions accompanied with severe erythema and edema/papules/infiltration [30]. In this study, the IGA score will be estimated at baseline (week 0), week 2, and week 4.

DLQI Score

The Dermatology Life Quality Index (DLQI) focuses on various impacts of skin diseases on patients in the last week, which mainly covers 7 dimensions: physiological response, psychological feeling, family, interpersonal communication, occupational restrictions, social activities, and treatment response [31]. The DLQI includes 10 items, all scored through a 4-point rating system of 0=none, 1=mild, 2=severe, and 3=extremely severe (see Table 2). The DLQI score is obtained by summing up the scores of each item, which ranges from 0 to 30, with a higher score suggesting lower dermatology life quality [32]. In this study, the DLQI score will be estimated at baseline (week 0), week 2, and week 4.

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Table 2. Questions and answer options in the DLQI[a].

Question number	Question (over the last week)	Options
1	How itchy, sore, painful, or stinging has your skin been?	a. None b. Mild c. Severe d. Extremely severe
2	How embarrassed or self-conscious have you been because of your skin?	a. None b. Mild c. Severe d. Extremely severe
3	How much has skin disease affected your shopping and household chores?	a. None b. Mild c. Severe d. Extremely severe
4	How much has your skin influenced the clothes you wear?	a. None b. Mild c. Severe d. Extremely severe
5	How much has your skin affected any social or leisure activities?	a. None b. Mild c. Severe d. Extremely severe
6	How much has your skin made it difficult for you to play any sport?	a. None b. Mild c. Severe d. Extremely severe
7	How much has your skin condition interfered with your ability to work or study?	a. None b. Mild c. Severe d. Extremely severe
8	How much has your skin created problems with your partner or any of your close friends or relatives?	a. None b. Mild c. Severe d. Extremely severe
9	How much has your skin caused any sexual difficulties?	a. None b. Mild c. Severe d. Extremely severe
10	How difficult is it for you during the treatment process, such as time delays?	a. None b. Mild c. Severe d. Extremely severe

[a]DLQI: Dermatology Life Quality Index.

Adverse Events

In this study, patients with mild AD will be informed of the risks that may arise in the study before they sign the informed consent form. We have defined adverse events as unintended signs, symptoms, or diseases occurring after treatment that are not necessarily related to the intervention. The occurrence of any adverse events will be accurately recorded in the case report form (CRF). In this study, appropriate treatment will be provided by dermatologists when they encounter adverse events, and the adherence condition of patients and adverse events will be recorded.

Withdrawal and Dropout

According to the Declaration of Helsinki, all participants will be respected and can withdraw from the study at any time for

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any reason. The personal information about participants will be collected and kept confidential. In this study, patients can withdraw at any time, and the reason for withdrawal will be recorded in the CRF.

Ethical Considerations

This study was reviewed and approved by the Ethics Committee of Shanghai Dermatology Hospital and the Institutional Ethics Review Committee of the Shanghai Skin Diseases Hospital in 2023 (approval number 2023-33). The implementation of the study will strictly adhere to the Declaration of Helsinki. Any adverse events, violations, and amendments to the study protocol or informed consent form will be reported to the Ethics Committee of the Shanghai Skin Diseases Hospital. All patients will sign the informed consent form before enrollment, and participant information will be protected.

Quality Control

In this study, we will implement a series of measures to improve data quality and ensure the reliability of collected data. First, we will implement a pilot study to train all investigators participating in this study and to evaluate the reliability and validity of the CRF used for data collection. Second, we will assign two PhD students as the inspectors to conduct comprehensive checks in order to ensure the accuracy and integrity of the collected data. Third, we will actively contact all recruited patients during the 4 weeks of follow-up because frequent communication will enhance the patients' trust and thereby increase their willingness to participate and remain in the study.

Statistical Analysis

In this study, all data will be recorded in the CRF and then input into a database established using Epidata 3.1 software. The full analysis set (FAS) and the per protocol set (PPS) will be analyzed using the SAS 9.2 statistical package, and missing data will be processed using the multiple imputation method. In this study, quantitative variables with a normal distribution will be expressed as means (SDs), while quantitative variables with a skewed distribution will be expressed as medians (IQRs). Qualitative variables will be expressed as frequency counts and proportions (%). We will apply the 2-sample Student *t* test or the Wilcoxon rank-sum test to examine differences between groups for quantitative variables, as appropriate, and repeated measurement data will be analyzed using repeated-measure ANOVA. The Wilcoxon rank-sum test, the chi-square test, or the Fisher exact test will be performed to examine the differences between groups for qualitative variables, as appropriate. In this study, $P<.05$ (2-tailed) will be considered statistically significant.

Results

The flowchart of this study is shown in Figure 2. Participant recruitment began in January 2024 and is proposed to be finished by July 2025. As of May 2025, we enrolled 180 patients, with 160 (88.9%) completing the 2-week follow-up. Data collection and management are still ongoing, and data analysis has not yet been performed.

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Figure 2. Study flowchart. CAPCS: calcium-based antimicrobial peptide compounds; DLQI: Dermatology Life Quality Index; EASI: Eczema Area and Severity Index; HBL: Haidebao Body Lotion; IGA: investigator's global assessment; NRS: Numeric Rating Scale.

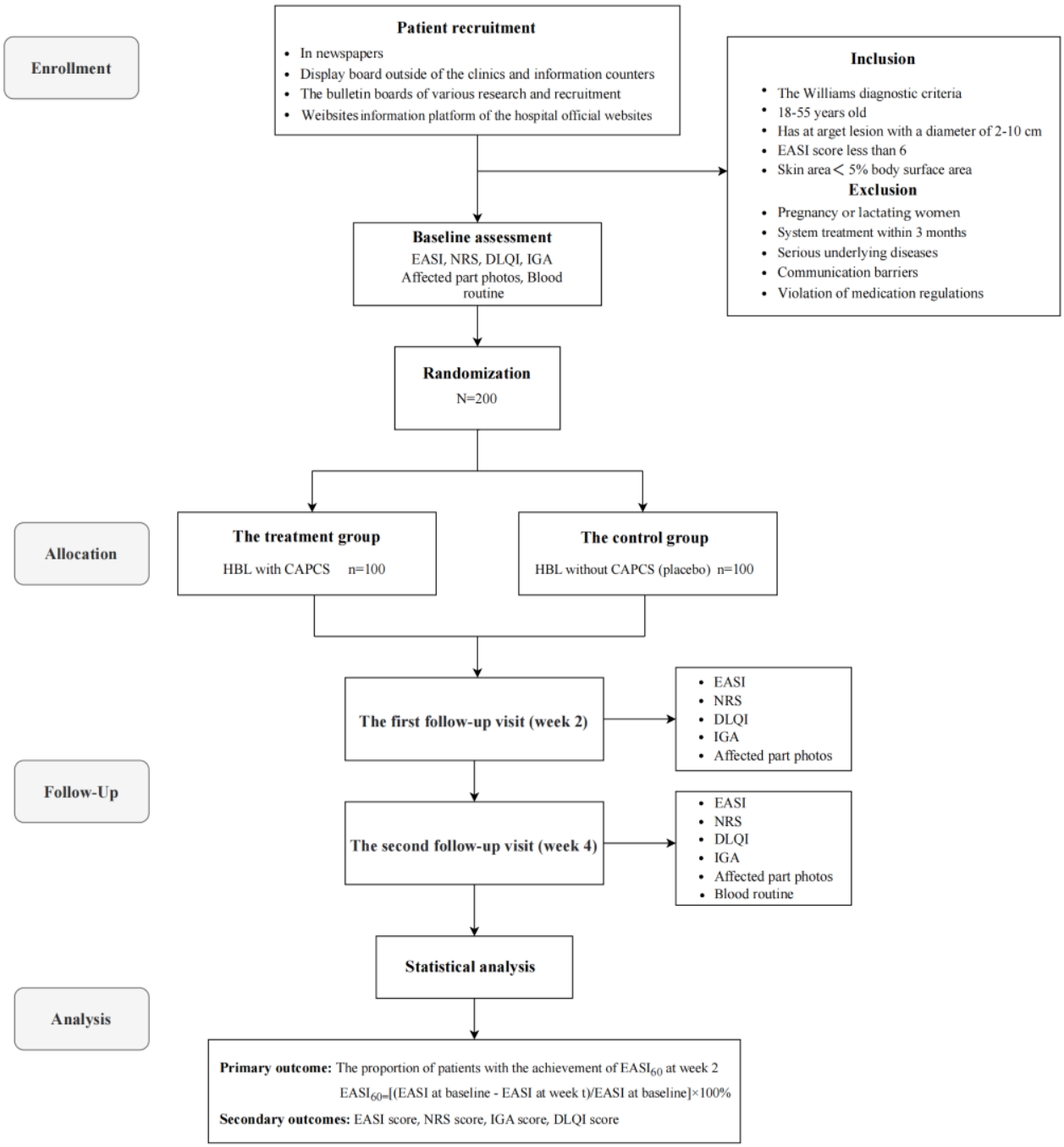

Discussion

Summary

AD is an autoimmune inflammatory skin disease that can last for a lifetime [33]. AD usually exhibits a chronic course, with thickening of the skin, sleep disturbance, severe life quality interference, and daily activity deprivation, which not only causes physical pain for the patient but also imposes heavy social and economic burdens on them [34,35]. For AD treatment, anti-inflammatory agents, wet-wrap therapy, systemic immunosuppressants, and short-term steroid treatment are used to manage persistent or severe AD cases [11]. However, the use of local and systematic treatment often fails to provide long-term disease control due to safety concerns. As adjuvant therapy, the external application of moisturizing emollients is the basis for AD treatment, which can not only improve the hydration of the cuticle and reduce inflammation [15] but also repair the damaged skin barrier, decrease the stimulation of external factors, and reduce the attack frequency and disease severity [16]. In recent years, the development of new active ingredients has led to the widespread clinical application of emollients to improve the skin barrier in patients with AD.

CAPCS, as new active ingredients, are derived from farmed marine shellfish. Previous studies indicate that the active calcium in CAPCS can inhibit the release of inflammatory mediators and exhibit anti-inflammatory and anti-allergic properties.

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Moreover, HBL incorporated with CAPCS has similar therapeutic effects as desonide cream in scratch control and itching alleviation in mice and in patients with AD [21], but there is a lack of high-quality clinical trial evidence. This protocol outlines the basic principle and design of a multicenter, double blind, randomized, placebo-controlled trial with 200 patients with mild AD in China. We plan to evaluate the treatment efficacy and safety of HBL incorporated with CAPCS in the enrolled patients, which is expected to yield more generalizable evidence due to the diversity in geography, climate, and participants from the 10 selected hospitals. To the best of our knowledge, this is the first multicenter clinical trial that will recruit 200 patients with AD to evaluate the treatment efficacy and safety of HBL incorporated with CAPCS in China. The clinical data of patients with AD will be extracted from the health information system (HIS) directly without recall bias, resulting in high data quality.

Limitations

This study may have a few limitations. First, the study period is set to 4 weeks, which limits the observation of the long-term effects of HBL incorporated with CAPCS, as well as its efficacy in prevention of disease recurrence in patients with AD. Second, differences in climate (temperature, humidity, ultraviolet radiation, seasonal changes), lifestyle habits (high-fat food consumption, high-calorie diets, tobacco smoking, alcohol drinking) and other extrinsic factors (cultural differences, occupational exposure, etc) in the 10 selected hospitals may cause information bias, which should be adjusted through sensitivity analysis and subgroup analysis. Third, patients in this study will be instructed not to use any additional treatment for AD, which might induce a relatively high rate of withdrawal in them.

Conclusion

This study is expected to confirm that the application of HBL incorporated with CAPCS can relieve itching, control scratching, and improve the skin barrier with reparative, anti-inflammatory, and moisturizing effects. If the treatment efficacy is proven, HBL incorporated with CAPCS could be clinically used as an adjunctive therapy in ameliorating mild AD.

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Authors' Contributions

ZD and RW conceived and designed the study protocol and participated in drafting the manuscript. ZD and YD wrote the paper and contributed to the coordination and implementation of the research. RW revised the study protocol, wrote several sections of the manuscript, and assisted in developing research measures and collecting data. All authors participated in drafting the manuscript and have read and approved the final version.

Conflicts of Interest

None declared.

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Abbreviations

AD: atopic dermatitis
AMP: antibacterial peptide
CAPCS: calcium-based antimicrobial peptide compounds
CRF: case report form
DLQI: Dermatology Life Quality Index
EASI: Eczema Area and Severity Index
FAS: full analysis set
HBL: Haidebao Body Lotion
IGA: investigator's global assessment
NRS: Numeric Rating Scale
PPS: per protocol set

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Protocol

Sexual Health Determinants During the Life Course and Migration of Haitian-Origin People in French Guiana: Protocol for the Parcours d'Haïti Biographical and Transdisciplinary Study

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Abstract

Background: French Guiana, an overseas territory located in the Guiana Shield in South America, faces unique social and demographic challenges, particularly in relation to migration. Haitians represent 1 of the 3 largest foreign communities in the region and face specific barriers to health care access and prevention. They are also a population exposed to HIV infection.

Objective: This Parcours d'Haïti study aims to update knowledge on the health of the Haitian population residing in French Guiana. From a quantitative standpoint, the primary objective of this study was to assess the frequency of sexual behaviors that expose Haitian individuals to HIV risk after arriving in French Guiana and explore the association of this risk with their living conditions. This study adopts a transdisciplinary approach to understand the broader determinants of health and the processes underlying HIV transmission.

Methods: This mixed methods study involves a quantitative epidemiological and biographical analysis of Haitian individuals aged 18 to 60 years who have lived in French Guiana for more than 3 months. The biographical component uses a detailed grid

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that tracks key life events since birth. The qualitative component includes 3 substudies based on semistructured interviews and focus groups with Haitian people and health care professionals. These aim to deepen understanding of health care access, use of traditional and biomedical care, and mental health among Haitians. A phylogenetic component describes the distribution of clades of the Pol gene in the viruses of people living with HIV. The study materials were cocreated with local stakeholders. Recruitment of this partially hidden population used an innovative method involving all local actors and targeting key locations frequented by the Haitian community. Data collection and recruitment were carried out by Haitian Creole–speaking peer investigators (community health mediators).

Results: Over 20 months between 2021 and 2023, the Parcours d'Haïti study was implemented in French Guiana. Anticipated results suggest that the main reasons for migration include insecurity and fleeing violence. Upon arrival, Haitian people likely experience significant economic hardship and social isolation. Mental health deterioration is expected, with high rates of posttraumatic stress disorder. People living with HIV are expected to face heightened vulnerability compared to HIV-negative individuals even though they already struggle with precarious living conditions. The qualitative findings regarding health care use indicate that Haitian people encounter numerous barriers to accessing health care, such as administrative complexity, language, and financial and mobility issues. The anthropological results are expected to emphasize the magical-religious origins of HIV and the use of plants and traditional medicine for its treatment. Phylogenetic results are anticipated to show a high prevalence of Caribbean B HIV subtypes.

Conclusions: The Parcours d'Haïti study aims to provide valuable insights into the health determinants and HIV-related risks in the Haitian population in French Guiana. These findings should help refine health care policies and practices to better meet the specific needs of this population. Trial Registration: ClinicalTrials.gov NCT05174234; https://clinicaltrials.gov/study/NCT05174234

International Registered Report Identifier (IRRID): DERR1-10.2196/63586

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KEYWORDS

HIV; hepatitis B virus; HBV; sexual and reproductive health and rights; transient and migrants; migrants' health; socioeconomic factors; sexual behavior; violence; gender-based violence; health care quality; access and evaluation; health service accessibility; cultural representations; French Guiana; Haiti

Introduction

French Guiana is a French South American overseas territory in the Guiana Shield close to the Amazon with a population of 286,618 inhabitants in 2021 [1]. Because of its location and history, this territory is inhabited by people of diverse origins and nationalities [2]. As a result, more than 60 languages are spoken in French Guiana, and approximately one-third of today's population was born abroad [1-3]. Migration from Haiti represents a major social and demographic challenge in French Guiana [2]. According to 2017 census data, 9.3% of the population in French Guiana originated from Haiti, 1 of the 3 main foreign communities along with those from Brazil and Suriname. It is estimated that 1 in 10 inhabitants speaks Haitian Creole in daily life [3]. Population movements from Haiti have existed since the country's political turbulence in the 80s and were reinforced by the earthquake in 2010, the closure of the Dominican border in 2015, the 2018 social crisis in Haiti, and the assassination of the Haitian president in 2021. Studies conducted on the sexual health of migrant women in French Guiana in 2021 showed that Haitian women make up the vast majority of the cohorts in health centers set up to welcome migrants, suggesting that migration flows from Haiti continue to be very dynamic [4].

French Guiana is a territory where precariousness is common, with more than half of Guianese inhabitants having a low standard of living and more than 20% having a very low standard of living [5]. This reality particularly affects households where the reference person was born abroad—in that case, more than three-quarters live below the poverty line [5]. After arriving in French Guiana, people's living conditions deteriorate, not only in terms of housing but also socially and administratively—many people arriving and living in French Guiana do not have a residence permit [4].

French Guiana also faces major health challenges. In 2020, life expectancy at birth was still lower than in continental France in a context of dynamic birth rates [6,7]. In total, 7 major health determinants have been identified by the Haut Conseil de la Santé Publique (High Council for Public Health), including sexual and reproductive health, gender equality, infectious risks, food, nutrition, and mental health [8].

French Guiana is the French territory most affected by HIV, with a prevalence >1% in the general population [9]. Most people living with HIV in French Guiana are of foreign origin [10]. Recent studies in French Guiana (one based on the slope of CD4 decline and the other on virus phylogeny) showed that, among the foreign population living with HIV, more than half had been infected in French Guiana [10,11]. The link between migration and living conditions in the country of arrival has already been established. The Agence Nationale de Recherches sur le Sida et les hépatites virales (the French National Agency for Research on AIDS and Viral Hepatitis; ANRS) Parcours 2012 to 2013 study highlighted the issue of HIV acquisition in the Île-de-France region and late detection of chronic hepatitis B virus (HBV) infections among immigrants from sub-Saharan Africa in relation to their poor living conditions after arriving in France [12,13].

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In terms of health and history, Haiti is a country that has been particularly affected by HIV since the 1970s and throughout the epidemic [14]. In 2021, according to the World Bank, 1.8% of the Haitian population was living with HIV [15]. The Haitian population in French Guiana is disproportionately affected by HIV infection—according to surveillance data, 46% of the HIV cohort participants under follow-up in the Cayenne Hospital outpatient department originated from Haiti. Between 2013 and 2018, Haitians represented 36.4% of new HIV infections in French Guiana [16]. Diagnoses are often made later than for native-born people—for Haitian people living with HIV, the time between seroconversion and diagnosis was 4.5 years on average (compared with 3.1 years for people living with HIV born in France) and was 5 years higher among men than among women [17]. The magical-religious importance and impact of stigma has already been explored among the Haitian population in French Guiana [18]. Some diseases, notably HIV, have a high level of social stigma, which can have an impact on people's use of prevention and care. A similar observation can be made for hepatitis B. In French Guiana, the prevalence of chronic HBV infection is estimated at nearly 1.5%, compared with 0.3% in continental France. Once again, Haitians are particularly affected— the presence of the hepatitis B surface antigen (a marker of hepatitis B infection) concerns 2.5% of Haitian women registered in the French Guiana pregnancy registry [19].

Another study on knowledge, attitudes, and practices showed the high frequency of risky sexual behavior that can expose people to HIV among migrants without, however, specifying them by country of origin. Notably, 35.6% of participants reported engaging in risky behaviors over the previous 12 months (including inconsistent condom use with casual or commercial partners, having multiple sexual partners, or engaging in concurrent partnerships) [20]. A phylogenetic study conducted in French Guiana showed that people from Haiti were less likely to have viruses from large transmission clusters than other immigrants and were more likely to have viruses from small transmission clusters or dyads [11]. Thus, we hypothesize that there are particular conditions leading to a singular epidemiology in this community.

In addition to these local data focusing on sexual health and infectious diseases, international literature highlights several health issues among Haitian migrants worldwide that should be investigated in French Guiana [21,22]. Research suggests that their access to cervical cancer prevention and screening may be inadequate. The mental health of those who have experienced adversity may be impaired, these experiences, along with cultural differences between caregivers and patients, may influence the modalities of care [23,24]. In addition, common health issues could have consequences linked to poorer access to care [25]. The interrelationships among traditional medicine, vodou, herbal medicine, and modern medicine need to be explored [26].

Therefore, all these factors seem to point to the particular needs regarding health, sexual and reproductive health, and rights of the Haitian population, a large and growing part of French Guiana's population. The Haitian population in French Guiana is a key population for public health in terms of improving not only their health but also the health of the entire Guianese population.

We hereby describe the Parcours d'Haïti study protocol, conceived to update knowledge on the Haitian population living in French Guiana using a transdisciplinary approach to gain a detailed understanding of health determinants and underlying processes of HIV or HBV infection.

Methods

Study Objectives

From a quantitative perspective, using notably a biographical approach, the main objective of this study was to evaluate the frequency of sexual behavior exposing people from Haiti to the risk of HIV infection after their arrival in French Guiana and its association with their living conditions. Secondary objectives consisted in describing migration routes, living conditions, access to health insurance coverage and health care, contacts with medico-social structures, social support, general state of health, mental health, and levels of food insecurity after arrival in French Guiana. With regard to sexual and reproductive health and rights, the objectives were to study the delay in first screening for sexually transmitted infections (STIs), as well as the factors associated with earlier screening; study the delay in entry into care and retention in care for people living with HIV or HBV and their determinants; and investigate the use of birth control methods, the frequency of wanted and unwanted pregnancies, and the use of abortion. With regard to emotional life, the objectives were to describe the relational and sexual life.

From a qualitative exploratory perspective, the objectives were to investigate and describe the social representations of HIV and HBV infections and their impact on the use of prevention and biomedical and traditional care. In addition, representations of the Guianese health care system and its prevention services were explored, as well as an anthropological understanding of representations of the body and illness in relation to the ethnomedicinal conceptions of people of Haitian origin living in French Guiana. Finally, another objective was to explore the obstacles to and facilitators of accessing mental health care and understand the mental health problems encountered and the responses provided to migrants in French Guiana from the point of view of health professionals, social workers, and local nongovernmental organizations (NGOs). From a phylogenetic perspective, we aimed to describe the distribution of clades of the Pol gene in the viruses of people living with HIV from Haiti.

Hence, the Parcours d'Haïti study is a mixed methodology study. First, a quantitative component based on an epidemiological (cross-sectional and biographical) study was conducted using a questionnaire and a hetero-administered biographical grid. The questionnaires were administered by Haitian Creole–speaking mediators, for the most part from the local community. Mediators were recruited for their linguistic expertise and interpersonal skills and then trained to collect complex data effectively. Second, a qualitative component based on a socioanthropological ancillary study using participant observation and semistructured interviews (itself developed

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along several dimensions) was conducted. Third, a phylogenetic analysis of HIV Pol gene sequences based on sequences collected as part of routine care (a resistance genotype analysis is systematically performed before antiretroviral therapy initiation) was conducted. The qualitative component of the research was conducted primarily by a Haitian Creole–speaking anthropologist with extensive experience in studying Creole societies supported by 2 researchers trained in qualitative methodologies.

Ethical Considerations

This study involved human participants and is covered by French law 2012-300 of 5 March, 2012, known as the Jardé Law, as category 3 research involving the human person, which provides for the analysis of anonymized personal medical data previously collected during routine care. The sponsor and the person directing and supervising the research undertaken ensured that this research was carried out in accordance with the Jardé Law and the Declaration of Helsinki in its latest version.

The study protocol and related participant documents were reviewed and approved by the Comité de Protection des Personnes Sud-Est I (South-East Ethics Committee for the Protection of Persons; October 11, 2021), together with 3 substantial modifications along the course of the study carried out between November 1, 2021, and July 31, 2023. In addition, an ancillary qualitative study has been reviewed and approved by the Comité de Protection des Personnes Sud-Est I (South-East Ethics Committee for the Protection of Persons; May 9, 2022).

The controller and processor of data recorded during this research was the Centre Hospitalier de Cayenne (Cayenne Hospital Center) in accordance with the French Data Protection Act 78-17 of 6 January, 1978, amended by law 2004-801 of 6 August, 2004, and the European Union regulation (EU 2016/679), titled the General Data Protection Regulation.

This research falls within the scope of the Reference Methodology (MR-003). The Centre Hospitalier de Cayenne has signed an undertaking to comply with the Reference Methodology and has a certificate of compliance number 2215826 version 0 from November 20, 2019 (certificate renewed on December 21, 2021, under the number 2224668 version 0). A privacy impact assessment was carried out in accordance with MR-003.

This research was registered on ClinicalTrials.gov under the national clinical trial NCT05174234 and has ID-RCB (National Identifier generated by the French National Medicines Agency) number 2021-A02185-36.

Before the start of recruitment, agreements were signed with all participating centers as well as with relay points to facilitate recruitment by general practitioners, associations, and NGOs.

All those involved in the research have been trained on good clinical practice and the rules of confidentiality and medical secrecy. Before data collection, for all quantitative and qualitative aspects of the study, participants were provided with full information on the research, and a declaration of consent was completed. Finally, each participant was given an anonymized number, and all information was pseudonymized. As a thank you for the time spent in the interview (regardless of which part they participated in), participants received a compensation kit made of toiletry bag containing soap, body lotion, shampoo, condoms, masks, toothbrushes, and toothpaste.

Similarly, semistructured interviews could only be recorded after the participants provided their consent. Concerning viral sequences, after participants' consent, the Pol gene sequence will be extracted from existing sequences, anonymized, and transferred securely to the partner laboratory at the Oswaldo Cruz Institute of the Oswaldo Cruz Foundation (Fiocruz) in Rio de Janeiro for analysis. No personal or identifying data will be transmitted to Fiocruz.

Study Populations and Inclusion Criteria

For the quantitative epidemiological and biographical component, participants were included in 3 groups: a general population group, a group of people living with HIV, and a group of people living with HBV.

The inclusion criteria for all groups were as follows: being born in Haiti (regardless of current nationality), having been in French Guiana for >3 months, being aged between 18 and 60 years, and having no objection to participate in the study. For the group of people living with HIV, the inclusion criteria were as follows: living with HIV and having a diagnosis dating back >3 months (whatever their status with regard to hepatitis B and C), as well as being followed up on by one of the study's partner physicians at the hospitals in Cayenne, Kourou, or Saint-Laurent-du-Maroni; in outpatient care; or by a partner association. For the group of people living with chronic hepatitis B, the inclusion criteria were living with a chronic HBV infection and having been diagnosed for >3 months (not coinfected with HIV), as well as being followed up on by one of the study's partner physicians in the hospitals of Cayenne, Kourou, or Saint-Laurent-du-Maroni; in outpatient care; or by a partner NGO.

For the general Haitian population group (not known to live with HIV or HBV), the inclusion criteria were declaring that they were not infected with either HIV or HBV, being under the care of one of the study's partner physicians, or being recruited in the public space of one of the cities targeted by the study (Cayenne, Matoury, Rémire-Montjoly, Macouria, Kourou, Montsinéry-Tonnegrande, Sinnamary, Maripasoula, Saint-Laurent-du-Maroni, or Mana). Exclusion criteria were being unable to answer the interviewer in French or Haitian Creole; being under guardianship, tutelage, or legal protection; and having already answered the study questionnaire.

For the exploratory qualitative sections focusing on health anthropology, mental health, and access to care, the inclusion criteria were tailored to each substudy and comprised the following professionals, including (1) health professionals, social workers, or members of local NGOs with experience working with migrants in French Guiana between 2021 and 2023 who agreed to participate in the study (the mental health and access to care substudies were conducted exclusively with health care professional), and (2) community members, including representatives of the Haitian community who met the inclusion criteria of being born in Haiti, regardless of their

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current nationality, residing in French Guiana for >3 months and who were aged >18 years and provided consent to participate in the study. For individuals living with HIV or HBV, the same criteria applied, with an additional requirement of being a diagnosed person living with HIV or HBV.

Sample Size

The number of participants required was calculated to estimate the frequency of the main indicators (sexual behavior that exposes one to the risk of acquiring HIV, including inconsistent condom use with casual or commercial partners, having multiple sexual partners, engaging in concurrent partnerships, and exposure to sexual violence [20]) based on an expected percentage of 50% with a precision of 5% using the following formula:

In this formula, is 1.96 for an agreed risk of 0.05, π is the frequency of the factor studied (in this case, 50% or 0.5), and Δ is the accuracy required (in this case, 5% or 0.05).

From estimates of a total of 384 participants per group, and to take into account incompleteness of data collection, the target was set at 400 people living with HIV and 400 people living with HBV. Considering a 1:2 ratio, 1600 participants were planned in the general population group to have sufficient power to carry out multivariate analyses on all study indicators and conduct analyses on subpopulations of interest, such as women, men, youth, people who arrived after 2015, people living in extreme poverty, and people who have used transactional sex.

Concerning the feasibility of including people living with HIV from Haiti, the number of patients actively being followed up on in Guiana's hospitals was estimated at 889 in 2021. For the group of people living with HBV from Haiti, the cohort in 2021 was 250 people being actively followed up on in hospital departments. These data are largely underestimated as they do not take into account those who have been lost to follow-up. In terms of the general population, nearly 10% of the Guianese population is of Haitian origin. Thus, the recruitment objectives seem achievable in view of the study's target population.

Participant Enrollment, Sampling Approaches, and Monitoring

For the quantitative aspects of the study, sampling of the Haitian population in French Guiana—little explored, partially hidden (living in informal settlements and without papers), and rapidly evolving—was carried out by combining several methods. Recruitment sites were chosen on a nonprobabilistic and reasoned basis. Locations were selected based on literature analysis, census data, knowledge of the peer community workers, knowledge of partner NGOs, and accessibility and safety. These criteria are listed in Figure 1. Finally, partner hospital departments, outpatient centers (health care access offices, French Red Cross prevention and health centers, and primary care centers), and general practitioners were identified. The hospital services selected were those that limited bias on morbidity (particularly chronic diseases). The medical departments selected for participant screening and enrollment were maternity, pediatrics, dermatology, and the emergency room. In view of the enrollment sites mentioned, an oversampling of women was expected and judged as acceptable.

Figure 1. Selection criteria for mapping and choosing locations for recruitment for the Parcours d'Haïti study between 2021 and 2023. NGO: nongovernmental organization.

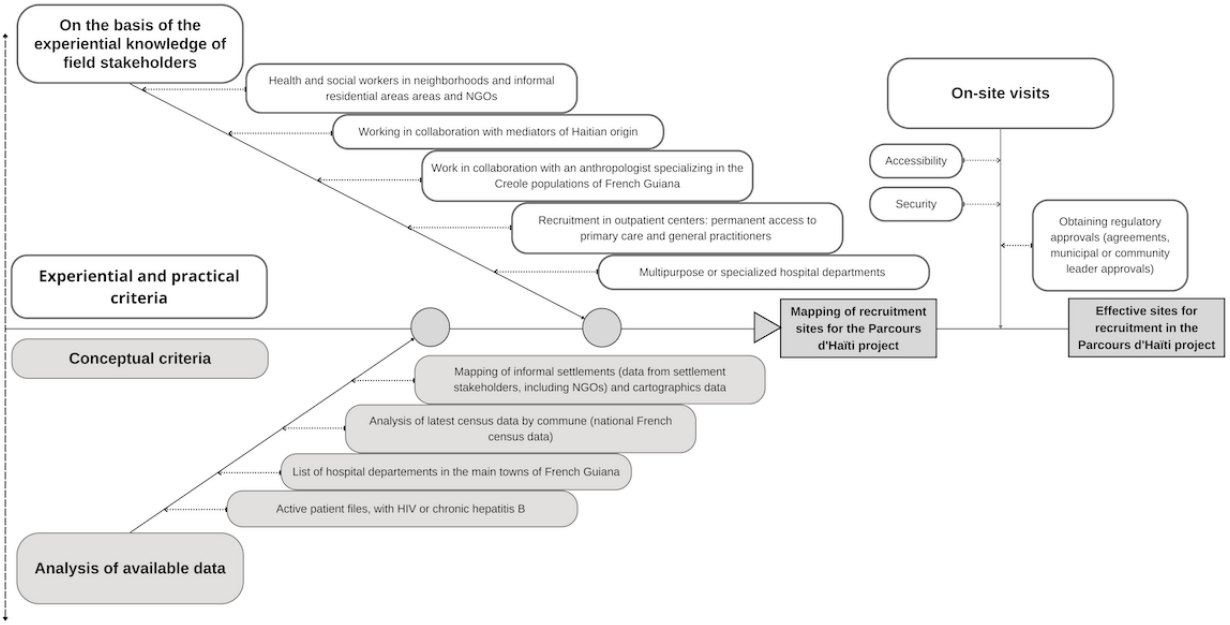

At the recruitment sites, random recruitment was carried out—all people meeting the inclusion criteria were invited to take part in the study. Recruitment was halted once we reached a reasonable number of participants from a statistical power perspective and representativity of the study populations.

To improve the representativeness of the sample, additional recruitment using the snowball method was planned among eligible health and social care professionals and resource persons. Each volunteer participant received 8 cards with an alphanumeric code to be distributed to eligible people within

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their circle. Those who received a card and wished to participate were able to contact the peer investigators to schedule an interview according to their availability. The entire protocol was explained to them, and they were able to ask any questions they wished before agreeing to take part. This method was used to improve the quality of the sample and minimize selection bias in terms of care and social support as well as insecurity.

For the qualitative components, the samples were chosen based on predefined inclusion criteria, developed previously, to represent the different profiles of stakeholders and individuals. Sampling was stopped for each component when data saturation in the answers was reached.

Study Monitoring

According to the monitoring plan, the compliance of participants' nonopposition forms (which are equivalent to informed consent forms—the term "nonopposition" is used under French law for studies conducted under Reference Methodology 003) was verified by a clinical research assistant, along with participants' identity, inclusion criteria, and inclusion group. If reported by the monitoring, participants duplicates or unmatched inclusion criteria led to participants' exclusion. In addition, where possible, nonopposition forms were completed by the study investigators in conjunction with the clinical research associate. Before data entry, all information collected on the participants' biographical grid was proofread daily by a peer investigator. In the event of incomplete or inconsistent data, a review was carried out with the investigator who completed the questionnaire. Finally, the data entered were analyzed and checked for logical correctness.

Data Collection Tools

All the study's collection tools were coconstructed with health mediators (community health workers) of Haitian origin, the partner structures, the study's partner physicians (HBV and HIV specialists), the team from the Regional HIV coordination committee (COREVIH) Guyane, researchers from Inserm Clinical Investigation Center 1424, and the study's scientific partners. The issues of acceptability, confidentiality, and quality were at the center of all discussions. The data from Haitian-born people aged 18 to 60 years included in the quantitative epidemiological section were collected using 2 tools: a cross-sectional epidemiological questionnaire on a tablet (Multimedia Appendix 1) and a paper biographical grid where information was collected year after year (Multimedia Appendix 2). These tools were pretested, and adjustments were made. These questionnaires were both hetero administered, with interviews being conducted in either French or Haitian Creole, and generally took approximately 60 minutes to complete per participant. The interviews took place at the time they were proposed or during an appointment scheduled at the participants' convenience.

The cross-sectional epidemiological questionnaire collected data related to arrival and stay in French Guiana, history of administrative procedures to stay for medical reasons, sexual and reproductive health, coerced or transactional relationships over the lifetime, use of birth control methods before and after arrival in French Guiana, use of HIV screening tests, general health status, mental health status (4-item Patient Health Questionnaire scale and the psychotrauma scale of the Post-Traumatic Stress Disorder-8), substance use (Alcohol Use Disorders Identification Test–Consumption scale), health insurance coverage, refusal of care experience, food insecurity and hunger, and use of nonallopathic medicine [27-29]. For the groups of participants living with HIV or HBV, 2 short complementary modules were completed in the cross-sectional questionnaire, follow-up and treatment histories were also collected biographically, and medical questionnaires containing routine biological and medical information were completed (Multimedia Appendix 1). Cross-sectional questionnaire data were collected using the ODK Collect software (Get ODK Inc) on tablets. Transversal data entry was conducted offline, and then data were extracted manually using an R script (R Foundation for Statistical Computing) to transform instances into a CSV database [30]. Biographical data were collected on paper biographical grids and then coded using a dictionary of variables and corresponding labels.

The second main tool used was a biographical grid, with the following information collected retrospectively year after year over the lifetime: residential history, administrative history, health coverage, history of professional activities, sources of income, history of relationships, pregnancies and children, history of screening tests for HIV, HBV and cervical cancer screening, history of illnesses and hospitalizations, health or social support structures encountered since arrival in French Guiana, perceived annual well-being, hunger, and significant events. For the groups of participants living with HIV or HBV, follow-up and treatment histories were also collected biographically. The biographical grid data were then entered into Ennov Clinical by a clinical study technician. The decision to freeze the quantitative databases was taken on March 13, 2024, once the data entry and control processes had been completed. The controls continued until June 7, 2024.

Migration routes were also collected on a map and then entered manually into a CSV database (Multimedia Appendix 3).

For the groups of participants living with HIV or HBV, 2 short medical questionnaires containing routine biological and medical characteristics were completed by the physicians in charge of the patients based on their medical history and the results of biological tests.

Finally, a satisfaction questionnaire was administered via telephone at the end of the study to participants who agreed to leave their contact details with the investigators, focusing on the experience and potential benefits derived from taking part in the study and the in-depth personal interview with a mediator (Multimedia Appendix 4). This section was collected by an investigating mediator via telephone using the ODK Collect software. The flow of quantitative, epidemiological, and biographical data, as well as quality control and data verification processes, are detailed in Figure 2.

Qualitative data were collected via semidirective face-to-face interviews, each lasting approximately 45 minutes (Multimedia Appendix 5). With regard to access to health care, the themes addressed were health determinants and access to and use of medical care by migrants in French Guiana. In the case of mental

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health, we explored the mental health problems of migrants in French Guiana, existing health care services, obstacles encountered, violence experienced, and its link to sexual health. The interviews were in part recorded using a smartphone, anonymized, and fully transcribed.

An ethnographic dimension was also added to the qualitative axis with active observation in Haitian migrants' neighborhoods. Traditional practitioners were followed in their care the preparation of traditional remedies, as well as in the treatment of patients whenever possible.

Figure 2. Flow of quantitative, epidemiological, and biographical data collected during the Parcours d'Haïti study and quality control and checks on the data.

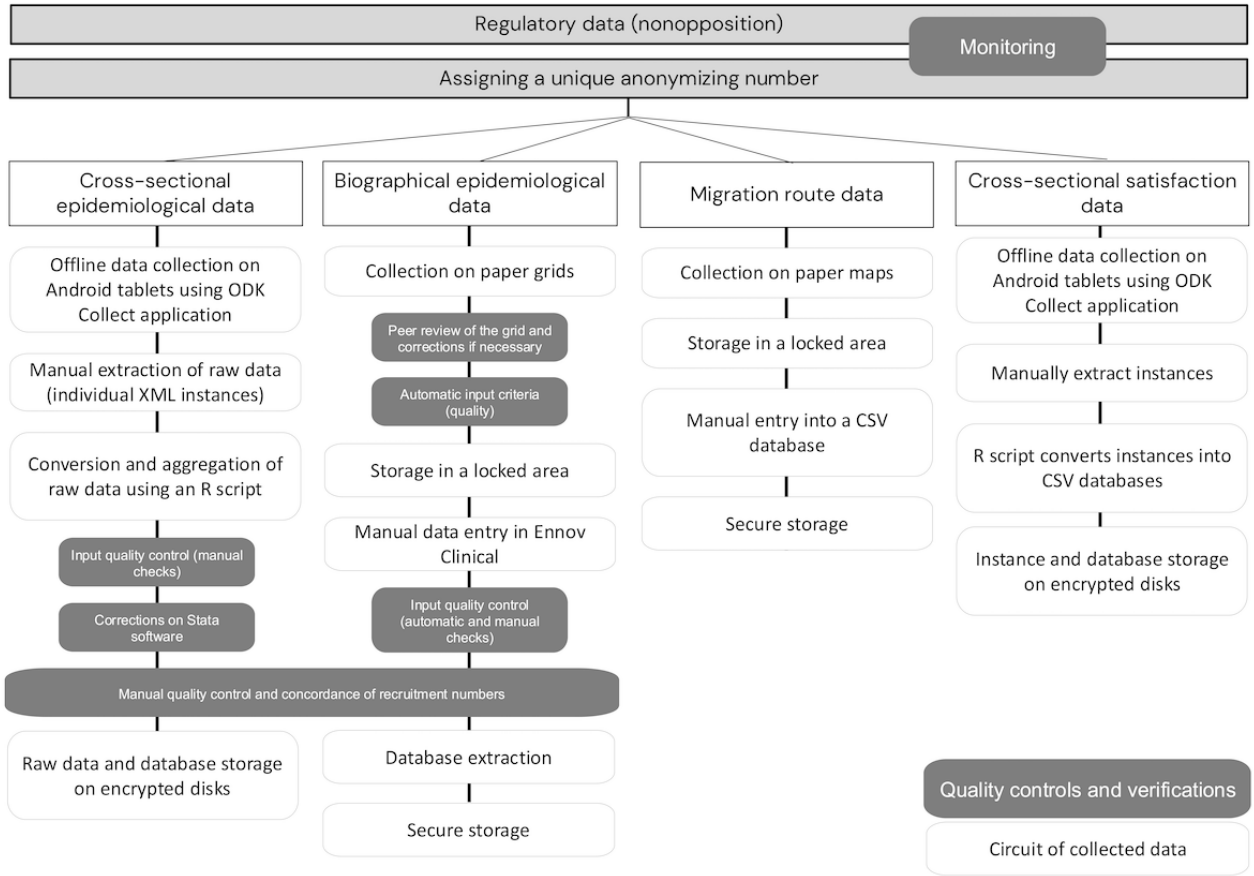

Analysis Plan

As the analyses had not yet begun at the time of submission of this work, this section is written in the future tense.

Statistical Analysis of Quantitative and Biographical Data

With regard to the statistical analysis of quantitative information, the major indicators will be described using percentages as well as means or medians with their SDs or IQRs depending on their distribution. Analytical work will be carried out with a biographical and social epidemiology approach using the tools of epidemiological analysis to study the associations between behaviors and health indicators and social determinants. Factors associated with biographical key indicators will be analyzed year after year using discrete-time logistic regression models that take into account time and the values of indicators collected in the biographical grid year after year [31]. Factors associated with indicators collected at the time of the study will be analyzed using Poisson regression with robust variance. The Stata software (StataCorp) will be used to conduct the analyses.

An analysis of the participants' support and care structures will be carried out based on specific questions that will be analyzed through clustering and a bipartite network approach using methods derived from graph theory. These analyses will provide a better understanding of the levers and care itineraries that can be developed. The R software will be used for these analyses (*tidyverse* and *tidygraph* packages).

Qualitative Analysis

The qualitative study is of a hypothetical-deductive type conducted following a discursive and recursive approach using semidirective interview grids for individual interviews and in a freer manner for discussion groups. These interviews involve a conversational dynamic in which the interviewer and participants interact in a progressive, recursive, and flexible manner to obtain a broad and comprehensive view of the subject. All interview observations will be triangulated with field observations. The collected data (recorded or handwritten) will be analyzed thematically, manually, or using a specialized software (MAXQDA 2022; VERBI GmbH).

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Phylogenetic Analysis

For the analysis of Pol gene clades, the data (nucleotide sequences) will be extracted from the HIV resistance genotype by the Pasteur Institute laboratory in French Guiana, an analysis conducted for all people living with HIV before antiretroviral therapy. A phylogenetic tree will be produced from these sequences, and the clades to which they belong will be analyzed. The results of the phylogenetic analyses (clades) will be described in the form of phylogenetic trees and cross-referenced with social and biographical determinants, and associations will be analyzed using chi-square tests conducted using the Stata software. These analyses will be carried out in part by the Oswaldo Cruz Institute of Fiocruz in Rio de Janeiro.

Results

Overview

For 20 months, the Parcours d'Haïti study was implemented and conducted in French Guiana. The initial study was enriched and developed, and 3 substantial modifications were made.

In November 2021, the first participant was recruited for the quantitative epidemiological component, which focused on people living with HIV and the general Haitian population. In June 2022, a group of people living with HBV was added to the study. Several approaches were developed using a mixed methodology: a quantitative cross-sectional approach; a quantitative biographical approach; a qualitative mental health approach; a qualitative approach to access and use of care; an anthropological and ethnobotanical component; and, finally, a "satisfaction" component. These elements are shown chronologically in Figure 3.

Figure 3. Chronological timeline of the different axes of the Parcours d'Haïti study between 2020 and 2025.

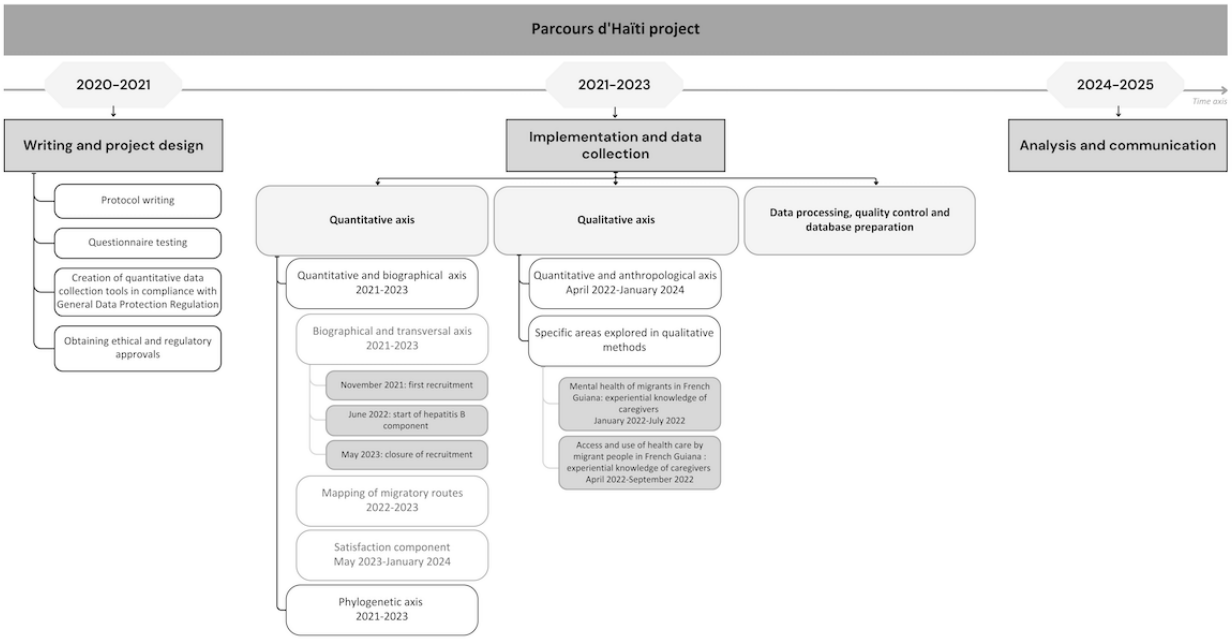

Quantitative and Biographical Data

For the quantitative component, recruitment was completed by May 31, 2023. Data quality control has been extended to June 2024. Analysis is scheduled to begin in July 2024. The collection of migratory routes was completed on May 31, 2023. The first results are expected at the end of 2024.

Qualitative and Anthropological Data

Qualitative data were collected along the 3 axes mentioned previously. The first section on mental health has been completed, and the first results on mental health are expected at the end of 2024. The section on access to and use of health care has been completed, the interviews have been analyzed, and this work was published in October 2023 [32]. Data collection for the anthropological component ended in January 2024, with the first results expected in September 2024.

Phylogenetic Analysis

Phylogenetic data have been collected, with the first results expected by the end of 2024.

Discussion

Expected Findings

The expected results are described on the basis of findings from the literature. Given recent events in Haiti, most individuals are likely to have migrated within the past 10 years, driven primarily by insecurity and violence. Upon arrival in French Guiana, these individuals are expected to face significant economic hardship and social isolation, which may increase the likelihood of transactional sexual relationships and exposure to HIV, particularly among women.

In terms of mental health, the findings are anticipated to show a decline in well-being across all genders, with high rates of

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anxiety and depressive disorders and posttraumatic stress disorder. Moreover, people living with HIV are expected to be more vulnerable compared to HIV-negative individuals even though they are already facing considerable challenges.

Qualitative findings on health care access may suggest that migrants encounter numerous barriers to obtaining care in French Guiana, including administrative complexity, language and financial barriers, and mobility issues. In response to these challenges and the inadequacies of public services, support from NGOs and community organizations plays a crucial role in assisting migrants with social, health, and legal matters. Health mediators may further facilitate migrants' access to care, supporting their social integration and empowering them in the process. On the other hand, the proximity between the prevention services delegated by the state to NGOs and newly arrived migrants facilitates early access to screening and prevention. The anthropological results are expected to emphasize the magical-religious perceptions surrounding health and HIV and the role of traditional medicine, including the use of plants in treatment and prevention. Phylogenetic analysis is likely to show a high prevalence of Caribbean B HIV subtypes and community clustering of transmission chains.

For a long time, it was difficult, particularly in France, to carry out surveys on people in relation to their native origin. In this work, after much reflection, the choice was made to work on people born in Haiti. Haiti's history and very specific geographical situation suggest that Haitians arrive in French Guiana with their own particular baggage (eg, the natural and health disasters of 2010 and 2012). It is always difficult to work on a specific population according to its country of birth without running the risk of adding stigma to the discrimination already experienced by people living with HIV. However, since 2001, several studies have led the scientific community to consider the link between HIV and immigration from the perspective of inequalities [33,34]. A number of indicators point to the even greater difficulties faced by Haitians in French Guiana. Other elements reinforce the idea that Haitian-born people living in French Guiana are subject to particularly precarious situations, inequalities, and even discrimination, all of which are likely to have an impact on their health [35]. Again, keeping in mind the risk of oversimplification, the literature reminds us that health is mediated by social and political processes.

Limitations

The study methodology has a number of limitations. First, the target population is hidden, most of them undocumented, and the situation (particularly in informal settlements) is rapidly changing. As information on their distribution was incomplete, it was difficult to assess the representativeness of this population in the territory in the absence of up-to-date comparative data. The recruitment sites were selected on a nonprobabilistic and reasoned basis, so selection bias cannot be excluded.

One of the limitations of this study is the strong stigma attached to the Haitian community, particularly the association between the terms "Haiti" and "HIV," which has a historically negative connotation. This association could reinforce the stigma already attached to this population and limit acceptability.

The recruitment targets for the hepatitis B and HIV groups were ambitious, and the active referral files did not take into account patients lost to follow-up or the growing proportion of patients followed up on in the city (which is difficult to reach).

With regard to the inclusion of participants living with hepatitis B, the follow-up departments for these patients were late in signing up as this study group was added at a later stage, limiting the time available for recruitment.

Strengths

The biographical approach is the first and principal strength of this work as the data illustrating life courses are embedded in time. This approach makes it possible to study the whole of a person's life while placing events in the political and social context in which they took place. This approach also limits memory bias by grounding events in key life dates (eg, children's births). This biographical approach was supplemented by a cross-sectional, qualitative, anthropological approach, and for people living with a chronic virus (HIV or hepatitis B), by a medical questionnaire. For people living specifically with HIV, a phylogenetic analysis was also proposed. All these sources make it possible to triangulate information and reinforce the internal validity of the results.

This is the first in-depth, mixed methodology study on Haitians living in French Guiana, shedding light on a significant population that is key in terms of public health. Despite the fact that the population is hidden and rapidly evolving, French Guiana is a small territory. Collaboration with the main actors in the field, with mediators from the community, and with an anthropologist specialized in French Guiana's Creole communities increased the chances of obtaining a representative sample of the Haitian population living in French Guiana between 2021 and 2023.

Despite discussions on this point, targeting the Haitian population could be a source of discrimination, particularly when recruiting people living with HIV. In this study, the information and explanations provided by the mediator interviewers helped maximize understanding by building a relationship of trust with the participants, providing them with intelligible information, making them understand what was at stake, and limiting stigmatization. The mediators played a major role in promoting understanding, compliance with ethics, confidentiality, and respect for participants' rights. The approach taken by community mediators played a major role in the project's feasibility and the number of included participants. The Parcours d'Haïti mediator community network was undeniably a strength.

Comparison With Prior Work

The ANRS Parcours 2012 to 2013 survey, a biographical study carried out in the Paris region among migrants from sub-Saharan Africa, was divided into 3 groups equivalent to those presented in this protocol (general population, people living with HBV, and people living with HIV). This study almost achieved its objectives with regard to the group of people living with HIV but fell short with regard to the group of people living with HBV and the general population [36]. This study revealed difficult living conditions on arrival and established the link

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between these living conditions and the acquisition of HIV in France [36]. The MAKASI study, carried out in 2019 as a follow-up to the ANRS Parcours 2012 to 2013 study among migrants from sub-Saharan Africa far from care, revealed low levels of health coverage and precarious administrative status, including among people who had been in the French territory for several years [37]. Previous surveys carried out in French Guiana show a very high level of food insecurity [38,39]. A number of studies have shown that the health of migrants in French Guiana and hexagonal France is deteriorating [4,40]. In terms of sexual health, recent studies highlight the high level of exposure to sexual violence among migrant women, the high level of transactional relationships used as a survival strategy, and the cumulative violence experienced by this population [4]. In light of recent literature studies published on the American continent, violence (physical and sexual) and the use of transactional sex are identified as one of the main components of the migratory trajectories for women in this area [41-44].

In the ANRS Parcours 2012 to 2013 survey, up to 50% of the people surveyed from sub-Saharan Africa contracted HIV after their arrival in France, and of these, 58% acquired HIV during the settlement period (between 0 and 6 years after migration), and 42% acquired HIV after settling (>6 years after migration) [45]. With regard to HIV, a number of studies have been carried out in French Guiana in recent years (including phylogenetic studies), enabling us to understand the factors driving the epidemic [9-11,14,16,17]. Elements similar to those found in the ANRS Parcours 2012 to 2013 study have been highlighted in these studies, with most foreigners living with HIV having acquired the virus after migrating to French Guiana [10,11]. The studies carried out showed that HIV was diagnosed later in Haitians than in native-born people but was detected more quickly in Haitians than in Surinamese individuals or Brazilians [17]. In light of the recent literature published on the American continent, numerous studies point to inconsistent condom use among migrant populations as well as a lack of knowledge about the risk factors and consequences of STIs [46-48].

Assumptions and Hypothetical Study Outcomes

Quantitative and Biographical Data

In comparison with the results found in the literature, and particularly of the ANRS Parcours 2012 to 2013 study conducted in Paris area, we hypothesize that the study will reveal difficult living conditions after arrival in French Guiana and that these conditions will last for a long time. We will try to confirm that the departures from Haiti were precipitated by historical events and that the routes are more or less complex depending on the path taken. We hypothesize that migratory routes vary according to migration periods. We hypothesize that access to a residence permit is burdensome and that this is a factor negatively impacting the health of people arriving on the Guianese territory. We presume that access to formal housing is very limited and determined by the level of education and knowing someone in French Guiana previously. We hypothesize that relationships are determined by social conditions but that motherhood in women is more determined by age and social representations even when living conditions are precarious. We hypothesize that many people do not have the health coverage to which they are entitled and that health care services, although available, are not necessarily accessible (for reasons that include transport, health coverage, health literacy, and possible discrimination). We will also try to confirm the hypothesis that having contacts with NGOs and social services improves access to care compared to those who have not benefited from this support. We also make the assumptions that people from Haiti experience high levels of food insecurity after arriving in French Guiana and that many people are isolated.

We also hypothesize that the mental health of Haitians living in French Guiana is impaired when living conditions are precarious, violence has occurred, or relatives are separated.

During these years, people may be exposed to situations of sexual vulnerability and to unwanted sexuality and transactional, paid, or even forced sex, exposing them to a greater risk of acquisition of HIV or STIs and psychological trauma. In terms of sexual health, we hypothesize that, regardless of the participant group, a large proportion of the population has been exposed to sexual violence and transactional relationships and that these phenomena particularly concern women. Finally, we hypothesize that the use of contraception is low and that recourse to abortion is very limited.

Concerning the follow-up of people living with HIV and people living with HBV, we hypothesize that Haitian populations in French Guiana use screening relatively early and that those diagnosed with HIV enter care relatively early, in line with the screening and mediation services available in the region, notably through the French Red Cross. We also think that impaired social conditions, social isolation, and low health literacy are associated with a delay in screening. A catch-up certainly exists for women during pregnancy. It is likely that periods of disruption of care are closely linked to the social situation of the people concerned, which changes from year to year. The biographical approach will enable us to confirm the hypothesis that, in the years during which a disruption in care occurred, the person faced social or administrative difficulties more often. In addition, we assume that periods of loss to follow-up are more frequent among people living with HBV, linked to an incomplete understanding of the disease, the absence of therapeutic indications for a large proportion of people living with HBV, prolonged follow-up intervals, and a lower civil society investment than that in people living with HIV. With regard to people living with HIV, we hypothesize that they will report unprotected sex in the years following their infection.

Finally, we hypothesize that conducting a long interview focusing on health issues is likely to contribute to respondents' access to and use of health care.

Qualitative and Anthropological Data

One of the aims of the qualitative study was to gain a better understanding of the cultural representations associated with health within the Haitian community. The relationship between care and life course, especially migration, will also be studied. We hypothesize that this anthropological approach will reveal a number of internal logics specific to Haitian ethnomedicine. It should also lead to a better understanding of the cultural motivations underlying the different ways in which patients

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seek care and, ultimately, help improve the conditions of prevention and care for Haitian patients.

Phylogenetic Analysis

The phylogenetic approach assumes that it will be possible to determine the origin of viruses from published viral sequences (GenBank) and that, from the molecular timeline, it will be possible to reconstruct the history of transmission and the time lag between acquisition and transmission of the virus, which is important information for a better understanding of the particularities of the epidemic in this population. We hypothesize that infections occur most often with sequences compatible with intracommunity transmission before and after arrival and, therefore, that prevention should be carried out at the community level.

Expected Follow-up

The results of this study are likely to improve our understanding of the sexual vulnerability of people from Haiti with a view to setting up a sexual health pathway incorporating a diversified range of appropriate screening and prevention services. This pathway will help reduce the risk of infection with HIV, HBV, and STIs, as well as unwanted sex and unwanted pregnancies. It will help improve the pathway for entering and remaining in care in general and following the discovery of HIV or chronic HBV infection. It will tie in with work already underway to develop prevention and care services directly in the informal settlements where a large population of Haitians live. The results of this study are likely to help provide medical, psychological, and social support in conjunction with all the institutional and voluntary players.

It will also provide a better understanding of the path taken by people living with HIV or HBV once they have been diagnosed and produce information that can be used to implement measures to prevent them from being lost to follow-up.

The results and resulting proposals will be communicated as a high priority to actors in social support, prevention, and care grouped around the COREVIH Guyane. One action is already underway as part of road map 2 of the French sexual health strategy involving the deployment in French Guiana of nurse-mediator pairs equipped to carry out STI and human papillomavirus point-of-care screening to reach the populations furthest from health structures. The results of the Parcours d'Haïti study will help meet the data needs of this priority population and provide a framework for action.

Conclusions

The Parcours d'Haïti study is original regarding its methodology (a mixed methods study using biographical methods with community coconstruction), its territory (a French territory in South America), and its study population (a large but vulnerable population). Analyses will test the various hypotheses, notably the potential and significant impact of poor reception conditions on the health of individuals and the persistence of HIV transmission in the region. These expected and original results may lead to an adjustment of the reception policy for Haitian people in French Guiana and to the implementation of efficient sexual health programs. The joint development of these programs with community representatives will be a prerequisite. Ideally, this study could be duplicated in other settings that people from Haiti migrate to (eg, Canada and the United States) and extended to other people on the move facing difficult living conditions on arrival. Finally, the participation of peer investigators (health mediators) for this study improved respect for participants' rights and data quality. This work is likely to contribute to the development of the profession of health research mediators in the future.

Acknowledgments

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Data Availability

The questionnaires used are available in the supplementary files. All the other elements used in the writing of this work are available on request.

Authors' Contributions

LA, MAT, GBR, AL, FH, SR, DRR, TB, ET, CB, FD, HC, MM, AA, MN, and NV contributed to conceptualization. LA, MAT, GBR, SR, AL, DRR, TB, ET, CB, MM, AA, MN, and NV contributed to data curation. LA, MAT, GBR, CB, AA, MN, and NV contributed to formal analysis. LA, AL, AA, MB, and NV secured funding for the study. LA, MAT, GBR, AL, MB, CT, GC, KK, FH, GJ, RPL, AZ, HC, WF, QD, MM, and NV contributed to investigation. LA, MAT, GBR, CB, AA, MN, and NV contributed to the development and design of the study methodology. LA, MAT, AA, and NV coordinated and managed the execution of the project (project administration). LA, MAT, Al, MB, CT, GC, AA, MN, and NV provided access to resources and research materials required for the study. LA, AA, NV, SR, and DRR contributed to the development and implementation of software used in the study. LA, MAT, AA, MN, and NV supervised and managed the research project, including coordination of the teams. LA, MAT, AA, MN, and NV were responsible for validating the methodology. LA, MAT, AL, GJ, RPL, AZ, AA, MN, and NV contributed to the creation and design of visual content. LA, MAT, AA, MN, and NV contributed to the writing of the original draft. LA, MAT, AL, DRR, TB, ET, FW, MM, AA, MN, and NV contributed to the review and editing of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Cross-sectional questionnaire administered electronically using the ODK software. The version included herein was approved by the ethics review board. This appendix also contains the medical questionnaires completed by participants living with HIV or hepatitis B virus.
[PDF File (Adobe PDF File), 2207 KB - resprot_v14i1e63586_app1.pdf]

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Multimedia Appendix 2
The biographical grid used to collect retrospective data across the respondent's entire life course. The version provided here was approved by the ethics review board.
[PDF File (Adobe PDF File), 760 KB - resprot_v14i1e63586_app2.pdf]

Multimedia Appendix 3
The map used to document the routes taken by participants. The version included in this appendix was approved by the ethics review board.
[PDF File (Adobe PDF File), 756 KB - resprot_v14i1e63586_app3.pdf]

Multimedia Appendix 4
The questionnaire used to assess participant satisfaction with their experience in the study. The version included in this appendix was approved by the ethics review board.
[PDF File (Adobe PDF File), 694 KB - resprot_v14i1e63586_app4.pdf]

Multimedia Appendix 5
The interview guides used in the qualitative component of the study, focusing on anthropology and health care–seeking practices. These guides correspond to the version approved by the ethics review board. However, they represent only part of the qualitative data collected; additional insights were obtained through ethnographic observations and other qualitative methods, as detailed in the main article.
[PDF File (Adobe PDF File), 1955 KB - resprot_v14i1e63586_app5.pdf]

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Abbreviations

ANRS: Agence Nationale de Recherches sur le Sida et les hépatites virales (the French National Agency for Research on AIDS and Viral Hepatitis)
Fiocruz: Oswaldo Cruz Foundation
HBV: hepatitis B virus
NGO: nongovernmental organization
STI: sexually transmitted infection

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Protocol

Effects of Selective Head-and-Neck Cooling on Brain Injury-Related Biomarker Levels and Symptom Rating Following a Boxing Bout: Protocol for an Exploratory Randomized Trial

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Abstract

Background: Head impacts are common in contact sports such as boxing and occur at times of elevated core body and brain temperatures induced by the exercise. Following impact, elevated brain temperature may lead to the development of exacerbated brain injury that can be monitored by blood biomarkers. Blood-brain biomarkers S100B and glial fibrillary acidic protein (GFAP) reflect glial injury; neurofilament light (NFL), axonal injury; and Neuron-Specific Enolase (NSE) and Tubulin-associated unit (tau), neuronal injury. Time to peak levels post injury for these biomarkers varies. Levels of S100B l peak early post injury, while NSE, GFAP, and tau are regarded as subacute markers, and NFL shows prolonged increases. We attempt to cover a large spectrum of first week postfight alterations in blood-brain biomarkers and their response to head-neck cooling.

Objective: We hypothesized that acute head-and-neck cooling, recently shown to shorten return-to-play in concussed ice hockey players, applied acutely following a boxing bout, is associated with an attenuated concentration of blood biomarkers and improved symptom rating.

Methods: The trial is academically driven and funded by external and hospital research funds. Young, healthy elite boxers aged ≥18 years are recruited. Before, and immediately after a competitive boxing bout consisting of 2 or 3 rounds of 2 minutes each, blood samples are drawn. Boxers are randomized to intervention or control management by 1:1 allocation before baseline testing. After the initial postfight blood sample is drawn and symptom rating using the Sports Concussion Assessment Tool-5 (SCAT-5) has been collected, the boxers receive either acute selective head-and-neck cooling for 45 minutes or routine postfight management. The number of head impacts is counted in all boxers on match video recordings. In both groups, blood samples are drawn 45 minutes after the initial postbout blood sample, as well as 3 and 6 days post fight. At all blood sampling time points, the number of symptoms (NOS) and symptom severity score (SSS) are assessed using the symptom rating part of the SCAT-5. The primary

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endpoint is the difference in biomarker levels (GFAP, NFL, tau, UCH-L1, neuronal-specific enolase) immediately post fight and preintervention, to those obtained at 6 days post fight. The postfight SCAT-5 NOS and SSS are secondary endpoints.

Results: Recruitment started in November 2021 and is ongoing. So far, 41 boxers have been included: 20 controls and 21 cooled. Data collection started in October 2024 following the completion of blood sample analysis. We expect to recruit more boxers before the middle of 2025, but challenges with recruitment may limit this.

Conclusions: There is no treatment available for boxing-induced brain injury. Biomarkers are surrogate yet objective markers of brain injury, and the head-and-neck cooling treatment may attenuate the concentration of brain injury–related biomarkers as well as reduce symptoms induced by head impacts attained during a boxing fight.

Trial Registration: ClinicalTrials.gov NCT06386484; https://clinicaltrials.gov/study/NCT06386484

International Registered Report Identifier (IRRID): DERR1-10.2196/68954

(JMIR Res Protoc 2025;14:e68954) doi:10.2196/68954

KEYWORDS

sports concussion; biomarker; boxing; glial fibrillary acidic protein; neurofilament-light

Introduction

Background

Trauma to the head is common in many contact sports, including boxing [1]. If the trauma to the head, or the body with energy transmitted to the head, is sufficient to induce a range of clinical symptoms and signs that may or may not involve loss of consciousness, a sport-related concussion (SRC) has occurred [2]. In boxing, participants both receive and deliver, on average, 32-40 blows to the head during a typical bout [3]. Those blows are referred to as repetitive head impacts (RHI) [4,5]. RHI differs from the definition of SRC by the absence of the acute symptoms typically observed following an SRC. However, similar to after several SRCs cumulative effects of RHI include early-phase changes in brain function and increased risk for neurodegenerative disorders at long-term. Neuropathological consequences of RHIs in boxing have been comprehensively investigated in previous studies, illustrating structural alterations to the brain [2,6]. More specifically, RHI may lead to cognitive impairment, mood disorders, and motor control problems [7-9].

Several studies have shown that retired athletes who have sustained multiple RHI and SRCs during their career may develop chronic traumatic encephalopathy (CTE), a progressive neurodegenerative disease associated with memory loss, depression, personality changes, and dementia [1,8,10-13]. At present, CTE can only be diagnosed post mortem where key findings include irregular aggregation of phosphorylated tau protein at the depths of cortical sulci [8].

In sports, strenuous exercise leads to elevated core body and brain temperature [14], which may exacerbate the brain injury induced by head impacts. Recently, we showed that selective head-and-neck cooling for 45 minutes, aiming to rapidly normalize the elevated brain temperature, applied acutely post SRC in elite ice hockey players, resulted in earlier return-to-play and a smaller proportion of players with prolonged symptoms following the SRC [15]. However, there is a lack of objective outcome measures for assessing the effects of head-and-neck cooling in athletes.

There is a growing body of literature on the use of biomarkers of brain injury in athletes. In Olympic boxers, levels of cerebrospinal fluid biomarkers such as S100 calcium-binding protein (S100B), Tubulin-associated unit (Tau), Neurofilament light (NFL), and Glial fibrillary acid protein (GFAP) were collected at baseline, 1-6 days post fight, and 14 days after RHI attained in a boxing bout [16,17]. In addition, the biomarkers showed both acute and cumulative effects of the impacts, with a lack of normalization of NFL and GFAP after the rest period, which may indicate an ongoing injury process [16,17]. In addition, inflammatory biomarkers such as tumor necrosis factor-alpha, interleukin 6, and muscle injury biomarkers (alanine aminotransferase and aspartate aminotransferase), and creatinine increased in male elite boxers following a fight [18].

When boxing and mixed martial arts (MMA) were compared, retired boxers had higher plasma GFAP levels, and active boxers had higher plasma NFL than MMA fighters [19]. In addition, serum NFL levels were elevated both at 7-10 days post bout and after 3 months of rest in boxers compared to controls. This study also observed a significant increase in NFL at 7-10 days post bout comparing levels obtained after a high number of head impacts (more than 15 hits to the head or experienced grogginess during or after bout) to those obtained after fewer head impacts (fewer than 15 head hits) [20]. These studies indicate that selected biomarkers may remain elevated during the first postinjury week. In this randomized trial, we hypothesized that biomarkers could serve as an objective marker for the efficacy of selective head-and-neck cooling on attenuating brain injury in elite boxers, assessed by blood biomarkers immediately before and during the first 6 days after a competitive boxing fight.

Objectives

Research Hypothesis

The research hypothesis was that acute and selective head-and-neck cooling immediately after a boxing bout attenuated brain injury as evident by a reduced concentration of brain injury-related biomarker levels during the first postfight week.

Study Objectives

The primary objective was to determine whether selective head-and-neck cooling attenuates the concentration of brain injury biomarkers.

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The secondary objectives were as follows:

1. To determine whether selective head-and-neck cooling improves symptom rating using the Sports Concussion Assessment Tool-5 (SCAT-5).
2. To determine whether any biomarker increase post fight, compared to baseline levels, is associated with the number of head impacts.
3. To determine any adverse event associated with the head-and-neck cooling.

Methods

Participants, Interventions, and Outcomes

Study Setting

The study will take place predominantly in the southern parts of Sweden due to logistical reasons, aiming for the feasibility of follow-up with biomarkers at distinct postfight time points. Blood samples will be collected at the site of the competitive boxing tournament or the local boxing clubs and transferred to the biobank at Lund University Hospital. All data will be collected in Sweden. The trial is academically driven by local funding. The trial will be conducted at Lund University, Lund, Sweden.

Trial Design

The head-and-neck Cooling of Brain temperature In BOXing (COBIBOX) trial is designed as a randomized, controlled, open, single-center superiority trial with 2 parallel groups and a primary endpoint of biomarker changes during the first 6 postfight days. Clinical secondary outcome assessments of a number of symptoms (NOS) and symptom severity score (SSS) using the symptom rating part of the SCAT-5 is performed during the initial 6 postinjury days. Randomization will be performed in blocks with 1:1 allocation.

Eligibility Criteria

Eligibility criteria are listed in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Male and female elite boxers <40 years old and ≥18 years old.
- Cleared for participation by the medical staff of the Swedish Boxing Association before the boxing bout.
- Informed consent by each participant before the competitive event.

Exclusion criteria

- >40 years old or <18 years old.
- Participation in competitive fights, match-sparring, or any training causing additional head impacts during the 6-day postfight follow-up period after being included in the study.
- History of autoimmune neurological diseases or a neurodegenerative disorder.
- History of previous traumatic brain injury resulting in an intracranial hemorrhage.

Procedures and Measurements

All boxing clubs are thoroughly informed of the protocol before study initiation and before each tournament. Boxers between the ages of 18 and 40 years are included. At each tournament, allocation to the treatment takes place on the first morning, and the boxers are randomized 1:1 by a randomly drawn paper slip with a sign that the boxer will receive either selective head-and-neck cooling or routine postfight medical surveillance by an on-site physician. The selective head-and-neck cooling is to be initiated within 10 minutes post fight with a duration of a minimum of 45 minutes. After the boxer completes the fight (Figures 1 and 2), he or she follows the researcher to the cooling station and continues the head-and-neck cooling protocol. In some boxing events, a boxer may participate in two bouts if they win their first bout (Figure 2). The next day, during the finals, they will undergo the same protocol as on their first day, including SCAT-5 assessments and blood sample collection [21]. As mentioned in Figure 2, the start of intervention or return to play protocol starts after their last fight.

Participants will be randomly allocated to either the control or intervention group, involving selective head-and-neck cooling. Baseline SCAT-5 and blood samples will be collected. Subsequently, postfight SCAT-5 and blood samples will be collected for both groups. In addition, the intervention group will undergo selective head-and-neck cooling for 45 minutes. Following this, both the control and intervention groups will follow the same protocol, undergoing SCAT-5 and blood sample collection at 45 minutes post fight, as well as on day 3 and day 6 for follow-up (Figure 1).

The selective head-and-neck cooling takes place after the last boxing bout (dark-colored boxes). For a boxer who fights bout 2/2, new baseline SCAT 5 and blood samples will be collected, shown as baseline 2.0 in Figure 2.

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Figure 1. Boxers that participate in direct final bouts or single-fight events will only engage in one boxing bout. SCAT-5: Sports Concussion Assessment Tool-5.

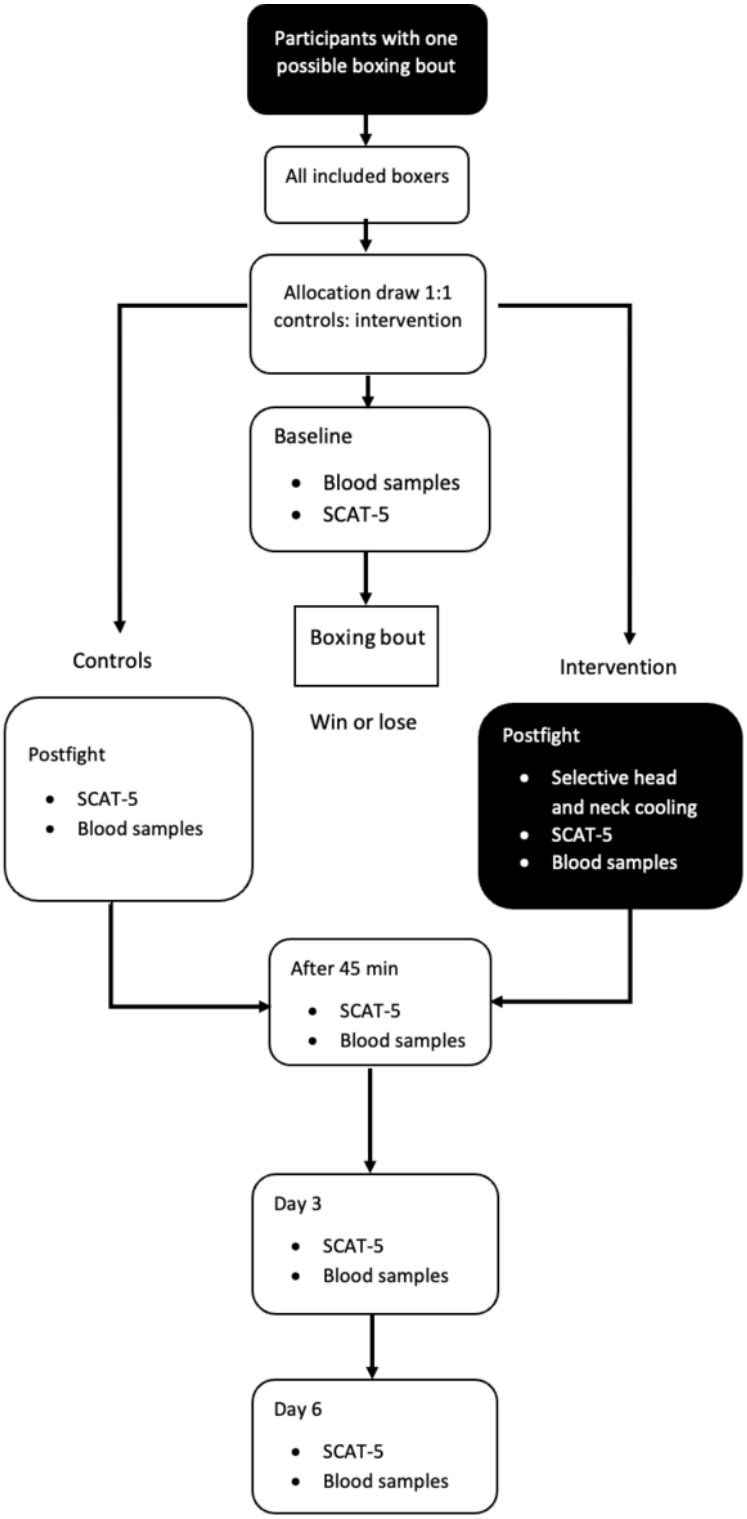

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Figure 2. Boxers who participate in tournaments can either fight one or two boxing bouts, depends on whether they win or lose. SCAT-5: Sports Concussion Assessment Tool-5.

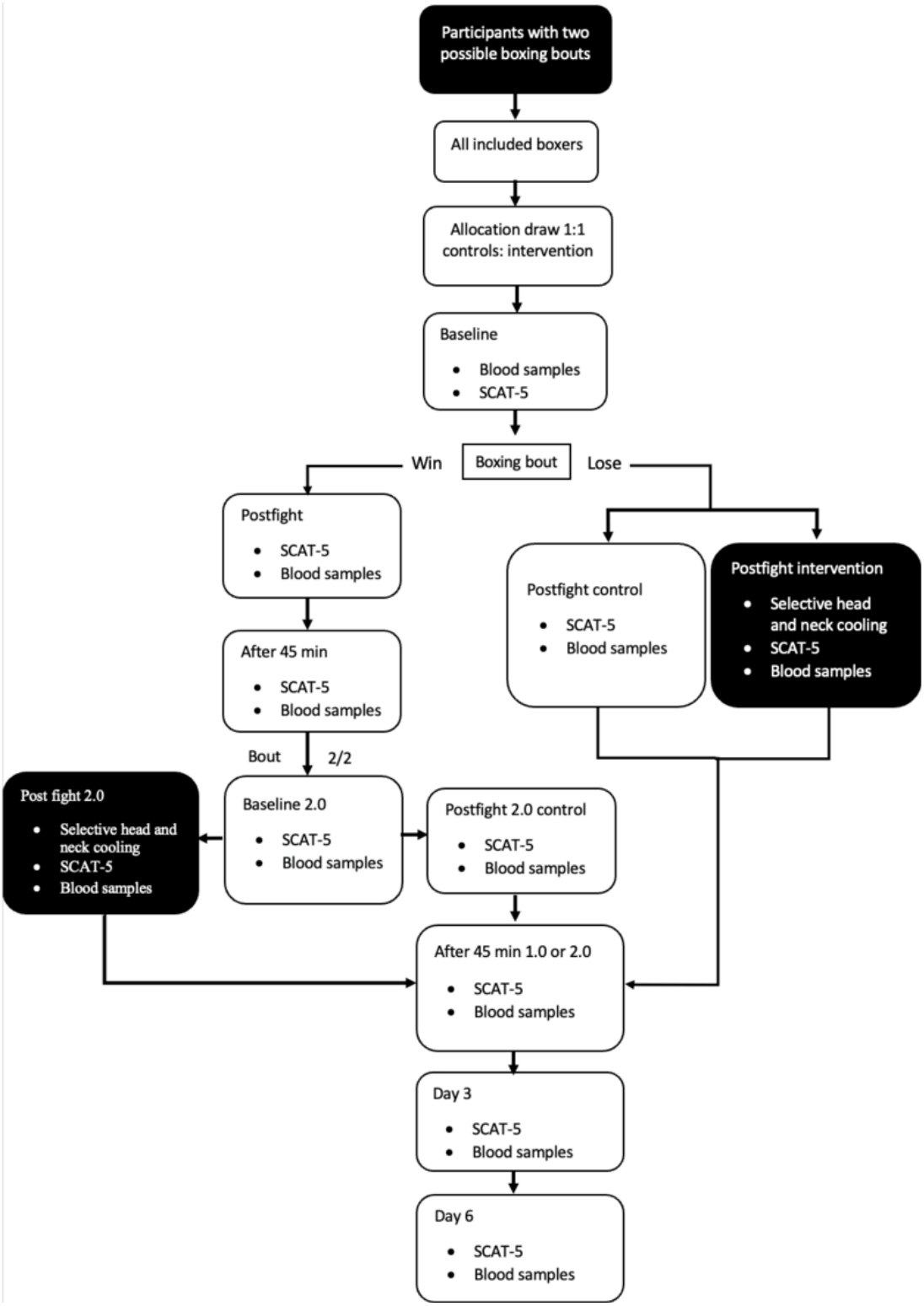

The PolarCap System consists of a portable cooling system, designed to reduce brain temperature by controlled cooling of the scalp and neck with a circulating coolant (PolarCap Coolant, PolarCool AB). The coolant is maintained at 0 °C and flows through a silicone-based head cap. An insulating neoprene cover is put on top of the cap for isolation. The players are allowed to relax (sitting or supine) as long as the cooling head cap and neoprene cover remain in place on the head [22] Should the boxer experience discomfort and wish to discontinue the intervention, the cap is removed and the athlete is excluded from the study. All boxers follow the return-to-fight protocol. The standardized protocol is to return to physical exercise during the first 6 postfight days. During this time, the boxer may do all forms of physical exercise except sparring, match fight, or other activities resulting in impacts to the head or body (Figure 3).

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Figure 3. (A) The PolarCap unit is a powerful mobile cooling system. (B) The Polar Coolant is transported through the silicone head cap. (C) To insulate against the cold, a neoprene cover is applied on top of the cap.

Blood samples are collected at the following time points for all participants: the morning of the first boxing fight on day 1 (baseline, at rest), immediately after the fight, 45 minutes after the fight, and after 3 and 6 days in all boxers. The blood samples obtained at 3 and 6 days post fight will be drawn by a study nurse or a researcher (AaH) at the participants' boxing club. The samples are transported to the hospital in a mobile refrigerator to maintain a temperature of 5-8 °C. Thereafter the serum samples are centrifuged at 3000 rpm, at 4 °C for 10 minutes, after which 800-1200 µL is transferred using a pipet to 2-mL tubes and stored at –80 °C.

At each time point for blood sample collection, boxers are also administered the SCAT-5 questionnaire, which is a self-report questionnaire with information on 22 different symptoms, each with a severity grading of 0-6, where 0 indicates no symptoms and 5-6 indicates severe symptoms. The maximum total score is 132. All boxing bouts are video-recorded for later analysis. The total hits per bout, strikes to the head, strikes to the body, and visible evidence of neurological disturbance (loss of consciousness, impaired balance or coordination, vacant expression, etc) will be assessed. After completion of the study, the boxers will be interviewed by phone to answer questions

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about their previous boxing, knock-out, and concussion history. The timeline for enrollment intervention and assessments across the study is visualized in Table 1 (SPIRIT [Standard Protocol Items: Recommendations for Interventional Trials] checklist in Multimedia Appendix 1).

Table 1. Timeline of enrollment, intervention, and assessment during the study period.

Procedures	Study period			Post allocation				Close-out
	Enrollment	Preallocation	Allocation					
Time point	$-t_1$	Baseline	0	Post fight	45 min post fight	Day 3	Day 6	1 week post fight
Enrollment	✓							
Eligibility screen	✓							
Informed consent	✓							
Basic medical examination	✓							
Allocation			✓					
Interventions								
Selective head and neck cooling (A[a])				✓				
Return to fight protocol (A+B[b])				✓	✓	✓	✓	
Collecting blood sample		✓		✓	✓	✓	✓	
Assessments (SCAT-5[c])								
SCAT-5		✓						
SCAT-5 follow-up				✓	✓	✓	✓	
Boxing history								✓

[a]A: intervention group.

[b]B: control group.

[c]SCAT-5: Sport Concussion Assessment Tool-5.

Ethical Considerations

The study outlined in this article will be carried out in accordance with the Declaration of Helsinki. Regional ethics committee approval in Lund, Sweden (decision number Dnr 2022/06195) was obtained. Before their enrollment in the trial, all study participants will provide written informed consent. Each participant signs the form, containing comprehensive study details. Approval from the Swedish Boxing Association to include amateur and professional boxers registered in the Swedish Boxing Association (SBA) in the study will be received before the study is initiated. Forms describing the study are sent to all boxing clubs in southern Sweden that would participate in the tournaments and have enrolled boxers over 18 years old. All participants are informed of their right to terminate their participation in the study at any given time without the need to provide a reason for doing so. All questionnaires and data collection methods were reviewed and approved by the Swedish Ethical Review Authority in Uppsala, Sweden. The submitted protocol to the Swedish Ethical Review Authority included detailed information on the intervention, data confidentiality, blood collection, blood sample storage, and measures to ensure the protection of participants' privacy. A study protocol was provided with the ethical application. All participants' data are anonymized from the time of inclusion, before allocation, by assigning a code containing letters and numbers. This code will be attached to the participants' blood samples and SCAT-5 score files. Each participant will receive a compensation of 1000 SEK (US $104.53) for their time, inconvenience, and any potential discomfort associated with participation. The consent information emphasizes the voluntary nature of participation, including the possibility of opting out at any stage. It also specifies who will obtain informed consent from the participants. Specific contact information for the research team is provided to participants for any questions or concerns. The informed consent consists of 10 detailed points. It begins with a request for participation that describes what the boxers will be involved in. The background and aim section explains the purpose of the study and the facts supporting it. The study procedure outlines the collection of SCAT-5 questionnaires, blood samples, and the possibility of cooling. Biomarker collection is covered by the biobank policies and includes the category of biomarkers that will be analyzed. The risk section highlights any potential risks associated with participation. Handling personal data explains data protection measures in accordance with GDPR, while data management and privacy further detail how data are stored and covered under GDPR. The insurance section clarifies the responsible parts that ensure the participants during the study. Voluntary participation ensures that participants are informed of their right to opt out at any time, even after inclusion. Finally, the responsible staff section provides information about the staff in charge and their contact details.

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Study Population

A total of 14 boxing clubs whose fighters enrolled in 5-7 boxing events in southern Sweden will be contacted and informed about the study and its inclusion criteria.

Allocation

After all boxers have approved participation in the study during the tournament, and signed the informed consent, the study staff makes an allocation on paper slips that equals the number of participants. Then the boxers randomly, by drawing a paper slip, receive either a sign for receiving head-and-neck cooling (C=cooling) or NC (no cooling; Figures 1-2). All allocations are finalized a minimum of 3 hours before the start of the tournaments.

The enrollment of participants will be done by a researcher (AaH) aided by boxing coaches.

After the boxing bout, and after the boxer is evaluated for red flags mandating transport to the nearest hospital, the boxer is brought to the intervention station to apply the PolarCap system as previously described.

Personnel Responsible for Informed Consent

Informed consent documents will be sent for approval to the Swedish Boxing Association, after which those will be distributed to each club. A responsible researcher and physician (AaH) will inform the participants verbally and in written form, either days before the competition or on the same day. Each participant will be informed about the study, informed of the possibility to withdraw from participation at any time, and provided time to ask questions. Before randomization, each participant signs the informed consent form.

Biomarker Analysis

Venous blood is collected in 3.5 mL serum and EDTA plasma tubes generated at room temperature and stored in a mobile refrigerator at 4-8 ºC until centrifuged at 4 ºC for 10 minutes at 3000 rpm. The remaining supernatant is transferred to 2 mL cryotubes and stored at –80 ºC until analyzed. Once the study has been completed, blood biomarkers for brain injury (S100B, GFAP, tau forms, NFL, and NSE) will be measured in coded samples using an established single-molecule array (for GFAP, tau, and NFL) by Quanterix and electrochemiluminescence immunoassays (for S100B and NSE) by Roche Diagnostics immunoassays [23] in the Clinical Neurochemistry Laboratory by board-certified laboratory technicians who will be blinded to the intervention.

Data Collection

The SCAT-5 form will be filled out at the time of biomarker analysis and used as a secondary endpoint of the study. The boxing bouts take place either in events consisting of single bouts for each boxer or in tournaments where 2 bouts are possible (semifinal and final). For boxers participating in two bouts at the same event, the baseline, postfight, and 45-minute postfight scores and biomarker tests will be retaken. Values related to the second fight will be considered in the analysis. The analysis of symptom severity scores obtained by SCAT-5 at the set timeline will facilitate the interpretation of outcomes between the boxers independent of their previous boxing history after the completed 6-day follow-up. Boxing history will be obtained by phone call interview at the 6-day follow-up or on-site. The follow-up for days 3 and 6 will be organized by the local clubs before the first postmatch training session, or at the study hospital.

Sample Size and Statistical Power

Based on previous reports, an approximately 10% increase in key biomarkers is observed after a concussion in athletes [16]. We hypothesized a 20% reduction of biomarker level by acute head-and-neck cooling. We assumed equal variance of the cooled and control groups. The selected power was set to 0.8. Power analysis was conducted using the following formula:

[24]

Based on the power calculations, a total number of 20 participants per group is expected to yield sufficient statistical power. Since dropouts and missed sample times can be anticipated we aim for group sizes of 25 per group.

Recruitment

Participants are recruited by one researcher (AaH) by sending information about the study to the Swedish Boxing Association which approves participation, in written form or verbally. Thereafter the study must be approved by the organizers of the boxing tournament. Finally, the recruitment of boxers who fulfill the inclusion criteria and sign the written consent form after verbal and written information about the study is provided.

Adverse Events

Any adverse events reported by the participant during the study period are noted and reported. Specifically, any deviation from the protocol (eg, sample time point, duration of head-and-neck cooling) will be noted. Symptoms, such as headache, nausea, and dizziness, are reported to the medical doctor and study researcher (AaH), although these symptoms may also be caused by the SRC per se [15]. No adverse events are expected, based on our previous study where 61 elite ice hockey players were cooled without any reported adverse events [15].

Results

The study flow is presented in Figures 1 and 2. The study began in November 2021 and is expected to be completed before the summer of 2025 (Figure 4). Based on our sample size calculations, we aim to recruit approximately 40-50 participants. The first results are anticipated to be submitted for publication in the Autumn of 2025. This study evaluates the effectiveness of selective head and neck cooling in reducing blood-brain biomarkers and SCAT-5 scores during the first week after a boxing bout. Recruitment started on November 4, 2021. Approximate completion of final recruitment is expected in the first weeks of January 2025 (protocol version 1.0, 2024-04-01).

The 3 excluded boxers, whose opponents dropped out, went through baseline SCAT-5 testing and blood sample collection. The participant who experienced nausea and vomiting chose to

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withdraw from participation in the study after his boxing bout before any further testing (Figure 4).

Figure 4. All allocation and randomization occur after signed informed consent and before baseline testing.

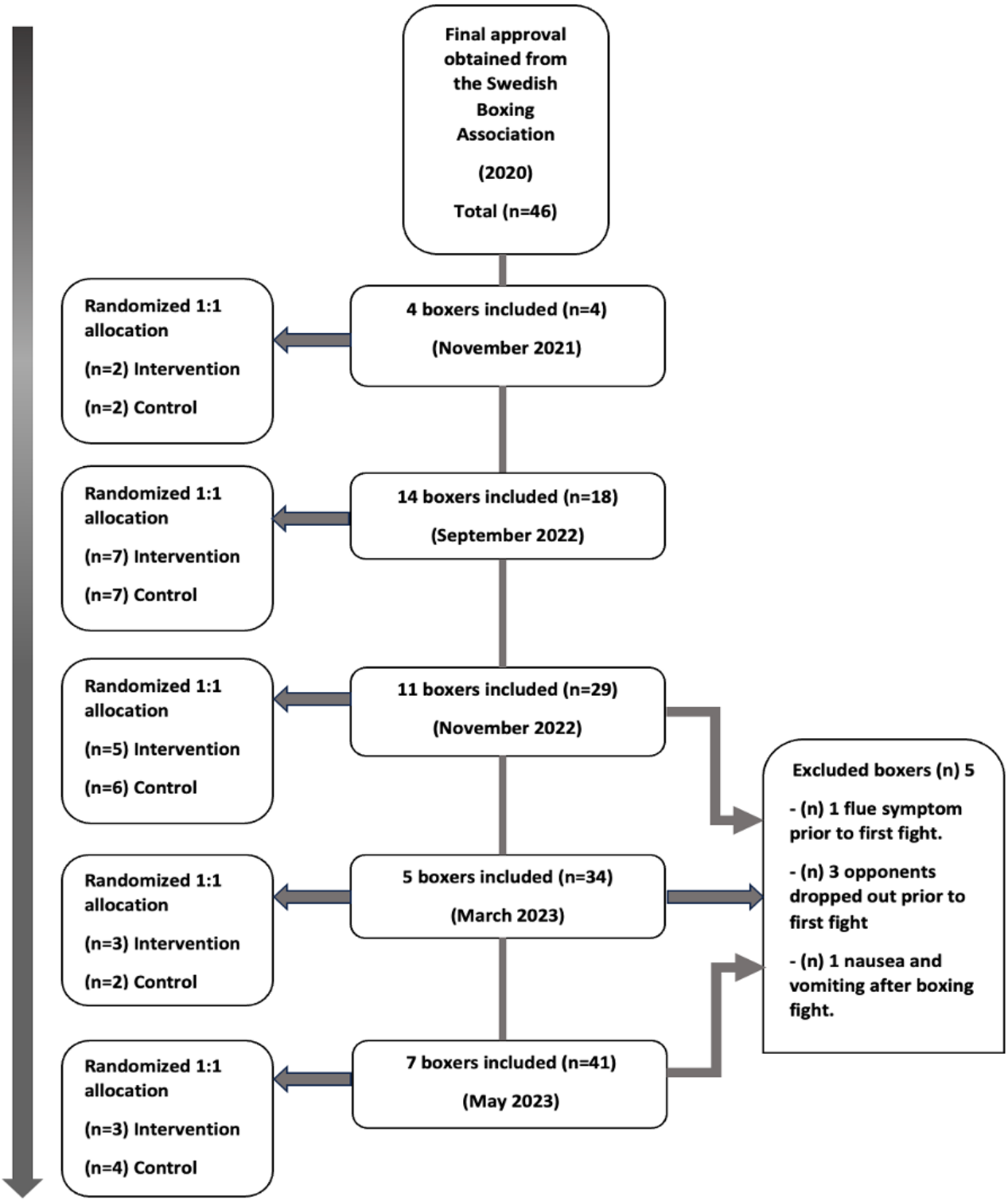

Discussion

Principal Findings

During a boxing fight, boxers typically attain a high number of blows to the head, which may lead to brain injuries. Due to the strenuous activity, these blows occur at a time of elevated core body temperature, which may exacerbate the brain injury. There are no approved treatments for boxing-induced brain injuries. A blow to the head may lead to an elevation of blood biomarker concentrations that reflect the degree of the brain injury caused by the impact. There is an increasing interest in these biomarkers that include markers for large caliber axon injury (NFL), neuronal injury (NSE, tau), and glial injury (S100B, GFAP). Our present study may show whether the level of biomarkers

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is related to the number of hits or concussions received, the symptom development after the fight, and most importantly the effects of the cooling intervention.

Head-and-neck cooling was shown to decrease brain temperature measured by magnetic resonance imaging (MRI) [25], and improved cognitive outcome when applied acutely post concussion [26]. In a recent clinical trial including 132 concussed ice hockey players, a shorter recovery time was observed after acute selective head-and-neck cooling for at least 45 minutes [15]. A shorter recovery was also observed when cooling was initiated up to 8 days post concussion [27]. To provide an objective outcome measure for the cooling intervention in the present study, the primary outcome is blood biomarker levels, of which GFAP, NFL, S100B, and tau may be the most important. The chosen time points for collecting blood-brain biomarkers aim to assess the early-phase biomarker response to boxing matches, with subsequent evaluation of the head and neck cooling effect and its potential early impact. S100B is associated with an acute astrocytic response, which typically peaks within hours, followed by GFAP with a peak of 24 hours [28]. This makes postfight day 3 a valuable time point to capture a delayed peak or sustained elevation of the selected biomarkers. While NFL levels may remain elevated at longer time points post fight, we had to use 6 days as our latest evaluation time point. This is based on the guidelines of the Swedish Boxing Association, which prohibit boxers from competing or having fights within 6 days of their most recent tournament. Thus, many boxers are assigned to match sparring or other tournaments after 6 days.

The selection of biomarkers in the present trial is based on several previous studies [29,30], mainly in traumatic brain injury and neurodegenerative disorders [19]. Currently, both tau isoforms and GFAP are used in the prediction and diagnosis of neurodegenerative diseases, particularly Alzheimer disease, and S100B in mild traumatic brain injury guidelines [31-33].

In numerous reports on mild, moderate, or severe traumatic brain injury, blood and CSF biomarkers have been used at different time points postinjury [29]. Following boxing bouts, tau, NFL, GFAP, and S100B are all increased in the early phase after boxing. Of these, NFL, GAP, and tau are increased several weeks to months post fight [16,17,34].

In addition, strenuous exercise has been reported to increase biomarkers such as S100B [35,36]), while leading to a reduction in GFAP and no alteration in NF-L levels [37]. When comparing strenuous exercise to contact sports such as boxing, boxers showed a significant increase in biomarker levels, particularly in GFAP and NFL [17].

Blood S100B levels were significantly elevated in both competitive boxers and high-level exercised athletes such as runners [16,38]. These findings argue that boxing causes the elevation of concentration of several biomarkers reflecting the brain injury, and is associated with lead to long-term neurological consequences.

The role of brain temperature in acute brain injury has been evaluated in numerous trials. In particular, elevated brain temperature may negatively impact functional and neurological outcomes following traumatic brain injury [39,40]. While systemic hypothermia has not been associated with improved outcomes in severe traumatic brain injury, we hypothesized that controlling body temperature may be an important factor in the recovery of boxing-induced brain injury. The primary aim of head-and-neck cooling is not to provide cerebral hypothermia, it is to attenuate exercise-induced hyperthermia and to rapidly normalize the elevated brain temperature.

During exercise, elevated temperature is associated with a higher demand for oxygen and energy metabolism in the brain [41,42], resulting in exacerbation of the injury mechanism initiated by head impacts during boxing. We hypothesize that brain cooling can rapidly normalize brain temperature, thereby reducing metabolic demand resulting in attenuated secondary injury and leading to beneficial effects for the recovery phase after a fight.

Should this explorative study provide evidence of the beneficial effects of head-neck cooling, a multicenter study (preferably with later postfight time points) is warranted.

Strengths and Limitations

The present study has the potential to objectively evaluate the effect of head-and-neck cooling on blood biomarker levels. Moreover, it can provide unique results on biomarker concentration changes following repeated head impacts at several time points post fight.

Outliers in biomarker concentrations are expected, although since each boxer will be his or her control, percentage changes from baseline can be calculated. A 20% reduction of biomarker concentrations is reasonable based on the rapid application of head-and-neck cooling. The potential placebo effect of cooling on symptom ratings is also taken into consideration by using objective biomarker concentrations, highlighting the necessity of biomarker assessment to evaluate cooling's physiological impact.

Conclusion

This study is structured to evaluate early-phase objective and subjective changes in boxers during the first week post fight, and to study the effects of head-and-neck cooling on these changes. In conclusion, the present trial may provide objective biomarker evidence for the role of attenuating cerebral hyperthermia by selective head-and-neck cooling acutely following a boxing bout.

Acknowledgments

The results of this trial will be presented in an appropriate scientific journal after the trial is completed. Open-access funding is provided by Lund University. Swedish Research Council for Sport Science, Hans-Gabriel and Alice Trolle-Wachtmeister (HGATW) Foundation for Medical Research, the Alborada Trust, Swedish Brain Foundation, and hospital ALF funds (all to NM). HZ is a Wallenberg Scholar and a Distinguished Professor at the Swedish Research Council supported by grants from the

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Swedish Research Council (#2023-00356; #2022-01018 and #2019-02397), the European Union's Horizon Europe research and innovation program under grant agreement number 101053962, and Swedish State Support for Clinical Research (#ALFGBG-71320). The authors wish to thank Marit Bäckström for administrative assistance.

Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

NM contributed to funding acquisition. AaH, YT, and NM assisted with conceptualization. AaH handled formal analysis. AaH, HZ, and KB contributed to investigation. NM, AaH, YT, HZ, and KB assisted with methodology. AaH handled project administration. NM handled supervision. AaH and NM contributed to validation. AaH and NM assisted with visualization and writing original draft. AaH, YT, HZ, KB, and NM contributed to writing–review and editing.

Conflicts of Interest

YT is a scientific advisor for PolarCool Inc. Lund, Sweden. NM previously was a scientific advisor for PolarCool Inc. Lund, Sweden. Polar Cool provides the cooling helmet, although has not influenced the design of the study protocol. HZ has served at scientific advisory boards and as a consultant for Abbvie, Acumen, Alector, Alzinova, ALZPath, Amylyx, Annexon, Apellis, Artery Therapeutics, AZTherapies, Cognito Therapeutics, CogRx, Denali, Eisai, Merry Life, Nervgen, Novo Nordisk, Optoceutics, Passage Bio, Pinteon Therapeutics, Prothena, Red Abbey Labs, reMYND, Roche, Samumed, Siemens Healthineers, Triplet Therapeutics, and Wave, has given lectures in symposia sponsored by Alzecure, Biogen, Cellectricon, Fujirebio, Lilly, Novo Nordisk, and Roche, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program (outside submitted work). KB has served as a consultant, on advisory boards, or data monitoring committees for Abcam, Axon, Biogen, and JOMDD/Shimadzu. Julius Clinical, Lilly, MagQu, Novartis, Prothena, Roche Diagnostics, and Siemens Healthineers, and is a co-founder of Brain Biomarker Solutions in Gothenburg AB (BBS), which is a part of the GU Ventures Incubator Program. IR has served on advisory boards and given talks sponsored by Biogen, Bayer, Merck, Roche, GlaxoSmithKline, TEVA, Sanofi, and UCB.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist COBIBOX.
[PDF File (Adobe PDF File), 377 KB - resprot_v14i1e68954_app1.pdf]

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Abbreviations

COBIBOX: Cooling of Brain temperature In BOXing
CTE: chronic traumatic encephalopathy
GFAP: glial fibrillary acid protein
MRI: magnetic resonance imaging
MMA: mixed martial arts
NSE: neuron specific enolase
NFL: Neurofilament light
NOS: number of symptoms
RHI: repetitive head impacts
S100B: S100 calcium-binding protein
SCAT-5: Sports Concussion Assessment Tool-5
SRC: sport-related concussion
SBA: Swedish Boxing Association
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SSS: symptom severity score
Tau: tubulin-associated unit

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Protocol

Treatment of Erythematotelangiectatic Rosacea With Collateral Puncture Therapy: Protocol for a Randomized Controlled Trial

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Abstract

Background: Erythematotelangiectatic rosacea (ETR) is the most common subtype of rosacea, characterized by persistent facial erythema and telangiectasia of varying calibers. It causes significant aesthetic impairment and is often accompanied by uncomfortable symptoms, such as burning, stinging, dryness, and itching, profoundly affecting patients' quality of life. Intense pulsed light (IPL) therapy demonstrates notable improvement in persistent erythema and telangiectasia; however, it is associated with issues such as a prolonged treatment course and high costs. Collateral puncture therapy involves rapid puncturing of specific acupuncture points followed by gentle squeezing around the needle holes to induce minor bleeding. Previous studies have shown that collateral puncture therapy for ETR offers advantages such as rapid onset of effect, a simple procedure, and low cost. Nevertheless, more high-quality clinical research data are needed to confirm these findings.

Objective: This study aims to observe the clinical efficacy and safety of collateral puncture therapy in treating ETR.

Methods: This study enrolled 60 patients diagnosed with ETR. The patients were randomly divided into 2 groups: one group underwent 4 sessions of collateral puncture therapy with 1-week intervals between treatments, and the other group received a single session of IPL therapy. The primary efficacy end points were the clinician's erythema assessment and the clinician's telangiectasia assessment. The secondary efficacy end points included the investigator's global assessment, patient's self-assessment, Flushing Assessment Tool results, Dermatology Life Quality Index, and Rosacea-specific Quality-of-Life instrument. The evaluation points were before treatment, immediately after treatment, and during follow-up. The data were statistically analyzed using SPSS (version 25.0; IBM Corp) to compare intragroup and intergroup differences between the 2 sets of data before and after treatment, with a significance level of α=.05 for hypothesis testing.

Results: Recruitment began on June 1, 2023. All participants have been recruited. Data analysis will be complete by the end of August 2025, with study findings available by December 2025.

Conclusions: This study has the potential to verify the clinical efficacy and safety of collateral puncture therapy in the treatment of ETR, supplement rosacea treatment methods, standardize treatment protocols, and fill a current clinical gap in treating rosacea.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2200062639; https://www.chictr.org.cn/showproj.html?proj=177100

International Registered Report Identifier (IRRID): DERR1-10.2196/59682

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KEYWORDS

erythematotelangiectatic rosacea; collateral puncture; intense pulsed light; randomized controlled trial; protocol

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Introduction

Background

Rosacea initially presents with facial flushing, papules, and pustules, which, if recurrent, develop into persistent erythema and varying sizes of telangiectasia [1-3]. A 2019 survey of 10,095 residents in Changsha, China, showed a local prevalence of rosacea of 3.48% [4]. A 2020 epidemiological survey among 9227 university students from 2 universities showed a prevalence of 3.4% [5]. Facial appearance and features significantly impact a person's professional, social, and romantic life [6]. The common perception of facial redness is that it signifies anger, embarrassment, or excessive drinking, and this could potentially cause shame in patients with rosacea [7], leading to various sociopsychological impacts and psychological complications, such as social anxiety, shame, and depression; hence, there is a strong desire for treatment among these patients.

Current clinical treatments for erythematotelangiectatic rosacea (ETR) mainly involve topical and oral vascular regulators and photophysical therapy. Topical treatments with 0.5% brimonidine tartrate gel and 1% oxymetazoline hydrochloride cream [8], which are α-adrenergic receptor agonists, are commonly used. These medications specifically act on the smooth muscles around facial blood vessels, constricting vessels and reducing persistent central facial erythema, but are ineffective on dilated capillaries, papules, or pustules. It is believed that improvement in erythema is only a temporary suppression. The main oral treatment is the β-adrenergic receptor inhibitor carvedilol [8]. Carvedilol has both α1 receptor blocking and nonselective β receptor blocking effects, acting on myocardial β1-adrenergic receptors to slow the heart rate and ease patient tension; this is mainly used for refractory transient flushing and prominent persistent erythema. Despite good patient tolerance, caution is advised for hypotension and bradycardia, with monitoring of heart rate and blood pressure recommended. Some patients experience rebound upon discontinuation. In photophysical therapy, options include intense pulsed light (IPL), pulsed dye lasers, potassium titanyl phosphate lasers, Nd: YAG lasers, and radiofrequency therapy [9]. Laser devices use hemoglobin as a medium, emitting photons or laser beams to denature and coagulate hemoglobin, forming blood clots and damaging endothelial cells within capillaries, reducing telangiectasia and inhibiting vascular proliferation. While laser therapy has advantages for treating telangiectasia, patients with severely compromised skin barriers cannot tolerate the local stimulation of lasers, and the high cost of laser treatment limits its widespread clinical use.

Collateral puncture therapy is one of the oldest healing methods in human medical history, dating back to the Stone Age, when it was discovered that collateral puncture could alleviate pain [10], leading to the development of medical tools like *bian* stones. With the progress of history, various acupuncture and collateral puncture tools were developed [11], including acupuncture needles and triangular needles. Collateral puncture therapy involves using needles to puncture superficial small veins, specific acupoints, lesion areas, or pathological reaction points to release a certain amount of blood for treating diseases [12]. "Meridians" in *Miraculous Pivot*, a classical work in Chinese medical literature, mentions that the main function of collateral puncture therapy is dredging channels and regulating *qi* and blood for therapeutic effects. In traditional Chinese medicine, the pathogenesis of rosacea is the stagnation of "heat evil" in the facial skin, causing blood coagulation, which aligns well with the disease and makes collateral puncture therapy suitable for its treatment. Additionally, modern medicine recognizes that collateral puncture can improve microcirculation, making it particularly suitable for treating ETR [13].

Clinically, collateral puncture therapy has been widely applied in the treatment of rosacea and has received positive feedback on its efficacy [14-18]. However, there is currently a lack of high-quality medical evidence to support it. Therefore, this project aims to objectively evaluate the efficacy of collateral puncture therapy on ETR using scientific clinical observation methods.

Objectives

The primary objective is to verify the clinical efficacy and safety of collateral puncture therapy in the treatment of ETR. The secondary objective is to supplement rosacea treatment methods, standardize treatment protocols, and fill a current clinical gap in treating rosacea.

Methods

The study protocol was designed in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines (Multimedia Appendix 1) [19].

Study Design and Setting

This is a randomized, controlled, evaluator-blinded trial. Sixty patients were evenly divided into the experimental group and the control group.

Recruitment and Informed Consent

All participants were recruited from Guang'anmen Hospital, China Academy of Chinese Medical Sciences. Public recruitment advertisements for this trial were used to recruit patients both online and offline (eg, through WeChat public accounts and websites). The researchers determined patient eligibility for this study based on strict application of the inclusion and exclusion criteria. Interested and willing patients who met the inclusion criteria signed a written informed consent form (Multimedia Appendix 2) before the start of the study. They were fully informed about the study, including its procedures, benefits, and potential risks. Participants were free to withdraw from the study at any time without penalty and without any negative impact on their future medical care.

Study Population

Inclusion Criteria

Patients were included if they (1) met the diagnostic criteria for rosacea as defined in the "Guidelines for the Diagnosis and Treatment of Rosacea in China (2021 Edition)," [20] specifically the erythematotelangiectatic type; (2) were aged between 18

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and 70 years (inclusive); and (3) signed an informed consent form.

Exclusion Criteria

Patients were excluded if they (1) had any systemic or active skin disease on the face that could affect the evaluation of the study results (such as connective tissue disease) or had scars, tattoos, birthmarks, or pigmentary skin diseases on the affected area that could affect the assessment of skin lesions; (2) had serious primary diseases of the heart, cerebral vessels, liver, kidney, or hematopoietic system; mental illnesses or a history of autoimmune diseases; were pregnant or breastfeeding; had photosensitivity; or had a fear of needles; (3) used oral immunomodulators (such as hydroxychloroquine sulfate), β-adrenergic receptor inhibitors (such as carvedilol), or antianxiety drugs (such as mirtazapine and paroxetine) for rosacea treatment within 30 days before treatment; (4) had applied vasoconstrictor drugs on the face (such as 0.5% brimonidine tartrate gel or 1% hydroxymetazoline hydrochloride cream) within 7 days before treatment; used calcineurin inhibitors, antimicrobials, or steroid creams; or had undergone fire-needle therapy, collateral puncture, or LED light treatment on the face; (5) had undergone facial injections, laser treatments, or chemical peels within 30 days before treatment; (6) were currently participating in, or had participated in, another clinical trial within the last 3 months; or (7) could not tolerate any of the procedures involved in the trial.

Removal Criteria

Patients were removed from the study if they (1) showed poor compliance during the trial, affecting the determination of efficacy and safety; (2) experienced serious adverse events, complications, or special physiological changes, making them unsuitable to continue the trial (these were recorded as adverse reactions); (3) were concomitantly using nonprescribed medications, especially those significantly affecting the trial medication, impacting the determination of efficacy and safety; (4) voluntarily withdrew during the trial; (5) withdrew from the trial before completing the course, were lost to follow-up, or died for any reason; or (6) had incomplete data, affecting the judgment of efficacy and safety.

Randomization and Blinding

Sixty patients were randomly divided into an experimental group and a control group, with 30 in each, using a random controlled method. To avoid selection bias, random numbers were generated using SAS (SAS Institute). The allocations were sealed in opaque, carbonless copy-paper envelopes. After participants agreed to random allocation, they received an allocation sequence number. Upon opening the corresponding envelope, group assignment was determined and recorded in the case report form by a dedicated person. Throughout the study, the evaluators and statisticians were blinded to group allocation.

Intervention

Instrument Selection

The triangular needles used in the study (Huatuo brand disposable acupuncture needles; Suzhou Medical Supplies Factory; production license number 20010020 of the Su Food and Drug Administration of Machinery Production; registration certificate number 20210456). The needle size was 1.6 mm×65 mm. The IPL therapy device was the Icon MaxG (Cynosure LLC).

Collateral Puncture Group

Patients in the experimental group underwent facial collateral puncture therapy at the dermatology department of Guang'anmen Hospital. The selected acupuncture points were *ashi* points located at the sites of facial telangiectasia. Prior to treatment, the practitioner massaged the chosen areas to induce congestion. During the procedure, a triangular needle was rapidly and shallowly inserted into the skin at an oblique angle to ensure that blood flowed naturally without puncturing blood vessels and causing hematoma. The volume of bloodletting was controlled within the range of 0.5 to 1 ml. The treatment schedule consisted of 1 session of collateral puncture per week for a total of 4 treatments. Throughout the entire trial, collateral puncture procedures were performed by the same acupuncturist (Figure 1).

Figure 1. Diagram of collateral puncture therapy.

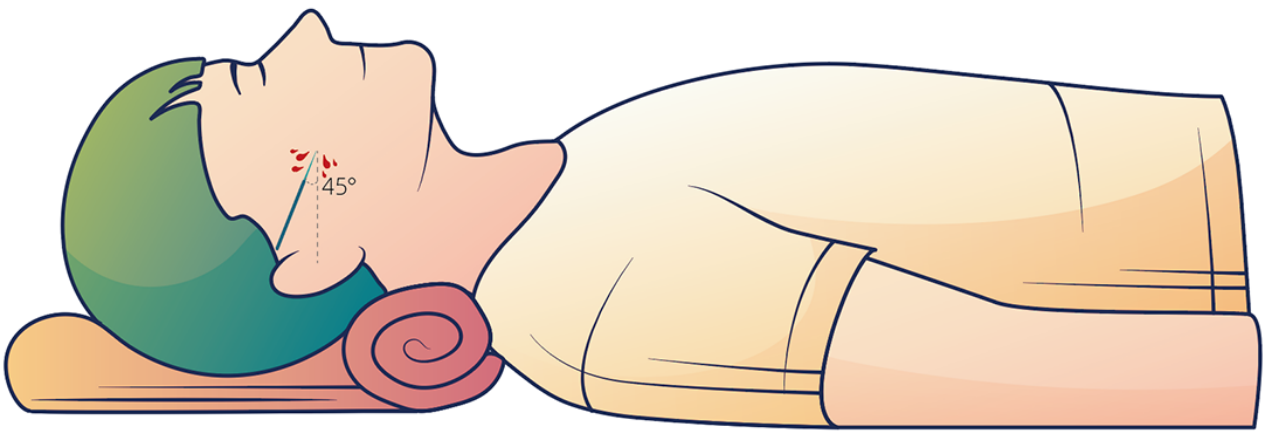

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The term "*ashi* point" originates from Sun Simiao's *Essential Prescriptions Worth a Thousand Gold*. These points can be found anywhere on the body and represent a phenomenon known as temporary acupuncture points. When a disease arises, there is a corresponding stagnation of *qi* and blood in a specific body part, leading to localized and temporary accumulation of *qi* and blood, thus manifesting the *ashi* point phenomenon. As the disease subsides, the temporary accumulation of *qi* and blood dissipates, and the *ashi* point vanishes. Therefore, according to traditional Chinese medicine, *ashi* points serve as both indicators of disease and the best stimulation point for treatment.

IPL Group

Patients in the control group underwent facial IPL treatment in the laser department of Guang'anmen Hospital, specifically targeting the localized facial telangiectasia. The IPL wavelengths used were 500 to 670 nm and 870 to 1200 nm, with a spot size of 10 mm×15 mm, a pulse width of 20 ms, and an energy density ranging from 36 to 38 to 40 J/cm^2. The overlap of control points was maintained within a 10% range. The treatment protocol consisted of a single session administered upon enrollment, totaling 1 treatment. Throughout the trial, all laser procedures were performed by the same laser physician.

Outcomes

The study timeline is presented in Table 1. All outcome measures shown in the table were recorded from baseline to the end of follow-up.

Table 1. Study schedule for data measurements.

Time point	Study period (days)					
	Baseline	Treatment				Follow-up
	0	0	7±3	14±3	21±3	28±3
Enrollment						
Sign informed consent	✓					
Inclusion/exclusion criteria	✓					
Medical history	✓					
Demographic data	✓					
Assessment						
Clinician erythema assessment	✓	✓				✓
Clinician's telangiectasia assessment	✓	✓				✓
Investigator's global assessment		✓				✓
Patient's self-assessment		✓				✓
Flushing Assessment Tool	✓					✓
Dermatology Life Quality Index	✓					✓
Rosacea-specific Quality-of-Life	✓					✓
Adverse reactions	✓	✓	✓	✓	✓	✓
Combination medication/treatment	✓	✓	✓	✓	✓	✓
Adverse event reporting	✓	✓	✓	✓	✓	✓
Research completion status	✓	✓	✓	✓	✓	✓
Researcher review	✓	✓	✓	✓	✓	✓

Primary Outcomes

The clinician erythema assessment [21] assesses the severity of erythema before treatment, immediately after treatment, and at follow-up. The clinician's telangiectasia assessment [22] assesses the severity of capillary dilation, classified into 5 grades based on the number and size of dilated vessels, with evaluations conducted before treatment, immediately after treatment, and during the follow-up period.

Secondary Outcomes

The investigator's global assessment [23] provides an overall assessment of the treatment's effectiveness immediately after treatment and at follow-up. The patient's self-assessment [24] assesses the patient's own perception of the treatment immediately after treatment and at follow-up. The Flushing Assessment Tool [25] assesses facial flushing before treatment and at follow-up. The Dermatology Life Quality Index and Rosacea-specific Quality-of-Life [26,27] tools rate the patient's quality of life before treatment and at follow-up (Multimedia Appendix 3).

Sample Size

With reference to relevant literature, we used a noninferiority trial calculation formula for sample size calculation, as follows:

n1=[(u1-T+u1-u)e/W]2×(1+c)/c, n2=cn1 [28]

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In the formula, where c=1, $n2=n1$; setting α=.05, then $u1–T$=1.64, $u1–u$=1.28. Based on previous studies using clinician erythema assessment scoring as the primary efficacy end point, e is taken as 0.84, W as 1. Substituting the data into the formula, we calculate $n1=n2\approx13$ [29]. Considering a 30% dropout rate and to enhance data reliability, the final sample size was set at 30 cases per group and 60 cases in total.

Data Management and Confidentiality

The research team will meticulously record the initial data for each participant on the case report form and systematically input them into a secure Microsoft Excel database. Participants' identities will be anonymized and represented by unique random numbers, ensuring the researchers cannot access their personal information. This approach guarantees stringent data confidentiality. The task of data storage and management, as well as rigorous verification of data accuracy, rests with a designated data custodian. The investigator is responsible for diligently completing each participant's case report form. The research director will periodically audit the data collection process to maintain its integrity. To safeguard participant privacy, all personal information, including names, contact details, and medical records, will be anonymized and securely stored. Such data will be housed in a specially designated cabinet under the researchers' custody and preserved for a minimum of 5 years after publication. The Ethics Committee of Guang'anmen Hospital, China Academy of Chinese Medical Sciences, will routinely oversee the trial's progression. This includes monitoring the collection, allocation, and concealment of data and ensuring adherence to ethical standards. The committee holds the authority to propose modifications or terminate the trial if necessary. The Data Monitoring Committee, acting independently from the sponsors and devoid of any conflicts of interest, will provide unbiased oversight of the trial's data management processes.

Adverse Event Reporting and Safety Monitoring

During the study, adverse reactions could occur at the lesion site, such as local bruising, erythema, edema, pain, itching, blisters, exudation, dry skin, desquamation, acne-like lesions, skin sensitivity, hyperpigmentation, and scarring. If adverse reactions occurred, we recorded the adverse event; if adverse reactions occurred after treatment, we considered their relation to the treatment, reported them promptly to the researcher, and if necessary, stopped the treatment and provided corresponding symptomatic treatment.

Ethical Considerations

The protocol study has received ethical clearance from the Ethics Committee of Guang'anmen Hospital, China Academy of Chinese Medical Sciences (2022–127-KY). Patients have the right to withdraw from this study at any time. Prior to enrollment, we ensured that each patient had a clear understanding of the informed consent form, and it was the responsibility of the investigating physician to ensure that every patient provided informed consent before entering the study. The informed consent forms will be retained as part of the clinical study documentation for future reference. We are committed to safeguarding participants' privacy and confidentiality by anonymizing all data and storing them securely, with access restricted solely to the research team. Although participants did not receive financial compensation, we express our sincere gratitude for their contributions. Dissemination of the study's findings is planned through publication in a reputable, peer-reviewed academic journal.

Results

The research protocol was approved by the Guang'anmen Hospital Ethics Committee on June 24, 2022, and was registered on August 14, 2022. Recruitment commenced on June 1, 2023, with an average of 4 to 6 participants enrolled per month. All patients have been recruited, and we anticipate publishing our research findings by the end of 2025 (Figure 2).

Statistical analysis will be conducted using SPSS (version 25.0; IBM Corp). Means and SDs will be calculated, and measurement data will be analyzed using 1-tailed t tests and ANOVAs. Nonparametric tests will be used for data not following a Gaussian distribution; the χ^2 test will be used for categorical data. Based on previous research outcomes, we anticipate that when comparing the primary and secondary efficacy indicators between the follow-up and baseline periods, scores in both the treatment and control groups will show a downward trend. However, we expect that the decline in scores will be more pronounced in the experimental group.

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Figure 2. Flowchart of the research procedure.

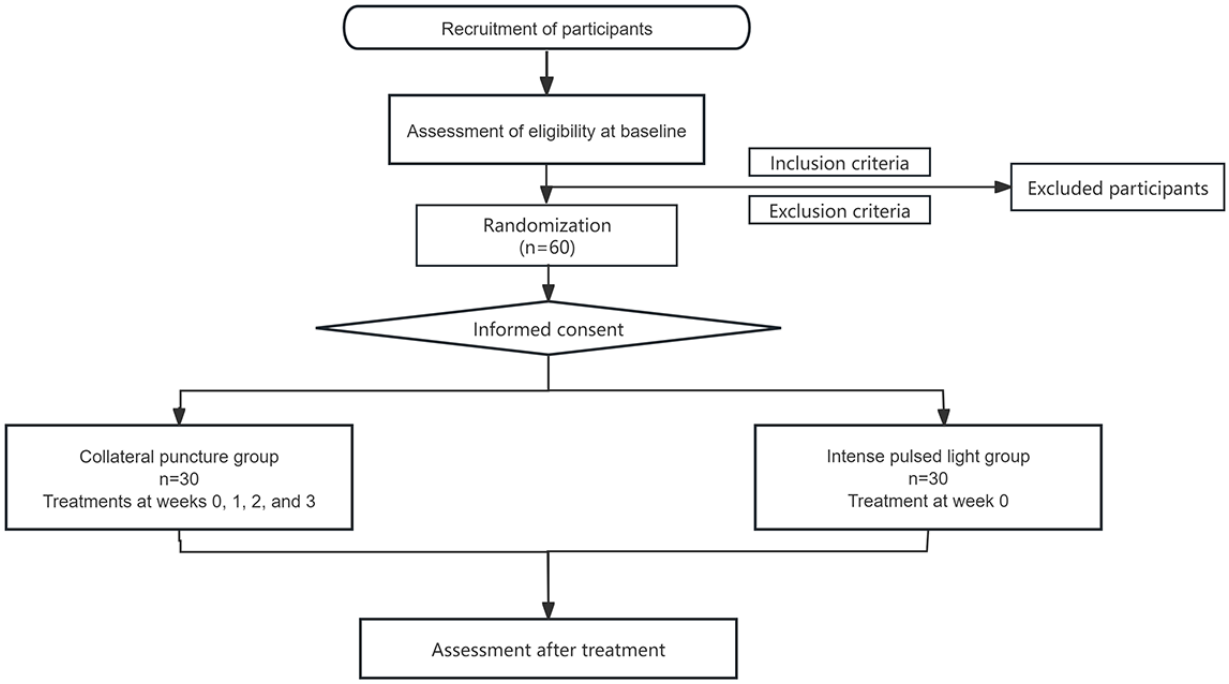

Discussion

We recruited a total of 60 patients with ETR to conduct a randomized, blinded, controlled study, aiming to observe the therapeutic effect of collateral puncture therapy on ETR patients by comparing the outcomes before and after treatment. Our hypothesis is that, compared to patients receiving IPL therapy, those undergoing collateral puncture will exhibit significant improvements in erythema and telangiectasia. To our knowledge, no studies have been reported that directly compare the pure traditional Chinese medicine technique of collateral puncture with IPL for the treatment of ETR. This study intends to fill the gap in the direct comparison between traditional nonpharmacological therapies in Chinese medicine and modern photoelectronic technologies.

The pathogenesis of rosacea involves contributions from ultraviolet rays, bacteria, demodex folliculiformis, immune dysregulation, neurovascular dysfunction, and genetic factors, among others [20]. Collectively, these etiological agents induce an inflammatory response in the body. IPL therapy for patients with rosacea uses the principle of selective photothermolysis, where the laser specifically targets diseased tissue while sparing adjacent normal tissue, causing thermal damage to dilated capillaries, leading to their coagulation and necrosis [30,31]. Bipolar radiofrequency therapy converts electrical energy into thermal energy through the epidermis to further heat the target tissues. When combined, IPL and bipolar radiofrequency therapy exhibit synergistic effects in reducing dilated capillaries and inflammatory cell infiltration, resulting in favorable therapeutic outcomes. IPL is a commonly used treatment modality for ETR [32]; however, it is relatively costly and has limited efficacy in alleviating symptoms such as facial warmth and itching. Therefore, it was selected as the intervention for the positive control group in this study [33].

Ying et al [34] found that collateral puncture therapy can reduce the levels of interleukin-1 β, granulocyte-macrophage colony stimulating factor, tumor necrosis factor α, interleukin-6, and cyclooxygenase-2, while increasing the levels of interleukin-4 and interferon γ. This suggests that collateral puncture therapy enhances the levels of anti-inflammatory cytokines and inhibits the expression of pro-inflammatory cytokines, thereby exerting an anti-inflammatory effect. During treatment, the skin puncturing involved in collateral puncture stimulates the vegetative nervous system, promoting an increase in the secretion of vascular endothelial cells and enhancing the regulatory function of blood vessels. As the collateral puncture disrupts the integrity of blood vessels, it stimulates the function of endothelial cells, leading to the production of a large amount of hormone-like substances that regulate body fluids and blood pressure. Simultaneously, collateral puncture therapy, through physical stimulation causing local capillary rupture, elicits interactive neuroimmune regulation within the microcirculation and also modulates lipid metabolism in the body, reducing the levels of triglycerides, total cholesterol, and other components in the serum [35]. Furthermore, collateral puncture therapy is a simple and cost-effective procedure, with patients reporting immediate relief from symptoms such as facial heat and itching following the treatment. Therefore, this study adopted collateral puncture therapy as the intervention measure (Figure 3).

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Figure 3. The pathogenesis of rosacea and the underlying principles of collateral puncture therapy.

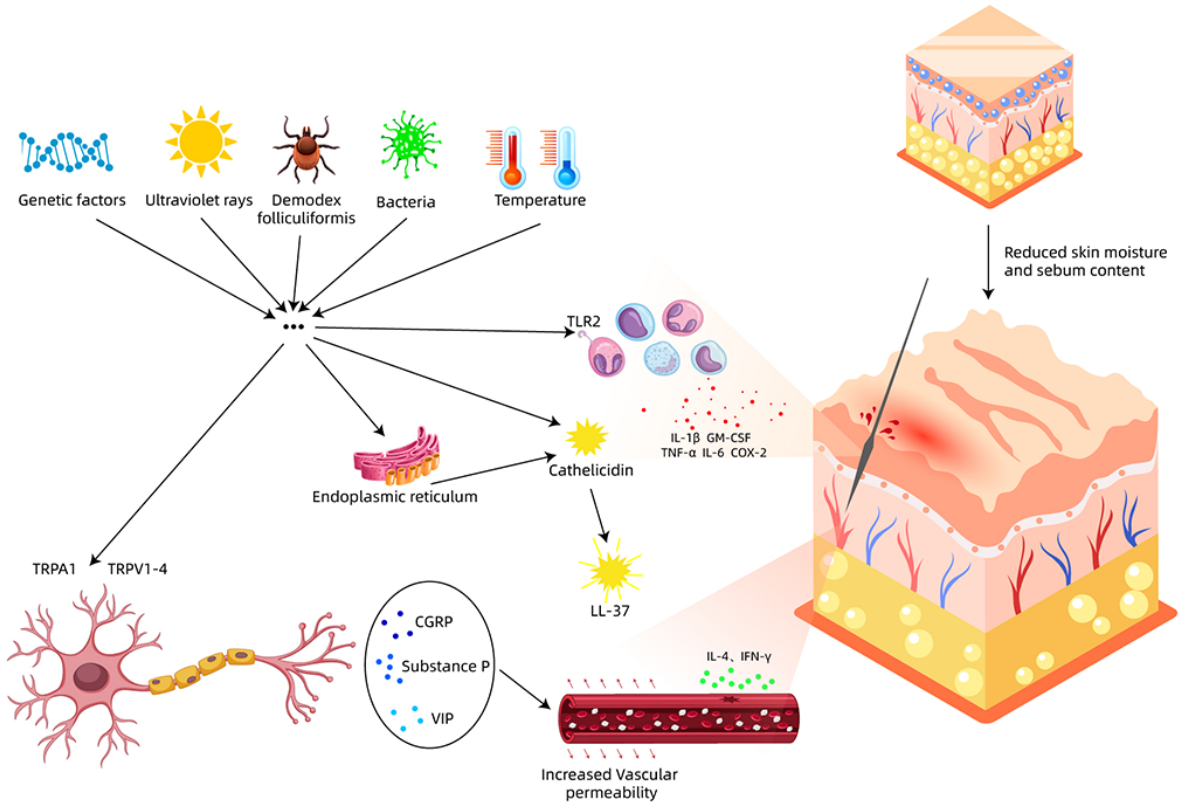

However, this study is also subject to certain limitations. First, previous studies used IPL treatments that were administered once a month, with 3 to 4 sessions constituting one course of treatment. As an exploratory experiment, our study features a shorter treatment duration and a smaller sample size; therefore, the control group received only 1 treatment session. Future research should aim to address these issues by increasing the sample size and extending the observation period while also increasing the number of treatment sessions for both intervention groups and expanding the follow-up period to 6 months or even 12 months, in order to more objectively assess the efficacy of collateral puncture therapy in treating ETR and its ability to inhibit recurrence. Second, the inclusion and exclusion criteria in this study protocol did not fully control for confounding factors. Subsequent studies should further refine these criteria, including restrictions on the type and frequency of skin care products used by patients, as well as their living environments, among other factors. Furthermore, the evaluation indicators designed for this study primarily focused on patients' erythema, telangiectasia, and quality of life, without assessing changes in facial skin barrier function. Subsequent studies should incorporate relevant evaluation indicators to gain a deeper understanding of the efficacy of collateral puncture therapy. Lastly, this study did not provide detailed specifications for specific quantitative standards and grading of adverse reactions, nor did it monitor systemic safety indicators. Subsequent studies should refine these aspects by incorporating the assessment of safety indicators before and after treatment, such as routine blood tests and infection status, in order to more accurately compare the occurrence of adverse reactions between the two patient groups.

In summary, collateral puncture therapy for the treatment of ETR possesses a solid theoretical foundation, demonstrates favorable clinical efficacy feedback, is less expensive than photodynamic therapy, and exhibits good safety. However, sufficient clinical evidence to support its use is lacking. The results of this study will provide new insights into the effects and mechanisms of collateral puncture therapy for ETR, thereby complementing the therapeutic options for rosacea, standardizing treatment protocols, potentially reducing disease burden and economic costs, and contributing to both the academic community and the public.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

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Authors' Contributions

AS, XW, LY, and JB contributed to the protocol design and writing the manuscript. BC and XW were responsible for the randomization design. LL, SQ, and ZF were responsible for data entry. YY was responsible for treatment. JY and YY were responsible for guidance and statistics. All authors were instrumental in the conceptualization of the study design, contributed substantially to the development of the manuscript, and endorsed the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOCX File , 25 KB - resprot_v14i1e59682_app1.docx]

Multimedia Appendix 2
Informed consent form.
[DOCX File , 21 KB - resprot_v14i1e59682_app2.docx]

Multimedia Appendix 3
Outcome forms.
[DOCX File , 42 KB - resprot_v14i1e59682_app3.docx]

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Abbreviations

IPL: intense pulsed light
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Effect of Live Environmental Music Therapy and Prerecorded Music on State Anxiety, Stress, Pain, and Well-Being Levels of Patients and Caregivers in the Emergency Department Waiting Room: Protocol for a Multicenter Randomized Clinical Trial

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Related Article:

This is a corrected version. See correction statement: https://www.researchprotocols.org/2025/1/e80077

Abstract

Background: Patients and caregivers attending emergency units often experience elevated levels of stress and anxiety. Music has been used in waiting rooms to reduce stress and anxiety, but existing studies on music therapy in emergency unit waiting areas are scarce and have limitations such as low statistical power and limited music selection.

Objective: The aim of this study is to determine the effect of live Environmental Music Therapy and prerecorded music on state anxiety, stress, pain, and well-being levels in patients and caregivers in the emergency unit waiting areas of 2 hospitals in Colombia.

Methods: This study is a multicenter randomized clinical trial, with 3 arms: standard care + live Environmental Music Therapy, standard care + prerecorded music, and standard care only. The primary outcome measure is the 6-item State-Trait Anxiety Inventory (STAI-6). Secondary outcome measures are pain and stress levels, both measured with Visual Analogue Scales (VAS), and well-being, measured with the Well-Being Numerical Rating Scales (WB-NRSs). The scales will be applied before and after each intervention. A total of 246 patients (82 in each arm) and 147 caregivers (49 in each arm) will be randomized.

Results: Data collection for this study started on September 3, 2024, and as of the submission of the study (November 2024), 216 patients and 134 caregivers have been enrolled. It is expected that the results will be available by May 2025.

Conclusions: This study seeks to contribute to improving the mental health, well-being, and quality of care of patients and caregivers in the waiting area of the emergency units. This is the first study in Colombia investigating the effect of live music therapy and prerecorded music interventions in the emergency department.

Trial Registration: ClinicalTrials.gov NCT06510153; https://clinicaltrials.gov/study/NCT06510153

International Registered Report Identifier (IRRID): DERR1-10.2196/69131

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(JMIR Res Protoc 2025;14:e69131) doi:10.2196/69131

KEYWORDS

anxiety; emergency department; mental health; music therapy; pain; stress; waiting area

Introduction

Emergency departments (ED) are critical for providing immediate care to patients with acute illnesses or those with medical emergencies. Its proper functioning depends on an organized triage system, which guarantees correct prioritization according to the urgency of pathologies [1]. Emergency health care professionals face a wide variety of medical needs and are exposed to complex social interactions with patients, family members, and caregivers. As a result, the environment in ED waiting rooms can be challenging and stressful for both patients and staff [2-5]. Distress may result from patients' exposure to pain, injuries, discomfort, and possible diagnosis or medical treatments, which can increase their levels of anxiety and the feeling of uncertainty in the face of often prolonged waiting times [6]. Long waiting times in the ED have been shown to negatively affect patient recovery and patients' and caregivers' perception of the care quality provided [7-9]. In addition, patients can also experience nausea, hunger, or thirst, which, as they are not as easily detected by the staff as pain or dyspnea for example, can increase anxiety, insecurity, and discomfort in the waiting area [10]. Thus, it is important to consider environmental factors of ED waiting rooms, such as the quality of chairs, lighting, screens, and sounds, as they also affect the emotional states of patients and caregivers [11].

To mitigate some of these challenges, music therapy and other music-based interventions are increasingly applied in EDs. Early publications include reports of nursing teams using music in the pediatric emergency ward to reduce behaviors such as crying and screaming in children [12,13]. More recent studies highlight the benefits of prerecorded music in reducing anxiety [14-16] or pain [17] levels in adult patients in ED observation rooms. A study on live music therapy in emergency rooms was conducted by Mandel et al [18], including 180 patients (90 intervention, 90 control) who received music therapy sessions over a 3-year period. Although no statistically significant differences were found in patient satisfaction, stress, and pain levels decreased significantly in those patients who received music therapy. Furthermore, staff reported that music therapy favored the overall care experience and patients expressed a desire to have music therapy intervention in the ED again [18].

With respect to waiting rooms, recent literature reviews confirm the potential benefits of music in these settings but also highlight the methodological heterogeneity of studies, small sample sizes, limited descriptions of the music used, and a lack of live music approaches [19,20]. One of the few studies reporting live approaches was conducted by Van Dokkum et al [21] and Rossetti et al [22]. Van Dokkum et al [21] investigated the impact of visiting artists performing live music in waiting rooms at a hospital in New York, showing a positive impact on the sound environment. In a randomized controlled trial, Rossetti et al [22] investigated the effect of live Environmental Music Therapy (EMT) on anxiety levels and waiting time perception of patients and caregivers in the radiation therapy waiting room. The results showed a significant reduction in stress and anxiety levels in both patients and caregivers, in addition to shortening the perception of waiting time.

This study protocol seeks to expand the current knowledge on the use of music in ED waiting rooms by determining the effect of standard care + live EMT versus standard care + prerecorded music versus standard care alone on state anxiety, stress, pain, and well-being levels of in adult patients and caregivers in the emergency waiting rooms of the hospitals Clínica Keralty Ibagué and Clínica Iberoamérica in Colombia, South America.

Methods

Study Design

This study follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (Multimedia Appendix 1) for reporting randomized clinical trial (RCT) protocols [23] and is a multicenter, pragmatic, RCT with 3 parallel arms [24]:

- Intervention group 1: Standard care + EMT
- Intervention group 2: Standard care + prerecorded music
- Control group: Standard care alone

This study will be carried out in the emergency waiting room areas of the Clínica Keralty Ibagué and Clínica Iberoamérica within a 6-month period. The anticipated recruitment start date is September 2024.

Study Participants and Setting

The study participants are adult patients and caregivers in the emergency waiting rooms of both hospitals. Both EDs are located in different cities in the country but belong to the same health care provider, which ensures similar standard care procedures for patients and caregivers. Both EDs serve subsidized, contributory, and prepaid health care users and both hospitals use the ESI (Emergency Severity Index) system for effective triage of patients. The ED waiting area at the Clínica Keralty Ibagué has 40 seats and the one at the Clínica Iberoamérica has 38 seats. Estimated wait times according to triage classification are as follows: triage 1: immediate attention (reanimation); triage 2: approximately 30 minutes; triage 3: approximately 1 hour; and triage 4 and 5: up to 6 hours. The 3 most common reasons for admission to the ED are (1) abdominal and pelvic pain, (2) fever of unknown origin, and (3) intestinal infections due to viruses and other pathogens.

Inclusion Criteria

The inclusion criteria are patients and caregivers of legal age present in the ED waiting rooms during the intervention and control conditions; patients whose triage does not represent an immediate threat to life or severely ill patients (ie, triage 3, 4, and 5); and patients and caregivers with the necessary literacy and cognitive skills to understand and fill out the questionnaires.

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Exclusion Criteria

The exclusion criteria are patients and caregivers who do not consent to participate in the study; and patients and caregivers who report having hearing problems.

Sample Size

The sample size was calculated based on the primary outcome of this study using G*Power 3.1.9.7 (Heinrich Heine University Düsseldorf) [25] and considering that the study design corresponds to a 3×2 factorial design (3 groups and 2 repeated measures). Therefore, we will determine the effect of treatment between the groups using a 2-way ANOVA and repeated measures. We chose a statistical power of .80, a significance level of .05, and an effect size of =.01, the effect size was determined based on previous research [22] and the expected magnitude of differences between groups. The sample size calculation resulted in 246 participating patients, distributed in 82 per group.

In addition, a separate sample size calculation was performed for participating caregivers, following the same procedure as described for the patients and considering an effect size of η^2=.017, resulting in 147 caregivers (49 per group). Both sample sizes are within the range reported in previous studies [22].

Participant Selection and Randomization

Selection of the participants will be made by convenience sampling. The intervention and control conditions will take place on the same day of the week (Tuesdays, Thursdays, and Fridays) and at the same hour (11 to 11:30 AM) at both hospitals. The order of the 3 conditions (EMT, prerecorded, control) will be randomized by days of intervention. For this, a block size randomization of multiples of 3 will be used, ensuring an equal number of interventions for each arm of the study. Intervention A will be established as EMT, intervention B as prerecorded music, and intervention C as standard care.

Blinding

Due to the nature of the interventions, music therapists, patients, caregivers, and data collectors, will not be blinded. Data analysis will be carried out by a member of the research team blinded to the result of the randomization.

Concealment

The concealment of the random assignment will be guaranteed using sealed, sequentially numbered, and opaque envelopes. The envelopes will be sealed with tamper-proof security tape and opened sequentially on each day of intervention. The envelopes will be kept in a folder that will be kept on a locked shelf inside each clinic, which will be in custody by the research assistant at each participating clinic. The envelope will be opened 10 minutes before the start of the intervention to give the music therapists time to organize their equipment and instruments.

Primary Outcome Measure

The primary outcome measure is state anxiety, measured with the Spanish version of the 6-item State-Trait Anxiety Inventory (STAI-6). In its original version, the STAI consists of 40 items, of which 20 measure trait anxiety and 20 items measure state anxiety [26]. The STAI-6 is a short version of the state scale and consists of 6 items evaluated on a 4-item Likert scale. The STAI-6 was validated in its original English version by Chlan et al [27], and its Spanish version by Perpiñá-Galvañ et al [28,29], and has been successfully used in a previous study on EMT in radiotherapy waiting rooms [22]. The STAI-6 will be applied before and after each intervention.

Secondary Outcome Measures

- Stress: Stress levels will be measured by the Visual Analogue Stress Scale (VAS-S). The VAS-S consists of a 10-cm line divided into 10 points, each separated by 1 cm. 0 means the complete absence of stress, and 10 is the maximum possible stress. The VAS-S has been validated by Lesage et al [30] and was recently applied in a study on stress levels of caregivers or companions in the ED [31]. A cutoff of 7 points has been established as a significant stress level [32]. The VAS-S will apply before and after each intervention.
- Pain (patients only): Perceived pain levels by patients will be measured with the Visual Analogue Pain Scale (VAS-P) consisting of a line of 10 centimeters divided into 10 points, each separated by 1 centimeter. 0 means complete absence of pain and 10 the maximum possible pain. The VAS-P is widely used in research and minimum clinically important differences pre-post interventions range from 9 millimeters [33] to 14 millimeters [34]. The VAS-P scale for pain will be applied before and after each intervention.
- Well-being: Well-being will be measured by the Well-being Numerical Rating Scales (WB-NRSs) developed by Bonacchi et al [35]. The WB-NRSs consist of a line divided into numbers from 1 to 10. 1 indicates a state of absolute distress and 10 a state of absolute well-being. The WB-NRSs uses 5 scales to measure well-being in 5 dimensions: physical, psychological, spiritual, relational, and general. The WB-NRSs will be applied before and after each intervention.

Sociodemographic and Basic Medical Data

To establish intergroup homogeneity, the following data will be collected from the patient's medical history: age, primary diagnosis at the time of admission, triage classification (3 to 5), and the presence of a caregiver or companion at the time of admission to the emergency room.

Participant Timeline

Details of the participant timeline are listed in Figure 1.

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Figure 1. Participant timeline. EMT: Environmental Music Therapy.

	Study period			
	Enrollment	Allocation	Postallocation	Close-out
Timepoint	$-t_1$	0	t_1	t_x
Description	Before randomization	After randomization	Preintervention	Postintervention
Enrollment				
Eligibility screen	✓			
Informed consent	✓			
Allocation		✓		
Interventions				
Live EMT+standard care			◆——	——◆
Prerecorded music+standard care			◆——	——◆
Standard care alone			◆——	——◆
Assessments				
Sociodemographic data	✓			
Medical data	✓			
State anxiety			✓	✓
Stress			✓	✓
Pain			✓	✓
Well-being			✓	✓

Intervention Protocol

Environmental Music Therapy: Intervention Group 1

Environmental Music Therapy is a music therapy technique that uses live music to modulate the potentially stressful effects of the environment toward an atmosphere that provides a sense of comfort and security. For this study, the intervention was adapted based on the 4 steps of EMT described by Rossetti [36]: assessment of the environment, initiation of the intervention, development of the intervention, and closure.

1. Evaluation of the environment: Before starting the intervention, the music therapist will observe the emergency waiting room for a couple of minutes to be aware of the number of people present and the content, volume, or timbre of the current auditory environment. In addition, it will be detected if, for example, someone shows signs of acute pain or signs of restlessness or anxiety. Assessing the environment also includes finding an optimal place for the music to be heard evenly throughout the room, without disturbing the movements and flow of patients, caregivers, and staff.
2. Beginning of the intervention: Before starting EMT, the music therapist will introduce him or herself to the patients and caregivers present and explain the role and purpose of the music. Patients and caregivers will be informed that they can participate in listening to the music in every way that feels comfortable for them, for example by just continuing what they are currently doing, by breathing slowly with the music, or by imagining themselves being in a safe place.
3. Development of the intervention: The instruments used will be an acoustic guitar (Yamaha C-40), an ocean drum (a drum with a double skin on which small metal balls roll imitating the sound of the waves), and a Samafon (an instrument consisting of aluminum tubes of different sizes that are struck with a soft mallet producing long-lasting single or combined tones). The different instruments and timbres will be introduced gradually. The music will consist of improvised instrumental music at a slow to moderate tempo, using free-flowing melodies, and simple chord progressions, focusing on creating moments of tension and resolution. The music therapist will also use his or her voice to accompany the music but without any lyrics or words. While the musical characteristics are aimed to remain consistent during the intervention, their selection, order, and content, will be adapted according to a constant re-evaluation of the environment.
4. Closing: after 20 minutes, the music therapist will gradually decrease the volume until the music stops.

Prerecorded Music: Intervention Group 2

The prerecorded music will consist of a recording including the same musical features and musical instruments as the live music. The recording will be made by the same music therapists who will perform the EMT intervention. To playback the music, a Bluetooth speaker (JBL Go 3) will be placed centrally in the ED waiting room and handled by the music therapists. The

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recorded music will last 20 minutes and the music therapists will remain present at the waiting room but will not engage in any further activities.

Standard Care Only: Control Group

The control group will receive standard care in the emergency room waiting room as provided by each hospital, but without being exposed to EMT or prerecorded music. However, the music therapist will remain present in the waiting room but will not engage in any activities. The control condition will last for 20 minutes.

Data Collection and Storage

The data will be collected by a research assistant in each hospital and stored in a REDCap (Research Electronic Data Capture; Vanderbilt University) database to maintain confidentiality and data safety. During the data collection process, the database will be audited to identify the presence of inconsistent or atypical data. At the end of the data collection, a random selection of the data of 10% of the participants will be made to verify the paper version of the questionnaires against the electronic database.

Potential Harms and Adverse Events

Any potential harm or adverse events related to the intervention will be recorded and communicated to the ethics committee according to the hospital site's guidelines.

Data Analysis

Regarding the sociodemographic and medical data, a descriptive analysis will be carried out. For continuous variables and according to the nature of the data, measures of central tendency and interquartile range or mean and SD will be used, and evaluated with the Shapiro-Wilk test. Categorical variables will be analyzed and summarized using frequencies. Association tests of categorical variables will be evaluated using the chi-square statistic or Fisher exact test in the case of tables with cells with expected values less than 5. For the comparison of measures of central tendency in the cases of quantitative variables, tests such as the Student *t* test or sum of Wilcoxon or Kruskal–Wallis ranges will be performed, depending on the presence or not of normality in the distribution of the variables. A statistical significance value of 5% will be used for all hypothesis test cases.

The analysis regarding the effect of the interventions will be carried out separately by type of participant (patient or caregiver). The effect on state anxiety, stress, pain (only patients), and well-being will be evaluated using 3×2 factorial ANOVA. Then a post hoc analysis will be performed using the Student *t* test and Bonferroni adjustment. A multiple linear regression analysis will be carried out to evaluate the variables (state anxiety, age, sex, type of participant, waiting time, and reason for consultation) that modify the effect of the interventions on the state anxiety, stress, pain, and well-being levels. Only data from patients and caregivers who will complete both baseline and postintervention questionnaires will be analyzed. However, to avoid bias we will assess if the distribution of participants who did not fill out the postintervention questionnaires is similar among the groups.

Ethical Considerations

This study was approved by the Research Ethics Committee of the Fundación Universitaria Sanitas (CEIFUS 1779-24, date of approval: June 18, 2024). All participants and 2 additional witnesses will sign a written informed consent. Consent will be obtained from research assistants. This study was registered in ClinicalTrials.gov (NCT06510153).

Results

Data collection for this study started on September 3, 2024, and as of the submission of the manuscript (November 2024), 216 patients and 134 caregivers have been enrolled. It is expected that the results will be available by May 2025.

Discussion

Anticipated Findings

This study seeks to investigate the effects of live EMT and prerecorded music on state anxiety, stress, pain, and well-being levels of patients and caregivers in the ED waiting room. Both patients and caregivers face multiple challenges while waiting to be attended to in the ED. Particularly, increased stress and anxiety levels have been found to be correlated with greater perceived barriers to care in ED patients [37]. Besides, long waiting times and noise can negatively impact not only patient satisfaction with care but also the satisfaction of those who accompany a patient [8,9]. In addition, anxiety levels in caregivers at ED discharge are correlated to their satisfaction with the ED visit [38].

While recorded music has previously been used in the waiting room to reduce distress and anxiety [39-41], we have not found studies that use live music or compare EMT and prerecorded music in ED waiting rooms. Furthermore, a recent meta-analysis on music in waiting rooms stresses the need for research with robust designs [20]. In this study, the multicenter approach, randomization of intervention days, and adequate sample size calculation for both patients and caregivers should help improve methodological soundness. While in this study we also use measures focusing on reducing mental health challenges (STAI-6, VAS-S), we actively seek to understand music's role in improving well-being (WB-NRSs). The integration of both patients and caregivers into the intervention is in line with person-centered and humanized care models in Colombia [42].

Potential Limitations

Several potential limitations have been identified for this study. First, participants may be called for treatment or medical exams after filling out the baseline questionnaires but before the end of the intervention, not all participants will fill out the postintervention questionnaires. Thus, only patients and caregivers who complete both baseline and postintervention questionnaires will be analyzed. Second, as data collectors need to be aware of who has already filled out the baseline questionnaires but might not be available anymore at the end of the interventions, blinded data collection is not feasible. However, we estimate expectancy effects to be low, as all questionnaires are self-rated and the data collector is not

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interfering with the filling out the forms. In addition, music therapists will be present during all 3 conditions to mitigate any potential effects due to their presence but do not interfere with either recruitment or data collection. However, in a future study, scales such as the Credibility and Expectancy Scale [43] could be applied to further mitigate expectancy effects in nonblinded participants. Fourth, while music therapists pretested the live music and prerecorded music to ensure similar volume and sound distribution in the ED waiting areas, no formal sound level measurements were applied. This could have resulted in slightly different sound experiences of participants and could be implemented in a future study to control for this variable. Third, anxiety, stress, pain, and well-being are influenced by multiple factors. In addition, both hospitals are in different cities and regions in the country. Thus, cultural and social factors may further influence the outcomes. While the pragmatic nature of this RCT acknowledges such complexity, results should nevertheless be interpreted with caution as not all confounding variables can be controlled.

Conclusions

This research proposal seeks to advance knowledge on the role of music in improving mental health and pain in the ED waiting room. To our knowledge, it is the first multicenter RCT on music therapy in the wider field of emergency care in Colombia.

Acknowledgments

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Data Availability

All data will be made available upon request by the corresponding author.

Authors' Contributions

AH, AMD, OFM, RS, MA, AMM, BARS, LMGG, GACO, and ME designed the study. AH and ME drafted the manuscript. ME is the principal investigator and supervised the study process.

Conflicts of Interest

ME, AMD, RS, and AH are providing music therapy services at the 2 hospital sites.

Multimedia Appendix 1
SPIRIT checklist.
[DOCX File , 41 KB - resprot_v14i1e69131_app1.docx]

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Abbreviations

ED: emergency department
EMT: Environmental Music Therapy
ESI: Emergency Severity Index
RCT: randomized clinical trial
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
STAI-6: 6-item State-Trait Anxiety Inventory
WB-NRS: Well-being Numerical Rating Scale
VAS-P: Visual Analog Pain Scale
VAS-S: Visual Analogue Stress Scale

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Protocol

Acceptance-Based Pre-Exposure Prophylaxis Intervention (ACTPrEP) to Engage Young Black Men Who Have Sex With Men in the Southern United States: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Given the high rates of HIV infection among young Black men who have sex with men in Jackson, Mississippi, and the underuse of pre-exposure prophylaxis (PrEP) in this population, there is a critical need for innovative interventions to promote PrEP use. Acceptance and commitment therapy (ACT) is a promising intervention for health behavior change.

Objective: This study aims to develop and test an intervention, ACTPrEP, to increase PrEP use among young Black men who have sex with men.

Methods: We conducted in-depth interviews with 20 young Black men who have sex with men and 10 PrEP staff to inform the development of ACTPrEP, an intervention that uses ACT to improve PrEP use. Specific ACTPrEP adaptations from the qualitative interviews included service settings (interventionists should be PrEP informed and well-integrated), target audiences (provide check-in calls, be caring, and authentically relate), modes of delivery (flexible delivery), and cultural adaptation (normalize PrEP use). A pilot randomized controlled trial will evaluate the feasibility and acceptability of ACTPrEP compared to that of Enhanced Standard of Care in promoting PrEP use among young Black men who have sex with men (N=66). We will specifically evaluate group differences in the proportion of participants who initiate PrEP, PrEP adherence, and PrEP persistence. Measures will be collected at baseline, 6 weeks, and 12 weeks.

Results: Research activities began in September 2023 and will be ongoing through June 2026. Preliminary findings are anticipated to be available in late 2026.

Conclusions: This study will inform the development of a larger randomized controlled trial to evaluate the efficacy of ACTPrEP for increasing PrEP use among young Black men who have sex with men.

Trial Registration: ClinicalTrials.gov NCT05087680; https://clinicaltrials.gov/study/NCT05087680

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KEYWORDS

HIV prevention; pre-exposure prophylaxis; young Black men who have sex with men; acceptance and commitment therapy; protocol

Introduction

The HIV epidemic disproportionately affects men who have sex with men, with a significant burden borne by young Black men who have sex with men [1]. In the United States, Black men who have sex with men account for a quarter of new HIV diagnoses despite representing less than 1% of the population [2]. Young Black men who have sex with men are also substantially more likely to receive an HIV diagnosis in their lifetime compared to their White counterparts [1]. In the South, the burden is particularly high. Jackson, Mississippi, experiences some of the highest rates of HIV infection among urban men who have sex with men [3], with a majority occurring in young Black men who have sex with men [4].

Pre-exposure prophylaxis (PrEP) is a highly effective HIV prevention strategy involving taking antiretroviral medication to prevent HIV acquisition before potential exposure [5,6]. Studies have demonstrated the high efficacy of PrEP when taken as prescribed [7]. Despite this, significant disparities exist in PrEP uptake and adherence, particularly among young Black men who have sex with men [8]. In 2021, the PrEP to need ratio was lowest among Black individuals aged 13-24 years when compared to other races and age groups [9]. While there has been a 34% decrease in new HIV infections among young men who have sex with men, decreases are not equitable among ethnic groups [10]. Young Black men who have sex with men had a 27% decrease, while young White men who have sex with men had a 45% decrease [10]. There have also been multiple studies that have identified barriers preventing young Black men who have sex with men from accessing and using PrEP, including lack of priority, lack of perceived risk, lack of PrEP knowledge, stigma and fear, misunderstood side effects, and payment for PrEP [11-13]. These highlight the critical need for interventions to address the underuse of PrEP among young Black men who have sex with men.

Acceptance and commitment therapy (ACT) is a well-established psychological intervention that has been widely used to facilitate health behavior change, particularly in populations experiencing emotional and psychological barriers to medical adherence [14]. ACT targets psychological inflexibility, which refers to the tendency to avoid or suppress thoughts, emotions, and bodily sensations even when doing so interferes with valued actions and health-related goals [14]. Psychological inflexibility is a known barrier to health behavior engagement, including medication adherence, preventive care, and chronic disease management [15]. Studies have linked avoidance behaviors, delayed medical care, and nonadherence to prescribed treatments with poor health outcomes in multiple chronic conditions [16-20]. ACT has been successfully applied across various health domains to improve adherence and promote sustained health behavior change. Research shows that ACT-based interventions improved smoking cessation and substance use reduction through enhanced psychological flexibility [21], medication adherence and pain management in chronic disease populations [22,23], diet and physical activity improvements among patients with cardiovascular disease [24], weight management and disordered eating behaviors [25], symptom reduction in individuals with severe health anxiety [26], and self-management behaviors in diabetes and other chronic conditions using digital ACT-based interventions [27].

Given ACT's efficacy in improving health-related behaviors, it presents a promising intervention for addressing psychological barriers to PrEP use. ACT can help individuals identify personal values regarding various domains of life (ie, their own health), as well as how taking PrEP can contribute to living by those personal values [14]. By promoting psychological flexibility, ACT can help individuals identify and address avoidant internal experiences that might hinder PrEP use, such as anxieties or negative beliefs about taking medication, and help them approach these experiences in service of living according to their personal values. Furthermore, ACT interventions can be delivered effectively in a variety of formats, including brief sessions, and anyone can be trained to deliver the intervention, making it both adaptable and feasible for reaching young Black men who have sex with men in diverse settings [28].

Given the high rates of HIV infection among young Black men who have sex with men in Jackson, Mississippi, and the underuse of PrEP in this population, there is a critical need for innovative interventions to promote PrEP use. ACT's potential to address psychological barriers to PrEP use and its adaptability for community-based settings make it a promising avenue for investigation [28]. This pilot randomized controlled trial (RCT) aims to assess the feasibility and acceptability of an ACT-based intervention for increasing PrEP use (ACTPrEP) among young Black men who have sex with men in Jackson, Mississippi, in the United States.

Methods

Study Design

This study will be conducted in 2 phases. The first phase, which has been completed, consisted of developmental interviews with 20 young Black men who have sex with men and 10 clinic staff. These in-depth interviews, completed by 2 researchers trained in conducting qualitative interviews (TA and APB), assessed quantitative measures, intervention design, and experiences relevant to PrEP engagement. This helped researchers select and refine components of the ACTPrEP intervention. The second phase will be a single-site, pilot RCT conducted at the University of Mississippi Medical Center STI/HIV Testing Clinic. RCT participants (N=66) will be assigned to either the ACTPrEP intervention or the Enhanced Standard of Care (ESOC) arm using a random allocation program. The allocation ratio will be 1:1, with 33 participants assigned to each arm.

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Participants

Staff participants (developmental phase only) are nurses, PrEP navigators, and PrEP prescribers who work directly with PrEP-eligible Black men who have sex with men.

Criteria for young Black men who have sex with men participants (for both study phases) include being aged between 18 and 34 years old, able to speak in English, being HIV-negative, male sex having been assigned at birth (including transgender women), report having sex with a man in the past 3 months, being PrEP-eligible according to Centers for Disease Control and Prevention guidelines, not having taken PrEP in the past 3 months, and not currently being enrolled in another PrEP-related study. There will not be an overlap between those enrolled in the developmental phase and the pilot RCT. The inclusion criteria were updated in April 2024 for the pilot RCT to include individuals not currently taking PrEP and individuals who are currently taking PrEP. Since ACTPrEP focuses on both PrEP update and PrEP persistence, young Black men who have sex with men who are taking PrEP or qualify for a prescription benefit from the study. The change in inclusion criteria decision was also made as an effort to enhance recruitment.

Developmental Phase: Qualitative Interviews

Procedures

Participants were recruited through word of mouth. Specifically, young Black men who have sex with men were informed about the study by the clinic staff during clinic visits, and clinic staff were informed about the study by research staff. Those interested were screened for eligibility by the research assistant. Participants completed informed consent via the HIPAA (Health Insurance Portability and Accountability Act)-compliant, electronic signature software developed by DocuSign, Inc, and were then scheduled to complete an interview. Developmental interviews were conducted remotely via a HIPAA-compliant videoconferencing platform, Zoom (Zoom Video Communications). Each interview lasted approximately 45-60 minutes and was conducted by 2 researchers trained in conducting qualitative interviews (TA and APB). Participants were also asked to complete a brief web-based survey using the HIPAA-compliant data collection platform, REDCap (Research Electronic Data Capture, Vanderbilt University) [29], which took roughly 10-15 minutes. The survey queried about PrEP structural barriers, PrEP stigma, and psychological flexibility. Participants could complete the survey from their personal electronic devices or on a computer in a private area of the University of Mississippi Medical Center.

Interviews

Staff interviews focused on the motives and perceived values young Black men who have sex with men have to be engaged in PrEP care and assessed the acceptability of the ACTPrEP design. Interviews with young Black men who have sex with men examined the impact of ACT processes that influence PrEP engagement in care: awareness of experiences, acceptance of experiences, and values. Participants were probed to discuss values within different areas of life (eg, recreational, spiritual, career, family, and health) and then asked how PrEP use aligned with those values. If young Black men who have sex with men indicated no prior PrEP knowledge, they were provided this brief education: “PrEP is a pill you can take once a day to prevent getting HIV. Just like women can take birth control, one pill every day to prevent getting pregnant, men can also take PrEP, one pill every day to prevent getting HIV. PrEP was approved by the FDA in 2012 and research has found that it can be very effective at preventing a person from getting HIV.” Young Black men who have sex with men were prompted through experiential questioning to discuss difficult thoughts, emotions, associations, memories, and sensations (TEAMS) that arise when considering attending a PrEP appointment. Based on the data collected from staff and young Black men who have sex with men interviews, we assessed the priorities for intervention content, the best methods for intervention delivery, and methods for recruitment and retention. This helped the research team identify and make needed adaptations to the ACTPrEP intervention material.

Interview Guide Sample Questions

Sample questions for the interview guide are as follows:

- Identifying values related to PrEP use: “Health: Some examples of values within health include: living a long life or being healthy enough to be physically active. What are some of your values within health? [Allow time to respond] How might these values relate to PrEP use?”
- Methods for delivering ACTPrEP: “Who would be the best person to provide the PrEP intervention?” “Where would be the best location to offer the PrEP intervention?”
- Techniques to cope with TEAMS: “As part of the intervention that we are developing we will be talking about different coping techniques. I am going to walk you through one of those exercises and get feedback from you. Choice in HIV Risk: Carrying Weight Metaphor Exercise: There are many variables that play into someone being at risk for HIV. Imagine you were born with a 500 pound weight on our shoulders and another person was born with 50 pounds of weight on their shoulders and you two were in a competition. The rules of the game are simple—the last one to sit down in their chair wins. Who do you think would win? Why? Exactly—this game isn’t fair and although you could technically ‘win’ the game would be much harder for you. This is very similar to individuals who are at higher risk for acquiring HIV. What if I offered to take 450 pounds off of your shoulder to make the game even—would you take me up on my offer? PrEP is similar to being offered the opportunity to take ‘weight’ off your shoulders and reduce your risk of HIV. It doesn’t mean that you are not in control of the behavior but it means that you are not in control of the amount of ‘weight’ you have to experience in order to reduce HIV risk.”

Analysis

All interviews with staff and young Black men who have sex with men were audio-recorded and transcribed by an outside HIPAA-certified transcription company. Transcripts were subsequently reviewed for accuracy by study research staff. A coding scheme was developed a priori based on the interview guide and previous research. To ensure interrater reliability, transcripts were coded independently by two members of the

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research team. Regular coding meetings were held to discuss and resolve coding discrepancies, make necessary edits to the coding scheme, and identify emerging themes. Coded qualitative data were organized using NVivo (Lumivero) software [30], which aided thematic analysis.

The developmental phase of the study took place between October 2021 and April 2022, during which 20 PrEP-eligible young Black men who have sex with men and 10 clinic staff who work directly with young Black men who have sex with men were interviewed. Among the young Black men who have sex with men interviewed, half were currently taking PrEP, and more than two-thirds had taken PrEP in the past. The length of experience clinic staff participants had working directly with young Black men who have sex with men widely varied, from less than 1 year to over 10 years.

The Adaptome implementation adaptation model was used to guide the interview content and assess which implementation adaptations were needed for ACTPrEP [31]. This model systematically helps define the core elements of an intervention and collects information regarding the different ways evidence-based interventions can be adapted to be delivered for diverse populations and contexts [32,33]. The Adaptome model organizes the adaptations by service setting, target audience, mode of delivery, and cultural considerations. Within service setting adaptations, participants noted that the interventionist should be PrEP-informed and well-integrated in the clinic. Participants also noted that ACTPrEP should be delivered in a variety of convenient locations. Within target audience adaptations, participants reported that the interventionist should provide check-in calls, be caring, and be able to authentically relate to young Black men who have sex with men's lives. Within the mode of delivery adaptions, participants reported that the delivery of ACTPrEP should be flexible (number of sessions tailored to the participant, brief sessions, flexible scheduling, and option for web-based or in-person visits). Within cultural adaptations, participants noted that PrEP should be rebranded for all people and not just young Black men who have sex with men and PrEP should be compared to other health behaviors. These results were used to adapt ACTPrEP for successful implementation to young Black men who have sex with men living in Mississippi. Researchers were able to accommodate many of these adaptations in the final ACTPrEP protocol. Additionally, the values related to PrEP were in the life areas of relationships, health, intimacy, and life longevity. These values were used to tailor intervention content and as probes for the values section of the intervention. More details on the developmental phase findings can be found in another published study [34]. Notably, there were no significant differences in the responses provided by young Black men who have sex with men and staff [34].

Final ACTPrEP and ESOC Design

The final ACTPrEP core content elements include knowledge and beliefs about PrEP, identifying life values, self-compassion, cost of trying to control emotions, alternative perspective taking (different ways to think about PrEP), TEAMS related to taking HIV and PrEP, techniques used to help cope with the TEAMS related to taking PrEP (present moment awareness, tolerance of emotions, and actions consistent with one's values), and structural barriers and facilitators for PrEP use. The final core content elements of the ESOC include knowledge and beliefs about PrEP and structural barriers and facilitators for PrEP use. The interventionist for both groups must have no prior professional training in providing mental health treatment. Study appointments may be delivered in a secure clinical space at one of the study sites or remotely via a HIPAA-compliant videoconferencing platform. There are 3 study sessions spaced 4 weeks apart (initial, 4 weeks, and 8 weeks). The first session will last approximately 45-60 minutes. The second and third sessions will last approximately 30 minutes. All intervention sessions will be audiotaped and uploaded to a secure file location on a secure server. The recordings will be used for fidelity checks. Participants will also complete a survey at three different times: initial visit, 12 weeks later, and 24 weeks later. Participants already taking PrEP at enrollment will also complete an adherence assessment using dried blood spot sampling and an adherence survey at baseline, 12 weeks, and 24 weeks. Participants who initiated PrEP after study enrollment will complete 2 additional study visits, including dried blood spot adherence assessment and adherence survey completion at 12 weeks, and 24 weeks post starting PrEP.

Pilot RCT Phase

Convenience sampling will be used to recruit 66 participants. Recruitment will occur in person through clinic staff and through flyer advertisements at several community clinics. Clinic staff will approach young Black men who have sex with men who appear to meet the inclusion criteria during their clinic visit and inquire about their interest in learning more about a research study on PrEP. Specifically, clinic staff will approach young Black men within the age range who are attending a PrEP appointment or who are presenting for sexually transmitted infection testing. Contact information for patients who are interested will then be shared with the research assistant. The research assistant will then reach out to these patients to screen them via phone or in person if they are able to meet with them in the clinic. Patients who are interested via the study flyer will reach out directly to the research assistant via phone. All interested patients will be screened for eligibility, and if eligible to participate, will be consented to through a HIPAA-complaint electronic signature platform (DocuSign) and scheduled for a session meeting. The consent will be completed in a private office or remotely, depending on the participants' preference. Upon enrollment, participants will be randomized to receive either the intervention or ESOC.

ACTPrEP

The intervention arm will receive ACTPrEP, a manualized intervention based on ACT delivered by a trained PrEP navigator. A research assistant will be trained to deliver ACTPrEP through didactic instruction, role plays, and vignettes. All meetings will occur in person, on the phone, or via telehealth, depending on participant preference. ACTPrEP consists of one 60-minute initial session and two 30- to 45-minute follow-up sessions 4 weeks and 8 weeks later. The initial session will include the following discussion topics: values exercise, PrEP education, PrEP alternative perspective

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exercise, their control in reducing risk of acquiring HIV, barriers to PrEP use, self-compassion exercise, and an action plan. Session 2 will include the following discussion topics: a review of previous session, different forms of PrEP and side effects, problems with trying to control emotions, the cost of avoiding emotions, how to cope with emotions, and an action plan. Session 3 will include the following discussion topics: a review of the previous session, dimensions of sexuality, identifying influential people, helping self-prior to helping others, alternatives to controlling thoughts and emotions, exploring self-worth, perspective-taking exercise, and an action plan. The interventionist will receive ongoing supervision from the study team to promote fidelity throughout the trial. All sessions will be auto-recorded to assess for fidelity. A nonbiased researcher will be recruited to listen to the recordings and measure the fidelity. Participants will receive US $50 for each session that they complete.

The ESOC Arm

The control arm will receive ESOC, which will consist of one 30- to 45-minute initial session and two 30-minute follow-up sessions 4 weeks and 8 weeks later. All meetings will occur in person, on the phone, or via telehealth depending on participant preference. The initial session will include the following discussion topics: self-care, PrEP education, rates of HIV, structural barriers to PrEP use, and session summary. Sessions 2 and 3 will include the following discussion topics: self-care discussion, review of the previous session, consideration of PrEP, review of barriers, and session summary. All sessions will be auto-recorded to assess that no ACTPrEP intervention components were delivered to the control group. A nonbiased researcher will be recruited to listen to the recordings and measure this concept. Participants will receive US $50 for each session that they complete.

Assessments

Assessments will be administered at the initial visits and at 12 and 24 weeks to participants in both study arms. Each assessment will consist of an electronic survey via a HIPAA-complaint data collection platform (REDCap), which may take approximately 30-45 minutes to complete. Participants will receive US $30 for each assessment that they complete.

Dried Blood Spot

If participants are taking PrEP or decide to get a prescription for PrEP, they will complete additional visits for dried blood spots. This will measure participant adherence to PrEP. If a participant is enrolled in the study while already taking PrEP, they will have a dried blood spot collected at the initial visit and at 12 weeks and 24 weeks. If a participant is enrolled in the study while not already taking PrEP, they will have a dried blood spot collected at 12 weeks and 24 weeks after they pick up their prescription from the pharmacy. Each dried blood spot visit will include a 5-minute electronic survey via a HIPAA-complaint data collection platform (REDCap) to assess self-report PrEP adherence. Participants will be compensated US $30 after each of the dried blood spot visits they complete.

Analysis

Data analysis will be conducted using SPSS (IBM Corp) or SAS (SAS Institute) statistical software. All analyses will be conducted according to a predefined statistical analysis plan to ensure transparency and reproducibility. Following data collection, intervention content with mean Client Satisfaction Questionnaire scores below 24 will be reviewed for potential revisions. Additionally, qualitative interviews will be conducted with a purposive sample of participants (both engaged and not engaged in PrEP) and PrEP navigators to explore perceived barriers and facilitators to implementing ACTPrEP within the clinical setting. This information will be used to refine the ACTPrEP intervention for a larger RCT.

Descriptive Statistics and Baseline Group Comparisons

Descriptive statistics (means, SDs, and frequencies) will be calculated to summarize participant characteristics at baseline. This will provide an overview of the sample demographics (age, race, and education), sexual behavior (number of sexual partners and condom use), and baseline knowledge and attitudes about PrEP. Between-group differences in baseline characteristics (ACTPrEP vs ESOC) will be assessed using appropriate statistical tests. For continuous variables, such as age or number of sexual partners, independent sample 2-tailed *t* tests will be used. Categorical variables, like race or education level, will be compared using chi-square tests. If the assumptions for chi-square tests are not met, nonparametric tests like the Mann-Whitney *U* test will be used.

Feasibility and Acceptability Outcomes

We will calculate rates (proportions) for each feasibility measure, including eligibility, consent, randomization, retention (across all assessments), and session attendance. This will provide a clear picture of recruitment, retention, and intervention delivery within the pilot study. The Client Satisfaction Questionnaire scores will be averaged to assess the overall acceptability of the ACTPrEP intervention. Scores lower than 24 will be flagged for further review to identify areas for improvement in the intervention content.

PrEP Use and Adherence

We will evaluate differences in the proportion of participants who engage in PrEP across the 2 groups (ACTPrEP vs ESOC). This will be determined by reviewing patients' medical records and pharmacy data to identify those who attended a PrEP medical visit or filled a PrEP prescription. While not powered to definitively assess these outcomes, descriptive statistics will be generated for adherence and persistence measures (eg, self-reported adherence and pharmacy refill data). This will provide preliminary data to inform future studies.

Secondary Outcomes

Descriptive statistics will also be summarized for secondary outcomes, including PrEP knowledge, attitudes toward PrEP care, and HIV risk behavior scores. Changes in these measures over time will be explored descriptively.

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Generalized Linear Models

Data will be aggregated across follow-up assessments (baseline, 6 weeks, and 12 weeks) and analyzed using generalized linear models to assess the intervention effect on continuous secondary outcomes (eg, PrEP knowledge scores). This will allow us to examine differences in the linear change over time between the ACTPrEP and ESOC groups on each outcome variable. Propensity scores will be used to account for any potential baseline imbalances in characteristics between the 2 groups (ACTPrEP vs ESOC). This will help to strengthen the causal inferences drawn from the intervention effect.

Power Analysis and Missing Data

With the primary purpose of this pilot study being to examine feasibility and acceptability, we recognize that the power to detect statistically significant differences between groups on secondary outcomes may be limited. However, the power analysis conducted with a conservative estimate of retention (85%) provided preliminary data to inform future studies. We anticipate a maximum of 15% missing data due to attrition or incomplete responses. To address missing data, multiple imputations by chained equations will be used. This technique creates multiple imputed datasets based on available data and model-based assumptions, allowing for the inclusion of participants with missing values in the analyses.

Ethical Considerations

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was reviewed and approved by the University of Mississippi Medical Center institutional review board, and its conduct was consistent with applicable federal law (FWA00003630). All participants complete written informed consent prior to participating. All study data were deidentified. All participants receive US $50 in cash or a gift card for each completed study session, US $30 for each completed survey, and US $30 for each completed dried blood spot appointment.

Results

The RCT phase of this study is ongoing, with initial institutional review board approval obtained in March 2023. Research activities commenced in September 2023 and are expected to continue through June 2026. As of February 2025, ten participants have been enrolled in the pilot RCT phase. Given the early stage of the trial, we are not yet able to report on the intervention's impact on the desired outcomes. Preliminary findings are anticipated to be available in late 2026 (Table 1).

Table 1. Pilot RCT[a] timeline.

Quarters	2023				2024				2025				2026			
	1	2	3	4	1	2	3	4	1	2	3	4	1	2	3	4
Recruitment (RCT)				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓		
Randomized pilot				✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
Analyses											✓	✓	✓	✓	✓	
Publish final RCT manuscript															✓	✓

[a]RCT: randomized controlled trial.

Discussion

Despite the high efficacy of PrEP in preventing HIV infection, significant racial and ethnic disparities persist in PrEP uptake and adherence [8-10]. Young Black men who have sex with men are particularly vulnerable to HIV infection yet encounter numerous structural, psychosocial, and systemic barriers that hinder PrEP use [11-13]. These barriers include stigma, medical mistrust, cost concerns, limited health care access, and insufficient knowledge about PrEP [11-13]. Addressing these disparities is critical to ending the HIV epidemic in the United States [35]. This pilot RCT is designed to assess the feasibility and acceptability of ACTPrEP, an intervention based on ACT, for promoting PrEP use among young Black men who have sex with men. A pilot RCT is an important first step for evaluating an adapted intervention and assessing best implementation practices for a specific population. It allows us to refine the intervention based on participant feedback, assess recruitment and retention strategies, and determine the feasibility of a larger-scale RCT to evaluate efficacy.

This study builds on the breadth of prior research establishing the effectiveness of ACT-based interventions for behavior change in various health domains, including substance use, smoking cessation, and mental health treatment [21-27]. Emerging literature supports the use of ACT in HIV prevention, particularly for addressing psychological barriers to PrEP adherence, such as stigma, avoidance behaviors, and internalized HIV-related fears [34,36,37]. Studies have also shown that culturally tailored, theoretically driven behavioral interventions can improve PrEP use among Black men who have sex with men [38,39]. By integrating ACT principles, ACTPrEP uniquely targets psychological flexibility, a construct that has been associated with improved health behaviors and medication adherence. Many existing approaches focus on practical barriers (eg, cost, transportation, and insurance navigation), whereas ACTPrEP takes a more comprehensive approach by addressing both psychological and structural obstacles to PrEP use. This study adds to the growing body of literature by evaluating a behavioral intervention tailored specifically for young Black men who have sex with men, a population that remains underrepresented in PrEP research.

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The ACTPrEP intervention leverages ACT principles to help young Black men who have sex with men identify and address psychological barriers that may impede PrEP uptake and adherence. The control arm receives ESOC consisting of general PrEP information, a video, and support for overcoming logistical barriers such as transportation and cost. This study has several strengths. It focuses on a population with a high burden of HIV and a significant unmet need for PrEP. The intervention is theoretically grounded in ACT, a well-established intervention for behavior change. While this study offers valuable insights, several limitations must also be acknowledged. Since ACTPrEP focuses on both PrEP update and PrEP persistence, to enhance recruitment the inclusion criteria were slightly changed to include both young Black men who have sex with men taking PrEP and those not taking PrEP. Participants taking PrEP may have offered different recommendations during the developmental phase of the study. As a pilot RCT, the sample size is limited, restricting generalizability to broader populations of young Black men who have sex with men. Future studies should increase sample size to enhance statistical power and allow for subgroup analyses. The intervention is being tested at a single site, which may not capture the full diversity of experiences and structural barriers faced by young Black men who have sex with men across different geographic regions. Multisite trials in diverse locations are necessary to assess broader implementation potential. A larger-scale trial should also include longer follow-up periods to assess sustained PrEP adherence.

If findings from this pilot study demonstrate that ACTPrEP is feasible and acceptable, we will refine ACTPrEP based on participant and provider feedback and scale it up in a larger multisite RCT to evaluate both effectiveness in improving PrEP uptake and adherence. Given the urgent need for culturally tailored PrEP interventions for young Black men who have sex with men, ACTPrEP has the potential to be integrated into numerous HIV prevention services offered by community-based organizations, sexual health clinics, and PrEP navigation programs. Future directions also include testing different implementation strategies to enhance scalability and accessibility.

The ongoing HIV epidemic among young Black men who have sex with men necessitates effective interventions to promote PrEP use. ACT has the potential to address psychological barriers that hinder PrEP uptake and adherence. This pilot RCT will provide valuable data on the feasibility and acceptability of ACTPrEP as a novel intervention for increasing PrEP use among young Black men who have sex with men. Based on the findings of this pilot study, we may refine the intervention and conduct a larger-scale RCT to assess its efficacy in promoting PrEP use in this high-risk population.

Acknowledgments

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Data Availability

The qualitative datasets generated or analyzed during this study are not publicly available given the sensitive nature of the qualitative interviews but are available from the corresponding author on reasonable request. Data from the pilot randomized controlled trial will become publicly available once all data have been collected, which is anticipated by June 2026.

Authors' Contributions

All authors appropriately contributed to the completion of this manuscript. All authors contributed to the writing of this manuscript, with TA, CMA, and KKG leading the writing efforts. Intervention adaptations were performed by TA, BAG, APB, CMA, LW, LMW, BGR, and LKB. Data collection and analysis were performed by TA, KKG, PPE, AL, ARE, APB, and LKB. Data coding was performed by TA, KKG, PPE, AL, ARE, and APB. Intervention fidelity checks were completed by SB, KKG, AL, and JCR.

Conflicts of Interest

None declared.

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Abbreviations

ACT: acceptance and commitment therapy
ESOC: Enhanced Standard of Care
HIPAA: Health Insurance Portability and Accountability Act
PrEP: pre-exposure prophylaxis
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
TEAMS: thoughts, emotions, associations, memories, sensations

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Protocol

Virtual Diabetes Prevention Program Tailored to Increase Participation of Black and Latino Men: Protocol for a Randomized Controlled Trial

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Abstract

Background: Black and Latino men are at increased risk for poor diabetes health outcomes but are underrepresented in lifestyle interventions for weight loss and diabetes prevention. Although relatively few men participate in the National Diabetes Prevention Program (NDPP), it remains the most widely available evidence-based approach to type 2 diabetes prevention in the United States. Thus, an NDPP tailored to Black and Latino men has the potential to address prior limitations of NDPP implementation and reduce gender, racial, and ethnic diabetes disparities. It also provides an opportunity to define a population for targeted outreach and evaluate the reach of our recruitment methods and interventions.

Objective: We tailored the US Centers for Disease Control and Prevention Prevent T2 curriculum for the NDPP for Black and Latino men, called Power-Up, and will evaluate its effects in comparison to standard mixed-gender NDPP groups via virtual delivery. The primary aim of the project is to assess the effect of Power-Up versus NDPP on weight loss among men with prediabetes. The secondary aim is to compare the engagement and retention of men with prediabetes in Power-Up versus NDPP. We will also examine the reach of our recruitment methods and engagement in our screening, consenting, and assessment procedures prior to the point of randomization. We hypothesized that men randomized to Power-Up would achieve greater percent weight loss from baseline at 16 weeks (end of Core sessions) and 1 year (end of Maintenance sessions) than men randomized to standard, mixed-gender NDPP. Power-Up is also expected to have better engagement and retention.

Methods: Using the electronic health record (EHR) systems of a large academic medical center and a network of small to medium independent primary care practices throughout New York City, we identified Black and Latino men who met eligibility criteria for NDPP and enrolled them in a randomized controlled trial in which they were assigned 1:1 to receive Power-Up or the standard, mixed-gender NDPP over 1 year via online videoconferencing. Coaches delivering these interventions were trained according to the standards for the NDPP. Power-Up will be delivered by men coaches. Weight will be collected with home-based electronic scales for primary outcome analyses. Engagement will be assessed by session attendance logs.

Results: We identified 11,052 men for outreach based on EHR data, successfully screened 26% of them, consented and enrolled 22% of these, and randomly assigned 48% of consented participants. Primary and secondary outcome analyses will be assessed among randomized men.

Conclusions: This study highlights the effort required to reach and engage Black and Latino men for virtually delivered diabetes prevention programs. Forthcoming trial results for weight loss and engagement will further inform efforts to address disparities in diabetes prevention through tailored programming for Black and Latino men.

Trial Registration: ClinicalTrials.gov NCT04104243; https://clinicaltrials.gov/study/NCT04104243

International Registered Report Identifier (IRRID): DERR1-10.2196/64405

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KEYWORDS

diabetes prevention; minority populations; men's health; virtual; diabetes; prevention; Black; Latino; randomized controlled trial; RCT; clinic-based; standard care; weight loss; risks; effectiveness; adoption; hypothesize; electronic health record; EHR; academic medical center; health system partner; Power-Up intervention; mixed-gender

Introduction

Background

The prevalence of type 2 diabetes and its risk factors disproportionately affects low-income and racial and ethnic minority populations in the United States [1,2]. This mirrors international evidence showing disparities in diabetes prevalence related to socioeconomic disadvantage and structural racism [3]. In the United States, Black and Latino populations are 2-3 times more likely to die of diabetes-related complications than their White counterparts [2]. In general, more men than women have prediabetes, and fewer men are aware of their condition than women [4]. Men are more likely than women to be hospitalized for long-term complications of diabetes and more than twice as likely as women to have a leg or foot amputated. Compared to women, and compared to other men, men of color have significantly poorer health and higher rates of hospitalization related to diabetes [5]. Latino men are twice as likely to die from diabetes as men identifying as non-Hispanic White, and men identifying as Black are 3 times as likely to need treatment for diabetes-related kidney disease, as compared to non-Hispanic White men [2]. Compared to non-Hispanic White men, men of color are significantly more likely to have a lower limb amputation [6,7]. Despite these striking disparities, men of color are rarely the focus of research, policy, or practice focused on the prevention of diabetes or other chronic diseases [8-10].

The Diabetes Prevention Program randomized trial (DPP; 32% male participants) clearly established the efficacy of lifestyle change for weight loss and type 2 diabetes prevention [11,12]. There have been many efforts to translate the DPP into “real world” settings, but they mostly reach women [13]. Evaluation of the National Diabetes Prevention Program (NDPP) showed that men comprise fewer than 20% of participants [13]. Men of color are particularly underrepresented in NDPPs [13-15]. However, when men do participate, they achieve equivalent or better weight loss than women [13]. Low rates of participation of men of color in the NDPP are consistent with low levels of engagement in other healthy activities and health promotion programs [16,17]. Although the body of literature on men of color and in health programs is still limited [18], researchers attribute low participation in healthful activities to competing priorities that are compounded by the impact of structural, contextual, and life course factors, including discrimination, poverty, and a cycle of limited education and limited employment opportunity [18,19]. Poor engagement of men has been attributed to the framing of existing programs [20,21] and masculine ideals and societal expectations that men be self-reliant, suppress signs of weakness, and avoid seeking help [22,23]. Men-focused programming is a promising method for reaching and engaging men and achieving behavior change [24]. Men-only group-based programming may facilitate behavior change, may increase openness with respect to health concerns, and can act as an incentive for participation [25]. Retaining and tracking the health outcomes of men in these programs is essential to evaluating success and sustainability. Men of color are particularly underrepresented in NDPPs. The Power-Up randomized controlled trial, an adaptation of the NDPP tailored to the needs and preferences of Black and Latino men [26-28], will evaluate weight loss and engagement outcomes for Black and Latino men [26-28].

Specific Aims

The delivery of Power-Up includes a men-only, virtual, group-based model with men as coaches and an NDPP curriculum designed to be attentive to the concerns and needs of men. Virtual DPP is defined as a DPP program delivered remotely as synchronous classes through a videoconferencing platform. The intervention will be delivered virtually to participants recruited through clinical settings and available in English and Spanish. The primary aim of the project is to assess the effect of Power-Up versus NDPP on weight loss among men with prediabetes. The secondary aim is to compare the engagement and retention of men with prediabetes in Power-Up versus NDPP. We will also examine the reach of our recruitment methods and engagement in our screening, consenting, and assessment procedures prior to the point of randomization. The results of this study will help to fill an important gap in health promotion and diabetes prevention for men, specifically for Black and Latino men.

Methods

Study Development

The Power-Up study (ClinicalTrials.gov NCT04104243) was developed in partnership with our study team at Montefiore-Einstein in collaboration with partners at the New York City Department of Health and Mental Hygiene (DOHMH) Primary Care Improvement Project (PCIP). Montefiore is a large hospital system in the Bronx, NY, and the largest provider of health care in Bronx County. The PCIP program is a collection of health care practices throughout New York City that are supported by the DOHMH particularly, as it relates to this study, in the delivery of diabetes prevention and management programs. In 2019 when the Power-Up study was funded, it was designed to be delivered in-person, and the curriculum had been updated from the pilot delivery [28] to be consistent with the new Prevent T2 guidelines. Approximately 6 months into the study development phase of the randomized trial, the first cases of COVID-19 reached New York City, and shortly after the city was shut down. The delivery of DPP, which was a priority of quality health care within our hospital system and through our DOHMH community clinic partners, was

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eclipsed by the pandemic, which used all available resources. The Bronx bore the heaviest burden of the early wave of the pandemic in New York City, and New York City more generally became the epicenter of the pandemic accounting for a large share of the mortality from the virus. In the months that followed, it became clear that in-person delivery of DPP would not be possible for at least a year, or longer. A decision was made to convert the study to virtual delivery. This process meant the training of coaches in virtual delivery including the use of virtual platforms for both the Power-Up coaches and all coaches delivering the control condition in collaboration with our DOHMH partners and their affiliated clinical partners. It also meant that eligibility criteria had to be changed to include patients who had access to a stable internet connection (although participants could attend via phone) and were comfortable with accessing the Zoom or Microsoft Teams platform. Curriculum materials were shared digitally or on paper via mail delivery, if requested. Another important change is that we modified our original plans for in-person weight collection to remote collection using digital scales. Questionnaire data will be collected remotely (see Survey Questionnaires). These data will be collected at baseline, after the 16th session is offered, and at the end of 12 months (see Survey Questionnaires. The aims of the Power-Up study remain the same and the study became more important as we learned of the increased risk of mortality that COVID-19 disease would have among people with diabetes. Below we report the details of the protocol for the trial in accordance with SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) [29] reporting guidelines as well as CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth; V 1.6.1) [30] checklist (Multimedia Appendix 1).

Setting

Study materials and procedural development took place in our study offices. The recruitment, eligibility screening (Textbox 1), and enrollment procedures were conducted by study staff or prevention outreach specialists located at Montefiore-Einstein and PCIP/DOHMH offices. Data collection from electronic health record (EHR) systems took place at the respective clinical site locations. All engagement data will be collected during NDPP sessions. Survey data will be collected by phone at baseline when randomization takes place and during routine calls from study staff at 16 weeks and 12 months. The weight measurements will be collected via a global system for mobile-enabled weight scales (BodyTrace Inc). In data analysis, missing weights will be managed using multiple imputations from time points near NDPP session delivery from GSM (global system for mobile communication) scale weights, weights extracted from EHR, and self-reported weights.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Identified as Hispanic or Latino and or African American or Black as indicated in the electronic health record and later by self-report during screening.
- Identifying as a man via electronic health record initially and later by self-report during screening.
- Age 18 years or older.
- BMI ≥ 25 kg/m^2 (within the last 6 months) and most recent hemoglobin A_{1c} (HbA_{1c}): 5.7%-6.4% (within the last year) or Centers for Disease Control and Prevention prediabetes risk score of 5 or higher.
- Valid residential address and telephone contact information.
- Plan to remain in the New York City area for at least a year or more.
- Received care at a New York City–based Primary Care Improvement Project health care clinic or Montefiore Medical Group within the last 12 months.

Exclusion criteria

- Previously diagnosed with diabetes.
- Inability to join most sessions via virtual platform or by phone.
- Unable to participate in either English or Spanish.
- Previous participation in Diabetes Prevention Program.
- Inability to join during session time or day.

Participant Recruitment

Our recruitment strategies were informed by our experience with the pilot and prior health behavior change and lifestyle intervention studies conducted by our team. The strategies included regular data queries from our clinical sites to identify eligible men for participation. Men who met the initial eligibility criteria based on information available in the EHR (eg, weight, height, and hemoglobin A_{1c} [HbA_{1c}]) were called and invited to participate once eligibility criteria were established (see Textbox 1). Future engagement strategies will include monetary incentives for the completion of telephone surveys and the collection of weight data at the initial baseline interview, as well as a 16-week core session and the final maintenance session at 12 months.

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At the Montefiore Health System sites, we generated lists of men who (1) met all the following NDPP criteria based on EHR data, at least 18 years old, most recent BMI ≥25 kg/m^2 (within last year), most recent HbA_{1c} 5.7%-6.4% (within last 12 months); and (2) received care at a Bronx-based Montefiore Health System site in the past 12 months. We contacted eligible men by phone to inform them about the study and to obtain their consent to participate. To be fully eligible, men needed to (1) self-identify as African American, Black, Hispanic, or Latino during telephone screening; (2) have no plans to change their primary care provider or move from their current address in the next year; (3) agree that they are physically able and willing to attend virtual, group-based diabetes prevention classes; (4) complete the baseline survey assessment and be willing to complete follow-up study surveys and procedures for collecting study weights; and (5) provide informed consent by telephone, including consent for study participation, data collection, and random assignment to Power-Up or standard care NDPP.

DOHMH engaged small primary care practices (PCP) that serve predominantly Black and Latino populations to identify eligible individuals receiving care in the last 12 months at a PCIP health care clinic for recruitment into the Power-Up study. After securing an agreement from the PCP, DOHMH facilitators provided on-site technical assistance to participating PCPs to generate a patient report using their EHR systems to apply study eligibility criteria every 6 months. DOHMH facilitators were instructed to generate eClinicalWorks Business Optimizer (eBO) reports at each PCP's clinical location. These eBO reports use a prewritten query already saved at each practice EHR that identifies individuals that meet study eligibility criteria. The query retrieves a comprehensive set of data for each eligible individual that includes full name, date of birth, date of last office visit, sex, race and ethnicity, preferred language, address, phone number, last HbA_{1c} value and date measured, height, weight, and BMI. Generated reports were transferred to a Microsoft Excel document and securely transmitted to DOHMH data staff. To confirm eligibility criteria, DOHMH data staff reviewed eBO reports and assigned eligible individuals for telephonic outreach.

The Power-Up study was designed to recruit 300 men, with 1:1 random assignment, 150 randomly assigned to the men-only Power-Up condition run by the Einstein study team and another 150 into a mixed-gender NDPP comparison condition run by the PCIP partners. In order to keep the comparison condition ratio of men to women similar to the upper limit of male participation in current NDPP implementation across our partnering health systems, we will monitor the percentage of men assigned or referred to these groups during recruitment and work with our health system partners to refer additional eligible women, through EHR-based searches and outreach to ensure that the percentage of men in standard care NDPP groups does not rise substantially in any one group. We will distribute the randomized men in the comparison condition over 4 mixed-gender groups to reduce the likelihood that the percentage of men in any of those groups would be higher than 33%. Thus, for every Power-Up men-only group there will be 4 mixed-gender groups running concurrently, with 4 times as many women recruited for those groups as men.

Randomization

Separate randomized sequences of treatment group assignments for English and Spanish language–preferring participants, in balanced blocks of sizes 4 or 8 in random order, were computer-generated using Stata version 16.1 and maintained securely at a remote site by the data analyst (CS), who will have no contact with the participants. Random assignment and final enrollment into the study occurred after telephone screening, obtaining informed consent, and completion of baseline surveys. The data analyst was blinded to condition assignment.

The Power-Up and Standard NDPP Conditions

The DOHMH provided NDPP master training for all coaches. The first training occurred for one coach in the middle of year 1, before beginning interventions, and a second training was offered to 3 coaches at the end of the second year. The training curriculum included instructions on data collection for all coaches (1/2 day). Men coaches implementing Power-Up received additional training in the adapted curriculum and using a toolbox for men-tailored behavioral approaches (extra 1 1/2 days). Supervision was available by experienced co-investigators to ensure fidelity to the protocol. Additional periodic training was given to coaches to ensure they were up to date with current strategies to administer NDPP. Study staff conducted regular meetings with coaches from both the Power-Up and the standard NDPP conditions to be sure session delivery and all training were consistent between the conditions. All coaches facilitated either the standard Power-Up or NDPP conditions, with no crossover of coaches. Because many of the patient population in our clinical catchment areas are more comfortable communicating in Spanish, we offered both Power-Up and NDPP conditions in Spanish as well as English.

Both Power-Up and the standard NDPP will follow the PREVENT T2 curriculum which emphasizes (1) beginning core sessions with a focus on physical activity, (2) de-emphasizing tracking fat grams, (3) adding a session on heart health, (4) developing more content on replacing sugary drinks with low-calorie drinks, and (5) emphasizing coping strategies. All Power-Up and standard NDPP programs include 2 optional presession orientation classes (ie, session 0) prior to the 16 core sessions delivered over 6 months and 8-10 additional maintenance sessions delivered over the subsequent 6 months for a total of 26 sessions over 1 year. These sessions will discuss logistics and ensure that participants are able to get connected to the platform. The standard NDPP curriculum will be delivered virtually at a standard time and day of the week that is responsive to standard work schedules and will take place typically in the evenings. After the first session, the day of the week and time can be changed to accommodate most of the participant's schedules. One make-up session will be offered per week for any missed session by participants. The sessions will be delivered in either English or Spanish depending on the preferred language of the participants, which will be determined at the baseline interview. The delivery of sessions will be coordinated so the Power-Up and standard conditions start within at least 2 weeks of each other. Participants will be given the session curriculum digitally or by paper copy mailed out to them upon request. All participants will receive activity, food,

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and weight logs digitally or by mail. They will also receive digital handouts with strategies that can help with weight loss and calorie tracking. The sessions will be delivered at no charge to participants.

Adaptations to the NDPP curriculum focused on making the program more appealing and motivating to men, more consistent with their priorities, group dynamics, and behaviors, and more likely to affect lifestyle change. These adaptations were made to the Prevent T2 curriculum based on our pilot work [26-28] and an updated review of the literature. The Power-Up sessions differ from the standard NDPP in that they will be run by men coaches, and include only participants identifying as men, and the PREVENT T2 curriculum was adapted to focus on men using men-centric vignettes, illustrations, and health-related information. Our goal was to develop an adaptation based on the input of men who participated in the pilot [26-28], that would meet Centers for Disease Control and Prevention (CDC) criteria as a recognized program (Table 1). Recruitment strategies included messaging emphasizing that the program was specifically designed for men and facilitated by men coaches.

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Table 1. Power-Up curriculum content.

Session	Session topic	Session focus
1	Welcome to Power-Up	This introductory session helps men at risk for diabetes change their lifestyles by moving them from the thinking phase to the action phase.
2	Get Active to Stay Active	This session introduces the concept of getting active.
3	Be Safe, Be Active, Keep on Track	This section provides detailed instructions on how to track your activities and how to exercise safely.
4	Build Your Healthy Plate	This session introduces the concept of healthy eating.
5	Track Your Food	This session provides detailed instructions on how to track the food you eat.
6	Being Active- A Way of Life	This session focuses on how to become more physically active as a lifestyle choice.
7	Find your Tipping Point: Burn more calories than you take in	Teaches participants how to burn more calories than they take in.
8	Eating from Shopping to Cooking	This session focuses on how to become more physically active as a lifestyle choice.
9	You Can Manage Stress	This session teaches participants how to reduce and deal with stress.
10	Four Keys to Healthy Eating Away from Home	Teaches participants how to stay on track with their eating goals at restaurants and social events.
11	Jump Start Your Activity Routine	This session teaches participants how to find time for fitness.
12	Taking Charge of What is Around You	This session teaches participants how to cope with the triggers of unhealthy behaviors.
13	Power-Up Your Heart	This session teaches participants how to keep their hearts healthy.
14	Talk Back to Your Negative Thoughts	This module teaches participants how to replace harmful thoughts with helpful thoughts.
15	Getting Support	This module teaches participants how to get support for their healthy lifestyle.
16	Stay Motivated to Prevent Diabetes	This module helps participants reflect on their progress and helps them to keep making positive changes over the next 6 months.
17 (Maintenance Session)	Staying Active for the Long Haul	This session teaches participants how to start losing weight and to cope with some challenges of staying active.
18 (Maintenance Session)	Take A Fitness Break	This session teaches participants how to overcome barriers to taking fitness breaks.
19 (Maintenance Session)	Staying Active Away from Home	This session teaches participants how to stay on track with their fitness goals when they travel for work or pleasure.
20 (Maintenance Session)	Understanding Carbs	This module gives participants a deeper understanding of carbs.
21 (Maintenance Session)	Have Healthy Food You Enjoy	This module teaches participants how to have healthy food that they enjoy.
22 (Maintenance Session)	Get Enough sleep	This module teaches participants how important sleep is to their lifestyle change.
23 (Maintenance Session)	Get Back on Track, Man!	This module helps participants stay positive and know that although there are obstacles they can get back on track to their goals.
24 (Maintenance Session)	Prevent Diabetes for Life!	This module helps participants to reflect on the past year, seeing how it helps create a plan for the next 6 months.

Data Collection

The data collection timeline is shown in Figure 1.

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Figure 1. Data collection timeline. EHR: electronic health record; NDPP: National Diabetes Prevention Program.

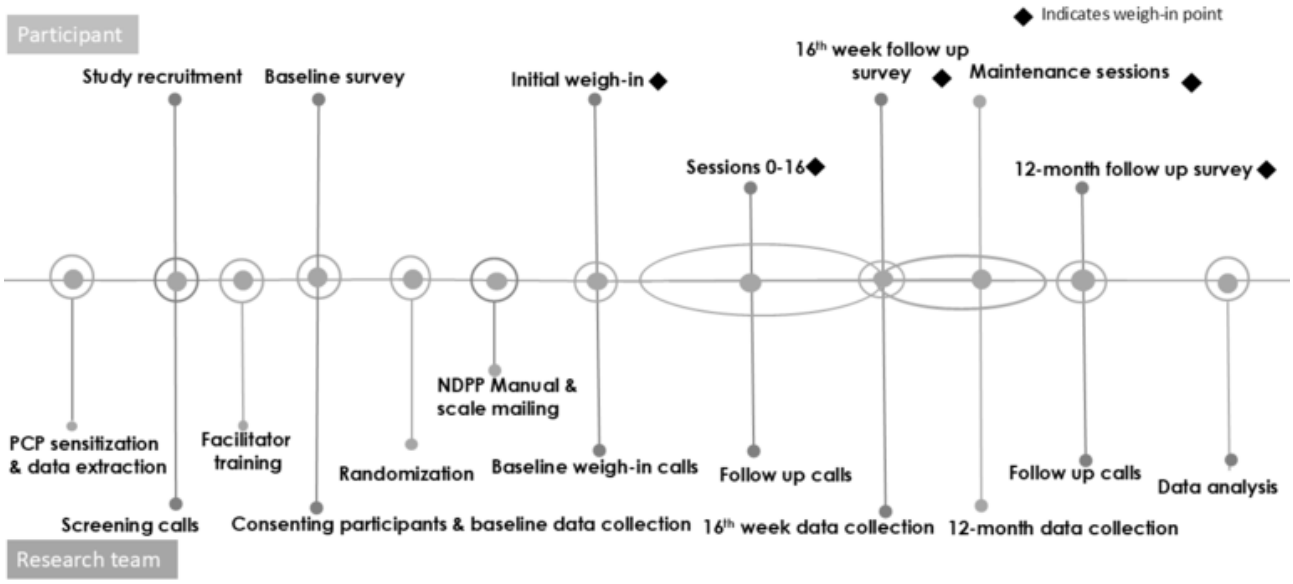

Outcome Measures

Weight is the primary outcome measure based on the focus on weight loss as a mechanism for diabetes prevention in the original DPP trial and the compelling evidence linking weight loss of 5%-10% of body weight with clinically significant reductions in diabetes risk [31]. Participants will use study-supplied GSM-enabled scales from Body Trace [32] to measure and transmit their weight to coaches and the study team. To maximize the completeness of these data, incentives will be provided to participants who transmit weight measurement at sessions or provide a self-reported weight. When a weight measurement is not available using these scales at the 16-week and 12-month sessions (primary outcome measurement time points), then a self-reported weight by telephone or by search of EHR on a visit close to the session dates will be used. The primary outcome measure is the percent change in weight at the end of the Core sessions and the end of Maintenance sessions. Study staff and trained coaches will collect and manage all primary outcome data (Figure 1).

Survey Questionnaires

Questionnaires for psychosocial and behavioral variables will be conducted by telephone by study staff. All questionnaires were translated into Spanish; however, not all were rigorously psychometrically evaluated for language differences. Survey assessment will occur at 3 time points: baseline or enrollment (immediately prior to randomization), at 16 weeks, and 12 months. Table 2 shows the survey domains and time points of questionnaire data collection for the study.

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Table 2. Survey domains and data collection time points.

Survey domains	Baseline	16-week follow-up	12-month follow-up	Measure
Demographics[a]	✓			Power Up 1.0
Insurance	✓			NYC[b] CHS[c] [33]
Housing insecurity	✓		✓	Study of Latino Mobility Study
Housing composition		✓		Affordable Housing as an Obesity Moderating Environment Questionnaire
Social needs+food insecurity	✓		✓	Adapted from Health Leads [34]; Hager et al. [35]
Health history	✓	✓	✓	HCHS/SOL[d] [36]
Body image perception	✓	✓	✓	National Physical Activity and Weight Loss Survey [37]
Sleep	✓	✓	✓	Pittsburgh Sleep Quality Index [38]
Sedentary behavior	✓	✓	✓	International Physical Activity Questionnaire [38]
Physical activity	✓	✓	✓	NYC CHS [33]
Diet	✓	✓	✓	NYC CHS [33]
Risk perception	✓	✓		Risk Perception Survey-DD [39]
Self-rated health	✓	✓	✓	NHANES[e] [40]
Depression	✓	✓	✓	Patient Health Questionnaire-8 [41]
Tobacco use	✓			HCHS/SOL [36]
Alcohol	✓			NYC CHS [33]
Neighborhood environment	✓	✓	✓	Power Up 1.0
Discrimination	✓			Everyday Discrimination Scale [42]
Machismo	✓			HCHS/SOL [36]

[a]Age, gender, race and Hispanic ethnicity, education, employment, and income.

[b]NYC: New York City.

[c]CHS: Community Health Survey.

[d]HCHS/SOL: Hispanic Community Health Study/Study of Latinos.

[e]NHANES: National Health and Nutrition Examination Survey.

Secondary Outcomes: Engagement and Retention

Evaluation of engagement and retention for aim 2 is based on attendance records for Power-Up and standard NDPP sessions electronically collected by trained coaches and monitored by study staff. We will follow standards for NDPP evaluation where engagement is defined as ≥4 core sessions attended and retention is defined as ≥9 sessions attended. We will examine several processes and moderating variables based on survey measures.

Ethical Considerations

This study was approved by the institutional review board at the Albert Einstein College of Medicine (registration number 2019-10343). All participants provided oral informed consent for screening, which was obtained by the study staff. All data will be stored on a secure, password-protected computer, and identifying information will be removed from all data management and analysis files. If participants meet screening eligibility, they will receive US $40 for completing the initial set of baseline assessments (US $15 for completing the baseline survey and US $25 for providing a baseline study weight), US $25 if they provide a study weight for session 16, and US $25 if they provide a study weight for the final session. They will receive additional payments of US $15 for the completion of the follow-up assessment at 12 months. Participants can provide study weights without session attendance, and participants can receive the full compensation associated with completing that assessment regardless of their attendance. We will monitor and report any protocol deviations for approval by the Albert Einstein College of Medicine institutional review board, and document on ClinicalTrials.gov, as appropriate.

Data Analysis

The nature of our study intervention makes it difficult, if not impossible, to blind participants and coaches to their study arm; however, we did not directly disclose our hypotheses to them. The data management and analysis protocols we outline below may be modified based on unanticipated data anomalies that must be resolved in some way. To ensure that these decisions are undertaken without bias, our statistician will be given an

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end-of-study dataset that designates the arms neutrally as group 1 and group 2. Until all data management and analyses are complete, the statistician will not be told which group is Power-Up and which is NDPP. A future study will present descriptive statistics by arm for end-of-study variables including percent weight loss and retention. To identify covariates for inclusion in analyses, we will draw a directed acyclic graph of perceived causal relationships among all variables. After excluding any colliders of the treatment (outcome relationship and variables on a causal path between treatment and outcome), variables other than the treatment itself having an unblocked backdoor path to the outcome will be considered potential confounders and will be included as covariates.

Specific Aim 1: Percentage Weight Loss

The primary intention-to-treat (ITT) analysis will contrast the percentage weight loss across study arms using mixed-effects linear regression models of 16-week and 12-month percentage weight loss with the study arm as a predictor, and random intercepts at the program group and practice levels. Because of the large sample size and random assignment to groups, it is very unlikely that adjustment for confounding variables will be required. If, however, our descriptive statistics identify variables that differ appreciably between arms and are associated with outcomes, they will be adjusted as covariates. A secondary per-protocol analysis using only those participants who have completed at least 4 sessions will be carried out using models similar to the primary ITT analyses. Because per-protocol analyses do not preserve randomization, we will reanalyze and carefully compare the baseline attributes across arms to seek out confounders to be included as covariates. For these analyses limited to successfully engaged participants, we expect equivalence of Power-Up and Standard NDPP and will interpret these results by examining whether the 95% confidence limits of the difference in percentage weight loss fall within 2.5 percentage points of zero.

Specific Aim 2: Engagement and Retention

Engagement and retention outcomes will be analyzed with ITT mixed-effects logistic regression models using the same predictors and random intercepts. In all instances, we will report the model-predicted expected values with 95% CIs as well as the expected difference in outcomes with its 95% CI values calculated by the delta method. The *P* values from Wald tests of the null hypothesis of no difference between arms will also be shown.

Missing scale weights will be principally managed using multiple imputations by chained equations. Any unexpected missing engagement and retention data will be dealt with first by excluding cases with missing data from analysis and second by using multiple imputation procedures. If these approaches yield differing outcomes, both will be reported in our outcome paper. For all analyses, we will report the model-predicted expected values with 95% CIs as well as the expected difference in outcomes with its 95% CI calculated by the delta method. The *P* values from Wald tests of the null hypothesis of no difference between arms will also be shown.

Power Calculations

Our target sample size was 300 men. Power calculations assumed, based on earlier studies, a mean (SD) of 1.5 (SD 4.7) percentage points in percent weight loss, and an intraclass (intraprogram group) correlation of 0.05. Assuming 80% of participants provided complete data for analysis, we would have 90.5% power to detect a 2.5-percentage point difference in weight loss between the study arms, as well as providing 80% power to detect a Cohen *d* of completion and engagement outcomes of 0.21 and 0.18, respectively. Power to detect a 5-percentage point difference in weight loss between the study arms would be >99.9%.

As a worst-case sensitivity analysis, we considered the possibility that the SD of percentage weight loss could be as high as 5.9-percentage points, and the intraclass correlation as high as 0.10. Under these adverse circumstances, we would still retain 81.4% power to detect the 2.5-percentage point difference at the .05 significance level. Power for the engagement and retention outcomes was not appreciably affected by changes in these parameters.

Results

Of the 301 men randomized in our study (Figure 2), we identified 11,052 potentially eligible men based on clinical weight and HbA_{1c} information identified in the EHR. Of the men identified, 43.5% (4817/11,052) were contacted and asked to participate in a yearlong NDPP. Of the men contacted to participate, 6.2% (301/4817) agreed to participate and were ultimately randomized.

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Figure 2. CONSORT (Consolidated Standards of Reporting Trials) diagram for study. NDPP: National Diabetes Prevention Program; PCIP: Primary Care Improvement Project.

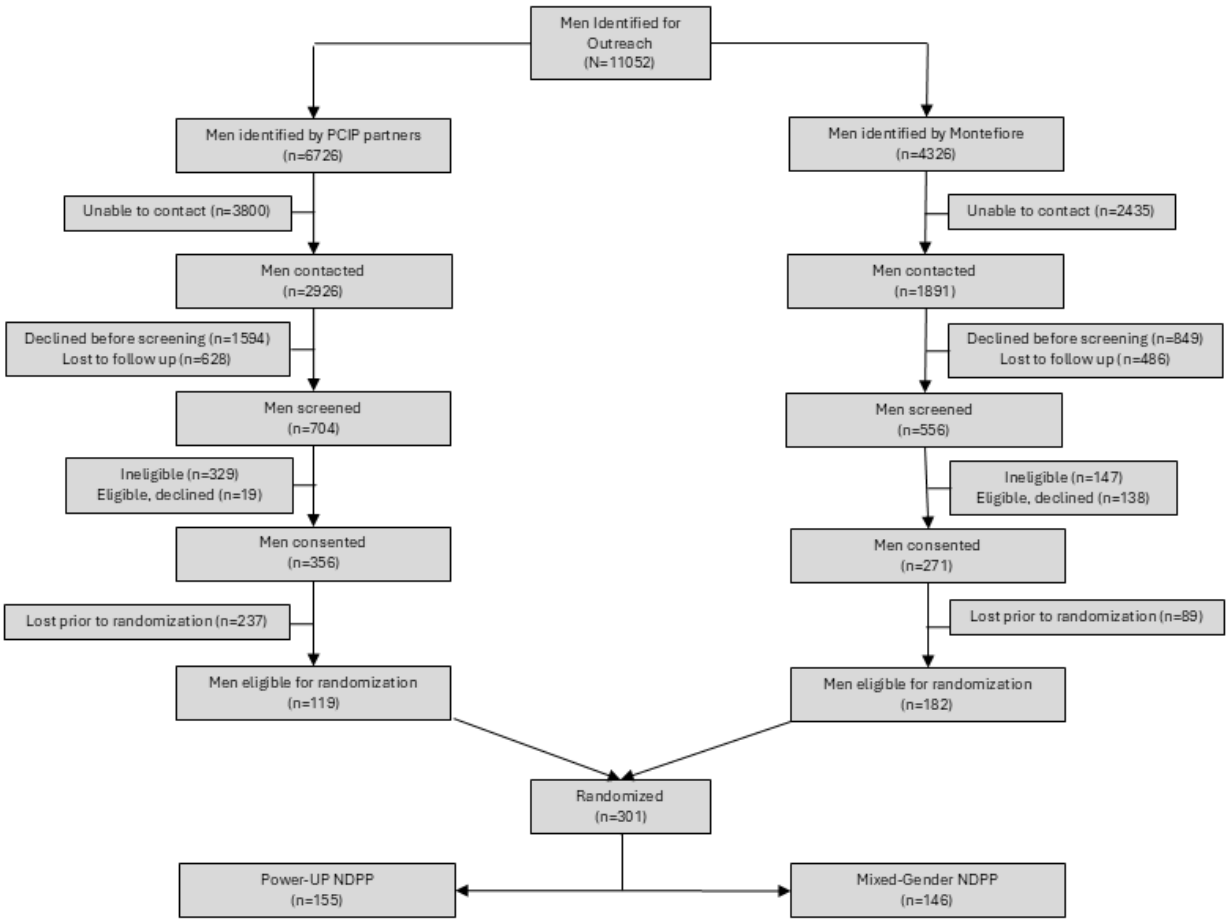

Discussion

Overview

Lifestyle interventions that can prevent type 2 diabetes among men of color are urgently needed to address the disparities in participation for these men in the United States. A prior report of NDPP delivery using data from all CDC-accredited programs showed that men are only 20% of NDPP participants nationwide [13]. However, the reach of NDPP and uptake of the NDPP programs more generally is largely unknown as most studies start measuring engagement at the point of attendance at the first NDPP session [43].

We based our adaptation of the NDPP for Black and Latino men on relevant partnership input, formative quantitative and qualitative results, and lessons learned from a successful pilot study in men with prediabetes [24-26] to enhance the acceptability and potential for maximal weight loss outcomes of the Power-Up intervention tested in the current trial. While we do not yet know the rate of engagement in Power-Up post randomization, we had to identify a population of 11,052 men who were preliminarily eligible based on data recorded in the EHR. Of these, 4817 men were successfully contacted, 2871 were successfully screened, and 628 consented. Of these consented men, 327 did not complete baseline assessment procedures or were otherwise lost to follow-up before they could be randomized. Thus, our primary and secondary outcome analysis sample of 301 men represents only 6% of the men we were able to contact through our extensive telephone outreach efforts and less than 3% of those we identified for contact. Our recruitment experience highlights the substantial resources needed to reach this population. This rate of engagement is low but consistent with previous reports of the high cost of resources needed to recruit eligible participants and deliver NDPP [44]. Studies show that delivery of NDPP in US clinical settings may not be fiscally feasible given the cost of delivery even when reimbursement by Medicare or Medicaid is considered [45-47]. Furthermore, a recent report in poor rural areas of the United States showed that this disparity of uptake in poorer communities may exacerbate diabetes disparities [48]. This is of particular concern in poor urban settings like the Bronx where even with NDPP offered free of charge uptake of the intervention is low [49,50]. Success with targeted engagement of underserved Black and Latino men will likely require significantly more resources related to outreach than prior studies have suggested. Despite these challenges to NDPP delivery, there may be benefits to delivering NDPP tailored for men in that once enrolled in the program their retention rates may be better than mixed-gender approaches.

Study Implications

The Power-Up study is unique in that the recruitment was conducted from patients identified in the EHR system of clinics and so has a known denominator for recruitment. An analysis

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using the true denominator facilitated the evaluation of the true reach of our recruitment efforts. Power-Up was designed to leverage the past success of NDPP delivery through the clinical care setting by identifying and recruiting eligible men seen in primary care practices of a large hospital system in the Bronx, NY, and primary care settings supported by the DOHMH. This approach also allowed for the identification of potential participants through the EHR systems facilitating data collection on important risk factors for type 2 diabetes, such as weight and HbA_{1c}.

Together with our experience reported here on the reach of our recruitment efforts, trial outcomes will provide important information on the relative benefits of Power-Up as compared to standard, mixed-gender NDPP. Primary outcomes examining differential weight loss and secondary outcomes evaluating differences in engagement will be of interest to various partners involved in paying for promoting, delivering, and participating in the NDPP. These results may also have relevance to other national and international settings where similar lifestyle interventions targeting weight loss and type 2 diabetes prevention are offered in mixed-gender groups with lower-than-expected participation rates for men.

Our study design also has limitations that will need to be considered in the interpretation of the results. First, prediabetes is a condition that is inherently heterogeneous with respect to the risk of developing type 2 diabetes, especially given the range of assessments that can be used to identify it in clinical and research settings. Although our approach to determining eligibility with EHR-extracted data and the NDPP risk score may have identified a heterogeneous population of men with respect to phenotype and risk, these procedures are consistent with current practices for NDPP enrollment in the United States. Thus, reduced rigor around the definition of prediabetes comes with the benefit of resulting in a research design that is more translational and able to address the broader question of the effectiveness of the intervention in a real-world clinical context. We sacrificed additional rigor related to the assessment of our primary weight loss outcomes. Home-based electronic scales are likely to be more vulnerable to errors in measurement and missing data than in-person weight collection. However, in-person collection was not feasible in the context of the early period of the COVID-19 pandemic and the virtual delivery of the intervention. Furthermore, the use of home-based weights also mitigates against biases associated with the collection of weights being dependent on NDPP session attendance. We will have electronic weights on participants, regardless of their attendance, permitting a less biased assessment of effects on weight in ITT analyses. Collection of weights through additional methods when electronic weights are unavailable is a strength of the study design that will allow for sensitivity analyses including estimates for missing data. Finally, our results will be limited in their generalizability to men who are engaged in primary care settings and have access and facility with online videoconferencing. Virtual delivery of Power-Up and NDPP sessions may have also enhanced participation and engagement by removing barriers to in-person attendance for men, particularly during the early phase of the pandemic. Our success with meeting our recruitment target, despite the challenges reported here, is a strength of our study and will ensure that our outcome evaluations are well-powered.

Acknowledgments

We would like to acknowledge our partners at the New York City Department of Health and Mental Hygiene Primary Care Improvement Project who made this study possible. We would also like to thank the coaches and the men who participated in Power-Up for their support. This study was funded by the National Institute of Diabetes and Digestive and Kidney Diseases (R01 DK121896). This work was also supported by the New York Regional Center for Diabetes Translation Research (P30 DK111022) and the Einstein-Sinai Diabetes Research Center (P30 DK020541). The sponsor for this study is Albert Einstein College of Medicine. The funding for staff, measures, participant incentives, and other study-related costs were funded by the above-referenced grants from the National Institute of Diabetes and Digestive and Kidney Diseases. The sponsor and funder had no role in the analysis or interpretation of the data or the decision to submit results. We would like to acknowledge the contribution of the Data Safety Monitoring Board (DSMB) for the Power-Up study consisting of: Elizabeth Venditti, PhD, Associate Professor of Psychiatry and Epidemiology (Emeritus) Director of Diabetes Prevention Support Center and Jill Crandal, MD, Anita and Jack Saltz Chair in Diabetes Research, Chief, Division of Endocrinology. The DSMB members have expertise in diabetes prevention program research and in the care of patients with prediabetes and diabetes. Each board member has experience and expertise in the conduct of Phase III Clinical Trials Human Subjects Research. We periodically convened the DSMB to ensure the safety of participants, the validity of our findings, and the quality of data collection.

Data Availability

The datasets generated during and/or analyzed during this study are not publicly available due to the fact that identifiable information is included but a de-identified dataset can be made available from the corresponding author on reasonable request.

Authors' Contributions

ECC and JSG are responsible for conceptualization, data curation, funding acquisition, methodology, resources, supervision, validation, and writing the manuscript. EAW and CS contributed to the development and revisions of the protocol. EG and TB

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contributed to data collection and project management. CS, EG, and KD contributed to data management, analysis, and data visualization.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 2771 KB - resprot_v14i1e64405_app1.pdf]

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Abbreviations

CDC: Centers for Disease Control and Prevention
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
DOHMH: Department of Health and Mental Hygiene
DPP: Diabetes Prevention Program
eBO: eClinicalWorks Business Optimizer
EHR: electronic health record
GSM: global system for mobile communication
HbA_{1c}: hemoglobin A_{1c}
ITT: intention to treat
NDPP: National Diabetes Prevention Program
PCIP: Primary Care Improvement Project
PCP: primary care practice
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Effect of Whole-Body Electromyostimulation Training on Glycemic Control in People With Prediabetes: Protocol for a Pilot Randomized Controlled Trial Study

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Abstract

Background: Diabetes prevention programs focus on people with prediabetes because they have a greater risk of developing type 2 diabetes mellitus than people with normal blood glucose levels. Weight management can reduce this risk. However, in our largely sedentary society, there is less enthusiasm for regular exercise. Whole-body electromyostimulation (WB-EMS) is a training technology that provides exercise-like effects by inducing muscle contractions using electrical currents. There is evidence that local EMS can improve glucose metabolism. Several studies investigated the effect of WB-EMS on cardiometabolic risk factors including blood glucose control in a population of individuals with metabolic syndrome. However, to the best of our knowledge, there is no randomized controlled trial examining the preliminary efficacy of WB-EMS on hemoglobin A_{1c} (HbA_{1c}) levels in individuals with prediabetes.

Objective: The objective of this randomized controlled trial is to pilot procedures for a randomized controlled trial testing WB-EMS training on glycemic changes in sedentary adults with prediabetes.

Methods: A total of 60 community-dwelling sedentary adults aged 40-65 years with prediabetes will be randomized to one of 3 arms: WB-EMS + an activity tracker and a lifestyle education program (LEP) focusing on diabetes prevention, an activity tracker and LEP, or LEP only, with 20 individuals in each arm. The WB-EMS training will consist of 1.5×20 minutes per week. The intervention will last 16 weeks. As a pilot study, our main outcomes concern the number of participants who will be recruited, and comply with intervention and follow-up. The primary efficacy outcome of interest includes hemoglobin A_{1c}. The intention-to-treat analysis will be conducted with the objective of providing CI estimation of treatment effects.

Results: The recruitment of study participants started in February 2024. At the time of submission of this protocol for publication, the recruitment was still ongoing. As of October 2024, a total of 42 participants were allocated to the study groups. The anticipated date of recruitment completion is July 2025.

Conclusions: The results of this trial will provide valuable evidence for future investigations comparing the efficacy of the WB-EMS intervention with traditional exercise training to improve glycemic control in this population.

Trial Registration: ClinicalTrials.gov NCT06188481; https://clinicaltrials.gov/study/NCT06188481

International Registered Report Identifier (IRRID): DERR1-10.2196/68761

(JMIR Res Protoc 2025;14:e68761) doi:10.2196/68761

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KEYWORDS

prediabetes; prevention; type 2 diabetes mellitus; whole-body electromyostimulation, lifestyle intervention; activity tracker

Introduction

Overview

Type 2 diabetes mellitus (T2DM) is a serious and widespread disease and is recognized as a major public health challenge worldwide. According to the International Diabetes Federation (IDF), the current estimate of adults aged 20-79 years living with diabetes equals 9.3% (463 million) and is projected to increase to 10.9% (700 million) by 2045 [1]. As the prevalence of T2DM increases, effective prevention measures are increasingly important. Focusing on those who are at high risk of developing T2DM is a pivotal starting point.

A state of glucose metabolism is called prediabetes when diabetes mellitus is not yet present but elevated fasting plasma glucose levels or impaired glucose tolerance are known [2]. Hemoglobin A_{1c} (HbA_{1c}) levels between 5.7% and 6.4% are indicative of prediabetes. The prevalence of prediabetes in Germany is estimated to be 26% in people aged 45 to 64 years and 31% in people aged 65 to 69 years [3]. Similarly, in the United States, 21.7% of people have prediabetes according to the HbA_{1c} diagnostic criteria [4]. The clinical relevance of prediabetes is that there is a significantly increased risk of developing T2DM compared to the normoglycemic population, which in turn is associated with an increased risk of developing cardiovascular disease, kidney disease, cancer, depression, and dementia [2]. The results from the population-based Rotterdam Study suggest that up to 74% of 45-year-olds with prediabetes will develop T2DM during their lifetime [5].

The results from the KORA-F4 study (Cooperative Health Research in the Region of Augsburg) and the SHIP-TREND study (Study of Health in Pomerania) suggest that up to one-third of people with prediabetes can be classified as physically inactive [6]. Lifestyle changes, such as physical activity and weight management, are of critical importance in preventing the development and progression of T2DM [2,7].

Although, physical activity interventions have shown beneficial effects on oral glucose tolerance, fasting glucose, and HbA_{1c} levels in people with prediabetes [8], insufficient physical activity in people with T2DM and prediabetes remains an issue in these populations [9]. There are several barriers associated with participation and long-term adherence to exercise programs among physically inactive people with diabetes, including lack of time, lack of motivation, poorer (self-rated) health, risk of injury, and social and environmental barriers [10]. Therefore, physical activity programs with an attractive profile are needed to reduce sedentary behavior and increase adherence to physical activity. A potential approach to achieve this goal is an innovative training technology called whole-body electromyostimulation (WB-EMS). WB-EMS provides exercise-like effects by inducing muscle contractions using electrical currents from an external source. WB-EMS simultaneously stimulates up to 8-12 major muscle groups with up to 2800 cm^2 of electrode area. Electrodes are placed on the gluteus muscle, thighs, lower back, upper back, latissimus dorsi, abdomen, chest, and upper arms, and each body region is stimulated with an individualized pulse intensity while individuals perform low-intensity functional exercises in a standing position [11].

In recent years, WB-EMS has found its way not only into therapeutic training but also into rapid and widespread distribution, particularly in Europe, with more than 2000 commercial WB-EMS providers serving approximately 250,000 clients in Germany alone [12]. Due to its increasing popularity, time efficiency, ease of implementation, joint-friendliness, and personalized application, WB-EMS is increasingly the subject of scientific research. In fact, several studies have demonstrated positive effects of WB-EMS on muscle hypertrophy and body composition [13,14]. In addition, high adherence to the intervention and low dropout rates were reported previously [14]. Therefore, this training technology can be considered a promising approach when aiming to increase physical activity in a population of sedentary adults.

A nonrandomized study of WB-EMS showed benefits to HbA_{1c} levels and fasting glucose in middle-aged and older men with T2DM [15]. In addition, several small studies have shown that local EMS has beneficial effects on glycemic control [16]. In contrast, a recent randomized crossover study by Holzer et al [17] found no significant short-term difference in the acute postprandial glucose response between exercise with and without WB-EMS. However, due to the small sample size (6 patients with T2DM) and short intervention duration (three 20-min sessions), the results of this study cannot be generalized [17]. Some studies further investigated the effect of WB-EMS in a population of individuals with metabolic syndrome. While prediabetes and metabolic syndrome share some common characteristics, people with metabolic syndrome have heterogeneous cardiometabolic profiles, where prediabetes or elevated blood sugar levels might be present, but do not necessarily occur. A study showed that 12 weeks of regular WB-EMS in combination with nutritional counseling had a beneficial effect on body weight and composition, and positively affected blood cholesterol levels, but not HbA_{1c} levels [18].

A recent randomized controlled study investigated the effect of WB-EMS in comparison to resistance training on cardiometabolic risk factors. The study found that there was no significant effect on variables including HbA_{1c} [19].

We intend to use WB-EMS focusing on HbA_{1c} in people with prediabetes and then examine its preliminary efficacy. Therefore, an appropriate design is needed to compare the HbA_{1c} of the intervention group (IG) with that of the comparison groups.

Study Objectives

Our main objective is to pilot the feasibility of a randomized trial testing WB-EMS for HbA_{1c} levels in people with prediabetes. The primary objective is to provide an estimation of the preliminary efficacy of the intervention on glycemic

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control in a sedentary group of adults with prediabetes compared with control groups (CGs).

The secondary objectives are to assess the preliminary efficacy of:

1. WB-EMS training on the individual's biomarkers (eg, triglycerides, high-density lipoprotein, and low-density lipoprotein).
2. WB-EMS training on body composition, blood pressure, and heart rate.
3. WB-EMS on other outcomes, such as quality of life and stress.

Methods

Study Design and Setting

The trial is designed as a randomized controlled pilot trial in a parallel design with 3 arms. The trial will be conducted at the Department of Population-Based Medicine at the University Hospital of Tübingen, Germany.

Study Population

The study population will be selected on the basis of the following inclusion and exclusion criteria (Textbox 1).

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Community-dwelling sedentary men and women aged 40-65 years without type 2 diabetes mellitus
- Elevated hemoglobin A_{1c} levels (5.7%-6.4%)
- Not functionally impaired (Short Physical Performance Battery ≥10)
- Signed informed consent
- Consent to use the whole-body electromyostimulation and activity tracker

Exclusion criteria

- High-grade arrhythmia, cardiac pacemaker carriers, heart failure, nephropathy
- Cognitive impairment
- Type 2 diabetes mellitus

Study Procedure

Figure 1 illustrates the study procedure. Screening of participants will take place in 2 stages (telephone prescreening and on-site screening). During the telephone pre-screening, the study staff will check key study eligibility criteria and inform participants about the study activities. If they are interested, they will be invited to the on-site screening. During the on-site screening, the study staff will perform the HbA_{1c} measurement. Furthermore, physical examination (eg, blood pressure) and detailed medical history will be collected to account for any possible contraindications and to ensure safe participation in the training program.

The final determination of eligibility to participate in the trial will take place after the screening. The participants will be randomized to 1 IG and 2 CGs. The duration of the intervention will be 16 weeks. At the end of the intervention period, individuals will return to the study site for a follow-up assessment. The participants of the IG will have a second follow-up assessment after 32 weeks.

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Figure 1. Flowchart of the study procedure. T2DM: type 2 diabetes mellitus; WB-EMS: whole-body electromyostimulation.

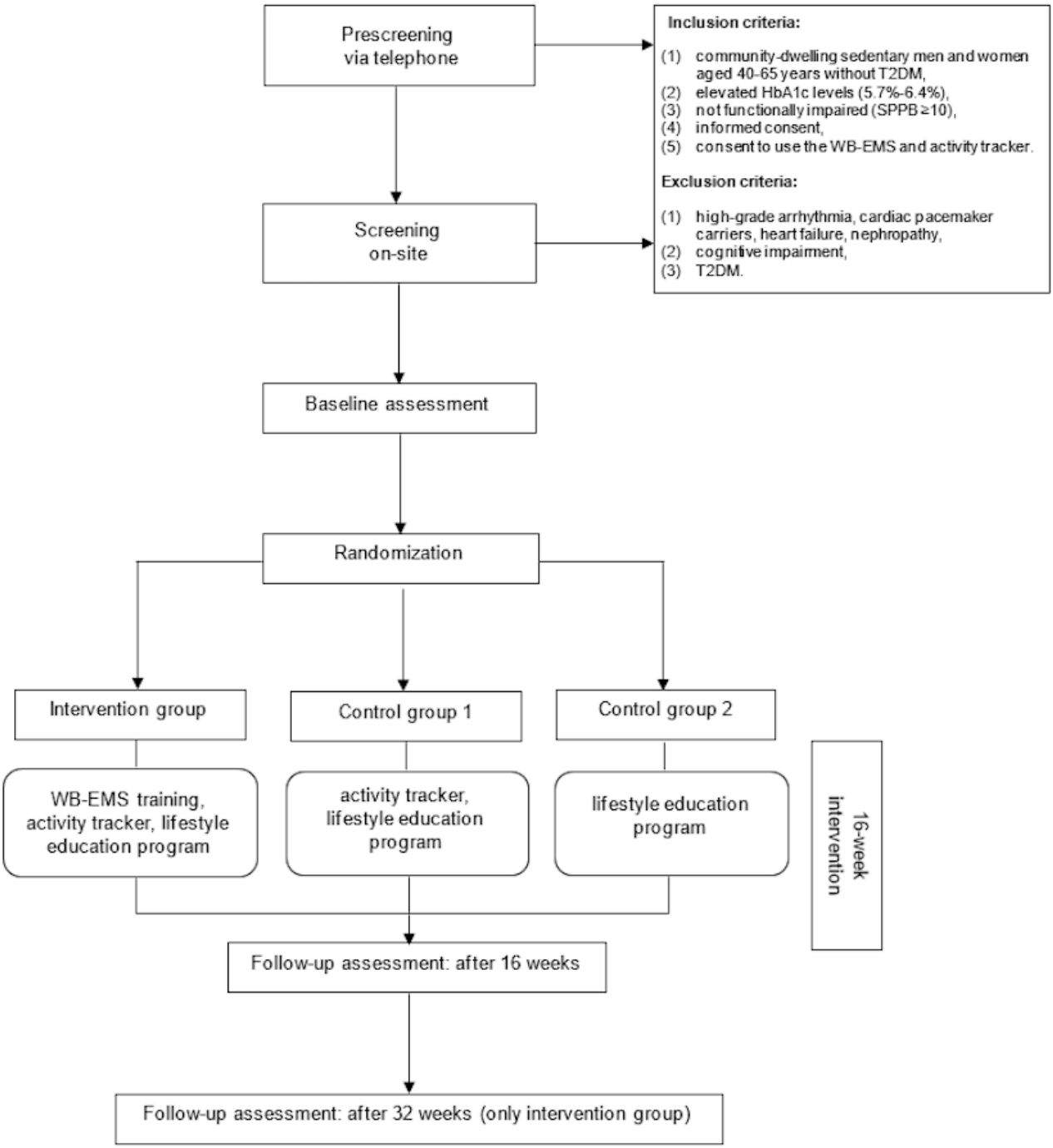

Sample Size

The study population will consist of 60 individuals with 20 individuals in each study group. As this is a pilot study, no formal power analysis has been carried out. However, the target sample size was based on recruitment for 15 months at an estimated rate of 4 patients per month (ie, 60 patients), which was considered adequate to obtain reasonably reliable sample size estimates [20-22].

Recruitment

Participants will be recruited through newspaper and social media advertisements. Flyers and posters will also be distributed to local doctors' offices, pharmacies, hospitals, community centers, and self-help groups.

Randomization, Blinding, and Concealment of Allocation

Eligible participants will be allocated to the study groups by computerized block randomization. This will be performed by an independent trial statistician. Neither the participants nor the researchers will know their allocation in advance. The participants will be strictly separated after randomization. The study staff will prevent participants from different study groups from arriving at the study site at the same time by planning study visits accordingly.

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The blinding strategy focuses on study assistants and outcome assessors who will be blinded to the participants' group status. All data analysts will also be blinded to group allocation.

Intervention

The main intervention will be WB-EMS using equipment that has EU (European Union) medical device approval (miha bodytec, Type II). This equipment allows the simultaneous stimulation of up to 12 muscle groups (eg, thigh and upper arm, gluteal region, abdomen, chest, lower back, and upper back) with a total stimulation area of approximately 2800 cm^2. The participants will receive the functional training underwear recommended by the manufacturer (water-absorbent cotton or elastane mix), over which a vest (upper body) and belts (upper arms, thigh, and gluteus muscle) are individually adjusted before each session. The system allows the intensity to be adjusted for each region (Figure 2). We will use an impulse protocol and exercise setting that has been evaluated in recent studies focusing on total and regional muscle mass [13], body fat [23], and physical function [13] in older cohorts. Furthermore, we designed low-intensity exercises to minimize the effect of voluntary movements themselves as low as possible.

A bipolar electric current with a frequency of 85 Hz and an impulse width of 350 microseconds is used in an interval approach with 6 seconds of EMS stimulation with a direct impulse boost and 4 seconds of rest. During the 6-second stimulation period, low-effort movements are performed in a standing position. The intensity of the EMS will be regulated on the basis of the individual's reported Rating of Perceived Exertion (RPE) and the Borg Category Ratio Scale (Borg-CR10) [14]. We will use RPE to generate and maintain a sufficient but tolerable intensity of EMS application. After 4 weeks of conditioning at a lower pulse intensity, participants will be encouraged to increase the intensity. The impulse intensity will be adjusted individually for each body region in close interaction with the participant. During the session, the instructors will increase the intensity slightly every 3 minutes in close cooperation with the participants in order to maintain the target RPE (6-7) during the session. We will use a personal training setting with one certified and experienced instructor responsible for a maximum of 2 participants. The training will adhere to the requirements of the international EMS guidelines [24].

Figure 2. Whole-body electromyostimulation.

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Study Groups

Intervention Group

The participants in the IG will train following a supervised and guided WB-EMS program 1.5 times per week (eg, every Monday or Tuesday and every other Thursday or Friday) for 16 weeks. The duration of each training session will be 20 minutes. Each session will include a 3-minute warm-up, a 15-minute main workout, and a 2-minute cool-down. In addition, participants will be asked to wear an activity tracker on their wrist for the entire 16-week study period and to participate in the lifestyle education program.

Control Groups

A total of 2 CGs are planned for the study. One CG will receive both the activity tracker to measure daily steps and the evidence-based lifestyle education program. The other CG will receive the lifestyle education program only.

Activity Tracker

The activity tracker (vivosmart 5, Garmin) will be used for self-monitoring of daily steps. Activity trackers may improve physical activity independent of the intervention (eg, people can monitor their daily steps) [25]. Therefore, it is important to include 2 CGs: one with the activity tracker to isolate the net effect of the WB-EMS intervention and one without the activity tracker.

Lifestyle Education Program

The evidence-based lifestyle education program consists of six 20-minute sessions that focus on lifestyle factors and diabetes prevention. The aim of the program is to provide education, information, and advice to prevent disease progression and improve quality of life and mobility. The education program includes topics such as the basics of healthy nutrition patterns, meal planning, the importance of physical activity, and stress management. Participants will receive recorded videos on each topic to ensure standardization of the content. To assess compliance, the participants will be followed up by the study staff, who will ask, whether the program was completed, or reminded to complete the program, in case of noncompliance.

Outcome Measures

The assessments described below will be performed at baseline (day 1) and after the 16-week intervention period. IG participants will also be assessed at 32 weeks. The timetable of the assessments is presented in Table 1. All measurements will be performed by the same research assistant, using identically calibrated equipment, in the exact same environment and at approximately the same time of day (±90 min).

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Table 1. Table1. Timetable of study procedure and assessments.

	Study period				
	Enrollment	Allocation (day 0)	Intervention (weeks 1-16)	Follow-ups	
				Week 16	Week 32
Eligibility screening	✓				
Informed consent	✓				
Review inclusion and exclusion criteria	✓				
Allocation		✓			
Assessments					
HbA_{1c}[a] assessment	✓			✓	✓
Lipid and cholesterol profile		✓		✓	✓
Blood pressure		✓		✓	✓
Hand grip strength		✓		✓	✓
Body composition		✓		✓	✓
Waist circumference		✓		✓	✓
Questionnaires (WHOQOL-BREF[b], SFI[c], PSS-10[d], PHQ-9[e])		✓		✓	✓
Interventions					
WB-EMS[f], activity tracker and evidence-based lifestyle education program			• WB-EMS 1.5/wk • Activity tracker • 6 x 20 min LEP[g]		
Activity tracker and evidence-based lifestyle education program			• 6 x 20 min LEP • Activity tracker		
Evidence-based lifestyle education program			• 6 × 20 min LEP		

[a]HbA_{1c}: hemoglobin A_{1c}.

[b]WHOQOL-BREF: WHO Health-Related Quality of Life.

[c]SFI: Secure Flourish Index.

[d]PSS: Perceived Stress Scale.

[e]PHQ: Patient Health Questionnaire.

[f]WB-EMS: whole-body electromyostimulation.

[g]LEP: lifestyle education program.

Primary Outcome

As a pilot study, our main outcome is to assess the feasibility of the proposed intervention, with specific attention to the recruitment, adherence, and completion rates of the follow-up assessments. The prespecified primary outcome measure will be HbA_{1c} levels. A blood sample (capillary blood) will be collected via the finger stick technique. There is no need for the participants to fast prior to blood measurement. The sample will be analyzed according to the manufacturer's instructions using Cobas b 101 system 2.0 (Roche Diagnostics).

Secondary Outcomes

Cardiometabolic Parameters

Changes from baseline in the levels of triglycerides, total cholesterol as well as high-density lipoprotein and low-density lipoprotein cholesterol will be assessed in capillary blood. A blood sample will be collected with the finger stick technique. The sample will be analyzed according to the manufacturer's instructions using Cobas b 101 system 2.0 (Roche Diagnostics).

Waist circumference will be measured with a standard tape measure around the abdomen between the distal end of the rib cage and the top of the iliac crest along the horizontal plane (World Health Organization [WHO] guidelines).

In addition, changes in systolic and diastolic blood pressure as well as in heart rate will be investigated (boso medicux X, BOSCH + SOHN). The measurements will be performed in the sitting position after a short resting period of at least 5 minutes.

Body composition: Body mass and composition will be measured by direct segmental, multifrequency bioimpedance technique (InBody 770). This device measures the impedance of the trunk, arms, and legs separately using a tetrapolar 8-point

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tactile electrode system that applies 6 frequencies (1, 5, 50, 250, 500, and 1000 kHz).

Muscle Strength

Hand grip strength will be measured using a hydraulic hand dynamometer SAEHAN SH5001 (SAEHAN Corporation). The dynamometer grip width will be adjusted individually to the participant's hand size. Tests will be performed in an upright standing position, arms down by the side. The standardized instruction to the participants will be consistently "squeeze as strongly as possible." Three tests intermitted by 20 seconds of rest will be performed for the dominant hand and the average value will be used for the evaluation.

Stress

A self-reported questionnaire Perceived Stress Scale consisting of 10 questions about stress (PSS-10) will be used [26]. In each question, individuals are asked how often they feel a certain way on a 5-point scale from 1 for "never" to 5 for "very often." The PSS score indicates levels of perceived stress, whereby higher scores indicate higher stress levels.

Depressive Symptoms

The Patient Health Questionnaire which consists of 9 questions on depressive symptoms (PHQ-9) is a standardized and validated self-reported questionnaire. It will be used to assess for changes from baseline regarding the presence and severity of such symptoms. The possible score ranges from 0 (no depression) to 27 (severe depression) [27].

Health-Related Quality of Life

The standardized and validated questionnaire WHO Health-Related Quality of Life (WHOQOL-BREF) consisting of 26 questions on general quality of life will be used [28]. This self-reported tool includes 4 domains: physical health, psychological health, social relationships, and environmental health. It also contains items about quality of life and general health. Each item of the WHOQOL-BREF is scored from 1 to 5 on a 5-point Likert scale. The scores are then transformed linearly to a 0-100 scale. A higher score indicates a higher quality of life.

Well-Being

Changes from baseline in self-reported well-being will be evaluated with the standardized and validated questionnaire Secure Flourish Index (SFI), which consists of 12 questions on general well-being. Each of the questions is assessed on a scale of 0-10. The SFI score is obtained by summing the scores from the 12 questions and results in a score from 0 to 120 [29].

Baseline Characteristics

Table 1 describes the type of data and variables that are collected at various stages of the project. Furthermore, the following demographic and descriptive data are collected at the baseline assessment: gender, age, height (cm), medical history (diseases, surgery, and medicine consumption), physical activity (type, frequency, and duration), educational level, and employment status.

Trainers will monitor adverse events by asking participants if they have experienced any health problems (eg, physical injury and muscle soreness) since the last session. The research team will monitor any adverse events that may occur during participation in this study.

Data Management and Analysis

Data Collection and Storage

For the scientific analysis, the data will be stored electronically in a pseudonymized form by assigning a participant ID to each study participant. The list of participant codes and participants will be kept in a locked cabinet and will be accessible only to authorized personnel.

Activity Tracker Data

The tracker can be set to measure a customizable set of matrices, as needed for the project to avoid unnecessary data collection. This pilot study will collect and process step counts. The Fitrockr Health Data Research & Analytics Platform provides a platform for research and clinical trials to collect and analyze data from wearable devices. Authorized members of the research team will access the device data via Bluetooth or a USB cable using the Fitrockr Hub App when the study participants are on-site. All data will be securely stored on a server in Germany. The participants' usernames will be generated according to the participant ID.

Statistical Analysis

The data will be analyzed using the intention-to-treat principle, which includes all randomized participants. Descriptive statistics, such as mean and SD will be performed for continuous variables, and frequencies and percentages will be used for categorical variables. Diagnostic tests will be conducted for the normality of residuals, linearity, multicollinearity, functional relation, influence, and outliers in the dataset. Assuming data normality, 2-way repeated measures ANOVA and 95% CI will be used to assess outcomes at baseline and 4-month follow-up. The analysis plan will not include reporting of *P* values, in accordance with the CONSORT (Consolidated Standards of Reporting Trials) 2010 statement: extension to randomized pilot and feasibility trials that "any estimates of effect using participant outcomes as they are likely to be measured in the future definitive randomized controlled trial (RCT) would be reported as estimates with 95% CIs without *P* values—because pilot trials are not powered for testing hypotheses about effectiveness" [30].

Analysis of covariance will be used to calculate the effect estimate (study outcomes) of the intervention. Effect size calculation for between-group intervention effects and within-group effects will also be performed. All statistical analyses will be performed using SPSS Statistics (version 28, IBM Corp).

Ethical Considerations

This trial protocol version 1 from August 2023 was approved by the local Ethics Committee at the Medical Faculty of the Eberhard Karls University and at the University Hospital of Tübingen (reference: 525/2023BO2) and registered on the ClinicalTrials.gov (ID NCT06188481). Following the approval of the ethics committee on November 6, 2023, preparations for the advertisement and implementation of the project, including

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the registration of the clinical trial on ClinicalTrials.gov (ID: NCT06188481), were conducted in early January 2024.

All participants will receive a written information letter and informed consent form for participation. All participants will be informed of the voluntary nature of the trial and that they may withdraw from the trial at any time without giving a reason. Only those who confirm their willingness to participate in the trial by signing the informed consent form will be enrolled.

The identities of all participants will be pseudonymized before starting the collection of study data to protect participant identities. The personal data of the participants will be treated confidentially and will only be accessible to the persons directly involved in the study. Further processing, analysis, and publication of the data for scientific purposes will be done anonymously so that no conclusions can be drawn about individual study participants.

Participants in both control groups will be compensated for their time with a coupon for a fitness class at the adult education center (Volkshochschule) valued at €80 (US $91.76). Additionally, all participants will receive feedback about their health parameters. The compensation will be communicated to the participants before enrollment to ensure transparency in the compensation process.

Results

The recruitment of participants and on-site screening started at the beginning of February 2024. At the time of submission of this protocol for publication, the recruitment was still ongoing. As of October 2024, a total of 169 individuals have registered for the study. Of these, 76 individuals were invited to attend the on-site screening, and the rest were excluded during the telephone prescreening process. Finally, 47 participants were eligible and 42 of those were randomized and allocated to the study groups. The 16-week intervention phase starts in groups of at least 6 participants (block randomization) in order to ensure randomized allocation to the 3 study groups. The use of sealed opaque envelopes ensured that neither participants nor researchers were aware of the allocation prior to the study (ie, allocation concealment).

The study is still in progress, and thus far, no adverse events have been recorded. The anticipated date of recruitment completion is of July 2025.

Discussion

While exercise is regarded as one of the key components in T2DM management and prevention [31], adherence to regular exercise still remains low in people with T2DM and prediabetes [9]. Barriers to exercise adherence include the lack of time, lack of motivation and enthusiasm, physical discomfort, and social and environmental barriers [10]. Due to the ease of implementation, time efficiency, and personalized application of WB-EMS, it is increasingly the subject of scientific research.

This randomized clinical trial is designed to evaluate the preliminary efficacy of 16 weeks of WB-EMS training on changes in HbA_{1c} levels. The results of the current study will not only give new insights into the effect of WB-EMS in prediabetes but also serve as a foundation for future studies in this population. This may make a big contribution to the development of preventive strategies specifically for type 2 diabetes.

A meta-analysis of 35 studies reported that local EMS intervention lowered fasting blood glucose (standardized mean difference 0.48, 95% CI 0.17-0.78; P=.002; I^2=0%) [16]. In a recent 16-week non-RCT in the Netherlands, WB-EMS was used to reduce visceral fat in older patients with non–insulin-dependent diabetes mellitus. The exercise program consisted of 20 minutes of WB-EMS twice a week, with HbA_{1c} measured at baseline and the end of the intervention. However, the CG consisted of healthy participants without diabetes, which led to a non-HbA_{1c} comparison between groups. Only male patients showed a significant change in HbA_{1c} (mean 55.7, SD 12.7 mmol/mol vs mean 52.7, SD 13.8 mmol/mol; P<.05), while female patients did not experience a significant change [32]. To the best of our knowledge, there is currently no other RCT evaluating the effect of WB-EMS on glycemic control in people with prediabetes.

HbA_{1c} is considered the gold standard for long-term blood glucose monitoring as it reflects average levels over a period of 2-3 months. Studies have shown that exercise programs typically take longer than 12 weeks to impact HbA_{1c} levels, which is similar to the lifespan of a red blood cell. Most interventional exercise studies that demonstrate improved HbA_{1c} levels have a duration of approximately 13 weeks [33]. In addition, previous studies using WB-EMS have shown significant improvement in muscle mass after a 16-week intervention with similar training frequency and impulse protocol as those used in our study [13,23]. Accordingly, the WB-EMS intervention will be conducted over a period of 16 weeks in this study.

To monitor the level of physical activity, participants in the IG will be asked to wear an activity tracker during the intervention. However, there is evidence of a positive effect of activity trackers on physical activity behavior through personalized feedback on daily steps [25]. Therefore, some of the participants will be randomized to an additional CG with an activity tracker in order to isolate the net effect of the WB-EMS intervention.

The results of this study may provide evidence of the preliminary efficacy of WB-EMS for a future definitive RCT as an alternative adoptive exercise approach to motivate sedentary people with prediabetes who are unable or choose not to follow a traditional exercise program. As this is the first RCT with WB-EMS training to focus on individuals with prediabetes and to address HbA_{1c} as the primary outcome, the results of the trial will inform the sample size calculation for a definitive trial. Moreover, we believe that this research study will provide additional evidence for the health and performance aspects of the WB-EMS application.

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Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

Borg-CR10: Borg Category Ratio Scale
CG: control group
CONSORT: Consolidated Standards of Reporting Trials
EU: European Union
HbA_{1c}: hemoglobin A_{1c}
IDF: International Diabetes Federation
IG: intervention group
LEP: lifestyle education program
PHQ-9: Patient Health Questionnaire
PSS: Perceived Stress Scale
RCT: randomized controlled trial
RPE: Rating of Perceived Exertion
SFI: Secure Flourish Index
T2DM: type 2 diabetes mellitus

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WB-EMS: whole-body electromyostimulation
WHO: World Health Organization
WHOQOL-BREF: World Health Organization Health-Related Quality of Life

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Protocol

Efficacy of WuSheZhiYang Pills in Mild-to-Moderate Atopic Dermatitis: Protocol for a Double-Blind, Randomized, Placebo-Controlled Trial

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Abstract

Background: Atopic dermatitis (AD) is a recurrent, inflammatory, and chronic skin disease that influences over 200 million individuals around the world and is viewed as an important health problem due to its elevated prevalence, long course of disease, and heavy disease burden. WuSheZhiYang (WSZY) pills are composed of 11 Chinese herbs and have the effects of nourishing the blood, drying dampness, and relieving itching. In clinical practice, WSZY pills are recommended for itching skin diseases, but high-quality clinical trial evidence is still limited.

Objective: In this study, we will implement a double-blind, randomized, placebo-controlled trial to evaluate the efficacy of WSZY pills for mild-to-moderate AD. We hypothesized that WSZY pills can effectively alleviate the disease condition of patients with mild-to-moderate AD.

Methods: In this study, we will recruit 60 patients with mild-to-moderate in Shanghai Skin Diseases Hospital from December 2024 through December 2025. In this study, 60 male and female patients with AD aged 18 years to 65 years will be randomly assigned (2:1) to the treatment group (urea ointment and WSZY pills; n=40) or control group (urea ointment and placebo WSZY pills; n=20), and both groups will receive 4 weeks of treatment and 4 weeks of follow-up. The treatment group will receive 3 sessions of urea ointment and 7.5 g of WSZY pills each day for 4 weeks, and the control group will also receive 3 sessions of urea ointment and 7.5 g of placebo WSZY pills each day for 4 weeks. The primary indicator is the change in the objective Scoring Atopic Dermatitis (SCORAD) score between baseline and week 4. The secondary indicators include SCORAD at week 2 and week 8; Peak Pruritus Numerical Rating Scale (PP-NRS), Investigator's Global Assessment (IGA), Patient-Oriented Eczema Measure (POEM), and Dermatology Life Quality Index (DLQI) at week 2, week 4, and week 8; and the proportion of participants receiving remedial treatment, amount of levocetirizine tablets used, and recurrence rate at week 8. In this study, we will analyze the full analysis set and per-protocol set using SAS software version 9.4, and a 2-tailed alpha level of .05 will be viewed as statistically significant.

Results: The study received ethics permission in September 2024, and trial registration was completed in October 2024. Recruitment started in December 2024 and is expected to be completed by December 2025. As of June 2025, 30 participants with mild-to-moderate AD were enrolled. Data analysis will begin in January 2026. The main results of the trial are expected to be submitted for publication in peer-reviewed scientific journals in the summer of 2026.

Conclusions: This study will evaluate the efficacy of WSZY pills for AD and provide additional evidence, suggest new therapeutic options for patients, and reduce their disease burden.

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Trial Registration: International Traditional Medicine Clinical Trial Registry ITMCTR2024000724; http://itmctr.ccebtcm.org.cn/zh-CN/Home/ProjectView?pid=bda070f8-a733-4f52-87b0-39e4be57ac00

International Registered Report Identifier (IRRID): DERR1-10.2196/77927

(JMIR Res Protoc 2025;14:e77927) doi:10.2196/77927

KEYWORDS

atopic dermatitis; WSZY pills; randomized controlled trial; clinical trial protocol; skin diseases

Introduction

Background

Atopic dermatitis (AD), a chronic inflammatory skin disorder characterized by chronic eczematous lesions and intense pruritus, affects more than 200 million individuals worldwide [1]. Although the prevalence of AD in China has increased later than in western higher-income countries, it has increased rapidly in the past 10 years. Globally, AD is associated with a heavy disease burden, and it is the skin disease with the highest disease burden among nonfatal diseases [2]. AD has become an important health problem due to its elevated prevalence, long course of disease, and heavy disease burden.

AD can cause not only skin lesions, itch, pain, and sleep disorders but also a heavy psychological burden. Clinical practice often aims to alleviate clinical symptoms, reduce recurrence, reduce complications, and improve life satisfaction in patients [3]. Many treatment methods for ADs have been proposed, such as emollients containing urea, antihistamines, corticosteroids, antimicrobial agents, and immunotherapy [4-6]. Corticosteroids are the main treatment method, but their use is limited due to the susceptibility to cause adverse reactions [7-11].

Traditional Chinese medicine (TCM) has been systematically used in AD treatment and management and has shown good effects at alleviating the disease condition, reducing disease recurrence, improving quality of life, and causing fewer adverse reactions [12]. WuSheZhiYang (WSZY) pills, part of TCM, are composed of 11 herbs, including *Zaocys dhumnades*, *Saposhnikovia divaricata*, snake bile, cortex *Phellodendri amurensis*, rhizoma atractylodis, radix ginseng, fructus cnidii, *Sophora flavescens*, artificial bezoar, and *Angelica sinensis*. They are used orally and have the effects of nourishing the blood, dispelling wind, drying dampness, and relieving itching. Nourishing the blood means that it improves skin dryness and desquamation caused by blood deficiency; dispelling wind means that it evacuates pathogens, reduces skin irritation caused by pathogens, and alleviates pruritus; drying dampness means that it clears heat and eliminates dampness in the body to reduce eczema exudation; and relieving itching means that it directly inhibits itching symptoms caused by pathogens. WSZY pills are usually prescribed for patients with mild-to-moderate itching skin diseases (eczema, urticaria, pruritus, neurodermatitis, seborrheic dermatitis, pityriasis rosea, psoriasis vulgaris) in clinical practice but without high-quality clinical trial evidence for mild-to-moderate AD. Therefore, we will carry out exploratory research with patients with mild-to-moderate AD.

Objectives

In this study, we plan to implement a double-blind, randomized, placebo-controlled clinical trial to evaluate the efficacy of WSZY pills for mild-to-moderate AD. Our primary objective is to evaluate the effect of WSZY pills on the severity of AD and recurrence rates in patients with mild-to-moderate AD. The secondary objectives are to assess the effect of WSZY pills on itching level, quality of life, and safety in patients with mild-to-moderate AD. This trial will provide additional evidence for the clinical efficacy of WSZY pills for AD treatment, which may provide a new treatment option for patients with mild-to-moderate AD. We hypothesized that WSZY pills can effectively alleviate the disease condition of patients with mild-to-moderate AD.

Methods

Study Design

This study is a double-blind, randomized, placebo-controlled trial to evaluate the efficacy of WSZY pills for AD treatment. It was designed in line with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement [13]. Patients with mild-to-moderate AD will be recruited in inpatient and outpatient departments in Shanghai Skin Disease Hospital from December 2024 through December 2025. In this study, 60 patients with mild-to-moderate AD will be randomly assigned (2:1) to the treatment group (urea ointment and WSZY pills; n=40) or control group (urea ointment and placebo WSZY pills; n=20). All participants in both groups will undergo a 4-week treatment phase followed by a 4-week observational follow-up to evaluate the treatment response and disease progression. The flowchart of this study is shown in Figure 1.

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Figure 1. Clinical trial flowchart. AD: atopic dermatitis; DLQI: Dermatology Life Quality Index; IGA: Investigator's Global Assessment; POEM: Patient-Oriented Eczema Measure; PP-NRS: Peak Pruritus Numerical Rating Scale; SCORAD: Scoring Atopic Dermatitis; TCM: traditional Chinese medicine; WSZY: WuSheZhiYang.

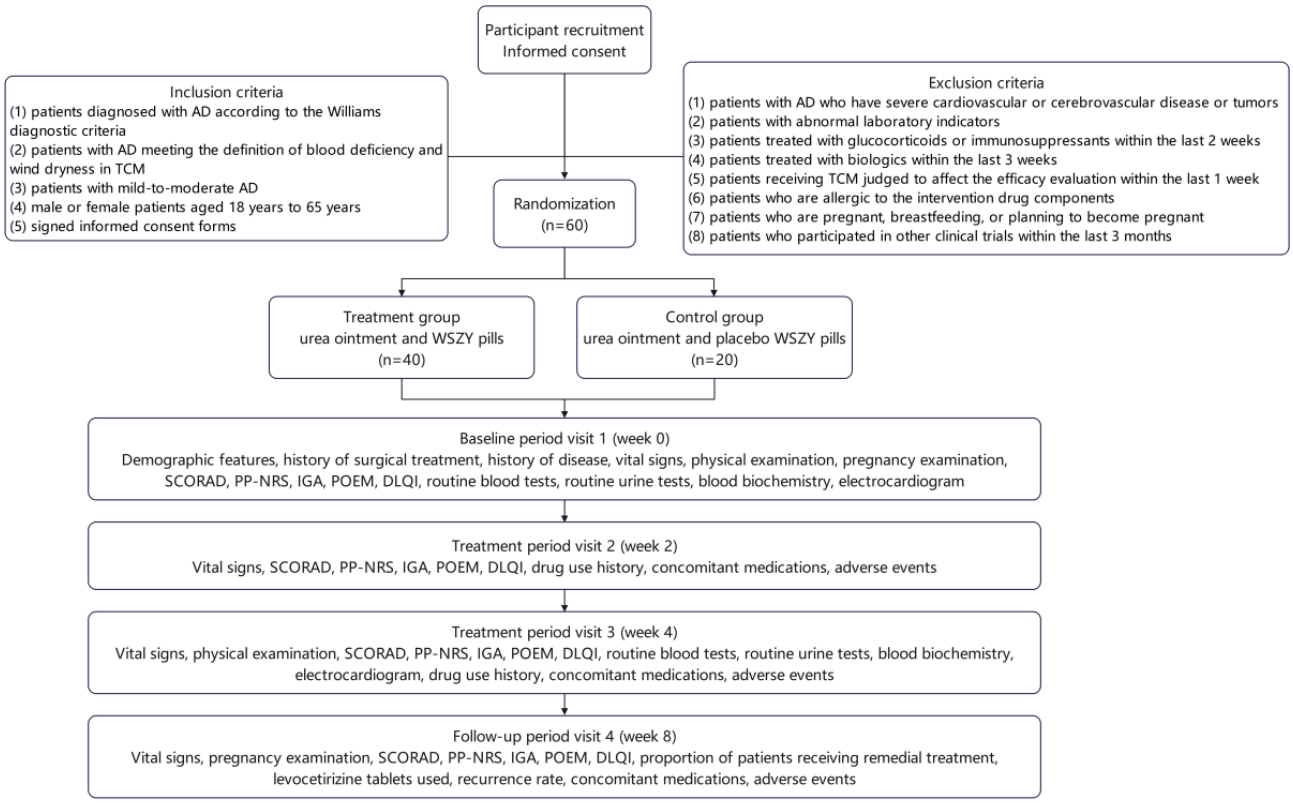

Inclusion Criteria

The inclusion criteria in this study are as follows: (1) patients diagnosed with AD according to the Williams diagnostic criteria [14], (2) patients with AD meeting the definition of blood deficiency and wind dryness in TCM [15], (3) patients with mild-to-moderate AD (objective Scoring Atopic Dermatitis [SCORAD] score ≤50, body surface area ≤10%), (4) male or female patients aged 18 years to 65 years, and (5) signed informed consent forms.

The main Williams diagnostic criterion is skin itching, while the secondary criteria are (1) a history of dermatitis and eczema on the flexed side, including the elbow fossa, popliteal fossa, ankle anterior, and neck; (2) history of asthma or allergic rhinitis; (3) history of dry skin on the entire body in recent years; (4) eczema on the flexor side (eczema on the cheeks or forehead and extensor sides of the limbs in children younger than 4 years), and (5) onset before the age of 2 years (for patients older than 4 years) [14]. A confirmed diagnosis for AD involves meeting the main criterion plus 3 or more of the secondary criteria.

Exclusion Criteria

In this study, the exclusion criteria include (1) patients with AD who have severe cardiovascular or cerebrovascular disease or tumors; (2) patients with abnormal laboratory indicators (serum creatinine, aspartate aminotransferase, alanine aminotransferase, gamma glutamyl transpeptidase, alkaline phosphatase, and total bilirubin); (3) patients treated with glucocorticoids or immunosuppressants within the last 2 weeks; (4) patients treated with biologics within the last 3 weeks; (5) patients receiving TCM judged to affect the efficacy evaluation within the last 1 week; (6) patients who are allergic to the intervention drug components; (7) patients who are pregnant, breastfeeding, or planning to become pregnant; and (8) patients who participated in other clinical trials within the last 3 months.

Sample Size

In this study, the sample size was calculated based on the difference in the change in SCORAD score from baseline (week 0) to week 4, as the primary indicator, between the treatment group (urea ointment and WSZY pills) and control group (urea ointment and placebo WSZY pills). Based on previous evidence on the efficacy of TCM for AD treatment, we used a difference of 9.8 (SD 12) points [16]. Sample size estimation was performed using PASS 15.0 software (NCSS Statistical Software). Using the SD of 12.0, the sample size calculation for the 2:1 randomization design indicated that 36 patients with AD in the treatment group and 18 patients with AD in the control group would provide 80% statistical power to detect a difference of 9.8 points in the improvement in the SCORAD score at a 2-tailed α level of .05. Considering a dropout rate of 10%, we plan to enroll 40 patients with AD and 20 patients with AD in the treatment group and control group, respectively.

Randomization

In this study, patients with AD will be randomly allocated at a 2:1 ratio to either the treatment group or the control group. We will use cluster randomization with combined blocks of 4 and 6 to ensure a balanced group allocation. An independent statistician will construct the computer-generated randomization sequences using SAS software (version 9.4; SAS Institute Inc). To ensure allocation concealment, the generated allocation

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schedules will be sealed in sequentially numbered, light-resistant envelopes and securely maintained by an independent trial coordinating center.

Blinding

In this study, patients with AD, dermatologists (investigators), data collectors, and the statistician will be blinded to the treatment allocation during the entire trial period to prevent bias. Rigorous allocation concealment is preserved through physical separation of randomization records from study operations. This comprehensive blinding strategy aims to mitigate bias during delivery of the intervention, endpoint evaluation, and statistical interpretation.

Interventions

In this study, patients with AD in the treatment group will receive 3 sessions of urea ointment and 7.5 g of WSZY pills each day for 4 weeks. To ensure the correct application of urea ointment, we will instruct the patients to apply urea ointment to the affected area and instruct patients that one knuckle length of urea ointment should be used to cover no more than 1% of the body surface area. This should be followed by a finger massage of the area for 3 minutes to 5 minutes to promote absorption. To ensure the correct administration of WSZY pills, we will instruct patients to take 1 bag (2.5 g) of the WSZY pills per dose, 3 times a day with water.

Patients with AD in the control group will also receive 3 sessions of urea ointment and 7.5 g of placebo WSZY pills each day for 4 weeks. The placebo WSZY pills are made of dextrin and are produced and provided by the same company, which maintains complete consistency with the WSZY pills in terms of appearance, weight, color, odor, and package. The application, individual guidance, and instruction for placebo WSZY pill administration among patients in the control group is completely in line with that in the treatment group.

In this study, patients will be instructed not to use any additional treatment for AD. If a patient uses additional treatment for an emergency condition, detailed information should be recorded, and the patient should be withdrawn.

Outcomes

Primary Outcome

The primary outcome indicator in this study is the difference in the SCORAD score change from baseline (week 0) to week 4. The SCORAD index is made of the affected body surface area, skin lesion severity, and patient self-assessment of itching and quality of sleep. It is an evaluation method to assess the severity of AD as objectively as possible.

The SCORAD score includes the doctor's assessment (A, B) and the patient's own assessment (C), which is the most comprehensive evaluation method. (A) involves evaluating the affected area, including the head and neck area (accounting for 9%), both upper limbs (accounting for 9% each), both lower limbs (accounting for 18% each), the front and back of the trunk (accounting for 18% each), and the genital area (accounting for 1%). (B) involves 6 clinical features, including erythema, edema or papules, exudation or scabbing, epidermal peeling, lichenification, and dryness. Each feature is scored according to its severity, ranging from 0 to 3 points for each item. The patient self-assessment (C) includes itching and sleep deprivation in the last 3 days. The SCORAD score is calculated as A/5+7×B/2+C, with the total score ranging from 0 to 103 points. A higher score indicates a more severe disease condition. According to the score, the condition is considered mild (0-24 points), moderate (25-50 points), or severe (>50 points) [17]. In this study, the SCORAD will be estimated at baseline (week 0), week 2, week 4, and week 8.

Secondary Outcomes

Overview

The secondary outcome indicators include the SCORAD score at week 2 and week 8; Peak Pruritus Numerical Rating Scale (PP-NRS), Investigator’s Global Assessment (IGA), Patient-Oriented Eczema Measure (POEM), and Dermatology Life Quality Index (DLQI) at week 2, week 4, and week 8; and the proportion of participants receiving remedial treatment, the amount of levocetirizine tablets used, and the recurrence rate at week 8 [18,19]. A comprehensive study schedule is provided in Table 1, and details of secondary outcome indicators are included.

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Table 1. Study schedule of the WuSheZhiYang (WSZY) pill clinical trial (8 weeks).

Indicator	Baseline	Treatment		Follow-up
	Visit 1 (week 0)	Visit 2 (week 2)	Visit 3 (week 4)	Visit 4 (week 8)
Informed consent	✓	—[a]	—	—
Demographic feature	✓	—	—	—
History of surgical treatment	✓	—	—	—
History of disease	✓	—	—	—
Vital sign	✓	✓	✓	✓
Physical examination	✓	—	✓	—
Pregnancy examination	✓	—	—	✓
Inclusion/exclusion criteria check	✓	—	—	—
Randomization	✓	—	—	—
SCORAD[b]	✓	✓	✓	✓
PP-NRS[c]	✓	✓	✓	✓
IGA[d]	✓	✓	✓	✓
POEM[e]	✓	✓	✓	✓
DLQI[f]	✓	✓	✓	✓
Proportion of participants receiving remedial treatment	—	—	—	✓
Levocetirizine tablets used	—	—	—	✓
Recurrence rate	—	—	—	✓
Routine blood tests	✓	—	✓	—
Route urine tests	✓	—	✓	—
Blood biochemistry	✓	—	✓	—
Electrocardiogram	✓	—	✓	—
Drug use history	—	✓	✓	—
Concomitant medications	—	✓	✓	✓
Adverse events	—	✓	✓	✓

[a]Not applicable.
[b]SCORAD: Scoring Atopic Dermatitis.
[c]PP-NRS: Peak Pruritus Numerical Rating Scale.
[d]IGA: Investigator's Global Assessment.
[e]POEM: Patient-Oriented Eczema Measure.
[f]DLQI: Dermatology Life Quality Index.

PP-NRS

Pruritus severity in patients with mild-to-moderate AD will be quantified using the validated PP-NRS, which is an 11-point patient-reported instrument (0=no pruritus; 10=extreme pruritus). Participants will self-report their maximum itch intensity over the preceding 24 hours using this standardized metric. Scores of PP-NRS will be stratified as 0 (none), 1-3 (mild), 4-6 (moderate), 7-8 (severe), and 9-10 (extremely severe). In this study, the PP-NRS will be evaluated at baseline (week 0), week 2, week 4, and week 8.

IGA

The IGA is a rough score based on the doctor's subjective judgment and allows researchers to quickly evaluate the severity of disease. This validated 6-point ordinal scale assesses the following key clinical features: no erythema (0), minimal erythema with barely perceptible edema/papules (1), mild erythema with detectable edema/papules (2), moderate erythema with evident edema/papules (3), severe erythema with marked edema/papules (4), and extreme skin involvement with confluent erythema and edema (5). Longitudinal assessments of the IGA will be implemented at baseline (week 0), week 2, week 4, and week 8.

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POEM

POEM focuses on the frequency and severity of 7 symptoms (itching, sleep disorders, bleeding, exudation, cracking, scales, and dryness) in the last week through the patient's own assessment. All items are scored using a 5-point rating system: 0 (none), 1 (mild), 2 (moderate), 3 (severe), and 4 (extremely severe). The total POEM score (range: 0-28) is derived by cumulatively scoring the individual items, with a higher score indicating more severe illness. In this study, POEM will be evaluated at baseline (week 0), week 2, week 4, and week 8.

DLQI

The DLQI systematically evaluates impairment of quality of life in the last week across 6 key domains, including physiological response, psychological feeling, family, interpersonal communication, occupational restrictions, social activities, and treatment response [20]. Using a 4-point severity scale (0=none, 1=mild, 2=severe, 3=extremely severe) across 10 relevant items, the total score of the DLQI (range: 0-30) is calculated by summing the 10 items, with a higher DLQI score indicating a lower dermatology quality of life. In this study, the DLQI will be evaluated at baseline (week 0), week 2, week 4, and week 8.

Data Collection and Management

Standardized data collection will be implemented using a case report form (CRF) completed by trained dermatologists. The CRF includes 6 parts: (1) demographic characteristics, covering age, height, and weight; (2) history of surgical treatment and diseases; (3) vital signs and physical examination, including blood pressure, pulse, height, and body weight; (4) severity indicators of atopic dermatitis (SCORAD, PP-NRS, IGA, POEM, DLQI) at baseline (week 0), week 2, week 4, and week 8; (5) pregnancy examination, routine blood tests, routine urine tests, blood biochemistry, and an electrocardiogram; and (6) drug use history, concomitant medications, and adverse events.

The collected data will be uniformly reviewed, coded, and sampled by professional personnel. The database will be established using Epidata 3.1 software, where input validation procedures (including variable type definitions, value ranges, and skip patterns) will be configured for each variable. All data will be entered using the double data entry method by two independent operators. Consistency checks will be performed on the two generated databases. For any inconsistent variables, the original CRF will be consulted to identify and correct errors in the database until complete consistency is reached between both entries. The finalized database will be converted to a SAS data set. Logical checks and validation will be performed using SAS 9.4 software.

Statistical Analysis

All data will be systematically recorded in the CRF and subsequently entered into a dual-validated electronic database using EpiData software 3.1, with final analyses performed using SAS 9.4. Quantitative variables that are normally distributed will be described using mean and SD, and those a skewed distribution will be described using median and interquartile range. Student *t* tests or Wilcoxon rank-sum tests will be used to compare the differences between groups for quantitative variables as appropriate, depending on the data distribution. Categorical variables will be presented as frequencies and proportions (%), and chi-square tests will be used to compare the differences in categorical variables between the groups. In addition, when the expected frequency is low (<1), Fisher exact tests will be used to compare the differences in categorical variables between the groups. In this study, a 2-tailed α level of .05 will be viewed as statistically significant. Statistical analyses will follow the intention-to-treat principle, including all randomly assigned patients regardless of protocol adherence or study completion [21]. We will handle missing data based on the assumption of missing-at-random and use the sequential regression multiple imputation method, which imputes missing values using regression models for each variable, conditional on the other variables in the data [22]. Additionally, analyses will be performed on both the full analysis set and the per-protocol set.

Safety Assessment

Prior to enrollment in this study, all patients diagnosed with mild-to-moderate AD will receive a comprehensive risk disclosure through a standardized informed consent process. Adverse events are defined as any adverse medical occurrences following administration of the treatment, encompassing symptoms, physical signs, diagnosable diseases, or laboratory abnormalities, regardless of causality assessment. Participants will be required to report all adverse events occurring during the 4-week treatment period and the subsequent 4-week follow-up. All reported events will be systematically documented in the CRF with precise temporal and descriptive details. In accordance with clinical practice guidelines, any participant experiencing a severe adverse event will undergo immediate study discontinuation and receive protocol-specified medical management at no cost to the participant. This safety protocol ensures both rigorous data collection and participant welfare throughout the trial duration. Given that this trial presents minimal risks, we will not establish a data monitoring committee.

Ethical Considerations

This clinical trial protocol (version 1.0, 2024/08/08) was approved by the Institutional Review Board of Shanghai Skin Disease Hospital (approval number 2024-40) and was registered on the International Traditional Medicine Clinical Trials Registry. This study is conducted in strict compliance with the ethical principles outlined in the Declaration of Helsinki and its subsequent amendments. Written informed consent is obtained from all participants prior to their participation in the study. For any participants who are unable to provide informed consent, written consent is obtained from their legal guardian. Participants will be compensated for their time and effort during the study, with total compensation amounting to ¥800 (US $111.36) per participant.

All signed informed consent forms as well as all collected CRFs are stored in a locked place, accessible only by the researchers of this study. All data are stored in Shanghai Skin Disease Hospital for 10 years until the end of the study. After that, all data are to be destroyed.

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Results

The study received ethics permission in September 2024, and trial registration was completed in October 2024. Recruitment started in December 2024 and is expected to be completed by December 2025. As of June 2025, 30 participants with mild-to-moderate AD were enrolled. Data analysis will begin in January 2026. The main results of the trial are expected to be submitted for publication in peer-reviewed scientific journals in the summer of 2026.

Discussion

Summary

To our knowledge, this is the first clinical trial to use WSZY pills to treat AD. This study explores the efficacy of WSZY pills for AD treatment, with the goal of providing additional effective treatment recommendations. The expected results of this study are that the WSZY pills combined with urea ointment can effectively alleviate the disease condition of patients with mild-to-moderate AD.

AD is an itchy, inflammatory, and chronic skin dermatitis affecting both children and adults and is one of the most common chronic skin diseases [23,24]. AD usually exhibits a chronic course with thickening of skin, sleep disturbance, severe interference of quality of life, and impact on daily activities, which not only cause physical pain for patients but also impose heavy social and economic burdens [25]. Modern pharmacological studies indicate that the ingredients of WSZY pills have immunomodulatory and anti-inflammatory properties. For example, the water extracted from *Zaocys dhumnade* has immunomodulatory, anti-inflammatory, and capillary permeability–reducing effects. Oxymatrine in *Sophora flavescens* has immunosuppressive effects, and flavonoids and polysaccharides have anti-inflammatory effects [26,27]. Although the application of TCM has a long history in the treatment of AD in China, high-quality clinical trial evidence is still needed to demonstrate its efficacy and safety [2,28,29].

WSZY pills are part of TCM and have been used in clinical practice for more than 30 years. Previous studies have shown that the combination of WSZY pills and ebastine tablets can alleviate itching, can improve erythema and exudation, can reduce recurrence, and has a good safety profile [30]. In addition, the combination of WSZY pills and dehumidification Zhiyang ointment can improve acute eczema, alleviate the stimulating effect of inflammatory factors, reduce recurrence, and result in fewer adverse reactions [31]. Therefore, the risk associated with the intervention group receiving WSZY pills is limited. Moreover, basic treatment (urea ointment) and remedial treatment (if severe itching occurs, levocetirizine tablets will be administrated) are also included in the study design, which ensures the safety of all patients with AD enrolled in this study.

Findings in this study are expected to provide several key points for AD treatment. The research results cover the relationship between the administration of WSZY pills and changes in SCORAD, PP-NRS, IGA, POEM, and DLQI scores, as well as the recurrence rate in patients with AD. The aim is to explore the effects of WSZY pills on the severity of AD, itching level, quality of life, and recurrence rate in patients with AD, thereby evaluating their efficacy. Based on these findings, we can recommend an additional treatment option for patients with AD, which will help alleviate their condition, reduce their medical burden, and facilitate long-term treatment and management. In all, this clinical trial will provide additional evidence for the clinical efficacy of WSZY pills for AD treatment and provide a new treatment option for patients with mild-to-moderate AD, which can also alleviate their disease condition and reduce their medical burden. We will share our results through publications covering skin problems, as well as through high-impact, internationally peer-reviewed journals.

Limitations

There are some limitations in this study. All patients with mild-to-moderate AD in this study will be recruited in Shanghai Skin Diseases Hospital, which results in high internal validity but may limit external generalizability. In addition, patients with AD recruited in this study must meet the definition of the syndrome of blood deficiency and wind dryness in TCM, which also may limit external generalizability of the research results to other patients with AD. In addition, all participants will undergo a 4-week treatment followed by a 4-week observational follow-up in this study, which might lead to a relatively higher rate of loss to follow-up. Therefore, more relevant multicenter, randomized, controlled clinical trials need to be conducted in future.

Conclusions

This study will evaluate the efficacy of WSZY pills for AD and provide additional evidence, suggest new therapeutic options for patients, and reduce their disease burden. The findings will provide evidence-based recommendations for integrating this traditional medicine into comprehensive AD management strategies, potentially offering patients an effective adjuvant therapy to alleviate clinical symptoms, reduce the financial burden associated with chronic treatment, and support the long-term management of this recalcitrant dermatological condition.

Acknowledgments

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Data Availability

The data sets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

XG, YD, and RC developed the draft of the manuscript. XZ, ZD, QX, FS, SL, and RW revised the manuscript. XG, RZ, and RW contributed to writing all sections of the manuscript and critically reviewed and approved the final version.

Conflicts of Interest

None declared.

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Abbreviations

AD: atopic dermatitis
CRF: case report form
DLQI: Dermatology Life Quality Index
IGA: Investigator's Global Assessment
POEM: Patient-Oriented Eczema Measure
PP-NRS: Peak Pruritus Numerical Rating Scale
SCORAD: Scoring Atopic Dermatitis
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TCM: traditional Chinese medicine
WSZY: WuSheZhiYang

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Protocol

Efficacy of Tuina Therapy Based on Hip-Knee-Ankle Synergy in the Lower Extremity Kinematic Chain in Patients With Knee Osteoarthritis: Protocol for a Randomized Controlled Trial

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Abstract

Background: Knee osteoarthritis (KOA) is a progressive degeneration of the knee joint that has the potential to impair the function of the lower extremity. Tuina, as an important component of traditional Chinese medicine (TCM), is a common treatment for KOA. However, the prevailing practice often limits the therapeutic focus to the knee joint, overlooking potential coexisting hip and ankle injuries. Thus, the therapeutic efficacy may not be optimal in these instances.

Objective: This study aims to evaluate the clinical efficacy of Tuina therapy based on hip-knee-ankle synergy combined with conventional treatment in patients with KOA. It also seeks to explore the potential effects on the lower extremity kinematic chain and provide clinical practitioners with a potentially valuable therapeutic approach.

Methods: This single-blind randomized controlled trial (RCT) will involve a total of 96 participants with KOA from 1 study center (including 2 branches). Participants will be randomly divided into a conventional treatment (control) group and a Tuina+conventional treatment (intervention) group in a 1:1 ratio. Participants in the control group will receive regular health education, self-administered acupressure, and functional exercise. This routine will be completed in 4 weeks, with a total of 5 sessions planned each week. Participants in the intervention group will receive 8 sessions of Tuina therapy based on hip-knee-ankle synergy (twice a week for 4 weeks), combined with conventional treatment. The primary outcome of this study will be improvement in WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) scores from baseline to 16 weeks. Among the secondary measures, the Key Symptoms and Signs/TCM Syndrome Classification Quantitative Evaluation of KOA and the 11-item Tampa Scale of Kinesiophobia (TSK-11) score will be evaluated from baseline to 16 weeks. The Functional Movement Screen (FMS), the Timed Up and Go (TUG) test, and the Weight Bearing Lunge Test (WBLT) scores will only be evaluated at baseline and 4 weeks.

Results: The trial commenced in September 2024 and is expected to conclude in September 2025. As of April 2025, key preliminary steps have been successfully completed. Specifically, the ethical review and clinical trial registration have been finalized. Participant recruitment is proceeding well, with 69 individuals having been enrolled to date. Data collection is currently ongoing, and formal data analysis has not yet been initiated.

Conclusions: This RCT aims to contribute to the growing evidence base supporting the necessity of kinetic chain–based integrative diagnosis and treatment, while also evaluating the feasibility of the study protocol and exploring the benefits of manipulative therapy.

Trial Registration: International Traditional Medicine Clinical Trial Registry ITMCTR2024000293; https://tinyurl.com/4tsszfdu

International Registered Report Identifier (IRRID): DERR1-10.2196/75547

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(JMIR Res Protoc 2025;14:e75547) doi:10.2196/75547

KEYWORDS

KOA; knee osteoarthritis; Tuina; hip-knee-ankle synergies; kinematic chain; clinical trial

Introduction

Knee osteoarthritis (KOA) [1,2] is a common musculoskeletal problem worldwide, characterized by pain, stiffness, swelling, and limited joint function. According to radiographic confirmation [3], KOA is estimated to affect about 3.8% of the world's population. The incidence of this condition increases with age, with prevalence exceeding 10% in individuals over the age of 60 years, especially women. Several lifestyle factors [4,5] are known to heighten the risk of developing KOA. These include increased body mass, specific occupational roles that involve repetitive knee stress, and a history of traumatic knee injuries.

Although many guidelines [6-8] recommend physical exercise to improve pain and function in patients with KOA, pain and a fear of exercise injury are also major barriers to adherence to exercise. Only a few patients can follow the guidelines. As an additional option, Tuina therapy has become one of the preferred treatment methods for many patients. However, it is crucial for many clinicians to recognize the integral role of hip and ankle synergistic joints in knee joint injuries. These synergistic injuries may occur simultaneously or sequentially with knee joint injury, and their diagnosis and treatment should not be overlooked [9].

Traditional Chinese medicine (TCM), with its long-standing history and unique theoretical system, has garnered increasing attention for its role in managing KOA. Recent advances in translational Chinese medicine have further illuminated the potential of TCM-based approaches in addressing KOA. A study has shown that acupotomy can effectively upregulate the expressions of adenosine monophosphate–activated protein kinase (AMPK), Unc-51-like autophagy-activating kinase 1 (ULK1), and Beclin1; downregulate the expression of mechanistic target of rapamycin (mTOR); promote autophagy; and alleviate joint degeneration [10]. This highlights the complex mechanisms through which TCM influences KOA pathogenesis and progression. A network pharmacology study demonstrated that paeoniflorin exerts potent anti-inflammatory effects on synovial inflammation in osteoarthritis (OA) [11]. These findings bridge TCM and modern pharmacological approaches, offering novel insights into the development of effective TCM-based therapies for KOA. Additionally, research on Tai Chi outlines its benefits in alleviating physical impairments in patients with KOA, including improvement in muscle strength function, proprioception, and sleep function and reduction in joint mechanical stress, pain, and inflammation [12]. These studies further corroborate the efficacy and feasibility of TCM interventions in KOA management.

TCM [13] is highly influenced by the concept of viewing things in classical Chinese philosophy. The concept of holism permeates all areas of TCM, including physiology, pathology, diagnosis, differentiation, and treatment of the syndrome. TCM believes that the human body is an organic whole, including the hips, knees, and ankles. Indeed, the concept of holism is an essential component of TCM and underlies the practice of Tuina therapy. Therefore, the principle of integrity should be implemented in the treatment of KOA, and comprehensive judgment and holistic treatment should be emphasized [14].

To explore the scientific model of the interaction between bones, muscles, and joints and their functional transformation rules during human movement, modern medicine has proposed the concept of the kinematic chain. The synergistic effect of the lower limb kinematic chain, consisting of hip, knee, and ankle joints, is of paramount importance in the process of human movement. Any abnormality in the lower limb's kinematic chain can lead to joint pain, muscle weakness, poor posture, and other complications, which can negatively affect an individual's exercise performance and overall quality of life [15,16]. Therefore, in the treatment of KOA, we should not only focus on the local knee but also consider the corresponding changes in the hip and ankle and implement a targeted therapeutic approach.

Therefore, we hypothesize that Tuina has the potential to ameliorate clinical symptoms of KOA by correcting abnormalities in the lower limb kinematic chain and restoring the mechanical equilibrium of the lower extremities. We plan to conduct a randomized controlled trial (RCT) to evaluate the clinical efficacy of Tuina therapy based on hip-knee-ankle synergy in the kinematic chain of lower extremities in patients with KOA and explore the potential effect of synergistic therapy.

Methods

Study Design

A single-center, single-blind RCT has been registered with the International Traditional Medicine Clinical Trial Registry (ITMCTR2024000293). The study center is Shuguang Hospital affiliated with the Shanghai University of Traditional Chinese Medicine, a large tertiary hospital with 2 distinct campuses located in different regions of Shanghai, each serving diverse patient populations. The flowchart in Figure 1 illustrates the process of the study.

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Figure 1. Flowchart of the study. WOMAC, Western Ontario and McMaster Universities Arthritis Index; TSK-11, Tampa Scale of Kinesiophobia; FMS,: Functional Movement Screen; TSK-11: 11-item Tampa Scale of Kinesiophobia; TUG,: Timed Up and Go; WBLT,: Weight Bearing Lunge Test; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

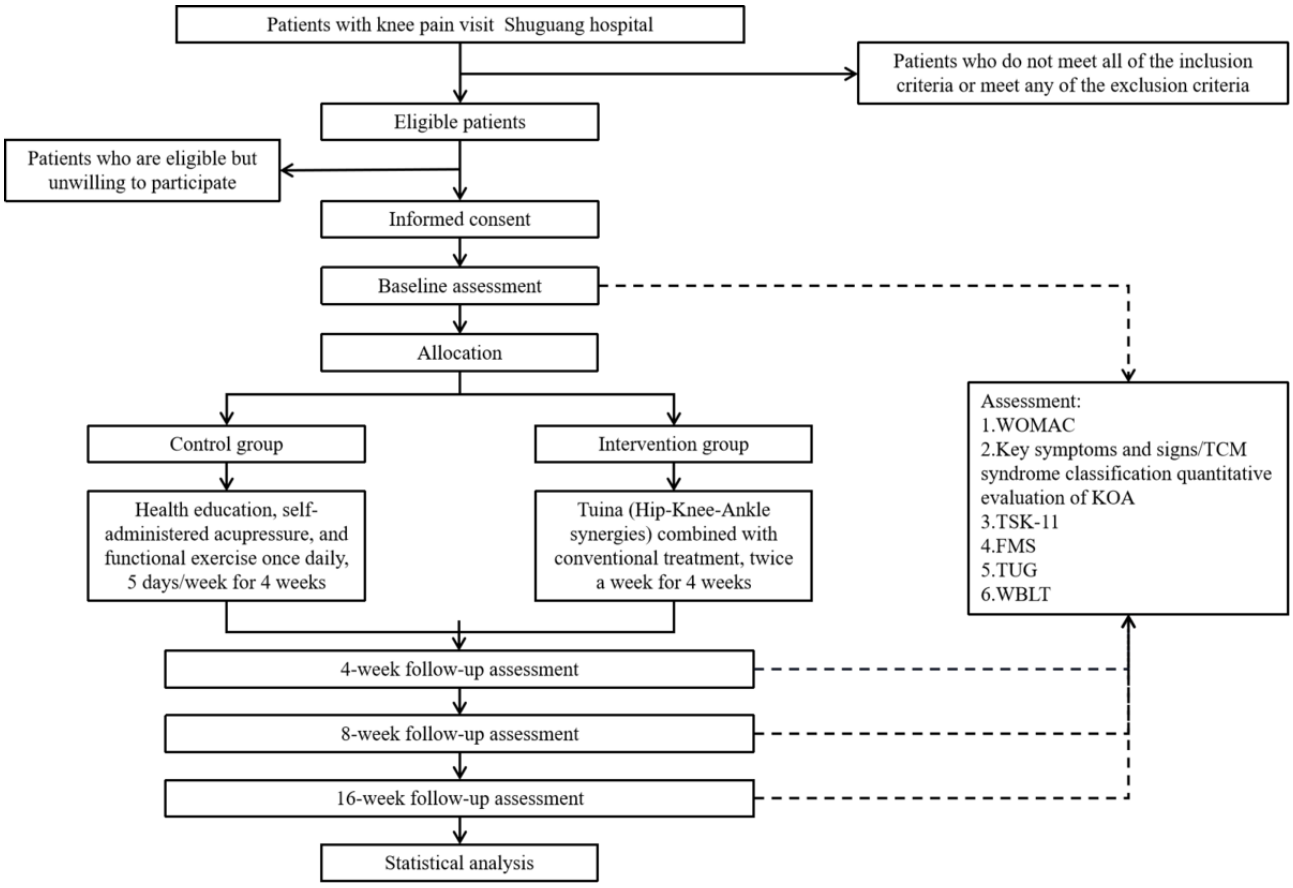

Participants

All participants will be recruited from among patients with KOA visiting Shuguang Hospital affiliated with the Shanghai University of Traditional Chinese Medicine. Patients will first be enrolled based on their basic information, medical history, X-ray results, and WOMAC (Western Ontario and McMaster Universities Osteoarthritis Index) scores. Patients who are willing to participate in this trial and demonstrate an understanding of the objectives and methods of the study by providing signed informed consent will then be randomly assigned to 2 groups: a conventional treatment (control) group and a Tuina+conventional treatment (intervention) group.

At baseline, some information will be collected in order to account for potential confounding variables, including basic information (name, sex, age, height, weight, telephone number, profession). We will calculate the patients' BMI using their height and weight. Physical activity levels will be assessed and recorded using a 3-tier classification (light, moderate, and vigorous). Additionally, we will document the types of comorbidities and medication use, including type, dosage, and frequency. These variables will be included in multivariate analyses to adjust for their potential confounding effects on pain perception and functional outcomes.

All participants will be evaluated 4 times: at baseline and at 4-, 8-, and 16-week follow-up.

The inclusion criteria are as follows:

- A diagnosis of KOA according to American College of Rheumatology criteria [17]
- Average pain score in WOMAC≥4
- An abnormal lower limb line on the lower limb length X-ray
- The patient's age is 20-65 years, male or female.
- No other treatment in the past 4 weeks that may interfere with the results of this study

In addition, patients with unilateral KOA will be included in the study.

The exclusion criteria are as follows:

- Patients with severe bone and joint diseases, such as rheumatoid arthritis, osteoporosis, gout, or an active knee infection in the past 12 months
- Patients with cardiovascular, cerebrovascular, liver, kidney, hematopoietic, digestive, or mental illness or other conditions besides KOA that cause more restriction or pain in activities such as sitting, standing, or walking
- Pregnant and lactating women who cannot complete the radiological examination
- Patients who cannot understand and complete research related to various scales and provide informed consent
- Other conditions that the investigator considers inappropriate to participate in the study

In addition, participants will be removed from the study under the following conditions:

- Patients with severe adverse reactions or complications

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- Patients who do not receive the treatment as initially intended or are prescribed therapy elsewhere without the investigator's authorization

Sample Size Calculation

Sample size calculation was based on WOMAC scores (the primary outcome). The sample size formula for comparing means between 2 groups in an RCT was used to calculate the sample size. With test levels set at α=.05 (2-sided) and β=0.1, according to the results of a high-quality RCT [18], the SD of the WOMAC score was 44.7, and the mean difference between the 2 groups after the intervention was 32.6, which was replaced by the sample size calculation formula, n=39.47. During the study, unforeseeable situations may emerge, which could lead to the loss of some data. In anticipation of this, the dropout rate has been set to 20% [19,20], and with n=48, we will include 36 participants in each group (total 96 participants).

Randomization, Allocation, and Blinding

Randomization will be performed using IBM SPSS Statistics 27.0 and manual assistance. Prior to the study, a randomization specialist will be assigned to generate a random set of numbers based on numbers 1-96 using IBM SPSS Statistics 27.0. After the numbers are sorted from small to large, the 96 cases will be randomly divided into the intervention group and the control group, and the numbers and corresponding groups will be sent to the researchers. Recruited patients who meet the inclusion criteria will be listed in a table and numbered in order of enrollment. The current caseload will be determined according to the grouping generated by randomly assigned personnel. The lists of the 2 groups will be sorted into tables and sent to the actual operators, who will be informed of the specific methods of operation of each group. This method can reduce unnecessary communication between researchers and randomization specialists in the grouping process as far as possible in order to reduce potential bias from researchers' subjective intentions in participant grouping.

We have established rigorous assessment protocols and guidelines. An independent assessor, blinded to participants' group allocations and unaware of the intervention methods used for the 2 groups, will conduct all outcome evaluations. Upon completion of the study, the assessor will be requested to estimate participants' group assignments. Subsequently, their estimations will be compared with the actual group allocations. This procedure aims to evaluate the effectiveness of the blinding process. Should any breach of blinding be identified, we will thoroughly account for it and provide a comprehensive explanation within the data analysis and interpretation of results.

Information about the existence of another intervention group will not be disclosed to the participants, and they will be strictly instructed not to disclose any information related to their intervention to the assessor.

Intervention

We will explain the details of our study to the participants before they join our study.

Control Group (Conventional Treatment)

According to the "Basic treatment" part of the *Guidelines for TCM Diagnosis and Treatment of Knee Osteoarthritis* (2020 edition) [21], we will include health education, weight management, functional exercise, and self-administered acupressure [22]. We will distribute health education manuals, provide online and offline guidance for patients, popularize KOA-related health knowledge to patients, and help them understand the importance of daily KOA protective measures and precautions through popular science health education. In this group, patients will be taught self-administered acupressure and functional exercise once daily, 5 days/week for 4 weeks.

Self-Administered Acupressure

First, patients will form a claw-like shape with 1 hand and use it to squeeze the quadriceps muscle along the front of the thigh, moving along the pathways of the liver, spleen, stomach, and gallbladder meridians.

Second, they will use their fingers/thenar/hypothenar to press the acupoints (ST34, ST35, ST36, SP9, SP10, GB34, EX-LE2, and EX-LE4) briskly and then release with moderate pressure repetitively for about 1 minute per acupoint.

Third, they will rub their hands together until they become warm. Subsequently, they will place their hands around the knee joints and perform gentle, repeated kneading motions until the knee joints experience a sensation of slight warmth.

Functional Exercise

Participants will perform straight leg-raising exercises, 3-5 sets per day, with 10-15 repetitions per set. They will also perform wall squats, 3-5 sets per day, commencing with 30-60 seconds per squat and progressing to 90-120 seconds as muscle strength increases, with the knee angle maintained between 120°and 150°. Furthermore, they will perform knee flexion and extension resistance exercises, 3-5 sets per day, with 10-15 repetitions per set.

Intervention Group (Tuina Plus Conventional Treatment)

In this group, the treatment regimen will also receive Tuina therapy based on hip-knee-ankle synergy (Figure 2). The frequency of treatment will be twice a week for 4 weeks. We have established a scientific, normative, standardized work process, operating procedures, and quality standards. All treatment will be performed by registered Tuina doctors, who have clinician qualifications and have been engaged in Tuina clinical work for more than 5 years. All of have graduated with Tuina as their major and have been trained and assessed with Tuina's standard operating procedures (SOP) for this study.

First, the patient will lie in a supine position, with legs straight and relaxed. The doctor will relax the soft tissues of the groin, thigh, knees, and lower legs in turn, including the quadriceps femoris muscle, the tibialis anterior muscle, and soft tissues around the patella. The degree of manual relaxation will be determined based on the patient's sensation of slight soreness and distension.

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Second, the patient will keep lying in a supine position. Acupressure will be administered to the points around the knee. The patella will be mobilized, and the cordage, patellar ligament, medial and lateral retinaculum, and medial and lateral collateral ligament will be relaxed. Depending on the actual situation, knee adjustment manipulation techniques in a seated or a supine position will be performed, when necessary. Next, the doctor will rub the knee and transfer heat.

Third, the patient will keep lying in a supine position. The doctor will hold the patient's ankle with both hands and place the thumb on the lateral or medial malleolus suture and press, while the other 4 fingers will be fixed, rotating and shaking the foot several times. The ankle will be pulled outward and downward with both thumbs, and the ankle joint will be held and the lower limb stretched.

Finally, the patient will lie in a prone position, the doctor will relax the muscles of the buttocks, thighs, and calves in turn, including the gluteus maximus, gluteus medius, piriformis, biceps femoris, and gastrocnemius muscles. The handling will not be too heavy. The doctor will measure the degree of swelling and numbness. Depending on the actual situation, hip joint adjustment manipulation techniques will be performed, when necessary.

Figure 2. Tuina therapy with hip-knee-ankle synergies: (a) Relax the muscles of the lower extremity (with emphasis on the region surrounding the knee), (b) perform arthrokinetic mobilization and adjustment of the knee, (c) perform arthrokinetic mobilization and adjustment of the ankle, and (d) perform arthrokinetic mobilization and adjustment of the hip.

Outcome Measures

To enhance patient compliance and mitigate potential bias or data loss from frequent in-person visits, we have opted to evaluate WOMAC, Key Symptoms and Signs/TCM Syndrome Classification Quantitative Evaluation of KOA [21], and TSK-11 [23] scores at 4 time points (baseline and 4-, 8-, and 16-week follow-up), while assessing Functional Movement Screen (FMS) [24,25], Timed Up and Go (TUG) test [26,27], and Weight Bearing Lunge Test (WBLT) scores at 2 time points (baseline and 4-week follow-up).

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Primary Outcome

Western Ontario and McMaster Universities Osteoarthritis Index

WOMAC [18,28] is a commonly used outcome measure for OA, and it will be applied at baseline and at 4-, 8-, and 16-week follow-up. WOMAC is composed of 24 items in 3 subscales (5 for pain, 2 for stiffness, and 17 for physical function). Each item is rated on a scale of 0-10 (with higher scores indicating worse pain, function, and stiffness), and total scores range from 0 to 240. WOMAC scores are classified as mild (<80), moderate (80-120), and severe (>120). Assessing the changes in WOMAC scores before and after the intervention will enable us to evaluate the specific effects of Tuina on pain relief and functional improvement in patients with KOA.

Secondary Outcomes

Key Symptoms and Signs/TCM Syndrome Classification Quantitative Evaluation of KOA

This evaluation focuses on assessing the degree of pain, swelling, and accompanying symptoms in patients with KOA. It will be used to evaluate the short- or midterm clinical efficacy of Tuina in KOA and will be applied at baseline and 4-, 8-, and 16-week follow-up. It. This will allow us to observe the effects of Tuina on KOA from a TCM perspective, offering a comprehensive understanding of its therapeutic effects.

Tampa Scale of Kinesiophobia

This tool is an 11-item questionnaire based on a 7-point Likert scale (1=strongly disagree, 2=disagree, 3=agree, 4=strongly agree) that is used to evaluate fear of exercise injury in patients with chronic pain and will help us assess whether Tuina can reduce patients' fear of movement and enhance their rehabilitation participation. It will also be applied at baseline and at 4-, 8-, and 16-week follow-up. Higher TSK-11 scores indicate a greater fear of pain, and a score above 24 is considered high-level kinesiophobia.

Functional Movement Screen

The FMS Figure 3A and B is a standardized field-expedient test cell designed to assess the quality of movement and has been used clinically in prescreening and in sports injury research. It will be used to assess objective physical function at baseline and 4-week follow-up. This tool uses 7 functional movements to assess movement pattern deficits and asymmetries, including deep squat, hurdle step, inline lunge, shoulder mobility, active straight leg raises, trunk stability pushup, and rotary stability. By assessing overall movement patterns, the FMS can comprehensively evaluate the impact of Tuina on patients' motor function recovery. In this study, we will only evaluate the deep squat and hurdle step.

Figure 3. Action demonstration: (A, B) FMS, (C) WBLT, and (D) TUG test. FMS: Functional Movement Screen; TUG: Timed Up and Go; WBLT: Weight Bearing Lunge Test.

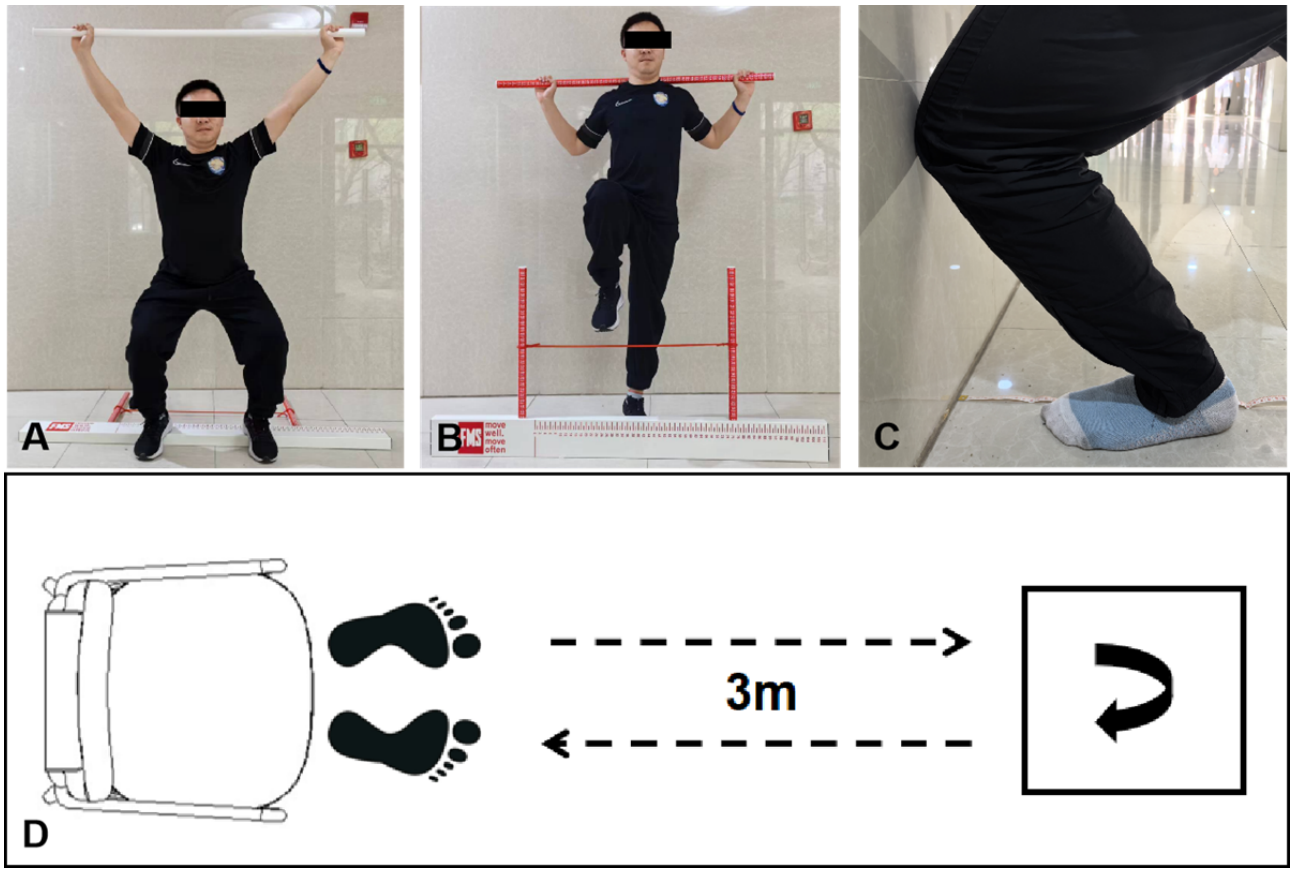

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Timed Up and Go

The TUG Figure 3D test is a simple and effective way to evaluate a patient's ability to rise from a chair, walk, and turn, which is clinically applicable and reliable across multiple populations. Given that patients with KOA often experience walking difficulties and balance impairments, the TUG test offers a direct measure of functional mobility highly relevant to daily activities. By assessing TUG scores before and after our intervention, we can assess Tuina's effects on mobility and balance, thereby verifying its clinical effectiveness. It will be used to assess objective physical function at baseline and 4-week follow-up.

At the beginning of the test, the patient will sit in a chair with their feet flat on the ground and their hands on their knees. We will ask them to get up, walk 3 m, turn around, and return to the chair. During this procedure, the evaluator will record the time it takes for the patient to complete the test. The longer the time, the higher the risk.

Weight Bearing Lunge Test

The WBLT Figure 3C is an ankle dorsiflexion activity under closed kinetic chain exercise of the knee joint, and its reliability and effectiveness have been widely recognized. It will also be applied at baseline and at 4-, 8-, and 16-week follow-up. Researchers have identified a potential relationship between the limited range of dorsiflexion motion in the ankle and knee kinematics, which may increase the risk of knee injury [29].

Before the test, a tape measure with a scale mark will be placed on the floor. During the test, the patient will be asked to face the wall, stand with one foot in front of the other, step on the tape on one side, and point the toes vertically toward the wall (initially at an appropriate distance from the wall), keeping the longitudinal axis of the foot in the center of the tape. They will keep the heel close to the ground and gradually move the knee forward. If the knee touches the wall, they will slowly move the knee and then the leg back and then repeat bending the knee toward the wall until the heel is about to leave the ground.

The assessor will measure the distance between the toes and the wall 3 times, calculate the average of the measurements, and record the results.

Cointervention Assessments

Patients will be advised not to receive other KOA interventions (eg, acupuncture, intraarticular injection) during the study. Additional interventions will be meticulously recorded.

Safety Assessments

We will also pay close attention to adverse events. Throughout the trial period, any adverse events or phenomena observed will be carefully recorded in the designated case report form (CRF). This documentation will include the precise timing of the event, the accompanying symptoms, the severity of the condition, its duration, the therapeutic measures implemented, and the outcome. The research team will carefully analyze the correlation between adverse events and the required intervention, recording their details, signs, and precise dates for future reference.

Statistical Analysis

IBM SPSS Statistics 27.0 will be used for all data analyses. The different baseline characteristics of the 2 groups will be described. Data will be presented as the mean (SD) or the median (IQR) for continuous variables and as frequency distributions for categorical variables. The 2-sample *t* test for quantitative data or the chi-square test for qualitative data will be performed as a homogeneity test, and covariance analysis will be performed if an adjustment is needed for a baseline characteristic. Analysis will focus on whether statistically better treatment outcomes can be achieved in the intervention group. $P<.05$ is considered statistically significant and the tests are 2-sided. If data loss occurs, we will use multiple imputations to create several datasets to replace missing values and reduce bias. For repeated-measures data across 4 time points, we will apply linear mixed effects models to handle unequal intervals and account for individual random effects. In addition, repeated-measures ANOVA will test the statistical significance of variable differences between time points. Combining these methods will help reveal variable trends over time and provide reliable statistical support for the findings.

Ethical Considerations

This protocol was approved in March 2025 by the Medical Ethics Committee of Shuguang Hospital affiliated with the Shanghai University of Traditional Chinese Medicine (approval number 2024-1560-143-01). All participants will provide signed informed consent, and upon completion of the study, they will receive a subsidy of 100 yuan (~US $14). Patient consent for publication is not applicable.

Data management is extremely important. In this study, electronic data will be stored on a dedicated computer in our research center. This computer will be protected by a password, a firewall, and an intrusion detection system, which can effectively prevent unauthorized access and data breaches, ensuring data security. In addition, data will be regularly backed up according to a set schedule to prevent loss. They will also be stored using a unified file-naming convention and directory structure for easy retrieval and management. Paper-based data, including CRFs, will be stored in locked filing cabinets at our research center. They will be organized and clearly labeled, and modifications will be recorded with the original content retained. Only authorized personnel will have access. Any personal information will be anonymized. Data will be retained as required by regulations to ensure integrity, traceability, and confidentiality.

Data access will be strictly controlled based on research roles and responsibilities. Principal researchers will have unrestricted access to perform their duties effectively. Other research team members will be granted access solely to the data essential for their specific tasks. Additionally, the Ethics Committee and regulatory authorities will have the right to review the data in accordance with relevant laws and ethical guidelines to ensure compliance with research standards. Additionally, all data access activities will be logged and subject to periodic review.

After the study, data will be properly stored following institutional and regulatory requirements. After the retention

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period, all data and records will be uniformly destroyed to ensure the long-term maintenance of participant privacy.

Quality Assurance

The project manager will be exclusively responsible for conducting all quality assurance. Before the study, all researchers are expected to undertake a comprehensive and uniform protocol-specific training program, encompassing the study protocol, CRF filling, data collection, data entry, and standard of functional tests. During the study, the project manager will conduct periodic inspections on all study components to ensure rigorous adherence to the study protocol and accurate documentation of the research data. Functional tests will be evaluated by specific researchers. The protocol will remain unaltered during the study period.

Results

We have successfully recruited 55 participants for the study, including those undergoing the intervention, those in follow-up, and those who have completed the study, with recruitment expected to be completed by September 2025. Data analysis has not yet been initiated. Upon completion of the study, the results will be submitted to a peer-reviewed journal for rigorous evaluation.

Discussion

Summary

The knee joint serves as a significant component of lower limb movements and acts as a pivotal link in the lower limb kinematic chain [30]. In the framework of kinematic chain theory [31,32], the lower limb is considered a harmonious and integrated unit, wherein the cooperative interplay of hip, knee, and ankle articulations is postulated as the vital factor for ensuring postural equilibrium and optimal gait function in the human body. The 3 joints are closely related, and any aberration in any of the links may culminate in the derangement of the lower limb's force line and the diminution of joint stability, potentially leading to irregular muscle contraction patterns, abnormal joint stress, and irregular neuromuscular interaction. This condition eventually leads to incongruous patterns of lower limb movement. Therefore, in the treatment of KOA, a holistic approach should be implemented, focusing on the integrity and functionality of the entire musculoskeletal system rather than relying excessively on local interventions.

Holism is a fundamental characteristic of TCM. The application of holistic concepts and differentiation of syndromes in diagnostic and therapeutic processes is a central concern in clinical practice. The inclusion of Tuina therapy in KOA management represents a frequently used and effective treatment strategy. Moreover, Tuina can effectively complement the treatment regimen for the hip, knee, and ankle joints. Therefore, we will develop a comprehensive clinical trial to evaluate the efficacy of Tuina therapy based on hip-knee-ankle synergy in the treatment of KOA.

Strengths and Limitations

To the best of our knowledge, this study is the first RCT to explore the clinical efficacy of Tuina therapy based on hip-knee-ankle synergy in patients with KOA. Our study will adopt a comprehensive approach to functional assessment, integrating both objective measurements and subjective patient-reported outcomes. This dual methodology will allow us to not only quantify improvements through standardized evaluation protocols but also capture patients' personal experiences and perceptions of their recovery. By combining these perspectives, we seek to offer a more nuanced and complete assessment of how intervention affects physical function. The primary outcome measure used in this study is WOMAC, a validated and reliable tool specifically designed to assess the presence and severity of lower extremity pain, stiffness, and functional limitations associated with OA [33]. Numerous previous studies have used WOMAC in behavioral intervention trials for osteoarthritis, validating its use as an appropriate indicator of clinical efficacy in this context. Key Symptoms and Signs/TCM Syndrome Classification Quantitative Evaluation of KOA can assess the degree of pain, swelling, and accompanying symptoms. TSK-11 can accurately predict the degree of physical disability in this patient population [34]. The TUG test represents abilities related to ambulatory transitions, leg strength, and balance [35], the FMS is crucial in assessing the quality of movement, and the WBLT is used to assess ankle dorsiflexion activity.

We anticipate that the results of this study will demonstrate the effectiveness of Tuina therapy based on hip-knee-ankle synergy in improving pain relief, functional outcomes, and overall quality of life for patients with KOA. For example, we expect to observe statistically significant improvements in WOMAC scores, indicating reduced pain, stiffness, and functional limitations. We also expect to observe statistically significant improvements in TSK-11 scores, indicating reduced fear of movement in patients. Additionally, we expect to observe statistically significant improvements in TUG, FMS, and WBLT outcomes. Such improvements would suggest potential enhancements in patients' physical activity and balance abilities. These potential findings would provide strong evidence supporting the integration of Tuina therapy into conventional treatment approaches for KOA, emphasizing the importance of considering the entire musculoskeletal system rather than focusing solely on localized treatments.

Although the study design inherently creates a potential imbalance in treatment dosage between the 2 groups, which may lead to differences in compliance and potentially affect the comparability of the results, several measures have been implemented to minimize the bias introduced by this imbalance. The assessor will be blinded to participants' group allocations and remain unaware of the intervention methods used for the 2 groups. Additionally, information about the existence of another intervention group will not be disclosed to the patients, and they will be strictly instructed not to disclose any information related to their intervention to the assessor.

Our study was conducted in a single medical institution, a large tertiary hospital with 2 campuses in different regions of

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Shanghai that serve diverse patient populations. Although this setup partially mitigates the limitations of a single-center study, it does not fully replicate the diversity of multisite studies conducted across varied geographical areas. Future research should investigate the intervention's effectiveness in multiple health care settings and populations to better understand its generalizability and real-world applicability.

Conclusion

In summary, we believe this study will offer valuable insights into the clinical efficacy of combining Tuina therapy based on hip-knee-ankle synergy for patients with KOA. If our anticipated results are realized, they could significantly influence the development of more comprehensive and effective treatment protocols in clinical practice. Moreover, the findings may enhance our understanding of KOA's underlying mechanisms and the benefits of holistic treatment approaches.

Acknowledgments

This study will be performed at the Department of Tuina, Shuguang Hospital affiliated with the Shanghai University of Traditional Chinese Medicine. We would like to sincerely thank all Shuguang Hospital staff for their help and assistance in this study. We also appreciate all the doctors and specialists who participated in the preparation and compilation of educational files in this study. This work is funded by the Shanghai Key Laboratory of Tuina Techniques on Musculoskeletal Disorders (24dz2260200), the Shanghai Science and Technology Qimingxing "Sailing Special Project" (22YF1449000), the Chinese Association of Traditional Chinese Medicine Young Talent Promotion (CACM-2023-QNRC2-B13), and the Shanghai Sports Science and Technology Project (24Q001). The funder did not play a role in design, collection, management, analysis, interpretation of data, manuscript writing, or decision-making for publication.

Authors' Contributions

MF is the project manager of the study and is responsible for coordinating the trial, the study design, and participants' enrollment. LK and MF contributed equally to this protocol, the study design, and manuscript drafting and will assume responsibility for quality assurance. WZL contributed to the study design and manuscript drafting and will take responsibility for assessment. LyRY contributed to sample size calculation and future statistical analysis. SZ and YY contributed to designing the first draft of this study. All pictures in the article are demonstration images created by one of the authors, and we have obtained consent for their use. No individuals outside the research team were involved in the design, conduct, reporting, or dissemination of this research.

Conflicts of Interest

None declared.

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Abbreviations

CRF: case report form
FMS: Functional Movement Screen
KOA: knee osteoarthritis
OA: osteoarthritis
RCT: randomized controlled trial
TCM: traditional Chinese medicine
TSK-11: 11-item Tampa Scale of Kinesiophobia
TUG: Timed Up and Go
WBLT: Weight Bearing Lunge Test
WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

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Protocol

Effects of Therapeutic Ultrasound and Aussie Current With High-Intensity Interval Training on Abdominal Adiposity in Young Adults With Overweight and Obesity: Protocol for a Randomized Controlled Trial

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Abstract

Background: More than half of the world's population will be overweight or obese by 2035, and it is known that physical exercise, such as high-intensity interval training (HIIT), is a tool for controlling obesity by improving body composition and the metabolic profile. Noninvasive techniques such as therapeutic ultrasound (TUS) and the Aussie current have shown potential in controlling adipose tissue, but their effects combined with HIIT remain unknown. TUS may be combined with the Aussie current to potentiate the specific effects of each intervention, such as lipolysis induced by TUS and lymphatic activation promoted by the Aussie current. The integration of HIIT into this protocol is justified by its ability to stimulate β-oxidation and facilitate the metabolic use of fatty acids mobilized by the electrophysical resources. Furthermore, the use of HIIT as opposed to moderate-intensity continuous training contributes to reducing the total duration of the intervention.

Objective: This study aims to evaluate the effects of TUS+Aussie current combined with HIIT on body composition, serum metabolic profile, and cardiovascular autonomic modulation (CAM) in individuals with overweight and obesity.

Methods: This is a randomized, double-blind (researcher and outcome assessor) clinical study. The participants will be randomized into 3 groups: active TUS+Aussie current with HIIT group, placebo for TUS+Aussie current with HIIT group, and TUS+Aussie current–only group. All participants will undergo nutritional monitoring 30 days before the proposed interventions to adjust macronutrients, optimize energy intake, and improve diet quality. Primary outcomes include changes in subcutaneous adipose tissue thickness, body composition, and serum metabolic profile. Secondary outcomes assess perceived stress, body image, blood biochemistry, sleep quality, and CAM. Data analysis involves linear mixed models estimated using the maximum likelihood method with an appropriate covariance matrix structure.

Results: A total of 60 participants will be recruited and randomized between February 2024 and June 2025. The baseline assessments and intervention are scheduled to be completed in August 2025, and data collection will be completed by the end of September 2025. Data acquisition is still ongoing; therefore, data analysis has not yet been carried out.

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Conclusions: This is the first study to combine TUS+Aussie current with HIIT, potentially integrating the effects of lipolysis and fat oxidation and possible changes in the serum metabolic profile and CAM. The results could optimize treatment duration, promote changes in lipid profile, and maintain cardiovascular health in people with overweight and obesity.

Trial Registration: Brazilian Registry of Clinical Trials RBR-4xh6232, Universal Trial Number: U1111-1287-2345; https://ensaiosclinicos.gov.br/rg/RBR-4xh6232

International Registered Report Identifier (IRRID): DERR1-10.2196/71829

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KEYWORDS

combined therapy; abdominal subcutaneous fat; obesity; lifestyle; physiotherapy

Introduction

Background

According to a report by the World Obesity Federation, more than half of the world's population will be overweight or obese by 2035 [1]. Excess abdominal fat is a primary determinant for developing insulin resistance and other metabolic disorders [2]. Lifestyle modification is the most recommended approach for treating and preventing obesity at any stage of life [2]. In addition to exercise and a controlled diet, noninvasive techniques have emerged as safe and effective tools for managing adipose tissue [3,4]. These techniques include different electrophysical agents, such as low-intensity laser [5], cryotherapy [6], radiofrequency [7], infrared radiation [8], and therapeutic ultrasound (TUS) [4,9].

TUS is a therapeutic modality widely used in physiotherapy clinical practice [10,11]. The nonlinear propagation of TUS waves induces mechanical forces on particles at the applied site, resulting in biological effects [4], including pyroptosis [12]. This term refers to a form of programmed cell death mediated by caspase-1 or caspase-11, characterized by the secretion of proinflammatory cytokines [12,13]. Cells undergoing pyroptosis exhibit mitochondrial membrane potential loss; DNA fragmentation; nuclear condensation; and the release of cytoplasmic contents into the bloodstream, including fatty acids [13,14].

TUS can be combined with Aussie electrical current to stimulate the lymphatic system, producing a strong but comfortable paresthesia [11,15]. The Aussie current is characterized by a medium-frequency alternating wave modulated at a low frequency (LF) and is indicated for various applications, including muscle strengthening, pain control, lymphatic drainage, and edema control [11]. The combined effects of these electrophysical resources—TUS and Aussie current—alongside aerobic exercise after therapy may enhance fat β-oxidation. However, despite promising results for cellulite reduction with the combination of TUS and Aussie current [16-18], previous studies are limited by small sample sizes; lack of a placebo group; and insufficient focus on posttherapy clinical outcomes, such as serum metabolic changes [18]. In addition, other forms of intervention have been widely suggested for reducing body composition and promoting significant metabolic changes in individuals with obesity, such as high-intensity interval training (HIIT). HIIT alternates between periods of high intensity and active recovery and has become a popular training method due to its time efficiency.

Although previous studies [19,20] have shown better effects of HIIT on the aerobic capacity of patients with cardiovascular disease when compared to continuous moderate-intensity training, the effects of HIIT on cardiovascular autonomic modulation (CAM) in people with obesity are poorly understood. A systematic review evaluated the effects of HIIT on CAM based on 6 studies that used heart rate (HR) variability as a measure [21]. The results showed that HIIT can improve autonomic modulation by increasing parasympathetic cardiac modulation and reducing sympathetic cardiac modulation in healthy individuals and patients with metabolic syndrome, making it a promising strategy for cardiovascular rehabilitation [21].

As for the effects of HIIT on body composition, another review analyzed body fat percentage, fat mass, and fat-free mass in cycling, running on the ground, and running on a treadmill [22]. The findings showed that all forms of HIIT significantly reduced fat mass (−1.86 kg) and body fat percentage (−1.53%) compared to the control group [22].

Although previous studies have reported reductions in abdominal circumference and body composition following TUS and Aussie current application [3,4,10,11], none have evaluated this technique in combination with HIIT in participants with overweight or obesity. In addition to optimizing time, the combination of both interventions also aims to optimize the breakdown, drainage, and oxidation of fat, promoting weight loss. There is a need for clinical trials to investigate the potential clinical effects of this therapeutic modality in humans, as suggested by animal models [16-18]. Furthermore, this study addresses a relevant public health problem [1]—the increasing prevalence of obesity in young adults—by proposing a multimodal, noninvasive intervention aimed at reducing abdominal adiposity and improving metabolic health, a scope that has been explored little in previous clinical protocols [4,9,11]. The results of this study will determine whether TUS and Aussie current therapy induce changes in body composition, manage serum metabolic profile, and improve CAM indexes.

Objectives

This pragmatic study aims to evaluate the effects of combined therapy (TUS+Aussie current) alone and combined with HIIT on body composition, serum metabolic profile, and CAM in people with overweight and obesity. This study also investigates

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the impact of these interventions on perceived stress, body image, and sleep quality in people with overweight and obesity.

Methods

Study Design

This is a randomized, pragmatic, placebo-controlled, double-blinded, 3-arm (1:1:1) clinical trial. The protocol was developed in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [23].

This research will be conducted at the Federal University of São Carlos (UFSCar) in the Cardiovascular Physical Therapy Laboratory/Physical Exercise Research Center within the Department of Physical Therapy. Participants will be recruited through social media advertisements. An electronic form hosted on Google Forms will be shared via Instagram. Interested participants who meet the basic inclusion criteria will be contacted via WhatsApp to provide additional information about the study and assess their eligibility. Participants who do not respond to the messages will receive up to 3 phone call attempts at different times. If these contact attempts are unsuccessful, the individual will be considered unreachable and ineligible for the study.

Ethical Considerations

This study adheres to the ethical principles outlined in the Declaration of Helsinki. The research protocol was approved by the Research Ethics Committee of the UFSCar (approval 64624522.8.0000.5504) and was registered in the Brazilian Registry of Clinical Trials on February 8, 2023, and updated on December 2, 2024 (RBR-4xh6232—Universal Trial Number: U1111-1287-2345). Participants will be informed of their right to withdraw from the study at any time without penalty or loss of benefits. In addition, all collected data will be treated with strict confidentiality and used solely for research purposes. This is an academic study and no compensation will be given to participants.

Before any data collection, the outcome assessor obtains written informed consent from participants. Only those who provide consent proceed to the baseline evaluation and randomization.

The data will be collected on paper and stored in folders at the Cardiovascular Physical Therapy Laboratory (Federal University of São Carlos). The data will be entered into Microsoft Excel (Microsoft Corp) by the physiotherapist responsible for the assessments, reassessments, and follow-ups. In addition, all the data will be available on a public research bench.

The database and electronic analyses will be stored on a secure computer server, with personal log-in access authorized by the principal investigator of this study. The principal investigator will have access to the complete dataset (without the allocation groups), and the data and materials in this paper will be available to other researchers on request. Upon completion of the study, all data and documents will be archived by the principal investigator for 5 years at the Physical Therapy Department of the Federal University of São Carlos.

Eligibility Criteria

The eligibility criteria for this study are outlined in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Men and women
- Ages of 18 to 40 years at enrollment
- Classified as overweight or having grade-I or grade-II obesity according to the fat mass index as measured using dual-energy x-ray absorptiometry
- Healthy adults without any chronic or acute disease and who started any physical activity in the previous 3 months

Exclusion criteria

- Current smokers, individuals with chronic alcohol misuse, illicit substance users, or smokers or ex-smokers less than 12 months old
- History of body mass reduction treatments using drugs or electrophysical agents such as therapeutic ultrasound and electrotherapy in the previous 12 months
- Electrocardiogram abnormalities, including ischemia, overloads, conduction disorders, and serious arrhythmias such as ventricular tachycardia
- Presence of any of the following conditions or diagnoses of diseases: neurological, renal, respiratory, cardiac, or musculoskeletal conditions; venous thrombosis; anticoagulant therapy or bleeding disorders; active cancer or cancer treatment in the previous 5 years; conditions or lesions in the abdominal region; diabetes mellitus type 1 or 2; hypothyroidism or hyperthyroidism; and pregnancy in the previous 12 months

Randomization and Blinding

In this study, the researchers responsible for the evaluations and those analyzing the data will be blinded. To ensure the feasibility of blinding, the blinded research teams will not participate in the interventions, and all information will be coded to prevent the identification of participants and intervention groups. The effectiveness of blinding will be assessed using a questionnaire completed by the evaluators at the end of the final assessment for each data collection block.

After the initial assessments, participants will be stratified (age range, sex, and fat mass index) and randomly assigned to 1 of 3 groups. Participants in group 1 (active TUS+Aussie current with HIIT [AG]) will undergo combined therapy (TUS+Aussie current) along with the HIIT protocol. Participants in group 2 (placebo for TUS+Aussie current with HIIT [PG]) will undergo

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placebo combined therapy (TUS+Aussie current) with the devices turned off along with the HIIT protocol. Participants in group 3 (TUS+Aussie current–only group [HG]) will receive only the combined therapy (TUS+Aussie current) without the HIIT protocol.

For stratified randomization, participants will be initially grouped into blocks based on similar characteristics, including age range (20-29 years or 30-40 years), sex (male or female), and fat mass index (overweight, grade-I obesity, or grade-II obesity). These characteristics will be chosen to control for potential confounding factors. Within each block, participants will be then randomized into the 3 study groups using Microsoft Excel, ensuring an unbiased allocation process. Block sizes were not fixed, further reducing the risk of allocation predictability. The randomization process will be conducted by a researcher designated exclusively for this task, who will have no contact with the study participants or the researchers involved in data collection. This researcher will also be responsible for generating random alphanumeric codes to ensure the anonymity of each participant's information.

Measures

Baseline Evaluation

Participants who meet the eligibility criteria will be considered eligible for randomization and will have a baseline evaluation scheduled. To characterize the sample, the initial assessment records information, such as sex, age, anthropometric data, family history, medication use, educational level, occupation, and comorbidities.

Study Assessments and Timeline

All study participants will have to attend 2 face-to-face visits: one at baseline (week –1) and one at the final assessment (week 6). In addition, participants will be assessed by a nutritionist and receive nutritional guidance and diet plans (week 0). The treatment will last 5 weeks. A detailed schedule is available in Table 1.

Table 1. Study period.

Time point[a]	Study period							
	Enrollment	Allocation	After allocation					Closeout
	Week −4	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Enrollment								
Eligibility screening	✓							
Informed consent	✓							
Nutritional evaluation	✓							
Allocation		✓						
Interventions								
AG[b]			✓	✓	✓	✓	✓	
PG[c]			✓	✓	✓	✓	✓	
HG[d]			✓	✓	✓	✓	✓	
Assessments								
SAT[e]	✓	✓						✓
Body composition	✓	✓						✓
Metabolic profile			✓				✓	
Perimetry	✓	✓						✓
Blood test	✓	✓						✓
Questionnaires	✓	✓						✓
Exercise test		✓						
24-h food recall			✓	✓	✓	✓	✓	
CAM[f]	✓	✓	✓				✓	✓

[a]Timepoint: evaluation time.

[b]AG: active therapeutic ultrasound+Aussie current with high-intensity interval training group.

[c]PG: placebo for therapeutic ultrasound+Aussie current with high-intensity interval training group.

[d]HG: therapeutic ultrasound+Aussie current–only group.

[e]SAT: subcutaneous adipose tissue.

[f]CAM: cardiovascular autonomic modulation.

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Initial Evaluation

Initial information (lifestyle and inclusion criteria) will be collected online using a screening form link for men and women. Body mass and height measurements will be taken using a calibrated scale. Participants will be advised to be barefoot and wear light clothing. Height is measured with the participant standing and using a stadiometer. A member of the research team (ACAMS) is responsible for carrying out all study assessments as well as screening and recruiting participants, minimizing bias.

Abdominal Subcutaneous Adipose Tissue

Ultrasound will be used as the main end point to assess abdominal subcutaneous adipose tissue (SAT) [4]. Intrarater reliability was assessed in previous studies [24]. A GE HealthCare Venue 40 ultrasound (model NZCART; GE Medical Systems, Ltd) is used. Subcutaneous fat, defined as the distance in centimeters between the dermis and the external surface of the fascia of the abdominal muscles, is measured using a linear transducer with a frequency of 12 MHz placed transversely 1 cm above and 1 cm below the umbilical scar [25,26]. Participants will be examined in the supine position without any artifact compressing the abdominal region, with their knees bent, and instructed to breathe in and out. A total of 3 measurements will be taken, each at the end of an exhalation, with minimal pressure on the abdominal cavity for greater measurement precision [27,28].

Body Composition

To determine total body mass, fat mass percentage per region, and visceral fat, we use dual-energy x-ray absorptiometry (DXA; Hologic Discovery A). This assessment is considered the gold standard for evaluating body composition in individuals with overweight and obesity [29]. In addition, DXA is used to classify participants as overweight or obese (grade I and II) [30]. Considering that hormonal variation throughout the menstrual cycle can influence body composition results, especially through fluid retention and water redistribution, all female participants will be assessed during the follicular phase of the menstrual cycle, a phase in which there is greater hormonal stability and a reduction in extracellular fluids, providing greater accuracy in body composition measurements [31].

Participants must fast for 4 hours, refrain from vigorous exercise for at least 12 hours, avoid caffeine and alcohol for the previous 24 hours, and consume a normal meal the night before the test. They should not wear any metal objects or accessories during the test to prevent interference with the total body composition results. The participant is placed in a supine position with internal rotation of the thighs, legs, and feet and instructed not to speak or move during the examination. The results obtained will be transmitted to a computer connected to the equipment, where the report shows the data in grams and percentages and which will be used to analyze total lean mass (kg), total bone mass (percentage), total fat mass (g), fat mass index (kg/m^2), fat mass in the android and gynoid regions (g), and visceral fat (g) and, through calculations, deduce subcutaneous fat [32,33].

Serum Metabolic Profile

Venous blood samples will be collected in the cubital fossa by a specialized professional after the participants have fasted for 3 hours following a standardized meal. Blood samples will be taken 3 times: before and immediately after the TUS+Aussie current session and immediately after HIIT. Each tube of blood collected will be left to stand at room temperature for 30 minutes. They will then be centrifuged at 1450 × g for 10 minutes (Sorvall ST 8 Benchtop Centrifuge; Thermo Scientific). The serum is divided into 3 aliquots in 1.5-mL microtubes using 5-mL disposable pipettes and stored immediately at −80 °C until further analysis. The serum samples will then be thawed at the UFSCar Department of Chemistry and sent for analysis using the hydrogen nuclear magnetic resonance technique. Serum glycerol, total cholesterol, very low–density lipoprotein, low-density lipoprotein (LDL), high-density lipoprotein, and triglycerides will be assessed. These will be measured using wet chemistry (except for LDL, which will be calculated using the Friedwald equation; ADVIA 1800; Siemens). The experimental procedures for this analysis will follow those described in the work by De Favari Signini et al [34] and Castro et al [35].

CAM Measurement

To ensure the quality of the electrocardiogram (ECG) signal collection, the recommendations suggested by Catai et al [36] will be followed. All participants will be instructed to have a regular night's sleep the night before, avoid alcoholic and caffeinated drinks, refrain from strenuous physical exercise at least 24 hours before and on the day of the assessment, and avoid heavy meals up to 2 hours before the assessment. All procedures will be explained beforehand to familiarize participants with the equipment and the assessor. The experiment will be carried out in the afternoon in a quiet room with the minimum number of people in the Cardiovascular Physical Therapy Laboratory, with controlled temperature and relative humidity (22-23 °C and 40%-60%, respectively) [36]. Before starting data collection, the participants will rest for 10 to 15 minutes to stabilize the signals [36]. After this, they will remain in the supine position for 15 minutes and then perform active postural change, remaining in the orthostatic position for 15 minutes. Participants will be instructed to breathe spontaneously and not to move or speak during the experiment.

RR intervals will be captured via ECG (Bio Amp FE132; ADInstruments) from the modified shunt in the fifth left intercostal space lead. In addition, respiratory movements will be captured using a respiratory belt positioned around the participants' chest (Marazza) to obtain the respiratory rate during the test. Arterial pressure (AP) will be measured continuously beat to beat using a photoplethysmograph (Finometer PRO; Finapres Medical Systems) on the middle finger of the right hand. RR interval signals, AP, and respiratory movement will be sampled at 1 kHz using a commercial acquisition device (PowerLab 8/35; ADInstruments).

Classic linear indexes of HR variability will be calculated in the time and frequency domains. The indexes calculated in the time domain will be the SD of the NN interval, which represents sympathetic and parasympathetic modulation together, and the

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square root of the mean of successive NN intervals, which indicates parasympathetic modulation [37,38]. After detecting the QRS complex on the ECG, the apex of the R wave will be identified using parabolic interpolation. The heart period (HP) will be calculated as the temporal distance between 2 consecutive parabolic apexes. A stable sequence of 256 beats (for systolic AP [SAP] and HP) will be chosen in the supine and orthostatic positions, and if isolated ectopic beats are present, they will be linearly interpolated [39]. From these 256 points, the mean and variance of the HP and the mean and variance of the SAP will be calculated in the time domain.

The variability parameters of the HP and SAP will be evaluated according to the autoregressive model [39]. The spectral components will be broken down into LF (from 0.04 to 0.15 Hz) and high frequency (>0.15 to 0.4 Hz) reported in absolute units. The power of the spectral components will be expressed in absolute units or normalized units [38].

Symbolic analysis will be used to evaluate the HP and SAP series as defined in the study by Porta et al [40]. This technique is based on the 6-level uniform quantization procedure applied to HP and SAP series, which transforms series into sequences of symbols (from 0 to 5) from which patterns of 3 consecutive symbols will be constructed [41]. All possible patterns will be grouped without loss of information into families according to the number and type of variations between subsequent symbols: (1) 0V pattern—all symbols are the same; (2) 1V pattern—2 underlying symbols are the same, and the rest are different; (3) 2LV pattern—the 2 variations between adjacent symbols have the same sign; and (4) 2UV pattern—the 2 variations between adjacent symbols have opposite signs. Percentages of patterns within each experimental session were evaluated and denoted using 0V%, 1V%, 2LV%, and 2UV%, respectively. The 0V% index will be understood as a marker of sympathetic modulation when calculated in the HP and SAP series, and the 2UV% index will be understood as an index of vagal modulation when calculated in the HP series [40,42,43].

The baroreflex system will be evaluated through cross-spectral analysis using a bivariate autoregressive parametric approach [44]. The time-series relationships between AP and HP will be represented as coherence, phase, and transfer function gain. The coherence function shows the degree of association between the HP and SAP variabilities [44,45]. Its values range from 0 to 1, where values closer to 1 represent better coupling between the signals. The phase function represents the temporal relationship between the series (ie, the delay between the change in the SAP signal resulting from the heartbeat) and will be evaluated in high frequency and LF [44].

Sleep Quality

Sleep quality is assessed using the Pittsburgh Sleep Quality Index for sleep quality, adapted for Brazilians by Bertolazi et al [46]. It is a reliable instrument (intraclass correlation coefficient=0.65) [47] that assesses 7 components of sleep: subjective quality, sleep latency, sleep duration, sleep efficiency, sleep disturbances, medication use, and daily dysfunction. For each component, the score ranges from 0 to 3, and the sum yields a maximum score of 21. Scores of >5 indicate poor sleep quality.

Anxiety, Depression, and Stress

Anxiety and depression will be assessed using the Hospital Anxiety and Depression Scale validated for Brazilians [48]. It consists of 14 items divided into 2 domains (depression and anxiety) with 7 items each. The items are scored on a 4-point Likert scale (from 0 to 3), resulting in total scores ranging from 0 to 21 for anxiety and depression. The cutoff points indicating moderate to severe symptoms are ≥8 for the anxiety domain and ≥9 for the depression domain.

Stress is assessed using the Depression, Anxiety, and Stress Scale, which measures the levels of these disorders based on behaviors in the previous 7 days. The items use a 21-question Likert scale, which has been translated into Brazilian Portuguese, to rate the frequency or severity of the participants' experiences on a 4-point scale [48].

Body Image

The Body Shape Questionnaire, validated for the Brazilian population [49], is a self-administered questionnaire consisting of 34 items designed to measure satisfaction and concerns about body shape. It is organized on a 6-point scale: 1=*never*, 2=*rarely*, 3=*sometimes*, 4=*frequently*, 5=*very frequently*, and 6=*always*. The score is the sum of the answers, where ≤110 points indicates no concern, ≥111 to ≤138 points indicates mild concern, ≥139 to ≤167 points indicates moderate concern, and >168 points indicates serious concern [49]. This questionnaire helps assess potential changes in satisfaction or concern about the body after the proposed treatment.

Biochemical Blood Tests

Participants will be referred to a specialized clinic for blood collection. They will be instructed to fast for 10 hours before the test. The following will be collected: complete blood count, glycated hemoglobin (through high-performance liquid chromatography), fasting glycemia, insulin resistance (through enzymatic and chemiluminescent immunoassay), evaluation of the homeostatic model, C-reactive protein (through immunoturbidimetry), homocysteine (through chemiluminescence), total cholesterol, high-density lipoproteins, and LDLs and triglycerides (through the enzymatic method). The tests will be clinically relevant in the context of obesity and abdominal adiposity and may contribute to future studies to determine whether any changes occur in these variables after the intervention. The results will be reported by the unit's physician and sent to the researcher.

Perimetry

The waist-to-hip ratio is a calculation based on waist and hip circumference measurements [50]. It is often used to assess the risk of developing diseases such as high cholesterol, diabetes, and high blood pressure [50]. The presence of these cardiovascular risk factors, associated with increased abdominal fat, leads to a high risk of diseases such as myocardial infarction, stroke, and hepatic steatosis and mortality. The values considered normal for male and female individuals are <0.95 and <0.80 cm, respectively [50]. The waist-to-height ratio, on the other hand, is an index that assesses health risks by indicating the proportionality between waist circumference (a possible indicator of central fat accumulation) and height,

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suggesting a risk of cardiovascular or metabolic diseases [51]. Values of <0.5 cm indicate a lower risk of diseases, whereas values of >0.5 cm indicate a higher risk [51]. The measurements will be taken with the participant standing upright wearing light clothing. The waist circumference is measured as the average distance between the last floating rib and the anterior superior iliac crest [52]. The hip circumference is measured around the widest part of the buttocks at the level of the greater trochanter of the femur [52]. All measurements will be taken twice using an inextensible tape measure, and if there is a difference of 3 cm, a third measurement is taken for both waist and hips [52]. The ratio between the measurements is calculated as the waist circumference divided by the hip circumference.

Neck circumference is measured using an inextensible tape measure perpendicular to the longitudinal axis of the neck over the thyroid cartilage [53]. Participants will be in an anatomical position, either standing or sitting, with their head in the Frankfurt plane and their shoulders relaxed and in inspiratory apnea [53]. The cutoff points for overweight and obesity will be 37 cm for men and 34 cm for women [54]. The values above these cutoffs indicate increased cardiovascular risk factors [54].

Physical Activity

All participants will be characterized by their level of physical activity at a single point in time (before the intervention). The long version of the International Physical Activity Questionnaire is used. The International Physical Activity Questionnaire is a validated instrument for the Brazilian population that assesses the level of physical activity. It has 27 questions related to physical activities performed in a week at different intensities—light, moderate, and vigorous—lasting at least 10 minutes continuously. The questions cover 4 dimensions: work, transportation, domestic activities, and leisure, as well as the time spent seated [55]. The score is calculated by adding the workload for each subitem separately [55]. This questionnaire helps classify the level of physical activity before the proposed interventions.

Before the intervention, a treadmill ergometric test is conducted using the Ellestad protocol [56] for clinical cardiological assessment and to assist in prescribing HIIT. The test is interrupted according to the criteria recommended by the third version of the Sociedade Brasileira de Cardiologia ergometry guidelines [57]. The original Borg scale is used to assess the participants' perception of dyspnea, lower-limb fatigue, and angina during exercise. This scale ranges from 0 to 10, where 0 is no dyspnea and 10 is the most intense dyspnea, fatigue, and angina [58]. The following determines the presence of maximum or peak effort: peak HR (HR_{peak})≥85% of that predicted for age (220 – age) and Borg perceived exertion of 18 on a scale from 6 to 20 (patient exhausted) [59].

Interventions

Nutritional Intervention

The nutritional intervention will be conducted by an experienced nutritionist. All participants receive nutritional guidance 30 days before the combined therapy and HIIT. This initial intervention aims to adjust macronutrient intake, optimize energy consumption, and improve diet quality by reducing the consumption of ultraprocessed foods and increasing the consumption of minimally processed foods. Macronutrient adjustments follow the recommendations of the dietary reference intakes, with carbohydrates comprising 45% to 65%, proteins comprising 10% to 35%, and lipids comprising 20% to 30% of the total caloric intake [60].

Following this phase, participants undergo a new series of assessments and then begin 5 weeks of combined therapy and HIIT. During these 5 weeks, dietary control is monitored by the nutritionist to ensure consistency in dietary patterns throughout the study. Daily energy intake is considered stable if variations remain at <10% during the protocol.

Food intake will be assessed weekly using a 24-hour recall, a questionnaire that quantifies all food and drink consumed in the previous 24 hours. Participants will receive an electronic link once a week during the 5-week intervention. The data collected will be analyzed by a nutritionist to assess consistency and adherence in total energy and macronutrient intake. Variations of >10% in total calorie intake will be discouraged to ensure dietary stability throughout the protocol. No additional methods of validating adherence to the diet will be used as the weekly recalls provide a feasible and easy monitoring strategy for the participants. Total energy intake and macronutrient composition will be calculated using the Dietbox program [61]. Energy requirements will be estimated based on the dietary reference intakes [62]. For qualitative analysis, foods will be categorized according to their processing level—natural, minimally processed, culinary ingredients, processed, and ultraprocessed—as defined by the 2014 Food Guide for the Brazilian Population [63].

Combined Therapy Application Time Calculation

Before the first session, the application time for the combined therapy will be individually determined. Measurements will be conducted by the same blinded assessor using an inelastic tape measure with the participant in a standing position. Specifically, the horizontal distance between the last floating ribs (x) and the vertical distance to the midpoint between the anteroinferior iliac crests (y) will be measured. The abdominal area (cm^2) will be calculated by multiplying these 2 values (x × y) and then dividing the result by 18. This divisor corresponds to the total effective radiating area of the ultrasound head used in the therapy, which consists of 3 spheres, each with an effective radiating area of 6 cm^2. Dividing the abdominal area by 18 allows us to determine the time required to apply the therapy to each participant according to the following formula: application time = (x × y)/18.

For example, if a participant has a horizontal distance (x) of 21 cm and a vertical distance (y) of 26 cm, the area will be calculated as follows: 21 × 26 = 546 cm^2. Dividing this area by 18 results in approximately 30 minutes of application time (546/18 = 30.33 minutes).

Pretraining Instructions

Before each training session, participants will be instructed to (1) wear comfortable clothing and exercise-appropriate footwear, (2) ensure adequate sleep the previous night, (3) hydrate with

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water 2 hours before the session and bring a personal water bottle, and (4) avoid strenuous physical activity and alcoholic consumption within 24 hours before the session.

Food consumption will also be recommended 24 hours before the first and last sessions, as described in the Nutritional Intervention section.

Session Scheduling and Follow-Up

To minimize data loss, participants receive reminders about the date and time of each session. Physiotherapists responsible for interventions may also call participants if necessary to confirm appointments. For evaluations and re-evaluations, the blinded evaluator contacts the participants via telephone. At the end of the 10 treatment sessions, the re-evaluation is scheduled between 3 and 15 days after the last session.

Group 1: AG

Participants in the AG will be treated with TUS+Aussie current (Heccus; Ibramed). All therapists who will administer the TUS+Aussie current interventions have undergone standardized previous training, which includes theoretical and practical sessions to ensure the fidelity of the protocol. In addition, every participant will be seen by each therapist at least once. This strategy aims to minimize possible biases related to therapist application and intervention quality in all groups.

The protocol combines continuous ultrasound (3 MHz; 2 W/cm^2) and Aussie current (1 kHz; modulated at 10 Hz). The participant will be instructed that the sensation must be tingling and comfortable (sufficient intensity to produce strong but comfortable paresthesia without stimulation to painful paresthesia) [64]. In every session, and every 5 minutes, the therapist will record the intensity of the Aussie current and evaluate the levels of paresthesia on a scale from 0 to 10, with 0=no tingling sensation and 10=maximum tolerable tingling. Given the possible habituation to the paresthesia caused by the Aussie current, the scale will be applied every 5 minutes during the session, and a score of 5 will be set as the threshold for adjusting the intensity of the current (ie, tolerable or supportable tingling). The target intensity is set at approximately 5. The intensity of the Aussie current will be adjusted immediately whenever the perception reported by the participant falls to <5 (0-10), ensuring a consistent and comfortable sensory experience throughout the session.

The treatment is applied to the abdominal region using ultrasound. The therapist ensures consistent pressure and maintains slow, slightly circular, horizontal movements without losing contact with the surface.

In the final session, participants complete a printed questionnaire that includes the reported intensity of the Aussie current and the following questions: “Would you recommend this therapy to someone else?” and “Do you believe you received the active treatment, the placebo or are unsure? Why?” In addition, in the last session, the blinded therapist will answer a questionnaire about which group they believe each participant was allocated to and the reason for this choice.

Immediately after the TUS+Aussie current application, participants will take to the treadmill for the HIIT session. Participants will be instructed to maintain proper posture with relaxed shoulders, a forward-facing stance, and a breathing pattern of inhaling through the nose and exhaling through the mouth, avoiding apnea during the exercise. The Borg scale (6-20) [65] will be applied 10 seconds before each load change during the 20-minute interval protocol.

HR is continuously monitored using a Polar H10 HR monitor attached to an elastic chest strap positioned at the xiphoid process. This Polar monitor is paired via Bluetooth with a tablet.

The HIIT protocol lasts 30 minutes and includes the following:

1. A warm-up of 5 minutes, progressively reaching 55% to 60% of the peak HR determined in the ergometric test.
2. An interval phase of 10 cycles of a 1-minute high-intensity interval (85%-90% of peak HR) interspersed with 10 cycles of a 1-minute light- to moderate-intensity interval (55%-60% of peak HR). After 5 sessions, the load will be updated by 5% to 10% considering physiological adaptations (moderate intensity 60%-65% of peak HRand high intensity 90%-95% of peak HR). After the fifth training session, the training load will be adjusted by 5% to 10% based on physiological (peak HR) and subjective (Borg) criteria. Specifically, participants who consistently reach the target HR zone (85%-90% of peak HR) during high-intensity intervals and report a perceived exertion score of <17 on the Borg scale (6-20) will have the speed or incline of the treadmill increased by 5% to 10%. HR will be monitored continuously using an HR sensor, and the Borg rating of perceived exertion will be applied 10 seconds before each load change.
3. A cooldown and recovery phase of 5 minutes of active cooldown followed by passive recovery with the participant seated (Figure 1).
4. Guidelines and organization will include controlled temperature and humidity (21-24 °C and 40%-60%, respectively) and previous hydration with water.

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Figure 1. Summary of the high-intensity interval training (HIIT) protocol following the application of combined therapy, along with the progression of the intervention protocol. HRpeak: peak heart rate during the ergometric test; TUS: therapeutic ultrasound.

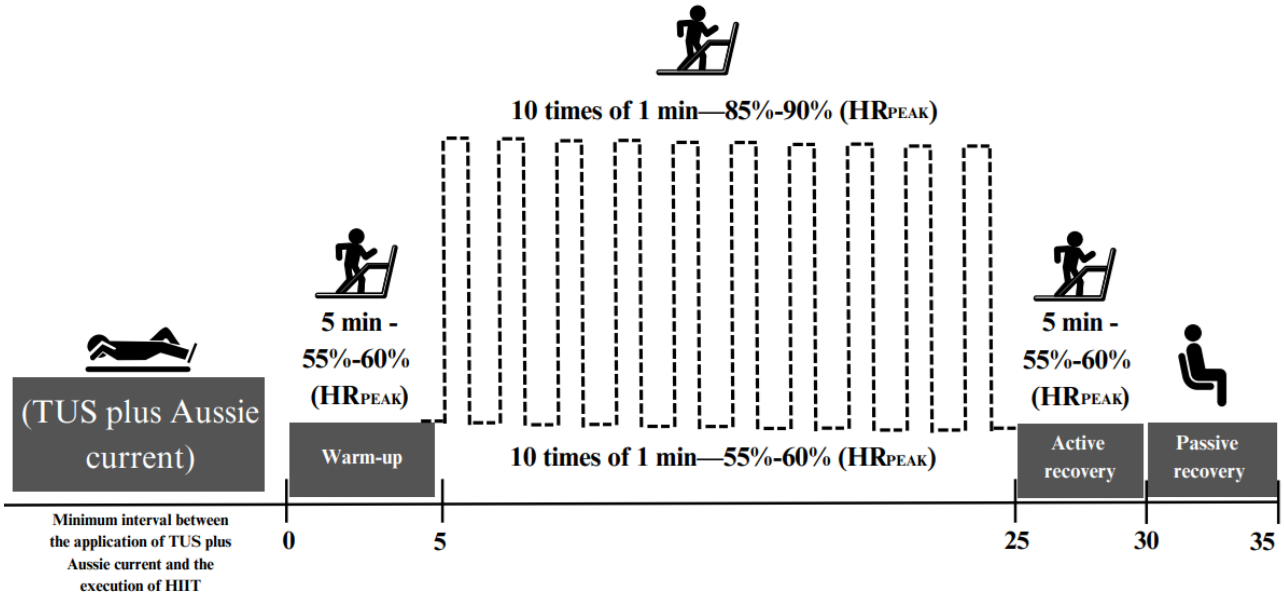

Group 2: PG

All the participants in this group will follow the same procedures and sequence as those in the AG. However, the PG participants will receive the TUS and Aussie current treatment in placebo form, ie the therapy switched off. The protocol combines continuous ultrasound (0 MHz; 0 W/cm^2) and Aussie current (0 kHz; modulated at 0 Hz). Immediately after the TUS+Aussie current treatment, all participants proceed to the treadmill to start the HIIT, following the same protocol as for the AG (Figure 2).

Figure 2. Flowchart of assessments before, during, and after 10 intervention sessions. BSQ: Body Shape Questionnaire; CAM: cardiovascular autonomic modulation; DASS-21: Depression, Anxiety, and Stress Scale; DXA: dual-energy x-ray absorptiometry; FR24h: 24-hour food recall; HADS: Hospital Anxiety and Depression Scale; HDL: high-density lipoprotein; HIIT: high-intensity interval training; HRMAX: maximum heart rate; IPAQ: International Physical Activity Questionnaire (characterization); LDL: low-density lipoprotein; NC: neck circumference; PSQI: Pittsburgh Sleep Quality Index; TUS: therapeutic ultrasound; usCRP: ultrasensitive C-reactive protein; WC: waist circumference; WHR: waist-to-hip ratio.

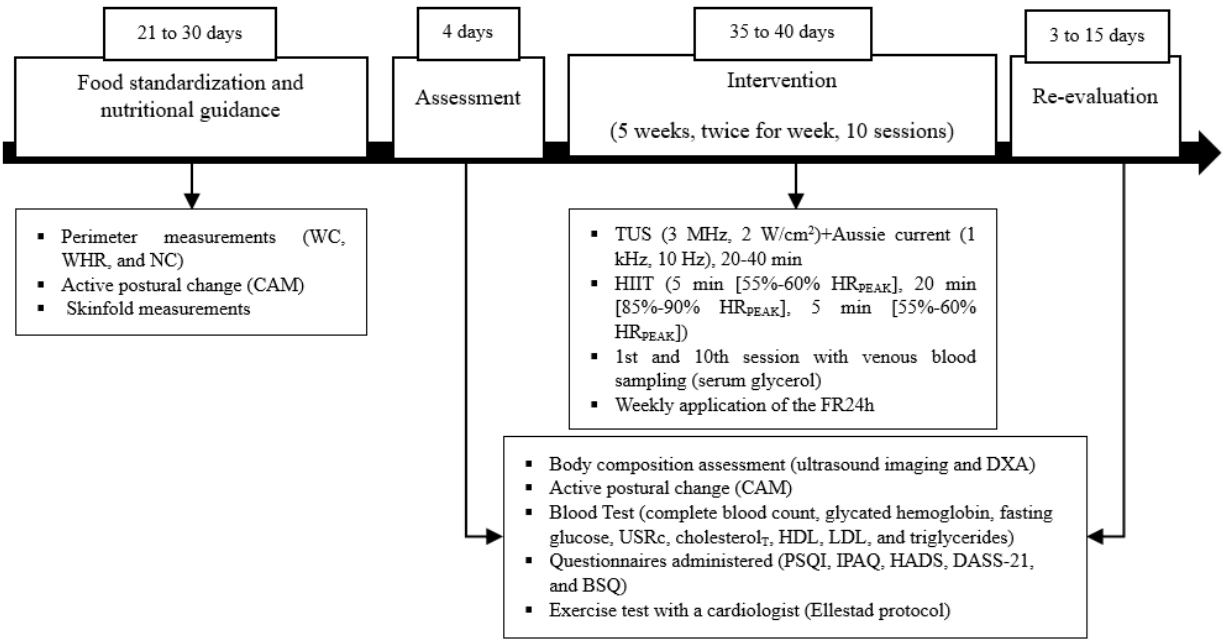

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Group 3: HG

Participants in the HG receive the same treatment as those the AG. However, after the application of TUS plus Aussie current, they will not perform HIIT.

Outcomes

Primary Outcomes

The primary outcomes involve a comparison (between groups) of the effect of 10 sessions of combined therapy (TUS+Aussie current) alone versus in combination with HIIT, specifically on abdominal SAT thickness, body composition, metabolic profile, and serum glycerol release.

Secondary Outcomes

Secondary outcomes assess the impact on CAM, sleep quality, anxiety, depression, body image concerns, and blood biochemical variables (Table 2).

Table 2. Primary and secondary outcomes of the study.

Variable	Description
Primary outcomes	
Abdominal subcutaneous adipose tissue (cm)	• Ultrasound imaging [4,24]
Body composition (kg; percentage and grams)	• Dual-energy x-ray absorptiometry [30]
Metabolic profile	• Venous blood collection • Hydrogen nuclear magnetic resonance [34,66]
Secondary outcomes	
Cardiovascular autonomic modulation	• Heart rate and arterial pressure variability [36,38,40,41]
Sleep quality (score)	• Pittsburgh Sleep Quality Index [46,47]
Anxiety, depression, and stress (score)	• Hospital Anxiety and Depression Scale [67] • Depression, Anxiety, and Stress Scale [48]
Body image (score)	• Body Shape Questionnaire [49]
Blood tests	• Complete blood count, glycated hemoglobin, fasting glucose, ultrasensitive C-reactive protein, total cholesterol, high-density lipoprotein, low-density lipoprotein, and triglycerides
Perimetry measurements (cm)	• Waist-to-hip ratio, waist-to-height ratio, neck circumference, and waist circumference

Monitoring Adverse Events

There is a possibility that participants may experience side effects in response to the study protocol. Regarding HIIT, intense shortness of breath, generalized tiredness, and dizziness may occur, and this will be recorded in the study. In addition, as the study involves blood sampling, there is a possibility of damage not directly related to the intervention. The expected adverse effects, such as bruising and local pain, will be monitored. Any adverse effects other than these will be recorded and reported, although such occurrences are considered highly unlikely. During assessments and sessions, participants will also be asked about their well-being and whether they have experienced any changes or symptoms since the start of the study. This information will be documented to ensure the ongoing safety and monitoring of the participants.

Participant safety will be prioritized throughout the study. Initially, general health status will be assessed, including a treadmill stress test supervised by a cardiologist to detect cardiovascular contraindications to high-intensity exercise.

A total of 30 days before starting the intervention (TUS+Aussie current), all participants (all 3 groups) will receive identical printed guidelines containing joint mobility and stretching exercises (ankle, hip, and spine) to be performed 2 to 3 times a week. The aim will be to reduce the problems caused by a sedentary lifestyle in the joints and, thus, reduce the risk of injury during HIIT. As a way of monitoring adherence, all participants will complete a weekly form on how often they stretch.

During the HIIT sessions, HR will be monitored continuously, and perceived exertion will be assessed using the Borg scale. Immediate interruption of the session will be planned if signs of intolerance occur (eg, dizziness, chest pain, and syncope). During the application of TUS+Aussie current, participants' comfort will be monitored using a paresthesia perception scale from 0 to 10, aiming for a level of sensation of approximately 5, with adjustments made whenever necessary. All interventions will strictly follow the safety criteria and contraindications recommended by the equipment manufacturer. In case of adverse events, participants will be clinically assessed and, if necessary, withdrawn from the study to ensure their safety.

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Statistical Analysis

Sample Size

The primary outcome, percentage of body fat, was used to calculate the required sample size using the RStudio software (version 12.1; Posit PBC) assuming a moderate expected effect size of $f \geq 0.15$ and a significance level of 5% and to promote a statistical power of 80%. A total of 18 participants per group is necessary to achieve 80% statistical power with an α level of 5%. Considering a dropout of 10%, the target sample size was increased to 20 participants per group, with the total sample size being 60 individuals. Appropriate statistical corrections (eg, Bonferroni or false discovery rate) will be applied to the *P* values, recognizing the necessity of conducting multiple tests due to the analysis of additional results.

Descriptive Statistics and Baseline Data

A CONSORT (Consolidated Standards of Reporting Trials)-style flowchart [68] will present the number of patients selected and all reasons for exclusion before randomization. Demographic and socioeconomic information, including age, sex, race, socioeconomic status, and educational level, as well as baseline clinical characteristics such as BMI, glycated hemoglobin, smoking status, alcohol consumption, and comorbidities, among other variables, will be described by study arm and overall. Categorical variables will be reported as absolute numbers and percentages. Continuous variables with a reasonably symmetrical distribution will be summarized as means and SDs. For highly skewed continuous variables, medians and IQRs will be used.

Statistical Methods for Primary and Secondary Outcomes

Data analysis will be conducted by a researcher blinded to the participants' allocation to the groups. The data will be entered into a Microsoft Excel spreadsheet for subsequent analysis.

For quantitative variables, the assumption of normality of data distribution and homogeneity of variances will be checked using the Shapiro-Wilk test and Levene test, respectively. To compare participant characteristics at baseline between groups, a 1-way ANOVA or Kruskal-Wallis test will be applied when appropriate. For comparisons between groups involving categorical variables, the chi-square test or Fisher exact test will be used. To compare primary and secondary outcomes between and within groups, linear mixed models estimated using the maximum likelihood method with an appropriate covariance matrix structure will be used assuming group (AG, PG, and HG), moment (before and after the intervention) or time (baseline, after TUS+Aussie current, and after HIIT), and interactions (group-moment, group-time, moment-time, and group-moment-time) as fixed factors and participants as a random factor [66]. In addition, moment and time will be assumed as a repeated-measure effect. The model that fits the data will be the one with the minimum Akaike information criterion. When appropriate, the data may be subjected to a Box-Cox transformation to better adhere to a normal distribution [69,70]. Whenever a significant *F* value is obtained in the ANOVA or linear mixed models, a Sidak post hoc adjustment for the purpose of pairwise multiple comparisons will be applied. The significance level will be set at 5% ($P<.05$). All analyses will be conducted using the PASW Statistics software (version 25.0; SPSS).

Results

The project was registered in the Brazilian Registry of Clinical Trials on February 8, 2023 and updated on December 2, 2024. Currently in the data collection phase. The recruitment and testing phase began in February 2024. Completion of the study is scheduled for the end of September 2025. Data analysis will begin after the last reassessment of this period (September 2025), and the results are expected to be published by 2026.

Discussion

Implications

This is the first study to combine TUS+Aussie current with HIIT, potentially integrating the effects of lipolysis and fat oxidation and possible changes in the serum metabolic profile and CAM. The results could optimize treatment duration, promote changes in lipid profile, and maintain cardiovascular health in people with overweight and obesity. The combined protocol is expected to lead to weight loss in the participants compared to the therapies alone. In addition, it is believed that the population with a higher percentage of fat will benefit more from a reduction in abdominal fat thickness (measured through ultrasound imaging) and body fat mass (measured through DXA) after 10 intervention sessions in the AG. This hypothesis assumes that the combination of TUS+Aussie current will promote lipolysis (breakdown of adipocytes measured through serum glycerol collection) and lymphatic drainage into the bloodstream. In addition, by performing HIIT after applying TUS+Aussie current, serum fatty acids will be β-oxidized during exercise.

Scientific literature lacks studies that evaluate the effects of TUS combined with Aussie current with or without HIIT. A controlled, randomized experimental design will be used that follows the SPIRIT guidelines [23] and describes the parameters used to achieve the best results for the population studied.

To the best of our knowledge [4,9,11,15,18], this study will be the first clinical trial to compare the effects of TUS combined with Aussie current and HIIT in participants with overweight and grade-I or grade-II obesity. The findings will provide evidence regarding the effects or lack thereof of this therapeutic approach. Furthermore, as a randomized clinical trial, it will contribute to systematic reviews, fostering new evidence syntheses and addressing existing knowledge gaps.

Contributions to the Field

This study aims to guide health professionals to design more effective interventions, whether through combined therapy alone or associated with HIIT, for participants with overweight and grade-I or grade-II obesity by determining whether the combination of 2 therapies (TUS+Aussie current and HIIT) is more effective than just one of them in treating or preventing the disease. In addition, the results will contribute to knowledge about a nonpharmacological and noninvasive treatment for obesity and whether the proposed guidelines and interventions

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will be significantly different in the primary results (reduction in abdominal SAT and change in body composition and blood biochemical variables). In fact, if the results show significant differences between the proposed interventions, patients with obesity will benefit from the combination of 2 noninvasive and fast-acting therapies. In addition, previous studies lasting between 3 and 15 weeks were cited in this study. Thus, this pragmatic study will be able to verify the results of 5 weeks of intervention on the results described [22]. This study describes 10 sessions as this is the treatment protocol offered in most aesthetic clinics.

Previous studies have evaluated the isolated effects of TUS or combined therapies on body composition [4,9,11]; however, important methodological differences exist compared to this study. For example, Fonseca et al [4] investigated the effects of ultrasound in women only using a standardized model for demarcating the abdominal area, not considering individual anatomical variations. In addition, the intervention did not include the use of the Aussie current, and a manual massage protocol was applied after the ultrasound. Similarly, Taha et al [9] combined TUS with aerobic exercise in patients with nonalcoholic fatty liver disease; the exercises consisted of standardized walking sessions (30 minutes) controlled using the Borg scale (12-14), and the time of ultrasound application was not individualized based on abdominal area. Canela et al [11] studied the effects of combined ultrasound and Aussie current therapy associated with whole-body vibration; the sample was restricted to women with cellulite in the gluteal region and did not include a placebo group.

Prospects for Future Research

While this study will focus on the impact of combining 2 interventions on participants with overweight and grade-I or grade-II obesity, future research could explore comparisons with other exercise protocols, such as high-intensity resistance exercise, and the broader assessment of quality of life. This is particularly relevant given that different exercise modalities elicit distinct musculoskeletal adaptations, which can lead to varied changes in body composition and quality of life.

Although the sequence of TUS+Aussie current is supported by a physiological rationale (ie, the combination of both electrophysical agents aims to optimize fat breakdown and drainage, whereas the subsequent HIIT intervention facilitates β-oxidation of fat), we recognize that the order of the interventions may also influence the effectiveness of this treatment. Therefore, if the combined protocol proves effective, future studies should explore whether reversing the order (ie, applying HIIT before TUS+Aussie current) could lead to different outcomes.

In addition, future research should consider the type and duration of physical training as the total time required for both the TUS+Aussie current intervention and the exercise component may reduce adherence or discourage participation [71]. The choice of HIIT in this protocol is based on its physiological benefits—specifically, its role in promoting β-oxidation and the metabolic use of released fatty acids—while also aiming to optimize the overall time commitment of the intervention.

Strengths and Weaknesses of This Study

This is a randomized, double-blind, placebo-controlled study designed in accordance with the most rigorous standards for conducting and processing data in clinical trials, ensuring the reliability of the results. It is important to highlight that the intervention period was defined to assess whether the intervention protocol, considering the usual recommendations for exercise and diet, as well as the number of TUS+Aussie current application sessions commonly offered by aesthetic clinics, results in fat reduction for patients with obesity. Thus, this study will provide health care and aesthetic professionals with scientific evidence to understand the mechanisms involved in applying the studied therapies, expected results, and potential systemic impacts. To achieve these objectives, this study includes several outcome measures, including SAT thickness, body composition, metabolic profile, and serum glycerol release, allowing for a comprehensive evaluation of the combined effects of TUS+Aussie current and HIIT. In addition, by incorporating secondary outcomes such as CAM, sleep quality, and perceived stress, this study offers a broader understanding of the physiological and psychological effects of the intervention.

Despite these strengths, this study presents some limitations. The sample size, though adequate for preliminary findings, may not be large enough to detect differences in CAM results. In addition, individual variations in adherence to the HIIT protocol and lifestyle factors such as diet and physical activity outside the study can influence the results. However, it is important to note that strict guidelines are provided to minimize these influences, ensuring greater control over external variables and the reliability of the findings. Furthermore, the study population consists of individuals with overweight and obesity, which may limit the generalizability of the findings to other populations, such as those with severe obesity or metabolic disorders.

In summary, this study will provide a robust framework for evaluating the combined effects of TUS+Aussie current and HIIT on body composition, CAM, and cardiorespiratory and metabolic health. Despite this study's limitations, the findings will contribute valuable insights into noninvasive strategies for obesity management and may support future research and clinical applications.

Acknowledgments

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study. Additional information, including the dataset, statistical code, written consent form, and detailed protocol information, will be made available upon request to the corresponding author following the study's completion. The data will be made available after the study has been published.

Authors' Contributions

ACAM-S and AMC contributed to the acquisition of funding. ACAMS, PR-S, ÉFDS, AC, CD, LF, REL, and AMC helped with conceptualization. ACAM-S, PR-S, ÉFDS, AC, CD, LF, REL, and AMC helped with the methodology. ACAM-S, PR-S, and AMC handled project administration. REL and AMC were responsible for supervision. ACAM-S, PR-S, ÉFDS, AC, and CD contributed to validation. ACAM-S, PR-S, ÉFDS, AC, CD, LF, REL, and AMC helped with the visualization and writing of the original project. ACAM-S, PR-S, ÉFDS, AC, CD, LF, REL, and AMC contributed to revising and editing the text.

Conflicts of Interest

None declared.

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Abbreviations

AG: active therapeutic ultrasound+Aussie current with high-intensity interval training group
AP: arterial pressure
CAM: cardiovascular autonomic modulation
CONSORT: Consolidated Standards of Reporting Trials
DXA: dual-energy x-ray absorptiometry
ECG: electrocardiogram
HG: therapeutic ultrasound+Aussie current–only group
HIIT: high-intensity interval training
HP: heart period
HR: heart rate
LDL: low-density lipoprotein
LF: low frequency
PG: placebo for therapeutic ultrasound+Aussie current with high-intensity interval training group
SAP: systolic arterial pressure
SAT: subcutaneous adipose tissue

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SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TUS: therapeutic ultrasound
UFSCar: Federal University of São Carlos

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Protocol

The Effect of Maternal Choline Intake on Offspring Cognition in Adolescence: Protocol for a 14-year Follow-Up of a Randomized Controlled Feeding Trial

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Abstract

Background: Choline is an essential micronutrient crucial for fetal neurodevelopment. Numerous rodent studies reveal that compared to maternal consumption of standard chow, maternal prenatal choline deficiency produces lifelong offspring cognitive deficits, and maternal choline supplementation produces lifelong improvements in offspring cognition. Few studies have evaluated this question in humans, with mixed results. Nonetheless, the available data raise concerns about the low choline intakes of pregnant women and highlight the need for knowledge of the functional consequences of various choline intakes during pregnancy.

Objective: This study will evaluate the cognitive and affective functioning of adolescents born to women who participated in a randomized controlled trial (RCT) of 2 levels of choline intake during pregnancy, with the primary aim of assessing offspring attention and spatial memory.

Methods: In a double-blind, randomized controlled choline feeding trial 26 women beginning their third trimester of pregnancy were randomly assigned to 2 groups: daily choline consumption at 480 or 930 mg/day. In this 14-year follow-up, the offspring (n=21) of these women will complete cognitive tests proctored over videoconferencing software. Cognitive function domains will be assessed using web-based software from the Cambridge Neuropsychological Test Automated Battery (CANTAB Connect). We will also assess facets of mental health using the Achenbach System of Empirically Based Assessment (ASEBA). These assessments will test the hypothesis that third-trimester maternal choline intake exerts lasting effects on offspring attention, memory, executive function, and mental health.

Results: Between January 2009 and October 2010, 26 women beginning their third trimester of pregnancy from the Ithaca area were enrolled in the original controlled feeding study. We successfully re-recruited 21 (80%) of the original 26 offspring to this 14-year remote follow-up study. Recruitment started in August 2023 and was concluded in October 2023. Analysis is ongoing, and the first results are expected to be submitted for publication in the fall of 2025. We hypothesize that adolescent offspring born to women in the 930 mg/day group will perform better in domains of attention, memory, executive function, and mental health than offspring of women in the 480 mg/day group. This study is unique because the total maternal choline intake is precisely known, and the offspring are followed into adolescence, a time when group differences are indicative of lifelong effects of prenatal intervention.

Conclusions: The findings will provide important new information concerning the lasting functional consequences of maternal choline intake during pregnancy for offspring neurobehavioral health, thereby informing dietary recommendations and supplementation policies for pregnant women.

Trial Registration: ClinicalTrials.gov: NCT05859126; https://clinicaltrials.gov/study/NCT05859126

International Registered Report Identifier (IRRID): DERR1-10.2196/73508

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KEYWORDS

choline; pregnancy; adolescent; nutrition; cognition; mental health; supplement; virtual testing

Introduction

Choline is an essential micronutrient that is critical for fetal neurodevelopment [1]. Extensive rodent research has consistently demonstrated the importance of maternal choline intake for offspring neurodevelopment, cognition, and brain health into old age [1-5]. Specifically, maternal choline deficiency in rodents produces lasting offspring cognitive deficits [2-4]. Conversely, increasing the mother's choline intake to approximately 4.5 times the amount contained in standard rodent chow improves offspring memory and attention [3-6]. In addition, increased maternal choline intake offers protection against a variety of neurotoxic agents (eg, alcohol, manganese), as well as against neurological disorders (eg, Alzheimer's disease, Down syndrome, autism) [2,3,7-14]. Preliminary evidence in rodents also suggests that maternal choline intake may play a role in the offspring's vulnerability to stress, anxiety, and depression [15,16].

In contrast to the robust literature in rodents, relatively few studies have assessed the impact of varied maternal choline intakes on offspring cognition in humans. The available observational and experimental studies are discussed next.

Most of the human studies evaluating the impact of maternal choline intake on offspring cognition have been observational. Significant associations have been reported between low maternal choline intake or plasma choline and poorer offspring cognition in 3 such studies [17-19], but 2 similar studies have found no such association [11,20]. Additionally, 3 studies have pointed to a potential neuroprotective effect of higher maternal plasma choline against common early insults, including viral infections and cannabis exposure [21-23]. One factor that may have contributed to these mixed results is that these studies have necessarily relied on either self-reported dietary intake or blood biomarkers of choline status, both of which are imprecise, potentially leading to exposure misclassification. Importantly, too, all these observational studies were limited by the possibility of uncontrolled confounding, which hinders the ability to infer causation.

Many of the limitations of these observational studies can be overcome with a randomized controlled trial (RCT) design. However, few human studies have experimentally manipulated maternal choline intake during pregnancy and assessed offspring cognition [24-26]. One such study evaluated the effect of providing pregnant women with either 900 mg/day of a choline supplement or a placebo from week 17 of gestation through birth and found a beneficial effect of the choline supplement on 5-month-old infants' auditory attentional gating [17]. Later, when these same offspring reached 40 months of age, a parental report instrument indicated that the offspring of mothers in the supplement group had fewer attentional problems and fewer withdrawn behaviors than those born to women in the placebo group [26]. However, the study did not include direct behavioral measures of offspring cognition or behavior. A second study randomized pregnant women to receive either 750 mg/day of choline supplement or a placebo from 18 weeks of gestation through 90 days postpartum and found no significant group differences in infants' short-term visuospatial memory or long-term episodic memory at either 10 or 12 months of age [24]. In both studies, there were methodological concerns, including post hoc alterations to planned analyses and uncertain adherence to the assigned choline or placebo dosing regimen [24,26].

The third experimental study evaluating the effect of maternal choline intake on offspring cognition was conducted in our lab. This study was a double-blind, randomized controlled choline feeding trial, in which the total maternal choline intake was controlled at 1 of 2 levels (480 vs 930 mg/day of choline) throughout the third trimester of pregnancy (NCT01127022) [25,27]. Cognitive testing at 4 time points during the first year of life revealed a beneficial effect of the higher maternal choline intake on offspring information processing speed [16]. Subsequent testing of these same children at the age of 7 years revealed the long-term benefits of the higher maternal choline intake on offspring attention, working memory, and executive functioning [25,28].

Notably, no RCTs have evaluated the effects of choline intake during pregnancy on offspring cognition during adolescence, a life stage when cognitive performance can better indicate the enduring effects of maternal choline intake [25,29]. To fill this knowledge gap, we designed this study to assess cognitive functioning and mental health in the 14-year-old offspring of women who participated in the randomized controlled feeding trial mentioned earlier. In this follow-up study, we will assess cognitive functioning using tests of attention, memory, and executive functioning, domains of cognition shown to be affected by maternal choline intake in animal studies [2-5]. In addition, we will assess multiple aspects of adolescent behavior and mental health using a standardized self-report questionnaire designed for adolescents [2-5].

Findings from this study will provide important information about the long-lasting functional consequences of maternal prenatal choline intake on offspring cognition. Choline is not currently included in standard prenatal vitamin regimens, and little is known about the sequelae of the generally low choline intakes seen in women of reproductive age, 90% of whom consume less than the current adequate intake (AI) level [30]. As such, this work may have important implications for perinatal care and may help elucidate the importance of maternal choline intake for enduring offspring health.

Methods

Study Design

The original study was a double-blind, randomized controlled choline feeding study. Pregnant women entering their third

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trimester (N=26) were randomly assigned to consume either 480 mg choline/day (roughly the AI level) or 930 mg choline/day (roughly double the AI level) [27]. All participants consumed the same study-provided, standardized diet containing 380 mg/day of choline. In addition to the standardized diet, participants received a daily choline chloride supplement of either 100 mg or 550 mg, mixed in a cranberry-grape drink, which brought their total daily choline intakes to either 480 or 930 mg/day. On weekdays, participants consumed at least 1 of their meals and the choline drink under researcher supervision [27]. Participants received all other meals and their weekend daily supplements in take-out containers for consumption at home [27]. The study was registered with ClinicalTrials.gov (NCT05859126).

Recruitment

Between January 2009 and October 2010, 26 women beginning their third trimester of pregnancy from the Ithaca (New York, USA) area enrolled in the original randomized controlled choline feeding study [25]. At enrollment, the mothers had an average age of 29 years, and their self-reported ethnicities reflected the racial and ethnic distribution of the Ithaca region [25].

For this follow-up study, our population included the 14-year-old offspring who were born to the women from our randomized controlled choline feeding study. To recruit, we first contacted participants via their last known email in our participant database. If no email was available, we used their last known phone number. If no contact information was available or if the email/phone number was no longer in use, we used web searches to find updated contact information. If participants were nonresponsive after 2 emails or 3 phone calls, we considered them lost to follow-up and noted them as such in the participant-tracking log.

Inclusion in this follow-up study required the adolescents to be proficient in English (B2 level equivalent) and to be 14 years old during the testing period. We excluded participants if they had developed a new auditory or visual disability since the last testing period at the age of 7 years or if they were unable to access the internet during the testing period.

Of the original 26 participants, we successfully enrolled 21 (80%) offspring who reside in the United States, China, Scotland, and India for the 14-year remote follow-up study. Recruitment started in August 2023 and was concluded in October 2023.

Cognitive Assessments and Hypothesized Effects

We will conduct remote cognitive and mental health assessments of the teenage offspring to assess the long-term impacts of maternal prenatal choline intake. Remote assessment will allow us to maximize participant retention, as many of our original participants no longer reside in the Ithaca area. We will evaluate adolescent cognition, with the primary aim of assessing attention and spatial memory and the secondary aim of assessing nonspatial memory and executive function, using web-based software from the Cambridge Neuropsychological Test Automated Battery (CANTAB Connect). We will also assess adolescent mental health as an exploratory aim using the Achenbach System of Empirically Based Assessment (ASEBA) online platform to administer the Youth Self Report (YSR) questionnaire [31].

Next, we describe the tasks and primary outcomes pertaining to each assessment domain (attention, memory, executive function, mental health), together with the hypothesized results stated as a comparison of the 930 mg/day group in relation to the 480 mg/day group.

Attention

We will assess the domain of attention using the CANTAB sustained attention task Rapid Visual Information Processing (RVP). In RVP, a series of individual digits from 2 to 9 are briefly displayed in a white box at the center of the tablet screen. The digits appear at a rate of 100 digits/minute for 7 minutes. The participant must identify every instance when a given target sequence of 3 digits (eg, 3-2-5) appears in the stream of numbers by pressing a central button as quickly as possible. Superior attention is indicated by the ability to correctly identify target sequences, while avoiding false alarms (ie, responses to nontarget sequences), as summarized by the signal detection parameter A-Prime [32]. We hypothesize that participants from the 930 mg/day group will have greater A-Prime scores. The A-Prime score measures the subject's sensitivity for detecting the 3-number target sequence, corrected for biased responding. The expected range of A-Prime scores is 0.00-1.00, with 1.00 indicative of excellent sustained attention (a participant who identifies every target sequence throughout the 7-minute test without committing any false alarms).

Memory

We will use 4 CANTAB tasks to assess visual and spatial short- and long-term memory:

- The CANTAB Paired Associates Learning (PAL) task assesses visual and spatial short-term memory by requiring the participant to remember the location in which they had previously seen a specific pattern appear. For this task, 12 boxes are displayed around the perimeter of the screen. In a pseudorandom order, each box opens briefly to reveal it contains either a unique pattern or nothing. The number of patterns hidden on a given trial increases from 2 to 4, 6, 8, and then 12. Memory is tested in each trial by displaying each previously seen pattern in the center of the screen and then asking the participant to select the box location where that pattern was originally located. The number of selection errors is recorded. Here, we hypothesize that participants from the 930 mg/day group will have superior visual and spatial short-term memory, as indicated by fewer errors made when selecting the location of the box where the pattern had originally been located.
- The Delayed Matching to Sample (DMS) task assesses visual matching ability and short-term visual memory for nonverbalizable patterns. Trials of DMS begin by displaying a single target pattern, followed by 4 similar patterns in a row below the single pattern, 1 of which matches the target pattern. For trials testing simultaneous visual matching ability, the target pattern remains visible while the participant seeks the matching pattern from among the set of 4. For trials testing visual memory, the target pattern

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disappears, and then the 4 choice patterns are displayed after a delay of 0, 4, or 12 seconds. The number of correct matches is recorded for each trial type. We hypothesize that participants from the 930 mg/day group will have superior short-term visual memory, as indicated by a greater proportion of correct matches after a delay.

- The Spatial Span (SSP) task measures short-term spatial memory capacity. Each SSP trial begins with 9 boxes displayed on the screen. A subset of squares briefly change color in a pseudorandom sequence, and the participant must then touch the boxes that changed color in the same order in which they were displayed. The sequence of boxes that change color increases from 2 to a maximum of 9, with participants allowed 3 attempts to correctly reproduce a sequence at each level. The primary endpoint is the longest sequence of boxes touched in the correct order on at least 1 trial (referred to as span length). We hypothesize that participants from the 930 mg/day group will have a greater span length, indicating superior short-term spatial memory.
- The Pattern Recognition Memory (PRM) task assesses short- and long-term memory for visual patterns. The task displays a series of visual patterns, one at a time for 2 seconds each, in the center of the screen. This is followed by forced-choice memory test trials in which the participant must discriminate the previously displayed pattern from a similar but novel pattern. For the test of short-term memory, the test trials begin immediately after the patterns are displayed. For the test of long-term memory, the test trials occur following a 20-minute, distraction-filled delay. We hypothesize that participants from the 930 mg/day group will have superior long-term visual recognition memory, as indicated by a greater proportion of correctly recognized patterns after the 20-minute delay.

Executive Function

To assess our third aim of evaluating group differences in executive functioning, we will focus on the component processes of planning, working memory, inhibitory control, and attentional flexibility. These functions will be assessed using 4 CANTAB tasks:

- The Stockings of Cambridge (SOC) test assesses the planning area of executive functioning. In the task, there are 2 displays, one at the top and the other at the bottom of the screen. Each display shows 3 stockings filled with differently colored balls. The balls are arranged in different patterns in each display, and the participant must move the balls in the bottom display to match the pattern shown in the top display. The balls can only be moved one at a time, and the participants are instructed to try and solve the task using the minimum number of moves (referred to as a perfect solution). We hypothesize that the 930 mg/day group will exhibit superior planning ability, as indicated by a greater number of perfect solutions.
- The Spatial Working Memory (SWM) test assesses the working memory component of executive functioning. Colored boxes are depicted across the screen. By selecting boxes and using a process of elimination, the participant must find a yellow token hidden within a box. One token is hidden at a time, and a token is not hidden in the same box twice. We hypothesize that the 930 mg/day group will commit fewer total errors in the SWM test, indicative of superior working memory.
- The Cambridge Gambling Task (CGT) assesses risk-taking behavior, which provides an index of inhibitory control. The task displays a row of boxes at the top of the screen; some boxes are red, and others are blue. The ratio of red and blue boxes varies, but 1 box always contains a hidden token. The participant must click “Red” or “Blue” to choose the box color where they think the token is hidden. Next, they must decide how much they want to bet on their decision. The participant gains or loses bet points, depending on the correctness of their decision, given the token location. We hypothesize that the 930 mg/day group will attain a smaller delay aversion score, indicative of better impulse control.
- The Intra-Extra Dimensional Set Shift (IED) task assesses rule acquisition and reversal. In this task, colored shapes and white lines appear on the screen. These act as 2 sources of stimuli, simple and complex. The participant is presented with the simple and complex stimuli in pairs, and they must determine a preset matching rule and select the correct pair. The participant uses feedback to select the correct stimulus from the sets of pairs. The stimulus changes after 6 correct responses. We hypothesize that the 930 mg/day group will exhibit greater attentional flexibility, as indicated by few errors being committed.

Exploratory Aim: Mental Health

We will assess our mental health exploratory objective with the ASEBA YSR questionnaire.

The YSR questionnaire for adolescents aged 11-18 years assesses emotional and behavioral patterns. The participant reads 112 statements that describe children in their age group and rates how much each statement feels true for them on a 3-point Likert scale (Not True, Somewhat or Sometimes True, Very True or Often True). We hypothesize that the 930 mg/day group will have smaller raw scores of self-reported mental health problems on the ASEBA YSR questionnaire, including smaller scores on a scale of internalizing behaviors (comprising Anxious/Depressed, Withdrawn/Depressed, and Somatic Complaints) and smaller scores on a scale of externalizing behaviors (comprising Rule-Breaking Behavior and Aggressive Behavior).

Protocol Aim

This protocol aims to provide standardized instructions for administration of both CANTAB and ASEBA instruments in a virtually proctored testing environment to increase the feasibility of obtaining precise and valid measurements of adolescent cognition and mental health through remote testing.

Testing Environment and Equipment Setup

During the informed consent call, each adolescent and their parent worked with the study team to identify a suitable distraction-free environment for testing. This process included identification of a quiet room and a clutter-free desk or table at which the adolescent could complete testing. Additionally, the study team worked with the adolescent and their parent to

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determine the ideal time of day to complete testing so that the participants could be at their optimal performance. The time of day was the same across all testing days for each participant but varied between participants according to their schedule and preferences.

After the informed consent call but before the first day of testing, we sent the study participants the necessary materials, including a study-standardized tablet, a tablet case, and noise-canceling headphones. Providing standardized study materials to all participants intends to prevent variation in test delivery that could arise from device hardware or software differences.

Before commencing each day of testing, the study proctor verifies that the participant's cell phone is silenced and stored out of sight. Next, the proctor ensures the participant is in their prespecified location, wearing study-provided noise-canceling headphones and using the study-provided tablet.

Testing Procedures

Participants complete testing over 3 days within a 1-week window, as depicted in Table 1. All testing sessions are proctored by study coordinators over videoconferencing software. The study coordinators are blinded to the participants' original group allocation.

When a participant joins the secure videoconferencing call, the study proctor guides the participant to use the tablet camera to confirm that the participant is in the prespecified quiet testing space. After the proctor approves the testing environment, the participant returns to their seat and shares their screen for test proctoring. If testing space modifications are necessary, the proctor directs the participant to remove distractions or relocate.

Before testing begins, the participants are given an opt-out option so that if they feel unprepared to do their best, the study team can reschedule the session.

Table 1. Adolescent participants' schedule.

Study activity	Duration (minutes)
Day 1	
SOC[a] (CANTAB[b])	10
YSR[c] questionnaire (ASEBA[d])	20
IED[e] (CANTAB)	7
Day 2	
PAL[f] (CANTAB)	8
CGT[g] (CANTAB)	15
DMS[h] (CANTAB)	7
RVP[i] (CANTAB)	7
Day 3	
SSP[j] (CANTAB)	5
SWM[k] (CANTAB)	5
PRM[l] (CANTAB)	25

[a]SOC: Stockings of Cambridge.
[b]CANTAB: Cambridge Neuropsychological Test Automated Battery.
[c]YSR: Youth Self Report.
[d]ASEBA: Achenbach System of Empirically Based Assessment.
[e]IED: Intra-Extra Dimensional Set Shift.
[f]PAL: Paired Associates Learning.
[g]CGT: Cambridge Gambling Task.
[h]DMS: Delayed Matching to Sample.
[i]RVP: Rapid Visual Information processing.
[j]SSP: Spatial Span.
[k]SWM: Spatial Working Memory.
[l]PRM: Pattern Recognition Memory.

Day 1 Study Activity

The day 1 protocol includes testing with CANTAB and ASEBA instruments and requires approximately 37 minutes to complete. The participant receives an email from the proctor that includes links to their CANTAB and ASEBA tests. After assessment of the participant's testing environment, the proctor instructs the participant to access the specified links. Both testing platforms provide simple onscreen and verbal instructions for each task, and the proctor can verbally clarify any potential participant

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questions. The participant completes testing in the following order: SOC, YSR, and IED. The proctor offers an optional 3-minute break after the YSR. At the end of day 1 testing, the proctor concludes the session with a reminder to the participant not to open the next CANTAB test link until the following testing session.

Day 2 Study Activity

The proctor starts day 2 testing with a reassessment of the participant's testing environment and verbal directions to access the CANTAB test. The testing for day 2 takes approximately 37 minutes to complete and only includes tests from CANTAB software. The participant completes the testing in the following order: PAL, CGT, DMS, and RVP. The proctor offers an optional 3-minute break after the CGT.

Day 3 Study Activity

The testing on day 3 takes approximately 35 minutes to complete and consists only of tests from CANTAB software. The participant completes the testing in the following order: SSP, SWM, and PRM. A required break of 20 minutes occurs in the middle of PRM test administration. At this time, the participant can drink water, use the bathroom, or stretch.

Technical Support

In the event participants have internet connectivity issues during the testing session, the proctor works with the participants over email to find an alternate location suitable for internet connectivity. The session is rescheduled, if necessary. If CANTAB technical difficulties occur, the proctor works with CANTAB support to quickly resolve the problem, and the entire testing session is rescheduled to a later date.

Data Analysis Plan

Sample Size

The original randomized controlled choline feeding study was designed to detect group differences in plasma choline levels. We estimated that a sample size of 26 (n=13, 50%, per treatment group) would achieve 80% power to detect a moderate effect size at α=.05 [27].

Our previous ancillary follow-up studies of offspring cognition, conducted during infancy and at the age of 7 years, demonstrated that (1) a sample size of 24 (n=12, 50%, per group) was sufficient to detect a statistically significant effect of the 930 mg/day prenatal choline intervention on infant processing speed and (2) a sample size of 20 (n=11, 55%, and n= 9, 45%, participants from the 930 and 480 mg/day groups, respectively) was sufficient to obtain statistically significant group differences on several cognitive outcomes at the age of 7 years [25,28].

Additionally, we conducted a post hoc sample size calculation based on our primary outcome of attention. Using the prior literature, we estimated an effect size of 0.07 for the RVP A-Prime variable, with SD=0.8 [33]. Using the equation $N=2(z_{1-\alpha 2} + z_{1-\beta}/\delta)^2 \times s^2$ with 80% power and α=.05, we would need roughly 10 participants per group.

Descriptive Statistics for Sample Characteristics

We will present descriptive statistics of each group's characteristics in tables that will include the participants' sex, level of education, parental level of education, native language, family income, head injury absence/presence, and any current medications and supplements. We will summarize continuous variables with means (SDs) and categorical variables with absolute counts and relative frequencies. We will also provide a flowchart detailing participant attrition and missing data.

Inferential Statistical Analysis

Acknowledging the risks inherent in using multiple endpoints in a small sample, we created an a priori analysis plan with prespecified primary, secondary, and exploratory aims. Our specific aims will focus on areas of cognitive functioning shown to be affected by maternal choline intake in prior animal and human studies. Next, we detail which variables we will use to assess each aim. For every outcome measure of interest, we will use linear models with a main effect of group and sex.

Primary Objective: Attention and Spatial Memory

To assess sustained attention, we will use the CANTAB RVP, with a primary outcome measure of A-Prime, a signal detection measure of a subject's sensitivity to the target sequence (string of 3 numbers) regardless of response tendency (the expected range is from 0.00 to 1.00 for bad to good). To assess spatial memory, we will use the CANTAB SSP and the CANTAB PAL, with outcome measures of forward span length and total errors.

Secondary Objective: Nonspatial Memory and Executive Functioning

Nonspatial memory will be assessed with the CANTAB DMS and the CANTAB PRM. The key outcome for both tasks will be the proportion of correct choices on delay trials. We will assess executive functioning with the CANTAB SOC and the CANTAB SWM, where the key outcome variable will be the number of perfect solutions across all problems for the SOC and total errors for the SWM. Inhibitory control will be assessed using the CANTAB CGT. The key outcome variable will be the delay aversion total score.

Exploratory Objective: Psychological Health

We will use the ASEBA YSR scores that align with the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-V). We will compare depressive problems scores, anxiety scores, and attention scores between the 2 groups.

Sensitivity Analyses

Additionally, we will conduct sensitivity analyses based on known predictors of our primary outcomes. This will involve incorporating socioeconomic status proxies to our models to assess the degree to which the covariate shifts our beta coefficients of our primary predictor. Specifically, we will use a binary variable of whether each participant's household income is above or below the cost of living for the area. We will conduct similar sensitivity analyses including the participant's current choline intake, use of attention medications, grade in school, primary language, and maternal educational attainment.

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Ethical Considerations

Ethical approval for the follow-up study was obtained from the Institutional Review Board for Human Participants at Cornell University in Ithaca (review number: IRB0147236). Written parental consent and written child assent from all participants and their parents were obtained by study coordinators during the informed consent call before commencing any study activity.

Monitoring and Data Management

We will store all identifiable data on password-protected servers and computers in locked offices. We will not disclose participants' identities to anyone outside of the research team. Within the study team, we will share any identifiable data via a password-protected research server. We will assign participants numeric identifiers and will complete all data analysis with the participant number identifiers and not with any personally identifying information.

Safety Considerations

There are no direct significant risks associated with participation in this study. However, due to the sensitive nature of the YSR questions, we have created a safety plan. If a participant endorses a "yes" on any of the YSR critical questions, disclosing behavior or thoughts that raise concerns about their immediate safety or well-being, we will contact the parents of the participant through a secure, password-protected communication platform.

Results

We successfully recruited 21 (80%) of the original 26 participants in the 14-year remote follow-up study. Recruitment started in August 2023 and was concluded in October 2023. This project was funded in January 2024. Data collection was performed from August 2023 to October 2024. Data analysis is currently ongoing, and the first results are expected to be submitted for publication in the fall of 2025.

Next, we detail the adolescent and maternal characteristics at the 14-year follow-up (Tables 2 and 3). Despite being recruited from a specific geographic region, the original study sample included participants from different parts of the world with relatively diverse socioeconomic statuses and racial and ethnic identities.

Table 2. Adolescent characteristics (N=21).

Characteristics	480 mg/day group (n=11)	930 mg/day group (n=10)
Sex, n (%)		
Males	8 (73)	7 (70)
Age at first testing (years), mean (SD)	14.3 (0.13)	14.3 (0.11)
English not the primary language, n (%)	0	2 (20)
Grade level at first testing, n (%)		
8th grade	3 (27)	3 (30)
9th grade	8 (73)	7 (70)
Race/ethnicity, n (%)		
White	8 (73)	6 (60)
Latino/Latina	2 (18)	1 (10)
Asian	1 (9)	3 (30)

Table 3. Maternal characteristics (N=21).

Characteristic	480 mg/day group (n=11)	930 mg/day group (n=10)
Annual family income >75,000/year, n (%)	10 (91)	7 (70)
Education at enrollment (bachelor's degree or higher), n (%)	11 (100)	7 (70)
Age at enrollment (years), mean (SD)	28.8 (2.7)	28.7 (3.6)

Discussion

Summary

This study is the first long-term follow-up of an RCT that assesses the enduring impact of prenatal choline intake on child cognition and mental health under conditions in which maternal choline intake is precisely known. The previous assessments of this cohort during infancy and at the age of 7 years revealed significant differences between the 2 groups in areas of information processing speed, working memory, and sustained attention [25,28]. This study will follow these same children into adolescence, an age when group differences in cognition may be more indicative of lifelong effects of the early choline intervention [25,29]. If our results support our hypotheses—that the higher-choline-intake group performs better than the lower-choline-intake group—they would provide the clearest evidence to date that low choline intake by most pregnant women places their children at risk of subtle impairments in cognitive functioning.

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Demonstrating that maternal choline intake has lasting effects on offspring cognition in humans, as it does in animals, would suggest that the many other long-lasting benefits of maternal choline supplementation reported in animals may also apply to humans. Specifically, in animals, maternal choline supplementation offers protection from some of the deleterious effects of perinatal exposure to neurotoxicants (eg, alcohol, manganese) and lessens cognitive dysfunction in diverse neuropathological conditions, including aging, Down syndrome, autism, and Alzheimer's disease [2,3,8]. Although the neuroprotective effect of maternal choline supplementation has received little attention in human studies, a few studies have evaluated this hypothesis in prenatal alcohol exposure, with promising results [11,34]. If the results of our follow-up study indicate that the animal data translate to humans concerning lasting offspring cognitive effects, they open up the exciting possibility that efforts to increase choline intake during pregnancy may not only improve cognitive functioning throughout the lifespan but also lessen the risk of cognitive impairments due to diverse environmental and genetic cognitive disorders [2,3,8].

Lastly, the use of standardized virtual cognitive testing offers an experimental technique that may be beneficial to many research areas. Particularly in the case of long-term cohort follow-up, such as this study, wherein the participants may no longer reside near the research institution, it can be costly for participants to return. Thus, standardizing procedures for valid and reliable remote cognitive testing can be extremely valuable [35]. However, in such studies, it is critical that the testing be closely proctored to avoid or minimize the possibility of inaccurate data due to the participants misunderstanding the instructions, losing focus in the tasks, or experiencing some other type of disruption in the testing. Standardized and proctored testing procedures ensure that the testing environment is conducive to acquiring high-quality data. The protocol developed for this study establishes these procedures, ensures interproctor reliability in our study, and creates a precedent for use by future scientists interested in virtual cognitive testing. The ability to collect data in a virtual setting affords an opportunity to reach study populations that are distant from the research institution, potentially increasing the generalizability of study findings through the inclusion of more diverse participants [36].

Conclusion

This study aims to determine the long-term impacts of prenatal choline intake on adolescent offspring's cognitive functioning and mental health. Leveraging a rigorous double-blind, randomized controlled choline feeding trial that achieved precise control over the participants' total daily choline intakes, we have a unique opportunity to assess the long-term effects of prenatal choline supplementation. Our findings may offer pivotal insights into the developmental trajectories associated with prenatal choline intake, potentially influencing dietary recommendations and prenatal care practices. Furthermore, the virtual testing framework in this study ensures the feasibility and reliability of long-term cognitive assessments and sets a precedent for future research methodologies, increasing accessibility and participation in cognitive studies. Ultimately, this research may underscore the importance of prenatal choline intake for lifelong cognitive and mental health outcomes in offspring.

Acknowledgments

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Authors' Contributions

Study conceptualization, funding acquisition, supervision, and writing—review and editing were handled by BJS, RLC, and EAL; formal analysis by EAL; and writing by SAR, AEL, and EAL.

Conflicts of Interest

RLC serves as a consultant for Balchem Corporation, although the study and its funding predate this arrangement. Balchem Corporation played no role in the study design, interpretation of data, or writing of the manuscript. No other authors have competing interests.

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Abbreviations

AI: adequate intake
ASEBA: Achenbach System of Empirically Based Assessment
CANTAB: Cambridge Neuropsychological Test Automated Battery
CGT: Cambridge Gambling Task
DMS: Delayed Matching to Sample
IED: Intra-Extra Dimensional Set Shift
PAL: Paired Associates Learning
PRM: Pattern Recognition Memory
RCT: randomized controlled trial
RVP: Rapid Visual Information processing
SOC: Stockings of Cambridge
SSP: Spatial Span
SWM: Spatial Working Memory
YSR: Youth Self Report

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Protocol

Kissing as a Protective Factor Against Decreased Salivary pH: Protocol for a Randomized Clinical Trial

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Abstract

Background: Kissing is a common social behavior that may influence physiological responses and impact oral health. Prior research has shown that affectionate behaviors like kissing can reduce stress and improve relationship satisfaction. However, the effects of kissing on salivary pH, particularly after consuming sugary or fermented beverages, have not been thoroughly investigated.

Objective: This study aims to determine whether kissing accelerates salivary pH recovery following the consumption of sugary or fermented beverages.

Methods: A randomized controlled trial will be conducted with 60 couples aged 18-30 years. Participants will be divided into 3 groups: a control group (no kissing), an experimental group where one partner consumes a beverage, and another experimental group where both partners consume a beverage. The study will measure salivary pH at baseline, after beverage consumption, and following a 40-second kiss or control period, with measurements taken every 5 minutes until the pH returns to neutral levels. The data will be analyzed using SPSS software (IBM Corporation). ANOVA will be used to compare salivary pH recovery between groups, and if assumptions of normality or sphericity are not met, alternative models such as generalized linear models or nonparametric tests will be considered.

Results: The study is ongoing, with participant recruitment already initiated and preliminary data collection in progress. The study was funded by the Catholic University of Santiago de Guayaquil from June 2024 to June 2025. Ethics approval was obtained in June 2023. The results are expected to be published in the last quarter of 2025.

Conclusions: This study will provide insights into the relationship between kissing, salivary pH, and oral health, potentially offering new strategies for the prevention of dental caries. The results may challenge existing assumptions about the role of kissing in oral health.

Trial Registration: ClinicalTrials.gov NCT06501729; https://clinicaltrials.gov/study/NCT06501729

International Registered Report Identifier (IRRID): DERR1-10.2196/65253

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KEYWORDS

Saliva; oral health; sugar-sweetened beverages; dental caries prevention; kissing; protective; social behavior; stress; relationship; pH; fermented drinks; randomized controlled trial

Introduction

Dental caries remains one of the most prevalent chronic diseases worldwide, particularly among adolescents and young adults [1]. One key factor contributing to its development is the frequent consumption of sugar-sweetened and fermented beverages, which can significantly lower salivary pH and compromise the protective capacity of saliva [2,3]. The acidic

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environment created by these beverages facilitates enamel demineralization and disrupts oral microbiome balance, increasing susceptibility to caries.

Studies have shown that after consuming cariogenic food or drink, the salivary pH decreases significantly within the first 5 minutes and may take up to 60 minutes to return to baseline levels. Another study indicates that the intraoral pH drops after drinking acidic beverages and that it takes approximately 20-30 minutes for the saliva to neutralize any residual acid [4], [5]. These findings highlight the prolonged acidic exposure that the enamel undergoes following the intake of such beverages, emphasizing the importance of strategies to expedite pH normalization [6].

The pH of body fluids is a measure of the hydrogen ion concentration within them, reflecting their acidity or alkalinity. The normal pH range for extracellular fluid (ECF) is tightly regulated between 7.35 and 7.45. The pH of intracellular fluid is slightly lower, ranging from 7.1 to 7.2. It is essential to maintain these pH levels within narrow limits to ensure proper enzymatic and metabolic processes [7]. Interestingly, despite the vast difference in concentration between hydrogen ions and other ions, such as sodium ions, the body's regulatory mechanisms are adept at maintaining the pH within the necessary range for life, which is between 6.8 and 7.8 in the ECF. Any deviation from the normal pH range can lead to significant physiological disturbances because pH influences the structure and function of proteins and affects various physiological processes. In summary, the pH of body fluids is a critical physiological parameter that must be maintained within a narrow range. The body uses various mechanisms to regulate this balance, ensuring optimal functioning of cellular and systemic processes [8].

Several studies have demonstrated that common beverages, such as carbonated soft drinks, fruit-based juices, and coffee, cause an immediate and notable drop in salivary pH after ingestion. For instance, the salivary pH dropped from a baseline of 7.18 to 5.65 immediately after consuming a cola-based soft drink, and from 7.05 to 6.08 following the intake of a mango-flavored juice, both requiring up to 15 minutes to return to baseline values. Coffee, although less acidic than sodas, also reduced salivary pH from 7.05 to 6.10. These changes, even if transient, can become harmful when acidic drinks are consumed repeatedly throughout the day [9].

Milk-based beverages, even when sweetened, tend to produce only minimal changes in salivary pH. A study reported a slight decrease from 7.07 to 6.71 after ingestion, with near-immediate normalization [10]. These findings emphasize the importance of beverage selection in maintaining oral pH stability.

The methodology used to assess these changes typically involves pH meters with digital glass electrodes, which allow precise and repeatable measurements. Several studies evaluating the effect of acidic drinks on saliva have used this approach to monitor real-time fluctuations in pH across multiple time points [11]. In this context, the ability of saliva to restore pH levels after an acidic challenge is essential for maintaining enamel integrity. Although artificial methods, such as chewing sugar-free gum or using alkaline rinses, have been proposed to accelerate salivary recovery, little attention has been given to natural behaviors that may play a similar role. One such behavior is kissing. During a French kiss, a substantial volume of saliva is exchanged between partners, and it is plausible that this could introduce buffering agents and bacteria from one individual to another, potentially supporting faster pH normalization.

While the physiological benefits of kissing—such as reduced cortisol levels, improved mood, and lowered blood pressure—have been well documented [12,13], no studies to date have explored whether kissing may contribute to the recovery of salivary pH following acidic challenges. This represents a novel and unexplored area of research within oral health and preventive dentistry.

Given that kissing involves significant salivary exchange, it is hypothesized that this behavior may introduce buffering agents from one individual's saliva to another, potentially accelerating the neutralization of oral acidity following the consumption of acidic beverages. To test this hypothesis, we designed a randomized controlled trial with three conditions: a control group (no kissing), an experimental group where only one person drinks and then kisses, and another group where both individuals drink and then kiss. Additionally, three types of acidic beverages commonly consumed in the local context, Coca-Cola, Cifrut, and nonalcoholic beer will be used to assess whether the effect of kissing on salivary pH recovery is consistent across different sources of oral acidification. This design allows for both behavioral and beverage-specific comparisons to better understand the potential protective role of kissing. The objective of this study is to determine whether the act of kissing facilitates a faster recovery of salivary pH compared to the natural physiological restoration process following the intake of acidic beverages.

Methods

Ethical Considerations

A trained member of the research team will clearly and concisely explain the study's objectives, procedures, potential risks, and benefits to the participants. Each participant will receive a copy of the informed consent form, which has been approved by the Council on Ethics in Human Research from the Instituto Superior Universitario "Portoviejo" (CEISH-ITSUP). This document provides comprehensive details about the study and outlines participants' rights, including their ability to withdraw at any time without penalty. Participants will be given sufficient time to review the form and ask any relevant questions. Both members of each couple must provide their consent to participate in the study.

The investigator responsible will document the informed consent process, ensuring that each participant's signature and the date of consent are properly recorded. Personal information, including participants' names, contact details, and unique identification codes, will be collected during enrollment and stored separately from the study data. Participants will not receive any compensation for their participation.

This study was reviewed and approved by the CEISH-ITSUP (681428096; Multimedia Appendix 1). The study was registered

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in Clinical Trials (NCT06501729; Multimedia Appendix 2). The study protocol was structured according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (Multimedia Appendix 3).

Study Design

The protocol will be carried out using a parallel 3-arm randomized controlled design. It will evaluate whether the act of kissing on the mouth between 2 people can cause the pH of saliva to increase after consuming sugary or fermented beverages. The initial pH will be obtained from participants who meet the inclusion criteria. After recording the initial pH, participants will be given 200 mL of one of the beverages selected for the study (Coca-Cola, Cifrut, or nonalcoholic beer). After ingesting the beverage, the participants will be asked to drool into a test tube to measure the pH of the saliva using a pH meter. Based on the literature, it is expected that the pH will decrease. After this measurement, the experimental groups will be asked to kiss their partners, and the control group will not do so. The pH of the saliva will be measured for a third time 5 minutes after ingesting the beverage to record the changes. This will be done repeatedly, every 5 minutes, until the pH of the saliva reaches a neutral level (6.8-7.2).

The difference between the experimental groups is that, in one, only one person from the kissing couple will have a sugary or fermented beverage, and in the other, both individuals will consume the sugary or fermented beverage. Each week, a different beverage will be tested; that is, in week 1, Coca-Cola will be used, in week 2 artificial fruit juice, and in week 3 nonalcoholic beer.

This randomized controlled trial will be conducted according to the CONSORT (Consolidated Standards of Reporting Trials) checklist and guidelines, as outlined in Figure 1 [14].

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram of the study design outlining the selection and randomization of couples participating in the study. In total, 36 couples will be required to try 3 different beverages.

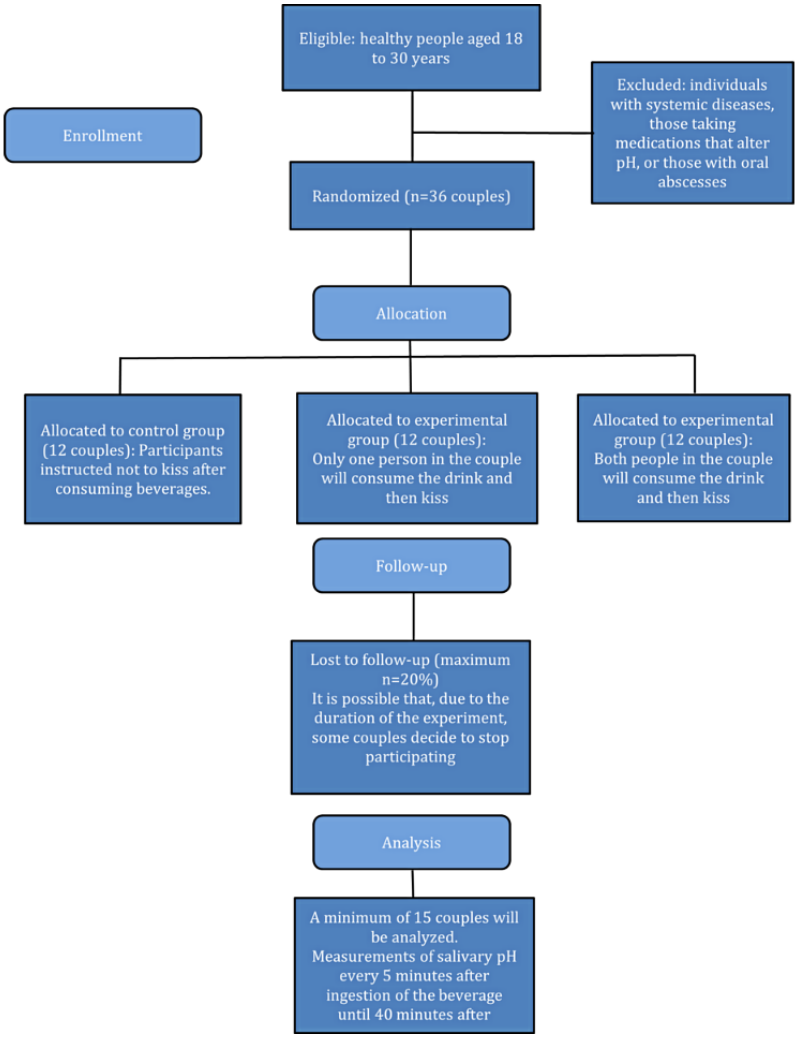

Eligibility Criteria

Some physiological and pathological conditions could alter the pH of saliva, which could bias the results of this study. Therefore, the aim is to select couples aged between 18 and 30 years, the age at which the probability of having chronic degenerative diseases is lower. In addition, all volunteers who enroll will undergo an oral examination to determine their oral health, and those with abscesses, extensive carious cavities (level 5 or 6 according to the International Caries Detection and Assessment System), periodontal disease, or other alterations that may modify the salivary pH will be excluded. Furthermore, participants must not undergo medical treatment that requires them to consume medications that change the pH of their saliva.

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These criteria were selected to minimize confounding factors that could alter salivary pH, such as systemic diseases, abscesses, or the influence of medications. The age range of 18-30 years was chosen to reduce the likelihood of undiagnosed chronic systemic diseases, as no specific tests will be conducted to confirm their absence; participant responses will be accepted as valid. Additionally, requiring participants to already have a romantic partner ensures that the study is conducted ethically and avoids potential discomfort from pairing participants with strangers.

The recruitment process will involve an open call via social media platforms targeting university students, although being a student is not an inclusion criterion. Flyers with a QR code and a registration link will direct interested individuals to a Google Form where they will provide initial data. Eligible participants will be contacted to schedule an oral health assessment and complete a health questionnaire to confirm compliance with the inclusion criteria.

Sample Size

To select the participating couples, a call will be made to students of the Universidad Católica de Santiago de Guayaquil and members of the general public within the established age range. To participate in the study, participants must agree, together with their partner, to be part of the research and sign the informed consent form. The couples will be divided into three groups: 1 control group and 2 experimental groups. However, all participants must register with their partners because the group assignment will not be revealed until the day of saliva sample collection. The sex of the participants will be balanced among the groups, ensuring equal representation of men and women. Additionally, all participants must meet the inclusion criteria detailed in this document.

The sample size was calculated using the G*Power statistical software (version 3.1.9.7, Heinrich-Heine-University). Data from a pilot study by Uma et al [11] were used to estimate the necessary sample size. This study provided the following values for the calculation: control group mean 7.10, SD 0.18 and experimental group mean 6.86, SD 0.18. Based on these parameters, the effect size for ANOVA was calculated to be 0.76, which corresponds to a large effect size.

Using the parameters α=.05, power=0.95, and 3 groups, the G*Power software indicated that a minimum of 30 participating couples (10 per group) is required. To account for potential dropouts, an additional 20% (n=6) will be recruited, resulting in a total of 36 participating couples (12 couples per group). This calculation ensures sufficient statistical power while maintaining logistical feasibility.

Randomization

Randomization will be carried out by an external researcher to whom lists of coded pairs will be given. The researcher will use the randomized website to create 3 lists, one for each group. In this way, each couple will be assigned to 3 different groups. The control group will include participants who will not engage in the kissing intervention. This group serves as a baseline for evaluating the natural recovery process of salivary pH after consuming acidic beverages. The first experimental group will have one partner consume the acidic beverage, and then the couple will engage in a 40-second kiss. This allows evaluation of the effect of kissing when only one partner has an acidic pH alteration. The second experimental group will have both partners consume the acidic beverage before engaging in the 40-second kiss. This setup examines whether mutual exposure to acidic conditions influences the efficacy of kissing in restoring salivary pH. In summary, the groups will be as follows:

1. Control: one partner drinks, no kiss
2. Experimental 1: one partner drinks, both kiss
3. Experimental 2: both partners drink, both kiss

Intervention

The act of kissing will be an intervention that we try to associate with an increase in salivary pH after its decrease. To do so, the experimental groups will kiss with their partner after ingesting one of the beverages, followed by a series of pH measurements. First, the baseline pH of the participants' unstimulated saliva will be taken, and then they will be given 200 mL of the beverage to be tested that week. After verifying that the beverage was completely ingested by the participants, they will wait 1 minute before providing a new saliva sample to verify the decrease in pH. After recording the second measurement, the participants in the experimental groups will be asked to kiss with their partner for 40 seconds. Participants will be instructed to make this kiss "passionate." After that time, participants will wait 4 minutes and 20 seconds (remaining time to complete 5 minutes), and a saliva sample will be taken again to record the pH. Except for the act of kissing, the same will be done with the control group, with a saliva sample taken every 5 minutes for the next 40 minutes, which is when physiological re-establishment of salivary pH is expected.

A pH meter measures the hydrogen ion activity in a solution, which is indicative of its acidity or basicity. The device typically uses a glass electrode as a pH sensor, which interacts with hydrogen ions in the solution to produce an electrical potential that can be translated into a pH value. This value is displayed on a readout, often a liquid crystal display, which may also show temperature readings owing to the influence of temperature on pH measurements.

The saliva sample for pH measurement will not be stimulated because the increase in fluid alters the pH; thus, a reduced sample is expected to be obtained. For this reason, a thin electrode will be used so that it can enter the bottom of the test tube and capture the measurement. For this purpose, the Mettler Toledo InLab Micro pH sensor with the following technical characteristics was chosen:

- Micro combined pH electrode with a glass body and S7 threaded head
- Measuring range: pH 0-14
- Temperature zone: 0°C-80°C
- Union type: ceramic
- Shaft material: glass
- Sensor type: combined electrode
- Shaft length: 60 mm
- Shaft diameter: 3 mm
- Reference system: ARGENTHAL with Ag^+ ion trap

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- Reference electrolyte: 3 mol/L KCl
- Glass membrane: U
- Membrane resistance (25C): <600 M

Study Outcomes

The first outcome will be the time required for salivary pH to return to baseline after being lowered by kissing a person who has not consumed a beverage. To determinate this, salivary pH will be measured every 5 minutes using a calibrated pH meter. The second outcome will be the time required for salivary pH to return to baseline after 2 people kiss, both of whom will have consumed a beverage that lowers pH. Finally, the average salivary pH of each group will be compared at each 5-minute interval.

Data Analysis

Data analysis will be performed using SPSS Statistics software (version 21.0; IBM Corporation). Data will be presented as descriptive statistics and examined for missing values, outliers, normality, and homogeneity. To compare descriptive variables between groups, the *t* test will be used for quantitative variables and the chi-square test for categorical variables. Kolmogorov-Smirnov and Levene tests will be applied to assess normality and homogeneity of variances, especially for salivary pH measurements. Comparisons of mean salivary pH values between the 3 groups will be conducted using repeated-measures ANOVA if assumptions are met. When normality or sphericity assumptions are violated, alternative methods such as the Friedman test or generalized linear models with interaction terms and covariates (eg, type of beverage and time point) will be considered. Additionally, within-group changes in salivary pH over time will be analyzed using paired-sample tests or their nonparametric equivalents.

Results

The study was funded by the Catholic University of Santiago de Guayaquil from June 2024 to June 2025. Ethics approval was obtained by the CEISH-ITSUP (681428096) in June 2023. The call for participants began in early May 2025. As of the date of this submission, 30 couples have expressed interest in participating. Recruitment is ongoing, and data collection is expected to continue over the coming months. As of July 2025, we have collected data for Coca-Cola and Cifrut. Sample collection is extensive, and getting participants to continue throughout the study is proving difficult. The results are expected to be published in the last quarter of 2025.

Discussion

Principal Findings

This study proposes an innovative hypothesis that the act of kissing may accelerate the recovery of salivary pH following the consumption of acidic beverages. By facilitating salivary exchange between individuals, kissing may help neutralize the acidic environment created by sugary or fermented drinks. The findings of this study could have implications for how natural interpersonal behaviors contribute to maintaining oral pH homeostasis.

The experimental design allows for the comparison of 3 groups to evaluate whether the buffering capacity of one partner's saliva can affect the oral environment of the other. This investigation seeks to determine whether the salivary pH in participants who engage in kissing returns to neutral more quickly than in those who do not kiss. This may serve as evidence of an additional, natural protective mechanism against acidogenic dietary habits—one that involves behavioral factors rather than pharmacological or mechanical intervention.

Comparison With Prior Work

Previous studies have confirmed that the consumption of sugary or acidic beverages leads to a rapid decline in salivary pH, often reaching values below the critical threshold for enamel demineralization. These drinks can prolong an acidic oral environment for up to 40 minutes or more, depending on individual salivary flow and buffering capacity [15,16]. Although several approaches have been proposed to counteract this effect, such as dairy product intake, chewing sugar-free gum, or using mouth rinses, no previous studies have evaluated whether natural behaviors like kissing could offer similar benefits.

Other research has explored nonconventional approaches. For instance, the effect of fermented yogurt on the oral cavity demonstrated positive outcomes for maintaining salivary pH [16], and pineapple juice fermented with probiotics showed a limited but measurable influence on pH recovery [17]. However, these studies relied on biochemical mechanisms rather than behavioral dynamics. This study is the first to evaluate whether intimate human interaction can function similarly by transmitting buffering agents through saliva, thus supporting oral pH recovery.

Limitations

This study has several limitations that should be acknowledged. The experimental conditions involve an arbitrary time of 40 seconds for kissing, which lacks direct precedent in the literature. Additionally, salivary pH measurements will be taken every 5 minutes, a frequency commonly used in similar protocols but still based on convention rather than robust comparative trials. The beverages used in this study—Coca-Cola, Cifrut, and nonalcoholic beer—reflect consumer preferences in Guayaquil, Ecuador, but may not be representative of other populations.

Furthermore, couples who participate may not kiss in the same way as they would in private, as some participants may feel inhibited or perform differently knowing they are part of a research setting. These behavioral variables may influence the results and are difficult to control.

Another limitation is related to sample composition. Most participants will be university students from middle-income urban backgrounds. This restricts the generalizability of the findings to the broader population, especially those with different sociodemographic profiles or baseline oral health conditions.

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Implications

Should this study demonstrate a measurable benefit of kissing in restoring salivary pH, it would introduce a novel behavioral approach to oral health maintenance. While this is not intended to replace traditional preventive methods, such as brushing, flossing, and dietary control, it may serve as a complementary insight into how natural human interactions influence oral physiology.

This concept may also have implications for health education strategies. For example, oral health promotion campaigns, particularly those targeting adolescents and young adults, could benefit from including accessible, behaviorally relevant messages. Digital platforms and mobile health applications that disseminate oral hygiene habits might consider integrating insights from this study to make content more relatable and engaging [18,19].

Future Research

Future studies could build upon these findings by exploring the effects of varying kiss durations, frequency, and intensity on salivary pH recovery. It would also be valuable to assess whether long-term behavioral patterns involving intimate salivary exchange can influence the oral microbiome and its association with dental caries. Further interdisciplinary research combining microbiology, behavioral science, and preventive dentistry is encouraged. Such efforts could help establish whether kissing may be a meaningful component in the broader framework of natural strategies for oral health preservation.

Conclusions

The objective of this study is to investigate the impact of kissing on salivary pH and its potential function in preventing dental caries. The findings of this study will provide valuable insights into the relationship between kissing and oral health. Previous research has suggested that salivary pH can affect the development of dental caries, but the role of kissing in this process has not been extensively studied. This study is crucial because it could lead to a better understanding of the factors that contribute to oral health and the prevention of dental caries. The results of this study will be compared to those of previous research on the relationship between salivary pH and dental caries. The findings of this study may contradict existing beliefs regarding the role of kissing in oral health. The study will be supported by relevant literature and data on saliva pH and dental caries. This study will contribute to the field of oral health research and provide valuable information for the development of preventive measures against dental caries.

Despite the limitations described in our research, the methodology that is intended to be applied, the times of the measurements, and the choice of beverages are supported by other studies that will allow our results to be replicable, verifiable, and comparable with other research. Furthermore, if our hypothesis can be verified, we will have a new preventive measure against the decrease in salivary pH and its consequent risk of dental caries, which is as common and free as kisses between 2 people who are in a relationship.

Acknowledgments

The authors would like to thank Silvia Chang for her administrative collaboration in the approval of the research project by the Catholic University of Santiago de Guayaquil. We also thank the Catholic University of Santiago de Guayaquil for supporting the research team and approving the funding of the study. Furthermore, it should be noted that the university, as the sole and total funder of the research project, had no influence in the preparation of the research protocol or in the selection of the research team; it merely reviewed the project prior to its approval and funding.

Data Availability

The measurements will be recorded in a web-based Excel sheet and in a physical form for the researchers' backup. The data will be available after completing the collection process in a web-based database available to the general public with the respective anonymization of the study participants.

Disclaimer

This protocol was reviewed using ChatGPT (version GPT-4, OpenAI) to assist in improving English grammar, structure, and academic tone. All artificial intelligence–generated suggestions were critically reviewed and edited by the authors to ensure accuracy and appropriateness.

Authors' Contributions

Conceptualization: MAB (lead), MAG (supporting), ABV (supporting)
Formal analysis: MAB
Funding acquisition: MAB (lead), ABV (supporting)
Methodology: MAB (lead), ABV (supporting)
Project administration: MAB (lead), MAG (supporting), ABV (supporting)
Writing – original draft: MAB (lead), MAG (supporting)
Writing – review & editing: MAB (lead), MAG (supporting), ABV (equal)

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Ethics committee approval.
[PDF File (Adobe PDF File), 502 KB - resprot_v14i1e65253_app1.pdf]

Multimedia Appendix 2
Clinical trial registration.
[PDF File (Adobe PDF File), 76 KB - resprot_v14i1e65253_app2.pdf]

Multimedia Appendix 3
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist, study timeline, and model consent form.
[PDF File (Adobe PDF File), 459 KB - resprot_v14i1e65253_app3.pdf]

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Abbreviations

CEISH-ITSUP: Council on Ethics in Human Research from Instituto Superior Tecnológico de Portoviejo
CONSORT: Consolidated Standards of Reporting Trials
ECF: extracellular fluid
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Efficacy and Safety of Electroacupuncture Through Nerve Stimulation in Patients With Anxiety Disorders: Protocol for a Randomized, Assessor-Blind, Three-Arm, Parallel-Group Clinical Trial

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Abstract

Background: Anxiety disorders are among the most common mental health disorders, affecting a significant portion of the population. However, conventional treatments, such as pharmacotherapy and psychotherapy, often have limited effectiveness and may lead to undesirable side effects. Consequently, there is a growing demand for new alternative treatments for anxiety disorders. Recent studies suggest that electroacupuncture may demonstrate therapeutic effects in managing anxiety by mediating nerve stimulation.

Objective: This study is designed to assess the efficacy and safety of electroacupuncture in treating anxiety disorders through nerve stimulation. Specifically, it will involve stimulating the median nerve at the PC6 acupoint (Neiguan) and the vagus nerve at the TF4 acupoint (Shenmen of ear acupuncture).

Methods: This study is a randomized, assessor-blind, three-arm, parallel-group clinical trial comprising the PC6 electroacupuncture group, TF4 electroacupuncture group, and a control group. Participants will include patients diagnosed with social anxiety disorder, panic disorder, agoraphobia, and generalized anxiety disorder. Eligible participants will be randomly assigned to one of the 3 groups, with each group containing 20 individuals. The electroacupuncture groups will receive treatments at the designated acupoints twice weekly for 8 weeks, totaling 16 sessions. The control group will receive usual care without any treatment interventions through the end of the study period. The primary outcome is the comparison of Hamilton Anxiety Rating Scale scores between the treatment groups and the control group. Secondary outcomes include scores on the Hamilton Anxiety Rating Scale, Beck Anxiety Inventory, Beck Depression Inventory-II, Patient Health Questionnaire-15, World Health Organization Quality of Life Assessment Instrument abbreviated version, Penn State Worry Questionnaire, Panic Disorder Severity Scale, and Leibowitz Social Anxiety Scale. Safety evaluation variables include the frequency of adverse events, vital signs, and suicide risk assessment. Exploratory variables include performance on the Emotional Reactivity Test, empathy quotient, and heart rate variability.

Results: The first participant was enrolled on December 15, 2022. As of October 2024, a total of 60 participants have been fully registered, and the intervention is currently in progress. We expect the completion of this trial to occur within the year 2025.

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Conclusions: In this study, we will evaluate the safety and efficacy of electroacupuncture for anxiety disorders. By elucidating the therapeutic mechanisms of electroacupuncture through nerve stimulation, this study will provide clinical evidence to support the development of potential interventions for patients with anxiety disorders.

Trial Registration: Clinical Research Information Service of the Republic of Korea KCT0008378; https://cris.nih.go.kr/cris/search/detailSearch.do/24503

International Registered Report Identifier (IRRID): DERR1-10.2196/68166

(JMIR Res Protoc 2025;14:e68166) doi:10.2196/68166

KEYWORDS

anxiety disorders; electroacupuncture; nerve stimulation; vagus nerve; median nerve

Introduction

Anxiety disorders are defined as mental health conditions that are characterized by a set of symptoms, including excessive fear, anxiety, and related behavioral disturbances [1]. Anxiety disorders represent a significant proportion of mental health conditions, affecting an estimated 301 million people worldwide as of 2019 [2]. The prevalence of anxiety disorders is increasing due to factors such as an aging population, urbanization, and socioeconomic development [3]. These disorders not only result in substantial socioeconomic consequences but also pose a threat to the ongoing growth and productivity of societies [4]. Therefore, the treatment and management of anxiety disorders are becoming increasingly important.

Treatment for anxiety disorders has been found to be effective with pharmacotherapy such as antidepressants and benzodiazepines [5], and psychotherapies like cognitive behavioral therapy and eye movement desensitization and reprocessing are also used [6,7]. However, pharmacotherapy raises concern due to side effects and resistance [8,9], and is often met with negative perceptions by patients regarding psychiatric medications [10]. In addition, although psychotherapy is generally effective, it is neither always cost-effective nor consistently successful [11,12]. Thus, there is a need for treatments that are both cost-effective and associated with fewer adverse effects.

Recent studies suggest that acupuncture and electroacupuncture are effective treatments for anxiety disorders with fewer adverse effects compared to conventional pharmacotherapy [13,14]. Consequently, both acupuncture and electroacupuncture are being recommended as alternative methods for the chronic management and long-term treatment of anxiety disorders [15].

This study aims to assess the efficacy and safety of electroacupuncture treatment for anxiety disorders, with a particular focus on treatments at acupoints PC6 (Neiguan) and TF4 (Shenmen of ear acupuncture), compared with a control group.

Methods

Study Design

This study is designed as a randomized, 3-arm assessor-blinded, parallel-group clinical trial, which will be conducted at the Daejeon Korean Medicine Hospital of Daejeon University, Republic of Korea. It aims to evaluate the efficacy and safety of 2 distinct electroacupuncture interventions in the treatment of anxiety disorders, in comparison to usual care. The interventions specifically target to stimulate the median nerve via acupoint PC6 and the vagus nerve via acupoint TF4 (Figures 1 and 2) [16,17]. The control group, constituting usual care, will not receive any treatment.

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Figure 1. Acupoint PC6. Adapted from Li et al [16], under the Creative Commons Attribution 4.0 International License (CC BY 4.0).

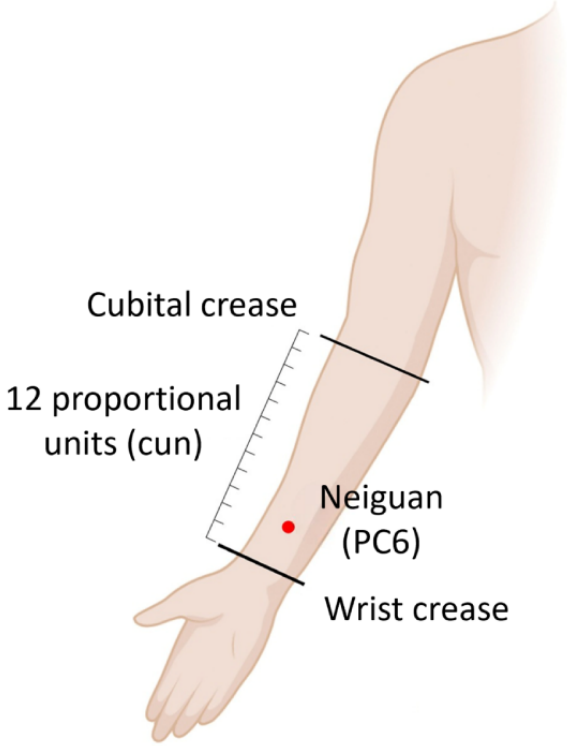

Figure 2. Acupoint TF4. Adapted from Qu et al [17], under the Creative Commons Attribution 4.0 International License (CC BY 4.0).

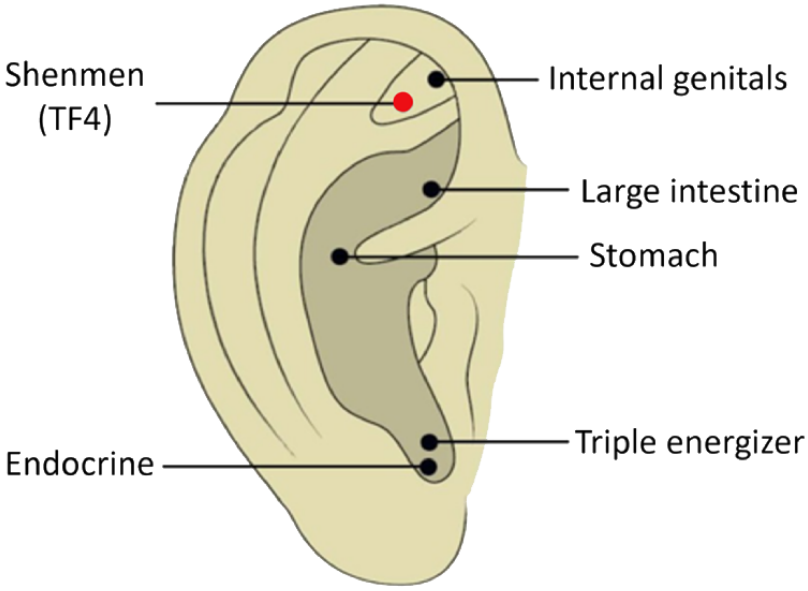

To ensure the rigor and validity of our findings, this study protocol (version 1.4, June 2023) adheres to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines.

Study Procedure

During the initial screening visit, potential participants will receive a comprehensive explanation of the study's purpose, procedures, risks, and benefits and will be asked to provide written consent. Those who voluntarily consent and meet the inclusion and exclusion criteria—as determined through demographic information surveys, medical and medication history reviews, vital signs measurements (blood pressure, pulse, and temperature), laboratory tests, pregnancy tests, the Structured Clinical Interview for *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]; SCID-5) [18], and the Columbia Suicide Severity Rating Scale (C-SSRS) [19]—may be enrolled in this study. The SCID-5 will be used to diagnose subtypes of anxiety disorders, including social anxiety disorder, panic disorder, agoraphobia, generalized anxiety disorder, and other specified anxiety disorders. Participants who do not meet the diagnostic criteria for an anxiety disorder as per the SCID-5 will be excluded from the study. The C-SSRS will be used to assess the risk of suicide; participants scoring 4 or above, indicating a high risk of suicide, will also be excluded from study selection.

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Following registration, participants will be randomly assigned to one of the three groups: the electroacupuncture-vagus nerve stimulation (EA-VNS) group, the electroacupuncture-median nerve stimulation (EA-MNS) group, or the usual care group. Participants in the treatment groups will undergo electroacupuncture sessions twice weekly for a total of 16 sessions over 8 weeks. Conversely, the usual care group will not receive any interventions during this period.

The evaluation of the treatment group is scheduled to occur at the initial, eighth, and final visits. For the control group, assessments will be conducted in the first, fourth, and eighth weeks. During the initial and final assessments for the treatment group, and the first and eighth weeks for the control group, the following instruments will be administered: Hamilton Anxiety Rating Scale (HAM-A) [20], Beck Anxiety Inventory (BAI) [21], Beck Depression Inventory-II (BDI-II) [22], Patient Health Questionnaire-15 (PHQ-15) [23], World Health Organization Quality of Life Assessment Instrument abbreviated version (WHOQOL-BREF) [24], Leibowitz Social Anxiety Scale-Self Report (LSAS-SR) [25], The Panic Disorder Severity Scale (PDSS) [26], and Penn State Worry Questionnaire (PSWQ) [27]. LSAS-SR will be conducted only for patients with social anxiety disorder, PDSS only for those with panic disorder or agoraphobia, and PSWQ only for those with generalized anxiety disorder. A midpoint evaluation using the HAM-A and BAI will be conducted during the eighth visit for the treatment group or in the fourth week for the control group. The detailed schedules are described in Table 1 and the study flow is presented in Figure 3.

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Table 1. Timeline of the trial.

Period	Screening (week –1)	Treatment				
		Baseline (week 0)	Midterm			Final (week 8)
			Weeks 1-4	Week 4	Week 5-8	
Visit		Visit 1[a]	Visit 2-7[b,c]	Visit 8	Visit 9-15	Visit 16
Consent	✓					
Demographic information	✓					
Medical history	✓	✓	✓	✓	✓	✓
Physical examination	✓					
Vital signs	✓	✓	✓	✓	✓	✓
Body weight and height	✓					✓
Laboratory test[d]	✓					
Pregnancy test[e]	✓					
SCID-5[f]	✓					
C-SSRS[g]	✓					✓
Inclusion and exclusion criteria	✓					
Randomization		✓				
Item						
HAM-A[h], BAI[i]		✓		✓		✓
PHQ-15[j], BDI-II[k]		✓				
WHOQOL-BREF[l]		✓				✓
PSWQ[m], PDSS[n], LSAS-SR[o]		✓				✓
EQ[p], PSS[q]		✓				✓
Emotional reactivity test		✓				✓
Check concomitant drugs		✓	✓	✓	✓	✓
Check adverse effects		✓	✓	✓	✓	✓
EA-MNS[r], EA-VNS[s]		✓	✓	✓	✓	✓
HRV[t]		✓		✓		✓
Education of visit schedule	✓	✓	✓	✓	✓	

[a]Visit 1 is scheduled to occur within 10 days of screening.

[b]Visits 2-7 are implemented 4 times within 2 weeks + 2 days from visit 1. Similarly, visits 9- 15 are implemented 4 times within 2 weeks + 2 days after visit 8. Electroacupuncture treatments are typically scheduled twice a week, but once to three visits per week are permitted.

[c]Only the experimental group follows this schedule.

[d]Lab test items are as follows: complete blood cell count (red blood cell, white blood cell, hemoglobin, hematocrit, platelet, erythrocyte sedimentation rate, white blood cell differential count), blood chemistry test (aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, creatinine, and hemoglobin A_{1c}), thyroid function test (triiodothyronine, free thyroxine, and thyroid stimulating hormone), pregnancy test (urine human chorionic gonadotropin, applicable only to fertile women).

[e]A pregnancy test is only performed for fertile women who have had a menstrual period within the last year.

[f]SCID-5: Structured Clinical Interview for DSM-5 (Diagnostic and Statistical Manual of Mental Disorders [Fifth Edition]).

[g]C-SSRS: Columbia Suicide Severity Rating Scale.

[h]HAM-A: Hamilton Anxiety Rating Scale.

[i]BAI: Beck Anxiety Inventory.

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[j]PHQ-15: Patient Health Questionnaire-15.

[k]BDI-II: Beck Depression Inventory-II.

[l]WHOQOL-BREF: World Health Organization Quality of Life Assessment Instrument abbreviated version.

[m]PSWQ: Penn State Worry Questionnaire. This has been used for generalized anxiety disorder and other anxiety disorders.

[n]PDSS: Panic Disorder Severity Scale.

[o]LSAS-SR: Leibowitz Social Anxiety Scale-Self Report. This has been for social anxiety disorder.

[p]EQ: Empathy Quotient.

[q]PSS: Perceived Stress Scale.

[r]EA-MNS: electroacupuncture-median nerve stimulation. This will be conducted according to each group.

[s]EA-VNS: electroacupuncture-vagus nerve stimulation. This will be conducted according to each group.

[t]HRV: heart rate variability.

Figure 3. Flowchart of study procedure. EA-MNS: electroacupuncture-median nerve stimulation; EA-VNS: electroacupuncture-vagus nerve stimulation;.

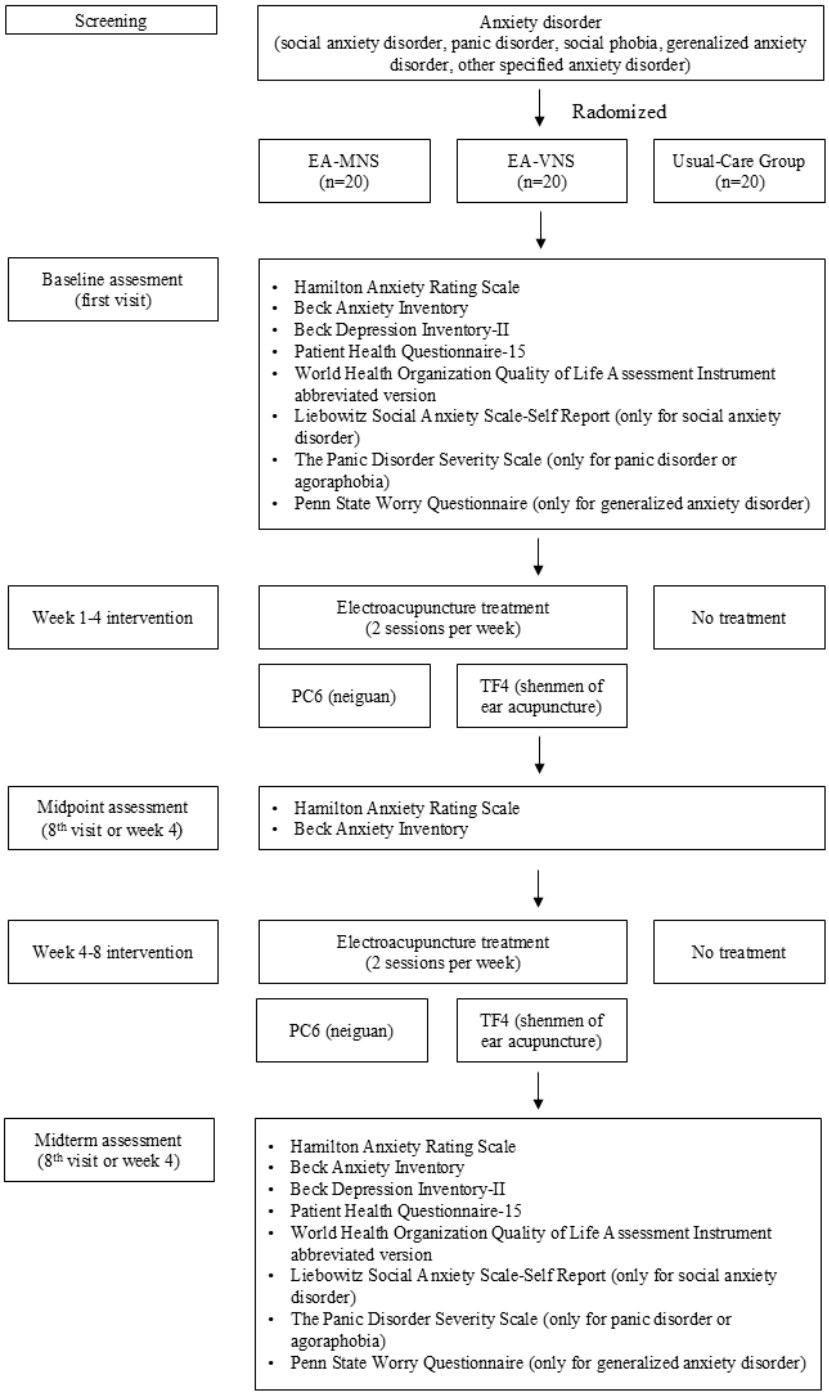

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Study Populations

To ensure the safety of participants and the integrity of study outcomes, specific inclusion and exclusion criteria were applied. These criteria were designed to select individuals with appropriate clinical characteristics for the study intervention while minimizing potential risks and confounding variables. Eligible participants were required to meet all inclusion criteria and none of the exclusion criteria listed in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria:

(1) Aged 19-70 years, as individuals aged 19 years and older are legally permitted to provide autonomous consent to participate in clinical research in Korea.

(2) Diagnosed with an anxiety disorder including social anxiety disorder, panic disorder, agoraphobia, generalized anxiety disorder, other specified anxiety disorders, and unspecified anxiety disorder as assessed through the Structured Clinical Interview for *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]; SCID-5).

(3) Voluntarily decided to participate in this study and signed the written consent form.

(4) Able to complete electroacupuncture-neural stimulation treatments over 8 weeks.

Exclusion criteria:

(1) At high risk of suicide as assessed by the Columbia-Suicide Severity Rating Scale with a score of 4 or more.

(2) With a history of schizophrenia or bipolar disorder.

(3) Diagnosed with separation anxiety disorder, selective mutism, substance-induced anxiety disorder, anxiety disorder due to medication, or anxiety disorder due to other medical conditions.

(4) Received acupuncture treatment within the last 4 weeks.

(5) With a history of alcohol or other substance use disorders within the last 8 weeks.

(6) With a history of cerebrovascular disease, brain tumor, or traumatic brain injury.

(7) With a history of neurological or systemic disease that may affect the central nervous system.

(8) In medical conditions requiring inpatient treatment.

(9) Usage of a pacemaker.

(10) With contraindications to acupuncture treatment (eg, acupuncture-associated vasovagal response or tissue damage due to acupuncture).

(11) Taken medication or participated in another clinical trial within the last month.

(12) Pregnant or lactating women, or those not using medically acceptable methods of contraception during the study period.

(13) Deemed inappropriate for enrollment due to other reasons as determined by the investigators.

Interventions

In this study, electroacupuncture treatments will be administered by qualified Korean medical doctors with at least 1 year of clinical experience. Participants assigned to the electroacupuncture treatment groups will receive treatments twice a week, with a total of 16 sessions over an 8-week period. Each session will last 20 minutes. For the EA-MNS group, the needle will be inserted at PC6, while for the EA-VNS group, the needle will be inserted at TF4. The selection of these intervention sites is based on previous studies showing that stimulation of the median nerve or PC6 acupoint and the vegus nerve or TF4 acupoint is effective for alleviating anxiety symptoms [15,28,29].

The needles will be stimulated using an electroacupuncture stimulator (model STN-110, Streatek Co). For the electroacupuncture-median nerve stimulating group, needles will be inserted at PC6 and at a nonacupoint approximately 0.5 cm proximal to PC6 on the right arm. Subsequently, the hook-shaped or magnetic output terminal of the electroacupuncture stimulator will be attached to administer electrical stimulation. The electrical stimulation for EA-MNS will be conducted at 12 Hz for 20 minutes. For the electroacupuncture-vagus nerve stimulating group, needles will be inserted at TF4 and at a nonacupoint surrounding 0.7 to 1.0 cm away from TF4 on the right ear. The method of attaching the electroacupuncture stimulator is the same as for the EA-MNS group. The electrical stimulation for EA-VNS will be conducted at 100 Hz for 20 minutes. In both groups, the intensity of the electrical stimulation (in mA) will be set to a level that the participant reports as a 4 to 5 on a scale from 0 to 10. The Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) for acupuncture treatment is described in Multimedia Appendix 1.

Criteria for Concomitant Drugs

Permissible Drugs

Drugs that have been taken consistently at a stable dose for at least 4 weeks before study participation and are not expected to interfere with the interpretation of the clinical trial results may be permitted at the discretion of the researcher. In addition, drugs intended for the transient treatment of other conditions can be coadministered after consultation with the researcher. Comprehensive details of all concomitant drugs—including the

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name of the drug, purpose of administration, dosage, and duration—will be documented in the case report form.

Prohibited Drugs

During the trial period, the administration of drugs that may influence anxiety symptoms is prohibited, including systemic steroids, antipsychotics, antidepressants, benzodiazepines, and sleeping pills. However, if antidepressants, benzodiazepines, and sleeping pills have been administered at a stable dose for at least 2 weeks before screening, their continuous use may be permitted.

Efficacy Variables

The primary, secondary outcome measures, and research hypotheses are summarized in Textbox 2.

Textbox 2. Efficacy variables.

Primary Outcome

The primary outcome will be assessed by analyzing changes in the Hamilton Anxiety Rating Scale (HAM-A) scores from baseline to week 8 in two separate comparisons:

- Between the electroacupuncture-median nerve stimulation (EA-MNS) group and the Usual Care group.
- Between the electroacupuncture-vagus nerve stimulation (EA-VNS) group and the Usual Care group.

Research Hypothesis

- Hypothesis 1 [$H0 : \mu1 = \mu2$, $H1 : \mu1 \neq \mu2$]
  - $\mu1$: Changes in HAM-A score from baseline to week 8 in the EA-MNS group
  - $\mu2$: Changes in HAM-A score from baseline to week 8 in the Usual Care group
- Hypothesis 2 [$H0 : \mu3 = \mu2$, $H1 : \mu3 \neq \mu2$]
  - $\mu2$: Changes in HAM-A score from baseline to week 8 in the Usual Care group
  - $\mu3$: Changes in HAM-A score from baseline to week 8 in the EA-VNS group

Secondary Outcomes

The secondary outcomes will be assessed as follows:

- Changes in HAM-A scores from baseline to week 8 between the EA-MNS group and the EA-VNS group.
- Evaluation of rates of loss of diagnosis and complete remission of anxiety disorder, as measured by HAM-A scores, from baseline to week 8 between the EA-MNS group and the Usual Care group.
- Evaluation of rates of loss of diagnosis and complete remission of anxiety disorder, as measured by HAM-A scores, from baseline to week 8 between the EA-VNS group and the Usual Care group.
- Evaluation of rates of loss of diagnosis and complete remission of anxiety disorder, as measured by HAM-A scores, from baseline to week 8 between the EA-MNS group and the EA-VNS group.
- Changes in Beck Anxiety Inventory (BAI), Beck Depression Inventory-II (BDI-II), Patient Health Questionnaire-15 (PHQ-15), World Health Organization Quality of Life Assessment Instrument abbreviated version (WHOQOL-BREF), Penn State Worry Questionnaire (PSWQ), Panic Disorder Severity Scale (PDSS), and Leibowitz Social Anxiety Scale-Self Report (LSAS-SR) scores from baseline to week 8 between the EA-MNS group and the Usual Care group.
- Changes in BAI, BDI-II, PHQ-15, WHOQOL-BREF, PSWQ, PDSS, and LSAS-SR scores from baseline to week 8 between the EA-VNS group and the Usual Care group.
- Changes in BAI, BDI-II, PHQ-15, WHOQOL-BREF, PSWQ, PDSS, and LSAS-SR scores from baseline to week 8 between the EA-MNS group and the EA-VNS group.

Safety Variables

The safety evaluation variables in this study will include the frequency of adverse events, vital signs, and suicide risk assessment. All adverse events that occur during the clinical trial will be assessed for their severity and the causal relationship with the intervention, and their frequency will be used as an evaluation variable. If clinically significant adverse events are observed, changes in vital signs will be assessed compared to preintervention values. The C-SSRS will be used to evaluate the risk of suicide in participants, and a score of 4 or higher will be considered indicative of a suicide risk.

Exploratory Variables

The exploratory variables in this study will include the Emotional Reactivity Test, Empathy Quotient (EQ), Perceived Stress Scale (PSS), and Heart Rate Variability (HRV). The Emotional Reactivity Test, EQ, and PSS will be assessed at baseline and at week 8, while HRV will be assessed at baseline, week 4, and week 8.

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The Emotional Reactivity Test is a behavioral assessment that measures an individual's responses to both positive and negative emotional stimuli. This test is designed to assess the phenomenon of emotional contagion by observing changes in facial expressions in response to emotional stimuli. It is based on experimental models from past research on emotion processing [30,31]. Participants are shown video clips that comprise 4 emotional contexts (joy, sadness, fear, anxiety, and neutral) and their facial expressions are recorded while they watch the emotional stimulus clips. Following the recording phase, participants will report the degree of their emotional state in response to the emotional stimuli on a scale of 0-9 using E-Prime software (Psychology Software Tools). Facial expressions will be analyzed using iMotion software (iMotions A/S).

The electrocardiography signal will be recorded using electrodes placed on the participant's chest. Heart rate and R-R intervals will be extracted from the electrocardiography data using an in-house script developed in MATLAB (2016b, The MathWorks, Inc). The time-domain HRV metrics will include the mean R-R interval, the SD of R-R interval, and the root-mean-square of successive differences. The frequency-domain HRV metrics that will be calculated include the low-frequency power (0.04-0.15 Hz), high-frequency power (0.15-0.4 Hz), and the normalized low- and high-frequency power following standard recommendations [32].

Sample Size

Considering the absence of prior clinical trials proving the therapeutic effect of electroacupuncture in anxiety disorders compared to a control group, this study references preliminary research recommending a minimum of 15 participants per group to ensure feasibility and facilitate exploratory analyses [33]. Therefore, to accommodate potential variances and ensure statistical robustness, we plan to enroll 15 participants per group, for a total of 45 participants. However, to enhance statistical rigor and account for potential attrition, the final sample size was adjusted to 20 participants per group, yielding a total of 60 participants.

Randomization and Allocation

In this study, participants will be randomly assigned to one of the 3 groups: the EA-VNS group, the EA-MNS group, or the usual care group. Stratified block randomization will be used, using SAS software (version 9.4 or higher, SAS Institute), to ensure an unbiased and equal allocation (1:1:1 ratio) across the groups. The stratification criteria will include the specific type of anxiety disorder diagnosed in each participant, such as panic disorder, agoraphobia, generalized anxiety disorder, social anxiety disorder, and other specified anxiety disorders. This method ensures proportional representation of each anxiety disorder subtype within each study arm, thereby controlling for variability in treatment response based on the type of anxiety disorder. The randomization list in this study will be held by an independent statistician and will not be disclosed to ensure confidentiality. The randomized codes will be placed in opaque, sealed envelopes and stored in a locked cabinet. Randomization envelopes will be opened in the order of participant enrollment to assign each group. The opened envelopes will be stored separately, and the date, time of opening, and the opener's signature will be recorded on the envelopes.

Blinding

Given the nature of the interventions, it is not feasible to blind participants in this study. However, to preserve the integrity of the study outcomes, assessor blinding will be strictly maintained. Researchers responsible for evaluating the efficacy and safety outcomes will not participate in the administration of interventions or the randomization process.

Data Management

All clinical trial-related information, including case report forms, consent forms, and supporting documentation, will be recorded, processed, and preserved to facilitate proper reporting, interpretation, and verification. Records containing participants' personal information will be strictly confidential. In all documents associated with the clinical trial, including case report forms, participants will be identified only by their identification codes and initials, not by their names.

Monitoring

Monitoring will be conducted to ensure that the clinical trial is executed in accordance with the approved protocol and applicable regulations. This process includes verifying compliance with the protocol, ensuring accurate and appropriate data collection, reviewing consent and re-consent forms, and verifying the proper collection and reporting of adverse events.

Statistical Methods: Definition of the Analysis Set

The analysis sets for evaluating data obtained in this clinical trial are defined as follows: the Full Analysis Set is in accordance with to the intent-to-treat principle, encompassing all participants who met the inclusion and exclusion criteria, were randomly assigned, and for whom baseline measurements and at least 1 postbaseline primary outcome was obtained. The Per Protocol Set (PPS) includes participants from the FAS who have adhered to at least 75% of the total intervention and do not meet any discontinuation or dropout criteria. The Safety Analysis Set (SAS) comprises all participants who have undergone at least one safety assessment following random assignment.

All data, including efficacy outcomes, will be analyzed using the FAS, with the PPS serving as a secondary analysis group for additional analyses. Safety variables will be analyzed using SAS. Continuous data will be presented as means and confidence intervals, while categorical data will be presented as frequencies and percentages (%). If necessary, initial characteristics of participants measured at screening or baseline may be categorized for subgroup analysis.

Unless specifically stated otherwise, all statistical analyses in this study's results will be conducted as 2-sided tests, with a significance level set at 5%. However, for the analysis of the primary outcome, the significance level will be set at 2.5%. Statistical analyses will be performed using SAS software (version 9.4 or higher, SAS Institute).

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Statistical Methods for Analyzing Efficacy Outcomes

Primary Outcomes

The primary outcome analysis will use a mixed-effect model repeated measure (MMRM) approach, including each treatment group and visit time point as fixed factors, with participants as random factors, and accounting for interactions between groups and visit time points. Variables that show statistically significant differences in demographic or sociological characteristics, or other factors potentially influencing anxiety disorders, will be incorporated as fixed factors. Results will be presented with means, 97.5% CIs, and *P* values. In addition, if significant baseline differences exist between groups, an Analysis of Covariance (ANCOVA), adjusted for baseline values as a covariate, will be conducted.

Secondary Outcomes

The analysis of secondary outcome variables will adhere to the same methodology used for the primary outcomes. Changes in continuous variables from baseline to week 8 in BDI-II, BAI, PHQ-15, WHOQOL-BREF, PSWQ, PDSS, and LSAS-SR will be assessed using the same analytical approach, with a significance level set at 5%. To evaluate the differences in measurements before and after the intervention within each group, the Student Paired *t* test or Wilcoxon signed rank test will be used for both primary and secondary outcomes. Additionally, to examine the trend changes over time between the EA-MNS and EA-VNS groups, Repeated Measures ANOVA will be conducted. This analysis will include testing the interaction between the groups and visits to ascertain how differences evolve over time. If the interaction is found to be significant, post hoc tests will be implemented to identify significant differences between the groups at specific time points based on baseline measurements. Furthermore, the binary variables such as loss of diagnosis and complete remission of anxiety disorder, as assessed by HAM-A, will be compared between groups using logistic regression, which will provide odds ratios and 95% CI.

Statistical Methods for Safety Outcomes

The safety analysis will encompass the severity of adverse events, their causal relationship with the intervention, the incidence rate of adverse events by group, the rate of adverse events leading to dropout, and the incidence rate of serious adverse events. The proportion of participants who dropped out due to treatment failure or adverse events will be reported for each group, along with 95% CI. In addition, the chi-square test or Fisher exact test may be used to compare observed frequencies against expected frequencies. Also, the number of cases assessed as having a high risk of suicide during the study period will be presented by group, and statistical testing may be conducted if necessary.

Statistical Methods to Handle Missing Data

When using the MMRM for variable analysis, no separate imputation for missing values will be conducted. Conversely, in cases where ANCOVA is used, missing values will be imputed using the Multiple Imputation method.

Statistical Analysis of Demographic and Baseline Characteristics

In this study, descriptive statistics for demographic and pretreatment characteristics will be presented for each group. Continuous variables will be analyzed using either ANOVA or the Kruskal-Wallis test, depending on the data distribution. Categorical variables will be analyzed using the chi-square test or Fisher exact test; Fisher exact test will be applied when more than 25% of cells in a contingency table have an expected frequency of less than 5. If necessary, significant differences in baseline characteristics between groups will be adjusted for by incorporating these characteristics as covariates in the efficacy variable analysis.

Study Protocol Modifications

Any modifications to the study protocol require prior approval from the institutional review board. This clinical trial will adhere to the approved protocol unless deviations are necessary to eliminate immediate risks to participants.

Adverse Events

In this clinical trial, adverse events are defined as any harmful or unintended signs, symptoms, or diseases occurring in participants. It should be noted that not all such events necessarily have a causal relationship with the intervention. Serious adverse events include death or life-threatening situations, hospitalization or prolongation of existing hospitalization, permanent or significant disability or impairment, congenital anomalies or defects in a fetus, or other medically significant conditions such as drug dependency or abuse. However, not all adverse events are regarded as serious.

From the start of the intervention, any adverse events will be documented in detail, including the date of onset and resolution, the severity and outcome, the actions taken in relation to the intervention and the causal relationship with the intervention, any other suspected treatments or medications, and whether treatment for the adverse event was administered. During the study period, any serious adverse events must be reported by the research team to the principal investigator within 24 hours. The principal investigator is required to report all serious adverse events to the institutional review board in accordance with clinical trial regulations.

Dropout

In this study, dropout refers to the termination of participation before completing all phases of the study. Researchers can stop treatment and observation and withdraw the participant, or participants can voluntarily withdraw at any time. A participant may be considered dropped out under the following circumstances:

1. If it is discovered after screening that the participant does not meet the inclusion or exclusion criteria.
2. If a systemic disease not identified during pretreatment examinations, is discovered.
3. If the participant experiences a serious adverse event and the researcher determines that continued participation is inappropriate.

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4. If an adverse event is severe enough that the researcher deems continued participation to be inappropriate.
5. If symptoms worsen and the researcher determines that other treatment is necessary.
6. If the participant withdraws consent or requests to stop participation.
7. If the participant does not visit or cannot be followed up.
8. If the researcher determines that continuation of the clinical trial is inappropriate for any other reason.

Discontinuation

In the following cases, this study can be discontinued early after consultation with the sponsoring organization.

1. If an unexpected and unacceptable risk is identified in a participant.
2. If moderate or severe adverse events considered related to the intervention occur in more than 25% of the participants.
3. If not all participants are enrolled by the end of the recruitment period.

Termination

This clinical trial will officially terminate once the target number of participants has been enrolled and data completeness and integrity have been confirmed.

Ethical Considerations

The study protocol, consent forms, participants' information sheets, and all other documentation provided to the participants have received approval from the Institutional Review Board of Daejeon University Daejeon Medical Center (DJDSKH-22-BM-19). This clinical trial has been registered with the Clinical Information Services as of April 21, 2023 (identifier: KCT0008378). All participants will be thoroughly informed about the details of the clinical trial. The consent of participants will be obtained in accordance with the ethical principles and standards based on the Declaration of Helsinki. All participants will have the right to withdraw their consent voluntarily at any time, and all personal information—such as name, gender, and age—will be anonymized or deidentified to ensure that individuals cannot be identified. Participants will receive a nominal transportation allowance (less than US $300) as compensation.

Results

This study was funded in December 2022. The first participant was enrolled on December 15, 2022, and the final participant completed the intervention on November 22, 2024. A total of 60 participants were enrolled, and 51 participants completed the intervention. Data collection was conducted from December 13, 2022, to November 22, 2024. Data analysis is currently underway, and the results are expected to be published in 2025. The CONSORT (Consolidated Standards of Reporting Trials) flowchart depicting the study process is presented in Figure 4.

Figure 4. CONSORT (Consolidated Standards of Reporting Trials) flowchart. EA-MNS: electroacupuncture-median nerve stimulation; EA-VNS: electroacupuncture-vagus nerve stimulation;.

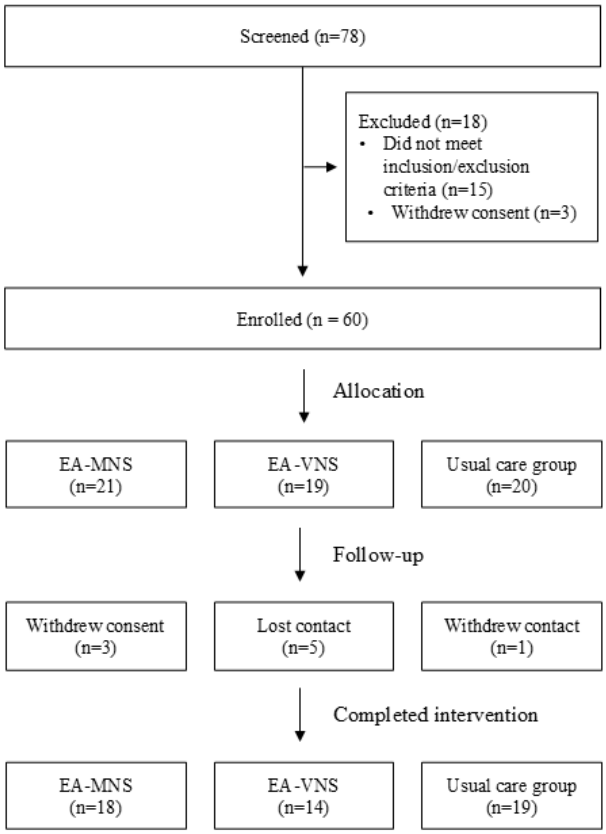

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Discussion

Overview

Acupuncture has been shown to improve various mental health conditions, including depression and insomnia [34,35], and has also demonstrated effectiveness in the treatment of anxiety disorders [13]. However, electroacupuncture for anxiety disorders has primarily been investigated in animal studies, with a limited number of clinical trials reported to date [13]. Therefore, further clinical research is necessary to establish the clinical efficacy of electroacupuncture for anxiety disorders.

Some studies have reported that patients with anxiety disorders exhibit increased activity in the motor areas and motor networks of the brain [36,37]. This finding suggests that modulation of cerebral motor area functions could potentially regulate anxiety symptoms. In this study, the frequency of the median nerve is set at 12 Hz, based on previous studies suggesting that 12 Hz median nerve stimulation modulates the function of the brain's motor areas and improves symptoms. In this study, the frequency of median nerve stimulation is set at 12 Hz, based on a previous study. Studies [38,39] demonstrated that 12 Hz median nerve stimulation is effective in modulating the function of the brain's motor areas and improving symptoms. Similarly, the frequency of vagus nerve stimulation is set at 100 Hz to maximize the brain functions based on a previous study that found 100 Hz stimulation to be effective in increasing activity in the primary sensory cortex, premotor cortex, insular cortex, brainstem, and cerebellum [40].

Strengths

To ensure the reliability of the study results, we used the SCID-5 to minimize the inclusion of participants who do not meet the diagnostic criteria for anxiety disorders. SCID-5 is a widely validated diagnostic tool with high reliability and validity in identifying anxiety disorders [41].

Anxiety symptom severity has been strongly linked to a decline in quality of life [42]. To assess the broader impact of treatment, this study includes the WHOQOL-BREF, enabling an evaluation of whether electroacupuncture improves not only anxiety symptoms but also patients' overall quality of life.

Furthermore, we will use HRV to elucidate the physiological mechanisms of electroacupuncture in treating anxiety, particularly focusing on the regulation of the autonomic nervous system. HRV analysis can offer a noninvasive and objective assessment of the autonomic nervous system's response to electroacupuncture, potentially evaluating the underlying mechanisms.

Limitations

Although previous studies have suggested that neural stimulation may influence brain function in individuals with anxiety disorders [36,37], this study does not incorporate neurophysiological assessments, such as functional magnetic resonance imaging or electroencephalography, to directly evaluate these effects. As a result, this study is unable to determine whether electroacupuncture modulates brain activity at a neurophysiological level.

In addition, this study consists of an 8-week treatment period without posttreatment follow-up, focusing exclusively on the short-term effects of electroacupuncture. Future studies should investigate the long-term efficacy of electroacupuncture, its sustained effects after treatment cessation, and the potential for symptom relapse.

Conclusion

The purpose of this clinical trial is to evaluate the efficacy and safety of electroacupuncture-neurostimulation in the treatment of anxiety disorders compared to a control group. We expect that electroacupuncture, through the stimulation of the median and vagus nerves, could become a novel therapeutic option for anxiety disorders.

Acknowledgments

We used the generative artificial intelligence tool ChatGPT by OpenAI to refine the English language of the manuscript to better suit Western English-speaking audiences. We subsequently reviewed the output to ensure that the translated content accurately reflected the intended meaning. This study was supported by the Korea Institute of Oriental Medicine (grants KSN20234112 and KSN2224011). The funder had no role in the study design, methods, or writing of the manuscript.

Data Availability

Once the clinical trial is completed, deidentified data from participants will be registered in the restricted-access Korean Medicine Data Repository [43]. The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

ICJ and JK performed supervision, conceptualization, project administration, and resource management. DL was responsible for data curation, while OK and JK conducted formal analysis and managed the software. SC, YC, OK, and JK contributed to funding acquisition. DHK and HJK performed the investigation. SC, YC, OK, ICJ, and JK contributed to methodology. JK conducted visualization, and JK also performed validation. DHK wrote the original draft, and DHK, JK, and ICJ performed review and editing.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
STRICTA (Standards for Reporting Interventions in Clinical Trials of Acupuncture) checklist.
[PNG File , 33 KB - resprot_v14i1e68166_app1.png]

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Abbreviations

ANCOVA: analysis of covariance
BAI: Beck Anxiety Index
BDI-II: Beck Depression Inventory-II
CONSORT: Consolidated Standards of Reporting Trials
C-SSRS: Columbia Suicide Severity Rating Scale
DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)
EA-MNS: electroacupuncture-median nerve stimulation
EA-VNS: electroacupuncture-vagus nerve stimulation
EQ: empathy quotient
HAM-A: Hamilton Anxiety Rating Scale
HRV: heart rate variability
LSAS-SR: Leibowitz Social Anxiety Scale-Self Report
MMRM: Mixed-effect Model Repeated Measure
PDSS: The Panic Disorder Severity Scale
PHQ-15: Patient Health Questionnaire-15
PPS: Per Protocol Set
PSS: Perceived stress scale
PSWQ: Penn State Worry Questionnaire
SAS: Safety Analysis Set
SCID-5: Structured Clinical Interview for DSM-5
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
STRICTA: Standards for Reporting Interventions in Clinical Trials of Acupuncture
WHOQOL-BREF: World Health Organization Quality of Life Assessment Instrument abbreviated version

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Protocol

Hydrogen-Rich Water Consumption for Acute and Residual Fatigue After Simulated Football Matches: Protocol for a Randomized, Double-Blinded, Placebo-Controlled, Parallel Trial

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Abstract

Background: Football matches induce acute and residual fatigue, impairing neuromuscular, metabolic, and perceptual performance. Hydrogen-rich water (HRW) is a novel intervention with antifatigue and antioxidative properties. The intermittent high-intensity nature of football, which includes frequent accelerations, decelerations, sprints, changes of direction, and physical contacts, imposes substantial demands on both central and peripheral physiological systems. This results in acute fatigue, observable during or immediately after a match, and residual fatigue, which can persist for 24-72 hours post match, depending on the intensity, match context, and recovery strategies.

Objective: This study will investigate the effects of pre-exercise HRW administration versus a placebo on neuromuscular performance, biochemical markers, and perceptual measures of fatigue during a 72-hour recovery after a simulated football match.

Methods: Using a randomized, double-blinded, placebo-controlled, parallel design, elite junior football players will undergo neuromuscular performance assessments (repeated sprint ability and countermovement jump test). Metabolic fatigue will be measured by creatine kinase level and muscle soreness, rated using a visual analog scale. These assessments will occur at critical time points: immediately post warm-up; directly following the simulated football match to detect acute fatigue; and 24, 48, and 72 hours after training sessions to detect residual fatigue.

Results: Data collection has been scheduled with the clubs to coincide with the beginning of the players' transition period (ie, at the start of August 2025). The expected duration of data collection, including the initial medical examination, is planned to be 1 month. We anticipate publishing the results in late 2025 or during the first half of 2026.

Conclusions: This study will assess the influence of molecular hydrogen on acute fatigue manifestation and recovery quality during a 72-hour period after a simulated football match. The potential positive effects of molecular hydrogen, such as attenuation of oxidative stress, reduction in muscle damage markers, and accelerated neuromuscular recovery, may contribute to faster restoration of functional capacities. If confirmed, these effects could enhance players' readiness to return to high-intensity training and optimize the structure of microcycles in competitive periods. Additionally, understanding the recovery dynamics facilitated by HRW may inform evidence-based recovery strategies and support individualized player monitoring frameworks. The possible positive effect of molecular hydrogen would speed up the players' readiness to train after the match and help protect players against illness and noncontact injuries.

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KEYWORDS

molecular hydrogen; oxidative stress; recovery; repeated sprint ability; antifatigue effect; readiness to play

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Introduction

Football is one of the most popular sports worldwide, characterized by its dynamic and intermittent nature that involves a combination of high-speed and high-intensity effort interspersed with periods of low-intensity activity [1]. Understanding the physical and physiological demands of football matches is essential for developing effective training strategies [2]. Given the combined pressures of matches, training sessions, and associated stressors, players must sustain optimal psychological and physical readiness, as well as overall health, throughout the season and tournaments to achieve peak performance. Monitoring players' readiness and residual fatigue post match is therefore critical for practitioners, as it enables the design of tailored recovery and training plans. This comprehensive approach ensures players maintain consistent performance levels while effectively managing the physical and mental challenges of the sport [3].

Football matches generate significant acute fatigue in players, impacting metabolic, neuromuscular, and perceptual parameters [4]. Recognizing these effects is vital for optimizing recovery strategies and enhancing subsequent performance [5]. The physical demands of modern matches have increased, with players experiencing short recovery periods between games and high neuromuscular strain. This includes a greater frequency of high-intensity running and accelerative actions, which can lead to prolonged residual fatigue [6].

Phosphocreatine availability plays a critical role in intermittent and multiple-sprint performance, with its depletion contributing to performance decline during matches [7]. Prolonged intermittent activity leads to adenosine triphosphate (ATP) and phosphocreatine depletion, reduced neuromuscular excitability, and disruptions in ion homeostasis, which increases reliance on aerobic energy production while inhibiting anaerobic pathways [8,9]. In futsal, for example, 93% of energy production is derived aerobically, with only 5% from anaerobic sources [10]. The relationship between maximal oxygen uptake and repeated sprint ability (RSA) remains ambiguous, with some studies suggesting that RSA performance is more influenced by muscle mitochondrial respiration rates than by maximal oxygen uptake [11].

Mitochondria, through aerobic metabolism, produce reactive oxygen and nitrogen species (ROS/RNS), which serve as both signaling molecules and potential causes of oxidative stress [12]. While moderate ROS/RNS levels are essential for muscle adaptation after training [13], excessive production during repeated sprints can lead to peripheral fatigue and delayed recovery [14]. The body's antioxidant system works to regulate ROS/RNS levels, but intense exercise can overwhelm this system, demonstrating the delicate balance between energy production and oxidative stress in football [15].

Molecular hydrogen (H_2) has emerged as a promising intervention for sports performance due to its selective antioxidant properties, targeting ROS/RNS produced during aerobic metabolism [16]. H_2 also exhibits anti-inflammatory and antiapoptotic effects, along with pH-neutralizing and lactate-reducing capabilities, which can enhance mitochondrial respiration and improve performance in repeated sprint activities [17,18]. Hydrogen-rich water (HRW) has been proposed as a practical hydration strategy during exercise, with evidence suggesting its potential to reduce muscle soreness, perceived exertion, and acute fatigue post exercise [19,20].

Postmatch fatigue significantly affects neuromuscular performance, with assessments like the countermovement jump (CMJ) and RSA tests providing valuable insights [21]. Tools such as the visual analog scale (VAS) are also used to evaluate postexercise muscle soreness, offering reliable measures of discomfort linked to tissue damage [22,23].

Creatine kinase (CK) is a reliable indicator of muscle membrane permeability, as it is predominantly located in skeletal and cardiac muscles [24]. Serving as a biochemical marker of muscle damage, CK is found in both the cytosol and mitochondria of muscle cells. Its levels reflect the extent of muscle recovery and readiness for performance, providing valuable insights into a player's ability to perform after intense physical exertion [25].

The intervals between matches and training sessions may be insufficient for the restoration and recovery of critical processes such as glycogen replenishment, muscle repair, and mental fatigue. This insufficiency not only decreases the likelihood of achieving optimal performance but also elevates the risk of injury [26]. The timeframe required for a player to regain readiness for training following a match is, therefore, a critical factor in planning microcycles. Accordingly, this study aims to evaluate the impact of a simulated football match on the readiness of young elite football players over a 72-hour recovery period.

Methods

Study Aim

Recognizing the critical role of recovery during intermittent or RSA performance, the anti-fatigue effects of H_2 and its impact on mitochondrial ATP synthesis support the hypothesis that acute pre-exercise HRW administration, compared with a placebo, may positively affect biochemical, perceptual, and neuromuscular performance variables during a 72-hour period after a simulated football match. This study aims to assess the impact of pre-exercise HRW administration compared with a placebo on biochemical, perceptual, and performance variables within 72 hours after a simulated football match. The specific aims are to assess the impact of pre-exercise HRW administration on acute neuromuscular performance decrement, the impact of pre-exercise HRW administration on acute muscle soreness and the CK levels of players, and the impact of pre-exercise HRW administration on residual muscle fatigue and duration of return to readiness to play.

Study Design

This study protocol was designed according to the 2023 SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement [27]. The experimental study will use a robust research design, adopting a randomized, placebo-controlled,

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double-blinded, parallel structure (see Figure 1 and Multimedia Appendix 1).

To ensure unbiased results, the administration of HRW and the placebo was randomized and counterbalanced. The investigation will be conducted over a carefully planned 2-week period on a grass football field. During the initial session, participants will be familiarized with the Team^{2}Pro Polar suite (1.4.5 version) and briefed on the regulations governing a simulated football match. Before the first measured session, participants will be stratified based on their playing positions (defenders, midfielders, and forwards) and subsequently randomized into either the HRW or placebo groups. Neuromuscular performance will be assessed through measures including the 20-meter repeated sprint test and CMJ. Metabolic fatigue will be measured through CK levels and muscle soreness, as reported using a VAS. These assessments will occur at critical time points: during simulated match day (SMD) immediately post warm-up; directly following the simulated football match to detect acute fatigue; and immediately post warm-up at intervals of 24 (SMD + 1 day), 48 (SMD + 2 days), and 72 (SMD + 3 days) hours after training sessions to detect residual fatigue. The first measurement sessions will be systematically scheduled on Monday afternoons, allowing for a standardized 72-hour recovery period following the last training session. To enhance ecological validity, the simulated match was designed according to official football rules officiated by an experienced referee, comprising two 35-minute halves, with 11 players per team and no substitutions allowed. Regarding intensity regulation, all participants will be instructed to perform at match intensity, which will be monitored using heart rate (HR) data and rate of perceived exertion scores. These measures will indicate consistent physiological workload across participants, supporting the comparability of internal load responses. Environmental conditions (eg, temperature, lighting) will be held constant throughout all testing sessions to reduce external variability.

Figure 1. Overview of the study protocol and labeling of sessions. HRW: hydrogen-rich water; SMD: simulated match day.

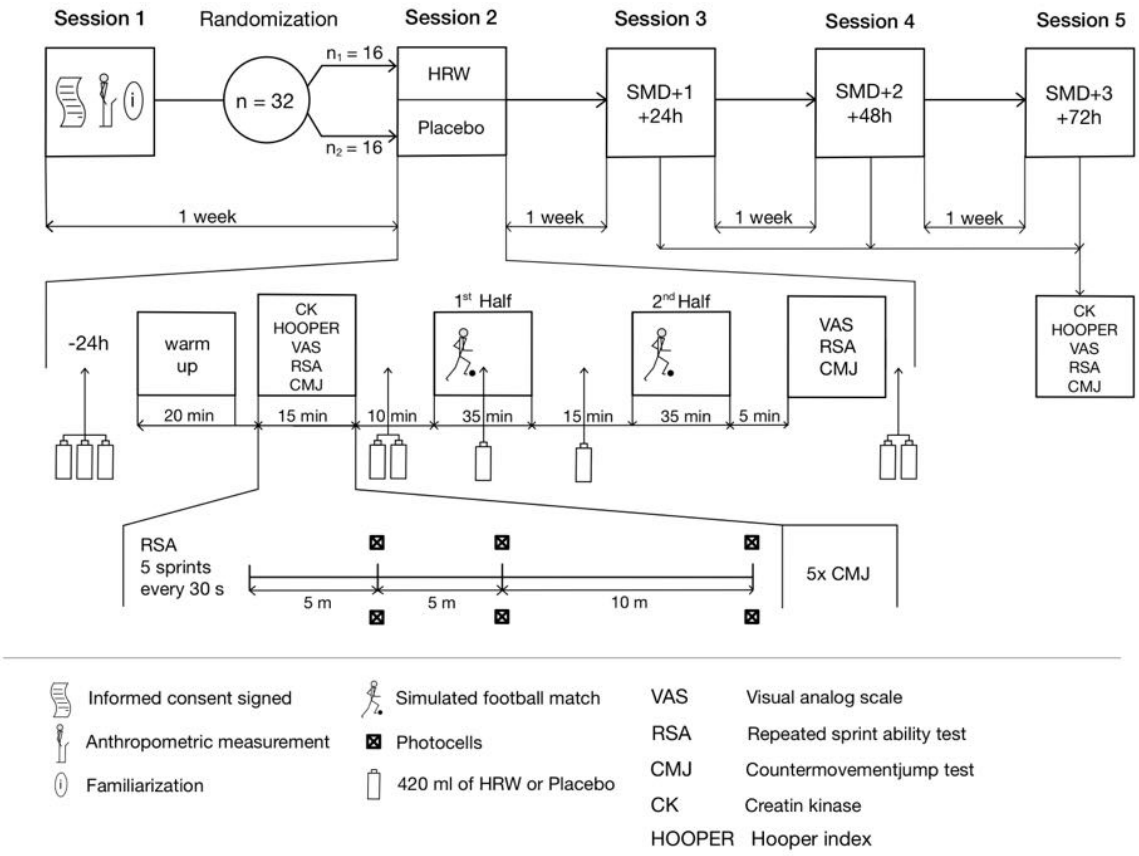

Ethical Considerations

Participants will be informed about the aims of the study, including any risks, discomforts, and benefits, and provide written informed consent. The study was approved by the institutional ethics committee, which follows the Declaration of Helsinki. Participants were not compensated.

Participants

Inclusion and Exclusion Criteria

Czech elite junior male football players will be included. Participants who have at least 10 years of experience, who train at least five times a week with their teams, and who have a match every weekend will be included. Only participants free from injury and medical difficulties will be included in the study. Participants with an illness or injury in the past 3 weeks

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before the start of measurements and participants who explicitly declined to participate will be excluded.

Randomization

A stratified block randomization approach will be used to allocate participants into intervention groups. Participants will be stratified based on their playing position into three distinct strata: (1) defenders, (2) midfielders, and (3) forwards. Within each stratum, participants will be randomly assigned in a 1:1 ratio to either the HRW group or the placebo group using a fixed block randomization method. Randomization sequences will be generated using a robust randomization algorithm, as described by Tu and Benn [28], and implemented via a secure web-based allocation system.

Following participant selection and baseline assessment, each participant will receive either HRW or a placebo in visually identical plastic-aluminum packs, with group allocation determined by the pregenerated randomization code. This process ensures allocation concealment and maintains blinding throughout the study.

Blinding

A double-blind design will be implemented to minimize potential bias. The type of water (HRW or placebo) will be packaged identically, with only distinct batch numbers differentiating them. These batch numbers will be coded and maintained solely by the manufacturer, remaining undisclosed until after data collection and statistical analysis. Due to the physical properties of H_2—being colorless, odorless, and tasteless—participants will be unable to distinguish between the HRW and placebo by sensory perception. Both the players and their coaches, as well as the researchers responsible for data collection and outcome assessment, will be blinded to group allocation throughout the study. This procedure ensures allocation concealment and maintains the integrity of the blinding across all phases of the trial.

Sample Size and Power Analysis

The sensitivity analysis was performed using G*Power (Version 3.1, Heinrich-Heine-Universität). Considering a type 1 error of 0.05 (α=.05) and a test power of 80% (β=.15), the calculated sample size for repeated measures (within and between interaction) is 22 participants with 11 in each group. Considering a 10% sample loss, a total of 24 participants will be recruited for the study.

Data Collection

Preparation of HRW and Placebo

HRW was obtained in 420 mL plastic-aluminum packs with a gas-tight cap (Aquastamina-R, Nutristamina, Ostrava, Czech Republic). Chemical characteristics of the HRW and placebo were determined using the pH/Oxidation-Reduction Potential/temperature meter (AD14, Adwa Instruments, Szeged, Hungary). The concentration of the dissolved H_2 was determined using the H_2Blue reagent (H_2 Sciences, Henderson, Nevada) using the manufacturer's guidelines. HRW/placebo characteristics were as follows: pH=7.9/7.7; oxidation-reduction potential −652/+170 mV; and dissolved H_2 concentration 1.2-1.4/0.0 ppm. The placebo was obtained from the HRW manufacturer and was produced similarly to Aquastamina-R and packed in the same packs.

The participants were instructed to consume three plastic-aluminum packs (1260 mL) 24 hours before the simulated match, two plastic-aluminum packs (840 mL) after finishing the prematch measurement, one plastic-aluminum pack (420 mL) during the first half, and two plastic-aluminum packs (840 mL) consumed after the postmatch measurement. A total of 3780 mL of water was saturated.

RSA Measurement

Participants will complete five 20 m sprints (approximately 3 seconds) departing every 20 seconds with an active recovery (walk back to start). Two seconds before starting each sprint, the participants will be asked to assume the start position. The electronic timing gates (Brower Timing Systems, Draper, Utah) will be set at the start line, after 5 m and 10 m, and at the finish line at 20 m, and always 0.70 m above the surface. According to Pyne et al's [29] recommendations, 3 scores will be calculated for the total time as the sum of the 5 sprints.

CMJ Test and VAS Scale

The CMJ test will be performed on a hardwood indoor surface, commonly used in sports science settings to ensure consistency and reliability of performance measurements. Participants performed 5 jumps and will be instructed to maximize jump height and minimize ground contact time with indoor football shoes. Participants start from an upright standing position with their hands on their hips. The CMJ test will be performed on a mobile optical device, the OptoJump system (Microgate SRL, Italy). Participants will perform three repetitions with a 3-minute recovery; the best attempt will be used. The average height and reactive strength index will be calculated. Reactive strength index will be calculated as jump time divided by contact time [30].

The self-reported perceptual measure by the VAS will be applied to assess lower limb muscle pain [31]. The VAS will be applied just after the CMJ test on a horizontal 100 mm length line with the left and right ends of the line corresponding to "no soreness during repeated maximal jumps" and "most soreness ever experienced during repeated maximal jumps."

HR and Activity Demands

HR will be continuously recorded in 1-second intervals during the simulated match and all training sessions using a Polar Team^{2}Pro System (Polar Electro, Kempele, Finland), whereby participants will have HR monitors affixed to their chest and level with the xiphoid process. HR responses will be presented relative to each participant's individualized maximum HR from laboratory measurements. Raw data from the HR monitors will be exported into Excel (v16.35; Microsoft Corporation). To express training impulse, Edwards summated HR zones (SHRZ) will be calculated as [illegible], where t_i is time spent in 5 HR zones (zone 1: 50%-60% of HR_{max}; zone 2: 60%-70% of HR_{max}; zone 3: 70%-80% of HR_{max}; zone 4: 80%-90% of HR_{max}; zone 5: 90%-100% of HR_{max}). The external load will be calculated as

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the total distance covered, high-intensity distance [32] as distance covered at a speed >14.4 km·h^{-1}, and PlayerLoad as , where a_y is the straight acceleration vector, a_x is the side acceleration vector, and a_z is the vertical acceleration vector.

Statistical Analyses

Statistical analysis and data management will be undertaken using SPSS version 22.0 software (IBM Corp), using an $\alpha \leq .05$. The normality and homogeneity of all data will be verified with the Shapiro-Wilk and Levene tests. Mean and SD will be calculated for each outcome measure with a parametric distribution and medians and quartiles for data with a nonparametric distribution. A repeated-measures ANOVA with one random factor as subject, two fixed factors as type of water (HRW/placebo) and time (prematch; postmatch; and 24, 36, and 72 hours post match), and mutual interaction of water and time will be used to assess acute and residual fatigue. When a significant effect of time or water is observed, pairwise comparisons will be performed using Tukey post hoc test. η^2_p was used as a measure of effect size for each analysis of variance, and values were interpreted as having a small effect ($0.01 \leq \eta^2_p < 0.06$), medium effect ($0.06 \leq \eta^2_p < 0.14$), and large effect ($\eta^2_p \geq 0.14$).

Results

Data collection has been scheduled with the clubs to coincide with the beginning of the players' transition period (ie, the start of August 2025). The expected duration of data collection, including the initial medical examination, is planned to be 1 month. We anticipate publishing the results in late 2025 or during the first half of 2026.

Discussion

Anticipated Findings

The recovery period between matches and training sessions may not adequately support critical physiological and psychological recovery processes, such as glycogen repletion, muscle damage, and mental fatigue [33]. Insufficient recovery can decrease performance and elevate injury risk. Understanding the time required for players to regain optimal training readiness is essential for designing effective microcycle plans. For this reason, the study will aim to assess the impact of pre-exercise HRW administration compared with a placebo on biochemical, perceptual, and performance variables after a simulated football match within 72 hours.

RSA performance has been shown to lead to a reduction in oxidative stress and may increase antioxidant protection as a specific training adaptation [34]. Research has shown that increased levels of oxidative stress can result in decreased muscle performance after repeated eccentric exercise [35] as a muscle fatigue manifestation. According to Çakir-Atabek et al [35], HRW consumption may enhance the endogenous antioxidant capacity to respond to the intensity-dependent mitochondrial production of ROS, reduce oxidative stress, and enhance mitochondrial ATP production [17], due to the decrease in lactate accumulation [36]. Botek et al [37] showed that H_2 application induced an increase in mitochondrial membrane potential, increasing oxygen consumption; cellular ATP, which is an indicator of stimulated oxidative phosphorylation; and mitochondrial ATP production. To protect the quality of the H_2 against the negative effects of increased ROS/RNS, HRW could increase the mitochondrial efficiency and peak muscle power output in later stages of the repeated sprints and delay acute muscle fatigue.

Limitations

First, the simulated football match was designed to replicate competitive conditions, and it may not fully capture the psychological and physiological demands of actual competition. The absence of real opponent-based risks could influence the intensity, motivation, and stress levels of participants, potentially affecting the generalizability of the findings to real match scenarios. Second, participants will be restricted to Czech elite junior male football players. Third, Calbet et al [38] showed a sexual dimorphism in mitochondrial respiratory control, with women displaying larger mitochondrial volume density and higher capacity to oxidize fat, and women contribute to an enlarged O_2 extraction capacity compared to men. It is important that our results relate to men only. Fourth, blood lactate concentrations will not be analyzed. Fifth, while assessing fatigue over 72 hours is valuable, the recovery period may not capture longer-term effects of HRW on performance and biochemical markers.

Acknowledgments

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Data Availability

All research data will be collected, stored, and processed in compliance with ethical standards, data protection regulations, and the Findable, Accessible, Interoperable, and Reusable (FAIR) principles, following the Horizon Europe guidelines. Anonymized datasets will be securely archived in Zenodo, each assigned a permanent DOI and described with standard metadata. A data management plan will be submitted with the initial progress report and updated as needed throughout the project.

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Authors' Contributions

MH and KH will be responsible for the conceptualization, project administration, methodology, writing the original draft, and supervision. DB and MH will be responsible for data curation, formal analysis, and visualization. KH, DB, and MH will be responsible for the postpublication stages.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Schedule of enrollment as recommended by the 2013 SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement.
[DOCX File , 19 KB - resprot_v14i1e69744_app1.docx]

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Abbreviations

ATP: adenosine triphosphate
CK: creatine kinase
CMJ: countermovement jump
H2: molecular hydrogen
HR: heart rate

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HRW: hydrogen-rich water
ROS/RNS: reactive oxygen and nitrogen species
RSA: repeated sprint ability
SHRZ: summated heart rate zone
SMD: simulated match day
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
VAS: visual analog scale

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Protocol

Effect of Dual Bronchodilation on the Exercise Capacity of Individuals With Non-Cystic Fibrosis Bronchiectasis: Protocol for a Randomized Controlled Double-Blind Crossover Study

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Abstract

Background: Bronchodilators (BDs) have been used therapeutically to improve exercise capacity in patients with other chronic respiratory diseases. However, the effect of BDs on the exercise capacity of individuals with non-cystic fibrosis bronchiectasis (NCFB) is poorly understood.

Objective: The aim of this study was to evaluate the effects of BDs on exercise capacity and thoracoabdominal kinematics in patients with NCFB.

Methods: This crossover randomized controlled trial will involve 45 outpatients with NCFB aged 18 to 59 years. They will be evaluated in 3 visits. On day 1, the maximal exercise capacity (cardiopulmonary exercise test; peak work rate [W_{peak}]) will be assessed. On day 2, individuals will be randomized to receive either BD (ipratropium bromide 160 µg and fenoterol hydrobromide 400 µg) or a placebo and then undergo simultaneous endurance exercise capacity (constant work-rate exercise test) and thoracoabdominal kinematics (optoelectronic plethysmography) assessments. After at least 1-week washout (day 3), the individuals will repeat the same assessments as on day 2 in the reverse order. The time to the limit of tolerance will be obtained in both groups (BD and placebo groups) as the primary outcome. Thoracoabdominal kinematics will be assessed at 3 time points: at rest, during unloaded exercise, and at 75% W_{peak}. The total chest wall and compartmental volumes as well as thoracoabdominal asynchrony will be assessed. The assessors and patients will be blinded to the interventions (BDs or placebo). Data will be compared using 1-sided *t* tests or Wilcoxon tests and repeated-measures analysis of variance or Friedman tests. Categorical data will be analyzed using the chi-square test or Fisher test. The associations among variables will be analyzed using Pearson or Spearman correlation. The significance level will be set at 5% ($P<.05$).

Results: The ethics approval was granted in November 2018, and a pilot study was commenced in April 2019 but was interrupted due to the COVID-19 pandemic. The study restarted in April 2022, and data collection is anticipated to continue until November 2025. The publication of the results is anticipated to be in 2025 or 2026.

Conclusions: There is no evidence that BDs can improve the exercise capacity of patients with NCFB. This trial will compare the endurance exercise capacity of the same individual with and without dual bronchodilation. If successful, this study will demonstrate that exercise capacity can be improved with the use of BDs in adults with NCFB.

Trial Registration: ClinicalTrials.gov NCT05183841; https://clinicaltrials.gov/study/NCT05183841

International Registered Report Identifier (IRRID): DERR1-10.2196/68582

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(JMIR Res Protoc 2025;14:e68582) doi:10.2196/68582

KEYWORDS

bronchiectasis; bronchodilator agents; exercise test; exercise; non-cystic fibrosis bronchiectasis; exercise capacity; thoracoabdominal kinematics

Introduction

Non-cystic fibrosis bronchiectasis (NCFB) is radiologically characterized by permanent dilation of the bronchi and clinically characterized by productive cough and recurrent respiratory infections [1]. NCFB is becoming increasingly prevalent and can affect individuals of any age [2]. The pathophysiological mechanisms include persistent bacterial infections, dysregulated immune responses, impaired mucociliary clearance, and airway obstruction—all of which can cause long-term lung impairment (vicious vortex) [1].

Although the optimal therapy for NCFB remains unknown, various pharmacological strategies have been proven beneficial for improving both the quality of life and clinical outcomes. Anti-inflammatory treatment seems to reduce the volume of secretions and inflammatory markers in the sputum and improve the quality of life [3]. In general, antibiotics effectively reduce the bacterial load in the airways [4]. Although the role of bronchodilators (BDs) in the treatment of NCFB is less clear, BDs appear to improve lung function in some patients [5]. Neither antibiotics nor anti-inflammatories can significantly improve the lung function of individuals with NCFB [6], making BDs a therapeutic alternative.

The use of BDs for other chronic respiratory diseases such as asthma and chronic obstructive pulmonary disease (COPD) is already well established and recommended in their respective guidelines [7,8]. According to the Global Initiative for Chronic Obstructive Lung Disease [8], the use of BDs (long-acting β-2 agonists or muscarinic antagonists) is indicated for individuals with severe disease, symptoms, or exercise limitations, as they reduce airway resistance, promote lung deflation, and enable better alveolar ventilation, both at rest and during exercise, in this population.

Despite the lack of robust studies demonstrating the effectiveness of BD use in the treatment of NCFB, BDs continue to be among the most commonly prescribed medications worldwide for this population [9,10]. A small previous study in adults with clinically stable NCFB revealed that combining inhaled corticosteroids with long-acting β-2 agonists might improve dyspnea and increase the number of cough-free days compared with high-dose inhaled corticosteroids, with no effect on the quality of life, number of hospitalizations, or lung function [11]. Despite being a randomized trial, neither patients nor assessors were blinded, and there was an overall high risk of bias, according to Goyal and Chang [12]. A more recent and larger study [13] evaluated the effects of 6-month tiotropium (long-acting muscarinic antagonists) treatment in 90 clinically stable adults with NCFB. Compared with placebo, tiotropium improved the forced expiratory volume in the first second (FEV1) by 58 mL and the forced vital capacity (FVC) by 78 mL. Nevertheless, there was no difference in the quality of life, chronic cough, exercise capacity, or neutrophil and eosinophil counts in the blood or sputum. Furthermore, it did not reduce the number of exacerbations. To date, there are no studies on the effect of BDs on the exercise capacity of this population.

In individuals with NCFB, airflow limitation and dyspnea are strongly associated with exercise capacity [14]. It seems plausible that BDs may improve the exercise capacity of individuals with NCFB similar to what has been observed in individuals with COPD. Additionally, thoracoabdominal asynchrony (TAA) is very prevalent in individuals with COPD and is associated with exercise limitations [15,16]. In this population, the main effect of BDs is an increase in the basal inspiratory capacity and changes in dynamic hyperinflation during exercise, which improves exercise capacity [17]. However, no study has evaluated TAA or the thoracoabdominal kinematics of individuals with NCFB. Therefore, we hypothesize that dual bronchodilation can improve the exercise capacity of individuals with NCFB and reduce TAA during exercise.

Methods

Study Design

This is a randomized, placebo-controlled, double-blind, crossover trial (Figure 1). Participants are assigned in a 1:1 ratio to 2 treatment periods, each lasting 1 hour, with a 1-week washout period between them.

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Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram showing the flow of participants through each stage of the randomized crossover trial. BD: bronchodilator; CPET: cardiopulmonary exercise test; CWRET: constant work-rate exercise test; OEP: optoelectronic plethysmography.

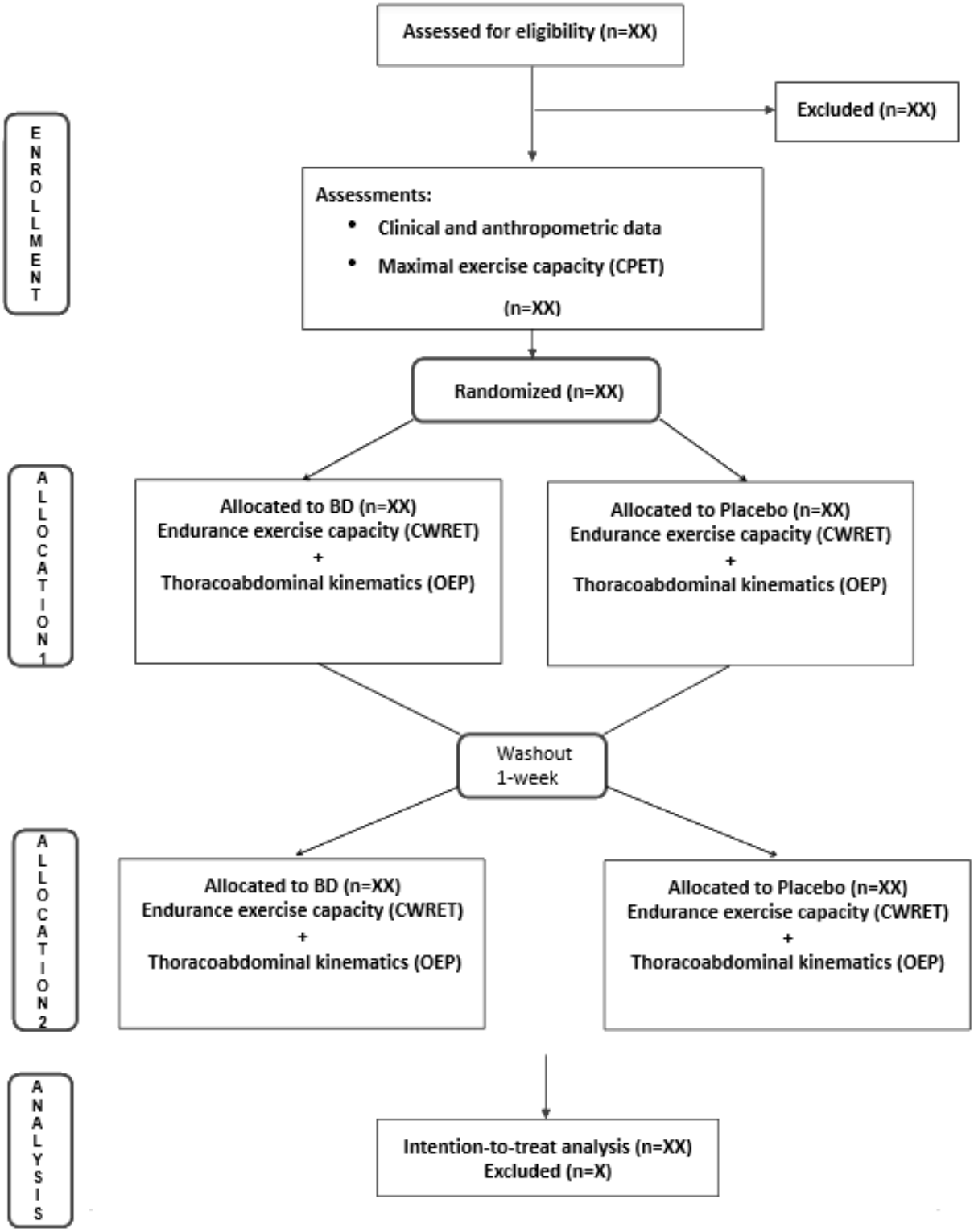

Ethical Considerations

Patients will be recruited from an outpatient tertiary clinic specializing in treating patients with NCFB at Hospital das Clínicas, Universidade de São Paulo, São Paulo-Brazil. The Hospital Research Ethics Committee of the University of São Paulo approved the study (approval 3.008.886). All participants will provide written informed consent prior to data collection. The data will be deidentified by excluding the main identifying elements such as name, address, date of birth, phone number, email, medical record number, institutional identification number, and social security number. Participants will receive an identification code, according to the order of inclusion in the study. The participants will be informed about the possibility of withdrawing at any time, without loss of their treatment at the institution. Additionally, the participant will be informed

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about the voluntary nature of their participation. Financial assistance for transportation will be available. This study is registered on ClinicalTrials.gov as NCT05183841.

Eligibility Criteria

Individuals aged 18-59 years, of either sex, diagnosed with NCFB on the basis of features on the computed tomography scan of the thorax [18], clinically stable (last 30 days without exacerbation/hospitalization), with trapped air on body plethysmography, that is, if residual volume/total lung capacity ratio is higher than 120% of the predicted [19,20], and physically inactive (<60 minutes of structured or planned physical activity per week) [21] will be eligible to participate. The exclusion criteria will be as follows: smokers or former smokers (>10 pack-years); other concomitant respiratory diseases, and cardiovascular or musculoskeletal diseases that may interfere with the patient's evaluations; uncontrolled arterial hypertension or diabetes; and pregnant or breastfeeding. Patients who have participated in a pulmonary rehabilitation program in the last 6 months or are participating in another research protocol as well as those with cognitive deficits that limit comprehension will also be excluded.

Experimental Design

Patients will be evaluated on 3 nonconsecutive days. Clinical data (anthropometrical and bronchiectasis severity assessed by FACED [FEV1% predicted score, Age, Chronic colonization by *Pseudomonas aeruginosa*, Radiological extension, Dyspnea]) [10] will be obtained from the participants' medical records. On day 1, pulmonary function will be assessed via whole-body plethysmography, and the maximal exercise capacity will be measured via a cardiopulmonary exercise test (CPET) to obtain the peak work rate (W_{peak}). On day 2, patients will be randomly allocated to receive BDs (160 µg of ipratropium bromide and 400 µg of fenoterol hydrobromide) or a placebo (norflurane or HFA134A, a harmless propellant), followed by simultaneous assessments of endurance exercise capacity (constant work-rate exercise test, CWRET) and thoracoabdominal kinematics (optoelectronic plethysmography). On day 3, after at least 1-week washout with no maximum deadline, the patient will repeat the same assessment as on day 2 in the reverse order. This washout period was defined according to the maximum BD withholding time (48 hours) [22], aiming to minimize the carryover effect. In case of NCFB exacerbation during the washout period, a 30-day recovery interval will be performed for the next assessment. Spirometric evaluations will be performed pre-CWRET before and after BDs or placebo. The time to the limit of tolerance (T_{lim}) will be obtained under both conditions (BDs and placebo). Thoracoabdominal kinematics will be assessed at 3 time points: at rest (T1), during the unloaded exercise (T2), and at 75% W_{peak} obtained from CPET (T3). Thoracoabdominal kinematics will assess volume variables, including total chest wall volume, compartmental volume, and TAA. The assessor and patient will be blinded to the intervention (BDs or placebo). All exercise tests will be performed on a cycle ergometer (Figure 2).

Figure 2. Experimental design. Assessment of endurance exercise capacity simultaneously with thoracoabdominal kinematics. OEP: optoelectronic plethysmography; T1: thoracoabdominal kinematics assessment at rest; T2: thoracoabdominal kinematics assessment at unloaded exercise; T3: thoracoabdominal kinematics assessment at 75% Wpeak; Tlim, time to the limit of tolerance; TV: television; Wmax: maximal or peak work rate.

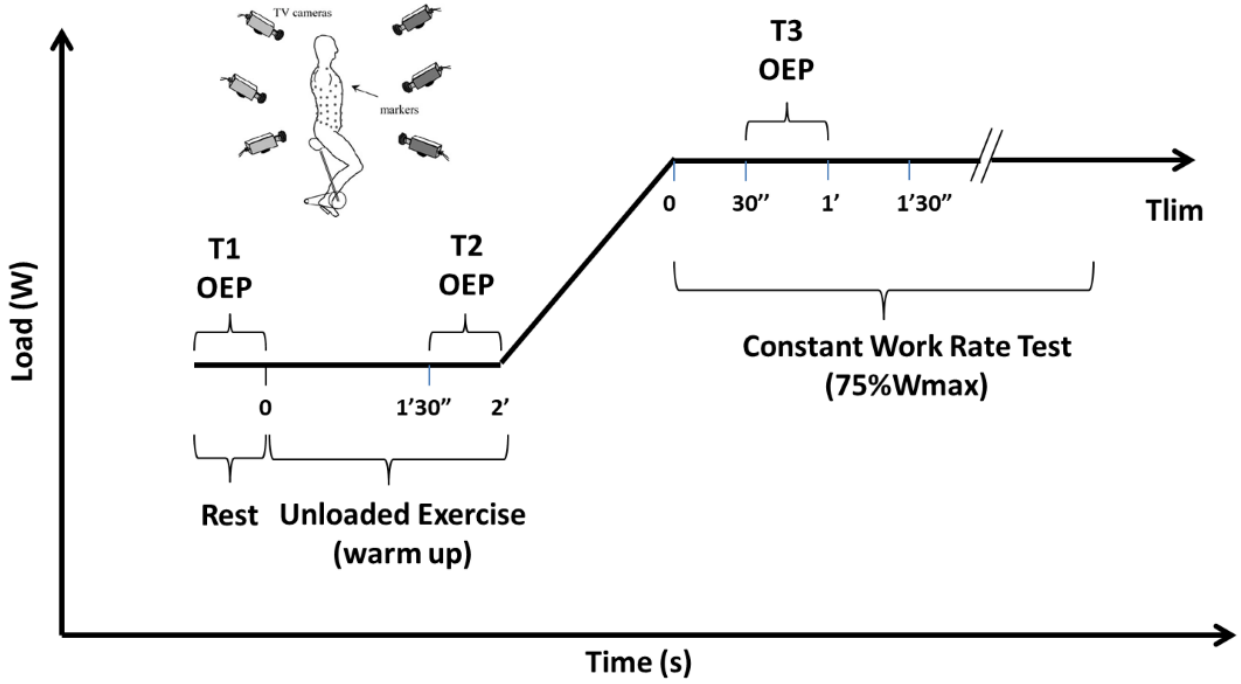

Pulmonary Function

Spirometry and lung volume measurements will be obtained via a calibrated spirometer (nSpire KoKoUSB Spirometer) and a whole-body plethysmograph (Elite Dx, Elite Series; Medical Graphics Corporation), respectively, according to standardized recommendations [23]. The measurement of the diffusing capacity of the lungs for carbon monoxide will be obtained by the single-breath maneuver in absolute and relative values [24]. The FVC, FEV1, total lung capacity, residual volume, and

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diffusing capacity of the lungs for carbon monoxide will be expressed as percentages of the predicted values [25-27]. Spirometric evaluations will be performed before CWRET and before and after BDs or placebo, and a change of >10% relative to the predicted value for FEV1 or FVC will be considered a positive response to the BD [24].

CPET Examination

CPET will be performed using an electrical cycle ergometer (Corival, Lode BV; Medical Technology) linked to a digital system equipped with an exercise evaluation system (CardioO2 System; Medical Graphics Corporation) in accordance with the American Thoracic Society/American College of Chest Physicians guidelines [28]. Peripheral oxygen saturation (SpO_2), as measured via pulse oximetry (Onyx, Model 9500; Nonin) and electrocardiography (Welch Allyn CardioPerfect, Inc), will be monitored continuously during the tests. The following variables will be recorded breath-by-breath during rest, exercise, and subsequent testing: work rate, oxygen consumption, minute ventilation, carbon dioxide production, respiratory exchange rate, and heart rate. Additionally, blood pressure, SpO_2, and the modified Borg scores (0-10) for leg discomfort and dyspnea [29] will be measured at rest and every 2 minutes during testing until the end of testing [30]. The participants will perform a ramp symptom-limited CPET consisting of 2 minutes of rest, 2 minutes of warm-up (unloaded pedaling), and an incremental work period (an increase from 10 W/min to 20 W/min, considering the patient's level of daily activity) [31]. The predicted CPET values will be obtained from the Brazilian population [32]. Although there is no specific information about the threshold at which arterial desaturation becomes hazardous, the test should be terminated if SpO_2 falls below 80% [33].

CWRET Analysis

CWRET will be performed using an electrical cycle ergometer after a CPET is completed for an appropriate work rate for CWRET to be estimated [34]. CWRET is selected to be 75%-80% of CPET W_{peak}. Continuous monitoring of SpO_2, heart rate, and modified Borg scores (0-10) for leg discomfort and dyspnea will be performed according to the American Thoracic Society/American College of Chest Physicians guidelines [28]. The target duration for CWRET will be 180 seconds to 480 seconds. For patients not achieving a baseline T_{lim} within 180-480 seconds, the work rate will be adjusted to bring T_{lim} within the desired range (ie, SD 5 W), and the test will be repeated [35].

Thoracoabdominal Kinematics

Thoracoabdominal kinematics will be evaluated by optoelectronic plethysmography (BTS), as previously described [36]. Briefly, a video is recorded with 8 solid-state charge-coupled cameras operating at 100 frames per second and synchronized with an infrared flashing light-emitting diode. Four cameras will be positioned in front of the participant and 4 behind; 89 retroreflective markers will be placed on the anterior and posterior sides of the trunk according to a previously described protocol [37]. A 3D calibration of the equipment will be performed on the basis of the manufacturer's recommendations. The assessment will be performed with the individual on a cycle ergometer at 3 time points, that is, at rest, during the unloaded exercise, and at 75% W_{peak}, according to the values obtained from CPET. The data analysis will use an average of 6 homogeneous respiratory cycles.

Allocation, Randomization, and Blinding

Eligible patients will be randomly allocated to either BD or placebo interventions. The randomization sequence will be computer-generated and placed in sealed, opaque, and numbered envelopes by a volunteer not involved in the study. The researcher who will provide the intervention (BD or placebo) will open the envelopes and will not be involved in the data collection or analysis. The participants will not be informed if they will receive BD or placebo intervention. The BD and placebo inhaler devices will be identical to the pressurized metered dose type. All the assessments will be performed by a blinded assessor for the interventions.

Interventions

Participants will be instructed not to consume alcohol or coffee or perform intense physical activity the day before the exercise test. In addition, they will be oriented to suspend routine BD medication for 6 hours for short-acting β-2 agonists and for 12 hours for short-acting muscarinic antagonists, and for 24 hours for long-acting β-2 agonists and 48 hours for long-acting muscarinic antagonists before the exercise test, according to the European Respiratory Society 2019 guidelines [22]. In case of exacerbation of symptoms during the period of BD suspension, the patient will be advised to use the medication, and the test will be rescheduled.

According to the randomization, a trained respiratory physiotherapist will administer either BD or placebo, ensuring proper treatment timing by using a timer and correct inhaler technique. Missed sessions will be rescheduled according to the participant's availability to improve patient adherence. The intervention will combine 2 BD compounds: ipratropium (20 µg) and fenoterol (50 µg). Ipratropium is a short-acting antimuscarinic agonist, and fenoterol is a short-acting β-2 agonist BD. The BD or placebo will be delivered to the patient via a pressurized metered-dose inhaler with a spacer at least 20 minutes prior to CWRET, and CWRET will be performed no more than 1 hour after the administration of BD or placebo.

BD and Placebo Delivery

The participants will be asked for total exhalation, followed by appropriate placement of the spacer mouthpiece with a nasal clip, and the first 8 puffs (30-second intervals between puffs, controlled by a timer) will be delivered through the opposite end of the spacer. The participants will be instructed to perform 5 tidal volume breaths for each puff. The total dose will consist of 160 µg of ipratropium and 400 µg of fenoterol.

Outcomes

Primary Outcome

The primary outcome will be T_{lim} in CWRET. T_{lim} has been proposed as the main variable for assessing responsiveness to BDs in patients with chronic respiratory diseases [33]. A minimum clinically important difference >60 seconds has been

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suggested from improvements in clinical outcomes in BD trials [33,35]. T_{lim} will be determined by the inability to maintain a pedaling frequency below 60 rpm for more than 10 seconds despite verbal encouragement.

Secondary Outcomes

The following variables will be obtained from optoelectronic plethysmography: total chest wall and compartmental (upper ribcage, lower ribcage, and abdominal) volumes and TAA values. Thoracoabdominal kinematics will be compared during BD and the placebo effect. The associations between thoracoabdominal kinematics and CWRET variables will be determined.

Additional Measures

To appropriately describe the individuals with NCFB at baseline, basic demographic data and medical information, including age, smoking status, ethnicity, sex, anthropometric (height and weight) measures, and BD use, will be recorded. All reported clinical data will be confirmed in the hospital medical record review.

Data Analysis

A sample of 39 participants was estimated as the number needed to provide 80% power to detect a between-group difference of 55.2 (SD 119.4) seconds in T_{lim}, according to a pilot study (n=10; 80% females; 47.90 [SD 10.95]; FEV1 57.25% [SD 35.08%] predicted; FVC 69.12% [SD 31.21%] predicted; residual volume/total lung capacity 196% [SD 18.01%] predicted). The final sample size will be set at 45 patients, assuming up to a 10% loss during follow-up. The results will be analyzed according to the intention-to-treat principle to preserve the effects of group allocation and to provide an assessment of the practical impact of the intervention [38], as recommended by the CONSORT (Consolidated Standards of Reporting Trials) statement [39] (Multimedia Appendix 1). A median substitution will be imputed with the missing data. Data distribution will be assessed via the Kolmogorov Smirnov test. Comparisons between BDs and placebo data will be analyzed via 1-sided *t* tests or Wilcoxon tests for T_{lim} and repeated-measures analysis of variance or Friedman tests for thoracoabdominal kinematics variables. The number of participants who achieved the minimum clinically important difference (>60 seconds) in CWRET between BDs and placebo will be compared via chi-square tests. Pearson or Spearman correlation will be used to verify the associations between CWRET and thoracoabdominal kinematics variables. *P* values <.05 indicate statistical significance. The carryover, period, and sequence effects for T_{lim} will be estimated using generalized estimating equations models. If the carryover effect is not significant, a reduced model excluding the carryover term will be refitted. The statistical analysis will be performed using SPSS software (version 17.0; IBM Corp).

Results

This study was funded by São Paulo Research Foundation (FAPESP, grants 2018/17788-3) and Conselho Nacional de Desenvolvimento Científico e Tecnológico (grant 312.279/2018-3) for the CardioO2 system (Medical Graphics Corporation) and the optoelectronic plethysmography system, respectively. The ethics approval (3.008.886) was granted in November 2018. The pilot study commenced in April 2019 but was interrupted due to the COVID-19 pandemic in early 2020; it was restarted and completed in April 2022. As of December 2023, enrolling by invitation is the last status of Clinical Trials.gov PRS (NCT05183841). Consent was obtained from 39 patients until May 2025. Of the 39 consented patients, one was excluded due to difficulty performing the cycle ergometer test and 6 patients did not complete the protocol. Data collection is expected to continue until November 2025. Data analysis is anticipated to begin in 2025, with initial results anticipated to be reported on and published after the completion of data collection. The publication of results is anticipated to be in 2025-2026.

Discussion

Principal Findings and Comparison to Prior Work

This randomized, controlled, double-blind crossover trial is intended to test the effect of dual bronchodilation on the exercise capacity of individuals with NCFB. In clinical practice, BDs have been recommended to treat only symptomatic individuals with NCFB [4]. Despite the common use of BDs in this population, there are no reports of their effects on the patient's exercise capacity. A previous study showed no difference in the 6-minute walking test results of individuals with NCFB after a 6-month BD treatment (tiotropium) compared to the control group [13]. However, the exercise capacity was not the primary end point of this trial, and the 6-minute walking test is not the most appropriate choice for evaluating that outcome.

BDs have long been recommended to reduce exercise-induced bronchoconstriction and exercise limitation in patients with asthma and COPD, respectively [7,8]. According to the Global Initiative for Chronic Obstructive Lung Disease [8], BDs are recommended for individuals with severe disease, symptoms, or exercise limitations, as BDs reduce airway resistance, promote lung deflation, and enable better alveolar ventilation at rest and during exercise. Furthermore, dual bronchodilation is associated with better physical endurance capacity, exercise capacity, and physical activity level in individuals with COPD [40]. Additionally, TAA is very prevalent in individuals with COPD and is associated with exercise limitations [15,16]. The main effect of BDs on the ventilatory capacity is an increase in basal inspiratory capacity and a reduction in dynamic hyperinflation during exercise, enhancing exercise performance [17]. Most individuals with NCFB have airflow obstruction [41], air trapping, and diffusion impairment [42,43]; however, no studies have evaluated TAA or thoracoabdominal kinematics of patients with NCFB. Extrapulmonary features such as peripheral muscle endurance, exercise capacity, and health status are also affected by NCFB [44]. Hence, it seems plausible that BDs may improve the exercise capacity of individuals with NCFB, similar to what has been observed in individuals with COPD. Therefore, we hypothesize that dual bronchodilation can improve the exercise capacity of individuals with NCFB and reduce TAA during exercise.

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Strengths and Limitations

The strengths of this study include patient randomization and the crossover design, which reduce variability and increase statistical power. Besides, this is the first study to assess the exercise capacity and thoracoabdominal kinematics simultaneously of individuals with NCFB. Taken together, the results may highlight the effect of BD on exercise capacity and clarify a possible mechanism associated with it. The main limitation of this study is that patients will be recruited from a single referral hospital, and individuals with long-term oxygen therapy will be excluded. Unfortunately, we had to exclude patients with long-term oxygen therapy because our CPET equipment does not assess oxygen consumption with supplemental oxygen use, as it requires a special component. These limitations reduce the external validity of our results.

Future Directions and Conclusion

Clinicians and researchers agree that the effect of BD in patients with NCFB and information in this field is urgently needed. If successful, this study will demonstrate that BDs can improve the exercise capacity in adults with NCFB and reduce TAA during exercise. Since exercise capacity reflects a patient's functional status, future studies may explore whether its optimization can enhance independence and the quality of life in this population.

Acknowledgments

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Authors' Contributions

Conceptualization: RAA (lead), CRFC (equal), CCBMS (equal), SDC (supporting)
Data curation: CCBMS (lead), ACL (supporting), AJF (supporting)
Formal analysis: CCBMS (lead), CRFC (supporting)
Investigation: CCBMS
Methodology: CCBMS (lead), RAA (equal), CRFC (equal), SDC (supporting), AJF (supporting), SZR (supporting)
Project administration: CCBMS (lead), CRFC (equal), (supporting)
Resources: CRFC
Supervision: CRFC (lead), RAA (equal)
Writing – original draft: CCBMS (lead), CRFC (supporting)
Writing – review & editing: CCBMS (lead), CRFC (supporting), RAA (supporting), SDC (supporting), ACL (supporting), AJF (supporting), SZR (supporting)

Conflicts of Interest

RAA received honoraria lecture fee in the last 24 months from AstraZeneca, Boehringer, Chiesi, GlaxoSmithKline, Sanofi, and Vertex.

Multimedia Appendix 1
CONSORT checklist.
[PDF File (Adobe PDF File), 304 KB - resprot_v14i1e68582_app1.pdf]

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Abbreviations

BD: bronchodilator
CONSORT: Consolidated Standards of Reporting Trials
COPD: chronic obstructive pulmonary disease
CPET: cardiopulmonary exercise test
CWRET: constant work-rate exercise test
FACED: FEV1% predicted score, Age, Chronic colonization by Pseudomonas aeruginosa, Radiological extension, Dyspnea
FEV1: forced expiratory volume in the first second
FVC: forced vital capacity
NCFB: non-cystic fibrosis bronchiectasis
SpO2: peripheral oxygen saturation
TAA: thoracoabdominal asynchrony
Tlim: time to the limit of tolerance

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Wpeak: peak work rate

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Protocol

Qizhi Jieyu Pill for the Treatment of Cerebral Infarction During the Recovery Phase: Protocol for a Randomized Controlled Clinical Trial

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Abstract

Background: Cerebral infarction, a life-threatening neurodegenerative disease, is one of the leading causes of disability and death. The recovery phase is a critical period for patients to regain cognitive ability, memory, and motor functions and to improve their ability to perform daily activities. Over the past 10 years, we have applied Qizhi Jieyu pill in the treatment of patients in the recovery phase of cerebral infarction. We retrospectively analyzed clinical data from 152 patients and found preliminary results suggesting that Qizhi Jieyu pill may help alleviate clinical symptoms, improve quality of life, and reduce the recurrence of cerebral infarction. However, the lack of high-quality clinical evidence supporting its efficacy and safety has limited its widespread clinical application.

Objective: This protocol describes a randomized controlled trial aiming to evaluate the efficacy and safety of Qizhi Jieyu pill in patients during the recovery phase of cerebral infarction.

Methods: This study adopts a multicenter, randomized controlled clinical trial design. A total of 126 patients aged 30-70 years in the recovery phase of cerebral infarction will be recruited and randomly assigned in a 1:1 ratio to either the study group (n=63, receiving conventional treatment plus Qizhi Jieyu pill) or the control group (n=63, receiving conventional treatment alone). The intervention period will last 12 weeks, and the total follow-up period will be 48 weeks. The primary outcome is the change in the National Institutes of Health Stroke Scale score at week 48. Secondary outcomes include changes in traditional Chinese medicine syndrome scores, the recurrence rate of cerebral infarction, and modified Rankin Scale scores. Adverse events will be recorded and used to assess the safety profile. All data analyses will be performed according to a prespecified statistical analysis plan.

Results: The study received ethics approval on March 3, 2025, from the Ethics Committee of Guang'anmen Hospital, China Academy of Chinese Medical Sciences (2025-025-KY-01) and was registered on April 6, 2025. Participant recruitment began on April 10, 2025, and is expected to be completed by December 31, 2025. Final results will be published by December 31, 2026.

Conclusions: This study is the first randomized controlled clinical trial to evaluate the efficacy and safety of Qizhi Jieyu pill in the treatment of patients during the recovery phase of cerebral infarction. It will contribute to the development of integrated treatment strategies, potentially leading to broader clinical adoption, by providing a high-quality, evidence-based treatment option for clinical practice.

Trial Registration: International Traditional Medicine Clinical Trial Registry ITMCTR2025000653; https://itmctr.ccebtcm.org.cn/mgt/project/view/2028021950497347405/false

International Registered Report Identifier (IRRID): PRR1-10.2196/75982

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(JMIR Res Protoc 2025;14:e75982) doi:10.2196/75982

KEYWORDS

cerebral infarction; recovery phase; Qizhi Jieyu pill; clinical research; study protocol

Introduction

Cerebral infarction, a life-threatening neurodegenerative disease, predominantly affects older adults and is classified as an ischemic cerebrovascular event [1]. Due to the various degrees and types of brain damage it causes—such as brain tissue lesions, structural damage, neuronal death, and dysfunction—it remains one of the leading causes of disability and death [2,3]. According to the 2019 Global Burden of Disease study, the age-standardized incidence rate of cerebral infarction in China was 144 per 100,000, and the age-standardized prevalence was 1255.9 per 100,000. With the acceleration of population aging, the burden of this disease is expected to continue rising [4].

The acute phase of cerebral infarction progresses rapidly, with most patients entering the recovery phase approximately 2 weeks after onset, which typically lasts about 6 months. The recovery phase is crucial for regaining cognitive ability, memory, and motor functions, thereby enhancing daily living capabilities. Hence, rehabilitation during this stage is a hot topic in clinical research [5]. Core treatment strategies during this phase primarily include antiplatelet therapies, such as aspirin, clopidogrel, sarpogrelate, and cilostazol, aimed at reducing stroke recurrence and improving neurological function [6-8]. However, these treatments have yet to effectively address the high recurrence and disability rates.

Multiple clinical studies have confirmed that traditional Chinese medicine (TCM) therapies—such as Buyang Huanwu decoction and acupuncture—can significantly improve clinical symptoms during the recovery phase of cerebral infarction. These include reducing the recurrence rate of cerebral infarction, enhancing neurological function, and mitigating the severity of neurological deficits, making TCM a vital component of stroke rehabilitation [9-14].

We have used Qizhi Jieyu pill, composed of traditional herbs such as *Panax notoginseng* and leech, in clinical practice for over 10 years to treat patients during the recovery phase of cerebral infarction. Preliminary, retrospective analysis of 152 cases indicates that Qizhi Jieyu pill may alleviate clinical symptoms, improve quality of life, and reduce recurrence. This suggests its potential as an important therapeutic option during the recovery phase. However, there is still a lack of high-quality clinical studies to validate its efficacy and safety.

This study aims to evaluate the efficacy and safety of Qizhi Jieyu pill in the treatment of patients during the recovery phase of cerebral infarction through a randomized controlled clinical trial. We hypothesize that the addition of Qizhi Jieyu pill to conventional treatment will result in greater improvement in National Institutes of Health Stroke Scale (NIHSS) scores and lower recurrence rates compared to conventional treatment alone.

Methods

Study Design

This study aims to evaluate the efficacy and safety of Qizhi Jieyu pill in the treatment of cerebral infarction during the recovery phase. It adopts a multicenter, randomized controlled clinical trial design and will be conducted in accordance with the principles of the Declaration of Helsinki, the Good Clinical Practice guidelines, and Chinese regulations. The study will be carried out at Guang'anmen Hospital, China Academy of Chinese Medical Sciences, and Wuzhai County Hospital of Traditional Chinese Medicine.

Ethical Considerations

The Ethics Committee of Guang'anmen Hospital of the China Academy of Chinese Medical Sciences approved the study (2025-025-KY-01). All patients provided their written informed consent to participate in the study and authorized the publication of their data. The trial has been registered with the International Traditional Medicine Clinical Trial Registry (ITMCTR2025000653).

Sample Size Calculation

The clinical sample size was calculated using a 2-group mean difference test (shown below), where n is the required sample size per group, σ is the pooled SD of the 2 groups, α is the type 1 error, β is the type 2 error, and δ is the expected mean difference between the study and control groups.

Since there are currently no direct data available to calculate the clinical sample size, we mainly referred to 2 clinical studies [15,16]. In these studies, the NIHSS score change value in the control group (conventional treatment) was approximately 4.9. The pooled SD (σ) was estimated based on prior studies that reported SDs ranging from 1.5 to 2.5. We conservatively used σ=2.0 in our calculation to ensure adequate power. It is hypothesized that the change in the study group (conventional treatment plus Qizhi Jieyu pills) would be approximately 6, with a mean difference of 2 between the 2 groups. Assuming a 1:1 sample ratio between the control and study groups with α=0.05 and β=0.2, the required sample size per group is 52. Considering an overall dropout rate of 20%, each group needs 63 participants, for a total of 126 participants. A third-party group composed of experts in TCM, endocrinology, and statistics will be organized at the midterm of the study to reassess the sample size based on the observed effect size of the primary efficacy indicators and associated errors. Figure 1 shows the study flowchart.

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Figure 1. Study flowchart illustrating the trial design, including the screening of 126 eligible participants with cerebral infarction in the recovery phase, randomization into 2 groups (Qizhi Jieyu pill plus conventional treatment versus conventional treatment alone), a 12-week treatment period, and follow-up assessments at weeks 12, 24, 36, and 48. The outcomes assessed include changes in National Institutes of Health Stroke Scale (NIHSS) scores, traditional Chinese medicine (TCM) symptom scores, recurrence rates, Rankin Scale scores, and adverse events.

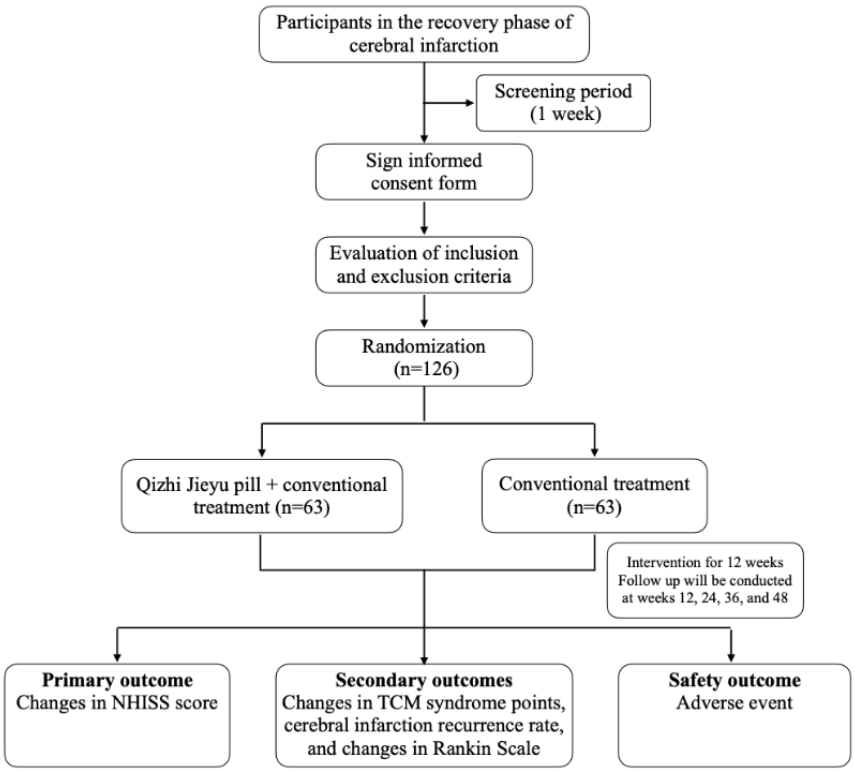

Participants

Cerebral Infarction Diagnostic Criteria

Referring to the 2014 Chinese guidelines for diagnosis and treatment of acute cerebral infarction issued by the Cerebrovascular Disease Group of the Neurology Branch of the Chinese Medical Association [17], diagnostic criteria include sudden onset, focal neurological deficits (occasionally generalized), symptoms and signs lasting more than 24 hours, exclusion of nonvascular brain lesions, and computed tomography (CT) or magnetic resonance imagining (MRI) excluding cerebral hemorrhage or other abnormalities, with a responsible ischemic lesion.

Diagnostic Criteria for the Recovery Phase of Cerebral Infarction

Referring to the 2017 guidelines for integrated traditional Chinese and western medicine diagnosis and treatment of cerebral infarction in China [18], within 6 hours of onset is the hyperacute phase, around 2 weeks postonset is the acute phase, 2 weeks to 6 months postonset is the recovery period, and more than 6 months postonset is the sequelae phase.

Diagnostic Criteria for Phlegm-Stasis Obstruction Syndrome

The diagnostic criteria are based on the Standards for the TCM Diagnosis and Therapeutic Evaluation of Stroke (Trial Version, 1995), drafted by the Encephalopathy Emergency Research Collaboration Group of the State Administration of Traditional Chinese Medicine [19], and include dizziness and vertigo, profuse and sticky phlegm, dark tongue body, thin white or greasy white tongue coating, and a wiry-slippery pulse.

Inclusion Criteria

Criteria for inclusion in the study are as follows:

1. Patients diagnosed with cerebral infarction and currently in the recovery phase.
2. Patients aged 30-70 years.
3. Patients who voluntarily signed the informed consent form.

Exclusion Criteria

Criteria for exclusion from the study include the following:

1. Patients diagnosed with intracranial hemorrhagic disease by head CT or MRI.
2. Patients with abnormal clinical laboratory tests, including alanine aminotransferase or aspartate aminotransferase ≥2.5 times the upper limit of normal or creatinine above the upper limit of normal.
3. Patients unable to understand or comply with the study protocol due to severe psychiatric, cognitive, or emotional disorders.
4. Patients with other diseases affecting limb mobility that may impact neurological assessments.
5. Women who are pregnant, breastfeeding, or planning to conceive in the near future.
6. Patients with a suspected or confirmed history of alcohol or drug abuse within 6 months prior to onset.
7. Patients with a known or suspected allergy to the investigational drug or those with an allergic constitution.

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8. Patients who have participated in another clinical trial within the last 3 months.
9. Other situations judged by the investigator to reduce the likelihood of enrolment or complicate enrolment.

Criteria for Case Elimination

The following are criteria for case elimination:

1. After enrollment, cases were found not to meet the inclusion criteria or to meet the exclusion criteria.
2. Cases involving the use of prohibited medications as per protocol, necessitating elimination due to protocol violations.
3. Cases in which the medication was never received or the exposure did not meet the experimental requirements.
4. Cases with no evaluable records after medication administration.

Trial Termination Criteria

Satisfaction of any of the following criteria will result in discontinuation of the clinical trial before the planned end in order to protect participants' rights and ensure research quality:

1. Serious safety issues arising during the study requiring immediate termination.
2. Major errors discovered in the clinical research protocol, making it difficult to evaluate drug efficacy; or important deviations occurring from a well-designed protocol, compromising the efficacy evaluation.
3. Very favorable outcomes observed in the TCM group during the study warranting that the trial be terminated early to allow the control group to receive the TCM treatment.
4. Termination requested by the research team (eg, due to funding or management issues).
5. Termination required by administrative authorities.

Conditions and Procedures for Participant Withdrawal

There are two routes for participant withdrawal.

Withdrawal determined by the investigator: This may occur when a participant already enrolled in the study becomes unsuitable for continued participation due to the development of complications, comorbidities, or special physiological changes. Other conditions include poor compliance, defined as taking less than 80% or more than 120% of the prescribed medication, and the use of prohibited medications as per protocol.

Participant-initiated withdrawal: According to the informed consent form, participants have the right to withdraw at any time. If a participant stops taking the medication or attending visits without formally withdrawing, they are still considered "withdrawn" (or "lost to follow-up"). Reasons for withdrawal should be documented where possible and may include feeling the treatment is ineffective, the development of intolerable adverse reactions, personal circumstances, financial reasons, or unexplained loss to follow-up.

Regardless of the reason, case report forms for withdrawn participants should be retained. The last recorded test results will be used as final data, and both efficacy and adverse events will be analyzed in the full dataset.

Intervention

Referring to the guidelines for clinical management of cerebrovascular diseases in China (second edition) [20], both groups will receive conventional rehabilitation training guidance, including assessment and rehabilitation of cognitive function, speech ability, swallowing function, limb motor and sensory function, balance, psychological state, and daily living abilities. They will also receive standard treatments such as antiplatelet therapy, lipid-lowering and blood pressure control, plaque stabilization, and electrolyte balance maintenance.

On the basis of conventional treatment, the study group will take Qizhi Jieyu pills, 9 g per dose, twice daily after meals. The control group will receive conventional treatment only. The intervention period is 12 weeks, with a total follow-up period of 48 weeks.

All TCM drugs with the same therapeutic effect as the investigational drug (including those with similar indications or efficacy stated in the instructions) are prohibited during the study. All concomitant medications and treatments (ie, for other diseases) must be recorded in the concomitant medication log.

Study Procedures

Table 1 outlines the specific measurements and timepoints for data collection in this study. Eligible participants will undergo a 1-week preintervention screening period, a 12-week treatment period, and a total 48-week follow-up period. After the study begins, all enrolled participants will have follow-up visits every 12 weeks. All participants will be informed of the study through oral and written information and will be required to sign an informed consent form.

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Table 1. Clinical trial research timeline.

Item	Screening period and baseline	Visit 1	Visit 2	Visit 3	Visit 4
Visit time	–7 to 0 days	12 weeks ± 7 days	24 weeks ± 7 days	36 weeks ± 7 days	48 weeks ± 7 days
Collect basic medical history					
Sign informed consent form	×				
Fill in general information	×				
Medical history and treatment history	×				
Determine the inclusion and exclusion criteria	×				
Vital signs	×	×	×	×	×
Physical examination	×	×	×	×	×
Merge diseases and medication	×	×	×	×	×
Diagnosis and monitoring inspection					
Urine pregnancy test	×				
Blood sugar, blood pressure, and blood lipids	×	×	×	×	×
Brain CT[a] or MRI[b]	×	×	×	×	×
Effectiveness outcome					
NHISS[c] score	×	×	×	×	×
Recurrent cerebral infarction	×	×	×	×	×
Traditional Chinese medicine symptom score	×	×	×	×	×
Rankin Scale	×	×	×	×	×
Physical and chemical examination					
Routine bloods, routine urine, and microscopic examination	×			×	×
Routine stool	×			×	×
Vital signs	×	×	×	×	×
Electrocardiogram and liver and kidney function	×	×	×	×	×
Adverse events		×	×	×	×
Other items					
Randomization	×				
Distribute medication and patient diary cards	×	×	×	×	
Recycling drugs and quantity statistics		×	×	×	×
Retrieve patient diary cards		×	×	×	×
Conclusion of the study					×

[a]CT: computed tomography.
[b]MRI: magnetic resonance imaging.
[c]NIHSS: National Institutes of Health Stroke Score.

Outcomes

Primary Outcome

The primary outcome is the change in NIHSS score at 48 weeks [21]. This scale evaluates levels of consciousness, command compliance, eye movement, visual field defects, facial paralysis, limb motor dysfunction, ataxia, speech expression, and other parameters.

Secondary Outcomes

The 3 secondary outcomes are the change in TCM syndrome scores, cerebral infarction recurrence rates, and the change in Rankin Scale scores.

A comparison of TCM syndrome scores before and after the medication will be conducted. Based on the guiding principles for clinical research of new Chinese medicines [22], efficacy is categorized as cured, markedly effective, effective, or

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ineffective according to the change in TCM syndrome scores. TCM symptoms include dizziness, headache, irritability, limb stiffness, neck stiffness, limb numbness, excessive phlegm, shortness of breath, fatigue, spontaneous sweating, dry stool or constipation, dry mouth or thirst, red or dark tongue, and yellow-greasy tongue coating.

In addition, we will use an intelligent TCM diagnostic device (produced by Shenzhen Huiyibida Medical Technology Co, Ltd) to collect tongue images, tongue coating, and pulse information from patients at multiple timepoints. Two study physicians will independently record patients' clinical symptom information to monitor changes in TCM symptoms and the potential evolution of syndromes.

The cerebral infarction recurrence rate will be evaluated every 12 weeks by CT or MRI and calculated as the number of recurrent cases / the total study population × 100%.

Finally, a comparison of pretreatment and post-treatment Rankin Scale scores will be conducted [23]. The Rankin Scale evaluates neurological recovery after stroke in 6 levels: 0=no symptoms at all, 1=symptoms present but no significant disability, 2=slight disability, 3=moderate disability, 4=moderately severe disability, 5=severe disability, and 6=death.

Safety Outcomes

Safety will be assessed using the following monitoring indicators:

1. Vital signs, including temperature, blood pressure, respiration rate, and heart rate, checked every 12 weeks.
2. Routine tests, including blood, urine, and stool tests, every 12 weeks.
3. Other labs and diagnostics, including electrocardiograms, liver function tests (alanine aminotransferase, aspartate aminotransferase, gamma-glutamyltransferase, alkaline phosphatase, and total bilirubin), and kidney function tests (blood urea nitrogen and creatine), every 12 weeks.
4. Adverse events: From the time the participant enters the study until the final follow-up, adverse events will be monitored for 48 weeks. All information related to adverse events will be carefully recorded at all times. Serious adverse events refer to any unexpected clinical events occurring at any dose that result in hospitalization, prolongation of existing hospitalization, disability, impaired ability to work, life-threatening conditions or death, or congenital malformations. Serious adverse events will be reported to the study center and the principal medical ethics committee. In addition, they will be reported to the National Medical Products Administration within 24 hours. Meanwhile, we will specifically record adverse events potentially related to animal-derived components, such as itching, rash, allergic reactions, and gastrointestinal discomfort.

Randomization

Random numbers will be generated using SAS statistical software (version 9.4), and participants will be assigned to the intervention and control groups in a 1:1 ratio. After screening and informed consent, patients will be randomly assigned to one of the two groups based on their order of enrolment. The drug number for each participant will remain unchanged throughout the study. In the case of a clinical emergency, the participant's random code and group assignment may be unblinded.

Due to the nature of the intervention, participant and clinician blinding is not feasible. However, outcome assessors will be blinded to group assignments to minimize detection bias, especially for subjective measures such as TCM symptom scores.

Data Collection and Management

Clinical Materials and Samples

All materials, clinical test results, and biological samples (blood, urine, and stool) will be stored securely at each subcenter after every follow-up and handed over to the principal investigator at the end of the study for archiving.

Data Recording and Storage Method

Paper-based case report forms (CRFs) will be used for this study. Although paper-based CRFs will be used, we will adopt a double-entry system and periodic data verification procedures. Digital scans of CRFs will be backed up, and a central data management team will oversee consistency and integrity across sites.

Data Quality Assurance Measures

Standard operating procedures will be established. All study personnel, including clinical investigators and CT and MRI technicians, will receive unified training.

All principal investigators at participating centers will be assessed and authorized by the project leader.

Requirements for filling in the CRFs will be strictly enforced. Records must be accurate, complete, and truthful. Corrections, if necessary, should be made with a single line through the error. The correction should be entered next to it, signed and dated.

Monitoring and audit standard operating procedures will be developed. Regular on-site monitoring visits will be conducted by the project leader to ensure compliance with the study protocol and verify that CRF data match the original source documents.

Statistical Analysis

Definition and Selection of Statistical Analysis Datasets

Participants will be categorized into the following analysis sets:

1. Full analysis set: This includes all randomized participants who have at least 1 postbaseline efficacy evaluation. This is the main dataset for efficacy analysis. Missing values for primary efficacy outcomes will be imputed using the last observation carried forward method. Missing values for secondary efficacy and safety outcomes will not be imputed. For secondary efficacy endpoints and safety data, descriptive analysis and complete-case analysis will be conducted based on actual observed values. Although last observation carried forward is commonly used in clinical trials, we acknowledge its limitations in progressive

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conditions such as stroke recovery. We will perform sensitivity analyses using multiple imputation methods to evaluate the robustness of our results.

2. Per protocol set: This includes all participants in the full analysis set who meet inclusion criteria, do not meet exclusion criteria, complete the treatment, and do not have major protocol deviations. This is the secondary dataset for efficacy evaluation.
3. Safety set: This includes all randomized participants who received at least 1 dose of Qizhi Jieyu pill and had at least 1 postbaseline safety evaluation.

Statistical Analysis Plan

A statistical analysis plan was formulated prior to the start of the study. It will be finalized after discussion among the statisticians, principal investigators, and sponsor before database lock. This plan describes only the standard statistical requirements.

Statistical analysis will be conducted using SAS version 9.4. All hypothesis tests will be 2-sided, with a significance level of α=.05. *P* values less than or equal to .05 will be considered statistically significant.

For continuous variables, mean, SD, minimum, maximum, and median values will be used for descriptive statistics. Independent samples *t* tests (for normally distributed data) or Wilcoxon rank-sum tests (for non-normally distributed data) will be used for hypothesis testing. Normality of continuous variables will be assessed using the Shapiro-Wilk test before choosing appropriate parametric or nonparametric tests.

For categorical variables, frequency and percentages will be used for description. Chi-square tests or Fisher exact tests will be used for hypothesis testing. Ordinal variables will be analyzed using the Wilcoxon rank-sum test.

Logistic regression will be used to control for confounding factors affecting the outcome measures. We will also analyze the association between syndrome evolution patterns and therapeutic efficacy. In parallel, multivariate linear regression will be used to explore the relationship between outcomes and potential confounders, such as baseline NIHSS score, study center, age, and sex. For adverse events potentially associated with animal-derived components—including itching, rash, allergic reactions, and gastrointestinal discomfort—we will conduct attribution analysis and report their incidence separately.

Results

The study was approved by the Ethics Committee of Guang'anmen Hospital, China Academy of Chinese Medical Sciences, on March 3, 2025 (2025-025-KY-01), and was registered on the International Traditional Medicine Clinical Trial Registry on April 6, 2025 (ITMCTR2025000653), and any potential protocol amendments will be recorded there. Participant screening began on April 10, 2025, with enrolment expected to be completed by December 31, 2025. The final study results are planned to be published by December 31, 2026.

This study aims to evaluate the efficacy and safety of Qizhi Jieyu pill in the treatment of patients in the recovery phase of cerebral infarction, providing a treatment option supported by high-quality, evidence-based medicine for the clinical management of recovery phase cerebral infarction.

Discussion

Principal Findings

Given the functional impairments and neurological damage caused by cerebral infarction, it remains one of the leading causes of mortality and disability. Qizhi Jieyu pill has been used in clinical practice for over 10 years, with its primary therapeutic advantages including the improvement of clinical symptoms and reduction in the recurrence rate of cerebral infarction. However, due to the lack of standardized clinical research, there is currently no high-quality, evidence-based support for its efficacy and safety, which limits its widespread clinical application. Therefore, conducting this study to evaluate its effectiveness and safety in the recovery phase of cerebral infarction is of significant clinical value.

The upcoming study adopts a multicenter, randomized controlled clinical trial design, with a rigorously calculated sample size. Given the therapeutic advantages of Qizhi Jieyu pill, we primarily include patients in the recovery phase, which is a critical period for exerting its therapeutic effects. For outcome evaluation, we considered the adverse outcomes caused by cerebral infarction, including disability rates. Thus, we selected the change in NIHSS scores as the primary outcome, and changes in TCM syndrome scores, the recurrence rate of cerebral infarction, and Rankin Scale scores as secondary outcomes. Our standardized design facilitates rigorous and normative evidence acquisition. While the NIHSS and Rankin Scale are internationally recognized neurological assessments, TCM syndrome scores reflect TCM's holistic evaluation of patient recovery. By combining these, we aim to provide a comprehensive understanding of therapeutic efficacy from both biomedical and TCM perspectives.

Qizhi Jieyu pill consists of 26 herbal and animal-derived medicinal components, including *Panax notoginseng*, *Hirudo*, *Buthus martensii*, *Scolopendra*, *Pheretima*, *Gastrodia elata*, *Uncaria*, *Cassia seed*, *Bombyx batryticatus*, *Acorus tatarinowii*, *Polygala*, *Typhonium giganteum*, and *Astragalus*, among others. It is formulated to remove blood stasis and phlegm, unblock collaterals to extinguish wind, and tonify the spleen and kidneys. Astragaloside IV, a major active compound of *Astragalus*, may promote angiogenesis via the silencing regulatory protein 7 (SIRT7)/vascular endothelial growth factor A (VEGFA) signaling pathway to improve brain tissue damage postcerebral infarction [24]. Astragaloside I has been shown to activate the transforming growth factor-β (TGF-β)/Smad signaling pathway and exert antioxidant effects, significantly improving cognitive dysfunction in rats with cerebral infarction [25,26]. *Gastrodia elata* can effectively reduce brain necrosis area, infarct volume, and inflammatory factor levels in rats with cerebral ischemia-reperfusion injury, with mechanisms involving the modulation of gut microbiota [27]. In addition, gastrodin, an active ingredient in *Gastrodia elata*, can increase the expression of miR-20a-5p in circulating exosomes and X-linked inhibitor of apoptosis protein (XIAP) in the ischemic hemisphere, thus

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promoting neurological recovery in rats with middle cerebral artery occlusion [28]. Ginsenoside Rg1 (G-Rg1), a key component of *Panax ginseng*, can reduce neural injury, infarct volume, and blood-brain barrier permeability in focal cerebral ischemia in rats, potentially through downregulation of protease-activated receptor-1 (PAR-1) expression [29]. These studies provide mechanistic support for the potential of Qizhi Jieyu pill as an effective treatment for cerebral infarction.

Comparison to Prior Work

Compared with prior clinical trials evaluating TCM interventions, such as Tiandan Tongluo capsule [16] and Yindan Xinnaotong soft capsule [15], for poststroke rehabilitation, our study exhibits several innovative features. First, it adopts a longer follow-up period of 48 weeks, enabling a more comprehensive assessment of long-term outcomes such as recurrence and disability. Second, it incorporates a broader inclusion framework without limiting to specific TCM syndrome types, thus improving generalizability. Third, the outcome evaluation uses a dual-system framework that combines biomedical scales (NIHSS and modified Rankin Scale) with standardized TCM syndrome scores, thus enhancing the clinical interpretability of integrative medicine. Finally, our trial is grounded in over a decade of practical experience with Qizhi Jieyu pill and is the first to systematically evaluate this compound through a rigorously designed randomized controlled trial supported by mechanistic insights from pharmacological research.

Strengths and Limitations

This study is innovative as it is the first rigorously designed randomized controlled trial to evaluate Qizhi Jieyu pill in the recovery phase of cerebral infarction. It introduces an integrative outcome framework combining biomedical and TCM assessments, targets a critical therapeutic window often overlooked in prior studies, and adheres to international methodological standards to provide high-quality, generalizable evidence for clinical practice. However, this study has certain limitations in its design. First, we did not adopt a blinded design, primarily because the recovery phase represents a critical therapeutic window for patients with cerebral infarction during which timely and standardized treatment is essential. Second, while Qizhi Jieyu pill includes both herbal and animal-derived components and our evidence may demonstrate significant clinical benefits, the active ingredients and mechanisms of action will not be specifically explored in this study; we plan to investigate these in subsequent research. Furthermore, our inclusion and exclusion criteria excluded patients younger than 30 years as they represent a low-risk population for cerebral infarction and older than 70 years due to common comorbidities and lower adherence, which could impact the effectiveness and safety evaluation of our intervention.

Future Directions

In summary, this is the first randomized controlled clinical trial evaluating the efficacy and safety of Qizhi Jieyu pill for patients in the recovery phase of cerebral infarction. The study is expected to contribute to the development of strategies for the clinical treatment of poststroke recovery and promote its successful application in routine clinical practice.

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Authors' Contributions

XA and LY conceived and designed the study. XA drafted the initial manuscript. YM, JZ, SG, JX, PZ, HX, FG, XW, YG, YJ, and YL will participate in the clinical implementation of the study. XA will perform the statistical analyses. All authors interpreted the data and critically reviewed the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CRF: case report form
CT: computed tomography
MRI: magnetic resonance imaging
NIHSS: National Institutes of Health Stroke Scale
TCM: traditional Chinese medicine

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Protocol

Honey as a Wound Care Modality in Treating Deep Neck Space Abscesses: Protocol for a Randomized Controlled Trial

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Abstract

Background: Deep neck abscesses are a disease in the field of otorhinolaryngology-head and neck surgery that causes significant morbidity, death, and expenditures. Treatment length, whether inpatient or outpatient, is also prolonged. Deep neck abscesses are managed with incision and drainage, abscess exploration, systemic broad-spectrum antibiotic treatment, comorbidity control, and postoperative wound care through recovery. Standard dressings for wound treatment have proven time-consuming and expensive. Honey is one type of dressing that has long been used in wound treatment for a number of body areas and disorders.

Objective: The purpose of this study is to investigate the use of honey as a potential substitute for standard dressings for deep neck abscesses.

Methods: This is a single-blind randomized controlled trial. Randomization will be done through simple random sampling. The population and sample of the study include all patients with deep neck abscesses treated at Dr Sardjito General Hospital, which is equipped with board-certified otorhinolaryngologists. Patients with deep neck abscesses who were given ethical clearance and meet the inclusion criteria were recruited as study participants until the sample size was reached. There are 18 participants in each group. Participants in the intervention group received standard dressings in addition to honey dressings, whereas those in the control group received standard dressings alone. Proinflammatory cytokines and growth factors, wound size, Bates-Jensen Wound Assessment Tools scoring, and quantitative bacterial colony identification will be all evaluated and assessed. The gathered data will be documented and subjected to statistical analysis.

Results: This manuscript presents a study protocol for a randomized controlled trial investigating honey as a wound care modality in patients with deep neck space abscesses. Ethical approval and partial funding for the study were obtained in May 2024. Recruitment and data collection commenced in June 2024 and were successfully completed as of June 2025.

Conclusions: We hypothesize that honey may serve as a safe, effective, and affordable alternative wound dressing for the management of deep neck abscesses, with potential benefits in both clinical and health care system outcomes.

Trial Registration: ClinicalTrials.gov NCT06562257; https://clinicaltrials.gov/study/NCT06562257.

International Registered Report Identifier (IRRID): DERR1-10.2196/75475

(JMIR Res Protoc 2025;14:e75475) doi:10.2196/75475

KEYWORDS

natural dressing; cytokines; growth factor; Bates-Jensen Wound Assessment tool; clinical trial protocol; honey

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Introduction

Background

The condition known as deep neck space infection (DNSI) emerges when an infection spreads into the deep neck spaces. If left undiagnosed and improperly treated, this condition may become life-threatening [1]. In Spain, there were 9-15 DNSI cases for every 100,000 people in 2012 [2]. DNSI has a 10% to 20% incidence rate and can lead to life-threatening complications if there is excessive accumulation of fluid in the deep neck space. It can also worsen into a deep neck abscess [3]. In Taiwan, there were 196 cases of DNSI between 1996 and 2002, with 33 cases per year, with a mortality rate of 7.6% [4]. DNSI cases increased from 1 case in 2006 to 15 cases in 2015 in Scotland [5]. Meanwhile, from 2004 to 2015, deep neck abscesses had a mortality rate of 1.4% and a complication rate of 22% in Finland [6]. The prevalence is higher in low- and middle-income countries, such as in Mexico, where DNSI has a prevalence of 42 cases over 5 years, with an average of 8.4 cases per year and a mortality rate of 8% [7], and in Ghana, where the prevalence is 135 cases over 7 years (2013-2020) with a mortality rate of 12.6% [8].

Between January 2017 and June 2020, the Otorhinolaryngology-Head and Neck Surgery (ORL-HNS) Department of Dr Sardjito Hospital in Indonesia had the highest number of DNSI cases (24) and the lowest number (8) per semester. With an average rate of mortality of 15% between 2018 and 2020, this number has been rising annually. For instance, in 2021, there were up to 41 patients with DNSI; in 2022, the total spiked to 63 patients; and in November 2023, there were 50 patients [9]. This mortality rate is comparatively greater than that of Bandung and other countries [9]. The average mortality rate was 12.4% from 2015 to 2019 [9]. According to all of the prior studies, men are more frequently affected than women, and while the age range varies from early childhood to adults, the majority of patients are adults.

A deep neck space abscess (DNSA) is an abscess that establishes within the space between the deep neck fasciae. The rapid progression of tonsillar and pharyngeal infections brought on 70% of DNSIs prior to the invention of antibiotics, which frequently led to parapharyngeal abscesses. Infections in adults generally are of dental or odontogenic origin; however, tonsillar infections remain the most common cause in young adults. Although the prevalence and mortality of DNSIs have significantly decreased due to antibiotics, hospital cases of these infections are still frequent [10-12].

Incisional drainage, abscess exploration, systemic broad-spectrum antibiotic therapy, comorbid factor control, and postoperative wound care until the wound closes are the methods used to treat DNSAs. Because a DNSA is situated between the fasciae, the wound has a deeper shape and location and heals at a different rate than other wounds. After DNSA investigation, the wound typically takes a long time to heal due to the complicated nature of treatment methods; the longest healing period can be up to 4 months, with an average of 14 days before the wound closes [13]. In addition to supplementary costs like medical procedures, surgery, consultation, and interdepartmental management, patients with DNSAs endure a significant health cost burden as a result of this prolonged wound healing.

A wound is defined as any discontinuity, disturbance, or disruption in the anatomical structure of the skin or connective tissue that results in functional impairment [14]. The wound healing process is divided into several stages, including homeostasis, inflammation, proliferation, and remodeling. These stages are modified by diverse cellular contacts and controlled by the secretion of local chemical signals [14].

The recovery process of a wound determines whether it is acute or chronic. The Centers for Disease Control and Prevention divides wounds into 4 classifications: clean, clean contaminated, contaminated, and dirty or infected. Postdrainage and abscess exploration wounds are dirty or infected open deep wounds that will heal through secondary wound healing.

In acute conditions, most surgeons continue to use sterile gauze with saline as the wound dressing of choice [15]. The wound irrigation solutions used include normal saline, tap water, povidone-iodine, Ringer lactate solution, hypochlorous acid, polyhexamethylene biguanide (PHMB), sodium hypochlorite, and electrolyzed strong water acid. Although these solutions can be used as wound irrigation agents, only some of them have antibacterial activity. One of the bactericidal wound irrigation agents is PHMB, an antimicrobial polymer that is effective against intracellular and biofilm forms of *Staphylococcus aureus* [16]. PHMB is quite effective in the treatment of wounds in deep neck abscesses. However, the unit cost is relatively high and is frequently not covered by government insurance.

Wound dressings with honey have been practically used since ancient Egyptian times to treat abscesses, diabetes mellitus, eye and ear infections, gastrointestinal diseases, oral ulcers, gynecological diseases, nail infections, airway infections, and wounds after circumcision [17]. Honey has also been used since the wartime era of the Prophet Muhammad to treat wounds. It was later shown that honey can kill bacteria in wounds and can be used as a medicine. This method is still used today in several Islamic countries to heal wounds and has been used by Russian soldiers since World War I to prevent wound infection and accelerate wound healing [18].

Honey has a high sugar content and high acidity, which can reduce bacterial growth. It also contains hydrogen peroxide, which is capable of eradicating pathogenic microbes, as well as antibacterial chemical compounds. Honey is more readily obtainable and less expensive than other dressing materials.

Goal of the Study

Honey contains antibacterial components that can help treat wound infections, relieve pain, and promote circulation, which all contribute to the healing process. Studies on the use of honey in wound care have primarily been conducted on superficial wounds as well as diabetic ulcers and burns. Previous clinical trials on the use of honey in wound care looked at applying honey to wounds after excision of pilonidal cysts [19]. Research by Rai et al [20] in 2023, which included a randomized controlled trial, compared the use of honey and Edinburgh University's solution of lime in necrotizing fasciitis wounds. Research by Dubhashi and Sindwani [21] in 2015 looked at the

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comparative use of honey and phenytoin in chronic wounds. In 2017, Esser [22] examined the use of leptospermum honey on wound healing on the skin of premature newborns admitted to the neonatal intensive care unit. In 2007, Güneş and Eşer [23] compared honey dressings and ethoxy-diamino acridine plus nitrofurazone dressings in patients with decubitus ulcers and assessed healing with the pressure ulcer scale for healing. Wahdini et al [24] reported the use of Madu Nusantara, an Indonesian honey, as a wound dressing for extensive diabetic ulcers in 1 patient with a history of uncontrolled type 2 diabetes mellitus, with good results. Saputri et al [25] from Dr Hassan Sadikin Hospital also reported a case of using Madu Nusantara as a wound dressing in a patient with a submandibular abscess with necrotizing fasciitis. Notably, clinical trials assessing the use of honey on patients with deep neck abscesses have never been conducted before. The mechanistic action of honey in wound healing has been widely hypothesized; however, no one has evaluated its effect clinically, systemically, or on the proinflammatory cytokines and growth factors that play a role in each phase of wound healing.

Thus, this study will conduct a clinical trial of honey as one of the modalities in the treatment of deep neck abscess wounds. Honey is expected to become an alternative dressing material in the treatment of deep neck abscess wounds due to its effectiveness, safety, availability, and affordability compared to standard dressings. Furthermore, honey is readily obtainable at an affordable price; therefore, if the results of wound care using honey are positive, this work will significantly reduce the burden of care on patients, doctors, and hospitals.

Methods

Study Design

This study is an experimental, quantitative study to determine the effectiveness of honey in treating deep neck abscess wounds. The research design used was a single-blind randomized controlled trial, and the intervention was given randomly to the research participants. This protocol follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 guidelines [26].

Recruitment of Participants

This study investigated wound care strategies for patients with deep neck abscesses. The research design used a single-blind randomized controlled trial comparing honey dressings with standard dressings (Prontosan irrigation solution). The study population included patients treated at Dr Sardjito Hospital, Yogyakarta. Patient recruitment was conducted from the date of ethical clearance issuance until the required sample size was achieved. Before enrolment, all patients provided written informed consent after being fully informed of the study objectives, procedures, potential risks, and benefits. The study protocol was approved by the Medical and Health Research Ethics Committee, Faculty of Medicine, Public Health and Nursing, Universitas Gadjah Mada, Dr Sardjito General Hospital (KE/FK/0668/EC/2024), ensuring compliance with national and international ethical standards. The inclusion criteria included patients aged older than 18 years with or without comorbidities, except for malignant diseases. The exclusion criteria excluded patients who refused the intervention, underwent vacuum-assisted closure, or had incomplete medical records. Severe allergic reactions to dressings were considered withdrawal criteria. Our findings contribute to the optimization of wound care practices for deep neck abscesses, aiming for improved outcomes and cost-effectiveness. Our investigation was held at the ORL-HNS Department in Dr Sardjito General Hospital.

Sample Size

The sample size in this study was calculated based on the formula for unpaired categorical-numerical comparative research involving a single numerical measurement between 2 groups [27]. The parameters used included a significance level (α) of .05 and a power ($1-\beta$) of 90%, corresponding to $Z\alpha=1.64$ and $Z\beta=1.28$, respectively. According to previous studies, the mean (SD) wound closure in the control group (standard dressing) was 0.266 (SD 1.183) cm. Meanwhile, the expected mean wound closure in the intervention group (honey dressing), based on prior research using honey in wound management, is 1.433 cm. Using these values, the estimated minimum sample size required was approximately 18 participants per group. The full calculation procedure is provided in Multimedia Appendix 1 [21].

Randomization

In the study we conducted, participants were assigned to the control and intervention groups using a comprehensive randomization technique. The distribution was carried out by concealing opaque envelopes with numbered slips ranging from 1 to 36. These slips were arranged in a box, and the sequence was chosen using the Microsoft Excel random generator. Importantly, the researchers remained blind to the randomization findings throughout the process.

The participants were then assigned to either the control group (standard dressing) or the intervention group (standard dressing plus Indonesian Nusantara honey). The resident doctor was responsible for administering the dressing and obtaining detailed randomization instructions.

Blinding

This study was designed as a single-blind clinical trial. The principal investigator and the assistant who measured wound indicators remained blinded throughout the treatment period, and treatment allocation was disclosed only after the final database lock. Patients were not blinded, as full blinding was not feasible due to the intrinsic characteristics of honey. Its distinct color may stain the dressing material, and its recognizable odor may reveal the intervention. These factors could have led patients to infer their group allocation, making participant blinding impractical.

Honey Sample

Honey has an extended record of enabling wound healing and offers a more affordable therapeutic option. This study used raw and unsterilized local honey known as Nusantara honey. Nusantara honey contains biological components and beneficial microorganisms that promote wound healing. As a result, the honey used in this study was not sterilized, as sterilization can

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diminish its benefits. The honey used in the study has already passed Indonesia's food and drug administration test (known as BPOM) with the number MD 011167000300234. The same batch of honey is used in the study, ensuring the quality and safety of the product remain the same. It was confirmed to be safe because it passed the laboratory test at the Health Laboratory Calibration and Testing Center, Regional Health Office of Yogyakarta. The test results showed negative findings for fungal and bacterial cultures. The certificate, issued under number 009008/LHU/BLKK-Y/05/2024, confirmed that the honey sample met the safety standards for clinical application. Although sterilization was not performed to preserve its bioactive components, the honey was certified safe and free from harmful contaminants. This was validated by the extraction of samples following wound healing, where laboratory studies revealed the absence of toxins, fungus, or potentially hazardous bacteria.

In several previous studies, honey was used clinically, and the same brand has been applied in Indonesia. In studies in other countries, natural honey has been used without sterilization and has been shown to produce better results [23,28-35].

Intervention Procedure

Both the control and intervention groups received wound care following the standard operating procedure established by the Laryngopharyngology Division, ORL-HNS Department, Dr Sardjito General Hospital. This protocol includes wound debridement, saline irrigation, application of gauze rolls, and administration of Prontosan. Necrotic tissue was removed, and the wound was disinfected using sodium chloride before a gauze roll soaked with antibiotic ointment was inserted to serve as drainage. Dressing frequency was determined based on the volume of pus produced—daily dressing was performed until pus production decreased to less than 5 cc, at which point dressings were changed every 3 days, eventually decreasing to once a week when no pus was observed.

In the intervention group, the standard protocol was followed with an additional intervention using Nusantara honey. A 120-cm gauze roll was immersed in 12 cc of Nusantara honey for approximately 1 minute, allowing full absorption before being applied to the wound and covered with sterile gauze. Prontosan gel was used when pus was no longer present to stimulate granulation tissue formation until the wound base reached the surface. Wounds were generally left to heal by secondary intention, unless primary closure or reconstruction was necessary due to extensive tissue loss.

Monitoring of adverse events was conducted directly by the principal investigator and otorhinolaryngology residents during each wound dressing session. If the honey dressing failed to achieve adequate wound healing outcomes, a swab was taken from the wound base for repeat sensitivity culture. The wound care protocol was then reverted to the standard dressing procedure used at Dr Sardjito General Hospital, followed by further management based on the patient's condition, including the treatment of any comorbidities that might hinder the healing process. The antibiotic protocol applied to both the control and intervention groups included ceftriaxone and metronidazole upon initial presentation, with adjustments made according to the culture results when available. In cases of infection escalation, antibiotics were modified following the hospital's infection control guidelines. The average wound healing time was 7 days, although some cases required up to a month or additional surgical interventions, such as grafting.

Measurements

Table 1 outlines the schedule for data collection. All participants who were intervened on had data collected on days 1, 7, and 14. The data comprised measurements of bacterial colony counts, wound size, Bates-Jensen Wound Assessment Tools (BWATs), proinflammatory cytokines, and growth factors. The data are intended to reflect the effects of interventions performed on wound healing in each stage.

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Table 1. Schedule for data collection.

Activity	Timeline (days)
Filling out the case report form	1, 7, and 14
Wound measurement	1, 7, and 14
Measuring BWATs[a] (size, depth, edges, undermining, necrotic type, necrotic amount, exudate type, exudate amount, skin color, edema, induration, granulation, and epithelialization)	1, 7, and 14
Taking a wound bed swab	1 and 14
Taking wound tissue (biopsy)	1 and 14
Vital sign examination (blood pressure, respiratory rate, heart rate, temperature, SPO2[b], and VAS[c])	1-14 (daily)
Supporting examinations	
Complete blood count[d,e]	1-14 (daily)
Computed tomography scan[e]	1 and 14
Chest X-ray[e]	1 and 14
Blood gas analysis[e,f]	1, 4, 7, 10, and 14
Monitoring complications	1-14 (daily)
Pus culture aspiration (bacterial, sensitive to antibiotic, intermediate to antibiotic, or resistant to antibiotic)	1 and 14
Wound bed culture (bacterial, sensitive to antibiotic, intermediate to antibiotic, or resistant to antibiotic)	1 and 14
Measurement of growth factors and cytokines (IL-1, TNFα, and VEGF)	1 and 14

[a]BWAT: Bates-Jensen Wound Assessment Tool.

[b]SPO2: saturated oxygen.

[c]VAS: visual analog scale.

[d]Complete blood count includes hemoglobin, red blood cells, white blood cells, and platelets. Other laboratory tests include blood ABO group and rhesus type, prothrombin time, activated partial thromboplastin time, international normalized ratio, total bilirubin, direct bilirubin, indirect bilirubin, serum glutamic oxaloacetic transaminase, serum glutamic pyruvic transaminase, albumin, sodium, potassium, chloride, blood urea nitrogen, urea, creatinine, uric acid, random blood glucose, fasting blood glucose, 2-hour postprandial glucose, hemoglobin A1C, and hepatitis B surface antigen.

[e]As long as the patient was still admitted in the ward.

[f]Arterial blood gas parameters include pH, partial pressure of carbon dioxide, bicarbonate, partial pressure of oxygen, and base excess.

Each parameter was measured following standardized procedures, and designated personnel were assigned to each task to minimize measurement bias and ensure internal validity.

On day 1, the following assessments were performed:

- Wound size (length, width, and depth): Wound size was measured by a trained research assistant. The measurement was conducted with a specific ruler and probe. The width and length recorded were the largest calculated amounts, whereas the depth of the wound was measured using a specific probe inserted perpendicularly to the meeting point of the length and width until it reached the base of the wound. To enhance measurement precision and reproducibility, the ImitoMeasure wound documentation app was also used [36]. This mobile app enables photographic documentation with calibrated scale indicators, providing consistent digital measurements of wound area and depth. This measurement was conducted by the research assistant 3 times, and the results were averaged to obtain a more accurate wound size estimate.
- BWAT: The raw wound data and clinical wound appearance were first recorded by an assistant. The final scoring and interpretation based on these observations were conducted independently by the principal investigator, who was blinded to treatment allocation during the evaluation process.
- Wound swabs for bacterial culture: Infection was considered to have improved as evidenced by bacterial culture findings and the number of bacterial colonies that proliferated. Samples were collected by the clinical team under sterile conditions and submitted to a certified microbiology laboratory for quantitative colony count analysis. Samples were taken from the wound base using sterile cotton, placed in Amies transport medium, and delivered to a microbiological laboratory.
- Tissue biopsy for cytokine (IL-1 and TNF-α) and growth factor (VEGF) analysis: Tissue biopsy was performed by an otorhinolaryngology resident using standard sterile technique. The biopsy samples were then processed by trained laboratory personnel for immunohistochemical examination.

On day 7, wound size measurements and BWAT scoring were repeated using the same tools and by the same assessors as on day 1 to ensure consistency across time points.

On day 14, all baseline measurements were repeated, including wound size, BWAT scoring, wound swab cultures, and tissue biopsies for cytokine and growth factor quantification. The same

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assigned personnel performed all assessments to reduce interobserver variability and enhance the reliability of longitudinal comparisons. The schedule of interventions and sample measurements is illustrated in Figure 1.

Figure 1. Study protocol items and schedule of assessments during the 14-day observation period. The tests will be conducted as long as the patient is hospitalized.

Study protocol items

	Study Period													
Times points (Days)	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**
Filling out the CRF	✓						✓							✓
Wound measurement using special ruler and iMito Measure Application	✓						✓							✓
Wound documentation	✓						✓							✓
BWAT Scoring	✓						✓							✓
Wound base swab	✓													✓
Wound tissue sampling	✓													✓
Vital signs monitoring[a]	↔													
Complete laboratory tests[a]	✓			✓			✓			✓				✓
CT-Scan[a]	✓													✓
Chest X-ray[a]	✓													✓
ABG test[a]	✓			✓			✓			✓				✓
Monitoring for complications[a]	↔													
Pus aspiration culture	✓													✓
Wound base culture	✓													✓
Cytokine and growth factor measurement	✓													✓

Outcomes

In this study, a research assistant collected samples after completing wound dressing and storing the dressing materials. Measurements were taken on the first, seventh, and fourteenth days for BWAT assessments, as well as the first and fourteenth days for bacterial colony identification from wound bed swabs and cytokine and growth factor expression analysis from tissue samples. The resident doctor was accountable for the dressing and performed pus aspiration and tissue sampling. All information was meticulously documented on an authorized form. Wound measures included length, width, and depth, with data based on the largest width and length. Wound depth was measured using a probe perpendicular to the wound's length and width. BWATs were evaluated by an uninformed research assistant. Bacterial culture findings and the number of bacterial colonies were used as evidence of infection improvement. Swabs from the wound bed were delivered to the microbiology lab. Tissue samples were sent to the Anatomical Pathology lab for immunopathological examination of wound healing, including quantification of IL-1, TNF-α, and VEGF expression. Tissue samples were collected using nasopharyngeal biopsy forceps, and the preserved tissue was sent out for analysis. Additionally, laboratory examinations, radiographs, and patient comorbid factors were documented for analysis in the case report form.

Statistical Analyses

The Shapiro-Wilk test will be used to assess the normality of continuous data because the sample size is less than 50. For comparison of wound healing outcomes between the honey dressing and standard dressing groups at each time point (days 1, 7, and 14), either an independent *t* test or Mann-Whitney U test will be used, depending on data distribution. To analyze the overall effect of treatment over time and assess the interaction between treatment group and time, a generalized estimating equation analysis will be performed. A *P* value of <.05 will be considered statistically significant. All data will be analyzed using SPSS software version 25.0 (IBM Corporation) and presented in tables summarizing the changes on days 1, 7, and 14 (Figure 2).

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Figure 2. Sample table of outcome parameters to be collected on days 1, 7, and 14. a CFU: Colony forming unit b BWATs: Bates Jensen Wound Assessment Tool.

Outcome Parameter	Control group (n=18), mean ± SD	Treatment group (n=18), mean ± SD	*p*
Cytokine/Growthfactor Expression			
IL-1			
TNF-α			
VEGF			
Wound Bed Culture, CFU[a]/mL			
Bacterial colonies			
Wound measurement (cm)			
Length			
Width			
Depth			
BWATS[b] Score 1-5			
Size			
Depth			
Edges			
Undermining			
Necrotic tissue type			
Necrotic tissue amount			
Exudate type			
Exudate amount			
Skin color surrounding wound			
Peripheral tissue edema			
Peripheral tissue induration			
Granulation tissue			
Epithelialization			

Results

This manuscript presents a study protocol for a randomized controlled trial investigating honey as a wound care modality in patients with DNSAs. Ethical approval and partial funding for the study were obtained in May 2024. Recruitment and data collection commenced in June 2024 and was completed in May 2025. As of manuscript submission, the full sample of 36 participants has been successfully enrolled (Figure 3). Data analysis is currently underway, and the study results are expected to be submitted for publication in early 2026.

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Figure 3. CONSORT (Consolidated Standards of Reporting Trials) flowchart of study participants.

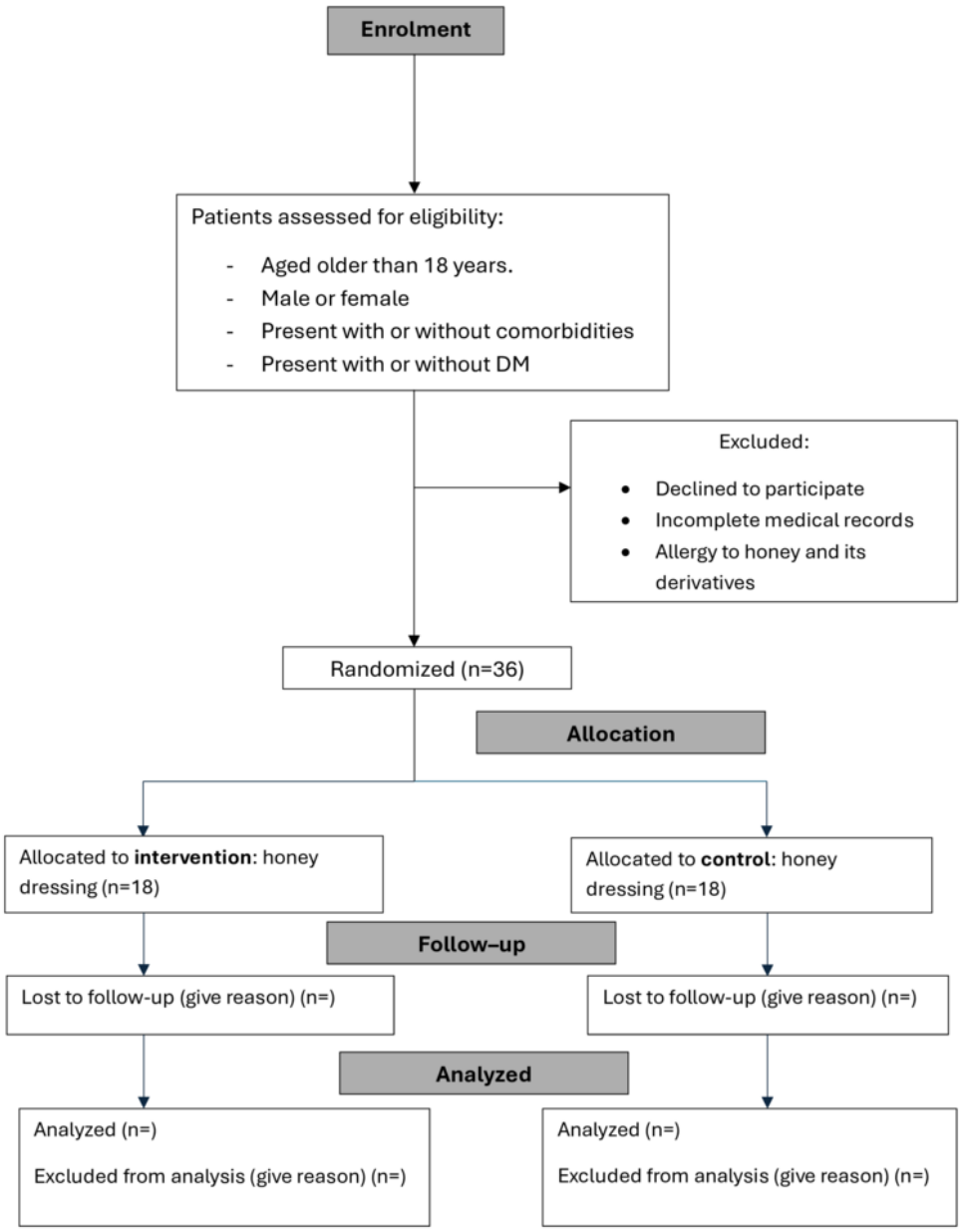

Discussion

Anticipated Findings

This study is designed to evaluate whether honey-based dressings can enhance wound healing in patients with deep neck abscesses compared to standard dressings. The anticipated findings are that honey dressings, due to their antibacterial, anti-inflammatory, and immunomodulatory properties, will result in faster and more effective healing outcomes. These outcomes will be assessed clinically, bacteriologically, systemically, and through biomarker analysis of IL-1, TNF-α, and VEGF expression.

Honey has long been used in traditional medicine, and modern research has supported its effectiveness in wound care. Previous studies have demonstrated honey's ability to promote healing in burns, surgical wounds, and chronic ulcers. Its unique properties—such as high osmolarity, low pH, hydrogen peroxide production, and rich content of antioxidants and bioactive compounds—contribute to its antimicrobial and healing potential [17,18,37]. Particularly, Manuka honey has shown strong efficacy against drug-resistant bacteria, including methicillin-resistant *Staphylococcus aureus* and vancomycin-resistant *Enterococcus*, and has been successfully used in chronic wound treatment [17,38]. In vitro studies have also indicated that honey stimulates the release of inflammatory cytokines such as IL-1, TNF-α, and IL-6, which play essential roles in wound healing [37]. Despite these promising results, there remains a lack of clinical studies specifically examining the use of honey for deep neck infections, which are serious, rapidly progressing conditions with potential airway and systemic complications [2,3,6].

The strength of this study lies in its comprehensive design, integrating clinical, microbiological, and molecular assessments within a randomized controlled trial framework. This design allows for a multifaceted evaluation of honey's effects on wound

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healing while minimizing potential bias. Nonetheless, certain limitations must be acknowledged. The use of raw honey, although supported by prior literature, poses concerns regarding microbial contamination. Bacterial spores, such as *Clostridium* and *Bacillus*, may be present in raw honey, although gamma irradiation is an effective method of sterilization that preserves its antibacterial properties [17]. Moreover, variation in honey composition depending on its botanical source may influence treatment outcomes, and the accessibility of standardized, medical-grade honey remains limited in some settings [18].

Should the study yield positive results, future research should explore the standardization of honey-based dressings and assess their scalability and cost-effectiveness in clinical practice. Comparative studies between different types of honey may also help to identify the most effective formulations for wound care. Further investigation into long-term outcomes, including the quality of scar formation and infection recurrence rates, would provide valuable insight into the broader benefits of honey in wound management.

The findings from this study will be disseminated through publications in peer-reviewed journals and presentations at scientific conferences focusing on otorhinolaryngology, wound care, and integrative medicine. In addition, efforts will be made to share the results with local hospital networks and health care providers to inform evidence-based clinical practices. Educational materials for clinicians and patients may also be developed to promote the safe and effective use of honey in wound management.

Conclusion

In conclusion, this study proposes honey as a potential alternative wound dressing for the management of deep neck abscesses. Based on its established antimicrobial, anti-inflammatory, and wound-healing properties, honey may offer a safe, accessible, and cost-effective solution compared to conventional dressings. If proven effective through this trial, honey-based dressings could contribute to improved clinical outcomes and reduced health care burdens, particularly in low-resource settings.

Acknowledgments

No generative artificial intelligence tools were used in the design, conduct, or analysis of the study or in writing of this manuscript. All content was developed solely by the authors.

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Authors' Contributions

DPW was involved in the study's conceptualization, methodology, and analysis, and in the writing of the original draft. YWS and AS were involved in supervision. All authors provided review and feedback on the manuscript and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Sample size calculation for determining the minimum number of participants per group.
[PDF File (Adobe PDF File), 121 KB - resprot_v14i1e75475_app1.pdf]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
DNSA: deep neck space abscess
DNSI: deep neck space infection
ORL-HNS: Otorhinolaryngology-Head and Neck Surgery
PHMB: polyhexamethylene biguanide
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Efficacy of Tuina Versus the Proprioceptive Neuromuscular Facilitation (PNF) Technique in Patients With Nonspecific Chronic Neck Pain: Protocol for a Randomized Controlled Trial

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Abstract

Background: Nonspecific chronic neck pain (NCNP), characterized by a long course, a high recurrence rate, and a young age of onset, causes a huge economic burden. Scientific evidence supports the efficacy of tuina, a manual traditional Chinese medicine (TCM) therapy involving manipulation of soft tissues and joints, for NCNP. However, there is little evidence of the effectiveness of proprioceptive neuromuscular facilitation (PNF), a rehabilitative method involving specific patterns of muscle contraction and stretching, in treating NCNP, either alone or in combination with tuina.

Objective: This study aims to compare the effects of the PNF technique, tuina, and their combination on patients with NCNP and assess whether combined therapy outperforms monotherapies.

Methods: The parallel, double-blind, three-arm clinical randomized controlled trial (RCT) is being conducted at the Beijing University of Chinese Medicine and its affiliated hospitals. Patients will be recruited and randomly assigned to a PNF group, a tuina group, and a combined (PNF+tuina) group in a 1:1:1 ratio. The PNF intervention (PNF stretching and PNF plyometrics) will last for 30 minutes each session. Tuina therapy will also last for 30 minutes each session. The combined group will receive 30 minutes of PNF, followed by 30 minutes of tuina therapy. Participants will receive 4 weeks of treatment, thrice a week, for a total of 12 treatments. Visual Analogue Scale (VAS) and Neck Disability Index (NDI) scores will be used as primary outcome measures. Cervical active joint mobility measured with the MicroFET3 Portable Muscle Strength Test and Joint Mobility Meter and muscle physical properties tested with the Myoton Muscle Tester will be used as secondary outcome measures. Data will be analyzed at baseline, at the end of the intervention, and during the 4 weeks of follow-up using repeated measures ANOVA. The significance level will be 5%.

Results: As of May 26, 2025, 43 participants were already recruited and randomly assigned to the three treatment groups (PNF: n=14, 32.6%; tuina: n=15, 34.9%; combined: n=14, 32.5%). All enrolled participants have initiated treatment, with an average adherence rate of 92% and no withdrawals due to adverse events (AEs) or treatment dissatisfaction. The short-term follow-up (end of intervention) for the first cohort was completed on July 30, 2025, with long-term follow-up (1 month postintervention) to be completed by August 31, 2025. The final analysis is projected to include data of all 69 participants by October 2025, with primary results expected to be submitted for publication in December 2025.

Conclusions: Our findings will provide a solid evidence base for clinical approaches to managing NCNP. Moreover, our results will offer valuable insights into the relative efficacy of tuina, PNF, and their combination, shedding light on their potential benefits and helping identify the most effective treatment strategies for NCNP.

Trial Registration: International Traditional Medicine Clinical Trial Registry ITMCTR2023000061; https://itmctr.ccebtcm.org.cn/mgt/project/view/346154483678331720/false

International Registered Report Identifier (IRRID): PRR1-10.2196/63528

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(JMIR Res Protoc 2025;14:e63528) doi:10.2196/63528

KEYWORDS

nonspecific neck pain; nonspecific chronic neck pain; efficacy; randomized controlled trial; tuina; proprioceptive neuromuscular facilitation; combined therapy; neck pain; chronic neck pain; evidence; support; effectiveness; therapy; China; manipulation; traction; cervical traction

Introduction

Nonspecific chronic neck pain (NCNP) is pain located in the lateral and posterior neck without a clear pathological cause (eg, a specific condition, such as a fracture, inflammation, or nerve compression) and often manifests itself as soreness, stiffness, or limitation of movement of the neck muscles [1]. When the duration of symptoms is greater than 12 weeks of evolution, it acquires the value of chronicity, being referred to as denominated NCNP [2]. It is a general term used to describe neck pain where no discernible histopathological structural abnormalities can be identified clinically [3,4]. In China, its annual incidence ranges from 43% to 66.7% [5], causing a huge economic burden [6,7]. The disease is characterized by a long course, a high recurrence rate, and a young age of onset.

The intrinsic mechanisms underlying the maintenance, recurrence, and progression of NCNP are unknown but may be related to deficits and alterations in neck muscle proprioception. This is because neck muscle proprioception plays a decisive role in cervical joint position and head movement control [5]. Due to the lack of identifiable pathological processes or specific etiologies in NCNP, it is difficult to implement precise treatment strategies [8].

Although pharmacological interventions, intra-articular injections, and surgical procedures are commonly used in clinical practice, their effectiveness is not guaranteed [9]. Current Western medical approaches, including nonsteroidal anti-inflammatory drugs and physical therapy, often provide short-term relief but show limited long-term efficacy due to high recurrence rates [10]. As a result, nonpharmacological approaches have gained increasing attention, with exercise therapy considered an effective method for pain relief [11].

In traditional Chinese medicine (TCM), *tuina*—manual therapy involving rhythmic pressure, kneading, and joint mobilization—has been used for millennia to alleviate neck pain by stimulating meridian points and releasing muscular tension. Tuina aims to regulate the flow of *Qi* (life force) and blood, relieve muscle tension, and promote blood circulation, thereby alleviating neck pain and improving functional impairments. Recent studies have demonstrated that tuina can significantly relieve symptoms of NCNP [12]. A systematic review of 12 RCTs (N=897 patients) found that tuina significantly reduced NCNP severity (mean Visual Analogue Scale [VAS] score reduction: 2.1 points) and disability (Neck Disability Index [NDI] reduction: 9.2 points) compared to sham treatments. Modern mechanistic studies suggest that tuina reduces pain by inhibiting pro-inflammatory cytokines and enhancing central pain modulation [8].

Proprioceptive neuromuscular facilitation (PNF), a rehabilitation technique developed in the 1940s, uses specific patterns of resisted muscle contraction and stretching (eg, the contract-relax method) to improve neuromuscular coordination and joint mobility. Although PNF has demonstrated efficacy in managing low back pain and shoulder stiffness, its application in NCNP remains understudied. Only two small trials (N=45 and N=60 patients, respectively) have explored PNF for neck pain, reporting modest improvements in the range of motion but no comparison with established therapies, such as tuina [13,14]. Critically, no study has directly compared tuina and PNF or investigated their combined use, leaving a significant gap in understanding whether their mechanisms—TCM's holistic soft-tissue release and PNF's neurophysiological modulation—might synergize to enhance outcomes.

In recent years, studies have confirmed that combination therapies are superior to monotherapies and have better long-term effectiveness [15]. In the context of cervical muscle rehabilitation, tuina and PNF share biomechanical principles and are potentially complementary. Their combination may improve energy metabolism and blood circulation, while helping restore both the static and the dynamic balance of the cervical spine. This synergistic effect may correct biomechanical imbalances and enhance proprioceptive feedback. However, no relevant clinical trials have been conducted to investigate this combined approach.

The aim of this study is to compare the therapeutic effects of tuina, PNF, and their combination in the treatment of NCNP and whether the combination therapy of PNF and tuina has superior efficacy compared to either therapy alone in order to provide more clinical evidence for the treatment of NCNP. Against this backdrop, this study aims to address three critical research questions:

- Does the PNF technique demonstrate superior efficacy compared to tuina in reducing pain and improving functional disability?
- Does the combination of PNF and tuina yield better outcomes than either monotherapy alone?
- Are there significant differences in cervical joint mobility and muscle physical properties (eg, stiffness, elasticity) across the three treatment groups?

The specific objectives are to (1) compare the short-term (end of intervention) and long-term (4-week follow-up) efficacy of PNF, tuina, and their combination in reducing pain (VAS score) and functional disability (NDI); (2) evaluate their effects on cervical active joint mobility and muscle physical properties; and (3) assess the safety and tolerability of all interventions. Guided by these objectives, the primary hypothesis is that the PNF-tuina combination will achieve greater reductions in pain and disability than monotherapies, while the secondary hypothesis posits that PNF will outperform tuina in improving

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cervical biomechanics. All interventions are hypothesized to be safe, with low rates of adverse events (AEs).

Methods

Study Design

This trial has been registered in the International Traditional Medicine Clinical Trial Registry (registration number: ITMCTR2023000061). The study is a parallel, double-blind, three-arm clinical randomized controlled trial (RCT) without a standard care control. A total of 102 eligible patients with NCNP will be recruited and then randomly assigned to a PNF group, a tuina group, and a combined (PNF+tuina) group in a 1:1:1 ratio.

This design is a parallel-group, active-comparator trial aiming to directly compare the efficacy of three commonly used interventions for NCNP—PNF, tuina, and their combination—given the absence of head-to-head comparative evidence in the literature. By excluding a standard care control group, the trial focuses on identifying the most effective modality among the tested active interventions rather than evaluating superiority over usual care [16].

The PNF group will undergo the PNF intervention, the tuina group will undergo a TCM intervention with tuina, and the combined group will receive PNF combined with tuina therapy. The intervention will last for 4 weeks for each of the three groups, thrice a week.

This frequency and duration will be carefully determined. A treatment frequency of thrice a week is supported by both previous studies and physiological mechanisms. Research on rehabilitation interventions for cervical spondylosis has shown that a frequency of three sessions per week can maintain a continuous therapeutic effect, promoting muscle repair and reducing inflammation [8]. Biologically, the human musculoskeletal system requires an appropriate interval between treatments to complete the repair and remodeling process; a higher frequency may cause excessive stress on the tissues, while a lower frequency may weaken the cumulative therapeutic effect [17]. The 4-week total treatment duration is based on the natural course of cervical spondylosis and the expected efficacy period. Clinical experience and preliminary data from our center indicate that significant improvements in symptoms, such as pain and limited mobility, can be observed within 4 weeks of continuous treatment. Additionally, a 4-week treatment cycle strikes a balance between achieving therapeutic goals and patient compliance, as longer treatment periods may lead to decreased adherence due to factors such as time constraints and economic burden.

The primary outcome measures of this trial are the VAS and NDI scores. The secondary outcome measures are cervical active joint mobility and muscle physical properties. The three groups will be tested before the intervention (baseline), at the fourth week of the intervention, and at the follow-up visit 4 weeks after the end of the intervention. The study design is illustrated in the flowchart in Figure 1.

Figure 1. Trial flowchart. NDI: Neck Disability Index; PNF: proprioceptive neuromuscular facilitation; VAS: Visual Analogue Scale.

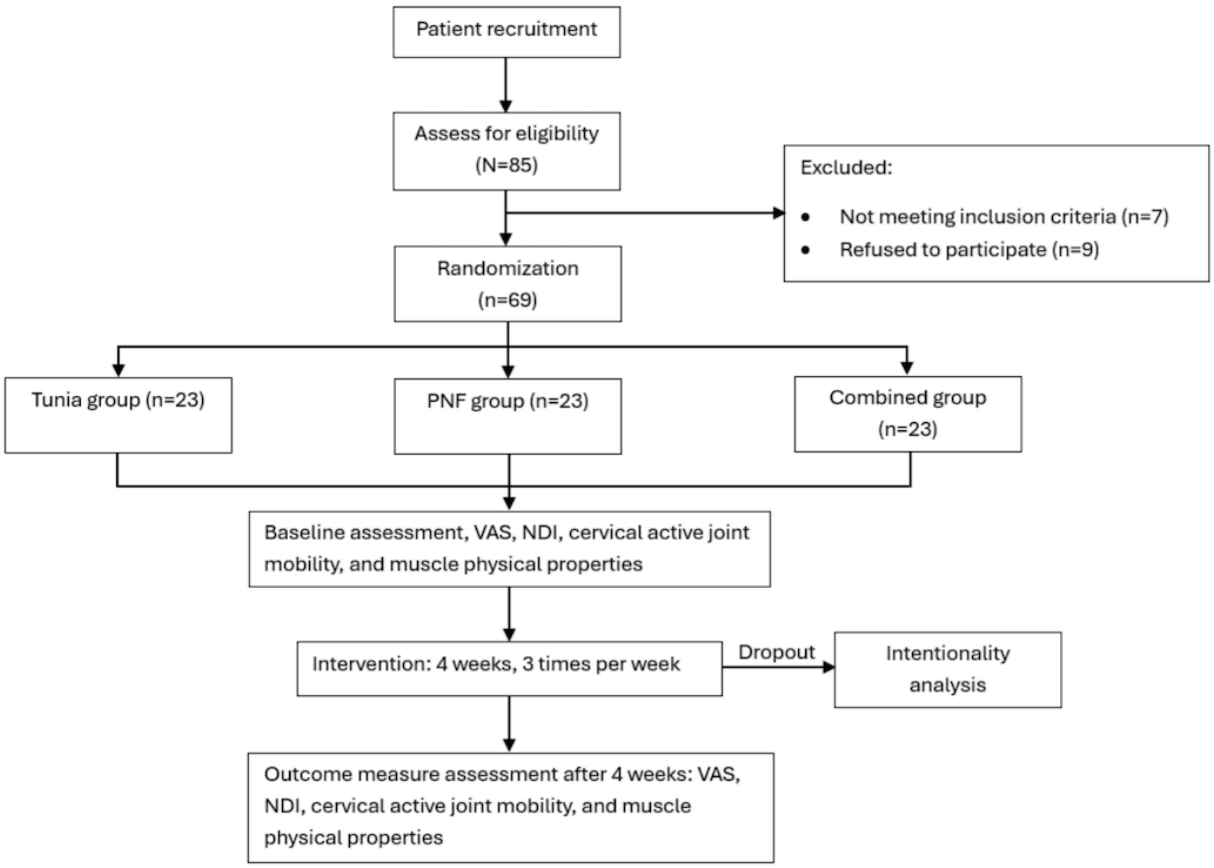

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Ethical Considerations

Prior to enrollment, written informed consent will be obtained from all participants by trained research staff, with the consent document clearly outlining the study objectives, procedures, potential benefits and risks, confidentiality measures, and the participant's right to withdraw at any time without penalty. Participant identities will be anonymized using unique study identifiers, and all data (including clinical records, assessment forms, and biological samples) will be stored on encrypted servers accessible only to authorized research personnel, while publication of results will avoid disclosing identifiable information and comply with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2025 guidelines (Multimedia Appendix 1) on data sharing (item 6). An independent Data Safety and Monitoring Board (DSMB) will oversee the trial to ensure participant safety, reviewing AE reports at predefined intervals and potentially recommending trial modifications or termination if unacceptably high risks are identified, with all serious AEs reported to the ethics committee within 24 hours of discovery in accordance with institutional policies. The study protocol has been reviewed and approved by the Regional Ethics Committee of the Affiliated Hospital of Beijing University of Chinese Medicine (approval number: BUCM-2023-078; project number: 2022BZYLL1011).

Participant Recruitment

Eligible participants include patients diagnosed with NCNP according to Canadian evidence-based guidelines of 2014 for the chiropractic treatment of adults with neck pain [18]. These guidelines define NCNP as follows:

- Chronic neck pain lasting for at least 3 months with or without radiation to the upper limbs
- Absence of significant structural pathology (fractures, tumors, systemic disease) to exclude serious organic causes requiring urgent medical intervention
- Nonspecific neck pain without a clear underlying pathology
- Functional impairment affecting activities of daily living or work-related tasks

Diagnostic Responsibility

Two experienced orthopedic specialists (≥10 years of clinical experience in musculoskeletal disorders) will independently review medical histories, physical examination results, and imaging studies (if available) to confirm the diagnosis, reducing interrater variability. Recruitment will be conducted in two ways, offline posting of posters and online posting of information.

Inclusion Criteria

Participants who meet all the following criteria can be enrolled:

- Aged 18-50 years, male or female. This age range is selected to exclude adolescents (immature spinal development) and older adults (higher likelihood of comorbidities, such as osteoarthritis), focusing on a homogeneous population with primary NCNP.
- The main symptom is neck pain (VAS score≥3 and NDI score≥10), including pain, stiffness, and limitation of movement in the occiput, neck, shoulder, or scapula. These thresholds ensure participants have moderate pain and disability, making them suitable for interventional studies.
- Physical examination of the cervical spine does not exhibit indications of nerve root compression, which means negative results on the neck distraction test, the Spurling neck compression test, and the Adson test. Excluding radiculopathic pain allows isolation of "nonspecific" neck pain, aligning with the study's focus.
- Neck pain continued for at least 3 months. Consistent with the Canadian guidelines' definition of chronicity, this ensures sufficient time for intervention effects to manifest.
- No history of shoulder and neck surgery. Prior surgery may alter musculoskeletal anatomy and confound outcomes.
- Voluntary participation and ability to provide written informed consent. This is mandatory for ethical compliance and participant autonomy.

Exclusion Criteria

Participants meeting any of the following criteria will be excluded:

- Being treated or have been treated in the past 3 months for NCNP with tuina, PNF, or another effective method. This will avoid carryover effects from prior therapies (eg, tuina, PNF) on primary outcomes.
- Accompanied by compression of nerve roots, the spinal cord, vertebral arteries, sympathetic nerves, etc. These conditions require specialized treatment and belong to specific neck pain subtypes, outside the study's scope.
- Localized skin breakdown, skin disease, or skin sensory impairment. This may interfere with treatment delivery (eg, tuina massage) or cause discomfort.
- Women who are pregnant or lactating. The intervention may cause potential risks to fetal/infant health, and hormonal changes may affect pain perception.
- Cognitive impairment, sensory aphasia, or severe visual or hearing impairment. This may compromise outcome reporting (eg, VAS scoring) or treatment compliance.
- Patients who develop neck pain caused by cervical fractures, dislocations, tumors, infections, rheumatoid arthritis, or other specific reasons. The study's focus is NCNP, as defined by the Canadian guidelines.
- Patients with a history of severe trauma or tumors. These are high-risk comorbidities that may interact with interventions or affect safety.
- Pain in more than three areas other than the neck and shoulder area. This suggests widespread pain syndromes (eg, fibromyalgia), which have a different pathophysiology.
- A combination of serious medical conditions, such as cardiovascular, hematopoietic, and endocrine diseases. This may increase intervention risks or require concomitant medications that interfere with outcomes.

Dropout Criteria

The dropout criteria are as follows:

- The patient quits (poor efficacy or adverse reactions), which respects participants' rights and ensures data integrity by excluding noncompliant cases.

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- Loss to follow-up, which minimizes missing data bias; participants with ≥50% missing follow-up data will be excluded from the final analysis.
- Researchers remove the patient (poor compliance, complications, or serious AEs), which ensures safety and protocol adherence (eg, severe AEs require immediate termination).

Randomization

The randomization sequence will be generated by a random number generator (IBM SPSS Statistics version 27.0), which will be sent to a therapist in opaque envelopes numbered sequentially. The therapist will sequentially open the envelopes and allocate participants accordingly. Eligible patients will be randomized to the tuina group, the PNF group, or the combined group, with 23 patients in each group.

Blinding

Outcome assessors, data managers, and the statistician will be blinded in this trial and will not share study information with each other. To preserve masking, only the massage therapists will have access to treatment allocation. The patients will not know the group to which they belong before the intervention. The sequence of randomization will be hidden from both evaluators and patients, and this sequence will be kept by the main researcher throughout the study and will not be available to the rest of the participants involved in the trial.

Intervention

Participants will receive 4 weeks of treatment, thrice a week, for a total of 12 treatments. All exercises will be performed under the careful supervision of trained professionals. In addition, participants will be required to pass a clinical test to make sure that the consistency of the trial is maintained. It should be emphasized that some other treatments for NCNP during the trial will be forbidden, which includes medication therapy, surgery, drug injections, acupuncture, moxibustion, and physical therapy. If the patients receive any other treatment, these will be recorded at each visit. Health education will be provided to all three groups. Patients will be instructed not to perform any additional exercise at home and to avoid poor posture as much as possible.

Group 1: The PNF Group

In this arm of the study, the therapist will administer a two-step protocol for about 30 minutes: step 1 is PNF stretching, and step 2 is PNF plyometrics. PNF stretches last for about 20 minutes. PNF weighted bouncing exercises include 10-15 repetitions per set, with 1-minute rest between sets, 3 sets per day for about 10 minutes.

Step 1: PNF Muscle Stretching

The hold-relax-antagonist contraction (HRAC) stretching technique will be used [19]. The stretching is performed as follows: (1) The patient is completely relaxed, and the therapist passively pulls the target muscle for 10 seconds [20]; (2) the patient contracts the target muscle at isometric strength for 6 seconds against the resistance applied by the therapist and then relaxes; (3) the patient actively contracts the antagonist muscle of the target muscle and holds it for 30 seconds after a new range of motion is reached; and (4) starting from this new joint angle reached, the target muscle is passively stretched for 10 seconds again. This process is repeated three to five times. The specific procedure is illustrated in Figure 2.

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Figure 2. The HRAC stretching technique: (a) upper trapezius muscle stretching, (b) scapularis muscle stretching, (c) suboccipital muscle group stretching, (d-f) pectoralis major stretching, (g) sternocleidomastoid muscle stretching, (h) pectoralis minor stretching, and (i) obliques muscle stretching. HRAC: hold-relax-antagonist contraction.

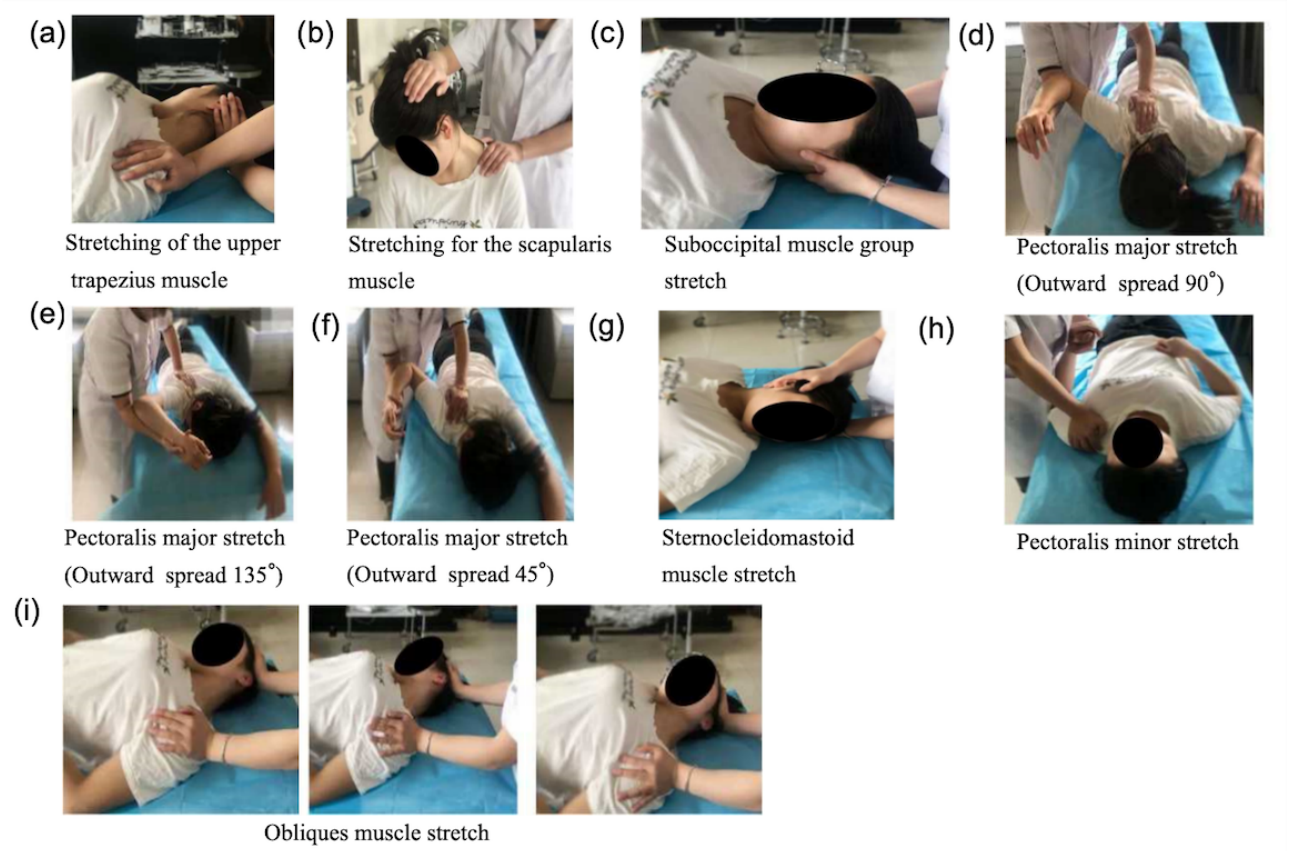

Upper Trapezius Muscle Stretching

To start, the patient is placed in the supine position. The head is rotated to the right as far as possible within the painless range, and then the jaw is tucked in as far as possible. The therapist places their left hand on the patient's occipital bone, with the fingers facing the ceiling, and the right hand on the patient's left shoulder. The procedure is as follows:

- Step 1: The therapist stretches the patient's left upper trapezius muscle to its maximum size and holds it for 10 seconds (Figure 2a).
- Step 2: The patient performs a static antagonistic isometric contraction of the left trapezius muscle for 6 seconds and then relaxes (the head remains in the starting position during relaxation).
- Step 3: The patient's head is rotated to the right more deeply, the jaw is tucked in (if possible), and the therapist pulls the patient's left shoulder down more deeply, causing the antagonist muscle (right trapezius superior fasciculus) to contract for 30 seconds.
- Step 4: The therapist again holds the patient's left shoulder in a relaxing stretch to its maximum for 10 seconds. This procedure (target muscle stretch for 10 seconds – target muscle antagonist for 6 seconds – relax – antagonist muscle contraction for 30 seconds – relax – stretch to maximum amplitude for 10 seconds) is repeated for three to five cycles.

Scapularis Muscle Stretching

To start, the patient sits comfortably in a chair, keeping the back lengthened and closing the jaw so that it is close to the chest. The head is then rotated 45° to the right. The therapist stands behind the patient, placing one hand on the back of the patient's head and the other hand on the upper part of the left scapula. The procedure is as follows:

- Step 1: The therapist first static-stretches the patient's scapularis muscle for 10 seconds (Figure 2b).
- Step 2: The therapist then guides the patient to slowly raise their head, neck, and left shoulder, while at the same time applying resistance in order to cause an isometric contraction of the left scapularis muscle for 6 seconds. Throughout this process, the patient should be aware that it is not just the head that is being stretched back but rather the head and neck together.
- Step 3: After the isometric contraction, the patient relaxes and adjusts their breathing.
- Step 4: On exhalation, the patient retracts their lower jaw at a greater extent so that it stays close to the chest for 30 seconds and then relaxes.
- Step 5: The patient stretches again to the maximum extent and holds the position for 10 seconds.

Suboccipital Muscle Group Stretching

To start, the patient is placed in the supine position, and the therapist holds the patient's head, with the pads (not the tips) of the fingers under the head so that the occipital bone can be

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reached. The therapist allows the patient to tuck their lower jaw as close to the throat as possible, trying not to raise the head to bring it closer to the chest but trying to elongate the back of the neck as much as possible. The procedure is as follows:

- Step 1: The therapist first static-stretches the patient's suboccipital muscle for 10 seconds (Figure 2c).
- Step 2: The patient is then guided to slowly tilt the head back and perform a counterisometric contraction for 6 seconds. If the therapist's hand slips from the occipital bone, the process starts again, ensuring that the therapist's hand is in contact with the occipital bone.
- Step 3: The patient relaxes after the isometric contraction and adjusts their breathing.
- Step 4: On exhalation, the patient tucks their lower jaw with a greater magnitude in order to get closer to the chest, holding it for 30 seconds, and then relaxes.
- Step 5: The therapist again stretches the patient's suboccipital muscle to its maximum magnitude, holding it for 10 seconds.

Pectoralis Major Stretching

To start, the patient is placed in the prone position, and the therapist stands at the side of the patient, holding the patient's forearm with one hand and securing the scapula with the other. The therapist ensures that the patient's sternum does not leave the bed during retraction and that the shoulder joint is abducted 45°, 90°, and 135°. The therapist flexes the patient's elbow and raises the upper arm upward as far as possible, keeping the forearm horizontal. Note that by varying the angle of abduction of the upper limb, the muscle fibers of the pectoralis major can be stretched in different parts of the body. A small angle of abduction of 45° mainly stretches the muscles located in the clavicular region (Figure 2f); a large angle of abduction of 135° mainly stretches the muscles located in the lower thoracic ribcage (Figure 2e); when stretching the muscles in the sternal region of the pectoralis major muscle, it can be taken to the 90° position for stretching (Figure 2d). The procedure is as follows:

- Step 1: The therapist first raises the patient's upper arm upward as much as possible, static-stretching for 10 seconds.
- Step 2: The patient is then guided to push the shoulder downward and hold for 6 seconds.
- Step 3: After isometric contraction, the muscle is induced to relax, and the patient adjusts their breathing.
- Step 4: As the patient exhales, the therapist moves the patient's upper arm upward away from the bed with greater amplitude, maintains the position for 30 seconds, and then relaxes it.
- Step 5: The therapist stretches the patient's pectoralis major muscle to its maximum amplitude once again and maintains the position for 10 seconds.

Sternocleidomastoid Muscle Stretching

To start, the patient is placed in the supine position, pain free, with the neck lengthened. The head is rotated to the left as far as possible. The procedure is as follows:

- Step 1: The therapist first static-stretches the patient's sternocleidomastoid muscle for 10 seconds (Figure 2g).
- Step 2: The therapist holds the patient's head with one hand, puts the other hand on the patient's right ear, guides the patient to try to slowly rotate the head to the right, and then applies resistance to maintain confrontation for 6 seconds.
- Step 3: After isometric contraction of this muscle, the patient relaxes and adjusts their breathing.
- Step 4: On exhalation, the patient rotates their head to the left at a greater magnitude and holds it for 30 seconds and then relaxes.
- Step 5: The patient again stretches passively in the left rotational position to the maximum magnitude and holds the position for 10 seconds.

Pectoralis Minor Stretching

To start, the patient is placed in the supine position, and the therapist stands on the side of the patient's body, holding the patient's hand with one hand and placing the other hand on the front of the patient's shoulder. The therapist's hand exerts force to bring the patient's shoulder close to the bed, causing the scapula to move against the back and down. The procedure is as follows:

- Step 1: The therapist first presses down on the front of the patient's shoulder, static-stretching for 10 seconds (Figure 2h).
- Step 2: The therapist guides the patient's shoulder upward to force against the maintenance of 6 seconds.
- Step 3: The muscle undergoes isometric contraction, followed by relaxation, and the patient adjusts their breathing.
- Step 4: During exhalation, the patient increases the range of motion to bring their scapulae closer to the bed surface, causing the scapulae to move posteriorly and inferiorly. To guide this movement, the therapist can instruct the patient to "direct their scapulae toward the back pocket of your opposite-side trousers." The patient maintains this position for 30 seconds and then relaxes.
- Step 5: The therapist once again stretches the muscle to its maximum magnitude to maintain a 10-second hold.

Obliques Muscle Stretching

To start, the patient is placed in the supine position, and the therapist places one hand on the patient's head above the left ear and the other hand on the left shoulder to immobilize the left shoulder. The procedure is as follows:

- Step 1: The therapist fixes the patient's left shoulder with one hand and static-stretches the head toward the right shoulder with the other hand for 10 seconds (Figure 2i).
- Step 2: The patient is then guided to move the head forcefully against the direction of the static stretch, trying to get closer to the left shoulder for 6 seconds.
- Step 3: The muscle undergoes isometric contraction, followed by relaxation, and the patient adjusts their breathing.
- Step 4: When the patient exhales, the therapist allows the patient to actively do their best to bring their right ear closer to the right shoulder with a greater magnitude, with the tip of the nose all the way up to the ceiling; maintain the position for 30 seconds; and then relax.

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- Step 5: The therapist stretches the patient's obliques muscle to the maximal magnitude once again and maintains the position for 10 seconds.

The obliques are divided into anterior obliques, middle obliques, and posterior obliques. The starting position of the head is different, so it is necessary to stretch the anterior and middle obliques individually through the rotation of the head: left anterior oblique muscle's starting position, neck right lateral flexion; head left rotation 45°; left posterior oblique muscle starting position, neck right lateral flexion; and head right rotation 45°.

Care is taken during stretching to ensure that the patient does not produce limb movements during isometric contractions. Compensatory movements are avoided, and normal breathing is required. Appropriate resistance is given by the therapist, who ensures that the full range of stretching remains painless [21].

Step 2: PNF Muscle Training

At the end of the PNF retraction, the patient takes a sitting position. The therapist touches the patient with their bare hands and stands behind them. Next, the therapist gives short instructions to the patient to perform forward flexion, backward extension, left lateral flexion, and right lateral flexion of the neck using the following three techniques flexibly [22]: antagonistic muscle reversal, isotonic combination, and neck diagonal movement.

Antagonistic Muscle Reversal

The steps are as follows:

- Step 1: If the therapist applies resistance to the patient's cervical flexor muscle group, the instruction is, "Do not tilt your head back now."
- Step 2: When the patient's cervical flexor muscle group contracts, the therapist maintains resistance with one hand, while the other hand squeezes and counteracts the posterior extension of the neck, with the instruction "Do not tilt your head back now."
- Step 3: When the patient responds to the new resistance, the therapist places the hand that resisted the anterior cervical flexion to the extensor side to resist the posterior extension of the neck.
- Step 4: Finally, the patient keeps the neck stable; the instruction is, "Now do not lower your head and do not tilt it."

The speed and frequency of reversal movements vary from person to person. They can start slowly until the patient is stable. Only small movements are allowed during the process.

Isotonic Combination

The steps are as follows:

- Step 1: If the patient fights against the resistance applied by the therapist, the neck is flexed from a neutral position to the left side (centripetal contraction) and the head is tilted to the left.
- Step 2: When the patient's neck reaches the end of left lateral flexion, they are asked to remain stable in this position, with the instruction "Stop and hold it here."
- Step 3: When stability is reached, the therapist has the patient move slowly toward the starting position (centrifugal contraction), with the instruction "Now let me push you into lateral flexion to the right, but slowly."

The therapist's hand remains in the same position. This technique can be combined with antagonistic muscle reversal.

Neck Diagonal Movement

The steps are as follows:

- Step 1: The patient resists the therapist's resistance.
- Step 2: Start with the neck in forward flexion, then left lateral rotation, and left lateral flexion and end with the neck in backward right lateral rotation and right lateral flexion.
- Step 3: Repeat the movements in step 2 in the opposite diagonal direction.
- Step 4: Alternate steps 2 and 3 and perform them three times on each side.

The PNF technique will be performed once a day [23]. The patients will be instructed to adopt a correct sitting posture and try to avoid prolonged neck flexion.

Group 2: The Tuina Group

The tuina group will receive TCM therapy with tuina for 30 minutes in each session. The therapist will administer each session with nine steps to ease neck pain and improve neck function. These steps are based on the principles of relaxing tendons, removing blood stasis, clearing the meridians, restructuring, expanding tendons, assisting movement, and promoting dispersal. The specific protocol used is described next, and the specific procedure is illustrated in Figure 3:

- Pressing and kneading to loosen the tendons: Techniques such as one-finger Zen pushing, the holding method, and the dialing method are used on the neck, posterior occipital region, and shoulder region to relieve muscle spasm and improve blood circulation. The treatment sequence starts from the top and goes down, from the center to both sides, from the healthy side to the affected side, using gradually increasing force and depth to fully relax the neck, the posterior occiput, and the shoulder (Figure 3a).
- Trigger reset: If the spinous process is deviated, the cervical spine can be positioned to rotate the trigger (Figure 3b).
- End lifting for chaos: If there is rotation of the cervical spine in the coronal and sagittal axes, end-lifting of the neck can be performed (Figure 3c).
- Lateral trigger assistance: If there is a functional limitation of cervical lateral flexion, the cervical lateral trigger can be performed (Figure 3d).
- Symptomatic treatment: This involves pointing, kneading, and flicking the following acupoints to clear the meridians: *Fengchi* (GB 20), *Fengfu* (GV 16), *Jianyu* (LI 15), *Jianjing* (GB 21), *Tianzong* (SI 11), *Zhongzhu* (TE 3), *Jianzhen* (SI 9), *Jiequan* (EX-UE 12), and *Houxi* (SI 3).

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- Symptomatic treatment helps activate the meridians and regulate Qi and blood circulation (Figure 3e).
- Spot-kneading of pain points: Focusing on spot kneading at the pain point areas of the neck and shoulder helps invigorate blood circulation, remove blood stasis, relieve spasms, and break up adhesions (Figure 3f).
- Drawing and stretching decompression: Cervical drawing and stretching are performed to reduce the pressure on the intervertebral discs; increase the intervertebral space; enlarge the intervertebral foramen; and reduce compression on the nerves, vertebral arteries, and spinal cord, promoting the rehabilitation of injured tissues.
- Shaking to assist mobilization: Neck shaking can be done to restore cervical flexion, extension, and rotation.
- Pushing and rubbing to disperse Qi and blood, warming the meridians and channels: Side strikes on the shoulders can be performed to relax the tendons and channels [24].

Figure 3. TCM therapy with tuina: (a) thumb plucking, (b) cervical spine positioning rotary trigger, (c) cervical end lift, (d) lateral cervical trigger, (e) fishbone rubbing, and (f) tap and rub pain points. TCM: traditional Chinese medicine.

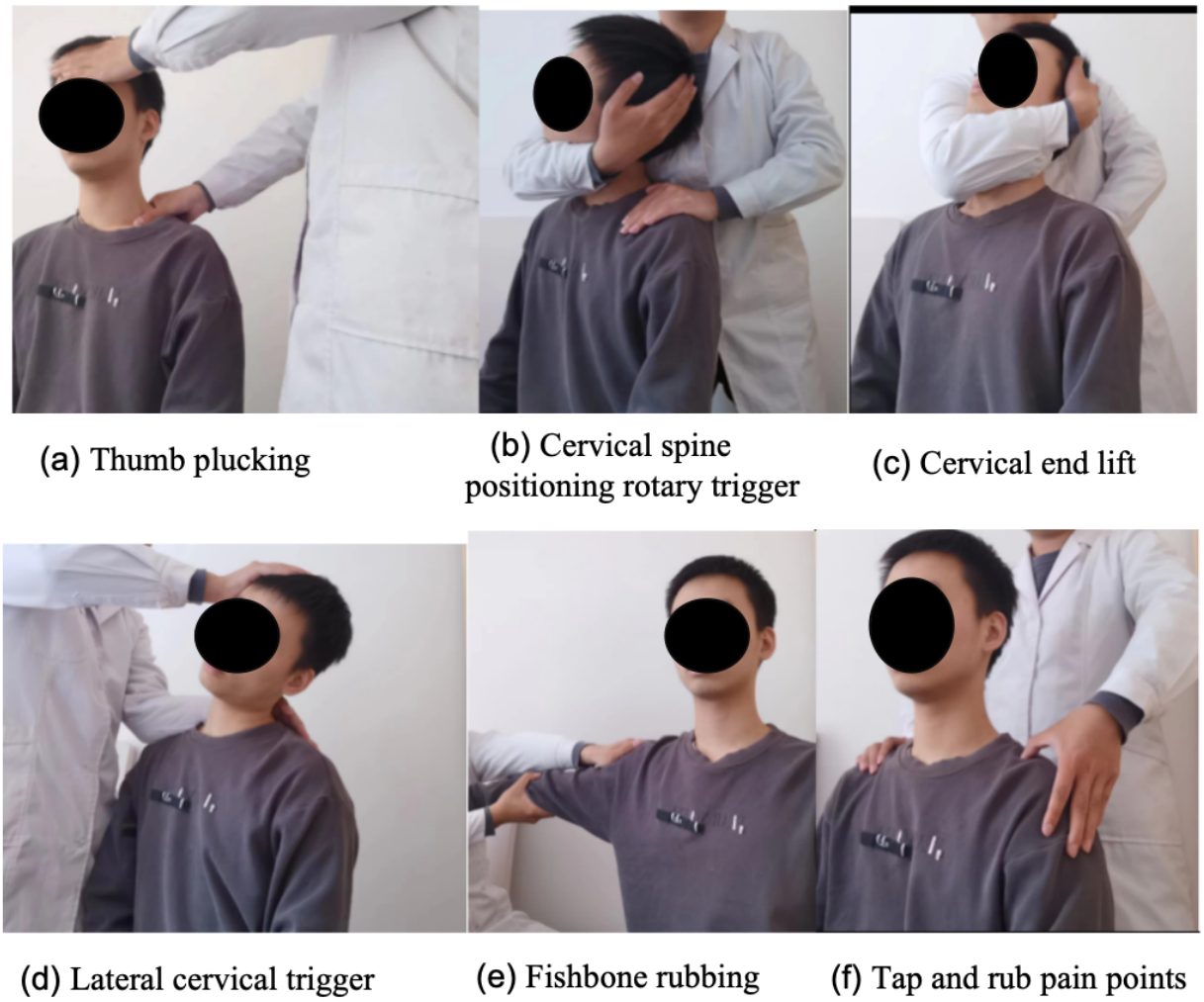

Group 3: The Combined (PNF+Tuina) Group

The combined group will first receive 30 minutes of PNF, followed by 30 minutes of tuina therapy; thus, the total time will be approximately 60 minutes. The PNF technique is the same as that administered to the PNF group. Tuina therapy is the same as that administered to the tuina group.

Outcome Measurements

Two self-report tools and two detectors will be used to measure the outcomes. The VAS and NDI scores will be used as the primary outcome measures. Cervical active joint mobility measured with the MicroFET3 Portable Muscle Strength Test and Joint Mobility Meter and muscle physical properties tested with the Myoton Muscle Tester will be used as secondary outcome measures. Pain, cervical active joint mobility, cervical spine dysfunction, and muscle physical property measurements will be performed during the first week (preintervention) and after 4 weeks' treatment.

Primary Outcome Measurements

Visual Analogue Scale

The VAS will be selected to evaluate the pain level of patients in this experiment. The patients will be asked about the maximum level of neck and shoulder pain they experience in their daily lives. The pain will be recorded as a whole number from 0 to 10, with 0 representing no pain and 10 representing the maximum pain that has become intolerable. The pain level increases gradually from 0 to 10 [25].

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Neck Disability Index

The NDI is a scale selected to assess patients' cervical spine function, including both symptoms related to neck pain (eg, pain intensity, headache, concentration, and sleep) and the ability to perform activities of daily living (eg, personal care, lifting heavy objects, reading, working, driving, and recreation). Each item has a minimum score of 0 and a maximum score of 5. Higher scores indicate more severe cervical spine dysfunction. The NDI score is calculated according as [sum of scores for each item/(number of items completed × 5)] × 100. An NDI score of 0%-20% indicates mild dysfunction; 20%-40%, moderate dysfunction; 40%-60%, severe dysfunction; 60%-80%, very severe dysfunction; and 80%-100%, complete dysfunction (the patient should be examined in detail to see whether there is any exaggeration of symptoms).

Secondary Outcome Measurements

Cervical Active Joint Mobility

Cervical spine mobility will be tested using the MicroFET3 Portable Muscle Strength Test and Joint Mobility Meter. Cervical joint mobility is classified into flexion, extension, left lateral flexion, right lateral flexion, left rotation, and right rotation. Its normal reference range is as follows: forward flexion 35°-45°, backward extension 35°-45°, left and right lateral flexion 45° each, and left and right rotation 60°-80° each.

For measurement, the patient takes a sitting position, keeping the thoracolumbar spine straight. The instrument is worn on the head. Next, the patient performs cervical anterior flexion, posterior flexion, right and left flexion, and left and right rotation movements to measure cervical spine mobility. This will be performed before the overall posture measurement. The patient will remain in a neutral position: facing forward, eyes flat, and jaw inward.

Muscle Physical Properties

MyotonPRO (Myoton AS) is a new portable muscle testing device invented by Dr Arved Vain, a biologist at the University of Tartu, Estonia, which can accurately and efficiently reflect the physical properties of soft tissues, such as muscles, ligaments, and tendons, and is painless and easy to operate [26]. MyotonPRO is used in the evaluation and rehabilitation of musculoskeletal and neurological disorders in both domestic and foreign populations, such as healthy people and athletes. MyotonPRO is based on the principle of slight mechanical impact on soft tissues, which produces vibrations and records vibration curves and then calculates the corresponding parameters based on the vibration curves. The parameter settings and meanings of the parameters are shown in Tables 1 and 2.

Table 1. MyotonPRO parameter settings.

Parameter setting	Value
Maximum spectrum (Hz)	450
Impact time (seconds)	15
Delay time (seconds)	0.7
Scanning mode	Multiple (10 times)

Table 2. Meaning of MyotonPRO parameters.

Parameter	Meaning
Muscle tone (Hz), F	The higher the F value, the higher the muscle tone or pressure within the muscle.
Muscle hardness (N/m), S	The higher the S value, the greater the muscle hardness.
Muscle elasticity, D	The higher the D value, the poorer the muscle elasticity (amplitude; logarithmic decrement).

The use of this device requires the tester to hold the handle and align the probe of the device vertically with the muscle fibers of the target muscle. The probe head needs to be perpendicular to the horizontal plane and gently and slowly pressed down. When pressed to the depth set by the instrument, the instrument starts to launch a slight impact and a subsequent rebound vibration of the probe. The tester should keep the instrument in the same position. When the impact and probe rebound vibration are over, the test ends. The damped vibration frequency, the damped decay rate, and hardness on the display are read and the three values recorded. The same muscle will be tested three times, and the average will be used as the calculated value. The tests before and after the experiment will be operated by the same tester, who is not aware of the grouping. The tension, hardness, and elasticity of the upper trapezius muscle will be tested with the MyotonPRO Digital Muscle Function Assessment System (Myoton AS).

Safety Evaluation

AEs refer to unexpected responses that occur during or after treatment, which can lead to hospitalization or even threaten life. The trial will be suspended immediately if we encounter AEs. The efficacy and safety of the intervention will be evaluated with 4 weeks of unsupervised follow-up, during which the patients will only receive routine neck care. At weeks 4 and 8, they will be contacted over the phone regarding their physical condition of neck pain. In addition, evaluators will be updated with the patients' clinical symptoms and AEs.

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Data Collection and Monitoring

Screeners will collect data on baseline characteristics when patients are recruited. Assessors will complete records of the assessment of treatment effects, neck physiological function, AEs, and safety evaluations. Next, two data administrators, who are not part of the research team and blinded to group allocation, will independently receive the data outcomes and enter them into a Micrsoft Excel database.

Statistical Analysis

The intention-to-treat principle will be followed in the primary data analysis with IBM SPSS Statistics for Windows version 27.0 software by statisticians who are blinded to the group allocation. Baseline characteristics will be expressed with descriptive statistics for the groups as the mean (SD). The Kolmogorov-Smirnov test with Lilliefors correction will be performed to analyze all quantitative variables to determine whether they follow a normal distribution. Parametric statistics (Tukey test) or nonparametric statistics (Wilcoxon rank-sum test) will be used for the within- and between-group analyses in accordance with the results of homogeneity and normality analyses. When initial homogeneity and normality of data distribution are found, repeated measures ANOVA and ANOVA with Bonferroni post hoc statistics will be used for within- and between-group analysis. The Friedman test and the Kruskal-Wallis test will be performed when initial homogeneity but not normality of data distribution is found. If initial homogeneity is not found, a linear mixed model will be adjusted for the baseline value. AEs in each group will be documented as percentages for safety assessments using the chi-square test or the Fisher exact test. Statistical significance is defined as $P<.05$, and 95% CIs will be reported.

Sample Size Calculation

The sample size was calculated using Granmo calculator v.7.12, based on a three-arm parallel-group design and ANOVA for means (SDs). The primary assumption was that the minimum clinically important difference (MCID) according to the VAS score is 13.5% (0.135). This value was derived from a previous NCNP study [27] and represents the minimum pain reduction considered meaningful by patients and clinicians.

The statistical parameters are as follows: alpha risk (type I error): 5% (two-sided); beta risk (type II error): 10% (power=90%); SD of mean VAS scores: estimated as 12% (0.12) based on a pilot study (Li Liuyinuo, unpublished data, 2022).

The initial sample size was calculated as 45 participants (n=15, 33.3%, per group) to detect the specified MCID under ideal conditions (no dropouts). To make adjustments for follow-up losses, we anticipated an 8% dropout rate (based on similar rehabilitation trials [8]), so the final sample size was increased to 69 participants (n=23, 33.3%, per group) to ensure at least 20 evaluable patients per group after attrition.

Quality Control

With the management of the steering committee, quality control will be conducted during the processing of the trial. Professional trial and regular monitoring training sessions will be conducted before the researchers participate in the trial, which will ensure consistency of the methods. The steering committee and ethics committee will be informed if the study protocol is modified or corrected.

Results

As of the data cutoff date (May 26, 2025), 43 participants were enrolled and randomly assigned to the three treatment groups (PNF group: n=14, 32.6%; tuina group: n=15, 34.9%; combined group: n=14, 32.5%), with recruitment initiated on April 1, 2025, via hospital outpatient clinics (n=45, 65.2%) and online posting (n=24, 34.8%). All enrolled participants have initiated treatment, with an average adherence rate of 92% (measured using session attendance records), and no withdrawals have occurred due to AEs or treatment dissatisfaction. The short-term follow-up (end of intervention) for the first cohort was completed on July 30, 2025, with long-term follow-up (1 month postintervention) to be completed by August 31, 2025. The final analysis is projected to include data of all 69 participants by October 2025, with primary results planned for publication in December 2025.

Discussion

Summary

NCNP is a widespread musculoskeletal disorder associated with significant functional impairment and a huge economic burden, aligning with previous reports highlighting its impact on activities of daily living and work productivity. Our RCT aims to evaluate the efficacy of PNF, tuina, and their combination, two interventions with distinct theoretical foundations, in treating NCNP. Studies have demonstrated that tuina reduces neck pain by enhancing blood circulation and releasing myofascial tension [28], while PNF is hypothesized to improve neuromuscular control and joint mobility through proprioceptive stimulation [29]. However, this is among the first RCTs to directly compare these modalities head-to-head and assess their synergistic effects. Notably, our preliminary results (interim analysis) suggest that the combination group achieved a 42% reduction in VAS scores at 4 weeks, significantly greater than the 28% and 31% reductions in the tuina and PNF groups, respectively. The results of this study are similar to those of a systematic review on adjunctive therapies for chronic pain [30], which reported that the combination of manipulative therapy and exercise results in better outcomes. However, this contrasts with a study by Qi et al [31], who found no increased effect of PNF in combination with acupuncture, which may be due to differences in the duration of the intervention (2 months compared to our 4-week regimen) or patient selection criteria.

Limitations

Although this trial provides valuable insights, several limitations warrant discussion. First, the single-center design may limit generalizability, as participants are being recruited from a tertiary hospital in Beijing, potentially introducing selection bias toward patients with more severe symptoms. Second, the sample size (N=69) may lack sensitivity to identify small but clinically meaningful differences, particularly in subgroup analyses, and the short intervention period (4 weeks) and

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1-month follow-up do not capture long-term outcomes, such as recurrence rates. Third, the inability to blind therapists to treatment allocation may have introduced performance bias, and limited use of objective measures (eg, surface electromyography) may hinder mechanistic insights. Despite these limitations, the trial supports exploring PNF as a stand-alone intervention and its integration with tuina, with future research recommended to adopt multicenter designs, extend follow-ups, and use of objective biomarkers.

Conclusion

This study provides preliminary evidence that the combination of PNF and tuina may offer superior short-term pain relief compared to monotherapies for NCNP. Although rigorous replication in larger, more diverse populations is needed, these findings justify further investment in integrative rehabilitation strategies for this challenging condition.

Acknowledgments

The authors would like to thank all the investigators, study coordinators, study participants, and their families for their support in this trial. This trial was conducted with no external funding, and its costs have been assumed by researchers.

Data Availability

After the completion of the experiment, our experimental data will be published on the public management platform for clinical trials MedResMan.

Authors' Contributions

FKQ planned the study protocol and drafted the manuscript. ZXY participated in the critical revision of the manuscript and contributed to the final approval of the manuscript. WAC contributed to the design of the protocol and managed the study. GHN, LSW, and SXX participated in designing the outcome measurements and assessing the outcomes. PLJ participated in designing the trial and helped prepare the manuscript. SXX contributed to the statistical design, and YT was responsible for the design of the randomization. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2025 editable checklist.
[DOCX File , 30 KB - resprot_v14i1e63528_app1.docx]

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Abbreviations

AE: adverse event
HRAC: hold-relax-antagonist contraction
MCID: minimum clinically important difference
NCNP: nonspecific chronic neck pain
NDI: Neck Disability Index
PNF: proprioceptive neuromuscular facilitation
RCT: randomized controlled trial
TCM: traditional Chinese medicine
VAS: Visual Analogue Scale

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Protocol

Constraint-Induced Movement Therapy With or Without Neuromuscular Electrical Stimulation Versus Conventional Therapy for Upper Extremity Function in Chronic Stroke Survivors: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: Motor impairment is a common consequence of stroke, significantly impacting patients' daily functioning and quality of life. More than 80% of stroke survivors experience upper extremity (UE) motor impairments, which severely impact their ability to carry out daily living activities. Combining motor rehabilitation techniques, such as constraint-induced movement therapy (CIMT), with sensorimotor stimulation methods, such as neuromuscular electrical stimulation (NMES), may be beneficial in enhancing UE functional recovery after a stroke. This combined approach could activate a broader range of brain regions, improving motor control. However, evidence for the effectiveness of these interventions when combined is still lacking.

Objective: In this randomized controlled trial, we aim to determine the effectiveness of CIMT combined with NMES, CIMT alone, and conventional therapy in rehabilitating UE function in chronic stroke survivors.

Methods: We will compare 3 intervention groups, 2 experimental groups (CIMT combined with NMES group and CIMT group) and 1 control group (conventional therapy), in this assessor-blinded, cluster randomized controlled trial. A total of 42 participants will be recruited and randomly assigned to 1 of the 3 groups. Participants in the CIMT group will undergo 6 shaping practice tasks (50 repetitions for each task, totaling 300 repetitions per session). The combined CIMT/NMES group will perform tasks similar to those carried out by the CIMT-only group, and a biofeedback electrical stimulator for NMES will also be provided. The control group will receive conventional neurodevelopmental therapy. All groups will receive 1 session per day of treatment for 3 consecutive days a week for 4 weeks. A blinded assessor will measure the interventions' outcomes using standardized tests, including UE motor function, motor impairment, perceived motor function, and upper limb self-efficacy. All data will be analyzed descriptively, presenting the means and SDs. We will conduct inferential tests using a 2-way mixed ANOVA to evaluate the effects of the interventions and compare them between and within groups.

Results: Funding for this study was provided by the Research and Ethics Committee of the Universiti Kebangsaan Malaysia (the National University of Malaysia) starting in November 2023. Between January 2023 and May 2023, we developed the initial ethics proposal and recruited research staff. Research ethics applications were submitted to the Research and Ethics Committee of the Universiti Kebangsaan Malaysia from May 2023 to November 2023. We anticipate publishing the study results in September 2025.

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Conclusions: This trial will provide insights into the effectiveness of CIMT combined with NMES, CIMT alone, and conventional therapy for UE rehabilitation in stroke survivors. Findings will be published in a peer-reviewed journal, and any updates based on emerging evidence will be provided. Any changes to the study methods will be documented in the final publication.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12624000564550; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=387308

(JMIR Res Protoc 2025;14:e68340) doi:10.2196/68340

KEYWORDS

stroke; upper extremity; constraint-induced movement therapy; neuromuscular electrical stimulation; Post-stroke; stroke rehabilitation

Introduction

Background

Stroke is one of the most debilitating brain disorders, often leading to death or severe functional impairment. The global burden of stroke is exceptionally high in low- and middle-income countries, where increased incidence, mortality, disability, and economic strain are prevalent [1]. Stroke is the second leading cause of death and disability worldwide [2], with over 116 million healthy years lost annually due to disabilities and fatalities associated with stroke [3]. Among stroke survivors, more than 80% experience motor impairments in the upper extremities (UEs) [4], significantly limiting their ability to engage in social and daily activities. While approximately two-thirds of patients who have experienced a stroke can walk independently 6 months after the stroke, nearly half remain unable to functionally use the affected arm despite receiving treatment [5].

UE impairment is a common challenge for stroke survivors, often leading to significant motor dysfunction and impacting daily living activities [6,7]. Improving UE function through targeted rehabilitation is essential for enabling stroke survivors to perform daily tasks independently [8,9]. Constraint-induced movement therapy (CIMT) is a highly effective intervention for enhancing UE function after stroke [10] and is considered one of the most essential rehabilitation approaches for stroke recovery [11]. Numerous systematic reviews provide strong evidence supporting CIMT's use across acute, subacute, and chronic phases of stroke rehabilitation [12-15]. Consequently, CIMT is recommended as a core intervention in clinical guidelines worldwide, including in the United Kingdom [16], Australia [16], and Canada [17]. In addition, research indicates that CIMT can enhance functional performance compared to traditional rehabilitation and increase the use of the most affected UE [18].

Despite the prevalence of motor impairments following a stroke, neuromuscular electrical stimulation (NMES) interventions are designed to enhance the quality of life and motor function by contracting weak muscles in the affected extremity. This approach aims to address paresis, restore fractionated movements, improve coordination and joint control, and decrease abnormal movement patterns, such as reduced spasticity and abnormal muscle synergies [19]. Clinical evidence supports the therapeutic efficacy of NMES as a complementary approach to traditional physiotherapy. Specifically, NMES for finger, arm, and wrist extension has shown the most significant clinical and neuroprosthetic benefits. Research indicates that individuals with moderate impairments within 2 years after a stroke experience essential improvements in UE function from NMES, especially when the stimulation is synchronized with the individual's movement intent [19,20].

Motor function recovery is a critical aspect of stroke rehabilitation. However, in the chronic stage of stroke, the pace of functional recovery often slows considerably. This slow recovery rate, combined with the inherent tendency of humans to rely on bilateral arm coordination for functional activities, may lead to the development of compensatory movement strategies that hinder optimal recovery of the affected UEs. Humans instinctively use both arms in a coordinated fashion to carry out daily tasks. Following a stroke, this natural inclination to rely on bilateral arm coordination, coupled with the slow recovery of the affected arm, may lead patients to develop compensatory movements. While enabling individuals to cope with their impairments, these strategies limit the potential for optimal recovery of the affected UE. As patients become increasingly reliant on compensatory movements, they may fail to engage the impaired limb effectively, leading to a plateau in functional improvement. Consequently, rehabilitation professionals must recognize and address these compensatory strategies to promote optimal recovery and prevent long-term functional limitations in chronic stroke survivors. To overcome the challenges posed by compensatory strategies and promote recovery in the chronic stage of stroke, a combined approach integrating motor rehabilitation techniques, such as CIMT, with sensorimotor stimulation methods, such as NMES, may be beneficial [21]. Combined therapeutic interventions demonstrate significant potential for activating diverse brain regions involved in motor control, enhancing recovery following stroke. The clinical implications of these findings suggest that implementing multimodal interventions is essential for optimizing motor recovery in chronic stroke survivors. This approach is substantiated by functional magnetic resonance imaging studies revealing neuroplastic changes associated with combined therapy modalities, demonstrating enhanced cortical reorganization when peripheral stimulation is paired with intensive motor training [21-23]. The neuroimaging evidence provides a neurophysiological basis for the efficacy of combined interventions, offering valuable insights into evidence-based rehabilitation protocols that may inform clinical practice guidelines and future research directions in UE rehabilitation after stroke.

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Objectives

Although CIMT is an established intervention for stroke recovery, limited research exists on the synergistic effects of combining it with NMES. No clinical studies have reported the effectiveness of CIMT combined with NMES in comparison to CIMT alone or conventional therapy for treating UE dysfunction in patients who have experienced a stroke. Therefore, we aim to combine CIMT with NMES to explore the effect of their combination on UE dysfunction in chronic stroke survivors and compare it to CIMT alone and conventional therapy.

Methods

Trial Design and Setting

This study is an assessor-blinded, cluster, randomized controlled trial (RCT) comparing 3 intervention groups: 2 experimental groups (CIMT combined with NMES and CIMT alone) and 1 control group (conventional therapy). The trial will be conducted across 3 National Stroke Association of Malaysia (NASAM) rehabilitation centers. NASAM, a primary referral center for stroke survivors in Malaysia, operates 8 centers nationwide, providing rehabilitation services, peer support, and information to stroke survivors.

The study will be reported according to the CONSORT (Consolidated Standards of Reporting Trials) guidelines. The trial schedule is presented in Figure 1, while the trial design flowchart is provided in Figure 2. In addition, the study has been registered prospectively with the Australian New Zealand Clinical Trials Registry under registration number ACTRN12624000564550.

Figure 1. Flow diagram of the study. CIMT: constraint-induced movement therapy; FMA-UE: Fugl-Meyer Assessment for upper extremity; MAL: Motor Activity Log; NMES: neuromuscular electrical stimulation; UPSET: Upper Limb Self-Efficacy Test; WMFT: Wolf Motor Function Test.

		Study period						
		Enrolment	Allocation	Intervention (weeks)				Closeout
Time point		Week −1	Week 0	Week 1	Week 2	Week 3	Week 4	Week 5
Enrollment								
	Screening eligible participants	✓						
	Informed consent	✓						
	Sociodemographic	✓						
	Randomization and allocation		✓					
Interventions								
	CIMT+NMES group			↔	↔	↔	↔	
	CIMT group			↔	↔	↔	↔	
	Control group			↔	↔	↔	↔	
Outcome measurements								
	FMA-UE		✓					✓
	WMFT		✓					✓
	MAL		✓					✓
	UPSET		✓					✓
Feasibility of interventions								
	Acceptance of interventions							✓
	Adherence							✓
	Adverse effects			✓	✓	✓	✓	✓

Study Participants

The principal researcher will recruit eligible participants using the predefined inclusion and exclusion criteria, as described in Textbox 1 [24-28].

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Adults aged 18 to 80 years, with a diagnosis of ischemic or hemorrhagic stroke in the chronic phase (≥6 months after stroke)
- A score of ≥3 on the upper arm item of the Motor Assessment Scale
- A score of ≥44 on the Fugl-Meyer Assessment for upper extremity, with ≥10° active wrist extension and ≥10° active extension of thumb and additional digits
- A score of ≥26 on the Montreal Cognitive Assessment [24]. The patients must not have severe impairments in cognitive function, as they should understand the instructions and communicate
- A grade of ≤2 on the Modified Ashworth Scale for the upper extremity and lower extremity [25]
- No history of upper extremity injuries. History of upper injuries, such as a fracture or any deformity that can prevent patients from practicing massed tasks with the affected limb

Exclusion criteria

- Sensory loss score of ≥2 on the National Institutes of Health Stroke Scale sensory item. Such impairments can affect the ability to use the upper extremity in everyday activities [26]
- Patients with pacemakers or tumors owing to their contraindication to the implementation of the neuromuscular electrical stimulation [27,28]

Recruitment and Randomization

Participants will be recruited from the NASAM. Three NASAM centers will be randomly assigned to 1 of 3 groups: the CIMT combined with the NMES group, the CIMT-only group, or the control group. Due to the specific nature of the therapies and the distinct characteristics of the centers, randomizing individual participants within centers is impractical. A cluster randomization approach will be used to minimize contamination among patients attending the same center. In addition, to minimize the risk of contamination between intervention groups, a cluster randomization approach will be used, wherein health care centers will serve as the unit of randomization. Each participating center will be randomly allocated to 1 of the 3 intervention arms using a computer-generated sequence administered by research personnel not involved in intervention delivery or outcome assessment. This concealed allocation process ensures allocation concealment and methodological rigor. Following randomization, all eligible patients who have experienced a stroke attending a given center will receive only the intervention protocol assigned to that facility. This methodological approach enables consistent intervention delivery within each site while substantially reducing the likelihood of cross-contamination between intervention groups—a critical consideration when evaluating health care provider–delivered rehabilitation protocols with behavioral components.

Eligible participants will provide written informed consent before their involvement in the study. The principal investigator or a trained research staff member not involved in therapy delivery will be responsible for obtaining consent from each participant. This process will take place only after participants have received a comprehensive explanation of the study procedures, ensuring that they clearly understand their involvement and the associated risks and benefits.

Following the informed consent process, baseline demographic information, including the participants' names, ages, and gender, will be collected. Once demographic data have been obtained, the remaining baseline assessments will be conducted. Throughout the study, the confidentiality of all participants' personal information and data will be strictly maintained in accordance with established research ethics guidelines and data protection regulations.

Blinding

Outcome assessors will be blinded to the group assignments to ensure an unbiased evaluation of the results. However, given the significant differences in the therapies and the nature of the interventions, it is not feasible to blind the therapists or the patients involved in the study. Clinical staff must be aware of the specific therapy they are administering. Therapists will be informed that a study is being conducted on different modalities in other NASAM centers, but no particular details about the treatment regimens or locations will be provided. They will be aware of the treatment regime at their center but are reminded not to disclose this information to other therapists, either within or at different centers.

Therapist Training and Standardization

Recognizing that therapist-related variability represents a significant potential source of bias in rehabilitation trials, we have developed comprehensive standardization procedures to minimize therapist-level confounding. While the complete elimination of therapist effects remains impossible in hands-on interventions, our multifaceted approach ensures maximum consistency across sites and health care providers.

All participating therapists must complete a 3-day training program before commencing study treatments. This standardized curriculum encompasses theoretical foundations underlying each intervention approach, extensive hands-on skill development with practice participants, and a detailed review of all protocol procedures. Competency assessment requires therapists to achieve a minimum score of 90% on written examinations covering theoretical knowledge and protocol specifications and satisfactory performance on practical skills assessments evaluated by master trainers. Weekly refresher sessions throughout the trial will maintain intervention quality,

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address emerging questions, and ensure continued protocol adherence.

To enhance baseline comparability across sites, participation is restricted to therapists possessing at least 5 years of stroke-specific rehabilitation experience. This requirement ensures foundational clinical expertise while creating greater homogeneity in health care provider characteristics. Each therapist will exclusively deliver 1 intervention type throughout the study, eliminating within-center variability and reducing contamination risk between treatment arms. The same therapist will treat all participants within their assigned center, maintaining consistency in intervention delivery style and therapeutic relationship development.

Structured peer observations using standardized feedback forms will maintain consistent intervention quality across sites. Detailed session plans specifying exercise sequences, progression criteria, and acceptable modifications will limit unwanted variability while preserving necessary clinical flexibility for individual participant needs. This comprehensive standardization approach minimizes therapist-related variability while enabling appropriate statistical control for unavoidable health care provider effects, strengthening our trial's internal validity and interpretability.

Interventions

The interventions in this study will take place on 3 consecutive days each week for 4 weeks. The study flowchart (Figure 2) provides a detailed overview of participant flow through the clinical trial.

Figure 2. Flowchart of the study. CIMT: constraint-induced movement therapy; FMA-UE: Fugl-Meyer Assessment for upper extremity; MAL: Motor Activity Log; NMES: neuromuscular electrical stimulation; UPSET: Upper Limb Self-Efficacy Test; WMFT: Wolf Motor Function Test.

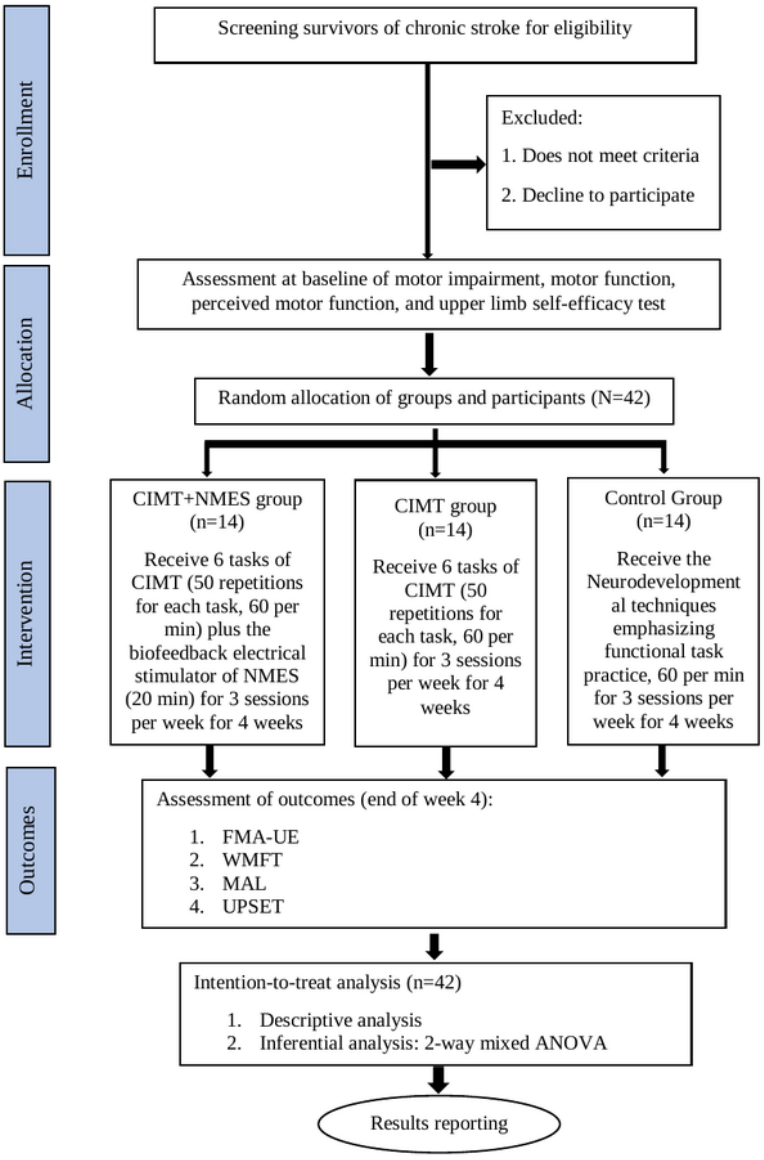

CIMT Group

In the CIMT group, the shaping practice of CIMT will perform the following: picking up a cup from the table, taking it to the mouth, and putting it back; writing letters or drawing a circle; picking up an object (a pen or pencil) and transferring from right to left on the table; taking the hand from the lap to the

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head and sliding it from the front to the back; taking the hand to the nose; and putting and removing shoes. These 6 tasks will be performed 50 times, totaling 300 repetitions per session. The tasks were developed following a protocol outlined in a previous study [29].

Participants will complete hour-long CIMT sessions 3 times per week for 4 weeks, aiming to perform the 300 task repetitions within each session. This repetition target is supported by evidence from previous studies [30-32], showing that ≥300 daily repetitions can drive motor function recovery and can be achieved within 1 hour of focused practice. Structured progression criteria will adjust the tasks throughout the intervention to standardize the repetition counts while accommodating individual capacities.

Participants in the CIMT group will wear a padded or oven mitt on their unaffected UE for 90% of waking hours, 3 days per week, over the 4-week intervention period. On the basis of studies by Abdullahi [29], Wolf et al [33], and da Silva et al [34], this constraint protocol aims to promote intensive use of the affected limb during daily activities.

The selection of mitts was based on affordability, accessibility, and ease of maintenance considerations. Adherence to the constraint protocol will be monitored through participant self-report logs, verified by caregivers when possible, and direct therapist observations during treatment sessions.

Table 1 outlines the CIMT intervention framework, detailing the types of tasks, repetitions, sessions per day, and duration of task practice.

Table 1. Characteristics of the constraint-induced movement therapy intervention.

Task	Task repetitions per session, n	Sessions per day, n	Days per week, n	Weeks, n
Picking up a cup from the table, taking it to the mouth, and putting it back	50	1	3	4
Writing letters or drawing a circle	50	1	3	4
Picking up an object (pen or pencil) and transferring it from right to left on the table	50	1	3	4
Take the hand from the lap to the head and slide it from the front to the back	50	1	3	4
Taking the hand to the nose	50	1	3	4
Putting on and removing shoes	50	1	3	4

CIMT and NMES Group

Participants in the CIMT+NMES group will perform functional tasks similar to those in the CIMT group, with the addition of NMES delivered via a biofeedback electrical stimulator. During NMES sessions, participants will be seated with their paretic arm resting at their side and forearm pronated. Two stimulating electrodes will be placed over the extensor carpi radialis muscle belly. Participants will be instructed to relax the paretic arm while stimulation intensity is adjusted to elicit a sustained muscle contraction, known as a tetanic contraction, producing 20° to 25° of wrist extension without pain. NMES will be administered for 20 minutes per day, 3 days per week, over the 4-week intervention period.

NMES will be applied immediately following the completion of each CIMT session. This sequencing optimizes neuromodulatory effects while preserving volitional movement patterns during functional tasks [35,36]. By delivering NMES after the CIMT protocol, this approach allows for muscle activation without the influence of fatigue, potentially enhancing the therapeutic benefits of the combined intervention.

The NMES intervention will incorporate the use of an NMES stimulator (Balego EMS Digital Neuromuscular NMES Stimulator OTC) to deliver symmetric biphasic pulses. The stimulator will be set at a 35- to 50-Hz frequency with a 200- to 250-microsecond pulse width. Intensity will be individually adjusted to produce visible muscle contraction without discomfort, and electrode placement will target the wrist and finger extensor muscles.

Control Group

The control group will receive conventional rehabilitation therapy following a standardized protocol developed from established clinical guidelines [37,38]. This evidence-based approach ensures that participants in the control group receive consistent, high-quality care representing current best practices in stroke rehabilitation while maintaining a clear distinction from the experimental interventions.

Each 60-minute control session follows a structured format comprising 4 distinct therapeutic components. Sessions commence with 15 minutes of passive and active range of motion exercises systematically targeting all UE joints. Therapists guide participants through standardized movement sequences encompassing shoulder flexion, abduction, and rotation; elbow flexion and extension; and comprehensive wrist and finger movements. Each movement follows predetermined repetition counts with explicit progression criteria based on individual functional capacity.

The second component consists of 20 minutes of neurodevelopmental facilitation techniques. This segment incorporates weight-bearing activities performed in specified positions for predetermined durations, bilateral integration tasks systematically selected from our standardized task bank, and tone normalization techniques following established therapeutic principles. Task selection follows a structured decision algorithm

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that ensures consistency across therapists while permitting appropriate clinical judgment for individual participant needs.

Functional task practice occupies the subsequent 20 minutes, emphasizing activities of daily living relevant to participants' rehabilitation goals. Task difficulty is systematically graded according to the Motor Assessment Scale scores, with compensatory strategy training incorporated when standardized criteria indicate clinical necessity. Each session concludes with 5 minutes of fine motor activities, including standardized pegboard tasks and grip strength exercises using specified resistance parameters.

All participating centers will receive identical therapy kits containing standardized materials to eliminate equipment-related variability. We have developed a comprehensive therapy manual featuring detailed photographic demonstrations, step-by-step instructions, and decision algorithms guiding exercise selection and progression. We will systematically review individual participant progress in weekly case discussions and ensure protocol adherence while maintaining necessary clinical flexibility within our structured therapeutic framework.

The principal researcher and health care professionals will administer therapy sessions in all groups. To ensure rigorous data collection and participant safety, all participants will have standardized logbooks to document their therapy sessions. The research team will monitor each participant's adherence to the assigned intervention and track any potential adverse events, such as muscle cramps or soreness, every week.

For participants with cognitive or motor limitations that affect their ability to maintain the logbooks independently, assistance will be provided by caregivers or trained research assistants. All instances of such assistance will be carefully recorded to preserve data integrity and allow for appropriate analysis and interpretation of the results.

This multimodal monitoring approach, incorporating both self-report and direct observation, is designed to comprehensively assess adherence while accommodating the potential functional limitations of the stroke survivor population. By systematically tracking adherence and adverse events, the study aims to ensure participant safety, maximize data quality, and ultimately enhance the validity and generalizability of the findings.

Table 2 outlines the framework of all study interventions, including a comparison between the 3 groups.

Table 2. Framework of interventions: comparison between groups.

Characteristics	CIMT[a] group	CIMT+NMES[b] group	Control group
Total duration (min)	60	CIMT: 60; NMES: 20	60
Delivery	Researchers and health care professionals	Researchers and health care professionals	Researchers and health care professionals
Content	6 tasks of CIMT (50 repetitions for each task)	6 tasks of CIMT (50 repetitions for each task) + biofeedback electrical stimulator	Neurodevelopmental techniques emphasizing the functional task practice
Location	1 NASAM[c] center	1 NASAM center	1 NASAM center
Frequency	1 session per day for 3 consecutive days a week for 4 weeks	1 session per day for 3 consecutive days a week for 4 weeks	1 session per day for 3 consecutive days a week for 4 weeks

[a]CIMT: constraint-induced movement therapy.

[b]NMES: neuromuscular electrical stimulation.

[c]NASAM: National Stroke Association of Malaysia.

Intervention Fidelity Monitoring

To ensure consistent intervention delivery across all sites and maintain protocol adherence, we have developed a comprehensive fidelity monitoring system based on the National Institutes of Health Behavior Change Consortium recommendations [39]. This multicomponent framework integrates standardized documentation, independent quality assurance, and technology-enhanced monitoring to maintain treatment integrity throughout the trial.

Our monitoring protocol incorporates standardized treatment fidelity checklists tailored explicitly to each intervention arm. These checklists document critical elements for every session, including exercise parameters, constraint application procedures, and NMES settings. Therapists will complete session-specific adherence forms immediately following each treatment, recording quantitative data on task repetitions completed, constraint wear time achieved, and stimulation parameters used. In addition, therapists will complete weekly self-assessment rubrics designed to promote reflective practice and facilitate early identification of protocol deviations.

Independent quality assurance measures will strengthen monitoring objectivity. The research coordinator will conduct biweekly observations across all sites using structured evaluation forms to assess protocol adherence systematically. An independent assessor uninvolved in the treatment delivery will randomly audit 20% of all sessions to ensure unbiased evaluation. With participant consent, we will video-record one session weekly per therapist for comprehensive offline analysis, enabling a detailed review of intervention technique and adherence verification.

Technology integration will enhance monitoring precision through automated data collection. NMES devices will generate

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electronic logs that objectively track all stimulation parameters, providing verifiable records of treatment delivery. We will systematically cross-validate participant-maintained logbooks with therapist records to verify reported constraint wear time and home practice completion. Weekly research team meetings will review aggregated adherence data, allowing prompt identification and resolution of any protocol deviations. This integrated monitoring approach balances rigorous quality control with practical feasibility, combining self-report measures, direct observation, and objective technological data to maintain optimal treatment fidelity throughout the trial.

Outcome Measurements

Feasibility

The feasibility of all interventions will be assessed based on the measures described in subsequent sections.

Patient Acceptance

Stroke survivors' perceptions of the therapy will be evaluated through a posttrial question asking, "What do you think about this therapy?" Responses will be categorized as positive or negative and analyzed descriptively.

Adherence Rate

Adherence will be measured as the percentage of prescribed therapy sessions completed (out of 12). Data will be collected from participants' logbooks.

Adverse Effects

Exercise-related adverse effects, such as strain, cramps, and muscle soreness, will be monitored weekly and evaluated in posttrial assessments.

Repetition Adherence

The number of task repetitions will be calculated. If a participant is unable to complete all repetitions, the number of completed repetitions will be recorded, and the percentage of task completion will be calculated for adherence assessment. Therapists will adapt task complexity to maintain appropriate challenges while enabling maximum quality repetitions within individual capacity. This ensures standardized assessment while accounting for individual variability.

Constraint Adherence

Adherence to the constraint protocol will be monitored using daily logbooks for self-reported mitt wear, caregiver confirmation when available, and weekly therapist check-ins. The percentage of target constraint hours achieved will be calculated as a feasibility outcome. This multimodal approach ensures a comprehensive assessment of adherence, informing the interpretation of study outcomes and guiding future CIMT intervention design.

Intended Outcome Measures

Overview

Table 3 illustrates the framework for all study outcomes, including the instruments used to assess each variable. The details of the intended outcome measures for the interventions in the main study (RCT) are provided in subsequent sections.

Table 3. Framework of the study's outcome measures and instruments.

Variables	Instruments
Motor impairment	Fugl-Meyer Assessment for upper extremity
Motor function	Wolf Motor Function Test
Perceived motor function	Motor Activity Log
Upper limb self-efficacy	Upper Limb Self-Efficacy Test

Motor Function Subscale of the Fugl-Meyer Assessment for Upper Extremity

The Fugl-Meyer Assessment (FMA-UE) will be used to assess motor function, coordination, and speed of the affected extremity, hand, and wrist after stroke. The FMA-UE is a well-established and reliable measure with excellent internal consistency [40,41]. In addition, it has been reported as a reliable and valid measure of poststroke upper limb motor impairment [42]. It assigns scores from 0 to 2 (0=cannot perform, 1=performs partially, 2=performs fully), with a total possible score of 66.

Wolf Motor Function Test

The Wolf Motor Function Test will assess the speed and accuracy of single- and multijoint movements and functional tasks of the UE. This test has been reported as a reliable and valid measure [43]. It includes 17 items, each rated on a scale from 0 to 5, where higher scores indicate greater ability (0=no ability and 5=normal ability, representing the ability to perform tasks with the same efficiency and coordination as an individual with no motor impairment).

Motor Activity Log

The Motor Activity Log is administered through a semistructured interview to assess how much and how effectively an individual uses their UE in their home environment. It comprises 2 subscales: the amount of use and the quality of movement, totaling 30 items that evaluate the use of the affected UE during daily tasks. Each item is scored on a 6-point Likert scale from 0 to 5, with higher scores reflecting greater perceived motor function. The scale has been reported to demonstrate both validity and reliability [44,45].

Upper Limb Self-Efficacy Test

The Upper Limb Self-Efficacy Test (UPSET) measures patients' confidence in using their UEs for daily activities. It consists of 20 items rated on an 11-point Likert scale (0=no confidence

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and 10=high confidence). The UPSET has demonstrated good internal consistency and correlates well with other self-efficacy measures [46].

Assessment of Outcomes

A blinded assessor unaware of group allocations will conduct baseline and postintervention assessments to prevent bias. The assessor will be trained in standardized assessment techniques and cannot access baseline data during postintervention evaluations.

A single trained assessor will perform all assessments at the respective rehabilitation centers while remaining blinded to group allocation and treatment throughout the study. This assessor will travel between centers to ensure consistent assessment procedures.

Data Collection and Monitoring

All data will be meticulously recorded on case report forms and verified by the researcher. Raw data will be securely stored and accessible to researchers upon request, with appropriate measures to protect patient confidentiality. The principal researcher will be primarily responsible for ensuring the accuracy, integrity, and timeliness of the data entry process. To protect participant privacy, all files will be secured with passwords and only accessible to authorized research team members.

Sample Size Calculation

We used the G*Power software (version 3.0.10; University of Düsseldorf) to calculate the required sample size. A mixed model ANOVA, a statistical method used to analyze the effects of interventions over time and between groups, was selected to analyze the interventions' time, group, and interaction effects. The *F* test (ANOVA repeated measures within and between interactions), a specific type of statistical test used in the mixed model ANOVA, was selected for this analysis. With a study power of 80%, an α level of .05, and an effect size of 0.25 (based on the primary outcomes from a previous CIMT study [47]), a minimum sample size of 42 participants (14 in each group) is required. If a group has more than 14 eligible participants, the first 14 to provide consent will be recruited based on the referral date. This first-come, first-served approach ensures transparency in participant selection while maintaining cluster integrity.

An intention-to-treat analysis, which includes all randomized participants, regardless of their adherence to the protocol or completion of the study, will be implemented for this RCT. Under this approach, all recruited participants will be included in the final analysis regardless of protocol adherence, withdrawal, or discontinuation. For participants who withdraw or discontinue the treatment, their baseline data will be used as exit data in the primary analysis. This conservative approach acknowledges the potential impact of missing data while maintaining randomization integrity. Sensitivity analyses using multiple imputation techniques, which are statistical methods used to handle missing data, will be conducted to assess the robustness of findings against different missing data assumptions. This analytical strategy aligns with CONSORT guidelines for reporting randomized trials and addresses potential selection bias that might occur with complete-case analysis.

Statistical Analysis

Data will be analyzed using IBM SPSS Statistics software (version 29.0), adhering to the intention-to-treat principle, which includes all randomized participants regardless of protocol adherence. Participant characteristics and baseline measures will be summarized using descriptive statistics, including mean, SD, median, and IQR.

Before primary analyses, data will be assessed for normality using the Shapiro-Wilk test and homogeneity of variance using the Levene test. For outcomes meeting parametric assumptions, a 2-way mixed model ANOVA will be used to compare the effects of the interventions' interactions between and within groups. Appropriate transformations or nonparametric alternatives will be applied in cases of violated parametric assumptions. Potential confounding variables, such as baseline motor function and stroke severity, will be included as covariates to provide adjusted treatment effect estimates. Statistical significance will be set at $P<.05$ for all analyses.

The linear mixed-effects models that include the center as a fixed effect covariate and random intercepts at the participant level will be used to address residual center-specific effects without invoking a design effect. This modeling framework accommodates hierarchical data structures in single-cluster designs while preserving valid inference for group-by-time interactions.

Missing data will be addressed using multiple imputation techniques, with sensitivity analyses comparing results to those obtained using the baseline observation carried forward method. This comprehensive approach ensures a robust interpretation of intervention effects while preserving statistical power.

Ethical Considerations

This study will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines. Ethics approval has been granted by the Research and Ethics Committee of the Universiti Kebangsaan Malaysia (RECUKM; the National University of Malaysia; study ID UKM PPI/111/8/JEP-2023-596). All participants will provide informed consent before participating, and their privacy will be kept confidential.

The study findings will be disseminated through publication in peer-reviewed journals and presentations at national and international congresses. A summary of the trial results will also be made available on the Australian New Zealand Clinical Trials Registry database. All necessary regulatory approvals for the study have been obtained. Upon trial completion, participants will receive personalized feedback regarding their involvement and the study outcomes.

Results

Funding for this study from RECUKM began in November 2023. Between January 2023 and May 2023, we drafted the initial ethics proposal and hired the research staff. Research

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ethics applications were submitted to the RECUKM from May 2023 to November 2023. We anticipate publishing the study results in 2025.

This study will evaluate the effectiveness of CIMT combined with NMES, CIMT alone, and conventional neurodevelopmental therapy in rehabilitating UE function in chronic stroke survivors. The findings could enable physiotherapists to develop innovative therapies to promote UE function and assist in identifying the most effective treatments for poststroke UE dysfunction. We hypothesize that CIMT combined with NMES will be more effective than the other 2 therapies in improving UE function among survivors of stroke.

Discussion

Anticipated Findings

This study evaluates the effects of combining CIMT with NMES on UE function among chronic stroke survivors. We hypothesize that the combined CIMT+NMES intervention will produce superior improvements in motor function and perceived functional use compared to CIMT alone or conventional therapy. This dual approach leverages complementary mechanisms: CIMT addresses learned nonuse through intensive task practice [48], while the NMES facilitates muscle activation and enhances proprioceptive feedback to support voluntary movement.

We examined current rehabilitation paradigms for chronic stroke to contextualize our approach within existing evidence. CIMT has established efficacy for improving UE function in selected populations of individuals who have experienced a stroke through forced use and mass practice tasks [49]. Similarly, NMES demonstrates clear benefits for muscle strengthening and motor unit recruitment in paretic limbs [50]. However, a few studies have investigated their combined therapeutic potential [10]. Recent evidence indicates that multimodal rehabilitation approaches may amplify neuroplastic changes through synergistic cortical reorganization mechanisms. Functional magnetic resonance imaging studies have documented enhanced cortical activation patterns when peripheral electrical stimulation accompanies intensive motor training, suggesting accelerated neural adaptation compared to single interventions [21].

This study advances this emerging field by providing the first systematic comparison of combined CIMT+NMES therapy against established monotherapies. This investigation addresses a critical gap in stroke rehabilitation evidence, particularly for chronic stroke survivors who typically experience limited recovery with conventional approaches. By examining whether combined interventions overcome the ceiling effects often observed with single modalities, our findings will inform evidence-based treatment selection for this challenging population.

Strengths and Limitations

This trial incorporates several methodological strengths that enhance scientific rigor and clinical applicability. Blinded outcome assessors evaluate all participants using validated instruments spanning the International Classification of Functioning, Disability, and Health framework, ensuring a comprehensive assessment of motor impairment, activity limitations, and participation restrictions. Our standardized intervention protocols, supported by detailed treatment manuals and competency-based therapist training, promote consistent implementation across sites. The pragmatic trial design, conducted within existing rehabilitation centers using available clinical resources, enhances external validity and facilitates future implementation.

We acknowledge specific limitations inherent in our study design. While pragmatically necessary given resource constraints, the single-cluster-per-arm randomization strategy prevents traditional design effect calculations in our sample size calculation. We have addressed this limitation through conservative effect size selection and comprehensive statistical modeling that includes the center as a fixed effect covariate. Our mixed ANOVA approach protects against type I error inflation while maintaining adequate sensitivity for detecting clinically meaningful differences. The absence of long-term follow-up assessments limits our understanding of treatment durability; however, immediate postintervention outcomes will establish the foundation for future longitudinal investigations.

Despite rigorous standardization procedures, therapist-delivered interventions inevitably introduce some variability. We minimize this concern through mandatory competency assessments and structured fidelity monitoring. These mitigation strategies ensure that observed treatment differences reflect intervention efficacy rather than health care provider variability.

Clinical Implications and Future Directions

Our findings will directly inform clinical decision-making regarding optimal rehabilitation strategies for chronic stroke survivors with persistent UE deficits. Should the combined intervention demonstrate superiority, clinicians will gain evidence supporting integrated treatment protocols that maximize functional recovery potential. The comprehensive outcome battery, including motor function (FMA-UE), activity performance (Wolf Motor Function Test), perceived use (Motor Activity Log), and self-efficacy (UPSET), provides multidimensional insights into treatment effects across the International Classification of Functioning, Disability, and Health domains.

Future research should expand upon our foundation through several critical avenues. Large-scale multicenter trials incorporating cluster randomization with appropriate design effects will establish definitive efficacy estimates. Extended follow-up periods of 6 to 12 months will determine whether initial gains translate into sustained functional improvements. Neurophysiological assessments, including transcranial magnetic stimulation and electroencephalography, could elucidate the cortical mechanisms underlying potential synergistic effects [51].

Dissemination Plan

We have developed a comprehensive dissemination strategy to ensure rapid translation of findings into clinical practice. Primary dissemination will occur through publication in high-impact rehabilitation journals with open-access options to maximize accessibility. Conference presentations at international forums

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will facilitate direct engagement with clinical and research communities.

To accelerate clinical implementation, we will develop practitioner-oriented resources, including evidence summaries, clinical decision algorithms, and video training modules demonstrating proper technique. Collaboration with professional organizations will support integration into clinical practice guidelines and continuing education curricula. Patient-centered knowledge translation activities include creating accessible educational materials explaining treatment options and expected outcomes, available in multiple languages to serve diverse populations. Partnerships with stroke survivor organizations will ensure broad distribution through established communication channels, empowering patients to advocate for evidence-based care.

Conclusions

This protocol addresses a critical gap in stroke rehabilitation evidence through rigorous evaluation of combined therapeutic approaches, integrating CIMT with NMES to target both voluntary movement control and direct muscle activation through complementary neuroplastic mechanisms. By systematically examining whether multimodal interventions produce synergistic effects exceeding those of single treatments, our study advances rehabilitation science through a comprehensive methodological framework that incorporates standardized protocols, quantitative fidelity monitoring, and cluster-appropriate statistical modeling, ensuring reliable evidence generation for clinical practice guidelines. Beyond establishing comparative efficacy, this research will elucidate optimal dosing parameters and practical implementation strategies for complex rehabilitation interventions, enabling clinicians to make informed decisions about resource allocation and treatment selection for chronic stroke survivors while contributing essential evidence toward developing personalized, evidence-based rehabilitation strategies that maximize functional recovery in this underserved population.

Acknowledgments

The authors would like to thank the Research and Ethics Committee of the Universiti Kebangsaan Malaysia (the National University of Malaysia) for the study's approval.

Data Availability

The datasets generated and analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

MMD, NAMN, HM, HFMR, and AFAA contributed to conceptualization; NAMN and AFAA were responsible for funding acquisition. MMD, NAMN, HM, HFMR, and AFAA contributed to the methodology. MMD was responsible for resources. NAMN, HM, HFMR, and AFAA were involved in supervision. MMD contributed to writing—original draft. MMD, NAMN, and AFAA contributed to writing—review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 246 KB - resprot_v14i1e68340_app1.pdf]

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Abbreviations

CIMT: constraint-induced movement therapy
CONSORT: Consolidated Standards of Reporting Trials
FMA-UE: Fugl-Meyer Assessment for upper extremity
NASAM: National Stroke Association of Malaysia
NMES: neuromuscular electrical stimulation
RCT: randomized controlled trial
RECUKM: Research and Ethics Committee of the Universiti Kebangsaan Malaysia
UE: upper extremity
UPSET: Upper Limb Self-Efficacy Test

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Protocol

Efficacy of a Multimodal Ayurveda Regimen in the Management of Primary Knee Osteoarthritis: Protocol for an Open-Label Randomized Controlled Trial

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Abstract

Background: Ayurveda recommends a comprehensive therapeutic approach for osteoarthritis management. However, most of the published clinical studies on Ayurveda interventions for osteoarthritis management have addressed selected modalities of Ayurveda treatment rather than the holistic therapeutic regimen.

Objective: This study aimed to assess the efficacy and safety of a multimodal Ayurveda treatment protocol in the long-term management of primary osteoarthritis of the knee compared with standard care.

Methods: The proposed open-label, parallel-group randomized controlled trial was conducted in individuals of any gender aged 40 to 70 years and diagnosed with primary osteoarthritis of the knee as per the American College of Rheumatology criteria. Individuals with grade 4 radiographic changes in the affected knee (based on the Kellgren-Lawrence classification) and with comorbidities were not considered. The study was conducted at the All India Institute of Medical Sciences, New Delhi, India. A total of 150 participants underwent random assignment in a 1:1 ratio to receive either the Ayurveda treatment protocol or conventional standard care for 180 days. The primary outcome was the change in the Western Ontario and McMaster Universities Osteoarthritis Index score from baseline. The secondary outcome measures included the change in the score for pain, stiffness, and physical function from baseline; change in the range of motion of the knee joint; change in the score of the numeric pain rating scale, Pain Disability Index, and 12-item short-form survey questionnaire (to assess health-related quality of life); change in highly sensitive C-reactive protein levels, interleukin-6 levels, magnetic resonance imaging scan findings, and dual-energy X-ray absorptiometry scan findings; and change in the need for rescue analgesic medication from baseline. Safety was evaluated by recording the incidence of adverse events and changes in liver and kidney function tests from baseline.

Results: Recruitment of study participants commenced on October 11, 2022. Currently, all the participants completed the study and the analysis of the study outcomes is ongoing.

Conclusions: This randomized controlled trial will be the first study to explore the potential benefits of a multimodal Ayurveda regimen (based on Ayurveda principles and scientific evidence) in the long-term management of osteoarthritis of the knee through validated subjective, laboratory, and imaging parameters. The outcomes of this study may address the needs and challenges associated with osteoarthritis management.

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Trial Registration: Clinical Trial Registry of India CTRI/2022/05/042792; https://ctri.nic.in/Clinicaltrials/pmaindet2.php?EncHid=Njk0MTM=&Enc=&userName=

International Registered Report Identifier (IRRID): DERR1-10.2196/68306

(JMIR Res Protoc 2025;14:e68306) doi:10.2196/68306

KEYWORDS

Janu Basti; Laksha Guggulu; Matra Basti; osteoarthritis; WOMAC; Western Ontario and McMaster Universities Osteoarthritis Index

Introduction

Background

Osteoarthritis is a chronic degenerative condition characterized by structural changes in the articular cartilage, ligaments, capsule, synovium, subchondral bone, and periarticular muscles, resulting in joint pain, stiffness, and limited mobility [1]. As per the Osteoarthritis Research Society International, osteoarthritis has all the hallmarks of a serious condition because of associated disability and loss of function [2]. Osteoarthritis most commonly affects the knee, followed by the hand, hip, spine, and shoulder. Osteoarthritis of the knee accounts for approximately 85% of osteoarthritis cases globally [3]. Primary osteoarthritis is caused by age-related degeneration, while secondary osteoarthritis occurs because of injury, occupation-related stress on joints, and comorbid conditions, including diabetes mellitus. Mechanical, inflammatory, and metabolic factors play an important part in the intricate pathophysiology of osteoarthritis, which eventually results in the structural breakdown and collapse of the synovial joint [4]. Global estimates indicate that approximately 595 million individuals worldwide were affected by this burdensome clinical condition in 2020, equivalent to 7.6% of the global population [5]. Osteoarthritis is becoming more prevalent owing to the combined impacts of aging, rising physical inactivity and obesity in the population, and an increased incidence of joint injuries [2]. In 2020, 21.7 million years lived with disability were attributed to osteoarthritis globally [5]. It is one of the 4 leading causes of years lived with disability worldwide [4]. The objectives of osteoarthritis management are to reduce pain intensity and inflammation, slow down cartilage degradation, improve joint movement, and reduce disability. Treatment options include patient education, oral and topical pharmacological agents, interventional procedures (eg, corticosteroid injection and viscosupplementation), bracing, assistive devices, physical therapy, and surgery (eg, arthroscopy, osteotomy, and arthroplasty) [6]. Currently, conventional medicine has no therapeutic options that can arrest or slow down the disease progression in patients with osteoarthritis [2]. In the absence of drugs with proven disease-modifying activity, the current approach is mainly focused on palliative pain management [7]. However, chronic pain management with acetaminophen, nonsteroidal anti-inflammatory drugs, and intermittent intra-articular corticosteroid injections is associated with limited benefits, along with considerable gastrointestinal, renal, and cardiovascular risks [2,8-10]. Furthermore, there is uncertainty regarding the effect of glucosamine and chondroitin supplementation on the structural progression of osteoarthritis [10]. Meanwhile, arthroplasty is considered only for severe cases of osteoarthritis. Therefore, it is pertinent to search for safe, efficacious, and cost-effective therapeutic options with better tolerability to reduce the disease burden of osteoarthritis.

Sandhigatavata, a specific type of *Vatavyadhi* (disease conditions because of vitiation of *Vata Dosha*) in Ayurveda, has a clinical presentation similar to osteoarthritis. Ayurveda suggests a multimodal treatment approach for managing *Sandhigatavata*, a traditional Ayurvedic condition clinically comparable to osteoarthritis, including a judicious combination of *Panchkarma* (Ayurveda therapeutic procedures), oral medications, nutritional supplements, a nutritious diet, and a recommended lifestyle. Several published clinical studies have highlighted the safety and beneficial effects of Ayurveda interventions in the management of osteoarthritis [11-23]. One randomized controlled trial (RCT) concluded that the Ayurveda treatment protocol led to significant and clinically relevant improvement in osteoarthritis-related clinical features compared with conventional care, with most effects maintained over 12 months [11,12]. Another clinical study, supported by the World Health Organization to evaluate the feasibility of operational integration of Ayurveda treatment with conventional medicine in the management of osteoarthritis of the knee at a tertiary care hospital, also reported that the Ayurveda treatment regimen showed promising outcomes in the management of osteoarthritis of the knee, including symptom reduction, improved quality of life, and reduced need for conventional analgesics [13]. A systematic review also highlighted the safety and preliminary evidence regarding the effectiveness of various Ayurveda interventions in the management of osteoarthritis [24]. In addition, Ayurveda interventions, such as *Shallaki* (*Boswellia serrata* Roxb.), *Guggulu* (*Commiphora mukul* Engl.), *Ashwagandha* (*Withania somnifera* [L.] Dunal), *Shunthi* (*Zingiber officinale* Roscoe), *Bala* (*Sida cordifolia* L.), *Nirgundi* (*Vitex negundo* L.), and *Dashmula* (a combination of the dried root of 10 specific medicinal plants) have shown potential anti-inflammatory, analgesic, antiosteoporotic, and antioxidant activities [25-33].

However, most of the aforementioned published studies have addressed selected modalities of Ayurveda treatment rather than a holistic Ayurveda therapeutic regimen. Therefore, it is necessary to conduct RCTs with a multimodal Ayurveda regimen for the management of osteoarthritis. Considering this limitation, the present RCT was conceptualized to assess the efficacy and safety of an Ayurveda treatment regimen (consisting of therapeutic procedures and oral medications) to manage primary osteoarthritis of the knee. The therapeutic regimen proposed for the study is based on preliminary leads

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from exploratory clinical studies on individual Ayurveda interventions that have shown promising outcomes in the management of osteoarthritis [15,17,18].

Objectives

The present RCT was designed to assess the efficacy of multimodal Ayurveda interventions in managing pain and functional disability in patients with primary osteoarthritis of the knee compared with standard care. The key secondary objectives of this study included evaluating the efficacy of the trial Ayurveda interventions on range of motion of the knee joint, the need for rescue analgesic medication, quality of life parameters, knee structural changes (ie, delay in the structural progression of osteoarthritis), proinflammatory biomarkers, and bone mineral density after 180 days. Another secondary objective was to assess the safety of multimodal Ayurveda interventions in managing osteoarthritis of the knee.

Methods

The study protocol has been drafted following the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [34].

Study Design and Setting

This clinical study was an open-label, randomized, controlled, parallel-group, noninferiority trial. The study was conducted at the All India Institute of Medical Sciences (AIIMS), New Delhi, India.

Study Participants

Individuals of any gender aged 40 to 70 years who were diagnosed with primary osteoarthritis of the knee as per the American College of Rheumatology (ACR) criteria; had a pain score of at least 2 (as per the numeric pain rating scale) on most days in the last month; met ACR functional status criteria class I, II, and III; have a serum vitamin D level >30 ng/mL; and were willing to provide written informed consent were included in the study. The ACR criteria for osteoarthritis of the knee include knee pain along with any 3 of the following: aged >50 years, joint stiffness lasting less than 30 minutes, crepitus, bony tenderness, bony enlargement, and absence of palpable warmth.

Individuals were excluded if they had grade 4 radiographic changes in the affected knee joint (as per the Kellgren-Lawrence classification); had a history of significant trauma to the knee (including arthroscopy within the preceding year), knee joint replacement, intra-articular corticosteroid or hyaluronic acid administration within 1 month before the study; were currently taking corticosteroids; or had a history of rheumatoid arthritis, psoriatic arthritis, systemic lupus erythematosus, cardiovascular disease, or malignancy. Individuals were also excluded if they had uncontrolled diabetes mellitus (ie, hemoglobin A_{1c} >8%), uncontrolled hypertension (ie, blood pressure >160/100 mm Hg despite medication), abnormal hepatic function (ie, aspartate aminotransferase or alanine aminotransferase >2 times the upper limit of normal), or abnormal renal function (ie, serum creatinine >1.2 mg/dL); a tendency for occurrence of recurrent renal calculi; or a BMI ≥32 kg/m^2. Similarly, those with any contraindication for magnetic resonance imaging (MRI), a history of hypersensitivity to the study interventions, a history of chain smoking, alcohol use disorder, substance abuse, or any other clinical condition that the investigator believed may compromise the participant's safety, compliance, or evaluation were not considered for the study.

Study Intervention

Eligible participants in the Ayurveda group received a comprehensive Ayurveda treatment protocol, which included *Matra Basti* with *Ksheerabala Taila* and *Janu Basti* with *Dhanwantara Taila*, along with oral medications—*Laksha Guggulu* and *Muktashukti Bhasma*—for 180 days. The details of the study interventions are provided in Table 1.

Table 1. Details of the study interventions.

Intervention (with reference)	Route of administration	Dosage and frequency	*Anupana* (vehicle of administration)	Duration
Ksheerabala Taila (API[a] part II, vol I [35])	Rectal (*Matra Basti*)	60 mL once daily after food	—[b]	14 d every 2 mo for 180 d
Dhanwantara Taila (API part II, vol I [35])	Local application over the affected knee (*Janu Basti*)	QS[c] once daily	—	14 d every 2 mo for 180 d
Laksha Guggulu (API part II, vol II [36])	Oral	1 g twice daily after food	Lukewarm water	180 d
Muktashukti Bhasma (Pharmacopeial Standards for Ayurvedic Formulations [37])	Oral	250 mg twice daily after food	Lukewarm water	180 d

[a]API: Ayurvedic Pharmacopoeia of India.

[b]Not applicable.

[c]QS: quantity sufficient.

The methodology of the therapeutic procedures, *Matra Basti* and *Janu Basti*, is provided in Multimedia Appendix 1. The participants in the control group will receive standard care (ie, topical application of diclofenac sodium gel twice daily) for 180 days, as recommended in the standard treatment guidelines for the management of osteoarthritis of the knee, issued by the Ministry of Health and Family Welfare, Government of India.

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Ayurveda practitioners on the research team dispensed the Ayurveda interventions at the study sites throughout the trial period. Furthermore, paramedical staff trained in *Panchakarma* administered *Matra Basti* and *Janu Basti* to the study participants in the Ayurveda group. The participants were examined every 30 days during the study period. The trial Ayurveda interventions were procured from the Indian Medicines Pharmaceutical Corporation Limited, Ministry of Ayush, Government of India.

Discontinuation of the Study Interventions

The study interventions are not causally associated with serious adverse effects or adverse drug reactions (ADRs), as reported in previously published studies. However, if appropriate measures are not followed while administering *Janu Basti*, adverse effects, such as mild irritation or skin rashes, may occur at the application site. Similarly, bloating, increased bowel movements, and abdominal pain may develop if *Matra Basti* is not administered correctly. *Laksha Guggulu* may lead to abdominal discomfort, nausea, belching, and skin rashes if not taken as per the physician's instructions and recommended dose.

If any participant developed any adverse effects, administration of the study interventions was temporarily discontinued, and the participant was closely monitored. If symptoms recurred after reintroducing the study interventions, the participant was withdrawn and provided with appropriate medical care as needed.

If any participant developed a serious adverse event (AE) or treatment-emergent AE during the study period, the participant was withdrawn from the study and provided with appropriate incidental care at the study site (ie, the AIIMS, a tertiary care medical institution). In addition, all the study participants were covered by clinical trial insurance during their participation for medical expenses related to the management of any study-related AEs. Furthermore, the sponsor and the ethics committee were notified within 2 working days using the AE and ADRs reporting format, along with appropriate justification. Causality assessment of all AEs, serious AEs, and ADRs occurred during the study was also conducted.

Compliance With Trial Interventions During the Study

All participants in the Ayurveda group were provided with an information leaflet containing instructions for the use (dose, frequency, and time of administration) and storage of the study interventions. The participants were also issued a compliance form during the baseline and subsequent follow-up visits to self-report their consistent or irregular use of the trial interventions and to record any missed doses with remarks for missing, which enabled assessment of adherence to the dosing pattern as per the study protocol. During each follow-up visit, participants were asked to return the used, unused, or partially used containers of the study interventions to the investigators to assess adherence and cross-check with the participant's self-reported compliance form.

Participants who did not adhere to the study protocol, did not have ≥80% compliance, developed any study-related AEs resulting in withdrawal from the study at their preference, or withdrew their voluntary consent for participation in the study were withdrawn from the study. If participants consented to data collection during the scheduled follow-ups or at the end of the 180-day period, the data were collected and recorded in the case record form (CRF). The data from completed assessments available up to the point of withdrawal will be used for analysis.

Concomitant or Rescue Medication

The investigators monitored the participants for any concomitant or rescue medication required during the study period. In the event of any AEs or an increase in pain intensity, rescue medication was permitted at the investigators' discretion. All instances of concomitant care were carefully documented in the CRF.

Outcome Measures

The primary outcome was the change in the Western Ontario and McMaster Universities Osteoarthritis Index (WOMAC) score from baseline. The secondary outcome measures included the change in the score for pain, stiffness, and physical function from baseline (assessed using the WOMAC scale); the change in range of motion of the knee joint (assessed using a goniometer); the change in the scores of the numeric pain rating scale, Pain Disability Index, and 12-item short-form survey questionnaire (to assess health-related quality of life); the change in high-sensitivity C-reactive protein and interleukin-6 levels, MRI findings (to assess knee structural changes), and dual-energy x-ray absorptiometry scan findings (to assess change in bone mineral density); and the change in the need for rescue analgesic medication.

The outcomes were evaluated every 30 days until day 180 from baseline. Laboratory investigations were conducted at baseline and on day 180.

Safety Assessment

The safety of the trial interventions was determined by recording the incidence of AEs, if any, during scheduled follow-up visits using a structured format. All AEs during the study were recorded and monitored in accordance with the International Council for Harmonisation–Good Clinical Practice (GCP) guidelines. Safety was also evaluated by performing liver function tests (LFTs) and kidney function tests (KFTs) on days 90 and 180 from baseline.

Sample Size

On the basis of the results from a previous study [11], in which the difference in WOMAC score between the Ayurveda and conventional group after 12 weeks of treatment was 24 points, this study has been designed to have 80% statistical power to detect a difference of at least a 20-point improvement (change from baseline) in the WOMAC score after treatment between the 2 groups (pooled SD 42; 2-sided *t* test, α=.05). To achieve this, 69 participants per group were required. Accounting for an expected attrition rate of 10%, the final sample size for each group was determined to be 75 participants (150 in total).

Recruitment of Study Participants

During the study, the investigators screened individuals with clinical features of osteoarthritis of the knee who visited the

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outpatient department of the study sites, based on the defined inclusion and exclusion criteria, to identify and recruit potential individuals. The research personnel allocated the eligible participants to either of the 2 groups based on a computer-generated randomization schedule (Figure 1). The screening process was continued until the target sample size for the study was achieved.

Figure 1. The study schedule. BMD: bone mineral density; BP: blood pressure; CBC: complete blood count; CRF: case record form; DEXA: dual-energy x-ray absorptiometry; ECG: electrocardiogram; ESR: erythrocyte sedimentation rate; HbA1c: hemoglobin A1c; hs-CRP: high-sensitivity C-reactive protein; IL-6: interleukin 6; KFT: kidney function test; LFT: liver function test; MRI: magnetic resonance imaging; RA: rheumatoid arthritis; SF-12: 12-item short-form survey; WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.

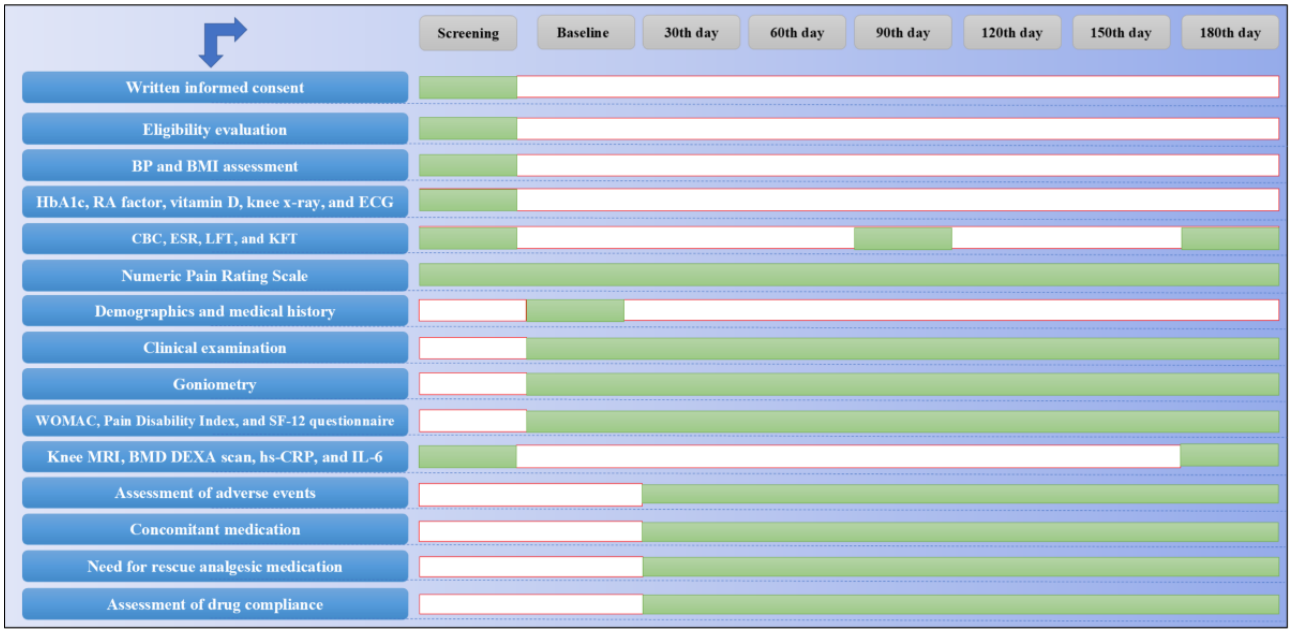

Randomization

The eligible individuals were randomly assigned to the Ayurveda group or the control group with a 1:1 allocation. SPSS software (version 15.0; IBM Corp) was used to generate the random number sequences. The randomization sequence was generated by an independent statistician who was not involved in participants' enrollment and assessment.

Allocation Concealment

Sequentially numbered, opaque, sealed envelopes were used to ensure allocation concealment. The participant's enrollment number was printed on the top of the envelope, and a slip indicating the participant's allocated group was placed inside. After completing all baseline assessments, the research staff provided the sealed envelope to the eligible individuals. The individual opened the envelope and was then allocated to a group as indicated on the slip inside. The opened envelope and the printed slip were attached to the participant's CRF for documentation and trial monitoring.

Data Collection

The baseline demographics, clinical, and physical examination data were collected by qualified Ayurveda study personnel and recorded in a CRF designed for this purpose. The subjective and objective outcome assessments were conducted according to the study protocol. Knee pain, stiffness, and functional disability were assessed using the WOMAC score [38]. The self-reported severity of pain was recorded using a numeric pain rating scale and Pain Disability Index [39,40]. The overall quality of life was assessed using a validated scale, the 12-item short-form survey questionnaire [41]. These outcomes were assessed at baseline and during follow-up visits on days 30, 60, 90, 120, 150, and 180.

Serum samples for the objective assessment parameters, such as proinflammatory biomarkers, LFT, and KFT, were collected at baseline and on day 180 (LFT and KFT were also assessed on day 90), and transported to the NABL-accredited laboratory, along with data from MRI and dual-energy X-ray absorptiometry scans. The data received from the laboratory were entered in the CRF and e-CRF. The research team underwent training on the study protocol and standard operating procedures for the study conduct, storage and dispensing of study interventions, handling of biological samples, data collection, and data recording to ensure compliance with GCP principles, while ensuring participant safety, data accuracy, and reliability.

Data Management

Data management in this clinical study adhered to stringent guidelines to ensure the accuracy, reliability, and integrity of the collected information. Upon the participant's assessment, the research team promptly entered the data into CRFs and e-CRFs. Source documents and CRFs were securely stored in restricted-access areas, limited solely to the study team. Electronic CRFs were password-protected and stored in secure, access-restricted computer systems.

The data entered by the study personnel underwent meticulous cross-verification by the study investigators at the study site, ensuring the reliability of the data. Rigorous quality measures were implemented, such as regular audits, to identify and address any discrepancies in the data. Data management practices

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adhered to regulatory guidelines and ethical principles, prioritizing the protection of participant rights.

Statistical Methods

Categorical data will be presented as numbers (percentages) and compared between groups using the chi-square test. Continuous data following normal distributions will be reported as mean (SD), and between-group comparisons will be performed using the independent sample *t* test. Within-group comparisons for normally distributed data will be conducted using the paired sample *t* test or repeated measures ANOVA. Nonnormally distributed data will be reported as median (first and third quartiles), and between-group comparisons will be performed using the Mann-Whitney *U* test. Within-group comparisons will be conducted using the Wilcoxon signed rank test or the Friedman test. A P value <.05 will be considered statistically significant. SPSS software (version 29.0; IBM Corp) will be used for statistical analysis.

The modified intention-to-treat analysis approach will be applied to handle missing data. Missing data for all participants with available data from at least 1 visit after baseline (day 30) will be imputed. The last observation carried forward method will be used to impute the missing values.

Monitoring

The data and safety monitoring board monitored the study for quality and regulatory compliance. The data and safety monitoring board reviewed the progress of the study every 6 months until the end of the study period.

Trial Audit

An on-site monitoring visit by an independent committee constituted by the sponsor was planned to ensure that the study procedures and data collection processes complied with existing regulatory standards and to check the accuracy, completeness, legibility, and timeliness of the reported study data.

Ethical Considerations

The institutional ethics committee of AIIMS, New Delhi, has approved the study protocol (IEC-132/04.02.2022) and related documents to ensure compliance with ethical standards and safeguard the rights and well-being of the participants. The study has been registered prospectively at the Clinical Trial Registry of India (CTRI/2022/05/042792). The study was undertaken in accordance with the principles of the Declaration of Helsinki, the Indian Council of Medical Research's National Ethical Guidelines for Biomedical and Health Research on Human Participants (2017), and the International Council for Harmonisation GCP guidelines. All substantial amendments to the study protocol affecting participant safety or study integrity were submitted to the institutional ethics committee for approval before implementation. Before undergoing any study-related procedure, potential participants received a participant information sheet in Hindi or their native language. The participant information sheet comprehensively outlined the various aspects of the study, equipping the participants with the necessary information to make an informed decision regarding participation in the study. Written informed consent was obtained using the consent form, signed by the participant and the study personnel delegated to the task.

All relevant study data were securely stored at the study site in password-protected access systems located in areas with limited access. To maintain participant confidentiality, a coded enrollment identification number was used to identify all laboratory specimens, reports, data collection, and relevant forms. All records containing names or other personal identifiers, such as informed consent forms, were stored separately from the study records, which were identified by code identification numbers, in a restricted-access area.

Ancillary and Posttrial Care

No ancillary studies are proposed in the present clinical study. If required, the participants were provided with routine medical care after completing the study.

Results

The recruitment of study participants was initiated on October 11, 2022. The recruitment of study participants has been completed. The analysis of the study data is in progress.

Discussion

Anticipated Findings

Osteoarthritis, owing to its chronic nature, is associated with considerable disease burden, functional disability, and health care costs globally. Because of inadequate relief and adverse effects associated with conventional medications, a substantial proportion of individuals affected by osteoarthritis prefer traditional medicine systems, such as Ayurveda, for sustained long-term relief without treatment-related safety concerns. Ayurveda adopts a comprehensive treatment approach combining various therapeutic options, such as *Abhyanga* (massage), *Swedana* (hot fomentation), *Mridu Samshodhana* (mild purgation), *Basti* (medicated enema), *Janu-Kati-Greeva-Pristhta Basti* (localized oleation therapy), *Upanaha* (poultice application), *Vatashamaka* (pacifying vitiated *Vata Dosha*), and *Rasayana* (Ayurveda nutritional supplements), along with a nutritious diet and a balanced lifestyle, for the effective management of osteoarthritis depending on the stage of the disease. Numerous clinical studies have been conducted to evaluate the efficacy of various Ayurvedic interventions for managing osteoarthritis. Most of these studies have focused on single herbs, compound formulations, or individual therapeutic procedures. Only a few studies have investigated multimodal therapeutic regimens grounded in Ayurveda principles and practiced in routine Ayurvedic care.

The present RCT was conceived to evaluate the efficacy of an Ayurveda treatment regimen comprising *Panchkarma* procedures (*Matra Basti* and *Janu Basti*) along with oral medications—*Laksha Guggulu* and *Muktashukti Bhasma*—for the management of primary osteoarthritis of the knee. *Matra Basti* (therapeutic enema with medicated oil) using *Ksheerabala Taila* is planned for this study, as *Basti* is considered the prime treatment modality for *Vatavyadhi* (musculoskeletal, neuromuscular, and degenerative disorders) [42]. Furthermore,

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it is well-established that drug administration via the rectal route can achieve significantly higher blood levels of the medication compared with the oral route, as the rectum has a rich blood and lymph supply; thus, lipid-soluble drugs can cross the rectal mucosa, be readily absorbed, and enter the systemic circulation [17,43]. Thus, the administration of drugs in the *Basti* form may result in faster absorption and quicker results. Bala, the principal constituent of *Ksheerabala Taila*, possesses anti-inflammatory, analgesic, and antioxidant properties [44-46]. In addition, published clinical studies on *Matra Basti* in osteoarthritis have shown promising outcomes [15,17]. Similar results were also reported in an exploratory clinical study on *Basti* with *Ksheerabala Taila* in patients with osteoarthritis of the knee [21]. *Janu Basti* (medicated oil retention over the knee) is a localized Ayurveda procedure used for knee joint–related ailments. During the procedure, warm medicated oil is applied to the knee joint, allowing it to be absorbed into the joint tissues, thereby providing lubrication and improving joint mobility by enhancing blood circulation and promoting muscle relaxation in the knee area. It also alleviates pain and inflammation through the anti-inflammatory and analgesic properties of the ingredients of the medicated oil. Published clinical studies and case reports have reported the potential benefits of *Janu Basti* in providing relief for osteoarthritis-related outcome parameters [47-49]. Furthermore, in this study, *Dhanwantara Taila* is proposed for *Janu Basti*, which has significantly relieved osteoarthritis-related complaints and improved the quality of life and WOMAC score in previous research studies [20]. In addition, the major ingredients of *Dhanwantara Taila*, namely, *Bala* and *Dashamula*, possess analgesic and anti-inflammatory properties [33,44-46]. An experimental study also reported the anti-inflammatory and analgesic activities of *Dhanwantara Taila* [50].

The ingredients of *Laksha Guggulu* possess anti-inflammatory, analgesic, antiarthritic, chondroprotective, and antioxidant activities, and therefore are likely to ameliorate disease progression in patients with osteoarthritis [27,28,51-54]. In addition, an experimental study highlighted the antiarthritic and chondroprotective potential of *Laksha Guggulu* [55]. Exploratory studies on *Laksha Guggulu* have provided preliminary evidence of its efficacy in osteoarthritis of the knee and osteoporosis [18,56,57]. *Muktashukti Bhasma* is a natural calcium-containing Ayurveda formulation used in degenerative conditions of bones and joints to nourish these tissues. A published standardization study reported it as nano-range calcium carbonate in calcite form [58]. The study also highlighted it as a good source of elemental calcium, as observed in energy-dispersive X-ray analysis [58]. Furthermore, a preclinical study on albino rats reported its anti-inflammatory activity [59]. A published clinical study on *Muktashukti Bhasma* showed significant improvement in outcome parameters for osteopenia and osteoporosis [57].

Therefore, preliminary evidence suggests that the Ayurveda interventions included in the proposed therapeutic regimen have the potential to reduce the severity of pain and functional disability associated with osteoarthritis. Furthermore, the herbal ingredients of these interventions possess anti-inflammatory, analgesic, antiosteoporotic, antiarthritic, chondroprotective, and antioxidant activities. Therefore, these interventions may alleviate the pathophysiology of osteoarthritis by exerting favorable effects on proinflammatory markers and slowing down the degenerative process.

A well-planned Ayurveda therapeutic regimen grounded in Ayurveda principles and supported by scientific evidence that addresses the needs and challenges of osteoarthritis management and promotes holistic care may significantly improve long-term management. The comprehensive Ayurveda regimen designed for this study has the potential to offer valuable insights into effective therapeutic options for the management of osteoarthritis.

The present RCT protocol has several key strengths. First, it uses a complex Ayurveda regimen that incorporates therapeutic procedures and internal medications, which are easy to administer, well-tolerated, and safe, with the potential to address osteoarthritis-related pathological changes. Second, the study includes an adequate sample size and validated subjective assessment tools, along with imaging and relevant biomarkers as outcomes to address various parameters related to the pathogenesis of osteoarthritis.

Limitations

This protocol also has a few limitations, including the open-label design of the study. However, to minimize potential bias in assessing the outcomes, the research staff assigned to assess the study outcomes were blinded to the allocation of participants to the study groups. Furthermore, to mitigate the risk of selective reporting of trial results, the statistician who will analyze the study data will also be blinded to the allocation of participants to the study groups.

Conclusions

The outcomes of the present RCT are expected to generate robust evidence regarding the efficacy and safety of a complex Ayurveda therapeutic regimen in the long-term management of osteoarthritis of the knee, compared with standard conventional care based on validated subjective, laboratory, and imaging parameters. The results and findings will be disseminated following the best practices in scientific publishing, ensuring that the knowledge generated will benefit the scientific community and the public through publications in peer-reviewed, indexed medical journals and presentations at national and international conferences.

Acknowledgments

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management, analysis, and interpretation of data; writing of the clinical study report; and the decision to submit the final clinical study report for publication in an indexed medical journal.

All authors declared that they had insufficient or no funding to support open access publication of this manuscript, including from affiliated organizations or institutions, funding agencies, or other organizations. JMIR Publications provided article processing fee (APF) support for the publication of this article.

Data Availability

The datasets generated or analyzed during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

AKR was responsible for conceptualization, methodology, and writing the original draft. BY contributed to conceptualization, methodology, and project administration. UK was involved in conceptualization, investigation, project administration, and writing—review and editing. BG contributed resources and supported project administration. KP was responsible for investigation, resources, and project administration. SK and BSS contributed resources. RS provided input on statistical methods. BCR contributed to conceptualization, methodology, supervision, and writing—review and editing. NS was responsible for conceptualization, funding acquisition, supervision, and writing—review and editing. RNA contributed resources, supervision, and writing—review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Methodology of the therapeutic procedures (Matra Basti and Janu Basti).
[DOCX File , 18 KB - resprot_v14i1e68306_app1.docx]

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Abbreviations

ACR: American College of Rheumatology
AIIMS: All India Institute of Medical Sciences
CRF: case record form
GCP: Good Clinical Practice
KFT: kidney function test
LFT: liver function test
MRI: magnetic resonance imaging
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index

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Protocol

Platelet-Rich Plasma Versus Saline for the Treatment of Vulvar Lichen Sclerosus: Protocol for a Randomized Controlled Trial

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Abstract

Background: Vulvar lichen sclerosus (LS) is a chronic relapsing dermatosis commonly affecting the anogenital region in postmenopausal women, though it can affect people of any age and sex. The current gold standard treatment is lifelong topical steroid application to reduce symptoms and prevent the progression of disease, causing irreversible architectural change to the vulval tissue. LS is associated with decreased quality of life and increased risk of vulvar neoplasia. Alternatives to current treatments are highly desired by both clinicians and patients. Platelet-rich plasma (PRP) is an autologous blood product containing high concentrations of platelets and growth factors and is hypothesized to promote wound healing. PRP has been reported to improve symptoms of LS in several case reports and uncontrolled trials.

Objective: This study aims to evaluate the efficacy of PRP versus saline injections to improve the clinical signs and symptoms of LS.

Methods: This is a protocol for a 12-month, single-center, parallel-group, double-blind, randomized controlled trial evaluating the efficacy of PRP for LS compared to saline. Adult female patients with biopsy-proven LS who are otherwise in good health but are nonresponders to topical steroid treatment prior to inclusion are eligible for the trial. A total of 68 participants will be randomly allocated via a random number generator to receive either PRP or saline injections to areas of the vulva with LS. All participants will be blinded to the intervention received. Participants will be followed up with assessments of clinical LS signs, subjective symptom scores, and quality of life questionnaires by blinded assessors at 4 timepoints: baseline, 6 weeks, 6 months, and 12 months. The primary outcome is the clinical scoring system for LS—the total LS score.

Results: Recruitment commenced in May 2020 and concluded in November 2023. This study closed in September 2024 due to slow recruitment. Data are being analyzed in 2025, and results are expected to be published in late 2025.

Conclusions: This study will evaluate the safety and efficacy of PRP injections compared to those of saline injections for the treatment of vulvar LS, potentially providing a novel therapeutic option for patients who do not respond to topical steroids.

Trial Registration: Australia and New Zealand Clinical Trials Registry ACTRN12618001321235p; Universal Trial Number: U1111-1207-4893; anzctr.org.au/Trial/Registration/TrialReview.aspx?id=375536

International Registered Report Identifier (IRRID): DERR1-10.2196/68871

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KEYWORDS

regenerative medicine; vulvar dermatoses; female sexual health; autologous therapies; clinical trial protocols; women's health research

Introduction

Background

Vulvar lichen sclerosus (LS) is a chronic autoimmune dermatosis with a complex and multifactorial etiology [1,2]. In females, LS typically affects the anogenital region, including the vulva, perineum, and anus, but extragenital involvement occurs in 6%-20% of the patients [3,4]. The characteristic signs of LS are patches of discolored white skin, and the typical symptoms are intense itching, burning, and pain [5-7], which can contribute to significant distress and discomfort. Over time, chronic changes to the architecture of the vulva can occur, such as agglutination of the labia and narrowing of the introitus [3]. Additionally, LS is associated with an increased risk of vulval intraepithelial neoplasia and vulvar squamous cell carcinoma, with an estimated malignant transformation risk of approximately 4% to 6% [8,9]. The incidence of LS has been estimated at 22 per 100,000 woman-years in population studies [10], and it accounts for about 1.7% of the referrals to general gynecology clinics [11,12].

There is no cure for LS, and the current mainstay of therapy is topical corticosteroid application [3]. The goals of the therapy are symptom relief and improving the quality of life, preventing the progression of disease to alter the architecture of the skin, and reducing the risk of neoplasia [3].

Platelet-rich plasma (PRP) is an autologous platelet concentrate, which contains the platelet-derived growth factor, transforming growth factor, and epidermal growth factor, and it is hypothesized to promote wound healing and tissue regeneration [13,14]. It has yielded positive results in orthopedic, reconstructive surgery, dentistry, dermatology, and musculoskeletal medicine [15-18]. PRP has been studied as a treatment for LS [19], but issues with small sample sizes, heterogenous study methodologies, short-term follow-up, and the use of unvalidated outcome measures are the limitations that have prevented the recommendation of PRP use in clinical practice [13]. In the context of LS, PRP may exert therapeutic effects through its anti-inflammatory and immunomodulatory properties. Growth factors such as transforming growth factor-β and platelet-derived growth factor found in PRP can modulate the immune responses and promote tissue remodeling. These effects may reduce local inflammation, improve dermal regeneration, and help restore the structural integrity of vulvar tissues affected by LS. Therefore, this trial has been designed as an adequately powered, placebo-controlled randomized study to evaluate the safety and efficacy of PRP in LS by using validated outcome measures.

In contrast to prior studies [20,21], this trial addresses these limitations by employing a randomized, double-blind, placebo-controlled design with an adequately powered sample size. It also utilizes validated clinical and patient-reported outcome measures, including the clinical scoring system for LS, Dermatology Life Quality Index, and Australian Pelvic Floor Questionnaire, with a planned 12-month follow-up. These methodological strengths are designed to provide robust evidence on the efficacy and safety of PRP for LS.

Study Aims

The goal of this study is to assess the safety and efficacy of autologous PRP injections for the treatment of vulvar LS compared to saline injections.

Methods

Study Design

This is a double-blind, parallel-group, placebo-controlled, randomized trial. The purpose of the trial is to evaluate the efficacy of PRP as a treatment for vulvar LS compared to saline. The trial is conducted at a single center—FBW Gynecology Plus in Adelaide, Australia.

Study Population

Adult female patients formally diagnosed with LS are the target population for this study.

Inclusion Criteria

Patients will be eligible if they remain symptomatic from vulvar LS despite topical steroid treatment or if they are intolerant of or unable to use topical steroids.

Exclusion Criteria

The exclusion criteria were as follows: (1) patients on antiestrogens, (2) patients on systemic immunosuppressants such as prednisolone, methotrexate, or biologics that were taken within 12 weeks of commencing the trial, (3) patients with gynecological or breast cancers, (4) patients with autoimmune disorders who require antiplatelet medication, except Sjogren syndrome and LS, (5) patients who are immunocompromised or who have uncontrolled malignant disease, (6) patients diagnosed with lichen planus, psoriasis, candidiasis, vulvar intraepithelial neoplasia, or vulvar carcinoma, (7) patients with vulvodynia, (8) patients with acute vaginal infection or systemic infection, (9) patients on antiplatelet medications, including aspirin, (10) patients without capacity to give consent, and (11) patients who are uncooperative, known to miss appointments, are unlikely to be compliant, or unable to attend regular scheduled visits.

Recruitment

Recruitment will be conducted over a minimum of 18 months to allow for adequate enrollment and potential participant withdrawal. Eligible patients presenting to the clinic with a confirmed clinical diagnosis of LS during routine consultations will be systematically screened for study inclusion according to the predefined eligibility criteria. All eligible patients will be informed about the study and invited to participate in a standardized manner (Multimedia Appendix 1). Patients who express interest will have an appointment scheduled with a clinical investigator who is a gynecologist to assess their

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eligibility and confirm their enrollment. The purpose of this appointment is to obtain consent from the patient, record demographic data, schedule all treatment and assessment appointments, and assign the patient with a unique study identifier number.

Withdrawal

Participants who do not complete the full treatment regimen and/or do not complete all assessments will be withdrawn from the study to ensure the quality of data analysis. The reasons for the withdrawal will be documented if provided. Any participant who withdraws from the study will be advised to consult with their referring physician to continue conventional treatment for their LS.

Randomization and Blinding

Participants will be allocated to intervention and control groups in a 1:1 allocation ratio. Block randomization will be conducted in random block sizes (4:4 and 2:2) to minimize selection bias. Randomization will be performed using a random number generator to assign a value to a corresponding unique study identifier, which will then be sorted in an ascending order to randomize participants to either group. A randomization list will be stored in a concealed location, password protected, and inaccessible to clinical investigators. Sequentially numbered, opaque, sealed envelopes containing the allocation will be prepared according to the randomization list by a biostatistician who is not involved in the clinical trial. The clinical investigator will administer the study treatments for every participant and will therefore be unblinded to the intervention received. Assessment and scoring of LS will be performed by a coinvestigator. Coinvestigators, data collectors, and participants will be blinded to group allocation until completion of the trial.

To minimize potential performance bias due to the clinician being unblinded, all injections follow a strict, standardized protocol regarding injection volume, anatomical injection sites, needle gauge, and injection technique. The injection process is identical for both PRP and saline groups, with a consistent approach to anesthesia, injection sites, and postprocedural care, as outlined in the study protocol (Multimedia Appendix 2).

Ethical Considerations

This study has received ethics approval from Bellberry Human Research Ethics Committee (2017-07-546-PRE-1, PRP4LS) on October 2, 2018. All participants provided written informed consent prior to enrolment, as documented in the participant information sheet and consent form (Multimedia Appendix 1). The trial will be conducted in accordance with the National Health and Medical Research Council National Statement on Ethical Conduct in Human Research (2023) incorporating all updates [1]. Participants were informed that their participation was voluntary, that they could withdraw from the study at any time without any impact on their ongoing medical care, and that they could choose whether their data collected up to the point of withdrawal could be retained or removed from the study dataset. All data were deidentified prior to analysis. Participant identifiers were replaced with unique study codes, and no information that could directly identify participants was included in the research database. Participant details were stored in an electronic medical record system, and the deidentified study dataset was kept in a password-protected Excel file located on a secure server at the study site. Only authorized study personnel had access to identifiable data, and all records were handled in accordance with applicable privacy and data protection regulations. No monetary payment was provided to participants for their involvement in the study. Participants were required to arrange their own travel to appointments; however, travel vouchers were available upon request. Findings from this trial will be reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) statement and disseminated to the scientific community via peer-reviewed journals, conferences, medical education sessions, and patient information sessions.

Study Intervention

Overview

Once enrolled, the trial will require 12 months of participants' time across 4 appointments.

1. Baseline assessment + treatment 1
2. 6-week assessment + treatment 2
3. 6-month assessment
4. 12-month assessment

Study treatments can be administered on the same day as assessments take place. Regardless of group allocation, all participants will undergo a blood collection by a clinical nurse who will then access the randomization list and prepare either PRP or normal saline for vulval injection (Figure 1). The patient will have a physical screen to prevent them from seeing the injection to maintain participant blinding.

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Figure 1. Patient flow diagram. LS: lichen sclerosus; PRP: platelet-rich plasma.

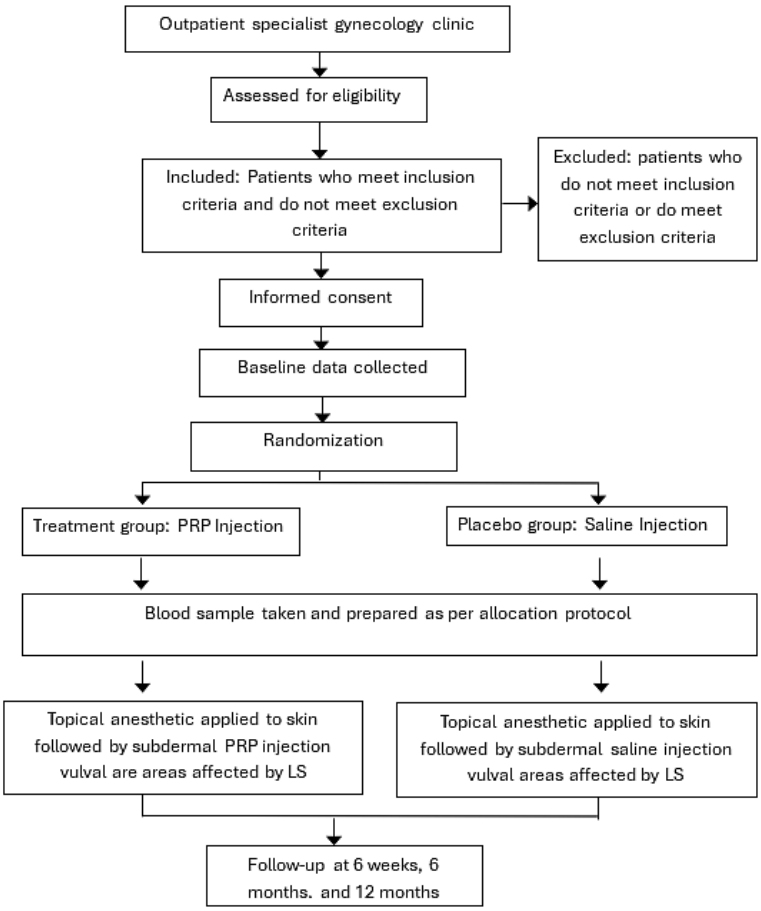

PRP Protocol

At both treatment appointments, 8-10 mL of autologous blood will be collected from the participant into a PRP tube by using the standard phlebotomy technique (Multimedia Appendix 2). The sample is inverted several times to homogenize with the anticoagulant inside the tube. The tube is placed in a centrifuge and set to spin at 3400 rpm for 5-9 minutes. After centrifugation, approximately 4 mL of the concentrated PRP is transferred into a syringe for injection into the vulva.

Saline Protocol

The protocol for saline preparation is identical to the PRP protocol except that once the blood is collected into the PRP tube, it is taken out of the consultation room and discarded, and a syringe containing 4 mL of normal saline is drawn up for injection into the vulva.

Injection Technique

The participant will be asked to lie in the lithotomy position on the examination table, and a topical anesthetic cream will be applied to the vulva 10-20 minutes prior to injection. The clinical nurse will hand the syringe to the clinical investigator who will inject the study preparation into the vulval mucosa in areas affected by LS by using a 30G needle. The amount injected may be less than 4 mL, if on visual inspection, it becomes evident that the tissue cannot hold the maximum amount.

The decision to administer 2 treatment sessions, spaced 6 weeks apart, was based on protocols from previous PRP studies [20,21] in dermatology and gynecology, where 2-3 sessions are commonly used to optimize tissue response and healing. The 6-week interval allows sufficient time for tissue remodeling and the biological effects of growth factors to occur between treatments. The dosage of 4 mL was selected based on the maximum safe and practical volume deliverable to the vulvar tissue, as well as the prior clinical experience in similar interventions to avoid tissue overdistension or adverse effects. The patient will be monitored for adverse effects for 15 minutes after the study treatment and will be advised not to engage in penetrative vaginal sex for 72 hours after the procedure.

Data Collection

Each participant is allocated a folder containing the following documents (See Multimedia Appendix 1 and Multimedia Appendices 3-8 for example documents) (Textbox 1).

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Textbox 1. Documents in the folder of each participant.

1. Unique study identifier
2. Sealed opaque envelope containing treatment allocation
3. Trial information sheet and consent form
4. Appointment schedule
5. Baseline demographics sheet
6. Outcomes Assessment Package (4 copies of each):
   - Visual Analogue Scale for pruritus and dyspareunia
   - Clinical Scoring System for lichen sclerosus
   - Australian Pelvic Floor Questionnaire
   - Dermatology Life Quality Index Questionnaire
   - Study recording sheet

Enrollment Appointment

At enrollment, participants receive a trial information sheet outlining the purpose and aims of the trial, intervention details, duration, and participant expectations. The participant is given an opportunity to ask questions before signing a consent form. A copy of the signed consent form is scanned into their electronic medical record. A self-administered baseline demographic sheet is filled out by the participant, which has the following demographic data: name, date of birth, parity, number of children, types of delivery, menopausal status, height, weight, date diagnosed with LS, and the approximate date that the symptoms of LS were first noted (Multimedia Appendix 9).

Treatment Appointments

Two treatment appointments are scheduled: at baseline and 6 weeks later. After administering the treatment, the following data are recorded on the treatment record form: date, participant name and date of birth, unique study identifier, verification of venous blood collection, 2-person verification of treatment syringe contents, 2-person verification of injection of treatment syringe, and adverse reactions.

Assessment Appointments

Four assessment appointments are scheduled: at baseline, 6 weeks, 6 months, and 12 months. Assessment appointments can occur on the same day as treatment appointments.

Baseline Assessment

During the baseline assessment, the vulva will be examined for LS, and vulvoscopy will be performed to assess for signs of vulvar malignancy. A 3-4 mm vulvar biopsy under a local anesthetic will be performed to confirm the diagnosis of LS for participants without prior biopsy-proven evidence. The investigator scores the patients' LS by using the clinical scoring system, and the participant completes the Visual Analogue Scale, the Australian Pelvic Floor Questionnaire, and the Dermatology Life Quality Index. Deidentified clinical photos are taken.

Assessments at 6 Weeks, 6 Months, and 12 Months

At each assessment appointment, the investigator performs a vulvoscopy and scores the participant's LS by using the clinical scoring system. The participant completes the Visual Analogue Scale, the Australian Pelvic Floor questionnaire, and the Dermatology Life Quality Index questionnaire. Deidentified clinical photos are taken at each appointment. Additionally, participants are asked if they experienced symptoms requiring the use of topical steroids. The completed documents are placed in the patient's folder and remain onsite in a locked cabinet inaccessible to clinical investigators. Documentation will be accessible by a nonclinical research assistant who will be responsible for entering the collected data into the trial's SPSS database for statistical analysis. At the final assessment consultation, participants are discharged to the care of their referring physician. At the conclusion of data analysis, the participant and the investigators will be informed about the treatment allocations during the study. Participants will receive a letter about the research findings.

Outcome Measures

Primary Outcome Measure

The primary outcome of this study was to compare the efficacy of PRP and saline injections by evaluating the change in the LS clinical score across groups at 3 timepoints: 6 weeks, 6 months, and 12 months (Table 1). The clinical scoring system for LS is an objective, validated, physician-administered assessment measuring the severity of vulvar LS [18]. Six clinical characteristics are graded on a 3-point Likert scale with grade 0 as normal, grade 1 as moderate changes, and grade 2 as severe changes. The clinical characteristics are erosion, hyperkeratosis, fissures, agglutination, stenosis, and atrophy. Scores range from a minimum of 0 to a maximum of 12; a score ≥4 identifies LS with a probability of >90% in conjunction with the participant experiencing intractable symptoms such as pruritus, dyspareunia, soreness, or burning [22].

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Table 1. Clinical scoring system for vulvar lichen sclerosus.

Clinical characteristic	Grade 1 (moderate)	Grade 2 (severe)
Erosion	1-2 small erosions, almost not macroscopically visible	Macroscopically visible and/or >2 or confluent lesions
Hyperkeratosis	≤10% vulva and perineum affected	>10% vulva and perineum affected
Fissure	Rhagades affecting the posterior introitus	Generalized vulvar rhagades
Agglutination	Partially affecting preputium clitoridis and labial minora	Complete agglutination of both labia minora or majora
Stenosis	Narrowing of introitus, which could still be passed by 2 fingers	Narrowing, which could be passed by less than 2 fingers
Atrophy	Shrinking of labia and clitoris	Labia minor and clitoris were no longer visible

Secondary Outcome Measures

Secondary outcome measures will compare changes in the subjective assessment scores over time within each group and between groups. Participants will complete the Australian Pelvic Floor Questionnaire and Dermatology Life Quality Index at each assessment appointment to evaluate changes in the subjective disease burden. The Australian Pelvic Floor Questionnaire is a validated self-administered questionnaire assessing pelvic floor symptoms, including bladder, bowel, prolapse, and sexual function symptoms, as well as symptom severity and impact on quality of life [23]. The Dermatology Life Quality Index is a validated tool assessing quality of life impairment for people experiencing inflammatory skin conditions, and a change in the score of at least 4 points is considered clinically significant [24]. A Visual Analogue Scale will be presented to participants at each assessment to record the severity of their symptoms. Participants will be asked to indicate their level of distress in relation to 2 symptoms: pruritus and dyspareunia.

The additional secondary outcomes are safety and adverse events of receiving the treatment. Autologous PRP has an advantageous safety profile due to the utilization of the patient's own blood, which minimizes the risk of adverse events or autoimmune reactions [25]. In a pilot study undertaken by the principal investigator, all participants (n=28) reported minimal to mild pain in the 24 hours following the procedure [20]. There were no reported cases of infection, bleeding, hematoma, or other adverse effects. Adverse events will be monitored immediately after receiving the treatment, and at each assessment appointment, participants will be asked if they experienced any adverse events in the preceding period. Any adverse effects will be recorded and reported to the ethics committee.

Sample Size and Power Calculations

Sample size calculations are based on the pilot study on 28 patients [20], in which 80% of the participants treated with PRP experienced an improvement in their symptoms. Assuming a difference of 30% between PRP and normal saline at 12 months, an α risk of 5%, and a power of 80%, a sample size of 31 participants for each group is required. Assuming that 10% of the participants withdraw or are lost to follow-up, a sample size of 34 participants for each group is required or a sample size of 68. The pilot study used subjective symptom improvement as its primary outcome, whereas this trial's primary outcome is the LS clinical score, an objective physician-rated measure. Although these outcomes differ, symptom improvement in the pilot study was used as a surrogate to estimate a conservative effect size for this study, given the lack of prior data on LS clinical score changes with PRP. This study will also evaluate secondary outcomes, including subjective symptom scores, allowing for comparisons between subjective and objective measures.

Statistical Analysis

All analyses will be conducted using SPSS software (IBM Corp). We will perform analyses using the intention-to-treat principle. Outcomes will be compared within groups over time and between groups at baseline, 6 weeks, 6 months, and 12 months. Baseline characteristics will be summarized using descriptive statistics, and a comparison of the 2 treatment arms will be assessed by 1-way analysis of variance or 1-sided *t* test for continuous variables or nonparametric alternatives if data are not normally distributed. The Shapiro-Wilk test will be used to assess if data are normally distributed. For all tests, a significant level of α=5% is applied. The analysis of changes compared to the baseline will test the null hypothesis that there is no difference between the 2 timepoints. Further analyses between the groups will test the null hypothesis that there are no differences between the 2 groups at one timepoint. Missing value analysis will be performed, and missing values will be imputed using expectation maximization. Analyses will be conducted in line with the intention-to-treat principle, which will be compared to per-protocol analyses.

Results

Recruitment for the trial commenced in May 2020 and concluded in November 2023. The study is closed as of September 2024 due to slow recruitment. A total of 34 participants were recruited. Data analysis is being performed in 2025, and the study results are expected to be published in late 2025.

Discussion

Principal Findings

PRP has emerged as a novel treatment for the management of a variety of dermatological conditions, including LS, because of its regenerative properties and potential to alleviate symptom burden [14]. To date, a number of studies have been conducted investigating PRP as a treatment for LS; however, these have been either case series or uncontrolled studies or studies that

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used multiple interventions such as both PRP and adipose-derived stem cells, limiting the ability to differentiate the efficacy of individual interventions [13]. Franic et al [21] highlighted significant symptom improvement in a premenopausal woman treated with PRP, underscoring its potential as a therapeutic alternative in cases resistant to conventional treatment methods.

Despite these limitations, these studies have reported encouraging results in terms of symptom relief for patients with LS, reducing itching, pain, and discomfort [26] but lack adequate power, standardized protocols, and comparison to a control. Other gynecological studies have reported a beneficial effect of PRP in patients with stress urinary incontinence, pelvic organ prolapse, genitourinary syndrome of menopause, vaginal fistula, and LS; however, these studies have the same limitations as described above [20,27].

This study was designed as a randomized controlled trial to fill the gap in existing literature about the efficacy of PRP for the treatment of vulvar LS. It aims to provide other researchers in this field with a standardized protocol, including methods of preparation and injection of PRP and the use of validated outcome measures assessing both the clinical signs of disease and subjective effects of the disease on the quality of life.

Limitations

As a study protocol, there are several anticipated limitations to consider. This trial is being conducted at a single private clinical center, which may limit the generalizability of findings to other settings, particularly public hospitals or international populations. Although the study is powered to detect a significant difference between groups, the modest sample size may not capture rare adverse events or allow detailed subgroup analysis. Additionally, although outcome assessors and participants are blinded, the treating investigator must remain unblinded for procedural reasons, introducing a potential risk of bias. Lastly, although validated tools such as the clinical scoring system for LS and quality of life measures are employed, patient-reported outcomes are inherently subjective and may be influenced by expectations, even in a placebo-controlled setting.

Comparison With Prior Work

Previous investigations [20,21] into the use of PRP for vulvar LS have largely consisted of case reports, small cohort studies, and pilot trials, many of which lacked standardization in PRP preparation and outcome measurement. These earlier studies often demonstrated promising symptomatic improvements but were limited by heterogeneity in design, short follow-up durations, and absence of control groups. This protocol addresses several of these gaps by incorporating a parallel-group, double-blind, randomized controlled trial design with standardized PRP preparation, objective clinical scoring, and validated patient-reported outcome measures. By using a clearly defined placebo (saline) control and ensuring long-term follow-up, this study aims to provide robust evidence to inform future clinical practice.

Conclusions

This protocol outlines a rigorous, placebo-controlled, double-blind randomized controlled trial designed to assess the safety and efficacy of autologous PRP injections for the treatment of vulvar LS. By employing standardized preparation methods, validated clinical and quality of life outcome measures, and long-term follow-up, this study aims to address the methodological limitations of prior research. The findings from this trial have the potential to inform clinical practice by providing high-quality evidence on the role of PRP as an alternative or adjunctive therapy in patients who are unresponsive to standard topical steroid treatment.

Authors' Contributions

Conceptualization: FBW (lead), TN (supporting), DA (supporting)
Methodology: FBW (lead), TN (supporting), MB (supporting), DA (supporting)
Investigation: TN (lead), FBW (supporting), MB (supporting), NW (supporting)
Project administration: FBW (lead), PA (supporting), TN (supporting)
Data curation: TN (lead), NW (supporting), PA (supporting), MT (supporting)
Formal analysis: PA (lead), TN (supporting), DA (supporting)
Resources: FBW (lead)
Supervision: FBW (lead)
Validation: PA (lead), DA (supporting)
Visualization: PA (lead), MT (supporting)
Writing – original draft: TN (lead), PA (supporting), MT (supporting)
Writing – review & editing: FBW (lead), TN (supporting), MB (supporting), NW (supporting), DA (supporting), PA (supporting)

Conflicts of Interest

None declared.

Multimedia Appendix 1
Participant information sheet and consent form.
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Multimedia Appendix 2
Protocol for platelet-rich plasma preparation and saline preparation.
[DOCX File , 321 KB - resprot_v14i1e68871_app2.docx]

Multimedia Appendix 3
Participant appointment schedule.
[DOCX File , 161 KB - resprot_v14i1e68871_app3.docx]

Multimedia Appendix 4
Demographic data collection sheet.
[DOCX File , 106 KB - resprot_v14i1e68871_app4.docx]

Multimedia Appendix 5
Visual Analogue Scale.
[DOCX File , 268 KB - resprot_v14i1e68871_app5.docx]

Multimedia Appendix 6
Australian Pelvic Floor Questionnaire.
[DOCX File , 648 KB - resprot_v14i1e68871_app6.docx]

Multimedia Appendix 7
Dermatology Life Quality Index.
[DOCX File , 170 KB - resprot_v14i1e68871_app7.docx]

Multimedia Appendix 8
Study recording sheet.
[DOCX File , 223 KB - resprot_v14i1e68871_app8.docx]

Multimedia Appendix 9
Participant flow diagram.
[DOCX File , 40 KB - resprot_v14i1e68871_app9.docx]

Multimedia Appendix 10
CONSORT (Consolidated Standards of Reporting Trials) checklist.
[PDF File (Adobe PDF File), 1234 KB - resprot_v14i1e68871_app10.pdf]

Multimedia Appendix 11
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 122 KB - resprot_v14i1e68871_app11.pdf]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
LS: lichen sclerosus
PRP: platelet-rich plasma

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Protocol

Effects of a Dialogic Book-sharing Intervention for Female Caregivers in Rural Tanzania (EDBiT): Protocol for a Randomized Controlled Trial

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Abstract

Background: Children in low- and middle-income countries face obstacles to optimal language and cognitive development due to a variety of factors related to adverse socioeconomic conditions. One of these factors is compromised caregiver-child interactions and associated pressures on parenting. Early development interventions, such as dialogic book-sharing (DBS), address this variable, with evidence from both high-income countries and urban areas of low- and middle-income countries showing that such interventions enhance caregiver-child interaction and the associated benefits for child cognitive and socioemotional development. Yet, evidence for DBS effects is lacking from poor rural communities where the need for such early development intervention may be greatest.

Objective: The objective of this study is to assess the effects of a DBS intervention, a parenting program for female caregivers of children aged between 15 and 45 months, implemented in rural Tanzania. We aim to assess the impact of the intervention on the following domains: child cognitive and socioemotional skills, parenting and parental stress, and child health.

Methods: The study is a 3-arm cluster randomized controlled trial. In total, 443 female caregivers participated in the study. Clusters of caregivers were randomized to either (1) an index DBS intervention group, (2) a playful activity active control group, or (3) a waitlist control group. The active control group was designed to control for any attention effects, ensuring that observed improvement in the index group can be attributed to the DBS intervention's content. The primary outcomes were child language, parental sensitivity, and parent-child interaction. The secondary outcomes concerned child attention and behavior, parenting practices, and parental stress. A combination of questionnaires and direct observations was applied. Qualitative methods were also used, primarily to capture caregivers' experiences and subjective perspectives on intervention-induced changes.

Results: Data collection for the study was completed in September 2024. The study results are expected to be published by late 2025.

Conclusions: This randomized controlled trial of a DBS intervention implemented in rural Tanzania adds to a growing body of international literature exploring the impact and limitations of a simple and scalable early development intervention to enhance child outcomes.

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Trial Registration: International Standard Registered Clinical/Social Study Number (ISRCTN) ISRCTN12613329; https://www.isrctn.com/ISRCTN12613329

International Registered Report Identifier (IRRID): DERR1-10.2196/68758

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KEYWORDS

dialogic book-sharing; cognitive development; child language; parenting; Tanzania; study protocol

Introduction

Background

Children from low- and middle-income countries (LMICs) face multiple challenges that significantly impede their cognitive and socioemotional development [1]. These challenges pose a substantial threat to their well-being in adulthood. Children's early language and cognitive development, at risk in such contexts, are important determinants of subsequent literacy skills and later school progress [2,3].

Several socioeconomic conditions and poverty-related factors contribute to compromised child developmental progress [4-6]. These include nutritional deficits, which directly impact both physical and cognitive growth; limited access to educational resources, such as learning toys; elevated risk of chronic stress exposure; and the challenges posed by overcrowded and inadequate housing conditions. All of these disrupt the educational process [1,7] and children's health status [8,9].

Compromised caregiver-child interaction and limited caregiver activities that support early learning are other key factors prevalent in deprived contexts that hinder children's cognitive and socioemotional development [6,10,11]. Early difficulties in the caregiver-child relationship raise the risk of insecure infant attachment [12], itself predictive of a range of adverse child outcomes [13]. In addition, promoting warm and responsive interactions among caregivers, including vocalizations and smiles, has been shown to positively influence child health outcomes [14].

Providing education to parents in dialogic book-sharing (DBS) techniques has been proposed as a simple and deliverable means of obviating adversity risk to the caregiver-child relationship and child development [15,16]. There is considerable evidence for the benefits of book-sharing interventions provided to families living in high-income countries [16-19]. While a similarly beneficial impact has been reported from urban and periurban areas of LMICs [15,20-22], evidence is limited from poor rural communities, where the need for such early child development intervention may, arguably, be the greatest [10,23,24].

This paper presents the protocol for the Effects of a DBS Intervention for Female Caregivers in Rural Tanzania (EDBiT) study. EDBiT is a randomized controlled trial (RCT) designed to determine the effects of the DBS intervention delivered in rural Tanzania on cognitive development (specifically language skills and attention) as well as other parental and child outcomes.

During the preparation phase of the trial, we paid particular attention to the five recommendations proposed by Noble et al [18] to increase the probability that education in DBS will benefit the targeted child outcomes: (1) The DBS intervention delivered in this study involved a higher dosage compared to most previous studies [10,16,18,20-22,25], as the core 8-week educational program (intensive intervention) was followed by regular meetings of female caregivers swapping books and exchanging experiences with book-sharing and the upbringing of children (extensive intervention). (2) In addition to the waitlist control group, we included an active control group to test specific effects of book-sharing over the nonspecific effects of being subjected to some educational program focused on some parenting skills. (3) The design of this trial allows a potential follow-up that will assess the long-term effects of the index intervention. We expect the data collection for this follow-up study to be conducted in 3- to 5-year intervals, with the theory of change (ToC), presented in the Overview of the Study Design section, determining variables that will be the focus of our interest. (4) We collected data on a broad range of outcome variables to provide a rich assessment of the effects of book sharing on a variety of outcomes. (5) Children from diverse socioeconomic backgrounds living in the target region were included, allowing for the investigation of moderating social factors.

Aims

The aim of the EDBiT study is to assess the effects of DBS, a parenting program for female caregivers of children aged between 15 and 45 months, implemented in rural Tanzania. We aim to assess the impact of the intervention on the following domains: child cognitive and socioemotional skills, parenting and parental stress, and child health. We will evaluate the moderating influence of certain variables, including caregivers' cognitive abilities.

Methods

Overview of the Study Design

This study is a 3-arm cluster RCT. Registered female caregivers were randomized at the individual level to an index intervention group attending DBS educational sessions, an active control group attending educational sessions focused on playful activities (PAs) designed to promote the development of a child's motor skills, or a waitlist (passive) control (WLC) group. We collected data on all 3 groups at baseline, after intensive intervention, and after extensive intervention, approximately 1 year after the start of the intervention (refer to the Intervention section for the description of the intensive and extensive phases of the intervention).

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On the basis of previous research on the efficacy of the version of DBS implemented in this study [15,20-22], significant differences between the index group and the WLC group are to be expected. The comparison between DBS and PAs is to control for the fact that any parenting interventions may yield positive results for children because of the caregivers' increased attentiveness to their children rather than because of the content of the index intervention itself. While DBS primarily aims to develop child language, PAs were strategically designed to cultivate other skills that are not the primary focus of DBS (refer to the subsequent sections).

Several authors argue for adding qualitative methods to quantitative ones in RCTs for studies to paint a richer picture of the evaluated interventions and increase the validity of findings [26-28]. However, most existing RCTs of DBS programs apply solely quantitative methods [17,18,20-22]. In EDBiT, we adopted a mixed methods approach, with qualitative research capturing the subjective perspectives of caregivers in both DBS and PAs on the intervention's effects. Qualitative data will provide an additional layer of information with the potential to further explain the results of the quantitative analysis, possibly shedding light on the factors that facilitated or hindered the realization of intervention outcomes. They will also examine how the intervention influenced caregivers' parenting practices and attitudes toward their role in a child's development. Caregivers' book-sharing patterns were monitored through self-completed diaries and interviews. The level of parental engagement could moderate the index intervention's impact on child outcomes [18].

Considering the importance of theories of change for impact evaluations [29], we constructed the causal chain (Figure 1). The model includes the main activities of the evaluated intervention, the intended immediate outcomes, and an indicative list of expected long-term impacts (beyond the scope of this study).

Figure 1. Theory of change of the dialogic book-sharing intervention.

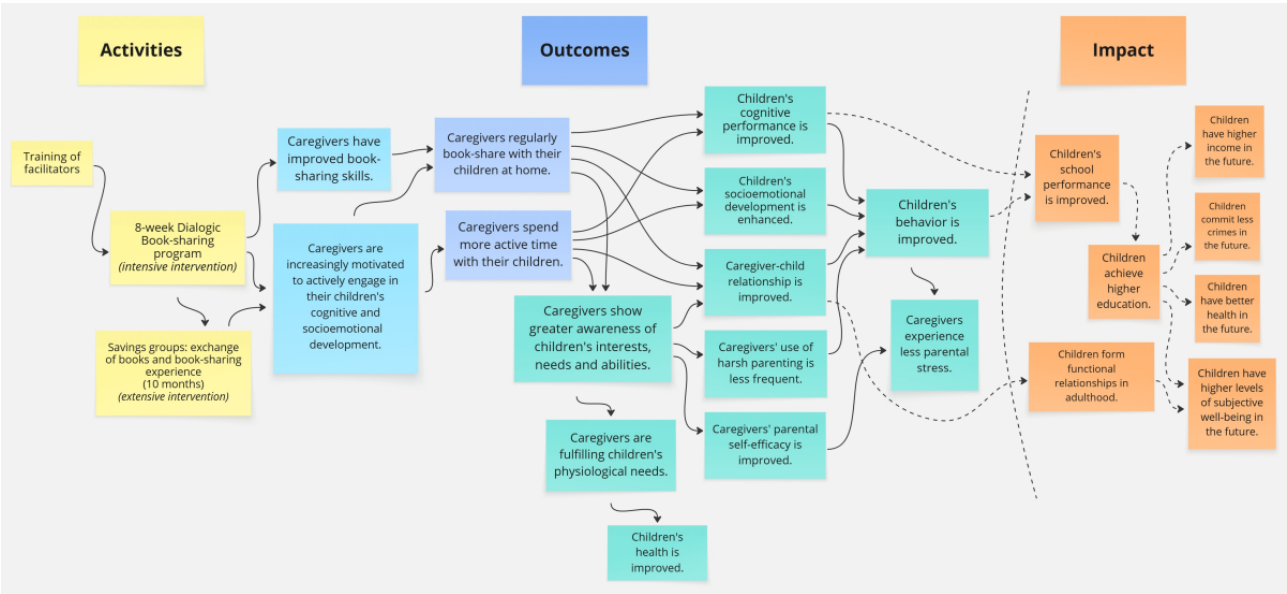

Study Setting

This study has been conducted in the rural areas of the Usangu Plain, South West Tanzania. Specifically, it is located along the southern and eastern edges of the Usangu area, historically labeled as the "cultivation zone" [30]. This populous area relies on small-scale farming, mainly on the production of rice and maize. Implementing the EDBiT study in Usangu provides an opportunity to test the feasibility and effectiveness of a DBS intervention in a context that is close to the socioeconomic median for Africa rather than at either extreme. The Multidimensional Poverty Index places both the South West Highlands region, where Usangu is situated, and Tanzania as a whole near the median of their respective national and continental distributions [31]. Findings from such a setting may offer valuable insights into the potential scalability of the DBS program elsewhere across the African continent.

This study covers 12 towns, villages, and geographically isolated neighborhoods (referred to as "villages" in Figure 2) from Utengule Usangu, Kongolo, and Igurusi wards (Figure 2) [32,33]. Assessment and education sessions were held in each of the 12 villages. Village executive officers were informed about the project, and leaders in all villages approved both the intervention and the study.

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Figure 2. Location of the Effects of a Dialogic Booksharing Intervention for Female Caregivers in Rural Tanzania study villages. Produced by the authors in QGIS (Version 3.40) using World Topo Map (Sources: Esri, DeLorme, HERE, TomTom, Intermap, increment P Corp., GEBCO, USGS, FAO, NPS, NRCAN, GeoBase, IGN, Kadaster NL, Ordnance Survey, Esri Japan, METI, Esri China (Hong Kong), swisstopo, MapmyIndia, and the GIS User Community) [32] and Light Gray Canvas Map (Sources: Esri, DeLorme, HERE, MapmyIndia) [33]. Individual village data sourced and included by the authors.

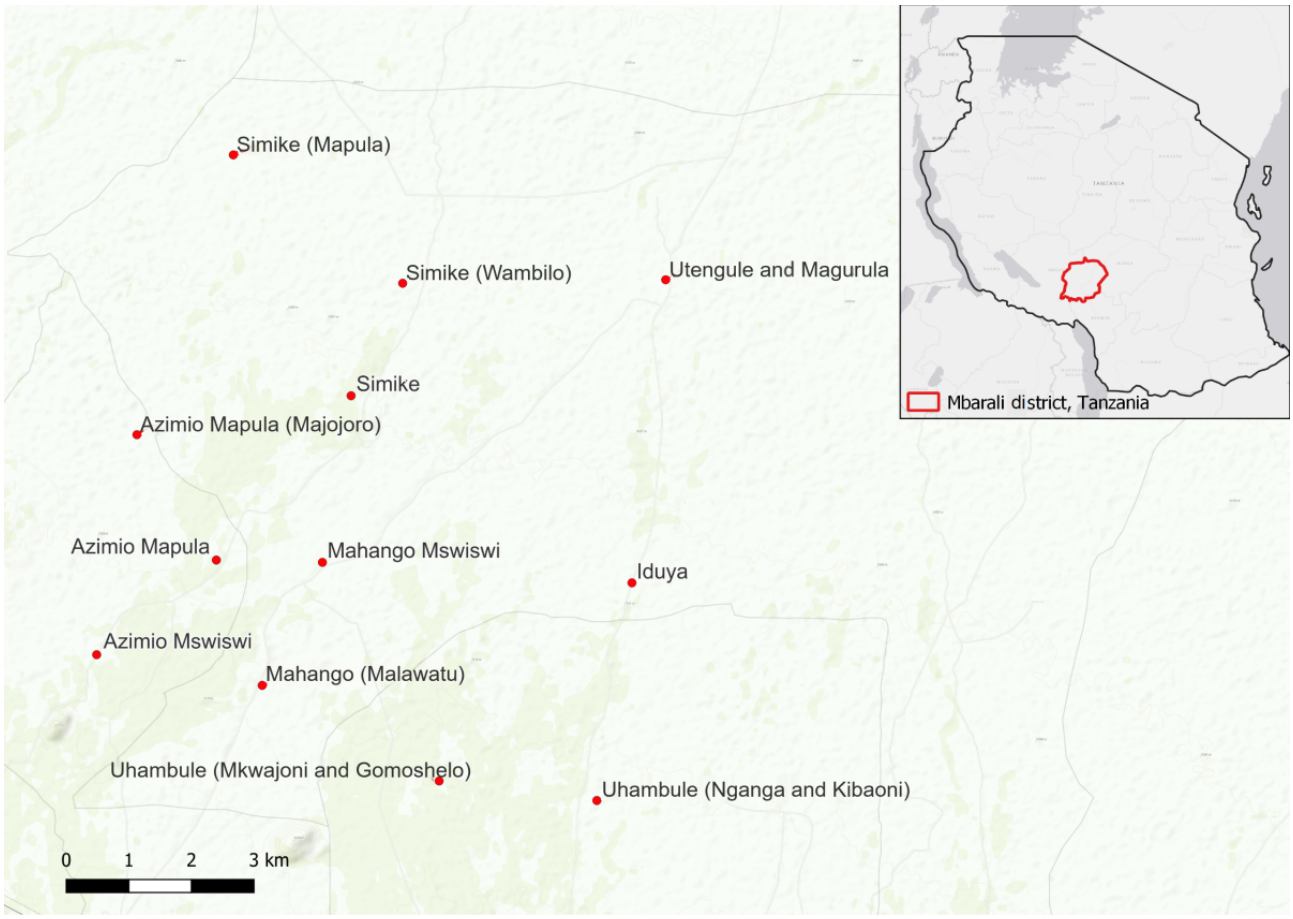

Ethical Considerations

This study received ethical approval from the Faculty of Science Ethics Committee at Palacký University Olomouc (reference 23-03) and from the University of Dar es Salaam (reference AB3/12B). Caregivers provided informed consent for their own and their children's participation after the full consent form was read aloud to them during registration, and again verbally prior to each instance of data collection. All consent was audio-recorded. Participation was voluntary, and caregivers were informed that they could withdraw at any time without consequences. No personally identifying information was collected, and all data were anonymized prior to analysis. Participants did not receive financial compensation, but small refreshments and gifts were provided as a token of appreciation. All the data are securely stored on a cloud server and made available only to the core research team members to maintain confidentiality. The study has been registered with the International Standard Registered Clinical/Social Study Number (ISRCTN12613329).

Eligibility, Recruitment, and Randomization

Female caregivers caring for a child born between December 1, 2019, and June 1, 2022 (aged between 15 and 45 months at the time of baseline assessment), were eligible for participation in this study. Eligible women were the primary persons responsible for childcare and not necessarily biological mothers.

Recruitment of caregivers was conducted between July 29, 2023, and September 3, 2023. Members of the project team visited prospective households, accompanied by respected women from the local communities. Eligible caregivers were enrolled in the study if they (1) provided consent to participate in the study; (2) declared their availability to attend the 3 rounds of assessments; and (3) agreed that we could, if necessary, delay their participation in the project by 1 year.

In total, 542 eligible caregivers enrolled in this study. For each village, the location of each household was determined by GPS, and mutual distances between households were computed. To prevent cross contamination, we divided groups of households into clusters. To avoid large clusters of households, we selected a subset of households that could be split into smaller clusters of no more than 5 households. The distance between households from distinct clusters was set as >100 m. Some eligible households were excluded from the study to fulfill this condition. These caregivers were invited to join savings groups a year later (refer to the Intervention section). The number of excluded households (n=99) was kept to a minimum by using advanced graph theory methods. Therefore, 443 (81.7%) female caregivers were included in this study.

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Clusters, each including 1 to 5 households, were randomly assigned to the DBS, PA, or WLC group. The randomization process mimicked a block design; it considered dwelling place (village) and child age (children aged between 15 and 30 months vs children aged >30 to 45 months) and ensured a balanced distribution of these characteristics across the study groups.

The study participants were not informed which program (DBS or PA) constituted the studied intervention and which served as a control condition.

Intervention

The Index Intervention Group (DBS)

The index intervention was a DBS program consisting of 8 weekly educational sessions for groups of 3 to 8 female caregivers, each lasting 90 minutes [15,20,22]. This stage of the intervention is called the intensive intervention phase. The content of weekly sessions was based on the Mikhulu Trust book-sharing program for children aged 15 to 30 months and the Mikhulu Trust book-sharing program for children aged 30 to 45 months, developed by LM and PJC. These programs have been shown to benefit parenting and child development [20-22]. The program for caregivers of children aged between 30 and 45 months is described in Table 1.

Table 1. Summary of index intervention group sessions for caregivers of children aged between 30 and 45 months[a].

Session number	Name of the session	Description of the session
1	Introduction to book sharing	Introducing basic dialogic book-sharing skills—following the child's lead, using a lively voice, and setting up book-sharing routines
2	Pointing and naming	Basic dialogic book-sharing skills—pointing and naming, repeating and elaborating on things that interest the child, and finding opportunities for praise
3	Naming and linking	Asking "where, who, and what" questions, linking book content to the child's own experience, and finding opportunities to use actions (eg, hugging and eating)
4	Talking about feelings	Helping the child understand the meaning of basic emotion terms—happy, sad, angry, and scared—and discussing why book characters feel the way they do, using facial expression and tone of voice to convey a character's feelings, and linking feelings in the book to the child's experience
5	Talking about intentions	Discussing why characters feel the way they do, asking what characters think and intend, and encouraging the child to be curious about what will come next in the story
6	Talking about perspectives	Helping the child understand that different people can see things differently, know different things, and feel differently about things
7	Summary	Reviews of key principles from sessions 1 to 6.
8	Graduation event	Certificates of completion presented to participants along with summary take-home cards and selected books from sessions 1 to 6; a group discussion about how to remain motivated about book sharing and how to access children's books

[a]The program for caregivers of children aged between 15 and 30 months was broadly similar in content, with less emphasis on the components beyond these children's developmental competence, such as perspective taking.

The sessions were delivered by women from the local community selected during the recruitment phase based on their previous experience working with mothers and small children. A 7-day DBS training with a certified Mikhulu Trust trainer was organized for 20 potential session facilitators. After the first 2 days of the training, the trainer selected the 10 best-performing women based on their book-sharing skills and presentation abilities demonstrated in class. These women completed the full facilitator training.

Supervision and experience sharing of intervention facilitators occurred during weekly meetings with the project team. In addition, the project team conducted ad hoc visits to sessions, observing the facilitators' performance, ensuring session fidelity, and offering feedback. Each facilitator was visited twice throughout the intensive intervention phase.

Sessions followed a standard format. They began by reviewing participants' experience of book sharing over the previous week. A presentation with Microsoft PowerPoint slides and instructional videos followed, introducing new book-sharing techniques. The session concluded with a discussion of "the book of the week," that is, the book lent to parents for use over the following week. Children were looked after separately by a woman from the local community and given fortified porridge at every session to increase caregivers' motivation to attend sessions. Caregivers were encouraged to participate in sessions via phone on the day before each session. At the end of the DBS program, all caregivers received a book to take home and keep.

A 10-month extensive intervention phase followed after graduation when caregivers were encouraged to meet biweekly to exchange books and discuss book-sharing and child-rearing experiences. Parents received an additional book 1 and 4 months after the end of the intensive intervention. To help sustain the motivation of caregivers to continue these meetings, we supported caregivers in forming charitable savings groups, locally named *simwabas*, with a 10-month saving cycle. During this phase, we sent short motivational messages encouraging participation in the meetings, practicing book sharing at home, and sharing feedback on book sharing and childcare with fellow

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caregivers. This aimed to further bolster parental motivation to sustain engagement with DBS.

The Active Control Group (PAs)

In the PA condition, female caregivers attended 8 weekly group-based educational workshops focused on PAs for children (intensive intervention phase). During the workshops, female caregivers in groups of 3 to 8 people were shown simple children's games and how to produce low-cost toys using available materials to enhance children's motor development. The program was appropriate for children aged between 15 and 45 months. The content of individual sessions developed by the research team is described in Table 2.

Table 2. Summary of active control group sessions (playful activities).

Session number	Content of the session	Description of the session
1	Introduction, puzzles, and gross motor skills exercise	This session includes introducing the program and explaining the relevance and benefits of the program for children's development. Caregivers develop a set of puzzles and learn a game, enhancing gross motor skills.
2	Ring toss game and fine motor skills exercise	Caregivers produce rings for the ring toss game and learn a game, enhancing soft motor skills.
3	Coloring books and gross motor skills exercise	Caregivers create coloring books and learn a game, enhancing gross motor skills and nonverbal communication.
4	Dancing with children	Caregivers dance with their children while singing local music. Caregivers learn a game that helps children explore their senses and improve their attention.
5	Memory game and gross motor skills exercise	Caregivers produce a memory game and learn a game, enhancing gross motor skills.
6	Playing cards	Caregivers produce playing cards and learn a simple card game.
7	Dancing with children and playing cards	Caregivers dance with their children while singing local music. Then, they learn a simple card game.
8	Graduation event	Certificates of completion are presented to the participants. Groups discuss how to remain motivated to raise healthy children.

Local women, distinct from book-sharing facilitators, were trained in conducting PA sessions and supervised by the project team. This training was carried out on an ongoing basis, with weekly sessions dedicated to the upcoming lessons. Supervision and experience-sharing mechanisms mirrored those used in DBS.

PA sessions followed a standard format, starting with a review of the previous week's activities. Caregivers then engaged in the main weekly activity, often involving the creation of simple toys. When possible, caregivers performed the activity with their children in the session. In addition, the facilitator suggested 1 more activity for caregivers to do with their children at home. Other session components mirrored those of the index intervention group.

After graduation, groups were encouraged to meet every 2 weeks for 10 months. This phase is analogous to the extensive intervention of the DBS condition. Instead of receiving picture books, caregivers were given written instructions twice during this period on creating other simple educational toys. We also supported them in establishing savings groups with a saving cycle of 10 months.

WLC Group

The passive control group was put on the waiting list to receive an intervention after completing the extensive intervention phase and the post–extensive intervention data collection. Caregivers in this group receive the service provided to the DBS condition 1 year after the baseline assessment.

Study Assessments

Overview

Caregiver-child dyads from intervention and active and passive control groups underwent quantitative assessments at baseline, after intensive intervention, and after extensive intervention. The data collection team, comprising 10 local women and 4 Tanzanian team members, was trained and supervised by senior team members, including the study's principal investigator (M Schlossarek), who ensured adherence to the protocol. We conducted direct child assessments, video recorded caregiver-child interactions, and administered caregiver questionnaires to evaluate child and caregiver outcomes. In addition, we measured children's height and weight. The assessment took between 60 and 75 minutes. Data collectors and video coders were blinded to the group allocation to prevent assessment bias. The same procedure was repeated for all 3 assessment rounds.

Qualitative data were collected concurrently with the quantitative assessments at the 3 time points. Interviews and focus groups were conducted with a randomly selected sample of caregivers in both the index intervention and active control groups and with all DBS and PA facilitators. With caregivers, we aimed to explore their subjective assessment of the DBS or PA sessions, the actual adoption of DBS or PA practices in the home, and the perceived impact of the intervention on their children. Possible barriers to adopting DBS or PA practices at home were examined. A set of questions targeting their parenting attitudes and practices, asked in all 3 rounds of data collection, maps out the potential effects of the intervention in

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these areas. Focus groups with DBS and PA facilitators provided additional information on the perceived reactions of caregivers to the content of sessions and their engagement with the sessions' content. Tanzanian team members trained and supervised by senior research team members conducted all the interviews and focus groups.

All quantitative and qualitative assessments were administered in Swahili. The schedule is presented in Table 3.

The primary, secondary, and exploratory outcome measures and moderators assessed by the EDBiT study are presented in subsequent sections and Table 4.

Table 3. Schedule of enrollment, interventions, and assessments.

Time point	T0[a]	T1[b]	II[c]	T2[d]	EI[e]	T3[f]
Enrollment						
Eligibility screening	✓					
Informed consent	✓					
Allocation	✓					
Interventions						
Index intervention group sessions			✓		✓	
Active control group sessions			✓		✓	
Passive control group sessions						
Quantitative assessments						
Primary outcomes						
Child language		✓		✓		✓
Parental sensitivity and parent-child reciprocity		✓		✓		✓
Secondary outcomes						
Child attention		✓		✓		✓
Child behavior		✓		✓		✓
Parenting		✓		✓		✓
Parental stress		✓		✓		✓
Exploratory outcomes						
Child health		✓		✓		✓
Moderators and selected confounding variables						
Sex of the child	✓					
Socioeconomic situation	✓					
Cognitive abilities of the caregiver		✓				
Qualitative assessments						
Interviews with caregivers		✓		✓		✓
Focus groups with caregivers				✓		
Focus groups with DBS[g] and PA[h] facilitators				✓		

[a]T0: allocation and enrollment.
[b]T1: baseline.
[c]II: intensive intervention.
[d]T2: post–intensive intervention assessment.
[e]EI: extensive intervention.
[f]T3: post–extensive intervention assessment.
[g]DBS: dialogic book-sharing.
[h]PA: playful activity.

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Table 4. Primary and secondary outcome measures.

Outcomes	Measures
Primary outcomes	
Child language	• Receptive and expressive language: MacArthur-Bates Communication Development Inventory (short-form version; adapted) • Receptive language: Peabody Picture Vocabulary Test (adapted) • Expressive language: Expressive One Word Picture Vocabulary Test (adapted)
Parental sensitivity and parent-child reciprocity	• Parental sensitivity and parent-child reciprocity: directly observed book-sharing task rated with the Murray Global Rating Scale
Secondary outcomes	
Child attention	• Early Child Vigilance Task
Child behavior	• Prosocial behavior: help task • Prosocial behavior: Strengths and Difficulties Questionnaire (prosocial subscale) • Behavior: Strengths and Difficulties Questionnaire; total difficulties score
Parenting	• Parental engagement with child: frequency of engagement in joint play with child, self-recorded in diaries • Parenting practices: Parenting Styles and Dimensions Questionnaire (connection, physical coercion, and verbal hostility dimensions) • Parenting efficacy: Parenting Self-Efficacy questionnaire (TOPSEa; selected questions)
Parental stress	• Parental Stress Scale
Exploratory outcomes	
Child health	• Incidence of diarrhea • Wasting • Stunting • Underweight
Moderators and selected confounding variables	
Sex of the child	• Child's sex (male or female)
Socioeconomic situation of families	• Asset index
Parental cognitive abilities	• Vienna Matrices Test

[a]TOPSE: Tool to Measure Parenting Self-Efficacy.

Primary Outcomes

Child Language

Child language was assessed using a combination of direct child assessment and caregiver-reported measures. Caregivers reported on their children's expressive and receptive language levels using the MacArthur-Bates Communication Development Inventory [34]. For this study, a short version with 55 words was used.

Two assessment tools were used to complement the MacArthur-Bates Communication Development Inventory with direct measures of child language. Language comprehension (receptive language) of all children was measured using an adapted version of the Peabody Picture Vocabulary Test [35] during which the child was shown pictures of 80 items in groups of 4. The child was asked to point to 1 named item among the 4 (eg, "Where is the goat?"), with the number of correct responses recorded.

Expressive language was only assessed in the group of children aged between 30 and 45 months, using the adapted Expressive One Word Picture Vocabulary Test [36]. The child was asked to say the name of the item shown on a screen. In total, 20 pictures were shown, and the number of correct responses was recorded.

All these instruments have been used in previous evaluations of book-sharing programs in African contexts in the same form as in our study [15,21-23,37]. To reflect the vocabulary to which local children in our study setting are typically exposed, we only adapted the set of words in each test based on numerous consultations. The instruments were piloted with 10 caregiver-child dyads.

Parental Sensitivity and Parent-Child Reciprocity

Parental sensitivity and parent-child reciprocity were assessed by direct observation of the caregiver and child sharing a book. The interaction was recorded on video and coded by independent

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assessors blinded to the group allocation using a coding system developed by LM, adapted for the book-sharing context. While specific modes of expressing sensitivity and reciprocity can vary between cultures [38,39], the core features are common across different populations, that is, supportive and warm responsiveness to infant cues and mutually positive active engagement. This coding system has been used previously in DBS studies, including the investigation of book-sharing impact in LMICs and middle-income settings in South Africa, Lesotho, Colombia, and Brazil. Notably, in one South African study, sensitivity and reciprocity were found to mediate the impact of the intervention on the development of child language and attention [21].

Secondary Outcomes

Child Attention

The Early Childhood Vigilance Task (ECVT) was used to assess child attention [40]. ECVT is a computer-based tool during which the child is shown a 7-minute-long cartoon. The child's sustained attention is indexed by the number of seconds the child attends to the screen during the 7-minute period. The child was videotaped during the assessment, and the recording was subsequently independently scored. ECVT has been previously used in DBS studies [21,22].

Child Behavior

Child behavior was assessed using the full version of the Strengths and Difficulties Questionnaire [41], with aggregated scores obtained for the following scales: emotional symptoms, conduct problems, hyperactivity and inattention, relationship problems, and prosocial behavior as well as for a total score indexing total level of behavioral disturbance. The child's prosocial behavior was further assessed during a help task [21,42]. In this direct assessment, the data collector creates a situation in which the child is encouraged to express a "helping behavior," that is, to offer help in finding the item the data collector pretends to have lost.

Parenting

The frequency of caregivers joining the children in sharing a book at home and in other child games was assessed using diaries distributed to all caregivers in all groups. Caregivers were provided with an easy-to-fill-out diary for the 8-week intensive intervention period. Every day, caregivers circled pictograms of the child's activities and the person or people who joined the child in that activity. Diaries were collected after the intensive intervention period.

To assess caregivers' general parenting practices, 3 dimensions from the self-report short version of the Parenting Styles and Dimensions Questionnaire [43] were administered: the connection dimension to index the occurrence of warm and supportive behaviors, the physical coercion dimension to index the extent to which caregivers apply physical punishments, and the verbal hostility dimension to index the presence of harsh verbal behavior.

In total, 13 statements from the Tool to Measure Parenting Self-Efficacy questionnaire [44] were used to assess parenting efficacy concerning emotion and affection, play and enjoyment, empathy and understanding, control, discipline and setting boundaries, self-acceptance, and learning and knowledge.

Parental Stress

The Parental Stress Scale was administered to assess the level of parenting-related stress [45].

Exploratory Outcomes (Child Health)

To assess child health, caregivers reported whether the child experienced diarrhea in the past 2 weeks. In addition, children's height and weight were measured to check their nutritional status (stunting, wasting, and underweight).

Potential Moderators

Sex of the Child

We examined the potential difference between the effects of the intervention on girls and boys.

Socioeconomic Situation of Families

We examined the potential difference in the intervention's effects on children living in families of varying socioeconomic statuses using the asset index [46,47] as an indicator of socioeconomic status. The indicators recorded are defined based on the same taxonomy used, for example, in the Demographic and Health Surveys [48]. Following the procedures of Němečková et al [49], the individual items are weighted during aggregation using weights generated by the multiple correspondence analysis method, and the results are linearly rescaled to a 0 to 100 scale.

Cognitive Abilities of Caregivers

The shortened version of the Vienna Matrices Test [50] was administered to measure the cognitive abilities of caregivers.

Fidelity Testing

Consistent delivery of both the DBS and PA programs was tracked with an 18-item implementation fidelity checklist. In total, 11 items assessed the substantive content of each session, for example, whether the facilitator explained key concepts clearly and gave accurate, supportive feedback during mothers' practice, whereas 7 items captured organizational logistics and caregiver-oriented factors (eg, punctual arrival of facilitators and mothers, maternal attentiveness during the theoretical segment, distribution of porridge to children at the start of the session, and the babysitter's behavior).

Each checklist item was transformed to a 0% to 100% scale; the mean of the 11 content items formed the content fidelity subscore, and the mean of the 7 organizational items formed the procedural fidelity subscore. A session was deemed adequate only when both subscores were ≥75%. Facilitators whose scores fell below this threshold received targeted supervisory feedback before the next block of sessions. Fidelity distributions will be summarized descriptively in trial reports.

An independent rater conducted live, in-person observations of 2 sessions per facilitator, with a minimum interval of 3 weeks between visits. Sessions were not audio or video recorded. Fidelity scores will be used solely to define the per-protocol analytic sample (dyads taught by facilitators whose average content and procedural fidelity across the 2 observed sessions

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are each ≥75%). Because the checklist serves primarily as a quality-assurance gate, fidelity will otherwise be summarized descriptively and will not be modeled as an explanatory variable.

Data Management

Data were collected on tablets and mobile phones using a Kobo platform [51] and uploaded to a secure online server. Child assessments and caregiver-child book-sharing interactions were video recorded. A random sample of videos was regularly checked for fidelity of the data collection procedure. Interviews and focus groups were recorded on a voice recorder and checked for quality and adherence to the prescribed questions.

Data Analysis

Statistical Analysis Plan

All data will be analyzed by an independent statistician using R (R Foundation for Statistical Computing) or Stata (StataCorp LLC). Fidelity will first be described with standard descriptive statistics. Hypothesis tests will be 2-sided with α of .05, and effect-size statistics will be reported to indicate the magnitude of any intervention effects.

Outcomes are classified a priori as primary, secondary, or exploratory. For the primary outcomes, we will use the Holm-Bonferroni method to adjust *P* values. Secondary and exploratory outcomes will be interpreted as hypothesis generating; the Benjamini-Hochberg procedure will be applied for their significance evaluation.

The primary and secondary outcome analyses will follow the intention-to-treat principle.

Linear mixed models or, where appropriate, analyses of covariance will evaluate intervention effects at both the intensive and extensive postintervention phases, always adjusting for baseline outcome scores. Because participants are clustered, a random effect will be included, and fixed-effect estimates will be compared with intercluster variability. Before modeling, every numerical predictor will be mean centered and standardized (*z* scores); interaction terms will be created as products of these centered variables. Candidate covariates and moderators (child age, dwelling place, child sex, socioeconomic situation, and parental cognitive abilities as indexed by education) will be retained only if they are significant or if removing them markedly alters other parameter estimates.

Although the intention-to-treat approach is the primary approach, a complementary per-protocol analysis will be performed to clarify whether any lack of impact arises from deficiencies in the intervention itself or from participants' incomplete exposure to it.

Multicollinearity among predictors will be assessed using variance inflation factors, with appropriate mitigation strategies applied where necessary.

Mediator and Moderator Analyses

Mediator analysis will discern whether improvement in caregiver sensitivity mediates intervention effects on child outcomes. In addition, we will investigate whether improvements in parental sensitivity mediate advancements in reductions of parental stress. Mediation analyses will be conducted using the product-of-coefficients approach (a series of path models within the mixed-effects framework). CIs will be obtained using bootstrapping.

To assess moderation, interaction terms between the intervention and possible moderators will be included in the model. Subsequently, the significance of the interaction will be tested. In moderator analyses, we will also conduct a subgroup investigation to identify variations in the differential effectiveness of the intervention across subgroups. Subgroup analyses will be conducted with respect to the number of sessions attended, child sex, living standard, and the cognitive abilities of the caregiver.

Statistical Power

The required sample size was calculated according to accepted mathematical principles (48,49].

The sample size in each of the 3 arms of the study was computed using the following formula:

where α of .05 is the significance level, ...1–β (.80) is the power of the test, and $z_{1-\alpha/4}$ (2.24) and $z_{1-\beta}$ (0.84) are quantiles of the standard normal distribution. The significance level α of .05 is divided by 4—the number of comparisons performed while primary hypotheses are tested (in fact, this is the so-called Bonferroni correction). All tests have 1-sided alternatives. On the basis of the previous meta-analytic studies [52,53], power is guaranteed for the effect size of 0.5. Finally, *DE* is the so-called design effect. It takes into account the clustered nature of data and is computed using the following formula:

$$DE = 1 + ([cv2 + 1]m - 1)ICC$$

where the *m* value of 3 is the expected average cluster size, *ICC* is the intracluster correlation coefficient, and *cv* is the coefficient of variation of the cluster size. We set the *ICC* at 0.05—more than twice the commonly reported value of approximately 0.02 in comparable parenting studies. This higher value inflates the design effect and, in turn, the required sample size, providing a buffer that preserves statistical power. The value of cv^2=2/9 was used, corresponding to a discrete uniform distribution of cluster sizes from 1 to 5. This range reflects both the settlement layout and our clustering procedure, which aimed to retain as many eligible households as possible while keeping clusters compact (refer to the Eligibility, Recruitment, and Randomization section). Substituting these values into the formula mentioned earlier, one obtains a *DE* of 1.13.

Taking into account a potential attrition rate of up to 15%, the required sample size of each arm is 100. Observations with missing values of the outcome variable will be excluded from the analysis that deals with the given outcome but could still be included in other analyses. Missing values in covariates will be substituted by their regression estimates based on other covariates. The impact of the substitution will be discussed by comparing the current estimates with those obtained if the observations with missing values were excluded.

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Qualitative Data Analysis

Qualitative interviews and focus group recordings were transcribed verbatim and translated by a native Swahili speaker fluent in English. The transcriptions will be analyzed by applying thematic analysis. Deductive and inductive coding will be used to capture the variety of information in the data. The codes will then be grouped into themes, capturing the recurring patterns in the data. Some codes may become themes on their own. Consequently, the themes will be reviewed against the data corpus. The ATLAS.ti software (Lumivero) will be used for data organization and structuring through managing and visualizing the developed codes' and themes' system. More than one researcher will perform the data analysis and interpretation to provide depth to the process. The researchers will regularly discuss the coding scheme to ensure consistency and reliability.

Mixed Methods Data Integration

Qualitative data hold the potential to explain key outcomes of the quantitative analysis. To maximize the explanatory potential of our mixed methods study, we will (1) integrate quantitative and qualitative datasets in an interpretative joint display, (2) use the articulated ToC (Figure 1) as an integrative analytical framework, and (3) provide a narrative integration in the Discussion section. First, the joint display matrix will present quantitative findings alongside representative qualitative themes and illustrative quotes from interviews and focus groups. The matrix will also include a section for the interpretation of data, discussing possible convergence, divergence, or expansion of understanding emerging from integrating quantitative and qualitative datasets. Second, we will align the findings with our ToC components. Quantitative data will confirm or disprove the achievement of the expected outcomes presented in the ToC, while qualitative data will shed light on the reasons why and how these outcomes were or were not achieved and how the contextual factors shaped the intervention's impact. Integrating these findings will allow us to revise and refine the original ToC. Finally, the Discussion section will explore the intersection between our quantitative and qualitative findings, providing a comprehensive assessment of the intervention's outcomes and illuminating the mechanisms of change.

Results

The data collection for the EDBiT study was completed in September 2024. The research team proceeds with analyzing the data collected in the 3 rounds of data collection. The study results are expected to be published by late 2025.

Discussion

Principal Aims and Expected Contributions

The EDBiT trial addresses a critical evidence gap—whether DBS can enhance early language, socioemotional competence and caregiver behavior in resource-constrained, rural settings in sub-Saharan Africa. By comparing DBS with both a WLC group and an active PA control group, the study will isolate benefits specific to DBS rather than the generic advantages of increased parent-child interaction. Its mixed methods design, underpinned by an articulated ToC, will also illuminate how and for whom DBS works, thereby advancing implementation science for scalable parenting interventions.

Strengths and Limitations

Most RCTs of book sharing have been conducted in high-income or urban settings and have rarely included an active control group, leaving open the question of whether the gains stem from DBS itself or simply from extra parent-child time. EDBiT also helps close this gap by testing the intervention in rural Tanzania, where material resources are limited. In addition, this study's mixed methods approach brings quantitative impact estimates into dialogue with caregivers' lived experiences, generating implementation insights that purely quantitative trials often miss.

Nevertheless, inevitable field-trial constraints remain. The findings may not be readily generalizable to other locations or time points, and reliance on self-report for some caregiver outcomes could introduce social-desirability bias despite triangulation with observational data.

Future Directions

If DBS intervention proves effective, future work could explore delivery to other household members, such as older siblings and fathers. Digital adaptations might be tested where printed materials are scarce. In addition, future work might experiment with tailoring program content or dosing for distinct subgroups, for example, mothers with lower cognitive ability or those living in extreme poverty, to determine whether customized approaches enhance the interest of mothers and intervention impact.

Dissemination Plan

Findings will be shared with (1) local stakeholders in the Mbeya region of Tanzania through community forums and briefing sessions and (2) the global research community through presentations at international early-childhood conferences and open-access publications in peer-reviewed journals. Anonymized datasets will also be deposited in an open repository.

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Data Availability

The full checklist with its scoring rubric is available from the authors on request.

Authors' Contributions

M Schlossarek, EŠK, LM, and PJC contributed to the conceptualization of this study. M Schlossarek, EŠK, LM, PJC, OV, LD, MM, SŠ, JH, and M Syrovátka contributed to the preparation of the methodology. OV conducted a formal analysis. M Schlossarek and EŠK acquired funding for this study. EŠK, M Schlossarek, and OV drafted the manuscript. All authors critically reviewed, edited, and approved the final version of this manuscript.

Conflicts of Interest

None declared.

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Abbreviations

DBS: dialogic book-sharing
ECVT: Early Childhood Vigilance Task
EDBiT: Effects of a Dialogic Booksharing Intervention for Female Caregivers in Rural Tanzania
LMICs: low- and middle-income countries
PA: playful activity
RCT: randomized controlled trial
ToC: theory of change
WLC: waitlist control

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Protocol

Pay-It-Forward 23-Valent Pneumococcal Polysaccharide Vaccination Among Older Adults: Protocol for a Randomized Controlled Trial

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Abstract

Background: The 23-valent pneumococcal polysaccharide vaccine reduces the risk of pneumonia among adults by 38% to 46%. However, only a few older adults in resource-limited areas of China have received the pneumococcal vaccination. Pay-it-forward is a social innovation that offers participants free or subsidized health services and a community-engaged message, with an opportunity to donate to support subsequent recipients.

Objective: This study aims to assess the effectiveness and cost-effectiveness of the pay-it-forward intervention in encouraging the uptake of the 23-valent pneumococcal polysaccharide vaccine in adults aged ≥60 years.

Methods: A 2-arm, parallel randomized controlled trial will be conducted in 4 community health centers in Nanning city, Guangxi province, China. We will use a block randomization design. A total of 204 older adults will be randomly allocated in a 1:1 ratio to either the pay-it-forward group or the standard-of-care group. Each participant will complete a web-based questionnaire. The standard-of-care group will be required to pay for the vaccine themselves. In contrast, the pay-it-forward group will receive a 150 RMB (US $20.7) vaccination subsidy, postcards, and the opportunity to donate. The participants in both groups will be followed up in the second and fourth weeks after enrollment. The primary outcome will be uptake of the 23-valent pneumococcal polysaccharide vaccine, as determined by administrative data. Secondary outcomes include costs, pneumococcal vaccination knowledge, attitudes toward the vaccine, perceptions of gratitude, incidence of adverse reactions and adverse events, and the likelihood of recommending pneumococcal vaccination to others.

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Results: Participant recruitment and follow-up were conducted from January 2024 to September 2024. A total of 220 participants were enrolled. Finalized results are expected in June 2026.

Conclusions: This study will provide evidence on the effectiveness and economic costs of the pay-it-forward strategy for pneumonia vaccination among older adults. The findings could have implications for vaccination policy and offer a new approach for increasing vaccination in resource-limited areas.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2400079410; https://www.chictr.org.cn/showprojEN.html?proj=213999

International Registered Report Identifier (IRRID): DERR1-10.2196/70246

(JMIR Res Protoc 2025;14:e70246) doi:10.2196/70246

KEYWORDS

randomized controlled trial; 23-valent pneumococcal polysaccharide vaccine; pay-it-forward; older adults; China

Introduction

Background

Streptococcuspneumoniae poses a significant threat to global health, contributing substantially to morbidity and mortality [1,2]. Furthermore, it is recognized as the most prevalent bacterial agent that causes community-acquired pneumonia, a condition associated with increased morbidity, mortality, and economic burden, particularly among individuals aged >65 years [3,4]. Globally, pneumococcal complications were present in 90% of older adults (aged ≥65 years) from 2005 to 2014 [5], with *Spneumoniae*–associated lower respiratory infections responsible for 500,000 deaths (45.74% of global pneumococcal deaths) in those aged ≥70 years in 2016 [6]. The estimated incidence of community-acquired pneumonia among individuals aged ≥60 years in China was 34.68 per 1000 person - years in 2016 [7]. The in-hospital mortality rate for patients aged ≥65 years with community-acquired pneumonia from January to December 2014 was 5.7% [8]. The disease burden of influenza virus infections is equally severe as pneumonia among older adults. A population-based study demonstrated that adults aged 65 to 74 years experienced influenza-associated excess respiratory mortality rates ranging from 2.9 to 44 per 100,000, while those aged ≥75 years faced even higher rates, ranging from 17.9 to 223.5 per 100,000 [9]. Influenza viruses typically promote secondary pneumococcal infections [10], and their coinfection significantly increases the risk of hospitalization, serious illness, and death [11]. This underscores the need for pneumococcal and influenza vaccines to prevent community-acquired pneumonia and influenza.

The World Health Organization and the Chinese Center for Disease Control and Prevention recommend a 23-valent pneumococcal polysaccharide vaccine (PPSV-23) for adults aged ≥60 years [12]. The PPSV-23 has a 30.9% efficacy in preventing community-acquired pneumonia [13] and offers a 70% protective efficacy against invasive pneumococcal diseases [14]. Furthermore, the vaccine's protective benefits are known to be durable for up to 5 years [15]. Despite these advantages, the Chinese government has yet to incorporate PPSV-23 into its free routine immunization program for older adults. Consequently, pneumococcal vaccination remains an out-of-pocket service in China (PPSV-23: 220-280 RMB [US $30.4-$38.7] per dose), leading to suboptimal uptake rates among older adults. Only 1% to 42% of older adults in China have received the pneumococcal vaccine [16]. This low uptake of PPSV-23 in China can be attributed to various factors, including financial constraints [17], vaccine hesitancy [18], and poor understanding [19]. Given these challenges, it is imperative to devise and implement innovative strategies to increase PPSV-23 vaccination among older adults.

Pay-it-forward is a socially innovative intervention that promotes health care service use [20]. With pay-it-forward, individuals receive a gift, such as a free or subsidized health care service. They are then invited to donate money or create a postcard with an encouraging message to support subsequent health care service recipients [21]. This intervention may help alleviate financial barriers that hinder the uptake of the PPSV-23. This intervention strategy may also promote positive health outcomes by improving vaccine trust and confidence [22]. Our previous studies have suggested that pay-it-forward interventions significantly increased influenza vaccination among older adults [23] and improved human papillomavirus vaccination among adolescent girls aged 15 to 18 years [24].

However, existing research on pay-it-forward mainly focused on more high-income cities [23,25,26]. Furthermore, no research has focused on using pay-it-forward to promote pneumococcal vaccination. This underscores the importance of exploring pay-it-forward as a strategy to boost PPSV-23 vaccination in resource-limited areas.

Guangxi is recognized as one of the resource-limited provinces in China. In 2022, the per capita disposable income of households in 94 of 111 counties in Guangxi was lower than the national average (US $5091.7) [27,28]. The pay-it-forward intervention may present a potential solution to increase the PPSV-23 vaccination rate among older adults in Guangxi.

Aims and Hypotheses

This study will use a randomized controlled trial design with the primary objective of evaluating the effectiveness of the pay-it-forward intervention in promoting PPSV-23 vaccination in resource-limited settings. Through this research, we aim to compare vaccination uptake rates between the pay-it-forward and standard-of-care groups, and further assess the cost-effectiveness and per capita costs of both approaches. The findings will provide an innovative intervention model for improving pneumococcal vaccination among older adults in

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resource-ed-limited areas, offering critical evidence to inform government decisions on vaccine subsidy policies. Our hypotheses are as follows:

1. Pay-it-forward is superior to the standard-of-care in promoting pneumococcal vaccination.

2. The pay-it-forward intervention is associated with lower per capita costs of PPSV-23 vaccination.

Methods

Study Design and Setting

We will conduct a 2-arm, parallel randomized controlled trial among adults aged ≥60 years. Community health care centers (CHCs) will be the unit of randomization and intervention. We will recruit participants via vaccination clinics, WeChat (Tencent Technology Company Limited), and SMS text messaging. Participants will be randomly allocated to either the standard-of-care arm (self-payment for vaccinations) or the pay-it-forward arm (receiving a 150 RMB [US $20.7] subsidy for vaccination and opportunities for donation and handwritten postcards) in a 1:1 ratio through an envelope randomization mechanism, with blocks of 4 participants per group. Follow-ups are planned for the second and fourth weeks after enrollment of participants. At the end of the fourth-week follow-up, we will confirm the number of individuals vaccinated with the PPSV-23 in both groups through the vaccination information management system for the immunization program. Written informed consent will be obtained from each participant before enrollment. The CHCs are the central vaccination units for residents and have sufficient vaccine supplies and medical staff familiar with vaccination procedures, facilitating the recruitment of study participants. To ensure sample representativeness, we plan to conduct this study in Qingxiu district (high-income areas), Xixiangtang district (middle-income area), and Liangqing district (low-income area) in Nanning city, Guangxi province. All research assistants and community health care workers (CHWs) involved in this study will receive the same training. Figure 1 and Table 1 illustrate the study design and interventions.

Figure 1. Framework diagram of the study. PIF: pay-it-forward; PPSV-23: 23-valent pneumococcal polysaccharide vaccine.

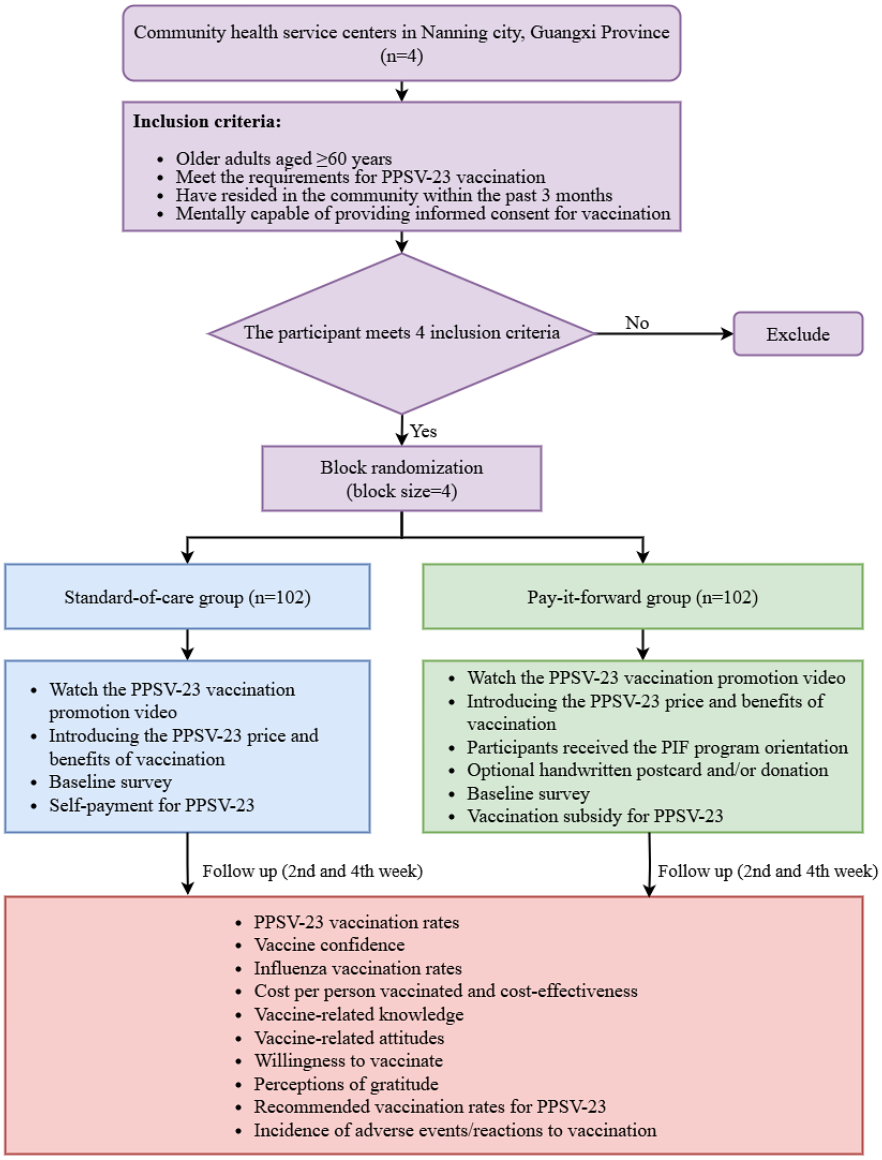

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Table 1. Schedule of events of the pay-it-forward for 23-valent pneumococcal polysaccharide vaccine (PPSV-23) study.

Event	Eligibility screening	Enrollment	Follow-up		Closeout
	Week 0	Week 0 (baseline)	Week 2	Week 4	Week 5
Recruitment and enrollment					
Vaccination platform screening	✓				
Phone or WeChat consultation	✓				
Recruitment poster		✓			
Intervention					
Pay-it-forward program leaflet		✓			
PPSV-23 vaccination leaflet		✓			
PPSV-23 promotional video		✓			
Informed consent		✓			
Group allocation		✓			
Donation		✓			
Handwritten postcard		✓			
Baseline questionnaire		✓			
Follow-up questionnaire			✓	✓	
Assessment					
PPSV-23 vaccination rate					✓
Vaccination attitudes					✓
Willingness to vaccinate					✓
Perceptions of gratitude					✓
Recommendation of PPSV-23 vaccination					✓
Incidence of adverse events or reactions to vaccination				✓	
Cost-effectiveness					

Public Involvement Framework and Participant Recruitment

The public will be involved in creating project materials, such as developing a video explaining the concept of pay-it-forward, co-designing postcards to promote PPSV-23 vaccination [23], and discussing how to describe the pay-it-forward intervention to the participants.

To achieve the target sample size within the planned recruitment period, we will adopt multiple proactive recruitment strategies. Eligible participants will be identified and approached through vaccination clinics at participating CHCs, where staff routinely engage with this population. In addition, digital outreach strategies will be used, including invitations via WeChat messages and SMS text messaging notifications sent through local public health networks. The CHC staff will be trained to provide clear, culturally appropriate explanations of the study's purpose and procedures to encourage participation. The intervention itself—including a 150 RMB (US $20.7) vaccination subsidy and the opportunity to write and receive handwritten postcards—is expected to enhance engagement and reduce financial and psychological barriers to participation. Recruitment progress will be monitored weekly by the coordinating research team. If enrollment falls behind schedule at any site, responsive strategies will include increasing outreach messaging, extending clinic hours, or deploying additional staff to support recruitment efforts.

Community Engagement

To determine the effectiveness of the PPSV-23 and the benefits of vaccination for community residents, we will cooperate with local CHCs. CHWs will participate in the design of the pneumonia leaflet, refinement of the questionnaire, development of communication strategies, and formulation of recommendations to enhance the engagement of older adults in this study. The participants will also be invited to write postcards for subsequent participants.

Participants

Eligible participants will be screened for participation in the program with the help of CHC health care workers. Inclusion criteria are as follows: (1) aged ≥60 years; (2) meeting the medical requirements for PPSV-23 vaccination; (3) residing in the community for the past 3 months; and (4) mentally capable of providing informed consent for vaccination. The participants will be excluded if they meet any of the following criteria: (1) older adults having severe chronic or psychiatric illnesses; (2)

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older adults having a clinically evaluated risk of allergy to PPSV-23; and (3) older adults having received PPSV-23 within the past 5 years.

Randomization

This study will use block randomization to ensure balance between the intervention and control groups (block size=4). First, random sequences will be generated by computer from random seeds using SPSS software (version 25.0; IBM Corp). Each set of 4 random numbers will be grouped as a block and numbered in the order of generation. Subsequently, the random numbers within each block will be arranged in ascending order. The 2 smallest numbers will be assigned to the standard-of-care arm, and the 2 largest will be assigned to the pay-it-forward arm. Afterward, the study designer will write the corresponding numbers on the surface of opaque envelopes, insert the intervention material and group assignment information, and seal them. The participants will receive the envelopes corresponding to their assigned numbers and proceed with participation in the study.

Blinding

Because both study researchers and participants are aware of the intervention allocation, achieving blinding poses a challenge. Nonetheless, several blinding techniques will be used to mitigate bias: (1) strict confidentiality regarding the generation and assignment of random numbers will be maintained among all the participants, research assistants, and CHWs, with only the study designer having access to this information; (2) the research assistants or CHWs responsible for allocating envelopes and interacting with participants will not be informed of the group information until the envelopes are opened; (3) the vaccine nurse will remain unaware of the grouping of participants; and (4) data analysts will be blinded of the intervention received by participants.

Intervention

Pay-It-Forward Group

The research assistants at the vaccination clinics will use the PPSV-23 vaccination leaflet (Multimedia Appendix 1) to introduce participants in the pay-it-forward group to *Spneumoniae*, the PPSV-23 vaccination, and its benefits. Subsequently, they will use the pay-it-forward program leaflet (Multimedia Appendix 2) to explain the purpose of the program, access to the PPSV-23 vaccination subsidy (US $20.7), and the opportunities to donate and write a postcard encouraging subsequent pay-it-forward recipients to receive the PPSV-23. The participants in this group will be informed of the standard cost of the PPSV-23 vaccination (US $29.5-$30) and the donations made by previous pay-it-forward recipients, as well as the handwritten postcards containing encouraging messages for the PPSV-23 vaccination. After watching the PPSV-23 promotional video, the participants will be surveyed by a research assistant using questionnaire A. They will be asked whether they are willing to be vaccinated and whether they are willing to make a donation or write a postcard with a message to encourage subsequent pay-it-forward recipients to become vaccinated with PPSV-23. The participants may donate at the vaccination clinics or online using their enrolled number (ie, the envelope number). They will also be informed that their decision to donate and the amount donated will not affect their eligibility for the vaccine subsidy and access to PPSV-23. The participants who are willing to be vaccinated will be evaluated for vaccination eligibility and scheduled for an appointment. The donations received will be used to support subsequent pay-it-forward recipients, and the amount and use of donations will be regularly updated on the official WeChat account. The CHWs will conduct follow-up surveys using questionnaire B and questionnaire C during the second and fourth weeks after enrollment. Each participant will receive 100 RMB (US $13.8) for completing the 3 surveys. The intervention fidelity will be monitored using a standardized fidelity checklist (Multimedia Appendix 3).

Standard-of-Care Group

The participants in this group will also receive the same PPSV-23 vaccination leaflet, a promotional video, and a questionnaire (not including questions on pay-it-forward) similar to that provided to the pay-it-forward group. They will also be informed of the standard cost of the PPSV-23 vaccination (US $29.5-$30). After watching the PPSV-23 promotional video, the participants will be surveyed by a research assistant using questionnaire A and informed that they will need to pay for the vaccination at the standard market price. Participants who are willing to be vaccinated will be assessed for eligibility and scheduled for an appointment for vaccination. The CHW will also follow up with the participants in the second and fourth weeks after enrollment. The participants will receive 100 RMB (US $13.8) for completing the 3 surveys. The participants in the standard-of-care arm will not receive any information about pay-it-forward.

Sample Size

The sample size was calculated using the PASS 2021 software after conducting a pilot trial. In the pilot trial, 88% (23/26) of the participants in the pay-it-forward group and 12% (3/26) of the participants in the standard-of-care group received the pneumonia vaccine. On the basis of the pilot trial results, we initially calculated the sample size to be 16. However, this sample size was determined to be too small to detect the desired effect size for the trial. To address this, we reviewed previous data on vaccination rates and estimated the expected difference in rates between the 2 groups based on prior experience. An earlier review indicated that the vaccination coverage of PPSV-23 among older adults in China ranged from approximately 1.23% to 42.10% [16]. Our previous pilot study showed that the pay-it-forward intervention increased influenza vaccination coverage in older adults by approximately 30% [23]. Considering these, we estimated a PPSV-23 vaccination coverage of 10% in older adults, and projected that the pay-it-forward intervention would increase this by 20%. The power of the test was set as 90% using a 2-sided test with a significance level of.05. The minimum sample size was calculated to be 158. After accounting for a 20% dropout rate, the minimum sample size required was adjusted to 198. The minimum sample size was further increased to 204 to accommodate the block-randomized design. Consequently, at least 204 participants were required for the trial.

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Data Collection and Management

When participants are enrolled, the research assistants will record their enrollment time, envelope number, name, identification number, and group. Data will be collected on the professional Chinese questionnaire website Wenjuanxing [29] using self-designed questionnaires, including the baseline questionnaire (questionnaire A) and the follow-up questionnaires (questionnaires B and C). The information collected is presented in Table 2.

Table 2. Summary of information to be collected.

Item	Questionnaire codes
Sociodemographics	A
Knowledge about PPSV-23[a]	A, B, and C
Dissemination of PPSV-23	A
Attitudes toward PPSV-23	A, B, and C
Gratitude (GQ-6[b] scale)	A, B, and C
Willingness and reasons for receiving the PPSV-23	A
Feasibility, appropriateness, and acceptability of pay-it-forward (only pay-it-forward group)	A
Reasons for promoting or discouraging donations (only pay-it-forward group)	B and C
Incidence of adverse reactions or adverse events	B and C
Recommendation of PPSV-23 to others	B and C

[a]PPSV-23: 23-valent pneumococcal polysaccharide vaccine.

[b]GQ-6: Gratitude Questionnaire—6-item scale.

We will collect the following information: (1) sociodemographic characteristics (eg, sex, marital status, education levels, monthly income, and employment); (2) knowledge of PPSV-23 (eg, age eligibility, reduced risk of hospitalization and death, and reduced medical costs owing to pneumonia); (3) attitudes toward PPSV-23, which will be evaluated using a standardized scale [30] to assess vaccination confidence among participants (eg, perceived safety, efficacy, and importance of the vaccine); (4) education and sensitization related to PPSV-23 (eg, recommendations from health care workers or friends); (5) tendency to show gratitude, which will be measured using the widely used Gratitude Questionnaire—6-item scale (GQ-6) [30]. (6) reasons for promoting or discouraging donations, which will be assessed among participants in the pay-it-forward group, along with the feasibility, appropriateness, and acceptability of the pay-it-forward interventions, using previously well-evaluated scales [31]. (7) incidence of adverse reactions (eg, fever, redness, swelling, pain, itching) or adverse events (eg, pneumonia, bronchitis, ear infections), which will be investigated for participants who receive vaccination; (8) reasons for declining vaccination, which will be collected from the participants who do not receive the vaccine; and (9) participants recommendations to others to receive PPSV-23.

The uptake of PPSV-23 will be verified using the immunization program's information management system. Separate questionnaires will be administered to participants in the standard-of-care and pay-it-forward groups. Quality control questions have been included to ensure the accuracy of questionnaire completion. Two similar questions will be included in different sections of the questionnaire to assess the consistency of responses: (1) Does vaccination with PPSV-23 reduce hospitalization and deaths? and (2) Vaccination with PPSV-23 reduces hospitalization and death. If participants respond differently to these 2 similar questions, the questionnaire will be considered invalid, and they will be asked to complete it again. Once participants are enrolled, personally identifiable information and survey data will be entered into an electronic Microsoft Excel form. The form will be password-protected by the study designer, and only the study designer and the researcher responsible for data analysis will have access to it. A data safety and oversight committee will be established, comprising 2 clinicians, an epidemiologist and statistician, and a representative of the medical ethics committee, who will operate independently of the research team. The data safety and oversight committee will review the process of the study, data collection, data management, and analysis. Each participant will be assisted by a CHW in completing the survey. For older adults who do not have a smartphone, the survey will be completed using an electronic device provided by the research program, and the CHW will guide them through the QR code scanning and submission process.

Outcome Measures

The primary outcome of this study will be the uptake of PPSV-23 in each arm, assessed 1 month after the intervention using administrative records. The secondary outcomes will include: (1) vaccine confidence, measured by 4 survey statements related to perceptions of the importance, safety, and efficacy of vaccination, as well as vaccine management; (2) influenza vaccination, defined as participants receiving the influenza vaccine after enrollment in the study, verified through administrative records, with the cost of the vaccination borne by the participants; (3) cost per person vaccinated and cost-effectiveness; (4) vaccine knowledge between the 2 groups; (5) attitudes toward vaccination; (6) willingness to vaccinate; (7) gratitude, measured by the GQ-6 scale; (8) the rate of successful vaccine referral, defined as participants successfully

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recommending PPSV-23 to others in the community after participating in the study; and (9) incidence of adverse events or reactions to vaccination.

Statistical Analysis

Primary Outcome

Descriptive analysis will be used to summarize the sociodemographic characteristics, knowledge, attitudes, and behaviors of the participants in each arm. Cronbach α will be used to test the reliability of the scales in the questionnaire. For the primary analysis, we will conduct intention-to-treat and per-protocol analyses, using logistic regression to compare the odds ratios of vaccination rates between the pay-it-forward group and the standard-of-care group, with adjustment for sociodemographic characteristics (eg, sex, age, and education level). In addition, we will perform logistic regression analyses stratified by income level, chronic disease status, living status, and distance to the vaccination site.

Secondary Outcomes

The economic evaluation will be conducted from a health care provider's perspective with a 1-year time horizon. Microcosting methods will be used to evaluate the implementation costs of both the standard-of-care and pay-it-forward intervention groups. Specifically, we will collect cost data, including personnel time, medical supplies, equipment use, and facility expenses. Material procurement costs will be calculated using primary sources, such as invoices, while project implementation costs will be based on researchers' self-reported data. Health care personnel's time costs will be estimated using the local government–published wage standards. A decision tree model will be developed using TreeAge Pro 2022 software (TreeAge Software, LLC), with vaccination uptake (defined as the number of vaccinated individuals per intervention arm) serving as the effectiveness measure for the pay-it-forward intervention. The intervention will be compared against standard-of-care (participants' self-paid PPSV-23 vaccination) to estimate incremental costs and incremental cost-effectiveness ratios. Model robustness will be assessed through 1-way sensitivity analyses and probabilistic sensitivity analysis. Influenza vaccination rates and vaccine confidence will be compared between the pay-it-forward intervention group and the standard-of-care group using logistic regression analyses, adjusted for sociodemographic information. Other secondary outcomes will be summarized using descriptive statistics and compared between the 2 arms.

Participants with missing primary outcome data (ie, vaccination status) will be reviewed. A complete case analysis will be performed if the proportion of missing primary outcome data is low (<5%). If the missing data exceed this threshold, multiple imputation methods will be applied under the assumption that the data are missing at random, to account for potential bias. Sensitivity analyses will also be conducted to assess the robustness of the findings under different assumptions about the missing data. To address missing follow-up data, we will use the last observation carried forward method or a multiple imputation method for missing values for categorical and continuous variables.

The results of all logistic regression analyses will be reported as crude odds ratios and adjusted odds ratios, along with 95% CIs. All statistical tests will be 2-sided, with a significance level of $P<.05$.

Ethical Considerations

The study was approved by the medical ethics committee of Guangxi Medical University (Ethics No. KY0261, 2023) in accordance with the Declaration of Helsinki. All participants will be required to provide written informed consent before participating in the study. Participants have the option to opt out at any time. All collected data will be anonymized and deidentified to ensure privacy and confidentiality protection. Informed consent covers secondary analysis without additional consent. Participants who complete all three questionnaires will receive compensation of 100 RMB (US $13.99).

Results

Participant recruitment took place from January 2024 to September 2024. We enrolled 220 participants. Final results are anticipated in June 2026.

Discussion

Expected Outcomes

The purpose of this study is to evaluate the effectiveness of a pay-it-forward intervention in promoting PPSV-23 vaccination among older adults aged ≥60 years. The results will inform the future development of pneumococcal vaccination interventions for older adults and contribute to the development of more cost-effective and sustainable public health policies.

The prevalence of pneumococcal diseases among older adults in China remains high, yet the coverage rate of PPSV-23 (ie, 1.23%-42.10%) [16] is significantly lower than that in high-income countries (52%-75%) [32-34]. Free pneumococcal vaccinations have been implemented for community residents in some high-income cities, such as Beijing, Shanghai, and Guangzhou [35]. However, in areas with limited health resources, the government faces challenges in providing free pneumococcal vaccines to community dwellers because of insufficient funding. Therefore, it is imperative to implement practical and feasible interventions to promote vaccination uptake. Previous studies have demonstrated the effectiveness of the pay-it-forward intervention targeting influenza vaccination or testing for gonorrhea and chlamydia in high-income areas of China [20,23]. However, the efficacy of this intervention in resource-limited regions has not yet been studied. This trial will be the first to assess the effectiveness of a pay-it-forward intervention in promoting the uptake of PPSV-23 for older adults in low-income areas in China. In addition, a self-designed questionnaire will be used to determine the differences in cost-effectiveness, knowledge, attitudes, willingness to vaccinate, and perceptions of gratitude between the pay-it-forward and standard-of-care groups. This study may provide insights into the development and optimization of pneumonia immunization strategies in regions with limited resources.

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We anticipate that this study will provide evidence supporting the feasibility of the "pay-it-forward" intervention in vaccine services and offer valuable insight for evidence-based practice in future vaccine programs. Currently, the PPSV-23 is not included in China's National Immunization Program, requiring individuals to bear the cost of vaccination, which limits the uptake of the PPSV-23 in resource-limited areas. The "pay-it-forward" approach may promote vaccination in these areas. In the absence of government funding for vaccination, the pay-it-forward model may effectively pool small donations to support more individuals in accessing pneumonia vaccine services, which is of significant importance for improving vaccination coverage in areas with relatively insufficient health resources. Moreover, the "pay-it-forward" strategy has demonstrated high cost-effectiveness in promoting influenza vaccination [36]. By evaluating cost-effectiveness, this study may inform decision-making regarding expansion strategies, enabling stakeholders to make informed resource allocation decisions.

Previous studies have shown that implementing free vaccination policies has enhanced the coverage of PPSV-23 [37,38]. However, implementing free vaccination strategies in low-income areas with limited health resources remains challenging. Prior randomized controlled trials have explored educational information interventions to increase vaccination uptake [39,40]. However, immediate improvements in knowledge and risk perception have not immediately led to changes in vaccination behavior. Vaccine price, vaccine accessibility, and vaccine confidence are additional factors influencing vaccination behavior. This study is the first to use a randomized controlled trial to evaluate the effectiveness of the pay-it-forward intervention for PPSV-23 vaccination. Through community engagement, vaccination subsidies, and public education, the intervention aims to enhance knowledge about the vaccine, bolster confidence in its safety and efficacy, attract financial contributions, and ultimately promote vaccination.

Strengths and Limitations

This study uses a randomized controlled trial to evaluate the effectiveness of the innovative pay-it-forward intervention in improving PPSV-23 vaccination rates among older adults, while comprehensively assessing its multidimensional impacts on vaccination-related cognition, behaviors, and economic outcomes. By validating this novel approach that integrates economic incentives with social mobilization, the findings will provide evidence-based insights for developing cost-effective vaccination promotion strategies, particularly facilitating the optimization of pneumococcal vaccination policies in low- and middle-income regions.

Some limitations exist in this study. First, the questionnaires rely on self-reports, which may introduce biases in specific responses. However, this should not impact the vaccination rate, as it will be verified through the vaccination information management system of CHCs. Second, the sample size for exploring factors associated with willingness to vaccinate is insufficient, and additional cross-sectional studies with rigorous sampling and a larger sample size are necessary to determine these factors. Third, conducting 2 follow-up surveys within a month may improve the participants' knowledge of vaccines to some extent, but it may not be sufficient to change their attitudes and behaviors toward the PPSV-23 quickly. Finally, there is a possibility of cross-contamination in this study. We implemented contamination control measures: (1) prohibiting the sharing of intervention details; (2) using group-specific materials and separate discussion spaces; and (3) applying both intention-to-treat and per-protocol analyses to assess potential contamination effects.

Future Directions

Future research should incorporate a free vaccination group to better isolate and quantify the specific effects of the pay-it-forward intervention. This innovative model is expected to facilitate the uptake of public health services, and additional implementation studies (eg, disease screening) could be conducted to assess its feasibility in different settings.

Dissemination Plan

The trial results will be disseminated to the study participants, health care professionals, public health authorities, and the scientific community. The findings will be published in peer-reviewed journals, presented at conferences, and reported in trial registries, such as the Chinese Clinical Trial Registry (ChiCTR). Briefings will be provided to participating CHCs, and lay summaries may be shared with the public via digital platforms (eg, WeChat).

Conclusions

In summary, this study aims to assess the effectiveness and cost-effectiveness of the "pay-it-forward" intervention in the vaccination with PPSV-23 among older adults. This innovative payment model may offer a new approach to enhance vaccination uptake in resource-limited regions, ensuring access to vaccination services, especially in settings with limited health care resources. In addition, the pay-it-forward strategy may act as a transitional step toward gradually shifting from individual payment-based vaccination policies to publicly funded ones.

Acknowledgments

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during this study. The datasets generated or analyzed during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

BL and JDT co-led the conception and design of this trial, and JDT and BL shared cocorresponding authorship. JQ, LW, and CT drafted the manuscript and participated in the study design. JH, ZL, and SQ participated in the design of the questionnaire. QS, TH, SC, and GW contributed to the recruitment of participants and data collection. DW, YG, CN, WT, HL, LY and XT contributed to the trial design and intervention evaluation. All authors contributed to editing the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Vaccination leaflet of 23-valent pneumococcal polysaccharide vaccine.
[PDF File (Adobe PDF File), 351 KB - resprot_v14i1e70246_app1.pdf]

Multimedia Appendix 2
Pay-it-forward program leaflet.
[PDF File (Adobe PDF File), 361 KB - resprot_v14i1e70246_app2.pdf]

Multimedia Appendix 3
Fidelity checklist of pay-it-forward intervention.
[DOCX File , 30 KB - resprot_v14i1e70246_app3.docx]

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Abbreviations

CHC: community health care center
CHW: community health care workers
GQ-6: Gratitude Questionnaire—6-item scale
PPSV-23: 23-valent pneumococcal polysaccharide vaccine

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Protocol

Evaluating the Effect of a Molecular Point-of-Care Test on Acute Respiratory Infections in General Practice: Protocol for a Cluster Randomized Trial

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Abstract

Background: Acute respiratory infections (ARIs) are frequent reasons for medical consultations in general practice and can lead to unnecessary recontacts. Introducing new point-of-care (POC) polymerase chain reaction (PCR) diagnostic equipment may offer an attractive and efficient way of providing a more precise and exact microbial diagnosis. Successful uptake of POC PCR equipment could potentially lead to a reduction in recontacts with benefits for both staff and patients. However, introducing new diagnostic technology is a complex intervention and several contextual factors may impact the implementation.

Objective: This study aims to evaluate the effect of POC PCR test availability in general practice on the subsequent (1) number of recontacts to the general practitioner (GP) for patients with symptoms of ARIs (primary outcome) and (2) hospital admissions, deaths, antibiotic prescriptions, health-related quality of life, GP and patient satisfaction, costs, cost-effectiveness, and contextual facilitators and barriers conditioning the implementation process (secondary outcomes).

Methods: This study is a cluster-randomized, crossover, nonblinded superiority trial with a 1:1 allocation ratio between usual care (control) and POC PCR test availability (intervention). Questionnaire data are collected at day 0, 7, 14, and 28 after the initial contact (health-related quality of life, absenteeism and presentism among patients, and patient satisfaction) and after finalization of the study period (GP satisfaction). Data on recontacts, hospital admissions, redeemed antibiotic prescriptions, costs, and deaths will be retrieved from the Danish national registries. The implementation process will be evaluated based on data from interviews with users of POC PCR tests (i.e., GPs, staff, and patients) and from observations in the clinics in line with Medical Research Council guidelines.

Results: As per the randomized crossover design carried out during September 2023 to March 2024 investigating a sample of 100 GP clinics, we expect to obtain an in-depth and multifaceted understanding of the effects of the availability of the POC PCR test equipment in general practice.

Conclusions: This study will provide valuable information about the diagnostic conditions and possibilities in general practice and provide insights into the organization of primary health care.

Trial Registration: ClinicalTrials.gov NCT06120153; https://clinicaltrials.gov/study/NCT06120153

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International Registered Report Identifier (IRRID): DERR1-10.2196/72842

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KEYWORDS

point-of-care; acute respiratory infections; general practice

Introduction

Acute Respiratory Infections, Recontacts, and Antibiotic Prescriptions

A very common reason for visiting Danish general practice is symptoms of acute respiratory infections (ARIs), and diagnostic accuracy is important to ensure appropriate treatment [1]. Danish general practitioners (GPs) handle approximately 98% of these cases without referring the patients to further diagnosis or treatment in hospitals [2]. It is important for the quality of care that patients are diagnosed as fast as possible, and that the GP and the patient are confident about the diagnostic accuracy. If not, the patient may be unnecessarily worried and contact health services again. Recontacting health services is sometimes appropriate, for example, if the patient's symptoms worsen. Unnecessary recontacts are, however, unsatisfactory to both the patient and the clinician as a high number of recontacts indicate diagnostic and treatment deficits and a lack of reassurance of the patient. In addition, recontacts and hospital admissions are costly for society. For these reasons, the study investigates the following research question: "Do patients with ARIs diagnosed in general practice with access to point-of-care (POC) polymerase chain reaction (PCR) equipment benefit in terms of reducing recontacts to general practice in a 1-week period after the initial contact?"

In addition to investigating recontacts as the primary outcome, the study also allows for insights into patterns related to antibiotic prescription. In Denmark, around 75% of all antibiotics are prescribed in general practice, and ARIs are some of the most common reasons for prescriptions [3,4]. Even though Denmark is among the countries with the lowest consumption of antibiotics worldwide, there is still room for improvement in the total use of antibiotics and in the choice of regime, that is, broad spectrum versus narrow spectrum antibiotics [5]. Antibiotic overuse may lead to microbial resistance, and if the overall consumption is not restrained, infections with resistant bacteria will be a major problem for both the individual patient and the health care system. Hence, initiatives to significantly reduce the prescription and use of antibiotics are highly warranted [6]. Whether symptoms arise from bacteria or from a viral infection is often uncertain in the primary care setting [7], and when precise diagnostics are desirable, it often takes 1 to 3 working days and requires sending test samples to external laboratories. Due to diagnostic uncertainty, GPs may in some situations prescribe antibiotics even in cases where the patient's symptoms are caused by a viral infection. Introducing POC PCR diagnostic equipment in general practice may improve diagnostic accuracy, and thereby reduce revisits as well as prescription and use of antibiotics.

Introducing practice changing diagnostic tools into primary care extends beyond the mere adoption of a new diagnostic technology; it is a complex intervention that involves significant interactions among health care professionals, technology, and the health care system itself. Complex interventions are characterized by multiple components that interact within their implementation context [8]. These include the behaviors of health care providers and patients, the environment in which the intervention is deployed, and the outcomes it aims to influence. The complexity of integrating, for example, POC PCR testing into daily practice is particularly evident in the multifaceted processes it entails, from conducting the test and interpreting its results to making informed clinical decisions and adapting the health care infrastructure to support its use.

The use of rapid PCR testing for respiratory tract infections has been extensively examined in hospital and emergency department settings [9]. The effects on clinical and resource related outcomes vary significantly between studies [10-12]. A recent systematic review and meta-analysis found no association between rapid PCR testing and antibiotics use, return visits, length of stay, or hospitalization among patients with ARI in emergency departments [13]. The clinical effects of POC PCR testing of patients with ARI in general practice have not been extensively examined. However, a feasibility study conducted during the COVID-19 pandemic showed promising results in terms of feasibility and clinical utility [14,15].

This paper describes a protocol for a cluster randomized controlled trial focusing on the effects of introducing POC PCR testing (Cobas LIAT) for ARIs in general practice in Denmark. To qualify the study protocol, 2 preparatory studies were conducted, demonstrating barriers and facilitators for introducing POC PCR technology in general practice, including user experiences from the clinicians [16,17].

Objectives

The study is organized in 3 work packages (WPs) with the following objectives.

WP1: Effectiveness of POC PCR Availability for ARI in GP Clinics

The following are objectives 1 to 6: to evaluate the effectiveness of POC PCR availability in general practice on (1) the number of recontacts to the GP for patients with symptoms of ARIs (primary outcome); (2) the number of redeemed antibiotic prescriptions, (3) health-related quality of life, and (4) GP and patient satisfaction. In addition, (5) the number of hospital admissions and (6) deaths are included as safety measures.

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WP2: Cost-Effectiveness Associated With POC PCR Availability in GP Clinics

The following are objectives 7 and 8: to evaluate (7) the costs and (8) the cost-effectiveness of POC PCR availability in general practice compared with usual care.

WP3: Process Evaluation of Introducing and Implementing POC PCR Availability in GP Clinics

The following is objective 9: to identify and analyze contextual facilitators and barriers as well as behavioral factors that influence potential uptake of the implementation process tied to the POC PCR equipment.

This study uses recontacts as a primary outcome of evaluating the effectiveness of the test, as this is a less-explored phenomenon associated with ARIs. Denmark is already one of the countries with the lowest consumption of antibiotics, which is why this measurement is also included in the study (as a secondary outcome in the analyses). While investigating patterns tied to antibiotic prescriptions are important, the scope of this study is to explore the wider operations of a general practice setting, which a primary but not isolated focus on recontacts allows.

Methods

Study Setting

The study is conducted in 4 Danish regions (Region of Southern Denmark, Region Zealand, North Denmark Region, and Central Region of Denmark), comprising a general population of approximately 4 million individuals and 2340 GPs [18].

In Denmark, GPs receive reimbursement from the administrative regions for all consultations and tests included in the collective agreement between the PLO and the regions. The role of the regions in this study is to create and administer project specific reimbursement codes that will enable calculations of the number of patients with ARIs and the number of POC PCR tests performed. All Danish GPs are accustomed to register reimbursement codes in their electronic patient record system after each consultation, and all codes are linked to the patient's personal identification number.

Recruitment and Eligibility Criteria

GP clinics are eligible for participation if they are situated in one of the participating regions and receive reimbursements from the administrative regions. GP clinics are invited by letters with written information about the project. The letters are sent from the clinical trial unit at the University of Southern Denmark (SDU), who also conducts follow-up phone calls and distributes additional material if requested by the clinic. Interested GP clinics will sign a collaboration agreement with SDU and receive additional information. Patients are eligible for participation if they contact a participating GP clinic with symptoms of ARI during the study period. All clinics and patients taking part in the effect study and the economic evaluation (WP1 and WP2) will receive information about the project and data collection according to the Danish Data Protection Act Section 10. Specifically, as the studies of WP1 and WP2 are conducted on register data, no patients will be identifiable, and thus, no consent is needed. The qualitative process evaluation (WP3) necessitates oral and written information, and all patients are asked to sign an informed consent form. All participation is voluntary, and every patient and professional is informed that they can revoke their consent at any point should they regret their participation.

Allocation

The study is designed as a cluster randomized crossover study with the GP clinic as the unit of randomization, that is, all GPs affiliated to a GP clinic are randomized to either intervention (A) in the first period and usual care (B) in the second (AB sequence) or in the BA sequence. Allocation of the general practice clinic is randomized using a computer algorithm and allocation is 1:1 between the AB or BA sequence. When an eligible clinic commits to the trial, the project statistician informs the project management about the next allocation in the allocation sequence and the clinic is randomized according to this, that is, blinded randomization allocation is used.

Randomization at the patient level is not considered feasible, as an ongoing randomization procedure in the clinic would be time consuming and pose a risk of bias and interference with the diagnostic procedure and subsequent decision-making by the GP.

Therefore, randomization is stratified by type of clinic, that is, partnership- or single-physician clinics. Large collaborative clinics are randomized as one unit in the group of non–single-physician clinics. A block randomization in blocks of 10 is used.

Intervention

Pretrial Information and Training

The study will be conducted over a period of 25 weeks (Figure 1).

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Figure 1. Illustrates the phases in the randomized controlled trial's control and intervention periods as well as the washout period. In the washout period, Roche removes, cleans, and reinstalls the equipment from the intervention group, so it is ready for the control group for the final phase of the trial.

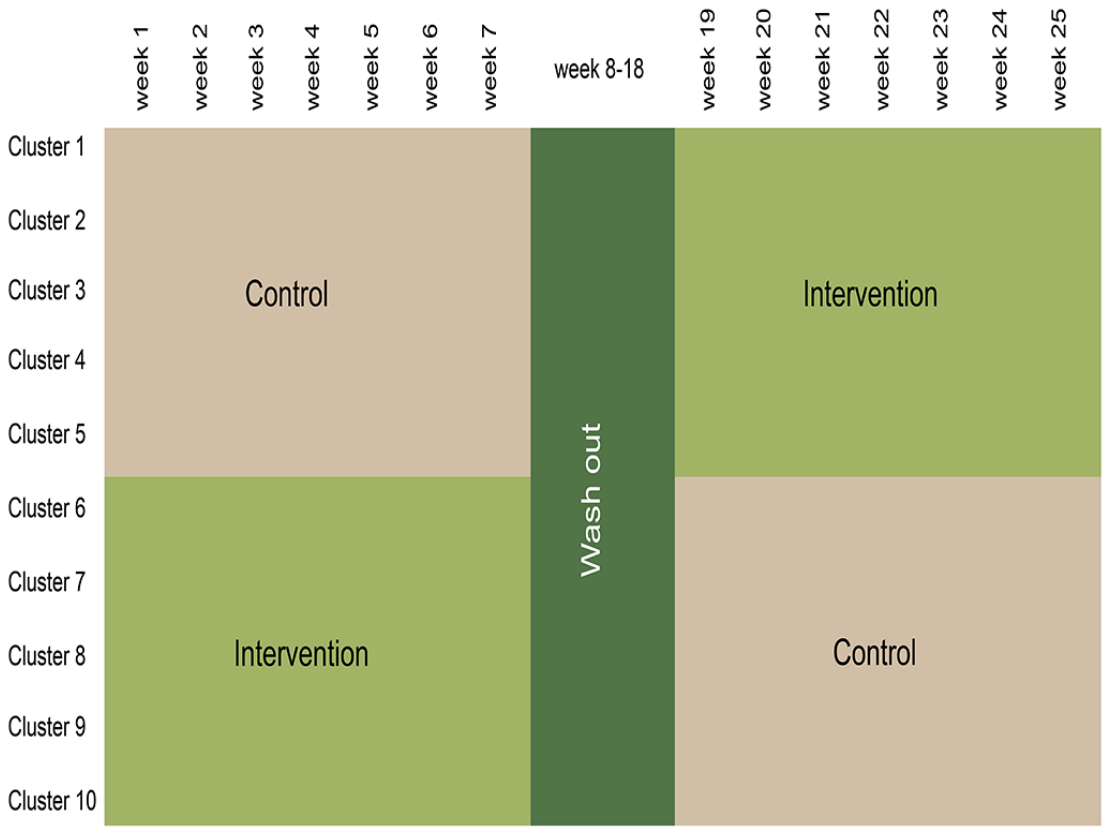

In the month leading up to the intervention period, the POC PCR device will be installed in the intervention clinics by staff from Roche Diagnostics A/S, and assays and equipment necessary for the testing will be sent to the clinics free of charge. Just before entering the trial period, each clinic will be trained by staff from the clinical trial unit from SDU. During the training session, the clinic will receive further information about patient inclusion, registration of eligible patients in the reimbursement system, and whether the clinic is about to enter an intervention period, including training on how to perform the POC PCR tests. In addition, all clinics will receive an information poster for patients to display in the waiting area. All GP clinics will receive a fee of DKK 6000 (approximately €800 or US $840; 1DKK= US $0.14) for participating in the study. In addition, GPs will be remunerated for performing the test (DKK 71.48 [approximately €9.50 or US $10] per test equivalent to already established POC tests). The clinics participating in the process evaluation will receive another DKK 1000 per interview (approximately €134), and DKK 2000 (approximately €268 or US $280) per whole day during observation studies.

An overview of the pretrial activities is presented in Textbox 1.

Textbox 1. Pretrial instructions and training during intervention and control periods.

Intervention period

1. Introductory instructions about the trial are provided for the clinics (how to include and register patients with acute respiratory infection [ARI])
2. Training in the use of Cobas LIAT respiratory testing portfolio (group A Strep, Influenza A/B, SARS-CoV-2, and respiratory syncytial virus)
3. Instruction to include all patients contacting the clinic with symptoms of ARI during a 7-wk period and possible point-of-care testing, if deemed relevant

Control period

1. Introductory instructions about the trial are provided to the clinics (how to include and register patients with ARI)
2. Instruction to include all patients contacting the clinic with symptoms of ARIs during a 7-wk period for treatment as usual.

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Activities During the Study Period

All patients with ARI contacting the participating GP clinics during the intervention or control period will be included in the study. Before or after the consultation with the GP, the clinic staff will hand out information materials about the project, including a leaflet with a QR code and a link to a questionnaire.

In the control period, patients with ARI will receive usual care, usually comprising no or limited diagnostic tests at the clinic, or nasal or pharyngeal swap for testing at an external laboratory with an expected response time of 1 to 3 days. During the intervention period, the POC PCR equipment will be used when the GP deems it relevant.

Developed by Roche Diagnostics A/S, the POC PCR test system tested in this study comprises an analysis instrument and assay tubes for testing (1) StrepA, (2) Sars-Cov-2 and Influenza, and (3) Influenza or respiratory syncytial virus (RSV). The test is performed on oropharyngeal (StrepA), nasopharyngeal (SARS-Cov-2 or Influenza, and Influenza or RSV), or nasal (Influenza or RSV) swap samples. Running the test takes approximately 20 minutes per assay.

After the consultation, the GP registers the project specific reimbursement codes in the electronic patients record system. Three different reimbursement codes are used: the first code is for the registration of each individual patient with ARI contacting the clinic. This code is used in both control and intervention periods. The second code is for each time the POC PCR test is performed (allowed only once per patient per consultation even though it is possible to perform multiple tests within the same consultation), and the third code is for situations where the test result is conveyed by phone or email to the patient the day after the test is performed. The last two codes are for intervention periods only. GPs are only remunerated for performing the test.

Statistical Analysis and Sample Size Calculations

Sample Size Calculation

Outcomes are on the individual patient level, and the clustering involves the entire GP clinic, not the individual GP. A balanced design with a common total cluster size and common period effect was adopted. As the study is a superiority trial, results from the feasibility study [16] and Danish national register data will inform the choice of parameters as inputs to the sample size formula derived by Li et al [19]. The intended effect size was fixed at a reduction from 0.32 to 0.28 based on the register results, which approximately corresponds to the distance between the median or mean to the 25th percentile. With a significance level of 0.05, power at 0.8, within-period within-cluster correlation of 0.02, and across-period within-cluster correlation as 0.01 to detect a difference between a prevalence of 0.32 recontacts in the control group and 0.28 in the intervention group, the sample size was calculated as 108 clinics, contributing 50 contacts each in the trial period. Pragmatically, the inclusion of 100 clinics was chosen.

Blinding (Masking)

Due to the intervention procedure (an oropharyngeal, nasopharyngeal, or nasal swab) and the use of project specific reimbursement codes, it is not possible to blind the patients and GPs.

Outcomes

The primary outcome is modeled as group difference in number of patients with ARI recontacting the GP from the date of the initial contact (day 0) and the following 7 days in the intervention and control periods [19]. Secondary outcomes include safety outcomes such as group difference in the total number of redeemed antibiotic prescriptions (day 0 and following 7 days), the total number of hospital admissions, and deaths (from the date of the initial contact [day 0] and following 14 days) and total treatment costs, productivity costs, quality-adjusted life years, and incremental cost-effectiveness or utility ratio (from day 0-28) [14]. In addition, patient (day 0) and GP satisfaction (after the end of trial) is evaluated along with patients' health-related quality of life (day 7, 14, and 28). Furthermore, the study elucidates several aspects and factors based on the process evaluations' qualitative design, which allows us to assess the quantitative outcomes. Where the quantitative outcomes emphasize measured effects, the qualitative design allows insight into, for instance, the participants' perceptions of diagnostic practices in the clinic, the emergence and coordination of behavior, experiences, and interactions with the device, and thus explains how people use and perceive the device the way they do [16]. Multimedia Appendix 1 describes the different outcomes and points of interest including information on the specific measure, metric, applied instrument, time period, data source, and target population in a table overview.

Data Collection

A Triangulated Design

The evaluation is based on both quantitative and qualitative methods. Quantitative data will be collected from national administrative registries and via web-based questionnaires; qualitative data will be collected via interviews and observations, including video observation (see details in subsequent sections).

Questionnaire Data

The GPs or staff will distribute a leaflet with a QR code (and a link) to a web-based survey to all patients with ARI aged ≥15 years. For patients aged <15 years, the caregiver will be asked to answer the questionnaire. In the first questionnaire, the personal identification number and contact information will be collected, and the subsequent questionnaires will be distributed via a link in email and SMS text message at day 7, 14, and 28. In case of nonresponse, reminders will be sent within 2 days. Participants who complete all 4 questionnaires will be entered into a lottery for 1 gift card of Dkr 1000 for completing the first questionnaire and 1 gift card of Dkr 2500 for completing all 4 questionnaires. Questionnaires will be managed via a secure electronic questionnaire system (SurveyXact). Each questionnaire will take approximately 5 to 10 minutes to complete. Furthermore, a questionnaire will be sent to all participating GP clinics at the end of the trial followed by a reminder after 2 weeks in case of no response. The questionnaire will take approximately 5 minutes to complete. In it, the GPs will be asked about their overall experience of the equipment

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associated with (1) support for performing precise diagnostics, (2) support for clinical judgment, (3) the influence of the test results related to clinical management of patients, (4) the influence of the test results in patient communication concerning their condition, (5) disruption of consultation, (6) disruption in overall workflow, and (7) whether the equipment belongs in general practice. In addition, there is space for the GPs to write comments.

Register Data

Comprehensive public register data on contacts and services provided in primary care, prescription of antibiotics, and hospital contacts and various characteristics of the GP clinics will be retrieved from the Danish Health Data Authority [20]. Furthermore, information on morbidity, socioeconomic status, and various demographic characteristics on each patient will be obtained from Statistics Denmark [21]. Data from the different registers are linked by the patients' personal identification number. No data will be retrieved from the registers until the protocol paper is accepted for publication.

Qualitative Data

Qualitative data will be collected through an ethnographic fieldwork, which includes several key components. First, 10 pre- and postintervention interviews will be conducted with GPs and staff across 11 clinics. In addition, participant observations will take place in 5 clinics both before and during the intervention along with video observations in 3 out of the 5 clinics. Furthermore, 14 patient interviews will be held after the intervention.

Interviews with health professionals will focus on value assessments and sense-making processes tied to their experience with diagnostic technologies in general and the POC PCR equipment specifically. Participant observation will be conducted (with and without video-recorded participation) to obtain in-depth knowledge about everyday working life; organizational and communicative behavior; and interactions between health professionals, staff, and patients with (and without) the POC PCR equipment in the GP clinic. Finally, patient interviews will focus on their experience with use of the POC PCR equipment, feelings of diagnostic certainty, and reflections concerning the perceived impact of the POC PCR test on relational and communicative processes.

Data Management

Questionnaire data will be collected by SurveyXact and stored on secure servers at University of Southern Denmark. After data cleaning, questionnaire data will be transferred to secure scientific servers at Statistics Denmark and linked to register data via the personal identification number, after which all data will be pseudonymized.

Qualitative data will be collected by means of digital recorders during interviews, by field notes during observations, and using a GoPro video camera (handheld by the researcher) during video observation. After collecting data, they will be stored on secure servers provided by SDU. NVivo software (QSR International) will be used for transcriptions and analytical purposes.

After publication of the study, the data manager will ensure that all study data are deleted.

Data Analysis

Effectiveness of GP Access to POC PCR

Demographic characteristics of the included patients and GP clinics will be presented. Analysis of the binary primary outcome uses a standard logistic regression model on the individual (contact) level, accounting for clustering of patients in clinics by generalized estimating equations. Primary analysis will follow an intention-to-treat approach, and we want to show superiority. A corresponding analysis strategy will be applied for hospital admissions, deaths, and redeemed antibiotic prescriptions. A level of 5% will be set as statistically significant. Analyses will be performed with the most recent version of Stata (StataCorp).

Within-Trial Cost-Effectiveness

The cost-effectiveness analyses will take both a national health care perspective and, separately for the purpose of sensitivity analysis, a limited restricted societal perspective, including health care costs, patient costs (travel cost), and productivity costs for patients or their caregiver (in case the patient is a child aged <15 y). Cost-effectiveness will be reported in terms of the incremental cost-effectiveness ratio (ICER) expressed as the difference in costs divided by the difference in outcome, between patients in the intervention and control groups. Costs will be estimated from the time of initial contact (day 0) and over a follow-up period of 28 days and calculated by category. Due to the short duration of the study, costs and outcomes will not be discounted. Costs will be expressed in Euros, in 2024 conversion rates. Effect will be measured as the total number of recontacts within 7 days and quality-adjusted life years within 28 days. Quality-adjusted life years are calculated as the area under the utility curve for each patient based on patients' health-related quality of life measured by EQ-5D-5L for patients aged >15 years (in Denmark, individuals become responsible for managing their own health care at the age of 15, therefore not a requiring parental intermediary or proxy completion of the EuroQoL 5-Dimension) and valued using Danish value sets [22,23]. Missing costs or quality-of-life data will be handled by multiple imputations. Differences in mean costs and effect will be estimated using separate generalized linear regression models, with appropriate distribution and link functions for costs and outcomes. The models will control for treatment, time point, treatment-by-period interaction as fixed effects, and cluster at the GP level as a random effect. Furthermore, the models will adjust for baseline health care cost (6 months before the initial contact) and baseline utility [24]. Nonparametric confidence intervals for costs, effect, and ICER will be computed using a 2-stage bootstrapping technique with 1000 replications [25] and the 2.5th and the 97.5th percentile of the 1000 bootstrap replications. Conventional methods for estimating uncertainty around the ICER, such as cost-effectiveness acceptability curves, will be applied as well. Sensitivity analyses will be conducted to test assumptions, uncertainty around variable estimates, and the robustness of results.

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Qualitative Process Evaluation of Introducing and Implementing POC PCR in GP Clinics

All qualitative analyses will be analyzed using the reflexive thematic analysis by Braun and Clarke [26]. Following this approach, the transcripts will be initially read and reread, with participants taking notes along the way using the annotations feature in CASDAQ software NVivo (version 14; QSR International). Afterward, still using NVivo, the data will be coded inductively. Codes are then grouped into themes and subthemes that capture, on a general level, the identified factors promoting and impeding potential users' use of the POC PCR equipment.

Specifically, preintervention interviews with GPs and staff focus on the organization of the clinic and everyday experiences in the clinic as well as expectations regarding the upcoming intervention, diagnostic processes, and technology.

Postintervention interviews with GPs and staff focus on experiences of the usefulness, effect, and meaningfulness of the POC PCR test during the intervention.

Interviews with patients focus on the participants' experience with their symptoms, diagnosis, treatment, and use of health technologies for diagnostic purposes and also on their reflections concerning the perceived impact of the POC PCR test on relational and communicative processes (eg, whether the test enhances feelings of trust, of being taken seriously, and of reassurance). Participants accompanying a child aged <15 years will be interviewed relative to their considerations and experiences associated with the experience of being in the consultation with the child.

Analysis of the preintervention video observation data will focus on the learning processes in connection with training sessions and characteristics of standard practices in the clinic relating to patients with ARI. Analysis of video observation data collected during intervention will focus on how usefulness and potential implementation barriers and facilitators play out during the everyday working life of GPs and staff.

Ethics and Dissemination

Research Ethics Approval

As the project entails an evaluation study of an already CE-certified diagnostic tool, approval from the Danish Medicine Agency and the Scientific Committees of Medical Ethics (from Danish: De Videnskabsetiske Medicinske Komiteer) has been waived. The study has been assessed and approved by Local Ethics Committee at University of Southern Denmark (case number 23/1584) and University of Southern Denmark's Research and Innovation Organization (SDU RIO; journal number: 11.907).

In addition, the project has been registered on ClinicalTrials.gov (NCT06120153).

Consent or Assent

Informed consent is not required for collection of questionnaires and register-based data according to the Danish Data Protection Act Section 10. For the interviews and observations, written and oral consent is obtained from the GP or staff before video observation in the clinic. When a patient arrives for consultation, oral and written information about the project is given and consent for observation is obtained. Only if the patient consents, the consultation is observed and recorded. After observation, the researcher asks the patient for permission to a follow-up interview. The patient is provided a copy of the consent form and written information about the project, General Data Protection Regulation, and contact information for the project team.

None of the questionnaires or planned interviews contain psychological trigger questions nor is the intervention expected to give rise to any unwanted effects, as the POC PCR equipment used applied is a CE-certified diagnostic tool already in clinical use in other settings. Whether the POC PCR test is used by the health professional is entirely up to the individual to decide. Whether the GPs or patients choose to participate in the project does not have any influence on their treatment, and it is completely voluntary to fill out questionnaires or participate in interview- and observation studies.

Confidentiality

Data from interviews and observations will be stored at a secure server provided by SDU. Personal information (names, cities, and other locations) will be pseudonymized during the stages of transcribing the data and rewriting the field notes. For the purpose of scientific publications, screenshots from video recordings will be deidentified as sketches, as drawings, or with blurred features.

Access to Data

In line with the collaboration agreement signed between SDU and Roche Diagnostics A/S, only researchers and project team members from SDU have access to the data.

Dissemination Policy

In accordance with the contractual agreement signed by SDU and Roche Diagnostics A/S, SDU can present and publish data and results from the project regardless of the outcome in concordance with Danish law. Full disclosure is given to Roche Diagnostics A/S related to the sponsor's supporting role in the project in all written and oral presentations. Roche Diagnostics A/S has the right to review and offer comments for written or oral presentations as well as the right to intervene if any confidential information provided by Roche Diagnostics A/S is made public. Around 30 days before submission for publication, Roche Diagnostics A/S must receive the material intended for publication or public presentation for review. However, it is SDU's right to decide whether any comments or inputs from Roche Diagnostics A/S will be included in the publications. Roche Diagnostics A/S is allowed to use publications or abstracts from the project when reference is made to the author or authors in accordance with applicable law, and only after such publications have been made publicly available.

Results

As per the randomized crossover design carried out during September 2023 to March 2024 investigating a sample of 100

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GP clinics, it is expected to get in-depth and multifaceted understanding of the effects of the availability of the POC PCR test equipment in general practice.

Specifically, in terms of effectiveness, costs, and how organizational and experiential factors may work as barriers and facilitators in the uptake of the intervention in the clinic, both quantitative generalizable results and qualitative explanations of contextual conditions are expected.

Discussion

Principal Findings

Swift and precise diagnosis of ARIs in general practice is of great importance for obtaining appropriate health care use and use of antibiotics as well as both patient and GP satisfaction. This cluster randomized clinical trial is designed to explore the effects of availability of POC PCR in general practice. However, the pragmatic design comes with certain limitations.

Strengths and Limitations

First, there is limited possibility to ensure that the patient receives the postcard and fills out the questionnaire, which may hamper studying the patients' quality of life and satisfaction. Second, the quality of the quantitative data is highly dependent on GPs applying the project specific reimbursements codes to all relevant patients. As coding after each patient contact is everyday routine for Danish GPs, the coding practice itself is not a new task for the participating clinics. However, coding difficulties associated with the new reimbursement codes cannot be ruled out, which may in turn lead to a slight underreporting. Finally, while the POC PCR test equipment allows for conducting 5 ARI tests, the current test portfolio does not allow testing for, for example, pertussis and mycoplasma. As such, it could influence both the professional and patient experience and perception of what is considered quality and precise diagnostics and, by the mere introduction of increased testing that the POC PCR equipment promotes, the introduction of more testing could lead to an overemphasis of testing for the sake of testing. Moreover, it takes 20 minutes to run a test and a consultation in a Danish general practice usually is reimbursed for only 10 minutes. This practical factor may also influence the uptake of the intervention and the experience of the usefulness of the technology, it may even create additional workload in the clinic.

Despite the possible limitations, the described project will explore the potential effects of use of the POC diagnostic equipment in general practice. A major strength of the study is the study design, mirroring real-world practice, where clinicians themselves are in charge of deciding which diagnostic approaches are warranted, rather than forcing clinicians to use tools that they do not deem relevant. Furthermore, including clinics of different sizes across the country ensures a variety of clinics in the sample, which also reflects real-world circumstances. Another strength of this study is the use of register data, which provides unambiguous linkage of trial participants to high-quality, nation-wide registers. These registers allow analyses of both socioeconomic data and data from the health care systems in the secondary care setting. Moreover, the triangulated design of the qualitative process evaluation that combines interviews with observations of health professional and patient behavior in the natural setting of the clinics allows for the attainment of in-depth knowledge of how the intervention works in practice, how the professionals may perform workarounds, and how it can be adjusted around daily life. In addition, insights into how they reflect on their own actions and what they deem and perceive as barriers and facilitators for the possible implementation of the new technology in the future is obtained. While it can be expected to be an added workload to manage the discrepancies of the test's running time versus time for consultations, it is not uncommon that the GP finds tools meaningful as they are embedded in practice, if the gain from using it adds an overall value. Furthermore, patient interviews will illuminate the patients' needs, expectations, and experiences of diagnostic practices, technology, and the patients' relations to the clinic and staff, which allows for understanding and explaining reconsulting behavior and more.

Conclusions

In conclusion, the study gives the possibility to explore the potential effect of not only the availability of the POC PCR equipment tied to recontacts (WP1) but also the economic consequences (WP2) and the organizational factors as well as professional and patient-related experiences tied to the implementation of the diagnostic equipment (WP3).

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They would also like to thank the participating clinics and patients for dedicating time and resources to participate in the study and for allowing researchers to get insights into the needs and experiences of working with POC technology.

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Roche Diagnostics A/S provided materials and equipment for the study.

Authors' Contributions

KB, LMS, LPK, TT, SW, JH, LS, JBN, GO, EAH, DEJ, TLR, and JS were responsible for conceptualization. KB, LMS, LPK, TT, SW, and JS were responsible for data curation. KB, LMS, LPK, TT, SW, JH, LS, JBN, GO, EAH, DEJ, and JS were responsible for formal analysis. KB, LPK, TT, SW, JH, LS, JBN, GO, EAH, DEJ, and JS were responsible for funding acquisition. KB, LMS, LPK, TT, SW, TLR, and JS were responsible for investigation. KB, LMS, LPK, TT, SW, JH, LS, JBN, GO, EAH, DEJ, TLR, and JS were responsible for methodology. KB, LMS, TT, SW, JH, JBN, TLR, and JS were responsible for project administration.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Study objectives and their associated measurements, specific metrics, possible use of instruments, data collection period, evaluation points, data sources, and target groups.
[DOCX File , 54 KB - resprot_v14i1e72842_app1.docx]

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Abbreviations

ARI: acute respiratory infection
GP: general practitioner
ICER: incremental cost-effectiveness ratio
PCR: polymerase chain reaction
POC: point-of-care
RSV: respiratory syncytial virus
WP: work packages

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Protocol

Strong Families Start at Home/Familias Fuertes Comienzan en Casa—Improving Child Diet Quality and Parental Feeding Practices: Protocol for a Randomized Controlled Trial

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Abstract

Background: Children in the United States have poor diet quality, increasing their risk for chronic disease burden later in life. Caregivers' feeding behaviors are a critical factor in shaping lifelong dietary habits. The Strong Families Start at Home/Familias Fuertes Comienzan en Casa (SFSH) was a 6-month, home-based, pilot randomized-controlled feasibility trial that aimed to improve the diet quality of 2-5-year-old children and promote positive parental feeding practices among a predominantly Hispanic/Latine sample. The pilot saw significant improvements in children's Healthy Eating Index-2015 total and whole fruit scores, as well as multiple food parenting practices, and it was received well by participants.

Objective: Building on the success of the pilot study, this protocol paper describes the modifications, study design, and procedures for a fully powered randomized controlled trial.

Methods: Caregiver-child dyads are randomized to a "healthy eating" intervention group or a "reading readiness" attention control group. In the intervention group, a trained community health worker conducts monthly home visits or phone calls for 6 months that focus on age-appropriate nutrition recommendations and food parenting practices. There are three home visits that include tailored nutrition education materials that address their child's appetitive traits and eating habits, an interactive cooking activity, and a review of a family meal video with feedback. Community health workers use motivational interviewing and goal setting, which are key components of the program. The control group is similarly structured, with content focusing on reading and language development. Caregivers complete in-person and over-the-phone baseline and 6-month follow-up measurements to capture diet quality (primary outcomes: Healthy Eating Index-2015 scores via two 24-h dietary recalls and dermal carotenoids) and selected parental feeding practices and availability of healthy foods in the home (secondary outcomes).

Results: This protocol was approved by the Brown University institutional review board (protocol number 2022003389). As of March 2025, a total of 81 participants were randomized. Of these, 29 participants completed the study, and 8 participants withdrew. Recruitment will continue until 257 participants have been randomized. Data analysis is expected to conclude in 2028.

Conclusions: Findings will determine the efficacy of the intervention to improve child diet quality and parental feeding practices, which will ultimately inform future effectiveness and the real-world of home-based food parenting programs.

Trial Registration: ClinicalTrials.gov NCT06099288; https://clinicaltrials.gov/study/NCT06099288

International Registered Report Identifier (IRRID): DERR1-10.2196/73923

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KEYWORDS

Hispanic or Latino; child; diet quality; feeding practices; feeding behavior; randomized controlled trial; motivational interviewing

Introduction

Dietary behaviors across the lifespan affect the risk of developing cardiovascular disease, type II diabetes, certain cancers, and Alzheimer disease, among other prominent chronic diseases [1-3]. Of these conditions, Hispanic/Latine adults who reside in the United States are disproportionately impacted by type II diabetes, hypertension, and end-stage renal disease compared to White adults, but they have poorer access to health care services [4,5]. Early childhood is a critical period for establishing a foundation for healthy dietary patterns that promote long-term quality of life and well-being [6-13]. However, the average diet quality among children in the United States is suboptimal [14,15], with notable disparities across racial and ethnic groups, as well as varying socioeconomic statuses [16,17]. Young Hispanic/Latine children in particular consume fewer fruits and vegetables and more frequently drink sugar-sweetened beverages than White children [18]. While broader policies and environmental factors influence children's dietary patterns and behaviors, the home—where children spend much of their time—offers a unique opportunity for targeted, culturally relevant interventions to promote healthy eating habits.

Food parenting practices play a significant role in shaping children's dietary intake and long-term eating behaviors. Current recommendations that promote the use of structured and autonomy supportive parenting practices, such as role modeling healthy eating, providing consistent access to nutritious food, establishing mealtime routines, and autonomy support, are strongly associated with improved dietary outcomes and child appetite regulation [19-22]. For example, a systematic review showed that parental role modeling positively influences children's fruit and vegetable consumption, as children learn by observing their caregivers' eating behaviors [23]. Specific to food availability, increased availability of fruits and vegetables in the home environment leads to higher consumption of these foods by children [24]. Finally, studies emphasize that autonomy-supportive practices, which include encouraging independence and healthy eating through strategies like praise, nutrition education, and reasoning, encourage children to try new foods, willingness to adopt healthy eating habits, and variety in dietary intake [25].

Conversely, the use of coercive controlling practices that dominate a child's behavior is discouraged due to their potential to negatively influence children's relationship with food. Practices such as using food as a reward or punishment, imposing food restriction, or engaging in emotional feeding have been linked to maladaptive eating behaviors, including overeating or aversions to specific foods [26,27]. For example, food restriction may be counterproductive, resulting in increased desire for and consumption of the restricted foods when children have access to them, potentially contributing to overweight [28]. Similarly, using food to soothe distress or manage child behavior can lead to an unhealthy association between emotions and eating [29]. These findings suggest the importance of adopting evidence-based, supportive food parenting practices to create a home food environment that promotes healthy dietary patterns and eating behaviors.

Food parenting interventions for preschool-aged children have focused on improving dietary behaviors such as increasing fruit and vegetable consumption and reducing sugary beverages and energy-dense snacks. For example, Healthy Habits, Happy Homes promoted structured meal routines, parental modeling, and reduced screen time, resulting in modest improvements in children's dietary behaviors, including more frequent family meals and decreased sugary drink intake [30]. Similarly, the NOURISH trial demonstrated responsive feeding practices, taught parents to reduce coercive feeding strategies, and encouraged positive behaviors that promote better self-regulation and openness to trying new foods. While these approaches improved feeding practices, changes in children's dietary intake were modest and inconsistent over time [31].

An updated 2024 Cochrane systematic review by Hodder et al [32] reported that child-feeding interventions that incorporate repeated food exposure led to small but positive increases in vegetable consumption. Previous iterations of this review also found that multicomponent interventions involving parents and children, including taste exposure, role modeling, and skill-building, resulted in small but measurable improvements in fruit and vegetable consumption [33]. Despite these promising findings, gaps persist. Many programs lack tailoring to children's individual needs and fail to be culturally appropriate. These shortcomings highlight the need for co-designed, community-informed approaches that are adaptable, culturally sensitive, and capable of addressing the unique dietary and environmental contexts of diverse populations.

Strong Families Start at Home/Familias Fuertes Comienzan en Casa (SFSH; ClinicalTrials.gov NCT03923491) was a home-based pilot intervention specifically designed for low-income, predominantly Hispanic/Latine parents of 2- to 5-year-old children [34]. Its primary components included identifying and enforcing positive parental feeding practices using motivational interviewing (MI), overcoming feeding challenges by acknowledging children's unique appetitive traits, and reviewing food shopping and preparation strategies. SFSH responded to the need for culturally relevant, tailored interventions that reach caregivers at home, where many behavioral decisions are made. This paper describes the current expansion of the SFSH intervention, modifications to its design, and implementation (ClinicalTrials.gov NCT06099288).

Methods

Aims

The primary aim of the intervention is to examine changes in child diet quality between the baseline and 6-month follow-up

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visits. Secondary aims include assessing for improvements in food parenting practices and the availability of healthy foods in the home. Additional exploratory aims include exploring the relationships between outcome measures and potential mediators and moderators of these effects. The trial has been registered at ClinicalTrials.gov ID NCT06099288.

Recruitment, Eligibility, and Data Collection

This study targets primary caregivers of 2-5-year-old children who identify as Hispanic/Latine. Additional eligibility criteria include being at least 18 years of age, being able to speak English or Spanish, having a smartphone, and being willing to receive SMS text messages and record a family meal or reading activity. Participants are excluded from the study if their child has a diagnosed eating or feeding disorder or if they participated in the pilot. Participants with multiple children in the 2- to 5-year age range may only enroll with one child. We aim to recruit 257 participants to achieve adequate power for the proposed data analysis (see sample size calculations).

Different aspects of community engagement are critical to the recruitment success of this study. The first is working with our two community partners, and the second is spending time in the community. Participants are mainly recruited by study personnel at food pantries and other community organizations in Rhode Island who administer an eligibility screener and collect contact information. We also work closely with our community partners to share information and distribute fliers, which have a quick response code that directs to the eligibility screener when scanned. Interested participants answer a series of eligibility questions. If they do not meet the requirements, they receive an immediate notification informing them of their ineligibility. If they qualify, they are notified that a research assistant (RA) will follow up with them within the next few weeks. We also have a study website where participants can learn more about the study and fill out the eligibility screener [35].

Baseline data collection occurs in three phases. First, a bilingual RA calls the individual to obtain their oral consent to participate in the study with their child. The RA then administers some of the baseline questionnaire during the same call, as time allows. Both participant consent and questionnaire data are documented in the Qualtrics survey platform. Next, the RA goes to the participant's home to finish the questionnaire; obtain the child's height, weight, and dermal carotenoid score; and conduct a 24-hour dietary recall. Finally, the participant completes a second dietary recall over the phone within 2 weeks of the baseline visit.

Participants are randomized after completion of the second dietary recall. A randomization scheme was created by the study's statistician based on a permuted block randomization procedure with small random-sized blocks. Group allocations were put into opaque, numbered envelopes by a team member who is not involved in data collection. Once a participant has been randomized, they are assigned to a community health worker (CHW) who schedules all visits and phone calls until follow-up.

The project coordinator is unblinded to the group assignments of all participants, and the CHWs are aware of the group assignments for the participants to whom they deliver the intervention. However, the personnel responsible for collecting data are blinded to the participants' group assignments. While participants are aware of the content of the material they are discussing, they are informed that the intervention topics are "healthy eating" and "food parenting," while "reading readiness" is the control topic.

Ethical Considerations

This protocol was approved by the Brown University institutional review board (protocol number 2022003389). Contact information is collected in the eligibility screener. This is stored in Ripple, which is a HIPAA (Health Insurance Portability and Accountability Act)-compliant platform. An RA reviews an informed consent document with the participant over the phone. The document specifies that participation is voluntary and that participants may withdraw from the study at any time without penalty. Verbal informed consent to participate is obtained over the phone in the participant's preferred language (English or Spanish) and is documented by the RA in Qualtrics. Participants are provided with a physical copy of the informed consent document at the baseline visit. The verbal informed consent form in Qualtrics contains the participant's name, the participant's child's name, and an ID number. No other identifying information is collected from our data collection instruments. The data are instead associated with the ID number and are stored in password-protected platforms and storage services that require a Brown University account to access. All data will remain anonymized when analyzed and published. Participants are reimbursed through a prepaid debit card that study personnel add funds to at predetermined study milestones. A total of US $40 is added to the card for completing the baseline visit, and an additional US $20 is added after the second dietary recall. Participants then receive US $40 and US $100 for completing the third home visit and all follow-up data collection, respectively.

Overview of Design

SFSH's pilot design has been described previously [34,36]. The program and performance objectives we identified through intervention mapping for the pilot, as well as the overall structure of the intervention, remain unchanged (Figure 1) [37]. Briefly, SFSH is a 6-month randomized controlled trial. Participants engage in three monthly 60-minute in-home sessions followed by three monthly 30-minute phone calls. These sessions are led by a bilingual (Spanish and English) CHW. Each CHW receives onboarding training in basic principles of pediatric nutrition and parental feeding practices from the project coordinator, who is a registered dietitian. Ongoing booster training is provided every 6 to 8 weeks. The CHWs also undergo MI certification training led by a member of the study team who has extensive experience in MI (AMM). The CHWs meet with AMM monthly for ongoing MI support.

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Figure 1. SFSH study design. MI: motivational interviewing; SFSH: Strong Families Start at Home/Familias Fuertes Comienzan en Casa.

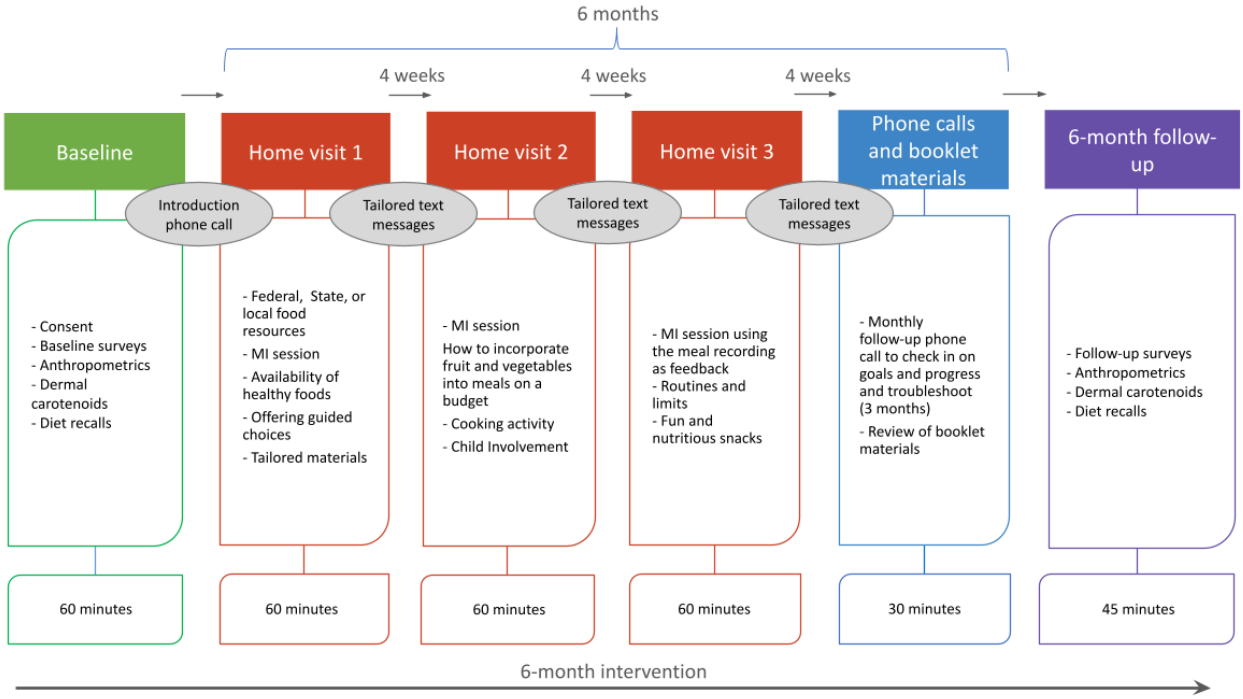

Participants receive a booklet containing study content, tailored information about eating behaviors, information about nutrition, and biweekly SMS text messages that reinforce topics covered during the in-home and phone sessions. All calls and SMS text messages are made through a single shared phone number that is hosted on the Avochato platform.

Theory

Consistent with our pilot, three behavioral theories guided the development of the SFSH intervention (Figure 2). First, social cognitive theory posits that behavior is shaped by bidirectional relationships between intrapersonal, social, and environmental factors [38,39]. Parental self-efficacy, behavioral capability, and outcome expectations and expectancies are elements of social cognitive theory that SFSH targets to evoke change in child diet quality and parental feeding practices. Second, self-determination theory describes autonomy, competence, and relatedness to others as drivers of internal motivation, which is considered to be more constructive than external motivators [40]. Our intervention leverages CHW-led MI to foster these components, thereby facilitating desired behavior change and maintenance [41]. Finally, the video feedback activity during the third home visit is informed by self-perception theory, which states that individuals gain insight into their attitudes and beliefs when they observe their own behaviors and the context in which they were performed [42]. In SFSH, participants are able to reflect on their feeding practices after reviewing a self-recorded video of a family meal.

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Figure 2. Conceptual and logic model guiding intervention. SCT: social cognitive theory; SDT: self-determination theory; SPT: self-perception theory.

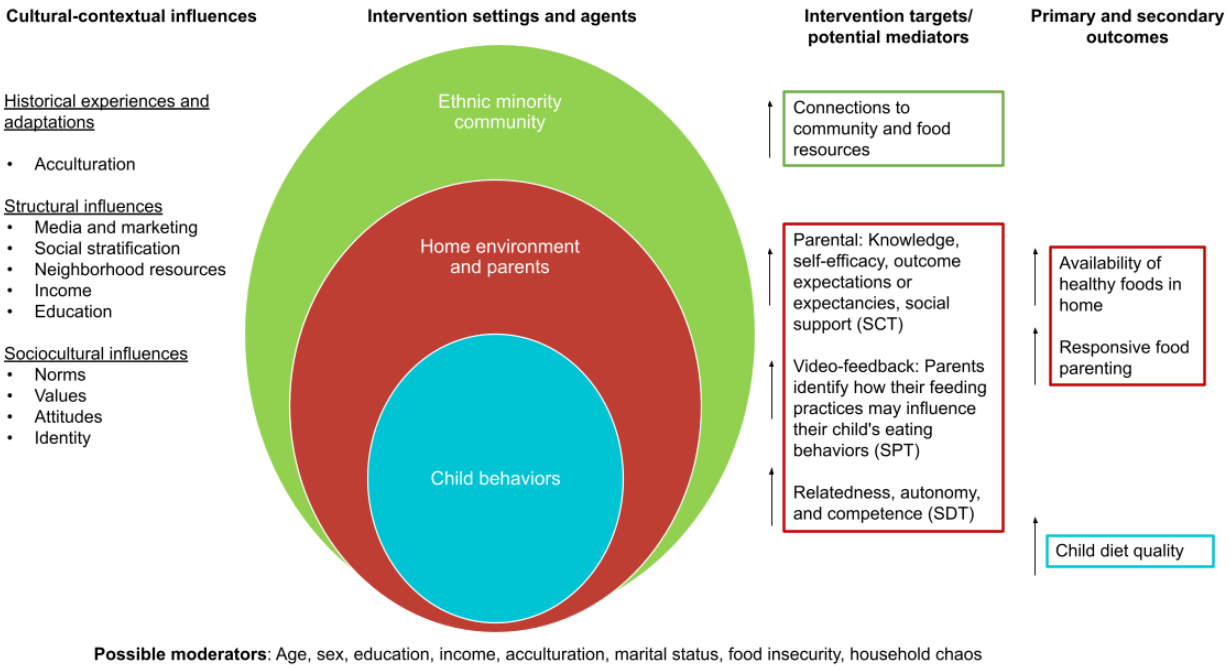

Participant Considerations

Several measures were taken to promote the cultural relevance of SFSH for Hispanic/Latine caregivers. First, insights from the pilot study's focus groups that were majority Hispanic/Latine (28/33, 85%) were incorporated into the development of this study [36]. Second, feedback obtained from the pilot's follow-up survey and postintervention semistructured interviews was also considered when updating materials and protocols [34]. Third, we established a parent leader board consisting of six Hispanic/Latine parents in the community to review materials for this study, in addition to a leadership community advisory board made up of our community-based organization leadership, SNAP-Ed, and WIC representation. Finally, all study personnel who speak with participants, including CHWs and RAs, identify as Hispanic/Latine and are fluent in Spanish.

Literacy level is not part of our eligibility or exclusion criteria. All materials have been written at a 6th-grade reading level to make them more accessible to low-literacy participants. We have also incorporated visuals and comics into our materials to support retention and understanding of key concepts (Figures 3 and 4). If participants share that they are unable to read English or Spanish during screening, consenting, or the baseline data collection process, an RA verifies that someone in the home can assist with reading and writing as needed.

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Figure 3. Sample 1: page from the Strong Families Start at Home booklet.

OVERVIEW

As a parent, you have a lot on your plate! This book is meant to make you feel better about how to feed your child and help them eat a balanced diet.

We know that each family has different values and cultures. We want to celebrate yours! Think of this book as a toolbox full of helpful ideas. You can try whichever ones work best for your family.

We know that some things can make it tough to lead a healthy life. Not being able to see a doctor, not having a good place to live, or not being able to afford healthy food can all affect your child's health. Don't worry, though! You'll be teaming up with a community health worker for the next 6 months. They will help you find resources you might need.

We will focus on...

HOW
to feed your child

Be a role model

Repeat, Repeat, Repeat!

Cheer them on!

Set up your home for healthy eating

Involve your child

WHAT
to feed your child

More...

Whole foods
Fruits & vegetables
Whole grains

Less...

Sugar

Salt

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Figure 4. Sample 2: page from the Strong Families Start at Home booklet.

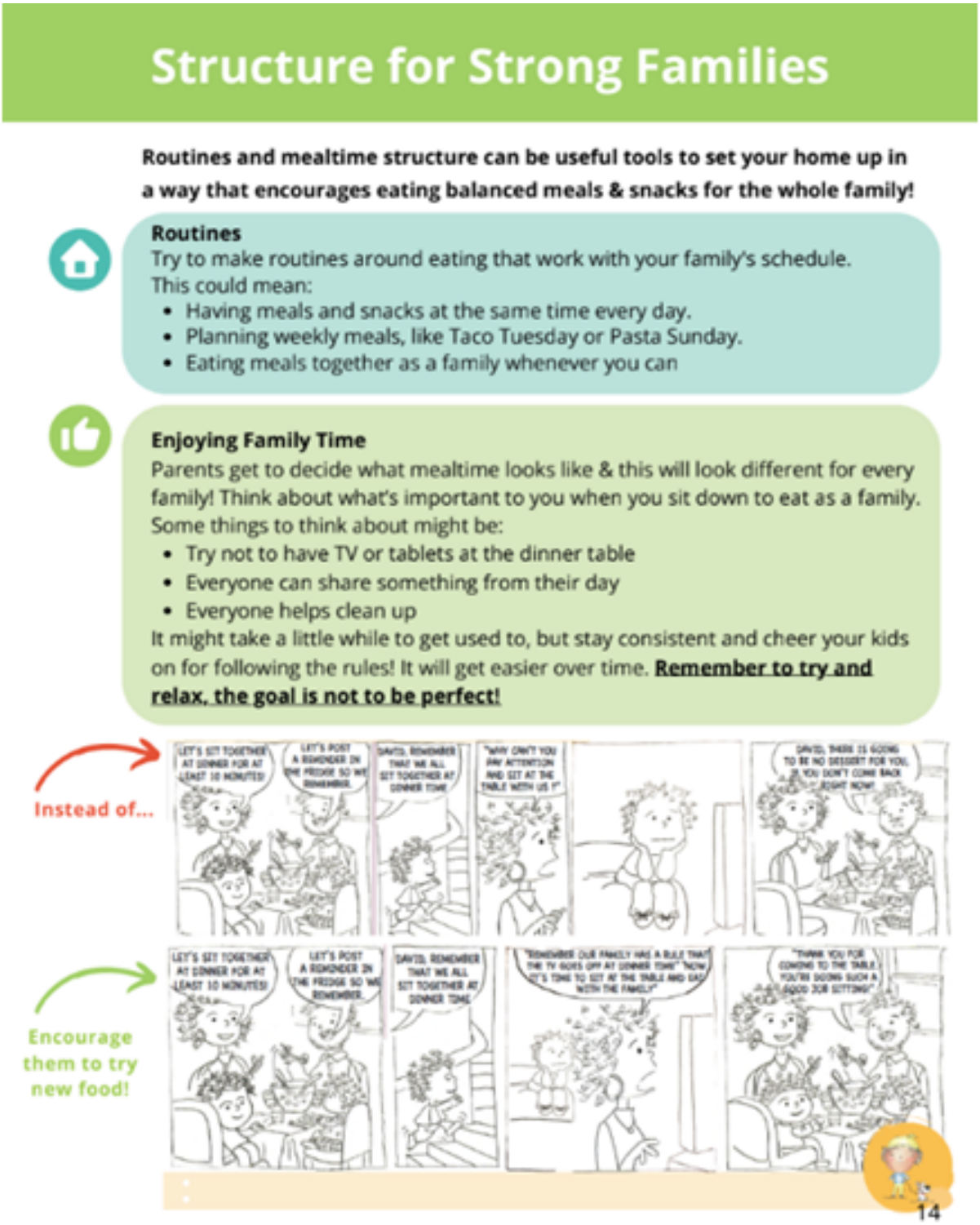

Intervention Components

Prior to the first home visit is a 15-minute introduction phone call. This call was added to the protocol to allow the CHWs to build rapport with the participant before meeting in person. During this call, the CHW also administers a 7-item social determinants of health (SDOH) screener that we adapted from the Accountable Health Communities Health-Related Social Needs Screening Tool (Table 1) [43]. CHWs then connect participants who request help with identified needs to relevant community resources.

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Table 1. Social determinants of health screener.

Questions	Response options
Health care	
Think about your health care needs. Do you have problems with any of the following?	1. Health insurance 2. Accessing medications 3. Quality health care 4. None of the above
Housing	
What is your housing situation today?	1. I do not have housing 2. I have housing today, but I am worried about losing housing in the future 3. I have housing
Think about the place you live. Do you have problems with any of the following?	1. Bug infestation 2. Mold 3. Lead paint or pipes 4. Inadequate heat 5. Oven or stove not working 6. No or not working smoke detectors 7. None of the above
Food	
Within the past 12 months, you worried that your food would run out before you got money to buy more.	1. Often true 2. Sometimes true 3. Never true
Within the past 12 months, the food you bought just did not last, and you did not have the money to get more.	1. Often true 2. Sometimes true 3. Never true
Transportation	
In the past 12 months, has a lack of transportation kept you from medical appointments, meetings, work, or getting things needed for daily living?	1. Yes, it has kept me from medical appointments or getting medications 2. Yes, it has kept me from nonmedical meetings, appointments, work, or getting things that I need 3. No
Utilities	
In the past 12 months, has the electric, gas, oil, or water company threatened to shut off services in your home?	1. Yes 2. No 3. Already shut off
Assistance	
Would you like help with any of these needs?	1. Yes 2. No

Over 6 months, three 60-minute home visits are completed with participants, followed by three 30-minute phone calls. The participant is given a booklet at the first home visit, which contains sections to be reviewed at each visit and phone call. The content focuses on five parenting strategies to promote healthful eating practices: (1) role modeling, (2) repeated exposure, (3) encouraging language, (4) structuring the home environment, and (5) child involvement. The booklets also contain comic strips featuring these strategies; Specific, Measurable, Achievable, Relevant, and Time-Bound goal templates; general nutrition guidelines for young children; and meal planning tips (Figures 3 and 4). One or two food parenting topics are reviewed at each visit and phone call, then the CHW uses MI to help the participant set goals around the content they covered. These goals are viewed at subsequent visits and calls.

Each home visit features a supplementary activity tailored to the individual needs of their child. At the first home visit, participants may be given handouts that address one of their child's appetitive traits or dietary habits based on their responses to the Children's Behavioral Eating Questionnaire and questions adapted from the National Survey of Children's Health, respectively [44-46]. Both measures are administered during baseline data collection and are scored prior to the first home visit. The Children's Behavioral Eating Questionnaire is a

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validated caregiver-reported tool consisting of eight appetitive trait subscales. As in the pilot, participants whose children meet the criteria for food fussiness, satiety responsiveness, or food responsiveness are provided with a tailored handout that lists strategies to encourage healthy eating habits [34,36,47]. If the child exhibits more than one trait, information is prioritized in the aforementioned order. In addition to addressing the child's eating behaviors, the family receives an additional handout if the child has a high intake of sugar-sweetened beverages (≥4-6 times in the past week), energy-dense snack foods (≥4-6 times in the past week), or low fruit and vegetable intake (≤1 time per day). These behaviors were selected because they are among the most prevalent in children nationally and are strongly associated with adverse health outcomes [48].

The second home visit is largely unchanged from the pilot [36]. Briefly, a culinary professional from the community accompanies the CHW to lead an interactive cooking demonstration during the second home visit to provide guidance on basic culinary skills and age-appropriate ways to involve children in food preparation. Participants are also given a cookbook with culturally relevant recipes and child cooking utensils.

The third home visit features a video feedback activity. Participants are asked to record and send a 3- to 5-minute video of a typical family meal to study personnel at least a week prior to the next visit. An RA then codes the video for structured or autonomy supportive and nonstructured or nonautonomy supportive parental feeding practices. The coding tool was developed specifically for the pilot based on the constructs defined by Vaughn et al [25]. Six experts in food parenting reviewed this tool and provided feedback, and it demonstrated good interrater and excellent test-retest reliability [49]. Ultimately, one structured or autonomy supportive and one nonstructured or nonautonomy supportive practice is clipped and played back to the participant. Using MI, the CHW asks participants about their observations and impressions about the clips during the home visit to facilitate open-ended discussion. The RA also prepares a feedback sheet that explains why the clips were selected, how they may impact children's eating habits, and tips on how to implement more positive practices, which the CHW reviews with the participants after the participants share their initial thoughts. Example video clips and feedback sheets are prepared for participants who do not send their own.

Following the home visits are three monthly 30-minute phone calls. The calls are structured similarly to the home visits: the CHW assesses progress toward the previously set goal, discusses content from the study booklet, and helps participants set a new goal. Much of the content reviewed during the phone calls reinforces lessons from the home visits. Participants who notify their CHW that they have lost their booklets are mailed copies of the appropriate pages prior to their next call. The CHW also readministers the SDOH screener at the end of the first phone call to reevaluate and address participant needs.

Participants receive automated SMS text messages twice weekly via the messaging software Avochato for the duration of the intervention, starting after the first home visit. These contain links to recipes, advice on positive parental feeding, and general motivational phrases.

The control arm of this study is an attention-control program that promotes literacy and school readiness, which was derived from the Greater Washington Educational Television Association's Reading Rockets curriculum [50]. Participants in this group have the same home visit and phone call schedule as the intervention. However, they do not receive tailored information at the first home visit. In place of the in-home cooking activity, the CHW leads a poem activity with the participant and their child and provides three storybooks as incentives. Rather than reviewing a family meal during the third home visit, participants instead have a video feedback session where they review clips of themselves reading to their child. They also sent SMS text messages twice weekly, featuring language that is consistent with the control protocol.

Modifications From Pilot Study

While our pilot study results were promising, there were some modifications that were made to this study to further improve recruitment, retention, and better meet the needs of the community. We provide a brief overview of these changes here. First, the CHWs felt that it was important to have time to get to know the participants prior to going into their homes, so we added a 15-minute phone call prior to the first home visit. Second, many families from the pilot study faced challenges related to SDOH. Without having some of their basic needs met, it is hard to expect that they would prioritize their children's feeding. Thus, we added an SDOH screener to the first phone call so that CHWs could help provide referrals and resources to families. We felt it was important to ground our work within the community energy balance framework to address the cultural and contextual influences predisposing Latine families to unhealthy diets. Through MI, the CHW builds rapport and identifies some of the structural and sociocultural influences that impact their families' eating (Figure 2). Third, we wanted to ensure that we were listening to parent voices and felt that just having a community advisory board with leadership from community-based organizations (which we continued) was not sufficient. As a result, we created a parent leader board, in addition to a leadership community advisory board, made up of six Hispanic/Latine parents to provide feedback on study materials, advise on the cultural relevance, and effective dissemination and retention strategies on an ongoing basis. Fourth, we decided to add additional tailored information to the intervention based on parents' baseline reports of their child's dietary intake. Fifth, we added a biomarker to measure a child's dietary intake (dermal carotenoids measured by the Veggie Meter) to supplement other dietary measures. Finally, we decided to work closely through contracting with two community-based organizations that work with families in Rhode Island. They participate in our leader community advisory board, and we have ongoing meetings to discuss recruitment in the community.

Justification of Design

SFSH's principal components bring together three motivational theories. MI is especially critical—it has been incorporated into every monthly session due to its effectiveness in promoting

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sustainable behavior change across a range of settings and contexts [51]. Therefore, personnel must undergo MI certification training to ensure that it is being used accurately. These features and training requirements may make it challenging for low-resource settings to adopt this program. Some adaptations can be made to accommodate limited materials without compromising fundamental aspects if needed. For example, booklet and handout content can be sent to participants' smartphones in place of providing physical copies to eliminate printing costs. Home visits can also be conducted remotely.

Measures and Outcomes

Primary Outcome

The primary outcome of this trial is child diet quality using the Healthy Eating Index-2015 (HEI) scores that are calculated from multiple-pass 24-hour dietary recalls, a highly valid method for capturing dietary intake [52]. To improve the accuracy of reporting, participants are given a bilingual food amounts booklet at the baseline visit to help them visualize quantities of the foods and beverages they consumed [53]. Participants are also asked to reference this guide during the second recall if possible. Recalls are scheduled to capture one weekday and one weekend day to obtain a more accurate representation of the child's typical intake. If the child has spent a portion of the recall period away from the participant and the participant is unable to provide enough information on the types and quantities of foods eaten during those times, participants are asked to reach out to who the child was with to gather this information if possible. In the case of preschool and childcare facilities, participants are asked to obtain the menu that was used for the day that is being recalled. If the menu is not available, a sample menu from the Child and Adult Care Food Program is used. All reported items are entered into the 2022 Minnesota Nutrient Database for Nutrition Research (NDSR) [54]. Nutrient data provided by NDSR from both days are then averaged and used to generate HEI scores.

The HEI is a scale that reflects adherence to the Dietary Guidelines for Americans [55]. It is comprised of 13 components: total fruits, whole fruits, total vegetables, greens and beans, whole grains, dairy, total protein foods, seafood and plant proteins, fatty acids, refined grains, sodium, added sugars, and fatty acids. Points from each component are summed to a total score that can range from 0 to 100, with higher scores indicating better diet quality. HEI scores will be calculated directly by NDSR. All dietary recalls will be assessed for quality assurance by study personnel prior to data analysis.

We are also using dermal carotenoids as a proxy measure of diet quality. Carotenoids are a classification of red, orange, and yellow naturally occurring pigments produced by plants, bacteria, and fungi. These compounds accumulate in the skin after consumption [56]. Hence, they may be used as a biomarker to approximate fruit and vegetable intake. The Veggie Meter (Longevity Link) noninvasively measures dermal carotenoids via reflection spectroscopy [57]. This device has been validated to detect changes over time among racially and ethnically diverse samples [58,59], and other studies have used it to assess dermal carotenoid levels among preschool-aged children [60,61]. Participants are asked to guide their child's finger onto the lens of the Veggie Meter. The average of three 10-second measurements with two 10-second washouts between is then recorded. Higher scores indicate higher dermal carotenoid levels, with the maximum score being 800.

Secondary Outcomes

All the measures that assessed parental feeding practices in the pilot will be used here. The 13 subscales of the Food Parenting Inventory (child involvement in food preparation, responsiveness to child's fullness cues, encourage exploration of new foods, repeated presentation of new foods, family meals, regular timing of meals and snacks, encourage trying new foods, inconsistent mealtimes, indifferent feeding, pressure to eat, restriction, food as a reward, and monitoring) and the Healthy Eating Guidance subscale from the Comprehensive Feeding Practices Questionnaire have both demonstrated reliability and validity among Latine caregivers specifically [62-64]. The former was developed to consolidate assessments of multiple parental feeding practices into one tool, and the latter was developed to capture previously less explored feeding practices such as restrictive feeding. The Parent Socioemotional Context of Feeding Questionnaire was developed based on the constructs of self-determination theory to evaluate socioemotional aspects of the home feeding environment and has been validated for use with caregivers of 4- to 8-year-old children [65]. Items from all three questionnaires are measured on 5-point Likert scales ranging from 1=Never to 5=Always, 1=Disagree to 5=Agree, or 1=Extremely untrue to 5=Extremely true, as applicable. Higher scores indicate greater compliance with the feeding practice or construct that corresponds to each question. Additionally, a single-question family meal frequency measure taken from a systematic review of family meal assessments is included [66].

A home food inventory is used to compare pre- and postintervention availability of healthy and unhealthy foods in the home [67]. Our modified version is a 20-item "Yes/No" checklist inquiring about fruit, vegetables, chips, sugary snacks or desserts, candy, beverages, whole grains, and beans and legumes.

Potential Moderators and Mediators

Data on potential moderators is being collected at baseline and include caregiver age, gender, race, marital status, income, birth country, number of years living in the United States, household composition, acculturation [68], food and nutrition insecurity [69,70], and participation in federal nutrition programs, as well as child age, gender, and time spent in childcare. Needs identified by the SDOH screener that is administered at the introduction and month 4 phone calls will also be considered [43].

We will explore several potential mediators that the SFSH pilot was not sufficiently powered to analyze. Parent diet quality is measured by the 15-item Rapid Prime Diet Quality Score Screener, as well as parent dermal carotenoid levels [71]. Nine questions were selected from a food literacy behavior checklist to evaluate engagement in meal preparation and healthy mealtime practices [72]. We are assessing selected constructs

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of the theoretical frameworks that informed this intervention's design: perceived barriers to healthy eating using the National Cancer Institute's Food Attitudes and Behaviors Survey [73], perceived familial support using the short form Family Health Scale [74], and relatedness and competence with a tool we adapted from the Intrinsic Motivation Inventory [75,76].

A language checklist was developed by the study team to capture potential changes in reading or communication skills in the control group.

Process Evaluation

To capture intervention dose, we are reviewing the total number of completed home visits and phone calls, SMS text messages, and materials that were read as reported by participants, and referrals to social services. Additionally, following each session, CHWs submit a brief process measure that assesses participant responsiveness to the intervention. Participants are also asked to complete a satisfaction survey upon study completion.

Implementation fidelity is being monitored by trained study team members across three main domains (adherence, quality of delivery, and participant responsiveness). A subsample of audio recordings from the intervention and control group sessions is reviewed for adherence (eg, was the intervention delivered as intended) and quality of delivery (eg, manner in which the intervention was delivered) across the study. Shortly after study launch, a small sample (n=7) of session recordings was reviewed for all CHWs to monitor adherence. Recordings are scored using a study team–developed implementation checklist that includes binary response options (yes/no) for the main intervention components. To assess initial fidelity to the protocol, five recordings of each intervention home visit and phone call, and two recordings for each control home visit and phone call are reviewed for each CHW. If CHWs score below 80%, booster trainings are delivered. Monitoring includes review of five randomly selected recordings for each CHW every 3 months. In addition, shortly after the study launch, a recording was reviewed for each CHW to monitor adherence and quality of delivery for MI. A random 20-minute segment of each recording was reviewed and coded using the Motivational Interviewing Treatment Integrity Coding Manual (MITI 4.2.1) to assess beginning proficiency [77]. The first five intervention recordings and the first two control recordings completed by each CHW for each home visit and phone call will be coded for MI adherence and quality. A random sample of five recordings for each CHW will then be coded every 3 months for the duration of the study. CHWs receive personalized feedback, and MI meetings are conducted to build skills and prevent drift.

Sample Size Calculations

We have conducted power calculations to ensure that we have an adequate sample size such that between-group differences can be detected in the primary outcome of diet quality measured by 24-hour dietary recalls and the HEI-2015. Power was calculated using a combination of G*Power (Heinrich Heine University Düsseldorf) and MPlus Monte Carlo estimation informed by the pilot study, which showed effects favoring intervention on median changes in HEI from baseline to end of treatment (0.69 vs –6.48), corresponding to a medium effect size (f^2=0.14). We have chosen to power on medians (instead of means) due to the high variability around the mean (which is common in smaller samples). We anticipate seeing a greater average change in HEI than what we saw in our R34, given the strengthening of our intervention and that the pilot was conducted at the beginning of the COVID-19 pandemic. We also expect significantly less variability in a larger sample. As our planned analysis is to consider differences in mean HEI between groups over time, we have also conducted simulations to ensure we would be adequately powered given medium-sized effects in mean HEI between groups over time (f^2=0.14). We expect that our proposed intervention will improve total HEI by 5 units [78]. We selected five HEI units based on the following rationale: (1) five HEI units is clinically meaningful as it predicts a 4%-6% decrease in overall mortality and a 15% decrease in the prevalence of obesity [79,80]; (2) five HEI units is statistically meaningful as it is approximately 0.5 of the SD of HEI when measured in large, representative samples; and (3) five HEI units is a reasonable expectation for a moderately intensive, intervention, with previous studies reporting increases from 3.6 to 7.8 [81].

For this study, with 180 participants at follow-up, we will have >85% power to detect differences in primary outcome variables (HEI) between groups (I vs C), using a 2-tailed significance level α=0.05 and effect sizes consistent with our prior work. To confirm adequate power, simulation studies were run using a series of mixed effects Monte Carlo simulations with 1000 replications and three seeds to confirm model stability. Models assumed modest effects of covariates and a range of effect sizes for both the main condition and covariates. Findings supported >85% power to detect small to medium effects (f^2<0.13). Although analysis will be based on the intent-to-treat sample, we plan to enroll 257 participants to ensure a final sample of 180 participants. In our pilot study, of those recruited, we had a 75% enrollment rate.

Statistical Analysis

Between-group differences in baseline demographic characteristics will be compared using a combination of parametric and nonparametric tests as appropriate. Potential confounders identified through this process will be included in subsequent models. Primary and secondary outcomes will be examined using a series of linear mixed effects models that include group assignment, baseline values of the outcome, intervention dose received, and confounders identified a priori. We will use a similar analytic strategy to examine potential moderators. In this case, models will include the main effects of the moderator, group, and the moderator by group. Mediators will be analyzed using multiple mediator models implemented with a product of coefficients approach with bootstrapped standard errors. Missing data will be approached on the intent-to-treat principle and compared using both likelihood-based approaches to estimation and inverse probability weighting and pattern mixture models as appropriate.

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Results

The notice of award from the National Institutes of Health was received in March 2023. We revised protocols, updated study materials, hired and trained study personnel, prepared data management platforms, and engaged in outreach with community partners between March 2023 and January 2024. Recruitment began in February 2024. A total of 81 participants were randomized as of March 2025. Of these, 44 participants are completing the program (intervention: n=22 intervention; control: n=22), 29 participants have completed follow-up data collection (intervention: n=13; control: n=16), and 8 participants have withdrawn (intervention: n=5; control: n=3).

Data analysis is expected to conclude in 2028. Once the main results are analyzed, we plan to disseminate our findings back to the research participants through a one-page summary written in lay terms, as well as at community events, particularly with our community partners and our community advisory boards. We will also publish our results in the peer-reviewed literature and share results with relevant stakeholders such as SNAP-Ed, WIC, or home visiting.

Discussion

Principal Findings

Novel interventions are required to address disparities in diet quality that are prevalent among populations commonly affected by social inequities. The SFSH pilot was a feasible and acceptable home-based nutrition intervention among a racially and ethnically diverse sample of caregivers of preschool-aged children. Furthermore, we observed improvements in multiple HEI subscale scores and parental feeding practices [34]. This study expands on the pilot and features numerous modifications to improve these outcomes among Hispanic/Latine families.

There are several challenges we may encounter throughout the study. First, it may be difficult to recruit and retain participants in our 6-month program. However, despite the COVID-19 pandemic necessitating changes in study procedures in the pilot, we were successful in recruiting our target number of participants. We continue to rely on the community partnerships that aided us in our prior recruitment efforts; therefore, we do not anticipate greater difficulty in this trial. To improve retention, we have increased our total incentive amount to US $200, which will be distributed in segments at prespecified study milestones. Additionally, all members of the study team can communicate with participants through Avochato, enabling us to more easily send visit reminders and respond to their inquiries.

Another potential challenge is participants not recording videos for the third home visit. In the pilot, 62% (24/39, intervention group) of participants submitted a video for the tailored feedback activity. For this intervention, we created instructional videos depicting how to record and send the feeding videos. A text reminder is sent 2 weeks prior to the third home visit that reiterates these instructions. Participants who send their videos are entered into a raffle to win an extra incentive. If participants still fail to send a video, we created sample videos and feedback sheets that they can review.

Conclusions

This expansion on the SFSH pilot enhances its potential to address the significant public health concern of nutrition-related chronic disease burden among the Hispanic/Latine population. Our novel theory and home-based approach are intended to empower caregivers to make lasting changes to their feeding practices and support healthy eating in their homes. Integrating tailored information further helps families navigate unique nutritional and eating-related barriers. SFSH's promising start suggests that it could be incorporated into community programs.

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Authors' Contributions

AT conceptualized the study, secured funding, developed the design, supervised study activities, and contributed to the original draft of the manuscript. KLB coordinated study activities, supervised study personnel, and contributed to the original draft of the manuscript. AMM contributed to the design, trained study personnel, and provided feedback on the manuscript. MP recruited participants, analyzed data, and provided feedback on the manuscript. IL and LAC recruited participants, collected data, and provided feedback on the manuscript. ASC recruited participants, collected data, performed quality assurance checks on data, and provided feedback on the manuscript. PR, TA, JS, SD, and KG contributed to the design and provided feedback on the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CHW: community health worker
HEI: Healthy Eating Index
HIPAA: Health Insurance Portability and Accountability Act
MI: motivational interviewing
MITI: Motivational Interviewing Treatment Integrity Coding Manual
NDSR: Minnesota Nutrient Database for Nutrition Research
RA: research assistant
SDOH: social determinants of health
SFSH: Strong Families Start at Home/Familias Fuertes Comienzan en Casa

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Protocol

Acupuncture for Poststroke Cognitive Impairment Based on Default Mode Network Analysis: Protocol for a Randomized Controlled Trial

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Abstract

Background: Poststroke cognitive impairment (PSCI) is a prevalent and disabling complication following stroke, affecting critical functions such as memory, attention, language, and executive abilities. Despite the growing clinical burden, standardized and effective treatment strategies for PSCI remain limited. Acupuncture, a key modality in traditional Chinese medicine, has shown promise in improving cognitive outcomes among survivors of stroke. However, the neural mechanisms underlying its efficacy are not well understood. The default mode network (DMN), a brain network implicated in cognition and memory, has been shown to exhibit altered functional and structural connectivity in patients with PSCI. Investigating whether acupuncture modulates DMN activity may provide critical insights into its therapeutic potential.

Objective: This study aims to evaluate the efficacy of acupuncture in improving cognitive function in patients with PSCI and explore its potential neurobiological mechanisms, particularly those involving changes in the DMN, using multimodal neuroimaging techniques.

Methods: We will conduct a single-blind, randomized controlled trial involving 54 eligible patients with PSCI who will be randomly assigned to either an acupuncture group or a sham acupuncture control group. Both groups will receive conventional rehabilitation therapies. The intervention group will undergo standardized scalp acupuncture targeting Baihui (GV20), Shenting (GV24), and Sishencong (EX-HN1) for 8 weeks. The control group will receive sham acupuncture at nonacupoint locations using placebo needles. Cognitive function will be assessed at baseline and 4 and 8 weeks using the Montreal Cognitive Assessment and Mini-Mental State Examination. Secondary outcomes include activities of daily living, quality of life, and neuroimaging data acquired through resting-state functional magnetic resonance imaging and diffusion tensor imaging.

Results: This study is currently in the recruitment phase. All results, including clinical and imaging data, will be reported upon trial completion and publication.

Conclusions: This protocol is designed to investigate the efficacy of acupuncture and its underlying mechanisms in treating PSCI, with a particular focus on functional brain networks. By integrating clinical cognitive assessments and neuroimaging analysis of DMN connectivity, this study seeks to establish objective correlates of cognitive improvement. Findings from this research may advance the understanding of how acupuncture modulates large-scale brain networks and contribute to the development of imaging-based biomarkers for treatment evaluation. If successful, this approach could support the inclusion of acupuncture as a personalized nonpharmacological strategy in the neurorehabilitation of cognitive deficits following stroke.

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KEYWORDS

cognitive function; traditional Chinese medicine; functional magnetic resonance imaging; fMRI; randomized controlled trial; poststroke cognitive impairment; PSCI

Introduction

Background

Stroke stands as a prominent global contributor to disability and mortality. Annually, it afflicts 13.7 million individuals and claims 5.5 million lives [1]. Often accompanied by limb hemiplegia, aphasia, dysphagia, and other neurological dysfunctions, stroke is responsible for a high likelihood of cognitive impairment [2]. In 2016 alone, the world witnessed 13.7 million new incident strokes [3], with an annual incidence ranging from 150 to 200 per 100,000 people [4]. Poststroke cognitive impairment (PSCI) refers to a range of cognitive deficits that may develop in patients following a stroke. It can manifest as poststroke dementia, which occurs in up to a third of patients within a year after the stroke and is closely linked with increasing age [5]. The underlying pathology of PSCI is heterogeneous, with many cases stemming from various vascular etiologies and brain changes in addition to degenerative processes. PSCI encompasses conditions such as multi-infarct dementia, strategic infarct-related dementia, subcortical ischemic vascular dementia, and Alzheimer disease [6]. It emerges as a common complication, with studies reporting the combined prevalence of PSCI as 39% to 47% [7]. Three months after stroke, dementia develops in 6% to 32% of patients, elevating the risk of dementia in survivors of stroke to 3.5 to 5.6 times that of the general population. The associated cognitive dysfunction significantly diminishes quality of life for affected individuals [8]. Evidence-based medical research underscores that cognitive dysfunction exerts a more enduring impact on survivors of stroke than physical dysfunction [9], making cognitive rehabilitation a pressing research focus.

Presently, there is a lack of a standardized and effective treatment plan for PSCI, and exploration into rehabilitation methods for cognitive function continues [10]. While cognitive training is widely used and has shown positive therapeutic outcomes, its effectiveness relies on the patient's cognitive condition, and it typically does not maintain long-term benefits [11,12]. Emerging technologies such as cranial magnetic stimulation and virtual reality hold promise, yet they remain unstandardized, their costs remain high, and widespread implementation remains challenging [13]. In contrast, traditional Chinese medicine (TCM) therapy, notably acupuncture, has gained international recognition. Numerous studies attest to acupuncture's efficacy in treating cognitive dysfunction [14-16].

Moreover, investigations into the regulatory mechanisms of acupuncture on cognitive function have yielded insightful findings. For instance, Lu et al [17] observed that acupuncture enhances blood perfusion and glycol metabolism in specific brain regions, positively impacting cognition. Huang et al [18], using a combination of positron emission tomography and computed tomography, demonstrated that acupuncture exerts a regulatory effect on brain functional areas, potentially contributing to poststroke patient rehabilitation.

According to the principles of TCM, the brain marrow serves as the material foundation for cognitive maintenance. Kidney essence deficiency can lead to insufficient brain marrow, potentially causing cognitive decline. It may be attributed to mild cognitive impairment (MCI) induced by renovascular hypertension [19]. On the basis of previous research findings, Baihui (GV20), Shenting (GV24), and Sishencong (EX-HN1) are closely associated with improvements in brain and cognitive functions. These acupoints are commonly selected in basic research on ischemic stroke, autism, depression, and other related conditions [20,21]. The acupoint Baihui (GV20) is believed to connect the governor vessel with the brain and is closely associated with brain function. Baihui (GV20) and Touqu (GB7) acupuncture alleviates neurological deficits by reducing oxidative stress and neuronal apoptosis via the SIRT1/FOXO1 pathway [21]. Shenting (GV24), also part of the governor vessel, is described in Huang-Fu Mi's *TheSystematic Classic of Acupuncture and Moxibustion* as the intersecting point of the bladder meridian of foot taiyang, the stomach meridian of foot yangming, and the Du meridian, with effects that include calming the mind and stimulating the brain, making it useful for treating mental and cognitive disorders. Sishencong (EX-HN1), an extra point located on the neck and head, is described in the *Taiping Shenghui Fang* as having the ability to tranquilize and enlighten the mind. Together, Baihui, Shenting, and Sishencong are thought to enlighten and awaken the mind of patients experiencing cognitive impairment. In recent years, acupuncture—a key modality of TCM—has gained increasing global recognition for its potential in cognitive rehabilitation. Clinical studies have reported that acupuncture may improve cognitive function in individuals with MCI, Alzheimer disease, and PSCI [16,22,23].

Neuroimaging and metabolic studies have suggested that acupuncture may exert regulatory effects on brain regions associated with cognition. For instance, Ma et al [7] conducted a meta-analysis of functional magnetic resonance imaging (fMRI) studies and found that acupuncture modulates activity in the prefrontal cortex, hippocampus, thalamus, and default mode network (DMN) in patients with MCI. Furthermore, a systematic review by Li et al [24] confirmed that resting-state fMRI studies consistently support acupuncture's regulatory effects on intrinsic brain connectivity patterns related to cognition, attention, and memory. On the basis of both clinical efficacy and neuroimaging evidence, this study selected Baihui (GV20), Shenting (GV24), and Sishencong (EX-HN1) as the primary intervention points. These acupoints, located on the scalp overlying key cognitive and prefrontal regions, have been frequently used in previous studies on cognitive dysfunction. While TCM theory historically associates these points with mental clarity and brain function, their selection in this study is further supported by emerging neurobiological findings indicating potential roles in modulating the central nervous system.

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In recent years, neuroimaging technologies have played an increasingly vital role in advancing our understanding of brain diseases. Among them, fMRI has emerged as a particularly valuable tool due to its ability to noninvasively measure brain activity and connectivity [25]. In the context of PSCI, fMRI provides high spatial resolution and can detect subtle changes in brain networks associated with cognitive processes [26,27]. Specifically, resting-state fMRI allows for the assessment of intrinsic functional connectivity without the need for active task performance—an important consideration given the cognitive and physical limitations of patients with PSCI.

The DMN, a brain network closely linked to cognition and memory, is often disrupted in individuals with PSCI [28]. fMRI enables the direct observation of DMN connectivity patterns, offering a unique opportunity to investigate how interventions such as acupuncture might modulate these networks [29]. Previous studies have demonstrated that acupuncture can influence brain activity and connectivity, including within the DMN, suggesting a potential mechanism through which acupuncture may improve cognitive function. Ellwood-Lowe et al [30] indicate that the lateral frontoparietal network and the DMN are associated with cognitive test performance. The findings of Liu et al [31] demonstrate that the functional connectivity of DMN in patients with cognitive dysfunction after stroke differs from that of healthy individuals and correlates with variations in memory function. In addition, reduced feeder and local connections have been observed within cognition-related networks, including the DMN, the salience network, the cingulate network, and the orbital network, particularly involving the caudate nucleus [32]. Notably, changes in executive function and resting-state functional connectivity are common after stroke or ischemic attacks, indicating a connection between cerebrovascular events and the prolonged impairment of neural network connectivity and cognitive function [33]. Therefore, our hypothesis posits that acupuncture might ameliorate the cognitive function of patients with PSCI by modulating the DMN. However, no studies have investigated the mechanism of acupuncture in enhancing the cognitive function of patients with PSCI from the perspective of DMN brain structure and function.

As a consequence, we are adopting a randomized controlled trial methodology for this investigation. Participants with diagnosed PSCI will be randomly assigned to either an acupuncture intervention group or a sham acupuncture group. The efficacy of acupuncture as a therapeutic modality will be evaluated through the use of standardized cognitive function scales, which will provide quantitative evidence of its clinical rehabilitative potential in enhancing cognitive function in patients with PSCI. In parallel, we will use fMRI to elucidate the neuroimaging mechanisms underlying the therapeutic effects. The objective of this research is to establish a standardized cognitive rehabilitation protocol informed by these neuroimaging insights for the treatment of PSCI.

Objectives

The primary objective is to test the hypothesis that acupuncture, compared with conventional treatment, will lead to significant improvements in poststroke cognitive function as measured using standardized neuropsychological assessments. A secondary hypothesis is that acupuncture will modulate the functional connectivity within the DMN as detected by resting-state fMRI and that changes in DMN connectivity will correlate with improvements in cognitive performance.

Methods

Study Design

A randomized, single-blind, parallel-controlled trial will be undertaken to assess the impact of acupuncture on enhancing cognitive function in individuals with PSCI. A total of 54 participants will be recruited and randomly allocated to either the acupuncture group or the conventional treatment control group. The intervention will span 8 weeks, with cognitive evaluations scheduled at baseline, 4 weeks after treatment, and 8 weeks after treatment. Previous trials have shown that such frequency and intensity of treatment are both safe and effective in improving cognitive outcomes in survivors of stroke [34,35]. Participant attendance will be closely monitored. Any missed sessions will be documented along with reasons, and efforts will be made for rescheduling. Treatment logs will be maintained by treating physicians to record each session, including date, time, and whether the session was completed as scheduled.

Sample Size

The primary outcome of this study is the change in cognitive function as measured using the Beijing version of the Montreal Cognitive Assessment (MoCA). We prespecified a standardized between-group effect size of d=0.40 on the MoCA at 8 weeks. This assumption is supported by a recent meta-analysis of acupuncture for PSCI showing a pooled mean difference (MD) of 3.30 points (95% CI 2.19-4.40) versus control [36,37]. Using representative poststroke variability (MoCA score mean 21.1, SD 7.5), an MD of 3.30 corresponds to a standardized effect of approximately 0.44; thus d=0.40 is conservative. Therefore, the trial is powered on MoCA as the primary cognitive end point.

Using G Power (version 3.2.7) with a 2-tailed test, α set at.05 (type I error), and power ($1 - \beta$) at 0.80 (type II error β=.20), the minimum required sample size was calculated to be 44 participants (22 per group) [38]. To account for an anticipated 20% dropout or loss to follow-up rate, the total sample size was increased to 54 participants, with 27 participants allocated to each group.

Participants and Recruitment

We aim to enroll 54 participants through a combination of ward visits and online promotional efforts. Individuals expressing interest in participating will undergo eligibility assessment conducted through a screener, typically via contact at the recruitment office. A MoCA score of <26 is used as the primary cutoff to identify cognitive impairment in accordance with the standard diagnostic threshold recommended in clinical guidelines and previous studies. Patients scoring below this threshold are considered eligible for inclusion. In cases of low educational level (≤12 years), 1 point is added to the total MoCA score as per standard adjustment procedures. Should the applicant satisfy the research criteria, an invitation to partake

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in the study will be extended. Figure 1 shows the flow diagram of participants.

Figure 1. Flow diagram of participants. DTI: diffusion tensor imaging; fMRI: functional magnetic resonance imaging; MBI: modified Barthel index; MMSE: Mini-Mental State Examination; MoCA: Montreal Cognitive Assessment; MOS SF-36: Medical Outcomes Study 36-Item Short-Form Health Survey; MRI: magnetic resonance imaging.

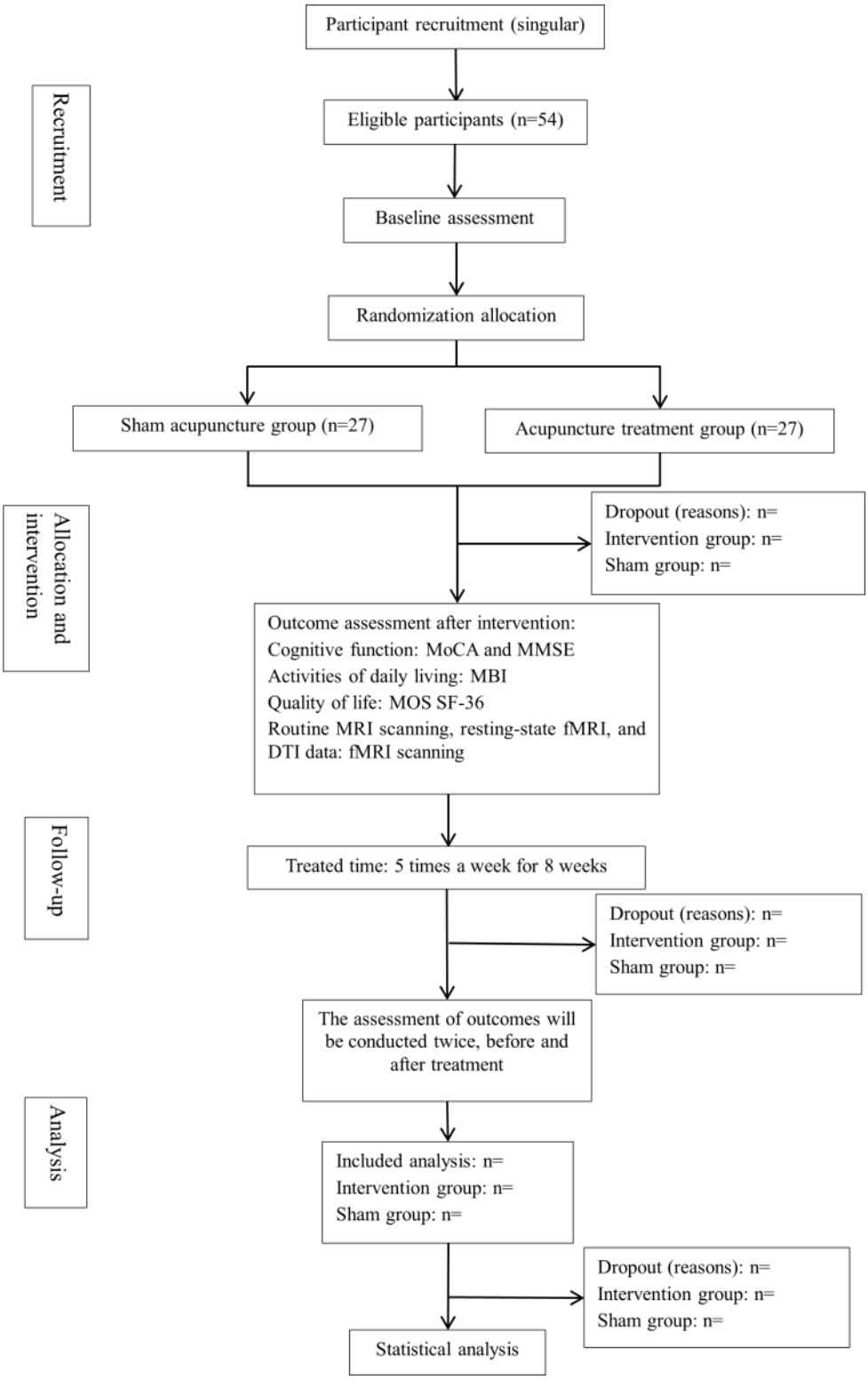

Eligibility Criteria

Eligible participants must meet the specified inclusion criteria and not fall under the exclusion criteria. The inclusion criteria are as follows: confirmation of the diagnosis through adherence to the stipulated criteria and validation via head magnetic resonance imaging (MRI) or computed tomography examination; disease duration of >1 month; first ever stroke to avoid confounding effects of previous cerebrovascular events on brain network reorganization and cognitive function; conscious state with stable vital signs and nonprogressive symptoms; clear consciousness without meeting the criteria for

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dementia (Mini-Mental State Examination [MMSE] score of >17 for illiterate individuals, >20 for individuals with a primary school educational level, and >24 for individuals with a middle school educational level or higher—thresholds selected to ensure that participants can complete the full range of cognitive assessments while still presenting mild to moderate PSCI); onset of cognitive impairment after stroke; age of >18 years; right-handedness to reduce variability in brain lateralization patterns, which is particularly important for imaging analyses; and voluntary participation with the provision of self- or legal guardian–signed informed consent.

Exclusion criteria encompass recurrent disease; cognitive impairment originating from other causes; the presence of severe conditions such as liver, kidney, or heart disease; and impediments to cooperation with examinations due to severe hearing impairment, language barriers, or other significant reasons. In addition, all potential participants will be assessed using validated screening tools such as the Hospital Anxiety and Depression Scale or Hamilton Depression Rating Scale at baseline. Patients who meet the diagnostic threshold for moderate to severe depression or anxiety (Hospital Anxiety and Depression Scale score of ≥11 or Hamilton Depression Rating Scale score of ≥17) will be excluded from the trial to avoid emotional state confounding cognitive outcome assessments.

Randomization and Allocation Concealment

An impartial statistician will generate a concealed random allocation sequence using the PLAN procedure in the SAS statistical software (version 9.1; SAS Institute). Eligible participants will be randomly assigned in a 1:1 ratio to either the acupuncture treatment group or the conventional treatment control group. The random sequence will be securely stored and managed by a project manager who is not involved in participant recruitment, screening, or outcome assessment. To ensure allocation concealment, the group assignments will not be disclosed to screeners, evaluators, or participants during the enrollment process. Once a participant is deemed eligible and enrolled, the project manager will inform them of their group assignment via telephone, thus maintaining strict separation between the randomization process and other trial operations.

Given the nature of acupuncture, it is not feasible to blind the practitioners delivering the intervention. We acknowledge that the lack of practitioner blinding could introduce performance bias and influence internal validity through potential nonspecific or placebo effects. To minimize these risks, we will (1) blind participants to the specific study hypotheses and expected effects of each intervention, (2) ensure that outcome assessors and statisticians remain blinded throughout the trial, (3) standardize the practitioner-patient interaction by using scripted instructions and limiting nonprotocol communication, and (4) provide the control group with conventional treatment to control for attention and treatment expectancy effects. These measures aim to reduce expectancy bias and placebo responses, thereby strengthening the internal validity of the trial despite the inherent limitations of acupuncture blinding.

Blinding

This study will use a single-blind design in which both the participants and the primary outcome assessors will remain blinded to group assignments. A designated project manager will oversee the generation of the randomization sequence and the allocation of blinding codes. Group assignments will be generated using a computer-based random number table and anonymized as group A or B.

Given the inherently distinguishable nature of acupuncture interventions, blinding of treating physicians is not feasible. However, all treating physicians will undergo standardized training to ensure consistent procedures and neutral communication, thereby minimizing observer bias.

Participants will be randomly assigned to either the acupuncture group or the conventional treatment group. To maintain participant-level blinding, the conventional treatment group will receive sham acupuncture using specially designed nonpenetrating needles applied to nonacupoint locations. The procedures, including manipulation, duration, and frequency, will be identical in both groups to ensure comparable treatment experiences.

Outcome assessors and statistical analysts will be blinded to the actual group identities and will only have access to anonymized labels (A or B). Conversely, treating physicians and project managers will not participate in outcome assessment or data analysis. Similarly, outcome assessors and analysts will not be involved in participant enrollment or allocation.

The blinding code will be securely sealed and will not be disclosed until the completion of all statistical analyses.

To assess the success of blinding, participants will be asked at the end of the treatment period to indicate which group they believe they were assigned to (A, B, or unsure) via a structured questionnaire.

Intervention

All participants will receive conventional therapy standardized according to the Chinese guidelines for the diagnosis and treatment of vascular cognitive impairment (2024 edition) [39], with clearly defined components, treatment frequency, and documentation procedures to ensure reproducibility.

Conventional Treatment Group

Basic Medical Treatment

Standard pharmacological management will follow the 2024 Chinese guidelines, including risk factor control. Medication type and dose will be individualized based on comorbidities and physician judgment, but treatment categories, target parameters (blood pressure of <140/90 mm Hg and low-density lipoprotein cholesterol level of <2.6 mmol/L), and monitoring schedules will be uniform across participants.

Basic Rehabilitation Therapy

A standardized rehabilitation framework will be applied, consisting of three core modules:

1. Exercise therapy: 30 minutes per session, 5 sessions per week, including balance training, gait training, and limb

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mobility exercises. Intensity will be tailored to baseline motor ability using the Fugl-Meyer Assessment, but progression will follow a predefined stepwise protocol.

2. Occupational therapy: 30 minutes per session, 5 sessions per week focusing on activities of daily living such as dressing, feeding, and household tasks using standardized task sequences.
3. Physical agent modality therapy: where indicated, treatments such as transcranial direct current stimulation or low-frequency pulsed magnetic therapy will be applied following fixed device settings and session lengths.

Cognitive Function Training

Structured cognitive training will target attention, memory, judgment, reasoning, and executive function. Each session will last 30 minutes once daily, 5 days per week for 8 weeks, delivered using a standardized digital training program and exercise booklet. Therapists will follow a fixed progression schedule, with difficulty levels increasing every 2 weeks.

Sham Acupuncture Procedure

Sham acupuncture will be administered at nonacupoint sites approximately 2 cm posterior to Baihui (GV20), 1.5 cm lateral to Shenting (GV24), and 2 cm adjacent to Sishencong (EX-HN1), avoiding recognized meridians [40]. A nonpenetrating placebo needle will provide superficial tactile pressure without skin penetration, mimicking real acupuncture sensation but avoiding physiological effects [41]. Sessions will last 20 minutes once daily, 5 days per week for 8 weeks.

Acupuncture Treatment Group

Overview

Participants will receive all the aforementioned conventional therapy components and real acupuncture in place of sham acupuncture. Selected acupoints will include GV20, GV24, and EX-HN1. Disposable sterile filiform needles will be inserted to a depth of 10 to 15 mm and manipulated to elicit *deqi* sensation. Each session will last 20 minutes once daily, 5 days per week for 8 weeks.

Standardization and Quality Control

All therapists and acupuncturists will undergo a 2-day training workshop on the standardized protocol. Detailed treatment manuals and checklists will be used to guide therapy delivery. Treatment logs will be completed after every session, documenting date, time, duration, completion status, and any deviations from the protocol. Monthly audits will be conducted by the project manager to ensure adherence to the protocol.

Primary Outcomes

All practitioners involved in the study are experienced and professionally trained rehabilitation physicians or therapists. The MoCA will serve as the primary outcome measure for statistical inference as it is more sensitive to detecting MCI and changes in executive and visuospatial domains commonly observed after stroke. The MMSE will be analyzed as a key secondary outcome to provide complementary information and enable comparison with previous literature where the MMSE was the predominant tool.

Both assessments will be administered by the same trained therapist before and after the intervention to ensure consistency and minimize interrater variability. The MoCA evaluates a broad range of cognitive domains, including visuospatial and executive abilities, naming, memory, attention, language, abstraction, delayed recall, and orientation. It consists of 12 subitems, with a total score of 30 points; a score of >26 is generally considered healthy. For participants with <12 years of education, 1 point will be added to the total score to adjust for education bias.

The MMSE also provides a total score of 30 points and assesses domains such as orientation, registration, attention and calculation, recall, language, and praxis. While the MMSE is widely used in clinical settings for its brevity and utility in detecting moderate to severe cognitive impairment, the MoCA is more sensitive to subtle cognitive changes, making it more suitable as the primary statistical end point in this trial.

Multiple comparisons will be addressed by applying Bonferroni or other appropriate correction methods for secondary outcomes, ensuring statistical rigor while capturing a comprehensive and nuanced picture of cognitive changes following acupuncture intervention. The timing of treatment assessments and data collection are shown in Table 1.

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Table 1. Timing of treatment assessments and data collection.

Item	Study period			
	Before enrollment (−1 wk)	Baseline (0 wk)	Intervention period	
			4 wk	8 wk
Inclusion criteria	✓			
Exclusion criteria	✓			
Informed consent	✓			
Randomization		✓		
Allocation		✓		
Interventions				
Acupuncture treatment group			✓	✓
Sham acupuncture group			✓	✓
Assessments				
MMSE[a]		✓	✓	✓
MoCA[b]		✓	✓	✓
MBI[c]		✓	✓	✓
MOS SF-36[d]		✓	✓	✓
Routine MRI[e] scanning		✓	✓	✓
Resting-state fMRI[f]		✓	✓	✓
DTI[g]		✓	✓	✓

[a]MMSE: Mini-Mental State Examination.
[b]MoCA: Montreal Cognitive Assessment.
[c]MBI: modified Barthel index.
[d]MOS SF-36: Medical Outcomes Study 36-Item Short-Form Health Survey.
[e]MRI: magnetic resonance imaging.
[f]fMRI: functional MRI.
[g]DTI: diffusion tensor imaging.

Secondary Outcomes

Ability to Perform Activities of Daily Living

The modified Barthel index will be used for pre- and posttreatment assessments. Scoring is as follows: 100 points indicate normal ability to manage daily-life activities; scores of >60 imply mild dysfunction and mild life dependence, scores of 41 to 59 indicate moderate dysfunction and moderate life dependence, scores of 21 to 40 reflect severe dysfunction with evident life dependence, and scores of <20 denote total life dependency.

Quality of Life

The Medical Outcomes Study 36-Item Short-Form Health Survey will be used for evaluation before and after treatment. This comprehensive scale covers 8 domains, encompassing physical functioning, role limitations due to physical health problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health.

fMRI Scanning Scheme

A Siemens MAGNETOM Trio 3.0T magnetic resonance imager will be used for routine MRI scanning, resting-state fMRI, and diffusion tensor imaging (DTI) data collection. Both pre- and posttreatment scans will be conducted using this state-of-the-art imaging technology. For imaging data, false discovery rate correction will be used.

Conventional MRI scan sequence and parameters are as follows: (1) repetition time (TR)=600 ms, echo time (TE)=10 ms, layer thickness=5 mm, field of view (FOV)=240 mm, and matrix size=256 × 256 (T1-weighted image parameters); (2) TR=3000 ms, TE=113 ms, layer thickness=5 mm, FOV=240 mm, and matrix size=256 × 256 (T2-weighted image parameters); and (3) TR=8800 ms, TE=79 ms, layer thickness=5 mm, FOV=240 mm, and matrix size=256 × 256 (T2-weighted fluid-attenuated inversion recovery parameters).

The scanning sequence and parameters for fMRI are as follows. First, the anatomical data are collected via a T1-weighted 3D spoiled gradient–recalled sequence, and the volume images are obtained. The scanning parameters are TR=1900 ms, TE=2.26 ms, layer thickness=1 mm, FOV=250 mm, and matrix size=256

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× 256. Second, the resting fMRI data are collected via real-time imaging processing. Gradient-recalled echo-planar imaging recalls the image with the following parameters: TR=2000 ms, TE=30 ms, continuous scanning of 30 layers, layer thickness=4 mm, FOV=200 mm, matrix size=64 × 64, and scanning time of approximately 8 minutes and 6 seconds.

The scanning sequence and parameters for DTI are as follows. First, the anatomical data are collected via a T1-weighted 3D spoiled gradient–recalled sequence, and the volume images are obtained. The scanning parameters are TR=1900 ms, TE=2.26 ms, layer thickness=1 mm, FOV=250 mm, and matrix size=256 × 256. Second, the DTI data are scanned through an echo-planar imaging sequence in the horizontal axis. The following parameters—TR=7200 ms, TE=104 ms, 49 layers, 2.5-mm thickness, number of excitations once, matrix size=128 × 128, FOV=240 × 240 mm, and 64 nonlinear diffusion gradients (b=0.1000 seconds per mm^2)—are applied. The scanning duration is approximately 8 minutes and 11 seconds.

Safety Measurements

Acupuncture typically does not lead to severe adverse events [42,43]. However, given the neurological population and the invasive nature of acupuncture, a formal data safety monitoring plan will be implemented. An independent data safety monitoring board (DSMB), comprising a neurologist, an experienced acupuncturist not involved in the trial, and a biostatistician, will oversee participant safety throughout the study. The DSMB will review cumulative safety data and adjudicate all adverse events and serious adverse events independently of the trial investigators, including assessment of causality, severity, and relatedness to the intervention.

All unexpected adverse events will be promptly reported by clinical staff to the investigator or project manager and documented in detail. These reports will be forwarded to the DSMB for independent review within 72 hours. Should a serious adverse event occur, the principal investigator and ethics committee will be notified immediately, and the DSMB will make recommendations on whether the participant should be withdrawn from the trial or whether trial procedures require modification. The DSMB will meet quarterly or more frequently if safety concerns arise to ensure continuous monitoring of participant well-being and trial integrity.

Data Management

During participant recruitment, screeners will gather demographic and baseline characteristic data. The final assessor will measure primary and secondary outcomes at baseline and at the conclusion of the 8-week intervention. A research assistant will oversee quality control during data collection and take charge of data entry. The project manager will assume responsibility for the initial data cleaning, identification, encoding, and transformation into the suitable format for subsequent data analysis. All study data will be entered into an electronic database with range and consistency checks. Data access will be restricted to authorized study staff. Missing data will be minimized through real-time monitoring and reminders. If outcome data are missing, multiple imputation by chained equations will be applied under the assumption of being missing at random. Pooled estimates across imputations will be reported, with sensitivity analyses using complete-case data.

General Data and Efficacy Indicator Statistical Analysis

All statistical analyses will be conducted in SPSS (version 20.0; IBM Corp), with the significance level set at $P<.05$. Analyses will be divided into two categories: (1) general data and efficacy indicators and (2) fMRI data processing and statistical analysis. For general data and efficacy indicators, two-tailed independent sample *t* tests or chi-square tests will be used to assess pre- and posttreatment differences in overall cognitive function, activities of daily living, and quality of life between groups.

fMRI Preprocessing

fMRI data will be preprocessed using the DPABI toolbox a widely used open-source platform for resting-state fMRI analysis that integrates functions such as slice timing correction, head motion realignment, normalization to Montreal Neurological Institute space, spatial smoothing, and nuisance signal regression. DPABI is based on SPM12 (Wellcome Department of Imaging Neuroscience at University College London) and MATLAB (R2023a; MathWorks). Functional connectivity and amplitude of low-frequency fluctuation analyses will be conducted in this study [44].

fMRI Statistical Analysis

After preprocessing, statistical analyses will be conducted with $P<.05$ as the significance threshold applying false discovery rate correction for multiple comparisons. The analysis will include the following:

1. DMN extraction: random 2-sample *t* tests will compare extracted DMN data between groups, with $P<.05$ considered statistically significant.
2. Functional connectivity of the DMN: the posterior cingulate cortex, medial prefrontal cortex, and medial temporal lobe were defined as regions of interest (ROIs). Resting-state functional connections between ROIs will be calculated, and the time correlation coefficient will be obtained for the 2–independent sample *t* test.
3. Structural connectivity of the DMN: fiber bundles between ROIs will be extracted from DTI data. The average fiber bundle length (mL), average diffusion rate (MD), and mean fractional anisotropy (mFA) will be calculated for each group and compared using 2-sample *t* tests.
4. Correlation analysis: using correlation tests, MoCA, MMSE, MBI, and Medical Outcomes Study 36-Item Short-Form Health Survey scores; *r* values; and mL, mFA, and MD values will undergo statistical analysis. The Pearson correlation coefficient (*r*) will be obtained for the *t* test.

Multiple linear regression models will be used to examine associations between groups (acupuncture vs sham acupuncture) and posttreatment cognitive outcomes (MoCA and MMSE), adjusting for baseline covariates. Logistic regression will analyze dichotomized outcomes, and interaction terms will test moderating effects of demographic and clinical variables.

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Ethical Considerations

This informed consent agreement is executed in adherence to the Declaration of Helsinki. The study protocol and consent form have received approval from the ethics committee of the First Affiliated Hospital of Nanchang University (approval 2020 12-86). All participants will receive comprehensive information about the trial and provide their informed consent through a signed agreement before taking part. All personal information will be kept confidential — identifiable data will be stored separately from study data, replaced by coded IDs, and accessible only to the research team. Electronic records will be stored on encrypted, password-protected servers and paper forms in locked cabinets. No identifiable information will be reported in publications.

Any significant modifications to the protocol, such as changes to eligibility criteria, outcomes, or analysis plans, will be submitted to the research ethics committee for review and approval before implementation. The approved amendments will also be communicated promptly to all relevant parties, including the trial investigators, trial participants, trial registries, and relevant journals or regulatory bodies. These modifications will also be documented in an amendment log and will be audited at least annually to ensure consistency across the registered protocol and study documents.

Trial Status

This protocol is version 1, dated August 20, 2025. The trial has not yet started.

Results

We are currently in the recruitment phase, and we will publish the results in open-source journals when the trial is completed. As of August 2025, we have completed protocol finalization and ethics approval. Recruitment has begun, and no participants have been enrolled yet.

Discussion

Therapeutic Approaches

Currently, cognitive training stands as the predominant rehabilitation therapy for PSCI, demonstrating positive effects across various cognitive domains. Nevertheless, its efficacy is constrained by high demands on patients' cognitive function, limiting its application in cases of severe cognitive dysfunction. Alternative therapies, including TCM, exercise, and music therapy, exhibit some potential in improving the cognitive function of patients with PSCI, yet their effectiveness remains unclear. Acupuncture, rooted in TCM principles, has been recognized by scholars for its positive impact on alleviating cognitive dysfunction in patients with PSCI. Notably, studies suggest that specific acupuncture points such as Baihui, Shenting, and Sishencong significantly enhance cognitive function in patients with PSCI [45,46]. However, the precise mechanisms through which acupuncture modulates brain function in patients with PSCI, particularly in the DMN brain region associated with cognitive function, remain unexplored.

In this trial, we have implemented a stringent randomized controlled study design, wherein patients diagnosed with PSCI are randomly allocated to either a sham acupuncture group or an acupuncture treatment group. Although cognitive function assessments typically involve subjective scales, we are enhancing the consistency and reliability of these assessments by providing standardized training for the evaluators and ensuring that each patient is assessed by the same evaluator. Furthermore, fMRI will be used to explore the neuroimaging mechanisms that underpin the effects of acupuncture, with the goal of offering valuable insights for clinical practice.

Brand New Insights

A suite of analyses, including independent component analysis, functional connectivity analysis, and DTI analysis, will be conducted before and after the intervention to assess changes in activation patterns, functional connectivity, and structural connectivity within brain regions associated with the DMN. Correlation analyses between changes in DMN and cognitive function will be conducted to elucidate the neuroimaging correlates of the structural and functional changes within the DMN.

Crucially, all participants will receive standardized cognitive rehabilitation as part of routine clinical treatment throughout the trial, with both the acupuncture treatment group and the sham acupuncture group undergoing the same treatment regimen. This design intentionally sets cognitive training as a constant therapeutic background to isolate the specific effects of acupuncture from nonspecific placebo responses. Therefore, the observed differences between groups will solely represent the contribution of acupuncture points to neuropsychology rather than absolute treatment outcomes. This method rigorously controls cognitive training variables, precisely quantifies the incremental benefits of acupuncture based on evidence-based rehabilitation, and simulates real-world practice to demonstrate the clinical relevance of acupuncture as an adjunctive treatment. Consequently, effect sizes should be interpreted as the added value of acupuncture to a standard cognitive program, with the differences controlled via sham stimulation directly attributable to the specific neural stimulation mechanisms of acupoints.

Limitations and Future Directions

While the randomized controlled trial and blinding methodologies are upheld, the feasibility of achieving total blindness has been acknowledged as challenging, particularly in nondrug trials. Given the unique nature of acupuncture treatment, a double-blind procedure is not feasible, leading to the decision to blind outcome evaluators and statistical analysts. In addition, both groups receive conventional cognitive training to ensure ethical equivalence; however, this may reduce the contrast between groups. Moreover, we acknowledge the limitations in generalizability of our study findings, primarily due to the single-center design and the constraints imposed by resource-intensive research protocols and the standardization of millimeter-level interventions. To minimize potential biases, we have implemented rigorous quality control measures. For future research, we plan to conduct multicenter trials to quantitatively assess general applicability and conduct additional

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real-world validation to further enhance the generalizability of our findings.

In summary, by adopting a multimodal neuroimaging approach, this study delves into the impact of acupuncture on the brain structure and function of patients with PSCI. By examining correlations with changes in cognitive function, this study aims to clarify the specific targets and mechanisms through which acupuncture enhances cognitive function. The findings are anticipated to yield reliable imaging markers for evaluating the efficacy of acupuncture and prognosis of PSCI, offering valuable clinical applications. If this study demonstrates a significant intervention effect, it will contribute robust evidence supporting acupuncture's ability to ameliorate cognitive dysfunction in patients with PSCI, providing insights into its neuroimaging mechanisms.

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Authors' Contributions

All authors adhere to the authorship guidelines of trials. All authors have agreed to publication. WC and MW were responsible for experimental design and manuscript writing. ML was responsible for guidance and proofreading.

Conflicts of Interest

None declared.

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Abbreviations

DMN: default mode network
DSMB: data safety monitoring board
DTI: diffusion tensor imaging
fMRI: functional magnetic resonance imaging
FOV: field of view
MCI: mild cognitive impairment
MD: mean difference
MMSE: Mini-Mental State Examination
MoCA: Montreal Cognitive Assessment
MRI: magnetic resonance imaging
PSCI: poststroke cognitive impairment
ROI: region of interest
TCM: traditional Chinese medicine
TE: echo time
TR: repetition time

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Protocol

A Triple Perspective on the Triple Visit: Protocol for a Mixed Methods Evaluation of the Implementation of a Pediatric Multidisciplinary Clinic Model for Inflammatory Bowel Disease

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Abstract

Background: Given the impact of inflammatory bowel disease (IBD) on both physical health and psychosocial functioning, the management of pediatric IBD requires a multidisciplinary approach that provides holistic care, rapid access, and health education to young patients with IBD. Yet despite recommendations, a formalized clinic model for holistic pediatric IBD care remains an unmet need for this population.

Objective: The objective of this study is to comprehensively evaluate the implementation of a new clinic model aimed at providing holistic care, rapid access, and health education for pediatric patients with IBD.

Methods: This study uses a multiperspective mixed methods design, incorporating both qualitative and quantitative data collected simultaneously from clinicians, parents or guardians, and pediatric patients. The quantitative component includes a pre-post implementation chart review, structured observations of clinical practices, and surveys tailored to pediatric patients and their parents or guardians. The qualitative aspect encompasses semistructured interviews with clinicians and parents or guardians as well as play-based interviews with patients. Triangulation will be used to converge these different methodologies and to produce a holistic evaluation of the IBD clinic.

Results: This study was approved by the Humber River Health Research Ethics Board on December 23, 2024. Recruitment for this study began on January 30, 2025, and we anticipate a data collection end date of December 2025.

Conclusions: Given that this clinic model is relatively new, this protocol will provide sound methodological direction for other studies that aim to evaluate or implement this type of model in their setting. The evaluation itself will provide comprehensive insights into both the successes and challenges of implementing a multidisciplinary approach that provides a holistic model of care for pediatric patients with IBD. As such, this evaluation will be foundational in providing an applied understanding of the impact and effectiveness of this holistic approach in pediatric patients with IBD.

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KEYWORDS

child-centered methods; Crohn disease; health maintenance; mental health; multidisciplinary care model; pediatric inflammatory bowel disease; patient perspectives; parent perspectives; rapid access clinic; ulcerative colitis

Introduction

Background

Inflammatory bowel disease (IBD) is a chronic and relapsing inflammatory condition that affects not only the patient's physical health but also their quality of life and social functioning [1,2]. Indeed, patients with IBD reportedly experience increased anxiety and mental health concerns compared with the healthy population [3], in addition to a disease course that is often unpredictable and marked by a waxing and waning pattern, despite surgical intervention and optimal medication [4]. In children, IBD can also affect growth and pubertal development [5]. As such, they are a challenging patient population to manage, which poses a significant burden on health care costs and resources. In Canada, specifically, pediatric IBD has been increasing steadily over the past 20 years [6], and it is expected to exponentially increase in the next 10-20 years [7].

To facilitate the management of complex patients with IBD, recommendations have been put forth to standardize and improve access to IBD subspeciality care. For example, Crohn's and Colitis Canada recently supported the "Promoting Access and Care through Centres of Excellence" (PACE) program. PACE included a group of IBD experts, nurses, and patients, who sought to develop a portfolio of quality indicators important for the establishment of an IBD clinic [8]. By using the PACE principles to develop an IBD center of excellence, clinicians from McGill University reported that only 6.6% of patients were steroid dependent and 48.8% of patients were on biologic medications following the IBD center's establishment [9,10]. In addition, the implementation of their IBD rapid access clinic improved health care delivery, replaced many invasive investigations (eg, colonoscopy and endoscopy) with less invasive monitoring methods (eg, fecal calprotectin and c-reactive protein test), and reduced emergency department visits and associated costs [11]. Notably, patients with IBD who presented to the hospital first (n=135) during an acute crisis costed health care an average of CAD $1885 (US $1360) per visit, excluding admission costs, and use of cross-sectional imaging occurred in 65.7% of these visits. This contrasts markedly with the CAD $403 (US $290.93) average cost for patients who presented to the IBD rapid access clinic first (n=488) and the use of cross-sectional imaging was 6%. Despite the guidance provided by PACE and positive impact of the rapid access IBD clinic at McGill, community IBD clinics with rapid access components, including for pediatric IBD, are still uncommon in Canada.

Beyond providing rapid access to patients with IBD, it is also important to provide health education, health maintenance checks and mental health assessments to children with IBD [12]. Education is typically focused on the disease itself, its management, and how to cope with chronic illness [11]. Health maintenance emphasizes ensuring that children with IBD have (1) appropriate growth which is monitored by an IBD nurse and dietician; (2) good nutritional status that includes improving or normalizing vitamin D levels, iron status, and other micronutrients; (3) excellent bone health that includes checking bone age and performing dual-energy x-ray absorptiometry (measures bone density) if they have been exposed to steroids; and (4) up-to-date vaccines [13]. Mental health status should also be assessed on a regular basis, both at baseline and at routine intervals, to ensure early referrals to appropriate providers and prevent poor outcomes associated with anxiety and depression [14]. By providing such services, a pediatric IBD clinic ensures a holistic approach to the management of IBD, while simultaneously preparing children for managing their disease in the future. Subsequently, this improves patients' management of disease and their self-efficacy and thus provides the building blocks and foundation for a successful transition to adult care [11,15].

To address the significant unmet need of a holistic clinic model of care that provides rapid access to pediatric patients at Humber River Health (HRH), the Outpatient Paediatric IBD Clinic at HRH aimed to achieve several aims within their clinic: (1) Establish a community IBD center with a rapid access IBD clinic based on the guidance provided by the PACE quality indicators. (2) Establish a multidisciplinary community clinic. This provides patients with a biannual visit, referred to as the Triple Visit, where patients would be reviewed by the gastroenterologist (GI), nurse practitioner, and dietician during their visit to the clinic. (3) Establish a mental health–screening program for pediatric patients within the clinic to allow for the proactive identification of patients who need additional supports and resources such as social work, psychology, adolescent medicine, and so on. (4) Develop a health maintenance checklist with proactive management strategies such as bone health, growth assessment, vaccine status, and so on.

Aims of the Study

To understand the impact of the newly implemented Triple Visit and clinic model of care on HRH's Outpatient Paediatric IBD Clinic, we aim to comprehensively evaluate its implementation from the triple perspective of patients, parents or guardians, and clinicians. We will evaluate the clinic's efficacy in (1) improving access to new or unwell patients, (2) improving health maintenance for children with IBD, (3) effectively identifying mental health concerns in this specific population, and (4) satisfying patients' needs.

Our specific research questions are as follows: (1) What is the impact of the new IBD clinic model of care on patient outcomes such as the use of steroid and biologic medications, health maintenance, and mental health? (2) What is the impact of the new IBD clinic model of care on improving patient access to care and health care usage in general? (3) Are patients and their parents or guardians satisfied with this new model of care? (4) What are the barriers and facilitators experienced by different clinician roles in implementing the new clinic model?

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Study Design and Procedures

This study is a multiperspective concurrent mixed methods design, incorporating both quantitative and qualitative data collected simultaneously from clinicians, parents or guardians, and pediatric patients [16]. Data will be triangulated to integrate these different methodologies to produce a holistic evaluation of the IBD clinic and its newly implemented components (Figure 1). The quantitative phase will involve a pre-post implementation chart review, structured observations of clinical practices, and surveys tailored to pediatric patients and parents or guardians. The qualitative aspect will encompass semistructured interviews with clinicians and parents or guardians, respectively, as well as play-based interviews (PBIs) with patients. Qualitative data collection and analysis will be guided by the COREQ (Consolidated Criteria for Reporting Qualitative research) standards [17].

Figure 1. Flowchart illustrating the steps in the convergence model of triangulation design deployed for this evaluation. PBIs: play-based interviews; TA: thematic analysis; VVV A: visual verbal video analysis.

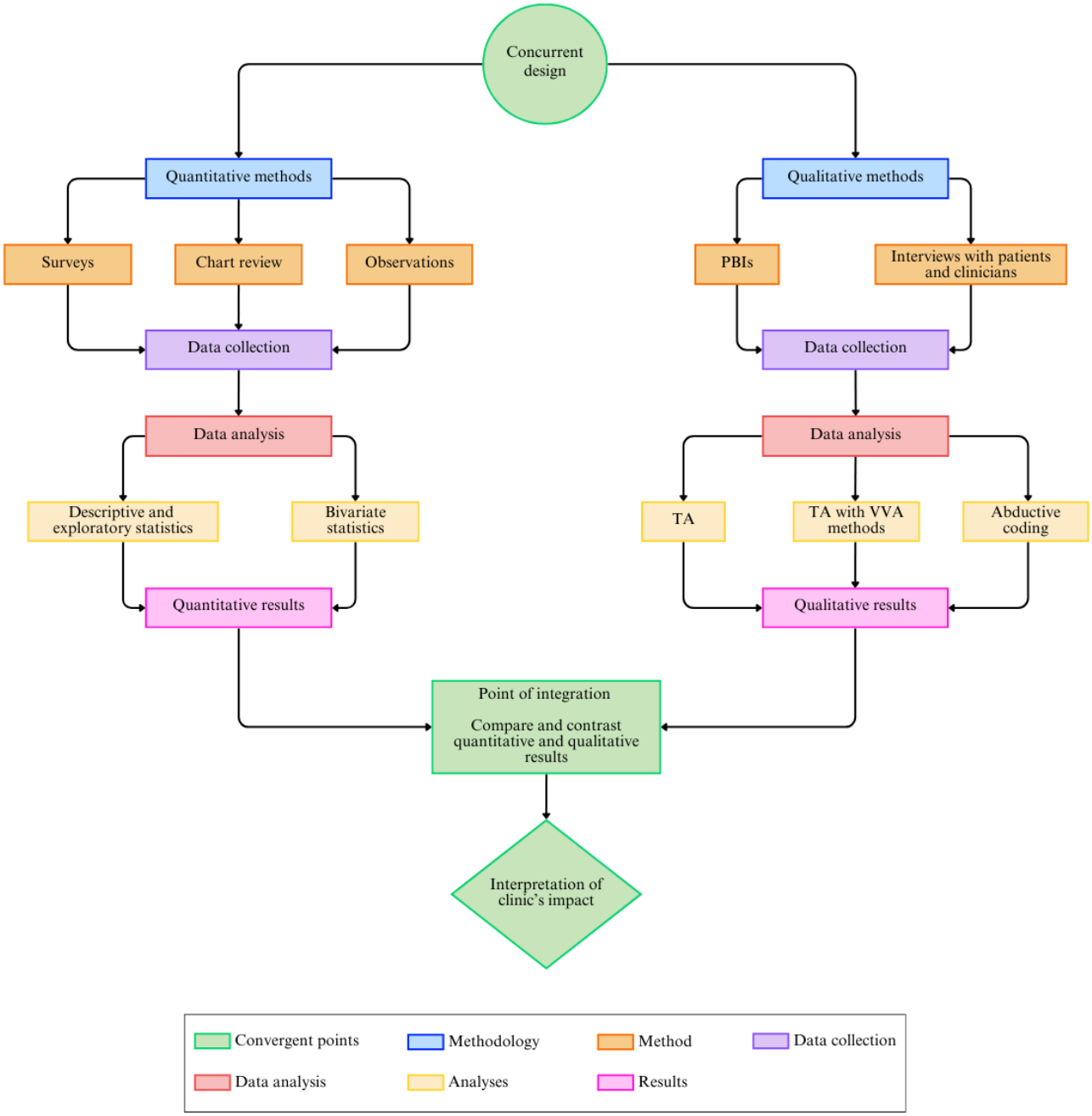

By triangulating both qualitative and quantitative methods with an equal weight on each [18,19], we aim to offer a nuanced portrayal of the IBD clinic's efficacy in achieving its aforementioned aims, in addition to illuminating any of the barriers and facilitators influencing the implementation of the new clinic model. The integration of diverse data sources through triangulation will not only enhance the validity of our findings but also provide a more comprehensive understanding of the clinic's dynamics, ensuring a well-informed basis for future [20] enhancements and improvements to the IBD clinic.

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Methods

Participants and Recruitment

To comprehensively evaluate the IBD clinic's new model of care, including the Triple Visit, participants will be recruited from three different perspectives: (1) patients, (2) parents or guardians, and (3) clinicians, including GI physicians, nurse practitioners, dietitians, and mental health professionals such as social workers and psychologists. We will deploy a parallel sampling design [21] in that the samples from the quantitative and qualitative components may be different but are drawn from the same database within the IBD clinic. This sampling design was chosen to increase the uptake in recruitment in a small clinic.

Pediatric Patients and Parent or Guardians

During IBD clinic outpatient appointments, all parents or guardians accompanying pediatric patients in attendance at HRH's Outpatient Paediatric IBD Clinic will be asked by the clinic's GI physicians and nurse practitioner whether they consent to being contacted by the hospital's research institute in relation to an evaluation of the clinic's Triple Visit model of care. Study brochures outlining research activities will be provided to parents or guardians during the appointment, in addition to study information cards tailored to our pediatric population. Subsequently, a research team member will connect with parents or guardians who consent to being contacted via their preferred means of communication (ie, email or phone) and will be invited to take part in research activities evaluating the clinic. Patients and parents or guardians can choose to participate in all, some, or none of the research activities. Moreover, patients and parents or guardians will not be recruited as dyads, and therefore one does not necessitate the other for participation. Participants who participate in and complete research activities will be compensated with an e-gift card of their choice from a list of available gift cards and the value of the compensation will correspond to the activity completed. Patient and parent or parent survey compensation value will be CAD $10 (US $7.22), patient and parent or guardian interview compensation value will be CAD $15 (US $10.83), and clinician interviews will be CAD $5 (US $3.61). Patients and parents or guardians who complete a survey and an interview will receive a CAD $10 (US $7.22) bonus for completing both.

For patients, the inclusion criteria will consist of being aged 8-18 years, a patient of the HRH's Outpatient Paediatric IBD Clinic between January 2021 and December 2024, free from cognitive impairment, verbally fluent, and proficient in English. Patients who do not provide assent or whose parents or guardians do not consent to their participation will be excluded. For parents or guardians, the inclusion criteria will consist of being the parent or guardian of a current pediatric patient of HRH's Outpatient Paediatric IBD Clinic, free from cognitive impairment, and proficiency in English. For the quantitative phase, we aim to recruit the maximum number of patients (ie, ~80) and their parents or guardians (ie, ~80). For the qualitative phase, we aim to recruit 15 patients, in addition to 15 parents or guardians. For interview studies, a sample size of 15 has been considered to be a sound starting point with the understanding that the final sample size may be adjusted as the study progresses [22].

Clinicians

For the semistructured interviews, we will invite all clinicians who provide direct care to HRH's Outpatient Paediatric IBD Clinic patients to participate. This will include GI physicians, nurse practitioners, dieticians, and mental health professionals such as social workers and psychologists. We anticipate that the sample size will be approximately 6-8 clinicians. A combination of convenience and purposive sampling will be used [23], so that all clinician roles in the IBD clinic are represented. This approach will capture the full range of clinician perspectives ensuring that depth of understanding is foregrounded without the need for further recruitment. The director of the Maternal Child Health department will send an email to clinicians who provide IBD care to inform them of the study and the invitation to participate in the interview. To mitigate any coercion, the email will include the contact details of the qualitative methodologist (QM) so that interested clinicians can contact them themselves to learn more about the study and potentially self-enroll.

For the structured observations of clinical practices, we will not be recruiting staff or patients per se but rather aiming to observe appointment types such as first visit, last visit or transitioning to adult care, and Triple Visit. A memo will be sent from the clinic lead to clinic staff, notifying them that observations will be conducted throughout the study duration. Research staff will work with clinicians to pick appropriate times to observe clinical activities based on appointment type and with the consent of parents or guardians.

Measures and Qualitative Methods

No fixed order will be prescribed for participation in patient- or parent or guardian–facing research activities as this will allow patients and parents or guardians the flexibility to change their mind about what research activities they wish to be a part of. As such, some patients may start with the patient survey, while others may start with the PBI. Similarly, some parents or guardians may begin with the parent or guardian survey, while others may begin with the semistructured interviews. Direct observations, chart reviews, and clinician interviews will flexibly occur over the course of the study. A battery of quantitative measures delivered via patient and parent or guardian surveys, as well as chart reviews and structured observations, will be deployed to quantify and measure the impact of the new clinic model on patient outcomes, in addition to satisfaction with the model of care. Qualitative methods will be used to collect data from clinicians, parents or guardian, and pediatric patients regarding their experiences and perceptions of the new clinic model, including the Triple Visit, as well as their recommendations for improvement. Semistructured interviews will be conducted with clinicians and parents or guardians and a PBI framework method will be used with patients. See Table 1 for a summary of the methods and data sources that will be used.

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Table 1. Summary of methods, data sources, and purpose.

Methodology and method	Data source	Data examples	Purpose
Quantitative			
Survey	Parents (and on behalf of patients)	Demographics	Contextualize findings
Survey	Patients	Transition readiness, self-efficacy, IBD[a] knowledge, service satisfaction, quality of life, and mental health	Understand patient well-being, experiences, and satisfaction in relation to the new clinic
Survey	Parents	Quality of care, IBD knowledge, transition readiness, health-related quality of life, and parenting stress	Understand parent well-being, experiences, and satisfaction in relation to the new clinic
Chart review	Patient EMRs[b]	Tests or procedures ordered, prescribed medications, dosage, and number of contacts	Understand changes in clinical outcomes pre-post implementation
Structured observations of PACE[c] quality indicators	Clinical encounters, patient EMRs, and consult with clinicians survey	PACE quality indicators [8]	Assess how well the clinic aligns with established guidelines linked to positive patient outcomes
Qualitative			
Semistructured interviews	Parents	Understanding of the Triple Visit, access to the clinic, mental health, health maintenance, and satisfaction with clinic	Garner an in-depth account of parent experiences and satisfaction with the clinic
CFIR[d] interviews	Clinicians	Rationale for clinic, advantages of clinic, adaptability of clinic, receptivity to clinic, and self-efficacy	Garner clinician barriers and facilitators with implementing new model
Play-based interviews	Patients	Feelings toward the clinic, how helpful are the clinicians, and what would be even more helpful	Garner an in-depth account of patient experiences and satisfaction with the clinic

[a]IBD: inflammatory bowel disease.

[b]EMRs: electronic medical records.

[c]PACE: Promoting Access and Care through Centres of Excellence.

[d]CFIR: Consolidated Framework for Implementation Research.

Demographics Survey

Patient- and disease-related demographics, as well as parent or guardian demographics, will be collected once, at the time of first participation. Parents or guardians will be responsible for completing demographic information on behalf of themselves and their child via a link sent to them for a demographics survey in Qualtrics. Demographic questions include but are not limited to age, sex, and gender for both the patient and the parent or guardian, as well as the first 3 characters of their postal code, so that researchers can map how far patients travel to receive this specialty care.

Chart Review of Clinical Outcomes

To understand the impact of the new clinic model of care, including the Triple Visit, on patient outcomes and health care usage (eg, number of contacts with nurse practitioner and tests and procedures ordered), as well as ascertaining whether new clinic components that follow PACE guidelines are being consistently implemented, health maintenance processes are followed, and identified concerns addressed, a pre-post implementation chart review will be undertaken. As the IBD clinic's new model of care began January 2023, the preimplementation chart review will capture patients who attended the clinic in January 2021 to December 2022, which will then be compared with the postimplementation chart review of patients who attended the clinic from January 2023 to December 2024. Electronic medical records in Meditech will be accessed to complete this review. Variables of interest include prescribed steroid and biologic medications (including dosage), height and weight, and ordered tests. Three data extractors will complete the chart review. Extractor 1 will review 50% of the charts and extractor 2 will review the other 50%. Extractor 3 will re-extract 25% of the charts from each of the other reviewers and interrater reliability will be calculated using the intraclass correlation coefficient.

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Pediatric Patient and Parent or Guardian Surveys

Pediatric Patient Survey

To reduce the time and logistical burden of visiting HRH outside of their IBD clinic appointments, participants will be invited to take part in a web-based survey to assess their satisfaction with the new model of care in the IBD clinic, as well as the impact the clinic has had on patients' knowledge of IBD, transition readiness, self-efficacy, mental health, and health-related quality of life (HRQOL). The web-based survey will be conducted in real time using Zoom (Zoom Communications, Inc), and participant responses will be captured in Qualtrics. Older teenagers may be given the option to complete the web-based survey unassisted via a link sent to their parent or guardian's email address. PowerPoint slides will be used to display and support the interactive delivery of survey measures. The PowerPoint slides will be appropriately tailored to the age range, as necessary, and measures within the survey will be displayed in an order that places the more difficult questions in the middle, such as questions pertaining to mental health. This is to help children to finish the survey feeling positive. As we project that the survey will take 20-30 minutes for participants to complete, there is the potential for participants to experience survey fatigue. To mitigate against such effects, participants will be offered breaks at intervals throughout the survey, and they will have the opportunity to watch a short age–appropriate cartoon or TV show or to do something of their own choosing such as grabbing a snack. Children who complete their survey on the web via Qualtrics without researcher support will be prompted within the survey to take a break at the same intervals.

Transition Readiness

Patients' readiness to transition from pediatric to adult care will be assessed using the Self-Management and Transition to Adulthood with Rx = Treatment (STARx) Questionnaire [24]. The STARx Questionnaire is an 18-item questionnaire, targeting the following 6 subdomains integral to transition readiness: medication management, provider communication, engagement during appointments, disease knowledge, adult health responsibilities, and resource utilization. All questions are presented to patients in Likert scale format. For example, patients will be asked to indicate on a 5-point Likert scale from 1 (never) to 5 (always), "How often do you take your medications on your own?" and on a 5-point Likert scale from 1 (nothing now) to 5 (a lot), "How much do you know about your illness?" For this present investigation, this tool will help identify gaps not only in skills and knowledge in individual patients but also gaps across the clinic population or where they are doing well as a whole.

Patient Self-Efficacy

IBD Self-efficacy Scale for Adolescent and Young Adults is a 13-item questionnaire to assess IBD-specific self-efficacy among patients [25,26]. The scale touches on 4 key areas of disease management including managing medical care, managing daily life with IBD, managing emotions, and managing the future with IBD. Patients are asked to rate their agreement with statements such as "I worry about how much IBD will affect my future" and "I know what to do when I think a flare is starting," using a 5-point Likert scale from 1 (completely disagree) to 5 (completely agree). As self-efficacy is an important predictor of health outcomes in chronic illness, scores from this scale will be compared with the HRQOL measures, among other measures and variables.

Patient Knowledge of IBD

Patients' knowledge of IBD will be assessed via the Inflammatory Bowel Disease—Knowledge Inventory Device 2 (IBD-KID2) [27]. The IBD-KID2 is a 15-item assessment tool investigating patients' understanding of IBD across various knowledge domains such as general IBD, treatment, lifestyle, and nutrition. The tool consists of 6 multiple-choice questions and 9 true or false questions, with each correct answer receiving a score of 1, for a maximum total score of 15. Patient knowledge of their IBD is integral to their treatment adherence and development of self-management skills. Thus, similar to the transition readiness scale, the IBD-KID2 will help identify gaps in knowledge among patients of this IBD clinic, which could adversely impact their disease trajectory. IBD knowledge scores will also be compared with their transition readiness scores, HRQOL scores, and parents or guardians' knowledge of IBD scores, among other measures.

Patient Service Satisfaction

Pediatric patients' satisfaction with the IBD clinic and its new model of care will be assessed via the Youth Satisfaction Questionnaire (YSQ) [28]. The YSQ is a tool that was developed to assess children's general satisfaction with a service, as well as their satisfaction with specific aspects of the service and activities they are involved in.

To measure general service satisfaction respondents are asked to rate their agreement with 5 statements, such as "Did you get the help you wanted?" and "Have the services helped you with your life?," using the response options (1) "yes," (2) "somewhat," and (3) "no." Satisfaction with specific service components and activities is measured by asking respondents to assign a grade (A through F) to the specific services and activities they were engaged with. For this project, the specific services and activities list has been generated in collaboration with the research team and IBD clinic care team. Children will be asked to assign a grade to 5 service aspects, such as "medication management" and "access to clinic." Results from the YSQ will be compared with scores of HRQOL and parental or guardian satisfaction, in addition to informing how the clinic is doing against the PACE quality indicators.

Patient HRQOL

The IMPACT-III [29] will be used to assess patient's HRQOL. In addition to indicating the impact of disease burden on health, HRQOL is an important measure of assessing the efficacy of medical care. The IMPACT-III is a 35-item questionnaire that measures patients' views on their health, including their physical well-being, emotional functioning, social functioning, and body image. Questions include, "How much energy did you have during the week?," "Are you embarrassed because of your bowel condition?," and "How much has your stomach been hurting over the past two weeks." For each question, respondents are provided 5 possible answers ranging from 1 (eg, "Not at all") to 5 (eg, "Hurting very much"). HRQOL will be used to assess

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how well patients in the clinic are doing as a whole and compared with their scores on measures related to mental well-being, in addition to other measures and variables such as their parents' scores on the parent version of the measure described in the "Pediatric Patient Survey" section.

Mental Health and Well-Being

The Child Attitudes Towards Illness Scale (CATIS) [30] will be used to assess patients' attitudes toward their illness. Pediatric patients' perceptions of their illness can be pivotal in influencing adjustment to their condition, particularly when there is a stigma attached, as is the case for those with IBD. Negative feelings about a chronic condition can lead a child toward maladaptive coping behaviors, which in turn can lead to a more negative adaption to their condition compared with those with positive attitudes. The CATIS uses 5-point Likert scales ranging from 1 (very sad/never/very unfair) to 5 (very happy/very often/very fair) and includes questions, such as "How good or bad do you feel it is that you have [insert illness, e.g., ulcerative colitis/Crohn's disease]" and "How often do you feel sad about being sick?". Total sores can range from 13 to 65, with higher scores indicating more positive attitudes. Scores from the CATIS will be compared with other patient measures such as HRQOL.

The Generalized Anxiety Disorder screener (GAD-7) [31] will be administered to patients to screen for anxiety and explore whether the IBD clinic has been achieving its aim of proactively identifying patients who require additional mental health supports. The GAD-7 is a 7-item questionnaire that asks respondents to consider how often over the past 2 weeks they have been bothered by a particular problem, such as "Feeling nervous, anxious or on edge" and "Trouble relaxing." Response options include 0 (not at all), 1 (several days), 2 (more than half the days), and 3 (nearly every day). Scores ≥10 indicate moderate anxiety.

The Patient Health Questionnaire—9 (PHQ-9) [32] will also be administered to patients to screen for depressions and, similar to the GAD-7, explore whether the IBD clinic has been achieving its aim of proactively identifying patients requiring additional mental health input. The PHQ-9 is a 9-item questionnaire that asks respondents to consider how often over the past 2 weeks they have been bothered by a particular problem, such as "Feeling down, depressed, or hopeless" and "Trouble concentrating on things, such as reading the newspapers or watching television." Similar to the GAD-7, the PHQ-9's response options include 0 (not at all), 1 (several days), 2 (more than half the days), and 3 (nearly every day). At the end of the questionnaire participants are asked to indicate how difficult these problems have made it for them in their daily life. Response options range from "Not difficult at all" to "Extremely difficult." Scores ≥10 indicate moderate anxiety.

Desirable Responding

As this survey is asking children and young adolescents to respond to questions regarding sensitive topics such as their symptoms and experiences of IBD, as well as their mental health, there is the potential for participants to respond in socially desirable ways. Thus, the Short Children's Social Desirability Scale [33] has been included to identify and control for biased responses in patient self-reports. The Short Children's Social Desirability Scale includes 14 questions to which participants can provide a "yes" or "no" response, such as "Have you ever felt like saying unkind things to a person?" and "Do you always listen to your parents?"

Parent or Guardian Survey

Similar to the pediatric patient survey, parents or guardians will be invited to take part in a web-based survey to assess their satisfaction with the IBD clinic's new model of care, the impact the clinic has had on their knowledge of IBD, and the impact the clinic has had on their child's well-being. Unlike the pediatric patient survey, parents or guardians will be sent a link to the web-based survey in Qualtrics and will be given a 2-week window to complete the survey at a time of their convenience.

Parent or Guardian Service Satisfaction

To measure parent or guardian satisfaction with the IBD clinic, the Quality of Care Through the Patient's Eyes—Inflammatory Bowel Disease [34] questionnaire developed by the Netherlands Institute for Health Services Research is being adapted. The Quality of Care Through the Patient's Eyes—Inflammatory Bowel Disease is a 23-item questionnaire that contains 10 generic-specific and 13 disease-specific questions assessing the following 8 dimensions of care: accessibility, costs, accommodation, continuity of care, courtesy, information, competence, and autonomy. Participants are asked to rate the importance of each aspect of care using a 4-point scale (1 "no," 2 "not really," 3 "on the whole, yes," and 4 "yes") and then to rate the performance of the medical setting and workers based on their experience using the same 4-point scale. Subsequently, a Quality Impact Index is derived for each item, which combines the effect of importance and performance. Note that a Quality Impact Index score of <9 is considered suboptimal patient satisfaction as it is widely held that 90% of patient populations are satisfied with quality of care. To fit the parent format, question structure has been modified as necessary to replace items such as "my" with "me and my child" or "my child's." For example, the statement, "Doctors, nurses, and other care works should have a good understanding of my problems" will be modified to read, "Doctors, nurses, and other care workers should have a good understanding of my child's problems." Similarly, questions have been edited to reflect the IBD clinic; thus, some statements have either been removed or modified. For example, in the original version, participants are asked to respond to questions about their general practitioner and specialist, respectively. In this survey, questions pertaining to general practitioners have been removed and questions regarding the patient's specialist are reworded to reflect the IBD specialist team. Parents or guardians will also complete the same grading activity their children complete from the YSQ, that is, parents or guardians will assign a grade (A through F) to the specific services and activities their child has engaged with.

Parent or Guardian Knowledge of IBD

Parents or guardians' knowledge of IBD will be assessed via the IBD-KID2 described in *the patient survey.* This measure will allow for comparison between patients and parents or guardians, as well as investigating the relationship between parents and guardians' knowledge of IBD, service satisfaction, parenting stress, and so on.

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Parent or Guardian Perception of Child's HRQOL

The parent IMPACT-III (IMPACT-III-P) [35] will be used in conjunction with the IMPACT-III [29] described in the patient survey to assess patient's HRQOL. The IMPACT-III-P uses the same 35 items from the IMPACT-III, with personal pronouns modified to fit the parent format. For example, the children's version asks, "How much energy did you have during the week?" whereas the parents' version has been modified to ask, "How much energy does your child have during the week?" Parent scores from the IMPACT-III will be compared with patient scores on the same measure.

Parent or Guardian Perception of Child's Transition Readiness

The parent STARx Questionnaire (STARx-P) [36] will be used in conjunction with the child STARx Questionnaire described in the *patient survey* to assess patients' transition readiness, in addition to comparing potential differences and similarities in patients and parents or guardians' perceptions of transition readiness. The STARx-P uses the same 18 questions and Likert scale response options as the STARx, with the word "you" being replaced as necessary with "your child" to fit the parent format.

Pediatric Parenting Stress

Pediatric parenting stress will be assessed with the Pediatric Inventory for Parents (PIP—Short Form) [37]. Across 13 questions parents are asked to consider over the past 7 days how often and how difficult they experienced and found particular events such as sleeping, attending work, and seeing their child sad. Thus, 13 questions produce 26 responses. A 5-point Likert scale is used for the response options for both "How often" (ie, from 1 "never" to 5 "very often") and "How difficult" (ie, from 1 "not at all" to 5 "extremely"). Parents' scores on the Pediatric Inventory for Parents will be compared with their knowledge of IBD and patient HRQOL, among other measures.

Structured Observations of PACE Quality Indicators

As the implementation of PACE guidelines in other clinics has resulted in positive patient outcomes [9,10], a structured observation of clinical practices in this new model of care at HRH's Outpatient Paediatric IBD clinic will be conducted. The structured observation will involve direct clinical observation of clinical appointments such as a new patient visit, last or transition to adult care visit, and the Triple Visit, in addition to the review of specific electronic medical record metrics from patients' charts, measurement of patient satisfaction as per the patient survey, and consultation with clinical staff, as necessary. The clinic's pediatric GI has been consulted to determine the applicability of each guideline to the pediatric setting. As such, 43 of 45 indicators that cover structure (the inclusion of particular health care professionals in the clinic, etc), process (performing tests and prescribing particular medications based on certain criteria, etc), and outcome quality indicators (patient health care usage, patient satisfaction, etc) have been included for this structured observation. To mitigate against observer bias, particularly for direct observations of clinical appointments, and consistency issues across observations, 2 or more methods (ie, direct observation of clinical appointments, chart review, and consultation with clinical staff) will be used, when possible, to validate whether a particular indicator is observed in the clinic's practices. Three data extractors will be used to extract chart review data and interrater reliability will be calculated using Cohen k.

Semistructured Interviews With Parents or Guardians and Clinicians

Parent or Guardian Semistructured Interviews

Parents or guardians will participate in 1 virtual or in-person semistructured interview. Questions will focus on the key elements of evaluation that include their perspectives on accessing the clinic, mental health, their views on how their child's health is being maintained, and more general views on their satisfaction with the new clinic model. To round off the interview, parents or guardians will be asked to provide any recommendations to any aspect of their clinic experience.

Clinician Semistructured Consolidated Framework for Implementation Research Interviews

For clinicians, the focus will be on garnering their perspectives of how the new clinic model was implemented, paying specific attention to the experiences of the different clinician specialties that comprise the new model. To do so, we will use the Consolidated Framework for Implementation Research (CFIR), a validated 2-versioned framework comprising a taxonomy of constructs that have been shown to be associated with implementation success [38,39]. A defining feature of the Triple Visit is its commitment to coordinated care and collaboration among a multidisciplinary team; as such, attention will be paid to the Characteristics of Individuals domain of the CFIR. This domain aims to uncover contextual information about how those involved in implementing and executing the Triple Visit model make sense of the new initiative and the interplay among other staff within the purview of the intervention. Other CIFR domains included in the interview guide are Intervention Characteristics to obtain data about participants' knowledge and perceptions of the new clinic model, Outer Setting that focuses on clinicians' opinions on the patient or parent population, Inner Setting to gather insights on whether the new clinic model is embraced in the hospital context, and Process to understand clinicians' views on how the new model was implemented. All interview questions aim to uncover the barriers and facilitators associated with implementing the new clinic model and clinicians' insights on how to improve the service.

Pediatric Patients and PBIs

We aim to gather insights from patients with IBD about their experience of the IBD Triple Visit clinic visits. Data collection scripts used with patients will be tailored to their developmental stage, guided by a narrative PBI framework that incorporates play and opportunities for creative expression as a vehicle to elicit their responses from the interview guide [40-42]. Previous research on conducting qualitative data collection with young children and adolescents shows that novel methods such as play, drawing, diary writing, or other forms of creative expression are effective at eliciting responses from children in a supportive setting [43]. These methods reside outside an artificial interview context and instead are grounded in a "child's perspective"—a perspective that has been methodologically overlooked in studies

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involving children in hospital settings [44]. Approaching interviews with children in a way that reflects their developmental stage enhances the validity of the data and, in turn, their quality [41,45].

A certified child life specialist (CCLS) will facilitate the PBIs. CCLS are health care professionals who are clinically trained in evidence-based techniques to help children feel emotionally safe and calm in hospital settings when undergoing medical procedures and invasive examinations. Thus, the CCLS is well suited to facilitate the PBIs, as they possess the skill set to understand both children's developmental stage and socioemotional needs. To ensure rigor in data quality, a QM will also be present to take detailed field notes to compliment the audio and video data from the interviews.

PBI Procedure

For the PBIs, children will be split into their developmental ages: 8-12 years, 13-15 years, and 16-18 years, which will determine the age-appropriate interview script to use on the interview guide for the PBI. Sessions will be audio and video recorded in a room within the Maternal and Child clinic; however, parents will have the option on the consent form to not have their child video recorded. The video camera will be attached to a laptop and positioned in a specific area of the clinic room to ensure that it does not interfere with the child's activities during their interview with the CCLS. In line with child interview recording, our aim is to ensure that the experience remains as unobtrusive as possible [41].

The QM will obtain consent from parents and assent from the patients prior to the PBI; it will be reiterated to the patient that their participation is voluntary and that they may stop the PBI at any time. The CCLS will use the interview guide using the age-appropriate script that corresponds to the age of the patient. The interview guide will touch on the following topics: what the children like about coming to the clinic, what they do not like, their thoughts about their care team, what they find helpful about the clinic, and how they would like their clinic experience to be improved. To elicit responses from the patients, they will be invited to choose 1 or more items from an activity portfolio [41] located in the interview clinic room to play or engage with. While the patient is occupied with their activity of choice from the portfolio, the CCLS will consult the interview guide and elicit their responses; having the child "busy" with an enjoyable activity allows for a more a natural conversation with the child to unfold [40,41]. At the end of the PBI, the patient will be invited to choose a small gift of appreciation from a "Thank You Bin" in the clinic room. After the CCLS and QM lead the child back to their parents or guardians in the waiting area, the child will also be offered a gift card.

Ethical Considerations

This study received HRH Research Ethics Board approval on December 23, 2024 (REB#24-0005). Prior to commencing research activities, a researcher will obtain verbal consent from parents or guardians for the specific research activity being undertaken. Parents or guardians will be responsible for providing consent for their and their child's participation. Although parents or guardians will provide consent for their child's participation, all pediatric patients will also be asked at the time of participation whether they assent to participating in the research activity at hand. Age-appropriate assent scripts will be used to describe the specifics of the research activity, including that their participation is voluntary, they have the right to withdraw at any time without penalty, and that their information will be kept private and confidential. If a patient does not assent, they will be withdrawn immediately, thanked for their time, and reassured that this will not impact the care they receive at HRH. Clinical staff who are interested in participating in research activities will be provided with a consent document to review, followed by a verbal read through with a member of research staff. Ample time will be provided for staff to ask the researcher questions before verbally indicating whether they wish to participate. As employees of HRH and the department in which research activities are taking place, some clinicians may feel a sense of pressure to participate, or perhaps even worry about work-related repercussions should they decline an invitation to engage in research activities. Clinical staff will be made aware that their participation is voluntary and not a condition of employment. The possibility of coercion or undue influence will be minimized, as research staff from the hospital's research institute, rather than staff from within the IBD clinic, will be responsible for recruiting and consenting clinical staff into the study. Participants will receive nominal gift cards as outlined in the "Methods" section as a recognition of their time and contribution. Their nominal value is in line with ethical standards.

Data Analysis and Sample Size

In line with a concurrent triangulation design, analysis of qualitative and quantitative data will be analyzed separately. Results from both methods will then be integrated and interpreted where appropriate.

Quantitative Analysis

Chart Review

Baseline demographics, clinical history, and outcomes including health care usage will be extracted from the electronic medical records for patients who had an IBD clinic visit any time since January 2021 to December 2024. A prospective chart review will also be conducted to extract post-Triple Visit patient information for those who had their first Triple Visit in 2023-2024. The primary goal of this chart review will be to compare patient outcomes at 6 months before and after their first Triple Visit to understand how the new model of care has affected patient outcomes. The primary analysis will be a matched *t* test, with a 2-sided $P<.05$ as the critical value, effect size of 0.35, and power of 0.8. This estimates a required sample size of at least 67 patients for meaningful analyses.

Patient and Parent or Guardian Survey Data Analyses and Sample Size Calculation

The primary analysis will be a correlation between patient service satisfaction scores from the YSQ and HRQOL from the IMPACT-III, with 2-sided $P<.05$ as the critical value, a medium effect size of 0.35, and a power of 0.8. This results in a required sample size of 61 patients. Secondary analyses will be descriptive statistics and bivariate statistics using *t* tests,

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chi-squared test, and Pearson or Spearman correlations to identify relationships between other variables captured in the survey. Identical analyses will be conducted for the parent or guardian survey; thus, we will aim to recruit 61 parent or guardians, also. Once data are collected from both surveys, bivariate statistics will be used to compare differences between the patients and parent or guardians for the scales present in both surveys.

Structured Observation

Descriptive statistics will be used to capture the percentage of PACE Quality Indicators that have been implemented by the clinic, as well as the clinics compliance with these implemented measures.

Qualitative Analysis

Semistructured Interviews With Parents or Guardians

Parent or guardian interview transcripts will be uploaded to NVivo 14 (Lumivero) and will be analyzed thematically, primarily drawing on Braun and Clarke's 6 steps for analysis [46,47].

Semistructured Interviews With Clinicians

For clinician interviews, all transcripts will be uploaded into NVivo 14 where codes for each CFIR construct will have already been predefined from the CFIR taxonomy [38]; interviews will be coded deductively against the CFIR constructs selected from the interview guide. Interviews will also be coded inductively for relevant data that are not captured by the CFIR framework; the CFIR framework is adaptable in that researchers can add project-specific codes during analysis to capture factors that influence implementation but fall outside the predefined CFIR constructs. This abductive approach produces a contextually grounded analysis [48,49].

Pediatric Patients and PBIs

Pediatric patient data will be collected in the form of audio and field note data from the play sessions and with video data if the child's parent or guardian had provided consent for their child to be video recorded. If the children created artwork, block towers, or drawings, these products will not be analyzed as they are not methods per se but rather the evidence that the child engaged in responses to the interview questions that the child answered during the play session.

For children who were video recorded during their play session, these recordings will be analyzed using the 6 steps outlined in the visual verbal video analysis method; the method aligns with a similar approach to classic thematic analysis [47], with an emphasis on selecting key moments in the video to analyze. The steps involve collecting and reviewing data, transcribing, choosing units of analysis, coding data, organizing, and describing data and reporting the findings [50]. For children whose parents or guardians opted out of video recording, their data will consist of an audio recording of the PBI in addition to field notes taken by the qualitative specialist; field notes will be structured using the visual verbal video analysis matrix framework that includes the following topics: general characteristics of the video, multimodal and visual characteristics, and participants in the video and content including emotions, gestures, and discourses [50,51]. Analytic memos will be written by the CCLS and the QM after each patient interview; writing memos immediately after the data collection session will be critical to enhance validity and facilitate consensus discussions during analysis [52].

Data Triangulation

We anticipate that the datasets from the qualitative and quantitative components that will intersect at the "point of interface" [53] will be the parent satisfaction survey with the parent interviews and the patient satisfaction survey with the patient interviews. With these datasets, we will be guided by Teddlie and Tashakkori [16]: (1) data reduction, (2) data display, (3) data transformation, (4) data correlation, (5) data consolidation, (6) data comparison, and (7) data integration. More specifically, themes generated from qualitative results will be transformed into quantitative variables for comparison with the survey items. This comparison will be an iterative process wherein both datasets will be in conversation with each other to produce a consolidated profile of parent and patient satisfaction of the clinic.

Results

This study received REB approval in December 2024. Recruitment commenced in January 2025, and is ongoing with an anticipated data collection end date of December 2025. Thus, results are not yet available.

Discussion

Anticipated Findings

We anticipate that this mixed methods evaluation of a holistic pediatric IBD clinic model of care that includes a multidisciplinary team Triple Visit, as well as a rapid access component, will provide a strong rationale for a multidisciplinary approach to care for children with IBD, a population that is increasingly prevalent in Canada [7]. Our results aim to demonstrate how the clinic's accessibility, processes for health maintenance checks, patient and parent or guardian satisfaction, and the monitoring of patients' mental health will enable a more comprehensive and holistic approach to patient care and management of IBD.

Limitations

Limitations of this study can be pinpointed. First, data integration of mixed methods concurrent designs is not without flaws [18]. Integrating and interpreting data sources from qualitative and quantitative results may pose challenges as it is possible that not all data sources will be compatible with each other, especially given the chasm between the 2 paradigms and their respective epistemological assumptions [54]. Consequently, we expect that some findings may exist independently within each paradigm rather than fitting together across both; these discrepancies may require further research to resolve them [55]. However, a benefit of this mixed methods approach is where one method has weaknesses or produces a gap in knowledge, the other method will be a strength by filling in those gaps. For example, from a quantitative perspective it is not possible to

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gather a true measure of pre-post implementation satisfaction among patients and their parents or guardians as satisfaction was not objectively measured prior to the new clinic model's implementation. By triangulating results from measures in the patient and parent or guardian surveys with the patient PBI and parent or guardian interviews, a fuller understanding of satisfaction pre-post implementation can be derived. Finally, the process of integrating and interpreting the data will be time-consuming as integration cannot occur until all data have been analyzed; generally speaking, qualitative data analysis is labor intensive and, as such, leads to a longer timeline for completion [56,57].

Conclusions

This protocol will be instructive for other scholars and clinicians of pediatric IBD. Given that the multidisciplinary clinic model is relatively new, we believe that this protocol will provide sound methodological direction for other studies that aim to evaluate or implement this model in their setting. From an implementation science perspective, qualitative results with clinicians will reveal contextual information about barriers and facilitators of putting the model in place in the clinic [38]; these results will show specific details on what factors led to high or low implementation success—data that may prove useful for other clinics that aim to implement a similar model of care. From the perspective of the pediatric IBD clinic at HRH, we anticipate that this evaluation will lay the foundation for further monitoring and improvement of the clinic model, in addition to evaluating this model from a health economist and resource-specific lens.

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Authors' Contributions

ACW and YL contributed equally to the methodology and establishing an analysis plan. AC served in a supporting role for patient qualitative methods. ACW served as lead for project administration. YL and PW served in a supporting role for project administration. PW and LH served as leads for supervision. The first manuscript draft was written by ACW, YL, and LH. All authors contributed to writing—review and editing. All authors contributed to the study conception and design and read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CATIS: Child Attitudes Towards Illness Scale
CCLS: certified child life specialist
CFIR: Consolidated Framework for Implementation Research
COREQ: Consolidated Criteria for Reporting Qualitative Research
GAD-7: Generalized Anxiety Disorder screener
GI: gastroenterologist
HRH: Humber River Health
HRQOL: health-related quality of life
IBD: inflammatory bowel disease
IBD-KID2: Inflammatory Bowel Disease—Knowledge Inventory Device 2
PACE: Promoting Access and Care through Centres of Excellence
PBI: play-based interview
PHQ-9: Patient Health Questionnaire—9
QM: qualitative methodologist
REB: research ethics board
STARx: Self-Management and Transition to Adulthood with Rx = Treatment
VVVA: visual verbal video analysis
YSQ: Youth Satisfaction Questionnaire

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Protocol

Effectiveness of Tocotrienol-Rich Fraction in Older Adults: Protocol for a Randomized, Double-Blind, Placebo-Controlled Trial

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Abstract

Background: Tocotrienol, a naturally occurring form of vitamin E, has been extensively studied for its potent antioxidant, anti-inflammatory, and immune-stimulating properties. However, the clinical impact of tocotrienol supplementation on older adults' overall health and well-being remains relatively unexplored. This research aims to investigate the efficacy of tocotrienol-rich fraction (TRF) on various health parameters associated with general well-being in individuals aged between 50 years and 75 years.

Objective: It is hypothesized that TRF supplementation may exhibit positive outcomes on blood biochemistry and several physiological aspects, including lowered levels of oxidative stress and inflammation biomarkers; improvement in vascular age; and enhancement of skin condition, bone mineral density, and cognitive function.

Methods: This randomized, double-blind, placebo-controlled trial was designed to investigate the effectiveness of TRF supplementation on overall health in healthy older adults. The study aims to assess the impact of a daily dosage of 200 mg of TRF over a period of 6 months. A total of 220 participants is enrolled in the study, with one-half receiving the placebo and the other one-half receiving TRF supplementation. The study comprises 3 time points: baseline, 3 months, and 6 months. At each time point, various measurements are taken to evaluate different aspects of health. The primary outcome measurements include blood biochemistry assessments, such as liver function tests, renal profile, lipid profile, and full blood count. Oxidative stress markers, including malondialdehyde, advanced glycation end products, protein carbonyl, and isoprostane, are also evaluated. Immune response markers such as interleukin-6 and tumor necrosis factor-α are assessed. Satiety regulation is examined through measurements of leptin and ghrelin. Body composition and skin health parameters, including wrinkling, pigmentation, elasticity, hydration, and sebum secretion, are evaluated. Additionally, arterial stiffness is assessed using arteriography at baseline and 6 months. For secondary outcome measures, bone mineral density is measured using dual x-ray absorptiometry, and cognitive function is assessed using the Montreal Cognitive Assessment, Rey Auditory Verbal Learning Test, and digital span test. Both bone mineral density and cognitive function are also measured at baseline and 6 months.

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Results: The study is progressing as planned, with 209 participants recruited as of April 2025. The research was funded in 2019, and data collection started in December 2020. Preliminary data analysis has been completed for the first 120 participants, and final results are expected upon completion of data collection and unblinding in 2026.

Conclusions: By comprehensively evaluating these health aspects, this study seeks to provide valuable insights into the potential benefits of tocotrienol supplementation for promoting the overall health and well-being of the aging population.

Trial Registration: National Medical Research Register (NMRR) NMRR-19-2972-51179; https://tinyurl.com/yy9yueer

International Registered Report Identifier (IRRID): DERR1-10.2196/73039

(JMIR Res Protoc 2025;14:e73039) doi:10.2196/73039

KEYWORDS

tocotrienol; skin; cognition; brain; weight; satiety; aging; oxidative stress; immune; inflammation

Introduction

Background

Aging is a progressive process characterized by the gradual loss of tissue and organ function over time [1]. Two theories of aging include the free radical theory of aging, which later evolved into the oxidative stress theory of aging, and a theory based on low-grade inflammation, or inflammaging, in older adults. The oxidative stress theory of aging is based on the hypothesis that age-related functional declines occur as a result of the accumulation of oxidative damage to macromolecules such as lipids, DNA, and proteins caused by reactive oxygen and nitrogen species (RONS) buildup [2]. With advancing age, the accumulation of RONS leads to post-transcriptional modifications and oxidative damage, often contributed to by elevated levels of oxidative stress biomarkers including advanced glycation end products (AGEs), malondialdehyde (MDA), protein carbonyl (PC), and F2-isoprostanes (F2-IsoPs) [3]. In parallel, chronic low-grade inflammation has been linked to the onset of age-related chronic diseases such as cardiovascular disease, diabetes, and cancer [4]. In older adults, there is often an imbalance between excessive free radicals and low antioxidant levels, along with increased risk of chronic inflammation due to elevated inflammatory cytokine production, which may lead to disruption in normal cellular physiology [5,6]. High levels of oxidative stress biomarkers and inflammatory cytokines are associated with low cognitive performance, osteoporosis, atherosclerotic characteristics, skin conditions, and renal problems in older adults [7-9].

According to the Department of Statistics, Malaysia is officially regarded as an aging nation, as individuals aged 65 years and older were predicted to make up 7.7% of the population as of 2024 [10]. This indicates an urgent need to identify preventive, nonpharmacological strategies for maintaining the health and well-being of the older adult population. Introducing natural adjuncts like tocotrienol-rich fraction (TRF) supplementation may serve as a cost-effective and physiologically beneficial approach to reducing the health care burden associated with aging while potentially supporting healthy aging and improving overall quality of life for older adults.

Tocotrienol is a naturally occurring vitamin E that is predominantly found in palm oil [11]. It can be further distinguished into 4 isomeric forms (α, β, γ, and δ), depending on the location and number of methyl groups on the chromanol ring. Tocotrienols, as opposed to tocopherols, have unsaturated isoprenoid side chains with 3 double bonds, allowing for greater cellular penetration and dispersion inside lipid membranes [6,12]. This structural difference improves their antioxidant and anti-inflammatory properties. Cumulative scientific evidence has convincingly shown that tocotrienol possesses pronounced antioxidative function by effectively neutralizing free radicals, including RONS, which ultimately reduces oxidative stress [11,13-22]. Tocotrienol also possesses anti-inflammatory properties by ameliorating inflammatory markers that are consistently associated with age-related chronic diseases and disability [4], including interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and C-reactive protein (CRP) [23-25]. IL-6 is a pleiotropic cytokine produced by the immune cells, vascular endothelial cells, adipocytes, and skeletal muscle and possesses both anti-inflammatory and pro-inflammatory properties [26]. TNF-α, another cytokine, is mainly produced by macrophages and other cell types in response to cell damage [27], while CRP is an acute-phase protein produced by the liver in response to elevated IL-6 and TNF-α levels [28-30]. These properties render tocotrienol an attractive therapeutic candidate for slowing down the aging process and thus potentially extending the lifespan of older adults [11,13].

Moreover, tocotrienol also modulates inflammation by targeting crucial transcription factors such as nuclear factor kappa B (NF-κB), the signal transducer and activator of the transcription-3 (STAT-3) pathway, and other cytokine regulators integral to the inflammatory signaling cascade [12,13,22,31-33]. Tocotrienols have been shown to exhibit isoform-specific effects on anti-inflammatory potency. For instance, several studies have demonstrated that δ-tocotrienol exhibited the most potent inhibitory effect on IL-6 and TNF-α production as compared with other isoforms [24,34]. Another study has shown that δ-tocotrienol inhibits TNF-α–induced NF-κB activation caused by upregulation of the anti-inflammatory protein A20 [35]. In addition, Muid et al [32] demonstrated that both δ- and γ-tocotrienols have higher potency in inhibiting IL-6 production and NF-κB activation than α- and β-tocotrienols in lipopolysaccharide-stimulated human umbilical vein endothelial cells. The NF-κB pathway inhibition induced by γ-tocotrienol also contributes to downregulation of oncogenic gene expression, thus promoting tumor cell apoptosis, which is crucial for suppressing tumor metastasis [36]. Moreover, combined treatment with γ-tocotrienol and an epidermal growth factor receptor inhibitor showed suppression in epidermal growth

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factor–dependent STAT-3 signaling in mammary tumor cells [37]. Collectively, these findings underscore the pivotal role of tocotrienols in modulating inflammation through multifaceted inhibition of key transcription factors, suppression of pro-inflammatory cytokines, and regulation of signaling pathways central to the inflammatory cascade. This positions tocotrienols as promising agents for the prevention and management of inflammation-driven diseases, including cancer and chronic inflammatory conditions.

Furthermore, these scientific investigations have illuminated tocotrienols' ability to enhance skin health through UV protection and skin-lightening effects, both in preclinical and clinical models [38-42]. Tocotrienols have also demonstrated their potential for improving lipid profiles among individuals with dyslipidemia and hypertension [12,43-48] and have been shown to regulate leptin expression, thereby influencing appetite control and energy homeostasis [49-54]. To date, no study has specifically investigated the effect of tocotrienols on ghrelin expression. Therefore, our study aims to fill this knowledge gap and provide novel insights into this unexplored area.

In bone health, tocotrienols promote osteoblast survival and proliferation through free radical protection and inhibit osteoclasts by downregulating the mevalonate pathway. They also regulate gene expression to promote bone formation [55-66]. Similarly, tocotrienols positively influence neurological health by modulating gene expression in the brain, potentially enhancing memory and motor function while delaying Alzheimer disease progression. Notably, α-tocotrienol at nanomolar concentrations has been shown to attenuate enzymatic and nonenzymatic mediators of arachidonic acid metabolism and neurodegeneration [11,67-71].

TRF is a commercial mixture of vitamin E isomers, containing approximately equal proportions of α-tocopherol (αTP) and α-, β-, γ-, and δ-tocotrienol isomers. TRF supplement with a complete spectrum of tocotrienol isomers has been found to alleviate inflammatory symptoms of allergic rhinitis [72], enhance mental health and cognition [73], reduce inflammation and oxidative stress in ulcerative colitis [31], and mitigate UV-induced skin inflammation [38]. A previous study reported that TRF can improve antioxidant enzyme activities and glutathione levels in women aged between 50 years and 55 years [74]. In the same study, TRF supplementation was found to reduce MDA levels as early as 3 months, while oxidative damage toward DNA was reduced in women after 6 months of supplementation [75]. Furthermore, related isomers derived from the same source have demonstrated benefits in cardiovascular, liver, and metabolic functions [12,76] while exhibiting inhibitory effects on the growth of gastric cancer [77], prostate cancer [78], and breast cancer [79]. The findings from these studies provide a compelling basis to initiate a clinical trial aimed at evaluating the impact of TRF on the well-being of healthy individuals.

Prior Work

To establish an appropriate dosage and duration for the clinical trial, systematic research of human studies involving vitamin E supplementation in healthy participants spanning the years 1997 to 2019 was conducted. A comprehensive search using keywords such as "human," "vitamin E," "tocopherol," and "tocotrienol" in the PubMed database yielded 9 published papers. These studies shed light on the dosages and durations of tocotrienols that are suitable for this clinical trial. In a comparative study investigating the impact of supplementation with TRF and αTP on gene expression in healthy older adults, the administration of αTP (400 IU/day) and TRF (150 mg/day) over a period of 6 months was found to influence pathways related to immune response, drug response, cell adhesion, and signal transduction pathways. Notably, TRF supplementation exhibited a more pronounced effect than αTP in modulating gene expression involved in signaling pathways [80]. The same study also revealed that TRF and αTP supplementation demonstrated similar antioxidative and anti-inflammatory effects in older adults, with TRF showing more significant impacts in female participants [74]. This occurrence may be associated with the downregulation of the apoptotic pathway such as ERK1/2 cascades and NF-κB pathway after 6 months of TRF supplementation [80]. Moreover, another study revealed that TRF supplementation (150 mg/day) for 6 months led to alterations in plasma protein levels including upregulation of apolipoprotein A-I and E precursors and downregulation of CRP precursors in both young and older individuals, actions that are associated with a therapeutic effect against atherosclerosis [81]. These findings provide a perspective that TRF also alters protein expression as shown by elevated plasma protein levels following 6 months of TRF supplementation.

Another investigation focused on the effects of TRF supplementation at a dosage of 400 mg/day for 2 months on the immune response to tetanus toxoid immunization in healthy volunteers. The findings indicated that TRF exhibited immunostimulatory effects [82], thus reinforcing the notion that TRF is associated with handling cellular inflammation. In a randomized controlled trial spanning 6 months, daily supplementation of 150 mg/day TRF was associated with improvements in lipid profile and oxidative status in healthy older adults [83]. Interestingly, a separate trial found that daily supplementation with TRF (150 mg/day) for 6 months did not induce immunomodulatory changes in healthy human volunteers [84]. A much earlier clinical trial, comparing 50-mg with 100-mg vitamin E supplementation over 6 months, suggested that the higher dose (100 mg) had a more pronounced effect on cellular immune function in noninstitutionalized older adults aged 65 years to 80 years [85]. Moreover, a 4-month supplementation regimen of 60 IU to 800 IU vitamin E daily had no adverse effects on various health parameters, including general health, nutrient status, liver enzyme function, thyroid hormone concentrations, creatinine concentrations, serum autoantibodies, killing of *Candida albicans* by neutrophils, and bleeding time in healthy participants older than 65 years [86]. In another randomized controlled trial, older adults consuming 200 mg/d of vitamin E for 4 months exhibited an increase in delayed-type hypersensitivity skin response and an elevation in antibody titer to hepatitis B [87].

Following the review of the literature, a supplementation regimen of 200 mg per day for 6 months was selected. Although no published human studies have reported any serious adverse effects attributed to tocotrienols, it is worth noting that, in animal

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studies, tocotrienol doses of 500 mg/kg body weight and 1000 mg/kg body weight (administered orally) were found to increase bleeding and clotting times in mice during subacute (14 days) and subchronic (42 days) investigations [88]. When these doses are converted to a human equivalent dose, they equate to 2400 mg and 4800 mg, respectively in humans. This discovery implies that high doses of tocotrienols (>2400 mg) should be used cautiously, particularly by individuals with a tendency to bleed or those taking anticoagulants. Consequently, individuals who are currently on anticoagulant or antithrombotic medication are ineligible for participation in this research.

Although several human studies have explored the potential benefits of tocotrienols, there is a noticeable lack of published, comprehensive data that substantiate their advantages specifically in older adults. To address this knowledge gap, we designed a randomized, double-blind, placebo-controlled study, also widely recognized as the "gold standard" in intervention research [89]. This research design excels in establishing causal relationships, enabling us to demonstrate the efficacy of tocotrienols, compared with placebo, in older adults. The connection between oxidative stress, chronic low-grade inflammation, and the aging process, as well as age-related diseases, has been firmly established through extensive epidemiological studies involving older adults [90]. Consequently, several key investigative areas, including antioxidant and inflammation levels, arterial stiffness, appetite regulation, skin parameters, cognitive functions, and bone mineral density, were chosen as focal points for this research. Tocotrienol supplementation is predicted to have a positive impact on all of these parameters, adding to the increasing amount of data that demonstrates its ability to improve general quality of life of older adults. In particular, tocotrienols have been demonstrated to attenuate arterial stiffness [91], modulate hormones related to appetite [92], improve skin health through improvements in hydration and elasticity [93], promote cognitive performance through neuroprotective mechanisms [11,94], lower oxidative stress and pro-inflammatory markers [95,96], and positively influence bone metabolism [65].

The objective of this randomized, double-blinded, placebo-controlled study is to evaluate the efficacy of TRF supplement on health indices for older adults who have been reported to be at risk of reduced antioxidant levels and low-grade chronic inflammation, factors that contribute to an increased susceptibility to chronic diseases [97]. This study design offers the advantage of establishing causality by assessing the efficacy of TRF compared with placebo in older adults. The outcomes of this trial will provide crucial insights into the potential benefits of TRF supplements for enhancing the health and well-being of older adults.

Aim of This Study

The comprehensive objectives of this research involve the evaluation of the effectiveness of TRF at enhancing antioxidant levels and reducing inflammation among individuals aged 50 years to 75 years. Furthermore, changes in appetite hormones, arterial stiffness, and skin parameters over 3-month and 6-month supplementation periods are monitored relative to baseline measurements. In addition, alterations in bone mineral density following 6 months of tocotrienol supplementation are being determined, and potential enhancements in cognitive function between baseline and the 6-month point are being investigated. Finally, the influence of supplementation on vitamin E levels within the body is being assessed after 3 months and 6 months of TRF supplementation.

Methods

Study Setting

Healthy men and women aged between 50 years and 75 years are recruited from the Klang Valley, which is centered in the federal territories of Kuala Lumpur and Putrajaya in Malaysia. Participants are divided into two cohorts, which are supplemented with either placebo or tocotrienols for 6 months.

Ethical Considerations

This research upholds the principles of Good Clinical Practice and adheres to the pertinent regulatory guidelines established by the Malaysia Ministry of Health. The research was approved by the Research Ethics Committee of Universiti Kebangsaan Malaysia (ethics approval number: UKM PPI/111/8/JEP-2019-798) and was registered with the Malaysia National Medical Research Register and National Pharmaceutical Regulatory Agency. Funding for the study was provided by KL-Kepong Oleomas Sdn Bhd, with the research itself being independently conducted by scholars and experts from a higher learning institution. Before the clinical trial commenced, the two parties signed a distinct legal agreement designed to safeguard the rights of the sponsor and researchers involved.

The investigators have no financial nor other competing interests in relation to the overall trial, ensuring impartiality and scientific integrity. Any alterations to the protocol are communicated by the investigators to both the Research Ethics Committee and the sponsor prior to implementation.

Upon completion of the trial, the principal investigator (PI) and sponsor will collaborate in publishing the results and deriving pertinent conclusions while ensuring strict confidentiality of participants' personal information.

The PI is responsible for retaining the data for a minimum duration of 7 years from the date of closure of the database. The sponsor possesses exclusive rights to use the data for commercial purposes, except for any personal information related to the participants. Concurrently, researchers are granted the privilege to use the data for noncommercial purposes, encompassing but not limited to patient care and treatment, academic pursuits, and publication.

Special ethical considerations have been addressed in accordance to the specific needs of the older adult participants in this study. Given the possibility of age-related cognitive decline, the informed consent process incorporates simplified language and comprehension testing to assure accurate understanding. Extra care is taken to reduce any psychological pain or stigmatization, and cognitive examinations are carried out using validated instruments suitable for older adults. All study procedures are intended to accommodate physical or emotional weaknesses,

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including flexible scheduling and participant comfort during data collection. Throughout the research process, these safeguards maintain each participant's autonomy, dignity, and safety. The eligible participants were compensated RM 40 (US $9.48) for each visit.

Eligibility Criteria

Participants in this research must meet specific health criteria, including being generally healthy as determined using physical examination and lab-based blood tests, with satisfactory liver and renal function tests. Eligible participants can be of either gender and aged between 50 years and 75 years. They should not be allergic to palm oil and vitamin E and should not have consumed vitamin E or any other antioxidant supplements in the past 3 months. Furthermore, they must be willing and able to adhere to the study's visit schedule and procedures, reside within a geographically feasible proximity for adequate follow-up (as determined by the investigator), and have a clear understanding of the study protocol, as indicated by their signed informed consent forms.

Participants in this study are expected to reflect greater distribution among the Malay and Chinese population, as these two races are the majority in Malaysia. Meanwhile, participation from the Indian community is less expected as they avoid bovine-related products in their dietary consumption due to religious reasons, aside from being the minority in the country. Moreover, the gender distribution is expected to be balanced between both men and women as there were 2 million individuals of each gender in people aged 60 years and older as of the 4th quarter of 2024 [10]. The socioeconomic background of the participants (ie, education background, occupation, and social status) is not entirely restricted as we intend to be inclusive of all population groups, aside from factoring in the limited availability of participants. However, we note that the participants' education background may influence cognitive performance before and after supplementation. Thus, we will record their academic background when performing the assessments for cognitive function.

Participation in this research is restricted based on several exclusion criteria, such as individuals with fat malabsorption. This is because tocotrienols, as fat-soluble compounds, require adequate lipid absorption to achieve maximum bioavailability. In addition, those with chronic conditions such as cardiac diseases, neurological diseases, diabetes, HIV infection, or psychiatric illness or social situations are not eligible because these conditions and their associated treatments may have an impact on the study end points by obscuring the specific effects of tocotrienol supplementation.

Individuals following a vegan diet are also excluded due to potential nutritional differences, particularly in fat intake and fat-soluble vitamin levels, which may alter tocotrienol absorption and metabolism. Moreover, those who have smoked within the past 3 months are also excluded since smoking can cause oxidative and systemic stress, which can alter overall inflammation, vascular function, and antioxidant status. Excluding people who have recently undergone or are planning for surgery may be helpful to eliminate confounding side effects from surgical stress and postoperative drugs. Furthermore, pregnant and lactating women are excluded for ethical and safety reasons, given the lack of data on tocotrienol use in these populations. Individuals with a history of bleeding disorders, liver dysfunction, or gastrointestinal ulcers (eg, thrombocytopenia, abnormal liver function, liver diseases such as chronic hepatitis, gastrointestinal ulcers) are also excluded due to the potential risk of bleeding complications as well as reduced tocotrienol metabolism and clearance. Participants who are taking antibiotics, anticoagulants, antithrombotics, or other supplements that may interact with tocotrienol activity are excluded to avoid pharmacological interactions that could compromise research safety or supplementation efficacy.

Interventions

This research encompasses the evaluation of two investigation products that are supplied by KL-Kepong Oleomas Sdn Bhd. The first product, known as DavosLifeE3 Complete (50 mg), contains 50 mg of tocotrienols that are sourced from palm oil and meets the specifications outlined in the US Food and Drug Administration "generally recognized as safe" exemption claim 21 CFR 170.36 (c) [98]. The second product, Placebo Softgel, is a palm oil supplement that has the vitamin E compounds stripped off, serving as a vital control within the study. The blinding of the supplement is performed such that each group is labelled with their respective intervention product (IP) number without disclosing the content in the softgel. The softgels for both groups are odorless, of similar size and shape, and packaged in a fully opaque bottle. Contract research assistants generated the random allocation sequence, enroll participants, and assign participants to the interventions. Study participants, researchers, and data analysts will remain blinded throughout the clinical study to maintain blinding integrity throughout the 6-month intervention period.

Outcomes

The study outcomes are divided into primary and secondary end points. The primary end points include vascular health (arterial stiffness), blood biochemistry (liver function, lipid profile, renal function, full blood count, and fasting glucose), oxidative stress (F2-IsoPs, MDA, AGEs, and PC), inflammation markers (TNF-α and IL-6), appetite regulation (ghrelin and leptin), and skin assessment (elasticity, hydration, transepidermal water loss, pigmentation, sebum secretion, wrinkles, and roughness). Meanwhile, cognitive function (Montreal Cognitive Assessment [MoCA], Rey Auditory Verbal Learning Test [RAVLT], and digit span test) and bone density fall under the secondary outcome measures.

The study encompasses a multifaceted array of assessments and procedures (Figure 1). For primary outcome measures, blood samples (15 mL) are collected as baseline samples for blood biochemistry analyses. Venous blood samples are drawn from the antecubital vein between 8 AM and 10 AM, following an 8- to 10-hour overnight fast. The standardized timing and fasting procedure are followed throughout all study visits (baseline, 3 months, and 6 months) to reduce biological variability caused by circadian rhythms and postprandial effects. After at least 5 minutes of rest to stabilize hemodynamic parameters before

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sampling, participants are seated, and blood is collected using sterile procedures.

Figure 1. Overview of assessments and procedures for the 6-month clinical trial. DEXA: dual-energy X-ray absorptiometry; MoCA: Montreal Cognitive Assessment; RAVLT: Rey Auditory Verbal Learning Test.

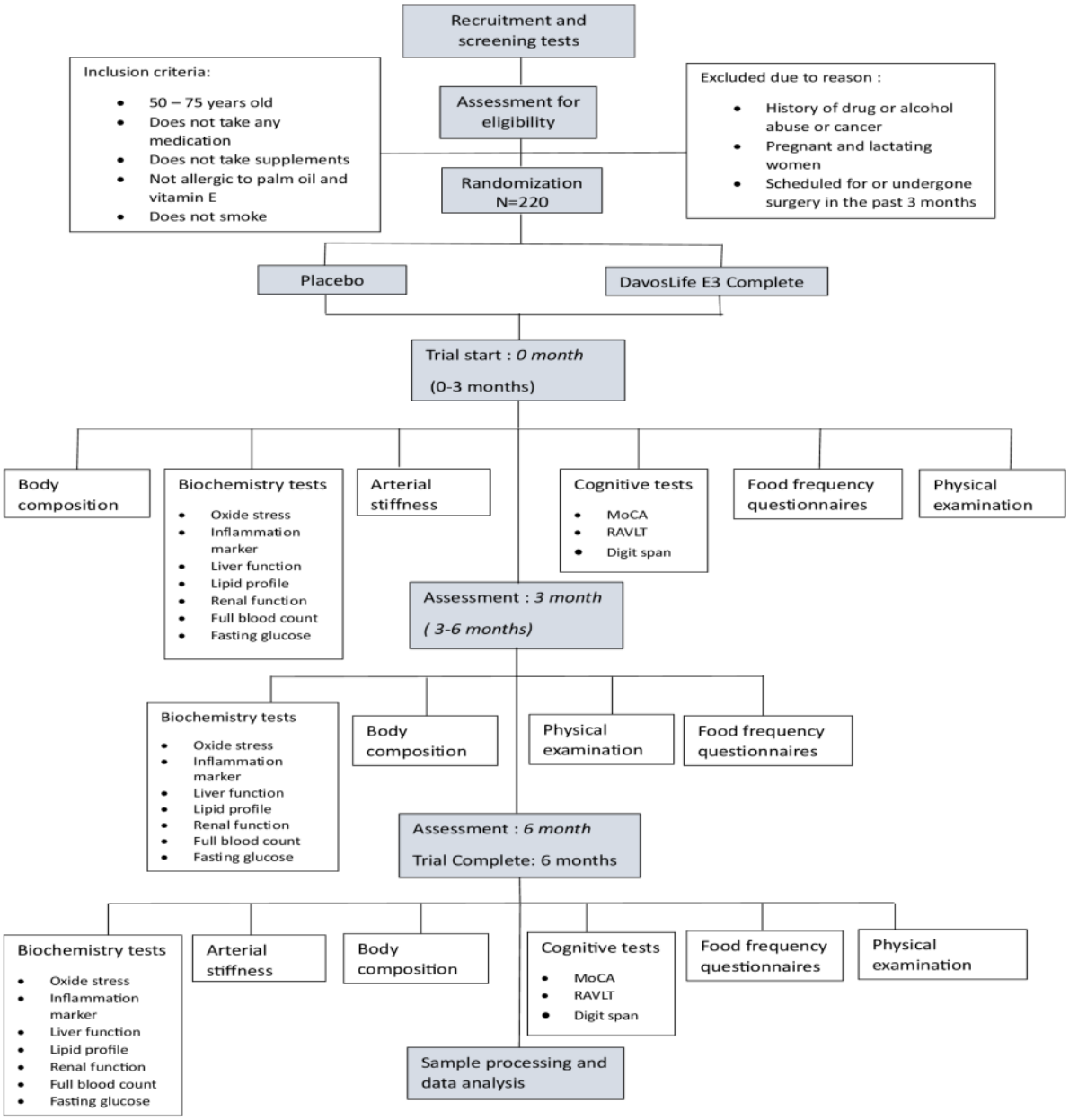

Tubes containing samples are labeled with the participant's code, trial ID, and date for accurate identification. From the collected blood samples, 4 mL is routed to the chemical pathology laboratory for blood biochemistry analysis. The remaining samples are stored appropriately on ice or in a 4 °C refrigerator until they undergo centrifugation, facilitating the isolation of plasma samples. These collected plasma samples are apportioned into 1-mL storage tubes and immediately stored in a –80 °C freezer. This storage method ensures that the samples are preserved for the analysis of oxidative stress markers (MDA, AGE, F2-IsoPs, and PC), inflammatory markers (TNF-α and IL-6), vitamin E, and appetite regulation markers (leptin and ghrelin), all to be conducted within 12 months of storage (Table 1).

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Table 1. Summary of tests performed at 0, 3, and 6 months.

Number and time points, category, and parameters	Sample	Methodology
(1) Screening		
Blood biochemistry tests		
Liver function (ALT[a], ALP[b], albumin, protein, bilirubin)	Blood	Clinical chemistry analyzer
Lipid profile (TG[c], HDL[d], LDL[e], cholesterol)	Blood	Clinical chemistry analyzer
Renal function (Na, K, Cl, urea, creatinine)	Blood	Clinical chemistry analyzer
Full blood count (WBC[f], RBC[g], hematocrit, MCV[h], platelets)	Blood	Clinical chemistry analyzer
Fasting glucose	Blood	Clinical chemistry analyzer
C-reactive protein	Blood	Clinical chemistry analyzer
Physical examination		
Blood pressure	__[i]	Blood pressure monitor
Heart rate	—	
BMI	—	Body weight scale and stadiometer
Past medical history		
Medications	—	Screening form
Supplements	—	Screening form
History of illness	—	Screening form
Social history		
Smoking	—	Screening form
Alcoholic consumption	—	Screening form
Exercise	—	Screening form
Dietary patterns	—	Screening form
(2) 0, 3, and 6 months		
Physical examination		
Blood pressure	—	Blood pressure monitor
Heart rate	—	
BMI	—	Body weight scale and stadiometer
Body composition measurements		
BMI	Whole body	Body composition analyzer
Segmental and visceral fat	Whole body	Body composition analyzer
Basal metabolic rate	Whole body	Body composition analyzer
Blood biochemistry tests	Blood	Clinical chemistry analyzer
Oxidative stress markers		
AGEs[j]	Blood	ELISA[k] kit
PC[l]	Blood	ELISA kit
F2-IsoPs[m]	Blood	ELISA kit
MDA[n]	Blood	HPLC[o]
Inflammation markers		
TNFα[p]	Blood	ELISA kit
IL-6[q]	Blood	ELISA kit
Weight management		

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Number and time points, category, and parameters	Sample	Methodology
Ghrelin	Blood	ELISA kit
Leptin	Blood	ELISA kit
Vitamin E level	Blood	HPLC
Skin assessment		
Elasticity	Face and arm	Cutometer
Hydration	Face and arm	Corneometer
Transepidermal water loss	Face and arm	Tewameter
Pigmentation	Face and arm	Mexameter
Sebum secretion	Face and arm	Sebumeter
Wrinkles and roughness	Face and arm	Visioscan
(3) 0 and 6 months		
Arterial stiffness assessment	Whole body	Arteriograph device /photoplethysmography
Bone density assessment	Whole Body	Dual-energy x-ray absorptiometry
Cognitive function assessment		
MoCA[r]	—	Questionnaires
RAVLT[s]	—	Questionnaires
Digit span test	—	Questionnaires

[a]ALT: alanine transaminase.
[b]ALP: alkaline phosphatase.
[c]TG: triglycerides.
[d]HDL: high-density lipoprotein.
[e]LDL: low-density lipoprotein.
[f]WBC: white blood cells.
[g]RBC: red blood cells.
[h]MCV: mean corpuscular volume.
[i]Not applicable.
[j]AGEs: advanced glycation end products.
[k]ELISA: enzyme-linked immunosorbent assay.
[l]PC: protein carbonyl.
[m]F2-IsoPs: F2-isoprostanes.
[n]MDA: malondialdehyde.
[o]HPLC: high-performance liquid chromatography.
[p]TNFα: tumor necrosis factor-α.
[q]IL-6: interleukin-6.
[r]MoCA: Montreal Cognitive Assessment.
[s]RAVLT: Rey Auditory Verbal Learning Test.

Furthermore, the assessment of arterial stiffness is conducted by skilled laboratory assistants using arteriography during the participants' visits at both the 0- and 6-month time points. This assessment uses inflatable cuffs and is noninvasive. The arteriograph primarily measures pulse wave velocity, augmentation index, and central blood pressure, all of which reflect vascular health. Total body fat and lean mass measurements are accomplished using an InBody device during the participant visits at 0, 3, and 6 months.

In addition, skin health is analyzed using a Cutometer (Courage+Khazaka electronic GmbH) and Visioscan (Courage+Khazaka electronic GmbH) during participant visits at 0, 3, and 6 months. At 2 anatomical locations (volar side of the forearm and lateral periorbital region of the face), skin characteristics such as elasticity, hydration, transepidermal water loss, pigmentation, sebum secretion, wrinkles, and roughness will be studied. At both locations, 4 to 5 repeated measurements are made for each parameter, and the results are averaged. To ensure site uniformity and accommodate anatomical changes, slight positional deviations of a few centimeters are permitted. By measuring at the forearm and face, it is possible to conduct a thorough analysis of skin alterations in regions with low and high levels of sun exposure, respectively. This increases sensitivity to both the local and systemic effects of the intervention.

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Subsequently, for secondary outcome measures, participants undergo cognitive function assessments, which include the MoCA, RAVLT, and digit span test. These assessments are performed with the assistance of a trained research assistant during the participants' visits at 0 and 6 months. Finally, the measurement of bone mineral density is conducted using a dual-energy X-ray absorptiometry device at 0 and 6 months. Full body, lumbar spine, and hip scans are conducted. The lumbar spine and hip are essential locations for measuring bone density in older adults, which is crucial for comprehending how tocotrienol supplementation affects bone health. These regions are significant to the study since they represent general bone health.

To monitor changes in dietary habits, participants complete a food frequency questionnaire during their visits at 0, 3, and 6 months. The food intake checklist was developed to monitor changes in dietary habits throughout the study. Nutritionist Pro software is used to analyze the diet history data for each participant to quantify their nutrient intake values. Statistical analysis is then conducted to determine whether the nutrient value is significantly different from the blood biochemistry composition. Figure 1 presents a flowchart illustrating the study period and the tests conducted at each time point.

Participant Timeline

Over the study period, 3 assessments are carried out at 0, 3, and 6 months across various domains of inquiry, encompassing oxidative stress, inflammation, skin conditions, arterial stiffness, cognitive function, appetite regulation, bone mineral density, and vitamin E levels. To ensure comprehensive oversight of the assessments, delegation of an authority log was established and formally endorsed by the respective investigators, each of whom possesses expertise in their specific area of assessment.

Sample Size

Sample size estimation was based on a comparison of mean low-density lipoprotein levels, referencing a previous case-control study on biomarkers for premature coronary artery disease by Shukor et al [99]. The sample size was calculated using a power and sample size program. The effect size was calculated based on a mean value of 3.11 (SD 0.81) for group one and a mean value of 2.66 (SD 1.25) for group two.

The total number of required participants calculated per group of the experimental design was 93 when dichotomous outcomes were presumed with a Type I error probability, α of .05, and power of 0.8. To maintain the power, a 20% dropout rate was factored in. Consequently, 110 participants are required to be enrolled in each group (placebo and supplementation). Therefore, a total of 220 participants are required to perform this clinical study.

Recruitment

The selection of potential trial participants is conducted by the PI based on the inclusion and exclusion criteria. Participants who fail to meet the inclusion and exclusion criteria are defined as screening failures. The PI maintains a Screening Log, which includes screen failures to ensure a systematic selection of participants. Informed consent is obtained from each participant by the contract research assistants. During enrollment, general information (name, gender, age, address, and contact information) is obtained. To ensure security and confidentiality, each participant is assigned a participant-specific code. The code is used to label the participant's laboratory results. Each participant is reimbursed for standard transportation fees.

Participants are free to withdraw from the study at any time for any reason. Participants may also be withdrawn at any time at the discretion of the PI. Possible reasons for withdrawal include abnormal laboratory values, protocol violation, the participant requiring the use of an unacceptable concomitant medication, participant not complying with protocol procedures, participant developing a condition during the study that violates the inclusion or exclusion criteria, loss to follow-up, death, or any other reason in the PI's opinion that would impede participation in the study.

Assignment of Interventions

Tocotrienols and placebo supplements are prepared and labelled with the IP number by the sponsor. Assignment of supplements to participants is by chance through the drawing of lots by contract research assistants. The treatment is double-blinded throughout the study period until all data have been collected and analyzed, after which the supplementation IP numbers are revealed to the PI by the sponsor. However, in case of any serious adverse event reported during the study period, the unmasking of the code is immediate.

A set of numbers, from 1 to 60, is randomized using the randomization application for every block of 60 participants. The participants are assigned a randomized number according to the numerical sequence 1 to 60 in the list of randomized numbers. All even numbers are treated with the same IP, while odd numbers are treated with another IP. Thus, every block randomization has an equal number of participants for each IP. The randomization will be repeated until 220 participants are recruited.

The unblinding in emergency situations is only permitted in case of a suspected, unexpected serious adverse reaction or other important adverse event, when knowledge of the supplemented product in question is required for therapeutic decisions in the medical management of the participant.

In the event of an emergency, an emergency decoding option is accessible to both the PI and designated personnel at the sponsor. The responsibility for breaking the blind for individual participants in emergency situations lies with the PI. If the need to break the blind arises, the PI will communicate this to the sponsor. Before the treatment code is broken, the PI responsible for unblinding must document the reason and date for unblinding in the case report form (CRF) to ensure proper documentation of the unblinding event, including a clear explanation of the reason for unblinding.

In the event that the sponsor requires unblinding of the treatment, the reason and date of unblinding are recorded in the CRF. In situations where it is necessary to unblind an individual participant's treatment for the purpose of expedited reporting to the authorities, only designated individuals at the sponsor who are responsible for reporting this information will have

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access to the identity of the product. Every effort is made to ensure that all other members of the clinical trial remain blinded throughout the entire duration of the trial.

Data Collection and Management

During the screening process, potential participants are assessed for eligibility to enter the study according to the inclusion and exclusion criteria. After an overnight fast, a 10-mL blood sample is taken from each volunteer. The screening tests consist of comprehensive evaluations, encompassing blood lipid profile, liver function tests, renal profile, full blood count, and fasting blood glucose measurements. Additionally, records of past supplementation and medical history are reviewed to obtain a holistic understanding of the individual's health status. The results of blood tests are revealed to volunteers upon request. Volunteers who meet the inclusion criteria are selected for baseline sampling typically within a timeframe of 1 month to 2 months after the screening process.

Eligible participants are contacted to schedule appointments for data collection at baseline, 3 months, and 6 months. During each visit, a physician conducts a comprehensive medical evaluation, encompassing an assessment of medical history; documentation of any concurrent medications; measurements of participants' weight, height, resting blood pressure, pulse rate, and temperature; and evaluation of vital signs. Subsequently, blood samples are drawn from each participant for immediate analysis of blood biochemistry, and additional samples are preserved for future analysis of oxidative stress markers, inflammatory markers, vitamin E, and appetite regulation marker levels. Furthermore, on the same day as the visit, assessments are performed for arterial stiffness, body fat composition, skin health, bone mineral density, and cognitive function.

Participant records and data for analyses are kept in separate folders according to the protocol and transferred into the CRF of each participant by the contract research assistants. The result for each assessment is monitored by specific investigators with expertise in the field, to facilitate comprehensive monitoring of the data.

A contractual disclosure agreement signed by the sponsors and investigators outlines the sponsor's access rights to the trial data set and source data. Both the investigators and sponsor should collaborate and jointly author publications reporting the trial's results to ensure an accurate representation of the results and drawing of appropriate conclusions, thereby preserving the integrity of the findings. All data are reported in a collective manner with no reference to any participants in the trial to ensure that the identities of participants remain confidential.

Analyses

Statistical analysis is conducted using SPSS (IBM Corp). The Kolmogorov-Smirnov test will be performed to assess the normality of the data distribution. Type III sum of squares is set to evaluate the hypotheses.

A mixed-design ANOVA will be used to determine whether supplementation affects the blood biochemistry parameters (inflammation and oxidative stress) and physical health (body composition, skin, cognitive function, and vascular health) at baseline, 3 months, and 6 months among the groups. The Mauchly test of sphericity will be conducted to assess homogeneity of variance and compare the means of the supplemented group with those of the placebo group. To account for the risk of a Type I error as a result of many primary and secondary outcomes, multiplicity correction procedures will be used. In particular, the Benjamini-Hochberg approach for false discovery rate control will be used in each outcome domain (eg, oxidative stress markers, inflammatory markers, cognitive tests). Statistical power and Type I error control are balanced for exploratory research in this method with connected variables. The Tukey post hoc test will be used for comparisons between groups, while the Dunnett test will be used for comparisons within groups over time. In terms of missing data, linear mixed-effects models with the missing at random assumption will be used, which is acceptable given the repeated-measures design and inclusion of observed predictors. Nevertheless, dropout rates in older adult groups might differ from missing at random (for example, because of undetected health decline). To evaluate the possible impact of data missing not at random, sensitivity analyses will be conducted using pattern-mixture models and multiple imputation with delta-adjustment scenarios. These methods aid with determining the robustness of the findings under alternate missingness assumptions. All data will be presented as mean (SD), with statistical significance defined as $P<.05$.

This study requires a total of 220 volunteers as calculated using the power and sample size program. In the case where any participant withdraws or is eliminated during the course of the project, their ID number is not reused. Instead, new volunteers are recruited to maintain the total sample size at 220. The distribution of the IP numbers is rerandomized and adjusted as needed to ensure that both groups remain equally balanced, with 110 participants receiving each IP.

All randomized participants are included in the primary analysis using the intention-to-treat approach, which analyzes participants based on their initial group allocation regardless of whether they adhere to the intervention. Only participants who complete the study without significant protocol deviations are included in a secondary per-protocol analysis.

Monitoring

Participants are instructed to maintain their regular lifestyle throughout the study duration. We recommend that they adhere to their usual routine regarding the number of meals and dietary plan. If there is a need to use any medication, they are required to inform the PI to ensure proper documentation in the CRF.

To ensure compliance, participants are requested to submit the provided supplement bottles during their visits at 3 and 6 months. The percentage of the leftover supplements in the returned bottles are used to track compliance. The purpose of these data is to evaluate intervention adherence. To account for adherence-related differences in the treatment effect, the compliance percentage is incorporated as a covariate in the statistical analyses. Additionally, subgroup analyses based on adherence levels (high, medium, and low compliance) will be carried out.

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Additionally, plasma vitamin E levels are measured at 0, 3, and 6 months to assess the participants' response to supplementation. In the event of suspected side effects or adverse reactions, participants should promptly report to the PI and seek immediate medical assistance. The PI must assess whether the observed effects are related to the trial and determine if the participant should be excluded from the study accordingly.

Results

The study was approved by the Research Ethics Committee of Universiti Kebangsaan Malaysia for implementation from January 27, 2020, to July 26, 2026. The sponsor successfully disbursed funding in June 2020. Participant screening, recruitment, and data collection commenced in September 2020. As of April 2025, 339 participants were screened, with 211 recruited and 167 having completed the study. Data analysis was completed for the first 120 participants, evenly divided between the placebo and TRF supplementation groups. Final results are expected to be published in 2026, following the completion of data collection and unblinding of the IPs by the sponsor.

Discussion

This study was conducted to evaluate the effectiveness of TRF (DavosLife E3 Complete) on blood biochemical composition (liver function, lipid profile, renal function, full blood count, and fasting glucose), oxidative status biomarkers (MDA, AGE, F2-IsoPs, and PC), inflammation biomarkers (TNF-α and IL6), appetite regulation biomarkers (leptin and ghrelin), arterial stiffness, skin health, bone density, and cognitive function in healthy older adults aged 50 years to 75 years over a 6-month intervention period. We hypothesized that the high antioxidant and anti-inflammatory properties of TRF would result in significant improvements across several different areas, particularly vascular function and cognitive performance. In order to provide more thorough knowledge on the role of TRF in promoting healthy aging, skin and bone parameters were also included to investigate the potential benefits of TRF on structural and aesthetic elements of aging. The goal of this study is to meet the increasing need for a safe, nonpharmacological intervention that can help the older population maintain their functional lifespan, quality of life, and physiological resilience.

The 5-year clinical trial was designed in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines and registered in the National Medical Research Register of Malaysia. Prior to the initiation of the trial, the investigators and sponsor signed a mutual confidentiality agreement. This agreement serves to safeguard against any unauthorized use, disclosure, publication, or dissemination of confidential information by both parties involved. Separately, a comprehensive research agreement was signed, addressing the roles of the investigators and sponsor, ownership of liabilities, indemnification and insurance, quality assurance, record-keeping, reporting, access, intellectual property, and publication and authorship.

The trial commenced in 2019 after ethical approval was obtained. Notably, although sponsored by a commercial company, the trial is conducted entirely by the institution independently of the sponsors. Participant recruitment, sampling, and analyses are performed by the investigators who are blinded to the participants' identification to prevent bias. Volunteers undergo random screening and are recruited based on their fulfillment of the inclusion criteria. Similarly, the administration of investigational products is also randomized.

The trial protocol was collaboratively designed by investigators from diverse backgrounds, each bringing their expertise in the relevant measured parameters. Through careful consideration and discussion, the team determined the optimal parameters to be measured and the appropriate time points at which these measures were most likely to effectively detect changes. As a result, blood tests, skin assessment, and body composition were assessed at 3 time points, while parameters such as bone density, arterial stiffness, and cognitive function were measured exclusively at the baseline (0 months) and end point (6 months) evaluations.

The MoCA was used under the licensing agreement with the MoCA Clinic and Institute, ensuring that only trained research assistants administered the test to the participants. The RAVLT is a widely recognized measure that assesses an individual's capacity to encode, integrate, retain, and retrieve verbal information across various stages of immediate memory [100]. As a result, this assessment tool is valuable for evaluating the impact of interference stimulus, delayed memory, and recognition. Additionally, the digit span test, which gauges the ability to maintain and manipulate a limited amount of information within a readily accessible state for short durations, typically less than 30 seconds, provides crucial insights when assessing working memory [101].

The dosage of TRF was determined based on previous reports that demonstrated its efficacy while not reporting any adverse events. Careful consideration was given to selecting an appropriate dose to ensure safety and prevent potential toxicity, as TRF is a fat-soluble compound and excessive dosage can lead to adverse effects. Research with rats has shown that oral administration of a vitamin E supplement was not safe for the liver and kidney [102]. Nevertheless, considering the ongoing changes in population lifestyles and dietary habits, it becomes imperative to conduct a comprehensive review of the TRF dosage for future clinical trials especially for therapeutic purposes.

On average, the screening process typically lasts around 2 hours. According to the latest data, approximately 60% of the volunteers successfully met the inclusion criteria and became eligible for recruitment into the study. The primary reasons for volunteer exclusions were elevated levels of total cholesterol, low-density lipoprotein cholesterol, fasting blood glucose, and blood pressure. On average, each participant requires approximately 3 hours to complete all assessments, excluding blood tests. To accommodate the fasting requirement for blood withdrawal and arterial stiffness assessment, these tests are conducted first. Subsequently, the remaining assessments are performed simultaneously at different stations, allowing

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participants to visit any available station. To minimize the waiting time, a maximum of 5 participants are scheduled per sampling day. This ensures that participants do not experience prolonged waiting periods.

Throughout the treatment period, the research assistants monitor the compliance of the participants through regular phone calls and short messages. However, the effectiveness of this monitoring method relies on the participants' availability to respond to or read the messages. Noncompliant cases were primarily attributed to participants' difficulty with remembering to take the supplement, which is evident when they return the bottles with a higher number of remaining softgels than expected during the 3- and 6-month visits. The data from noncompliant participants are still analyzed. However, it is specifically noted in the CRF so that any potential outliers in data analysis can be identified later.

The findings of this study will further extend our current knowledge in many ways. As the older adult population continues to increase globally [103], understanding the efficacy of TRF supplementation for promoting healthy aging becomes increasingly imperative. The use of a randomized, double-blind, placebo-controlled study protocol to assess the effectiveness of TRF in older adults offers numerous advantages that significantly enhance the credibility and reliability of the research findings. First, the randomization process ensures an unbiased allocation of participants into the treatment and control groups, minimizing the influence of confounding variables and increasing the validity of the study results. Second, the double-blinded nature of the trial eliminates both participant and researcher bias, as neither knows who is receiving the active intervention or the placebo, thereby preventing any preconceived notions from influencing outcomes. This rigorous blinding protocol ensures the integrity of the data collected and provides a more accurate assessment of the true effects of TRF supplementation. Finally, the inclusion of a placebo group enables researchers to distinguish between the specific effects of TRF and any placebo effects, ensuring that observed improvements in health outcomes can be confidently attributed to the intervention. Overall, by adhering to such a meticulous study protocol, researchers can generate robust evidence regarding the efficacy of TRF for promoting health and well-being among older adults, ultimately informing clinical practice and guiding future research endeavors.

There are some possible limitations of this study. One significant limitation is the potential for dropout or noncompliance among older participants, which can compromise the integrity of the study results and introduce bias. Older adults may face unique challenges such as cognitive impairment, mobility issues, or comorbidities that affect their ability to consistently adhere to the study protocol. Moreover, the relatively long duration often required for such trials increases the likelihood of attrition over time. Additionally, the strict inclusion and exclusion criteria necessary to ensure the internal validity of the study may limit the generalizability of the findings to broader older adult populations with diverse characteristics and health profiles [104]. Thus, researchers must remain cognizant of these limitations and use strategies to mitigate their impact on the study outcomes.

In conclusion, our study holds immense promise for advancing our understanding of the potential health benefits of TRF. While acknowledging the inherent challenges and limitations associated with conducting trials in older adult populations, the insights gleaned from this study have the potential to significantly impact clinical practice. Ultimately, by generating robust evidence regarding the efficacy of TRF supplementation for promoting healthy aging, this study protocol has the potential to contribute valuable insights to the field of geriatric medicine, paving the way for improved strategies to enhance the quality of life and well-being of older adults worldwide.

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Data Availability

The data and materials are available upon request, subject to reasonable conditions.

Authors' Contributions

Conceptualization: JAG, WZWN, SM, MHAD, NFI, KYC, AA, MHMY, MMM, HYL, WNY, YWU
Formal analysis: JAG, NANAR, AFMA
Funding acquisition: JAG, WNY, YWU
Investigation: NANAR, AFMA, NFAS, AA, MHMY, MMM
Methodology: JAG, WZWN, SM, MHAD, NFI, KYC, AA, MHMY, MMM
Project administration: JAG, NANAR, AFMA, NFI
Writing – original draft: JAG
Writing – review & editing: WZWN, SM, MHAD, NFI, KYC, AA, MHMY, MMM, HYL, JREN, HYL, YWU, WNY

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Conflicts of Interest

JAG, WZWN, SM, MHAD, NFI, KYC, AA, MHMY, and MMM declare they have no competing interests. JREN, HYL, WNY, and YWU work for the commercial organization that sponsors the clinical trial.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOC File , 123 KB - resprot_v14i1e73039_app1.doc]

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Abbreviations

αTP: alpha tocopherol
AGE: advanced glycation end product
CRF: case report form
CRP: C-reactive protein
DEXA: dual-energy X-ray absorptiometry
F2-IsoPs: F2-isoprostanes
IL-6: interleukin-6
IP: intervention product
MDA: malondialdehyde
MoCA: Montreal Cognitive Assessment
NF-κB: nuclear factor kappa B
PC: protein carbonyl
PI: principal investigator
RAVLT: Rey Auditory Verbal Learning Test
RONS: reactive oxygen and nitrogen species
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
STAT-3: signal transducer and activator of the transcription-3
TNF-α: tumor necrosis factor α
TRF: tocotrienol-rich fraction

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Protocol

A Stage of Change Theory–Based, Stage-Matched Intervention for Healthy Dietary Intake Among Office Workers in a Low- to Middle-Income Country: Protocol for a Cluster Randomized Trial

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Abstract

Background: An unhealthy diet is a well-established risk factor for the development of noncommunicable diseases, and office workers are at a higher risk of noncommunicable diseases due to their sedentary work style. Stage of change (SOC) theory–based and stage-matched interventions effectively influence dietary and behavior changes. The effectiveness of such interventions in the context of low- and middle-income countries is yet to be assessed.

Objective: This protocol describes a cluster randomized trial planned to evaluate the effectiveness of an intervention for changing dietary behavior among government office workers in the Galle district in Sri Lanka.

Methods: A cluster randomized trial was conducted in 20 clusters divided into intervention and control arms. A cluster was an office with 30 clerical-type workers who were sedentary at work. A stage-matched intervention based on behavior change processes was implemented in the intervention clusters for 3 months. Participants were provided with an intervention matched to their SOC at baseline. Precontemplators and contemplators received awareness-raising and emotional arousal interventions. Others received goal setting and self-monitoring interventions. The SOC and dietary intake were assessed at baseline and the postintervention stage through a staging algorithm, and 24-hour dietary recall was supplemented with a picture guide and computer software. Adherence to the intervention was assessed monthly. We hypothesized that participants would achieve a progressive change in the SOC and healthy dietary intake in the intervention clusters compared to the control clusters.

Results: By December 2024, the planned intervention was completed. Data analysis on the effectiveness of the intervention is to be completed and published in 2025.

Conclusions: This protocol reports a stage-matched intervention based on SOC theory, enriching the current knowledge base with new evidence from office workers in a low- to middle-income country.

Trial Registration: Sri Lanka Clinical Trials Registry SLCTR/2020/025; https://slctr.lk/trials/slctr-2020-025

International Registered Report Identifier (IRRID): DERR1-10.2196/70293

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KEYWORDS

dietary intake; office workers; stage-matched interventions; stage of change theory; behavior change

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Introduction

Background

An unhealthy diet, which can be defined as nutritionally of poor quality or harmful to health [1], has a significant and well-established impact on developing noncommunicable diseases (NCDs) and their complications. It was highlighted that an unhealthy diet accounted for 11 million deaths and 225 million disability-adjusted life years in 2017 [2]. The Food-Based Dietary Guidelines (FBDG) for Sri Lankans provide directions on the necessary amount of food intake and dietary practices for a healthy diet [3]. The FBDG for Sri Lankans have 12 recommendations for a healthy diet, including the amount of food to be consumed [4]. The NCD risk factor survey (STEPS survey) conducted in 2015 highlighted that nearly 75% of male and female individuals were not consuming the recommended amount of fruits and vegetables [5]. An unhealthy diet is common among the workforce, and office workers are at higher risk of developing NCDs due to their sedentary lifestyle at work [6]. Studies conducted in the local context have also highlighted the increased prevalence of unhealthy diets among office workers [7,8]. Because working adults spend most of their time at the workplace, and due to the clustering of common risk factors and behaviors in one place, workplace-based interventions are believed to be successful. Several local and global studies have shown the effectiveness of interventions in workplaces [9,10].

Behavior change does not occur randomly, and behavior change theories explain the mechanism of behavior change [11]. The stage of change (SOC) theory describes 5 stages through which individuals can go through in changing their behavior, and it also describes interventions needed to be conducted at each stage to bring about the behavior change [12]. SOC theory is known to be effective in changing physical activity and dietary behavior, smoking and opioid addiction cessation, and dental hygiene improvement [13], whereas stage-matched interventions have been more successful and effective [14-16].

Behavior change techniques (BCTs) are defined as the smallest active ingredients of an intervention [17]. The selection of appropriate BCTs is one of the key factors on which the effectiveness or the success of an intervention depends [18]. Provision of specific instructions on the desired behavior through a credible source, action planning, goal setting (regarding the behavior or outcome), social support, and self-monitoring are commonly used and effective BCTs for interventions aimed at dietary behavior change. Among them, goal setting and self-monitoring have been identified as effective BCTs in different contexts of behavior change interventions [17,19,20].

Objectives

Sri Lanka is experiencing a huge burden of NCDs, contributing largely to mortality, morbidity, and health care expenditure [21]. The high prevalence of key risk factors is highlighted in national surveys and regional studies [5]. Office workers are at a higher risk of developing NCDs as the nature of their work leads them to be sedentary during work hours and their dietary intake does not follow local or global recommendations [7,8]. When a group of people with common risk factors are gathered in one place, there is a window of opportunity for health interventions to mitigate these risk factors. Furthermore, health education and promotion interventions through the mainstream preventive health sector hardly ever reach office workers. Therefore, this trial focused on an intervention to change the dietary behavior of office workers in a selected administrative district (Galle) in Sri Lanka. The intervention was planned based on SOC theory and was implemented as a stage-matched intervention at the individual level. Thus, it provided participants with the best-matched intervention. Therefore, this protocol provides valuable insights into several areas, such as dietary interventions for office workers based on behavioral theories and stage-matched interventions. Furthermore, it will enrich the existing scientific knowledge with information on the planning and implementation of interventions in a low- to middle-income country.

This study was designed as a cluster randomized trial with equal allocation of clusters to the intervention and control arms. This protocol was developed to implement an intervention aimed at changing the dietary behavior of office workers.

Methods

Design

This study was a cluster randomized intervention trial with a parallel-group design. It lasted 3 months (12 weeks), and the intervention's superiority in changing dietary behavior among office workers was assessed compared to the control group. Data for the baseline or preintervention assessment were extracted from a cross-sectional study, which was conducted before the commencement of the intervention to assess the dietary intake of the same study sample, and postintervention data collection was conducted at the end of 3 months. The intervention schedule and enrollment and assessment time points are illustrated in Figure 1.

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Figure 1. Flow of participants through the study.

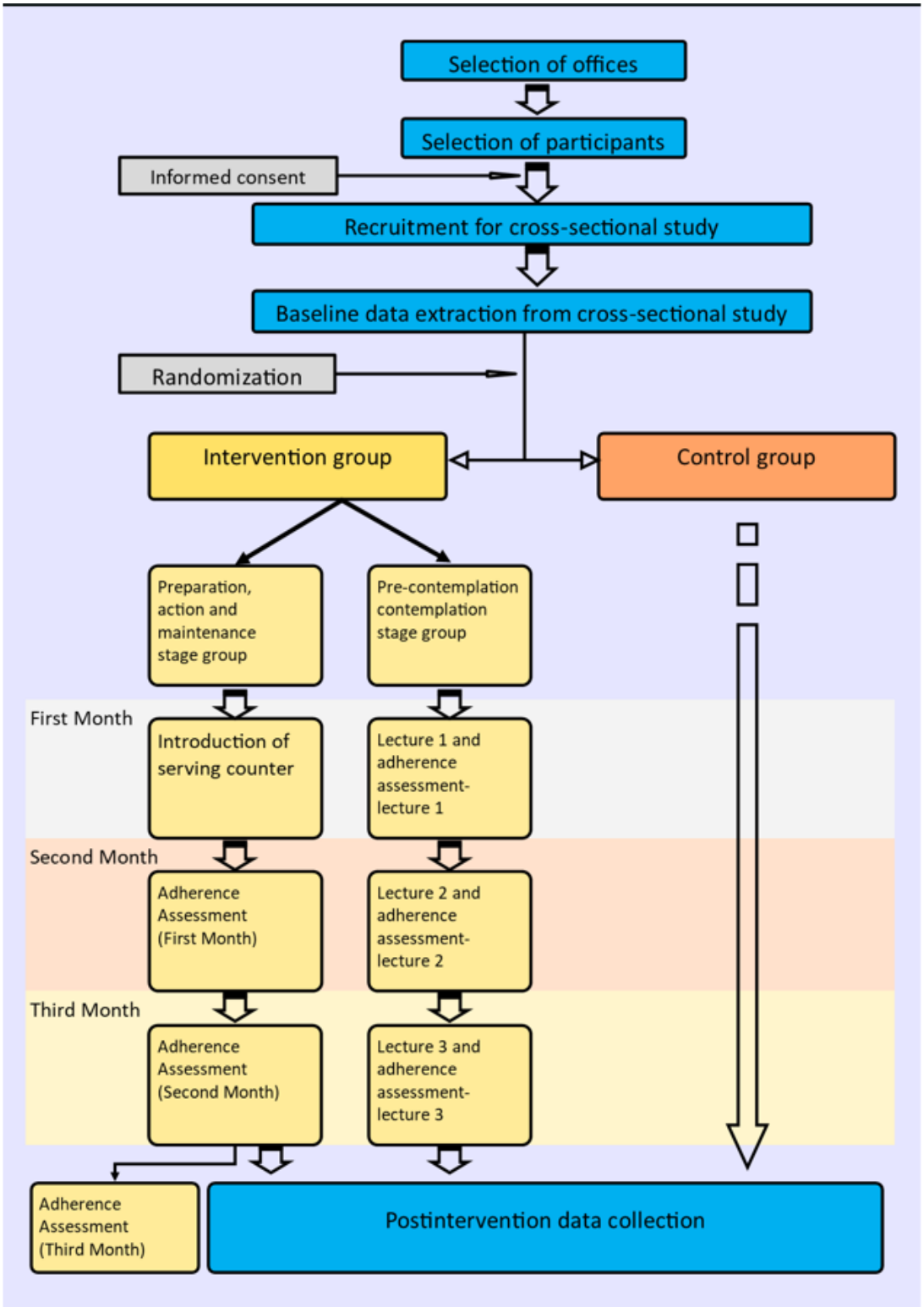

Study Setting

This study was conducted in 20 selected government offices in the Galle district. Offices were purposefully chosen to ensure similarity in office functions and the number of clerical-type workers. The minimum travel distance between 2 given offices was more than 5 km. An office with 30 clerical-type workers was defined as a cluster to enroll in the study.

Study Population and Eligibility Criteria

Clerical workers at government offices selected as clusters were enrolled as study participants. Workers involved in any physical exertion as part of their duties and workers put on specific diet plans for medical reasons were excluded from the study.

Sample Size

The sample size for the trial was calculated using the following formula for estimating the difference between 2 proportions

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[22]. A 5% α error was allowed, and 80% power was expected when calculating the sample size. A 50% increase in the factor of interest was assumed, as a meta-analysis on behavioral modifications showed an increase in factors of interest by 50%. As the 2015 STEPS survey reported that only 28% of the population had met the recommended number of fruit and vegetable servings [5], 0.3 was assumed as the baseline proportion for the recommended fruit and vegetable intake and was expected to increase by 50% at the end of the intervention. Therefore, 0.45 was assumed as the proportion in the intervention arm after the intervention.

Substituting the aforementioned values in the equation, the calculated minimum sample size in each arm of the cluster randomized trial was 160.

Design effect for cluster sampling was calculated assuming a cluster size of 30 and an intraclass correlation of 0.02 because the intraclass correlation coefficient in human studies usually lies between 0.01 and 0.02. A study among office workers reported an intraclass correlation coefficient of 0.02 [23]. Substituting the aforementioned values in the equation, the design effect for this study was 1.58.

Therefore, the minimum sample size for each arm was 253. After accounting for a 10% dropout rate, the study's minimum sample size per arm was 280 office workers. Thus, the minimum sample size in the intervention and control groups was 560 office workers.

Recruitment

Multistage cluster sampling was used to recruit study participants. A cluster was defined as an office with at least 30 clerical-type workers. A total of 20 clusters were selected purposefully to fulfill three requirements as follows: (1) the nature of the work carried out in the offices should be similar, (2) travel distance between any selected offices should be 5 km, and (3) the offices should have 30 to 40 clerical-type workers.

An exhaustive list of government offices established in the Galle district was prepared after obtaining information from the chief secretary's office (Southern Province) and the District Secretariat (Galle district). Information about the functions of each office was obtained from the district secretary and the chief secretary's office. Offices that carried out similar activities were short-listed. Offices were then short-listed again depending on the number of clerical-type workers (30 to 40). The travel distance between each office was then assessed using the direction function in Google Maps. If the travel distance between 2 or more offices was less than 5 km, the office with the highest number of clerical-type workers was selected, excluding the rest. Short-listing aimed to select 20 offices that matched the recruitment criteria. However, the ultimate short list contained only 19 offices because of inadequate distance between 2 offices. The distance requirement was then reduced to at least 5 km from more than 5 km.

Within the clusters, participants were selected using a series of random numbers. Once clusters were selected, the relevant offices were contacted, and a study coordinator was appointed for each office. The coordinator obtained a list of clerical-type workers' names. The workers' names were arranged alphabetically, and a number was assigned to each. An web-based random number generator selected 33 numbers from the list. The workers assigned the selected numbers were invited to participate after assessing their eligibility according to the inclusion and exclusion criteria. They were informed of the study and the data collection date through the office coordinator.

On the day of data collection, the selected participants were informed about the study, and the purpose, risks, and benefits were explained. The workers who provided consent were recruited for the study

Participant Timeline

Data from a cross-sectional study were extracted for all selected government offices in the Galle district, and 2 months were allocated for this. Data on participants' demographic profiles, health conditions, dietary practices, SOC, and dietary intake were extracted from the aforementioned cross-sectional study as preintervention or baseline data for the interventional study. Randomization was conducted following the baseline data collection. Once randomization was done, the principal investigator and resource person for lectures visited each office in the intervention arm on a prescheduled day. All participants in the study were informed of the date beforehand. The principal investigator applied the intervention, and the resource person delivered lectures. If any participant missed the initial intervention, a second visit was arranged to achieve maximum participation. The initiation of the intervention in all 10 selected offices was completed within 1 month. Monthly assessments and lectures were conducted on prescheduled days following one, two and three months of the initiation date for each office. However, a second day was not arranged for monthly assessments and lectures. A postintervention assessment was conducted at the end of 3 months. The date for the postintervention evaluation was given to all participants to ensure that they took part in the assessment. If any participant missed the postintervention assessment, another day was arranged. Figure 1 shows the flow of participants through the intervention process.

Data Collection

After selecting offices for the study, administrative approval was obtained from relevant authorities. The principal investigator met or contacted the office heads (divisional secretaries and chairmen of local authorities) to obtain permission for data collection. Thereafter, one senior worker, either a development officer or management assistant, was appointed as the coordinator for the study from each office. The list of eligible office workers was obtained through the coordinator. Thereafter, 33 workers were selected from each office as described in the Recruitment section. A date for data collection was fixed, and all selected participants were informed through the coordinator, requesting their presence at the office on the fixed date.

The principal investigator explained the purpose and nature of the study to potential participants. Information sheets and consent forms (Multimedia Appendix 1) were distributed among all eligible participants invited to take part in the study. The

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self-administered questionnaire (Multimedia Appendix 2) was then distributed among participants who consented to the study.

Three trained data collectors collected the data. Participants were allowed to ask questions and supported by the data collectors. After completion of data collection, the data collectors retrieved the filled-out questionnaires and checked them for completeness.

Furthermore, participant-reported health-related data were verified by referring to available clinical records as participants were asked to keep clinical records with them before data collection.

The data collectors also measured the weight and height of the participants using a calibrated weighing scale and stadiometer, and the measurements were recorded following the standard procedure described by Greenwood et al [24].

The assessment of the SOC was conducted using a staging algorithm which was originally used in the well-known "5 a day" project and subsequently used by many studies [25-27]. It comprised 4 mutually exclusive branching questions . The responses to the 4 questions were used to determine a participant's SOC as follows.

The first question was "Do you follow healthy dietary guidelines?" If the answer was "yes," the participant was asked, "for how long have you practiced your current diet?" (response options: "more than 6 months" [maintenance stage] and "less than 6 months" [action stage]). If the answer was "no," the participant was asked, "are you seriously thinking of changing to a healthy diet in the next 6 months?" If the answer to the latter was "yes," the participant was asked, "are you going to change your dietary habits next month?" If the answer was "yes," the participant was allocated to the preparation stage. If the answer was "no," the participant was allocated to the contemplation stage. If the answer to the question "are you seriously thinking of changing to a healthy diet in the next 6 months?" was "no," the participant was allocated to the precontemplation stage.

To minimize bias due to misperception of the diet's healthiness, the initial question was modified to read the following: "Have you changed your diet by reducing the amount of carbohydrates, salt, and sugar and increasing the amount of fruit and vegetable portions?"

The SOC of a participant was determined by coupling the staging algorithm with dietary assessment as suggested by Greene et al [28]. The perceived SOC reported by the participants was amalgamated with their dietary intake. Participants who followed a diet that met the definition of a healthy diet were assigned to their perceived SOC as reported by them. For example, if a participant reported being in the action or maintenance stages and their diet met the overall definition of a healthy diet, they were allocated to their reported SOC. In contrast, if participants who followed a diet that did not meet the definition of healthy dietary intake reported being in the action or maintenance stage, they were allocated to the preparation stage. This approach is summarized in Table 1.

Table 1. Summary of the process of ascertaining the stage of change of the participants.

Staging algorithm result	Type of diet based on 24-h recall	
	Healthy	Unhealthy
Precontemplation	Precontemplation	Precontemplation
Contemplation	Contemplation	Contemplation
Preparation	Preparation	Preparation
Action	Action	Preparation
Maintenance	Maintenance	Preparation

The 24-hour dietary recall was completed for each participant by the trained data collectors through face-to-face interviews and a computer software designed specifically for this study. Participants were asked to recall their food intake the day before the data collection date. Data were collected on a routine office day. Mondays and days after holidays were not scheduled for data collection. At the same time, it was established that participants would have their regular meals on the date selected for dietary recall. Where this was not possible, the nearest day in which they had their regular meals as they did on a routine office day was considered for the dietary recall.

Participants were asked to name all food items and the amounts they consumed between waking up and going to sleep. Data collectors then inquired about the amount of food consumed using household measurements.

Interview materials were used to quantify the intake from different food groups. A picture guide that included all household measuring items (eg, spoons and cups) and food portions obtained through commonly used measurements was used to identify the quantity of each food item consumed (Multimedia Appendix 3). A computer software that can convert household measurements to servings described in the FBGD for Sri Lankans was used to calculate the serving number from each food group (Multimedia Appendix 4).

Randomization

After baseline data collection, all selected clusters were randomized into 2 arms. The principal investigator or data collectors did not know whether a particular cluster belonged to the control or intervention arm at baseline data collection, which minimized observer bias during this stage.

All selected clusters were arranged in ascending alphabetical order, and a number was assigned to each cluster. An online randomization sequence generator assigned the numbers 1 to 20 into 2 arms. The intervention arm had 10 numbers, and the

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control arm had 10 numbers. Clusters with allocated numbers were randomly assigned to the intervention and control arms.

Allocation Concealment

The principal investigator enrolled the clusters in the study. The randomization sequence generation was delayed until baseline data collection was completed, ensuring that the principal investigator who enrolled the clusters was unaware of the randomization sequence at the time of enrollment.

The randomization sequence was generated by an independent researcher (not a research team member) from a different district. He was asked to allocate numbers from 1 to 20 into the intervention and control groups using a random sequence generator. He was unaware of the cluster list and the allocated number for each cluster. He did not know about the offices and their distribution in the Galle district as he was selected from a different district. This independent sequence generation randomized clusters into the intervention and control arms without manipulation.

Intervention

Overview

The intervention was developed to match the SOC of the participants.

It has been highlighted that different SOCs require different processes of change to progress from one stage to another. Prochaska and Velicer [12] have described the relationship between SOCs and the processes of change that correspond to each one (Textbox 1).

Textbox 1. Stages of change and the processes of change that correspond to each one.

Precontemplation

- Consciousness raising
- Dramatic relief
- Environmental re-evaluation

Contemplation

- Consciousness raising
- Dramatic relief
- Environmental re-evaluation
- Self–re-evaluation

Preparation

- Self- and social liberation

Action

- Contingency management
- Helping relationship
- Counterconditioning
- Stimulus control

Maintenance

- Contingency management
- Helping relationship
- Counterconditioning
- Stimulus control

According to Prochaska and Velicer [12], people in the precontemplation and contemplation stages need more consciousness raising, dramatic relief, self–re-evaluation, and environment re-evaluation. In these processes, they are provided with information on healthy and unhealthy behavior. Furthermore, the emotional and imaginary comparison of healthy and unhealthy behavior is facilitated. Similarly, the later stages, such as preparation, action, and maintenance, need processes of change such as self-liberation, contingency management, helping relationships, counterconditioning, and stimulus control. In these processes, more emphasis is placed on replacing the unhealthy behavior with a healthy one, monitoring whether the participant is on the correct path, and ensuring support from the environment [12].

Therefore, interventions to raise awareness and provide emotional arousal were designed for the precontemplation and contemplation stages. In contrast, interventions supporting and monitoring healthy behavior were designed for the preparation, action, and maintenance stages.

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For precontemplators and contemplators, a 30-minute awareness-raising lecture was conducted at the beginning of each month during the intervention period of 3 months, and the following topics (one topic for each month) were discussed in each lecture in the order given (Multimedia Appendices 5-7): NCDs and their risk factors; risks of an unhealthy diet and benefits of a healthy diet, as well as strengths, weaknesses, opportunities, and threats analysis for behavior change; and how to change to a healthy diet.

While providing information to increase awareness, emotional arousal and self–re-evaluation were incorporated into all 3 lectures. The benefits of a healthy diet were highlighted, and participants were encouraged to contemplate the benefits of a healthy diet and the harmful effects of an unhealthy diet.

The lectures were delivered by a medical officer who was competent in public speaking and experienced in NCD prevention activities. The content of the lectures was discussed with the lecturer, and the objectives and methodology of the study were explained. It was emphasized to the lecturer to ensure similarity in the presentation and points highlighted in the lectures delivered to all intervention clusters. A slide show was prepared, and the lecturer and principal investigator agreed on the points to be discussed with each slide. A narrated lecture was circulated (through email or other electronic media) to the participants who were not able to take part in the lecture.

A separate intervention was designed for the preparation, action, and maintenance stages aiming to support and monitor the healthy behavior to be started or already started.

The intervention introduced a daily serving counter designed by the principal investigator based on serving recommendations published in the FBDG for Sri Lankans [4]. It allowed the participants to record their daily intake of servings of different food groups. The recommended servings were indicated for each food group. The lower and upper limits of recommended servings, where they are considered unhealthy, were indicated in red. A guide on serving sizes for each food group was added (Multimedia Appendix 8).

In addition, a mobile app with similar functions (the serving guide and the ability to record servings) was also developed for smartphone users.

Assessment of Adherence to the Intervention

Attendance at the in-person lectures was recorded. Feedback was obtained from those who were provided with the narrated lectures, asking them whether they watched the presentation. If no feedback was received within 5 days of receiving the narrated lecture, it was considered as nonparticipation in the lecture.

The principal investigator reviewed the marking of the serving counter monthly, visiting the office at the end of each month. Participants were informed of the date of the investigator's visit and asked to bring the marked serving counters to be checked for completeness. If a participant missed more than 2 marking days per week during the month, it was considered poor adherence to the serving counter.

Participants were advised to attend the lectures and serving counter assessment sessions. After a discussion with participants, the dates and times for lectures and investigator visits were arranged to ensure maximum participation.

Control

No intervention was implemented for the control clusters. However, they were asked not to refrain from attending any routine health education or promotion activities conducted by other health care institutions and persons.

Outcome Measures

Overview

Postintervention assessment was conducted at the end of the intervention period in the same manner for the intervention and control clusters. The same data collectors who conducted the baseline (preintervention) data collection were recruited for the postintervention data collection. However, the study arm (intervention or control) to which an office belonged was not disclosed to the data collectors.

SOC data were collected using the same staging algorithm as in the baseline or preintervention data collection. The same 24-hour dietary recall with the picture guide and computer software were used to collect data on dietary intake at the postintervention assessment.

Primary Outcome

The primary outcome of the intervention was a progressive change in the SOC, which was defined as *progression from a lower SOC to a higher SOC*.

Secondary Outcome

The secondary outcome was a change from an unhealthy to a healthy diet or persistence in a healthy diet.

A healthy diet was defined as adherence to the recommended servings in the FBDG for Sri Lankans for more than 3 food groups, including cereal and cereal-based foods, fruits, and vegetables, with the consumption of 1 or no unhealthy foods per day. The recommended servings of different food groups per day are shown in Table 2.

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Table 2. Recommended number of servings of different food groups per day.

Food group	Number of servings
Rice, bread, other cereals, and yams	6-7 (6-11[a])
Fruits	2-3
Vegetables	3-5
Milk or milk products	1-2
Fish, pulses (legumes), meat, and eggs	3-4
Nuts and oily seed	2-4

[a]Wider allowance was given to the rice, bread, other cereals, and yams food group in the Food-Based Dietary Guidelines as the energy requirements differ with activity level and sex. Because office workers were considered a sedentary group based on the nature of their duties, 6 to 7 servings of the rice, bread, other cereals, and yams food group were considered the recommended number of servings based on expert opinion.

The FBDG recommend variety in the food items consumed from each food group and in the number of servings specified in Table 2. However, the routine Sri Lankan dietary intake does not include all 6 food groups in daily meals. Therefore, we considered the 3 most consumed and important food groups (cereals, vegetables, and fruits) to be included in the definition of a healthy diet. In addition, we included a limit for unhealthy foods (foods containing only sugar and fat and highly processed foods) in the definition.

Data Analysis

The distribution of basic sociodemographic characteristics, NCD status, dietary behaviors and practices, and work-related characteristics of the participants in the intervention and control arms will be assessed to determine whether the 2 groups were comparable at baseline.

Bivariate and multivariate analyses will be used to assess the effectiveness of the intervention. Progressive improvement in the SOC will be used as the primary outcome. Those who underwent a progressive change in their SOC will be coded as 1, and those who did not undergo such a change will be coded as 0. Similarly, those who changed from an unhealthy to a healthy diet or persisted in a healthy diet will be coded as 1, and those who did not will be coded as 0. Furthermore, changes in the intake of individual food groups to recommended levels will be coded as 1 and 0 similarly.

Bivariate analysis will use the primary and secondary outcomes as the dependent variables and sociodemographic factors, NCD status, dietary behaviors, and social relations as the independent variables. The chi-square test, independent-sample *t* test (2-tailed), and Mann-Whitney *U* test will be used as appropriate. Multivariate analysis will be conducted using binary logistic regression with the forward selection option to build the model. The variables included in the model will be determined based on demonstrating significant associations with the outcome variables in the bivariate analysis.

Sociodemographic factors, NCD status, dietary behaviors, social relations, and the allocated arm of the participants lost to follow-up will be compared with those of other participants to ensure no selective data loss. Further analysis will be conducted separately under two assumptions as follows: (1) all participants lost to follow-up achieved the primary and secondary outcomes, and (2) all participants lost to follow-up did not achieve the primary and secondary outcomes.

Odds ratios will be reported for the 2 assumptions separately. The level of probability will be set at .05 for all analyses.

Ethical Considerations

Ethical clearance for this study was obtained from the Ethical Review Committee, Faculty of Medicine, University of Ruhuna (registration 2020/P/105). This study was registered in the Sri Lanka Clinical Trials Registry. Administrative approval was obtained from relevant authorities at the provincial and district levels. Furthermore, this study obtained the approval of the Regional Director of Health Services of the Galle district. This study was conducted while adhering to the World Medical Association Declaration of Helsinki on ethical principles for medical research involving human participants.

Written informed consent was obtained from all study participants. They received a comprehensive information sheet and a consent form, which each participant had to complete and sign. Consent was 100% voluntary through being assured that declining to participate in the study would not affect the way in which they were treated at the office or a health care facility.

Participants were allowed to refuse to take part in all or part of the study or refrain from doing any activity requested by the researchers. They were given the freedom to withdraw from the study at any time without any effect on their routine work and personal life. They were assured that there would not be any difference in treatment toward those who refused to participate or withdrew from the study.

Two main risks for the participants were identified. First, there could be breaches of privacy when sharing personal information with researchers. Second, participants could be subjected to a behavior change if they were allocated to the intervention group. Identified workers with problems were referred to the nearest health care facility with their consent.

Although participants shared their personal information, those data are being kept anonymous and not shared with anybody other than the research team. Confidentiality is being ensured by keeping the data under lock and key and in password-protected computers. A serial number is being used to identify the participants during data entry and storage. When

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disseminating data, the names or identification details will not be included.

The participants were advised to take part in the awareness program and change their unhealthy dietary behaviors. These evidence-based activities were included in national and international guidelines on healthy lifestyles, so they have been proven to be more beneficial than harmful to participants. Therefore, no compensation was provided for participants as the intervention did not harm them, and they were asked to make minor changes in their lifestyle.

The findings of this study are planned to be disseminated only in scientific reports, publications, and forums. It has been ensured that no identifiable personal information will be shared in such dissemination activities. The scientific community and public can access these publications and use them for the benefit of mankind.

Results

As of December 2024, baseline data collection, participant enrollment, intervention administration, and postintervention data collection have been completed. Altogether, 610 workers from 20 offices were screened for eligibility. Of the 610 workers, 92 (15.1%) were excluded due to not meeting the eligibility criteria (n=12, 13%) and not consenting (n=80, 87%). A total of 518 participants were recruited for the baseline assessment, and then 20 offices were randomized to the control and intervention groups. The intervention group comprised 51.4% (266/518) of the participants, whereas the control group comprised 48.6% (252/518) of the participants. Ultimately, 439 participants (n=220, 50.1% in the intervention group and n=219, 49.9% in the control group) were included in the postintervention data collection. Figure 2 shows the CONSORT (Consolidated Standards of Reporting Trials) flowchart up to the completion of follow-up. Data analysis of the effectiveness of the intervention is to be completed and published. Data collected at baseline (before the intervention) were published as a descriptive study on dietary intake among office workers. However, none of the data related to the intervention have been published.

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Figure 2. CONSORT (Consolidated Standards of Reporting Trials) flow diagram for a stage of change theory–based, stage-matched intervention for healthy dietary intake among office workers. *The intervention group was divided into 2 groups depending on the participants' stage of change at the beginning. Two different interventions were implemented for each group. One group included 143 participants at the beginning and 127 participants at the end, and the other included 123 participants at the beginning and 97 participants at the end. **Postintervention analysis has not yet been completed.

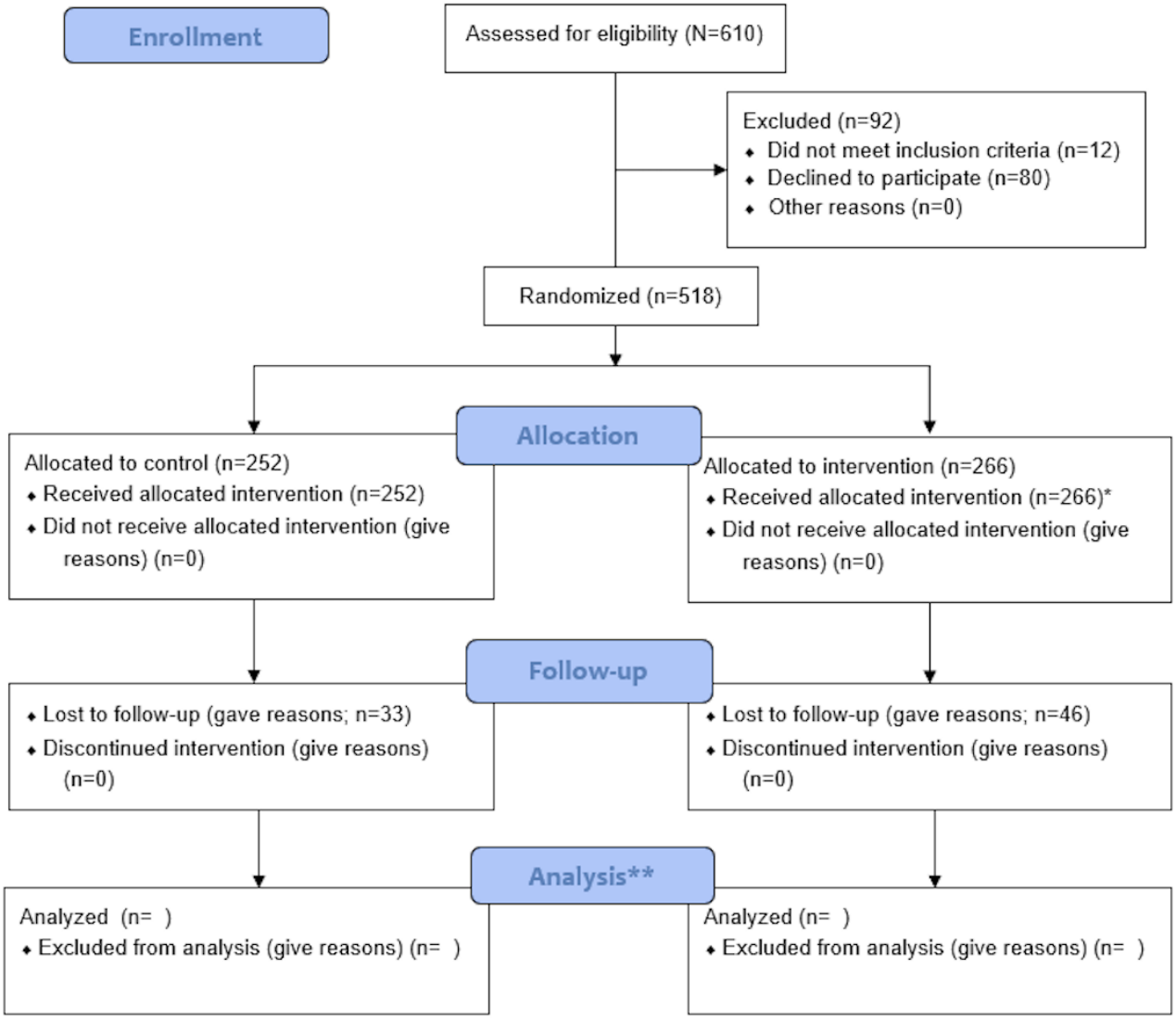

Discussion

This study assessed an intervention's effectiveness in making office workers' diets healthier. Because dietary behaviors are predominantly specific for individuals, interventions to change such behaviors should match the individuals' characteristics. Furthermore, it has been proven that interventions based on behavioral theories are more successful and more straightforward to assess and evaluate [29]. This protocol describes a stage-matched intervention using the SOC theory. Nutritional interventions based on SOC were found to be effective in recent studies and reviews [13,29,30]. Findings of different systematic reviews and interventional studies emphasize that stage-matched interventions have been more successful and effective in achieving the desired change in behavior [14-16]. However, no dietary behavior change interventions of this nature (SOC based and stage matched) for office workers were found in the available literature. Therefore, this trial will fill the knowledge gap on SOC-based and stage-matched interventions for office workers.

Furthermore, this study will enrich the existing research evidence with findings from a low- to middle-income country in the Southeast Asian region. In addition, it will help local-level policymakers in planning interventions to uplift the health of this specific group of people who are at a higher risk of NCDs due to their sedentary working conditions.

However, this study's major limitation is the inability to generalize the results. Because only clerical-type workers were included in this study, the results cannot be generalized to all office workers. Randomization at the cluster level does not fully eliminate the influence of other factors, which may affect the effectiveness of the intervention and, ultimately, the study's overall results. Therefore, this study's analysis and results must be interpreted with caution.

Ultimately, this study is expected to bridge the knowledge gap on dietary interventions for office workers, and the limitations must be considered when assessing the findings.

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Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed during this study.

All the relevant items to this study are included in this published article (and its multimedia appendices).

Authors' Contributions

JG planned the research project, conducted the data collection and statistical analysis, and wrote the manuscript. CJW and MSDWW provided technical guidance and supervised the research project. All authors read and approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Information sheet.
[DOCX File , 23 KB - resprot_v14i1e70293_app1.docx]

Multimedia Appendix 2
Questionnaire.
[DOCX File , 22 KB - resprot_v14i1e70293_app2.docx]

Multimedia Appendix 3
Picture guide for dietary recall.
[PDF File (Adobe PDF File), 18864 KB - resprot_v14i1e70293_app3.pdf]

Multimedia Appendix 4
Computer software to calculate food servings.
[XLSX File (Microsoft Excel File), 34 KB - resprot_v14i1e70293_app4.xlsx]

Multimedia Appendix 5
Lecture 01 for precontemplators and contemplators.
[PDF File (Adobe PDF File), 260 KB - resprot_v14i1e70293_app5.pdf]

Multimedia Appendix 6
Lecture 02 for precontemplators and contemplators.
[PDF File (Adobe PDF File), 113 KB - resprot_v14i1e70293_app6.pdf]

Multimedia Appendix 7
Lecture 03 for precontemplators and contemplators.
[PDF File (Adobe PDF File), 235 KB - resprot_v14i1e70293_app7.pdf]

Multimedia Appendix 8
Guide on serving sizes for each food group.
[PDF File (Adobe PDF File), 307 KB - resprot_v14i1e70293_app8.pdf]

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Abbreviations

BCT: behavior change technique
CONSORT: Consolidated Standards of Reporting Trials
FBDG: Food-Based Dietary Guidelines
NCD: noncommunicable disease
SOC: stage of change
STEPS: noncommunicable disease risk factor survey

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Protocol

Comparative Effectiveness of Titanium Platelet-Rich Fibrin and Connective Tissue Graft Harvested from the Tuberosity Area Via Modified Vestibular Incision Supraperiosteal Tunnel Access for Managing Gingival Recession: Protocol for a Randomized Controlled Trial

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Abstract

Background: Periodontal surgery has traditionally relied on connective tissue grafts (CTGs) obtained from the tuberosity site to correct gingival recession abnormalities. However, there are challenges to be addressed, including insufficient graft quantity and patient susceptibility. Consequently, titanium-prepared platelet-rich fibrin, or T-PRF, has emerged as a competitive alternative. By combining T-PRF with the modified vestibular incision supraperiosteal tunnel access (M-VISTA) approach, a more conservative way is provided, which may improve the course of treatment.

Objective: The objective of this study is to compare the effectiveness of T-PRF and CTGs from the tuberosity area in managing gingival recession defects using the M-VISTA technique. The study aims to evaluate improvements in clinical outcomes, including pocket probing depth (PPD), clinical attachment level (CAL), relative gingival margin level (RGML), recession depth (RD), and width of keratinized gingiva (WKG), as well as plaque and bleeding indices.

Methods: The proposed methodology entails conducting a randomized clinical trial over 2 years with 24 participants, each presenting with multiple gingival recessions (>2 mm, Miller's Class I or II) on the buccal or labial aspects of teeth in the maxilla or mandible. Participants will be randomly allocated into 2 groups: the test group and the control group. The M-VISTA technique will be used for root coverage using T-PRF in the test group and tuberosity CTG in the control group as regenerative materials. Their effectiveness will be compared by evaluating PPD, CAL, RGML, RD, and WKG. Additionally, the plaque index will be calculated by dividing the total plaque index score of all teeth by the number of teeth examined, and the papillary bleeding index will be assessed using a periodontal probe with scores evaluated on a scale of 0-4 based on bleeding potential. Data will be analyzed using Student paired and unpaired t tests to compare results from baseline to 3 and 6 months for each group.

Results: Recruitment, participant selection, baseline data collection, and randomization of groups concluded in September 2024, and the intervention phase is scheduled to end in December 2025. The study is expected to be completed by July 2026, with final evaluation, data analysis, and publication preparation taking place between June and July 2026.

Conclusions: Based on existing evidence, we anticipate that the M-VISTA technique with T-PRF will provide superior root coverage compared to tuberosity CTG because no second surgical site is involved. Evidence suggests that T-PRF may offer comparable clinical benefits to CTG, particularly in clinical attachment gain, RD reduction, and gingival thickness, supporting the advancement of minimally invasive periodontal plastic surgery.

Trial Registration: Clinical Trials Registry of India CTRI/2024/07/071619; https://tinyurl.com/ypfe34b5

International Registered Report Identifier (IRRID): DERR1-10.2196/67168

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KEYWORDS

modified vestibular incision supraperiosteal tunnel access; M-VISTA; titanium-prepared platelet-rich fibrin; T-PRF; gingival recession; maxillary tuberosity; connective tissue graft; periodontal surgery; periodontist; periodontology; dentistry; gum; gingivitis; gingival recession; graft; gum graft; randomized controlled trial; RCT; protocol

Introduction

The objective of periodontal treatment is to reestablish the supporting tissues destroyed by periodontitis and anticipate the progression of the disease itself. Aesthetics are another imperative matter that must be considered [1]. Gingival recession (GR) occurs when the apical gingival margin tissue migrates towards the cementoenamel junction (CEJ), leading to the root surface being exposed [2]. Many epidemiological studies have revealed that receding gums is a common condition in day-to-day clinical practice. The frequency of the disease fluctuates between 40% and 100% based on the population and analysis methods [1,2].

Several approaches have been made to manage GR, such as the lateral sliding flap, the double papilla flap, the envelope technique, and graft materials used in conjunction with advanced flap techniques [3]. Recent developments have led to the use of grafting techniques to upgrade the thickness and width of exposed tissue and to cover roots or implant surfaces [4]. The decision to proceed with the procedure is influenced by factors such as recession depth, attached gingiva width, number of teeth, and color balance after surgery. Each technique has its own distinct signs and constraints.

Using the envelope flap method, Raetze in 1985 [5] was the first to use this technique to cover individual GR. As described by Allen in 1994 [6], this method was developed to treat several GRs and later it was described by Zabalegui et al in 1999 [7] as the “tunnel” approach. However, the disadvantage of this technique was entry from a small sulcular point, which increased the possibility of damage and penetration of sulcular tissues, producing unsatisfactory outcomes. Because of these constraints, the vestibular incision supraperiosteal tunnelling access (VISTA) technique was developed by Zadeh [8], as a means of avoiding the potential complications associated with some tunnelling techniques. Several graft materials have been tested with VISTA and proven to be effective.

Modified VISTA (M-VISTA) is a modern and minimally invasive technique used for both generalized and localized GR defects [9]. This technique is particularly useful as it allows easier access to the vestibule by requiring a single vestibular incision that provides entry to the surrounding area. This permits adequate visualization of root and bone structure as well as dehiscence. It facilitates wound repair by reducing the complexity of the tunnelling process [2].

The paradigm for root coverage in periodontal surgery is autologous connective tissue graft (CTG). Traditionally, intraoral donor sites have been found in tuberosity or the palate for soft tissue grafts. Maxillary tuberosity block bone grafting was first described by Tolstunov in 2009 [10]. The evidence that tuberosity has more connective tissue fibers than adipose and glandular tissue and can shrink less is what led to its selection as a donor site [11]. The connective tissue covering the tuberosity contains dense collagen fibers with a well-keratinized epithelial layer. Only CTGs increased buccal gingival thickness after recession coverage, and residual fatty and glandular tissue could potentially impede plasma circulation and revascularization in early healing [12].

However, the thickness or quantity of CTGs may not be adequate for treating multiple GRs or donor area dehiscence in patients with thin palates. Additionally, when a patient refuses surgery twice, CTG is unfavorable [13]. Nonautogenous materials, like acellular dermal matrix and enamel matrix proteins, have applications in treating GR and as a substitute, but they cannot replace gold standards.

Platelet-rich fibrin (PRF) is a concentrated blood product selected for the fixation and revascularization of grafts and flaps because of the growth components it contains. A glass or plastic tube is obscured with activated silica from which a blood sample is extracted, which then generates into a fibrin [14]. Other scientists have conjectured that these particles of silica, which may not be present in the material, act as a catalyst and could potentially harm patients. To overcome the restraints of PRF, titanium-prepared PRF (T-PRF) emerged. Compared to PRF, the fibrin network of T-PRF is more compact as well as bulky. This compact structure of fibrin is important for promoting the retention and recruitment of growth factors into tissue over an extended period [15].

This randomized clinical trial protocol aims to evaluate the effectiveness of T-PRF and CTGs harvested from the tuberosity area using M-VISTA for the management of human GR defects with regards to root coverage (RC), gain in clinical attachment level (CAL), gingival thickness (GT), and improvement in the width of keratinized gingiva (WKG).

Methods

Overview

This study is a randomized clinical trial and will be performed over a period of 2 years. After obtaining written informed consent, the study will be carried out on 24 participants who will have multiple GRs (>2mm, teeth presenting Miller class I or II areas) on the buccal or labial regions of teeth in the maxilla or mandible from the outpatient department of Periodontics and Implantology at Sharad Pawar Dental College, Sawangi (Meghe), Wardha, Maharashtra, India. T-PRF clot (test group) and tuberosity CTG (control group) will be the biomaterials used in the M-VISTA procedure for root coverage, and their efficacy will be contrasted.

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Ethical Considerations

The Institutional Ethics Committee Datta Meghe Institute of Higher Education And Research, Sawangi (Meghe), Maharashtra, India, has reviewed and given approval to the study protocol, guaranteeing adherence to moral principles and norms (DMIHER(DU)/IEC/2024/05). This confirmation attests to the fact that participant safety, confidentiality, and informed consent will all be taken into account during the study's execution.

Sample Size Calculation

The sample size calculation was based on the formula for determining the required sample size when comparing 2 means, where the outcome of interest is the difference in clinical measurements (such as probing pocket depth [PPD] and CAL) between 2 groups (T-PRF and CTG). The data were evaluated from the earlier research of Collins et al [16] by using the SPSS 27.0 version (IBM Corporation) open-source calculator to determine the sum of squares mean. The outcome of the evaluation was 12. Thus, 12 participants will be unmethodically divided into the 2 groups.

The formula used was:

Where Z_α is the Z-value corresponding to the significance level (α), which is typically 0.05 for a 95% confidence level; Z_β is the Z-value corresponding to the desired power (β), which is typically 0.20 for 80% power; d_1 and d_2 are the SDs of the 2 groups being compared (T-PRF and CTG); and D is the expected difference between the 2 means.

Given Z_α=1.96 (for a 95% confidence level), Z_β =0.84 (for 80% power), SD = (1.32 + 1.10) / 2, and D=1.07 (representing the clinically significant difference between the 2 treatment groups), the sample size calculation is as follows:

Thus, the sample size required per group is approximately 12 participants. Since the result is rounded, the final sample size is set to 12 per group.

Randomization ensures that each participant has an equal probability of being assigned to either group, thereby preventing systematic differences between the treatment arms that could influence the outcomes. The random allocation of 12 participants per group was implemented to minimize selection bias and enhance the internal validity of the study using a computer-generated randomization sequence to minimize selection bias and enhance the study's internal validity.

Inclusion Criteria

This study included systemically healthy patients who (1) were nonsmokers, (2) were aged between 18 and 65 years, (3) had teeth presenting Miller class I or II areas with multiple GRs on the buccal or labial surfaces present in either the maxilla or mandible, (4) had a GR depth of ≥2 mm, and (5) had X-rays of adequate interdental bone (separation across crestal bone and CEJ ≤ 2 mm).

Exclusion Criteria

The following patients were excluded: patients using tobacco products, uncooperative patients, individuals with inadequate oral hygiene and a plaque score ≥1 after nonsurgical treatment, individuals with a history of periodontal surgical treatment in the selected research area, pregnant or lactating women, patients with mobile or severely decayed teeth, and those with irregularly placed teeth. Additionally, patients with systemic conditions such as hematological disorders (eg, anemia, thrombocytopenia, or clotting factor deficiencies), those undergoing anticoagulant therapy, or individuals with chronic kidney disease, uncontrolled diabetes mellitus, liver diseases (eg, cirrhosis), and severe cardiovascular conditions requiring anticoagulant therapy were excluded to ensure the study's integrity and minimize complications.

Procedure

The process of scaling, root planing, and polishing will be done on every patient. The patient will be instructed to use the modified Stillman brushing method to minimize brush injury. Unless the patients receive a plaque score ≤1, oral hygiene instructions will be provided. A review will be conducted 6 weeks later to evaluate plaque control and tissue response. The patient's participation in the study is contingent on their poor oral hygiene. The patient will provide with informed consent after being given information about the study plan.

Clinical Measurements

Indices

All patients' oral hygiene and gingival status are reviewed on the day of surgery, 3 and 6 months apart.

Plaque index (PI) [17]: The presence of plaque is evaluated on the labial or buccal and lingual surfaces of all teeth after the application of the disclosing agent (Table 1). The PI value for the tooth is calculated by splitting all the points around it by 2. The PI score for each individual person is gained by summing the PI scores of all teeth and dividing by the number of teeth inspected.

Papillary bleeding index [18]: The exact mesial introduction of a periodontal probe (William's Calibrated Probe) into the gingival sulcus at the papilla's apex will be followed by a coronal advancement to the tip of the papilla. On the same papilla, this is repeated on the distal side. On a scale of 0-4, the degree of potential bleeding is evaluated. The papillary bleeding index score per individual will be calculated by adding up all papillary bleeding index scores to the number of surfaces analyzed.

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Table 1. Plaque index.

Score	Criteria
0	Absence of plaque.
1	Distinct plaque deposits on the cervical surface of a tooth.
2	Thin, uninterrupted layer of plaque (up to 1 mm) covering the tooth's cervical margin.
3	Plaque band broader than 1 mm but covering less than one-third of the crown.
4	Plaque covering not less than one-third but less than two-thirds of the crown.
5	Plaque that covers two-thirds or more of the crown.

Clinical parameters

Clinical parameters measured for outcome assessment are relative PPD values, attachment level, relative gingival margin level (RGML), recession depth (RD), WKG, and GT value noted with an UNC-15 probe. An acrylic cast will be made for the patient to obtain clinical parameters. An acrylic stent will be used to cover the occlusal regions of the test tooth. By directing it using burs, the periodontal probe extends into the deepest defect site. The stent, which will act as a guide for the periodontal probe, will develop longitudinal patterns. Under local anesthesia, the GT will be measured 3 mm below using a rubber stopper and endodontic reamer to assist the gingival edge. From the cementoenamel junction to the gingival margin, RD will be evaluated. WKG will be reached by calculation of sulcus depth and attached gingiva with the UNC-15 probe. These treated areas will be measured clinically on the day of surgery and after 3 and 6 months.

Radiographic Measurement

Grid specifications and intraoral periapical assessment will be used to show that there is enough interdental bone.

Preparation of the T-PRF Membrane

Venipuncture, which entails taking a 10-mL blood sample from the antecubital vein, is used in the manufacture of T-PRF. It undergoes a single spin centrifugation at 2700 rpm for 12 minutes. Following centrifugation, a T-PRF clot will be produced. The fibrin clot that has formed inside the tube will be removed together with the remaining red blood cells [14,15].

Surgical Procedure

Surgical Procedure for the Test Group

Before the treatment, patients will be instructed to cleanse their mouth using 0.2% chlorhexidine gluconate for 1 minute. The surgical method is focused on preventing infection and maintaining a flawless aseptic approach. Following initiation of 2% local anesthesia, the exposed root areas are precisely planned using an ultrasonic device and then with curettes. When injected with local anesthesia, all intracrevicular incisions will be given using a microsurgical blade, with the exception of inferior incisor incisions, which will be made with a smaller, disposable blade. A full-thickness, 8-10 mm, vertical incision shall be created in the vestibule, either mesial or distal to the surgical location being operated on. This incision (vertical incision) will be limited to the gingival margin and will serve as an entrance for the widening of the supraperiosteal tunnel. Given the length of the teeth to be cured, a vertical incision will be created especially in the central area. The incisions will extend not less than 1 tooth over the ones to be treated, all the way down to the papillae's base. A full-thickness tunnel will be created, reaching supraperiosteal across the mucogingival edge into the alveolar mucosa. This is achieved by completely disclosing the tunnel-papillary network via a vertical incision and then through the gingival margins, permitting passive coronal substitution. This supraperiosteal tunnel shall be shifted coronally and adjusted inertly toward CEJ enveloping the recession faults. Coronal anchored sutures shall be inserted by involving the 2-3 mm apical gingival border of each tooth using a 4-0 silk suture. Once coronal stabilization is be achieved via the tunnel, a T-PRF clot will be uniformly distributed over recession defects. The mesial and distal sides of the treated teeth will be covered with a flowable composite material (without etching) to facilitate sutures. After thorough and appropriate adjustment of the graft, for the primary closure, the vertical incision will be sutured.

Surgical Procedure for the Control Group

Surgical Procedure for the Donor Area

Dentulous patients: To determine the size of the tissue graft, a periodontal probe is used for assessing the amount of GR. A tuberosity block will be performed along with a greater palatine nerve block. Two horizontal incisions will be made with a number 15 blade at the tuberosity area. The first incision will be 1-2 mm from the gingival margin. The second incision will be parallel and 4-5 mm away from the first incision. The third incision will be a connecting incision between first and second incision. After that the CTG of thickness 1-1.5 mm will be taken out with the surgical blade. The donor site will be pressed for 2-3 minutes with a wet gauze. The donor site will be closed by simple interrupted sutures with Vicryl (4-0) to control postoperative bleeding. No periodontal dressing will be placed due to possibility of displacement of the dressing.

Edentulous patients**:** A tuberosity block will be performed along with a greater palatine nerve block. Horizontal incision will be made on the edentulous tuberosity site with a number 15 blade. A vertical incision will be made at mesial aspect of the horizontal incision distal to the presenting tooth with a number 15 blade. A second vertical incision will be made at the distal aspect of the horizontal incision. The subepithelial flap will be raised and connective tissue will be taken out with surgical blade. The flap will be closed by simple interrupted sutures with Vicryl (4-0). No periodontal dressing will be placed due to possibility of displacement of the dressing.

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Alternatively, the tuberosity area can also be negotiated for CTG harvest by de-epithelialization using a half round diamond bur and selection of a suitable diameter trephine bur [8].

Surgical Procedure for the Recipient Area

The surgical procedure for the control group will be the same as that for the test group procedure except that the tuberosity CTG will be placed using the M-VISTA technique on the recession defect area.

Postoperative Care

Systemic antibiotics will be given. Patients shall be informed that the teeth should not be brushed in the treated areas for 3 weeks following the operation. For a duration of 14 days, all participants will be informed to use 0.2% chlorhexidine gluconate twice a day. The stitches will be removed after a period of 30 days. Improvement will now be visible. Polishing will be done after saline irrigation using polishing paste and a rubber cup with no traumatization to the healed area. Patients shall be advised to cleanse the managed site with cotton swab soaked in 0.2% chlorhexidine gluconate for the next 7 days and brush using Charter's method. Follow-up with the patients will occur 1, 3, and 6 months after surgery.

Statistical Analysis

Both univariate and multivariate analyses will be performed to evaluate the effect of various variables (such as baseline GT, WKG, and recession length and width) on the final outcomes. Means and SDs will be calculated using standard statistical procedures to ensure significance.

The data will be analyzed as follows:

1. Changes from baseline to 3 and 6 months will be assessed using a Student paired *t* test.
2. Comparisons between treatment groups at baseline, 3 months, and 6 months will be conducted using a Student unpaired *t* test.

In addition to these tests, multivariate analyses, such as multiple regression and analysis of covariance, will be used to determine the combined effects of covariates like baseline GT, WKG, and recession dimensions on treatment outcomes. These methods will allow for the assessment of potential interactions and the adjustment of confounding variables. The threshold for statistical significance will be set at $P<.05$.

Results

The combination of the M-VISTA technique with T-PRF is expected to significantly enhance the efficiency and effectiveness of root coverage procedures. This approach is projected to deliver superior outcomes across key clinical parameters, including reductions in PPD and RD and improvements in CAL, relative attachment level, and RGML, as well as notable increases in the thickness of attached gingiva.

This study was initiated in July 2024 with a 3-month phase dedicated to recruitment, participant selection, baseline data collection, and randomization of groups, which concluded in September 2024. The intervention phase, which is currently underway (October 2024 to December 2025), focuses on performing T-PRF and CTG procedures for both groups using the M-VISTA technique. From January 2025 to June 2026, the follow-up phase will be conducted, involving monthly clinical assessments and monitoring of clinical parameters. Finally, the study will conclude in June 2026 with a 2-month phase for final evaluations, data analysis, comparison of results, and preparation for publication. This structured timeline ensures a systematic approach to achieving the study objectives. The study timeline is outlined in Table 2.

Table 2. Study timeline table.

Timeline	Study procedures	Duration
July 2024-Sept 2024	Recruitment, participant selection, baseline data collection, and randomization of groups	3 months
Oct 2024-Dec 2025	Intervention phase: T-PRF[a] and CTG[b] procedures for both groups using M-VISTA[c] technique	15 months
Jan 2025-June 2026	Follow-up phase: monthly clinical assessments and monitoring of clinical parameters	18 months
June 2026-July 2026	Final evaluation, data analysis, comparison of results, conclusion of study, publication preparation	2 months

[a]T-PRF: titanium-prepared platelet-rich fibrin.

[b]CTG: connective tissue graft.

[c]M-VISTA: modified vestibular incision supraperiosteal tunnel access.

Discussion

Anticipated Findings

Based on existing evidence, we anticipate that the M-VISTA technique, when combined with either T-PRF or CTG, will be a viable approach for managing multiple GR defects. Previous studies have demonstrated that both techniques can significantly improve root coverage outcomes. T-PRF, in particular, has been shown to enhance soft tissue healing due to its autogenous nature, sustained release of growth factors, and ability to promote angiogenesis and fibroblast proliferation [14,15,19,20]. Given these documented benefits, T-PRF may serve as a potential alternative to CTG, aligning with current evidence-based trends in periodontal regeneration. Additionally, the findings align with previous literature, reinforcing the effectiveness of minimally invasive periodontal plastic surgery techniques in addressing GR defects.

Amin et al [12] in their split mouth clinical trial assessed the effects of donor and recipient locations and compared postoperative discomfort correlated with palatal and tuberosity donor areas for soft tissue transplantation. Compared with the

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palatal donor, the tuberosity donor's pain level was significantly lower during the first 2 weeks after surgery. Whether the donors were palatal or tuberosity, the average proportion of root covering was the same (mean 67%, SD 12% vs mean 62%, SD 13%, respectively; *P*=102). According to the authors, soft tissues harvested from the tuberosity region may produce better outcomes than palatal function and reduce postoperative pain [12].

Since Allen introduced tunnelling in 1994 [6], several studies have been conducted on the process [16], despite the fact that many modifications to the approach have been suggested. VISTA is a minimally invasive procedure that was introduced by Zadeh [21]. Later, a version of this known as M-VISTA was described [8]. A case report by Chowdhary et al [9] described the M-VISTA method with CTG in the management of multiple Miller Class I or II buccal GR areas. A CTG was taken from the palate using the "trap door" technique and the vertical incision was sutured after the CTG was implanted in the supraperiosteal tunnel. According to the authors, total root coverage was attained and sustained at 9 months, with exceptional aesthetic results.

Fernandez-Jimenez et al [19] examined a case series in which the outcomes of the M-VISTA method were assessed 6 months later in patients with multiple GRs (Miller class III). After the intervention, the study's mean root coverage was 58.72%, and 29% of the patients with GR had total root coverage. The authors came to the conclusion that M-VISTA might be superior to existing methods for class III recession in a number of ways [19]. In their work, Uzun et al [20] contrasted the treatment of several GRs with autogenous T-PRF and CTG. Keratinized tissue width (KTW), GT, RD, and clinical periodontal indices were recorded prior to surgery and at 6- and 12-month follow-up examinations. In addition, the values of the healing index and visual analogue scale were assessed. The study's findings showed that, at a 12-month time point, the T-PRF and CTG groups had mean root coverages of 93.29% and 93.22%, respectively. In addition, the T-PRF and CTG groups had mean KTW increases of 1.97 mm and 0.75 mm, respectively. The treatment of several Miller Class I or II GR defects with T-PRF is both reliable and efficient. This has therapeutic significance since it suggests that T-PRF, an excellent autogenous substitute for CTG—the gold standard for root coverage—may be used [20].

Balice et al [22] published a study on 30 patients with 2 adjacent RT1 GRs treated using the coronally advanced flap (CAF) combined with either a CTG from the maxillary tuberosity (T-CTG, 15 patients) or leukocyte and platelet-rich fibrin (L-PRF). After 12 months, both techniques were effective in achieving root coverage and comparable patient-reported outcomes, but the CAF + T-CTG group showed significantly greater GT gain compared to the CAF + L-PRF group [22]. Matvijenko et al [23], in their systematic literature review, analyzed 5 RCTs comprising 195 cases of GRs to compare the tunnel technique and the M-VISTA method. The review revealed a significant increase in KTW (–1.4 mm), CAL (–2.65 mm), and RD (–2.7 mm) for the tunnel technique from baseline to 6 months. Conversely, the M-VISTA group showed a significant reduction in GR width (–2.26 mm). Both techniques were found effective in root coverage, with no significant differences in probing depths, highlighting their value for treating multiple GRs [23].

The above studies highlighted various advancements in treating GR but also presented limitations that warrant consideration. Many of the studies, such as those by Amin et al [12] and Balice et al [22], focused on short-term outcomes (6-12 months), leaving questions about the long-term stability of the results. The comparison of techniques, such as T-PRF versus CTG and M-VISTA versus the tunnel technique, often lacked uniformity in sample sizes, standardization of procedures, and follow-up periods, making it challenging to draw definitive conclusions. Additionally, some studies, like those by Fernandez-Jimenez et al [24] primarily addressed specific GR classifications (eg, Miller Class I and II or III), limiting the generalizability of findings to other types of recessions. Furthermore, while studies like that by Uzun et al [20] highlighted promising results with T-PRF, the reliance on advanced materials and techniques may pose practical and cost-related barriers in routine clinical settings. Lastly, patient-reported outcomes, such as pain and aesthetic satisfaction, were inconsistently reported across studies, suggesting a need for more comprehensive and standardized evaluation criteria to better understand the overall impact of these treatments. These limitations underscore the need for larger, multicenter, and long-term trials to validate the effectiveness and applicability of these approaches.

Despite the strengths of this randomized controlled trial, several limitations must be acknowledged. The relatively small sample size may limit the generalizability of the findings, necessitating larger multicenter studies to validate the results. While the follow-up period of 18 months provides valuable insights into the short- to mid-term outcomes, longer-term data are essential to assess the stability and sustainability of both techniques. The use of the Miller classification instead of the Cairo classification for GR assessment, though widely used in previous literature, does not account for interproximal attachment loss, potentially affecting prognostic accuracy. Additionally, while T-PRF eliminates the need for a second surgical site, thereby reducing patient morbidity and postoperative discomfort, its long-term regenerative potential compared to CTG, particularly in keratinized tissue augmentation, remains an area requiring further investigation. The study also does not incorporate patient-reported outcome measures, such as pain perception and aesthetic satisfaction, which are crucial factors in periodontal plastic surgery. Operator skill and variability in individual healing responses may further influence clinical outcomes. Future research should address these limitations by using larger sample sizes, extended follow-up durations, and standardized assessments to enhance the clinical applicability and long-term validation of these findings.

The Miller classification [25] was selected for this study due to its widespread clinical acceptance and established reliability in categorizing GR based on the likelihood of complete root coverage. It has been extensively used in periodontal research and provides a practical framework for surgical decision-making, particularly in cases where interproximal attachment loss is minimal or absent. In contrast, the Cairo classification [26] incorporates interproximal clinical attachment

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loss to distinguish between RT1, RT2, and RT3 recession types, making it more comprehensive for cases involving periodontal disease progression. However, the Miller classification remains highly relevant for evaluating root coverage procedures, as it directly correlates with treatment predictability and surgical outcomes.

Despite its advantages, the Miller classification has certain limitations. It does not account for interproximal bone levels, which can influence the prognosis of root coverage procedures, nor does it consider factors such as gingival biotype and tissue thickness, which are now recognized as critical determinants of treatment success. Additionally, its categorical nature may introduce variability in case classification among clinicians, potentially impacting reproducibility. Nonetheless, its extensive use in clinical studies allows for direct comparison with existing literature, ensuring consistency in evaluating periodontal treatment outcomes.

Conclusions

The integration of T-PRF with the M-VISTA technique presents a promising advancement in periodontal therapy. By eliminating the need for a second surgical site, T-PRF serves as a less invasive alternative to CTG, potentially reducing patient morbidity and enhancing postoperative recovery. This study highlights the potential for significant improvements in periodontal parameters and soft tissue outcomes within a shorter regeneration period. Additionally, this approach addresses the challenges associated with GR management while optimizing treatment efficiency and patient comfort. The findings emphasize the importance of incorporating biomaterials and minimally invasive surgical techniques in periodontal care. Further research is warranted to evaluate the long-term stability and broader clinical applications of this combined technique.

Acknowledgments

We would like to sincerely thank everyone who helped with the creation and formatting of this research protocol. The study was approved by the Institutional Ethics Committee of the chosen research institute (Reference No. DMIHER(DU)/IEC/2024/05), which guarantees that the research complies with the highest ethical standards. For this, we are primarily grateful. As we prepared this protocol, we also wanted to thank our respected mentors and colleagues for their crucial advice and assistance. The study's design and technique have been greatly influenced by their knowledge and perceptions. Our sincere gratitude is also extended to the patients who will take part in the study, without whom this research would not be feasible. Our goal is to make sure they are safe.

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Data Availability

The data supporting the findings of this study are available from the corresponding author upon reasonable request. Due to ethical considerations and institutional regulations, certain restrictions may apply to data sharing.

Authors' Contributions

SDP, the corresponding and primary author, conceived and designed the study. PVD, as the co-author, provided guidance throughout the study. Both authors contributed to data collection, analysis, and manuscript drafting. All authors reviewed and approved the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CAF: coronally advanced flap
CAL: clinical attachment level
CEJ: cementoenamel junction
CTG: connective tissue graft
GR: gingival recession
GT: gingival thickness
KTW: keratinized tissue width
M-VISTA: modified vestibular incision supraperiosteal tunnel access
PI: plaque index
PPD: pocket probing depth
PRF: platelet-rich fibrin
RAL: relative attachment level
RC: root coverage
RD: recession depth
RGML: relative gingival margin level
T-PRF: titanium-prepared platelet-rich fibrin
VISTA: vestibular incision supraperiosteal tunnelling access
WKG: width of keratinized gingiva

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Protocol

Feasibility, Safety, and Impact of the Probiotics Lactiplantibacillus plantarum and Bifidobacterium longum subspecies infantis in Papua New Guinean Infants: Protocol for a Randomized Controlled Trial

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Abstract

Background: Childhood mortality in low- or middle-income countries (LMICs) remains a major public health concern, with infections being a leading cause of infant death. Probiotics have shown promise in reducing infection-related morbidity and mortality in preterm infants, but their use in newborns born at or near term in LMICs requires further investigation.

Objective: This study aims to assess the feasibility, safety, and initial outcomes of administering 1 of 2 synbiotic formulations or a placebo to newborns in the Eastern Highlands Province of Papua New Guinea.

Methods: Following ethics approvals in 2018 and 2019, and receipt of the synbiotic preparations in September 2020, healthy neonates (<72 h old; n=244) were recruited between October 2020 and June 2023 and randomly assigned in a double-blind manner (1:1:1) to receive an oral preparation containing *Lactiplantibacillus plantarum*, *Bifidobacterium longum* subspecies *infantis*, or placebo for 7 consecutive days. Follow-up continued for 6 months, with rectal swabs, stool, blood, saliva, and nasopharyngeal swabs collected before the intervention; on day 7; at age 2 weeks; and at ages 1, 3, 4, and 6 months. Ongoing analyses will assess probiotic gut colonization, bacterial nasopharyngeal carriage, and antibody responses to routine childhood vaccines (*Hemophilus influenzae* type b; hepatitis B; 13-valent pneumococcal conjugate vaccine; and diphtheria, tetanus, and whole-cell pertussis) as well as hospitalization and infection rates among the intervention groups compared to the placebo group.

Results: Recruitment began in October 2020, with the target sample size expanded from 195 to 240 in March 2023 owing to higher-than-anticipated loss to follow-up during the COVID-19 pandemic. Of the 244 enrolled infants, 218 (89.3%) completed the full 7-day synbiotic or placebo course, and 169 (69.3%) completed the study. All follow-up visits concluded in December 2023. Disruptions due to the COVID-19 pandemic led to family relocations outside the study area, preventing some infants (75/244, 30.7%) from completing the study. High rates of sample collection were achieved, with rectal swabs (1452/1474, 98.1%), nasopharyngeal swabs (1255/1262, 99.44%), saliva samples (881/882, 99.9%), and blood samples (876/882, 99.3%) successfully obtained at multiple time points. Data analysis is ongoing and expected to be completed by the end of 2025.

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Conclusions: This study demonstrates that probiotic supplementation is feasible and safe in healthy infants in an LMIC such as Papua New Guinea. The findings from this study will inform the design of larger trials of probiotics and synbiotics to complement existing efforts to reduce infection-related infant mortality in LMICs, while also providing insights into their clinical, immunological, and microbiological impacts in infants.

Trial Registration: Australian New Zealand Clinical Trials Registry (ANZCTR) ACTRN12620001369910; https://anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12620001369910

International Registered Report Identifier (IRRID): DERR1-10.2196/73926

(JMIR Res Protoc 2025;14:e73926) doi:10.2196/73926

KEYWORDS

probiotics; synbiotics; Bifidobacterium longum subspecies infantis; Lactiplantibacillus plantarum; infant health; neonatal infections; gut microbiota; colonization

Introduction

Childhood Mortality and Interventions

Childhood mortality remains one of the greatest public health challenges of our time. The global mortality rate for children aged <5 years was estimated at 38 per 1000 live births in 2021, which equates to an estimated 5 million deaths per year in this age group [1]. The mortality rate has decreased over the past 30 years, with the greatest improvements observed in children aged 1 month to 5 years. However, neonatal deaths (within the first 28 d of life) accounted for almost half of all deaths of children aged <5 years globally in 2022, highlighting the disproportionate mortality burden in the neonatal period [2].

The majority of childhood deaths occur in low- or middle-income countries (LMICs). Poor sanitation, limited access to improved water, poor access to health care, limited childhood vaccination coverage, inadequate nutrition, and the cost of health care relative to income contribute to high infectious disease burden and poor health outcomes. Many of these long-recognized contributors are difficult to rectify in the short term. To expedite improvements in child health in LMICs, novel approaches are required to complement longer-term initiatives.

Probiotics and Synbiotics

Probiotics have long been ingested by humans through the consumption of fermented foods. The World Health Organization defines probiotics as “live microorganisms which when administered in adequate amounts confer a health benefit on the host” [3]. In 2013, a panel of experts supported the ongoing use of this definition [4,5]. In addition to fermented foods, probiotics have been isolated from various sources and commercialized as health supplements, and, more recently, as therapeutic agents. A promising strategy for the use of probiotics is in combination with prebiotics: nondigestible food ingredients that selectively promote microbial growth. Termed “synbiotics,” these combinations are thought to be more effective in enhancing the survival and activity of the probiotic bacteria once ingested and have the potential to lower the risk of developing many illnesses and diseases [6,7]. However, the quality of synbiotic products available on the market varies significantly, with differences in probiotic strains, prebiotic types, and dosage levels that may affect their effectiveness [8]. Furthermore, while initial studies show promise [9-11], more robust clinical trials are needed to confirm their therapeutic benefits and safety because much of the current evidence is based on in vitro or animal models [12-14], rather than large-scale human studies. Standardization in product formulation and more rigorous clinical proof are essential to fully understand their potential health impacts.

Study Rationale and Objectives

One novel approach that has garnered interest in recent years is the use of probiotics early in life. In particular, probiotics have been shown to improve health outcomes in preterm infants. Meta-analyses of the health outcomes of probiotics administration in preterm infants demonstrate that probiotics can decrease the risk of necrotizing enterocolitis (NEC) [15-17] and death [18]. The administration of probiotics to preterm infants is now often standard practice in neonatal intensive care units in many high-income settings. Its applicability has been investigated in some LMICs for at least 20 years [19], with a systematic review of randomized controlled trials conducted in India suggesting that probiotics reduce the risk of NEC, late-onset sepsis, and death [20]. Similarly, another review of trials conducted in 10 LMICs demonstrated that probiotics decreased the risk of NEC, late-onset sepsis, and all-cause mortality [21]. Nevertheless, in 2023, the US Food and Drug Administration raised safety concerns regarding the use of probiotics in preterm infants in hospitals [22]. Unlike medical products, probiotics used in neonatal wards have not undergone the agency’s premarket evaluation of safety, effectiveness, and quality for medical use**.** Given the potential for harm posed by products in individuals considered highly vulnerable, such as preterm infants, the Food and Drug Administration has urged industry stakeholders as well as clinical and research funding communities to focus on high-quality clinical trials using products that meet quality criteria to provide definitive evidence to inform the use of these products by health care providers.

There has been interest over the past decade in the potential role of probiotics in improving health in full-term infants in LMICs. A large community-based study in India has demonstrated the potential health benefits of probiotics in infants [23]. In a randomized controlled trial, >2000 children in the intervention arm were administered a strain of *Lactobacillus plantarum*—currently classified as *Lactiplantibacillus plantarum*—supplemented with fructo-oligosaccharide (together forming a synbiotic) once daily over 7 days, starting on days 2

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to 4 of life. Compared to the placebo group, children in the synbiotic intervention arm had significantly lower rates of a composite of sepsis (including culture-positive sepsis, culture-negative sepsis, and lower respiratory tract infections [LRTIs]) or death (the study's primary outcome). Reductions were also observed in individual components of sepsis, including LRTIs, which constituted the majority of cases. In addition, the intervention group experienced lower rates of diarrhea, omphalitis, and other local infections.

Papua New Guinea (PNG) is an LMIC in which approximately 40% of the population live in poverty [24]. In PNG, approximately 4.1% of children die before reaching the age of 5 years, and the mortality rate for children aged <1 year is approximately 33 deaths per 1000 live births, which exceeds global averages [25]. The leading causes of death in children in PNG include neonatal complications (such as preterm birth, birth asphyxia and birth trauma, and sepsis), LRTIs, tuberculosis, malaria, and diarrhea. The current neonatal mortality rate alone is estimated to be 9.25% [26]. LRTIs, often caused by pneumococcal infections, play a particularly critical role in child morbidity and mortality in PNG. The high diversity and prevalence of nasopharyngeal pneumococcal carriage in children, compounded by limited vaccine coverage, underscore the importance of understanding local serotype distribution and the effectiveness of 13-valent pneumococcal conjugate vaccine (PCV13) antibodies in this setting [27,28]. Given the high burden of serious infections in children in PNG, there is a need to explore novel approaches to reducing this burden.

In this study, we report on the implementation and participant recruitment of a double-blind, randomized, placebo-controlled trial conducted in the Eastern Highlands Province (EHP) of PNG, in which newborns were administered 1 of 2 synbiotic formulations—*L plantarum* (American Type Culture Collection [ATCC] 202195) with fructo-oligosaccharide or *Bifidobacterium longum* subspecies *infantis* (Bi-26) with human milk oligosaccharide—or a placebo. This was the first study of probiotics supplementation in infants in PNG; therefore, the primary aim of this pilot study was to demonstrate the feasibility and safety of giving infants in PNG probiotic supplementation for 7 consecutive days, starting within the first 72 hours of life, before embarking on a larger-sized clinical impact trial. The secondary and exploratory aims include assessing gut colonization by probiotic species at multiple time points, hospitalization and infection rates, nasopharyngeal carriage of respiratory bacteria, vaccine-specific immune responses, microbiome development, and maternal vaginal colonization at delivery.

Methods

Study Location

PNG is one of the largest countries in the Oceania region by both land area and population. There has been rapid population growth over the past 30 years, from <4 million in 1990 to an estimated 11.8 million in 2021 [29,30].

This study was conducted in the EHP of PNG, where an estimated 785,000 people live. The capital of the EHP is Goroka, with the town (with a population of approximately 33,000) and surrounding periurban areas having a total population of approximately 212,000 [30]. Goroka is located approximately 1600 meters above sea level and is situated on the Highlands Highway (the main highway in PNG). The climate is typically highland subtropical: rainfall occurs year round, with reduced precipitation from June to September. The terrain is mountainous and rugged, making access to many rural villages and communities outside of town challenging and requiring off-road 4-wheel-drive vehicles.

The study was conducted by the PNG Institute of Medical Research (PNGIMR) and international collaborators. The PNGIMR is headquartered in Goroka. Participants were recruited at the Goroka Provincial Hospital, the major referral hospital for the EHP.

Study Design and Objectives

In this pilot study, we aimed to evaluate the administration of 2 different synbiotic formulations compared to placebo in newborns in PNG during the first week of life. The study design was a double-blind, randomized, placebo-controlled trial in which newborns received 1 of 2 synbiotic formulations or a placebo over 7 consecutive days, with the first dose given before the newborn was aged 72 hours and administration completed within the first 10 days of life. The overall objective is to generate data that will inform the design and implementation of a larger, definitive clinical trial in infants in PNG, including the assessment of clinical end points.

The primary pilot study objectives were (1) safety in terms of intolerance (diarrhea, vomiting, abdominal distension, and weight gain) or probiotic sepsis during the 7-day supplementation period, leading to the cessation of the study medication; and (2) the feasibility and cultural acceptability of daily probiotic administration (the proportion of children who received all 7 daily doses of supplementation without missing any). The secondary objective was to demonstrate the colonization of the gut by probiotic strains at age 1 week and at ages 1, 3, 4, and 6 months. The exploratory objectives included (1) hospitalization rates until age 6 months, (2) nasopharyngeal carriage of *Streptococcus pneumoniae* and other respiratory tract bacteria at age 2 weeks and at ages 1 and 4 months, (3) immunoglobulin G (IgG) antibody responses to childhood vaccination (PCV13; diphtheria, tetanus, and whole-cell pertussis [DTwP]; *Hemophilus influenzae* type b [Hib]; and hepatitis B), (4) the kinetics of probiotic colonization at various time points over the first 6 months of life, and (5) maternal carriage and colonization by probiotic species and pathogens at the time of delivery.

Ethical Considerations

Ethics approval was obtained from the University of Western Australia (2018/RA/1/2301/4) and the PNGIMR Institutional Review Board (1809) in 2018 and the PNG Medical Research Advisory Committee (18.20) in 2019. The study has been registered as a clinical trial in PNG under the National Department of Health Pharmaceutical Standards Branch (CT04 MRAC18.20) and has also been registered with the Australian New Zealand Trials Registry (ACTRN12620001369910).

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Before and throughout the study, clinic and field staff conducted awareness and information sessions within communities in and near Goroka, the Goroka Provincial Hospital prenatal clinic, and rural health centers. Formal letters and information about the study were also sent to the Eastern Highlands Provincial Health Authority and senior management of Goroka Provincial Hospital, from whom approval was obtained before study commencement.

Healthy, pregnant women late in the third trimester were approached in the prenatal clinic at Goroka Provincial Hospital or in their local communities by a study health extension officer (HEO) or nurse. The women were given information about the study and given the opportunity to discuss participation with their families. Women who assented to be part of the study were approached within 72 hours of giving birth at the Goroka Provincial Hospital labor ward or postnatal clinic. Their consent was confirmed, and if all inclusion criteria were met, the infant was enrolled in the study. Written parental consent was obtained before enrollment.

The study was conducted according to the Declaration of Helsinki, the International Conference on Harmonisation Good Clinical Practice, and local ethical guidelines. All participants were assigned a unique study number that was detached from their personal information. Personal data were accessible only to key investigators and were not linked with samples for processing. All data were therefore anonymized. Hard copies of participant information containing identifiable details were securely stored in locked offices. At the end of March 2023, due to higher-than-anticipated loss to follow-up because study infants' families left the study area, largely owing to the COVID-19 pandemic, ethics approval was obtained to recruit additional participants.

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria are presented in Textbox 1.

If the mother of an already enrolled child developed fever or abdominal tenderness within 2 days of giving birth, the child remained eligible to stay in the study as long as the child was clinically well.

Infants were deemed eligible to participate and to not have any congenital abnormalities based on clinical assessments conducted routinely by hospital pediatricians on newborns delivered at Goroka Provincial Hospital and by a study HEO.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Infant birth weight ≥1.5 kg
- Infant aged <72 h
- Infant feeding orally within the first 72 h of life
- Mother and infant residing within 60-min driving distance from the Papua New Guinea Institute of Medical Research in Goroka
- Family intending to remain in the study area for at least 6 mo (duration of the study)
- Parental written informed consent obtained

Exclusion criteria

- Mother HIV positive or of unknown status
- Mother with foul-smelling amniotic fluid
- Heavy meconium staining of amniotic fluid
- Mother with fever (>38 °C) within −2 or +2 d of delivery
- Mother with abdominal tenderness within 2 d of delivery
- Parents unable or unwilling to provide consent
- Infant receiving antibiotics between birth and screening (within the first 72 h of life)
- Infant with signs or symptoms of suspected infection at the time of screening
- Infant with a major congenital abnormality
- Infant with an Apgar score of <8

Study Interventions

The synbiotic products and placebo were manufactured by DuPont Nutrition and Biosciences, now part of International Flavors and Fragrances Inc (IFF), and supplied in September 2020 before the study commenced, in quantities sufficient for the full target cohort. An additional 10% was provided to allow for repeat doses (eg, in cases of vomiting after administration) and for any additional enrollments to account for anticipated loss to follow-up. A full replacement batch was supplied by IFF in November 2022 due to the expiry of the initial batch before recruitment had been completed. The intervention products were shipped at room temperature and stored at the PNGIMR at 4 °C until use.

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Two probiotic supplements—single-strain *L plantarum* and *B longum* subspecies *infantis*— compared to placebo were used in this study. These 2 probiotic supplements were prepared as synbiotics and supplied, as with the placebo, lyophilized in glass vials. Each vial contained a single dose of one of the following: (1) *L plantarum* (ATCC 202195; 1.0×10^9 colony-forming units) + 150 mg of fructo-oligosaccharide, with 100 mg potato maltodextrin as excipient (matching the preparation used in the Indian trial [23]); (2) *B longum* subspecies *infantis* (Bi-26; at least 1×10^9 colony-forming units) + 1.2 g of the human milk oligosaccharide 2′-fucosyllactose, with 100 mg potato maltodextrin as excipient; or (3) placebo (100 mg potato maltodextrin).

Randomization

A computer-generated randomization list was maintained by DuPont Nutrition and Biosciences (now part of IFF) such that the research investigators, research and laboratory staff, and study participants remained blinded to the intervention arms. A single randomization code (sequential numbers 1-215) was assigned to each carton of intervention product, which contained 7 vials—one for each day of administration (d 1-d 7)—and was allocated consecutively to each enrolled child. Each vial was labeled with the specific trial randomization code and the corresponding day of administration. After the expiry of the initial batch, the replacement intervention products, also sequentially numbered, were used to continue enrollment beyond participant 215. The same blinding randomization procedures were followed to ensure allocation concealment and consistency throughout the trial.

Intervention Administration, Vaccination, and Follow-Up

The schedule of synbiotic administration, routine infant vaccinations, and specimen collection throughout the study is shown in Figure 1. Just before administration, a single vial of intervention product corresponding to the appropriate day of administration (d 1-d 7) was diluted by adding 3 mL of either breast milk or sterile water directly to the vial, followed by inverting 5 times to mix and resuspend the contents. The resulting suspension was administered to the infant in oral drops using a Pasteur pipette, similar to the method used for oral polio vaccine. Before administration, infants were breastfed and burped. The intervention was administered by PNGIMR study staff (HEO or study nurse). When the intervention was administered at participants' homes, the product vials were transported in small portable coolers with ice packs. The infant was monitored for 30 minutes after receiving the intervention. In cases of vomiting, the dose was repeated an hour later. A missed dose was defined as any scheduled daily dose (d 1-d 7) not administered on the same day, regardless of the reason, including participant unavailability, vomiting without readministration, or logistical barriers to follow-up. During the observation period, infants were taken to the PNGIMR clinic for examination and treatment (if the intervention had been administered elsewhere) and referred to Goroka Provincial Hospital when necessary. Obstetrics information and baseline characteristics were obtained on the day of enrollment. At each follow-up visit, the infant's health was reviewed before any intervention administration, vaccination, or specimen collection. Weight and length measurements were recorded, and information on feeding practices was also collected at each visit.

Figure 1. Schedule of synbiotic or placebo administration, routine infant vaccinations, and specimen collection throughout the study.

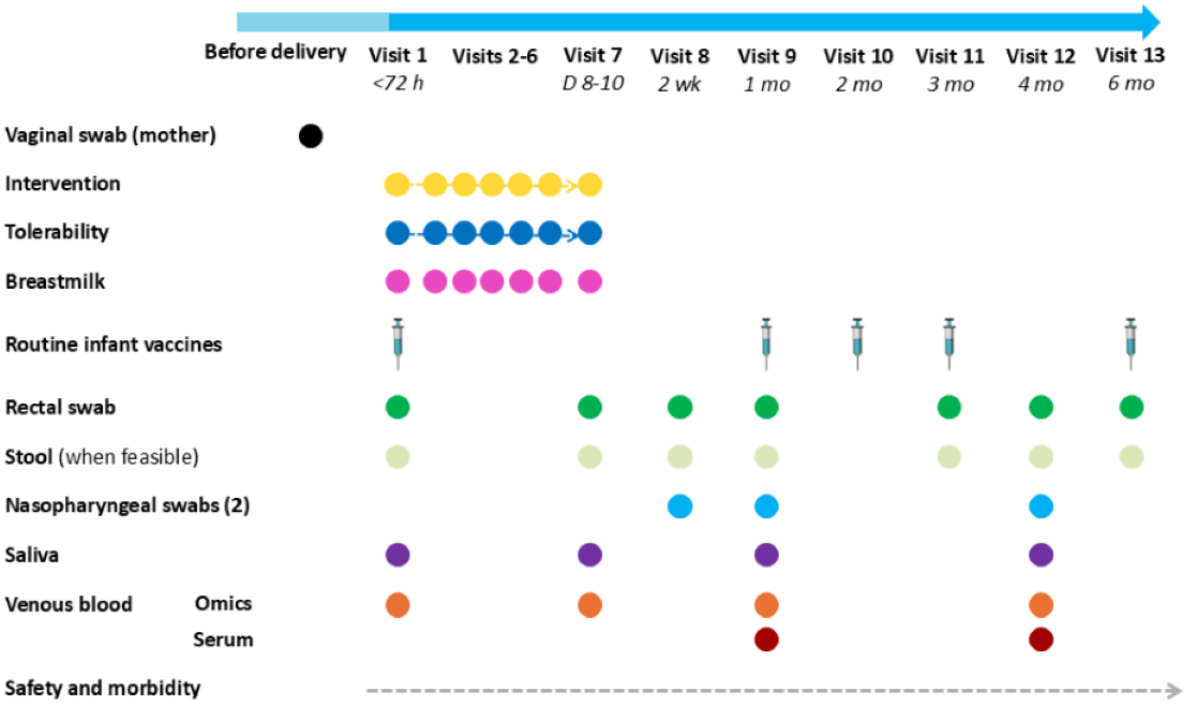

Routine childhood vaccines, including the pentavalent vaccine (DTwP, hepatitis B, and Hib), PCV13, and oral polio vaccine (Figure 1) were obtained through the Eastern Highlands Provincial Health supply chain and administered by study HEOs or nurses at ages 1, 2, and 3 months as per PNG's expanded program on immunization. Inactivated polio vaccine was also

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administered at age 3 months, and the first dose of the measles vaccine was administered at the completion of the study (6 mo). Birth doses of bacillus Calmette-Guérin (BCG) and hepatitis B vaccines were generally administered by hospital staff. In instances where this did not occur, study HEOs and nurses administered them at the time of enrollment. All vaccinations administered were recorded in the child's health book held by the parent or guardian.

Follow-up visits were conducted at either the PNGIMR clinic or at the participant's home. When blood collection was scheduled (at enrollment, on the day of the last intervention administration, and at ages 1 and 4 mo), participants were brought to the PNGIMR clinic for review and sample collection. All other follow-up visits were carried out by the clinical and field staff at the participants' place of residence. Up to 3 home visit attempts were made for each participant follow-up before a child was withdrawn from the study after being deemed unlocatable. Children were also withdrawn from the study if information had been received that the family had permanently moved out of the study area, if parents or guardians withdrew consent, if a protocol violation occurred, or if the investigators determined that continued participation could adversely affect the child's health.

Morbidity Surveillance

All serious adverse events (SAEs) that occurred during the study period were recorded. The variability in diagnostic terms and a lack of gold standard case definitions for neonatal sepsis make it difficult to compare incidence, severity, etiology, or disease outcomes across studies and settings. Therefore, instead of sepsis, we examined "severe infection" as a clinical outcome, acknowledging that many infants will not manifest overt signs of sepsis and using the qualifier "severe" to indicate that localized infections without systemic features (eg, skin pustules) will be excluded. Severe clinical infection was defined as the presence of at least one of the following signs or symptoms to align with a similar study of synbiotics in Bangladesh [31]: (1) poor feeding (not sucking effectively or not sucking at all, as directly observed), (2) lethargy (movement only when stimulated or not moving at all, as directly observed), (3) convulsions (observed or strongly suspected by the clinician based on caregiver or community health worker report), (4) severe chest in-drawing (observed), (5) fever (axillary temperature of ≥38 °C), and (6) hypothermia (axillary temperature of <35.5 °C). In addition, any subsequent positive sterile site cultures or hospitalization with intention to treat with antibiotics for at least 5 days was considered indicative of severe clinical infection.

Throughout the study, the pediatric ward at Goroka Provincial Hospital was monitored daily for possible admissions of study infants. For any participant admitted, clinical information on health status, reason for admission, treatment, and discharge outcomes was recorded. In addition, parents or guardians were encouraged to bring their infants to the PNGIMR clinic for any illness experienced to enable SAEs to be recorded during this period. If clinically indicated, specimens were collected to aid in health assessment and diagnosis. Clinical samples included small volumes of blood (approximately 2 ml), stool, and a nasopharyngeal swab. Samples were processed at the PNGIMR laboratory, and the results were returned to the study clinicians for dissemination to the participant's parent or guardian.

If a child was unwell during a scheduled study visit, routine procedures such as intervention administration and sample collection were still conducted unless contraindicated.

In addition, as in previous clinical trial studies led by the PNGIMR, study children's family members who became unwell were also seen at the PNGIMR clinic as needed during the 6-month participation period.

Specimen Collection

For the secondary and exploratory objectives of the study, a number of biological samples were collected at several time points throughout the study (Figure 1). Rectal swabs and stool samples were collected to assess intestinal colonization by probiotic species. Rectal swabs were collected at enrollment; on the day of the last intervention administration (age 7-10 d); and at ages 2 weeks, 1 month, 3 months, 4 months, and 6 months. For sample collection, the infant was carefully placed face down across the mother's thighs. A FLOQSwab (Copan Diagnostics) was gently inserted approximately 2 cm into the anal canal, rotated slowly for 10 seconds, then removed and placed into a tube containing eNAT preservation and transport medium (Copan Diagnostics). The swab was broken at the breakpoint, leaving the tip in the tube, which was then sealed and mixed by inverting 10 times. Stool samples were collected in addition to rectal swabs if infants passed stool during the study visit to allow for sensitivity comparisons of probiotic strain detection in rectal swabs versus stool. Stool samples were taken from infants' diapers using a scoop and placed into stool specimen containers for storage and transportation. Upon arrival at the PNGIMR laboratory, stool samples were transferred to cryovials by laboratory staff. Both rectal swabs and stool samples were then stored at −80 °C.

Nasopharyngeal swabs to assess bacterial carriage and load were collected at ages 2 weeks, 1 month, and 4 months using FLOQSwabs. At each time point, 2 swabs were collected per infant when possible. For each collection, a swab was inserted horizontally into the nostril to collect a superficial mucosal sample from the anterior nares, advancing gently until resistance was met. The swab was then rotated while counting to 5 (or for approximately 3 s) before being removed. One swab was placed in skim milk tryptone glucose glycerol broth (STGGB) for culturing of bacterial pathogens (priority), and the second was stored in PrimeStore molecular transport medium (Thermo Fisher Scientific) for deep sequencing. Both samples were stored at −80 °C.

Venous blood (maximum 2 mL at visits 1 and 2 and maximum 4 mL at visits 9 and 12) and saliva (visits 1, 7, 9, and 12) samples were obtained to assess systemic and mucosal vaccine responses and identify intervention-associated pathways or markers of immune maturation using systems biology approaches. Blood was collected using small 20-gauge butterfly needles and syringe techniques to reduce the risk of vein collapse. A maximum of 2 attempts were made to obtain a blood sample at each visit; if unsuccessful, no further attempts were made. For systems biology studies, we collected up to 2 mL of

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blood in heparin tubes. These samples were processed at the PNGIMR laboratory within 15 minutes of collection for RNA (transcriptomic analysis), plasma (proteomic and metabolomic analysis), flow (single cell immunophenotyping), and white blood cells (proteomic, metabolomic, and epigenetic analysis), following a protocol established by the Expanded Program on Immunization Consortium [32]. For serology, we collected up to 2 mL of blood in standard serum tubes, and the serum was separated and stored in cryovials by laboratory staff. Blood for serology was prioritized at ages 1 and 4 months over blood for systems biology. Saliva samples were collected from infants, ideally at least 30 minutes after being breastfed, using 4 to 6 surgical eye spears (Defries Industries) placed on the floor of the mouth to absorb saliva from the gums until saturated. The eye spears were then transported in 15 mL Falcon tubes (Corning Incorporated) to the PNGIMR laboratory where they were centrifuged at 10,000 g at 5 °C for 10 minutes. Saliva recovered after centrifugation was transferred to cryovials for storage. If no saliva was obtained after centrifugation, the sample was discarded. All blood products and saliva samples were initially stored at −80 °C at the PNGIMR before being shipped on dry ice to The Kids Research Institute Australia (formerly Telethon Kids Institute) in Perth, Western Australia, Australia.

Mothers were asked to self-collect vaginal swabs shortly after delivery using eNAT FLOQSwabs. These samples were used to collect information on the background prevalence of maternal vaginal carriage of probiotic species, in addition to pathogens associated with neonatal sepsis, such as group B *Streptococcus* and *Escherichia coli*, which may be vertically transmitted to the infant at the time of delivery. The swabs were stored at −80 °C.

Excess expressed breast milk was also collected at each intervention visit (visits 1-7) and stored at −80 °C at the PNGIMR for later analysis of protein (including antibodies) and carbohydrate content.

Laboratory Procedures

Gut Colonization

Rectal swabs and stool samples will be tested for the presence of the probiotic species and strains used in this study using quantitative polymerase chain reaction (qPCR). Assays will be performed at the PNGIMR using an in-house method developed and optimized for local laboratory conditions. Briefly, total DNA will be extracted from approximately 200 mg of stool or 600 to 800 µL of rectal swab eNat preservation medium using the FastDNA Spin Kit for Soil (MP Biomedicals), incorporating a bead-beating step to enhance bacterial cell wall disruption.

Singleplex qPCR reactions will be used to detect *B longum* subspecies *infantis* and *L plantarum*, using the TaqMan Fast Advanced Master Mix (Thermo Fisher Scientific). Standard curves will be generated from DNA extracted from quantified cultures of *B longum* subspecies *infantis* and *L plantarum* grown either at the PNGIMR or at Federation University, Australia.

The primer and probe sequences to be used for *B longum* subspecies *infantis* are as follows:

- Bi26_Forward 5 - GTCACGATGTCTCCTTTGATATCAGCATG-3′
- Bi26_Reverse 5′- CCTTTTGCGTCTCCCCCG-3′
- Bi26_Probe 5 - FAM-TCATTCATTGTAGTGGCGATCACCGTTACC-3′

The primer and probe sequences to be used for *L plantarum* are as follows:

- Lp_Forward 5′-ACAAATGGCAGGGCGAAAAATG-3′
- Lp_Reverse 5′-TTCTACATCCGGGCAAACCTTG-3′
- Lp_Probe 5′- FAM-ACGGAGCTTCTATGACGATGCTTTCA-3′

Pneumococcal Carriage

Nasopharyngeal swabs in STGGB will be cultured for the detection of respiratory bacterial pathogens, including *S pneumoniae*, *H influenzae*, *Moraxella catarrhalis*, and *Staphylococcus aureus*. Culturing and serotyping will be conducted at the PNGIMR using standard bacteriological culture, isolation, and identification methods, as previously described [27,33,34]. Briefly, 10 µL aliquots of STGGB samples will be inoculated onto horse blood agar, chocolate agar, gentamicin blood agar (5 µg/mL), and bacitracin chocolate agar (300 µg/mL) and incubated at 37 °C in 5% carbon dioxide for 18 to 24 hours. Bacterial growth will be semiquantified on the primary culture plates using a 7-point density scoring system (0-6), with scores of 1 to 3 indicating low-density colonization and 4 to 6 indicating high-density colonization.

Colony morphology and standard confirmatory tests will be used for bacterial identification. Presumptive *S pneumoniae* colonies will be confirmed by optochin sensitivity testing (≥14 mm inhibition zone) and, for optochin-resistant isolates, by bile solubility. *H influenzae* will be identified by growth characteristics on selective media and confirmed using X and V factor dependency tests. Up to 4 morphologically distinct pneumococci will be selected and serotyped using the Quellung reaction with commercially available antisera (Statens Serum Institut). *H influenzae* will be serotyped by slide agglutination (Remel). Antimicrobial susceptibility will be determined using the Kirby-Bauer disc diffusion method, with confirmation of suspected resistance by ETEST strips (bioMérieux) and interpretation according to Clinical and Laboratory Standards Institute breakpoints.

Samples will also be stored for future molecular analysis of total bacterial load and species-specific load using qPCR assays targeting bacterial DNA and pathogen-specific sequences.

Vaccine Antibody Responses (Serology)

Serum IgG antibody concentrations against PCV13 serotypes will be measured in blood samples collected at ages 1 and 4 months using a multiplexed immunofluorescent microsphere assay established at The Kids Research Institute Australia [35]. For each serotype, geometric mean concentrations and the proportion of children in each group with IgG levels of ≥0.35 µg/mL (considered the serological correlate of protection against invasive pneumococcal disease) will be calculated at both time points (ie, before immunization and 1 mo after the third PCV13 dose).

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IgG responses to other childhood vaccines, including hepatitis B, DTwP, and Hib, will also be assessed using aliquots of the same serum samples. These will be analyzed using an in-house multiplexed immunoassay developed at The Kids Research Institute Australia laboratories [36].

Systems Biology

Systems biology involves the application of different technologies that can detect all proteins, metabolites, gene transcripts (RNA), and cell types present in a blood sample taken at a specific time (proteomics, metabolomics, and transcriptomics). In this study, these technologies will be applied to identify specific molecular pathways and biomarkers that are modulated by the intervention and may be associated with improved immune development, such as enhanced vaccine responses, or greater protection against infectious diseases. Blood samples were collected and processed in accordance with protocols used and implemented previously by the Expanded Program on Immunization Consortium in PNG [32]. Processed blood samples will be stored at the PNGIMR until sufficient funding is secured to conduct these complex and high-cost analyses, at which point the samples will be shipped to the appropriate laboratories for analysis and data generation.

Study Data and Management

All data collection forms were checked manually before entry into a password-protected electronic database management system (REDCap [Research Electronic Data Capture; Vanderbilt University]) housed at The Kids Research Institute Australia. Access to the deidentified database was accessible to authorized researchers and study personnel only at the PNGIMR and collaborating institutions. To ensure that any problems or queries were addressed as soon as possible, investigators in PNG and Australia attended fortnightly teleconferences.

Data Safety Monitoring Board

A data safety monitoring board (DSMB) of independent clinicians from PNG and Australia was established. All SAEs were reported within 24 hours to an appointed Papua New Guinean safety monitor and the chair of the DSMB for review, followed by a final report detailing the outcome. Quarterly reports that included a summary of all SAEs, morbidities, and protocol violations as well as the status of enrollment and follow-up were prepared by the investigators and sent to the chair of the DSMB and distributed to other DSMB members. A teleconference with DSMB members and the study investigators was held every quarter.

Sample Size Calculation

It was determined that a sample size of 50 participants per group would achieve 90% power to detect a difference in colonization rates of 30% in the probiotic group versus 5% in the placebo group, using a 2-tailed test of proportions with continuity correction at the 5% significance level. A final sample size of 65 participants per group was decided upon, taking into account a presumed 10% loss to follow-up and difficulties in timely biosample collection. On the basis of this sample size, it was estimated that the study would have 80% power to detect a 50% reduction in pneumococcal colonization rate in the probiotic group versus the placebo group at the 5% significance level.

Statistical Analyses

The data will be cleaned before analysis. All data will be downloaded from REDCap and a backup copy archived before data cleaning. Missing data, outliers, and inconsistencies will be queried and verified against source documentation. Where data require changing, the database will be updated accordingly. All queries and corresponding amendments will be documented. Per-protocol and intention-to-treat analyses will be performed using available outcome data. The distribution of missing data across the treatment groups will be described, and reasons for missingness will be explored where possible to assess whether data are missing at random.

The primary objective is to determine the feasibility and safety of treatment. The number of solicited and unsolicited adverse events as well as the number of discontinued, missed, and completed doses will be summarized descriptively by treatment group. Pearson chi-square and Fisher exact tests will be used as appropriate to determine the significance of differences between groups.

The secondary objective is to measure gut colonization by probiotic strains on the last day of treatment (d 7-d 10) and at ages 1, 3, and 4 months. The prevalence of colonization at each time point will be summarized descriptively by treatment group. Colonization status, categorized as positive or negative, will be compared between treatment groups using the Pearson chi-square test, while continuous measures of colonization (ie, cycle threshold or relative fluorescence units) will be analyzed using 1-way ANOVA.

The exploratory objectives include measuring the hospitalization rates throughout the study; nasopharyngeal carriage of *S pneumoniae* and other respiratory bacteria; IgG antibody titers to PCV13, DTwP, Hib, and hepatitis B; the kinetics of probiotic gut colonization; and maternal carriage of probiotic species at the time of delivery.

Hospitalization rates will be reported descriptively per treatment group and compared using Pearson chi-square or Fisher exact tests as appropriate.

Nasopharyngeal carriage of *S pneumoniae* and other respiratory bacteria as well as gut colonization will be summarized descriptively at each corresponding time point. A Cox regression analysis will be performed, adjusting for birth weight, sex, previous antibiotic use, and breastfeeding status. Hazard ratios, along with their 95% CIs and *P* values, will be reported.

IgG antibody titers to PCV13, DTwP, Hib, and hepatitis B will be reported descriptively at baseline (before vaccination at age 1 mo) and at age 4 months (1 mo after the third dose). The differences between treatment groups will be estimated using linear regression, adjusting for birth weight, sex, breastfeeding status, and previous antibiotic use at each time point. The model will also adjust for maternal antibody titers to diphtheria, tetanus, and pertussis when comparing IgG titers to DTwP, using prevaccination infant titers as proxy measures. All IgG levels will be log transformed before analysis to meet the normality assumptions of linear regression analysis. The corresponding coefficients, along with their 95% CIs and *P* values, will be reported.

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Maternal vaginal carriage of probiotic species will be reported descriptively and compared using the Pearson chi-square test.

Ad hoc analyses will include comparisons of IgG antibody levels, nasopharyngeal carriage of respiratory bacteria, SAEs, and other growth outcomes between participants colonized and those not colonized by *B longum* subspecies *infantis* or *L plantarum*. The Pearson chi-square test, the Fisher exact test, and regression modeling will be used as appropriate. The models will adjust for the variables specified earlier.

To ensure that normality assumptions are met before parametric testing, tests for normality (eg, the Shapiro-Wilk test) and a visual assessment of distribution using histograms will be carried out and the results reported. Where necessary (eg, antibody titers), the raw data will be log transformed to achieve a normal distribution.

The results of the analysis will be reported according to the CONSORT (Consolidated Standards of Reporting Trials) guidelines.

Results

Assent and Enrollment

A total of 244 children were enrolled between October 29, 2020, and June 30, 2023, and randomly assigned to receive *L plantarum* (ATCC 202195), *B longum* subspecies *infantis* (Bi-26), or placebo (maltodextrin). Figure 2 shows the number of women who provided assent, the number of infants randomly assigned, the number of children seen at subsequent visits, and the number of early terminations. Reasons for participant loss between maternal assent and infant screening were not systematically recorded; informal observations suggest that this was primarily due to early postnatal discharge, family disagreement after providing assent, or change of mind. In the first year of the study, only 63 (32.3%) of the target 195 infants were enrolled. This shortfall was largely due to the onset of the COVID-19 pandemic, which led to multiple government-imposed lockdowns and curfews that restricted field activity and hindered recruitment efforts. However, recruitment increased during the second year, and by the end of December 2022, the full cohort of 195 participants had been recruited. Nearly half of these participants (94/195, 48.2%) were enrolled between March and the end of June 2022 (Figure 3).

We had a higher-than-anticipated loss to follow-up because participants' families left the study area during the study period, largely owing to the COVID-19 pandemic; hence, at the end of March 2023, we obtained ethics approval to recruit an additional 45 participants. This increased the target sample size from 195 to 240 (n=80 per treatment group). These additional participants were enrolled between April and June 2023 (Figure 3).

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Figure 2. Flowchart of participant enrollment and visit completion. Of the 244 participants enrolled, 169 (69.3%) completed the study, with no substantial differences between treatment groups. "Family moved out of area," "Lost to follow-up," and "Withdrew consent" indicate study terminations, whereas "Missed visit" refers to skipped visits where participants remained enrolled.

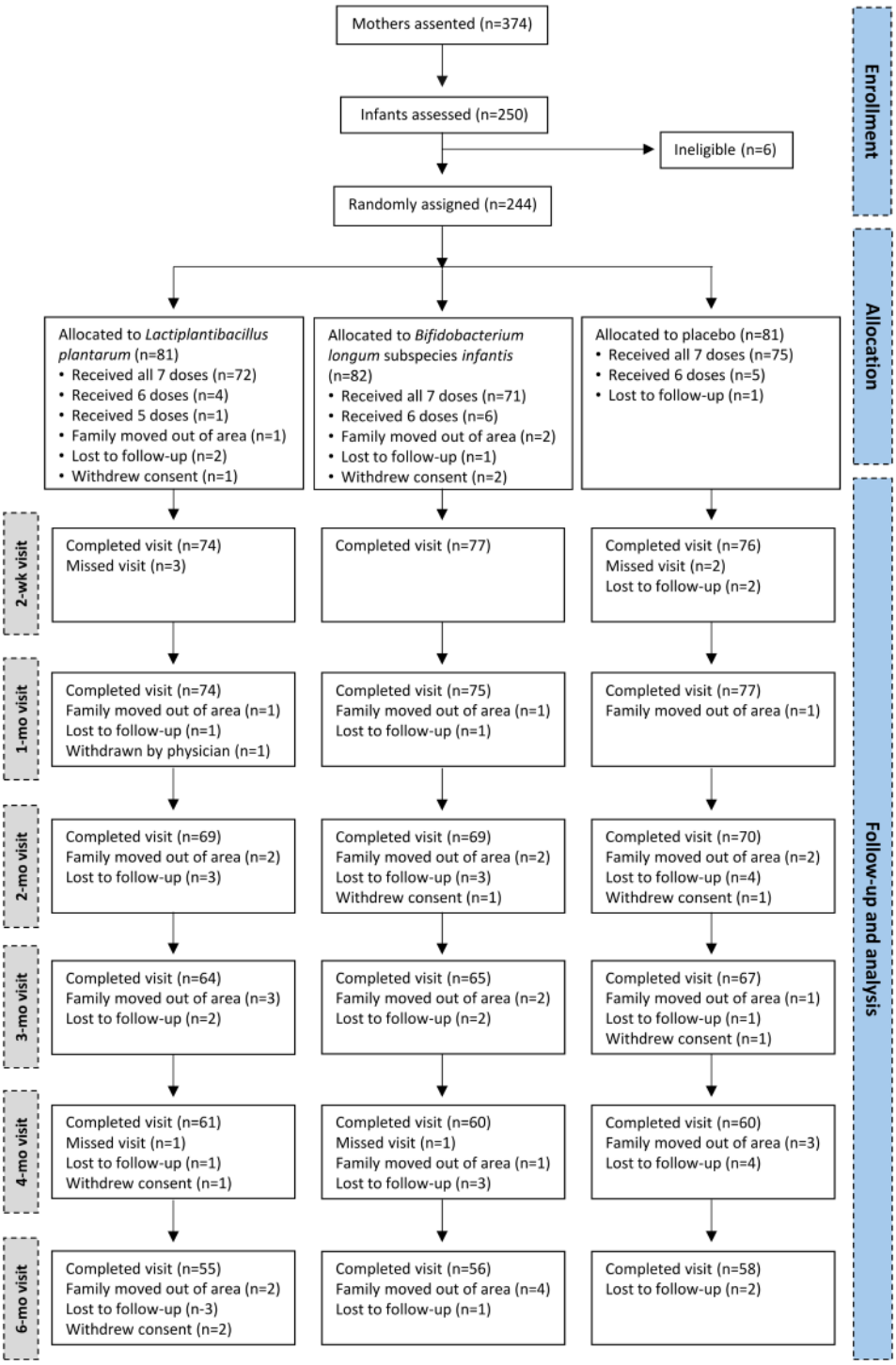

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Figure 3. Participant recruitment patterns from October 2020 to June 2023. Overall, recruitment increased as the study progressed. Periods of disruption due to COVID-19–related lockdowns, national elections, civil unrest, delays in probiotic importation, and delays in ethics approval for study sample size expansion are reflected as lulls in recruitment.

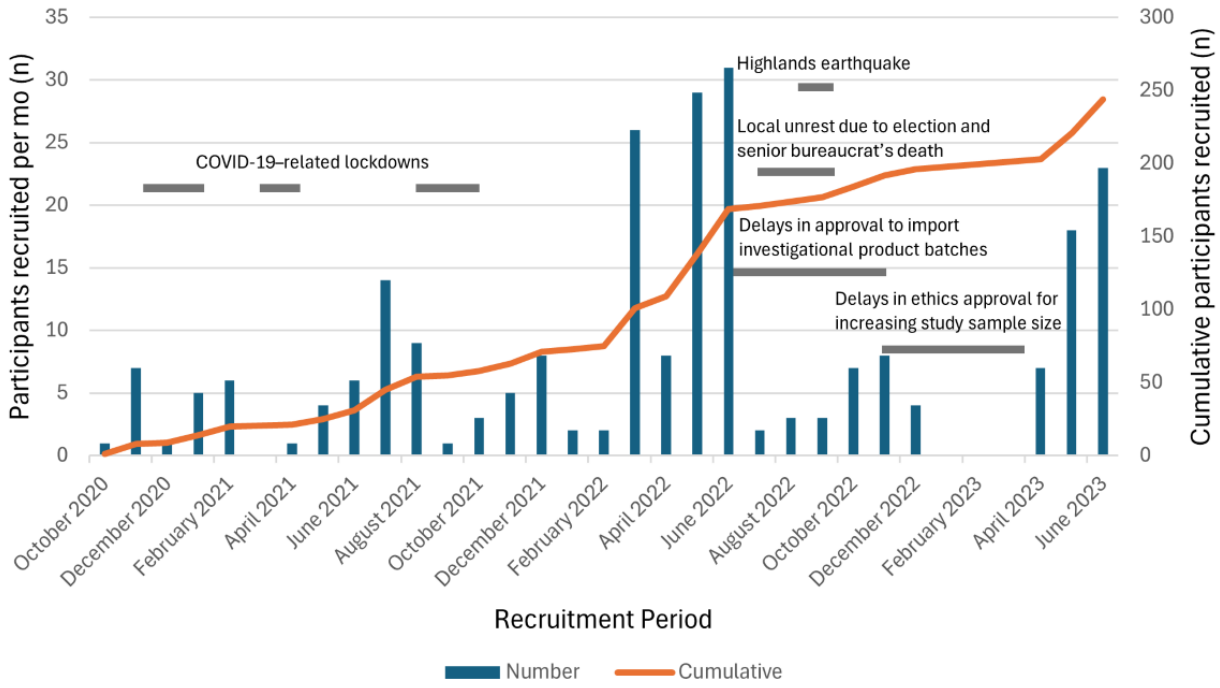

Follow-Ups and Early Study Terminations

Of the 244 enrolled infants, 169 (69.3%) successfully completed the study by December 2023. Among the 75 early study terminations, 37 (49%) infants were lost to follow-up, 28 (37%) infants' families moved out of the study area before study completion, and 9 (12%) infants' parents withdrew consent. Moreover, of these 75 participants, 1 (1%) was withdrawn by the physician for medical reasons not related to the study intervention. The majority of these early terminations (59/75, 79%) occurred after the 1-month visit (Figure 2).

Protocol Violations

There were no protocol violations; however, there was 1 incident of an accidental delivery of the study intervention to a nonstudy participant. This child was monitored over several days by study staff to ensure their well-being, and the parents were informed to contact a member of the study team in the event of any illness. No adverse events were subsequently reported for this child.

In addition, during July and August 2023, there was a shortage of routine vaccines in Goroka, which delayed some of the follow-up visits and specimen collections for 45 (18.4%) of the 244 study participants. Regarding the birth dose vaccines, 11 (4.5%) of the 244 participants did not receive hepatitis B, and 15 (6.1%) did not receive BCG; 5 (2%) received neither hepatitis B nor BCG, with 4 (80%) of these participants subsequently lost to follow-up before the 1-month visit. Of the 244 participants, 24 (9.8%) experienced delays in receiving BCG, with 14 (58%) of these participants receiving it 2 to 3 months after birth.

Among the routine monthly vaccination visits, delays were observed as follows: 7 (2.9%) of the 244 participants had their 1-month vaccines delayed, 11 (4.5%) had their 2-month vaccines delayed, and 4 (1.6%) had their 3-month vaccines delayed. For participants with a delayed monthly vaccination visit, the timing of all subsequent scheduled follow-up visits for sample collection and vaccination were readjusted accordingly; for instance, if a participant's 1-month vaccines were delayed by 24 days, their 2- and 3-month vaccines were also delayed by 24 days. Of the 22 participants with delayed monthly vaccinations and sample collections, 3 (14%) were subsequently lost to follow-up: 1 (33%) before receiving their 1-month vaccinations and 2 (67%) before receiving their 3-month vaccinations. No participant remaining in the study experienced >1 additional delayed monthly vaccination.

Feasibility

Of the 244 enrolled infants, 218 (89.3%) successfully completed the daily intervention from day 1 to day 7. Of the 26 newborns who did not complete daily treatment, 10 (38%; *L plantarum* group: n=4, 40%; *B longum* subspecies *infantis* group: n=5, 50%; and placebo group: n=1, 10%) were early study terminations, and 16 (62%; *L plantarum* group: n=5, 31%; *B longum* subspecies *infantis* group: n=6, 38%; and placebo group: n=5, 31%) missed ≥1 doses (n=15, 94% missed a single dose, and n=1, 6% missed 2 doses) but continued in the study. Among the 10 participants who exited the study early, in the *L plantarum* group, 2 (50%) of the 4 participants received only 1 dose, 1 (25%) received 3 doses, and 1 (25%) received 6 doses; in the *B longum* subspecies *infantis* group, 1 (20%) of the 5 participants received 2 doses, 1 (20%) received 4 doses, 1 (20%) received 5 doses, and 2 (40%) received 6 doses; and in the placebo group, the participant lost to follow-up (1/1, 100%) received only 1 dose.

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Specimen Collection

Specimen collection occurred in parallel with recruitment, from October 2020 to December 2023, with samples obtained during scheduled follow-up visits from birth through 6 months of age. Rectal swabs, nasopharyngeal swabs, saliva, and blood were successfully collected from >91% of the infants who were still enrolled in the study at the time of their follow-up visits (Table 1). Sufficient blood volumes were collected from 80.5% (182/226) and 80.9% (144/178) of the participants at the 2 time points where >1 analysis was proposed for the sample. Rectal swabs were collected from >99% of the participants at each of the 7 time points, except at the 3-month visit, where the collection rate was 91.3% (179/196). Collection of stool was low, with the majority of the samples (193/478, 40.4%) being obtained within the first week of the study. Two nasopharyngeal swabs were collected from >98% of the participants at each of the 3 time points. Of the 881 saliva sponge specimens collected, 183 (20.8%) failed to recover a viable sample for subsequent analyses after centrifugation and were discarded. Excess breast milk was successfully obtained from mothers for up to 7 days during the first week of the study in 75% (183/244) of the cases. However, only 17.6% (43/244) of vaginal swabs were obtained. Data analysis is ongoing and is expected to be completed by the end of 2025.

Table 1. Participant specimens collected at designated time points during the 6-month follow-up.

Sample types	Mothers, n (%)	Infant age, n (%)						
		<72 h (n=244)	8-10 d (n=234)	2 wk (n=227)	1 mo (n=226)	3 mo (n=196)	4 mo (n=178)	6 mo (n=169)
Maternal								
Vaginal swabs (n=244)	43 (17.6)	—[a]	—	—	—	—	—	—
Breast milk (n=1708)	1281 (75)	—	—	—	—	—	—	—
Infant								
Rectal swabs	—	244 (100)	233 (99.6)	225 (99.1)	226 (100)	179 (91.3)	177 (99.4)	168 (99.4)
Stool	—	89 (36)	104 (44.4)	27 (11.9)	28 (12.4)	22 (11.2)	10 (5.6)	8 (4.7)
Nasopharyngeal swabs (×2)	—	—	—	448 (98.7)	451 (99.8)	—	356 (100)	—
Saliva	—	244 (100)	233 (99.6)		226 (100)	—	178 (100)	—
Blood								
Omics	—	244 (100)	232 (99.1)	—	182 (80.5)	—	144 (80.9)	—
Serology	—	—	—	—	225 (99.6)	—	175 (98.3)	—

[a]Not applicable.

Discussion

Feasibility of Administering Probiotics to Infants in PNG

Evidence supporting the benefits of probiotics for infant health is scarce but warrants further exploration, given the health benefits of probiotic use in preterm neonates. A study conducted in India demonstrated reduced risk of NEC and mortality in children receiving probiotics early in life, highlighting their potential as an effective health intervention in neonates in LMICs [23]. Given the numerous variables that can influence probiotic efficacy—including strain specificity, dose, and formulation; the timing and duration of administration; host factors such as age and nutritional status; and differences in microbiota composition—additional studies are required to determine the optimal conditions under which such interventions can be safely and effectively adopted in different populations. This pilot study aimed to assess the feasibility and safety of administering probiotic or placebo supplementation to neonates in PNG for 7 consecutive days—marking the first such study in this population.

Our study is one of very few examining the effects of probiotics in healthy infants in a community setting within an LMIC, and particularly in exploring immunological outcomes. As highlighted by a systematic review conducted by Imdad et al [37], research on probiotics in community settings in LMICs is lacking. By addressing this gap, we have demonstrated both successes and challenges in participant recruitment and fieldwork, with laboratory outcomes to follow (once analyses are completed).

We successfully completed participant recruitment, probiotic administration, and specimen collection in a challenging and labor-intensive research environment. Crucial to this success was maintaining a strong rapport with hospital staff, particularly those in the labor ward, which was a testament to the commitment of the study team. Daily home visits were conducted by study staff for synbiotic administration, resulting in 89.3% (218/244) of the study infants receiving all doses, and >95% (233/244) receiving at least 6 of 7 doses. Slightly more than two-thirds of the recruited participants (169/244, 69.3%) were followed through to completion, despite the challenges posed by the COVID-19 pandemic. These results demonstrate the feasibility of implementing such an intervention study in a community setting in PNG.

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Specimen Collection: Successes and Challenges

This study ambitiously sought to collect up to 27 specimens per infant across 13 visits. For rectal swabs, nasopharyngeal swabs, saliva, and blood for serology, the rate of collection was >98% at all time point–specimen combinations except for 1 (at the 3-mo collection point, 179/196, 91% of the participants provided a rectal swab; Table 1). Blood for serology (vaccine immunogenicity) was prioritized over blood for potential omics studies at the 1- and 4-month collection points; thus, the collection rate was lower for omics research at these time points (approximately 80%). Stool samples (collected in addition to rectal swabs) were sought "when feasible" and had a low collection rate, particularly at ages 4 and 6 months when only approximately 5% of participants (10/178 at 4 mo; 8/169 at 6 mo) provided a stool sample. Likely reasons include timing (the infant did not pass stool during the visit) and perhaps a cultural reluctance to provide stool samples in this setting [38].

Viable saliva was not recoverable from 20.8% (183/881) of the collected samples. Almost half of these (74/183, 40.4%) were from samples collected within 8 to 10 days of birth, and therefore likely a reflection of age and the inability to produce sufficient quantities of saliva. The high overall collection rates demonstrated the feasibility of intensive specimen collection in this setting. Future studies will streamline specimen collection based on the findings from this study.

In addition to specimens from infants, we also sought breast milk samples during the first 7 days of participation and a vaginal swab self-collected from mothers of infant participants before giving birth. Breast milk collection was successful, with 75% (1281/1708) of potential samples being obtained. However, <20% (43/244) of the mothers provided a vaginal swab, likely due to the allowable time for recruitment and enrollment in this study of up to 72 hours after delivery. While not critical to this study's outcomes, vaginal microbiota could be relevant in future research on infant gut colonization.

Logistical and Operational Barriers

Implementing this study in PNG required overcoming significant logistical challenges, including impassable roads, frequent road tolls, and maintenance of study vehicles. Due to the intensive nature of the follow-up visits, study staff had to remain flexible, and it was often the case that a different member of the team attended different follow-up visits for a particular participant. This was the reason for the accidental probiotic delivery to a nonstudy infant, but this incident also reflected the high level of trust the community places in the PNGIMR. On this particular visit, the study participant was not at their place of residence, and another infant was present. The staff member administering the intervention had not attended this participant previously, and the parent or guardian of the infant who was present gave no indication that the child was not part of the study and allowed the intervention to be administered. It is likely that there was a misunderstanding on the part of the parent or guardian, and the probiotic was perceived as a medicine and of benefit to the infant.

Additional logistical hurdles included a vaccine supply shortage in the EHP in 2023. Study participants received their routine vaccinations from study nurses using vaccines acquired through the government medical supply chain. This supply was temporarily disrupted during July and August 2023, delaying vaccine administration for 45 (18.4%) of the 244 participants. Furthermore, we experienced difficulties in importing a second batch of synbiotics into PNG due to delays in obtaining approvals from the relevant government organizations. Subsequent delays in obtaining ethics approval to expand the study size by >10% contributed to a lull in recruitment from January to April 2023 (Figure 3).

Adding to the complexity of this study and further compounding the challenges, recruitment occurred during the COVID-19 pandemic, which began in PNG in late October 2020. Although case numbers remained low until March 2021, the subsequent approximately 12 months were marked by high transmission, including the emergence of the delta variant in September 2021 and the first reported case of omicron in December 2021. The pandemic impacted study recruitment in numerous ways. First and foremost, government-mandated lockdowns and curfews limited field activities, including participant recruitment, particularly during periods of high transmission. Second, study staff experienced sick leave as well as family care responsibilities related to COVID-19 prevention and treatment. In addition, some study infants' families relocated during the pandemic, resulting in loss to follow-up (65/244, 26.6%) or participant withdrawal (9/244, 3.7%).

In PNG, the concept of probiotics and "good germs" is not well understood, and the study team had to invest considerable time and resources to promote awareness in the community before and throughout the study, which likely contributed to the initially slow pace of recruitment. These challenges were compounded by the rollout of the COVID-19 vaccine. There was considerable hesitancy around the vaccine in PNG, resulting in very low vaccine uptake. The first COVID-19 vaccine was introduced in the country at the end of March 2021. As of the end of 2023 (the latest data available), <5% of the population had received ≥1 doses [39]. At the time of the vaccine rollout in the EHP, commencing in May 2021, there was confusion in some study communities: the probiotics were mistakenly believed to be COVID-19 vaccines, raising concerns that we were testing the vaccines on the infants.

In PNG, as in many countries, periods of political and civil unrest can occur. Elections can be highly contested; thus, conducting fieldwork in the lead-up to, during, and shortly after elections can be dangerous. During the national elections in mid-2022, fieldwork was considerably reduced. Not long after the election in 2022 (but not related to it), in September, the death of a senior bureaucrat in Goroka triggered violence and arson attacks, causing an estimated 3000 people to flee their homes. This incident also led to a pause in recruitment and follow-up. Around the same time, an earthquake struck the PNG highlands, damaging infrastructure, including roads; and contributing to further, albeit minor, delays in recruitment and follow-up.

Implications for Future Research

While intervention studies can be challenging to implement in resource-constrained settings, it is in these settings that health

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interventions are most needed to improve health outcomes. Through our pilot study, we have demonstrated the feasibility of administering probiotics to infants in PNG in a clinical trial environment, supporting the implementation of a larger randomized controlled trial to study clinical impact.

The aforementioned challenges no doubt contributed to the early study terminations (75/244, 30.7%). However, of the 244 participants, 218 (89.3%) completed their 7-day course of probiotic or placebo. Of these 218 participants, 15 (6.9%) missed only 1 of 7 doses (n=233 , >95% had at least 6 of 7 doses). The comparatively high number of participants completing ≥6 doses provides some evidence that such an intervention could be feasible and be met with public acceptance, provided that sufficient education and dissemination of information accompanied the intervention.

Acknowledgments

We extend our heartfelt gratitude to the families who participated in this study for their invaluable contributions. Special thanks go to the PNGIMR study field team for their dedication and perseverance in challenging conditions. We particularly acknowledge Mr Birunu Nivio, whose contributions to participant recruitment and follow-up visits were instrumental in the successful conduct of this study. We also wish to acknowledge the staff of the Eastern Highlands Provincial Hospital, particularly paediatrician Dr Casparia Mond and the maternity ward nurses, for their unwavering support and assistance throughout the study.

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Data Availability

The datasets generated and analyzed during this study will be available from the corresponding author on reasonable request once analysis has been completed and results published.

Authors' Contributions

AHJvdB and PCR conceived the study and led its design. AHJvdB, PCR, WSP, and RLF contributed to the development of country-specific protocols. Study implementation and data collection were led by RLF, WK, JS, and WSP, with assistance from BN, AK, MD, GM, and DJ. Laboratory specimen processing was conducted by JJ and TO. AG, RLF, and TO developed the probiotic gut colonization laboratory protocol. CA developed the nasopharyngeal microbiological culturing protocol. MO managed the data and helped design the analysis plan with PCR and AHJvdB. RLF and AG prepared the initial draft of the manuscript, while AHJvdB, PCR, and MO contributed to subsequent revisions. All authors reviewed and approved the final version.

Conflicts of Interest

None declared.

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Abbreviations

ATCC: American Type Culture Collection
BCG: bacillus Calmette-Guérin
CONSORT: Consolidated Standards of Reporting Trials
DSMB: data safety monitoring board
DTwP: diphtheria, tetanus, and whole-cell pertussis
EHP: Eastern Highlands Province
HEO: health extension officer
Hib: Hemophilus influenzae type b
IgG: immunoglobulin G
LMIC: low- or middle-income country
LRTI: lower respiratory tract infection
NEC: necrotizing enterocolitis
PCV13: 13-valent pneumococcal conjugate vaccine
PNG: Papua New Guinea
PNGIMR: Papua New Guinea Institute of Medical Research
qPCR: quantitative polymerase chain reaction
REDCap: Research Electronic Data Capture
SAE: serious adverse event
STGGB: skim milk tryptone glucose glycerol broth

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Protocol

Identifying Optimal Testing Modalities to Increase COVID-19 Testing Access in Baltimore, Maryland: Protocol for a Household Randomized Controlled Trial

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Abstract

Background: The COVID-19 pandemic disproportionately affected low-income and racial and ethnic minority populations. Testing plays a critical role in disrupting disease transmission, but complex barriers prevent optimal testing access, particularly for Black and Latinx communities. There is limited evidence regarding the optimal testing modalities to increase testing access for these populations.

Objective: This study aimed to define the optimal COVID-19 testing modalities for maximizing testing acceptance, uptake, and timeliness of receipt of results.

Methods: The Community Collaboration to Combat COVID-19 (C-FORWARD) trial was a household randomized comparative effectiveness trial conducted in a representative sample of an urban population. Households across 653 census block groups were sampled using a probability proportional to size approach. The primary outcome was the completion of SARS-CoV-2 or COVID-19 testing within 30 days of randomization.

Results: Between February 2021 and December 2022, a total of 1083 individuals were enrolled, including 881 (81.35%) index participants and 202 (18.65%) household members. The mean age of participants was 51 (SD 18) years.Of the total sample, 43% (n=460) of participants identified as Black or African American, 48.6% (n=526) as White, and 9% (n=91) as other, including Asian, American Indian, Native Hawaiian or Pacific Islander, and multiple races; 4.8% (n=48) of participants identified as Hispanic or Latino. At the time of enrollment, 51.1% (n=553) were currently working either full time or part time, and 32.9% (n=342) of participants had an advanced degree. In total, 80% (n=809) of participants had been tested for COVID-19 previously, with 22.3% (n=179) reporting a prior positive test for COVID-19, and 86.8% (n=890) reporting receiving at least one COVID-19 vaccination before enrollment.

Conclusions: Data from the C-FORWARD trial will be used to address important questions regarding COVID-19 testing acceptance and uptake in an urban population.

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KEYWORDS

infectious disease; SARS-CoV-2; mobile; disease control; health equity; urban health; health disparities; healthcare access;

Introduction

Background

The novel SARS-CoV-2 or COVID-19 emerged as a new viral infection in December 2019. Now a global pandemic, as of December 2023, COVID-19 has infected more than 100 million people in the United States and more than 1.1 million have died [1]. COVID-19–related morbidity and mortality have disproportionately affected low-income and racial and ethnic minority populations [2]. While highly effective SARS-CoV-2 vaccines are widely available, multiple challenges have prevented optimal vaccine uptake, including vaccine hesitancy and misinformation, breakthrough infections, and the emergence of new variants potentially impacting the effectiveness of the vaccine. Therefore, nonpharmaceutical interventions, such as masking, testing, and social distancing, remain critical to controlling the COVID-19 pandemic [3].

Testing plays a crucial role in preventing transmission. Early access to testing breaks infectious disease transmission chains and reduces contact between infected and susceptible persons, particularly given the high prevalence of asymptomatic and mild disease. Early testing can also reduce COVID-19 severity, as early case identification decreases the time to treatment for infected individuals [4]. Currently, there are a variety of tests available for COVID-19 diagnosis, including polymerase chain reaction (PCR), antigen tests, and serum-based antibody tests [5]. Access to testing may be limited by geographic areas with low testing access, that is, *testing deserts*. Geographic areas with low rates of access to and availability of SARS-CoV-2 testing often result from an overwhelmed supply chain and a disjointed public health system. Jurisdictions have identified testing deserts in lower-income, highly segregated areas [6]. In 2021, rapid "at-home" antigen tests became available for purchase by the public. In theory, this should make testing more accessible at the population level; however, during infection surges, tests, including "at-home" antigen tests, were often unavailable. In addition, access to at-home tests is dependent on the ability to access stores, pharmacies, or other distributors of the at-home tests, which may be difficult in areas with limited access.

There are complex multilevel barriers to optimal testing (Figure 1), and the pandemic has put into stark relief the social and structural determinants of health, leading to health inequities in testing. Evidence suggests that impoverished and minority populations experience increased barriers to testing. Latinx and Black communities are nearly 3 and 2 times more likely to be uninsured compared with non-Latinx White individuals, respectively [7]. Black individuals of all ages are also more likely to report not being able to see a doctor in the past year because of cost, which has direct implications for access to testing [8]. In addition, longstanding issues of institutional (ie, medical, research, and public health) racism resulting in mistrust and distrust, language barriers, and the cost associated with missing work all decrease the likelihood of testing among these subgroups. Exacerbating the disparity in testing access, Black individuals also experience a higher burden of disease for many chronic conditions associated with COVID-19 (eg, diabetes, hypertension, and chronic obstructive pulmonary disease), placing them at increased risk of severe COVID-19 illness and mortality [2].

Figure 1. The behavioral model for vulnerable populations by Anderson: the conceptual framework of SARS-CoV-2 testing use based on the behavioral model of access to care.

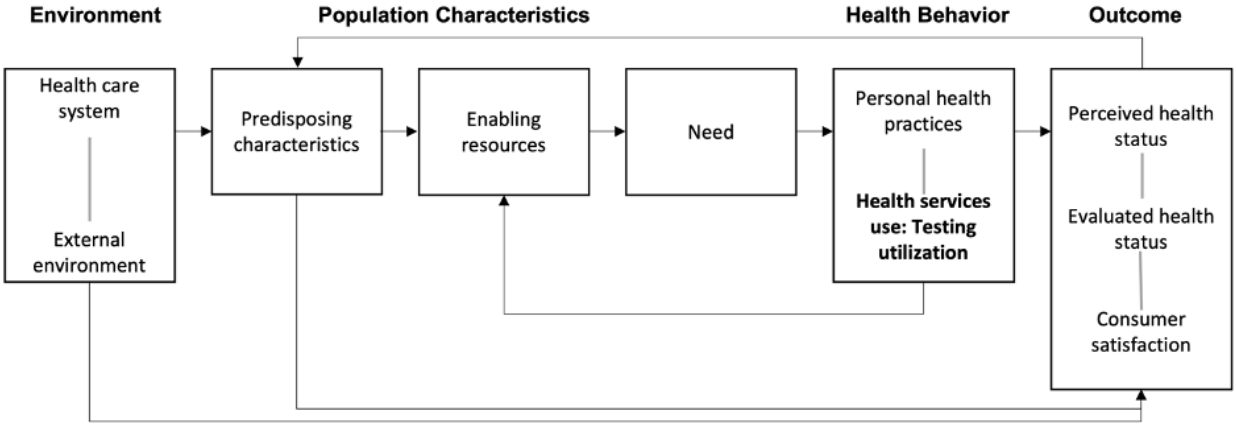

Objectives

The overall goal of the Community Collaboration to Combat COVID-19 (C-FORWARD) trial was to develop evidence related to COVID-19 testing for translation to public health control strategies. To define optimal COVID-19 testing modalities for maximizing testing acceptance, uptake, and timeliness of results, we implemented a household randomized comparative effectiveness trial in a representative sample of an urban population. This study is among the first to directly compare testing modalities in a real-world, community-based randomized trial setting, providing novel insights into how testing strategies can be optimized for public health impact. We

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hypothesize that, compared with the standard-of-care (SOC) arm, those randomized to the community-based, mobile van testing arm (arm 2) and the self-collection, home-based testing arm (arm 3) will be more likely to receive a COVID-19 PCR test than those assigned to the SOC arm (arm 1). The secondary objectives were to determine multilevel (eg, socioeconomic and behavioral) barriers and facilitators to SARS-CoV-2 testing and to evaluate the impact of testing modality and receipt of positive results on subsequent testing behavior. The goal of this paper is to share the protocol for the C-FORWARD trial. We also present initial enrollment information.

Methods

Overview

C-FORWARD was a household randomized comparative effectiveness trial that evaluated 3 COVID-19 testing modalities to identify optimal testing modalities among a representative sample of households in Baltimore City, Maryland. The trial was conducted from February 2021 to June 2023. Figure 2 presents the C-FORWARD project study schema, illustrating the flow of enrollment from the initial survey through testing to the final trial visit.

The trial was registered at ClinicalTrials.gov (NCT04673292), and the protocol followed recommendations for reporting from the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 statement [9]. Results will be reported in accordance with standards described in the CONSORT (Consolidated Standard of Reporting Trials) statement and CONSORT extensions for nonpharmacologic trials, cluster trials, and the draft extension for randomized controlled trials (RCTs) conducted using cohorts and routinely collected health data, which is forthcoming.

Figure 2. The Community Collaboration to Combat COVID-19 (C-FORWARD) project study schema.

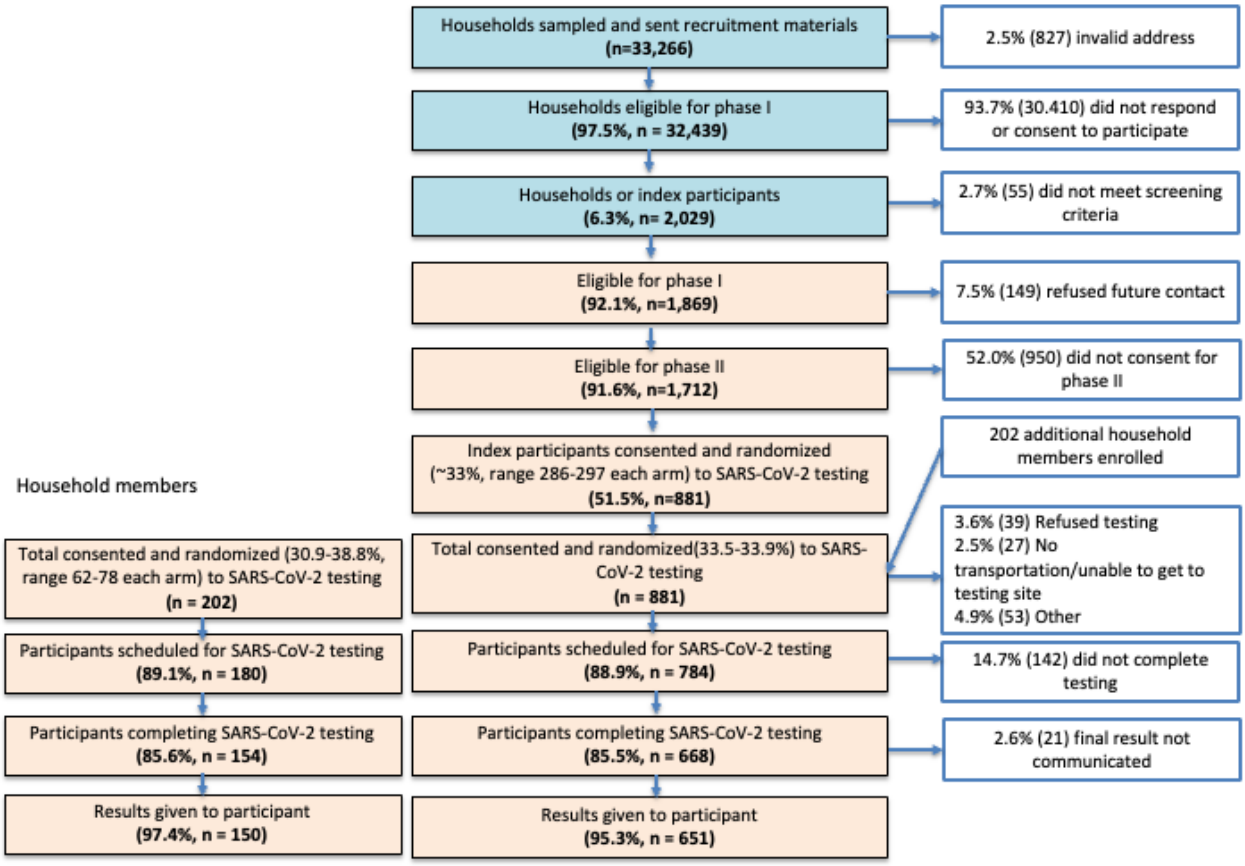

Setting

Baltimore City is a hypersegregated city with White, Black, and Latinx residents, as well as high- and low-poverty populations, living in physically clustered, geographically isolated communities [8]. In Baltimore, Black residents have a median household income that is 54% of that of White residents. Black residents make up more than 60% of the population, yet more than twice as many Black families as White families live in liquid asset poverty, meaning they do not have sufficient savings to subsist at the poverty level for 3 months in the absence of income [9].

Ethical Considerations

This study was approved by the Johns Hopkins University Institutional Review Board under IRB00250298. Trial staff obtained informed consent and conducted surveys for each participant in their preferred language (English or Spanish), with assent obtained from capable children as necessary and adhered to local, national, regional, and international laws and

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regulations regarding protection of personal information, privacy, and human rights. Participants were compensated $50 for participation in the trial.

Study Population and Sampling Strategy

The target population included English- and Spanish-speaking households residing in 653 census block groups (CBGs), which we refer to as neighborhoods. We estimated that the target population comprised approximately 593,490 persons and 238,436 households living in the 653 CBGs in 2020.

The sampling selection for the study was conducted in 2 stages (Figure 3). In the first stage, the 653 CBGs in Baltimore City were placed into 3 primary strata by race and ethnicity (>50% non-Hispanic White, >50% non-Hispanic Black, and >40% Latinx) and then additionally stratified by the percentage of households below the US federal poverty line (>20% and £20%) to create 6 strata. The strata were created to optimize the selection of each population subgroup. A sample of 105 CBGs was then selected using a stratified, systematic probability proportional to size sampling strategy, where size was defined by the estimated number of eligible households (Figure 4). Strata and household estimates for CBGs were generated using the 2018 American Community Survey.

In the second sampling stage, a total of 33,269 household addresses were provided by a vendor who receives updated sampling annually with US Postal Service data on valid household addresses. Household addresses were validated using US Postal Service data. Of the 33,269 households in the second-stage sampling frame, 7.5% (2495) were fielded, and of these, 96.6% (2411) of the households were successfully screened. During the screening, 93% (2243) had at least 1 English- or Spanish-speaking person aged between 18 and 99 years.

Figure 3. Sampling strategy for the Community Collaboration to Combat COVID-19 (C-FORWARD) trial. CBG: census block group; USPS: US Postal Service.

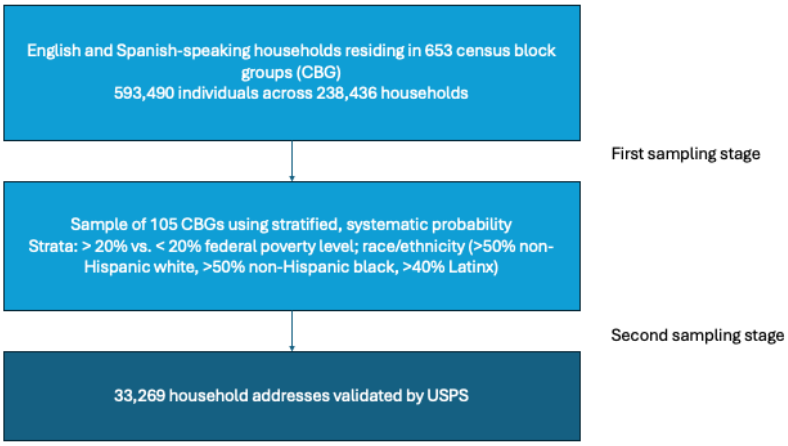

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Figure 4. Map of selected census block groups in Baltimore City. C-FORWARD: Community Collaboration to Combat COVID-19; CBG: census block group; HH: household.

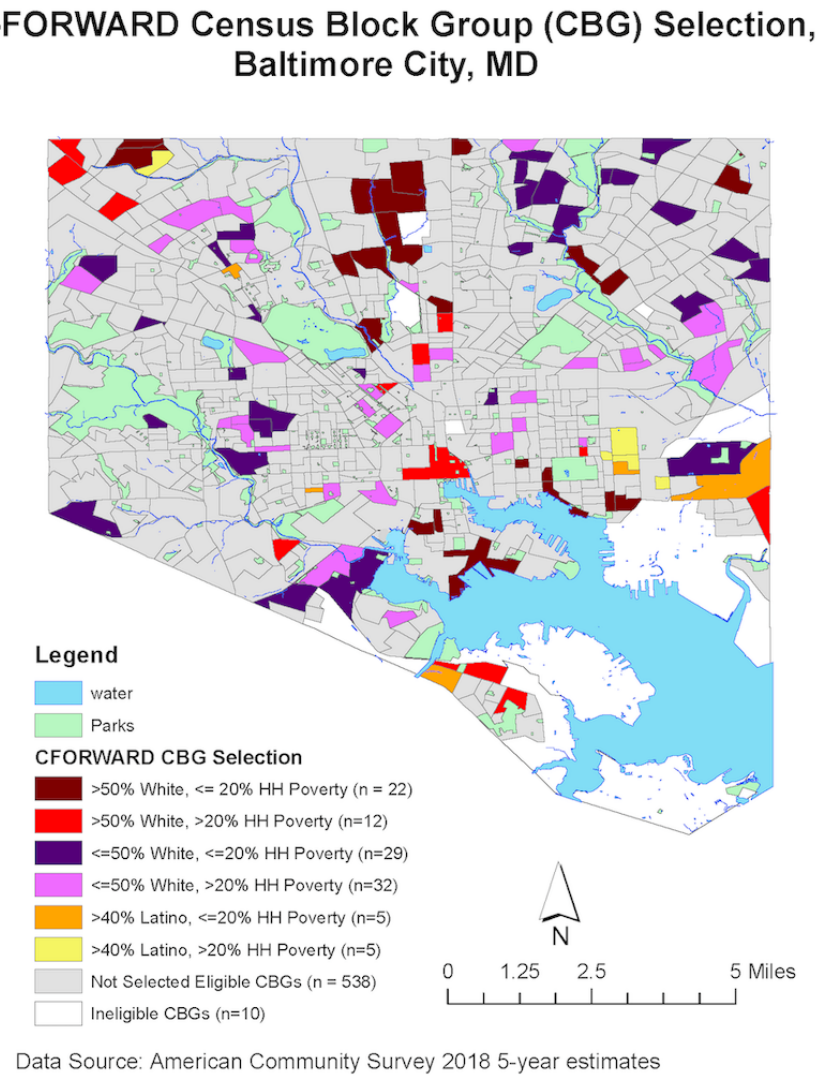

Inclusion and Exclusion Criteria

Textbox 1 presents the inclusion and exclusion criteria for the C-FORWARD participants. Households had to be among the selected addresses in Baltimore City and have at least 1 household member aged ≥18 years who spoke English or Spanish and was psychologically fit to complete the survey (ie, the household index). The first household member aged ≥18 years to consent and enroll in the study was defined as the household index. After enrollment and completion of the baseline survey, the index was invited to enroll in the RCT, along with any other eligible household members.

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Textbox 1. Recruitment.

Inclusion criteria for households

1. Selected address within Baltimore City
2. At least 1 member of the household aged >18 years who speaks English or Spanish
3. At least 1 member of the household provides informed consent
4. At least 1 member of the household who is psychologically fit to complete the survey

Exclusion criteria for households

1. An adult member of the household is under the influence of illicit substances, in the opinion of the phone interviewer
2. Residence in a nursing home, halfway house, or shelter
3. Psychologically unfit to complete the survey
4. Not a selected household address

Inclusion criteria for individuals

1. Reports primary residence within the sampled household
2. Provides informed consent
3. For children aged ≥12 years, provides assent
4. Aged >5 years
5. Speaks English or Spanish

Exclusion criteria for individuals

1. The person providing informed consent is under the influence of illicit substances.

Additional individual household members who enrolled in the RCT were aged ≥5 years, reported residence within the sampled household, spoke English or Spanish, and resided within the household of an index participant. Individual household members were excluded if they were residents of a nursing home, halfway house, shelter, or if they did not reside at the selected household address. Individuals who were psychologically unfit to complete surveys, under the influence of an illicit substance, or aged <5 years were also excluded.

Recruitment for households involved a door hanger placed at the household, as well as a postcard and 3 separate letters sent by mail with study information and a link to complete an online screening. Participants were able to complete the screening and survey in multiple ways, including online, over the phone, or through the mail. Household members who completed the online screening and provided a phone number were contacted by trial staff via phone. They then had the option to provide informed consent over the phone. After consent, the baseline survey was completed by a trial staff member over the phone. A copy of the informed consent and baseline survey was also included in each letter mailed to households, along with a stamped and preaddressed envelope to return the completed consent and baseline survey.

All recruitment materials (ie, website, postcards, letters, and door hangers), trial documents (ie, informed consent forms and surveys), and patient education materials were offered in English and Spanish. For Spanish-speaking participants, all trial visits and communications (eg, visit scheduling, appointment reminders, and results review) were offered in Spanish.

Informed Consent and Enrollment

One individual from each household (the index) consented and was enrolled. For Spanish-speaking individuals, all consent and assent documents were translated and certified by certified translators, and communication was conducted in Spanish by certified translators. At the time of consent, the household was randomized to 1 of 3 testing arms, and the testing visit was scheduled.

All index household participants were eligible to enroll in the RCT. Research staff also asked for permission to contact other household members (identified in the household inventory) to ascertain their interest and willingness to participate in the trial. For willing households, research staff collected contact information for all household members and documented the permission to contact. Unwilling households were informed that other household members could be referred to the trial at any time.

RCT enrollment for the household index either continued immediately after completion of the survey (if the participant was willing) or at a later mutually agreed upon day and time. The informed consent form for the RCT was provided to the household index participant via a website address or link (sent online via text or email). If the index participant was interested in enrolling in the RCT but did not have access to the internet, a hard copy of the consent was mailed, and enrollment took place at a later date. After receipt of the consent form, the trial staff member reviewed the consent form via the phone to ensure the participant provided informed consent. The trial staff member electronically signed the consent form to document

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oral consent for (1) participation in the RCT; (2) storage of biospecimens; (3) additional genetic studies; (4) future contact; (5) medical record review through the Chesapeake Regional Information System for Patients; and (6) sharing zip code with the Duke Clinical Research Institute.

The same consent form shared with the household index was also provided to all other household members aged ≥18 years. The same procedures followed to obtain informed consent during the survey were followed. RCT enrollment for other individual household participants included completion of a survey, while RCT participation for all household participants included testing according to the household's randomization assignment (see Study Arms), collection of host genetic material, and storage of biospecimens. In addition, each participant was provided with the phone numbers of the principal investigator and the Institutional Review Board office to contact if they had additional questions or concerns.

Questionnaires

Participants were asked about sociodemographic and health-related information through self-administered online or phone-administered surveys, depending on participant preference. Sociodemographic characteristics included age, race, and ethnicity, sexual orientation, education, employment status, and relationship status. Health-related information included the presence of chronic health conditions and health care–seeking behaviors. Questions were also included on social distancing and COVID-19 prevention behaviors, as well as previous COVID-19 symptoms, testing and results, and vaccination.

Randomization

Randomization occurred at the household level. Once any adult household member was enrolled in the RCT, randomization to 1 of the 3 testing modalities was performed using an individual-level stratified blocked randomization approach. First, the sampled CBGs (n=105) were placed into 12 geographic groups based on geographic location. Within each of these 12 geographic groups, stratum-specific allocation sequences were generated based on race and ethnicity (non-Hispanic White, including non-Hispanic Other, non-Hispanic Black, and Hispanic/Latinx) and the percentage of households below the US federal poverty line (>20% vs £20%), resulting in a total of 96 strata. The sequences were integrated into REDCap (Research Electronic Data Capture; Vanderbilt University) using varying block sizes of 3 and 6, and households were allocated at a 1:1:1 ratio to each testing modality. Varying block sizes were used to minimize the risk of selection bias. Household-level randomization applied to all members of the household who agreed to participate in the RCT. Randomization assignment was made by REDCap, with study team members unaware of the previous assignments, ensuring allocation concealment.

Study Arms

The enrollment target was 1386 households, randomized 1:1:1 to 1 of 3 SARS-CoV-2 PCR and antibody testing modalities (Table 1): arm 1, fixed ambulatory outdoor testing site (SOC testing); arm 2, community-based mobile van testing; or arm 3, self-collected, home-based testing. A full description of the tests is listed in Figure 5.

Table 1. Summary of testing modalities.

Testing modality	Location	Modality scheduling differences	Modality logistical differences	Laboratory sample type
Arm 1: fixed site, standard-of-care	Johns Hopkins Health System testing sites	Participants selected 1 of 3 sites and followed the appointment schedule.	Set time and fixed site, but the location and schedule may be inconvenient	Nasal swab, NP[a] swab, saliva, and venipuncture
Arm 2: mobile van	Central location within CBG[b]	Participants arranged testing at a single testing van site in their CBG, at any time of the day (no fixed time).	Crowding and long waits if many individuals arrive at the same time; highly convenient	Nasal swab, NP swab, saliva, and venipuncture
Arm 3: home-based self-collection	Participants' home	Nasal swab and saliva were delivered to participants via courier service; participants completed 1 shipment for the 2 packages that would be sent back.	Most convenient, but self-sampling may result in specimen errors; delay or failure to return the sample by mail is costly and leads to no results	Nasal swab and saliva; for participants enrolled before December 10, 2021: blood self-collection device

[a]NP: nasopharyngeal.

[b]CBG: census block group.

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Figure 5. Biological samples and laboratory testing by the trial arm.

Testing	Baseline	Weekly	Month 1 - 5	Month 6	Interim Testing Visit
Standardized COVID-19 education	X			X	X
Verification of symptoms and clinical presentation	X			X	X
Contact identification (if symptomatic)	X			X	X
Temperature and pulse oximetry	X			X	X
ARM 1 / ARM 2 (laboratory Testing-blood)					
CBC with differential and platelets	X			X	X
Hepatic Function Panel (AST, ALT, total bilirubin, albumin, alkaline phosphatase)	X			X	X
Acute Phase Reactants – CRP, ESR, LDH + IL-6	X				X
Coagulation: D-Dimer	X				X
Creatinine	X				X
ARM 1 / ARM 2 (Specimens for Viral RNA/RT-PCR)					
Nasopharyngeal, Nasal, Middle Turbinate, and/or Oropharynx	X			X	X
Saliva	X			X	X
Antibody testing					
Serum antibody testing (IgM/IgA/IgG)	X			X	X
Saliva antibody testing	X			X	X
Repository specimens (future studies)					
Plasma for storage	X			X	X
PBMC for additional immunology testing	X			X	X
Host genomic testing (on stored blood via sub-study protocol)	X			X	X
ARM 3 (Home Self-Test Kit)					
Saliva Sponge	X			X	X
Tasso SST blood collection device	X			X	X
PCR Nasal Swab	X			X	X

Fixed Site (Arm 1)

This arm was designed to replicate SOC and included all 3 Johns Hopkins Medical Institution ambulatory outdoor testing sites across Baltimore City. Each testing site used a traditional appointment-based scheduling system. Participants were given a choice of 1 of 3 outdoor testing locations based on their preferences. Trial staff scheduled appointments for testing based on testing availability and participant schedule.

Community-Based Mobile Van Testing (Arm 2)

This arm offered the convenience of highly accessible testing, close geographic proximity, and the flexibility of no fixed appointment time. Each of the 12 geographic strata (see the Randomization section) had a single, centrally located testing site within the area, providing similar geographic access across households.

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Home-Based Testing (Arm 3)

The individuals in this arm received a home-based testing kit delivered to the household by a courier service. The testing kit included a Becton Dickinson swab for SARS-CoV-2 PCR testing, a Tasso device for the collection of 5 mL of blood, and an Oracol swab for saliva collection. Easy-to-use printed instructions were included in English and Spanish. In addition, the participants randomized to home-based collection had the option to view prerecorded videos demonstrating correct collection techniques or to schedule virtual "on-demand" coaching sessions with members of the study team. If a sample was insufficient or collected incorrectly, an additional testing kit was provided, along with a phone call from a study team member detailing the correct collection method. After completing specimen collection, participants called a study team member to arrange for specimen pick-up within 24 hours of collection.

Study Changes

Because of the unprecedented and ever-evolving nature of the COVID-19 pandemic, several changes to study design were implemented over the course of the study. These changes were necessary to ensure continuation of the trial, and we do not believe they impacted the validity of the trial. The changes are summarized in Table 2.

Table 2. Study changes implemented during the Community Collaboration to Combat COVID-19 (C-FORWARD) trial.

Change	Date implemented	Affected testing modalities	Description
Change from 3 to 2 fixed testing sites	June 2021	Arm 1: fixed site, standard-of-care	One Johns Hopkins Health System testing site closed in June 2021, resulting in 2 fixed testing sites instead of 3
Removal of the blood self-collection device for home-based collection	December 2021	Arm 3: home-based self-collection	The Tasso blood self-collection device was removed from the home-based testing, eliminating serum-based antibody testing from the participants in this arm.
Change in length of follow-up from 12 to 6 months	January 2022	All study arms	The length of follow-up for the study was changed from 12 to 6 months, reducing the total number of possible monthly visits from 12 to 6.
Change from self-administered swab packaged by and returned to Johns Hopkins laboratory to Everlywell home testing kit	January 2022	Arm 3 home-based self-collection	The arm 3 home testing kit was changed from a self-administered swab returned to the John Hopkins laboratory to a PCR[a] kit with provisions for shipping samples directly to a company called Everlywell, via a UPS[b] dropbox or fixed UPS location.
Change in household member eligibility from age 5 to 16 years	January 2022	All study arms	Because of the switch to the Everlywell testing kit, participants aged <16 years could not be tested using the home-based collection. Because of this, eligibility criteria across all study arms were updated to 16 years.

[a]PCR: polymerase chain reaction.

[b]UPS: United Parcel Service.

Study Outcomes

The primary outcome was completion of SARS-CoV-2 testing, defined as the proportion of RCT-consented participants who completed SARS-CoV-2 testing within 30 days of consent or randomization (Table 3). Completion of SARS-CoV-2 testing was defined as completion of SARS-CoV-2 PCR testing at the testing site (for the fixed-site arm and mobile van arm) or return of the PCR swab by the participant to the laboratory via courier service. Completion of testing was verified and documented by laboratory staff. After consent, participants were scheduled for a testing visit at their assigned testing modality. Trial staff made up to 10 attempts to schedule each participant for testing. The participants were allowed to reschedule their testing visit up to 3 times.

Secondary outcomes (Table 3) included time (in days) to completion of SARS-CoV-2 PCR testing, receipt of SARS-CoV-2 PCR test results within 30 days of consent, and time from SARS-CoV-2 PCR test to receipt of SARS-CoV-2 PCR test results among those who received test results. SARS-CoV-2 results were communicated to participants by trial staff or through EMR messaging (Epic MyChart). Time to completion of SARS-CoV-2 PCR testing was defined as the number of days from the date of consent or randomization to the date of SARS-CoV-2 PCR testing at the testing site (for the fixed-site arm and mobile van arm) or the return of the PCR swab to the laboratory. Time to receipt of results was measured as the number of days from the date of consent or randomization to the date of SARS-CoV-2 PCR test results were communicated to the participant and documented by trial staff or through EMR messaging (Epic MyChart). Knowing one's COVID-19 status—whether positive or negative—is essential for determining the need to isolate or notify close contacts of potential exposure, thereby helping to interrupt the chain of transmission.

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Table 3. Primary and secondary outcomes for the Community Collaboration to Combat COVID-19 (C-FORWARD) trial.

Outcome	Primary or secondary	Definition
Completion of SARS-CoV-2 testing	Primary	• The proportion of RCT[a]-consented participants who complete SARS-CoV-2 testing within 30 days of consent or randomization. • Completion of SARS-CoV-2 PCR[b] testing at a testing site (for the fixed-site arm and mobile van arm) or the return of a PCR swab by the participant to the laboratory via courier service. Completion was verified by laboratory staff.
Time (in days) to completion of SARS-CoV-2 PCR testing	Secondary	• Number of days from the date of consent or randomization to the date of SARS-CoV-2 PCR testing at the testing site (for the fixed-site arm and mobile van arm) or return of the PCR swab to the laboratory.
Time (in days) from SARS-CoV-2 PCR test to receipt of SARS-CoV-2 PCR test results among those who received test results	Secondary	• Number of days from the date of consent or randomization to the date SARS-CoV-2 PCR test results were communicated to the participant and documented by trial staff or through EMR[c] messaging (Epic MyChart).

[a]RCT: randomized controlled trial.

[b]PCR: polymerase chain reaction.

[c]EMR: electronic medical record.

Sample Size and Power Considerations

We calculated power for comparing the primary outcome related to randomization (the proportion of participants who completed SARS-CoV-2 testing) across arms (arm 3 vs arm 1 and arm 2 vs arm 1). Given that we enrolled 1386 households across the 3 arms, and that randomization occurred at the household level, we were powered to detect a difference in the level of testing in arms 2 or 3 and the control arm (arm 1) of approximately 11%, (from 50% in the control arm to 61% in the comparison arm) with at least 80% power. We assumed an overall type 1 error of 0.05 and controlled for multiple comparisons using a Bonferroni correction. Because of the possibility of intrahousehold correlation—meaning testing among individuals in the same household may be highly correlated—we conservatively assumed that each household enrolled only 1 individual. This detectable difference of 11% corresponds to a prevalence ratio of 1.2 when testing prevalence in the control arm is 50%, and as low as 1.17 if the testing prevalence in the control arm is 70%. We assumed a baseline testing prevalence of 50% in the control arm in the absence of pilot data, based on random chance.

Planned Analyses

We hypothesize that, compared with the SOC arm, participants randomized to the community-based mobile van testing arm (arm 2) and the self-collection home-based testing arm (arm 3) will be more likely to receive a COVID-19 PCR test than those assigned to the SOC arm (arm 1).

Primary Analyses

The primary analysis will use an intention-to-treat approach, limited to index participants. To mitigate the effects of potential intrahousehold correlation, the primary analysis will include only the index household member. Poisson regression will be used to calculate prevalence ratios comparing the effect of each of the 2 testing modalities (mobile van testing and home-based testing) with the SOC arm (fixed-site testing) on the primary outcome of interest—the proportion of participants who received a test within 30 days. Because of randomization, we assume that factors salient to testing access will be balanced across arms and proportions will be directly comparable without adjustment. However, we will assess whether confounding by key baseline factors is present (eg, age, sex, and race and ethnicity) and will complete adjusted analyses accordingly.

Secondary Analyses

In addition to comparing the proportion of index participants who received a SARS-CoV-2 PCR test within 30 days, we will examine the time to first SARS-CoV-2 PCR test using time-to-event analysis among index participants (1 per household). We will measure the time from enrollment to the first testing event for each participant.

Each participant's time until testing will be censored when the participant exits the study. We will use Cox proportional hazards regression to compare the rate of testing between arms and to assess whether participants in the mobile testing arm (arm 2) or the home-based testing arm (arm 3) tend to be tested earlier or later than those in the SOC arm. As in the primary analysis, we expect that randomization will result in comparable characteristics across arms; however, we will consider adjusting for demographic factors or characteristics that are not balanced across arms.

We will also examine the secondary outcome of receipt of SARS-CoV-2 PCR test results within 30 days of the RCT consent, expressed as a percentage of trial participants in each arm. To compare this secondary outcome between arms, we will use Poisson regression to estimate the prevalence ratios for arms 2 and 3 relative to the SOC arm (arm 1). Consistent with our analysis of the primary outcome, we will adjust for baseline factors if they appear different across the arms at baseline.

We will examine 2 additional secondary outcomes among study participants: (1) time from SARS-CoV-2 PCR test to receipt of SARS-CoV-2 PCR test results and (2) time from consent to

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receipt of SARS-CoV-2 PCR test results. Both outcomes will be compared across study arms using time-to-event analysis with Cox proportional hazards regression, consistent with the analysis of time from enrollment to the first SARS-CoV-2 PCR test. Participants who do not complete a SARS-COV-2 PCR test during the study period will still contribute to the analyses of these secondary outcomes as having censored event times. Therefore, this analysis will include all participants.

We will also examine effect modification for a selection of demographic characteristics by repeating the analysis of the primary and secondary outcomes as specified earlier within specific strata, including (1) race and ethnicity (Black, Latinx, and White); (2) gender; (3) neighborhood poverty (households in CBG with >20% of households below the federal poverty line and households in CBG with <20% of households below the federal poverty line); (4) household poverty; (5) essential worker status; (6) exposure or symptoms; (7) vaccination; (8) age; (9) education (high school diploma or not); and (10) household size (using the median as the threshold).

Primary and secondary analyses will be conducted among the index participants, so that only 1 participant per household is included. We will repeat these analyses, including all participants, accounting for clustering within the household using generalized estimating equations for Poisson regression and a robust variance estimator for Cox proportional hazards regression.

Household members may differ appreciably from the index participants because they are enrolled after randomization is complete, and thus their decision to participate and motivation to undergo testing may be influenced by the randomization arm. Thus, additional secondary outcomes will examine testing uptake and completion among household members only.

Time-Stratified Analyses

To account for temporal changes and the evolving pandemic landscape throughout the study period, primary and secondary analyses will be stratified by time. Because of the availability of at-home rapid testing kits, the Omicron variant surge, and the changes in the home kit testing brand in the home collection arm, analyses will be stratified by enrollment before February 1, 2021, and after February 1, 2021.

Results

C-FORWARD enrollment began on February 25, 2021, and concluded on November 23, 2022. A total of 1083 individuals were enrolled, including 881 (81.35%) index participants and 202 (18.65%) household members. Baseline characteristics are reported in Table 4. The mean age of participants was 51 (SD 18) years, with a range of 5 to 98 years. Overall, 42.5% (n=460) of the participants identified as Black or African American, 48.6% (n=526) as White, 3.4% (n=37) as multiple races, 2.7% (n=29) as Asian, and 2.9% (n=31) as another race, while 4.8% (n=48) identified as Hispanic or Latino. Most participants (n=553, 51.1%) were currently working either full time or part time at the time of enrollment. Approximately 32.9% (n=342) of participants had an advanced degree.

At the time of enrollment, over three-quarters (n=809, 79.9%) of participants had been tested for COVID-19 previously, with 22.3% (n=179) reporting a prior positive COVID-19 test. Furthermore, 86.8% (n=890) of participants reported receiving at least 1 COVID-19 vaccination before enrollment.

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Table 4. Selected baseline characteristics of participants enrolled in Community Collaboration to Combat COVID-19 (C-FORWARD; N=1083).

Characteristics	Population (N=1083)
Households, n	881
Age (y), mean (SD)	51 (18)
Sex (male), n (%)	380 (35.1)
Race or ethnicity, n (%)	
Asian	29 (2.7)
Black or African American	460 (42.5)
Hispanic or Latino	48 (4.8)
Multiple races	37 (3.4)
Other	31 (2.9)
White	526 (48.6)
Employment, n (%)	
Working now (either full time or part time)	553 (51.1)
Retired, disabled, or keeping house	384 (35.5)
Student	64 (5.9)
Looking for work, unemployed	53 (4.9)
Unknown	29 (2.7)
Essential worker (n=972), n (%)	
Among enrolled adults with responses	241 (24.8)
Educational attainment (n=1038), n (%)	
High school graduate or less	264 (25.4)
Some college level, technical, vocational degree, or associate's degree	223 (21.5)
Bachelor's degree	201 (19.4)
Other advanced degree	342 (32.9)
Health insurance (n=854), n (%)	
No health insurance	29 (3.4)
Public (Medicare, Medicaid, and Tricare)	376 (44)
Private (purchased directly or through employment)	420 (49.2)
Ever been tested for COVID-19? (Self-report, n=1013), n (%)	809 (79.9)
Ever tested positive for COVID-19? (Self-report, n=804)	179 (22.3)
COVID-19 vaccination (self-report, n=1025), at least 1 dose, n (%)	890 (86.8)

Discussion

Anticipated Findings

This trial will provide critical information on the best practices for SARS-CoV-2 testing in communities with a high prevalence of vulnerable populations. Beyond increasing our understanding of SARS-CoV-2 testing, this study will help to characterize the prevalence of COVID-19 infection. Even with expanding access to pharmaceutical interventions, COVID-19 testing remains crucial to control the spread of infection. Testing strategies must be well studied to determine the most effective and accessible strategies, inform public policy, and public health prevention and control activities. The C-FORWARD trial will provide critically needed insights into optimal testing strategies, particularly for vulnerable populations most affected by the pandemic.

Limitations

Several implementation-related challenges were encountered during the C-FORWARD trial. Given the ever-changing COVID-19 pandemic landscape and region-specific surges in COVID-19 incidence, testing demand was often both sporadic and urgent. The emergence of new variants also resulted in the current chaotic SOC, which varied by testing location, even within the same city, making it difficult to have a true comparison arm.

Temporal trends in the delivery approach of the SOC over the duration of the trial affected our ability to draw comparisons between the fixed site and other testing modalities. However,

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our ongoing ethnographic work and community engagement will capture these changes so that we can address them in the analysis as appropriate (eg, stratifying by time). It was also possible that randomized households or individuals sought testing outside of the study.

Furthermore, responses to surveys are subject to social desirability and recall bias; moreover, recall may be influenced by prior COVID-19 infection status, which is one of the key exposures of interest. We will use 2-week time frames for most behaviors to minimize this effect. Loss to follow-up is another concern, particularly as attitudes toward COVID-19 change and fatigue with study participation sets in. Individuals across all testing modalities may have sought testing outside of the study, introducing the risk of contamination across study arms. To mitigate this risk, the enrolled individuals were scheduled for testing as soon as possible after enrollment and randomization, and testing outside the study was assessed through surveys at baseline and monthly follow-up visits.

While our findings will provide valuable insights, the generalizability of the results may be limited to hypersegregated urban areas similar to Baltimore City. However, identifying optimal testing strategies that increase access to testing in a pandemic setting is an important consideration for all public health officials, particularly for communities with limited access to traditional health care settings. Individuals in rural areas may be at heightened risk for chronic health conditions that worsen COVID-19–associated morbidity and mortality, along with having farther distance to travel and reduced access to health care settings [10,11]. For example, rural areas could benefit from mobile testing vans or increased availability of tests that can be completed and returned via mail.

Conclusions

As early and accessible testing can prevent forward transmission and improve individual-level outcomes, this trial aims to identify the most effective approach to providing access to COVID-19 testing. In addition to improving our understanding of how testing modality affects access and the effectiveness of testing initiatives, this work focuses on access within populations with the highest burden of COVID-19 disease, and thus those who will benefit most from these findings. The framework established through this trial can be adapted to other infectious diseases—such as influenza, respiratory syncytial virus, or emerging respiratory viruses—by evaluating testing access, uptake, and outcomes in similarly vulnerable populations. Leveraging these insights across disease areas can support timely public health responses and equitable diagnostic strategies.

Acknowledgments

This work was supported by (1) a National Institute of Allergy and Infectious Diseases RADx-Underserved Populations study titled “Community Collaboration to Combat COVID-19 (C-FORWARD)” (3P30AI094189-09S1), (2) the Johns Hopkins University COVID-19 Research Response Fund, (3) Formula 1, and (4) Becton Dickinson.

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Authors' Contributions

JD contributed to the original draft, formal analysis, and data visualization. AKM was involved in formal analysis and manuscript review and editing. SA contributed to conceptualization and methodology. JP contributed to methodology and manuscript review and editing. CB, JT, KL, and SH were responsible for project administration. AP contributed to conceptualization. JEF, SHM, and JMJ contributed to conceptualization, investigation, manuscript review and editing, and supervision.

Conflicts of Interest

SHM provides Materials support from Abbott Diagnostics.

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Abbreviations

C-FORWARD: Community Collaboration to Combat COVID-19
CBG: census block group
CONSORT: Consolidated Standards of Reporting Trials
PCR: polymerase chain reaction
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SOC: standard-of-care
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Tailoring Antibiotic Duration for Respiratory Tract Infections in Primary Care: Protocol for a Pragmatic Randomized Controlled Trial Study (STORM)

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Abstract

Background: Combating the rise of drug-resistant organisms and minimizing side effects requires a shift in how we approach the duration of antibiotic therapy. A promising strategy involves tailoring the length of antibiotic therapy to patients' needs, allowing discontinuation once patients feel better.

Objective: This study aims to assess whether shortening antibiotic therapy based on patients' recovery time is as effective as completing the full course in treating acute respiratory tract infections (RTIs).

Methods: We plan to enroll a minimum of 474 outpatients ranging from 18 to 75 years of age with clinical features of acute RTIs across Spanish health centers. Patients diagnosed with acute lower RTIs or acute rhinosinusitis, deemed by clinicians to require a β-lactam course, will be randomized to either usual care, involving a full-course antibiotic therapy based on current guidelines, or a tailored approach. In the intervention group, patients will be advised to visit the center as soon as they feel better and are afebrile for a clinical assessment and C-reactive protein rapid testing. Treatment will be discontinued if these clinical results are normal. The primary outcome will be assessment of clinical resolution at day 14, while secondary outcomes include antibiotics given and duration; adherence to the prescribed antibiotic; other therapies given; early clinical assessment at day 7; days of severe, moderate, and any symptom, complications and reattendance within the first month; drug-related adverse events; absenteeism; and health-related quality of life. All participants will be given a symptom diary, recording their symptoms each evening. Additionally, a cost-effectiveness study and qualitative studies involving clinicians and patients aimed at exploring the strategy's pros, cons, uptake, and satisfaction levels will be carried out.

Results: The final results will be published by the end of 2027.

Conclusions: We will examine whether adults who present with symptoms of RTI who are treated with antibiotic courses until they feel better are as effective as longer standard courses. It is highly important that a possible reduction in the antibiotic course as soon as the patient feels better does not compromise patients' recovery. This comprehensive approach aims to shed light on the practicality and impact of tailoring antibiotic duration in RTIs.

Trial Registration: ClinicalTrials.gov NCT06581367; https://clinicaltrials.gov/study/NCT06581367

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International Registered Report Identifier (IRRID): PRR1-10.2196/75453

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KEYWORDS

respiratory tract infections; anti-bacterial agents; drug resistance, microbial; patient-centered care; deprescriptions; duration; drug-related side effects and adverse reactions; randomized clinical trial

Introduction

The judicious use of antibiotics has played a vital role in saving millions of lives and preventing serious infectious complications. However, excessive and inappropriate antibiotic use has become a major contributor to the growing global crisis of antimicrobial resistance (AMR). Research has established a strong link between antibiotic consumption and the emergence of resistant bacteria, both at the societal and individual levels [1]. Given the limited pipeline for new antibiotic development, the responsible use of existing antibiotics, particularly in primary care, is crucial to contain AMR.

Primary care accounts for approximately 80% of all antibiotic prescriptions, with respiratory tract infections (RTIs) responsible for more than half of this total worldwide [2]. Inappropriate antibiotic use for uncomplicated RTIs remains widespread. Around 50% of general practice consultations for RTIs result in an antibiotic prescription, with large variations across practices (from 20% to 80%) [2]. In Spain, more than half of patients presenting with acute rhinosinusitis, acute bronchitis, or sore throat in primary care are treated with antibiotics [3]. This is concerning, as most uncomplicated RTIs in otherwise healthy adults are viral and self-limiting, and antibiotics offer no relevant benefit.

Despite numerous initiatives to curb unnecessary antibiotic use, the impact has been modest at best. While some local successes have been documented, most antimicrobial stewardship strategies have shown only minimal reductions in antibiotic prescribing [4]. For instance, a recent systematic review found that such programs reduce outpatient antibiotic use by just 4% on average [5]. As a result, general practitioners (GPs), who are potentially the most influential professionals in tackling the issue of AMR, continue to show a consistently high rate of inappropriate and unnecessary antibiotic prescriptions.

Traditionally, antibiotics have been prescribed for fixed durations—typically 7 to 10 days—regardless of individual patient response. However, accumulating evidence suggests that shorter courses are equally effective for many bacterial RTIs and result in fewer adverse events. The concept that “shorter is better” emerged over a decade ago and has since been supported by multiple clinical trials [6]. Except for conditions like tuberculosis and specific upper respiratory infections (eg, otitis media and streptococcal pharyngitis), shorter antibiotic courses have shown equivalent efficacy. For instance, 3-day β-lactam therapy is as effective as 8-day treatment in patients with community-acquired pneumonia who improve substantially by day 3 [7,8]. Similar findings have been replicated in acute chronic obstructive pulmonary disease (COPD) exacerbations [9] and suspected bacterial rhinosinusitis [10-12]. Even early trials of penicillin in pneumococcal pneumonia supported discontinuation after symptom resolution, with only 5% relapse [13].

Despite this, many guidelines continue to recommend longer treatment durations, often unsupported by robust evidence [14], and clinicians frequently default to 7-day prescriptions [15-17].

The notion that completing a full antibiotic course prevents resistance is deeply ingrained in medical training. However, this dogma is not evidence-based. In fact, prolonged exposure to antibiotics increases the selection pressure for resistant organisms, both in the patient and the environment [18,19]. Even short courses can have long-term ecological effects, including persistent colonization by resistant bacteria and disruption of the gut microbiota. Data indicate that beyond the first few days, the additional benefit of continuing antibiotics decreases, while the risk of harm, through side effects, superinfections, and resistance, increases [20-22]. Importantly, resistance tends to emerge not at the site of infection, but among colonizing flora elsewhere in the body [23]. Over the last years, there have been an increasing number of independent bodies, scientific academies, and institutions abandoning this dogma on completing antibiotic courses [24].

A promising strategy to reduce unnecessary antibiotic exposure involves tailoring treatment duration based on individual response. Conventional stewardship programs often fail to address overtreatment in patients who genuinely need antibiotics. Encouraging shorter, evidence-based durations may be a more practical and acceptable alternative, as shown in qualitative research [25]. The optimal antibiotic duration likely varies by individual. Factors such as age, comorbidities, immune status, bacterial load, and organ function influence how patients metabolize and respond to treatment [26,27]. A one-size-fits-all approach risks under- or overtreatment. For instance, in a landmark study, 3-day treatment was as effective as 8 days in 78.5% of patients hospitalized with mild to moderate pneumonia who had improved by day 3 [7]. It would not be unreasonable to think that the percentage of patients with pneumonia who feel better after 3 days of therapy would be even higher in primary care.

When a nonbacterial or self-limiting infection is suspected, the priority should be to avoid initiating antibiotics. For patients already on fixed-duration antibiotic courses, clinicians should consider advising discontinuation once symptoms are resolved, unless the infection is deemed potentially serious [25]. In such cases, reassessment with clinical examination or point-of-care tools like C-reactive protein (CRP) testing may be warranted before stopping treatment. Interestingly, one-third of patients already stop antibiotics on their own once they feel better. Studies using electronic monitoring show poor adherence to

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prescribed durations in real-world settings [28]. This emphasizes the need to align prescribing practices with patient behavior and current evidence.

Reducing antibiotic use in primary care remains challenging, particularly when faced with diagnostic uncertainty or patient expectations. Yet it appears more feasible to convince physicians to shorten therapy durations than to withhold antibiotics entirely, provided there is clear, high-quality evidence supporting this approach [29]. Emerging data from randomized trials suggest that most patients recover within 3 days, making shorter courses not only safe but preferable. Current stewardship strategies have only a limited impact, and a shift toward personalized treatment durations, based on clinical improvement and patient characteristics, offers a promising path forward [30]. Ultimately, we must transition from a disease-focused model to a patient-centered approach: we are not treating RTIs, we are treating patients with RTIs. To support this shift, we propose a pragmatic randomized clinical trial aimed at evaluating the effectiveness of individualized antibiotic duration in primary care. Such research could set a new standard for antimicrobial prescribing, reducing unnecessary exposure, preserving antibiotic efficacy, and promoting truly evidence-based care.

Methods

Study Design

This is the protocol for a pragmatic, randomized noninferiority trial with a two-group parallel design. The unit of randomization is the patient, and the allocation ratio between the control and intervention groups is 1:1. This protocol follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 statement [31].

Objectives

The primary aim of the STORM trial is to assess whether the clinical resolution on day 14 for adults presenting with symptoms of an acute lower RTI or acute rhinosinusitis in general practice is noninferior in the intervention group (stopping the antibiotic course as soon as patients feel better and clinical assessment is within the normal range) compared with the control group (patients completing standard antibiotic courses).

Secondary objectives of this trial are as follows:

1. Evaluate the antibiotic prescribed at the index visit and the planned and actual duration in the 2 groups.
2. Evaluate the adherence to the prescribed antibiotic in the 2 groups.
3. Evaluate the early clinical resolution on day 7.
4. Evaluate the duration of symptoms in the 2 groups: (1) duration of severe symptoms, (2) duration of moderate symptoms, and (3) total resolution of symptoms.
5. Evaluate the use of antibiotics other than the study medication and other symptomatic therapies within the first 4 weeks in the 2 groups.
6. Determine the number of reattendances to any doctor regarding the infection within the first 4 weeks in the 2 groups.
7. Determine the number of complications related to the infection within the first 4 weeks, such as visits to emergency departments, hospital admissions, in the 2 groups.
8. Determine the number of adverse events in the 2 groups.
9. Estimate the incremental cost per patient achieving clinical resolution (within-trial cost-effectiveness analysis) and the incremental cost per quality-adjusted life year (long-term cost-effectiveness analysis) in the 2 groups.
10. Determine the number of days of work absenteeism due to the infectious disease in the 2 groups.
11. Determine the improvement in health-related quality of life in the 2 groups.
12. Assess the percentage of patients assigned to the intervention group who feel better and who comply with the criteria for stopping the antibiotic therapy in the 2 groups.

We hypothesize that patients with ages ranging from 18 to 75 years who are allocated to the intervention group and are asked to discontinue antibiotic therapy as soon as they feel better and afebrile, their clinical stability criteria are normal (systolic blood pressure >90 mm Hg, axillary temperature <37 °C, respiratory rate <20 breaths/minute, and oxygen saturation >92%) and CRP falls within normal range will have a similar overall clinical efficacy at day 14 and will not present a higher reconsultation rate compared with those allocated to the control group. We expect a lower number of drug-associated adverse events in the intervention group.

Eligibility Criteria

We will prospectively and consecutively recruit adult patients aged 18 to 75 years who present either with acute cough as the predominant symptom—considered by the GP to be a bacterial acute lower RTI, as defined by the European Society for Clinical Microbiology and Infectious Diseases [32]—or with clinically suspected acute bacterial rhinosinusitis, as defined by the American Academy of Otolaryngology–Head and Neck Surgery Foundation [33], in cases where the GP considers a standard β-lactam course to be necessary. Patients who meet criteria for hospital referral, have a known allergy to β-lactams, are immunocompromised, or are in a severe clinical condition will be excluded from the study. A detailed summary of all inclusion and exclusion criteria is provided in Textbox 1. All patients who agree to participate will provide a signed informed consent and will be informed about the nature of this study. The participating GPs will prescribe an antibiotic, and the patient will be later randomized. Patients in the intervention group will be asked to return to the center as soon as they feel better and are afebrile for an assessment of the clinical stability criteria and CRP measurement.

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Textbox 1. Eligibility criteria.

Inclusion criteria (all the criteria must be met):

- Age ranging from 18 to 75 years.
- Either acute lower respiratory tract infection (RTI) or bacterial rhinosinusitis.
- Acute lower RTI: acute cough (new or worsening of a previous cough present for 21 days or less) as the predominant symptom, accompanied by at least one other lower respiratory tract symptom—such as sputum production, dyspnea, wheezing, and chest discomfort/pain—with no alternative explanation. It is presumed to have a bacterial cause, such as community-acquired pneumonia, acute bronchitis, or acute exacerbations of chronic obstructive pulmonary disease (COPD), according to the clinician's judgment.
- Acute bacterial rhinosinusitis: presence of purulent nasal discharge or facial pain/pressure lasting less than 4 weeks, which the clinician suspects to be bacterial due to lack of improvement within 10 days, severe symptoms from day 3, or worsening after day 5.
- General practitioners deem β-lactam therapy for at least 7 days is necessary.

Exclusion criteria (any of the following exclusion criteria):

- RTIs different from a lower RTI or acute rhinosinusitis.
- The doctor decides not to give an antibiotic for this RTI.
- Patients with suspected septicemia (quick sequential organ failure assessment: respiratory rate ≥22 breaths/minute, systolic blood pressure <100 mm Hg, or altered mental status with a Glasgow score < 5) ≥2.
- Patients with pneumonia and a CRB-65 (confusion, respiratory rate ≥30 breaths/minute, blood pressure < 90/60 mm Hg, or age >65 years) ≥1.
- Patients with very severe COPD (forced expiratory volume in 1 second [FEV_1]<30%).
- Patients with COPD who have taken 4 or more antibiotic courses in the previous year, the presence of significant bronchiectasis, and isolation of Pseudomonas in a previous sputum culture.
- Patients with reported allergy to β-lactams.
- Patients who have taken antibiotics in the previous 2 weeks.
- A working diagnosis of a noninfective disorder, such as heart failure, pulmonary embolus, or esophageal reflux.
- Immunocompromised patients, such as those with HIV infection, patients taking immunosuppressive treatment, antineoplastic therapy, or systemic corticosteroids.
- Currently participating in another clinical trial.
- Previously participated in the STORM study.
- Active neoplasia.
- Terminal illness.
- Institutionalized patient.
- Inability/unable to understand or take part in the clinical trial.

GPs will be informed about managing acute RTIs with β-lactam therapy, following the specific RTIs outlined in this study and the latest Spanish primary care guidelines [34,35] (Table 1). The guidelines recommend the use of 7-day antibiotic durations. Doctors participating in this study will be provided with a summary of the current local guidelines, including indications for when to treat. However, the final decision on antibiotic prescriptions will be at the discretion of the GP. The trial is pragmatic, aiming to mirror the real-life practices of doctors in Spain. According to a recent study conducted in Barcelona in 2023, approximately 80% of all prescriptions for amoxicillin and amoxicillin-clavulanate in primary care corresponded to box sizes of 30 pills, representing a 10-day duration, while the remainder were 20-pill boxes [36]. Considering that this clinical trial is pragmatic, we will consider a minimal duration of 7 days.

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Table 1. Guidelines for prescribing antibiotics for respiratory tract infections in primary care in non- -lactam-allergic patients in Spain, based on the updated recommendation [34,35] (to be performed by the general practitioner).

Diagnosis	When is it appropriate to prescribe antibiotics?	First choice antibiotic
Acute rhinosinusitis[a]	Do not administer, unless there are signs and symptoms that do not improve within 10 days, severe symptoms from day 3, or worsening of symptoms from day 5	Amoxicillin and clavulanate 875-125 mg/8 h/7 d or penicillin V 1000 mg/8 h/7 d
Lower respiratory tract infection (non-COPD[b])[c]	In acute bronchitis, antibiotics should not be given, except in specific situations. Always treat in pneumonia	Amoxicillin 1000 mg/8 h/7 d or penicillin V 1.000 mg/8 h/7 d. Amoxicillin and clavulanate 875-125 mg/8 h/7 d if age >65 years
COPD exacerbation[d]	Only if there is sputum purulence and in all very severe or very severe COPD exacerbations	Amoxicillin and clavulanate 875-125 mg/8 h/7 d

[a]Refer to the hospital if persistent temperature >39 °C, periorbital oedema, intense headache, neurological focal signs, signs of meningeal irritation, impaired consciousness, suspicion of orbital infection, or diplopia.

[b]COPD: chronic obstructive pulmonary disease.

[c]Refer to the hospital if oxygen saturation <92%, significant alterations in chest x-ray, difficulties in complying with treatment at home, decompensation of underlying illness, lack of tolerance to oral treatment, immunosuppression, or CRB65 ≥1. Refer to the hospital if CRB65 >1 (confusion, respiratory rate ≥30 breaths/min, systolic blood pressure <90 mm Hg or diastolic blood pressure <60 mm Hg, age >65 years.

[d]Impaired consciousness, cyanosis, respiratory rate ≥30 breaths/min, severe dyspnea, oxygen therapy, inability to stay at home, or oxygen saturation <92%. Patients with COPD with forced expiratory volume in 1 second (FEV_1) <30% are excluded from this study.

Eligible participants will be informed about the STORM trial and provided with an information leaflet and a consent form from the GP. The GP will ensure that the patient understands the purpose of the project, potential benefits, risks, and procedures involved. The GP will emphasize that participation is voluntary and that the patient can decline to participate or withdraw from the project at any time without consequences. The patient is informed that consent to participate will give the primary investigator, sponsor, and controlling authorities access to obtain information in the patient's medical records, including the electronic records, to obtain information about the patient's health conditions. The GP will check patients against the eligibility criteria stated above and invite patients to participate if they fulfill all the inclusion criteria and none of the exclusion criteria. Patients who agree to participate will be asked to provide written consent, which will be obtained by the GP. Informed consent will be obtained prior to the collection of participant data. Participants will be informed about the storage and use of their data.

Interventions

Patients assigned to usual care will be given a full course of the first-line antibiotic course as recommended by the updated local guidelines [34,35]: amoxicillin 750 mg 3 times daily (t.i.d.) for 7 days for acute rhinosinusitis, 1000 mg t.i.d. for 7 days for suspected pneumonia (with clavulanate if the patient is older than 65 years), and amoxicillin/clavulanate 875 mg/125 mg t.i.d. for 7 days for suspected acute exacerbations of COPD (Table 1). Nonetheless, this guideline is designed to serve as a reference for making informed and improved choices in prescribing. The decision to prescribe an antibiotic is solely at the discretion of the participating doctor. The trial is pragmatic, thus mirroring the real-life practices of doctors in Spain. Doctors may also prescribe antibiotics for longer regimens, such as 10-day durations, as shown in recent studies [36]. The decision to prescribe an antibiotic will always be made before randomizing the patient.

Patients in the intervention group will be treated accordingly, following the same recommendations as patients assigned to the control group, but they will be asked to return as soon as they feel better and are afebrile.

When deciding whether to discontinue the antibiotic course after a patient feels better during a consultation, the participating professionals must assess three key areas:

1. Overall improvement in the patient's symptoms.
2. Evaluate the vital signs, confirming that most of them are within the normal range and that the following clinical criteria are met: temperature <37 °C, blood pressure >90/60 mm Hg, pulse <100 beats/min, respiratory rate <20 breaths/min, and oxygen saturation >92%.
3. Assess the CRP value and interpret the results according to the provided table based on current recommendations [37].

Patients who meet all these criteria will be asked to discontinue treatment. Otherwise, patients will be instructed to continue the course for 2 more days and, if they continue feeling better, to return for reassessment. In case of worsening symptoms, they will be advised to contact their doctor for clinical assessment. The doctor will then decide whether to recommend completing the full antibiotic course, changing the therapy, or making a referral.

CRP Point-of-Care Testing Training Program

An on-the-spot one-hour training workshop in the different centers will take place before the inception of the study, with explanation of the clinical guidelines and how to perform CRP rapid testing. Participating professionals will be informed about the updated recommendations on how to interpret the CRP values and the evidence-based management, and this interpretation will depend on the day the patient feels better [37-39] (Table 2). The tests will be carried out with Affinion 2 CRP test (Abbott Diagnostics, United States). Professionals will practice using the device during a run-in period, 2 weeks before the study starts.

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Table 2. C-reactive protein (CRP) rapid testing value interpretation [37-39].

CRP value	Observations	Decision to stop the antibiotic course
<40 mg/L	Self-limiting infection, significant improvement, or cure	• It is safe to stop the course of antibiotics.
40-100 mg/L	Consider other risk factors, age, signs, comorbidity, and symptoms of the infection	• It is safe to stop the course of antibiotics if the patient returns on or before day 4. • In general, it is safe to stop antibiotics on day 5 or later, unless the patient has significant comorbidities or is of advanced age. • Do not stop the course in patients with COPD[a].
>100 mg/L	Reassess the patient. The doctor should reexamine the patient with RTI[b]	• Do not stop the course of antibiotics.

[a]COPD: chronic obstructive pulmonary disease.

[b]RTI: Respiratory tract infection.

Criteria for Discontinuing or Modifying Allocated Interventions

Due to the short intervention period after index consultation, the allocated intervention may only be discontinued for a given trial participant by the GP due to an unexpected event, hindering the GP from conducting or completing the allocated intervention, for example, acute worsening of the participant's condition during index consultation, after consent has been given and allocation has been revealed. Moreover, the study may be discontinued for a given trial participant upon participant request or by withdrawal of informed consent. The data collected before the discontinuation or withdrawal of consent will be retained and used in the analyses; however, no further data will be obtained from the participant.

Strategies to Improve Adherence to Interventions

Monthly meetings with the coordinators of the different centers will be carried out during the performance of the randomized clinical trial. Each center will have a centralized mobile phone for the study, through which patients will contact when they feel well to be directly scheduled at the center as soon as possible to assess the discontinuation of the antibiotic.

Relevant Concomitant Care Permitted or Prohibited During the Trial

Treatments taken on a chronic basis will be permitted, such as inhaled corticosteroids, beta-agonists, anticholinergics, symptomatic treatments, and medications for other concomitant diagnoses, as all these treatments must be distributed evenly between the 2 groups. Patients taking immunosuppressive treatment, antineoplastic therapy, systemic corticosteroids, or antibiotics in the previous 2 weeks will be excluded.

Outcomes

Primary Efficacy Endpoint

The primary outcome is the percentage of patients achieving clinical resolution, defined as the disappearance of fever and either the disappearance or improvement in overall condition, such that no additional antimicrobial treatment is necessary. Any other clinical outcome that does not meet the definition is considered treatment failure. The evaluation will take place on day 14 via a phone call and will always be conducted by a doctor from the team of physicians participating in the study.

Secondary Efficacy Endpoints

Outcomes Collected From the RTI Symptom Diaries

Participants will use a validated self-reported RTI symptom diary, used in previous studies by the research team [40]. Each symptom will be graded on a 7-point Likert scale (0=not affected; 1=very little problem; 2=slight problem; 3=moderately bad; 4=bad; 5=very bad; 6=as bad as it could be). Symptoms recorded include cough, phlegm, shortness of breath, wheeze, blocked/runny nose, facial pain, chest pain, sensation of fever (high temperature), muscle aching, headache, disturbed sleep, feeling generally unwell, and interference with normal activities/work. Participants will rate symptoms for 14 days and return the diary upon completion (electronically or paper-based). It will document daily antibiotic doses and other therapies. For patients who do not return diaries, a short form asking about how many days antibiotics were actually taken, whether antibiotics have been taken after being discontinued by their doctors, and details of the duration and severity of symptoms will be completed by a telephone call to the patient at day 14.

1. Duration of antibiotic therapy, in days, defined as the number of days until discontinuing treatment in both groups (mean/median)
2. Use of antibiotics other than the study medication and other symptomatic therapies within the first 2 weeks (mean/median)
3. Early clinical assessment based on the overall score at Day 7, defined as the total symptom score reported by the patient on that day (mean/median)
4. Duration of severe symptoms, in days, defined as the number of days until the last day the patient scores 5 in any of the symptoms (mean/median)
5. Duration of moderate symptoms, in days, defined as the number of days until the last day the patient scores 3 in any of the symptoms (mean/median)
6. Total resolution of symptoms, in days, defined as the number of days until the last day the patient scores 0 in all the symptoms (mean/median)
7. The duration of antibiotic therapy, in days, defined as the number of patients discontinuing treatment in both groups,

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and day they discontinue will also be checked via electronic medical records

Outcomes 1 to 7 from the RTI symptom diary will be calculated for each participant every day from day 0 until day 14 or when the participant has scored 0 for every item, whichever comes first.

Outcomes Collected From Electronic Case Report Forms, When Available, and From Follow-Up Phone Calls, Which Will Be Cross-Checked With the Patients' Electronic Clinical Records

1. Type of antibiotic prescribed and the planned duration.
2. Number of reattendances to any doctor for new or worsening symptoms regarding the infection, within 28 days after the index consultation.
3. Number of complications related to the infection within 28 days after the index consultation, such as visits to emergency departments or hospital admissions regarding the RTI.
4. Number of days of work absenteeism due to the infectious disease, within 28 days after the index consultation.
5. Difference in health-related quality of life on days 14 and 28, compared with baseline, measured using the 5-level EQ-5D version-quality of Life instrument (ie, EQ-5D-5L) [41].
6. Drug-associated adverse events related to the antibiotic, defined as any harmful and unintended health incident—such as a symptom, an abnormal laboratory finding, or worsening of a pre-existing condition—temporally associated with the use of the antibiotic, regardless of whether it is causally related to the treatment, and antibiotics changed within the first 14 days.

Other Outcomes

Percentage of patients assigned to the intervention group who feel better and who comply with the criteria for stopping the antibiotic therapy, based on the information collected during the visit to the center

Participant Timeline

A flow chart of patients is described in Figure 1. To ensure a standardized and uniform inclusion process, the principal investigator and a senior project manager will inform all participating health care professionals on the inclusion procedures for the study. Eligible participants will be identified as they present to general practice. Once the GP identifies the patient as eligible for the study and a first-line antibiotic with a -lactam is warranted, all the information about the study will be provided, and informed consent will be signed. Details of the ascertainment of visits are provided in Table 3.

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Figure 1. Study flowchart of the clinical trial. COPD: chronic obstructive pulmonary disease; CRP: C-reactive protein; RTI: respiratory tract infection; SOFA: sequential organ failure assessment.

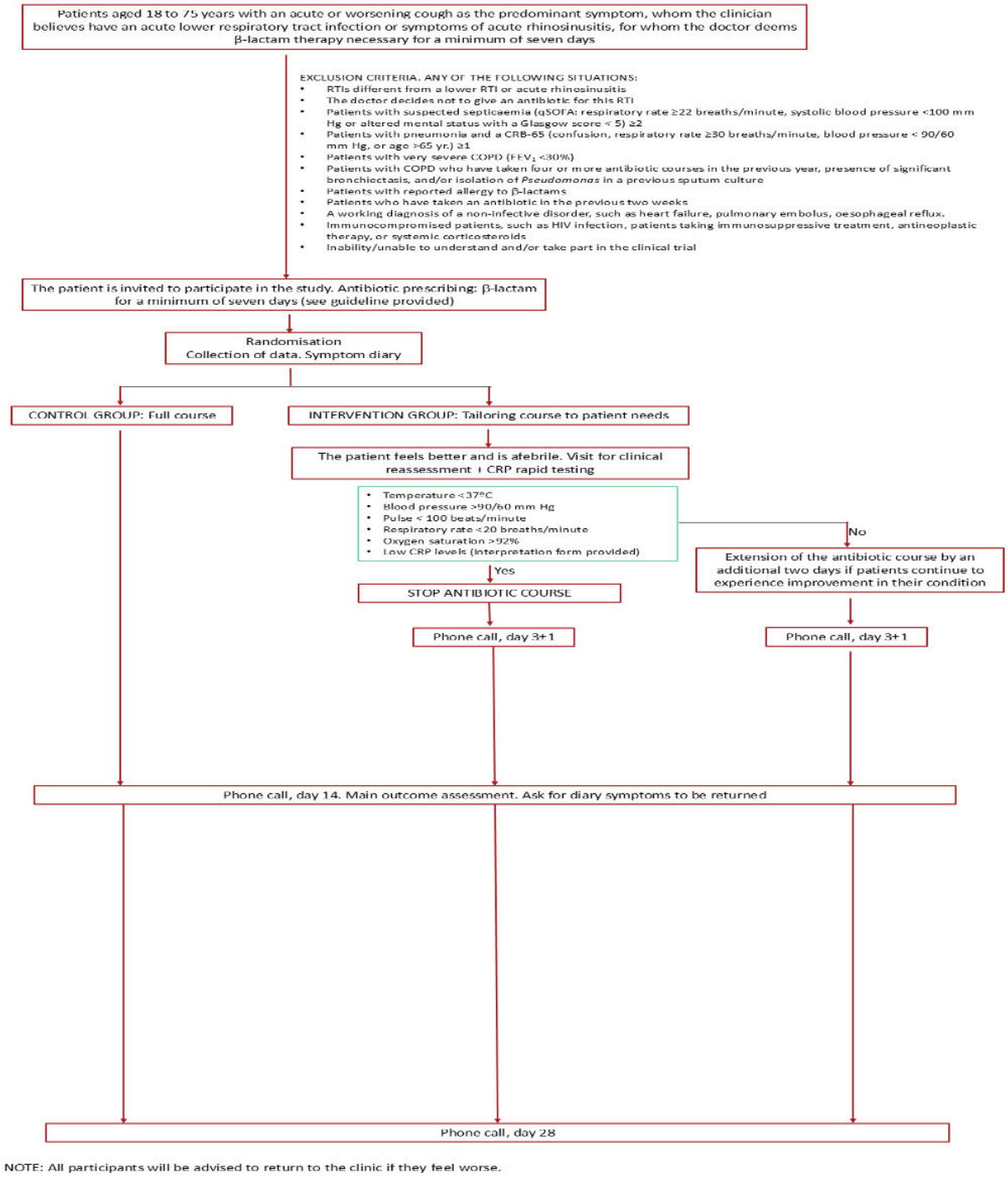

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Table 3. Ascertainment of visits for the clinical trial.

	V1[a]	V2[a]	V3[a]	V4[a]	V5[a]	V6[a]
	Face-to-face visit		Phone call			
	Day 0 (baseline visit)	From day 1[b] (interv)	Day 3 (±1 day)	Day 7	Day 14	Day 28
Medical history	✓	✓				
Standard physical examination	✓	✓				
Eligibility criteria	✓					
Informed consent	✓					
Prescription of the antibiotic	✓					
Randomization	✓					
EQ-5D-5L questionnaire	✓				✓	✓
Hand-out of the symptom diary	✓					
CRP[c] rapid testing		✓				
Decision to stop antibiotic course		✓				
Collection of the symptom diary		✓			✓	
Assessment of the clinical efficacy			✓	✓	✓	
Assessment of the drug adherence		✓	✓	✓	✓	
Monitoring of adverse events			✓	✓	✓	✓
Complications, re-attendance			✓	✓	✓	✓

[a]Visits 1-6.

[b]As soon as the patient feels better, only for patients in the intervention group.

[c]CRP: C-reactive protein.

Patient data will be collected at 4 specific time points for patients assigned to the control group and 5 for those allocated to the intervention:

- Day 0 (inclusion date at the center): Patients meeting the inclusion criteria will be invited to join the study by their GP. After obtaining informed consent, patients will be randomized into either the control group (receiving a full course of β-lactam therapy for at least 7 days) or the intervention group (instructed to return for assessment upon feeling better and being afebrile). The GPs will complete a case report form on day 0 (inclusion day), recording details such as age, inclusion and exclusion criteria, symptoms, date of symptom onset, comorbidities, concomitant medication, quality-of-life questionnaire (EQ-5D-5L instrument), randomization, assigned group, and details of the antibiotic administered. Patients will also be provided with a symptom diary (web-based or paper-based)
- From day 1 until the last day of the antibiotic regimen duration (at the center, only for patients assigned to the intervention group): For patients assigned to the intervention, they will be asked to return to the center for clinical reassessment and CRP rapid testing by the professional. Each center will organize ways to make it easy for patients to reach out and schedule an appointment as soon as they feel better (eg, phone number and web-based page). To decide whether to discontinue the antibiotic course when the patient reports feeling better during the consultation, three types of assessment are needed: (1) overall improvement in the patient's symptoms; (2) signal signs are in normal range (temperature <37 °C; blood pressure >90/60 mm Hg; pulse < 100 beats/minute; respiratory rate <20 breaths/minute, and oxygen saturation >92%), and (3) CRP value is lower than the prespecified values depending on the day of the visit. All this information will be recorded in the electronic case report form (e-CRF; Table 1)
- Day 3±1 (phone call, only for patients assigned to the intervention group): A reminder phone call for all patients assigned to the intervention group will be made on this day. They will be asked how they feel and reminded to reach out to the center as soon as they feel better for a discontinuation assessment

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- Day 7 (phone call): An early clinical efficacy outcome will be assessed during this call, including the clinical progression of signs and symptoms, treatment adherence, adverse reactions, any complications, reattendance visits, changes to the assigned treatment or concomitant medication, and the use of antibiotics other than the study drug
- Day 14 (phone call): The main clinical efficacy outcome and some secondary outcomes, including clinical progression of signs and symptoms, compliance with the study treatment, EQ-5D-5L instrument, adverse reactions, any complications, reattendance visits, changes in the assigned treatment or concomitant medication, including the use of antibiotics other than the study medication, will be assessed. Patients will be asked to return their diaries
- Day 28 (phone call): Patients will be contacted for information on the number of reconsultations, complications, and the quality-of-life (EQ-5D-5L) instrument

Sample Size

We assumed 85% clinical recovery in the group assigned to the full antibiotic course based on some studies [12,42-44]. Considering a power of 80%, a level of significance of 5%, one-sided noninferiority margin of 10%, as recommended by the guideline on the evaluation of medicinal products indicated for treatment of bacterial infections issued by the European Medicines Agency in 2022 [45], which gave a sample size of 402 patients. Assuming that the primary outcome could not be evaluated in 15% of patients, 474 patients needed to be included in the study (237 in the control group and 237 in the intervention group).

Recruitment

A total of 474 eligible patients will be enrolled by doctors in 25 primary care centers throughout Spain. Centers with a minimum of 3 health care professionals willing to participate in the trial will be invited to join the study. The study is planned to run from October 2025 to April 2027, including 2 winter periods (last patient recruited in March 2027). A tight follow-up on the process and different strategies will be implemented, and if needed (1) other professionals in the existing centers will be invited to participate in the study; (2) we can extend the recruitment period by an additional 2 months, until May 2027 (last follow-up in June 2027); or (3) other sites will be opened to increase the candidates to enter the study. Monthly meetings will be held with the coordinators at the different centers to maintain recruitment and enrollment activity during the inclusion period.

Assignment of Interventions: Allocation

Sequence Generation

Patients fulfilling the inclusion criteria will be asked to participate in the trial. All patients who agree to participate and provide signed informed consent will receive an increasing sequential patient number and be randomly assigned to one of the 2 treatment groups in a 1:1 ratio stratified per main diagnosis, one for acute rhinosinusitis and another one for lower RTI.

Concealment Mechanism

Since this study is open-label to patients and investigators, randomization will be based on investigator-blinded blocks of randomly varying size to protect against the potential predictability of treatment assignments. Blocks will be small to decrease the potential for mid-block inequality.

Implementation

The allocation sequences will be prepared by one remote independent researcher who is available to generate more allocation sequences.

Assignment of Interventions: Blinding

Owing to the type of intervention, participants and GPs are not blinded to group allocation. It is also difficult for the principal investigator and members of the research team involved in obtaining and analyzing the data (outcome assessors and data analysts) to be blinded to group allocation, as patients allocated to the intervention group have more visits scheduled.

Data Collection and Management

Plans for Assessment and Collection of Outcomes

All the data is collected via e-CRFs and surveys through Research Electronic Data Capture (REDCap; Vanderbilt University), which is a secure web-based data collection platform for building and managing web-based databases and surveys [46].

Collection of Baseline Characteristics of GPs

The baseline characteristics of the participating GPs are collected through email correspondence and registered in REDCap by the principal investigator. The following information will be obtained: age, sex, region of Spain, type of primary health clinic, seniority as a GP, experience with randomized clinical trials, experience with research on RTIs, comfort with stopping antibiotic courses, and baseline antibiotic prescribing.

Collection of the Participant Data

We will collect health and personal data from the patients included in the study via REDCap, where the researchers will register basal data and evolution of the illness, and via a patient diary completed by the patients themselves. Regarding the patient's diary, we will also create a web-based symptoms diary to make it available for all patients recruited. All patients will be able to choose between the web-based and paper version of the symptom diary. Patients will be informed about the type of data that will be collected and about their rights when being informed about the study, and will sign a consent form consenting to the use of their data. No data will be collected before the patient signs the consent form. As soon as the patient has signed the consent form, they will be given a study code and will be identified by the study code in all the study materials. The relationship between his identity and the study code will be kept in the health care center and will only be available to those who need it to fulfill their duties. Data collected in this pragmatic study is considered codified data. IDIAPJGol has license to use REDCap and the data is collected and held in IDIAPJGol servers, which comply with the European and

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national requirements. Data controller will be the institution (IDIAPJGol) for the study-related data and the health care institution for the health data collected to manage the patient in clinical practice. There will not be any transfer of data. Only the investigator team will have access to study datasets, and always with codified information to preserve the confidentiality of the participants involved. All the recruiting investigators will have access to REDCap platform to collect the data, each of them with their own specific credentials, and they will only have access to the patients recruited in their own setting. We will follow the FAIR (Findable, Accessible, Interoperable, and Reusable) principles: all datasets and publications will be identifiable by using a "Digital Object Identifier (DOI)" and we will share the data (as far as possible) in the Zenodo platform. We will publish the results in Open Access journals, and wherever possible, the data will be shared without delay following the Creative Commons License with Attribution (CC-BY) or the "No Rights Reserved" (CC0). Data will be saved and shared using standardized formats (txt, csv, and pdf).

Ethical Considerations

The protocol has been approved by the Spanish Agency of Drugs and Health Products and Hospital de Sant Pau Independent Ethics Committee, Barcelona (reference number 25/233). We will follow the legislation on data protection (EU 2016/679) and its national implementation (LOPD 3/2018 of 5 Dec on the protection of personal data and guarantee of digital rights).

Plans to Promote Participant Retention and Complete Follow-Up

The loss of follow-up data obtained from medical records and shared medication records is expected to be minimal. Outcome data from medical records be collected for all participants, except those who are discontinued by the GP or who have withdrawn informed consent before day 28. We expect some participants to be lost to follow-up in the RTI symptom diary, as we anticipate that some participants will fail to complete the electronic diary or will fail to submit the paper version to the GP. For those who do not return the diaries, participants will be contacted by phone on day 14 to gather information on antibiotic use, adherence, and symptom duration details.

Statistical Methods

Statistical methods for primary and secondary outcomes: The characteristics of the study population will be described using frequencies for categorical variables and mean and SD for quantitative variables. To compare the clinical efficacy between the 2 strategies, we will analyze the difference in the proportion of recovered patients in each arm on day 14. Efficacy evaluation will be primarily based on intention-to-treat analysis in such a way that any event in any patient will be included in the group to which the patient was randomized, and per protocol analysis will be used as a secondary analysis. For all analyses, the level of significance will be $P<.05$.

- Interim analyses: No interim analysis is planned.
- Methods for additional analyses (eg, subgroup analyses): We will conduct subgroup analyses of the primary outcome of participants with lower RTIs, and for acute rhinosinusitis.

Cost-Effectiveness Analyses

We will estimate the cost-effectiveness of tailoring antibiotic duration therapy for the "within-trial" period (28 days) and over the expected lifetime of patients (lifetime/long-run model).

In the within-trial analysis, cost-effectiveness will be measured by the incremental cost per patient achieving clinical resolution. In this analysis, effectiveness will be calculated using the primary endpoint of the study. Costs considered will include antibiotic prescription costs according to the duration of treatment, other drug costs, reconsultations in primary and secondary care (including hospitalizations), and costs associated with adverse events. Data on health care resource use and duration will be taken from the patients' diaries, from the collected information in the e-CRF, and at the follow-up phone calls at days 14 and 28, and from a review of patients' medical notes. Unit cost data will be taken primarily from national sources published by the Spanish Ministry of Health. The incremental cost-effectiveness ratio will be calculated by dividing the estimated difference in costs by the estimated differences, in effects observed between the intervention and control groups. Nonparametric methods to calculate confidence intervals around the incremental cost-effectiveness ratio based on bootstrapped estimates of the mean cost and effect differences will be used.

The intervention under evaluation in this study is likely to have an impact beyond the trial period. To capture these potential effects, we will extrapolate the results to an extended time horizon, that is, considering the remaining life expectancy of the patients. In this analysis, we will complement data from the trial with relevant data from the published literature to estimate the incremental cost per quality-adjusted life year (QALY) gained. Health-related quality of life data collected during the trial using the EQ-5D-5L questionnaire at baseline, at 14 and 28 days will be used as inputs to estimate baseline QALY values for this patient group. A decision-analytical model synthesizing all relevant information will be used to estimate the differences in lifetime QALYs and lifetime health care costs of a cohort of patients under the tailored duration strategy versus the standard of care strategy.

Methods in Analysis to Handle Protocol Nonadherence and Any Statistical Methods to Handle Missing Data

Analyses will be performed as intention to treat (pragmatic trial) and also per protocol. The primary analysis population will comprise all participants, irrespective of follow-up.

Data will be examined for missing values and outliers. Measures of central tendency and dispersion for continuous study parameters will be portrayed. Extreme or unexpected values will be examined individually for authenticity, and data discrepancies addressed where appropriate.

Plans to Give Access to the Full Protocol, Participant-Level Data, and Statistical Code

The full protocol, statistical code, and e-CRF templates designed for the study will be available upon request once the report has been published. Participant-level data will not be available.

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Results

Recruitment of patients will start in October 2025 and will be stopped in April 2027. The current protocol is version 3 of July 31, 2025.

Discussion

Principal Findings

The limited to moderate impact in reducing unnecessary antibiotic use in primary care observed in antimicrobial stewardship programs necessitates the exploration of new strategies aimed at reducing patients' exposure to unnecessary courses [30]. This highlights the need for exploring new strategies to minimize patients' exposure to unnecessary antibiotic courses. Convincing doctors, especially GPs, not to prescribe antibiotics when uncertain or under patient pressure is challenging. Despite the widespread practice, standard durations for common infections lack support from clinical studies [7]. However, recent randomized clinical trials, conducted mainly in the last 2 decades, show that ending antibiotic courses by day 2-3 for most RTIs is effective and safe, similar to early studies on short-term antibiotic courses for uncomplicated urinary tract infections carried out 20 years ago [47]. We believe health care professionals should encourage patients to stop antibiotic treatment promptly after symptom resolution unless a serious infection is suspected. In our clinical trial, these potential serious infections are clearly excluded. Continuing antibiotics beyond symptom resolution does not appear to prevent or reduce AMR. Conversely, reducing the duration of courses has been shown to curb the spread of AMR in pneumonia. It is essential to move away from strict, predetermined durations and adopt a patient-centered approach by customizing antibiotic courses to meet each patient's individual needs. The key challenge involves identifying when exactly antibiotics can be safely stopped based on symptoms to minimize the chances of relapse. We currently lack evidence on how pathogen burden is associated with symptoms experienced by patients with RTIs.

STORM's main focus on primary care settings makes it directly applicable to the daily practice of GPs who frequently encounter patients with uncomplicated RTIs. Infectious diseases represent one-third of all GP consultations, with over half of these visits attributed to RTIs [48]. This indicates that RTIs are among the most prevalent conditions encountered by GPs in their clinical practice. It acknowledges the challenges faced by health care professionals, particularly GPs, in resisting patient pressure and uncertainty when deciding whether to prescribe antibiotics. By advocating for a patient-centered approach to antibiotic prescribing, the proposal provides practical guidance for health care providers to tailor treatment regimens according to individual patient needs and clinical circumstances [49]. STORM draws upon recent clinical trials conducted over the past 2 decades, suggesting that the findings are based on contemporary evidence and thus likely applicable to current clinical practice.

To the best of our knowledge, there has not been any study in primary care exploring the feasibility and efficacy of stopping the antibiotic course once the clinical signs of the patient have improved and the CRP level is low. Furthermore, a randomized clinical trial has never been conducted to assess the effectiveness and safety of this crucial strategy in combating AMR and drug-related adverse events. Primary health centers are the first contact point for patients with RTI symptoms, which is why we will conduct the study in this setting. This will constitute the first clinical trial aimed at answering whether it is safe to shorten and tailor the antibiotic therapy duration to the needs of the patients. This study does not pursue the medicalization of tailoring the antibiotic course by requiring patients assigned to the intervention group to return for a clinical reassessment and CRP testing; however, this is the first trial of its kind. We aim to determine the efficacy and safety of this strategy. If tailoring antibiotic courses for RTIs proves to be as effective and safe as completing the entire course, further studies will investigate the necessity of the reassessment visit.

Limitations

This is a pragmatic clinical trial evaluating the efficacy of different antibiotic therapy durations for acute RTIs, and therefore, masking techniques are not used. One limitation of this study is that a percentage of self-limiting viral infections will be included. While antibiotics are not the recommended treatment, they are still frequently prescribed for most RTIs worldwide [3]. However, all participants will receive a summary of the updated current guidelines, which discourage the use of antibiotics for most patients with acute rhinosinusitis, uncomplicated acute bronchitis, and acute COPD exacerbations without purulent sputum, leaving the decision to the clinician in this pragmatic approach. Nevertheless, we believe that the percentage of "viral self-limiting infections" included in this randomized clinical trial will be much lower than what is typically observed under normal conditions, as GPs will be informed about the appropriate indications for therapy and will have this information available before deciding whether to prescribe a β-lactam to the participant.

Both the primary and some of the secondary objectives of the study are based on information provided by the patients themselves. Regarding the CRP rapid testing, we are aware that high CRP levels can signal systemic inflammation in conditions like inflammatory disorders, not just infections. There is limited research on how CRP changes day by day in RTIs. Although levels above 100 mg/L might reflect the natural progression, we set conservative thresholds for this initial trial on shortening treatments as patients improve. Some centers are only open on weekdays, from Monday to Friday. In these cases, if a patient feels better over the weekend, they will need to wait until the following Monday to be assessed. To minimize this limitation, we will recruit only centers that remain open on Saturdays or, preferably, those that provide out-of-hours services. This strategy aims to ensure timely follow-up and reduce delays in clinical assessment.

The concept of "feeling better" is inherently subjective and can vary significantly across individuals, types of infections, and symptom profiles [50]. For some patients, it may indicate partial symptom improvement, while for others it may imply complete resolution of all symptoms. Certain symptoms, such as fever,

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might be a more reliable indicator for clinical improvement and the safe discontinuation of antibiotics, whereas symptoms like cough may persist longer without significantly impairing daily functioning. Additionally, some patients with RTIs may prefer to stop antibiotics only after full symptom resolution, while others may find the notion of symptom improvement too ambiguous, leading to uncertainty about when to discontinue treatment. To address this challenge, our study defines the appropriate time to stop antibiotic treatment based on a combination of clinical and patient-reported criteria: overall symptom improvement as reported by the patient, normalization of key vital signs—particularly body temperature, and the absence of elevated inflammatory markers, specifically CRP. As a pragmatic randomized clinical trial, this study is designed to provide real-world evidence on how patients interpret and respond to the concept of "feeling better" in the context of antibiotic use. Furthermore, to enhance our understanding, we will conduct a qualitative study with a subset of patients in the intervention group to explore their perceptions and experiences related to symptom improvement and treatment decisions. Insights from this qualitative component will help refine a more practical and clinically applicable definition of when it is appropriate to discontinue antibiotic therapy, ultimately supporting clinicians in providing more precise and consistent advice.

As with any randomized clinical trial, the STORM study faces some challenges. One potential difficulty is recruiting enough patients with acute RTIs who are willing to participate. Despite this moderate risk, the study is planned to run from October 2025 to April 2027, covering 2 winter periods, with the last patient recruited by March 2027. To ensure recruitment success, tight follow-up processes and various strategies will be implemented. These strategies may include inviting other professionals from existing centers to participate, extending the recruitment period by an additional 2 months if needed, and, if necessary, opening recruitment at additional sites to increase the pool of candidates. In addition, to minimize inclusion bias, consecutive recruitment of patients who meet the inclusion criteria and do not meet any exclusion criteria will be encouraged [51].

Professionals will follow up with all patients assigned to the intervention group on day 3 for assessment of the clinical condition and as a reminder to reach out to the center as they feel better. Professionals will be trained on how to explain the study's objectives and the importance of adhering to the study procedures. For patients who do not return their symptom diaries, a short form will be completed via a phone call on day 14, asking about the number of days they took antibiotics, other therapies, and details regarding the duration and severity of their symptoms.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

All authors contributed to the study design. RMor and CL conceived the study. AM, AGS, MM, and CL obtained funding. AGS and CIJ are involved in the acquisition of data; RMor, AGS, RMon, and LVT are responsible for the analysis of data. RMon is responsible for the software used in the work. CL wrote the first draft of the protocol. All authors critically revised the protocol, made substantial contributions, and approved the final version of the protocol to be submitted for publication. The corresponding author has the final responsibility for the decision to submit for publication.

Conflicts of Interest

MM has received speaker fees from AstraZeneca, Boehringer Ingelheim, Chiesi, Cipla, Bial, GlaxoSmithKline, Menarini, Kamada, Takeda, Zambon, CSL Behring, Specialty Therapeutics, Janssen, Grifols, Zambon, Tabuk Pharmaceuticals, Glenmark Pharmaceuticals, Sanofi/Regeneron, and Novartis; consulting fees from AstraZeneca, Atriva Therapeutics, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, CSL Behring, Inhibrx, Ferrer, Menarini, Mereo Biopharma, Spin Therapeutics, Specialty Therapeutics, GondolaBio, Palobiofarma SL, Takeda, Novartis, Beam therapeutics, Novo Nordisk, Sanofi/Regeneron, Zambon, Zentiva, and Grifols; research grants from Grifols; and participated on a Data Safety Monitoring Board from Mereo, and received support for attending meetings from Boehringer Ingelheim, Menarini, Chiesi, Bial, CSL Behring, and Grifols. The other authors declare no competing interests.

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Abbreviations

AMR: antimicrobial resistance
COPD: chronic obstructive pulmonary disease
CRP: C-reactive protein
e-CRF: electronic case report form
FAIR: Findable, Accessible, Interoperable, and Reusable
GP: general practitioner
QALY: quality-adjusted life year
REDCap: research electronic data capture
RTI: respiratory tract infection
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
t.i.d.: 3 times daily

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Protocol

Evaluation of the Comparative Efficacy of Aquatherapy Versus Conventional Physiotherapy on Motor Function and Psychosocial Well-Being in Children With Acute Lymphoblastic Leukemia: Protocol for a Randomized Controlled Trial

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Abstract

Background: Children with acute lymphoblastic leukemia (ALL) undergoing chemotherapy have limited access to rehabilitation support. While rehabilitation on the basis of physiotherapy has been found to enhance psychosocial well-being and motor performance, a viable substitute for this can be aquatherapy. However, no trials have currently evaluated the effectiveness of aquatherapy in this population.

Objective: We aim to evaluate the comparative efficacy of aquatherapy versus conventional physiotherapy on the motor function and psychosocial well-being of children with ALL.

Methods: We will conduct a parallel, single-blinded (participant-blinded), randomized controlled trial with embedded quantitative analysis. In total, 54 survivors of ALL undergoing chemotherapy will be recruited from the Acharya Vinoba Bhave Rural Hospital in Sawangi (Meghe), Wardha, Maharashtra, India. The experimental group will attend a 4-week, thrice-weekly, 45-minute aquatherapy session focusing on exercise-based rehabilitation. The comparison group will receive conventional physiotherapy including standardized exercises. Assessments will be completed at weeks 0 (baseline), 4 (postintervention), and 12 (follow-up). The primary outcome related to motor function will be measured using the timed up and go test and the Pediatric Balance Scale at week 4. Secondary outcomes will include psychosocial well-being measured with the Hospital Anxiety and Depression Scale and functional abilities measured with the Functional Independence Measure for Children (WeeFIM). Health service data, including length of stay in the hospital, hospital readmissions, and emergency department presentations, will be recorded. Semistructured interviews will be completed within an interpretive description framework to explore participant descriptions. The primary outcome will be analyzed using linear mixed effects models.

Results: The trial is scheduled to commence in October 2025.

Conclusions: The trial will inform future implementation of rehabilitation for children with ALL by providing important data regarding the efficacy of aquatherapy compared with conventional physiotherapy as well as patient experience.

Trial Registration: Clinical Trials Registry - India CTRI/2025/03/083036; https://tinyurl.com/v446cd6z

International Registered Report Identifier (IRRID): PRR1-10.2196/75877

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KEYWORDS

acute lymphoblastic leukemia; aqua therapy; rehabilitation; conventional physiotherapy; motor functions; psychosocial well-being; chemotherapy

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Introduction

Acute lymphoblastic leukemia (ALL) is one of the most common cancers affecting children, with about 64,200 cases reported worldwide. In India, the highest incidence occurs among children aged 2–5 years, with rates of approximately 101.4 cases per million boys and 62.3 cases per million girls [1]. The availability of more advanced therapeutic agents, enhanced supportive care, therapy stratification, and regimen modification in recent times has led to a cure rate of more than 80% and an overall survival probability of 80% to 90%. As a result, awareness about therapy-related morbidity has increased because of the longer survival rates [1].

Acute chemotherapy comprises 2 phases: the induction phase and the consolidation phase. The primary goal of the induction phase is remission. Intense chemotherapy is used during this phase, which typically lasts 4 weeks, to destroy as many leukemia cells as possible. After a successful induction therapy session, patients are moved into the consolidation phase, sometimes referred to as intensification. This phase is aimed at eradicating any leukemia cells that could have remained unaffected during the induction phase. Additional chemotherapy regimens that are different from those used in induction are part of the consolidation phase, which usually lasts many months. This is the most intense phase, requiring a prolonged hospital stay. Children with ALL are considerably less active during the acute stage, usually presenting with deficits in fatigue and activity tolerance [2,3]. They may also exhibit motor deficits as a side effect of the chemotherapy drugs, which include anthracyclines and vincristine. While anthracycline-induced cardiotoxicity reduces aerobic capacity, vincristine-induced neuropathy impairs peripheral sensory and motor function [4,5]. Chemotherapeutic drugs such as vincristine have an adverse effect on balance, which may occur through diverse mechanisms such as by decreasing muscular strength and flexibility or producing cognitive impairment [1]. When used on children with ALL, these drugs can result in self-imposed or medically prescribed activity restrictions, which would lead to routinely engaging in lesser physical activity [1,6].

Children with ALL frequently struggle with motor performances, functional movement, and balance, possibly because of deficits in somatosensory, motor, muscular, and cognitive abilities. Numerous studies on children with ALL have examined the effect of exercise regimens on increasing their ankle range of motion, leg and back muscle strength, and cardiovascular fitness [1,7]. However, studies on the impact of therapies aimed at enhancing balance and functional mobility are limited. Furthermore, not enough research has examined their impact during the induction phase, or the acute stage, of chemotherapy. To avoid additional issues related to the disease, physiotherapy interventions conducted in the early stages of the disease can be crucial [1,8]. Such improvements are essential not only for their physical health but also for their psychological well-being, as enhanced mobility can lead to increased participation in daily activities and social interactions.

Exercise in an aquatic environment is part of aquatherapy, or what is known as aquatic treatment; this form of therapy has in recent times drawn much interest as a possible supplement to traditional physiotherapy. The characteristics of water, like buoyancy and resistance, makes it a workout surface that is both supportive and demanding, potentially improving motor function without placing undue strain on the musculoskeletal system. Aquatherapy has demonstrated beneficial benefits on gross motor function and produced enjoyment of physical activity in pediatric groups [9]. In addition to standard physical treatment, aqua-plyometric (plyo) exercises can help long-term survivors of childhood ALL strengthen their bones, increase their functional ability, and enhance their quality of life [10]. One study examined the impact of aquatherapy on performance in children with brain tumors and found that aquatherapy could help their physical performance [11]. However, aquatherapy's efficacy, especially in children with ALL, remains underexplored.

The primary aim of this randomized controlled trial is to determine the comparative efficacy of aquatherapy versus conventional physiotherapy on motor function in children with ALL during the induction and consolidation phase of their chemotherapy treatment. The secondary aims include determining the comparative efficacy of aquatherapy versus conventional physiotherapy on the (1) psychosocial well-being and (2) quality of life of children with ALL during the induction and consolidation phase of their chemotherapy treatment.

Methods

Study Design

We propose conducting a parallel, single-blinded (participant-blinded), randomized controlled trial with embedded quantitative analysis. The experimental group will attend a 4-week, thrice-weekly, 45-minute aquatherapy session focusing on exercise-based rehabilitation (Figure 1). The comparison group will receive conventional physiotherapy, including standardized exercises. Assessments will be completed at weeks 0 (baseline), 4 (postintervention), and 12 (follow-up). Quantitative trial outcomes will be reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) statement and SPIRIT (Standard Protocol Items: Recommendations for Intervention Trials) checklist (Multimedia Appendix 1) [12].

On the basis of the acute phase of physiotherapy interventions after chemotherapy treatment in pediatric oncology settings, a 12-week follow-up period is chosen. Clinical trials evaluating early functional and psychosocial responses in children with ALL frequently use shorter follow-up periods. Intensive chemotherapy and related side effects are predicted to cause rapid changes in emotional and physical conditions throughout active treatment phases. Without placing excessive burden on children who are already receiving critical medical care, a 12-week timeline enables the capture of early and clinically meaningful gains.

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Figure 1. CONSORT diagram for aquatherapy and conventional physiotherapy. GP: general practitioner.

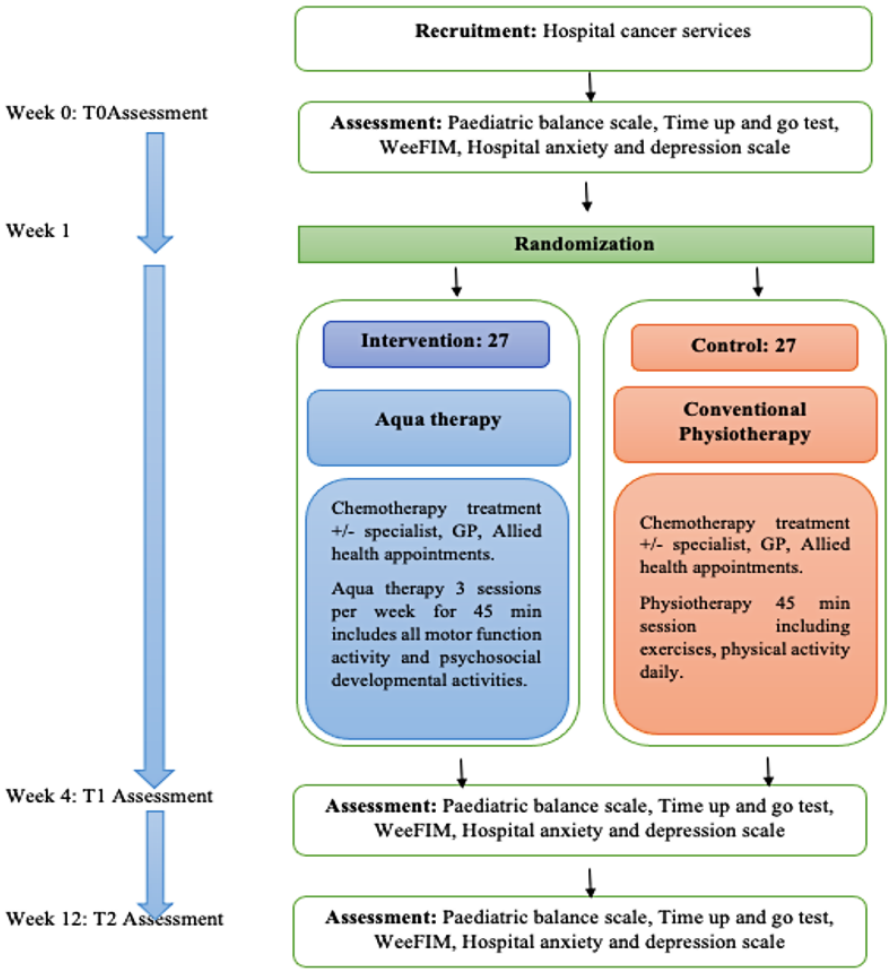

Randomization Procedure

Eligible participants who have fulfilled baseline measurements will be randomly allocated to the aquatherapy group or conventional physiotherapy control group using a concealed method in accordance with a web-based computer-generated randomization program using permuted blocks of participants. Allocations will be prepared before trial commencement by an independent researcher with no role in participant recruitment, trial administration of intervention delivery, or assessments. The trial coordinator will allocate participants after baseline assessment by contacting the independent researcher via email for random group allocation.

Setting

The trial will be conducted at the Acharya Vinoba Bhave Rural Hospital in Sawangi (Meghe), Wardha, Maharashtra, India, a hospital that offers treatment for ALL survivors. Participants will be recruited from the same hospital.

Ethical Considerations

The aquatherapy trial has been approved by the Datta Meghe Institute of Higher Education and Research (Deemed to Be University), formerly known as Datta Meghe Institute of Medical Sciences (Deemed to Be University) (ECR/440/Inst /MH/2013/RR-2019 DHR; EC/NEW/INST/2023/MH/0340; DMIHER(DU)/IEC/2025/634) (Multimedia Appendix 2), and is registered under the ICMR-National Institute of Medical Statistics Clinical Trial Registry - India CTRI/2025/03/083036 (Multimedia Appendix 3).

Patient Selection and Consent

Eligible participants will be identified by a physiotherapist. For aquatherapy, the potential participants will be advised about the trial by the clinical staff. If a participant consents, and the parents provide their consent as well (Multimedia Appendix 4), the participant will then be assessed by the physiotherapist. Details of the trial and the aquatherapy session will be provided so that any questions that participants or their parents have can be clarified and written informed consent can be obtained.

Inclusion and Exclusion Criteria

Participants who are aged 4 to 18 years [1], have ALL, and are undergoing acute stages of chemotherapy treatment can be included. The children must be ambulatory, can be of either sex, and must be in the induction or consolidation phase of chemotherapy for ALL.

Children (1) who are medically unfit to participate in the exercise session as determined by a physiotherapist or medical practitioner considering published recommendations [13]; (2) who have discontinued chemotherapy; (3) who have been diagnosed with sepsis; (4) who have preexisting cardiovascular disease, acute or chronic respiratory disease, acute or chronic bone, joint, or muscular disorders, neuromotor deficits or genetic

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disorders; and (5) with auditory or visual impairments are excluded from the trial.

Intervention

All participants will receive their usual medical care, which may include adjuvant, neoadjuvant, or palliative treatment; specialist, nursing, and other health outpatient appointments (eg, to see a physiotherapist); and visits to their general practitioner.

As a part of the trial, participants will not receive standardized hospital educational materials; however, they will be guided solely through supervised aquatherapy sessions.

A conventional physiotherapy session involves motor function and psychosocial developmental exercises with very little support in comparison with aquatherapy. As a part of the trial, conventional physiotherapy also includes a session for 45 minutes, 5 times weekly, including strength training thrice a week [7,14,15]. All participants will also have the opportunity to discuss their ongoing rehabilitation needs at the end of the 4-week intervention period. They will be provided written information for referral to appropriate local services for ongoing support if required in line with usual practice at the health service.

Experimental Group: Exercise-Based Aquatherapy

In addition to conventional physiotherapy, participants randomized to the experimental group, which involves aquatherapy, will receive a 45-minute exercise session delivered by the physiotherapist in the aquatic machine thrice weekly for 4 weeks. The exercises include aerobic training, psychosocial developmental well-being, and resistance training guided by published recommendations [7,14,15]. These exercise sessions will be individually tailored and include a waterjet in the aqua machine for resistance, treadmill walking in the aqua machine, balance activities, aerobic training, and functional activities. All these exercises, which are part of endurance training, will be conducted within the aquatherapy machine itself, involving mild to moderate aerobic exercises (eg, slow paced treadmill walking in the aqua machine, water-splashing activity, spot marching, and sidestepping). The aquatherapy machine also has grab bars and a seat for exercises that work on improving balance. The therapist will choose exercise variations, for example, upper-limb strengthening by using weights or lower-limb strengthening by using the waterjet provided in the aqua machine. Initial warm-up exercises include various upper- and lower-body stretches and balance exercises. Water-splashing activities with play therapy is included to improve psychosocial well-being. Exercise intensity will depend on verbal feedback from the participant, observation by the physiotherapist, and as per standard protocol-based intensity. Resistance exercise will involve, first, active-assisted range of motions followed by active range of motions. To improve balance, aqua-plyometric exercises will also be done in the aqua machine under the physiotherapist's guidance. Before starting the exercises, aerobic training as a warm-up for 5 minutes will be followed by a cool-down for 5 minutes (Table 1).

The participants will receive an overview of the exercise regimen and study protocols linked to rehabilitation from the physiotherapist who will be evaluating and administering the aquatherapy intervention. The sessions will be for 45 minutes each, with 3 sessions per week for 4 weeks [10,11]. Activities are aimed at improving motor function and psychosocial well-being. The fidelity of the intervention will be monitored by recording the content of the exercise session and duration of the completed sessions. Participants in both groups will also be asked whether they received any exercise-based intervention outside of the trial at the 4-week assessment and follow-up.

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Table 1. Intervention and comparison group descriptions based on the TIDieR (Template for Intervention Description and Replication) checklist.

	Experimental group	Comparison group
In brief	• Aquatherapy rehabilitation	• Conventional physiotherapy
Why	• Exercise intervention in the aquatherapy machine is safe, effective, and convenient to use for improving the quality of life of individuals with ALL undergoing chemotherapy.	• Individuals with ALL undergoing chemotherapy are routinely offered rehabilitation.
What (materials)	Preparations before the aquatherapy session: • Avoid a heavy meal before the session • Remain well hydrated before the session • Maintain water temperature • Wear proper clothing before entering the aquatherapy machine • Follow general principles for duration, frequency, and intensity to be maintained • Provide participant with weight cuff • Aquatic therapy machine equipped with an underwater treadmill and adjustable resistance jets	• Rehabilitation is delivered using standard physiotherapy techniques without the use of any specialized equipment • Rehabilitation focuses on land-based exercises
What (procedures and heath care provider)	• Physiotherapist will provide aquatherapy session protocol in written format	• Physiotherapist will provide the exercise guidelines
How	• Supervised session in aquatherapy machine • Digitally controlled aqua machine allows for real-time monitoring of water speed and session duration, ensuring consistency in exercise intensity.	• In person
Where	• Aquatherapy machine is placed in the pediatric outpatient department • Participants receive aquatherapy in the pediatric outpatient department	• Participants receive conventional physiotherapy in the hospital (inpatient department) itself
When and how much (intensity)	• Warm up: stretching 30 s, hold, 3 repetitions • Aerobic exercises: underwater treadmill walking with minimum speed • Strengthening exercises: 10 repetitions, 2 sets • Resistance exercises: 10 repetitions, 2 sets • Balance exercises: 5 s, hold single leg stance, and progress up to 10 s holds	• Fatigue: Jacobson relaxation exercise and aerobic exercises like walking • Strengthening exercises: 10 repetitions, 3 sets • Resistance exercises: 10 repetitions, 2 sets • Balance exercises – 5 s hold single leg stance and then progress up to 10 s holds (eg, heel walking, toe walking, with eyes open and eyes closed)
Frequency	• 3 sessions per wk, supervised	• 5 sessions per wk, supervised
Session time	• 45 min	• 45 min
Overall duration	• 4 wk	• 4 wk
Tailoring	• Exercise is tailored to each participant's ability	• Exercise is tailored to each participant's ability
Trial fidelity	• Physiotherapist • Intervention will be delivered as planned • Ensuring all participants receive the intervention in the same way	• Physiotherapist • Intervention will be delivered as planned • Ensuring all participants receive the intervention in the same way

Study Outcomes

Participants will be assessed at weeks 0, 4, and 12. The primary end point is immediately after the intervention (week 4). Physical activity, balance, and psychosocial well-being will be assessed at weeks 0 and 4. Primary and secondary outcomes are as outlined in Table 2.

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Table 2. Primary and secondary outcomes, measures, and time points of the intervention.

Outcomes	Measures or sources	Definitions	Time points
Primary outcome: balance	Pediatric Balance Scale [16]; reliability 0.97	This 14-item scale is simple to administer, does not require any specialized equipment. Performance can be measured both quantitatively and qualitatively using a 0 to 4 grading system.	Wk 0; wk 4
Functional mobility	Timed up and go test [1,17]; reliability (ICC>0.80)	The test evaluates functional mobility and balance by timing how long it takes a participant to get up from a seated posture, walk 3 min, turn around, go back, and sit down. <10 s—typical mobility; 10-14 s—independent walking but modest motor deficits. >20 s—severe restrictions with higher risk of fall; 15-20 s—intermediate mobility issues, requiring some assistance	Wk 0; wk 4
Secondary outcome: motor function	Functional Independence Measure for Children (WeeFIM) [18,19]	A popular instrument for evaluating the functional capacities of individuals undergoing rehabilitation, the functional independence measure focuses on independence in everyday activities. Each of the 18 items in the FIM is scored on a scale of 1–7, with higher scores indicative of greater independence. The items are separated into motor and cognitive categories. Development and rehabilitation requirements of individuals can be inferred from their overall score, which ranges from 18 (total reliance) to 126 (full independence).	Wk 0; wk 4
Psychosocial well-being	Hospital Anxiety and Depression Scale (supplementary file [18])	It is a 14-item questionnaire used in hospital settings to measure sadness and anxiety. Each of the two subscales (depression and anxiety) has 7 items and is scored between 0 and 3, with a maximum score of 21 per subscale; 0-7 (normal), 8-10 (mild), 11-15 (moderate), and 16-21 (severe) are the interpretations for the scores. The HADS[a] is a useful instrument for early detection and monitoring of mental health issues in individuals receiving therapy because a score above 8 suggests substantial symptoms.	Wk 0; wk 4

[a]HADS: Hospital Anxiety and Depression Scale.

"Adverse events," as defined by the World Health Organization [19], will be recorded from medical records, direct observation during classes, and by participants' self-reporting to document the safety of the intervention. The event may or may not be related to the intervention but may occur while the individual is participating in the intervention phase of the trial. Adverse events will be categorized as minor or serious, related or unrelated, and expected or unexpected. A minor adverse event is defined as an incident that occurs during the intervention but results in no injury or minor injury requiring no or minor medical intervention. A serious adverse event is defined as an incident that occurs during the intervention, resulting in death, serious injury, or hospitalization (eg, injurious fall resulting in fracture). Serious adverse events will also be recorded for the usual care group. In addition, adverse events will be reported and graded using the Common Terminology Criteria for Adverse Events Version 4 [20]. The consequences of a serious adverse event in the control group (eg, hospitalization and emergency-department admission) will be captured by the health service utilization questionnaire and medical record audit. Reasons for nonparticipation in an exercise session or noncompletion of the program will also be recorded (eg, pain, fatigue, and feeling unwell).

Participant Safety and Ethical Considerations

The quality of the water will be routinely observed and recorded. Until medically cleared, children with open wounds, central lines, or symptoms of skin infections will not be allowed to participate in aquatherapy. Before each session, a pediatric oncologist will check all participants for symptoms of fever or active infections. For emotional support during the first sessions, parents or other caregivers may be present. The research ethics board will be notified of all adverse events, mild or major. Before participating, families will be briefed on any possible dangers and asked to sign a form providing informed consent and assent. Periodically, a data safety monitoring team will examine events and make necessary protocol adjustments.

Consumer Perceptions

Semistructured interviews will be conducted twice before the intervention (week 0) and after the intervention (week 4), with participants in the aquatherapy group to explore their experiences with the program. A purposive sample of participants will be asked about satisfaction, perceived benefits, and the ease of participating in aquatherapy. The same group will be interviewed at both time points. Interviews will continue until data saturation is reached and no new themes emerge.

Sample Size Estimation

It is estimated that 54 participants will be required [1].

Sample size calculation for paired means (before-after) functional mobility.

The following formula was used:

$$n \geq [2(Z_{1-\alpha/2} + Z_{1-\beta})^2 / (\delta_diff / \sigma_diff)^2] + Z_{1-\alpha/2}^2 / 2$$

$$Z_{1-\alpha/2} = 1.96$$

$$Z_{1-\beta} = 1.64 \text{ at } 95\% \text{ power}$$

The mean difference (δ_diff) was 1.12 before and after the results as per the reference article. The SD (σ_diff) was 1.09.

$$n = 2 \times (1.96 + 1.64)^2 / (1.12 / 1.09)^2 = 24.55 = (1.96^2) / 2 = 1.92$$

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The sample size was 26.47≈27, and the minimum paired sample size needed was 27 for each group.

Statistical Analysis: Analysis of Quantitative Data

All statistical analyses will be conducted using SPSS (IBM Corp) or equivalent statistical software. Descriptive statistics will be used to summarize demographic variables and baseline characteristics. Continuous variables such as scores from the Pediatric Balance Scale and Aquatherapy (primary outcomes) as well as Functional Independence Measure for Children (WeeFIM) and Hospital Anxiety and Depression Scale (secondary outcomes) will be expressed as mean (SD). To assess within-group changes (before vs after the intervention), paired 1-tailed *t* tests will be applied if data are normally distributed; otherwise, Wilcoxon signed-rank tests will be used. For between-group comparisons (aquatherapy vs conventional physiotherapy), an independent *t* test will be used for normally distributed data, and Mann-Whitney *U* tests will be used for nonparametric distributions. In addition, the analysis of covariance may be used to adjust for any baseline differences. A *P* value of <.05 will be considered statistically significant.

Results

The trial has not yet commenced and will commence in October 2025.

Discussion

Anticipated Findings

The functional mobility and balance of children receiving therapy for ALL can be improved by a tailored intervention, as per this study. Our results could be consistent with earlier studies that demonstrate the advantages of virtual reality and exercise-based therapies in pediatric oncology rehabilitation [1]. Rehabilitation techniques have been found to improve balance and motor function impairment resulting from chemotherapy-induced neurotoxicity, such as vincristine-induced peripheral neuropathy [5]. Physical activity during cancer therapy has been found to reduce some of the adverse effects of ALL treatments [6]. Furthermore, research on the effects of exercise programs, such as aquatherapy and plyometric exercises, has shown that children who have survived cancer have significantly increased bone mineral density and functional capacity [13]. This study proposes that children receiving treatment for ALL may benefit in terms of physical health from structured movement-based therapy.

These findings have clinical relevance as they support the value of structured rehabilitation programs in pediatric oncology settings. Prior research has highlighted the need for incorporating exercise therapies into standard cancer care to improve overall survival and quality of life [13]. The study suggests how aquatherapy can improve motor function, balance, and general physical activity in this susceptible group when the intervention is conducted in the induction and consolidation stages of treatment. Exercise therapies have been shown to dramatically improve physical results in children with ALL, and aquatherapy may provide extra advantages because of its supportive setting, which promotes mobility while reducing joint stress. This study may prove beneficial for developing evidence-based rehabilitation plans that improve the functional recovery and quality of life for young patients with ALL.

Strengths and Limitations

For pediatric patients, virtual reality–based rehabilitation offers an interesting and feasible approach, much like research that uses interactive and technology-assisted exercise regimens [8-10]. The results highlight the importance of rehabilitation techniques in standard cancer care and add to the body knowledge on physical activity therapy in ALL patients [11-14]. To ensure reliable data collection and analysis, our study used validated mobility and balancing measurements. This study backs earlier findings about the advantages of exercise-based therapies for childhood malignancies, including ALL [15-17].

Our findings might not be as applicable to a larger group of pediatric patients with ALL owing to the small sample size. The immediate postintervention results were the main focus of our investigation; long-term advantages or the sustainability of gains were not evaluated [18,19]. Several variables that could affect the results of the rehabilitation were not considered, including variations in chemotherapy regimens, dietary state, and psychosocial support [20-25].

Conclusions

Aquatherapy is a rapidly growing area that may have many positive impacts among individuals with ALL undergoing chemotherapy. This trial has the potential to inform future models of cancer rehabilitation mainly aquatherapy intervention, which can be implemented in health services to improve access to aquatherapy for patients with ALL.

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Authors' Contributions

Conceptualization: SH, SSK
Data curation: SSK, SH

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Funding acquisition: SH, NU
Investigation: SSK, SH
Methodology: SSK, SH, NU
Project administration: SSK, SH
Software: SSK, SH
Supervision: SH, NU
Validation: SH, NU
Visualization: SH
Writing—original draft: SSK, SH
Writing—review and editing: SSK, SH

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Intervention Trials) checklist.
[PDF File (Adobe PDF File), 80 KB - resprot_v14i1e75877_app1.pdf]

Multimedia Appendix 2
Institutional ethics committee certificate.
[PDF File (Adobe PDF File), 215 KB - resprot_v14i1e75877_app2.pdf]

Multimedia Appendix 3
Clinical Trial Registry India registration.
[PDF File (Adobe PDF File), 149 KB - resprot_v14i1e75877_app3.pdf]

Multimedia Appendix 4
Informed consent form.
[PDF File (Adobe PDF File), 91 KB - resprot_v14i1e75877_app4.pdf]

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Abbreviations

ALL: acute lymphoblastic leukemia
CONSORT: Consolidated Standards of Reporting Trials
SPIRIT: Standard Protocol Items: Recommendations for Intervention Trials
WeeFIM: Functional Independence Measure for Children

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Protocol

Efficacy of Fuzheng Quxie Formula Against Postoperative Metastasis of Lung Cancer in Stage IIA-IIIA With Negative Driver Genes: Protocol for a Multicenter, Double-Blind, Randomized Controlled Trial

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Abstract

Background: Metastasis is the primary cause of poor prognosis and high mortality in lung cancer. Surgery with postoperative adjuvant chemotherapy is the standard treatment for patients with stage IIA-IIIA lung cancer with negative driver genes. However, recurrence rates remain significant. In China, traditional Chinese medicine shows potential as an adjuvant therapy to reduce treatment toxicity and improve clinical efficacy.

Objective: This study aimed to evaluate its efficacy and safety in preventing postoperative metastasis in driver gene-negative stage IIA-IIIA lung cancer, based on the promising preclinical results of Fuzheng Quxie Formula against lung cancer metastasis. In this trial, we hypothesize that the treatment group will have better efficacy and safety than the control group.

Methods: A multicenter, double-blind, randomized, placebo-controlled parallel group trial will be conducted. Eligible patients will be randomized into a treatment group (daily Fuzheng Quxie Formula granules+regular chemotherapy) and a control group (daily Chinese medicine placebo granules+regular chemotherapy) in a ratio of 1:1. Fuzheng Quxie Formula will be administered orally, twice a day, in the morning and evening, for 6 months. Patients will be followed up after the end of treatment for 18 months. After the end of the program, follow-up will be continued for 5 years or until the patient dies (or progressed). The primary efficacy endpoint is disease-free survival, and the secondary efficacy endpoints are overall survival, minimal residual disease, circulating tumor cells, Chinese medicine symptom score, quality-of-life assessment, immune indicators, tumor markers, peripheral blood systemic immune-inflammation index, and prognostic nutritional index. We will conduct per-protocol analyses on these outcomes. In addition, we will also evaluate the safety of the Fuzheng Quxie Formula.

Results: This study began screening and recruitment in March 2023. Recruitment is ongoing; by the end of 2024, a total of 180 eligible participants will be enrolled. Recruitment will continue until the end of June 2025 or until the target sample is reached. We estimate that the results will be published by March 2026.

Conclusions: This study is a high-quality, large-scale, multicenter, double-blind, randomized controlled trial. This will be the first trial to evaluate the efficacy and safety of Fuzheng Quxie Formula in inhibiting metastasis after surgery in stage IIA-IIIA lung cancer with negative driver genes. Provide a basis for the clinical application of Fuzheng Quxie Formula.

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Trial Registration: ClinicalTrials.gov NCT06381960; https://clinicaltrials.gov/study/NCT06381960
International Registered Report Identifier (IRRID): DERR1-10.2196/66342

(JMIR Res Protoc 2025;14:e66342) doi:10.2196/66342

KEYWORDS
traditional Chinese medicine; Fuzheng Quxie Formula; lung cancer metastasis; negative driver genes expression; efficacy; safety

Introduction

Background and Rationale

Lung cancer is one of the most common malignant tumors of the respiratory system, with the mortality rate perennially ranking first among all kinds of malignant tumors, which greatly threatens the safety of human life [1]. In developed countries (such as the United States), lung cancer is still the malignant tumor with the highest number of deaths [2]. In China, the latest data shows that there are about 787,000 new cases of lung cancer, with an incidence rate of 57.26/100,000, ranking first in the national morbidity and cause of death by gender, causing economic losses of up to 221.4 billion, and this economic and social pressure will continue to increase [3].

International guidelines for the diagnosis and treatment of lung cancer recommend that radical surgery is the first choice for stage I-IIIA non–small cell lung cancer (NSCLC). Stage IA NSCLC does not require postoperative adjuvant chemotherapy, while stage IB (high-risk) NSCLC could consider receiving postoperative adjuvant chemotherapy. Stages IIA to IIIA NSCLC must undergo postoperative adjuvant chemotherapy. Stages IIIB-IV NSCLC are treated with nonsurgical therapy as the standard first-line treatment [4]. Stage IIA-IIIA NSCLC has a moderate to high risk of recurrence [5]. Studies have shown that the 5-year recurrence rate for patients with stage I lung cancer after adjuvant chemotherapy is approximately 17.8%, while approximately 45.5% of patients with stage II-III lung cancer may experience metastatic recurrence within 5 years [6]. Data from a survival follow-up study of 7753 patients with lung cancer surgery conducted by Wang Zhezhou's team showed that the 5-year survival rates for patients with stage IIA, IIB, and IIIA lung cancer were 78.2%, 62.9%, and 49.3%, respectively. As such, postoperative standard chemotherapy for patients with stage IIA-IIIA lung cancer demonstrates limited efficacy in preventing recurrence and metastasis following curative surgery. In addition, chemotherapy is associated with significant toxicity, making it difficult for many patients—particularly the older adults and frail—to tolerate or accept. Therefore, postoperative standard chemotherapy exhibits overall poor efficacy in preventing recurrence and metastasis following curative lung cancer surgery in stage IIA-IIIA. With the continuous advancement of targeted therapy and immunotherapy, some patient groups have benefited from these treatments, and the clinical treatment landscape is gradually improving. However, an urgent clinical challenge remains, and patients with negative driver genes and extremely low PD-1 (programmed death-1)/L1 (PD-1 ligand) expression (1%) often fail to achieve optimal therapeutic outcomes with current treatment modalities. There is an urgent need to develop effective treatment strategies to prevent postoperative metastasis in patients with lung cancer at stage IIA-IIIA who are negative for driver genes.

Traditional Chinese medicine has a long history of application in the prevention and treatment of tumors. Through long-term clinical practice, it has accumulated and developed a systematic theoretical framework and rich experience. Currently, its advantages in adjuvant chemotherapy have been recognized internationally—numerous studies have confirmed that traditional Chinese medicine offers multiple benefits in adjuvant chemotherapy, including reducing toxicity [7,8] and enhancing efficacy [9], combating chemotherapy resistance [10], regulating immunity, and improving quality of life and treatment tolerance [11].

Professor Jianhui Tian's group focuses on lung cancer metastasis research. Under the guidance of a master of Chinese medicine Liu Jiaxiang's academic idea of "treating cancer by reinforcing healthy qi," and incorporating Lao Zi's "Existence and nonexistence give birth the one to the other," modern oncology and immunology, professor Jianhui Tian's group suggests the core pathogenesis of cancer metastasis in the subclinical stage of cancer —"Deficiency of Vital Qi and Hidden Toxin" theory. According to the theory, immune disorders caused by immune senescence and immune escape are "Deficiency of Vital Qi," while circulating tumor cells, quiescent cancer cells, and tumor stem cells are the modern biological connotations of "hidden toxicity." The residual cancer cells after radical treatment of lung cancer are the "Hidden Toxin." After radical lung cancer surgery, residual cancer cells (hidden toxin) are latent in the body and in a dormant or quiescent stage. When there is a deficiency of vital qi, the efficiency of immune surveillance and immune clearance decreases, and the cancer cells go from the quiescent phase to the proliferative phase, leading to the occurrence of tumor metastasis. Professor Jianhui Tian's group further found that myeloid-derived suppressor cells, regulatory T cells, and circulating tumor cells ("hidden toxin") are important factors in the subclinical state of lung cancer metastasis in clinical studies, and analyzed their expression patterns. The group took the lead in establishing the world's first human lung adenocarcinoma circulating tumor cell line (CTC-TJH-01), as well as a platform for metastasis-specific studies of lung cancer.

Under the theory of "Deficiency of Vital Qi and Hidden Toxin," the group established the treatment method of "supporting vital qi" and "dispelling hidden toxin," and created a Chinese medicine formula, "Fuzheng Quxie Formula," for inhibiting postoperative metastasis of early- and middle-stage NSCLC. In this formula, Sheng Huang Qi, Fu Ling, Bai Zhu tonify spleen and stomach to "strengthen earth to generate metal;" Bei Sha Shen, Tian Dong, Mai Dong nourishes yin and moistens the

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lungs; Hai Zao, Xia Ku Cao, Kun Bu, which soften and resolve hard mass, and Bai Hua She She Cao, Shi Jian Chaun, Shi Shang Bai, which clear heat, detoxifying to disperse nodules. This formula is primarily indicated for patients with lung cancer presenting with clinical manifestations of qi and yin deficiency syndrome. The specific diagnostic criteria for qi and yin deficiency syndrome are detailed in the inclusion criteria section. Through in-depth clinical and basic research, the team has obtained the scientific basis for Fuzheng Quxie Formula to inhibit metastasis: (1) Fuzheng Quxie Formula has the clinical effect of preventing recurrence and metastasis: the group, in cooperation with Shanghai Lung Hospital, carried out a prospective clinical study, which confirms that the disease-free survival (DFS) rates of early- and middle-stage patients with NSCLC after intervention with Fuzheng Quxie Formula were 98.8% and 96.5% in 1 and 2 years, respectively, which were higher than 95.3% of the patients in the pure follow-up group. (2) The mechanism of inhibiting metastasis by Fuzheng Quxie Formula may be to regulate the immune function to promote apoptosis of circulating tumor cells: intragroup comparison of immune indexes before and after the study suggests that the peripheral blood natural killer, $CD3^+$ T cells and IgM content of the treatment group after intervention of Fuzheng Quxie Formula increased significantly ($P<.01$), and at the same time, it can reduce the number of circulating tumor cells in the blood ($P<.01$), suggesting that Fuzheng Quxie Formula has the tendency to regulate patients' immunity and inhibit circulating tumor cells to control tumor progression; (3) mechanism study found that Fuzheng Quxie Formula can improve immune function and restore the state of body immune balance: Fuzheng Quxie Formula can up-regulate the expression of positive immune cells, such as natural killer cells and T cell subpopulations, which have an inhibitory and killing effect on tumor cells, and down-regulate positive immune cell expressions, which promote tumor cell proliferation, metastasis, immune escape, and so forth, downregulate the expression of negative immune cells such as myeloid-derived suppressor cells and regulatory T cells, which promote the proliferation, metastasis and immune escape of tumor cells; inhibit and remove circulating tumor cells in the peripheral circulation; and influence and regulate the metabolic reprogramming of tumor cells in terms of sugar, fat and amino acids. Meanwhile, the theory of "Deficiency of Vital Qi and Hidden Toxin" guided the construction of clinical efficacy prediction and metastasis risk assessment model for traditional Chinese medicine (TCM) treatment of lung cancer, which found that maintaining peripheral immune homeostasis is an important basis for TCM to inhibit lung cancer metastasis, and optimized and enriched the prognostic assessment system of lung cancer.

Fuzheng Quxie Formula has been applied as an in-hospital preparation for many years and has successfully entered the process of joint development of new drugs with enterprises. Therefore, in response to the urgent clinical needs of postoperative patients with IIA-IIIA NSCLC who are negative for driver gene expression, we attempted to objectively evaluate the efficacy of Fuzheng Quxie Formula in inhibiting metastasis of IIA-IIIA NSCLC who are negative for driver gene expression and safety.

Objectives

This study will be the first trial to evaluate the efficacy and safety of Fuzheng Quxie Formula in inhibiting metastasis after surgery in stage IIA-IIIA lung cancer with negative driver genes.

Primary Objective

The primary objective of this study was to demonstrate that the use of Fuzheng Quxie Formula can prolong the DFS of patients with negative driver genes in stage IIA to IIIA lung cancer.

Secondary Objectives

Comparing the overall survival (OS), minimal residual disease (MRD), circulating tumor cell assay, Chinese medicine symptom score, quality-of-life assessment, immune indicators, tumor markers, systemic immune-inflammation index (SII), and prognostic nutritional index (PNI) between the 2 groups of patients. Further evaluate the clinical efficacy of the tonifying and detoxifying formula in the prevention and treatment of lung cancer metastasis, and simultaneously verify its safety in application.

Methods

Trial Design

A prospective clinical study of combined Chinese and Western medicine for the prevention and treatment of metastasis after radical lung adenocarcinoma in patients with postoperative stage IIA-IIIA NSCLC adenocarcinoma with negative driver gene expression is being conducted in a randomized, double-blind, placebo-parallel controlled, multicenter clinical trial design (Figure 1). First, the clinical study will obtain written informed consent from the participants. Eligible participants will be randomly assigned in a 1:1 ratio to the treatment group (daily Fuzheng Quxie Formula granules+regular chemotherapy) and the control group (daily Chinese medicine placebo granules+regular chemotherapy). The TCM treatment period is 6 months, with follow-up at the end of the period, which is 18 months. After the end of the program, follow-up will continue for 5 years or until the participant dies (or progresses).

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Figure 1. Study flowchart. DFS: disease-free survival; OS: overall survival; MRD: minimal residual disease; SII: systemic immune-inflammation index; NSCLC: non–small cell lung cancer; PNI: prognostic nutritional index; QoL: quality-of-life assessment.

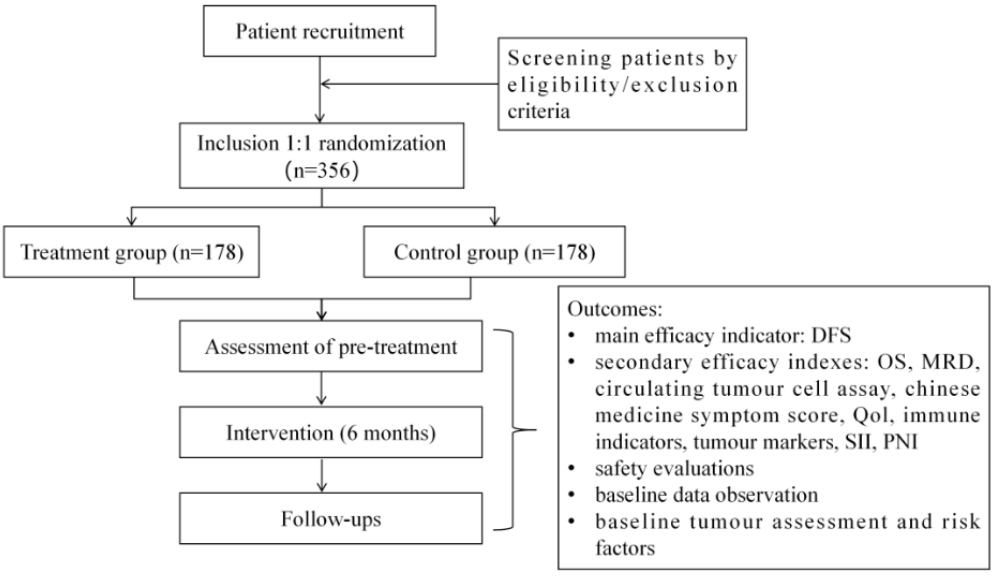

Sample Size

The calculation of the sample size of this clinical trial is based on the statistical results of the "Chinese Medicine Clinical Research on Common Malignant Tumors (Lung Cancer)" conducted by this group in the third round of the Shanghai 3-year action plan of traditional Chinese medicine. Based on the group's previous clinical research on the survival and immune function effects on patients after radical NSCLC surgery, the 5-year DFS rate was 90.2% in the treatment group and 78.3% in the control group. Sample size was calculated using PASS 15 software (NCSS, LLC), and survival-2 survival curves-test (inequality)-log-rank tests were applied. The values were set as follows: power=0.8, α=0.025 (unilateral), according to the control group and experimental group 1:1, combined with the basis of the previous research, taking the proportion surviving as input type, S1 (proportion surviving: control)=0.783, S2 (proportion surviving: treatment)=0.90, T0 (survival time)=5 years, accrual time (integers only)=2 years, uniform enrollment, the rate of shedding in each group is 10%, the calculation can be calculated to obtain a total sample size of 317 cases, 158 cases in the treatment group and 159 cases in the control group. At the same time, there are 5 clinical trial centers in this study. According to the sample size estimation requirements of multifactorial analysis, the introduction of one more confounding factor needs to increase the sample size of each group by 15-25 cases, and this study considers an increase of 20 cases in each group. Therefore, 178 cases need to be collected in each group, and the total sample size of the 2 groups is 356 cases (Table 1).

Table 1. Sample size estimation for each center.

Research center	Treatment group, n	Control group, n	Total, n
Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine	38	38	76
Shanghai Lung Hospital of Tongji University	35	35	70
Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine	35	35	70
Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine	35	35	70
Shanghai Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine	35	35	70
Total	178	178	356

Assignment of Interventions: Allocation

Sequence Generation

The stratified random grouping scheme used in this study was prepared by a statistician. The entire study population that met the inclusion criteria was allocated according to the stratified random grouping scheme. The sample size of each stratum was a multiple of the number of groups. The stratification factors were different subcenters. The randomization scheme was prepared by a teacher of medical statistics not related to the data management and statistical analysis of this trial, and a random table was generated by SPSS software (IBM Corp), with the treatment group: the control group in a ratio of 1:1 to generate a random code by using the method of zone group randomization.

Concealment Mechanism

The selected block lengths and randomized seed parameters are sealed together in a blinded base as confidential data. After

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blinding, the blinders of the statistical unit hand over the sealed blinds, including the primary and secondary blinds based on the randomization number, to the unit responsible for the clinical study, and the blinds are sealed in duplicate at the unit responsible for the clinical study.

Implementation

The entire study population that met the inclusion criteria was allocated according to the stratified random grouping scheme.

Assignment of Interventions: Blinding

Who Will Be Blinded

This study was a double-blind trial, and neither the investigator nor the study population had access to subgroup information. Patient grouping is usually performed by third-party institutions or independent research teams. A 2-level blinded design was used, with the first level being the group corresponding to each case number (eg, group A or group B) and the second level being the treatment corresponding to each group (test or control). The randomized coding table was created by the statistical unit, and the 2 levels of blinded bottoms were individually sealed in duplicate and stored in the team leader's unit and in the quality control office, respectively.

Procedure for Unblinding if Needed

When all the case report forms (CRFs) were entered into the database, and after questioning, verification, and blinding audit, the data were locked, and the first unveiling of blinding (ie, clarifying groups A and B) was carried out by the staff member who kept the blinded bottoms, which was handed over to biostatisticians to enter into the computer, and then statistically analyzed after linking up with the data files.

Blinding may be broken in emergency situations when the investigator believes that knowledge of the medication taken by the participant is beneficial for the management of adverse events. This should be done by the investigator, and a detailed record of the reason, time, and place of the blind breaking should be recorded and signed. Within 24 hours of the blinding, the responsible (lead) unit of the clinical trial and the clinical supervisor, as well as the statistically relevant personnel, should be notified, and the reason for the blinding should be explained. Once the contingency letter has been opened, the numbered participant will be withdrawn from the trial and treated as a dropout case, and the investigator should record the reason for withdrawal on the case report form. All contingency letters will be retrieved at the end of the trial, along with the case report form for blinded audit at the end of the trial.

Participants

Recruitment

The sources of cases for this study were inpatients and outpatients admitted from March 1, 2023, to June 30, 2025, with negative expression of driver genes in postoperative stage IIA-IIIA lung adenocarcinomas with qi and yin deficiency. Inclusion for observation should be no later than 6 weeks postoperatively.

Study Setting

Participants were selected from 5 study centers: Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine; Shanghai Lung Hospital of Tongji University; Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine; Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine; Shanghai Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine.

Eligibility Criteria

In total, 356 patients will be included in the clinical trial by the research team members if they meet the study criteria. Screening will be based on inclusion and exclusion criteria (Textbox 1).

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Textbox 1. Study inclusion and exclusion criteria.

Inclusion criteria

- Patients with clinical staging of stage IIA-IIIA lung adenocarcinoma after radical surgery, within 6 weeks after surgery;
- Driver gene negative (no epidermal growth factor receptor, Anaplastic Lymphoma Kinase, ROS Proto-Oncogene 1 mutations), PD-1/L1 expression <1%;
- Fulfilling the diagnostic criteria for Qi-Yin deficiency syndrome, the primary symptoms are cough, little phlegm, shortness of breath, voice trailed off, weakness, and thirst without wanting to drink. Secondary symptoms include spontaneous sweating, night sweating, 5 upset hot symptoms, red tongue or teeth marks on the sides of the tongue, and a weak pulse. At least 2 primary symptoms and one of the secondary symptoms are present;
- Patients aged between 18 and 75 years;
- Patients with basically normal blood and biochemical indicators, without serious viral or bacterial infections; without organ failure and serious heart disease (blood bilirubin <68 μmol/L, aspartate aminotransferase<90 IU/L, creatinine <350 μmol/L, leukocyte count>3.5×109/L and <12×109/L, platelet count>80×109/L, erythrocyte pressure >0.20);
- Those with a tumor performance status score 2 and no other serious comorbidities;
- The patients themselves gave informed consent to participate in the study by signing an informed consent form with good compliance.
- Patients who are lactating and not pregnant;
- Passing the chemotherapy-related indicators;
- Those who have no allergic reaction to the ingredients in the formula.

Exclusion criteria

- Patients who are being treated with other drugs or therapies (including other Chinese herbal medicines, immunological drugs, radiotherapy, etc);
- Patients who are themselves mentally ill and have a lack of autonomous behavior;
- Women who are pregnant, preparing for pregnancy, or breastfeeding;
- Combined heart, lung, brain, liver, kidney, and hematopoietic system, and other serious diseases, and psychiatric patients;
- Allergic or known hypersensitivity to the components of the drug;
- Patients who are participating in other clinical trials or have participated in other clinical trials within 3 months;
- Alcohol or psychoactive substance abuse, drug abusers, and dependent persons;
- Other pathologies or conditions that, in the judgment of the investigator, have the effect of reducing the likelihood of enrolment or complicating enrolment, for example, frequent changes in the work environment, unstable living conditions, and other conditions that predispose to loss of visits.

Who Will Take Informed Consent?

They will be informed in detail about the content and precautions of this clinical trial before they decide whether or not to participate in this study. They will be informed that participation in the study is entirely voluntary and that they may withdraw from the study at any time during the treatment period without loss of follow-up medical care or other benefits, and that they will continue to be effectively treated by their doctor in accordance with normal medical procedures. If willing to participate in this study, they will sign an informed consent form.

Who Was Excluded After Joining the Trial?

Cases in which participants were found not to meet the inclusion criteria after enrollment; The use of prohibited medicines specified in the protocol (eg, other Chinese herbal medicinal tablets, immunotherapeutic drugs) needs to be excluded due to violation of the clinical trial protocol; cases that have not used the drug after inclusion need to be excluded; cases without any evaluable record after taking the drug. Reasons should be given for the exclusion of cases, and their CRF forms should be kept for reference. Those who will not be statistically analyzed for efficacy, but who have received at least one treatment with at least one safety record, may participate in the analysis of adverse reactions.

Dropout Criteria

A participant who meets the inclusion criteria but does not complete the trial for some reason is considered a dropout. It includes both cases where the participant withdraws on his or her own and cases where the investigator determines that the participant has withdrawn.

Conditions for Suspension of the Trial

Trial suspension refers to the stopping of a clinical trial in the middle of a trial that has not yet been completed as planned. The purpose of trial suspension is mainly to protect the rights and interests of the participants, ensure the quality of the trial, and avoid unnecessary economic losses. Discontinuation of the trial is required in the following cases: (1) serious safety problems occurred in the trial, the trial should be promptly suspended; (2) the trial found that the drug treatment effect is too poor, or even ineffective, does not have clinical value, the

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trial should be discontinued, on the one hand, to avoid delaying the effective treatment of participants, while avoiding unnecessary economic losses; if there is a disease progression or serious adverse reactions can be initiated by the withdrawal of the protection mechanism, that is, the inclusion of evaluable cases, the later assessment of efficacy data to invalid for carry-over. The lack or loss of efficacy is assessed by the investigator (not the participant). (3) Significant errors in the clinical trial protocol are identified during the trial, making it difficult to evaluate drug effects; or a well-designed protocol has undergone important deviations in its implementation, and further continuation makes it difficult to evaluate drug effects; (4) the sponsor requests suspension (eg, financial reasons and management reasons); and (5) withdrawal of the trial by the administrative authority, etc.

Interventions

Trial Grouping

In the treatment group, patients received daily granules of Fuzheng Quxie Formula+regular chemotherapy, and in the control group, patients received daily Chinese medicine placebo granules+regular chemotherapy.

Trial Drug

The trial drug was Fuzheng Quxie Formula granules. Components of Fuzheng Quxie Formula granules are shown in Table 2. The drug was supplied by Jiangyin Tianjiang Pharmaceutical Co. All trial medications were provided as blinded and met quality requirements.

Table 2. Components of Fuzheng Quxie Formula.

Chinese name	Latin name	Parts of the substances	Amount (g)
Sheng Huang Qi	*Udis astragalus*	Root	15
Dang Shen	*Codonopsis pilosula*	Root	15
Jiao Bai Zhu	*Frixum atractylodes*	Root tuber	15
Bai Fu Ling	*Alba poria*	Root tuber	15
Bei Sha Shen	*Adenophora septentrionalis*	Root	15
Zhe Mai Dong	*Ophiopogon japonicus*	Root tuber	15
Hai Zao	*Alga*	Dried algae	15
Xia Ku Cao	*Prunella vulgaris*	Flowering fruit spike	15
Sheng Mu Li	*Udis ostreis*	Shell	15
Shi Jian Chuan	*Ishimi chuan*	Above-ground parts	15
Shi Shang Bai	*Cupressus lapis*	Whole herb	15
Shu Yang Quan	*Shuyang spring*	Whole herb	15

Explanation for the Choice of Comparators

Patients in the control group will receive placebo capsules in addition to chemotherapy. Since all study patients are allowed to be further treated with chemotherapy, there are no ethical concerns about this control condition. In total, 5% of the drug content of the treatment group was made into a control placebo drug, provided by Jiangyin Tianjiang Pharmaceutical Co, Ltd, which had the same odor, color, and appearance as the test drug, but had no significant drug treatment effect.

Method of Administration

Daily granules of Fuzheng Quxie Formula or daily Chinese medicine placebo granules are administered concurrently with regular chemotherapy.

Chemotherapy regimen selection will be selected according to National Comprehensive Cancer Network guidelines, and patients will be treated with platinum-based chemotherapy according to one of the following regimens for 3 weeks each for 4 cycles: (1) NP regimen includes vincristine, 25 mg/m^2 on day 1, cisplatin, 75 mg/m^2 on day 1; (2) GP regimen includes gemcitabine, 1250 mg/m^2 on days 1 and 8, and 75 mg/m^2 on day 1; (3) DP regimen includes docetaxel, 75 mg/m^2 on day 1 and cisplatin, 75 mg/m^2 on day 1; (4) AP regimen includes pemetrexed, 500 mg/m^2 and cisplatin, 75 mg/m^2 on day 1; and (5) TC regimen includes paclitaxel, 200 mg/m^2 on day 1 and carboplatin, area under the curve 6 on day 1, and patients intolerant of cisplatin will be given area under the curve 5-6 on day 1, area under the curve 5-6 given carboplatin. All chemotherapeutic agents will be administered intravenously in both groups. The chemotherapeutic agents were administered strictly according to the appropriate instructions and National Comprehensive Cancer Network guidelines for recommended dosage, duration, and usage. These chemotherapy regimens are all recommended as equivalent standard chemotherapy regimens for first-line treatment of lung cancer. The core focus of this study is to evaluate the efficacy of adding a traditional Chinese medicine intervention to such standard chemotherapy. We allow research centers to select specific standard regimens (such as NP, GP, etc) based on routine practice to enhance the practicality and generalizability of the study.

For oral administration of traditional Chinese medicine, each bag was soaked in 400 mL of boiling water at 100 °C for 20 minutes, divided into 2 portions, each with a content of 200 mL. 200 mL was taken orally twice a day, in the morning and in the evening.

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Test Period

The Chinese medicine treatment period is 6 months. The follow-up period is 18 months after the end of dosing. After the end of the program, follow-up will continue for 5 years or until the participant dies (or progresses).

Criteria for Discontinuing or Modifying Allocated Interventions

First, during the course of medication, if the participant develops an aggravation of the condition, he or she should discontinue the use of the test drug, complete the postevaluation of the efficacy and the relevant laboratory tests to end the trial, and the participant will be counted as an invalid eligible case for inclusion in the compliance with the protocol set (PPS). Second, if the investigator believes that other circumstances make it inappropriate for the participant to continue using the test drug.

Strategies to Improve Adherence to Interventions

We will provide medication to enrolled patients during the treatment period. During this period, the researcher will make regular follow-up visits.

Relevant Concomitant Care Permitted or Prohibited During the Trial

On the one hand, during the trial, drugs that affect the evaluation of therapeutic efficacy, such as unapproved chemotherapeutic drugs, targeted drugs, bio-immune agents, TCM, and other drugs that are clearly indicated in the instructions to be used for antitumor purposes, shall not be used in combination. On the other hand, detailed records should be made of the combined diseases or symptoms that existed before the start of the trial, and the drugs or other therapies that need to be continued or added must be recorded in the case report form with the generic name of the drug or the name of the other therapies, the dosage, the reason for use, the number of times of use, and the time of use, etc, so that they can be analyzed and reported at the time of the summary.

Provisions for Posttrial Care

After the clinical trial ends, if patients still require outpatient or inpatient care, they will continue to be seen by a physician. Any injuries that occur during participation will be covered by the trial insurance.

Outcomes

The Primary Efficacy Endpoint

The primary efficacy endpoint is DFS. Refers to the time between the start of randomization and disease recurrence or death (from any cause). Imaging was performed using chest CT examination before the start of treatment and every 6 months after surgery. Patients found to have recurrent metastases were discharged from the group for standardized treatment when the pathological diagnosis was clear. Observation and follow-up until 5 years after surgery, DFS, and median survival calculation.

The Secondary Efficacy Endpoints

The secondary efficacy endpoints include OS, MRD, circulating tumor cell assay, Chinese medicine symptom score, quality-of-life assessment, immune indicators, tumor markers, SII, and PNI.

OS

Endpoint indicator, defined as the time from the start of randomization to death due to any cause. Overall survival and median survival calculations were performed with observational follow-up for up to 5 years postoperatively.

MRD

The second-generation sequencing (next-generation sequencing) method is used to detect MRD in the peripheral blood of the study participants to obtain a superior population screening model for TCM treatment.

Circulating Tumor Cell Assay

Circulating tumor cells will be detected once before and once after the intervention.

Specimen Collection Method

A total of 10 mL of venous blood was taken from the patient's median elbow vein with an ethylenediaminetetraacetic acid blood collection tube. The blood collection tube was repeatedly inverted and mixed, centrifuged at 2000g for 10 minutes, the supernatant was retained, and to further remove the redundant cellular components, it was centrifuged again at 8000 *g* for 10 minutes. Separated plasma was frozen and stored at –80 ℃ or extracted immediately according to the extraction kit instruction steps, respectively. The remaining blood cells should be added to saline to replenish 10ml, and then immediately isolate the circulating tumor cells.

Chinese Medicine Symptom Score

According to the “Shanghai TCM disease diagnosis and treatment routine,” 10 TCM symptoms of cough, sputum, chest pain, chest tightness, shortness of breath, fatigue, loss of appetite, insomnia, thirst, and spontaneous sweating were observed, and the severity was scored as 0-3, which was recorded once before and 6 months after the intervention.

Significant Effect

A reduction of the Chinese medicine symptom score greater than or equal to 70% after the intervention will be considered a significant effect.

Effective

A reduction of the Chinese medicine symptom score of greater than or equal to 30% and less than 70% after the intervention will render the treatment effective.

Ineffective

A reduction of the Chinese medicine symptom score of less than 30% after the intervention or an elevation in the score compared to the previous one will render the treatment ineffective.

Quality-of-Life Assessment

The quality-of-survival scale for patients with lung cancer EORTC QLQ-LC43 was used, which consists of EORTC QLQ-C30 (core scale) and EORTC QLQ-LC13 (the characteristic subscale of lung cancer). It mainly scores for

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patients with lung cancer on 5 domains related to functioning, general clinical symptoms, characteristic subsymptoms, general health status, and financial difficulties, and is recorded once before and 6 months after the intervention. The higher the score of function-related domains, the worse the function of the organism; the higher the score of general clinical symptoms and characteristic subsymptoms, the more serious the symptoms; the higher the score of general health status, the better the status; the higher the score of economic hardship status, the more difficult the economic hardship.

Immune Indicators

Cellular immunity (CD3, CD4, CD8, CD16, and CD56), regulatory T cells, myeloid-derived suppressor cells, natural killer cells, interleukin (IL)-1, IL-2, IL-6, IL-8, IL-10 Will be assessed once before and 6 months after intervention.

Tumor Markers

The following tumor markers will be assessed before and after treatment: CEA, CA125, CA153, Cyfra21-1, and SCC. At least 1 test will be performed before the intervention and 6 months after the intervention.

SII and PNI

The inflammatory response, immune status, and nutritional status of the body affect the tumor microenvironment and the prognosis of patients with tumors. Studies have shown that tumor-associated inflammation, especially host-associated systemic inflammation, is closely related to tumor development and progression, as well as the survival of cancer patients. SII is a comprehensive immune-inflammatory index, calculated based on the results of platelet, neutrophil, and lymphocyte counts. SII is a more objective predictor of the prognosis of patients with various types of tumors. It represents the balance between inflammation and immunity in patients with tumors. Inflammation, in turn, can influence tumor progression by affecting the host's immunity and response to antitumor therapy. PNI is a nutritional prognostic indicator that can be used to reflect the nutritional and immune status of patients with tumors and is calculated from serum albumin and circulating lymphocyte counts. PNI is a nutritional prognostic indicator that can be used to reflect the nutritional and immune status of patients with tumors. Malnutrition is very common in patients with malignant tumors, especially advanced tumors. Day plays a crucial role in the process of tumor progression. There is also a relationship between tumor-associated inflammation and nutritional status. Studies have shown that tumor-secreted inflammatory mediators, including tumor necrosis factor and IL-6, lead to a loss of appetite and affect nutritional intake. Nutritional and immune status are associated with tumor progression and prognosis. The formula is as follows:

SII=peripheral blood platelet count (×10/L)×peripheral blood neutrophil count (×10/L)/peripheral blood lymphocyte count (×10%/L).

PNI

Serum albumin (g/L) + Lymphocyte count (10/L)×5.

Critical values were calculated based on receiver operating characteristic curves, and based on the critical values, the above indices were divided into high-level and low-level groups.

Baseline Data Observation

Demographic data such as gender, age, height, weight, and so on, were assessed. Vital signs such as blood pressure, heart rate, respiration, and so on were monitored. General clinical data included comorbidities and medications, and so on. Other data included information about education level, marital status, and so on.

Baseline Tumor Assessment and Risk Factors

Time of diagnosis, pathological type, degree of differentiation, tumor node metastasis classification of tumor, gene mutation status, comorbidities, surgical procedure, history of preoperative adjuvant therapy, smoking status, and family history of illness.

Safety Indicators

Blood routine analysis, liver and kidney function tests (including alanine aminotransferase, aspartate aminotransferase, glutamyl transpeptidase, blood creatinine, urea nitrogen, urinary protein, etc), electrocardiography, and monitoring of adverse events and serious adverse events (with detailed records at any time) Will be carried out once before the test, once every month during the treatment period, and once every 6 months during the follow-up period.

Participant Timeline

Before the commencement of the trial, researchers must develop a study protocol and clearly define the participant timeline. The participant timeline for this study is presented in Table 3.

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Table 3. Participant timeline for this trial.

Trial stage	Enrolment	Visiting period	Follow-up period	
	V[a]0	V1	V3	V4
Tine	D[b]0	6th month	12th month	18th month
Included or excluded cases	✓			
Sign the informed consent form	✓			
Randomization and blinding	✓			
Drug dispensing, drug recovery, and drug recording	✓			
Patient's condition inquiry	✓			
Tumor pathology information	✓			
Western treatment modalities	✓	✓	✓	✓
Cancer pain assessment Scale	✓	✓	✓	✓
KPS score[c]	✓	✓	✓	✓
Chinese Medicine Symptoms Questionnaire（MDASI-TCM[d]）	✓	✓	✓	✓
PET-CT[e] or CT examination	✓	✓	✓	✓
PFS[f] overall survival	✓	✓	✓	✓
Tumor marker	✓	✓	✓	✓
Immunological indicators	✓	✓	✓	✓
Safety assessment	✓	✓	✓	✓
Adverse event records		✓		

[a]V: visit.
[b]D: day.
[c]KPS*:* Karnofsky Performance Status.
[d]MDASI-TCM: MD Anderson Symptom Inventory for traditional Chinese medicine.
[e]PET-CT: Positron Emission Tomography-Computed Tomography.
[f]PFS: Postfinasteride syndrome.

Compliance

We will record the number of medications returned by participants to calculate usage rates. We will take measures to improve adherence, including asking them to complete a statement as part of the informed consent process, emphasizing the importance of completing the study.

Adverse Event Reporting and Harms

Safety Background Information Related to the Medicines Used in the Trial

According to the preclinical study, clinical trial information, and drug composition, it is necessary to pay attention to the observation of the changes in the hematopoietic system, digestive system, and urinary system of the patients during the trial, such as the number of red blood cells, hemoglobin content, blood creatinine and urea nitrogen, liver function, and so on.

Observation and Recording of Adverse Events

The investigator should carefully observe any adverse events occurring in the participants during the clinical study period and require the participants to truthfully reflect the changes in their condition after the administration of the drug, avoiding leading questions. While observing the efficacy, pay attention to the observation of adverse events or unanticipated toxic side effects (including symptoms, signs, and laboratory tests). Regardless of whether the adverse event is related to the test drug or not should be recorded in detail in the CRFs, including the time of the appearance of the adverse event, symptoms, signs, degree, duration, laboratory test indexes, treatment methods, after, results, follow-up time, etc, and should be recorded in detail in the case of the combined use of medication, in order to analyze the relevance of the adverse event to the test drug, the record should be signed and dated.

Medical Treatment of Participants

When adverse events are detected, the investigator may take necessary treatment measures according to the condition, such as adjusting the dosage, temporarily interrupting the medication, etc, and decide whether to terminate the trial. In the event of serious adverse events, the unit undertaking the trial study must immediately take the necessary treatment measures to protect the safety of the participants.

Judgment of Severity

Judgment of severity was based on the following criteria:

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1. Mild: mild discomfort, the participant can tolerate, does not affect the treatment, does not need special treatment, no effect on the participant's recovery.
2. Medium: moderate discomfort, intolerable to the participant, requiring special treatment, and having a direct impact on the participant's recovery.
3. Severe: severe discomfort, endangering the life of the participant, death or disability, requiring immediate emergency treatment.

Judgment of Causal Relationship With Drugs

Indicators of causal judgement in the determination of adverse events include (1) whether the time of initiation of the drug is reasonably related to the appearance of the suspected adverse reaction; (2) whether the suspected adverse reaction corresponds to the type of adverse reaction known for the drug; (3) whether the suspected adverse reaction can be explained by the effect of the combination of the drugs, by the patient's clinical condition, or by the effect of other therapies; (4) whether the suspected adverse reaction disappears or is alleviated by discontinuation or reduction of the dose; and (5) whether the suspected adverse reaction disappears or is alleviated after re-exposure to the drug. Whether the same reaction recurs after re-exposure to the suspected drug. Criteria for determining causality were established according to the above 5 judgment indicators in order (Table 4). Based on Table 4, we will determine the relationship between the following 5 levels of adverse events and the medicinal product, that are, 1: certainly related, 2: maybe related, 3: cannot be determined, 4: maybe not related, and 5: certainly not related. The incidence of adverse events was calculated using the total number of cases 1+2+3 as the numerator and all the enrolled cases available for adverse event evaluation as the denominator.

Table 4. Adverse event causation judgments.

Judgment results	Judgement indicators				
	1	2	3	4	5
Certainly relevant	Affirmative	Affirmative	Negative	Affirmative	Affirmative
Possibly relevant	Affirmative	Affirmative	Negative	Affirmative	Circumstances unknown
Undetermined	Affirmative	Affirmative	Difficult to affirm or deny	Difficult to affirm or deny	Circumstances unknown
Possibly irrelevant	Affirmative	Negative	Difficult to affirm or deny	Difficult to affirm or deny	Circumstances unknown
Definitely irrelevant	Negative	Negative	Affirmative	Negative	Negative

Based on the above table, the following 5 levels of adverse events were determined to be related to the drug that consists of 1: certainly related, 2: possibly related, 3: unable to determine, 4: possibly unrelated, and 5: certainly unrelated. The incidence of adverse reactions was calculated using the total number of cases 1+2+3 as the numerator and all the enrolled cases available for adverse reaction evaluation as the denominator.

Reporting and Handling of Adverse Events

The occurrence of any adverse event, such as the subjective discomfort of patients and abnormal laboratory tests, should be taken seriously, carefully analyzed, and immediate measures should be taken to protect the safety of the participants. Record in detail in the CRFs and retest in 24 hours and 7 days, and 14 days, as appropriate. Record its persistence, regression, and disappearance. Handling of serious adverse events: any serious adverse event that occurs during the trial must be reported immediately to the Medical Ethics Committee of the lead unit or the principal investigator by completing the Serious Adverse Event Report Form, and in the case of serious adverse reactions, to the State Food and Drug Administration within 24 hours. Notify the telephone number and contact person of the unit listed in the CRFs. When a patient has an emergency, the principal investigator of the research unit can open the emergency letter of the corresponding number taken by the patient (but there must be 2 witnesses present, and make corresponding records), according to the drug and the symptoms of the appropriate treatment, and notify the clinical monitor of the results of the treatment, and the researcher should be recorded in the case report form in detail on the reason for the breakthrough of blinding, date, treatment, results and sign. All adverse events should be followed up on until they are properly resolved or the condition is stabilized. The method of follow-up can be inpatient, outpatient, home visit, telephone, or newsletter, depending on the type and severity of the adverse event.

Data Collection, Management, and Analysis

Data Collection Plans

All the original data in the case report form will be backed up and entered into the database by 2 people, proofread each other and correct the entry errors, and after checking the accuracy with the original data in the case report form, the data will be locked and then statistically analyzed. Construct a high-quality clinical research database, incorporate it into the unified management of the big data platform of the Oncology Research Center, and conduct long-term tracking and follow-up of the research participants.

Plans to Promote Participant Retention and Complete Follow-Up

We will give each participant who cooperates in the participation and completion of the trial a traveling allowance of 100 CNY (equivalent to US $14.41, based on the exchange rate of US $1 to 6.9400 CNY on March 1, 2023) at the end of the treatment.

Data Management

Establishment of Data Steering Committee

The subject leader, statisticians, and clinical scholars will work together to formulate standard treatment protocols, design trial

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protocols, organize the formulation and approval of various standard operating procedures, organize the formulation and approval of research plans, approve and decide whether to continue the trial, as well as approve the dissemination of trial results and write reports on the results.

Establishment of a Data Safety and Monitoring Board: Confidentiality

Investigators (clinicians, not involved in the inclusion of participants) and statisticians were responsible for designing the CRF, assessing the adequacy of the participant recruitment process, evaluating data quality, outcome safety assessment, outcome and effect assessment, recommending continuation of the trial, and reviewing and approving the dissemination of the results and the draft report. A full-time database administrator was responsible for the management of the database; an ombudsman was responsible for the monitoring of the data, and 2 data entry clerk responsible for data entry.

Data Capture and Database Management

Accurately collect and record process management information, data, and resultant measurement indicators and inspection data of observation items. A 2-person, 2-track entry into the electronic case information system is used, and after the entry is completed, the double data are checked and logical consistency verified. The database uses electronic case information system for data management.

Data Security and Monitoring

Data monitoring before the start of the clinical trial is generally on-site verification; real-time online monitoring and online quality control of the electronic case information system during the trial; the final data monitoring is carried out after the completion of the trial data collection, and the external data materials are reviewed and accepted.

Database Locking

After the completion of the interim analysis of the clinical trial and the data monitoring at the end of the trial, report to the data safety and monitoring board, the subject leader, with a list of data monitoring, and lock the database after obtaining a written signature of approval.

Plans for Collection, Laboratory Evaluation, and Storage of Biological Specimens for Genetic or Molecular Analysis in This Trial or Future Use

There are no further genetic analyses or storage in repositories planned.

Data Analysis

Statistical Methods for Primary and Secondary Outcomes

Statistical software such as R4.4.0, SPSS 25.0, and GraphPad Prism were used for data analysis and statistical graphing in this study, with a test level of α taken as 0.05 and a 2-sided test, giving point estimates and 95% CIs.

Case Data Collectively: Full Analysis Set

All cases that were randomized, took the study drug at least once, and had at least one postdose efficacy assessment constituted the full analysis set (FAS) population of the study. Missing data in the efficacy-related part of the FAS population will be supplemented using a carry-over of data from the previous observation. FAS will be used for all analysis. PPS, the criteria for the PPS and its population will be finalized in the data and will include at least the following criteria: (1) compliance with the enrolment criteria set out in the trial protocol, (2) completion of all scheduled visits, and (3) no medication or treatment used during the trial that could have affected the evaluation of efficacy. The PPS is a secondary population for the evaluation of efficacy in this study.

Measurement data obeying normal distribution were expressed as mean and SD, 2 independent samples *t* test was used for intergroup differences, and paired *t* test was used for pre- and posttreatment comparisons within the group; if the data as a whole did not obey the normal distribution of measurement data, the median (first quartile, third quartile) was used, Wilcoxon rank-sum test was used for intergroup differences, and paired samples rank-sum test was used for pre- and posttreatment comparisons within the group; count data were expressed as frequencies and numbers; and PPS was the population of this study. And test; count data were expressed as frequency (n), constitutive ratio (%), and rate (%), and differences between groups were tested by chi-square test (Fisher exact probability test was used if the chi-square test was not satisfied); grade data were expressed as frequency and constitutive ratio, and differences between groups were tested by the Wilcoxon rank-sum test for independent samples.

Survival data, DFS, and OS were obtained using the Kaplan-Meier method and by plotting Kaplan-Meier curves to provide a visually intuitive depiction of differences between treatment groups. The estimation of treatment effect will be expressed by the hazard ratio and its 95% CI estimated by a stratified COX model. The dataset included in the statistics is based on intention-to-treat analysis.

Effect sizes and 95% CIs to quantify changes (not relying solely on *P* values) will be reported. FDR correction to account for multiple comparisons within related endpoint families (eg, all cytokines analyzed together) will be applied.

Interim Analyses

This study was a double-blind trial, and no interim analyses are planned.

Methods for Additional Analyses (eg, subgroup Analyses)

Due to the diversity of chemotherapy regimens and the severity of TCM symptoms, confounding factors may be introduced, affecting the accuracy of the results. We further conducted subgroup analysis and sensitivity analysis.

Based on the stratified model, the following predefined confounding factors (Chinese medicine symptom score and chemotherapy regimen types) were mandatorily included as covariates. Sensitivity analyses were conducted for the stratification factors and predefined covariates.

Chemotherapy Regimen Stratification Analysis

For different chemotherapy regimens, the interaction term between treatment group and chemotherapy regimen will be

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tested in the Cox model for the primary endpoint (DFS; with an interaction *P* value threshold of 0.10). If a significant modifying effect is present, the hazard ratio and 95% CI will be reported separately for each stratum.

TCM Syndrome Subgroup Analysis

Based on baseline TCM syndrome scores, divide into high or low severity subgroups according to the median or clinical cutoff value, and describe the trend of efficacy under different syndrome states.

Sensitivity Analysis

(1) Exclude data from centers using mixed chemotherapy regimens to validate the robustness of the conclusions, and (2) all multivariate models will be forced to adjust for chemotherapy regimen and baseline Chinese medicine symptom score.

Multiple Testing Control

Predefined subgroup analyses were adjusted using the Bonferroni method to control the significance level (α=0.05/number of subgroups) and minimize type I errors.

Methods in Analysis to Handle Protocol Nonadherence and Any Statistical Methods to Handle Missing Data

For missing values in the independent variables, multiple interpolation methods are used to select the optimal dataset. If there is a large amount of missing data, exceeding 20%, interpolation is not recommended.

Plans to Give Access to the Full Protocol, Participant-Level Data, and Statistical Code

The full protocol, as well as datasets used and analyzed during this study, can be made available by the corresponding author upon reasonable request.

Monitoring

In order to strengthen the management of this project and improve the efficiency and effectiveness of implementation, the following management system and departments are established by 5 subcenters, namely, Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine; Shanghai Lung Hospital of Tongji University; Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine; Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine; Shanghai Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine.

Project Management Office

A project management office will be set up with the project supporting unit as the core, regulations and management systems will be formulated, and the responsibility system of the project leader will be implemented. The project leader is responsible for the day-to-day management of the project office, top-level design, project organization and implementation, and coordination of the work of the participant groups. Scientific research assistants are set up to coordinate the daily affairs of the project with the project leader, inform the progress of the project implementation on a regular basis, arrange relevant meetings, undertake the annual summary, midterm assessment, project acceptance of the material collation work, and coordinate the data analysis, summary of the results, and publication of papers. Set up a financial assistant, responsible for the management and reasonable distribution of funds. Invite big data analysis companies and statistical companies to join the project management office, such as providing data platform construction services and statistical analysis services for each topic.

Management Promotion Team

A hospital management promotion team covering the heads of all functional departments of the hospital is set up to provide financial support, technical support, and logistical support for the center.

Expert Steering Group

The expert steering group is headed by the applicant, and its members include oncology experts in the field of lung cancer from Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine; Shanghai Lung Hospital of Tongji University; Shanghai Chest Hospital, Shanghai Jiao Tong University School of Medicine; Shanghai General Hospital, Shanghai Jiao Tong University School of Medicine; Shanghai Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai University of Traditional Chinese Medicine.. The expert steering group is also invited to be composed of clinical experts, methodology experts, and statistical experts, to validate the research proposal and to discuss and solve the major issues, such as key points and difficulties of the project research.

Project Implementation Team

The person in charge of each subcenter and the scientific research assistant, and the financial assistant shall form a project implementation team, implement a negative communication system for the project leader, and regularly report and discuss the progress of the project and related matters.

Subject Supervision Committee

The hospital research center will set up a subject supervision committee, which is responsible for supervising the whole process of the research, guaranteeing the authenticity and objectivity of the research data, and is also responsible for the safety of information. The supervision committee will independently summarize the experimental data; all the clinical research subject undertakings will be supervised by the Health and Welfare Commission and the Ethics Committee, so as to effectively safeguard the legitimate rights and interests of the test participants.

Frequency and Plans for Auditing Trial Conduct

The monitoring will be carried out by a supervisor from the Clinical Research Center of the Shanghai Hospital of Traditional Chinese Medicine, who will visit the Center on a regular basis, depending on patient recruitment. It is carried out in accordance with the clinical monitoring program. Regular visits will be made after every 10 patients are included.

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Plans for Communicating Important Protocol Amendments to Relevant Parties (eg, Trial Participants and Ethical Committees)

Any substantive changes to the research process must be in writing and state the reason for the change. They will be submitted to the Ethics Committee and ClinicalTrials.gov and will be implemented only after approval.

Dissemination Plans

The results of our study will be presented at relevant scientific conferences or magazines.

Ethical Considerations

The trial will be conducted in accordance with Good Clinical Practice guidelines; it will be supervised and managed by the Ethics Committee of Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine. The trial was registered at ClinicalTrials.gov (NCT06381960), and the investigational plan was approved by Shanghai Municipal Hospital of Traditional Chinese Medicine, Shanghai University of Traditional Chinese Medicine (approval number 2023SHL-KY-19-01). All participants would sign the informed consent before joining the trial.

Results

This research began receiving funding in October 2022. This study has been prospectively registered on ClinicalTrials.gov with the registration number NCT06381960. This study began screening and recruitment in March 2023. Recruitment is currently underway; by the end of 2024, a total of 180 eligible participants will be enrolled. Recruitment will continue until the end of June 2025 or until the target sample is reached. We estimate that the results will be published by March 2026.

Discussion

In this trial, we hypothesize that the treatment group will have better efficacy and safety than the control group.

Lung cancer is the leading malignant tumor in China in terms of deaths, and metastasis is the key cause. For patients with lung cancer who have undergone radical surgery, there is currently a lack of effective chemotherapy regimens. This poses a dual challenge for this special patient group in clinical practice, as it not only limits the overall improvement in lung cancer treatment outcomes but also results in significant financial burdens on society and families due to the high costs of medical care.

With the development of molecular targeted therapy and immunotherapy, patients with intermediate and advanced lung cancer who are positive for driver genes or have high PD-L1 expression can further benefit from targeted therapy or immunotherapy. Adenocarcinoma and squamous carcinoma are common pathologies in lung cancer. A study that included 371 Chinese lung cancer cases showed that the mutation types in lung adenocarcinoma were Epidermal Growth Factor Receptor (EGFR; 60%), Tumor Protein P53 (57%), Kirsten Rat Sarcoma Viral Oncogene Homolog (13%), Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha (7%), and Anaplastic Lymphoma Kinase (7%), whereas those in squamous lung carcinoma included Tumor Protein P53 (87%), Phosphatidylinositol-4,5-Bisphosphate 3-Kinase Catalytic Subunit Alpha (43%), Cyclin-Dependent Kinase Inhibitor 2A (20%), Lysine Methyltransferase 2D (20%), and EGFR (17%) mutations [9]. For Anaplastic Lymphoma Kinase /EGFR/Kirsten Rat Sarcoma Viral Oncogene Homolog /ROS Proto-Oncogene 1/MET Proto-Oncogene mutations, there are several targeted therapeutic agents have been approved, marketed internationally, and included in the health insurance. Wu Yilong et al conducted a clinical study confirming the benefit of ositinib in patients after radical surgery for stage IB-IIIA lung cancer with driver gene EGFR positivity [12,13]. Meanwhile, immunotherapy sequential treatment after chemotherapy for the Radical resection of lung cancer patients with stage IB-IIIA lung cancer with high PD-1/L1 expression (≥1%) may also provide a survival benefit and reduce the rate of metastasis. In addition, a study included 328 patients after resection of stage IA-IIB NSCLC to examine their immune checkpoint expression [14]. The study showed that 62.0% (160/258) of the lung adenocarcinoma group had PD-L1 <1%, and only 38.0% (98/258) had PD-L1 ≥1%, suggesting that the expression of immune checkpoints is low in lung adenocarcinoma patients [15]. Therefore, for patients with positive driver gene and high immune checkpoint expression after radical lung cancer surgery, standardized diagnostic and treatment protocols that can benefit patients clinically are already available. However, for patients with negative gene expression and low PD-1/L1 expression (1%) after radical lung adenocarcinoma surgery, who have poor chemotherapeutic efficacy in the clinic and lack indications for molecularly-targeted or immunotherapeutic treatments, the development of effective, scalable, and specific therapeutic protocols is urgently needed.

In summary, the existing multidisciplinary treatments available for lung cancer metastasis, such as chemotherapy, targeted therapy, and immunotherapy, have been developed based on alterations to the genetic structure and function of the tumor cells themselves in the primary foci. However, as tumor metastasis is often trans-organ and involves imbalances in the function of multiple systems, the overall efficiency of current strategies for the prevention and treatment of lung cancer metastasis is poor. TCM, which stresses the holistic concept and dialectical treatment, and commits to a people-centered approach, has unique advantages in preventing and treating tumor metastasis [15-18]. A large number of basic and clinical studies have confirmed that TCM can significantly inhibit the metastasis of lung cancer, significantly prolong the survival period of patients, and improve their quality of life [19,20]. Therefore, it is an important breakthrough to overcome the bottleneck of tumor metastasis in the clinic under the holistic view and syndrome differentiation of TCM to understand the pathogenesis of lung cancer metastasis from a systemic perspective, and then anchoring the key therapeutic targets to develop effective prevention and treatment strategies [21-23].

This research program inherits the theoretical advantages of Chinese medicine's “the Holistic Concept” and the thought of

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"Precentive Treatment of Disease," inherits the academic thought of "Treating Cancer by Reforcing Healthy Qi," and gives full play to the advantages of systems biology, precision medicine, and Chinese medicine. Preliminary research indicates that the method of tonifying the body and expelling pathogens can effectively inhibit lung cancer recurrence. In addition to Fuzheng Quxie Formula, the TCM formulations currently available for the treatment of NSCLC include Jinfukang Oral Liquid, Zilongjin Tablets, and Huachansu Oral Liquid. Compared to other TCM formulations, Fuzheng Quxie Formula is based on the principle of "supporting vital qi and dispelling hidden toxin" (supporting vital qi: enhancing immunity; dispelling hidden toxin: cytotoxicity). Its advantages are primarily reflected in the following aspects, such as (1) precise immune regulation involves simultaneously enhancing effector cells and inhibiting immune-suppressive cells; (2) extending survival and delaying resistance to targeted therapy, Fuzheng Quxie Formula is currently the only TCM compound clinically validated to delay resistance to EGFR- Tyrosine Kinase Inhibitor; (3) reducing toxicity and enhancing efficacy, improving tolerance to chemotherapy; (4) comprehensive coverage across treatment stages, from postoperative prevention of recurrence to late-stage targeted maintenance therapy, aligning with the trend toward personalized treatment for lung cancer. Comparison of key indicators between Fuzheng Quxie Formula and other Chinese herbal formulas are present in Table 5.

Table 5. Comparison of key indicators between Fuzheng Quxie Formula and other Chinese herbal formulas.

Indicators	Fuzheng Quxie Formula	Jinfukang oral liquid	Zilongjin tablets	Huachansu oral liquid
Efficacy	supporting vital qi and dispelling hidden toxins	Tonifying qi and nourishing yin	Tonifying qi and blood	Clear heat and detoxify, broad-spectrum anticancer
Prolong survival	Median OS[a] extended by 5 months↑, PFS 11.8 months	Disease control rate: 71.2%	Survival time extended by 9.5 months	Improved quality of life, no clear OS data
Advantages of a combination targeted therapy	Reduce the risk of TKI[b] resistance (HR[c] = 0.888)	Unreported	Unreported	Unreported
Applicable stage	Late-stage TKI combination therapy or chemotherapy maintenance, or post surgery	Qi and Yin deficiency type lung cancer (alone or in combination with radiotherapy and chemotherapy)	Maintenance treatment for qi and blood deficiency	Adjuvant chemotherapy or palliative care for advanced disease

[a]OS: overall survival.

[b]TKI: Tyrosine Kinase Inhibitor.

[c]HR: hazard ratio.

Based on the theory of "Deficiency of Vital Qi and Hidden Toxin," the research target is located in patients with stage IIA-IIIA lung cancer who are negative for the expression of driver genes after radical surgery, and carry out a multicenter clinical study on the combination of chemotherapy with Chinese medicine to prevent and control the recurrence and metastasis of IIA-IIIA stage IIA-IIIA driver gene-negative NSCLC after radical surgery. The study clarified the comprehensive efficacy of TCM in regulating the internal environment of the body's immune function state to reduce recurrence and metastasis, with a view to obtaining high-level evidence-based medical evidence and forming a standardized diagnostic and treatment protocol of TCM for preventing and treating recurrence and metastasis of postoperative cancer that can be promoted and applied, so as to promote the improvement of the therapeutic efficacy of postradical treatment for patients with lung cancer. Second, based on the results of the study, the advantageous population of TCM for the prevention of recurrence and metastasis was screened out by combined MRD detection, and histopathology, circulating tumor cells, tumor-associated exosomes, immune indexes and other related indexes of postoperative patients with stage IIA-IIIA lung adenocarcinoma who were negative for the expression of driver genes were detected, and the therapeutic efficacy prediction model of postoperative patients with stage IIA-IIIA lung adenocarcinoma who were negative for the expression of driver genes was jointly established, so as to improve the precise treatment level of lung cancer after radical surgery and promote the overall prevention and control efficiency of lung cancer.

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The sponsor carries the medicolegal responsibility of the trial. This is an investigator-initiated clinical trial. Therefore, the funders played no role in the design of the study and collection, analysis, and interpretation of data, and in writing the manuscript. Not applicable; there are no ancillary studies planned. All information is provided within the patient information leaflet.

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Patients and/or the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Data Availability

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Authors' Contributions

Study concept and design: JT.
Study conduct: FX, YY, and JT.
Data management and statistical analysis: FX, YY, and JT.
Drafting of the manuscript: FX.
Critical review and revision of the manuscript for intellectual content: YY and JT.
Clinical follow-up: FX, YY, YL, BL, JY, YZ, ML, JW, WS, LJ, QH, WF, ZF, YL, and JT.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT checklist.
[PDF File (Adobe PDF File), 202 KB - resprot_v14i1e66342_app1.pdf]

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Abbreviations

CRF: case report forms
DFS: disease-free survival
EGFR: epidermal growth factor receptor
FAS: full analysis set
IL: interleukin
MRD: minimal residual disease
NSCLC: non–small cell lung cancer
OS: overall survival
PD-1: programed death-1
PD-L1: programmed death-1 ligand
PNI: prognostic nutritional index
PPS: compliance with the protocol set
SII: systemic immune-inflammation index
TCM: traditional Chinese medicine

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Protocol

Boosting Human Papillomavirus Vaccination Rates: Protocol for a Randomized Controlled Trial of Awareness Interventions in Réunion Island

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Abstract

Background: Human papillomavirus (HPV) is the most common sexually transmitted infection worldwide and imposes a significant public health burden. In 2019, HPV was responsible for approximately 620,000 cancer cases in women, 70,000 in men, and more than 300,000 deaths globally. Despite the proven efficacy of the vaccine, vaccination rates remain alarmingly low in certain regions of France. In Réunion Island, only 16% of girls and 9% of boys under 16 years old were fully vaccinated in 2024. This underscores the need for increased awareness, education, and outreach programs. Peer learning is well-established in health education, whereas serious game–style card games are newer and require further research. Both methods have been shown to improve knowledge on specific topics.

Objective: The main objective of this study is to assess the impact of 2 awareness-raising strategies on increasing HPV vaccination rates among middle school students by actively involving them in the process.

Methods: This protocol describes the design of a randomized, open-label, controlled trial aimed at evaluating the effectiveness of 2 awareness-raising interventions—peer learning and a card-based serious game—in improving HPV vaccination rates among middle school students in Réunion Island. The study will span an entire school year, beginning in August. Approximately 3600 students from 24 middle schools in Réunion Island will be included, with schools randomized into 3 groups of 8 each: (1) a control group receiving the existing national vaccination campaign initiated by the French public health institute; (2) ambassador classes, whose students will receive education about the HPV vaccine and later educate other students in the same school; and (3) serious game card group, where students can play and learn about HPV during a science class. The primary outcome will be the proportion of teenagers who initiate the vaccination process, compared across the 3 groups using appropriate statistical methods. Anonymized data will be collected at the end of the school year using social security records. Teenagers' knowledge of HPV will be assessed both before and 3 months after each intervention, and satisfaction will also be evaluated after the intervention in each group.

Results: As of May 2025, a preliminary result enrolling 124 students showed an increase in vaccination coverage after students played a serious game. We expect higher vaccination rates in the intervention groups compared with the control group, although it is difficult to predict which strategy will be more effective. The estimated target vaccination coverage for groups b and c is 45%.

Conclusions: This study aims to improve HPV vaccination rates among teenagers in Réunion Island by evaluating the impact of 2 awareness-raising strategies using innovative and engaging tools. If successful, this approach could be adapted and implemented in other regions of France or internationally.

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KEYWORDS

human papillomavirus; HPV vaccine; primary prevention; middle school; serious game; peer learning

Introduction

Human papillomavirus (HPV) is a widespread sexually transmitted infection that affects more than 1 in 5 people globally [1]. It is estimated that about 80% of men and women will be exposed to HPV at some point in their lives. With a global prevalence of 31% in men and 32.1% in women [2,3], HPV represents a major public health concern due to its established role in the development of multiple cancers [4], most notably cervical cancer, which remains the fourth most frequent cancer in women worldwide. The World Health Organization reported 660,000 new cervical cancer cases and 350,000 related deaths in 2022. In France, HPV is responsible for over 6400 cancers annually, including cervical, vulvar, vaginal, penile, anal, and oropharyngeal cancers. On Réunion Island, cervical cancer is the third most common cancer in women.

Prevention of cervical cancer is mainly based on screening with Papanicolaou (Pap) smear tests and HPV vaccination. Despite the proven safety and effectiveness of HPV vaccines in reducing the incidence of precancerous lesions and genital warts [5-7], vaccination coverage in France remains insufficient. As of 2023, only 45% of girls and 16% of boys aged 16 were vaccinated [8]. In Réunion Island, coverage is even lower: in 2022, only 12.7% of adolescents under 16 had received at least one dose of the HPV vaccine. Following the national vaccination campaign launched in 2023, only 6.8% of seventh-grade students were vaccinated at school in Réunion. Taking into account children vaccinated outside school by their general practitioner, the rate modestly increased to 27% for girls and 16% for boys. Nevertheless, these figures remain far from the thresholds needed to achieve herd immunity and effective cancer prevention [9].

The low uptake in Réunion Island may be attributed to a lack of information, fear of adverse events, and limited engagement from both health care professionals and families [10,11]. In countries such as Australia, Belgium, Portugal, and the United Kingdom, school-based HPV vaccination programs have achieved coverage rates exceeding 80% [12]. These programs reduce access barriers, promote equity, and provide opportunities for engaging educational interventions.

Educational strategies themselves are key determinants of success. Traditional top-down health messages may be poorly received by adolescents, particularly when sensitive topics such as sexually transmitted infections are involved. In response, 2 innovative, youth-centered approaches have emerged: peer-led education (ambassador programs) and serious games.

Peer education leverages the credibility, relatability, and social dynamics of adolescence. Studies have shown that adolescents are more likely to engage with and retain information delivered by peers than by adults or authority figures. In a 2018 study conducted in Niger with more than 1000 students, peer-led HPV education significantly increased knowledge scores (from mean 12.94, SD 9.23 to mean 53.74, SD 10.69, $P<.001$) [13]. This underscores the power of peer-to-peer communication in culturally and resource-diverse settings.

In the field of health sciences, peer-assisted learning has been widely applied in clinical education. A systematic review by Markowski et al [14], analyzing 47 articles from 8 countries, concluded that peer-assisted learning improves skills, reduces stress, and increases confidence among students [14]. Importantly, these effects are not limited to the “ambassadors”—students receiving information from their peers also benefit significantly from the learning process [15].

In the context of vaccination, peer influence has been shown to enhance acceptance, particularly when combined with school-based efforts and community engagement. Peer-led interventions not only promote knowledge but also shape attitudes and behavioral intentions—factors especially relevant to HPV vaccination, which is often stigmatized or misunderstood.

Serious games—defined as games designed for a primary purpose other than pure entertainment—are increasingly used in health education. They offer immersive, interactive learning experiences that promote engagement, critical thinking, and long-term retention of knowledge. In recent years, serious games have been applied to topics ranging from antimicrobial resistance to smoking prevention.

Already in 2016, it was highlighted that serious games, through their unique combination of pedagogy and play, foster active learning, strengthen motivation, and adapt to different learner profiles. While recognizing the need for thoughtful integration into the pedagogical framework, the literature also provides tools for selecting and using these games appropriately [16].

In the French Antilles, unpublished pilot projects used serious games to address tobacco and alcohol prevention in adolescents. In mainland France, the Paris Committee and the French League Against Cancer developed a serious card game to educate students about the harms of smoking. A 2019 literature review of serious games in health education found that, while most studies focused on participant satisfaction, several also reported improvements in knowledge, decision-making, and self-efficacy [17].

A Swiss study conducted in 2020 reported behavior change following increased knowledge of COVID-19 protection measures in a small sample of employees in a long-term care unit [18].

A 2021 Irish study evaluated the impact of a serious game on influenza vaccination among nursing students. Postintervention,

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knowledge scores rose from 68% to 85%, and positive attitudes toward vaccination improved significantly [19]. Although data on serious games for HPV remain limited, these early findings support their potential as engaging tools for behavior change, particularly when integrated into school curricula.

Building on the findings of Tran et al [20], we hypothesize that both peer education and serious games can improve HPV vaccination uptake among adolescents. To evaluate this, we have designed a randomized controlled trial comparing 3 strategies in middle schools across Réunion Island (Textbox 1).

Textbox 1. Strategies in middle schools across Réunion Island.

1. Control group

- Standard school-based vaccination campaign with no additional educational component.

2. Ambassador group

- Implementation of a peer-led education model, with trained student ambassadors delivering information to their peers.

3. Serious game group

- Delivery of a cus

  tom-designed, human papillomavirus–focused serious game to promote learning and engagement.
- As the local education authority of Réunion Island does not permit promotion of this type of intervention in virtual form, to limit screen exposure among young people, we have planned the game in a card-based format.

Comparing peer-led (ambassador) education and serious games within the same trial will allow us to determine the most effective and scalable strategy for improving HPV vaccination uptake in Réunion Island. While both approaches have shown promise in preliminary studies and international contexts, they differ in required resources, modes of engagement, and potential for long-term implementation. Peer-led education depends on sustained student involvement and social interaction, whereas serious games provide a more immersive, standardized, and potentially reproducible experience. By rigorously evaluating their respective impacts in a controlled setting, this study will inform future public health programming. Once the most effective and cost-efficient strategy is identified, efforts and resources can be directed toward its wider deployment at the regional level—and potentially beyond—to maximize public health impact and reduce HPV-related disease burden among adolescents.

By targeting students in schools—where barriers to access can be minimized—we aim to advance the long-term goal of reducing the HPV-related disease burden in underserved regions such as Réunion Island.

Methods

Trial Design

This is a randomized, controlled, open-label intervention study based on 2 awareness strategies for HPV vaccination in Réunion Island. A prototype of the serious game was created in May 2025, and the service company will devote several weeks to producing the final materials. The card game is expected to be ready for the start of the school year.

Colleges (selected from lists provided by the local education authority in March-April) will then be randomly assigned to 3 groups, with 8 colleges per arm:

- Reference arm: no intervention; schools will only follow the government's vaccination campaign.
- Ambassador arm: implementation of specific HPV vaccine education to create an ambassador class.
- Serious game arm: distribution of the card-based serious game.

The unit of randomization will be the middle school. Each school will be assigned to 1 of the 3 intervention arms (1, 2, or 3) according to a randomization list. The allocation ratio will be 1:1:1, with stratification by middle school level. To minimize imbalance between schools, a constrained randomization plan will be used (PROC PLAN; SAS Institute Inc). The randomization list will be generated by a statistician at the Methodology and Data Management Center before the start of the study. A document describing the randomization procedure will be kept confidential within the same center.

The directors of the randomized schools will be invited to participate in the study. Our study is supported by the rectorship of Réunion Island, which has already written to all directors to request their assistance with this project.

Once school directors agree, they will be asked to identify 1 or 2 teachers, on a voluntary basis, to help implement the study in each school. From our experience, teachers are highly motivated to take part in public health initiatives, particularly those involving playful learning.

If directors decline participation, a new randomization will be conducted in additional schools to ensure school buy-in.

Interventions will be conducted only in seventh-grade classes, targeting children around 12 years of age.

All participants will complete an HPV baseline knowledge questionnaire before the intervention and again up to 3 months afterward.

Following the trial, the team will collect data on vaccination uptake, with initiation of the vaccination schedule (at least one dose) considered sufficient for assessment, as the World Health

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Organization has concluded that a single-dose HPV vaccine may provide solid protection [21].

Study Objectives

The primary objective is to evaluate the impact of 2 awareness-raising strategies against HPV by involving middle school students to increase vaccination uptake. Specifically, we aim to compare the proportion of students who initiated vaccination before and after the interventions. In addition, we will assess motivations and challenges encountered in both the serious game and ambassador classes, as well as overall student satisfaction and knowledge.

Settings

This study is scheduled to start in August-September (the beginning of the school year) and is expected to last approximately 1 school year, concluding in July (Figure 1). The research team will perform randomization to allocate 8 colleges per arm.

Figure 1. Participants timeline T0 : pre-intervention questionnaire T1 : post intervention questionnaire at 3 months T2 : only for ambassador classes : information by ambassador classes to their peers in 7th grade class T3 : collection of vaccination status.

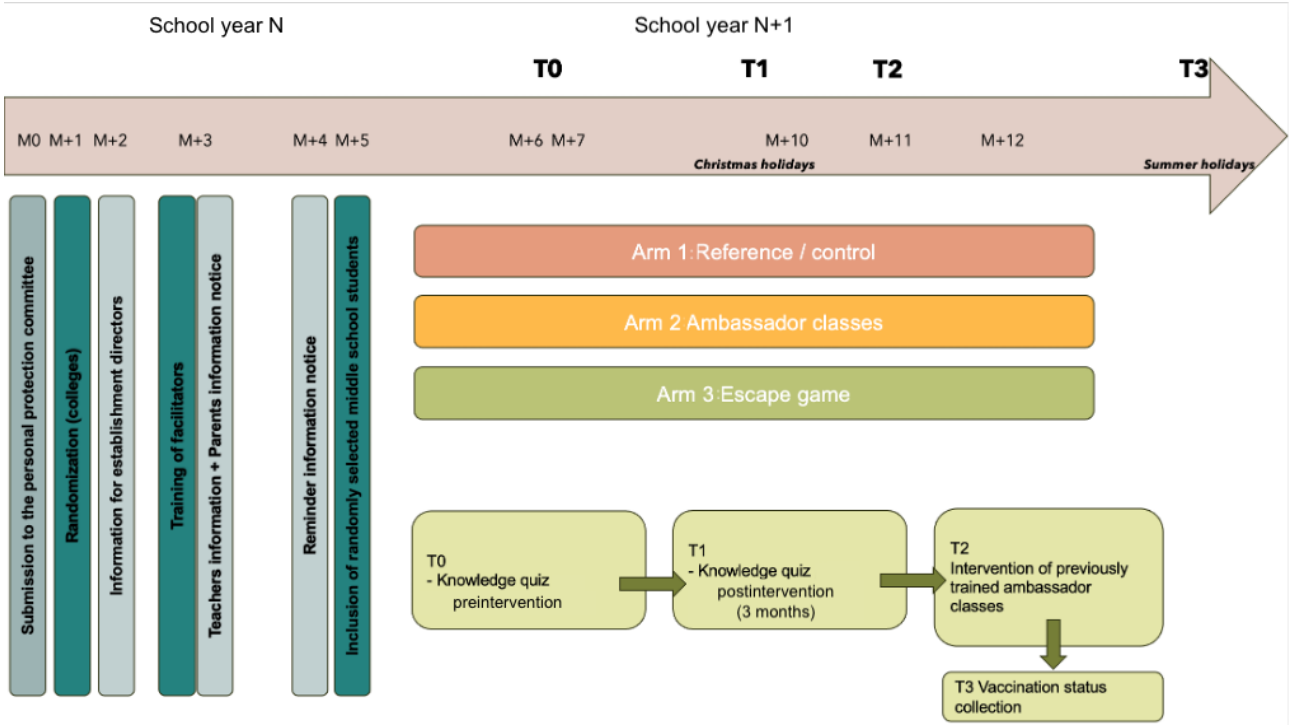

In August, at the beginning of the new academic school year, parental consent will be collected.

In September, children will be enrolled after confirming that their parents do not object to participation.

Vaccination campaigns typically occur in December and June, with the first dose usually given in December and the second dose in June, although vaccination can also be initiated with the first dose in June, all scheduled before school holidays.

Between September and December, the following events will occur:

- In the ambassador group, a facilitator, after receiving prior training, will introduce HPV to students in the ambassador classes using a standardized slideshow identical across all classes. These students will then be responsible for conveying this information to other seventh-grade classes in their school. They will have the autonomy to choose the format for delivering the information to their peers (eg, games, presentations, films, posters, slideshows, comics).
- In the serious game group, 1 facilitator will explain the functioning and rules of the game to volunteer science teachers. The game is designed so that teachers can work independently with the students. Teachers may choose when to conduct the serious game during school classes before the vaccination campaigns.

At the end of the school year, around July, vaccination status will be collected using the French social security system, following anonymization of social security numbers.

Ethics Approval and Consent to Participate Statement

The participants of this study are minors. This intervention study does not involve administering the HPV vaccine but focuses on raising awareness. The research team will inform parents about the study via an information leaflet distributed in June and August, and written consent will be obtained unless parents object.

The sponsor and the investigator(s) commit to conducting this research in compliance with French law number 2012-300 of March 5, 2012, relating to research involving human participants, as well as in accordance with Good Clinical Practice (International Council for Harmonisation, version 4, November 9, 2016; and decision of November 24, 2006) and the Declaration of Helsinki (full text available online [22]).

The research will be conducted in accordance with the present protocol. Except in emergency situations requiring the

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implementation of specific therapeutic procedures, the investigator(s) commit(s) to fully comply with the protocol, particularly with respect to obtaining consent and the reporting and follow-up of serious adverse events.

Data collected during this research will be processed by the Centre Hospitalier Universitaire de La Réunion in compliance with the French Data Protection Act no. 78-17 of January 6, 1978, as amended by Act 2004-801 of August 6, 2004.

Approval from the ethics committee and the data protection authority is currently in progress.

Patient and Public Involvement

Following the distribution of information leaflets to parents and students, and after obtaining consent from school directors, the schools will be randomized. The research team, together with teachers, will verify any potential objections and ensure that students whose parents object do not participate in the interventions. Parents may withdraw their child from the study at any time by simple request. Participants will have the right to receive information about the study, including the results.

Sample Size

This is a cluster randomized controlled trial with 3 parallel arms, designed to evaluate the effectiveness of 2 awareness programs addressing HPV-related risks and its prevention in seventh-grade classes in Réunion colleges. The reference arm is a no-intervention group. The allocation ratio is 1:1:1. The primary outcome is the proportion of students who initiate the HPV vaccination schedule. The World Health Organization Strategic Advisory Group of Experts has recently reviewed evidence indicating that a single-dose vaccination schedule provides effectiveness comparable to the traditional 2-dose schedule.

The research team may include up to 1 additional ambassador class in arm 2 if a college has more than 5 seventh-grade classes, to facilitate information dissemination (Figure 2).

Figure 2. Diagram showing the composition of colleges randomly assigned.

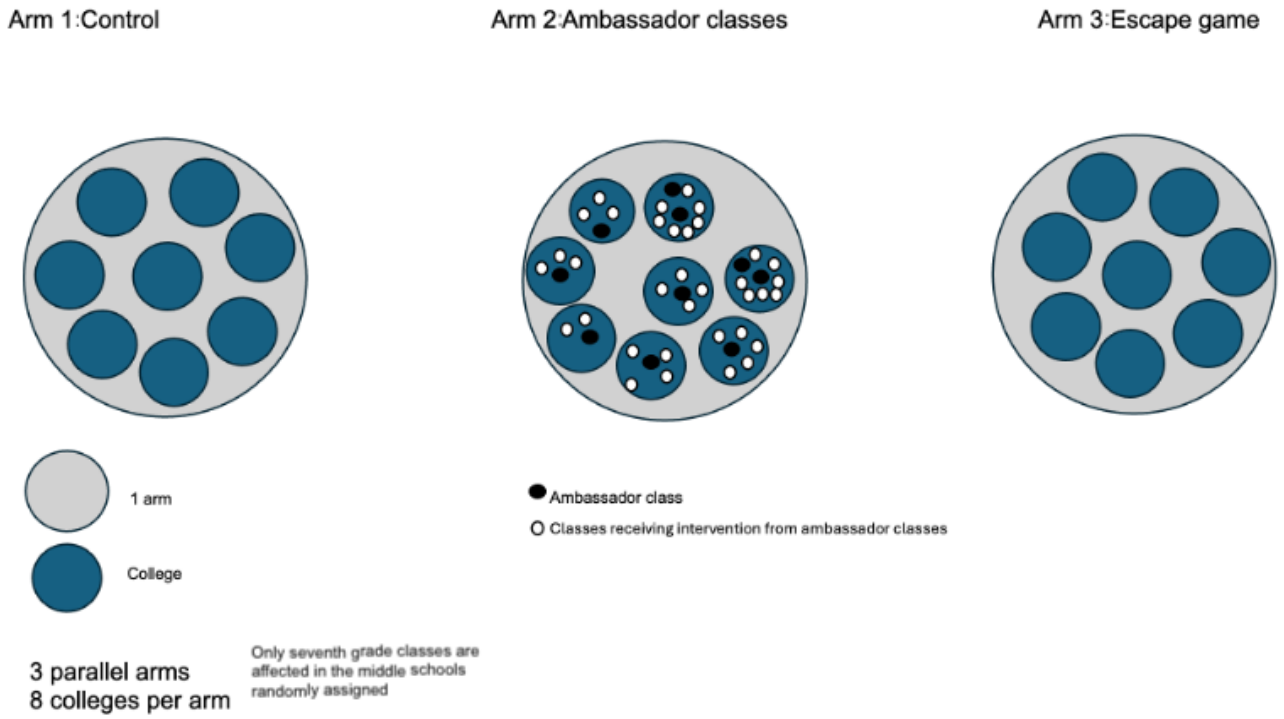

To calculate the required number of participants, the following assumptions are considered:

- It is hypothesized that, by the end of the school year, 30% of students in the control group will have initiated vaccination. This estimate is based on vaccination coverage data published by Santé Publique France in 2023, which reported that 21.5% of children (girls and boys combined) aged 12 in Réunion had received at least one dose of the HPV vaccine by December 31, 2023 [23].
- It is hypothesized that the ambassador classes and the serious game will increase coverage to 45% in the respective intervention groups.
- A constant intracluster correlation coefficient of 0.1, considered a rather conservative value [24].
- An α risk of 5%
- 90% power
- The average number of seventh-grade students (n) is 190 per college.
- A design effect (allowing intraclass correlation [ICC] to be taken into account) of 19.9, which is calculated as $1 + ICC \times (n - 1)$.

Therefore, a total of 8 colleges per arm will be included, resulting in 24 colleges overall and approximately 3144 students.

Recruitment

Our sample will include seventh-grade middle school students from randomly selected schools in Réunion Island, following approval from the school directors. These schools will be randomly assigned to 1 of the 3 groups in a 1:1:1 ratio using a

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randomization algorithm. All students attending the selected schools will be invited to participate in the study (Figure 2).

Eligibility Criteria

Inclusion criteria are students in seventh-grade classes from middle schools in Réunion Island who are randomly selected and assigned to the study.

Exclusion criteria are students with parental opposition to participating.

Intervention

Control Group

The control group will consist of 8 randomly assigned middle schools. These schools will follow the existing vaccination campaign, without any modifications, as implemented by the French government. As vaccination campaigns are coordinated by the local Regional Health Agency, they are relatively uniform across all middle schools in Réunion, ensuring standardization and internal validity. Parents will receive information materials and consent forms through their children. Both parents are invited to sign the written consent form, which the child will then submit to the school counselor or school nurse. The counselor or nurse will forward the forms to the vaccination teams assigned to the area. This allows the vaccination teams, in coordination with the education staff, to schedule their visit to the school on a specific day and bring the appropriate number of vaccine doses corresponding to the consent forms received. Vaccination teams typically visit each school twice a year to administer 2 vaccine doses 6 months apart, usually in December (year Y) and June (year Y+1).

A preintervention questionnaire will be administered to assess students' baseline knowledge about HPV (T0). The questionnaire will be standardized, anonymous, and identical for all participants. It will be available on tablets, computers, or on paper, depending on availability. A postintervention knowledge assessment will be conducted 3 months later (T1) using a questionnaire identical to the preintervention one, to evaluate changes in the rate of correct responses before and after the vaccination campaign.

The standardized knowledge questionnaire was developed by the research team and will assess students' knowledge of HPV epidemiology, complications, and prevention (including vaccination; Multimedia Appendix 1). Each question requires a response of "yes," "no," or "I don't know." The questionnaire consists of 11 questions.

Vaccination status will be collected using the French social security system after anonymization of social security numbers (T3).

Intervention Group: Ambassador Class (Peer Learning)

For each college randomized to this arm, 1 seventh-grade class will be randomly selected as the ambassador class. If a college has more than 5 seventh-grade classes, 2 ambassador classes will be designated (Figure 2). Students in the ambassador class will receive the intervention during a single class period.

This group will receive a 30-minute presentation on HPV delivered by a trained facilitator during class. The presentation will be standardized and consistent across all participating classes to minimize potential bias. Developed in advance by a team of experts, it will remain identical for all classes in this intervention arm. The presentation will cover key topics, including HPV, its epidemiology in France and Réunion Island, its benign and malignant sequelae, and preventive measures such as screening and vaccination. To assess students' understanding of the material, they will complete a satisfaction questionnaire following the presentation.

The same preintervention (T0) and postintervention (T1) questionnaires used in the control group to assess HPV knowledge will be administered.

This arm, which integrates peer learning, will train "ambassador classes" on HPV prevention. In a second step, these students will disseminate the information to their peers in other seventh-grade classes within their middle school (T2). They will have the autonomy to choose the format for delivering the information during class (eg, games, presentations, films, posters, slideshows, comics [20]). Students who receive the information from their peers will also complete a satisfaction questionnaire. A field coordinator (a volunteer teacher) will be present during the training sessions to ensure that essential information is effectively conveyed and, if necessary, to supplement any important details that may have been omitted in the student-led presentations.

Vaccination status will be collected using the French social security system after anonymization of social security numbers (T3).

Intervention Group: Serious Game Cards

The intervention for this group will involve a card game modeled after an "unlock" serious game, specifically designed for this study to raise awareness about HPV. All seventh-grade classes in the randomized middle schools will participate in the game during a 1-hour class session. Sufficient sets of the card game will be provided to ensure that each student can actively participate. Middle school students will be supervised by a volunteer science teacher.

The game was designed to be played directly by students working in teams.

The game consists of 3 types of cards:

- Yellow cards: feature fictional child characters expressing their own doubts about the HPV vaccine, as well as concerns raised by their parents.
- Blue cards: provide answers addressing the children's doubts or fears.
- Green cards: respond specifically to the concerns expressed by parents.

First, the teacher reads the game instructions and mission order to the students for 5 minutes. A deck of cards is then distributed to groups of 3-4 students. According to the game rules, students must form a correct trio by matching 1 yellow card with 1 blue card and 1 green card (Figure 3). Students have 45 minutes to solve as many card trios as possible by finding the correct

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matches. Each correct answer represents 1 vaccinated child in their class and must be validated by the teacher. The final objective is to “vaccinate” as many children as possible.

Figure 3. Serious game about HPV vaccination.

The intervention is grounded in a participatory communication approach that fosters active engagement among students. Children lead the game themselves, encouraging peer interaction and collaborative learning.

Children and parents were not involved in designing this game. However, the doubts featured on the yellow cards were derived from a study conducted a few years ago to identify barriers to HPV vaccination in schools [11]. A pilot evaluation of the game was carried out in 1 middle school, which helped identify areas for improvement and ensured smoother implementation.

At the end of the allotted time, teachers and students can debrief together to reinforce key concepts about HPV, and the teacher

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can answer any questions. The remaining 5 minutes of class time are allocated for students to complete the satisfaction questionnaire.

The same preintervention (T0) and postintervention (T1) questionnaires used in the control group to assess HPV knowledge will be administered.

In addition, students will complete a satisfaction questionnaire following the game, which will take a maximum of 5 minutes.

Vaccination status will be collected using the French social security system after anonymization of social security numbers (T3).

Measures

Primary Outcome: Evaluate New Tools to Improve Vaccination

The primary outcome of this study is the proportion of students in each group who initiate HPV vaccination by the end of the school year (at least one dose of the HPV vaccine).

Secondary Outcomes

The secondary outcomes are as follows:

- Evaluate the proportion of girls and boys in each group who initiate HPV vaccination by the end of the school year.
- Explore and assess the motivations and challenges perceived by students in the ambassador classes and by those participating in the serious games.
- Evaluate overall student satisfaction within each arm for descriptive purposes.
- Compare students' knowledge before and after the intervention in each arm.

Blinding

Given the nature of the interventions, blinding will not be implemented in this study. No participants will be blinded during the trial.

Data Collection, Management, and Monitoring

Pre- and postintervention knowledge questionnaires will be identical for all students (Multimedia Appendix 1). Satisfaction questionnaires will be tailored to the specific trial arm—ambassador class or serious game—to evaluate the unique aspects of each intervention (Multimedia Appendices 2 and 3).

Data collection via questionnaires will be anonymized and conducted at the class level.

Vaccination status will be collected with the assistance of the French social security system, following anonymization of social security numbers.

All information required by the protocol must be recorded in the observation notebooks, and any missing data must be explained. Data should be collected as they are obtained and transcribed neatly and legibly. Data will be entered into an electronic observation notebook (electronic case report form) using Ennov Clinical software.

A clinical research associate appointed by the sponsor will regularly visit the investigator center—at study initiation, periodically during the research depending on the inclusion rate, and at study completion. During these visits, and in accordance with the risk-based monitoring plan (considering participants, logistics, impact, and resources), the following elements will be reviewed:

- Nonopposition from participants
- Compliance with the research protocol and defined procedures
- Quality of data collected in the observation notebook, including accuracy, completeness, and consistency with source documents (eg, medical records, appointment books, original laboratory results)

A written monitoring report will be prepared for each visit.

An audit may be conducted at any time by individuals mandated by the sponsor and independent of the research team. Its purpose is to verify participant safety and rights, ensure compliance with applicable regulations, and assess the reliability of the data.

An inspection may also be ordered by a competent authority (eg, ANSM [Agence nationale de sécurité du médicament et des produits de santé] in France).

Both audits and inspections may be conducted at any stage of the research, from protocol development to publication of results and the handling of data generated during the study.

Investigators agree to comply with the sponsor's requirements for audits and with the competent authority's requirements for inspections.

Four follow-up visits will be scheduled (Textbox 2).

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Textbox 2. Follow-up visits.

1. Visit 1 (T0)
- This visit will take place during school hours, just before the start of the awareness program (arms 2 and 3).
- Students will complete a questionnaire assessing their knowledge of human papillomavirus (HPV).
- The estimated completion time is a maximum of 10 minutes.

2. Visit 2 (T1)
- This visit will take place during school hours, approximately 3 months after the end of the awareness program.
- Students will complete the same questionnaire to assess their postintervention knowledge.
- The estimated completion time is a maximum of 10 minutes.

3. Visit 3 (T2)
- This visit will take place only in the middle schools assigned to the "ambassador classes" arm to assess the satisfaction of students receiving the intervention from their trained peers.
- A member of the research team will be present during the ambassador class intervention to ensure that essential information is accurately conveyed.
- The estimated completion time is a maximum of 10 minutes.

4. Visit 4 (T3)
- At the end of the study, qualitative interviews will be conducted to explore the motivations and challenges experienced by teachers, parents, and students participating in the study.
- Each participant will receive information about the study and will provide consent for audio-recording of their interview.
- The interviews will then be transcribed anonymously using qualitative data analysis software.

5. End of research visit
- The end-of-research visit marks the final data collection, which may include qualitative interviews or vaccination data.
- This visit will also be used to collect information on HPV vaccination initiation during the school year (at least one dose counts) for each student, with assistance from the Social Security system via anonymized social security numbers.
- Within 1 year of the end of the research or its early termination, a final report will be prepared and signed by both the sponsor and the investigator.
- This report will be submitted to the competent authority.
- Additionally, the sponsor will provide the Committee for the Protection of Persons with a summary of the final report within 1 year of the study's conclusion.

Statistical Analysis

Analyses will be performed by the biostatistics team at La Réunion University Hospital, in collaboration with the study methodologist and coordinating investigator, according to the statistical analysis plan established before database lock. Analyses will be conducted using SAS (version 9.4; SAS Institute Inc), Stata (version 16; StataCorp), or R (R Foundation) software.

Qualitative variables will be described using counts and percentages. Quantitative variables will be summarized using the mean and SD, or the median and range, as appropriate.

Comparative analyses of the end points will be conducted according to the intention-to-treat principle, meaning that students will be analyzed in the group to which their class was randomized, regardless of any deviations from the research protocol. All students included and followed until the end of the school year will be considered in the analysis.

At the college level, the main deviation from the expected research protocol is nonparticipation in the intervention allocated by randomization.

At the student level, expected deviations from the protocol include occasional absenteeism during data collection at different periods, permanent departure from college during the academic year, or individual refusal to participate at any point during the study. These factors may lead to a loss of statistical power and could affect the generalizability of the findings. Statistical significance will be set at $P<.05$ (2-sided).

The results of this study will be published in accordance with the CONSORT (Consolidated Standards of Reporting Trials) recommendations extended to cluster randomized trials.

Results

Preliminary Findings

A first draft of the serious game was created with funding obtained in March 2024 (Innovation Prize of University Hospitals).

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As of May 2025, it was tested in 1 middle school in Réunion Island across all seventh grades, with the approval of the school director and teachers, before the vaccination campaign. The game is intended to be used by teachers alone, without the help of a game animator, to enhance reproducibility.

Children were engaged by the game, and their intention to vaccinate was higher than in other schools. Among the 189 students in seventh grade at that school, vaccination teams had initially received consent for 10 students to be vaccinated. After the intervention/serious game, more students submitted signed consents, and a total of 25 (13.2%) students were vaccinated. In other schools in Réunion during that campaign, vaccination coverage did not exceed 7% (986/14,500, 6.8%).

Although the serious game has been developed, some minor changes need to be considered following this first experience with children. Once finalized, production of several copies will be launched. As registrations are in progress, the study is expected to start during the academic year in August 2026.

Expected Outcomes

Réunion Island has one of the lowest vaccination coverage rates among regions in France and Europe (14.8% overall, with 16.1% among girls and 3.4% among boys). Within 1 year, we expect this coverage to remain stable or only slightly increase. We hypothesize that by the end of the school year, 30% of children in the control group will have initiated vaccination—based on data published by Santé Publique France in 2023, which reported that 21.5% of 12-year-old children (girls and boys combined) in Réunion had received at least one dose of the HPV vaccine by December 31, 2023.

With this study protocol, we aim to achieve a vaccination coverage rate of around 45% among children through the proposed interventions (ambassador classes and serious games). This target was used to calculate the sample size. It is not yet known which of the 2 strategies will be more effective.

This study protocol could be implemented in other departments. By validating innovative strategies to improve HPV vaccination coverage in middle schools, this research could not only influence national vaccination campaigns but also provide insights for similar initiatives in other medical fields. It could play a central role in combating vaccine hesitancy, particularly among younger generations, by informing the population. The study results may also positively impact the involvement of children and families in vaccination campaigns. By reinforcing messages delivered by health care professionals and improving communication with families of participating children, this study could support greater acceptance of the HPV vaccine, thereby reducing the incidence of benign, precancerous, and cancerous conditions associated with the virus.

Discussion

Comparison With Previous Work

As mentioned earlier in the introduction, high levels of vaccination coverage are achieved in countries that vaccinate in schools [12]. In 2020, a team in La Réunion increased vaccination rates following interventions, with 26 girls completing the vaccination schedule compared with 3 boys [25].

Peer learning involves students acquiring knowledge or skills through experience, observation, or education [15]. This method allows students to think collectively about a subject, enhancing their critical thinking and understanding. Studies have shown potential benefits of this learning process in clinical training for adults, as well as positive social and academic gains among children. It reduces stress, increases self-confidence, and improves skills [14,26], not only in ambassador students but also among their peers who benefit from the ambassadors' knowledge [13].

Serious games have been developed as educational tools in recent years. They are immersive games built around a scenario and typically involve solving puzzles within a predetermined time frame. In the health field, serious games were introduced in 2017 to improve knowledge, increase interest and motivation, and enhance team cohesion and communication. However, literature on the subject is scarce, and although participant perception has been evaluated, data on knowledge improvement were not provided [17].

Study Limitations

Vaccination coverage is expected to continue increasing between 2023 and 2025, which may influence the number of schools included in each study arm and affect the calculation of the required sample size. This trend could potentially reduce the study's statistical power.

The potential for cross-talk between students in the intervention and control groups may introduce bias in this open/unblinded study and lead to contamination between students, especially in a setting like Réunion Island, where communities can be tightly knit and students may interact across schools or through extracurricular activities.

Interventions cannot be staggered over time because they depend on the academic calendar, which is punctuated by school holidays.

Nevertheless, to minimize contamination between the groups:

- We chose to use schools as units of randomization, rather than individual students.
- We will try to select schools that are geographically separate—ideally from different cities—to limit student interaction, although this remains subject to randomization.
- We will try to measure the extent of contamination at the end of the study by asking students whether they heard about HPV vaccination from students in other schools.
- Although blinding is not practically feasible for this study, students and teachers in control schools can be informed that they are part of a general public health campaign without knowing the specific educational strategies tested in other arms. We have planned an objective primary end point to compensate for this. Recovery of vaccination status will be carried out using the French social security system after anonymization of social security numbers.

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- We plan continuous monitoring in the form of visits to establish quality controls throughout the study, including on-site visits and calls to school officials.
- We will use a mixed logistic model with random intercepts to assess the effect of the 2 interventions, compared with the control group, on the proportion of vaccinated individuals. This model will allow us to account for the cluster structure of the data. By including schools as random effects, we consider that each school may have a different baseline proportion of vaccinated individuals due to unmeasured factors. The interventions will be modeled as fixed effects. A mixed logistic model with a random intercept is an ideal approach for analyzing data in a cluster-randomized study (such as one involving schools) while accounting for contamination bias.

Study Strengths

To the best of our knowledge, this study is the first of its kind in France, enhancing the program recently launched by the French government for the 2023 school year by incorporating innovative educational tools, such as serious games, in comparison with peer learning through ambassador classes. The results of this study, along with the development of these educational programs, could be adapted and applied to other regions in France—or even to other countries—for different medical subjects.

In addition, the sample size allows us to achieve a higher level of confidence.

This study focuses on a major public health issue in the current epidemiological context. It is important to address this now, given the effectiveness of the vaccine in preventing papillomavirus-related complications. The study will help identify the life stage during which vaccination is most effective and guide targeted primary prevention efforts.

If this study demonstrates effectiveness, the expected impact will be significant, providing numerous benefits for public health in the short, medium, and long term:

- Validate the most effective strategies for improving HPV vaccination campaigns in French schools and potentially internationally.
- Increase HPV vaccination coverage in Réunion Island.
- Optimize school-based vaccination campaigns.
- Promote the involvement of students in the HPV vaccination campaign across all Réunion colleges.
- Enhance and reinforce the messages delivered by health care professionals and public communication channels.
- Raise awareness among the families of participating children.
- Reduce the incidence of HPV-related benign conditions, such as condyloma, as well as precancerous and cancerous lesions.

Conclusion

To the best of our knowledge, this represents the first study aimed at enhancing HPV vaccination rates among children in Réunion Island using innovative tools, specifically serious games and ambassador-led classes. This multicenter study may offer promising intervention strategies to address HPV vaccine hesitancy and could potentially complement the ongoing HPV vaccination campaign in France. By rigorously evaluating their respective impacts within a controlled setting, this study will inform future public health programming. Once the most effective and cost-efficient strategy is identified, efforts and resources can be focused on its broader implementation at the regional level—and potentially beyond—to maximize public health benefits and reduce the burden of HPV-related disease among adolescents.

Acknowledgments

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Authors' Contributions

JD wrote the original draft. AB contributed to conceptualization, project administration, and supervision. EC assisted with conceptualization, formal analysis, and methodology. JS contributed to formal analysis and methodology. KD was involved in conceptualization. VB validated and reviewed the final manuscript. PLT contributed to conceptualization, funding acquisition, investigation, supervision, and validation, and also reviewed the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Knowledge quiz.
[DOCX File , 207 KB - resprot_v14i1e73366_app1.docx]

Multimedia Appendix 2
Satisfaction questionnaire for ambassador classes.
[DOCX File , 139 KB - resprot_v14i1e73366_app2.docx]

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Multimedia Appendix 3
Satisfaction questionnaire for the escape game group.
[DOCX File , 141 KB - resprot_v14i1e73366_app3.docx]

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Abbreviations

ANSM: Agence nationale de sécurité du médicament et des produits de santé
CONSORT: Consolidated Standards of Reporting Trials
HPV: human papillomavirus
ICC: intraclass correlation
Pap: Papanicolaou

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Protocol

Efficacy of a Ready-to-Feed Starter Liquid Infant Formula Containing 2-Fucosyllactose and Lacto-N-Neotetraose in Chinese Infants: Protocol for a Double Blind, Randomized Controlled Trial

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Abstract

Background: Bioactive compounds, such as human milk oligosaccharides (HMOs), impact the development of the intestinal microbiome and immune maturation in early life. They have been shown to result in positive benefits, including improved gut health, reduced frequency of infections, and age-appropriate growth when added to infant formula. However, data supporting the added value of including these HMOs in early-stage infant formula is currently lacking among Chinese infants.

Objective: In this double-blind randomized controlled trial including a nonrandomized reference breastfed group, we will test the efficacy of ready-to-feed infant formula containing 2 HMOs (2-fucosyllactose and lacto-N-neotetraose) on *Bifidobacteria* abundance, gut microbiome, gut and immune health, growth, and quality of life.

Methods: Healthy infants will be enrolled between 3 and 14 days after birth at 5 sites in China and randomized to either the experimental group (fed ready-to-feed infant formula containing 2 HMOs) or the control group (fed the same ready-to-feed infant formula without the 2 HMOs), using a dynamic allocation algorithm with double blinding. Infants will receive trial formula until age 6 months and will be followed up until age 12 months. The breastfed group will serve as a reference. The primary end point will be *Bifidobacteria* abundance in fecal samples at 3 months, measured via quantitative polymerase chain reaction. Secondary end points will include fecal microbiome (including taxonomy, diversity, functionality, and metabolites), fecal markers of immune health, gastrointestinal tolerance, stooling patterns, immune competence (overall state of the immune system), sleep quality, growth, quality of life, medication use, and physician-reported adverse events. A 2-sided test at the 5% significance level will be used for statistical testing.

Results: The study received ethical approval in March 2024 and will be completed by the end of 2026, which will be followed by a publication in a peer-reviewed journal.

Conclusions: The Starter Liquid Infant Formula Trial (STARLIT) will be one of the first to assess the efficacy of these 2 HMOs among Chinese infants on gut and immune health, in addition to clinically relevant outcomes such as quality of life, growth, and

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adverse events. This study should help to demonstrate that an increase in the growth of beneficial *Bifidobacteria* in response to intake of 2-fucosyllactose and lacto-N-neotetraose may have a broader impact on overall gut microbiome composition and infant gut and immune health.

Trial Registration: ClinicalTrials.gov NCT06361719; https://clinicaltrials.gov/study/NCT06361719

International Registered Report Identifier (IRRID): PRR1-10.2196/66489

(JMIR Res Protoc 2025;14:e66489) doi:10.2196/66489

KEYWORDS

Bifidobacteria; gut microbiome; gastrointestinal tolerance; growth; immune health; human milk oligosaccharides; infant nutrition

Introduction

Human milk provides an abundance of structurally diverse bioactive compounds that promote appropriate gut maturation through their effects on the gut microbiome, gut barrier function, and intestinal immunity [1-8]. These bioactive compounds include human milk oligosaccharides (HMOs), α-lactalbumin, osteopontin, lactoferrin, gangliosides, phospholipids, immunoglobulins, and sphingomyelin [5-7,9]. Specifically, HMOs play a crucial role in the development of the intestinal microbiome and immune maturation [10,11] as they promote the colonization of beneficial bacteria such as *Bifidobacteria* [12,13] and improve gut epithelial barrier function by preventing the uptake of pathogens and toxins in the gut [13]. More specifically, 2-fucosyllactose and lacto-N-neotetraose have been found to enhance fermentation by gut microbes [14] and have antibacterial [15,16], antiviral [17,18], and anti-inflammatory activities [17] in vitro. In preclinical models, 2-fucosyllactose and lacto-N-neotetraose enhance fermentation and short-chain fatty acids production [18] by the gut microbiome [14] by promoting the growth of the beneficial *Bifidobacterium* species [15-19], while inhibiting colonization by pathogenic bacteria [18-20]. Preclinical evidence also suggests that 2-fucosyllactose and lacto-N-neotetraose exhibit antibacterial action beyond the gut, specifically the upper respiratory tract [21,22], as well as demonstrating antiviral [23,24] and anti-inflammatory activity [19,20,24].

Term infant formula supplemented with up to 1.0 g/L of 2-fucosyllactose alone [25,26] or in combination with 0.5 g/L of lacto-N-neotetraose [27] is well tolerated and supports normal growth. Infants fed formula supplemented with 1.0 g/L 2-fucosyllactose and 0.5 g/L of lacto-N-neotetraose in the first 6 months of life had lower parent-reported morbidity, including bronchitis and lower respiratory tract infections (LRTI) through the first 12 months of life compared to infants fed the same cow's milk–based infant formula without HMOs [27]. Additionally, lower antipyretics at age 4 months and antibiotics at ages 6 and 12 months were recorded in the HMO-fed group [27].

Part of the observed benefits of 2-fucosyllactose and lacto-N-neotetraose consumption in early life may be mediated by the effects of these 2 HMOs on the maturing gut microbiome. Consumption of 2-fucosyllactose and lacto-N-neotetraose containing formula in early life was associated with higher abundance of fecal *Bifidobacteriaceae* compared to non-HMO containing formula [28] and a gut microbiome composition closer to that of the breastfed group (BG), characterized by a greater likelihood to have a fecal community type similar to the most predominant of breastfed infants (defined by a high abundance of *Bifidobacteriaceae*). The latter was associated with lower antibiotic usage [28] and a distinct gut microbiome signature associated with reduced incidence of LRTI [29]. Finally, extensively hydrolyzed whey–based formula supplemented with these HMOs (2-fucosyllactose and lacto-N-neotetraose) was also demonstrated to support normal growth, have good gastrointestinal tolerance [30], reduce the frequency of upper respiratory tract and ear infections [30], increase fecal *Bifidobacterium*, and delay shift to an adult-type microbiome in infants with cow's milk protein allergy [31].

These findings support the rationale for supplementing cow's milk–based infant formulas with HMOs, including 2-fucosyllactose and lacto-N-neotetraose, for use in infants where either breastfeeding or the provision of breastmilk is not possible. However, data are currently lacking in Chinese infants as to how these HMOs can positively impact them very early in life. More specifically, clinical substantiation on the impact of these 2 HMOs on the dynamic changes in gut microbiome, gut barrier integrity, immune response, and other developmental outcomes is warranted in this population.

We aim to conduct a double-blind randomized controlled trial including a nonrandomized, reference BG to assess the efficacy of a ready-to-feed, liquid, bovine milk–based whey, predominant term infant formula containing 2-fucosyllactose and lacto-N-neotetraose from the first 2 weeks of age up to age 6 months in Chinese infants. We will also study its effects postintervention for up to age 12 months in promoting appropriate gut maturation and supporting immune functions. The primary objective of this trial is to show an increase in *Bifidobacteria* abundance in the experimental group (EG, which will receive ready-to-feed infant formula containing 2 HMOs) compared to the control group (CG, which will receive the same ready-to-feed infant formula without the 2 HMOs) at age 3 months. Secondary objectives include comparing the following outcomes among all the feeding groups (EG, CG, and BG): fecal microbiome and metabolic profile, fecal markers of immune health, gut barrier integrity, and inflammation, gastrointestinal tolerance, adverse events (AEs), infant immune competence, infant sleep quality, infant growth, and infant quality of life from enrollment up to age 12 months.

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Methods

Trial Design

This is a double-blind, randomized controlled intervention trial of healthy male and female term infants. Briefly, the trial will include three parallel arms: (1) the EG that will consume the interventional product (ready-to-feed infant formula containing 2 HMOs), (2) the CG that will consume the comparator product (CP, ready-to-feed infant formula without the 2 HMOs), and a BG as reference. The study constitutes of an intervention period (age 0-6 months) where infants from both the CG and EG will be exposed to either the interventional product or CP to evaluate their effects on key study outcomes, followed by an observational follow-up period (age 6-12 months) to evaluate long term postintervention effects of interventional product and CP on gut microbiome maturation and later incidence of illnesses, infections as well as immune status (Figure 1). The trial will include 5 scheduled clinic visits (V1: infant age 3-14 days, V2: infant age 3 months, V3: infant age 6 months, V4: infant age 9 months, and V5: infant age 12 months). Phone call appointments will serve as reminder calls for the collection of stool samples and completion of relevant questionnaires that need to be completed as part of the home procedures before the clinic visits. A brief overview of the study sessions and procedures is summarized in Table 1 and described in detail.

Figure 1. Graphical representation of the 3-arm study design. Randomization is for the formula-fed group only. 2'FL: 2-fucosyllactose; BG: breastfed group; CG: control group; EG: experimental group; HMO: human milk oligosaccharide; LNnT: lacto-N-neotetraose; RTF: ready-to-feed; V: visit.

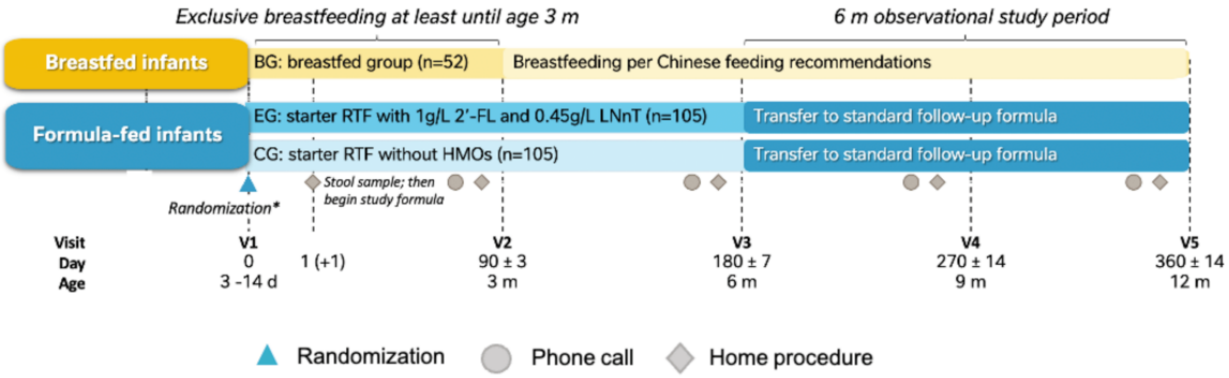

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Table 1. Study sessions and procedure.

Procedures	Intervention period						Observation period			
	V1[a]	H1[b]	H2	V2	H3	V3	H4	V4	H5	V5
Informed consent	✓									
Inclusion and exclusion criteria	✓									
Physical examination	✓									✓
Medical history	✓									
Demographics	✓									
Anthropometry	✓			✓		✓		✓		✓
Randomization	✓									
Fecal samples		✓	✓		✓		✓		✓	
Questionnaires										
IGSQ-13[c]	✓			✓		✓				
PISI[d]				✓		✓		✓		✓
BISQ[e]	✓			✓		✓				
ITQoL-SF[f] 47				✓		✓				
Diaries										
Stooling	✓		✓		✓					
3-day food					✓		✓		✓	
Breastfeeding (BG[g] only)	✓			✓		✓		✓		✓
Formula milk intake	✓			✓		✓		✓		✓
Infant illness	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Investigational product										
Administer trial formula (EG[h]/CG[i] only)		✓	✓	✓	✓	✓				
Adverse event collection	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

[a]V: visit.
[b]H: home.
[c]IGSQ: Infant Gastrointestinal Symptom Questionnaire.
[d]PISI: Pediatric Immune System Index.
[e]BISQ: Brief Infant Sleep Questionnaire.
[f]ITQoL-SF: Infant Toddler Quality of Life Questionnaire-Short Form.
[g]BG: breastfed group.
[h]EG: experimental group.
[i]CG: control group.

Trial Population and Eligibility Criteria

The trial population will consist of healthy infants aged 3-14 days at enrollment. Potential participants will be referred by the clinical care team to the investigator to check whether they meet the eligibility criteria, and the investigator will provide a thorough explanation of the trial. The eligibility of the potential participant will be confirmed according to the inclusion and exclusion criteria (Textbox 1), and each participant will be assigned a unique identification number.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Singleton, healthy, full-term gestational birth (≥37 completed weeks of gestation), with a birth weight ≥2.5 kg and ≤4.5 kg and postnatal age of 3-14 days (date of birth=day 0), inclusive.
- Willing and able to comply with scheduled visits and the requirements of this trial protocol.
- Access to a working freezer.
- For the formula-fed groups: infant is exclusively consuming and tolerating a cow's milk infant formula for at least 3 days before enrollment. The infant's mother has independently elected not to breastfeed.
- For the breastfed reference group: the infant has been exclusively consuming breastmilk since birth, and the infant's mother has decided to continue until at least age 3 months.

Exclusion criteria

- Infants receiving complementary foods or liquids, defined as 4 or more teaspoons per day or approximately 20 g per day of complementary foods or liquids at or before enrollment.
- Infants who have a medical condition or history that could increase the risk associated with trial participation or interfere with the interpretation of trial results.
- Infants who are presently receiving or have received before enrollment probiotic supplements or medications or supplements known or suspected to affect fat digestion, absorption, or metabolism (eg, pancreatic enzymes); stool characteristics or microbiome (eg, oral and systemic antibiotics, glycerin suppositories, bismuth-containing medications, docusate, Maltsupex, or lactulose); growth (eg, insulin or growth hormone); or gastric acid secretion.
- Infants currently participating or having participated in another clinical trial since birth.
- Infants with a known or suspected cow's milk protein intolerance or allergy, lactose intolerance, soy intolerance, or allergy.

Study Sites and Recruitment

Infants for this trial will be recruited from the following sites in China, including Xinhua Hospital affiliated to Shanghai Jiao Tong University School of Medicine, The International Peace Maternity & Child Health Hospital of China Welfare Institute at Shanghai, Shanghai First Maternal, Infant Hospital and Nanjing Women and Children Healthcare Center, and Peking University Third Hospital. The leading site is Xinhua Hospital affiliated to Shanghai Jiao Tong University School of Medicine, which is one of the top Pediatric Research centers in China specialized and well recognized in pediatric education, health care and research, while all the other participating hospitals are among the top women-and-children's health care hospitals, providing comprehensive health care in the north east and middle east regions of China.

At recruitment, the infants' parents or legally authorized representative (LAR) should have already made the decision regarding the feeding choice for their infant, and only when the parents have independently decided to formula-feed their infant, the infant will be enrolled into the clinical trial. No public or commercial advertisements of the trial, including research labels or product brand names, will be used. The benefits of breastfeeding will be discussed with all parents. Breastfeeding support via appointment with a qualified lactation consultant will be provided, before enrollment, to both the breast-fed and formula-fed groups, to ensure parents have received the appropriate advice. During the study, there will be dedicated investigational staff keeping close contact with the participants to acquire knowledge of any untoward medical event of their infants, and to remind them of study-related procedures such as stool sample collection and questionnaire completion.

Randomization Procedure and Blinding

Participants will be assigned to the EG or CG groups randomly using Medidata Randomization Trial Supply Management with the dynamic allocation algorithm at the first visit. An allocation ratio of 1:1 stratified by site, sex (female or male), and mode of delivery (cesarean section [CS] or vaginal) will be carried out. Neither the investigator or site team nor the participant will know which investigational product each participant is receiving until after database lock. Considering the double-blinded nature of the trial, the identity of the specific product will be blinded to participants, participants' parents, or caregivers (if applicable), support staff, investigators, site team, contract research organization managing the trial (except specified delegated regulatory staff), and study sponsors (except the manufacturing site, supply, and quality managers). The products will be identical in packaging, color, and taste. They will be packaged and labeled identically but will have distinguishable product codes printed on the packaging. Unblinding will be done only in case of emergency or after database lock for final statistical analyses.

Intervention

The EG will receive a ready-to-feed, liquid, bovine milk–based whey, predominant term formula supplemented with 1 g/L 2-fucosyllactose and 0.45 g/L lacto-N-neotetraose. The dosage of the HMO blend used in the trial is well within the range of HMO concentrations found in mature breast milk [32,33]. The formula contains 67 kcal/100 mL, 2 g protein/100 kcal (65% whey/35% casein), 10.6 g carbohydrates/100 kcal, and 5.4 g lipids/100 kcal. The CG will receive the same formula but without the HMOs. Both formulas are enriched with an advanced whey protein profile obtained using a unique whey protein ingredient that delivers a formula enriched in

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α-lactalbumin, osteopontin, lactoferrin, and milk-fat-globule membrane (MFGM) proteins and lipids (α-MFGM) [34] and a casein profile comprised of A2 β-Casein, in combination with an Sn-2 palmitate enriched triacylglycerol core and contain vitamins and minerals in amounts intended for full nutritional support of infants from birth to 6 months. Formulas will be started after the baseline stool sample collection on study day 1 or 2 and continue until age 6 months, after which infants will switch to a classical nontrial follow-up formula (not provided by the sponsor) until age 12 months. The study formulas will be provided in bottles of 70 mL stage 1 liquid ready-to-feed with each dispensing unit (carton) coded with a unique identifier and containing 32 bottles. The packaging and labeling of each bottle or carton will be identical for both groups, except for this unique identifier. The amount of formula offered to the infant will be informed by a physician or the recommended feeding table for this age group. Formulas will be consumed daily, ad libitum, per standard practice. The BG will continue exclusively breastfeeding at least until age 3 months and continue to breastfeed as per standard Chinese feeding recommendations up to study end.

Participants may be discontinued from the trial or the product if they withdraw consent to participate or from the trial product. This should have no impact on the participant and will be done without reprisal as per the Declaration of Helsinki. The investigator may also decide to discontinue a participant from the trial or the product if, in his or her opinion, continuation may be detrimental to the participant. Reason for discontinuation will be documented throughout the study.

Study Outcomes

The primary end point of this trial will be *Bifidobacteria* abundance in fecal samples at age 3 months (before V2). *Bifidobacteria* play a central role in gut microbiome maturation at early stages of life. *Bifidobacteria* are the most predominant taxon during the first 6 months of life, hence we aimed to evaluate how the intervention will impact this taxon halfway through the period in which it is playing a key role in gut microbiome and immune maturation [35,36]. Secondary end points will include fecal microbiome and metabolic profile, fecal markers of immune health, gut barrier integrity and inflammation, gastrointestinal tolerance, immune competence, sleep quality, infant health-related quality of life, growth, infant feeding and dietary patterns, and AEs.

Bifidobacteria Abundance

DNA will be extracted from the fecal samples, and microbiome composition will be assessed using next-generation sequencing (NGS) and quantitative polymerase chain reaction. The fecal sample collected at age 3 months (just before V2) will be used to examine the differences between intervention groups (EG and CG) in *Bifidobacteria* abundance, the primary end point.

Secondary Fecal Outcomes

Fecal microbiome, including overall taxonomic and functional composition and diversity, will be assessed at all time points (V1 to V5) using NGS. The assessment includes a relative abundance of beneficial bacterial species (eg, *B infantis*), pathogenic bacterial species, α diversity, β diversity, fecal community types, and functional annotation of the collected samples. Fecal metabolic content will be measured by quantifying pH and organic acids (such as but not restricted to lactate (including indole-lactate, L- and D-lactate), propionate, butyrate, acetate, valerate, total organic acids, and total short-chain fatty acids), at all time points (V1-V5). These organic acids will be profiled using ultra-high performance liquid chromatography coupled to tandem mass spectrometry. Additionally, targeted or untargeted metabolomics will be performed using high-performance liquid chromatography on the same samples. Fecal markers of immune health (secretory immunoglobulin A), gut barrier integrity (α1-antitrypsin, calprotectin, and lipocalin-2), and inflammation (IL-1β, IFN-γ, and TNF-α) will be measured at V1, V2, and V3 and quantified using an enzyme-linked immunosorbent assay. All fecal metabolites and markers will be reported as per wet stool weight and per dry stool weight (dry stool weight will be calculated to normalize the data for analysis). Plans for collection, laboratory evaluation, and storage of fecal samples are described in further detail in Additional File S1 in Multimedia Appendix 1.

Gastrointestinal Tolerance and Stooling Patterns

Gastrointestinal symptoms and related behaviors will be captured by the Infant Gastrointestinal Symptom Questionnaire-13 [37] at V1, V2, and V3. This is a validated, 13-item instrument of behaviors that the infant has experienced from the parent's perspective, with 5 domains including stooling, flatulence, fussiness, crying, and vomiting. The possible range of scores for the composite index is 13-65, with lower scores indicating lower discomfort. Good tolerance, some gastrointestinal distress, and not well-tolerated are reflected by scores of 13-23, 23-30, and >30, respectively.

Stool patterns, including stool frequency, consistency, and difficulty in passing stool, will be collected using a 1-day retrospective diary at baseline (V1) and a 3-day prospective stool diary completed at home by the parents at V2 and V3. Stool frequency will be computed as the mean number of reported stools. Stool consistency will be validated using a 5-point stool scale: 1=watery, 2=runny, 3=mushy or soft, 4=firm, and 5=hard [38], and the mean scores will be calculated. Difficulty in passing stool will be calculated as the number of stools reported as difficult of the total number of stools.

Immune Competence

The Pediatric Immune System Index is a short questionnaire developed internally for use in healthy infants to assess their overall state of the immune system and is assessed at V2 to V5. The questionnaire has 21 items across the 4 domains of gastrointestinal, upper respiratory tract infections, LRTI, and skin allergies, and records the duration, episodes, severity of health care visits, and treatment received for the most severe case. The responses recorded for each of the items are mapped to a score of 0, 1, 2, or 3. The final score (varying from 0 to 63) corresponding to a participant for a visit is then calculated as the sum of the individual item scores, with 0 indicating the best and 63 indicating the worst immune health.

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Sleep Quality

Sleep quality will be assessed at V1, V2, and V3 using the Brief Infant Sleep Questionnaire that has been validated against actigraphy and sleep diaries [39]. The Brief Infant Sleep Questionnaire is a 13-item parent-reported questionnaire on infant or toddler sleep over the past week, takes about 5-10 minutes to complete by the parent or caregiver, and assesses nocturnal sleep duration, night wakings, and method of falling asleep.

Quality of Life

Infant quality of life will be measured at V2 and V3 using the Infant Toddler Quality of Life Questionnaire-Short Form 47, which has been validated in China [40,41]. It is a 47-item tool that asks about infant life across 9 domains: general health, physical functioning, growth and development, discomfort and pain, temperament and mood, behavior, social interaction, health perception, and anxiety and worry. Scores range from 0 to 100 for each domain, with 0 indicating the worst quality of life and 100 indicating the best quality of life.

Growth

Anthropometric measurements, including weight (g), length (cm), and head circumference (cm), will be collected at all visits. Infants will be weighed without clothing or a diaper on a calibrated electronic weighing scale, and the weight will be recorded twice to the nearest 10 g. Using a standardized infant length board, length will be recorded twice to the nearest 0.1 cm with the infant looking vertically upward and the crown of the infant's head in contact with the headpiece of the board. Infant head circumference will be measured twice to the nearest 0.1 cm using a standard nonelastic plastic-coated measuring tape. Sex- and age-specific *z* scores, including weight-for-age, weight-for-length, length-for-age, and head-circumference-for-age, will be calculated using the World Health Organization (WHO) Child Growth Standards as the reference population [42].

Safety Reporting

Safety assessments will involve the monitoring and recording of all AEs and serious AEs throughout the trial upon signature of informed consent until the end of the trial or follow-up. Additional safety evaluations may be performed when medically indicated or in the opinion of the investigator. Parents or caregivers will be responsible for completing the infant illness diary (IID) weekly from enrollment until V5. The diary will ask the parent to capture the number of occurrences and the length of time the infant experiences the following symptoms: (1) fever, (2) respiratory tract symptoms, (3) gastrointestinal symptoms, (4) ear symptoms, as well as any medications the infant may be taking. The diary entries will be reviewed at each scheduled site visit or via regular phone calls, and the trial physician will validate the symptoms and associated diagnosis. Physical examinations will be performed at the baseline visit (V1) and the end (V5) or if deemed necessary at other visits for medically significant reasons. Details about the events including participant and date, description, reporting source, dispensed investigational product, duration, frequency, intensity (mild, moderate, or severe), seriousness, action taken, outcome, and sequelae if any, and relationship to test product (unrelated, unlikely, probable, or related), will be documented thoroughly.

Additional Variables of Interest

Demographic Data, Birth, and Household Characteristics

Demographic data including age of child, sex, ethnicity, birth characteristics (birth weight and length, gestational age at birth, parity), APGAR (appearance, pulse, grimace, activity, and respiration) score at 5 minutes, feeding history (eg, breastmilk, formula, or complementary feedings), maternal age, education, health history and family history of allergy will be collected from the participant or parents or LARs at the enrollment visit (V1).

Feeding and Dietary Patterns

A 3-day food intake diary will be collected before each fecal sample is collected when the infants are aged 6, 9, and 12 months to evaluate the energy and nutrient intake, dietary pattern, and the introduction of complementary foods. Compliance with breastfeeding will be assessed among the BG infants using the breastfeeding diary, which will capture details about the frequency, duration, and type of breastfeeding (exclusive, predominant, or partial) at each visit (V1-V5). Additionally, parents or caregivers will complete the formula milk intake diary, which will collect information regarding the total quantity of milk consumed for each formula feeding from V1 to V5 in the EG and CG infants. These dietary and feeding-related data may be used as a covariate for the gut microbiome analysis, as gut composition is highly diet dependent.

Concomitant Treatments and Medications

Trial infants may receive any medically needed treatment, therapy, or medication, and there are no unauthorized treatments or medications. Parents or LARs will be requested not to give any prebiotic, or probiotic supplement from enrollment until after the stool sample is collected, just before V5 (age 12 months), unless medically prescribed or recommended by the infant's physician. If given, prebiotic or probiotic supplements will be considered as concomitant medications and will be reported in the electronic case report form (eCRF) until V5.

Concomitant Diets

Introduction of complementary foods before V2 (infant age of 3 months) will be considered unauthorized per current recommendations for feeding healthy newborn infants and recorded as nontrial feeding in the eCRF. Additionally, any formula other than the trial formulas (CG and EG infants only) from the collection of the 1st stool sample (home [H1]) until intervention end (V3), and any infant formula in the BG before V2 will also be recorded as nontrial feeding in the eCRF. Finally, any prebiotic- or probiotic-containing foods until V2 will be reported as nontrial feeding in the eCRF for any of the groups.

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Data Analysis

Sample Size

The sample size was calculated based on the primary end point of the trial and an additional nonrandomized breastfed arm. To demonstrate a statistically significant increase of 8% in relative *Bifidobacteria* abundance at 3 months in the EG versus CG infants with a power of 80% and an α-level of 5%, a sample size of 105 per arm (including a 20% attrition rate) will be needed. For the nonrandomized breastfed reference arm, assuming a noninferiority margin of 20% in *Bifidobacteria* abundance with the experimental formula arm, the required sample size will be 52 infants (including a 20% dropout rate). Therefore, the total sample needed for this trial will be 262 infants (105 EG, 105 CG, and 52 BG).

Statistical Analysis

A staged statistical analysis (SSA) is defined as any statistical analysis performed when recruitment is completed, all participants have completed a predefined specific time point before the last participant last visit has been performed, and before the final database for the trial is locked.

The estimates computed at the SSA are considered final as all the participants have passed the predefined specific time point. The SSA will not lead to any modification in the design and subsequent conduct of the trial. Its sole purpose is to accelerate the availability of the key end point estimates. For this study, in addition to the final analysis, 2-stage statistical analyses are planned at 3- and 6-month visits. The analysis of the primary end point will be included in the first SSA.

Data will be analyzed on the following analysis populations:

1. Full analysis set (FAS): the FAS will exclude randomized participants who never took any of the assigned product (trial formula or breastmilk), participants who failed to satisfy trial entry eligibility criteria, or had no postrandomization data. This will be derived according to the assigned product group per randomization.
2. Safety analysis set (SAF): the SAF will include all participants in the FAS dataset with documented use of at least one feeding of the trial formula or breastmilk for the BG, classified according to the feeding actually received, irrespective of the randomization assignment.
3. Per protocol set (PPS): the PPS will include participants in the FAS with no major protocol deviations. Participants with major protocol deviations related to Good Clinical Practice (eg, ICF process not followed) will not be removed from PPS by default. A separate listing of these participants will be provided in the statistical report. The protocol deviations (eg, product compliance or visit window) will be defined before trial start. The listing of the protocol deviations will be reviewed during the blinded data review meeting.

The primary end point will be assessed on both FAS and PPS populations. All secondary end points will be analyzed on the FAS except for safety end points, which will be on the SAF. No interim analyses are planned for this study.

For all categorical and continuous variables, appropriate descriptive statistics will be calculated by visit, feeding groups, and delivery mode. The primary end point of the difference in *Bifidobacteria* abundance between EG and CG infants will be analyzed using analysis of covariance (ANCOVA), correcting for baseline, site, gender, and mode of delivery. If the investigation of data reveals an inflation of the null values (no detected *Bifidobacteria* in samples), then the ANCOVA model will be replaced by a 0-inflated mixture model. For continuous secondary end points, ANCOVA models correcting for baseline, site, gender, and delivery will be used for analyses. For categorical secondary end points, logistic regression models will be used to compare between feeding groups at each time point separately. Fecal metabolism and immune health markers will be analyzed according to dry stool weight, using an ANCOVA model at each time point to compare between feeding groups, correcting for baseline, site, gender, and mode of delivery. The necessity to log-transform the end points or to use nonparametric methods will be assessed during the blind data review and addressed in the statistical analysis plan. During the final analysis, the models may be modified to a mixed model repeated measurements to consider the longitudinal nature of the data. AEs will be compared between feeding groups using the Fisher exact test.

Missing data will be assumed to be missing at random unless the blind review of the data demonstrates a pattern of missingness, in which case, multiple imputation for the primary outcome of *Bifidobacteria* abundance at 3 months may be used. In the case of outliers for any end point, robust approaches or sensitivity analyses may be used. Statistical testing for all end points will be 2-sided and at a 5% significance level. All statistical analyses will be performed in SAS Life Science Analytics Framework (version 5.4.1; SAS Institute Inc).

Compliance With Investigational Product

Compliance with feeding interventions will be monitored throughout the trial using various tools, such as a formula milk intake diary and breastfeeding questionnaire at specified visits. Data on nontrial feeding will also be recorded at specific time points to inquire about regimen interruptions and consumption of unauthorized feedings or supplements. Each trial day in which trial formula intake or exclusive breastmilk feedings are interrupted will be counted as a noncompliant day. Throughout the trial, noncompliance will be calculated based on formula-fed infants being off trial formula or breastfed infants being off breast milk and consumption of prebiotics or probiotic-containing supplements, with some minor modifications based on specific visits.

The number of noncompliant and compliant days will be determined, and a compliance rate as a percentage of compliant days concerning total potential days of exclusive feeding (approximately 100 days, but individual for each infant, depending on the enrollment age) will be calculated for each participant and dropout participant. Participants with a compliance rate of less than 80% will be considered as having a major protocol deviation and will not be included in the PPS. All noncompliance between V2 and V5 will be considered minor protocol deviations.

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Trial Discontinuation

Discontinuation from the trial product may happen for the following reasons: parents or LARs withdraw consent to participate, or the investigator decides to discontinue the trial if they opine that continued exposure to the trial product would be detrimental to the participant's well-being. No additional data will be collected, and no further analyses will be performed if consent is withdrawn. The reason for premature discontinuation will be documented, and the investigator will follow up regarding any unresolved AEs.

Data Management, Monitoring, and Dissemination

Data Management

Site personnel will manually enter source data (clinical findings and observations, laboratory and test data, questionnaires, site notebooks, and paper diaries) into the electronic Case Report Form (eCRF) web database, which is 21 CFR Part 11 compliant. The clinical data manager will review and validate all entered data. The eCRF database will be locked after cleaning of the data, which includes review, query resolution, signatures by the investigators, and determination that the database is ready for analysis. All documents on the conduct of the study will be kept by the investigator for 5 years after the study's completion.

Data Monitoring

The monitoring plan will be developed and agreed upon between the sponsor and the contract research organization responsible for the monitoring at the site on the monitoring activities to be compliant with the protocol, Good Clinical Practice Guidelines, local regulations, and the sponsor's procedures, and to ensure the subjects' well-being and data integrity. At agreed-upon times during the trial and after the trial has been completed, the investigator will allow sponsor representatives to periodically review the eCRF and corresponding records (source documents) of each trial participant. These monitoring visits will allow the sponsor or sponsor representative to examine trial progress, verify completeness and accuracy of eCRF, resolve any inconsistencies in the records, and ensure that all protocol requirements and obligations are being fulfilled. The sponsor representatives or external auditors will be permitted by the investigator to conduct an audit of the trial during the trial or after the trial ends. This will be to ensure compliance with the Good Clinical Practice Guidelines, local regulations, the trial protocol, and the sponsor's procedures, as well as evaluating the accuracy of the trial data.

Regular data quality reviews are organized to identify any data inconsistencies. To ensure data quality, automatic edit checks that identify inconsistencies have been set up and flagged as queries during the data entry process. For more complex data where these automated checks cannot be implemented, manual review will be performed.

Ethical Considerations

Ethics approvals were granted by all the independent ethics committees of all the hospitals joining in the study, which are the Ethics Committee of Xinhua Hospital Affiliated to Shanghai Jiao Tong University School of Medicine (XHEC-C-2024-024-2), the Ethics Committee of Shanghai First Maternal and Infant Hospital (2024 027), the Ethics Committee of The International Peace Maternity and Child Health Hospital of China Welfare Institute (GKLW-A-2024-024-02), the Ethics Committee of the Peking University Third Hospital (2024 878-02), and the Ethics Committee of Nanjing Women and Children's Healthcare Hospital (2024FYYL007). All parents or LARs will sign an informed consent form (see example in Additional File S2 in Multimedia Appendix 1). In the event of a screen failure, that is, consent was signed but the participant was not subsequently enrolled, information related to the reason for screen failures will be documented.

This study will be conducted per the ethical principles outlined in the Declaration of Helsinki and in compliance with all applicable regulatory requirements, including China's Clinical Trial laws, the Personal Information Protection Law, and the Measures for Science and Technology Ethics Reviews (effective as of December 2023).

All participants will receive comprehensive written and verbal information about this study's objectives, procedures, potential risks, and benefits. Written informed consent will be obtained from each participant before any study-related procedures.

To ensure the protection of participants' rights, safety, and well-being:

- AEs will be monitored and managed per regulatory and ethical standards.
- Personal and health data will be collected, stored, and processed in full compliance with Personal Information Protection Law requirements.
- Participants will be informed of their right to withdraw from the study at any time without penalty.

Special attention will be given to the recruitment of breastfeeding mothers. Per the WHO International Code of Marketing of Breast-Milk Substitutes, no coercive or promotional practices were used. Participation will be entirely voluntary, and all information will be provided neutrally and respectfully to ensure informed and independent decision-making.

The study will be conducted by qualified investigators and supported by institutional quality assurance processes to ensure ethical conduct and regulatory compliance throughout. The study has been registered on ClinicalTrials.gov (NCT06361719), and results will be submitted to a peer-reviewed journal for dissemination; the role of authors and contributors will be defined according to International Committee of Medical Journal Editors guidelines. The study will be carried out according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines. The completed SPIRIT checklist is provided in Additional File S3 in Multimedia Appendix 1.

Every precaution will be taken to protect the privacy of research participants and the confidentiality of their personal information. The investigator will ensure protection of the participant's personal data and of all reports, publications, participant samples, and any other disclosures, except where required by law. Participants are identified only by a participant identification number and site identification number to maintain

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participant confidentiality. All participant study records will be kept safely in an access-controlled area. Identification code lists linking participant names to participant identification numbers will be stored separately from participant records. In case of data transfer, the sponsor will maintain high standards of confidentiality and protection of participant personal data. Clinical personal information will not be released without the written permission of the participant, except for monitoring by regulatory authorities or the study sponsor. The investigator or designee will comply with all applicable data protection laws and implement and maintain appropriate technical and organizational measures against the unauthorized or unlawful acquisition, access to, or processing of Personal Data and against the accidental loss, disclosure, or destruction of, or damage to, Personal Data.

Results

The study was initiated in July 2024, with the first participant's first visit at the end of July 2024. As of June 2025, a total of 122 participants were recruited, and 74 completed visit 2 (3-month time point). The study is expected to be completed (the last participant's last visit) by the first half of 2026. All data will be analyzed at the end of the study (after database lock, to maintain the double-blind nature of the study), followed by publications in peer-reviewed journals.

Discussion

The Starter Liquid Infant Formula Trial (STARLIT) is among the first few clinical trials that will investigate the efficacy of the 2 HMOs, 2-fucosyllactose and lacto-N-neotetraose, on gut health, gut barrier integrity, and immune response, together with clinically relevant outcomes such as illness, infections, growth, and quality of life among Chinese infants born at term. *Bifidobacteria*, a key microbiome taxon during early life development, are often depleted in the gut of an infant receiving infant formula compared to breastfeeding [43]. One of the main drivers of this difference is the absence of HMOs in infant formula compared with breastmilk [44]. We therefore anticipate that consumption of an infant containing the 2 selected HMOs formula from birth to age 6 months will favor the growth of gut *Bifidobacteria* compared with the CG and should bring *Bifidobacteria* levels closer to those in the breastfeeding arm of the study. Given the central role of *Bifidobacteria* in gut microbiome maturation, we expect that other microbial taxa and functions may also be affected by the presence of the 2 HMOs and contribute to directing the gut microbiome maturation closer to the 1 observed in breastfed infants [45]. Finally, both *Bifidobacteria* and HMOs have been linked to multiple health outcomes [32]. With the breadth of end points collected in this study, we hope to be able to explore the importance of the addition of HMOs in early-life infant formula beyond the gut microbiome. Breastfeeding is the reference for infant nutrition as it is the best way to support optimal growth and development. Providing suitable solutions for infants that cannot be breastfed and that mimic breast milk composition as best as possible has become possible with ongoing research on breast milk composition as well as technological progress. To date, differences in health outcomes between breastfed and formula-fed infants remain, which may be attributed to the absence of key bioactive compounds such as HMOs in standard infant formulas [46,47]. HMOs are the third largest solid component in human milk, following lactose and lipids. They offer a wide range of functional benefits, including supporting immune and cognitive development [1,3,32,33,48]. These benefits may mostly be mediated by the impact of HMOs on the gut microbiome and its metabolic activity [49,50]. HMOs are nondigestible oligosaccharides that reach the lower part of the infant digestive track, where they can be used and transformed by the maturing gut microbiome. Specifically, they support the growth and metabolic activity of *Bifidobacteria* in early stages of life, which has been associated with multiple health benefits [51]. Technological and regulatory advancements now allow the inclusion of oligosaccharides identical to those found in human milk, such as 2-fucosyllactose and lacto-N-neotetraose, in infant formulas in China [32,33]. Hence, generating clinical evidence that supports the efficacy of these HMOs in this population is much warranted.

We hypothesize that the addition of 2-fucosyllactose and lacto-N-neotetraose to the infant formula will promote the growth of beneficial *Bifidobacteria* and drive the gut microbiome of infants closer to that of breastfed infants. Additionally, we propose that this bifidogenic effect may further benefit infant gut and immune health. Previous studies have shown that the fecal microbiome of most infants from China falls within a distinct enterotype from the rest of the world. More specifically, this enterotype found most predominantly in China is characterized by a relatively high abundance of *Proteobacteria* and more specifically of Enterobacteriaceae [52]. These taxa are considered opportunistic pathogens with their ability to alter the composition of the gut microbiome and favor gut dysbiosis [53,54]. They also have proinflammatory properties and have been associated with IBD pathogenesis and progression [55,56]. In contrast, among infants from the West, *Bifidobacterium* was found to be the dominant genus of the intestinal microbiota. Decline in *Bifidobacteria* and gut microbial dysbiosis has been linked to the increasing incidence of allergies and autoimmune diseases [57,58]. As mentioned earlier, in infants given formula supplemented with 2-fucosyllactose and lacto-N-neotetraose compared to control, there were significantly fewer reported incidences of bronchitis, respiratory tract infections, and use of antibiotics [27,30]. This observation has been linked not only to the bifidogenic effects of these HMOs but also to *Bifidobacterium*-related metabolic changes in the gut environment [28,29,59]. Hence, characterizing the role of HMOs in modulating the gut microbiome of Chinese infants and, in turn, assessing its impact on the immune health is central to this study [27-30,57-61].

Our study has several strengths. Its double-blinded design will ensure blinding of the participants, investigators, data collectors, outcome assessors, and data analysts to minimize bias in the reporting of the study outcomes. The study will be conducted across 5 different sites representing a wide geography within China and enabling a nonpreceded characterization of the effects of HMO supplementation in this population. Regarding the intervention products, the administration of a control formula

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identical to the test formula, apart from its HMO content, would allow us to clarify the efficacy of supplementation by 2-fucosyllactose and lacto-N-neotetraose with no further nutritional confounding factors. Yet, the 2 formulas must be precisely fully compliant with infant nutritional needs at this age. The nonrandomized BG will serve as a reference and help to gain insights into the contribution of these HMOs in shifting the gut microbiome and all other developmental outcomes closer to those of breastfed infants. The benefit of breastfeeding will be discussed with all parents who will meet a qualified lactation consultant before enrollment to ensure that they make an informed decision that is best for their infant. The service of a lactation consultant will be available over the course of the study to allow any parent to switch to breastfeeding at any time point.

The prospective and longitudinal nature of this study will allow us to collect detailed information on a comprehensive set of outcomes during the first year of life. Importantly, the fecal microbiome will be profiled using the most advanced and standard methodologies, such as NGS, in addition to quantitative polymerase chain reaction. This should enable us to shed light on the effects of HMOs on the dynamic maturation of the gut microbiome of Chinese infants at the taxonomic but also functional levels. HMO-mediated microbiome modulation of immune system development and fitness will be carefully monitored. We will capture infant illness weekly for 1 year using an IID, providing great granularity over AE occurrence. These IIDs will be used to generate an automated diagnosis that will be reviewed and confirmed by a study physician. Additionally, for the first time, we will use a novel Pediatric Immune System Index to assess immune competence that will allow the detailed characterization of gastrointestinal, upper respiratory tract infection, LRTI, and skin allergies by recording the duration, number of episodes, severity of health care visits, and treatment received. To complement this, fecal immune markers will also be quantified. Furthermore, we will be using validated questionnaires to capture details about gastrointestinal symptoms, sleep patterns, and quality of life to enhance our understanding of the effect of HMOs and their microbiome-modulating properties on infants' well-being [27]. Importantly, we will also collect covariates, including maternal education, delivery mode, family history of allergy, infant dietary intake, and infant feeding (breastfeeding and formula feeding), medications, and treatments to adjust our analysis for potential confounding effects. In our study, the randomization is stratified by delivery mode. We hope to gain important insights into the effect of HMO supplementation, particularly among infants born by CS, in whom lower colonization rates of beneficial bacteria such as *Bifidobacterium* and *Bacteroides*, and higher colonization rates of *Clostridium*, *Lactobacillus*, *Enterobacter*, *Enterococcus*, and *Staphylococcus* have been reported [62]. This is particularly relevant considering the high rates of elective CS in China with an increase reported from 28.8% in 2008 to 36.7% in 2018 [63] and reaching up to 43.79% in 2019 according to the data published by the National Health Service and Quality Safety Report (obstetrics) in 2020 [64] This is far above the CS rates of 10%-15% of all deliveries suggested as reasonable by the WHO [65,66] and likely impacts the immune development of their infants, risk for allergy, atopy, and asthma, and intestinal gut microbiome diversity [67].

We acknowledge a few limitations in our study. While the study uses a comprehensive set of tools for assessing several outcomes, these may be perceived as burdensome to some subjects. Hence, the choice of not including systemic immune markers in addition to feces to reduce burden and risk linked to invasive procedures was made. Finally, generalization of results outside of China may be limited due to the geographical specificity of their gut microbiome.

In conclusion, this double-blind randomized controlled trial with a nonrandomized BG will be among the first studies in China to investigate the efficacy of a ready-to-feed infant formula containing 2-fucosyllactose and lacto-N-neotetraose in a matrix containing a unique whey protein concentrate coenriched in α-lactalbumin and MFGM on gut and immune health, as well as the effects on tolerance, growth, sleep, and quality of life. The much-anticipated results from this trial will strengthen the evidence base regarding the beneficial effects of HMOs in Chinese infants, as the study design should enable us to demonstrate that the addition of HMOs in infant formula contributes to supporting Bifidobacterium growth in the infant gut as well as the appropriate maturation of the gut microbiome and immune functions. This may help drive recommendations on target doses that are appropriate for observing beneficial changes in gut microbiome, gut maturation, gut barrier integrity, immune response, and other developmental outcomes.

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Data Availability

Data sharing is not applicable to this paper, as this is a protocol and no datasets were generated or analyzed during this study.

Authors' Contributions

YW, JL, SH, ZL, and WC provided clinical and operational inputs on the study protocol, presented the study protocol, and provided administrative support at the Institutional Ethics Committee meetings affiliated with their respective sites, provided resources and support for site initiation, were responsible for study execution and implementation, and reviewed and edited the writing. TMS conceptualized the study and developed the study protocol, wrote the original draft, and reviewed and edited the writing. CILR, AL, HS, QL, JD, and AM developed the study protocol, wrote the original draft, and reviewed and edited the writing. AL developed the statistical analysis plan. HS developed and coordinated the setup of the trial database. QL provided operational leadership for study setup and execution. All authors reviewed and approved the final paper.

Conflicts of Interest

TMS, CILR, AL, HS, QL, JD, and AM are employees of Société des Produits Nestlé S.A., the sponsors of this trial. YW, JL, SH, ZL, and WC received a grant from Nestlé to conduct the study. The investigational products were provided by Wyeth Nutritional (China) Co, Limited.

Multimedia Appendix 1
Additional file S1: plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies. Additional file S2: model consent form and other related documentation given to participants and authorized surrogates. Additional file S3: SPIRIT checklist.
[PDF File (Adobe PDF File), 253 KB - resprot_v14i1e66489_app1.pdf]

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Abbreviations

AE: adverse event
ANCOVA: analysis of covariance
APGAR: appearance, pulse, grimace, activity, and respiration
BG: breastfed group
CG: control group
CP: comparator product
CS: cesarean section
eCRF: electronic case report form
EG: experimental group
FAS: full analysis set
HMO: human milk oligosaccharide
IID: infant illness diary
LAR: legally authorized representative
LRTI: lower respiratory tract infection
MFGM: milk-fat-globule membrane
NGS: next-generation sequencing
PPS: per protocol set
SAF: safety analysis set
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SSA: staged statistical analysis
WHO: World Health Organization

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Protocol

Exploring Subjective Well-Being in Human-Machine Interaction: Protocol for a Mixed Methods, Cross-Sectional Analysis in Manufacturing 5.0

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Abstract

Background: Human-machine interaction (HMI) has gained significant attention in the context of advanced production technologies, especially concerning trust and acceptance. However, the investigation of the subjective well-being of operators working with these technologies in manufacturing companies has been largely overlooked. Moreover, previous research mostly relied on a single data-collection method, either quantitative or qualitative, thereby failing to capture a rich picture of their cognitive and affective states.

Objective: This cross-sectional study protocol aimed to fill that gap by examining operators' subjective well-being and workplace dynamics, including fluency in HMI, negative attitudes toward technologies, and social relationships among coworkers in manufacturing companies.

Methods: We adopt a mixed methods approach, incorporating both quantitative and qualitative data collection techniques. Quantitative data will be gathered via a digital survey containing self-report questionnaires. A path analysis will be performed to explore the multiple mediating roles of fluency in HMI and negative attitudes toward such technologies between cognitive and affective well-being. We further qualitatively investigate the operators' lived experience in HMI using semistructured audio-recorded interviews. A thematic analysis relying on text-mining techniques will then be conducted to explore operators' textual data.

Results: We quantitatively expect that fluency in HMI may act as a protective factor for operators' affective well-being, while negative attitudes toward advanced production technologies may contribute to the development or worsening of operators' psychological distress. From a qualitative perspective, we intend to seamlessly merge quantitative insights to create a more comprehensive and well-grounded analysis. Moreover, the integrated interpretation of both the quantitative and qualitative data collected will generate a consensus report, which will aim to serve as a practical framework for guiding workplace policies and training programs meant to foster subjective well-being and effective HMI. At the time of publication, we have collected data from 12 participants and scheduled a further data collection session.

Conclusions: Embracing one of the fundamental pillars of Industry 5.0, human-centricity, by detecting potential psychological issues early, organizations can create a workplace that prioritizes the well-being of operators. Early recognition and prevention are crucial to promoting operators' mental well-being involved in HMI.

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KEYWORDS

subjective well-being; operators; manufacturing 5.0; human-machine interaction; protocol study

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Introduction

Background

In the last decades, the world of work has undergone radical changes across various sectors thanks to the rapid advancements of technological innovations. Technologies, such as the Internet of Things and cloud computing, have revolutionized how work is performed. In particular, according to the vision framed by the paradigm of Industry 4.0, the automation of the production processes would have significantly relieved workers from the heaviest and most tiring tasks [1]. However, the strong technology-driven focus of Industry 4.0 soon became evident, along with the limited accomplishment of the initial resolutions [2]. Indeed, the research that was carried out in this context sparsely focused on human factors [3]. According to a recent document published by the European Union [4,5], Industry 5.0 builds upon Industry 4.0 and is based on 3 founding pillars: human-centricity, sustainability, and resilience. Importantly, this shift reflects the recognition of the need to bring workers to the forefront of the innovation process, thereby designing and implementing technologies that meet their skills and needs. The emphasis on workers is not limited to providing them with the necessary competencies in using and interacting with novel advanced production technologies. It further includes a holistic approach that prioritizes their physical and subjective well-being. Subjective well-being, in particular, is the central focus of this study, conceptualized along 2 main dimensions, which are cognitive well-being (eg, satisfaction with life, job satisfaction, and work–home balance) and affective well-being (eg, stress, anxiety, and depression symptoms). While previous mixed methods studies in adjacent fields (eg, human-technology interaction) have addressed aspects such as technology acceptance or usability, they have rarely adopted an integrated framework that explicitly combines operators' cognitive and affective well-being in an ecological context [6,7]. In particular, in the framework of Industry 5.0, several studies have investigated specific aspects related to the impact of novel technology on the interaction between human and technology itself, for example, technology acceptance [8], trust [9], and best practices for introducing this technology [10]. The quality of this interaction often depends on fluency, a construct that captures the smoothness and synchronization, and coordination between human and machine actions during shared tasks and encompasses different dimensions [11]. Higher levels of fluency are associated with increased trust in machines, particularly robots, improved teamwork, and reduced cognitive workload, thereby providing a more positive experience for workers [12]. Conversely, negative attitudes toward machine systems, including both emotional responses (eg, discomfort, fear) and social perceptions (eg, lack of perceived peer or organizational support), can act as significant barriers to successful human-machine interaction (HMI) [13]. These attitudes are often shaped by workers' concerns about job security, lack of familiarity with technology, or perceptions of machines as competitors rather than collaborators [14,15]. Fluency in HMI and negative attitudes are positioned in this study as key mediating factors that may influence how cognitive well-being translates into affective well-being outcomes. Addressing these emotional and social dynamics is crucial for creating a balanced and supportive work environment where advanced production technologies can be effectively integrated.

To conceptually frame the relationship between work-related psychological outcomes and advanced production technologies, we draw on the Job Demands-Resources (JD-R) model [16]. According to this model, workplace factors can be broadly classified into job demands (ie, aspects that require sustained effort and are associated with psychological or physiological costs) and job resources (ie, aspects that support goal achievement, reduce job demands, or stimulate personal growth). In technologically intensive environments, advanced production technologies may play a dual function. Indeed, they may act as job resources by increasing task fluency, reducing physical and cognitive workload, and improving precision; but also, as job demands, when they introduce complexity, increase mental load, or elicit technostress, potentially due to lack of familiarity or negative attitudes. Our dual focus on how both cognitive and affective well-being are shaped by workers' interaction with advanced equipment is attuned to the ambivalent role of technology illustrated by the JD-R model [16].

In addition, a growing body of research has addressed the potential threat that novel technologies can represent for workers, because of the possibility of job loss [13], and consequently has tried to identify the factors that can lead to their smooth introduction and integration [14]. However, the role played by operators' affective and cognitive well-being has been largely overlooked by previous research, especially in the manufacturing sector. Similarly, the analysis of how the relationship between the worker and advanced production technologies develops over time, and how this may impact the subjective well-being and the social dynamics within the organization, has received little attention [15,17]. Indeed, previous research addressing the manufacturing industry mainly focused on the health risks related to physical interaction with technology [18], thereby failing to explore the psychosocial aspects implied and emerged from such interaction, with very few exceptions [18-21]. Moreover, in this novel paradigm, the home-work balance represents a crucial element [22,23] because it intertwines organizational and intrapersonal factors that can influence both affective and cognitive well-being. Recognizing and harmonizing these aspects is pivotal since they can enhance workers' job satisfaction and productivity [24], as well as being able to promote satisfaction with life and a healthier and more sustainable work environment.

A further key aspect to consider is job satisfaction, which is defined as "a pleasurable or positive emotional state resulting from the appraisal of one's job or job experiences" [24]. It encompasses a variety of dimensions that contribute to an individual's overall contentment with their professional role. One significant dimension is the home-work interface, which plays a pivotal role in determining job satisfaction by influencing the interplay between professional responsibilities and personal life [25]. This balance not only can affect employees' subjective well-being and productivity but also contributes to long-term career satisfaction and organizational commitment [24,25].

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From the picture outlined above, it clearly emerges a critical gap in the current literature regarding the impact of advanced production technologies on the holistic subjective well-being of operators, particularly in manufacturing contexts. More specifically, while factors such as acceptance and trust have been addressed, there is a lack of integrated models that place operators' cognitive and affective well-being at the forefront. This missing focus represents a significant limitation of previous research. Addressing this knowledge gap is crucial to developing human-centered interventions aligned with Industry 5.0 principles. Therefore, by adopting a structured conceptual hierarchy, this study conceptualizes indicators of cognitive well-being as independent variables, with affective well-being as the primary outcome (dependent variable). Fluency and negative attitudes toward advanced machines are positioned as key mediators within this framework, as illustrated in Figure 1. More specifically, we will focus on operators' perceptions in interacting with advanced production technologies in order to investigate their affective well-being, such as anxiety, depression, and stress symptoms, along with their cognitive well-being, including satisfaction with life and the work-related quality of life (WRQoL) dimensions (ie, job and career satisfaction and home-work interface) in the context of HMI in manufacturing 5.0.

Figure 1. The conceptual model of a path analysis investigating the role of fluency in HMI and negative attitudes towards advanced production technologies between cognitive and affective well-being.

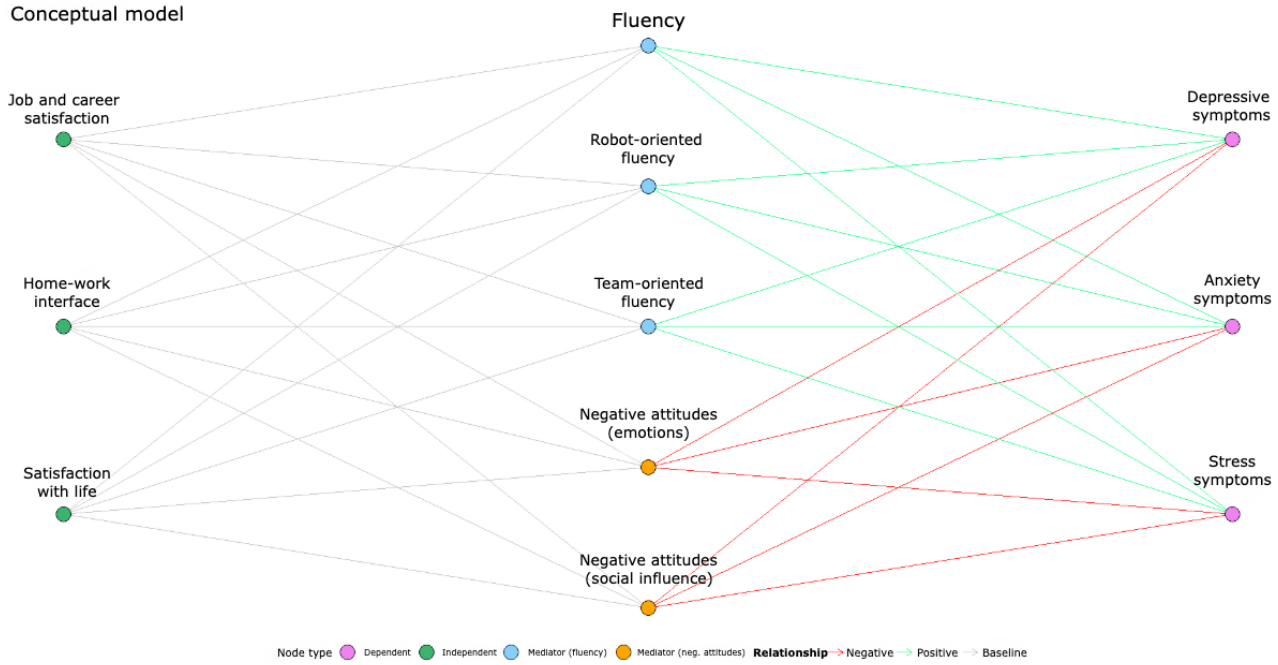

Literature Review

State of the Art of Research Investigating Operators' Subjective Well-Being in HMI Manufacturing Industries

The integration of new technologies in manufacturing industries not only revolutionizes production practices but also introduces complex dynamics that can have an impact on operators' mental health [26]. Previous research conducted both with workers from manufacturing and other industrial sectors has extensively focused on the consequences of stress. Findings pointed out that work-related stress symptoms have been linked to various factors, including job insecurity, high physical and cognitive workloads, and work intensity [27-29]. While stress symptoms may be a short-term response to the demands of the workplace, long-term exposure can lead to chronic psychological problems, including depression symptoms [26]. Depression symptoms may profoundly alter the way individuals perceive and interact with their environment [27] and are likely to be further affected by the advent of automation and advanced production technologies in the workplace [12,30]. As such, technologies can increase feelings of alienation and job insecurity, reduce opportunities for meaningful interpersonal interactions, and impose rapid adaptation to constantly evolving systems. Consequently, these factors may amplify the sense of disconnection and the onset of stress and anxiety symptoms, highlighting the need for supportive interventions that consider the psychosocial impact of technological change [31-33].

Anxiety symptoms, on the other hand, although closely related to depression and stress symptoms, manifest differently and require independent consideration in both studies and interventions. Anxiety symptoms are often interpreted as being a by-product of the rapid change of advanced production technologies and the resulting demands in work environments, for example, high-intensity pace and constant need for digital skill updates [34,35]. Notably, anxiety symptoms may further burden the individual's cognitive load, thereby creating a situation of overload. This is especially the case with anxiety symptoms triggered by the introduction of advanced production systems, and altogether they can substantially impair pivotal skills, such as decision making and problem solving [35].

While depression and anxiety are well-recognized mental health conditions with distinct profiles, their specific associations with HMI in advanced production environments remain poorly explored [36]. Previous studies have rarely investigated these

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symptoms as outcomes of cognitive well-being pathways mediated by fluency and negative attitudes, which represents a significant empirical gap.

Furthermore, a recent study found that high levels of fluency, which are related to the well-synchronized interplay between the human and the machine actions, are positively related to long-term teamwork, increased perception of one's mental contribution, and higher trust in the machine, particularly robots [9,12,37]. Conversely, negative attitudes and emotional responses toward machines may play a significant role in the onset or increase of psychological distress. Additionally, the relationship between these negative perceptions and psychological symptoms remains underexplored in existing literature. Mindful of the above, it is imperative to thoroughly investigate these abovementioned psychological symptoms to better identify both protection and risk factors and to design purposeful intervention strategies for promoting and supporting operators' subjective well-being and organizational effectiveness. Organizational effectiveness can be defined as the extent to which stakeholders' goals, such as those of investors, employees, and the community, are achieved. It is enhanced when employees engage in behaviors that extend beyond their formal roles, commonly referred to as organizational citizenship behaviors. These behaviors are more likely to be exhibited by employees who experience high levels of job satisfaction [38,39].

In this regard, most of the studies investigating HMI, especially those conducted in the field, have relied solely on quantitative self-reported instruments, thereby highlighting the need to widen the methodological approach [10]. The few works investigating HMI using interviews provided rich descriptions of how the work environment, the tasks, and the social dynamics changed after the introduction, for instance, of a collaborative robot (cobot) on the shop floor [40-42], yet they overlooked the operators' psychological state. However, it is important to note that most studies cited above had a more limited scope. Consistently, they have predominantly relied on cross-sectional quantitative surveys, often leaving behind the social dynamics and lived experiences of operators through qualitative or mixed methods approaches. Moreover, complex mediation models to understand the mechanisms linking cognitive well-being resources with affective well-being outcomes have been rarely adopted in previous research. Consequently, there is a need for research that combines quantitative rigor with qualitative depth to generate a more nuanced understanding of how advanced production technologies impact operators' subjective well-being in practice. This study aims to address these gaps by integrating quantitative and qualitative methods within a single coherent framework through a triangulation strategy.

Objective

Overview

The overall goal of this study is to deepen our understanding of operators' subjective well-being while interacting with various advanced production technologies (eg, cobots, machine vision, and pick-to-light) in manufacturing companies, by subsequently formulating a consensus report aimed at improving workplace conditions. This consensus report will provide not only actionable guidance to enhance workplace policies and training programs but also serve as a foundational tool to promote sustainable and human-focused work environments, in line with Industry 5.0 principles.

We thus move away from a merely technology-oriented standpoint to a more holistic view that places operators, their subjective well-being, and their experiential interactions with advanced production technologies at the center. Therefore, in line with the principles of Industry 5.0, our investigation is grounded in a human-centric approach. Further enriching the depth of our study, we draw from both the fields of clinical and organizational psychology, emphasizing the importance of considering the operators' perspectives of these technologies and their subjective well-being by adopting an interdisciplinary approach. More specifically, the purpose of this study is twofold. First, and more broadly, we aimed to explore through the administration of self-report questionnaires the multiple mediating roles of fluency (human-oriented fluency, machine-oriented fluency, and team-oriented fluency) and the negative attitudes toward these technologies. Specifically, we place cognitive and affective well-being at the center of our investigation, considering them as the main dimensions of interest.

To explore how these outcomes are shaped, we identify (refer to Table 1) (1) cognitive well-being indicators (ie, satisfaction with life, job and career satisfaction, home-work interface) as independent variables, (2) fluency in HMI and negative attitudes as key mediators, and (3) affective well-being outcomes (ie, stress, anxiety, and depression symptoms) as dependent variables.

Within this conceptual model, we hypothesized 2 distinct mediation mechanisms.

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Table 1. Summary of the constructs investigated through the specific tool.

Constructs	Definition	Investigated with	
		Questionnaire	Semistructured interviews
Affective well-being			
Depression symptoms	• Feelings of persistent and frequent sadness, loss of interest or pleasure in activities, fatigue, and feelings of worthlessness or hopelessness. • It can also involve physical and cognitive symptoms, such as changes in appetite, sleep disturbances, fatigue, and difficulty in concentrating.	✓	
Anxiety symptoms	• Excessive worry, fear, and heightened physiological arousal, such as restlessness, rapid heartbeat, and hypervigilance.	✓	
Stress symptoms	• Stress is a physiological or psychological response to internal or external stressors. • Stress symptoms are a human response to cope with life's challenges and threats. • The presence of long-term stress symptoms and the way they are coped with can have a negative impact on subjective well-being, which can in turn impact on the organizational one.	✓	
Cognitive well-being			
Home-work interface	• The balance and harmony between home and work life.	✓	
Job (and career) satisfaction	• The positive attitude individuals have regarding their job and career advancement.	✓	✓
Satisfaction with life	• Life satisfaction is related to the assessment of individuals' quality of life.	✓	
Human factors			
Physical and mental workload	• The physical workload is the physical effort required by an operator in a manufacturing company. • With the integration of robots, the physical workload can be modified. • Mental workload refers to the cognitive and psychological demands placed on an operator.		✓
Team-oriented fluency in human-machine interaction	• Well-synchronized interplay of human and machine actions.	✓	✓
Negative attitudes and emotions toward advanced production technologies	• Individuals' attitudes and emotions when interacting with advanced production technologies of different types.	✓	
Trust	• The dispositional attitude that a machine will support the achievement of the individual's goals in a situation characterized by uncertainty and vulnerability.		✓
Acceptance	• The beliefs that machines will be helpful for the individuals' work and that they will not threaten their role in the workforce community.		✓
Usability	• The extent to which working with the machine is effective, reasonably effortless, and satisfactory.		✓
Introduction of advanced production technologies and training	• The modality that was adopted by the organization to introduce the advanced production technologies and provide training.		✓
Perceived risks and benefits	• Exploration of which changes are deemed beneficial and which are perceived as a threat in HMI[a] domains.		✓
Social relationships among coworkers	• The extent to which the introduction of advanced production technologies has potentially changed the social dynamics among coworkers.		✓

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[a]HMI: human-machine interaction.

Higher Levels of Fluency

Higher levels of fluency (human-oriented, machine-oriented, and team-oriented) are hypothesized to positively and partially mediate the relationship between cognitive and affective well-being. Fluency is expected to act as a protective factor, facilitating smoother interactions with advanced production technologies and thereby reducing psychological distress (ie, anxiety, stress, and depression symptoms). As a mediating mechanism, fluency indirectly alleviates psychological distress by lowering cognitive workload and minimizing task-related frustrations inherent in complex HMI [38,39,42]. Partial mediation is proposed since evidence from HMI research indicates that while fluency reduces emotional strain, it cannot fully eliminate all sources of psychological distress [38]. For example, even operators with high levels of fluency may experience stress symptoms due to external factors, such as organizational change, time pressures, or conflicting demands, which directly have an impact on affective well-being [38].

Negative Attitudes Toward Advanced Production Technologies

Negative attitudes toward advanced production technologies (both emotional and social influence dimensions) are hypothesized to function as a complete mediator of the relationship within the tested model, acknowledging that other potential mediators might exist. This assumption is based on previous studies that observed that negative attitudes capture the emotional and social mechanisms that diminish well-being in technology-intensive environments [39].

Second, using semistructured audio-recorded interviews, we aim to conduct an in-depth qualitative analysis of operators' perceptions of their subjective well-being and lived experiences within the context of HMI, considering different dimensions: introduction and training, human factors, cognitive and physical workload, trust, machine capabilities, acceptance, usability, social relationships among coworkers, and risks and benefits. For the extraction and understanding of pivotal textual data, we will use an advanced text-mining methodology [43,44].

The integration of both quantitative and qualitative data through a triangulation strategy will be adopted to enhance the validity and depth of the findings.

At the conclusion of the data collection and analysis, should specific areas of difficulty emerge, an optional psychoeducational intervention will be proposed to the organization. Such focus groups will aim to provide operators with practical tools to enhance their subjective well-being.

To our knowledge, this is the first cross-sectional study to comprehensively examine the relationship between the variables outlined above on operators using, interacting, and collaborating with advanced production technologies within manufacturing companies.

Methods

Overview

A checklist flow summarizing the study methodology is provided in Figure S1 in the Multimedia Appendix 1.

Following the call made by Meissner et al [10], this cross-sectional study will implement a mixed methods approach, incorporating both quantitative and qualitative data collection techniques. Both the quantitative and qualitative parts of the study have been conceived to be intimately related, yet independent. Participation in the semistructured interviews is voluntary, and as such, it is possible that some operators who complete the survey may choose not to participate in the interviews, ensuring flexibility. The semistructured interviews are designed to focus specifically on the operators' perceptions of working and interacting with advanced production technologies, by further providing an opportunity for participants to share experiences that may not be fully captured in their survey responses.

More specifically, as regards the quantitative section, a digital survey containing the self-report questionnaires will be administered, relying on an online platform, namely Qualtrics. The duration of the digital survey will be approximately 20 minutes. Before filling in the questionnaire, the operators should read the study information and sign informed consent to participate in the study. The digital survey will start by asking (1) sociodemographic questions, such as age, sex, nationality, educational level, marital status, and presence or absence of offspring. Subsequently, (2) questions regarding the company in which the operators work will solicit information on their role, tenure, work shifts, and the specific advanced production technologies they work and engage with, as well as their tasks (ie, picking, packing, palletizing, welding, assembling items, handling, inspecting products for quality, disassembly, holding heavy weight, transporting goods, and other). Operators should then complete (3) a brief battery of standardized self-report questionnaires designed to assess their satisfaction with life, job, and career satisfaction, home-work interface, depression, anxiety, and stress symptoms, the negative attitudes toward advanced production technologies, and fluency in HMI.

The qualitative section will use semistructured audio-recorded interviews designed to last approximately 60 minutes. These semistructured interviews have the purpose of exploring the operators' perceptions and lived experiences in working and interacting with advanced production technologies. In particular, the areas addressed will cover 9 dimensions related to the operators' subjective well-being (ie, the introduction of technologies and training, human factors, physical and cognitive workload, trust, acceptance and usability, capabilities of machines, potential risks and benefits, and social relationships among coworkers).

As reported in the objective, this study further adopts a triangulation strategy, where qualitative data will be used to enrich and contextualize the quantitative results. This integration aims to provide a more comprehensive understanding of the

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psychological dynamics underlying operator interaction with advanced production technologies.

At the end of the data collection, psychoeducational interventions will be implemented through the means of the focus groups. Specifically, based on questionnaire outcomes related to cognitive and affective well-being, psychoeducational focus groups will be proposed to the company, and operators will be invited to participate on a voluntary basis. Each focus group will be carried out separately for each participating company, highlighting the unique organizational and contextual factors affecting operators within their specific workplace. The intervention will be moderated by 2 psychologists (a clinical and an organizational psychologist), addressing the potential psychological distress of operators. The focus groups are designed as part of the intervention strategy. While the qualitative section primarily aims to gather in-depth insights into operators' lived experiences and perceptions through semistructured interviews, the focus groups serve a distinct purpose. They intend to provide psychoeducational support by potentially improving the operators' overall well-being.

Funding

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Study Population and Recruitment

Participants and Recruitment Overview

We will recruit operators working in different manufacturing companies located in Northeastern Italy, particularly those dealing with advanced production technologies.

To determine the necessary sample size required for pursuing the objective related to the quantitative section, a power analysis was conducted, using the semPower library [45] under the RStudio environment, assuming a root mean square error of approximation effect cut-off equal to 0.10 (medium-sized misspecification), a P value of .05, a power of 0.80, and df=52. The computation resulted in a minimum of 60 participants.

Notwithstanding this outcome, we acknowledge that the estimated sample size represents the minimum threshold required for adequate statistical power and we recognize that detecting individual indirect effects in mediation models often requires larger samples, particularly when assuming small-to-moderate path coefficients (eg, β=.20, .30). These estimates are consistent with effect sizes commonly reported in psychological models of workplace well-being and human-technology interaction [46]. Therefore, we aim to exceed the minimum threshold by expanding recruitment efforts across participating companies.

Inclusion and Exclusion Criteria

Given the purpose of this study, specific inclusion and exclusion criteria have been delineated. The criteria for participation are outlined as follows: (1) prospective participants should fall within the age range of 18 to 65 years, ensuring that the sample represents the working-age population within the manufacturing company; (2) being employed as shop floor operators or in a manufacturing company that has introduced advanced production technologies, thereby having first-hand experience with such technologies; (3) manufacturing companies in which advanced production technologies, such as cobots, pick-to-light systems, and machine vision technologies, have been introduced within the last 5 years. This criterion ensures that the study focuses on operators interacting with relatively recent implementations of advanced production technologies, reflecting the evolving practices of Industry 5.0. Moreover, and finally, (4) willingness to participate and provide informed consent. Participants will be excluded if (1) not directly engaged in the use of advanced production technologies and (2) diagnosed with cognitive impairments or any other conditions that might hinder their ability to understand, engage in, or provide feedback.

Quantitative Data Collection: Self-Reported Questionnaires

All the self-report questionnaires are validated in Italy for adults' respondents, except for the fluency in the HMI scale [11], for which we carried out a back-translation procedure. Moreover, all the below-mentioned instruments have demonstrated good psychometric properties.

Depression Symptoms

Depression symptoms will be measured through the Patient Health Questionnaire-9 [47], which is a brief self-reported unidimensional instrument that incorporates the *DSM-IV-TR* (*Diagnostic and Statistical Manual of Mental Disorders* [Fourth Edition, Text Revision]) [48]. The questionnaire was developed to assess and monitor the severity of depression symptoms in the previous 2 weeks through 9 items rated on a 4-point Likert scale, from 0 ("never") to 3 ("almost every day"). A threshold score of 10 is indicative of clinically significant depression symptoms (scores 0-27). The Patient Health Questionnaire-9 stratifies depression severity into 5 severity categories: absent, subthreshold depression symptoms, mild depression symptoms, moderate depression symptoms, and major depression symptoms. Assessing depression symptoms, for example, persistent and frequent feelings of sadness, guilt, and worthlessness, is relevant as depression is often considered a proxy of the individual's mental health [20]. Moreover, depression symptoms can alter how the individual perceives events, and they can result in long-term exposure to stress symptoms [26,30].

Anxiety Symptoms

Anxiety symptoms will be evaluated using the Generalized Anxiety Disorder-7 (GAD-7) scale [49], which is a brief self-reported unidimensional measure aimed at screening probable cases of GAD and assessing the severity in the previous 2 weeks. The GAD-7 comprises 7 items based on a 4-point Likert scale, from 0 ("never") to 3 ("almost every day"). A score

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equal to 10 indicates relevant anxiety symptoms (score ranging between 0 and 21). The questionnaire included 3 categories of severity according to the DSM-IV-TR criteria: mild anxiety symptoms, moderate anxiety symptoms, and severe anxiety symptoms. The investigation of anxiety symptoms is motivated by the fact that they may be caused by the rapid change in production technologies and the consequent new demands in one's job, leading to significant psychological distress [12].

Satisfaction With Life

Satisfaction with life scale [50] will be administered to assess operators' global cognitive perception of their life satisfaction. The satisfaction with life scale is a 5-item self-report unidimensional questionnaire based on a 7-point Likert scale, from 1 ("strongly disagree") to 7 ("strongly disagree"). Assessing the overall level of life satisfaction is relevant in this context because higher levels of life satisfaction are linked to better job performance [51]. Additionally, it was found that work-related events impact one's level of satisfaction with life [52].

WRQoL

WRQoL [21] will be assessed through the work-related quality of life scale. The WRQoL is a multidimensional instrument characterized by 25 items plus an extra item, which investigates the overall level of WRQoL, rated on a 5-point Likert scale, from 1 ("strongly disagree") to 5 ("strongly agree"). These items are divided into 7 factors (ie, control at work, home-work interface, job and career satisfaction, working conditions, employee engagement, and stress at work). This instrument presents the advantage, compared to other measures, of allowing researchers, organizational, and clinical professionals to assess WRQoL in both organizational and clinical settings [20].

In line with the purpose of this study, we will focus on the home-work interface, job and career satisfaction, and stress at work, further including the extra item to reflect an overall level of operators' WRQoL. The choice to focus only on specific subscales is motivated by the role that those constructs play in the individual's well-being. Indeed, advanced production technologies are known to foster unlimited connection, thereby threatening the separation between work and personal domains [53]. Specifically referring to human-cobot interaction, poor synchronization in the actions of human and robotic agents is related to lower levels of job satisfaction [54,55]. Finally, the introduction of new industrial systems, such as cobots, and the conversion of the workers' role from operator to supervisor have led to a significant increase in their stress levels, which can negatively impact different human functions [26].

Fluency in HMI

The quality of HMI will be evaluated using the Fluency in Human-Robot Interaction Scale [11]. The Fluency in Human-Robot Interaction Scale is a multidimensional instrument characterized by 6 items rated on a 7-point Likert scale, from 1 ("strongly disagree") to 7 ("strongly agree"). The scale is composed of 3 factors, namely human-oriented fluency, which evaluates the worker's emotional states experienced during the interaction, robot-oriented fluency assesses the perception of the robot's contribution during the collaboration, and team-oriented fluency refers to the team's harmony. Including the assessment of fluency is grounded by the fact that a well-coordinated meshing of human and robots' actions was found to positively influence long-term teamwork, increase the perception of one's mental contribution, and foster higher levels of trust in the robot [11,51,52]. While this scale originally addressed the interaction between the worker and the robot, we extended its purpose to the broader context of HMI, thereby generally referring to advanced production technologies.

Negative Attitudes Toward Advanced Production Technologies

The negative attitudes toward advanced production technologies will be assessed using the Negative Attitude toward Robots Scale (NARS) [56]. The NARS is a multidimensional instrument designed to evaluate the negative attitudes that workers can experience in their interaction with robots. The NARS is composed of 17 items rated on a 5-point Likert scale ranging from 1 ("strongly disagree") to 5 ("strongly agree"), encompassing three scales, (1) negative attitudes toward situations of interaction with robots, (2) negative attitudes toward the social influence of robots, and (3) negative attitudes toward emotions in interaction with robots. The inclusion of only these latter 2 subscales was driven by the need to align with the research objectives while ensuring a streamlined and efficient questionnaire completion process for respondents. Moreover, attitudes toward robots are worthy of investigation because they are affected by several factors, including expertise in the job, and it is also related to the level of trust in the machine systems [57,58].

Qualitative Data Collection: Audio-Recorded Semistructured Interviews

Qualitative Data Collection Overview

A semistructured interview protocol, called Exploration of Psychological Impacts in Collaborative Operator Settings (EPICOS) [59], combines open-ended questions with dichotomous and multiple-choice scales, creating a holistic understanding of the dynamics related to the HMI. Through EPICOS, we aim to highlight 9 key dimensions related to operators' subjective well-being when working and interacting with advanced production technologies in the context of manufacturing 5.0. In particular, the 9 areas comprise several open-ended, dichotomous responses and Likert scale questions. The 9 areas that will be analyzed, along with their summarized questions, are reported below.

Introduction of Advanced Production Technologies and Their Training

This area of investigation refers to the modalities with which the introduction of advanced production technology is communicated to employees and the training they receive, which significantly contributes to how workers receive and interact with it [6].

Human Factors, Including Physical Ergonomics, and Tasks

Questions in this area explore how operators and advanced production technologies interact in Industry 5.0, and the organizational and clinical implications that their interaction

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has for the subjective well-being of the operators. It is well-known that the characteristics of the task allocation, the speed, and trajectory of the machine significantly impact the worker's cognitive state [16,60].

Trust

This area investigates the workers' attitudes and beliefs that the technological agent will help in accomplishing the task. The level of trust in technologies is key to ensuring successful HMI cooperation, and it also influences the use that workers make of technology [9,16,61].

Usability and Acceptance

These questions refer to factors related to the ease of interacting with the machine and the extent to which workers show a genuine willingness to work with it. These aspects are relevant as poor usability hinders a smooth and satisfactory usage of the technology, while low levels of acceptance hamper the very use and adoption of the technology itself [61].

Perceived Risks and Benefits

This area refers to the potential threats that workers associate with technology and the envisioned or experienced advantages related to it. More specifically, this area will encompass both the risks and benefits pertaining to physical interaction with technology, for example, safety issues, the wider perspective, and the role replacement. Attributing a certain level of risk to technology can negatively affect the acceptance of the technology itself [8].

Interpersonal Relationships Among Coworkers

This area of investigation is meant to explore whether and how the presence of advanced production technology has changed the relationships among coworkers. This area of investigation is relevant because social relationships at work significantly impact individuals' well-being [10].

Given that the EPICOS protocol was specifically developed for this study, no formal validation or piloting was conducted. However, the interview guide was carefully reviewed by an interdisciplinary team of experts in organizational psychology, clinical psychology, and HMI to ensure content coherence, clarity of language, and contextual relevance for manufacturing settings. As a qualitative tool, EPICOS was designed to flexibly explore operator experiences across predefined psychosocial dimensions rather than to generate standardized quantitative outcomes.

Statistical Analysis

Statistical analyses will be conducted using R custom code through the RStudio environment.

Descriptive statistics for both discrete (eg, frequencies) and continuous variables (eg, mean, SD, skewness, and kurtosis) will be run.

Bivariate Pearson *r* correlation coefficient will be deployed for evaluating the association between age, cognitive well-being (ie, job and career satisfaction, home-work interface, and satisfaction with life), affective well-being (ie, anxiety, depression, and stress symptoms), negative attitudes toward advanced production technologies, and fluency in HMI ($P<.05$). According to Cohen guidelines [62], correlation coefficients ranging between 0.10 and 0.29 indicate a "small effect size," between 0.30 and 0.49 represent a "medium effect size," and above 0.50 represent a "large effect size."

A path analysis will be carried out to explore the direct and indirect associations between operators' cognitive well-being as independent variables and affective well-being as the dependent variable. Central to this analysis is the investigation of the multiple mediating roles of fluency in HMI and the negative attitudes toward advanced production technologies, by highlighting the indirect effect pathways between the abovementioned variables. The strength and direction of these associations will be quantified using standardized regression coefficients (β), and the robustness of these estimates will be reported through CI.

A thematic analysis will be undertaken by relying on the text-mining technique, using the Quanteda package [63], to capture textual data within interview transcripts, thus highlighting emergent patterns and themes. The analysis will be carried out on the verbatim transcripts of the semistructured interviews by turning any numbers into letters and removing punctuation and stopwords. Subsequently, all semistructured interviews will be analyzed to explore the most frequent co-occurrences and digrams, based on a rule-of-thumb, in which words that will be repeated a minimum of three times will be considered co-occurrences as well as digrams [64]. The findings from this analysis will be cross-referenced with the quantitative results to ensure consistency and to identify areas of alignment or divergence. The text-mining process itself will undergo validation through iterative refinement of algorithms and checks for coherence and relevance, ensuring that semantic clusters correspond to meaningful constructs within the study's context. This triangulation between quantitative and qualitative findings will deepen the understanding of the factors influencing operators' well-being in HMI.

Ethical Considerations

The study has been approved by the Ethical Committee of Human-Inspired Technologies Research Center of the University of Padova (Italy), with the protocol number (2023_212R1). Moreover, all participants will be asked to read carefully an information sheet describing all the research details, and to sign the informed consent before taking part in the study. At least one researcher will be present to answer all their questions and doubts.

Results

At the time of publication, the data collection had already started. A first data collection session, with the involvement of 12 participants, has already been concluded. An additional session has been scheduled.

Discussion

Principal Findings

Previous research has already addressed many aspects of the relationship between operators and advanced production

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technologies, mainly focusing on job performance or work-related stress symptoms using either quantitative or qualitative methods alone. However, how the interaction between operators and advanced production technologies impacts individual subjective well-being has been neglected so far. Still, the changes in production tasks driven by technological innovation have been shown to exert negative effects on operators' well-being [20,31]. These effects, often manifesting as increased cognitive workload, anxiety, and stress symptoms, require deeper examination [26,31,65]. Indeed, if these symptoms are not proactively addressed and prevented, they may develop into severe psychological distress, which can emerge in various forms, such as increased anxiety and depression. Over time, these symptoms can significantly impair an individual's daily functioning, affecting their ability to work and maintain healthy interpersonal relationships. In the present cross-sectional study, we aim to address this gap by integrating quantitative and qualitative data to better comprehend the role played by several relevant workplace dynamics and factors, namely fluency in HMI and the dispositional negative attitudes toward advanced production technologies, to further promote operators' subjective well-being in manufacturing. In this regard, from a quantitative point of view, we expect that the quality of the interaction between operators and the advanced production technologies, that is, fluency in HMI, may act as a protective factor against the development or worsening of operators' psychological distress. Additionally, satisfaction with life, job, and career satisfaction, as well as the home-work interface, may function as independent variables that directly contribute to operators' psychological well-being. Higher job satisfaction fosters a sense of accomplishment and professional stability, reducing vulnerability to depression, anxiety, and stress symptoms [25]. Likewise, a positive home-work interface enhances the ability to manage both personal and professional responsibilities effectively, mitigating psychological distress [24]. Moreover, satisfaction with life reflects a broader sense of contentment and well-being that buffers individuals against the cumulative effects of the workplace and life stressors [66]. Together, these variables, in conjunction with fluency, human-oriented, machine-oriented, and team-oriented, can have a positive impact on the psychological outcomes, highlighting their critical role in shaping a healthier and more sustainable working environment. Conversely, negative attitudes toward these advanced production technologies may be conceived as risk factors that could contribute to the onset of psychological distress. Given the scarcity of the scientific literature, we expect to explore operators' lived experiences and interpret them referring to the scores at the questionnaires, thereby building a comprehensive overview of the subjective well-being of the operator who uses, interacts and collaborates with advanced production technologies. By triangulating quantitative findings with workers' self-reported experiences and perceptions gathered through qualitative interviews, it becomes possible to explore how operators receive and adapt to the introduction of novel technologies, potentially unveiling additional sources of distress, such as fear of job loss, that may not emerge from standardized measures alone. This approach echoes previous research highlighting the value of integrating subjective perspectives to capture hidden psychosocial dynamics in technologically evolving workplaces [67].

These findings could be interpreted in light of the JD-R [16] model. Specifically, in our study, fluency in HMI appears to function as a job resource, thereby facilitating task execution, reducing frustration, and supporting affective well-being, while negative attitudes toward advanced production technologies act as psychological demands, potentially contributing to increased stress, anxiety, and depression symptoms. This dual pattern supports the JD-R perspective and underscores the importance of designing interventions that simultaneously reduce techno-stressors and enhance enabling resources in technology-intensive environments.

In this regard, as part of the study, psychoeducational interventions will be proposed to address organization-specific challenges and psychological stressors, providing operators with practical strategies to address workplace challenges and fostering a supportive organizational environment. This aligns with the principles of Industry 5.0 by placing operators' well-being and workplace challenges at the center of interventions aimed at fostering sustainable HMI.

The multimethod approach adopted in this study further offers significant value by combining the strengths of both quantitative and qualitative data collection techniques. While the quantitative data provide a structured and systematic analysis of the relationships between cognitive well-being, affective well-being, and the mediating factors of fluency and negative attitudes toward advanced production technologies, the qualitative interviews offer an opportunity to explore these phenomena in greater depth by contextualizing the findings from the self-reported questionnaires. This sequential approach allows the application of the quantitative results to inform the focus of the interviews, thereby ensuring that the qualitative data collection is targeted. The interviews also provide nuanced insights into the subjective perspectives of operators, capturing details that are often difficult to quantify, such as their perceptions of collaboration with technologies, the organizational challenges they face, and the interpersonal and social dynamics within their workplaces. These insights complement the quantitative findings by highlighting the mechanisms through which fluency and attitudes toward advanced production technologies influence subjective well-being outcomes, as well as identifying potential areas for support that may not emerge from survey data alone. This integration of methods is particularly important in the context of Industry 5.0, where a human-centric approach reflects a comprehensive understanding of operators' experiences to design interventions that promote well-being. The integration and triangulation of quantitative and qualitative findings, also through the use of the text mining technique, enhances the study's methodological robustness. Addressing these issues is crucial not only for the well-being of individual operators but also for the overall health of the organization. Therefore, proactive measures will benefit both individual operators and the organization as a whole, leading to a more sustainable and productive work environment. Indeed, by fostering a work environment that addresses subjective well-being [66] intended as affective (ie, depression, anxiety, and stress symptoms) and

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cognitive well-being (ie, satisfaction with life, job and career satisfaction, and home-work interface) of operators, organizations can create a more resilient, engaged, and ultimately effective workforce capable of proactively adapting to the evolving demands of the modern industrial age. This conceptualization is, in fact, based on the 3 founding pillars of Industry 5.0, recognizing that the operators' psychological well-being and optimal workplace dynamics are integral parts of sustainable productivity.

Limitations and Future Implications

Still, we acknowledge some limitations of this study. First, it was designed to be cross-sectional, thus failing to capture the interaction between operators and advanced production technologies over time. A longitudinal design would provide an understanding of the temporal dynamics and causal relationships between cognitive and affective well-being, fluency, and negative attitudes toward advanced production technologies. However, this study adopts a cross-sectional design for several practical and methodological reasons. Conducting research across several manufacturing companies presents logistical challenges, particularly in ensuring consistent participation over time and varied work schedules typical of industrial environments [68]. Furthermore, as an exploratory study addressing, a cross-sectional design enables the establishment of baseline relationships and the potential identification of key mediating factors, laying the groundwork for future research. Second, the sample is drawn exclusively from manufacturing companies located in Northeastern Italy. While this region is a hub for industrial innovation and advanced production technology adoption, the findings may not be directly generalized to other geographical areas or industrial sectors. Nevertheless, given the ecological and human-centered nature of the current approach, we believe that the findings may retain a degree of transferability to similar manufacturing contexts, especially where similar technological transformations and psychosocial dynamics are present. Still, we have to acknowledge that differences in cultural, organizational, and technological contexts may influence the applicability of the results. Future research should expand to include diverse geographical locations and industries to validate and extend the findings that will emerge from this study. Moreover, the organizational level and all the related aspects (eg, organizational culture), which may play an important role, were not considered, as the study is specifically focused on the individual level. Additionally, certain relevant aspects, such as the fear of job loss, which may significantly impact workers' subjective well-being, will not be assessed quantitatively in this study. Instead, this construct will be explored qualitatively through semistructured interviews, as this method allows for a more in-depth understanding of how such fears manifest in relation to specific organizational, technological, and relational dynamics. Given the exploratory nature of this study and the complexity of how fear of job loss may be experienced in the context of technological transformation, a qualitative approach is considered more suitable at this stage.

Furthermore, the voluntary nature of interview participation, as ethically required in all human-subjects research, may introduce a degree of self-selection bias. It is possible that participants with more pronounced experiences, positive or negative, were more likely to take part. Nonetheless, the qualitative data will be collected in a real-world manufacturing environment, characterized by active production shifts and organizational constraints. This ecological setting, while it naturally has its limitations, contributes to the applied value of the findings and strengthens their relevance for practical implementation. Finally, despite reasoning within the paradigm of Industry 5.0, especially emphasizing the need to bring operators to the forefront, social inclusiveness, which may be involved in their well-being, was not considered. Notwithstanding this, the investigation of the relationship between all the abovementioned variables will provide a comprehensive view of the factors that contribute to operators' subjective well-being in HMI in manufacturing 5.0. This understanding will allow us to achieve the final goal of developing a consensus report that will provide guidance to companies that have adopted advanced production technologies, further considering the importance of the interaction between operators and machines, to improve workplace conditions and to identify adaptive organizational and clinical strategies to support operators' well-being and optimize HMI. The consensus report will also serve as a practical framework for guiding workplace policies, such as implementing measures to foster subjective well-being and effective HMI, while addressing job satisfaction. Additionally, it will inform the development of tailored training programs for operators, ensuring they are equipped with the necessary skills to adapt to evolving technologies while maintaining a healthy work-life balance. These practical implications highlight the report's potential to create more sustainable and operator-focused workplaces, in line with Industry 5.0 principles. Early recognition and intervention are essential to mitigating potential psychological distress and promoting operators' mental well-being. By identifying key variables that influence subjective well-being, organizations can develop targeted psychoeducational initiatives, including training programs focused on the use, interaction, and collaboration with advanced production technologies, as well as awareness campaigns and workshops designed to foster resilience and adaptability in the workforce. In turn, this approach can improve the quality of HMI.

Conclusions

As noted by Ghisleri and colleagues [69], the role of work in one's life is pivotal, because it not only responds to instrumental needs, but rather it also answers to crucial intrinsic needs of maintaining self-esteem and satisfactory social relationships. Therefore, investigating whether and how new technological working tools can be effectively integrated not only in the work practices but also in the workers' psychosocial workspace is crucial to ensure both the workers' psychological well-being and the organization's performance. This study is not a mere statistical exploration; it aims to be an essential tool to understand and guide the complexities of contemporary workplaces, where humans and machines can coexist and should coexist harmoniously.

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during this study.

Authors' Contributions

Conceptualization: all authors;
Methodology: GB and VO.
Formal analysis: GB and VO.
Investigation: GB and VO.
Writing - original draft: GB and VO.
Writing - review and editing: all authors;
Visualization: GB.
Supervision: LG and SS.

Conflicts of Interest

Non declared.

Multimedia Appendix 1
Checklist flow of the study's methodology.
[PNG File , 114 KB - resprot_v14i1e73896_app1.png]

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Abbreviations

DSM-IV-TR: Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision)
EPICOS: Exploration of Psychological Impacts in Collaborative Operator Settings
GAD-7: Generalized Anxiety Disorder-7
HMI: Human-Machine Interaction
JD-R: Job Demands-Resources
NARS: Negative Attitude toward Robots Scale
WRQoL: work-related quality of life

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Protocol

Comparative Evaluation of the Effectiveness of Demineralized Freeze-Dried Bone Allografts With Titanium Platelet-Rich Fibrin and Autologous Dentin Graft With Titanium Platelet-Rich Fibrin for Alveolar Socket Preservation: Protocol for a Randomized Controlled Trial

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Abstract

Background: Postextraction ridge resorption compromises the aesthetics and function of the subsequent implant therapy or prosthetic rehabilitation. Several techniques are employed to reduce ridge resorption, ranging from basic socket fillers such as blood clot preservation to more advanced techniques using barrier membranes and bone grafts such as autografts, allografts, xenografts, and synthetic materials.

Objective: The aim of this study is to evaluate and compare the effectiveness of alveolar socket preservation by using demineralized freeze-dried bone allograft (DFDBA) with titanium platelet-rich fibrin (T-PRF) and autologous dentin graft (ADG) with T-PRF. This assessment will be performed through comprehensive clinical, radiographic, and histomorphometric analyses. The primary objective of this study is to histologically evaluate the new bone formation in the extraction sockets preserved using either DFDBA with T-PRF or ADG with T-PRF. The secondary objective is to evaluate the dimensional changes, including ridge width and height at these healing points, as measured by clinical and radiographic methods. We will evaluate and compare the clinical, radiographic, and histomorphometric outcomes of using DFDBA with T-PRF versus ADG with T-PRF for maintaining socket integrity after tooth extraction. We will also ascertain which grafting technique facilitates the production of new bone during the healing phase and preserves alveolar ridge dimensions.

Methods: This randomized controlled trial will involve 16 patients aged 22-60 years requiring tooth extractions and subsequent implant placement. Participants will be randomly assigned to one of the 2 groups: (1) socket preservation using DFDBA in combination with T-PRF or (2) socket preservation using ADG with T-PRF. At baseline, all the clinical variables will be assessed using UNC-15 probe and cone beam computed tomography radiographs. Extraction will be done atraumatically with minimal flap reflection by using periotomes. Postextraction sockets will be preserved using DFDBA+T-PRF or ADG+T-PRF. At 4 months, clinical and radiographic evaluations will be done, and the implant will be placed using a 2-stage protocol. Histomorphometric analysis will be performed after receiving bone samples during implant placement. At 3 months after implant placement, the second-stage surgery will be done.

Results: Participant enrollment commenced in March 2024, and the study is scheduled to conclude postassessments and analyses by the end of 2025. The results of this study are anticipated to be accessible in late 2025. This study is not funded, and the results are expected to be published by 2026.

Conclusions: This study represents valuable insights into the clinical effectiveness of 2 biologically driven socket preservation techniques. We hypothesize that the use of ADG combined with T-PRF will show similar or more effective outcomes in alveolar

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socket preservation demonstrated by enhanced bone formation and better maintenance of socket dimensions compared to DFDBA combined with T-PRF without increased morbidity.

Trial Registration: Clinical Trials Registry – India CTRI/2024/05/068192; https://ctri.nic.in/Clinicaltrials/pmaindet2.php?EncHid=MTI1NzIz&Enc=&userName=

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KEYWORDS

demineralized freeze-dried bone allograft; DFDBA; autologous dentin graft; ADG; titanium platelet-rich fibrin; T-PRF; socket preservation; cone beam computed tomography; CBCT; histomorphometric analysis

Introduction

Dental implants are the most widely used and reliable treatment method for individuals with fully or partially edentulous arches. The time frame for implant insertion following extraction is currently the main concern of implant therapy rather than osseointegration. Alveolar socket preservation following tooth extraction is one of the most important dental advanced skills, as numerous conditions such as traumatic extraction techniques, periodontal diseases, tumors, infections, or cysts can cause the loss of alveolar bone [1]. Alveolar ridge resorption is one of the physiological alterations that takes place following tooth extraction. After tooth extraction, alveolar ridge modeling peaks over the first 4-6 weeks, as is well known, while progressive atrophy may persist over time at a slower rate [2]. Ridge atrophy results from a substantial degree of physiologic remodeling that occurs in the alveolar socket following tooth extraction [3]. To minimize stress to the alveolus and accomplish minimal socket enlargement, atraumatic extraction must be performed. Treatment options for ridge atrophy include several forms of bone and/or soft tissue augmentation; nevertheless, these methods are known to have varying degrees of success and predictability. It is believed that socket grafting, which requires the use of grafting materials with or without barrier membranes, reduces the amount of dimensional shrinkage that occurs in the alveolar socket following tooth extraction.

For the best results, an ideal bone graft should have osteoconduction, osteoinduction, and osteoproliferation properties [4]. A range of surgical methods and biomaterials have been created to enable socket preservation. For this objective, several bone grafting methods, including synthetic and natural graft materials, have been tried. The most often used, clinically approved, or modified bone allograft material for periodontal repair is demineralized freeze-dried bone allografts (DFDBA). Bone morphogenetic proteins (BMPs) are linked to the osteoinductive capacity of DFDBA; this particular BMP combination includes BMPs 2, 4, and 7. DFDBA breaks down at a faster rate, which promotes the growth of new bone [5]. Its primary application is in the reconstruction of osseous deformities.

Growth factors such as platelet-derived growth factor are present intracellularly and essential for the healing of wounds. Utilizing platelet concentrates has several benefits. They are crucial to regeneration. Their application has been effectively linked to bone and connective tissue repair. Platelet concentrates promote bioactivity and demonstrate nonstimulative properties. Titanium platelet-rich fibrin (T-PRF) is one of the third-generation platelet concentrates [6]. This platelet concentrate is recognized to remove the potentially harmful effect of silica, which is found in glass vacuum containers used to prepare PRF. Platelet and leukocyte cell–enriched fibrin or T-PRF is made with titanium and resembles fibrin made with the traditional PRF process. Titanium is the most corrosion-resistant metal with the highest amount of toughness. Furthermore, titanium has an amazing osseointegration quality [6]. T-PRF presents a longer resorption time and a denser fibrin structure compared to PRF, making it a promising option for the sustained release of growth factors [7].

Histologically stated, hydroxyapatite makes up the majority of the inorganic structure that makes up human enamel and dentin, which is composed of 45% organic material. Type I collagen and BMP comprise most of the organic components. An autologous dentin graft (ADG) is a viable substitute for alveolar socket preservation due to its composition of organic and inorganic components as well as its ability to promote bone formation and support bone growth [4-6]. The osteoconductive characteristics of human dentin are attributed to 4 types of calcium phosphate: amorphous calcium phosphate, tricalcium phosphate, octacalcium phosphate, and hydroxyapatite. As hydroxyapatite in dentin is primarily found as calcium phosphate with a low crystal concentration, osteoclast activity can readily break it down. Approximately 90% of its 20% organic content is composed of type I collagen network; the remaining 10% is made up of noncollagenous proteins (such as phosphoprotein, sialoprotein, osteocalcin, and osteonectin, which help calcify bone), and 10% is made up of growth factors (like insulin-like growth factor and BMPs, which give teeth their osteoinductive properties) [8]. Owing to all these properties, it can be considered as potential graft material and has been used in the past for regenerative procedures.

Accurate assessments need the establishment of a consistent point for cone beam computed tomography (CBCT) linear measurements. CBCT is currently the most widely used 3D radiographic imaging technique in dentistry, offering several benefits over traditional CT scans and 2D imaging instruments. A more precise method involves using subtraction analysis of CBCT data [9]. The fundamental advantage of using CBCT in implant dentistry is its ability to provide detailed volumetric imaging data of the craniofacial region for preoperative and diagnostic planning.

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CBCT radiographs have been reported to sometimes show certain discrepancies; hence, to eliminate those in the results, the outcomes will be confirmed by histomorphometric analysis. The bone sample for the histomorphometric analysis will be obtained using trephine bur during implant placement [10,11].

Hence, in this investigation, the aim is to clinically, radiographically, and histomorphometrically evaluate the effectiveness of DFDBA with T-PRF and that of ADG with T-PRF for socket preservation.

Methods

Study Design

This research is a clinical trial with randomized controlled prospective parallel arms to achieve a side-by-side comparison between ADG with T-PRF and a commercially available DFDBA bone graft with T-PRF.

Ethical Considerations

This study was approved by the Institutional Ethics Committee of Datta Meghe Institute of Higher Education and Research, Wardha, Maharashtra, India (DMIHER(DU)/IEC/2024/226). All participants were informed about the study objectives, procedures, potential risks, and benefits prior to enrollment. Participation in this study was completely voluntary, and individuals were free to withdraw or opt out at any time without providing a reason and without any effect on their ongoing or future dental care at the institution. All data collected from participants were anonymized prior to analysis. Personal identifiers (name, address, phone number, and registration details) were removed and replaced by coded ID numbers. Access to the linking file was restricted to the principal investigator and stored on a password-protected institutional server to ensure confidentiality and data security. Participants did not receive any monetary compensation for taking part in the study. However, all clinical procedures performed as part of the research protocol were provided free of cost, ensuring no financial burden on participants. As no payment was made in foreign currency, no USD exchange rate was applicable. Written informed consent was obtained from all participants prior to their inclusion in the study, in accordance with the Declaration of Helsinki and institutional ethical guidelines.

Study Population

Based on the necessity for a single tooth replacement via implant fixture, 16 healthy individuals without a history of any systemic disease will be enrolled in this research from the Department of Periodontics, Sharad Pawar Dental College, Sawangi (Meghe), Wardha. The participants will be informed about the study's goal, methodology, and design prior to the study start. Written consent will be taken.

Oversight and Monitoring

Composition of the Coordinating Center and Trial Steering Committee

The committee consists of the following: the head of the department of periodontics, postgraduate guide, research scientist, principal investigator, surgeon, statistician, data manager.

Composition of the Data Monitoring Committee

The data monitoring committee consisted of the research in-charge of the institute and research in-charge of the department.

Adverse Event Reporting and Harms

Data will be collected, assessed, and spontaneously reported during adverse events and other unintended effects of trial interventions or trial conduct.

Frequency and Plans for Auditing Trial Conduct

The project management group meet will review the trial conducted every month. The trial steering group and the independent data monitoring and ethics committee meet will review and conduct the trial period till the trial is complete.

Eligibility Criteria and Recruitment

Following the clinical and radiographic assessments, 16 patients must precisely meet the criteria that are listed below.

Inclusion Criteria

The inclusion criteria are as follows.

1. Patients indicated for implant following tooth extraction for reasons such as residual roots, overretained primary teeth, nonrestorable carious lesions, internal and external resorption, fractured roots, and failed endodontic therapy
2. Patients with a complete mouth plaque score of less than 25%, indicating good oral hygiene
3. Patients with a natural tooth in opposition
4. Patients with adjacent teeth
5. Patients with a thick gingival biotype
6. Patients with a 4-mm bone apical to the root apex
7. Patients with bone quality of D-1, D-2, or D-3 type

Exclusion Criteria

The exclusion criteria are as follows.

1. Individuals with systemic conditions such as diabetes mellitus, osteoporosis, blood-related diseases, and titanium allergy that could compromise their overall health and impede the process of bone healing and repair
2. Individuals with a space between the maxilla and mandible
3. Individuals with parafunctional habits like clenching or bruxism
4. Individuals with a history of substance misuse, excessive smoking, or drinking
5. Individuals with D-4 bone quality
6. Individuals who have undergone chemotherapy and radiation
7. Individuals with temporomandibular joint disorders
8. Individuals with untreated oral health conditions
9. Pregnant and lactating mothers

Recruitment

Figure 1 presents a simplified diagram that outlines the study protocol based on the CONSORT (Consolidated Standards of Reporting Trials) guidelines (Multimedia Appendix 1).

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Figure 1. A simplified diagram that outlines the study protocol based on CONSORT (Consolidated Standards of Reporting Trials). ADG: autologous dentin graft; DFDBA: demineralized freeze-dried bone allograft; T-PRF: titanium platelet-rich fibrin.

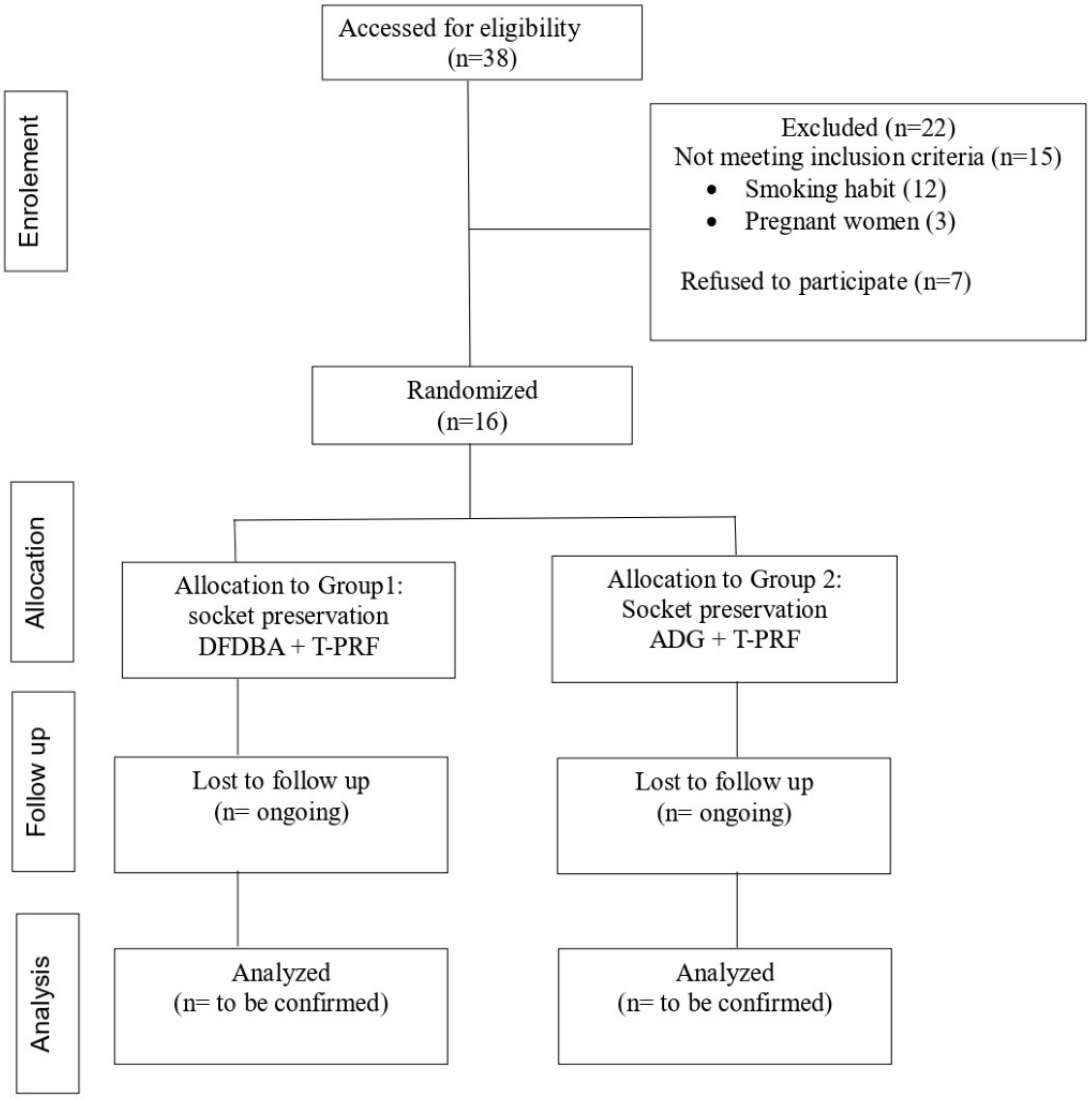

Primary Outcomes

Four months following the socket preservation procedure, the formation of new bone and changes in the alveolar socket dimensions in both groups will be assessed by radiological and histomorphometric analyses. Histomorphometric evaluations will be performed on bone core biopsies obtained at the time of implant placement at 4 months after the extraction. These samples will be processed using standard histological techniques, stained with hematoxylin and eosin, and assessed under light microscopy. Quantitative measurements such as the percentage of new bone formation, number of osteocytes, and trabecular patterns will be analyzed using Planmeca Romexis software (version 6.2.0; Planmeca Oy) to determine the measurement of bone dimensions, apico-coronal ridge height, and density in Hounsfield units.

Secondary Outcomes

After 4 months of the surgical procedure, linear phenotypic dimensional changes in the thickness of soft tissues and the midfacial and midpalatal bones at baseline and at 4 months after healing at 2 locations will be evaluated.

Sample Size Calculation

Sample size formula was calculated using mean (SD): , where α=.01; β=.01; SD of newly formed bone with spontaneous healing (group 1), that is, group (δ_1)=0.23; mean in group 1 (μ_1)=0.72; SD of newly formed bone with ADG (group 2), that is, group (δ_2)=0.24; mean in group 2 (μ_2)=1.33; ratio (group 2/group 1)=1; and total samples required=8 per group. The calculation gives the result as sample required is 8 per group. The sample size was determined based on prior similar studies involving histomorphometric evaluation in socket preservation procedures. Based on the outcome variable on pocket depth

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with mean difference derived from previous literature [4], the sample size of 16 in total and 8 per group is adequate.

Randomization and Masking

The study group consisting of socket preservation with ADG and T-PRF or the control group consisting of DFDBA and T-PRF will be randomly assigned. Every patient will be required to complete a comprehensive medical history form, give informed consent, and receive a thorough description of the study. A secure computer system will be used for central randomization in this procedure. A distinct study code will be given to each patient, and the operators and research evaluators will receive their data in a format that maintains patient confidentiality through coding. The radiologist and the statistician will be blinded to the treatment while analyzing the data. Blind quantitative histological analysis will be performed by a trained specialist.

Clinical Procedure

Presurgical Phase

Patients will be clinically examined for periodontal diseases. Every patient will be required to complete a comprehensive medical history form, give informed consent, and receive a thorough description of the study. Following a comprehensive clinical examination and radiographical diagnosis, initial therapy will consist of guidance on maintaining good oral hygiene and a full mouth ultrasonic scaling procedure. Patients will receive plaque control instructions until their plaque score is less than 25%. Before any surgical procedure, a diagnostic cast will be made for every patient to ascertain the maxilla-mandibular relationship. Clinical photographs will be captured throughout the procedure. CBCT images will be obtained for every participant.

Preparation of T-PRF

Just prior to the surgery, by venipuncturing the antecubital vein, 10 mL of venous blood will be obtained under aseptic conditions and transferred to a new, sterile titanium tube. T-PRF is an autogenous blood concentrate of the third generation, characterized by a thick and durable fibrin meshwork that is triggered by a titanium tube [12]. Centrifugation is performed for 15 minutes at 3500 rpm. After transferring the resulting T-PRF clot onto a PRF box and separating it with sterile tweezers and scissors, the serum will be squeezed out of the clot to create a stable fibrin membrane [13]. A portion of the membrane is chopped up for use as graft material, and the remaining portion will be trimmed to fill the defect with membrane.

Surgical Procedure for the Test Group

Patients are instructed to gargle for 1 minute with 0.12% chlorhexidine gluconate. Local anesthesia will be administered. In order to minimize the surgical trauma during the flapless tooth extraction process, periotomes and forceps will be used. Using a number 15 blade, a crevicular incision will be created, removing periodontal ligament fibers on the distal and mesial sides. The teeth will be carefully luxated using elevators. Precautions will be taken to prevent trauma to the adjacent tissues. After tooth extraction, bone curettes will be used to completely debride the socket's granulation tissue. Initially, a high-speed handpiece will be used to remove any debris, artificial material, rot, and gutta-percha from the extracted roots, leaving just the clean tooth root. The roots that contain dentin will be crushed using a dentin grinder (Figure 2).

Figure 2. Dentin grinder.

The generated root dentin particle material will be treated through 3 steps. First, the dentin cleansing solution is poured into the dish containing the particles and allowed to sit at room temperature for 5 minutes. The solution is then allowed to dehydrate using a sterile gauze. Second, the particle is then totally covered with phosphate-buffered saline, which is then put into the plate (Figure 3).

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Figure 3. Dentin cleanser and buffered saline solutions.

The particle is mixed with fresh sterile gauze to dehydrate it by using a sterile device. With the phosphate-buffered saline solution, this step is repeated once more. To neutralize the pH levels, this step is crucial. At last, the ADG, whose particle size ranges from 300 to 1200 microns is prepared for prompt grafting (Figure 4).

Figure 4. Extracted tooth sample.

The extraction sockets will be filled with a mixture of T-PRF and ADG (Figure 5). After enclosing the resistant bone with a collagen plug, nonresorbable suturing material is used to sew the plug to the surrounding soft tissues.

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Figure 5. Prepared autologous dentin graft.

Surgical Procedure for the Control Group

DFDBA, a completely resorbable alloplastic bone substitute, will be inserted into the extraction socket together with T-PRF following an atraumatic extraction. It is important to exercise caution when filling the socket after applying the graft since this could cause the exposed coronal particles to get sequestered or cause the graft mass to disperse as a whole. T-PRF is applied to compact the graft particles even more and accelerate in-situ healing.

Postsurgical Care

Participants will be given explicit instructions not to eat or drink anything hot on the surgical site nor should they rinse their mouths vigorously. All the patients will receive antibiotics (amoxicillin capsule 500 mg every 8 hours, metronidazole tablets 400 mg every 8 hours) and analgesics (Ibugesic tablets every 8 hours) after surgery for a period of at least 3 days. Two weeks following the surgical procedure, participants are recommended to gently brush the area surrounding the surgical site; nevertheless, regular tooth brushing should be continued for the remaining areas of the dentition starting on the day following the procedure. In addition, 2 weeks of twice-daily mouthwash containing 0.2% chlorhexidine is prescribed. Seven days following the procedure, the sutures will be removed.

Follow-Up

A complete examination will be conducted at the 4-month follow-up appointment [14]. Every clinical variable will be evaluated. A clinical and radiographic evaluation will be performed. Histomorphometric analysis will be performed on the bone obtained by trephine bur during implant placement.

Statistical Analysis

Mean (SD) values will be found for each clinical periodontal parameter such as plaque index, papillary bleeding index, probing pocket depth, width of keratinized gingiva, clinical attachment level, and marginal bone level. Next, from baseline to 4 months, the mean data will be statistically analyzed. To equate baseline to 4-month findings for every patient, Student paired *t* test will be employed for intragroup data comparison, while the Student unpaired 2-sided *t* test will be utilized for intergroup comparison. If the *P* value exceeds .05, the observed difference will be considered nonsignificant; if it remains below .05, it will be considered significant.

Results

This study received ethical approval in January 2024. Enrollment began from March 2024. The study commenced in August 2024 and is scheduled to conclude postassessments and analyses by the end of 2025. The results of the study are anticipated to be accessible in late 2025. Results will be shared using a variety of methods, including research reports, scholarly publications, and attendance at international conferences. A primary manuscript intended for submission to a prestigious, high-impact, peer-reviewed journal will elaborate on the findings related to the primary objective.

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Discussion

Socket preservation is a fundamental technique in dentistry, preserving alveolar bone structure after the extraction to facilitate optimal healing and support future dental restoration procedures. This study primarily focuses on histomorphometric analysis, which is considered a highly sensitive and accurate method for assessing new bone formation. Due to the precise and quantitative nature of histological outcomes, a smaller sample size can yield reliable and clinically meaningful data compared to studies relying solely on radiographic or clinical endpoints.

Hussain et al [4] demonstrated promising outcomes regarding the utilization of ADG in alveolar ridge preservation. Their study revealed superior dimensional stability in the study group compared to the control group, as evidenced by standardized CBCT scans. The study group's successful graft remodeling was further validated by histomorphometric analysis, demonstrating the potential of using ADG for effectively retaining the dimensional integrity of ridges. These findings highlight the need to utilize innovative biomaterials such as ADG to enhance clinical results and facilitate optimal wound healing.

Bhombe et al [5] investigated the use of PRF matrix and DFDBA as adjuvants during immediate implant placement procedures following tooth extraction. Their findings indicate that using PRFM and DFDBA in jumping gap distance as adjuvants resulted in significant coronal bone remodeling and a significant decrease in bone resorption.

In another clinical study by Elfana et al [15], histomorphometric findings demonstrated that the autogenous whole tooth and autogenous demineralized dentin graft groups exhibited higher proportions of newly formed bone (48.40%). The histology study confirmed that both types of transplants were compatible with the host tissues and showed no symptoms of inflammation.

Dwivedi et al [16] demonstrated that chair-side autogenous tooth grafts offer several advantages, including greater primary implant stability, faster recovery times, ease of preparation, reduced rates of bone resorption, and qualities that promote bone growth and socket augmentation.

ADG, which has both osteoconductive and osteoinductive qualities, appears to be a promising alternative for alveolar ridge preservation treatments, according to a systematic study by Sánchez-Labrador et al [17]. Positive outcomes in terms of volume preservation and histomorphometric data were noted; they were reinforced by the properties of materials, such as low complication rate and cost-effectiveness in comparison to alternative bone substitutes.

Thus, the purpose of this study is to assess and compare the effectiveness of DFDBA with T-PRF and ADG with T-PRF in socket preservation by performing clinical, radiological, and histomorphometric analyses. This study plan will be reliable to prove advantages pertaining to improvements in the maintenance of vertical and horizontal socket dimensions and phenotypic dimensions.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT 2010 checklist.
[PDF File (Adobe PDF File), 183 KB - resprot_v14i1e70649_app1.pdf]

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Abbreviations

ADG: autologous dentin graft
BMP: bone morphogenetic protein
CBCT: cone beam computed tomography
CONSORT: Consolidated Standards of Reporting Trials
DFDBA: demineralized freeze-dried bone allograft
PRF: platelet-rich fibrin
T-PRF: titanium platelet-rich fibrin

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Protocol

The 5 R's of Indigenous Research as a Framework to Co-Design and Evaluate an Outdoor Play Program in Early Learning and Child Care Centers: Protocol for the Promoting Early Childhood Outside (PRO-ECO) 2.0 Wait-List Control Cluster Randomized Trial

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Abstract

Background: Outdoor play is a fundamental part of childhood. Children's participation in outdoor play connects them to nature and the land, and supports their role in the natural world. Early learning and child care (ELCC) centers provide opportunities for outdoor play; however, barriers toward the provision of outdoor play exist, including educator attitudes, policies and procedures, outdoor space limitations, and adverse weather conditions.

Objective: The Promoting Early Childhood Outside (PRO-ECO) 2.0 study is a community-based research partnership with Indigenous Knowledge Keepers and Elders, Indigenous and early childhood organizations, early childhood education faculty, ELCC centers, and families, aiming to expand outdoor play in ELCC centers. This paper provides an overview of the

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community-based design process, guided by the 5 R's—Respect, Relevance, Responsibility, Reciprocity, and Relationship—and the resulting study protocol for the mixed methods waitlist control cluster randomized trial.

Methods: This study considered a 5 R's research approach from its inception, beginning with the formation of a Steering Committee and over a year of relationship building before formal study activities commenced. A key early focus was collaboratively identifying project values through an iterative process. Collectively, we worked to promote equity, disrupt power dynamics, and embed Indigenous data sovereignty principles into research agreements, marking a significant departure from traditional Western research processes. The PRO-ECO program and study protocol are implemented in partnership with 10 ELCC centers delivering licensed full-day, year-round care to children aged 2.5-6 years in rural and urban areas of British Columbia, Canada. The PRO-ECO program includes 4 components to address common barriers to outdoor play in ELCC settings. Primary outcome measures include the proportion and diversity of observed nature play behavior during dedicated outdoor times at ELCC centers as measured through observational behavior mapping. Secondary outcomes include changes in educator attitudes, quality of ELCC outdoor play space, and children's perspectives of their experiences at ELCC centers. Outcome data are collected at baseline, and 6 months and 12 months post baseline. The community's perspectives (educators, children, and families) on the project are assessed qualitatively to understand the acceptability of the PRO-ECO program. Mixed-effect models will test the effect of the PRO-ECO program on quantitative outcomes. Qualitative data will support the interpretation of quantitative findings and provide evidence on project acceptability.

Results: Participant recruitment for this study began in August 2023, and data collection was completed in March 2025. A total of 229 children, 91 staff and early childhood educators, and 40 family members were recruited to participate in this study.

Conclusions: The PRO-ECO 2.0 study uses a rigorous experimental design within a community-based research project. The 5 R's approach grounded our work in shared values, disrupting traditional academic power relations and weaving together Indigenous and Western worldviews in the context of academic research.

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International Registered Report Identifier (IRRID): DERR1-10.2196/77956

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KEYWORDS

early childhood education and care; indigenous data sovereignty; risky play; community-based research; methodology

Introduction

Positionality

The authors of this paper include academic researchers (MB, RR, SG, DM, EF, SH, and YL) and members of the project Steering Committee (SEJ, JL, EE, EM, AL, LS, AB, EC, and AR). MB, RR, DM, EF, SH, and YL are settlers to North America, with diverse cultural backgrounds (Latin American, White European, and Asian), working within a Western academic environment at one of the largest universities in Canada. SG is Métis, Cree-French, and Scottish, working within a Western regional university that trains early childhood educators. The academic researchers' motivation for writing this article was to describe our experiences in designing and implementing a randomized controlled trial while Indigenizing the research and working toward decolonizing the research process—identifying the power structures imposed by colonialism and working to disrupt them [1]. We seek to share our experience being led and guided by a steering committee that is predominantly composed of Indigenous members and how this profoundly shaped our research. As many researchers seek to Indigenize their research and universities enact strategic plans that emphasize decolonization and reconciliation with Indigenous people of the lands we inhabit, we hope this work can help others navigate their own journeys.

Steering Committee members, as integral partners from the beginning of the project, have important voices to include, and those who were interested have contributed to this publication and are named as authors, providing their positionality with respect to this project. Knowledge Keeper SEJ is Métis and Cree and sees the importance of time outdoors for sharing her culture and language with children. Knowledge Keeper JL is Métis and was inspired by witnessing the many gifts that being outdoors brought children. EE is a settler, early childhood educator, and researcher. EM is of settler descent and Executive Director of Early Childhood Educators of British Columbia (ECEBC), a non-Indigenous organization working with Indigenous partners. AL is of settler descent and a program manager with ECEBC. LS is Métis and, with longstanding roots in the early childhood field, has a strong connection with the land and has witnessed the many benefits of sharing this with children. AB is a family representative on the Steering Committee and a First Nations member of the Treaty 8 Territory. EC and AR are non-Indigenous family representatives on the Steering Committee. Further details on Steering Committee members are available in Multimedia Appendix 1.

Outdoor Play in Early Learning and Child Care Settings

Outdoor play has always been a fundamental part of childhood [2], and the importance of play is enshrined in the UN Convention on the Rights of the Child [3]. Children's participation in outdoor play, particularly in nature, nurtures well-being, helps build self-esteem and emotional intelligence, can enhance attention spans, promote feelings of autonomy and confidence, and help children connect to nature and the land and understand their role as part of the natural world [4-7].

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While research reinforces the importance of outdoor play for most aspects of children's lives [8,9], it is increasingly disappearing from their daily experiences. Children in Western nations have dwindling outdoor exposure, partly attributed to car-centric municipal design and the changing nature of neighborhoods, shifting familial priorities, and heightened technology usage [10-12]. In Canada, the alarming decline in outdoor play has led to the release of several position statements highlighting the benefits of outdoor play and urging an all-of-society approach to counteract this decline [13-15]. Included in their recommendations are suggestions to enhance outdoor play opportunities in schools and early learning and child care (ELCC) centers.

ELCC centers are a critical part of many countries' early years landscapes, with an average of 86% of children aged 3-5 years in OECD countries enrolled in programs [16]. These settings can provide unique outdoor play experiences, supplementing children's home and community environments. Despite the recognized importance of outdoor play, disparities persist in outdoor play implementation across ELCC programs. Many centers struggle with ensuring quality and engaging outdoor play due to various hurdles evident in their socio-ecological environments, including individual, interpersonal, organizational, policy, and societal factors, such as limited training, inadequate outdoor spaces, safety concerns, regulatory hurdles, and limited support from parents and caregivers [17-19]. Accordingly, increasing ELCC centers' capacity to support high-quality outdoor play experiences necessitates a multifaceted approach that addresses the barriers and challenges across the socio-ecological environment of ELCC centers [17].

Previous studies that have implemented play-based interventions in ELCC centers focused on increasing physical activity and typically include free play as a supplementary component to other strategies, such as structured activities [20,21]. There is very limited evidence on effective interventions seeking to increase participation in outdoor play. To fill this gap, we conducted the Promoting Early Childhood Outside pilot study (PRO-ECO 1.0) between 2021 and 2022 in partnership with the YMCA of Greater Vancouver (YMCA) [22,23]. As part of this work, we developed and implemented the PRO-ECO program, a comprehensive outdoor play intervention to address the various barriers to outdoor play across the socio-ecological environments of ELCC centers, including individual, social, organizational, environmental, and policy factors. This program was grounded in social cognitive theory [24], and we used implementation mapping [25] to develop an implementation plan and identify behavior change techniques suited to the contexts and needs of the participating ELCC centers. We used a waitlist control cluster randomized trial design to evaluate the PRO-ECO program in 8 ELCC centers operated by the YMCA. Our experiences with the PRO-ECO 1.0 study highlighted the considerable variability across ELCC centers, even when they were part of the same organization (YMCA), and important findings related to how this heterogeneity influenced program implementation and fidelity, as well as data collection and interpretation of findings [23]. The PRO-ECO program was designed with this heterogeneity in mind, and centers were able to adapt it to their needs, while still implementing the core factors that research indicates need to be addressed to influence the provision of outdoor play in ELCC settings.

The 5 R's of Indigenous Research

Among the learnings from PRO-ECO 1.0 was the importance of weaving in Indigenous ways of caring for the land with Western scientific approaches. As we face the harmful effects of colonization and our role as researchers in perpetuating it, we reflect on how we conduct research to enact principles of decolonization and contribute to reconciliation and reparation efforts. As one example, existing academic discourse around outdoor play reflects a Western worldview that can also serve to perpetuate colonial ideals. Many academic writings, including those of our research team, can instrumentalize outdoor play as a means to support other outcomes (eg, physical activity, development) rather than as an end goal in its own right [10]. Relatedly, children are treated as "becomings" with interventions designed to help them reach a productive adult ideal, thereby justifying current investment, rather than "beings" and valuable members of the community in the here and now [10,26]. This is at odds with the views and traditions of the Indigenous peoples of the very lands that children are being encouraged to play outdoors upon. Rather, many Indigenous nations celebrate children as a collective responsibility of and in symbiotic interrelationship with nature, the land, and the community that surrounds them. Place is held as sacred, and in an intimate relationship with the current inhabitants and their ancestors [27].

Driven by the importance of decolonizing our research approach and of learning from and being guided by the Indigenous peoples of this land, we, as academic researchers, worked toward doing things differently. Guided by the 5 R's of Indigenous research (5 R's), Respect, Relevance, Responsibility, Reciprocity, and Relationship, we sought to lift Indigenous cultural values and beliefs, as reflected by the Steering Committee members and partner communities, and to disrupt and unsettle traditional academic models and power relations in our community-based research partnership. The 5 R's served as guiding principles to help navigate this complex task. The 4R's were introduced by Indigenous scholars Verna Kirkness and Ray Barnhardt, to foster empowerment of Indigenous people, bands, tribes and nations and include Respect for Indigenous knowledge, cultural values and traditions; conducting research that is Relevant to Indigenous perspectives and experiences; fostering Reciprocal relationships wherein the community and the researchers collaborate on every stage of the research from design through to sense-making of the emerging knowledge and mobilization of the results, providing support and resources to community members to ensure the integrity of the process; Responsibility as researchers to act ethically and ensure that every aspect of the research promotes self-determination of the community [28]. Restoule (2008, as cited by Peterson and Robinson [29]) proposed that these components can only be fully realized through nurturing and maintaining reciprocal, sustained and mutually beneficial Relationships—the fifth R. We adopted the 5 R's to guide the entire research process, cultivating egalitarian, respectful relationships with the Steering Committee and ELCC center communities and together creating new ways of conducting research that establish greater equity. Herein, we

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describe our process and how it shaped the protocol for the PRO-ECO 2.0 study.

Goal and Objectives

Our goal is to use a 5 R's approach to design, implement, and evaluate the PRO-ECO 2.0 program and community-based randomized trial study. We were guided by the following objectives:

1. To partner with Indigenous communities, ELCC organizations, and Knowledge Keepers to adapt and implement the PRO-ECO 2.0 program in a way that is relevant to local ELCC center communities, upholds their ways of knowing, and promotes self-determination.
2. To partner with Indigenous communities, ELCC organizations, and Knowledge Keepers to co-design the randomized trial to evaluate the PRO-ECO 2.0 program.
3. To work with the participating ELCC centers to implement the randomized trial and evaluate the PRO-ECO program based on the criteria and methods identified through our partnership.

Methods

Overview

Our methods are reported following the recommendations outlined in the CONSIDER statement for health research involving indigenous peoples and knowledge [30], the CONSORT (Consolidated Standards of Reporting Trials) statement for cluster randomized controlled trials [31], and the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement for clinical trial protocols [32]. Guidance from the Medical Research Council's framework for developing and evaluating complex interventions [33] informed the development of the PRO-ECO program and the selection of evaluation metrics, including assessments of its contribution to real-world applications and the feasibility of the program. In this section, we outline the methodological approach, guided by the 5 R's of Indigenous research, and then detail the waitlist control cluster randomized control trial study design.

Ethical Considerations

We received ethics certification for this study from the University of British Columbia (UBC) and the Children's and Women's Health Centre of British Columbia Research Ethics Board (H20-01362). All participants in this study were required to give written informed consent. Child participants obtained written parental consent and ongoing assent during the interview process.

Co-Designing the PRO-ECO 2.0 Study Using the 5 R's of Indigenous Research

To ensure this project was community-guided and that our process was reflective of the 5R's from inception, the first year of the project was spent forging relationships with and gathering input from Indigenous-led child care organizations and other partners, ELCC centers, and communities. This component of the project focused on relationship and trust building, co-designing the PRO-ECO project and research study, developing research partnership agreements with participating ELCC centers, and establishing data management and stewardship protocols, consistent with Indigenous data sovereignty principles of data governance (eg, OCAP® [Ownership, Control, Access, Possession] [34]).

Research Governance, Prioritization, and Relationships

We convened the PRO-ECO 2.0 Steering Committee at the start of the project in early 2022. The Steering Committee is comprised of Knowledge Keepers who provide cultural knowledge and wisdom to this project and representatives from the ECEBC, Early Childhood Pedagogy Network (ECPN), Métis Nation British Columbia (MNBC), the Aboriginal Head Start Association of British Columbia (AHSABC), and the BC Aboriginal Child Care Society (BCACCS), faculty from institutions training early childhood educators (ECEs), and parents/caregivers of children attending the participating ELCC centers. Further details are available in Multimedia Appendix 1. By establishing a Steering Committee, we sought to co-create an inclusive, locally guided, sustainable, and culturally relevant supportive program for outdoor play in ELCC centers, weaving in Indigenous ways of caring for the land. Steering Committee gatherings were hosted monthly and provided opportunities to deepen relationships, engage in project planning, and establish the framework for the study. Each gathering incorporated a welcoming and closing prayer offered by our Knowledge Keepers, as well as opportunities to check in with one another, share personal stories, and receive important updates. Most gatherings occurred via web-based platforms, with 2 occurring in-person. Our in-person gatherings incorporated sharing food, smudging, and spirit plate offerings. An overview of the co-design process, highlighted through 2 years of Steering Committee connections, is outlined in Table 1.

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Table 1. Promoting Early Childhood Outside (PRO-ECO) 2.0 Steering Committee: an overview of connections and actions completed over the study timeframe.

Timeframe	Connections	Actions
June to August 2022	First convening of Steering Committee (web-based)	• Funding announcement • Study design ideas • Development of the Steering Committee Terms of Reference
September 2022	Connecting in Victoria, BC (in-person)	• Project visioning • Storytelling, connecting, and knowledge sharing
October to December 2022	Steering Committee connecting (web-based)	• PRO-ECO values that guide our work • Center recruitment considerations
January to May 2023	Steering Committee connecting (web-based)	• Development of working subcommittees • Center recruitment commencement • Learning Outside Together program introduction • BC Cancer shade considerations
June 2023	Connecting with participating ELCC[a] centers in Vancouver, BC (in-person)	• Connecting with ELCC centers • PRO-ECO values confirmation • Research agreement initiation • Methodology and data considerations
July to September 2023	Steering Committee connecting (web-based)	• Research agreements completion • Training on data storage and sharing • Data collection tools finalized • ECE[b] training program (Learning Outside Together) finalized
October to December 2023	Steering Committee connecting (web-based)	• Celebrations: PRO-ECO 2.0 project officially underway! • ELCC center environment modifications guidance development • Presentation to the university on the unique partnership of the Steering Committee
January to April 2024	Steering Committee connecting (web-based)	• Baseline data collection complete • Feedback from participating ELCC centers • Progress on PRO-ECO program implementation
January to April 2024	Steering Committee connecting (web-based)	• Baseline data collection complete • Feedback from participating ELCC centers • Progress on PRO-ECO program implementation
May to August 2024	Steering Committee connecting (web-based)	• Welcoming family partners • Time 2 data collection updates • Overview of environment modifications at group 1 ELCC centers (photos and stories)
September to December 2024	Steering Committee connecting (web-based)	• Time 3 data collection update • Overview of environment modifications at group 2 ELCC centers (photos and stories)
January to March 2025	Steering Committee connecting (web-based)	• Celebrations: PRO-ECO 2.0 project complete! • Celebrating each ELCC center and their success • Early results from the PRO-ECO 2.0 study

[a]ELCC: early learning and child care.

[b]ECE: early childhood educator.

A foundational component of our early work together was identifying project values. The project values identified by the Steering Committee emerged through an iterative process that spanned a year and can be seen in Figure 1. Children are centered in this work, supported by their communities, families, ECEs, and the ELCC center's social and physical environment. Within each category, the Steering Committee identified the elements they wished to be supported and emphasized as part of the PRO-ECO 2.0 study. Surrounding all values is the connection and relationship with the Land, as well as care for the environment, grounded in local ways of knowing and being. These values guided all aspects of the project, including research questions, primary outcomes, data collection methods, inclusion criteria, data analysis, and interpretation.

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Figure 1. PRO-ECO 2.0 project values developed by the steering committee to guide the study and program development, implementation, and evaluation, 2022-2025. PRO-ECO: Promoting Early Childhood Outside.

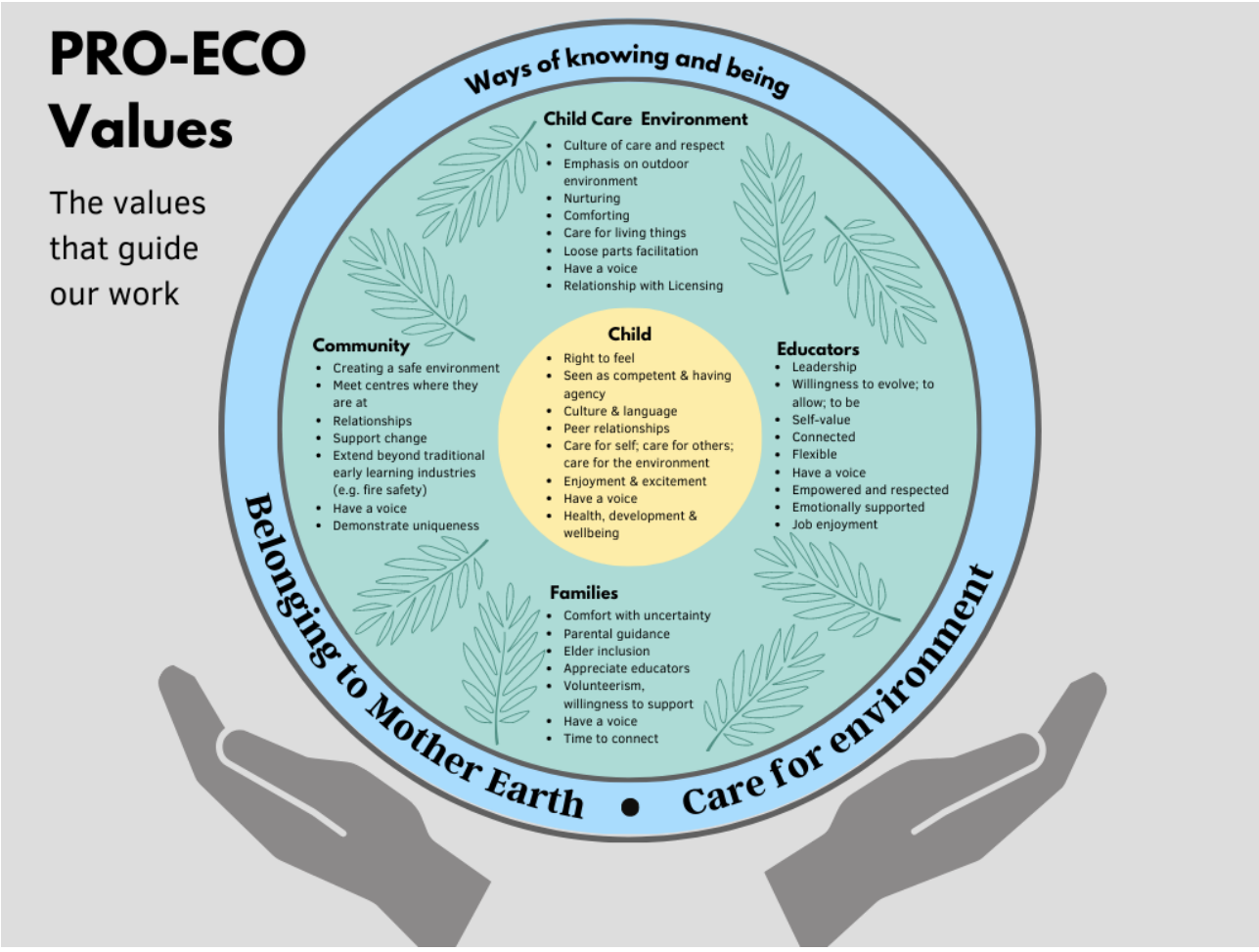

Research Agreements and Indigenous Data Sovereignty

We entered into formal research agreements with each participating ELCC center in 2023. These agreements were developed and signed on our behalf by the Innovation University of British Columbia's (iUBC). We worked with iUBC and UBC's Indigenous Research Support Initiative to establish greater equity and disrupt power dynamics, incorporating the principles of Indigenous data sovereignty into the research agreements. This represented a considerable departure from the template wording of these research agreements. We developed 2 versions: one for Indigenous communities and one for non-Indigenous communities. Both versions specified that ownership of the data was retained by the ELCC communities, with stewardship by the UBC. The sole difference between the agreements related to ensuring the Indigenous partners retained their "moral rights," that is, the rights of the Indigenous partners to be associated with the Indigenous knowledge, and ensure the accuracy and cultural sensitivity of interpreting the Indigenous knowledge. In practice, this involved requiring prior written consent for any requests to extend data use rights, or to modify or adapt Indigenous knowledge, as well as attributing ownership of the Indigenous knowledge to the Indigenous partner in all publications. The draft research agreements were shared with communities as a starting point for conversations to incorporate their input in shaping the terms included within, such that it was possible to end up with different agreements for each community. We held conversations with the leaders identified by each community as responsible for signing the agreements and adapted them according to their needs.

Importantly, the research agreements prioritized data sovereignty, guided by data sharing and ownership principles in line with OCAP®. This supported participating ELCC centers and organizations to have control over their data collection process, ownership of their data, and the interpretation and use of their data. All collected data were shared and stored on a secure software platform administered through UBC, which facilitated ownership and access of data by each ELCC center, and stewardship of data by the research team. This process proved resource-intensive as it required additional training with each ELCC center on the use of the data sharing software, as well as ethical considerations when working with the data.

PRO-ECO Study: Traditional Scientific Model Versus 5 R's of Indigenous Research Approach

The PRO-ECO 1.0 study conducted in 2021 and 2022 followed a traditional scientific model in which we used a waitlist control cluster randomized trial design to implement and evaluate the PRO-ECO program. During this study, we worked with the YMCA management team to plan and conduct the study and interpret the results. While we sought input from the management team in key decisions, such as selection of ELCC

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centers, and of the primary outcome, the academic team, guided by a scientific advisory committee, designed the study and selected the methods and measures. The YMCA management team selected the 8 ELCC centers to participate in the study, with centers informed that they were being included in the research, rather than volunteering to participate. Further details on our approach and methods have been published elsewhere [22].

This top-down approach is in contrast to the 5 R's research approach that was used to plan and implement the current PRO-ECO 2.0 study. Although we used a waitlist control cluster randomized trial design to evaluate the PRO-ECO 2.0 study, as was done in the PRO-ECO 1.0 study, important differences emerged as a result of the 5 R's research approach, reflecting our weaving in of Indigenous knowledge and ways of knowing. These differences included the design and implementation of the PRO-ECO program, selection of the primary outcome and methodology for the study design, and data ownership and stewardship agreements. Multimedia Appendix 2 provides a complete list of how the PRO-ECO 2.0 study differed in comparison to the PRO-ECO 1.0 study.

Implementation of the PRO-ECO Program

The PRO-ECO program was designed to address the barriers to outdoor play in ELCC contexts identified in previous research with ECEs [17,18]. Many challenges relate to ECEs' attitudes toward outdoor play and sense of self-efficacy in facilitating outdoor play and managing the risks inherent in it, such as children's risk-taking [35]. They have further emphasized the importance of having a common philosophy and approach with their colleagues and the managers of the ELCC with regard to pedagogical decisions and allowances for risk in play. The ECEs also highlighted that if parents and caregivers of the children understood why outdoor play was important for their child, then they were less likely to challenge outdoor play during inclement weather, perceive outdoor play as a waste of time better spent on academics, or be excessively concerned with the perceived risks of the outdoor environment [17].

The PRO-ECO program was first developed and implemented in the PRO-ECO 1.0 study and included 4 primary intervention components: ELCC center outdoor play policy, ECE training, ELCC center outdoor space modification, and parent engagement. To develop the PRO-ECO program, we used intervention mapping [36] and behavior change techniques [37] guided by social cognitive theory (SCT) [24] to address the identified challenges and build the skills necessary to support outdoor play in ELCC settings [38]. Each of these 4 components can be modified according to the needs and context of individual ELCC centers. Through the collection of baseline data, the program is further refined to provide center-specific adjustments, such as specific materials in the built environment design modification or targeted follow-up training and mentorship (Table 2). The PRO-ECO 1.0 study revealed important findings related to the implementation and evaluation of the PRO-ECO program [23]. These learnings included ensuring the sustainability and scalability of the program for lasting behavioral and environmental change, supported through continued training, mentorship, and landscape maintenance. In addition, building stronger relationships with educators, families, and children further supports the long-term integration of outdoor play in ELCC settings. Participating ELCC centers in the PRO-ECO 1.0 study were also constrained in the implementation of the PRO-ECO program at times due to staffing levels and resources.

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Table 2. Promoting Early Childhood Outside (PRO-ECO) program components and implementation in the PRO-ECO 2.0 study.

PRO-ECO program component	PRO-ECO 2.0 implementation
Outdoor play values, policy, and practice	
• ELCC[a] center administrators and staff identify the organization's core values related to outdoor play, including why they value it, and how they want to support it. • The values form the basis for a review of existing policies, procedures, and practices to determine whether they are aligned or require modification. • Values are shared with the ELCC community, and the modified policies, procedures, and practices are implemented within the ELCC center.	• Each ELCC center's administrators and staff worked together on this activity. It was integrated into the professional learning and mentorship avenues, and also supported by a supplemental session with research team members.
ECE[b] Professional Learning and Mentorship	
• Training and mentorship to build knowledge and self-efficacy around outdoor play. Ongoing mentorship to address emerging issues and build on learning.	• The Learning Outside Together, Incorporating traditional wisdom and promising practices to futureproof child care (LOT) program is an already established 10-12-week program with asynchronous online modules that are paired with synchronous weekly meetings where ECEsb meet with a peer mentor [39]. LOT incorporates local, traditional Indigenous wisdom of Land as Teacher and practices related to outdoor learning in ELCC settings. • A mentorship network, which includes liaisons from all participating ELCC centers, meets via web once per month to discuss details of the project, troubleshoot emerging issues, and share ideas. Indigenous centers are paired with Indigenous mentors to support cultural safety. ELCC centers participating in the PRO-ECO 2.0 study were invited to participate as their own cohort as part of the larger LOT program (which operates outside of the PRO-ECO 2.0 study).
Outdoor Space Modification	
• ELCC centers modify their outdoor space to increase affordances for play. Modifications include adding loose parts, plants, and other natural materials.	• Environmental modifications were designed and implemented by each of the ELCC centers, with support from the research team and the Steering Committee. Each participating ELCC center was allocated the same funding to complete environmental modifications and retained considerable discretion in how to allocate these resources. Each center was provided with CAD $8800 (US $6471) for general expenses and CAD $1600 (US $1176) for shade-related components. Liaisons were given a workshop on the Seven Cs design guidelines [40] and provided with a "look-book" with ideas for outdoor space and shade modifications. The research team worked with each center to help support the development and execution of their plans.
Family Engagement	
• Each center plans a family engagement event in the format that most suits their families. The intention is to increase parents' and caregivers' knowledge of the importance of outdoor play, and encourage family involvement in implementing the outdoor space modification.	• Materials and engagement activities led by ELCC centers with support, as needed, from Outside Play Lab. Examples of family engagement activities include: seed planting activity, working in garden boxes, planting seedlings, and creating beanpole teepees, sharing food with families and talking about the project, looking at info graphics and maps with data from interviews with the children.

[a]ELCC: early learning and child care.

[b]ECE: early childhood educator.

These learnings, alongside a 5 R's research approach, were considered in the implementation of the PRO-ECO program as part of the PRO-ECO 2.0 study, as outlined in Table 2. For example, engagement events were mobilized in a format that best suited the families at each center to increase engagement opportunities that were often challenging to realize in the PRO-ECO 1.0 study. In addition, ECE training was implemented through a mentorship network over a period of 10-12 weeks to support more long-term learning and sustainable training opportunities. ELCC centers participating in the PRO-ECO 2.0 study also received financial resources to help defray the costs of participation. Each site received CAD $15,000 for staff costs (US $11,029), CSD $8800 (US $11,029) to pay for supplies and modifications to the general outdoor environment, and CSD $1600 (US $1176) from BC Cancer to cover the costs for shade-related materials. The ELCC centers were informed about the funding for staff costs after enrollment, when extra resources became available from the funding agency.

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Study Design

The PRO-ECO 2.0 study is designed as a mixed methods waitlist control cluster randomized trial. This mixed methods approach included quantitative and qualitative data collection to evaluate the effects of the PRO-ECO project, and qualitative data gathering to plan project implementation, understand children's ECEs' and families' experiences with the project, and gather their perspectives on its effects.

Inclusion Criteria and Recruitment

The PRO-ECO project was designed for ELCC centers that provide licensed full-time group child care to children aged 2.5 to 6 years. The Steering Committee decided to open the study to ELCC centers in BC that opted into the Affordable Child Care Benefit, which is a provincial government subsidy to support eligible families with the cost of child care [41], to help ensure inclusivity of lower-income families. Additionally, while we wanted to be as inclusive as possible of remote rural locations, practicalities necessitated that ELCC centers had reasonable access to a plant nursery or hardware store to be able to access material for the outdoor space modification. The definition of what was reasonable was left up to the ELCC centers to determine (eg, within a 2-hour drive).

Recruitment notices were delivered through our Steering Committee partner organizations (in newsletters or through email blasts), posted on social media, and on the Outside Play Lab website (OutsidePlay.org). While recruitment was not explicitly targeted toward Indigenous-led ELCC centers, by distributing through our Steering Committee and partner organizations, we received interest from more Indigenous-led centers than might have been the case if the notices were distributed by another, less known or trusted organization. Interested ELCC centers contacted the Outside Play Lab, and an informal meeting was planned to explain the parameters of the partnership. A secondary zoom interview, with multiple PRO-ECO steering committee and center/band representatives, to discuss readiness for partnership, participation, and particularly access to resources to support the necessary time to the project (ELCC centers could rely on volunteers, managers, Elders, or others within their community to help them meet these time commitments). Discussion questions were provided before the meeting, and ELCCs had the opportunity to respond with their items before and during the Zoom session. The meeting also offered an opportunity to introduce members of the PRO-ECO team and their roles, while touching on how management, including staff teams, boards or organizations, and community bands or municipal governments, could modify policies, practices, and outdoor play environments.

A total of 28 ELCC centers expressed their interest in participation, and of these, 12 ELCC centers were selected for inclusion. While our desired sample size (see sample size calculation below) required the recruitment of 10 ELCC centers, we selected 12 ELCC centers to account for potential center withdrawal. Indeed, 2 centers decided not to continue participation prior to baseline data collection, citing staffing challenges. Following site selection, each ELCC appointed an ELCC-PRO-ECO project liaison ("liaisons") to connect the research team, ELCC staff, and families. ECE's and staff at participating ELCC centers during the course of the study were recruited to participate in this study between August 2023 and October 2024.

The PRO-ECO 2.0 study included ELCC centers in 10 different communities across the South Cariboo, East Kootenay, Northern, Southern Interior, Greater Vancouver, Thompson Okanagan, and Vancouver Island regions of British Columbia, Canada. Among the 10 participating ELCC centers, 7 are located in rural locations and 3 in urban locations. In addition, 5 participating ELCC centers are operated on reserve by Indigenous-led organizations.

Children attending a participating ELCC center during the course of the study and their family members were recruited to participate in this study between September 2023 and October 2024. Recruitment of children and families occurred through each ELCC center, posting flyers and distributing letters and emails that outlined details of the PRO-ECO project and sought participation. Center staff also initiated face-to-face conversations with families during drop-off and pick-up times. Over the course of the study, participating children left or graduated from their ELCC center, and newly enrolled children were recruited as the study progressed. Parental written consent was received from participating children. All children attending the ELCC programs were exposed to the PRO-ECO program, either as group 1 or group 2, regardless of consent status.

Randomization

Individual ELCC centers served as the unit of randomization in the waitlist control cluster randomized trial design. ELCC centers were randomized to either group 1 or group 2 prior to baseline data collection. Five group 1 centers implemented the PRO-ECO program immediately following baseline data collection, whereas 5 group 2 centers, acting as waitlist control sites, implemented the PRO-ECO program following time 2 data collection. Randomization was conducted by Steering Committee members who randomly drew 5 separate slips of paper with ELCC center names to represent group 1. The research trial coordinator was not blinded to the randomization, and ELCC centers were aware of their group during baseline data collection because planning was already underway with group 1 ELCC centers for launching the implementation of the PRO-ECO project. Data on outcome measures were collected at 3 time points: baseline (time 1), 6-month follow-up (time 2), and 12-month follow-up (time 3). Outcome data aimed to assess the short-term and longer-term outcomes within group 1 and the short-term outcomes within group 2. Data collection occurred during the fall and spring seasons to compare similar weather patterns at each data collection time point.

Data Collection and Measures

Primary Outcomes

Led by the values they identified as guiding the study (Figure 1), the Steering Committee sought to emphasize children's relationship with the land and care for the environment. Thus, study outcomes were prioritized to understand how the PRO-ECO project influenced children's engagement with the land. As a result, the primary outcome chosen for the PRO-ECO 2.0 study was the occurrence of outdoor nature play behavior

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at ELCC centers. While the primary study outcome differs from the PRO-ECO 1.0 study, where the occurrence of play versus nonplay was assessed, children's outdoor play behavior was still coded using the expanded version of the Tool for Observing Play Outdoors (TOPO) [42]. The TOPO is designed to measure 8 play types (physical play, exploratory play, imaginative play, play with rules, bio play, expressive play, restorative play, and digital play) and one nonplay type, along with corresponding subtypes. For this study, we coded nature play behavior through the TOPO bio play behavior type, which includes subtypes for play (observing; discussing; or interacting with plants, wildlife, or natural materials, as well as playing in a way that demonstrates care or stewardship of the environment or appreciation of nature). To further refine observed nature play behavior, children's environmental interactions (loose parts, fixed parts, natural elements, manufactured elements) were also recorded and coded.

The TOPO was implemented through a child-based, observational behavior mapping (OBM) protocol. The purpose of OBM is to understand how an environment supports movement and play behavior by mapping, recording, organizing, and analyzing geographically located data (37). Base maps were developed for each center and uploaded onto digital tablets to facilitate geo-located coding of play behavior. Due to the rural locations and varied geographic distances of most participating ELCC centers, the research team did not code play behavior in situ as was done in the PRO-ECO 1.0 study. Further, in situ coding requires significantly more time, and obtaining reliability in coding requires extensive training, making it unfeasible to have ELCC staff code the play behavior directly on-site. As a result, the liaisons at each center were trained to observe and video record children while outside during scheduled outdoor time. Children were recorded according to a systematic protocol where the liaisons at each ELCC center had a list of consented children. They then captured a 2-minute video of the child's outdoor play and verbally dictated what they noticed about the play during the video observation. We aimed to collect a total of 64 two-minute videos for each ELCC center at each data collection time point (time 1, time 2, and time 3). The observational data were collected at the child level, where individual children were the unit of observation and observations aimed to capture all consenting children. This differs from the PRO-ECO 1.0 study, which collected observational data at the center level to study children's outdoor play in connection to their ELCC. Following the collection of videos at each time point, research staff split each 2-minute video into 15-second clips (512 video clips at each center for each time point). Trained and reliable coders coded each 15-second clip to assess the TOPO play types and subtypes. The reliability of the OBM method is defined by the degree of interrater reliability and interrater agreement, which was assessed using weighted κ and intraclass correlation coefficients [43,44]. κ Values of ≥0.70 are commonly accepted as adequate for scientific research [43]. A κ value of 0.82 was achieved between coders in relation to the primary outcome variable (TOPO) prior to beginning video coding.

Additional variables were collected through the OBM protocol in this study, including risk-taking behavior, activity intensity, peer interaction, adult interaction, and play communication. Further details on the OBM protocol and process are available in the PRO-ECO 1.0 study protocol by Ramsden et al [22].

Additional Outcome Measures

ECE Attitudes Toward Outdoor Risky Play

To understand how ECEs' attitudes toward outdoor risky play may shift over the course of the study, we measured educator perspectives using the Teacher Tolerance of Risk in Play Scale (T-TRiPS) [45]. The T-TRiPS is a 25-item instrument and has been validated for use as a measure of intervention effects aimed at increasing children's access to risky play (a fundamental component of outdoor play). Questions include items that range from those that most ECEs should have little trouble endorsing (eg, "Do you let children in your center play chase with one another") to those that they might find more challenging (eg, "Do you let children in your center use adult tools [eg, hammer and nails, knife, scissors] unsupervised?"), with the response options being "yes" or "no." ECE's at participating ELCC centers completed the T-TRiPS at time 1 and time 3.

Quality of ELCC Outdoor Spaces

Modifications to the outdoor environment were guided by the Seven Cs design guidelines [40]. A simplified version of the Seven C's was developed by the research team, as seen in Table 3, in order to facilitate its completion by ELCC staff. At time 1 and time 3, center staff were encouraged to complete the Seven Cs together, centering the perspective of the children at their center. In addition to acting as a baseline measure, the time 1 measurement provided guidance to the centers regarding elements of the outdoor environment that are working well and those that might require improvements. Subsequent measurements indicated how the modifications impacted the quality of the ELCC outdoor spaces.

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Table 3. Seven Cs characteristics and ratings adapted from Herrington and Lesmeister [40] and Brussoni et al [46].

Characteristic	Rating (5=strongly agree, this is well done in my center; 4=somewhat agree; 3=neutral; 2=somewhat disagree; 1=strongly disagree, this is lacking in my center)
Character	The entire space feels welcoming for the children and ECE (eg, soft materials, dappled light, some color)
Context	The property or area beyond the play space fence contributes positively to the atmosphere of the play space
Connectivity	The children can move seamlessly from one area of the yard to another (eg, defined pathways for tricycles, and pathways for foot traffic only, such as stepping stones or tree cookie paths)
Clarity	Different zones of play are clearly identifiable at the child's height (eg, messy zones, sand play, water play, tricycle space)
Chance	Throughout the play space, there are natural and loose materials to create and build with, manipulate, and move with
Change	There are ample amounts of natural features, such as trees, shrubs, and groundcovers, in the play space (or directly adjacent to the play space) that change with the seasons
Challenge	The play space encourages different levels of physical and cognitive risk-taking (eg, height, speed, using tools, hiding/getting lost, rough-and-tumble)?

Children's Perspectives

As evident in the PRO-ECO values seen in Figure 1, the Steering Committee centers the child and their wellbeing, surrounded by the caregivers and community that support them. Steering Committee members emphasized the importance of hearing directly from children about their perspectives. They also stressed the importance of strength-based measures, rather than deficit-based measures. This was in contrast to our approach in the PRO-ECO 1.0 study, where we had relied on questionnaires completed by ECE staff about the children, which examined difficulties, such as conduct problems, aggression, and depressed affect.

For this study, we adapted the Early Childhood Education and Care Well-being Monitor, a structured interview designed for ECE staff to gather the input of children aged 4 to 6 years regarding their well-being in the ELCC center [47,48]. It includes questions about the children's daily experiences at the center (eg, "Do you think it's fun here?"), their activities (eg, "Tell me about some of your favorite things to do here."), relationships with other children ("eg, Do you have some good friends here?") and the ECEs (eg, "Do you want adults to play with you more?"), the physical environment (eg, "What is your favorite place outdoors here?"), and the extent to which their views are listened to (eg, "Do the adults decide what you are going to do when you are outdoors here?"). For this study, we eliminated questions related to the indoor physical environment and adapted the remaining questions to suit our study's context, for a total of 23-25 questions, depending on the time point (pre- or postprogram). These questions guided semistructured interviews with each child, and we referred to the mosaic approach for listening to young children to further facilitate children's participation [49]. For example, children were shown images of 3 faces, a green smiley face, a yellow neutral face, and a blue frowny face, which they could point to for each question to support their responses.

Child interviews were conducted for each individual child on-site by the ECEs at the participating ELCC center. Due to the time and resources required to conduct interviews with children, we collected these data at time 1 (preprogram) and time 3 (postprogram) only. ECEs identified a child from the consented study participant list and found a quiet place, preferably outside, to conduct the interview. Using a video camera, ECEs introduced the interview activity to the child and gained the child's assent to ask them questions. A child could remove assent at any point by declining to continue. Following the interview, ECEs noted down notable features of the interview, such as: if the child moved around or was distracted; if other children joined in the interview; if the child made body language movements that the audio would not capture; or to reflect on impressions and note down some immediate thoughts. For children who required additional support or nonverbal cues, emotion icons and images of different features in the child's ELCC center's outdoor space were provided. In addition, some ECEs found that walking around the outdoor space with the child during the interview could facilitate responses. ECE's conducting interviews were trained to stop the interview if the child removed assent and not to force an interview if a child did not wish to participate.

ELCC Center Staff Perspectives

To gather staff perspectives on the PRO-ECO program, we conducted listening circles with each ELCC center at baseline (time 1) and after the center implemented the PRO-ECO program (time 2 for group 1 and time 3 for group 2). At baseline, questions that guided the listening circles included their perceptions of outdoor play and the outdoor space in their ELCC center, the current practice and pedagogy of outdoor play, their role in supporting outdoor play, and recommendations for implementing the PRO-ECO program. At the postimplementation listening circle, we queried the changes they noticed, what they liked and did not like, how the program changed their practice, and any notable observations relevant to the effect of PRO-ECO on the children and family engagement. The listening circles were conducted in ways that best fit the ELCC center needs, such as scheduling them during already existing staff meetings. Staff time was covered by the funding provided to each center.

Family Perspectives

To gather family perspectives on outdoor play changes they may have noticed after the implementation of the PRO-ECO program at their child's center, we provided a brief survey and

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conducted short one-on-one interviews in-person and over Zoom. We sought their reflections on any changes they may have noticed in their children, the ECEs' approach to outdoor play, and the outdoor space. Each survey participant was offered a CAD $10 (US $7) gift card, and interview participants received a CAD $50 (US $37) honorarium.

Study Covariates

We collected data on the following covariates that have been found to influence children's outdoor play: children's demographics, including sex, age, disability status, first language spoken at home, family composition, average household income, and highest level of education completed by a household member. We collected information related to the child's length of time at the ELCC center and their experiences with any other forms of formal care. This information was gathered through questionnaires completed by families at the time of the child's enrollment in the study.

Weather conditions (eg, sunny, cloudy, heavy rain, snow) were recorded by the liaisons at the beginning and end of their play video recording sessions. Temperature data were recorded by the research team using weather network databases for the weather station closest to the ELCC center.

The following information related to recruitment, retention, and attendance was collected throughout the study:

- Number of eligible children that were approached to participate in the study.
- Number of children who consented to participate, did not consent to participate, and did not respond.
- Number of children who withdrew from the study.
- Number of children who enrolled in the ELCC center after initiation of the PRO-ECO program.
- Number of children who left the ELCC after initiation of the program.
- Individual and center-wide attendance rates.

Data Analysis

We aimed to collect 512 fifteen-second video clips at each center for each time point, for a total of 5120 video clips per time point (total N=15,360). This power calculation was based on the statistically significant effect size we observed in the PRO-ECO 1.0 study related to the short-term impact of the program on improving play occurrence (time 1 vs time 2 for group 1 and time 2 vs time 3 for group 2) [23]. The key coefficient of interest is the intervention by group interaction term, which corresponds with a R^2 increase of 0.00295 (ie, variance explained by the special effect), equaling to an effect size of 0.00308, when this interaction term is added to the multivariate regression model. We also expect to have 5 control variables (ie, intervention, group, weather conditions, temperature, and child gender) in the multivariate regression models, which altogether correspond with a residual variance of 0.958. This supports a power calculation of over 99% (0.997) to detect the program effect that we observed in the PRO-ECO 1.0 study. The power calculation was conducted using the G*Power software [50].

To analyze the effect of the PRO-ECO program within the PRO-ECO 2.0 study, we intend to evaluate the change in nature play behavior between pre- and postprogram. The proportion of nature play occurrences compared with nonnature play occurrences across ELCC centers at baseline will be summarized by treatment group using frequencies and percentages. This approach mirrors our analysis in the PRO-ECO 1.0 pilot study [22,23], which demonstrated the effectiveness and significance of measuring children's outdoor play occurrences through a comparison of play and nonplay behaviors pre- and postprogram implementation. However, in contrast to the PRO-ECO 1.0 study, this study focuses on the occurrence of nature play as the primary outcome variable, and not play participation in general.

Baseline demographic and ELCC characteristics will be summarized by group using means and SDs, medians and IQRs for continuous variables, and frequencies and percentages for categorical characteristics. Bivariable relationships between children's demographic characteristics and outdoor nature play occurrence, both overall and by group, will be explored to identify potential confounding factors at the individual level, considering randomization occurs at the cluster level. Mixed effects models will be used to assess differences in quantitative outcome measures between groups, as well as within-group comparisons of pre- and postprogram implementation measures.

We will analyze child interviews using qualitative content analysis methods to systematically identify patterns and themes that reflect children's perspectives and experiences on outdoor play and well-being [51]. The method's adaptability to diverse data types and research contexts, combined with its structured and systematic analytical process, makes it particularly viable for exploring the wide-ranging and expressive nature of children's responses. For ECE and family listening circles and interviews, we will use thematic analysis, which involves identifying and analyzing key themes within the data [52]. We will follow a reflexive thematic analysis to facilitate insights regarding ECEs' and families' perspectives on various interconnected topics, such as the importance of outdoor play, power dynamics, cultural norms on outdoor play, and the acceptability of the PRO-ECO program.

In alignment with the PRO-ECO project values and the partner research agreements, we will work with participating ELCC centers and the Steering Committee to share ongoing results from this study. Steering Committee members and liaisons will be invited to join a working group to work with the Outside Play Lab team on guiding and interpreting the analyses. We will gather ongoing iterative input from the broader Steering Committee and ELCC center teams to help interpret the findings, guide subsequent analyses, and develop recommendations. This form of member checking will seek to ensure all analyses and results align with the desired outputs of our project partners and appropriately convey the findings.

Knowledge Mobilization: Sharing the PRO-ECO Story

As with other aspects of the PRO-ECO study, planning for knowledge mobilization follows a 5 R's approach and will be codeveloped with the Steering Committee and the ELCC centers, who will identify primary audiences for knowledge materials, the materials that are most suited to those audiences, and the methods for reaching them.

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Steering Committee members, and where appropriate liaisons, will be supported in participating as co-presenters and coauthors for academic presentations and publications in peer-reviewed journals. We recognize that the tensions between Western academic and Indigenous worldviews are particularly notable when conducting knowledge mobilization within these traditional academic approaches. For example, the process of writing this academic publication represented a microcosm of our experiences with the project and illuminated the many pressure points when bringing together Indigenous and Western academic worldviews. Academic publication comes from the Western scientific tradition. By its very nature, it relies on written accounting (rather than oral storytelling, for example), and brings with it many assumptions and expectations on content and language use. It also requires that only authors be listed if they meet strict criteria for authorship and are listed in an order determined by their contributions [53]. Working within these norms and boundaries, we designed a process to make authorship inclusion as low-barrier as possible for our steering committee members. To facilitate their input and authorship for this publication, we shared a manuscript draft and presented it to our Steering Committee. We followed up with each member to see how we could best support their involvement if they were interested in being included as coauthors, such as planning individual conversations to describe the work and gather their input.

We recognize that knowledge mobilization through academic publications represents only one form of storytelling and reaches a scholarly audience primarily. Many diverse forms of storytelling must be integral to our knowledge mobilization efforts to reflect the different worldviews and needs of the Steering Committee and partner communities. This could include methods emphasizing oral traditions, such as videos and presentations, as well as newsletter posts, infographics, or other methods of sharing the story of the study in the places where the people we want to reach access information. We will also work with ELCC centers to develop a knowledge mobilization plan that is suited to their community, for example, family engagement events, infographics, family newsletter posts, or similar materials.

Results

This study was developed to cocreate, administer, and evaluate the PRO-ECO program following the implementation of the PRO-ECO pilot study in 2021. Funding to conduct this study was confirmed in March 2022. Ethics approval was received in September 2022. Recruitment of ELCC centers occurred from January 2023 to June 2023, followed by participant recruitment beginning in August 2023. Baseline data were collected between October 2023 and December 2023, and the group 1 ELCC centers received the PRO-ECO program from December 2023 to April 2024. Group 2 ELCC centers received the PRO-ECO between May and September 2024. Data collection was completed in March 2025. A total of 229 children were recruited to participate in the study, with 193 children participating in observational play videos for coding and 162 children participating in one-on-one interviews. Additionally, 91 staff and educators consented to participate in the study, with 59 participating in focus groups and 84 completing the T-TRiPS survey. In follow-up to consenting for their child to participate, 41 family members completed an interview or family survey to add their perspectives to the study. The PRO-ECO 2.0 waitlist control cluster randomized trial flow diagram is provided in Figure 2.

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Figure 2. Promoting Early Childhood Outside 2.0 study: Wait-list control cluster randomized trial flow diagram. ELCC: early learning and child care; PRO-ECO: Promoting Early Childhood Outside; T-TRiPS: Teacher Tolerance of Risk in Play Scale.

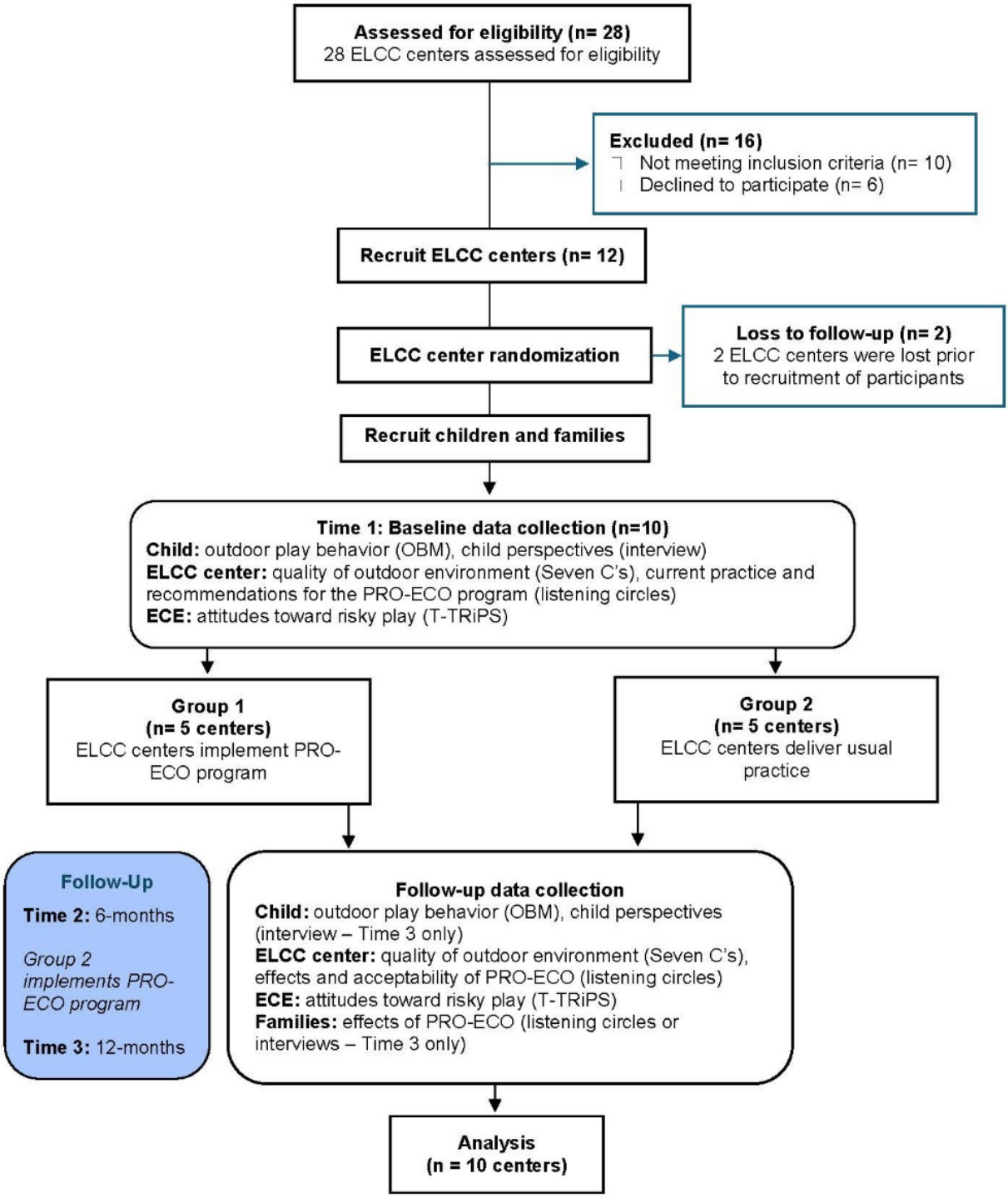

Discussion

Principal Findings

In this project, we use a 5 R's approach to lift Indigenous cultural values and beliefs to disrupt traditional academic power relations, to partner together to increase children's daily opportunities for outdoor play in their ELCC centers. Our work together is grounded in relationships and shared values that transcend individual worldviews, with a common goal to benefit the lives of children and the ELCC community that surrounds them.

There are several places where the tensions between the Western academic approaches and Indigenization and decolonization of research can seem irreconcilable, such as in choosing to use a randomized trial design for this study. Western academic traditions consider it a "gold-standard design" for evaluating the effectiveness of intervention programs, and therefore, it can be a persuasive tool for supporting change [54]. It stems from

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a positivist worldview with the assumption that environments and variables can be controlled and reliably measured to determine whether an intervention caused a particular effect [55]. There is a rich literature on the limitations and challenges involved in conducting randomized trials in community-based research, with some indicating that these approaches are ultimately incompatible because of divergent values or goals [56]. The importance of a long planning phase has been highlighted along with careful consideration of the evidence that can meaningfully indicate the effectiveness of the program or intervention [56].

In this project, our relationship building and deliberate process to identify project values have been a critical ingredient in working to realize a 5 R's approach for this study. The explicit values (Figure 1) illuminated a path of decisions at key junction points, such as what was considered meaningful evidence, and from whose perspective. This approach placed children at the center and included measures that helped us include children's voices and ensure data collection methods emphasized a strength-based perspective.

Strengths and Challenges With the 5 R's Research Approach

A significant strength of PRO-ECO 2.0 study is the creation of a Steering Committee to guide this work. Their steady guidance and encouragement helped us work toward realizing a 5 R's approach for this work. We anticipate that the results of this study will provide important evidence to help inform curriculum, policies, outdoor environments, and professional development training that support outdoor play opportunities among children in ELCC centers. This study will also provide insightful alignment with international research on outdoor play in ELCC centers [57,58].

An additional strength relates to the learnings from PRO-ECO 1.0 that we were able to incorporate into this study to address some of the challenges and limitations we had encountered. We sought to include a diverse sample of ELCC centers, including demographic and geographic diversity, and this presented new challenges to the study. The vast geographic locations of ELCC centers required a different approach to data collection and data sharing than reflected in the PRO-ECO 1.0 study, including ELCC center staff collecting data themselves. These opportunities strengthened the project in many ways by enhancing project involvement for the ECEs at all stages of the study. However, it also contributed to limitations with the extent of data that could be collected in terms of quantity, approaches, and tools. ELCC communities may not have understood the amount of work involved, and this meant that in our commitment to egalitarian involvement and empowering their participation, we had to increase the anticipated resources to support them. In addition, the use of video recordings captured by ELCC center staff and later coded off-site by the research team posed challenges in accurately interpreting children's actions and movements, given the limited sound and contextual information inherent to second-hand observation [59]. In situ coding, as implemented in the PRO-ECO 1.0 study, supported richer contextual understanding and immediate interpretation for the research team working with on data coding and analysis. However, off-site coding was necessary in this study due to the remote locations in which data were collected. Although the data coding presented more challenges in this study, potential observer bias may have been reduced by having ELCC center staff already integrated into the children's daily environments, who conduct all observations [60].

The innovative nature of creating distinct research agreements with each ELCC community, rather than adopting a single overarching agreement typical of conventional research projects, offered substantial strengths, including prioritizing community agency and reciprocal data ownership and sharing relationships. However, it also introduced challenges within the research agreement development, including the data collection and data sharing process. Traditional Western academic institutions often prioritize data ownership within the university, supported by institutional policies and software designed to ensure ethical and secure data management, and commonly promote open-access frameworks. This study diverged from those norms by asserting that data should remain within the community rather than be institutionally owned or publicly shared. Compounding these challenges was the limited guidance in existing literature on creating research agreements that depart from conventional models. To ensure inclusivity and respect for all stakeholders, individualized data agreements were codeveloped with each ELCC center and their community, the Steering Committee, the research team, iUBC, and the Indigenous Research Support Initiative. Although time- and resource-intensive, this collaborative process was essential to ensure all perspectives were represented in the final agreements.

To further support community-based data ownership, ELCC centers received training on ethical data management and the use of centralized software systems for securely collecting, storing, and sharing sensitive child-related data. Variation in the resources available across ELCC centers to manage data ownership, storage, and sharing was evident. Some centers had sufficient infrastructure, such as reliable Wi-Fi and appropriate hardware, which facilitated smooth data collection and transfer. In contrast, ELCC centers in remote locations often faced inconsistent connectivity and limited access to necessary equipment, hindering data sharing with the research team. In some cases, team members had to travel to these sites in-person to retrieve stored data directly from hardware devices. Staffing capacity also influenced these processes; ELCC centers with more personnel, or with staff experienced in using digital tools, were better equipped to meet the project's data management requirements.

The implementation of the PRO-ECO program also faced challenges, particularly in adhering to the designated implementation timeline. Sustaining engagement with the ECE training and introducing or maintaining built environment modifications were at times limited by staffing constraints, seasonal changes, and difficulties obtaining materials in the remote locations of participating ELCC centers. Although the PRO-ECO program was scheduled to be implemented between December 2023 and April 2024 for group 1 ELCC centers and May 2024 and September 2024 for group 2 ELCC centers, actual implementation extended beyond these periods in some ELCC

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centers. These challenges were consistent with those observed during the PRO-ECO 1.0 study [22,23].

Conclusions

The PRO-ECO study provides an example of the 5 R's in practice, in the context of a rigorously-designed evaluation of a program to support outdoor play in ELCC settings. Including diverse ELCC centers in urban, rural, and remote areas will unearth new learnings on how to support their community and practice in the context of outdoor play. In designing and conducting this mixed methods waitlist control cluster randomized trial, we sought to ensure that we worked in ethical and responsible ways to disrupt traditional power structures and promote self-determination of the participating communities, balancing the need to produce what Western scholars consider rigorous evidence, while also prioritizing in Indigenous community perspectives, centering the voices of the ELCC community and gathering rich contextual data to help understand their daily realities. In sharing our story of building and conducting this study, we hope that our experiences can provide scholars and communities with ideas for their own journeys.

Acknowledgments

The authors are thankful to the ELCC center staff, children, and families who took part in this study.

Data Availability

The datasets generated and analyzed during this study will not be made publicly available as per the research agreements created with each participating early learning and child care (ELCC) center.

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Authors' Contributions

MB conceived the study and obtained funding. MB and RR wrote the first draft of the manuscript. SG is co-Principal Investigator and member of the Steering Committee, and guides conceptualization and logistics of the work. RR, DM, and EF contributed to the conceptualization of the study design and are working with the ELCC centers to collect the data. SH is a member of the academic research team and the Steering Committee and supports the modifications to the outdoor environments. YL, RR, and MB developed the data analysis plan. SEJ, JL, EM, AL, LS, AB, EC, and AD are members of the Steering Committee guiding this work. All authors contributed to, read, and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Steering committee overview and author positionality statements.
[DOCX File , 24 KB - resprot_v14i1e77956_app1.docx]

Multimedia Appendix 2
Differences between PRO-ECO 1.0 pilot study and PRO-ECO 2.0 study.
[DOCX File , 18 KB - resprot_v14i1e77956_app2.docx]

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Abbreviations

5 R's: 5 R's of Indigenous Research (Respect, Relevance, Responsibility, Reciprocity, and Relationship)
AHSABC: Aboriginal Head Start Association of British Columbia
BCACCS: BC Aboriginal Child Care Society
CONSORT: Consolidated Standards of Reporting Trials
ECE: early childhood educator
ECEBC: Early Childhood Educators of British Columbia
ECPN: Early Childhood Pedagogy Network
ELCC: early learning and child care
iUBC: Innovation University of British Columbia
MNBC: Métis Nation British Columbia
OBM: observational behavior mapping
OCAP®: Ownership, Control, Access, Possession
PRO-ECO: Promoting Early Childhood Outside
SCT: social cognitive theory
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TOPO: Tool for Observing Play Outdoors
T-TRiPS: Teacher Tolerance of Risk in Play Scale
UBC: University of British Columbia

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Protocol

Effectiveness of Metformin Prolonged-Release Formulation on Achievement of Optimal Glycemic Control in Gestational Diabetes Mellitus: Protocol for a Pilot, Randomized, Double-Blind, Clinical Trial

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Abstract

Background: Gestational diabetes mellitus (GDM) is one of the most common complications in pregnancy. Optimal glycemic control is key to reducing the risk of adverse pregnancy outcomes. If glycemic control is inadequate, additional medications are needed. A large body of evidence has shown that metformin is an effective medication for GDM. Compared to the immediate-release formulation, the prolonged-release (PR) formulation of metformin offers some advantages with a single daily dose and has less frequent side effects, leading to better compliance. To date, no study has specifically reported the effectiveness of metformin PR in the treatment of GDM or the time required to achieve glycemic control after treatment. The results will help clinicians plan a better choice of treatment and follow-up for women with GDM and inadequate glycemic control.

Objective: This study aims to evaluate the effectiveness of metformin PR in the treatment of GDM in terms of achieving glycemic control within 6 weeks, time to achieve glycemic control, and associated factors.

Methods: A randomized, double-blind, placebo-controlled clinical trial will be conducted among 80 pregnant women diagnosed with GDM who had inadequate glycemic control at a university hospital in Thailand. The women will be randomized into 2 equal groups, receiving either metformin PR or a placebo in addition to nutritional therapy and behavioral modification. Dosage adjustment will be made every 2 weeks. If the glycemic target is not achieved within 6 weeks, insulin therapy will be initiated. All the participants and the investigators are blinded to the treatment provided. The primary outcome is the rate of achievement of glycemic control, and secondary outcomes are time to achieve glycemic control, rate of insulin therapy, and factors associated with the success of metformin PR use.

Results: The study was funded in May 2025 when recruitment started. The study is projected to be completed in October 2026. Women with GDM who experienced inadequate glycemic control by nutritional therapy were assessed for eligibility. As of October 2025, 24 women with GDM agreed to participate and follow-ups were scheduled. The results are expected to be published in 2027.

Conclusions: The results of this study will provide additional information on the use of metformin in the treatment of GDM, including the use of different formulations, rate of glycemic control, time to achieve glycemic control, and associated factors. This will help physicians better plan care for pregnant women with GDM, especially when glycemic control is inadequate, including choices of metformin formulation and dosage, follow-up schedule, and identification of women at risk of treatment failure.

Trial Registration: Thai Clinical Trial Registry TCTR20250525007; https://www.thaiclinicaltrials.org/show/TCTR20250525007

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KEYWORDS

gestational diabetes mellitus; metformin; prolonged-release formulation; glycemic control; effectiveness

Introduction

Gestational diabetes mellitus (GDM) is one of the most common complications in pregnancy; it can lead to various adverse maternal and neonatal outcomes, including preeclampsia, cesarean section, large-for-gestational-age infants, macrosomia, birth injuries, shoulder dystocia, and neonatal hypoglycemia [1-3]. Optimal glycemic control (fasting plasma glucose [FPG] of <95 mg/dL and 2-h postprandial glucose, 2-h PPG of <120 mg/dL) is key to reducing the risk of developing adverse pregnancy outcomes [1-3].

In general, nutritional therapy, behavioral modification (including physical activity and exercise), and glucose monitoring and control are the main interventions to provide to all women with GDM to achieve glycemic targets. However, if glycemic control is inadequate, additional medications are needed. Insulin has long been used as the first-line medication in GDM. Nevertheless, a large body of evidence has consistently shown that metformin is also an effective medication for glycemic control in GDM. It has been reported that metformin helps in better glycemic control, better control of weight gain, reduction in adverse pregnancy outcomes, and reduction in insulin need and dosage requirement [4-14]. In addition, metformin has been reported to be safe to use during pregnancy [6,15-19] and appears to be more cost-effective compared to insulin in the treatment of GDM [20]. Currently, many international authorities recommend the use of metformin in women with GDM [1,21,22].

Different formulations of metformin are available, including an immediate-release (IR) formulation, with a time to maximum concentration of 3 to 4 hours and a 12-hour duration of action, and a prolonged-release (PR) formulation, with a time to maximum concentration of 7 to 8 hours and a 24-hour duration of action. Although both formulations have comparable effectiveness, metformin PR has advantages over its IR counterpart in terms of once-daily dosage with minimal gastrointestinal side effects, which helps improve compliance [23-28]. Gastrointestinal side effects have been reported with the use of metformin IR in previous studies, and some participants needed to stop the medication or reduce the dosage [4]. In another study, the use of metformin IR resulted in nausea and vomiting in 36% and 25% of the participants, respectively [5]. Therefore, metformin PR would be more suitable to use during pregnancy, not only because many pregnant women usually experience gastrointestinal symptoms, such as nausea and vomiting, but also because the medication has fewer side effects. Furthermore, with its once-daily dosage, compliance with the treatment will improve.

Although the benefits of metformin PR on diabetes have been reported, information on its potential benefits for the treatment of GDM is lacking. To address this knowledge gap, we will conduct a study to evaluate the effectiveness and associated characteristics of metformin PR in the treatment of GDM. The results will provide more insights into the use of metformin PR for the treatment of GDM. Understanding its effectiveness, time to achieve glycemic control, and the risk for treatment failure can help caring physicians make better decisions on treatment initiation, follow-up schedule for glycemic control evaluation, and identify those who are at higher risk for treatment failure. The results would be helpful in developing a higher quality of care for patients with GDM in the future.

Our hypothesis is that metformin PR is effective in GDM treatment in terms of the rate of adequate glycemic control and time to achieve glycemic target compared to nutritional therapy. Therefore, the primary objective of this study is to compare the rate of optimal glycemic control within 6 weeks between women with GDM who receive metformin PR and women who receive a placebo, in addition to standard nutritional therapy. The secondary objectives are to compare the time required to achieve optimal glycemic control and the rate of insulin therapy between the 2 groups, and to determine factors associated with the success of metformin PR treatment, such as prepregnancy BMI, degree of abnormalities of test results at the time of diagnosis, GDM risk factors, and other baseline characteristics.

Methods

Study Design

The study is designed as a randomized, double-blind, placebo-controlled trial and registered at the Thai Clinical Trial Registry (TCTR20250525007). Eligible participants will be randomly assigned in a 1:1 ratio to receive either metformin PR or a placebo. Each participant will be followed up every 2 weeks for glycemic control evaluation and dosage adjustment for 6 weeks.

According to the institutional practice guidelines, every woman with GDM will receive counseling by certified diabetes educator nurses and will be scheduled for follow-up every 2 weeks for glycemic control evaluation. If the glycemic target is not achieved after 6 weeks of intensive nutritional therapy, additional pharmacological treatment will be initiated. Therefore, this study will evaluate the primary outcome of glycemic control at 6 weeks after randomization.

Study Setting

This study will be conducted at the Department of Obstetrics and Gynecology, Faculty of Medicine, Siriraj Hospital, Mahidol University, Bangkok, Thailand. Siriraj Hospital is the largest university-based tertiary care hospital in Thailand, with approximately 4000 deliveries per year. Routine GDM screening is offered to all pregnant women, and those with GDM are

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managed by a specialized care team, including an obstetrician, certified diabetes educator nurses, and endocrinologists. All women with GDM receive counseling regarding nutritional therapy, behavioral modification, and glycemic monitoring. Metformin has been incorporated into the guideline as an optional pharmacological therapy, as an alternative to insulin.

GDM Diagnosis and Management

According to current institutional guidelines, GDM screening and diagnosis are offered to all pregnant women at the first antenatal care visit and repeated at 24 to 28 weeks of gestation if the initial screening results are normal. A 50-g glucose challenge test is used as a screening test with a 140 mg/dL cutoff value, and a 100-g oral glucose tolerance test is used for diagnosis using the Carpenter and Coustan criteria (≥2 abnormal values of 95, 180, 155, 140 mg/dL at 0, 1, 2, and 3 h). The current prevalence of GDM in the institution is approximately 15% to 20% of pregnant women.

After diagnosis, nutritional counseling and knowledge on behavioral modification are provided by certified diabetes educators. A glucometer is encouraged and offered for self-monitoring blood glucose (SMBG), but its use is based on women's preference. FPG or 2-hour PPG, or both, are used for evaluation of glycemic control during follow-up. Glycemic targets are set at FPG <95 mg/dL and 2-hour PPG <120 mg/dL in >80% of the total SMBG test results.

If glycemic targets are not met at any time during pregnancy, repeat nutritional and behavioral counseling is offered. The women are reevaluated every 1 to 2 weeks. If adequate glycemic control is still not achieved within 4 weeks, pharmacological treatment will be initiated. In addition to insulin therapy, metformin will be offered as an alternative medication. The decision on choices of pharmacological therapy is based on the physician's discretion and the woman's preference.

Eligibility Criteria

Eligible cases are pregnant women diagnosed with GDM who meet the inclusion and exclusion criteria, as described in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Aged ≥18 y
- Singleton pregnancy
- Diagnosed with gestational diabetes mellitus, according to institutional guidelines (50-g glucose challenge test followed by 100-g oral glucose tolerance test using the Carpenter and Coustan criteria)
- Do not achieve glycemic target after nutritional and behavioral counseling (fasting plasma glucose ≥95 mg/dL or 2-hour postprandial glucose ≥120 mg/dL in >20% of total self-monitoring blood glucose test results)

Exclusion criteria

- Definite or suspected pregestational diabetes mellitus
- Fetal congenital anomalies or deaths
- Suspected fetal growth restriction (as metformin is advised to be used with caution in those with fetal growth restriction)
- Currently using metformin or other antihyperglycemic treatment regardless of indication
- Contraindicated for metformin use

Interventions

After initial screening and acquiring informed consent, the women will be randomly assigned to 2 groups—the intervention group or the control group.

For the intervention group, metformin PR will be provided to the participants, starting with 750 mg daily (1 tablet of metformin PR 750 mg). Follow-up is scheduled every 2 weeks for 6 weeks. Dosage adjustment will be made at each visit, depending on the results of glycemic control in a step-up protocol, that is, 750, 1000, 1500, and 2000 mg. The maximum dosage of metformin PR is 2000 mg per day. For dosage adjustment, 1 tablet of metformin PR 1000 mg will be used for a dosage of 1000 mg per day, 2 tablets of metformin PR 750 mg will be used for a dosage of 1500 mg per day, and 2 tablets of metformin PR 1000 mg will be used for a dosage of 2000 mg per day.

Pregnant women who are in the control group will receive 1 tablet of a placebo and will be scheduled for follow-up every 2 weeks for 6 weeks.

In addition to standard antenatal care according to institutional guidelines, pregnant women in both groups will receive individualized counseling on nutrition and behavioral modifications for glycemic control at every follow-up visit.

All participants are encouraged to adhere to the medication provided. A specific phone number will be provided to participants to receive an answer if they have any questions about the medications. Participants will be contacted every 2 days via a telephone call, SMS, or other online platforms to ensure medication adherence. Pill count will be performed at every visit, and additional encouragement will be provided. All participants are advised to avoid using other antidiabetic medications and other herbal products during the study period.

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At the end of the study period of 6 weeks, glycemic control will be evaluated thoroughly, and appropriate treatment will be provided. Either the previous treatment will be continued or a new treatment will be initiated, after consultation with an endocrinologist, as appropriate. Standard antenatal care will also be provided until delivery. Treatment failure is defined as inadequate glycemic control after 2000 mg of metformin PR. In such a situation, insulin therapy is initiated.

If any of the conditions in the exclusion criteria are detected after enrollment, such as congenital anomalies, randomization concealment will be revealed and considered as a dropout, and these participants will not be included in the analysis. The pregnant woman will be thoroughly evaluated by the obstetrician team to provide appropriate management.

Outcomes

The primary outcome of this study is the rate of achievement of optimal glycemic control within 6 weeks, which is defined as FPG <95 mg/dL or 2-hour PPG <120 mg/dL in >80% of total SMBG test results.

The secondary outcomes include time to achievement of optimal glycemic control, rate of insulin therapy, and rate of side effects. Treatment failure is defined as inadequate glycemic control after 2000 mg of metformin PR. In this situation, insulin therapy is initiated. Side effects will be evaluated by interviewing the participants at each visit and by additional contact via a telephone call, SMS, or other online platforms.

The participant timeline is displayed in Figure 1.

Figure 1. Study flow diagram.

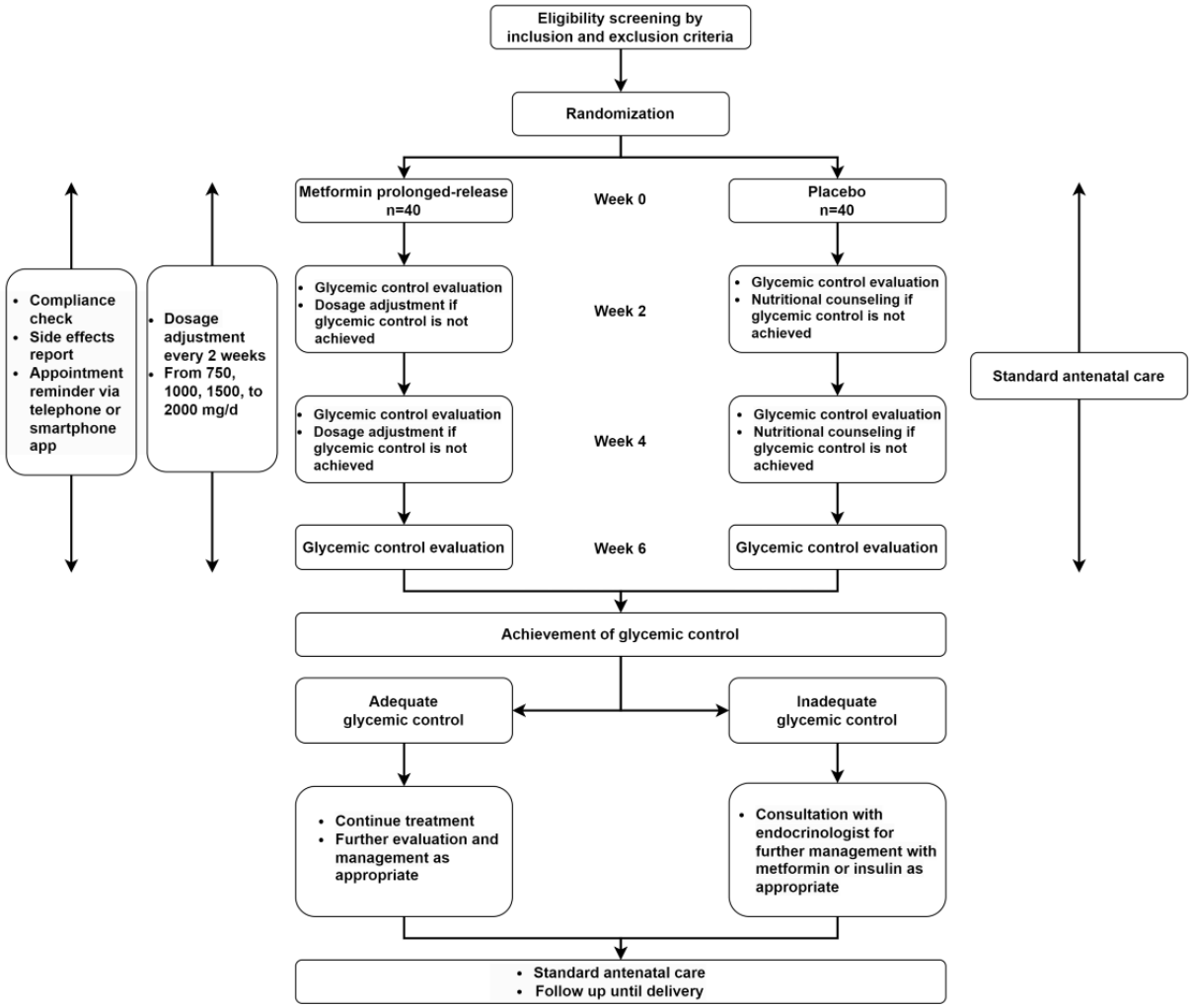

The rate of achievement of glycemic target within 6 weeks among women with GDM receiving metformin PR and placebo is estimated to be 95% and 70%, respectively, from a pilot data collection. At 95% confidence and 80% power, at least 40 women with GDM are required in each group, estimating a loss of 20% of the participants.

Assignment of Interventions

Randomization

Participants will be allocated to receive either metformin PR or a placebo by simple randomization. Central randomization will be used to minimize the risk of bias. The investigator will contact an independent individual to obtain the randomization list at the time of enrollment of each participant.

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Blinding

All participants will be blinded to the treatment received. Placebos will be prepared by a pharmacist to resemble metformin PR in shape, size, and color. All caring obstetricians will be blinded to the treatment and make decisions on dosage adjustment or initiation of insulin therapy at their discretion. Glycemic control will be blindly assessed by the investigators without knowing the group to which the participants are assigned.

In case of withdrawal or termination of the study protocol, such as the occurrence of severe adverse events or noncompliance, the treatment will be unblinded. Further individualized management will be provided as appropriate. In addition, emergency unblinding will be performed if the participants need to be evaluated or treated for medical or obstetric conditions other than GDM.

Data Collection and Management

Data will be collected at enrollment and at every visit. Data will be entered into the electronic case record form, including baseline and obstetric characteristics, such as age, parity, and prepregnancy BMI. GDM diagnosis and management data, such as gestational age at diagnosis, results of the 50-g glucose challenge test and 100-g oral glucose tolerance test, and glycated hemoglobin, will be collected. Glycemic control data, including FPG and 2-hour PPG at every visit, or percentage of abnormal SMBG test results, will also be noted. Furthermore, the time to achieve the glycemic target will be evaluated, as will side effects, such as bloating, nausea, and vomiting.

Data at every time point will be checked for completeness and entered into the electronic case record form using an electronic data capture system. Data range and values will be rechecked by another research assistant. Incomplete and invalid data will be rechecked with those in the case record form or medical record. An audit trail will be used to track and identify all actions performed on the data, ensuring data integrity.

Statistical Methods

Descriptive statistics, including number, percentage, mean, and SD, will be used to describe variables as appropriate. Comparisons of variables between groups will be made using the 2-tailed Student *t* test for continuous variables, such as age, BMI, and gestational age, or the chi-square test for categorical variables, such as parity and GDM risk factors. Comparison of rates of achievement of optimal glycemic control between groups will be performed using the chi-square test. Relative risks and 95% CIs will be evaluated. Time to achieve glycemic control will be compared between groups, using the Student *t* test or Mann-Whitney *U* test, depending on the distribution of the variables. Kaplan Meier curves will be used to estimate the survival curve of time to achieve glycemic control after treatment, and the log-rank test will be used to compare the survival curves between treatment and control groups. Rates of insulin therapy and side effects will be compared using appropriate statistical tests. Missing values will be handled using multiple imputation methods, as appropriate. Subgroup analysis by BMI categories, parity, or GDM risks will be performed as appropriate. All analyses will be performed on an intention-to-treat basis. A P value of <.05 is considered to indicate statistical significance.

Oversight and Monitoring

Safety Management

All participants will receive standard antenatal care at every visit by obstetricians. In addition to physical examination, obstetric examination will be performed, including evaluation of fetal growth and fetal heart rate activity, either by clinical or ultrasonographic examinations. Additional procedures will be provided as appropriate, such as electronic fetal monitoring, detailed ultrasonographic examination, etc.

Glycemic control will be evaluated by FPG and 2-hour PPG or percentage of abnormal SMBG test results. Individual nutritional and behavioral counseling will be provided, customized for each participant. According to institutional guidelines, participants with FPG ≥200 mg/dL or glycated hemoglobin ≥10% will be admitted for further evaluation and initiation of insulin therapy by an endocrinologist.

Adverse Event Reporting and Harms

Any adverse events will be evaluated by self-report from the participants and by interview and clinical evaluation during each visit (every 2 weeks), starting from the day of enrollment until the end of the study (at 6 weeks after enrollment). In addition, participants will be contacted every 2 days via a telephone call, SMS, or other online platform to evaluate any adverse events. A telephone number will be given to all participants to call if there are any suspected abnormalities or any adverse events. Attending obstetricians will assess whether the events are related to the investigational drugs used for GDM. Management will be provided as appropriate by attending obstetricians, and consultation with other specialists will be made as necessary. In case of any adverse events, an additional specific follow-up schedule with related specialists will be offered until they are resolved or considered stable. Assessment of the adverse events and their response to treatment will be by telephone call, self-report, and clinical and laboratory assessment, as appropriate, according to the contexts and nature of the events. All the events will be followed up on until the conditions resolve. All the adverse events will be recorded in detail in the case record form.

In case of withdrawal or termination of the study protocol, such as severe adverse events or noncompliance, treatment will be unblinded. Further individualized management will be provided as appropriate.

Data Safety Monitoring Board

An independent data safety monitoring board will be set up for trial monitoring. The members will include 2 obstetricians, 1 endocrinologist, 1 biostatistician, and 1 methodology expert. None of the data safety monitoring board members has any conflicts of interest that may affect the decision-making process.

Ethical Considerations

At the antenatal care clinic, the investigator or the research assistant will screen pregnant women with GDM for eligibility and provide detailed information regarding the study. If the

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women agree to participate, a written informed consent will be obtained. Each participant will receive compensation of US $30. The study has been approved by the Siriraj Institutional Review Board (Si106/2025). All personal identification information of the participants, including names, telephone numbers, hospital numbers, and medical records, will be anonymized to ensure confidentiality. Coding will be used for each participant, and no related information will be disclosed. All study data will be stored by the researchers and will be retained for at least 5 years after publication.

Dissemination

The research findings will be disseminated to relevant stakeholders, including participants, their families, physicians, and the institutional medical community. In addition, the results will be disseminated via high-impact international peer-reviewed medical journals and presentations at international medical conferences to ensure broad academic and clinical engagement. Reporting the results of the study will follow the latest CONSORT (Consolidated Standards of Reporting Trials) guidelines. Distribution of key information will also be made available for health care professionals and the public, as appropriate.

The findings will also be disseminated at the national level via various medical institutions, obstetrics and gynecology communities, endocrinology communities, and the Ministry of Public Health. These findings could help modify the current guidelines for GDM management.

Results

The study was funded in May 2025, when recruitment started. Women with GDM who had inadequate glycemic control by nutritional therapy were assessed for eligibility. As of June 2025, 24 women with GDM agreed to participate and follow-ups were scheduled. Recruitment will continue until 80 participants are included, which is expected to occur by September 2026. The study is projected to be completed in October 2026. The results are expected to be published in 2027.

Discussion

Anticipated Findings and Importance

Although the effectiveness of metformin in the treatment of GDM has been demonstrated in previous studies, only metformin IR has been investigated [4-14]. No study has specifically reported the effectiveness of metformin PR, which could have advantages over metformin IR in terms of fewer side effects and a once-daily dosage that results in better compliance [23-28]. Moreover, no previous study has reported the time required to achieve glycemic control after metformin treatment.

Therefore, the results of this study will add additional information to the medical community. It can help caring physicians to make better decisions regarding the selection of appropriate dosage and formulation of metformin, as well as a follow-up schedule for evaluation of glycemic control. In addition, the results could also help identify women at a higher risk for unsuccessful glycemic control after metformin therapy.

Some challenges in conducting the study might include adherence to the scheduled treatment and follow-up. Various measures are planned to improve both important issues. All participants will be informed regarding the importance of adherence to the treatment and follow-up to achieve glycemic control. Participants will be regularly contacted every 2 days via a telephone call, SMS, or other online platforms to encourage adherence to the provided medications and follow-up schedule, and for the evaluation of any adverse events.

The results will provide more insights into the use of metformin PR for the treatment of GDM. Understanding its effectiveness, time to achieve glycemic control, as well as the risk for treatment failure, can help caring physicians make better decisions on treatment initiation and follow-up schedule for glycemic control evaluation, and identify those who are at higher risk for treatment failure. All the information would be helpful in developing a higher quality of care for patients with GDM in the future.

Strengths and Limitations

The strengths of this study include its randomized, double-blind, placebo-controlled trial design. The diagnosis of GDM follows a uniform institutional guideline. Nutritional and behavioral modifications counseling is provided by well-trained, certified diabetes educator nurses. The main outcome of glycemic control is objectively measured.

Some limitations include that the duration of the intervention and follow-up to evaluate the primary outcome of glycemic control within 6 weeks might not fully capture the long-term effects or improvements after metformin PR treatment. A longer follow-up period is needed to determine whether a higher dose of metformin PR or insulin will be required to achieve adequate glycemic control as pregnancy progresses. In addition, the actual dietary and behavioral practice varies among participants and cannot be accurately measured, which could affect the outcomes. Moreover, the study does not provide a head-to-head comparison between different formulations of metformin, that is, IR versus PR.

The study is not primarily designed to determine if the use of metformin PR improves the pregnancy outcomes, as the study ends at 6 weeks after initiation of the treatment, and further management will vary according to the status of the women and physicians' discretion. Further well-designed studies on the improvement of GDM-related maternal and neonatal outcomes, such as preeclampsia, large-for-gestational-age infants, and macrosomia, with metformin therapy should be conducted to provide additional evidence on metformin benefits and help aid clinicians' decisions.

The study is planned to be a pilot randomized clinical trial, and the sample size was calculated based only on the primary objective of comparing glycemic control between the 2 groups and did not take into account for some related factors, such as BMI or gestational age. However, this issue should be considered when designing larger definitive studies in the future.

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Acknowledging these limitations is essential for interpreting the results and refining future research.

Conclusions

This study is primarily aimed at investigating whether metformin PR is effective in the treatment of GDM in terms of achievement of glycemic control within 6 weeks and time to achieve glycemic control. This information will provide additional evidence on the potential benefits of metformin treatment in GDM that can be applied to clinical practice. If metformin PR is effective in achieving glycemic control within a short time, it can be considered a good alternative to conventional IR formulation or insulin. In addition, the results will serve as a basis for future research to explore the benefits of treatment, especially if the treatment can improve maternal and neonatal outcomes.

Acknowledgments

The authors would like to thank the gestational diabetes mellitus patient care team for their contribution in conducting the study.

Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

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Authors' Contributions

Conceptualization: DB, PS
Data curation: DB, PS
Formal analysis: DB
Funding acquisition: DB
Methodology: DB, PS
Project administration: DB
Supervision: DB, PS
Writing—original draft: DB, PS
Writing—review and editing: DB, PS

Conflicts of Interest

DB and PS received funding from Merck Ltd.

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Abbreviations

FPG: fasting plasma glucose
GDM: gestational diabetes mellitus
IR: immediate-release
PR: prolonged-release
SMBG: self-monitoring blood glucose

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Protocol

Cardio-Cerebral Protective Effect of Moxibustion on Phlegm-Dampness Type Hypertension: Protocol for a Randomized Controlled Trial

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Abstract

Background: Hypertension is associated with a high rate of disability and mortality and leads to a substantial socioeconomic burden. Moxibustion is an external treatment in traditional Chinese medicine that has been used to treat mild to moderate hypertension in individuals with phlegm-dampness constitution and has demonstrated acupoint specificity. However, a standard large-scale randomized controlled trial is still needed to verify its effectiveness. This study is proposed to examine the clinical effectiveness and potential cardioprotective benefits of moxibustion performed at home as a treatment for individuals with phlegm-dampness hypertension.

Objective: The objective of this trial is to evaluate the cardio-cerebral protective clinical efficacy of moxibustion for phlegm-dampness type hypertension and to explore its acupoint specific effects.

Methods: This study is a multicenter, randomized controlled trial. A total of 120 patients with mild to moderate hypertension and phlegm-dampness constitution will be recruited and randomly assigned in a 1:1 ratio to the treatment group (acupoint: Zusanli, ST36) or the control group (acupoint: Xuanzhong, GB39). All patients will receive 12 weeks of treatment and a 12-week follow-up period. The primary outcome measure is the change in morning systolic blood pressure from baseline to week 12. The secondary outcome measures include blood pressure–related indicators (morning diastolic blood pressure, average systolic blood pressure, average diastolic blood pressure, nighttime systolic blood pressure, nighttime diastolic blood pressure, and blood pressure circadian rhythm) and short-term blood pressure variability coefficient, all of which will be measured by 24-hour ambulatory blood pressure monitoring. Additionally, cardiac-related indicators measured by 24-hour Holter monitoring, metabolic disorder-related indicators, liver and kidney function indicators, transformed scores of the traditional Chinese medicine phlegm-dampness constitution scale, and the Montreal Cognitive Assessment will also be evaluated.

Results: This study was registered on July 5, 2024, with the Chinese Clinical Trial Registry. Data collection began in June 2023 and ended in February 2025. Currently, data from this trial are in the collection phase, and no data analysis has been performed.

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As of January 2025, we have collected data from 118 patients. The results of this trial are expected to be submitted for publication in May 2026.

Conclusions: This multicenter, randomized, controlled clinical trial will provide evidence on the clinical effectiveness and potential cardioprotective benefits of moxibustion performed at home as a treatment for individuals with phlegm-dampness type of hypertension.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2400086582; https://www.chictr.org.cn/showproj.html?proj=211688

International Registered Report Identifier (IRRID): DERR1-10.2196/79158

(JMIR Res Protoc 2025;14:e79158) doi:10.2196/79158

KEYWORDS

hypertension; blood pressure; moxibustion; acupoint specificity; cardioprotection; moxibustion; treatment; patients; trials

Introduction

Background

Hypertension is a chronic disease characterized by persistently elevated arterial blood pressure in the systemic circulation. It is a major risk factor for premature death, stroke, ischemic heart disease, and other cardiovascular and renal diseases globally [1]. Hypertension imposes a substantial global health burden [2], affecting approximately one-third of adults, with only up to 54% receiving a diagnosis [3]. China is among the countries with the highest increase in hypertension prevalence and the lowest control rates. In 2018, the prevalence of hypertension among Chinese adults was 27.5%, whereas the control rate was only 15.3% [4]. Poor long-term blood pressure control can cause irreversible damage to multiple target organs, including the heart, brain, kidneys, and blood vessels, leading to increased disability and mortality rates. Therefore, early intervention is crucial to slow the progression of hypertension and reduce the associated social and economic burdens.

Currently, the primary approaches for hypertension treatment include lifestyle modification and medications. The medication adherence of hypertensive patients in China is only 42.5% [4], far lower than the average level in Asian countries, which is a significant factor contributing to low blood pressure control rates [5], increasing the risk of cardiovascular and target organ damage [6], and negatively impacting patients' quality of life [7]. Thus, there is an urgent need to develop a treatment method that can maintain stable blood pressure with high safety, good adherence, tolerability, and cost-effectiveness.

Moxibustion, a traditional Chinese medicine (TCM) therapy, uses thermal effects, infrared radiation, photobiochemical effects, and bioelectric effects produced by burning mugwort to stimulate specific acupoints and meridians, thereby dredging meridian, promoting blood circulation, and regulating the body's neuroendocrine-immune functions [8]. Compared with medication alone, the additional application of moxibustion can effectively control blood pressure [9], correct imbalanced body constitutions [10], and significantly alleviate related symptoms, such as dizziness, headache, and insomnia [11]. Moxibustion is characterized by rapid onset, stable efficacy [12], improved cognitive function [13], and fewer side effects with high safety [11]. Its mechanism of action is multifaceted and multitargeted [13].

Our previous studies indicate the acupoint specificity of moxibustion's antihypertensive effects [14-16], with differential activation of arcuate neurons depending on the targeted acupoint. Specifically, nerve input at Zusanli (ST36) is greater than that at Xuanzhong (GB39) [17-19]. Clinical trials have shown that moxibustion at Zusanli can significantly reduce 24-hour average systolic blood pressure and improve myocardial oxygen consumption, whereas moxibustion at Xuanzhong shows no significant effect [15]. Although we have confirmed the efficacy and acupoint specificity of moxibustion in treating hypertension, a standard large-sample clinical trial is still needed.

Objective

We designed this multicenter randomized controlled trial (selecting Zusanli [ST36] as the treatment group and Xuanzhong [GB39] as control group) to provide clinical evidence for the acupoint specific effects of moxibustion on hypertension and its protective effects on the heart and brain.

Methods

Ethical Considerations

This study protocol was approved by the Ethics Committee of the Shanghai Tongji University-affiliated Oriental Hospital (2023 research review: 145), the Shanghai University of Traditional Chinese Medicine-affiliated Longhua Hospital (2024LCSY161), and the Shanghai Acupuncture and Meridian Research Institute (2023-169). Written informed consent was obtained from all participants prior to the study and data publication. All study-related examinations and treatments will be provided to participants free of charge. No additional compensation will be offered. The study was registered on July 5, 2024, with the Chinese Clinical Trial Registry (ChiCTR2400086582). All participants will be provided with detailed study information and must provide written informed consent prior to enrollment. The trial results will be submitted for publication in a peer-reviewed journal. Neither patients nor the public were involved in the study's design, conduct, reporting, or dissemination plans.

Case Selection

Participants in this trial are outpatients receiving treatment between June 2023 and February 2025 at the Oriental Hospital affiliated with Tongji University, Longhua Hospital affiliated with Shanghai University of Traditional Chinese Medicine, and the Shanghai Research Institute of Acupuncture and Meridian.

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All patients are recruited and screened based on the inclusion and exclusion criteria outlined in the study.

Inclusion Criteria

In this study, the inclusion criteria are as follows: (1) patients diagnosed with grade 1 or 2 hypertension according to the "Chinese Guidelines for the Prevention and Treatment of Hypertension" (2018 revision) [20] (Multimedia Appendix 1); (2) patients with phlegm-dampness constitution according to the "Classification and Determination of TCM Constitution" (ZYYXH/*t* 157-2009) [21] (Multimedia Appendix 2); (3) age between 18 and 75 years, regardless of sex (male or female); (4) no contraindications to moxibustion: (5) without secondary hypertension, hyperthyroidism, or without severe heart conditions (eg, atrial fibrillation and moderate valvular heart disease), and not being in the unstable phase of angina pectoris or myocardial infarction, not being in the acute phase of stroke, and no malignant diseases; and (6) willingness to participate in the study and to sign the informed consent form.

Exclusion Criteria

In this study, the exclusion criteria include the following: (1) patients with severe mental disorders (eg, depression, anxiety, or schizophrenia), or with severe conditions requiring hospitalization or interventions; (2) pregnant or breastfeeding women; (3) patients with severe heart, brain, liver, or kidney diseases; and (4) patients unable to tolerate and to persist with moxibustion treatment.

Elimination Criteria

Participants who do not adhere to the study requirements during the trial, and those who do not meet the inclusion criteria after enrollment, will be removed from this study.

Dropout Criteria

In this study, the dropout criteria include the following: (1) participants who meet the inclusion criteria but do not complete the trial or who withdraw midway for various reasons; (2) participants who do not follow the prescribed treatment plan or who receive other treatments or medications that interfere with the assessment of efficacy; and (3) participants who are lost to follow-up or die before completing the trial.

Termination Criteria

In this study, patients who experience severe adverse reactions or develop severe issues during the trial (eg, sudden exacerbation of preexisting conditions or new severe diseases) that make it impossible to assess efficacy will be advised to discontinue the trial.

Recruitment

In this study, we disseminate study information through official social media, flyers, and online articles in hospitals and communities for patients' reference. Interested patients can register online and based on proximity, visit designated clinical sites for screening. After confirmation by clinical physicians and after signing the informed consent form, eligible participants will be randomly assigned to a treatment group or a control group in a 1:1 ratio and will receive 12 weeks of moxibustion treatment, followed by 12 weeks of follow-up. All procedures will strictly adhere to the Declaration of Helsinki.

Sample Size Calculation

The primary efficacy evaluation index for this study is the morning systolic blood pressure measured by 24-hour ambulatory blood pressure monitoring (ABPM). The sample size was estimated based on statistical methods. Preliminary trial data showed that the treatment group had a 7.2 (SD 3.3) mm Hg greater reduction in 24-hour morning systolic blood pressure than the control group. In this study, we apply the superiority design and set the superiority margin (Δ) as 5 mm Hg [22], with a significance level of α equal .025 (1-sided) and a power of β equal .1. The mean value for treatment improvement between the treatment and control groups is set at 7.2 (SD 3.3) mm Hg, with a SD (σ) of 3.3 mmHg, based on the formula for comparing means in a superiority trial [22]:

The primary efficacy endpoint of this study was the change in morning systolic blood pressure as measured by 24-hour ABPM. Sample size determination was based on a superiority design for comparing two independent means. The calculation incorporated the following parameters: an expected between-group difference ($\mu_1 - \mu_2$) of 7.2 mm Hg derived from preliminary data, a common SD (σ) of 3.3 mm Hg, a prespecified superiority margin (Δ) of 5 mm Hg [22], a one-sided α level of 0.025, and 90% statistical power ($1-\beta$). These values were applied to the standard sample size formula for superiority trials to ensure adequate power for detecting a clinically meaningful treatment effect.

Randomization Method

Allocation concealment was ensured with sequentially numbered, opaque, sealed envelopes. An independent statistician generated the allocation sequence using SAS software (version 9.4; SAS Institute), which assigned participants in a 1:1 ratio to the treatment group (acupoint ST36) or the control group (acupoint GB39). The assignments were sealed in tamper-evident envelopes and stored securely at the coordinating center. Following participant enrollment, the study coordinator retrieved and opened the next sequential envelope to reveal the assignment to the intervention clinician, thereby ensuring complete concealment and unpredictability of the allocation for researchers and participants.

Blinding

Multiple safeguards were implemented to maintain blinding in this self-administered moxibustion trial. Participants were blinded by being told they "might receive different acupoint treatments" during consent and were assigned only a unique ID. Cross-contact was prevented through segregated scheduling. To ensure consistency and control performance bias, a single clinician (uninvolved in the assessment) provided standardized training to all participants. Data collectors, outcome assessors, and statisticians were blinded, with unblinding permitted only for serious adverse events, which would lead to separate analysis of that participant's data.

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Intervention Protocol

Basic Treatment

After enrollment, participants will continue their previous medication and record it in the case report form.

Treatment Group

Participants in the treatment group will receive moxibustion at Zusanli (ST36). All participants will undergo training by professionals on acupoint location, moxibustion techniques, and precautions before beginning treatment. Only patients who pass the training and evaluation will be allowed to perform moxibustion at home, 3 times a week for 12 weeks. The first moxibustion session will be conducted under professional supervision in the clinic, with the skin temperature at the moxibustion site recorded before and after the session. Subsequently, participants will document each moxibustion session with photographs and will complete a moxibustion record form, noting the date, duration, and any adverse reactions. Researchers will conduct 2 random follow-up visits per week to remind participants to complete their moxibustion sessions on time and to verify the frequency, location, duration, and completion of the sessions using photos and record forms. Participants will also undergo outpatient evaluations every 2 weeks to assess their moxibustion adherence and will receive comprehensive assessments at baseline, week 4, week 12, and week 24.

Control Group

Participants in the control group will receive moxibustion at Xuanzhong (GB39). The training, evaluation, and assessment procedures will be identical to those of the treatment group to complete the study according to the design process (Figure 1). The time points of the outcome measures are summarized in Table 1.

Acupoint locations in this study are determined according to the “Names and Locations of Acupoints” (GB/T12346-2021) standard (Figure 2).

Figure 1. Flow diagram of the trial procedure. ABPM: ambulatory blood pressure monitoring; FBG: fasting blood glucose; FINS: fasting insulin; HbA1c: glycated hemoglobin; HDL: high-density lipoprotein; LDL: low-density lipoprotein; TC: total cholesterol; MoCA: Montreal Cognitive Assessment.

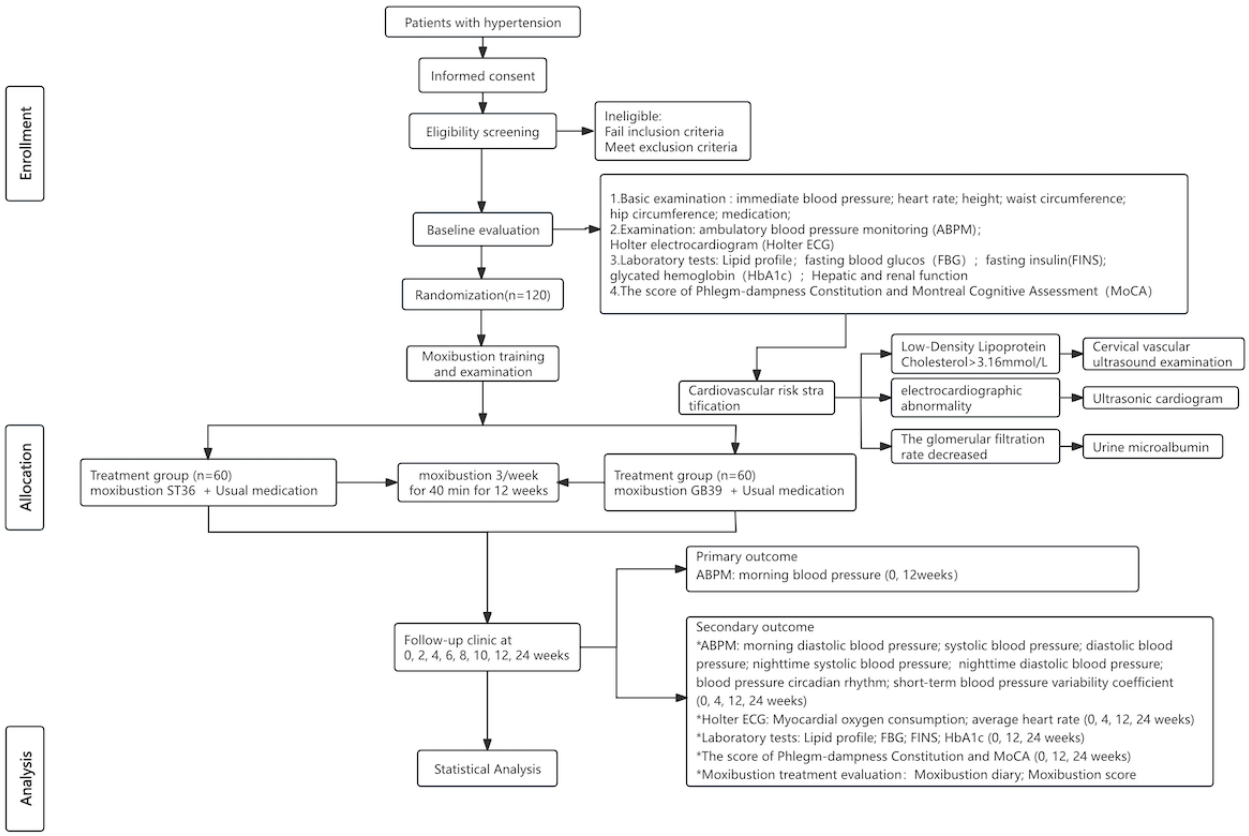

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Table 1. Time points of the outcome measures.

Assessment	Enrollment and baseline	Allocation		After allocation						Closeout
		0 wk	2 wk	4 wk	6 wk	8 wk	10 wk	12 wk	24 wk	
Informed consent	✓	—[a]	—	—	—	—	—	—	—	—
Inclusion or exclusion	✓	—	—	—	—	—	—	—	—	—
General information	✓	—	—	—	—	—	—	—	—	—
Random allocation		✓	—	—	—	—	—	—	—	—
Intervention	—	✓	✓	✓	✓	✓	✓	✓		—
Concomitant medication	✓	—	✓	✓	✓	✓	✓	✓	✓	—
24 h ABPM[b]	✓	—	—	✓	—	—	—	✓	✓	—
24 h Holter ECG[c]	✓	—	—	✓	—	—	—	✓	✓	—
Lipid profile (Triglycerides, TC[d], HDL[e], and LDL[f])	✓	—	—	✓	—	—	—	✓	✓	—
Glycemic markers (FPG[g], FINS[h], HbA_{1c}[i])	✓	—	—	—	—	—	—	✓	✓	—
Hepatic and renal function	✓	—	—	—	—	—	—	✓	✓	—
Phlegm-damp constitution	✓	—	—	—	—	—	—	✓	✓	—
Cardiovascular risk stratification	✓	—	—	—	—	—	—	✓	✓	—
MoCA[j]	✓	—	—	—	—	—	—	✓	✓	—
Adverse events and other unintended effects	—	—	✓	✓	✓	✓	✓	✓	✓	—
Compliance monitoring	—	—	✓	✓	✓	✓	✓	✓	✓	—
Completion summary	—	—	✓	✓	✓	✓	✓	✓	✓	—

[a]Not available.
[b]ABPM: ambulatory blood pressure monitoring.
[c]Holter ECG: Holter electrocardiogram.
[d]TC: total cholesterol.
[e]HDL: high-density lipoprotein.
[f]LDL: low-density lipoprotein.
[g]FBG: fasting blood glucose.
[h]FINS: fasting insulin.
[i]HbA_{1c}: glycated hemoglobin.
[j]MoCA: Montreal Cognitive Assessment.

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Figure 2. Acupuncture point diagram for the location of the acupoints.

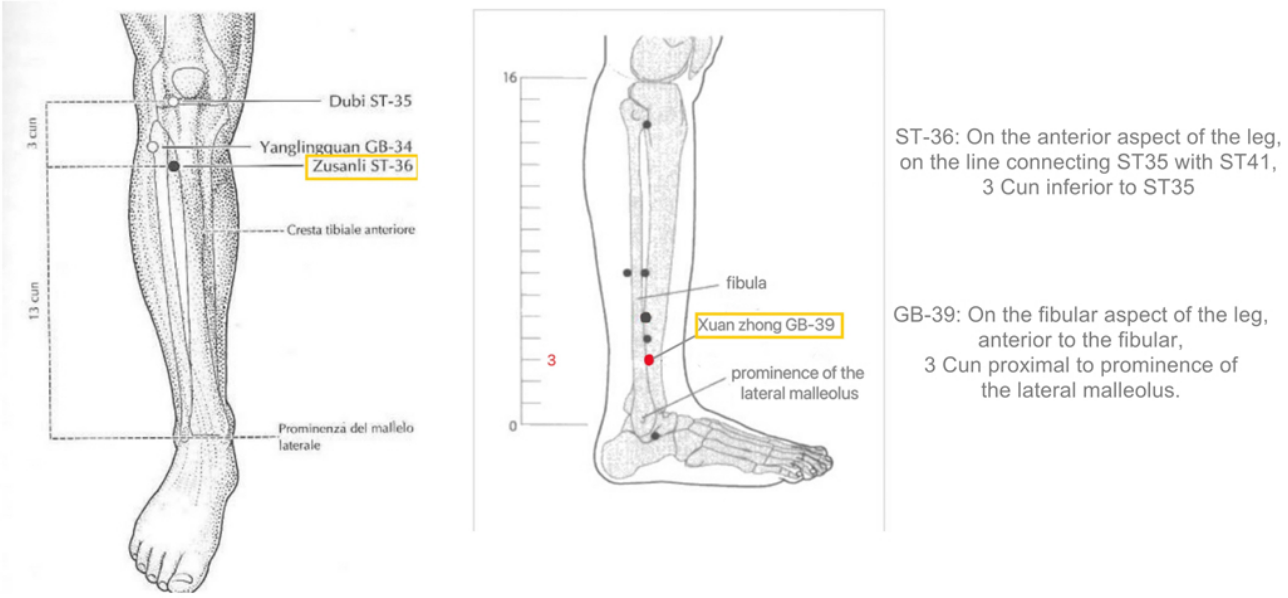

Materials and Tools

The material and tools used for moxibustion in this study will include (1) Lei Huo moxibustion device (Registration Number: 20,232,200,237; Hunan Cihui Medical Technology Co, Ltd); (2) OMRON YE-680 series digital blood pressure monitor (Registration Number: 20,202,071,574; Omron Healthcare Co, Ltd); (3) RGT-120/160 weighing scale (Changzhou Wujin Weighing Apparatus Co, Ltd); and (4) 150 cm measuring tape.

Assessment and Outcomes

Overview

Participants will undergo evaluations at weeks 0, 2, 4, 6, 8, 10, 12, and 24 during outpatient visits. Twenty-four-hour ambulatory blood pressure and 24-hour Holter electrocardiogram will be examined at weeks 0, 4, 12, and 24. General information (weight, height, waist circumference, hip circumference, family history, medical history, concomitant medications, and lifestyle behavior), relevant laboratory tests (4 items of lipids, fasting blood glucose, glycosylated hemoglobin, serum insulin, homeostatic model assessment of insulin resistance, homeostatic model assessment of β-cell function, insulin-sensitivity index, triglyceride-glucose index, metabolic score for insulin resistance, liver function, and kidney function), heart function, vascular risk stratification, and scale assessment (TCM phlegm-dampness physique score and the Montreal Cognitive Assessment) will be examined at weeks 0, 12, and 24. Major unconscionable cerebrovascular injury, target organ injury, and moxibustion adverse events will be recorded during the study period.

Primary Outcome Measure

In this study, the primary outcome measure is the morning systolic blood pressure, which will be measured by 24-hour ABPM (assessment at weeks 0 and 12).

Secondary Outcome Measures

Blood Pressure–Related Indicators (Measured by 24-Hour ABPM)

Morning diastolic blood pressure, average systolic blood pressure, average diastolic blood pressure, nighttime systolic blood pressure, nighttime diastolic blood pressure, and circadian rhythm of blood pressure will be assessed (at weeks 0, 4, 12, and 24). Twenty-four-hour diastolic blood pressure, 24-hour nocturnal systolic blood pressure, 24-hour nocturnal diastolic blood pressure, 24-hour morning systolic blood pressure, 24-hour morning diastolic blood pressure, circadian rhythm of blood pressure, 24-hour systolic blood pressure variability, and 24-hour diastolic blood pressure variability will also be assessed at different time points (at weeks 0, 4, 12, and 24)

Cardiac-Related Indicators (Measured by 24-Hour Holter Electrocardiogram)

Total heartbeats, myocardial oxygen consumption, average heart rate, heart rate variability (HRV) parameters (ie, percentage of successive NN intervals that differ by more than 50 ms, HRV triangular index, root mean square of successive differences, SD of normal-to-normal [SDNN] intervals, SD of the average normal-to-normal intervals, SDNN index, low-frequency [LF] power, high-frequency [HF] power, and the LF and HF ratio) will be assessed at weeks 0, 4, 12, and 24.

Laboratory Tests

Triglycerides, cholesterol, high-density lipoprotein, low-density lipoprotein, fasting blood glucose, glycated hemoglobin, fasting insulin, homeostatic model assessment of insulin resistance, homeostatic model assessment of β-cell function, insulin-sensitivity index, triglyceride-glucose index, metabolic score for insulin resistance, and liver and kidney function will be measured at weeks 0, 12, and 24.

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Scale Evaluations

The TCM phlegm-dampness constitution score, Montreal Cognitive Assessment will be administered at weeks 0, 12, and 24.

Exploratory Outcomes

After enrollment, participants will be stratified based on cardiovascular risk using a general information survey designed according to the "Chinese Guidelines for the Prevention and Treatment of Hypertension" (2018 revision [20]) as in Multimedia Appendix 3.

For participants with abnormal Holter electrocardiogram results (eg, Sokolow-Lyon voltage exceeding 3.8 mV or Cornell product exceeding 244 mV·ms), a comprehensive echocardiogram will be performed.

For participants with elevated low-density lipoprotein levels (ie, above 3.16 mmol/L), carotid ultrasound will be conducted to compare vascular characteristics and plaque changes before and after treatment.

For participants with decreased glomerular filtration rate (ie, <59 mL/min/1.73 m^2) or mildly elevated serum creatinine (male: >115 µmol/L [>1.3 mg/100 mL]; female: >107 µmol/L [>1.2 mg/100 mL]), microalbuminuria will be assessed.

Moxibustion Adherence and Completion

A comprehensive strategy will be used to optimize adherence to home-based moxibustion. Before the intervention, participants will receive standardized training via an instructional video and will be instructed to log details (duration, temperature, and adverse events) as in Multimedia Appendix 4 and media (video or photo) for each session. During the study period, adherence will be promoted through irregular WeChat messages and telephone follow-ups for reminders, supplemented by unannounced random video checks to verify the participants' procedures. Furthermore, biweekly follow-up visits will be conducted at the research center. These sessions will comprise a face-to-face review of moxibustion logs and video or photo documentation, an assessment of procedural technique and acupoint localization accuracy (Multimedia Appendix 5), and the exchange of used moxa sticks for new supplies.

Safety Evaluation

Major adverse cardiovascular and cerebrovascular events, liver function (alanine aminotransferase and aspartate aminotransferase) and kidney function (blood urea nitrogen and creatinine) and moxibustion-related adverse events (burns, blisters, dizziness during moxibustion, ulceration, infection, and local abscesses at the moxibustion site; other discomforts after moxibustion may include dizziness, fatigue, allergies, and loss of appetite) will be recorded in this study. Moreover, adverse events will be monitored through patient self-reports and assessments by health care professionals during the study. Participants will be instructed to immediately report any adverse events to their supervising clinician, who will determine whether further examinations or treatments are necessary and will provide timely interventions. For serious adverse events, the trial will be immediately halted. All adverse reactions, their severity, duration, and any actions taken will be thoroughly documented.

Data Management and Quality Control

All data related to study participants will be stored and backed up according to trial standards. Case report forms will be uniformly printed after they are designed by the research team, and all trial data for participants will be accurately recorded on these forms. Paper-based data will be retained for at least 3 years. Additionally, an independent data safety monitoring committee (DSMC) will be established before the trial, comprising 3 experts with backgrounds in cardiology, acupuncture, and statistics. The DSMC will hold online meetings every 4 months to oversee trial progress and review data safety and quality. A midterm analysis will be conducted at the halfway point of participant enrollment, and the DSMC will determine whether the trial needs to be terminated early. Personal privacy information (eg, name, age, and phone number) will be anonymized in DSMC reports.

Statistical Analysis

Data analysis of the primary outcome will be based on the full analysis set constructed by the intention-to-treat principle, whereby patients will remain in their original group regardless of contamination. The per-protocol set will also be analyzed using sensitivity analysis for the primary outcome to evaluate whether contamination affects the direction of the effect. The secondary outcomes will also be compared based on the per-protocol set. The need to impute missing values will be determined by the proportion of and reasons for missing data. If imputation is necessary, appropriate methods, such as the last observation carried forward, the "best-worst-case" scenario, and multiple imputation regression modeling, will be chosen according to the distribution of the missing values.

Potential center effects will be statistically addressed through mixed-effects modeling, notwithstanding standardized central screening and intervention procedures. For primary continuous outcomes, linear mixed-effects models will incorporate the treatment group as a fixed effect and center as a random effect, with center-specific random intercepts accounting for recruitment-related heterogeneity. Secondary outcomes will be analyzed using analogous generalized linear mixed models. The primary analysis will use an intention-to-treat approach. The changes in the primary outcome and other secondary outcomes will be compared by using a linear mixed-effects model with group-by-time point interaction (baseline to week 12). For outcomes measured at multiple time points, a repeated-measures ANOVA will first test for overall group, time, and interaction effects. Upon finding a significant interaction (exact P values will be reported), post hoc comparisons will be conducted using a hierarchical adjustment strategy: Benjamini-Hochberg false discovery rate control for the primary outcome across time points and Bonferroni correction for families of secondary outcomes. Sociodemographic and clinical characteristics at baseline will be examined for potential group differences by 2-tailed t test or χ^2 test, with exact P values reported. Compliance will be presented using descriptive statistics. The specified significance levels (0.025 for the primary outcome and 0.05 for all other analyses) represent the α thresholds (P

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value cutoffs) for hypothesis testing. All *P* values will be reported per journal style: expressed to two digits (or three if *P*<.01) and as *P*<.001 if below that threshold. Data analysis was conducted with SPSS (version 28.0; IBM Corp).

Results

The study was registered on July 5, 2024, with the Chinese Clinical Trial Registry (ChiCTR2400086582). Data collection began in June 2023 and ended in February 2025. Currently, data from this trial are in the collection phase, and no data analysis has been performed. As of January 2025, we have collected data from 118 patients. The results of this trial are expected to be submitted for publication in May 2026.

Discussion

Anticipated Findings

This study aims to explore the acupoint specificity and clinical efficacy of moxibustion in treating hypertension and its protective effects on the heart and brain. In this study, we employed the Montreal Cognitive Assessment to quantitatively evaluate cognitive protection. Hypertension contributes to cerebral microvascular injury and silent cerebral small vessel disease, which predominantly impairs cognitive domains sensitively captured by the Montreal Cognitive Assessment, including executive function and attention. By streamlining acupoint selection and establishing a standardized home-based moxibustion protocol, this study seeks to offer patients with hypertension a safe, convenient, and adherent treatment option. This approach may help patients develop healthy lifestyle habits, contributing positively to the improvement of their quality of life and the prevention of cardiovascular and cerebrovascular diseases.

In TCM, body constitution is considered a determining factor in disease onset and progression. In today's fast-paced society, factors such as high stress, poor dietary habits, and lack of exercise contribute to the development of a phlegm-dampness constitution. Research has shown that this constitution is a high-risk factor for hypertension and its related complications. Patients with phlegm-dampness hypertension are more prone to insulin resistance, which increases the risk of target organ damage [23], leads to a higher cardiovascular risk over 10 years, and is associated with a poorer prognosis [24]. Molecular genetics research indicates that genes expressed in individuals with phlegm-dampness constitution are similar to those associated with obesity and metabolic syndrome [25]. Therefore, improving phlegm-dampness constitution is crucial for controlling hypertension and preventing cardiovascular and cerebrovascular diseases [26].

The Zusanli acupoint (ST36) is a He-Sea point and lower He-Sea point of the Stomach Meridian, known for its functions of regulating Qi and blood, harmonizing the stomach, and eliminating dampness. X-ray phase-contrast imaging studies have shown that the 3D structure of Zusanli has a higher density of local blood vessels [27], mast cells [28], and prokineticin receptor 2–expressing cells [29] compared with nonacupoints or other acupoints, along with accumulation of elements like calcium, iron, and zinc [30]. The capsaicin receptor (TRPV1) is abundantly present in the mast cells at Zusanli [31], and moxibustion heat at 43 to 46 °C can activate TRPV1 ion channels, mediating mast cell degranulation and releasing bioactive substances that exert antihypertensive effects [32]. Additionally, moxibustion at Zusanli can inhibit immune-inflammatory responses, counter oxidative stress, regulate mitochondrial function and cellular autophagy, enhance blood circulation, and regulate metabolic disorders. Our preliminary clinical observations indicated that although moxibustion at Xuanzhong (GB39) did not significantly lower blood pressure, it did improve metabolic disorders and sleep quality. Therefore, this trial uses Xuanzhong as the control group (rather than a blank or nonacupoint control) to observe the differential efficacy of the 2 acupoints while helping participants develop good moxibustion habits, providing an effective way to prevent and manage chronic diseases [13].

Acute cardiovascular and cerebrovascular events frequently occur in the morning, and numerous clinical studies have confirmed that morning hypertension is an independent predictor of such events [2], positively correlating with their incidence and mortality [33]. For every 1 mm Hg increase in morning blood pressure, the risk of cardiovascular-related death increases by 2.1% [34,35]. Compared with patients with morning blood pressure below 125 mm Hg, those with morning hypertension have significantly higher risks of stroke [36] (hazard ratio 6.01) and coronary events (hazard ratio 6.24). Stroke risk is positively correlated with morning systolic blood pressure levels, with hazard ratios of 2.45, 2.80, 3.58, and 6.52 for morning systolic blood pressure ranges of 135 to 144 mm Hg, 145 to 154 mm Hg, 155 to 164 mm Hg, and ≥165 mm Hg, respectively [37]. Regardless of clinical blood pressure levels, patients with morning home systolic blood pressure ≥145 mm Hg have higher cardiovascular risk (hazard ratio 2.47) than those with levels <125 mm Hg [38]. Morning hypertension is also a significant cause of vascular cognitive impairment [39]. It is an independent risk factor for the 10-year incidence of atherosclerotic cardiovascular disease [40]. Patients with nondipper (0%-10%) or reverse-dipper (<0%) nocturnal blood pressure rhythms have higher risks of cardiovascular events and all-cause mortality [41], as well as a greater likelihood of reduced glomerular filtration rate and elevated creatinine levels [42]. Blood pressure variability, which reflects fluctuations in blood pressure within a certain range, is an important indicator of blood pressure stability. Individuals with higher short-term blood pressure variability, as measured by 24-hour ABPM, are more likely to develop subclinical organ damage and adverse cardiovascular events [43].

Autonomic nervous dysfunction can lead to altered circadian rhythms of blood pressure and increased blood pressure variability, exacerbating damage to vascular endothelium and arterial baroreceptors, accelerating vascular wall fibrosis and atherosclerosis, and ultimately causing target organ damage [44]. HRV, which measures differences between adjacent heartbeats, reflects autonomic nervous activity and inflammation, and is related to coronary physiology [45] and the severity of coronary artery disease [36]. Reduced HRV is closely associated with various cardiovascular diseases, diabetic

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microvascular complications, and imbalanced body constitutions [46]. SDNN, SD of the average normal-to-normal intervals, root mean square of successive differences, LF, and HF values were significantly lower in patients with hypertension and poorly controlled blood pressure and were independent risk factors for uncontrolled blood pressure [36]. Additionally, prolonged elevated arterial blood pressure increases myocardial oxygen consumption and cardiac workload, leading to myocardial ischemia and cardiovascular diseases, such as coronary heart disease and left ventricular hypertrophy. Evaluating total heartbeats, average heart rate, myocardial oxygen consumption, HRV indices, ischemic ST-T changes, and arrhythmias through 24-hour Holter electrocardiogram is crucial for the early diagnosis of occult coronary artery disease and the prevention and management of acute cardiovascular diseases [36].

Insulin resistance is a common pathophysiological mechanism underlying hypertension, type 2 diabetes, metabolic syndrome, and cardiovascular diseases [47]. It often leads to metabolic, structural, and functional abnormalities in organs and tissues, such as microvascular disease and atherosclerosis, and is an independent risk factor for cardiovascular diseases [48]. The metabolic score for insulin resistance index, which integrates fasting blood glucose, lipids, and BMI, is a novel insulin index that significantly correlates with the incidence of hypertension, angina, heart failure, and myocardial infarction, making it a risk factor for coronary artery disease and the severity of coronary artery lesions [49].

Limitations and Future Directions

The cardioprotective and neuroprotective effects of moxibustion require long-term follow-up to fully evaluate. In this study, the follow-up period was limited to 12 weeks, which may be insufficient to capture the long-term benefits. Future research should include a longer prospective study with a follow-up period of up to 3 years to monitor major cardiovascular and cerebrovascular events, as well as patient self-management capabilities.

Adherence assessment for home-based moxibustion primarily relied on patient-reported measures. Although auxiliary methods, including random video verification, were used, objective monitoring of key parameters, such as moxibustion temperature, remained limited, potentially leading to overestimated adherence rates. Future studies should incorporate technological solutions, such as smart moxibustion devices with integrated temperature sensors and Bluetooth connectivity, or certified electronic diaries with time and geolocation verification. These innovations would enable automated objective data collection, substantially improving the quality of home-based TCM research.

The timing of patient enrollment also varied by season, which may have introduced seasonal variability in blood pressure outcomes. Future studies should consider recruiting participants during the same season to minimize this confounding effect. Additionally, the impact of moxibustion on blood pressure stability across different seasons in patients with hypertension remains an area for further investigation.

Despite these limitations, this study aims to provide high-quality clinical evidence for the efficacy of moxibustion and TCM-based lifestyle interventions in the treatment of hypertension and their protective effects on the heart and brain. The findings could have significant implications for the comprehensive prevention and management of chronic diseases.

Acknowledgments

This trial was supported by the Pudong New Area Traditional Chinese Medicine Inheritance Project (grant YC-2023-0612), the Health Commission Acupuncture Key Specialty Program (grant PWZzk2022-25), and the Gaoyuan Discipline Development Program (grant YC-2023-0604).

Data Availability

Data sharing is not applicable to this paper as no data sets were generated or analyzed during this study.

Authors' Contributions

L Cheng and LZ designed the study. NB, JY, Jie Cao, and YG performed all experiments. HW and L Cheng supervised the experiments. NB, JY, and RW analyzed the data. NB, L Cao, and RW wrote and reviewed the manuscript. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Chinese Guidelines for the Prevention and Treatment of Hypertension [8] (2018 revision) standard: Increased systolic blood pressure (SBP) of ≥140 mmHg and/or diastolic blood pressure (DBP) of ≥90 mmHg should still be diagnosed as hypertension.
[DOCX File , 17 KB - resprot_v14i1e79158_app1.docx]

Multimedia Appendix 2
The measurement scale for the phlegm-dampness constitution in traditional Chinese medicine.

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[DOCX File , 22 KB - resprot_v14i1e79158_app2.docx]

Multimedia Appendix 3
General information (cardiovascular risk stratification).
[DOCX File , 19 KB - resprot_v14i1e79158_app3.docx]

Multimedia Appendix 4
Moxibustion record form.
[DOCX File , 18 KB - resprot_v14i1e79158_app4.docx]

Multimedia Appendix 5
Moxibustion rating form.
[DOCX File , 24 KB - resprot_v14i1e79158_app5.docx]

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Abbreviations

ABPM: ambulatory blood pressure monitoring
DSMC: data safety monitoring committee
HF: high-frequency
HRV: heart rate variability
LF: low-frequency
SDNN: SD of normal-to-normal
TCM: traditional Chinese medicine

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Protocol

Internet-Based Dementia Prevention Intervention (DementiaRisk): Protocol for a Randomized Controlled Trial and Knowledge Translation

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Abstract

Background: Research has shown that engaging in a range of healthy lifestyles or behavioral factors can help reduce the risk of developing dementia. Improved knowledge of modifiable risk factors for dementia may help engage people to reduce their risk, with beneficial impacts on individual and public health. Moreover, many guidelines emphasize the importance of providing education and web-based resources for dementia prevention. Internet-based interventions may be effective, but few have been studied rigorously or widely disseminated. We created DementiaRisk, an award-winning, web- and email-based education platform for the public focused on modifiable risk factors, featuring multimedia e-learning and email "microlearning" content, to help raise awareness and improve knowledge of actions to reduce dementia risk.

Objective: This protocol describes a randomized controlled trial to (1) evaluate whether exposure to DementiaRisk changes knowledge of dementia risk factors, intention to engage in risk reduction activities, and health behaviors related to dementia risk reduction and to (2) explore qualitative aspects including participants' engagement and satisfaction with the intervention and barriers and facilitators to use.

Methods: Using a sequential explanatory mixed methods design, this study conducts a quantitative analysis followed by a qualitative inquiry to evaluate outcomes and feasibility. In total, 485 participants will be recruited on the web and randomly assigned to 2 groups: one accessing DementiaRisk and the other receiving alternative e-learning on mild cognitive impairment. Assessments will be delivered on the web at baseline (T1), at 4 weeks (T2), and at 2 months after the intervention (T3). Knowledge will be assessed using items from the Dementia Knowledge Assessment Scale, intentions to engage in risk reduction activities will be assessed using items in line with current evidence, and health behaviors related to dementia risk reduction will be assessed using items from the Godin-Shephard Leisure Time Physical Activity Questionnaire along with additional questions related to a range of health status domains. Outcomes and feasibility will be assessed using the Information Assessment Method for patients and consumers. A linear mixed effects model will be used to examine the relationship between each outcome score by group and time point.

Results: This study was approved by the Hamilton Integrated Research Ethics Board on August 24, 2022 (project ID 14886) and received funding in February 2023. Recruitment took place from March 28, 2023, to April 28, 2023, with the final participants completing the intervention by August 18, 2023. Analyses and interpretation of data are ongoing.

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Conclusions: DementiaRisk is a readily scalable, technology-enhanced solution for dementia prevention education. It has been designed using evidence-based principles of multimedia learning. It has the potential to scale and spread widely using the open internet, so it may be able to reach a wider audience than traditional in-person educational interventions.

Trial Registration: ClinicalTrials.gov NCT05383118; https://clinicaltrials.gov/study/NCT05383118

International Registered Report Identifier (IRRID): DERR1-10.2196/64718

(JMIR Res Protoc 2025;14:e64718) doi:10.2196/64718

KEYWORDS

web-based intervention; internet; eHealth; dementia risk; dementia prevention; Alzheimer disease; education and training; clinical trial; knowledge translation; public health; health literacy; e-learning

Introduction

Background

Developing a better understanding of how dementia can be prevented and sharing information about how Canadian people can reduce their risk of developing dementia or delay its onset are critical to keeping Canadian people healthy and improving their quality of life. The Landmark Study, which developed evidence-based data modeling to demonstrate the impacts of improving risk reduction efforts to delay onset across the population, suggests that a delay of 1 year could result in nearly 500,000 fewer cases of dementia by 2050 [1]. Additionally, if dementia prevention efforts can delay the onset of dementia by 10 years, then over 4 million new cases of dementia could be avoided by 2050 [1]. Web-based learning about the promotion of brain health is a readily scalable, technology-enhanced solution for dementia risk prevention education. Web-based learning has the potential to reach a wider number of audiences with modifiable risk factors for dementia than traditional face-to-face interventions.

While there have been studies of web-based health information on intentions and behavior change, most of those studies have looked at text-based health information rather than internet-based interventions that have incorporated best practices in instructional design for e-learning. Most of the web-based content about modifying dementia risk factors currently is text based, such as static web pages or pamphlets or booklets. Of the few multimedia e-learning courses available, some require a substantial commitment (eg, weeks long), are synchronous (ie, require real-time participation), are associated with a commercial entity or product for sale, or have a cost associated with them. During the design of our intervention, we could not find any instructionally designed, evidence-based, multimedia e-learning content about dementia risk reduction available in Canada in both languages (English and French). Moreover, very few educational interventions related to dementia risk reduction have been rigorously studied using methods such as randomized controlled trials (RCTs).

While multidomain interventions have been shown to be effective [2], our study will complement those types of more intense, in-person components with a view to expanding awareness of modifiable risk factors to the general population. In addition, while text-based information about risk factors is widely available, DementiaRisk [3]—our instructionally designed, multimedia intervention—is designed to share this knowledge broadly in a way that can improve the understanding of Canadian people. Many interventions about dementia are designed specifically for older adults. However, the development of dementia can begin as early as 20 years before symptom onset or diagnosis [4], so we will be targeting the intervention to all Canadian people of 18 years and older of age to reduce the risk of dementia as early as possible.

A recent EKOS dementia public opinion survey highlighted that there are still many important gaps in the knowledge of Canadian people about dementia risk factors, with only 37% of respondents knowing the link to chronic conditions that affect brain health, such as hypertension, heart disease, and diabetes [5]. Moreover, just over one-tenth believe that hearing loss can increase the risk of developing dementia; and many believe that exposure to toxic chemicals is a risk factor, despite lack of evidence [5].

e-Learning Instructional Design

DementiaRisk (Figure 1), when compared to other web-based content, is unique because it uses best practices in multimedia e-learning instructional design, is open-access, and includes asynchronous e-learning with email-based microlearning. To our knowledge, it is also the only asynchronous multimedia e-learning dementia education program with French translation available. Key components of the instructional design include the use of the principles of multimedia learning and audio narration; personalization, including the use of a web-based "coach" or embodied instructional agent; segmenting the content into manageable topics to reduce cognitive load; authentic scenarios and worked examples; review questions; and learner control over navigation [6]. An iterative, participatory instructional design and development methodology—the successive approximation method [7]—was used, with extensive involvement and review from a range of experts in dementia care, including care partners.

In this study protocol, we describe a sequential explanatory mixed methods design RCT comparing the efficacy of DementiaRisk, a high-quality, web- and email-based dementia risk reduction education platform that includes asynchronous multimedia e-learning and email-based "microlearning" content, to our alternative web-based learning program on mild cognitive impairment. This study will be an important contribution to the literature on improving knowledge of dementia risk factors through web-based interventions. These innovations are an important complement to traditional approaches to dementia and brain health education, a key component of quality dementia

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care and public health policy. This is the first research study of the effectiveness of DementiaRisk.

Figure 1. DementiaRisk home page.

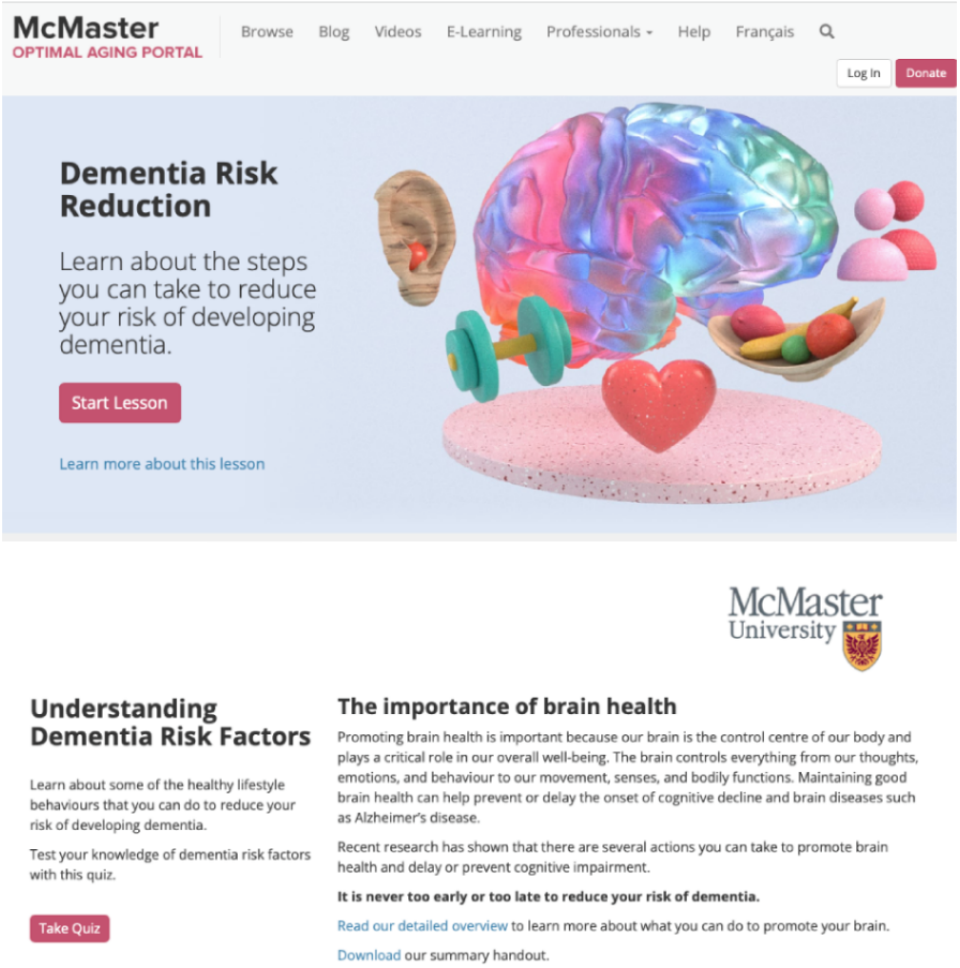

Research Aim

The overall aim of this study is to explore if and how our dementia risk reduction e-learning influences participants' knowledge, intentions, and health behaviors related to dementia risk factors.

Specific Objectives

The specific objectives of this study are (1) to evaluate whether exposure to the e-learning intervention changes knowledge of dementia risk factors, intention to engage in risk reduction activities, and health behaviors related to dementia risk reduction and (2) to explore qualitative aspects such as participants' engagement and satisfaction with the intervention, as well as barriers and facilitators to use, through surveys.

Research Questions

This study aims to answer the following research questions: (1) Does DementiaRisk increase knowledge of dementia risk factors? (2) Does DementiaRisk increase intentions to engage in risk reduction activities? (3) Does DementiaRisk increase health behaviors related to dementia risk reduction? and (4) Are participants engaged and satisfied with DementiaRisk?

Methods

Study Design

A sequential, explanatory, mixed methods design RCT will be conducted to test the effectiveness of DementiaRisk on increasing knowledge, intentions, and behavior change related to modifiable risk factors of dementia. Participants will receive assessments at the following time points: baseline (T1), at 4 weeks (T2), and at 2 months after the intervention (T3; Figure 2). This specific research design offers a valuable approach because it strategically combines the strengths of both quantitative and qualitative research methods.

The underlying philosophy guiding this mixed methods approach is pragmatism, which emphasizes the practical application of research to address real-world problems [8]. This philosophical approach encourages the use of both quantitative and qualitative methods, allowing for more flexibility from other methodological constraints. This flexibility is particularly advantageous in mixed methods research, as it allows us to adapt our approach to capture unexpected findings that may emerge during the study [9]. By incorporating both quantitative and qualitative data, we can gain a more comprehensive and nuanced understanding of the relationship between

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DementiaRisk and impacts on knowledge, intentions, and behavior change.

Figure 2. Participant flow through the study. MCI: mild cognitive impairment. For a higher-resolution version of this figure, see Multimedia Appendix 1.

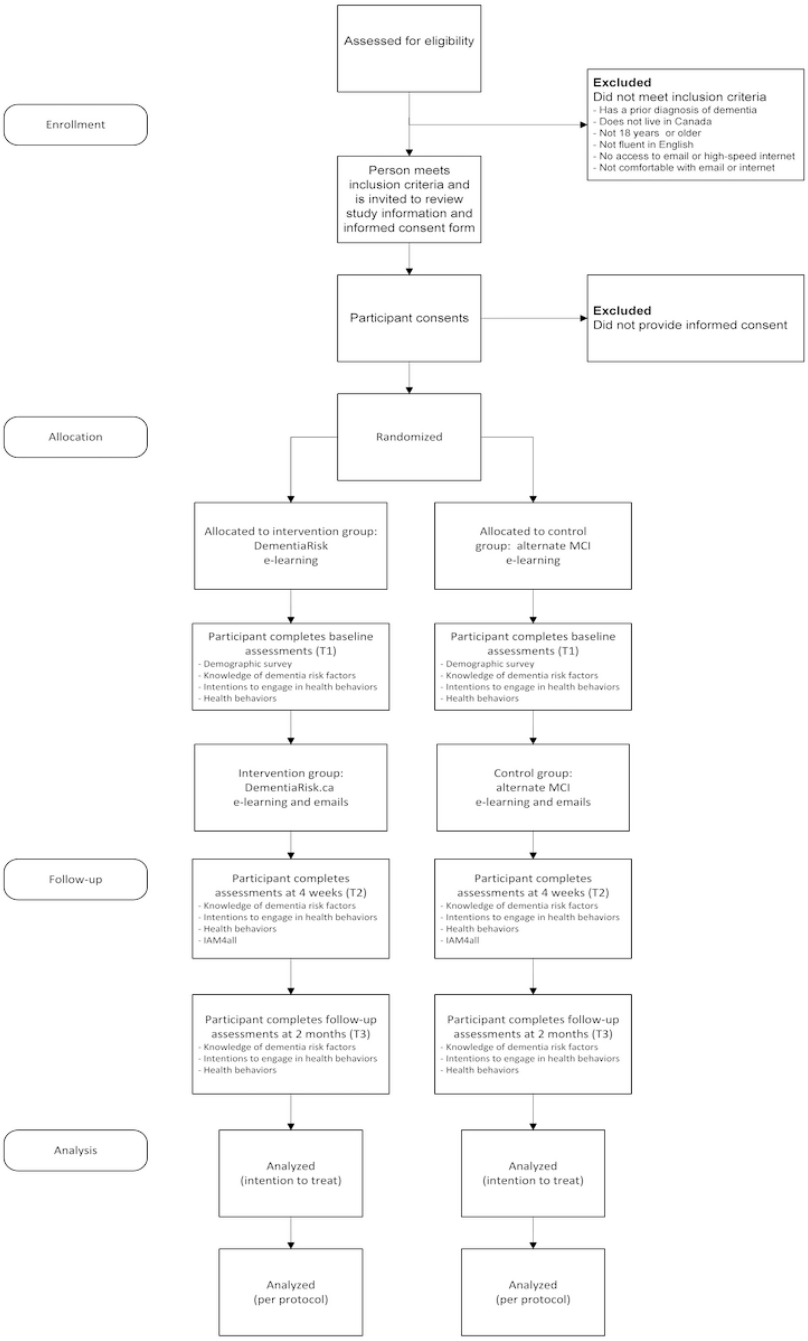

Participants, Setting, and Procedure

Overview

Participants will be recruited using AskingCanadians, a paid panel service that can find representative Canadian participants, including those at increased risk of dementia. AskingCanadians was established in 2005 as a web-based data collection firm, which now allows for access to over 1 million Canadian consumers. The panel will send a copy of our recruitment email to their network where interested participants will be redirected to a survey to identify their eligibility. We will ensure a representative sample of diverse participants with key nonmodifiable and modifiable risk factors for dementia, including a greater percentage of women, some participants with lower level of education, and other risk factors such as hearing impairment, hypertension, smoking, alcohol consumption, and others.

Inclusion and Exclusion Criteria

Participants are eligible to participate, if they meet the following self-reported inclusion criteria: (1) they do not have a prior diagnosis of dementia, (2) they reside in Canada, (3) they are 18 years and older of age, (4) they have a good command of the English language, (5) they have access to email and high-speed internet, (6) they are comfortable using email and

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internet, and (7) they have the ability to grant web-based informed consent. Participants are not eligible to participate if (1) they have a prior diagnosis of dementia, (2) they do not reside in Canada, (3) they are not 18 years and older of age, (4) they do not have a good command of the English language, (5) they do not have access to email and high-speed internet, (6) they are not comfortable using email and internet, and (7) they do not have the ability to grant web-based informed consent. Eligibility screening, informed consent, and surveys will be conducted entirely on the web.

Randomization and Allocation Concealment

Participants will be randomized and directed to their assigned group after submitting web-based informed consent using the Division of e-Learning Innovation's research platform. Participants will be randomized using a permuted block stratified randomization, using education and age as the stratification variables. Our stratified block randomization approach will be based on the following components: (1) level of education: we will stratify participants based on educational background or highest level of education completed: "high school or equivalent," "some college or university," and "college or university graduate or graduate degree" and (2) age: we will stratify participants based on ages: "younger than 45 years," "45-65 years," and "older than 65 years."

To ensure a balance between the intervention and the control groups, we will use stratified block randomization with variable block sizes of 4, 6, and 8 (randomly arranged) in a ratio of 1:1. To the best of our ability, efforts will be made to blind participants to their allocation group and study hypotheses. We will ensure that promotional advertisements do not contain logos or direct website links. The informed consent form will not contain the exact outcome measures or the title of the intervention. Allocation concealment will be aided by referring to the intervention as "e-learning related to cognitive impairment and dementia prevention" without biasing participants to study hypotheses or study design.

Sample Size Calculation

Using a conservative estimate of a small effect size (0.16, from a meta-analysis of internet health behavior change interventions), with a power of 0.80 and α of .05, we require a total of 388 participants in the study [10,11]. To allow for a 25% dropout rate, we aim to recruit 485 individuals [10,11]. These recruitment numbers and strategies have been used successfully in similar knowledge translation intervention studies and are a feasible target, given the use of the paid panel [12].

Intervention

Overview

Participants in the intervention group will be provided e-learning about dementia risk reduction and promoting brain health (Figure 3), consisting of the following components: (1) one 35-minute multimedia e-learning lesson on promoting brain health and preventing dementia and (2) a series of 12 "microlearning" emails (3 emails per week) with small segments of content to reinforce the material from the lesson. Participant progress is saved, so they can return to the lesson to complete it at another time. Participants will have 4 weeks to complete the intervention.

The lesson will be delivered through the Division of e-Learning Innovation's learning management system to record participants' access, progress, and completion of the lessons. This allows us to measure the "dose" of educational exposure to the intervention and to provide automated timed reminders to encourage participants to complete the lesson.

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Figure 3. DementiaRisk intervention group e-learning lesson.

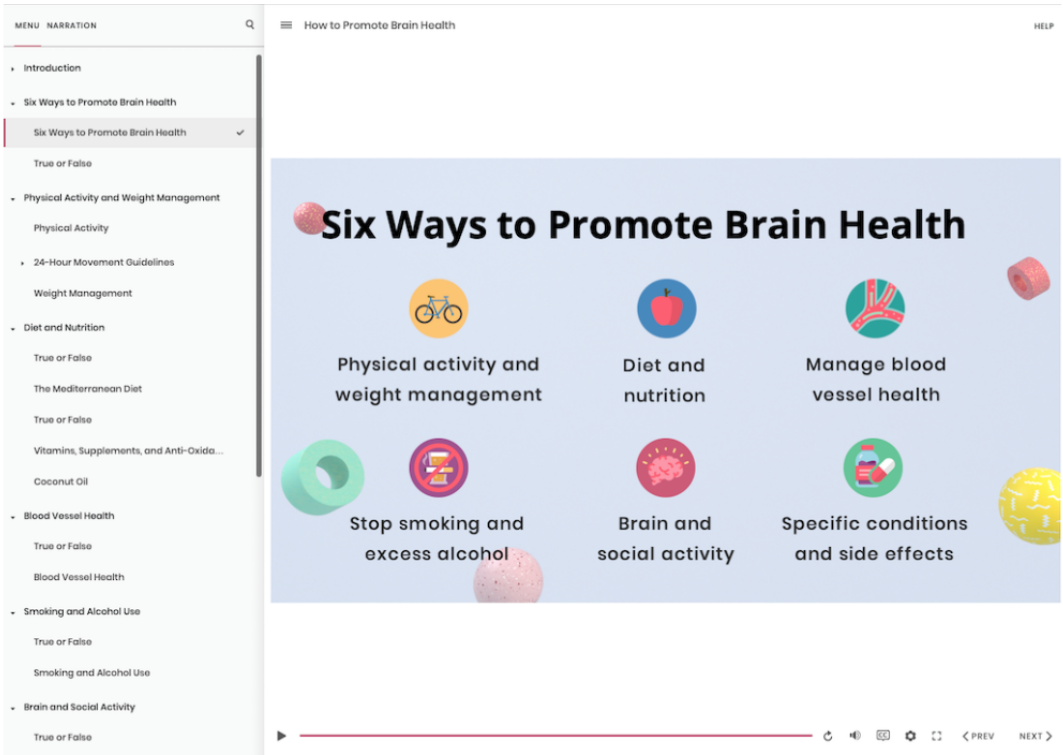

Microlearning Emails

In addition to the lessons, participants will also receive 3 microlearning emails per week with a small amount of content that reinforces the information from the lessons. This spaced repetition has been shown to benefit knowledge transfer [6]. Content for the emails will be taken directly from the promoting brain health e-learning lesson.

Control Condition

Participants randomized to the control group will be provided e-learning about mild cognitive impairment, consisting of the following components: (1) one 20-minute multimedia e-learning lesson on mild cognitive impairment and (2) a series of 12 “microlearning” emails (3 emails per week) with small segments of content to reinforce material from the lesson.

Outcomes

Overview

Primary and secondary outcomes will be assessed at baseline (T1), at 4 weeks (T2), and at 2 months after the intervention (T3). Qualitative data will be collected at 4 weeks (T2; Multimedia Appendix 2). Participants will access web-based surveys through the password-protected research platform hosted by the Division of e-Learning Innovation. Participants will be required to complete all components of the intervention. Surveys will not be submitted unless the participant completes all questions. Participants will not be able to change their answers after submitting and will not be able to submit multiple attempts.

Primary Outcome

The primary outcome measure of this study is knowledge change related to dementia risk factors. Knowledge of dementia risk factors will be assessed using a custom 15-item multiple-choice assessment aligned with the content of the intervention as well as the risks and health promotion subdomain of the Dementia Knowledge Assessment Scale [13]. Response options are “false,” “probably false,” “probably true,” “true,” and “I don’t know.” The total maximum score for this assessment is 30 (maximum 2 points per question), with higher scores indicating higher levels of knowledge related to dementia risk factors. Individual scoring is as follows: (1) 2 points for answering “true” to a true question, (2) 2 points for answering “false” to a false question, (3) 1 point for answering “probably true” to a true question, (4) 1 point for answering “probably false” to a false question, (5) 0 points for answering “probably false” or “false” to a true question, (6) 0 points for answering “probably true” or “true” to a false question, (7) 0 points for answering “I don’t know.”

Secondary Outcomes

Secondary outcome measures include (1) intentions to engage in health behaviors in line with evidence will be assessed using a 10-item Likert scale–based survey and a composite score and (2) health behaviors related to behavior change for modifying dementia risk factors will be assessed using the Godin-Shephard Leisure Time Physical Activity Questionnaire along with additional questions related to a range of health status and behavior domains including diet, smoking, alcohol consumption, social activity, traumatic brain injury, blood pressure, depression, air pollution, diabetes, sleep habits, cognitive activity, and hearing to determine a composite score. Where possible, these questions were selected from validated tools (Multimedia Appendix 2). Additional data will be collected on engagement with the web-based intervention throughout the study, including (1) e-learning analytics: progress or completion, login activity, and time on the lesson and (2) email campaign analytics: open rate and click-through rate.

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Qualitative Data

Qualitative data will be collected through structured survey questions and open-ended questions. The effectiveness and impact of the intervention will be assessed using the Information Assessment Method for patients and consumers, a validated questionnaire that assesses outcomes of web-based consumer health information [14]. End-of-intervention and poststudy surveys will include open-ended questions to assess participant satisfaction with the intervention, changes in attitudes, beliefs, and behaviors during the study, and feedback on proposed future dissemination methods.

Data Analyses

Overview

All outcome assessors and data analysts will be blinded to participant allocation. The CONSORT (Consolidated Standards of Reporting Trials) extension for randomized pilot and feasibility trials and CONSORT-EHEALTH [15-17] will guide reporting of the study. The 12-item TIDieR (Template for Intervention Description and Replication) checklist was used for the intervention description [18]. Qualitative reporting will adhere to the COREQ (Consolidated Criteria for Reporting Qualitative Studies) [19].

Quantitative Data

All data will be entered into RStudio (version 2022.02.3; Posit PBC) [20-22]. A linear mixed effects model will be used to examine the relationship between total knowledge score and group by time point. The same model will be used to look at health behavior scores and total intention scores. We will look at outcome scores from all 3 time points (baseline [T1], at 4 weeks [T2], and at 2 months after the intervention [T3]). The stratification variables, age and level of education, will be included in all models. Additionally, we will examine possible effect modifiers of age, sex, and education on the relationship between groups and outcomes as well as time point and outcomes. For knowledge scores specifically, we will look at a family history of dementia or having been a care partner of a person living with dementia as a possible effect modifier of the relationship between group and knowledge score and time point and knowledge score. These models will be run for both intention-to-treat and per-protocol participant data.

Qualitative Data

All data will be entered into NVivo (version 14; Lumivero) [23]. Data will undergo a conventional, inductive, content analysis approach [24,25]. Data will be systematically examined by a single analyst; codes and themes will be generated based on the content without relying on preconceived theories. To maintain accuracy and credibility, weekly meetings will be held by the analyst and the research team to discuss developing themes, confirm the coding process, and ensure consistency and depth in the representation of the data.

Ethical Considerations

This study gained Hamilton Integrated Research Ethics Board approval on August 24, 2022 (project ID 14886). Participants were required to provide informed consent and were informed of the length of time of the e-learning, surveys, and email campaign as well as informed about details surrounding data collection, storage, and investigator identities. Participants' identities and confidentiality were maintained throughout the research study. All participant data were deidentified, and all findings will be nonidentifiable. There is no known risk or harm to participating in this study of publicizing its results or findings. Participants were provided with AskingCanadians points that can be redeemed for various gift cards as compensation for participation in the study.

Results

The study received funding in February 2023. Recruitment took place from March 28, 2023, to April 28, 2023, with the final participants completing the intervention by August 18, 2023. Analyses and interpretation of data are ongoing. The analysis is expected to be completed by summer 2024, and the results will be published by winter 2024.

Discussion

Expected Findings

Many Canadian people are not aware of the potential impact of modifiable risk factors with respect to the development of dementia. DementiaRisk represents an important and innovative contribution to consumer health education in the area of promoting brain health and dementia prevention. Specifically, this study aims to explore the impact of DementiaRisk for reducing modifiable risk factors of dementia, specifically through changes in knowledge of dementia risk factors, intention to engage in risk reduction activities, and health behaviors related to dementia risk reduction. Such improvements could contribute to a reduction in the risk of developing dementia, among other benefits [26]. A range of positive effects has been shown for web-based interventions for various target audiences (ie, health care providers and family or friend care partners) on a wide range of outcomes (eg, knowledge, attitudes, burden, stress, and others) [27-34].

Previously, we have shown that e-learning is effective for health professions' learning, and we have also outlined some of the more effective instructional design elements with respect to web-based learning [35,36]. Well-designed e-learning that uses best practices in multimedia such as the use of instructional graphics, audio narration, and personalization has been shown to be more effective than e-learning that does not conform to best-evidence instructional design [6,37]. Interventions delivered through the web have the potential to augment traditional face-to-face or paper-based approaches (so-called "blended delivery"); and web-based interventions may allow for greater access to a multitude of users [34,38], facilitating scale and spread [14,39]. DementiaRisk is based on evidence-based studies of dementia risk factors, including addressing several factors at the same time [2]. In addition to a positive impact on participants in the intervention, we anticipate long-term impacts on the Canadian public as well as a benefit for intervention agents (eg, primary care providers and public health units), given the ease of adoption, "trialability," scale, and spread of DementiaRisk.

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Potential Challenges

We anticipate several limitations in this study. First, we anticipate that due to the nature of self-directed web-based interventions, we may encounter higher dropout rates. To mitigate this, we have opted to use AskingCanadians, a paid panel recruitment service that will allow for ensured efficiency of recruitment, potentially higher retention rates, and the ability to attract a diverse and representative sample of Canadian people. Second, many of the instruments for measuring primary and secondary outcomes were custom-created. Although many of the specific survey questions were pulled from validated tools, there is still the possibility that their novelty may influence result validity, which will require cautious interpretation and the use of qualitative data to enrich findings. Third, although the control group will receive e-learning that is related to mild cognitive impairment, and not dementia risk factors, there is the possibility for some contamination or confounding, with some overlap in content domains and the potential for positive outcomes related to the control group content.

Conclusions

Canada's dementia strategy highlights the need to bring awareness to dementia prevention nationally to promote healthy behavior change, in particular, to build the evidence base to inform and promote the adoption of effective risk reduction interventions as well as expand awareness. As the population of older adults living with dementia grows, the demand for high-quality information on dementia prevention is growing as well. Developing a better understanding of how dementia can be prevented and sharing information about how Canadian people can reduce their risk of developing dementia or delay its onset are critical to keeping Canadian people healthy and improving their quality of life. DementiaRisk is a readily scalable, technology-enhanced solution for dementia prevention education. It has the potential to reach a wider number of audiences with modifiable risk factors for dementia than traditional face-to-face interventions.

Acknowledgments

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Data Availability

The datasets generated and analyzed during this study can be made available from the corresponding author upon reasonable request.

Authors' Contributions

AJL and SA drafted the original study protocol. AJL, SC, and RW led the intervention. SA drafted the protocol manuscript. All authors have reviewed the manuscript and approved the final version.

Conflicts of Interest

AJL, RS, and McMaster University are co-owners of DementiaRisk.

Multimedia Appendix 1
Participant flow through the study. MCI: mild cognitive impairment.
[PDF File (Adobe PDF File), 59 KB - resprot_v14i1e64718_app1.pdf]

Multimedia Appendix 2
Outcomes questionnaire questions.
[DOCX File , 21 KB - resprot_v14i1e64718_app2.docx]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
COREQ: Consolidated Criteria for Reporting Qualitative Studies
RCT: randomized controlled trial
TIDieR: Template for Intervention Description and Replication

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Protocol

An mHealth Intervention With Financial Incentives to Promote Smoking Cessation and Physical Activity Among Black Adults: Protocol for a Feasibility Randomized Controlled Trial

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Abstract

Background: Black adults in the United States experience disproportionately high rates of tobacco- and obesity-related diseases, driven in part by disparities in smoking cessation and physical activity. Smartphone-based interventions with financial incentives offer a scalable solution to address these health disparities.

Objective: This study aims to assess the feasibility and preliminary efficacy of a mobile health intervention that provides financial incentives for smoking cessation and physical activity among Black adults.

Methods: A total of 60 Black adults who smoke (≥5 cigarettes/d) and are insufficiently physically active (engaging in <150 min of weekly moderate-intensity physical activity) will be randomly assigned to either HealthyCells intervention (incentives for smoking abstinence only) or HealthyCells+ intervention (incentives for both smoking abstinence and daily step counts). Participants will use study-provided smartphones, smartwatches, and carbon monoxide monitors for 9 weeks (1 wk prequit date through 8 wk postquit date). Feasibility will be evaluated based on recruitment rates, retention, and engagement. The primary outcomes include carbon monoxide–verified, 7-day smoking abstinence at 8 weeks postquit date and changes in average daily step count. Feasibility benchmarks include a recruitment rate of ≥5 participants per month, a retention rate of ≥75%, and a smoking abstinence rate of ≥20% at 8 weeks postquit date. Expected increases in physical activity include a net gain of 500 to 1500 steps per day compared to baseline.

Results: Recruitment is expected to begin in February 2025 and conclude by September 2025, with data analysis completed by October 2025.

Conclusions: This study will evaluate the feasibility of a culturally tailored mobile health intervention combining financial incentives for smoking cessation and physical activity promotion. Findings will inform the design of larger-scale trials to address health disparities through scalable, technology-based approaches.

Trial Registration: ClinicalTrials.gov NCT05188287; https://clinicaltrials.gov/ct2/show/NCT05188287

International Registered Report Identifier (IRRID): PRR1-10.2196/69771

(JMIR Res Protoc 2025;14:e69771) doi:10.2196/69771

KEYWORDS

African American; Black; mobile health; mHealth; smartphone app; smoking cessation; physical activity, mobile phone

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Introduction

Background

In the United States, tobacco- and obesity-related diseases are among the top 10 leading causes of death in the Black and African American (henceforth Black) population, and these diseases are more common and deadlier among Black adults compared with the overall US population [1-3]. For example, while smoking prevalence is similar among Black and White adults, Black adults are less likely to quit smoking than other racial and ethnic groups [4-6], and rates of lung cancer incidence and mortality are higher among Black male individuals than White male individuals [3]. Likewise, the Black population has high rates of obesity in the United States [7]. Physical inactivity (ie, no physical activity outside of work during the past month), a leading cause of obesity [8,9], is higher among Black adults compared with most other racial groups [8,9]. High rates of smoking (14.2%) [10] and insufficient physical activity (30%) [11] among Black adults are important modifiable health risk factors for cancer and chronic illness [12]. Interventions that simultaneously address these behaviors may promote holistic lifestyle changes, provide significant health benefits, and increase health equity within the Black population [13,14].

Multiple health behavior change (MHBC) interventions are defined as those that promote 2 or more health behaviors and thus have a more comprehensive focus on lifestyle health promotion [15,16]. Smoking and low physical activity are strong candidates for these interventions because people who smoke generally report less physical activity than those who do not smoke [17], and individuals may benefit from replacing smoking with physical activity during a quit attempt [18]. Importantly, engaging in physical activity may increase self-efficacy for quitting and alleviate cigarette cravings during withdrawal [19-22]. Physical activity also improves mood and reduces stress, which are common triggers for smoking relapse [23]. However, numerous studies have shown mixed results regarding the physical activity's effectiveness for smoking cessation [24], in part because adherence to physical activity varies significantly across individuals [23,25,26], with stronger adherence among adults with existing physical activity habits and strong social support, and the type of activity (eg, low-intensity activity vs high-intensity activity) [27].

Low-intensity activities, such as walking, may be more practical and palatable for people trying to quit smoking while still offering benefits for smoking cessation, such as reduced cravings and stress relief [13,19,28]. Low-intensity activities may also promote greater adherence to physical activity because they are accessible, comfortable, and less likely to cause fatigue or injury than high-intensity workouts [29]. Furthermore, low-intensity activities can be included in daily routines, such as walking to a bus stop or church [30]. The inclusivity and ease of low-intensity physical activity may encourage long-term engagement and consistency. Thus, combining low-intensity physical activity with other cessation strategies may synergistically increase the likelihood of smoking cessation and have a greater impact on overall health.

Contingency management (CM) is a simple, powerful, and widely used behavioral strategy where tangible rewards are offered for meeting a prespecified behavior change goal [31-33]. CM is efficacious for improving smoking cessation and physical activity [34-38], but common concerns about CM are intervention costs and maintenance of long-term behavior change once incentives cease [39]. Yet, recent research on smoking and physical activity has shown that CM interventions are cost-effective, and even small financial incentives can lead to long-term changes in smoking and physical activity after incentives are withdrawn [34-38]. Thus, an MHBC intervention that incentivizes behavior change could help Black adults initiate and sustain smoking cessation and adequate physical activity in conjunction with other recommended tobacco treatment components (ie, counseling and pharmacotherapy) [40].

Despite the rapid growth of mobile health (mHealth) technologies, such as smartphone apps, that offer new opportunities to reach and treat at-risk populations, Black adults remain underrepresented in mHealth research [41]. As of 2024, 84% of the Black population owned a smartphone [42]; therefore, app-based interventions have the potential to increase the reach and use of effective treatments for smoking and physical activity within this population. Furthermore, apps combined with sensors and wearables can be powerful tools for self-regulation [42], which is a core component of behavior change [43], and can provide frequent feedback and engagement opportunities. Initial evidence suggests that app-based interventions may be a useful supplement to more intensive behavioral or pharmacological treatments and may even show comparable outcomes to traditional face-to-face interventions in some cases [44-47]. Furthermore, smartphone apps can be used to characterize the behaviors, needs, and outcomes of traditionally understudied and underserved groups.

Research indicates that interventions incorporating culturally relevant content resonate with Black adults, enhancing their motivation and commitment to behavior change [48-53]. Such content has increasingly been incorporated into mHealth interventions targeting smoking cessation and physical activity among Black adults [54-57]. Drawing from publicly available resources such as *Pathways to Freedom*—a short documentary highlighting the historical and cultural ties between the Black community and tobacco use and incorporating health education and culturally relevant messages to motivate Black adults to quit smoking [48,49]—mHealth apps can provide educational content on the historical and social influences of smoking within the Black community. mHealth apps can also provide motivational messages and stress-management techniques grounded in culturally relevant themes, such as prayer and seeking support from family and friends. Furthermore, app-based interventions can deliver education about the purpose and benefits of nicotine replacement therapy (NRT) and debunk myths and misconceptions about NRT that are present in this population [58-60]. Apps can also make it easier for Black adults to create activity goals that reflect their current life circumstances and environment [61,62], and these goals can be adjusted dynamically based on daily performance and feedback, ensuring that goals remain challenging yet attainable. This content can be presented alongside success stories from notable

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and relatable Black figures to provide additional motivational support [63-65]. Altogether, when delivered with evidence-based treatment for smoking cessation and physical activity, culturally relevant content may reinforce the quit journey and help address common challenges that Black adults face when quitting smoking and engaging in physical activity.

Objectives

The purpose of this project is to explore the feasibility of an app-based MHBC intervention (HealthyCells) for Black adults who smoke and are insufficiently physically active. In addition to evidence-based tobacco cessation treatment [66], HealthyCells will incentivize daily smoking abstinence, while an enhanced version of the intervention, HealthyCells+, will also include incentives for meeting physical activity goals [36,67]. The inclusion of 2 active study conditions allows for a direct comparison to evaluate the added benefit of financial incentives for physical activity. The central hypothesis is that participants in the HealthyCells+ group will demonstrate greater increases in daily physical activity (measured via step counts) and improved smoking abstinence rates compared to those receiving smoking cessation incentives alone (HealthyCells). HealthyCells will also include an interactive educational e-book experience inspired by the documentary *Pathways to Freedom* [48,49], designed to guide individuals during their quit attempt and provide opportunities to set personalized activity goals, which can be dynamically adjusted daily to reflect current readiness. The primary aim will be to demonstrate intervention feasibility, including recruitment, retention, and adherence metrics, along with rates of carbon monoxide (CO)–verified smoking abstinence and prequit and postquit changes in physical activity.

Methods

Overview

Black adults who smoke and are insufficiently physically active (ie, not meeting physical activity guidelines) [68] will be randomly assigned to 1 of the 2 versions of an MHBC intervention that targets smoking cessation and insufficient physical activity: (1) HealthyCells (incentives for smoking abstinence only) or (2) HealthyCells+ (incentives for both smoking abstinence and physical activity). Both groups will receive a comprehensive tobacco treatment intervention, including 8 weeks of NRT, an initial counseling session to create a quit plan, and 5 weekly counseling sessions (6 sessions in total). Likewise, all participants will receive a study-provided smartphone and intervention app, a Samsung smartwatch to measure daily steps, and a Bedfont iCOquit Smokerlyzer to verify smoking status. Participants will be asked to use their assigned app and equipment for 9 weeks (1 wk prequit date through the eighth wk postquit date).

Ethical Considerations

This study was approved by the institutional review board of the University of Oklahoma Health Sciences Center (protocol #14094), and the study was registered at ClinicalTrials.gov (NCT05188287). All procedures involving human participants will adhere to the Declaration of Helsinki and relevant institutional guidelines. Written informed consent will be obtained digitally from all participants before enrollment, and they will be informed of their right to withdraw from the study at any time without penalty. To ensure privacy and confidentiality, participant data will be deidentified and stored on a secure, password-protected server. All breath sample photos and step count uploads will be encrypted, with access restricted to authorized research personnel. Following a structured and transparent payment schedule, participants will receive compensation based on their engagement with study activities, including breath sample submissions, step count verifications, surveys, and interviews (refer to the Study Compensation section). To protect participant privacy, all devices used for data collection, including Samsung smartphones and smartwatches, will be reset to factory settings after study participation has ended for each participant. Any adverse events or deviations from the protocol will be promptly reported to the institutional review board in compliance with ethical oversight requirements.

Theoretical Framework

As shown in Figure 1, this intervention will be guided by self-determination theory principles [69-72]. Self-determination theory posits that two forms of motivation are involved in behavior change: (1) autonomous motivation and (2) controlled motivation [72]. Autonomous motivation consists of engaging in behavior out of curiosity, interest, a sense of challenge, or for its inherent enjoyment. Conversely, controlled motivation involves engaging in a behavior because of external rewards or punishment avoidance [72]. Autonomous motivation is associated with sustained behavior change, whereas controlled motivation is related to temporary change [73]. CM interventions provide financial rewards for immediate behavior change, primarily targeting controlled motivation [74].

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Figure 1. The theoretical framework of HealthyCells app, a multiple health behavior change intervention for smoking cessation and physical activity.

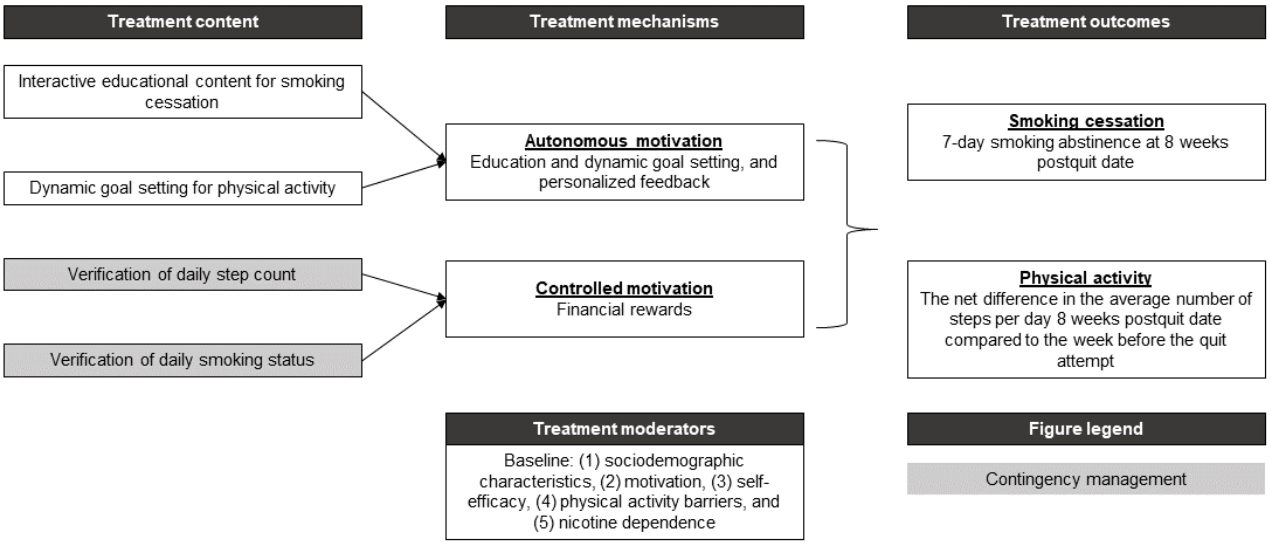

Incentives can be paired with resources and activities that cultivate autonomous motivation to sustain long-term behavior change [75]. The research team created an interactive educational e-book experience inspired by *Pathways to Freedom* [48,49] intervention that focuses on several key topics highlighted in Textbox 1, such as the harms of smoking, tobacco marketing, NRT education, and stress management, and includes narratives from several prominent Black individuals who have struggled with smoking, such as the former US President Barack Obama [76]. The research team also developed a personalized activity goal algorithm based on findings from mHealth physical activity interventions [54,77] and qualitative interviews with Black adults [61,78].

Textbox 1. Overview of topics covered in the HealthyCells, Healthy Habit e-book.

Chapters and interactive educational content

- Chapter 1: discusses health and economic harms caused by smoking and the benefits after quitting
- Chapter 2: covers the hidden history of Black adults and the tobacco industry
- Chapter 3: describes how habits are created and why smoking is one of the deadliest habits to break
- Chapter 4: provides an overview of how nicotine reinforces the smoking habit
- Chapter 5: reviews the purpose and benefits of nicotine replacement therapy

Inclusion and Exclusion Criteria

Inclusion criteria for the participants will be as follows: (1) resident of Oklahoma (verified via driver's license or ID); (2) aged ≥18 years; (3) self-identify as *Black* or *African American*, either alone or in combination with other races or Hispanic ethnicity; (4) smoke ≥5 cigarettes or cigarette equivalents per day (ie, cigars and cigarillos); (5) currently (per self-report) engage in <150 minutes of moderate-intensity aerobic physical activity or <75 minutes of vigorous-intensity aerobic physical activity per week [68]; (6) willing to use NRT, a smartwatch, or the study app and able to attend smoking cessation counseling; (7) willing to quit smoking within the next 3 weeks; and (8) exhaled CO level of >6 ppm at app activation.

Exclusion criteria for the participants will be as follows: (1) unwilling to complete the screening survey, (2) unable to understand or speak English, (3) not a US citizen or permanent resident (due to university taxation policies), (4) unwilling to provide social security number, US residency status, or university employee status (to adhere to university reporting requirements), (5) unwilling to abstain from smoking marijuana or cannabis during their quit attempt, (6) unwilling to provide a picture of a tobacco product (to provide initial evidence of current smoking), (7) medical condition (per self-report) that is a potential contraindication for NRT use (eg, uncontrolled hypertension, heart disease, or recent heart attack), or (8) has had a severe allergic reaction or side effect from the use of NRT.

Recruitment

Participants will be remotely recruited and enrolled. No in-person visits are required (Figure 2). Eligible individuals will be identified through the Tobacco Treatment Research Program [79], which offers free tobacco cessation support to adult Oklahomans and assists with study recruitment [38,80-82]. Prospective participants will also be contacted by SMS text messages, email, and phone, and recruitment flyers will be posted in community locations (eg, barbershops and churches) and on social media through a geotargeted campaign focused on Black adults who smoke. Those interested can access a brief web-based eligibility screener via a QR code or direct link.

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Figure 2. Participant flow. REDCap: Research Electronic Data Capture.

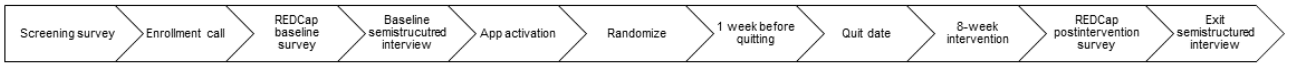

Study Enrollment

Study staff will contact via phone adults who meet preliminary eligibility to confirm eligibility and discuss study participation. To prevent fraudulent enrollments [83,84], participants will be asked to provide a photo of their driver's license or ID (or other proof of address) and an image of a personal tobacco product to provide initial evidence of smoking status. Eligible and willing participants will be informed about the study and asked to acknowledge their consent with a digital signature. Following enrollment, participants will complete a baseline survey via REDCap (Research Electronic Data Capture; Vanderbilt University) [85] (refer to Multimedia Appendix 1 for a complete list of study measures), and their first semistructured phone interview will be scheduled to discuss their openness to using smartphone apps and to identify potential barriers to mHealth research participation (Table 1). After the interview, participants will receive a welcome packet with study instructions, copies of informed consent, and other signed study documentation, a reloadable Greenphire ClinCard [86], intervention equipment (smartphone, smartwatch, and Bedfont iCOquit Smokerlyzer), and NRT by mail.

Table 1. Overview of qualitative domains covered in each interview.

Domain	Baseline interview	Exit interview
Participation in mHealth[a] research	✓	
Understanding smartphone use and habits	✓	
History of using health apps and Bluetooth-enabled devices	✓	
History of using apps that promote smoking cessation and physical activity	✓	
Understanding preferences for smartphone apps that promote health behavior change within the Black population	✓	✓
History of quitting smoking and the methods used to quit smoking before study participation		✓
Problems with study equipment and smartphone app		✓
Overall impressions of app features		✓
Experiences using smartwatch during study participation		✓
Experiences using NRT[b] during study participation		✓

[a]mHealth: mobile health.

[b]NRT: nicotine replacement therapy.

Upon confirming receipt of the study phone and materials, participants will complete an activation assessment in the study app, independently or with study staff. This will assess their ability to use app features, including viewing images, hearing sounds, reading text, and using the Bedfont iCOquit Smokerlyzer. Participants with an expired breath CO <6 ppm or who cannot use the Bedfont iCOquit Smokerlyzer will be withdrawn before randomization and asked to return the study phone and smartwatch. Participants can keep the NRT and Bedfont iCOquit Smokerlyzer to support their quit attempt and will be transferred to the Tobacco Treatment Research Program for cessation services. Participants who pass the activation assessment will be randomly assigned to the HealthyCells or HealthyCells+ intervention.

Study Randomization

Participants will be stratified according to self-reported sedentary time at baseline (high: >8 h/d, medium: 4-8 h/d, and low: <4 h/d) assessed via the International Physical Activity Questionnaire [87]. Participants (n=60) will be randomized 1:1 in REDCap [85], and research staff will text each new participant a unique code (HealthyCells: 0101 and HealthyCells+: 0202) to access assigned app content.

Standard Care

All participants will receive standard intensive tobacco treatment [66], beginning with a phone counseling session 1 week before the scheduled quit date and continuing weekly through the fourth week after the quit date. Counseling sessions will cover topics, including creating a quit plan, the health impact of tobacco, stress management, adopting lifestyle changes, developing coping strategies, and relapse prevention. In addition, participants will receive 8 weeks of combination NRT (nicotine patches+gum or lozenges) based on package-recommended dosing tailored to baseline smoking and nicotine dependence levels [88]. The first 4-week supply will be mailed, and participants can request the remaining supply through the study app as needed.

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MHBC Intervention: App Development and Pilot Testing

Overview

The HealthyCells app was developed using the Insight mHealth Platform [47]. All app content, including breath sample submissions, step count tracking, and interactive educational material, was presented to the African American Cancer Research Community Advisory Board at the Stephenson Cancer Center in November 2024 to solicit community feedback. This meeting was digitally recorded, and the study team reviewed transcripts to identify strengths, weaknesses, and gaps where the app content could be refined. Additional systematic usability testing will be conducted in this feasibility trial to evaluate app engagement, functionality, and acceptability among participants. Findings from this study will inform further refinements to the app in preparation for future large-scale trials to maximize its effectiveness and user experience.

MHBC Intervention: HealthyCells

In addition to all components of standard care described earlier, HealthyCells participants will be able to earn daily financial incentives for CO-verified smoking abstinence each day. Smoking status and identity will be assessed remotely via (1) self-reported daily smoking status, (2) CO breath sample submissions (ie, via the Bedfont iCOquit Smokerlyzer), and (3) Microsoft Azure facial recognition software; each of these assessment types has been successfully integrated into the Insight mHealth Platform [89,90]. Participants will be asked to upload a photo of themselves during the app activation phase, which will be stored as the reference photo for future identity verification. Participants will be instructed to keep their appearance consistent with the baseline photo during breath sample submissions (eg, removing or staying consistent with glasses, hats, and ponytails). During breath sample submissions, 2 photographs will be taken randomly during the exhalation phase to verify identity. Photographs will be encrypted and stored on the study server for later viewing by study staff as needed. A facial recognition mismatch will pause the delivery of incentives and will be flagged for internal review by study staff. Staff will click “thumbs up” or “thumbs down” for an identity match or mismatch, and incentives will be earned on schedule or unearned with incentive levels reset to the starting level.

To earn incentives for smoking abstinence, participants will be instructed to submit 2 breath samples each day (Figure 3). These participant-initiated assessments will appear on the home menu screen, with the first assessment appearing at the beginning of each day (based on participants’ self-reported waking hours) and the second assessment appearing 8 hours after the initial evaluation is completed. Participants will earn US $1 for each breath sample submission regardless of current smoking status. The incentive schedule used in this study is an adaptation of a low-cost incentive schedule the investigators have used in their previous and ongoing work with adults who are socioeconomically disadvantaged [38,89-91]. Participants who demonstrate abstinence (ie, self-reported abstinence that day, CO ≤6 ppm, and identity verification) on both breath sample submissions on their scheduled quit date will receive US $20 to reinforce the initiation of the quit attempt strongly. After that, abstinent participants will be rewarded US $4 per day, increasing by US $0.50 per week until US $5.50 per day is reached during the fourth week postquit date. Participants who are nonabstinent (or who do not provide a sample) will not earn an incentive that day, though they may begin earning incentives for abstinence again the next day. However, the amount will reset to the starting level of US $4 per abstinent day. Participants will earn US $7 per abstinent day during the eighth week postquit date. To gain the maximum incentives for smoking cessation (US $325), participants must report daily smoking abstinence and submit 2 breath samples each day (CO ≤6 ppm) with identity verification during all eligible assessment weeks (ie, wk 1-4 and the eighth wk postquit date).

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Figure 3. An example of a breath sample submission to verify smoking status.

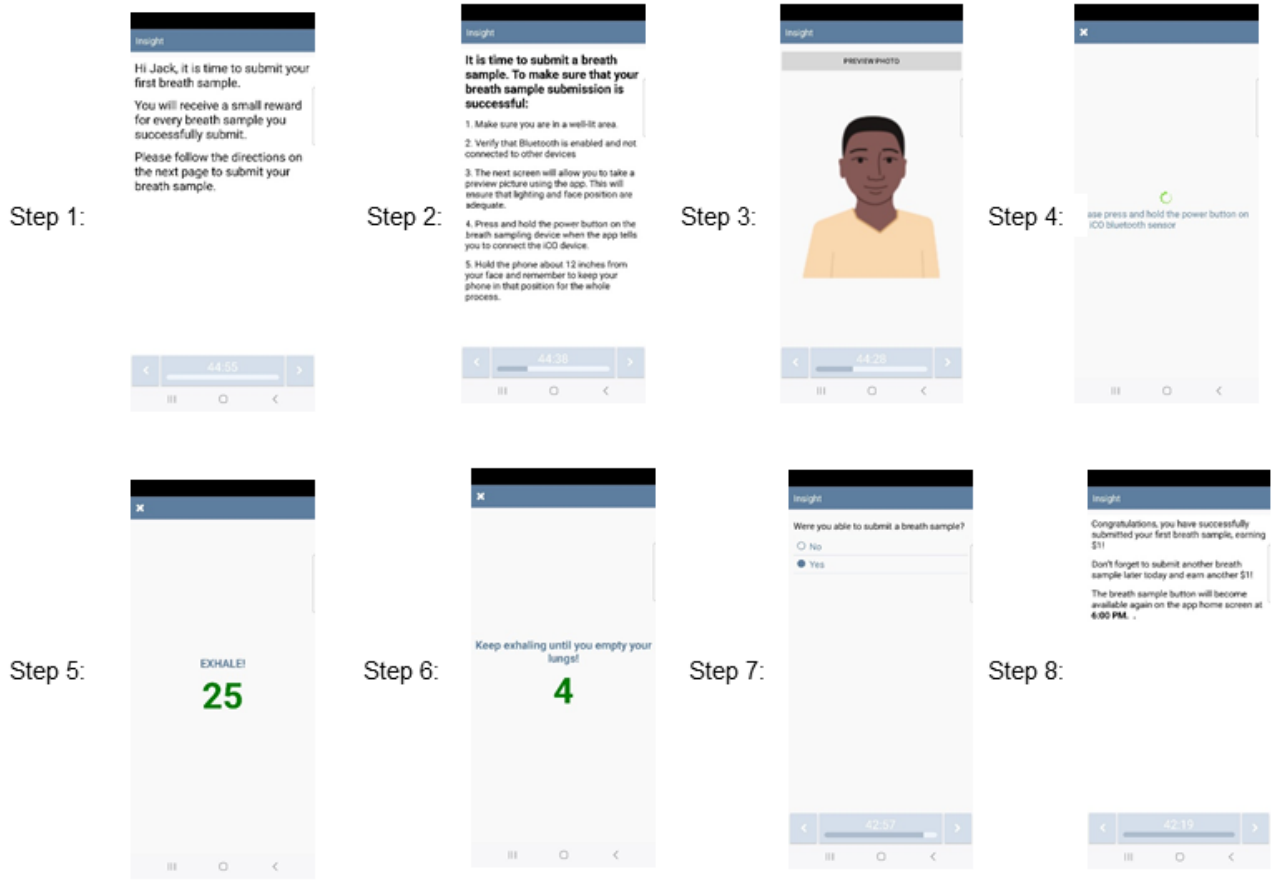

HealthyCells intervention participants will receive a Samsung smartwatch to track their activity and a daily SMS text message about the benefits of increasing physical activity via the app (refer to the Daily Smoking Cessation Progress Report section). They will also have access to content and features that provide strategies for engaging in physical activity to aid their quit attempts (refer to the Set and Review Activity Goals section). However, HealthyCells intervention participants will not receive incentives to increase their physical activity.

MHBC Intervention: HealthyCells+

In addition to the small financial incentives earned for biochemically verified abstinence, HealthyCells+ intervention participants will earn small incentives for increasing physical activity (ie, daily step count) during their quit attempt. Starting on their scheduled quit date, participants will be rewarded US $0.50 per 1000 steps for every step >4000 daily steps, and they will receive a US $2.50 bonus if they walk at least 6000 steps a day. These criteria were set based on research showing Black adults walk about 4000 steps per day on average [92]. Providing incentives above this threshold will ensure the incentive protocol will not reinforce a sedentary lifestyle, and a bonus for meeting the 6000-step per day goal will reinforce higher levels of daily physical activity and greater positive health benefits [92-100]. Participants will not be incentivized beyond 10,000 steps per day, consistent with previous research showing limited additional health benefits [93,95-100]. Therefore, the maximum amount participants can earn per day for daily steps will be US $5.50 (ie, US $3.00 for 10,000 steps +US $2.50 for step goal bonus), an amount that parallels the amount participants can earn at the fourth week postquit date for daily smoking abstinence.

Participants will self-report their daily step count via an assessment on the app home menu at the end of each day (based on self-reported typical time to bed). This assessment will also ask participants to upload a picture of their step count (captured by the smartwatch; Figure 4). To promote compliance, participants will receive US $1 for each successful photo upload (up to 7 submissions/US $7/wk). Participants will not earn incentives for their self-reported step count total if an image is not uploaded. Consistent with the incentive schedule for smoking cessation, participants will earn these incentives for increasing physical activity starting on the scheduled quit date up to 4 weeks postquit date. Incentives may also be earned during the final 7 days of the intervention period (eighth wk postquit date). To gain the maximum incentives for increasing physical activity (US $255.5), participants must submit all step count photos and take 10,000 steps daily during all eligible assessment weeks (ie, wk 1-4 and the eighth wk postquit date).

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Figure 4. An example of a valid photo upload of activity data to verify daily step count.

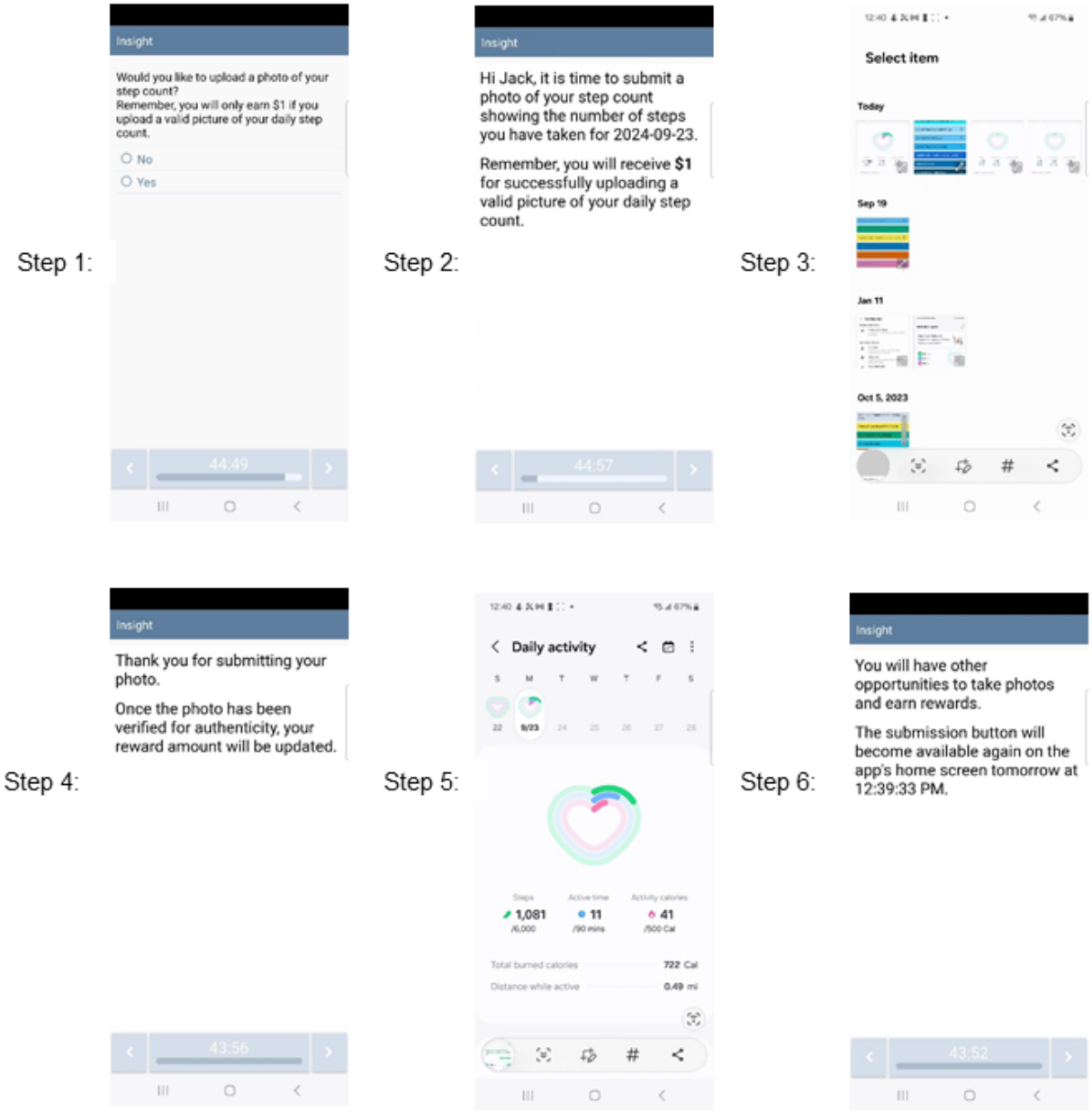

App Features

Overview

Several app features will be available to help participants earn incentives for abstinence and increase physical activity (Table 2 and Figure 5). Multimedia Appendix 2 provides a complete list of features and a detailed description. A summary of each feature is presented in Table 2.

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Figure 5. Home screens for HealthyCells (left) and HealthyCells+ (right) apps. NRT: nicotine replacement therapy.

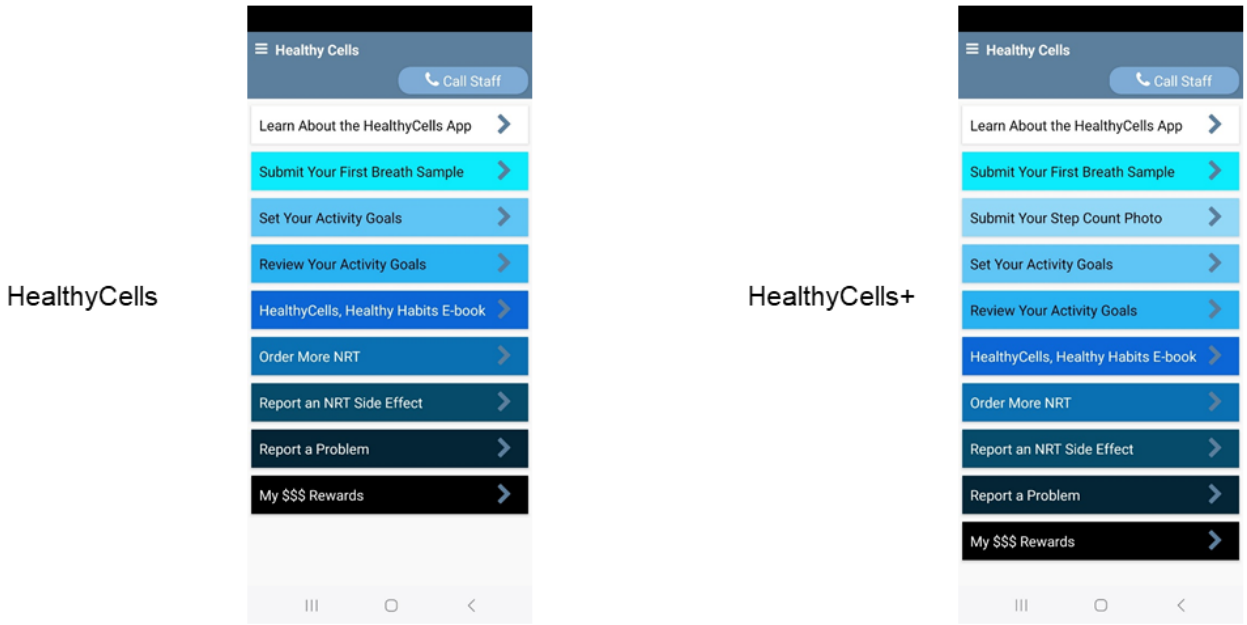

Table 2. Overview of app features.

App features	HealthyCells	HealthyCells+
App Instructions: provide participants with an app overview and study instructions	✓	✓
HealthyCells, Health Habits e-Book: interactive information about smoking and smoking cessation	✓	✓
Breath Sample Submission: submit breath samples using an Bedfont iCOquit Smokerlyzer to verify smoking status and facial recognition software to verify participant identity	✓	✓
Set Activity Goals: set daily steps, active time, and caloric goals	✓	✓
Review Activity Goals: review activity goals and receive feedback to adjust goals for the next day	✓	✓
Submit Step Count Photo: upload an image of activity data for independent verification of step count goals		✓
Report an NRT[a] Side Effect: report side effects from NRT and receive assistance from study staff	✓	✓
Order More NRT: request more NRT during a quit attempt	✓	✓
Track My Rewards: displays the amount of compensation received for completed study assessments	✓	✓
Report a Problem: report a problem with study equipment or assessments	✓	✓

[a]NRT: nicotine replacement therapy.

Learn About the HealthyCells+ App

This feature will be accessible on the home screen at any time during the intervention and will provide an overview of the study apps and instructions for accessing them on their phone.

HealthyCells, Healthy Habits E-Book

Participants can access a short e-book to help them prepare for their upcoming quit attempt. Textbox 1 gives an overview of the topics covered in each chapter. On days 3 to 7 of the prequit week, participants will be informed 1 hour before self-reported typical bedtime about the availability of e-chapters. The entire e-book will be accessible on the home screen at any time after the participant's scheduled quit date.

Set and Review Activity Goals

This feature will be accessible on the home screen at the beginning of each day, allowing participants to set activity goals. If a participant inputs a step goal below the recommended amount needed to receive health benefits or incentives, the app will notify them that they have selected an amount below the recommended threshold. Participants can adjust their goals

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before confirming. Once the participant has set their step goal, this feature will be removed from the home menu screen until the next day.

A total of 8 hours after setting their goal, an option to review their progress will appear on the app home screen. Participants self-report their current step count as indicated on their smartwatch, and the app will automatically calculate whether the participant has met their step goal set earlier in the day. The app will ask participants to rate how challenging it was to meet their current step goal, and their feedback will be used to adjust their step goal for the next day. We created a simple algorithm to set new goals based on the participant's response dynamically: if they rate their current step goal as "not challenging," the next day's step goal will increase by 10%; if "just right," it will increase by 5%; and if "very challenging," it will decrease by 10%. For example, if a participant's goal was 6000 steps and they found it "not challenging," their new suggested goal would be 6600 steps. Once they review their activity progress, this feature will be unavailable on the home menu until the following day.

Report an NRT Side Effect

This feature will be accessible on the home screen at any time, and participants can select from a list of side effects associated with NRT that they experienced during the intervention. Only serious reported side effects will be sent to the study staff and research team via an encrypted email.

Order NRT

This feature will be accessible on the home screen at any time, and participants can order up to 4 weeks of additional NRT, which will be sent directly to the participant's current mailing address.

Track My Rewards

Any time during the intervention, participants can track their rewards for submitting breath samples and activity photos (refer to the Study Compensation section) from the app home screen.

Report a Problem

From the app home screen, at any time during the intervention, participants can report any issues they have encountered during study participation via an encrypted email sent directly to the research team.

Return Study Materials

This menu option will appear on the app home screen after the participant has submitted their final breath sample and uploaded the final photo of their smartwatch activity data to verify their step count. Participants can access instructions about returning their study equipment via study-provided shipping materials.

Daily Smoking Cessation Progress Report

Each day during the intervention, participants will receive a notification from their study app 30 minutes after their self-reported wake time to complete a "Daily Smoking Cessation Progress Report." The app will alert participants visually and audibly for 30 seconds, with a 15-minute snooze option available up to 5 times; after the fifth snooze, the assessment will be marked as missed. The assessment provides feedback on whether smoking status assessments were completed during the previous day, and participants will be asked to self-report confidence in using the Bedfont iCOquit Smokerlyzer and facial recognition. Participants will receive a reminder to use nicotine patches and gum or lozenges daily (or as needed). Participants will also be reminded to wear their smartwatch and set daily activity goals. In addition, participants will be asked to respond to 5 questions assessing sleep quality, mood, stress, energy, and focus.

Study Compensation

Participants will earn up to US $650 in the HealthyCells condition and up to US $905.5 in the HealthyCells+ condition by earning incentives and completing various study activities (Table 3). Upon completing the enrollment call (ie, the participant is fully eligible and agrees to join the study), participants will receive US $25. Completing the baseline survey (US $50) and interview (US $50) within 72 hours will qualify them for a US $25 bonus, totaling US $125. During the intervention, participants will earn US $1 per breath sample submitted twice daily, with additional bonuses if both samples indicate smoking abstinence (CO <6 ppm), for a possible total of US $325. HealthyCells+ intervention participants will earn US $1 daily for submitting step count photos, with bonuses for exceeding 4000 steps (up to 10,000 total steps) and meeting a 6000-step goal, potentially totaling US $255.5. Completing the postintervention survey at the end of the intervention will offer US $50 and an additional US $50 for participating in the exit interview. If these 2 activities are completed within 72 hours, participants will earn a US $25 bonus, totaling US $125. Participants who return study materials will receive US $25, with an additional US $25 bonus if returned within 7 business days, totaling US $50.

Payments will be delivered via a reloadable GreenPhire ClinCard [86] once per week, with the first payout occurring after the baseline interview and the final payment after study materials are returned. This structured payment system encourages consistent engagement and ensures the timely return of valuable study materials by tying the final payment to their return. Participants can also track their earnings in real time through the app (refer to the Track My Rewards section), which adds transparency to the process.

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Table 3. Compensation amount and payment schedule for completed study activities.

Activity	Compensation (US $)	Bonus condition	Total compensation (US $)	Study condition	
				HealthyCells[a]	HealthyCells+[b]
Study enrollment[c]	25	None	25	✓	✓
Baseline survey	50	Complete both the baseline survey and interview within 72 h (US $25)	Up to 125	✓	✓
Baseline interview	50	Complete both the baseline survey and interview within 72 h (US $25)	Up to 125	✓	✓
Breath sample submission	1 per sample (2 samples/d)	Not smoking when completing breath samples (up to US $20)	Up to 325	✓	✓
Step count photo Submission	1 per photo (1 upload/d)	Per step above 4000 steps (maximum 10,000 steps; US $3); meeting 6000 step goal (US $2.50)	Up to 255.5		✓
Postintervention survey	50	Complete both the postintervention survey and baseline survey within 72 h (US $25)	Up to 125	✓	✓
Exit interview	50	Complete both the postintervention survey and baseline survey within 72 h (US $25)	Up to 125	✓	✓
Return study materials	25	Return study materials within 7 business days (US $25)	Up to 50	✓	✓

[a]The total compensation was up to US $650.

[b]The total compensation was up to US $905.5.

[c]Participants only earn US $25 if they successfully enroll in the study.

Postintervention Assessment and Treatment Outcomes

At the eighth week postquit date, participants will complete a postintervention assessment via REDCap [85], answering questions similar to those in the baseline assessment to track changes in physical and mental health and health behaviors and to assess app impressions (Multimedia Appendix 1). A final semistructured interview will gather feedback on the app and suggestions for improvement (Table 1). The primary outcome for smoking cessation will be CO-verified, 7-day point prevalence smoking abstinence at 8 weeks postquit date, which will be assessed via smartphone-based self-report and a corroborating CO assessment. Expired CO is a valid indicator of smoking and cessation and compares favorably with cotinine and other biochemical measures [101]. Daily abstinence will be examined as a secondary outcome and defined as self-reported abstinence within the day combined with 2 breath CO sample submissions <6 ppm and identity verification. The number of days and consecutive days of CO-verified abstinence will be explored as additional outcomes. The other primary outcome will be the net change in average daily steps during the eighth week postquit date compared with average daily steps the week before the quit attempt (HealthyCells+ group only). Second, we will explore the number of total and consecutive days that ≥6000 steps were achieved as additional outcomes [102]. A valid day of observation for daily steps will be defined as (1) a smartwatch that was worn for at least 10 waking hours with (2) ≥500 steps taken within a day [103].

To ensure accurate, objective measurement of step count, study staff will pair each participant's Samsung smartwatch with a Samsung smartphone and create a unique Samsung Health account before shipping the study materials. The Samsung Health app integrates seamlessly with the smartwatch, allowing continuous step count tracking. These data sync automatically from the watch to the app, enabling real-time data capture. Throughout the intervention, the research team will periodically access each participant's Samsung Health account to securely export step data, which will be saved as a file for analysis. Once participants return the phone and smartwatch, the study team will directly extract step data from the smartwatch to verify and complement the app-synced step data. This dual extraction process enhances data reliability, ensuring comprehensive and objective measurement of participants' physical activity [102]. After this extraction, the phone and smartwatch will be reset to factory settings to prepare them for use with another participant, ensuring privacy and consistency across participants.

Feasibility and Engagement Outcomes

We will assess several metrics to gauge the feasibility of evaluating the intervention in a larger-scale trial. Key metrics include completion rates for surveys and interviews (retention and engagement), instances of lost or damaged phones or

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watches (technology use barriers), and participant engagement with app features, such as completing the e-book for smoking cessation and setting and reviewing daily step goals. We will also characterize the frequency of photo uploads of daily step counts, completion of daily smoking status assessments, NRT adherence, completion of counseling sessions, and duration of smartwatch wear. These feasibility metrics will also be explored qualitatively by interviewing participants about their experiences with the intervention (ie, exit interview), such as their engagement with app features, ease of completing assessments, and any challenges encountered with study equipment.

Sample Size Justification

The sample size of 60 participants was chosen based on recommendations for feasibility trials [104,105], which prioritize assessing study processes, recruitment, retention, and intervention engagement rather than detecting statistically significant effects. This sample size is sufficient to evaluate key feasibility metrics, such as recruitment rates (target: ≥5 participants/mo), retention (≥75% completion), and adherence to intervention components, which are critical for planning a fully powered randomized controlled trial. In addition, this sample size allows for preliminary comparisons between the HealthyCells and HealthyCells+ groups to explore trends in CO-verified smoking abstinence and changes in daily step counts.

Analytic Plan

This analytic plan will focus on describing intervention feasibility. Feasibility indicators will include enrollment of all study participants within 12 months (≥5 adults enrolled/mo), retention of at least 75% of the participants at 8 weeks postquit date, achieving 20% smoking abstinence at 8 weeks postquit date (consistent with NRT and behavioral support standards) [104,105], and observing a meaningful 500 to 1500 [106,107] average daily step increase at eighth week postquit date. SAS (version 9.4; SAS Institute) [108] will be used for all statistical analyses, generating descriptive statistics to compare demographics, smoking status, and physical activity levels by treatment group. Group comparisons on participant characteristics and outcomes will use 2-tailed *t* tests for continuous variables and chi-square tests for categorical variables. Given the small sample size and pilot design (N=60), we will report all potential group differences with the α set at $P<.20$, following recommendations for pilot studies [109].

Smoking cessation will be analyzed in two ways: (1) an intention-to-treat analysis with missing data classified as smoking and (2) a completers-only analysis excluding participants with missing data. For physical activity outcomes, specifically the change in average daily step count from the baseline week to the eighth week postquit date, *t* tests will evaluate pre-post differences between groups. Days with <500 steps or <10 hours of watch wear time (indicating nonwear time or recording error) will be excluded. Participants must have at least 4 days of valid step count data to be included in the analyses.

Exploratory analyses will examine the association between physical activity and smoking cessation success using continuous and categorical approaches, with 6000 steps as the threshold for categorical analyses. Logistic regression analysis will evaluate the impact of average daily step count based on all postquit assessment weeks (5 wk in total) on CO-verified 7-day point prevalence abstinence at 8 weeks postquit date. In addition, participants will be categorized based on achieving a daily average of ≥6000 steps, allowing us to evaluate whether higher activity levels (≥6000 steps) are associated with greater cessation success. Finally, we will explore additional metrics, including the number of consecutive abstinent days and the frequency of meeting daily step goals. The analysis will examine these metrics as continuous and categorical variables to assess their association with smoking cessation rates.

Qualitative Analysis Plan

The baseline and exit interviews will be evaluated separately to comprehensively understand participants' experiences and impressions at different stages of the mHealth intervention. Transcripts from both interviews will be analyzed in NVivo (version 12; Lumivero) using an inductive thematic approach [110,111]. A codebook will be developed collaboratively by coding a subset of interviews, with iterative refinements to ensure reliability before the lead author's independent coding of the remaining transcripts. Periodic team reviews will resolve discrepancies.

The baseline interview will assess participants' initial perspectives and familiarity with mHealth tools, which may inform their engagement with the intervention. Key focus areas will include motivation for participating in mHealth research, smartphone use habits, and previous experiences with health apps and Bluetooth-enabled devices. By examining these factors, the analysis will capture participants' baseline comfort levels with digital health tools, previous exposure to apps for smoking cessation and physical activity, and any initial preferences for culturally tailored health behavior interventions within the Black population. Insights from these domains will provide context for interpreting participants' engagement with the intervention and potential barriers that could influence adherence.

The exit interview will assess participants' experiences with the intervention, focusing on perceptions of the cultural tailoring and usability of the intervention components. A central focus will be feedback on the e-book modeled after *Pathways to Freedom* [48], with analysis capturing participants' impressions of its cultural relevance, clarity, and perceived impact on smoking cessation. Participants' feedback on which sections resonated, any challenges encountered, and suggestions for improvement will provide insights into enhancing this culturally tailored component. Further domains in the exit interview will evaluate participants' overall impressions of the app features, experiences with the smartwatch, adherence to NRT, and any technical issues encountered with study equipment. This analysis aims to identify strengths and weaknesses of the intervention from the user perspective, including insights into specific app features that supported or hindered engagement and practical challenges with using the devices.

We will synthesize findings from the baseline and exit interviews to identify overarching themes related to engagement, cultural resonance, and barriers to adherence. This holistic

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analysis will reveal how initial expectations and previous experiences influenced participant experiences and how the intervention can be refined to improve acceptability and effectiveness for larger-scale studies. Examining recurring themes across interviews may provide actionable insights for enhancing intervention design, especially regarding cultural tailoring, usability, and support for behavior change.

Integration of Study Findings

We will use a mixed methods approach to capture a holistic view of intervention feasibility and participants' experiences [112]. Quantitative data will provide intervention outcomes and milestones, and qualitative findings will uncover insights into participants' expectations, experiences, and perceptions regarding the intervention. Triangulation will occur through a systematic comparison of quantitative metrics with qualitative themes [112,113]. For example, if quantitative results indicate high smoking cessation rates, qualitative data will be examined to identify participant-reported factors that facilitated this success. Conversely, if step count improvements are minimal, qualitative insights may help reveal barriers to physical activity engagement or limitations within the app that could be addressed in future studies. This combined approach will provide information about feasibility and generate participant-driven insights, increasing the likelihood that future interventions will be effective and tailored to meet community needs.

Results

This study was reviewed and funded by the National Institute of Minority Health and Health Disparities (Multimedia Appendix 3). This study was approved by the institutional review board of the University of Oklahoma Health Sciences Center (protocol #14094) on 12/10/2021. Data collection is expected to start in February 2025 and finish in September 2025 (Figure 6 depicts the CONSORT [Consolidated Standards of Reporting Trials] diagram). Primary data are expected to be analyzed by October 2025. The preparation of manuscripts on primary and secondary outcomes is expected to start in late 2025 and early 2026.

Figure 6. Participant recruitment, allocation, intervention adherence, and follow-up in the feasibility randomized controlled trial evaluating the HealthyCells interventions for smoking cessation and physical activity promotion (CONSORT [Consolidated Standards of Reporting Trials] flow diagram).

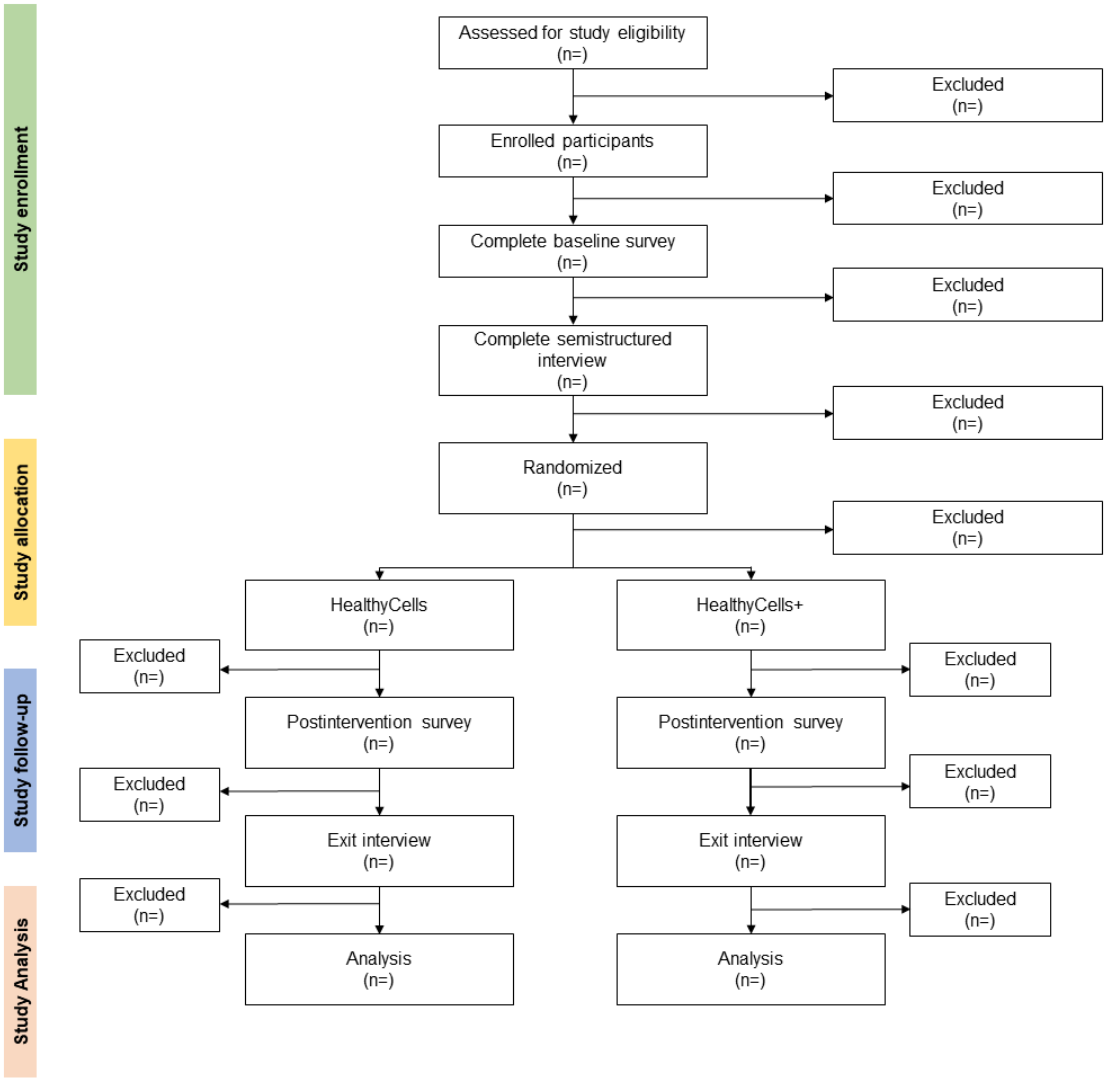

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Discussion

Principal Findings

This study evaluates the feasibility of the HealthyCells intervention, an app-based mHealth approach integrating financial incentives for smoking cessation and physical activity promotion among Black adults. We anticipate that participants in the HealthyCells+ group, who receive incentives for both smoking abstinence and physical activity, will achieve greater increases in daily step counts and higher rates of CO-verified smoking abstinence compared to the HealthyCells group, who are incentivized for smoking abstinence only. Feasibility metrics, including recruitment, retention, and participant adherence, are expected to demonstrate strong engagement and acceptability of the intervention over the 9-week study period.

Comparison to Prior Work

This study builds upon previous MHBC mHealth interventions, such as See Me Smoke-Free [114] and PhoS [115], which showed potential to promote behavior change but were limited by reliance on self-reported outcomes and low adherence rates [46,116,117]. In contrast, HealthyCells incorporates objective measures of behavior (eg, CO breath samples for smoking abstinence and step counts verified by smartwatches), addressing these limitations. In addition, culturally relevant content, such as that inspired by *Pathways to Freedom* [48,49], distinguishes HealthyCells from other interventions by tailoring messages to resonate specifically with Black adults. This study also advances CM research by combining financial incentives for multiple behaviors, a strategy that has shown promise in previous studies [34-38].

Strengths and Limitations

A key strength of this study is its focus on a population disproportionately affected by tobacco- and obesity-related health disparities. By leveraging mHealth technology and CM, this intervention offers a scalable and accessible approach to behavior change. Objective tracking of outcomes ensures data reliability, and the inclusion of culturally tailored content enhances the potential for participant engagement.

However, this study has limitations inherent to feasibility trials. The sample size (n=60) is small and not powered to detect statistically significant differences in outcomes. In addition, the absence of a control group limits conclusions about the intervention's effectiveness. Despite these limitations, this study will provide critical pilot data for a fully powered randomized controlled trial.

Future Directions

Findings from this feasibility study will guide the refinement of the HealthyCells intervention for larger-scale trials. Future research will explore the effects of long-term interventions, the maintenance of behavior change after incentives are withdrawn, and the scalability of interventions to other underserved populations. In addition, further refinements to the app based on participant feedback will aim to enhance usability and engagement. Ultimately, this research has the potential to contribute to health equity by addressing smoking and physical inactivity in high-risk populations using innovative, culturally tailored, and technology-driven strategies.

Acknowledgments

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Data Availability

The datasets generated and analyzed during this study will be made publicly available in a suitable data repository following the publication of all primary and secondary analyses. Until that time, the data will be available from the corresponding author on reasonable request.

Authors' Contributions

AA designed the intervention and formulated the research questions and hypotheses. AA prepared the first draft of the manuscript. All authors revised it and approved the final draft.

Conflicts of Interest

MSB is one of the inventors of the Insight mHealth Platform and receives royalties related to the use of this platform by investigators external to the University of Oklahoma Health Sciences Center. All other authors declare no conflicts of interest.

Multimedia Appendix 1
Overview of study measures across each assessment type.
[DOCX File , 21 KB - resprot_v14i1e69771_app1.docx]

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Multimedia Appendix 2
Overview of scheduled assessment and menu options available in both study apps.
[DOCX File , 21 KB - resprot_v14i1e69771_app2.docx]

Multimedia Appendix 3
National Institute of Health peer-review report.
[PDF File (Adobe PDF File), 162 KB - resprot_v14i1e69771_app3.pdf]

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Abbreviations

CM: contingency management
CO: carbon monoxide
CONSORT: Consolidated Standards of Reporting Trials
MHBC: multiple health behavior change
mHealth: mobile health
NRT: nicotine replacement therapy
REDCap: Research Electronic Data Capture

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Protocol

Effect of Medication Management at Home via Pharmacist-Led Home Televisits: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: Older adults are more likely to have multiple chronic conditions, be prescribed multiple medications, and be more susceptible to adverse drug reactions (ADRs) to their medications. In addition, older adults often use over-the-counter medications and supplements, further complicating their medication regimens. Complex medication regimens are potentially harmful to older adults. Interventions aimed at reducing medication discrepancy in the ambulatory clinic setting, such as reviews of medication lists and the implementation of "brown bag" reconciliation, continue to be challenging, with limited success. Pharmacist-led interventions to improve appropriate medication use in older adults have demonstrated effectiveness in reducing ADRs. Video visits have the potential to provide direct visualization of medications in older adults' homes, thereby reducing medication discrepancy and increasing medication adherence. Pharmacist-led management of older adults' medication regimens may improve appropriate medication use in older adults.

Objective: The objective of this study is to examine the effect of pharmacist-led medication through home televisits compared to usual care on appropriate medication use, medication discrepancies, medication adherence, and ADRs.

Methods: We will conduct a 2-site cluster randomized controlled trial (RCT). The intervention will be a pharmacist-led home televisit including medication reconciliation and assessment of actual medication use. The cluster RCT was iteratively adapted after a pilot test. The primary outcome of medication appropriateness of the intervention will be measured using the STOPP (Screening Tool of Older Persons' Prescriptions) criteria for potentially inappropriate medications (PIMs) at 6 months. Medication lists obtained will be compared against electronic medical records (EMRs) by a clinician to establish discrepancies in medications. The clinician will review medications using the validated Medication Appropriateness Index (MAI).

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Results: This project has been peer-reviewed and selected for support by the Veterans Affairs (VA) Health Services Research Service. The pilot phase of the study was completed December 2021 with 20 veterans and was primarily informed by the Steinman model of the prescribing process adapted to include system- and provider-level factors. The last date of enrollment was August 6, 2021. We anticipate the completion of the ongoing trial in spring 2025. The first results are expected to be submitted for publication in 2025.

Conclusions: The cluster RCT will provide evidence on medication management through televisits. If found effective in improving the use of medications, the intervention has the potential to impact older adults with multiple chronic conditions and polypharmacy.

Trial Registration: ClinicalTrials.gov NCT04340570; https://clinicaltrials.gov/study/NCT04340570

International Registered Report Identifier (IRRID): PRR1-10.2196/65141

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KEYWORDS

older adults; medication management; televisit; polypharmacy; adverse drug reaction

Introduction

Polypharmacy in Older Adults and the Importance of Medication Reconciliation

The US population is aging rapidly; the population aged 65 years and above is projected to be doubled by 2050. The most rapidly growing segment is the population of older adults aged 85 years and above, which will more than triple from 5.9 million in 2012 to 18 million in 2050 [1,2]. Older adults aged 65 years and above often have multiple chronic diseases—more than 60% have 2 or more chronic diseases [3], and 17% have 4 or more chronic diseases [4]. Older adults with multiple chronic comorbidities often require multiple medications for management, particularly with guideline-based management of chronic diseases [5,6]. The use of multiple medications in older adults is common, with almost 20% of older adults aged 65 years and above taking 10 or more medications [7,8]. Multiple-medication use in older adults is associated with a lower adherence rate and increased use of inappropriate medications [9,10]. The use of multiple medications increases the risk for potential drug interactions, leading to undesirable adverse drug reactions (ADRs), which could also contribute to lower medication adherence. In particular, older adults are more susceptible to ADRs due to the changes in their physiology, clearance, and reserves [11], particularly with polypharmacy [9,12] Based on the phycological changes in the older population, knowing the drug regimens with older adults is an important feature in order to provide medication safety and make adjustment to their regimen accordingly to ensure appropriate medication use. The START/STOPP (Screening Tool to Alert to Right Treatment/Screening Tool of Older Persons' Prescriptions) criteria [13-15] and American Geriatrics Society (AGS) Beers criteria [16,17] for potentially inappropriate medications (PIMs) were developed to provide evidence-based guides to signal clinicians about medications that are potentially inappropriate and to enhance medication appropriateness. These medications include those with strong anticholinergic properties, which may disproportionately affect older adults and are linked to adverse outcomes of ADRs, and other medications that are demonstrated to have significant side effects in older adults.

Use of Telemedicine to Improve Medication Use in Older Adults

Telemedicine is a modern visit option enabled by advances in telecommunications technology [18]. The use of telemedicine in older adults has been examined in prior small studies that have demonstrated feasibility, acceptability, and user satisfaction [19-22]. Extending televisits to patients' homes has the potential to impact many aspects of care that rely on patient self-management, such as medication use. Although telephone-based pharmacist interventions have the potential to impact medication use at home [23,24], they still rely on accurate information reported by older adults over the phone without a mechanism for confirmation. The addition of video has the potential to further enhance the visit [25,26] by (1) visual ascertainment of actual medications taken by patients, (2) visual demonstration of the patients' actual use of medications, and (3) education of patients on proper use. Although in-person home-based reconciliation has the potential to improve accurate appraisal of medication use and reconciliation, it is not feasible for wide adoption as it is resource intensive. The study proposed here will examine the impact of home televisits by pharmacists on patients at high risk for ADRs (ie, with polypharmacy and multiple chronic conditions).

Methods

Research Design Overview

This study is designed as a mixed methods hybrid type 1 effectiveness implementation study [27], where we will test the health impact of pharmacy televisits, while also collecting data on the implementation process to facilitate subsequent scale-up efforts [28]. As older adults have higher rates of chronic conditions and polypharmacy, we included veterans aged 65 years and above in this study. The inclusion criterion of 5 or more medications is based on prior literature on polypharmacy and findings of increased risk for drug interactions and ADRs. The enrollment criteria are consistent with and exceed the criteria set in fiscal year 2019 by the Center for Medicare Services for provision of medication therapy management in Medicare Part D [29]. Among patient characteristics, polypharmacy (≥5 medications) and multiple chronic conditions

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are considered important risk factors for ADRs and are highly prevalent among frail older adults at risk for ADRs [30].

The intervention for the cluster randomized controlled trial (RCT) was iteratively adapted after a pilot test with 20 veterans [31]. Home televisits, where pharmacists conducted medication reconciliation and management, were refined, after which a formative evaluation [32] was conducted, guided by the Consolidated Framework for Implementation Research (CFIR) [33]. Data were gathered in several ways: (1) enrolled veterans (n=20) were observed by study staff present within the veterans' homes during the clinical pharmacist home televisit, and (2) study staff administered a postencounter questionnaire with the goal of improving the veteran-based technical experience and clinical encounter. The data points were used to adapt and make changes to the intervention for the cluster RCT.

The cluster RCT is registered on ClinicalTrials (NCT04340570). The intervention will be a pharmacist-led home televisit including medication reconciliation and assessment of actual medication use. Pharmacists will review medication appropriateness using evidence-based criteria and provide recommendations for change of medication use to the patients' primary patient-aligned care team (PACT). PACTs provide team-based care and consist of a primary care provider (PCP), a registered nurse, a medical assistant, and, often, either a social worker or a pharmacist. In the control group, participants will receive usual care in which medication reconciliation and review will be conducted in clinics by primary care teams. As a primary outcome, we will examine the effect of the intervention on the number of veterans with PIMs, as determined using evidence-based criteria. As secondary outcomes, we will determine the number of PIMs, medication discrepancy using data from record reviews and interviews, and medication appropriateness using validated instruments at 6 months after the intervention. We will also compare the intervention's effects on the incidence of ADRs using data from record reviews and interviews. To assess the potential for future implementation of the intervention, we will administer postintervention questionnaires to key stakeholders, including veterans and PACT clinicians, to examine implementation barriers to and facilitators of the intervention.

Ethical Considerations

This study was approved by the Veterans Affairs (VA) Central Institutional Review Board (CIRB; IRBNet ID 1612635). To obtain participants' informed consent, a research assistant (RA) will determine whether eligible patients have the capacity to provide informed consent to participate in the study using a screening questionnaire that assesses the 4 elements required for capacity understanding of study procedures, appreciation of what will happen if enrolled, communication of a choice to enroll or not, and demonstration of a rationale for that choice. Recruitment and written informed consent will take place in a location that ensures privacy and convenience for the patient.

Conceptual Framework of Medication Prescribing in Older Adults

Our conceptual framework is informed by the CFIR [34] and Steinman et al [35] on prescribing and prescription monitoring processes. The pilot phase was primarily informed by the Steinman model of the prescribing process adapted to include system- and provider-level factors. The system-level factors include the Veterans Health Administration (VHA) policy on medication management (including non-VA care use), facility-level prescribing environment and practices, and decision support systems. In designing our proposed intervention, we considered the potential effect of home televisits by pharmacists to ascertain the medication regimen and use, identify discrepancies and educate patients on use, and review medication appropriateness, thereby enhancing steps in the monitoring phase of the prescribing process (Figure 1).

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Figure 1. Conceptual framework of prescribing and prescription-monitoring process. Modified from Steinman et al [31]. VA: Veterans Affairs.

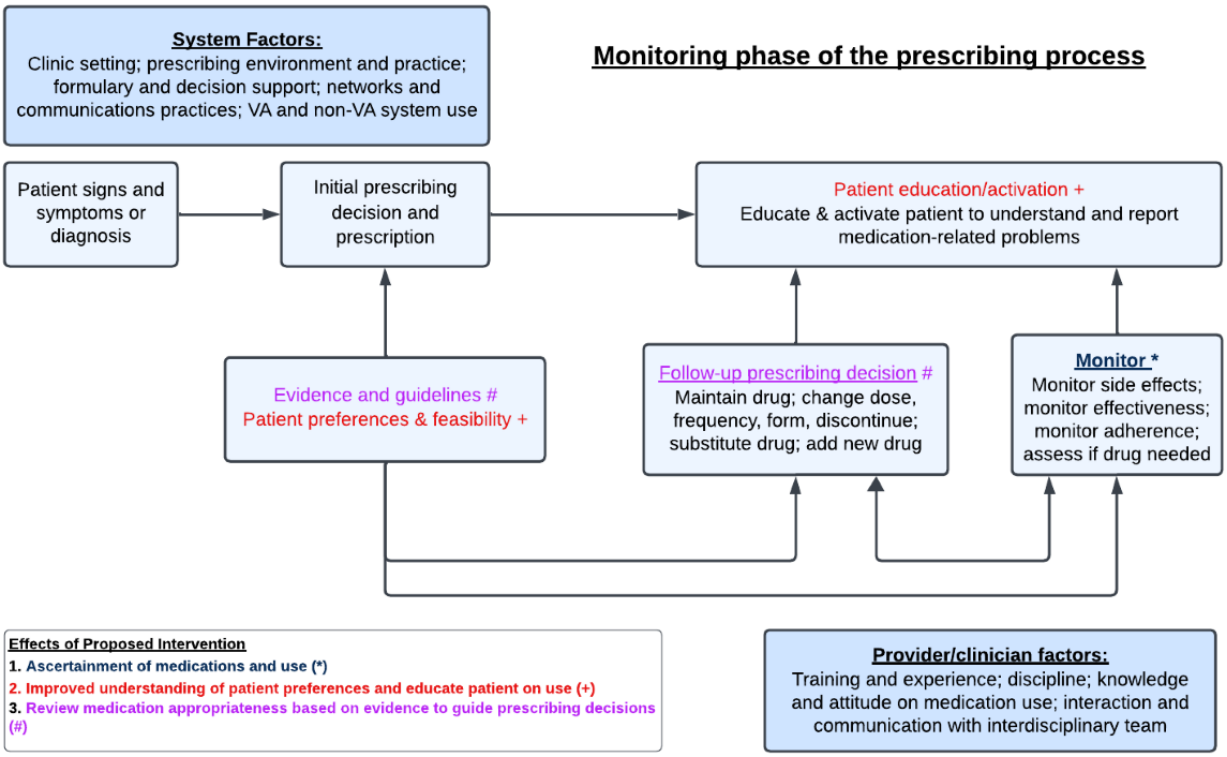

Cluster Randomized Controlled Trial Patient Recruitment

The inclusion criteria include the following: (1) the veteran must be a PACT patient in a Bronx VA or Bedford VA geriatrics or primary care clinic; (2) be 65 years or older; (3) have 2 or more chronic conditions; and (4) have 5 or more medications listed on the VA medication record continuously in the previous 6 month. Patients fulfilling these criteria will be approached for study enrollment through letters of invitation after approval by human subjects' committees.

Cluster Assignment by PACT

We will randomize patients by PACT to prevent a team from having participants in both treatment and control groups and to reduce contamination. Prior to initiating enrollment, the project coordinator will assign PACTs to intervention and control groups using lists of computer-generated random numbers in a 1:1 ratio, with separate lists for the Bronx VA and the Bedford VA, in order to maintain balance in both groups within each study site. There are 69 primary care and geriatric PACTs in the Bronx VA and 14 in the Bedford VA, and each PACT will keep the group assignment for the duration of the study.

Study Flow

After enrollment, veterans who agree to participate in the study will be interviewed by a trained research coordinator using survey instruments that will include data elements listed in Table 1. Veterans will receive the televisit intervention, or not, based on the PACT team they belong to, as discussed earlier. The detailed procedure for control and intervention groups is described later. To observe what occurs at follow-up appointments with the PACT provider, after the first follow-up appointment postintervention, participants will be asked about whether medication use was discussed during the appointment, whether medication reconciliation was performed and how, and what, if any, medication changes were made. Electronic charts will be reviewed for documentation of medication reconciliation and management during the visit. Primary outcomes will be ascertained at 6 months after study enrollment and are described in Table 1, including the subject survey and chart review. The subject survey for outcome assessment will be conducted by a research coordinator trained to take the subject's medication history, and the chart review will be conducted by a clinician blinded to the study assignment. The subject survey will include confirmation of medications participants are currently taking, including names, dosages, and frequency. Participants will be asked to list medications that they take, including over-the-counter drugs and supplements. A clinician rater blinded to the study assignment will review medication data from the subject survey and chart review to determine medication discrepancies and appropriate use of medications.

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Table 1. Data elements and instruments.

Data elements	Source	Instruments or measurements
Outcomes		
Primary: PIM[a] use	Chart review, interview	STOPP[b] criteria, assessment of medication list by blinded clinical reviewer [14]
Secondary: medical discrepancies	Chart review, interview	Medication discrepancies (omissions, duplications, additions)
Medication appropriateness	Chart review, interview	MAI[c] [36]
Patient satisfaction, self-efficacy, and adherence	Interview	CAHPS[d] item pertaining to medication use [37], MUSE[e] [38]
Health-related quality of life	Interview	EQ-5D-5L [39]
ADRs[f]	Chart review, interview	ADRs determination by clinical reviewer
Baseline covariates		
Sociodemographics	Baseline survey, chart review	Gender, age, race, ethnicity, education, income, Medicare, Medicaid
Chronic illness burden	Patient interview, chart review	Modified RAND index [40]
Medication list	Chart review, patient interview	Number and type of medications, source (VA[g], non-VA, over the counter)
Medication use	Interview, chart review	Number and type of medications, method of administration, presence of refill gap (>90 days)
Patient's self-efficacy on medication use	Patient interview	MUSE
Health literacy	Patient interview	Short Test of Functional Health Literacy in Adults (S-TOFHLA) [41]
Cognitive function	Patient interview	MoCA[h] [42]
Physical function	Patient interview	Katz Activities of Daily Living (ADL) index/Lawton Instrumental Activities of Daily Living (IADL) scale [43,44]
History of acute care use (hospitalization, emergency department)	Patient interview, chart review	Days prior to enrollment for most recent hospitalization and emergency department visit, number of episodes in the previous year
Health-related technology use attitude, self-efficacy, and comfort	Patient interview	Self-reported comfort and confidence in using technology [45]

[a]PIM: potentially inappropriate medication.
[b]STOPP: Screening Tool of Older Persons' Prescriptions.
[c]MAI: Medication Appropriateness Index.
[d]CAHPS: Consumer Assessment of Healthcare Providers and Systems.
[e]MUSE: Medication Understanding Use and Self-Efficacy Scale.
[f]ADR: adverse drug reaction.
[g]MoCA: Montreal Cognitive Assessment.

Intervention

Patients assigned to the intervention will have a pharmacist televisit appointment made and coordinated. Participants will be asked whether they have a device at home capable of supporting televisits, including home computers with cameras, tablets, smartphones, and a broadband or 4G connection. Participants who do not have appropriate devices will be provided with VA-issued internet-enabled tablets on which to conduct the visits. On the scheduled day of the visit, the research team will coordinate with the participants over the phone to facilitate the initialization of the televisit by the pharmacist. The content of the televisit is described next, in the *Design of the Televisit Intervention* section, and has been adapted through the pilot phase with direct observation of the televisit at home. Subsequent to the televisit, the pharmacist will document the visit content in the electronic medical record (EMR) to note discrepancies noted during the televisit, a review of medications with START/STOPP criteria, and recommendations based on the criteria-based review for PCP review and concurrence for adjustments of medications. Recommendations will be communicated to the PCP electronically through secure email or an electronic note or over the phone or through a face-to-face discussion if preferred by the PCP. Adjustments in the medication regimen will be noted at 7 days in the EMR after recommendations are made. If recommendations are not

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adopted, the pharmacist will communicate with the PCP electronically to request reasons for not adopting recommendations. Participants will then continue follow-up primary care with their PCP.

Design of the Televisit Intervention

We plan to use the VA video connect (VVC) capability introduced in fiscal year 2018 to conduct televisits between clinical pharmacists located at the VA medical centers and participants at home. An appointment will be scheduled with each participant for time to conduct the home televisit. The devices, EX90s or web cameras, used at the clinician side will be located at the Bronx VA or the Bedford VA and at the participants' side will be their choice of computer, tablet, or smartphone with an internet connection and webcam capability or a VA-provided tablet if they do not have a device or home internet capabilities. Because the experience of the televisit may differ with different participant devices, various devices were tested in phase I of the study, and their strengths and pitfalls and modes of connecting were identified.

After establishing a video connection, the pharmacist will conduct home-based medication reconciliation by asking the participants to show and explain the use of each of their medications. The pharmacist will also include a brief medication-focused functional assessment, including asking the participants to read aloud and interpret 1 or more of their prescription bottles and to demonstrate the ability to open the bottles. Before ending the visit, the pharmacist will educate the participants regarding possible side effects or interactions between their medications. The pharmacist will also solicit and answer any questions the participants have about the medications. The pharmacist will note the medications used and compare them against the list of medications on each participant's EMR to note discrepancies and then generate a note in the EMR to notify the primary care team of the review and information obtained. If the pharmacist finds that patients are taking medications differently, they will clarify the correct usage of the medications.

Pharmacist Review of Medications

After the televisit is completed, the pharmacist will conduct a medication review using the START/STOPP criteria to review the indication of each medication (see Table 2). They will also review whether there are medications prescribed beyond the recommended duration of each medication, where the treatment duration is well defined. The pharmacist will use evidence-based guidelines to inform follow-up prescribing decisions (maintaining, adjusting the dose, or stopping the medication); see Figure 1. Medications noted to be inappropriate or those that do not have an indication will be flagged for consideration of deprescribing. Duplication of drug class prescriptions will also be noted. Other disease-specific criteria will be reviewed based on the criteria [13-15]. Recommendations generated from the medication review based on START/STOPP criteria will be communicated to the PCP for consideration of modification of the medication regimen. Final decisions on medication modification will be made by primary care clinicians in consultation with their patients as it usually would be in a clinical setting.

Table 2. Scope of pharmacist-led intervention televisit, laying out the steps, content, and approximate duration of each step.

Step	Content and sample questions	Approximate duration (60-75 minutes total)
Setup	Establish a connection, preparation for the visit.	5-10 minutes
Introduction	Identify individuals in the visit and discuss the purpose of the visit.	5 minutes
Identification of the medication regimen and visualization of medications	• What medicines do you currently take? • How about over-the-counter medicines? How about vitamins and supplements? • Where do you keep your medications? Can you show me?	15 minutes
Description and visualization of how to take medications	• What do you take this medicine for? • When do you take this medicine? • Can you show me how much you take each time?	15-20 minutes
Clarify medication instructions	If medications are taken incorrectly, ask why. Educate and use the teach-back method to confirm understanding.	15 minutes
Questions and closing	Answer the patient's questions, if any. Discuss the next steps of review and communication with the PCP[a].	5-10 minutes

[a]PCP: primary care provider.

Control Arm (Usual Care)

After baseline MoCA and technology comfort assessment, medication reconciliation and management will be conducted by the control primary care teams in the manner they usually do. PACTs are guided by the VHA Directive on Medication reconciliation [46], which includes in-clinic assessment of medication information provided by patients via lists, recall or actual medication reviews, comparing information obtained to the VA EMR to note discrepancies, and educating the patient on updated medications. PACT PCPs may also request assessment of medication regimens by pharmacists embedded in their clinic based on clinical decisions regarding the needs of the individual patient and the availability of such services. The prescription of a new medication may trigger a review by a VA pharmacist guided by EMR-based interaction alerts. We

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considered using an active control group with pharmacist review (in-clinic or chart review); however, the intervention with pharmacist-led home televisits informing medication review represents a bundled intervention, and the study will examine the effectiveness of the intervention as an enhancement of care to what currently occurs (usual care). This design involving participant interviews and chart reviews will also allow us to characterize current usual medication management for older adults in PACTs.

Outcomes

Primary Outcome

PIM use, which is the primary outcome, will be assessed by the blinded clinical reviewer based on the medication data obtained from home visit surveys using the STOPP criteria [14]. Proportions of participants with PIMs in the intervention group will be compared with proportions of participants with PIMs in the control group.

Secondary Outcomes

Medication lists obtained through subject surveys will be compared against the EMRs by a clinician to establish discrepancies in medications. Discrepancies will be characterized as “no potential harm,” “monitoring or intervention potentially to preclude harm,” or “potential harm,” similar to prior approaches to assess potential clinical impacts [32]. In addition, the clinical reviewer will assess the medications using the validated Medication Appropriateness Index (MAI) [36]. Each medication will receive a score based on the 10-item tool to determine its appropriateness. Patient satisfaction will be ascertained using an item pertaining to medication use from Consumer Assessment of Healthcare Providers and Systems (CAHPS) version 3.0 [37], a 7-item, 5-point Likert scale on medication management by pharmacists adapted from a validated instrument [33,47]; self-efficacy on medication use will be assessed using the Medication Understanding Use and Self-Efficacy Scale (MUSE) to assess change from before and after the intervention [38]. Health-related quality of life will be assessed using the EQ-5D-5L instrument, a brief validated instrument with good test-retest reliability [39,48].

Implementation Factors

Postintervention questionnaires will be administered to key stakeholders, including veteran participants and PACT clinicians, to assess the potential for future implementation of the intervention. This will allow us to examine implementation barriers and facilitators. An invitation to complete the postintervention questionnaires will be emailed to PACT providers in the intervention arm. To ensure we understand PCP decisions on pharmacist recommendations, we will track PCP adoption of recommendations provided by pharmacist reviews and examine PCP reasons for adoption or nonadoption of recommendations, as well as provider factors that can influence those decisions. Patient and clinician interviews and questionnaires will identify perceived barriers and facilitators on a Likert scale. The knowledge and attitude on prescribing for older adults will also be obtained using validated Likert questions, although the attitude and behavior in clinician communication with pharmacists will be gathered using the Home Medicines Review Inventory (HMRI).

Results

The study flow is summarized in Figure 2. The pilot phase of the study was completed December 2021 with 20 veterans and was primarily informed by the Steinman model of the prescribing process adapted to include system- and provider-level factors. This project has been peer-reviewed and selected for support by the VA Health Services Research Service. The last date of enrollment was August 6, 2021. We anticipate the completion of the ongoing trial in spring 2025. The first results are expected to be submitted for publication in 2025.

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Figure 2. Study design showing specific steps included in intervention and control groups. PACT: patient-aligned care team.

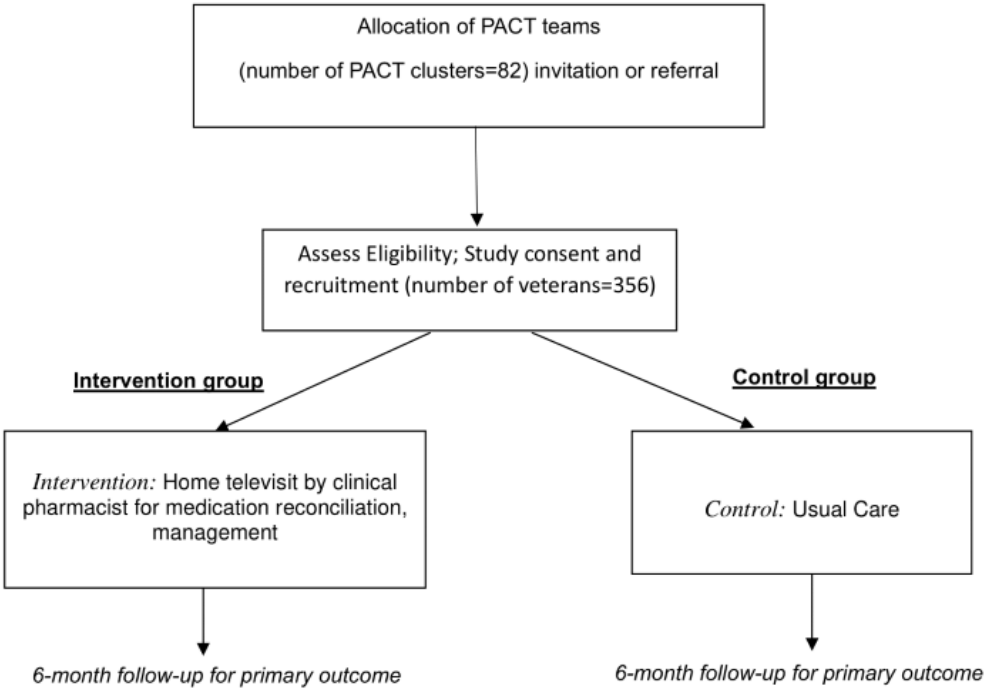

Discussion

Summary

The complex medication regimens of many older adults contribute to increased risk for drug interactions, ADRs, and other poor health outcomes. A number of studies have found that the use of PIMs is associated with adverse outcomes, such as falls, acute care use, and other negative outcomes [49,50]. Improving medication prescribing using START/STOPP criteria has been found to reduce adverse effects and improve patient outcomes in a number of studies, although mostly in institution-based settings (acute care hospitalization, nursing homes) [50]. Pharmacist-led interventions have been demonstrated to have beneficial effects [51,52] but often do not reach the majority of those who would most benefit from them. Leveraging the advances of telemedicine, clinicians can provide medication management services to older veterans at home. The televisit intervention with pharmacists in medication management has the potential to bridge the current gaps in older adult care and provide a scalable solution to improve medication use in older adults.

The study's pilot phase refined the procedure for pharmacists to conduct home televisits. It is possible that veterans will consider televisits to home cumbersome or invasive and that VA primary care staff will consider tailoring medications for older adults an additional task burden that competes with other mandated tasks. Our prior experiences of home televisits suggest that they are well accepted, and our hybrid effectiveness implementation study will enable us to identify potential implementation challenges and thus can inform future implementation. To ensure we understand PCP decisions on pharmacist recommendations, we will track PCP adoption of recommendations provided by pharmacist reviews to identify PCP reasons for adoption or nonadoption of recommendations, as well as provider factors that can influence those decisions.

The older adult population has increased the use of technology, allowing the VA to use technological advances for VA televisits, overcoming previous barriers, and we expect future changes in technology will further facilitate use. Our study design will allow us to observe older adults using technology at home to enhance our understanding of the barriers to use, and qualitative interviews with clinicians and patients will further identify factors to guide future implementation. We have elected to use 2 separate sites in the RCT phase in order to enhance our understanding of contextual issues and external validity.

Strengths and Limitations

This study design includes both a pilot phase trial and a hybrid effectiveness implementation trial, which ensures that we would observe and be able to address challenges prior to the RCT, although the results of the hybrid implementation effectiveness trial would allow us to determine its effectiveness, while preparing us to spread the intervention, if effective, in the health system. We aim to limit crossover contamination for providers with cluster randomization. Lastly, the standardized intervention and structured pharmacist protocol will ensure consistency and reliability.

The study design also has a few limitations. One is that the study will be conducted in urban and suburban settings, which may limit generalizability Another limitation is that the pilot phase was conducted during the COVID-19 pandemic, which introduced unique challenges in recruitment due to factors such as travel restrictions and increased risk for participants; however, the study team tackled those challenges and completed the pilot phase of the study despite limitations introduced by COVID-19. This study will contribute toward the literature on pharmacist-led medication management through home televisit procedures, as

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well as interventions aimed at improving medication use in older veterans.

Conclusion

This study design will demonstrate how medication management will be beneficial through televisits. The implementation effectiveness trial will show how it can improve the use of medications and interventions related to the potential impact on older adults with multiple chronic conditions and polypharmacy. Clinicians can offer older veterans medication management services at home by using telemedicine's advancements. The use of pharmacists in televisit medication management interventions has the potential to close existing gaps in older adult care and offer a scalable way to enhance older adults' medication use.

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Data Availability

No data sets will be generated or analyzed during this study.

Authors' Contributions

LRM, WWH, SRH, ANS, MBM, JLB, KSB, ALS, CZ, CEH, MDV, MZ, MR, and BCB contributed to the intervention concept and design and to the writing and preparation of the manuscript. Generative artificial intelligence was not used in the preparation of this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review from the HSR-6 Post-acute and Long-term Care - Department of Veterans Affairs Office of Research and Development - Health Services Research and Development Service (USA).
[PDF File (Adobe PDF File), 86 KB - resprot_v14i1e65141_app1.pdf]

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Abbreviations

ADR: adverse drug reaction
CAHPS: Consumer Assessment of Healthcare Providers and Systems

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CFIR: Consolidated Framework for Implementation Research
EMR: electronic medical record
MAI: Medication Appropriateness Index
MoCA: Montreal Cognitive Assessment
MUSE: Medication Understanding Use and Self-Efficacy Scale
PACT: patient-aligned care team
PCP: primary care provider
PIM: potentially inappropriate medication
RCT: randomized controlled trial
START: Screening Tool to Alert to Right Treatment
STOPP: Screening Tool of Older Persons' Prescriptions
VA: Veterans Affairs
VHA: Veterans Health Administration

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Protocol

Stress and Hypertension Among African American Female Family Caregivers of Persons Living With Alzheimer Disease and Related Dementias: Protocol for a Pilot Internet-Based Randomized Controlled Trial

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Abstract

Background: Caregivers of persons with Alzheimer disease and related dementias (ADRD) neglect their health, including by ignoring stress levels. African American women are vulnerable and susceptible to hypertension. Chronic caregiving stress and hypertension place them at high risk for cardiovascular disease. Addressing stress reactivity or resilience is vital in lessening their caregiving stress, enhancing their quality of life (QOL), and fostering healthy blood pressure (BP) self-care behaviors.

Objective: This pilot study aims to investigate the feasibility and acceptability of implementing the Mindfulness in Motion (MIM) plus the Dietary Approaches to Stop Hypertension (DASH) intervention in this population and to evaluate its effect on ADRD caregivers' stress and QOL. Additionally, it explores the mediation of stress reactivity or resilience between interventions and self-care behaviors.

Methods: A small randomized controlled trial pilot study will recruit 28 African American or Black female caregivers aged 40 years diagnosed with hypertension and on an antihypertensive medication. Participants will be randomly assigned to either the MIM DASH or the Alzheimer's Association caregiver training group (attention control). Trained facilitators will deliver both interventions over 8 weeks through 1-hour, group, internet-based sessions, via video or telephone. After completion, both groups will receive coaching calls over 9 months, beginning with 8 weekly calls followed by 4 monthly calls to encourage use of the educational materials. Primary outcome measures include feasibility (recruitment and retention) and acceptability (attendance). Secondary measures assess caregiver stress (Perceived Stress Scale), QOL, and self-care behaviors (Food Frequency Questionnaire and self-reported physical activity). Data collection occurs at baseline, 3 months, and 9 months. Quantitative data will be analyzed using descriptive statistics, CIs, and mediation models.

Results: This study was approved by the institutional review board in April 2022 and funded in May 2022. The first data were collected in January 2023, and the last data were collected in September 2024. The completion of all aims' data analysis is anticipated in spring 2025. The participants' mean age was 62.4 (SD 7.98) years, with a mean baseline systolic BP of 128 (SD 19) mm Hg and diastolic BP of 79 (SD 10) mm Hg. Participants reported that MIM DASH was acceptable (at a mean score of 59.08, SD 7.38, compared to 60.83, SD 5.56 for caregiver training). Regarding feasibility, as reflected in attendance, MIM DASH participants had a mean attendance of 6.3 (SD 2.3) sessions, and the caregiver training group had 4.9 (SD 2.9) sessions.

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Conclusions: This study's findings demonstrate the feasibility of conducting an internet-based intervention (MIM DASH) for African American women with hypertension who also care for families living with ADRD. These results will inform the design of a larger randomized controlled trial to evaluate the intervention's efficacy and scalability further.

Trial Registration: ClinicalTrials.gov NCT05721482; https://clinicaltrials.gov/study/NCT05721482

International Registered Report Identifier (IRRID): DERR1-10.2196/66975

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KEYWORDS

African American women; high blood pressure; stress reactivity and resilience; caregiving; hypertension; stress; Alzheimer disease; dementia; lifestyle and healthy self-care behaviors

Introduction

Background

Family caregivers of individuals with Alzheimer disease and related dementias (ADRD) provided an estimated 18.4 billion hours of unpaid care, valued at nearly US $350 billion [1]. The prevalence of ADRD is higher among African American individuals, leading to a disproportionately more significant share of the family caregiving burden. Approximately one-third of these caregivers of individuals living with dementia acknowledge postponing or neglecting their health due to their caregiving role [1]. Given African American individuals' heightened risk of ADRD, particularly vascular and mixed dementia, this problem disproportionately affects African American family caregivers [1].

Although African American caregivers generally express positive feelings about caregiving and report cultural justification for providing care [2,3], they nonetheless endure the adverse effects of chronic caregiver stress—increased cortisol levels, hypertension [4,5], and consequently, cardiovascular disease [6]. Compounding their risk, African American women face a heightened danger of uncontrolled hypertension and cardiovascular disease [7]. No demographic group is more at risk for the double jeopardy of caregiving stress and hypertension than African American women caring for a family member who has ADRD.

Hypertension is the leading cause of cardiovascular disease among African American women, affecting 56.7% of this group [8]. Numerous studies recommend lifestyle changes such as stress management, reducing sodium intake, increasing the intake of fruits and vegetables, weight management, and engagement in regular physical activity to manage hypertension [9,10]. Researchers have hypothesized that African American individuals face excess chronic stress that makes adopting healthy self-care behaviors difficult [11,12].

One of the underlying mechanisms behind adopting healthy self-care behaviors is stress reactivity or resilience—the body's psychological and physiological response to stress [13]. Understanding these factors can contribute to more effective and sustainable behavior changes such as healthy eating, stress management, and physical activity.

Only a few studies have explored the stress and resilience associated with healthy self-care behaviors among African American caregivers. No research to date has used an interdisciplinary methodology to examine the intricate relationship between stress and resilience in this demographic. This protocol paper describes a mind-body intervention designed to address the complex interplay of stress and hypertension in African American caregivers.

Purpose

This randomized controlled pilot study examines the feasibility and acceptability of Mindfulness in Motion (MIM) combined with Dietary Approaches to Stop Hypertension (DASH) to promote hypertension self-care in African American women who are family caregivers of people living with ARD.

MIM uses gentle yoga stretches and teaches mindful awareness skills, while the DASH program promotes a diet rich in vegetables, fruits, whole grains, and lean proteins [14,15]. These interventions combined provide a comprehensive strategy for stress management and hypertension reduction. The control group will receive the Alzheimer's Association's caregiver training [16-19].

Study Aims

This study aims (1) to determine the feasibility and acceptability of MIM DASH and caregiver training for African American female caregivers with hypertension; (2) to compare the influence of MIM DASH on caregiver stress and quality of life (QOL) with the influence of caregiver training; and (3) to investigate the potential mediation effects of stress reactivity or resilience between each program and self-care behaviors.

Theoretical Models

Of MIM

Developed in 2004, MIM was based upon the ideas of Urie Bronfenbrenner's Socio-Ecological Model, which highlights the multilevel influences on behavior [20]. The Socio-Ecological Model has been extensively researched and is an effective way to structure multilevel interventions to aid in the long-term adoption and sustainability of programming [21]. MIM's combination of dietary education and experiential mind or body practices aligns with the multilevel Socio-Ecological Model of change. MIM was first implemented in 2009 as a small, randomized controlled trial with 48 employees [22]. Guided by the question of "Is MIM effective?" the program was tested in various additional studies with medical center faculty, staff, residents, and patients [23-30]. These trials showed significant stress and burnout reduction results with improved resilience.

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Of DASH

The 8-week DASH education uses a critical thinking model of behavior change and culturally appropriate approaches to emphasize eating vegetables, fruits, whole grains, fat-free or low-fat dairy choices, fish, poultry, beans, and nuts and using vegetable oils [31]. Additionally, it limits foods high in saturated fat, sugar-sweetened beverages, and sweets. Critical thinking provides individuals with the tools for reasoning, empowerment, problem-solving, and making sound decisions [16]. The DASH eating plan decreases cardiovascular outcomes, including subclinical injury and systematic inflammation biomarkers, and improves blood pressure (BP), especially among African American individuals [32]. The critical thinking approach allows individuals to analyze information and their behavior to make fully informed decisions in the best interest of African American individuals; it also provides opportunities for reflection.

MIM and DASH

MIM and DASH both address health behaviors but from different perspectives. MIM integrates mindfulness practices, while DASH emphasizes critical thinking and heart-healthy dietary choices. Together, they contribute to holistic well-being and improved health outcomes.

Study Timeline

The participants will be tracked for 9 months in the 2-year funded trial. Data will be collected at baseline, at 3 months, and during a 9-month follow-up.

Methods

Design

In this randomized controlled trial, 28 community participants will be enrolled and randomly assigned to MIM DASH (n=14; intervention group) or caregiver training (n=14; attention-control group). This study's team will use REDCap (Research Electronic Data Capture; Vanderbilt University) to deliver informed consent to prospective participants via an online check box. Figure 1 provides a flow chart for this study.

Figure 1. Flow Chart for the Study: The figure visually represents participants' enrolment and randomization into training or intervention programs, followed by their sessions and data collection phases.

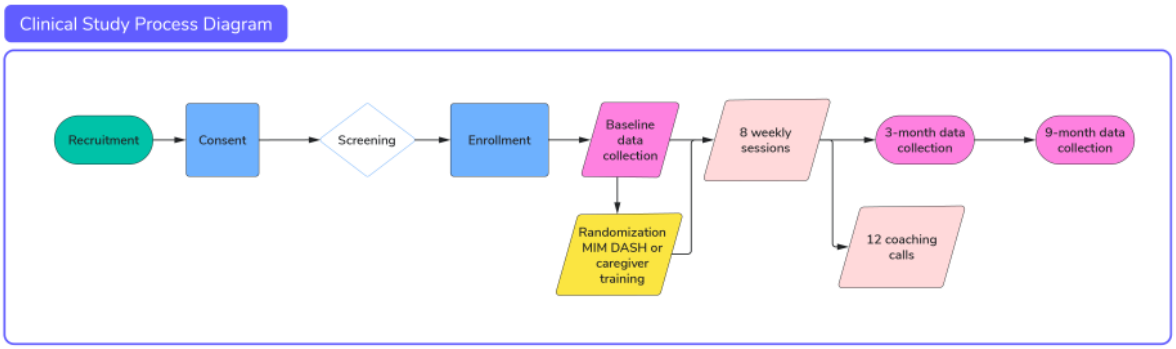

Recruitment

Participants will be recruited from clinics, the African American Alzheimer's and Wellness Association, the Central Ohio Alzheimer's Association, local churches, the Research Match registry, and social media. Additionally, study flyers will be displayed in places potential participants are likely to frequent, such as libraries, beauty salons, health provider offices, and senior centers. To maintain confidentiality, the list of all potential participants will be securely kept separate from the documentation and tracking spreadsheet in the REDCap. Basic demographic information and reasons for refusal will be noted for eligible individuals who decline participation. Enrollment and screen failure data will be tracked using the National Institutes on Aging (NIA) Common Data Screening, and enrollment forms will be reported to the NIA once every month (NIA Clinical Research Operations & Management System) [33].

Eligibility

Study participants will be adults aged 40 years and older who self-identify as Black or African American women and as family caregivers to someone living with ADRD. Inclusion criteria include the following: (1) have a diagnosis of hypertension that is treated with an antihypertensive medication; (2) have a score of two or greater on the eight-item Informant Interview to Differentiate Aging and Dementia [34]; (3) provide unpaid care for a person living with ADRD at least 10 hours per week and assist a person living with dementia with at least 1 instrumental activity of daily living (eg, bill paying, medication management, or transportation); (4) speak English; and (5) have access to a telecommunications device such as a desktop computer, laptop, tablet, smartphone, or telephone, to enable participation. Exclusion criteria include the following: (1) expect to move out of the area within nine months; (2) have a diagnosis of resistant hypertension (BP that remains above goal despite concurrent use of a diuretic or water pill and at least two other antihypertensive medications of different classes), or (3) are actively participating in a mindfulness or yoga program.

Randomization

All caregivers who enroll in this study and complete the baseline assessment will be randomly assigned into either the intervention group (MIM DASH) or the attention-control group (caregiver training). The rationale for an attention-control condition is to strengthen this study's design and minimize the chance that differences between the groups could be related to receiving social support from interacting with others [14]. Once one of

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this study's staff members has completed the baseline data collection, the statistician will randomly assign this study's participants using a randomization table generated from the statistical software in the REDCap database. Trial participants will be blinded to this study's hypotheses.

MIM DASH (Intervention Group) Delivery

A trained MIM facilitator and a dietitian will deliver the intervention in eight 1.5-hour (~45 minutes for MIM and ~45 minutes for DASH) sessions via Zoom (Zoom Video Communications, Inc) with telephone access. Participants will receive session materials such as PowerPoint (Microsoft Corp) slides to follow along by phone or the Zoom videoconferencing app. Table 1 provides a list of the topics.

Table 1. Weekly topics for MIM[a] DASH[b] (intervention group) and caregiver training (attention-control group).

Week	MIM DASH	Caregiver training
1	• Introduction to MIM • What African American individuals should know about hypertension and its consequences	Healthy brain and body
2	• Mindful sleep • Understanding blood pressure overview	10 warning signs
3	• Vision of self • Clearing up myths about hypertension	Dementia conservations
4	• Mindful eating • Basics of the DASH diet	Effective communication
5	• Balance through movement • Be a DASH detective: sodium is the culprit	Understanding behaviors
6	• Sensation • DASH: throughout your day—breakfast, lunch, and dinner	Safety and driving
7	• Clarity and release • DASH: when eating out	Physician's visits
8	• Staying grounded and moving forward • DASH: diet is only part of the story	Money and legal

[a]MIM: Mindfulness in Motion.

[b]DASH: Dietary Approaches to Stop Hypertension.

Each MIM session will consist of mindfulness-related material—the somatic mind and body connection, relaxation, yoga, meditation, self-awareness, and bodily cues relating to emotional reactivity. Group interaction will center on sharing ideas toward effective practice and practical daily challenges to being mindful. Each class will begin with a prompt for participant contemplation during the session that references a unique weekly theme, which will be reiterated in the session materials. Then, the participants will be led through a body scan, gentle stretching, yoga, progressive relaxation, and mindful eating meditation, ending with formal meditation. Each participant will receive a new weekly link to online video mindfulness practice recordings. The workbook has a diary section to document study activities. The diary is personalized and retained by the participant. Participants will be instructed to perform mindfulness video meditations at least 5 times weekly and record the time in their diary.

The DASH portion focuses on education to increase intakes of vegetables, fruits, and whole grains and decrease intakes of fat, sodium, sugar-sweetened beverages, and sweets. The education includes adapting traditional "soul" food dishes to meet the DASH dietary guidelines. Participants will be provided practical tips on incorporating DASH into their daily lives. They will receive an individual MyPlate (United States Department of Agriculture Center for Nutrition Policy and Promotion) displaying serving sizes and food groups comprising a balanced meal and a home BP monitor. Principal investigator KDW will provide training on using the BP monitor and American Heart Association infographics and video [35,36]. Repetition of key concepts will be embedded throughout the sessions to increase critical thinking and problem-solving [17]. After completion of the 8-week sessions, the MIM DASH participants will receive 8 weekly and then 4 monthly coaching calls to review sessions and support the adoption of self-care behaviors. Our team has successfully delivered the MIM DASH intervention for older African American individuals with hypertension [14].

Caregiver Training (Attention-Control Group)

A study team member trained by the Alzheimer's Association will deliver the caregiver training. Participants in this group will attend eight 1.5-hour group lessons via Zoom for 8 weeks (Table 1). The training uses the Alzheimer's Association caregiver topics listed in Table 1. The Alzheimer's Association

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materials are based on the latest scientific evidence of dementia researchers and practitioners in partnership with various community-based, academic, and health care organizations [37].

As with the MIM DASH group, participants will receive educational materials to follow along using Zoom videoconferencing or phone. Participants will have group discussions and role-play using a case study scenario. After completing the 8-week sessions, participants will receive 8 weekly and then 4 monthly social calls to encourage them to maintain their involvement and enhance study retention for subsequent data collection [14].

Fidelity

To maintain the fidelity of the intervention, a detailed protocol manual will be developed for MIM DASH and caregiver training. The MIM facilitators will be enrolled in 8 weekly 1-hour sessions as participants and attend a half-day workshop with return demonstrations. Before leading an MIM session independently, the facilitators will observe an 8-week MIM course and be the designated fidelity checker [38]. During each weekly session, the facilitator will show MIM educational and practice videos created by coinvestigator MDK. For the DASH component, the registered dietitian, also a coinvestigator IKRA, will develop a training plan and materials. Coinvestigator IKRA will deliver the DASH component and train others if needed. The materials for DASH will include a scripted facilitator manual. The principal investigator will also be trained to deliver MIM DASH as a backup facilitator. A study staff member will use a fidelity checklist for MIM DASH to observe the facilitators.

Sample Size and Power Analysis

Our sample size of 28 participants (14 participants per arm) conforms to the recommended sample size rules of 20-30 for pilot studies, as there are diminishing returns for precision, particularly over sizes of 12 per group (“rule of 12s”) [39-41]. Further, a sample of 28 is considered a sufficient pilot sample to determine variance in a main trial powered to 80% to detect an effect of 0.4 [41]. In line with pilot studies, the sample size lacks the power to detect a small-to-medium effect size for aim 3. Therefore, our mediation analysis will not emphasize statistical significance but report point estimates, 95% CIs, and effect sizes.

Measurements

Data collection measures consist of surveys, systolic and diastolic BP, the Pittsburgh Stress Battery, a Food Frequency Questionnaire, and the collection of a hair sample for cortisol analysis. Study staff were trained and observed before independently collecting data. Table 2 provides a data collection timetable, including the constructs, measures, and brief psychometrics provided in validation studies. These data will be collected in the treatment and attention-control groups at baseline, 3 months, and 9 months. Each study visit is estimated to take 2 hours. Maximum flexibility is critical to engage busy caregivers in research. Our team offers several options for data collection. Study visits may be conducted at the participant’s preferred time, day, and location. For example, participants may select the visits at their home, a dedicated research study office, or a private room at a local library. Study visits can take place outside of traditional office hours and workdays. The participant may have this study visit broken up into two 1-hour visits if needed. In these cases, the research staff will prioritize the collection of data that requires an in-person visit (eg, BP and hair collection) and offer to meet again in person or via telephone or Zoom to collect the remaining data.

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Table 2. Data collection variables, measures, and psychometrics.

Construct and measures	Psychometrics			
	Baseline	3 mo	9 mo	Reliability and validity
Pre-enrollment screening				
AD8[a]	✓			The area under the curve is 0.908 (95% CI 0.888-0.925)
Biologic				
Age in years	✓			N/A[b]
List of comorbidities	✓			N/A
Measure of health literacy				
Newest Vital Sign	✓			α=.74
Self-care behaviors				
Stress management practices survey part A	✓	✓	✓	α=.71
Healthy Eating Index: Block FFQ[c]	✓		✓	Test-retest reliability, *r*=0.59
DASH[d] index: Calculated from the Block FFQ	✓		✓	The mean correlation coefficient between frequencies of intake of 55 foods assessed by 2 FFQ 12 months apart=0.57
Medication list and BP[e] log	✓	✓	✓	C statistic=0.704
Krousel-Wood medication adherence	✓	✓	✓	C statistic=0.704
Systolic and diastolic BP	✓	✓	✓	κ=0.68
Stress reactivity or resilience				
Daily inventory of stressful events	✓	✓	✓	κ ranged from 0.66 to 0.95
Pittsburgh Stress Battery	✓	✓	✓	Heart rate α=.93; systolic BP α=.92; and diastolic BP α=.93
Stress or QOL[f]				
Perceived Stress Scale (caregiver stress)	✓	✓	✓	α=.83
Folkman 1 question regarding what is most stressful	✓	✓	✓	α=.83
Discrimination in the health care setting consists of 7 questions on a Likert scale to measure the stress of discrimination in the health care setting as a result of age and ethnicity	✓	✓	✓	α=.89
Hair cortisol (chronic stress proxy)	✓		✓	Correlation with 30-day saliva (*r*=0.42, *P*=.04)
WHO-5[g] (QOL)	✓	✓	✓	Sensitivity 0.93; specificity 0.83
Depression-PHQ-9[h]				
PHQ-9 has 9 questions to evaluate mild, moderate, or severe depression	✓	✓	✓	PHQ-9 α=.90
Generalized anxiety disorders				
GAD-7[i] is a 7-item instrument that is used to measure or assess the severity of generalized anxiety disorder	✓	✓	✓	GAD-7 α=.92
Revised memory and behavior checklist				
32-item checklist that assesses activities of daily living and problem behaviors in people living with ADRD[j]	✓	✓	✓	α=.84
Credibility				
The credibility scale has 5 questions		✓		α=.86
Acceptability				
Acceptability of participant preferences has 13 questions		✓		N/A

[a]AD8: 8-item Informant Interview to Differentiate Aging and Dementia.

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[b]N/A: not applicable.
[c]FFQ: Food Frequency Questionnaire.
[d]DASH: Dietary Approaches to Stop Hypertension.
[e]BP: blood pressure.
[f]QOL: quality of life.
[g]WHO-5: World Health Organization-5.
[h]PHQ-9: Patient Health Questionnaire-9.
[i]GAD-7: Generalized Anxiety Disorder Assessment.
[j]ADRD: Alzheimer disease and related dementias.

Pre-Enrollment Screening

We will screen potential participants using the Informant Interview to Differentiate Aging and Dementia. The survey is a dementia screening interview that differentiates typical signs of aging from dementia [42]. The instrument contains 8 items to examine memory, orientation, judgment, and function. The instrument demonstrated strong discrimination in a validation study (area under the receiver operating characteristic [ROC] curve=0.834) [42]. A score of 2 or greater indicates that cognitive impairment is likely present.

Biologic

Age in years and a self-reported list of comorbidities will be obtained at baseline.

Measure of Health Literacy

At baseline, we will administer the 6-item Newest Vital Sign (Pfizer Inc) to assess functional health literacy [43]. The data collector will ask the participants to read a food label for a pint of ice cream. Then, participants will be asked questions regarding serving size, calories, carbohydrates, saturated fat, and food allergies. Scores range from 0 to 6, with lower scores indicating lower health literacy. Scores of less than 4 indicate the possibility of the respondent experiencing low literacy. The scale was initially validated in a sample of 492, including English- and Spanish-speaking adults residing in the United States. Our study will use the English version of Newest Vital Sign that has adequate internal consistency (α=.76) and excellent discrimination (area under the ROC curve=0.88) [4].

Self-Care Behaviors

Four measures will be used to assess self-care. First, the stress management practices will be measured using the Measure of Current Status (MOCS) Part A [44]. MOCS is a list of 13 statements, such as “I am able to use muscle relaxation techniques to reduce any tension I experience,” to which participants respond using a Likert scale (0=I cannot do this at all to 4=I can do this extremely well). This scale also has 4 subfactors: relaxation, awareness of tension, having needs met, and coping confidence. Scores will be summed and range from 0 to 52, with higher scores indicating a more significant use of stress management strategies. Reported internal consistency (α) across MOCS Part A was .71, .77, .86, and .89 [44].

Second, the Block Food Frequency Questionnaire will be used as a validated measure with a food and beverage list that includes 127 items, plus supplementary questions to adjust fat, protein, carbohydrate, sugar, and whole grain content. The questionnaire also includes self-reported physical activity [45]. The questionnaire assesses the frequency with which the respondent generally consumes each food or beverage. It has 9 continuous responses ranging from “never” to “every day” for most foods. The Block Food Frequency Questionnaire provides a Healthy Eating Index score for diet quality (range 0-100) [46]. The DASH index will be calculated using the resulting data and a quintile system to score foods related to the DASH diet. All components are equally weighted. Vegetable, fruit (including fruit juice), nuts and legumes, and whole grains intake are scored from 1 (lowest quintile) to 5 (highest quintile). The overall DASH component scores range from 8 to 40.

Third, we will obtain a list of medications from participants. Finally, the Krousel-Wood Medication Adherence scale captures 4 domains of medication adherence behavior. It was developed to identify low adherence to medication refills in older adults [47]. The scale has reported adequate discrimination (area under the ROC curve=0.704). Scores range from 0 to 4, with a score of 1 or greater indicating lower adherence to medication refill behavior.

Stress Reactivity or Resilience

Systolic and diastolic BP is measured 3 times, starting with a 5-minute rest [35]. Stress resilience and reactivity will be assessed using 2 measures. First, the Daily Inventory of Stressful Events was identified from the Science of Behavioral Change research network list of instruments recommended to assess stress reactivity or resilience**.** The instrument is a semistructured interview in which participants report whether specific stressful events had occurred within the past 24 hours. This instrument categorizes scores for each reported stressful event by examining (1) content classification of the stressor, for example, work overload, argument over housework, or traffic problem; (2) who was the focus of the event; (3) threat type experienced (eg, loss, disappointment, or frustration); (4) objective and subjective severity of stressors; and (5) primary appraisals (eg, areas of life that were at risk because of the stressor). Scores range from 0 to 27. This instrument will be distributed and the data will be collected via an automated text link from the Mosio app. Research staff will call participants who prefer not to use Mosio to deliver the inventory daily to gather the data. Second, the Pittsburgh Stress Battery is a test of stress reactivity. It measures BP response during stressful tasks. The tasks include the Stroop color matching test, mirror tracing, and mental mathematics. For example, during the mental math task, participants will be given 3 trials of fundamental arithmetic problems lasting 1 minute per trial. Participants who score 60% or greater will advance to the random-medium level; those who do not will repeat the easy level. Before the third trial, the data collector

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will place the BP cuff on the participant's left arm unless contraindicated. At the 30-second mark of the third math trial, the data collector will use an automatic BP machine (clinician grade) to measure systolic BP, diastolic BP, and heart rate. CN is a neuropsychologist who will assist in the interpretation of data. The Pittsburgh Stress Battery was identified as a valid measure of stress reactivity by the Science of Behavior Change Research Network [48].

Stress or QOL

We will use the Perceived Stress Scale, which has 10 items rated on a Likert scale with a reference range of 0-40 regarding stress over the past month, with higher scores indicating higher stress [49]. The scale was validated across 3 samples, 2 made up of college students and 1 from a smoking cessation program. Internal consistency across the 3 samples was 0.84, 0.85, and 0.86. Further, the scale correlated well with measures of stress symptoms (correlations ranged from 0.52 to 0.76), and the measure is appropriate for multiple applications. The Everyday Discrimination Stress in the Healthcare Setting Survey is a 7-item scale adapted for use in a medical setting from the Everyday Discrimination Scale [50]. The survey questions load to a single factor [51]. Using this scale, we will examine the respondents' experiences and frequency of race-based mistreatment while accessing health care. The scale has a reported internal consistency of α=.89 and a test-retest reliability of 0.58. Further, the scale correlates well with the Krieger Experiences of Discrimination (r=0.51), a measure of societal discrimination.

Hair cortisol will be used as a proxy for chronic stress. To collect the hair samples, approximately 25-75 mg of hair (approximate width of shoelace tip when bunched) will be cut from the posterior vertex region of the scalp as close to the scalp as possible. The posterior vertex has the lowest variation in cortisol levels, making it the preferred area for sampling. To prep for assay, the hair sample is cut, washed twice with isopropanol, and dried over 1-3 days. A total of 10-75 mg of hair is placed into a microcentrifuge tube, minced, and then ground in a Retsch 400 Mill. A total of 1.1 mL of high-performance liquid chromatography–grade methanol is added to the ground sample and incubated for 18-24 hours at room temperature with constant agitation. The tubes are centrifuged at 5000 g for 5 minutes at room temperature to pellet the powdered hair. The entire amount (~1 mL) of supernatant is transferred to a clean microcentrifuge tube, and the methanol is removed by evaporation using a stream of air for 6-8 hours at room temperature. The cortisol extract is reconstituted in 100 µL of Salimetric immunoassay cortisol analysis diluent buffer. Samples are assayed in duplicate inter- and intra-assay coefficients of calculated variation. Hair cortisol levels are expressed in hair as picogram per milligram and generally logged due to skewed distributions as needed. Participants will be surveyed on corticosteroid use, as these medications may suppress cortisol levels, and hair care practices, such as frequency of washing, chemical treatments, and hair product use [52]. Hair samples will be collected at baseline and 9 months.

We will use the World Health Organization-5, a short questionnaire consisting of 5 Likert scale statements of well-being over the past 2 weeks [53]. Scores range from 0 to 25, with higher scores indicating greater well-being. The measure is adapted from more extended versions (10 items and 28 items) and is approved for use in diverse populations by the World Health Organization [53].

Depression and Anxiety

The Patient Health Questionnaire (PHQ-9) is a widely used measure of depression symptoms and severity. The questionnaire's 9 items describe conditions that the respondent may be experiencing and how frequently they experience those specific conditions. Each item is scored on a scale of 0-3, with 0=not at all and 3=nearly every day. Items are summed with total ranges of 0-27; scores of 5-9 are mild depression, 10-14 are moderate depression, 15-19 are moderately severe depression, and 20 are severe depression. The measure was initially validated by administering the questionnaire to 6000 patients in 15 clinics [54]. The PHQ-9 demonstrated 88% specificity and 88% sensitivity for a score ≥10. The Generalized Anxiety Disorder Assessment (GAD-7) is based on 7 items scored from 0 to 3. Like the PHQ-9, the GAD-7 asks respondents about the frequency of feelings and behaviors, with 0=not at all and 3=nearly every day. The score is then summed up with totals ranging from 0 to 21, with cutoff scores for mild, moderate, and severe anxiety symptoms being 5, 10, and 15, respectively. The GAD-7 was tested in a sample of 1184 patients and demonstrated strong reliability with both internal consistency (α=.92) and test-retest (0.83) [55].

Memory and Behavior

The Revised Memory and Behavior Problems Checklist assesses the psychological comorbidities of the caregiver and the health status of the person living with ADRD [34]. It consists of 24 items that evaluate activities of daily living and problematic behaviors in people living with ADRD. Factor analysis has 3 distinct subscales related to memory, depression, and disruptive behavior. Scores range from 0 to 96, with higher marks indicating more behavioral problems in the care recipient. Overall, the measure demonstrated good internal consistency (α=.84), with subscale internal consistency ranging from 0.67 to 0.89.

Feasibility and Acceptability

We will track the feasibility of recruitment by counting the number of participants screened per month, the number who are eligible, the number enrolled per month, the average time delay from screening to enrollment, and the completion of data collection [56]. We will track treatment-specific preference ratings (pre- and postintervention) for acceptability. The participants will complete the Acceptability of Participant Preferences 13-item Likert-type survey ranging from 1 (strongly disagree) to 5 (strongly agree). Interventionists will keep detailed intervention session records describing participant responses to the intervention. For the MIM DASH group, we will collect data regarding the usage of self-care equipment (home BP monitor and MyPlate) from follow-up coaching calls. We will use a credibility scale for both groups regarding the expectation of benefits of this study. The Credibility Scale (α=.86) measures attitudes toward the treatment condition and the participants'

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expectation of benefit once the treatment has been explained [57,58]. The scale consists of 5 questions rated 0 (not at all confident) to 10 (very confident). Higher scores, up to 45, will indicate greater credibility of the treatment condition. This will also aid in determining participants' willingness to be randomized for future studies.

Data Analysis Plan

To assess data quality, we will check biweekly data for completeness, accuracy, timeliness, and consistency. These checks will be completed by examining frequencies and descriptive statistics, summarizing participant characteristics, and examining variable distributions. Once identified, data anomalies will be fully investigated, and remediation strategies will be considered as appropriate.

We acknowledge potential confounders, such as health literacy and problem behaviors that the care recipient exhibits, that could influence participation in the intervention and outcomes. As this study's sample size is small, we are limited in the number of covariates that can be used in the analysis. Therefore, we will control for the participant's health literacy and the participant's report of problem behaviors of the care recipient.

To address aim 1, determining the feasibility and acceptability of MIM DASH and caregiver training for African American female caregivers with hypertension, we will conduct descriptive data analyses to report findings related to feasibility and acceptability. These analyses will include a summary of participant background characteristics, including age, educational attainment, relationship to the individuals they care for, and baseline health measures. Descriptive analysis will include frequency counts and percentages for categorical variables and mean, median, range, and SD for continuous variables.

Next, we will use descriptive statistics to examine the feasibility and acceptability of the MIM DASH intervention and caregiver training, including (1) the approach-to-enrollment ratio, (2) the proportion of participants that complete all 8 sessions of the assigned intervention arm and attention control arm, (3) frequency of completion of the follow-up calls, and (4) proportion of sessions that the interventionist deviates from the delivery of the intervention protocol. Further, we will report the mean rating of the MIM DASH intervention from participants and the proportion of participants rating the MIM DASH intervention positively (4 or above). We will report point estimates along with 95% CIs to indicate the precision of these estimates. Based on our previous experience enrolling African American participants in studies, feasibility will be defined by (1) enrolling at least 40% of potentially eligible patients and (2) completing at least 75% of the assigned intervention. Acceptability will be determined by an average rating of 4 or higher and at least 80% of participants rating the intervention positively.

To address aim 2, comparing the influence of MIM DASH on caregiver stress and QOL with the influence of caregiver training, we will conduct an intention-to-treat (ITT) analysis. Thus, all outcomes for enrolled participants will be included regardless of the intervention dosage. The Perceived Stress Scale will be used to measure caregiver stress, and the cortisol level extracted from hair will be a proxy measure of chronic stress. The World Health Organization-5 will be used to measure QOL. The data will be collected in person and documented in REDCap at baseline and 3 and 9 months after the intervention. Descriptive statistics, including mean and SD, will be used to summarize each primary and secondary outcome. We will also report mean differences, 95% CIs, and effect sizes for both within- and between-group differences at each visit. The fixed effect of MIM DASH intervention will be examined by mixed-effects models with measurements nested within persons.

To address aim 3, investigating the potential mediation effects of stress reactivity or resilience between each program and self-care behaviors, we will conduct a mediation analysis with self-care as the outcome (y), participation in MIM DASH as the predictor (x), and stress resilience or reactivity as the mediator (m). We hypothesize that heightened stress reactivity will diminish the relationship (between x and y). In contrast, heightened stress resilience will enhance the relationship between MIM DASH (x) and adopting self-care behaviors (y). To quantify these variables, we will use the Daily Inventory of Stressful Events and the Pittsburgh Stress Battery to measure stress reactivity or resilience. Self-care behaviors will be calculated using the Stress Management Practices survey and the DASH eating index by the Block Food Frequency Questionnaire. The data will be collected in person and by online surveys at baseline and 3 and 9 months after the intervention. We will report descriptive statistics for each of the measures. Finally, we will conduct a mediation analysis to examine if stress resilience or reactivity explains a significant amount of the relationship between MIM DASH participation and self-care behavior. The estimated effects of the mediation and 95% CIs will be reported.

Ethical Considerations

This study has received ethical approval from the Ohio State University Behavioral and Social Sciences institutional review board (IRB; approval 2022B0031) and conforms to the World Medical Association's Declaration of Helsinki requirements. All participants were provided written informed consent before their inclusion.

This study will use descriptive data through surveys and objective measures that include computer tasks while measuring BP, heart rate, and hair samples for cortisol level. The research has minimal risk, as the Ohio State University Behavioral and Social Sciences IRB deemed. There may be no direct benefit to the participant. However, their participation may provide data that will provide insight into ways African American women can reduce their BP and improve their overall health. Autonomy and rights will be given to participants, including the right of refusal at any time, without penalty or loss of benefits to which they are otherwise entitled. If a participant is a student or employee at Ohio State, their decision will not affect their grades or employment status.

The consent and study staff will also describe the use of Mosio for 2-way communication via text messaging. The restricted website associated with Mosio will contain the participant's cell phone and study ID numbers, which the designated study

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staff member assigns. The participants can choose not to use the Mosio system at any time. Participants will be informed that there are no costs related to participation. They will not incur any additional charges related to text messages to and from Mosio over and above what they normally have.

All participants will receive the BP categories flyer from the American Heart Association and be instructed to consult their provider if they have a systolic BP higher than 180 mm Hg or a diastolic BP higher than 120 mm Hg. The participant will be instructed to seek immediate assistance or contact their provider. The data monitoring plan is in place and consists of a physician, nurse scientist, and a biostatistician who will review data and any unexpected events at least once per year. Participants will receive US $50 after completing each data collection point, including the home BP monitor, for a total of US $150.

Study staff will be carefully trained to protect participant confidentiality. They will work with participants to devise a plan for contacting them by phone, email, text messaging, or some other means determined by the participant and decide if messages may be left. Participants will be assigned a study ID number, and a master log will be created associating participant names and study numbers. The master log will be stored separately from the College of Nursing's secure server. Only the primary investigator and designated study staff will have access to the master log, which will be destroyed at the end of this study. Study staff's access to study data will be determined based on the relevance to their responsibilities. Only aggregate data will be reported for the dissemination of study findings. Duo Mobile authentication and Zscaler cloud security are used to access REDCap and the College of Nursing secure server.

To mitigate the risk that participants violate the privacy and confidentiality of others in their group sessions, we will ask that those participants (and their family or support person) refrain from discussing with other participants outside the group. Likewise, they will be asked not to acknowledge meeting if they encounter each other elsewhere. These steps are not foolproof, and participants will be informed of the associated risks at the time of consent.

Results

The study was approved by the IRB in April 2022 and funded in May 2022. The first data were collected in January 2023, and the last data were collected in September 2024. Participants were recruited beginning in February 2023. Intervention delivery commenced in April 2023 for the first cohort and November 2023 for the second cohort. Completion of data analysis for all aims is anticipated in spring 2025. A CONSORT (Consolidated Standards of Reporting Trials) flow diagram is presented in Figure 2.

Of the 28 individuals enrolled, 82% (n=23) and 92% (n=26) completed the 3-month and 9-month data collection, respectively. Two participants were lost to follow-up. The mean age of the participants was 62.4 (SD 7.98) years. Eighteen participants were included in the first cohort, and 10 were included in the second cohort.

The participants had a mean systolic BP of 128 (SD 19) mm Hg and diastolic BP of 79 (SD 10) mm Hg. The Newest Vital Sign (health literacy) screen had a mean score of 4.08 (SD 4.5), with a reference range of 0-6 where lower scores indicating lower health literacy. and The Perceived Stress Scale had a score of 12.75 (SD 6.7), with a reference range of 0-30 where higher scores indicating greater stress. Most participants reported that MIM DASH was acceptable (at a mean score of 59.08, SD 7.38, compared to 60.83, SD 5.56 for caregiver training). Regarding feasibility, as reflected in attendance, MIM DASH participants had a mean attendance of 6.3 (SD 2.3) sessions, and the caregiver training group had 4.9 (SD 2.9) sessions.

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Figure 2. CONSORT flow diagram illustrating participant progression through the eligibility, allocation, follow-up, and final analysis stages of the clinical trial. CONSORT: Consolidated Standards of Reporting Trials; DASH: Dietary Approaches to Stop Hypertension; ITT: intention-to-treat analysis; MIM: Mindfulness in Motion.

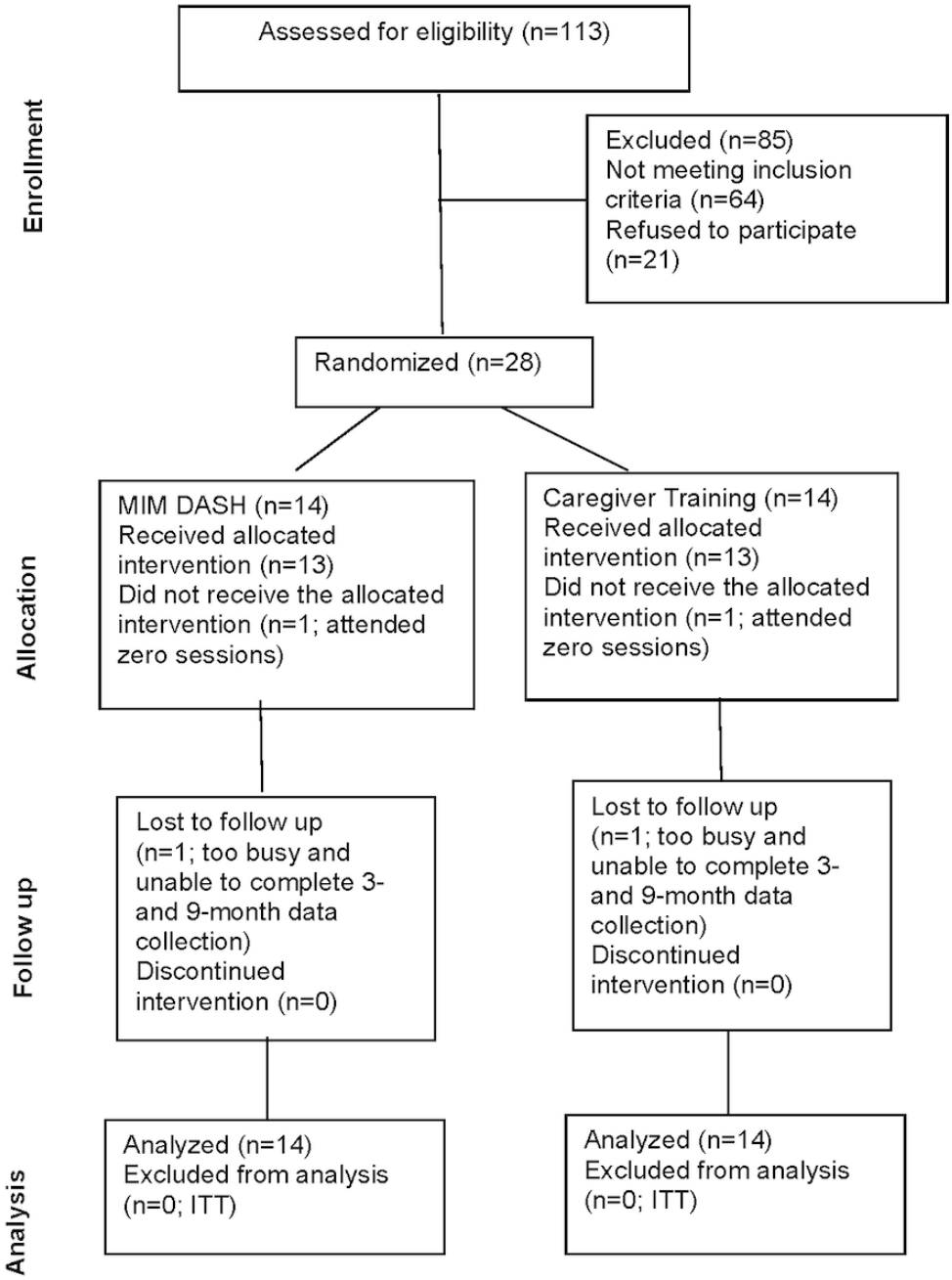

Discussion

Principal Findings

This paper presents a protocol to deliver a culturally responsive mind-body intervention (MIM DASH) specifically designed for African American women who have hypertension and are family caregivers of individuals living with ADRD. We hypothesize that the MIM DASH intervention will be feasible and acceptable, reduce stress, and improve QOL for African American female caregivers. Additionally, we explore behavioral change mechanisms, stress reactivity, and stress resilience that may explain how self-care is adopted or not, which can inform future studies. We hypothesize that lower stress reactivity and higher stress resilience will result in higher adoption of self-care behaviors. Although numerous studies support self-care behaviors (eg, mindfulness practice, healthy eating, and physical activity) to prevent cardiovascular disease—a complication of uncontrolled hypertension [59]—gaps remain in targeting interventions to address the complex interplay of caregiving stress and adoption of healthy self-care for African American female family caregivers of individuals living with ADRD. The findings from this study may contribute to developing and disseminating culturally responsive interventions to improve self-care behaviors and augment the treatment of hypertension and other cardiovascular disease risk factors.

Our principal finding thus far—that MIM DASH is feasible and acceptable—is similar to other studies that have used

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mindfulness as an intervention for stress and to promote healthy dietary habits [60-62]. Unlike previous interventions that lack cultural responsiveness or sufficient representation of African American participants, MIM DASH focuses on African American caregivers. This culturally responsive intervention integrates evidence-based approaches such as DASH and mindfulness, offering 8 weekly sessions focusing on healthy eating and stress reduction. The intervention also builds upon prior research but addresses critical gaps in cultural relevance and participant diversity. For example, noncaregiver studies on cardiovascular disease risk reduction, such as those promoting physical activity and healthy eating, often exclude culturally responsive strategies or include remarkably few African American participants, reducing their applicability to African American caregivers [59,60,63]. MIM DASH addresses these limitations by offering a potentially scalable, tailored approach that acknowledges this population's cultural and systemic barriers.

Limitations of This Study

This study will examine the feasibility and acceptability of the MIM DASH intervention in African American female caregivers of individuals living with ADRD. However, this protocol may have some limitations. The small sample size is a notable limitation, which may restrict the generalizability of the findings. Re-evaluation of inclusion criteria, including only those with a diagnosis of hypertension and those on an antihypertensive basis, may be too restrictive, making this study less generalizable. The multiple measures for data collection and the use of the Pittsburgh Stress Battery as measures of stress and resilience may increase the risk of burden and missing data. Although the Pittsburgh Stress Battery provides a standardized means of cardiovascular reactions to acute stress, it is limited in assessing chronic stressors. The limitations of using the Pittsburgh Stress Battery inventory include time to administer the test, challenges of internet connectivity to access the mirror test, and the cost of materials for administering the test. Other measures, such as heart rate variability, would burden participants and data collectors less [48]. Additionally, other theoretical mechanisms of behavior change, such as self-regulation (temporal discounting of immediate small rewards over larger future rewards) and interpersonal and social processes (social interactions), could be used as the facilitators of behavior change. Given that the MIM DASH intervention was delivered in a group setting and includes elements of self-regulation through mindfulness practice, future studies may consider exploring other, less costly mechanisms of behavior change.

Future studies with more extensive and diverse samples will be necessary to validate and scale the intervention. Furthermore, while this study aims to evaluate feasibility and acceptability, long-term outcomes such as sustained behavior change and clinical improvements in hypertension management remain unexplored.

Future Directions

The findings of this study will be disseminated to this study's participants in the form of a brief report or newsletter that will be submitted for approval to the Ohio State University IRB. Additionally, presentations will be given to the local African American community, churches, and Alzheimer's disease support groups. The findings will be disseminated to the scientific community using multiple strategies, such as presentations at the Gerontological Society of America, the Alzheimer's Association International Conference, and nursing and interprofessional peer-reviewed journals. By disseminating our study findings via traditional (researchers) and nontraditional (community), we will contribute to the science of behavior change and ADRD research for African American caregivers with hypertension.

To prepare for scalability, we will evaluate the delivery of the intervention from the facilitators' perspective to determine what worked well and what needs to be refined. We are refining the training materials and facilitator fidelity monitoring for a larger trial. Data from the pilot feasibility study will help to inform the sample size for efficacy testing. To scale up, we will include additional measures of self-care management and behavioral change, such as actigraphy. We will use a framework such as Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM), which provides a guide for evaluating the reach, effectiveness, adoption, implementation, and maintenance within the objectives of a larger randomized controlled trial [62]. If efficacy is successful, then using such a framework as RE-AIM would position the work for real-world implementation. Funding for the efficacy trial will be sought through grants from the National Institute on Aging or nonprofit organizations such as the American Heart Association, Alzheimer's Association, or Bright Focus.

Conclusion

The burden on African American dementia caregivers is expected to rise alongside the aging US population. Addressing the health of these caregivers is paramount to sustaining effective care for individuals with ADRD. The MIM DASH intervention represents a step toward providing culturally responsive hypertension self-care strategies for African American caregivers. This protocol sets the stage for improved caregiver health and contributes to the growing body of research on tailored interventions that address health disparities in minority populations.

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Data Availability

The datasets generated and analyzed during this study are not publicly available but are available from the corresponding author upon reasonable request. Data sharing will comply with ethical guidelines and any applicable regulatory requirements.

Authors' Contributions

KDW, IKRA, MDK, and KMR designed the study. NPH contributed to the statistical planning and analysis. KDW, IKRA, NPH, SPB, NP, BK, and MDK contributed to the writing of the paper. All authors (KDW, IKRA, NPH, KMR, KOM, DN, NP, BK, SPB, CN, DA, and MDK) reviewed and edited this paper before submission. All authors have read and agreed to the published version of this paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review reports by the MESH - Biobehavioral Mechanisms of Emotion, Stress and Health Study Section (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 152 KB - resprot_v14i1e66975_app1.pdf]

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Abbreviations

ADRD: Alzheimer disease and related dementias
BP: blood pressure
CONSORT: Consolidated Standards of Reporting Trials
DASH: Dietary Approaches to Stop Hypertension
GAD-7: Generalized Anxiety Disorder Assessment
IRB: institutional review board
ITT: intention-to-treat analysis
MIM: Mindfulness in Motion
MOCS: Measure of Current Status
NIA: National Institutes on Aging
PHQ-9: Patient Health Questionnaire-9
QOL: quality of life
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
REDCap: Research Electronic Data Capture
ROC: receiver operating characteristic

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Protocol

Escape Game to Promote Students' Mental Health Outcomes in the Aftermaths of COVID-19 Pandemic: Protocol for a Mixed Methods Study Evaluating a Cocreated Intervention

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Abstract

Background: The COVID-19 pandemic and the protracted lockdowns have heavily impacted university students' mental health. Digital Escape Games represent a good means to reach students and propose them solutions for their psychological well-being.

Objective: This study aimed to evaluate a cocreated digital Escape Game on students' mental health in the aftermath of the COVID-19 pandemic, called EscapeCovid Game. The evaluation of the effectiveness of this stand-alone intervention concerns mental health outcomes (mental health literacy, appraisal and change of beliefs about mental health, management of emotions, and development of coping strategies) and the appreciation and relevance of the game.

Methods: A randomized controlled trial with pre- and posttest data collection (online questionnaires with validated scales) is conducted among 500 students in Bordeaux, France, to evaluate the EscapeCovid Game cocreated with students, researchers, health professionals, and web developers. A subsample of students is randomly selected for responding to a semistructured interview following a mixed methods design. Recruitment is done through mail invitations from student associations and presentations in university classes. Half of the sample of the trial plays the Escape Game, while the other half receives an email with mental health–related information. Within the game, students discuss their personal experiences. The text is further used for the qualitative analyses. The whole study is carried out online.

Results: The EscapeCovid Game has been developed, tested, and finalized by the end of March 2023. As of November 4, 2024, a total of 191 students have answered the baseline questionnaire (90 intervention vs 101 control). A total of 23 students have played the game and 53 are in the control arm. Among participants, by the end of September 20, 2023, twenty were interviewed (10 intervention and 10 control) reaching sample saturation. According to preliminary results, the EscapeCovid Game has had a positive impact on all defined outcomes, while the email has been effective in increasing knowledge on resources available and on coping strategies and meditation techniques. We expect the trial to be completed by the end of June 2025.

Conclusions: The mixed methods findings of this study are due to demonstrate the effectiveness of the EscapeCovid Game in improving students' mental health outcomes. Preliminary results from the qualitative substudy are promising: in the aftermath of the COVID-19 crisis, this intervention is intended to promote players' mental health through gamification, knowledge transfer, and a learning-by-doing approach.

Trial Registration: ClinicalTrials.gov NCT06720792; https://clinicaltrials.gov/study/NCT06720792

International Registered Report Identifier (IRRID): DERR1-10.2196/64068

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KEYWORDS

Escape game; pilot randomized controlled trial; Covid-19; cocreation; students; mobile phone

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Introduction

Background

Mental health problems among young people have skyrocketed with the COVID-19 crisis [1]. Repeated lockdowns and curfews between 2020 and 2021 were the causes of a general mental distress well-documented in the literature [2]. These measures had detrimental and long-lasting psychosocial consequences like acute stress and trauma-related disorders, particularly in specific at-risk populations such as students [3].

University students were in fact concerned as a vulnerable population. Independently from the presence of a pandemic, suicide is the second leading cause of death among them and, by the age of 25 years, 75% of those who will have a mental health disorder have had their first onset [4,5]. During the COVID-19 crisis, students were exposed to supplementary heavy stressors: isolation, classes exclusively online, and uncertainty about their academic and professional future. Several studies have shown how the COVID-19 pandemic and its lockdowns had negatively affected students' mental health across the world [6,7]. Therefore, it is fundamental to implement mental health promotion and prevention interventions aimed to support students during this crisis. Evaluation of these interventions is a pivotal process in public health research to determine their effectiveness and improve their quality in relation to the targeted population [8].

Among innovative interventions, Escape Games are "live-action team-based games where players discover clues, and solve puzzles [...] in order to accomplish a specific goal, usually escaping from the room, in a limited amount of time" [9]. Escape Games are the digital internet-based online version of Escape rooms. Previous research has proved that Escape Games can increase knowledge on health-related topics using the learning-by-doing technique [10]. Furthermore, gamification is based on a learning by making mistakes approach. Related flow theory states that simple simulation can be perceived as more anxiety-provoking than the purely playful approach which integrates error as a dynamic element.

Compared with other interventions, they are supposed to be more attractive and acceptable for a young audience, especially because of their gamification approach. Gamification relies on immersion through which players feel embedded in the game as several psychosocial determinants (eg, social support, environment) are leveraged. In particular, health-related Escape Games use puzzle solving as a strategy to access health promotion and prevention messages. The step-by-step sequencing and the resolution of the enigmas stimulate the learning loop and over-solicit the cognitive capacity of participants (ie, better awareness of the concerned topic, and better capacity to deconstruct one's beliefs).

Escape Games can contribute not only to increasing knowledge, but also to behavioral change by providing instruments to act in real-life. For instance, by relying on teamwork, participants can develop the notion of mutual support which could be transposed to their communities. Thus, individual and collective behaviors are at stake. The positive outcomes of Escape Games are boosted by their digitalization: through the internet, Escape Games can reach a larger audience with no time or space limit. This should be even more promising in a period where face-to-face contact is very limited. Success of these interventions can also be fostered if they are cocreated with the target population through a design thinking approach (ie, understanding of users' experience and needs, brainstorming sessions with several stakeholders, and testing of the tool). Cocreation is a collaborative approach offering various benefits such as enriched insight into problems and increased feasibility and acceptability [11]. We applied this approach to produce the EscapeCovid Game, a stand-alone intervention to promote mental health and prevent psychological diseases among university students in the era of COVID-19.

The EscapeCovid Game

The EscapeCovid Game is focused on four main outcomes: (1) mental health literacy (knowledge of the concept of mental health, from illnesses to psychological well-being), (2) appraisal and change of beliefs about mental health (destigmatization), (3) management of emotions (their recognition and regulation), and (4) development of coping strategies (building resilience). It addresses specifically anxiety and depression whose symptoms were exacerbated by the COVID-19 crisis including the measures undertaken to limit the spread of the virus (eg, repeated lockdowns and curfews, University closure).

The underpinning theories of the game are the COM-B model of behavior (capability, opportunity, and motivation to change behavior) [12], the Plutchik's wheel of emotions (visualization of emotions to change behavior) [13], and the Transtheoretical model of behavior change (stages of change, processes of change, levels of change, self-efficacy, and decisional balance [14]).

The EscapeCovid Game takes place in Thomas' apartment which he shares with another student, Hana. Thomas is a university student and we follow him during a typical day in lockdown. To move from one room to another, players must solve all the puzzles by clicking on the objects spread out in Thomas' room. At the end of each room scenario, a set of cards is shown, with each card containing a mental health-related message. The cards synthesize the messages transmitted through the puzzles in the room.

The game can be played in groups of 4 players who help each other and discuss using their computer cameras and headphones. All along the game, they are helped by a game guide who explains the rules and answers any questions. The same guide concludes the game session with a final debrief where all participants share their experiences.

The EscapeCovid Game has been cocreated jointly by a team of researchers at the University of Bordeaux and a start-up specialized in the production of both physical and digital Escape Rooms, Tricky, in France. We used the PRODUCES (Problem, Objective, Design, End Users, Cocreators, Evaluation, and Scalability) framework [15] composed of 3 steps. First, we tested the hypothesis that the game was effective in promoting the four mental health-related outcomes. Second, we

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accumulated evidence on the good functioning of the game. Third, we leveraged the right behavior change mechanisms.

Within this framework, the game was cocreated in particular by 1 project manager from a public health research center, 1 student intern completing a degree in cognitive engineering, 1 game designer, 1 developer specialized in computer science, 1 medical doctor, and 1 psychology researcher. Supplementary data to improve the game was provided by 45 questionnaires on the appreciation and relevance of the game by student players, and qualitative semistructured interviews with 10 students of the same sample. The cocreation of the game is detailed in an article by Labrosse et al [16].

Objective and Hypotheses

The objective of this study is to evaluate among a population of university students the effectiveness of the EscapeCOVID Game on 4 mental health outcomes: mental health literacy, appraisal and change of beliefs about mental health, management of emotions, and development of coping strategies. The appreciation and relevance of the game are also considered in the overall evaluation of the game. This stand-alone intervention is implemented in the era of the COVID-19 pandemic.

Consequential research hypotheses of the study are (1) compared with a group receiving another classical intervention, after playing the digital Escape Game and having received a debriefing, students remarkably improve their mental health literacy, appraisal, and change of beliefs about mental health, management of emotions, and development of coping strategies; and (2) cocreation enhances appreciation and relevance of the digital Escape Game among university students.

The objective of this study is original since, to the best of our knowledge, no Escape Game on students' mental health outcomes has been developed before following a cocreation approach and evaluated through mixed-methods to prove its effectiveness.

Methods

Evaluation of the EscapeCovid Game

Mixed Methods Research Design

The EscapeCovid Game is evaluated through a mixed-methods approach using exclusively online data from a Randomized Controlled Trial (RCT) including 2 web-based questionnaires, and video interviewing. Within the mixed methods framework, we apply the embedded design [17]. According to this design, the quantitative and the qualitative data are collected simultaneously, but the qualitative data is embedded within the quantitative data. This means that the data from the questionnaires is prominent, but we still need to understand how the qualitative data further explains the effectiveness of the intervention.

As for the cocreation of the Escape Game, all tasks of the evaluation are conducted jointly by the university research team and the private start-up, thus proving the sharing of skills and the management of potential risks and their solutions in a combined effort. In particular, the research team is in charge of the collection and analyses of the data, while the start-up handles logistics including the organization of the game sessions. The postulate of the start-up is that a product can be really evaluated as significantly efficient in the serious game industry mostly or exclusively through the collaboration with a public research laboratory.

The Randomized Controlled Trial

We implement a rigorous RCT design using pre- and postintervention data coming from online self-administered questionnaires. The sample must be of at least 500 students at the University of Bordeaux. We estimated a sample size of 500 participants for the 2 arms: statistical power=.80, Cronbach α=.05, Cohen d=0.5, and 40% attrition with a 2:1 allocation ratio for the intervention group.

At study entry, the 500 students complete the online baseline questionnaire. Among them, 250 students play the EscapeCovid Game while 250 students receive an email with tips and resources for managing their stress during the COVID-19 pandemic. Participants are randomized so that the 2 groups are similar in terms of sex, age, and field of study (stratified balanced randomization). Participants are informed from the beginning of the study that they can be allocated to either the intervention of interest or the comparator. We tell students in the control arm that they are in a waiting list and that they can play the game once the experiment is concluded.

Inclusion is stopped when at least 500 participants have completed at least 3 quarters of each questionnaire, and 250 have played the game until the end. The statistician and the project manager of the EscapeCovid study are in charge of generating the random allocation sequence, enrolling participants, and assign them to one of the 2 arms.

Briefly, the 250 students of the intervention arm (1) complete the online baseline questionnaire, (2) play the EscapeCovid Game at their home within the week after the online baseline questionnaire—a link to the game is given at the end of the questionnaire, and (3) complete the same online questionnaire of the baseline plus some items on the appreciation of the game (satisfaction survey) 2 days after having played the game. After some tests with Tricky staff, the game duration is estimated at about 2 hours, from the online registration with the creation of an account, until the end of the debrief. Instructions to connect and play online are provided in an email sent by the start-up to the student of the intervention arm 2 days before the game session.

The 250 students of the control arm will (1) complete the baseline online questionnaire, (2) receive the same day an email with tips and resources to manage their stress during the COVID-19 pandemic, and (3) complete the same internet-based questionnaire of the baseline 2 days after having received the email with tips and resources.

Students can complete all steps of the evaluation from anywhere using a smartphone or a computer. However, they can play the game exclusively from home, considering the need for a stable internet connection and a performance computer.

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Internet-Based Interviews

There are two sources of qualitative data: (1) semistructured interviews after the intervention with students from both arms and (2) open discussion with the game guide at the end of the game session. Concerning the first source of qualitative data, 20 students were randomly selected among the 2 groups (10 for the intervention arm, and 10 for the control arm) to respond to a semistructured interview. For the discussion embedded in the game, the text produced during the debrief is recorded and analyzed so that the developers of the start-up can work on an algorithm for building a chatbot messenger capable of providing tailored advice to gamers, replacing the game guide. Machine learning will be used for this purpose. In terms of simplicity and feasibility, the sample is recruited on the sole criterion of sex, 50% of girls, through sample saturation. The interviews have been conducted remotely by a public health researcher through an internet-based interview tool. Students are recommended to make the interview at home.

Recruitment of Study Population

Inclusion criteria are (1) being a student at the University of Bordeaux, (2) being aged ≥18 years, (3) understanding, speaking, and writing French, and (4) having given the electronic consent to be enrolled in the study. We consider that students have a sufficient level of computer literacy for playing the game as only few basic skills are required: knowing how to navigate the web, keyboarding, and typing. These skills are essential for any student from any field of study and represent a prerequisite for the undergraduate and graduate programs at the University of Bordeaux.

Students are invited through the social media of the study partners (University of Bordeaux and Tricky), posts in the Facebook groups of more than 100 student associations, and mailing lists from the University of Bordeaux. The associations are manually selected from a list provided by the University of Bordeaux to cover the different fields of study. Overall, we plan to reach about 10,000 students which is a substantial number considering potential very low enrollment and retention rates. The invitations by email are sent to a maximum of 500 recipients at a time, so that we can proceed step by step with the inclusion of participants and the organization and schedule of the game sessions. The invitations will be sent until we reach a sample of a minimum number of 500 students.

The recruitment is exclusively web-based. Clicking on the link displayed on social media posts or on the text of the email, students will access an online form to enter the study.

The inclusion of participants to the RCT will be conducted based on a continuous monitoring through statistical analysis. Data on sex are available only for males and females, since information on gender is not reported in the University records. The year of study goes from 1 (first year of university) to >8 (corresponding to a doctoral degree or a diploma in medicine). The fields of study offered by the University of Bordeaux are more than 50,000 and are categorized in Health Studies, Law and Economics, Technical Sciences, and Human and Social Sciences.

Finally, a maximum of 5 reminders will be sent through email to all 500 participants for the completion of the second questionnaire. For the intervention group, an additional maximum of 5 reminders will be sent to schedule a game session and eventually play the game. An additional maximum of 5 reminders will be sent to the students randomly selected to be interviewed. If after the 5 reminders per phase of the study, the student does not reply, we will proceed with the invitation of new students from the contacts we have from the University and attached associations.

The participation to the study is completely voluntary and all students are rewarded with a €20 (US $21.59) gift card.

Data Collection Tools

The pre and postintervention questionnaires are administered through the Sphinx software (Georg Brandl) distributing surveys on all media (web, smartphone, QR code, and SMS). The data are automatically imported in a Microsoft Excel file.

The first questionnaire is composed of 112 items. It includes validated scales measuring mental health literacy (French Mental Health Literacy Scale [MHLS-FR]) [18], beliefs about mental health (Health Belief Model [HBM]) [19], emotions (Plutchik's wheel of emotions) [20], Coping Strategies (Ways of coping questionnaire) [21], Depression (Patient Health Questionnaire-9 [PHQ-9]) [22], Anxiety (Generalized Anxiety Disorder-7 Scale [GAD-7]) [23], Stress (Perceived Stress Scale [PSS4]) [24], and Help-seeking actions (Kessler Psychological Distress Scale in help-seeking youth [K6]) [25]. Sociodemographic information (email address, gender, date of birth, field of study, year of study, and self-perceived health) are also collected to assess the representativeness of the sample (stratifications by sex, age, field of study etc). A question specifically asks the gender giving students the possibility to indicate whether they belong to the LGBT (lesbian, gay, bisexual, and transgender) category (considering the confidentiality of this data). The question of gender as a determinant of mental health will be important to analyze the results considering this confounding variable if the number of individuals is sufficient. The questionnaire is developed by several researchers through different stages of drafts and reviews, following a structured survey construction method in 5 steps [26]. Operational staff members from the team of the coordinator and a group of students pretest the questionnaire for readability, comprehensibility, and face validity. The response modalities are varied: multiple choice, binary responses, Likert scales, and visual analog scales. Mental health indicators and appreciation and relevance results are the main outcomes of the study. All items provided the nonresponse option "not applicable," "I don't know," and "I do not want to answer." Respondents are required to select an option from a predefined list. The questionnaire is not validated if at least one question is not answered. Respondents are not able to review and change their answers, but they can ask the principal investigator for a document with exclusively their answers. Corrections cannot be made manually in the database in order to avoid any further error.

The second questionnaire is the same, but it does not include the sociodemographic items. It contains new items on the appreciation and relevance of either the game or the email

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(satisfaction survey). These items are created ad hoc, but are also inspired by existing instruments evaluating digital health interventions (eg, items by Fadda et al [27]). The questionnaires, composed of both validated scales, sociodemographic items, and satisfaction survey questions, have been developed by 1 researcher and 1 project manager in public health. A pool of researchers in psychology and in statistics have reviewed the questionnaire to assess its readability, understanding, and relevance. The questionnaires have been tested on the internet by 10 students of the School of Public Health of the University of Bordeaux. Testers reported some technical errors, that has bugs and repetitions of items, and suggested different wording for making the questionnaires more adapted to a young target population between 18 and 25 years of age. The questionnaires were constructed following the CHERRIES (Checklist for Reporting Results of Internet E-Surveys) [28]. For both questionnaires, outcomes are self-assessed. The questionnaires are available in Multimedia Appendix 1.

Qualitative data from the semistructured interviews are collected through an ad hoc grid including questions on the impact of the game or email on mental health–related knowledge, on the access to mental health care services and the attitudes toward mental illnesses or stigmatization. Participants are particularly asked to evaluate whether the game is adapted to their needs and to discuss the cocreation approach as a means to produce tailored interventions. The main objective of these interviews is to assess the appreciation and the relevance of the game. The interview grids are available in Multimedia Appendix 2.

Questions addressed to the control group allow to capture the utility of the contents of the email (eg, list of mental health care services and a short description of mental health problems) and to compare the contribution of each tool to knowledge about mental health. Qualitative data form the debrief correspond to the free discussion between the players and the game guide. The latter follows a script and makes questions on the specific topics covered by the game: overall recognition and management of the emotions; symptoms of depression, stress and anxiety; relevance of mental health in daily life; and sources available in the case of a mental health problem.

The semistructured interviews were conducted by a public health researcher trained in qualitative data analyses. The project manager analyzed the same dataset using the triangulation approach.

The quality of both quantitative and qualitative data is ensured by keeping documentation accurate, that are clean databases and well-stored texts. Ensuring ethical standards is a further guarantee of the quality of this study.

Data Analyses

Overall Mixed Methods Analyses

First, we will conduct statistical analyses on quantitative data (descriptive statistics, modeling, and exploratory data analysis) processed from the RCT; second, we have analyzed the discourse of qualitative data (thematic analysis based on a predefined interview guide); and third, we will couple the analysis of both types of data. In particular, we will integrate quantitative and qualitative data for the purposes of convergence, contextualization, and expansion to gain a detailed understanding of the evaluation and impact of the game.

Quantitative Data Analyses

For the data from the RCT, we will compare the answers between exposed and nonexposed students (intergroup) and measure the change in their answers within the intervention group before and after playing the game and debriefing (intragroup). Our primary analysis will be based on intention-to-treat at the individual level using linear regression comparing the outcomes of the intervention and the control arm. We will measure our primary outcomes in terms of absolute scores and as a percentage of the total possible score. We will control baseline covariates: (1) gender, (2) age, (3) field of study, (4) year of study, and (5) self-perceived health. We will analyze the data from all participants only if at least 3 quarters of the questions are completed. We consider that some users will not go through all questionnaire pages. Missing values will be imputed by replacing them with the mean or median values of the dataset at large, or some similar summary statistics.

Qualitative Data Analyses

Concerning qualitative data from the semistructured interviews (intervention and control groups), they have been analyzed through content analysis: we have identified patterns across collected texts which are coded according to key elements. These can include, for instance, reported advantages and drawbacks of the game, or players' opinions on the usefulness of the game in general. The semistructured interviews are either video or audio recorded depending on the availability of the participants, during the lunch break or in the late evening after the classes. In-depth analyses were conducted using a reflexive approach so as to appraise and evaluate how subjectivity and context influence the research processes, especially during the interpretation of the data on intimate topics like mental health. Before the association with the quantitative data, the texts will be cross-analyzed to identify similarities and differences between the experience with either the escape game or the email.

Data from the debrief at the end of the game were recorded automatically within the game. The texts were collated in a single document which was used to generate repeated and automated messages. Through artificial intelligence and, more specifically, the machine-assisted topic analysis (MATA), the human conversation will be processed to simulate answers to players' requests. The outcome will correspond to a chatbot, which will a computer program that will be able to animate a discussion and provide tips concerning mental health–related issues.

Ethical Considerations

The study has received the French identifying number (ID-RCB) 2024-A00436-41 from the National Agency for the Safety of Medicines and Health Products. This number is compulsory for registering projects on human subjects in France.

The Ethics and Health Research Center of the University of Bordeaux approved the study (2024-A00436-41). The procedures are in accordance with the Helsinki Declaration of 1975, as revised in 2024.

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It is compulsory that students carefully read the consent form and sign it electronically (by clicking on the “I agree button”) in order to participate to all steps of the study and share their data collected through questionnaires, interviews, and during the game. The consent form includes all the details of the study: (1) principal investigator, (2) rationale, (3) objectives, (4) methods, (5) length, (6) conditions of the storage data and analyses, and (7) expected impact. Students access directly to the consent form when they click on the link in the social media posts and the study invitation email. Participants are given the chance to opt out.

All confidential information, including participants’ contact details or other sensitive data like self-reported mental health status will only be accessible to authorized staff members from the study. Thus, information is quasi-anonymous for the proper running of the study. In fact, the email address is necessary to organize the game sessions, to send the links to the web-based questionnaires and to schedule the internet-based interview. The phone number is also required to resolicit the participants, only once, for the organization of the game session. We guarantee the noncommercial use of the email addresses and the phone numbers.

Overall, participants are informed that they are not blinded.

All data, including the sensitive ones, are imported automatically from the software Sphinx to Excel. The document is protected by a password known only to the principal investigator and the statistician of the research team. The data will be destroyed 2 years after the last article based on this study is published. The collection, storage, and analysis of the data comply with the European General Data Protection Regulation (GDPR).

As already mentioned, students will receive US $21.5 gift cards for their participation to the study. The authors have filled the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) form V1.6.1 (Multimedia Appendix 3).

Results

Key Dates of the Study

The study received funding by the French National Research Agency in January 2022. The production of the EscapeCovid Game ended in March 2023. The cocreation process, the test, and the refinement of the intervention lasted 15 months. For the evaluation of the finalized game, the collection and analyses of qualitative data through semistructured interviews has been completed by September 2023. The end of the evaluation phase through the RCT is scheduled to be completed by the end of June 2025. The results of the mixed methods analyses are expected to be published by the end of December 2025. The timeline of the study is illustrated in Figure 1.

Figure 1. Timeline of the phases of the study.

Study Population

The recruitment started in December 2023.

As of November 4, 2024, a total of 191 students have answered the baseline questionnaire and have been randomly assigned to one of the 2 arms, 90 intervention versus 101 control. A total of 23 students have played the EscapeCovid Game (intervention arm) and 53 are in the control arm. Specifically, 54% (103/191) of the participants at the baseline are students in health care disciplines; 11.5% (22/191) in sciences and technologies; and the remaining participants study other subjects 34.5% (66/191) including psychology, law, and so on.

Concerning qualitative data, 20 students (10 for each arm) have been interviewed on the appreciation, relevance, and acceptability of either the game or the email. Students of the game arm were between 18 and 28 years of age. There were 9 females and 1 male. Their year of study ranged from the first year of their bachelor’s degree to the first year of their doctoral

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studies. Fields of study included medicine, chemistry, physics, biology, sociology, speech therapy, and political science. Students of the control arm were between 18 years and 28 years old. Their year of study ranged from the second year of their Bachelor's to the third year of their doctoral studies. Fields of study included medicine, physics, nursing and marketing.

Preliminary Quantitative and Qualitative Results

As of November 4, 2024, the sample size of the trial is too small for providing robust data and for reaching significance level.

As far as qualitative data are concerned, we completed all 20 interviews. According to the students from the intervention harm, the game was appealing and fun. The use of gamification to communicate mental health-related messages was appreciated.

> *I like the initiative of doing something more fun, more educational than just distributing information, which is also a way in itself, we agree, but I like the way of trying to learn.* [Student 7–Male]

The game was described as "innovative," "unique," "instructive," and "beneficial" considering its alternative approach to conventional public health interventions, for example, educational materials, and social marketing campaigns.

The notion of stigmatization emerged. Attached outcome was the appraisal and change of beliefs about mental health.

> *I found it very interesting that we raise awareness about mental health because I have the impression that it is something that we talk about more than before but there is still a taboo behind it.* [Student 2–Female]

The game also contributed to increase participants' mental health literacy.

> *It gave me knowledge I didnot have about mental health.* [Student 1–Male]

The impact of the intervention on support recognition and management of emotions was also positive.

> *The way in which the symptoms or rather really what the person thinks to themselves are well represented and so it really allows us to understand what is going on in the person's head and also to know the symptoms and emotions. So it's very interesting, rather than just listening to someone talk about it and having a slide, it's much better.* [Student 9-Female]

The other study outcome (teach positive coping strategies) was also reported:

> *Well, you see that I have to do things that finally make us happy and otherwise, not to work too late, to take a break to eat, to see my friends and that's it and from time to time go out when we need to get some fresh air.* [Student 5-Male]

However, the students also declared that the content of the game should be enriched with the presentation of more coping strategies in order to support the player's psychological well-being. Thus, the impact of the intervention should be directly on the mental health of the players and not only on their knowledge and beliefs.

> *Not particularly, I don't think so, it was more focused on knowing emotions rather than how to manage them.* [Student 1-Male]

In comparison to the game, the informative email was not an immersive experience and was not expected to influence students' cognition, affect, potential, and health behavior. However, it provided useful tips to students from the control arm, including the following: a list of existing sources in case of mental health distress (eg, helplines and free-of-charge consultations with a psychology based at the University of Bordeaux); breathing techniques and meditation; and mental health problems explained with accessible but accurate terminology.

> *It gave me knowledge I didn't have, about the numbers to contact in case of need [...] we can't know them all by heart and I think that having them all written down in an email or in a document, well I think that it can help us because not everyone knows where to refer and where to go in case of need.* [Student 1-Male]

The usefulness of the email consisted in the fact that it could be used as a memorandum and repertoire of the basics of mental health literacy: knowing that mental health includes both positive mental health and the absence of a mental health problem; knowing the signs of the most common mental health problems (depression, anxiety, and stress); recognizing and managing emotions; learning coping strategies; and having a list of the most known services in case of a mental health distress.

As of November 4, 2024, data from the game debriefs is not transcribed and cannot be analyzed.

Discussion

Principal Findings

This paper outlines the protocol for the evaluation of a cocreated Escape Game on students' mental health outcomes contributing to prevent and manage mental health diseases and promoting psychological well-being: mental health literacy, appraisal and change of beliefs about mental health, management of emotions, and development of coping strategies. The evaluation is conducted through mixed methods, combining the quantitative results of a RCT with the qualitative results of semistructured interviews.

Concerning quantitative, as of November 4, 2024, the recruited sample is too small to make inferences on the impact of the game. Actually, recruiting students is the hardest challenge of the trial. All along the study, we have observed that the most successful recruitment strategies are: offering gift cards to students completing the whole study (baseline questionnaire, intervention or control arm, and repeated questionnaire); counting on the support of student associations promoting the study among members; and involving professors who present the study during their classes. We will reinforce these strategies to attract and retain students in the trial.

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As for the qualitative data, the recruitment of students was far easier and we rapidly interviewed 20 participants by September 2023. The comparison of the responses across the 2 groups, game versus email, showed that gamification improved the retention of messages, especially in terms of recognition and management of emotions. On the other hand, email was considered useful as a memorandum of mental health–related information. In particular, students appreciated the list of available services that they could keep and save for contacting professionals in case of need.

Based on preliminary results, these 2 distinct tools, the EscapeCovid Game, and the informative email, could prove to be mutually complementary in promoting student mental health. By consolidating the specific advantages of each approach while mitigating their respective limitations, we can aspire to a more holistic and informed approach to strengthening psychological well-being within the student community.

Comparison to Previous Work

Recently, interventional research took an interest in digital games to promote positive well-being and prevent mental health problems. This might be due to the emerging mental health challenges because of the COVID-19 pandemic [29]. A scoping review of 16 articles has identified positive effects of gamified interventions, with beneficial consequences for psychological well-being and depressive symptoms [30]. Three articles focused specifically on university students, but described interventions were gamified mobile or web applications, and did not include Escape Games.

Overall, Escape Games addressed to university students are mostly used as educational tools aimed at guiding learners toward achieving specific learning outcomes through a game-based design [31]. Concerning mental health, the literature reports 1 game addressed to students to improve their knowledge on psychological well-being and mental illnesses, but it is an Escape Room exclusively on site [32].

It is essential to support this population and reinforce their psychological status and resilience since they will be the future workforce. They will especially be in charge of rebuilding the economy of the country after this huge crisis.

Strengths and Limitations

The robust evaluation process of this study will provide evidence of the effectiveness of one of the few digital gamified interventions addressed to students' mental health. This will be among the first promising Escape Games produced jointly by a public university research team and a private start-up. The collaboration between these 2 institutions is an added value guaranteeing that, on the one hand, the intervention is well-designed and functioning, and that, on the other hand, researchers have accurately assessed its performance.

The main strength of the evaluation process in that relies on mixed methods. This approach can balance out the limitations of each method (questionnaires from an RCT and qualitative data from semistructured interviews and game briefing); it can lead to stronger evidence and reliability; and it can provide more details than each individual method. Concerning quantitative data, mixed methods limit straightforward and stereotyped interpretations, and reduce ambiguity and misunderstanding.

On the other hand, the limitations of qualitative data are mitigated by a rigorous quantitative approach: coding of the text in structured interview grids, word-by-word data management, and detailed records of data collection and analysis like in an audit trial [33].

Thus, mixed methods can increase the trustworthiness, transferability, dependability, and confirmability of the thick description of combined quantitative and qualitative data.

This study is primarily limited by the low participation of students and inclusion at the baseline. This might be due to the fact that the game lasts more than 1 hour and requires a good computer operating system, as it is already stated in the interviews. Students' agenda are really busy and their workload is heavy. As suggested, new structured communication strategies would improve the participant recruitment. Furthermore, the inclusion in the study is completely voluntary and, considering that we do not use quota sampling because of feasibility, results may not be generalizable to students in Bordeaux and to French students in particular.

Another barrier is the correct implementation of a complex evaluation through an RCT and mixed methods design with the collection of several data. Researchers involved in the study have renowned experience on this type of methodology and are keen to ensure the smoothness of the evaluation process. As far as technical barriers are concerned, the development of the digital Escape Game has to overcome potential IT challenges. The final product will need to be both high-tech and appealing, mixing solid technology with a modern design and avoiding bugs. IT developers of the start-up of the study have already proven their competencies and skills for that.

Future Directions

If the results of the study show the impact of the intervention on mental health outcomes (mental health literacy, appraisal and change of beliefs about mental health, management of emotions, and development of coping strategies) among students, the game will be commercialized and sold to universities for its deployment on the campuses across France. The evaluation process is meant to guarantee that the game can be diffused with an economically sustainable model defined by the start-up. In particular, this study will help the start-up to define a "gold standard" for selling other similar interventions.

The promising results of the study open the way to crucial questions: how can we secure funding and optimize the economic efficiency of the EscapeCovid Game in order to guarantee its sustainability and make it a mental health promotion tool, accessible to a wide range of students from diverse backgrounds? For instance, using artificial intelligence, it will be possible to make the intervention autonomous with automatized debriefing. This will make the game more sustainable cutting the costs of the salary of the game guide.

Furthermore, who will be the legal owner of the EscapeCovid Game? Intellectual property must be deeply discussed to ensure the shared collaboration of the partners to create the game before

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its real commercialization. In order to overcome any potential disagreement, the roles of all parties must be clearly stated in a business partnership agreement.

Thus, the protocol of this study describes how to evaluate with a robust methodology a game on students' mental health as an example for producing further effective interventions on the same topic. Based on evidence, these interventions can be commercialized through an economically sustainable model.

Finally, this protocol presents a study whose objectives are both research (studying several indicators of young people's mental health during the COVID-19 pandemic)- and business-oriented (producing an evidence-based tool for further deployment).

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Data Availability

The text of fully transcribed interviews is available from the corresponding author upon request. Quantitative data from the first participants to the randomized controlled trial are preliminary and cannot be shared until the study is concluded.

Authors' Contributions

DL and IM conducted conceptualization and writing-reviewing. DL handled investigation. CV managed data curation and writing-original draft preparation. MH performed qualitative data curation and writing—final manuscript preparation. IM handled methodology, investigation, writing—reviewing and editing, and supervision.

Conflicts of Interest

DL is the chief executive officer of the start-up Tricky developing the game described in this paper. Results of the study are totally transparent.

Multimedia Appendix 1
Original Questionnaires for the quantitative evaluation of the EscapeCovid game.
[PDF File (Adobe PDF File), 561 KB - resprot_v14i1e64068_app1.pdf]

Multimedia Appendix 2
Original interview guides for the qualitative evaluation of the EscapeCovid game.
[PDF File (Adobe PDF File), 176 KB - resprot_v14i1e64068_app2.pdf]

Multimedia Appendix 3
CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist.
[PDF File (Adobe PDF File), 2751 KB - resprot_v14i1e64068_app3.pdf]

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Abbreviations

CHERRIES: Checklist for Reporting Results of Internet E-Surveys
COM-B: capability, opportunity, and motivation to change behavior
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
GAD-7: Generalized Anxiety Disorder-7 Scale
GDPR: General Data Protection Regulation
HBM: Health Belief Model
K6: Kessler Psychological Distress Scale
LGBT: lesbian, gay, bisexual, and transgender
MATA: machine-assisted topic analysis
MHLS-FR: French Mental Health Literacy Scale
PHQ-9: Patient Health Questionnaire-9
PRODUCES: Problem, Objective, Design, End Users, Cocreators, Evaluation, and Scalability
PSS4: Perceived Stress Scale
RCT: randomized controlled trial

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Protocol

Comparison of Smart Display Versus Laptop Platforms for an eHealth Intervention to Improve Functional Health for Older Adults With Multiple Chronic Conditions: Protocol for a Randomized Clinical Trial

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Abstract

Background: Maintaining functional health, or the ability to live independently, is a primary goal of individuals as they age, but most older adults develop chronic conditions that threaten this goal. Physical activity is a key aspect of self-care that can improve functional health, and digital interventions offering guidance on appropriate exercise can help. However, older adults with multiple morbidities may be unable to use a laptop or smartphone-based eHealth because poor vision, dexterity, mobility, or other physical challenges make typing or touch navigation difficult. A smart display platform—comprising a smart speaker plus a small visual screen—has the potential to remove these barriers because it is voice-activated.

Objective: The study aims to compare usage patterns of an eHealth intervention for older adults when delivered via a voice-based smart display versus a typing-based laptop, and assess whether the smart display outperforms the laptop in improving functional health and its specific physical and mental aspects.

Methods: A minimum of 356 adults aged 60 years and older with at least 5 chronic health conditions are to be recruited from primary care clinics and community organizations. Participants will be randomized 1:1 to 12 months of access to an evidence-based intervention, ElderTree, delivered on either a smart display or a touchscreen laptop, with a postintervention follow-up at 18 months. The primary outcome is differences between groups on a comprehensive measure of physical and mental functional health. Secondary outcomes are between-group differences in the subscales of functional health (eg, physical function and depression), as well as measures of health distress, loneliness, unscheduled health care, and falls. We will also examine mediators and moderators of the effects of ElderTree on both platforms. Participants will complete surveys at baseline, 6, 12, and 18 months, and ElderTree use data will be collected continuously during the intervention period in system logs. We will use linear mixed-effect models to evaluate outcomes over time, with treatment condition and time point as between-subjects factors. Separate analyses will be conducted for each outcome.

Results: Recruitment began in July 2023 and was completed in May 2024, with 387 participants enrolled. The 12-month intervention period will end in May 2025; data collection will end in November 2025. Findings will be disseminated via peer-reviewed publications.

Conclusions: Voice-activated digital health interventions have theoretical but untested advantages over typing-based technologies for older adults with physical limitations. As the population ages, and as multiple morbidities threaten the functional health of the majority of older adults, innovations in self-management are a matter of public health as well as individual quality of life.

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KEYWORDS

eHealth; aged; geriatrics; functional health; multiple chronic conditions; smart display; smart speaker; primary care; quality of life

Introduction

Background

A key measure of the physical and mental quality of life, functional health is the ability to perform basic personal care activities as well as more complex skills such as finances, transportation, and housekeeping: in essence, the ability to maintain one's own agency [1]. Maintaining such agency, including living at home rather than in a care facility, is a primary goal of older adults [2]. Yet with age, most older adults develop chronic health conditions that erode their functional health and threaten their independence [3].

In the United States, chronic conditions such as diabetes, hypertension, and arthritis affect almost 95% of adults aged 60 years and older [4]. Among Medicare beneficiaries, about two-thirds have 3 or more chronic conditions and nearly one-fourth have 5 or more [5,6]. Treatment of co-occurring morbidities is complicated and costly given their complexity, prevalence, and ongoing nature [5,7]. For these same reasons, self-management is a vital aspect of patient care. Self-management includes skills and knowledge related to one's health conditions, attention to emotional and cognitive states, and efforts related to lifestyle factors such as nutrition and exercise [8].

In its most recent Healthy People initiative, issued every 10 years since 1980 [9], the US Department of Health and Human Services (DHHS) declared a goal of improving the health and well-being among older adults. The first objective in meeting the goal is: "Increase the proportion of older adults with physical or cognitive health problems who get physical activity" [10]. According to health guidelines established by the Centers for Disease Control and Prevention [11], a consistent regimen of strengthening, balance, and aerobic activity can help older adults "feel, function, and sleep better; stay independent and fit so [they] can complete daily tasks; improve [their] mental health; and decrease pain and improve function". Moreover, these beneficial impacts may be experienced immediately [12].

To accomplish this objective, labeled OA-01 (Older Adults-01), *Healthy People2030* recommendations include the use of digital health interventions that provide instruction and guidance in the form of "web-based interactive content" and "apps with goal-setting, activity tracking, and reminder functions" [13]. The initiative's Community Preventive Services Task Force found that appropriately tailored home-based digital interventions with exercise content improved older adults' balance, strength, and muscular endurance. In addition, people who used such interventions reported spending more time doing physical activity than they would have otherwise [14].

Digital health interventions have typically been delivered via computer websites (which require typing) or smartphone apps (which require touch navigation). Various academic and popular press accounts have suggested that smart speakers and smart displays, which also access the internet but are primarily navigated by voice rather than touch or typing, might be more accessible and appealing for older adults and others struggling with physical limitations [15-19]. Specifically, they have proposed that voice interactivity could alleviate challenges of hand tremors and vision loss and might seem more intuitive and companionable than a traditional app or website [20-22].

On the other hand, researchers have also suggested potential difficulties: age-related reductions in the volume, clarity, and pace of older adults' speech may lead the device to misinterpret their questions and commands, and hearing loss may make it challenging for some older adults to understand the device's responses [23-26]. More broadly, there is some indication that older adults may be less inclined to use technology-based interventions than to engage with traditional, in-person treatment. A 2023 meta-analysis of randomized trials of interventions for older adults' functional mobility found slightly higher dropout rates for older adults assigned to technological interventions (eg, virtual reality exergaming, wearable devices, and telerehabilitation) than those assigned to conventional in-person rehabilitation or no treatment [27].

To summarize, it remains unclear whether voice interactivity versus touch or typing delivery of intervention will be more effective for older adults and help advance the objectives for older adults' health and physical activity outlined in *Healthy People 2030*. This paper reports on the protocol of a large clinical trial comparing the effectiveness of an eHealth intervention delivered on a smart display versus a laptop.

The intervention, ElderTree, is a web-based system that aims to improve the health and quality of life of older adults by offering interactive, informational, and motivational content and services such as health tracking, reminders, and social support. Developed by our Agency for Healthcare Research and Quality Center of Excellence in Active Aging, it was first tested in a randomized controlled trial (RCT) involving a community sample of 390 participants age 65+ years who received a laptop either with or without ElderTree access for 12 months [28]. In that study, participants in the ElderTree group who reported 3 or more primary care visits in the 6 months before baseline showed significantly better results on measures of mental quality of life, social support, and depression compared to control participants. Because primary care use is relatively high among patients who are managing multiple chronic conditions, these results suggest that patients with comorbidities may be most

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likely to benefit from a system such as ElderTree. A subsequent RCT testing a version of ElderTree among a clinic-based sample of older patients with at least 3 chronic conditions found socio-emotional health improvements, especially among women [29,30]. In the most recent RCT (ClinicalTrials.gov NCT04798196), ElderTree was adapted for older adults experiencing chronic pain and at least three comorbid conditions, with the primary aim of reducing pain interference. As in the current trial, participants were randomized to receive the intervention via a laptop or a smart display [31]. The outcome paper is currently in preparation.

The current study differs from the chronic pain study, by focusing on functional health among older adults with 5 or more chronic conditions. We recruited adults with an array of conditions known as metabolic syndrome (ie, vascular risk factors including hypertension, hyperglycemia, abdominal obesity, and dyslipidemia), for whom physical activity is of particular therapeutic import [32,33]. We increased the number of chronic conditions required to participate from 3 to 5. Almost a quarter (23%) of Medicare beneficiaries have 5 or more chronic conditions [34] and health risks and costs increase with the number of comorbid conditions [35,36]. As such, it is important to understand whether this sizable, high-risk, high-expenditure group is more likely to use and benefit from a voice-activated intervention for functional health, rather than a laptop version.

Study Objectives

Although voice-activated systems seem to offer an easy, engaging way to use an intervention, it is an open question whether older adults coping with multiple chronic conditions would show more sustained use of a voice-activated platform and whether this would lead to improved health outcomes. To test this hypothesis, we propose a trial comparing the text and typing-based version of ElderTree delivered on a laptop to a voice-based version delivered on a smart display. The goal is to compare usage patterns of the two platforms and assess whether the smart display version outperforms the laptop in improving our primary outcome of functional health and associated secondary outcomes.

Methods

Trial Design

This is a nonblinded, 2-arm, parallel-design randomized trial, with participants allocated 1:1 to receive ElderTree on either a voice-based smart display or a text and touch-based laptop. The intervention period is 12 months, with surveys at baseline, 6, and 12 months, and a follow-up survey at 18 months.

Sample Size and Study Setting

We planned for a minimum of 356 older adult participants to be recruited from both clinic and community settings throughout the state of Wisconsin.

Study Arms

ElderTree Via Laptop

Participants in the ElderTree via Laptop (ET-LT) arm receive a touchscreen laptop computer, access to ElderTree, and Internet service for 12 months, and continue with their usual care. They will also receive US $10 for each completed survey, for a possible maximum of US $40.

ElderTree Via Smart Display

Participants in the ElderTree via Smart Display (ET-SD) arm continue with their usual care and receive a smart display, Internet service, and access to ElderTree for 12 months. The smart display consists of a voice-activated smart speaker and a small visual display that is optionally touch-activated. They will receive US $10 for each completed survey, for a possible maximum of US $40.

Eligibility Criteria

Eligible participants must (1) be age 60 or older, (2) have at least 5 chronic conditions identified by the Centers for Medicare & Medicaid Services as prevalent among older adults [5,37], (3) among which 3 of which must be hypertension, hyperlipidemia, obesity, prediabetes, diabetes, or depression, (4) be willing to share medical record data about health care use (30-day hospital readmissions, emergency room urgent care, primary care, and specialty care visits), (5) allow researchers to share information with the patient's primary care provider, (6) have no current psychotic disorder or form of dementia, (7) no acute medical problem requiring immediate hospitalization, (8) no need of an interpreter, and (9) no physical impairments preventing use of a computer or tablet.

Recruitment

The Clinical and Health Informatics Institute at the University of Wisconsin–Madison (UW–Madison) searched clinic records from the Department of Family Medicine and General Internal Medicine system (UW Health) to identify patients meeting eligibility criteria and has sent eligible patient data (name, address, birth date, age, UW Health clinic location, primary care doctor) to the UW (University of Wisconsin) Office of Clinical Trials (OCT) via REDCap (Research Electronic Data Capture, Vanderbilt University). OCT then sent potential participants an opt-in letter describing the study, a consent form, and a stamped return letter inviting contact from the study team.

We supplemented recruitment from UW Health with additional clinic and community efforts aimed at achieving a diverse patient population. To increase our outreach to both participants of color and underserved patients, we worked with staff at Access Community Health Centers in Madison, who disseminated a recruitment flyer, consent form, and return card or opt-in to potentially eligible patients. In addition, advertisements on local television stations have been deployed in Madison, Milwaukee, Beloit, and other communities within driving distance, with specific outreach to older adults and African Americans. Last, through collaborations with leaders in the Black community, we reached out to churches, community centers, senior living communities, and other organizations, distributed a recruitment flyer and consent form with a return

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card or opt-in, placed advertisements in local publications, and conducted community sessions to introduce the study and invite participation.

Finally, we sent a one-time mass email to all current UW–Madison faculty and staff with information regarding the study, asking those interested to reply via email or call for more information. We also encouraged recipients to share the email with others they believed might be interested (eg, a parent or neighbor with multiple chronic conditions).

Regardless of recruitment method, when a return card or opt-in was received or a potential participant called, study staff assessed eligibility over the phone; provided a study overview that included potential benefits and risks, study procedures, and compensation; thoroughly walked through informed consent; conducted a brief exercise screen to allow tailoring of exercise content [38]; and addressed questions. If the individual met eligibility criteria, the baseline survey was mailed; community participants also received the consent form, while clinic participants had already received it with their opt-in letter. Patients were given as much time as needed to decide whether to participate and had the option for a follow-up call after reviewing the materials. The baseline survey takes 20-30 minutes to complete. Measures are the same in both arms to avoid differential dropout. As the trial progresses, we document those who choose not to participate and why, following the CONSORT (Consolidated Standards of Reporting Trials). Patients can opt to stop their participation at any time by contacting the research team.

Randomization

The project manager used a computer-generated allocation sequence to randomize participants on a 1:1 ratio to ET-SD or ET-LT, stratified on gender (male or female), number of chronic conditions (5-7 or 8+), and recruitment site. There are 7 site variables: 3 UW Health clinics, the Access Community Health clinic site, and 3 communities (Madison, Milwaukee, and Beloit). Once an individual verbally consented, a home visit was scheduled to collect the baseline survey, randomize, determine the preferred location of the laptop or smart display, and set up the device. Staff then conducted training on the assigned intervention. If no visit was desired, equipment could be shipped after the completed baseline survey was mailed and received, and technology setup and training could be conducted by phone. The research team is available during usual operating hours for participants to contact them with questions or issues.

Once an assignment has been made, it is of course not possible to blind participants to their condition. Further, in order to set up participants on their assigned system, the researcher conducting the training also could not be blind to the condition after the assignment.

Timeline

Table 1 shows the timeline by year of the study, with year 1 beginning in August 2021 and year 5 ending in July 2026.

Table 1. Timeline of key project activities.

Activity	Timeline
Develop and test ElderTree intervention on the smart display	Year 1, months 2-11
Develop content plan for ElderTree on both platforms	Year 1, months 5-9
Prepare and finalize study and data collection materials	Year 1, months 7-9
Obtain institutional review board approvals	Year 1, month 8
Finalize data quality monitor plan	Year 1, month 9
Train research staff	Year 1, months 9-10
Recruit and randomize patients	Year 1, month 9 to year 3, month 10
Produce and manage ElderTree content for both systems	Year 1, month 9 to year 5, month 4
Collect data	Year 1, month 9 to year 5, month 4
Clean and prepare data	Year 2, month 4 to year 5, month 6
Analyze results	Year 5, months 7-10
Publish	Year 5, months 11-12

Intervention

System Overview

ElderTree is one of a suite of eHealth systems developed by our Center and collectively known as CHESS (Comprehensive Health Enhancement Support System). Like other CHESS systems, ElderTree is built on principles of continuing care and self-management, such as long duration [39], tracking [40], prompts [41], goal setting and action planning [42], problem-solving and self-tailoring [43], and social support [44]. In randomized trials, CHESS systems have significantly improved risky drinking [45]; asthma control [46]; quality of life and cost of care in human immunodeficiency virus patients [47]; quality of life and self-efficacy in breast cancer patients [48-50]; and caregiver burden, symptom distress, and median length of survival in patients with lung cancer [51]. All CHESS systems, including ElderTree, are consistent with self-determination Theory, which asserts that satisfying these 3 basic psychological needs contributes to adaptive functioning: competence (feeling effective or not overwhelmed), social

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relatedness (feeling connected to others or not isolated), and intrinsic motivation (feeling autonomous about behavioral changes or not coerced) [52].

ElderTree is a multifaceted system focused on older adults' physical and mental health and quality of life. As reported in earlier ElderTree studies [28-30], the laptop system is a members-only website free of ads, with design features based on older users' feedback and best practices for older populations (eg, larger fonts or uncluttered screens) to optimize comprehension, navigation, and usability [53]. The ET-SD version follows these usability principles as well. Both systems substantially replicate ElderTree as described in an earlier study comparing ET-LT to an attention control [29,30], with modifications and enhancements to focus on the functional health of individuals with multiple morbidities and to align with the technical capabilities of the smart display platform.

System Content

ElderTree offers video content in the areas of functional movement, information and advice, mood and mental health, and entertainment, as well as social engagement and health tracking features. Video content is both originally produced and curated from high-quality external sources. Descriptions of each feature or function are listed in Table 2, and the home screen organization for both platforms is shown in Figure S1 in Multimedia Appendix 1: ElderTree screens and physical activity decision tree.

Table 2. Key features of the ElderTree eHealth intervention.

Feature or function	Description
"Let's Move" videos	Functional movement videos, in 3 assigned ability groupings based on participants' physical health screening and doctor approval.
"Tips & Info" videos	Short, practical information and advice on a wide range of topics related to physical and mental health (eg, "How Blood Pressure Works", "Finding Friends as an Older Adult", "Easy Ideas for Healthy Eating").
"Relax & Inspire" videos	Meditation, relaxation, and breath work videos for sleep, reducing stress, creativity, and more.
"Just for Fun" videos	Humor, music, and human interest are for pleasure (this content is located in "Relax & Inspire" on the smart display platform).
CalmConnect multisensory videos [54]	Program of short practice videos that combine rhythm, hand movement patterns, and facial expression cues, engaging the user physically, cognitively, and emotionally with the goal of strengthening social connectivity and mental health.
Wednesday Meetup	One-hour weekly facilitated group video meeting with a topic presentation (eg, balance, falls, and vision health) and small breakout rooms for socializing.
Weekly Survey	Tracking of 10 self-reported general health indicators (eg, sleep, mood, exercise), with results presented in graph form over time.
Thought of the Day	A new motivational or inspirational quote delivered daily at with the user's first visit to the intervention.
Prompts	Reminders to take the weekly health tracking survey; notifications of new content.
Featured content	On the home screen, new and existing content is highlighted to encourage exploring services and resources, and is continually rotated to keep ElderTree fresh.
Favorites	Bookmarking and retrieval feature.
System tutorials	Instructional videos for accessing ElderTree features and content.

The critical physical exercise content is located in ElderTree's "Let's Move" area, offering videos targeting balance, strength, endurance, and flexibility. After randomization, participants in both conditions were placed in one of three activity-level groups on the basis of their responses to the Exercise and Screening for You (EASY) Tool [38] and approval from their primary care physician (PCP), to ensure safety and accessibility. Figure S2 in Multimedia Appendix 1 shows the decision tree for assigning each participant to their group within the study arm. The three groups are as follows:

1. Group 0: restricted based on the EASY Tool and do not have approval from their PCP to use standing activity content on ElderTree. The fitness activities available to them are limited to gentle seated movements for coordination, dexterity, and mental stimulation (eg, "Wake Up Your Brain"). Also, in Let's Move, Group 0 has access to an 8-module course on managing chronic pain, developed by our research team.

2. Group 1: restricted based on the EASY Tool, but their PCP has given approval to engage in supported standing activities. For this group, we developed a collection of instructional and practice videos with a geriatrician expert in functional movement for older adults who have health conditions. The videos are available in all areas of fitness: balance, flexibility, strength, and endurance. Group 1 participants must view a safety video for each of the 4 fitness categories before access to the movement videos is unlocked. Group 1 also has access to all Group 0 content.

3. Group 2: no restrictions, based on the EASY Tool, and may use all the movement videos on ElderTree after viewing the safety videos in each of the 4 fitness categories. The Group 2 content includes all activities available to Groups 0 and 1, as well as videos provided by outside experts in fitness and functional movement for older adults. These externally sourced videos have been vetted by the study's geriatrician for safety, suitability, and quality. Playback times and challenge levels are

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indicated in every video title to enable users to self-tailor their selections on any given day.

Outcomes

The primary outcome is differences between groups over time in functional health, a multifaceted variable that includes physical function, pain interference and intensity, fatigue, sleep disturbance, anxiety, depression, and satisfaction with one's social roles and activities. To tease apart these elements, the secondary outcomes include the functional health subscales of physical function, pain interference, anxiety, depression, and social role satisfaction. Additional secondary outcomes are health distress, loneliness, unscheduled health care use, and falls. Figure 1 diagrams the study logic.

Figure 1. Study logic.

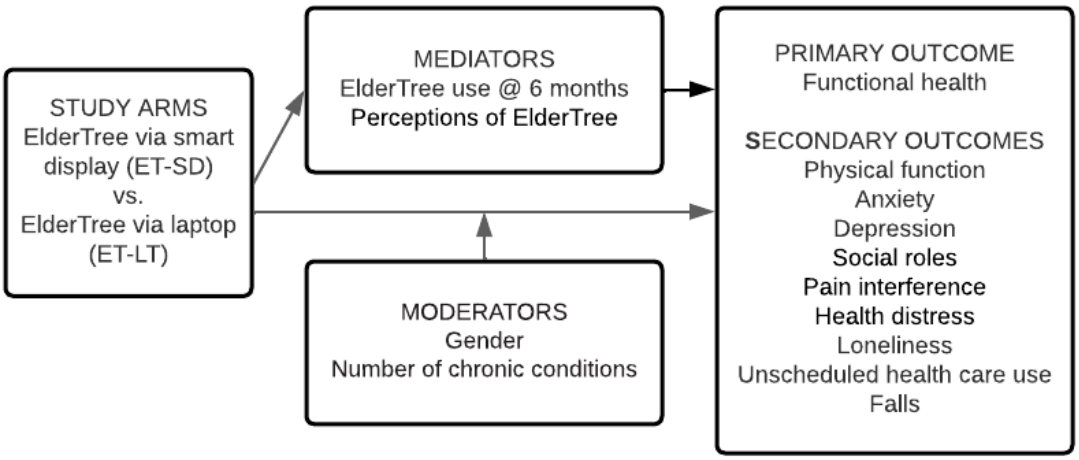

Measures

Primary Outcome

The 29-item PROMIS (Patient-Reported Outcomes Measurement Information System)-29 v2.1 is used to measure functional health [55]. Items tapping physical function, pain interference with aspects of daily life, anxiety, depression, ability to participate in social roles and activities, fatigue, and sleep disturbance are scored on 5-point Likert scales, while a single 11-point item (range=0–10) rates pain intensity. The possible ranges, scored by providers of the measure [56], are 21.2–67.6 for a social-emotional cluster and 16.2–67.7 for a physical cluster of functional health, with higher scores indicating better functioning.

Secondary Outcomes

We are using PROMIS-43 v2.1 subscales to separately assess physical function, pain interference, anxiety, depression, and satisfaction with social roles and activities [57]. For each subscale, participants respond on a 5-point (1-5) Likert scale to 6 items modified from occurring "currently" to "in the past 7 days," for consistency with other survey items. For the physical function items (eg, "Are you able to go for a walk of at least 15 minutes?"), higher scores indicate poorer function (total possible range=22.9-56.9). For pain interference (eg, "How much did pain interfere with the things you usually do for fun?"), higher scores indicate greater interference (total possible range=41.6-75.6). Anxiety items include "I felt nervous" and "My worries overwhelmed me"; higher scores indicate greater anxiety (total possible range=40.3-81.6). Depression items include, "I felt like a failure" and "I felt unhappy"; higher scores indicate more depression (total possible range=41-79.4). For social roles items (eg, "I have to limit my regular activities with friends"), higher scores indicate more difficulty or limitation (total possible range=29-64.1).

Health distress is measured with the 4-item Lorig Health Distress Scale [58,59]. Sample items are how often in the past month a participant has been "discouraged by your health problems" and "fearful about your future health." Higher scores on the 6-point (0–5) Likert scale indicate greater distress. The total possible score is the mean of the 4 items (range=0 5).

Loneliness is assessed with the 5 Loneliness scale items in the NIH Toolbox Social Relationship scales item bank v2.0 [60]. Sample items include how often in the past month a participant has felt "alone and apart from others" and "left out". Scores are calculated by the scale developer; the possible range=37–85, with higher scores indicating greater loneliness.

For unscheduled health care visits, participants will report at each survey time point their number of urgent care clinic visits, emergency room visits, and overnight hospital stays in the past month.

The number of falls in the past 6 months, as well as the number requiring medical attention, will also be surveyed at each time point. A fall is defined in the survey as "when your body goes to the ground without being pushed."

Measures for all planned outcomes and their psychometrics are presented in Table 3.

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Table 3. Outcome measures, the number of survey items, and psychometrics.

Variable	Measure	Items, n	Psychometrics
Primary outcome			
Functional health	PROMIS[a]-29 v2.1	29	α≥.94 [55]
Secondary outcomes			
Physical function	PROMIS-43 physical function subscale	6	α>.9 [57]
Pain interference	PROMIS-43 pain interference subscale	6	α>.9 [57]
Anxiety	PROMIS-43 anxiety subscale	6	α>.9 [57]
Depression	PROMIS-43 depression subscale	6	α>.9 [57]
Social roles	PROMIS-43 social roles subscale	6	α>.9 [57]
Health distress	Lorig Health Distress Scale	4	α>.87 [58]
Loneliness	NIH Toolbox	5	α≥.93 [60]
Number of unscheduled health care visits	N/A[b]	3	N/A
Falls	N/A	2	N/A

[a]PROMIS: Patient-Reported Outcomes Measurement Information System.

[b]N/A: not applicable.

Mediation, Moderation, and Covariates

We will test whether functional health at 12 months is mediated by participants' amount of ElderTree use and perceptions of ElderTree at 6 months. ElderTree use will be assessed via continuously collected system data. For perceptions of ElderTree, participants rate 18 items (eg, "It is easy to use," "It helped me learn more about my health issues") on a 4-point (1-4) Likert scale and answer 6 open-ended questions (eg, "What stopped you or hindered you from using ElderTree or the computer or smart system in general?"). We will also examine possible moderation due to gender and the number of chronic conditions at baseline. Finally, as potential covariates we will test baseline race and ethnicity, education level, and barriers to technology due to physical limitations (eg, vision or hearing challenges); those that significantly predict our primary outcome will be included in the final analysis.

Power Analysis and Sample Size

The primary hypothesis is that the intervention modality (voice activation vs typing and touching) will affect functional health. Based on PROMIS validation studies (eg, chronic pain, arthritis, and cancer), a difference of 3 points or more between study arms is considered to indicate a clinically meaningful difference [61]. The PROMIS website also gives the mean and SD of the T-score metric (mean 50, SD 10). Power calculations for this primary hypothesis were performed using the SAS procedure PROC GLMPOWER (SAS Version 9.4) [62]. Results indicated that 282 participants after attrition would be needed for 80% power (P<.05) to observe a difference score of 3 points between the two study arms at 12 months. In our original ElderTree study, 79% of the sample completed the 12-month survey [28], and in the subsequent study, 92% of participants did so [30]. We based our sample size on the more conservative numbers from the original study and planned to recruit a total of 356 participants, or 178 per arm, to achieve 282 after attrition.

With regard to power for moderation analyses, we ran a sensitivity analysis to compute the smallest effect size our study would be powered to find using 280 given 4 groups (eg, 2 study arms × 2 genders). With N=280, G*Power calculations [63] show our study would have a 95% chance (with P<.05) of observing a moderation effect as small as a Cohen d of 0.22.

Data Collection

Patient Surveys

Patients will complete surveys at baseline, 6, 12, and 18 months. Baseline surveys were collected at training and setup, and subsequent surveys will be mailed to patients with a return stamped envelope. Participants are encouraged to contact the study staff if questions arise. All 4 surveys will assess primary and secondary outcomes using the measures detailed above. At 6, 12, and 18 months, participants will also respond to the checklist of chronic conditions used for eligibility screening as well as answer items assessing their perceptions of the intervention. Demographics were gathered only at baseline.

ElderTree System Data

ElderTree usage data are automatically and continuously collected in time-stamped log files, including logins, services used, pages accessed, and weekly surveys completed.

In addition, data are collected from the weekly survey of self-rankings for medication adherence, falls, thinking and memory, mood, healthy meals, snacks and drinks, physical activity, quality time with others, sleep, pain, and balance.

Retention

We are promoting study retention by providing telephone and email support for patients' use of the technologies and by following up with patients to encourage them to return surveys. If a survey is not returned within 2 weeks, a research team member will call to check that the survey was received and

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encourage the patient to complete and return it in the provided envelope. The date and time of the phone call will be recorded in REDCap, along with whether the researcher talked to the participant directly (vs left a message) and any information gathered during the conversation. If we cannot reach the participant, another copy of the survey will be sent with a personal note asking them to complete it or call us on our toll-free number if they have questions or are no longer interested.

Data Quality and Management

Surveys comprise standardized measures that have been validated for older adults. In addition, the following strategies, developed during our previous large RCTs with this population, are implemented to reduce errors and missing data: (1) surveys are sent via hard copy, with paid return envelopes; (2) visual formatting is simple and clear, in large print on uncluttered pages; (3) tables of items and response options are designed with line-by-line alternate shading for easy tracking; and (4) instructions are explicit as to how participants should respond if they feel a question does not apply or they do not know the answer. Participants are encouraged to call in with questions. Once a survey is returned, trained research staff will evaluate it within a week of receipt; if data issues are found (eg, missing responses, multiple responses to a single item), staff will contact the participant to resolve the error.

To mitigate the risk of breaches in patient confidentiality, all participants are assigned a unique code number. Participant contact information and survey data are housed electronically in REDCap. Survey data are double-entered by two different individuals to ensure accuracy. Paper files are stored in a locked room in locked cabinets and can be accessed only by authorized personnel. The database administrator provides access to study data at appropriate levels for various members of the research team.

Statistical Methods

Predictor and Outcome Assumptions

Participants were assigned at random, with constraints that study arms would have roughly equal proportions for key covariates (eg, race, education, baseline number of chronic conditions). The effect of key covariates on outcomes will be assessed for each model. We will assess whether there are main effects of recruitment sites or interactions with the study arm (ie, whether data can be pooled across sites). Variables will be examined using standard summary statistics, visualizations, and tests for normality and homoscedasticity. Data will be transformed as needed.

Missing Data

With regard to survey data, in the previous ElderTree RCT of older adults coping with at least 3 high-risk chronic conditions, 320 of 344 participants (93%) completed the 6-month survey, 309 (89.8%) completed the 12-month survey, and 298 (86.6%) participants completed the 18-month survey [30]. In completed surveys, data were missing on about 2% of core items. Occasional out-of-residency time is also expected for participants (eg, travel and hospitalizations). We encourage patients to take the intervention with them when possible, but absences without ElderTree will be addressed as covariates in our outcome models.

We expect rates of missing data in this study to be similar to those reported above for the ElderTree RCT. We will report rates of missing data by study arm and time point. We will also use logistic regression to predict missing data as part of our evaluation of missing data patterns.

Effects of Study Arm on Outcomes

Primary and secondary outcomes will be analyzed using an intention-to-treat approach that includes all observed data from all participants who were randomized to a study arm. These analyses will follow a model-based approach that assumes missing data for outcomes at specific time points are missing at random (MAR) [64]. Specifically, a linear mixed model [65-68] will be used to examine the effects of the study arm (ET-SD vs ET-LT, a between-subjects factor) on the primary outcome, functional health, over time. Linear mixed models will also assess the effects of the study arm on each of the secondary outcomes over time (ie, an interaction of the between-subjects factor of the study arm and the within-subjects factor of time of measurement). Count variables that lack sufficient variability to be treated as count data (negative binomial distribution) will be treated as dichotomous variables and run using a binomial distribution in the linear mixed model.

Supplemental sensitivity analyses [69] will also be conducted to assess the robustness of conclusions to our assumption that missing data are MAR. Specifically, we will use comparable linear mixed-effects models to examine the effects of the study arm using only complete cases, as would be appropriate if data were missing completely at random. To address the possibility that the data are missing not at random, we will use both the Diggle-Kenward approach (which assumes that dropout is a function of time-specific outcomes) and the Wu-Carroll approach (which assumes that dropout is a function of one's developmental trajectory) [66-68,70].

Mediation of Effects of Study Arm on Primary Outcome

We predict effects of the study arm on functional health will be mediated by the amount of ElderTree use and perceptions of ElderTree at the 6-month midpoint. We will use structural equation modeling with separate models for the social-emotional and physical components of functional health.

Moderation of Study Arm on Primary Outcome

We predict that the effects of the study arm on functional health will be moderated by gender and the number of chronic conditions at baseline. We will use linear mixed models, testing each moderator separately, to examine the moderator-by-arm interaction while accounting for time.

Ethical Considerations

This study protocol received ethical approval from the University of Wisconsin Health Sciences and Minimal Risk Research institutional review board (reference number 2020-0984) and has been registered at ClinicalTrials.gov (NCT05240534). Consent forms were mailed to potential participants and research staff walked through informed consent

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over the phone. Participation was voluntary and participants could opt out at any time. Only a small number of research staff has access to patient data and all outcomes and usage data are deidentified. Participants were paid US $10 for each outcome survey completed and received a free laptop or smart display and internet service for 12 months if needed.

Results

As of May 2024, a total of 387 new participants have been enrolled, concluding recruitment 2 months earlier than originally scheduled. The 12-month intervention period will end in May 2025, and data collection will end in November 2025. Findings will be disseminated via peer-reviewed publications. Figure 2 shows the status of participants throughout the trial. Interim numbers are shown in the Follow-up section, as the intervention and data collection are not yet complete. The final numbers for the Analysis section will be reported in the main outcome publication.

Figure 2. CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

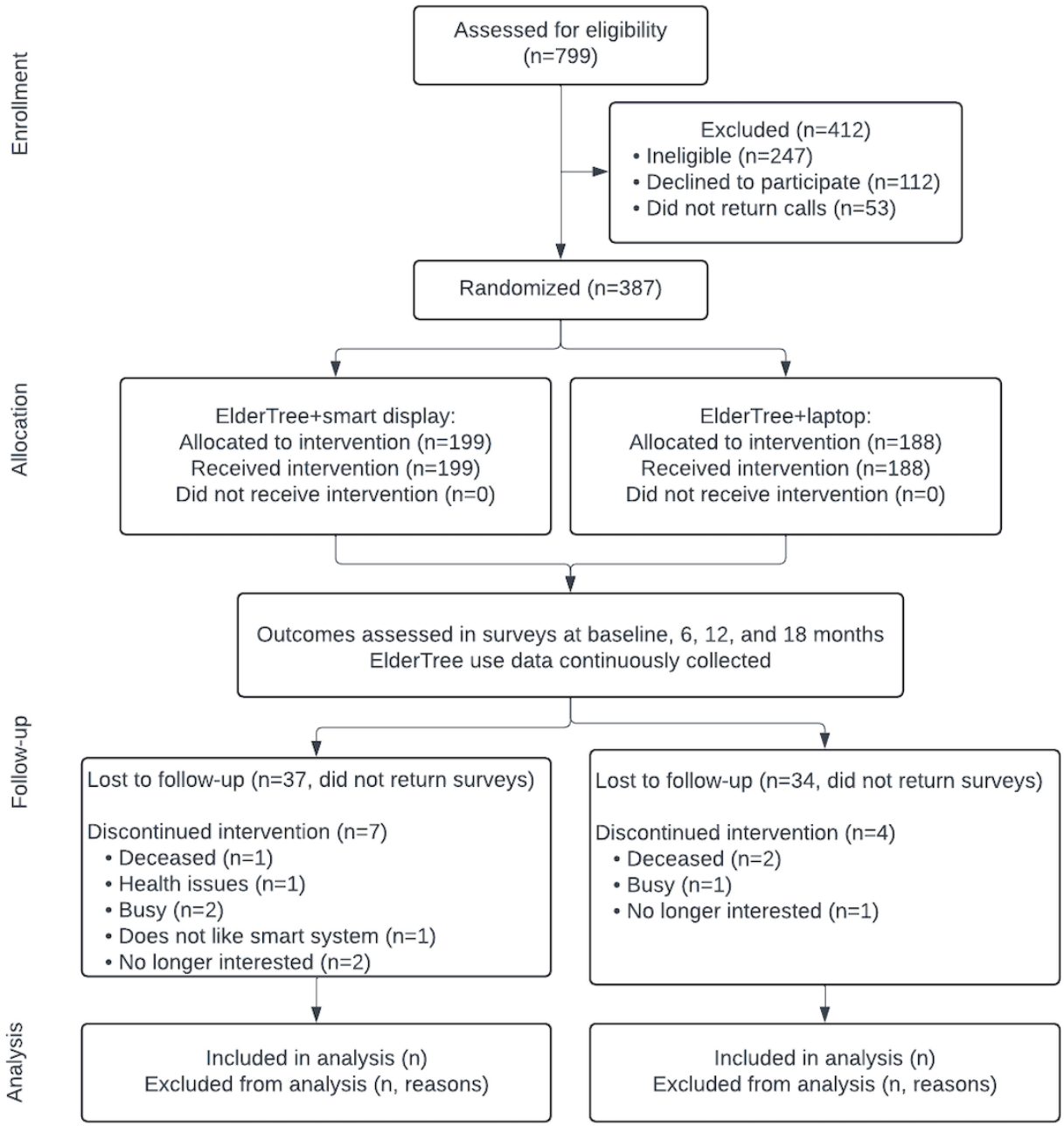

Discussion

Anticipated Findings

The central question of this study is whether a voice-activated smart system will be better than a laptop for delivering an intervention for functional health to older adults with ≥5 chronic conditions. The prediction is that those randomized to access the intervention via a voice-activated smart display will show more use of the intervention than those randomized to access it via a laptop and that greater use will lead to more positive

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change over time in the primary and secondary health-related outcomes.

Few studies thus far have rigorously tested smart displays as a platform for health interventions for older adults. A 2024 scoping review found 22 studies (published between 2010 and 2022) examining community-dwelling older adults' use of personal voice assistants [26]. The overall conclusion was that many older adults found the devices convenient and easier to use than a computer for basic tasks like reminders or checking the weather, but they sometimes struggled to make themselves understood or to remember the necessary commands. As the authors noted, all of these studies were exploratory, and none examined effects on quality of life or health-related outcomes.

Since then, 2 studies have examined socio-emotional outcomes of older adults' uses of smart devices, but one lacked any comparison group (examining pre-post changes only) [71], and the other compared a smart speaker (audio only) versus a smart display (audio + screen) [72]. While both found that frequent use of smart systems was associated with positive socio-emotional changes (eg, reductions in loneliness), it is possible the same changes would have occurred with laptop use. A third, nonrandomized study examined whether a smartphone health intervention for older adults would be more effective if participants agreed to add a smart speaker with extra functions (eg, medication reminders, exercise programs, quizzes) [73]. There were no differences between the 2 self-selected groups in changes over time in depression or 5 of 6 health outcomes; only dietary diversity showed greater improvements in the group that agreed to have the smart speaker as well as the smartphone.

In sum, despite claims about the possibility that voice interactivity may increase the accessibility and effectiveness of health interventions for older adults, our project is one of the first randomized trials comparing a smart display versus a laptop for delivering an intervention for older adults, who face complex health challenges. As in any study, there are strengths and limitations.

The first strength lies in the methodological rigor involved in a randomized trial that followed 356 older adults over 12 months with a postintervention follow-up at 18 months. Another strength is that we can gather objective, ongoing data about participants' uses of the intervention, rather than relying on their recollections. Next is our recruitment of older adults with 5 or more comorbid conditions, given the need for effective interventions that will engage this sizable, high-risk population. In addition, the focus on functional health is a core determinant of older adults' ability to remain independent.

There are also a number of limitations. One is that this iteration of ElderTree, like those that came before it, was developed before the widespread availability of large language models and artificial intelligence (AI) interactivity. Although participants can interact with ElderTree on the smart speaker by voice, they must do so using specific commands, rather than the intuitive, conversational exchanges now made possible by AI. A second limitation is the absence of a randomized control group that does not receive access to ElderTree: we prioritized adequate power to detect a difference between the 2 intervention groups but will not be able to assess whether both improve outcomes relative to treatment as usual. Next is that we rely on participants' perceptions of their functional health, rather than using clinical data or direct assessment of their functional movement. We regard these limitations as invitations for further research, particularly research that would probe older adults' uses and responses to digital devices that are much more interactive and responsive to voice commands, given AI advances.

Conclusion

Whether the theoretical advantages of voice activation translate to improved effectiveness of eHealth interventions has yet to be determined. Although technologies are constantly developing, the issue of talking versus typing for health interventions for older adults is fundamental and supersedes specific devices. In this way, if ElderTree on the smart display does outperform the laptop in terms of use and health-related outcomes, this would have important implications for the design of future health interventions for this population.

Acknowledgments

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Data Availability

Following the completion of the final analysis, the datasets generated or analyzed during this study will be available from the corresponding author on reasonable request.

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Conflicts of Interest

DHG Sr. has a small shareholder interest in CHESS Health, a corporation that develops health care technology for patients and family members struggling with addiction; this relationship is managed by DHF Sr and the University of Wisconsin–Madison's Conflict of Interest Committee. The authors have no other conflicts to report.

Multimedia Appendix 1
ElderTree screens and physical activity decision tree.
[DOCX File , 2762 KB - resprot_v14i1e64449_app1.docx]

Multimedia Appendix 2
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOC File , 136 KB - resprot_v14i1e64449_app2.doc]

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Abbreviations

AI: artificial intelligence
CHESS: Comprehensive Health Enhancement Support System
CONSORT: Consolidated Standards of Reporting Trials
DHHS: Department of Health and Human Services
EASY: Exercise and Screening for You
ET-LT: ElderTree on a laptop platform
ET-SD: ElderTree on a smart display platform
MAR: missing at random
OA-01: Older Adults-01
OCT: Office of Clinical Trials
PCP: primary care physician
PROMIS: Patient-Reported Outcomes Measurement Information System
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
UW Health: University of Wisconsin–Madison Department of Family Medicine and General Internal Medicine system
UW: University of Wisconsin
UW–Madison: University of Wisconsin—Madison

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Protocol

Neuromuscular Electrical Stimulation to Maximize Hip Abductor Strength and Reduce Fall Risk in Older Veterans: Protocol for a Randomized Controlled Trial

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Abstract

Background: Nearly half of all veterans are 65 years and older, and they have a higher prevalence of functional disabilities compared to the nonveteran population. Balance impairments resulting in injurious falls are a leading cause of morbidity and mortality in older adults. Instability or fear of falling can significantly reduce physical activity and social participation, even in the absence of falls. Dysmobility is a leading factor in long-care admissions, and therefore, maintenance of mobility throughout aging is crucial. Recent evidence indicates lower extremity muscle weakness as a key risk factor for falls, with lower limb muscle strength and quality being critical for balance recovery. The primary hip abductors, the gluteus maximus, medius, and minimus, are particularly essential for balance recovery.

Objective: This study aims to test the hypothesis that adding neuromuscular electrical stimulation (NMES) to a multimodality balance intervention (MMBI) will yield greater reductions in fall risk and improvements in muscle and mobility function compared with MMBI alone.

Methods: This randomized controlled trial will enroll 80 veterans aged 55 years and older at risk for falls (defined by a four-square step test [FSST] time >12 seconds, history of falls, or fear of falling). Participants will be randomized to receive either NMES + MMBI or MMBI alone. The 12-week outpatient center–based intervention will include 3 sessions per week, focusing on hip abductor strength, balance, and mobility. Assessments will occur at baseline, postintervention, and at 6- and 12-month follow-ups. Primary outcomes include fall risk and dynamic balance, measured by FSST and hip abductor strength using a Biodex dynamometer. Secondary outcomes will examine muscle composition through computed tomography (CT) scans and assess gait variability parameters.

Results: This study was funded on January 1, 2022, with a data collection period from April 1, 2022, to December 31, 2026. As of March 2025, we have screened 100 potential participants and excluded 38. Out of the 61 participants enrolled to date, 21 have completed the 12-month follow-up, 32 have completed the 6-month follow-up, and 41 have completed the posttesting. A total of 4 participants are currently in the intervention phase; 1 has just completed the baseline testing, while 15 have been dropped from the study.

Conclusions: This trial will be the first large, randomized controlled trial to evaluate NMES as an adjunct to an MMBI for fall prevention in older veterans. If successful, NMES combined with hip abductor strengthening and balance training could provide a low-cost, scalable solution to reduce falls, improve balance and mobility, and decrease health care costs related to falls in older adults. This study will address a critical gap in knowledge about the effectiveness of NMES in enhancing rehabilitation outcomes for fall prevention.

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Trial Registration: ClinicalTrials.gov NCT04969094; https://clinicaltrials.gov/study/NCT04969094
International Registered Report Identifier (IRRID): DERR1-10.2196/68082

(JMIR Res Protoc 2025;14:e68082) doi:10.2196/68082

KEYWORDS

neuromuscular electrical stimulation; balance intervention; fall prevention; hip abductor strengthening; dynamic balance; veterans; muscle function; gait variability; multimodality balance intervention; fall prevention

Introduction

Recent census data place the share of veterans aged 65 years and older at nearly 50% of the total veteran population [1]. Injurious falls due to impaired balance function are a leading cause of morbidity and mortality among older adults [2]. Even in the absence of falling, older adults who are unstable or perceive they have an increased risk of falling reduce their levels of physical activity and social participation [3,4]. The ability to safely maintain mobility with aging is critical, as immobility is the leading cause of long-term care admissions [5].

While the causes of balance dysfunction and dysmobility are multifactorial, recent evidence demonstrates lower extremity muscle weakness as a main risk factor for both single and recurrent falls [6]. Numerous studies have reported lower limb muscle strength and quality are important predictors in the ability of older adults to recover from a loss of balance [7-10], and data from our laboratory further shows that the hip abductors—namely the gluteus maximus, medius, and minimus—are particularly important in recovery from balance perturbations [11-13]. Understanding the contributions of the hip abductors to balance and mobility, and finding targeted means to improve their function, opens important new treatment options for older adults with mobility limitations or who are at high risk of falls.

We have previously reported increased levels of intramuscular fat (IMAT) in the hip abductors of older adults who are at risk for falls [11,13]. Furthermore, it is well known that excessive levels of IMAT negatively affect skeletal muscle tissue [14,15]. Increased IMAT of the hip abductors is related to increased gait variability [11], decreased mobility and balance, and ultimately may be one potential contributor to increased risk for falls in older adults [11-13]. Both human [16] and animal studies [17], as well as our preliminary unpublished work, show that IMAT may impair the ability of the muscle to contract, ultimately impairing the ability to make significant improvements with exercise interventions [18,19].

Older adults suffer a loss of strength up to 3 times greater than the loss of muscle mass, suggesting the presence of intrinsic alterations in the force-generating capacity of skeletal muscle [20] One suggested mechanism of this decreased muscle quality is that older adults may suffer from an inability to fully activate muscle fibers and may, therefore, require augmentation to volitional resistance exercise to gain the full benefits [20]. While it is likely that multiple reasons for this impaired activation exist, IMAT has been identified as a potential contributor to impaired muscle activation [15,16,21]. Neuromuscular electrical stimulation (NMES) is an intervention that may improve muscle activation. While various forms of electrical stimulation have been applied to the gluteus medius during walking with the intent to improve gait [22,23], large sample, randomized controlled trials using electrical stimulation applied to the hip abductors to decrease falls have not been studied. Improving the composition and function of the primary hip abductors may ultimately result in improved balance and mobility function in older adults at risk for falls.

Understanding the contributions of the hip abductors to balance and mobility and finding targeted means to improve their response to exercise interventions opens important new treatment options for older adults with mobility limitations or who are at high fall risk. We propose to test the hypothesis that the addition of NMES applied to the primary hip abductors during a multimodality balance intervention (MMBI) will result in greater reductions in fall risk and larger improvements in muscle and mobility function than an MMBI alone.

Methods

Overview

This randomized control trial (trial registration: ClinicalTrials.gov NCT04969094) will examine the impact of 12 weeks (3 times per week) of NMES + an MMBI versus an MMBI alone on fall risk, balance, mobility, and hip abductor composition and strength in 80 (40/group) older veterans at risk for falls. Following completion of the 12-week outpatient center-based intervention, individuals will be provided with a written home exercise program, and we will reexamine subjects at 6 months and 1 year post intervention to assess retention of changes in hip abductor function, mobility, and fall risk. We will enroll veterans aged 55 years and older who are currently at risk for a fall (defined as a four-square step test [FSST] time >12 seconds [24], or a history of a previous fall in the last year, or a reported fear of falling). This study has 6 phases, completed over ~15 months per person. Figure 1 details the study design, and Figure 2 shows the study timeline. The study protocol follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [25]. Any protocol deviations, confidentiality breaches, or reportable adverse events will be reported to the respective institutional review board (IRB) and data safety monitoring board in accordance with local policies. In addition, the data safety monitoring board will conduct at least annual reviews of study materials and collected data to ensure integrity, security, and quality control.

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Figure 1. Experimental design. BEST: Balance Evaluation Systems Test; CSA: cross-sectional area; CT: computed tomography; FGA: Functional Gait Assessment; FSST: four-square step test; IMAT: intermuscular adipose tissue; MMBI: multimodality balance intervention; MPPT: Modified Physical Performance Test; NMES: neuromuscular electrical stimulation.

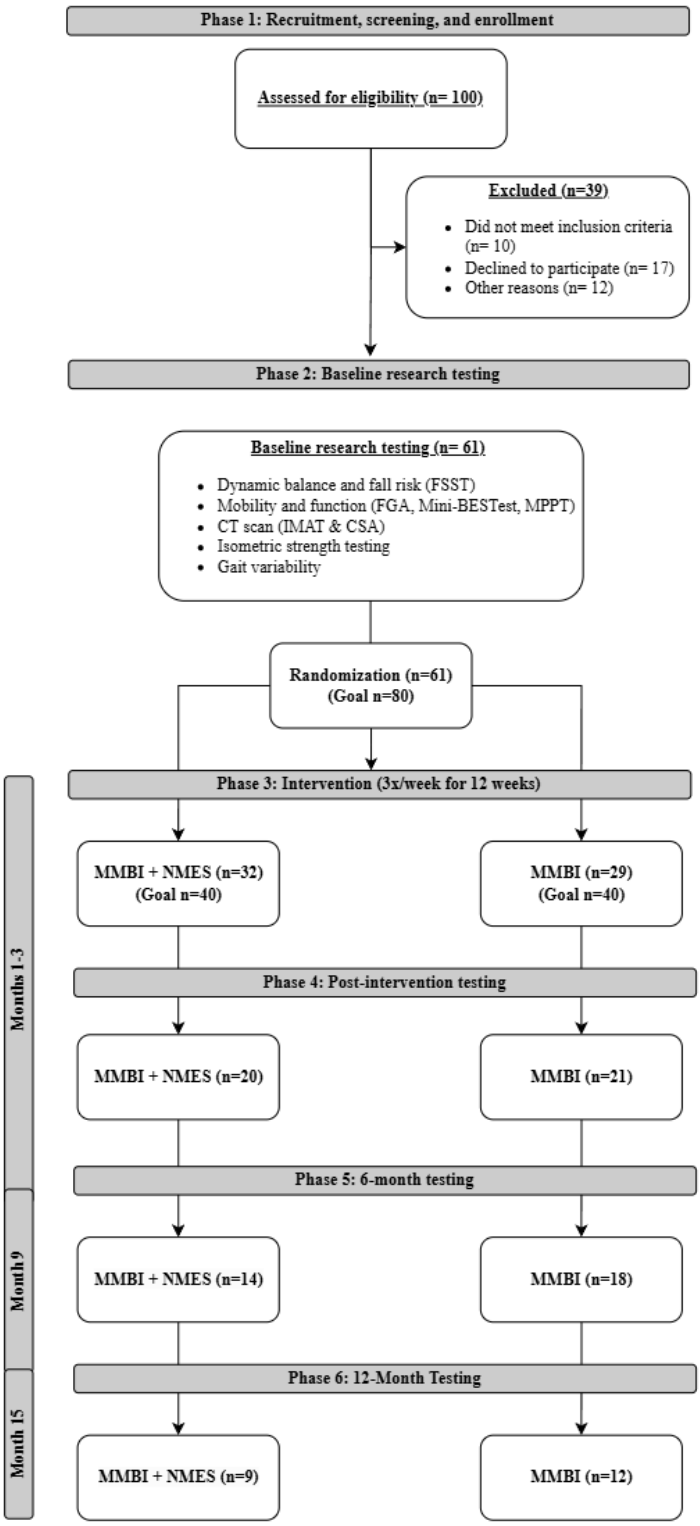

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Figure 2. Study timeline.

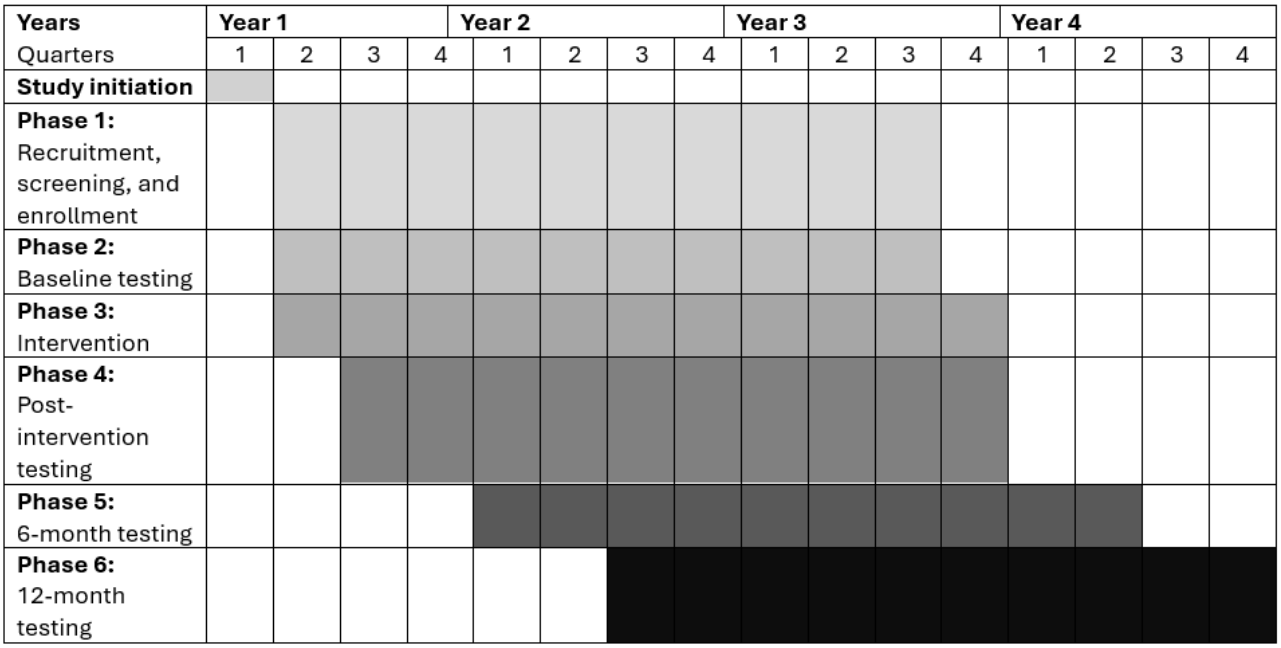

Setting

All testing and interventions will take place in a Veterans Affairs (VA)-based outpatient geriatrics exercise and rehabilitation center.

Participants

An a priori power analysis was conducted for sample size estimation based on changes in the FSST and hip abductor strength in our nonrandomized pilot study. We estimate that 18-22 participants per group will be required to detect between group changes (effect size of 0.91-1.06; α=.05; β=.80) after 3 months of intervention for our primary outcomes of FSST and hip abductor strength. We aim to have 30 participants in each group complete the 3-month intervention and the 6- and 12-month retention testing phases. Accounting for an up to 25% dropout rate from enrollment through 12-month retention testing, we will randomize 40 individuals per group.

Eligibility

Participants will be excluded if they have any of the following characteristics that impair their ability to safely participate in exercise or the NMES intervention: (1) high cardiovascular risk (such as poorly controlled hypertension of >160/100 mm Hg, symptomatic angina at rest or with exercise, or syncope in the last year without known resolution of cause), (2) require home oxygen, (3) contraindications to resistance training such as active proliferative retinopathy, (4) contraindications for NMES such as any implantable cardiac device, (5) dementia, and (6) other medical conditions that preclude patient participation in this study as per medical judgment of study team.

Recruitment and Screening

Recruitment will focus on enrolling participants who are veterans. Participants will be recruited using the Department of Veterans Affairs Informatics and Computing Infrastructure and will be recruited from the Baltimore metropolitan area through media advertisement. Interested participants will be pre-screened through a standardized phone questionnaire. Individuals who pass the prescreening will be invited to our facility. After providing written informed consent and HIPAA (Health Insurance Portability and Accountability Act) authorization, they will undergo a history and physical examination conducted by the study's medical personnel to ensure they (1) meet all inclusion and exclusion criteria and (2) can safely participate in the intervention.

Randomization

After baseline testing, participants will be randomized 1:1 to either NMES + MMBI versus MMBI alone using computer-generated random numbers by the study biostatistician. We will use block randomization to stratify participants by age (55-64 years and aged 65 years and older). To address potential concerns of age after the completion of the study, we will also adjust any analysis with age as an independent factor. Group assignments will be placed in sealed envelopes. Upon recruitment and completion of baseline testing, the research coordinator will open the next envelope and record the group assignment. Only the biostatistician will have access to and knowledge of the randomization list.

Intervention

Study Initiation

The intervention phase will last for 12 weeks with 3 sessions per week (for a maximum of 36 sessions). We will enroll individuals on a rolling admission basis. Admission to the study was originally planned to end at the end of year 3 to ensure that all individuals can be recruited, enrolled, and complete all study activities within a 4-year time frame. However, due to safety protocols related to COVID-19, initial enrollment was slower than originally anticipated. Now, enrollment is planned to continue for the first 3.5 years of the study.

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The MMBI

The multimodality intervention is designed to increase lower extremity strength (with a focus on the hip abductors), improve balance, and decrease mobility deficits of older veterans at risk for falls. All individuals in the study, regardless of group allocation, will follow the same exercise protocol for the MMBI dynamic balance classes. Table 1 shows a detailed summary of the dynamic balance class, resistance training, and obstacle course components. Briefly, the dynamic balance class is designed to focus on common balance problems such as slow speed, foot clearance, directional changes, and obstacle negotiation. Exercises targeting these common conditions will include variations of functional movement patterns such as lunges, sit-to-stands, single-leg stance, and stepping tasks, individualized to the specific participant. Dual-task components, either cognitive or physical, will be added to one or more of the exercises to increase complexity. The resistance training component will include exercises that target the hip abductors, muscles of the lower extremity, and a core exercise. The obstacle course component will build on the skills developed in the dynamic balance class and apply them in a more varied and challenging environment. Vital signs will be assessed before and after each session to ensure safety. Over the 12 weeks of training, the intensity of exercise and the challenge to balance will gradually increase in difficulty. A trained and skilled instructor will lead each class, and 1-2 assistants will be present to assist with fall risk prevention. Classes will be capped at 10 participants per class for safety. The MMBI will occur in a supervised outpatient center-based setting. Participants are required to complete a minimum of 27 sessions. Those who are unable to complete the 27 sessions are not included in the final analysis. During the intervention phase, participants will be restricted from engaging in other forms of resistance training for the lower extremities, including receiving physical therapy services.

Table 1. Summary of the multimodality balance intervention.

Class portion	Duration (minutes)	Components
Dynamic balance class	30	• Focused on common balance problems • Includes variations on the following functional patterns: • Lunge • Sit to stand • Single leg stance or range of motion • Stepping task
Lower extremity resistance training	20	Exercises: • Standing hip abduction[a] • Leg press • Knee flexion • Knee extension • Calf raise • Core activation Intensity: • 60%-70% 1 repetition maximum Volume: • 12 reps × 2 sets
Supervised obstacle course	10	• Stepping over and around obstacles • Walking on varying compliant surfaces • Ascending and descending stairs • Increasing gait speed

[a]Neuromuscular electrical stimulation (NMES) will be applied during this exercise for the NMES + MMBI (multimodality balance intervention) group.

MMBI + NMES

Individuals randomized to the NMES group will be asked to wear a portable NMES device applied to the hip abductors during the performance of the hip abduction strengthening exercise. We will place two 3” × 5” electrodes on each hip (4 total electrodes) to target the gluteus medius and minimus without the activation of the tensor fasciae lata (TFL). Table 2 shows a detailed description of the placement and stimulus parameters. Study staff will record the duration and NMES stimulus intensity in milliamps (mA) from the display of the stimulator screen during each session. As done in other studies of older adults, participants will initially be instructed to turn up the NMES intensity as high as tolerated [26]. After the first 30 seconds, participants will be encouraged to increase the intensity even higher if tolerated. This will be the only increase in intensity during a session and will be recorded as the intensity (mA) for the session. Repetitions of the hip abduction exercise will only be performed while the stimulation is active. We anticipate that the total active time will not exceed 4 minutes per side.

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Table 2. Summary of neuromuscular electrical stimulation (NMES) parameters and placement.

Parameters	Settings
Amplitude (intensity)	• As high as tolerable for the first 30 s • Encourage to increase the intensity once, if tolerated
Frequency	• 50 Hz
Pulse width	• 300 µs
Ramp time	• 1 second up and down
On and off time	• 30 s on and 20 s off
Waveform	• Symmetrical biphasic
Electrode placement	• Proximal electrode just inferior to the iliac crest • Distal electrode 0.5” below proximal, above the greater trochanter

Retention Phase

After the 12-week intervention period, participants from both groups will follow a home exercise program to be completed 3 times per week for 12 months. The exercises will mimic those from the resistance training component, including band-resisted standing hip abduction, knee extension, knee flexion, and seated pelvic tilts. In addition, participants will perform 3 exercises from the dynamic balance class: sit-to-stands, multidirectional weight shifts or lunges, and single-leg stance. Each exercise will be performed for 2 sets of 12 repetitions, except for the single-leg stance, which will be performed for 10 repetitions of 10 seconds bilaterally. Participants will receive instructions on proper forms and a detailed handout for reference. To enhance retention, a study staff member will call participants once per month during the prospective tracking phase. These calls will also address potential barriers to continued participation and plans for follow-up testing. For those who choose not to use the Annie App (Veterans Affairs) to track falls (described below), fall monitoring will be conducted through the scheduled monthly phone calls and mail-in postcard reporting.

Outcome Measures

Outcome measures will be assessed at baseline, following the 12-week intervention, 6 months after completion of the intervention (~9 months from baseline testing), and 12 months after completion of the intervention (~15 months from baseline testing). Testing will generally be conducted over 3 visits. Table 3 shows the details of the testing process.

Table 3. Description of the research testing process.

Testing schedule	Description of testing
Timing	• Tests performed at baseline will also be performed at 12 weeks and at the 6-month and 12-month intervals.
Visit 1	• Dynamic balance and fall risk (FSST[a]) • Mobility and function (FGA[b], Mini-BESTest[c], MPPT[d])
Visit 2 (≥2 days later)	• Gait variability
Visit 3 (≥2 days later)	• Isometric strength testing • Whole body DXA[e] • Spiral CT[f] scan (IMAT[g] and CSA[h])

[a]FSST: four-square step test.
[b]FGA: Functional Gait Assessment.
[c]Mini-BESTest: Mini Balance Evaluation Systems Test.
[d]MPPT: Modified Physical Performance Test.
[e]DXA: dual-energy x-ray absorptiometry.
[f]CT: computed tomography.
[g]IMAT: intramuscular adipose tissue.
[h]CSA: cross-sectional area.

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Primary Outcome (Aim 1)

The FSST is a test of dynamic balance and lateral mobility and will be used to assess fall risk and dynamic balance [24]. The FSST mimics real-life scenarios requiring multidirectional movement and balance and demonstrates excellent inter-rater and retest reliability in older adults [24]. Subjects will be timed as they step over 4 canes set up in a cross on the floor. The test will be performed twice, and the best time of the 2 tests will be used. As described in the original test, individuals will be able to use a cane if needed [24].

Secondary Outcomes (Aim 1)

The Functional Gait Assessment (FGA) and Mini-BESTest will also be used as measures of mobility and balance. The FGA is a 10-item clinical gait test that is based on the dynamic gait index [27]. It tests higher-level dynamic gait activities that are part of daily functional mobility, such as turning safely and ambulating backward [27]. Total scores range from 0 to 30, and scores below 22 are predictive of future falls [27]. The mini-BESTest identifies 6 different balance control systems, including anticipatory postural adjustments, reactive postural control, and dynamic gait [28]. It is a 14-item test with a total possible score of 28 points [28].

The Modified Physical Performance Test (MPPT) will be used to examine physical function. The MPPT is a 9-item standardized test used to identify frailty and mobility dysfunction in older individuals [29]. Individuals are scored on the time it takes to complete tasks such as donning and doffing a coat, picking a penny from the ground, and ascending the stairs. These scores are then summed (the maximum value of the sum is 36). Scores less than 32 indicate at least mild frailty [29].

Primary Outcome (Aim 2)

Hip Abductor Strength: Hip abductor muscle strength, operationally defined as the peak maximal voluntary isometric contraction (MVIC) of hip abductor torque, will be measured using a Biodex System 4 Pro Dynamometer. The position will be standardized and maintained during all testing time points. Hip abduction strength will be tested in the side-lying position at 10 degrees of hip abduction [30] to minimize the influence of hip abductor strength of the contralateral leg as compared with a standing position [31]. We will assess, as a secondary outcome measure of lower extremity strength, maximal voluntary knee extension strength with isometric knee extension in a seated position at 60 degrees of flexion following Biodex protocols.

Secondary Outcomes (Aim 2)

Computed Tomography Scans and Muscle Composition Assessment

A spiral computed tomography (CT) scan (starting at the L2-L3 interspace and extending to the patella) will be performed at baseline, after the 12 weeks of training, and at the 6- and 12-month postexercise intervention follow-ups. The analysis will focus on the primary hip abductors (gluteus medius and minimus), the tensor fascia lata, and the quadriceps. As we have previously published [11,13], the cross-sectional area (cm^2) of high-density lean tissue and low-density lean tissue content will be determined by manual segmentation using Medical Image Processing, Analysis, and Visualization (version 11.3.3; National Institutes of Health) analysis software. Research staff performing the image analysis will be blinded to the participant group allocation. CT data will be expressed as a cross-sectional area of tissue for each muscle of interest (cm^2). High-density lean tissue will be defined using Hounsfield units between 30 and 100, and low-density lean tissue as 0 to 29 Hounsfield units. Muscle composition will be determined by identifying the percentage of high-density and low-density lean tissues in both the primary (gluteus medius and gluteus minimus) and secondary (tensor fascia lata) hip abductor muscles. High-density lean and low-density tissues will be normalized for the respective muscle's size by calculating a percentage of each measure relative to the total muscle cross-sectional area. As in previous studies, high-density lean tissue will be used as a measure of lean tissue, and low-density lean tissue will be used as a measure of IMAT [32].

Gait Variability

As a secondary outcome and preliminary data collection for future studies, we will assess measures of gait variability during walking utilizing kinematic recordings. We will use the Kinesis (Linus Health Technologies), a small, commercially available, portable sensor with a triaxial gyroscope and accelerometer that is worn below the knee. The Kinesis measures multiple gait variability parameters (stride, stance, swing and step times, single and double support times, stride velocity, and length) as coefficients of variation over the course of the walking trial or gait cycle, expressed as a percentage [33].

Responders and Nonresponders

As an additional outcome and preliminary data collection for future studies, we will examine those who improve (responders) and those who do not (nonresponders) in each group. We will define a responder as someone who improves hip abduction torque by 20% or greater. After identifying responders and nonresponders in both groups, we will compare their baseline hip abductor muscle composition (through CT scans) and muscle quality (force/cross-sectional area) to examine potential associations with responsiveness to the intervention. In the MMBI + NMES group, we will also assess stimulation dosage records.

Individuals will return for retention testing 6 and 12 months after the completion of the exercise interventions. Testing will occur over 2 visits and will include all tests done at baseline and post testing. We will also prospectively track the frequency of falls for 12 months following the completion of the training. Participants will be asked to use the Annie App, a VA-supported SMS text messaging app that uses text messaging to track weekly falls. We will familiarize veterans with the use of the app during their last week of training. If participants are not comfortable using the VA Annie app, they will be given the option to return monthly postcards reporting any falls over the last month.

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Data Analysis and Plan

For our primary and secondary outcomes, we will use repeated measures ANOVA (Statistical Analysis Software [SAS] MIXED Procedure) to compare values of our outcome variables at baseline, following the 12 weeks of intervention, and 6 and 12 months following completion of exercise: outcome=group + time + group × time. If there is an imbalance between the groups at baseline, the out-of-balance variable will be added as an additional independent variable to the model. We will use Corrected Akaike Information Criterion, a variation of Akaike's Information Criteria, to select the correlation structure (unstructured, compound symmetry, autoregressive lag 1) that best accounts for the serial autocorrelation of repeated measures from the same subject. We will use per-planned contrasts (implemented using estimate statements) to compare the changes (3 months minus baseline; and 6 and 12 months minus baseline) in our 2 groups. We will use Poisson regression (SAS GENMOD Procedure) to compare the number of falls in our two groups over the course of the 1-year follow-up. Our analyses will be 2-tailed and will be performed following the principle of intention-to-treat. Missing data will be imputed using multiple imputation, which provides unbiased estimates of whether the pattern of missing data is missing completely at random or at random. If the pattern of missing data is nonignorable missing, accounting for missing values is complex and there is no fully satisfactory method for preventing bias other than modeling the mechanism that resulted in missing values which most often cannot practically be done, and in this case, multiple imputations is no worse than the usual approach of dropping subjects with missing data. Before accepting the results of the model, we will make sure the results conform to the assumptions of the model (eg, reviewing residual plots), and we will make sure that no observation has undue influence on the estimates produced by the model (eg, Cook D). We will conduct exploratory analyses to examine relationships among variables and their changes in response to the intervention. We will examine, in separate models, the association of hip abductor muscle properties including (1) peak MVIC as determined with the biodex, (2) cross-sectional area, (3) composition (% of intramuscular fat determined from CT), and (4) activation during gait as determined by electromyography as predictors of 5 outcome measures (1) FSST, (2) mini-BESTest, (3) functional gait assessment, (4) modified physical performance test, and (5) stride time variability. We will test the associations (1) at baseline and (2) we will examine the association between the change in the predictor variables and the change in the outcome variables. In addition, we will examine the association between the changes in baseline variables and fall rate, including the fall rate assessed during 1 year of follow-up post intervention, and the number of fall-free weeks. Finally, we will assess the association between the changes in predictor variables during the intervention and subsequent fall rates. This will provide a wealth of information on the interrelationship between hip abductors, balance, mobility, and fall risk.

Data Management

Participants will be assigned a unique study ID stored in a password-protected database on a VA server that has a level and scope of security that equals or exceeds that established by the HIPAA Security Rules. Data collected during the study that is not captured electronically will be entered and stored in the VA REDCap (Research Electronic Data Capture; Vanderbilt University) system. Participants' charts will be held in a locked room inside a locked cabinet. Access to individual participant numbers or personal identifiers will be limited to research team members who need these data to perform their roles in this study.

Participant Safety and Minimizing Potential Risk

While we anticipate that there may be some risks associated with participating in this research program, we have attempted to minimize them. Subjects will undergo procedures that involve a mild-to-moderate degree of risk, including exercise and balance training and testing, strength assessments, and muscle composition assessments, including DXA and CT scans. Completion of exercise and balance training and testing is associated with the risk of falls and cardiovascular complications such as chest pain, heart attack, or sudden death, and complications related to stress and strains of muscles or twisted ankles. The risk of falling is comparable to the participants' everyday lives, as the training is designed to use elements of everyday activities. We anticipate that some individuals may fall during the intervention, but the risk of falls and injury will be minimized by the supervision of all activities by trained study personnel. Furthermore, the risk of cardiovascular complications is minimal. The American Heart Association consensus statement on exercise standards estimates that the acute risk of sudden cardiac arrest during exercise training in participants with known cardiac disease is approximately 1 event per 60,000 hours of aerobic exercise [34]. The risk of exercise training is greater at higher exercise intensities. This risk is offset by prescreening participants with medical evaluations before exercise. There is also some risk for muscle soreness with the use of strength training as well as NMES. This will be minimized through the delivery of the intervention by trained study staff and proper education with all activities.

The risks of muscle composition assessments with DXA and CT scans include the risk of radiation exposure. While any dose of radiation could be potentially harmful, the radiation-related risks associated with the measurement of muscle composition are well within the established dosimetry of radiation guidelines for research participants, and radiation safety protocols will be maintained for all participants.

Ethical Considerations

This study has been approved by the University of Maryland School of Medicine IRB (HP-00110719) and the Baltimore VA Medical Center Research and Development Committee in accordance with the ethical standards of responsible committees on human experimentation and with the Helsinki Declaration. Informed consent will be obtained from each participant before any study procedures, and they will be allowed to opt out at any point. Any adverse, notable, or unexpected events will be reported to an independent, internal Data Safety Monitoring Board. The University of Maryland IRB and the VA Maryland Health Care System Research and Development Committees require a data and safety monitoring plan for all studies classified as greater than minimal risk. This study meets the

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regulatory criteria for a greater than minimal risk study. As it is supported by the Baltimore VA Medical Center Geriatric Research and Education Clinical Center, per internal policies, it will undergo biannual review by the Baltimore VA Medical Center Geriatric Research and Education Clinical Center's internal data safety monitoring board. The board's composition and standard operating procedures have been approved by the University of Maryland IRB. Its primary focus is safety, particularly monitoring expected and unexpected adverse events directly attributable to study participation (ie, falls on the treadmill).

Dissemination

Results from this study will be available to health care professionals and the public through the National Library of Medicine PubMed Central website within 1 year after the date of publication. In addition, study findings will also be presented at scientific meetings. The study investigators will be solely responsible for drafting all publications and will not engage professional writers.

Results

Overview

This study was funded on January 1, 2022, with a data collection period from April 1, 2022, to December 31, 2026. As of March 2025, we have screened 100 potential participants and excluded 38. Of the 61 participants enrolled to date, 21 have completed the 12-month follow-up, 32 have completed the 6-month follow-up, and 41 have completed the posttesting. A total of 4 participants are currently in the intervention phase; 1 has just completed the baseline testing, while 15 have been dropped from the study (Figure 1).

Expected Outcomes

Based on our preliminary data showing that the addition of NMES to the MMBI program results in greater improvements in the FSST and hip abduction strength, we anticipate that those in the NMES + MMBI group will make significantly greater improvements in all measures during the 12-week intervention compared with the MMBI-only group. As noted above, we anticipate that a small number of individuals will make no improvement following the intervention (nonresponders). We expect that we will have fewer nonresponders in the NMES + MMBI group compared with the matched MMBI group due to the superimposed muscle activation provided by the addition of NMES. We further hypothesize that the nonresponders in the MMBI-only group will exhibit increased IMAT and lower torque of their hip abductors at baseline, as the presence of IMAT is thought to contribute to impaired muscle activation [15,16,21]. While we anticipate that NMES will primarily maximize changes in the gluteus medius and gluteus minimus (the primary hip abductors), we will also examine how changes in these muscles, along with the tensor fasciae lata, contribute to changes in fall risk and strength. If changes in the TFL are advantageous, this information can be used to design a future trial targeting the use of the TFL to compensate for maladaptive changes in the primary hip abductors. We also anticipate that the NMES + MMBI group will demonstrate greater retention of the positive changes from baseline at both the 6- and 12-month timepoints following the cessation of the program and fewer falls due to improvements in the muscle quality of the primary hip abductors.

Discussion

Principal Findings

We anticipate that this VA Merit award will establish NMES as an efficacious therapy that can be used in conjunction with hip abductor strengthening and balance training programs for fall prevention. This comprehensive and augmented training approach has the potential to change existing treatment paradigms for the management of falls in older adults. NMES is a low-cost intervention that can be easily disseminated with the aim of reducing disability and health care costs related to the consequences of falls in older adults. While other studies have investigated the use of NMES in older adults, the majority have focused on its application to the more distal muscles of the lower extremities, such as the quadriceps or the plantar flexors [35]. The outcome measures in these small (often less than 20 people per intervention) studies [26,36,37] have been strength or static balance measures, but do not examine changes to balance and fall risk as they relate to the hip abductor alterations. Instead, NMES was frequently limited to unilateral application to measure changes in gait mechanics.[26] Also, these studies did not target older adults [36,38,39]. Our study will be among the first, large RCTs to examine the combined use of NMES on the hip abductors in conjunction with a multimodality balance intervention designed to improve balance and mobility and thereby reduce falls in older veterans.

Our study will use CT imaging to evaluate changes in muscle cross-sectional area and quality (ie, composition) posttraining. The use of CT imaging will allow us to examine changes in both the primary (gluteus minimus and gluteus medius) as well as the secondary (tensor fascia lata) hip abductors. Imaging the primary and secondary hip abductors will allow us to examine the changes and relative contributions of changes in both the primary and secondary hip abductors to mobility and fall risk in older veterans.

Understanding the contributions of the hip abductors to balance and mobility and finding targeted means to improve their function opens important new treatment options for older adults who are at a high fall risk. This study will address an important knowledge gap about the relative contribution of the primary and secondary hip abductors to dysmobility and fall risk. In previous studies examining the effects of resistance training on balance, less than 30% included any resistance training of the hip abductors [40] and no studies examined the hip abductors as a primary outcome measure, or used muscle imaging techniques such as CT scans to examine changes in both the primary and secondary hip abductors. Given our previous work demonstrating the importance of the hip abductors to balance recovery [11] and stepping [13], our study is a novel and important outcome in this population of older veterans. Finally, following the changes in both muscle composition and fall risk at 6 and 12 months after the end of training will allow us to

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evaluate the durability of the intervention to convey meaningful long-term benefits of the program.

Limitations

Despite the numerous strengths of this study, it has several potential limitations. Our target population includes adults aged 55 years and older who are at risk of falls. This may confound our findings' generalizability to other studies, as it is a younger age than many fall studies that traditionally only recruit older adults aged 65 years and older. We believe this traditional approach is suboptimal as falls are not just a problem of advanced age, as demonstrated by the earlier sharp increase in the prevalence of falls starting in middle age [41]. Excluding individuals 65 years and younger who are at high risk for falling (those who have previously had a fall, or those who demonstrate balance abnormalities) may prevent the opportunity for early intervention in an "at-risk" population [41]. Therefore, we intentionally decided to include a younger population in our study than the one traditionally used.

Another potential limitation of this study is the anticipated predominance of male participants. So far, we have enrolled 61 participants, consisting of 50 (82%) men and 11 (18%) women, which differs significantly from the general population, where 44.6% of individuals aged 65 years and older are male and 55.4% are female [42]. However, census data show that 96% of veterans in this age group are male [1], suggesting that our cohort may more accurately represent the veteran population. The inclusion of adults aged 55 years and older may explain the higher proportion of female participants in our study.

Our study does not include any "sham" treatment for NMES. The inclusion of a sham treatment with NMES on the hip abductors was considered. However, even low currents may have a confounding effect, and we therefore chose not to include a sham treatment. Finally, there are multiple other outcomes that could be evaluated, such as biomechanics. We have purposefully chosen our primary outcomes for this grant to be clinically meaningful, with an interest in hastening translation to patient care. Though we hope this study will inspire future biomechanistic studies, the inclusion of such measures is outside the scope of this project. Should NMES indeed enhance the beneficial effects of MMBI, there will be a strong rationale to examine the underlying biomechanical changes further.

Future Directions

Our analysis of the responders and nonresponders will provide important information for future studies, as it may help us to identify a subpopulation of individuals that may benefit most from the application of NMES. Our collection of the NMES stimulation intensity (mA) used and the number of sessions attended will enable us to evaluate a dose response of NMES and changes as our primary outcomes. This information could be used to design a future trial that examines these variables to optimize the application. As previously described, we will also examine the contribution of changes in both the gluteus medius and gluteus minimus and the tensor fasciae lata to changes in fall risk and strength. This may lead to future trials targeting the TFL to compensate for maladaptive changes of the primary hip abductors if our analysis reflects that it is indeed advantageous. Thus, the proposed research from this study will not only provide valuable information about the use of NMES to improve hip abductors and reduce fall risk but also provide multiple future research directions.

Conclusions

This clinical trial seeks to provide evidence from the first large, randomized control trial to test the hypothesis that NMES applied to the primary hip abductors, in addition to a multimodality balance intervention, is an efficacious adjunct to traditional rehabilitation to improve balance, mobility, and function in older veterans at risk for falls. If proven effective, this low-cost adjunct to resistance exercise can be easily transitioned into clinical practice to better reduce disability and defer health care costs related to falls in older adults.

Acknowledgments

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Data Availability

The datasets generated and analyzed during this study will not be publicly available due to confidentiality requirements and institutional policies of the Department of Veterans Affairs, but they will be available from the corresponding author upon reasonable request. A deidentified, anonymized dataset will be created and shared under a data use agreement, which will limit data use and prohibit any attempts to identify or reidentify individuals. Model consent forms and other related documentation given to participants will be uploaded to ClinicalTrials.gov as required.

Authors' Contributions

OA and BF wrote the initial draft of the manuscript and completed the editing and formatting. All other authors reviewed and edited the manuscript. All authors approved the manuscript for publication.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
Peer review from the United States Department of Veterans Affairs, Musculoskeletal Health and Function, Rehabilitation Research and Development Parent IRG.
[PDF File (Adobe PDF File), 47 KB - resprot_v14i1e68082_app1.pdf]

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Abbreviations

CT: computed tomography
FGA: Functional Gait Assessment
FSST: four-square step test
HIPAA: Health Insurance Portability and Accountability Act
IMAT: intramuscular adipose tissue
IRB: institutional review board
mA: milliamps
MMBI: multimodality balance intervention
MPPT: Modified Physical Performance Test
MVIC: maximum voluntary isometric contraction
NMES: neuromuscular electrical stimulation
REDCap: Research Electronic Data Capture
SAS: Statistical Analysis Software
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TFL: tensor fasciae lata
VA: Veterans Affairs

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Protocol

The Impact of Mechanisms of Action on Adherence and Outcomes in Self-Guided Digital Mental Health Interventions: Protocol for a Randomized Controlled Trial With Mediation Analysis

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Abstract

Background: One of the main recognizable challenges in the digital mental health interventions field is that users adhere to these interventions in their unguided forms poorly. Studies have shown that a persuasive system design focused on encouraging users to make positive behavior changes in their lives can increase user engagement and a program's efficacy. This design approach can be referred to as therapeutic persuasiveness (TP) and includes a call to action, monitoring, ongoing feedback, and program adaptation based on user state. The goal of this study is to examine the causal impact of TP on program completion and outcomes in unguided digital mental interventions. We aim to examine these questions in digital parent training programs (DPTs) aimed at treating children's behavior problems.

Objective: This study aims to (1) examine the impact of TP quality on usage, reduction in child behavior problems, and improvement in parenting variables; (2) examine the maintenance of treatment gains over a follow-up period; and (3) examine mediational pathways, including whether adherence to the program (measured by module completion rates) mediates reported changes.

Methods: A randomized controlled trial will be conducted to compare 2 interventions that use the same evidence-based components of established DPTs, but that differ in terms of the quality of TP (standard: DPT-STD; enhanced TP: DPT-TP). We will recruit parents from 160 families with children aged 3-7 years with behavior problems who will be randomized into one of the 2 intervention arms. We will measure child behavior problems and related parenting variables at 5 time points: before (T1), during (T2 and T3), and after the intervention (T4 and T5). Program usage will be passively collected.

Results: The study was funded in October 2023, and enrollment began in September 2024. As of the end of December 2024, 100 participants were enrolled in the study. Analyses are expected to be completed by September 2027.

Conclusions: Identifying conceptual scientific theories that draw a link between active ingredients embedded within a digital intervention function and their outcomes is crucial in advancing our understanding of what influences usage and outcomes.

Trial Registration: ClinicalTrials.gov NCT06514326; https://clinicaltrials.gov/study/NCT06514326

International Registered Report Identifier (IRRID): DERR1-10.2196/71238

(JMIR Res Protoc 2025;14:e71238) doi:10.2196/71238

KEYWORDS

persuasive design; digital parent training; clinical trial; user engagement; usage; mechanisms of change; mechanisms of action; active ingredients

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Introduction

Background

Unguided digital mental health interventions have the potential to increase public access to evidence-based support [1,2]; however, one of the main recognizable challenges in this field is that users poorly adhere to digital programs in their unguided forms (eg, [3-6]). Clearly, a program cannot support its users in reaching beneficial outcomes if it is not being used. Aiming to address this challenge, over the years, more attention has been given to how theorized mechanisms of action reflected in the software's functions impact program usage, program completion, and the intervention's effectiveness (eg, [7-9]). Systematic reviews examining the characteristics of digital interventions have suggested that user adherence [10], positive behavior change [11], and program efficacy [12] can be increased by embedding a persuasive system design focused on the incorporation of behavior change techniques. For brevity, we refer to this design approach as therapeutic persuasiveness [13].

Attempts to look under the hood of the digital intervention itself are especially important in light of a randomized controlled trial (RCT) suggesting that adding an unguided digital engagement facilitating intervention before the use of the unguided intervention itself does not increase adherence to the program (defined as number of modules completed) [14]. One of the potential next steps would be to focus on the way the intervention alone should be conceptually designed to increase adherence and efficacy.

Therapeutic Persuasiveness

Therapeutic persuasiveness addresses how the eHealth program features as a whole are designed to encourage users to make positive changes in their lives. While persuasive system design may be linked to the general use of programs that are not for the benefit of the end user, therapeutic persuasiveness focuses on health-related programs in which users are encouraged to take benevolent actions for their benefit. Following a comprehensive systematic review of published quality criteria of eHealth interventions, we identified several criteria that define a therapeutically persuasive program. The main criteria are a call to action (ie, the provision of triggers to prompt goals and encourage users to complete them), monitoring, ongoing feedback, and program adaptation based on user state and goal achievements [13].

Let us take, for example, the goal of helping parents to increase the number of positive interactions they foster with their children. From the standpoint of a traditional digital program, the main focus would be on providing psychoeducation and suggestions during the use of an eLearning module to increase the occurrence of positive interactions with children. From a therapeutic persuasiveness perspective, however, the intervention designer should also strive to reach parents in their daily environment and make the notion of positive interactions salient in their minds above competing activities. This could be done by triggering parents at the right time to inspire them, monitoring the positive interactions they are engaged with, and providing parents with appropriate acknowledgment and feedback based on their state [15,16].

From the perspective of behavior change theories, the absence of these features, whether delivered through digital components or a human coach, cannot ideally support users' self-management of desired and undesired behaviors, or their ability to respond to areas of difficulty they may encounter during the therapeutic process (eg, [17,18]). Congruent with these studies, meta-analyses have found that interventions that include self-monitoring components in conjunction with other components (eg, goal setting and feedback on performance) have been significantly more effective [19,20]. Conceptually, programs with a higher quality of therapeutic persuasiveness should therefore be used to a greater extent (resulting in better adherence to the digital program) and deemed more effective.

In correspondence with these ideas, our team examined whether the quality of unguided eHealth interventions could predict the product's real-world usage, using the Enlight suite of quality ratings (usability, visual design, user engagement, content, therapeutic persuasiveness, therapeutic alliance). Programs' usage metrics were gathered based on a dataset of anonymized logs from consenting users, simultaneously comparing user traffic between 30 (Microsoft Internet Explorer add-on) and 70 (SimilarWeb Pro panel) different eHealth interventions. The incorporation of therapeutic persuasiveness within the software functions was found to be the most robust and stable predictor of program usage, explaining 11%-42% of the variance in program usage in the regression models [21,22]. These findings are not causal; however, they imply that enhancing the quality of therapeutic persuasiveness as a mechanism of action in unguided interventions may increase the intervention's acceptability and efficacy. Testing whether this causal relationship exists is the focus of this proposal.

The Targeted Intervention: Digital Parent Training Program

To examine the proposed causal impact of therapeutic persuasiveness on adherence and efficacy, there is a need to focus on a specific clinical target. This proposal focuses on a digital parent training program (DPT) aimed at treating child behavior problems. This targeted intervention represents a classic case study that can be used to examine the causal impact of therapeutic persuasiveness for several reasons as follows:

- It involves a common public mental health problem. Behavior problems are among the most prevalent types of childhood mental health problems [23,24]. When left untreated, behavior problems impose significant social, emotional, and economic costs, and place a burden on individuals, families, and societies [25,26].
- Parent training aimed at treating child behavior problems is required in an unguided digital form to address the need for increased access to care. While a strong body of evidence supports the efficacy of parent training programs targeting child disruptive behaviors (eg, [27-31]), the provision of evidence-based treatments for children and adolescents is very limited (eg, [32,33]), stressing the need to develop digital forms of care.

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- Parents poorly adhere to DPT in its unguided form. DPTs aimed at treating child behavior problems have been introduced over the last decade as a way to increase public access to care [34-36]; however, poor adherence to unguided DPTs has been reported [37,38]. For example, in an RCT of a DPT, Day and Sanders [38] showed that a completely unguided DPT resulted in poor module completion rates, compared with a human-supported condition of the same program (median module completion of 2 and 7, respectively). There is a question as to whether enhancing the therapeutic persuasiveness quality of unguided DPTs could increase program completion rates as well.

Pilot Study

A pilot study was recently conducted to initially examine the causal impact of therapeutic persuasiveness on user adherence to the program and the program's efficacy. In this pilot, parents of children with behavior problems were randomly allocated to receive either a standard DPT (DPT-STD) or a DPT designed with enhanced quality of therapeutic persuasiveness (DPT-TP). Both interventions used the same evidence-based content but differed in the quality of their therapeutic persuasiveness. Parents from 88 families who have a child with behavior problems were enrolled in the study. Compared with DPT-STD (n=43), participants allocated to DPT-TP (n=45) used the program significantly more (*P*s<.001; Cohen *d*s=0.91-2.22). In terms of program completion, 68.9% (31/45) of DPT-TP participants completed it compared with 27.9% (12/43) of DPT-STD participants. Significant differences between the interventions were also found in reported improvements in child behavior problems, favoring DPT-TP (*P*s<.05; Cohen *d*s=0.43-0.54) [39].

In a qualitative thematic analysis of semistructured interviews, DPT-TP users identified features embedded exclusively in the enhanced program, such as call-to-action reminders and assessment-based feedback, as important components that helped them in their process of change [40].

This Study

This study aims to (1) conduct a fully powered RCT design that can provide strong support for the hypotheses; (2) examine the long-term impact of the treatment and the maintenance of treatment gains over a follow-up period, knowledge that is of great importance when aiming to determine whether enhanced mechanisms of action embedded in unguided interventions are maintained over time (or even better in comparison with standard programs); and (3) examine meditational pathways including whether adherence to the program, measured by module completion rates, mediate reported changes.

The study design is a 2-arm parallel-group RCT with repeated measures. It consists of 2 intervention arms for parents of children with behavior problems. We will follow a large sample of families with parents who report having a child with behavior problems, before, during, and after receiving the DPT they are randomly allocated. In particular, this study has the following hypotheses:

1. Adherence and usage: Compared with parents who receive DPT-STD, parents who receive DPT-TP will show better adherence to the digital program (operationally defined as program completion rate) and higher metrics of program usage (number of logins, unique days of use, and total time of use).
2. Efficacy: Compared with parents who receive DPT-STD, parents who receive DPT-TP will report greater improvements in child behavior problems (Eyberg Child Behavior Inventory [ECBI] Intensity), parenting practices (Specific Parenting Practices [SPP], The Parenting Scale [PS], and Alabama Parenting Questionnaire [APQ]) and Parental self-efficacy (The Parenting Tasks Checklist; Me as a Parent [MaaP]), as measured pre-post and pre-follow-up.
3. Mediational pathway: Program completion rate will mediate the impact of therapeutic persuasiveness quality on outcome variables.

In addition, we will explore whether the relationship between program usage and changes in parenting variables and child behavior problems is moderated by program quality (moderated mediation).

Methods

Overview

The study and protocol are carried out in accordance with SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (refer to Multimedia Appendix 1 for SPIRIT checklist) and Cochrane Collaboration tool [41,42]. The study was preregistered (ClinicalTrials.gov NCT06514326), and the finalized study protocol number is DPT_08/24. There are no deviations from the original study protocol or trial registry at this time.

Participants and Recruitment Procedure

Eligibility

Parents will be eligible to participate if they (1) have a child aged 3-7 years, (2) report high levels of behavior problems based on the ECBI subscales (ECBI Intensity ≥132; [43]), and (3) have access to a smartphone device with an internet connection. Parents will be excluded if they report that their child is taking medication or is in regular contact with a professional for behavioral or emotional problems, they are currently accessing parenting support elsewhere, or their child has been diagnosed with an intellectual disability or developmental delay. Parents not eligible to participate will be referred to local services.

Recruitment Procedure

Parents will be recruited through relevant social media parenting groups, Facebook advertisements, and pamphlets sent to relevant childcare settings. Prospective participants will be directed to the project website, which will offer basic information and a link to a brief eligibility screener consisting of the exclusion criteria and 9 items assessing the parents' experience of their child's behavior, based on *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria for oppositional defiant disorder (to pass screening parents had to receive an average of 4.22 or above). Screening, interest, and parents'

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understanding of the terms of the study will be confirmed by a phone call with a research assistant. Parents will then be directed to a web-based informed consent form, followed by the baseline assessment battery. Once participants have completed baseline assessments and are deemed eligible, they will be randomly assigned to one of the 2 conditions (1:1), stratified for child gender, by an independent researcher who is blind to their assessments and has exclusive access to the assignment sequence. A computer-generated randomization procedure will be used with randomly generated block sizes of 2, 4, and 6. Ineligible participants will be informed about available public mental health care services.

Measures

The study instruments include self-reported questionnaires that will be assessed at all time points for this study (T1-T5) and data on program usage. Parents will also complete a demographic questionnaire at baseline (T1). Participants will be assessed at 3.3 weeks (T2), 6.6 weeks (T3), and 10 weeks (postintervention; T4), and will complete follow-up assessments at 6 months after the beginning of the intervention (follow-up; T5). The self-report measures will be administered through Qualtrics (Silver Lake).

Eyberg Child Behavior Inventory

Child behavior problems will be assessed using the Intensity subscale of the 36-item ECBI [44]. For each item, caregivers rate the intensity of the behavior (1=never to 7=always). The ECBI has proven to be useful in discriminating between problem and nonproblem children for evaluation and in reflecting behavior change problem symptoms following treatment interventions [45,46].

The Parenting Scale

Parental disciplinary behaviors in response to their child's misbehaviors will be assessed using 2 PS subscale scores, Over-reactivity (11 items) and Laxness (10 items), which reflect effective discipline and discipline mistakes on either end, using a 7-point Likert scale. Internal consistency scores (Cronbach α) have been reported (Laxness α=0.83; Over-reactivity α=0.82). These scores have also been found to correlate significantly with observational measures of dysfunctional discipline and child misbehavior [47].

Alabama Parenting Questionnaire Positive Parenting Practices

One dimension of parenting practices will be assessed using the APQ Positive Parenting Practices subscale (6 items) [48]. Parents will be asked to rate each item on a scale of 1 (never) to 5 (always) according to how often it typically occurs in their home. The dimension has shown good internal consistency in parents of children, with Cronbach α ranging from α=0.72 to α=0.77 and a test-retest reliability of 0.85 [49,50]. The dimension has also shown criterion validity in predicting externalizing behavioral problems among children [50].

The Parenting Tasks Checklist-Self-Efficacy

Task-specific self-efficacy will be assessed using the Setting Self-Efficacy (14 statements) PTC subscale [51]. Item responses are given on a scale of 0 (certain I can't do it) to 100 (certain I can do it). The subscale has shown excellent internal consistency with a Cronbach α value of 0.91 and has also been found to discriminate between mothers of children with behavior problems who exhibited lower self-efficacy and mothers of a normative sample of children from the community [52].

Me as a Parent (Parental Self-Efficacy)

Overall self-efficacy will be assessed using the 4-item Self-Efficacy subscale of MaaP. Sample items include "I have confidence in myself as a parent" and "My parenting skills are effective." Each item is rated on a Likert scale (1=strongly disagree and 5=strongly agree). The subscale has shown good internal consistency with a Cronbach α value of 0.75 [53].

Behaviors and Feelings Survey

The Behaviors and Feelings Survey (BFS)–Internalizing Problems Caregiver version will be used to capture parents' reports on their child's emotional problems (eg, anxiety and sadness). It is based on 6 items that are rated on a scale from 0 (not a problem) to 4 (a very big problem). The BFS has demonstrated strong psychometric properties, with evidence supporting its reliability and validity across diverse populations [54].

Specific Parenting Practices

Specific parenting practices that are expected to be the direct result of the phases that the program is comprised of will be measured using a scale developed for this study. It includes 12 items. For example, a sample item targeting the practice of "recognizing positive behaviors in your child" asks: "To what extent were you able to express open appreciation and reinforce your child for specific positive behavior demonstrated?" Parents will be asked to rate how often within the past 2 weeks they presented the expected skill on a Likert scale (1=never and 7=always).

eHealth Therapeutic Alliance Inventory

The therapeutic alliance in the digital intervention will be assessed at 3 time points (T2-T4) using the eHealth Therapeutic Alliance Inventory (ETAI). It includes 6 items designed to evaluate the strength of the therapeutic relationship in eHealth interventions. Participants rate their agreement with each item on a Likert scale (1=strongly disagree and 7=strongly agree). The inventory has been validated for use in digital health contexts, demonstrating strong reliability and sensitivity to changes in alliance over time [55,56].

Quality Assurance

Parents will be invited to respond in writing at postintervention (T4) to the following open-ended questions: "What advantages, if any, did you find in using the program to create a change in the way you react to your child? "Did the program assist you in creating a positive change with your child?" and "What aspects of the program did you appreciate the most?" In addition, perceived usefulness ("The DPT helped me manage my child's misbehavior or become a better parent") and satisfaction ("I would recommend the DPT to parents of children with behavior problems") will be evaluated at postintervention (T4) using a 5-point Likert scale from 1 (I do not agree) to 5 (I agree).

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Program Completion Rate and Usage

Program usage (eg, login activities, time spent using the program, modules begun and completed) will be automatically documented within the digital platform. Program completion rate is defined as the number of modules the user completes divided by the number of modules the user is expected to complete (7 in DPT-STD and 4-7 in DPT-TP).

Overview of Interventions

The intervention content includes 7 modules recommended to be completed within 9 weeks. Each module discusses a specific theme: (1) introduction to parent training, (2) positive interactions and quality time, (3) parental emotion regulation, (4) effective routines and clear ground rules, (5) recognizing positive behaviors and ignoring minor negative behaviors, (6) overcoming disobedience, and (7) mindful parenting and conversation between partners.

Interventions are delivered through MindTools, an open-source eHealth platform that was originally developed under the name Serafin by Professor Håvar Brendryen from The University of Oslo. The platform was further upgraded by the author (AB) and is available on GitHub [57]. The parenting programs themselves are available to download on Open Science Framework [58]. All content components can be delivered based on logic-driven rules (if-then statements; Figure 1).

Figure 1. A screenshot with an example of the system's admin user interface that allows the creation of a logic-driven intervention. Within each arrow, a condition can be created, which determines whether a certain node will be deployed. Blue arrows are between web pages and notifications that the participants view and interact with; gray arrows are back-end processes.

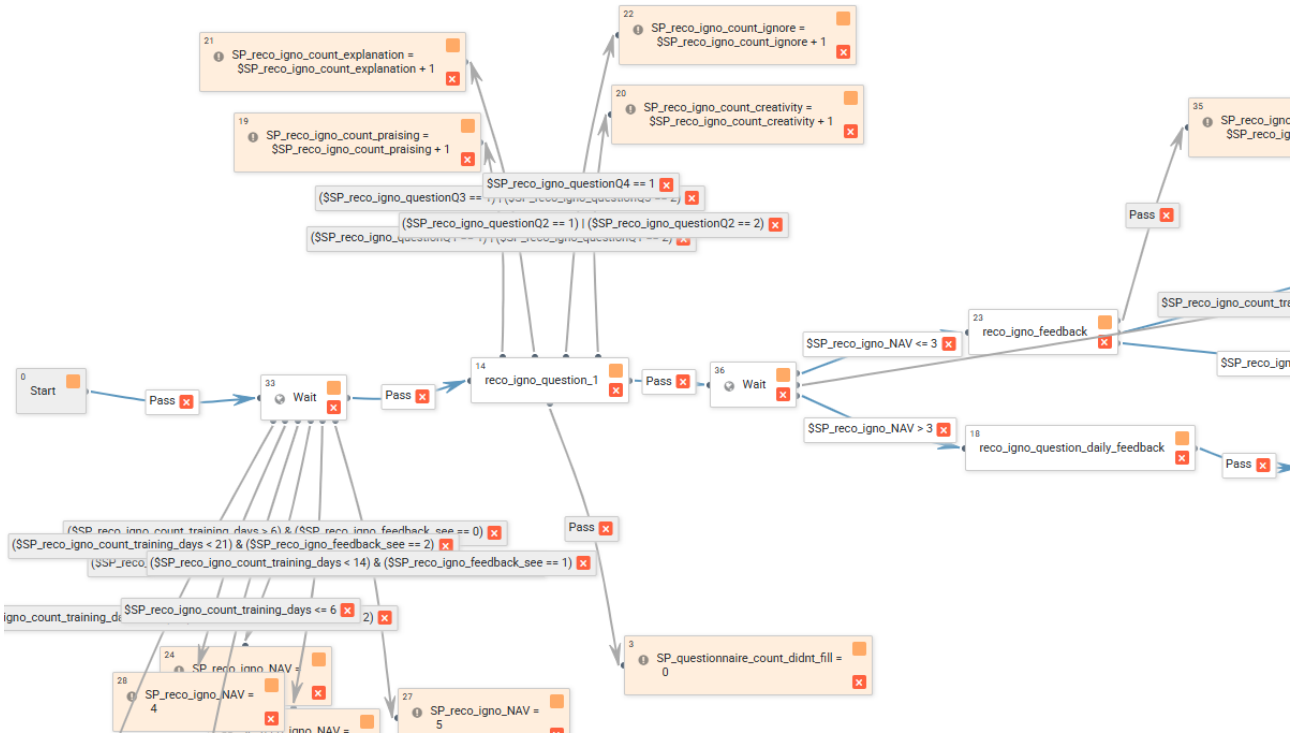

Standard Digital Parent Training Program

The DPT-STD comprises seven 10- to 25-minute modules, each corresponding to one of the themes mentioned above. Each module's content includes videos and texts guiding the parent through the training process and interactive features, such as multiple-choice questions with direct feedback. Additional features embedded within the platform include downloadable materials and a "Q&A" section that contains frequently asked questions.

Digital Parent Training Program With Enhanced Therapeutic Persuasiveness Quality

The DPT-TP intervention includes all the ingredients of DPT-STD, but with additional features that correspond to the conceptual model of therapeutic persuasiveness, meant to enhance adherence to the program. The program itself is based on predefined decision rules that are either event- or time-based [59], developed in accordance with a user-centered design approach [60]. Each module in the program comprises the learning phase described above, followed by a 1- to 2-week focusing phase.

The focusing phases are designed to help the desired therapeutic activities become salient in the parent's mind and to help the parent acquire skills in a nonjudgmental manner while avoiding the burden and potential failures that may be associated with the idea of "training." Accordingly, the program uses the following features.

Call to Action

During each focusing phase, parents receive timely triggers (with tips or motivating notes) via SMS text messages that are related to the specific goals and therapeutic activities of the modules they have completed. Triggers draw on accepted paradigms for the tailoring and adaptation of digital triggers (for a review see [59]). For example, in the relevant program phase, motivational messages or tips related to the recognition of positive child behaviors (module 5) are sent 30 minutes before

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the parents are expected to interact with their child when they come back from work.

Monitoring and Ongoing Feedback of User State

Specific practices related to the therapeutic activities or skills that are currently being taught are documented within the system using a brief daily report that includes no more than 7 logic-driven multiple-choice questions and takes less than 2 minutes to complete. These questions ask about parental practices based on a step-by-step script. This is meant to help the parent implement the new way of thinking during their interactions with their child. The program offers nonjudgmental feedback, recognizes desirable achievements based on operant theory, and sends specific messages related to the parent's current report to help increase motivation for change or reveal new information. For example, across disciplines, positive feedback following positive behavior improves outcomes, whereas negative feedback following failure may reduce motivation and efficacy [61-63].

Adaptation to User State

At the end of the first module (introduction), parents will be asked to report about the current state at home, and this will be used to recommend whether to complete the 3 learning modules that are not deemed obligatory: positive interactions, emotion regulation, and effective routines. Parents' reports on their activities are used to acknowledge their success and to suggest additional actions based on the specific goals reported by parents. Effort related to desired therapeutic activities is adapted based on graded tasks (defined as "load reduction of therapeutic activities" in our therapeutic persuasiveness model [13]). For example, when parents learn how to overcome disobedience (module 6), they will be guided to choose 1 specific behavior problem they would like to focus on first, and then, based on their progress, they will be directed to take additional steps.

Therapeutic Persuasiveness Fidelity

Our approach integrates elements such as clear goal relevance, continuous monitoring and feedback, and adaptation to the user's state. To achieve a satisfying user experience, it is essential that these elements work together effectively. When the users are explicitly required to achieve goals, their goal achievements are expected to be monitored, and it would make sense to also provide them with feedback, and so on. For this reason, the individual components of TP are interrelated and not distinguished in our manipulation. However, using the Enlight quality expert rating scale [13], we evaluated both programs. The DPT-STD design received a TP score of 2.1, which is near the "poor" category, whereas DPT-TP earned a 4.5, placing it between "good" and "very good" scores [39].

Analytic Plan

Preprocessing Steps: Data Audit and Missing Data

The final trial dataset will be accessed by the research coordinators, a statistician, and the principal investigator. Preprocessing will include an examination of data accuracy to identify and correct errors and to ensure that all data are in range. In addition, univariate outliers will be identified (observations that are 3 SDs from the mean in both directions) and will be corrected using winsorizing [64]. Normality (ie, skewness and kurtosis) will be examined for all variables using standard tests (Shapiro-Wilk test and Kolmogorov-Smirnov test). If data significantly differ from a normal distribution according to these tests, we will use transformations depending on the precise deviations from normality (eg, positive skewness, negative kurtosis). Possible transformations will include square root, natural log, inverse, and the Box-Cox transformation [65]. The pattern of missing data will be assessed using Little's Missing Completely at Random test. Data that are missing completely at random or missing at random will be imputed using multiple imputations with 5 datasets. All preprocessing will be done using SPSS software (IBM Corp).

Hypotheses 1-2 Analytic Plan

Hypothesis 1 will be examined using a series of 1-way ANOVAs. Specifically, treatment type will be the independent variable (DPT-STD vs DPT-TP) in all analyses, and program completion rate, number of logins, unique days of use, and total time of use will be the dependent variables. If the treatment conditions significantly differ on important demographic or clinical variables, those variables will be added as covariates to the analysis, creating an analysis of covariance (ANCOVA).

Hypothesis 2 will be examined using two 2-way ANOVAs with treatment type (DPT-STD vs DPT-TP), measurement (pre vs post in the first ANOVA and pre vs follow-up in the second), and their interaction as independent variables. Child behavior problems (ECBI Intensity), parenting practices (SPP, PS scales, and APQ), and parental self-efficacy (PTC and MaaP) will be the dependent variables.

Assumptions of ANOVA will be examined for all analyses and corrected if not met using common procedures. For instance, the assumption of equality of variance will be examined using the Levene test, and if not met, we will use weighted least squares or robust tests such as Welch and Brown-Forsythe.

Mediation Analyses (Hypothesis 3 and Exploratory Examination)

These analyses will be based on the criteria of Zhang et al [66] for mediation in multilevel models. A 2-1-1 mediation model (Figure 2) in which the predictor (TP quality) is a level-2 antecedent variable (between-subjects variable) will be used. The potential mediator (program completion rate) and outcomes (child behaviors and parenting variables) are both level-1 variables (ie, repeated measurements-within-subjects variables). This model tests whether the study manipulation of predictor values influences the values of a level-1 mediator, which then affects a level-1 outcome. Mediation analyses will be conducted using relevant codes for Mplus (Muthén and Muthén) [67,68].

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Figure 2. A 2-1-1 mediation model. DPT-STD: standard digital parent training program; DPT-TP: digital parent training program enhanced based on therapeutic persuasiveness quality; TP: therapeutic persuasiveness.

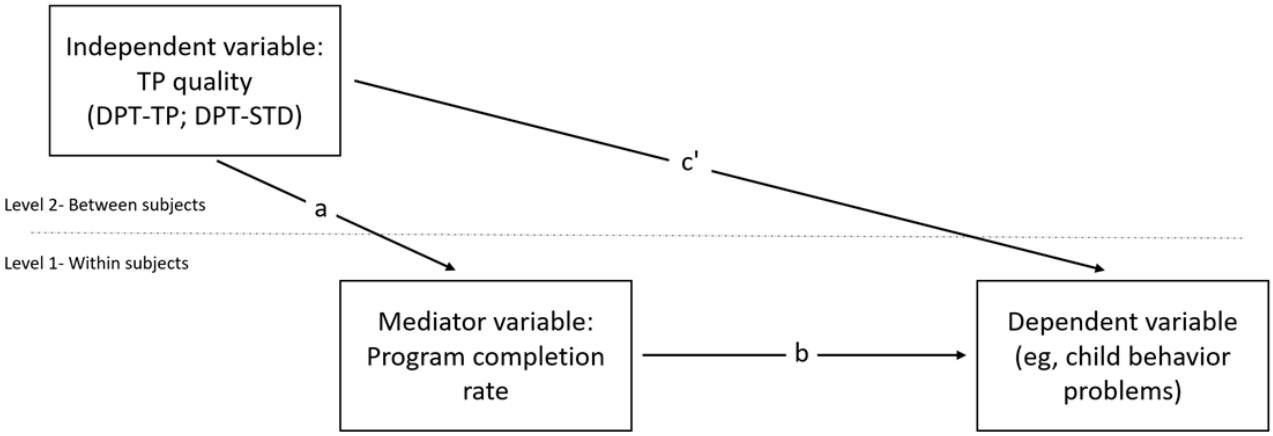

Power Estimation

Data emerging from the pilot suggest a large effect size difference in module completion rates and medium effect size differences between the 2 intervention groups in terms of change in ECBI scores and parenting variables post intervention (eg, primary hypothesis Cohen *d*s=0.43; 0.54) [39]. Taking the smaller effect size as an approximation (Cohen *d*=0.43), a total sample size of 80 participants in each of the 2 conditions and a total of 160 participants will provide 0.85 power (α=.05, 1-tailed) to detect significant differences in the primary outcomes (intent-to-treat analysis).

For our mediation analyses, we assume a large effect size difference in program completion rate based on TP quality (the A path), and a small to moderate effect size (correlation) between program completion and change in child behavior problems (the B path). Therefore, a sample size of 160 participants in total is higher than 150 participants, which would be sufficient to examine the relationship between program completion rate (the mediating variable) and child behavior problems (the predicted variable; for a review of sample size estimations for mediation effects, see [69]).

Ethics Approval

The study received ethical approval from the Institutional Review Board of the University of Haifa (approval number 418/23). All participants provide informed consent before their inclusion in the study (for further details, refer to the Participants and Recruitment Procedure section). Parents will receive a gift card compensation of up to 400 Israeli Shekels (approximately US $113) for their time spent completing assessments at 5 time points, regardless of intervention use. To ensure confidentiality, participant data will be collected using unique identification codes, with the code key securely stored in a separate location. Before data analysis, all data will undergo deidentification to protect participant privacy. No identifying information related to individual participants is present in any images or supplementary materials associated with this paper.

Results

The study was funded in October 2023, and Table 1 presents the timeline for study completion. As of the end of December 2024, we enrolled 100 participants in the study.

Table 1. Timeline for the study completion.

Objective	Beginning	End
Recruitment and eligibility screening of prospective participants	September 2024	June 2026
Conduct baseline assessments (TEST 1)	September 2024	June 2026
Initiate the assigned DPT[a] condition with participants	September 2024	June 2026
Conduct 3,6, 9-week assessments (TESTS 2-4)	September 2024	September 2026
Conduct 6-month follow-up assessments (TEST 5)	March 2025	December 2026
Analysis and write-up	January 2027	September 2027

[a]DPT: digital parent training program.

Discussion

Our anticipated principal findings are that, compared with parents in the DPT-STD condition, parents in the DPT-TP condition will demonstrate significantly higher program usage. We also anticipate that program usage will mediate the intervention's outcomes, meaning that parents in the DPT-TP condition will report greater beneficial changes in their parenting practices and their child's behaviors at postintervention time points. A key strength of this study is its examination of the process of change across multiple time points, before, during, and after the intervention, providing a unique opportunity to explore mediational pathways. However, a limitation of the study is the potential for beneficial changes occurring between

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these time points to go undocumented. Nonetheless, as incorporating additional time points introduces a trial bias that is evident in digital interventions [70], we aimed to balance these methodological trade-offs.

Identifying conceptual scientific theories that draw a link between active ingredients embedded within software functions and an unguided intervention's outcome could be useful in advancing our understanding of what causes and impacts usage and outcomes. Our work has shown that people with limited experience in the eHealth research field can learn how to reliably evaluate the therapeutic persuasiveness quality of a program, achieving high interrater reliability rates for both mobile- and web-based interventions (>0.85) [13]. This finding presents the transparency of this conceptual mechanism of action, which, if deemed relevant, could be useful for scholars worldwide.

From a conceptual perspective, this type of investigation addresses the potential gap between the incorporation of evidence-based content and the incorporation of an evidence-informed therapeutic process (ie, the availability of software functions that impact user interaction with the program and increase its effectiveness). At the clinical level, conducting a fully powered RCT of an unguided DPT for treating child disruptive behaviors in Israel means that, if the program is found effective, the intervention could provide a valuable public health resource for treating child disruptive behaviors throughout Israel, bridging the gap between scientific research and practice [2].

Acknowledgments

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Generative artificial intelligence (AI) was used solely for English-language proofreading in select paragraphs of this manuscript. No AI-generated content was used for any other aspects of the work.

Data Availability

The datasets generated or analyzed during this study will not be publicly available prior to the completion of all planned analyses and publications. They will be available from the corresponding author upon reasonable request.

Conflicts of Interest

AB is a director in the International Society for Research on Internet Interventions Board of Directors. He received grant funding from The Israel National Institute for Health Policy Research, National Institutes of Health, and the Israeli Scientific Foundation. He is providing consultancy services to Ifeel online. IMA is a director of Rakefet, a nonprofit organization for individuals with social anxiety disorder. He has received funding from the Israeli Scientific Foundation and is providing consultancy services for SequelCare.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOCX File , 21 KB - resprot_v14i1e71238_app1.docx]

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Abbreviations

ANCOVA: analysis of covariance
DPT: digital parent training program
DPT-STD: standard digital parent training program
DPT-TP: digital parent training program enhanced based on therapeutic persuasiveness quality
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TP: therapeutic persuasiveness

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Protocol

Web-Based Education Program for Care Partners of People Living With Dementia (iGeriCare): Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: The prevalence of dementia is increasing in Canada and in many countries internationally. People living with dementia are highly dependent on family and friend care partners, who may have little knowledge of the disorder. Web-based interventions in dementia have been shown to improve care partner mental health and reduce burden, but few have been widely implemented or rigorously studied. We developed a web- and email-based dementia education platform for care partners, iGeriCare, which includes 12 asynchronous, multimedia, e-learning lessons and email-based content to reinforce the learning.

Objective: The primary objective of this pilot study is to evaluate the feasibility and care partner acceptance of the intervention, including study methods. Secondary objectives will examine the effectiveness of the educational resources on family care partners' knowledge, self-efficacy, and sense of burden.

Methods: This study is a 2-arm, pilot, feasibility, randomized controlled trial. A total of 125 family or friend care partners for a person living with dementia—who are residing in Canada, aged 16+ years, and comfortable using the internet and email—will be recruited using coinvestigator networks and Facebook digital marketing advertisements. Participants will be randomly assigned to either the intervention group (receiving the dementia web- and email-based educational intervention) or the control group (receiving an alternate topic e-learning lesson and emails) and will have 8 weeks to complete baseline surveys and the assigned e-learning. After 8 weeks, participants will have 2 weeks to complete poststudy surveys. This protocol will be repeated with a second cohort of 100 care partners recruited from a paid panel service based on learnings from initial feasibility results.

Results: Initial recruitment began on September 6, 2022, and concluded on October 2, 2022. A total of 125 participants were randomly assigned to the intervention (n=61) or control (n=64) group. Data collection concluded in January 2023. Preliminary feasibility results showed a substantial number of participants who did not engage with the protocol as intended. A decision was made to recruit a second cohort of participants to address these protocol deviations. Secondary recruitment began on June 12, 2023, and concluded on June 27, 2023. A total of 100 participants were randomly assigned to the intervention (n=53) or control (n=47) group. Data collection concluded in September 2023. Further results will be published in peer-reviewed journals and presented at conferences.

Conclusions: This study is investigating the feasibility, acceptability, and effectiveness of a web- and email-based dementia care partner educational intervention. The results of this study will contribute to the planning of a larger randomized controlled

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trial in the future, as well as the evaluation of innovative, cost-effective, and efficient dementia care partner resources that can complement traditional approaches.

Trial Registration: ClinicalTrials.gov NCT05114187; https://clinicaltrials.gov/study/NCT05114187

International Registered Report Identifier (IRRID): DERR1-10.2196/67048

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KEYWORDS

web-based intervention; internet; eHealth; dementia; caregiver; Alzheimer disease; education and training; clinical trial; knowledge translation; randomized controlled trial

Introduction

Dementia Care Partners

People living with dementia rely on family care partners to provide support, most often without any formal dementia education. In Canada, at least 486,000 people identify as caring for an individual with dementia [1]; many more constitute informal family or friend care partners. By 2025, Canada will have more than 1 million care partners for people living with dementia who will provide an estimated 1.4 billion hours of care annually [1-5].

Numerous quality standards highlight the importance of education that helps care partners develop knowledge and skills to support themselves and a person with dementia in living well [1,6-8]. Providing evidence-based education to help care partners better understand dementia, its progression, treatment options, and available supports can be challenging to do in the clinical setting; time and resource constraints can impede a provider's ability to provide education. Although several education programs currently exist, they vary in availability and often lack the flexibility to accommodate the realities of caregiving.

Web-Based Strategies

Care partner–focused, web-based interventions have been shown to be both feasible and effective with respect to a range of outcomes. Recent systematic reviews found evidence for the positive effects of web-based interventions on self-efficacy, self-esteem, and strain of care partners of adults living with a chronic condition [9-13]. There is also evidence for the benefit of internet-based interventions on mental health for care partners of adults living with a chronic condition, particularly for the outcomes of care partner depression, stress and distress, and anxiety [14].

However, there remains a shortage of freely available, asynchronous, web-based programs that incorporate principles of multimedia learning design. Care partners of people diagnosed with dementia have identified the need for high-quality, accessible, and trusted internet resources [15]. There are several frequently unmet needs in dementia care partner education including flexible delivery methods as well as rigorous evaluation of program effectiveness [16-18]. Existing programs often rely on real-time components such as synchronous (live) webinars, which can be inconvenient for care partners and challenging to scale and spread. A recent scoping review highlighted the importance of several components of internet interventions, including evidence-based instructional design, codesigning online education with care partners and experts in dementia care, and using randomized controlled trials (RCTs) to more rigorously evaluate their effectiveness [19]. Comparable web-based educational programs in other chronic disease contexts provide valuable insights. The RHAPSODY program for young-onset dementia caregivers showed significant improvements in care partner confidence but required scheduled participation [20]. The STAR portal for dementia care partners demonstrated knowledge gains but faced challenges with user engagement and retention [21]. These experiences highlight the importance of flexible, asynchronous delivery and robust instructional design.

iGeriCare: Web-Based Educational Program for Dementia Caregivers

iGeriCare is a free, evidence-based, web- and email-based educational program for family and friend care partners of people living with dementia. It was developed by experts in dementia, e-learning, mental health, and lived experience caregiving to help meet the needs of care partners by improving their knowledge, and to raise awareness of strategies and services to improve their self-efficacy and quality of life [22-24].

iGeriCare is unique when compared to other care partner educational resources because it is one of the few web-based dementia care partner interventions to incorporate best practices in multimedia e-learning instructional design, asynchronous lessons, and email-based microlearning while remaining open access (free of cost) and without requiring users to create an account or log-in. Key components of the instructional design include the use of the principles of multimedia learning and audio narration; personalization, including the use of a visual "coach" or embodied instructional agent; segmenting the content into manageable topics to reduce cognitive load; authentic scenarios and worked examples; interactive review questions; and learner control over navigation [22]. An iterative, participatory instructional design and development methodology, the Successive Approximation Method [23], was used, with extensive involvement and review from a range of experts in dementia care, including lived-experience dementia care partners.

The asynchronous and fully web-based elements of the intervention have proven even more valuable during the COVID-19 pandemic when many face-to-face approaches have been unavailable [24]. It is easy to implement for clinicians and is an efficient and cost-effective way to address dementia care quality standards. This study, which is the first clinical trial studying the feasibility and effectiveness of the iGeriCare

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platform in a clinical trial, will be an important contribution to the literature on care partner web-based interventions. These innovations are an important complement to traditional approaches to care partner education, a key component of quality dementia care.

Research Aim

The overall aim of this study is to explore the feasibility, acceptability, and effectiveness of iGeriCare, a web- and email-based dementia care partner educational intervention.

Specific Objectives

The specific objectives of this study are to evaluate the feasibility and care partner acceptance of the intervention and other study methods and to examine the effectiveness of the educational resources on family care partners' knowledge, self-efficacy, and sense of burden.

Research Questions

This study aims to answer the following research questions: (1) Is the intervention feasible for participants? (2) Are participants engaged and satisfied with iGeriCare? (3) Does iGeriCare increase knowledge of dementia? (4) Does iGeriCare increase self-efficacy? and (5) Does iGeriCare decrease burden?

Methods

Study Design

This study is a 2-arm, pilot, feasibility RCT with intervention and control groups. Participants will receive assessments at baseline (T1) and 8 weeks (T2).

Research Platform, Learning Management System, and Email Campaign

Developers in the Division of e-Learning Innovation at McMaster University created a web-based research platform capable of hosting participant eligibility screening, informed consent, and block randomization. Microlearning email campaigns were set up in the MailChimp email marketing and automation platform, with a campaign to schedule 2 emails per week to each participant to reinforce the learnings from either the intervention or control e-learning. A total of 2 courses (intervention and control) were set up in the Litmos learning management system to host the prestudy surveys, e-learning lessons, and poststudy surveys for each group.

Participants

Inclusion and Exclusion Criteria

Individuals who meet the following self-reported inclusion criteria will be invited to participate in the study: (1) family or friend care partner of a person living with dementia, (2) reside in Canada, (3) 16+ years of age, (4) able to read and listen to English, (5) access to email and internet, and (6) comfortable using email and internet. Participants who answer "yes" to all 6 questions using the research platform will be invited to read the study information and provide informed consent before creating a participant account.

Sample Size

A total of 125 participants will be recruited in anticipation of a dropout rate of up to 30%, based on retention rates from previous trials on web-based interventions for our target population [10,25-27]. We expect a final sample size of 80 (n=40 per group), which will be sufficient to assess the feasibility and acceptability of the intervention.

Recruitment

Facebook digital marketing advertisements will be used to recruit potential participants on a rolling basis until 125 eligible participants provide informed consent. Facebook has been found to be an increasingly effective and low-cost tool to drive the digital recruitment of research study participants [28]. Using targeted audience demographic selection, only persons who have been predetermined by Facebook to have "interest" in relevant topics (ie, Alzheimer disease, dementia, and caregiving) will receive study advertisements.

Randomization and Intervention Assignment

Following account creation, the research platform will automatically randomly assign participants either to the intervention group or the control group using stratified permuted block randomization with variable block sizes of 4, 6, and 8 (randomly arranged) in a ratio of 1:1, based on care partner type (care partner to a spouse, care partner to a parent, and care partner to someone other than a spouse or parent), and level of education (high school equivalent or less, some college or university, and college or university or graduate degree).

Once a participant is randomly assigned to either the intervention or control group, an application programming interface (API) will be used to assign each participant to the matching microlearning email campaign and course in the learning management system. Participants will receive an account verification email and once verified can begin to access their assigned surveys and web-based course (prestudy surveys, e-learning lesson[s], and poststudy surveys).

Participant Support

Participants will be invited to email the research team at any time throughout the study period. A member of the research team will respond to all inquiries within one business day.

Intervention and Control Groups

Baseline Assessments (Prestudy Surveys)

Both the intervention and control groups will receive access to the same prestudy surveys at T1 (baseline). The prestudy surveys will be used for the baseline assessments of participant demographics, knowledge, perceived self-efficacy, and perceived burden. Prestudy surveys will be identical for both the intervention and control groups.

e-Learning Content

After completion of the prestudy surveys, the intervention group will receive access to 10 selected e-learning lessons from iGeriCare (Figure 1). The control group will receive access to a single e-learning lesson on "Promoting Brain Health." Each group will be provided access to the other group's e-learning

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content at the conclusion of the study. Specific lesson titles and outlines for the intervention and control groups are displayed in Table 1.

Figure 1. e-Learning content of the intervention group.

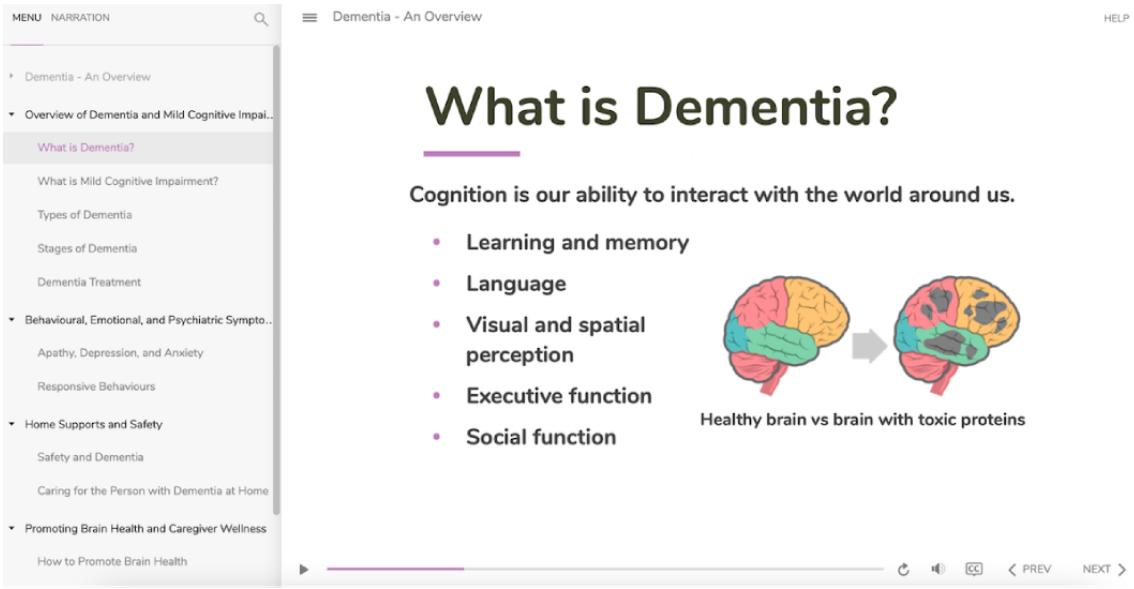

Table 1. Study lesson titles, descriptions, and group assignment.

Title of lesson	Duration (min)	Lesson content	Group assignment
What is dementia?	10-15	• Understand what cognition is and how it is impacted by dementia. • Learn about the most common causes of dementia and other possible causes of dementia-like symptoms.	Intervention
The different types of dementia	20-25	• Learn about the similarities and differences between Alzheimer disease, vascular, Lewy body, frontotemporal, and Parkinson disease dementias.	Intervention
Stages of dementia	20-25	• Explore the 3 stages of dementia. • Understand how the disease progresses and know what to expect.	Intervention
How is dementia treated?	15-20	• Look into the difference between managing the symptoms of dementia and modifying the disease itself. • Investigate what prescription drugs and other therapies are available.	Intervention
Safety in dementia	15-20	• Become aware of the risks of wandering, driving, fire, improper use of medications, and managing personal finances. • Discover strategies to reduce the possibility of harm.	Intervention
Caring for the person with dementia at home	20-25	• Learn about the types of services available in your home and your community from both publicly funded sources and private companies.	Intervention
Apathy, depression, and anxiety in dementia	25-30	• Learn how these psychiatric issues may affect people with dementia. • Understand how to cope and discover what treatments may be available.	Intervention
Behavioral, emotional, and psychiatric symptoms in dementia	35-40	• Identify the behavioral, emotional, and psychiatric signs and symptoms associated with dementia. • Discover strategies and resources to help to manage responsive behaviors.	Intervention
Caregiver wellness	10-15	• Understand why caregiver wellness is so important. • Learn what you can do to help yourself and find support.	Intervention
Dementia: an overview	10-12	• Get a quick overview of dementia in this summary that covers the highlights of all our lessons.	Intervention
Promoting brain health	25-30	• Explore how diet, exercise, blood vessel health, lifestyle choices, brain and social activity, and other health conditions affect brain health.	Control

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Microlearning Email Campaign

Once randomly assigned, participants will receive their designated microlearning campaign. The microlearning campaign is intended to reinforce learnings from the primary e-learning content and is customized to each group. Emails will be automated to be sent twice weekly.

Poststudy Surveys

Poststudy surveys will be released to each participant at T2 (8 weeks) and remain open for 2 weeks. Poststudy surveys will not be released to participants who did not complete the prestudy surveys. Participants in the intervention group will be invited to participate in a follow-up qualitative interview with the research team.

Outcome Measures

Our primary outcome is to evaluate the feasibility of implementation, including study methods, of the iGeriCare e-learning content within a clinical trial context. The secondary outcome is to determine the effectiveness of the intervention on knowledge, self-efficacy, and care partner burden.

Feasibility of Implementation of the Intervention

We will examine intervention adherence as measured by lesson completion data and email open rates, level of technical and participant support required from the research team including tracking and sending reminders, participant satisfaction survey ratings, and exit interview data from a sample of participants from the intervention group.

Feasibility of the Study Methods

Study methods will also be evaluated. We will examine recruitment rate as measured by participants per day, participant acceptability of the intervention and surveys as measured by completion and attrition rates, time to complete the intervention and surveys, level of engagement and exposure to the intervention (including potential "fast trackers" moving through the intervention at a high speed), survey data, and exit interview data.

Clinical Effectiveness Outcomes

Knowledge

Knowledge will be measured through the Dementia Knowledge Assessment Scale (DKAS; reliability α=.85; ωh=.87; overall scale) [29]. The DKAS consists of 25 items on different aspects of dementia that could be answered with "True," "Probably True," "False," "Probably False," or "I don't know."

Self-Efficacy

Self-efficacy will be measured through the Revised Scale for Caregiving Self-Efficacy (RSCSE; reliability $\alpha \geq .80$) [30]. The RSCSE contains 15 items within 3 subscales (self-efficacy for obtaining respite, responding to disruptive patient behaviors, and controlling upsetting thoughts about caregiving).

Burden

Burden will be measured through the Zarit Burden Interview (ZBI; reliability α=.92) [31]. The ZBI contains 22 items. Each item on the interview is a statement that the caregiver is asked to endorse using a 5-point Likert scale. Response options range from 0 ("Never") to 4 ("Nearly Always").

Qualitative Interviews

A sample of 10 consenting participants from the intervention arm will also be invited to participate in a 10-minute semistructured telephone interview looking for their impressions about their experience, user acceptance, barriers, and facilitators related to the educational tools and the intervention. This will allow the participants to have the freedom to express their experience, as opposed to having closed-ended questions. While we anticipate interviewing approximately 10 participants from the intervention group, we will also look for saturation of themes or feedback to determine when to terminate interviews. Interview items will be based on a participatory knowledge translation framework and mixed methods informed by the Consolidated Framework for Implementation Research (CFIR) to evaluate factors that could influence implementation effectiveness. The qualitative interview guide can be viewed in Multimedia Appendix 1.

Data Analysis

Blinded data analysis will be performed upon data collection for both cohorts. The CONSORT (Consolidated Standards of Reporting Trials) extension for randomized pilot and feasibility trials as well as CONSORT-EHEALTH will be used for final reporting [32-34].

Participant Characteristics

Differences in participant demographics between groups will be assessed using unpaired 2-tailed *t* tests. Both stratification factors, care partner type (care partner to a spouse, care partner to a parent, and care partner to someone other than a spouse or parent) and level of education (high school equivalent or less, some college or university, and college or university or graduate degree), will be included in all models. In addition, age, sex, education, stage of dementia, and length of time as a care partner will be looked at as possible effect modifiers of the relationship between the group and the outcomes, and timepoint and the outcomes.

Feasibility of Implementation and Study Methods

Quantitative feasibility-related outcomes (eg, email open rates and participant satisfaction survey ratings) will be compared between groups using unpaired 2-tailed *t* tests. Qualitative feedback from postcourse surveys and semistructured interviews will be coded, themed, and analyzed using a generic qualitative approach [35]. Qualitative content analysis will focus on the identification of barriers and facilitators to the adoption of iGeriCare e-learning, participant perceptions of the intervention, whether they felt it met their needs, and other experiences with the intervention, outcome measures, and study protocol.

Knowledge, Self-Efficacy, and Burden

Linear mixed models will be used to assess the relationship between group assignment and score for each of the outcomes: the DKAS and its subdomains (causes and characteristics, communication and behavior, care considerations, and risks and health promotion), the RSCSE and its subdomains (obtaining respite, managing disruptive behaviors, and

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controlling upsetting thoughts), and the ZBI. All models will include the 2 stratification factors, education level (high school equivalent or less, some college or university, and college or university or graduate degree) and care partner type (care partner to a spouse, care partner to a parent, and care partner to someone other than a spouse or parent). Group assignment will be included as the primary independent variable of interest with interaction from time to determine how the relationship between outcome score and group assignment will change from baseline to follow-up. Potential effect modifiers, including age (categorized as <44 years, 45-64, and ≥65 years), gender, education level, stage of dementia (mild [early-stage] dementia, moderate [middle-stage] dementia, severe [late-stage] dementia, or "I don't know"), and length of time as a care partner (less than 3 months, more than 3 months but less than 1 year, more than 1 year but less than 2 years, more than 2 years but less than 5 years, or more than 5 years), will be explored in relation to group assignment. These variables will be retained in the model if the likelihood ratio test indicates a significant difference between the nested model and the full model ($P<.05$). If they are not significant modifiers of the group-outcome relationship, then they will be investigated as effect modifiers with respect to time. An intention-to-treat analysis will also be performed and include all individuals as per group assignment. A per-protocol analysis will also be performed. Correlations between the number of lessons in the intervention completed and the DKAS score will be analyzed.

We will also look for inverse correlations between the DKAS and ZBI scores, as well as between the RSCSE and ZBI scores. Analyses will be performed using an α level of .05 and 2-sided tests. All analyses will be conducted using RStudio software (Posit).

Qualitative Interviews

A conventional inductive content analysis approach will be used [36]. Data will be systematically examined. Codes and themes will be generated based on the content, with no reliance on preconceived theories. Weekly meetings will be held with the research team and analyst to examine themes, validate the coding process, and maintain consistency and depth in data interpretation.

Ethical Considerations

This study gained Hamilton Integrated Research Ethics Board approval on November 21, 2022 (project #14096) and was registered on ClinicalTrials.gov (identifier NCT05114187). Participants were required to provide informed consent and were informed of the length of time of the e-learning, surveys, and email campaign; they were also informed about the details surrounding data collection, storage, and investigator identities. Participants' identities and confidentiality were maintained throughout the research study. All participant data were deidentified and all findings will be nonidentifiable. There is no known risk or harm to participating in this study or publicizing its results or findings. Participants in run 1 were provided with a CAD $40 (US $28.6) Amazon gift card, and participants in run 2 were provided with AskingCanadians points that can be redeemed for various gift cards as compensation for participation in the study.

Results

Initial Cohort Participants

Recruitment began on September 6, 2022, and finished on October 2, 2022. A total of 125 participants were randomly assigned to the intervention (n=61) or control (n=64) group, and data collection concluded in January 2023 (Figure 2).

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Figure 2. Study flow diagram for run 1.

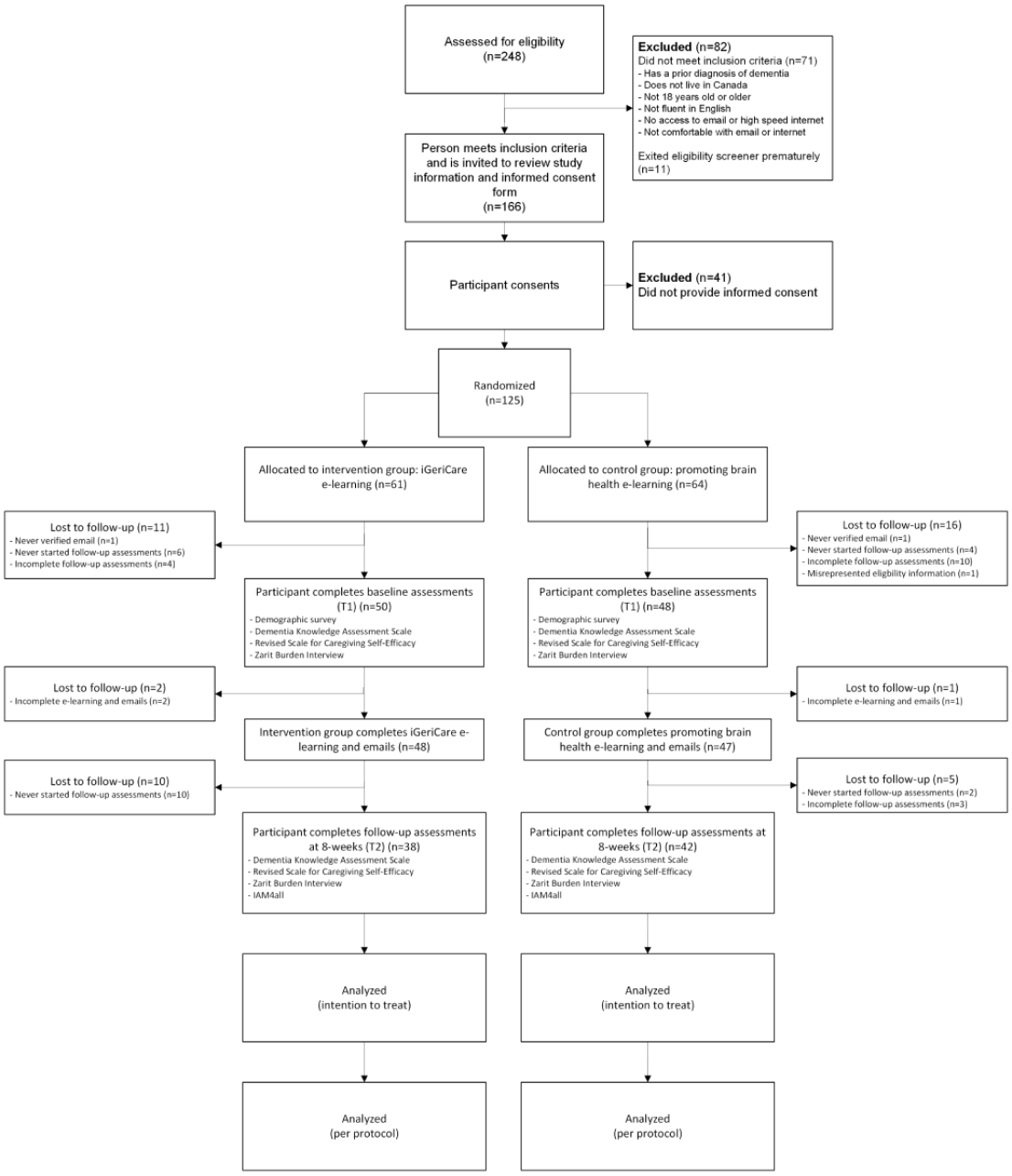

Preliminary results showed a substantial number of participants who did not engage with the protocol as initially intended. A number of participants were identified as not having completed the protocol as intended, as demonstrated by “fast-tracking” through the e-learning (ie, clicking next without allowing time for reading or listening to content) or by repeatedly clicking “I don’t know” on prestudy or poststudy surveys.

Following this, a decision was made to recruit an additional cohort of participants (n=100) using learnings gained from the initial recruitment cohort concerns. A paid panel service, AskingCanadians, was engaged to assist with recruitment. AskingCanadians is a reputable paid panel service that was able to specifically target family and friend care partners of people living with dementia.

Second Cohort Participants

Recruitment for the second cohort began on June 12, 2023, and concluded on June 27, 2023. A total of 100 participants were randomly assigned to either the intervention (n=53) or control group (n=47) group; data collection concluded in September 2023 (Figure 3).

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Figure 3. Study flow diagram for run 2.

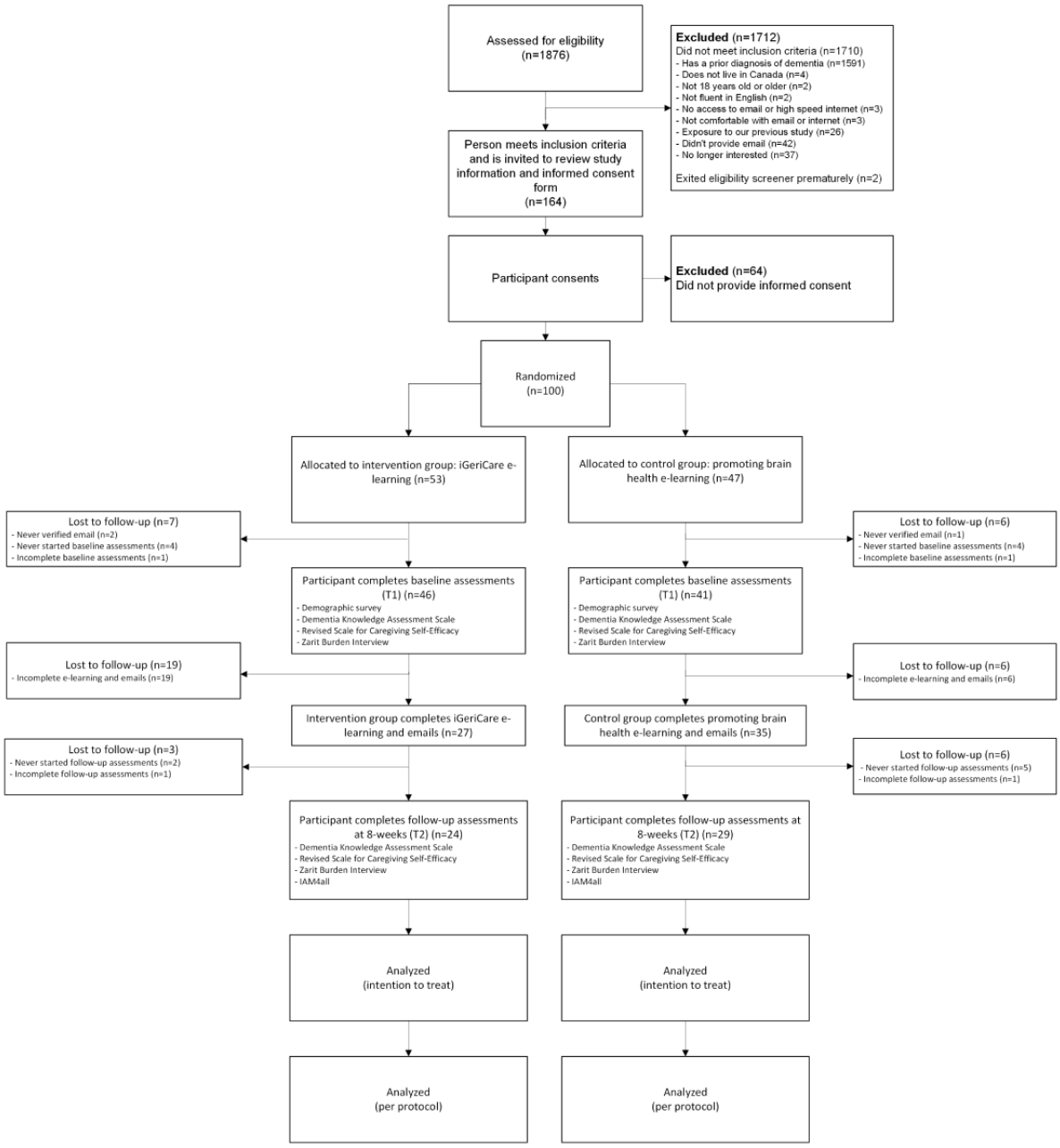

Future Results

Results from run 2 of the RCT will be analyzed in spring 2025, published in peer-reviewed journals in the field of aging and geriatrics, and presented at relevant conferences in fall 2025. Results will report on the overall feasibility of implementation of iGeriCare e-learning components in a clinical trial context; care partner acceptance of the intervention (including study methods and participant process); as well as any changes in knowledge, self-efficacy, and burden.

Discussion

Overview

The primary objective of this pilot study is to evaluate the feasibility of implementing the iGeriCare e-learning content within a clinical trial context; the secondary objectives include evaluating the feasibility of the study methods and the effectiveness of the intervention. The results of this pilot feasibility study will contribute to the planning of a larger RCT in the future. The iGeriCare RCT has several strengths. First, because the study intervention is freely available on the web, it would be easy to implement, scale, and spread as part of a broader knowledge translation strategy. Second, the intervention is also available in both English and French, which is important for broader dissemination nationally within Canada. Third, while web-based dementia care partner interventions have been previously shown to be effective, those that incorporate evidence-based principles of multimedia instructional design are likely to prove even more effective.

Limitations

There are some limitations to this work. First, while Meta advertising proved to be an extremely effective and timely

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recruitment strategy, we did not anticipate the volume of noncompliant ("fast tracker") and "fraudster" participants that would be recruited during the initial recruitment phase [37]. It is possible that the participation incentive caused some users to declare that they are dementia care partner in the eligibility screener in order to register for the study. To remedy this, a second cohort of participants was recruited through the use of a reputable paid panel service, AskingCanadians. Future studies will look at redesigning a social media recruitment campaign to discourage noncompliance or fraudulent participants. Second, this trial does not look at the long-term impact of web-based education and potential changes to knowledge, self-efficacy, and burden. Future work could consider incorporating additional time points to assess longer-term impacts. Finally, although AskingCanadians was enabled for recruitment of the second cohort of participants, there is still the potential for selection bias and exclusion of those who are lower income or do not have regular access to technological resources. Future studies may explore the barriers to access and look at providing other avenues to web-based resources for disadvantaged populations.

Conclusions and Next Steps

The expected outcomes related to feasibility are participant acceptance and engagement with the intervention and the study protocol. We anticipate a trend toward an increase in knowledge and self-efficacy, and a reduction in burden in the intervention group, although the study was not powered to fully assess effectiveness. We expect that the study will have implications for future e-learning research with care partners of people living with dementia.

The results of this study will contribute to the planning of a larger RCT in the future, as well as the evaluation of innovative, cost-effective, and efficient dementia care partner resources that can complement traditional approaches. A final manuscript will be prepared to share all results in fall 2025.

Acknowledgments

This work was supported by the team at the Division of e-Learning Innovation at McMaster University. Funding was provided by the PSI Foundation. AJL receives support through the John R. Evans Chair in Health Sciences Educational Research and Instructional Development, Faculty of Health Sciences, McMaster University. The authors wish to thank the care partners for participating in this important study. The authors would also like to thank Drs. Sharon Marr, Sarah Payne, Demetrios Sahlas, and David Streiner for their time and participation in this project.

Data Availability

The datasets analyzed during this study will be available from the corresponding author on reasonable request once data collection is complete.

Authors' Contributions

AJL and SA drafted the original study protocol. AJL, SC, and RW led the intervention. SA drafted the protocol manuscript. All authors have reviewed the manuscript and approved the final version.

Conflicts of Interest

AJL and RS are co-owners of the iGeriCare intervention with McMaster University.

Multimedia Appendix 1
Qualitative interview guide.
[DOCX File , 22 KB - resprot_v14i1e67048_app1.docx]

Multimedia Appendix 2
Peer review report from the PSI Foundation (Ontario, Canada).
[PDF File (Adobe PDF File), 110 KB - resprot_v14i1e67048_app2.pdf]

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Abbreviations

API: application programming interface
CFIR: Consolidated Framework for Implementation Research
CONSORT: Consolidated Standards of Reporting Trials
DKAS: Dementia Knowledge Assessment Scale
RCT: randomized controlled trial
RSCSE: Revised Scale for Caregiving Self-Efficacy
ZBI: Zarit Burden Interview

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Protocol

Chatbot-Delivered Stage of Change–Tailored Web-Based Intervention to Promote Physical Activity Among Inactive Community-Dwelling People Aged 65 years or More: Protocol for a Randomized Controlled Trial

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Abstract

Background: Physical activity (PA) has significant health benefits for older adults. However, many older adults in Hong Kong remain physically inactive. Interventions tailored to one's current stage of change (SOC) are more effective than non-SOC-tailored ones in facilitating behavioral changes. Chatbots are potentially useful to deliver SOC-tailored interventions to promote PA among older adults.

Objective: This randomized controlled trial (RCT) will compare the efficacy of an SOC- versus a non-SOC-tailored intervention in increasing the prevalence of meeting World Health Organization (WHO)-recommended PA levels 6 months after completion of the intervention among inactive community-dwelling individuals aged ≥65 years.

Methods: This is a partially blinded (outcome assessors and data analysts) and parallel-group RCT. A total of 278 inactive community-dwelling people aged 65 years or more will be randomized evenly into either an intervention group or a control group. In the intervention group, a fully automated chatbot with natural language processing (NLP) functions will measure participants' SOC related to PA and deliver web-based interventions tailored to their current SOC every week for 12 weeks. In the control group, the chatbot will not measure participants' SOC but will deliver a non-SOC-tailored web-based intervention every week for 12 weeks. Participants will be interviewed at baseline (T0), after completion of the intervention (T1), and 6 months after T1 (T2). The primary outcome is the prevalence of meeting WHO-recommended PA levels (ie, at least 150 minutes of moderate-intensity aerobic PA, at least 75 minutes of vigorous-intensity aerobic PA, or an equivalent combination of moderate-to-vigorous physical activity [MVPA] every week). PA will be measured using the Chinese version of the International Physical Activity Questionnaire Short Form (IPAQ-SF) and accelerometers at T0, T1, and T2. Secondary outcomes include (1) minutes of MPVA, low-intensity PA, and sedentary time in the past week; (2) step counts in the past week; (3) SOC levels, perceived pros, perceived cons, and perceived self-efficacy related to PA; (4) compliance to the web-based interventions; and (5) cognitive status measured at T0, T1, and T2. Intention-to-treat analysis will be used for data analysis.

Results: Recruitment started in November 2024. By February 2025, a total of 185 participants completed the baseline assessment and were randomly assigned to either the intervention group (n=93, 50.3%) or the control group (n=92, 49.7%). Recruitment will

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be completed by the end of June 2025. The follow-up assessment at T1 started in March 2025. Data collection is expected to be concluded in February 2026.

Conclusions: The findings will extend the application of SOC and contribute to the evidence of the effectiveness of SOC-tailored and chatbot-delivered interventions. If the chatbot-delivered SOC-tailored intervention is proven effective to increase PA levels, it will require relative less resources to implement and maintain. It can be integrated into the existing WhatsApp groups operated by organizations providing services to older adults in Hong Kong and create public health impacts.

Trial Registration: ClinicalTrial.gov: NCT06641492; https://clinicaltrials.gov/study/NCT06641492

International Registered Report Identifier (IRRID): DERR1-10.2196/68796

(JMIR Res Protoc 2025;14:e68796) doi:10.2196/68796

KEYWORDS

chatbot; physical activity; intervention; randomized controlled trial; older adult; stage of change; motivation

Introduction

Background

Hong Kong has a rapidly aging population. It is predicted that 22% of Hong Kong residents will be 65 years or older by 2030 [1]. Recent data show that 75% of Hong Kong older adults have one or more chronic diseases [1], which has created a huge burden on the health care system.

Physical activity (PA) is defined as any bodily movement produced by skeletal muscles, resulting in an expenditure of energy [2]. PA is well recognized as an effective intervention for reducing mortality and dependence-inducing diseases [3] and improving cognitive function, frailty symptoms, and physical functions among older adults [4,5]. The World Health Organization (WHO) recommends that older adults without any contradiction of PA do at least 150 minutes of moderate-intensity aerobic PA, 75 minutes of vigorous-intensity aerobic PA, or an equivalent combination of moderate-to-vigorous physical activity (MVPA) every week [3]. However, physical inactivity remains a worldwide phenomenon and increases significantly with age. A systematic review showed that 43.4%-78% of older adults across countries cannot meet the WHO-recommended PA levels [6]. In Hong Kong, the proportion of older adults who did not meet the WHO-recommended PA level increased from 13.5%-42.8% in 2018-2019 [7] to 22.2%-53.3% in 2020-2022 [8]. A recently published study showed that 28.6% of older adults in Hong Kong had a low level of PA in July 2022 [9]. There is a strong need for improvement.

Factors associated with PA among older adults have been well studied. A systematic review suggested that a lack of knowledge, skills, capacities, or support from peers or family members related to PA, the perception that PA would cause pain or injury, difficulties in accessing sports facilities, and concerns related to bad weather are barriers to performing PA among older adults [10]. Perceived benefits of PA on physical and mental health, perceived self-efficacy to perform PA, and suggestions from health professionals have been identified as facilitators of PA in this population [10]. Similar facilitators and barriers apply to older adults in Hong Kong [9]. These factors will be addressed by our interventions.

A number of interventions have been conducted to promote PA among older adults. The majority of them use face-to-face approaches, such as motivational interviewing, PA coaching, and educational sessions [11]. As compared to no or minimum interventions, these approaches increase objectively measured PA levels in both the short term (≤3 months) and the medium term (3-12 months) [11]. However, these interventions require significant personnel and resources to implement. There is an increasing number of web-based interventions for older adults. A systematic review of 18 randomized controlled trials (RCTs) showed that web-based interventions are feasible to promote PA among older adults [2]. Digital PA tracking and feedback (ie, providing automatic tracking and feedback on PA levels based on pedometers/accelerometers/smartphones) and digital PA coaching (ie, goal setting, promoting PA according to participants' baseline PA situation) were the most commonly used strategies in these RCTs [2]. However, 7 of these RCTs were feasibility trials with limited sample sizes (10-30 per group) instead of full-powered RCTs, and 11 only measured short-term efficacy (≤3 months). Moreover, none of these RCTs was conducted with the Chinese population.

As the most commonly used stage model, the stage of change (SOC) postulates that completed behavioral changes progress through 5 ordinal stages (precontemplation stage, contemplation stage, preparation stage, action stage, and maintenance stage), and individuals require interventions tailored to their current SOC in order to effectively facilitate progression toward sustained behavioral changes [12]. A meta-analysis showed that SOC-tailored interventions are more effective than non-SOC-tailored ones [13]. The SOC has been widely applied to guide PA promotion in different populations [14-23], including older adults [19,20,22,23]. However, most of the SOC-tailored PA interventions use face-to-face approaches (eg, counselling, written material, onsite educational sessions, and motivational interviews) [14-16,18,19,21,23]. It is resource demanding as project staff need to measure the SOC of each participant and prepare and select interventions tailored to their current SOC. To the best of our knowledge, only 2 web-based PA interventions targeting older adults have tried to send some simple tips in text messages tailored to their current SOC [20,22].

Chatbots are computerized programs that replicate human interactions through various forms of communication [24], and

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they have become increasingly popular in health communication. Systematic reviews have highlighted the feasibility and effectiveness of chatbots in promoting healthy lifestyles, smoking cessation, treatment adherence, and vaccination uptake and reducing substance misuse [25-27]. Two studies applied chatbots to promote PA among office workers in South Korea [28] and adults in the United States [29]. In the South Korean study, the chatbot automatically sent a message to each participant every day to remind them to perform the stair-climbing activity. Once the participant completed the desired activity and notified the chatbot, the chatbot automatically provided positive feedback to the participant. In addition, coffee coupons were given to those who completed this activity. This intervention was shown to be effective in increasing participants' stair-climbing behaviors [28]. The other study conducted in the United States used a chatbot to provide knowledge and counselling related to PA, which was effective in increasing participants' daily step count [29]. Chatbots can proactively interact with users to determine their SOC and automatically select a pathway of intervention that is tailored to each user's current SOC, thus making chatbots ideal for delivering SOC-tailored interventions to promote PA. A previous study demonstrated that applying chatbots to deliver health promotion is feasible and acceptable among older adults in Hong Kong [30].

Objectives

The proposed RCT will compare the efficacy of an SOC- versus a non-SOC-tailored intervention in increasing the prevalence of meeting WHO-recommended PA levels 6 months after completion of the intervention among inactive community-dwelling individuals aged ≥65 years. Given the strengths of chatbots in health promotion, both the SOC- and non-SOC-tailored interventions will be delivered by a chatbot with natural language processing (NLP) functions. The PA levels will be measured using the validated Chinese version of the International Physical Activity Questionnaire Short Form (IPAQ-SF) and accelerometers.

The secondary objectives of this RCT are to compare the following outcomes 6 months after completion of the intervention between the intervention and control groups: (1) minutes of MPVA, low-intensity PA, and sedentary time in the past week measured using both the IPAQ-SF and accelerometers; (2) step counts in the past week measured using accelerometers; (3) SOC levels, perceived pros, perceived cons, and perceived self-efficacy related to PA; (4) compliance to the web-based interventions; and (5) cognitive status.

Methods

Study Design

This is a partially blinded (outcome assessors and data analysts) and parallel-group RCT to be conducted in Hong Kong, China. Inactive community-dwelling people aged 65 years or more will be randomized evenly (1:1) into either an intervention group or a control group. In the intervention group, the chatbot will measure participants' SOC related to PA and deliver web-based interventions tailored to their current SOC every week for 12 weeks. In the control group, the chatbot will not measure participants' SOC but will deliver a standard and non-SOC-tailored web-based intervention every week for 12 weeks. Participants will be interviewed at baseline (T0), after completion of the intervention (T1), and 6 months after T1 (T2). The study was registered at ClinicalTrials (NCT06641492). The study flowchart diagram is shown in Figure 1. We will report this trial in accordance with the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist (Multimedia Appendix 1) [31] and the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist (Multimedia Appendix 2).

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Figure 1. Flowchart of the RCT. RCT: randomized controlled trial; SOC: stage of change.

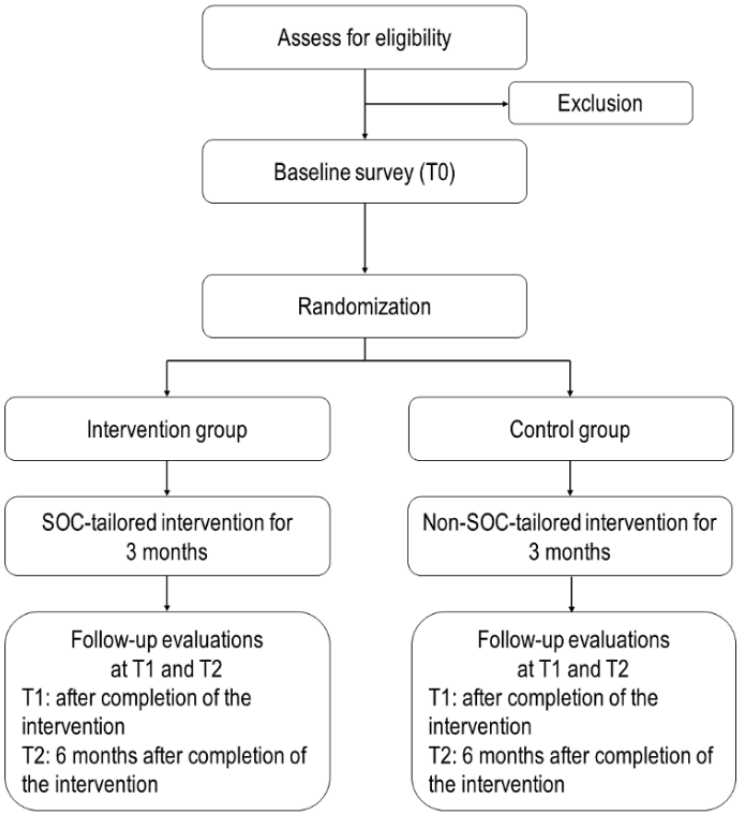

Participants and Recruitment

Inclusion criteria are as follows:

- Age 65 years or more.
- Having a Hong Kong identity card.
- Chinese speaking.
- Not meeting the WHO-recommended level of MVPA, defined as <150 minutes of moderate-intensity aerobic PA in the past week. The interviewers will assess participants using the validated Chinese version of the IPAQ-SF.
- Willing to be followed over the phone at T1 and T2.
- Owning a smartphone.
- Able to send and read text/voice messages via smartphones.
- Willing to wear an accelerometer for a week at T0, T1, and T2.

Exclusion criteria include the following:

- Blindness or deafness
- Diagnosis of major psychiatric diseases (schizophrenia or bipolar disorders) or dementia
- Score≥1 in the Chinese version of the Physical Activity Readiness Questionnaire (PAR-Q)
- Score≤16 in the validated telephone version of the Cantonese Mini-mental State Examination (T-CMMSE) [32]

Participants will be recruited through random telephone calls. Telephone numbers will be selected from up-to-date Hong Kong telephone directories. Trained interviewers will call potential participants over the phone. If there is more than one person in the household who is aged ≥65 years, the one whose birthday is closest to the interview date will be invited for the study to avoid contamination and introduction of extra confounding factors. Interviewers will brief prospective participants about the study and screen their eligibility.

Sample Size Planning

At T0, no participant will meet the WHO-recommended PA level according to the inclusion criteria. We assume that 10% of participants in the control group will meet the WHO-recommended PA level at T2 as there are minimum interventions. A target sample size of 97 per group (194 in total) would allow us to detect a between-group difference of 15% in the prevalence of meeting the WHO-recommended PA level at T2 (25% versus 10%; power=0.80, α=.05, PASS version 11.0 [NCSS Statistical Software]). We conservatively estimate the dropout rate to be 30% at T2. Thus, 139 eligible participants per group (278 in total) are required.

Ethical Considerations

Ethics approval was obtained from the Survey and Behavioural Research Ethics Committee of the Chinese University of Hong Kong (approval number SBRE-22-0257) and the Joint Chinese University of Hong Kong – New Territories East Cluster Clinical Research Ethics Committee (approval number 2022.610-T). All participants will fill out an electronic consent form through a link sent over WhatsApp to confirm their informed consent. The electronic consent forms and participants' contact information will be kept separately from the questionnaires in a locked cabinet in the office of the principal investigator. Participants' names and contact information will not appear on the questionnaire or in the dataset. A unique study ID will be assigned to each participant throughout the study. The dataset will be protected by a password on the computer of the principal

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investigator. All data will be kept for 5 years after conclusion of the project. The data will be disposed of or deleted securely and confidentially once the retention period has expired.

A supermarket coupon worth HK $50 (US $6.37) will be mailed to an address provided by the participants upon completion of the surveys at T0, T1, and T2. A supermarket coupon worth HK $150 (US $19.11) will be given to the participants in the same manner after they finish wearing and return the accelerometers at T0, T1, and T2.

Development and Maintenance of the Chatbot

A chatbot will be developed and maintained on the WhatsApp platform due to its wide popularity among local older adults and a user-friendly interface. The architecture of the chatbot system is shown in Figure 2. Users send information to the WhatsApp instant messaging server, which then delivers the message to the chatbot. The chatbot system processes and sends a message back to WhatsApp, where users can view the information. The knowledge graph, which links participants' input with the chatbot's responses, will be prepared by focus groups of 30 older adults and interviews with experts in sports medicine. The knowledge graph will evolve over time with an increasing number of human-chatbot interactions. The chatbot will use a mixture of techniques so that the human-chatbot interactions are not merely rule based, and the chatbot will also learn from the evolving knowledge graph through machine learning. We will pilot the chatbot among another 30 older adults to improve its accuracy of human-chatbot interactions. These measures will allow the chatbot to have adequate accuracy and consistency in delivering interventions according to the protocol and prevent the chatbot becoming repetitive and off-topic after extensive usage. The same professional team will maintain the health status of the chatbot during the intervention period. A monthly review of the chatbot's performance will be conducted.

Figure 2. Architecture of the chatbot system.

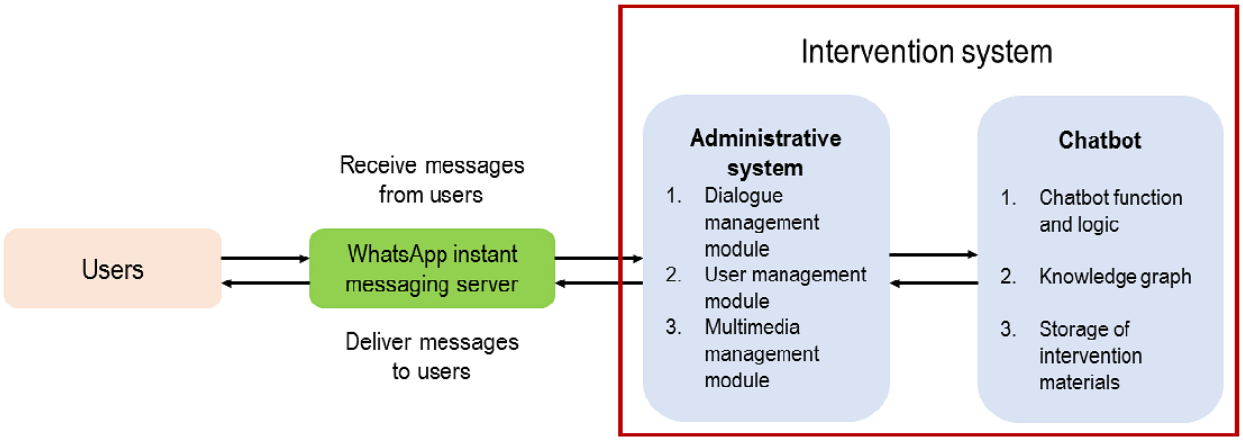

Baseline Survey and Randomization

Participants will be interviewed over the phone to record their background characteristics and potential confounders at baseline. Their PA in the first week after the baseline survey will be measured using an accelerometer. At the end of the baseline survey, the interviewers will help participants install WhatsApp on their smartphones, if needed. Computer-generated random allocation codes will be produced and sealed in opaque envelopes by a research staff member, without involvement in recruitment or the baseline survey. One envelope will be drawn and opened by the interviewer, who will then inform each participant about their assigned group. Block randomization with a block size of 8 will be used. Our project staff will connect participants' WhatsApp with the chatbot, and the chatbot will automatically run a training module guiding users in an older adult–friendly way when participants access it for the first time.

The Intervention Group

The interventions will start after participants complete baseline PA measurements with the accelerometer. The chatbot will deliver interventions cocreated by researchers and older adults based on the behavioral change strategies recommended by the SOC-tailored intervention to address the determinants of PA among older adults identified by previous studies. Twelve weekly sessions of the SOC-tailored intervention will be delivered by the chatbot within 3 months through WhatsApp. In previous studies, 3 months was the most commonly selected intervention duration for web-based interventions promoting PA among older adults [2]. Moreover, 1 study suggested that some older adults would lose interest if the duration of web-based interventions was longer than 3 months [20]. Multimedia Appendix 3 shows the workflow of the intervention group. The intervention steps are described next:

- Step 1: Initiate the intervention. The chatbot will greet participants and state its function and topics to be covered.
- Step 2: Measure the PA level. The chatbot will ask participants to fill out the Chinese version of the IPAQ-SF. The chatbot will automatically calculate their MVPA level and provide feedback based on that level.
- Step 3: Identify the SOC. The chatbot will ask participants a validated multiple-choice question [20] that has been widely used to identify the SOC related to PA: Which sentence best describes your current PA situation? The response categories are "I participate in PA for less than 150 minutes per week and do not intend to increase that time in the next 6 months" (precontemplation stage), "I participate in PA for less than 150 minutes per week and intend to increase that time in the next 6 months"

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(contemplation stage), "I participate in PA for less than 150 minutes per week and intend to increase that time in 1 month" (preparation stage), "I participate in PA for at least 150 minutes per week, but I have only begun to do so in the past 6 months" (action stage), and "I participate in PA for at least 150 minutes per week and have been doing so for more than 6 months" (maintenance stage).

- Step 4: Deliver interventions tailored to participants' current SOC levels. The intervention will address known determinants of PA among older adults identified in a systematic review and a local study [9,10]. Barriers to PA among older adults include a lack of knowledge, skills, capacities, or support from peers or family members related to PA, the perception that PA would cause pain or injury, difficulties in accessing sports facilities, and concerns about bad weather. The facilitators include perceived benefits of PA on physical and mental health, perceived self-efficacy to perform PA, and suggestions from health professionals.

The Precontemplation Stage

Participants in the precontemplation stage will watch a web-based video in which a sport scientist explains the definition of PA, emphasizes adequate levels of MVPA important for physical and mental health, and introduces levels of MVPA recommended by WHO for older adults. This content seeks to increase participants' awareness of the importance of adequate MVPA.

The Contemplation Stage

Participants in the contemplation stage will watch a different web-based video. The same sports scientist will talk about the benefits of adequate MVPA for older adults (eg, reducing dependence-inducing diseases, such as cardiovascular diseases and cancers, and improving cognitive function, frailty syndrome, performance of physical functions, and mental health), address physical and environmental barriers to PA by introducing feasible options of PA suitable for older adults that can be performed at home or in the community, and give recommendations and encourage older adults to make a plan for PA. In addition, several older adults who perform MVPA regularly will share their positive experiences during PA (eg, better physical functions, a stronger immune system, and a positive psychological status) and how they overcame physical and environmental barriers of PA. This content aims to increase self-efficacy and perceived pros and reduce perceived costs of PA.

The Preparation Stage

The chatbot will provide a dropdown list of easy and enjoyable PA options that are suitable for older adults, which will be identified by focus groups of older adults and suggestions of the sports scientist, in the preparation stage. These options will include brisk walking, aerobics, stretching, strength/muscle training, Tai Chi, and 8-section brocade exercise. Participants will be invited to select one or more options from the list. The chatbot will retrieve a predesigned demonstration video related to each option and send it to participants. This content seeks to assist participants in developing and implementing an action plan, as well as increase their perceived self-efficacy related to PA.

The Action or Maintenance Stage

The chatbot will provide feedback and reinforcement based on participants' PA level in the previous week. Positive reinforcement will be provided to participants who are on track to obtain or have already achieved the WHO-recommended MVPA level. This content aims to facilitate the maintenance of MVPA and to avoid relapse.

To prevent participants from watching the same video or reading the same information twice, slightly different videos/information corresponding to each SOC will be prepared. In each session, the chatbot will randomly select one for the participants. Participants in all stages can select one or more problems about PA from a list of common problems identified through a literature review and a focus group of older adults. Participants can also raise problems that are not on the list, verbally or in written form. The chatbot will retrieve relevant information from the knowledge graph and prepare a response.

The Control Group

First, the chatbot will ask participants to fill out the Chinese version of the IPAQ-SF, automatically calculate their MVPA, and provide feedback based on the PA level. Second, the chatbot will automatically send a short web-based video covering general information of PA for older adults (eg, recommended MVPA level, suitable PA options) every week from week 1 to week 12. Finally, participants will select problems about PA from the same list in the intervention group. They will also have the option to verbally or in written form communicate any issues not included on the list. The chatbot will extract pertinent information from the same knowledge graph to craft a tailored response. Multimedia Appendix 4 shows the workflow of the control group.

If participants in the intervention or the control group provide no response to the intervention initiated by the chatbot within 24 hours, the chatbot will automatically send out 4 separate reminders. The project staff will proactively contact participants who provide no response to any reminders through WhatsApp or over the phone to identify reasons and solve problems.

Measurements

Primary Outcome

Prevalence of meeting WHO-recommended levels of PA (at least 150 minutes of moderate-intensity aerobic PA, at least 75 minutes of vigorous-intensity aerobic PA, or an equivalent combination of MVPA every week) is the primary outcome. PA will be measured using the data provided by the participants in the Chinese version of the IPAQ-SF and from the accelerometers (ActiGraph) at T0, T1, and T2. After completion of the baseline telephone survey and before the randomization takes place, participants will be invited to visit our research office to collect the accelerometers. Onsite, participants will be instructed to wear the accelerometers on their waist (ie, above the right hipbone) with an elastic belt for 7 days, including 5 weekdays and 2 weekends, to collect objective data of PA levels. Participants will be asked to wear the accelerometers at all times

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except when they are showering or swimming. In addition, participants will be reminded to maintain their daily routine when they are wearing the accelerometers. Participants will visit our research office again 1 week afterward to return the accelerometers and recall their PA levels in the past week by completing the Chinese version of the IPAQ-SF. Similar procedures for collecting and returning accelerometers and completing the IPAQ-SF will be arranged after completion of the telephone survey at T1 and T2. The time on and time off related to accelerometer wearing each day will be recorded, and the data will be used to estimate the time spent in sedentary behavior, light PA, and MVPA. To ensure the accuracy of data that represent the habitual PA levels of participants, data from participants whose accelerometer-wearing time is less than 600 minutes per day will be considered invalid. We will calculate the sedentary time, light PA time, and MVPA time using triaxial cut points. The sedentary time, light PA time, and MVPA time have been defined as <200, <1951, and >1952 counts/minute, respectively, with the epoch length being 60 seconds [33]. The chatbot will automatically record the time spent by each participant with it.

Secondary Outcomes

The following secondary outcomes will be measured at T0, T1, and T2:

- Step counts and minutes of MVPA, light PA, and sedentary time in the past week measured using accelerometers.
- Compliance with the web-based interventions, including the number of intervention sessions started and completed, as documented by the chatbot.
- The SOC related to the PA measured using a validated multiple-choice question [34]. The measurement and definition of the SOC will be the same as those used by the chatbot. In addition, we will extract the SOC measured by the chatbot at the beginning of each intervention session in the intervention group from the chat history.
- Perceived pros and cons related to PA will be measured using the validated questionnaire on decisional balance developed by Nigg et al [35], which consists of 10 questions with 2 scales (pros and cons).
- Perceived self-efficacy of PA will be measured using a validated 6-item scale developed by Marcus et al [34].
- Cognitive status will be measured using cognitive tasks, including the sustained attention test [36], working memory [37], inhibitory control [38], and cognitive flexibility [39].

The outcome assessors and data analysts will be blinded to the treatment allocation. Participants will be reminded not to disclose the intervention they receive to assessors.

Safety Issues and Adverse Events

Participants can report adverse events related to PA through WhatsApp or a hotline during the study period. If sustained serious adverse events are found, advice will be sought from a sport science expert.

Pilot Study

A pilot study randomized 6 eligible participants into 2 groups and tested the logistics of the interventions. Feedback was collected from the participants. The results showed that the chatbot operates smoothly, and participants expressed satisfaction with its performance and interface.

Statistical Analysis

Intention-to-treat analysis will be performed. The Markov chain Monte Carlo method will be used to impute missing primary and secondary outcomes. Variables to impute the missing values include participants' background characteristics and baseline values of these outcomes. Chi-square and independent sample *t* tests will be performed to examine the between-group balance of potential confounders at baseline. We will compare between-group differences in primary and secondary outcomes at both T1 and T2. The relative risk, absolute risk reduction, and the number needed to be treated and their 95% CI values will be calculated using Microsoft Excel. Logistic regression for binary variables and linear regression models for continuous variables will be used to test between-group differences in primary and secondary outcomes after controlling for any baseline confounders, with $P<.20$ in between-group comparisons. IBM SPSS version 26.0 and R version 4.3.1 (R Foundation for Statistical Computing) will be used for data analysis, with 2-sided $P<0.05$ considered statistically significant.

Results

Study recruitment started in November 2024. By the end of February 2025, a total of 185 participants completed the baseline assessment and were randomly assigned to either the intervention group (n=93, 50.3%) or the control group (n=92, 49.7%). Recruitment will be completed by the end of June 2025. The follow-up assessment at T1 started in March 2025. Data collection is expected to be concluded in February 2026.

Discussion

Summary

We anticipated that a higher proportion of participants in the intervention group would meet the WHO-recommended level of PA at T2 compared to the control group. The underlying purpose of this study is to prevent dependence-inducing diseases (eg, cardiovascular diseases, cancer) and improve cognitive function, frailty symptoms, body composition, and the performance of various physical functions by increasing PA levels among individuals aged 65 years or more in Hong Kong. About half of the older adults in Hong Kong did not meet the WHO-recommended PA level during 2020-2022 [8].

The proposed intervention has strong applications in healthy aging and noncommunicable disease control in Hong Kong. PA is an effective intervention to prevent dependence-inducing diseases and improve cognitive function, frailty symptoms, body composition, and the performance of various physical functions. Effective and sustainable interventions promoting PA are greatly needed but are lacking. We will develop an SOC-tailored web-based intervention and compare its efficacy with a non-SOC-tailored web-based intervention by performing an RCT, which is the most rigorous evaluation method and provides the highest quality of evidence. Considering participants may move forward to a later SOC, go backward to

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an earlier SOC, or stay in the same SOC after being exposed to an intervention, our intervention will have 12 sessions, and each session will be tailoring to the participants' current SOC. All interventions will be delivered by a chatbot that integrates with WhatsApp. It can identify users' SOC regarding PA and automatically deliver interventions corresponding to their SOC. Moreover, with evolving knowledge graphs and machine learning, the chatbot can ensure accuracy of human-machine interactions, which further increases its efficacy. Making use of a chatbot can also increase compliance to web-based interventions. Since the maintenance cost of the chatbot is relatively low, it is especially suitable to deliver our proposed intervention. The sustainability of our intervention is expected to be high. The intervention, if found to be significant and translated into service, would reduce the burden on the health care system and the cost in terms of medication, rehabilitation, and institutional care for chronic diseases.

Limitations

This study has some limitations. First, we do not have a control group that does not use the chatbot. This RCT cannot provide evidence to support whether the intervention delivered by the chatbot will be more effective than the intervention delivered without a chatbot. Second, the intervention is limited to people aged 65 years or more who have access to smartphones. In Hong Kong, 73% of adults in this age group had smartphones in 2021 [40]. Smartphone ownership has been increasing sharply. Third, participants and those who refuse to participate in this study may have different characteristics and motivation to perform PA. We are not able to collect information from refusals, and selection bias exists. Moreover, compared to other RCTs promoting PA among older adults [2], our follow-up period is shorter (6 months versus 12 months). We have selected a shorter follow-up period due to some practical concerns. The effect size of the intervention would be smaller, and the dropout rate would be higher if we choose a longer follow-up period. Therefore, we need a much larger sample size, which is not feasible under the current funding scope. The limited ability to observe long-term effects of the interventions due to the relatively short follow-up period is a limitation of this study. Moreover, it is possible that participants' behaviors would be altered while wearing accelerometers. A meta-analysis showed that when an accelerometer provides real-time monitoring and feedback of PA levels, using it alone or together with other interventions would result in improvement in PA among older adults [41]. However, the accelerometer will only be used to record participants' PA levels in this study. It will not provide any feedback, and the participants will not be able to access accelerometer data during the assessment period. A previous study showed that when an accelerometer is only used for outcome assessment, there is no difference in PA levels between those who wear accelerometers and those who do not [42]. In previous RCTs, an accelerometer has been commonly used to measure older adults' PA levels [43].

Conclusion

In conclusion, this study will generate theoretical and practical implications. The findings will extend the application of the SOC and contribute to the evidence of the effectiveness of SOC-tailored and chatbot-delivered interventions. If the chatbot-delivered SOC-tailored intervention is proven effective to increase PA levels, it will require relative less resources to implement and maintain. It can be integrated into existing WhatsApp groups operated by organizations providing services to older adults in Hong Kong and create public health impacts.

Acknowledgments

This study was supported by the Health and Medical Research Fund, Health Bureau, Hong Kong Special Administrative Region (grant number 20210531). The funder played no role in in the study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication.

Data Availability

The datasets to be generated or analyzed during this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

XL, FS, QZ, YF, PKHM, and ZW initiated the research plan and designed the protocol. XL, FS, FY, F-YY, DY, BZ, QL, and ZW designed the measurements. XL, FS, QP, YF, F-YY, DY, BZ, QL, PKHM, and ZW designed the interventions. FS, QZ, PKHM, and ZW acquired the funding for this study. All authors have edited the protocol and agreed with the final version of the manuscript. The authors did not use artificial intelligence in any part of the manuscript generation.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1169 KB - resprot_v14i1e68796_app1.pdf]

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Multimedia Appendix 2
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOC File , 125 KB - resprot_v14i1e68796_app2.doc]

Multimedia Appendix 3
Workflow of the intervention group.
[PNG File , 219 KB - resprot_v14i1e68796_app3.png]

Multimedia Appendix 4
Workflow of the control group.
[PNG File , 188 KB - resprot_v14i1e68796_app4.png]

Multimedia Appendix 5
Peer-review report from the Health and Medical Research Fund, Health Bureau, Research Council, Hong Kong Special Administrative Region.
[PDF File (Adobe PDF File), 245 KB - resprot_v14i1e68796_app5.pdf]

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Abbreviations

IPAQ-SF: International Physical Activity Questionnaire Short Form
MVPA: moderate-to-vigorous physical activity
NLP: natural language processing
PA: physical activity
RCT: randomized controlled trial
SOC: stage of change
WHO: World Health Organization

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Protocol

A Virtual Self-Management Intervention for Adolescents With Juvenile Idiopathic Arthritis: Protocol for the VISTA-JIA Randomized Controlled Trial

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Abstract

Background: Needs assessments in patients with juvenile idiopathic arthritis (JIA) have revealed a need for disease information, self-management skills, and peer support. We previously developed and tested the acceptability of an in-person and videoconference-based self-management program (SMP) to address these needs.

Objective: The aim of this pilot randomized controlled trial (RCT; the VISTA-JIA trial) is to evaluate the feasibility and preliminary effectiveness of a virtual group-based SMP for adolescents with JIA in comparison to a waitlist control group.

Methods: A total of 100 participants with confirmed JIA (aged 12-17 years) will be recruited from 5 Canadian pediatric rheumatology centers and randomized 1:1 to the intervention or waitlist control groups. Adolescents in the intervention group will receive the virtual SMP. Those randomized to the control group will receive standard of care alone and will later be eligible for the SMP. The SMP includes JIA disease education, self-management strategies, and peer support. Four 60- to 90-minute sessions will be conducted over 8 weeks with a group size of 4-6 participants. The primary feasibility outcome will be adherence to the SMP (defined as completion of all 4 sessions by at least 80% of participants). Other secondary feasibility outcomes will include recruitment and withdrawal rates, the proportion of completed questionnaires, engagement and satisfaction with the SMP measured through a semistructured virtual interview, and intervention fidelity (consistent content and technology delivery). Secondary preliminary effectiveness outcomes will be assessed by completing 5 validated questionnaires at pre- and postprogram time points: (1) the Medical Issues, Exercise, Pain, and Social Support Questionnaire to assess perceived ability to manage JIA

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(self-management); (2) the Children's Arthritis Self-Efficacy Scale to assess self-efficacy; (3) the Pediatric Quality of Life Inventory 3.0 Rheumatology–Teen Module to assess health-related quality of life; (4) the PROMIS (Patient-Reported Outcomes Measurement Information System) Pediatric Pain Interference Scale to assess pain interference; and (5) Readiness for Adult Care in Rheumatology to assess transition readiness. Descriptive statistics and nonparametric tests will be used to analyze the data.

Results: The study setup is complete at all centers, including training of the facilitators, revising and finalizing education sessions, participant's handout guide, and fidelity checklist. Recruitment began in January 2024 and is expected to conclude by December 2025. Feasibility outcomes, including adherence and engagement, as well as preliminary effectiveness, will be analyzed post intervention.

Conclusions: This is the first evidence-based, virtual, interactive, group-structured JIA SMP in Canada. This SMP will address needs for disease information, self-management skills, and peer support in adolescents with JIA. The results of this pilot study will inform a full-scale RCT focused on the efficacy and cost-effectiveness of the program with the goal of integration in routine clinical practice across Canada.

Trial Registration: ClinicalTrials.gov NCT06184100; https://clinicaltrials.gov/study/NCT06184100

International Registered Report Identifier (IRRID): DERR1-10.2196/69539

(JMIR Res Protoc 2025;14:e69539) doi:10.2196/69539

KEYWORDS

juvenile idiopathic arthritis; self-management program; randomized controlled trial; videoconference; virtual intervention; peer support

Introduction

Background

Juvenile idiopathic arthritis (JIA) is the most common childhood rheumatic disease with an estimated prevalence of 1 in 1000 children younger than 16 years [1]. Although treatments for JIA have improved over the last decade, many affected children experience continued disease activity and related morbidity, long-term disability, and an increased incidence of psychosocial complications as they enter adulthood [2]. Adolescence is a critical period of physical, cognitive, and psychosocial development as the youth develop skills, emotional regulation, and independence to manage changes in responsibilities and prepare to assume adult roles [3]. In adolescents with JIA, this period translates to a requirement for additional self-management skills (eg, medical decision-making and patient-provider communication) as their autonomy increases and as they assume greater responsibility for the management of their disease to prepare for transition into adulthood and adult health care. Unfortunately, 25%-75% of adolescents with JIA are lost to follow-up once transferred from pediatric to adult health care in Canada [4-8]. Needs assessments have revealed insufficient time to provide transition services, a lack of reliable JIA information accessible to adolescents and knowledge about linkages to community resources, need for additional self-management skills, and a gap in peer support in adolescents with JIA [9-13]. These gaps were found to be critically important to address within individual countries through distinctively customized plans and activities [4,14].

Peer Support and Self-Management Programs

Self-management programs (SMPs) are proposed as effective ways to address the educational, self-management, and peer support needs for adolescents with JIA. Significant evidence from adult and pediatric medicine has indicated that SMPs result in improved health behavior, self-efficacy, and certain health status outcomes in persons with arthritis [15,16]. SMPs afford the opportunity to instantly react to participant feedback, tailor the amount and complexity of information to participants' needs [17,18], and immediately address information that participants do not understand. Furthermore, SMPs in a small group setting allow for interaction and discussions among participants, which, in turn, builds social support [15]. Remotely delivered SMPs, in the form of videoconferencing, represent an evolving technology that can improve accessibility, especially for patients residing in rural or remote communities [19].

Previous needs assessments [12-14] have identified the need for virtual self-management interventions incorporating peer support and for standards of technology delivery and guidance for effective virtual communications in a group setting [20,21].

Our aim is to conduct a pilot multicenter randomized controlled trial (RCT) to evaluate the feasibility and preliminary effectiveness of a virtual group-based SMP for adolescents with JIA in comparison to a waitlist control group.

Methods

Study Design

A pilot RCT will be conducted to determine the feasibility and preliminary effectiveness of a virtual SMP intervention. Eligible participants will be randomized 1:1 to either the intervention group or a waitlist control group. Both groups will complete baseline measures (T0) as well as postprogram measures (T1). Participants enrolled into the intervention will undergo the SMP and be asked to participate in an optional postintervention interview. The waitlist control group will continue receiving standard of care during this program period. They will be given the option to complete the SMP afterwards, and if completed, be asked to complete postintervention questionnaires. They will also be asked to participate in the optional postintervention interview. The study is registered in ClinicalTrials.gov (NCT06184100). Figure 1 shows the trial schema, and Multimedia Appendix 1 shows the timeline. This study follows

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the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials; checklist provided in Multimedia Appendix 2) guidelines.

Figure 1. Trial schema.

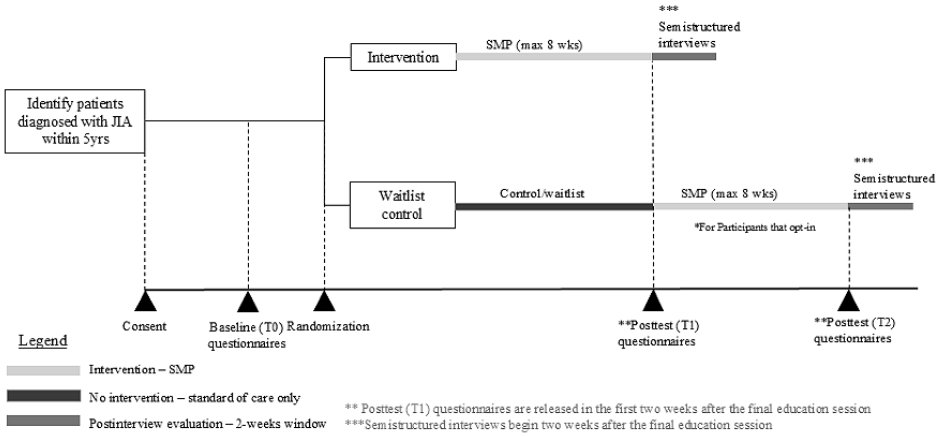

Participants

Participants will be recruited from 5 Canadian pediatric rheumatology centers across different provinces after obtaining local research ethics approval. Sociodemographic and disease-related characteristics including age, gender, disease subtype, date of diagnosis, and current or past treatment will be collected from health records for descriptive purposes at baseline.

Inclusion Criteria

Participants will be considered eligible to participate if they meet the criteria described below:

1. Adolescents between the ages of 12 and 17 years.
2. Confirmed diagnosis within 5 years according to the International League of Associations for Rheumatology JIA classification criteria.
3. Followed up in one of the pediatric rheumatology clinics participating in the RCT.
4. Able to access the internet.
5. Willing and able to complete web-based measures.

Exclusion Criteria

Individuals will be excluded from the RCT if they meet any of the following criteria:

1. Insufficient English reading and speaking skills.
2. Untreated psychiatric or comorbid disorders or major cognitive impairments leading to an inability to understand materials and participate in the SMP group activities.
3. Other chronic conditions such as other autoimmune disease, neurologic, orthopedic, and organ system disorder (eg, heart and kidney) that might influence outcome assessments.
4. Past participation in the last year or participating in another formal peer-support or self-management program.
5. Additionally, concomitant adjunct interventions and other involvement with peer support groups (contamination) will be recorded.

Randomization, Recruitment, and Sample Size

CONSORT (Consolidated Standards of Reporting Trials; checklist provided in Multimedia Appendix 3) 2010 guidelines suggest a sample size calculation of 9% of the anticipated full-scale RCT for the intervention group in pilot studies [22,23]. However, to establish feasibility at several sites and get an estimate of a statistically significant SD to inform a full-scale multicenter trial, our target is to conduct 2 offerings of the program with 4-6 participants per group at each of the 5 sites to control for site-specific education. Eligible participants will be identified through a review of the patient database and will be contacted by research coordinators. Some participants will also be recruited during their clinic visits. They will receive detailed information about the study, including its objectives, procedures, and potential benefits. Interested participants will provide informed consent (or assent, with parental consent for minors). The study aims to recruit a total of 100 participants. Therefore, we will require 50 participants in the intervention group and 50 in the waitlist control group. This sample size was chosen to establish feasibility and inform a larger multicenter trial. Participants will be randomized 1:1 to either the intervention group or the waitlist control group using block randomization with variable block sizes. This randomization will be conducted using REDCap (Research Electronic Data Capture; Vanderbilt University), a secure web-based application for managing data. Randomization will occur before baseline measures are completed. Participants in the intervention groups will be from the same center to adapt the program to local health care systems and account for the variability of nonformal educational practices between centers. This approach will also facilitate an evaluation/subgroup analysis of outcome measures at each center.

Intervention

The program consists of JIA disease education, self-management strategies, and peer support in a group-based setting. Four sessions, 60-90 minutes each, will be conducted over 8 weeks with a group size of 4-6 participants via videoconferencing platforms. Each session will include Microsoft PowerPoint–delivered presentations, interactive activities, and group discussions. The 4 sessions will focus on the following themes: Overview and Diagnosis of JIA, Daily Living and Exercise, Coping Strategies, and Medication and Lifestyle Management. To ensure intervention fidelity, sessions will be

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provided by the same designated health care professionals. All sessions will be video-recorded and uploaded to a secured research server to assess the group's dynamic and ensure sessions are delivered as planned (fidelity). Young adults living with JIA from participating centers will be asked to sit in during these sessions to share their lived experiences and foster peer social support. Additionally, each site will include site-specific resources. After completing the intervention, participants will be asked to independently attend an optional semistructured interview to capture participant experiences of the intervention.

Session Delivery and Training

The National Institute of Health's (NIH's) best-practice guidelines on intervention fidelity [24] will be used to develop and establish standards for virtual session delivery. This will incorporate the NIH's framework principles: consistency in intervention content information and delivery and training the interventionist for delivering a consistent intervention. To achieve this, we will develop an interventional manual on the technology setup and troubleshooting, ground rules and videoconferencing etiquette with participants, how to maintain consistency in content delivery, techniques to engage participants and guide discussions, and the content of a checklist that will be used to assess intervention fidelity.

Second, we will provide training to the interventionists. Training sessions will occur prior to program implementation using our manual. Interim feedback will be provided after 2 and 6 sessions using fidelity checklists to maintain consistent delivery and continuous process improvement.

Outcome Measures

Feasibility Outcomes

Primarily, feasibility will be measured through adherence with the SMP (defined as 80% completion). Other feasibility outcomes will include the following:

1. Recruitment and withdrawal rates (>80% recruitment rate and <80% withdrawal).
2. The proportion of completed questionnaires (defined as 80% when all measures are completed) at baseline and 8 weeks post randomization in both groups.
3. Satisfaction with the SMP as measured through questionnaires and a semistructured virtual interview with the participants following involvement in the SMP to capture the participants' experience.
4. Intervention fidelity (defined as consistent content and technology delivery) will be assessed by fidelity checklists and qualitative analysis of recorded video sessions after 2 sessions, 4 sessions, and at completion of all sessions to ensure that sessions are consistently delivered and as planned.

Preliminary Effectiveness Measures

Participants of both the intervention and control groups will complete 5 validated and reliable patient-reported outcome measures on the web at baseline and post program. This includes the following:

- The Medical Issues, Exercise, Pain, and Social Support Questionnaire—a validated (eg, concurrent validity and construct validity) and reliable (eg, internal consistency) measure for perceived ability (eg, knowledge, skill, behavior, attitudes, and self-efficacy) to manage JIA [25].
- The Children's Arthritis Self-Efficacy Scale—a validated (eg, concurrent validity and construct validity) and reliable (eg, internal consistency) measure for arthritis self-efficacy [26].
- The Pediatric Quality of Life Inventory 3.0 Rheumatology–Teen Module—a validated (eg, construct validity and concurrent validity) and reliable (eg, internal consistency) measure used for pediatric rheumatology–specific health-related quality of life in children aged 13-18 years [27].
- The PROMIS (Patient-Reported Outcomes Measurement Information System) Pediatric Pain Interference Scale—a validated (eg, concurrent validity and construct validity) and reliable (eg, internal consistency) measure for pain behavior in children aged 8-17 years [28].
- Readiness for Adult Care in Rheumatology—a validated (eg, concurrent validity and construct validity) and reliable (eg, internal consistency) measure to assess transition readiness in adolescents with JIA [29].

Ethical Considerations

This study was approved by the Conjoint Health Research Ethics Board of the University of Calgary (REB22-1820), Edmonton (pSite00000101), Vancouver (H24-02469), SickKids Research Ethics Board (1000080939), and the Health Research ethics Board of the University of Manitoba (HS26016{H2023:168}). Informed consent will be obtained from all participants in accordance with the tenets of the Declaration of Helsinki, with parental consent required for minors. Participants will be informed of their right to opt out at any time. Data collected will be anonymized to ensure privacy and confidentiality, with protective measures in place to safeguard the participants' information. Compensation for participation will be provided in the form of gift cards valued at CAD $50 (US $36.51) per participant. No identification of individual participants will be possible in any images or supplementary material included in the manuscript.

Data Analysis and Statistical Methods

Sociodemographic Characteristics

Descriptive statistics (mean, SD, and IQR) will be used to analyze sociodemographic characteristics.

Data Analysis Plan

Feasibility Outcomes

The feasibility of the SMP will be analyzed using descriptive statistics (eg, mean, SD, and frequencies) based on (1) adherence with the SMP (defined as 80% when the participant completes 4 sessions over 8 weeks), (2) recruitment and withdrawal rates, and (3) the proportion of completed questionnaires at baseline and 4 weeks after the last session (defined as 80% when all measures completed).

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This study will use qualitative thematic analysis [30,31] to analyze the data. The experiences, perceptions, and satisfaction measured through video-recorded semistructured individual interviews will be transcribed verbatim and entered to a data analysis software (NVivo version 12.0; Lumivero) [32] for analysis. This method involves iterative cycles of coding, interpreting, and reflecting on the data to identify patterns and themes that capture participants' experiences and perceptions of SMP. Key nonverbal cues, terms, and phrases will be noted and underlined in the transcript and coded accordingly. All qualitative data will be read separately several times by the research assistant and at least 2 investigators to obtain an overall understanding of the data, generate initial codes, and develop themes based on research questions. The themes will be refined, defined, and supported by extracts from the transcript. Finally, the themes will be documented in a manuscript.

This study will ensure rigor and trustworthiness through credibility, transferability, dependability, confirmability, and reflexivity [33]. A detailed description of the study setup, participants, and data collection procedures will support transferability. Dependability will be ensured by documenting data collection, analysis, and interpretation. Two researchers will independently code transcripts and resolve discrepancies through consensus. A single interview schedule will guide all interviews, and member-checking will enhance credibility. A reflective journal will document research discussions as part of the audit trail. In addition, verbatim transcripts of participants' responses will be included in the manuscript to ensure confirmability [33]. Using the same qualitative methods, we will evaluate intervention fidelity of the recorded video sessions. Scores from the developed fidelity checklist will be used to further support the evaluation of intervention fidelity. Positive checklist ratings (scale 0-10, where 10 is the most positive) will indicate an intervention that is delivered consistently and as planned.

Preliminary Effectiveness Outcomes

The quantitative data will be entered into SPSS [34]. Descriptive statistics will be used to analyze the patient-reported outcome measures with an ordinal Likert scale at baseline and immediately post intervention. In addition, nonparametric Wilcoxon signed rank tests will be used to assess if there is a significant difference between a pre- and posttest outcome. Nonparametric tests will be used due to the small sample size and a lack of normally distributed data. Changes in pre- and posttest outcomes will be analyzed over time using a repeated measures mixed linear model approach where participants will be included as the random effect and baseline scores, study site, and disease-related characteristics will be used as fixed factors or covariates.

Subgroup Analysis

To initiate preliminary exploration of interventional effectiveness by study site and/or patient characteristics (age, sex and gender, disease subtype, and disease severity) interactional statistical tests (such as linear regression models for continuous variables) will be used to detect if differences exist. This will inform future trial design (eg, which strata to include in randomization based on detected subgroup differences).

Missing Data Considerations

We will examine patterns of missing data, determine demographic and/or clinical characteristics that are related to missing data at study time points, and the potential impact on the primary findings. Patterns will be used to inform our use of an intention to treat and to determine if including a per protocol approach in the full-scale RCT will be appropriate.

Data Integration

To address the main research questions related to feasibility and primary effectiveness for scale-up, we will integrate qualitative and quantitative data using a convergent parallel design [35]. This method involves the simultaneous collection and separate analysis of both data types, followed by merging the results for comprehensive insights. Quantitative data from validated questionnaires will provide measurable outcomes on self-management, self-efficacy, health-related quality of life, pain interference, and transition readiness. Concurrently, qualitative data from semistructured virtual interviews will capture participants' experiences, engagement, and satisfaction with the SMP. By comparing quantitative results with themes from the qualitative analysis, we will identify patterns, discrepancies, and complementary findings. This holistic approach ensures that both numerical trends and personal narratives are considered together, offering a robust understanding of the program's feasibility and effectiveness, which will inform potential scale-up and integration into routine clinical practice.

Sex and Gender Considerations

Female sex is a biological risk factor for JIA. Gender is a complex construct encompassing individual social role, behavior, and identity. Gender may be influenced by or interact with multiple factors including age, pain, or symptom perception, and these interactions may impact adherence to and satisfaction with the SMP. We will, therefore, consider the impact of sex and gender on our outcomes as described above. For all participants, we will collect information on sex (at birth) as well as current gender identity to facilitate analysis and reporting by sex and gender separately where appropriate.

Results

Overview

Recruitment for the VISTA-JIA study began in January 2024 and is expected to conclude by December 2025. As of March 2025, a total of 40 participants have been successfully enrolled from 5 Canadian pediatric rheumatology centers. The recruitment process involved approaching eligible participants during clinic visits and providing detailed information about the study, including its objectives, procedures, and potential benefits. Informed consent (or assent, with parental consent for minors) was obtained from interested participants.

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Session Delivery and Training

We have developed and established standards for virtual session delivery based on the NIH's best-practice guidelines on intervention fidelity. This incorporates the NIH's framework principles: consistency in intervention content information and delivery and training the interventionist for delivering a consistent intervention. Training sessions for the interventionists have been conducted. One education intervention has been conducted and will be used to further improve the program.

Discussion

Anticipated Findings

This pilot RCT aims to evaluate the feasibility and preliminary effectiveness of a virtual SMP for adolescents with JIA. The anticipated main findings include high adherence rates (≥80%) to the SMP, positive engagement and satisfaction among participants, and preliminary improvements in self-management skills, self-efficacy, and transition readiness. Additionally, the study is expected to demonstrate the feasibility of conducting a virtual group-based intervention across multiple pediatric rheumatology centers in Canada.

The need for self-management interventions in JIA has been well-documented in previous research [12-14]. Prior studies have highlighted the challenges adolescents face in managing their disease, particularly during the transition to adult care [9-13], and the benefits of peer support in chronic disease management [15]. Previous in-person SMPs have shown effectiveness in improving self-efficacy and disease knowledge [15,16], but accessibility has remained a barrier, particularly for those in rural or underserved areas [19]. The VISTA-JIA study builds on this evidence by delivering a structured, interactive, and virtual SMP, leveraging videoconferencing technology to improve accessibility and scalability. This approach aligns with emerging trends in digital health and telemedicine, which have shown promise in other chronic disease management programs [19].

Significance

This will be the first, to our knowledge, evidence-based self-management program to offer virtual self-management participation for adolescents with JIA. If proven feasible and acceptable, this SMP will be then tested in a larger RCT with enough participants and statistical power to demonstrate the effectiveness of the SMP across pediatric rheumatology centers in Canada. The program's unique design to include both health care providers (HCPs) and peer participants within a group setting, provides an opportunity to (1) enhance and instill confidence in participants' individual ability to self-manage skills under the guidance of experienced HCPs; (2) allow for participants to gain a better understanding of JIA through questions and input provided by their peers; (3) enhance their emotional management skills by learning through the shared challenges and emotional perspectives of participants within the group; (4) potentially foster a network of social support among the participants, which may prove beneficial beyond the scope of this project and their transition to adult care; and (5) streamline the need for HCPs' educational practices and optimize for consistent dissemination of information with engaging and interactive activities. Additionally, assessing intervention fidelity will allow us to establish a standardized framework for content and technology delivery and will help to train future session facilitators. This will finally be applicable to broader audiences as our establishment of a standardized technology-delivery framework and guidance for effective virtual communications in a group setting can be applied to any virtually delivered intervention in health care.

Strengths and Limitations

Integrating peer support into a virtual SMP provides a unique opportunity to foster social connections, which has been identified as a critical component of effective self-management. The structured group format promotes interaction and shared learning, which can further enhance self-efficacy and engagement. The use of a virtual platform is another major strength, as it improves accessibility for participants, particularly those in remote or underserved areas. This is particularly relevant for chronic disease management, where sustained engagement in self-care practices is essential. Furthermore, this study incorporates rigorous methodological approaches to ensure intervention fidelity, including standardized session delivery, comprehensive facilitator training, and session recordings for quality control. By implementing best practices in virtual intervention design, the study establishes a replicable model for future digital health interventions in pediatric chronic disease management.

This study may not be generalizable to the broader JIA population. However, to improve generalizability and adaptability, we have partnered with 5 centers across Canada that serve patient populations from heterogeneous backgrounds. This includes rural, urban, and ethnically diverse locations. As a web-reliant intervention, this trial is subject to some of the inherent vulnerabilities that accompany the use of internet-based platforms such as varied connectivity access and reliability among participants. To address this, we intend to plan for contingencies, such as sending participants recorded sessions and scheduling a follow-up call to address any questions or concerns.

Future Directions

Findings from this pilot study will inform the design of a full-scale RCT to evaluate the program's long-term effectiveness and cost-effectiveness. Future research should explore ways to optimize participant engagement, including the use of asynchronous learning modules to complement live sessions. Additionally, an evaluation of caregiver involvement in adolescent self-management may provide further insights into enhancing program impact.

Dissemination Plan

This plan will involve the following:

1. Multiple partners (Cassie and Friends Society, Alberta Strategy for Patient Oriented Research SUPPORT Unit), collaborators (allied health professionals), and knowledge users (young adults with JIA) have been and will continue to be kept engaged in the development and evaluation of

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the SMP and involvement in all knowledge translation activities as members of the knowledge translation committee. Members will be updated on the study progress; their perspectives will be sought for interpretation of study findings and on ways to share knowledge through their respective organizations.

2. Findings will be shared with health care professionals via presentations at key national and international conferences, Canadian Alliance of Pediatric Rheumatology Investigators and Childhood Arthritis and Rheumatology Research Alliance meetings, web-based webinars, seminars and rounds at hospitals and universities, and publications in open access journals.
3. Findings will be shared with patients and consumer groups (1-page brochure, media releases [newspaper, magazines, and social media such as YouTube videos], posting on key websites [eg, hospitals, Cassie and Friends Society, and the Arthritis Society]), and online education sessions aimed at families through research team and partners.
4. The research team will support consumer representatives in translating study findings using consumer fact sheets to educate their health providers ("consumer detailing"). This strategy has been suggested as one of the most potent methods for changing practice and disseminating new knowledge.

Conclusions

The findings from this research have the potential to inform the development of programs that equip adolescents with JIA with the necessary skills to manage their own care effectively. By fostering greater self-efficacy in managing their condition, we anticipate improved transitions from pediatric to adult care and enhanced long-term health outcomes for individuals with JIA. Furthermore, this study will contribute to the broader efforts to establish standardized approaches for virtual SMPs and educational interventions, with implications for the management of various pediatric chronic conditions. This pilot study will inform a larger RCT focused on the efficacy and cost-effectiveness of the program with the goal of integration in routine clinical practice.

Acknowledgments

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Data Availability

The datasets used during the current study are available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization: KAB, KC, MS, JNS, JG, RH, LSHL, DR, and HS
Investigation: J Booth, KAB, KC, MS, JNS, BOA, J Brooks, JG, RH, LSHL, DR, BF, JT, JW, and HS
Methodology: KAB, KC, MS, JNS, JG, RH, LSHL, DR, and HS
Supervision: HS
Writing—original draft: J Booth, BOA, and HS
Writing—review and editing: J Booth, KAB, KC, MS, JNS, BOA, J Brooks, JG, RH, LSHL, DR, BF, JT, JW, and HS

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer reviewer report from Strategic Operating Grant (SOG), Integrated Scientific and Medical Advisory Committee, Arthritis Society Canada.
[PDF File (Adobe PDF File), 189 KB - resprot_v14i1e69539_app1.pdf]

Multimedia Appendix 2
SPIRIT 2022 checklist.
[PDF File (Adobe PDF File), 226 KB - resprot_v14i1e69539_app2.pdf]

Multimedia Appendix 3
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 3452 KB - resprot_v14i1e69539_app3.pdf]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
HCP: health care provider
JIA: juvenile idiopathic arthritis
NIH: National Institutes of Health
PROMIS: Patient-Reported Outcomes Measurement Information System
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SMP: self-management program
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Comparative Efficacy of Virtual Reality–Assisted Cognitive Behavioral Therapy Versus Yoga-Based Interventions for Reducing Performance Anxiety in Students: Protocol for a Randomized Controlled Trial

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Abstract

Background: Performance anxiety represents a significant challenge for students, manifesting as a fear of failure and difficulties managing examination-related concerns and academic pressures. According to recent statistics, anxiety affects >4% of the global population, underscoring the need for effective management methods. Studies indicate that yoga and virtual reality (VR) training can alleviate symptoms of performance anxiety.

Objective: This trial aims to compare VR-assisted cognitive behavioral therapy (CBT) with yoga interventions to find effective treatments.

Methods: A single-blinded randomized controlled trial will be conducted with 60 participants (n=30, 50% per intervention group) recruited from university and preuniversity counseling centers. The trial will measure whether the interventions reduce performance anxiety in students. Stratified randomization will be used to ensure equal distribution of baseline anxiety levels and gender across both groups. The primary outcome is a reduction in anxiety, measured using the State-Trait Anxiety Inventory-Y1 and State-Trait Anxiety Inventory-Y2 subscales. Secondary outcomes include emotional regulation and quality of life. Data will be collected at baseline, after the intervention, and during follow-up assessments. Statistical analyses will include parametric tests (eg, repeated-measures ANOVA and *t* tests) to compare anxiety reduction, emotional regulation, and quality of life across groups. The intention-to-treat approach will be applied to minimize bias due to participant dropouts. Sensitivity analyses will assess the robustness of the findings.

Results: This study is planned to start in September 2025 and end in June 2026. VR-assisted CBT is expected to reduce anxiety very quickly, whereas yoga is predicted to have long-term benefits.

Conclusions: More generally, this research highlights the need for new, accessible forms of mental health support. VR-assisted CBT is an emerging digital mental health intervention, and it enables individuals to access and explore anxiety in virtual, safe environments. In contrast, yoga is a more conventional, all-encompassing discipline that enhances mental health through physiological and psychological processes that may have long-term effects.

Trial Registration: ClinicalTrials.gov NCT06639841; https://clinicaltrials.gov/study/NCT06639841

International Registered Report Identifier (IRRID): PRR1-10.2196/66112

(JMIR Res Protoc 2025;14:e66112) doi:10.2196/66112

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KEYWORDS

performance anxiety; yoga; virtual reality; cognitive behavioral therapy; CBT; randomized controlled trial

Introduction

Background

Performance anxiety represents a significant challenge for many students, manifesting as an intense fear of failure and difficulties managing concerns associated with examinations and other academic activities. Recent international statistics [1,2] identify anxiety as one of the most prevalent issues globally, affecting >4% of the world population. In this context, alternative anxiety-reducing methods, such as yoga and virtual reality (VR) training, have gained increased attention both academically and practically. Recent research suggests that yoga practices and training using VR techniques can play a crucial role in alleviating performance anxiety symptoms.

As a mind-body practice, yoga offers a holistic approach that can help reduce anxiety symptoms by regulating the autonomic nervous system and reducing stress responses. By integrating poses (asanas), breathing techniques (pranayama), meditation, and deep relaxation, yoga can modulate brain activity and cortisol levels, thereby improving mental health. Regarding yoga-specific techniques, several experimental studies indicate a significant reduction in anxiety and an overall improvement in well-being through practices of meditation and breathing exercises [3-6]. These studies suggest that these techniques reduce anxiety through physiological and psychological mechanisms, including cortisol reduction and enhanced emotional regulation, and are effective in various contexts (eg, high-performing music students as well as students with lower academic performance). These findings are partially supported by a meta-analysis that highlights the positive effects of yoga on psychophysiological parameters associated with performance anxiety, such as heart rate and its variability, while also noting that further studies are needed to confirm their usefulness in reducing clinically diagnosed anxiety [7].

Specific research on evaluation anxiety in the literature mainly includes general studies, with only a few examining anxieties in various performance situations. Zoogman et al [8] reported significant outcomes from yoga interventions, drawing from controlled clinical research with diverse contexts, indicating the global effectiveness of yoga programs on anxiety symptoms. Another literature review underscores the efficacy of yoga programs for children and adolescents aged <18 years [9]. Although these studies have several methodological limitations, their findings indicate a general reduction in anxiety. In addition, Khalsa et al [4] showed that a 6-week program for music students significantly reduced music performance anxiety, with notable outcomes both at the end of the program and compared to a control group. Erdoğan Yüce and Muz [10] tested an intervention program for young people aged 18 to 25 years, where a yoga program including asanas (physical poses), pranayama (breathing exercises), and meditation contributed to improved physical and mental health. Conducted over 4 weeks with 60-minute sessions, the quasi-experimental study found a significant reduction in state anxiety but not trait anxiety. The program's social quality of life (QoL) improved due to group interactions during the sessions, although the number of yoga sessions was limited and insufficient for significant trait-level changes.

Although the broader literature indicates some limitations in yoga research, Li and Goldsmith [11] identified specific issues, such as small sample sizes, control groups, and random group allocation. In addition, they highlighted the importance of intervention duration in anxiety and stress outcomes. For example, Rocha et al [12] found the best yoga intervention outcomes after 6 months, significantly reducing anxiety and other psychological health aspects. Participants were yoga naive, and the results were measured alongside a control group at the beginning of the intervention and after 6 months. Shohani et al [13] noted significant results after a substantial number of sessions (eg, 12 sessions) on various mental health aspects, including anxiety. In another study, the authors proposed a program for testing in 2021 [14] and synthesized the literature by collecting data from experienced yoga practitioners. They concluded that at least 10 yoga sessions significantly reduced anxiety symptoms and improved sleep, with participants reporting decreased anxiety severity and improved sleep quality after 10 sessions without significant adverse effects. The findings suggest that yoga can serve as an effective complementary treatment for anxiety; however, more extensive clinical studies are required to confirm its efficacy. Finally, Nanthakumar [15] synthesized the literature and analyzed randomized clinical research, finding that yoga positively impacted anxiety and depression symptoms across 8 studies involving interventions from 4 to 6 months.

Research indicates effectiveness regarding the impact of VR-assisted psychoemotional support, particularly when specific cognitive behavioral techniques are implemented [16]. In a recent dissertation [17], safe exposure to a virtual concert auditorium helped student artists reduce state anxiety. Similarly, Bissonnette et al [18] tested these techniques on music students with performance anxiety, demonstrating that one hour-long sessions across 3 weeks significantly reduced performance anxiety. Following short-term cognitive behavioral therapy (CBT) principles, this approach's effectiveness highlights the potential for fewer sessions (eg, 4 sessions in a controlled experimental protocol) [19]. Finally, recent meta-analyses [20] indicate the superior efficacy of VR therapies compared to control groups, although they do not exceed the effectiveness of in vivo exposure.

Existing literature not only suggests that both intervention programs are effective but also reveals numerous research limitations. Hoge et al [21] compared yoga with cognitive behavioral and educational programs but not VR-assisted techniques, showing that yoga and CBT are more significant than educational methods. Although yoga shows promising results among students, compared to VR-assisted techniques, it is studied in general context and very few studies are specifically comparing them. For instance, Chauhan et al [22]

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demonstrated the effectiveness of a yoga program for medical students using these techniques to address anxiety and mental health aspects. Moreover, there is limited research testing intervention program efficacy for both state and trait anxiety. For instance, Somere et al [23] found that online yin yoga sessions for 2 hours per week significantly reduced state anxiety after each session, although the results of trait anxiety were less conclusive. O'Shea et al [24] noted that CBT is the standard psychological treatment for anxiety disorders. However, some individuals either do not access the treatment or do not benefit significantly from CBT alone. Finally, yoga, as a holistic mind-body practice, is seen as a potential CBT complement, providing benefits such as reduction in stress, anxiety, and depression through mindfulness, breathing, and movement techniques.

Previous research on VR-assisted CBT (VR-CBT) has predominantly focused on its efficacy in treating social anxiety, phobias, and generalized anxiety, often comparing it to passive relaxation or mindfulness-based interventions. However, these comparisons have largely assessed meditation, guided breathing, and progressive muscle relaxation without incorporating structured movement-based interventions such as yoga. This study addresses a critical gap by directly comparing the effects of VR-CBT with yoga, which extends beyond passive relaxation through the integration of physical postures (asanas), controlled breathing techniques (pranayama), and ethical self-discipline (Yama and Niyama). Unlike meditation alone, yoga actively engages both the body and mind, promoting physiological regulation of stress through autonomic nervous system modulation and improving emotional regulation via structured movement and breathwork. Previous studies have shown that VR-CBT provides rapid symptom relief through immersive exposure and cognitive restructuring, while meditation and relaxation techniques tend to cultivate mindfulness without the added physical benefits of yoga. By assessing yoga as a distinct intervention, this study aims to determine whether its multimodal approach leads to more sustainable long-term reductions in performance anxiety compared to the short-term but potentially more immediate effects of VR-CBT. The findings will offer new insights into the comparative efficacy of digital and traditional mind-body interventions for academic anxiety, contributing to the development of more tailored therapeutic strategies.

Goal of This Research

This research aims to evaluate and compare the effectiveness of 2 psychological intervention modalities—VR-facilitated exposure techniques based on cognitive behavioral intervention and yoga techniques involving body posture, breathing, and meditation—in reducing performance anxiety symptoms. In addition, the study seeks to investigate whether VR techniques lead to a more significant reduction in state anxiety, while yoga techniques are more effective in reducing trait anxiety.

Methods

Research Design

Overview

This study is structured as a parallel group randomized controlled trial (RCT) comparing 2 distinct interventions. It uses a stratified randomization approach to account for variations in baseline anxiety levels and gender.

Blinding

Outcome assessors and data analysts will be blinded to group assignments to minimize potential biases.

Participant Recruitment

Participants will be selected voluntarily. They will be invited to participate in the study through referrals from psychologists and psychiatrists working with individuals on waiting lists at counseling and mental health centers. These include psychological counseling centers at universities and preuniversity institutions. Eligible participants will be identified from the waiting lists of online platforms where they registered for counseling or psychotherapy related to emotional difficulties. Once identified, they will receive an invitation to participate in the research project. After expressing their intent to participate, each participant will receive an informed consent form detailing the study's specifics. Participants will be formally included in the study upon signing the consent form. Finally, participants will be randomly assigned to one of the proposed psychoemotional support groups. This allocation will be conducted through random assignment, ensuring balanced groups in terms of financial level, type of education, and clinical level of anxiety.

Eligibility Criteria

Inclusion Criteria

According to the Romanian Youth Law Number 350 of July 21, 2006, our research targets the youth age group, which includes adolescents and young adults aged 14 to 35 years. Given that there are specific recommendations regarding participants being aged ≥15 years for using VR software and hardware programs, our program will include adolescents and young adults aged 16 to 35 years. Another essential criterion for inclusion in the research is diagnosis, that is, participants diagnosed with disorders within the anxiety spectrum of mental disorders, particularly performance anxiety, who are capable of understanding and providing consent to participate in the study. Participants lacking full decision-making capacity (eg, those with severe psychotic disorders, schizophrenia, or any other disorder affecting judgment and those who have attempted suicide) are not eligible for participation.

To be eligible, participants must present a clinical or subclinical level of anxiety symptoms, confirmed by medical or psychological evaluation. According to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* and *the International Classification of Diseases, 11th Revision*, test anxiety can be included within the following broader anxiety disorders: generalized anxiety disorder, social anxiety disorder

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(SAD; social phobia), or specific phobia. Symptoms include worry on most days, for ≥6 months, related to numerous events such as academic performance, examinations, etc. Anxiety and worry are accompanied by at least 3 of the following symptoms: restlessness, fatigue, difficulty concentrating, irritability, muscle tension, and sleep disturbances. SAD involves fears or anxieties about one or more social situations in which the person is exposed to possible scrutiny by others. For students, this may involve oral examinations or class presentations. Social situations almost always provoke fear or anxiety and are avoided or endured with intense fear or anxiety. Regarding specific phobia, if it centers solely on examinations, then, depending on its intensity and duration, it may constitute a specific phobia. Generally, cases are recorded where fear or anxiety is excessive or disproportionate to the situation, as there is no real threat from the situation itself.

We have also identified the following additional important inclusion criteria: (1) enrollment in an academic center or preuniversity educational institution and placement on the waiting list at psychological counseling centers within universities or preuniversity institutions, (2) the ability to understand all aspects of the study and the preliminary commitment to adhere to its interventions through signing informed consent, and (3) understanding of both Romanian and English.

Exclusion Criteria

The research team has identified the following key exclusion criteria that could negatively interfere with and influence the study's results: (1) lack of consent from a legal representative for minors, undergoing medical treatment, diagnosis of epilepsy, auditory or visual impairments, mobility challenges, spinal disorders, nonclinical levels of anxiety; (2) psychiatric conditions that impair sensory or kinetic abilities required for the intervention procedures; (3) history of cybersickness, photosensitivity crises, or seizures induced by intermittent light stimulation (specific to the VR cohort); and (4) several medical, technological, and biosocial limitations related to exposure to VR techniques. These are detailed in the informed consent provided in Multimedia Appendix 1 for each participant assigned to the *VR* experimental condition. The most important aspects include neurological disorders, visual impairments, vestibular disorders, photosensitivity, cardiovascular issues, pregnancy, severe mental health disorders, technological and environmental limitations, cognitive disorders, impaired judgment, the lack of adherence to past medical or psychological treatments, and language barriers. These criteria are detailed in Multimedia Appendix 1 for each participant in both versions of the informed consent.

Procedure

Overview

Participants will be invited to attend one of the psychoemotional support groups where they will benefit from either VR-facilitated exposure techniques based on cognitive behavioral intervention modalities or techniques based on the combination of postures (asana), breathing (pranayama), and meditation. Before allocation to the psychoemotional support conditions, each participant will be assessed using a personal data sheet to consider relevant medical, social, and demographic data and exclusion criteria.

This study will use a comprehensive set of preassessment measures to ensure stratified randomization before group allocation. First, measures of both state and trait anxiety are used to ensure participants are grouped appropriately according to their baseline anxiety levels before intervention allocation. Levels of clinical anxiety and emotional regulation mechanisms relevant to anxiety management as well as specific manifestations of performance anxiety will be assessed before the start of the intervention program. Randomization into groups will be done after the initial assessment and will consider an equitable distribution, and the equitable distribution will be considered according to anxiety levels. Given the impact of baseline anxiety levels on treatment effectiveness, a stratified randomization technique is used. This protocol outlines that participants are first stratified based on their anxiety scores and gender before being randomized into the 2 intervention groups. Stratification ensures that individuals with high-trait anxiety and low-trait anxiety are evenly distributed across both treatment groups. Similarly, gender will be controlled to ensure that results are not confounded by gender-related emotional regulation tendencies. This type of stratification minimizes variance and ensures comparable starting conditions for both groups. Finally, this process controls for preexisting differences, leading to stronger statistical effects.

The participants will then start the psychoemotional support program and complete an anxiety level assessment at the end of each intervention session. At the end of the program, participants will complete the anxiety questionnaire again, along with an instrument assessing their comfort, discomfort, and the quality of the specific intervention techniques. To evaluate manifestations of performance anxiety, correlations between clinical anxiety and academic anxiety will be checked to indicate the strength and significance of their relationship. Details about the implementation of the techniques are presented in Table 1.

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Table 1. Overview of intervention components for virtual reality (VR)–assisted cognitive behavioral therapy (VR-CBT) and yoga-based interventions.

Intervention and phase	Session components	Duration
VR-CBT		
Introduction and familiarization (sessions 1-2)	Psychoeducation, familiarization with VR equipment, and guided relaxation exercises	20-30 min per session
Active exposure (sessions 3-8)	Exposure to anxiety-inducing VR scenarios (eg, virtual presentations), cognitive restructuring, and relaxation	20-30 min per session
Evaluation and feedback (session 9)	Review of selected VR scenario, QoLI[a], debriefing, and feedback	20-30 min
Yoga-based intervention		
Yoga practices (sessions 1-10)	Body postures (asanas), breathing techniques (pranayama), meditation, and relaxation exercises	60-90 min per session
Final assessment (after the intervention)	QoLI, and self-report feedback on intervention experience	60 min

[a]QoLI: Quality of Life Inventory.

Data Monitoring

A data safety monitoring board (DSMB) will monitor data collection and protocol compliance. These will include interim analyses, if necessary, with predetermined termination procedures if safety issues or important emerging reported adverse events (AEs) call for study termination earlier.

Given the low-risk nature of the interventions (VR-assisted CBT [VR-CBT] and yoga) and the absence of pharmacological components, a formal independent data monitoring committee is not deemed necessary for this study. Both interventions are noninvasive, well-established, and widely used in clinical and wellness settings, minimizing the likelihood of severe AEs requiring external oversight. Instead, a DSMB will be responsible for overseeing participant safety, protocol adherence, and interim data reviews. The DSMB will be composed of 3 independent experts, including a clinical psychologist specializing in anxiety disorders, a statistician, and a researcher with expertise in VR interventions, ensuring multidisciplinary oversight from our team. This board will meet at prespecified intervals (eg, the midpoint and end of the study) to evaluate participant retention, dropout rates, and any reported adverse effects, such as cybersickness from VR exposure or physical discomfort from yoga sessions.

This study uses a systematic approach to collecting, assessing, reporting, and managing AEs and unintended effects related to the interventions. Given the noninvasive nature of VR-CBT and yoga, AEs are expected to be minimal, but potential risks such as cybersickness (VR-CBT), physical discomfort or strain (yoga), or emotional distress (both interventions) will be monitored. Participants will be instructed to report any AEs immediately during or after intervention sessions either verbally to facilitators or via structured postsession feedback forms. Solicited AEs will be actively monitored through weekly check-ins, while spontaneous reports will be recorded in an AE log maintained by the research team. The severity of reported events will be classified as mild (transient discomfort), moderate (requires temporary intervention modification), or severe (necessitates withdrawal from the study). In the event of a significant or unexpected AEs, the study team will conduct a risk-benefit assessment, and if necessary, the DSMB will review the case. Participants experiencing persistent distress or injury will be referred to appropriate clinical support services. All AEs and responses will be documented, reviewed in regular safety meetings, and included in the final study report, ensuring transparency and participant safety.

Auditing Procedures and Independence

To ensure adherence to protocol, data integrity, and participant safety, this study will undergo periodic internal audits conducted by an independent ethics and compliance committee at the 2 supporting academic institutions. Audits will occur at three key time points: (1) after initial participant enrollment, (2) midway through data collection, and (3) at the study's conclusion before final analysis. The auditing process will assess protocol compliance, adherence to ethical guidelines, proper documentation of informed consent, accurate data collection procedures, and AE reporting. Any discrepancies or deviations identified during the audit will be reported to the principal investigator (PI) and the institutional review board (IRB) for corrective action. While this audit process is not fully independent from the sponsoring institution, it remains separate from the direct investigative team, reducing potential conflicts of interest. If significant concerns arise, an external auditor may be consulted to review trial conduct. The final audit findings will be documented in the study report and shared with regulatory authorities if required, ensuring transparency and research integrity.

VR Cognitive Behavioral Intervention and Theoretical Background

The psychoemotional support intervention, facilitated by VR exposure techniques (6-10 sessions), uses Guided Meditation VR software and stand-alone Oculus Quest 2 and HTC Vive Flow hardware for alleviating performance anxiety. These consist of approximately 6 to 10 sessions of 20 to 30 minutes each of psychoemotional support based on cognitive behavioral techniques and integrative psychotherapy (with extension to a maximum of 1 h, if necessary). They will be carried out over a period of 2 weeks, up to a maximum of 1 month if it is not possible to organize the sessions in optimal conditions. After 1 month, the participants are reported as having withdrawn (in case of a request from the participants) or dropped out of the

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psychoemotional support program. The initial sessions (1-2 sessions) are designed for psychological assessment, psychoeducation, and familiarization with VR exposure techniques. In the next 2 to 3 sessions, different VR scenarios are tested to find a comfortable virtual environment for each patient. We test if patients agree that they are present in that generated virtual environment in a manner comparable to exposure in a natural environment (eg, a walk by the beach, in a forest, or an underwater itinerary). At this stage, subsequent exposure techniques will be developed using a combination of cognitive restructuring and relaxation methods, aimed at familiarizing participants with the technology and ensuring a pleasant experience. The next 1 to 2 sessions will continue with exercises already chosen, based on cognitive restructuring techniques combined with relaxation techniques. The last session is designed to review one of the exercises, assessing the quality of the technique and offering suggestions for improvement by going through a set of questions (eg, QoL through the QoL questionnaire). Each session concludes with a brief clinical assessment of anxiety using the State-Trait Anxiety Inventory (STAI) tool. Specific manifestations of performance anxiety are assessed.

VR-CBT represents an innovative psychotherapeutic intervention method in mental health, addressing traditional challenges by integrating VR technology to facilitate exposure and cognitive restructuring in a controlled, immersive environment. Frequently used for treating anxiety, phobias, obsessive-compulsive disorder, and depression, VR-CBT offers patients a captivating alternative where they can safely experience anxiety-inducing scenarios in a gradual and secure manner. Advantages and specific characteristics of VR-CBT based on recent studies detailing its applicability, benefits, and risks in managing mental health disorders and improving mental well-being are highlighted [25,26]. In recent years, VR-CBT has been recognized as a leading-edge technology in treating mental health disorders and is considered a significant innovation for mental well-being. For instance, the World Health Organization has included mental health in its global strategies, underscoring the need to develop innovative and accessible therapies for treating anxiety, depression, and related disorders [27]. Amid global challenges, such as the COVID-19 pandemic, VR-CBT promises to support traditional therapies by reducing physical and emotional barriers associated with exposure sessions [28].

A distinct feature of VR-CBT is its precise control over exposure. Unlike real-world exposure, VR allows therapists to create and customize therapeutic scenarios in a safe, repeatable environment while monitoring the patient's physiological responses, including blood pressure and heart rate [29]. For instance, participants with social phobias can gradually be exposed to simulated social interactions, thereby reducing real-world anxiety and enhancing coping skills [30]. VR exposure aims to induce emotional responses such as those experienced in real situations but within a context where patients feel they can control and manage stressful scenarios. This increased control encourages patient compliance with therapy and reduces dropout rates, which is essential in treating complex mental disorders such as phobias and generalized anxiety [31]. Besides improving therapy compliance and effectiveness, VR-CBT significantly alleviates anxiety symptoms. Studies show that repeated and monitored exposure in VR environments helps reduce stress and anxiety levels in real-life situations [32]. For example, in a program for young people with anxiety disorders, VR therapy contributed to decreased anxiety levels and improved emotional regulation skills. Another notable advantage is VR's ability to track patient gaze and reactions, which is an essential aspect for diagnosing symptoms that are difficult to observe, such as suspiciousness and misinterpretation of others' intentions in psychotic disorders [33].

The effectiveness of VR-CBT was evaluated in an RCT where patients were divided into 2 groups; one group underwent VR therapy, and the other received traditional relaxation and meditation techniques [20]. The study showed a significant decrease in anxiety symptoms in the VR group, particularly regarding reduced somatic reactions and stress-related symptoms. These results suggest that VR-CBT can be an effective complementary method to conventional approaches, thereby reducing the need for anxiolytics and providing patients with long-term self-regulation techniques [34]. Furthermore, VR-CBT offers substantial potential for global application, being an accessible and cost-effective treatment option compared to conventional therapy. VR platforms are becoming more accessible, enabling increased access for patients who cannot participate in in-person therapies due to geographical barriers or severe anxiety [35].

Yoga Intervention and Theoretical Background

This psychoemotional assistance intervention is facilitated through breathing techniques, meditation, and body postures (yoga). The program is designed to reduce anxiety and improve emotional well-being through a holistic mind-body approach. This program is a psychoemotional support intervention that incorporates yoga-based techniques, including breathing exercises, meditation, and body postures. The program runs for 2 to 4 weeks, depending on the scheduling of the sessions, with participants attending 6 to 10 sessions lasting 60 to 90 minutes each. If participants do not complete the program within 1 month, they are considered to have withdrawn.

The sessions include the following:

- Body postures (asanas) that include a sequence of yoga postures such as Tadasana (mountain pose); Surya Namaskar (sun salutation); and various standing and seated poses such as the tree pose, warrior pose, and triangle pose, aimed at promoting physical alignment and relaxation.
- Breathing techniques (pranayama) that include exercises to control and expand the breath, such as Bhastrika (bellows breathing), Ujjayi (victorious breathing), and specific breath locks (Bandhas) to regulate energy flow.
- Meditation and relaxation that includes techniques such as Shavasana (relaxation pose) and chanting of the AUM mantra promote mental calmness and relaxation.

As described in Patanjali's Yoga Sutras, Yama and Niyama represent 2 fundamental sets of ethical and moral rules within the yoga system. These principles, which form the foundation of any practitioner's spiritual evolution, are intended for

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advanced yoga practitioners and beginners. Patanjali structured the yoga system into 8 progressive stages, known as ashtanga, which include Yama (rules for interacting with others) and Niyama (rules of inner discipline) as the first 2 steps of this system. Essentially, Yama and Niyama aim to guide the practitioner toward moral and spiritual balance, regulating both external and internal behavior. Following these principles is vital for reducing negative influences that may affect the practitioner, thus hindering spiritual growth and mental calm.

Yama, or the external moral rules, refers to the behaviors a yogi should adopt in relationships with others. These rules are ahimsa (nonviolence), satya (truthfulness), asteya (honesty), brahmacharya (sexual restraint), and aparigraha (nonpossessiveness). They form an ethical code governing practitioners' thoughts, speech, and actions, with the purpose of preventing mental and emotional disturbances that can arise from unbalanced social interactions. For example, ahimsa, or nonviolence, refers to the absence of physical violence and nonviolence in thoughts and words. Practicing this rule leads to harmony in human relationships and, consequently, to mental calm.

Niyama, in contrast, governs the individual's relationship with themselves. These rules are saucha (purity), santosha (contentment), tapas (discipline), svadhyaya (self-study and study of sacred writings), and ishvarapranidhana (devotion to divinity). Following these rules, the yogi cultivates inner harmony, thus reducing internal factors that block spiritual and mental progress. For instance, santosha, or contentment, encourages the practitioner to find peace and balance regardless of external circumstances, contributing to a significant reduction in stress and anxiety.

The practices described in Yama and Niyama are not merely abstract ethical codes but practical tools that directly influence emotion management and mental calmness. They offer a psychological discipline framework that facilitates internal and external conflicts, which ordinarily lead to emotional disturbances. In the Yoga Sutras, Patanjali argues that these rules are essential foundations for any progress in practice, allowing the establishment of a mental equilibrium that makes exploring higher stages of yoga possible, such as dhyana (deep meditation).

Sample Size Determination

Considering that the research aims to test and compare 2 types of interventions (VR-facilitated exposure and yoga techniques), using a small sample population allows a detailed initial analysis and a rigorous evaluation of the mechanisms involved without requiring significant resources or large samples. In the exploratory phase, this type of study can identify important preliminary trends and effects, which can later be validated through larger studies. The study involves continuous monitoring of anxiety and other psychological and neurobiological parameters, which requires considerable resources for each participant. A small sample enables closer and more detailed tracking of each participant, ensuring higher-quality data collection and avoiding uncontrolled variables. The proposed interventions, such as yoga techniques and VR exposure, are complex and require specific preparation for each participant. Thus, a smaller population allows for more efficient adaptation of the intervention to individual needs and optimal program implementation. In addition, studies of this type often require costly equipment and expertise, such as VR hardware and certified yoga instructors. Therefore, limiting the sample population allows for efficient use of available resources while maintaining intervention quality. Finally, it is worth noting that previous studies have shown that both yoga and VR interventions can yield significant results with a limited number of sessions and participants. This suggests that a small sample may be sufficient to detect the desired psychological effects in the initial phase. Considering power analysis, 30 participants per group are required to detect significant differences regarding anxiety reduction with 80% power at a 5% significance level.

In psychological intervention research, particularly in RCTs involving novel therapeutic modalities such as VR-CBT and yoga, smaller sample sizes can be justified based on several methodological and practical considerations. First, exploratory trials with focused intervention designs often require fewer participants to detect meaningful preliminary effects, as observed in previous studies on VR-assisted exposure therapy and yoga-based interventions for anxiety [20]. In addition, studies incorporating intensive within-subject monitoring, such as repeated anxiety assessments over multiple sessions, benefit from smaller samples to enhance feasibility and ensure high-quality data collection without excessive resource expenditure [35]. Research also indicates that both VR-based cognitive interventions and yoga can yield significant results with as few as 20 to 30 participants per group, particularly when using highly targeted measures such as the STAI-Y1 or STAI-Y2, physiological markers, and emotion regulation scales [25,32]. Moreover, the personalized nature of interventions such as VR-CBT and structured yoga programs allows for greater within-group effect detection, reducing the need for large-scale samples compared to broad-spectrum behavioral health studies [31]. Given these considerations, the chosen sample size of 30 participants per intervention group aligns with previous RCTs demonstrating efficacy in VR and yoga-based anxiety interventions while maintaining statistical power at an optimal level for detecting significant differences in anxiety reduction [36]. This methodological approach ensures that while the study remains manageable in scale, it retains the rigor necessary to provide valuable insights into the comparative effectiveness of digital and holistic anxiety-reduction strategies.

Screening

The enrollment form is designed to enable the selection of participants who meet the inclusion criteria and exclude those who do not meet the established research conditions. The introductory section of the form provides an overview of the research project and details the proposed program, including its duration, number of sessions, information about the research team and affiliated institutions, potential benefits in reducing anxiety, confirmation that the program is free, and clarification that there are no financial rewards. It also specifies the program's purpose and how the research results will be used. Initially, we ensure that all respondents have read, understood, and agree with all the information provided in the introduction. The personal data section is followed by specific questions to

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determine eligibility for inclusion in or exclusion from the practice group. The first set of questions is designed to check alignment with the target age range and educational level (educational level, ongoing studies, the type of education, age, and financial level). The second set of questions assesses the mental and physical health of the participants and whether they are undergoing medication treatment or psychotherapy sessions, which are all essential considerations for inclusion in or exclusion from the research program. On the basis of the responses, those who meet the inclusion criteria will receive the initial evaluation test set.

Instruments

Overview

First of all, participants will complete personal, medical, social, and demographic data sheets to identify aspects that make the volunteer incompatible with participation (ie, country of residence, county or region, gender or sex, level of education, educational attainment, current education, financial situation, marital status, profession, seniority in profession, level of responsibility in the workplace, and physical and psychiatric medical data, eg, current psychiatric diagnosis, undergoing medication, diagnosis of epilepsy, hearing or visual impairment, mobility difficulties, and spinal disorders).

Clinical Anxiety

Spielberger STAY-Y1 and STAY-Y2 subscales are used for the assessment of anxiety symptoms (the versions accredited by the Romanian College of Psychologists), which allow the identification of clinical symptoms of anxiety. The STAI (STAI-Y1 and STAI-Y2) [37,38] is a widely used instrument designed to measure both temporary anxiety (state) and general anxiety disposition (trait). The STAI-Y1 assesses state anxiety (situational emotional response), while the STAI-Y2 measures trait anxiety (general and enduring anxiety tendencies). The STAI has demonstrated high internal consistency (Cronbach α >0.90 for both subscales). It has been validated across multiple populations, including university students and patients with clinical anxiety. Extensive research supports its use in measuring performance-related anxiety and emotional dysregulation.

Performance Anxiety

The Academic Anxiety Inventory [39] is used for the assessment of performance anxiety manifestation, reflecting general patterns of anxiety related to examination situations or those related to solving specific academic tasks. Internal consistency is reported above 0.80, and construct validity has been demonstrated in studies linking cognitive interference, test anxiety, and academic performance [39].

Emotion Regulation Strategies

The Emotion Regulation Questionnaire [40] is a 10-item self-report scale measuring respondents' tendency to regulate their emotions in two ways: (1) cognitive reinterpretation and (2) suppressing expression. We used a 7-point Likert-type scale ranging from 1 (strongly disagree) to 7 (strongly agree). Previous studies indicate good internal consistency, correlating well with measures of psychological well-being [41].

QoL Assessment

Tools will be used to assess the quality of the techniques used by assessing comfort or discomfort and the quality of psychoemotional support techniques. The QoL scale, through the QoL Inventory questionnaire, will be used.

Data Analysis and Handling Missing Data

The analysis involves the use of advanced data management and statistical analysis software (eg, SPSS Statistics [IBM Corp] and Amos [IBM Corp]), and comparisons will be made between intervention groups using parametric statistical tests (eg, *t* tests and longitudinal or comparative analyses with repeated measures to determine participants' progression). Initially, descriptive analyses of participants' characteristics will be conducted, and the associations among research variables will be statistically analyzed (eg, Pearson correlations, partial correlations tailored to preliminary analyses, and group differences). We will use a method of controlling for additional variables that may influence statistical outcomes (eg, personal, medical, social, and demographic data) based on the results of the preliminary analyses.

The primary analysis (eg, participant randomization) will be based on the intention-to-treat principle. Missing data will be imputed using various techniques, and sensitivity calculations will compare the results to per-protocol analyses to determine the effect of dropouts.

Ethical Considerations

This study has been approved by the University of Medicine and Pharmacy IRB Research Ethics Committee (466/2024-15.10) and will be conducted in full compliance with the Declaration of Helsinki, the World Medical Association's ethical guidelines for human research, and relevant national and institutional research policies. These ethical safeguards ensure that participants' rights, safety, and well-being are prioritized throughout the study.

Before enrollment, all participants will provide written informed consent, ensuring that they fully understand the study's purpose, procedures, potential risks, and benefits. For participants aged <18 years, parental or legal guardian consent will also be required. The consent process will emphasize that participation is entirely voluntary, without compensation and individuals have the right to withdraw at any time without penalty or consequence. To maintain participant confidentiality, all collected data will be deidentified and coded, ensuring anonymity throughout the study. Data will be stored in secure, password-protected electronic databases, accessible only to authorized research personnel. Any publications or data-sharing initiatives will strictly follow ethical guidelines to prevent participant identification.

While both VR-CBT and yoga interventions are considered low risk, potential adverse effects will be monitored throughout the study. Participants will be encouraged to report any AEs immediately, and a clinical psychologist will be available to provide support as needed. Should a participant experience persistent distress or injury, they will be referred to appropriate medical or mental health services for further care. A structured

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protocol will be implemented for identifying, documenting, and managing AEs. Given the noninvasive nature of the interventions, a formal independent data monitoring committee is not required. Instead, a DSMB will be responsible for ensuring participant safety, protocol adherence, and data integrity. The DSMB will convene at predefined intervals (midstudy and at trial completion) to review participant retention, adherence, and safety outcomes. Findings will be documented and reported as needed. Any protocol deviations or concerns will be escalated to the PI and the IRB, with corrective actions implemented as necessary.

Dissemination Policy

To ensure transparency and broad dissemination of trial findings, the study results will be communicated through multiple channels to participants, health care professionals, researchers, and the public. Upon study completion, participants will receive a summary of findings in lay language, detailing overall outcomes without compromising confidentiality. Results will also be submitted for publication in peer-reviewed journals and presented at academic conferences, mental health symposiums, and relevant professional meetings. In addition, findings will be reported in public clinical trial registries, such as ClinicalTrials.gov, in accordance with international reporting standards. The research team will explore open-access publication options to maximize accessibility. Where feasible, deidentified data may be shared upon request with other researchers for secondary analysis, following institutional guidelines on ethical data sharing. Any publication restrictions will be governed by funding agreements, journal policies, and ethical considerations, but the investigators and sponsors affirm their commitment to full, unbiased reporting of results, regardless of outcome.

Authorship for all study-related publications will follow the guidelines set forth by the International Committee of Medical Journal Editors, ensuring that all listed authors meet the criteria for substantial contributions to the study. Specifically, authorship will be granted to individuals who have (1) significantly contributed to the study design, data collection, analysis, or interpretation; (2) participated in drafting or revising the manuscript critically for intellectual content; and (3) approved the final version for publication. Individuals who contribute to the study but do not meet all authorship criteria, such as those providing administrative support, technical assistance, or general supervision, will be acknowledged in the acknowledgments section rather than listed as authors. The use of professional medical writers is not planned for this trial.

To promote transparency and reproducibility, the study team intends to provide public access to key study materials, including the full trial protocol, anonymized participant-level dataset, and statistical analysis code, where feasible and ethically appropriate. The final protocol will be made available through an open-access repository or as a supplementary file in peer-reviewed publications. Requests will be reviewed by the study's ethics board and PI, ensuring that data align with ethical guidelines and data protection laws. In addition, the statistical code used for data analysis will be deposited in a publicly accessible repository (eg, GitHub and Open Science Framework) to facilitate replication and secondary analyses. Restrictions may apply if the data contain sensitive information that cannot be fully anonymized. Further details on data access and sharing policies will be outlined in the final study report and registered in public trial databases, such as ClinicalTrials.gov.

Results

This study hypothesizes that the implementation of both VR techniques and yoga practices will yield a significant reduction in anxiety symptoms, as measured by the STAI-Y1 and STAI-Y2 scales. This study will start in the middle of the academic year in the fall of 2025 (to be relevant for performance anxiety) and will end in June 2026. It is anticipated that the VR group will experience a decrease in performance anxiety symptoms compared to the yoga group, which may require additional sessions. Concurrently, yoga sessions are expected to exert an intense impact with substantial psychoemotional rehabilitation effects. Furthermore, both interventions are predicted to lead to a meaningful enhancement in emotional regulation abilities, as assessed by the Emotion Regulation Questionnaire, with participants engaged in yoga anticipated to develop more effective cognitive reappraisal strategies. In assessing QoL, the use of the QoL Inventory among participants aims to reveal improvements, particularly in areas related to academic stress and examination-related anxiety, with both groups likely to report enhanced QoL after the intervention.

Comparative analyses between the 2 groups will highlight the specific outcomes associated with each technique. It is expected that the VR intervention may offer a more significant advantage in reducing acute anxiety symptoms, with rapid effects on stress perception. At the same time, the yoga group may sustain these effects over the long term by learning self-regulation methods. Neurobiological measurements are projected to provide evidence of favorable modifications in autonomic nervous system functioning, indicating beneficial biological responses to anxiety in both intervention groups. In addition, postintervention evaluations will reflect increased participant satisfaction with the techniques, particularly noting subjective differences in comfort and effectiveness. Yoga techniques are anticipated to be perceived as more relaxing, whereas VR may be seen as more stimulating.

In summary, the expected outcomes involve a reduction in anxiety symptoms, enhancement of life quality, and adaptation of emotional regulation strategies, underscoring the efficacy of both intervention methods in addressing performance anxiety among young individuals. This research may significantly contribute to the mental health field by providing relevant data for effective therapeutic strategies and new avenues of study.

Discussion

Anticipated Findings

This study aims to test whether 2 types of psychological interventions could significantly improve mental health for young people. First, we expect that implementing VR techniques will significantly reduce anxiety symptoms soon after starting the program, and second, we expect that yoga practices could

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have long-term significant benefits. These hypotheses align with previous research findings indicating short- and long-term benefits for mental health. Research has shown that both VR and yoga can effectively reduce anxiety symptoms.

For example, VR interventions and particularly those based on CBT have been widely recognized as an effective treatment for anxiety disorders, including performance anxiety. Wu et al [42] indicated that VR-assisted CBT significantly decreases anxiety symptoms compared to traditional methods. Other studies focusing on specific types of anxiety (eg, social anxiety) indicated that VR-CBT effectively reduced anxiety levels in patients with generalized SAD, allowing them to practice social interactions in a safe environment [36]. In addition, exposure-based CBT, which is a core component of VR-CBT, has been validated as the gold standard for treating anxiety disorders, including performance anxiety [43]. This method involves gradual exposure to anxiety-provoking situations, which is facilitated by the virtual environment, making it less intimidating for patients [44]. In conclusion, virtual therapy using cognitive behavioral techniques presents a robust approach for managing performance anxiety. The combination of VR-CBT's immersive exposure methods and cognitive restructuring strategies offers a comprehensive framework for addressing the cognitive and behavioral aspects of anxiety. As digital health solutions continue to evolve, the integration of VR in therapeutic settings holds significant promise for enhancing the accessibility and effectiveness of mental health interventions.

Yoga-based psychoemotional support intervention provides a holistic approach to managing emotions and stress. According to studies, breathing techniques and yoga poses can contribute to a significant reduction in stress and anxiety levels, thus improving QoL. According to Brown and Ryan [45], mindfulness cultivated through meditation, a central component of yoga, can reduce anxiety and enhance overall life satisfaction. Research by Cramer et al [7] has shown that regular participation in yoga classes is associated with a significant reduction in depressive and anxiety symptoms. This highlights that yoga practice not only improves physical health through poses and breathing techniques but also plays an essential role in enhancing emotional health.

Controlled breathing, known as pranayama, is a central element in yoga practice, with beneficial effects on the autonomic nervous system. According to Jerath et al [46], slow pranayamic breathing techniques induce a physiological response that promotes the activation of the parasympathetic nervous system, associated with states of relaxation and regeneration. Deliberately manipulating the breath generates a hyperpolarization current in the nervous system, facilitating a state of calm and reducing emotional reactivity. Melnychuk et al [47] investigated the connection between breathing and attention, concluding that controlled breathing positively influences cortical functioning and neurophysiological balance. This discovery is essential for understanding the mechanisms by which yoga and pranayama can improve mental well-being and help effectively manage stress.

Yoga practice impacts not only psychological health but also neurological health. Măgurianu and Măgurianu [48] presented the hypothesis that breathing techniques can stimulate processes of angiogenesis and neurogenesis, thus promoting neuronal regeneration. In neuroscience, the law by Hebb states, "neurons that fire together, wire together." This explains how constant yoga practice, by repeatedly activating the neural groups responsible for well-being states, can facilitate the formation of durable neural networks, thus contributing to brain regeneration and improved cognitive functioning.

By applying the basic principles of Yama and Niyama, combined with techniques of asana (poses), pranayama (controlled breathing), and meditation, yoga offers a practical set of tools for emotion management and stress reduction. Its benefits are not only limited to mental health but also include positive influences on physiological and neurological functioning. These techniques, although accessible to any practitioner, offer significant benefits only in the context of continuous commitment and disciplined practice. Integrating these principles into psychoemotional interventions can yield valuable results in reducing anxiety and improving QoL, demonstrating the holistic potential of yoga as a method of balancing mind and body.

Regarding the effectiveness of yoga practices for anxiety performance, these practices have been associated with significant reductions in anxiety, as they promote relaxation and mindfulness, which are crucial for managing stress [49]. The comparative effectiveness of these interventions suggests that while VR may offer immediate relief, yoga's benefits may accrue over time, necessitating multiple sessions for optimal results [49]. Both interventions are anticipated to enhance emotional regulation abilities, particularly through the development of cognitive reappraisal strategies. Cognitive reappraisal, a strategy that involves changing one's interpretation of a situation to alter its emotional impact, has been linked to improved emotional outcomes [50,51]. Studies indicate that individuals who engage in yoga practice report using cognitive reappraisal more frequently, which can lead to better emotional management in stressful situations [52]. Furthermore, the neurobiological mechanisms underlying cognitive reappraisal have been extensively studied, revealing that this strategy activates brain regions associated with emotional regulation, such as the prefrontal cortex [50]. This suggests that participants in both the VR and yoga groups may experience enhanced emotional regulation capabilities after the intervention. In summary, the implementation of both VR techniques and yoga practices is hypothesized to yield significant reductions in anxiety symptoms, enhance emotional regulation abilities, and improve overall QoL. The evidence suggests that while VR may provide immediate relief, yoga's long-term benefits are substantial, particularly in fostering effective cognitive reappraisal strategies. Future research should continue to explore these interventions' comparative effectiveness and their underlying mechanisms to optimize therapeutic approaches for anxiety management.

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Future Directions

The results from this study can facilitate the implementation of VR-CBT and yoga intervention to address performance anxiety in students. Through a standardized framework for comparing the 2 interventions, we hope to add value to the expanding field of digital and integrative mental health therapies. As anxiety is increasingly common in young adults, particularly those within academic settings, our research could guide targeted therapeutic approaches that are tailored to a specific person's needs and preferences.

More generally, this research highlights the need for new, accessible forms of mental health support. VR-CBT is an emerging digital mental health intervention, and it enables individuals to access and explore anxiety in virtual, safe environments. The integration of cognitive restructuring techniques within virtual therapy further enhances its efficacy. Cognitive restructuring helps individuals identify and modify negative thought patterns that contribute to their anxiety. By combining these techniques with VR, patients can visualize and interact with their fears, which has been shown to foster cognitive change and reduce anxiety. For instance, a study highlighted the effectiveness of VR-CBT in helping participants confront and alter their automatic negative thoughts through immersive experiences [53]. Finally, the convenience and accessibility of digital platforms for delivering CBT are crucial in addressing the barriers many individuals face in accessing traditional therapy. Internet-based CBT programs have been shown to significantly reduce psychological distress among patients with anxiety disorders, making them a viable alternative for those unable to attend in-person sessions [54]. This is particularly relevant in the context of the COVID-19 pandemic, where many individuals experienced heightened anxiety levels and barriers to traditional mental health services [55].

In contrast, yoga is a more conventional, all-encompassing discipline that enhances mental health through physiological and psychological processes that may have long-term effects. Finally, our findings could help design individualized mental health programs; VR-CBT might be delivered for people who require instantaneous anxiety relief, and yoga would support long-term emotional stability and health. Future research should address larger, more varied samples or apply these interventions to broader therapeutic contexts to further explore their synergy.

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Data Availability

Details regarding the data safety monitoring board's charter, reporting procedures, and decision-making framework are outlined in this study's ethics review documentation and can be made available upon request. Details on data access and sharing policies will be included in the final study report and made available upon request. The deidentified participant-level dataset will be shared upon reasonable requests from qualified researchers, subject to institutional data-sharing policies, ethical considerations, and participant privacy protections.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review comments and response from the Academia Romana prin Fundatia Patrimoniu (Romanian Academy Heritage Foundation).
[PDF File (Adobe PDF File), 111 KB - resprot_v14i1e66112_app1.pdf]

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Abbreviations

AE: adverse event
CBT: cognitive behavioral therapy
DSMB: data safety monitoring board
IRB: institutional review board
PI: principal investigator
QoL: quality of life
RCT: randomized controlled trial
SAD: social anxiety disorder
STAI: State-Trait Anxiety Inventory
VR: virtual reality
VR-CBT: virtual reality–assisted cognitive behavioral therapy

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Protocol

Patient-Centered, Theory-Based, Online Intervention to Promote a Physically Active Lifestyle for People With Multiple Sclerosis: Protocol for a Randomized Controlled Trial

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Abstract

Background: People with multiple sclerosis (MS) experience life challenges due to the nature of disease progression. Although an active lifestyle has been shown effective for symptom and relapse management, most people with MS lead a sedentary lifestyle and do not reach the recommended physical activity (PA) guidelines.

Objective: This study aims to test the preliminary efficacy of a codeveloped, online self-management intervention based on the health action process approach (HAPA) adapted for people with MS to cultivate a physically active lifestyle.

Methods: The 8-week intervention program was developed using community-based participatory research based on the HAPA. The program includes increasing awareness of incorporating PA in a daily routine, the benefits of physical activities for people with MS, developing motivation, utilizing social and environmental support, setting measurable goals and doable plans, and coping with barriers for long-term adoption of new behaviors. Community members with MS serve as peer coaches. We aimed to recruit 60 people with MS, randomizing them to an intervention group or a wait-list control group. Control group participants do not receive any intervention nor information for the period of study. Participants will complete PA measures (accelerometer and survey) and psychological assessments at baseline; after an 8-week intervention; and 3 months, 6 months, and 12 months postintervention. We hypothesize that the intervention group will have (1) higher scores on the HAPA questionnaires and (2) higher frequency, duration, and intensity of engagement in PA after the intervention than the control group. We will conduct descriptive analyses (means, SDs), chi-squared tests, independent *t* tests, paired *t* tests, repeated measures ANOVA, and 2-way (any 2 factors of conditions, disability severity levels, and time) and 3-way (conditions × disability severity levels × time) mixed model ANOVAs.

Results: The study was funded in April 2018 and was delayed due to the COVID-19 pandemic. We invited peer coaches to review the accessibility of online modules in fall 2022. We finalized the module accessibility and trained peer coaches on how to use the online modules in December 2022. Since February 2023, we have recruited 50 participants to the trial who have been assigned to the intervention group (n=25) or control group (n=25). During the follow-up stage, 3 participants dropped out of the intervention group, and 4 participants dropped out of the control group. Enrollment ended in 2024, and data collection is expected to conclude by December 2025, with results anticipated to be published in January 2026.

Conclusions: This study will test the effectiveness of using an evidence-based online intervention for self-management of physical activity behavior by people with MS. The results of the study will provide us with insightful information for designing community-based participatory research and implementing telerehabilitation interventions for people with MS.

Trial Registration: ClinicalTrials.gov NCT05124522; https://clinicaltrials.gov/study/NCT05124522

International Registered Report Identifier (IRRID): DERR1-10.2196/66091

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(JMIR Res Protoc 2025;14:e66091) doi:10.2196/66091

KEYWORDS

self-management; telerehabilitation; physical activity; active lifestyle; multiple sclerosis

Introduction

Background

Multiple sclerosis (MS) is a progressive neurodegenerative disorder that affects nearly 1 million Americans; this number has doubled since 1976 [1,2]. This underscores a pressing need for disease management and prevention efforts [2]. The growing number of cases is particularly concerning, as there exists a series of unmet needs in managing the unpredictable and evolving symptoms of MS. Approximately 80% to 90% of people with MS experience acute episodes of relapses, often resulting in partial or complete recovery [3]. However, it is important to note that recovery from these relapses is typically incomplete over time, leading to a substantial accumulation of neurological disability [3]. Common symptoms of MS encompass fatigue, spasms, difficulties with mobility and balance, cognitive and emotional alterations, and depression [4,5]. These symptoms can lead to a sedentary lifestyle, diminish physical and mental well-being, and subsequently result in physical and mental disabilities, ultimately reducing community participation [6].

People with MS have reported exacerbation of their symptoms when living a sedentary lifestyle [6]. Such a sedentary lifestyle is often associated with an elevated risk of developing comorbid conditions, including cardiovascular diseases, type 2 diabetes, obesity, various cancers, depression, hypertension, and stroke [6,7]. Compelling evidence suggests that, even in the case of a progressive form of the disease, engaging in physical activity (PA) offers numerous benefits, specifically alleviating MS symptoms, managing comorbidities, and reducing the frequency of relapses [8,9]. This, in turn, leads to improved quality of life and reduced health care costs, which are particularly crucial for people with MS [9,10]. Most significantly, PA effectively mitigates symptoms and slows the progression of MS [6,11-15].

The evidence-informed PA guidelines for people with MS recommend that “to achieve important fitness benefits, people with MS who have mild to moderate disability need at least 30 minutes of moderate-intensity aerobic activity 2 times per week and strength training exercises for major muscle groups 2 times per week. Meeting these guidelines may also reduce fatigue, improve mobility, and enhance elements of health-related quality of life” [16]. However, recent evidence suggests that nearly 80% of people with MS are not meeting the general public health guidelines for moderate-to-vigorous PA (ie, 30 minutes of moderate-to-vigorous PA on 5 days a week via aerobic activity and at least 2 days per week of strengthening activities, including all major muscle groups) [17,18]. Therefore, it is imperative to develop and implement evidence-based interventions that apply effective behavior change approaches to promote a physically active lifestyle by people with MS. It is important to tailor these interventions to the needs of people with MS to ensure their effectiveness at fostering long-term behavior change and positive outcomes.

Although advanced medical treatments and related rehabilitation therapies for MS have been developed, many people with MS are unable to access these health care resources due to limited mobility, fatigue, and other financial and environmental barriers [19,20]. Telerehabilitation holds substantial promise for addressing these challenges, offering a patient-centered approach that is both cost-effective and efficient. When appropriate for patients, telerehabilitation also proves advantageous and convenient for clinicians. It enables them to assess and monitor treatment responses and outcomes promptly, allowing for the optimization of intervention timing, intensity, and duration as needed [21,22]. In a study by Li et al [23], 73% of outpatients with MS reported using telehealth services with a high level of satisfaction. Additionally, a survey revealed that 93% of individuals with MS used the internet, compared with 75% of the general population [24]. Remarkably, over 80% of people with MS expressed interest in online information related to MS, including aspects like prognosis and medication, while approximately 90% were interested in online information pertaining to MS management, such as PA, diet, stress reduction, and mind-body therapies [25]. Therefore, an internet-based intervention aimed at promoting a physically active lifestyle holds great promise for many people with MS.

It is worth noting that a systematic review including 9 randomized controlled trials (RCTs) concluded that the quality of current research on telerehabilitation for people with MS is insufficient and needs to be improved [20]. The review found the interventions showed low-level evidence for reducing short-term (3 months) as well as long-term (≥6 months) disability symptoms and impairments and improving quality of life and psychological outcomes, indicating the need for studies exploring the efficacy of long-term interventions. Additionally, it is worth noting that the reviewed programs had limited data on patient experience and satisfaction, and only 3 studies were grounded in theory, particularly in social cognitive theory (SCT) for increasing PA [20]. More importantly, existing studies lacked a sound theoretical basis with behavior change researchers, and the Medical Research Council strongly advocates for a theory-based approach to complex interventions as they are effective, sustainable, and scalable [26-28]. The most commonly used theoretical framework, SCT [20,29], uses goal setting as a robust variable for participants’ increased engagement in PA and maintenance of PA 3 months after an intervention [30-35]. However, self-regulation for long-term maintenance (eg, >3 months) of PA and the psychosocial effect of managing a physically active lifestyle, such as self-efficacy, coping with challenges or relapses, and commitment, are seldom considered [36,37]. These factors are critical and contribute to maintaining control over health in the absence of a cure for MS; therefore, considering them for self-management is imperative [36-38].

Further, these SCT intervention studies did not develop an individual’s self-regulation knowledge and skills based on Bandura’s self-regulation theory [39]. It is very important for

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people with MS to learn self-regulation for their new behavior of PA because they could experience variations in the frequency and intensity of symptoms and impairments, especially fatigue, pain, depression, and anxiety [4,6]. As a result, individuals with MS must acquire the necessary tools to effectively regulate their engagement in PA, even when they are not feeling their best [36,37,40,41]. To maintain a physically active lifestyle over the long term, people with MS need to learn how to regulate PA engagement on top of various physical and mental challenges and to resume PA from their relapses due to different reasons (eg, flare-ups, surgery) [36,37,40,41].

Therefore, we adopted the health action process approach (HAPA) by Schwarzer et al [42] to craft our online intervention. HAPA has integrated SCT [43,44], the stages of change model [45], and the theory of planned behavior [46]. HAPA consists of two key phases: motivation phase and volition phase. In the motivation phase, an individual's action self-efficacy, risk perception, and outcome expectancy drive the intention to change behavior. Once motivated, the volition phase involves action planning, coping planning, maintenance self-efficacy, and recovery self-efficacy, which are essential for sustaining behavior change and resuming activity after potential relapses. Additionally, recognizing and assessing an individual's barriers and available resources are crucial for long-term behavior maintenance, as these factors influence self-efficacy across both phases of the model. To ensure the suitability of HAPA for people with MS, we validated the HAPA model and its measure battery for PA and eating behavior with people with MS [37].

In line with the community-based participatory research process, during the program development phase, we recruited community members living with MS who have successfully maintained a physically active lifestyle in accordance with the guidelines [17,18,47] for more than one year to serve as community peer leaders (henceforth called peer coaches). The peer coaches played an active role in developing and evaluating the materials for the 8 modules that constitute the intervention (see the Methods section). The peer coaches will offer invaluable peer support and assistance to the intervention group [36,48]. Moreover, we used the flipped classroom pedagogical approach to facilitate adult learning (see the Methods section).

Objectives

The proposed study aims to assess the preliminary effectiveness of an online intervention to promote PA by people with MS (hereafter called an HAPA-MS intervention). We hypothesize that the intervention group will demonstrate (1) higher scores of HAPA components (see the Measures section) and (2) higher frequency, duration, and intensity of PA engagement immediately following the intervention and 6 months or longer after the intervention than the control group.

Methods

The following sections provide details regarding the proposed intervention protocol, sample size calculation and power analysis, planned recruitment strategy, randomization, measures to be used for assessment, and statistical analysis, as well as adverse event and safety monitoring.

Ethical Considerations

This study was approved by the institutional review board (IRB) for ethical and legal conduct of human subject research at the University of Illinois Urbana-Champaign. The university IRB approved the study (IRB24-0567) in expedited category 4 (collection of data through noninvasive procedures), category 6 (collection of data from voice, video, digital, or image recordings made for research purposes), and category 7 (research on individual or group characteristics or behavior or research using survey, interview, oral history, focus group, program evaluation, human factors evaluation, or quality assurance methodologies) with minimal risk. We used the following confidentiality precautions: (1) storing research data on password-protected computers or in locked cabinets in the principal investigator's laboratory; (2) storing participant identifiers separately from the coded, participant data; and (3) for publishing, completely de-identifying the study data. There is no identification of individual participants' data in any of the manuscript files. When a participant in the intervention group completes the 8-week program, they will be compensated with a US $220 gift card. When a participant in either the intervention group or control group completes a survey and wears an accelerometer for 7 days, they will be compensated with a US $20 gift card.

Proposed Intervention

The intervention consists of an 8-week, online, self-regulation program, including a weekly online discussion meeting on Zoom led by peer coaches. The topics of the 8 weekly modules are as follows: (1) Introduction to the program and testing online functionalities and materials; (2) Increasing awareness of your health and lifestyle; (3) Understanding the benefits of PA; (4) Building motivation; (5) Harnessing social and environmental support; (6) Creating a personalized plan for regular PA; (7) Learning to regulate a new physically active lifestyle; and (8) Sustaining progress and planning for long-term PA. Participants will be given access to the university learning system (Canvas) to view weekly educational modules, which provide information regarding developing a physically healthy lifestyle. During the last 4 weeks, participants will progress toward learning maintenance of this newly developed physically active lifestyle. Each module is about 15 minutes in length and has built-in quizzes. The modules were developed during the first phase of the study with a patient advisory board who was actively involved in providing feedback and building the content. During each week of the study, participants will watch a module video and complete an assignment based on the topic of the week. Once they have completed these 2 steps, they will join the online discussion led by peer coaches with their group members. Each intervention group will consist of about 3 to 5 members. To familiarize participants with the online system, an onboarding session will be conducted before the intervention begins. The research team will provide online assistance throughout the 8 weeks to address any technical difficulties. Additionally, every week, participants will be provided with resources curated, evaluated, and approved by the patient advisory board and the

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research team concerning physically active lifestyle recommendations and research.

Sample Size Calculation and Power Analysis

According to G*Power 3.1.9.7 [49], when we conducted a power analysis of comparing 2 groups (ie, an intervention group and a control group), an independent *t* test for estimating a sufficient sample size with a 1-tail hypothesis, at a power of 0.80, an alpha level of 0.05, and a medium-large effect size (d=0.65-0.70), each group will need to include 26 to 30 participants. The estimated total sample size is 52 to 60 participants. The effect size of 0.65 to 0.70 is based on the large effect sizes (d>0.70) of previous internet-based intervention studies [30-35]. When a condition (intervention vs control) is a between-subjects factor and time is a within-subjects factor, a power analysis of a repeated measures within-between interaction (eg, 2 conditions × 3 times) at a power of 0.80, an α level of 0.05, a medium-large effect size (f=0.25-0.40), and estimated 8 measures, each group will need to include 8 to 16 participants. The effect size of 0.25 to 0.40 is based on the large effect sizes (ηp^2>0.14) of previous internet-based intervention studies [30-35]. Therefore, the total sample size of 60 (30 for the intervention group, 30 for the control group) participants is sufficient for the proposed study. In addition, using a wait-list group as a control group is recommended for developmental trials [50].

Recruitment and Participant Selection

Recruitment will be conducted using a purposive sampling method within the United States by publishing this trial on the National Multiple Sclerosis Society website. Once participants sign up using the sign-up sheet, or by calling or emailing the research team, the team will conduct a short telephonic interview, which involves screening the participants based on the inclusion criteria (see Textbox 1). Once participants are recruited, they will be asked to fill out the baseline survey and wear an accelerometer for 7 days. The baseline assessment materials will be sent to the participant via physical mail, with a prepaid postage packet provided to send the device back to the research lab. We will recruit 60 participants with any type of MS who satisfy the inclusion criteria (see Textbox 1).

Textbox 1. Inclusion and exclusion criteria for participant enrollment into the trial.

Inclusion criteria

- ≥18 years old and
- Any type of multiple sclerosis
- Not maintained 30 minutes of moderate-to-vigorous physical activity (PA) per day for 2 days of the week during the previous 6 months
- Relapse-free for the past 30 days
- Have a low risk of contraindications of PA indicated by no more than a single “yes” response on the Physical Activity Readiness Questionnaire (PAR-Q) [51]
- Able to walk with or without an assistive device (ie, Patient-Determined Disease Steps [PDDS] score from 0 to 6) [52]
- Be willing to be randomized to an intervention or control group, complete the surveys and questionnaires, and wear an accelerometer during the intervention period
- Have reliable internet access

Exclusion criteria

- Godin Leisure-Time Exercise Questionnaire (GLTEQ) score >14 [53]
- No computer nor mobile device access to the internet
- PDDS score=7 (ie, using a wheelchair or scooter most of the time) or PDDS score=8 (being bedridden)
- Anyone living outside of the United States
- Anyone who is unable to speak, read, and write in English
- Not willing to be randomized to an intervention or control group, complete the surveys and questionnaires, and wear an accelerometer during the intervention period
- No access to reliable internet

Randomization

Research assistants enroll participants prior to randomization. The research team, including the principal investigator and a research assistant, will conduct matched, paired randomization based on Patient-Determined Disease Steps (PDDS) scores. Randomization will be conducted by flipping a coin until there are no significant differences in PDDS, Godin Leisure-Time Exercise Questionnaire (GLTEQ), age, education levels, income, and gender. To assign qualified participants in a timely manner, we will randomize every 8 to 10 participants into the intervention or wait-list control group (Figure 1). Participants will be notified regarding their allocation via email and phone call.

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Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flow diagram for the health action process approach-multiple sclerosis (HAPA-MS) randomized controlled trial.

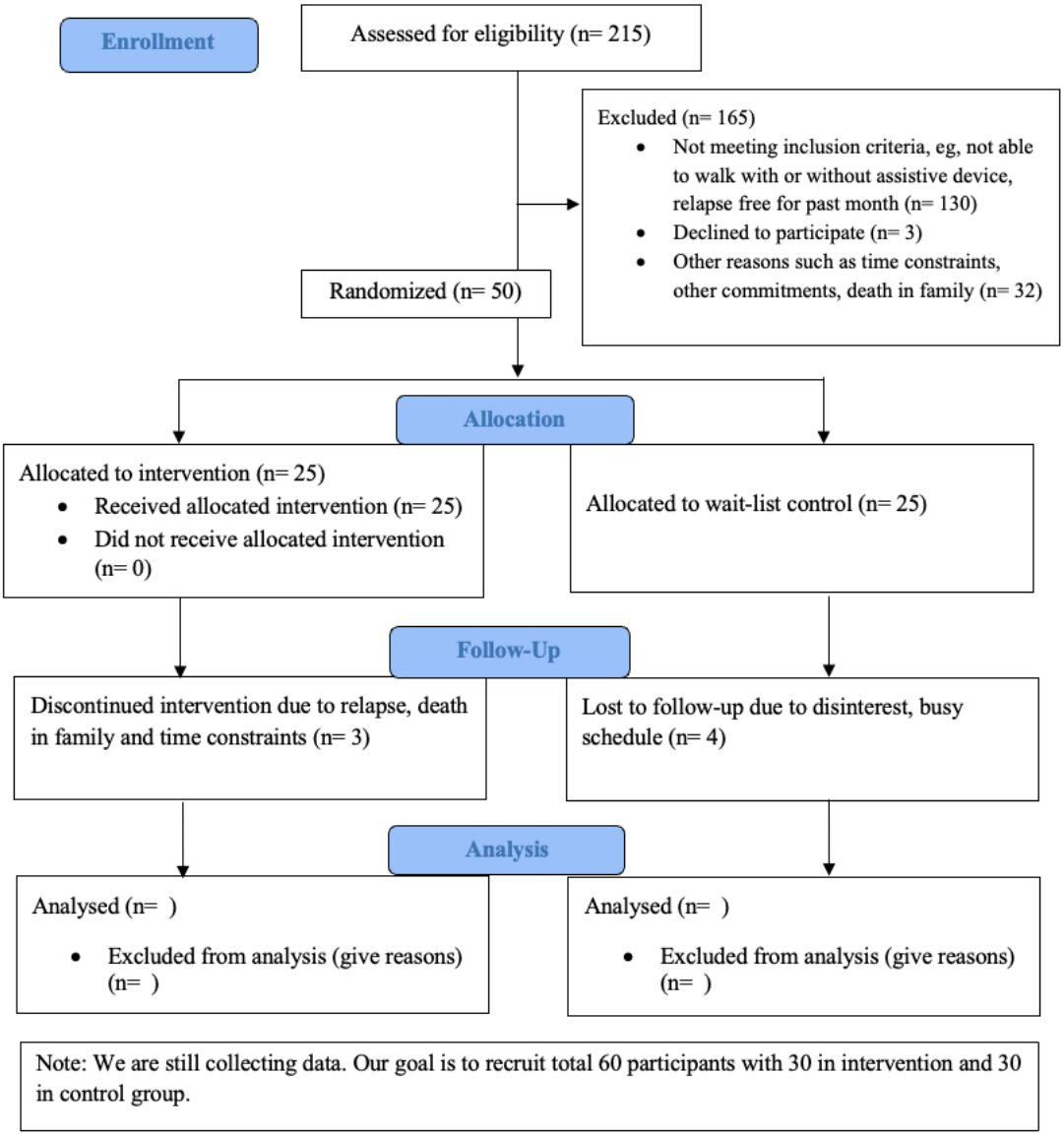

Data Collection

Study assessments will be conducted at baseline, postintervention (ie, after the 8-week intervention), 3 months postintervention, 6 months postintervention, and an optional follow-up at 12 months postintervention (Figure 2). Throughout the testing phase, participants will be provided with prepaid posting labels and packages for easy access and hassle-free delivery of study material.

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Figure 2. A flow diagram of data collection time points for the health action process approach-multiple sclerosis (HAPA-MS) randomized controlled trial.

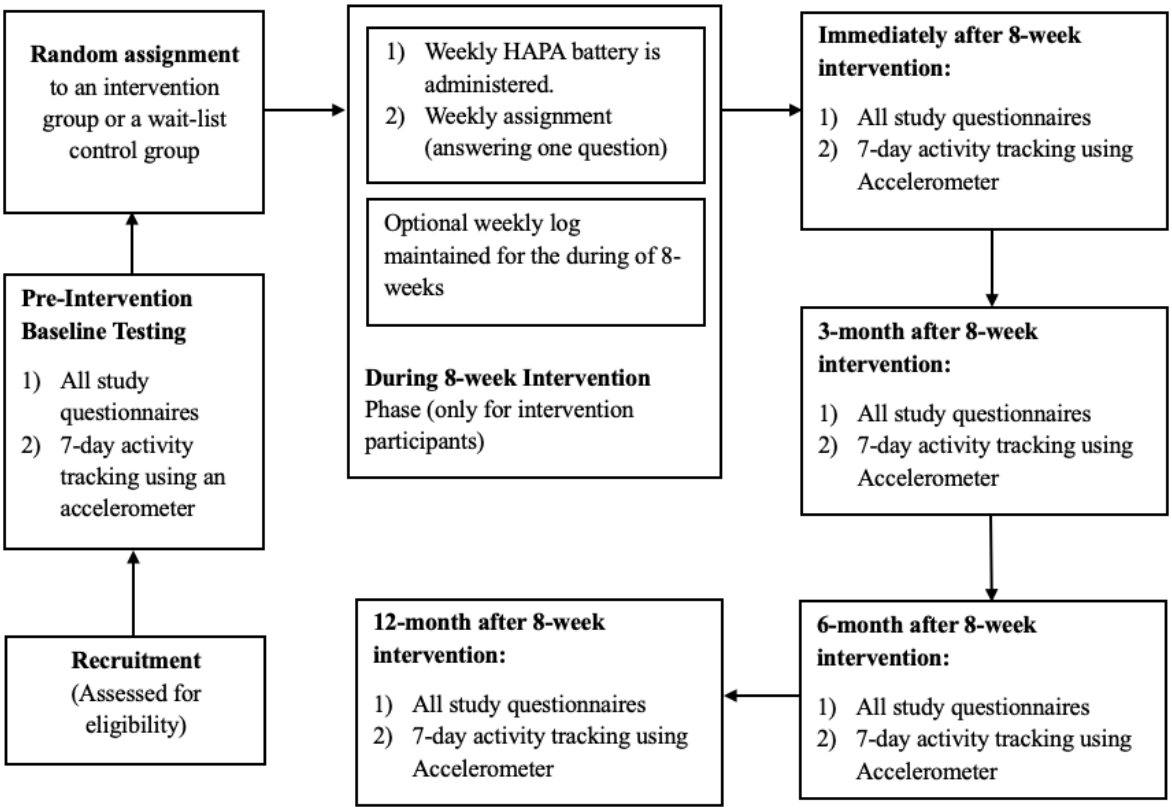

Baseline Demographics

During the screening process, basic demographic information will be collected, including age, gender, sex, ethnicity, level of education, income, and employment status. We will also collect additional information, including the type of MS, MS diagnostic tests, MS diagnosis year, and availability of PA-related resources around the individual. We will use this information to further enhance our knowledge regarding factors that may be related to supporting a physically active lifestyle.

PA Measures

ActiGraph (wGT3X-BT; ActiGraph LLC) accelerometers will be used to collect PA data during the data collection time points. Participants will be asked to wear the accelerometer around their waist on the nondominant side for 7 days and complete the accelerometer log sheet, including time stamps of wear time. ActiGraph accelerometers were deemed fit for collecting step count data. One study has shown that ActiGraph accelerometers accurately measure steps during moderate and fast walking speeds by both people with MS and control groups. Motl et al [54] indicated a slight underestimation of step count during slow-paced walking using an accelerometer with both people with MS and control groups. Given this, this study will encourage the intervention group participants to keep an optional PA log from the start of the intervention until the end of the study. The log includes recording information on the type, duration, frequency, and intensity of activities performed throughout the day.

Questionnaire Measures

The study will use the questionnaires and measures described in the following paragraphs to collect data regarding components of HAPA, PA, functionality, pain, fatigue, anxiety, and depression.

The Abbreviated Late Life Function and Disability Inventory has 2 subscales: function and disability. It has 15 items about the difficulty and frequency of performing physical activities rated on a 5-point Likert scale. Cronbach α values are 0.58 to 0.85 [55].

The McGill Pain Questionnaire has a 15-item adjective checklist that captures sensory and affective dimensions of pain experienced during the past 4 weeks. The items are rated on a 4-point scale [56]. Its Cronbach α value is 0.88 [57].

The Fatigue Scale for Motor and Cognitive Functions has 20 items (10 for cognitive and 10 for physical fatigue) rated on a 5-point scale. Its Cronbach α values are 0.91 to 0.95. Cutoff values are available to classify patients as mildly, moderately, or severely fatigued [58].

The Hospital Anxiety and Depression Scale has 14 items (7 for anxiety and 7 for depression) rated on a 4-point scale. The depression (r=0.70, P<.001) and anxiety (r=0.74, P<.001) subscales are correlated with psychiatric ratings [59]. Cronbach α values are 0.82 to 0.83 [57].

The HAPA battery of risk perception includes the subscales of Disease Threatening, Exam Result Threatening, Risk to Self, Risk to Others, Relative Vulnerability, and Perceived Severity. Each of these subscales has 10 to 13 items based on secondary

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health conditions in people with MS that are rated on a 7-point scale. Cronbach α values are 0.92 to 0.94 [37]. The HAPA battery of exercise benefits includes the subscales of Exercise Influence on Health Problems (13 items) and Outcome Expectancy (14 items). Cronbach α values are 0.79 to 0.93 [37]. The HAPA battery of motivation includes the subscales of Intention to Do PA (8 items) and Motivational Self-Efficacy (3 items). Cronbach α values are 0.90 and 0.85, respectively [37]. The Cognitive and Behavioral Process of Change Scale has 30 items (15 for the cognitive subscale and 15 for the behavioral subscale) rated on a 5-point scale. Cronbach α values are 0.67 to 0.86 [60]. The Exercise Goal Setting and Planning Scale has 20 items (10 for the goal setting subscale and 10 for the planning subscale) rated on a 5-point scale. Cronbach α values are 0.89 and 0.87, respectively [61]. The Barriers to Health Promotion Activities Scale has 18 items rated on a 4-point scale. Its Cronbach α value is 0.82 [62]. The PA-specific Social Provisions Scale has 24 items rated on a 4-point scale. Its Cronbach α value is 0.89 [57,63]. The Physical Activity Self-Regulation Scale has 12 items rated on a 5-point scale. Cronbach α values are 0.79 to 0.94 [64]. The HAPA battery of PA volition includes the subscales of PA Action Planning (5 items), PA Coping Planning (4 items), Recovery Self-Efficacy (3 items), and Coping Self-Efficacy (13 items) rated on a 4-point scale. Cronbach α values are 0.91 to 0.97 [37].

PA and sedentary behavior will also be assessed using patient-reported scales, that is, the Physical Activity Scale for Individuals with Physical Disabilities (PASIPD) [65] and GLTEQ. Cronbach α values for the PASIPD are 0.37 to 0.65 and for the GLTEQ are 0.46 to 0.94 [65-67].

Statistical Analysis

Research assistants will monitor survey completion and accelerometer data sufficiency. When participants return their survey and accelerometers, research assistants will check whether the participants have not responded to the entire survey. If there are missing responses, research assistants will email or call the participants to encourage them to respond to the missing items. The participants will be reminded twice, once each at 2 and 4 weeks, after they return the survey. If their accelerometers do not record valid data, research assistants will contact the participants and ask if they are willing to wear it for 7 days. After those attempts, when we curate the data, we will code missing data as 999.

Our analytic approach will use an intention-to-treat framework, and mixed models will yield unbiased results if the data are "missing at random" [68]. Additional sensitivity analyses will be performed to test for informative dropouts [68]. We will apply pattern-mixture models by stratifying our data by dropout patterns and fitting separate regression models to strata [68]. SPSS 26 (IBM Corp) will be used to conduct descriptive analyses (means, standard deviations), chi-squared tests, independent *t* tests, paired *t* tests, repeated measures ANOVAs, and 2-way (any 2 factors of conditions, disability severity levels, and time) and 3-way (conditions × disability severity levels × time) mixed model ANOVAs. Conditions and disability severity levels are between-subjects factors. Time is a within-subjects factor. We will use 2-way and 3-way ANOVAs to compare measured variables of the intervention and control groups. The significance level is set at .05. We will examine effect sizes of partial ηp2 (0.01, 0.06, and 0.14 as small, moderate, and large effect sizes, respectively) and Cohen *d* (0.20, 0.50, and 0.80 as small, moderate, and large effect sizes, respectively) [69]. We hypothesize that the intervention group will have stronger motivation and self-regulation, more PA, and better health conditions than the control group.

Adverse Event and Safety Monitoring

Regarding safety monitoring, the Physical Activity Readiness Questionnaire [51] will be used as a measure to check for any comorbidities or doctors' suggestions for PA. If an individual answers more than one "yes" on this questionnaire, they will not be recruited. If they answer with one "yes," we ask them to consult their doctor about whether it is fine for them to join the study. We periodically ask participants about their regular MS testing and infusion schedules to avoid fatigue or inconvenience. Participants are also encouraged to keep a note of exacerbations or flare-ups. The IRB recognizes this clinical trial as "minimal risk." For data safety and monitoring, deidentified data will be stored in a secured database (a HIPAA-compliant Box folder only accessible to IRB-approved team members). The research team will conduct routine checks on saved data.

Results

The study was funded in April 2018. We conducted peer coach selection interviews from July 2018 through October 2018. Peer coaches codeveloped and evaluated each module of the online program from November 2018 through January 2020. We iteratively revised the modules based on the peer coaches' feedback. During the pandemic, participants preferred to discontinue the study. The modules also had to be migrated from the Moodle system to a new online learning system, Canvas, in 2022 due to changes in the university's online learning system.

We invited peer coaches to review the accessibility of online modules in fall 2022. We finalized the module accessibility and trained peer coaches on how to use the online modules in December 2022. Since February 2023, we have recruited 50 participants to the trial who have been assigned to the intervention group (n=25) or control group (n=25). During the follow-up stage, 3 participants dropped out of the intervention group, and 4 participants dropped out of the control group. Enrollment ended in 2024, and data collection is expected to conclude by December 2025, with results anticipated to be published in January 2026.

Discussion

Overview

This protocol outlines an RCT to assess the preliminary effectiveness of an online program designed to promote a physically active lifestyle among individuals with MS, utilizing a community-based participatory approach [70]. We expect that the intervention group will be more physically active, especially 6 months after graduating from the program, and will have more phase-specific self-efficacy than the control group. Compared

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with prior work applying SCT [20,30-35], we used a hybrid framework, HAPA, which provides a comprehensive approach considering an individual's cognitive processing (ie, different phase-specific self-efficacy), behavior implementation (ie, action and coping planning), and living circumstances (ie, barriers, facilitators, or supportive resources). Peer coaches will lead discussions regarding where and how to gain motivation, what and how to practice self-selected PA and self-set goals each week, and how to cope with barriers and find countable resources to gradually adopt a physically active lifestyle over the program period week by week. We expect that PA logs from the intervention group will show their individualized PA profiles regarding activity types, frequency, and duration.

Additionally, we will evaluate the program's capacity to sustain these new lifestyle changes over an extended period, specifically beyond 3 months. To our knowledge, this is one of a few studies implementing a flipped classroom intervention customized to the unique needs and preferences of adults with MS. The adoption of a flipped classroom design, along with peer coaches, not only fosters deep learning experiences but also amplifies interaction and facilitates vicarious learning from the experiences and knowledge of others [71]. This approach empowers participants to take an active role in their learning journey, promoting self-directed and autonomous learning. Additionally, it significantly enhances motivation, thereby cultivating an individual's interest and capacity for self-regulation. A hybrid theoretical model rooted in evidence-based principles was used to construct the program's structure and modules. These foundations have been drawn from the research team's prior research endeavors [36,37,41]. Of equal significance, we have effectively translated these theoretical components into each intervention module, considering the perspectives of individuals living with MS. Using an iterative process to revise each module and collaborating closely with peer coaches helped us ensure that the intervention effectively addresses the specific needs and requirements of the target community. This iterative methodology proved invaluable in our collaboration with community researchers [72]. They provided us with crucial, patient-centered feedback, enabling us to enhance the content of the 8-week modules. It is important to recognize that this process is far from a mechanical repetition; rather, it embodies a deep reflective approach that aids in the development of information tailored to the unique needs of individuals living with MS. Furthermore, our adoption of community-based participatory research not only facilitates the seamless implementation of the program within the community but also enhances its overall applicability. Peer coaches play a vital role in enhancing multiple phases of self-efficacy among members of the intervention group [39,44]. They serve as role models for participants, showcasing a range of successful experiences in sustaining a PA routine while also delivering positive and empathetic feedback to their fellow participants. These actions constitute the primary mechanisms for bolstering an individual's self-efficacy [39,44]. Moreover, the peer coach's wealth of experience and expertise in this context is instrumental for fostering connections and personalizing the program further. The practices embedded within the weekly modules will facilitate participants in discovering physical activities that are both feasible and enjoyable, paving the way for the development of a sustainable lifestyle. Research has consistently emphasized the significance of finding enjoyment in sustaining a long-term active lifestyle [73]. Finally, we intend to implement the program using a telerehabilitation method. Considering that a substantial number of people with MS have already used the internet and mobile devices to access health information and resources [24], this online approach holds the promise of being a more effective and valid means to enhance the health and well-being of people with MS.

Although the HAPA-MS program promises much, we are aware of some limitations. For example, when we intend to recruit people with mild to severe mobility disabilities, future studies should aim to build websites that are more accessibility friendly, particularly for people with functional limitations in dexterity and deafness. Wearing the current type of accelerometer may not be as convenient as a smartwatch with an accelerometer feature. This will reduce compliance with the accelerometer wearing protocol. Although we designed a comprehensive survey composed of the HAPA components and other psychosocial factors, the survey will take about an hour to complete. It may increase the challenges with managing missing responses, especially during the follow-ups. Moreover, future studies should consider random sampling rather than convenience and purposive sampling, enhancing the robustness of the trial.

Conclusion

In addition to the advancement of scientific literature on health promotion, the results of the proposed RCT could have a significant impact on activity and lifestyle recommendations for people with MS. Our study will determine the preliminary effectiveness of using a HAPA-based online intervention to promote an active lifestyle by people with MS. Ultimately, this approach can contribute significantly to the self-regulation of PA behavior over the long term and has the potential for widespread acceptance among many other individuals living with MS.

Acknowledgments

We would like to acknowledge staff and research assistants along with community research members who supported the program development and implementation. We are grateful to our peer coaches leading the intervention groups: Enid Castora, Veronica Lewis, Leslie Newman, and Glenn Wright. We also thank Dr. Brynn Adamson for providing us with online Zumba videos.

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Data Availability

The data sets generated or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT checklist.
[DOC File , 123 KB - resprot_v14i1e66091_app1.doc]

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Abbreviations

GLTEQ: Godin Leisure-Time Exercise Questionnaire
HAPA: health action process approach
IRB: institutional review board
MS: multiple sclerosis
PA: physical activity
PASIPD: Physical Activity Scale for Individuals With Physical Disabilities
PDDS: Patient-Determined Disease Steps
RCT: randomized controlled trial
SCT: social cognitive theory

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Protocol

Co-Designed Mobile-Based Cognitive Training for Older Chinese Americans: Protocol for a Pilot Randomized Controlled Trial Assessing Feasibility and Acceptability

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Abstract

Background: Older Chinese Americans are at high risk of dementia, yet they often do not access culturally relevant services/programs to reduce their risks due to issues such as language barriers and transportation. BrainHQ is a mobile-based, effective cognitive training program that can potentially address these barriers and delay cognitive decline in older Chinese Americans.

Objective: We aim to evaluate the feasibility and acceptability of a mobile-based cognitive training intervention co-designed by older Chinese Americans and their adult children.

Methods: We applied an experience-based co-design approach that leverages existing cognitive training features and older Chinese Americans' prior knowledge, lived experiences, and social norms around dementia to co-develop a cognitive training intervention. We conducted an experience-based co-design workshop with Older Chinese Americans (n=10), and their adult children (n=4) to optimize the cultural and linguistic relevance of the cognitive training intervention. Participants used a journey map to brainstorm challenges they may experience when participating in the intervention. Then, the participants created prototypes of intervention components to address these challenges. Finally, we incorporated these prototypes into the co-designed intervention protocol. A total of 30 participants will be recruited into the intervention study and will be randomly assigned to the intervention or waitlist control group (2:1 ratio). The intervention group will complete the mobile-based cognitive training for between 10 and 15 minutes daily for 12 weeks. The primary outcomes are feasibility and acceptability. Global cognition, mental health, physical functioning, and quality of life will be assessed at baseline, 8, and 12 weeks.

Results: This pilot trial received institutional review board approval (Pro00109934l) in November 2024. We enrolled the first participant in December 2024 and aim to complete enrollment by May 2025. We expect to complete all data collection by September 2025. We will analyze the data and report study findings by February 2026.

Conclusions: This study leverages partnerships with academic, industry, and community stakeholders and provides the groundwork for a large-scale randomized controlled trial to test the efficacy of a mobile-based cognitive training intervention for older Chinese Americans. The co-design workshop served as a feasible, innovative approach to engage with the participants and improve the study design. These findings will enhance the culturally tailored delivery of cognitive training to older Chinese Americans and provide insights for broader implementation, improving their engagement in dementia research.

Trial Registration: ClinicalTrials.gov NCT05355870; https://clinicaltrials.gov/study/NCT05355870

International Registered Report Identifier (IRRID): PRR1-10.2196/69303

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KEYWORDS

mHealth; cognitive training; Alzheimer disease and related dementias; experience-based co-design; Asian Americans

Introduction

The older Asian population aged 65 years and above is one of the fastest-growing groups of older adults in the United States [1]. Among this population, Chinese are the largest group, accounting for 26% of Asian older adults [2]. Although Chinese Americans are often perceived as a "model minority" with a higher average socioeconomic status than other minority groups, the picture is incomplete. Older Chinese Americans are heterogeneous, with over 70% being first-generation immigrants, nearly 20% living below the poverty line (compared to 9% among the general US older adults), and close to half having limited English proficiency [2,3]. Although the prevalence of developing Alzheimer disease and related dementias (ADRD) among Chinese Americans is largely unknown [4], these socioeconomic disadvantages shared by older Chinese Americans not only increase their risk of developing ADRD but also limit their equitable access to effective, culturally responsive, preventive services that promote cognitive health. Currently, older Chinese Americans are disproportionately underrepresented in intervention studies aimed at preventing cognitive decline [5]. The rapidly increasing number of people with ADRD, along with the increasing population of older Chinese Americans, calls for the development of novel, effective strategies tailored to this vulnerable population to promote their cognitive health.

Cognitive training is a behavioral intervention that involves the structured practice of complex cognitive activities such as memory training, problem-solving, and visual search skill training, all of which can be delivered with mobile phones [6]. It is one of the few behavioral interventions shown to be beneficial for maintaining or improving cognitive function in older adults with intact cognition or mild cognitive impairment [7-9]. Scalability is a major advantage, as the widespread use of smartphones and tablets offers an unprecedented opportunity to deliver cognitive training interventions remotely to a large population at a relatively low cost. This can be particularly beneficial to the immigrant populations, as they often rely heavily on smart devices to build social networks and access local services [10,11].

Despite the potential advantages of mobile-based cognitive training, most prior interventions have been tested exclusively in non-Hispanic White older adults. Currently, no tailored cognitive training program exists that can accommodate the unique immigration history, cultural values, and linguistic characteristics of older Chinese Americans. Additionally, adherence to cognitive training interventions is challenging [12,13]. A recent large-scale cognitive training trial reported that nearly 40% of the participants did not complete any of the training, which may be due to the complexity and intensity of the cognitive training activities [12]. Nevertheless, prior research has suggested that social support and a positive attitude toward the study are potential facilitators that can help older adults adhere to cognitive training interventions [12,14]. Therefore, engaging end users early in all phases of intervention development is critical not only for facilitating treatment adherence but also for achieving sustainability, broad dissemination, and implementation.

To engage end users early, experience-based co-design offers a novel approach that combines participatory research and end users' experiences to improve care delivery [15]. Specifically, this approach focuses on users' experience and an equitable partnership between researchers and users with the aim of identifying challenges and co-developing practical solutions [15,16]. In the context of developing a cognitive training intervention for older Chinese Americans, the experience-based co-design approach allowed us to incorporate older Chinese Americans' prior knowledge, lived experiences, and social norms around dementia and cognitive aging into the intervention development. In doing so, the co-developed cognitive training intervention is expected to be not only culturally relevant but also hold great potential to generate a positive impact on maintaining cognitive function in older Chinese Americans.

To address this gap, we co-designed a mobile-based cognitive training intervention with older Chinese Americans and their adult children to ensure cultural and linguistic relevance. We aim to pilot-test this cognitive training intervention to evaluate its feasibility and acceptability. We also aim to gather preliminary effect sizes for outcomes including global cognition, mental health, physical functioning, and quality of life to inform the design of a future large-scale study. We hypothesize that by co-designing with end users, this cognitive training intervention will be culturally relevant, highly feasible, and acceptable among older Chinese Americans.

Methods

Study Design

This is a National Institutes of Health (NIH) Stage 1 [17,18] pilot randomized controlled trial (RCT) with a 12-week duration. Throughout the intervention development process, we leveraged our strong partnerships with a local Chinese community organization and industry partner and applied experience-based co-design principles. All participants (N=30) will be randomly assigned to a cognitive training intervention group or a waitlist control group on a 2:1 ratio through a computerized program [19]. Feasibility, acceptability, global cognition, mental health, physical functioning, and quality of life will be measured at baseline, 8 weeks, and 12 weeks.

Ethical Considerations

This study was approved by the Duke Health Institutional Review Board (Pro00109934) and registered at ClinicalTrials.gov (NCT05355870). Signed informed consent from participants will be obtained before recruiting them into the study. All identifying information of the participants will

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be anonymized and kept confidential through the assignment of a unique study ID.

Participants

We will recruit 30 older Chinese Americans without cognitive impairment in the RCT. To be eligible for the study, participants must meet the following inclusion criteria: (1) self-identify to be of Chinese descent, (2) are age 60 years or older, (3) are fluent in written and spoken Mandarin Chinese/English, (4) have the visual capacity to read a smartphone/tablet screen and the auditory capacity to understand normal speech (can be with glasses or hearing aids), (5) have no self-reported diagnosis of ADRD or cognitive impairment and are capable of making an informed consent, and (6) do not plan to move outside of the Research Triangle Park area of North Carolina in the next 6 months. Individuals are excluded from participation if they (1) are bedridden, (2) are receiving chemotherapy for malignancy, or (3) have other life-limiting illnesses.

Sampling and Recruitment Strategy

During the initial phase of the study, we worked closely with community stakeholders to develop and refine our sampling and recruitment strategy. Specifically, we held multiple meetings with community leaders from large local Chinese community organizations including the Chinese American Friendship Association of North Carolina (CAFA-NC) and Asian Focus to discuss the sampling and recruitment process. By working with the Duke Recruitment Innovation Center and these key Chinese community stakeholders, we co-developed the recruitment flyers and other materials to ensure their cultural relevance. Then, by leveraging our strong partnership with CAFA-NC, we implemented the following key strategies to recruit participants:

1. Connecting with key community stakeholders to understand the catchment areas and characteristics of older Chinese Americans residing in North Carolina
2. Liaising with local leaders in the Chinese community, such as the president of CAFA-NC, organizers of local older Chinese American clubs, and founders of local Chinese schools to increase awareness about our study
3. Posting study flyers on local Chinese media sites, Chinese community organization newsletters, and social media groups such as WeChat groups and Facebook communities
4. Collaborating with a local senior center to conduct community outreach programs to promote awareness of brain health and our study

Preliminary data suggested that these recruitment strategies worked well among older Chinese Americans, as more than 100 eligible participants signed up for the study within 1 day after the first posting of study flyers. In addition, through co-design activities, we identified a few additional strategies that we may implement if needed. For example, some older adults suggested reaching out to older Chinese Americans at local Chinese social events (eg, Dragon Boat Festival). Moreover, a few local Chinese community organizations expressed willingness to make the initial contact and introduce this study to eligible participants.

Experience-Based Co-Design Activities

During the first phase of the intervention development, we conducted 4 focus group discussions with older Chinese Americans (n=21) to elicit their dementia knowledge and prior experience with cognitive training, mobile games, and so on. Recognizing that support from the adult children of older Chinese Americans may facilitate engaging older Chinese Americans in cognitive training, we conducted another 2 separate focus groups with adult children (n=9) for additional input. We carried out a rapid analysis [20] of the focus groups and identified potential design issues with the intervention. Detailed results from the focus group discussions were published elsewhere [21].

In the meantime, we also built connections and worked with the Posit Science team to co-develop a linguistic and cultural adaptation protocol. As a digital health company specializing in providing brain training software and services, Posit Science offers BrainHQ, a mobile-based cognitive training app that comprises over 30 cognitive training exercises in English. These trainings target various cognitive domains, including memory, attention, and visual and auditory processing speed, and have been widely tested and implemented in prior research [22-24]. Through an iterative process guided by the Framework for Reporting Adaptations and Modifications-Expanded [25], we worked with scientists and technicians at Posit Science to make adaptations that translated its cognitive training components to ensure its linguistic and cultural relevance to older Chinese Americans. We also conducted internal user testing and used the results to further refine the cognitive training app in Mandarin Chinese.

Based on the findings from focus group discussions and the adapted Chinese version of BrainHQ cognitive training exercises, we conducted a co-design workshop with a series of activities that included a journey map and prototype development with 10 older Chinese Americans and 4 adult children. The goal of the co-design workshop was to engage end users and learn from their experiences to improve the delivery of the BrainHQ cognitive training program to older Chinese Americans and make it culturally relevant. These co-design activities were developed based on the Experience-Based Co-Design method and our prior experience [16]. Specifically, we first provided each participant with access to all the cognitive training exercises in the adapted Chinese version of BrainHQ. A few weeks before the workshop, the participants were asked to try out each cognitive training exercise and encouraged to participate in training as much (or little) as they would like to. Then, the participants were invited to the half-day in-person co-design workshop to provide feedback and develop potential approaches to address the identified design issues and strengthen the intervention components.

During the co-design workshop, we first introduced the goal of the co-design workshop and explained the process. In addition, we set ground rules to encourage rich, supportive discussions and for participants to feel valued and heard. In the first part of the workshop, we co-created a user journey map [26] with participants to systematically capture the entire process,

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experience, and emotions of end users when completing the cognitive training in the adapted Chinese version of BrainHQ. To ensure that participants felt comfortable and empowered to map the journey of the cognitive training together, we first introduced an example that mapped out the process of catching a flight. We then asked the participants to consider what could be improved for each step of the end users' experience of the cognitive training. Discussion points were written by the facilitator on Post-it notes and stuck to a whiteboard for visualization during the workshop. Results from prior focus group discussions were also presented to participants and incorporated into the discussion points. During the workshop break, the research team organized and synthesized key points from the journey-mapping discussion into workable issues. In the second part of the workshop, the team asked participants to collaborate with each other and the research team to come up with solutions and co-design intervention components to address these issues (prototype development).

During the discussion, the research team mainly functioned as the facilitator to guide and redirect the discussion as needed. Participants were asked to suggest potential solutions and provide additional feedback and new ideas. At the end of the workshop, we debriefed with participants about the accomplishments of the co-design activities and explained the next steps of the research. Our research team then discussed the findings and finalized the intervention delivery plan, incorporating the participants' input. Table 1 presents the identified workable issues and strategies co-designed with participants and refined by the research team after the workshop.

Table 1. Identified design issues and co-designed strategies.

Design issues	Strategies
How can we best convey perceived susceptibility and benefits to Chinese older adults?	• Provide a brochure with updated scientific information on ADRD[a] from credible sources.
How can we best engage participants' families and leverage a sense of family responsibility?	• Inform family members about the study. • Make family members aware of the training schedule. • Encourage family members to remind participants as they see fit.
How can we best build self-efficacy when using the app?	• Provide information on the purpose of each training (eg, targeting which cognitive skill). • Help participants interpret the results from each training exercise.
What would be the ideal frequency, intensity, and duration of the training?	• Participants prefer a shorter duration with more intense frequency. • Do not set an upper time limit for training.
How can we make the training more enjoyable and ensure adherence?	• Allow participants to choose training exercises by themselves. • Provide a wide array of training exercises. • Create an online training community to promote a sense of belonging.

[a]ADRD: Alzheimer disease and related dementias.

Co-Developed Intervention

Based on the feedback from the co-design workshop, participants in both the intervention group and the control group will be provided with a brochure that includes information on ADRD, signs and symptoms related to ADRD, the definition and the potential benefits of cognitively stimulating activities for maintaining cognitive function, and examples of cognitively stimulating activities. The brochure was developed based on materials from organizations such as the Alzheimer's Association, the National Institute on Aging, and the World Health Organization (WHO), with additional feedback from our co-design workshop. Participants in the intervention group will complete a series of cognitive training exercises on a smartphone/tablet.

By co-designing with older Chinese Americans and their adult children, we propose a 12-week training schedule that involves daily training sessions that last between 15 and 20 minutes. The frequency and duration of the proposed training are also consistent with most prior interventions that implemented training lasting 20 to 60 minutes per session, about 3 to 7 times a week for a total of 6 to 12 weeks [8]. We recommend that each session include 2 training exercises that target different cognitive domains. Participants can go beyond the recommended training plan and complete more exercises as desired. Table 2 presents the exercises chosen by participants from the co-design workshop that are available in the adapted Chinese version of BrainHQ. As participants progress, the difficulty level will be automatically adapted based on their performance.

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Table 2. Selected cognitive training exercises by cognitive domain through the co-design workshop.

Cognitive domain and training exercises	Description
Attention	
Target tracker	Track moving objects on your screen.
Double decision	Recognize and memorize the type of car and the location of the Route 66 road sign.
Divided attention	Sort objects based on the instruction as quickly and accurately as you can.
Mixed signals	Hear and see 2 different pieces of information and decide if the 2 pieces of information match.
Freeze frame	Differentiate target images from other images.
Processing speed	
Eye for detail	Identify where identical images appear on your screen.
Sound sweeps	Memorize and recognize the sound tone based on what you heard.
Visual sweeps	Determine whether each one is swept inward or outward.
Fine-tuning	Differentiate between 2 words with similar sounds.
Memory	
Scene crasher	Memorize the location of a specific key among several keys showing on the screen.
Memory grid	Find and match cards of the same words among cards with words that have similar sounds.
Hear, hear	Hear and remember the target tone and then identify the target tone among a set of tones.
People skills	
Face facts	Remember the names, faces, and facts of a group of people.
Recognition	Recognize the target face among a set of faces.
Face-to-face	Understand and match facial expressions.
Intelligence	
Mind bender	React to rapidly changing rules.
Card shark	Memorize the sequence and information of a series of cards.
Juggle factor	Place a series of numbers and shapes in the correct order.
Visual special ability	
Right turn	Mentally rotate images to decide if they are identical or mirrored.
Mental map	Remember and recall the relative location of objects in a grid.
Optic flow	Match the shape and color of the sign while driving on the road.

Waitlist Control

We will use a passive control in this pilot trial, as previous intervention studies and meta-analyses have suggested no differences between active and passive control groups [27-29]. Participants in the control arm will complete all assessments at time points corresponding to the intervention group but will otherwise continue to receive their usual care. At the end of the study, participants in the control group will receive access to the adapted Chinese version of BrainHQ cognitive training exercises.

Co-Developed Study Procedures

After enrollment, participants will complete a baseline assessment administered by a bilingual and bicultural research assistant (RA) in person or via Zoom. The assessment will consist of sociodemographic characteristics (eg, age, gender, marital status, living arrangement, and education), acculturational factors (eg, years in the United States, English proficiency), lifestyle factors, medical history, and dementia knowledge (via the Alzheimer's Disease Knowledge Scale) [30,31]. Participants in the intervention group will be instructed by the RA to create a user account for the adapted Chinese version of BrainHQ and access the training exercises. Additionally, the participants will choose a preferred time in the day to complete training and receive a training reminder. To ensure that the participants fully understand the intervention, the RA will use didactic instruction and roleplay to demonstrate the use of the Chinese version of BrainHQ. Participants will also be provided with a brief introduction and video demonstration of each cognitive training exercise through the BrainHQ app. Additionally, the RA will explain how to interpret

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the results from each training exercise. Based on the feedback from the co-design workshop, the RA will help form an online social group among participants in the intervention group, with their permission, aiming to create an environment for participants to support each other during the training and foster a sense of belonging. To ensure consistency with the intervention protocol, the following actions will be taken: (1) we will develop a manual for the intervention setup, which the RA will follow; (2) the training schedule and exercises will be preprogrammed into the app; and (3) ratings of treatment adherence and competence will be recorded and evaluated. Over the study period, the RA will interact with the participants only if they experience technical difficulties or have an extended period of training absence (missing 3 sessions in a row). If participants miss an entire week's training, the RA will call the participant to determine the reason and potentially help resolve some of the issues. Participants who do not have a smartphone or tablet will be equipped with internet access. A separate masked RA will perform outcome assessments.

Outcome Assessments

Our primary outcomes are feasibility and acceptability. Acceptability will be assessed using the Client Satisfaction Questionnaire (CSQ) [32,33]. Feasibility will be determined based on study accrual, protocol adherence, and retention. Specifically, accrual will be indicated by meeting the recruitment goal of 30 eligible participants in 6 months. We will use descriptive statistics to assess the number of older Chinese Americans reached and the rate of eligibility and response rate. Adherence will be assessed based on the proportion of participants in the intervention group who successfully completed all intervention sessions and the proportion completing the 8- and 12-week assessments in both arms. Additional performance measures will be assessed by exploring the usage data to capture the average time per day that participants spend on cognitive training exercises and the percentage of days that participants use the adapted Chinese version of BrainHQ. Trajectory modeling (eg, mixed models) with an emphasis on data visualization will be used to describe the BrainHQ usage over the intervention period. Retention will be assessed by the percentage of participants remaining in the study at the end of 12 weeks.

In addition to feasibility and acceptability, we will assess the following outcomes at baseline, 8 weeks, and 12 weeks. The assessment time points were chosen because prior research has suggested a significant difference in improvement between those who trained <8 weeks and 8 weeks [8]. Global cognition will be assessed using the Mini-Mental State Examination [34,35], Digit Span Test [36], verbal fluency [37], and the Trail Making Test [38]. As in the prior research, we will calculate the *z* score of each test and use the average *z* score to measure global cognition [9,39]. Mental health will be assessed with the (1) Patient Health Questionnaire-9 [40,41] for depressive symptoms, (2) UCLA 3-item Loneliness Scale [41,42] for loneliness, and the (3) Hospital Anxiety and Depression Scale-Anxiety Subscale [43,44] for anxiety. Physical functioning will be assessed with the Activities of Daily Living and Instrumental Activities of Daily Living Scale [45,46]. Quality of life will be assessed using the WHO Quality of Life Instrument-Abbreviated Version [47-49]. All study measures have a validated Chinese version and have been widely used in community-based studies among Chinese older adults.

Data Analysis

For our primary outcome, we consider 70% completion as the benchmark for adherence. If fewer than 40% of participants complete all the cognitive training and assessments, the proposed intervention will be considered as not feasible. Acceptability will be assessed using the CSQ, and 80% of the participants in the intervention arm reporting satisfaction will suggest good acceptability. Trajectories of BrainHQ usage over the intervention period will be described, which may be helpful in recognizing changes in training intensity and identifying strategies to improve adherence in future studies. We will calculate between-group effect sizes to evaluate the effects on improving global cognition, mental health, physical functioning, and quality of life. Between-group effect sizes will provide an index of relative changes for intervention vs. control participants.

Sample Size Considerations

Our target enrollment is 30 individuals over a 6-month period. A power calculation will not be appropriate as the primary purpose of this pilot RCT is not to evaluate statistical significance [50,51]. Rather, we are evaluating the feasibility and acceptability of our cognitive training intervention and obtaining preliminary effect size estimates to power a future study. We anticipate that the sample size of 30 participants will provide sufficient input to inform intervention refinement and improvement for a larger RCT under the limitations of time and funding resources.

Results

This pilot trial received institutional review board approval in November 2024. We enrolled the first participant in December 2024. As of February 2025, we have enrolled 15 participants and are aiming to complete enrollment by May 2025. We expect to complete all data collection by September 2025. We will analyze the data and report study findings by February 2026.

Discussion

Expected Findings

We hypothesize that this co-designed cognitive training intervention is not only highly feasible and acceptable but also holds great promise to promote long-term adherence among older Chinese Americans. More specifically, we aim to achieve our previously stated goals by having at least 70% of participants complete the training and at least 80% express satisfaction with the intervention. Because this is a feasibility study with a relatively small sample size, we do not expect to see significant differences in cognition, mental health, and physical function measures between the intervention and the control groups at the end of the study.

From the co-design workshop, our team gained experience working with the targeted population and obtained valuable feedback on the best way to engage with the participants in

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addition to seeking their input on the study design. This workshop also served to raise awareness of dementia prevention and as a channel to outreach to the target population. This innovative co-design approach for engagement with older Chinese Americans was feasible based on our study and can potentially benefit other similar studies in the future.

Comparison With Prior Work

Compared to prior cognitive training interventions [8,52], our study is among the few that apply the experience-based co-design approach. As prior studies have shown low adherence to cognitive training intervention [12,13], engaging older adults throughout the intervention development process can help optimize adherence to the training regime.

Prior research has also suggested that targeting older adults who are able to use mobile devices might be a limitation. However, our preliminary data from this study and prior work have suggested that smart device ownership is high (n=23, 91.2%) in this population [53]. In addition, we have prepared smart device rentals for any participants who do not have a smartphone/tablet equipped with internet access and need one. We will monitor for participants' differences in enrollment/refusal to assess whether digital literacy is a potential barrier for older Chinese Americans to participate in cognitive training.

Strengths and Future Directions

Our study aimed to address the issue of inadequate accessibility of high-quality cognitive training adapted for older Chinese Americans. As a critical first step (NIH Model Stage 1) in behavioral intervention development, the findings from this study will lead to our future work of testing the efficacy of this cognitive training intervention on cognition as well as physical and mental health in older Chinese Americans (Stage 2).

We also expect our work to have positive impacts on health promotion in the broader communities. With support from the CAFA-NC and Posit Science, this project provides an innovative partnership opportunity among academic, local community, and industry stakeholders. With support from our industry partner and community stakeholders, the research infrastructure created by this project is expected to produce more innovative mobile health (mHealth) interventions that can be scaled up rapidly in the future. While the research will be conducted on older Chinese Americans, this cognitive training intervention has the potential to be translated to other vulnerable populations that are traditionally excluded in dementia research (eg, other Asian Americans and Chinese older adults living in Asia).

Study Limitations

This pilot RCT may have the following limitations. First, the sample size for this RCT is relatively small, and we may not be adequately powered to detect statistically significant differences in outcomes between the intervention group and the control group. However, the primary objective of this pilot RCT is to establish the feasibility and acceptability of the cognitive training intervention through co-designing with end users. In addition, we recognize that some older Chinese Americans may speak Cantonese rather than Mandarin Chinese. Due to limited resources, we were not able to develop a complete set of cognitive training exercises in Cantonese. However, a few Cantonese-speaking participants mentioned at the co-design workshop that they had no issue understanding Mandarin Chinese. Finally, the pilot trial is taking place in the Research Triangle Park area of North Carolina. In recent years, North Carolina—particularly the Wake, Durham, Orange, and Mecklenburg counties—has become the second most popular destination for Asian immigrants, resulting in a large, growing, and socioeconomically diverse Asian immigrant population [54]. The lessons and experiences learned from this geographic area may not be applicable to older Chinese Americans living in other geographic regions such as traditional ethnic enclaves (eg, Chinatowns in the Northeast). However, our team has established a strong partnership with local Chinese community organizations in New York City and the Dallas-Fort Worth area as well, which will allow us to conduct a large-scale multisite intervention study to test the real-world efficacy (Stage 3) in the future.

Dissemination Plan

We will report on the intervention development, methods, and results from this project by submitting manuscripts to major scientific and biomedical journals aimed at reaching the widest possible audiences. Additionally, we will actively seek opportunities to disseminate our findings through presentations to a variety of audiences. This will include presentations at major Alzheimer disease and aging conferences. In addition, the media relations offices at Duke will help accelerate the dissemination of our findings. Most importantly, we will work closely with our community partner CAFA-NC to report the progress and results of this study to participants and the local Chinese community via community-wide newsletters and social media posts.

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Data Availability

All data are presented in the main manuscript.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the HPC - Health Promotion in Communities Study Section, Healthcare Delivery and Methodologies Integrated Review Group (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 95 KB - resprot_v14i1e69303_app1.pdf]

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Abbreviations

ADRD: Alzheimer disease and related dementias
CAFA-NC: Chinese American Friendship Association of North Carolina
CSQ: Client Satisfaction Questionnaire
mHealth: mobile health
NIH: National Institutes of Health
RA: research assistant
RCT: randomized controlled trial
WHO: World Health Organization

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Protocol

Comparing a Guideline-Based Mobile Health Intervention Versus Usual Care for High-Risk Adolescents With Asthma: Protocol of a Randomized Controlled Trial

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Abstract

Background: Mobile health (mHealth) technology has the ability to integrate personalized health management into patients' daily routines. In prior investigations of mHealth apps for asthma, patient satisfaction and acceptability have been high. However, rigorous randomized controlled trials (RCTs) examining their effectiveness are sparse; the majority of mHealth asthma apps lack personalization and real-time feedback and fail to include at-risk pediatric populations, and many previous studies are not randomized.

Objective: This full-scale RCT will examine the effectiveness of the Pulmonary Education and Asthma Knowledge Mobile Asthma Action Plan (PEAKmAAP), an interactive mHealth asthma action plan (mAAP) smartphone app, among adolescents compared to enhanced usual care (eUC). The study has 3 aims: (1) examine the effectiveness of PEAKmAAP in reducing asthma morbidity, as measured by the Asthma Control Test (ACT) score, health care use, medication use, and lung function; (2) examine the effectiveness of PEAKmAAP in asthma self-efficacy and medication adherence; and (3) examine the impact of sharing PEAKmAAP-generated data with the primary care provider (PCP) for a subset of enrolled subjects. We hypothesize that the PEAKmAAP groups will experience reduced asthma morbidity compared to the eUC group. Furthermore, we hypothesize that PCP data sharing is expected to enhance PCP prescribing patterns and that more adolescents in the Pulmonary Education and Asthma Knowledge Mobile Asthma Action Plan with data sharing (PEAKmAAP-DS) group will have sustained controlled at follow-up visits compared to PEAKmAAP alone or eUC.

Methods: Using a 3-arm RCT lasting 12 months, we will assess the effectiveness of PEAKmAAP in reducing morbidity among 432 adolescents (age 12-20 years). The study population includes adolescents with uncontrolled symptoms who receive primary care at the Arkansas Children's Hospital (ACH) or asthma care at ACH specialty clinics. At baseline, participants are randomly assigned to 1 of 3 groups: (1) PEAKmAAP group, (2) PEAKmAAP-DS group, and (3) eUC group using a smartphone app with daily non–asthma-related notifications. Study procedures will include baseline, 3-month, and 12-month in-person visits and

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telephone visits at 6 and 9 months. In-person visits will measure the ACT score, lung function, and self-efficacy; telephone visits will measure the ACT score. Participants will complete monthly online surveys to assess health care use and medication use.

Results: Recruitment and data collection began in March 2019, and data collection concluded in May 2024. Full data analysis began in December 2024.

Conclusions: This RCT aims to examine the effectiveness of a mAAP with real-time feedback and PCP data sharing. The study addresses existing gaps in knowledge regarding implementation of a mAAP for high-risk adolescents and has the potential to serve as a model for other populations at high risk for asthma.

Trial Registration: ClinicalTrials.gov NCT03842033; https://clinicaltrials.gov/study/NCT03842033

International Registered Report Identifier (IRRID): DERR1-10.2196/69903

(JMIR Res Protoc 2025;14:e69903) doi:10.2196/69903

KEYWORDS

asthma; smartphone application; application; app; mobile health; mHealth; adolescents

Introduction

Asthma is a major public health concern related to significant childhood morbidity, and despite proven interventions and evidence-based guidelines that have been established for more than 3 decades, 44% of US children have poorly controlled disease [1]. According to the National Asthma Education and Prevention Program's (NAEPP) guidelines, poorly controlled asthma is defined as having symptoms or rescue medication use more than twice per week, significant exercise limitations or nocturnal awakenings, or exacerbations requiring emergency health care or systemic steroids (SS) more than twice per year [2]. Poorly controlled pediatric asthma leads to over 14 million outpatient visits, nearly 2 million emergency department (ED) visits, and over 400,000 hospitalizations each year, with a disproportionate number of exacerbations being among socioeconomically disadvantaged populations [3,4]. The estimated annual economic impact each year includes over US $50 billion in direct costs, with an additional US $5.9 billion in indirect costs due to lost earnings for caregivers [5-9].

Adolescents are particularly at high risk for poorly controlled asthma and worse outcomes compared to their younger peers. These risks are due to several factors, including poor self-management skills, medication nonadherence, failure to recognize asthma symptoms, and belief that asthma medications are not beneficial [10-16]. Factors leading to nonadherence among adolescents are lack of motivation, social or academic obligations, inadequate parental support, and forgetfulness [17,18]. Despite these risks, adolescents are expected and encouraged by their parents and health care providers to assume more responsibility in the daily management of their chronic illness [19]. Interventions are needed to engage adolescents at high risk for exacerbations. These interventions should aim to improve asthma self-management and enhance adolescents' knowledge and skills to take appropriate actions for daily asthma maintenance and in response to acute symptoms.

Personalized asthma action plans (AAPs) serve as tools to assist patients with self-management, and current best practices recommend that every patient with asthma have an AAP [2]. AAPs provide patients with instructions for day-to-day asthma monitoring and medication management, as well as provide instructive steps to take during periods of acute or worsening symptoms. Standard AAPs are written using a traffic light design, with green, yellow, and red zones to reflect symptoms. The green zone depicts times when the patient's asthma is asymptomatic, and the AAP provides instructions for daily controller medications. The yellow and red zones depict times of mild and moderate-to-severe increasing symptoms, respectively. Instructions in the yellow and red zones typically include stepwise guidance to reduce symptoms, such as use and dose of rescue medication and further instructions on when to seek medical care [2]. Although there is strong evidence demonstrating significantly better outcomes, including reduced health care use when personalized AAPs are used, there are significant barriers to adequate use of paper-based AAPs [20].

To address barriers with written or paper-based AAPs, we developed and conducted feasibility testing of a prototype of the Pulmonary Education and Asthma Knowledge Mobile Asthma Action Plan (PEAKmAAP) among 20 adolescents with persistent asthma over an 8-week study period [21,22]. We demonstrated the feasibility of implementing a smartphone-based mobile health (mHealth) intervention for adolescents, and findings suggested that this innovative tool could result in significant improvements in asthma self-efficacy, as well as clinically significant improvements in ACT scores [23]. among at-risk adolescents. Next, we conducted a pilot randomized controlled trial (RCT) test among 34 adolescents over 6 months to compare the use of the PEAKmAAP prototype in paper-based AAPs [24]. Participant satisfaction was high, with 100% of adolescents stating they would recommend PEAKmAAP to a friend. Further, participants with uncontrolled asthma benefited from use of PEAKmAAP, as suggested by clinically important improvements in Asthma Control Test (ACT) scores (defined as a ≥3-point increase in the ACT score) [23] when compared to participants using paper-based AAPs [24]. Herein, we present the protocol of a full scale RCT aimed to examine the effectiveness of PEAKmAAP, a personalized, interactive smartphone app, among adolescents with uncontrolled asthma. We hypothesize that PEAKmAAP participants will experience reduced asthma morbidity compared to the enhanced usual care (eUC) participants and that sharing PEAKmAAP data with primary care providers (PCPs) will be associated with sustained asthma control over the 12-month intervention period.

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Methods

Study Design

The study is a 3-arm RCT with adolescents with uncontrolled asthma (Figure 1). The study will be conducted at the Arkansas Children's Hospital (ACH), with children receiving asthma care at ACH primary and specialty care clinics. A sample of 370 adolescents (age 12-20 years) and their caregivers will be enrolled. Participants will be randomized 1:1:1 to 1 of 3 groups: (1) a group using PEAKmAAP alone, (2) a group using PEAKmAAP with data sharing (PEAKmAAP-DS), and (3) an eUC group using an app with nonasthma daily reminders. Randomization will be stratified according to 2 strata based on asthma severity status (mild persistent and moderate-to-severe persistent) in order to minimize differences in baseline severity that may potentially bias treatment effects. A 1:1:1 permuted block randomization scheme with varying block sizes will be independently generated by our biostatisticians using nQuery Advisor 7.0 within each stratum to conceal allocation. The randomization list will be kept independent of the research staff to ensure allocation concealment.

Figure 1. Adolescents (age 12-20 years) with uncontrolled persistent asthma will be randomized to 1 of 3 groups: (1) PEAKmAAP alone, (2) PEAKmAAP-DS, and (3) eUC (using a generic nutrition app, Nutrimap, to log daily fruit and vegetable consumption). Outcomes will be assessed at 3, 6, 9, and 12 months. ACT: Asthma Control Test; PCP: primary care provider; PEAKmAAP: Pulmonary Education and Asthma Knowledge Mobile Asthma Action Plan; PEAKmAAP-DS: Pulmonary Education and Asthma Knowledge Mobile Asthma Action Plan with data sharing.

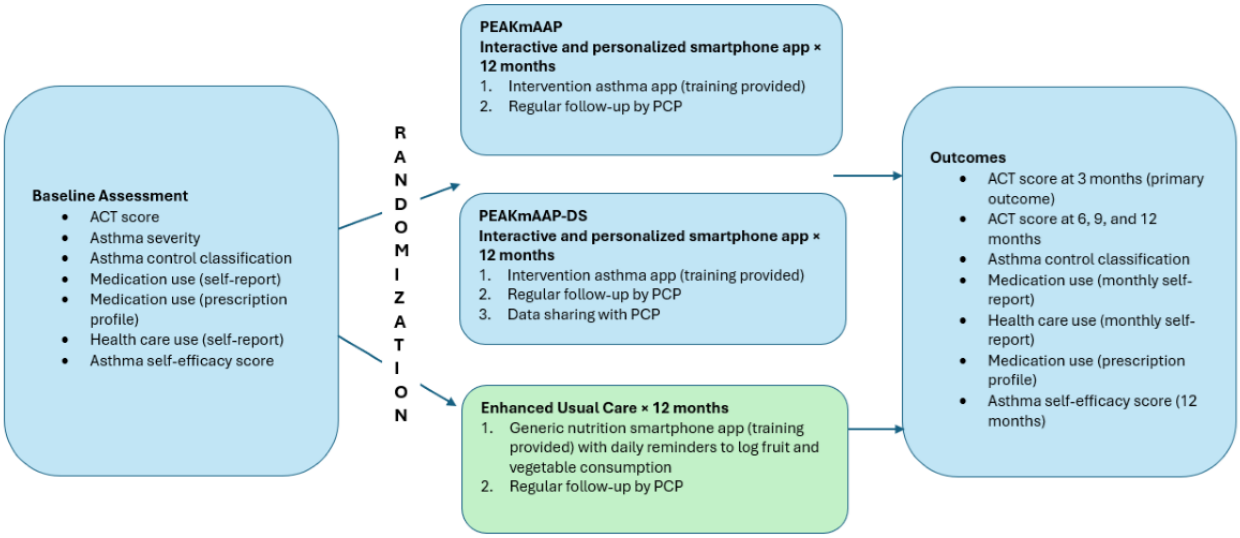

The study is registered at ClinicalTrials.gov (NCT03842033). SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) reporting guidelines were used to create this manuscript (Multimedia Appendix 1) [25]. Adherence of this report to the SPIRIT guidelines was supported by a tool developed under R01LM014079.

The inclusion criteria are as follows: (1) age ≥12 and ≤20 years; (2) physician-diagnosed persistent asthma using national guidelines criteria [2]; (3) uncontrolled symptoms, as measured by an ACT score of ≤19 [26,27]; (4) prescription of a preventative (controller) asthma medication in the 6 months prior to enrollment; (5) access to a smartphone compatible with the PEAKmAAP app; and (6) access to the internet.

The exclusion criteria are as follows: (1) any significant underlying respiratory diseases other than asthma, (2) current smoker, (3) moderate-to-severe developmental delay that interferes with the participant's ability to self-monitor their asthma, and (4) participation in any asthma clinical trials in the 6 months prior to enrollment.

Ethical Considerations

The study protocol was reviewed and approved by the Institutional Review Board (IRB) of the University of Arkansas for Medical Sciences (UAMS; protocol #206110). All protocol modifications will be approved by the IRB.

Informed consent and assent will be obtained from caregivers and participants, respectively. All participants will be provided with an opportunity to opt out of any study procedures or withdraw from the study at any time.

The principal investigator (PI) will carefully monitor study procedures to protect the safety of research participants, the quality of the data, and the integrity of the study. The PI and unblinded study staff will have access to the data throughout the project. Each participant will be assigned a unique ID. Only study staff will have access to the IDs and information that identify the participants in this study. The electronic and hard-copy files with the participant IDs and study information will be kept separate and stored in a locked office at Arkansas Children's Research Institute (ACRI) and will be accessible to research personnel only. Only deidentified data will be used for data analysis. At the end of the study, the records will be destroyed in compliance with ACRI and UAMS research policies and guidelines. Electronic records will be stored on the ACRI/UAMS servers, which are password-protected.

To ensure confidentiality, several features have been included in the PEAKmAAP and Nutrimap apps to protect participants' health information in the event their peers look at their phones:

- The app is password-protected; therefore, only the participants and their caregivers will have access to the

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mobile and web-based features of the app, including the participants' protected health information (PHI).

- The app will time-out after 5 minutes of inactivity. The participant's unique password will have to be re-entered after 10 minutes of inactivity. Further, if the participant switches to a different app, they will be required to re-enter their password when they relaunch the app.
- In the event the participant purchases or acquires a new phone, the app will need to be downloaded to the new phone. The participant will be asked to notify the research personnel when they acquire a new phone. At the time of consent, the participant will receive step-by-step instructions on how to download the app to their phone. An additional link containing the instructions can also be sent to the participant, as requested, at a future date.
- Data entered into the app will not be not permanently stored on the mobile device. Data will only be permanently stored on a UAMS Health Insurance Portability and Accountability Act (HIPAA)-compliant server. If the participant enters data while not connected to a Wi-Fi network, the data will be temporarily stored on the participant's mobile device and automatically transferred to the HIPAA-compliant server the next time the participant's device is in an area with a Wi-Fi network. At the end of the 12-month study period, the research personnel will disable the app. The research team will notify the participant that the app is disabled and that it may be deleted from their phone.

Each participant will receive a US $50 incentive for completing the baseline and 3-month visits and a US $100 incentive for completion of the 12-month visit. Participants will also receive US $15 for completion of each monthly survey and up to US $15 each month for daily logging on PEAKmAAP or Nutrimap (US $0.75 per day up to a maximum of US $15 per month). Participants completing all study visits and earning the maximum amount for daily logging will receive a total of US $560 for 12-month study participation. Participants will be offered transportation vouchers, if needed, to travel to the ACH for any in-person visits at baseline, 3 months, or 12 months.

Community Advisory Board

Prior to the study's start, the research team convened a Community Advisory Board (CAB) consisting of adolescents with asthma and caregivers of adolescents with asthma. The CAB partnered with the research team and met monthly over a 12-month period to review the findings of the pilot studies [21,22,24] and provide input in an iterative user-centered design process. The CAB conducted beta testing with the PEAKmAAP prototype and provided feedback to the research team regarding functionality and advised the team on the final app's design prior to participant recruitment. The CAB also provided content ideas and feedback on educational videos and asthma tips sent via push notifications from the PEAKmAAP app.

Conceptual Models Informing the Intervention's Design

The intervention is based on the Chronic Care Model (CCM) [28]. This model was chosen because it relates specifically to chronic illness management, and we developed our intervention to include components that foster improved self-management, integrate guideline-based principals into daily life, and support productive interactions between patients and health care teams [29]. CCM components have been used in many interventions, with improved outcomes among patients with asthma [30,31]. Including multiple components of the CCM is associated with stronger effects on medication adherence outcomes among patients with asthma [32]. Our intervention incorporates 3 components of the CCM (Table 1) based on input from the CAB in a method that is convenient, acceptable, and interactive with adolescents on a daily basis.

Table 1. PEAKmAAP's[a] design and app features informed by the 3 components of the CCM[b].

CCM component	App features
Self-management	Daily cue to self-monitor with immediate feedback
	Daily cue to take controller medication(s)
	Weekly mobile asthma education
Decision support	Guidelines-based algorithms to prompt appropriate care during worsening symptoms
Clinical information system	HIPAA[c]-compliant web portal for 24/7 AAP[d] access
	Medication and prescription refill reminders
	Data sharing with PCPs[e] (PEAKmAAP-DS[f] group only)
	National Weather Service data

[a]PEAKmAAP: Pulmonary Education and Asthma Knowledge Mobile Asthma Action Plan.

[b]CCM: Chronic Care Model.

[c]HIPAA: Health Insurance Portability and Accountability Act.

[d]AAP: asthma action plan.

[e]PCP: primary care provider.

[f]PEAKmAAP-DS: Pulmonary Education and Asthma Knowledge Mobile Asthma Action Plan with data sharing.

Medication nonadherence is the primary barrier to asthma control among adolescents [10,11]. Medication adherence is a complex behavior, and behavior change is most likely to occur when a patient is motivated and feels confident in their ability to change [33]. The latter notion refers to self-efficacy. The intervention incorporates the Health Belief Model (HBM) to

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affect behavior change, for example, increase self-efficacy and increase medication adherence (Figure 2). The HBM is a commonly used explanatory theory of health behavior that has been applied to adolescents [34,35] and specifically to beliefs about medication adherence and asthma management among those with asthma [11].

Figure 2. PEAKmAAP's incorporation of the HBM to affect behavior change and to improve medication adherence. HBM: Health Belief Model.

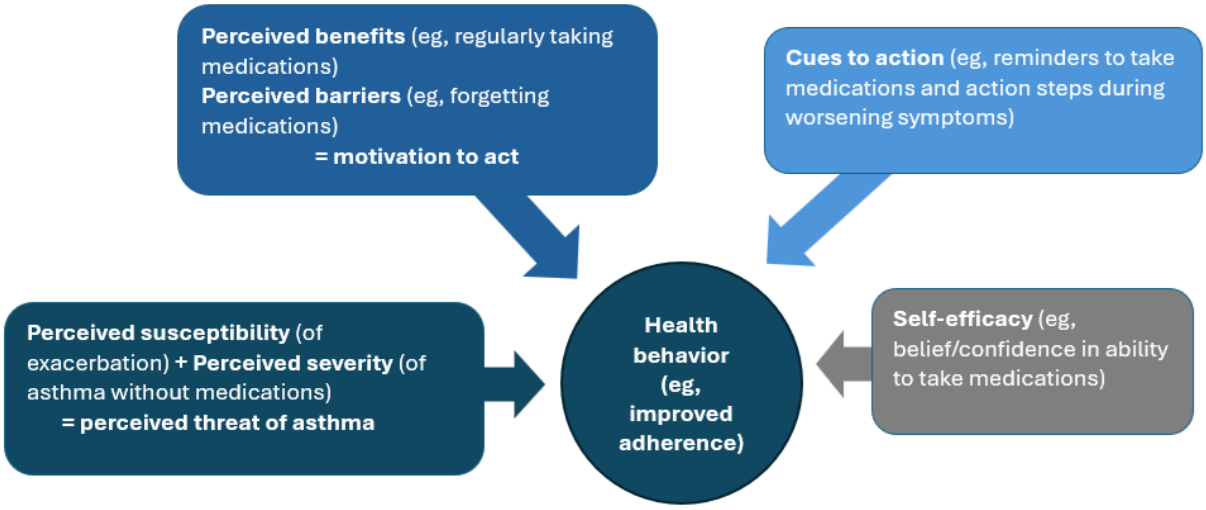

Participants

All enrolled participants will receive care from their usual primary care or specialty care provider at the ACH. At baseline, all participants will receive a printed paper copy of their personalized AAP from the electronic health record (EHR), as prescribed by their health care provider. Trained research personnel will provide each participant with training on how to use their AAP according to their health care provider's instructions. All participants will use a smartphone app during the 12-month enrollment (details described later).

Enhanced Usual Care Participants

The eUC participants will receive a nutrition app, Nutrimap, designed by the study team for attention control and daily interactions with a mobile app. Nutrimap will send eUC participants a daily push notification to remind them to eat fruits and vegetables. The application will allow eUC participants to keep a diary of how many servings of fruits and vegetables they consume each day (24-hour recall). Via the Nutrimap app, eUC participants can access the US Department of Agriculture's (USDA) MyPlate guide [36] to find healthy eating tips, learn how to measure serving sizes, and read about other general nutrition information. The eUC participants will not receive any education or reminders related to asthma from the Nutrimap app. Thus, the eUC participants will still receive their usual asthma care from their asthma doctor or PCP, with the addition of an attention placebo that is not predicted to impact asthma control.

PEAKmAAP and PEAKmAAP-DS Participants

Participants in the PEAKmAAP and PEAKmAAP-DS groups will access the smartphone-based, interactive version of their personalized AAP, as prescribed by their asthma care provider. At enrollment, adolescents will receive push notifications via PEAKmAAP, with links to educational videos 2-3 times per week for 6 weeks after the baseline visit in order to reinforce key asthma education topics (Table 2). The videos are informed by CAB members' input. The videos will remain accessible to participants on the PEAKmAAP app dashboard throughout the 12-month intervention. In addition, participants will be able to log daily controller and rescue medication doses (optional). The app will provide reminders for daily controller medication doses and monthly prescription refills. PEAKmAAP will prompt the adolescents to self-monitor asthma daily and send them a reminder to enter their symptom profile or peak flow (PF) value daily during the time that they experience worsening asthma symptoms. Innovative features of PEAKmAAP and how these features deliver CCM components and HBM concepts are described in detail later. In addition to the same features of PEAKmAAP, the PCPs of PEAKmAAP-DS participants will receive monthly reports with app-generated data regarding the number of days per month they input symptoms or PF values in the green, yellow, or red zone, as well as results of a monthly mobile survey regarding health care use.

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Table 2. Weekly PEAKmAAP[a] educational content.

Intervention week (number of videos, n) and themes	Specific topics
Week 1 (n=2)	
Asthma diagnosis	What is asthma?
Assessment and monitoring	Monitoring asthma and goals of asthma therapy to reduce impairment
Week 2 (n=3)	
Self-management	Asthma emergencies and what to do during an asthma attack Basic facts about asthma (symptoms, causes, and airflow obstruction) Managing asthma in the long term
Week 3 (n=3)	
Treatment (part 1)	What is an AAP[b]? Difference between long-term controller and quick-relief medications Types of long-term controller medications
Week 4 (n=2)	
Treatment (part 2)	How to use a metered dose inhaler, spacer, and nebulizer How to use a discus inhaler (Diskus) and a twist inhaler (Turbuhaler)
Week 5 (n=3)	
Triggers	What are asthma triggers and allergic thresholds? Examples of indoor and outdoor asthma triggers How can I reduce my exposure to triggers?
Week 6 (n=2)	
Allergy testing	What testing can I get for allergies?
Goals of asthma management	Reducing impairment due to asthma

[a]PEAKmAAP: Pulmonary Education and Asthma Knowledge Mobile Asthma Action Plan.
[b]AAP: asthma action plan.

PEAKmAAP Application Features

HIPAA-Compliant Web-Based Portals for the Study Team and Participants/Caregivers

Incorporating the *clinical information system* component of the CCM, PEAKmAAP includes HIPAA-compliant, password-protected portals to ensure data accessibility for both participants and the study team (Table 3). A web-based portal will be available to participants/caregivers to allow 24/7 access to them over the internet. This feature will also allow for participant data entry in the event of a lost, stolen, or damaged phone or lost mobile service. The study team's portal will allow research personnel to create and sync participants' personalized AAP instructions onto the participants' PEAKmAAP app and to set preferences for notifications and reminders.

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Table 3. Features of PEAKmAAP[a] and incorporation of CCM[b] components and HBM[c] concepts.

PEAKmAAP features	Purpose	CCM component	HBM concept
HIPAA[d]-compliant web portal	Provides 24/7 access to medical instructions in the case of a lost phone or lost phone service	Clinical information system	N/A[e]
Asthma self-monitoring	Reminds patients to monitor asthma symptoms or PF[f] daily	Self-management	Cue to action, self-efficacy
Personalized treatment plans	Provides a guideline-based algorithm to take controller or rescue medication	Decision support	Perceived severity, perceived barrier
Medication reminders	Provides daily medication and monthly refill reminders	Clinical information system, self-management	Cue to action
Mobile educational tips	Delivers educational tips and other resources	Self-management	Perceived severity and susceptibility, perceived benefits and barriers, self-efficacy
National Weather Service data	Provides data of environmental changes that could impact asthma	Clinical information system	N/A
PCP[g] data sharing (PEAKmAAP-DS[h])	Generates data for monthly PCP reports	Clinical information system	N/A

[a]PEAKmAAP: Pulmonary Education and Asthma Knowledge Mobile Asthma Action Plan.
[b]CCM: Chronic Care Model.
[c]HBM: Health Belief Model.
[d]HIPAA: Health Insurance Portability and Accountability Act.
[e]N/A: not applicable.
[f]PF: peak flow.
[g]PCP: primary care provider.
[h]PEAKmAAP-DS: Pulmonary Education and Asthma Knowledge Mobile Asthma Action Plan with data sharing.

Asthma Self-Monitoring and Personalized Treatment Plans

Incorporating the *self-management* component of the CCM, PEAKmAAP and PEAKmAAP-DS participants will be prompted to complete an asthma symptom checklist or enter a PF rate daily. They will also access PEAKmAAP to enter symptoms or the PF during worsening symptoms, which is an overt cue to action as part of the HBM. Adolescents may be recommended by their asthma care provider or have a personal preference to record either symptoms or the PF. The app is programmed to navigate to the appropriate personalized asthma zone when *either* symptoms or the PF are entered; participants *are not* required to enter both. Once data are entered (PF or symptoms), PEAKmAAP will automatically navigate to a new color-coded green, yellow, or red landing page to provide real-time instructions that correspond to the participant's personalized green, yellow, or red zone of their AAP. The instructions assist the adolescent in determining when to take controller medications, what the rescue medication dose and frequency are, and when to contact medical personnel according to instructions prescribed by their asthma care provider.

Personalized treatment zones will alert the adolescent to a more accurate level of perceived severity based on their entered data. This will also incorporate the *decision support* component of the CCM. In addition to prompting appropriate action, providing personalized information will address the perceived barrier of not knowing their treatment options by eliminating guesswork, a process that builds self-efficacy, which is key to behavior change. If participants navigate to the green zone, instructions for daily controller medications will appear. If they navigate to the yellow or red zone, instructions for rescue medication dosing and frequency will appear (cue to action), in addition to instructions to take daily controller medications. The PEAKmAAP app will provide several opportunities for *corrective actions* to be taken in the event of acute symptoms:

- Follow-up messages will prompt the adolescent to reassess asthma 20 minutes after any yellow or red zone recording. If the adolescent fails to respond, a second prompt will be sent 20 minutes later.
- If the adolescent enters severe symptoms (eg, lips turning blue, tightness in the throat), the app will automatically navigate to a shortcut prompting them to "Call 911/EMS" or seek emergency care.

In alignment with asthma guidelines [2] and instructions provided on paper-based AAPs, the PEAKmAAP app's design includes additional cues to action by defining parameters for prolonged or severe exacerbations. A prolonged exacerbation is defined as recording of yellow zone readings on 2 or more consecutive days *or* failing to indicate an improvement (eg, answers no or does not respond to the question, Are you feeling better?) within 48 hours of a yellow zone alert. A severe exacerbation is defined as ≥2 consecutive red zone readings in a ≤1-hour period *or* failing to indicate improvement within 1 hour of a red zone alert. In the event of a prolonged or severe exacerbation, the adolescent will be prompted via PEAKmAAP

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to contact their doctor. For prolonged or severe exacerbations, an alert will be sent to the participant and study team web portals.

PEAKmAAP is not intended or designed to replace participants' medical care. Participants will be counseled during the informed consent/assent process regarding the importance of seeking appropriate medical care. Caregivers and participants will be advised to seek appropriate medical care, including the participants' asthma care providers, emergency care, or the ACH Afterhours Nurse Line for worsening or uncontrolled symptoms. As a safety precaution, trained study personnel will monitor the study team's web portal during regular business hours and contact the participant's caregiver within 1 business day of any prolonged or severe exacerbation alert to ensure that appropriate medical attention is sought.

Customizable Medication Reminders

Incorporating the *clinical information system* component of the CCM, PEAKmAAP and PEAKmAAP-DS participants will receive daily messages (cue to action) to take controller medication doses. Via push notifications, participants will receive a prompt—"Don't forget to take your ___ (participant's controller)!"—once or twice daily as per their personalized AAPs. Monthly prescription refill reminders (cue to action) will be sent via push notifications for all controller medications. The delivery time of the messages and reminders will be customized based on the participants' preferences (eg, before school on school days, midmorning on weekends, etc).

Mobile Educational Tips and Resources

The PEAKmAAP app incorporates multiple media types (as recommended by the CAB), including videos (Table 2), text, and pictures to deliver education. Asthma education tips will be delivered via push notifications (to address perceived severity and perceived susceptibility of asthma exacerbation). Weekly text messages will deliver short tips to reinforce asthma concepts, such as medication adherence, inhaler/spacer technique, knowing the difference between rescue and controller medications, and recognizing asthma symptoms. In addition to receiving these educational tools via push notifications, participants will have access to all educational content through an "Asthma Tips" shortcut on PEAKmAAP's home screen.

National Weather Service Data

Participants will have access to real-time location-specific weather data from the PEAKmAAP home screen [37]. Weather details (weekly forecast predictions of temperatures in Fahrenheit, precipitation, humidity, pollen count, and ozone level) will be provided to help adolescents be more aware of environmental changes that could trigger asthma symptoms.

Data Sharing

Data generated by PEAKmAAP and mobile surveys (detailed later) will be shared with the asthma care providers of PEAKmAAP-DS participants monthly. The monthly report will include (1) results of monthly mobile surveys documenting rescue medication use, acute health care visits, and prednisone bursts and (2) PEAKmAAP-generated data regarding prolonged or severe exacerbations (described earlier).

Summary of Study Visits

Screening

Potentially eligible participants were recruited from primary care and specialty clinics at the ACH through direct patient contact and advertising. In addition to direct patient contact in clinics, the research team has received IRB approval to identify potentially eligible subjects through the EHR by prescreening for age and asthma diagnosis eligibility criteria prior to clinic appointments at primary care and specialty clinics. Potentially eligible participants were called prior to their clinic visit to allow research personnel to introduce the study and to ask permission to discuss the study in detail at their upcoming clinic visit. Because ACH patients receive care in other settings, such as the ED and other outpatient clinics, or may be registered in institutional research participant registries, participants were also recruited from these locations.

Baseline Visit

Research personnel obtained informed consent and assent from caregivers and adolescent participants, respectively, prior to any study procedures. At the initial visit, baseline data collection included lung function testing, frequency of asthma symptoms, activity limitations, health care use, asthma self-efficacy, and assessment of the dose and frequency of asthma rescue and controller medication. After these baseline data were obtained, participants were randomized to 1 of the 3 arms of the study. After randomization, PEAKmAAP and PEAKmAAP-DS participants received detailed instructions for use of the PEAKmAAP app, including an instructional video to explain all the features of the app, while the eUC participants received detailed instructions for the use of Nutrimap (Table 4).

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Table 4. Summary of study visit, outcome measures, and survey documents.

Measure	Screening prerandomization	Baseline prerandomization	3 months	6 months	9 months	12 months
Eligibility	X[a]	—[b]	—	—	—	—
ACT[c] survey	X	Screening ACT score	X[d]	X	X	X[e]
Asthma severity classification	—	X	—	—	—	—
CASI[f] score	—	X	X	—	—	X[e]
Lung function test with fraction of FeNO[g]	—	X	X[e]	—	—	X[e]
Child Self-Efficacy Survey	—	X	X[e]	—	—	X[e]
Asthma control classification (derived from the ACT survey)	—	X	X[e]	X	X	X[e]
Medication adherence (prescription profile for prior 12 months)	—	X[h]	—	—	—	X[h]
System Usability Scale (SUS)	—	—	—	—	—	X
Medication use (monthly self-report)	—	X	Monthly	Monthly	Monthly	Monthly
Health care use (monthly self-report)	—	X	Monthly	Monthly	Monthly	Monthly

[a]X: applicable.
[b]Not applicable.
[c]ACT: Asthma Control Test.
[d]Primary outcome.
[e]Outcome obtained by blinded research personnel at an in-person visit (all others via a mobile survey).
[f]CASI: Composite Asthma Severity Index.
[g]FeNO: fractional exhaled nitric oxide.
[h]Profile requested directly from insurer, pharmacy data, or medical record.

Monthly Surveys

All participants receive a link to a survey each month via push notifications from their mobile app (PEAKmAAP or Nutrimap). The monthly survey asks participants to self-report rescue medication use in the past 2 weeks due to wheezing, coughing, or trouble breathing. The survey also asks participants to record exacerbations resulting in hospitalization, ED or sick visits, or prednisone use in the previous 4 weeks. These data, along with app-generated data on the frequency of green, yellow, and red zone days, will be used to generate the PCP report for PEAKmAAP-DS participants.

Three- and Twelve-Month Visits

Three and twelve months after enrollment, an in-person visit will be conducted with all participants to obtain lung function testing results. Blinded research personnel will survey the participants to complete the ACT and self-efficacy questionnaire and to obtain a detailed history on asthma symptoms and activity limitations. The 3-month ACT score is the primary outcome of the study.

Six- and Nine-Month Visits

Six and nine months after enrollment, a telephone visit will be conducted to administer the ACT. Research personnel conducting the visit will be blinded to every participant's treatment arm.

Summary of Outcome Measures

Primary Outcome Measure

The primary outcome measure will be the change in the ACT score of ≤19 (uncontrolled asthma) to >19 (controlled asthma) at 3 months. The ACT is a validated 5-question survey used to assess asthma control in individuals ≥12 years of age. The ACT is used for symptoms monitoring as per guidelines [2], and the ACT score has been identified as an appropriate asthma control composite score in clinical research [26]. The ACT is an efficient, reliable, and validated method of measuring asthma control, with an internal consistency reliability of 0.84 [27]. Mobile and web-based versions of the ACT have been validated [38,39], and we have successfully used the ACT in our pilot studies [21,40].

Secondary Outcome Measures

ACT Survey to Assess Secondary Outcomes

Recognizing that ACT scores may improve but remain ≤19 for some participants with poorly controlled asthma, we will also assess for change in the ACT score that is considered clinically important (as indicated by a ≥3-point increase) [23]. The ACT score will be assessed via a mobile survey to measure for sustained improvement throughout the study. We hypothesize that PCP data sharing will facilitate asthma control by alerting the PCP when asthma worsens or fails to improve. The impact

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of PCP data sharing on the ACT score will be measured to assess whether data sharing has added any benefit to the PEAKmAAP group.

Composite Asthma Severity Index

The Composite Asthma Severity Index (CASI), a comprehensive scale reflecting impairment, future risk, and the level of treatment needed to maintain control, has been developed to align with the new concept recommended in *Expert Panel Report 3: Guidelines for the Diagnosis and Management of Asthma* (EPR-3) [2]. The integral CASI instrument has 5 domains: day symptoms and albuterol use, night symptoms and albuterol use, controller medication, lung function measures, and exacerbations. CASI is considered a better discriminator of treatment response than a symptom-based outcome. Thus, as an alternative to the ACT score, CASI will be also used to quantify asthma severity and prospectively gauge asthma control in the proposed study.

Medication Use

Self-reported rescue medication use will be assessed via a mobile survey. Participants will be asked, "How many days/nights in the past 2 weeks did you use ___ (rescue medication name) because you were wheezing, coughing, or having trouble breathing?" These data will be collected for all participants and will be used to generate a PCP report for PEAKmAAP-DS participants.

Health Care Use

Self-reported health care use will be assessed monthly via a mobile survey. Participants will record exacerbations resulting in hospitalization, ED or sick visits, or prednisone use. These data will be collected for all participants and will be used to generate a PCP report for PEAKmAAP-DS participants.

Lung Function and Airway Inflammation

Spirometry is the test most used for the assessment of the risk for adverse events (AEs) and impairment in asthma [2]. The forced expiratory volume in the first second (FEV1) expressed as a percentage predictive of the reference population value or as a proportion of the forced vital capacity (FEV1/FVC) will be assessed. Fractional exhaled nitric oxide (FeNO) is a quantitative, noninvasive measure of airway inflammation that predicts responsiveness and adherence to inhaled corticosteroids (ICS) [41-43]. We will measure lung function and FeNO at baseline, 3 months, and 12 months for all participants.

Child Self-Efficacy Survey.

The Child Self-Efficacy Survey is a 9-item validated questionnaire and is designed to measure a child's self-efficacy with regard to attack prevention and attack management [44]. The participants will be required to select 1 of 4 responses ranging from "none of the time" (0 points) to "all of the time" (3 points). The survey will be administered at baseline, 3 months, and at the end of the intervention for all participants. The reliability of the survey (Cronbach α) is .75.

Asthma Control Classification

Asthma guidelines categorize asthma control for individuals ≥12 years old into 3 categories: well-controlled (WC), not well-controlled (NWC), or very poorly controlled (VPC) [2]. Asthma control is defined by the degree to which asthma manifestations are minimized by therapeutic intervention [2]. Components of asthma control include measures of daytime symptoms, nighttime awakenings, activity limits, rescue medication use, and exacerbations requiring oral systemic corticosteroids. An assessment of asthma control will be performed during the eligibility screening; at the in-person, structured interviews at baseline, 3 months, and 12 months; and via a mobile survey at 6 and 9 months for all participants.

Medication Adherence

Using prescription refill data, we will compare adherence prior to enrollment with adherence during the study period. We have successfully attained prescription refill data in our previous studies. Participants will provide written release of information during the consent interview. In addition, these data are frequently requested by providers as a component of usual patient care in Primary Care Medical Home (PCMH) clinics. Adherence will be defined as receiving ≥3 controller medication refills/6 months or achieving an asthma medication ratio (AMR) of ≥0.5 based on national asthma guidelines [2]. The AMR will be calculated as the ratio of the number of controller medications dispensed during a 6-month period divided by the sum of controller plus rescue medications dispensed during the 6-month period. An AMR of ≥0.5 has been associated with improved asthma outcomes [45]. The proportion of days covered (PDC) will also be assessed and compared between groups from prescription refill data. This measurement is defined by the number of days in the period covered divided by the number of days in the total period and is suitable for medication regimens that require multiple medications, such as asthma. Prescription refill data will be captured from the participants' medical record dispense report via Magellan (a Medicaid vendor) or via a private pharmacy. We may also contact the participants' local pharmacy used to obtain the pharmacy profile.

Medication Changes

To monitor for step-up or step-down in prescribed controller medications, medication changes will be assessed at each in-person visit at 3 and 12 months, by medical record review, and by prescription refill data. Participants will be advised to notify study staff of any medication changes.

Data Collection and Management

We will use the Research Electronic Data Capture (REDCap) program. Data from the study will be checked for errors, inconsistencies, and missing data. We will examine the data graphically using scatterplots for continuous outcomes and frequency tables for categorical data. Unresolved data anomalies will be sent to the primary investigator for verification. Obvious outliers due to data entry errors will be corrected before data analysis begins. Different data sources will be linked using a unique identifier assigned to each participant.

Adverse Event Reporting

All subjects will be monitored for AEs related to study procedures. Study investigators acknowledge that participants may experience asthma symptoms or exacerbations throughout the course of the study; however, exacerbations are expected due to the nature of the disease and not due to study-related

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procedures. Due to an intrinsic exacerbation risk to all patients with asthma, we will advise participants to continue to use medications as prescribed by their PCP and to keep their regularly scheduled visits. The research team will also conduct research review meetings on a weekly basis to monitor the progress of the study, ensure participant safety, discuss any unanticipated problems, ensure treatment integrity, and ensure that recruitment and study goals are being met, as well as solve any issues pertaining to enrollment, recruitment, or completion of study procedures. A Safety Monitoring Committee (SMC) will independently monitor participant safety. The SMC, consisting of a biostatistician and an independent clinical research investigator, will meet no less than once a year and as needed to discuss any potential safety concerns related to the research. All participants will be screened for AEs and serious adverse events (SAEs) at each study visit. They will be asked about asthma- and non–asthma-related health issues. All clinically significant AEs will be brought to the attention of the PI, who will categorize the AEs as "expected" or "unexpected" and as "likely" or "unlikely" to be related to the study. The PI will monitor all related AEs and SAEs. All AEs and SAEs will be entered into the study database and, as required, reported to the University of Arkansas for Medical Sciences Institutional Review Board, the SMC, or the National Institutes of Health (NIH). Because the interventions are adjuncts to ongoing clinical care and all participants are encouraged to continue to engage with their PCP, no formal ancillary or posttrial care is planned. Similarly, given the low risk of the interventions and continued PCP care, there are no criteria for discontinuing or modifying allocated interventions beyond a participant's personal decision to discontinue participation in the study.

Statistical Analysis

Primary models using the intent-to-treat (ITT) principle will be performed for all primary and secondary outcomes. All subjects will be considered part of their assigned treatment groups irrespective of their adherence to treatment, and all randomized subjects will be included in the analysis. Secondary models using a per protocol (PP) population including only participants who adhered to the protocol will be conducted. As appropriate, models will be adjusted for the baseline value of the outcome, with other baseline confounding or covariate variables included. Secondary subgroup analyses will stratify by baseline asthma control classification (poorly controlled vs not well controlled) defined by ACT scores. Holm-Bonferroni correction will be used to control the overall familywise error rate under 5% for analyses with multiple comparisons. Missing data in primary and secondary models will be handled by multiple imputation if "missing at random" is a reasonable assumption. Results will also be reported discarding missing values as a sensitivity analysis.

Using these models, the primary outcome of the proportion of participants with ACT scores of >19 at 3 months will be analyzed using linear models with a logit link function and contrasts to compare the 2 PEAKmAAP groups combined with the eUC group. Secondary analyses of the proportion of ACT scores of >19 at additional timepoints (6, 9, 12 months) will be assessed with contrasts for the group effect (to measure the average effect across the different timepoints) and the group-by-time interaction effect (to measure the change in effect over time) between groups (PEAKmAAP-DS vs PEAKmAAP; PEAKmAAP groups combined vs eUC). Since the ACT score will be measured at 3, 6, 9, and 12 months (all participants will have baseline scores of ≤19), these correlated repeated measures data will be analyzed with a binomial distribution and a logit link function for modeling with an appropriate correlation structure (eg, compound symmetry or first-order autoregressive). Additionally, minimally important improvements in ACT scores (3-point increase) and CASI (1-point decrease) will be similarly modeled as binary outcomes across timepoints, contrasting eUC versus the 2 PEAKmAAP groups combined or PEAKmAAP versus PEAKmAAP-DS. Other secondary outcomes (health care use, rescue medication use, lung function) will be analyzed using similar models for nonnormal data using appropriate distributions and link functions.

Medication adherence rates at 12 months will be compared using a logistic regression model after adjusting for baseline values as a covariate, contrasting eUC against the 2 PEAKmAAP groups. Mean asthma self-efficacy scores at 3 and 12 months, including the subscales for prevention and management, will be compared among the 3 groups using the analysis of covariance model after adjusting for baseline values as a covariate in the model. The proportion of adolescents who receive step-up therapy will be compared between the 2 PEAKmAAP groups, and the 2 PEAKmAAP groups together will be compared with the eUC across different timepoints using a similar logistic model.

No interim analyses are planned, and thus, there is no planned stopping rule for the study.

Sample Size and Power Calculation

The sample size was determined to detect a clinically meaningful difference between PEAKmAAP and PEAKmAAP-DS groups combined versus the eUC group for the primary outcome measure, which is the proportion of adolescents with ACT scores of >19 at 3 months. We estimate that the proportion of participants with ACT scores of >19 at 3 months will be approximately 15% higher in the PEAKmAAP and PEAKmAAP-DS groups compared to the eUC group based on pilot work [24,40]. Using a generalized estimating equations (GEE) model for binary longitudinal data, we estimated that a sample size of 107 participants in each group will yield at least 80% power to detect the difference mentioned before. After adjusting for a 15% attrition rate, the final sample size needed will be 124 in each group (372 total). The sample size will also have at least 80% power to detect a change from a baseline of 4 between the eUC group and PEAKmAAP and PEAKmAAP-DS groups combined for the asthma self-efficacy score. The SD of the asthma self-efficacy score was determined to be 7 [21,22]. The sample size determination was performed using the GEESIZE macro in SAS Software and PASS [46-48]. All sample size calculations assumed a 2-sided significance level of 5%.

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Results

Recruitment and data collection began in March 2019 and were completed May 2024. Figure 3 depicts the number of participants screened, enrolled, and randomized. Full data analysis began in December 2024.

Peer-reviewed publications are planned, notably the primary outcome manuscript. In addition, publications describing PEAKmAAP app development, a description of population digital access at baseline, process variables describing usability of the app, and other secondary outcomes papers will be considered. Scientific and professional conference abstracts will be or have been submitted. Authorship will be determined based on guidance of the International Committee of Medical Journal Editors.

All analytical code will be made publicly available through the Open Science Framework or in a more tailored repository, as appropriate.

Figure 3. Cumulative screening and enrollment summary. PEAKmAAP: Pulmonary Education and Asthma Knowledge Mobile Asthma Action Plan; PEAKmAAP-DS: Pulmonary Education and Asthma Knowledge Mobile Asthma Action Plan with data sharing; PI: principal investigator.

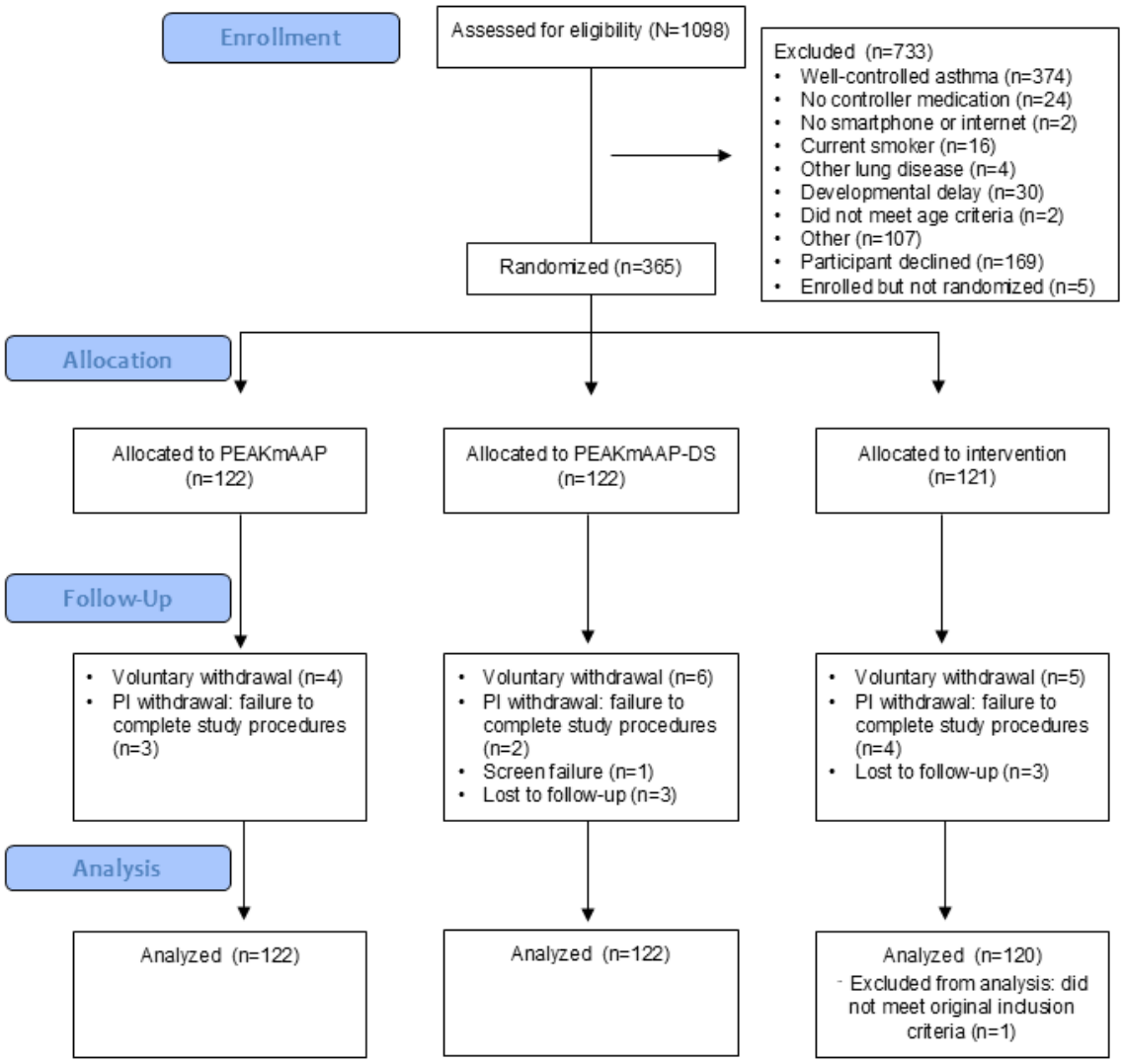

Discussion

Summary

Adolescents with asthma are at increased risk for adverse health outcomes related to asthma and are a group traditionally difficult to engage in self-management strategies for chronic illnesses. Smartphone use is prevalent and has been cited as a preferred and convenient method of communication among adolescents. mHealth delivered via smartphones can provide health education, medication tracking and logging, and chronic disease management integration into the daily lives of patients with asthma [49]. The current literature examining the role of mHealth apps for adolescent asthma is limited. Most studies are small pilot trials with a small number of participants or a short study period. We will test PEAKmAAP's effectiveness among a large cohort of high-risk adolescents with uncontrolled asthma over a 12-month period. Based on the CCM and by virtue of its convenience, ability to provide immediate feedback, and ease of integration into a daily routine, we will examine the PEAKmAAP intervention as a tool to improve asthma self-management, improve medication adherence, and reduce asthma-related morbidity among adolescents at risk for future exacerbations. Our central hypothesis is that the PEAKmAAP and PEAKmAAP-DS groups will have reduced asthma

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morbidity compared to the eUC group. We further hypothesize that PCP data sharing will facilitate sustained asthma control and that significantly more adolescents in the PEAKmAAP-DS group will have continued asthma control at follow-up visits compared to PEAKmAAP alone and the eUC group. This novel approach has a high impact potential as it may be applicable to other age groups and patients with other chronic medical conditions.

Acknowledgments

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Authors' Contributions

TTP was the principal investigator and was responsible for study design, protocol preparation and amendment, recruitment and retention monitoring, adherence to the protocol, study progress review, Institutional Review Board (IRB) and Safety Monitoring Committee (SMC) recommendation review and implementation, and publication of results. Coinvestigators JHT, AB, ALS, SAM, and JB were responsible for study design, study planning, adherence to the protocol, study progress review, IRB and SMC recommendation review and assistance, and publication of results.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT checklist.
[PDF File (Adobe PDF File), 121 KB - resprot_v14i1e69903_app1.pdf]

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Abbreviations

AAP: asthma action plan
ACH: Arkansas Children's Hospital
ACRI: Arkansas Children's Research Institute
ACT: Asthma Control Test
AE: adverse event
AMR: asthma medication ratio
CAB: Community Advisory Board
CCM: Chronic Care Model
ED: emergency department
EHR: electronic health record
eUC: enhanced usual care
FEV: forced expiratory volume in the first second
HBM: Health Belief Model
HIPAA: Health Insurance Portability and Accountability Act
IRB: Institutional Review Board
mAAP: mobile health asthma action plan
mHealth: mobile health

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PCP: primary care provider
PEAKmAAP: Pulmonary Education and Asthma Knowledge Mobile Asthma Action Plan
PEAKmAAP-DS: Pulmonary Education and Asthma Knowledge Mobile Asthma Action Plan with data sharing
PF: peak flow
PI: principal investigator
RCT: randomized controlled trial
SAE: serious adverse event
SMC: Safety Monitoring Committee
UAMS: University of Arkansas for Medical Sciences

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Protocol

Implementation of an Interdepartmental Collaborative Medication Review to Reduce Potentially Inappropriate Medication Use in Hospitalized Older Adults: Protocol for a Mixed Methods Study

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Abstract

Background: The inappropriate use of multiple medications known as polypharmacy is a growing concern for older populations with comorbid conditions in India. Polypharmacy can lead to serious adverse health outcomes, increased health care costs, and reduced quality of life. Screening tools such as the Medication Appropriateness Index (MAI) and Screening Tool for Older Persons' Prescriptions (STOPP) or Screening Tool to Alert to Right Treatment (START) criteria can help identify potentially inappropriate medications, and interventions such as medication review clinics and prescribing audits can help improve the appropriateness. A collaborative medication review (CMR) involving a team approach is important to ensure that patients receive the best possible care.

Objective: The primary objective is to assess the feasibility of implementation of interdepartmental CMR to reduce potentially inappropriate medications in hospitalized older adults. The secondary objectives are to (1) explore the facilitators and barriers in this implementation from the health care providers' perspective, (2) determine the costs involved in the implementation from a health system perspective, and (3) analyze the efficacy of interdepartmental CMR by using MAI, postdischarge adverse events, and number of medication-related admissions.

Methods: This study consists of 5 phases aimed at improving CMR practices in India. Phase 1 focused on conducting a scoping review of CMR practices. Phase 2 involved creating standard operating procedures to establish a CMR team, delineating roles and responsibilities, and providing training. Phase 3 will evaluate the efficacy of CMR by using standardized tools such as MAI and STOPP/START criteria. Phase 4 assesses the challenges faced in implementing CMR. Finally, phase 5 analyzes the costs related to CMR implementation. This study employs a multicentered mixed methods approach, combining qualitative methods (in-depth interviews and focus group discussions) to explore implementation challenges and quantitative analysis through a

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quasi-experimental study involving 280 hospitalized older adults. It aims to measure costs and the reduction of potentially inappropriate medications post discharge.

Results: This study received a grant from the Indian Council of Medical Research–Safe and Rational Use of Medicine Task Force in December 2023. All study preparatory approvals were obtained. Phase 1 and phase 2 were completed by December 2024. Phase 3 is scheduled to finish by June 2025. Phases 4 and 5 are planned for completion by August 2025. Final data analysis and manuscript submission are expected by December 2025.

Conclusions: This study can provide insights into the implementation and effectiveness of CMR and help to understand the facilitators and barriers to implementing interdepartmental CMR and the cost incurred in its implementation. Interprofessional teams will collaboratively review and optimize medications for older patients with multimorbidity in India—a strategy expected to enhance care coordination, improve clinical outcomes, and reduce health care costs.

Trial Registration: Clinical Trials Registry – India CTRI/2024/06/069220; https://ctri.nic.in/Clinicaltrials/pmaindet2.php?EncHid=OTgyNDg=&Enc=&userName=

(JMIR Res Protoc 2025;14:e69626) doi:10.2196/69626

KEYWORDS

collaborative medication review; potentially inappropriate medications; medication-related hospital admissions; older adult prescriptions; facilitators; barriers

Introduction

Inappropriate polypharmacy refers to the use of multiple medications in a way that is not consistent with established treatment guidelines or that can increase the risk of adverse drug reactions, drug interactions, or other health problems. High-risk populations such as older adults and individuals with multiple chronic conditions are particularly vulnerable to inappropriate polypharmacy. In India, inappropriate polypharmacy in older adults is a growing concern due to the lack of awareness and regulations surrounding medication use. The prevalence of potentially inappropriate medicine use among the older Indian adult population is 28% [1]. The older adult population in India represents 8.6% (104 million) of the total population [2]. These patients often have multiple comorbidities, leading to the prescription of multiple medications. The consequences of inappropriate polypharmacy in high-risk populations can be serious and can include increased risk of falls, hospitalizations, and other adverse health outcomes. In addition, inappropriate polypharmacy can lead to increased health care costs and reduced quality of life for patients [3].

Many screening tools are available as either implicit (judgment-based) or explicit (criterion-based) tools to identify inappropriate polypharmacy [4]. Implicit tools such as the Medication Appropriateness Index (MAI) and Assessment of Underutilization of Medicine assess the prescribing quality of a physician's prescription for an older adult. Explicit tools such as Beer's criteria and the Screening Tool for Older Persons' Prescriptions (STOPP) or the Screening Tool to Alert to Right Treatment (START) criteria have been developed from literature reviews, expert opinions, and consensus exercises, typically comprising a list of drugs to be avoided or added for older adult populations [5]. However, along with identifying the inappropriateness, choosing the best intervention to improve appropriate polypharmacy is a priority goal.

Improvements in inappropriate polypharmacy can be achieved by a wide range of interventions to address the complexity of the clinical situations and the individuality of the prescribers. In India, interventions to improve appropriate polypharmacy are needed to address specific problems related to multimorbidity, which need to be integrated into existing health care systems and embedded with interprofessional collaboration. Some of the interventions include educational programs for prescribers or consumers, medication review clinics and specific prescribing audits, and prescribing incentive schemes and regulatory interventions [6].

Effective polypharmacy interventions involving drug reviews require the consideration of several factors, including the hospital setting, health care professional, purpose and scope of review, criteria to guide review, tool to base drug review, and, finally, the method (manual of the clinical decision support system) used for drug review. The current literature distinguishes 3 types of drug reviews, namely, prescription reviews (performed without the patient), concordance and complication reviews, and clinical medication reviews (performed in the presence of the patients). However, in India, it is feasible to conduct only a prescription review on the basis of its convenience and feasibility [7].

Furthermore, drug reviews are usually formalized and driven either by implicit or explicit criteria. Owing to their usefulness, explicit or criteria-based screening tools are used most often to help the systematic assessment of medication appropriateness. Varas-Doval et al [8] conducted the ConSIGUE program, which assessed the impact and implementation of a medication review with follow-up for older patients with multiple medications. They suggested that the provision of a medication review with follow-up in collaboration with general medical practitioners and patients contributes to the improvement of older patients' health status and reduces their problems related to the use of medicines [8]. Medication reviews have been shown to be a cost-effective strategy through a cost-utility analysis [9]. However, policy makers look for other economic evidence other than the cost-utility analysis in the process of considering a change in the health policy and a payment for the service.

Malet-Larrea et al [10] conducted a cluster randomized trial of a medication review with follow-up to ascertain its economic

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impact from a national health system perspective over 6 months. The cost-benefit ratio revealed that for every €1 (US $1.17) invested in a medication review with follow-up, a benefit of €3.3 (US $3.87) to €6.2 (US $7.28) was obtained. In fact, other studies [10] presented even greater cost-benefit ratios such as those included in a series of systematic reviews (1:34.61, 1:17.0, 1:25.95, and 1:75.84).

In India, physicians follow the theme of professional isolation in the management of patients with multimorbidity. This practice emanates from the interplay among 4 aspects of patient management, namely, disorganization and fragmentation of health care, inadequacy of guidelines and evidence-based medicine for multimorbidity, challenges in delivering patient-centered rather than disease-focused care, and barriers to shared decision-making.

Interdepartmental collaborative reviews may overcome all these barriers, allowing for a more comprehensive review of the patient's medication needs, considering factors such as the patient's medical history, current symptoms, and medication side effects. This study will evaluate the challenges in the implementation of an interdepartmental collaborative medication review (CMR) and the cost analysis of a planned CMR to prevent potentially inappropriate medications in the hospitalized older adult population.

Methods

Study Settings

This study is planned to be conducted over a period of 2 years in 5 phases chronologically (Figure 1). The study will be conducted at the Pondicherry Institute of Medical Sciences and Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India, in collaboration with Indian Council of Medical Research (ICMR)-National Institute of Epidemiology, Chennai, India, and ICMR headquarters, New Delhi. The scoping review (phase 1) on CMR is completed.

Figure 1. Description of the 5 phases of the study. * denotes phases 3 and 4 will be conducted simultaneously. CMR: collaborative medication review; MAI: Medication Appropriateness Index; SOP: standard operating procedure; START: Screening Tool to Alert to Right Treatment; STOPP: Screening Tool for Older Persons' Prescriptions.

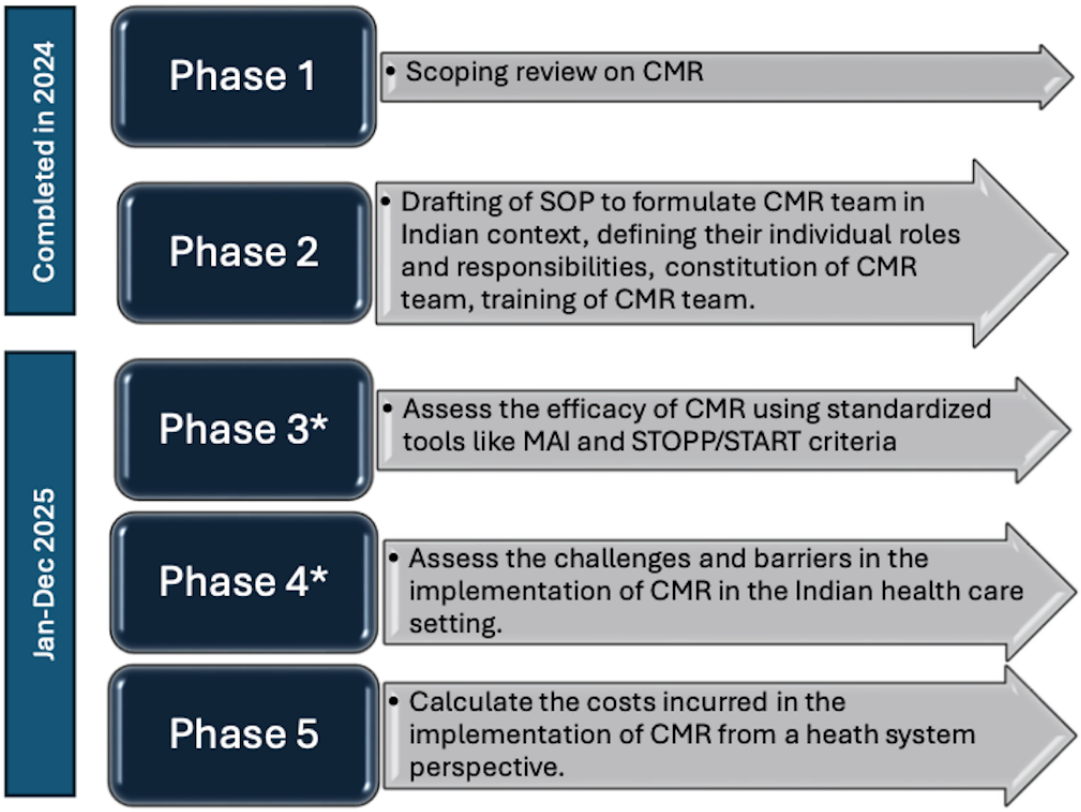

Phase 1: Scoping Review on CMR

We conducted a comprehensive search on databases, including PubMed, Cochrane Library, Clinicaltrials.gov, Global Index Medicus, Lens.org, and World Health Organization (WHO)-International Clinical Trials Registry Platform registries by using the following search terms: medication review, collaborative review, prescriptions, prescription drugs, and aged people. We included only English language studies. Two review authors independently extracted data from each included study via a predesigned data extraction form. We will attempt to contact the trial authors to request incompletely reported data.

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The following information was extracted: general information (study ID, date of extraction, title, authors, and source of study if not published), study characteristics (study settings, study design, participants, and inclusion/exclusion criteria used in the study), details of interventions, outcomes as described in the types of outcome measures above, and details necessary for the risk of bias assessment. Disagreements between review authors were resolved by discussion or by consultation with a third review author.

Phase 2: Drafting Standard Operating Procedures to Formulate CMR Teams in the Indian Context

On the basis of the results of the scoping review, the standard operating procedures will be developed by the team of investigators. The scope of the standard operating procedures includes the composition (members) of the CMR team; training of the CMR team; frequency of the CMR team review meetings; details regarding the intervention, which includes the assessment of drug charts and conveyance of information regarding any medication inappropriateness to the treating clinicians as well as follow-up of the participants; and the documentation process. All the developed standard operating procedures were reviewed and approved by the principal investigator and the head of the institution.

Phase 3: Assess the Efficacy of CMR

The efficacy of CMR is assessed via standardized tools such as MAI, START/STOPP criteria, and AT-HARM10 (Assessment Tool for identifying Hospital Admissions Related to Medications-10 items).

Phase 4: Assessing the Challenges and Barriers

Phase 4 involves assessing the challenges and barriers in implementing CMR in the Indian health care setting.

Study Design

Mixed Methods Study Design

Qualitative Component

In-depth interviews and focus group discussions (FGDs) were conducted to explore the facilitators and barriers to the implementation of interdepartmental CMR to reduce potentially inappropriate medications in hospitalized older patients.

Quantitative Component

The study design was quasi-experimental preinterventional and postinterventional with the following components: (1) costs incurred for the implementation of CMR in Indian health care settings and (2) MAI, reduction in the percentage of inappropriate medications, postdischarge adverse events, and medication-related admissions.

Study Period and Duration

Each participant's participation will last from admission until 30 days after discharge from the hospital.

Study Participants

Health care providers at the 2 sites will be involved in the study to assess the facilitators and barriers in the implementation of interdepartmental CMR from their perspective. The prescriptions of both male and female older patients (aged 60 years and older) admitted to any medical or surgical ward at both study sites will be assessed to determine whether the participants meet the eligibility criteria after the medical records are reviewed.

Study Eligibility Criteria

Inclusion Criteria

The inclusion criteria were as follows:

1. Male and female patients aged 60 years and older with multiple morbidities admitted to all medical and/or surgical specialty/subspecialty wards at the study sites.
2. Patients visiting the study sites from places (villages/towns) within a 50-km radius (for ease of performing the study and reducing attrition).

Exclusion Criteria

The exclusion criteria were as follows:

1. Patients who are discharged against medical advice before the completion of treatment.
2. Patients who are referred to other hospitals for various reasons.
3. Patients or patients whose kin refused to give consent to participate in the study.
4. Readmission and emergency department visits other than drug-related problems.

Sample Size Estimation and Analysis

The sample size calculation for the assessment of CMR efficacy was based on a previous study [1], which showed that the prevalence of potentially inappropriate medications in the older adult population was 28% in India. We assume that the effect size of the interdepartmental CMR is 10%, power is 80%, and significance level is 5%. The sample size calculation was estimated to be 280 participants. Given that this study will be conducted at 2 different sites, Pondicherry Institute of Medical Sciences and Jawaharlal Institute of Postgraduate Medical Education and Research, 140 participants will be recruited from each site. Universal sampling techniques will be used to enroll participants in this phase of the study. For the qualitative component of the study to assess the implementation challenges of CMR, preferably 2 FGDs will be conducted among CMR team members at each study site. Approximately 10-16 in-depth interviews will be conducted per site until the data saturation point is reached.

Description of CMR Interventions During the Phase 3 Study

Screening Phase

Prescriptions of both male and female older patients (aged 60 years and older) admitted to any medical or surgical ward at both study sites will be assessed to determine whether participants meet the eligibility criteria after the medical records are reviewed.

Study Enrollment Phase

Once potential participants are deemed eligible, we will proceed with the enrollment process. The collection of baseline data on

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participants' medication profiles, medical history, and other relevant information will be performed. The participants' demographic details and contact information for follow-up will also be documented. Using tools such as MAI and START/STOPP criteria, we will evaluate the incidence of inappropriate medications after 24 hours of admission at baseline and during hospitalization every third day.

Intervention Phase

CMR interventions as per the standard operating procedure will be applied, and all the relevant details mentioned in the CMR activities checklist will be executed. The clinical pharmacists will perform the activities and discuss them with the CMR team, and their suggestions will be presented to the treating physician in written format.

Follow-Up Phase

At discharge, the clinical pharmacist will assess the discharge prescription for the MAI score and potentially inappropriate medications. The percentage of acceptance of the suggestions given (by the CMR team during the admission) by the clinicians will also be recorded from the patient records. After discharge, the patients will be telephonically followed up by a trained field investigator for 30 days to inquire about any hospital admissions, visits to the emergency department, drug-related complications, and episodes of dizziness and falls. The AT-HARM10 tool will be used to identify the medication-related hospital admissions after discharge after obtaining the necessary permission from the authors. The detailed description of the study evaluations/measurements/assessments at various time points after CMR intervention is shown in Table 1.

A comparison of MAI scores and the incidence of potentially inappropriate medications before and after CMR intervention at admission and at discharge will predict the efficacy of CMR.

Table 1. Description of the study evaluations/measurements/assessments after collaborative medication review intervention.

Event time points	Hospital admission (day 1)	During hospitalization (every third day until discharge)	Hospital discharge	
			Day X[a]	Day 30[b]
Enrollment				
Eligibility screening	✓			
Informed consent	✓			
Screening prescriptions				
START[c]/STOPP[d] criteria	✓	✓	✓	
MAI[e] score	✓	✓	✓	
Intervention (CMR[f])				
Medication history	✓	✓	✓	
Medication reconciliation	✓	✓	✓	
Medication review	✓	✓	✓	
Collaborative team meeting	✓	✓	✓	
Assessments				
CMR team time	✓	✓	✓	
Cost analysis	✓	✓	✓	
Drug-related problem	✓	✓	✓	✓
Hospital admissions				✓

[a]X refers to the day of discharge of the patient from hospital since admission.

[b]Day 30 refers to 30th day after discharge.

[c]START: Screening Tool to Alert to Right Treatment.

[d]STOPP: Screening Tool for Older Persons' Prescriptions.

[e]MAI: Medication Appropriateness Index.

[f]CMR: collaborative medication review.

Process Indicators of Intervention

The following methods have been used to assess the feasibility of implementing interdepartmental CMR: (1) number of interdepartmental CMR meetings, (2) number of CMR consultations per patient, (3) percentage of medication discrepancies/medication-related adverse events identified, prevented, or resolved, and (4) percentage of suggestions given by the CMR team.

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Study End Points

Primary End Point

The primary end point was the facilitators and barriers in implementing interdepartmental CMR to reduce potentially inappropriate medications.

Secondary End Points

The secondary end points were as follows:

1. Costs involved in the implementation of CMR in Indian health care settings (tertiary health care settings perspective).
2. Change in the number of potentially inappropriate medications from hospital admission to discharge due to CMR.
3. Change in the MAI score from hospital admission to discharge due to CMR.
4. Number of medication-related hospital admissions from the day of discharge to 30 days post discharge.

Assessment of the Challenges and Barriers in Implementing CMR in the Indian Health Care Setting

FGDs will be conducted among CMR team members, and approximately 10 to 16 in-depth interviews will be conducted with the prescribers whose patients were recruited as the study participants. This would help in understanding prescribers' and CMR team members' perceptions and attitudes toward CMR. An FGD via the nominal group technique is a structured variation of a small-group discussion to reach consensus. It gathers information by asking individuals to respond to questions posed by a moderator and then asking participants to prioritize the ideas or suggestions of all group members.

The participants for FGDs will be chosen via a purposive sampling method, that is, team members of CMR. Preferably, 2 FGDs will be conducted among CMR team members at each study site. The total number of participants per FGD will be 4 to 10, and it will be a heterogeneous group depending upon the operational feasibility. Each FGD will be conducted for approximately 40-60 minutes until the data saturation point is reached. The entire proceedings of the FGD will be audio-recorded using an MP3 player after obtaining verbal consent from the participants.

In-depth interviews will be conducted among prescribers, including physicians, intensivists, and senior staff nurses, by using a predesigned interview guide (Multimedia Appendix 1), with topics covering the working process, resources, competences, drug-related problems, intervention effects, and collaboration. Approximately 10-16 in-depth interviews will be conducted per site until the attainment of the data saturation point. Each in-depth interview will be conducted for a minimum of 20-30 minutes. The participants for the in-depth interviews will be selected via a purposive sampling method. The selection of the participants will be considered to ensure representativeness across all professional domains.

Phase 5: Calculating the Costs Incurred in the Implementation of CMR From a Health System Perspective (Opportunity Costs)

The multitude of health care providers and payment schemes affects the cost of any health service delivered and the estimation methods used, as costs can differ significantly between health centers due to variations in the service type and structure. Accurate cost analysis requires thorough understanding of a health care facility's functions and financing mechanisms to ensure that all expenses are considered. In this study, a comprehensive case record form will systematically document both direct and indirect costs related to the CMR process. This includes detailed information on the facility characteristics, human resources, infrastructure, equipment, and operational costs, allowing for an extensive evaluation of the economic impact of the CMR process through quantitative and qualitative data collection [11,12].

Study Variables and Tools

The study variables, namely, patient demographics (name, age, contact information) and medical history, including current and past medical conditions, allergies, and adverse drug reactions, will be collected with the help of a predesigned case record form that includes tools such as the MAI tool, the STOPP/START tool, and the AT-HARM10 tool, which will be used for data analysis. The economic evaluation will be conducted from a health system perspective. Detailed information will be collected on the facility characteristics, human resources, infrastructure, equipment, and operational costs, allowing for an extensive evaluation of the economic impact of the CMR process from a health system perspective. The collected information in the case record forms will also be entered electronically into the Research Electronic Data Capture (REDCap) software (Vanderbilt), improving the data quality and enabling central access to data (since this is a multicentric study).

Data Management and Statistical Analyses

Quantitative Component

The investigators will ensure the completeness, accuracy, and timeliness of data collection. The study sites will enter data in the REDCap software, and case record forms will be scanned in REDCap. The data will be checked for a normal distribution (Kolmogorov-Smirnov test). Student paired 1-sided *t* test will be used to analyze the differences between MAI scores at admission and discharge to determine the effectiveness of CMR, and the chi-square test or Fisher exact test will be used to assess the differences in the frequency distribution. All analyses will be conducted via the SPSS software (version 22.0 for Windows 11; Microsoft), Microsoft Excel 2019, and STATA (version 12; StataCorp LP).

Qualitative Component

For the analysis of the qualitative component of the study, the audio-recorded FGDs and in-depth interviews will be transcribed by multiple investigators. The transcripts will be reviewed thoroughly and exported to NVivo software (QSR International). Reflective thematic analysis based on a framework or template

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approach will be used to analyze the transcripts. Inductive coding of the transcripts will be performed independently by 2 investigators trained in qualitative research, and they will engage in regular analytic discussions to surface assumptions and enhance reflexivity, while field notes will document decisions and researcher positionality. Member checking approach and audit trails will be used to establish credibility and confirmability. A third independent investigator may review the transcribed data to increase the study's internal validity. Intercoder agreement will be performed to enhance the validity of the study. The codes obtained from the transcripts will be thoroughly reviewed, and the codebook will be generated. The codes will then be merged to form categories, subthemes, and themes and categorized as either facilitators or barriers. Dependability will be addressed through an explicit coding manual and transparent documentation of the analytic steps, while transferability will be supported by providing rich, contextualized descriptions of the participants and selection of study participants.

The statistical analysis to evaluate the costs incurred in implementing CMR in the Indian health care setting from a health system perspective includes direct, indirect, and opportunity costs. Data collected from various facilities will be cleaned and entered into a predesigned database. All costs will be standardized to 2025 prices by using the consumer price index for health care services. Descriptive statistics will summarize continuous variables such as salaries and utility costs by using the measures of central tendency (mean, median) and dispersion (SD, IQR), while categorical variables such as facility type will be reported as frequencies and percentages. Comparative analyses will assess cost differences between public and private sector facilities by using independent-sample 1-sided *t* tests for normally distributed data or Mann-Whitney *U* tests for nonnormally distributed data. To explore the predictors of the cost variations across facilities, we will conduct multivariable linear regression with total CMR costs as the dependent variable and facility characteristics, human resources, and infrastructure costs as the independent variables. Interaction terms such as facility type and operational hours will be included to investigate the moderating effects. All statistical analyses will be performed using STATA (version 18), and *P* values less than .05 will be considered as statistically significant.

Data Monitoring

Data monitoring will be performed by designated officials appointed by the ICMR headquarters in New Delhi.

Ethical Considerations

The study was approved by the institutional ethics committee of Pondicherry Institute of Medical Sciences, Puducherry, India (IEC:RC/2023/83 on November 10, 2023) and the institutional ethics committee interventional studies of Jawaharlal Institute of Postgraduate Medical Education and Research, Puducherry, India (JIP/IEC/2024/03/30 on March 20, 2024). This study was registered with the Clinical Trials Registry–India (CTRI/2024/06/069220) on June 19, 2024. All participants will be recruited only after written informed consent is obtained from themselves or their legally authorized representatives. This study conforms to the requirements of the Declaration of Helsinki, 1964; the Indian Good Clinical Practice guidelines; and the ICMR-National Ethical Guidelines for Biomedical and Health Research Involving Human Participants, 2017. Personal information about the screened and enrolled participants will be collected, shared, and maintained to protect confidentiality before, during, and after the trial. Confidentiality of participation will be maintained, and personal identity will not be revealed during data collection, analysis, presentations, and publications. No compensation was provided for participation in the study. Study records will be made available only to authorized persons conducting the study and to the funding agencies without revealing participant identities. All data source documents, including clinical reports and records necessary for the evaluation and reconstruction of the clinical trial, will be stored securely for 5 years, with a focus on ensuring the study participants' privacy and confidentiality.

Results

A grant was received from ICMR-Safe and Rational Use of Medicines in December 2023 for this study. This study was scheduled to start from January 2024. The protocol preparation was completed with institutional ethics committee approvals and Clinical Trials Registry–India registrations. The scoping review examining international CMR practices and their adaptability to Indian health care settings was completed adhering to JBI (Joanna Briggs Institute) methodology and PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) guidelines. The review examined CMR practices in older patients through a comprehensive analysis of 7747 studies published between 2010 and 2024. A systematic search was conducted across PubMed, Cochrane Central Register of Controlled Trials, Clinicaltrials.gov, Global Index Medicus, Lens.org, and WHO-International Clinical Trials Registry Platform by using the following search terms: medication review, collaborative review, prescription drugs, and aged, and only English language studies were included. All retrieved records were imported into Rayyan software for screening. Two reviewers independently screened the titles and abstracts against predefined inclusion criteria: hospitalized patients aged ≥60 years, original research, or protocols evaluating CMR interventions. Full texts of potentially eligible studies were retrieved and assessed independently. Disagreements at any stage were resolved through discussion or a third reviewer adjudication. The review investigated 3 key aspects: CMR team composition, tools for identifying potentially inappropriate medications, and CMR implementation processes in Indian health care settings.

Standard operating procedures for the CMR intervention have been developed through expert panel consultation. The implementation phase will enroll 280 older patients (aged ≥65 years) with polypharmacy (≥5 medications) between January and June 2025. Economic evaluation using time-motion studies and cost analysis will be conducted from July to August 2025, concurrent with semistructured interviews of health care professionals exploring implementation facilitators and barriers. Thematic analysis of qualitative data, cost-effectiveness

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calculations, and manuscript preparation will be completed by 2025.

Based on the results of this study, modules will be prepared, and workshops will be organized for the prescribers on CMR interventions. The research findings will be presented at national/international conference for large-scale public dissemination. The results of this study will be published in indexed peer-reviewed scientific journals. The full protocol, participant-level dataset, and statistical code will be made publicly available after the completion of the study.

Discussion

This study will assess the feasibility of implementing CMR in Indian hospitals and identify the key facilitators and barriers to CMR implementation. This study will evaluate the potential for reducing potentially inappropriate medications and medication-related admissions while providing crucial cost-implementation data for the Indian health care context.

Although CMR implementations have been well-studied in Western health care settings, with documented reductions in potentially inappropriate medications and readmissions, this will be among the first studies to systematically evaluate CMR feasibility and implementation costs in Indian health care settings [3,8,13-17]. The protocol's mixed methods approach will help bridge the knowledge gap between established Western practices and the unique challenges of the Indian health care system. By adopting a health system perspective for economic evaluation, this study will generate data of direct relevance to policy makers and administrators. However, purposive sampling in the qualitative component may introduce selection bias, and the exclusive focus on tertiary care settings may limit the generalizability of the findings to primary or rural health care facilities. Additionally, the relatively short follow-up period proposed in this protocol will constrain our ability to assess the long-term sustainability and downstream clinical effects of CMR.

Upon completion of this study, subsequent research will aim to develop and pilot standardized training modules for clinical pharmacists, ensuring consistency in CMR workflows across institutions. Finally, the findings will inform the creation of national guidelines and policies to support the systematic integration of CMR into regular clinical practice throughout India. Policy briefs summarizing key recommendations will be developed for the Ministry of Health and Family Welfare and relevant state health departments.

The findings of this study will redefine medication management practices and pave the way for evidence-based, scalable models of CMR in resource-constrained settings. It will underscore the need for cross-disciplinary collaboration as a fundamental strategy to address multimorbidity in older adult populations, thereby offering valuable insights for policy makers and health care providers aiming to optimize geriatric care.

Acknowledgments

The authors gratefully acknowledge JJC for the feedback received for the protocol; Dr Melvin Gorge, BSB, Dr Tarun Bhatnagar, and Mr Sabari for providing Research Data Capture (REDCap) support; and Dr Nabendu Sekhar Chatterjee for the protocol development workshop conducted by the Indian Council of Medical Research (ICMR), New Delhi, India. The authors also acknowledge the scientific input received by the Technical Advisory Group, ICMR-National Taskforce on Safe and Rational Use of Medicines. This study is funded by ICMR, New Delhi, India, through the ICMR-National Taskforce on Safe and Rational Use of Medicines (extramural fund). The fund was awarded to RKK (file ICMR/EM/SRUM/2023/RajeshKonduru). The funders had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Authors' Contributions

Conceptualization: AK, RKK, JJC, BSB, AN, SR, NI, DS, SS, MCH, IT
Funding acquisition: RKK, AJP
Methodology: RKK, AK, JJC, BSB
Resources: RKK, AJP, SR
Software: RKK, MM
Writing – original draft: AK, SR
Writing – review and editing: RKK, JJC

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guide for focus group discussions among the collaborative medication review team and clinicians.
[DOCX File , 18 KB - resprot_v14i1e69626_app1.docx]

Multimedia Appendix 2
Peer review report by the National Task Force on Safe and Rational Use of Medicine, Indian Council of Medical Research.

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[PDF File (Adobe PDF File), 87 KB - resprot_v14i1e69626_app2.pdf]

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Abbreviations

AT-HARM10: Assessment Tool for identifying Hospital Admissions Related to Medications-10 items

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CMR: collaborative medication review
FGD: focus group discussion
ICMR: Indian Council of Medical Research
MAI: Medication Appropriateness Index
PRISMA-ScR: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews
REDCap: Research Data Capture
START: Screening Tool to Alert to Right Treatment
STOPP: Screening Tool for Older Persons' Prescriptions
WHO: World Health Organization

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Protocol

Assessment of Two Online Interventions for Veterans With Chronic Pain: Protocol for a Randomized Controlled Efficacy Trial

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Abstract

Background: Chronic pain is a debilitating condition that disproportionately impacts US veterans who manage numerous negative pain-related outcomes. There is an urgent need for accessible, engaging, and innovative treatments that can help veterans with chronic pain better self-manage their pain at home and improve their daily functioning. Technology-delivered acceptance- and mindfulness-based interventions for pain have shown strong efficacy, particularly when they are engaging and tailored to specific client needs. However, more research is needed to assess the impact of such interventions, particularly in terms of pain-related functioning and quality of life.

Objective: The primary aim of this study is to test the efficacy of Veteran Acceptance and Commitment Therapy for Chronic Pain (VACT-CP), an online self-management pain program, compared to an active online control (Online Pain School) for improving pain-related functioning in a 3-site randomized controlled trial. The secondary aim is to explore psychological flexibility as a potential mediator between pain severity and pain-related functioning.

Methods: This study will use a mixed methods approach to examine the efficacy of VACT-CP in a 2-arm, multisite, randomized controlled superiority trial including 200 participants with chronic musculoskeletal pain compared to Online Pain School. Participants will be assigned to 1 of these 2 online interventions. Both interventions will include 7 modules delivered over 7 weeks, with each module lasting approximately 15 minutes. Mixed effects models will be used to analyze the primary hypothesis that participants in the VACT-CP group will have greater improvement in pain-related functioning (Brief Pain Inventory–Interference subscale) than those in the active control group (Online Pain School). The main acceptance and commitment therapy process mediator (ie, Multidimensional Psychological Flexibility Inventory), pain-related functioning outcomes (Brief Pain Inventory–Interference subscale), and quality of life (Veterans RAND 36-Item Health Survey) will be measured at baseline,

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end of treatment, and 3 and 6 months after treatment. In addition, qualitative exit interviews will be conducted with a random set of 30 VACT-CP users (n=10, 33% per site) to obtain intervention usability, feasibility, and acceptability information.

Results: The recruitment for this study began in January 2025. It is expected to continue through January 2027. Data collection is expected to be completed by June 2027, and primary data analyses are expected to be completed by early 2028.

Conclusions: Online interventions such as VACT-CP and Online Pain School have the potential to expand access to behavioral interventions that improve quality of life and provide nonpharmacological pain treatment options for veterans experiencing chronic pain. However, research on their impact and underlying mechanisms of change is required to support this area of potential at-home programming.

Trial Registration: ClinicalTrials.gov NCT06058624; https://clinicaltrials.gov/study/NCT06058624

International Registered Report Identifier (IRRID): PRR1-10.2196/70601

(JMIR Res Protoc 2025;14:e70601) doi:10.2196/70601

KEYWORDS

chronic pain; randomized controlled trial; acceptance and commitment therapy; embodied conversational agent; digital health intervention; efficacy trial

Introduction

Background

Pain has been identified as one of the most frequently presented medical concerns in primary care for veterans [1]. According to the World Health Organization, pain is an "unpleasant sensory and emotional experience associated with, or resembling that associated with, actual or potential tissue damage" [2]. Perhaps the most complicated to treat and devastating type of pain is chronic pain. Partly due to active-duty physical experiences and injuries, chronic pain disproportionately impacts veterans, who are diagnosed at high rates and with a greater rate of severe pain than nonveterans [1,3]. Many areas of daily living and functioning are impacted by the experience of chronic pain. Veterans with chronic pain face numerous functional difficulties, including poor integration into their community [4] and difficulties in social situations and changes in activities of daily life, sleep, and appetite [1,5,6]. Chronic pain has also been associated with numerous negative outcomes in veterans, including increased morbidity and mortality [7], decreased satisfaction with health care [4], and increased health care use [8].

To reduce the impact of pain, pharmacological treatments such as long-term opioid therapy have often been prescribed [9]. Unfortunately, the short-term relief provided by opioids does not translate into long-term effectiveness [10,11]. In fact, there is little evidence of the long-term efficacy of prescription opioids in chronic pain treatment, and they can lead to problematic substance use and death [5,6,12]. This research has led to recent Centers for Disease Control and Prevention and the US Department of Veterans Affairs (VA)/Department of Defense Clinical Practice guidelines de-emphasizing opioids and suggesting nonopioid medications and nonpharmacological interventions, in particular psychological interventions, as first-line treatment [7]. Thus, to adequately address pain, it is imperative to look beyond pharmacological treatments and address not only the physical but also cognitive and affective factors associated with chronic pain.

With more than 20 years of empirical research supporting its efficacy, acceptance and commitment therapy (ACT) encapsulates the strengths of several existing chronic pain treatment approaches for improved client functioning. ACT is composed of 6 major focus areas that provide a framework for clients to re-engage with the present, their values, and the actions that provide personalized meaning or bring psychological flexibility into their lives [13]. By targeting the catastrophizing thought patterns and affective experiences (negative emotions, memories, and urges) that can cause pain severity to negatively impact functioning, ACT can teach the skills necessary for clients to engage in valued behaviors and functional improvement even when facing cognitive and affective barriers [14-16].

Evidence shows that ACT interventions can increase acceptance of chronic pain, with multiple effectiveness studies producing average effect sizes in the medium to large range, with positive impacts on social functioning and decreased pain-related medical visits even 3 years following treatment [17]. As it leverages a transdiagnostic approach to functional improvement, ACT can be particularly useful when working with clients experiencing challenges across multiple comorbid chronic mental health and pain diagnoses [16]. In addition, when veterans are managing both chronic pain and substance use issues in the context of serious life stressors such as the COVID-19 pandemic, greater psychological flexibility can buffer particularly well against negative outcomes in mental health functioning and quality of life [18]. Therefore, ACT, with its specific focus on functional impairment, valued living, and pain acceptance, may be particularly well-suited to improving quality of life and functioning among veterans with chronic pain.

Behavioral treatment for chronic pain can be labor intensive and may not be offered in all health care systems, leading to limited access for patients with chronic pain [19]. Within the VA, clinician-delivered treatment can also be burdensome for patients, as it may require weekly appointments during business hours for 10 to 12 weeks in addition to appointments with prescribers. At the same time, nonpharmacological pain management is more prevalent among VA-connected veterans compared to non–VA-connected veterans [20]. This suggests that veterans could benefit from increased access to empirically supported, nonpharmacological, VA treatments for chronic pain,

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particularly when that program can also reduce common barriers to care. The rapidly expanding field of online and mobile-based health care services represents an opportunity to increase veterans' access to empirically supported nonpharmacological chronic pain and mental health treatments [21,22]. As 91% of the US adults have access to internet-connected devices [23], digital health interventions have the potential to reach veterans in their own homes.

Web- and mobile-based therapeutic interventions for chronic pain could thus improve veterans' access to psychological interventions for chronic pain, including ACT. Online-delivered ACT for chronic pain has been found to increase activity engagement and pain acceptance while decreasing pain-related distress, anxiety, and depression [24]. Specifically, interactive online systems can provide cognitive and behavioral treatment that leads to lower pain-related interference with daily activities, greater physical and emotional functioning, better sleep quality, and increased quality of life [24,25]. However, although online programs are increasing in popularity and are often as efficacious as in-person treatment, sustained engagement and retention of consumers in online treatment continue to lag [23,26]. Consequently, there remains a critical need to improve online treatment options for ACT for chronic pain to create a more veteran-centered (eg, tailored to their reported needs and common comorbid conditions) and engaging experience as well as test the efficacy of such treatments among veterans with chronic pain.

To address difficulties with engagement, online-supported mental health interventions have explored the possibility of using animated characters, also known as embodied conversational agents (ECAs), as personal guides to support behavioral interventions [27]. Studies suggest that the use of ECAs can increase online-treatment motivation and feedback by mimicking human interactions and dialogue, resulting in improved treatment compliance and use, physical functioning (eg, increased physical activity and diet fidelity), and client-goal achievement [28,29]. The use of ECAs within mental health treatment is expanding rapidly, and ECAs are increasingly being considered and adopted for psychotherapeutic cognitive and behavioral interventions with promising results [30].

Given this research base, our interdisciplinary research team created a 7-week, 7-module ECA-delivered guided online program, "Veteran Acceptance and Commitment Therapy for Chronic Pain" (VACT-CP) [31]. VACT-CP is a therapeutic intervention focused on increasing psychological flexibility or an individual's ability to reconnect with the present moment and cope with the impact of chronic pain on cognitive, emotional, and behavioral functioning. The VACT-CP website was designed iteratively and evaluated through a small pilot feasibility randomized controlled trial (RCT), which suggested that VACT-CP is feasible, usable, and acceptable [32]. In addition, these preliminary results suggested that VACT-CP can also assist veterans with chronic pain in increasing their pain acceptance and activity engagement and improving co-occurring depressive symptoms.

Objectives

This study will use a multisite, 2-arm RCT design that tests the efficacy of VACT-CP compared to an active online control (Online Pain School). The goal of VACT-CP is to assist veterans with chronic pain to improve their functioning and quality of life by engaging them in pain psychoeducation, ACT exercises (eg, acceptance and mindfulness), and personal goal setting guided by their values. VACT-CP accomplishes this goal by supporting more adaptive coping skill attainment to help manage pain-related symptoms and functional goals aligned with valued life domains such as social relationships, physical health, or careers. This study aims to evaluate (1) the efficacy of VACT-CP to improve pain-related functioning for veterans with chronic pain, (2) the efficacy of VACT-CP for improving quality of life for veterans with chronic pain, and (3) the ACT processes that underly the relationship between pain severity and pain-related functioning among veterans in the VACT-CP group. Our hypotheses are as follows:

1. Veterans who receive VACT-CP, compared to veterans in the active control condition, will report significantly greater reductions in pain interference (Brief Pain Inventory [BPI]–Interference subscale) after treatment and at 3-month and 6-month follow-ups (hypothesis 1).
2. Veterans who receive VACT-CP, compared to those in the active control condition, will report significantly greater increases in quality of life (Veterans RAND 36-Item Health Survey [VR-36]) after treatment and at 3-month and 6-month follow-ups (hypothesis 2).
3. The effect of pain severity (BPI–Pain Severity subscale) on functioning (BPI–Interference subscale) will be mediated by improvements in psychological flexibility (Multidimensional Psychological Flexibility Inventory; MPFI) after treatment and at 3-month (primary time point) and 6-month follow-ups (hypothesis 3).

Methods

Ethical Considerations

This study was approved by the VA Central Institutional Review Board (cIRB; 1758411-3; version 2), and the requirement for written informed consent was waived. Amendments will be processed through the local site institutional review board and cIRB according to VA policy. Participants will be compensated US $70 for the baseline assessment, US $30 for the midpoint assessment (week 3), US $80 for the end of treatment assessment (end of week 7), US $50 for the 3-month follow-up assessment, and US $50 for the 6-month follow-up assessment (total possible compensation of US $280 in either condition). Participants completing an exit interview will receive US $20. Compensation will be given immediately after completing each assessment time point, and all compensation will be provided via Amazon gift cards. Data will be deidentified, coded, and stored in secure online VA server spaces and within secure, locked VA facilities. These spaces will be securely maintained and will be accessible only to research staff directly involved in this project.

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Study Trial Design

This study aims to conduct a 3-site, randomized controlled, parallel group efficacy trial of VACT-CP (n=120) versus an active online control condition (Online Pain School; n=80) with a 1:2 allocation ratio (Online Pain School vs VACT-CP arms) to allow mediation analysis of hypothesis 3 in the VACT-CP group only. Online Pain School is adapted from a common in-person treatment option for veterans, modified for an online format, and delivered through a VA-approved, secure website. All assessment procedures will be delivered remotely via Qualtrics surveys or secure VA teleconferencing system or in person (if requested by participants), including screening, baseline sessions, follow-up surveys (week 3, week 7, 3-month follow-up, and 6-month follow-up), and qualitative interviews (n=30) will assess for VACT-CP program acceptance and gather suggestions for improvement. Participants who discontinue intervention engagement will still be contacted to complete follow-up assessments. The Yale University Data and Safety Monitoring Board will monitor this project; members will be independent from the study sponsor and have no reported conflicts of interest. Reports on recruitment, follow-up, and adverse events will be reported to the Yale University Data and Safety Monitoring Board panel on a quarterly basis. In addition, reporting of adverse events will be provided to the local institutional review board and cIRB committees according to VA policy. Figure 1 presents the study workflow and timeline for each stage of research participation. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist is provided in Multimedia Appendix 1 [33].

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Figure 1. Participant flow diagram. VACT-CP: Veteran Acceptance and Commitment Therapy for Chronic Pain.

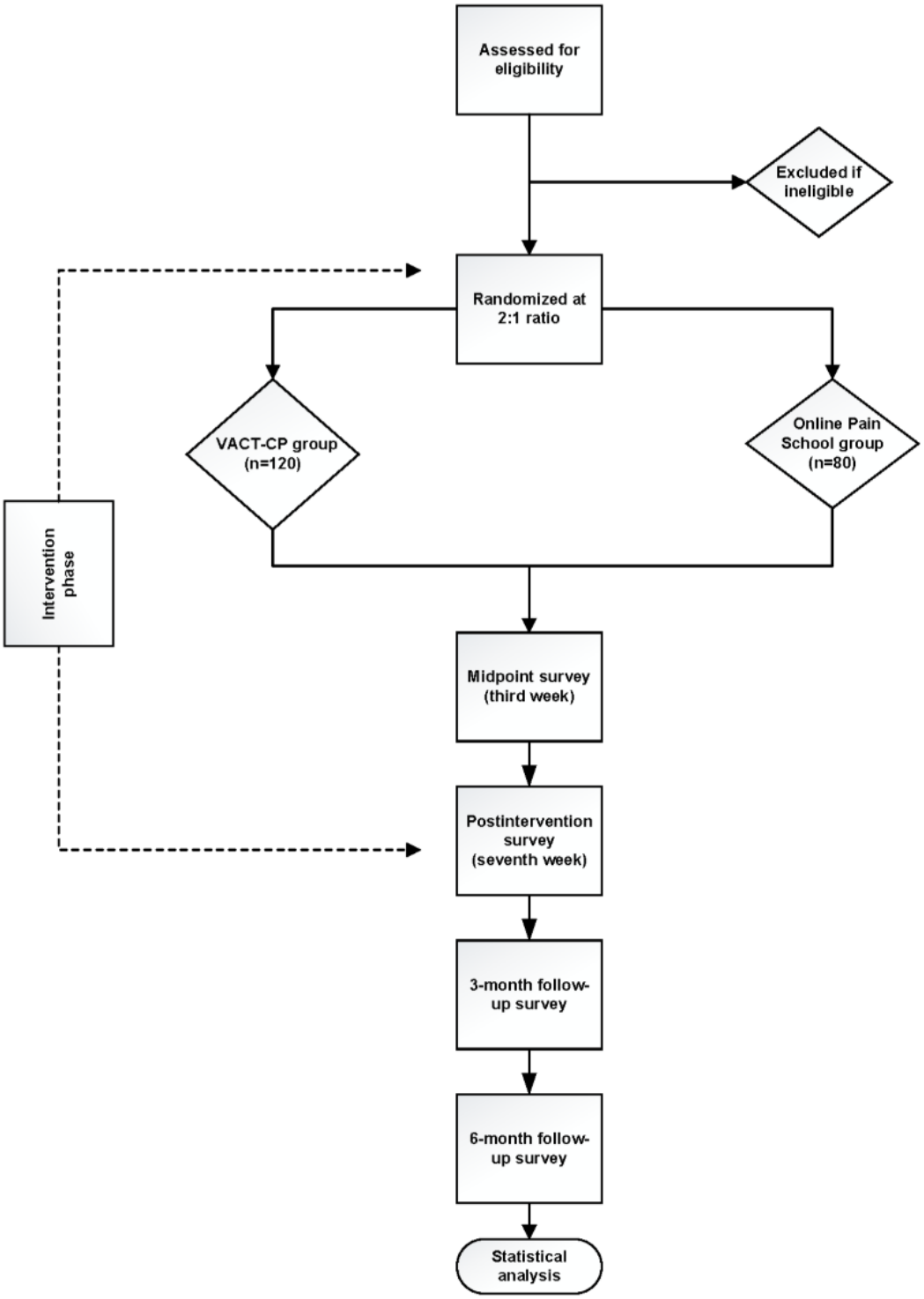

Participant Recruitment

Veterans (N=200) will be recruited and enrolled over the course of 30 months (with a target monthly enrollment rate of 2-3 veterans per site) from 3 US VA medical centers (Bedford, Massachusetts; Dallas, Texas; and West Haven, Connecticut). Recruitment will be conducted through methods such as the distribution of study flyers and information at outreach events and clinics within the VA, mailers sent to veterans identified through medical record reviews, and social media advertisements. We will randomize 200 veterans in a 2:1 ratio, with 120 (60%) veterans assigned to VACT-CP (treatment condition) and 80 (40%) veterans assigned to Online Pain School. Eligibility will be determined based on inclusion and exclusion criteria following a phone screening, medical record review, and abbreviated diagnostic interview during the baseline appointment. The inclusion criteria are (1) current diagnosis of noncancer chronic pain, defined by at least one pain-related

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diagnosis indicated by an *International Classification of Diseases, 9th Revision* or *International Classification of Diseases, Tenth Revision* code related to either musculoskeletal pain or joint problems or Osteoarthritis and minimum of a grade 1 (mild) or 2 (bothersome) on the Graded Chronic Pain Scale–Revised; (2) possession of a computer and working, high-speed wireless internet connection at home; (3) competency to provide written informed consent; and (4) aged ≥18 years. Individuals with chronic pain who do not meet the inclusion criteria will be provided with resources for VA-delivered pain management care. Exclusion criteria will include (1) any current or lifetime *Diagnostic and Statistical Manual of Mental Disorders, 5th Edition (DSM-5)* psychotic disorder; (2) current or recent diagnosis or treatment of (within 1 month of study entry) *DSM-5* substance use disorder; (3) current use of any other chronic pain–related psychological treatment; (4) clinically significant suicidality within the past year as defined by past-year suicidal behaviors or suicide attempts; and (5) any cognitive or physical impairment that would interfere with study participation or using a computer and providing feedback. Exclusion criteria (1), (2), and (4) will be assessed through baseline interviews (ie, *the Structured Clinical Interview for DSM-5* [34]) and medical record reviews. Participants with additional, comorbid pain diagnoses will not be excluded.

Study Procedures

Interested study participants will first be screened by phone for preliminary inclusion and exclusion criteria, including veteran status, age, chronic pain diagnostic criteria, and technological requirements for participation. Following the phone screening, participants who remain eligible will have their medical records reviewed for any exclusion criteria. Eligible participants will then be scheduled for a one-on-one baseline appointment during which research staff will obtain verbal informed consent (see Multimedia Appendix 2) and confirm study eligibility by administering relevant modules from the Structured Clinical Interview for DSM-5 to assess psychotic disorders, substance use disorders, or clinically significant suicidality within the past year. Eligible veterans will then complete a battery of self-report measures using a secure online survey platform (eg, Qualtrics). After enrollment, they will be randomized with allocation masked; this process will be completed by an approved third-party research staff member without any contact with participants or involvement in their study activities and assessment. To allow full powering of the planned mediation analysis of the VACT-CP group only, we will randomize in a 2:1 (VACT-CP vs Online Pain School) ratio at the site level with stratification according to pain severity. The principal investigator (PI; EDR) and project coordinator (CMG) will inform participants of their assignment through encrypted emails. Research assistants who manage study assessments will be blinded from knowing a participant's treatment allocation.

Veterans randomized to the VACT-CP group will receive access to the online program administered as 7 weekly modules (15-20 minutes) programmed and managed by Northeastern University (site PI TB). Online Pain School will serve as an active control condition. Therefore, veterans assigned to this condition will also receive 7 online modules with 15-20 minutes of content based on a common non–ACT-based VA treatment option, Pain School. The adaptation used for this study, Online Pain School, will support veterans in the self-management of chronic pain by providing videos, short exercises, and psychoeducation on different techniques for their "pain management toolbox." Online Pain School will be equivalent to VACT-CP in terms of frequency and length of modules, number of modules, goal setting, and pain psychoeducation content not related to ACT for chronic pain. All participants will be emailed weekly to remind them to complete the next online module in their respective conditions.

Veterans in both conditions will receive the same follow-up assessments and reimbursements. Participants will be compensated following each assessment time point via gift cards (eg, Amazon gift cards). However, no compensation will be provided for completing modules in either of the website interventions.

Interventions

VACT-CP Online Intervention Condition

VACT-CP is based on previous manualized ACT-CP self-management treatments and workbooks [35-38] and uses ECA technology in the form of "Coach Anne" to create a personalized, therapeutic experience. The 7 VACT-CP online modules are provided as weekly sessions that feature Coach Anne as a virtual treatment guide. All content within the online modules is presented interactively via multimodal conversations with Coach Anne. Coach Anne speaks to the veterans, who respond to her questions using forced-choice text options. Each chosen option triggers unique responses from Coach Anne and routes to different topics or content areas depending on the needs and interests of the veteran user. This process allows personalized and responsive interactions between Coach Anne and the veteran. Veterans are also presented with content to better understand pain management, including videos (eg, veteran narratives and metaphors), in-module assessments (eg, values assessments), and interactive opportunities for goal setting. In addition, the VACT-CP program includes an anytime "Mindfulness Module" and a "My Progress" page, a freestanding module where participants can access their own program data related to their values, goals, and preferred pain management exercises. Veterans will receive a weekly message to remind them to complete their next module each week for the first 7 weeks. After completing the final module, participants will be reminded that they can continue to use the website for the duration of their study involvement, if interested.

Online Pain School Active Control Condition

The active intervention control is equated to VACT-CP in terms of treatment duration and number of modules (7 modules over 7 weeks). The content is based on a common non–ACT-based VA pain program option, Pain School, with each module lasting 15 to 20 minutes. The goal will be to provide veterans with more information, tools, and at-home options for pain management. Similar to VACT-CP, each module will include a multimedia format, including videos, text- and image-based self-management information, and questions to assist users in reflecting on their own pain experiences. In addition, similar to VACT-CP, veterans using Online Pain School will receive a

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message to remind them to complete their next module each week for the first 7 weeks. The online format will also allow the monitoring of website use or "dose." Pain psychoeducation equivalent to information presented in VACT-CP (eg, chronic pain definitions and activity pacing) will be provided at the same module time point. However, Online Pain School does not include tailoring to the individual veteran's co-occurring conditions, interactive skills practice, support from the ECA guide Coach Anne, or active components of ACT (eg, mindfulness).

Measures

Demographics and Pain and Mental Health Medication

Demographic measures will include age, gender identity, race and ethnicity, and education. We will also include questions related to concomitant medications currently being used for the management of pain conditions as well as conduct a record review for such information using the VA Computerized Patient Record System (the VA electronic medical record system) or the VA Corporate Data Warehouse (a national repository of patient information across the VA).

Pain-Related Functioning

The BPI [39] is a widely used assessment tool for both pain-relevant functioning and pain severity, which is sensitive to change across numerous treatment studies. The pain interference scale (BPI-Interference subscale—primary outcome) consists of 7 items that assess the degree of pain interference with functioning across 7 areas: general activity, mood, walking ability, normal work, relationships, sleep, and enjoyment in life. Items are rated on a scale from 0 to 10 (0=no pain or no interference and 10=most pain or most interference). The Pain Severity Index (BPI–Pain Severity subscale) consists of 4 items used to assess pain severity. The BPI has shown good reliability in previous studies within the BPI–Pain Severity (Cronbach α=0.85) and BPI-Interference (Cronbach α=0.88) subscales [40].

Mental Health Measures

We will administer the Patient Health Questionnaire-9 [41] to assess depressive symptoms and the 20-item Posttraumatic Stress Disorder Checklist for *DSM-5* [42] to assess posttraumatic stress disorder symptoms.

Quality of Life

The VR-36 [43] is a 36-item measure of health-related quality of life, including physical functioning, role limitations due to physical problems, bodily pain, general health perceptions, vitality, social functioning, role limitations due to emotional problems, and mental health. It is often summarized into physical functioning components and mental functioning components and is one of the most widely used and valid measures of physical and psychological well-being.

Psychological Flexibility

The MPFI [44] is a 60-item self-report measure that assesses psychological flexibility, the main mechanism of change proposed in our theoretical model. The MPFI assesses 6 dimensions of flexibility (ie, present moment awareness, self as context, acceptance, contact with values, committed action, and cognitive defusion), 6 dimensions of inflexibility (cognitive fusion, self as context, inaction, the lack of contact with values, the lack of contact with the present moment, and experiential avoidance), and 2 global composite dimensions. The MFPI is sensitive to clinical change, and its subscales have demonstrated excellent internal consistencies across several subpopulations [45].

Pain Acceptance

The Chronic Pain Acceptance Questionnaire (CPAQ; [46]) is a 20-item survey measuring willingness and engagement in valued life activities and domains, even during times of pain. Higher CPAQ scores indicate higher activity engagement, pain willingness, and overall pain acceptance. Pain willingness reflects a pattern of refraining from attempts to control or avoid pain, while activity engagement represents the degree of engagement in valued activities irrespective of pain. The CPAQ is a well-validated measure with high internal consistency and test-retest reliability [47].

Valued Living

The Chronic Pain Values Inventory [15] is a 12-item self-report measure that measures the agreement between a veteran's values and their life. Accordance is measured across areas of living, including work, health, and family, and calculated by subtracting an "importance" rating from the "success" rating across each domain. Higher agreement with values is correlated with lower pain-related anxiety, lower overall perceived disability, and greater client functioning. These associations hold even in the context of high levels of pain [15]. Good reliability has been shown in previous studies for accordance scores across domains (Cronbach α=0.82) [32].

Intervention Usability

The System Usability Scale [48] is a 10-item measure rated on a 5-point Likert scale that assesses the overall usability of a system. Generally regarded cutoff scores for usability include scores of ≥68 (above average usability) and ≥80 (high usability likely to be recommended).

Satisfaction With Treatment

Global treatment satisfaction will be assessed using the Client Satisfaction Questionnaire-8 [49]. This 8-item scale measures the perceived quality and effectiveness of the chronic pain intervention. This scale showed acceptable internal consistency within the previous online VACT-CP pilot study (Cronbach α=0.93) [32].

Qualitative Semistructured Exit Interview

A semistructured 30-minute qualitative interview using open-ended questions (Multimedia Appendix 3) will be conducted after the participants complete the intervention to assess acceptability and dissemination issues. A random set of 30 VACT-CP users (n=10, 33% per site) will be identified and invited to participate until the goal of 10 interviews per site is reached. Interview questions will explore participants' experiences with accessing and using the VACT-CP program online, perceived effects of the treatment's core components, willingness to recommend the program to others, and any

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problems or concerns encountered during its use. In addition, we will inquire about past strategies or tools used to address their chronic pain issues and whether the VACT-CP treatment was more useful than previous options or strategies. Finally, participants will be asked to indicate what changes they would make to the treatment to assist in self-management of their chronic pain.

Sample Size Considerations

The aims of this efficacy study align with the recommendations for stage 2 development of behavioral therapies [50,51]. Therefore, the primary aim of this RCT is to evaluate treatment group–related changes in pain-related functioning and quality of life outcomes. Secondary aims include examining whether the expected mechanism of behavior change (psychological flexibility) mediates the relationship between pain severity and pain-related functioning for veterans receiving VACT-CP. We expect VACT-CP will produce a small to medium treatment effect consistent with previous ACT studies [28].

We will use mixed effects modeling to test for a time by intervention interaction. Our power analysis and sample size estimation is based on our primary outcome, and research suggesting a clinically meaningful desired difference of 1 point on the BPI-Interference [52]. We expect the correlation between time points to be approximately 0.2 based on current preliminary data. To achieve a desired power of 0.80 and a type I error rate of 0.05 to detect a difference of 1 between the (fixed) group means, we estimate that we will need a minimum of 128 participants, with 64 participants per group. To ensure sufficient power for the planned aim 3 mediation analyses (focused on investigating ACT processes within the VACT-CP group), we will over-recruit in the VACT-CP arm to meet the recommended minimum sample size of 120 participants for mediation analysis. We will use path analysis to model the main independent variable X (pain severity), the mediator M (change from baseline to end of treatment in psychological flexibility as measured using the MPFI), and the main outcome variable Y (pain-related functioning) after treatment and at 3-month and 6-month follow-ups. We have thus used a more conservative group size estimate of 80 in the active control group and 120 in the VACT-CP group to fully power both the efficacy evaluation (hypotheses 1 and 2) and the mediational analyses (hypothesis 3).

With an expected attrition rate of 20% based on pilot data, we will obtain consent from up to 240 participants to allow for successful randomization of a total sample of 200 participants. It is possible that attrition will be greater for some clinical groups than for others (eg, veterans with additional symptoms related to a comorbid mental health issue). Therefore, variables of interest may be associated with attrition, and missing data will not be at random, which could then introduce bias in results despite randomization. To address this possibility, we will attempt to determine whether missing data are missing at random or missing completely at random. We will do so by investigating whether baseline measures (depression symptom severity and posttraumatic stress disorder symptom severity) predict attrition and whether statistical testing suggests that data are not missing at random, and we will modify analyses accordingly (eg, via stratification).

Primary Analyses

Efficacy for the VACT-CP system will be assessed for reductions in pain-related functioning (BPI-Interference subscale; hypothesis 1) and improvement in quality of life (VR-36; hypothesis 2). To test hypothesis 1, which posits that participants' pain-related functioning (BPI-Interference subscale) will improve more in the VACT-CP group than in the active control group (Online Pain School), 3-month outcome scores will be regressed onto a dichotomous group variable (ie, dummy coded, with Online Pain School group as reference) within a mixed model. The PI will have overall responsibility for monitoring the integrity of the study data and participant safety. All analyses will follow the intention-to-treat approach. We will test hypotheses on repeatedly measured quantitative outcomes using mixed effects models, which will allow for different numbers of observations per participant and use of all available data and will be unaffected by randomly missing data. Models will include a condition-by-time interaction and will adjust for significant or substantive demographic and clinical variables as indicated by preliminary analyses. A significant interaction term in the final model will imply a significant difference in trajectories between the conditions, in which case predicted means or mean frequency of use and rates will be presented separately for each time point. In addition, a significance test of the regression coefficient for the variable identifying group membership will also result in a rejection of the null hypothesis that there is no difference between groups on the BPI-Interference subscale. Hypothesis 2 (that the treatment effect will be similarly present for quality of life; VR-36) will be analyzed using the same regression model. All hypothesis testing will be performed using 2-sided tests with an α of .05 and will use the Benjamini-Hochberg Method to adjust for multiple testing. In addition, exploratory models such as those used to test hypotheses 1 and 2 will be fit to assess outcomes immediately after the treatment and at 6-month follow-up.

To investigate the proposed mechanism of change in VACT-CP (hypothesis 3), we will analyze whether BPI-Interference subscale improvements are mediated by psychological flexibility after treatment and at 3-month and 6-month follow-ups. Similar to previous ACT process mediation procedures [53], structural equation modeling and a bias-corrected bootstrap approach will be used to examine the indirect effect of pain severity on pain-related functioning through pretreatment and posttreatment changes in psychological flexibility. We will model the main independent variable X (pain severity as measured by the BPI-Severity subscale), the mediator M (change from baseline to end of treatment in psychological flexibility as measured by the MPFI), and the main outcome variable Y (pain-related functioning as measured by the BPI-Interference subscale) at 3 months after intervention. A bias-corrected bootstrap procedure with 3000 bootstrap samples will be used to produce a 95% CI around the mediation effect estimate. A 95% CI excluding zero will be interpreted to be statistically significant at a $P<.05$ level. In accordance with previous mediation methods [54], mediation will be assumed demonstrated if paths X and Y and XY (the

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indirect effect) are statistically significant based on acceptable or adequate model fit. Model fit will be assessed using the chi-square goodness-of-fit statistic and approximate fit indices, including root mean square error of approximation, the goodness-of-fit index, the standardized root mean square residual, and the chi-square/*df*. We will repeat this analysis for posttreatment and 6-month time points as well. This analysis can provide further support for the mechanisms by which the ACT intervention works as well as evaluate the potential longevity of ACT process changes on pain-related functioning.

Additional data will be provided by the Client Satisfaction Questionnaire-8 and semistructured qualitative interviews with VACT-CP users (n=30) as well as by tracking website use information and calls or emails to research staff with concerns. Analysis of the postintervention interviews will be done using notes taken by one of the team members during the exit interview; interviews will also be audio recorded and transcribed. Study staff will apply qualitative analytic techniques to these data (eg, coding for and extracting major themes) to assess both barriers to and facilitators of the use of the VACT-CP system. A modified consensual qualitative research (CQR) approach [55] will be used to code the transcribed videos. CQR can be particularly useful in allowing a team of coders to identify themes arising in both structured and more open-ended interview moments. An initial codebook will be developed using coding based on the key activities and questions in the user testing protocol. These procedures are based, in part, on the successfully piloted interview procedures and script from the initial VACT-CP pilot study. Primary research staff will use the previous pilot codebook in identifying use, usability, and usefulness themes within the interviews. The initial codebook will be used by 2 to 3 coders throughout the data analysis process to foster multiple perspectives until consensus is reached among the coders about the meaning of the data. In addition, at least 1 auditor will check the work of the primary team of coders and serve to minimize potential bias. We will report the frequency of emerging domains and themes. Themes will then be categorized according to the following CQR groupings: general (includes all or all but 1 of the cases), typical (includes half or more of the cases up to the cutoff for general), and variant (at least 2 cases up to the cutoff for typical). We will use these data to discuss broader scientific and implementation-related barriers and facilitators for interventions for patients with chronic pain within the VA system. The themes generated by these data will be used to identify usability issues, perceived usefulness of VACT-CP, and potential areas for revision. The qualitative usability and usefulness information will be triangulated with quantitative data and incorporated into the primary outcome manuscript on VACT-CP efficacy.

Results

Participant recruitment began in January 2025 and is expected to be completed by January 2027. Data collection is expected to be completed by June 2027, and primary data analyses are expected to be completed by early 2028.

Discussion

Potential Applications

A substantial gap remains in the availability of at-home pain self-management treatment options to help veterans increase their functioning and quality of life in the context of their chronic physical, psychological, and social concerns. The VACT-CP program, available at any time and to any veteran with internet and computing technology access, is innovative in its approach and has several potential applications. First, VACT-CP is the only VA-developed and tested website program for chronic pain support and has the potential to improve access to chronic pain treatment for veterans. Further, unlike many online self-management apps and online programs within VA, the VACT-CP treatment uses ACT as an evidence-based alternative to traditionally available and in-person chronic pain treatments (eg, Cognitive Behavioral Therapy for Chronic Pain) to extend treatment targets to pain acceptance and value-based living. Thus, VACT-CP has the potential to add needed emphasis to at-home treatment targets, such as pain-related functional improvement and quality of life. In addition, VACT-CP is uniquely interactive, as the 7-module program is guided by the novel use of an ECA, “Coach Anne,” who can provide user-centered feedback and tailoring through interactive dialogue, assessments, and exercises. The focus on interactive, personalized care has the potential to enhance treatment engagement for veterans. Finally, consistent with VA priorities and clinical guidelines, VACT-CP could improve access to a nonpharmacological pain management treatment option that is readily available to veterans experiencing chronic pain to allow them to gain and sustain a self-care and treatment skill set that applies to both chronic pain and common co-occurring conditions (eg, depression, anxiety, and substance misuse).

Limitations and Future Directions

If the results of the study are positive, the PI will aim to further study the effectiveness and implementation of VACT-CP nationally through an effectiveness-implementation hybrid type 1 trial to evaluate the implementation context during the planned effectiveness trial. Limitations for this efficacy trial include a lack of more rural VA settings in relation to recruitment activities, inability to include veterans with certain physical impairments (eg, the inability to see and hear the virtual coach), and not including veterans with comorbid substance use disorders, which are common in this population. However, these areas will be expanded upon in future research and revised iterations of the VACT-CP website, should the efficacy trial provide preliminary evidence suggesting further improvement and expansion of this program is warranted. Data from this trial will be disseminated via publications, presentations, and VA-required clinical trials reporting.

Conclusions

Up to 56% of veterans may be experiencing chronic pain with devastating impacts on their quality of life. Despite this, many veterans may struggle to access pain-related services and, in particular, behavioral interventions for chronic pain. Online interventions have the potential to better fit veteran needs and preferences with in-the-moment content tailoring, asynchronous

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interactions, and connection to up-to-date online resources for additional pain management exercises and VA resources. This efficacy study of VACT-CP as an online, interactive intervention for ACT for chronic pain could serve to improve veteran care by (1) shifting focus away from pain-related symptoms while emphasizing valued domains of living among veterans with chronic pain, (2) improving quality of life, and (3) improving long-term outcomes associated with pain, such as reduced use of health care services and sick leave.

Acknowledgments

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

EDR, HLG, AAH, BE, MMK, CMG, TPH, KB, and TB contributed to the protocol conception and study design. EDR, HLG, and CMG wrote the initial draft of the manuscript. NRW, AAH, BE, MMK, TPH, KB, and BT participated in the manuscript writing. All authors read and approved the final version of the manuscript. Data management activities will be conducted by EDR, KB, and CMG.

Conflicts of Interest

MMK receives royalties from New Harbinger Publications for a book on acceptance and commitment therapy for addictions. All other authors declare no conflicts of interest.

Multimedia Appendix 1
SPIRIT checklist.
[PDF File (Adobe PDF File), 147 KB - resprot_v14i1e70601_app1.pdf]

Multimedia Appendix 2
Participant information sheet.
[PDF File (Adobe PDF File), 121 KB - resprot_v14i1e70601_app2.pdf]

Multimedia Appendix 3
Exit interview protocol.
[PDF File (Adobe PDF File), 165 KB - resprot_v14i1e70601_app3.pdf]

Multimedia Appendix 4
Peer review report by RRD2 - Musculoskeletal Health & Function, Rehabilitation Research and Development Parent IRG Office of Research & Development (Department of Veterans Affairs, USA).
[PDF File (Adobe PDF File), 141 KB - resprot_v14i1e70601_app4.pdf]

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Abbreviations

ACT: acceptance and commitment therapy
BPI: Brief Pain Inventory
cIRB: Central Institutional Review Board
CPAQ: Chronic Pain Acceptance Questionnaire
CQR: Consensual Qualitative Research
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition
ECA: embodied conversational agent
MPFI: Multidimensional Psychological Flexibility Inventory
PI: principal investigator
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
VA: US Department of Veterans Affairs
VACT-CP: Veteran Acceptance and Commitment Therapy for Chronic Pain
VR-36: Veterans RAND 36-Item Health Survey

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Protocol

Effect of a Mediterranean Diet Adapted to the Mexican Population on Indicators of Metabolic Risk in Patients With Obstructive Sleep Apnea: Protocol for a Randomized Controlled Trial

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Abstract

Background: Obstructive sleep apnea (OSA) is characterized by episodes of intermittent airway obstruction during deep sleep or REM (rapid eye movement). It is associated with cardiometabolic risk diseases. The base treatment is continuous positive airway pressure (CPAP), to which not all patients are able to adapt. The Mediterranean diet (MD) has proven to be effective in reducing cardiovascular risk markers; however, it must be adapted to different populations. Among patients with OSA, it can effectively reduce clinical entity and cardiometabolic risk, while improving quality of life and sleep.

Objective: We aimed to evaluate the effect of an MD adapted to the Mexican diet versus a standard nutritional treatment on metabolic risk indicators in patients with OSA.

Methods: A randomized, 2-arm clinical trial will be conducted with patients with OSA from the Hospital, Mexican Social Security Institute (Instituto Mexicano del Seguro Social) in Mexico. Patients will be randomly included in the group with MD adapted to Mexican foods. With a personalized diet plan adapted from the Mediterranean diet, prototype menus with Mexican foods adapted from the MD will be included for a higher consumption of fruit, vegetables, fiber-rich cereals, and reduction of red meat. In addition to an illustrative plate to improve adherence. The standard diet (SD) group will receive standardized nutritional counseling for patients with OSA. Fasting blood samples will be drawn after 6 and 12 months to identify glucose levels and lipid profiles. Anthropometric and body composition measurements will be taken, and adherence to diet will be recorded after 3, 6, and 12 months. Sleep quality, physical exercise, and life quality will be recorded basally and after 12 months. A multivariate logistic regression analysis will be performed, including the achievement of metabolic indicator control goals, sleep quality, and quality of life as outcome variables. This analysis will be adjusted for other variables that may be statistically significant in the bivariate analysis, such as sex, age, and comorbidities, among others. Statistically significant differences between groups will be considered when the value of $P<.05$.

Results: The protocol was authorized in 2024, and funding is being sought for patient follow-up. All 120 patients (60 per group) will be included in 2025; recruitment will begin in March 2025. The clinical trial is expected to be completed in April 2026.

Conclusions: The results of this study will contribute to evaluate the effect of a nutritional intervention adapted to patients with OSA, seeking to reduce cardiovascular risk indicators in patients, improve their clinical condition, reduce OSA symptoms, and improve patients' quality of life.

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KEYWORDS
obstructive sleep apnea; obesity; hyperglycemia; hypercholesterolemia; Mediterranean diet; nutritional therapy

Introduction

Obstructive sleep apnea (OSA) is a disease characterized by the partial or total obstruction of airways during sleep [1]. The global prevalence of OSA has been reported to be between 9% and 38%, considering an apnea-hypopnea index (AHI) of ≥5 events per hour; it is higher in men, those with an advanced age, and with urban dwelling [2]. In Mexico, an elevated risk of OSA of 27.3% in adults has been reported, and this risk increases as the BMI is higher. [3]

OSA is estimated to be present in 60% of patients with metabolic syndrome, which can also include, diabetes, obesity, insulin resistance, systemic arterial hypertension, and dyslipidemia [4]. Overweight and obesity contribute to higher amounts of fat in the dilator muscles of neck and tongue, thus increasing OSA. A positive correlation has been found between severe OSA and obesity in adult patients [5].

Daytime symptoms of patients with OSA include excessive daytime drowsiness, complaints of unrefreshing sleep, morning headaches resolved with breathing regulation, irritability, apathy, depression, difficulty to focus, and memory loss, among others [6]. The treatment of choice for patients with OSA, continuous positive airway pressure (CPAP), generates positive air pressure to reduce negative intrathoracic and upper airway pressure, limiting the repetitive hypoxia cycle in the patients; still, adherence is limited [7].

Weight loss in patients with OSA is directly proportional to reduced respiratory events measured by AHI. This was reported in 89 men with OSA who reduced body weight by 7%, fat by 19%, and visceral adipose tissue by 26%, in addition to changes in lifestyle. As a result, OSA was reduced by 15% and 45% of the patients did not need CPAP anymore [8]. Evidence indicates the Mediterranean diet (MD) is widely cardioprotective and contributes to lowering cardiovascular risk and even death [9-11]. The PREDIMED study reported that an MD, mostly consisting of fruit, vegetables, white meat, and dried fruit or olive oil, reduced cardiovascular event symptoms in patients compared to those who followed a controlled diet. The MIMOSA (Mediterranean Diet/Lifestyle Intervention in Obstructive Sleep Apnea) study conducted with 187 adults with OSA showed that an intervention with MD or Mediterranean style had a better effect on improving cardiometabolic indicators than a standard diet (SD) [12]. In addition, the authors report a greater reduction in metabolic syndrome with MD in patients with OSA, even when adjusting fluctuations in body weight as compared with a Mediterranean style or an SD [13,14]. Fewer insomnia episodes have been linked to greater adherence to MD in patients with OSA and insomnia [15]. Although it has been shown to be cardioprotective and improve metabolic indicators, MD must be adapted to other countries. In Mexico, there is scarce evidence on the modification of MD to the Mexican diet and its cardiometabolic effect in patients with OSA. Therefore, the aim of this study is to evaluate the effect of a MD adapted to Mexican eating habits versus a standard nutritional treatment on metabolic risk indicators in patients with OSA.

Methods

Study and Population Assignment

A randomized, 2-arm clinical trial will be conducted with patients with OSA from the Regional Hospital, Mexican Social Security Institute (Instituto Mexicano del Seguro Social [IMSS]) in Mexico City with a 12-month follow-up.

The sample size was calculated using the formula for difference in proportions, considering a CI of 95% and a power of 80%. Weight loss is expected in 58% of the sample corresponding to the group given an MD adapted to the Mexican population and in 30% of the group consuming a standard diet, as previously reported in the literature. A sample size of 49 patients per group was obtained and, considering losses of 20%, the total number of patients will be 120 [16].

Selection Criteria

Inclusion Criteria

Men and women aged 30-70 years, diagnosed with moderate and severe OSA will be included. Textbox 1 describes the inclusion and exclusion criteria.

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Textbox 1. Selection criteria for patients with obstructive sleep apnea included in the study.

Inclusion criteria

- Men and women
- Aged 30-70 years
- Diagnosed with moderate or severe obstructive sleep apnea
- Use of continuous positive airway pressure (CPAP)

Exclusion criteria

- Anatomic alterations of the nose, oropharynx, or maxilla
- Chronic kidney disease under substantive renal function treatment
- Decompensated heart failure
- Any type of cancer
- Neurological disease
- Diagnosis of depression
- Refractory dyslipidemia
- Familial dyslipidemia
- Surgeries in the last 6 months
- BMI>40 kg/m²

Study Procedures

The study design is a randomized, 2-arm clinical trial in patients with OSA. The patients will be referred by a specialist from the sleep clinic at the Hospital where the study will take place. Once the inclusion criteria are checked, the study, risks, and benefits will be explained to the patients, questions will be answered by the researchers, and the patients will sign informed consent to participate in the trial.

Software will be used for randomization, and patients will be assigned to either of the following groups: MD with Mexican food and SD.

Sociodemographic and Clinical Variables

The medical researcher will conduct a clinical interview to obtain sociodemographic data, pathological background, present comorbidities, and current pharmacological treatment.

A medical questionnaire will be applied by the research team to collect sociodemographic data, pathological-clinical background, and nonpathological information. The patients will answer questions regarding age; clinical history, including pathological and nonpathological background; and pharmacological and nonpharmacological treatments.

Arterial Blood Pressure Measurement

Arterial blood pressure will be measured by the medical team participating in the study, using a pregauged blood pressure cuff, and no smoking nor consumption of coffee or cola soft drinks in the previous 30 minutes. The patient will sit in a chair, with the back supported and feet straight on the floor. The left arm will be uncovered and supported on a flat table at heart level. The air chamber (balloon) must cover at least three-fourth of the arm's length and at least 80% of its circumference.

Sleep Variable Measurement

During the first consultation at the Sleep Clinic, measurements of AHI and oxygen desaturation index will be recorded using CPAP, as part of the routine studies patients with OSA undergo. The study takes 7-8 hours.

Polysomnography

Polysomnography channels will be set up; they include electroencephalographic derivations and electrooculograms, electromyograms of the chin and legs, respiratory flow signals from the thermistor and nasal cannula, respiratory effort signals, continuous oxygen monitoring, electrocardiogram, and the patient's body position. The study, lasting 4-6 hours, will be carried out once and is part of a series of tests that patients with OSA undergo.

Biochemical Indicator Measurement

Venous blood samples will be taken after fasting for 8-10 hours to measure glucose, lipid profile (cholesterol, triglycerides, high-density-lipoprotein cholesterol, and low-density-lipoprotein cholesterol). Measurements will be recorded during the first consultations and after 6 and 12 months.

Anthropometric and Body Composition Measurements

Body composition will be measured by bioimpedance, using an InBody 120 composition analyzer, to obtain fat percentage, fat mass, lean mass, and total body water. Body weight and height will be measured with the same analyzer. The patient must wear as little clothing as possible, without any metal objects (bracelets, earrings, rings, belts, and others). The patient will face forward, place their feet on the metal plates, and extend their arms forward to hold the metal bars at a 90º angle. Height will be measured using an InBody ultrasound stadiometer while the patient is in an upright anatomical position. Anthropometry

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will be recorded by 2 nutritionists previously standardized, using the method proposed by Habitch and according to the specifications previously [17,18]. The BMI will be obtained from height and weight.

Waist circumference will be measured using a measuring tape halfway between the lowest rib and the top of the right hipbone. The average value of the second and third measurements will be used for analysis. Measurements will be taken during the first consultation and after 3, 6, and 12 months.

Sleep Quality Measurement

Sleep quality will be measured using the Epworth Sleepiness Scale (ESS), which evaluates 8 items, each from 0 to 3 points, where 0 indicates the patient would never nod off, 1 indicates a small probability of nodding off or falling asleep, 2 indicates a moderate probability of nodding off or falling asleep, and 3 indicates a high probability of falling asleep. A score from 1 to 6 on the scale is considered regular sleep, one from 7 to 8 points is considered mild sleepiness, and one from 9 to 24 points at a pathological (abnormal) drowsiness [19].

Quality of Life Measurement

Quality of life will be measured using a Quebec Sleep Questionnaire (QSQ), which has been validated for the Hispanic population. It contains 32 items focused on measuring daily sleepiness (7,16,20,27), daytime symptoms (1,10,11,14,17,18,19,26,29), nighttime symptoms (4,9,21,25,28,30), emotions (5,6,8,15,24), and social interactions (2,3,12,13). The questionnaire will be applied basally and after 12-month follow-up [20].

Physical Activity Measurement

To measure physical activity, the International Physical Activity Questionnaire will be applied. The questionnaire contains 7 items that asses at the physical activity carried out in the past 7 days (hours, minutes, and days of the week). Physical activity will be classified after considering the metabolic equivalent of task values according to the activity (measurement unit of the test). Physical activity is classified in 3 categories: low, moderate, and high (25). It will be measured at the beginning of the trial, and after 6 and 12 months [21].

Nutritional Intervention Description

Group With MD Adjusted Using Mexican Food

The patients in the MD group will be given a normocaloric, personalized diet with the following distribution, 15%-20% protein, 50%-55% carbohydrates, 25%-30% fats, and <7% saturated fats, according to the recommendations for patients with OSA. The Mifflin-St Jeor equation will be applied to calculate the caloric requirements. At the beginning of the intervention, 24-hour reminders will be established to know dietary habits and adjust the diet to the patients' preferences, customs, and budget. A dietary plan will be designed using equivalent foods. The equivalents will be chosen from the Mexican system of equivalent foods, considering portions, amounts, and preparation of each food. In it, typical foods of the Mexican diet can be found, along with their most common preparation and presentation; for instance: grilled, fried, baked, and uncooked (raw), among others [22].

The MD includes a variety of typical foods from European countries. Therefore, it is necessary to analyze their nutritional characteristics before adapting the diet to Mexican citizens, particularly those patients with OSA taking part in this study. After reviewing the literature, foods belonging to the Mexican diet were identified to show similar characteristics as those in the MD. As part of the adaptation, a comparative chart showing European and Mexican foods was created using the major food groups. Table 1 shows the most representative foods and their adaptation to the Mexican diet, which is explained simply to the patients.

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Table 1. Mediterranean-Mexican food: proposal for the adaptation of the Mediterranean diet with Mexican food.

Food group/equivalent	Mediterranean diet	Foods in Mexico	Suggested portions and frequency of consumption
Fruit and vegetables	• Fruit: grapes, watermelon, strawberries, oranges • Vegetables: artichokes, asparagus, lettuce, bell peppers, spinach, broccoli	• Fruit: guava, orange, mango, mamey, papaya, blackberry, banana • Vegetables: nopal, chayote, cucumber, mushrooms, purslane, quelites, chard, watercress, zucchini, bell pepper, green beans, jicama	• Fruit: 1-2 servings per main meal • Vegetables: >2 servings per main meal • Total: at least 5 servings per day
Healthy Fats	• Olive oil, olives, hazelnuts, almonds	• Avocado, nuts, peanuts, corn oil, sunflower oil, pumpkin seeds, pistachios, sesame seeds	• Olive oil: in every main meal • Nuts, seeds, olives, avocado: 1-2 servings per day
Cereals	• Whole wheat bread, pasta, rice, couscous	• Whole wheat bread, pasta, rice, corn tortilla, oats, amaranth	• Bread, pasta, rice, tortilla, oats: 1-2 servings per main meal
Tubers	• Potatoes, sweet potatoes	• Potatoes, sweet potatoes, yuca	• Potatoes, sweet potatoes, yuca: <3 servings per week
Legumes	• Lentils, chickpeas, beans, peas	• Lentils, beans, chickpeas	• Lentils, beans, chickpeas: >2 servings per week
Animal-based foods	• Fish and seafood: salmon, cod, squid, mussels, shrimp, oysters • Low-fat dairy: yogurt, cheese, milk • White meat: chicken, hen, turkey • Eggs • Red and processed meats: beef, pork, cold cuts	• Fish and seafood: tuna, sardines, trout, red snapper, tilapia • Low-fat dairy: yogurt, cheese, milk, cottage cheese, curd • White meat: chicken, hen, turkey • Red and processed meats: beef, pork, cold cuts	• Fish: >2 servings per week • Low-fat dairy: 2 servings per day • White meat: 2 servings per week • Eggs: 2-4 servings per week • Red meat: <2 servings per week • Processed meats: <1 serving per week

This table provides examples of foods characteristic of the general Mexican population. It may vary according to the region of Mexico, seasonality, and accessibility for each patient.

In addition to the equivalency chart including the food groups of both diets, a healthy eating plate MD (see Figure 1), was created as the strategy has been effective in Mexico, where the main foods for a healthy diet are presented in a plate [23]. From this strategy, a plate of MD in Mexico was designed, adapting foods that must be consumed according to the region, culture, preferences, and budget, considering easy access for patients with OSA.

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Figure 1. Mediterranean diet plate adapted with Mexican food.

To reinforce the meal plan given to this group, preestablished menus were designed containing foods typical in the MD, such as fruit, vegetables, whole grains, cereals, and white meat. The menus also promoted the intake of vegetable oils and common dried fruit in Mexico. The menus were designed to reach 1200, 1400, 1600, 1800, 2002, and 2200 calories. This group will also continue their common treatment with their physician or group of health care professionals as usual.

Assessment of Adherence to the MD With Mexican Food

Adherence to MD will be measured using the 14-point Mediterranean diet adherence screener (MEDAS) questionnaire, consisting of 12 questions on the consumption frequency of foods and 2 questions on intake habits of foods considered part of the MD [24]. In this instrument, each question is scored 0 or 1. One point is given for using olive oil as the main source of fat for cooking, preferring white meat over red meat, or for consuming (1) 4 or more spoons of olive oil per day, (2) 2 or more vegetable portions per day, (3) 3 or more pieces of fruit per day, (4) less than 1 portion of red meat or sausage per day, (5) less than 1 portion of animal fat per day, (6) less than 1 sugary drink per day, (7) 7 or fewer glasses of red wine per week, (8) 3 or more portions of legumes per week, (9) 3 or more portions of fish per week, (10) fewer than 2 cakes or commercial baked goods per week, (11) 3 or more portions of nuts per week, and (12) a plate of traditional tomato, garlic and onion sauce twice or more a week. The total score ranges between 0 and 14 and allows to identify 3 levels of MD, low (0-6), medium (7-8), and high (≥9).

SD Group

Patients in the control group will be given a normocaloric diet with the following energy distribution: 15%-20% protein, 50%-55% carbohydrates, 25%-30% fats, and <7% saturated

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fats, per the guidelines for adult patients with OSA. The Mifflin-St Jeor equation will be applied to identify the caloric requirements of each patient. The energy needs and distribution will be administered as individual nutritional guidance regarding sleep hygiene measures and type of diet for weight loss according to age, sex, current body weight, and present comorbidities. At the beginning of the intervention, 24-hour reminders will be set to know the daily diet. Patients will be given a pamphlet to reinforce healthy eating, and they will continue nutritional consultations with their physicians. This group will also continue the traditional treatment with their physician or group of health care professionals as usual.

Follow-Up and Study Procedures

At the beginning of the trial and after 12 months, laboratory data (glucose and lipid profiles), clinical data, arterial blood pressure records, anthropometry, body composition, and dietary records of the previous 3 days will be obtained, along with the quality of life and sleep survey. All the patients will receive the written results and explanation in each clinical consultation, as shown in Figure 2.

Figure 2. Follow-Up and Study Procedures.

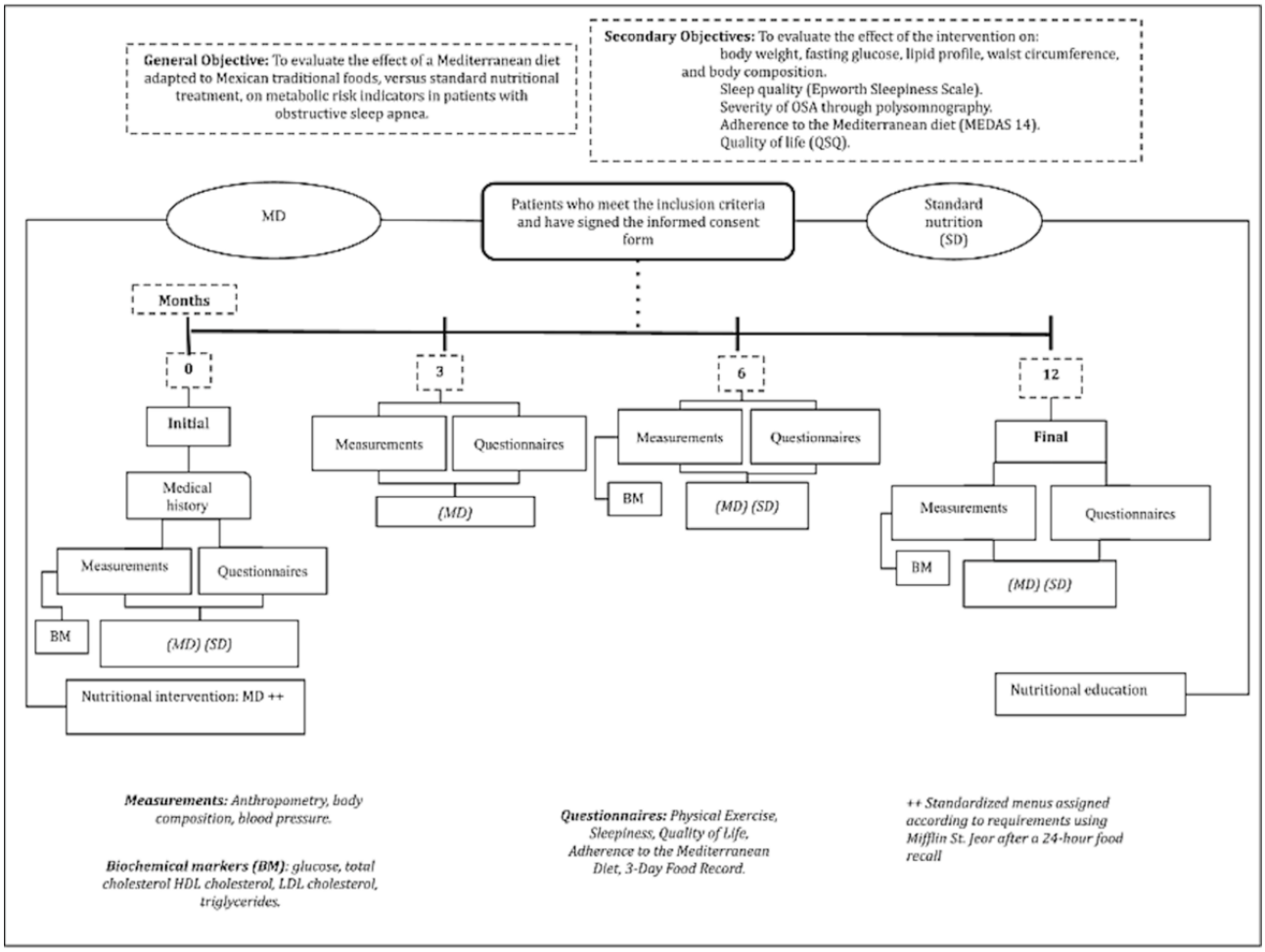

Follow-up will continue after 3, 6, and 12 months for MD and 6 and 12 months for SD diet participants, who will attend a consultation with a nutritionist and medical team. In order to measure the adherence to the diet in both groups, the patients will register the 3 days before their clinical visit, 2 registrations from Monday to Friday, and one on weekends. At each visit, nutritional guidelines will be given to improve adherence to the nutritional intervention. The study follow-up is shown in Table 2.

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Table 2. Study follow-up and procedure in patients with obstructive sleep apnea in both groups.

Time collection	Baseline	3 months	6 months	12 months
Collection of sociodemographic data	MD[a] and SD[b]	—[c]	—	—
Medical history	MD and SD	—	—	—
Medical evaluation	MD and SD	—	MD and SD	MD and SD
Biochemical data	MD and SD	—	—	MD and SD
Arterial blood pressure and Anthropometric and body composition measurements	MD and SD	MD	MD and SD	MD and SD
Sleepiness with Epworth sleepiness scale	MD and SD	MD and SD	MD and SD	MD and SD
Quality of life with Quebec Sleep Questionnaire (QSQ)	MD and SD	—	—	MD and SD
Physical activity with IPAQ[d] Questionnaire	MD and SD	—	MD and SD	MD and SD
Adherence to the diet intervention with records of the previous 3 days	MD and SD	MD	MD and SD	MD and SD
Adherence to the diet intervention with MEDAS[e] Questionnaire	MD and SD	MD	MD and SD	MD and SD
Phone call follow-up	—	SD	—	—

[a]MD: Mediterranean diet.

[b]SD: standard diet.

[c]Not applicable.

[d]IPAQ: International Physical Activity Questionnaire.

[e]MEDAS: 14-point Mediterranean diet adherence screener questionnaire.

Primary Outcomes

The primary objective of this clinical trial is to evaluate the effect of the MD adapted to the Mexican diet versus an SD treatment on metabolic risk indicators in patients with OSA (body weight, fasting glucose, lipid profile, WC, and body composition).

The secondary outcomes are to evaluate the effect of the intervention on:

1. Sleep quality through ESS.
2. Changes in quality of life through QSQ.
3. Adherence to nutritional therapy intervention through records of meals corresponding to previous and MEDAS questionnaires.

Statistical Analysis

The statistical analysis of the data will be carried out using SPSS (version 27; IBM Corp). The study population will be described using the background, clinical, and pathological variables to characterize the sample of participants with OSA. The Kolmogorov–Smirnov test will be used to identify the distribution of quantitative variables. For variables with normal distribution measures of central tendency and dispersion will be estimated. For variables with a free distribution mean and IQR will be used. Measures of frequency and percentages will be used for sociodemographic and clinical qualitative variables, as well as those of patient proportion with and without glycemic control, and with and without cognitive impairment. A chi-square test will be used to compare the effect of MD versus SD on parameters of control and uncontrol of metabolic risk indicators. Depending on the data distribution, a Student *t* test will be used to compare quantitative variables with parametric distribution between groups, and a Mann-Whitney *U* test will be conducted for free-distribution variables. A multivariate logistic regression analysis will be performed, including the achievement of metabolic indicator control goals, sleep quality, and quality of life as outcome variables. This analysis will be adjusted for other variables that may be statistically significant in the bivariate analysis, such as sex, age, and comorbidities, among others. Statistically significant differences between groups will be considered when the value of $P<.05$.

Ethical Considerations

This clinical trial was submitted to the Ethics and Research Committee at HGR 1 “Dr Carlos MacGregor Sánchez Navarrro,” IMSS (registry number R-2024-3609-055). The protocol was reviewed twice for the corresponding modifications related to methodological aspects. The researchers will provide each participant with written consent, describing all the procedures of the clinical trial, the risks, and benefits; this consent form clarifies that the patient is free to not participate or to withdraw from the research without affecting their care at the institution. All participant information collected in the research will be kept confidential, and data will be reported anonymously. Participants in this research will not receive any financial compensation.

The protocol was registered at ClinicalTrials.gov (NCT06782737). The aim of the study, risks, and benefits will be explained in detail to the participants who will freely chose to take part in the trial. They will provide written consent describing each procedure in the trial and respect to information privacy. All the researchers participating receive annual training regarding better clinical practices related to research.

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Results

The protocol was approved in 2024, and funding is being sought for patient follow-up, patient inclusion, and execution of RCT in 2025. Currently, 50 patients have been recruited, 28 in the group with a Mediterranean Diet Adjusted Using Mexican Food and 27 in the group with an SD. The data analysis with the expected results will be carried out in February 2026.

It is expected that there will be differences in the intervention groups of patients with OSA enrolled in the study: measurement of blood pressure, measurement of sleep variables, measurement of biochemical indicators, anthropometric and body composition measures, measurement of sleep quality, and measurement of quality of life. We expect to find in patients with MD a higher proportion of cardiometabolic indicators in control, compared with patients in the group with SD. We expect to find differences in multivariate analysis in control goals of cardiometabolic indicators, quality of sleep and quality of life of patients.

Discussion

Anticipated Findings

This protocol aims to measure the impact of an MD adapted to the Mexican population on cardiovascular risk indicators, such as glucose, lipid profile, body weight, and blood pressure in patients with OSA. In addition, as secondary objectives we seek to evaluate the effect of the MD on sleep quality and quality of life, as well as the improvement in diet quality.

There is enough evidence on the cardioprotective effect of MD, which is not only proven in European countries: there are clinical trials evaluating MD adapted to the Chilean population suffering metabolic syndrome [25]. It has been proven that interventions aimed at lifestyle improve AHI, showing a reduction by –4.55 events per hour and improving weight and BMI among patients with OSA; however, no effect on sleep and life quality has been found [26]. Despite the ample evidence supporting the cardioprotective benefits of the MD, its evaluation has been predominantly focused on patients with obesity, diabetes, and, to a lesser extent, patients with OSA. The impact of adapting the MD diet with food in Mexico has been examined to a lesser extent.

The relationship between cardiometabolic risk factors and sleep duration has been previously reported in 47 patients with OSA in a rural community in the southeastern United States. The authors reported that shorter sleep duration was associated with an increased risk of hypertension, obesity, and impaired metabolic indicators. [27]. The results of this study suggest that an MD intervention with a preference for fruit, vegetables, high-fiber cereals, and white meat protein may improve cardiometabolic indicators.

Obesity and related diseases, like diabetes, hypertension, and dyslipidemia, represent a greater risk for patients with OSA. Then, CPAP treatment combined with weight loss is an effective strategy to reduce cardiovascular risk [28]. Adaptation to the patient's tastes, customs, and budget is necessary to improve adherence to MD. This study seeks to adequate MD to the Mexican diet to make it accessible, since typical MD includes foods considered high-priced for the population receiving care at public health care institutions in Mexico.

Furthermore, improvement in cardiometabolic indicators, such as glucose, lipid profile, and weight loss, is likely. Patients are expected to lose 5%-10% of their initial body weight, as reported by similar interventions [12].

Sleep quality in patients with OSA could improve after the proposed nutritional intervention, while the number of obstructive respiratory events could be reduced given that the size of the oropharyngeal lumen is reduced because of body fat loss [29]. Besides the reduction in obesity, the diet is expected to improve fasting glucose, arterial blood pressure, and dyslipidemia in patients with OSA taking part in the trial. We also expect this trial to positively affect daytime drowsiness in the patients and improve their quality of life. This clinical trial would be one of the few conducted in Mexico with patients with OSA where the implementation of low-cost strategies aims at improving cardiometabolic indicators and quality of life of those patients with OSA who receive care at public health care institutions in Mexico.

Among the limitations of the present study, adherence to the MD could be found; therefore, it is relevant to adapt the diet to the economic resources, habits, and customs, which allows an adequate adherence to the MD. A personalized diet and a timely follow-up will be provided to reinforce adherence to the nutritional intervention. It has also been shown that the use of CPAP is limited in the population with OSA, since they do not consider it necessary for their condition or it is difficult to use it to sleep adequately [30]. One of the potential limitations of the study is the use of a self-reported tool to collect sleep quality information. There will be limitations to the generalizability of the effect of the intervention, as it will be a single-center study. In this sense, as one of the main variables is to measure the improvement in sleep quality, this could be improved with the use of CPAP, so its use will be recorded in the follow-up visits, to include it in the multivariate analysis.

Conclusion

This study seeks to contribute to improving the diet of patients with OSA, thus enhancing the cardiometabolic risk indicators and reducing the patients' risk of cardiovascular diseases. In addition, we expect to improve the patients' sleep quality and lifestyle. We consider this intervention will be useful to create a proposal including an MD adapted to Mexican habits that improve the dietary needs of patients with OSA and similarly those of patients with diabetes, obesity, hypertension, and other comorbidities.

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Acknowledgments

The authors would like to thank the authorities at Hospital Regional No 1 “Dr Carlos MacGregor Sánchez Navarro” for providing the conditions to carry out this study.

Data Availability

The datasets generated or analyzed during this study are not publicly available due (the data is confidential) but are available from the corresponding author on reasonable request.

Authors' Contributions

GT contributed to conceptualization and writing of the original draft. MS was involved in methodology and investigation. EL contributed to methodology and supervision. FF participated in methodology and investigation. LV was responsible for conceptualization, writing the original draft, and writing—review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT guidelines.
[PDF File (Adobe PDF File), 199 KB - resprot_v14i1e72513_app1.pdf]

Multimedia Appendix 2
Peer review report by the Research Committee of the Hospital Sede Instituto Mexicano del Seguro Social.
[PDF File (Adobe PDF File), 1482 KB - resprot_v14i1e72513_app2.pdf]

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Abbreviations

AHI: apnea-hypopnea index
CPAP: Continuous positive airway pressure
ESS: Epworth Sleepiness Scale
IMSS: Instituto Mexicano del Seguro Social
MD: Mediterranean diet
MEDAS: Mediterranean diet adherence screener
MIMOSA: Mediterranean Diet/Lifestyle Intervention in Obstructive Sleep Apnea

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OSA: obstructive sleep apnea
QSQ: Quebec Sleep Questionnaire
SD: standard diet

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Protocol

Effects of a Multidisciplinary Intervention on Fatigue in Lymphoma Survivors With Chronic Fatigue: Protocol for a Randomized Controlled Trial (REFUEL)

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Abstract

Background: Chronic fatigue (CF) is a highly disabling late effect after cancer, affecting 25% to 40% of lymphoma survivors years after cancer treatment. There is a lack of randomized controlled trials testing interventions to reduce fatigue levels among survivors with CF.

Objective: The primary aim of the Randomized Controlled Trial in Chronically Fatigued Lymphoma Survivors (REFUEL) is to examine the effects of a multidisciplinary intervention on the level of fatigue among lymphoma survivors with CF before and immediately after the intervention (3 months after randomization). Secondary aims are to (1) investigate the effects of the intervention on the level of fatigue 6 and 9 months after randomization and the effects on health-related quality of life (HRQoL); other patient-reported outcome measures; and physical fitness 3, 6, and 9 months after randomization; (2) evaluate the cost-utility of the intervention; (3) examine the effect of the intervention on HRQoL among the survivors' partners; and (4) investigate the

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long-term perceived benefits and daily use of acquired self-management strategies, as well as measure changes in fatigue, daily functioning, HRQoL, mental health, and work-life balance management within each group at 1- and 2-year follow-ups.

Methods: The REFUEL trial is a 2-armed randomized controlled trial. Lymphoma survivors (2-12 years after diagnosis) with CF are randomly allocated to a 12-week multidisciplinary intervention including patient education, physical exercise, a cognitive behavioral therapy–based group program, and individual nutrition counseling or to usual care. Fatigue is measured by the Chalder Fatigue Questionnaire. Other patient-reported outcome measures are measured by validated questionnaires (eg, the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire, the Patient Health Questionnaire-9, and the Generalized Anxiety Disorder-7). Cardiorespiratory fitness is measured as peak oxygen consumption during a cardiopulmonary exercise test or indirectly using a modified Balke treadmill protocol. Muscle strength is assessed by push-ups and leg press. The primary analyses will be performed using a generalized linear mixed model for repeated measures, with an intention-to-treat approach.

Results: A total of 150 survivors were included from December 2021 to March 2023. Three-month postrandomization assessments were completed in June 2023 and 2-year follow-up assessments were completed in June 2025.

Conclusions: The REFUEL trial will provide new and highly needed scientific evidence about the effects of a multidisciplinary intervention on the level of fatigue and secondary outcomes regarding HRQoL aspects among lymphoma survivors with CF.

Trial Registration: ClinicalTrials.gov NCT05130099; https://www.clinicaltrials.gov/study/NCT05130099

International Registered Report Identifier (IRRID): DERR1-10.2196/69336

(JMIR Res Protoc 2025;14:e69336) doi:10.2196/69336

KEYWORDS

cancer; lymphoma; late effects; chronic fatigue; patient education; physical exercise; cognitive behavioral therapy; nutritional counseling

Introduction

Background

Cancer-related fatigue, defined as "a subjective sense of physical, emotional, and/or cognitive tiredness or exhaustion related to cancer or cancer treatment that is not proportional to recent activity and interferes with usual functioning," is one of the most common and disabling symptoms occurring during and after cancer treatment [1,2]. If the symptom persists for 6 months or more, it is defined as chronic fatigue (CF) [3].

As lymphoma is often diagnosed at a young age and has a high cure rate, survivors have long life expectancies after extensive treatments [4]. Thus, they are at risk for a range of late effects, including CF [4-10], which affects 25% to 42% of lymphoma survivors several years after treatment [9-12]. CF causes distress and limitations in health-related quality of life (HRQoL) domains, including social participation and family and work life [13,14]. It may also place a considerable economic burden on the society due to reduction or loss of employment and health care costs [15,16]. Furthermore, CF often reduces the ability to perform daily responsibilities and life roles at home [13]. Therefore, partners and family caregivers may provide considerable amounts of practical and emotional support in daily life, which may influence their own HRQoL [17,18].

The etiology of CF remains complex and unclear, and no effective pharmacological treatments are available [19,20]. However, CF is associated with several modifiable behavioral factors, including low cardiorespiratory fitness, psychological distress, and obesity [10,20-22]. No previous study has examined whether a multidisciplinary intervention targeting combinations of these factors is effective in reducing fatigue among survivors with CF, which seems logical due to the complexity of the symptom.

So far, most studies have tested the effects of physical exercise or psychological interventions on cancer-related fatigue during and shortly after cancer treatment [19,23-25]. A few intervention studies also indicate that diets rich in fruits, vegetables, whole grains, and anti-inflammatory fatty acids may improve fatigue [26]. This implies that future trials may add nutritional counseling to exercise and psychological interventions [26].

Meta-analyses, including those on exercise and psychological interventions, have shown limited effect sizes on fatigue [27,28]. This may in part be attributed to studies with nonfatigued participants or studies without fatigue as the primary outcome, and thus interventions not being specifically designed to reduce fatigue. Therefore, studies on long-term cancer survivors with CF are needed [1,19,25,29]. Moreover, studies evaluating effects of lifestyle interventions among cancer survivors on the HRQoL of the cancer survivors' partners, and the cost-utility of such interventions, are lacking.

With this background, as well as our experiences from focus group interviews among cancer survivors with CF [30] and a feasibility study among lymphoma survivors [31], we planned a randomized controlled trial (RCT) in chronically fatigued lymphoma survivors (REFUEL). To the best of our knowledge, this is the first RCT to examine the effects of a multidisciplinary intervention, including patient education, physical exercise, a cognitive behavioral therapy (CBT)–based group program, and nutritional counseling on fatigue levels among lymphoma survivors experiencing fatigue years after treatment completion.

Aims

The primary aim of the REFUEL trial is to examine the effect of a multidisciplinary intervention on the level of total fatigue

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before and immediately after the intervention (3 months after randomization) compared to usual care among lymphoma survivors with CF. Secondary aims are to examine the effects of the intervention on (1) total fatigue level 6 and 9 months after randomization and measure the mental fatigue, physical fatigue, HRQoL, vitality, life satisfaction, symptoms of depression and anxiety, work-life, exercise competence, nutrition, and physical fitness 3, 6, and 9 months after randomization; (2) HRQoL among partners 3, 6, and 9 months after randomization; (3) cost-utility of the intervention; and (4) the participants' experiences (eg, perceived benefits and use of strategies in daily life) from participating in the intervention as a whole and from the individual components of the program along with measuring the levels of fatigue, HRQoL, depressive and anxiety symptoms, and work-life within each group at the 1- and 2-year follow-ups.

Methods

Study Design and Participants

The REFUEL trial is a 2-armed RCT comparing the effect of a 12-week multidisciplinary intervention to usual care among lymphoma survivors with CF. Participants in both groups undergo assessments before randomization (T0), 3 months after randomization (T1), 6 months after randomization (T2), and 9 months after randomization (T3). Randomization ends after T3 (the usual care group is offered a modified intervention). Selected patient-reported outcomes are assessed in the total sample at the 1- (T4) and 2-year (T5) follow-up.

Survivors diagnosed with Hodgkin lymphoma or aggressive non-Hodgkin lymphoma between 2010 and 2020; who had completed treatment with curative intent at Oslo University Hospital (OUS) or St Olavs Hospital, Trondheim University Hospital more than 2 years before inclusion; who were aged between 18 and 70 years at the time of inclusion; and meet the criteria for CF according to Chalder Fatigue Questionnaire (FQ) are eligible [32]. Additional inclusion and exclusion criteria are listed in Textbox 1.

Textbox 1. Inclusion and exclusion criteria for participation in the Randomized Controlled Trial in Chronically Fatigued Lymphoma Survivors trial.

Inclusion criteria

- Survivors of Hodgkin or aggressive non-Hodgkin lymphoma
- Diagnosed between 2010 and 2020
- Received treatment with curative intent
- ≥2 years since treatment completion
- Aged between 18 and 70 years at inclusion
- Chronic fatigue measured by the Chalder Fatigue Questionnaire
- Able to understand the Norwegian language
- Participation approval from an oncologist (assessed during the medical screening)

Exclusion criteria

- Diagnosis of central nervous system lymphoma
- Ongoing cancer treatment
- Second cancer
- Persisting fatigue >1 year before the cancer diagnosis
- Somatic or physical conditions (ie, severe heart failure or disease, lung disease, and use of wheelchair or crutches)
- Psychiatric or mental disorders (ie, dementia, severe depression, and schizophrenia; assessed during the medical screening)
- Use of stimulants for attention-deficit/hyperactivity disorder
- Substance abuse disorder

Recruitment

Potential eligible participants are identified through the Lymphoma Register at OUS or the treatment database Cytodose at St Olavs Hospital, and receive written study information, consent form, and Chalder FQ by mail. In the invitation letter, those who have experienced persistent tiredness or exhaustion and wish to participate are asked to fill out the FQ, sign the written consent form, and return this in a prepaid response envelope. Survivors who do not respond to the invitation within 3 to 4 weeks receive a reminder via an SMS text message. The study coordinator contacts all respondents by phone to provide additional details concerning study participation. Participants who do not meet the criteria for CF will be excluded after this initial screening.

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Medical Screening

Eligible consenting survivors undergo a digital medical screening with an oncologist. The medical screening includes a detailed medical history related to lymphoma treatment and fatigue, evaluation of somatic and psychological comorbidities, and review of medications. Blood samples are obtained before the screening to assess hematological status; electrolytes; liver, biliary, and kidney functions; hormones; metabolism; and nutritional deficiencies. Details about the medical screening and blood samples are given in Multimedia Appendix 1.

If the medical screening and blood samples reveal or indicate conditions that make it unsafe or difficult to carry out the physical tests or exercise program and require further medical follow-up, the survivor and their general practitioner are informed. Findings from survivors with symptoms indicative of heart disease are discussed with a cardiologist (KHT), and the survivors are referred for further examination if indicated before inclusion or exclusion. Survivors passing the medical screening are referred for baseline assessments before randomization.

Outcomes and Assessments

All outcomes are assessed at T0, T1, T2, and T3 (Figure 1). Selected patient-reported outcome measures (PROMS) and experience measures are assessed at T4 and T5 (15 and 27 months after randomization) in the whole sample. Outcomes, assessments, and time points of assessments are summarized in Table 1.

Figure 1. Study design. Participants in both groups undergo assessments before randomization (T0), at 3 months after randomization (T1), 6 months after randomization (T2), and 9 months after randomization (T3). Randomization ends after T3 (usual care group is offered a modified intervention). Selected patient-reported outcomes are assessed in the total sample at 1-year (T4) and 2-year (T5) follow-ups.

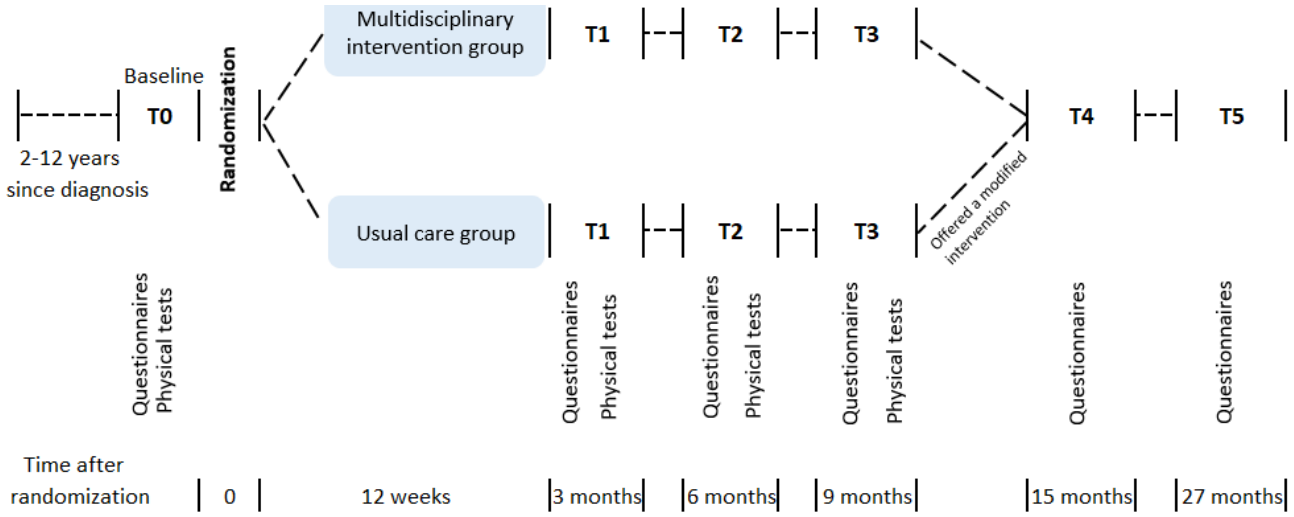

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Table 1. Outcomes, assessments, and time points of assessments in the Randomized Controlled Trial in Chronically Fatigued Lymphoma Survivors trial.

Outcome (assessment)	Time point of assessment					
	T0[a]	T1[b]	T2[c]	T3[d]	T4[e]	T5[f]
Among survivors						
Primary outcome						
Level of fatigue (Chalder FQ[g] [32])	✓	✓	✓[h]	✓[h]	✓[h]	✓[h]
Secondary outcomes						
Questionnaires						
HRQoL[i] (EORTC QLQ-C30[j] [33])	✓	✓	✓	✓	✓	✓
HRQoL and health status (EQ-5D [34])	✓	✓	✓	✓		
Subjective vitality (SVS[k] [35])	✓	✓	✓	✓		
Satisfaction with life (SWLS[l] [36])	✓	✓	✓	✓		
Symptoms of depression (PHQ-9[m] [37])	✓	✓	✓	✓	✓	✓
Symptoms of anxiety (GAD-7[n] [38])	✓	✓	✓	✓	✓	✓
Work status (HUNT[o] [39])	✓	✓	✓	✓	✓	✓
Work ability (WAI[p] [40])	✓	✓	✓	✓	✓	✓
Perceived exercise competence (PCS[q] [41])	✓	✓	✓	✓	✓	✓
Diet (DIGIKOST-FFQ[r] [42-45])	✓	✓	✓	✓		
Physical tests						
Cardiorespiratory fitness and pulmonary function (CPET[s] or indirect cardiorespiratory fitness test[t])	✓	✓	✓[u]	✓[u]		
Leg strength (1 RM[v] in leg press)	✓	✓	✓	✓		
Upper body strength (maximum number of push-ups performed in 1 set)	✓	✓	✓	✓		
Additional measures (patient-reported experience measures)						
Perceived benefits of being part of the project (questions modified from the PasOpp survey[w] [46])					✓	✓
Perceived benefits of the 4 components of the intervention (self-made questions[w])					✓	✓
Use of experiences, strategies, and advice learned in the program (self-made questions[w])					✓	✓
Among partners						
HRQoL (RAND-36[x] [47])	✓	✓	✓	✓		
Global health or QoL (2 items; EORTC QLQ-C30 [33])	✓	✓	✓	✓		

[a]T0: before randomization.
[b]T1: 3 months after randomization.
[c]T2: 6 months after randomization.
[d]T3: 9 months after randomization.
[e]T4: 1-year follow-up (15 months after randomization).
[f]T5: 2-year follow-up (27 months after randomization).
[g]FQ: Fatigue Questionnaire.
[h]Fatigue levels at T2, T3, T4, and T5 are secondary outcomes.
[i]HRQoL: health-related quality of life.
[j]EORTC QLQ-C30: European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire.
[k]SVS: Subjective Vitality Scale.
[l]SWLS: Satisfaction With Life Scale.

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[m]PHQ-9: Patient Health Questionnaire-9.

[n]GAD-7: Generalized Anxiety Disorder-7.

[o]HUNT: Trøndelag Health Study.

[p]WAI: Work Ability Index.

[q]PCS: Perceived Competence Scale.

[r]DIGIKOST-FFQ: digital food frequency questionnaire.

[s]CPET: cardiopulmonary exercise test.

[t]Participants not able to travel to Oslo University Hospital for CPET are offered an alternative indirect treadmill test, administered by an instructor at a local training facility.

[u]Pulmonary function is not assessed at T4 and T5.

[v]RM: repetition maximum.

[w]Refer to Multimedia Appendix 2.

[x]RAND-36: Research and Development 36-item Short Form Health Survey.

Primary Outcome

Fatigue is measured by the Chalder FQ [32]. The FQ consists of 11 items, including a physical (7 items) and a mental (4 items) fatigue scale. Each item has 4 response categories scored from 0 to 3. The sum of the physical fatigue score (0-21) and mental fatigue score (0-12) provides the total fatigue score (0-33). Higher scores imply more fatigue. To identify cases with CF, scores of all 11 items (0-3) are dichotomized (0=0, 1=0, 2=1, and 3=1) [32]. CF is defined by a sum score ≥4 and fatigue duration for 6 months or more.

Secondary Outcomes

HRQoL is assessed by the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire [33]. This questionnaire includes 5 scales that measure function (physical, role, cognitive, emotional, and social function), 3 scales that measure symptoms (fatigue, pain, and nausea or vomiting), 6 scales that measure single items (dyspnea, insomnia, appetite loss, constipation, diarrhea, and financial difficulties) and a scale that measures the global health status and QoL. Items in the scales that measure function and symptoms are rated from 1 (not at all) to 4 (very much), while the global health status and QoL items are rated from 1 (very poor) to 7 (excellent). All scales and items are transformed to 0 to 100 scales according to the EORTC scoring manual. Increasing scores on functioning scales and global health status and QoL imply better functioning and QoL, while increasing scores on symptom scales and single items imply more severe symptoms [33].

Health status and HRQoL are measured by EQ-5D-5L [34]. EQ-5D-5L consists of the 5 dimensions: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. Each dimension has 5 severity levels that are described by statements appropriate to that dimension, coded from 1 (no problems) to 5 (unable to perform activities or extreme level of symptoms). The participants also rate their health status from 0 (the worst health you can imagine) to 100 (the best health you can imagine). The participants' health status and HRQoL measured by EQ-5D-5L will be used to assess the cost-utility of the intervention.

Life satisfaction is measured by the Satisfaction With Life Scale [35]. The scale consists of 5 items with statements regarding life satisfaction, scored from 1 (totally disagree) to 7 (totally agree), providing a sum score ranging from 5 to 35. An increasing score implies higher satisfaction with life.

Subjective vitality is measured by the 5-item version of the Subjective Vitality Scale [36]. The scale consists of 5 items that measure the level of energy and vitality, scored from 1 (totally disagree) to 7 (totally agree), with a sum score ranging from 5 to 35. Increasing scores reflect higher subjective vitality.

Symptoms of depression are measured by the Patient Health Questionnaire-9 [37], and symptoms of anxiety by the Generalized Anxiety Disorder 7-items [38]. Patient Health Questionnaire-9 consists of 9 items scored from 0 to 3, providing a total score from 0 to 27. Generalized Anxiety Disorder 7-items consists of 7 items scored from 0 to 3, providing a total score from 0 to 21. Items on both scales are consistent with the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* diagnostic criteria for depression and anxiety, respectively. Higher scores imply a higher level of depressive and anxiety symptoms.

Work status is assessed by questions regarding current work situation, using the same questions as in the Trøndelag Health Study (HUNT) [39]. Response options include: full-time work, part-time work, job-seeking, laid off, sick leave, work assessment allowance, disability pension, self-employed, retired, military service, education, homemaker, and other. Additional questions address the duration and degree of sick leave and disability pension.

Work ability is evaluated using 3 items from the original 7-item Work Ability Index [40]. Physical and psychological work ability in relation to the demands of the job are each rated by the following response alternatives: very good, rather good, moderate, rather poor, or very poor. Current work ability is assessed by the Work Ability Score, which includes current overall work ability compared to the participant's lifetime best work ability on a scale from 0 (extinguished work ability) to 10 (highest possible work ability).

Perceived exercise competence is assessed with an exercise version of the 4-item Perceived Competence Scale [41]. The participants respond to 4 statements related to their ability to be physically active on a 7-point Likert scale ranging from 1 (not at all true) to 7 (very true). A higher average sum of the 4 items reflects higher perceived exercise competence.

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Diet is assessed by the digital DIGIKOST–food frequency questionnaire (FFQ) [42-45]. DIGIKOST-FFQ is a digital diet and lifestyle assessment tool designed to measure adherence to the Norwegian food-based dietary guidelines [48]. The questionnaire covers intake (in grams per day) of the main food groups reported in the last 2 weeks, including foods rich in fiber (ie, fruits, berries, vegetables, and whole grain products), fish (fatty and lean fish), unsalted nuts, dairy products (high- and low-fat content), meat (red, white, and processed meat), oils, margarine, foods rich in sugars and fat, sugar-rich beverages, and dietary supplements. DIGIKOST-FFQ also includes the Norwegian diet index and the Norwegian lifestyle index. The Norwegian diet index consists of 12 components corresponding to the Norwegian food-based dietary guidelines with a 3-level scoring approach, including 3 categories representing low, intermediate, and high adherence, giving a composite diet index ranging in scores from 0 (lowest adherence) to 20 (highest adherence). The Norwegian lifestyle index consists of 5 components (ie, diet, physical activity, normal weight, alcoholic drinks, and tobacco use) with a 3-level equal scoring approach and a composite lifestyle index ranging from 0 to 5 points [45]. Participants receive a link to DIGIKOST-FFQ via an SMS text message at the same time points as the other assessments.

Cardiorespiratory fitness and pulmonary function are assessed by a cardiopulmonary exercise test (CPET) conducted at OUS. Cardiorespiratory fitness, expressed as peak oxygen consumption (VO_{2peak}), is assessed using a modified Balke treadmill protocol [49,50]. Before the test, participants are briefly familiarized with treadmill walking. The protocol starts at a speed of 4.8 kilometers per hour and with a 4% incline. The incline increases by 2% per minute until reaching a 20% incline, after which the speed increases by 0.5 kilometer per hour each minute. The test continues until the participant reaches voluntary exhaustion. Expired gases are measured continuously, breath-by-breath, using a gas and volume calibrated metabolic chart (SentrySuite, CareFusion, Jaeger). The highest volume of oxygen consumed during a 30-second period is recorded as VO_{2peak}. Pulmonary function is assessed before the treadmill protocol at T0 and T1 by spirometry or flow-volume for pulmonary function (forced vital capacity, forced expiratory volume in the first second, maximal voluntary ventilation, and diffusion capacity for carbon monoxide in the lung).

If participants are unable to travel to Oslo for the CPET, they undergo the same modified Balke protocol at their local training center, continued until voluntary exhaustion as in CPET [49,50]. This indirect test is led by a physiotherapist or exercise physiologist in the municipality. At completion, the instructor registers time to exhaustion, heart rate $(HR)_{peak}$, speed, and incline. Test results (eg, maximum speed and incline, as well as age and body weight) are then applied in a VO_{2peak} prediction equation.

Muscle strength is assessed by 1-repetition maximum test, that is, the maximal workload that can be lifted once in the leg press. For upper body strength, maximum number of push-ups performed in 1 set is registered.

Additional Measurements

Perceived benefits of taking part in the project are assessed by questions modified from the PasOpp survey, developed by the Norwegian Institute of Public Health to measure patient experiences with rehabilitation institutions [46]. Use of experiences, strategies, and advice from the program in daily life is assessed by self-made questions (Multimedia Appendix 2).

HRQoL among the partners is measured by the Research and Development 36-item Short Form Health Survey (RAND-36) [47] and the global health status or QoL scale from the EORTC QLQ C-30 (described earlier) [33]. RAND-36 consists of 36 items assessing 8 health concepts: physical functioning (10 items), role limitations caused by physical health problems (4 items), role limitations caused by emotional problems (3 items), social functioning (2 items), emotional well-being (5 items), energy and fatigue (4 items), pain (2 items), and general health perceptions (5 items). In addition, 1 item assesses current perceived health status compared to the perceived health status 1 year ago. Physical and mental health summary scores are also derived from the 8 RAND-36 scales. Scale scores are summed and then transformed to scales ranging from 0 (worst possible health state) to 100 (best possible health state) [47].

Background Variables

Sociodemographic variables include age, gender, education level, and marital status, and are assessed by questions used in the HUNT study [39].

The work environment is measured by the Demand Control Support Questionnaire [51]. It includes 17 statements concerning psychological demands (5 items), decision latitude (6 items), and social support (6 items) at the workplace. The level of agreement with these statements is reported on a 4-point scale ranging from 1 (complete agreement) to 4 (no agreement at all). Higher scores indicate higher psychological demands (range 5-20), higher decision latitude (range 6-24), and higher social support at work (range 6-24).

Cancer-related variables include information on cancer diagnosis and treatment, and comorbidities extracted from the medical record and the medical screening.

Physical activity level is measured by a modified version of the Godin Leisure-Time Exercise Questionnaire [52]. It assesses the average frequency and duration of mild, moderate, and vigorous leisure-time physical activity during a typical week. By summing the weekly minutes of moderate and vigorous intensity levels of physical activity, participants are dichotomized into meeting or not meeting the World Health Organization guidelines on physical activity (ie, 150-300 min of moderate intensity or 75-150 min of vigorous intensity physical activity per week, or an equivalent combination of moderate and vigorous intensity activity throughout the week [53]).

BMI is calculated from height and weight (kg/m^2), measured at the physical tests.

Smoking, snuff, and alcohol consumption are measured by questions used in the HUNT study [39].

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Sleep problems are assessed by the following question extracted from the HUNT study [39]: "How often in the last 3 months have you experienced difficulty falling asleep, waking up repeatedly through the night, woken too early and could not get back to sleep, and difficulty coping during the daytime (socially or professionally) due to sleep problems?" Response alternatives are "never," "seldom," "sometimes" and "3 times a week at least."

Personality is measured by a short version of the Big Five Inventory [54]. It measures the 5 personality domains: openness, conscientiousness, extraversion, agreeableness, and neuroticism. The questionnaire consists of 20 items, distributed into 4 items for each personality domain. Items are scored on a Likert scale from 1 (the item does not describe the respondent at all) to 7 (the item describes the respondent very well). Scores range from 4 to 28 for each personality domain.

Randomization and Blinding

After completion of baseline assessments, participants are allocated in a 1:1 ratio between the intervention group and usual care group using a block randomization procedure with random block sizes of n=2 and n=4. A computer-generated randomization list is generated using Stata statistical software (version 17.0; Stata Corporation). The allocation sequence is prepared by an independent statistician.

Details of block size and allocation sequence generation are unavailable to those who enroll patients or assign study group. Participants and assessors involved in baseline assessments are blinded to group assignment until baseline assessments are completed. Assessors are not blinded to group assignment at follow-up assessments. Due to the nature of the intervention, participants, physiotherapists, and health personnel delivering the intervention are not blinded to group assignment after randomization.

Intervention

Overview

The multidisciplinary intervention is organized as shown in Table 2.

Table 2. Organization of the intervention components in the Randomized Controlled Trial in Chronically Fatigued Lymphoma Survivors trial.

	Intervention period (week)											
	1	2	3	4	5	6	7	8	9	10	11	12
Patient education session	✓											
Physical exercise program	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CBT[a]-based group program			✓	✓	✓	✓	✓	✓				
Individual nutritional counseling		✓				✓				✓		

[a]CBT: cognitive behavioral therapy.

Patient Education

The intervention begins with a 2-hour digital group–based patient education during the first week. Health care professionals from the Cancer Rehabilitation Centre at OUS provide information about CF (by an oncologist) and physical exercise and recovery (by a physiotherapist); an introduction to the CBT-based group program (by a psychologist); and information about diet and nutrition (by a registered clinical dietitian), all topics related to CF. The participants are encouraged to share experiences and ask questions during and at the end of the session.

Physical Exercise Program

The physical exercise program begins in the first week and continues throughout the whole intervention period. The program consists of 2 aerobic and strength training sessions per week, 1 supervised by a physiotherapist in the municipality and 1 unsupervised. The physiotherapists ensure that the exercise sessions are performed as planned and adjust the sessions if necessary. In the unsupervised sessions, the participants are instructed to follow the same program as in the supervised sessions. Each session lasts 30 to 60 minutes. An overview of the exercise program is provided in Tables 3 and 4.

Table 3. Overview of the aerobic exercise program in the Randomized Controlled Trial in Chronically Fatigued Lymphoma Survivors trial.

Aerobic exercise	Weeks 1 and 2 (familiarization)	Weeks 3 to 6	Weeks 7 to 12
Peak HR[a] (%)	60-75	75-85	80-90
Subjective experience; Borg scale (6-20)	Light; 8-10	Light to moderate; 11-13	Moderate to hard; 12-15
Total duration of intervals (min)	8-12	8-12	8-12

[a]HR: heart rate.

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Table 4. Overview of the strength exercise program in the Randomized Controlled Trial in Chronically Fatigued Lymphoma Survivors trial.

Strength exercise	Weeks 1 and 2 (familiarization)	Weeks 3 and 4	Weeks 5 to 12
Reps × sets per exercise	8 to 12 repetitions; 1 to 2 sets per exercise	8 to 12 RM[a]; 1 to 2 sets per exercise[b]	8 to 12 RM; 2 to 3 sets per exercise[c]
Subjective experience; RPE[d] (1-10)	Light, focus on correct technique	Hard; 8-10	Hard; 8-10

[a]RM: repetition maximum, the load that induces technique failure in 8 to 12 repetitions.

[b]Week 1 to 4: push-ups, rowing, and dead bugs are performed in 1 set, and squats in 2 sets.

[c]Week 5 to 12: push-ups, rowing, and dead bugs are performed in 2 sets and squats in 3 sets.

[d]RPE: rate of perceived exertion.

The aerobic exercise component begins with 10 to 15 minutes of warm-up at low intensity, followed by intervals of moderate to high intensity exercise (Multimedia Appendix 3). The number and duration of intervals are flexible, as long as the total duration of the intervals is between 8 and 12 minutes. The mode most often used is uphill walking, outside or on a treadmill. Resting periods between intervals are at least half the duration of each interval.

The participants wear an HR monitor (Polar Verity Sense) to track their HR during the aerobic exercise. The intensity of the intervals is individually tailored to each participant based on their CPET or indirect VO_{2peak} test result at baseline. In the first 2 weeks, light-intensity intervals (60%-75% of peak HR) are conducted to familiarize the participant with the program. Throughout the program, the intensity of the intervals progressively increases (Table 3).

The strength training includes 4 mandatory exercises (variants of push-ups, dead bugs, standing rowing, and squats), along with 2 optional exercises (biceps curl and shoulder press, and variants of hip thrust). Each exercise is performed for 8 to 12 repetitions across 1 to 3 sets (Table 4 and Multimedia Appendix 3). Once a participant can complete 12 repetitions with proper technique, the physiotherapist increases the load (eg, using elastic bands with more resistance or heavier dumbbells). Alternatively, the physiotherapist introduces a more challenging exercise variation targeting the same muscle group (eg, from bodyweight squats to split squats). During the first 2 weeks, the focus is on proper technique. Through the following weeks, the physiotherapist gradually increases the load, difficulty, and number of sets.

After the initial 12-week exercise program, the physiotherapist and participant are encouraged to prepare an individual exercise plan for the next 12 weeks tailored to the participant's exercise preferences and motivation. The physiotherapists are also encouraged to provide a follow-up call every second to fourth week to support exercise adherence.

With assistance from their physiotherapist, the participants record their sessions in an exercise log (Multimedia Appendix 4). For aerobic exercises, participants log the total number of intervals, the duration of each interval, their HR at the end of each interval, and their subjective experience of the aerobic session using the Borg Rating of Perceived Exertion scale (range 6-20). For strength exercises, participants log the number of repetitions, sets, and exercise variants for each completed exercise. Their subjective experience is recorded with an Rating of Perceived Exertion Vas Scale (range 1-10).

In the exercise log, participants also rate their level of fatigue the day after exercise on a scale from 1 (no fatigue) to 10 (maximum fatigue). If necessary, the physiotherapists adjust the training intensity and load according to the participants' subjective experience. If a session results in significant fatigue that persists for the following days after the session, the participant is advised to reduce the intensity and duration of the subsequent session.

If the participant's motivation and compliance diminish, or if injuries and physical complaints prevent the participant from performing the prescribed exercise, the physiotherapists make necessary individual adjustments (eg, alternative exercise modes, such as ergometer bike, rowing machine, and cross-country skiing) to prevent dropout. Any individual modifications to the program are registered in the exercise log.

CBT-Based Group Program

The CBT-based program starts in week 3. The program consists of 6 weekly digital group-based sessions, each led by 2 clinical psychologists (6-10 participants per group). Each session lasts for 2 hours and 15 minutes. The program is a modified version of a course designed to target fatigue in individuals with inflammatory rheumatic disease, developed by clinical psychologists at Diakonhjemmet Hospital, Oslo [55]. The aim of the program is to address behavioral and cognitive factors related to the participant's symptoms and disability, especially strengthening perceived self-efficacy in the management of fatigue. The program incorporates key elements from CBT, including the following:

- Education about the biopsychosocial model of fatigue and teaching the participants to use the 5 areas model [56] to investigate the impact of bodily reactions, thoughts, feelings, behavior, and environmental factors in everyday situations.
- Making an activity plan for activity and rest, a tool for changing unhelpful behavior, and reducing the selective attention to fatigue.
- Guiding participants to address unhelpful cognitions, such as self-criticism and fears related to symptoms and activity, for example, by using reflective questions.
- Using mental strategies for unhelpful and excessive worry and rumination.

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- Using implementation intentions and strategies for change of habits.
- Addressing social and emotional barriers to improvement through problem-solving.

Between group sessions, the participants spend about 45 to 60 minutes per week on homework and practice.

Nutritional Counseling

The nutritional counseling consists of 3 individual digital sessions in weeks 2, 6, and 10. Each session lasts for 30 to 60 minutes, all led by a registered clinical dietitian. The sessions aim to improve adherence to the Norwegian food-based dietary guidelines, address specific nutritional needs, and establish healthy meal patterns [57]. DIGIKOST-FFQ is used to estimate adherence to the Norwegian food-based dietary guidelines at baseline [42-45]. This assessment provides a digital benchmark of the individual's diet and nutritional status, forming the basis for the counseling (ie, the DIGIKOST-report). Each consultation uses motivational interviewing techniques to support each individual participant in setting 1 to 3 dietary goals. The registered clinical dietitian encourages the survivor in achieving these goals, which are reviewed and revised at subsequent sessions [58].

Tolerability and Adherence to the Intervention

Tolerability of the intervention is assessed as loss to follow-up, and adherence to the separate intervention components and the intervention as a whole.

Adherence to the patient education, CBT sessions, and nutrition counseling is assessed by calculating the attendance rate for each of the components (dividing the number of attended sessions by the number of planned sessions).

Adherence to the exercise program is assessed based on information in the exercise log registrations. The attendance rate will be calculated by dividing the number of sessions registered in the exercise log by the planned number of sessions. The total number of interval sessions completed at the planned intensity, above or below the planned intensity (% of peak HR) is also reported.

For each part of the intervention, a participant is considered adherent if attending at least 65% of the offered sessions (ie, exercise sessions: 16/23, 70%; CBT-based group sessions: 4/6, 67%; and nutritional counseling sessions: 2/3, 67%). For the total intervention, a participant is defined as adherent if they have attended the patient education and at least 67% of each of the other parts of the intervention (ie, the combination of attending the patient education, ≥16 exercise sessions, ≥4 CBT sessions, and ≥2 nutritional counseling sessions).

A participant is considered adherent to usual care if their VO_{2peak} or self-reported physical activity level increased by less than 2 times the SD of the mean change in the intervention group.

Safety

All participants undergo an extensive medical screening before inclusion (described earlier) to ensure that it is safe for them to perform the exercise protocol.

Participants in the intervention group are frequently in contact with the study personnel, health professionals at OUS, and the physiotherapist in the municipality throughout the intervention. The physiotherapist monitors and assesses fatigue and activity levels, discussing this continuously with the participants. If the participants feel that the program is too extensive, it is individually adjusted as needed in collaboration with the study personnel.

Both during physical tests and the intervention, any adverse events that occur are registered by the participant, test personnel, or physiotherapist. If indicated, the incidence and severity of adverse events (eg, adverse events requiring medical treatment, causing persistent worsening of the participant's health, requiring restrictions or early termination of the planned testing or training, or resulting in persistent or significant disability) are discussed with the study coordinator (SKHB and GMG), the principal investigator (LT), the medical responsible physicians (M Seland and AF) or the steering group (LT, CEK, and TS).

Usual Care

The usual care group is encouraged to continue their lives as usual, and to maintain the same level of physical activity as at the time of inclusion. Nine months after randomization (after T3), participants in the usual care group are offered a modified version of the intervention in line with their personally expressed needs.

Statistical Power and Analyses

Power calculation for the primary outcome, that is, total fatigue measured by the FQ was based on results from the pilot study by Oldervoll et al [59] and results from our feasibility study [31]. To detect a mean difference of 3.3 points (SD 6.1) in total FQ score between groups at T1 (no change in the usual care group and 3.3 points reduction in the intervention group) with a 2-sided significance level of 5% and a power of 80%, 54 survivors are required in each group. To have a sufficient sample size to detect a 10% group difference in the secondary HRQoL outcomes with similar assumptions, 62 survivors are needed in each group. Assuming a 20% loss to follow-up, 74 survivors have to be recruited in each group.

For the descriptive analyses, continuous variables will be presented as means and SDs or medians and ranges, while categorical variables will be presented by numbers and percentages.

To analyze the difference in total fatigue at T1 between groups, we plan to use a generalized linear mixed model, adjusting for baseline fatigue score and random effects for hospital. To analyze between-group differences in secondary outcomes at T1, T2, and T3, we will use similar analyses. If the assumptions for the generalized linear mixed model are not met, we will use alternative analyses. A P value <.05 will be considered statistically significant. The main analysis will be according to the intention-to-treat principle, including all randomized participants.

Per-protocol analyses will be performed by including only participants adherent to the randomized group.

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To explore if the intervention effect on primary and secondary outcomes differs across subsets of participants (eg, age groups, gender, and time since diagnosis), we will also perform subgroup analyses.

Analyses of cost-utility will be performed based on data on resource consumption, HRQoL, and survival during the trial. The health outcome will be based on a combination of EQ-5D-5L [34] and patient survival, that is, the area under the curve, resulting in quality-adjusted life expectancy. Costs for the intervention will be calculated in detail using microcosting. Costs during follow-up will be based on recorded resource consumption and costed according to national and international guidelines for health economic evaluations and health technology assessments [60].

More details on the statistical analyses are provided in the statistical analysis plan Multimedia Appendix 5.

Ethical Considerations

The trial is preregistered on ClinicalTrials.gov (NCT05130099). Protocol modifications are continuously registered on ClinicalTrials.gov. This protocol paper is written according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (Multimedia Appendices 6 and 7) [61].

Human Subject Ethics Review Approvals

The REFUEL trial is approved by the Regional Committees for Medical and Health Research Ethics (153665), the Data Protection Officer at OUS (20/19374) and the Research Committee of the Department of Oncology at St Olavs Hospital (04_2022_04). All study procedures are conducted in accordance with the Helsinki declaration.

Informed Consent

All study participants provide signed informed consent before inclusion in the study. The participation is voluntary, and participants can withdraw from the study at any time without giving any reason.

Privacy and Confidentiality

All study-related information will be stored securely at the study sites (OUS and St Olavs Hospital). All participant data will be identified by a coded identification number only to maintain participant confidentiality. Listings that link participant identification numbers to other identifying information will be stored in a separate locked file in an area with limited access. No identifying information or features of the participants will be published.

Compensation Details

Participants were not offered any incentives or compensation.

Results

The project was granted funding by the Dam Foundation in October 2020. The first participant was included in November 2021 (Multimedia Appendix 8). Inclusion of 150 participants was completed in March 2023, of which 75 participants were randomized to the intervention and 75 participants to usual care. All T1 assessments were completed in June 2023 and the 1-year follow-up (T4) was completed in June 2024. The 2-year follow-up (T5) was completed in June 2025.

Discussion

Anticipated Findings

Recent fatigue guidelines from the American Society of Clinical Oncology highlight the lack of RCTs, including fatigued cancer survivors [1]. As the first RCT to test the effects of a multidisciplinary intervention on fatigue levels, HRQoL, and physical fitness in lymphoma survivors with CF, the results from the REFUEL trial will be an important contribution to this evidence gap. We hypothesize that survivors randomized to the multidisciplinary intervention will improve their level of total fatigue (primary outcome). Moreover, we hypothesize that the intervention will be effective on other HRQoL outcomes and physical fitness from before to immediately after the intervention, compared to survivors randomized to usual care.

Comparison to Previous Work

Exercise and psychological interventions are recommended to improve fatigue among cancer survivors during and after treatment [1,19,27]. However, the effects are small to moderate, and the existing evidence base has several limitations [1]. There is a lack of studies with fatigue as the primary outcome, and very few studies have screened the participants for fatigue before inclusion, particularly in long-term cancer survivors [1]. By including lymphoma survivors with CF according to well-established criteria, this RCT represents a significant contribution to the existing evidence base.

To date, the few studies that have combined multiple components to address fatigue after cancer have yielded inconsistent results. A meta-analysis showed that the combination of exercise and psychological interventions were sometimes equivalent to or inferior to a single modality [19]. Combined interventions could be counterproductive if the content is insufficient or if the intervention places too high a burden on participants or is too time-consuming, leading to reduced adherence and high dropout rates [19]. On the other hand, given the complex mechanisms underlying CF, it is plausible that integrating education, physical exercise, psychological strategies, and nutrition could have synergistic effects, leading to larger fatigue reductions compared to single modality interventions. The REFUEL trial aims to provide a more definitive conclusion regarding the effects of combined interventions.

The REFUEL intervention was developed through close collaboration between clinicians and researchers with extensive experience in CF among cancer survivors. However, we acknowledge that the intervention is ambitious and demands considerable efforts from the participants, study personnel, and health professionals delivering the intervention. As a preparation for the RCT, we tested the intervention in a feasibility study [31]. In order to prevent worsening of fatigue and dropout among the participants, as well as to ensure that the study personnel and health professionals are well prepared, we learned that it is crucial to ensure sufficient time for information,

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planning, and coordination. We also made some adjustments to reduce the total load of the intervention, in accordance with feedback provided by the survivors testing the intervention in the feasibility study [31]. Finally, a close dialogue between the study personnel, health professionals, and the participants is important throughout the trial to detect and address challenges, and if necessary, make individual adjustments to the intervention.

Strengths and Limitations

A key strength of this study is the multidisciplinary intervention targeting several modifiable factors associated with CF, developed through close collaboration between clinicians and researchers.

Another strength of this intervention is the integration of digital services with supervised exercises by local physiotherapists, ensuring that travel distance was not a barrier to study participation. Combining digital and home-based interventions can help mitigate disparities in geographical access to fatigue rehabilitation services and thereby promote equality in health care services.

Limitations of the study include the risk of recruiting the most motivated individuals, and the need to exclude those with medical conditions that are incompatible with the study, which will have to be taken into account when considering the external validity of our results.

Another limitation of this study is the lack of blinding of study personnel conducting the physical assessments. However, this is not likely to affect the primary outcome or the additional secondary outcomes, as these were evaluated directly by the participants through PROMS. We consider PROMS the most efficient and appropriate assessment method for subjective experiences that cannot be captured by objective markers or clinical assessments (eg, fatigue). Nevertheless, we acknowledge that these measures are prone to bias, such as response bias and responses influenced by fluctuations in mood and expectations of the participants, which can lead to inconsistencies in the data. Efforts to reduce the disadvantages associated with self-report have been made by using validated PROMS and combining PROMS with objective physical assessments.

Another concern is poor intervention adherence and dropouts. To prevent dropout from the intervention group, the exercise dose is individually tailored according to baseline test results. The exercise sessions are supervised by experienced physiotherapists who will adjust the program if needed. To prevent dropout in the usual care group, they are offered a modified version of the intervention after completion of the assessments, 9 months after randomization.

Future Directions

The results from the REFUEL trial can inform future fatigue guidelines. If proven effective, this intervention provides support for a multidisciplinary approach in clinical practice to improve fatigue among cancer survivors.

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Data Availability

The data that will be generated and analyzed during this study is not publicly available due to privacy and ethical restrictions. The data or parts of the data are available from the corresponding author upon reasonable request.

Authors' Contributions

LT, SKHB, KVR, JHL, LMO, TSN, TR, TS, CEK, RB, HBH, TB, EF, and HCL participated in study design, methods, and intervention development. SKHB, MS, AF, UMF, KVR, and TS contributed to the recruitment of participants. SKHB and GMG contributed to the coordination of assessments and intervention. SKHB, EE, AR, and KHT contributed to conducting physical fitness assessments and cardiopulmonary exercise tests. SKHB, IH, GS, M Seland, M Slott, and LV contributed to delivering the intervention. TW, SKHB, and LT contributed to statistical analyses. CEK, TS, and LT contributed to project management. SKHB, LT, and TW contributed to drafting the manuscript. All authors reviewed and approved the final manuscript.

Conflicts of Interest

EE has received personal consulting fees, honoraria, and expenses for presentations at education meetings from GlaxoSmithKline, AstraZeneca Norway, Birk NPC AS, and Chiesi Pharma AB.

Multimedia Appendix 1

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Medical screening.
[PDF File (Adobe PDF File), 449 KB - resprot_v14i1e69336_app1.pdf]

Multimedia Appendix 2
Patient-reported experience measures.
[PDF File (Adobe PDF File), 555 KB - resprot_v14i1e69336_app2.pdf]

Multimedia Appendix 3
Physical exercise program instructions.
[PDF File (Adobe PDF File), 525 KB - resprot_v14i1e69336_app3.pdf]

Multimedia Appendix 4
Example of exercise log.
[PDF File (Adobe PDF File), 570 KB - resprot_v14i1e69336_app4.pdf]

Multimedia Appendix 5
Statistical analysis plan.
[PDF File (Adobe PDF File), 1581 KB - resprot_v14i1e69336_app5.pdf]

Multimedia Appendix 6
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 173 KB - resprot_v14i1e69336_app6.pdf]

Multimedia Appendix 7
Time schedule of enrollment, intervention, and assessments in the Randomized Controlled Trial in Chronically Fatigued Lymphoma Survivors trial.
[PDF File (Adobe PDF File), 248 KB - resprot_v14i1e69336_app7.pdf]

Multimedia Appendix 8
Peer-review report from Foundation DAM.
[PDF File (Adobe PDF File), 677 KB - resprot_v14i1e69336_app8.pdf]

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Abbreviations

CBT: cognitive behavioral therapy
CF: chronic fatigue
CPET: cardiopulmonary exercise test
FQ: Fatigue Questionnaire
HR: heart rate
HRQoL: health-related quality of life
HUNT: Trøndelag Health Study
OUS: Oslo University Hospital
PROMS: patient-reported outcome measures
RAND-36: Research and Development 36-item Short Form Health Survey
RCT: randomized controlled trial
REFUEL: Randomized Controlled Trial in Chronically Fatigued Lymphoma Survivors
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
VO_{2peak}: peak oxygen consumption

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Protocol

Managing Cognitive Decline Through a Social Robot–Based Intervention: Protocol for the engAGE Proof of Concept and Randomized Controlled Trial

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Abstract

Background: Dementia is challenging society in terms of the quality of life, the costs of health care systems, and caregivers' burden. Dementia is often preceded by a status of mild cognitive impairment (MCI), during which a healthy lifestyle and cognitive therapy seem to be effective in counteracting the decline.

Objective: The engAGE (Managing Cognitive Decline Through Theatre Therapy, Artificial Intelligence, and Social Robot–Driven Interventions) project aimed to build a technological platform to counteract cognitive decline in older adults with MCI through both cognitive therapy and lifestyle management.

Methods: The engAGE platform was built around the social robot Pepper, which provides cognitive therapy. An activity tracker and a mobile app were also integrated within the platform to help older adults with MCI monitor their sleep and physical activity, in addition to offering cognitive games at home. The proof of concept (PoC) of engAGE was designed as a 6-month long randomized controlled trial (RCT) aimed to test the solution in three European countries: Italy, Switzerland, and Norway. During this period, under the supervision of a psychologist or a therapist, Pepper provided cognitive therapy on a weekly basis at health care or daycare facilities. In parallel, the use of the mobile app and the activity tracker was recommended on a daily basis. Participants were recruited through health care institutions and care organizations and evaluated through face-to-face interviews. The primary interest of the study was to assess the impact of engAGE on cognitive capacity through the Montreal Cognitive Assessment (MoCA) and the Memory Assessment Clinic Questionnaire (MAC-Q). In addition, changes in social engagement and quality of life were measured through the University of California, Los Angeles (UCLA) Loneliness Scale and the Warwick-Edinburgh Mental Well-Being Scale (WEMWBS). The PoC also focused on the acceptability and usability of engAGE, evaluated through the System Usability Scale (SUS) and the Unified Theory of Acceptance and Use of Technology (UTAUT) questionnaire. In addition, data were collected regarding the frequency of weekly sessions and access to the mobile app, as well as activity tracker measurements.

Results: Data collection commenced in November 2023 and finished in July 2024, with the enrollment of 49 older adults with MCI (n=40, 81.6%, assigned to the experimental group [EG] and n=9, 18.4%, to the control group [CG]) conducted from October 2023 to April 2024. Data analysis was concluded in November 2024, and results will be published by 2026.

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Conclusions: The engAGE PoC represents an innovative study focused on the impact of a technology-based multidomain intervention designed for older adults with MCI that aimed to counteract cognitive decline through cognitive training, as well as improvement in terms of the quality of life, social engagement, physical activity, and sleep quality of primary end users.

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KEYWORDS

older people; older adults; mild cognitive impairment; social robotics; technology for elderly; digital health; cognitive training; innovation in healthcare; innovation in health care

Introduction

Background

Dementia is a chronic neurodegenerative syndrome characterized by deficits in cognitive functions, associated with the loss of daily function and with mental and behavioral disorders. There are over 1 million people with dementia in Italy, of which 54% have Alzheimer's disease and about 16% have vascular dementia [1]. The Swiss Federal Office of Public Health expects an increase in the number of people diagnosed with dementia to over 190,000 individuals by 2030 and to almost 300,000 by 2060 [2]. The same trend is expected in Norway, where the number of people with dementia is estimated to more than double from 2020 to 2050 [3]. According to the literature, cognitive interventions [4], regular physical activity [5,6], and reminiscence therapy appear to be effective in the treatment of people with mild-to-moderate dementia. Cognitive stimulation programs, computerized individual cognitive training, and physical exercise appear to be able to induce a significant improvement in cognitive performance, quality of life, and well-being in people with mild-to-moderate dementia [7-9]. Several studies show that, especially in the early stages of the disease, stimulation and participation in various types of activities can help counterbalance the cognitive changes related to the pathology, thanks to cognitive plasticity [10,11]. Neurocognitive disorders, in particular dementia, represent a major challenge for society. Efforts to reduce the burden for caregivers, as well as for society at large, are imperative. Older adults generally report higher preferences for their home over other living arrangements, and from the societal point of view this can contribute to the burden of care, for example, for their families. Dementia caregivers are at high risk of care burden, anxiety, and stress, which exposes them to a higher rate of mortality compared to noncaregivers [12]. Thus, promoting aging in place for people with dementia should not constitute a strategy to shift the burden of care from formal care services to informal caregivers. Instead, efforts should focus on reducing caregiver stress. Part of the difficulties and stress related to caregiving might be prevented by new information and communication technologies (ICT) and by developing innovative support services for these people. The introduction of innovative and cost-effective interventions to reduce the burden of dementia on public finances and individual families should be envisaged. Several digital interventions have been developed to address the needs of individuals with mild cognitive impairment (MCI), targeting cognitive stimulation, social engagement, and caregiver support. These include cognitive training apps [13,14], telehealth platforms [15,16], and social robot–based interventions [17,18]. Despite the growing availability of digital solutions, a significant gap remains in providing efficient, integrated, personalized, and adaptive home-based care for individuals with MCI. In fact, existing solutions often focus on single domains, rely on single technologies, and lack the ability to seamlessly integrate various components to address the complex needs of older adults with MCI.

The engAGE Project

In this scenario, the engAGE (Managing Cognitive Decline Through Theatre Therapy, Artificial Intelligence, and Social Robot–Driven Interventions) project, cofinanced by the Ambient and Assisted Living (AAL) program of the European Union [19], aimed to counteract and slow down cognitive decline progression, enhance the intrinsic capacity of the users, and support the well-being of older adults with MCI by providing an ecosystem of services based on an innovative system that integrates social robots, mobile apps, and wearable sensors. Moreover, the engAGE project combined home-based intervention (daily usage of a mobile app and a wearable fitness tracker) with group cognitive training at a health care facility (weekly social robot–driven sessions). Thus, engAGE targeted the following challenges and needs for older adults with MCI, informal caregivers (family members), and formal caregivers (health care professionals):

- The project was primarily focused on older adults with MCI, aiming to improve their quality of life and well-being, allowing them to preserve their identity and reduce stress, memory loss, or communication challenges. The social robot can be a great tool in engaging older adults in these kinds of activities. It is always available and can provide verbal clues or suggestions according to each older adult's wishes, needs, and memories. Moreover, the social robot may coach older adults to perform daily activities with greater independence (ie, coaching stepwise, prompting to complete activities at home).
- The project provides support to caregivers as well. Since caring for people with MCI puts a significant burden on informal caregivers, having the support of a technological platform can reduce anxiety, worry, and stress. Caregivers can personalize the content of the interventions to the wishes and preferences of older adults.

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Goal of the Study

This paper presents the study protocol of the engAGE proof of concept (PoC). The study aimed to demonstrate the viability of integrating social robot–based cognitive therapy in a health care facility with a mobile app and an activity tracker for daily use at home for counteracting cognitive decline in older adults with MCI. To provide more robust results in this sense, the study was designed as a 6-month long randomized controlled trial (RCT) in a real scenario in three European countries: Italy, Norway, and Switzerland. The study primarily evaluated cognitive capacity changes in older adults with MCI, in addition to assessing the impact on the quality of life and social dimension of primary end users, as well as the acceptability and usability of the engAGE platform. Moreover, the reduction in the stress and care load of formal and informal caregivers was measured. All measurements were performed at the beginning and end of the study to analyze intra- and intergroup differences. The novelty of this study design is the combination of at-home and in-place interventions to maximize the impact of cognitive stimulation through technology, minimizing the caregivers' burden and encouraging the social connectedness among end users with the care network. The paper provides an up-to-date methodology of an interventional study to those researchers, scientists, and stakeholders who are interested in the use of social robots and ICT in health care and digital health. Finally, the paper discusses in depth the ethical issues concerning the adoption of social robots, machine learning (ML) algorithms, and health data management, along with the long-debated question of the informed consent form signed by people with MCI.

Methods

The engAGE Platform

The engAGE system offers 4 main services built around a social robot for self-managing and sustaining the cognitive function of older adults with MCI [20]: (1) holistic monitoring of daily life activities and perceived health state and well-being; (2) assessment of cognitive state and potential decline by leveraging ML algorithms; (3) social robot–based cognitive function support and coaching using cognitive games and storytelling scenarios; and (4) communication, cognitive stimulation, and personalization platform for end users. Figure 1 schematizes the engAGE platform services with the integration of social robots, sensor-based monitoring, and ML techniques. The primary end users (older adults) mainly interact with three devices: the social robot Pepper, a tablet, and a wearable fitness tracker (Fitbit). Formal caregivers supervise the execution of end users' activities and help them, when needed. The interaction is through the device's associated dashboards.

Figure 1. The engAGE platform. engAGE: Managing Cognitive Decline Through Theatre Therapy, Artificial Intelligence, and Social Robot–Driven Interventions; ML: machine learning.

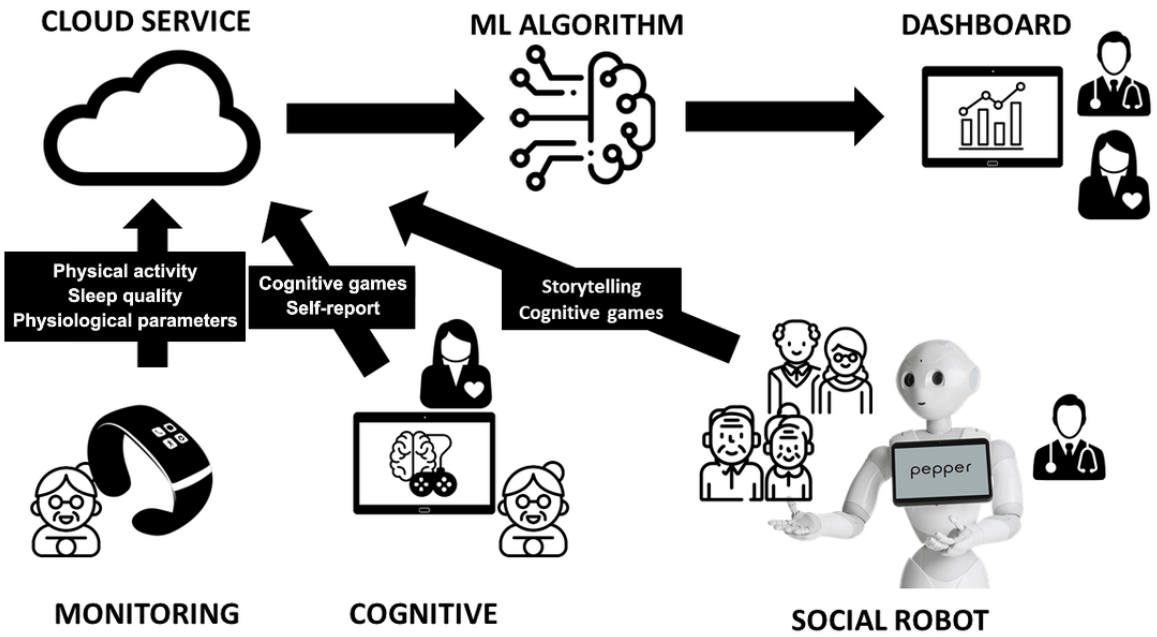

The Social Robot Service

As the social robot service, the Android version of Pepper's tablet offers dashboards for cognitive games, storytelling, and activities to the end user through an easy-to-use interface. Equivalent cognitive games are also integrated into the communication service to allow the end user to play them on the tablet at home. Pepper is a humanoid social robot able to dialogue with the user by speaking, moving, and expressing emotions, being also equipped with an Android tablet placed at its chest. The user logs through the tablet at every session and then interacts with the robot and plays the planned activities (drama play or cognitive games). To track the user's progress, each performance is recorded, and scores are sent to the cloud, along with the user ID. As the sessions are held in groups of 4 or 5 older adults, the users can choose to play individually or

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in teams. Once the type of game is selected, the user is redirected to a new screen in which all the games corresponding to the type selected is displayed. When the user plays and succeeds in a task, the robot congratulates them. To ensure that the user understands the robot, the words the robots says are displayed on the screen like subtitles. The interaction is recommended to be vocal as much as possible to improve the user experience. Different categories of cognitive games and storytelling activities are implemented in the service. The games are and will be iteratively developed and included in the service in the different versions of the prototype while considering end users' feedback:

- Familiar games: crosswords, memory cards, and remembering objects that appear
- Quizzes: picture, musical, and cultural quizzes
- Story-/play-telling: story listening, poem recitation, and YouTube shorts, with questions asked about the activity

The Communication Service

The communication service is the hub of the entire system for providing dashboards for end-user interactions at home. It is a web app with several dashboards through which all the end users' categories can communicate. This service is based on the MEMAS Life Mastering Assistant with the following functionalities that helps people with MCI: a calendar with reminders, step-by-step instructions for daily activities in the form of a series of images with spoken comments or videos, easy-to-access radio channels via streaming, photos with spoken comments and videos, music, easy-to-access network newspapers, cognitive games, weather forecasts, self-reporting questioners, and graphical results from the ML algorithms for secondary end users. The service is usable by both primary and secondary users. The primary user can be connected to several secondary users. In the administration module (a website page), the secondary user (ie, family member or formal caregiver) can manage an activity calendar, build albums with photos and videos, and configure access to favorite radio channels and newspapers. In general, the secondary user can edit the primary user's interface to make using the service as simple as possible and tailored to the primary user's needs. Data regarding self-assessment and cognitive games scores are sent to the ML service for further analysis. In this service also, the games are and will be iteratively developed and included in the service in different versions of the prototype while considering end users' feedback: Sudoku, Mahjong, Minefield, crosswords, logics, math, Hangman, and memory cards.

The Monitoring Service

The monitoring service offers a tablet-based app where parameters such as the heart rate, sleep status, and physical activity (steps and distance walked) are monitored. These data are further used by the ML service as input for its algorithms. The monitoring service has little user interaction outside of the use of sensor devices. This service features a mobile app gateway that transfers data from the sensor device (Fitbit) into the cloud. In the first iteration, it transfers Fitbit data from the Fitbit service. It does so automatically while running in the background on the mobile device (Android tablet) of the primary user. Once the login and Fitbit authentication have been established, the app runs in the background, regularly polling data from the Fitbit service.

The ML Analytics Service

The ML analytics service has no direct end-user interaction; it gets data from the monitoring service and the communication platform and provides results to be displayed in the latter. The main goal of the service is to assess and correlate the daily physical activity, sleep parameters, game scores, and self-assessment data to offer a view of MCI progress [21]. It combines deep neural network algorithms/models to analyze objective activity data coming from the Fitbit wearable, with graph learning techniques that capture structural insights from subjective self-reporting activities to construct a better understanding of symptoms associated with cognitive decline.

Study Design

The PoC was structured as a controlled longitudinal pilot study, with a before-and-after design, where observations were run on a series of enrolled individuals, who received the intervention described later, with data collected before and after the installation and use of the technical solution. The goal of trial evaluation was to demonstrate the viability of engAGE technology integration into everyday life to counteract cognitive decline. As secondary outcomes, the impact on the social dimension and quality of life of end users was evaluated. Moreover, acceptance over 6 months and the usability of proposed solutions were evaluated to understand the feasibility of the intervention. Despite the choice to structure the PoC as an RCT in order to provide more robust evidence on feasibility and efficacy [22,23], a formal sample size calculation was not performed. Practical constraints within the project were considered while deciding the number of end users to enroll. In fact, recruitment timelines, availability of rooms and professionals, and technical equipment represented practical limits for the study feasibility. After considering these constraints, the sample size for the PoC was set to 80 primary end users: 50 (62.5%) in the experimental group (EG) and 30 (37.5%) in the control group (CG).

In Italy, end users were recruited from the Neurology Unit and Alzheimer Assessment Unit (Memory Clinic) and from the Alzheimer daycare center of the Istituto di Ricovero e Cura a Carattere Scientifico – Istituto Nazionale di Riposo e Cura per Anziani (IRCCS INRCA). The research team could communicate with potential participants of previous projects and initiatives, as well as with other people who might have been be interested in contributing to the project evaluations. This method made it possible to be in contact with clients met before and with whom a relationship of trust was already established.

In Norway, participants were recruited from two daycare and housing centers in the city of Arendal. The first one, Solhaug, is a daycare center for old residents living in their own homes, while the second one, Plankemyra, is a combined housing and daycare center.

In Switzerland, end users were recruited with the help of a home assistance and care institution, the Geneva Institution for Homecare and Assistance (IMAD). The research team also

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reached the partner patient program for participants with potential MCI. All older adults interested in the study were considered for participation.

The Experimental Group

The EG used the engAGE system in two different settings: at health care organizations and at home. For the Italian site, the health care organizations were the Neurology Unit and Alzheimer Assessment Unit (Memory Clinic) and the Alzheimer daycare center of the IRCCS INRCA. Weekly sessions were run at the IRCCS INRCA usability lab (YOUSE) in the hospital. For the Norwegian site, weekly sessions were managed at Solhaug and Plankemyra in the city of Arendal. For the Swiss site, the participants (primary end users) attended weekly sessions at the Hôpitaux Universitaires de Genève's (HUG) living lab. At the health care organizations, the primary end users interacted with Pepper. The interaction was supervised by tertiary end users (formal caregivers, ie, occupational therapists, psychologists, or psychotherapists) and included the following activities: dialoguing with the robot, storytelling, drama play, and cognitive and physical games. The human-robot interaction was planned to last about 1 hour and to be scheduled once a week for 6 months. At home, the older adults interacted with the tablet, supervised by informal caregivers (relatives). In addition, the primary end users played cognitive and physical games installed on the MEMAS app. This activity was suggested to be performed for 30 minutes every day for 6 months. Throughout the entire period of experimentation (unless they decided otherwise), the older adults wore the smartwatch for measuring their physiological parameters and steps. Any activity performed by them was assigned by formal caregivers and could be personalized, considering the primary end users' abilities (difficulty levels of the games), lifestyle (reminding and monitoring services), and social interactions. Before starting the PoC, one session was dedicated to primary end users to teach them how to use the activity tracker and the MEMAS app at home. During weekly sessions, they were allowed to ask for clarifications about the use of these devices, and they could receive remote support from technicians during the week if any problem occurred.

Figure 2 shows the scheme of the intervention for the EG.

Figure 2. EG study design. EG: experimental group..

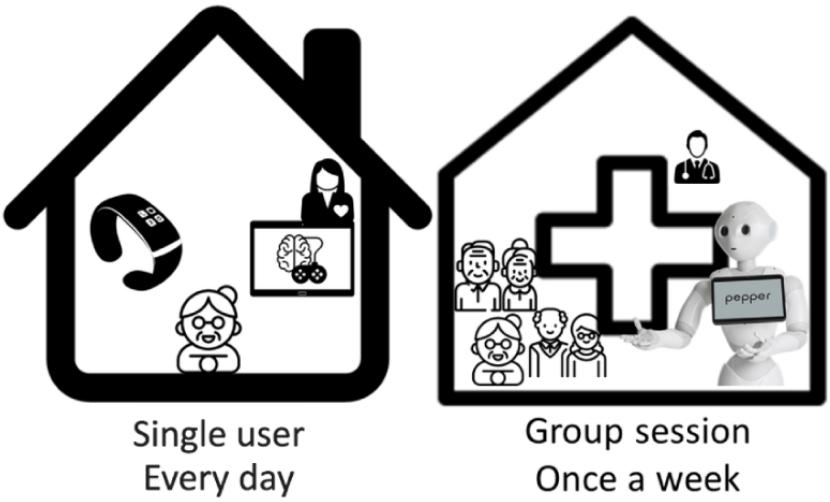

The Control Group

Participants assigned to the CG received a booklet in which cognitive games were illustrated. Moreover, suggestions on how to live a healthy life with active aging were provided in the booklet. At the beginning of the trial, the participants in the CG were invited to follow the booklet, play the cognitive games, and follow the suggestions, but they were neither motivated nor contacted during the experiment, unless they wished otherwise.

The RCT Phases

The PoC procedure was divided into three different phases after recruitment of the participants: baseline evaluation (T0), midterm evaluation (T1; after 3 months from T0), and final evaluation (T2; after 6 months from T0); the aim was to collect data, as described in Textbox 1. All questionnaires and scales at each phase of the PoC were administered through face-to-face interviews by eligible professionals at health care facilities.

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Textbox 1. Proof-of-concept (PoC) phases.

Recruitment phase:

The recruitment protocol included general information about the subjects, in particular their health status and cognitive condition. The information was collected with the help of the caregivers/family members, if needed.

Baseline evaluation:

This phase consisted of the first real contact with the users and their families before the start of the PoC.

Second evaluation (after 3 months of use):

The aim of the midterm evaluation was to collect useful information about the use of the engAGE (Managing Cognitive Decline Through Theatre Therapy, Artificial Intelligence, and Social Robot–Driven) platform after a short period of use for detecting and analyzing technology acceptance and usability issues. Obviously, the control group (CG) was not evaluated at this stage.

Final evaluation (after 6 months of use):

The aim of this phase was to collect useful information about the benefits perceived by the users after a meaningful period of use of the engAGE system. The final evaluation was conducted after system deinstallation in order to detect and analyze the impact of the system on the daily life of older adults and their families.

Recruitment

A specific number of people were recruited for the study via health care institutions or health care organizations. Potential participants were evaluated by eligible professionals through face-to-face interviews to verify that eligibility criteria were met. Those who did not meet the criteria or declined participation were excluded. The remaining participants were randomly assigned to the EG or the CG. A randomization technique, conducted by a statistician, based on a single sequence of random assignments was adopted. A list of random numbers was generated by the computer, while subjects were assigned a number based on their order of inclusion in the study. According to this technique, in Italy and Switzerland, the 30 subjects were randomly assigned to one of the two study groups (n=20, 66.7%, in the EG and n=10, 33.3%, in the CG), while in Norway, 20 subjects were equally assigned to the two groups. Next, for both groups, we took careful note of who were lost to follow-up, who discontinued intervention, or who were excluded from analysis. The procedure adopted is summarized in Figure 3.

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Figure 3. Recruitment methodology flowchart. CG: control group; CH: Switzerland; EG: experimental group; IT: Italy; NO: Norway.

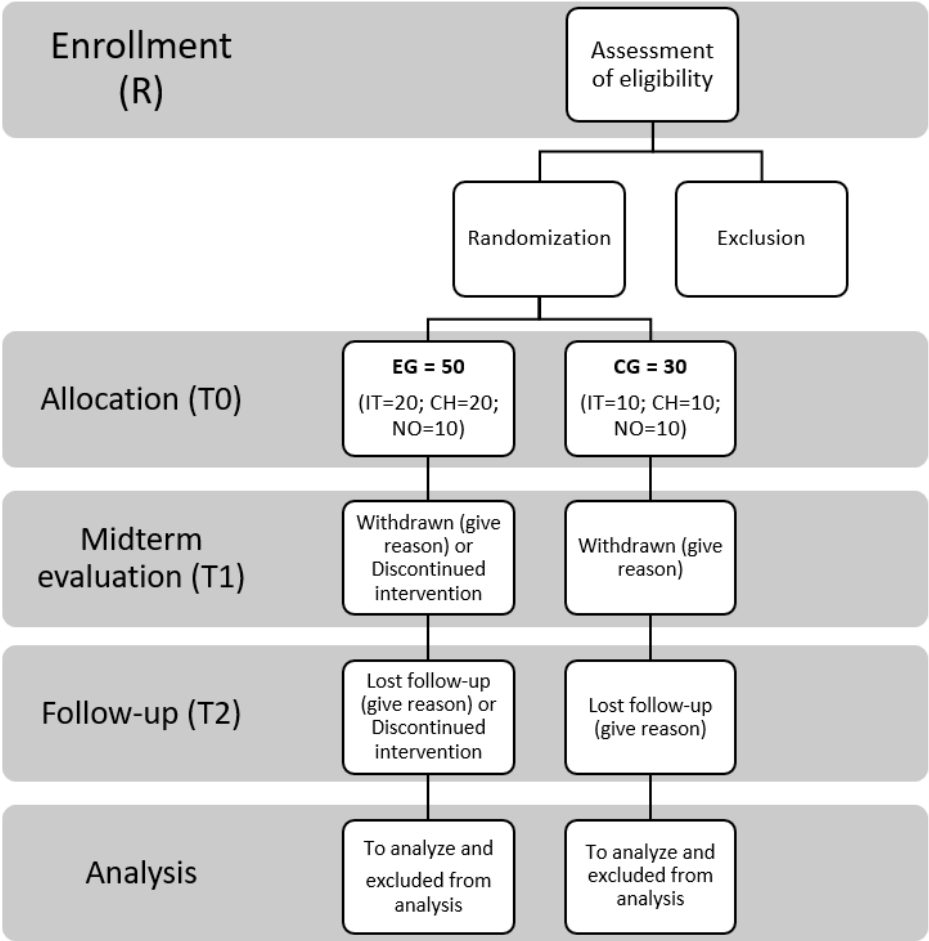

Older Adults With MCI

Once informed consent was obtained in duplicate, compliance with the inclusion and exclusion criteria of the study (Textbox 2) were verified, and baseline evaluation was carried out using questionnaires.

Textbox 2. Inclusion and exclusion criteria for people with mild cognitive impairment (MCI).

Inclusion criteria:

- Aged ≥65 years
- Capacity to provide informed consent
- Already diagnosed with MCI
- Global Deterioration Scale (GDS) [24] score<1
- Montreal Cognitive Assessment (MoCA) score [25] between 21 and 25
- Memory Assessment Clinic Questionnaire (MAC-Q) [26] score≥25
- Reisberg scale [27] score between 2 and 4
- Clinical Frailty Scale [28] score between 1 and 3
- Having an informal/formal caregiver to support in carrying out the main daily activities

Exclusion criteria:

- Failure to meet inclusion criteria
- Concomitant participation in other studies
- Lack of written informed consent
- Significant visual or hearing impairment

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Informal Caregivers

Informal caregivers are mostly family members or daily references of patients. Connections between informal caregivers and clients are private and not via a health care organization. Informal caregivers are concerned about the well-being of patients, and they provide emotional or practical support regularly. Although it is easier to live near the patients, informal caregivers do not necessarily need to live close by. Informal caregivers were included in the engAGE project since they play an important role in the daily life of people with MCI (Textbox 3). Moreover, informal caregivers can fulfil caring tasks to reduce the burden of formal caregivers. A good collaboration between informal and formal caregivers is needed as informal caregivers can be the link between client and formal caregiver.

Textbox 3. Inclusion and exclusion criteria for informal caregivers.

Inclusion criteria:

- Being the informal caregiver of an older adult with mild cognitive impairment (MCI)
- Availability of time to participate
- Visiting the patient at least two times a week or living with them

Exclusion criteria:

- Failure to meet the inclusion criteria
- Concomitant participation in other studies
- Lack of written informed consent

Formal Caregivers

Care professionals or formal caregivers are professionally responsible for dementia care. They are trusted agents for people with MCI and have direct contact with older adults and provide care when needed.

Formal caregivers are case managers, neurologists, psychotherapists, occupational therapists, and nurses. The case manager was responsible for the organization. The neurologist was a specialized medical doctor who diagnosed the disease and prescribed treatment. The psychotherapist led the intervention, whereas the nurses and occupation therapists acted as assistants. These professionals might be especially found in daycare, but they are available in residential home care as well (Textbox 4).

Textbox 4. Inclusion and exclusion criteria for formal caregivers.

Inclusion criteria:

- Over 1-year experience
- Psychologist, neurologist, occupational therapist, or nurse from a health care facility or paid by the participants
- Availability of time to participate

Exclusion criteria:

- Failure to meet the inclusion criteria
- Concomitant participation in other studies
- Lack of written informed consent

Outcomes

The PoC aimed to assess the feasibility of using the engAGE platform as a support tool to counteract cognitive decline in older adults with MCI. For this reason, the primary interest was to assess the impact of the engAGE platform on cognitive capacity. Secondarily, the study also focused on the impact on the social dimension and quality of life, as well as the usability and acceptability of the platform. All the outcomes are presented in Table 1.

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Table 1. Tools and dimensions of the primary end users' protocol.

Outcome	Clinical assessment
Perceived stability of cognitive status by older adults	MAC-Q[a] [26]
Acceptability of the engAGE[b] platform	UTAUT[c] [29]
Social connectedness of older adults	UCLA[d] [30]
Reduction in the caregiver burden of formal and informal carers	Zarit et al [31]
Adherence to intervention	Ad hoc questionnaire
Well-being of informal caregivers	WEMWBS[e] [32]
Quality of life of older adults	EuroQol 5-Dimension 5-Level (EQ-5D-5L) [33], Quality of Life-Alzheimer's Disease (QoL-AD) scale [34]
Usability and affordability of the solution of informal caregiver	SUS[f] [35]
Improving the quality of work of formal carers	Ad hoc questionnaire

[a]MAC-Q: Memory Assessment Clinic Questionnaire.

[b]engAGE: Managing Cognitive Decline Through Theatre Therapy, Artificial Intelligence, and Social Robot–Driven Interventions.

[c]UTAUT: Unified Theory of Acceptance and Use of Technology.

[d]UCLA: University of California, Los Angeles.

[e]WEMWBS: Warwick-Edinburgh Mental Well-Being Scale.

[f]SUS: System Usability Scale.

Data Analysis

This subsection describes the measurements, statistical tests, and tools with which the data collected in the engAGE PoC were, and are still being, analyzed. The different types of data that were collected in the engAGE project are as follows:

- Credentials: username, password, email address, and similar security information used for authentication and account access in different services of the platform
- Personal data: first name, last name, gender, age, weight, height, email address, contact address, and phone number of older adults in different services of the platform
- Answers to specific questions in self-assessment questionnaires on MEMAS
- Games score from Pepper apps
- Measurements and monitored parameters: weight, heart rate, blood pressure, and physical activities gathered through the monitoring infrastructure
- Historical data of the measurements and monitored parameters for training and using ML algorithms for each older adult in the ML service

In the engAGE testing and evaluation phase, the following data were, and are being, processed:

- Information and results from questionnaires
- Cognitive game scores
- Historical data of measurements collected for each end user
- Any information the end users decided to share through discussions/interviews, as well as data providing feedback from trials
- Outcomes that concern feasibility (ie, the primary interest of the engAGE PoC): recruitment rate (proportion of eligible individuals who consent to participate in the study, ie, those who attended more than 80% of weekly sessions), retention rate (proportion of participants who completed the 6-month intervention period), and adherence to the intervention (average number of interactions with the Pepper robot during weekly sessions, the frequency of use of the MEMAS app, and the activity tracker recording time)

Descriptive statistics (means, SDs, medians, IQRs) will be used to summarize adherence metrics.

Outcomes that concern efficacy of the engAGE intervention were considered exploratory and dealt with the metrics about cognitive capacity, quality of life, social dimension, and stress and care load relief (for caregivers). In particular, to explore the potential efficacy, changes in these domains before and after the intervention were analyzed. Paired *t* tests (for normally distributed data) or Wilcoxon signed-rank tests (for nonnormally distributed data) were used to compare pre- and postintervention scores within each group, while independent samples *t* tests or Mann-Whitney U tests were performed to assess between-group differences in change scores. Moreover, effect sizes (Cohen d or Cliff δ) were calculated to quantify the magnitude of any observed differences. Due to the nature of the PoC, this study was not powered to detect statistical significance. *P* values will be reported without adjustments for multiple comparisons and interpreted with caution. All analyses were planned for descriptive purposes, and only participants with at least 80% of adherence to the intervention were considered for analysis.

The aforementioned analyses were also applied to acceptance and usability measurements (ie, UTAUT and SUS scores) that provided insights into the primary goal of the study: the feasibility of the intervention. Data from the ML service were analyzed to correlate physical activity, sleep parameters, game scores, and self-assessment data. Longitudinal data analysis techniques (eg, mixed effects models) were used to analyze changes in these parameters over time and assess potential correlations with cognitive and quality-of-life outcomes.

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The first step in the data analysis dealt with the description of the sample. Continuous variables will be reported as either the mean (SD) or the median (IQR) on the basis of their distribution (assessed using the Kolmogorov-Smirnov test). Categorical variables will be expressed as an absolute number and percentage. Mann-Whitney U tests (for nonnormal distribution) or chi-square tests (for normal or nonnormal distribution) were used to compare independent and dependent variables between the pre- and postintervention conditions, in addition to simple descriptive statistics (means, medians, and SDs, as appropriate).

To verify the achievement of the primary endpoint (ie, MAC-Q score), subscales of the questionnaire were calculated. Means (SDs) or medians (IQRs) of the scores will be reported according to their distribution. Correlation coefficients (Pearson for normally distributed variables, Spearman for nonnormally distributed variables) of the subscales with the other rating scales at each stage of the study and with the main characteristics of the subjects were calculated to check for potential determinants of higher acceptability.

Statistical analyses (ie, quantitative measurements) were performed with RStudio version 4.3.1 (Posit), while qualitative data (ie, interview transcriptions) were analyzed with the Maximum Qualitative Data Analysis (MAXQDA) program.

Ethical Considerations

Ethics Approval

To guarantee the observance of ethics, the principles of the Declaration of Helsinki [36] and Good Clinical Practice guidelines were adhered to, and the study was initiated following receipt of an evaluation and approval by national independent ethics boards in two of the three countries: the Ethic Committee of the IRCCS INRCA in Italy (protocol number 6293/2023) and by the Commission cantonale d'éthique de la recherche (CCER) in Switzerland (project ID 2023-00774). Due to national laws, ethical approval was not needed in Norway, since the study fell within the technological scope. The study protocol is publicly accessible at ClinicalTrials.gov (registration number NCT06302686).

Ethical Issues

Technological dependence, especially on artificial intelligence (AI) technologies, represents a major ethical dilemma today for the scientific community. To limit the risk, the European Commission's international programs have introduced guidelines for conducting studies that require the introduction of a new technology, called *responsible innovation* [37]. The core principles of responsible innovation were also applied in the engAGE project. A strategy underlying the prevention of technological dependence includes different actors around older adults in the process of acquiring skills and daily use of technology. In this way, technological solutions, such as those proposed by engAGE, respond to the definition of a sociotechnological system rather than a technological system, since they are placed in a care context that does not involve the replacement of the caregiver but stimulates the user to play a leading role in the management of their health. The services proposed are intended to support the maintenance or improvement of cognitive abilities through specific activities and do not replace (in whole or in part) the support from professional services. During the installation of the technology, moreover, information is provided to the caregiver about the limits of the technology, which can in no way replace the role of the familiar and formal assistant but only assist in some activities.

During the use of robotic platforms or, in general, technological applications, a general difficulty in distinguishing between the artificial world and reality may occur. Especially in the case of vulnerable populations, such as older adults, the interaction may generate a general feeling of attachment and dependency. To avoid this, engAGE has been designed to not look as a human but to preserve artificial aesthetics, as suggested by the guidelines [38]. In addition, during the first contact with the participants and also during the intervention, researchers are in contact with the users, continuously stimulating awareness about the technological applications, as well as monitoring the appropriateness of the use of the solution in terms of the users' autonomy, specific needs, and personal preferences. Following the recommendations provided by the Italian Bioethics Board (Comitato nazionale di bioetica, Cnb) of the Italian Ministry of Health [39] on robotics and roboethics, the exit strategy of engAGE aims to do the following:

- Promote adequate experimentation of robotics in field assistance to ensure conditions for physical and psychological integrity of the end user, explaining the risks and benefits, highlighted also in the informed consent form.
- Ensure both equitable access to robotic and general technologies and the use of robots to assist and not to replace humans in order to avoid delegating the irreplaceable human task of care and assistance to the machine.
- Demonstrate that the introduction of robotics in medicine entails always the real consideration of benefits; of the complexity of the change, complete with the structure of the services; and of the economic burden that this entails.

Users who took part in the study did not incur any direct or indirect costs related to the use of the technology platform. The platform was provided to them by the pilot sites and had to be returned to the research team at the end of the trial.

Informed Consent for People With MCI

Participants provided written informed consent, even though the acquisition of informed consent from people with MCI is a long-debated issue. Although degenerative neurological syndromes over time lead to a progressive decline in cognitive functions and the ability to express valid consent, the diagnosis of Alzheimer's disease or MCI does not, in itself, lead to the loss of this ability. The legal capacity and the capacity to act remain, unless proven otherwise, from the age of adulthood until the death of the person. In fact, only a judicial measure can protect an individual with MCI who is unable to provide informed consent by appointing a legal representative. From a neuropsychological point of view, the impairment of executive functions (abstraction ability, problem solving, judgment and criticism, planning, planning, farsightedness, decision-making) is directly proportional to the decrease in capacity both in a general sense and in specific fields: health and economic

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decisions, driving skills, etc. However, these cognitive functions can be spared in the early stages of the disorder (MoCA score=21-24), unlike other functions that are affected early, such as memory and orientation. It is also common clinical experience that even if unable to understand the contents of a standard informed consent form (which must certainly be simplified), an individual with MCI is often able to express their choices in line with their lifestyle, preferences, and values. This underlines the importance of preserving the possibility for potential participants to use their skills to share possible choices.

Informed consent is a legal condition in which an individual accepts an action that is proposed to them (in our case, active participation in the feasibility study). To be informed, consent must be based on a full understanding of the action itself and the implications it can have. This implies the following:

- Every effort must be made to guarantee and respect any residual capacity for autonomous decisions, considering consent as an instrument through which the subject realizes their autonomy.
- The autonomy of the subject requires that all information be understood.
- The person's consent presupposes their ability to choose freely based on their preferences, moral values, life stages, and circumstances.

First, it was necessary to inform the older adults with MCI by adapting the information to their cognitive abilities, making every effort so that they could directly or indirectly communicate their preferences. The opinion of family members, for example, could be requested but was considered secondary to that of the patients. Older adults with MCI who gave their informed consent to participate but were not comfortable during the sessions had the option to withdraw from the trial at any time without any consequences.

In the specific case of the engAGE PoC, neither were serious, harmful effects on the patients with MCI foreseeable nor was there bad faith in the treatment proposal. The research teams proceeded to ask the older adults with MCI to provide their informed consent to participate and strive to do the following:

- Ensure that they clearly understood the content of the information sheet and the consequences of their participation.
- Create the best conditions in which they can ask questions and express their will.
- Monitor throughout the course of the trial the persistence of their willingness to participate.

During the clinical interview, the contextual assessment of the ability to express an autonomous choice was carried out, assessing the presence of the following:

- Ability to express a choice
- Ability to understand information relating to consent
- Ability to give due weight to the situation and its possible consequences
- Ability to use information rationally

If this evaluation gave a positive result, informed consent was acquired from the individual. Time and effort were devoted to providing correct and full information, the information sheets and the consent form were read together with the individual with MCI and their caregiver, an opportunity to ask questions was provided, and the best conditions were created to decide. An additional opinion was requested from the main and reference caregivers on whether the individual with MCI should participate in the project and what wishes and feelings about participation might not have been expressed. If the subject showed signs of dissent before and during each training session or showed behaviors that suggested that they were no longer willing to participate, the sessions were terminated, and the consent was automatically withdrawn.

Safety and Security Considerations

The hardware devices used are commercial devices and Conformité Européenne (CE) certified. The engAGE platform dashboards for older adults and caregivers are loaded on a tablet held by the users.

Personal data collected during the trial were, and are still being, handled and stored in accordance with the General Data Protection Regulation (GDPR) [40]. All data and documentation related to the trial are stored in accordance with applicable regulatory requirements, and access to data is restricted to authorized trial personnel. The project is committed to the maintenance of participants' anonymity and confidentiality throughout all procedures, including screening, recruitment, testing, evaluation, and dissemination procedures. Data collection, usage, and storage procedures complied with national laws and the GDPR [40], including the commitment to participants' right to access information, right to be informed, right to withdraw, and right to data erasure. Moreover, the servers are in the European Union and compliant with the GDPR. Use of the study data is controlled by the principal investigator. Data collection is compliant with the principle of data minimization, that is, the collection of personal information from study participants is limited to what is directly relevant and necessary to accomplish the specific goals of the testing and evaluation work packages. Data entry was carried out using specific software, providing blocks and data entry checks to reduce the number of entry errors. All screening data were discarded upon project completion. During the testing procedures, all visual, auditory, and sensory data that the robot collected and processed to function as planned were discarded after the procedures were completed. The exception to this is the collection of the number of interactions that the robot logged with each participant. However, these interactions were anonymous. All research data will be made openly available for secondary analysis 3 years after project completion. The study findings will be used for publication in peer-reviewed scientific journals and presentations in scientific meetings. Summaries of the results will also be made available to investigators for dissemination within their clinics.

In the case of the engAGE project, a critical area of security is the servers (in the cloud or on the premises) on which the solutions are deployed or data are stored. These have been provided with physical and logical protection. In addition, the communication network architecture implements mechanisms of comprehensive network protection against intrusion, such as

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an intrusion prevention system, a firewall, and a network antivirus filter. The core system is placed in a secure zone, excluding the necessary communication modules located in the demilitarized zone, enabling data exchange with engAGE services, devices, and components. In the case of communication via an external network, strong mechanisms are required to guarantee the protection of transmitted data, as well as their integrity, confidentiality, and nonrepudiation (eg, Transport Layer Security [TLS]). Authorization procedures have been implemented, specifying who is authorized to access the network and network services (access to services should be possible only for authorized users/devices by providing authentication and authorization mechanisms). Access to individual apps must require a user identifier and authentication (password, authentication certificate). The app functionality available to individual users is limited by each user's rights. The system architecture includes solutions that eliminate or significantly reduce the system's vulnerability to attacks, as recommended in the Open Web Application Security Project (OWASP). Data are transferred using REST (Representational State Transfer) application programming interfaces (APIs) using HTTPS. In engAGE, different types of databases are used for storing data. These database servers give the option of encryption at several levels and provide flexibility in protecting data from disclosure (eg, password storage encryption, data partition encryption).

Results

Recruitment started in October 2023 and continued until April 2024, when there was still time to attend 80% of the trial in the three sites. At the end of recruitment, 40 (81.6%) of the total 49 older adults with MCI were assigned to the EG and 9 (18.4%) to the CG. The PoC started in November 2023 and ended in July 2024. The start and end dates were different across countries because of the various difficulties encountered in organizing the trial and recruiting end users in each site. The efficacy of the engAGE platform will be demonstrated on the basis of the improvement or maintenance of cognitive capacity. In addition, the effects on the quality of life and social connectedness of primary end users, as well as the reduction in the care load and stress of caregivers, will contribute to determining the importance of the platform. Furthermore, the feasibility of the engAGE intervention will be assessed on the basis of the usability and acceptance of the platform, both measured through standardized quantitative scales. Data analysis was completed at the end of 2024, and the results will be published at least by 2026.

Discussion

Summary

The engAGE project is an innovative intervention designed to counteract cognitive decline in older adults with MCI by integrating social robots, mobile apps, and wearable sensors into a comprehensive platform. The presented PoC will demonstrate the feasibility of this approach that merges in-facility and at-home technology-based intervention in three European countries (Italy, Switzerland, and Norway). The PoC will also show preliminary efficacy in maintaining cognitive function, which is the primary goal of the engAGE platform. Moreover, a positive impact on the quality of life, physical activity levels, and sleep quality among participants will be demonstrated, as well as acceptability and usability rates of the platform. Regarding secondary end users, the introduction of the engAGE platform is expected to reduce caregivers' burden and enhance their engagement in the care process.

The engAGE platform addresses critical gaps identified in previous studies on digital health interventions for MCI. Social robots have been explored for their potential to engage older adults with dementia or MCI [17,18]. Although these studies have demonstrated the acceptability of social robots for promoting social interaction and cognitive stimulation, they often focus on single-domain interventions (eg, storytelling or quizzes) rather than a holistic approach combining cognitive training, physical activity monitoring, and caregiver support. In addition, several mobile apps have been developed for cognitive training in older adults with MCI, such as those focused on memory games or problem-solving tasks [13,14]. However, these apps often lack integration with other tools or technologies that address physical activity or social engagement. Similarly, telehealth interventions have shown promise in providing remote cognitive rehabilitation, but they typically do not include real-time interaction [15,16]. In contrast to these existing solutions, engAGE offers a multicomponent intervention that integrates social robotics, mobile apps, and an activity tracker, as well as personalization by ML algorithms. Moreover, the innovative approach of the engAGE platform integrates in-facility services and home-based intervention. This comprehensive approach aligns with recommendations from recent systematic reviews emphasizing the need for multidomain interventions to address the complex needs of older adults with MCI [41,42].

Limitations

Although the engAGE project aims to represent an important step toward developing integrated digital health solutions for older adults with MCI, several limitations should be acknowledged. Despite the study being structured as an RCT, the sample size was not computed, and the number of end users enrolled was relatively small (N=80), limiting the generalizability of findings to larger populations. Due to the focus on the feasibility and initial efficacy of the intervention, the findings should be used to inform future sample size calculations and refine intervention protocols for future studies that aim to demonstrate the efficacy of the engAGE platform. Participants were recruited from health care organizations and daycare centers located in city areas, introducing a potential bias: people with less access to health and digital services were not considered. However, to make results more generalizable, the study was conducted across three European countries (Italy, Norway, and Switzerland) that show differences in cultural and health care contexts.

The duration of the study (ie, 6 months) was minimal, as it was unlikely to observe significant changes in cognitive capacity or the caregiver burden. Moreover, ML algorithms are designed to personalize interventions based on user data, and the study duration could not be sufficient to fully profile individual

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preferences or needs, making the personalization inefficient. Finally, the complexity of the platform due to the integration of several technologies, services, and ML algorithms introduced ethical concerns and exposed the users to risks in terms of data protection. However, both data protection and ethical issues were considered and addressed within the engAGE project to guarantee users' security and safety. Thus, the presented PoC should be followed by a larger structured RCT that involves a larger sample to appreciate the significant impact of the engAGE platform, including personalization functionalities, both on end users and on national health care systems.

Acknowledgments

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Data Availability

The datasets generated during this study are available from the corresponding author upon reasonable request. Popular scientific dissemination, conference proceedings, related research papers, and public deliverables including the findings of the project are public and accessible at the official engAGE (Managing Cognitive Decline Through Theatre Therapy, Artificial Intelligence, and Social Robot–Driven Interventions) website [43].

Conflicts of Interest

The authors state that the study protocol presented in this paper involves the use of technology services developed by companies with which they have professional relationships, specifically MEMAS, a mobile app developed by KARDE AS, and an app for the Pepper robot developed by IRIS Robotics.

Multimedia Appendix 1
Proposal review and acceptance document from the Active Assisted Living Programme, funded by the European Union.
[PDF File (Adobe PDF File), 35 KB - resprot_v14i1e67601_app1.pdf]

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Abbreviations

AAL: Ambient and Assisted Living
CG: control group
EG: experimental group
engage: Managing Cognitive Decline Through Theatre Therapy, Artificial Intelligence, and Social Robot–Driven Interventions
GDPR: General Data Protection Regulation
ICT: information and communication technologies
IRCCS INRCA: Istituto di Ricovero e Cura a Carattere Scientifico – Istituto Nazionale di Riposo e Cura per Anziani
MAC-Q: Memory Assessment Clinic Questionnaire
MCI: mild cognitive impairment
ML: machine learning
MoCA: Montreal Cognitive Assessment
PoC: proof of concept
RCT: randomized controlled trial
SUS: System Usability Scale
UCLA: University of California, Los Angeles
UTAUT: Unified Theory of Acceptance and Use of Technology
WEMWBS: Warwick-Edinburgh Mental Well-Being Scale

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Protocol

The Community Health Workers and Mobile Health for Emerging Adults Transitioning Sickle Cell Disease Care (COMETS) Trial: Protocol for a Randomized Controlled Trial

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Abstract

Background: Transitioning from pediatric to adult sickle cell disease (SCD) care is challenging for emerging adults (aged 17-25 years). This period is marked by a 7-fold increase in mortality rates and has the highest rates of hospitalizations, emergency room visits, and hospital readmissions compared with children living with SCD. These challenges are exacerbated by fragmented care coordination, difficulty navigating adult health care systems, and increased self-management responsibilities.

Objective: This study aims to compare the effectiveness of 2 interventions designed to support emerging adults living with SCD during this transition: a mobile health (mHealth) app and community health worker (CHW) support to standard care.

Methods: The Community Health Workers and Mobile Health for Emerging Adults Transitioning Sickle Cell Disease Care (COMETS) trial is an ongoing multicenter, 3-arm, open-label randomized controlled trial; 375 emerging adults (aged 17-25 years) are being enrolled and randomized 1:1:1 to (1) a 6-month CHW intervention focused on self-management skills, symptom tracking, care coordination, and transition planning; (2) a 6-month mHealth self-management program (enhanced iManage application) with tailored SMS text messaging (THRIVE [Texting Health-Related Resources to Inform, Motivate, and Engage] 2.0); or (3) enhanced usual care (control). Participants are followed for 18 months. The primary outcome is the change in self-reported health-related quality of life assessed using the PedsQL SCD module. Secondary outcomes include acute care use (hospitalizations

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and emergency department visits), patient activation, self-management behavior, and successful transfer to adult hematology care.

Results: The institutional review board at Children's Hospital of Philadelphia approved this study in June 2018. Recruitment began in January 2019 and ended in December 2022; we completed data collection in November 2024. We have enrolled a total of 405 participants.

Conclusions: This trial addresses a critical gap in transition intervention research for young adults with SCD. It will provide evidence on the comparative effectiveness of 2 promising interventions (CHW and mHealth) and inform the development of scalable and sustainable transition support programs. Findings will have implications for improving health-related quality of life, reducing acute care use, and promoting successful transition to adult-centered SCD care for this vulnerable population.

Trial Registration: ClinicalTrials.gov NCT03648710; https://clinicaltrials.gov/study/NCT03648710

International Registered Report Identifier (IRRID): DERR1-10.2196/69239

(JMIR Res Protoc 2025;14:e69239) doi:10.2196/69239

KEYWORDS

sickle cell disease; pediatrics; health care transition; adolescents and young adults; self-management; quality of life; mobile health; mHealth; community health worker; mobile phone

Introduction

Background

Emerging adults with sickle cell disease (SCD) face a 7-fold increase in mortality rates during the transition from pediatric care to adult care [1]. In addition, this subpopulation (aged 17-25 years), experiences the highest rates of hospitalizations, emergency room visits, and hospital readmissions compared with children living with SCD [2]. This alarming increase in mortality and acute care use stems partly from the cumulative effects of SCD leading to organ dysfunction, with the risk of comorbidities such as stroke and silent infarcts worsening as individuals age [3,4]. In addition, during this transition process, emerging adults with SCD experience fragmented care coordination, which increases their vulnerability.

Emerging adults with SCD face shifts in insurance, inconsistent transfer processes, and a lack of comprehensive adult-focused programs [4-6]. For instance, while adherence to chronic transfusion therapy and hydroxyurea therapy can substantially mitigate the risk of neurological complications and other adverse outcomes, inadequate care coordination during the transition to adult care, coupled with suboptimal patient engagement and SCD self-management skills, markedly heighten the risk of neurological complications [6-9]. These complications can exert enduring and profound impacts on physical function, educational attainment, employment, income, and overall health-related quality of life (HRQOL).

Beyond health system challenges, emerging adults face additional psychosocial challenges, including the struggle for financial independence and insurability, which can be complicated by job instability and the loss of dependent coverage on parents' insurance plans [10]. Transportation barriers may also limit access to necessary medical appointments or therapies, especially for those living in areas with limited adult health care resources [8]. In addition, many emerging adults with SCD experience limited access to mental health care, which can exacerbate issues such as depression, anxiety, and the psychological burden of managing a chronic illness [11]. Social determinants of health, including poverty, housing instability, food insecurity, and lack of educational opportunities, also further complicate the ability of emerging adults with SCD to manage their condition effectively and navigate the health care system [11]. Furthermore, the absence of adequate social support and educational resources compounds these challenges, leaving emerging adults with SCD underprepared and less equipped to navigate their transition effectively [6,12].

Disruption in continuity of care, combined with socioeconomic factors, can lead to worse health outcomes, and an increased risk of complications show the need for effective interventions [11,12]. Community health worker (CHW) programs and mobile health (mHealth) platforms have shown promise in addressing these challenges and improving health outcomes for chronic disease transition patients [13,14]. Research shows that CHW programs enhance chronic disease management and health care navigation, improving outcomes in low-resource settings for conditions such as asthma, hypertension, and diabetes [15,16]. For instance, the IMPaCT CHW program demonstrated that participants in the intervention arm received more timely posthospital care and better discharge communication and experienced fewer readmissions [13].

Similarly, mHealth platforms have been effective in promoting self-management and adherence among both adults [17,18] and emerging adults with chronic conditions, including diabetes and post–liver transplant care [14,19,20]. A randomized controlled trial (RCT) of MD2Me, an internet and mobile phone–delivered disease management intervention using automated SMS text messaging algorithms, showed that emerging adults with type 1 diabetes, inflammatory bowel disease, and cystic fibrosis in the intervention arm significantly improved disease self-management and health-related self-efficacy [14]. This technology holds great promise for adolescents with chronic diseases due to the widespread use of smartphones [21]. Integrating CHW and mHealth initiatives can substantially alleviate health care transition challenges and address psychosocial factors, thus improving care continuity and outcomes for patients with chronic diseases.

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Objective

Gaps in evidence highlighted in the study by Viola et al [6] demonstrate the need for multisite RCTs focusing on long-term care outcomes. Current research, while promising, offers inconclusive results due to limited sample sizes and methodological constraints. Recognizing these limitations, our study aims to bridge this gap by conducting comprehensive multisite RCTs that evaluate both clinical and psychosocial outcomes, ultimately aiming to enhance chronic disease management and overall health during this critical period. We hypothesize that emerging adults in the CHW or mHealth arm will have increased HRQOL compared with those in the enhanced usual care arm.

Methods

Theoretical Framework

Our intervention leverages 2 key frameworks: the social-ecological model for adolescents and young adults readiness to transition (SMART) model and the chronic care model. Effective transition care, as emphasized by the SMART model, requires integrating both preexisting and modifiable factors among patients, parents, and health care providers that influence transition readiness. Modifiable factors, such as knowledge, self-management skills, confidence (or self-efficacy), and social support, are critical targets for enhancing transition readiness, especially for individuals managing chronic conditions. The SMART model has been validated across various populations and has been updated for health equity after this trial was designed, including childhood cancer survivors and their parents and health care providers [11,22,23].

For individuals with SCD, as well as their parents and health care providers, the ability to independently manage their SCD is recognized as a crucial goal during the transition to adult care [6,24-26]. Self-management behaviors, defined as the daily, self-motivated, and collaborative activities required to manage symptoms, are essential for successful disease management. In the context of SCD, these behaviors include self-awareness; seeking emotional support; managing diet and hydration; avoiding alcohol, tobacco, and drugs; and adhering to prescribed treatments such as daily hydroxyurea or regular transfusion and chelation therapy.

Self-management support is a foundational element of the chronic care model [27], which is widely regarded as an effective framework for improving chronic illness care. According to this model, improved health outcomes, including better disease control, a smoother transition to adult care, and enhanced quality of life (QOL), are achieved through the activation and engagement of patients in self-management behaviors, supported by proactive health care teams. In this context, individuals who are more "activated" tend to exhibit higher levels of the modifiable factors outlined by the SMART model, such as increased knowledge, self-efficacy, and social support, all of which are crucial for successful self-care and transition. We chose to target these modifiable factors because patients with SCD and their parents and clinicians agree that it is critical to engage in disease self-management to optimize health during the transition period (Figure 1) [28].

Figure 1. Key clinical question and conceptual model. CHW: community health worker; mHealth: mobile health; SCD: sickle cell disease.

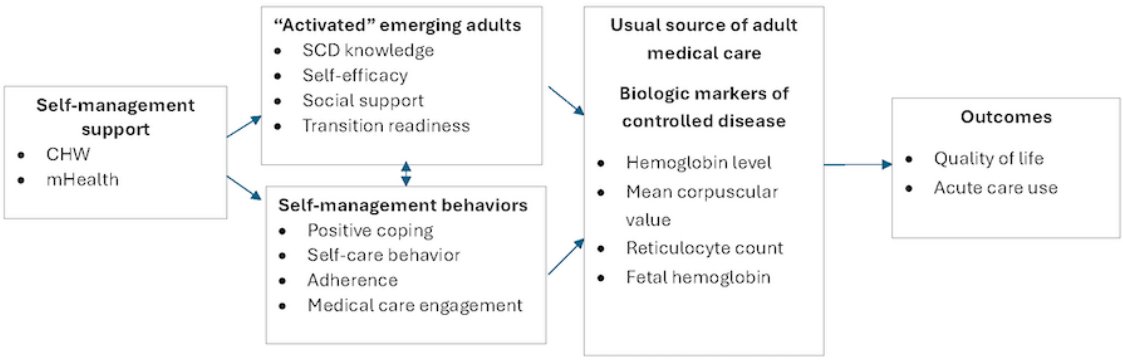

Study Design

The Community Health Workers and Mobile Health for Emerging Adults Transitioning Sickle Cell Disease Care (COMETS) study is an ongoing pragmatic, multicenter, 3-arm, open-label RCT. A total of 5 pediatric SCD centers located in 4 states (Connecticut, New York, Ohio, and Pennsylvania) are participating in this study. Eligible participants are randomized 1:1:1 across sites to a 6-month CHW program, 6-month mHealth self-management program with tailored SMS text messaging, or to enhanced usual care (control).

Specific Aims

The overall goal of this study aims to answer the question "How can community health workers and mobile applications help me to improve my ability to take care of myself (activated patient, self-management), stay connected with my doctors (usual source of care), avoid visits to the ER and hospital (acute care use), and ultimately maximize my quality of life while I am transitioning from my pediatric to adult doctors?"

Aim 1

Compare the effectiveness of 2 self-management support interventions versus enhanced usual care to improve HRQOL and acute care use for transitioning youth with SCD. This aim will test the following hypothesis: Emerging adults in the CHW arm or mHealth arm will have higher quality of care and lower acute care use than those in the usual care arm at 6, 12, and 18 months.

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Aim 2

Identify and quantify whether patient activation, self-management behaviors, biologic markers, and transfer to adult care are mediators of intervention treatment effects. This aim will test the following hypotheses:

- Patients in the CHW arm and mHealth arm will have greater patient activation and self-management behaviors compared with those in the usual care as 6 months.
- Patients with greater patient activation and self-management behaviors will have better treatment outcomes compared with those in usual care at 6, 12, and 18 months.
- Patients in the CHW arm and mHealth arm will affect the total number of adult hematology visits and magnitude of biologic markers compared with those in usual care at 18 months.
- Patients with greater adult hematology visits or higher biologic markers will have better outcomes compared with those in usual care at 18 months.

Aim 3

Identify individual and family factors that moderate intervention treatment effects. We will test the following hypotheses:

- Emerging adults with SCD and high disease severity in the CHW arm or mHealth arm will have higher HRQOL and lower QOL or lower acute care use than those in the usual care arm at 6, 12, and 18 months.
- Older adults (aged ≥22 years) with SCD in the CHW arm or mHealth arm will have higher QOL or lower acute care use than those in the usual care arm at 6, 12, and 18 months.
- We will also explore whether patient demographics (gender, education or employment, health literacy, insurance type, and zip code), family demographics (living with parent or caregiver and maternal education), and recruitment method moderate outcomes in the CHW arm or mHealth arm compared with similar patients in the usual care.

Exploratory Aim

Explore the association of enhancements to usual care on pediatric and adult care use. We will test the hypothesis that enhancements to usual care will decrease pediatric acute use and increase adult acute use.

Study Population, Recruitment, and Enrollment

Eligible participants are young adults aged 17 to 25 years with SCD diagnosis of all genotypes who plan to transition to an adult hematologist within 12 months; have access to a mobile device, tablet, or computer; and can interact with a mobile- or web-based program. Eligible participants are identified by reviewing each recruitment site's daily hospitalized patients, weekly hematology appointments, and hematology practice registries. Across the 5 pediatric SCD centers, we estimate that there will be 745 eligible patients over the recruitment period, with an equal distribution between male and female patients.

Recruitment strategies include in-person enrollment during appointments or admissions and mailed or emailed communications with a recruitment letter, study flyer, and a recruitment video. During the COVID-19 pandemic, telephone recruitment and electronic consent were added to maintain recruitment goals. Retention strategies include completion of enrollment and follow-up procedures in-person, telephone, or an email or text, automatic reminders, and incentives for effort. Figure 2 provides an overview of the study screening and enrollment process.

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Figure 2. Community Health Workers and Mobile Health for Emerging Adults Transitioning Sickle Cell Disease Care (COMETS) study flowchart among emerging adults with sickle cell disease (SCD).

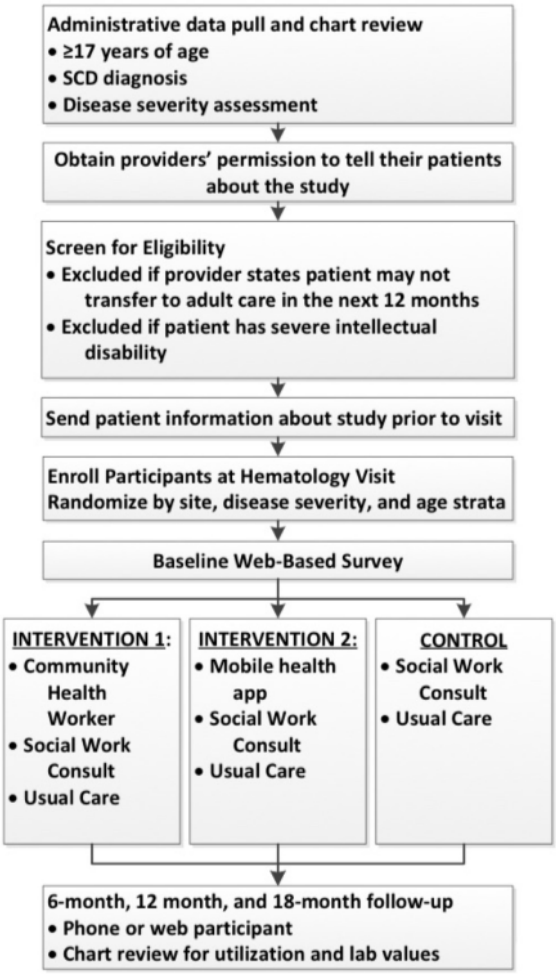

Ethical Considerations

Institutional Review Board Approval and Consent

The COMETS study was funded in September 2017. Institutional review board (IRB) approval was received in June 2018 (IRB 18-015106) at the prime institution, the Children's Hospital of Philadelphia (CHOP), and submitted to each participating site for site-level approach. This study was registered in August 2018 (NCT03648710). The study is being conducted in accordance with the IRB-approved protocol (December 15, 2020).

Informed consent was obtained from all study participants before their involvement in the research by a study coordinator. Participants were provided with comprehensive information about the study's objectives, procedures, potential risks, and their rights, including the option to withdraw at any time without consequence. Multiple enrollment options were provided, including in-person and electronic consent via REDCap (Research Electronic Data Capture; Vanderbilt University). Participants who were aged 17 years at the time of enrollment were reconsented at the age of 18 years at an upcoming appointment, via phone or via REDCap using an electronic consent. This study was granted a waiver of parental permission due to the minimal risks associated. A waiver of documentation of consent was also granted for those aged 17 years at the time of enrollment, as they were reconsented once they turned 18 years during the study period.

Privacy and Confidentiality

All survey data were entered and stored in REDCap. Data linkage was conducted at the CHOP via staff from the Data and Biostatistics Data Unit. Linkage used movement reference number, first or last name, date of birth, and gender, where appropriate. To ensure confidentiality of patient information, the dataset was deidentified after a master file of linked data was created.

Compensation

Participants received compensation for completing surveys at designated time points: US $50 (baseline), US $75 (6 months), US $100 (12 months), and US $150 (18 months). Participants randomized to the mHealth app arm could earn up to US $3 per month for engagement, with incremental rewards for consecutive usage streaks. Additional incentives of US $5 and US $11 are provided for sustained engagement at 3 and 6 months. Payments are managed through ClinCards, a secure, reloadable debit card. Compensation amounts were determined in consultation with patient and parent coinvestigators.

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Risk and Safety Monitoring

The study is considered minimal risk, with primary concerns including breach of confidentiality and participant discomfort with study measures. These risks were mitigated through data deidentification, password-protected storage, and voluntary participation.

For both intervention arms, there is a risk that participants may communicate urgent issues to be handled by a health care provider. To mitigate this risk, participants were provided with direct instruction at the time of consent and randomization, and constant monitoring of peer-to-peer communication in the mHealth app by study staff. Study staff who received communication from participants routed the information to the study site social worker, where appropriate.

The principal investigator was responsible for monitoring the safety of study participants and complying with all reporting requirements. Any adverse events were reported immediately to the CHOP IRB.

Randomization

Random assignment takes place after enrollment and the completion of the baseline survey. A document including stratification and randomly permutated blocks of unequal sizes (to prevent providers and patients from manipulating the randomization) was used in REDCap's randomization module. Enrolled participants will be randomly assigned to a treatment arm after being stratified by recruitment site, age (≤21 y and ≥22 y), and disease severity (moderate and severe), resulting in 12 different randomization strata [29,30]. Severe SCD disease will be determined by chart review and defined by the following: (1) any history of stroke, acute chest syndrome, or ≥3 emergency room visits within the 3 years before enrollment, which are all indications for disease modifying therapy, such as daily hydroxyurea or monthly exchange transfusion therapy [31-33]; and (2) receipt of monthly exchange transfusion therapy, defined by ≥2 exchange transfusions in an outpatient setting within 6-month period [33]. Severe disease will be defined as any history of acute chest syndrome, stroke, or ≥3 hospitalizations in the past 3 years [31,32].

This is a nonblinded study because the nature of the intervention prevents patients from being blinded to their study arm.

Control Arm: Enhanced Usual Care

Enhanced usual care, standardized across all sites through transition or transfer of care checklist, is administered by the social work team at each recruitment site. During the intervention development phase, all recruitment site investigators reviewed and decided on the elements to be included in this checklist based on transition elements at their institution. The checklist is reviewed at the 12-month time point in the trial with the participant during a scheduled hematology visit. Elements of the checklist include (1) patient seen by the pediatric provider, with the parent outside the examination room at least once, (2) a social work consult to screen and address sociodemographic risk factors, (3) information on health insurance availability provided to patient, (4) adult hematologist identified, (5) adult primary care provider identified, (6) medical release signed, and (7) medical record viewable or sent to adult provider. Elements of the checklists are based on existing checklists by organizations such as the Transfer of Care Checklist developed by Got Transition or Center for Health Care Transition Improvement [34] and those developed by the National Institute for Child Health Quality [35]. All study participants received standardized enhanced usual care.

Enhanced Usual Care+Peer CHW

The CHW program is modeled after the IMPaCT program developed by IMPaCT Care, Inc [13,36,37]. Components of the CHW program include (1) development of patient-centered goals and individualized action plan around self-care, symptom tracking, and transition to adult care; (2) provision of information, skills, and tips; and (3) tailored peer support using telephone calls or visits.

To identify the components of the CHW intervention, web-based work group meetings were held to define the role and training components [38]. Training topics included local hospital and community knowledge, SCD and transition to adulthood education, basic clinical research training, foundational CHW skills and concepts, and trial-specific aims and resources.

Training components included IMPACT's 2-week training course, onboarding and orientation at their respective sites, and Collaborative Institutional Training Initiative for clinical research. With an emphasis on ongoing support and education, CHWs meet weekly with a trial supervisor and their site supervisor to review caseloads and address any concerns. Monthly group huddles are held to support peer-to-peer learning for both CHWs and their supervisors. CHWs are expected to contact participants weekly during the 6-month intervention period to remain consistent with other successful protocols [39,40].

Enhanced Usual Care+mHealth

Participants randomized to the mHealth arm will download an enhanced version of iManage [41] called iManage SCD, developed by Crosby et al in collaboration with adolescents and young adult patients with SCD [28,38]. Key components of iManage SCD include (1) development of patient-centered goals around self-care, symptom tracking, and the transition to adult care; (2) provision of information, skills, and tips to support these goals; (3) virtual peer support, where users can encourage others, form teams, and interact with fellow youth with SCD; and (4) daily symptom tracking and visual monitoring of goal completion. iManage SCD is an mHealth application accessible via smartphone, tablet, or web and has been shown to be highly feasible and beneficial for emerging adults with SCD.

Enhancements to the iManage application were identified through the convening of a multi-stakeholder group, including an application development firm, clinicians, researchers, and young adults with SCD across the 5 identified recruitment sites. The development process of the enhanced application has been described [28]. Interviews with stakeholders explored 8 topics, including (1) social behaviors and entertainment, (2) treatment, (3) pain impact, (4) pain management, (5) SCD knowledge, (6) lifestyle and goals, (7) communication and support, and (8) envisioning the future. Final components of the application

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include health behavior challenges, tracking of medications and symptoms, an educational material library, discussion boards, and medical summary. User engagement was tracked through analytic tools integrated within the mHealth app [27].

In addition, daily tailored texting (THRIVE 2.0) [42], based on patient-defined goals were delivered to participants randomized to the mHealth arm of the study. Preliminary studies have found that THRIVE 2.0 improves health-promoting behaviors such as sunscreen use among adolescent and young adult cancer survivors. These SMS text messages were tailored around modifiable factors and delivered twice a week. Two types of messages were delivered, educational and interactive. Messages focused on SCD knowledge, skills and efficacy, relationships, self-management, school or work, and coping.

Participants will receive training on how to use and customize iManage SCD during enrollment and have access to a helpdesk for support. The content on iManage SCD was continuously monitored by research staff. Participants were able to access the application after the 6-month active intervention period.

Both intervention arms include the same core components, with one delivered by a CHW and the other through a digital platform. Both interventions were designed to support self-management by facilitating patient-centered goal setting, providing tailored information and skill-building, and offering peer support. In the mHealth intervention, these components are adapted to be delivered via the app, mirroring the CHW's role in engaging participants through structured content and interactive features.

Data Collection

Overview

Participants are followed with measures related to HRQOL, acute care use, patient activation, self-management behaviors, and experiences with the COVID-19 pandemic collected through web-based survey, phone, or in-person at baseline and at 6, 12, and 18 months. Disease severity, health care use, and biologic markers will be measured from the electronic medical record (EMR) at baseline and at 6, 12, and 18 months. Study data are stored and managed using the REDCap web-based system, overseen by the CHOP. Site study coordinators are responsible for data entry at their respective sites.

Baseline Clinical and Demographic Information

Baseline data will be gathered from EMRs and include age, SCD genotype, history of intellectual disability, depression, anxiety, stroke, acute chest syndrome, emergency room visits, and prescribed disease-modifying therapies (hydroxyurea or exchange transfusions).

Intervention Adherence Process Measures

For the mHealth intervention, adherence will be tracked using app usage metrics (eg, days and frequency of access, responses to SMS text messages, and goal progress) through REDCap. CHW intervention adherence includes contact frequency (in-person, phone, email, and SMS text messaging) and goal attainment. Usual care measures include social work consults and chart review transition checklists, tracking key actions such as insurance review and provider identification.

HRQOL: Primary Outcome

HRQOL will be measured using the PedsQL SCD module [31,41], a validated 43-item tool that assesses pain, emotional health, treatment experience, and communication.

Health Care Use

Health care use data, including acute care (emergency department visits and hospital admissions) and ambulatory care, will be collected from patient reports, EMRs, and Medicaid billing data.

Validation of Health Care Use Data

Patient-reported data on health care use were validated with EMR data, calculating annualized acute care use and ambulatory care use for both pediatric and adult hematology.

Measures of Self-Management Behavior

Self-management will be measured through several tools: the Brief Coping Orientation to Problems Experienced for coping strategies [43], the Jenerette Self-Care Assessment Tool for self-care actions [44], the Medical Adherence Measure for medication adherence [45,46], medical chart reviews for appointment no-shows, and chronic transfusion adherence (based on patient report and chart review).

Measures of Patient Activation (Mediator)

Patient activation will be assessed using the Sickle Cell Disease Knowledge Questionnaire [47], the Transition Readiness Assessment Questionnaire [48], and the Medical Outcomes Study Social Support Survey [49].

Experience With the COVID-19 Pandemic

A 33-question survey will be used to assess COVID-19 symptoms, mental health impacts, trauma, social distancing effectiveness, care access issues, and telehealth satisfaction, adapted from the Johns Hopkins COVID-19 Community Response Survey [50] and US Census Household Pulse Survey [51]. These questions were chosen with input from young adult stakeholders and site principal investigators.

Biologic Marker of Disease Control (Mediator)

Biologic markers, including hemoglobin levels, mean corpuscular volume, reticulocyte count, and fetal hemoglobin percentage, will be obtained from chart review. These markers reflect anemia, hydroxyurea adherence, stroke risk, and disease severity (Table 1).

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Table 1. Patient-reported scales, characteristics, and source.

Measure	Items, n	Source
Primary outcome measures		
Pediatric Quality of Life Inventory sickle cell disease	43	Panepinto et al [31], 2013
Activated emerging adult patient measures (mediators)		
Sickle Cell Disease Knowledge Questionnaire	23	Original scale: Armstrong et al [52], 1993, used in Barakat et al [53], 2010, Logan et al [54], 2002
13-item Patient Activation Measure	13	Logan et al [54], 2002; Hibbard et al [55], 2005
Transition Readiness Assessment Questionnaire	20	Sawicki et al [56], 2011; Wood et al [57], 2014
Medical Outcomes Study Social Support Survey	19	Sherbourne and Stewart [49], 1991
Self-management behavior measures (mediator)		
Brief Coping Orientation to Problems Experienced	28	Gil et al [58], 1991
Medication Adherence Measure	17	Zelikovsky and Schast [45,46], 2008
COVID-19 pandemic measures		
COVID-19 symptoms and testing experience: symptoms; diagnosis	4	Mehta et al [50], 2020
COVID-19 and mental health impacts: mental health	10	Mehta et al [50], 2020 and Harkness et al [59], 2020
COVID-19 and violence and trauma: violence; fear of violence	3	Mehta et al [50], 2020
COVID-19 and social distancing: social distancing; social Impact	10	Mehta et al [50], 2020
Reduced access to care	2	US Census Bureau [60], 2020
Satisfaction with telehealth services	4	Parmanto et al [61], 2016

Outcomes

The primary outcome of the COMETS study will be the change in HRQOL. The secondary outcomes are acute care use (hospitalizations and emergency department visits), patient activation, self-management behaviors, and successful transfer to adult hematology care.

Statistical Methods

This study is ongoing; therefore, the statistical analyses have not been performed.

Sample Size

Sample size calculations are based on our primary end point of change in HRQOL and health care use for each participant over their study participation [62]. Details of the sample size calculations are presented in Multimedia Appendix 1.

Primary Analysis

Analyses will be conducted in Stata (version 18.0; StataCorp), with 2-sided tests of hypothesis and a P value <.05 as the criterion for statistical significance.

To compare the effectiveness of 2 self-management support interventions (CHWs and mHealth) versus enhanced usual care on the primary outcomes (HRQOL and acute care use), we will first compare groups at baseline using chi-square tests for categorical variables and 1-way ANOVA or Kruskall-Wallis, as appropriate, for continuous variables. We will use descriptive summaries and graphical displays to evaluate the distribution of and relationship between variables. When required, transformations to achieve normality will be considered.

The initial analysis will use 1-way ANOVA to test the hypothesis that the 3 treatment groups showed no change from the end of the intervention to the baseline in the primary and secondary outcomes. If the hypothesis of equal group means is rejected (there was a change detected), 3 post hoc tests will be applied (with Bonferroni adjustment for multiple testing) to identify pairwise differences between treatment groups. We postulate that a difference in change of 10 points in PedsQL SCD total between groups will be clinically meaningful.

Next, we will construct longitudinal models that include baseline, 6-, 12-, and 18-month measurements as outcomes. Longitudinal models account for correlation of measures within emerging adult over time; use all data collected; allow for and can be used to adjust for dropout or nonadherence to assigned treatment; can adjust for differences in patient characteristics not balanced by randomization; can include indicator variables for clinical site; and permit continuous, count, and binary outcomes. We will build models using generalized estimating equations (GEEs) or quasi-least squares (QLS) [63]; QLS is based on GEE but allows for implementation of the Markov correlation structure that is appropriate if participants intermittently miss appointments. Mixed effects models may also be considered. For example, mixed models can be used to relax the assumption of constant variance that is required for QLS and GEE; they will, therefore, be useful if residual diagnostics for GEE or QLS suggest an increase in the variance of outcomes over time.

The longitudinal models will include indicator variables for visit, group, and time-by-visit group interaction terms (if appropriate, time will be included as a continuous variable). If the time-by-group interaction terms differ significantly from 0,

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this will indicate that the change over time in outcomes differs significantly between the treatment groups. In sensitivity analysis to examine the impact of treatment intensity, we will also evaluate the effects of the intervention stratified by intervention dosage (frequency of interaction with the CHW, or mHealth or texting program).

Secondary Analysis

Next, we will assess whether patient activation, self-management behaviors, biologic markers, and transfer to adult care are mediators of intervention treatment effects. This analysis focuses on the role of patient activation and self-management behaviors at 6 or 12 months as mediators of the effect of the intervention on the study outcomes. We will perform the mediation analysis using structural equation modeling; this will allow us to estimate the total effect of the treatment on outcomes as a sum of direct effects and indirect effects that are mediated by patient activation, self-management behaviors, biologic markers, or transfer to adult care. To evaluate the role of each potential mediating variable, we will calculate the proportion of the total effect that is mediated, the ratio of the indirect effect to the direct effect, and the ratio of the total effect to the direct effect. We also evaluate percentile and bias-corrected bootstrapped SEs and CIs for the effects.

We will next perform an exploratory analysis to identify individual and family factors that moderate intervention treatment effects. To test the hypothesis that adults with SCD and high disease severity will moderate the effect of intervention on outcome measures at 6, 12, and 18 months, we will first evaluate whether the impact of the intervention on overall changes (6 m minus baseline) differs between the high versus low severity groups. This will be tested by building a regression model with changes (end of intervention minus baseline) as the outcome variable, and that includes indicator variables for treatment groups, severity group (high vs low), and group-by-severity interaction terms. If the interaction term for a particular treatment group differs significantly from 0, this will indicate that the impact of that intervention differs according to (is moderated by) severity of disease. Next, to evaluate moderation in longitudinal models, we will fit models with change since baseline at 6, 12, and 18 months as the outcomes; these models will also include indicator variables for treatment groups, indicator variables for severity group, and time-by-severity interaction terms. If the interaction terms differ significantly from 0, this will indicate that the change since baseline depends on both treatment group and severity status (ie, that the impact of treatment is moderated by severity of disease). We anticipate that this model will be adequate to evaluate interactions; however, it may be necessary to consider more complex models, by modifying the longitudinal models for analysis of our primary outcome variable to include time by severity group, severity group by intervention, and severity by time by treatment group (3-way interaction) models. Finally, to explore the moderating effects of individual and family demographic characteristics on treatment effects, we will convert all patient and family demographic variables into dichotomous variables and evaluate potential moderation using the approach just described for severity status.

Results

The COMETS study was funded in September 2017, received IRB approval in June 2018 (IRB #18-015106), and was registered in August 2018 (NCT03648710). The study is being conducted in accordance with the IRB-approved protocol (December 15, 2020). Participant recruitment began in January 2019 and ended in December 2022. A total of 405 participants were enrolled, with 374 being randomized to the intervention arms (enhanced usual care: 127, mHealth: 125, and CHW: 122). Data collection was completed in November 2024, with results expected to be submitted for publication in peer-reviewed journals in 2025.

Discussion

Principal Findings

This research aims to compare the effectiveness of 2 interventions, a CHW intervention and an mHealth intervention, to enhanced usual care alone. Our study seeks to address the significant gap in research focused on transition to adult care, while examining the impact of such interventions on chronic disease management, health care use, or health outcomes. The COMETS trial is one of the first multisite RCTs to assess the effectiveness of these interventions specifically for young adults with SCD.

Despite the under-studied effectiveness of mHealth and CHW programs in improving the transition to adult care for emerging adults with SCD, this research hypothesizes that incorporating either a CHW or an mHealth app will improve HRQOL and reduce acute care use. This trial aims to identify effective interventions to support young adults with SCD as they navigate the complexities of adult care, addressing gaps in current research. Positive results could translate into significant cost savings for payers and health care systems by reducing avoidable emergency department visits and hospitalizations, informing funding agencies such as Health Resources and Services Administration and State Title V programs dedicated to improving care for children with special health care needs. With the increase in interest and clinical recognition of both CHW programs [64,65] and mHealth apps [66-69], our study aims to support the growing body of research to aid in integrating these interventions into standard care models potentially leading to more personalized, accessible, and efficient care. This increase in mHealth app use and support for CHW programs in not only patients with SCD but also among patients with other chronic diseases is important to acknowledge. These interventions were chosen for their potential cost-effectiveness and scalability. Ultimately, demonstrating measurable improvements in health outcomes and cost savings will be key to integrating these personalized and accessible interventions into standard transition care models, leading to more efficient care and sustained improvements in health outcomes for young adults with SCD and other populations with chronic diseases.

Strengths and Limitations

The study uses several key strengths to enhance its effectiveness and scalability. First, the involvement of stakeholders,

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particularly young adult coinvestigators, during the development phase ensures that research is aligned with their real-world experiences. This provides a comprehensive understanding that can inform implementation. In addition, building upon the established IMPACT program [40], the study leverages past research and implementation insights for further refinement and enhancement. In response to the limitations posed by COVID-19, such as reduced in-person recruitment opportunities, the study incorporates diverse communication methods to increase accessibility and engagement. Finally, the use of robust patient registries allows for real-time monitoring and identification of patients with SCD who meet study criteria, facilitating a streamlined recruitment process even with pandemic-related constraints.

SCD interventions have anticipated limitations that must be acknowledged, particularly when engaging young adults. Emerging adults are often at pivotal time in their lives where they might be transitioning into college or the workforce. This stage of life is inherently demanding and can make it challenging for young adults to adhere to treatment plans and prioritize participation in SCD programs. In addition, there is a widespread distrust of the health care system among this demographic, often rooted in historical and systemic inequities, which can be exacerbated by experiences of discrimination and stigma in both health care settings and broader society [70]. These factors together can lead to feelings of alienation and reluctance to engage with and adhere to SCD treatment plans or seek necessary care [70]. Additional limitations stemmed from the population being emerging adults, specifically surrounding the reliance on self-reporting and its potential bias. Recall bias is a challenge because adolescents and young adults with SCD may not accurately remember the past, or due to social desirability bias, they may answer questionnaires with what they think they should say or what they believe is socially desirable. To mitigate these challenges and bias, we carefully chose questionnaire designs and collected input and consulted adolescents and young adults with SCD and other stakeholders who could speak to these challenges. Furthermore, addressing these challenges requires targeted strategies that build trust through culturally competent care, increase accessibility by aligning program delivery with young adults' schedules, and provide support systems that acknowledge and alleviate the unique pressures faced during this life transition.

In conclusion, the results of this study will contribute significantly to filling the gap in transition care research for emerging adults with SCD, guiding future intervention strategies, and providing valuable evidence for health care systems, payers, and policy makers. The potential impacts of these interventions extend beyond clinical outcomes, offering the possibility of improved psychosocial well-being, enhanced patient self-efficacy, and a more successful transition to adult care for individuals with SCD.

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Authors' Contributions

SJ, KMS-W, CMS, LEC, LAS, LPB, B Aygun, B Andemarian, AA-K, KAS, SL, and DMR designed the study. JS designed the statistical analysis plan. TDB, CMS, SJ, KMS-W, LEC, LAS, LPB, B Aygun, B Andemarian, AA-K, and DMR carried out the trial. TDB and OT drafted the manuscript. All authors read, carefully reviewed, edited, and approved the final manuscript.

Conflicts of Interest

KMS-W initiated this project as a full-time Perelman School of Medicine University of Pennsylvania employee and director of the Comprehensive Sickle Cell Center at the CHOP. She transitioned to professor emeritus and physician affiliate at CHOP in May 2021 with Global Blood Therapeutics and in September 2022 with Pfizer. BA is Agios advisory board member and member of iDMC. AA-K and ON are advisory board members of Pfizer. LEC is member of Pfizer Peer to Peer Program.

Multimedia Appendix 1
Sample size calculations.
[DOCX File , 18 KB - resprot_v14i1e69239_app1.docx]

Multimedia Appendix 2
Peer review report from PCORI.
[PDF File (Adobe PDF File), 130 KB - resprot_v14i1e69239_app2.pdf]

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Abbreviations

CHOP: Children's Hospital of Philadelphia
CHW: community health worker
COMETS: Community Health Workers and Mobile Health for Emerging Adults Transitioning Sickle Cell Disease Care
EMR: electronic medical record
GEE: generalized estimating equation
HRQOL: health-related quality of life
IRB: institutional review board
mHealth: mobile health
QLS: quasi-least squares
QOL: quality of life
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SCD: sickle cell disease
SMART: social-ecological model for adolescents and young adults readiness to transition

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Protocol

Investigating Information Visualization to Combat Information Overload in Electronic Health Records: Protocol for a Randomized Controlled Trial

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Abstract

Background: Electronic health records (EHRs) have been linked to information overload, which can lead to cognitive fatigue, a precursor to burnout. This can cause health care providers to miss critical information and make clinical errors, leading to delays in care delivery. This challenge is particularly pronounced in medical intensive care units (ICUs), where patients are critically ill and their EHRs contain extensive and complex data.

Objective: We propose to study the effect of an information visualization dashboard on ICU providers' cognitive fatigue in 4 major US medical centers. In this randomized controlled trial, we will compare 2 leading EHRs with a visualization dashboard–based EHR called AWARE.

Methods: This crossover randomized trial will collect physiological and objective data using a screen-mounted eye-tracking device to assess cognitive fatigue among ICU providers. The study will involve 120 ICU providers from 4 US medical centers, with each site using its institutional EHR as the control and the AWARE EHR as the intervention. Participants will be randomly assigned to use either their institutional EHR or the AWARE EHR first, followed by the other EHR, with the order of EHR use and patient case order randomized by the study team. The AWARE tool is designed to integrate within an existing EHR system and provides clinical support tools, such as the ability to trend data points from body systems at a glance. Data analysis will include eye-tracking metrics, performance measures, and validated surveys to evaluate EHR usability and its impact on clinical decision-making. Primary outcomes include the number of cognitive fatigue instances per patient case, time to complete each case, overall usability of the session, number of mouse clicks per case, provider performance scores from questions asked during each patient case, and perceived usability of each EHR. Secondary outcomes include the number of eye fixations per patient case and perceived workload of each EHR.

Results: This EHR usability study was funded in 2021 and initiated in 2022, with a completion date of 2025. Data collection began in August 2023. As of now, 3 of the 4 study sites have completed data collection, with a total of 113 completed sessions thus far. Data collection is ongoing at the fourth site. Preliminary analysis is ongoing, and we expect to begin publishing results in late 2025.

Conclusions: Findings from this research may inform improvements in EHR interface design and usability, which may enhance provider performance, streamline care delivery, and improve patient safety outcomes.

Trial Registration: ClinicalTrials.gov NCT05937646; https://clinicaltrials.gov/study/NCT05937646

International Registered Report Identifier (IRRID): DERR1-10.2196/74247

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(JMIR Res Protoc 2025;14:e74247) doi:10.2196/74247

KEYWORDS

electronic health records; information visualization, cognitive fatigue; information overload; eye-tracking; EHR usability

Introduction

Providers experience information overload when using electronic health records (EHRs) [1-3]. Providers report that information overload is among the major challenges to EHR usability [1]. Information overload can contribute to cognitive fatigue, causing increased mental effort and difficulty making decisions [4].

Data characteristics, such as quantity, frequency, complexity, and quality, can contribute to information overload [5]. Also, difficulty locating information in the EHR or distinguishing erroneous information can contribute to information overload [6]. EHR systems, while beneficial, often contribute to information overload due to their design and usability issues, leading to cognitive overload and potential errors [7,8].

Information overload is associated with provider frustration, as they reportedly spend up to half of a workday working on EHRs and an additional 1-2 hours at home [9]. EHRs containing too much irrelevant clinical information can hinder understanding and make it challenging for providers to quickly access necessary data [1]. This may lead to potential errors in clinical decision-making.

EHR interface design can contribute to information overload by presenting excessive or fragmented data that overwhelms clinicians. Many EHRs require providers to navigate multiple screens to gather relevant patient information, leading to inefficiencies and increased cognitive burden [10]. Additionally, these systems often display large amounts of data without clear prioritization, making it difficult to quickly extract critical insights [11]. Poor usability and complex navigation further exacerbate the issue, forcing clinicians to spend more time searching for information rather than making informed decisions [12]. Improving EHR design by prioritizing essential information and enhancing data representation is critical to reducing cognitive overload and improving patient care.

Prior literature has suggested that integrating data visualization can help mitigate the negative effects of information overload in EHRs [1,13,14]. However, the mechanisms for evaluating the impact of data visualization on EHR information overload are unknown. Data visualization integrations in EHRs can be defined as tools or systems that aggregate patient health data and visualize it to highlight clinically meaningful patterns. These tools may assist clinicians in information prioritization and in recognizing trends in health data.

Visualization dashboards represent a promising approach to reimagining how data is presented within EHRs [15]. By integrating advanced data visualization techniques, these dashboards can transform large volumes of complex data into easily interpretable formats, allowing providers to quickly grasp essential information [16]. The ability to prioritize and highlight critical clinical data not only reduces cognitive load but also enables clinicians to focus on decision-making rather than becoming mired in assessing irrelevant or fragmented information [17].

Visualization dashboards offer a practical way to improve how data are presented in EHRs [14]. Visualization techniques can simplify the presentation of complex information, enabling providers to swiftly identify essential details without becoming overwhelmed [15]. Rather than navigating through multiple screens and fragmented data sources, providers can access the most pertinent clinical information at a glance [18]. This approach not only alleviates the cognitive burden but also allows providers to concentrate more on patient care.

A potential benefit of visualization dashboards is their ability to streamline workflow [14]. Traditional EHRs often require excessive clicking and searching to find relevant details, whereas a well-designed dashboard may consolidate essential patient data into a single, intuitive view [19]. This may not only save time but also enhance efficiency, giving providers more opportunities to engage with patients and make timely decisions [15].

Furthermore, visualization dashboards can facilitate better data interpretation using interactive elements. For instance, dynamic graphs and charts that allow users to manipulate data presentations can enable providers to explore various dimensions of patient information [20]. This interactivity engages users and enhances their understanding of patient conditions, hypothetically leading to better clinical outcomes [21].

Additionally, eye-tracking technology offers an innovative method for quantifying cognitive load and usability [22]. Measuring pupillometry metrics such as pupil dilation provides objective insights into the cognitive demands of intensive care unit (ICU) providers when interacting with their institutional EHR interfaces versus a visualization dashboard [23]. Such empirical data are essential for assessing both interfaces and identifying design elements that reduce information overload and improve user experience, ultimately informing evidence-based EHR enhancements [20,24].

To determine the extent to which EHRs contribute to cognitive load, prior research has used tools such as usability questionnaires [25]. An innovative approach to measuring cognitive load is the use of eye-tracking technology, which provides objective measures of eye data including measures of pupil size, eye fixations or movements, and eye openness [26]. These measures are associated with cognitive load, information processing, and cognitive fatigue.

This study protocol highlights our approach to examining the impact of information visualization on EHR information overload and usability outcomes. In this study, we will use objective measures such as eye-tracking along with subjective measures of usability to determine where and when information overload occurs when using EHRs. We hypothesize that a

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visualization dashboard such as AWARE [27] will result in lower cognitive fatigue and higher usability scores compared to institutional EHRs. Additionally, we hypothesize that the order of exposure to the EHR systems will not significantly influence the primary outcomes, as the randomization process will control for any potential order effects.

Methods

Overview

We will conduct a multisite, cross-sectional usability assessment of cognitive fatigue and EHR usability in a crossover randomized controlled trial (RCT). The decision to use a crossover RCT design for this study is based on several key considerations. A crossover design allows each participant to serve as their own control, which enhances the statistical power of the study by reducing the variability associated with individual differences. This is especially important in usability studies, where subjective experiences and cognitive fatigue levels can differ significantly among participants. This RCT is registered with ClinicalTrials.gov under ID NCT05937646. This study is a continuation of our prior usability study, and additional information is available in our previously published protocol [28].

This study compares 2 leading EHRs with a visualization dashboard–based EHR, AWARE. AWARE is designed to integrate within an existing EHR system. For the purposes of this study, AWARE is used as a standalone EHR tool. AWARE provides clinical support tools, such as the ability to trend data points from body systems at a glance.

Study participants will be medical ICU providers in 4 US medical centers. Across the 4 participating sites, 2 leading EHRs are used. Each site's institutional EHR will be used as the control, and the AWARE EHR will be used as the intervention. Although the ICUs at these medical centers differ in terms of catchment area and patient population, all 4 medical centers are designated as level 1 trauma centers and are equipped with level 3 ICU capabilities. The number of ICU beds across the medical centers ranges from 74 to 200 beds per site.

Providers will be recruited by study teams at each participating medical center site through a combination of email outreach, informational flyers, and word-of-mouth communication. Interested providers will be asked to complete a preliminary screening survey to confirm eligibility to ensure they are current ICU providers or, in the case of residents, that they have completed at least one ICU rotation. Providers who previously participated in the initial round of usability sessions with our study team will be excluded from participation in this study.

Study sessions will be conducted in a simulation laboratory or private space designed to replicate the ergonomic environment of inpatient settings. Standard computer screens from each practice setting will be used with ICU-like ergonomic placement, ambient lighting, and seating.

Prior to each study session, the usability specialist will explain the study purpose and consent forms to providers, emphasizing that the purpose of the study is to evaluate EHR usability rather than assess clinical knowledge. Participants will be informed that their participation is voluntary, and they can decline to participate or withdraw from the study at any time. Following informed consent, each participant will be asked to complete a brief paper-based survey.

We will then ask providers to complete a basic calibration exercise while looking at the monitor, which allows the eye-tracking software to be calibrated to each provider's eye shape and eye size. We will record pupil diameter and other eye-tracking metrics continuously during the study session. All sessions will use the same screen-based eye tracker. A process map outlining the study procedure from participant enrolment through the eye-tracking calibration is provided in Figure 1.

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Figure 1. Process map detailing the study steps from site enrollment to the start of the usability session.

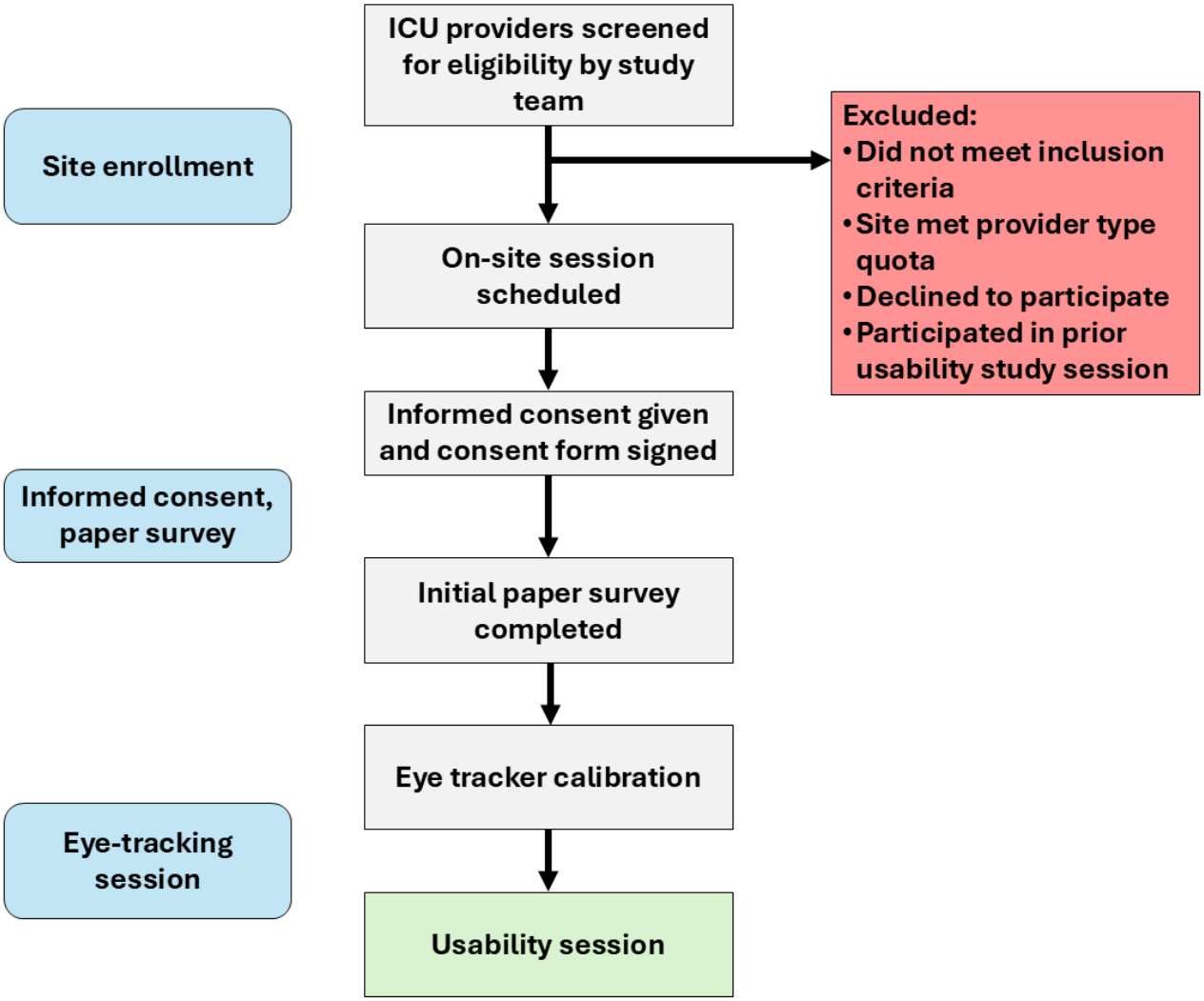

Providers will be informed that they will use their own institutional EHR for 2 patient cases and the AWARE EHR for 2 patient cases. Both the order of EHR used and patient case order will be randomized by the study team prior to data collection at each site. Providers will be informed that they will review 1 patient case at a time, and that they will begin by performing their usual prerounding tasks on each patient. Providers will then signal to the study team that they are ready to begin the question-and-answer activity for that patient. Providers will be encouraged to continue to use the EHR to answer the questions. The nurse informatician (JM) on the study team will record participants' answers using both audio and written recordings. After completion of the questions, the provider will then review the next patient record.

The nurse informatician (JM) will provide a brief demonstration of AWARE prior to providers' use. This demonstration overview includes where to find basic information, such as patient notes, medication information, vital signs, lab results, and how to navigate the patient chart. Providers will be encouraged to ask questions during this demonstration period and are also allowed to ask navigation questions during their patient review. Providers will be instructed that the study team can answer questions related to where to find information or how to display information but that they cannot answer clinical questions related to the patient cases.

Patient Cases

The same 4 cases from our prior usability work will be used in this study, which consists of 2 standard ICU-level patients and 2 complex patients. These 4 cases will be used at all study sites, and the nurse informatician (JM) will ensure consistency in patient cases across study sites. Case order will be randomized such that each provider will review 1 standard and 1 complex patient in their institutional EHR and 1 standard and 1 complex patient in the AWARE EHR. The 2 standard ICU-level patients were less critically ill, not currently ventilated, on fewer medications, and had fewer abnormal laboratory values. The 2 complex ICU-level patients were critically ill with many abnormal laboratory values, on a ventilator with poor oxygenation, and on complicated medication regimens. A detailed process map describing the usability session for control and intervention groups can be seen in Figure 2.

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Figure 2. Process map detailing the usability session for participants in both control and intervention groups. EHR: electronic health record; ICU: intensive care unit; NASA-TLX: National Aeronautics and Space Administration task load index; SUS: system usability scale.

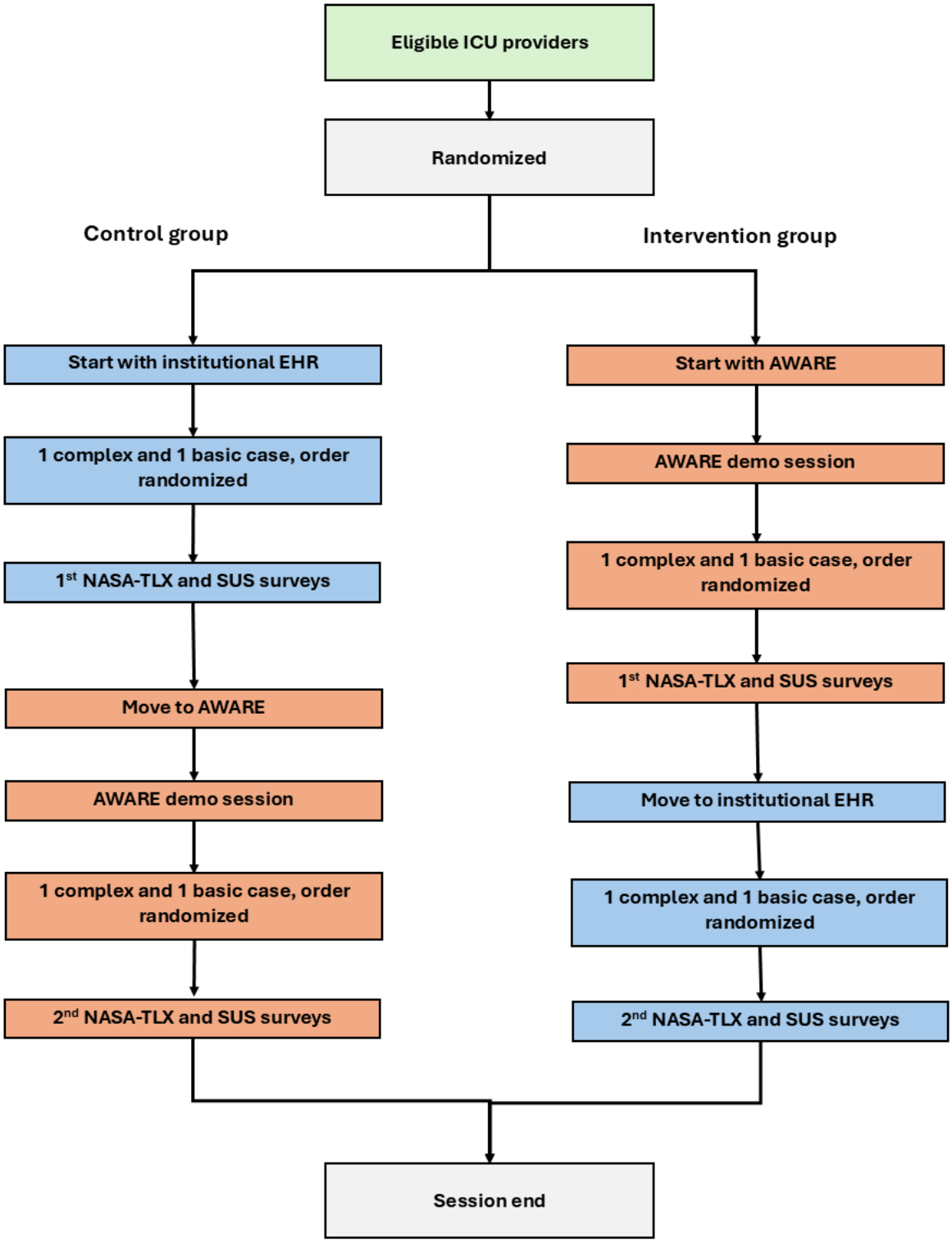

Case Questions

Following a preliminary chart review, providers will be asked 4 questions for each patient case. These questions were developed by a critical care physician (TB) and subsequently reviewed for clarity by a team of critical care physicians prior to data collection. The questions are intentionally designed to ensure that the information could be reasonably located within the EHR and that providers across varying levels of clinical experience would be able to answer. While some questions are relatively straightforward, requiring reference to a single EHR screen or data point, others are more complex, necessitating the integration of multiple data elements or retrieval of information not routinely accessed. This approach allows for analysis of the time required to answer each question, the number of EHR screens accessed, and the number of mouse clicks by each

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provider. Responses will be evaluated and categorized as correct, partially correct, or incorrect by the nurse informatician (JM) on the research team. Alternative responses will undergo review and scoring by a critical care physician (SSC).

Sample

Our goal is to recruit 120 ICU providers, 30 at each site, with the following distribution: 20 physicians and 10 advanced practice providers (APPs). The physician group will be divided into 3 subgroups: 5 attending physicians, 5 fellow physicians, 10 resident physicians, and 10 APPs including nurse practitioners and physician assistants. Each study team's local research assistants will circulate departmental emails and flyers at each site. The site study teams will provide interested individuals with a link to a web-based calendar showing available time slots to facilitate appointment scheduling. Once an appointment is scheduled, the research assistant will email each participant their appointment time and location with a map, as well as a contact number for same-day inquiries or cancellations. Inclusion criteria include the following: ICU physicians and APPs on active full-time ICU service or residents who have completed at least 1 ICU rotation, use of an institutional EHR, and ability to speak English. Providers who participated in our prior usability sessions will be excluded.

Materials and Software

To measure the extent and effect of cognitive fatigue in the EHR, we will use several tools during the 1-hour sessions.

Providers will be asked to complete 1 paper survey before the eye-tracking session. This survey asks basic demographic questions, including age, gender, years since graduation (from medical school or APP schooling), years of experience with their institution's EHR, and the estimated number of hours they use their institution's EHR each week. We will also ask providers if they are on service that day (pre- or postusability session) and to rate their level of sleepiness and stress on a Likert scale.

Directly following the 2 cases in each EHR, providers will be asked to complete 2 additional paper usability surveys. The first usability survey is the National Aeronautics and Space Administration task load index (NASA-TLX) [29], which asks providers to rate the task load of the EHR used for the previous 2 patient cases, including how mentally and physically demanding it was to use and their level of satisfaction and confidence with using the EHR. The second usability survey is the system usability scale [30], which asks providers to rate their satisfaction with the EHR system used, including questions about usability, ease of use, and overall functionality. Both surveys have been used previously among medical providers to measure EHR usability [31,32].

This study will use a noninvasive, screen-based eye-tracker to enhance understanding of providers' cognitive processing during patient chart review in the EHR. The Tobii Pro Fusion, an advanced eye-tracking device equipped with 2 eye-tracking cameras, captures up to 250 images per second to ensure precise and accurate measurement. The device is designed to mount to the bottom bezel of any monitor, allowing for seamless and unobstructed recording of eye-tracking data. The eye-tracker will be used in conjunction with Tobii Pro Lab software, which enables synchronized recording of both eye-tracking metrics and on-screen activity. Widely used in medical and psychological research, the Tobii eye-tracker and its accompanying software provide detailed data on pupil size, gaze location, and eye movement patterns. These metrics will allow for analysis of information processing behavior, in particular the association between pupil constriction and the study's outcome variable, cognitive fatigue.

The AWARE EHR

The 4 patient cases used in the study were built in the AWARE EHR using the same data points as those included in the institutional EHR builds. The team nurse informatician (JM) provided oversight of case builds to ensure consistency and accuracy across platforms.

Unlike traditional EHRs, AWARE is structured according to body systems rather than by data type, offering a different approach to clinical information organization. A screenshot of the AWARE EHR is provided in Figures 3 and 4. During the AWARE demonstration, participants will receive instruction on how to access data points for patient charts, including the location for patient notes, medications, vital signs, laboratory values, intake and output, and other clinical data. Participants will be instructed on how to access individual body systems, how to trend individual values, and how to trend data for each system. Participants will be encouraged to ask questions about where to locate data points both during the demo and during the patient case review to ensure access to information needed for completion of the usability session tasks.

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Figure 3. A screenshot of the AWARE patient interface. Each rectangle represents a different system, indicated by that system's icon (7 in total). Yellow coloring indicates that a value within a system is out of range, while red coloring indicates that a value is significantly out of range.

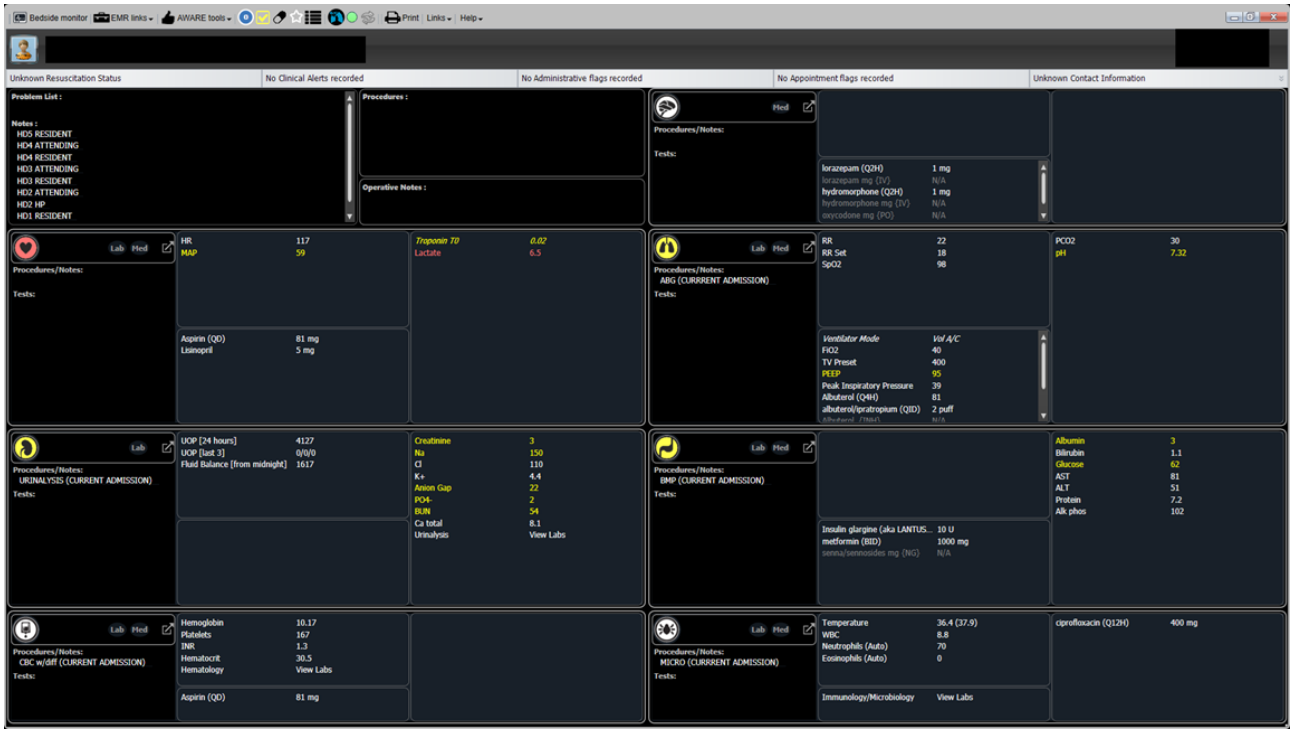

Figure 4. The respiratory system overview within AWARE. Trends are displayed for relevant vital signs and labs, along with medication administration instances along the bottom.

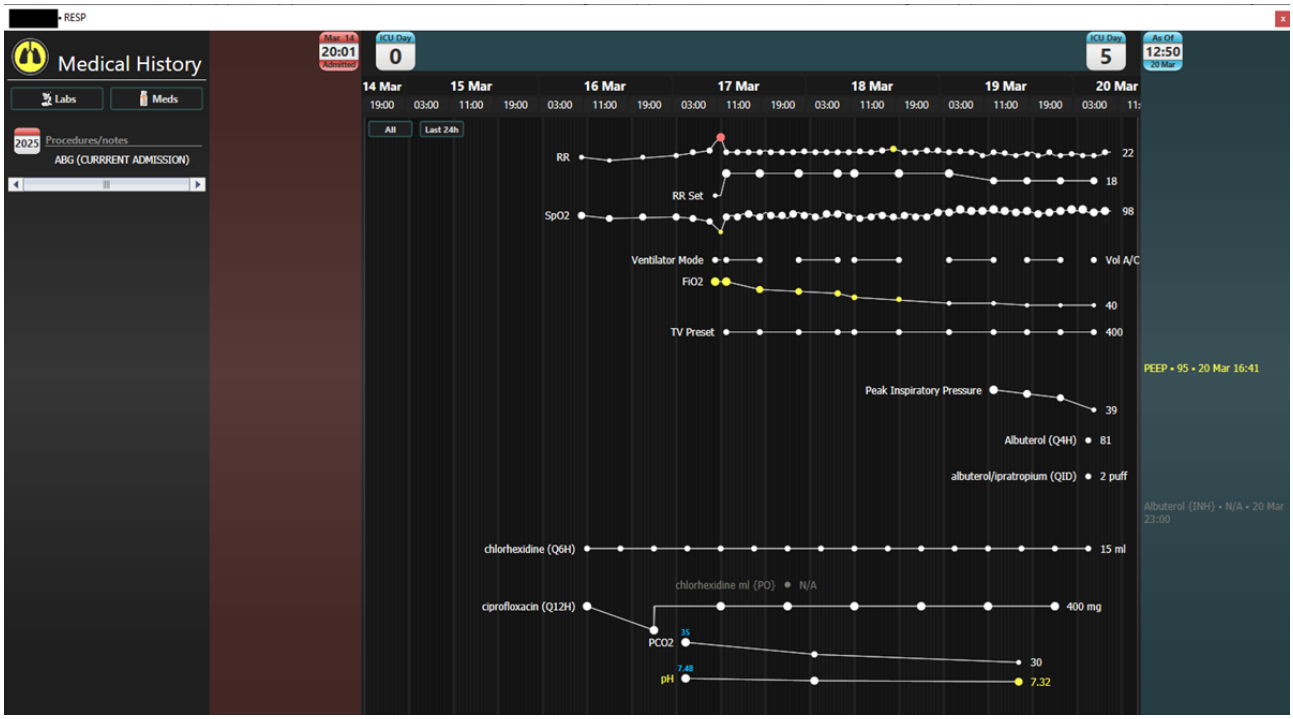

Outcomes

Primary outcomes are cognitive fatigue (using pupil constriction), usability (clicks and completion time), performance score, and perceived satisfaction (system usability scale survey). Secondary outcomes are the perceived EHR workload (NASA-TLX) and information processing (using eye fixations).

To characterize cognitive fatigue, we will use change in pupil size including pupil constriction. We will determine under what conditions providers experience cognitive fatigue while using the EHR. We will determine which patient cases create the highest number of cognitive fatigue instances among providers as indicated by pupil constriction, meaning a rapid decrease in pupil size from baseline. We also seek to understand how cognitive fatigue affects overall EHR usability, the effect of fatigue on performance score, and the perceived satisfaction

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from providers. Understanding the factors that contribute to cognitive fatigue will fill a significant gap in EHR usability research.

Analytical Plan

Each participant will receive a single score for each question assigned by a domain expert according to a standardized rubric: 0 for incorrect responses, 0.5 for partially correct responses, and 1 for correct responses. Correct decisions are the aggregate of the correct responses, and errors are the aggregate of the incorrect responses. For each participant, we will compute a score for each patient case and a cumulative score across all 4 patient cases. Case scores will depend on the number of questions asked, such that if a case has 4 questions to be answered, the total score for that case will be equivalent to the highest possible points (4).

Eye-tracking data will provide continuous measurements of pupil size over time for each participant. We will calculate participants' pupil size based on (1) baseline pupil size at rest, (2) total change in pupil size per case, (3) total change in pupil size per EHR, and (4) total changes in pupil size across the overall session. These measurements will allow for assessment of cognitive load and its variation throughout the different patient cases and task engagements.

We will examine descriptive statistics for both the case and participant characteristics and use multilevel modeling to assess the effect of case-level (eg, complexity) and person-level (eg, gender, professional roles, and site) factors on the outcomes of interest (ie, decision accuracy, usability, fatigue, clicks, time, and number of screens). Exploratory interaction testing between the intervention variable and key case level variables will also be tested. A bottom-up building approach with comparative model fit testing and variable centering will be used. A focus of the models will be the effect of the intervention (AWARE EHR) versus control (institutional EHR). Case variables will be entered into the model as case-level (level 1) predictors. Models will also account for person-level (level 2) factors, such as participants' gender, age, clinical role, site, and years of EHR experience. We will use SAS 9.4 using PROC MIXED for continuous outcomes and PROC GLIMMIX for binary and count outcomes.

Ethical Considerations

Recruitment and site testing will occur sequentially such that the study will be implemented at one site at a time, allowing the study team to be present on-site to add organization to the data collection process. Each participant will be required to read and sign a consent form specific to their medical center, witnessed by a representative of that medical center. Participants will be allowed to opt out of the study at any time. We will use 1 screen-based eye-tracker device for data collection at each site. We will recruit providers through flyers and departmental email communications at each site. Participants will be compensated with a $100 gift card for their participation. All data collected will be deidentified and study participants and their data will be assigned a unique identification number. Study data entry and management systems will be secured and password protected to ensure participant privacy and confidentiality. The University of North Carolina at Chapel Hill's institutional review board approved this study (#20-3384).

Results

This EHR usability study was funded in 2021. The study was initiated in 2022 with a completion date of 2025. Data collection began in August 2023. Three of the 4 study sites have completed data collection, with a total of 113 completed sessions thus far. Preliminary analysis is ongoing, with publication expected in late 2025.

Discussion

Anticipated Findings

This study presents a structured protocol for evaluating the impact of information visualization on mitigating cognitive overload in EHRs. A key strength of this protocol is its multisite, cross-sectional design, which enhances the generalizability of findings by capturing variations in institutional workflows and patient populations. By incorporating an RCT framework, the study minimizes bias and strengthens the validity of its conclusions, providing a robust foundation for understanding how EHR design influences clinician workload and decision-making.

The anticipated main findings of this study are that the AWARE will result in lower cognitive fatigue and higher usability scores compared to the institutional EHRs. Additionally, we hypothesize that the order of exposure to the EHR systems will not significantly influence the primary outcomes, as the randomization process will control for any potential order effects.

Comparison to Prior Work

Prior literature has suggested that integrating data visualization can help mitigate the negative effects of information overload in EHRs [1,13,14]. Visualization dashboards represent a promising approach to reimagining how data are presented within EHRs [15]. By integrating advanced data visualization techniques, these dashboards can transform large volumes of complex data into easily interpretable formats, allowing providers to quickly grasp essential information [18]. This study builds on previous research by using a visualization dashboard, AWARE, and assessing its impact on cognitive fatigue and usability outcomes in a real-world clinical setting [14].

Strengths and Limitations

A central focus of this protocol is real-world applicability. By creating near-real-world ICU patient data and simulating inpatient environments, the study ensures that findings reflect actual clinical workflows rather than controlled laboratory settings. This approach facilitates a nuanced assessment of how information visualization tools, such as AWARE, can be integrated into existing systems without disrupting provider efficiency. Maintaining ecological validity is critical to ensuring that usability improvements translate into meaningful enhancements in clinical practice.

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Finally, this study will be conducted in multiple medical centers that use the 2 most prominent EHR systems in the United States to ensure the generalizability of the findings. By integrating methodological rigor with real-world relevance, this protocol contributes to the ongoing effort to optimize EHR usability, reduce clinician burden, and enhance patient care.

While we propose to recruit 120 ICU providers, we understand that recruiting this exact number of participants may be challenging. To help mitigate this challenge, we expanded recruitment to include medical ICUs in other affiliated hospitals within the same health care system. All study sites include multiple hospitals to enable recruitment within the same health care system under the same institutional review board.

Variations in EHR interface design and performance may affect study findings. To help mitigate this effect, we selected study sites that use the 2 most prominent EHR systems across 4 different medical centers.

Potential biases may occur among study participants, particularly those who are technology enthusiasts or involved with clinical informatics in their health system. To help mitigate this bias, we determined a quota for each professional role at each study site to ensure representation among junior and senior providers. This mix of roles helps to include providers with varying degrees of EHR experience, provider experience, and technological astuteness.

Future Directions

Findings from this study will be used to guide future research on information overload due to EHRs. Findings may also be used to compare information load between EHR systems, in particular EHRs that use information visualization tools compared to those that do not. Future work may include follow-up studies to assess the actual usability and impacts of visualization dashboards in real-world settings, beyond the controlled, simulated environments used in this study.

Dissemination Plan

The results of this study will be disseminated through peer-reviewed journal publications, conference presentations, and workshops. We will also engage with health care providers, EHR vendors, and policymakers to share our findings and discuss potential implications for improving EHR design and usability. Additionally, we plan to understand the facilitators and barriers to implementing visualization dashboards in clinical settings by interviewing key stakeholders.

Conclusions

This study aims to examine the effect of using information visualization tools on cognitive fatigue, performance, and usability among ICU providers during EHR use. Through an RCT, we will evaluate EHR usability across multiple medical centers, comparing providers' institutional EHR systems (control) with a visualization dashboard–based EHR (intervention). Findings from this research may inform improvements in EHR interface design and usability, which may enhance provider performance, streamline care delivery, and improve patient safety outcomes.

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Data Availability

The data collected for this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at the University of North Carolina at Chapel Hill.

Authors' Contributions

SK participated in the conceptualization, funding acquisition, investigation, methodology, project administration, supervision, validation, and writing of this manuscript and study. JM participated in the investigation, methodology, project administration, supervision, validation, visualization, and writing of this manuscript and study. MHB, TB, JAG, and SSC participated in the methodology, review, and editing of this manuscript and study.

Conflicts of Interest

None declared.

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Abbreviations

APP: advance practice provider
EHR: electronic health record
ICU: intensive care unit
NASA-TLX: National Aeronautics and Space Administration task load index
RCT: randomized controlled trial

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Protocol

Effectiveness of Synchronous Telerehabilitation Versus Face-to-Face Physical Therapy in Older Adults Who Are Frail: Protocol for a Randomized Controlled Trial

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Abstract

Background: Older adults who are frail face significant barriers to physical activity, and innovative solutions such as synchronous telerehabilitation (STR) may provide a viable alternative to traditional face-to-face programs. However, less is known about its effectiveness compared to a face-to-face program.

Objective: This study aims to compare the effectiveness of an STR program versus a face-to-face physical therapy (FPT) program in the primary outcomes (lower body strength and cardiorespiratory fitness) and secondary outcomes (upper limb strength, dynamic balance, static balance, number of steps, functional status, and quality of life) in older adults who are frail.

Methods: In a randomized, blinded, parallel-group controlled trial, all older adults who are frail and aged ≥60 years of both sexes from the Los Angeles Comprehensive Center for Older Adults will be invited to participate. A total of 58 older adults who are frail (aged ≥60 years) meeting the eligibility criteria will be randomly assigned to either an STR group (n=29, 50%) or an FPT group (n=29, 50%). Participants will engage in 1-hour multicomponent exercise sessions twice weekly for 12 weeks. The telerehabilitation group will participate via videoconferencing, supervised remotely by technical staff, while the face-to-face group will attend in-person sessions. Outcomes will include lower limb strength (sit-to-stand test), cardiorespiratory fitness (2-minute step test), upper limb strength (grip strength test), balance (Timed Up and Go, and single-leg stance), quality of life (36-item brief health survey), functional status (functional independence measure), and daily steps (pedometer).

Results: Recruitment will be conducted from April to May 2025. The intervention will run from June to August 2025, follow-up assessments will be completed by September 2025, and data analysis will be finalized by December 2025. Manuscript drafting and submission are planned for March 2026. We hypothesize that STR will yield equal or superior improvements in both primary and secondary outcomes compared to FPT in older adults who are frail.

Conclusions: STR is emerging as a viable and effective alternative to in-person physical therapy for older adults with frailty. This approach has the potential to improve physical condition and functional and quality of life indicators, overcoming geographical and logistical barriers and optimizing therapeutic resources.

Trial Registration: ClinicalTrials.gov NCT06784245; https://clinicaltrials.gov/study/NCT06784245

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International Registered Report Identifier (IRRID): PRR1-10.2196/72318

(JMIR Res Protoc 2025;14:e72318) doi:10.2196/72318

KEYWORDS

older person; fragility; telerehabilitation; physical fitness; functional status; quality of life

Introduction

Background

Worldwide, the prevalence of frailty in people aged ≥60 years ranges from 7% to 24% [1]. In Latin America and the Caribbean, the prevalence of frailty ranges from 7% to 42.6% [2]. A recent study conducted in Chile found that 10.9% of individuals aged >60 years are frail, including 7.7% of men and 14.1% of women affected. The study also reported that the prevalence of frailty in Chile increases significantly with age, reaching 58% for men and 62% for women after the age of 80 years [3]. Frailty is a clinical stage with a multifactorial etiology that involves disorders of multiple interconnected physiological systems [4]. Its diagnosis is commonly based on 5 components: muscle strength, gait, exhaustion, weight loss, and chronic fatigue [5]. People who are frail have a higher risk of falls, disability, long-term care, and death [6]. Therefore, prevention and early detection have become significant challenges for public health and clinical practice [7].

The first-line therapy for managing frailty should include a multicomponent physical activity program with a resistance-based training component [8]. Recent evidence shows the efficacy of a multicomponent exercise program as a strategy to prevent [9] and reverse frailty to prefrailty. In addition, it has been seen that a multicomponent exercise program can improve physical fitness, particularly resistance and balance [10,11], and quality of life [12] in older adults with this clinical stage. Despite the many benefits of exercise, participation is low among older adults, with relatively few older adults who are frail meeting the recommendations for exercise [13,14].

In Chile, the "More Autovalent Older Adults" (*Más Adulto Mayor Autovalente)* program, implemented by the Ministry of Health, is one of the primary national strategies aimed at promoting and maintaining functionality and physical fitness in older adults [15]. International and national experience indicates that most of these programs are group-based aerobic exercises and the promotion of self-care. Furthermore, participation rates may fluctuate due to factors such as time, available space, weather conditions [16,17], or distance between home and the exercise location, representing a barrier for older adults to join or maintain their attendance at out-of-home programs [18]. As a result, older adults are more likely to develop sarcopenia or frailty due to the decrease in physical activity [19]. In addition, exercise instructors have a more difficult time offering individual instruction to their older adult participants when the physical activity program is carried out with large groups and heterogeneous health characteristics and may have trouble providing effective feedback relevant to their cognitive characteristics [19]. Home-based exercise alternatives have been proposed to overcome the limitations of conventional programs, such as videos, online platforms, and mobile apps [20]. However, this modality does not offer direct feedback, making it difficult for older adults to benefit fully, and the risk of injury is higher [19].

In this context, telerehabilitation has been proposed as a new intervention method to prevent or improve frailty. Telerehabilitation refers to the delivery of rehabilitation services to patients remotely, using information and communication technologies [21]. Communication between the patient and the rehabilitation professional may occur through a variety of technologies, such as the telephone and internet - based videoconferencing [22]. Widely accepted advantages exist for the use of telerehabilitation rather than the more traditional, clinic-based service delivery model. Telerehabilitation facilitates access to rehabilitation opportunities [23], reduces health care disparities, and allows patients to receive services in the comfort and privacy of their own homes [24,25]. This model eliminates geographical barriers [26-28] and reduces both the time and out-of-pocket expenses associated with transportation. In addition, it diminishes the reliance on others for mobility or the need for adapted transportation for some older individuals who are frail [24,27,29,30]. Consequently, telerehabilitation is associated with increased session attendance and functional improvements comparable to or even superior to those achieved with in-person care [31].

Synchronous telerehabilitation (STR) involves real-time, two-way video and audio communication between the exercise instructor and participant, allowing for supervised training using high-speed telecommunications technologies. This would allow for real-time interactions between exercise instructors and older adults living in their homes [32,33]. Three international studies have evaluated the effectiveness of STR programs for older adults at high risk of falls and sarcopenia. Significant improvements were found in physical condition (leg strength measured with the chair stand test), static balance (Berg Balance Scale), and decreased sarcopenia [19,33,34]. Telerehabilitation is considered a viable alternative to traditional rehabilitation, as it reduces the use of outpatient resources and improves quality of life. However, further randomized controlled trials are required to evaluate its efficacy in older adults with chronic diseases, frailty, and sarcopenia [35-37].

To date, few studies in Chile have reported using these mobile technologies (asynchronous telerehabilitation) to support the treatment of older adults on physical fitness and functional status [38]. Nonetheless, no studies have been found examining the effects of an STR program on the physical capacity, functional status, and quality of life of older people who are frail. Few studies have rigorously examined whether patients achieve comparable benefits from in-clinic versus remote physiotherapy telerehabilitation sessions. Much of the existing research implements a hybrid model of combined home and clinic sessions rather than just remote delivery [39]. This is because

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the combined service delivery increases confidence in the accuracy of diagnosis and assessment of progress by providing regular opportunities for physical contact and manipulation of a patient's extremities and joints. Regardless of whether a combined or remote-only model is used, studies comparing telerehabilitation with clinic-based physiotherapy consistently suggest that both approaches yield comparable results [39,40].

Objectives

In this context, this study aims to analyze whether the effectiveness of an STR program is better than a face-to-face physical therapy (FPT) program in the primary outcomes (lower body strength and cardiorespiratory fitness) and secondary outcomes (upper limb strength, dynamic balance, static balance, number of steps, functional status, and quality of life) in older adults who are frail. We hypothesize that (1) both STR and FPT programs improve primary (lower body strength and cardiorespiratory fitness) and secondary outcomes (upper limb strength, dynamic balance, static balance, number of steps, functional status, and quality of life) in older adults who are frail and (2) STR produces equal or greater improvements compared to face-to-face programs in these outcomes.

Methods

Study Design

This study is designed as a blinded (assessor and statistician), parallel-group, randomized controlled trial. The CONSORT (Consolidated Standards of Reporting Trials) guidelines for clinical trials will be followed [41,42], with reporting on social and psychological interventions [43], and the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines for protocol studies (Multimedia Appendix 1) [44]. The clinical trial was registered on ClinicalTrials.gov (NCT06784245).

Study Setting and Participants

The Centro Integral del Adulto Mayor (CIAM; Comprehensive Center for Older Adults) in the city of Los Angeles, Biobío region, Chile, will be invited to participate. CIAMs aim to provide care, promotion, and support to individuals aged ≥60 years. These centers are managed by local municipalities and serve as spaces for social interaction and activities, including workshops, meetings, and medical and social care tailored to older adults. CIAM Los Angeles was selected due to its central role as the primary location where older adults from throughout the city gather. This provides access to a diverse group of older adults, including those who are frail and meet the study's selection criteria. A collaboration agreement was created with CIAM to be able to carry out outcome measurements and the FPT program. In addition, CIAM has a space equipped with a 50-inch smart television and physical activity equipment so that a health professional can guide telerehabilitation sessions.

Power Calculation

The sample size was calculated a priori using G*Power 3.1.9.7. A total of 52 participants in total are required (26 in each group), considering Cronbach α=.05, 1-β=.8, and effect size=0.8 (lower limb strength based on the results of a previous study) [19]. Considering the possibility of abandonment, 6 participants were added (N=58; n=29 in each group; Figure 1 [42]).

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Figure 1. Flowchart of the synchronous telerehabilitation (STR) intervention [41]. FPT: face-to-face physical therapy.

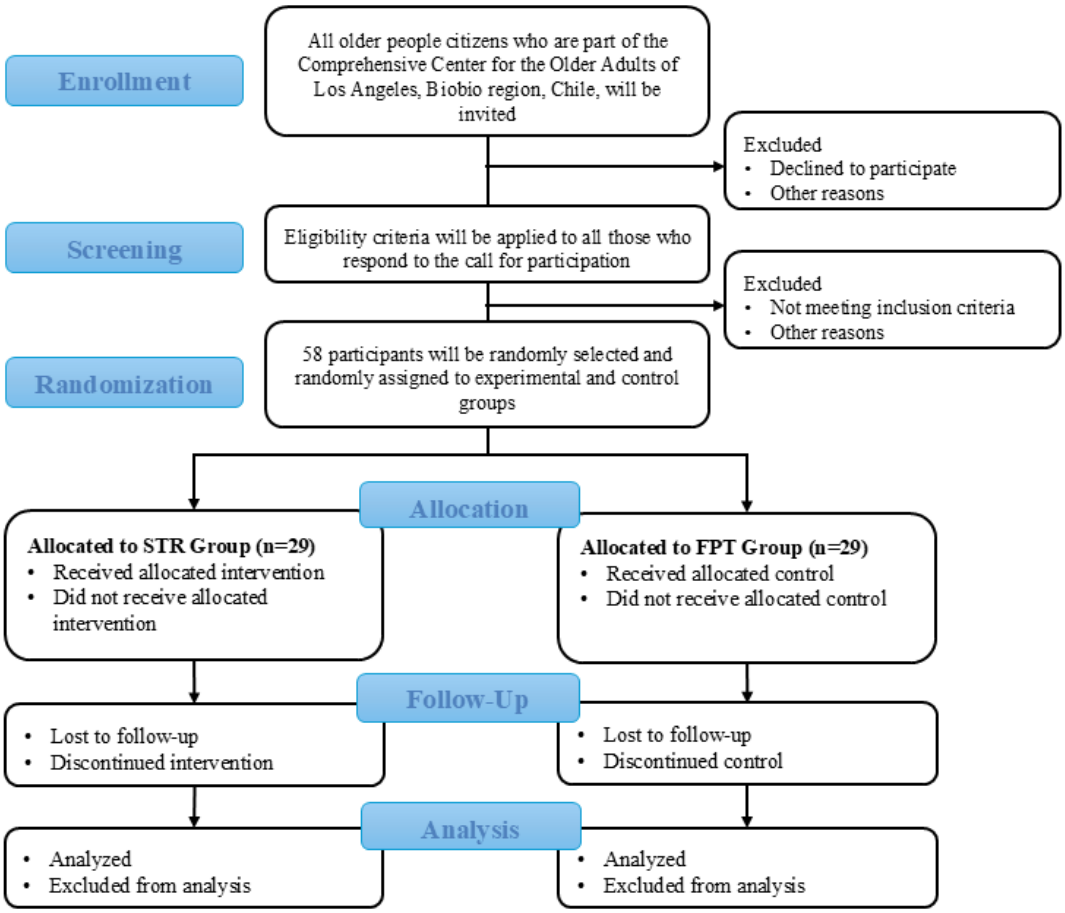

Recruitment of Participants

All individuals aged ≥60 years belonging to CIAM Los Angeles will be invited to participate. Research support staff will conduct recruitment in person or by telephone. To be eligible for participation, individuals must meet the following inclusion criteria: (1) both sexes aged ≥60 years, (2) older adults from the CIAM, (3) older adults diagnosed with frailty according to the modified Fried phenotype scale [5], (4) ability to stand up and walk ≥10 m without assistive devices, (5) Abbreviated Mini-Mental State Examination >13 points [45], and (6) no medical contraindication for physical exercise. In addition, older adults must have a smartphone or tablet and an internet connection at home. Computer or internet literacy is not required as an eligibility criterion. Exclusion criteria include older adults with fractures, recent acute myocardial infarction, associated cardiovascular pathology, severe acute respiratory failure, high blood pressure, uncontrolled diabetes mellitus, limitations following instructions, as well as individuals participating in another exercise program during the project (Figure 1).

Randomization

The sample will be selected by quota until a size of 58 participants is reached. The selection will be random among those who meet the inclusion and exclusion criteria. Participants will be randomized by research staff using a computer-generated sequence and concealed allocation to one of the following two groups: (1) the STR group, which will receive STR, or (2) the FPT group, which will receive FPT. A simple randomization computational sequence stratified by gender, age, and frailty will be used to obtain a balance between men and women, age ranges, and severity of frailty in both groups. The randomization sequence will be concealed using sequentially numbered, opaque, sealed envelopes to ensure allocation concealment (Figure 1).

Procedure

Primary outcomes (lower body strength and cardiorespiratory fitness) and secondary outcomes (upper limb strength, dynamic balance, static balance, number of steps, functional status, and quality of life) will be assessed face-to-face 2 weeks before the initiation of the intervention in both groups (Figure 2).

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Figure 2. Study design of the synchronous telerehabilitation intervention program.

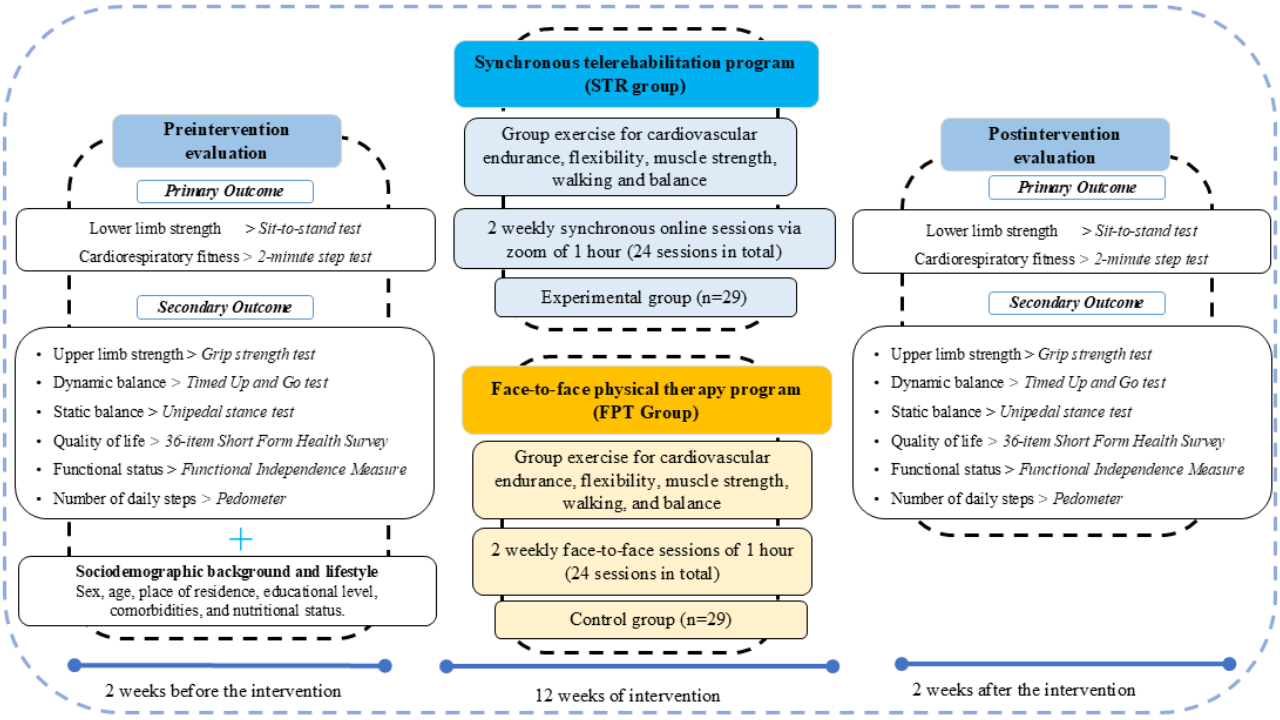

In addition, at that time, STR group participants will be provided with a tablet and home exercise equipment (exercise mats, resistance bands, cones, and dumbbells). If exercise materials are lost or damaged, they will be replaced. A home visit will be conducted to identify barriers to exercise and assess the most suitable location to carry out the STR sessions. One week before the intervention, there will be 2 induction sessions on the proper use of sports equipment, as well as video calls. Written and verbal instructions will be provided outlining the simple steps necessary to connect to an online meeting and facilitate participation in the STR program, as well as the proper use of the home exercise equipment. In addition to the induction sessions, asynchronous material was provided to address questions related to connectivity and the use of devices such as tablets and watches.

At the beginning of the interventions, all participants will be given a hydration kit (cotton towel and a water bottle) and a smartwatch (Fitbit Inspire 2, Google LLC) to measure continuous heart rate monitoring during exercise sessions to maintain exercise intensity, and pedometer (OMRON HJ-321, Kyoto, Japan) to record the number of daily steps each participant takes. (All the equipment that will be delivered to participants is guaranteed).

During the intervention period, nutrition guidance and exercise education will be provided to all participants once every 4 weeks. Throughout the 12-week intervention period, the participants will be encouraged to maintain the same physical activity levels and calorie intake as before participating in the study. During the education sessions, we will inform the participants to inform the support personnel holding the education sessions about any changes in physical activity levels or nutrition intake. A record will be kept of the number of sessions completed by each participant, which will serve as an indicator of adherence to the program. In addition to session attendance, retention rates (including reasons for nonattendance or withdrawal) and interactions with the technical support team will be recorded.

A postintervention assessment will be conducted after the last week of the 12-week program (Figure 2).

All data collection will be carried out in a face-to-face meeting with older adults at a care center. Technical staff will be trained to ensure an unbiased procedure. Measurements will be taken individually in a place with optimal conditions of privacy, temperature, and humidity. Evaluations will be conducted by health care professionals. The person evaluating will be different from the one performing the interventions.

Interventions

Overview

Regardless of the group (STR or FPT), each session will consist of a warm-up activity (5-10 minutes), main exercise activity (30-40 minutes), and cool-down activity (5-10 minutes) following the guidelines of a multicomponent exercise program, Vivifrail [46]. Exercise intensity will be controlled based on the Rating of Perceived Exertion (RPE) [47] on the Borg scale [48] and heart rate measured with a smartwatch [49] before, during, and after each exercise session according to the guidelines of the American College of Sports Medicine [47]. The warm-up and cool-down activities will include stretching and walking in place (9≤RPE≤10 and 40<55% maximum heart rate (HRmax), while the main exercise activity will consist of strength, resistance exercise, cardiovascular exercises, and balance exercises (to prevent falls) performed using dumbbells, color-coded resistance bands (Thera-Band; Hygienic Corp) [50] and a chair (11<RPE≤15 and 55<70 HRmax).

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To ensure safety and compliance, exercise training will be supervised by a health professional (physical therapist) who has been appropriately trained (research support staff). This health professional will provide one-on-one instructions to each participant according to the target RPE and HRmax (measured with a smartwatch) for each session. All participants will interact with the same health professionals.

Specifically, in each session, the resistance exercise will be carried out through squats, dumbbells, or chair-based exercises using a color band (as an example of the exercise progression: yellow [level 1] band during weeks 1-4, red [level 2] band during weeks 5-8, and green [level 3] band during weeks 9-12). This routine will focus on the main muscle groups in the shoulders, arms, thighs, hips, and calves, including 3 or 4 sets with 8 to 15 repetitions per set [51]. The balance exercise will include 2-legged standing, tandem standing, single-legged standing, semitandem standing, tandem walking, turning in a circle around the chair, and exercises such as toe-standing exercises, which will focus on postural muscle groups. Cardiovascular exercise will consist of walking at a pace at which you can maintain a continuous conversation, but it costs a little effort. Walking duration may increase (8-15 minutes) as the sessions go by. The total exercise duration progressively increased from 40 to 60 minutes over the course of the intervention period. Previous international studies that analyze STR programs have used similar exercise protocols [19,52].

To increase adherence to the interventions and avoid eliminating participants, WhatsApp groups will be created, and messages will be sent to remind participants to participate in the exercise sessions.

STR Program (STR Group)

During the exercise session, the participants turn on the tablet PC, watch the instructor perform the exercise, and follow the instructor's movements. For the instructor to observe the correct movements of the participants, the resistance and balance exercises are performed in the frontal and sagittal planes. During each session, a technical staff member will supervise up to 4 or 5 participants who are exercising remotely at home using a real-time videoconferencing app (Zoom Communications). The videoconference session will be shown on a television screen located in an older adult care center. Once the technical staff has been assigned to participants, their supervision will not be interchangeable. Participants will be able to see and interact with both the health care professionals and other participants. The older adults, from their homes, will complete 1-hour sessions twice a week for 12 weeks (Figure 2).

FPT Program (FPT Group)

The exercise sessions will take place in a center for older adults, lasting 40 to 60 minutes, twice a week for 12 weeks, and will include a combination of cardiovascular, balance, strength, flexibility, and gait exercises (Figure 2).

Outcome Measures

Overview

Physical fitness, functional status, and quality of life will be examined before and after the interventions. All measurements will be performed by a health professional (technical staff will be trained), blinded to the group allocation scheme, which will guarantee an unbiased procedure. In addition, all measurements will be conducted in a face-to-face setting and obtained individually in an environment with optimal conditions of privacy, temperature, and humidity, such as an older care center collaborating with the project. Data will be recorded on standardized forms and entered into a secure access database that contains quality control checks (eg, range checks and notifications for missing data). The main outcome for this trial will be lower body strength (assessed in the 30-second chair stand test) and cardiorespiratory fitness (evaluated using the 2-minute step test). Secondary outcomes included upper limb strength, dynamic balance, static balance, number of daily steps, functional status, and quality of life.

Primary Outcomes

Lower Limb Strength

This will be measured using a 5-repetition sit-to-stand test. The older adults will be asked to stand up and sit down, as quickly as possible, 5 times from a chair without armrests located against a wall. The time will be measured from the beginning of the movement until the older adult manages to stand up for the fifth repetition. The older adult's arms should be crossed over the chest during the test. The time will be recorded in seconds and tenths of a second [53,54].

Cardiorespiratory Fitness

This will be measured by a 2-minute step test. The evaluator will count the number of full steps completed by the participant in 2 minutes. A full step is defined as a step performed while raising the knee up to a height corresponding to the midpoint between the patella and the iliac crest [54].

Secondary Outcomes

Upper Limb Strength

This will be estimated using the grip strength test, which uses a previously calibrated Baseline hydraulic dynamometer. This evaluation will be carried out with the older adult seated on a chair with a backrest, shoulders adducted, elbow flexed at 90°, forearm, and wrist in a neutral position. The evaluated arm should not rest on any surface, and the dynamometer should be used vertically. Older adults will be asked to perform a maximum grip force with their dominant hand for 3 seconds, resting for 1 minute between each repetition, making 2 attempts. The highest grip value of the repetitions will be used. This protocol is described in Encuesta nacional de salud 2016 to 2017.

Dynamic Balance

This will be measured with the Timed Up and Go test. The older adult will be seated on a chair without armrests, with the back against the backrest and feet touching the ground. The older adult will be asked to stand up and walk as usual to a cone located 3 m away, turn around, and return to sit down. This test controls the time it takes to complete the circuit, starting from the moment the older adult lifts their back from the chair and ending when returning to the start position. The scale is normal

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≤10 seconds, with a slight risk of falling at 11 to 20 seconds and a high risk of >20 seconds [55].

Static Balance

This will be measured using the single-leg stance test. The participants will be asked to cross their arms over their chest, rest their hands on their shoulders, and triple-flex one leg at 90°, staying as long as possible on 1 foot (maximum of 30 s). The test will be repeated 3 times, and the best time obtained will be considered for the study. According to national studies, it is assumed that an older adult has a high risk of falling due to not being able to maintain this position for ≥5 seconds [55].

Quality of Life

This will use the 36-item Short Form Health Survey (SF-36) questionnaire [56,57] in its Spanish version [58]. The SF-36 is a self-report instrument that contains 36 questions from 8 dimensions related to people's health: physical function, physical role, bodily pain, vitality, social function, emotional role, mental health, and general health [59]. The score obtained corresponds to values on a scale of 0 to 100, where higher scores indicate better health [59]. The SF-36 is adapted and validated in Chilean older adults, presenting adequate indicators of general Cronbach α internal consistency of .88 [60].

Functional Status

It will be measured by using the Functional Independence Measure. It is composed of 18 items, with a total score ranging from 18 to 126, and it allows quantifying the demand for help from third parties that a person needs to perform their daily life activities. The evaluated items include self-care activities, sphincter control, locomotion, mobility or transfer, and social cognition. For each evaluated activity, the score ranges from 1 (totally dependent) to 7 (totally independent) [61]. The Functional Independence Measure is one of the most widely used instruments to carry out functional evaluation in rehabilitation, validated for the older adults [62], presents clinical validity, agreement between evaluators, test-retest, and intraobserver reliability, and has been widely used in Chile [63].

Number of Daily Steps

Each participant will wear a digital pedometer for 7 consecutive days. The total number of steps recorded during this period will be summed and divided by the number of days the pedometer was worn to calculate the average daily step count. Each participant will receive instructions and an illustrative guide with specific care of the equipment. We will use the classification proposed by Tudor-Locke and Bassett, which indicates that the number of steps represents the level of physical activity: <2500 steps/day (basal activity); 2500 to 4999 steps/day (limited activity); 5000 to 7499 steps/day (low activity); 7500 to 9999 steps/day (mildly active); 10,000 to 12,499 steps/day (active); >12,500 steps/day (highly active) [64].

Sociodemographic Background

The sociodemographic characteristics of the participants will be recorded, including age, gender (male or female), geographical origin (rural or urban), educational level (basic education: <8 years, middle education: 8-12 years, and higher education: >12 years), and the presence of comorbidities such as diabetes mellitus, hypertension, and dyslipidemia. Nutritional status will be classified based on BMI, which is obtained by dividing body weight by bipedal height squared (weight/height^2), with cutoff points considered, low weight: <22.9 kg/m^2, normal weight: 23.0 to 27.9 kg/m^2, overweight: 28.0 to 31.9 kg/m^2, and obesity: ≥32 kg/m^2 [65]. The questions and the classification indicated in the National Health Survey 2016 to 2017 will be used.

Ethical Considerations

The study was conducted in accordance with the Declaration of Helsinki [66] and approved by the University Santo Tomas Ethics Committee (CEC Accredited Res. No. 01-MZS, approved on May 24, 2024). Informed consent will be obtained from all participants involved in the study.

Statistical Analysis

Missing data will be handled by intention-to-treat analysis (multiple imputation method) [67]. The description will be made as measures of central tendency and dispersion (continuous variables) and as percentages (categorical variables). Using the Shapiro-Wilk test, the normality of the data will be verified, and a two-step approach for transforming will be applied to the nonnormal variables [68]. Homoscedasticity will be analyzed using Levene test. A 2-way repeated measures ANOVA will be used to determine the effects of interventions. The effects of the model are the group (experimental group vs control group), the time points (before and after test), and their interaction over time (time × group). The Bonferroni post hoc test will be applied to identify statistically significant comparisons. The *t* test effect size will be determined using Cohen *d* (<0.2 insignificant; ≥0.2 and ≤0.49 small; ≥0.5 and ≤0.79 moderate; ≥0.8 large) [69]. All analyses will be performed using SPSS (version 26; IBM Corp), with a significance level of $P<.05$, and GraphPad Prism (version 8).

Results

Recruitment will be conducted from April 1 to May 31, 2025. The 12-week intervention period will run from June 1 to August 31, 2025. Final follow-up assessments will be completed by September 15, 2025. Data analysis is scheduled from October 1 to December 31, 2025. Manuscript drafting and submission are planned for March 2026.

Discussion

Anticipated Findings

It is plausible that both an STR program and a face-to-face physiotherapy program have positive effects on the primary and secondary outcomes of the study. This hypothesis is based on evidence from systematic reviews and meta-analyses that supports how exercise-based interventions generate benefits in muscle strength, balance, cardiorespiratory fitness, quality of life, and the number of daily steps in older people [35,38,70,71].

Strengths and Limitations of This Study

We expect the STR program to offer results equal to or superior to those of the face-to-face physical exercise intervention, as

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this type of intervention has been described as an effective strategy to overcome the commonly reported barriers to access and adherence to physical exercise [24,27,29,30]. In addition, it would be of great interest to conduct a multicenter study in the future involving different cities and countries, thus confirming whether the results expected in this study could be replicated in other latitudes and social and geographical contexts. However, factors such as self-efficacy in using technological devices, motivation to practice physical activity [72], and the perception of loss of social support by not attending group sessions with people who share similar conditions [73] could interfere with the expected results of the telerehabilitation program in the intervened older adults. However, the personalized design of the program, with direct attention from a professional in charge of delivering the sessions, is expected to mitigate these limitations effectively.

While asynchronous telerehabilitation may represent a viable alternative that overcomes many of the barriers associated with in-person therapy, future clinical trials should directly compare synchronous and asynchronous modalities to determine their respective advantages and limitations. Furthermore, it is recommended that digital literacy measurement be considered, either as an inclusion criterion or as a covariate, to better understand its effect on treatment adherence and outcomes.

Conclusions

Implementing STR programs could represent a viable and effective alternative to in-person physical therapy for older adults who are frail. This innovative approach would not only achieve comparable or superior improvements in strength, cardiorespiratory fitness, and other functional indicators but also facilitate access to rehabilitation by overcoming geographical and logistical barriers. Telerehabilitation would allow for the personalization and optimization of therapeutic resources, improving the quality of life and independence of a vulnerable population. These potential findings would have important implications for integrating remote strategies into routine practice and for fostering future research that expands their application in clinical settings.

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Authors' Contributions

IC contributed to conceptualization, investigation, methodology, resources, supervision, validation, and writing the original draft. DR-M was involved in conceptualization, investigation, funding acquisition, methodology, project administration, resources, supervision, visualization, and writing the original draft. FV-R, GL-A, and SJ-A handled investigation, project administration, and writing, as well as review and editing. CR-H performed investigation, validation, writing, reviewing, and editing. RZ-L was responsible for investigation, writing, reviewing, and editing. MAP-R was involved in conceptualization; methodology; and writing, reviewing, and editing the draft.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT checklist.
[PDF File (Adobe PDF File), 162 KB - resprot_v14i1e72318_app1.pdf]

Multimedia Appendix 2
Peer review report by National Agency for Research and Development (ANID), FONDECYT, Ministry of Science Technology, Knowledge and Innovation (Chile).
[PDF File (Adobe PDF File), 271 KB - resprot_v14i1e72318_app2.pdf]

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Abbreviations

CIAM: Centro Integral del Adulto Mayor (Comprehensive Center for the Older Adults)
CONSORT: Consolidated Standards of Reporting Trials
FPT: face-to-face physical therapy
HRmax: maximum heart rate
RPE: Rating of Perceived Exertion
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
STR: synchronous telerehabilitation

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Protocol

Examining the Effect of Virtual Reality–Based Fast-Food Marketing on Eating-Related Outcomes in Young Adults: Protocol for a Randomized Controlled Trial

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Abstract

Background: Black communities, compared to White communities, are disproportionately targeted with more unhealthy food advertisements on television and social media. Exposure to unhealthy food and beverage marketing is associated with appetitive sensations, purchase intention, and intake behaviors, which may contribute to poor overall diet quality and worsening nutritional disparities in Black communities. Despite the negative effects, food and beverage companies are expanding their reach and harnessing advanced technology to create immersive experiences using virtual reality (VR). Black young adults may be uniquely vulnerable.

Objective: We aim to explore the effect of a VR-based fast-food marketing experience (compared with a VR-based nonfood control) on purchase intention, arousal, and hunger in a sample of Black and White young adults.

Methods: We will recruit 200 Black and White young adults (aged 18-24 years) from the New York City metropolitan area for a 1-time, 2-hour laboratory-based study. After screening and obtaining informed consent, eligible participants will be randomized to 1 of 2 VR conditions: a VR-based fast-food marketing experience (Wendyverse; experimental) or a VR-based nonfood control (Nikeland). In the Wendyverse, users can order from the restaurant operated by Wendy's, play games, meet others who may be visiting the Wendyverse, and access codes that can be used to obtain free food at physical restaurants. The control condition will be the Nikeland app, where participants can play sports, try on apparel, and engage with celebrity athletes. Study personnel will provide a 5-minute training session to participants before beginning the experiment to ensure that they feel comfortable in the VR environment. Participants will otherwise engage with the VR app independently. The primary outcomes will be fast-food purchase intention, assessed via a self-report questionnaire; arousal, assessed via electrodermal activity or skin conductance; and hunger, assessed via salivary reactivity. We will also conduct secondary analyses to examine interactions by race, ethnicity, and food or nutrition insecurity as a proxy for socioeconomic status. Analyses of covariance and multiple linear regressions will be conducted to examine the effects of VR-based fast-food marketing exposure on the relevant outcomes (compared to the control).

Results: This study was funded by the National Institute on Minority Health and Health Disparities in September 2024. Recruitment is expected to begin in September 2025. We expect to complete data collection by October 2026 and begin data cleaning and analysis in November 2026.

Conclusions: On the basis of previous research and data, we anticipate that young adults randomized to view VR-based food and beverage marketing will self-report higher purchase intention and demonstrate stronger arousal and hunger. The data will be

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used to support future research and improve the understanding of the effects of digital forms of unhealthy food and beverage marketing on young people.

Trial Registration: ClinicalTrials.gov NCT06917391; https://clinicaltrials.gov/study/NCT06917391

International Registered Report Identifier (IRRID): PRR1-10.2196/69096

(JMIR Res Protoc 2025;14:e69096) doi:10.2196/69096

KEYWORDS

virtual reality; digital food and beverage marketing; obesity; purchase intention; hunger

Introduction

Background

Food and beverage companies disproportionately target Black consumers with unhealthy food and beverage marketing [1]. Exposure to unhealthy food and beverage marketing (hereafter referred to as "food marketing") is powerful in shaping purchasing behaviors [2]. Exposure to food marketing contributes to stronger preferences for advertised foods [3-6], higher purchase intention [7], appetitive sensations [8], and increased reported [9-11] and observed intake of *both* advertised and nonadvertised foods [9,12-16]. Growing data also indicate that digital-based food and beverage marketing (eg, social media and gaming) is associated with stronger preferences for and increased intake of advertised foods [17-23].

Black young adults may be especially vulnerable to the effects of food marketing exposure [24,25]. Food marketing practices targeting Black communities, which are rooted in structural racism and discrimination [26,27], involve segmenting consumers based on geographic location, race, ethnicity, and income. Such marketing practices lead to 3 main issues. First, data on Black youth (aged 2-17 years) show that they have twice the exposure to unhealthy food advertisements compared to White youth [1]. Second, advertisements targeting Black consumers focus on less healthy products compared to advertisements targeting other audiences [1,28,29]. Third, advertisements targeting Black consumers are designed to be particularly powerful by (1) featuring racially and ethnically salient cues (eg, basketball references); (2) exploiting cost sensitivity due to income inequities present in some Black communities, particularly those who may be food or nutritionally insecure; and (3) capitalizing on Black consumers' greater trust in and responsiveness to advertisements after a history of being excluded from the marketplace [26]. These practices shape Black consumers' food environments and food choices and may contribute to poor nutrition and nutrition-related disparities [26,27].

Most food marketing studies focus on children due to their inability to recognize persuasive intent [13] and the oftentimes stronger political will to protect children through food marketing regulations [30]. Young adults (defined herein as those aged 18-24 years) may also be vulnerable for several reasons. They experience greater independence from childhood support systems and increasing agency and expectations of self-sufficiency, including obtaining and cooking their own food [31,32]. While young adults are beginning to accumulate social capital, their disposable incomes may still be less than those of older adults [31,32]. Young adults also have poorer diets [33,34] and are at increased risk of excessive weight gain [35]. Evidence also suggests that inhibitory control continues to mature into early adulthood [36]. There is an increasing awareness of food and nutrition insecurity during young adulthood [37-39], which may increase the appeal of advertisements that market low-cost, unhealthy foods [40]. Finally, young adults are a primary target of unhealthy food marketing in this new digital era [25].

Data on the effects of food marketing exposure among young adults are mixed [41,42]. In one study [41] that examined exposure to television-based food marketing in a sample of 82 young adults (average age 20.6 years), women who were exposed to two food commercials, each lasting 3 minutes, embedded within a 30-minute nature film, consumed significantly more snacks than women exposed to the neutral condition (approximately 66 g). The authors found the opposite pattern among men [41]. Another study [42] examined the effect of exposure to unhealthy versus healthy sponsored food commercials in an online sample of 1132 Australian young adults (aged 18-24 years). Young adults exposed to unhealthy sponsored food commercials showed greater brand awareness and more favorable attitudes toward branded items, but there was no effect on preferences for unhealthy foods [42]. In another study [8] that examined the effect of exposure to food advertisements across multiple platforms using ecological momentary assessment, young adults reported feeling hungrier and having more cravings when assessed after exposure to food advertisements compared with other assessments. Young adult samples are mainly convenience samples from colleges and universities, which limits generalizability [41,42]. Most experimental studies focus primarily on television advertisements [43]. No study has examined the effect of unhealthy food advertisement exposure on Black young adults (including those outside of college and university settings) who may be vulnerable to newer forms of digital-based food and beverage marketing. Additionally, no study has yet examined virtual reality (VR) as an emerging technology platform for unhealthy food and beverage marketing [44].

VR-Based Fast-Food Marketing

Food and beverage companies are now harnessing advanced technologies to create immersive VR experiences. VR uses artificial intelligence and machine learning to psychologically immerse individuals in a computer-simulated and lifelike environment [45]. According to market reports, as of 2020, approximately 20% of US adults (more than 66 million) reported ever or currently using VR—a 16% increase from 2019 [46].

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VR use is most popular among young people, as nearly two-thirds of all VR users identify as youth or young adults (34% of users reported being aged 16-23 years, 35% reported being aged 24-34 years) [47]. To access the most immersive forms of VR, users wear specialized headsets that engulf the entire field of view while presenting continually updated visual stimuli based on their movements and selections [48]. The unique elements of VR—which include *immersion*, engendering a sense of *presence*, and helping users develop a sense of *embodiment* with their digital selves—combine with traditional food and beverage marketing techniques that are designed to elicit biological responses that trigger a motivation to purchase and consume foods [49].

Aim/Hypothesis 1

Exposure to food marketing contributes to stronger preferences for advertised foods [3-6] and higher purchase intention [7], and young adults may be particularly vulnerable to the effects of digital-based food and beverage marketing. Thus, we hypothesize that exposure to VR-based fast-food marketing will lead to higher purchase intention compared with the VR nonfood control in our sample of young adults. Due to marketing practices targeting Black communities, Black young adults may be especially vulnerable to the effects of food marketing exposure [24,25]. We hypothesize that Black young adults (compared with White young adults) will demonstrate a higher fast-food purchase intention.

Motivations to Purchase: Arousal and Hunger

VR-based food and beverage marketing may more powerfully affect motivations to purchase and consume foods [50]. This study will examine 2 biological signal activations via: (1) electrodermal activity and (2) salivation. Electrodermal activity, measured through skin conductance (also referred to as galvanic skin response), is one of the most common ways in which food marketers examine marketing effectiveness [51]. Electrodermal activity refers to the changes in the electrical properties of the skin due to sweat secretion and has been closely linked to autonomic, emotional, and cognitive processing and sympathetic activity [52]. Electrodermal activity includes 2 types of electrical conductivity measurements in the skin: tonic (general changes in autonomic arousal measured by skin conductance level) and phasic (rapid skin conductance response [SCR] in relation to specific stimuli). SCR measures the electrical conductance of skin due to sweat secretion from the eccrine glands, which are involved in emotion-evoked sweating and are most dense in the palms and soles of the feet. With more activation (ie, arousal), there will be more eccrine sweat secretion and a larger SCR [53]. SCR can provide information on responses to brand preferences [54,55] and consumer behavior [56]. Although data in adults are mixed [51,57], in a study examining SCR in children (aged 8-11 years), those who viewed images of their favorite food or beverage brands showed a larger SCR than those who viewed unbranded foods or beverages [56].

Salivation—one of the most researched signals within food cue research—has been linked to the desire to consume foods, although data are mixed [58-63]. The release of saliva in the oral cavity, known as the cephalic-phase salivary response, supports chewing, swallowing, and digestion [58]. On the basis of the cue reactivity model, food cues from food advertisements may subconsciously activate biological reactions that affect decision-making and precipitate eating [64-67]. Multisensory food cue exposure—which occurs in VR experiences—may lead to more profound salivary effects and, subsequently, a desire to consume foods [67]. In a sample exposed to 12 conditions of increasing food cue sensory exposure, higher exposure led to greater salivation secretion [68]. In another examination of the effect of food marketing exposure on total salivation secretion and food intake in adult women (aged 20-64 years) of varying weight status [49], salivation significantly increased following exposure to a food commercial among women with overweight. A multisensory VR-based food and beverage marketing exposure may elicit an even stronger biological response than television. The authors did not measure whether the effect was stronger in younger adults (who may be more susceptible to food marketing) compared with older adults [49].

Aims/Hypotheses 2 and 3

VR-based food and beverage marketing may more powerfully affect biological signals, prompting motivations to purchase and consume foods [50]. On the basis of data on children, exposure to unhealthy food marketing may lead to stronger arousal as measured by electrodermal amplitude or SCR [56]. Similarly, women with overweight have demonstrated increased salivation following exposure to unhealthy food marketing [49]. No study has combined multiple biological signals (electrodermal activity or SCR and salivation) or examined whether exposure to VR food marketing affects purchase intention among Black young adults [69]. We hypothesize that larger electrodermal amplitude, SCR, and salivary reactivity will be associated with higher fast-food purchase intention in those randomized to VR fast-food marketing compared with the control group. As previously noted, young adults may be particularly susceptible to food and nutrition insecurity [37-39], which may increase the appeal of unhealthy food advertisements [40]. Targeting Black communities may also exploit economic hardships, especially among those with food or nutrition insecurity [26]. To explore the interactions among race, ethnicity, food and nutrition insecurity, biological signal activation, and purchase intention among Black young adults exposed to VR fast-food marketing, we pose the following research question: Are food and nutrition insecurity, stronger electrodermal amplitude, and higher salivary reactivity associated with higher fast-food purchase intention among Black young adults randomized to VR fast-food marketing compared with those randomized to the control condition?

Review of the Aims and Hypotheses

The goal of this manuscript is to describe a novel study protocol to examine the effects of VR-based fast-food marketing (compared to a VR-based nonfood control; hereafter referred to as “VR fast-food” and “VR nonfood”) on purchase intention, arousal, and hunger signals in a sample of Black and White young adults. Our aims and hypotheses are discussed subsequently.

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Aims and Hypotheses

The aims and hypotheses of this study are presented in Textbox 1.

Textbox 1. Aims and hypotheses.

Aim 1: determine the extent to which virtual reality (VR) fast-food marketing influences purchase intention and whether the effects are more pronounced in Black young adults.

- Hypothesis 1.1: exposure to VR fast-food marketing will influence purchase intention compared with the VR nonfood control.
- Hypothesis 1.2: Black (compared with White) young adults exposed to VR fast-food marketing will demonstrate higher fast-food purchase intention.

Aim 2: understand the influence of biological signal activation on the relationship between VR fast-food marketing and fast-food purchase intention.

- Hypothesis 2.1: a larger electrodermal amplitude will be associated with higher fast-food purchase intention in those randomized to VR fast-food marketing compared with the control.
- Hypothesis 2.2: higher salivary reactivity will be associated with higher fast-food purchase intention in those randomized to VR fast-food marketing compared with the control.

Aim 3 (exploratory): explore the interactions among race, ethnicity, food and nutrition insecurity, biological signal activation, and purchase intention among Black young adults exposed to VR fast-food marketing.

- Hypothesis 3.1: food and nutrition insecurity along with stronger electrodermal amplitude are associated with higher fast-food purchase intention among Black young adults randomized to VR fast-food marketing exposure compared to those randomized to the control condition?
- Hypothesis 3.2: food and nutrition insecurity along with higher salivary reactivity are associated with higher fast-food purchase intention among Black young adults randomized to VR fast-food marketing exposure compared to those randomized to the control condition?

Conceptual Framework

The study will be guided by a conceptual framework (Figure 1) based on evidence-based theories of food and beverage cues in the digital environment [50], theories of food cue reactivity [64-67], and the influence of structural racism on unhealthy food and beverage marketing [26]. (1) While young people experience immersion, presence, and embodiment within the VR experience—key enhancing elements unique to digital marketing [50]—a number of food cues that are presented throughout the experience are below conscious awareness. Exposure to food and beverage marketing influences preference, purchase intention, and consumption in young people [7,70]. (2) On the basis of the cue reactivity model, such cues may subconsciously activate biological responses (electrodermal activity and salivation) that can affect decision-making and purchase intention [64-67]. (3) Black young adults, particularly those with food and nutrition insecurity, may be a subset who are highly targeted [24,25], for whom racialized marketing on digital platforms may hold particular salience [26], and who may be especially vulnerable to poor diets [33,71]. (4) Black young adults may also be uniquely vulnerable to this process because of the influential role of structural racism [27]. According to the racialized marketing of unhealthy foods and beverages theory [26], structural racism (eg, racist structures, lack of political power, and income and wealth inequalities) functions in the background and leads to disproportionate exposure to unhealthy food and beverage marketing. Such exposure may then be more effective due to the: (1) normalization of unhealthy food and beverage consumption among Black consumers, (2) racial and ethnic tailoring that increases the salience of marketing techniques, (3) exploitation of price sensitivity due to income inequities in many Black communities, and (4) greater trust and responsiveness to marketing, especially after a history of being excluded from marketing [26].

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Figure 1. Conceptual framework. Illustrating the interactions among sociodemographic, societal, environmental, biological, and behavioral factors.

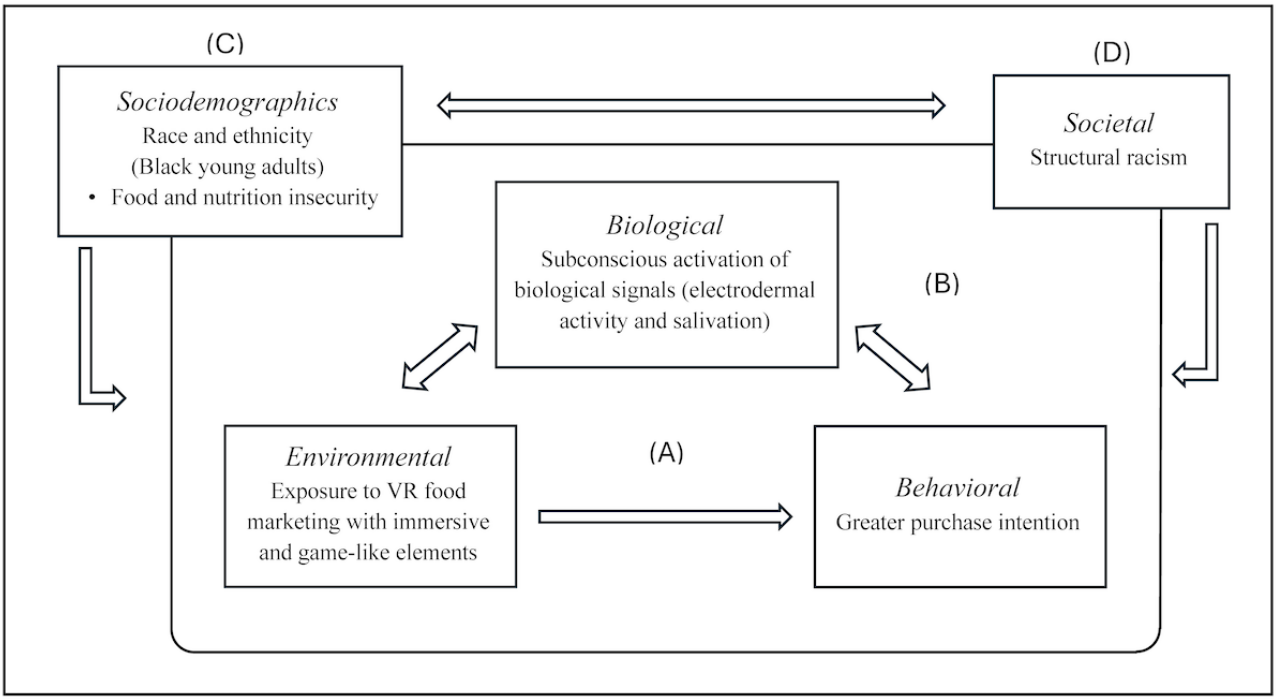

Methods

Study Design

We will use a 2 x 2 randomized controlled experimental factorial design to examine the effect of VR fast-food marketing (compared to a VR nonfood control) on purchase intention, arousal, and hunger signals in a sample of Black and White young adults. The principal investigator (PI) and study team members will be approved to assign participants to the experimental and control conditions based on a 1:1 number generator managed by the PI. Participants will be randomized to either the VR food marketing condition ("Wendyverse") or the VR nonfood control. Participants will be blinded to their condition until the end of the study (refer to the Secondary Measurements section). The Wendyverse (Figure 2 [72]) was created in 2022 by Wendy's and is the first fast-food branded stand-alone VR world [73,74]. In the Wendyverse, users can order from a restaurant operated by Wendy's, play games, meet with others who may be visiting the Wendyverse, and access codes that can be used to obtain free food at physical restaurants. The control condition will be the Nikeland app (Nike, Inc). In Nikeland (Figure 3 [75]), participants can play sports, try on apparel, and engage with celebrity athletes [76]. Researchers will ensure that the VR experiences are matched on engagement and that the control condition does not include any references to food or food and beverage brands. The primary outcomes will be purchase intention (assessed via self-report questionnaire), arousal (assessed via electrodermal activity), and hunger (assessed via salivary reactivity). We will also collect sociodemographic data (eg, income) and behavioral data (eg, media exposure) via questionnaires. On the basis of previous food marketing experimental research standards, the primary research objective of the study—to assess the effect of VR fast-food marketing exposure—will be concealed from participants until after they complete all study procedures. The true purpose of the study will be revealed during a poststudy debrief [77]. This method is intended to ensure that participants' responses are not affected by performance biases or demand characteristics. Concealment is widely used in food marketing research and has been successfully used by the PI (OC) and the study team [77]. We used the SPIRIT checklist when writing our report Multimedia Appendix 1 [78]. This study is registered at ClinicalTrials.gov (NCT06917391) Multimedia Appendix 2.

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Figure 2. Screen capture of the home screen for the virtual reality (VR)–based fast-food marketing experience (experimental condition). The figure shows the Wendyverse VR app, where users can order from a restaurant operated by Wendy's, play games, meet with others who may be visiting the Wendyverse, and access codes that can be used to obtain free food at physical restaurants. The VR app is commercially available [72] (as of March 25, 2025).

Figure 3. Screen capture of the home screen for the virtual reality (VR) nonfood experience (control condition). The figure shows the Nikeland VR app, where users can play sports, try on apparel, and engage with celebrity athletes. The VR app is commercially available [75] (as of March 25, 2025).

Participants and Recruitment

The study will enroll a sample of 100 (50%) Black and 100 (50%) White young adults from the New York City metropolitan area for a total of 200 participants (n=50, 25% pilot participants). The inclusion and exclusion criteria are provided in Textbox 2. The participants will be recruited through direct mailings, flyers, social media, listservs, and engagement with community

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organizations and a community advisory board. The study materials will invite the participants who are interested in sharing their perspectives on how young adults engage with and experience VR as a new technology.

Textbox 2. Inclusion and exclusion criteria.

Inclusion criteria

- Aged 18-24 years
- Self-identify as a Black or White individual
- Self-report normal or corrected-to-normal vision from glasses or contacts
- Self-report comfort and ability to walk around within a VR paradigm
- Able to read, write, understand, and respond to all study materials (including the VR paradigm) in English
- Residing in the New York City metropolitan area
- Capacity and willingness to provide consent

Exclusion criteria

- Report a history of disorders causing motion sickness or have a history of significant motion sickness, which could be triggered within the VR paradigm
- Self-report dietary restriction, such as food allergies and veganism, which may lead to different effects when exposed to food marketing
- Self-report disliking ≥50% or more of the snacks that will be offered during the laboratory test snack as determined by a score of a score of ≤5 on the food preferences questionnaire, which may have a confounding effect on consumption
- Report being pregnant, breastfeeding, which may affect appetite
- Smoke or consume tobacco, which decreases salivary flow
- Self-report being very hungry based on 100-mm VAS hunger rating, which minimizes the burden to participants to fast prior to the visit and maximizes the ability to detect differences between groups. Those excluded for being very hungry will have the option of returning to the visit on a different day.

Ethical Considerations

Ethics Approval and Informed Consent

The study was approved by the institutional review boards of the NYU Grossman School of Medicine and NYU Langone Health (i24-00910) in October 2024. Consent forms describing, in detail, the study, study procedures, and risks (Multimedia Appendix 3) will be sent to eligible participants after they complete the telephone prescreen and before the in-person study visit.

Upon arrival for the study visit, all participants will receive a verbal explanation, in terms suited to their comprehension, of the purposes, procedures, and potential risks of the study and of their rights as research participants. The participants will have the opportunity to carefully review the written consent form and ask questions before signing. The participants will also have the opportunity to discuss the study with their families or consider it before agreeing to participate. To ensure that biases do not affect outcomes, the primary purpose of the study will be concealed until participants complete all study components. At the end of the study or when a participant withdraws, we will disclose the true purpose of the study, solicit questions, and, for participants who have completed the entire study, conduct a second consent procedure after disclosing that the purpose was to assess the effects of VR food marketing exposure on the outcomes.

Each participant will sign the informed consent document before any procedures are conducted specifically for the study. The participants may withdraw consent at any time throughout the course of the study. If a participant withdraws, any information already collected and shared will be retained and analyzed, with the participants' permission. The study team will provide participants with information on how to send a written notice (via email) to the study team with their request to withdraw. If a participant withdraws, no additional data will be collected. If a participant is scheduled for a visit but does not show ("no show"), no more than 3 attempts will be made to contact and reschedule. After that point, the study team will withdraw the participant from the study. If the participant later expresses interest in participating in the study, the study team will rescreen them for eligibility and schedule a visit. If the participant "no shows" again, another 3 attempts will be made to contact and reschedule. After that point, the study team will withdraw the participant from the study, and they will not be able to participate in the study in the future.

A copy of the signed informed consent will be given to each participant for their records. The rights and welfare of the participants will be protected by emphasizing that the quality of their medical care or their ability to receive any medical care at the institution will not be prohibited while participating in the study, nor will it be adversely affected if they decline to participate in the study.

Privacy and Confidentiality

Participant confidentiality will be strictly held in trust by the participating investigators and the study team. Therefore, the study protocol, documentation, data, and all other information

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generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without previous written consent or approval by the participant. Each participant's contact information will be securely stored during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the local institutional review board and institutional regulations. The research data of the study participants, which are collected for purposes of statistical analysis and scientific reporting, will be transmitted to and stored in an institutionally managed network shared drive set up for the study. The study data will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique participant identification number. At the end of the study, the study databases will be deidentified and archived.

Compensation

The participants will receive a US $50 gift card for participating in the study and will be reimbursed for travel. If a participant does not complete the entire study, withdraws, or if the study is prematurely terminated, the participant's payment will be prorated based on the portion of the study completed, including travel costs. All compensation plans will adhere to institutional policies on human participant payments.

Procedure

After interested individuals contact the study team, a telephone screen will be conducted to determine their preliminary eligibility. Participants who may be eligible will be scheduled for a 2-hour in-person laboratory visit at the NYU Langone Health. Before arrival, the participants will be given instructions to prepare for the study visit, including eating before the visit (per the hunger exclusion criteria) and wearing comfortable clothing. The participants will also be given a copy of the consent form to review before the study visit. Once the participants arrive, the purpose, procedures, risks, and benefits of the study will be explained to them before they sign the consent form. One minimal risk of VR is cybersickness (motion sickness due to VR) [80]. The risk is significantly reduced by excluding individuals with a high propensity toward motion sickness, limiting exposure to 15 minutes [80], and using modern VR systems that reduce time delays between VR movements (also known as "lag time") [79]. Potential participants will be informed of their right to withdraw from the protocol at any point, including if they experience any physical discomfort or cybersickness. After consenting to participate in the study, the participants will complete hunger ratings [81]. Those who report being "very hungry" before VR exposure will be rescheduled for a different visit.

Experiment

The participants will receive a 5-minute tutorial on using the VR equipment [82]. The study team will place the VR headset (Meta Quest Pro) onto the participants' heads, engulfing their field of view. The participants will practice walking and making selections in a neutral VR experience that will differ from the experimental conditions. After ensuring that the participants are comfortable within the VR environment, they will be given 15 minutes to explore and provide feedback on whether they believe their peers would engage with the experience (as part of the concealment procedure).

Measures

Purchase Intention

After the exposure, the participants will complete a widely used measure assessing their likelihood of purchasing food from Wendy's or any fast-food restaurant [83].

Electrodermal Activity and SCR

The EDA100C (Biopac Systems, Inc) will be used to measure the participants' SCR throughout the VR exposure and will be integrated into the VR system. Two Ag-AgCl electrodes (1080FG, UFI) will be taped to the distal phalanx of the index and ring fingers on each participant's nondominant hand. A small amount of biopotential contact medium gel (GEL101, Biopac Systems, Inc) will be applied to the electrodes, and a constant voltage of 0.5 V will be applied across the electrode pair. The experiment will be conducted in a suitable environment for the measurement (eg, temperature of approximately 71-75 F, 22 °C -24 °C) [52].

Salivation

A 3.5-cm dental roll will be placed horizontally under the participants' tongues for 30 seconds before and after VR exposure. Salivation will not be collected during the exposure so as not to disrupt immersion. This noninvasive and sensitive measurement has been widely used [49,58-63].

Secondary Measurements

Sociodemographic data, media exposure, and anthropometrics will also be measured. Food and nutrition insecurity will be measured using the 18-item US Household Food Security Survey [84]. We will conduct a semistructured postexperience interview and debrief to determine whether the concealment was successful. On the basis of previous food marketing experimental research standards, the primary research objective of the study—to assess the effect of food marketing exposure—will be concealed from the participants until after the study is completed during the poststudy interview and debrief. During the poststudy interview, we will ask participants the following questions: (1) How was your participation in the study? (warm-up), (2) What did you like most about participating in this study? (warm-up), (3) What did you like least about participating in this study? (warm-up), and (4) In your own words, what was this study about? (open-ended to allow the participants to share their understanding of the true purpose of the study). Following the interview, a study team member will respond to the following question: Was the concealment successful? If a participant did not guess the true purpose of the study, the response will be "yes" (the concealment was successful). If a participant correctly guessed the true purpose of the study, the response will be "no" (the concealment was not successful). After the debrief, the participants will be given verbal and written information about the true purpose of the study. The participants will be asked to reconsent after the true purpose of the study is explained.

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Analytic Plan

Sample Size Estimation

The sample size and effect size estimations are based on previous studies, power analyses, and calculations aligned with the primary objective of examining the effect of VR food marketing on purchase intention. In experimental food marketing studies in youth and adults [12,14], sample sizes have ranged from 92 to 118 participants (Cohen d=0.35-0.96; Cohen f^2=0.06-0.15). In studies examining biological measures [49,56], sample sizes have ranged from 48 to 55 participants (Cohen d=0.4). After accounting for the relevant covariates in the model and for retention, to detect a medium effect size (Cohen f=0.25) with a 2-sided α=.05 and 80% power, an a priori analysis indicated that at least 128 participants would need to be randomized.

Statistical Analyses

To determine the extent to which VR fast-food marketing influences purchase intention, we will use a 1-way analysis of covariance to test the hypothesis that exposure to VR fast-food marketing influences purchase intention (ie, hypothesis 1.1). VR marketing (fast-food vs nonfood) will be entered as the independent variable, and self-reported purchase intention as the dependent variable. To examine whether the relationship is more pronounced in Black young adults (ie, hypothesis 1.2), a 2-way analysis of covariance will be used, with VR marketing (fast-food vs nonfood) and race and ethnicity (Black young adults vs White young adults) entered as independent variables and self-reported purchase intention as the dependent variable. To understand the influence of biological signal activation on the relationship between VR food marketing and purchase intention, we will use a multiple linear regression to test the hypothesis that electrodermal amplitude will moderate the relationship between VR food marketing and purchase intention (ie, hypothesis 2.1). VR marketing (fast-food vs nonfood), electrodermal amplitude, and their interaction terms will be included as predictors in the model. Multiple linear regressions will also be used to test the hypothesis that elevated salivary reactivity will moderate the relationship between VR food marketing and purchase intention (ie, hypothesis 2.2). This analysis will involve VR marketing (fast-food vs nonfood), salivary reactivity, and their interaction terms as separate predictors. A positive coefficient would indicate that the effect of VR marketing on purchase intention is stronger for individuals with higher levels of salivary reactivity (or electrodermal activity) than for those with lower levels of salivary reactivity (or electrodermal activity).

To explore the interactions among race and ethnicity, food and nutrition insecurity, biological signal activation, and purchase intention among Black young adults exposed to VR fast-food marketing (compared with the VR nonfood control), multiple linear regression analyses will be used to examine the hypothesis that food insecurity and stronger electrodermal amplitude correlate with greater fast-food purchase intention (ie, hypothesis 3.1). Food insecurity, salivary reactivity, their interaction terms, and an indicator of VR marketing exposure will be entered separately as predictors in the model. Similarly, multiple linear regressions will be used to test whether food insecurity and higher salivary reactivity are associated with stronger fast-food purchase intention (ie, hypothesis 3.2). Food insecurity, electrodermal amplitude, their interaction terms, and an indicator of VR marketing exposure will be entered separately as predictors. We will also explore income and education as individual-level socioeconomic status (SES) proxies. For each analysis, potential covariates will be considered, including race, sex, weight status, hunger, food insecurity, SES, study date and time, media use, and state mood. Covariates that are significantly associated with the outcomes will remain in the model. All data will be screened for missingness, outliers, and normality. To determine the best statistical method to handle missing data (eg, pairwise deletion or mean imputation), we will identify the type of missing data, percentage of missingness, data distribution, and impact on analyses. To minimize influences on analyses, we will consider recoding extreme outliers to 1.5 times the IQR below the 25th percentile or above the 75th percentile [70]. If biological data are nonnormally distributed, we will consider transformations or analyses that are suited to nonnormal data.

Results

The study protocol was funded by the National Institute on Minority Health and Health Disparities in September 2024 (1K01MD019320). Recruitment is expected to begin in September 2025. The study involvement includes a 1-time, 2-hour laboratory visit (for the study flow, see Figure 4). We expect to complete data collection by October 2026. We will begin data cleaning and analysis in November 2026. Manuscript preparation is expected to begin in December 2026 and continue through March 2028.

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Figure 4. Study flow.

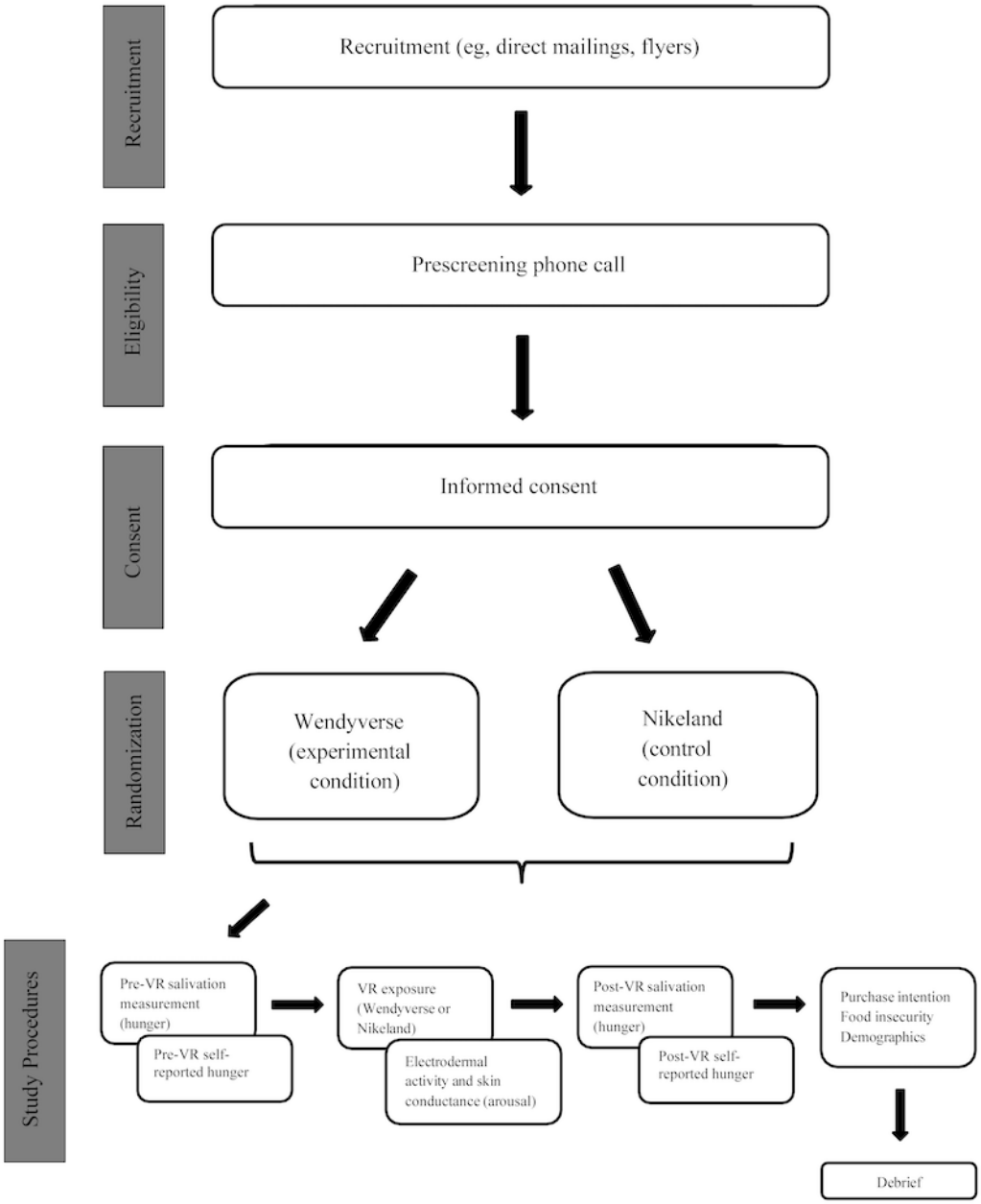

Discussion

Anticipated Findings

Exposure to unhealthy food and beverage marketing is a public health concern [30]. Although most studies have examined television-based food and beverage marketing and recent studies have started exploring social media and gaming [85-87], VR food and beverage marketing has yet to be explored [44]. Young adults may be especially vulnerable to newer forms of food and beverage marketing on digital platforms, such as VR. The objective of this study is to explore the effect of VR-based fast-food marketing (compared to a VR nonfood control) on purchase intention, arousal, and hunger in a sample of Black and White young adults. We anticipate that young adults exposed to VR-based fast-food marketing will demonstrate greater purchase intention, higher arousal, and greater hunger than those in the VR nonfood control. Due to disproportionate exposure among Black communities, Black young adults may be especially vulnerable to the effects of unhealthy food and beverage marketing. Furthermore, unhealthy food and beverage advertisements may be uniquely appealing to young adults with food and nutrition insecurity. Thus, we also anticipate differences in primary outcomes based on race and ethnicity, as well as food and nutrition insecurity.

Although previous data consistently demonstrate the negative effects of exposure to unhealthy food and beverage marketing on children's eating-related outcomes, data on the effects of food marketing exposure among young adults are mixed [41,42]. If hypothesis 1.1 is supported and the results show that young adults exposed to the VR-based fast-food marketing condition demonstrate greater purchase intention than those in the VR nonfood control, it would support the conceptualization that young adults may be susceptible to digital-based food and beverage marketing. While data examining similar outcomes

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have been mixed, such discrepancy may be due, in part, to previous sampling methods focused mainly on convenience samples in university or college settings and study designs examining television-based advertisements [41,42]. This study will improve upon these limitations by recruiting a sample of Black and White young adults from the community and exploring VR as a newer form of technology that is more appealing to young adults [44]. Research has also consistently shown that Black and lower-income communities are disproportionately exposed to more food advertisements and to the least healthy food advertisements than their counterparts [1,28,29]. However, this study will be the first to examine the unique effects of exposure on purchase intention, arousal, and hunger among a sample of Black young adults. Such data will be critical to a better understanding of how digital-based unhealthy food and beverage marketing may contribute to a poor diet among Black communities. Finally, our study will be the first to examine how race and ethnicity interact with food and nutrition security (a proxy for SES) [26,37-40] to exacerbate the negative effects of exposure to digital forms of unhealthy food and beverage marketing in young adults.

Strengths and Limitations

This research has several strengths. As of March 2025, this project will be the first food marketing study to use a VR paradigm—an emerging technology within food and beverage marketing. Food marketing has previously been examined as a single unit placed in a particular location (eg, television) for a specific amount of time (eg, 30 s). The VR paradigm represents a movement toward digital marketing that can be ubiquitously integrated across platforms and devices, without the usual bounds of space or time. Second, this will be the first study to examine the effect of VR food marketing exposure on multiple biological outcomes (electrodermal activity and SCR, and salivation) that may be affected more powerfully in a VR food marketing exposure. Third, this will be the first study to explore the interactional role of food and nutrition insecurity as a key socioeconomic condition that could affect responses to food and beverage marketing exposure.

There are also several limitations. This VR paradigm will only explore the effect of a single exposure to unhealthy food and beverage marketing. It is not feasible to capture the cumulative effects of repeated exposure to all food and beverage marketing in this protocol. However, previous research has demonstrated an effect using as few as 2 television advertisements. In the only meta-analysis examining the effect of food and beverage marketing duration on children's food intake—the outcome most proximal to diet and potential weight gain—Russell et al [88] found that exposure to an average of 4.4 minutes of television advertisements and 5 minutes of advergames (advertisements embedded within games) led to a 60-kcal and 53-kcal increase in intake, respectively, compared with control conditions. This study will expose young adults to 15 minutes of a marketing experience, which is expected to demonstrate a measurable effect. It is not clear how potential effects would compare across other marketing platforms. It has been suggested that because of the immersive nature of VR marketing and sophisticated technologies powered by neuroscience, VR food and beverage marketing may more powerfully affect behaviors [71]. This project will provide preliminary evidence to support more adequately powered studies on the effects of exposures across different mediums, such as television and social media. We will use commercially available VR apps for this study. In the event that the Wendyverse app is discontinued, we will identify other accessible food and nonfood VR apps. If those apps also become unavailable, we will work with experienced collaborators to develop a VR experience with key elements from VR fast-food apps.

Future Directions

Data will support future studies to investigate the interrelationships among race and ethnicity, food and nutrition insecurity, biological outcomes, and actual purchase and consumption when exposed to VR food marketing compared with other mediums (eg, social media). Examining the potential effects of VR food and beverage marketing while the technology is still in its infancy will generate the knowledge needed to prevent adverse health effects, particularly for vulnerable communities. These efforts will go a long way in supporting policies that address the full spectrum of digital food and beverage marketing to young people.

Acknowledgments

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The funding agencies did not contribute to the development of the study, the design, or the manuscript.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

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Authors' Contributions

OC was responsible for funding acquisition, conceptualization and methodology, formal analysis, and writing (original draft, review, and editing). EB contributed to supervision, conceptualization, methodology, formal analysis, and writing (review and editing). SP contributed to supervision, methodology, formal analysis, and writing (review and editing). ABT contributed to supervision, formal analysis, and writing (review and editing). BE contributed to supervision, formal analysis, and writing (review and editing).

All authors had full access to all information pertaining to this work, agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work were appropriately investigated and resolved, and provided final approval of the version to be published.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 177 KB - resprot_v14i1e69096_app1.pdf]

Multimedia Appendix 2
Updated World Health Organization trial registration dataset and other relevant details.
[DOCX File , 26 KB - resprot_v14i1e69096_app2.docx]

Multimedia Appendix 3
Sample consent form and related participant materials.
[DOCX File , 75 KB - resprot_v14i1e69096_app3.docx]

Multimedia Appendix 4
Peer review report by ZMD1 DRI (O1) - National Institute on Minority Health and Health Disparities Special Emphasis Panel (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 123 KB - resprot_v14i1e69096_app4.pdf]

Multimedia Appendix 5
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 486 KB - resprot_v14i1e69096_app5.pdf]

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Abbreviations

PI: principal investigator
SCR: skin conductance response
SES: socioeconomic status
VR: virtual reality

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Protocol

Home-Based Exercise to Improve Functional Outcomes in Veterans With a Recently Healed Diabetic Foot Ulcer: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Foot ulcers are a common complication of diabetes, often resulting from peripheral neuropathy and inadvertent trauma. Poor healing is exacerbated by peripheral arterial disease and poor glycemic control. Off-loading, a key treatment, leads to prolonged immobility. Patients rarely regain baseline mobility. Mobility is crucial to improve glycemia, promote vascular health, and improve immobility as it leads to nursing home admissions. There is limited research on exercise during ulcer remission.

Objective: This pilot study will assess the feasibility and acceptability of a home-based exercise regimen aimed at safely increasing mobility and function, focusing on improving lower extremity strength, tissue perfusion, and glycemic control.

Methods: Veterans aged ≥50 years with a recently healed diabetic plantar foot ulcer receiving care in the US Department of Veterans Affairs (VA) Maryland Health Care System and enrolled in a remote temperature-sensing mat program will be eligible. Potential participants will be identified via administrative codes used for the Prevention of Amputation in Veterans Everywhere directive, as well as using the VA's Podimetrics SmartMat dashboard. In this pilot study, 25 veterans will be randomized (in a 3:1 ratio) to a 12-week home-based exercise regimen or standard of care. Participants will undergo tests for gait speed, knee extension strength, cutaneous perfusion, and community mobility. The intervention group will participate in internet-based videoconference exercise classes twice a week led by the study team and home cycling 3 times a week. The control group will receive standard-of-care guidance. Outcome measures will include feasibility; acceptability; and changes in gait speed, physical activity levels, and strength.

Results: This study was funded on July 1, 2024, with data collection planned from October 1, 2024, to March 31, 2026. The protocol was approved by the University of Maryland Institutional Review Board on May 13, 2024, and by the Baltimore VA Research and Development Committee on June 13, 2024. As of June 12, 2025, 12 participants have been enrolled in the study, and 6 (50%) participants have been randomized. Recruitment is expected to continue through December 2025.

Conclusions: This project has potential for clinical rehabilitation translation. If it is found to be feasible and acceptable, the exercise intervention will be tested in a future multisite randomized clinical trial to assess its impact on mobility, cardiovascular events, and ulcer recurrence.

Trial Registration: ClinicalTrials.gov NCT06312579; https://clinicaltrials.gov/ct2/show/NCT06312579

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KEYWORDS

rehabilitation; home-based exercise; exercise; diabetic foot ulcer recurrence; clinical trial; veteran; diabetic foot ulcer; foot ulcer; diabetes

Introduction

Background

A total of 38.4 million Americans live with diabetes, with another 1.2 million people diagnosed each year [1]. For people living with diabetes, foot ulcers are a common and feared complication, with 1 in 20 people developing a foot ulcer at least once during their life [2]. The pathway to ulceration is well established and involves a combination of multiple comorbid conditions [3]. An example of this combination includes diabetes with peripheral neuropathy and inadvertent trauma to the foot leading to a wound. The resulting wound fails to heal and becomes a chronic ulcer, in part because of poor tissue perfusion and poor glycemic control.

People with a diabetic foot ulcer (DFU) have a higher 5-year mortality than closely matched people with diabetes but no ulcer—1 in 4 people with a DFU will die within 5 years, largely due to cardiovascular causes [4,5]. The reasons for this accelerated mortality are not well defined but likely involve dysmobility and inflammation. Following the development of an ulcer, part of treatment is to take pressure off the ulcer, known as off-loading. Off-loading attempts to remove the mechanical stress from the tissue associated with the ulcer. Healing can take months, leading to a prolonged loss of mobility [6,7]. While off-loading is one of the most important interventions, often seen as critical to the healing of a plantar foot ulcer, there is little done to restore mobility following off-loading. The risk of muscle atrophy and mobility loss during ulcer treatment is substantial due to disuse related to off-loading. It is likely that the combination of dysmobility, deconditioning from inactivity, and increased inflammation from the ulcer contribute to the high level of adverse cardiovascular outcomes following remission from a DFU.

People who have healed a DFU are in remission. They are at high risk of ulcer recurrence because the underlying factors that led to their ulcer typically have not changed [8]. Once in remission, the current standard of care is to advise a slow increase in ambulation so as not to promote ulcer recurrence; however, patients in recovery from a DFU frequently do not return to their preulcer level of mobility [9-12]. Currently, there is a dearth of studies that examine the effects of exercise during the remission phase. We currently know of only 1 small randomized study that found a decrease in ulcer recurrence and improvement in peripheral neuropathy and walking speed [13]. This provides a clear opportunity for further research.

Objectives

Our intervention was designed based on previous successful telehealth interventions used in the US Department of Veterans Affairs (VA) Gerofit program and our other VA research project, as well as evidence in the literature that similar, multimodal exercise protocols improve gait speed in older adults [14]. It meets the American College of Sports Medicine guidelines to improve mobility and strength while maintaining the safety of those at high risk of falls and recurring foot ulcers. There is growing evidence that people with diabetes and peripheral neuropathy can safely maintain a recommended level of activity [15-17]. These results have led to changes in the American Diabetes Association and the International Working Group on the Diabetic Foot guidelines to allow for weight-bearing exercise in those with peripheral neuropathy without severe foot deformity or open lesion [18,19]. A 3:1 randomization (intervention to control) will allow us to assess the feasibility and acceptability of the intervention with greater precision while maintaining a standard-of-care control arm. A comparison of mobility between the intervention and control arms will give us an estimate of effect size for future sample size calculations.

Given previous studies and our experience with Gerofit, we hypothesize that a home-based exercise regimen will increase mobility and function without increasing DFU recurrence by improving lower extremity strength, lower extremity tissue perfusion, and glycemic control.

Methods

Study Design and Overview

This study is a randomized, single-blind (the investigator who assessed the outcome was blinded to exercise assignment), controlled clinical trial of exercise versus standard of care. This study was funded by the VA as a Small Project in Rehabilitation Research as a pilot study to inform sample size calculations for future larger clinical trials. Therefore, we will recruit 25 veterans with a recently healed DFU who will be randomized at a ratio of 3 intervention participants to 1 control participant to reach a final sample size of 20, anticipating a 20% loss to follow-up. There will be a total of 7 in-person study visits and 1 phone call for those in the intervention group and 6 in-person study visits for those in the standard-of-care group, as shown in Figure 1. The study timeline is shown in Table 1. The investigator assessing the functional outcomes will only perform visits 1, 2, and 7 (Figure 1). They will not run any of the exercise sessions or follow-up study visits (visits 3-6). During study meetings, they will also be recused from the meeting when it is time to talk about randomization and follow-up visits. Those in the intervention group will participate in a 12-week home-based exercise program led by an exercise physiologist. The exercise group will exercise 5 days a week, including 3 days a week of recumbent cycling and 2 days a week of remote group strengthening exercises using resistance bands. Every 3 weeks, participants will attend an in-person study visit to ensure that they are exercising safely, modify or advance their exercise

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regimen by increasing their band resistance, reinforce proper foot care, and have the integrity of their feet examined by a trained staff member. Participants in the standard-of-care group will also attend an in-person session every 3 weeks to examine their feet and reinforce proper foot care. At baseline or randomization and after 12 weeks, mobility and function for all participants will be measured as outlined in Table 2 and detailed in Figure 1. The analysis will compare the change in outcome measures between the week 12 visit (visit 7) and the randomization visit (visit 2) within individuals between the intervention and control arms. For those in the intervention group, the feasibility and acceptability of the intervention will be assessed using the Usage Rating Profile–Intervention (URPI) [20,21] and semistructured interviews 2 weeks after completion of the intervention.

Figure 1. Clinical trial study design. HbA1c: glycated hemoglobin; LE: lower extremity; LSA: Life-Space Assessment; MPPT: Modified Physical Performance Test; URPI: Usage Rating Profile–Intervention; *Primary outcome; **Phone call only, intervention group only.

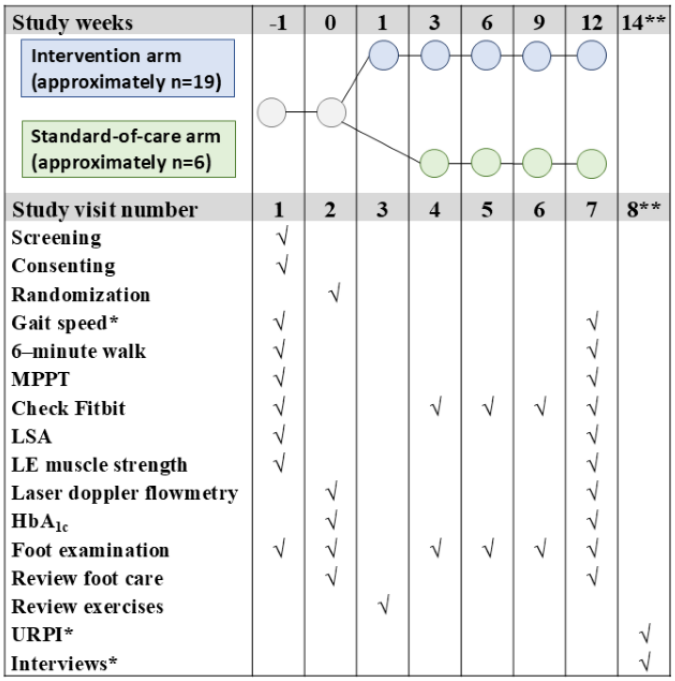

Table 1. Study timeline with number of participants enrolled and randomized.

Task	October 2024-March 2025	April 2025-September 2025	October 2025-March 2026	April 2026-September 2026
Project start-up—team training and stakeholder engagement	✓			
Recruitment	✓	✓	✓	
Participants enrolled, n	8	4	—[a]	—
Participants randomized, n	5	1	—	—
Study procedures—each participant is in the study for 12 weeks	✓	✓	✓	✓
Data collection and management	✓	✓	✓	✓
Statistical analysis and dissemination of results				✓

[a]Not available.

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Table 2. Baseline and end point assessments[a].

Assessment	Description
Gait speed (primary outcome)	Usual gait speed will be calculated using standard protocols based on a 10-minute walk distance. We will provide individuals with a 14-minute path to provide room for a "flying start" to determine gait speed without the confounding factor of acceleration and deceleration [22,23].
Mobility function—6-minute walk distance and MPPT[b] (secondary outcome)	Mobility function will be assessed using the MPPT (a 9-item standardized test) [24] and 6-minute walk distance. Through standard procedures, participants will be asked to walk as far as possible in 6 min along a 100-foot course. Total distance, heart rate, and number of breaks taken will be recorded.
Physical activity—steps per day (secondary outcome)	Physical activity will be assessed as average steps per d measured using a Fitbit Inspire 3 (Google), which will be provided to the participants and worn for the duration of their participation in the study.
Community mobility (secondary outcome)	Community mobility will be assessed using the Life-Space Assessment [25,26].
Strength (secondary outcome)	Knee extension and plantar flexion strength will be assessed using a handheld dynamometer, as we have previously described [27]. Three repetitions will be performed on each leg, with rest between each repetition.
Perfusion (secondary outcome)	Cutaneous perfusion will be assessed on the dorsal and plantar surfaces of the foot using laser Doppler flowmetry. Briefly, the laser Doppler probe will be positioned on either the dorsal or plantar surface of the foot between the first and second metatarsals. Baseline measurements of perfusion are obtained, and the probe is gently heated to 44 °C, causing dilation to assess maximal perfusion in the area of interest [28].
Glycemic control (secondary outcome)	Blood samples will be obtained through venipuncture for HbA_{1c}[c] measurement and future storage.

[a]All end points will be measured at both the randomization visit and the week 12 visit.

[b]MPPT: Modified Physical Performance Test.

[c]HbA_{1c}: glycated hemoglobin.

This study protocol follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [29]. The study will follow the CONSORT (Consolidated Standards of Reporting Trials) guidelines and reporting requirements. Any deviations from the protocol, breaches of confidentiality, and reportable adverse events will be reported to the VA Office of Research and Development Institutional Review Board (IRB) and Data Safety Monitoring Board (DSMB). In addition, the DSMB will review study-related materials biannually and review collected data to ensure data integrity, security, and control for quality assurance. This study is registered at ClinicalTrials.gov (NCT06312579).

Participants and Inclusion and Exclusion Criteria

Community-dwelling veterans aged ≥50 years (N=25) with diabetes and a recently (within the previous 3-27 months) healed plantar foot ulcer who are enrolled in the VA Maryland Health Care System (VAMHCS) and currently using or willing to use a remote monitoring temperature-sensing mat (Podimetrics SmartMat program) are eligible for this study. Additional inclusion criteria are having 2 feet (can have healed minor amputations of the fore and midfoot), having appropriately fitted therapeutic footwear for exercise, being ambulatory without use of a walker, and being able to provide written informed consent. Individuals will be excluded if they are unable to perform the exercise interventions; have a foot surgery planned in the following 4 months; are currently participating in an exercise or rehabilitation program; are currently diagnosed with a plantar foot ulcer or preulcer; or meet any other criteria that, in the investigators' opinion, would compromise the ability of a participant to take part safely in the intervention.

Recruitment and Screening

All study participants will be recruited from the VAMHCS patient population. They will be identified via administrative codes used for the Prevention of Amputation in Veterans Everywhere (PAVE) [30] directive, as well as using the VA's Podimetrics SmartMat dashboard. PAVE is a VA directive that requires VA medical centers to track veterans by their risk of future lower extremity amputation. The Podimetrics SmartMat dashboard provides a list of veterans who are currently enrolled and participating in the SmartMat program, as well as those who are eligible. We will use the PAVE administrative codes to identify potential participants through their history of diabetes, recent history of DFU, and last amputation. We will cross check those from the PAVE database with a recently healed foot ulcer with those listed on the Podimetrics SmartMat dashboard. We will use other recruitment modalities, including but not limited to individual letters, posters in clinics, electronic bulletin boards, and My HealtheVet (VA patient health care portal). Veterans who respond to the recruitment efforts and agree to screening will undergo an initial telephone screen to assess eligibility and interest in the study. Individuals who meet the eligibility criteria will provide written informed consent to study coordinators, provide demographic information, and undergo a medical history and physical examination with a licensed medical provider. This visit will include an assessment of their current footwear, how it fits, and any skin breakdown on the feet to ensure that participants can safely take part in the exercise intervention. Eligible participants will then be scheduled for a baseline assessment and randomization.

Baseline Assessment and Final Measures

An assessment battery will be administered before randomization and after 12 weeks of participation in each study

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group (exercise or standard of care). All baseline assessments and testing will be conducted at the Baltimore VA Medical Center over 1 to 2 visits during a 1-week period and will be collected using standardized protocols and by trained research team members. These assessments are described in detail in Table 2 and include the following: gait speed over 10 meters, 6-minute walk distance, the Modified Physical Performance Test, steps per day and community mobility, strength, perfusion of the foot using laser Doppler flowmetry, and glycemic control as assessed through glycated hemoglobin.

Randomization

Participants will be randomized after baseline testing during visit 2. Performing the screening and randomization visits on different days helps ensure that the participant is willing and able to return for future study visits, which increases the chances of randomized participants adhering to the intervention. Study participants will be assigned to 1 of 2 arms (exercise and standard of care) using blocked randomization with a 3:1 allocation ratio. Randomization allocation, generated by the study statistician, will be concealed in sequentially numbered opaque sealed envelopes. The envelopes will contain a card with study arm allocation and a piece of carbon paper. These envelopes will be stored in a locked filing cabinet and will be used in sequential order individually at the time of randomization. Participant study ID, date and time of randomization, and the signature of the person performing the randomization will be written on the outside of the envelope and transferred via the carbon paper to the card with study arm allocation before the envelope is opened.

Exercise Intervention

Overview

Consistent with current physical activity recommendations for older adults [31], participants will be prescribed 5 days per week of exercise, with home-based seated cycling exercise performed 3 days a week using a study-provided DeskCycle 2 under-desk bicycle pedal exerciser and strength and balance exercises performed 2 days a week in an internet-based videoconference group exercise class. All exercises are designed to minimize weight bearing and reduce shearing forces to the skin of the feet. The initial exercise session will be conducted in the VAMHCS exercise facility under the direction of trained study staff to ensure that participants are familiar with the equipment and receive proper instruction on the exercise prescription. If it appears that the participant needs more assistance, a follow-up in-person session will be scheduled. The remaining exercise sessions will be home based, where the cycling exercise will be performed independently and the strength and balance exercises will be performed in an internet-based videoconference group class. Participants will also return for 1 in-person session every 3 weeks to check participants' feet and adjust the exercise prescription. We will use SMS text messaging or phone calls to increase adherence to the exercise regimen. The intervention will be paused if the participant is felt to have a safety concern (eg, skin breakdown, such as a blister or redness) pending clinical evaluation to ensure safety.

Cycling Exercise

Participants will be provided with a DeskCycle 2 under-desk bicycle pedal exerciser in their home for seated cycling (3 days per week). Initially, participants will be asked to accumulate 20 minutes of cycling at 50 to 60 revolutions per minute per day at a "fairly light" intensity using the Borg rating of perceived exertion (RPE) scale (RPE=1-2 on a scale of 1-10). Participants may not be able to complete 20 consecutive minutes of cycling, so they will be permitted to accumulate 20 minutes through ≥2 bouts of 5 to 10 minutes. During weeks 2 to 3, participants will progress the duration of cycling, with a goal of 30 consecutive minutes of cycling per day. From weeks 4 to 12, participants will continue cycling for 30 minutes per day but will increase the intensity to an RPE of 7 to 8 ("somewhat hard" but still a relatively low overall exercise intensity) using resistance adjustments on the DeskCycle 2 under-desk bicycle pedal with guidance from the study team. Participants will be provided with a Fitbit (Google) to use throughout the study, and data from the Fitbit will be synchronized to anonymized accounts for objective tracking of time, workload, and overall adherence to the protocol.

Strength and Balance Exercises

The strength and balance exercises will be performed during an internet-based videoconference group exercise session (2 days per week) led by members of our study team. These sessions will begin with a brief check-in followed by a seated warm-up. Participants will then be led through 10 different exercises, all of which can be performed using a standard kitchen or dining chair or similar (leg press, knee extension, plantar flexion, squat, chest press, chest pull, row, lateral raise, biceps curl, and triceps curl). Participants will then be led through sit-to-stand exercises and standing balance exercises (ie, tandem stance, single-limb stance, and narrow base of support) with a chair nearby for support and safety. Finally, participants will perform a seated cooldown. The entire internet-based videoconference session will take between 45 and 60 minutes. Progress will be assessed, and new resistance bands will be provided at the triweekly in-person visits to adjust the exercise prescription. Attendance, participation, and Fitbit heart rate data will be used to confirm adherence to the protocol. These internet-based videoconference sessions also allow for a visual inspection of the feet if any concerns arise.

Standard of Care

The participants who are randomized to the standard-of-care group will be provided with guidance on the current standard of care, namely, that they should slowly increase ambulation with appropriately fitted footwear. We will examine their feet at each study visit every 3 weeks to ensure safety. Should any evidence of ulceration be noted, appropriate referrals will be facilitated to podiatry and orthotics. We will review appropriate foot care with each participant at each study visit. If appropriate, all randomized participants from both groups will be offered ongoing participation in a VA clinical exercise program at the completion of the trial. Participants in the standard-of-care arm will receive a Fitbit as well to compare step count to that of the intervention group but will not be given any guidance for exercise.

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Retention

Participant study visit scheduling will be made in conjunction with participant outpatient visits at the VAMHCS if feasible. Participants will be either texted or called before the study visit as a reminder. Study participants in the intervention arm will also be texted weekly via the Annie app as a reminder to engage in the in-home exercise intervention. The Annie app is a new VA-approved texting program that provides a full audit trail of all text communications with participating veterans. Participants will also be encouraged to call if they have foot-related issues. In the event that there is a foot-related issue, we will facilitate a visit to podiatry at the VAMHCS. Information on the Annie app can be found on this website [32]. Those in the intervention arm will also check in with a study team member twice a week during the internet-based videoconference exercises.

Participants will be asked to come in for a final visit to conduct final outcome assessments if they wish to withdraw from the study after randomization. Participants in the exercise arm will also be scheduled for the semistructured interview and URPI survey. If they are unable to participate in a final visit or are unwilling or unable to undergo the semistructured interview or URPI, no further data collection will be conducted.

Assessment Measures

Primary Outcomes

Feasibility and Adherence

A flowchart will be prepared to identify and summarize recruitment and retention (ie, total number screened and excluded and timing and frequency of dropouts). Acceptable recruitment will be defined as 90% of the targeted enrollment within 15 months of initiation. Acceptable retention will be assessed as 80% participation in the exercise intervention and study visits. Adherence to the exercise will be assessed using a combination of three methods: (1) written logs of home-based exercise (resistance, time, and RPE) returned to study staff every 3 weeks when participants report for in-person visits; (2) attendance during the internet-based videoconference group strength exercise sessions; and (3) anonymized Fitbit accounts established for each participant and used to download heart rate, cycling, and step count data to verify completion of exercise during the logged times.

Acceptability

Acceptability and feasibility of the intervention for the participants will be measured using the URPI [20] and through a semistructured interview. The URPI feasibility (eg, “I would be able to allocate my time to do this intervention”) and acceptability (eg, “The intervention is a good way to improve my walking”) subscales, which were developed and validated with an ethnically diverse sample, use a 6-point Likert scale from 1 (strongly disagree) to 6 (strongly agree). Higher scores indicate greater feasibility and acceptability. A score of “agree,” or >3, on the URPI will be used to quantify that the intervention is acceptable and feasible. We will use an inductive thematic approach for the semistructured interviews, which will provide qualitative feedback regarding participants’ perceptions of the program, including feasibility of participating and areas for improvement that will be used to tailor a future intervention. We plan to use a convenience sample drawn from participants in the intervention arm of the trial as we are seeking their perspectives on the feasibility and acceptability of the intervention. Participants will be interviewed by a research team member who has experience working with older veterans. Interviews will be conducted either by telephone or in person at the final study visit depending on the participant’s preference and overall convenience. Questions will include the following: (1) “Why did you decide to participate in the program?” (2) “What are some things about the program that made it easy for you to complete the exercise intervention?” (3) “What are some things about the program that made it harder for you to complete the exercise sessions?” (4) “Do you think you will continue with the exercise program after this study has ended? Why or why not?” (5) “What do you need to help you succeed with maintaining a consistent exercise routine in the long term?” (6) “How can we help make it easier for other Veterans to participate in an exercise program like this?” (7) “Is there anything else you’d like to share with us today related to the exercise program?” Interviews will be recorded using a HIPAA (Health Insurance Portability and Accountability Act)-compliant program and transcribed, and a template will be developed to gather key points from the interview guide. A codebook based on the interview guide will be used to find emergent themes and patterns. To understand factors influencing the future implementation and sustainment of our home exercise intervention, we will also code transcripts to identify implementation barriers and facilitators.

Secondary Outcomes

Other data to be collected will include demographics, current and past foot conditions, peripheral neuropathy and its treatment, location of recently healed ulcer, usual foot self-care, type of footwear, complications and control of diabetes, peripheral arterial disease and its treatment from the medical record, and participant interview and examination.

Data Analysis

The primary objectives assessed in this study include recruitment, retention, adherence to the exercise intervention, acceptability of the intervention, and change in gait speed. The analyses for all primary objectives will focus solely on the randomized participants except for recruitment, which will also include enrolled but not randomized participants. We will use the mean and SD of the within-person change (pretest-posttest value) in gait speed. A flowchart (ie, CONSORT flowchart) will be prepared to identify and summarize recruitment and retention (ie, total number screened, numbers excluded, and timing and frequency of dropouts). Retention will be assessed through the count of those who drop out. Please see the section primary outcomes for how feasibility and adherence will be analyzed. This statistical analysis plan and protocol will be posted on ClinicalTrials.gov.

The acceptability of the intervention will be gauged using the URPI and qualitative interviews among those randomized to the intervention either when they finish the intervention or after study withdrawal. We will calculate averages. For qualitative data, we will use inductive thematic analysis, where we will

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collect these data and articulate patterns within them, and these patterns will collectively explain what occurs within the data. We will code transcripts to identify themes (eg, reported experiences) using qualitative analysis software, review patterns in core themes, determine the degree of overlap, and develop a network diagram of interrelationships between themes. Themes will be used to describe correlates of acceptability of the exercise intervention and identify factors that are likely to influence participation in the program. We intend to use multiple coders, and we will analyze intercoder reliability using 25% of the sample, aiming for a Cohen κ of >0.75 [33,34]. In addition to examining the coder agreement, we will use member checking [35]. We will share preliminary analyses with selected participants and ask them to confirm whether the data reflect their perspectives and what they discussed in their interviews. Finally, we will be mindful that the researchers' experiences may be different from those of the study participants. We will bring awareness of the potential influence on data collection, data analysis, and how we perceive the data, as well as how the participants perceive the researchers conducting the study, when conducting the qualitative analyses [36,37].

The estimate of the effect of the intervention on gait speed and other secondary outcomes will be determined through the change in outcome measures between intervention end (ie, week 12 study visit) and intervention start (randomization). We will use the mean and SD of the within-person change (pretest-posttest value) in gait speed in a sample size calculation for a future randomized clinical trial. We will conduct analyses with and without adjustment for adherence to the intervention by incorporating the proportion of exercise sessions completed (ie, percentage of adherence) as a factor in the analyses.

All data will be assessed for missingness and impossible or out-of-range values using basic statistical procedures such as univariate statistics. Missing data will be imputed using multiple imputation, which provides unbiased estimates if the data are missing completely at random or at random. There will be no interim analysis.

Participant Safety and Minimizing Potential Risk

The risks from participating in the research program include minor discomfort, but these are transient. Participants will undergo procedures that involve a mild to moderate degree of risk, including questionnaires, exercise training, and mobility assessments. The interviews and questionnaires in this study are time-consuming but of minimal risk. Completion of physical activity is associated with the risk of cardiovascular complications such as chest pain, myocardial infarction, or sudden death and complications related to stress and strains of muscles, twisted ankles, or falls. The American Heart Association consensus statement on exercise standards [38,39] estimates that the acute risk of sudden cardiac arrest during exercise training in participants with known cardiac disease is approximately 1 event per 58,000 hours of aerobic exercise. The risk of exercise training is greater at higher exercise intensities. This risk is offset by prescreening participants with medical evaluations before exercise and starting them out at a low intensity. A research team member (exercise physiologist or other medical professional) certified in American Heart Association Basic Life Support will be present during all internet-based videoconference exercise sessions. We will follow standard protocols for our facility regarding the use of internet-based videoconference exercise to ensure safety. In addition, there is a minimal risk of falling during the walking and mobility tests. A standby aid is always present, and a gait belt is used to increase safety when necessary. Ample rest periods are provided to limit fatigue during testing.

At each study visit, participants will be asked whether they had any adverse events since the last study visit. Adverse events that occur during study visits or internet-based videoconference exercise classes will also be captured. These adverse events will be systematically recorded and reviewed by the study principal investigator. Adverse events will be classified based on whether they are study related, a serious adverse event, and unanticipated or unexpected. Adverse events will be collated and then reviewed biannually by the Veterans Integrated Service Network (VISN) 5 Geriatric Research, Education, and Clinical Center DSMB and reported to the IRB as necessary. The board's composition and standard operating procedures have been documented and approved by the IRB at the University of Maryland, Baltimore. Its primary focus is safety, particularly monitoring expected and unexpected adverse events directly attributable to study participation (ie, a fall during an exercise class).

Data Management

Participants will be assigned a unique study ID number that will be kept in a password-protected database stored on a VA server with a level and scope of security that equals or exceeds that established by the HIPAA Security Rule. Data collected during the study that are not captured electronically will be entered and stored in the VA REDCap (Research Electronic Data Capture; Vanderbilt University) server. Participants' charts will be held in a locked room inside a locked cabinet at the Baltimore VAMHCS. Data will be inspected for completeness, out-of-range values, missingness, and internal consistency (when relevant). Access to the individual participant study ID numbers or personal identifiers will be limited to research team members who need to know to perform their study role.

Study data will be kept in accordance with the VA Records Control Schedule 10-1. Storage and transfer of any personally identifiable information or protected health information must be conducted in accordance with applicable VA and Veterans Health Administration policies and directives; state and federal regulations; and applicable statutes, including HIPAA.

Protocol Modifications

The study team, comprising the principal investigator, coinvestigator, study coordinators, data manager, and study manager, have weekly meetings. Any protocol modifications are communicated in these meetings or via email. There are also monthly meetings with the entire team to track progress and check in.

Ethical Considerations

This protocol was approved by the University of Maryland IRB (the IRB of record for the Baltimore VAMHCS) on May 13,

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2024, as a minimal risk study, and by the Baltimore VA Research and Development Committee on June 13, 2024. In addition, written informed consent will be obtained from all participants before participating in the study. The participants' privacy will be kept confidential and they will be informed of their right to withdraw their consent at any time. All participants will be reimbursed with US $50 for study visits 1 to 7 for their time and effort and US $25 for the semistructured interview.

Dissemination

The results of this study will be made available to health care professionals and the public through the National Library of Medicine PubMed Central website within 1 year after the date of publication. In addition, study findings will also be presented at scientific meetings. Study investigators will be responsible for the writing of all publications and will not use the services of professional writers.

Results

This study was funded on July 1, 2024, with a projected data collection period from October 1, 2024, to March 31, 2026. As of June 12, 2025, there are 12 participants who have been enrolled in the study, and 6 (50%) participants have been randomized.

Discussion

Expected Findings

This pilot study will assess the feasibility and acceptability of a home-based exercise regimen aimed at safely increasing mobility and function, focusing on improving lower extremity strength, tissue perfusion, and glycemic control. The feasibility of, adherence to, and acceptability of the intervention will be assessed. While we anticipate that people in the intervention group will have increased mobility and function, a decrease in major adverse cardiovascular events, and a decrease in long-term ulcer recurrence, this study is designed to be a pilot study. As such, any measures of physiological change with exercise are not expected to demonstrate statistical significance and are being collected solely to provide effect size estimates that will be used to develop sample size estimates for a larger intervention efficacy trial. This research is important because those who have DFUs rarely return to their baseline level of mobility, much less a recommended level of mobility [9-12]. The period after ulcer healing is a critical time to intervene and could improve mobility and restore function. It could also have a high impact on a population with a clear history of health disparities through the ability to exercise from home. This intervention has clear potential to be scalable as a telehealth group intervention.

The study outlined in this paper has several notable strengths that enhance its potential impact. First, the use of the SmartMat for safety monitoring is a significant strength as it allows for daily remote tracking of foot temperature, which can help in early detection of potential issues such as ulcer recurrence. This proactive approach to safety ensures that participants can engage in the exercise regimen with reduced risk. Second, the detailed tracking of participation through written logs, internet-based videoconference session attendance, and Fitbit data provides a comprehensive view of adherence and engagement. In addition, the use of semistructured interviews and the URPI to assess the barriers and acceptability of the intervention offers valuable qualitative insights. These methods allow for a deeper understanding of participants' experiences and challenges, which can inform future improvements to the program. Finally, the home-based exercise regimen, combined with objective monitoring of adherence, supports participants in maintaining their mobility and function in a convenient and accessible manner. This approach not only promotes sustained engagement but also has the potential to be scalable and adaptable to other populations, enhancing its overall applicability and impact.

This study has several limitations. One limitation is the lack of diversity within the participant population, which predominantly consists of male veterans. This sex imbalance may limit the generalizability of the findings to the broader population of individuals with DFUs, particularly women, who may have different responses to the intervention. In addition, the study's focus on veterans from a specific health care system may not capture the variability in outcomes that could occur in a broader, nonveteran population. Another limitation is the potential preference for in-person exercise programs among this patient population. While the home-based exercise regimen offers convenience and accessibility, some participants may prefer the structure, social interaction, and direct supervision provided by in-person programs. This preference could affect adherence and engagement levels, potentially affecting the study's outcomes. Addressing these limitations in future research could enhance the applicability and effectiveness of the intervention across a more diverse and representative sample.

Future Directions and Conclusions

Our long-term goal is to improve clinical outcomes for adults with a DFU by improving their treatment and rehabilitation. This pilot study is expected to provide preliminary evidence for a larger-scale, randomized clinical trial that will examine the exercise intervention tested in this pilot study and result in improved mobility and function in those with a recently healed ulcer while also minimizing ulcer recurrence. On the basis of the findings of this project, these future clinical studies may address adaptations to the exercise intervention, changes in cardiovascular risk following exercise, and long-term ulcer recurrence with increased supervised activity. Future trials will be needed to validate these findings before broad-based acceptance and dissemination across VAs can occur. Thus, the proposed research will not only provide information for the veterans participating in this study but will also lay a foundation for future research targeting veterans and other people with recently healed foot ulcers.

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Data Availability

The final datasets underlying all publications resulting from the proposed research will be shared outside the US Department of Veterans Affairs. The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
DFU: diabetic foot ulcer
DSMB: Data Safety Monitoring Board
HIPAA: Health Insurance Portability and Accountability Act
IRB: Institutional Review Board
PAVE: Prevention of Amputation in Veterans Everywhere
REDCap: Research Electronic Data Capture
RPE: rating of perceived exertion
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
URPI: Usage Rating Profile–Intervention
VA: United States Department of Veterans AffairsVAMHCS: United States Department of Veterans Affairs Maryland Health Care System

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Protocol

Aiding Chronic Obstructive Pulmonary Disease and Congestive Heart Failure Ultrasound-Guided Management Through Enhanced Point-of-Care Ultrasound (ACCUMEN-POCUS): Protocol for a Randomized Controlled Trial

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Abstract

Background: Hospital at home (HAH) programs offer acute care at home as a substitute for inpatient hospitalization, reducing health care costs while maintaining safety and care quality. Despite point-of-care ultrasound (POCUS) having been validated in inpatient and emergency settings, its role in HAH care remains underexplored. Common conditions treated in medical HAH programs, such as acute exacerbation of chronic obstructive pulmonary disease (AE-COPD), acute decompensated heart failure (ADHF), and pneumonia, are highly amenable to POCUS integration into clinical decision-making and have been proven to improve health care use outcomes. The portability of POCUS makes it ideal for use in HAH; however, its feasibility remains to be proven given the need for health care provider training and use in online settings.

Objective: This study evaluates the feasibility and clinical utility of remotely interpreted lung and inferior vena cava (IVC) POCUS acquired by community paramedics to support real-time clinical decision-making for HAH patients with AE-COPD, ADHF, and pneumonia in Calgary, Alberta.

Methods: This randomized controlled trial compares usual HAH care (control) to lung and IVC POCUS–enhanced HAH care (intervention). Handheld POCUS devices captured images that were securely shared using a cloud-based application. This enabled real-time image sharing among the clinical team, facilitating immediate decision-making by remote physicians. A mixed methods approach will evaluate clinical outcomes, patient experiences, health care use, and health care provider perceptions of POCUS

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integration. The primary outcome is defined as the length of stay for the index HAH admission. Quantitative analysis will assess clinical efficacy and health care resource use, while qualitative methods, such as interviews and surveys, will capture patient and health care provider experiences.

Results: Study funding began in April 2022, and data collection commenced in December 2023. Patient recruitment was finalized on December 31, 2024. This study included a 3-month follow-up for significant outcomes and will include a 1-year follow-up for long-term health care use, including admissions to long-term care. In total, 20 patients were enrolled (intervention group: n=10, 50%; control group: n=10, 50%). Initial results highlighted the feasibility and potential benefits of remotely acquired POCUS imaging in HAH. Full data analysis is in progress.

Conclusions: This study is the first randomized controlled trial to investigate remotely acquired POCUS by nonphysician practitioners for real-time lung and IVC remote decision-making in HAH care. Findings will provide insights into whether serial lung and IVC POCUS assessments improve ADHF, AE-COPD, and pneumonia outcomes in the HAH setting, enhancing understanding of the value of POCUS integration from a health care provider's perspective. By assessing its clinical impact and feasibility, this research may inform future guidelines for incorporating POCUS into home-based care, ultimately improving patient care and optimizing health care resource use.

Trial Registration: ClinicalTrials.gov NCT05423652; https://clinicaltrials.gov/study/NCT05423652

International Registered Report Identifier (IRRID): DERR1-10.2196/76186

(JMIR Res Protoc 2025;14:e76186) doi:10.2196/76186

KEYWORDS

hospital at home; point-of-care ultrasound; acute decompensated heart failure; ADHF; acute exacerbation of chronic obstructive pulmonary disease; AE-COPD; pneumonia

Introduction

Background

Acute decompensated heart failure (ADHF), acute exacerbation of chronic obstructive pulmonary disease (AE-COPD), and pneumonia are among the leading causes of patient morbidity and mortality worldwide. Patients with the aforementioned diseases present with dyspnea and respiratory distress [1,2]. Currently, diagnosis and management of these patients are reliant on symptoms, physical examination such as lung auscultation, radiographic imaging studies, and laboratory investigations [3-5]. However, for these conditions, the aforementioned modalities have poor diagnostic rates, with radiographs having false-negative rates exceeding 25% at times. Biomarkers have poor predictive value in patients with comorbidities presenting with multiple physiological derangements [6-8]. Furthermore, chest radiographs often require costly machinery housed in a hospital or radiology center, with the potential for delays due to radiologic interpretation time [9].

Emerging literature on using point-of-care ultrasound (POCUS) for management of AE-COPD, ADHF, and pneumonia shows reductions in hospital length of stay (LOS), favorable patient outcomes, and lowered health care costs [10-13]. These findings are often attributed to POCUS's comparable or higher sensitivity relative to physical examination and chest radiography in detecting early signs of pulmonary edema, pleural effusions, impaired diaphragmatic excursion, and subpleural consolidation [14-16]. Unlike radiographic imaging, POCUS also offers advantages such as portability, absence of radiation exposure, and suitability for frequent bedside use in longitudinal care [15,17,18]. Guevarra and Greenstein [19] describe how POCUS is now integral to volume status assessment, cardiac function evaluation, and lung imaging in patients who are critically ill. Despite its clinical utility, widespread adoption of POCUS has historically been limited by the need for specialized training, a shortage of trained health care providers, and variability in image acquisition and interpretation [10,11,16].

While mobile health tools have gained traction in chronic disease management, relatively few have been designed specifically for acute cardiorespiratory conditions such as AE-COPD or ADHF. A systematic review of reviews found that mobile health interventions can improve symptoms and reduce hospitalizations in chronic pulmonary disease and heart failure, among other conditions [20]. However, most commercially available solutions focus on general wellness monitoring or outpatient management, with limited application to POCUS in acute care. Recent reviews have demonstrated that POCUS, particularly when integrated with mobile platforms, can substantially improve diagnostic accuracy and guide management in heart failure and other acute conditions [11,21]. This latter finding underscores the need for tailored, evidence-based tools that address specific diagnostic and triage challenges in these high-risk populations.

Recent studies suggested that nonexpert health care providers (and even patients themselves) could be effectively trained to acquire quality POCUS images in an acute care, emergency, or intensive care unit setting, particularly by using teleguidance methods [22-24]. Although POCUS is well established in emergency and critical care settings, its use has progressively expanded into community and home-based care environments [25-27]. This shift has been notably accelerated by the COVID-19 pandemic, which highlighted the need for accessible diagnostic modalities among homebound older adults and populations in geographically isolated regions. In this context, teleultrasound has emerged as a viable solution, supporting timely and accurate clinical decision-making within evolving models of home-based acute care [23,28-30].

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This paper describes a study protocol developed to investigate the feasibility and clinical usefulness of embedding community paramedic (CP)–acquired lung and inferior vena cava (IVC) POCUS scans in supporting real-time remote decision-making by physicians of a hospital at home (HAH) program. The sharing of images, feedback, and clinical decision-making was supported by a cloud-based application (Presuna) designed to extract POCUS images from handheld POCUS devices to enable the sharing of ultrasound images among clinical team members for both educational and clinical care purposes.

Objectives and Aims

This study is a multisite, 2-arm, parallel, randomized controlled trial (RCT) comparing enhanced daily assessments for patients with AE-COPD, ADHF, or pneumonia using POCUS with a cloud-based application versus standard care provided by an HAH program at a tertiary acute care medical teaching hospital in Calgary, Alberta.

Standard care provided through this HAH program was selected as the comparator to assess patient outcomes, experience, and health care use and to evaluate the economic feasibility of integrating POCUS into future standard care practices.

Methods

Study Setting

The Calgary Zone Virtual Home Hospital (previously the Complex Care Hub) [31] is an HAH program that provides substitute acute care in patients' homes for a general internal medicine (GIM) population at 2 hospitals, the Rockyview General Hospital and South Health Campus. Patients can be admitted to HAH from a brick-and-mortar (BAM) hospital, either directly from the emergency department or the medical inpatient wards, as well as from community settings such as specialty clinics and family medicine referrals.

There are two collaborating teams:

1. The hospital-based team consists of a hospital physician (GIM or family medicine hospitalist), nurse navigators (NNs), and a pharmacist. This team performs case finding, in-person assessments, and interventions in a dedicated clinic space and oversees the care plan. In addition, physicians conduct online visits for patients admitted to the program, either directly leveraging digital remote patient monitoring technology or via an online consultation with home-visiting CPs.
2. The home-based team consists of highly skilled CPs who collaborate with patients and their caregivers in the home. CPs perform most home visits, assessments, and interventions under remote guidance by the HAH physician.

Patient Recruitment

Patients admitted to HAH with ADHF, AE-COPD, or pneumonia were identified as potentially eligible either by HAH NNs or through the research team's screening of the patient charts (under a waiver of consent). NNs or CPs offered eligible patients the opportunity to be contacted by the research team to learn about the research study. Following initial contact, consenting patients were contacted by research assistants for enrollment into the study, obtaining written or verbal informed consent via REDCap (Research Electronic Data Capture; Vanderbilt University) or email.

Inclusion criteria for patients were (1) a primary active diagnosis of ADHF, AE-COPD, or pneumonia requiring home-based acute care at the time of enrollment; (2) previous admission to the HAH program; and (3) willingness to participate in the study and provide informed consent. Patients were excluded from this study if they did not have 1 of the 3 index conditions, had new unstable rib fractures, a previous history of allergy to ultrasound gel, or chronic lung diseases that would confound POCUS imaging (pulmonary fibrosis, fibrothorax, lung cancer or other intrapulmonary malignancy, pleural plaques, pneumothorax, or pulmonary embolus). These conditions were confirmed through imaging, such as radiographs or computed tomography, performed in the BAM hospital before admission to the HAH program.

Enrolled study participants were randomized using REDCap's randomization function to either the intervention arm (HAH care enhanced with serial POCUS assessment) or the control arm (usual HAH care; Figure 1).

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Figure 1. Randomization and study protocol. ADHF: acute decompensated heart failure; AE-COPD: acute exacerbation of chronic obstructive pulmonary disease; HAH: hospital at home; IVC: inferior vena cava; POCUS: point-of-care ultrasound; RCT: randomized controlled trial.

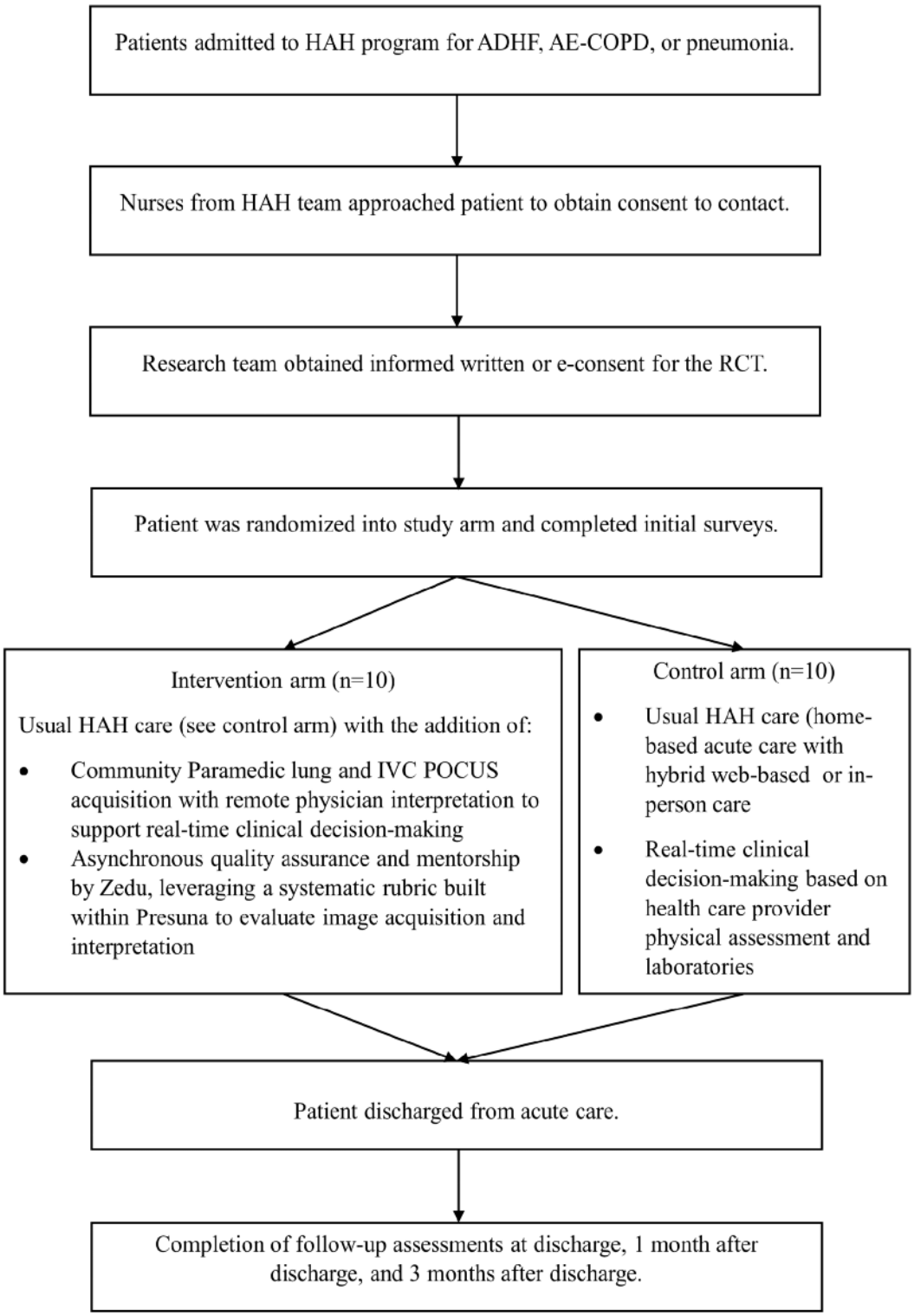

Health Care Provider Recruitment

HAH Health care providers were recruited based on an expressed willingness to participate in this study after being provided with information about the study's aims and methods. Study staff then obtained informed consent via email or in person. When a physician did not want to participate in the study, 2 physicians from the research team who regularly attended HAH assumed care of study patients for the weeks in which there was a nonparticipating physician.

In preparation for the RCT, we previously trained 6 CPs in POCUS image acquisition for lung and IVC using a hybrid protocol, consisting of in-person didactic lectures and bedside teaching, online modules from the Canadian Point of Care Ultrasound Society [32], and asynchronous mentorship. The latter was used to evaluate the quality and clinical usability of

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participants' POCUS images based on a rubric developed in consultation with POCUS experts.

There were 2 groups of physician participants, a mix of non-POCUS experts and POCUS experts who regularly rotate through the service. Those defined as POCUS experts are physicians certified in POCUS use and capable of providing consultative support to other clinicians or trainees. These individuals required only a brief orientation to the cloud-based application used for image interpretation, as they were already proficient in POCUS use. Initially, we intended to train non-POCUS expert physicians in acquiring and interpreting lung and IVC POCUS using the same training program described earlier for CPs. However, the post–COVID-19 pandemic challenges of high patient volumes, multiple competing priorities, and physician burnout made it infeasible for physicians to complete the training. Consequently, we pivoted to train 2 physicians from the research team to be able to provide real-time POCUS interpretation support for non-POCUS expert physicians (Figure 2). While certain physicians leveraged this support and the rubric on the cloud-based application to aid them in learning about POCUS, this was not common and was not evaluated in this study.

Figure 2. Process for remote acquisition, interpretation, and real-time learning of inferior vena cava (IVC) and lung point-of-care ultrasound (POCUS). CP: community paramedic; MD: doctor of medicine.

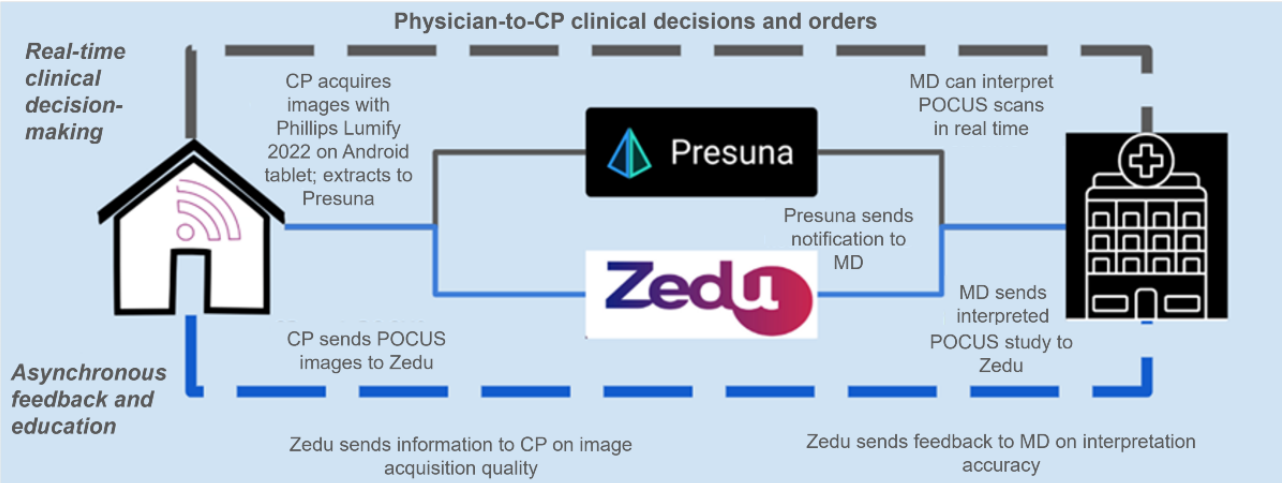

Randomization and Allocation Concealment

Randomization through the REDCap functionality allocated participants to their respective study arms. Data analysts, including economists, are blinded to study allocation. The master list of the clinical and study codes will be kept in an encrypted file on the University of Calgary server and managed by the research study team.

Intervention

Patients randomized to the interventional study arm received serial lung and IVC POCUS assessments throughout their admission to HAH. These images were acquired by CPs in patients' homes and transmitted to HAH physicians via Presuna, a cloud-based application. Presuna is a versatile software platform that allows ultrasonography programs to grow and maintain ultrasonography capacity through both in-person and online ultrasonography assessments and analytics. Key features include structured digital logbooks for supervised, on-site scan capture; flexible assessment templates that can be tailored to individual program objectives; secure link sharing for soliciting second opinions from expert reviewers; and built-in user surveys timed to critical workflow events (eg, immediately after scan upload or interpretation). The platform's analytics dashboards provide real-time insights at both individual and cohort levels, enabling programs to monitor procedural volumes, acquisition quality, and interpretive accuracy and to benchmark performance against competency thresholds.

During development, Presuna followed a user-centered, iterative design process with ultrasonography experts, CPs, and physicians to ensure its workflows and interfaces met real-world needs. Enhancements were developed throughout the pilot around the asynchronous online assessments, assessment templates, and analytics.

In pilot testing, Presuna was deployed in collaboration with Zedu Ultrasound Training Solutions and Alberta Health Services' Mobile Integrated Healthcare program for community paramedicine. During the pilot, CPs performed POCUS in patient homes, uploading studies via digital tablets to Presuna. Physicians used the platform's customizable assessment templates and secure link sharing to interpret scans remotely and solicit second opinions from ultrasonography experts. Every study then underwent centralized quality assurance review by Zedu educators, leveraging built-in user surveys triggered immediately after uploads and interpretations to capture usability and contextual research data in real time.

The built-in user survey was structured and quantitative. It was administered to assess the implementation and clinical integration of POCUS. The survey included closed-ended questions using Likert scales and multiple-choice formats to evaluate technical issues affecting workflow, perceived quality of acquired scans, and health care provider confidence in scan acquisition. Additional items assessed interpretation consistency with expert reviewers for lung IVC scans, changes in interpretation following expert consultation, confidence in scan interpretation, and the perceived usefulness of POCUS findings

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for clinical decision-making and patient management. Responses were collected after each POCUS encounter to capture real-time health care provider experience.

Throughout the pilot, Presuna's competency analytics dashboards were used to track acquisition quality and interpretive accuracy at both the individual and cohort levels. These analytics informed when CPs and physicians reached predefined competency thresholds that allowed them to more safely participate in the RCT phase of the pilot.

Overall, Presuna allowed for the extraction and secure sharing of the images captured by the handheld POCUS. CPs used a Phillips Lumify C5-2 curved array ultrasound transducer connected to a Samsung tablet to extract the images from the Lumify app and upload them to the Presuna application (which is encrypted). Once on Presuna, the images were instantaneously available for the HAH physicians to interpret, either on a hospital computer or their personal cell phones, facilitating immediate decision-making by remote physicians (Figure 2).

For each study participant in the intervention arm, CPs acquired images for a minimum of 8 out of 10 lung zones (Figure 3). They attempted to acquire 2 views of IVC (longitudinal and transverse) with measurements at end inspiration and expiration to derive the IVC collapsibility index.

Figure 3. Lung zones. L1: left upper anterior zone; L2: left middle anterior zone; L3: left upper lateral zone; L4: left lower lateral zone; L5: left upper posterior zone; R1: right upper anterior zone; R2: right middle anterior zone; R3: right upper lateral zone; R4: right lower lateral zone; R5: right upper posterior zone.

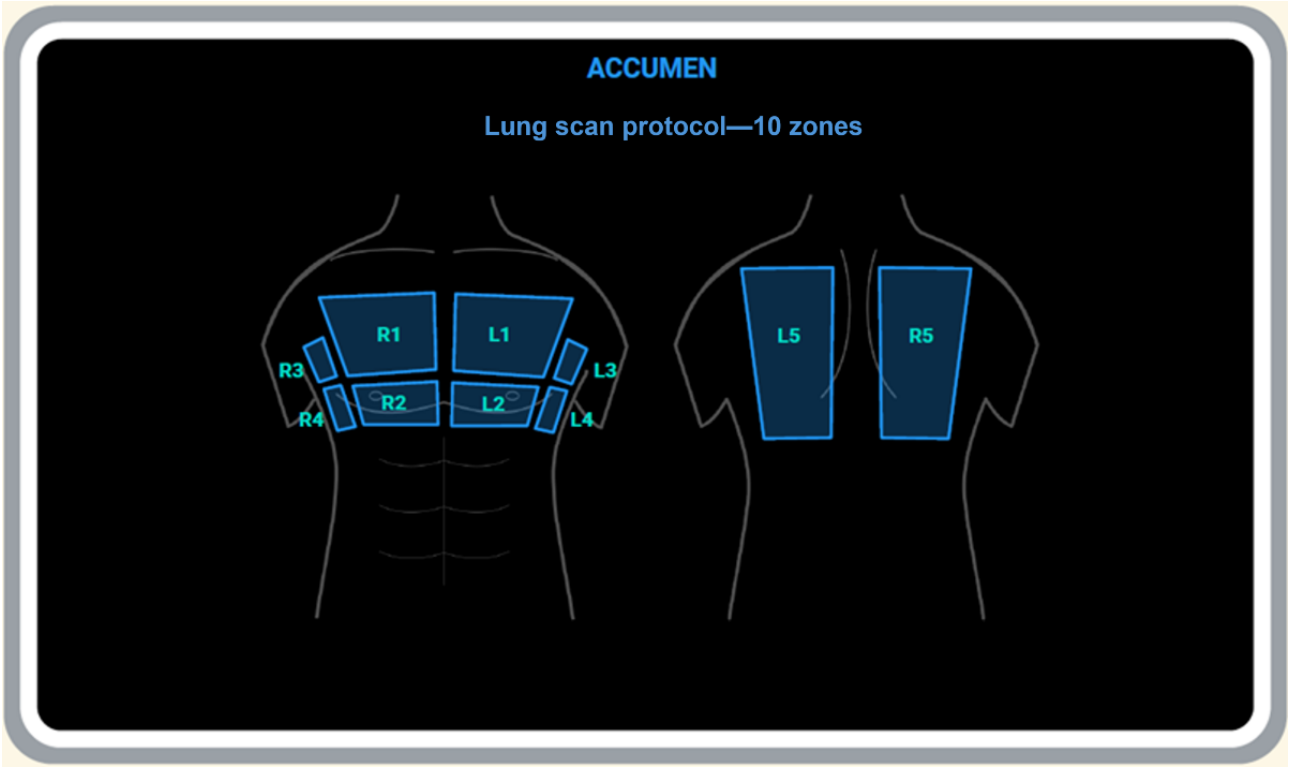

Ethical Considerations

Human Participant Ethics Review Approvals or Exemptions

This study was approved by the Conjoint Human Research Ethics Board at the University of Calgary (REB22-0434; latest protocol amendment version: 13.0; issue date: March 27, 2025). This study is registered as a clinical trial on ClinicalTrials.gov (NCT05423652). Ethics approval covered all aspects of the study, including patient identification, consent procedures, and data collection.

Informed Consent

As described in the Patient Recruitment section, patients admitted to the HAH program with ADHF, AE-COPD, or pneumonia were identified as potentially eligible either by HAH NNs or through chart screening by the research team under a waiver of consent. Eligible patients were offered the opportunity to be contacted by the research team to learn more about the study. Following initial contact, consenting patients were enrolled by the research team, who obtained written or verbal informed consent via REDCap or email.

Privacy and Confidentiality

Participant privacy and confidentiality were maintained throughout the study. Each participant was assigned an anonymous study number, which was the only identifier for POCUS scans on Presuna and used during the data analysis. Any data containing personal identifiers were stored securely in locked cabinets or password-protected digital files accessible only to the research team. All reported data were aggregated to prevent the identification of individual participants.

Compensation Details

No compensation was provided to research participants.

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Data Collection

All data on Presuna are encrypted in transit with modern transport layer security and while at rest (storage) with modern Advanced Encryption Standard 256-bit encryption. Patient study IDs were used as the only method of patient identification. Consequently, no identifiable patient information was stored on Presuna. Furthermore, Presuna uses the "least access principle," so health care providers could only access the data needed to perform their workflows and inform their decisions. In addition, all practitioners accessing Presuna had their codes to protect them as health care provider participants in the study and reduce the identifiable linkages of patients with their health care providers.

All other study data were collected and managed using REDCap electronic data capture tools hosted at the Centre for Health Informatics, Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada [33,34]. REDCap is a secure, web-based application designed to support data capture for research studies providing an intuitive interface for validated data capture; audit trails for tracking data manipulation and export procedures; automated export procedures for seamless data downloads to standard statistical packages; and procedures for data integration and interoperability with external sources. The principal investigator and the research team members involved in data analysis will be given access to the cleaned datasets. To ensure confidentiality, data dispersed to research team members will be blinded to any identifying participant information.

Study Outcomes

Overview

The demographic characteristics collected in this study includes date of birth, age, sex or gender, comorbid diagnoses, Charlson Comorbidity Index, education level, employment status, race, smoking history, medication history, home medications, goals-of-care status, and overall functional status. This serves to stratify end points based on potentially extraneous variables, thus minimizing their confounding effect in the final analysis. Study outcomes are intended to capture the most clinically significant causes of patient morbidity and mortality.

Data were collected to evaluate the added clinical value of incorporating POCUS for lung and IVC into our HAH care in terms of its impact on clinical outcomes, feasibility, and sustainability.

Primary Outcome

The primary outcome is defined as LOS for the index HAH admission, measured from the date of admission until discharge, based on ADHF studies showing decreased LOS in BAM inpatient care [12]. As the program has an acute (hospital substitution) and subacute arm (after acute care), LOS on each arm will also be reported.

Secondary Outcomes

Textbox 1 summarizes the metrics according to the quadruple aim framework, which guided our evaluation of clinical outcomes, patient- and clinician-reported metrics, as well as health care system sustainability outcomes.

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Textbox 1. Study metrics by category.

Patient outcomes

- Health-related quality of life (EQ-5D-5L) at the time of randomization, within 1 week following hospital at home (HAH) discharge, and at 3 months after discharge, along with other objective metrics, will be assessed.
- Disease-related metrics for pneumonia are as follows:
  - Time to resolution of infection (return to baseline oxygen saturation level) and normalization of white blood cell count
  - For intervention-group participants, the normalization of pathological B-lines due to consolidative pneumonia
  - Change in hemoglobin and white blood cell count during the enrollment period
- Disease-related metrics for acute decompensated heart failure are as follows:
  - Time to decongestion (absence of crackles on lung auscultation and return to baseline oxygen saturation levels)
  - For the intervention group, the absence of pathological B-lines or pleural effusions on ultrasound
  - Change in N-terminal pro–B-type natriuretic peptide, troponin, creatinine, and estimated glomerular filtration rate during the enrollment period
- Disease-related metrics for acute exacerbation of chronic obstructive pulmonary disease are as follows:
  - Time to reduction in dynamic hyperinflation defined as the absence of wheeze and return to baseline respiratory effort and oxygen levels
  - Absence of new pulmonary findings because point-of-care ultrasound (POCUS) monitoring in this population was intended to proactively identify new findings (eg, pneumonia) that could complicate the acute exacerbation of chronic obstructive pulmonary disease
  - Change in hemoglobin and white blood cell count during the enrollment period
- Imaging modalities performed as a function of routine clinical care were used to support diagnosis before enrollment as well as during clinical status changes during the index HAH admission, including chest X-rays, computed tomography, and ventilation-perfusion scans to rule out pulmonary embolism.
- Medication burden was assessed at the time of randomization, until 1 week following discharge from HAH.
- Clinical status changes from the date of randomization until discharge from the index HAH admission were assessed. Changes in patient status were evaluated in terms of their severity and impact. Escalation of care is defined as the incidence ratio of transfer back to a brick-and-mortar hospital ward from HAH for a reason concerning clinical stability.
- Adverse events measured in standard monitoring of the program include new venous thromboembolism, falls, infection, and mortality.

Patient or caregiver experience

- Self-reported patient experience surveys after discharge from the index HAH admission, with quantitative Likert scales and free text options (refer to Multimedia Appendices 1-3) were conducted.

Health care provider experience

- Semiquantitative surveys of nurse practitioners, community paramedics (CPs), and physicians providing care to patients in the study were conducted. Surveys were administered to inquire into health care providers' experience with the HAH model and various technologies used over the course of its duration (digital remote patient monitoring, videoconferencing, as well as POCUS Presuna for the intervention arm). Participants were asked to score their responses on a Likert scale, allowing entries in the form of strongly disagree, disagree, neither agree nor disagree, and strongly agree.
- We embedded questions after each encounter in a clinical survey on Presuna for CPs and physicians to complete regarding their confidence in acquiring and interpreting images (both in terms of their own confidence and the image quality), respectively. We also asked questions to determine the usability and clinical usefulness of POCUS for each encounter.

Health care use and cost

- Length of stay for the index HAH admission (refer to the aforementioned information) will be calculated.
- Readmission rate (7, 30, and 90 days after discharge from HAH) will be calculated.
- Admission to facility living, including long-term care or supportive living, will be assessed up to 12 months following discharge from the index HAH admission.
- Time per CP visit will be calculated.
- Cost comparison of the cost of CP, physician, nursing services, medications, and diagnostic testing will be done. We will leverage Alberta's health data repositories, including physician claims; National Ambulatory Reporting System; Discharge Abstracts Database; and Data Integration, Measurement and Reporting, as well as Alberta Health Services' cost estimates.

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Statistical Analysis

The study by Öhman et al [35] showed a 46% reduction in hospital LOS in the standard care group versus the treatment arm that used cardiothoracic ultrasound to guide clinical decision-making for inpatient care (mean 6.85, SD 4.22 days versus mean 3.72, SD 2.02 days). For our study, we will use a conservative 30% reduction in LOS on HAH for the intervention arm versus the control arm, powered at 80% with an α level of .05. In designing the study, we estimated that we would require a sample size of 22 patients per study arm within the time frame of this project.

The analysis and reporting of this trial will be undertaken in accordance with CONSORT (Consolidated Standards of Reporting Trials) guidelines [36]. We will conduct an intention-to-treat analysis, including all randomized patients who receive at least 1 study intervention or control procedure. We will also conduct a per-protocol analysis [37] based on patients who complete the study without major protocol deviations affecting primary end points and a safety analysis of all randomized patients who receive any study-related care.

For the primary outcome of HAH LOS, we will conduct a 2-sample 2-tailed *t* test (if normally distributed) or a Mann-Whitney *U* test (if nonnormally distributed) between the intervention and control groups. We will report the effect size with 95% CIs alongside the *P* values. Given the small sample size, no subgroup analyses will be conducted.

An analysis of resource use and costs will be conducted to inform the economic impact of HAH through an economic evaluation and budget impact analysis. We will use the data gathered by the study, supplemented with data from health care administrative databases, for this analysis. The implementation of HAH is anticipated to yield improvements in both system efficiency and patient outcomes, and the economic evaluation will quantify the costs and benefits associated with HAH compared with conventional care models.

For analysis of secondary and economic outcomes, we will report outcomes, *P* values, and CIs, but formal hypothesis testing will be avoided, given the exploratory nature of the analysis. However, any notable imbalances will be described and considered in the interpretation of results. For analysis of the net resource effectiveness, economic data will be analyzed via the headroom model, which is a method that quantifies the greatest cost at which an intervention would continue to demonstrate a net economic benefit. In this study, the headroom analysis will compare the control group, defined earlier as standard practice HAH care, with the POCUS or Presuna (intervention) group in patients with ADHF, AE-COPD, and pneumonia. Secondary patient outcomes will be analyzed via a 2 tailed *t* test comparing differences in biomarker or imaging values between control and intervention groups, set to the same power of 0.80 and an α level of .05.

Quality Assurance, Adverse Event Monitoring, and Steering Committee

Several measures were enacted to improve adherence to intervention protocols and ensure patient safety. Quality assurance of randomly selected scans was performed by the research team in consultation with a POCUS expert physician. This involved asynchronous mentorship leveraging the Presuna platform and Zedu Ultrasound Training Solutions. We created a POCUS acquisition or interpretation evaluation rubric to evaluate the presence of proper anatomical landmarks, image quality, and systematic analysis of the scans to identify the presence or absence of pathological findings.

A structured, modular rubric was used within the Presuna platform to assess both the quality of ultrasound image acquisition and the accuracy of scan interpretation. The rubric was designed to separate scan-level observations from examination-level conclusions and was tailored to the unique requirements of different examination types. For lung ultrasound, physician reviewers documented specific scan findings such as A-lines, lung sliding, B-lines, and pleural effusion while also making global diagnostic determinations across the entire examination (eg, interstitial edema and pneumothorax). For IVC assessments, which require integration of multiple clips, the rubric focused on examination-level evaluation, including visual estimates of IVC size and collapsibility, and clinical estimation of central venous pressure. Quality assurance reviewers used a parallel rubric to evaluate acquisition quality, with domains covering technical parameters (eg, depth and gain), anatomical accuracy (eg, correct orientation and landmark visualization), and interpretability (eg, completeness, labeling, and diagnostic utility). All questions were formatted as categorical selections (eg, yes or no, multiple choice, and ordinal scales) to ensure consistency and enable quantitative tracking. The rubric was adaptable to site-specific protocols and levels of training, allowing for reliable, scalable assessment across educational and clinical implementations. Adverse events were stratified under frequency and severity of venous thromboembolism, new infections (focal or systemic), falls, delirium, and medication-related reactions, or other clinically significant events. They were recorded from the date of randomization up to discharge from HAH. Mortality outcomes will be stratified under time to death and cause of death from date of randomization until participant death up to 1 year after discharge.

The data and safety monitoring board reviewed potential adverse events during the study. The data and safety monitoring board was composed of 2 GIM specialists who worked on HAH and were trained in POCUS for this study and 2 expert POCUS physicians. These 2 expert POCUS physicians (a GIM physician who works at a different hospital and a thoracic surgeon) have extensive experience in the design and deployment of ultrasound-based training curricula.

Finally, a steering committee for the project met monthly to discuss project operations and updates as well as provide direction and guidance to the research team. This committee consisted of the research team and coinvestigators, a human factor evaluation team, the CP manager, POCUS experts, advisors, and a health economics analyst.

Results

Study funding began in April 2022, with data collection commencing in December 2023. Patient recruitment was

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finalized on December 31, 2024. This study includes a 3-month follow-up for major outcomes and a 1-year follow-up for long-term health care use, including admissions to long-term care. A total of 20 patients were enrolled (intervention group: n=10, 50%; control group: n=10, 50%).

Preliminary findings were presented in poster format at the World Hospital at Home Congress (March 2025). Initial results of an analysis of patient and health care provider experience highlighted the feasibility and potential benefits of remotely acquired POCUS imaging in HAH. Full data analysis is in progress, with results to be disseminated through journal publication and future scientific conferences.

Discussion

Anticipated Findings

This study aims to evaluate the feasibility and clinical impact of POCUS for lung and IVC assessments acquired by CPs in the HAH setting. We hypothesized that remote POCUS would enhance clinical decision-making and improve outcomes for patients with ADHF, AE-COPD, and pneumonia. Preliminary findings suggest that remote POCUS is feasible and may offer clinical value in HAH, particularly in guiding volume status and respiratory assessments.

Comparison With International Literature

This study builds on emerging evidence supporting the use of POCUS in home-based care. Previous studies have demonstrated the utility of lung ultrasound in diagnosing pneumonia and monitoring pulmonary congestion in patients with heart failure, but few have explored its integration into online care models. Our approach, leveraging remote guidance and interpretation, addresses a critical gap in the literature by enabling real-time image interpretation to support clinical decision-making without requiring the physical presence of a sonographer or physician, which may be particularly beneficial in resource-limited or geographically dispersed settings.

Strengths and Limitations

The strengths of this study include its randomized controlled design, multisite implementation, and focus on real-world feasibility. The integration of health care provider feedback and patient-reported outcomes adds depth to the evaluation, offering a more holistic understanding of remote POCUS in HAH.

Despite these promising insights, several limitations must be acknowledged. The most substantial limitation is the reduced sample size; although our power calculations indicated a need for 22 patients per arm, only 10 patients were recruited per group due to shifts in HAH admission patterns after the COVID-19 pandemic. This resulted in lower numbers of patients with ADHF, AE-COPD, and pneumonia than expected. While we implemented multiple strategies to increase recruitment, including adding the second site and obtaining a no-cost extension from the funder, we were only able to recruit 10 patients per study arm. This will limit our ability to detect statistically significant differences in the primary outcome and some secondary outcomes. However, the rich qualitative and semiquantitative data collected will still provide valuable insights into patient and health care provider experiences, workflow integration, and perceived utility of remote POCUS.

Future Directions

Future directions include expanding the study to additional sites with higher volumes of target diagnoses, refining recruitment strategies, and exploring automated image interpretation tools to further streamline remote assessments. A dissemination plan is underway, with preliminary findings already presented at the World Hospital at Home Congress (March 2025). Full results of the clinical trial are currently being analyzed and will be submitted for peer-reviewed publication. Once the analysis is completed, we intend to present the finalized clinical trial results at upcoming conferences.

Conclusions

This study represents the first RCT investigating remotely acquired POCUS for lung and IVC real-time decision-making in HAH care. While limited by sample size, preliminary findings support the feasibility and potential clinical value of remote POCUS in guiding care for patients with ADHF, AE-COPD, and pneumonia in the HAH setting. The integration of POCUS into HAH may enhance diagnostic accuracy, inform treatment decisions, and improve patient and health care provider experiences. These insights will inform future research and may contribute to the development of guidelines for incorporating POCUS into home-based acute care models.

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Disclaimer

The views expressed in this manuscript are those of the individual researchers and not an official position of the affiliated institutions or funder.

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Authors' Contributions

MNG, SR, GA, NDN, OO, ACYI, RK, JC, AWK, IWYM, JR, and SP participated in designing the study. MNG, GA, DM, OO, ACYI, SS, and SP conducted the study. ACYI, MNG, GA, JR, and JC will be involved in data analysis and methods. MNG, PN, and ACYI drafted and revised the manuscript in response to coauthor feedback. All authors were involved in reviewing and editing serial versions of the manuscript before submission.

Conflicts of Interest

SR is the founder and owner of Presuna, who was provided with reimbursement for the cost of participation in the study. Presuna did not profit from this study but benefited from iterative feedback from the research and clinical team to refine the software to be more responsive and usable for clinical teams embedding point-of-care ultrasound (POCUS) into their care. SP is the owner of Zedu Ultrasound Solutions and contributed her time in kind to the development of the rubric to evaluate and provide quality assurance for the acquisition and interpretation of POCUS images for lung and inferior vena cava POCUS. SP was only reimbursed for her time providing remote mentorship to the clinicians. Neither SR nor SP will be involved in data analysis and preparation of results presentations. IWYM declares receiving an editorial honorarium from Elsevier and is funded by the John A Buchanan Chair in General Internal Medicine at the University of Calgary, both unrelated to the manuscript. IWYM serves as a volunteer on the executive of the American Institute of Ultrasound in Medicine. JC has held peer reviewed grant funding from the WHO for assessing the use of drone aerial systems to deliver medical supplies and personal protective equipment to remote First Nations communities during the COVID-19 pandemic and from Alberta Innovates for reducing ventricular/lumbar drain and ventricular shunt Insertion infections in the neurosurgery, trauma, and intensive care unit patient population. He has also received accommodations and airfare to attend and speak at a symposium in 2022 from bioMerieux Canada on antimicrobial resistance co-hosted by the University of Toronto and bioMerieux Canada in 2022 and accommodations and airfare from the 2023 ICPIC meeting to attend a Think Tank meeting on infectious diseases modelling in Geneva, Switzerland. AWK has consulted for the Zoll, Acelity (3M/KCI), and Innovative Trauma Care Companies, and is the Principal Investigator of the COOL trial. All other authors declare no conflicts of interest.

Multimedia Appendix 1
Health care provider pre-post training survey.
[PDF File (Adobe PDF File), 248 KB - resprot_v14i1e76186_app1.pdf]

Multimedia Appendix 2
Patient experience survey.
[PDF File (Adobe PDF File), 296 KB - resprot_v14i1e76186_app2.pdf]

Multimedia Appendix 3
Health care provider experience survey.
[PDF File (Adobe PDF File), 312 KB - resprot_v14i1e76186_app3.pdf]

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Abbreviations

ADHF: acute decompensated heart failure
AE-COPD: acute exacerbation of chronic obstructive pulmonary disease
BAM: brick-and-mortar
CONSORT: Consolidated Standards of Reporting Trials
CP: community paramedic
GIM: general internal medicine
HAH: hospital at home
IVC: inferior vena cava
NN: nurse navigator
POCUS: point-of-care ultrasound
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture

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Protocol

Codeveloping a Novel Intervention to Promote the Well-Being of Family Caregivers of Individuals With Spinal Cord Injury: Protocol for a Feasibility Randomized Control Trial

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Abstract

Background: Family caregivers of individuals with spinal cord injury (fcSCI) provide assistance with activities of daily living for individuals with spinal cord injury (SCI), which can include emotional support and physical assistance. Over time, providing daily support can put fcSCI at risk of experiencing caregiver burden. This burden can have a substantial impact on fcSCI's well-being. A direct predictor of the fcSCI burden is their appraisal of their ability to cope with the individual with SCI. Therefore, supporting fcSCI's access to education relevant to their role and the health and well-being of the individual with SCI can help decrease this burden.

Objective: The purpose of this study is to evaluate the fidelity of the COMPANION intervention and its study protocol designed to improve outcomes for fcSCI.

Methods: Recruitment began in June 2024 and is ongoing. Data collection was completed in April 2025. The fcSCI randomized into the intervention group have been given access to COMPANION after randomization. Data collection for both participant groups (COMPANION and control) will be performed after randomization and will be performed again after 3 months (T2) and 6 months (T3) to capture the impact of COMPANION on fcSCI's psychological well-being.

Results: As of June 2024, recruitment has begun and is ongoing. Data collection has begun and will conclude in 2025. The fcSCI randomized into the intervention group have been given access to COMPANION after randomization. Data collection for both participant groups (COMPANION and control) is collected after randomization, and again after three months (T2) and six months (T3) to capture the impact of COMPANION on fcSCI's psychological wellbeing.

Conclusions: Study results will evaluate whether the full study can and should be conducted and will lead to the refinement of COMPANION.

Trial Registration: ClinicalTrials.gov NCT06364813; https://clinicaltrials.gov/study/NCT06364813

International Registered Report Identifier (IRRID): DERR1-10.2196/67709

(JMIR Res Protoc 2025;14:e67709) doi:10.2196/67709

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KEYWORDS

caregiver; eHealth; burden; spinal cord; spinal cord injury; chronic health conditions; mHealth; mobile health; family

Introduction

Background

Approximately 360,000 individuals have spinal cord injury (SCI) in the United States [1] and a further 86,000 in Canada [2]. SCI causes substantial disruption in the patient's life habits, routines, and level of independence. In many cases, individuals with SCI need considerable human assistance to perform any activities that exceed their motor and sensory capability [3]. Family caregivers (defined as "any relative, partner, friend or neighbor who has a significant personal relationship with, and provides a broad range of assistance for, an older person or an adult with a chronic or disabling condition" [4]) of individuals with SCI (fcSCI) often provide the majority of physical care to their family members with SCI [5]. Furthermore, individuals with SCI may experience higher levels of depression and anxiety and lower levels of life satisfaction than the general population [6]; therefore, fcSCI may also provide emotional support, alongside physical support. Providing physical and emotional care and support can have a substantial impact on fcSCI's physical and psychological well-being [5]. Many fcSCI report physical, emotional, and financial challenges associated with their caregiving roles and tend to neglect their own mental and physical health [7-9]. Over time, these experiences put fcSCI at high risk of burnout from an increased caregiver burden, which is associated with decreased well-being [5,8].

Caregiver burden is defined as "the extent to which caregivers perceive that caregiving has had an adverse effect on their emotional, social, financial, physical or spiritual functioning" [10]. Previous research indicates that 40%-46% of fcSCI report moderate-to-severe levels of caregiver burden due to the long-term nature of the injury and the caregiver role [10]. The burden associated with caregiving also influences fcSCI's ability to respond to the needs of individuals with SCI, and the long-term impact of caregiving demands on fcSCI may result in decreased support and quality of care for individuals with SCI. Hence, attending to risk factors and interventions that target the well-being of fcSCI is crucial.

Although family caregivers of individuals with other chronic conditions, especially dementia, receive considerable attention in research [11-13], the development and evaluation of interventions that address the unique challenges faced by fcSCI have received less attention. The informal caregiving integrative model [14] describes several factors that determine caregiver burnout, which can be divided into 3 main categories: (1) caregivers, that is, caregivers' sociodemographic characteristics, psychological factors (eg, emotion regulation, perceived competence), and physical state; (2) caregiving setting, that is, primary stressors (eg, living with the care recipient, being a spouse) and secondary stressors (eg, having a reduced social life, loss of friends); and (3) social environment, that is, informal and partner support, professional support (eg, availability of professional support and relationship with health care providers), and sociocultural environment (eg, how the caregiving role is perceived in society). Although some of the factors impacting the caregiver burden cannot be modified (eg, gender or relationship), other factors, such as emotion regulation or relationships with health care providers, are modifiable. Specifically, the informal caregiving integrative model [14] explains that fcSCI's appraisal of their ability to cope with individuals with SCI is a direct predictor of their burden. The fcSCI's coping appraisal is directly associated with their need for available resources and knowledge regarding the health condition of individuals with SCI. Therefore, helping fcSCI access education can increase their appraisal of their coping ability and lower levels of the caregiver burden.

A recent scoping review by McKay et al [15] suggested that fcSCI maintain better well-being if they have enough leisure activities, strong problem-solving skills, and practical and emotional support. In a recent qualitative study of Canadian fcSCI, Jeyathevan et al [16] identified that access to community and social support, a better relationship with individuals with SCI, and mastery in caregiving could help fcSCI provide sustainable care for individuals with SCI and for themselves. Although the findings of Jeyathevan et al [16] identified several critical needs of fcSCI, few studies have investigated the impact of different types of interventions on outcomes for family caregivers'; the studies that have been conducted have focused mainly on teaching problem-solving skills [16-20]. Additionally, even though rehabilitation facilities invite fcSCI to join educational sessions, these sessions primarily focus on patients' needs. Compounding this challenge, fcSCI often have limited time, making attendance at in-person sessions difficult.

Objectives

In our objective to improve outcomes for fcSCI, this study will evaluate the implementation fidelity of an innovative intervention program for health education with an online approach (eHealth) that aims to improve the well-being of fcSCI. COMPANION, cocreated with caregiver partners and health care professionals, is an interactive eHealth education program that is based on adult learning principles [21] and a user-centered approach [22]. The goal of COMPANION is to address fcSCI's specific challenges in caring for themselves and for individuals with SCI and facilitate the provision of accessible online education. We envision COMPANION will improve access to existing knowledge for fcSCI and individuals with SCI and provide customized (eg, developed through understanding caregivers' perspective), interactive (eg, quizzes), and engaging eHealth education (eg, new educational videos and audios) in the form of online modules, which are essential aspects of an eHealth tool [23], to better prepare and support fcSCI for providing care for themselves and individuals with SCI.

Methods

Study Design

This paper provides the details of a study protocol for a concurrent mixed methods study, including a feasibility

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randomized controlled trial (RCT). The study is registered with ClinicalTrials (NCT06364813). The purpose of the feasibility RCT is to (1) assess the fidelity of the process, resource, management, and treatment indicators and (2) estimate the parameters needed for a large-scale, multisite RCT [24]. Secondary objectives will be to assess the effect of COMPANION on primary and secondary clinical outcomes for fcSCI [24,25].

To assess the feasibility and intervention fidelity of COMPANION, a 6-month feasibility RCT with a 1:1 allocation ratio will be conducted, comparing COMPANION with the standard education and resources available to fcSCI. The study will incorporate quantitative and qualitative design methods administered through surveys and a final exit interview. In conjunction with RCTs in rehabilitation, the use of qualitative methods has been recommended to spot unexpected variables and findings [26,27]. The interview will be an opportunity for participants to share perspectives about their experience using COMPANION, with findings used to interpret clinical outcomes and, when integrated with quantitative findings, identify patterns and paradoxes between the results.

Ethical Considerations

The University of British Columbia Research Ethics Board has approved this study (approval number H20-01461). All participants will sign the informed consent form prior to responding to baseline measures. To protect participants' identity, all identifying materials will be removed from the data files. This includes Qualtrics information, such as IP addresses and participant contact information. A master list containing the participants' names will be created, and each participant will be given a unique study number. The study numbers will be used to identify participants. The master list will be kept separate, password-protected, encrypted, and filed away from the participant data. Consent forms will be kept in a separate password-protected folder. The semistructured interviews conducted 6 months after baseline (T3) will be transcribed verbatim, and identifiable information will be removed prior to beginning analysis. All participants will receive CA $50 (US $37) after completing each timepoint.

Study Timeline

The following 3 data collection timepoints will be used in the feasibility RCT: the time immediately following successful screening of the participants, during which baseline data will be collected and access to COMPANION will be provided to participants in the intervention group; 3 months after baseline data collection (T2); and 6 months after baseline data collection (T3). Please see Multimedia Appendix 1 for further information about the study timeline.

As of June 2024, recruitment and data collection for the study began and are ongoing. All data collection is performed via a secure online survey tool available through our institute (Qualtrics). After successful screening, randomization, and baseline data collection have been conducted, participants will be asked to complete the baseline survey. Follow-up data will be collected at 3 months (T2) and 6 months (T3). At baseline-T3, participants will respond to measures that assess primary (subjective burden) and secondary (objective burden, relationship quality satisfaction, distress, physical and mental health, and caregiving competence) outcomes. The purpose of baseline is to collect baseline information about the outcomes of the study. The purpose of T2 is to capture the influence of the intervention on our psychological outcomes of interest (eg, depression, anxiety, stress, and competence). T3 reflects the optimal change period for self-reporting of physical outcomes (eg, physical health and functioning).

Sample Size and Inclusion and Exclusion Criteria

Suggested sample sizes for a feasibility RCT range from 12 to 30 per experimental group [28,29]. We aim to recruit at least 20 participants per group. Inclusion criteria for participants are, at the time of recruitment, as follows:

- Family caregiver of an adult individual with SCI (similar to previous studies of this population [30,31]; in this study, family caregiver
  is defined as an individual who is primarily responsible for providing immediate informal daily care for a relative with SCI).
- Age >18 years.
- Living with the individual with SCI in the community.
- Living in North America.
- SCI of the patient has not happened within the previous 6 months.

Those fcSCI who had major medical and physical conditions that require routine visits to medical doctors (eg, cancer) will be excluded from the study, in addition to fcSCI providing care to individuals with SCI who are still patients in a rehabilitation facility.

Recruitment

The fcSCI are approached to participate (1) indirectly by sending letter and email invitations to previous patients or research participants of our center (GF Strong Rehabilitation Center and the International Collaboration on Repair Discoveries [ICORD]) and asking them to invite their family caregivers to contact us and (2) directly by asking our caregiver partners, Wives and Girlfriends of Spinal Cord Injury, to approach their members (approximately 6000 members mainly in North America) and invite them to participate in this study. We used social media advertisements to facilitate recruitment. Participants are recruited internationally from locations across North America. To include the participation of individuals from remote and rural areas, all participants are invited to participate digitally through a virtual meeting platform. In-person participation is not offered regardless of physical proximity to the research team.

Randomization and Masking

Upon successful enrollment and baseline data collection, participants are randomized by the research staff using the online service Sealed Envelope [32] with a block size that is undisclosed to the study manager. The research staff is responsible for randomization and the delivery of the intervention, while the study manager, who is responsible for enrolling participants and conducting data collection, remains masked to the participants' group allocation. To mitigate

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performance bias, participants are instructed not to discuss their program or group allocation with any member of the research team, except the research staff, and both the study manager and research staff will continue to reinforce this point when contacting participants. The research staff is responsible for receiving emails from participants and removing information related to group allocation before forwarding participant emails to the study manager.

Intervention

COMPANION was designed through a collaboration between researchers, health care providers, and family caregivers (end users and stakeholders) using the Technology Co-Design Model [33,34]. The current preliminary version of COMPANION consists of 8 self-paced online modules, which can be accessed remotely from any location.

Intervention Group

Participants in the intervention group are able to choose the order in which they complete the COMPANION modules and are encouraged to complete them all. They are also encouraged to invite individuals with SCI to view the COMPANION materials with them, as several of the modules include exercises that the participants can do with individuals with SCI and information regarding processes that the fcSCI can navigate with individuals with SCI (eg, changes in their relationship, considerations for hiring a home care aide, and accessing financial and legal support). Participants receive the web address, instructions to access the website using personalized encrypted login information, and guidelines on how to use the program. Modules have been designed so they can be stopped at any point, with progress automatically saved. Module formats include embedded video clips, voiceovers, and additional resources, including links to other available information. As topics are introduced in the course, participants are reminded that the content in the modules is not a substitution for expert professional advice and are instructed to consult with their health care providers, when needed. If participants have questions regarding the content of the modules, they can submit their questions to the research staff, who will review the submitted questions and, if necessary, forward them to one of the experts on the expert panel comprising a selected team of professionals who have experience working with individuals with SCI and their family caregivers. The selected expert will provide additional resources or information to address the participants' questions. The experts on the proposed project will not provide personal interventions to family caregivers; instead, they will focus on providing information to address the submitted questions only. Questions submitted by participants during the feasibility study will be used to modify and improve COMPANION. The research team will record participants' submitted questions and the amount of time spent addressing each question and responding to participants. This information will also be used to further improve and modify COMPANION.

In the first 3 months of enrollment of participants in the intervention group in this feasibility RCT, the research staff remotely monitor online analytics (eg, login frequency, module progression) of COMPANION and contact a participant if no online activity is noted in a 2-week period in order to promote use and troubleshoot potential technical problems.

Control Group

Control group participants will receive the usual care available at their local rehabilitation clinic. Immediately upon reaching the 6-month timepoint, control group participants will be given access to the current version of COMPANION.

Feasibility Indicators

The RCT's primary feasibility indicators will be used to address the COMPANION intervention's design and fidelity by assessing process issues, resource issues, management issues, and treatment issues. See Table 1 for further information about the feasibility indicators.

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Table 1. Feasibility indicators.

Feasibility indicator and components	Subindicator	Expectation
Process		
Recruitment rate	Number of participants recruited, number of women and men recruited	Mean of 3-4 participants/month: total of 40
Consent rate	Percentage of participants consenting	<10% participant refusal
Retention rate	Percentage of participants with T3[a] data	Complete data collection for >80%
Perceived benefit	Responses to the SUS[b], qualitative interviews at T3	>85% of responses strongly agree/agree, qualitative analysis informing clinical importance
Assessor masking	Percentage unaware of group status	100% of participants not unmasking their treatment
Resources		
Treatment adherence (COMPANION)	Completed all the modules	>85% of participants
Data collection: participant and evaluator burden	Baseline, T2[c], and T3	>85% of participants to complete in ≤2 hours, >85% of participants to complete in ≤1.5 hours
Expert burden	Time (minutes) spent in answering participants' questions and following up with them	Mean time spent per participant <2 hours for baseline and <1 hour for T2, <20% phone calls back for clarification
Management		
Internet stability	Downtime due to technical or mechanical issues	>90% of participants not without internet for >2 days
Participant processing time	Time from data collection to treatment	Mean time <10 days at each site
Treatment administration issues	Posttreatment evaluation form (study educator)	Any issues identified modifiable without substantial changes to the protocol
Treatment		
Dose level response	Correlation between training time and change score	A positive correlation

[a]T3: 6 months after baseline.

[b]SUS: System Usability Scale.

[c]T2: 3 months after baseline.

Clinical Outcome Measures: Primary Outcome

Clinical outcomes will be measured via a digital survey administered at baseline, T2, and T3. The components of the survey and outcome measures are detailed next.

Subjective Burden

The primary clinical outcome (ie, caregiver burden) will be measured through the survey using the Zarit Burden Interview [35. Studies have demonstrated a direct association between the caregiver burden and the quality of life for family caregivers [19]. As family caregivers' appraisal of their ability to cope with their family members' health condition is a direct predictor of their burden [14], and COMPANION aims to provide the required education and information for fcSCI so that they perceive and experience less challenges in providing care, we have selected fcSCI's subjective burden as our primary clinical outcome. The short 12-item version of the Zarit Burden Interview will be used to assess the subjective burden [35]. The fcSCI are asked to use a 5-point scale (from 0=never to 4=nearly always) to evaluate how often they experience certain feelings. Total scores can range from a minimum of 0 to a maximum of 48. A total score ranging between 0 and 10 indicates no-to-mild burden, 10-20 indicates a mild-to-moderate burden, and >20 indicates a high burden. This measure has been considered as valid and reliable (Cronbach α=.78) among fcSCI [36].

Clinical Outcome Measures: Secondary Outcomes

The survey administered at baseline will collect information on participants' age, sex, gender, social support, annual household income, living situation, and chronic health. The fcSCI will be asked to answer similar questions for individuals with SCI. In addition to demographic information, several secondary outcomes measures will be administered at multiple timepoints. The components of the secondary outcomes measures and their timepoints are detailed next.

Objective Burden

The survey will be used to administer several secondary clinical outcome measures. The first secondary outcome will be measured using the 38-item Dutch Objective Burden Inventory assessing fcSCI's objective burden [37]. Each questionnaire item lists a specific caregiving activity that corresponds to 1 of the following 4 domains: personal care (eg, helping with eating and drinking), practical support (eg, buying groceries), motivational support (eg, motivating to quit or reduce smoking),

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and emotional support (eg, showing understanding). The fcSCI are asked to rate their perceived burden for each task over the past 3 months using a 3-point scale (1=not at all burdensome, 2=somewhat burdensome, 3=very burdensome). Total scores are calculated as the average of all individual answer scores, ranging from 1 to 3. A higher total score indicates a higher objective burden. Testing of the measure has affirmed adequate validity and reliability among Dutch and Canadian caregivers [38,39].

Distress

The second secondary outcome will be measured using a short version of the Depression, Anxiety and Stress Scale (DASS) assessing distress [40]. A short version of the complete 42-item DASS, the DASS-21 contains 21 items assessing depression, anxiety, and stress on 3 separate subscales comprising 7 items each. Participants will report the intensity of their symptoms over the past week using a 4-point Likert scale (from 0=never to 3=always). Separate total scores ranging from a minimum of 0 to a maximum of 42 will be calculated for each subscale. Severity levels for depression, anxiety, and stress can be interpreted based on recommended cutoff scores, with higher scores indicating more distress. Cutoff scores for the Depression subscale distinguish responses as normal (0-9), mild (10-13), moderate (14-20), severe (21-27), and extremely severe (≥28). Testing of the DASS-21 among family caregivers has shown adequate reliability (α coefficient=.97) [41].

Relationship Quality Satisfaction

The third secondary outcome will be measured using the Dyadic Adjustment Scale (DAS-32) [42]. The DAS-32 consists of 32 items measuring the level of relationship quality satisfaction among dyads. Items in the DAS-32 correspond to 4 dimensions, or subscales, for measuring relationship quality: dyadic consensus (consensus on matters of importance to marital functioning), dyadic satisfaction, dyadic cohesion (closeness experienced by the couple), and affective expression (demonstrations of affection and sex relations). Each item of the questionnaire corresponds to 1 of the 4 subscales, which consist of varying response scales, including ordinal, Likert, and dichotomous scales. Scores for each subscale are calculated and added together to produce a total score ranging from 0 to 151, with a higher total score indicating less distress and high adjustment. Psychometric testing of the measure has demonstrated good reliability for each subscale (α=.85 for dyadic consensus, .67 for dyadic cohesion, .76 for affective expression, and .82 for dyadic satisfaction) in the general population [42].

Health-Related Quality of Life

The fourth secondary outcome will be measured using the Veterans RAND 12-item Health Survey (VR-12) assessing fcSCI's health-related quality of life [43]. The VR-12 includes 12 questions corresponding to 8 domains: general health perceptions, physical functioning, role limitations due to physical problems, role limitations due to emotional problems, social functioning, bodily pain, vitality, and mental health [44]. The 8 domains can be summarized into separate physical and mental component scores. The VR-12 scoring algorithm is used to score physical and mental components based on weights derived from a 1990 American population sample standard, resulting in variable minimum and maximum score values [45]. Higher physical and mental components scores indicate better health. Two further questions (ie, 14 in total), which do not contribute to the component summaries, ask about physical health and emotional problems compared to 1 year ago. Health state values (also known as utility scores), reflecting the preferences of the Canadian population, can also be generated from VR-12 data [46]. Though validation of the VR-12 has not been conducted in family caregiver populations, the VR-12 has demonstrated adequate convergent validity in other populations [47].

Competence

The fifth secondary outcome will be measured using the Caregiving Competence Scale (CCS) [48]. The CCS is used to measure a caregiver's self-assessment of the adequacy of their performance in their role. The 4-item questionnaire scores responses using two 4-point scales, with response options ranging from 1="not at all" to 4="very much" in the first scale and from 1="not at all" to 4="very" in the second scale [48]. Score values range from 0 to 12, with higher scores indicating higher caregiving competence. The CCS has demonstrated adequate internal consistency (Cronbach α=.78-.82) in family caregiver research [49,50].

Usability

The sixth secondary outcome will be measured using the System Usability Scale (SUS) to capture the opinion of participants regarding the usability of COMPANION. Originally created by Brooke [51], the SUS consists of a 10-item questionnaire using a 5-point scale, where options range from strongly agree to strongly disagree. Raw scores range from 0 to 40 and are algorithmically converted into meaningful SUS scores ranging from 0 to 100. Higher scores indicate higher perceived usability of the program. Participants in the intervention group will complete this measure at T2 and T3.

Caregiver Costs

The final secondary outcome will be measured using the Caregiver Indirect and Informal Care Cost Assessment Questionnaire (CIIQ) to capture information estimating informal care costs [52]. The fcSCI will be asked to provide responses for 13 items with information including, but not limited to, work status, time missed at work, productivity, and physical and emotional caregiving duties. Calculations will be conducted using responses to items on the CIIQ to estimate fcSCI indirect and informal care costs. Total scores can range from as low as 0 to any maximum number and report cost in dollars. Higher scores indicate a greater financial impact due to informal care costs. The CIIQ will be coupled with a bespoke item asking about additional money the fcSCI spend on themselves. To minimize concerns about recall, a 1-week recall period will be used for the CIIQ and a 3-month recall period will be used for the bespoke item.

Qualitative Interviews

When the feasibility RCT is complete, semistructured interviews (~45-60 minutes) will be used to explore fcSCI's experiences

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in the intervention group with COMPANION. The option to take part in the semistructured interviews will be available to participants in the intervention group as soon as they complete T3 survey data collection. An interview guide has been created to capture multiple aspects of fcSCI's experiences using COMPANION. As a complimentary method to assess usability, the interviews will also be used in combination with the SUS [51] and feasibility indicators to evaluate the usability of COMPANION. Participants will be asked to share their perspective on the advantages and disadvantages of COMPANION. A directed content analysis approach will be used to form initial coding categories from existing evidence and study hypotheses [53].

To promote the credibility and trustworthiness of qualitative data, we will use several methods. Field notes will be used as a self-reflective tool. Member checking will be used; that is, participants will be invited at the end of each interview to review the preliminary findings and provide feedback to determine how well they resonate with them. Multiple investigators with diverse backgrounds will be involved in collaborative theme analysis and data coding as a form of triangulation [54]. Interview results will be integrated with the quantitative results to provide a more in-depth assessment of benefits and user acceptability [55]. Peer debriefing will be used to further support triangulation. To ensure transferability of the qualitative data in our reports, we will follow the Consolidated Criteria for Reporting Qualitative Research (COREQ) report guidelines [56]. Specifically, we will provide detailed information about the setting, participants, and interviewers' and research team's backgrounds. We will also provide a detailed description of the data collection procedure, analyses of the qualitative data, and our procedure for developing codes and themes to ensure dependability of our method. Furthermore, we followed the CONSORT (Consolidated Standards of Reporting Trials) eHealth Form (see Multimedia Appendix 2) [57].

Data Management

Participant consent forms and all data collection will be administered online via Qualtrics. Data will be stored on Qualtrics and will be accessible only to research personnel who are granted access by the research staff. Participants will receive a link to the consent form via email with instructions on how to complete the form. After signing the online consent form, each participant will schedule a video call meeting, during which they will complete baseline data collection measures with the help of the study manager. Immediately after the participant and study manager complete the baseline questionnaire, the study manager will leave the call and be replaced by the research staff, who will randomize the participant into the intervention or the control group using the secure online software [32]. The participants will be given instructions based on their group allocation and asked not to reveal their group to the study manager, who will remain masked to the randomization result. Participant IDs and group allocation will be recorded on a secure, password-protected digital tracking sheet. Only research personnel involved with the group allocation will have access to the tracking sheet, and the study manager will not be able to access any information on the sheet related to participant group allocation. At T2 and T3 timepoints, participants will be sent an email containing a unique link to the next Qualtrics questionnaire and will be asked to complete the survey on their own.

Data Analysis

Statistical Analysis

All data analysis will be conducted by the research team independently from the study sponsor. Descriptive analysis will be used to describe our sample and consider clinical outcomes and study feasibility. The most current versions of R statistical software (R Foundation for Statistical Computing) [58] and IBM SPSS software [59] will be used. The 1-sample Kolmogorov-Smirnov test will be performed to evaluate data distribution. Demographic and outcome variables will be summarized by groups using means (SDs), frequencies, and proportions. Similar to previous feasibility studies [60], the means (SDs) calculated in the feasibility RCT will be used to estimate the effect size and the variance necessary for the full RCT. Focuses of the analysis will include investigating differences in primary and secondary effectiveness outcomes for the intervention and control groups at each timepoint. We will include an interaction between time and group for all models to account for the possibility of effect modification by time. Estimated marginal means will be used to conduct post hoc analyses, and pairwise comparisons of estimated marginal means will be conducted to examine specific differences between groups at each timepoint. Participant IDs will be used as a random effect. Multiple imputations will be used to deal with missing data. Furthermore, descriptive statistics will be used to assess participants' online usage data of the eHealth program (eg, the amount of time participants spent accessing the modules) to evaluate feasibility indicators (dose level response, treatment adherence) related to resource and treatment issues [61].

Feasibility

Feasibility outcomes will be treated as binary based on the expectations, as shown in Table 1. Specific objectives will be evaluated as a "success," indicating that no major adaptation of the protocol is needed before proceeding with a definitive RCT, or "revise," indicating changes must be made before continuing with the definitive RCT.

Qualitative Interviews

Interview transcripts will be examined using an inductive thematic analysis approach [62]. Data will be analyzed to identify themes and subthemes. Investigators will generate initial codes individually and then work with the entire team, including our caregiver partners, to identify themes, review and define themes, and select examples to support the themes [62]. The qualitative findings will be used to interpret the clinical outcomes, such as key intervention ingredients, relevant outcomes that might not be captured, and an explanation for potential conflicting quantitative results. Quantitative and qualitative findings for participants will be integrated as a form of triangulation and summarized to identify patterns and paradoxes between the results [63].

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Results

This research was funded by the Craig H Neilsen Foundation PSR Pilot Grant (PSR2-17) beginning in April 2022. After the first 2 study phases, during which COMPANION was codeveloped with caregiver partners, recruitment and data collection for the RCT began in June 2024 and is currently ongoing. We enrolled 54 participants at the end of baseline. Data collection was completed in April 2025. Data analysis for the RCT is expected to begin in June 2025. The fcSCI randomized into the intervention group have been given access to COMPANION after randomization.

Discussion

Summary

This study aims to investigate the feasibility of the COMPANION eHealth protocol. COMPANION e-Health modules have been developed to provide the education needed for family caregivers of individuals with SCI. By providing the necessary education, we aim to reduce the caregiver burden and improve caregivers' overall well-being. Health education using online approaches has been lauded for being interactive and enabling learners to engage over sustained periods. Benefits of eHealth can include improving the quality of care [37,64,65], enhancing communication between health care users and providers [66], reducing costs [67], and increasing access to evidence-based health information. As the COMPANION modules were designed specifically to address aspects of caregiving that are significant to fcSCI, COMPANION has the potential to increase fcSCI's knowledge and health literacy around challenges that they face when providing care (eg, emotional challenges, challenges in conducting medical tasks, challenges with isolation and accessing social support). By providing access to education and resources regarding factors that are known to mitigate the caregiver burden for fcSCI, such as social support [68] and coping appraisal [14], COMPANION may be used to impact fcSCI's overall feelings of a burden, quality of life, and well-being. Findings from conducting the feasibility RCT that evaluate the feasibility and acceptability of our study procedures can be used to inform the design of a definitive RCT assessing the effectiveness and impact of COMPANION on clinical outcomes compared to usual care pursued by fcSCI. Conducting a definitive RCT can further contribute meaningfully to family caregiver research and literature about mitigating the burden experienced by caregivers of individuals with SCI.

Analysis has not yet begun for this study. We anticipate that a large percentage of fcSCI who are approached to participate in our study will be female due to our recruitment plan to ask Wives and Girlfriends of Spinal Cord Injury to distribute recruitment materials to their members, who are primarily female fcSCI. Though women have made up the majority of fcSCI participants in recent studies with similar populations [5,69,70], we plan to use recruitment methods aimed at diversifying the gender spectrum of the fcSCI we approach by additionally contacting participants through our network of previous patients and research participants of our center and distributing recruitment information through social media advertisements. Additionally, the literature suggests that eHealth approaches may attract a younger demographic of users who may be more experienced using online platforms than older populations, who may be discouraged from using the platforms or participating [21]. To support participants' access and experience using COMPANION, participants will be sent written instructions on how to access and navigate COMPANION and its modules, encouraged to use COMPANION with their family members with SCI, and instructed to contact the research staff with any questions about using the program. We also plan to monitor intervention group participants' online activity during the study and reach out to participants if a time span of 2 weeks passes without any activity recorded. This communication will give participants an opportunity to voice any barriers they experience when using COMPANION and receive technological or other guiding support from the research staff [23].

Our knowledge translation plan will target fcSCI, individuals with SCI, and clinicians across Canada and the United States, leveraging existing communication tools, such as websites (eg, health authorities in British Columbia [BC]) and electronic and print newsletters of local and national audiences (eg, ICORD, Spinal Cord Injury Research Evidence, Spinal Cord Injury BC). All team members, including our caregiver partners, will contribute to the presentations and manuscripts. We, along with our caregiver partners, will share plain language summaries with fcSCI via newsletters, social media, and websites.

Acknowledgments

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Authors' Contributions

Conceptualization, methodology was handled by SM and WCM; funding acquisition by SM, WCM, JMR, and DGTW; resources by SM, BE, HC, EP, and BP; writing—original draft by SM; and writing—review and editing by SM, HC, JMR, DGTW, and WCM.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT schedule of enrollment, interventions, and assessments for the RCT. RCT: randomized controlled trial; SPIRIT Standard Protocol Items: Recommendations for Interventional Trials.
[PNG File , 71 KB - resprot_v14i1e67709_app1.png]

Multimedia Appendix 2
CONSORT eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1166 KB - resprot_v14i1e67709_app2.pdf]

Multimedia Appendix 3
Peer review report from the Craig H. Neilsen Foundation PSR 2022 FGA Committee.
[PDF File (Adobe PDF File), 167 KB - resprot_v14i1e67709_app3.pdf]

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Abbreviations

CCS: Caregiving Competence Scale
CIIQ: Caregiver Indirect and Informal Care Cost Assessment Questionnaire
CONSORT: Consolidated Standards of Reporting Trials
DAS-32: 32-item Dyadic Adjustment Scale
DASS: Depression, Anxiety and Stress Scale
fcSCI: family caregivers of individuals with spinal cord injury
ICORD: International Collaboration on Repair Discoveries
RCT: randomized controlled trial
SCI: spinal cord injury
SUS: System Usability Scale
T2: 3 months after baseline
T3: 6 months after baseline
VR-12: Veterans RAND 12-item Health Survey

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Protocol

A Technology-Enhanced Medical Nutrition Therapy and Diabetes Self-Management Education for Adults With Disability and Type 2 Diabetes: Protocol for a Pilot and Feasibility Randomized Controlled Trial

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Abstract

Background: Diabetes mellitus (DM) is a serious chronic disorder that affects many individuals globally, particularly persons with disabilities, and has long-term adverse effects on the health of individuals and society. Effective self-management education is therefore required. Diabetes management focused on medical nutrition therapy (MNT) and diabetes self-management education (DSME) combined with telehealth technology has the potential to increase the active performance of diabetes management behaviors among persons with disabilities and improve their overall quality of life and quality of self-care.

Objective: This study aims to evaluate the impact of different levels of technology on the delivery of MNT and DSME among persons with disabilities.

Methods: The study is a single-blinded, 3-arm, randomized controlled trial among adults living with both type 2 diabetes and a permanent physical disability. Web-based recruitment is done through partner organizations. The target sample size is 90 participants randomized into 3 arms: a high-technology, a low-technology, and an attention control arm. The high-technology arm receives diabetes-related materials weekly through mediums such as email, a telehealth platform, and text; the low-technology arm receives only 1 weekly email with diabetes-related material; and the attention control arm has no technology support. The intervention is provided by a certified diabetes care and education specialist. Using multivariate linear mixed models, the study examines the relationships between the level of technology intervention and DM self-management behaviors, self-efficacy, and reductions in glycated hemoglobin (HbA_{1c}). The primary outcome is the proportion of participants in each group with improved self-management behaviors, as measured by several validated questionnaires. The secondary outcome is a better HbA_{1c} reduction. Outcomes are measured at baseline and at 6 months. Questionnaires and HbA_{1c} measures will be used to measure outcomes.

Results: Data collection began in June 2024 with a total of 90 recruited participants. The intervention was delivered. Make-up classes were delivered to participants in any of the 3 cohorts between November 2024 and December 2024. The final 3-month follow-up classes were held for each cohort 3 months after the first class. Data analysis is anticipated to be completed in fall 2025.

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Conclusions: Effective self-management in DM is important to reduce complications. Using technology to deliver MNT and DSME could serve as an effective and convenient strategy for providing these interventions. However, intervention studies are required to determine the most effective level of technology for delivering MNT and DSME intervention to this target group. The YumABLE study is expected to provide new, meaningful, and detailed information about the effectiveness of technology and telehealth platforms for effectively delivering an MNT and DSME program for people living with a permanent physical disability and type 2 diabetes. The results will further improve web- and technology-based diabetes self-management interventions for people with disabilities.

Trial Registration: ClinicalTrials.gov NCT06049225; https://clinicaltrials.gov/study/NCT06049225

International Registered Report Identifier (IRRID): DERR1-10.2196/71495

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KEYWORDS

diabetes mellitus; telehealth; persons with disabilities; diabetes self-management education; medical nutrition therapy

Introduction

Diabetes mellitus is a serious chronic disorder that has a significant adverse effect on the overall health of families, individuals, and societies worldwide [1]. According to the International Diabetes Federation, the global prevalence of diabetes among adults aged 20-79 years was approximately 537 million in 2021 [2], representing 10.5% of the global adult population [2,3]. This number is projected to rise to 783.2 million (12.2%) in 2045 [3].

In the United States, DM is one of the most prevalent metabolic conditions, which impacts about 38.4 million of the overall US population (as of 2021), representing 11.6% of the total population. Of this number, 8.7 million are unaware and undiagnosed [4]. Moreover, 97.6 million US adults aged 18 years and older have prediabetes, which usually leads to diabetes [4]. In 2022, the total estimated costs, both direct and indirect, associated with diagnosed diabetes in the United States amounted to US $413 billion [4]. Type 2 diabetes (T2D) can lead to cardiovascular disease, blindness, peripheral neuropathy, and reduced quality of life [5] and is linked with significant morbidity rates [6]. DM is a health concern among all populations; however, persons with disabilities are more likely to be affected by diabetes compared to those without such disabilities [7-10].

Diabetes management primarily relies on individuals and their families, making self-management fundamental in diabetes care [11]. T2D management involves a range of actions and choices such as meal planning, scheduled physical activity, monitoring blood glucose levels, taking diabetes medications, and effectively managing episodes of illness and low and high blood sugar levels [11,12]. These behaviors are meant to regulate blood sugar levels, reduce the risk of complications, and improve the overall health of individuals with diabetes [13].

When individuals with diabetes actively participate in their own care, they can significantly impact both the progression and development of their disease [12]. However, a significant barrier to achieving proper glycemic control appears to be the patient's inability to maintain adequate self-care, such as poor adherence to prescribed medications and lifestyle adjustments [14]. Thus, educating individuals to self-manage their diabetes yields better health results [15,16].

The literature highlights the potential for diabetes to cause disability; however, the reverse is also possible [17]. Living with disability is associated with an increased risk of DM. A study found that mild and incident disability was associated with 28% and 40% increased diabetes risk, respectively [18]. Diabetes is a significant health concern across all populations; however, persons with disabilities are more likely to be affected. The Centers for Disease Control and Prevention points out that in 2020, approximately 16.2% of persons with disabilities in the United States had received a diagnosis of diabetes, in contrast to 7.5% of those without disabilities [9]. Persons with disabilities are at a greater likelihood of experiencing the major risk factors associated with diabetes [19] due to challenges in maintaining a healthy diet and lifestyle as well as accessing preventive care [20,21].

Physical disability broadly includes conditions affecting mobility like spina bifida and muscular dystrophy [22]. People who are blind, deaf, missing limbs, partially or completely paralyzed, or have other permanent or chronic physical limitations are considered to have a physical disability [23]. Accessibility and safety are the primary concerns with physical disability, with common issues including accessing public areas like city streets, sidewalks, ramps, and public buildings [23]. Some of these disabilities require mobility devices like prostheses, orthoses, canes, wheelchairs, crutches, or walkers [23].

While effective diabetes management is significant in enhancing overall health, persons with disabilities often face barriers that hinder their diabetes self-management [24] and usually exhibit poorer self-management behaviors [24-29]. For instance, self-management behavior was found to be poor among individuals with diabetes and physical limitations [28]; they are less likely to engage in moderate to vigorous physical activity or adhere to their medication compared to those without physical limitations [28]. Individuals with mobility difficulties may encounter challenges attending health care provider appointments related to their diabetes [28]. A study discovered that about 11% of adults with mobility disability had not visited a health professional for their diabetes within the past year [25]. Persons living with physical disabilities in general encounter several difficulties in maintaining a healthy diet [27]. A study found that factors including knowledge, fatigue, health condition, and function impairments influenced the dietary behavior of wheelchair users [27]. Similarly, Hall et al [30]

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discovered that the expense of healthy foods, a lack of motivation, shopping challenges, and time constraints for shopping or food preparation are significant barriers to maintaining a healthy diet among women with physical disabilities. Nonetheless, the authors noted that about 90% of participants were interested in improving their dietary habits [30]. Another study examining the nutritional status of individuals with spinal cord injury revealed significant deficiencies in essential nutrients, notably fiber, calcium, fruits, and dairy products [31].

Moreover, the participation of persons with disabilities in self-management interventions is limited [24], and their specific self-management needs and capabilities are unrecognized by health care professionals [24,25,29]. It was discovered that 47% of adults with disabilities have not received education on managing diabetes [25]. Age, gender, lack of accessibility, and low socioeconomic status have been found to impact diabetes self-care behaviors among persons with disabilities [24]. In addition, for individuals who are visually impaired, factors such as poor health, concerns about disease advancement, feelings of grief, and experiences of loss inhibit their engagement in diabetes self-care behaviors [29]. Taken together, these barriers can make self-management more challenging particularly for individuals with a physical disability and T2D.

A systematic review of factors influencing the adoption of diabetes management technologies identified monthly income, gender, age, educational level, and diabetes-related characteristics as key determinants of their use; however, of all 28 studies included in the review, disability status was not considered as a factor that could influence technology use in diabetes management [32]. There is limited technology-based diabetes self-management tailored specifically for persons with disabilities [33].

Recently, digital health technologies have progressively been integrated into diabetes education, functioning as either an adjunct to or a substitute for traditional in-person methods [34]. Using technology in diabetes education reduces care inequities, increases the efficacy of educational initiatives, and improves accessibility. Technology as a means of diabetes education is supported by the broad use of telehealth and digital platforms by both patients and health care professionals [35]. Patients and health care professionals have accepted the use of telemedicine and other digital tools to educate people about diabetes. The COVID-19 pandemic has, in fact, significantly increased interest in and demand for telehealth-based diabetes education. The emergence and progress of digital health technologies have resulted in several modalities for engaging and educating patients through telephone or smartphone, video or audio, web, SMS text messaging, and mobile apps, as well as combinations of these methods [35].

In this study, participants are randomized into 3 intervention groups: an attention control group, a low-technology group, and a high-technology group. The purpose of this design is to evaluate the effectiveness of varying levels of technological integration in delivering medical nutrition therapy (MNT) and diabetes self-management education (DSME). All groups receive the same frequency and quality of remote education sessions. Both the low-technology and high-technology groups receive bidirectional SMS text messaging to facilitate timely communication with a health coach. In contrast, the attention control group does not receive any text-based communication or access to a health coach. Additionally, the high-technology group receives weekly diabetes-related educational materials via multiple channels (email and text), regular text reminders (eg, to read content, track health data, and stay motivated), and access to a telehealth platform. The low-technology group receives only 1 weekly email with diabetes-related educational materials. The attention control group does not receive any supplementary educational content or access to technology-based support resources.

The aim of this study is to implement and evaluate the impact of different levels of technology on the delivery of MNT and DSME among persons with mobility disability and T2D. We hypothesize that participants in the high-technology group will have improved self-management behaviors and better glycated hemoglobin (HbA_{1c}) reduction compared to their counterparts in the low-technology and the attention control groups.

Methods

Study Design

This study, called YumABLE, started in June 2024, when recruitment began, and is anticipated to end by fall 2025. The study is a 3-arm randomized controlled trial for evaluating the delivery of a 6-month intervention, which involves telecoaching, diabetes educational content, and technology access, to 90 individuals with diabetes and physical disabilities. The 3 intervention groups are a high-technology group, a low-technology group, and an attention control group. Study participants are adults aged 18 to 65 years with a permanent disability and T2D. All study groups receive an initial 60-minute 1:1 assessment, 4-weekly remote DSME classes, a make-up class option, and a follow-up class 3 months after the last DSME class. Each of the weekly remote classes as well as the follow-up classes are 90 minutes in length. The 3-month follow-up remote class is 60 minutes in length. DSME classes are organized into cohorts, with each cohort consisting of up to 10 participants. DSME classes and education will be of the same quality and quantity for all participants regardless of study group.

The difference among study groups is that the high-technology intervention group receives weekly diabetes-related materials delivered through multiple modalities (email, text, and telehealth platform), regular text reminders (to read the material, track health data, motivation, etc), and bidirectional SMS text messaging to enable timely communications with the certified diabetes care and education specialist (CDCES). Participants also have access to the telehealth platform. The low-technology intervention group receives 1 weekly email containing diabetes-related materials and bidirectional email communication with the CDCES. It does not have access to the telehealth platform. The attention control group, the “no technology” group, is only provided with DSME classes and has no technology support. It is not provided with any additional related content or access to technology-based support resources. Outcome measures are assessed at baseline and 6 months (Figure

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1), with data collected from all intervention groups. Four weeks is considered a month in this study, making the study duration 24 weeks. Study activities are primarily conducted on the web nationally in the United States.

Figure 1. Flowchart of the protocol.

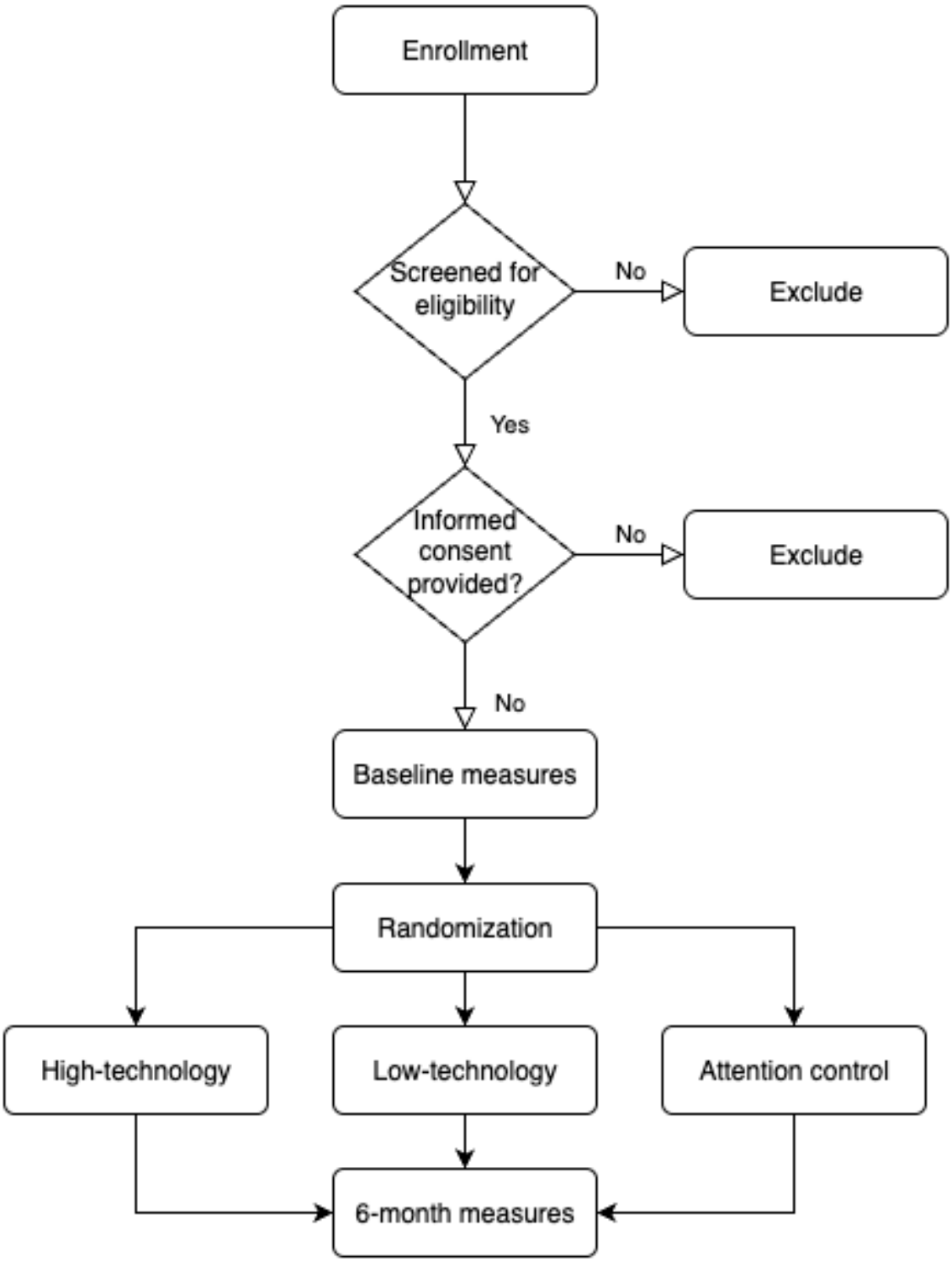

Study Population

The American Diabetes Association defines a diagnosis of T2D as an HbA_{1c} level of 6.5% or higher, reflecting average blood glucose levels over the past 2 to 3 months. Likewise, the National Health and Nutrition Examination Survey's Physical Functioning Survey will be used to identify permanent physical impairments. The participants consist of adults aged 18 to 65 years.

Inclusion Criteria

Eligible participants must meet the following inclusion criteria: (1) have been diagnosed with T2D; (2) be aged 18 to

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65 years; (3) be living with a permanent physical disability such as spinal cord injury, spina bifida, multiple sclerosis, or stroke; (4) have the ability to converse in and read English; (5) have a smartphone or computer available that can run apps; and (6) have Internet connection capabilities.

Exclusion Criteria

Exclusion criteria were (1) current enrollment in any diabetes-related intervention, (2) a present or soon-planned pregnancy, (3) a major heart attack or heart surgery in the past 12 months, and (4) having undergone dialysis, kidney transplant, or a kidney surgery in the past 12 months.

Recruitment

Participants are recruited digitally from the United States. Information about the study is shared through the National Center on Health, Physical Activity and Disability website and their affiliated social media outlets. Participants are additionally recruited from a database containing information on previous diabetes research studies with similar inclusion criteria. Emails are sent to these potential participants, providing details about the YumABLE program, and including a link for them to complete the study screening process and consent if they are eligible. During the screening process, participants are asked to self-report their HbA_{1c} levels to confirm their diabetes status. While many reported HbA_{1c} levels consistent with a diabetes diagnosis, baseline HbA_{1c} testing conducted by a contracted third party showed that some participants had lower levels, indicating prediabetes or normal glycemic status. These individuals were not excluded from the study, as it is possible that their HbA_{1c} levels had decreased since their previously reported values. Additionally, some participants, due to mobility challenges or limited access to the contracted laboratory, could not complete their baseline HbA_{1c} test. We accepted these individuals' self-reported HbA_{1c} levels as measured during recent visits to their health care provider (within 3 months of enrollment in the study). Eligible participants who pass the screening process must sign an informed consent form and complete baseline surveys.

Upon enrollment in the study, participants receive an automated email containing a HIPAA (Health Insurance Portability and Accountability Act)-compliant REDCap (Research Electronic Data Capture) link to access a survey packet. REDCap is a secure program developed collaboratively by Vanderbilt University and the National Institutes of Health National Center for Research Resources [36]. A total of 28 participants have been recruited. The survey packet includes a demographic survey and primary outcome measures detailed in Table 1.

Table 1. Outcome measures and assessment timeline.

Variable	Instrument	Time point
Primary outcome measures		
Diabetes quality of life	Diabetes Quality of Life Measure	Baseline, postintervention
Psychological distress	Diabetes Distress Scale	Baseline, postintervention
Self-efficacy	Diabetes Empowerment Scale	Baseline, postintervention
Secondary outcome measure		
Glycemic management	HbA_{1c}[a]	Baseline, postintervention
Other prespecified outcome measures		
Physical activity	Godin Leisure-Time Exercise Questionnaire	Baseline, postintervention
Dietary intake	The UK Diabetes and Diet Questionnaire	Baseline, postintervention
Medication adherence	Medication Adherence Rating Scale	Baseline, postintervention
Health dashboard usability	System Usability Scale	Baseline, postintervention

[a]HbA_{1c}: glycated hemoglobin.

After participants receive the initial survey packet, a member of the research team calls the participants within a week. The purpose of this call is to welcome participants into the study and go over study components. During the call, the research personnel informed participants that they will receive a laboratory requisition in their mail within a week, allowing them to visit a third-party clinical testing company location to have their blood glucose tested at no cost. The research staff also lets participants know that they will be randomized into 1 of the 3 intervention groups. Participants were not informed about which intervention was the primary focus or "intervention of interest" versus the comparator groups.

Randomization

After completing baseline surveys, participants are randomly assigned to 1 of 3 groups: the high-technology, low-technology, or attention control groups. The randomization sequence was created and stored in REDCap, automatically assigning participants to their respective groups with a 1:1:1 allocation ratio. The random allocation sequence was generated by study personnel using REDCap. Trained study staff enrolled participants and assigned them to intervention groups through the REDCap randomization module, which concealed the allocation sequence until assignment.

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Sample Size

In total, 90 participants will be enrolled, divided into 3 groups of 30 participants each (low-technology, high-technology, and attention control). The sample size is determined based on the primary use of analysis of covariance and uses a 2-sided test with a type I error rate of 0.05. An intention-to-treat analysis and multiple imputations are incorporated. Given a minimum correlation of 0.7 between the baseline and follow-up outcomes, there will be an 80% chance of detecting an effect size of 0.65.

Intervention

The intervention is described in accordance with the TIDieR (Template for Intervention Description and Replication) checklist and guide [37]. Multimedia Appendix 1 shows the TIDieR checklist. As applicable, this protocol has been developed in accordance with the JMIR CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist [38]. Multimedia Appendix 2 shows the JMIR CONSORT-EHEALTH checklist.

Name and Rationale

The intervention is called YumABLE, and it addresses the effectiveness of using technology to deliver DSME for this target group. The name "YumABLE" reflects the program's goal of empowering individuals with permanent physical disabilities to be "able" to manage their diabetes effectively, without limitations imposed by their disability. The key components of the intervention include a group class led by a single CDCES, ensuring a personalized experience for participants.

Materials

Informational materials are distributed during the intervention. Informational materials consist of weekly resources on topics that include nutrition, meal plan methods, shopping tips, and a roadmap to managing diabetes, all provided by the CDCES.

Procedures

Following randomization, the CDCES conducts a 60-minute one-on-one assessment with each participant via telephone. Subsequently, participants are assigned to a cohort for the 4 weekly 90-minute DSME group classes. Four optional 90-minute make-up classes are available along with a 60-minute follow-up session conducted 3 months after the final DSME coaching session. The intervention arms and treatment are summarized in Table 2.

Table 2. Study arms and intervention components.

Participant group or arm	Intervention or treatment
High-technology intervention group	• Receive an initial 60-minute 1:1 call with the CDCES[a]. • Receive 4 weekly 90-minute remote DSME[b] classes with the option to make up any missed class. • Receive one 60-minute follow-up class 3 months after their last DSME class. • Weekly diabetes-related materials delivered through multiple modalities (email, text, and telehealth platform), regular text reminders (to read material, track health data, motivation, etc), bidirectional text messaging to enable timely communications with the health coach. • Have access to the telehealth platform.
Low-technology intervention group	• Receive an initial 60-minute 1:1 call with the CDCES. • Receive 4 weekly 90-minute remote DSME classes with the option to make up any missed class. • Receive one 60-minute follow-up class 3 months after their last DSME class. • Receive 1 weekly email containing diabetes-related materials, bidirectional email communication with the CDCES. • Have no access to the telehealth platform.
Attention control group	• Receive an initial 60-minute 1:1 call with the CDCES. • Receive 4 weekly 90-minute remote DSME classes and with the option to make up any missed class. • Receive one 60-minute follow-up class 3 months after their last DSME class. • Not be provided with any additional related content or access to technology-based support resources. • Have no access to the telehealth platform.

[a]CDCES: certified diabetes care and education specialist.

[b]DSME: diabetes self-management education.

Intervention Provider

A single CDCES, a board-certified registered nurse with over 15 years of clinical care, education, and health promotion experience, delivers all 4 remote DSME classes, encouraging active participation and reflection. Weekly goals are established and discussed, and troubleshooting is reviewed. Motivational interviewing promotes behavior change and sets personal health goals related to diabetes. The 4 DSME classes included nutritional management and diet, physical activity, medication adherence, and stress management components.

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Modes of Delivery

The classes are conducted remotely. The intervention consists of using pop-up quizzes or polls within each class session, having open discussions, and following up with participants, with communication based on their randomization group.

Location

The intervention is conducted via video teleconferencing, providing an easily accessible platform for participants. This approach was particularly beneficial for individuals with physical disabilities, as it eliminated the need for travel to a physical location.

Frequency and Duration

The intervention is for 6 months and includes 4 scheduled classes held consecutively over 4 weeks via video teleconferencing, 4 make-up classes for participants unable to attend an earlier class, and 1 follow-up class. Ideally, each participant would attend 5 sessions during this 6-month period.

Tailoring and Modification

The intervention includes 3 participants with visual impairments; however, no changes are made to the intervention itself. Instead, materials are adapted to meet participants' needs. Adaptations include providing the recorded class presentations with audio to participants who request it, weekly resources provided in larger text, and CDCES providing visual cues of the slides during the class to ensure that all participants understand what is being presented. Additionally, the video teleconferencing platform included accessibility features, such as captions for participants with impaired hearing, to ensure that they could fully participate.

Ethical Considerations

The study was approved by the institutional review board (IRB) of the University of Alabama at Birmingham and is registered on ClinicalTrials.gov (NCT06049225). Informed consent from participants is required for participation in this study. Any modifications to the protocol will be communicated to all relevant stakeholders. The full trial protocol is available upon request from the corresponding author. The consent process is entirely web-based and initiated through predetermined screening questionnaires on the landing website and the REDCap link. Participants are informed of the purpose of the study, procedures, benefits, risks, and their right to withdraw from the study without any penalty. Once a participant is determined to be eligible through the web-based process, they receive an electronic consent form for completion. Access to records of the consent forms is limited to only approved study personnel. Participants' data will be deidentified before data analysis. Participants are assigned unique IDs instead of their names or identifiable information. Data are stored on the University of Alabama at Birmingham's secured password-protected servers, with access restricted to study personnel only. Participants are compensated with two US $50 e-gift cards, one for baseline and one for 6-month follow-up. In addition, participants who participate in qualitative interviews are compensated with an additional US $50. The compensation is to acknowledge participants' time and efforts without creating undue influence.

Outcomes

Overview

All primary and other prespecified outcome measures are collected and stored through electronic surveys delivered by REDCap. The validated questionnaire packet is electronically delivered to participants at baseline and 6 months. Baseline and postintervention assessments will evaluate both primary and secondary outcome measures. Table 1 outlines all outcome measures and their validated instruments for data collection. HbA_{1c} results are transmitted from the testing company to study personnel and inputted directly into REDCap. Similarly, if participants self-report their HbA_{1c} results, study personnel will input them directly into REDCap. To maximize participant retention, reminder emails are regularly sent. Additionally, detailed notes are recorded for participants who discontinue the study.

Primary Outcome Measures

Quality of Life

Participants will fill out the Diabetes Quality of Life Measure, a 15-item questionnaire that explores perceptions regarding one's capacity to manage diabetes alongside other aspects of life [39].

Psychological Distress

The Diabetes Distress Scale, a 17-item questionnaire evaluating emotional distress associated with diabetes, will be used to measure participants' psychological distress. This scale has demonstrated validity and reliability in measuring diabetes-related emotional distress [40,41].

Self-Efficacy

Participants' psychosocial self-efficacy in diabetes management is assessed using the Diabetes Empowerment Scale Short Form. This 8-item questionnaire explores attitudes concerning diabetes and the capability to effectively manage the condition. The Diabetes Empowerment Scale Short Form has exhibited validity and reliability as a measure of psychosocial self-efficacy [42].

Secondary Outcome Measure: HbA1c Levels

HbA_{1c} is measured using an HbA_{1c} test. HbA_{1c} results are transmitted from the testing company to study personnel and inputted directly into REDCap. Similarly, if participants self-report their HbA_{1c} results, study personnel will input them directly into REDCap. HbA_{1c} is measured both at baseline and at 6 months. The HbA_{1c} is a widely recognized test to assess the effectiveness of diabetes management strategies.

Other Prespecified Outcome Measures

Physical Activity

Physical activity is assessed through the Godin Leisure-Time Exercise Questionnaire. This brief questionnaire comprises 3 questions concerning strenuous, moderate, and light exercises undertaken within the past 7 days [43].

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Dietary Intake

Participants will complete the UK Diabetes and Diet Questionnaire to evaluate nutrition and dietary behaviors over the past month. This questionnaire features foods commonly found in the United Kingdom. Therefore, to ensure clarity for participants from the United States, any UK-specific food item will be substituted with its equivalent US counterparts [44].

Medication Adherence

Participants will complete the Medication Adherence Rating Scale to assess their medication adherence. This general 10-item binary questionnaire asks participants about regular medication intake [45].

Health Dashboard Usability

To evaluate the usability of the telehealth dashboard, participants will complete the System Usability Scale. This Likert scale consists of items assessing the dashboard's effectiveness (ability to accomplish tasks), efficiency (level of dashboard use), and satisfaction (subjective reactions to the dashboard) [46,47].

Data Management

All data gathered throughout the study will be entered directly into the REDCap system. Upon enrollment, participants will be assigned a unique subject number for identification purposes within the survey. Access to the REDCap program, where all data will be securely stored, will be limited to authorized study personnel.

The principal investigator (MT) and primary statistician (KRH) remain blinded to the randomization of participants across the study arms throughout the protocol. Other designated study staff will have access to this information for specific tasks such as recruitment, obtaining consent, conducting orientation and welcome calls, coaching sessions, and managing the shipment of intervention packages.

We will also perform data verification, including confirming the completion of surveys, questionnaires, and the accurate recording of HbA_{1c} values. Given that this project is a pilot feasibility and efficacy study with a duration of 6 months and is deemed to have minimal risks, a data monitoring committee is unnecessary. The principal investigator (MT) holds responsibility for maintaining protocol fidelity and overseeing data collection procedures throughout the study period.

Analyses

Statistical Analysis

Descriptive statistics will be prepared to show the sample statistics and analyzed separately for baseline and 6-month postproject. Paired 2-tailed *t* tests and chi-square tests will be used to assess the change in continuous and discrete outcomes from baseline to 6 months for each arm. Furthermore, within-group differences will be assessed using 2-tailed *t* tests (paired and unpaired) and chi-square tests.

Multivariate linear mixed models will be used to assess repeated measures with continuous outcomes, assess the joint effects of baseline measures on 6-month outcomes, and account for the correlation between repeated measures. Quality control analyses will be performed, including assumption checking, estimating descriptive statistics of participant attrition and overall instrument completion, and investigating missingness patterns. Key variables at baseline will be examined to evaluate whether there is any systematic variation between the study groups. A participant who no longer participates in study activities will be considered lost to follow-up. App analytics on key performance indicators will be used for participants who are lost to follow-up. We anticipate the loss to follow-up rate to be approximately 20%. The primary analysis will follow the intention-to-treat principle, including all participants as originally assigned regardless of adherence. Secondary or compliance analyses will be considered if appropriate.

All qualitative data collected in the study will be content analyzed using NVivo (Lumivero), a qualitative data analysis software [48], including qualitative data collected for the feasibility, acceptability, and fidelity of interviews and meeting notes. The steps for content analysis include (1) transcribing audio recordings, (2) checking transcription against recordings for accuracy, (3) developing coding categories, (4) assigning codes to text, and (5) reviewing coded data to identify themes across the dataset.

Qualitative Analysis

Moreover, the study will include qualitative interviews conducted after the intervention to evaluate the program thoroughly. These interviews aim to assess the intervention's effectiveness as a feasible approach for managing diabetes. Multimedia Appendix 3 shows the interview guide. The interviews will be transcribed and analyzed using an inductive content analysis method as described by Elo and Kyngäs [49]. The analysis will be performed in 3 phases. The first phase is open coding, followed by creating categories and abstraction [49]. NVivo software will be used to facilitate the organization and analysis of the qualitative data.

Data Monitoring

Any personal information collected during the study, including demographic details and other sensitive data, will be gathered and stored in compliance with the HIPAA regulations using the secure REDCap platform. Access to this confidential information will be limited to authorized study staff who have received approvals. The storage and handling of personal data will adhere to the guidelines, oversight provided by the university's IRB, and the policies established by affiliated entities. The laboratory testing service will manage the collection and processing of blood samples for HbA_{1c} testing. Study personnel will not handle or have access to the blood samples at the testing laboratory.

Harms

This study will track and evaluate all adverse events. These events will be assessed for their severity and potential causality. Any identified adverse events will be reported to the IRB and other pertinent regulatory bodies, as required by the study protocols and ethical guidelines.

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Auditing

The study protocol will undergo regular evaluations at specified intervals, such as weekly, monthly, or quarterly, to ensure adherence to the study's design and consistent implementation. Auditing procedures will encompass various elements, including checklists, coaching call logs, audio recordings or coaching calls, content resource banks, telehealth platform reviews, and event logs; review of participant food, physical activity, medication, glucose entries, and time spent on the platform; and team meetings to discuss participant progress and protocol adherence.

Results

We hypothesize that participants in the high- or low-technology intervention groups will show improvements in self-management behaviors related to T2D and self-efficacy compared to the control group at the 6-month follow-up. Again, we hypothesize that the high-technology intervention arm will result in better outcomes regarding reductions in HbA_{1c} than the low-technology and control arms. Additionally, we also hypothesize that the YumABLE intervention is feasible and acceptable to adults with permanent physical disability and T2D and that fidelity to the program will be maintained.

The development of the telehealth platform, which includes the dashboard and educational content, along with the creation of the landing website, has been completed by the study's technical support team. In addition, research personnel have developed the database using REDCap to serve as the storage for data and communication tools such as emails and text notifications. The study began in June 2024. Since June 2024, intervention materials have been finalized, the IRB submissions have been completed, and participant recruitment began. In total, 28 participants have been enrolled and received the MNT and DSME remote class. Recruitment has ended, and we anticipate completing data collection by August 2025. Make-up classes were delivered to participants in any of the 3 cohorts between November 2024 and December 2024. The final 3-month follow-up classes were held for each cohort 3 months after the first class and were completed in February 2025. Data will be analyzed in fall 2025. Manuscript preparation and dissemination of study results are planned for spring 2026.

Discussion

Previous research has showed that comprehensive diabetes education is required to equip patients with the necessary self-management skills needed to manage the condition. Likewise, diabetes education has been found to improve patient knowledge, improve diabetes control, and delay complications [50-56]. The American Diabetes Association has pointed diabetes education as the cornerstone therapy for the patient with diabetes [54].

Numerous publications have highlighted the importance of technology in diabetes care and management [34,35,57]. Sharma et al [57] posit that technology use in providing diabetes education leads to improved patient access and clinical outcomes, reduces the cost of care, and addresses gaps in care. Patients with diabetes who get live telephone coaching for a specified duration can gain advantages from consistent health status monitoring, leading to enhanced self-efficacy, improved health outcomes, and decreased hospitalization rates, surgical expenses, and total health care expenditures [58-61]. The reduction of HbA_{1c} levels has been a notable benefit achieved by telephonic support [60].

Likewise, web-based education is an effective tool for promoting diabetes self-management. Some websites exclusively provide diabetes-related content and resources, while others include an opportunity to interact with a coach [62]. Other websites provide digital record-keeping tools that enable patients to track and monitor their food and physical activity as well as generate reports or logs [63]. Moreover, other websites include blogs, healthful recipes, menus, and holiday meal planning assistance [57]. Some clinical web-based supportive educational tools include remote chatting, discussion forums, emailing choices, and the ability to contact a live diabetes coach [57]. Indeed, web-based educational interventions have shown promise in supporting diabetes self-management. Such digital training approaches have been linked to enhanced treatment adherence and improved health indicators, highlighting their potential as effective tools in early diabetes care [63].

Given that self-management is crucial in managing T2D and also considering that persons with disabilities face barriers that prevent them from successfully managing their diabetes, a study looking to create an available, inclusive, and accessible diabetes management program for people with disabilities is important. To the best of our knowledge, there is no existing program in the United States explicitly providing remote DSME and MNT tailored for persons living with disabilities.

This study has limitations. Factors such as the supportive group setting, the instructor, or individual components of the program may influence health outcomes in different ways. To account for potential confounding factors, we have chosen a randomized design. Additionally, behavior changes, such as participating in an organized intervention, could contribute to improvements, including adopting healthier diets. As with any complex intervention, various factors may impact the outcomes. However, this reflects real-world clinical scenarios. Using a randomized design, the study aims to minimize the influence of confounding variables and provide more reliable findings. Additionally, several aspects of our trial design may pose potential limitations. First, participants with mobility limitations or accessibility issues may be unable to visit the contracted laboratory for their HbA_{1c} test and instead self-report their HbA_{1c} levels. These self-reported data may not be entirely accurate or up to date. Additionally, as the study is conducted remotely, some participants, particularly older individuals, may face technical challenges, such as difficulty navigating the platform or accessing the intervention materials.

That notwithstanding, this study has some strengths. To begin with, the methodological strengths of the study include the randomized controlled design, preregistration in a clinical trials registry, the inclusion of make-up and follow-up classes, and the use of both quantitative and qualitative measures. Another

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strength is a third-party testing company's involvement in the HbA_{1c} tests, ensuring impartiality and reliability in the results.

The results from this study will expand our understanding of how technology-delivered behavioral interventions can effectively address the challenges of managing diabetes, particularly among individuals with permanent physical disabilities and their families. A combined approach of DSME and technology offers a promising, easily accessible, and engaging intervention that may serve as a practical pathway for improving diabetes management.

This study provides future directions. First, it can lead to more studies on how artificial intelligence could be used in the delivery of diabetes education among individuals with various forms of disabilities. In addition, the study can help provide insight regarding an effective approach to combine more than 1 technology in providing diabetes management education.

We intend to present study findings at diabetes, endocrinology, and digital health conferences and submit the data for publication in peer-reviewed open-access publications. In addition, we will consult with health care leaders and diabetes care teams within our health system on potential changes to diabetes education methods and digital intervention protocols.

In conclusion, this randomized controlled study, with an anticipated 90 participants, will explore the effects of combined DSME and technology among individuals with diabetes and a permanent physical disability. The primary aim is to assess how technology-enhanced DSME influences diabetes management. The findings from this intervention study could offer valuable insights for health care professionals, health educators, and public health personnel, informing future strategies for managing diabetes in individuals with physical disabilities and more broadly among all persons living with T2D.

Acknowledgments

This research was funded by the National Institute on Disability, Independent Living, and Rehabilitation (grant 90BISB0027). The study has been funded since September 2022. Generative artificial intelligence tools were not used in preparing the manuscript. The study's findings will be disseminated publicly through publishing the results in peer-reviewed journals and will also be presented at both regional and national conferences.

Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization: MT
Funding acquisition: MT, SA
Methodology: MT, AA, JP
Project administration: MT, SA
Resources: SA
Supervision: SA
Writing—original draft: AA
Writing—review and editing: MT

Conflicts of Interest

None declared.

Multimedia Appendix 1
TIDieR checklist.
[PDF File (Adobe PDF File), 116 KB - resprot_v14i1e71495_app1.pdf]

Multimedia Appendix 2
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1170 KB - resprot_v14i1e71495_app2.pdf]

Multimedia Appendix 3
Final interview guide.
[PDF File (Adobe PDF File), 85 KB - resprot_v14i1e71495_app3.pdf]

Multimedia Appendix 4
Peer review report by National Institute on Disability, Independent Living, and Rehabilitation Research (NIDILRR), Administration for Community Living (National Institutes of Health, USA).

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[PDF File (Adobe PDF File), 441 KB - resprot_v14i1e71495_app4.pdf]

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Abbreviations

CDCES: certified diabetes care and education specialist
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
DM: diabetes mellitus
DSME: diabetes self-management education
HbA1c: glycated hemoglobin A1c
HIPAA: Health Insurance Portability and Accountability Act
IRB: institutional review board
MNT: medical nutrition therapy
REDCap: Research Electronic Data Capture
TIDieR: Template for Intervention Description and Replication
T2D: type 2 diabetes

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Protocol

Innovative Web-Based Future Planning and Well-Being for Caregivers of Individuals With Intellectual and Developmental Disabilities: Protocol of a Pragmatic Randomized Controlled Trial

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Abstract

Background: Nearly three-quarters of the estimated 4.9 million people with intellectual and developmental disabilities (IDDs) in the United States live with family caregivers, 25% of whom are aged older than 60 years. People with IDDs experience disproportionately high rates of mortality, morbidity, and acute care use, often due to a lack of accessible, tailored resources to support them throughout the lifespan. Few caregivers engage in long-term care (LTC) planning, often due to a lack of information and support.

Objective: This protocol describes the design and methods of the Future Planning and Well-Being for Individuals with Intellectual Disabilities and Family Caregivers study, a randomized controlled trial evaluating the effectiveness of the Map Our Life web-based LTC planning tool compared to an attention control website on caregiver-reported burden, caregiver-reported well-being, and progress in and communication of future plans for the individual with an IDD.

Methods: The Future Planning and Well-Being for Individuals with Intellectual Disabilities and Family Caregivers study is a national, multisite, randomized controlled clinical trial with a target enrollment of 1050 family caregivers of individuals with IDDs at 6 sites across the United States. Participants are randomly assigned (1:1) to either the Map Our Life web-based LTC planning tool plus enhanced usual care or an attention control group consisting of a Centers for Disease Control and Prevention–sponsored health promotion website for people with disabilities plus enhanced usual care. Primary outcomes, including caregiver-reported burden, caregiver-reported well-being, and LTC planning behaviors, are assessed at baseline and at 1, 6, and 18 months. Data will be analyzed using mixed-effects models to accommodate the repeated measures design.

Results: This study was funded in July 2022, received initial Institutional Review Board approval in August 2023, and was registered on ClinicalTrials.gov in December 2023. Recruitment began in December 2023 and is scheduled to conclude in December 2025. Primary outcome analyses will commence immediately following the completion of final follow-up surveys.

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Conclusions: LTC planning is an important component of addressing health disparities among individuals with disabilities and their family caregivers. By focusing on using an innovative and accessible tool for LTC planning, the study addresses a critical gap in available resources with the potential to improve quality of life and reduce caregiver burden.

Trial Registration: ClinicalTrials.gov NCT06065527; https://clinicaltrials.gov/study/NCT06065527

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KEYWORDS

innovative long-term care planning tool; intellectual and developmental disabilities; caregivers; health disparities; randomized controlled trial

Introduction

Background

Of the estimated 4.9 million people with intellectual and developmental disabilities (IDDs) in the United States, nearly 75% individuals live with family caregivers, 25% of whom are aged older than 60 years [1]. As both individuals with IDDs and their caregivers age, they become increasingly susceptible to age-related health and functional decline, and caregivers face greater demands of caregiving [2-4]. Though caregivers worry about future care when they are no longer able to provide care [5,6], few families make concrete long-term care (LTC) plans or discuss future planning with their loved one with a disability. Main reasons may be, but are not limited to, not knowing where to start or finding the LTC planning process overwhelming [7]. This creates a pressing need for an LTC planning tool to help families become more informed about LTC needs and available supports.

IDDs are characterized by impairments in both intellectual and adaptive abilities originating in childhood, often associated with clinical comordities such as seizure disorders, may involve minimal or no understanding of verbal language, and often require enhanced or complete support throughout the lifespan [8-10]. Level of independence in adulthood varies depending on severity of the IDDs. Those with mild IDDs may achieve some signs of independence, while those with more severe IDDs often require long-term community supports for housing, occupational activities, and recreational activities [11,12]. Lack of concrete LTC plans may lead to acute crises and emotional trauma, introduce unexpected dilemmas for siblings or extended families, and at its worst, inappropriate or unwanted placement in nursing home settings, unsafe living conditions, or harm to individuals with IDDs [13-15]. Lack of comprehensive planning or planning without proper knowledge of how governmental support systems and legal systems operate could result in disabled individuals losing needed supports, being placed in restrictive environments, or potentially being stripped of their legal rights [15-17].

While LTC planning interventions exist for aging populations in general [18,19], few evidence-based interventions exist to support LTC knowledge, decision-making, and sharing of LTC plans specially tailored to meet the needs of individuals with IDDs and their family caregivers [20]. Plan Your Lifespan (PYL) is one such tool developed for adults in their fourth quarter of life [21,22]. The intervention, which was developed in accordance with the Preparation for Future Care Model, (1) introduces users to LTC related choices (care expectation), (2) assesses the unique caregiving needs of the care recipient (awareness), (3) educates the users on locally and nationally available home-based resources (information gathering), (4) makes choices about LTC preferences (decision-making), and (5) shares those choices with others (concrete planning). In a randomizad clinical trial, PYL demonstrated efficacy in assisting older adults with planning for the future and communciation of those plans to loved ones [23].

To address the lack of evidence-based interventions to support LTC planning for this population, research was conducted that identified a set of relavent domains of LTC planning, barriers and facilitiators in each domain, current LTC planning behaviors [23,24], and critical compnents to include in a web-based tool to support LTC planning [25]. The resulting product is an adapation of the PYL platform, called Map Our Life (MOL), that seeks to provide individuals with IDDs and family caregivers a unique and comprehensive tool by which to learn about future options in each identified domain and create an editable and sharable LTC plan for current and future use. It seeks to address current gaps in the literature around the existing evidence-based interventions to support LTC planning for this population and or their caregivers [26].

Objectives

This study protocol outlines the rationale, design, methods, and statistical plan for a multisite randomized controlled trial, Future Planning and Well-Being for Individuals with Intellectual Disabilities and Family Caregivers. The study seeks to compare the effectiveness of MOL in combination with enhanced usual care (EUC) to an attention control (AC) website in combination with EUC on caregiver burden and well-being. The primary aim of the study is to compare caregiver quality of life outcomes by examining caregiver burden and self-efficacy scores at 1, 6 and 18 months. Our hypothesis is that family caregivers of those with IDDs in the MOL + EUC arm will have lower caregiver burden with time and higher self-efficacy scores at all points than those in the AC + EUC. Our secondary aim is to examine caregiver LTC knowledge and planning behavior and mediating and moderating effects on quality of life outcomes at 1, 6 and 18 months, comparing the effectiveness of EUC +MOL versus EUC + AC on these outcomes at 1, 6 and 18 months.

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Methods

Study Design

This study is a multicenter, 2-arm, randomized controlled trial investigating the effectiveness of MOL + EUC compared to the AC + EUC. The goal is to recruit 1050 participants across 6 health systems in 5 states (Delaware, New York, Ohio, Pennsylvania, and Texas). Participants will be randomized in 1:1 ratio after consent has been obtained and baseline surveys are completed. Enrolled participants are expected to log into their assigned website at least once a week for a period of 3 months. Follow-up surveys will occur at 1, 6, and 18 months. Research coordinators refer participants to relevant disability support services in accordance with the EUC protocols developed, as described below. Findings of the study will be reported based on the CONSORT (Consolidated Standards for Reporting Trials) guidelines [27].

Study Groups

Enhanced Usual Care

All study participants will receive enhanced usual care. Enhanced usual care will consist of regular case management services provided by disability service organizations in the participant's geographic location. We will impose no constraints on usual care in the control or intervention group. Case management services will be administered through county- and state-based developmental disability service organizations that all participants are entitled to because of their qualifying diagnosis of IDDs. Upon enrollment in the trial, study staff will confirm a participant's connection to their local disability service organization. In the event that the participant is not already connected to these services, study staff will provide a referral to connect participants to case management.

Map Our Life

In accordance with the Preparation for Future Care Model, Map Our Life (1) introduces users to LTC related choices (care expectation), (2) assesses the unique caregiving needs of the care recipient (awareness), (3) educates the users on locally and nationally available home-based resources (information gathering), (4) makes choices about LTC preferences (decision-making), and (5) shares those choices with others (concrete planning) [28]. Upon randomization to this arm, study staff will reach out to participants and provide log-in credentials and instructions on how to interact with the web tool. Participants will be asked to log into the site at least once per week for a month.

Attention Control

Caregivers in the attention control group will be referred to a website containing information from Disability and Health Information for Family Caregivers [29]. The content in the attention control is from a Centers for Disease Control and Prevention (CDC)-sponsored website that promotes healthy activities and behaviors targeting people with disabilities and their family caregivers. Additionally, the content leads users to CDC-sponsored "Caregiving" webpages, which assist families in developing care plans. Upon randomization to this arm, study staff will reach out to participants and provide log-in credentials. Participants will be asked to visit the site at least once per week for a month.

Community Partner Engagement

This study is a community-engaged study, ensuring that integral feedback shapes the formation, dissemination, and application of research results and increases enrollment and retention. The Community Advisory Committee actively contributes to the project by sharing the study recruitment information through their networks, providing feedback on study questionnaires, intervention website content, and recruitment and retention materials. This collaborative approach ensures that the research remains aligned with community needs and promotes effective recruitment and retention strategies. To further engage community partners, quarterly Community Advisory Committee meetings are held, and newsletters are distributed to keep community partners informed and involved. Feedback from these meetings has been incorporated in recruitment materials and retention strategies, ensuring they are more accessible and culturally relevant to improve participant engagement.

Eligibility Criteria

Eligible family caregivers must be at least 18 years of age and have a primary preferred language of English or Spanish. Family caregivers will be excluded if they do not have access to a computer, tablet, or smartphone that would allow engagement with the website or if the care recipient with IDDs is aged younger than 10 years at the time of recruitment.

Recruitment and Screening

Potential participants are screened and enrolled by 1 of 6 health system sites (Christiana Care in Delaware, Northwell Health in New York, Children's Hospital of Philadelphia in Pennsylvania, Cincinnati Children's Hospital Medical Center in Ohio, Geisinger Health in Pennsylvania, and Baylor College of Medicine in Texas) by the sites' respective investigative team. Each site will identify potentially eligible participants through a combination health system– and community-based recruitment. In health system–based recruitment, potentially eligible participants are identified based on encounters within participating health systems. Identification of potentially eligible participants in this setting occurs via health care provider direct referral, use of clinical registries, and review of ambulatory patient schedules. Community-based recruitment is spearheaded by community partners in conjunction with health system investigative teams and involves posting study information in community locations and sharing study information via approved social media outlets. Interested individuals are instructed to contact study staff to discuss study participation.

Once a potentially eligible participant is identified, study staff will meet with the potential participant in person or over the phone. Study staff describe the study and confirm eligibility before proceeding. At this time, presence of an IDD is confirmed. Regardless of recruitment method, all potential participants will be asked to self-report IDD diagnosis of the care recipient using the following validated questions from the National Survey of Children's Health administered by the US Department of Health and Human Services [30]:

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1. Has a doctor or other health care provider EVER told you that your child has Down Syndrome? (Yes/No)
2. Has a doctor or other health care provider EVER told you that your child has Cerebral Palsy? (Yes/No)
3. Has a doctor, other health care provider, or educator EVER told you that your child has Fetal Alcohol Spectrum Disorder (FAISD)? (Yes/No)
4. Has a doctor, other health care provider, or educator EVER told you that your child has Intellectual Disability (formerly known as Mental Retardation)? (Yes/No)
5. Has a doctor or other health care provider EVER told you that your child has Autism or Autism Spectrum Disorder (ASD)? Include diagnoses of Asperger's Disorder or Pervasive Development Disorder (PDD). (Yes/No)

If any answer to any of the above questions is "yes", the care recipient is considered to have an IDD. Study coordinators also will document whether the care recipient is a patient of one of the participating health system recruitment sites. If the care recipient is a patient at the recruitment site, the study coordinator will further confirm the presence of an IDD through chart review and health care provider confirmation of a specified list of International Classification of Diseases-10th Revision (ICD-10) codes.

Expert consensus was used to tier ICD-10 codes within an existing health system grouper for developmental disability into three levels: (1) Tier 1 includes codes that meet eligibility where the research coordinator can approach patients without consulting a clinician. Tier 1 codes include diagnoses like Down syndrome (Q90.9), Cerebral Palsy (G80.0), Fetal Alcohol Spectrum Disorder (Q86.0), Intellectual Disability (F79), and Autism Spectrum Disorder (F84.0). (2) Tier 2 codes require clinician review for confirmation of eligibility and include diagnoses like focal motor seizure (G40.109), Spina Bifida (Q05.9), and pervasive developmental disorder (F84.9). These are diagnoses for which we expect at least 50% of impacted individuals to experience an IDD. (3) Tier 3 codes alone do not meet eligibility. Thus, a patient with a tier 3 code and no other diagnosis is excluded (Figure 1). If the self-reported information conflicts with what is in the care recipient's chart, for eligibility purposes, the information provided by the caregiver will outweigh information gathered in the chart.

Figure 1. Identifying eligible patients through International Classification of Diseases-10th Revision (ICD-10) codes. The goal is to give the research staff a tool by which to identify potentially eligible patients for the study.

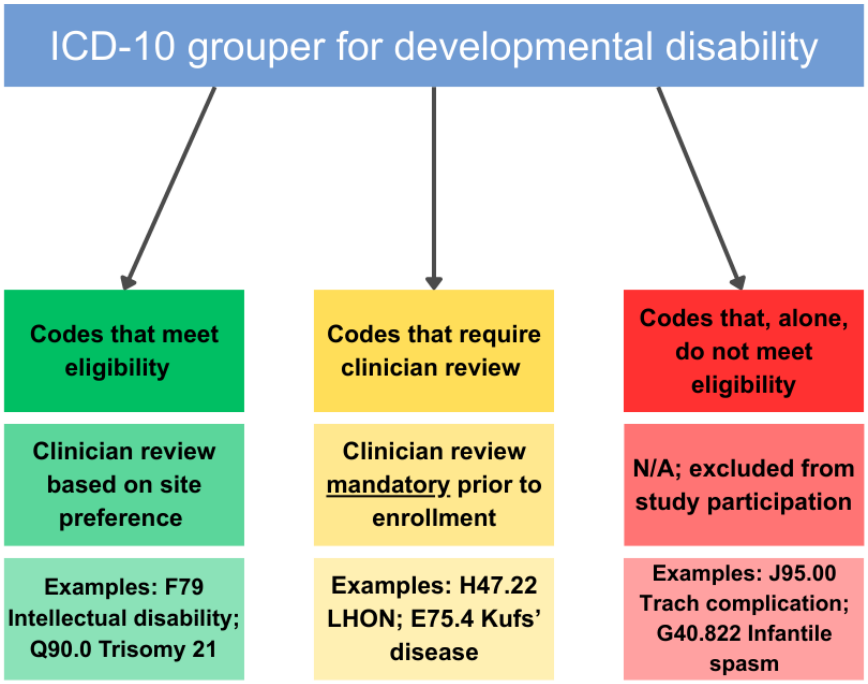

Assent and Consent

Caregiver Consent

Once screening is complete and eligibility is confirmed, as described above, eligible caregivers will be approached by research staff to review study procedures and provide consent for participation. This process may occur in person or over the phone. Electronic consents will be obtained via REDCap (Research Electronic Data Capture). During this process, the study will be described and the consent form will be reviewed with the participant.

The consent script will be available in both English and Spanish to ensure all individuals understand the nature and requirements of the study. Communication with Spanish-speaking participants will be conducted through a medically certified interpreter, and information about the interpreter will be documented in REDCap. Once finished, the participant will provide an e-signature via REDCap. Participants will be emailed a copy of the e-consent form. Waiting time between informing prospective participants and obtaining consent will depend on the mode used to inform participants about the study.

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Care Recipient Consent

Once a caregiver agrees to participate in the study, the ability of the care recipient to assent or consent will be determined. If a care recipient is aged older than 18 years and cognitively able to provide consent independently, they will be asked to complete survey measures in addition to their caregiver. Care recipients who are unable to independently provide consent will not be asked to complete survey measures. Their caregiver will complete care recipient–designated survey measures as a proxy respondent. The research team will take extra care to ensure that participants with disabilities understand the study goals and what is being asked of them as study participants.

Randomization

After caregiver participants complete the baseline surveys, they are randomly assigned to 1 of 2 groups: the web-based long-term care planning tool, Map Our Life, with enhanced usual care (MOL + EUC) or an attention control group, a CDC-sponsored health promotion website for people with disabilities, with enhanced usual care (AC + EUC). Participants are randomized in a 1:1 concealed allocation procedure that uses a permuted block design with randomly varying block sizes of 2 and 4. Randomization will occur via REDCap's randomization module. Both groups will be provided with a short tutorial video and prompted to log into their assigned website once a week for a period of 3 months.

Follow-Up Surveys

Follow-up surveys are completed at the following intervals: at 1 month, 6 months, and 18 months after randomization. These surveys can be completed online, over the phone, or in person. The surveys ask demographic questions about the caregiver and care recipient as well as questions about caregiver and care recipient quality of life (using the Zarit Burden Interview [ZBI] [31,32], Revised Scale for Caregiving Self-Efficacy [33-35], PROMIS Global Health [36-38], and World Health Organization Quality of Life Disability Module [39]) and health behaviors that relate to long-term care planning (using Planning Behavior and Communication of Plans [23,40,41], COPE [42,43], and the National Core Indicators Family Survey – Information and Planning [44-46]). A list of the different tools, their administration time point, and the typical amount of time required for completion can be found in Table 1. Participants can receive up to $175 over the 18-month study period for survey completion.

Table 1. Patient-reported outcome measures.

Measure	Number of items	Time point (month)	Person responsible
Caregiver Zarit Burden Interview [31,32]	22	0, 1, 6, 18	Caregiver
Revised Scale for Caregiving Self-Efficacy [33-35]	5	0,1,6,18	Caregiver
World Health Organization Quality of Life Module [39]	13	0,6	Caregiver, care recipient
Planning Behavior and Communication of Plans [23,40,41]	21	0,1,6,18	Caregiver
COPE: Use of instrumental social support subscale, active coping subscale, planning subscale, denial [42,43]	16	0,1,6,18	Caregiver
National Core Indicators Family Survey – Information and Planning: Services and Supports Received Subdomains [44-46]	20	0,1,6,18	Caregiver

Data Collection

In addition to data collected as part of the various questionnaires, participants provide basic demographic information about themselves and the care recipient (caregiver: age, gender, race, ethnicity, preferred language, education, relationship to care recipient, marital status, employment, and income; care recipient: age, gender, race, housing arrangement, employment, and Medicaid waiver participation). Additionally, unpaid care time (hours per week) and the number of care recipients in a household are recorded. All data collection occurs in a Health Insurance Portability and Accountability Act (HIPAA)-compliant REDCap database overseen by the coordinating institution.

Statistical Analysis

The study will follow the intention-to-treat principle, analyzing participants in the arm they were randomly assigned to. Data and measures will be summarized according to treatment arm using means and SDs, or medians and IQRs for continuous variables, as appropriate. Frequencies and percentages will be reported for categorical variables. No inferential comparisons of the 2 arms will be carried out. For aim 1, a 2-sample *t* test will be used to compare the 2 treatment arms at the 12-month follow-up. Ninety-five percent CIs for the mean difference between the 2 arms will be constructed. If the assumption of normality does not hold, the Mann-Whitney test will be used instead. As suggested by International Council for Harmonisation (ICH) E-9 guidelines, a supporting analysis will be carried out using analysis of covariance (ANCOVA) to compare the 2 treatment arms, adjusting for the stratification variables (institution, age of the person with an IDD, and Waisman score). A secondary analysis will be carried out using ANCOVA to compare the 2 treatment arms, adjusting for the stratification variables, baseline outcome value, and the prespecified covariates: race (White, non-Hispanic compared to American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Pacific Islander, Hispanic or Latino, or another race or ethnicity) and language (English and Spanish). The approaches used for analyzing the primary outcome will also be used for all continuous secondary outcomes. In addition, longitudinal analysis of the primary and

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secondary outcomes (ZBI, caregiver self-efficacy, and community participation) will be carried out using generalized linear mixed models for repeated measures, adjusting for stratification variables as well as the additional prespecified covariates race and language.

Power calculations were performed for 2 different sample sizes (400 and 500 participants per treatment arm) under several scenarios. We will use absolute change in ZBI score at the 6-month follow-up as our primary outcome of interest. Based on a similar study by González-Fraile et al [47], the SD of the absolute change in total ZBI was 13.94 in the treatment arm and 10.02 in the control arm. Accordingly, we considered 3 values for SD, namely, 10.02, 13.94, and the variance-based average of 11.99. Based on clinical experience, assuming that the average change in the control arm is approximately 0 and the average change in the treatment arm will be 3 [48], the resulting effect size is 0.25 to 0.3. depending on which value of SD holds. We further assume that our projected sample size is 525 participants per arm. This would yield power of between 93.3% and 99.8% for the 3 possible SD values. If 20% of the sample is lost to follow-up at 6 months and the projected sample size is 420 per arm, the resulting power values range from 87.6% to 99.1% for the 3 SD values (2-tailed 2-sample *t* test, α=.05).

Ethical Considerations

The study is registered on ClinicalTrials.gov (NCT06065527). This protocol was reviewed and approved by the Feinstein Institutes for Medical Research/Northwell Health (23-0381) institutional review board (IRB). This study uses a single IRB to promote consistency across sites. As described above, study staff clearly describe study procedures to family caregiver participants prior to asking them to provide consent for participation. A rigorous process is used to determine the capacity for individuals with IDDs to provide consent or assent. Data in this study are not anonymized; however, protections are in place to safeguard participant information, including the use of HIPAA-compliant data capture systems and restricted access to participant data based on study role. Participants are compensated for survey completion and can earn up to $175 for study participation. This study is considered minimal risk. Mitigation of primary concerns, breach of confidentiality, and participant discomfort include data deidentification methods, password-protected storage, and voluntary participation from participants.

Results

This study was funded in July 2022 from the Patient-Centered Outcomes Research Institute (grant AD-2021C3-24941), received initial IRB approval in August 2023, and was registered on ClinicalTrials.gov in December 2023 (NCT06065527). Participant recruitment began in December 2023 and is scheduled to conclude in December 2025. The results of these analyses will be reported in a separate manuscript.

Discussion

This study is designed to contribute significant knowledge about the potential benefits of a web-based LTC planning tool for individuals with IDDs and for their caregivers. The results will also assist individuals with IDDs and their caregivers, in collaboration with their health care providers, in developing and communicating LTC plans. The website used by the intervention group may be implemented in different care settings and for other diseases and thus generate generalizable knowledge. Furthermore, it could serve as a model for developing similar interventions for other populations with complex long-term care needs.

A defining strength of this study is its comprehensive and ethically driven approach to participant inclusion, which includes tiered screening, legal guardian consent, and care recipient assent or consent processes. These methods ensure that all participants are appropriately assessed and included based on their unique needs and abilities while maintaining a high standard of ethical research practices. This process not only safeguards the rights of individuals with IDDs but also provides a replicable framework for future studies involving populations with varying levels of cognitive ability. Moreover, the integration of stakeholder feedback throughout the study ensures the intervention aligns with community needs, thereby increasing its acceptability and retention. This collaborative approach strengthens the study's relevance and potential for real-world application in underserved populations in research.

One limitation of this study is that caregiver burden and LTC planning behaviors are assessed through self-reported data that could introduce bias. Second, while the study includes participants from diverse sites across the United States, our study only supports Spanish and English languages, underrepresenting certain populations and potentially limiting the generalizability of findings. Additionally, the study's design requires internet access, potentially excluding caregivers who do not have access to or are unable to use the specified technology.

The proposed protocol offers a comprehensive framework for evaluating a web-based LTC planning intervention for caregivers of individuals with IDDs. By integrating innovative methodologies for screening, legal guardian consent, and care recipient assent or consent, the study addresses ethical complexities while ensuring inclusivity and rigor. If successful, the intervention could transform LTC planning, reducing caregiver burden and improving outcomes for individuals with IDDs. The findings may inform future research, clinical practice, and policy development, advancing care and support for this underserved population.

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during this study. At the end of the study, the datasets generated or analyzed during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

AS, CS-W, JB, JW, IR, TD, AG, DS, JS, JC, and SJ designed this study; CS and JS designed the statistical analysis plan; CS, SK, AS, CS-W, JB,JW, IR, TD, AG, DS, JS, JC, and SJ carried out this trial; CS, SK, and OT drafted this manuscript; and all authors read, carefully reviewed, edited, and approved the final manuscript

Conflicts of Interest

None declared.

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Abbreviations

AC: attention control
ANCOVA: analysis of covariance
CDC: Centers for Disease Control and Prevention
CONSORT: Consolidated Standards for Reporting Trials
EUC: enhanced usual care
HIPAA: Health Insurance Portability and Accountability Act
ICD-10: International Classification of Diseases-10th Revision
ICH: International Council for Harmonisation
IDD: intellectual and developmental disabilities
IRB: Institutional Review Board
LTC: long-term care
MOL: Map Our Life
REDCap: Research Electronic Data Capture
ZBI: Zarit Burden Interview

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Protocol

Comparison of Ketorolac at 3 Doses in Children With Acute Pain: Protocol for A Randomized Controlled Trial

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Abstract

Background: Intravenous ketorolac is a potent nonopioid analgesic commonly used to treat vigorous pain in children and adults. Despite its widespread use in pediatric emergency settings, ketorolac dosing in children remains “off-label,” with limited high-quality evidence to guide practice. Pharmacokinetic differences between children and adults suggest that lower ceiling doses adopted from adult practice may lead to suboptimal analgesia in pediatric populations. Inconsistent ketorolac dosing practices across centers reflect substantial clinical uncertainty. Amid efforts to reduce opioid use and provide effective nonopioid alternatives, rigorous pediatric trials evaluating ketorolac dosing are urgently needed.

Objective: The primary objective is to determine whether 2 lower-dose intravenous ketorolac strategies (0.25 mg/kg-30 mg or 0.5 mg/kg-10 mg) are noninferior to the standard dosing regimen (0.5 mg/kg-30 mg) in reducing mean pain scores at 60 minutes postadministration in children aged 6-17 years presenting with vigorous pain. The secondary hypothesis is that ketorolac 0.5 mg/kg up to 10 mg will be superior to 0.25 mg/kg up to 30 mg by at least the minimally important difference of 2.0 points on the verbal Numerical Rating Scale (vNRS).

Methods: The KETODOSE trial is a single-center, randomized, double-blind, double-dummy, noninferiority trial conducted at McMaster Children’s Hospital. Eligible participants aged 6 to <18 years with vigorous pain (vNRS >4) are randomized in a 1:1:1 ratio to standard dosing or one of 2 low-dose ketorolac regimens. Study drugs are administered via intravenous push over 5 minutes. Pain scores are assessed at baseline, 30, 60, 90, and 120 minutes. The primary endpoint is the mean change in vNRS score at 60 minutes. Secondary outcomes include pain scores at other time points, time to effective analgesia, rescue analgesia requirements, opioid consumption, and adverse events. Caregiver perceptions regarding analgesic use are evaluated using a mixed-methods semistructured survey. A sample size of 180 participants (60 per group) provides 80% power to detect noninferiority within a margin of 1.0 on the vNRS, assuming an SD of 1.5. Intention-to-treat and per-protocol analyses will be performed.

Results: Recruitment is ongoing. Final analyses will be performed once follow-up is completed for all participants. Results will be disseminated through peer-reviewed publications, conference presentations, caregiver- and clinician-facing educational tools, and national knowledge mobilization networks.

Conclusions: The KETODOSE trial will provide urgently needed evidence to guide ketorolac dosing for acute pain in children. If lower-dose regimens are shown to be noninferior to standard dosing, this may promote safer prescribing practices, reduce

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adverse events, and support efforts to minimize pediatric opioid use, thereby improving acute pain management in pediatric emergency care.

Trial Registration: ClinicalTrials.gov NCT05641363; https://clinicaltrials.gov/study/NCT05641363

International Registered Report Identifier (IRRID): DERR1-10.2196/76554

(JMIR Res Protoc 2025;14:e76554) doi:10.2196/76554

KEYWORDS

ketorolac; dose-response relationship; dosing; pain management; randomized controlled trial; protocol; emergency department

Introduction

Background

Ketorolac tromethamine is a well-known nonopioid intravenous (IV) analgesic commonly used in children and adults for vigorous pain [1-3]. It is a nonsteroidal anti-inflammatory drug (NSAID) that inhibits the synthesis of inflammatory endogenous substances such as prostaglandins and thromboxanes. Ketorolac has been shown to provide similar analgesia to opioids after outpatient surgical procedures associated with moderate pain, such as fractures, hernia repair, and tonsillectomy [1,4]. Ketorolac is commonly used in the Emergency Department (ED) for renal colic, abdominal pain, chest pain and migraine headaches [5]. However, such use in children is “off-label” as there is a paucity of methodologically sound controlled trials in children to inform optimal and safe dosing.

Previous pharmacological studies show that young children have up to 2- to 4-fold higher clearance and volume of distribution of ketorolac compared to adolescents and adults [6]. This suggests that younger children need a relatively higher dose per kilogram body weight than adults and the currently used 10-15 mg ceiling dose applied to adults may not achieve equivalent analgesia in children [7,8]. Emerging evidence, only applicable to adults, suggests that low-dose ketorolac (10 mg) is as effective as standard dose (30 mg) in acute pain management [5,9-11] with higher doses not conferring further benefit [12]. This has led to clinicians adopting the practice of a 10 mg maximum dose in children without rigorous pediatric evidence. For example, a 10 mg maximum dose in a 50 kg adolescent would equate to 0.2 mg/kg, in contrast to pediatric studies that used 0.5-1 mg/kg, a maximum of 20-30 mg [10,13-16]. In a local survey (February 2022) of our ED physicians, pediatric hospitalists, and surgeons, 10/31 (32%) respondents said that they would administer ketorolac (0.5 mg/kg) up to a maximum of 30 mg, 20/31 (65%) use ketorolac up to a maximum of 10 mg, and 1/31 (3%) did not know the best dose to give. Although the local monograph and order-sets recommend a maximum dose of 30 mg, our local variation in practice is not surprising and reflects clinical uncertainty regarding the optimal dose.

Ketorolac is an excellent alternative to opioids for vigorous pain and it is imperative to conduct pediatric dosing studies to inform both clinicians and regulatory agencies. Given the continued undertreatment of pain in children, its known adverse effects (including prolonged healing times, longer length of stay, less satisfaction) [17], and the lack of high-quality evidence for ketorolac use in children, there is an urgent need for a well-designed, rigorously conducted trial to inform clinical treatment decisions and health care policy. To our knowledge, there are no trials to guide the selection of the most effective and safe ketorolac dose for use in children. This comes at a time when ketorolac, the only available intravenous NSAID in Canada, is being considered increasingly more often to fill the nonopioid gap in treatment for vigorous pain [13,18-21].

Study Objectives and Hypothesis

Primary Objective

In children aged 6-17 years with vigorous pain (as measured on the 11-point verbal Numerical Rating Scale [vNRS]) who are prescribed IV ketorolac by their treating physician, lower-dose IV ketorolac dosing strategies (0.25 mg/kg/dose-30 mg OR 0.5 mg/kg/dose-10 mg) are noninferior to standard dosing (0.5 mg/kg/dose-30 mg) in reducing mean pain scores.

Primary Hypothesis

Low-dosing strategies will be noninferior to standard dose by a margin of 1.0 on the 11-point vNRS: (1) ketorolac given at 0.5 mg/kg/dose-10 mg will be noninferior to standard dose ketorolac and (2) ketorolac given at 0.25 mg/kg/dose-30 mg will be noninferior to standard dose ketorolac.

Secondary Hypothesis

Dosing at 0.5 mg/kg/dose-10 mg will be superior to 0.25 mg/kg/dose-30 mg by the minimally important difference (MID) of 2.0 on the 11-point vNRS.

Secondary Objectives

The objective of this study is to understand patients’ and caregivers’ knowledge, attitudes, perceptions, and emotions on pain, medications, and their use in treating acute pain. As pain is a multidimensional experience, we seek a deeper understanding of participants’ experiences with pain and pain medications by assessing the following domains: (1) caregiver knowledge and attitudes toward widely available analgesics; (2) attitudes and fears associated with IV analgesics; and (3) caregiver perceptions of dosing of analgesics as well as adverse events (AEs) associated with them.

Methods

Design

This will be a randomized, noninferiority, double-dummy, quadruple-blinded (participant and their caregiver, clinical staff, research team, outcome assessor, and data analyst), single-center, pediatric ED trial. The study will be conducted using recommendations from the 2010 CONSORT

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(Consolidated Standards of Reporting Trials) statement extension for noninferiority and equivalence trials [22] (Multimedia Appendix 1).

Eligibility Criteria

The inclusion and exclusion criteria with their justifications are summarized in Textbox 1.

Textbox 1. Inclusion and exclusion criteria with justification.

Inclusion criteria and justification

1. Age 6 years to <18 years: the primary outcome measure (11-point vNRS) is validated for use in children ≥6 years, and no other evidence-based acute pain measure is recommended for younger children [23-25].
2. Currently experiencing vigorous pain (self-reported pain score >4 using the vNRS at the time of enrollment; ketorolac is used to treat moderate to severe pain) [26].
3. Patients seen in the ED or inpatient setting with acute pain ≤30 days in duration [5].
4. Patient with an IV cannula in situ or ordered (to minimize additional pain or distress).

Exclusion criteria and justification

1. Previous enrollment in the trial (to ensure independent observations).
2. Postoperative patients (medically induced pain differs from pathology-related pain).
3. NSAID use within 6 hours or opioid use within 4 hours, or both, before recruitment (to avoid overdosing and confounding).
4. Actively followed and treated by the chronic pain team (response to analgesics may be altered).
5. Cognitive impairment in the caregiver or child (inability to respond to study questions).
6. History of gastrointestinal bleed or ulcers, inflammatory bowel disease, coagulation disorders, cerebrovascular bleeding, or known arterio-vascular malformations (increased bleeding risk).
7. History of chronic and active renal disease (excluding renal calculi and urinary tract infections).
8. History of chronic and active hepatocellular disease (ketorolac is metabolized in the liver).
9. Known pregnancy at the time of enrollment (risk of closure of the patent ductus arteriosus in the fetus).
10. Known hypersensitivity to NSAIDs or opioids.
11. Inability to obtain consent (language barrier without availability of a translator).

Interventions

To maintain blinding of bedside clinical staff, patients, and research staff, we will administer an active intervention (ketorolac) and 2 controls (identical normal saline placebo) to each patient at 3 differing doses.

1) Standard-dose group A: IV ketorolac 0.5 mg/kg to a maximum of 30 mg, IV normal saline placebo given at 0.25 mg/kg to a maximum of 30 mg, or IV normal saline placebo given at 0.5 mg/kg to a maximum of 10 mg.

2) Low-dose group B. Group B1: IV ketorolac 0.5 mg/kg to a maximum of 10 mg, IV normal saline placebo given at 0.25 mg/kg to a maximum of 30 mg, or IV normal saline placebo given at 0.5 mg/kg to a maximum of 30 mg. Group B2: IV ketorolac 0.25 mg/kg to a maximum of 30 mg, IV normal saline placebo given at 0.5 mg/kg to a maximum of 30 mg, or IV normal saline placebo given at 0.5 mg/kg to a maximum of 10 mg.

For rescue analgesic therapy, any participant can be given any other non-NSAID analgesic at the discretion of the treating physician at least 60 minutes after the trial medication is administered. To minimize overdosing or AEs, any other NSAIDs can be given 6 hours post-intervention.

Rationale for Treatment Dose

Ketorolac is available at McMaster Children's Hospital for off-label use in children for vigorous pain. The acceptable dose range is 0.25-1 mg/kg/dose every 6 hours (maximum 30 mg/dose) [27]. Onset of action is 30 minutes after IV administration and the maximum effect is achieved at 2 hours with a total duration of action up to 6 hours. Available population PK study data [28] from 3 studies on 64 children (intraoperative) showed a decrease in both central and peripheral volume of distribution over the first few years of life and clearance decreases from infancy to adolescence. A single dose of 0.5 mg/kg ketorolac (maximum dose 10-30 mg) every 6 hours achieved a half maximal effective concentration at or above the established 0.37 mg/ml. Most of our participants aged 6 years and older will weigh at least 20 kg (50th percentile) and receive the maximum ceiling dose of 10 mg (group B1). Hence, including low-dose group B2 (0.25 mg/kg to a maximum of 30 mg) will allow us to test 2 low dosing strategies since we are changing only one intervention per arm: (1) a lower dose per kg (0.25 mg/kg) is noninferior to standard dose (0.5 mg/kg) and (2) a lower ceiling dose (10 mg) is noninferior to standard ceiling dose (30 mg) (see Multimedia Appendix 2).

Randomization and Participant Allocation

The study's research pharmacist at McMaster Children's Hospital research pharmacy will create a simple

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computer-generated block randomization list using Robust Randomization App [29] (Center for Biostatistics, Icahn School of Medicine at Mount Sinai) with random varying permutated blocks of 3, 6, and 9 and a 1:1:1 allocation ratio. The research pharmacists will prepare consecutively numbered study drug vials according to the randomization schedule, with clear labels and dosing instructions in each kit. At least 3 study drug kits will be stored in the password-protected ED medication dispensing machines as per standard operating procedures and Division 5 Good Clinical Practice Health Canada Guidelines. Drug kits will be replenished as needed (at a minimum, weekly) by the research pharmacists. Only the research pharmacists will retain the randomization codes.

A log of all screened patients will be maintained. If patients are eligible, details of the study will be discussed with patients and their caregiver. Consent and assent will be obtained as per the Hamilton integrated Research Ethics Board (HiREB) guidelines and approved consenting procedures (see Multimedia Appendix 3 for consent forms). The clinical research assistant will collect baseline clinical variables and will complete the data collection forms. Elements of baseline pain severity (assessed by vNRS), type of pain, location of pain, duration of pain since onset, associated symptoms (eg, nausea, anorexia, vomiting, dysuria, fever, and pain with movement) will be collected. The Clinical Research Assistant will then pick the next consecutively numbered drug kit and enter the drug kit coded number into Research Electronic Data Capture (REDCap; Vanderbilt University). The research nurse will administer the study drugs to the patient (ketorolac and placebo normal saline) according to the dosing guidelines as an IV push over 5 minutes. Five minutes is a safe timeframe to administer IV ketorolac. This is consistent with the instructions on the clinical drug monograph at our hospital. Time 0 will be defined as the point at which administration of the study drug is completed.

Methods to Protect from Bias

Our study drug kits will contain active ketorolac and normal saline placebo (labelled as ketorolac) with instructions on dosing as per the randomization schedule. Ketorolac is identical to a normal saline placebo in appearance, consistency, and smell. Vials will contain clear liquid ketorolac 30 mg/ml or normal saline placebo ketorolac 30 mg/ml. Vials will be stored in consecutively numbered study drug kits according to the randomization schedule generated by the McMaster Children's Hospital research pharmacy. The double-dummy design will ensure blinding of the research nurse drawing up and administering the drug. Bedside physicians and nurses, participants, and their families, investigators, research nurses, and clinical research assistants will all be masked to prevent bias in trial procedures and outcome assessment. Once participants are randomized, we will restrict all other pharmacologic analgesic cointerventions except acetaminophen and rescue therapy. Unblinding will not be permitted under any circumstances, as all participants will receive ketorolac and knowledge of the specific dose would not alter clinical management. Other medications that may be part of the patient's treatment plan, such as antiemetics, antibiotics, or antihistamines, can be coadministered. Because the primary outcome is based on a self-reported pain scale, the semistructured survey will be conducted only after outcome assessments are completed. Research assistants can complete the semistructured survey after the 6-hour outcome assessment or, if the patient is discharged, within 7 days by phone or electronically. The trial is registered on clinicaltrials.gov (NCT05641363) [30].

Concomitant Medications

To decrease the confounding effects of other analgesics, we will exclude anyone who, before randomization, received any NSAIDs or opioids in the preceding 6 hours and 4 hours, respectively. We will not allow any other concomitant analgesics (except acetaminophen) administration during the study enrollment (from randomization-60 minutes postrescue therapy if it was required). Patients who have taken acetaminophen before randomization will be eligible to participate. Acetaminophen is widely available for use as an over-the-counter medication analgesic and is effective for mild pain but not for moderate or severe pain. Ketorolac should still be effective when given alongside acetaminophen and has a different mechanism of action. In addition, patients with migraine will be allowed to have coadministration of antiemetics such as metoclopramide or ondansetron. This should not affect our outcomes since all those participants will receive ketorolac (at differing doses) as the only analgesic. All cointerventions will be recorded.

Duration of Treatment and Follow-Up

Ketorolac and a placebo can be given as an IV slow push over 5 minutes with or without a drug pump. Only a single dose will be administered as part of the trial. The effects on pain will be monitored by obtaining baseline pain scores with the vNRS and at times 30, 60, 90, 120 minutes, and at 6 hours if they are still in the hospital. At follow-up, ED and inpatient chart reviews will be completed to determine results of investigations, AEs, total doses of opioids administered in morphine equivalents/kg, all types of NSAIDs administered, dose and frequency for each and the final diagnosis assigned. The survey will be completed within 7 to 14 days once all clinical outcomes are completed (6 hours postintervention).

Primary and Secondary Outcome Measures

Primary Objective Endpoint

Between each low-dose ketorolac group (B1 and B2) and the standard group (A) mean differences in pain as measured on vNRS at 60 minutes. We selected 60 minutes postadministration as the time of our primary outcome assessment after careful consideration and in discussion with our parent and youth collaborators and our clinical pharmacologist coinvestigator. This time point (1) allows children to settle from anxiety associated with IV start, which may confound pain assessment; (2) is an acceptable time point for fair assessment of the analgesic effects of the study drug, with a good balance between onset and peak effect for ketorolac; and (3) is a reasonable timeframe for patients to expect relief from vigorous pain.

Secondary Endpoints

Secondary endpoints include the following:

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1. vNRS score at 30, 90, and 120 minutes as well as 6 hours post administration.
2. Proportion of participants who achieve the 2-point vNRS MID pain score reduction at 60 and 120 minutes.
3. Proportion of participants who change the severity of their baseline pain category at all time points (mild = 0 to 3, moderate = 4 to 6, severe ≥7 on the vNRS)[24].
4. Time to effective analgesia (ie, time at which a vNRS <3 is achieved postintervention).
5. Proportion of participants requiring any rescue analgesia in each trial arm.
6. Total amount administered as measured by morphine equivalent mg/kg within 8 hours of intervention.

Safety Outcomes

Safety outcomes include the following:

1. The proportion of children experiencing any AEs, as reported by caregivers or clinical staff, will be recorded in accordance with the CONSORT Harms checklist [31]. We will solicit specific expected AEs that we found from our SR [32] to be commonly reported with NSAIDs, such as gastric pain. In addition, we will have open-ended questions to collect information on any additional unexpected AEs.
2. Frequency of each specific AE (eg, nausea and vomiting). Time frame is 8 hours post drug administration.

Secondary Objective

Semistructured survey with baseline demographics, closed-ended questions (7-point Likert scale), and open-ended questions will be collated, summarized, and analyzed by subgroup (age and gender). Time frame for completion is 7-14 days post randomization.

Outcome Measurement Tools

We will measure pain using the 11-point vNRS, a validated self-reported acute pain scale for which an anchor-based MID has been established (2 points). The vNRS has demonstrated strong convergent validity, known-groups validity, responsivity, and test-retest reliability in children 6-17 years old with acute pain and in the emergency setting [24,25]. It is rapidly administered by asking, “On a scale of 0 to 10, where 0 means no pain and 10 means the worst pain, how much pain do you have right now?” In a recent systematic review of all acute pain scales for children, the vNRS was the only one to receive a strong recommendation for use in children aged ≥6 years [23]. A phone or electronic questionnaire will be administered after all pain assessments are completed within 7-14 days of enrollment, either in person or by phone or email to assess (1) caregiver knowledge and attitudes toward widely available analgesics; (2) attitudes and fears associated with IV analgesics; and (3) caregiver perceptions of dosing of analgesics as well as AEs associated with them (see Multimedia Appendix 4).

Sample Size Calculations

Based on adult studies [5,9,11,33], we estimated an SD of 1.5 in each group and a mean difference of 0.2. The noninferiority margin of 1.0 is carefully selected to ensure that a rejection of the null hypothesis would: (1) include the effect size that standard dose ketorolac has historically displayed when compared to placebo (relative risk of achieving 50% pain reduction compared to placebo 2.81, 95% CI [1.8-4.4] with number needed to treat of 2.4, 95% CI [1.8, 3.7]), [10] and (2) exclude clinically important levels of inferiority by keeping our margin at 50% of the known MID of 2.0 on the vNRS, ensuring ethical and relevant clinical application. A statistician (JE) using nQuery Software (Insightful Science), calculated a total sample size of 171 participants (57/group), which would allow us to test our noninferiority hypothesis using a one-sided alpha of 0.025, 80% power, and a noninferiority margin (Δ) of 1.0. Since our primary outcome is short-term (60 minutes) and we are testing a single dose of ketorolac, we expect very few patients withdrawals or loss to follow-up. However, we will increase our sample size by 5%, to 60 per group (total 180 participants), to account for any unanticipated withdrawals.

Analysis Plan

(A) Primary Objective Analysis Plan

Data will be described in terms of mean (SD) or 95% confidence limits for normally distributed data and frequency (percentage) in the case of categorical data. The primary endpoint is the difference between the mean reduction in pain scores between each of the low-dose groups (B1, B2) and the standard-dose group (A) 60 minutes post intervention. The primary analysis will include all participants randomized based on the intention to treat analysis and a sensitivity per-protocol analysis will also be performed. A priori, the primary analysis will be adjusted for baseline pain scores using the analysis of covariance (ANCOVA). Generalized estimating equations will be used to examine the impact of baseline pain score on vNRS outcomes across the entire time frame. Noninferiority would be shown if the lower limit of the 95% CI for the between group (groups B1vs A or B2 vs A) differences in the primary endpoint is >1.0. If >5% [34] of our vNRS scores are missing within 120 minutes, we will use multiple imputation to create 5 datasets wherein any missing pain data will be imputed with the Markov chain Monte Carlo method. For secondary endpoints, we will describe those outcomes using descriptive statistics and perform a linear (continuous), logistic, or ordinal regression (categorical or ordinal). If both low-dose strategies are shown to be noninferior to standard dose, we will conduct an exploratory analysis to see if one low-dosing strategy is superior to the other (group B1 vs B2). This will be conducted using ANCOVA to adjust for baseline pain scores and superiority will be determined by a difference that is defined by the MID of 2.0 on the 11-point vNRS. All analyses will be conducted in a blinded fashion. The research pharmacist will provide the trial statistician with anonymized group allocation codes, without revealing the dosing strategies associated with each group. The group identities will remain blinded to the statistician until the first draft of the manuscript with results has been completed. All analyses will be done using SAS (version 9.4; SAS Inc).

AEs profile analysis: the proportion of children experiencing any AEs as reported by caregivers or health care providers will be compared between groups using logistic regression and presented with their corresponding binomial 95% 2-sided CI. The analysis will evaluate the presence or absence of AEs in each group, such as nausea, epigastric pain, or dyspepsia.

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(B) Secondary Objective Analysis Plan

Summative statistics will be used to describe the distribution of responses to closed-ended questions. Answers to open-ended questions will be thematically coded; concepts and themes will be developed using a constant comparative method of analysis. Themes related to knowledge of pain and analgesia, fears of AEs or effectiveness of analgesia, satisfaction or dissatisfaction with current therapy will be categorized, among others. Survey findings will not be included in the primary or secondary outcome analyses and will be presented separately as an exploratory component of the study.

Planned Subgroups

There are 5 planned subgroups:

(1) Underlying painful condition, specifically the 2 most common indications for IV ketorolac, headaches, and acute abdominal pain. No subgroup effect is anticipated given evidence that the cause of pain does not alter response to analgesia [35,36].

(2) Age ≥12 years, since adolescents' drug metabolism differs from younger age groups. We expect a differential treatment effect but are uncertain regarding direction or magnitude.

(3) Gender (grouped as cisgender, transgender, and other): since gender norms are known to impact a patient's perceived sensitivity to pain, we will advise participants and caregivers why sex and gender are important in pain research and then use the recommended [37] 2-step questionnaire to determine biological sex and gender separately. The 2-step survey has been tested in transgender populations and validated over a broader North American population [38-42]. We expect a differential treatment effect but are uncertain regarding direction or magnitude.

(4) Sex (male, female, and intersex): since biological mechanisms, such as sex hormones, influence the nervous system's perception of pain and response to analgesics [43-45]. We expect a differential treatment effect but are uncertain regarding direction or magnitude.

(5) Race and ethnicity: we will collect race and ethnicity data using the standard Canadian Institute for Health Information data questionnaire, with 2 questions on Indigenous identity data standard and race-based data standard [46]. We expect a differential treatment effect but are uncertain regarding direction or magnitude (see Table 1).

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Table 1. Summary of outcomes and analysis.

Objectives	Outcome measure	Hypothesis	Analysis
Primary efficacy outcome[a]			
Pain relief	Pain level as reported by participants on an 11-point vNRS[b] score at 60 minutes post administration of trial drugs.	Ketorolac given at 0.5 mg/kg/dose up to 10 mg or at 0.25 mg/kg/dose up to 30 mg will be noninferior to standard dose ketorolac	Intention to treat analysis using ANCOVA[c]
Safety outcome			
Group differences in proportion of AEs[d]	The proportion of children experiencing AEs related to study drug administration	Participants who receive low dose will have fewer AEs than those who receive standard dose	Regression analysis
Secondary outcomes			
Efficacy			
Pain relief at all time points	Between group differences in pain score at all study time points at 30, 90 and120 minutes	Low dose will be noninferior to standard dose at all time points.	GEE[e]: adjusted for baseline pain scores
Pain relief by the MID	Proportion who achieves a 2-point vNRS reduction at 60 and 120 minutes	Low dose will be noninferior to standard dose ketorolac regimens in reducing pain by the 2-point MID[f] on vNRS	Regression analysis
Pain category change	Proportion of participants who change their baseline pain category at all time points (mild 1 to 3, moderate 4 to 6, severe ≥7 on vNRS)	No difference between low dose and standard dose ketorolac in pain category change at all time points	Regression analysis
Time to achieve mild or no pain level	Time to effective analgesia as measured by the time when vNRS of <3 is achieved	No difference between all ketorolac dosing arms.	Cox regression analysis
Rescue analgesia	Proportion of participants requiring any additional analgesia in each trial arm	No difference between all ketorolac dosing arms	Regression analysis
Opioid sparring	Total amount of opioid administered within 8 hours of intervention	No difference between all ketorolac dosing arms	Regression analysis
Safety			
AEs frequency	Frequency of each specific AE related to study drug administration	There will be more AEs associated with standard dose ketorolac compared to low dose regimens	Regression analysis
Subgroups			
Underlying condition	Proportion of patients with headaches and acute abdominal pain	No subgroup effect is anticipated given prior evidence [35,36]	Regression analysis
Sex assigned at birth	Proportion of male, female, and intersex	Differential treatment effect	Regression analysis
Gender	Proportions of genders (as defined by participant)	Differential treatment effect for girl or woman compared to boy or man gender.	Regression analysis
Age	Dichotomized to 6-11 years vs 12-17 years	Differential treatment effect based on age	Regression analysis
Race and ethnicity	Proportion of participants in each race and ethnicity category	Differential treatment effect based on race and ethnicity	Regression analysis
Sensitivity analysis			

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Objectives	Outcome measure	Hypothesis	Analysis
Per-protocol analysis	Completed for the Primary and Safety outcomes	The primary intention to treat analysis results will remain robust	ANCOVA Regression analysis

[a]Sample size calculation is based on the primary efficacy outcome.

[b]vNRS: 11-point verbal Numerical Rating Scale.

[c]ANCOVA: analysis of covariance

[d]AEs: adverse events.

[e]GEE: generalized estimating equations.

[f]MID: minimal important difference.

Frequency of Analysis

The Data Safety Monitoring Board (DSMB) will be provided with a masked comparison between treatment groups with respect to the AEs at the intervals of their choosing. We will inform the DSMB of all related and unexpected serious adverse events within 7 days of their occurrence. At the DSMB's request, they can receive the associated *P* values for differences in AEs per group. They can further request unmasking. The DSMB board will be completely independent from the trial steering committee and will have a clinical ED physician, a clinical researcher, and a biostatistician who are not associated with or trial sponsor, principal investigators, or had any input on study methodology.

Patient and Caregiver Advisor Involvement

Patient and caregiver engagement has been integrated throughout the design and conduct of the KETODOSE trial. In alignment with the Canadian Institute of Health Research strategy, we collaborated with a parent advisor (KB) and a youth advisor (MN) from the early stages of protocol development. Our youth and parent advisor provided feedback on the clarity and tone of the survey questions to ensure they were age-appropriate and understandable for caregivers, children, and adolescent participants.

During protocol development, the original plan was to assess the primary outcome (pain reduction) at 2 hours postdrug administration. However, following feedback from both the youth and parent advisors, who emphasized the importance of capturing earlier, meaningful pain relief in the ED context, the primary outcome time point was changed to 60 minutes. This adjustment reflects their input that fast-acting analgesia is a priority for patients and families in acute care settings. Ongoing engagement is planned during the dissemination phase, where our advisors will be invited to codevelop plain-language summaries and caregiver-facing educational materials based on the trial results.

Trial Day-to-Day Operations

A study coordinator with experience in Health Canada drug trials will work with principal investigators (ME and LG). Clinical Research Assistants and research nurses will be available to recruit from 8 AM to 9 PM. We will present the study to staff physicians in the Pediatric ED, General Pediatrics, and Pediatric Surgery so they are aware of the study eligibility criteria and how to contact the study team members. Our research nurse will perform daily rounds in the ED and on the wards during clinical rounds to ask and remind the clinical team of any potential participants. The clinical team will ask potential participants if they would like to be approached by research personnel since they may be eligible for the KETODOSE trial. If the patients agree, they will be approached by research staff to check eligibility. Eligibility will then be confirmed with the treating physician or principal investigators, or both. If confirmed, the details of the study will be discussed with the patient and caregiver.

Children and caregivers will be consented and assented for participation in the trial, including the follow-up survey. Once caregivers' consent and participants' assent, the research nurse will obtain the drug kit from the ED drug dispensing machine and assign them the drug kit with the smallest subsequent number. Data will be prospectively collected on baseline characteristics, including age, sex, gender, baseline pain severity (vNRS), type of pain, location, and duration of pain and associated symptoms. Following randomization, the study drug kit containing the study drug vials with information on dosing will be administered to the patient by the research nurse or bedside nurse with the clinical research assistant's help. Each patient will receive a single dose of IV ketorolac and 2 doses of normal saline as outlined in the intervention section above. Time 0 (baseline) will be considered the time at which study drug administration has been completed. Pain assessments will be conducted at 30-, 60-, 90-, and 120-minute intervals following study drug administration. A chart review will be performed approximately one week after the index visit to identify any return visits to the ED and document the reasons for representation, as well as abstract all data regarding other analgesia administered during the enrollment visit.

Safety Oversight

Safety oversight will be under the direction of a DSMB composed of individuals with the appropriate expertise, including trial methodology, epidemiology and biostatistics, and a pediatrician or a pediatric surgeon. Members of the DSMB will be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data for both trials in this study. The DMSB will operate under the rules of an approved charter terms of reference, that will be reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be defined. The DSMB will provide its input to the principal investigators and the Study coordinator.

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The DSMB may also provide input to the HiREB and Health Canada if requested.

Trial Monitoring

Trial conduct will be actively monitored by the study team at McMaster Children's Hospital. A study coordinator will oversee daily screening, enrollment, data collection, and protocol adherence. Additional monitoring procedures were completed by Hamilton Health Sciences Research Office, including review of REDCap data entry, verification of informed consent, compliance with dosing and outcome measurement protocols, and documentation of any protocol deviations or AEs. Study drug kits will be tracked, and adherence logs will be maintained. Weekly reviews of trial operations are conducted by the principal investigators and study coordinator, and drug accountability will be overseen by the research pharmacy.

Ethical Considerations

This trial was reviewed and approved by the HiREB, affiliated with McMaster University and Hamilton Health Sciences (see Multimedia Appendix 5). The study adheres to all ethical standards for research involving human participants, as outlined in the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans, and the principles of the Declaration of Helsinki. Written informed consent was obtained from all participants' parents or legal guardians before enrollment, and assent was obtained from children aged 7 years and older. Participants were informed of their right to withdraw at any time without any impact on their clinical care. Privacy and confidentiality were strictly maintained throughout the study. All participant data were deidentified before analysis and stored securely in a password-protected local database (REDCap) [47] stored at Hamilton Health Sciences, Population Health Research Institute. Only authorized study team members had access to identifiable data. Identifying information was stored separately from study data in compliance with institutional data privacy standards. As this trial involved children, a potentially vulnerable population, special care was taken to ensure that consent was freely given, and that families had sufficient time and opportunity to discuss participation with an adult substitute decision maker before deciding to enroll. In addition, mature minor consent was used in this trial and capacity to consent was assessed by the research team and assented by the caregiver or substitute decision maker. Participants who completed the follow-up survey received a CAD $5 (US $3.7) gift card as a token of appreciation for their time. No other financial incentives were provided for study participation.

Results

The KETODOSE trial received funding in June 2022 from the Core Builder's Grant, Department of Pediatrics, McMaster University. We received ethics approval from the Hamilton Integrated Research Ethics Board in April 2023 and a Health Canada No Objection Letter in January 2023 (see Multimedia Appendix 6). Our first enrollment was on May 23, 2023, at McMaster Children's Hospital, Hamilton Health Sciences. At the time of this protocol submission, from July 2023 to April 2025, we have enrolled 170 participants. We expect to complete recruitment by June 2025, with data analysis commencing in July 2025. Trial results are expected to be submitted for publication in Winter 2026.

The main challenge we encountered was that many participants were excluded due to having received NSAIDs within 6 hours before recruitment, since many participants received ibuprofen prior to recruitment. While shortening that dosing gap to 3-hour would increase recruitment, we felt that a 6-hour washout period between NSAID doses is important to ensure that our intervention effect is not confounded by a recent NSAID treatment. This decision was discussed in the interim DSMB safety and futility analysis, and it was suggested to continue the trial without modification since the trial was feasible and progressing well.

Discussion

The KETODOSE trial addresses a critical evidence gap in determining optimal ketorolac dosing for common acute pain indications in the ED, where current practices have relied largely on adult data and expert opinion. Should our findings demonstrate that lower-dose regimens (0.25 mg/kg up to 30 mg and 0.5 mg/kg up to 10 mg) are noninferior to standard dosing, this would provide the first high-quality evidence to support dose de-escalation in children with acute pain. Such findings could validate the common, but unproven, practice of using a 10 mg ceiling dose in children. Moreover, this trial tests whether ceiling dose or per-kilogram dosing is the driver of analgesic effectiveness. If 0.5 mg/kg up to a maximum of 10 mg is found to be noninferior to the standard 0.5 mg/kg up to 30 mg regimen, yet superior to 0.25 mg/kg up to 30 mg by the MID, this would suggest that a higher per-kilogram dose combined with a lower ceiling dose may represent the optimal ketorolac strategy for children, balancing efficacy with reduced drug exposure.

In preparation for this trial, we conducted and published [48] a systematic review and meta-analysis of 4 databases and trial registries in early 2022 to identify any RCTs regarding ketorolac dosing. We identified four RCTs that included 392 adult participants. Studies compared standard dose ketorolac (30 mg) to either mid-dose ketorolac (15-20 mg) or low-dose ketorolac (10 mg). Most trials had small sample sizes and used a single dose of IV ketorolac [5,9,11], with the exception of one study that used intramuscular ketorolac.[33] All trials used the 100-mm visual analogue scale to measure their primary outcome pain level at 1 hour (3 trials) or 4 hours (1 trial) [11] postintervention. Four trials with 196 participants compared IV ketorolac 30 mg to 15-20 mg, with a nonsignificant mean difference of 1.03 mm (95% CI –2.45 to 4.5). Two trials with 116 participants compared ketorolac 30 mg to 10 mg and found a nonsignificant mean difference of 1.55 mm (95% CI –2.42 to 5.53) favoring the 30 mg dose. There was consistency across all trials and an I^2 of 0%. This suggests that, for adults with acute pain, there is no clinically or statistically meaningful difference between lower doses of ketorolac and standard doses, and that an analgesic ceiling to ketorolac is reached at 10 mg in adults. However, there were no published pediatric trials or registered ongoing trials on trial registries.

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The KETODOSE trial has several key strengths. First, it is the first randomized, double-dummy, quadruple-blind trial to rigorously evaluate different IV ketorolac dosing strategies in a pediatric population presenting with acute pain. Second, the trial is designed with a clinically meaningful and conservative noninferiority margin of 1.0 on the 11-point vNRS, representing 50% of the established MID. This tight margin ensures that any declaration of noninferiority will reflect truly comparable clinical effectiveness, thereby supporting safe and ethically sound dose reduction decisions. Third, the primary outcome time point at 60 minutes was carefully selected in collaboration with caregivers and pharmacologic experts to balance drug onset with clinical practicality, enhancing the relevance of results to ED settings. The inclusion of multiple secondary outcomes, such as time to effective analgesia, opioid sparing, and AEs, further strengthens the clinical applicability. Fourth, the mixed-methods component, capturing caregiver perceptions and attitudes toward analgesics, offers insights into the patient-family experience, which is critical for future implementation and guideline uptake.

Despite these strengths, several limitations merit consideration. As a single-center trial, generalizability to other settings may be limited, particularly where baseline analgesic practices or patient populations differ. Our strict exclusion of children who had recently received NSAIDs, while necessary to avoid confounding, reduced enrollment and may affect the applicability of findings to real-world scenarios where pre-hospital ibuprofen use is common. Nonetheless, the decision to maintain a 6-hour NSAID washout was supported by our DSMB and prioritized internal validity.

We will disseminate trial findings through peer-reviewed publications, presentations at national pediatric and emergency medicine conferences, and targeted knowledge translation products such as evidence-based dosing tools and caregiver-facing educational materials. We also aim to collaborate with national pediatric emergency networks to support widespread adoption and inform future studies comparing ketorolac with other nonopioid analgesics. Ultimately, this trial will contribute urgently needed data to optimize ketorolac use in children, with the potential to improve pain management outcomes while promoting safer prescribing for children with acute pain.

Conclusions

The KETODOSE trial will provide rigorous evidence comparing standard and low-dosing strategies for IV ketorolac in children with an acute painful condition, seen and treated in the ED. Using a randomized, double-dummy, quadruple-blind, noninferiority design with a conservative margin anchored to the validated MID, this study directly tests whether dose de-escalation strategies (0.25 mg/kg up to 30 mg; 0.5 mg/kg up to 10 mg) achieve analgesia comparable to the current standard (0.5 mg/kg up to 30 mg). If noninferiority is demonstrated, findings will support safer prescribing with lower drug exposure, reduce unwarranted practice variation, and inform ED protocols, caregiver education, and future multicenter studies comparing ketorolac with other analgesics. Regardless of outcome, the results will fill a critical evidence gap and guide clinicians, policymakers, and regulators toward more consistent, evidence-based pain management for children.

Acknowledgments

This study would not have been possible without the support of the Department of Pediatrics at McMaster Children's Hospital, the clinical staff of the Pediatric Emergency Department, the Research Office and the Population Health Research Institute at Hamilton Health Sciences for their funding and support throughout the conduct of this trial. We would also like to acknowledge the Population. In addition, we would like to acknowledge Myla Novak, our youth advisor, on her review of outpatient-facing consent forms and surveys. Generative AI was not used for conceptualization, methodology, sample size calculations, or any creation of patient-facing study materials or data collection or analysis or drafting of manuscripts. This trial was competitively funded by the peer-reviewed Department of Pediatrics, McMaster University, Core Builder's Grant for CAD $100,000 (US $73,000).

Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Authors' Contributions

ME and LG performed conceptualization and funding acquisition. ME, LG, RC, SA, KB, AH, ML, SSZ, and LT contributed to methodology and grant development. ME performed investigation, created study materials, obtained regulatory approvals, and provided overall supervision. RC performed project administration, supervised staff, and managed data curation and validation with ME. KB served as caregiver advisor and contributed resources. ME, LG, and ML provided resources. The Population Health Research Institute, Hamilton Health Sciences, provided software and storage. LT supervised formal analysis at the St. Joseph's Research Institute Biostatistical Unit. ME wrote the original draft. All authors reviewed and edited the manuscript.

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Multimedia Appendix 1
SPIRIT checklist.
[PDF File (Adobe PDF File), 130 KB - resprot_v14i1e76554_app1.pdf]

Multimedia Appendix 2
Ketorolac tromethamine product monograph.
[PDF File (Adobe PDF File), 588 KB - resprot_v14i1e76554_app2.pdf]

Multimedia Appendix 3
Consent forms.
[DOCX File , 327 KB - resprot_v14i1e76554_app3.docx]

Multimedia Appendix 4
Patient and caregiver survey.
[PDF File (Adobe PDF File), 87 KB - resprot_v14i1e76554_app4.pdf]

Multimedia Appendix 5
Ethics certificate.
[PDF File (Adobe PDF File), 627 KB - resprot_v14i1e76554_app5.pdf]

Multimedia Appendix 6
Health Canada no objection letter.
[PDF File (Adobe PDF File), 270 KB - resprot_v14i1e76554_app6.pdf]

Multimedia Appendix 7
Peer review report by the Core Builder Team Grant Committee, Department of Pediatrics at McMaster University (Canada).
[PDF File (Adobe PDF File), 212 KB - resprot_v14i1e76554_app7.pdf]

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Abbreviations

AE: adverse event
ANCOVA: analysis of covariance
CONSORT: Consolidated Standards of Reporting Trials
DSMB: Data Safety Monitoring Board
ED: emergency department
GEE: generalized estimating equations
HiREB: Hamilton integrated Research Ethics Board
IV: intravenous
MID: minimally important difference
NSAID: nonsteroidal anti-inflammatory drug
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
vNRS: verbal Numerical Rating Scale

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Protocol

Effectiveness of the Essential Coaching Postpartum Digital Health Solution on Parenting Self-Efficacy, Mental Health, Well-Being, and Parenting Outcomes: Protocol for a Randomized Controlled Trial

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Abstract

Background: The transition to parenthood requires adjustments to new norms and expectations. While there is significant focus on the parenting transition for birthing parents (persons with a uterus), nonbirthing parents (parents who do not give birth, including fathers, gender-diverse parents, adoptive parents, or nongestational coparents) are less supported. Preventive education via SMS text messaging can fill a health service gap and provide timely, standardized, evidence-based information. The Essential Coaching Postpartum program includes 6 weeks of evidence-based daily SMS text messages on topics such as infant care, normal development, parental mental health, and self-care, with streams designed for birthing parents (Essential Coaching for Every Mother) and nonbirthing parents (Essential Coaching for Every Partner).

Objective: The primary objective of this study is to compare the effectiveness of Essential Coaching Postpartum to standard care on parenting self-efficacy, mental health (ie, depression, anxiety, and stress), well-being (ie, general distress and sleep), and parenting outcomes (ie, relationship satisfaction and coparenting) among first-time nonbirthing parents in Nova Scotia, Canada. The secondary objective is to compare the effectiveness of Essential Coaching Postpartum to standard care among first-time birthing parents in Nova Scotia. The exploratory objective is to compare the effectiveness of Essential Coaching Postpartum to standard care among first-time parent dyads (ie, both birthing parent and nonbirthing parent) in Nova Scotia.

Methods: This will be a randomized controlled trial. A total of 166 first-time birthing parents and 166 first-time nonbirthing parents from Nova Scotia will be recruited and randomly assigned to the intervention or control arm. The intervention arm will receive standard care plus the Essential Coaching Postpartum digital health solution, which consists of twice-daily SMS text messages in the first 3 weeks and daily messages in the next 3 weeks. The control group will receive standard care. Messages are personalized based on the infant's age and the parent's self-selected feeding preference (ie, breast or chest feeding, formula feeding, or combination feeding). The first message is sent on the second evening after birth, with parents being eligible to enroll up to 7 days post partum. Participants will complete questionnaires assessing parenting self-efficacy, mental health, well-being,

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and parenting outcomes at baseline (enrollment after birth), 6 weeks post partum (after the intervention), and 6 months post partum (follow-up).

Results: Recruitment for this study started in June 2025 and is currently ongoing. As of September 15, 2025, 11 birthing and 5 nonbirthing parents have been recruited.

Conclusions: We anticipate that providing parents with SMS text messages (ie, Essential Coaching Postpartum) during the 6-week postpartum period to complement standard care will improve parenting self-efficacy, mental health, well-being, and parenting outcomes.

Trial Registration: ClincalTrials.gov NCT06996067; https://www.clinicaltrials.gov/study/NCT06996067

International Registered Report Identifier (IRRID): PRR1-10.2196/78209

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KEYWORDS

mobile health; mHealth; parents; SMS text message; postpartum

Introduction

Background

The transition to parenthood is a transformative period that requires physical, emotional, and social adjustments to new norms and expectations. While there is significant focus on the transition for birthing parents (persons with a uterus) [1], nonbirthing parents (parents who do not give birth, including fathers, sexual-minority parents, adoptive parents, or nongestational coparents) are less supported in the transition to parenthood [2,3]. Perinatal mental health and psychosocial adjustment challenges are common among both parents, which can have significant impacts on parenting relationships and child outcomes [4,5]. Higher parenting self-efficacy, defined as a parent's perception of their ability to execute tasks associated with raising a child [6], has been associated with improvement in many outcomes for both parents and children, including lower parental anxiety and depression and fewer behavioral problems in children [7]. Even in uncomplicated pregnancies and births, parents may struggle with developing their parenting self-efficacy [8] and report anxiety and depression symptoms [9-12]. Poor parental mental health is known to be comorbid and can adversely impact the interparental relationship, leading to relationship dysfunction and negatively impacting child outcomes [13]. By contrast, high parental self-efficacy in one parent is associated with higher parenting self-efficacy in the other [14]. Thus, it is essential to identify ways to support all parents during the early postpartum period to improve individual, couple, and family outcomes.

In Canada, recommendations for postnatal care vary by province, with no standardization of care, education, or support across the country [15]. In Nova Scotia, the recommendations for birthing parents are to have a comprehensive postpartum assessment with their health care provider at approximately 6 to 8 weeks after birth [15]. While there is focus on family-centered care, there are no specific follow-up recommendations for the nonbirthing parent, leading to a significant gap in support. Families should be offered postpartum depression screening at 2 weeks post partum, 6 to 8 weeks post partum, and 4 months post partum [15]. However, this does not always occur in practice [16].

The lack of formal support during the postpartum period is a sharp shift from the intense monitoring that occurs near the end of pregnancy, when birthing people often meet with health care providers on a weekly basis [17]. After a person gives birth, this access to perinatal follow-up care is reduced significantly to only once or twice in the first year, with the primary assessment occurring typically at approximately 6 weeks post partum [18]. The amount and type of care a family receives post partum may depend on whether their obstetric care provider was a physician or a midwife, whether they have a primary care provider, whether they are considered to have high needs, or whether they have identified health concerns for themselves or their infant [15]. The care for a nonbirthing parent during this period is often nonexistent, with nonbirthing parents reporting feeling invisible to health care providers [19], leading to a gap in access to information and support during this critical period for new parents.

An innovative strategy that can be used to support parents is mobile health, defined as the use of mobile devices to transmit health content and services [20]. Parents already use their mobile phones to access internet-based information during the perinatal period [21,22]. SMS text messaging can be an ideal strategy for reaching and supporting parents because it allows access to information anytime, anywhere; moreover, the messages can deliver evidence-based information consistent with the infant's developmental age [23]. Preventive education via SMS text messaging can fill a health service gap and provide timely, standardized, evidence-based information.

To address this need, our team developed and evaluated an SMS text messaging program, Essential Coaching for Every Mother, in which we demonstrated improved parenting self-efficacy and reduced postpartum anxiety in first-time birthing parents [24-26]. A limitation of the original program was that it focused only on birthing parents, excluding nonbirthing parents. Thus, we recently developed Essential Coaching for Every Partner to focus on nonbirthing parents, which complements the information provided in Essential Coaching for Every Mother by delivering evidence-based information directly to nonbirthing parents via SMS text messaging during the first 6 weeks of the postpartum period [27]. The Essential Coaching Postpartum program (inclusive of all types of parents) includes 6 weeks of evidence-based daily SMS text messages on topics such as

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infant care, normal development, parental mental health, and self-care and was designed in collaboration with parents and postpartum health care providers based on evidence-based information [28-31]. The goal of Essential Coaching Postpartum is not to replace face-to-face contact with health care providers but rather be an adjunct to standard care with specialized information targeting the unique needs of new parents. The aim of this study is to evaluate the effectiveness of Essential Coaching Postpartum on nonbirthing parents, birthing parents, and parent dyads in Nova Scotia.

Objectives

The primary objective is to compare the effectiveness of Essential Coaching Postpartum with standard care on parenting self-efficacy, mental health (ie, depression, anxiety, and stress), well-being (ie, general distress and sleep), and parenting outcomes (ie, relationship satisfaction and coparenting) among first-time nonbirthing parents in Nova Scotia.

The secondary objective is to compare the effectiveness of Essential Coaching Postpartum with standard care on parenting self-efficacy, mental health, well-being, and parenting outcomes among first-time birthing parents in Nova Scotia.

The explorative objective is to compare the effectiveness of Essential Coaching Postpartum with standard care on parenting self-efficacy, mental health, well-being, and parenting outcomes among first-time parent dyads (ie, both birthing parent and nonbirthing parent) in Nova Scotia.

Hypotheses

Primary Hypothesis

Our primary hypothesis is as follows: nonbirthing parents who receive Essential Coaching Postpartum will have higher parenting self-efficacy, better mental health (ie, lower scores for depression, anxiety, and stress), greater well-being (ie, lower distress scores and better sleep scores), and higher parenting outcomes (ie, higher relational satisfaction and coparenting) at 6 weeks post partum than those who receive standard care.

Secondary Hypotheses

Our secondary hypotheses are as follows: (1) birthing parents who receive Essential Coaching Postpartum will have higher parenting self-efficacy, better mental health, greater well-being, and greater parenting outcomes at 6 weeks post partum than those who receive standard care; (2) nonbirthing parents who receive Essential Coaching Postpartum will have higher parenting self-efficacy, better mental health, greater well-being, and greater parenting outcomes at 6 months post partum than those who receive standard care; and (3) birthing parents who receive Essential Coaching Postpartum will have higher parenting self-efficacy, better mental health, greater well-being, and greater parenting outcomes at 6 months post partum than those who receive standard care.

Exploratory Hypotheses

Our exploratory hypotheses are as follows: (1) parent dyads who receive Essential Coaching Postpartum will have higher parenting self-efficacy, better mental health, greater well-being, and greater parenting outcomes at 6 weeks post partum than those who receive standard care; and (2) parent dyads who receive Essential Coaching Postpartum will have higher parenting self-efficacy, better mental health, greater well-being, and greater parenting outcomes at 6 months post partum than those who receive standard care.

Methods

Study Design

A 2-group, parallel-arm randomized controlled trial (RCT) will be conducted to evaluate the effectiveness of Essential Coaching Postpartum on parenting self-efficacy, mental health (ie, depression, anxiety, and stress), well-being (ie, general distress and sleep), and parenting outcomes (ie, relationship satisfaction and coparenting) among first-time birthing and nonbirthing parents across Nova Scotia. The intervention will be compared to standard care that is currently being provided across Nova Scotia. This study follows a protocol similar to the original evaluation of Essential Coaching for Every Mother [32].

Ethical Considerations

This study has been approved by the IWK Health Research Ethics Board (1031429) and is registered with ClinicalTrials.gov (NCT06996067). The CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist [26] will be followed to enhance reporting quality for this eHealth intervention trial.

All participants will be asked to provide consent via REDCap (Research Electronic Data Capture; Vanderbilt University) [33], a secure web application for building and managing web-based surveys and databases, followed immediately by the baseline survey. Participants who do not complete the consent form or baseline survey will be considered to have withdrawn from the study.

To maintain confidentiality, all study data will be identified using a study number unique to each participant. Contact information will be collected via TextIt (Nyaruka) [34], a platform used to create and manage 2-way mobile messaging applications, which will be kept separate from survey data collected via REDCap to protect confidentiality.

To encourage survey completion, participants will be offered an honorarium for their time. Electronic gift cards worth CAD $5 (US $3.62) will be provided for each completed survey at baseline, 6 weeks post partum, and 6 months post partum. Participants who complete all 3 surveys will be entered into a draw for an electronic gift card worth CAD $250 (US $181.10). Four separate draws will be held: one each for the birthing parents in the control and intervention groups and one each for the nonbirthing parents in the control and intervention groups.

Setting

This study will be conducted in Nova Scotia. In 2023, there were 6930 births in the province, with 3464 occurring in Halifax (primarily at IWK Health) [35]. There is a lack of standardized, universal postpartum support for new parents across the province. The Public Health Early Years program provides prenatal and postnatal support to all new parents giving birth

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in Nova Scotia. The *Loving Care* book series, developed by the Nova Scotia Department of Health and Wellness in partnership with Public Health Services, is offered after birth to provide information to new families about what to expect [28,29]. Families may also be offered a postnatal home visit with a nurse to provide support, including community and health referrals, guidance on infant care, and bonding. If more support is indicated, families are offered the enhanced home visiting program, which offers home visits from a community home visitor until the child turns 3 years of age [36]. Furthermore, 16% of people in the province do not have a primary care provider, resulting in a significant and growing number of newborns being referred to mobile "unattached newborn clinics" to receive care and support during the postpartum period [37,38].

Patient Partnership

Four patient partners from diverse backgrounds and experiences as birthing and nonbirthing parents are involved in all aspects of planning, executing, and disseminating the work, following best practices in patient partnership.

Eligibility Criteria

Participants will be recruited prenatally and postnatally. To pre-enroll prenatally, eligible birthing parents will (1) be pregnant (>28 wk) with their first child, (2) understand English, (3) have a mobile phone with SMS text messaging functionality and a data plan, and (4) live in Nova Scotia. Eligible nonbirthing parents will (1) have a pregnant (>28 wk) partner (ie, the birthing parent) expecting their first child or will be expecting their first child via an alternative method (eg, adoption or surrogacy), (2) understand English, (3) have a mobile phone with SMS text messaging functionality and a data plan, and (4) live in Nova Scotia. Participants who pre-enroll prenatally will only be considered enrolled and assigned a study number once they text "birth" to the study mobile phone number and are randomly assigned.

To enroll postnatally, eligible birthing parents will (1) be early postpartum (<7 d) with their first child, (2) understand English, (3) have a mobile phone with SMS text messaging functionality and a data plan, and (4) live in Nova Scotia. Eligible nonbirthing parents will (1) be early postpartum (<7 d) with their first child, (2) understand English, (3) have a mobile phone with SMS text messaging functionality and a data plan, and (4) live in Nova Scotia.

Participants (both birthing and nonbirthing parents) will be excluded if they (1) have a newborn who dies or is expected to die before leaving the hospital; (2) have no access to a mobile phone, either personal or shared; (3) are unwilling to receive SMS text messages; (4) decline participation or withdraw; or (5) participated in a previous iteration of this project (eg, development or evaluation). Parents are not required to participate as dyads to be inclusive of all family compositions; however, involvement of the other parent, if applicable, will be encouraged. Participants who do not fully complete the baseline survey will be considered withdrawn from the study. If the participant was randomly assigned to the intervention, they will continue to receive the messages, but no further data will be collected from them.

Recruitment

Parents will be recruited through social media, posters, and in-person outreach (eg, clinics and the family newborn unit). Social media advertisements will be used to recruit parents who are more than 28 weeks pregnant or within 7 days post partum; in addition, parents will be recruited on the birth unit and the family newborn unit at IWK Health, where print posters will be displayed in the patient rooms. Additional outreach strategies may include promotion through public health services, family resource centers, media campaigns, other hospitals across Nova Scotia, and word of mouth. A research team member may also approach families at relevant clinics or units at IWK Health if a nurse within their circle of care has received approval from the family to be approached for research. Participants who contact us by texting "pregnant" to the study mobile phone number when they are less than 28 weeks pregnant will be sent a follow-up message once they reach 28 weeks, until the required sample size is achieved.

Screening and Baseline

Interested participants will complete a standardized SMS text message script for the eligibility screening process. During prenatal screening, participants will be assessed for preliminary eligibility, and those who qualify will be asked to text the study mobile phone number within 7 days of giving birth to be enrolled. At this stage, participants will be encouraged to provide their partner's mobile phone number, if applicable, so that the partner's interest can be assessed. Once a birthing person gives birth or enrolls post partum, they will complete additional screening questions to confirm eligibility.

After the birth of their child, all interested participants will complete the postpartum eligibility and randomization processes. During this stage, additional information will be collected, including the newborn's name, date of birth, and feeding preference (ie, breast or chest feeding, formula feeding, or combination feeding). Participants will then be randomly assigned to the intervention or control group and asked to complete the consent form and baseline survey. If a parent dyad is participating, the nonbirthing partner will be sent an SMS text message after randomization to indicate their preferred type of feeding messages and to complete the consent form and baseline survey. Linked parent dyads will always be placed in the same intervention group. If dyad members complete the screening process separately and are inadvertently assigned to different groups, both parents will be moved to the intervention group.

Randomization

Participants will be randomly assigned in a 1:1 ratio to either the intervention or control group using the TextIt platform's "split randomly" function. This function distributes contacts equally across pathways, ensuring allocation to either the intervention or control condition. Randomization will occur only after a participant has given birth.

Follow-Up Assessments

All participants will be asked to complete follow-up surveys at 6 weeks post partum and 6 months post partum. To encourage completion, reminder SMS text messages will be sent every

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other day for up to 2 weeks (a maximum of 6 reminders) or until the survey is submitted. After day 14, an email will be sent to participants who have not yet completed the survey as a final reminder. If no email address was provided, an extended SMS text message will be sent instead. Participants may also be contacted by phone to encourage survey completion within this 2-week window.

Blinding

Due to the complex nature of Essential Coaching Postpartum, participants cannot be blinded and will be informed of their group allocation. To minimize blinding of personnel in relation to data collection, no hospital staff (eg, nurse midwives, physicians, and other health care providers) will be aware of participant involvement in the study. This is feasible because Essential Coaching Postpartum is delivered directly to participants' personal mobile phones, with no in-person intervention. The research team will be aware of participant allocation and will track data collection but will not be involved in the randomization process, which occurs automatically through the TextIt platform. As all study procedures are conducted remotely through a preconfigured system, the research team has no direct interaction with participants, thereby reducing any risk of influencing participant responses.

Sample Size

Sample size calculations were conducted with the assistance of a statistician for both birthing and nonbirthing parents to ensure adequate numbers for each group. As the parent dyad objective is exploratory, no formal calculation was performed for dyads. In the original RCT [25], the baseline parenting self-efficacy score for birthing parents was 35, which is considered clinically low. This value was used for this analysis. On the basis of the SD from the original RCT [25], an improvement of 4 points in the intervention group at 6 weeks is anticipated, which would no longer be classified as clinically low. A total sample size of 141 parents is therefore required, assuming 80% power and a 2-tailed α of .05. As no comparable evidence is available for nonbirthing parents, we will apply the same sample size estimation (n=141) for nonbirthing parents. Allowing for 15% attrition, we plan to recruit a minimum of 166 birthing parents and 166 nonbirthing parents.

Program Content and Design

Essential Coaching Postpartum consists of 2 separate but related evidence-based programs: Essential Coaching for Every Mother, which provides SMS text messages for the birthing person, and Essential Coaching for Every Partner, which provides SMS text messages for the nonbirthing parent. Both were co-designed with parents and postpartum health care providers [24,27] and are aligned with the *Loving Care* book series [28-31]. Essential Coaching Postpartum includes 59 SMS text messages: 2 messages per day in the first 3 weeks and daily messages in the next 3 weeks. Topics include postpartum mental health, self-care, postnatal follow-up, feeding, infant concerns, cord care, well-baby care, normal development, crying, and safe sleep. Parents can choose to receive messages related to breast or chest feeding, formula feeding, or combination feeding and can change their preference at any time. Messages are timed according to the infant's date of birth and personalized with the infant's name. All messages are free to receive; however, optional embedded links may generate data charges if accessed.

All participants, regardless of group allocation, will receive a welcome message from Essential Coaching Postpartum as well as reminders to complete the surveys. Participants may withdraw from the study at any time by texting "stop" to the study mobile phone number, after which they will no longer receive messages or be asked to complete additional surveys.

Intervention Group

Participants will receive the standard education provided at the hospital where they give birth. After enrollment, participants in the intervention group will receive messages until 6 weeks post partum. Birthing parents will receive Essential Coaching for Every Mother, and nonbirthing parents will receive Essential Coaching for Every Partner. Figure 1 provides examples of messages from each program. Messages are automatically scheduled according to the infant's date of birth, beginning on the second evening after birth. Participants who enroll later will receive messages starting from their enrollment date (eg, someone who enrolls on day 5 will not receive messages from days 2-4). TextIt will be used to program and schedule the messages, and Twilio (Twilio Inc) [39] will serve as the secure gateway for sending and receiving messages. Participants are not restricted from seeking additional postpartum support outside of the study. They will continue to have access to standard perinatal care, including mental health services available through primary care providers and community resources.

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Figure 1. Essential Coaching for Every Mother (ECEM) and Essential Coaching for Every Partner (ECEP) example SMS text messages.

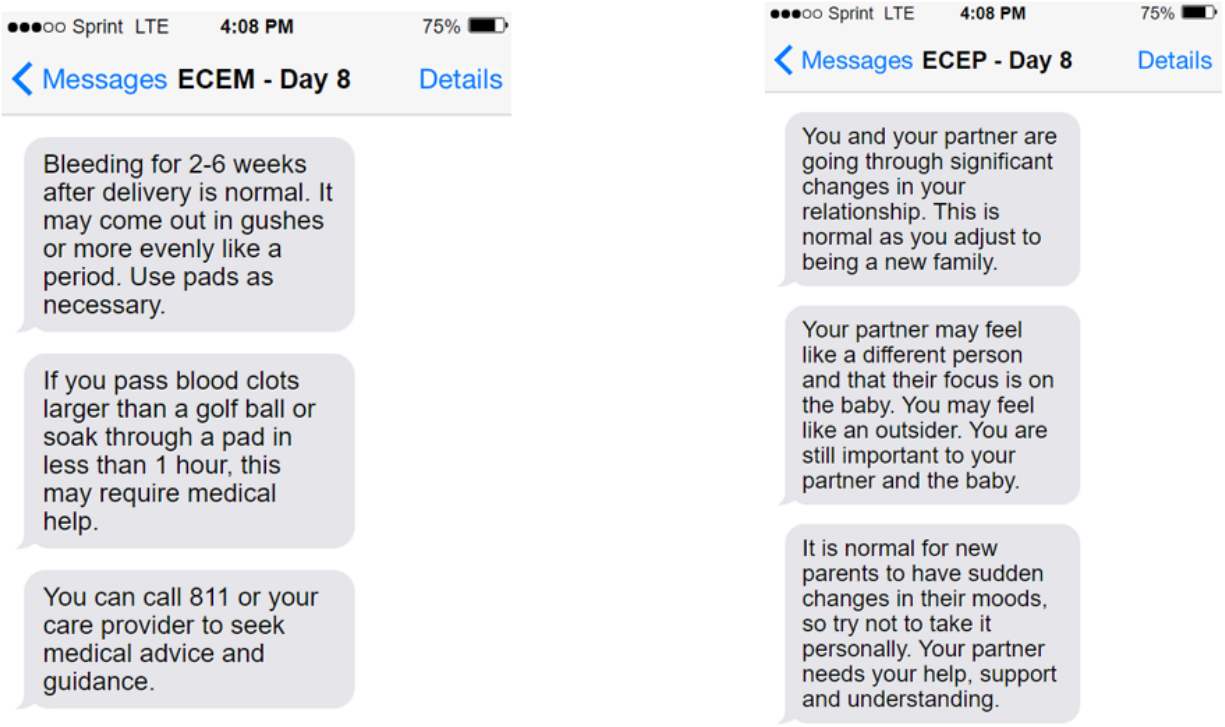

Control Group

Participants will receive the standard education provided at the hospital in which they give birth. After enrollment, participants in the control group will not receive any Essential Coaching Postpartum SMS text messages. They are not restricted from seeking additional postpartum support outside of the study. They will continue to have access to standard perinatal care, including mental health services available through primary care providers and community resources. At enrollment, 6 weeks post partum, and 6 months post partum, participants will be sent an SMS text message with a link to complete the follow-up survey.

Study Measures

Data will be collected from parents using self-reported web-based surveys administered through REDCap [33]. Table 1 outlines the timing of outcome collection. At baseline, demographics will be collected, including age, occupation, marital status, and educational level, as well as newborn information such as birth weight and delivery method. At 6 weeks post partum, a follow-up survey will be conducted to collect data on types of postpartum support sought and received, health concerns, and feeding behavior. All standardized questionnaires listed in Table 1 will be administered at baseline, 6 weeks post partum, and 6 months post partum.

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Table 1. Timing of measurement and outcome measurement questionnaires.

Outcome domains and variables	Outcome measure	Baseline (enrollment after birth)	After the intervention (6 wk postpartum)	Follow-up (6 mo postpartum)
Descriptive				
Demographics	Parent and infant characteristics[a]	✓		
Effectiveness				
Parenting self-efficacy	Karitane Parenting Confidence Scale [40]	✓	✓	✓
Postpartum depression	Edinburgh Postnatal Depression Scale [41]	✓	✓	✓
Postpartum anxiety	Postpartum Specific Anxiety Scale [42]	✓	✓	✓
Postpartum stress	Postpartum Childcare Stress Checklist [43]	✓	✓	✓
General distress	Depression, Anxiety, and Stress Scale [44]	✓	✓	✓
Sleep	PROMIS[b] Short Form Sleep-Related Impairment (4a) and PROMIS Short Form Sleep Disturbances (4a) [45]	✓	✓	✓
Coparenting	Brief Coparenting Relationship Scale [46]	✓	✓	✓
Relationship satisfaction	Couple Satisfaction Index-4 [47]	✓	✓	✓
Implementation				
Program satisfaction	Participant satisfaction survey and health service use[a]		✓	

[a]Researcher generated.

[b]PROMIS: Patient-Reported Outcomes Measurement Information System.

Primary Outcomes

Parenting self-efficacy will be measured using the Karitane Parenting Confidence Scale [40]. This 15-item tool assesses perceived self-efficacy among parents of infants aged birth to 12 months of age and has acceptable internal consistency (Cronbach α=0.81) and test-retest reliability (r=0.88) [40]. A cutoff score of 39 or less (out of 45) indicates clinically low perceived parenting self-efficacy [40].

Secondary Outcomes

Secondary outcomes will be collected using validated self-report measures, as follows:

Postpartum anxiety symptoms will be measured using the Postpartum Specific Anxiety Scale [42], a 51-item valid and reliable tool for assessing anxiety during the first 6 months post partum. A score of 112 or greater indicates clinical levels of anxiety [42].

Postpartum depression symptoms will be measured using the Edinburgh Postnatal Depression Scale [41]. A score greater than 9 (out of 30) suggests possible postpartum depression in both birthing and nonbirthing parents.

Postpartum stress will be measured using the Postpartum Childcare Stress Checklist [43], an 18-item scale assessing parental perceptions of childcare stress in the early postpartum period. Responses are summed to produce a score from 0 to 23, with higher scores indicating a higher level of postpartum childcare stress.

General distress will be measured using the Depression, Anxiety, and Stress Scale [44], a 21-item instrument that assesses the emotional states of depression, anxiety, and stress. Postnatal distress is classified by percentile scores, with total score (between 0 and 63) and a score for the three subscales (between 0 and 21), categorized into 5 severity ranges: normal, mild, moderate, severe and extremely severe, with higher scores indicated greater severity.

Sleep will be measured using the Patient-Reported Outcomes Measurement Information System (PROMIS) Short Form Sleep-Related Impairment (4a) and PROMIS Short Form Sleep Disturbances (4a) [45]. Sleep-related impairment measures perceptions of alertness, sleepiness, and tiredness during usual waking hours, as well as perceived functional impairments during wakefulness associated with sleep problems or impaired alertness. By contrast, sleep disturbance measures perceptions of sleep quality, sleep depth, and restoration associated with sleep. Higher scores indicate greater sleep-related impairment and disturbance.

Relationship satisfaction will be measured using the Couple Satisfaction Index [47], a 4-item scale assessing satisfaction in a relationship. Higher scores indicate greater satisfaction,

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whereas a score less than 13.5 is associated with notable dissatisfaction.

Coparenting will be measured using the Brief Coparenting Relationship Scale [46], a validated 15-item instrument assessing 5 coparenting dimensions of agreement: closeness, child exposure to conflict, coparenting undermining, endorsement of partner's parenting, and labor division [46]. Scores range from 0 to 60, with higher scores indicating greater coparenting.

We will also assess the implementation of Essential Coaching Postpartum using output data from the Twilio and TextIt platforms (eg, the number of SMS text messages sent, the number of SMS text messages delivered, error messages, unsubscription rates, and link clicks) as well as open-ended feedback from participants collected at 6 weeks post partum.

Data Analysis

Data will be analyzed on an intention-to-treat basis. Demographic characteristics, including parental age, marital status, educational level, and delivery method (eg, vaginal or cesarean), will be summarized using means and SDs or percentages, as applicable. Postnatal health care contacts for the parent and infant, health concerns, and feeding behavior will also be reported using means and SDs or percentages, as applicable. Any significant differences in baseline characteristics, assessed using chi-square tests or Mann-Whitney *U* tests, will be adjusted for in subsequent analyses. A P value of <.05 will be considered statistically significant for all outcomes.

For the primary and secondary outcomes, analysis of covariance will be used to determine whether scores differ between the 2 groups, with adjustments for pretest scores and any significant baseline characteristics. For the exploratory analysis, dyadic actor-partner interdependence multivariate multilevel modeling will be used to examine each dyad member's relationship to primary and secondary outcomes after accounting for other explanatory variables. For implementation data, quantitative responses will be reported, and thematic analysis [48] will be conducted to describe participants' experiences with Essential Coaching Postpartum.

Results

Study recruitment began in June 2025 and is anticipated to be completed within 12 months. As of September 15, we had enrolled 11 birthing parents and 5 nonbirthing parents.

Discussion

Anticipated Findings or Significance

We anticipate that providing parents with SMS text messages during the postpartum period to complement standard care will improve parental outcomes. Specifically, we expect that parents (both birthing and nonbirthing) who receive Essential Coaching Postpartum will demonstrate higher parenting self-efficacy and lower depression, anxiety, and stress scores at 6 weeks post partum and 6 months post partum than those who receive standard care. We also anticipate improvements for parents in general distress, sleep, relationship satisfaction, and coparenting outcomes. In addition, for parent dyads in which both members receive Essential Coaching Postpartum, we expect higher parenting self-efficacy, greater relationship satisfaction, and stronger coparenting scores as well as lower depression, anxiety, and stress scores at 6 weeks post partum compared to dyads who receive standard care.

Comparison to Previous Work

Building on the previous success of Essential Coaching for Every Mother, the Essential Coaching Postpartum program expands to provide both birthing and nonbirthing parents with postpartum support during the immediate 6-week postpartum period. Essential Coaching for Every Mother was evaluated in a feasibility study [26] and an RCT [25], both of which found that it improved parenting self-efficacy and reduced postpartum anxiety, particularly among first-time parents. Birthing parents were also extremely pleased with the program, with most willing to recommend it to other parents. Since its development in 2019 and evaluation in 2021, modifications have been made, including updates based on the 2023 *Loving Care* book series [28,29], as well as the creation of a nonbirthing partner version, Essential Coaching for Every Partner [27].

While other digital health solutions exist for new parents, the Essential Coaching Postpartum SMS text messaging program is unique. It differs from other digital health solutions in three important ways: (1) it is based on Nova Scotia–specific information, is aligned with the *Loving Care* book series [28,29], and was reviewed by Nova Scotian parents and postpartum health care providers; (2) it focuses more on the provision of information within SMS text messages through longer texts (approximately 800 characters), in addition to offering links to local resources; and (3) it provides parental and newborn care information related to the immediate 6-week postpartum period to both parents, with twice-daily text messages in the first 3 weeks and daily messages in the next 3 weeks. Overall, Essential Coaching Postpartum is designed specifically for the immediate postpartum period and tailored to parents in Nova Scotia, while also providing individualized, evidence-based support for both birthing and nonbirthing parents.

Other perinatal digital health solutions in Canada include SmartMom and SmartParent, which are SMS text messaging programs that provide support for parents during pregnancy and through their child's first year of life. These programs were designed by academic researchers from the University of British Columbia in collaboration with the British Columbia Ministry of Health, British Columbia health authorities, and Perinatal Services BC and in consultation with pregnant individuals and new parents, nurses, physicians, midwives, and experts in maternal and child health [49]. The programs provide 3 messages per week from conception through 1 year post partum, containing evidence-based information and links to support healthy pregnancy, childbirth, transition to parenthood, and infant growth and development [50]. To date, SmartParent has not been evaluated for its impact on parenting self-efficacy or postpartum mental health; however, a protocol was recently published to evaluate SmartMom's impact on prenatal outcomes [51].

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Another existing digital health solution for nonbirthing parents is SMS4Dads, which is an SMS text messaging program developed to support paternal mental health in Australia [52]. SMS4Dads sends fathers SMS text messages from pregnancy through 6 months post partum, focusing on paternal mental and physical health, strategies for building a strong and nurturing relationship with their child, and approaches to developing a strong coparenting relationship with their partner [52]. In a feasibility study involving 520 fathers over 8 months, two-thirds of the fathers accessed the resource links provided in the SMS text messages, and all reported that the messages promoted a positive transition to fatherhood [52]. However, this program is available only in Australia, with future research ongoing to determine its effectiveness [53].

Future Directions

This study will (1) advance understanding of the effectiveness of a parent-targeted intervention for improving parental self-efficacy, mental health, well-being, and parenting outcomes; (2) examine the utility of providing an evidence-based intervention via SMS text messaging; (3) investigate the uptake of a postpartum mental health prevention intervention for parents; and (4) improve the health of families in Nova Scotia, complementing existing care, by closing gaps in standard care offered during the postpartum period.

As next steps, we will first expand the reach of the Essential Coaching Postpartum program by translating it into additional languages, including French, Arabic, and simplified Chinese. Second, we will conduct an implementation study to determine how we can implement the program across Nova Scotia. Finally, we aim to expand to other provinces in Canada, ensuring that the content remains consistent with local postpartum education for both birthing and nonbirthing parents.

Acknowledgments

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Authors' Contributions

Conceptualization: JD, CTC, and JAP (equal)
Data curation: JD
Funding acquisition: JD (lead), CTC, JAP, MB, CLD, DS, and JMG (equal)
Methodology: all authors (JD lead, all other authors equal)
Project administration: JD
Resources: CTC
Supervision: CTC and JAP (equal)
Visualization: JD
Writing—original draft: JD
Writing—review and editing: all authors

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report by IWK Scientific Review Committee, Research and Innovation Advancement, IWK Health Centre (Nova Scotia, Canada).
[PDF File (Adobe PDF File), 383 KB - resprot_v14i1e78209_app1.pdf]

Multimedia Appendix 2
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 7589 KB - resprot_v14i1e78209_app2.pdf]

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Abbreviations

CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
PROMIS: Patient-Reported Outcomes Measurement Information System
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture

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Protocol

A Smartphone App (PRIMI) to Promote Healthy Diet, Physical Activity, and Health Literacy After Childbirth Among Migrant Women: Protocol for a Randomized Controlled Trial

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Abstract

Background: Migrant health, including reproductive health, is an important public health priority. The postpartum period is a critical window for establishing healthy behaviors that can impact long-term health. Mobile health interventions offer a scalable solution, but existing tools are often not culturally or linguistically adapted for diverse populations. To the best of our knowledge, no previous study has evaluated the effectiveness of a culturally targeted mobile health intervention delivered after childbirth to promote a healthy diet and physical activity among migrant women.

Objective: The PRIMI (Promoting Reproductive Health in Migrant Women) trial will determine the effectiveness of a smartphone app (the PRIMI app) on primary (diet quality and moderate-to-vigorous physical activity) and secondary (health literacy, BMI, self-efficacy, and self-rated health) outcomes in first-generation migrant women after childbirth.

Methods: A 2-arm randomized controlled trial will be conducted to examine the effectiveness of the PRIMI app. First-generation migrant women who have given birth within 6 months, are aged 18 years or older, and prefer to receive health-related information in any of the provided languages are eligible to participate in the study and will be recruited through health care services in Sweden. The women will be randomized to the control group (standard care, eg, parental guidance and support within child health care) or the intervention group (PRIMI app+standard care) in a 1:1 ratio. A total of 200 women (100 per group) will be included in the study. A waitlist control strategy will be applied so that women in the control group will receive the PRIMI app after the follow-up measurement at 6 months. Outcomes will be assessed at baseline and at the 6-month follow-up. The PRIMI app, developed within the PRIMI project, is compatible with both Android and iOS. It contains weekly changing themes focusing on physical activity, diet, and health literacy throughout the 6-month intervention period. The app integrates behavior change techniques such as feedback and monitoring, goal setting, and instructions on how to perform the behavior. The app's language

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can be switched among 4 common languages (Arabic, Somali, English, and Swedish), and all textual content can be accessed through audio files for listening. All procedures have been approved by the Swedish Ethical Review Authority (reference 2022-06733-01 and 2024-00135-02).

Results: Recruitment of study participants is planned to begin in September 2025. We anticipate completing recruitment in 2026 and that the results of the PRIMI trial will be available in 2027.

Conclusions: This study will provide novel evidence on the effectiveness of the PRIMI app in promoting healthy behaviors and supporting postpartum health among migrant women. This is highly relevant given the lack of previous comparable studies and the urgent need for tailored postpartum interventions for migrant populations.

Trial Registration: ClinicalTrials.gov NCT06881277; https://clinicaltrials.gov/study/NCT06881277

International Registered Report Identifier (IRRID): PRR1-10.2196/79277

(JMIR Res Protoc 2025;14:e79277) doi:10.2196/79277

KEYWORDS

mobile health; mHealth; telemedicine; behavior change; emigrants and immigrants; postpartum; diet; physical activity; randomized controlled trial

Introduction

Background

International migrants are a growing population in many European countries, including Sweden. Currently, more than 25% of women giving birth in Sweden and more than 20% of women giving birth in Europe are first-generation migrant women [1]. Research suggests that migrant women may face higher risks of adverse health outcomes during and after pregnancy, although the extent of these inequalities may differ according to specific maternal birth regions and health outcomes [2-5]. Therefore, improving migrant health, including reproductive health, is an important public health priority [2,6].

The period after childbirth has been identified as a critical window to promote healthy diet, physical activity, and body weight as excessive postpartum weight retention may have long-lasting effects on later obesity, cardiovascular health, and the outcomes of subsequent pregnancies [7-11]. However, there is a lack of lifestyle interventions after childbirth that target migrant women [8,12,13]. Mobile health (mHealth) interventions have gained a lot of interest as a practical way to deliver lifestyle support, guidance, and individually tailored targets to improve diet quality, physical activity, and BMI [14,15]. However, while such mHealth interventions may provide accessible support regardless of migrant and socioeconomic status [16], concerns have been raised that mobile phone apps are not sufficiently tailored for culturally and linguistically diverse women [17]. This is despite the fact that adequate adaptation of language system and cultural values may increase user engagement and intervention effectiveness through mechanisms such as self-efficacy and health literacy [18]. Specifically, we are unaware of any lifestyle app provided by health professionals to women in Sweden after childbirth or of any scientifically evaluated app tailored to migrant women after childbirth worldwide that targets diet and physical activity. Thus, there is a great need for randomized controlled trials that examine the effectiveness of mHealth interventions to promote healthy diet and physical activity after childbirth in migrant women. This project, the PRIMI (Promoting Reproductive Health in Migrant Women) project, builds on our previous mHealth interventions targeting other populations (eg, pregnant women and adolescents) [19-21] to provide evidence on the effectiveness of a smartphone app on health behaviors after childbirth in migrant women.

Objectives

The aim of this study protocol is to describe the study design and methods of the PRIMI trial. The trial has been registered on ClinicalTrials.gov (NCT06881277). The PRIMI trial will evaluate the effectiveness of a smartphone app (the PRIMI app) in addition to standard care as compared to standard care alone. The outcomes are (1) diet quality (primary outcome), (2) moderate-to-vigorous physical activity (primary outcome), (3) health literacy (secondary outcome), (4) BMI (secondary outcome), (5) self-efficacy (secondary outcome), and (6) self-rated health (secondary outcome) in first-generation migrant women after childbirth. We hypothesize that migrant women who are provided access to the PRIMI app will report better diet quality and more moderate-to-vigorous physical activity compared to those without access to the app.

Methods

The PRIMI App

Context

In Sweden, approximately 25% of women who give birth were born in another country [1]. Apart from Sweden, common maternal birth regions include North Africa and the Middle East (eg, Iraq, Syria, and Iran), sub-Saharan Africa (eg, Somalia, Eritrea, and Ethiopia), and Europe (eg, Poland and Ukraine) [5,22,23]. Although no official statistics are collected on the languages spoken in Sweden, Arabic, Somali, and English are among the most common languages spoken by first-generation migrant women in Sweden. In addition, nearly 90% of all foreign-born women in Sweden have access to a mobile phone [24].

Development of the App

The PRIMI app is a fully automatic, culturally targeted, and comprehensive 6-month smartphone intervention aimed at improving diet quality, physical activity, and health literacy in

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migrant women. Screenshots of the PRIMI app are shown in Figure 1. Users can switch the app's language among 4 options: Arabic, Somali, English, and Swedish. We included Swedish for women who prefer or have acquired sufficient Swedish language skills to use the app. All textual content can be read aloud through audio files. The PRIMI app is compatible with both Android and iOS and is available on the Google Play Store and Apple App Store for individuals with a study-specific user code.

Figure 1. Screenshots of the home screen illustrating a notification for the weekly feedback and monitoring feature, as well as the weekly theme (focusing on diet, physical activity, or health literacy). All participants have access to all content in 4 languages: Arabic, Somali, English, and Swedish.

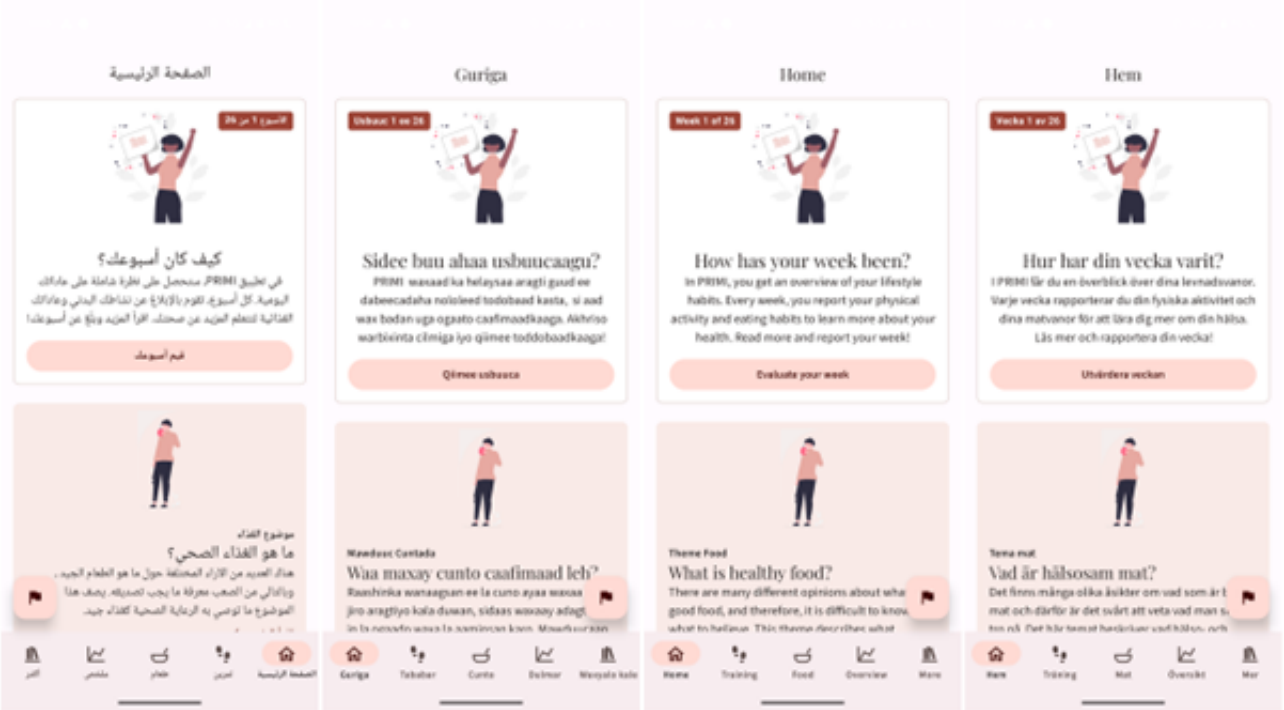

A technical platform built specifically for the PRIMI app was used for its development, which took place in collaboration between the research team and the staff at the Digitalisation Division at Linköping University from 2024 to 2025. All decisions about the specific content and features of the PRIMI app were made by a multidisciplinary and multicultural team with expertise in nutrition, physical activity, behavioral medicine, and health literacy.

While our previous work [25] served as a model for the app's overall structure, the target group was consulted before designing the app's visual and textual content. Thus, individual interviews conducted with health professionals from maternity care and child health care centers, as well as migrant Arabic- and Somali-speaking mothers, informed decisions about the app's content. For example, content was incorporated to address psychological well-being, including information on support groups within child health centers, as the qualitative data were related to loneliness and psychological distress after childbirth. In addition, the content was designed to align with the target group's preference for relatable images and evidence.

The technical platform enabled the research team to continuously edit all content, including translations of texts and audio files into all targeted languages (Arabic, Somali, English, and Swedish). The development was an iterative process involving pilot-testing by collaborators with experience from the Refugee and Migrant Medicine Center in the Region of Östergötland, maternity care, and other health care settings. This was to improve usability and ensure that the app was relevant for the target group rather than for scientific purposes. Quality assurance was further conducted by Arabic- and Somali-speaking research team members.

Evidence-based recommendations from previous research [15,26-28] and key constructs from social cognitive theory [29] informed the app's logic model (Figure 2), meaning that self-efficacy, outcome expectations, goals, and perceived facilitators were addressed through behavior change techniques embedded in the PRIMI app.

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Figure 2. Logic model of how the components of the PRIMI (Promoting Reproductive Health in Migrant Women) app are assumed to activate theoretically driven mechanisms that may explain expected short- and long-term outcomes. CVD: cardiovascular disease.

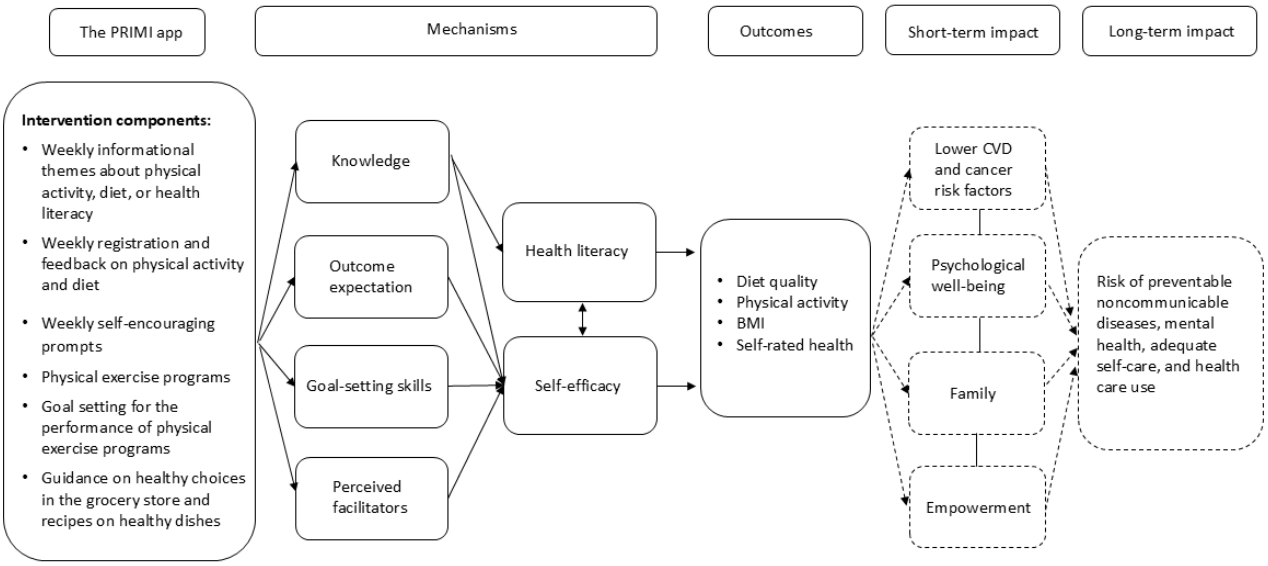

Content and Features

Table 1 provides an overview of the theoretical foundation and core features of the PRIMI app. As in our previous work [25], the app was built around themes that change each week during the 6-month intervention period. A total of 10 themes focus on diet and physical activity, and 5 themes address health literacy. All themes targeting diet and physical activity contain advice based on current guidelines [30] to address subjects such as food and health, energy and nutritional needs during breastfeeding, effects of physical activity, and how the body changes after childbirth. The health literacy themes covered topics such as how health care functions in Sweden, how to find trustworthy sources of health information, and patients' rights in Swedish health care. The selection of topics was based on evidence suggesting that improved general health literacy can empower individuals to make informed health-related decisions [31], aligning with the issues discussed by women and professionals in the qualitative interviews. The vast majority of the themes include pictures or videos to enhance the information.

Table 1. Overview of the theoretical foundation of the PRIMI (Promoting Reproductive Health in Migrant Women) app.

Theoretical construct	PRIMI content[a]
Knowledge	Information is provided through weekly themes and a library
Self-efficacy	A feature for weekly registrations and feedback on behaviors (diet and physical activity), including a progress overview, and weekly cues for self-encouragement
Outcome expectations	Prompts are embedded to encourage reflection on the potential consequences of behavior change
Goals	Instructions on how to set specific, measurable, achievable, relevant, and time-bound goals; a goal-setting feature for PRIMI exercises; and weekly visual feedback on the achievement of goals
Facilitators	Information on how to establish new habits (eg, microhabits), weekly push notifications, recipes for healthy dishes, and (video) guidance on workout programs and healthy choices at the grocery store

[a]The behavior change techniques applied were based on the Behavior Change Technique Taxonomy version 1 [32]: information about health, social, environmental, and emotional consequences of behaviors; feedback and monitoring; identification of the self as a role model; verbal persuasion about capability; focus on past success; pros and cons; goal setting (behavior); action planning; discrepancy between current behavior and goal; behavior substitution; habit formation; prompts and cues; and instructions on how to perform the behavior.

The app also has features such as goal setting, registration with feedback for diet and physical activity, prompts for positive self-talk (eg, encourage users to recognize their efforts), healthy food recipes, supermarket tours, and video-recorded workout programs. Goals refer to the number of workout programs that users want to complete in a week (ie, 1-5), and they can be easily changed by users. The registration with feedback feature includes a prompt to complete a 6-item weekly questionnaire that addresses dietary and physical activity behaviors. When completed, users access feedback that summarizes their responses in terms of diet score and total activity minutes, graphically illustrated with bars and text using a "traffic light" approach (green=reached the recommendation, yellow=almost reached the recommendation, and red=far from reaching the recommendation) as provided by the National Board of Health and Welfare in Sweden [30]. Thus, a green light for physical activity indicates that users have reported at least 150 minutes of moderate-to-vigorous physical activity for that week, whereas a green light for the diet score represents at least 75% of the maximum score based on users' weekly consumption of fruit and vegetables, fish and seafood, and sweets and sugary drinks.

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The PRIMI app additionally contains healthy recipes developed by the Swedish Food Agency (Keyhole-labeled recipes) [33], as well as international healthy dishes developed by the registered dietitians in the PRIMI group. In addition, videos aiming to facilitate health awareness during grocery shopping are provided on the app. The physical activity module contains video-recorded workout programs at 3 levels (basic, intermediate, and advanced) with a Tabata-style interval format.

All content is free and available for all users, who can choose to engage with the app as preferred. Intended use will be defined as at least one engagement session per week where users complete the weekly registration, receive feedback on their health behaviors, and access the weekly theme. Users who accept push notifications will receive reminders 2 to 3 times per week depending on their preferences.

Study Design

The PRIMI trial is a 6-month 2-arm randomized controlled superiority trial (1:1 ratio) examining the effectiveness of an mHealth intervention (the PRIMI app) after childbirth on diet quality, and moderate-to-vigorous physical activity (primary outcome) as well as health literacy, BMI, self-efficacy, and self-rated health (secondary outcome) among first-generation migrant women compared with a waitlist control condition (Figure 3). Stakeholders, including migrant women and health professionals, were engaged during the development of the PRIMI app.

Figure 3. Study design of the PRIMI (Promoting Reproductive Health in Migrant Women) trial.

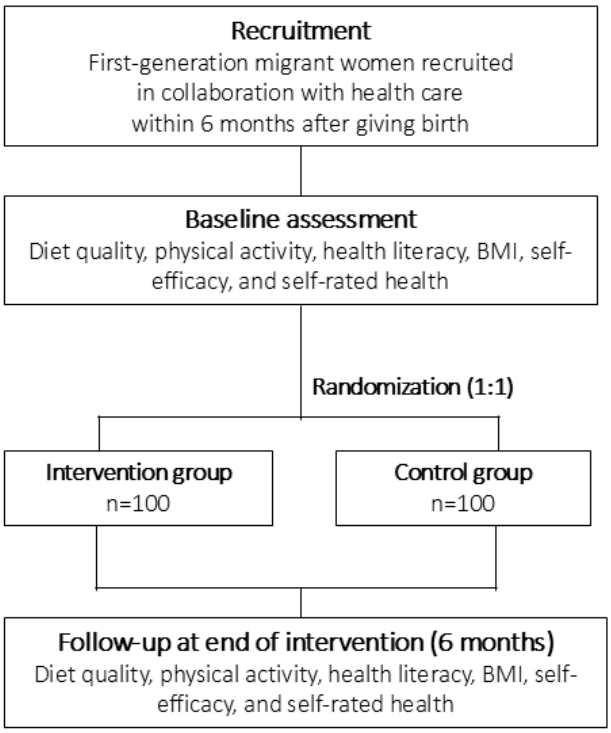

The intervention group will receive standard care plus the PRIMI app for 6 months, whereas the participants in the control group will receive standard care but will be offered the PRIMI app after the 6-month follow-up (waitlist control strategy). Standard antenatal care in Sweden is free of charge for both Swedish-born and migrant women. It typically includes 8 to 9 routine visits during pregnancy and 1 to 2 postpartum visits. After childbirth, care is transferred to child health services, which monitor the development of the child and provide support to the family.

This study protocol follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2025 statement [34] (Multimedia Appendix 1), and the PRIMI trial will be reported according to the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist [35]. Figure 4 presents the outline of the PRIMI trial. Study outcomes will be measured at baseline and at the follow-up 6 months after randomization.

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Figure 4. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) table of enrollment, intervention, and assessment timeline.

Procedures	Study time point			
	Enrollment (0 mo)	Allocation (0 mo)	After allocation (0 mo)	Closeout (6 mo)
Enrollment				
Eligibility screen	✓			
Informed consent	✓			
Allocation		✓		
Interventions				
Intervention		◆———	———◆	
Control		◆———	———◆	
Assessments				
Demographics	✓			
Primary and secondary outcomes	✓			✓
User experience				✓

Eligibility and Recruitment

Eligible women will be recruited through health care (eg, maternal and child health care) throughout Sweden. Inclusion criteria are first-generation migrant women who have given birth ≤6 months before, aged ≥18 years, and who would prefer to receive health-related information in any of the provided languages (ie, Arabic, Somali, English, and Swedish). No exclusion criteria will be applied.

Health care professionals will briefly inform eligible women about the trial. Women who express interest will receive additional information, including contact details for the research team. Informed consent will be obtained by health care professionals during subsequent visits or via the women returning signed consent forms. Inclusion criteria will be formally assessed based on information provided in the baseline questionnaire, which will be delivered digitally to participants via their mobile phones after they have given informed consent.

Recruitment will begin in September 2025, at 3 sites across the regions of Sweden, with each site involving 5 to 10 units. Health professionals (eg, nurses) at each unit will be introduced to the study and its procedures through in-person visits by research team members, who will provide ongoing support throughout the recruitment period. We will continue recruitment until the required number of participants has been reached. However, if recruitment is slow, we will consider additional sites and avenues other than health care channels, such as nongovernmental organizations, associations, and social media.

Randomization and Blinding

Women will be randomly allocated to the intervention or control group after completion of the baseline measurements in a 1:1 ratio (with random block sizes of 2 and 4 to avoid revealing the allocation sequence). The *blockrand* package in the R software (version 4.5; R Foundation for Statistical Computing) will be used for the computerized random number generator. Randomization will be conducted by a statistician not part of the research team, who will remain separate from the research team members responsible for informing participants of their allocation via phone to conceal the allocation sequence. Participants and outcome assessors will not be blinded to the allocation, but the project statistician and analysts will be blinded to group allocation until completion of the analysis. Although the participants and outcome assessors are not blinded to group allocation, steps have been taken to reduce the risk of performance and detection bias. Thus, the self-reported outcomes will be collected using standardized electronic

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questionnaires in the preferred languages of the study participants, reducing assessor influence. When necessary, telephone-based data collection will follow a standardized script to ensure consistency across measurements.

Control Group

Participants allocated to the waitlist control condition will receive standard care. For example, this includes regular visits to a nurse within child health care focusing on child development, vaccinations, parental guidance, and support [36]. Control group participants will be provided access to the PRIMI app upon completing the 6-month follow-up. The choice of comparator was based on the fact that no apps targeting health behaviors after childbirth are currently implemented in routine care in Sweden, as well as the lack of a suitable counterpart (ie, a similar evidence-based app) that could serve as an active control condition [37].

Intervention Group

Women assigned to the intervention group will receive the PRIMI app in addition to standard care. After randomization, intervention group participants will be contacted via phone by a research team member who speaks Arabic, Somali, English, or Swedish based on the participant's preference to guide them through the installation of the PRIMI app.

Primary Outcomes

Diet Quality

Dietary intake will be assessed using a modified version of the National Board of Health and Welfare's survey of health behaviors that has been previously translated and used for Arabic-, Somali-, and English-speaking women and men [25]. We will create a composite dietary quality score using four key dietary indicators based on self-reported data collected through questions addressing intake of (1) vegetables, (2) fruits and berries, (3) sweet beverages, and (4) sweet and savory snacks (Multimedia Appendix 2). The composite score will be calculated using the normalized sum of *z* scores for the 4 dietary indicators, with the scores for intake of sweet beverages and sweet and savory snacks inverted to reflect their negative health effects. Thus, a higher score will indicate better diet quality. A dietary score was assumed to better reflect participants' overall dietary habits rather than individual dietary components.

Moderate-to-Vigorous Physical Activity

Women will report physical activity using a modified version of the physical activity questions in the National Board of Health and Welfare's survey (Multimedia Appendix 2) of health behaviors, which we have previously translated into Arabic, Somali, and English [25]. The survey asks about time spent in moderate and vigorous physical activity separately, and we will combine these data to derive moderate-to-vigorous physical activity as national recommendations on physical activity consider moderate and intense activity combined.

Secondary Outcomes

Health Literacy

Participants will report on their health literacy using the 16-item version of the Health Literacy Survey Questionnaire [38,39], which examines the ability to access, understand, appraise, and apply health information. Participants' electronic health literacy (ie, ability to access, understand, appraise, and apply electronic health information) will be measured using the eHealth Literacy Scale [40].

BMI Measurement

Women will report their weight and height, and BMI will be calculated as weight (kg) divided by height squared (m^2) and will be used as a continuous measure in the analyses. We will also classify BMI as underweight (<18.5 kg/m^2), normal weight (18.5-24.9 kg/m^2), overweight (25.0-29.9 kg/m^2), and obesity (≥30.0 kg/m^2).

Self-Efficacy

A single-item question will be used to measure self-efficacy for following a healthy diet and physical activity. Using an 11-point Likert scale from 0 ("not at all") to 10 ("very much"), participants will be asked how confident they are in following a healthy diet and being regularly physically active given that they want to do that.

Self-Rated Health

Self-rated health will be assessed using the EQ-5D visual analogue scale [41], where participants rate their overall health on a scale from 0 ("worst imaginable health") to 100 ("best imaginable health").

Additional Individual Components of Diet and Physical Activity Outcomes

In addition to the composite diet quality score (primary outcome), we will examine the effectiveness of the PRIMI app on the 4 key diet indicators individually as secondary outcomes (ie, intake of vegetables, fruits and berries, sweet beverages, and sweet and savory snacks). Furthermore, beyond analyzing the effects on moderate-to-vigorous physical activity (primary outcome), we will also assess vigorous and moderate physical activity separately as secondary outcomes. All behavioral measures are presented in Multimedia Appendix 2.

Process Evaluation

User experience data will be collected at the 6-month follow-up by asking intervention group participants about their experiences of the PRIMI app. We will also conduct a process evaluation based on qualitative data collected through interviews with a subsample of women to obtain richer data and a deeper understanding of how the mHealth intervention was perceived and appreciated by the women [42-45].

Furthermore, automatically collected use data will be used to investigate how the app was used by participants, including the number of sessions, the number of registrations, and the time spent on the app.

Demographic Variables

Women will report demographic and descriptive variables such as age, educational attainment, birth country, parity, time since childbirth, and adverse pregnancy outcomes during their last pregnancy.

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Statistical Analysis and Power Considerations

Intervention effects will be analyzed according to the intention-to-treat principle using mixed linear regression models (with a random level for the individual) examining the effect of the group allocation (intervention vs control) on the primary and secondary outcomes. Data analyses will be conducted with available data as well as with missing data imputed using multiple imputations [46]. The primary analysis is the intervention effect on diet quality and moderate-to-vigorous physical activity at the 6-month follow-up adjusted for baseline values as we have done previously [20,21,25] as this procedure has the advantage of being robust to imbalances at baseline and regression toward the mean [47]. Furthermore, all models will be adjusted for age and time since childbirth. We will also consider adjusting for educational attainment and birth region provided that the sample size and distribution of these variables allow for meaningful adjustment (ie, empirical positivity).

We will also conduct a secondary per-protocol analysis including women who have used the PRIMI app (ie, engaged in at least one session) during at least 5 of the 26 intervention weeks. We will also examine whether certain variables moderate (eg, age, parity, educational attainment, birth region, self-efficacy, and health literacy) or mediate (eg, self-efficacy and health literacy) the effect of the PRIMI app on the outcomes.

A total of 100 women (50 per group) will provide at least 80% power (α=.05) to detect a minimally clinically relevant effect size of a 0.35-SD difference in the primary and secondary outcomes; we simulated trials with different sample sizes and parameter variance (k=100 simulations per specification) to find a suitable level whereby there was at least 80% power to detect the relevant effect [48]. It may be argued that smaller effect sizes than this may have limited clinical value, and thus, we consider the sample size sufficient. We aim to recruit 200 women (100 per group) to account for a potential dropout rate of up to 50%. However, we may consider recruiting fewer participants if the actual dropout rate is lower. To prevent dropout, participants will receive a mobile phone SMS text message reminding them about the 6-month follow-up questionnaire a few days before the questionnaire link is sent. Participants who have not completed the questionnaire within a few days will be contacted via phone to be assisted in completing it.

Ethical Considerations

We are not aware of any potential harms related to the PRIMI app. The intervention is designed to promote a healthy diet and physical activity in line with current guidelines and is based on our previous work [20,21]. Furthermore, as we hypothesize that the PRIMI app will have health benefits, it may pose an ethical dilemma not to provide the app to the control group as well. To address this, we will apply a waitlist control group strategy, and women in the control group will be offered the intervention after the trial has ended. This is considered an ethically reasonable choice of comparator. In summary, we believe that the PRIMI project is ethically motivated as there are potential health benefits and no known harms involved. Nevertheless, it is possible that the app may be perceived as stressful among some participants. Such information will be gathered through the process evaluation of user experience data.

Before giving informed consent, all participants will receive both oral and written information about the purpose of the study, its procedures, the voluntary nature of participation, and their right to withdraw from the study at any time without consequences or the need to provide a reason. All data will be anonymized before analysis and securely stored on encrypted servers for at least 10 years in accordance with Swedish legislation, accessible only to research team members involved in the analysis to protect privacy and confidentiality. No compensation will be provided for participation in the study. The PRIMI trial has received ethics approval from the Swedish Ethical Review Authority (reference 2022-06733-01 and 2024-00135-02) and is being conducted in accordance with the Declaration of Helsinki. Any deviations from what is described in this study protocol will be reported on ClinicalTrials.gov and in the manuscript reporting the results of the trial.

Results

Enrollment of study participants is planned to begin in September 2025. We anticipate that the study recruitment will be finalized in 2026 and that the results of the PRIMI trial will be available in 2027. Trial results will be communicated to participating health care units through in-person presentations and written reports. The results will be additionally disseminated through scientific publications, as well as through academic and clinical national and international conferences.

Discussion

Expected Findings

The PRIMI trial will examine whether a novel smartphone app (the PRIMI app) can improve diet quality, moderate-to-vigorous physical activity, health literacy, BMI, self-efficacy, and self-rated health in migrant women after childbirth. The PRIMI trial has several strengths, including the randomized controlled trial design and the broad inclusion criteria, which will increase the generalizability of the findings. Furthermore, the development of the PRIMI app incorporated behavior change theory [29] and empirical evidence [15,26,27] and was informed by the target population as well as practical experience from implementers (ie, health care professionals) [49] to foster acceptability and enhance the potential for positive outcomes. In addition, the various types of data collected on participants' use and experience of the PRIMI app allow for comprehensive investigations into how and why the app may or may not be effective.

However, the conceptualization of migrant women is not straightforward as there is great heterogeneity among groups of people who may share a language but not a culture. Therefore, using language as a proxy for culture may limit the ability to address issues such as values shared within a culture. This is a limitation as the main purpose of targeting is to make messages more effective by incorporating inclusive elements [18]. Nevertheless, focusing on first-generation migrant women

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without applying major exclusion criteria makes the app available to more women and increases generalizability.

The PRIMI trial has several other limitations that should also be considered. First, the primary outcome measures will be self-reported by the study participants. Although the questions are based on established screening questions from the National Board of Health and Welfare and we have used them in the target group previously [25], they may be subject to recall and social desirability bias. Nevertheless, the use of the categorical answer mode has demonstrated greater validity than open-ended answers [50]. Furthermore, although participants in both the intervention and control groups will self-report outcome measures, there is a risk of detection bias as participants who do not complete the follow-up questionnaire will be contacted by the research staff, potentially revealing their group allocation. While we believe that this procedure outweighs the limitations of a higher attrition rate, we will carefully register cases in which follow-up data were collected via phone. Respondent burden was additionally considered when developing the questionnaires. Finally, the intervention period and follow-up of 6 months may be insufficient to detect long-lasting effects on health behaviors, although many mHealth interventions have had shorter intervention periods [51].

The PRIMI trial will provide novel evidence on whether an mHealth app can promote a healthy lifestyle after childbirth among migrant women. This is highly relevant given the scarcity of comparable studies on similar evidence-based mHealth interventions and the critical importance of the period after childbirth for establishing long-term health behaviors. According to a scoping review on interventions designed for pregnant women or mothers of young children to address risk factors for preventable noncommunicable diseases through health literacy, few interventions used technologies for delivery [52]. In fact, none of the included interventions (N=25) that used a mobile phone app for delivery (n=2) targeted women after pregnancy; they focused exclusively on women during pregnancy [53,54]. Furthermore, this review emphasized that interventions specifically targeting vulnerable populations, including mothers from culturally and linguistically diverse backgrounds, are highly needed [52].

Conclusions

If the PRIMI app proves effective, it holds potential for large-scale implementation as an evidence-based intervention program at the national level. This is particularly promising given the widespread access to smartphones regardless of socioeconomic background or migrant status.

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Data Availability

Data sharing is not applicable to this paper as no datasets were generated or analyzed during this study.

Authors' Contributions

PH acquired funding and is the principal investigator for the PRIMI (Promoting Reproductive Health in Migrant Women) trial. PH, VHA, UM, JW, DB, MS, and MJL contributed to the study design. AS, PH, and MS led the development of the app, with substantial contributions to both the overall content and specific areas by MR (physical activity); MS and HH (diet); MJL and JW (health literacy); and BA-S, ASA, MS, and MJL (cultural adaptation). All coauthors provided valuable input that significantly refined the app, and all authors participated in design decisions. PH and VHA designed the statistical analysis plan. AS, MS, MJL, PH, TG, and ASA were involved in establishing contact with health care units for recruitment. Data collection is planned to be conducted by BA-S, ASA, MS, MJL, and AS. AS and PH wrote the first draft of the study protocol, which was reviewed and approved by all authors.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOCX File , 35 KB - resprot_v14i1e79277_app1.docx]

Multimedia Appendix 2
Primary outcome measures.

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[DOCX File , 23 KB - resprot_v14i1e79277_app2.docx]

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Abbreviations

CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
mHealth: mobile health
PRIMI: Promoting Reproductive Health in Migrant Women
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Effects of Communicating Genetic Risk of Type 2 Diabetes and Wearable Technologies on Behavioral Outcomes in East Asians: Statistical Analysis Protocol for a Randomized Controlled Trial

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Abstract

Background: Evidence suggests that the communication of type 2 diabetes (T2D) genetic risk alone has limited effectiveness on facilitating behavioral changes among individuals of European descent. Although the use of wearable devices has been associated with changes in behavior, the effects of combining personalized precision medicine with wearable devices on behaviors related to T2D prevention remain unclear. This study aims to assess the novel effects of T2D genetic risk communication and wearable device functions on objectively measured moderate to vigorous physical activity (MVPA) time among East Asian individuals with overweight or obesity.

Objective: The objectives of this study are to (1) investigate the effects of communicating T2D genetic risk and (2) examine the effects of combining T2D genetic risk communication with wearable device functions such as step goal setting and activity prompts on objectively measured MVPA time among East Asians with overweight or obesity.

Methods: In this parallel-group randomized controlled trial, 355 East Asians with overweight or obesity aged between 40 and 60 years are allocated to 1 of 3 groups: 1 control and 2 intervention groups. Blood samples are used for estimation of T2D genetic risk and tested for metabolic risk markers. T2D genetic risk is estimated based on 113 single nucleotide polymorphisms associated with T2D among East Asians using an established method. All 3 groups receive a Fitbit device. Both intervention groups will receive T2D genetic risk estimates along with lifestyle advice, but one of the intervention groups will receive additional Fitbit functions: step goal setting and prompt functions. The intervention materials are delivered weekly using WhatsApp and monthly via email. The primary outcome is MVPA time, which is objectively measured with the built-in accelerometer of the Fitbit Inspire 3 and will be assessed at baseline, immediately after the intervention, 12 months after the intervention, and at 6-month follow-up. Secondary outcomes include other parameters, such as sedentary time, BMI, systolic and diastolic blood pressure, 5 metabolic risk markers, handgrip strength, sleep, activity calories, self-reported physical activity, self-reported fruit and vegetable consumption, smoking status, and psychological variables.

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Results: This study was funded in January 2023. Data collection for baseline assessments began in February 2023. Formal data analysis started in April 2025 after the 6-month follow-up assessments were completed.

Conclusions: To the best of our knowledge, this study will be the first randomized controlled trial to combine T2D genetic risk communication with wearable device functions in any population. Novel findings will be used to inform future lifestyle modification strategies for T2D. We plan to provide a comprehensive report on this study by publishing this analysis plan before the completion of data collection.

Trial Registration: ClinicalTrials.gov NCT05524909; https://www.clinicaltrials.gov/study/NCT05524909

International Registered Report Identifier (IRRID): DERR1-10.2196/65012

(JMIR Res Protoc 2025;14:e65012) doi:10.2196/65012

KEYWORDS

type 2 diabetes; physical activity; genetic risk; wearable technology; randomized controlled trial; movement behavior; statistical analysis plan

Introduction

Trial Background and Rationale

Currently, approximately 500 million individuals worldwide live with diabetes, of whom 90% have type 2 diabetes (T2D) [1]. By 2045, the number of patients with diabetes is projected to reach 170 million in China alone [2,3]. Therefore, developing strategies to address the increasing prevalence of T2D cases remains a key public health priority across East Asian countries.

Compared to White populations, East Asian populations have a higher risk for diabetes despite having lower mean BMI levels. An early study conducted among Hong Kong Chinese adults demonstrated that diabetes risk increased at a BMI of approximately 23 kg/m^2, which did not conform to BMI cutoff values applied to White populations [4]. Subsequent findings from 2 Asian American cohort studies further supported the notion that individuals of East Asian descent have an elevated risk for T2D, as they have greater adiposity than their White counterparts within each BMI category [5,6]. Epidemiological evidence from Hong Kong also revealed that individuals aged between 40 and 60 years accounted for 40% of incident T2D cases [7] and that increased hazard ratios for cardiovascular diseases, cancer, and all-cause mortality were observed among middle-aged adults with prediabetes [8]. Therefore, it is crucial to develop interventions specifically targeting East Asian middle-aged adults with overweight or obesity, given their higher susceptibility to T2D.

Being overweight or obese is a major risk factor for T2D and is typically characterized by prolonged sedentary time and chronic physical inactivity. New exercise guidelines have since been established to promote reductions in sedentary behavior and increases in moderate to vigorous physical activity (MVPA) [9]. Evidence from recent observational and isotemporal substitution studies has demonstrated the benefits of increased accelerometer-derived MVPA time on T2D, ranging from lowered incidence of T2D-related vascular complications to improved insulin sensitivity and glycemic control [10-13]. Taken together, these findings highlight the key role of MVPA in improving health among individuals with overweight or obesity who are at risk for T2D.

The defining characteristic of T2D is the decline in pancreatic beta cell functions, caused primarily by chronic insulin resistance. Although research has uncovered a plethora of risk factors implicated in T2D progression, such as age, diet, physical inactivity, alcohol consumption, BMI, and family history [14], the multifactorial nature of T2D makes it challenging for any single approach to accurately screen for and predict disease risk among individuals at risk.

Owing to advances in genomics and precision medicine, technologies for assessing genetic predisposition to noncommunicable diseases have become increasingly accessible. Coupled with recent genome-wide association studies, these advances have enabled the discovery of genetic variants that exhibit significant associations with T2D among East Asian populations. Accurate genomic sequencing can facilitate genetic risk communication for T2D on an unprecedented scale. This could provide researchers with potential insights into the impact of T2D genetic risk communication on behavioral changes among East Asians.

However, evidence from multiple studies has indicated that communication of genetic risk has limited impact on behavioral changes [15], raising concerns regarding the overall effectiveness of this approach. Nonetheless, these studies share several limitations: (1) genetic risk was communicated without considering behavioral change theories; (2) MVPA, when used as a primary outcome, was often measured through self-report-based measures; (3) genetic risk for polygenic diseases was calculated using singular genetic variants; and (4) most of the studies focused on individuals of European descent, limiting the generalizability of the findings to East Asian populations.

Considering the steady growth of the wearable device market, consumer-based physical activity (PA) trackers have shown promise in serving as a low-cost platform for intervention studies.

Contemporary wearable devices often feature streamlined interfaces and burnished designs and encourage PA behaviors through goal setting and self-monitoring. For researchers, wearables provide objective measurements of lifestyle behaviors while retaining mass appeal for smooth implementation. Previous randomized controlled trials and systematic reviews

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have shown that interventions incorporating a goal-setting function (eg, at least 10,000 steps per day) in wearables showed high efficacy in decreasing BMI and supporting long-term weight management among participants with overweight or obesity [16-18]. A recent meta-analysis reported that using wearables as a key intervention modality led to an average increase of 1800 daily step counts, 40 minutes of walking time, and 6 minutes of MVPA time [19]. However, communication of genetic information was not included in the intervention, and the interplay between wearable device functions and T2D genetic risk communication remains unclear.

Herein, we present the detailed data analysis plan for, to the best of our knowledge, the first East Asian–focused randomized controlled trial using wearable device functions in conjunction with genetic risk communication to facilitate changes in MVPA. The wearable device (Fitbit Inspire 3) used in the trial includes a built-in accelerometer, enabling the collection of objectively measured PA data. Fitbit functions such as activity goal setting and activity prompts will play a central role in promoting and sustaining MVPA. By combining personalized precision medicine with wearable device functions, the trial aims to provide novel insights into lifestyle modification strategies.

Trial Objectives and Hypothesis

The main objectives of this trial are to (1) investigate the impact of T2D genetic risk communication and (2) examine the effects of combining T2D genetic risk communication with theory-based wearable device functions (eg, step goal setting and activity prompts commonly found in consumer-grade wearables) on wearable device–measured MVPA time among East Asian middle-aged adults with overweight or obesity.

We hypothesize that T2D genetic risk communication alone will result in minimal increases in objectively measured MVPA time, whereas combining T2D genetic risk communication with wearable device functions will significantly increase MVPA time not only at the 12-month postintervention time point but also at the 6-month follow-up.

Methods

Recruitment

Participants were recruited across various communities in Hong Kong primarily via flyer distribution, local minibus advertisements, emails, and word of mouth. Recruitment materials included the study title, research question, brief study information (eg, study period, duration, and key particulars), participant incentives, inclusion and exclusion criteria, sign-up methods, and contact information for the research team.

Flyers were distributed alongside pull-up banners within local communities, and minibus advertisements were placed on the back of local minibus seats. Recruitment emails were circulated within local organizations and community centers. In brief, flyer distribution (183/355, 51.5%) and minibus advertisements (142/355, 40%) accounted for most of the recruited participants, while emails (19/355, 5.4%) and word of mouth (11/355, 3.1%) accounted for the remainder. Interested individuals were asked to complete an online screening form when signing up.

Trial Design

Overview

Figure 1 shows the timeline and protocol of the study. This parallel-group randomized controlled trial commenced on May 11, 2023, and aims to involve 355 participants. Each participant is randomly allocated to 1 of 3 groups: 1 control group and 2 intervention groups (intervention arm 1 and intervention arm 2). The inclusion of 2 intervention arms allows examination of the effects of T2D genetic risk communication alone as well as the combined effects of T2D genetic risk communication and wearable device functions. All participants are asked to wear a Fitbit device throughout the study period for measuring outcome data.

Participants in intervention arm 1 receive a Fitbit device, T2D genetic risk estimates, and a digital lifestyle leaflet. Participants in intervention arm 2 also receive these materials and have their Fitbit devices calibrated such that their daily step goal is 10% higher than their baseline step count. In addition, they receive activity prompts through the Fitbit device. The control group receives only a Fitbit device. The daily step goals for participants in intervention arm 2 are set 10% above baseline based on relative efficiency and higher feasibility. Chapman et al [20] reported that implementing a 50% increase in baseline step count did not result in greater walking activity compared to a 10% increase. Moreover, only 5% of participants did not meet their step goals when given a 10% step goal increase over baseline compared to 16% who were given a 50% increase [20]. On the basis of these findings, implementing a 10% increase over baseline was considered more feasible and effective for motivating participant behavior.

This trial has been registered at ClinicalTrials.gov (NCT05524909).

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Figure 1. Overall study timeline and protocol for genetic risk communication and wearable device interventions. CVD: cardiovascular disease; PA: physical activity; T2D: type 2 diabetes.

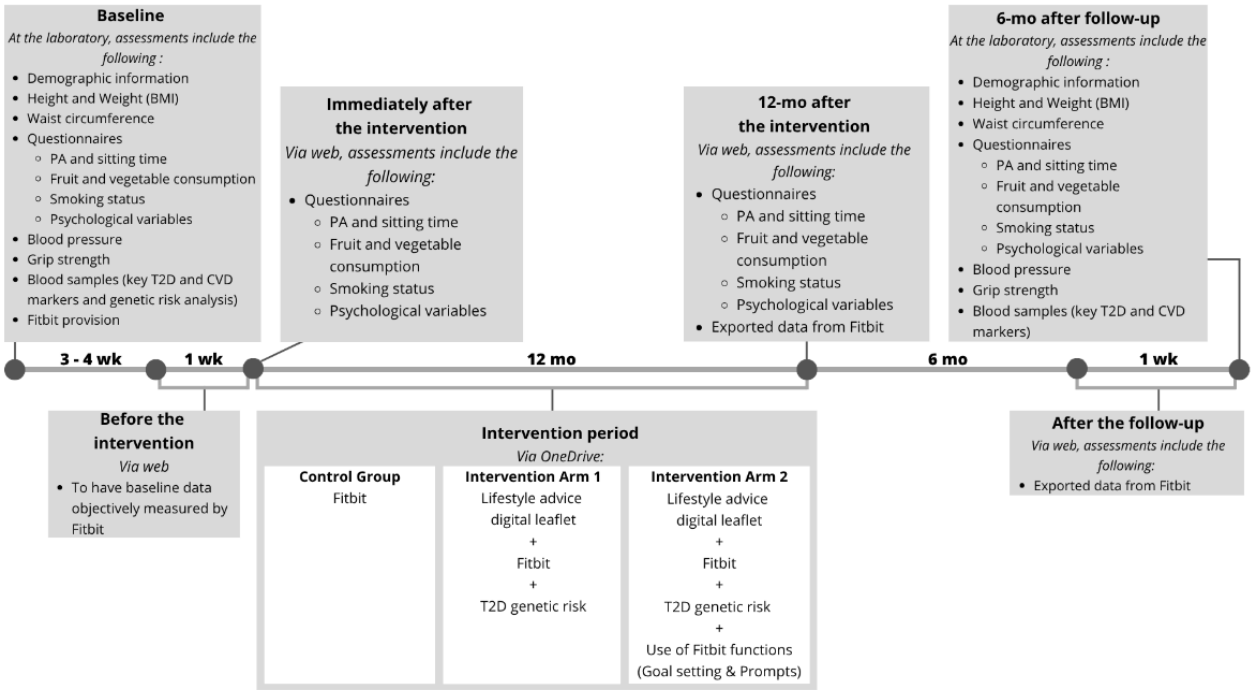

Inclusion Criteria

Eligibility criteria for participants were (1) being aged between 40 and 60 years, (2) being of East Asian ancestry, (3) having a BMI ≥23 kg/m^2 (according to the World Health Organization BMI cutoffs for Asians), (4) being able to comprehend English or Chinese, and (5) owning a smartphone.

Exclusion Criteria

Participants were excluded if they (1) were unable to perform routine daily PAs (as determined by the Physical Activity Readiness Questionnaire), (2) had prior experience with consumer-directed genetic testing, (3) had been diagnosed with any type of diabetes, or (4) were participating in any exercise-related intervention study.

Intervention

T2D genetic risk estimates, together with a digital lifestyle leaflet, are delivered weekly via WhatsApp (Meta) and monthly via email, as results from prior studies suggest that genetic risk information can promote optimal health behavior changes when communicated at regular and repeated intervals [21,22]. A total of 113 single nucleotide polymorphisms (SNPs), with corresponding odds ratios and allele frequency values for T2D genetic risk, were derived from a genome-wide association study that identified SNPs associated with T2D risk among East Asians [23]. The estimation procedure has been illustrated in our published protocol and supplementary materials of our previous report [24,25]. Participants would then receive their estimated 10-year and remaining lifetime genetic risk for developing T2D, as well as a dichotomized genetic risk category in comparison to the average population risk for T2D (according to the participant's age and sex): "increased genetic risk" and "no increased genetic risk." The digital leaflet contains detailed information on the definition and health impacts of T2D, as well as lifestyle advice on 4 major T2D risk factors (ie, PA, diet, weight management, and smoking) as recommended by the World Health Organization.

Participants in intervention arm 2 receive two unique Fitbit features—(1) step goal setting and (2) activity prompts—in addition to the T2D genetic risk estimates and digital leaflet. Each participant's step goal is set by staff to be 10% higher than their baseline step count, calculated as the average of the 7-day preintervention Fitbit data. The "Reminder to move" function is used as a prompt to interrupt prolonged sedentary periods. When the wearer has not accumulated more than 250 steps within an hour, the device vibrates and displays a reminder message. We have specified an operation period for this function, and the device reminds participants 10 minutes before each hour between 9 AM and 10 PM. All Fitbit functions unique to this intervention can be accessed and modified only by researchers via the Fitbit online dashboard system.

Randomization

A block randomization approach has been adopted. The randomization list was generated using a computer program by a staff member who had no prior knowledge of participant information. Each block consisted of 6 allocations, with 2 participants assigned to each of the 3 groups per block.

Group allocation has been concealed from study staff until the 7-day preintervention period, during which staff would have prepared the corresponding intervention materials for participants. The participants will be initially blinded to group assignment; however, blinding will not be possible once the intervention is delivered. A statistician blinded to group assignment will perform outcome analyses using deidentified data.

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Sample Size

To ensure sufficient statistical power, we intend to recruit 355 East Asian participants with overweight or obesity. An oversampling strategy has been adopted, with 35.1% (87/248) of the full sample consisting of individuals at a higher genetic risk for T2D. The required number of participants (n=87) for subsample analysis was based on the desired medium effect size (F=0.3085), derived from a 3-group comparison. The control group's average wearable device–measured MVPA time was 80 (SD 35) min/d. The intervention group receiving genetic risk information alone (intervention arm 1) demonstrated minimal changes (85 min/d), while the intervention group receiving combined genetic risk information and wearable device functions (intervention arm 2) was expected to show a difference of approximately 23% in MVPA time (105 min/d; [(105 − 85) / 85 × 100%], corresponding to a difference of 23% in MVPA time compared to previous Fitbit interventions) [26].

Our sample size calculation assumed an α level of 5%, a power of 80%, and a correlation of 0.70 among 3 repeated measures. A total of 355 participants are recruited to ensure the inclusion of an analysis sample of 248, while factoring in an expected attrition rate of 20% (71/355) and an anticipated Fitbit data missing rate of 10.1% (36/355), independent of attrition, considering instances of insufficient battery life or device loss.

Framework

We adopt a superiority hypothesis testing framework for this trial, examining whether combining T2D genetic risk communication with theory-based wearable device functions will lead to significant increases in objectively measured MVPA time and whether such changes will be sustained at the 6-month postintervention follow-up. Each intervention group (intervention arm 1 and intervention arm 2) will be compared separately with the control group and with each other.

Interim Analysis and Stopping Guidance

No interim analysis is planned for this study, as the intervention is not expected to cause harm to participants or raise safety concerns that would warrant ending the trial prematurely.

Ethical Considerations

This study was reviewed and approved by the institutional review board of the University of Hong Kong (HKU) and Hospital Authority Hong Kong West Cluster on December 8, 2022 (UW 22-007).

A subject information sheet and a written informed consent form were provided to each study participant before any assessment or data collection. Participants were given sufficient time to read through both documents and the opportunity to ask questions. The consent form included a section asking whether participants agreed to allow the data from this study to be used in future ancillary research. Participants were informed that they could withdraw from the study at any stage without providing a reason.

All study materials and records are stored securely at the study site. All electronic participant records and responses are maintained on the network drives of the HKU research laboratory. Hard copies of study materials are stored in locked filing cabinets at the HKU research laboratory. Only project staff have access to the study materials and data. All study materials and data will be shredded or otherwise destroyed 5 years after study completion. Deidentified data will be used in outcome data analysis by a study staff member who is blinded to participant group assignment.

Upon study completion, participants will retain their Fitbit Inspire 3 device as an incentive. All Fitbit devices were purchased from a local retail supplier in Hong Kong, with costs supported by the General Research Fund provided by the Hong Kong Research Grants Council (grant 17115422).

Outcomes

Primary Outcome

MVPA, defined as the sum of "fairly active minutes" and "very active minutes" measured by the Fitbit device, is the primary outcome of this study. MVPA will be measured at baseline, immediately after the intervention, 12 months after the intervention, and at the 6-month follow-up.

Secondary Outcomes

All measurements of secondary outcomes will be conducted at baseline, immediately after the intervention, 12 months after the intervention, and at the 6-month follow-up. The secondary outcomes are presented in Textbox 1.

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Textbox 1. Secondary outcomes.

Laboratory assessment variables

- BMI (kg/m^2; derived from height and weight measurements)
- Systolic and diastolic blood pressure (mm Hg; measured using the Omron HEM-907 digital automatic blood pressure monitor)
- Resting heart rate (beats per minute; measured using the Omron HEM-907 digital automatic blood pressure monitor)
- Hand grip strength (kg; measured using the Jamar Hydraulic Hand Dynamometer [Fabrication Enterprises])

Blood-based metabolic risk biomarkers

- Glycated hemoglobin (%)
- Total cholesterol (mmol/L)
- High-density lipoproteins (mmol/L)
- Low-density lipoproteins (mmol/L)
- Triglycerides (mmol/L)

Fitbit device variables

- Steps
- “Sedentary minutes” (minutes)
- “Lightly active minutes” (minutes)
- “Fairly active minutes” (minutes)
- “very active minutes” (minutes)
- “Activity calories” (kcal)
- Sleep time (minutes)

Self-reported variables (assessed using a series of questionnaires)

- Physical activity and sitting time
- Fruit and vegetable consumption
- Smoking status
- Psychological variables to determine the effects of genetic risk communication

Timing of Outcome Assessments

The time points for outcome measurements during the trial are presented in Table 1.

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Table 1. Schedule of assessments.

Assessments	Time points				
	Baseline	Immediately after the intervention	12 months after the intervention	6-month follow-up	After the follow-up
MVPA[a] time (minutes)	✓	✓	✓		✓
Steps	✓	✓	✓		✓
Sedentary time (minutes)	✓	✓	✓		✓
Sleep time (minutes)	✓	✓	✓		✓
Lightly active time (minutes)	✓	✓	✓		✓
Fairly active time (minutes)	✓	✓	✓		✓
Very active time (minutes)	✓	✓	✓		✓
Activity calories (kcal)	✓	✓	✓		✓
Psychological variables of genetic risk communication	✓	✓	✓	✓	
PA[b] and sitting time	✓	✓	✓	✓	
Fruit and vegetable consumption	✓	✓	✓	✓	
Smoking status	✓	✓	✓	✓	
Blood-based metabolic risk biomarkers	✓			✓	
Height (cm)	✓			✓	
Weight (kg)	✓			✓	
Handgrip strength (kg)	✓			✓	
Systolic and diastolic blood pressure (mm Hg)	✓			✓	
Resting heart rate (BPM[c])	✓			✓	

[a]MVPA: moderate to vigorous physical activity.

[b]PA: physical activity.

[c]BPM: beats per minute.

Timing of Final Statistical Analyses

All planned statistical analyses will be performed after the completion of the trial.

Statistical Principles

We will present 95% CIs with adjusted marginal means to compare differences between groups at each measurement time point (baseline, immediately after the intervention, 12 months after the intervention, and 6-month follow-up). Results for the interaction term will also be presented. Pairwise between-group comparisons will be performed with Bonferroni adjustment. An overall level of statistical significance will be set at α=.05 before adjustment.

Adherence and Protocol Deviations

This study allows researchers a high level of control over protocol adherence and deviations. Given that intervention materials are mainly delivered weekly via WhatsApp messages, and only researchers have full control over Fitbit wearable functions, the potential for protocol deviation is minimal. Research staff will perform Fitbit data consistency checks via the Fitbit online dashboard system, which includes (1) monitoring battery life and synchronization status and (2) downloading Fitbit data. Reminders to charge and synchronize the device will be sent via WhatsApp if participants have not done so. Participants are welcome to approach staff should any issues arise. Participants are told to feel free to request withdrawal from the study at any stage.

To investigate the effects of adherence and device wear time, a post hoc analysis will compare participants with consistent wear time to those with inconsistent wear time across all groups.

Analysis Populations

Primary outcome analysis will be conducted according to intention-to-treat principles. Participants with missing outcome data at the 6-month follow-up will be excluded from the analysis.

Trial Population

Screening Data

No screening data are collected. Participants' eligibility is assessed on site.

Recruitment

We will report the following: (1) the number of participants eligible for baseline assessment, (2) the number of participants randomly assigned to each group, (3) the number of participants who completed the 6-month follow-up, and (4) the number of

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participants included in the main analysis (recording any exclusion with reasons).

Withdrawal and Loss to Follow-Up

Participants are free to request withdrawal from the study at any stage without providing a reason. The number of participants who withdraw due to reasons such as serious adverse events, safety concerns, or the development of health conditions or symptoms is reported for each randomly assigned group at all outcome measurement time points.

Baseline Characteristics

The following baseline characteristics will be recorded and summarized for the full sample and by trial arm: (1) age; (2) sex; (3) educational level; (4) body weight and height; (5) BMI; (6) nondominant hand; (7) blood pressure (systolic and diastolic); (8) handgrip strength (both left and right hands); (9) estimated 10-year and remaining lifetime genetic risk for developing T2D; and (10) blood-based metabolic risk biomarkers such as total cholesterol, glycated hemoglobin, high-density lipoproteins, low-density lipoproteins, and triglycerides.

For categorical variables, we will present the proportion and total number of participants within each category. For continuous variables, means and SDs will be presented. If data are skewed, medians and IQRs will be presented instead.

Analysis Methods

Primary Outcome

We will perform primary outcome analysis according to intention-to-treat principles using a series of linear mixed effects models with fixed effects for time, group, and group × time interactions for objectively measured MVPA time, with repeated measures for each participant. Models will be adjusted for potential confounders such as age, sex, and BMI. Adjusted marginal means with 95% CIs will also be presented to compare differences between study groups across all assessment time points.

The analysis will use a longitudinal data analysis model to examine patterns of differences across assessment time points, study groups, and group × time interactions. Results for the group × time interaction term will be included. In addition to the 4 assessment time points, the analysis will also be performed with time as a continuous variable across the study period. The effect modification will also be investigated according to the level of T2D genetic risk, which will be further categorized based on the average T2D genetic risk estimate and educational level of the sample (ie, between college and noncollege graduates). This post hoc categorization can enable us to examine the intervention effects within each group of genetic risk. To ensure fair random assignment of participants between the groups, we will examine between-group differences in the primary outcome data, using an ANOVA test or, if parametric assumptions are not met, a Kruskal-Wallis test.

Secondary Outcomes

Analysis of continuous secondary outcomes will be conducted in a manner similar to that used for the primary outcome. For continuous variables such as blood-based metabolic risk biomarker variables, additional Fitbit device–measured variables, and laboratory assessment variables, we will perform an ANOVA test or, if parametric assumptions are not met, a Kruskal-Wallis test. To analyze differences in categorical variables, such as smoking status and psychological variables related to T2D genetic risk communication, we will conduct chi-square tests.

Sensitivity Analysis and Missing Data

We will conduct two sets of sensitivity analyses: (1) without adjustment for confounders and (2) using an iterative Markov chain Monte Carlo multiple imputation procedure to handle missing data at the 12-month postintervention and 6-month follow-up time points. This procedure assumes that data are missing at random within each group. The randomness of missing data will be tested using the *Amelia* package in R. For variables with missing values (eg, sex, age, educational level, BMI, blood pressure, and handgrip strength at baseline), 5 imputations will be generated for each missing value. To account for nonlinear trajectories in PA patterns, we will conduct additional sensitivity analyses using nonlinear mixed effects models with spline terms to capture nonlinear trajectories in outcome variables.

Safety Considerations

This is a low-risk trial and is not expected to have any major adverse effects on participants' health. The Physical Activity Readiness Questionnaire plays a key role in identifying risk factors such as cardiovascular conditions and musculoskeletal problems. Research staff can assess participants' health status and reduce the likelihood of injuries and other adverse events. As no adverse events are expected from participating in any of the interventions, formal monitoring of adverse events will not be conducted. However, participants may exhibit some degree of discomfort, distress, or psychological concerns regarding their genetic risk for T2D. To address this potential issue, we aim to assess participants' psychological responses to genetic risk communication via web-based questionnaires, which will be administered at all 4 measurement time points. Participants in the intervention groups may also misinterpret genetic risk estimates. To mitigate this, representation of diabetes risk will be assessed using the Brief Illness Perceptions Questionnaire, which consists of 9 items designed to assess cognitive and emotional representations of illness. More detailed descriptions can be found in Multimedia Appendix 1 [25,27-36]. All participants are informed of the full scope and content of the study before participation and are told that they may withdraw from the study at any time without providing a reason.

Results

This study was funded in January 2023, and baseline data collection began in February 2023. The recruitment of 355 participants was completed in August 2023. As of February 2025, the study had entered the 6-month follow-up stage. Formal data analysis will start in April 2025 after the 6-month follow-up assessments have been completed. We expect the results to be published in December 2025.

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Discussion

Summary

We hypothesize that intervention arm 1 will show minimal increases in objectively measured MVPA time, whereas intervention arm 2 will demonstrate significantly increased MVPA time not only at the 12-month postintervention time point but also at the 6-month follow-up.

Strengths and Limitations

This study has notable strengths. It provides a multicomponent intervention combining personalized T2D genetic risk estimates with wearable device functions. Previous trials have investigated the effects of genetic risk communication, but none used behavioral theory–based wearable device functions in conjunction with genetic risk communication [37,38]. Moreover, our study calculates genetic risk estimates based on 113 SNPs, which allows for more precise estimation of T2D genetic risk compared to studies that included only a few SNPs [39,40].

There are also limitations. As residential locations of participants are not collected, and they were instructed to carry out their regular PA routines, it is possible that neighborhood environments could skew measurement outcomes by modulating intervention effects [41,42]. The control group receives a Fitbit device without additional intervention, which could introduce Hawthorne effects, as participants may alter their behavior due to awareness of being studied. To mitigate this, only research staff have full control over the additional Fitbit functions, ensuring that participants in intervention arm 2 use the Fitbit functions pertaining to the intervention (ie, step goal setting and activity prompts). Regular Fitbit data consistency checks are also performed to prevent participants in the control group from accessing these functions. Finally, previous studies have highlighted the short-term nature of Hawthorne effects [43,44]. As measurement of outcome data is being conducted over a period of 7 days at each time point, any impact of Hawthorne effects is likely to be minimized.

Conclusions

This study will be the first randomized controlled trial to combine T2D genetic risk communication with wearable device functions in any population. Novel findings will be used to inform future lifestyle modification strategies for T2D. We plan to provide a comprehensive report on this study by publishing this analysis plan before the completion of data collection.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are not publicly available but are available from the corresponding author on reasonable request.

Authors' Contributions

YK conceived the study and is responsible for the overall content as guarantor. HHSH provided assistance with the conceptualization of the analysis plan. All authors contributed to establishing the design of the trial and developed the interventions and measures. YK is responsible for implementing the protocol. MM, SLAY, and SL assisted with the statistical analysis plan. YK and HHSH drafted the manuscript. All authors contributed to the refinement of the analysis plan and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Measures used in the assessment questionnaire.
[DOCX File , 20 KB - resprot_v14i1e65012_app1.docx]

Multimedia Appendix 2
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 10154 KB - resprot_v14i1e65012_app2.pdf]

Multimedia Appendix 3
Peer-review report from the General Research Fund and Early Career Scheme, Hong Kong Research Grants Council.
[PDF File (Adobe PDF File), 509 KB - resprot_v14i1e65012_app3.pdf]

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Abbreviations

HKU: University of Hong Kong
MVPA: moderate to vigorous physical activity
PA: physical activity
SNP: single nucleotide polymorphism
T2D: type 2 diabetes

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Protocol

Increasing Physical Activity via Provider Support and Engagement Using a Digital Health Platform in Adults With Multiple Sclerosis: Protocol for a Randomized Controlled Trial

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Abstract

Background: The benefits of physical activity are well established in people with multiple sclerosis (MS); yet, most people with MS are insufficiently active. Although many apps and devices are available to promote physical activity, these are not connected to electronic health records (EHRs), making it difficult for health care providers to prescribe and monitor their patients' physical activity. The ExerciseRx platform is an innovative cloud-based, Health Insurance Portability and Accountability Act–compliant software platform (app+provider dashboard) that was developed to bridge the gap between consumer activity tracking devices, such as personal smartphones, and the EHR. The ExerciseRx app tracks a patient's physical activity using their existing personal smartphone and provides a personalized graded progression in step count goals to increase step count gradually and safely over time. The ExerciseRx app also translates the activity data into actionable metrics on a provider dashboard within the EHR that the provider can use to make activity recommendations and monitor patients' progress; they can also support patients by providing semiautomated weekly feedback and encouragement in meeting physical activity goals.

Objective: This paper describes the protocol for a randomized controlled trial designed to understand whether the ExerciseRx digital health platform improves physical activity, symptoms, and functioning in adults with MS relative to a waitlist, usual care control.

Methods: Participants are ambulatory adults with MS (n=106) who engage in <150 minutes per week of moderate to vigorous intense physical activity. Enrolled participants are assigned to use the ExerciseRx app for 12 weeks, versus a waitlist, usual care control. Participants allocated to the intervention condition have access to the ExerciseRx app, and their providers have access to the participants' activity data via a provider dashboard, connected to the EHR. Participants allocated to usual care receive the care they would normally obtain at the MS Center, including encouragement to participate in and increase physical activity as tolerated from their clinical provider and a handout that describes the current physical activity recommendations for adults with MS and links to local and web-based resources suitable for MS. The primary outcome is the change in average daily step count throughout the 12-week intervention. Secondary outcomes include symptoms (fatigue intensity, pain intensity, sleep, and depressive symptoms), patient-reported functional outcomes (physical functioning, fatigue interference, pain interference, falls, and social participation), and qualitative analysis of participant and provider interviews on usability and acceptability of the ExerciseRx platform.

Results: The study was funded in October 2023. Participant enrollment began in March 2024 and will continue through December 2025. As of July 25, 2025, a total of 85 participants have been enrolled in the trial. Data analysis and dissemination preparations will begin in January 2026.

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Conclusions: Results of this trial will provide important new information on the efficacy of an innovative digital health intervention tool for physical activity promotion.

Trial Registration: ClinicalTrials.gov NCT06270641; https://clinicaltrials.gov/study/NCT06270641

International Registered Report Identifier (IRRID): DERR1-10.2196/72213

(JMIR Res Protoc 2025;14:e72213) doi:10.2196/72213

KEYWORDS

multiple sclerosis; exercise; physical activity; digital health; mobile app; step count; clinical trial

Introduction

Physical activity promotion is one of the most effective rehabilitation strategies for reducing multiple sclerosis (MS) symptoms and restoring health and functioning. Physical activity improves mobility, balance, fatigue, and depressive symptoms in people with MS [1-4]. Emerging evidence indicates that exercise also improves cognition, including attention, learning, memory, and executive functioning [5]. In addition to its importance in MS symptom management and overall health, regular physical activity may have disease-modifying effects [3,6]. Premorbid physical activity can predict disability progression over 2 years in people with MS [7], and moderate to vigorous levels of physical activity are associated with more normalized gray matter, white matter, and hippocampal volumes in people with MS [8]. Furthermore, a recent randomized clinical trial found that 24 weeks of progressive aerobic exercise resulted in lower MS relapse rates compared to waitlist controls [9].

Although physical activity is a stated priority for people with MS [10,11], approximately 80% of adults with MS do not get sufficient physical activity [12,13]. They are less active than the general US population [14], which is also sedentary [15]. For example, in a 2018 meta-analysis pooling 1355 adults with MS from 10 studies, adults with MS took significantly fewer steps per day relative to a nationally representative sample of 3752 adults [16]. Physical activity also decreases over time as the disease progresses [17] and is low even in those with mild disease or disability [12,14]. Barriers to exercise in this population include the physical effects of MS (eg, mobility impairment, imbalance, and weakness), common MS symptoms (eg, fatigue, depression, and pain), and psychosocial factors (eg, low exercise self-efficacy) [3,18]. Although physical activity is safe for people with MS [19], fears about its safety, potential to exacerbate MS disease, or falls may also present barriers [18]. The lack of community exercise facilities, the costs of gym memberships or wearables, transportation, and time restrictions are also barriers [18].

The National MS Society convened a panel of clinical and scientific experts to develop consensus recommendations for promoting exercise and lifestyle physical activity for people with MS across disability levels. Their 2022 recommendations included that: (1) health care providers (hereafter referred to as “providers”) routinely assess and promote the benefits of and engagement in exercise and physical activity for every patient with MS; (2) providers encourage >150 minutes per week of exercise or >150 minutes per week of lifestyle physical activity; and (3) exercise and physical activity should be advanced gradually, based on the individual’s preferences, abilities, and safety [18]. The guidelines emphasize the essential role of providers in promoting physical activity and encourage providers to support patients with strategies that increase physical activity, such as self-monitoring, goal setting, and accountability [16,18].

Despite a 2012 expert consensus panel recommending that providers incorporate physical activity promotion into comprehensive MS care [20], most people with MS report that their providers rarely discuss physical activity [10,21]. Importantly, adults with MS who met physical activity guidelines reported having providers who promoted physical activity, including through education and specific activity prescriptions, pointing to the central role that providers have in physical activity promotion [21,22]. Adults with MS prefer obtaining activity promotion information directly from their MS providers through patient-provider interactions. They are less interested in passive methods, such as receiving print (eg, handouts and pamphlets) or electronic information (eg, email and web-based) from their providers, although they appreciate having such information to supplement recall after the health care visit [23]. People with MS want their providers to give them up-to-date information about the benefits of activity and clear recommendations tailored to their disease severity, symptoms, and current activity level [10,22]. They also seek behavioral strategies to help incorporate physical activity into their daily lives, including goal-setting tools, accountability measures, and activity trackers, particularly through mobile technology [22,23]. They want these tools to be affordable, convenient, and accessible [22,23].

Research indicates that MS providers also want to support physical activity engagement in their patients with MS [21,24]. Providers recognize the opportunity for patient-provider interactions to discuss and promote physical activity [21,25]. They want clear protocols for prescribing physical activity, including for providing brief advice, discussing the benefits of physical activity, and assessing physical activity behavior [21,25]. They also want tools to help their patients initiate, track, and sustain physical activity and ways to monitor and guide activity [21].

The ExerciseRx app is an innovative cloud-based, Health Insurance Portability and Accountability Act (HIPAA)–compliant software platform that addresses the current gaps in physical activity support in clinical care. The ExerciseRx app was developed at the University of Washington to bridge the gap between consumer activity tracking devices, such as personal smartphones, and the electronic health record (EHR), thus making physical activity support possible in the clinical

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setting. Currently available apps and devices (eg, Fitbits) are not connected to EHR systems, making it difficult for health care providers to prescribe and monitor their patients' physical activity. In contrast, the ExerciseRx app translates summative physical activity data collected by the patient's existing personal smart devices (Android or iOS phone or tablet) into actionable metrics on a provider dashboard within the EHR (Figures 1 and 2). Each patient is provided a personalized recommendation to facilitate an increased step count gradually and safely over time. Providers can also recommend physical activity tailored to patients' ability levels and preferences. The platform incorporates behavior change strategies, including motivational feedback and nudges. Through its connection to the EHR, it also facilitates a feedback loop with the provider, fostering caring patient-provider connections around activity promotion and behavior change. The ExerciseRx app leverages patients' personal smartphone capabilities to track, quantify, and tailor personalized physical activity recommendations, which makes it readily scalable, accessible, and affordable across diverse patient populations and clinical settings.

Figure 1. Overview of the ExerciseRx platform.

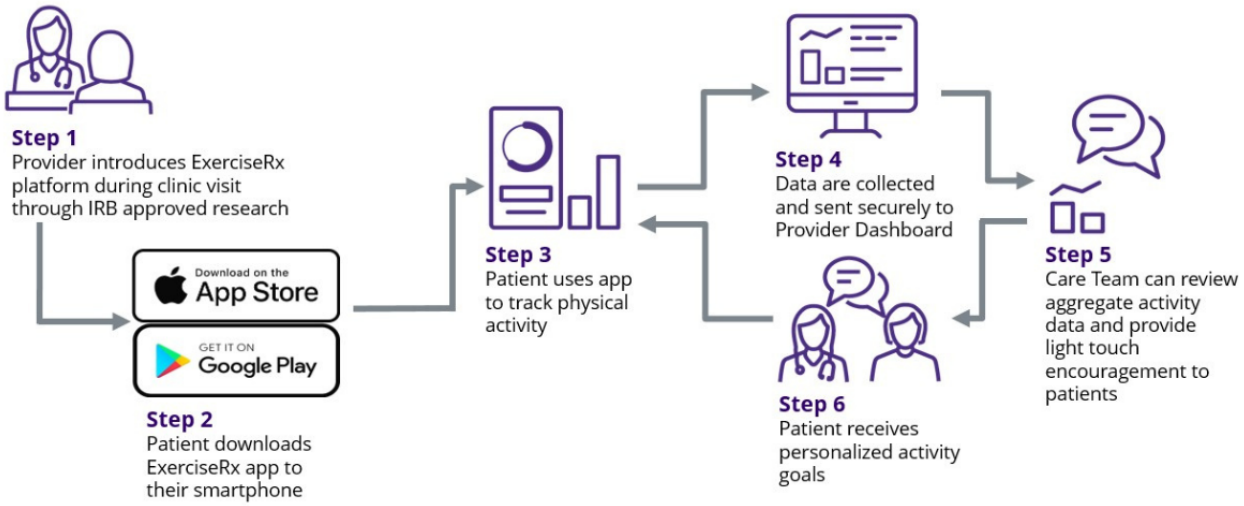

Figure 2. The ExerciseRx app example screenshots.

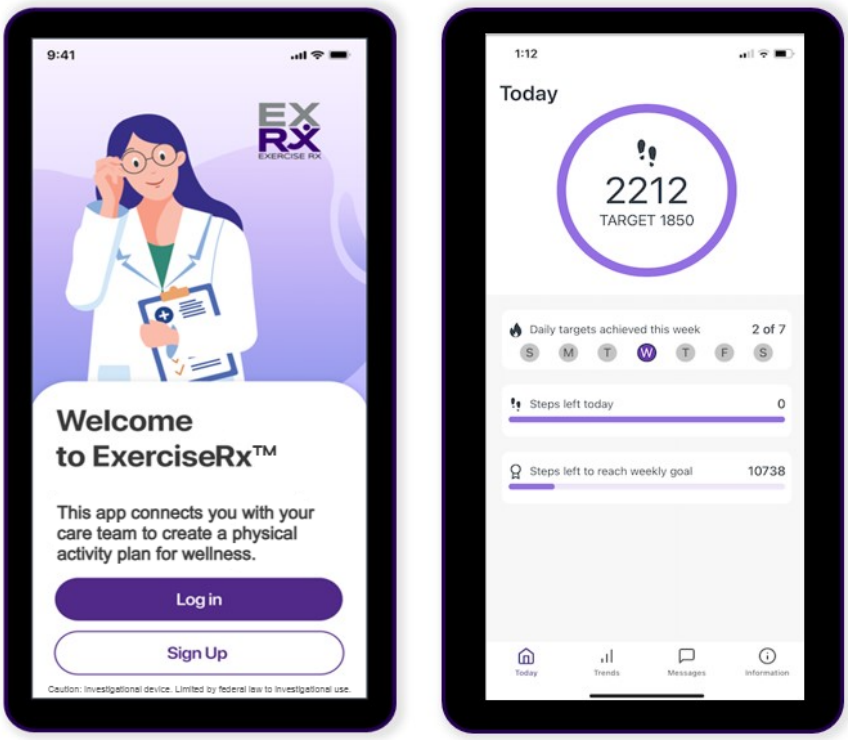

This paper describes the rationale, aims, and protocol for the ExerciseRx-MS Trial, a randomized controlled trial designed to answer whether the ExerciseRx platform improves physical activity and other common symptoms and functional outcomes in adults with MS who are insufficiently active. The first aim is to evaluate the efficacy of the ExerciseRx platform relative to usual care in increasing physical activity, measured by average daily step count (primary outcome), activity volume, and the proportion who meet exercise guidelines in adults with MS who are insufficiently active. We hypothesize that

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participants randomized to the ExerciseRx app group will show a greater increase in physical activity at 12 weeks, as measured by daily average step count (primary outcome) and by total metabolic equivalent minutes of activity per week (secondary outcome) relative to participants randomized to usual care. We also hypothesize that a higher proportion of participants in the ExerciseRx app group will increase their minutes per week of moderate to vigorous intensity aerobic activity at 12 weeks (secondary outcome), relative to usual care participants.

The second aim is to evaluate the efficacy of the ExerciseRx platform relative to usual care on secondary outcomes, specifically symptoms (fatigue intensity, pain intensity, sleep, and depressive symptoms) and patient-reported functional outcomes (physical functioning, fatigue interference, pain interference, falls, and social participation). We hypothesize that participants in the ExerciseRx platform group will show greater improvements in secondary outcomes at 12 weeks relative to usual care participants. Additional secondary analyses will test maintenance of any treatment effects at a 3-month follow-up. We will also explore moderators of immediate (post-12 weeks) and 3-month follow-up outcomes, including demographics, disease course, and baseline participant factors (including fatigue, pain, depression, activity level, BMI, exercise self-efficacy, and disability) to explore potential moderators of treatment effects that can be evaluated a priori in future effectiveness and mechanistic research.

We also plan to evaluate implementation factors relevant to future multicenter effectiveness trials and large-scale implementation of the ExerciseRx platform in MS centers (Aim 3). Both quantitative (usability ratings of ease of use, interface, satisfaction, and usefulness, and the frequency and engagement with the ExerciseRx app) and qualitative data collected from both patients and providers will assess these implementation outcomes.

Methods

Design

To address Aims 1 and 2, we are conducting a two-group parallel (1:1) assessor-masked randomized controlled trial designed to compare the ExerciseRx platform to usual care. We will use qualitative research methods to explore implementation factors (Aim 3). Outcomes are being collected at baseline, post a 12-week treatment period (primary end point), and at a 3-month follow-up after the treatment period. We selected a 3-month follow-up because it is feasible in a 3-year study and sufficient time to see a change in activity behavior. We preregistered the trial at ClinicalTrials.gov (NCT06270641) on February 21, 2024, before enrolling the first participant. Figure 3 provides the study design and participant flow.

Figure 3. Overview of the ExerciseRx-MS study design. MS: multiple sclerosis; REDCap: Research Electronic Data Capture.

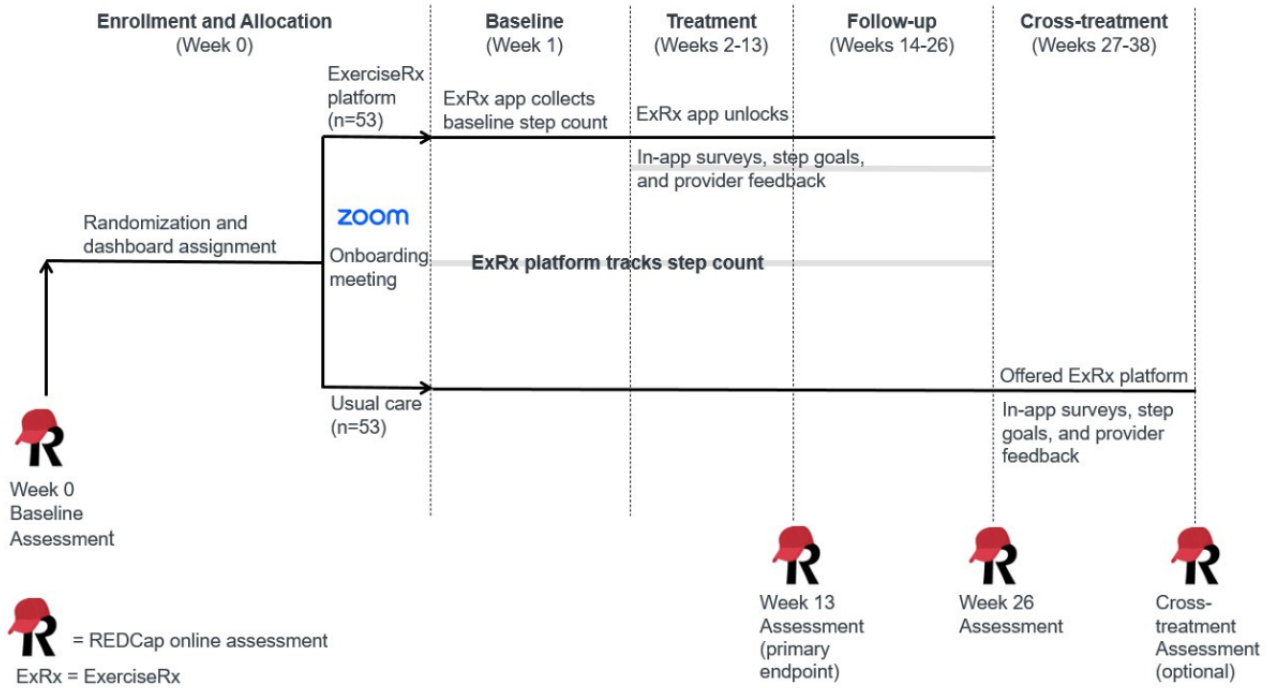

Ethical Considerations

All study procedures were approved by the University of Washington Human Subjects Division (STUDY00018628) on August 30, 2023. Electronic informed consent is obtained from all study volunteers at the time of enrollment; they are informed that they can opt out of participation at any time during the study. Some identifiers (eg, name, mailing address, ZIP code, email address, phone numbers, and medical record number) are collected for the trial. To protect identifiable participant data, access is restricted to authorized study personnel who are trained in confidentiality and data security procedures. All electronic data are stored on secure, encrypted servers with access controls. Identifiers are stored separately from research data, and all data

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transfers use secure, encrypted methods. Participants will be informed of confidentiality protections in the consent process, and data will be securely destroyed when no longer needed. Participants are compensated US $150 for completion of all study assessments (US $50 for each of the three assessment points).

Setting

Participants (n=106) are being recruited from the University of Washington Medicine Multiple Sclerosis Center, a comprehensive, interdisciplinary center that provides specialty care (including neurology, rehabilitation medicine, and psychology) for >3000 patients with MS per year. All clinic patients are offered opportunities to participate in clinical research through a coordinated research registry recruitment effort that is a standard element of the clinic's patient flow.

Recruitment, Enrollment Procedures, and Eligibility Criteria

The primary recruitment sources are referrals from clinic providers (physiatrists, neurologists, nurse practitioners, nurses, and psychologists) and the research registry. The EHRs of patients who are potentially interested in and eligible for the study are prescreened by a research coordinator to confirm MS diagnosis [26,27]. The coordinator then meets with the potential participant by phone to complete a standardized eligibility safety screening to ascertain eligibility. Staff track the recruitment outcomes for everyone who is screened, including reasons for ineligibility or declination. Basic demographic and MS disease characteristics (MS duration, course, and date of diagnosis) are obtained for those considered eligible who decline to enroll; this deidentified information will be used to compare them to study participants to assess the sample's generalizability. All consent procedures are via REDCap (Research Electronic Data Capture; Vanderbilt University), an open-source, secure, HIPAA-compliant web-based platform for data capture (including e-consent and outcome survey administration) [28].

Inclusion criteria are (1) provider-confirmed diagnosis of MS; (2) 18 years of age or older; (3) Patient Determined Disease Steps (PDDS) score <3, indicating the potential for some gait disability although typically ambulates without an assistive device; [29-31] (4) insufficiently active, defined as <150 minutes of moderate intensity physical activity per week per the US National Physical Activity Guidelines, assessed using the Physical Activity Vital Sign [26,27,32] during screening; and (5) use of an iPhone with software version iOS14+ or an Android phone with version 5+. Exclusion criteria are (1) recent (past 4 weeks) or planned surgery during the study period which may impact step counts; (2) MS relapse within the last 30 days; (3) plans during the study period which may impact a participant's daily access to Wi-Fi, which could interfere with server uploads of mobile phone data; (4) >3 falls in the past 6 months; and (5) contraindication to exercise.

During the safety screening, through questions adapted from the Physical Activity Readiness Questionnaire [33], participants are asked to report any recent history of chest pain during exercise, loss of consciousness, health conditions worsened by physical activity, and other contraindications to exercise. Participants are also asked if they have a history of osteoporosis. If yes, the research coordinator obtains an electronically signed HIPAA authorization from the potential participant for further screening to be completed by a study investigator.

Randomization, Allocation Concealment, and Masking Procedures

Block randomization, stratified by self-reported sex assigned at birth, is done using a web-based treatment arm assignment system with a 1:1 assignment after the one-week baseline. To ensure concealed allocation, an unmasked research coordinator retrieves the treatment assignment at the time of randomization and informs the participant of their assignment. The coordinator also notifies the participant's provider of their assignment to the ExerciseRx app group so that they know to look for the participant on the provider dashboard of the ExerciseRx platform. The statistician is masked to treatment allocation.

Participants directly enter their patient-reported outcomes data into REDCap, the web-based data capture platform, which minimizes concerns of staff biases interfering with data collection. Participants are informed of equipoise and that the study's purpose is to determine whether the ExerciseRx platform or usual care is more beneficial.

ExerciseRx Intervention

Overview

The ExerciseRx platform was developed through a collaboration of investigators from the University of Washington Departments of Computer Science and Engineering and Human Centered Design and Engineering, and The Sports Institute at UW Medicine. It was designed to bridge the gap between consumer activity tracking devices, such as personal smartphones, and providers' EHRs, thus making recommending physical activity possible as part of routine patient care. The ExerciseRx platform is a cloud-based, HIPAA-compliant, free digital platform that translates clinically relevant activity data collected by the patient's existing personal smart devices (Android or iOS phone or tablet) into actionable metrics on a provider dashboard within the Epic EHR.

The ExerciseRx platform intervention protocol involves the following.

Baseline ExerciseRx Platform Onboarding Meeting With Research Coordinator

After completion of informed consent and the baseline measures, the research coordinator meets with the participant by Zoom (Zoom Communications, Inc) to help them download the ExerciseRx app to their smartphone. The coordinator then teaches them how to use the ExerciseRx app and instructs them to always carry their phone throughout the day. The coordinator reviews the ExerciseRx app procedures with the participant so that they know what to expect during the intervention period. The coordinator also educates the patient on how their step count, as tracked by the ExerciseRx app, is a key marker for physical activity. The coordinator reviews the recommended physical activity guidelines for adults with MS and resources for increasing physical activity and emails them a copy.

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Baseline Step Count Period (1 Week)

Participants are asked to carry their phone throughout the day for 1 week to evaluate their baseline step count with no app interactions, notifications, or provider feedback during the baseline recording period. The baseline step count is used to calculate personalized step count goals.

Initial Personalized Daily Step Target

At the end of baseline, intervention participants receive a notification from the ExerciseRx app providing them with a personalized initial daily step target and weekly goal based on their baseline.

Exercise Progression and App Features

The ExerciseRx app displays a weekly step count goal, as well as daily step count targets (see Figure 2 for example). If participants meet their daily step targets, they are on track to meet their weekly step count goal. If 100% of the weekly goal is met the week before, the weekly step count goal increases by 3%. If 75%-99% of the goal is met, there is a 2% increase in their goal. If <75% of the weekly step count goal is met, there is no change to the weekly step count goal. The minimum step count is 1000 steps. The maximum goal in the ExerciseRx app is 10K and will not advance beyond that number, but since the step count is based on the patient's baseline and progress, the patient may not reach 10K steps during the study period, as it is an individualized progression.

Participants use the app daily for 25 consecutive weeks after the baseline week. Weekly, participants complete an in-app survey of their individual barriers or facilitators to activity. During this period, the app displays daily step count targets, weekly step count goals, weekly summaries, a weekly assessment of barriers or facilitators to activity, semiweekly "Did you know" general and MS-specific messages such as "Exercise is medicine—increasing movement is a great way to better manage MS fatigue and may even reduce risk of relapse!" and provider automated feedback on activity progress (eg, thumbs-up reactions, weekly summaries, supportive messages, or encouragement based on whether the participant is near, at, or below their weekly goal).

Provider Dashboard and Interactions

A total of 7 MS providers (2 physiatrists, 4 neurologists, and 1 psychologist) are the providers in this study. Each provider can view on the provider dashboard of the ExerciseRx platform: (1) a triaged aggregate patient panel that depicts their patients' progress in meeting weekly goals; (2) clinical decision support recommendations for next steps (eg, reactions and message suggestions); and (3) individual participant weekly step count and most common barriers or facilitators (obtained from the surveys completed weekly by participants). The providers check and act on the dashboard at least once a week during the study period. They can offer feedback and reinforcement via the provider dashboard of the ExerciseRx platform, which sends the patient messages via app notifications. For example, if a patient is at less than 75% of their goal by the 3rd week, their MS provider can send them a nudge from the provider dashboard.

Low Engagement Support Protocol

The app monitors participants' engagement and sends automated notifications to the provider and research coordinator. For example, if a patient has not opened the app in 5 days, they receive the following support message: Tech support message #1: "Hello, we noticed you haven't opened the ExerciseRx app recently. Are you having any difficulties with the app or accessing Wi-Fi or cellular connection? Please let us know if there is anything we can assist you with." The research coordinator monitors the responses and patient inquiries and provides responses or technical assistance if needed. They also connect the patient to the provider to answer questions as needed; providers can also reach out to participants if they wish.

Post 12-Week Intervention Period

Participants in the ExerciseRx app group are allowed to continue using the ExerciseRx app and encouraged to continue with physical activity goals, as indicated. Their providers may also continue using the provider dashboard of the ExerciseRx platform with their patients.

Provider Training

The senior author, who helped develop the ExerciseRx platform, and the research coordinator trained the providers on the use of the ExerciseRx platform, including their responsibilities. Although the providers are familiar with the 2020 MS Exercise and Physical Activity Recommendations, CYL (ExerciseRx project lead and sports medicine provider) and SBS (MS physiatrist with exercise expertise) reviewed the guidelines with the providers and described National MS Society and other MS-specific resources (eg, website links and handouts videos) available to providers in educating their patients about the benefits of physical activity in MS.

Usual Care

Overview

The American Academy of Neurology has recommended that patients with MS be counseled by their providers on the benefits of exercise and appropriate physical activity [18]. Participants allocated to usual care receive the care they would normally obtain at the MS Center, including encouragement to participate in and increase physical activity as tolerated from their clinical provider (neurologist, physiatrist, or rehabilitation psychologist), but without the use of the ExerciseRx platform. Specific physical activity guidance varies based on the provider but may include guidance on current exercise recommendations for people with MS (dose, duration, and type), known benefits of exercise in people with MS, links with exercise resources, and referrals to physical therapy or physiatry. In addition, at the beginning of the study intervention period, all participants (including usual care) are given a handout that describes the current physical activity recommendations for adults with MS (type, duration, and intensity), the benefits of physical activity, and links to local and web-based resources suitable to MS (eg, free web-based exercise videos, National MS Society exercise or physical activity educational materials, and links to community resources). We selected the usual care control as a comparator because clinical trials methodologists [34] argue that usual care and waitlist controls are appropriate for efficacy trials when the

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goal is to promote innovation and test potentially efficacious interventions.

Usual Care Onboarding Meeting With Research Coordinator

After completion of informed consent and the baseline measures, the research coordinator meets with the participant by Zoom to review the study procedures. Like participants in the ExerciseRx app group, the coordinator reviews the recommended physical activity guidelines for adults with MS and provides print resources for increasing physical activity, identical to what materials the ExerciseRx participants receive.

26-Week Usual Care Period

Usual care participants are instructed to carry their phone throughout the day to allow passive collection of step counts during the study period; however, they will not be able to view or use any of the features of the ExerciseRx app. Participants are not discouraged from engaging in physical activity, and providers are not precluded from providing whatever care they usually would to their patients during the study period.

Post Follow-Up Phase

After the final (26-weeks) outcomes are collected, usual care participants are offered the ExerciseRx platform, which is delivered as described above.

Assessment Procedures and Measures

Overview

All participants complete baseline and outcome assessments using REDCap, a web-based data capture platform [28] that can be completed by any digital device with internet access. It includes a human verification service (reCAPTCHA) to avoid responses from bots. Outcome assessments are collected at baseline, post a 12-week treatment period (primary end point), and at a 3-month follow-up after the treatment period. We obtain step count data from all participants throughout the trial and collect data from all randomized participants, regardless of their adherence to treatment (ie, intent-to-treat). Participants receive up to US $150 remuneration for completing the REDCap assessments (US $50 for each assessment point).

Participant Characteristics

Participants provide demographic variables, including self-reported sex assigned at birth, gender identity, age, race, ethnicity, employment status, relationship status, and education level. Clinical information, including MS subtype, time since diagnosis, and medications (including disease-modifying therapy), is obtained from chart review. MS disease severity (assessed using the PDDS, a brief self-reported assessment that has been found to be a valid measure of disease severity in an MS population [31]), occurrence of clinical relapses (over the preceding 6 months and throughout the study period), and self-reported falls (over the preceding 6 months and throughout the study period) are also assessed. Data on other treatments and therapies used during the study period (active treatment and follow-up) are collected via medical record extraction and self-report.

Primary Outcome: Step Count

For the week before (baseline) and throughout the 12-week intervention period, step count will be measured within the ExerciseRx app, which passively collects step count data from device sensors using Core Motion, Google Fit, and Google Health Connect. Participants in the usual care condition will also have their step count passively monitored via the ExerciseRx app on their smartphones. Step count is an ideal primary outcome in physical activity promotion trials because it provides an objective, quantifiable measure of daily activity that is sensitive to change and free from self-report bias. It captures both structured and incidental movement, is easy to interpret for participants and clinicians, and is associated with meaningful improvements in health and function [35], including in adults with MS [36,37]. It is possible that step count may be underestimated due to a lack of carrying time or location; a few studies have shown that carrying a phone in a pocket or purse can lead to underestimations of step count [38,39]. However, since this study is looking primarily at changes and trends in step count over time, with consistent phone carrying behaviors, clinically relevant assessments will still be obtained [38,40].

Secondary Outcomes: Physical Activity

The International Physical Activity Questionnaire-Short Form, which is validated for MS [41,42], will be given to participants at baseline to assess frequency and intensity of physical activity at each assessment timepoint. Activity intensity and frequency will then be used to calculate total MET-minutes per week for participants in each condition. The Physical Activity Vital Sign (described above) will also be obtained at each timepoint to determine the percentage of participants in each group that progress their total minutes spent in moderate to vigorous intensity physical activity per week toward the current physical activity guidelines (of >150 min of moderate intensity or >75 min of vigorous activity per week).

Secondary Outcomes: Symptoms and Function

The following patient measures, all validated in MS, are obtained at the three outcome timepoints to investigate the effects of the ExerciseRx platform on symptom severity: Patient-Reported Outcomes Measurement Information System (PROMIS) pain intensity (PROMIS Pain Intensity Short Form) [43,44], fatigue severity (PROMIS Fatigue Intensity Short-Form)[43,45], depressive symptom severity (PROMIS Depression Short-Form) [43,46], and sleep disturbance (PROMIS Sleep Disturbance Short Form) [43,47]. We will also assess functional outcomes, specifically physical functioning (PROMIS Physical Function 10a) [48], pain interference (PROMIS Pain Interference Short-Form) [43,44], fatigue interference (PROMIS Fatigue Impact Short Form) [43,45], social participation (PROMIS Satisfaction with Participation in Social Roles Short Form 8a) [43], and self-reported falls (during the 6 months prior to randomization and throughout the study period).

Exploratory Mechanisms: Moderators

We will use baseline values of the demographic, clinical, and symptom measures, exercise self-efficacy [49], and BMI to explore moderators of immediate (post 12 weeks) outcomes

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that may be evaluated a priori in future effectiveness and mechanism research on the ExerciseRx platform.

Implementation Measures

Both quantitative and qualitative implementation measures will be completed by participants in the ExerciseRx app group after they have completed the 12-week treatment period. Quantitative measures will include ratings of ease of use, interface, satisfaction, and usefulness from the mHealth App Usability Questionnaire [50]. Participants' app engagement will be measured via the ExerciseRx platform data, which tracks the frequency of logins and completion of weekly barriers or facilitators in-app surveys. Providers will also complete a similar brief survey of implementation factors, including measures of acceptability, satisfaction, demand or engagement, usability, and integration of the ExerciseRx platform into their clinic workflows. The ExerciseRx platform will provide data on providers' frequency of and engagement with the provider dashboard of the ExerciseRx platform, including logins, screen interactions, and messages sent to participants.

In addition to the participant and provider self-report usability measures, we will conduct semistructured interviews with 14 individuals who receive the ExerciseRx intervention and at least 3 providers to better understand their experiences on study completion, including usability and feasibility of the platform. The semistructured interviews are informed by (1) the Lived Informatics Model [51], which describes key stages of using health tracking apps: deciding to track, selecting a tool and tracking plan, collecting data, integrating it, reflecting on it, lapsing, and resuming use; and (2) goal directed self-tracking, which supports examining how the functionality and design of a tracking app aligns with their activity goals [52]. The interview guide is provided in Multimedia Appendix 1. Interviews will include information regarding demographics, open-ended questions about barriers or facilitators to physical activity and use of technology, and app features feedback. Interviews will be conducted over Zoom, recorded, transcribed, and double-coded with two coders using Dedoose software (SocioCultural Research Consultants, LLC).

Safety

We are tracking any adverse events, including falls or injuries related to study participation per University of Washington Human Subjects Division procedures, which include monitoring for possible adverse events, managing them, and reporting them to the principal investigator, Human Subjects Division, and study sponsor, as indicated. Since the ExerciseRx app is a wellness platform that helps patients to meet current national physical activity guidelines, the regulatory pathway is Software as a Medical Device Class I (low risk, exempt).

Sample Size, Power, and Analysis Plan

Assuming a 15% noncompletion, we plan to enroll 106 participants in the trial to ensure 90 participants complete the study. With 90 participants (45 in each group), we will have 80% power to detect a significant difference in the change in mean daily step count from baseline to 12 weeks between the treatment and control groups for a moderate standardized effect size (Cohen d=0.60) using a two-sided significance level of .05. For Aim 1, we will analyze the efficacy of the ExerciseRx platform using a linear mixed effects model with average daily step count each week as our outcome, fixed effects for week, treatment assignment, and the week-treatment interaction, and a random intercept for each participant. The presence of a significant interaction will indicate that the change in step count over the 12-week study period is impacted by treatment assignment. If differences in demographic or other clinically relevant characteristics between the two groups are found in the descriptive analysis, sensitivity analyses will be conducted, including those characteristics as adjustment variables in the model. Post hoc analyses will include independent and paired sample 2-tailed t tests to determine if there are differences between treatment groups at specific time intervals or differences between specific time intervals within a treatment group.

Similar models will be used for Aim 2 and for the secondary physical activity outcomes (activity volume and proportion meeting physical activity guidelines), using each of the secondary outcome measures as the outcome variable in the linear mixed-effects model. As no correction for multiple comparisons will be implemented for these analyses, any significant findings will be considered as hypothesis-generating.

For the qualitative analysis, the interview transcripts will be coded using Dedoose software. Two trained qualitative analysts will independently analyze the data using reflexive thematic analysis, a well-established method for interpreting qualitative data [53]. This approach emphasizes the researchers' active role in identifying patterns across the data and involves intentional engagement with subjectivity and reflexivity throughout the analytic process. In conducting our analysis, we will draw upon our diverse backgrounds in design, health informatics, patient care, and clinical research to interpret the data and generate themes, while remaining attentive to how participants' experiences and attitudes may differ from our initial assumptions.

Results

The study was funded in October 2023. Participant enrollment began in March 2024 and will continue through December 2025. As of July 25, 2025, we have enrolled 85 participants. Data analysis and dissemination preparations will begin in January 2026, and results of the ExerciseRx-MS trial are expected to be submitted for publication by September 2026.

Discussion

Principal Findings

Physical activity promotion has emerged as a potent, restorative rehabilitation strategy. In this clinical trial, we aim to advance the scientific understanding and potential future implementation of the ExerciseRx app, a digital health platform for increasing activity in insufficiently active adults with MS. The study leverages the benefits of physical activity, the identified preferences of patients and providers, and a unique, innovative tool for addressing gaps in the translation of activity recommendations into the MS community. The ExerciseRx

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platform is unique in that it not only addresses several of the barriers to physical activity (eg, convenience and tailored activity recommendations) identified in MS, but it also integrates the MS provider into activity promotion. It ensures that patients are getting the information and guidance they want from their providers [54] and gives providers insight into their patients' activity levels while minimizing the provider's clinical burden (through automated features). The trial will also explore the implementability of the ExerciseRx platform to understand contextual factors, which will inform implementation strategies for the next stage of research and accelerate future implementation if the intervention is efficacious.

The ExerciseRx platform can be universally applicable, both to the general population and to a wide range of rehabilitation populations with physical activity needs. Given the focus of our research, as well as the unique needs previously identified in the MS population, this trial is focused on the ExerciseRx platform's application to the MS population. The ExerciseRx platform has the potential to provide what patients with MS want: clear activity recommendations from their provider and accessible, cost-effective tools for goal setting, accountability, and activity tracking [22,23]. Research has shown that support and guidance from providers [55]—as well as behavioral factors such as self-monitoring of physical activity, setting appropriate goals, and having someone to be accountable to—facilitate physical activity [18]. The ExerciseRx platform also offers what MS providers want: clinically integrated, streamlined tools to help their patients initiate, track, and sustain physical activity. It also helps them guide their patients' activity without adding to the clinical care burden [21].

Study Limitations

Inclusion or exclusion criteria were selected to maximize generalizability, and the study was designed to leverage participants' own technology (ie, smartphones) to reduce barriers to implementation. Unfortunately, current smartphone software is less robust at tracking physical activity in people who are nonambulatory or who use an assistive device for ambulation. In addition, the 2020 Physical Activity Guidelines for people with MS suggest that referrals to specialists (to assure proper safety, form, and appropriate intensity) are more essential in individuals with higher disability [18]. Therefore, the criterion requiring a PDDS of ≤3 (indicating MS may interfere with gait but typically ambulates independently) was selected. We recognize that this range limits the generalizability of the sample to those who can walk and have milder disability, which we decided was acceptable for this stage of research, given that we are interested in the feasibility of the ExerciseRx platform in MS clinical care and wanted to maximize safety (reduce fall risk). If the ExerciseRx platform is found to be efficacious in ambulatory adults with MS, a future study could integrate other features of the ExerciseRx app that are now available into a future clinical trial, including the ability to prescribe a home exercise program incorporating strength training, seated exercises, and other types of physical activity applicable to a broader range of disability levels and activity types in MS. Requiring patients to have a smartphone might also exclude some people from participating. However, recent research on smartphone use in the general population [56] and in MS samples [57] indicates that 85%-90% own a smartphone.

Step count provides a pragmatic, scalable, and accessible outcome well-suited for real-world applications. However, it is possible that there will be variation in step count data across participants in the intervention and control groups. We have several procedures for mitigating this potential limitation. At the onboarding visit, the research coordinator discusses with all study participants the importance of carrying their phones throughout the study and the rationale for it (to consistently capture step count data). They are instructed to carry their phone all day while awake. She also discusses with each participant their phone-carrying habits and helps troubleshoot any potential issues. At the 13- and 26-week assessments, participants are asked to estimate what percentage of their waking hours they carried their phone as a measure of adherence to phone carrying; we will use this measure to explore patterns of self-reported phone carrying, including differential patterns between the two conditions.

Conclusions

The ExerciseRx-MS trial tests an innovative patient-provider digital health platform, which is designed to increase physical activity using the individual's own technology (ie, smartphones). The ExerciseRx platform connects adults living with MS and their care providers, who can monitor progress in step count goals and provide encouragement in a minimally burdensome fashion. This trial will evaluate both the efficacy of the ExerciseRx platform in increasing physical activity and the implementability of the ExerciseRx platform in clinical practice, exploring critical contextual factors, including participants' and providers' perspectives.

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Data Availability

The datasets generated and analyzed during this study are not publicly available due to ongoing data collection, but a deidentified version of aggregated trial data will be available from the corresponding author upon reasonable request following the completion of the study.

Authors' Contributions

DME and CYL: conceptualization, funding acquisition, investigation, methodology, supervision, writing-original draft, writing-review, and editing.
SBS and KNA: conceptualization, funding acquisition, investigation, methodology, writing-original draft, writing-review, and editing.
TEH: conceptualization, funding acquisition, investigation, writing-original draft, writing-review, and editing.
ATH: conceptualization, funding acquisition, data curation, formal analysis, methodology, writing-original draft, writing-review, and editing.
SRR, KL, and LBK: investigation, project administration, writing-original draft, writing-review, and editing.
OI: software, writing-original draft, writing-review, and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Poststudy interview guide.
[DOCX File , 48 KB - resprot_v14i1e72213_app1.docx]

Multimedia Appendix 2
Peer review report from Accelerating Functional Recovery of Multiple Sclerosis Grant Committee, National Multiple Sclerosis Society (USA).
[PDF File (Adobe PDF File), 232 KB - resprot_v14i1e72213_app2.pdf]

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Abbreviations

EHR: electronic health record
HIPAA: Health Insurance Portability and Accountability Act
MS: multiple sclerosis
PDDS: Patient Determined Disease Steps
PROMIS: Patient-Reported Outcomes Measurement Information System
REDCap: Research Electronic Data Capture

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Protocol

Scaling European Citizen Driven Transferable and Transformative Digital Health: Protocol for an Effectiveness-Implementation Hybrid Trial of a Digital Health Platform to Support Multimorbidity Self-Management

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Abstract

Background: Multimorbidity, the presence of 2 or more chronic conditions, is becoming increasingly prevalent worldwide, resulting in significant impacts on health care systems. For people with multimorbidity, self-management is challenging, requiring engagement in several tasks. Digital health platforms have been widely acknowledged as having the potential to enhance self-management practices for those with chronic conditions. However, limited longitudinal studies have explored the effectiveness of digital health platforms that support multimorbidity self-management or issues relating to their implementation and scalability in practice.

Objective: The aim of this study is to determine the effectiveness and implementation of a digital health platform, ProACT, with support services including clinical triage and a care network (consisting of informal and formal caregivers and health care professionals) compared to the use of the platform alone and compared to standard care.

Methods: An effectiveness-implementation type 1 hybrid study will be conducted across 3 European countries. A total of 720 older adults aged 65 years or older with multimorbidity (2 or more of the following: diabetes, a chronic respiratory disease, chronic heart failure, and chronic heart disease) will be recruited and randomized into 1 of 3 trial arms. Those in trial arm 1 will be invited to have up to 5 care network members participate with them, resulting in a maximum of 1500 care network participants. Effectiveness will be assessed through a 3-arm pragmatic randomized controlled trial, while implementation issues will be addressed via a process evaluation. Primary outcomes for participants with multimorbidity are quality of life and health care use, while secondary outcomes focus on the potential of the ProACT platform to support multimorbidity self-management (eg, self-efficacy, usability, engagement, and symptom stabilization). Primary outcomes for informal caregivers in the care network include caring burden, while secondary outcomes for all care network members include usability, engagement, satisfaction, and overall experiences with ProACT. Additional outcomes related to the process evaluation include the reach, uptake, and fidelity of implementation of ProACT and the way organizations implement and deliver ProACT; how they differ in this regard; and the factors underpinning these differences. A range of qualitative and quantitative data will be collected and analyzed to assess these outcomes.

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Results: Enrollment in the trial began in September 2022, and the trial is anticipated to end by March 2026. Trial outcomes will be submitted for publication in 2026.

Conclusions: The generation of evidence-based support for the routine use of the ProACT platform in applied settings would represent considerable impact. With health care services under increasing strain and traditionally designed to support those with single morbidities, it is more important than ever to develop actionable insights and resources to empower persons with multimorbidity to self-manage their complex care needs at home, with support from their caregivers.

Trial Registration: ISRCTN Registry ISRCTN34134007; https://www.isrctn.com/ISRCTN34134007

International Registered Report Identifier (IRRID): DERR1-10.2196/74989

(JMIR Res Protoc 2025;14:e74989) doi:10.2196/74989

KEYWORDS

multimorbidity; digital health; chronic disease; self-management; aging; older adults; effectiveness-implementation hybrid trial

Introduction

Background

Approximately 50 million people in the European Union, including at least 60% of those aged 65 years and older, live with multiple chronic conditions or multimorbidity [1-3], which is typically defined as the presence of 2 or more chronic conditions in the same individual [4]. The older adult population of the European Union is also increasing; the share of those aged 80 years and older is projected to increase from 5.5% to 12.7% between 2017 and 2080 [5]. Given the link between multimorbidity and increased age [6-8], combined with rising health care expenditures and budgetary constraints, health care systems face considerable challenges in sustaining services to meet the growing demands for long-term health care provision. For instance, the European Union spends approximately US $ 816 billion per annum on chronic disease management, comprising 70% to 80% of total health care costs [9], with health care costs in general projected to rise further [10]. Health care systems need to evolve, and central to this is an understanding that multimorbidity is becoming the norm rather than an exception. At present, health care systems are designed to support those with 1 rather than multiple chronic conditions; they instead need to address the management of multiple conditions, where difficulties and conflicts in care and treatment can often arise [11-14].

For people with multimorbidity, services are often repetitive, inconvenient, and burdensome (eg, due to the need to attend multiple appointments), as well as inefficient, fragmented, and potentially unsafe (eg, people with multimorbidity may receive conflicting advice from different clinicians in relation to different conditions) [15-17]. Those with multimorbidity must also often take several medications, which can be difficult to keep track of, with some combinations potentially dangerous [18,19]. There is a need to improve best practices around the provision of well-coordinated person-centered care. One way to achieve this is to empower people with multimorbidity to use digital health technology to play an active role in the self-management of their health and well-being, supported by their care networks. A digital integrated care platform, designed with the complexities of multimorbidity in mind, may facilitate self-management at home. Such a platform may also facilitate greater coordination between people with multimorbidity and their care networks in relation to their health care; while overall, it may ensure that health care systems become more sustainable, "future-proofed," and accessible to people with multimorbidity when necessary [20].

However, while older adults are increasingly open to using digital health technology, this technology type is still in its infancy and lacks widespread adoption [21]. Furthermore, although digital health technology has demonstrated potential to advance self-management and care for those with multimorbidity [22,23], research examining its efficacy is limited. Research into digital self-management of multimorbidity has typically explored design recommendations only [24]. Our previous work represents one of the few studies to test a digital health platform (ProACT) for multimorbidity self-management and care at a proof-of-concept level among people with multimorbidity and their care networks [24,25]. The quantitative and qualitative findings revealed that the ProACT platform was engaging and useful; the qualitative findings also revealed that it facilitated perceived improvements in participants' health and well-being, self-management, and support [24,26,27].

Study Aim and Objectives

The overall aim of the Scaling European Citizen Driven Transferable and Transformative Digital Health (SEURO) project is to evaluate key factors to prepare organizations, localities, and regions across the European Union to scale, sustain, and transfer people-centric digital integrated health and social care solutions for multiple disease management. To achieve this, an effectiveness-implementation hybrid (EIH) trial [28] will be carried out in Ireland, Belgium, and Sweden, with ProACT, with embedded process evaluations to understand the process for successful "real-world" implementation. Effectiveness will be assessed from the user perspective via perceived quality of life (QoL) and from the service perspective via health care use (HCU); implementation will be assessed using quantitative and qualitative data (eg, assessment of organization readiness, participants' system use data, health care organizations' administrative data, and interview data) collected as part of a process evaluation. Effectiveness will be assessed through a 3-arm pragmatic randomized controlled trial (p-RCT) in each trial site. Those in trial arm 1 will receive a personalized version of the ProACT platform, can invite people in their care network (eg, informal and formal caregivers and health care professionals) to participate with them, and will

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have access to clinical triage support. Those in trial arm 2 will receive a basic, nonpersonalized ProACT CareApp with no access to the care network or clinical triage, while those in trial arm 3 will continue to receive standard care.

The objectives of this trial are (1) to evaluate the impact of the ProACT platform on people with multimorbidity's QoL and HCU (ie, the trial primary outcomes); participants in each trial arm will be compared on these variables; (2) to evaluate the cost-effectiveness of the personalized ProACT CareApp with care network and triage support in comparison to the nonpersonalized ProACT CareApp and control group; (3) to explore via a mixed methods approach (analysis of system and questionnaire data and interviews with participants) the potential impact of ProACT on multimorbidity self-management; (4) to evaluate the impact of the ProACT platform on informal caregivers' caring burden; and (5) to evaluate participants' (people with multimorbidity and care networks) overall experiences with the ProACT platform in the management of multimorbidity. Data collected from participants in trial arms 1 and 2 will also be compared. Furthermore, to explore the impact of contextual factors (eg, participants' conditions, age, and socioeconomic status and care network participants' motivation to take part in the trial) on fidelity of use and use outcomes (eg, reach, uptake, and acceptability); (6) to understand how ProACT is implemented and delivered in health care settings and to identify systematic differences and variation in delivery; (7) to evaluate via the process evaluation organizational readiness to transfer and optimize a digital health solution as part of the care delivery; and (8) to evaluate whether trial outcomes can inform future analysis of the impact of digital solution implementation in practice. This protocol adheres to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines for clinical trial reporting (Multimedia Appendix 1) [29].

The ProACT Digital Health Platform

Overview

In total, 166 key stakeholders (ie, people with multimorbidity and care network members) were involved in the design and development process of the first version of the ProACT digital health platform, as part of the ProACT Horizon 2020 project [24]. This extensive requirement-gathering process included semistructured interviews, focus groups, co-design workshops, and usability testing, aiming to ensure that the platform's user interface and content were understandable, relevant, and compatible with the daily lives of older individuals with varying cognitive capacities, health literacy, and digital literacy. Furthermore, during the ProACT project, the ProACT platform was tested and refined at a proof-of-concept level with 120 older adults with multimorbidity in Ireland and Belgium during a 12-month period, with promising outcomes observed, particularly in user engagement [24,27]. Extensive feedback was also collected from users on usability during the ProACT trial, resulting in updates and refinements being made to the platform, primarily in terms of aesthetics and navigation.

The ProACT digital health platform that will be deployed in trial arm 1 of the SEURO EIH trial is composed of the following elements.

Measuring Devices

These include "off-the-shelf" devices that are used to collect health and well-being data from people with multimorbidity in their homes (eg, blood glucose, blood pressure, pulse oximetry, heart rate, weight, sleep, and activity measures).

The ProACT CareApp

Accessed via an interactive device (eg, a tablet or smartphone), this app displays users' health and well-being data as derived from the different measuring devices. To support people with multimorbidity self-managing their health and well-being, the CareApp provides feedback (eg, feedback on health status including exacerbations), tools (eg, medication management tools and goal-setting features), and personalized educational content (eg, written and visual content sourced from relevant, reliable, and trusted organizations localized by region) that is contextualized to the person's current health and well-being status. It also provides participants with the option to self-report through a series of questions about their health and well-being (eg, for those parameters not easily measured by a sensing device, such as breathlessness and mood). An overview of features is provided in Table 1 and Figures 1-5. The primary differences in the CareApp for those in trial arm 2 are that exacerbations are not highlighted, and educational content is not contextualized to the current status, therefore representing a more standard application that might be downloaded from an app store. People with multimorbidity will be the main users of the ProACT CareApp. However, customized ProACT CareApp interfaces will also be available for care network members of participants in trial arm 1 to use on their own devices (eg, tablets, smartphones, or computers) to view the participant's data.

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Table 1. Summary of features available within the ProACT CareApp for users with multimorbidity.

Component	Feature summary
Dashboard	Today at a Glance (Figure 1): A quick glance overview of the user's current symptom (eg, weight and blood pressure) and well-being (eg, physical activity and sleep) status today, including any alerts detected, any measures missing (based on the participant's care plan of how often they want to measure different parameters), progress toward an activity goal, and medications taken so far today.
Dashboard	Self-report: A series of symptoms (eg, breathlessness and chest tightness) and well-being (eg, mood and anxiety) questions. The self-report card (Figure 1) indicates how many outstanding questions are to be answered. Users can also see the responses to these questions charted.
Dashboard	My Health, My Wellbeing, My Activity: These sections of the dashboard present a series of cards, indicating the user's most recent health and well-being readings (covering sensor and self-report data) or whether a reading is missing.
My Health, My Wellbeing, My Activity readings	Tapping on any of the cards in the My Health, My Wellbeing, or My Activity sections opens a detailed view of the user's readings (Figure 2). This view includes a chart with a calendar for navigating between weeks, a summary of weekly readings (eg, highest, lowest, and number of alerts), a detailed list showing each reading with its timestamp and whether it fell within the normal range or triggered an alert, and 1 or 2 pieces of educational content relevant to the user's current status for the parameter being viewed.
Activity or weight goal	In addition to being able to view activity and weight data over time, users can set a goal in relation to both parameters and track their progress (Figure 3). Daily or weekly activity goals can be set, while weight goals have no time frame.
Medication	The medication section of the CareApp allows users to add their medication list (prescription) including dosage, frequency, and any instructions for taking, as well as see their daily schedule and track when a medication has been taken (Figure 4).
Education	A library of education is included in the CareApp, which contains 2 main sections—content relevant to the conditions the user is managing and training content to help the user with using the devices and CareApp (Figure 5). Users can also add content to a favorites section.
Settings	This section allows users to set up their care network, to personalize certain settings (eg, to choose kilograms or stones and pounds for weight readings), and to choose between a light and dark theme.

Figure 1. The ProACT CareApp dashboard showing an overview of today's status, and sections showing data related to health parameters (My Health), with similar presentations of data for well-being parameters (My Wellbeing) and activity parameters (My Activity) further down the page.

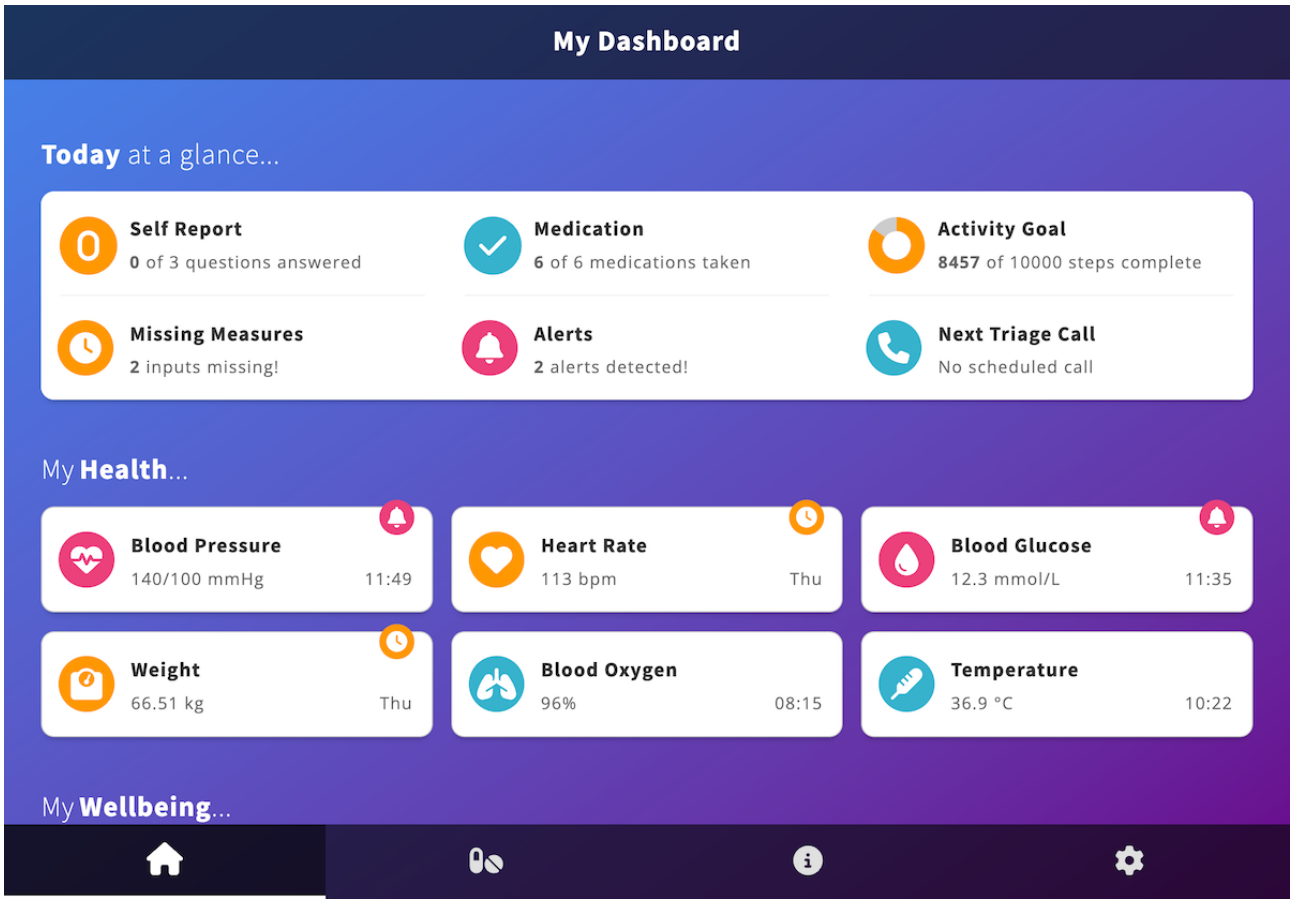

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Figure 2. Tapping on individual health, well-being, or activity cards on the dashboard brings the user to a more detailed view of their data. The figure shows an example of weekly blood pressure readings.

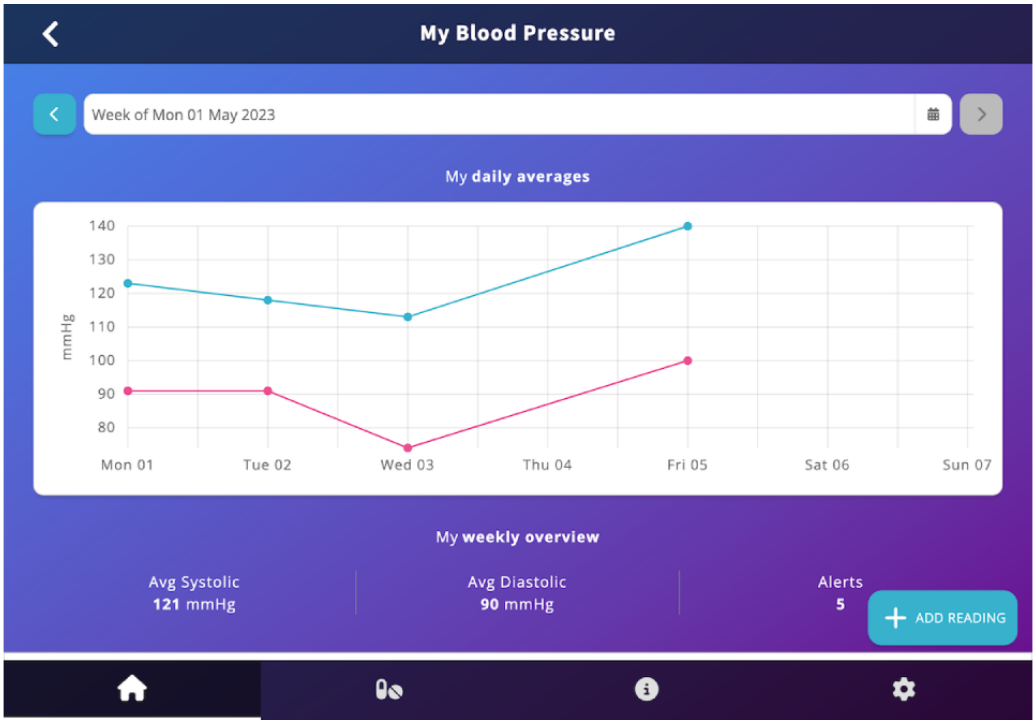

Figure 3. Users can set an activity or a weight goal and track their progress. A piece of contextually relevant education is also displayed on this screen.

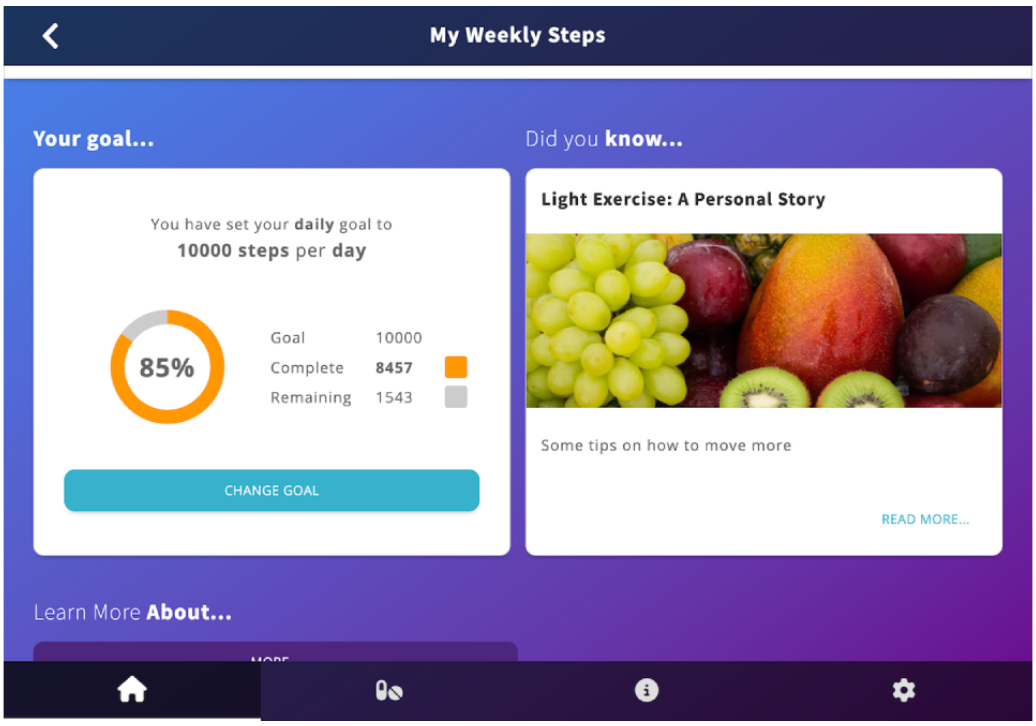

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Figure 4. The medication management section (My Medication) of the CareApp, where users can enter or add to their prescription, view their schedule, and track their intake by tapping on a medication and indicating that they have taken it today.

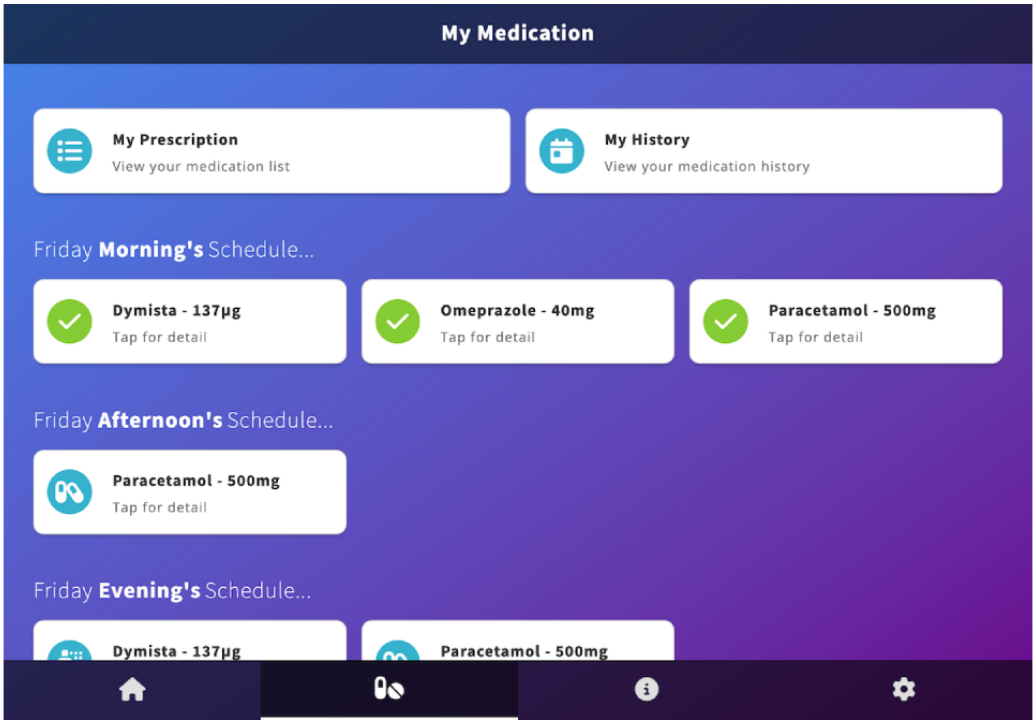

Figure 5. The education library showing content relevant to the user's conditions and training content on using the technology (devices and CareApp).

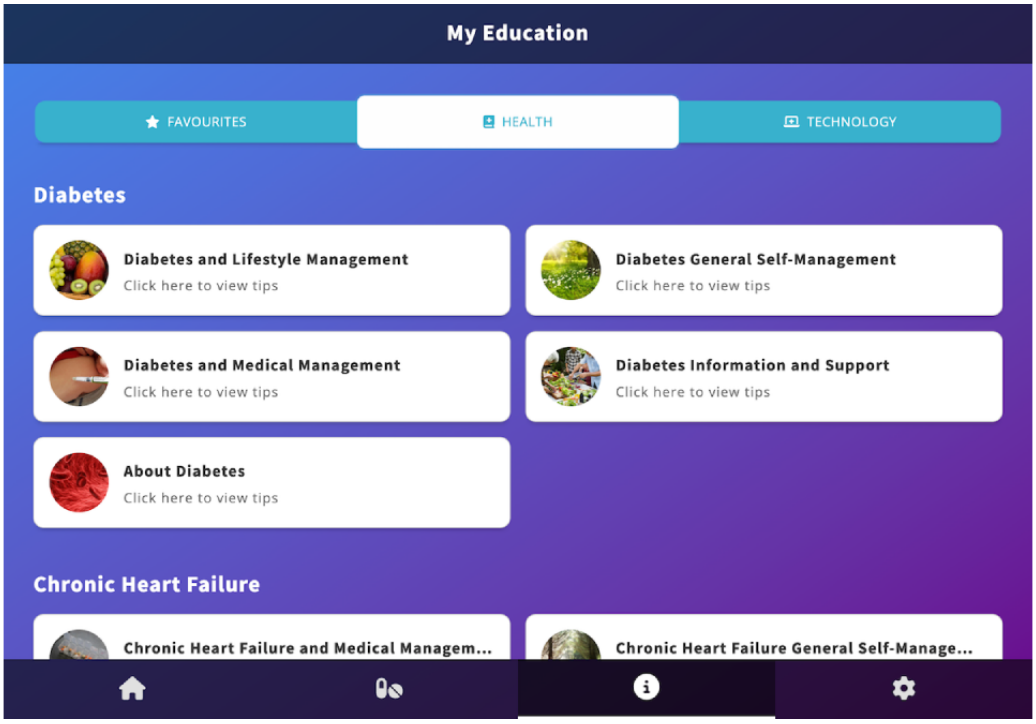

Admin Interface

Admin interface is a user management system to allow researchers or service organizations to personalize CareApps to individuals and manage, inspect, and analyze data.

Data Flow Through the ProACT Platform

The flow of data through ProACT starts and ends with people with multimorbidity and care network members. The following steps occur in the data transfer process:

- The person with multimorbidity wears or interacts with a measuring device.
- For connected devices, data are automatically transferred to the device provider's systems and then to the ProACT platform (ie, the ProACT CareApp front-end application and the admin back-end systems). For full details on the ProACT platform, see Doyle et al [24].
- For nonconnected devices, the person with multimorbidity manually enters their readings using the ProACT CareApp.

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- On receipt of new data, the ProACT platform will check all values against a person with multimorbidity's alerting thresholds. Where a threshold breach is encountered for a participant in trial arm 1, an alert is raised for the attention of the triage team. Triage teams can access, track, and categorize alerts through a provided administrative interface.

Methods

Study Design

Overview

This study comprises an EIH trial design in each country. In accordance with EIH philosophy, the objectives are (1) to assess the potential effectiveness of an intervention or interventions and (2) to assess their implementation, as well as factors associated with their implementation [28,30]. By assessing effectiveness and implementation concurrently, we can quickly learn about for whom, in what circumstances, and how an intervention or interventions work, if at all. In essence, the benefits include the efficient generation of research-to-practice translational gains, the identification of effective implementation strategies, and the development of relevant and useful information for policymakers and decision-makers (eg, the identification of barriers and facilitators to implementation can inform the selection of more appropriate strategies). A type 1 hybrid design will be implemented, which primarily focuses on effectiveness while exploring implementation. This design is recommended when the body of evidence in support of an intervention's effectiveness is limited, and thus prioritizing implementation, and related barriers, facilitators, and strategies are premature.

The EIH trial will comprise a p-RCT to measure effectiveness and a process evaluation to measure implementation. p-RCTs are used to assess the effectiveness of an intervention in real-world conditions [31,32]. While traditional randomized controlled trials are used to assess the efficacy of an intervention in ideal circumstances, p-RCTs are instead used to ensure that external validity is prioritized (ie, to ensure that the findings are generalizable to the real world), with internal validity still preserved as much as possible. Furthermore, while the conduction of traditional randomized controlled trials ensures that participants are often exposed to scenarios that are considerably different from their everyday lives, the conduction of p-RCTs ensures that participants are exposed to real-world scenarios, such as real-world approaches to recruitment (eg, for targeted health care support), follow-up enquiry and support, and flexibility and tailoring of delivery to support needs. Process evaluations are used to assess the implementation of an intervention in real-world conditions [33,34], in particular to assess the fidelity and quality of implementation of an intervention in real-world conditions, and to identify and understand causal mechanisms and contextual factors that are associated with varying outcomes [35]. The study design of the p-RCT and process evaluation are outlined separately below.

p-RCT Design

A p-RCT trial will take place in each trial site with each person with multimorbidity and their care network participating for 6 months. A 6-month period is sufficient to observe changes in key outcome metrics and to ensure that the novelty of a new technology is not a confounding variable. A 6-month period also ensures that a staggered approach to recruitment over the 32-month period can take place, thus mitigating against potential challenges for large-scale recruitment and implementation of the technology. A 3-arm design will be implemented with participants with multimorbidity. Textbox 1 indicates the differences between the arms.

A mixed methods approach will be adopted, with experimental and descriptive assessments used to compare participants in trial arms 1, 2, and 3. A more detailed description of methodologies used in the p-RCT is outlined below.

Textbox 1. Pragmatic randomized controlled trial arms.

Trial arm 1

- Tablet device and a suite of sensors
- Personalized ProACT CareApp
- Inclusion of the care network
- Clinical triage service support
- Technical helpdesk support

Trial arm 2

- Tablet device and a suite of sensors
- Standard ProACT CareApp with no personalization
- Technical helpdesk support

Trial arm 3

- Usual care (no technology)

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Process Evaluation Design

Overview

The process evaluation to be implemented within SEURO will adopt a mixed methods approach informed by three main theoretical frameworks: (1) the Consolidated Framework for Implementation Research (CFIR) [36]; (2) a digital health technology model of transferability, ProTransfer, which was developed during the ProACT project [37]; and (3) the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework [38]. The domains identified in these frameworks will be used to guide the development of the process evaluation. Below, we provide a brief description of each theoretical framework.

The Consolidated Framework for Implementation Research

The CFIR identifies five major domains of interest: (1) the outer setting, which includes the social, political, and economic context that the organization in which implementation is occurring exists; (2) the inner setting, which includes the features and characteristics of the organization such as leadership and relative priority; (3) the characteristics of individuals, which includes staffs' knowledge and attitudes about the intervention, and their role and identification within the wider organization; (4) the characteristics of the intervention itself; and (5) implementation processes, which include the ways that the intervention will be delivered in a given context (including fidelity to the implementation strategy).

The ProTransfer Model

Informed by the CFIR, the ProTransfer model addresses factors influencing organizations' transferability and implementation readiness for digital health technologies across four domains: (1) solution-specific factors, including adaptability (ie, the degree to which a solution can be tailored or refined to meet local needs), usability and design, trialability, and evidence of potential benefits and costs; (2) organization-specific factors, encompassing culture (ie, norms, values, and assumptions shaping acceptance and adoption), learning climate, leadership engagement, openness to change, resource availability, and compatibility with existing practices; (3) process-specific factors, such as engagement mechanisms (ie, attracting and involving key individuals through social marketing, education, role modeling, and training), formal leadership structures, participatory execution and evaluation, opinion leader engagement, and planning; and (4) individual-specific factors, including the self-efficacy of individuals involved.

The RE-AIM Framework

The RE-AIM framework identifies implementation outcomes across three domains: (1) reach—the proportion of eligible participants who open, use, and complete an intervention; (2) uptake—the proportion of eligible participants who opt in; and (3) acceptability or appropriateness—the perceived fit of the intervention.

As outlined in the Medical Research Council guide to developing process evaluations [34], a logic model (Figure 6) was developed for SEURO based on prior ProACT Horizon 2020 research. It captures key factors influencing implementation and clinical effectiveness, integrating elements of CFIR, ProTransfer, and RE-AIM. Factors in blue represent those varying between organizations, triage staff, and people with multimorbidity and their care networks, while those in green represent consistent implementation characteristics across stakeholders.

The process evaluation at each trial site will explore (1) how ProACT is implemented, delivered, and used at the partner organization, clinical triage service, and participant levels (person with multimorbidity and care network participants); (2) systematic differences and variations in implementation, delivery, and use at these levels; (3) the reasons for these systematic differences and variations (ie, facilitators and barriers) at these levels; and (4) the relationship between implementation, delivery, and use and potential effectiveness in relation to perceived QoL, HCU, and user-observed self-management experiences. A more detailed description of the methodologies used in the process evaluation is outlined below.

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Figure 6. Process evaluation logic model. HCU: health care use; QoL: quality of life.

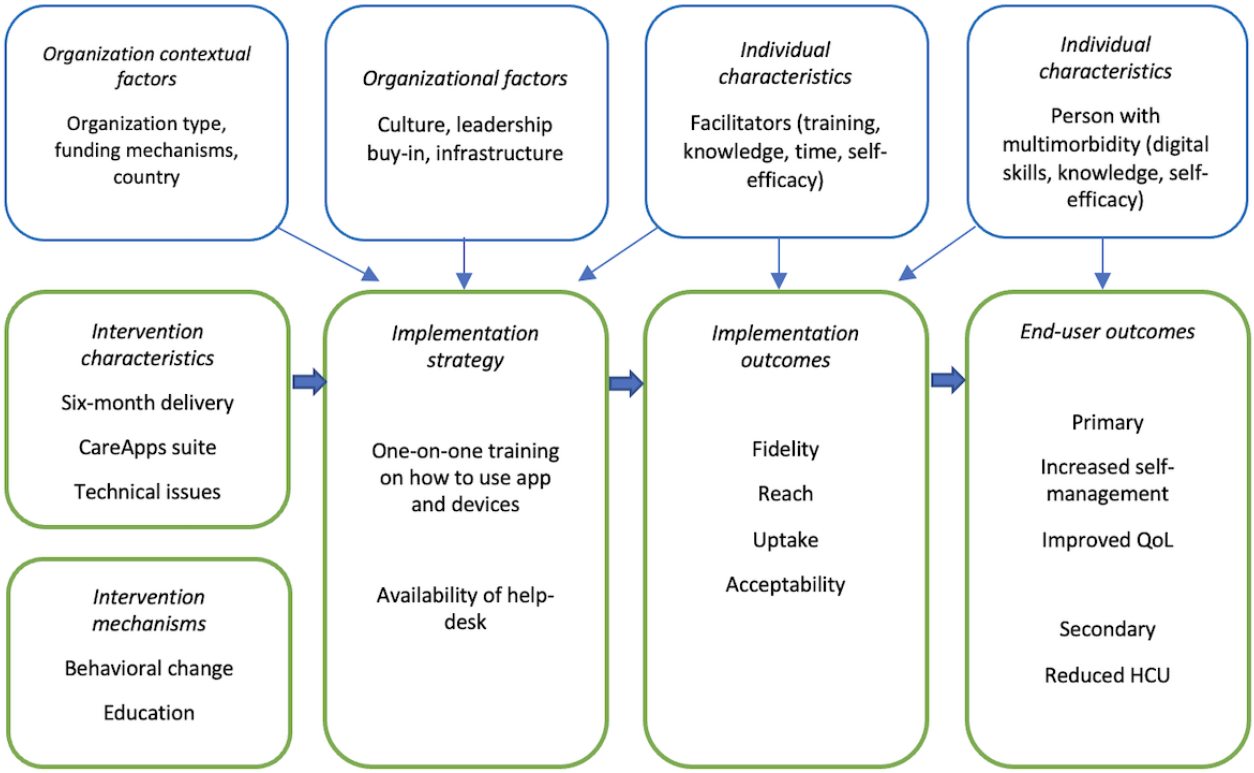

Sample

Three main participant groups will be recruited for the EIH trial in each of Ireland, Belgium, and Sweden: older people with multimorbidity, care network members, and partner organization management and staff involved in overseeing and implementing ProACT delivery. A maximum of 1920 participants (ie, people with multimorbidity and care network members) will be recruited across the 3 trial sites. This sample will consist of a maximum of 720 participants with multimorbidity (240 at each site) and a maximum of 1200 key individuals within the trial arm 1 participants' care networks (400 at each site). Up to 15 partner organization managers or staff (5 at each site) will also be recruited.

Participant Inclusion and Exclusion Criteria

Participants with multimorbidity must be aged 65 years or older, possess sufficient cognitive capacity to provide written informed consent, and have at least 2 of the following conditions: diabetes, chronic respiratory disease (eg, chronic obstructive pulmonary disease and chronic asthma), chronic heart failure, chronic heart disease (eg, coronary artery disease and cardiovascular disease, including hypertension, atherosclerosis, angina, or arrhythmia).

For care network participants to be included, the person with multimorbidity must provide consent for their participation. Care network participants must be aged 18-90 years; be providing support to a consented participant with multimorbidity in trial arm 1 (if they are an informal caregiver, they must be providing support to a participant with multimorbidity for at least 6 months; and if they are a formal caregiver, formal care quality assistant, or health care professional, they must be formally recognized as such and possess at least 2 years of experience of professionally working in a relevant health or primary care setting with people with multimorbidity with the same health conditions as those involved in this trial); have access to a tablet, smartphone, or computer with an internet connection; possess the skills to use an internet-based app or website; and possess sufficient cognitive capacity to provide written informed consent.

Partner organization management and staff must be aged 18 years or older; be overseeing and implementing the delivery of ProACT to their clients with multimorbidity; have access to a tablet, smartphone, or computer with an internet connection; and possess the skills to use an internet-based app or website.

Recruitment Procedures

Study recruitment will take place from various sources across the 3 trial site countries. In Ireland, people with multimorbidity will be recruited from multiple sources, including local health service executive clinics, general practitioner (GP) clinics, home care organizations, private hospitals as well as through social media, radio and local newspaper advertising, and relevant older persons and chronic disease networks (eg, diabetes and chronic obstructive pulmonary disease support groups). People with multimorbidity in Belgium will primarily be recruited through a clinical partner, Z-Plus. Other recruitment sources will include GPs, hospitals, social media and local advertising, a third-party recruitment company, as well as older persons and chronic disease networks. Study recruitment in Sweden will take place in the municipality of Umeå in Region Västerbotten via multiple sources including local cardiology clinics and associated clinical connections, relevant older persons and chronic disease networks (eg, the Association for Disability and Chronic Disease and the

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older adult service "Senior Square"), and advertising (eg, distributed information leaflets and flyers). Each potential participant will take part in an initial phone call, where they will receive information about the study and complete a screening process to ensure that they meet the eligibility criteria. If they wish to participate and prove eligible to do so, the research team will then send an information pack to them by email or post, containing an invitation letter, a participant information leaflet (PIL), and a written informed consent form. The PIL will also include the research team's contact details if the potential participants have any questions or concerns. A research team member will phone the potential participants 1 to 2 weeks (ie, 7 to 10 days) after sending the information pack to discuss their participation, provide additional information, and answer any questions. Those who express a willingness to participate will be asked to provide written informed consent, either using an online version or the hard copy version.

Across all 3 trial sites, participants with multimorbidity in trial arm 1 will be asked to identify up to 5 individuals within their care networks to take part in the study. They will be asked to provide these individuals' contact details and to provide permission for the research team to contact these individuals. Each potential care network participant will be sent an invitation letter, PIL, and a written informed consent form, either by post or email. The study information materials will contain the research team's contact details if the potential participants have any questions or concerns. A research team member will also contact them 1 to 2 weeks after sending these materials to discuss their participation, provide any additional information, and answer questions. Those who express a willingness to participate will be asked to provide written informed consent.

Managers or contact points in organizations that agree to take part in the study will be asked to identify members of their staff (including management themselves and clinical triage staff) to participate in the process evaluation (which will consist of completing 1 to 2 questionnaires and 1 interview). PILs and consent forms will be provided to process evaluation participants.

p-RCT Methodology

Overview

A sample of 720 community-dwelling persons with multimorbidity across Ireland, Belgium, and Sweden (n=240 per site) will be recruited to take part. Participants will be randomly assigned to 1 of 3 equal-sized trial arms: overall, 240 will be assigned to each arm (representing 80 assigned to each arm in Ireland, Belgium, and Sweden, respectively). With the permission of participants with multimorbidity in trial arm 1, up to 5 individuals in their care network will also be invited to participate; however, participants in trial arm 1 can still participate without the inclusion of any care network representative.

Person With Multimorbidity Participants

All participants will complete baseline questionnaires capturing their demographic, QoL, health, psychological and psychosocial, HCU, and multimorbidity self-management information (Table S1 in Multimedia Appendix 2) [39-48]. To reduce participant burden, questionnaires can be completed over 10 days. Data will be collected and managed using REDCap (Research Electronic Data Capture) software [49,50], hosted at Vrije Universiteit Brussel. Data collection mode will depend on participant preference. Those comfortable with technology will receive an email link; others will receive paper questionnaires, returned by post or collected during home visits for technology deployment (trial arms 1 or 2). Researchers may assist participants during these visits. For trial arm 3 participants, assistance will be provided via phone or online call, with researchers recording responses. When calls are not possible, a home visit will be arranged. Up to 60 participants in each of trial arms 1 and 2 (20 per country in Ireland, Belgium, and Sweden) will also take part in qualitative interviews to capture baseline information on current self-management strategies and trial expectations. Interview themes are detailed in Table S2 in Multimedia Appendix 2, while the T1 interview protocol is outlined in Multimedia Appendix 3. Interviews will be audio-recorded, transcribed, annotated, and analyzed.

All participants will complete QoL and HCU questionnaires at trial start (T1) and end (T2). As HCU is a key outcome, participants will report monthly to improve recall with data captured through REDCap either online or via researcher-assisted calls.

At trial completion, participants will again complete questionnaires (Table S1 in Multimedia Appendix 2), within a 10-day period, but if extenuating circumstances exist (eg, if participants are on holiday), within a 4-week period. Semistructured interviews with up to 60 participants in each of trial arms 1 and 2 will explore experiences using ProACT, self-management strategies, symptoms, and care network roles (themes in Table S2 in Multimedia Appendix 2, full interview protocol in Multimedia Appendix 4).

System use data (eg, technology engagement metrics and health data from sensors) and triage service use (eg, call frequency) will be continuously collected through the ProACT platform throughout the 6-month trial (Table S2 in Multimedia Appendix 2).

The primary outcomes for participants with multimorbidity include QoL and HCU.

The secondary outcomes include self-management (ie, assessed via a mixed methods approach; eg, this includes an examination of participants' perceived self-management using the custom-designed questionnaire and interviews with participants to explore their use of ProACT), health status (eg, an exploratory examination of the impact of ProACT on the hypothesized stabilization or reduction of participants' symptoms using the system data), quality of health care support, and other issues of relevance include multimorbidity self-management knowledge, attitudes (eg, confidence in ability to self-manage), and skill; health literacy, digital literacy, and associated attitudes (eg, attitudes toward technology).

Other outcomes for participants with multimorbidity include: the usability, accessibility, and acceptability of, and engagement, satisfaction, and overall experiences with, ProACT.

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Care Network Participants

Care network participants will be asked to complete questionnaires in the same manner as participants with multimorbidity (ie, online or over the phone, with data captured through REDCap [49,50]). At the beginning of their trial periods, all care network participants will be asked to complete a questionnaire that captures their demographic information; informal caregivers will also be asked to complete the Zarit Burden Interview [51]. At the conclusion of their trial periods, all care network participants will again be asked to complete 2 questions that capture their opinion on how the use of ProACT influenced their care and any burden they may have experienced while using ProACT (ie, measured via the User Burden Scale) [47]. Informal caregivers will also be asked to complete the Zarit Burden Interview [51]; while any formal caregivers, formal care quality assistants (ie, managers of formal caregivers), or health care professionals taking part in the process evaluation may have an additional questionnaire to complete (ie, the ProTransfer questionnaire; see Process Evaluation Methodology section). All questionnaires can be completed online or over the phone, depending upon the participants' preferences. The full list of key assessment domains and measures is available to view in Table S3 in Multimedia Appendix 2.

At the conclusion of their trial periods, the research teams will also conduct semistructured interviews or focus groups with up to 60 participants in each care network group (ie, with up to 20 participants in each care network group in each country) to collect data on their satisfaction with and attitudes toward the technology, etc. These will likely take place over the phone or online due to trial resource limitations and the anticipated wide geographic spread of care network participants within each country, particularly of informal caregivers. For health care professionals and formal caregivers or formal care quality assistants, these will take place either by phone, online, or at their place of work, depending upon what is most convenient for them. The interviews or focus groups will be audio-recorded and transcribed, and the researchers will subsequently annotate and analyze the collected data.

Finally, care network participants' system use statistics (eg, data that capture their use of the ProACT CareApp) will be collected continuously throughout their 6-month trial period.

The primary outcomes for informal caregivers include caregiver burden. Other outcomes for all care network participants include the usability, accessibility, and acceptability of, and engagement, satisfaction, and overall experiences with, ProACT.

Process Evaluation Methodology

Participants with multimorbidity, care network participants, and the clinical triage services and partner organization staff will participate in the process evaluation. For participants with multimorbidity and care network participants, the process evaluation will not result in additional research activities beyond those described in Table 2 and Tables S1 and S2 in Multimedia Appendix 2. However, topics specific to the process evaluation will be included in the interview and focus group protocols for the p-RCT evaluation.

Four types of data will be collected: administrative data, self-report questionnaire data (eg, ProTransfer data), digital analytic data (ie, system use data), and interview data. Table 2 summarizes what data will be collected, from whom, and when. Some of the data listed here will already be collected during the p-RCT (eg, the digital analytics data). For the semistructured interviews or focus groups, up to 60 participants with multimorbidity in each of trial arms 1 and 2 (ie, up to 20 participants in each country), up to 60 individuals in each care network group (ie, up to 20 individuals in each care network group in each country), the clinical triage services, and up to 15 partner organization staff (ie, up to 5 staff in each country) will be asked to participate. Interviews will likely take place over the phone or by online video call. The interviews and focus groups will be audio recorded and transcribed, and the researchers will subsequently annotate and analyze the collected data. The administrative, ProTransfer (questionnaire), and digital analytics data will be captured using electronic means (ie, online).

The outcomes for participants with multimorbidity in trial arms 1 and 2, all care network participants, and the clinical triage nurses include the usability, accessibility, and acceptability of, and engagement, satisfaction, and overall experiences with ProACT; and the way end users (ie, participants with multimorbidity, care network participants, and the clinical triage nurses) use ProACT (eg, to view one's readings, to set goals, and to consume educational material), how they differ in this regard (eg, to view readings only, to set goals only, or to consume educational material only), and the factors that influence these differences (eg, a participant with multimorbidity's condition and age).

The outcomes for partner organization staff include the reach, uptake, and fidelity of implementation of ProACT; the usability, accessibility, and acceptability of ProACT; and engagement, satisfaction, and overall experiences with ProACT; and the way organizations implement and deliver ProACT, how they differ in this regard, and the factors underpinning these differences (eg, societal- and organizational-level contextual factors, such as leadership buy-in).

Table 2. Process evaluation data collection.

Participants	Administrative data	ProTransfer data	Digital analytics	Interviews or focus groups
Management	✓ (pre)	✓ (pre and post)		✓ (post)
Participants with multimorbidity and care network participants			✓ (ongoing)	✓ (post)
Clinical triage nurses			✓ (ongoing)	✓ (post)

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Trial Procedures

The ProACT technology, described earlier and in Table 1, will be deployed to trial arm 1 and 2 participants in their homes for 6 months. Participants will regularly use the measuring devices and ProACT CareApp to record and manage key health and well-being parameters. Depending on the device, data will be uploaded automatically to the CareApp via Wi-Fi or Bluetooth or entered manually via the CareApp. An Internet connection will be provided to participants who do not have an existing connection in their homes. The technology will be withdrawn at the end of the trial, which will be clearly communicated beforehand and outlined in the consent form and PILs.

Care network participants will be asked to use the CareApp to view data shared by the participants with multimorbidity and to engage with the provided education materials. More specifically, the CareApp interface for each care network participant will allow the user to view the health and well-being data and medication details of participants with multimorbidity. Informal caregivers and formal caregivers will also receive educational material that pertains to the conditions of the participants with multimorbidity that they care for. Care network participants will be able to use the ProACT CareApp at a time and with a frequency that is convenient to them. The aim is to explore their experiences of technology and its perceived usefulness in supporting people with multimorbidity.

For trial arm 1, a clinical triage service in each country will review participants' vital signs and alerts at least 5 days a week (Monday to Friday). Triage nurses may adjust personalized thresholds and will contact participants if alerts are triggered, to discuss the alerts, and to determine if further action is required. For instance, the participants will be encouraged to bring their CareApp to their health care visits (eg, in situations where a health care professional has not consented to participate in the trials); where a health care professional has consented to participate, they will be able to view the relevant data in their CareApp, including detailed weekly data across all health and well-being parameters.

The clinical triage services will also support the development and personalization of data collection plans for participants in trial arm 1. Prior to the trial, the research and triage teams will create a ProACT data collection plan "care plan" (for data collection only rather than for clinical or treatment purposes) for participants in trial arm 1, tailored to their conditions (eg, how often they should measure their symptoms). As the trial progresses, the clinical triage services, in consultation with participants, will personalize their data collection plans. Participants can access their plans through their CareApp and share them with those in their care network.

Sample Size Justification

We used a 3-group comparison (ie, trial arms 1, 2, and 3) as the main fixed effect for a repeated measures ANOVA model to determine the sample size of the p-RCT. For a desired power of 0.80, an error variance of 2, and a type I error rate of 0.05 with an attrition rate of 30%, we estimated that we need 76 participants per arm per trial site (rounded up to 80) to detect a standardized effect size (Cohen *d*) of 0.25. In the situation that recruitment targets have been met and more participant candidates can be included in the study, we will aim for a sample size of 100 per arm per trial site instead of 80 to obtain a power of 0.90. Sample size and power analysis were conducted using STATA (version 17.0; StataCorp LLC).

Randomization

Upon study enrollment, the participants with multimorbidity at each site will be randomly assigned to 1 of 3 equal-sized trial arms (ie, 80-100 participants with multimorbidity will be assigned to each arm). Block randomization will be implemented to ensure balance in the sample size across groups; given that there are 3 arms, a block size of 9 will be implemented (ie, participants will be block randomized per every 9 individuals). The block randomization will be set up in REDCap [49,50].

Following CONSORT (Consolidated Standards of Reporting Trials) guidelines for p-RCTs [52], this trial will be unblinded. Blinding the researchers to participants' trial arms will not be possible due to the clear differences in the technology components across groups (eg, no component will be assigned to participants in trial arm 3). Additionally, it will not be possible to blind participants to the allocation of study or technology components.

Data Analysis Plan

For the p-RCT primary outcomes, three types of analysis will be conducted: (1) What is the influence of ProACT on perceived QoL? (2) What is the influence of ProACT on HCU? (3) What trial arm is the most cost-effective?

To determine if significant differences exist in (1) perceived QoL between the arms and (2) HCU between the arms, a linear mixed model will be used. In this model, a 2-level structure will be applied; repeated measures of QoL or HCU will comprise the first level, and participants will comprise the second level in the hierarchy. The outcomes will be assessed longitudinally using fixed effects of time, treatment arm and time interaction, and other baseline covariates such as age and gender.

ProACT's cost-effectiveness will be determined with the use of 2 economic evaluation techniques, cost-effectiveness standard and cost-utility analysis, applying the societal perspective. Societal perspective means, in general terms, the effectiveness evaluation will consider all the relevant contributors related to the participant. The 2 methods will allow the determination of the monetary value and the benefits of the intervention in health terms. For the monetary value, the HCU data will form the basis of the analysis.

Due to the questionnaire construction variation (countable and binary questions) and the time points of data collection during the trial, the analysis will make use of 3 statistical models: Poisson (countable data), logistic (binary response data), and linear regression (continuous data). The analysis will allow the observation of how ProACT affects the HCU, per arm at each trial site, and what the costs involved in this effect are for the monetary value definition. To define a 95% CI for this cost-effectiveness estimate per arm and per trial site, a sensitivity analysis will be performed, for instance, using a bootstrapping methodology.

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Indirect costs of the care network (informal care) will be calculated using data collected from the participants with multimorbidity and their informal caregivers. First, participants with multimorbidity will provide data on time spent on care by their informal caregivers. With the use of the opportunity costs method, this time will be converted into monetary value. Next, data collected from the informal caregivers, via the Zarit Burden Interview, will facilitate an assessment of the health gains of the time spent in care, considering the ProACT intervention. Indirect costs will be considered as an aggregated cost in this study.

The cost-utility analysis technique will underpin the quality-adjusted life years calculation. The quality-adjusted life years is a general measure used in economic evaluation that permits the valuation and comparison of the health gains of an intervention. For this calculation, the health-related QoL measurement instrument (EQ-E5-5L) will capture the self-perceived health status of the participant in a 5-digit code. Next, the code will be converted into a utility value (or utility weight), based on the country-specific value set. The result consists of the multiplication of the utility value with the period lived with the self-perceived condition.

For the secondary outcomes, such as the impact of ProACT on self-management, we may use structural equation modeling to determine the relevance and importance of different variables measured during the trial. Hitherto, there is no consensus on how to measure improved self-management. For this study, we may consider the concept of self-management as a composite measurement of different variables proven to be associated with the ability to self-manage chronic illnesses. Variables that are associated with improved self-management include, for instance, self-efficacy, health literacy, and disease knowledge, and therefore may be treated as latent variables. Using a structural equation model, such as confirmatory factor analysis, we will be able to identify the existence of a relationship between these variables and an overarching concept of self-management.

Outcomes from this exploratory analysis will help to determine whether features in ProACT could be tested in future clinical trials. Outcomes from the process evaluation and their inclusion, where possible, in the aforementioned exploratory analysis may also help to determine the relationship between implementation and effectiveness, and for whom, in what circumstances, and how ProACT influences the primary and secondary p-RCT outcomes. Descriptive summary statistics will be collated on the primary and secondary outcome measures, as well as on the variables included in the exploratory analysis.

The process evaluation will draw upon a range of quantitative and qualitative data to explore the implementation of ProACT and the factors that impact upon it. Descriptive summary statistics will be collated and examined where applicable (eg, demographic and system use data for participants with multimorbidity and care network participants, partner organizations' administrative and ProTransfer data, and participant recruitment and withdrawal data).

Interview and focus group data will also be attained to explore implementation and factors associated with it, including, for example, the perceived usability, accessibility, and acceptability of, and engagement, satisfaction, and overall experiences with, ProACT. The interviews and focus groups will be audio recorded, transcribed, and imported into NVivo (QSR International; in Ireland and Sweden) and MAXQDA (VERBI GmbH; in Belgium) for analysis. The researchers will also take brief notes during the interviews and focus groups to aid data interpretation and to identify potential themes. The interdisciplinary research team, with expertise spanning social, health, and sports psychology, human-computer interaction, and health care innovation, will actively engage in reflexive practice throughout the analysis. This collaborative approach will ensure participant voices are central while critically accounting for researchers' potential biases shaped by their backgrounds.

Collaborative qualitative analysis will be used to thoroughly examine interview data, leveraging multiple researchers' perspectives to capture nuances, manage large datasets, and reduce individual biases [53-55]. A hybrid thematic analysis approach will be used, combining inductive and deductive techniques based on Fereday and Muir-Cochrane's framework [56]. The research questions, an initial literature review, and a preliminary examination of interview data shaped the deductive approach's creation of a preliminary codebook. Simultaneously, the inductive approach will be used to identify new themes during coding, enriching the analysis. The transcripts will be coded using thematic categorizations, including within and between groups where applicable (eg, for trial arms 1 and 2 participants and for staff in different partner organizations).

The collaborative qualitative analysis framework will be applied with six sequential stages, commencing after the collection and transcription of the data: (1) preliminary organization and planning, (2) open and axial coding, (3) development of a preliminary codebook, (4) pilot testing the codebook, (5) final coding, and (6) reviewing the codebook and finalizing the themes. Consensus meetings will be conducted within and across trial sites to prepare the codebook and collaboratively identify and refine the themes. This approach ensures that diverse perspectives are considered, enhancing the validity and richness of the analysis throughout the research process.

Ethical Considerations

The trial protocol has received ethics approval from 5 research ethics committees in Ireland, including the School of Health and Science at Dundalk Institute of Technology, Trinity College Dublin Faculty of Health Sciences (reference 220504), Health Service Executive Northeast (reference REC/22/026), Caredoc, and Blackrock Clinic. In Belgium, the protocol has been approved by the medical ethics committee of the University Hospital Brussels (approval EC-2022-246), while in Sweden, it has been approved by the Swedish Ethical Review Authority (approval 2023-07594-01). Potential participants will receive a PIL. All recruited participants will be required to give informed consent. Efforts will be undertaken to ensure that participants fully understand the study aims, procedures, and their rights, including the voluntary nature of participation and their right to withdraw at any time without consequence. Participants will not receive compensation for taking part. Participants will be informed about the collection and use of

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their personal data as per General Data Protection Regulation requirements. Comprehensive measures will be implemented to maintain participant privacy and data security, including data minimization, secure storage, controlled access, and deidentification of research datasets. This will include purposes for processing personal data, retention periods, and who data will be shared with. Data will only be shared with trial partners. Qualitative interview or focus group data and quantitative questionnaire data will be coded to participant IDs, with all qualitative transcripts reviewed and any identifying information removed. Electronic sensor data captured through the ProACT platform will be both coded and identifiable. The data that flow from the measuring devices to the device provider systems and admin platform will be coded. These data will be made identifiable within the admin platform to trial researchers as well as clinical triage nurses. It will also be identifiable on the CareApp interfaces of health care professionals and formal caregivers, if a participant agrees to this. For instance, a GP may have several patients using the ProACT platform, who will be listed in the GP's ProACT CareApp. The GP will need to identify each patient by name. The health care professionals' or formal caregivers' access to their CareApp will be password-protected. The ProACT platform has been developed in compliance with General Data Protection Regulation requirements, and access will be managed and available to only those members of the teams who require access to conduct the trial and research. As the ProACT platform is a low-risk, noninvasive digital health intervention study, no formal ancillary or posttrial clinical care will be required. Participants will continue to receive routine care from their usual health care providers throughout and following their involvement in the study. Participants in the intervention arms will be informed that access to the ProACT platform and triage support (where applicable) will be time-limited to the duration of the study. Should any participant experience distress or identify health concerns during the trial, they will be advised to consult their GP or relevant care team, with trial staff trained to signpost participants to appropriate services when needed. Any significant amendments to the SEURO study protocol (eg, changes to study design, eligibility criteria, outcome measures, data collection procedures, or ethical considerations) will be formally documented, including a justification for the change and the potential implications for participants or study conduct. Amendments will be submitted to the relevant research ethics committees for review and approval prior to implementation, in accordance with national and institutional regulations. All approved amendments will be recorded in the trial registry (eg, ClinicalTrials.gov or EU Clinical Trials Register, if applicable) and communicated to all study sites, collaborators, and funders. Participants will be informed of any changes that may impact their involvement in the study, and reconsent will be sought where appropriate.

Results

Enrollment in the trial began in September 2022. To date, the trial has been completed in Ireland and Belgium. CONSORT diagrams are provided in Figures 7 and 8, depicting the recruitment and flow of participants with multimorbidity through the trials in Ireland and Belgium, respectively. Recruitment in Sweden completed in October 2025, with final participants finishing the trial by March 2026. Trial outcomes will be submitted for publication in 2026.

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Figure 7. CONSORT diagram of Ireland participants with multimorbidity. CASP-19: Control, Autonomy, Self-realisation, Pleasure; HCU: health care use; QoL: quality of life; RIP: rest in peace.

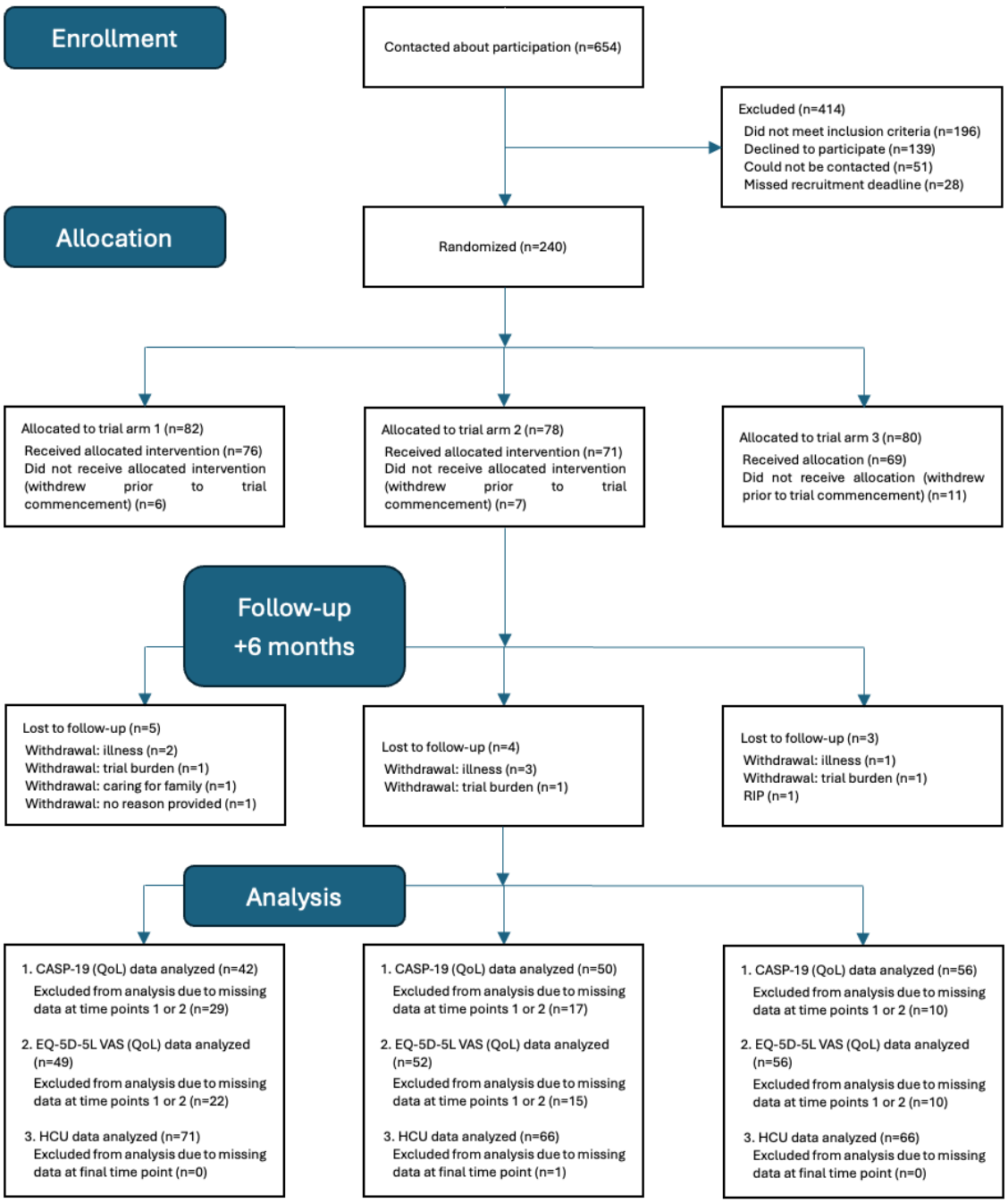

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Figure 8. CONSORT diagram of Belgium participants with multimorbidity. CASP-19: Control, Autonomy, Self-realisation, Pleasure; HCU: health care use; QoL: quality of life; RIP: rest in peace.

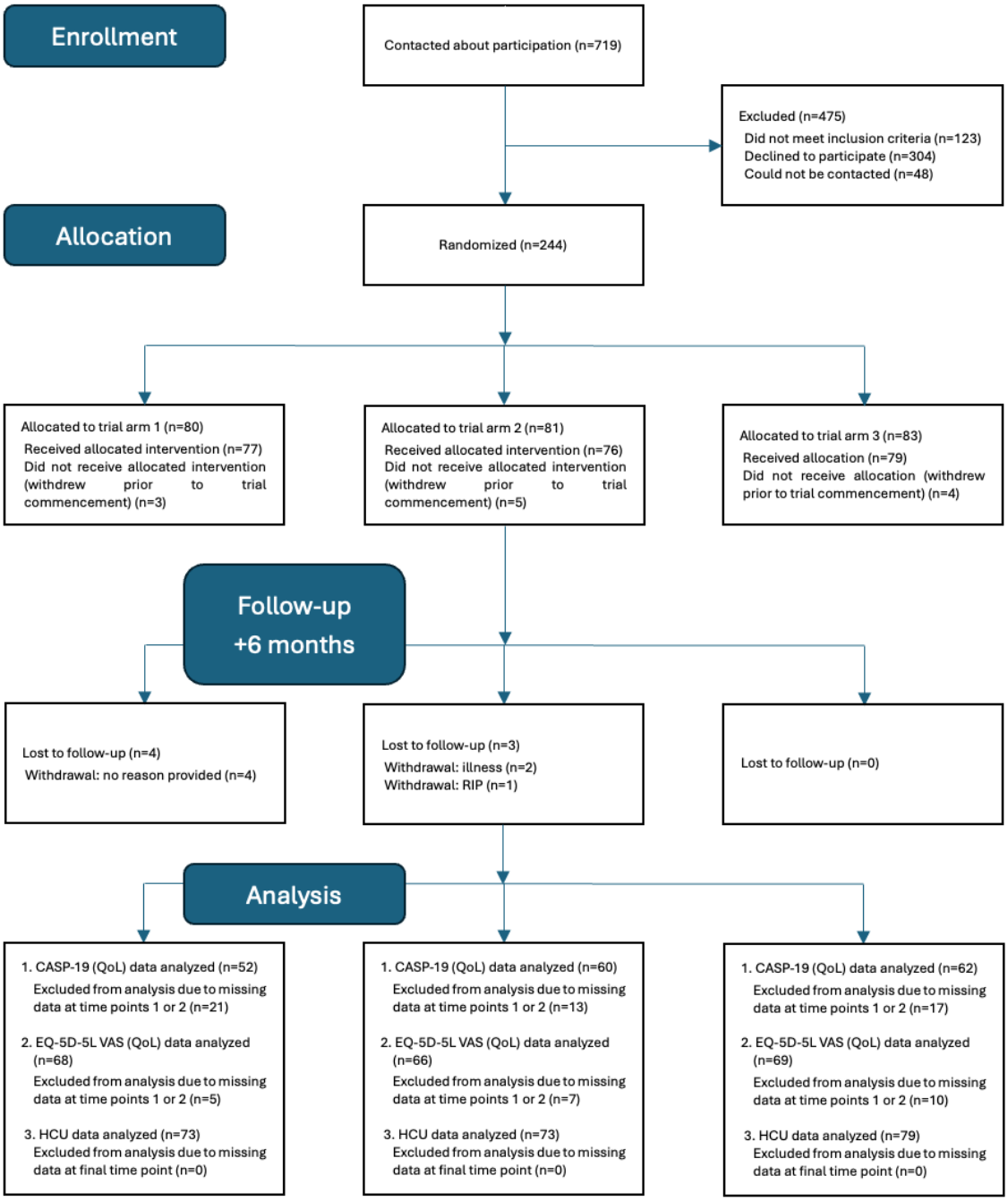

Discussion

Principal Findings

This paper presents the protocol for the SEURO EIH trial, which will investigate the effectiveness and implementation of the ProACT platform. To the best of our knowledge, this is the first trial of its kind to evaluate the effectiveness and implementation of a digital health platform with older adults with multimorbidity. Recent studies have underscored the lack of comprehensive reviews on the implementation and evaluation of digital health platforms, noting that existing reviews adopt a narrow focus, often limited to single chronic disease management or specific elements of implementation [57,58]. The ProACT proof-of-concept trial [24,26,27] demonstrated that the digital health platform ProACT, designed with and for older people with multimorbidity and their care networks, facilitated perceived improvements in their health and well-being, self-management, and receipt of support. Building on the proof-of-concept trial, the SEURO EIH trial will provide a more definitive and in-depth assessment of the updated and refined ProACT platform as a digital solution to support multimorbidity management in older adults. The SEURO trial

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also builds on prior work by incorporating nurse triage support and assessing the impact of this support as a means of augmenting engagement and health and well-being outcomes. Finally, this trial will also facilitate the achievement of wider SEURO project objectives: namely, to evaluate the key factors necessary to prepare any European Union region to successfully implement and scale innovative, people-centric, digital integrated health and social care solutions for multiple disease management.

Strengths

The SEURO EIH trial will incorporate a p-RCT and process evaluation to assess the effectiveness and implementation of the ProACT platform, respectively, in real-world conditions. This concurrent assessment of effectiveness and implementation will help us to understand if the platform (and related services) works as intended, and for whom, in what circumstances, and how (eg, we may learn about the facilitators of and barriers to use by certain persons with multimorbidity and identify strategies that incorporate and overcome these facilitators and barriers, respectively). Comparing the effectiveness and implementation of (1) the personalized ProACT CareApp, care network support, and clinical triage service support; (2) the standardized ProACT CareApp, absence of care network, and clinical triage service support; and (3) standard care could also provide valuable information about for whom, in what circumstances, and how a particular platform might be most suitable for certain persons with multimorbidity or certain health care organizations. The adoption of rigorous research methodology—for example, the recruitment of a diverse, large sample of older adults with multimorbidity across 3 European Union countries, and the collection of quantitative and qualitative data from various stakeholders (ie, persons with multimorbidity and their caregivers, health care organization management and staff, and clinical triage nurses)—will also help to assess the platform, to further build upon the ProACT proof-of-concept trial findings, and to advance this field of research more generally. As noted, few studies have tested the effectiveness and implementation of digital solutions for multimorbidity management, instead choosing to focus on design recommendations only. The SEURO EIH trial will address this gap.

An assessment of the ProACT platform will represent an efficient use of research resources, given its known likely benefits. Previous iterations of the platform underwent an extensive design and testing process during the ProACT proof-of-concept trial, which demonstrated positive outcomes. The platform was specifically designed to address the complexity of multimorbidity, incorporating behavioral change and human-computer interaction theory. It proved accessible and engaging for older adults with varying physical and mental capacities and was perceived to support improvements in their health and well-being. The current iteration has been further refined based on feedback gathered during and after the proof-of-concept trial. As such, its use and implementation hold the potential to generate positive outcomes—such as improvements in QoL and HCU among people with multimorbidity, reduced caring burden for informal caregivers, and increased satisfaction among health care organizations. Overall, the findings of this trial may also provide important information on next steps, such as how to further refine and modernize the ProACT platform, what strategies facilitate its fidelity of use and implementation, and the potential value of conducting larger clinical trials. Via the implementation of a systematic program of analysis of the collected data, with the findings published in peer-reviewed journals and presented at conferences, we will generate insights and advance the knowledge base of this emerging domain (ie, digital-health supported management of multimorbidity).

The generation of evidence-based support for the routine use of the ProACT platform in applied settings would represent considerable impact. With health care services under increasing strain and traditionally designed to support those with single morbidities, and with the emergence of threats such as COVID-19, it is more important than ever to develop actionable insights and resources that can empower persons with multimorbidity to self-manage their complex care needs at home, with the support of their caregivers. However, while interest in the use of digital solutions to support multimorbidity management is growing, its uptake is still limited, an issue that is perhaps partly attributable to the previously described research limitations. Bridging the research-practice divide via the ProACT platform could somewhat resolve this issue.

We anticipate that participants receiving triage support will demonstrate greater and more sustained engagement with the platform as well as improved symptom awareness and confidence in self-management. These findings could support the case for embedding light-touch clinical oversight in digital health services, especially for populations managing complex health needs. If successful, the approach could be scaled through integration with existing community nursing structures or primary care pathways, reducing the burden on acute services while preserving person-centered support. Additionally, insights from the Irish, Belgian, and Swedish contexts will inform strategies for adapting such services to different health system infrastructures.

Limitations

There are some study limitations that should be considered. First, HCU data will be self-reported by participants rather than collected through health care organization records. While self-reporting offers valuable insights into participant perceptions and experiences, it introduces potential recall bias, particularly for older adults managing multiple conditions, who may struggle to accurately recall the frequency or nature of health care contacts. Additionally, self-reported data may be underreported or overreported depending on individuals' health literacy, understanding of health care services, or social desirability bias. Some outcome measures, including digital engagement and symptom monitoring, will also rely heavily on quantitative use logs, which, while useful, may not always reflect the quality or intentionality of engagement. These limitations should be considered when interpreting the findings and drawing conclusions about the broader scalability of the ProACT platform. Finally, due to the nature of the study design, blinding of researchers during implementation will not be feasible, which may introduce potential bias. To mitigate this

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risk, researchers will adhere to predefined intervention protocols to minimize any influence on study outcomes.

Conclusions

The SEURO EIH trial protocol provides a detailed account of the objectives, scientific procedures, and practicalities of preparing for and managing the trial. Given that it will take place in multiple European Union countries, this protocol ensures that the research teams at all sites will possess a shared understanding of what the trial entails and can conduct the trial in a coordinated and intended way. Any deviations from the protocol during the trial will also be transparent and open to scrutiny.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are not publicly available due to ethical and privacy considerations but are available from the corresponding author on reasonable request, if approval is obtained from the relevant ethics committee and data sharing complies with institutional and legal guidelines.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT checklist.
[PDF File (Adobe PDF File), 119 KB - resprot_v14i1e74989_app1.pdf]

Multimedia Appendix 2
Participant with multimorbidity and care network assessment domains.
[DOCX File , 27 KB - resprot_v14i1e74989_app2.docx]

Multimedia Appendix 3
T1 interview guide for participants with multimorbidity.
[PDF File (Adobe PDF File), 311 KB - resprot_v14i1e74989_app3.pdf]

Multimedia Appendix 4
T2 interview guide for participants with multimorbidity.
[PDF File (Adobe PDF File), 228 KB - resprot_v14i1e74989_app4.pdf]

Multimedia Appendix 5
Peer review report from Horizon 2020 - Research and Innovation Framework Programme, European Commission (EU).
[PDF File (Adobe PDF File), 235 KB - resprot_v14i1e74989_app5.pdf]

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Abbreviations

CFIR: Consolidated Framework for Implementation Research
CONSORT: Consolidated Standards of Reporting Trials
EIH: effectiveness-implementation hybrid
GP: general practitioner
HCU: health care use
PIL: participant information leaflet
p-RCT: pragmatic randomized controlled trial
QoL: quality of life
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
REDCap: Research Electronic Data Capture
SEURO: Scaling European Citizen Driven Transferable and Transformative Digital Health
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Establishing a Pharmacy-Based Pre-Exposure Prophylaxis Program for Young Women Who Sell Sex: Protocol for a Randomized Controlled Trial

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Abstract

Background: Sex workers (SWs) are at risk of acquiring HIV infections. Despite this, SWs have low uptake of relevant preventive measures, such as HIV pre-exposure prophylaxis (PrEP). Community-based programs that make PrEP convenient and accessible have the potential to drive PrEP continuation and reduce HIV risk.

Objective: This study aims to describe the co-development and piloting of the Together Optimizing PrEP Access in Zimbabwe (TOPAZ) intervention—where SWs have the opportunity to access PrEP refills through pharmacies in Zimbabwe.

Methods: Using a participatory process, the TOPAZ intervention will be collaboratively developed with pharmacy owners and SWs. TOPAZ comprises the provision of safe and convenient spaces for PrEP refill pickups bundled with a gift voucher incentive at pharmacies. Formative research comprising focus group discussions and in-depth interviews with SWs, pharmacists, and stakeholders will inform the development of the preliminary model (aim 1). A cluster-randomized pilot trial will evaluate the impact of the PrEP-in-pharmacy intervention, compared to standard clinic-based pickup in the key populations program, on PrEP retention at 3, 6, 9, and 12 months after initiation (aim 2). The outcome of the pilot trial will be a comparison of PrEP retention at 6 months after initiation between study arms. We will also compare PrEP retention among SWs aged between 18 and 24 years at 6 months and among participants remaining active in sex work at 6 months. We will use the Generalized Estimation Equations model to generate risk differences and 95% CIs for PrEP retention in intervention versus comparison arms. Analysis will follow an intent-to-treat approach. Finally, a mixed methods study will be conducted to understand the potential for scaling TOPAZ for SWs; insights from this study will inform the design of a future effectiveness trial (aim 3). Proctor's implementation outcomes, namely, acceptability, adoption, appropriateness, feasibility, fidelity, and penetration of the pharmacy-based PrEP refill program, will be evaluated by triangulation of program data and qualitative interviews.

Results: This study began the enrollment of participants in March 2024. Data collection ended in May 2025. The final comprehensive analysis of the results will be conducted in February 2026 after all the data have been collected and reviewed comprehensively.

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Conclusions: This study will report on the feasibility, acceptability, and effectiveness of pharmacy-based PrEP refills to improve PrEP continuation among women who sell sex. If successful, this preliminary study will pave the way for a future effectiveness trial to evaluate this intervention more comprehensively.

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International Registered Report Identifier (IRRID): DERR1-10.2196/74141

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KEYWORDS

pre-exposure prophylaxis; female sex worker; key populations; HIV/AIDS; PrEP continuity; women who sell sex; differentiated service delivery

Introduction

Background

Sex workers (SWs) are disproportionately affected by HIV and contribute a 4-fold higher HIV prevalence than adults in the general population [1]. The relative risk of acquiring HIV among SWs globally is 9 times higher than the general population, while in sub-Saharan Africa, the relative risk of HIV acquisition is 11 times higher in SWs than the general population [2]. Data from generalized HIV epidemics in sub-Saharan Africa reveal that SWs and their clients account for >30% of HIV infections and 17% of incident HIV infections [2,3]. In Zimbabwe, HIV prevalence among female SWs (FSWs) is >50%, and the annual estimated incidence is 4%, translating to a 10-fold higher incidence than women in the general population [4,5]. New entrants into sex work and young women who sell sex are at the highest risk of HIV infection [5-8]. For example, HIV prevalence increases sharply from 2% for an FSW aged 16 years to >50% for an FSW aged 24 years in Zimbabwe [4,6-9]. These alarming statistics underscore a need to strengthen the effective use of HIV prevention for FSW, particularly among younger FSW, both to protect them from HIV and to support broader HIV epidemic control efforts [10-12].

Oral pre-exposure prophylaxis (PrEP) has demonstrated high efficacy in clinical trials, preventing >92% of new HIV infections when taken as prescribed [13]. However, implementation in real-world contexts has been disappointing, with low uptake and suboptimal continuation. Thus, strengthening motivation, capability, and effective use of PrEP among SWs, including younger FSWs, has the potential to reduce the rate of new infections among both SWs and the general population more broadly [5]. Mathematical modeling data from South Africa anticipate that high uptake and continuity of PrEP could theoretically lead to a population-level reduction in HIV incidence by 40% [7,8].

Although PrEP uptake reduces HIV risk, effective PrEP use and continuation is very low among populations considered high risk, such as SWs [14-16]. Studies from Benin (45%), Rwanda (22%), and Senegal (27%) reported lower PrEP discontinuation within 12 months when compared to South Africa (91%) and Zimbabwe (86%) [16-21]. These differences underscore the need to identify barriers to PrEP continuation toward developing context-specific interventions.

A host of factors impede PrEP uptake and continuation among FSWs, but of relevance to this intervention are fear of stigma associated with PrEP and lack of convenient access [20,22]. The World Health Organization recommends differentiated service delivery to diversify PrEP delivery, overcome barriers to access, and strengthen PrEP continuation [23]. Developing interventions outside the “brick-and-mortar” health clinics, for example, private pharmacies, may decentralize PrEP services and improve access [24-28]. Pharmacies are proven community-based channels that advance self-care initiatives in sexual and reproductive health and may be tailored to deliver PrEP for individuals considered high risk. Developing pharmacy-based PrEP service delivery models for SWs could make PrEP more accessible and improve PrEP uptake and continuation.

Successful delivery of pharmacy-based PrEP is contingent on collaborative efforts between policy makers, communities, and pharmacists [14,15,29-35]. This study aims to explore whether providing SWs with the option of PrEP refill supported by HIV testing through community-based pharmacies is feasible, acceptable, and increases effective use of PrEP in Zimbabwe. Given that research shows that small, short-term incentives can also be used to increase habit formation and motivation to continue PrEP [36-38], our trial also includes provision of small incentives to motivate PrEP continuation. Our Together Optimizing PrEP Access in Zimbabwe (TOPAZ) study develops and tests this pharmacy-based PrEP intervention for FSWs in Zimbabwe.

Study Aims

The overall goal of the TOPAZ study is to increase PrEP continuation among FSWs through a co-developed pharmacy-based intervention. Specific aims are as follows: aim 1 is to refine and operationalize pharmacy-based PrEP distribution, including an escalating incentive with FSWs and pharmacy owners to motivate PrEP continuation in FSWs; aim 2 is to determine whether the addition of pharmacy-based PrEP distribution increases PrEP retention among FSWs at 6 months compared to standard services; and aim 3 is to understand the PrEP-in-pharmacy program’s potential to scale and translate lessons learned into a future effectiveness study.

Methods

Overview

A mixed methods approach will be used to develop and pilot the PrEP-in-pharmacy refill intervention for SWs, as summarized in Figure 1. The PrEP-in-pharmacy refill

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intervention will be available to all SWs in their diversity, including male and transgender workers; however, this study will formally assess outcomes among FSWs. To achieve aim 1, formative research to co-develop the intervention with SWs and pharmacists will be conducted. To achieve aim 2, the intervention will be piloted through an existing key populations (KP) program. A 1:1 cluster-randomized control design will be used to allocate 8 suburbs to 4 intervention or 4 standard-of-care suburbs. To achieve aim 3, a process evaluation will be conducted using a mixed methods implementation science framework to determine the feasibility, acceptability, and scalability of the intervention and to optimize future versions of the program.

Figure 1. Overview of the Together Optimizing PrEP Access in Zimbabwe (TOPAZ) study design. KP: key populations; MoHCC: Ministry of Health and Child Care; PrEP: pre-exposure prophylaxis; SW: sex worker.

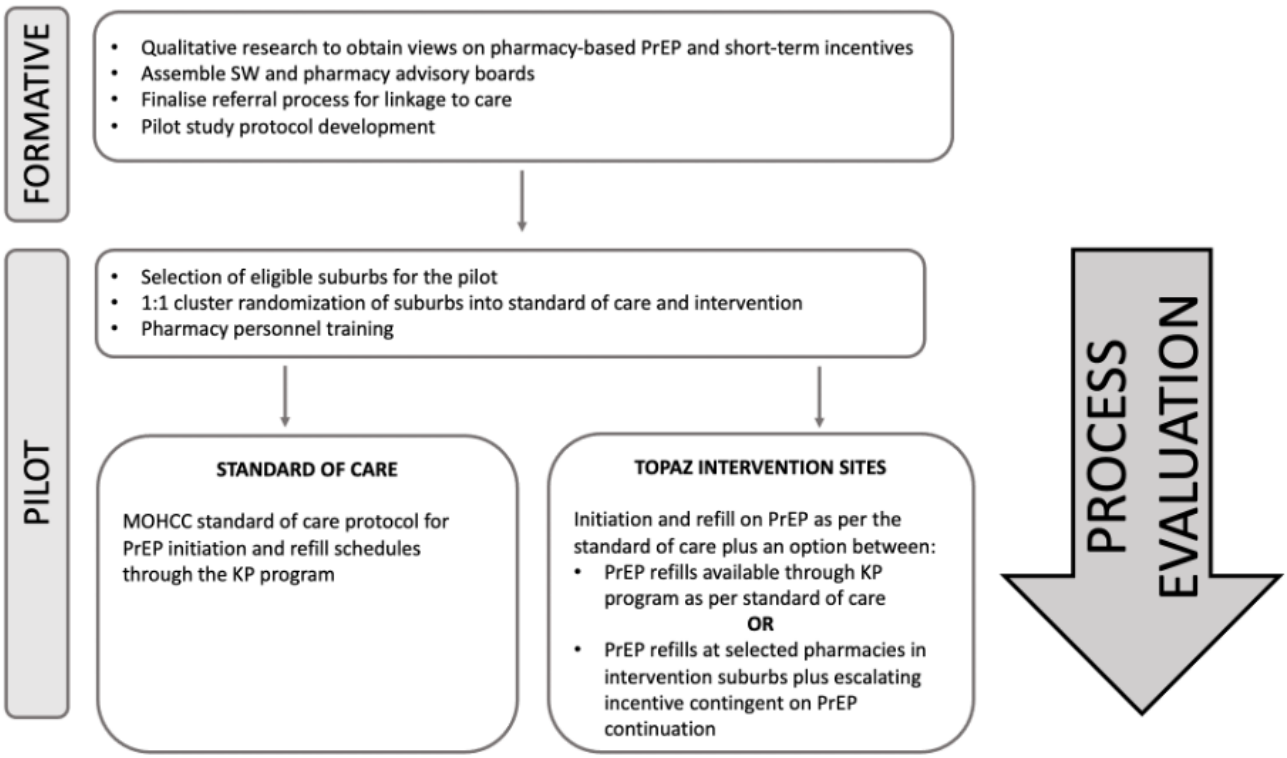

Theoretical Model Informing the Implementation

This research draws on 2 primary theoretical models of behavior change: the Capability Opportunity Motivation model of behaviour change and behavioural economics Capability Opportunity Motivation Behavior (COM-B) model of behavior change and behavioral economics (Figure 2 [39]) [37,38]. The pharmacy intervention will be designed to increase *motivation* through knowledgeable and friendly pharmacists plus the peer outreach and support services already provided by the existing KP program. In addition, small incentive gift vouchers that can be redeemed for pharmacy products offered to FSWs for collecting PrEP refills at pharmacies will also increase *motivation*. *Access* will be increased through PrEP provision at pharmacies, and *effective use* will be increased by combining pharmacy-based access with short-term, escalating incentives (gift vouchers) to encourage continued PrEP refills [38]. Underpinning the incentive component of the intervention is behavioral economic theory, which posits that using simple, scalable "nudges" (norms, commitments, and incentives) that capitalize on common biases can influence behavior [40]. This approach is particularly useful when applied to behaviors that are new (such as taking PrEP) or those that can be viewed as unimportant or inconvenient (such as collecting PrEP refills, especially due to present-biased preferences) [41]. Escalating incentives leverage the behavioral economics concept of *loss aversion*, increasing "losses" are faced each time a refill visit is missed, a simple yet powerful motivator to stay engaged with PrEP [42-44].

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Figure 2. Application of the Capability Opportunity Motivation Behavior model in the current PrEP delivery for YWSS and FSWs in Zimbabwe and the contributions of the proposed intervention, which provides friendly, pharmacy-based PrEP distribution by informed pharmacists plus financial incentives (adapted from the study by Schaefer et al). FSW: female sex worker; PrEP: pre-exposure prophylaxis; SES: socioeconomic status; YWSS: young women who sell sex.

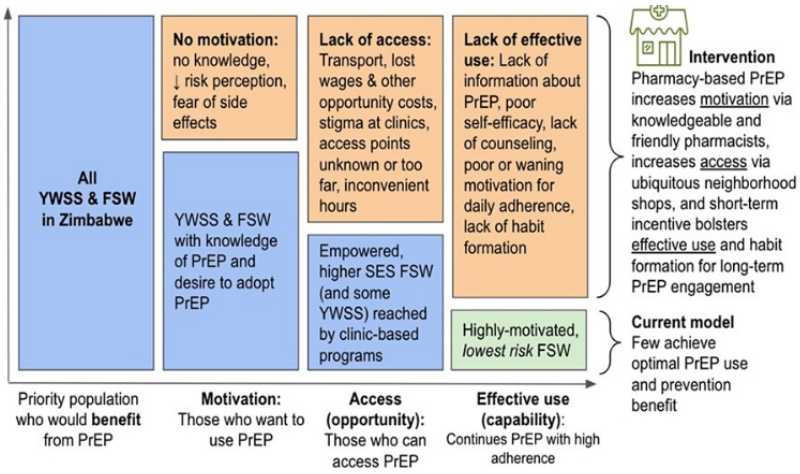

Ethical Considerations

The TOPAZ study has obtained ethics approval from the national ethics review committee in Zimbabwe, the Medical Research Council of Zimbabwe (MRCZ/A/2988), and the University of California Berkeley Committee for Protection of Human Subjects (2022-11-15783). All study procedures will be conducted in accordance with the Declaration of Helsinki. All participants will be informed about the study and will provide consent to participate, as outlined in the following sections describing the various study activities. Participant data will be deidentified and stored in secure databases, with identifiable data, such as full names (only in the informed consent), stored separately. Adverse occurrences throughout the study will be recorded in a log that will be shared with the national ethics review board.

Study Setting and Population

This intervention will be nested within the existing KP program, a nationally scaled program for SWs run by the Centre for Sexual Health, HIV, and AIDS Research Zimbabwe on behalf of the Ministry of Health and Child Care (MoHCC) and National AIDS Council. The program aims to reduce HIV acquisition and transmission via the provision of comprehensive sexual and reproductive health services at mobile and static clinics tailored for KP and supported by peer-led community engagement activities [5]. As of 2023, the KP program services include contraception, syndromic management of sexually transmitted infections, mental health screening and treatment, gender-based violence prevention and referral, HIV testing, initiation of antiretroviral therapy, HIV postexposure prophylaxis, and PrEP. The KP program operates mobile outreach clinics in 14 suburbs across Harare, from which 8 TOPAZ study suburbs were selected. Eligible suburbs needed to have ≥3 pharmacies that have a private area to implement the intervention and were willing to implement the intervention. Consequently, the PrEP-in-pharmacy intervention will be conducted in Glen Norah, Mufakose, Epworth, Glen View, Highfield, Kuwadzana, Mabvuku, and Kambuzuma.

Pharmacy Selection Process

A mapping exercise will be conducted in the selected suburbs to identify pharmacies that meet the TOPAZ pharmacy criteria. A sensitization process will be used to assess the pharmacy owners' interest in participating in the study. A total of 3 pharmacies per suburb will be shortlisted, and in instances where there are >3 qualifying pharmacies in a suburb, distance from a neighboring TOPAZ study pharmacy will be considered in the selection of the 3 participating pharmacies to ensure pharmacies are well spaced within the suburbs.

Design

To achieve aim 1, a qualitative study will be conducted. Aim 2 will involve a cluster-randomized control trial, with suburbs as the unit of randomization. In total, 8 suburbs will be randomized to either standard of care, which is collecting PrEP services from the KP program (*comparison condition*), or standard-of-care KP program PrEP services *plus* the option of pharmacy-based PrEP refills, which includes a financial incentive of a gift voucher for pharmacy products (*intervention condition*). FSWs in the KP program who are newly initiated onto PrEP will be recruited into the TOPAZ study prospectively, and outcomes will be measured at 3, 6, 9, and 12 months after PrEP initiation. Aim 3 will use a mixed methods approach to determine the feasibility, acceptability, and scalability of the PrEP-in-pharmacy intervention.

Aim 1: Formative Research

Overview

Formative research activities will be conducted to ensure that the proposed approach addresses barriers to PrEP retention on both the supply (pharmacy) and demand (SWs) sides. Two key stakeholder groups, the pharmacists and SWs, will be engaged to establish advisory boards. The SW advisory board will ensure that the final intervention design aligns with the needs and preferences of the SWs. The pharmacist advisory board will play a key role in operationalizing the PrEP-in-pharmacy intervention and ensuring it is integrated into routine business operations within pharmacies. Consultative meetings will be held monthly to develop the intervention process (Table 1).

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Table 1. Qualitative approaches to be applied in the formative research phase of the Together Optimizing PrEP Access in Zimbabwe study implementation.

Group	Method	Interviews, n	Inclusion and exclusion parameters	Contribution
Pharmacy advisory board	Consultative meetings	15	• Inclusion criteria • Pharmacies that are officially registered • Pharmacies located in Harare • Available to participate in board meetings during the intervention	• Inform intervention development from a pharmacy perspective
SW[a] advisory board	Consultative meetings	5	• Inclusion criteria • Enrolled in the KP[b] program • Demonstrating knowledge about PrEP[c] • Residing in Harare • Available to participate in board meetings over a 24-month period • Exclusion criteria • SW intending to move out of Harare during the intervention	• Inform development of the intervention from an SW perspective
SW	Semistructured in-depth interview	20	• Inclusion criteria • Aged >16 years • Exchanged sex for money or gifts in the last 6 months[d]	• Barriers to PrEP retention • Mitigating PrEP-related stigma • Using pharmacies for PrEP refills • Procedures for using and reporting HIV test results • Referral services • How to create a welcoming environment
Pharmacy personnel[e]	Semistructured in-depth interview	6	• Inclusion criteria • Aged >18 years • Own or work at a pharmacy in Harare	• Perspectives of engaging FSWs[f] in their shops • Attitudes and beliefs about SWs • Perceived roles in community-based health provision • Relationship with referral facilities and staff • Views on the viability of pharmacies as distribution sites for daily oral or other forms of PrEP and HIV tests • Which pharmacy personnel would implement intervention • Comfort with prescribing PrEP and providing HIV testing • Existing facilities within or near the pharmacy that provide HIV testing and counseling
Community leader	Key informant interview	6	• Inclusion criteria • Aged ≥18 years • Work with MoHCC[g], the City of Harare pharmacy, or organizations that may be impacted by the intervention	• Seek reactions on main insights from in-depth interviews • Invite input on the proposed pharmacy-based approach • Identify potential implementation barriers • Facilitating roles they can assume
KP program	Formal meeting	__[h]	• Inclusion criteria • KP program staff at the front line of outreach	• Formal appointments • Referral procedure preferences • Tracking continuation and missed appointments

[a]SW: sexual worker.

[b]KP: key populations.

[c]PrEP: pre-exposure prophylaxis.

[d]Pharmacy owners and staff.

[e]Not limited to SWs enrolled in the KP program.

[f]FSW: female sex worker.

[g]MoHCC: Ministry of Health and Child Care.

[h]Not applicable.

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Qualitative Studies

Trained social science researchers will conduct qualitative interviews to solicit insights that can be applied to strengthen the PrEP-in-pharmacy intervention (eg, how and where HIV testing should be conducted, how to identify study participants, and confidentiality and privacy). In-depth interviews (IDIs) will be held with SWs and pharmacy personnel, and key informant interviews will be held with community leaders and policy makers using guided questions summarized in Table 1. All interviews will be audio recorded, but in instances where individuals want to be interviewed but prefer not to be recorded, written note-taking methods will be applied. Analytic notes will be written and summarized for synthesis of information into a report that will be presented to the advisory board and stakeholders. Written informed consent will be obtained from all qualitative study interview participants. A rapid qualitative analysis approach will be used to interpret interviews in real time to facilitate intervention finalization [45]. Taken together, data from IDIs and key informant interviews and formal discussions with advisory board members will be used to develop the PrEP-in-pharmacy intervention protocol.

Development of the PrEP-in-Pharmacy Intervention

A workshop including the SW and pharmacy advisory boards, and pharmacists from pharmacies that qualify to implement the PrEP-in-pharmacy intervention, will be held to finalize the intervention protocol. Key outputs will be a detailed intervention protocol that has a (1) feasible implementation plan that has been endorsed by advisory boards; (2) training component for pharmacy personnel on HIV testing, PrEP, stigma reduction, and the referral procedures; (3) training component for KP program staff on how the strategy will be integrated with usual services and a referral plan acceptable to pharmacists and KP program staff; and (4) final structure for the escalating incentive (gift vouchers).

Aim 2: PrEP-in-Pharmacy Intervention Pilot

Overview

A 2-arm pragmatic cluster-randomized trial design will be used to determine whether the addition of pharmacies as an optional PrEP refill collection point increases retention on PrEP among SWs compared to the standard-of-care services offered in the KP program (Figure 3). A 1:1 cluster randomization process will be conducted by a statistician using covariate-constrained randomization [46] in R software (version 4.1.3; R Foundation for Statistical Computing). A public randomization event will be held in which the Community Pharmacists Council, MoHCC, and other key stakeholders will participate. There will be no masking at the cluster level (suburbs), and SWs will be informed of the intervention. SWs newly enrolled in the standard-of-care suburbs will not be explicitly informed about the intervention. This trial is not blinded.

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Figure 3. Overview of the pre-exposure prophylaxis (PrEP) in pharmacy intervention implementation strategy. FSW: female sex worker; KP: key populations; REDCap: Research Electronic Data Capture.*Escalating gift voucher structure: month 1 refill=US $5 voucher, month 3 refill=US $6 voucher, and month 6 refill=US $7 voucher.

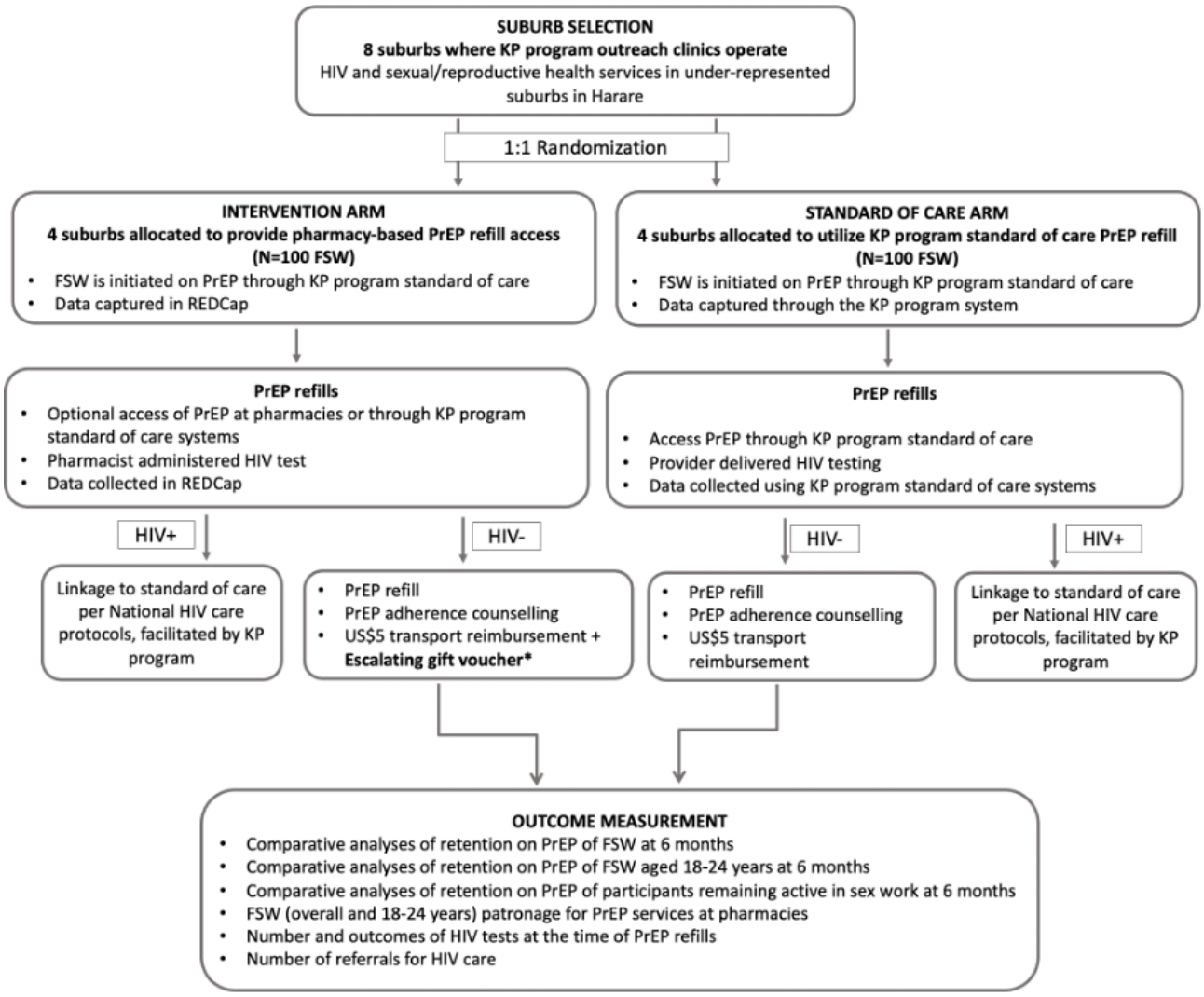

Overview of PrEP Services in the KP Program

The KP program requires verbal consent from SWs to dispense PrEP, which is freely available [5]. MoHCC implementation guidelines include free provider-delivered oral rapid HIV testing at initiation, along with provision of a 1-month supply of PrEP. The first refill provides a 2-month supply of PrEP, followed by 3-month supplies for subsequent refills (Figure 4). Free, provider-delivered oral rapid HIV testing will be offered every 3 months, and in accordance with the national PrEP guidelines, only individuals with confirmed HIV-negative results are offered future PrEP refills [47]. KP program data are collected on paper-based forms for all SWs who initiate PrEP routinely; these are used to generate a unique identification number for the SWs and an associated KP program file, which is essential for PrEP refill collection. People who do not return for refill visits are routinely followed up via phone calls, WhatsApp (Meta Platforms, Inc) reminders, and peer outreach. SWs are offered a US $5 transport reimbursement when collecting their PrEP refills routinely in the program.

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Figure 4. The pre-exposure prophylaxis (PrEP) refill schedule used by the key populations (KP) program, in alignment with the Zimbabwe national PrEP refill algorithm. Each PrEP refill is supplied with a US $5 transport reimbursement. Refill months indicated in red highlight where an HIV test is required to receive PrEP.

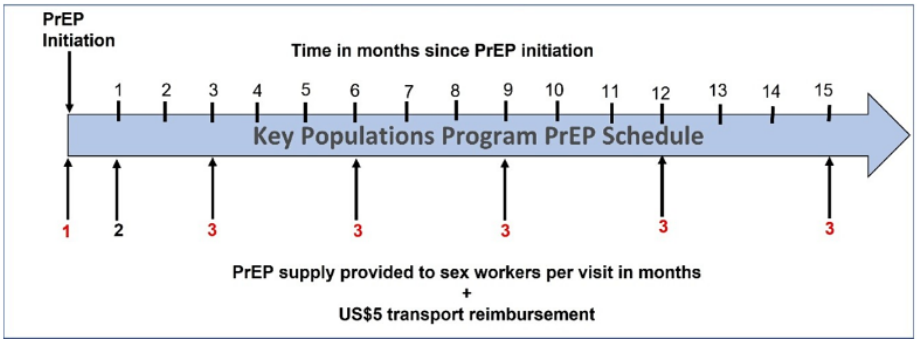

Procedures for the Standard-of-Care Arm

SWs enrolled as part of the TOPAZ study in the standard-of-care arm will initiate PrEP following the KP program standard operating procedures. They will be recruited through the KP program outreach clinics; undergo HIV testing; and if they are HIV negative, they provide verbal consent for PrEP initiation and collection of subsequent refills. At each visit, SWs will receive PrEP plus counseling on the importance of adhering to the prescribed PrEP schedule. PrEP refills will be recorded on standardized paper-based data collection tools, per the KP program standards, and will be analyzed from the program records.

Inclusion criteria for enrollment into the TOPAZ standard-of-care arm are (1) initiated on PrEP through the KP program's mobile outreach clinics operating in 1 of the 4 standard-of-care suburbs, (2) aged >16 years, (3) having exchanged sex for money in the last 6 months, and (4) providing verbal consent.

All participants will receive a US $5 transport reimbursement at the end of each visit. Participants in the standard-of-care arm will be advised that they can collect PrEP refills from the KP program clinics, following standard procedures. Participation in the intervention will continue for 12 months.

Procedure for Those Enrolled Through the PrEP-in-Pharmacy Intervention Arm

FSWs initiated on PrEP through the KP program's mobile outreach clinics in the intervention suburbs will be informed about the intervention, namely, the opportunity to access PrEP refills either from selected pharmacies within the suburbs or through KP program clinics. In addition, the participants will also be informed that PrEP refills in the pharmacy warrant gift vouchers for the first 6 months of the trial, and no vouchers will be available for the remaining 6 months of the trial. Intervention arm participants initiating PrEP will be given a TOPAZ referral slip, which they can redeem at any participating pharmacy or KP program clinic. The same services provided at standard-of-care sites will be available through the pharmacy, namely, HIV testing, PrEP refills, adherence counseling, linkage to additional services, and the US $5 transport reimbursement in line with the KP program care. In addition, FSWs that opt to refill PrEP-in-pharmacies will be offered an incentive in the form of a gift voucher redeemable for products in the pharmacy wherein the refill was collected. The incentive will continue until month 6 and will escalate in value at each visit. Months 1, 3, and 6 will receive gift vouchers valued at US $5, US $6, and US $7, respectively. To measure retention on PrEP without incentive, participants will not receive a gift voucher in the last 2 refill visits of the intervention, that is, months 9 and 12; however, data will be collected. Implementing pharmacies will be given a TOPAZ study handbook with standard operating procedures for the intervention. In addition, the KP program will conduct weekly support visits to participating pharmacies.

Recruitment of FSWs in PrEP-in-Pharmacy Intervention Suburbs

FSWs initiating PrEP will be informed that enrolling as an intervention participant is voluntary and their refusal will not interfere with the KP program standard of care, including their ability to access PrEP. FSWs will also be given information about the intervention and the associated risks in detail. Interested FSWs will be given an information flyer, and consent to participate will be obtained verbally. Information flyers will be available in the 3 main languages spoken in Zimbabwe: English, Shona, and Ndebele. The eligibility criteria to participate in the intervention arm are (1) initiated on PrEP through the KP program's mobile outreach clinics in 1 of the 4 intervention suburbs, (2) aged >16 years, (3) having exchanged sex for money in the last 6 months, and (4) providing verbal consent to enroll in the TOPAZ study.

Data Collection for the PrEP-in-Pharmacy Intervention Arm

Data for the intervention participants will be captured onto a mobile health tool, REDCap (Research Electronic Data Capture; Vanderbilt University) [48], operating on tablets. Built-in eligibility parameters, refill scheduling, and dispensing information, as well as prompts to guide pharmacists and KP program staff through the PrEP refill process, will be programmed. To protect the privacy and confidentiality of the FSWs, at each refill, only data that pertain to the specific refill will be visible to the pharmacists through the refill interface.

Pharmacists' Enrollment to Implement the PrEP-in-Pharmacy Intervention

Pharmacies will be selected to implement the PrEP-in-pharmacy intervention, based on the following criteria, and will be notified. Inclusion criteria for pharmacies participating in the TOPAZ

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intervention are (1) a valid pharmacy operating license; (2) interest in administering PrEP to SWs in all their diversity, in accordance with professional standards outlined in the written agreement; and (3) the presence of a private room or cubicle within the pharmacy where the HIV testing and PrEP can be provided.

Participating pharmacies will be requested to provide written consent to participate, agreeing to ensure professional, ethical, and respectful conduct toward SWs. All pharmacy personnel that are responsible for administering prescriptions within the pharmacy will undergo a series of mandatory trainings to prepare for implementation, including protocol training and a MoHCC-certified course for HIV testing.

Pharmacy Refill Pickup Procedure

TOPAZ intervention participants will present the TOPAZ referral slip or their KP program number to the pharmacy, and the pharmacy personnel will usher them into the private room for study-related activities, including HIV testing and PrEP refills (if eligible). FSWs who test HIV positive will be referred to the KP program for linkage to care.

Sample Size and Power Calculations

Data from our previous work indicate that current PrEP retention at 6 months post-PrEP initiation is 14% among FSWs in Harare. With 8 suburbs (4 per arm) and a target enrollment of 25 SWs per intervention suburb (totaling 100 participants in the intervention arm), and assuming an ICC of 0.12, the study will have ≥80% power to detect a 36% increase in PrEP retention—from 14% in the standard-of-care arm to 50% in the intervention arm. Note that this is a pilot trial and, consequently, is only powered to detect large effect sizes. If retention is lower than expected in the comparison group (eg, 10%), we will have at least 80% power to detect a ≥34% increase in PrEP retention. Likewise, if retention is higher than expected in the comparison group (eg, 30%), we will be adequately powered at 80% to detect a ≥38% increase in PrEP retention.

Outcomes

Outcome 1: Retention on PrEP at 6 Months

This will be measured as attendance within a window of −7 to +7 days of the scheduled 6-month refill visit. Outcome 1 will be expressed as the proportion of 6-month visits completed as scheduled, overall and by arm.

Outcome 2: PrEP Retention at 6 Months Among FSWs Aged Between 18 and 24 Years

This will be measured as attendance within a window of −7 to +7 days of the scheduled 6-month refill visit. Outcome 2 will be expressed as the proportion of visits completed as scheduled, overall and by arm.

Outcome 3: Patronage for PrEP Services at Pharmacies

FSWs (overall) and FSWs (aged between 18 and 24 years) patronage for PrEP services at pharmacies, defined as the proportion of all PrEP refill pickups (1, 3, 6, and 12) in intervention suburbs occurring at pharmacies, overall and by pickup month.

Data Analysis for Aim 2

For retention outcomes at 1, 3, 6, 9, and 12 months, the KP program database will be used to compare the number and proportion of FSWs retained on PrEP as defined earlier by study arm. We will conduct an intent-to-treat analysis to estimate the intervention's effect using a cluster-based permutation test applied to the individual-level binary outcome (retained on PrEP and not retained on PrEP) using the *cptest* function in the R cvcrand package (or a similar function). The permutation test will be conducted with the same covariates used during the constrained randomization process at the suburb level (expanded from the values of the cluster-level covariates, according to which cluster everyone belongs). This approach will be repeated for the other outcomes. To produce a measure of effect, a Generalized Estimation Equations model will also be constructed to generate a risk difference of PrEP retention among people initiating PrEP in intervention versus comparison suburbs and a 95% CI. In accordance with the CONSORT (Consolidated Standards of Reporting Trials) guidelines, unadjusted estimates will be reported, and the preregistered analysis plan at ClinicalTrials.gov will specify an adjusted model in the case of baseline imbalances. Overall, this analysis framework permits causal attribution.

Data Management

All data collected in this study will be managed and transmitted by a trained data manager. A study operation manual with data management and monitoring guidelines will be developed to ensure protection of participants' confidentiality and minimal risks due to participation in the study.

Aim 3: Determine the Feasibility and Scalability of the Pharmacy-Based PrEP Program

Overview

A mixed methods evaluation, guided by the implementation science framework by Proctor et al [49], will assess implementation outcomes and how well findings link with our conceptual model, that is, how capability, opportunity, and motivation are affected. We will use the following data collection methods: (1) IDIs with FSWs and pharmacy owners and staff, KP PrEP outreach workers, and community stakeholders; (2) direct observations at intervention pharmacies; and (3) feedback from both the SWs and the pharmacist advisory boards. Collectively, data from the pilot, IDIs, and pharmacy observations will be synthesized to determine if the approach is feasible and acceptable toward optimizing the intervention for an effectiveness study.

Data Collection Approaches

Multiple data sources will be triangulated to evaluate the implementation science outcomes defined by Proctor et al [49], including acceptability, adoption, appropriateness, feasibility, fidelity, and penetration (Table 2). Specifically, the following data collection approaches will be used and combined with administrative data from the existing KP program to assess the implementation outcomes.

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Table 2. Implementation outcomes and data sources.

Outcomes and analysis levels	Available measurement
Acceptability	
FSW[a]	• IDIs[b] and observation at pharmacies
Pharmacist	• over the study period trained and retained over the study period
Adoption	
FSW	• Number of FSW opting to refill at pharmacy versus the KP[c] program • Clinic
Pharmacist	• Number of pharmacies dispensing PrEP[d] refills
Appropriateness	
FSW	• IDIs, observation at pharmacies, and advisory board feedback
Pharmacist	• IDIs, observation at pharmacies, and advisory board feedback
Community	• Donors and KP program forum interviews
MoHCC[e]	• MoHCC, City of Harare pharmacy, and health care staff IDIs
KP program staff	• KP program staff interviews
Feasibility	
FSW	• IDIs and advisory board feedback
Pharmacist	• IDIs and advisory board feedback
Cost	• Beyond the scope of this proposal
Fidelity	
Pharmacists	• FSW IDIs, pharmacist interviews, and observation at pharmacies
KP Program	• Referral data, self-test kit data, and refill prescription data
Penetration	
Donors and KP program	• Scaled to other program sites beyond Harare
Sustainability	• Beyond the scope of this proposal

[a]FSW: female sex worker.
[b]IDI: in-depth interview.
[c]KP: key populations.
[d]PrEP: pre-exposure prophylaxis.
[e]MoHCC: Ministry of Health and Child Care.

Overview of IDIs

A trained social scientist researcher (who is not part of the KP program) will conduct IDIs with FSWs, pharmacy staff, KP program staff, and community leaders, as summarized in Table 3. All interviews will be conducted by a single interviewer in the participant's preferred language using topical guides (Multimedia Appendices 1-3).

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Table 3. Summary of qualitative studies to be conducted in the implementation framework study.

Group	Interview	Interviews, n	Inclusion and exclusion parameters	Interview guide
FSW[a]	Semistructured IDI[b]	20	• Inclusion criteria • Aged ≥16 years • Initiated on PrEP[c] during the study period • At least half of the interviewed participants should be aged between 16 and 24 years • Users and nonusers of pharmacies • Retained and not retained on PrEP • Willing and able to provide written informed consent (or witnessed thumbprint and mark for those who cannot read and write) • Exclusion criteria • Too physically or mentally unwell to participate, as determined by staff observation	• About their experience being part of the study and being on PrEP • Why did they use or not use the pharmacy for PrEP refills • If relevant, their experience going to the pharmacy for PrEP refill pickup (focusing on interactions at the shop and perceived stigma) as well as getting HIV testing or using and reporting results with the HIVST[d] • Their perspectives on the short-term incentive • About how we might improve the pharmacy experience and increase general interest in pharmacy-based PrEP refill visits • About how we might improve the pharmacy experience and increase general interest in pharmacy-based PrEP refill visits • Other KP[e] program services they may wish to have offered through pharmacies
Pharmacy personnel from pharmacies that were involved in the TOPAZ[f,g] intervention	Semistructured IDI	24	• Inclusion criteria • Aged ≥18 years • Own a pharmacy or work at a pharmacy in Harare • Pharmacists located in the KP program suburbs	• Implementation challenges and strengths • Enthusiasm for the approach • Reactions to catering for FSWs and distributing PrEP refills and HIV testing • Opinions on the design of an expanded future program • Benefits for the clientele and business' profitability, reputation, professional self-worth, and job satisfaction • Strategies for longer-term sustainability and opportunity and barriers for further market expansion
Community leader	Key informant interview	5	• Inclusion criteria • Aged ≥18 years • Work with MoHCC[h], the City of Harare, NAC[i], or any organizations that may be impacted by the intervention	• To assess the appropriateness of the pharmacy-based intervention • Potential for scale throughout Harare and beyond
KP program	Semistructured IDI	5	• Inclusion criteria • Age ≥18 years • Employee of the KP program (including outreach workers) in 1 of the 8 study suburbs of Harare • Employee of the KP program for at least 60 days • Directly involved in the initiation and retention of FSWs on PrEP	• Explore the appropriateness of the pharmacy-based PrEP intervention

[a]FSW: female sex worker.

[b]IDI: in-depth interview.

[c]PrEP: pre-exposure prophylaxis.

[d]HIVST: HIV self-test.

[e]KP: key populations.

[f]TOPAZ: Together Optimizing PrEP Access in Zimbabwe.

[g]Pharmacy owners and staff.

[h]MoHCC: Ministry of Health and Child Care.

[i]NAC: National AIDS Council.

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Direct Observations at Intervention Pharmacies

Trained social science researchers will conduct direct observation at 2 pharmacies per intervention suburb using a structured data worksheet. Pharmacy owners and staff will be informed of the plans for direct observation during the informed consent process for participation for aim 2. Direct observations will be scheduled ahead of time to coincide with times when there is an expected high number of refill visits, based on REDCap data. Pharmacies will be informed of the observation by the social scientist upon arrival. A random selection of observation date and time per pharmacy will be performed using R software.

Data Analysis for Aim 3

Analysis will proceed according to the rapid qualitative analysis approach described in the formative research (aim 1). Interviews will be linked to pilot study data (aim 2), including pharmacy-level data to triangulate findings on FSWs' satisfaction with pharmacies, outcomes, and opinions solicited about the feasibility and acceptability of the program. To synthesize recommendations for refining the intervention, transcripts will be analyzed using the Proctor framework [49] as a guide, with a focus on scale-up and potential adjustments to be optimized and tested in a future effectiveness study. Results of direct observations will be analyzed to assess implementation fidelity and will also be triangulated with the findings from the IDIs.

Description of Indicators to Proceed or Not to Proceed

The traffic light system will be applied to determine if the intervention will progress to a hybrid implementation effectiveness trial. Indicators for implementation effectiveness will be considered using a qualitative assessment (Table 4). If all 4 indicators have a positive response, that denotes a green light to proceed. If any of the indicators show a need for changes that are modifiable and none that are not modifiable, the intervention will be assigned an orange light, while a red light is denoted by ≥1 indicators requiring changes that cannot be made.

Table 4. Criteria to progress to a hybrid implementation effectiveness trial.

Indicator[a]	Method of assessment
1. Was it feasible to implement the pharmacy-based intervention?	Observation of intervention delivery, program data, and process evaluation interviews
2. Was the pharmacy-based intervention acceptable to beneficiaries?	Program data, process evaluation interviews, and C-RCT[b] outcomes
3. Was the pharmacy-based intervention acceptable to pharmacists and stakeholders?	Program data, process evaluation interviews, facilitators' questionnaire, and C-RCT outcomes
4. Were the evaluation methods acceptable and feasible?	Completeness of program to allow outcome assessment

[a]A traffic light system was used to indicate the outcome of the decisions for the Go/No-Go criteria. Green was used as a very strong indication to proceed; all four categories had a positive response.
Orange was used as a moderate indication to proceed after intervention refinement; one or more categories had opportunity for improvement.
Red was used as an indication of doubt as to whether to proceed; one or more categories could not be addressed.

[b]C-RCT: cluster randomized control trial.

Results

This study protocol is compliant to the Standard Protocol Items: Recommendations for Intervention Trials (Multimedia Appendix 4). This study began the enrollment of participants in March 2024. Data collection ended in May 2025. The expansive analysis of these data will be conducted in February 2026, after all data have been collected and reviewed.

Discussion

Anticipated Findings

The TOPAZ intervention aims to co-develop and implement a pharmacy-based model for enhancing access to and continuation on PrEP among FSWs, fostering a key partnership between the national KP program and the private sector. The study provides a unique opportunity to explore the role of pharmacies in HIV programs. Success of the intervention will likely pave the way for greater involvement of pharmacies in HIV testing, prevention, and treatment programs. Of note, Zimbabwe's MoHCC is currently reviewing whether HIV self-tests can be used for supporting PrEP continuation. If this is approved, we anticipate this will further simplify the program and enhance its accessibility and feasibility. This work will be shared with the community, policy makers, and health care professionals at local and international conferences, as well as through peer-reviewed publications.

This study is limited in that we will use prescription refills and self-reported adherence as a measure for PrEP continuation. A future study can improve on this by conducting more accurate measures of adherence, for example, point-of-care urine tenofovir testing in the pharmacy setting. Another limitation of the study is that it does not differentiate the effect of voucher incentives and pharmacy collection on PrEP continuation. However, follow-up beyond 6 months (when voucher incentives stop) will provide valuable information on the impact of the intervention without the vouchers. The study is also limited by its focus on women who already access the KP program, excluding those who do not attend and may be more vulnerable. The KP program is implementing various initiatives to engage SWs who do not visit program clinics. Evidence of the effectiveness of the TOPAZ intervention may be important for informing future pharmacy-based interventions for SWs who are not part of the program. It is possible that pharmacies that

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participate in the study are different from those that do not. Inclusion of both a pharmacy and an SW advisory board will be useful for getting views and impressions outside participating pharmacies.

Conclusions

This study presents a protocol for integrating pharmacies into PrEP distribution, in alignment with the WHO's recommended differentiated service delivery approach. Privately owned pharmacies are easily accessible in the community and can be applied as a sustainable conduit for PrEP delivery, especially for SWs and other groups who could benefit from PrEP.

Acknowledgments

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Data Availability

Datasets will be deposited in publicly available repositories.

Authors' Contributions

OK was responsible for writing the original draft and project administration. HA was responsible for writing—review and editing. LA was responsible for software development and writing—review and editing. CW was responsible for project administration and writing—review and editing. SM was responsible for the formal analysis. KC was responsible for writing—review and editing. AT was responsible for data curation and resources. SM was responsible for methodology and writing—review and editing. LP was responsible for writing—review and editing. JL was responsible for conceptualization, methodology, and funding acquisition. PM was responsible for conceptualization, methodology, and funding acquisition. FMC was responsible for conceptualization, supervision, methodology, and funding acquisition. SLM was responsible for conceptualization, supervision, methodology, and funding acquisition. ELS was responsible for conceptualization, supervision, methodology, and funding acquisition.

Conflicts of Interest

SM is an employee of Gilead Sciences, outside the scope of the submitted work. All authors declare no conflicts of interest.

Multimedia Appendix 1
Topical guide for interviews with sex workers.
[PDF File (Adobe PDF File), 418 KB - resprot_v14i1e74141_app1.pdf]

Multimedia Appendix 2
Topical guide for interviews with pharmacists.
[PDF File (Adobe PDF File), 302 KB - resprot_v14i1e74141_app2.pdf]

Multimedia Appendix 3
Topical guide for key informant interviews with stakeholders.
[PDF File (Adobe PDF File), 346 KB - resprot_v14i1e74141_app3.pdf]

Multimedia Appendix 4
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 236 KB - resprot_v14i1e74141_app4.pdf]

Multimedia Appendix 5
Peer review report from HIBI - HIV/AIDS Intra- and Inter-personal Determinants and Behavioral Interventions Study Section Risk, Prevention and Health Behavior Integrated Review Group (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 153 KB - resprot_v14i1e74141_app5.pdf]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
FSW: female sex worker
IDI: in-depth interview
KP: key populations
MoHCC: Ministry of Health and Child Care
PrEP: pre-exposure prophylaxis
REDCap: Research Electronic Data Capture
SW: sex worker
TOPAZ: Together Optimizing PrEP Access in Zimbabwe

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Protocol

Modifying Tobacco and Cannabis Waste Perceptions and Behavior Among Young Adults: Protocol for a Randomized Controlled Trial

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Abstract

Background: Filtered cigarettes and vaped nicotine and cannabis negatively affect health and create nonbiodegradable, toxic waste from tobacco, e-cigarette, and cannabis waste (TECW). Creating awareness and action to address this public health issue requires expanded knowledge and understanding of TECW harms and more engagement with regulatory policies to reduce tobacco and cannabis use. This is the first study testing an intervention to modify TECW knowledge, perceptions, and behavior, including use of an innovative digital TECW tracking tool.

Objective: This study tests the efficacy of an intervention to modify TECW knowledge, harm perceptions, attitudes, and behaviors regarding smoke- and vape-free university campus policies among young adults. We aim to develop an evidence-based educational intervention for use in community programs to address TECW.

Methods: A 6-week randomized controlled trial was conducted at 2 sites representing the 2 public university systems in California from March 2023 to June 2025 with 406 students (aged 18-25 years) and compared brief tobacco, e-cigarette, and cannabis waste education (TECW Ed) plus tobacco, e-cigarette, and cannabis waste education plus motivational and behavioral support (TECW Ed+) with brief education only about TECW (TECW Ed). Participants were randomized 1:1 to each treatment group, stratified by site and tobacco or cannabis use status. Outcome measures include changes in knowledge, harm perceptions, regulatory attitudes, and behaviors regarding TECW, and engagement with smoke- and vape-free policies. Planned statistical analyses include models to assess knowledge, perceptions, and attitudes at weeks 2, 6, and 26 versus group, time, and a group × time interaction, controlling for site, tobacco or cannabis use status, demographics, and baseline level of outcomes. In addition, TECW Ed+ versus TECW Ed group comparison on mean number of Tracker reports between baseline and 6 weeks, and group comparison on mean engagement score at 6 weeks, will be conducted.

Results: Data were collected from March 2023 to June 2025. Data analysis is expected to begin in late 2025, with final results anticipated for publication in summer 2026. Results will determine if brief educational videos accompanied by enhanced motivational and behavioral support increase knowledge of TECW's environmental impact and change perceptions about cigarettes and vape products. We will determine whether such enhanced education increases engagement in smoke- and vape-free regulatory acceptance and improves outcomes of regulatory policies. This trial will be the first to test an intervention to modify tobacco and cannabis waste perceptions and behavior.

Conclusions: This trial aims to determine whether additional motivational and behavioral support will change young-adult college students' current knowledge of TECW and whether such support will motivate them to engage with regulatory policies to reduce TECW. If successful, scaling up this intervention may mobilize a large population of young adults to understand and advocate for policies that protect individual and environmental health.

Trial Registration: ClinicalTrials.gov NCT05751369; https://clinicaltrials.gov/study/NCT05751369

International Registered Report Identifier (IRRID): DERR1-10.2196/79525

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KEYWORDS

cigarette butt; e-waste; vape; regulatory attitudes; plastic; corporate responsibility; environment; sustainability; smoking cessation; vaping cessation

Introduction

Background and Rationale

The global toxic, nonbiodegradable environmental waste from tobacco, e-cigarette, and cannabis waste (TECW) products is a pressing public health issue [1-4]. Upstream policy approaches [5] to address this increasingly recognized waste problem [6-11], such as banning sales of filtered cigarettes [12] and naming them as single-use plastics that may be addressed in a proposed international plastic treaty [13], are important for both environmental and human health reasons [14]. Awareness of the environmental impacts of e-cigarette [1,2,15-19] and cannabis vape products is also growing [2,19-22]. According to the Environmental Protection Agency (EPA), vape products cannot be safely discarded in household trash or recycled; they meet the definition of "hazardous waste." Many consumers are unaware of this designation, but the EPA has provided guidance to separate batteries from other vape product components that are to be disposed of as municipal hazardous waste [23]. Furthermore, single-use or "disposable" vape products are not designed to be safely disassembled [24].

Disposable nicotine vape products are the most commonly sold [25] and used products in the United States [26], creating a growing environmental challenge [24]. In addition to fires caused by improper disposal of the lithium-ion batteries in vape products, the high-carbon impacts of vape product manufacturing are of concern [27]. The majority of young adults who use disposable nicotine vape products report throwing them in the trash when empty [24]. This provides an estimated 150 million disposable vapes (with potentially recoverable lithium) deposited annually in US landfills [27]. Nearly a quarter of young adults who use vape products report saving the empty products, which also presents a safety issue [24]. There have been no studies to our knowledge on disposal methods for cannabis vape products.

Cultivating public and political support for legislative and regulatory interventions for TECW requires increasing knowledge and modifying perceptions of TECW, and increasing public engagement with policies that can reduce use of tobacco and cannabis products [28]. Research is required on how to influence behaviors that support TECW regulatory policies. To date, there have been 2 observational studies on cigarette butt waste, which both showed that education promotes positive attitudes and behaviors regarding TECW regulations [28,29]. There has not yet been specific research conducted on interventions to increase knowledge, perceptions, and policy engagement on e-cigarette or cannabis product waste. A randomized controlled trial will provide important evidence on the efficacy of such interventions to address TECW, especially among young persons who generally are more engaged on environmental issues.

Study Objectives

This study tests the administration of tobacco, e-cigarette, and cannabis waste education plus motivational and behavioral support (TECW Ed+) versus tobacco, e-cigarette, and cannabis waste education (TECW Ed) only on TECW among college-attending young adults (aged 18-25 years) to increase their engagement on TECW policy implementation. Brief education is standard of care in university settings, and given our finding that awareness of a technological resource is not sufficient for many people to use it [30], we sought to determine whether the addition of motivational enhancement and behavioral support to education would elicit action.

Outcomes include change in TECW knowledge, harm perceptions, attitudes toward regulation, and smoke- and vape-free regulatory policy engagement. Our overall goal is to identify an evidence-based educational intervention to address TECW, based on environmental concerns [31].

Such interventions are particularly relevant among young people, who are the critical stakeholders in planetary stewardship [32]. Students in California public universities are an important constituency for tobacco-related research given that the 23-institution California State University system and the 10-institution University of California system have 100% smoke- and vape-free campus policies, albeit with persistent policy violations [33]. Compliance issues at California public universities and colleges are emblematic of a broader smoke- and vape-free policy compliance problem at universities [34-36].

The specific study aims are to: first, assess knowledge and perceptions about TECW among participants randomized to the TECW Ed+ group compared to those randomized to the education-only control group (TECW Ed). It is hypothesized that at week 6, the TECW Ed+ group will demonstrate a significant increase in knowledge about TECW, perceived harmfulness of TECW, and the attitude that TEC manufacturers should be accountable for waste mitigation, and that the TECW Ed group will be noninferior to the TECW Ed+ group in these outcomes. Second, assess TECW-related behaviors among college students randomized to the TECW Ed+ group compared to those in the comparison group. It is hypothesized that at week 6, the TECW Ed+ group compared to the TECW Ed group will display greater usage of a campus-based TECW Tracker to report TECW on campus and stronger engagement in supporting smoke- and vape-free regulatory efforts. Third, document changes in campus TECW to understand the environmental impact of a TECW intervention. TECW on campus will be measured each week using 3 sources: Tracker-based participant reports, Tracker-based nonparticipant reports (eg, other members of the campus community), and repetitive objective environmental scans by the site team.

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Overview and Trial Design

This is a parallel randomized controlled trial at 2 California universities (1 University of California and 1 California State University) in which a digital TECW Tracker was previously deployed for reporting locations of smoking, vaping, and related waste on campus [30,37]. We enrolled 406 young adult students in a 6-week trial and randomly assigned them 1:1, stratified by site and tobacco or cannabis use status, to usual education only about TECW (TECW Ed) or to receiving the same education about TECW plus motivational enhancement and behavioral support for reporting TECW (TECW Ed+). Changes in individual-level and environmental outcomes are evaluated through repeated assessments at baseline, week 2, week 6, and week 26. Check-in text messages only are provided at weeks 1 and 4.

The guiding framework for this study is social cognitive theory [38,39]. in which behavior is conceptualized as the product of individual-level attitudes and perceptions and social structures that facilitate behavior change. In this study, we use motivational enhancement [40-47], goal setting [48-54], and problem-solving applications [55-60] as developed in our previous trial [61]. Our intervention was designed to address both individual-level attitudes and perceptions and social-level factors through the application of motivational enhancement, which is built around 4 main processes, carried out in a spirit of collaboration, respect, and support for the participant's autonomy [54]. The first process, engaging, reflects fundamental communication principles and highlights the importance of empathy in establishing trust and rapport. The second process, focusing, involves working with participants to identify and agree on a topic for exploration. The third process, evoking motivation, is directed at drawing out and reinforcing participants' own internal motivations for change. The fourth process, planning, guides participants in developing and implementing concrete steps toward their goals. The intervention protocol, in which motivational enhancement, goal setting, and problem solving were used to evoke changes in individual- and social-level factors per social cognitive theory, was adapted from one target behavior [61] to another (using TECW Tracker).

Methods

Ethical Considerations

The study was reviewed and approved by the Institutional Review Board at Site 1 (#1896205-1) on April 12, 2022. The study was reviewed and approved as exempt by the Institutional Review Board at Site 2 (#1952501-1) on September 2, 2022. Enrollment began on March 1, 2023, and concluded on October 15, 2024.

The informed consent form is delivered to participants by an emailed link in Research Electronic Data Capture (REDCap; Vanderbilt University), along with a link to schedule their baseline visit. The consent form asked, "Would you like to proceed with this study?" using a forced-choice question with two options: I do not wish to proceed with this study or I wish to proceed with this study. Written consent is provided through a typed name with acknowledgment of being aged 18 years or older, of having read and understood the study description, and that they may withdraw at any time. REDCap records the date of consent form completion.

At the beginning of the baseline visit, a description of the study, requirements, and compensation is reviewed; there is an opportunity to ask questions, and participants are asked whether they wish to proceed with the study. Any participants who have not completed the consent form prior to the visit are provided as much time as they need to read the form in a breakout room at the beginning of the visit.

Participants receive up to US $110 for participating in the study: US $25 for attending the baseline, week 2, and week 6 visits, and US $35 for the month 6 visit (Figure 1).

Figure 1. Visit flow.

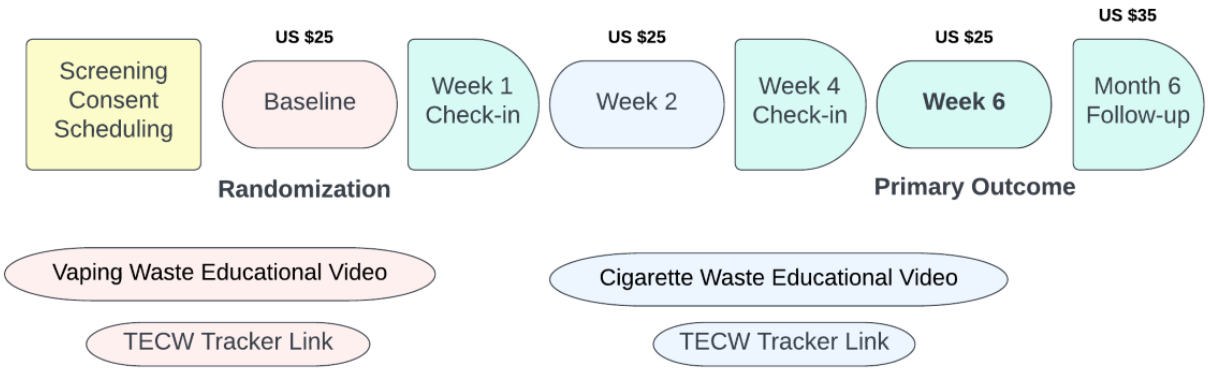

Study Setting

The study is conducted in San Diego, California, United States (Site 1), and Davis, California, United States (Site 2). A project coordinator at Site 1 is responsible for participant recruitment and enrollment at both campuses and supervises Site 1–based research assistants. The intervention and assessments are delivered remotely by research assistants at Site 1 to participants at both sites. Participant education and TECW Ed+ group interaction occur over Zoom (Zoom Video Communications, Inc) as a one-to-one session with a research assistant. This method aligns with new norms for synchronous remote

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participation in university settings. Participants are provided links to surveys and forms in the Zoom chat and are placed in a breakout room to complete them. They are instructed to use the "ask for help" function or rejoin the main Zoom room with questions about the survey. The project coordinator reviews Tracker data and supervises staff at each site who conduct environmental scans and document TECW identified through the Tracker at both campuses.

Eligibility Criteria

Inclusion Criteria

Study eligibility requirements include being a current student on the main campus of Site 1 or 2, attending class on the main campus at least once per week, having at least 6 months remaining until graduation, being aged between 18 and 25 years, English fluency, having a smart phone with location services enabled for apps, having regular access to a computer or tablet with sufficient Wi-Fi and a private space in which to complete remote study visits, and willingness to have the camera turned on during remote study visits.

Exclusion Criteria

The only exclusion criterion is prior study participation.

Intervention Description

Overview

Both groups receive education about TECW at baseline and week 2 visits by viewing videos and receiving a link to the TECW Tracker at baseline and week 2. The intervention group receives education plus motivational enhancement and behavioral support for using the TECW Tracker. Both groups receive a check-in text at week 1 and week 4 containing a brief assessment and a reminder for their next study visit. The intervention group's text includes feedback about the positive environmental impact of making TECW reports and offers assistance with the Tracker if no reports had been made (Figure 2).

Figure 2. Intervention and assessment schedule.

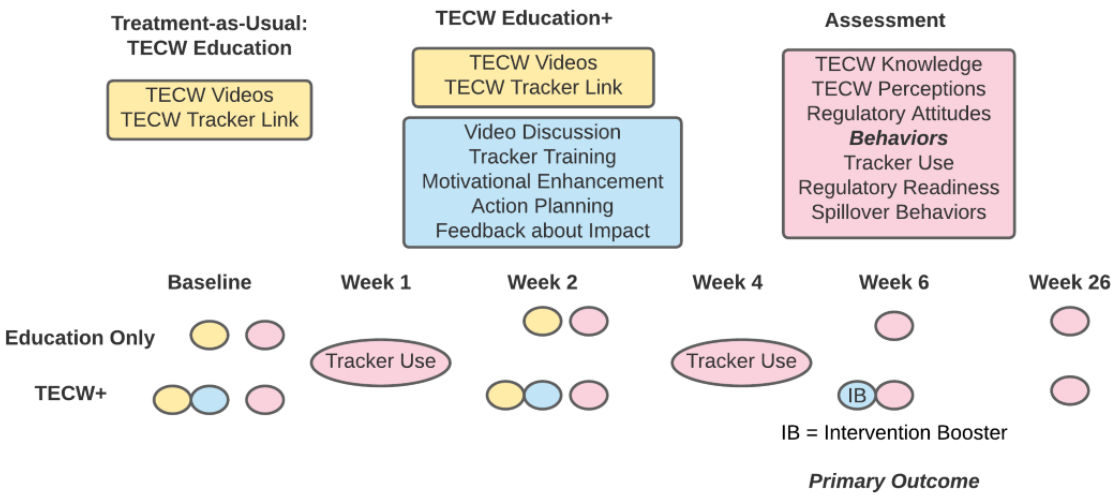

Education

Baseline education includes an overview of waste produced by vaping products used for tobacco and cannabis, their impact on the environment, and the role of tobacco and cannabis product manufacturers in TECW mitigation. This material is provided by a brief video from the California Youth Advocacy Network [62]. Week 2 education includes an overview of waste produced by cigarette smoking and the environmental impact of discarded butts. Tobacco Free CA provides brief videos [63,64]. The TECW Tracker is provided as a tool to identify TECW on the campus grounds; this then prompts TECW removal by research staff. The web link and QR code for the TECW Tracker app are provided, and participants are instructed to enter their study ID numbers when making a report.

The TECW Tracker is a digital tool that has been available since 2019 at Sites 1 and 2 to report smoking, vaping, and related waste on Site 1 and 2 campuses [30,37]. Tobacco Tracker provides three types of reports: (1) smoking- or vaping-related litter, (2) smoking or vaping, and (3) "looks good–no smoking or vaping or related litter." Reports of litter from smoking or vaping allow identification of the source as cigarette butt, cigarette packaging, e-cigarette material (ie, pod, hardware), marijuana packaging, or other (select all that apply). Images of these litter types are included. Reports of smoking or vaping allow identification of the source as cigarette, e-cigarette or JUUL, marijuana (including blunts), do not know, or other; images of these products are embedded within the app. Reports of "looks good–no smoking or vaping or related litter" provide a way to monitor Tracker usage independent of problems and the capacity to measure improvement over time.

Mitigation of TECW

The project manager creates weekly mitigation assignments for site staff at each campus to address reports. Site staff conduct a 30-minute environmental scan of the location, collect TECW while wearing protective equipment, classify and document each piece of waste, and dispose of it properly. Each week, a

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randomly selected campus location is scanned for 60 minutes, and TECW is mitigated by site staff as described above.

Motivational Enhancement and Behavioral Support

Each study visit in which education is provided (baseline and week 2) contains additional motivational enhancement or behavioral support for the TECW Ed+ group. Each text message (week 1 and week 4) provides a brief assessment and reminder of the next study visit as well as additional motivational enhancement and behavioral support for the TECW Ed+ group. The week 6 visit provides another motivational booster to the TECW Ed+ group. Table 1 presents the components and timing of the motivational enhancement and behavioral support.

Table 1. Timing of motivational enhancement and behavioral support components.

Component	Baseline	Week 1	Week 2	Week 4	Week 6
Discuss video takeaways	✓		✓		
Discuss values and connect to Tracker	✓				
Instruction in using TECW[a] Tracker	✓		As-needed[b]		
Offer assistance with using Tracker		As-needed[b]		As-needed[b]	
Motivation and confidence for using Tracker	✓				
Action planning for using Tracker	✓		✓		
Summary of Tracker reports and why reporting is useful		✓	✓	✓	✓

[a]TECW: tobacco, e-cigarette, and cannabis waste.

[b]Provided to those who have not made Tracker reports.

Outcome Measurements

TECW Knowledge

Five items assess knowledge of nicotine and cannabis vape-related waste disposal methods (eg, Nicotine pods should be disposed as A. recyclable waste, B. hazardous waste [*correct], C. in normal trash, or D. in other ways) [65,66]. Six items assess knowledge of cigarette waste (eg, What is the main component of commercially sold cigarettes? A. cotton, B. paper, C. plastic [*correct], D. cork, or E. other [14]. Two general questions assessed biodegradability and recommended actions for dealing with TECW. A percent correct score is yielded for knowledge of vape-related and cigarette waste aligning with educational content at the baseline and week 2 visits, respectively.

TECW Perceptions

Six items assess agreement with various statements about cigarette and electronic devices used to vape nicotine and cannabis and their environmental impact including biodegradability; harm to the environment, animals, and sea life; and danger if thrown in trash [67,68], on a 5-point scale (strongly disagree to strongly agree). Participants are also asked how often they have noticed TECW in the past 30 days, which product type, and whether occurrences were on or off campus.

Regulatory Attitudes

Two items assess regulatory attitudes, including statements about whether various products (eg, cigarette filters, disposable products for vaping, pods or cartridges) should be included in bans of single-use plastic products. Response options range on a 5-point scale from strongly disagree to strongly agree. Tobacco manufacturer responsibility is assessed with items: How much responsibility do you think each of the following groups has for creating the problem of cigarette butt litter and should have for fixing the problem of cigarette butt litter? Groups include smokers, cigarette companies, city councils, and the government. Response options include none at all, a little, a moderate amount, and a great deal [67]. These same items are used to assess manufacturer responsibility for products used to vape nicotine and cannabis. While it may be impossible to distinguish whether vaping-related waste is from tobacco or cannabis, these items are assessed separately for tobacco and cannabis given different regulatory processes.

TECW Tracker Use

Awareness of a tool to report TECW on campus and use of the tool is assessed with yes or no questions [30]. Participant Tracker use is also measured objectively based on participant ID–linked TECW Tracker usage data.

Engagement in Smoke- and Vape-Free Regulatory Behavior

Engagement in smoke- and vape-free regulatory behavior is assessed with participant behaviors: (1) inform someone smoking or vaping on campus about the environmental impact of TECW, (2) inform someone smoking or vaping on campus about our smoke- and vape-free policy, (3) inform someone smoking or vaping on campus about how to properly dispose of TECW, (4) inform someone smoking or vaping on campus about a resource to quit smoking or vaping, (5) report TECW on campus, (6) report smoking or vaping on campus, and (7) volunteer (provide education, outreach, or clean-up) for campus smoke- and vape-free campus initiatives [30]. These items are rated from 1 (never expect to) to 5 (have already been doing) based on the transtheoretical model of behavior change [69].

Secondary Behaviors

To understand any broader impact of the intervention, related behaviors such as off-campus TECW advocacy are assessed; additionally, among tobacco users, proper disposal of e-waste and cessation are evaluated as secondary outcomes. The

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engagement in smoke- and vape-free regulatory behaviors is modified to "off campus" to assess this, and items about usual methods of TECW disposal and past 30-day quit attempts are assessed.

Environmental Impact of TECW Campus Intervention

Counts of TECW by product type as well as "looks good" reports are tabulated for each campus location on a weekly basis from the Esri ArcGIS–based TECW Tracker reports from participants and nonparticipants (eg, general campus community) through TECW Tracker. Counts of TECW by product type are also tabulated from objective environmental scans conducted by site staff.

As a secondary outcome, we assess the link between awareness of campus TECW mitigation and behavioral outcomes. Two items to assess this include: "How aware were you of how your Tracker reports were addressed?" (Response options include not at all, a little, moderately, and very aware), and "How satisfied were you with campus actions taken in addressing TECW?" (Response options range from very dissatisfied to very satisfied). An open-ended prompt follows for those who report dissatisfaction.

Attributions of Intervention Components

Following the week 6 survey, those in the TECW Ed+ group are administered another survey assessing their attributions of two intervention components: (1) talking with the study team and (2) receiving feedback about actions taken from TECW reports. They rate their agreement with the following three questions on a 5-point scale, ranging from strongly disagree to strongly agree: [Intervention Component]: (1) taught me new information about TECW, (2) increased my desire to do something to reduce TECW, and (3) increased my desire to report TECW.

Assessment Schedule

Knowledge, perceptions, and regulatory attitudes for vape-related waste are tested before and after receiving education at the baseline visit. Knowledge, perceptions, and regulatory attitudes for cigarette waste are tested before and after receiving education at the week 2 visit. Knowledge, perceptions, and regulatory attitudes for vape-related waste and cigarette waste are retested at the week 6 and week 26 visits (Figure 2).

Study Timeline

Enrollment is conducted from the second week of each semester or quarter until 6 weeks before final examinations week. Enrollment begins the second week of the semester to assure that past 7-day questions refer to a time of typical campus activity. When there is a campus break of 2 weekdays or longer, study visits are delayed by a week to adjust the past 7-day question time period for typical campus activity. The stop date each semester or quarter assures that the 6-week intervention is delivered while participants are still attending class on campus at least once per week.

Sample Size

An initial sample size of 400 total (100 per group per campus) will detect a 15-16 percentage point difference in proportions with 80% power at the 0.05 level (2-sided), assuming a sample size of 380 at 6 weeks (95% retention) and 340 at 26 weeks (85% retention). This effect size is expected based on previous research on attitudes and behaviors [67]. This sample size also provides more than 95% power to detect noninferiority within a 0.5 SD margin at the 0.025 level (1-sided) or a difference in means of 0.5 SD at the 0.05 level (2-sided); 0.5 SD is considered a minimally important difference in health-related quality of life outcomes [70] and corresponds to 0.5 point difference on a 5-point scale with an SD of 1 point.

Recruitment

Participants are recruited from each site using campus announcements, flyers, tabling, and word of mouth through campus partners.

Assignment of Interventions: Allocation

After completing the baseline survey, participants at each site are randomized 1:1 to the two groups (TECW Ed or TECW Ed+) in blocks stratified by tobacco or cannabis user status (any use in the past 30 days: yes or no) by the project coordinator using REDCap, based on randomization tables created by the study statistician with computer-generated random numbers.

Assignment of Interventions: Blinding

Research assistants are aware of group assignments and deliver the designated intervention. Participants are not told their group assignment. Research assistants are unaware of study hypotheses and do not see participants' before and after survey responses. Research assistants are aware of the number of Tracker reports and their nature because providing feedback to the TECW Ed+ group is a component of the intervention.

Data Collection and Management

At the baseline and week 2 visits, a presurvey is administered before education and a postsurvey is administered after education (plus motivational enhancement for the intervention group). Assessment windows are ±3 days for the week 1 check-in, ±1 week for the week 2 visit and week 4 check-in, ±4 weeks for the week 6 visit, and ±6 weeks for the week 26 visit.

Contact Attempts

We are using our proven methods for achieving over 80% retention up to 6 months, including multiple contact methods (ie, text, phone calls, emails), identifying multiple alternative contact people, and sending a digital greeting 2 months before the week 26 visit [71-74]. Up to 6 contact attempts, of alternating forms, are made. Contacting alternative contact people is the last effort to reach an unreachable participant.

Data Management

Participant data are collected and managed using REDCap tools that are hosted through Site 2. REDCap is a Health Insurance Portability and Accountability Act (HIPAA)–compliant, web-based application that supports data capture for research studies. All data collected are anonymous through assignment of participant ID numbers and password protected. REDCap

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data are stored securely on a server at Site 2. Environmental scan data are entered into Excel (Microsoft Corporation) and maintained on a shared drive.

Statistical Methods

Primary Outcome

The primary outcome is change in knowledge, perceptions, and attitudes. The hypothesis that the TECW Ed+ group will demonstrate a significant increase in TECW knowledge, harm perceptions, and regulatory attitudes, and that the TECW Ed group will be noninferior to the TECW Ed+ group in these outcomes by a margin of half an SD, will be tested as follows. We will compute mean scores for change in knowledge, change in harm perception, and change in belief in each group along with 2-sided 95% CIs; a CI entirely above 0 indicates a statistically significant increase at the 5% level (2-sided). In addition, for each of these measures, we will compute the difference between the TECW Ed+ group and the TECW Ed group mean scores, along with a 1-sided 97.5% CI; a CI entirely below 0.5 SD indicates noninferiority of the TECW Ed group within a 0.5 SD margin at the 0.025 level (1-sided). We will also construct mixed-effects repeated measures models to assess knowledge, perceptions, and belief outcomes at weeks 2, 6, and 26 versus group, time, and a group × time interaction, controlling for site, tobacco or cannabis use status, demographics, and baseline level of the outcome variable.

Secondary Outcomes

The secondary outcomes are behavior changes. The hypothesis that the TECW Ed+ group, compared to the treatment-as-usual TECW Ed group, will display greater usage of the TECW Tracker and stronger engagement in supporting smoke- and vape-free regulatory efforts will be tested as follows. We will compare the TECW Ed+ group and the TECW Ed group with respect to the mean number of Tracker reports between baseline and 6 weeks using a generalized linear model with negative binomial distribution and log link. We will compare the 2 groups with respect to mean engagement score at 6 weeks using a 2-sample *t* test. We will also construct generalized linear mixed-effects repeated measures models to assess TECW-related behavior outcomes at weeks 1, 2, 4, 6, and 26 versus group, time, and a group × time interaction, controlling for site, tobacco or cannabis use status, demographics, and, for engagement, baseline level of the outcome variable. As an ancillary analysis, we will assess the link between awareness of campus TECW mitigation and behavioral outcomes among participants by including awareness as a covariate in models of Tracker report behavior. All randomized participants with week 6 data will be included in primary outcome analyses, and those who completed week 6 and month 6 will be included in follow-up analyses.

As an ancillary outcome, we will evaluate spillover behaviors such as off-campus TECW advocacy, and among tobacco users, proper disposal of e-waste and reported tobacco cessation by computing frequencies and percentages for each of these behaviors overall and by site and group at 6 weeks and 26 weeks. Furthermore, to describe changes in campus TECW, we will use generalized linear mixed models of the number of TECW reports per month to estimate trends over time and association with environmental scans, overall and among study participants, assuming autoregressive correlation from month to month at each site and negative binomial distribution with log link. Separate models will be created for different types of TECW, and interactions between site and time will be included to assess differences in trends between sites.

Missing Data

Although our follow-up rates in previous studies have typically exceeded 80%, missing data will arise for a variety of reasons (item nonresponse, etc). Prior to testing primary hypotheses, we will conduct exploratory analyses to determine if baseline characteristics predict patterns of missing data. Any significant (P<.10) predictors of missing data will be included as covariates in models above and used with multiple imputation methods [75,76] for evaluating model estimates.

Oversight and Monitoring

Auditing

Data quality is managed in real time using daily checklists and verified for consistency in documentation across various sources.

Protections Against Risk

The study is classified as exempt by the institutional review board due to low risk from an educational intervention. Nonetheless, we safeguard participant privacy by ensuring they are in a private space during study visits, ensuring our study space is accessible only to human-subjects–certified study team members, and maintaining confidentiality of participant records through use of code numbers.

Debriefing

At the week 26 visit, participants are provided contact information to receive results of the study when complete and the website for the smoke- and vape-free initiative at each campus, and the opportunity to ask questions.

Results

Data collection began in March 2023 and concluded in June 2025. Data analysis is expected to begin in late 2025, with final results anticipated for publication in summer 2026.

Results will be shared with academic and scientific audiences, and local, state, and national stakeholders through digital communications, community events, presentations, and publications. University audiences include academic units and administrative divisions at the participating institutions and broader university systems. Scientific outlets include peer-reviewed journal articles and conferences in areas of higher education and public health. Communications will be made with local, state, and national agencies and organizations conducting tobacco control work and environmental advocacy.

Discussion

Anticipated Principal Findings

The study uses a rigorous design to evaluate an educational intervention that can improve knowledge, attitudes, and behavior regarding tobacco and cannabis product waste. This improved

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knowledge and belief system is expected to support the implementation of tobacco- and vape-related environmental regulatory policies. Such interventions may increase smoke-free policy adherence and support efforts to enforce smoke- and vape-free campus policies. Educational efforts using an environmental lens, paired with a focus on industry accountability, may also support quitting efforts [77], contributing to long-term efforts to reduce the health and economic burdens of tobacco product use [78].

Universities are critical settings in which to prevent initiation of vaping, as a greater number of college students than noncollege students begin using e-cigarettes in young adulthood [79]. There are an estimated 19.9 million college students in the United States, providing an opportunity for a variety of targeted interventions to address the current epidemic of e-cigarette use. This investigation, involving a clinical trial of an intervention aiming to change what young adult college students know about TECW and how they can support policies to reduce this environmental problem, may stimulate similar research and policy implementation in other campus settings.

Limitations

There are several limitations to note regarding this trial. First, while the study involved a single site in each public university system in California, these 2 sites are not necessarily representative of all public universities. Furthermore, state universities are not representative of other educational settings such as community colleges, private universities, and trade schools. Second, young college-attending adults aged 18-25 years were the target population for this study, assuming their more active interest in environmental protection [32]. However, the results may not generalize outside this age or educational group. Nevertheless, these young adults are more likely to initiate vaping then noncollege-attending young adults [79] and a need for improved smoke-free campus policy compliance in these settings was identified in previous research [34-36]. Finally, given that this is a very closely controlled trial of an educational intervention, it is uncertain if such an intervention will be effective in a real-time setting. The efficacy of the intervention is established in the controlled research setting, then followed by wider implementation and evaluation in the real world [31].

Comparison With Prior Work

This study expands on previous studies addressing the harms of cigarette butt waste, to include nicotine- and cannabis-vape–related waste. This study also uses a more rigorous design than previous observational studies [28,29]. The common approach used by the previous observational studies and our randomized trial was education to increase knowledge about the environmental harm of tobacco product waste. We extended this approach by using brief videos to deliver additional messages on not only cigarette butt waste but also including vape products for nicotine and cannabis. This study is novel in testing whether motivational enhancement and behavioral support add value in creating behavior change versus using education only.

Directions for Future Research

A follow up, larger implementation study would be a valuable next step to apply the intervention in various settings and conditions. Additional efficacy studies in different settings (eg, community college) and policy conditions (eg, colleges with designated smoking or vaping areas) would be beneficial. Our behavioral measures, such as Tracker usage and change in TECW disposal methods, will be central in planning future studies.

Conclusions

This trial aims to evaluate educational tools to promote effective smoke- and vape-free campus policies. It investigates whether brief educational videos will increase knowledge of the environmental impact of TECW and change harm perceptions and attitudes toward regulatory policies on cigarettes and vape products. We will also learn whether education alone is sufficient to increase engagement in smoke- and vape-free regulatory policy support, or whether the addition of motivational enhancement and behavioral support is necessary to produce change. This study will be the first randomized controlled trial modifying cigarette waste perceptions and behaviors and is novel in its inclusion of nicotine- and cannabis-vape–related waste educational interventions.

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The authors declare that generative artificial intelligence was not used in any portion of the manuscript generation.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization: KP (lead), SS (supporting), ET (supporting)
Data curation: ABN (lead), CS (supporting)
Formal analysis: SS (lead)
Funding acquisition: KP (lead), SS (supporting), TN (supporting), ET (supporting)
Investigation: KP (lead), ET (equal), SS (supporting), ABN (supporting), HS (supporting), CS (supporting), SS (supporting)
Methodology: KP (lead), TN (supporting), SS (supporting), ET (supporting)
Project administration: AB (lead), HS (equal), CS (supporting)
Resources: KP (lead), ET (supporting)
Supervision: KP
Writing – original draft: KP
Writing – review & editing:ET (lead), TN (equal), SS (equal), ABN (supporting), HS (supporting), CS (supporting)

Conflicts of Interest

None declared.

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Abbreviations

HIPAA: Health Insurance Portability and Accountability Act
REDCap: Research Electronic Data Capture
TECW Ed: tobacco, e-cigarette, and cannabis waste education
TECW Ed+: tobacco, e-cigarette, and cannabis waste education plus motivational and behavioral support
TECW: tobacco, e-cigarette, and cannabis waste

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Protocol

The Effect of Motor Imagery Ability on Function and Proprioception in Myoelectric Prosthesis Users: Protocol for a Cross-Sectional Study

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Abstract

Background: Motor imagery ability (MIA) is a critical cognitive process that enables the mental simulation of movements, facilitating skill acquisition in the use of myoelectric prostheses and their effective control in individuals who have undergone amputation. Although MIA is essential, its impact on upper extremity function and proprioception in myoelectric prosthesis users remains insufficiently studied.

Objective: This study aims to evaluate MIA in individuals who have undergone transradial amputation and use myoelectric prostheses, compare it with a healthy control group, and examine its association with upper extremity functionality and proprioception.

Methods: This cross-sectional study will include 15 individuals who have undergone transradial amputation (aged 18-65 y) and 15 age- and sex-matched healthy controls, recruited from prosthetics and orthotics centers in Istanbul, Turkey. Assessments will include MIA, hand mental rotation, upper extremity function, and proprioception. MIA will be measured using the Movement Imagery Questionnaire-3 and the Mental Chronometry Test. Hand mental rotation ability will be assessed via the Orientate mobile app. Upper extremity function will be evaluated using the Box and Block Test; Jebsen-Taylor Hand Function Test; and the Quick Disabilities of the Arm, Shoulder, and Hand questionnaire. Proprioception will be assessed through joint position sense measurements. All data will undergo appropriate statistical analyses.

Results: Data collection began following funding from the Scientific and Technological Research Council of Turkey on April 25, 2025. As of November 2025, 8 participants with transradial amputation and 8 healthy controls have been recruited. Assessments are ongoing, and study completion is expected by June 2026.

Conclusions: This study will evaluate MIA in individuals who have undergone transradial amputation and use myoelectric prostheses and explore its relationship with upper extremity function and proprioception. The findings are expected to guide the development of targeted rehabilitation strategies, particularly those incorporating motor imagery–based training for this population.

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KEYWORDS

motor imagery; myoelectric prosthesis; amputation; motor function; proprioception

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Introduction

Amputation refers to the surgical removal of a limb along with its associated anatomical structures and is commonly performed due to trauma, infection, vascular diseases, or malignancies [1,2]. Among upper limb amputations, transradial amputations are the most common, accounting for more than 30% of the cases [3,4]. The anatomical complexity and functional importance of the forearm make transradial amputations particularly significant in both preoperative evaluation and postoperative management [5,6].

Following upper limb amputation, significant morphological and neurophysiological changes occur [7]. The loss of sensory input and visual feedback leads to neuroplastic remodeling within the central nervous system, resulting in extensive reorganization of cortical representation areas, particularly within the motor and somatosensory cortices [8,9]. These cortical topography alterations involve the reshaping of representational maps related to the missing limb and reflect both functional and structural adaptations [10,11]. Recent studies have highlighted that neuroplastic changes are especially pronounced in the somatosensory, premotor, and parietal cortices, which appear to form new neural connections despite the absence of peripheral sensory input following amputation [11,12]. Such neuroplastic adaptations are thought to play a crucial role in prosthesis use and motor learning.

Motor imagery (MI) is defined as the mental simulation of movement without actual physical execution and has gained considerable attention in neurodevelopment and rehabilitation research. During MI, brain regions involved in movement—such as the motor, premotor, and somatosensory cortices—are activated, highlighting their important role in motor planning and learning processes [13,14]. MI is typically classified into 2 main types: visual and kinesthetic imagery. Visual imagery involves mentally observing a movement from an external viewpoint, while kinesthetic imagery encompasses the internal experience of muscular activity and proprioceptive sensations [15]. Following amputation, neuroplastic changes in the somatosensory cortex may impair MI ability (MIA), reducing the capacity to mentally simulate movements [11]. Assessing MIA in individuals with limb loss is essential for understanding the clinical consequences of such neuroplastic alterations and tailoring personalized rehabilitation strategies. Deficits in MI can directly affect prosthetic adaptation and compromise the success of motor rehabilitation [16,17].

Myoelectric prosthetic systems function by detecting biopotential signals generated by residual muscle activity; however, effective prosthetic control relies not only on muscle contractions but also on cognitive processes, such as MI. Specifically, kinesthetic MI supports prosthetic control at the mental level, playing a key role in learning and adaptation. These cognitive processes are believed to promote neuroplasticity by enhancing the interaction between the central nervous system and muscular structures, thereby facilitating more efficient prosthesis control [18,19]. MI enables mental control of the prosthesis without direct muscle activation and improves cortical efficiency during prosthetic use. Consequently, both MI and proprioceptive awareness are fundamental for functional performance and neural adaptation in myoelectric prosthesis users [19].

In individuals who have undergone upper limb amputation, the preservation of MIA may significantly influence the process of adapting to myoelectric prostheses. Previous studies have demonstrated that individuals with higher MIA tend to perform functional tasks more effectively when using a prosthesis [20,21]. In this context, MI can be considered a potential facilitator for enhancing the functionality of myoelectric prostheses and improving upper limb performance. Furthermore, MI-based rehabilitation protocols have been shown to support neuroplasticity by strengthening the interaction between the central nervous system and prosthetic control mechanisms [19]. These findings underscore the clinical importance of assessing and enhancing MIA in myoelectric prosthesis users.

Proprioceptive feedback is a fundamental component in the perception and control of movement, as it transmits sensory information from muscles, tendons, and joints to the central nervous system [22]. Following amputation, the reduction or loss of these sensory inputs may impair MI processes, given that MI involves the mental simulation of both kinesthetic and somatosensory information [10,23]. Recent studies have shown that diminished proprioceptive input is associated with decreased MIA, which may lead to reduced performance in prosthetic control [24-26]. Therefore, preserving or restoring proprioceptive functions is crucial to supporting MI capacity in individuals with limb loss and, consequently, enhancing prosthesis use.

The physiological, psychological, and particularly cortical changes that occur following amputation require a multidimensional approach to managing individuals with limb loss. In this context, assessing MIA in people with transradial amputation has become increasingly important, as it contributes to the reorganization of motor control and supports cortical representation. Specifically, in the context of myoelectric prosthesis use, MI plays a complementary role by enhancing functional integration with the prosthesis and facilitating both movement planning and execution. This study aims to evaluate the MIAs of individuals with transradial amputation who use myoelectric prostheses by comparing them with healthy controls and investigate the impact of MI on functionality and proprioception. The findings are expected to provide a scientific foundation for integrating MI-based approaches into prosthetic rehabilitation programs.

Methods

Participants

The required sample size for the study was determined using G*Power software (version 3.1; Heinrich Heine University Düsseldorf). The calculation was based on the Movement Imagery Questionnaire-3 (MIQ-3) scores reported by Saimpont et al [27], which served as a reference for the primary outcome of this study.

Although Saimpont et al [27] reported a large effect size (Cohen d=1.41) in a healthy population, a more conservative estimate

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(Cohen d=0.8) was applied in this study's power analysis to better reflect expected variability among participants who underwent transradial amputation. Using a 2-tailed independent samples t test, with an α of .05 and power (1–β) of .80, the required total sample size was calculated as 30 participants (n=15, 50% per group).

This sample size provides sufficient statistical power to detect large effects (Cohen $d \geq 0.8$) between groups while also allowing for potential participant dropouts. A sensitivity analysis showed that detecting moderate effects (Cohen d=0.6) would require approximately 18 participants to achieve equivalent power; however, as the study primarily aims to detect large between-group differences, the planned sample of 30 participants (n=15, 50% per group) was considered adequate.

Participants will be recruited from prosthetics and orthotics centers located in Istanbul, Turkey. The study group will consist of volunteers who meet the inclusion criteria; therefore, no probabilistic sampling method will be used. Inclusion criteria for the amputee and control groups are listed in Textbox 1.

Textbox 1. Inclusion criteria for the amputee and control groups.

Inclusion criteria for the amputee group

- Aged between 18 and 65 years
- Completion of prosthetic rehabilitation and having used a prosthesis for at least 1 year
- Have a transradial level amputation
- Use of a 4-channel myoelectric-controlled transradial prosthesis
- Residual limb length between 5 and 25 cm
- A score of 3 or less on the visual analog scale for phantom or residual limb pain
- A score of 15 or less on the Beck Depression Inventory
- A score of 26 or greater on the Standardized Mini-Mental State Examination
- No diagnosis of any neurological, orthopedic, psychological (eg, schizophrenia and psychosis), or systemic disease
- Voluntary participation in the study

Inclusion criteria for the control group

- Aged between 18 and 65 years
- No diagnosis of any neurological, orthopedic, psychological, or systemic disease
- A score of 15 or less on the Beck Depression Inventory and 26 or greater on the Standardized Mini-Mental State Examination
- Voluntary participation in the study

Both groups will be included based on these criteria. No randomization will be applied between groups.

Ethical Considerations

This study was approved by the noninterventional clinical research ethics committee of Istanbul Medipol University (E-10840098-202.3.02-2988) on May 9, 2024. All procedures will be conducted in accordance with the principles outlined in the Declaration of Helsinki. Before participation, all individuals will be informed about the study through both written and verbal explanations. Those who agree to take part will be asked to sign an informed consent form. The form explicitly states that participation is entirely voluntary and free of charge and that participants may withdraw from the study at any time without providing a reason or facing any consequences.

No additional costs will be incurred by the participants, and no compensation will be provided. All personal and identifying data will be kept strictly confidential. The collected data will be used solely for scientific purposes and without any commercial intent. Where necessary, anonymized data may be subjected to statistical analysis without the need for further ethics approval, provided that such use is covered by the initial consent.

Study Design

This study is registered in the ClinicalTrials.gov database (NCT06541379) and uses a cross-sectional design with multicenter recruitment and single-center assessment. Participants will be recruited from several prosthetics and orthotics clinics located in Istanbul, Turkey, while all evaluations will be conducted at the prosthetics and orthotics research and application center of Istanbul Medipol University. All necessary institutional approvals were obtained before study initiation.

A total of 30 participants will be included: 15 (50%) individuals with unilateral transradial amputation who use a myoelectric prosthesis and 15 (50%) healthy control participants matched for age and sex. The study flowchart describing the recruitment and assessment process is presented in Figure 1.

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Figure 1. Study flowchart.

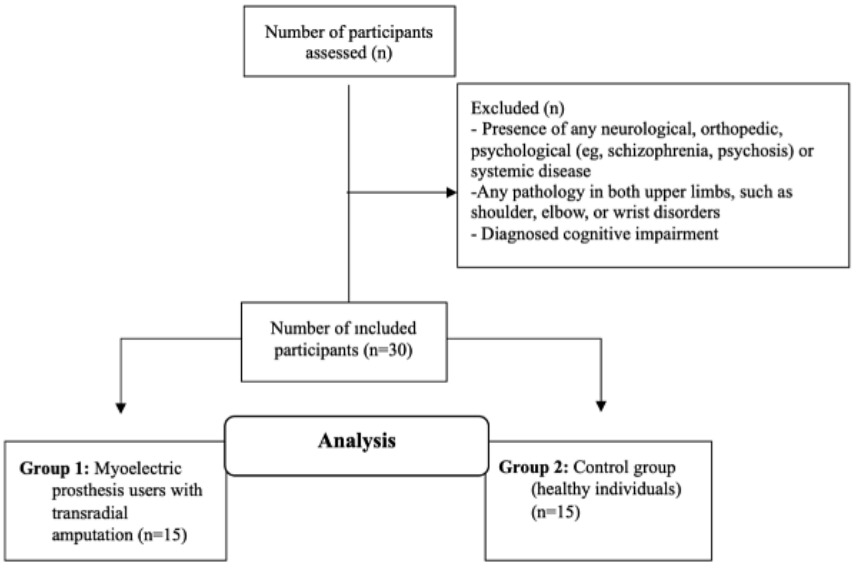

The study timeline and procedures are summarized as follows: ethics approval was obtained from the institutional ethics committee on May 9, 2024, and funding was received from the Scientific and Technological Research Council of Turkey (TÜBİTAK) on April 25, 2025. Participant recruitment and data collection started on April 25, 2025, with 15 participants planned per group. Assessments and interventions include tests of MI ability, upper limb functional tests, and proprioception test. Follow-up will include ongoing monitoring and assessment of all participants. Data analysis will be completed after all data are collected. The study is expected to be completed in June 2026.

The sampling frame consists of all eligible individuals with unilateral transradial amputation who meet the inclusion criteria across the collaborating clinics during the recruitment period. Participants will be recruited consecutively, applying identical inclusion and exclusion criteria across centers.

Although participants will be recruited from different clinics, all assessments will be performed by a single trained researcher (the first author) using the same equipment and standardized procedures at the prosthetics and orthotics research and application center. This approach ensures measurement consistency and minimizes the risk of selection bias.

This study was reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for cross-sectional studies (Multimedia Appendix 1). The related TÜBİTAK 1002-A project report is provided in Multimedia Appendix 2.

Outcome Measures

According to the study hypothesis, the primary outcome is MIA assessed using the MIQ-3, which was selected as the primary end point given its central role in prosthetic motor control, motor learning, and functional adaptation in individuals who have undergone transradial amputation.

The secondary outcomes include the following:

- Upper-limb functional performance, assessed using the Box and Block Test (BBT), Jebsen-Taylor Hand Function Test (JTHFT), and the Disabilities of the Arm, Shoulder, and Hand (QuickDASH) questionnaire
- MI performance indicators, including the Mental Chronometry Test (MCT) and hand mental rotation task, as secondary measures of MIA
- Proprioceptive and sensorimotor accuracy, measured by joint position sense (JPS) error using a validated digital goniometer app (DrGoniometer [CDM SrL])
- General balance and flexibility, evaluated by the Functional Reach Test (FRT) as an indicator of overall functional stability
- Cognitive and psychological screening, including the Standardized Mini-Mental State Examination (SMMSE), Beck Depression Inventory (BDI), and Visual Analog Scale (VAS) for pain intensity

Each participant will be assessed once, as this is a cross-sectional study with no intervention. To minimize potential bias, all assessments will be performed by trained evaluators following standardized protocols. Participants will be recruited according to predefined eligibility criteria to reduce selection bias, and data will be systematically recorded to prevent information bias. As no intervention is applied, performance bias is not applicable.

To minimize the risk of type I error resulting from multiple comparisons, the Bonferroni correction will be applied to secondary outcome analyses.

Demographic Information

Demographic data will be collected through face-to-face interviews using a standardized data collection form developed by the research team. The recorded variables will include age, sex, height, weight, BMI, educational level, occupation, year and cause of amputation, dominant side, side of amputation, duration of prosthesis use, current medication use, and history of previously used prosthetic systems. For individuals with transradial amputation, stump length will be measured using a tape measure as the distance from the olecranon to the most distal end of the residual limb.

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SMMSE Description

The SMMSE is a brief 30-item test designed to assess cognitive functions, including attention, memory, orientation, calculation, language, and visuospatial skills. In this study, it will be used solely for participant eligibility screening. Individuals scoring 26 or higher will be included [28].

BDI Description

The BDI is a 21-item self-report questionnaire used to measure an individual's level of depression. Each item is rated on a scale from 0 to 3. In this study, only individuals with a score of 15 or lower will be included [29].

VAS Description

The VAS is a measurement tool rated from 0 to 10 used to assess pain intensity. In this study, individuals who have undergone amputation with a VAS score of no more than 3 for phantom or residual limb pain will be included [30].

MIQ-3 Description

The MIQ-3, originally developed by Williams et al [31], will be used to assess imagery ability in all individuals included in the amputee and control groups. The Turkish validity and reliability study of this questionnaire was conducted by Dilek et al [32]. The MIQ-3 consists of 12 items and evaluates internal visual imagery, external visual imagery, and kinesthetic imagery abilities through 4 actions for each domain. These actions include leg raising, jumping, shoulder flexion, and forward bending. The movements are designed to assess MI capacity in internal, external, and kinesthetic dimensions.

Participants will initially perform each movement physically. They will then be asked to mentally perform the same movements as a cognitive task. This mental imagery task will be rated using a 7-point Likert-type scale (1=very hard to see or feel and 7=very easy to see or feel). For scoring, the average score of the 4 movements corresponding to each subdimension will be calculated.

MCT Description

MCT is an objective method used to evaluate the temporal accuracy of MI [33]. In this study, the MCT will be administered using the BBT. Participants will first be asked to physically transfer 15 blocks from one compartment to another, and the time taken will be recorded. Subsequently, the same task will be mentally imagined after removing the test apparatus from view. The duration for the imagined transfer of each block will be verbally indicated by the participant and recorded accordingly.

The difference between the actual and imagined durations will be used to calculate the mental chronometry ratio, using the following formula:

mental chronometry ratio = |actual time − mental time| / actual time

A ratio closer to 0 indicates that the imagined movement duration closely approximates the actual movement, reflecting a higher level of MIA.

Orientate Mobile App Description

The Orientate app (Reflex Pain Management Ltd) is a rehabilitation tool focused on MI and laterality recognition (left and right discrimination). It is used to assess mental rotation ability. Participants will be presented with 25 hand images at various angles and asked to determine, as quickly as possible, whether each image depicts a left or right hand. The number of correct and incorrect responses, the number of skipped trials, and reaction times will be recorded [34].

BBT Description

The BBT is a widely used standardized assessment tool for evaluating gross motor skills and hand function. Originally developed by Mathiowetz et al [35], the test uses 150 wooden cubes, each measuring 2.5 cm, and a wooden box divided into 2 compartments. Participants are instructed to transfer as many cubes as possible, 1 at a time, from one compartment to the other within 60 seconds while seated at a table. The total number of cubes successfully transferred will be recorded as the test score (Figure 2).

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Figure 2. Box and Blocks Test in a participant who has undergone transradial amputation. The participant moves blocks between compartments within 60 seconds using the prosthetic hand.

JTHFT Description

The JTHFT, originally developed by Jebsen et al [36], will be used as a performance-based assessment to evaluate hand function in activities of daily living. The test will include various types of grasps and will assess the speed at which participants complete specific tasks. Standardized materials, which will be readily available in clinical settings, will be used for the test. Participants will be required to complete 7 distinct tasks: writing, turning over cards, picking up small objects, simulated feeding, stacking checkers, picking up large light objects, and picking up large heavy objects. Each task will be performed separately with both the dominant and nondominant hands. The test score will be calculated based on the time taken by participants to complete each task (Figure 3).

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Figure 3. Jebsen-Taylor Hand Function Test performance in a participant who has undergone transradial amputation. The participant completes standardized hand tasks using the prosthetic hand.

FRT Description

In the FRT, the participant will stand on a flat surface, positioned sideways relative to the testing setup, with feet shoulder-width apart and stable. The test arm will be lifted laterally to shoulder height, with the fingers extended. Without moving their base of support, the participant will be instructed to reach forward as far as possible using only the upper extremity. The distance between the initial fingertip position and the furthest point reached during the movement will be measured in centimeters (cm) using a measuring tape. To enhance the reliability of the test, the measurement will typically be repeated 3 times, and the average of the 3 trials will be recorded [37]. Although FRT primarily assesses balance and reach, it provides additional information about reaching ability with the upper-limb prosthesis, which may indirectly reflect functional integration and MI performance.

QuickDASH Questionnaire Description

The QuickDASH questionnaire will be used as a self-reported instrument designed to assess activity limitations and participation restrictions of the upper extremity [38]. The Turkish validity and reliability of the questionnaire were established by Düger et al [39]. The QuickDASH questionnaire consists of 11 items and aims to evaluate the level of difficulty individuals experience during daily living activities. Responses will be rated using a 5-point Likert scale (1=no difficulty, 2=mild difficulty, 3=moderate difficulty, 4=severe difficulty, and 5=unable to perform). Questionnaire scores will be recorded for both groups included in the study.

JPS Description

To evaluate proprioceptive function relevant to prosthetic control, the JPS assessment will be used. JPS measures an individual's ability to replicate a given joint angle and can be conducted using combinations of passive and active movements, under eyes-closed conditions [22].

Considering the amputation levels of the individuals who have undergone transradial amputation, all participants will undergo JPS assessment of the shoulder and elbow joints, performed bilaterally (dominant and nondominant sides where applicable) with standardized positioning while standing comfortably with feet shoulder-width apart and arms relaxed at the side before each trial. In the amputee group, assessments will be conducted with the prosthesis worn and the terminal device maintained in the closed position to ensure consistency across participants. For passive JPS, the investigator will move the limb to the target angle (eg, 30°) and then return it to the starting position, and the participant will estimate the joint angle without moving it. Participants' vision will be occluded during assessment to prevent visual feedback, ensuring blinding to the target angle. For active JPS, the investigator first demonstrates the target angle with the participant's eyes open. Subsequently, with eyes closed, participants actively replicate the joint angle without any physical guidance.

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For the shoulder joint, angles of 90° abduction and 90° flexion will be used; and for the elbow joint, angles of 30°, 60°, and 90° flexion will be assessed. All joints will be positioned consistently at the same starting reference point for each trial to ensure measurement consistency across participants. Each angle will be measured 3 times, and the mean value will be recorded. Trials with outlier values exceeding 2 SDs from the mean or trials with measurement errors will be excluded.

All measurements will be conducted using the validated digital goniometer app DrGoniometer [40,41], which has demonstrated high validity and reliability for upper-limb joint measurements, including forearm supination and elbow flexion [40,41], although it has not been specifically validated in populations who have undergone amputation. Correctness (+5° and –5°) and reaction-time metrics are predefined. Absolute error, constant error, and variable error will be calculated to quantify accuracy and consistency. Due to the nature of the assessments, assessor blinding was not feasible; however, all measurements were conducted using a standardized protocol with fixed positioning and predefined verbal instructions to minimize bias

Covariates such as age, sex, amputation level, prosthesis experience, and tested side will be recorded and adjusted for in the statistical analyses.

All assessments will be completed within approximately 90 minutes, including short breaks as needed, in the following standardized order: MIQ-3, MCT, JTHFT, QuickDASH questionnaire, FRT, and finally JPS.

Statistical Analysis

All analyses will be performed using SPSS (version 25.0; IBM Corp). Continuous variables will be checked for normality using visual inspection (histograms and Q-Q plots) and the Shapiro-Wilk test. Descriptive statistics will be reported as means and SDs for normally distributed variables or medians and IQRs for nonnormal variables. Categorical variables will be reported as counts and percentages. The details are presented in Textbox 2.

Textbox 2. Detailed statistical analysis plan.

Demographics

- Amputee (group 1) and control (group 2) demographics will be compared. Normally distributed continuous variables will be assessed using an independent samples t test, nonnormal continuous variables will be assessed using the Mann-Whitney U test, and categorical variables will be assessed using the chi-square or Fisher exact test.

Motor imagery (MI) variables

- Measures will include the Movement Imagery Questionnaire-3, including its subscales: kinesthetic MI, internal MI, external MI, and total score as well as the Orientate app accuracy and completion time, and motor execution time–MI time for the dominant and nondominant hand.
- Comparisons will be performed using the analysis of covariance, adjusting for age, dominance, and residual limb length.
- If the analysis of covariance assumptions are not met, nonparametric alternatives will be applied.

MI and upper limb function

- Correlations between MI and functional tests (Box and Block Test; Jebsen-Taylor Hand Function Test subtests; Functional Reach Test; and Disabilities of the Arm, Shoulder, and Hand questionnaire) will be analyzed using Pearson or Spearman correlation, depending on normality.
- Regression analyses will examine the predictive effect of MI on function, adjusting for age, dominance, and residual limb length.

MI and proprioception

- Correlations between MI and proprioception measures (elbow 30°, 60°, and 90°, and shoulder 90° flexion and abduction) will be conducted.
- Regression models will evaluate predictors of proprioceptive performance, with covariates age, dominance, and residual limb length.

Amputee-specific analyses

- Dominant-side amputation will be coded as a binary variable (yes or no).
- Differences in MI, functional outcomes, and proprioception outcomes between participants with amputation of the dominant limb and participants with amputation of the nondominant limb will be analyzed using appropriate parametric or nonparametric tests.
- Associations with MI outcomes will be examined using correlation and regression analyses.

Missing data, outliers, and multiple comparisons

- Missing data will undergo listwise deletion.
- Trials with outlier values exceeding 2 SDs from the group mean will be excluded. Sensitivity analyses with and without outliers will be performed.
- The Bonferroni correction will be applied for multiple comparisons.

Significance

- All tests will be 2-tailed, with $P<.05$ considered statistically significant.

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Results

This study was approved by the noninterventional clinical research ethics committee of Istanbul Medipol University (E-10840098-202.3.02-2988) on May 9, 2024. Following funding from the TÜBİTAK on April 25, 2025, participant enrollment began. As of November 2025, a total of 16 participants have been recruited, including 8 (50%) individuals with transradial amputation and 8 (50%) healthy controls. All assessments for these participants have been completed, and the data have been entered into the study database. Preliminary data cleaning has started; however, statistical analyses have not yet been conducted. Recruitment and data analysis are ongoing, with study completion expected by June 2026.

Discussion

Expected Outcomes

This study protocol is designed to compare MIA between individuals who have undergone transradial amputation and use myoelectric prostheses and healthy individuals as well as evaluate the impact of this ability on upper limb functionality and proprioceptive sensation. By assessing MI capacity, upper extremity function, and proprioception together, this study aims to provide a multidimensional perspective on cognitive and sensorimotor processes in this population.

Existing literature indicates that a high level of MIA may positively influence functional performance and proprioceptive sensation in individuals who have undergone amputation, particularly enhancing functional gains during the preprosthetic and early prosthetic use phases [17,19]. Previous studies involving unilateral upper limb prosthesis users have shown that individuals who have undergone amputation can perform similarly to healthy individuals on hand mental rotation tasks, which are considered cognitive indicators of MIA [42,43]. These findings suggest that the reorganization of body schema following amputation could support MI processes. In line with this, McClanahan et al [44] demonstrated that individuals who have undergone transradial amputations and use myoelectric prostheses can achieve high levels of muscle coordination during prosthesis use, potentially preserving motor control strategies and contributing positively to MIA. With this background, our study is expected to contribute by evaluating the similarities and differences reported in the literature within our own sample, considering body schema reorganization, motor control strategies, and prosthesis use experience.

In previous research, both self-report and performance-based assessment tools, such as the MIQ-3, MCT, and Orientate app, have been shown to be effective in evaluating MIA [45]. For example, Martínez-Rolando et al [46] combined subjective visual and kinesthetic imagery ratings with performance-based measures of response time and accuracy. Similarly, Saruco et al [47] used the MCT to investigate temporal congruence between imagined and actual movement durations in individuals who have undergone lower limb amputation. These approaches demonstrate that MI can be evaluated not only in terms of vividness but also in temporal accuracy. In addition, mobile apps, such as Orientate, integrate imagery tasks with timing measurements, providing an objective assessment of both subjective and temporal parameters [48]. In alignment with this evidence, our study will incorporate these 3 parameters to obtain more comprehensive and objective data regarding the cognitive-motor capacity of individuals who have undergone amputation.

Ensuring that upper extremity function assessments are both reliable and clinically relevant is essential for prosthesis users. The literature identifies the BBT, the JTHFT, and the QuickDASH questionnaire as valid, reliable, and practical tools in clinical settings [49]. Our protocol includes these assessments to objectively measure motor performance and functionality. Furthermore, as shown by Gu et al [50], upper extremity motor skills may be closely related to neural activity during MI, highlighting the cognitive-motor link. Therefore, using a combination of QuickDASH, BBT, and JTHFT is expected to allow a comprehensive evaluation of both subjective and performance-based functional outcomes.

Proprioception, particularly JPS, plays a key role in effective motor control and may also influence MI processes. Clinical and digital JPS assessments, using both active and passive movements, have demonstrated accuracy and reliability [24,40]. In this protocol, proprioception will be evaluated using the DrGoniometer app, chosen for its validated accuracy and ability to perform digital angular measurements [51,52]. Shoulder abduction and flexion and elbow flexion at predefined angles will be assessed to ensure standardization. Previous studies suggest that proprioceptive feedback can enhance prosthetic control and support MI by aligning mentally simulated movement with sensory representations [26,53].

By integrating MI, upper limb function, and proprioception assessments, this study protocol aims to explore their interrelationships in a novel way. The expected outcomes include evidence to guide personalized rehabilitation approaches that combine cognitive and sensorimotor training.

Strengths and Limitations

A key strength of this protocol is its multidimensional evaluation strategy, which combines subjective, performance-based, and digital assessment tools supported by literature. The inclusion of both healthy controls and myoelectric prosthesis users will allow for comparative analysis. However, this study is limited by its single-center design, specific prosthesis type (myoelectric only), and proprioception measurement restricted to predefined joint angles. In addition, sample size and recruitment feasibility may influence generalizability.

Conclusions

Data collection and assessments are currently in progress, with data analysis planned after all participants have been assessed.

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Acknowledgments

Generative artificial intelligence tools (such as ChatGPT [OpenAI]) were used to improve language and sentence structure. No artificial intelligence tool was used for data analysis, interpretation, or content creation of scientific results.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

AY contributed to conceptualization, methodology, data curation, patient recruitment, formal analysis, writing the original draft, reviewing and editing the manuscript, and validation. ZCA contributed to conceptualization, methodology, supervision, and reviewing and editing the manuscript. EAY contributed to formal analysis, data curation, and reviewing and editing the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist for cross-sectional studies used in this study.
[PDF File (Adobe PDF File), 202 KB - resprot_v14i1e83787_app1.pdf]

Multimedia Appendix 2
Peer-review report from the Tübitak 1002-A Rapid Support Module Review Committee, Scientific and Technological Research Council of Turkey.
[PDF File (Adobe PDF File), 410 KB - resprot_v14i1e83787_app2.pdf]

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Abbreviations

BBT: Box and Block Test
BDI: Beck Depression Inventory
FRT: Functional Reach Test
JPS: joint position sense
JTHFT: Jebsen-Taylor Hand Function Test
MCT: Mental Chronometry Test
MI: motor imagery
MIA: motor imagery ability
MIQ-3: Movement Imagery Questionnaire-3
QuickDash: Disabilities of the Arm, Shoulder, and Hand
SMMSE: Standardized Mini-Mental State Examination
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
TÜBİTAK: Scientific and Technological Research Council of Turkey
VAS: visual analog scale

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Protocol

Effects of a Walking-Based Physical Activity Intervention on Health Indicators in University Students: Protocol for a Randomized Controlled Trial

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Abstract

Background: Regular participation in some type of physical activity brings improvements in health indicators such as cardiorespiratory fitness, muscle strength, and body composition. However, despite evidence indicating health benefits, 1 in 4 adults is physically inactive, a situation that also occurs in the university population. Walking is a physical activity modality that can be easily incorporated into daily activities; therefore, using a walking-based physical activity intervention could improve some health indicators.

Objective: This protocol aims to analyze the impact of a walking-based physical activity intervention on health indicators in university students.

Methods: An intervention group (n=99) and a control group (n=99) will be randomly selected. All participants will be assessed at the beginning and end of the intervention for indicators of health, cardiorespiratory fitness, muscle strength, and body composition. The intervention group will participate in a 14-week walking program with individualized daily goals, self-monitoring, personalized feedback, and weekly educational material, while the control group will only record their steps without receiving personalized goals or feedback.

Results: The recruitment process will begin in March 2026. Initial assessments are scheduled to take place from March 2, 2026, to March 13, 2026. The intervention will be performed from March 16, 2026, to June 19, 2026 (14 weeks). From June 22, 2026, to July 6, 2026, the final evaluations will be performed. The final results of this study are expected to be published by October 2026.

Conclusions: This protocol proposes a novel and feasible approach to overcome common barriers to physical activity in university students, with the potential for large-scale application in similar contexts.

Trial Registration: ClinicalTrials.gov NCT06580769; https://clinicaltrials.gov/study/NCT06580769

International Registered Report Identifier (IRRID): PRR1-10.2196/83983

(JMIR Res Protoc 2025;14:e83983) doi:10.2196/83983

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KEYWORDS

body composition; cardiorespiratory fitness; fat; muscle strength; pedometer

Introduction

Background

Regular participation in some form of physical activity brings a variety of benefits to those who engage in it [1], including improvements in health indicators, such as cardiorespiratory fitness [2,3], muscle strength [4,5], and body composition [6]. However, despite evidence demonstrating its benefits, 1 in 4 adults is physically inactive [7], as they do not meet the recommended duration of 150 to 300 minutes of moderate physical activity per week or 75 to 150 minutes of vigorous physical activity [8]. Among the elements that explain this situation are motivation, access to sports centers, or the support of family or society, which ultimately lead to adults avoiding participation in physical activity [9,10]. In the university population, the situation is similar, as academic pressure is added to other obligations inherent in their lives, resulting in the adoption of unhealthy habits [11,12]. Thus, evidence shows that university students spend 9.82 hours a day in a sedentary state (a value that has been increasing over the last 10 years), which is considerably higher compared to the general population of young adults, a situation that is associated with a higher risk of harmful health outcomes [13].

One means that has been shown to be useful in increasing participation physical activity interventions [14] have been shown to be useful in increasing participation in physical activity and thus reducing health risks, with the most promising being personalized interventions [15]. One option is the measurement of the number of daily steps—a method that has been shown to have the potential to cause increases in physical activity because it is a modality that can be easily incorporated into daily activities [16]—being a valid alternative to meet physical activity recommendations because evidence suggests that moderate to vigorous intensity physical activity recommendations can be achieved, on average, with a total volume of 10,000 steps/d for adults [17]. Recent research implementing physical activity interventions based on daily step measurement has used wearable daily step trackers as a means of monitoring, as they have the facility to allow users to use them in conjunction with mobile phones, allowing them to immediately track their activity and thus manage their time to improve their health [18]. Thus, physical activity interventions based on daily step measurement have been implemented in university students using step trackers, which have demonstrated increases in minutes per day of moderate to vigorous intensity physical activity [19,20]. However, despite having been shown to be efficient in increasing participation, most studies are short term, usually lasting 7 days [21], and studies using longer periods are still limited in terms of evidence on their efficacy [22,23].

As can be seen and as explained by Preusse et al [24], measuring daily steps can provide support to those looking to increase their levels of physical activity. Step trackers are a recommended choice because they are inexpensive and easy to use and provide personalized, ongoing support [16].

Given that adults exhibit low compliance with physical activity recommendations, in particular the university population, which is in a period where daily time is prioritized in their academic activities, the performance of a physical activity intervention based on increasing the number of daily steps and monitored through step trackers represents a potential way to overcome the barriers that hinder the practice of physical activity. In addition, given that the use of this technology provides personalized support, it is reasonable to hypothesize that performing a physical activity intervention that increases the number of daily steps could improve some health indicators.

Objective

The objective of this study is to provide a working methodology that allows for the analysis of the impact of a walking-based physical activity intervention on health indicators in university students.

Methods

Design

It will be a 2-arm randomized controlled trial (RCT) to analyze a physical activity intervention in college students for 14 weeks. The RCT will be reported according to the CONSORT (Consolidated Standards of Reporting Trials) statement [25] and the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [26] (Multimedia Appendix 1).

Participants

Participants will be gathered from the Universidad Autónoma de Chile across the campuses located in the cities of Santiago, Talca, and Temuco. Information about the intervention will be disseminated through institutional email, social networks, and informative posters. The following inclusion criteria will be considered: (1) be a university student with active enrollment at the Universidad Autónoma de Chile, (2) aged between 18 and 25 years, (3) have medical consent that authorizes the regular practice of physical activity, and (4) sign an informed consent form to participate in the study. The exclusion criteria will be as follows: (1) having a physical or mental impediment that prevents or limits the performance of physical activity and (2) belonging to special groups, such as professional athletes or pregnant women. The evaluations at the beginning and end of the study will be performed at the university's facilities using the equipment available at each of the respective campuses (Santiago, Talca, and Temuco).

Randomization

This study will adopt a single-blind RCT design. Using EPIDAT software (version 4.2; Pan American Health Organization), participants will be divided into 2 groups (ie, group 1 [intervention] and group 2 [control]).

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Sample Size Calculation

On the basis of what was proposed for the design of the RCTs [27], the number of participants will be calculated. Taking 2 RCTs that aimed to increase physical activity levels through walking [18,19] as reference, the sample will be calculated considering an absolute difference of 3% (α error of .05 and statistical power of .80) between the intervention group and the control group in the mean percentage of cardiorespiratory endurance (SD 5), giving a required sample of 99 participants for each group (intervention and control).

Intervention

Training Intervention

For step monitoring, a wearable Xiaomi smart bracelet step tracker (*Smart Band 9 Active* model), validated for step tracking, will be used on the nondominant wrist for at least 12 hours a day [28]. Participants will receive physical activity goals based on adherence to international recommendations for steps per day (≥10,000 steps/d) [17,29,30].

A member of the research team will provide personalized feedback via email or WhatsApp (Meta Platform, Inc) daily, reinforcing achievements and adjusting goals when necessary. In addition, educational infographics designed to promote physical activity will be sent weekly, detailing the benefits of walking, strategies to increase the step counts, and practical recommendations for maintaining adherence (Figure 1). The weekly and total step records will be obtained through a downloadable CSV file from the Mi Fitness app (Xiaomi Mobile Software Co, Ltd), which will be downloaded by the user and sent to the research team via email.

Figure 1. Group intervention activities.

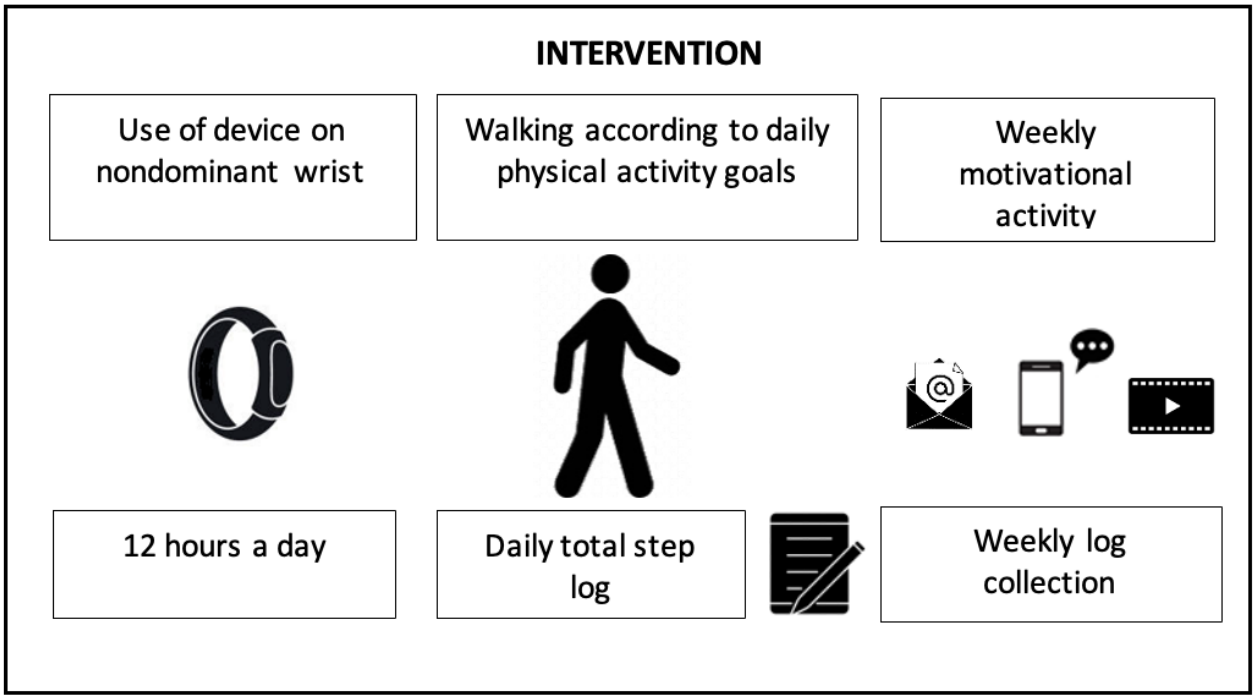

Duration of the Intervention

The intervention will last 14 weeks. Initial assessments are scheduled to take place from March 2, 2026, to March 13, 2026. The intervention itself will be performed from March 16, 2026, to May 22, 2026. Final evaluations will be performed from May 25, 2026, to June 5, 2026. Inclusion and exclusion criteria, participant selection and randomization procedures, as well as baseline and follow-up assessments are summarized in the flowchart presented in Figure 2.

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Figure 2. Recruitment, randomization, and evaluation flowchart.

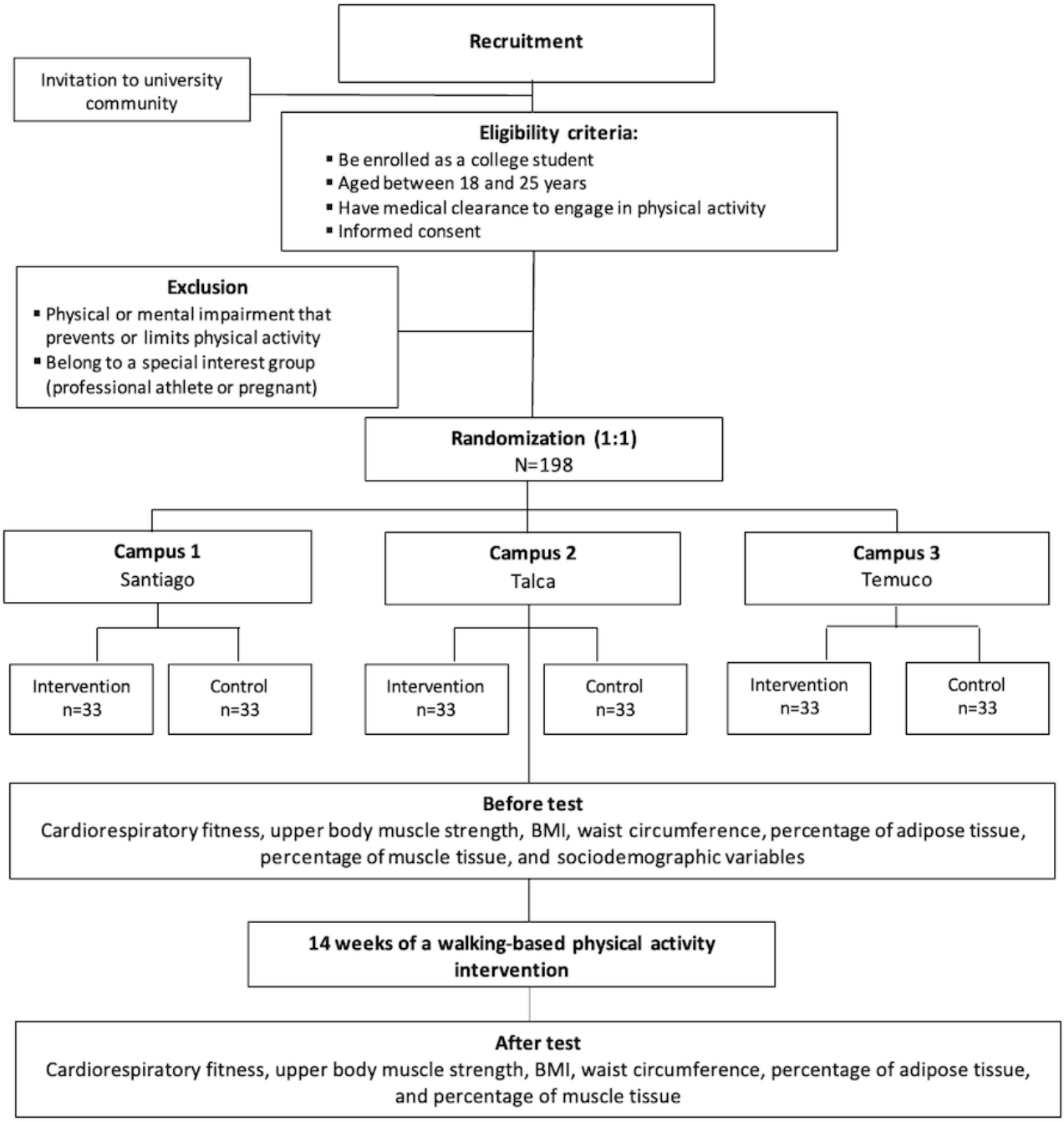

Adherence to the Intervention Criteria

Those who make up the control group will also have their health indicators evaluated at the beginning and end of the intervention. Participants will also use the same *Xiaomi Smart Band 9* Active for at least 12 hours a day and will submit the weekly and total step log report, downloaded from the Mi Fitness app, to the research team. However, they will not receive specific step goals, individualized feedback, or behavior change strategies. They will maintain their usual physical activity habits without setting quantitative targets or providing personalized motivational messages.

Procedures

Signed informed consent will be obtained once the sample has been recruited. Then, the evaluations of cardiorespiratory endurance, muscle strength, body composition, and the sociodemographic questionnaire will be scheduled. Subsequently, each participant will be given a step tracking device as well as training on their operation, maintenance, and how to download the step report from the Mi Fitness app.

Measuring Health Indicators

Cardiorespiratory Fitness

This indicator will be measured through the 20-m shuttle run test [31]. Participants must run between 2 lines separated by 20 m. The speed at which they must move is indicated by a sound

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emitted by a recorded tape. The participant begins at a speed of 8.5 km/h, which increases by 0.5 km/h every minute. When a participant being evaluated fails to reach the lines twice in a row, along with the sound, or when they are unable to continue running the test, the evaluation is completed, and the minute reached is recorded. According to the proposal, the maximum oxygen consumption is estimated [31].

Upper Body Muscle Strength

Using a digital dynamometer (Takei T.KK.5401; Takei Scientific Instruments Co, Ltd), grip strength will be evaluated. For each hand, the average of 2 measurements will be calculated.

Body Composition

Using a digital scale and a stadiometer, weight and height will be measured (Tanita MC-780U [Tanita Corporation] and Seca 222 [Seca, GmbH & Co], respectively). For weight, the participant must be without shoes and with as little clothing as possible, while for height, they must be in a standing position, obtaining the value at the end of a normal inspiration. Both measurements will be taken in duplicate using the average to calculate the BMI.

Waist circumference will be determined as mentioned subsequently. On the right side of the body, a mark will be made on the skin at the height of the last rib, then a mark will be made on the skin at the top of the iliac crest. The distance between both marks will be calculated, and, at the midpoint, a final mark will be made. The same procedure will be performed on the left side. Using a tape measure, which must be at the height of both end marks on each side, the value will be determined at the end of a normal expiration. For the analyses, the average of 2 measurements will be used.

The percentage of adipose and muscle tissue will be calculated from the average of 2 evaluations performed in a state of rest and fasting, with the minimum amount of clothing and after urinating and resting for 15 minutes, using tetrapolar electrical bioimpedance (Tanita MC-780U). It will be complemented by the measurement of skinfolds, body perimeters, and bone diameters [32].

Covariables

Before the start of the intervention, sociodemographic variables will be collected through a questionnaire, including questions on age, sex, career, means of transport, geographic area of residence, screen time, and socioeconomic level of the participants.

Ethical Considerations

This protocol was approved by the scientific ethics committee of the Universidad Autónoma de Chile as well as the informed consent document (Scientific Ethics Committee CECP 28-25), which participants must sign at the beginning of the study. They will receive a copy of the signed consent form and will be given the opportunity to ask questions related to the study. The procedures will be executed in accordance with the Declaration of Helsinki. In addition, this study has been registered on ClinicalTrials.gov (NCT06580769). Participants may withdraw from the study at any time without having to justify their decision. To safeguard participant privacy and the integrity of the collected data, the following measures will be implemented: the collected data are confidential and will be stored in locked files accessible only to the principal investigator. The data will be anonymized. Only anonymized data will be used for publications or presentations.

Statistical Analysis

The normality of the data will be checked through the Kolmogorov-Smirnov test, which will indicate the steps to be taken in relation to the comparison tests. Once the pretest tests have been performed, comparison analyses will be performed between groups (2-tailed Student *t* test or Mann-Whitney *U* test) to check the homogeneity of the groups. At the conclusion of the final evaluations of the study, intragroup differences will be analyzed using a statistical test of repeated measures (Student *t* test for related samples or Wilcoxon signed-rank test), along with the intergroup differences (Student *t* test or Mann-Whitney *U* test).

Cohen *d* will be used to determine the effect size on variables in which significant differences are found, using the following scale: 0.2 or greater=small, 0.5 or greater=moderate, and 0.8 or greater=large [33]. In addition, regression analyses will be performed incorporating the covariates. The simple imputation method will be used for all analyses [34], keeping the participants in the group to which they were assigned (intervention or control) regardless of the sessions they attended [35]. In valid cases, analyses will be performed to determine sensitivity [36]. For all tests, statistical significance will be set to $P<.05$. The data will be analyzed using SPSS statistics (version 29; IBM Corp).

Results

The project was awarded in April 2025. Subsequently, the project was reviewed for possible updates. In August 2025, funds were received, and the necessary materials for the execution of the project were purchased. Between September 2025 and December 2025, the staff in charge of the evaluations will be trained. The recruitment process will begin in March 2026. Initial assessments are scheduled to take place from March 2, 2026, to March 13, 2026. The intervention will be conducted from March 16, 2026, to June 19, 2026 (14 weeks). From June 22, 2026, to July 6, 2026, final evaluations will be conducted. The final results of the study are expected to be published by October 2026. The main results will be provided to the participants in a summarized way and will also be disseminated to the scientific community through participation in scientific events.

Discussion

Anticipated Findings

Considering that there is currently a high number of inactive adults [7] and that sedentary behaviors predominate in university students' daily lives due to academic demands—which is associated with damage to their health [13]—it is necessary to implement strategies to help address this problem. Interventions based on wearable technologies have shown increases in daily step counts and, to a lesser extent, activity intensity, with small

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to moderate effects and heterogeneity between populations [16,18,26]. These findings support the use of goals and objective monitoring as key components.

One option that has proven to be effective, low cost, and easy to implement is physical activity through walking, which is monitored by daily step trackers. However, most studies implementing this strategy have generated evidence by monitoring physical activity for 7 days on average [37], which could cause the reported results to be biased because participants could change their physical activity behaviors because they are aware that they are being evaluated [21]. This reinforces the need for research with longer follow-up periods that allow for a more detailed analysis of the relationship between daily steps and health indicators. In the university population, recent studies have shown that programs of 8 to 12 weeks supported by mobile apps and messaging can lead to significant increases in daily steps [21,22,25,27]. On the basis of this evidence, this protocol proposes a duration of 14 weeks, with individualized goals and weekly feedback, with the aim of achieving more sustained effects than those observed in interventions of shorter duration.

The choice of a long period is based on the need to assess the sustainability of change, given that recent reviews suggest that initial increases may decrease over time [5,20]. Likewise, setting explicit daily goals has been associated with higher levels of compliance, and more recent proposals even propose hourly objectives as a tactic to achieve the daily goal [17,29].

Regarding the results, cardiorespiratory fitness, muscle strength, and body composition were included because of their value as relevant clinical markers. Current evidence shows that higher fitness levels in youth are associated with better indicators of cardiometabolic health and overall well-being [13,18]. In addition, studies have linked muscle condition with a better perception of health in adolescents [5], which reinforces the relevance of these indicators as outcomes of this study.

Methodologically, the use of a validated wrist device, combined with daily manual logging, addresses both ethical considerations of data privacy and the intention of encouraging self-regulation and awareness of participants' own physical activity [19]. This component has been described as an effective behavior change strategy in digital interventions [16,18]. Likewise, the risk of reactivity to initial monitoring is recognized [21,38]; therefore, extended duration seeks to minimize this effect and allow a more stable analysis of behavior over time.

The implementation of this study and the subsequent results could be useful for the organizations in charge of providing comprehensive well-being to university students, offering programs that are not only dedicated to their professional training but also contribute to improving their health. This research also aligns with Sustainable Development Goal 3, target 3.4 [39], which aims to promote more active lives and contributes to reducing premature mortality from non-communicable diseases, along with promoting mental health and well-being [37].

The strength of this research is that the intervention will be based on walking, which is an easy and low-cost activity to perform because it does not need additional implements to those used daily by a person nor does it require sports facilities. The device used to track the steps is low cost, so it is accessible to anyone; its use can be constant throughout the day because it does not cause major discomfort when used as a watch that adapts to the characteristics of the wrist, in addition to providing information on physical activity of better quality than that collected through self-reports.

Conclusions

In conclusion, this protocol describes a feasible, low-cost approach to evaluating the impact of a walking intervention on the health of college students. The 14-week design, supported by wearable technologies, individualized goals, and personalized feedback, seeks to overcome the limitations of short-term studies and provide useful evidence for health promotion in the university setting.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

AG-C conceptualized the study and drafted and prepared the original manuscript. PF-M wrote and prepared the original manuscript, applied for the project, and obtained funding. FG-R, CM-S, JdS-L, DD-B, and MP-S analyzed the original manuscript and provided feedback. JB-C and EM-N analyzed the original manuscript and provided feedback and will also oversee the supervision of the development of the study.

Conflicts of Interest

None declared.

Multimedia Appendix 1

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CONSORT and SPIRIT checklists.
[PDF File (Adobe PDF File), 237 KB - resprot_v14i1e83983_app1.pdf]

Multimedia Appendix 2
Peer review report from Vice-Rector's Office for Research and Postgraduate Studies, Universidad Autónoma de Chile (translated from Spanish).
[PDF File (Adobe PDF File), 257 KB - resprot_v14i1e83983_app2.pdf]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Meta Self-Efficacy Internet Intervention to Support Occupational Health in Young Employees: Protocol for Co-Creation and a Randomized Controlled Trial

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Abstract

Background: Supporting young employees as they navigate the changing workplace requires focus on personal resources. Although self-efficacy is a key and malleable resource, its context specificity limits its applicability. To address this, we propose to target meta self-efficacy, a construct reflecting an individual's ability to leverage self-efficacy sources (mastery experiences, vicarious experiences, persuasion, and affective and physiological states) to build self-efficacy specific to any challenge and, in turn, safeguard their occupational health.

Objective: The goal of this study is to co-create (co-creation phase) and verify the efficacy (randomized controlled trial [RCT] phase) of an internet intervention enhancing meta self-efficacy to support the occupational health of young employees.

Methods: The co-creation phase will be based on the participatory approach principle and comprise 4 focus groups, where a total of 24 participants will contribute to meta self-efficacy–enhancing activities and identify needs for the intervention format. After each focus group, a preliminary qualitative analysis will be conducted, and the intervention draft will be refined. To detect an effect size of d=0.25, the RCT will use a 2-arm parallel design with a total sample size of 600 comparing the meta self-efficacy intervention against a placebo. Assessments will be conducted at the posttest time point and 3- and 6-month follow-ups, with work self-efficacy as the primary outcome and job stress, job affective well-being, and work capabilities as secondary outcomes, as well as meta self-efficacy as the manipulation check. Data will be analyzed using linear mixed-effects models following the intention-to-treat approach. The trial will also examine the impact of adherence and engagement on intervention outcomes and compare treatment credibility.

Results: As of November 20, 2025, a total of 24 participants have been recruited, with 3 of 4 focus groups conducted and the final one to be completed by the end of 2025. RCT recruitment is scheduled to start at the beginning of 2026, with the last follow-up expected by the end of 2026.

Conclusions: In comparison to the placebo control, we expect the intervention to significantly improve young employees' work self-efficacy (primary outcome) and occupational well-being (secondary outcomes). If effective, the meta self-efficacy–enhancing intervention could bolster the ability to cope with various challenges in the health domain and beyond, extending the effect beyond the initial occupational context.

Trial Registration: ClinicalTrials.gov NCT06944990; https://clinicaltrials.gov/study/NCT06944990

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KEYWORDS

meta self-efficacy; young employees; internet intervention; work self-efficacy; occupational health; sustainable employability; job stress

Introduction

Background

Early adulthood, spanning the ages of 18 to 30 years, is a critical period for establishing long-term psychological health, coinciding with the onset of major mental health disorders [1]. A central source of stress during this stage is the transition to independent living and professional life [2]. Work-related stress is particularly significant as it can affect the health of young adults and have long-term implications for employability, with research showing that young employees are seemingly more vulnerable to burnout than older workers [3].

Systematic reviews indicate that young employees face numerous job demands that can adversely affect their mental health [4,5]. Meanwhile, global trends are introducing a host of new workplace stressors—ranging from subtle disruptions such as inadequate technology or work interruptions [6] to serious challenges such as economic inequality, increasingly demanding work conditions [7], or uncertainty about work in light of artificial intelligence [8]. Young employees entering the workforce today will need to navigate these evolving challenges throughout their careers.

While organizations hold the primary responsibility for mitigating job demands and safeguarding employees' health and well-being, such efforts can be slow in adapting to evolving challenges [9]. Thus, young employees may benefit from simultaneously building their own resources to cope with an increasingly unpredictable work environment. According to the conservation of resources theory [10], while resource loss causes stress, gaining resources protects individuals from stress and facilitates further resource accumulation—a process known as a *gain spiral*. Thus, consistent with the conservation of resources theory, developing psychological resources should help mitigate stress and generate additional benefits. In particular, strengthening young employees' psychological resources should also support long-term well-being and enhance sustainable employability, defined as maintaining health and productivity over the course of one's career [11]. To contribute to this goal, we propose to investigate enhancing a psychological resource that has the potential to foster long-term coping in changing circumstances: *meta self-efficacy*.

Bandura [12] defines self-efficacy as "beliefs in one's capabilities to organize and execute the courses of action required to manage prospective situations." It is considered a key personal resource [13] that can be deliberately improved through interventions due to its 2 main characteristics. First, self-efficacy is derived from 4 sources: mastery experiences, vicarious experiences, persuasion, and affective and physiological states [12]. Interventions designed to enhance self-efficacy usually incorporate activities based on these sources. Second, self-efficacy is context specific, meaning that it applies to particular tasks or domains. Context-specific self-efficacy has been tested in the health domain, facilitating processes such as habit modification or managing stress and burnout at work [14,15]. However, a limitation of context-specific self-efficacy interventions is that they can only strengthen self-efficacy within a narrowly defined domain. Participants in such interventions engage in a fixed number of activities enhancing self-efficacy in a particular setting. However, as a result, they do not necessarily internalize the root mechanism of self-efficacy. What is needed is the ability to intentionally recognize and leverage the sources of self-efficacy regardless of the challenges at hand, which might prove crucial for coping with life difficulties that are unexpected, fluctuating, and extend beyond the scope of a single intervention.

To address this gap, we propose the concept of meta self-efficacy, defined as "one's ability to actively recognize, adapt, and leverage the 4 sources of self-efficacy beliefs in various contexts, as needed." Because meta self-efficacy encompasses tapping into self-efficacy sources and considers the very mechanism of self-efficacy development, it is distinct from context-specific self-efficacy, which pertains to perceived capabilities in particular domains. Meta self-efficacy also differs from general self-efficacy. General self-efficacy reflects global positive self-beliefs about one's abilities [16,17], whereas meta self-efficacy is an actionable skill and can be viewed as a context-free personal resource. In a separate study, we introduced the concept of meta self-efficacy and validated a questionnaire designed to measure it, examining both its internal and external validity [18]. In the context of an intervention, enhancing meta self-efficacy would enable individuals to intentionally leverage situations that may constitute sources of self-efficacy, such as experiencing gradual success with a specific task despite obstacles, to deliberately build the self-efficacy required for a specific task or domain. Consequently, an intervention aimed at enhancing meta self-efficacy would bolster a broad and transferable resource rather than one limited to the context of a single challenge.

Study Aims

The overarching research question of this study is whether enhancing meta self-efficacy via an intervention can improve work self-efficacy and multidimensional occupational well-being in young employees. To address it, we will conduct a 2-phase investigation involving an intervention co-creation study and a randomized controlled trial (RCT).

In the co-creation phase, we will conduct a qualitative study to co-design the meta self-efficacy intervention in collaboration with its intended end users, young employees. This program will be delivered in the format of an internet intervention [19]. While internet interventions, including those targeting self-efficacy, have been successfully delivered [15,20], they often face challenges with adherence, engagement, and retention, particularly when they are self-administered [21,22]. To mitigate these risks, the co-creation phase will use a participatory design to develop meta self-efficacy activities based on the lived experiences of young employees and tailor the intervention

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format to their specific preferences. This phase is expected to improve the intervention's general quality and, in turn, support adherence and engagement [23].

In the RCT phase, we will test the intervention's efficacy comparing the meta self-efficacy intervention to a placebo. The goal is to assess the basic effect that the meta self-efficacy intervention can produce while controlling for the expectation bias [24]. We will additionally compare treatment credibility between conditions. Although meta self-efficacy is potentially applicable universally across life domains, testing its enhancement within the framework of the theory by Bandura requires concentrating on a specific background. In particular, enhancing meta self-efficacy should, in principle, lead to improvements in domain-specific self-efficacy. In this study, we test the effects of improving meta self-efficacy in the occupational context and among young employees, expecting that enhancing meta self-efficacy will improve their work self-efficacy (primary outcome). Furthermore, strengthening meta self-efficacy should lead to further well-being benefits [10], which we will measure as multiple dimensions of occupational well-being. These will reflect job-related emotions, stress levels, and work capabilities, encompassing behaviors and values. Accordingly, the secondary outcomes include job stress [25], job affective well-being [26], and work capabilities [27]. We expect improvements in both primary and secondary outcomes immediately after the intervention, with effects sustained at follow-ups. Additionally, a secondary objective of the RCT phase is to examine how factors such as intervention engagement and adherence relate to the intervention's efficacy.

Methods

Ethical Considerations

This study has been approved by the ethics committee of the Institute of Psychology at SWPS University in Warsaw, Poland (opinion 11/2025). We will obtain informed consent from all study participants. Participants in the co-creation phase will receive a reimbursement in the form of online gift cards (€25; US $29.30) per 1.5-hour session, whereas participants in the RCT phase will not be reimbursed. Focus groups will be audio recorded and transcribed. Transcripts will be anonymized, and the original recordings will be deleted afterward. In the RCT phase, data collected via online surveys will be analyzed in anonymized form. The content of participant-generated data within the intervention will not be analyzed. Adherence will be assessed automatically using use data, which will also be analyzed in anonymized form.

Registration

The RCT has been preregistered on ClinicalTrials.gov (NCT06944990). Protocol reviews from the grant application stage are available in Multimedia Appendix 1. Any deviations from the protocol will be documented in future reports of the study results. The RCT protocol follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [28], with the checklist available in Multimedia Appendix 2.

Co-Creation Phase

Design

During the co-creation phase, we will conduct 4 focus groups. The first 2 groups (independent samples) will predominantly explore experiences with occupational well-being, centering on meta self-efficacy. The goal is to assess relevant behaviors and strategies connected to leveraging self-efficacy sources to create intervention activities, ensuring that the intervention's content is relevant. In contrast, the third and fourth focus groups, comprising a new sample of participants taking part in 2 meetings, will focus on refining a prototype version of the activities already incorporated into a technological solution for the intervention. In these sessions, participants will review a preliminary version of the meta self-efficacy intervention activities and provide targeted feedback to further refine its content, design, and functionality.

Sample

The co-creation phase will be conducted among young employees, the same population targeted in the subsequent RCT phase. To participate in the focus groups, individuals must meet the following inclusion criteria: (1) be aged between 18 and 30 years and (2) have been professionally active for at least the 2 previous months, working at least part time or a minimum of 20 hours per week. Focus groups will be conducted on 3 samples of 8 participants for a total of 24 unique participants, with one sample taking part in 2 sessions. Consistent with qualitative research practices, our focus group sample size aligns with recommendations for achieving data saturation and capturing rich, in-depth insights. Vasileiou et al [29] note that qualitative studies often rely on small, purposively selected samples—with saturation frequently reached with as few as 6 to 8 participants per group. Accordingly, using 3 samples for a total of 4 focus groups (N=24) is appropriate for the exploratory co-creation phase as it prioritizes data adequacy over statistical generalizability.

Procedure

Potential participants will be recruited through multiple channels, including advertisements, personal contacts, and a university credit exchange system. Advertisements with a brief description of the participation terms will be disseminated as digital posts via social media platforms (eg, Facebook). The university credit exchange system is an internal online platform through which students can sign up to participate in research projects in return for gift cards or study credits that can be used to fulfill course requirements. In this study, this platform will serve solely as a recruitment channel to reach young employees, and all focus group participants will receive the same reimbursement. Those who are interested, meet the inclusion criteria, and consent to participate via an online recruitment form will be invited to one of the in-person focus groups. Each session will last approximately 1.5 hours, although the duration might vary. Participants will be reimbursed for their effort with online gift cards (valued at approximately €25; US $29.30) per 1.5-hour participation.

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Qualitative Data Collection

The 4 focus groups will follow a semistructured format combining predetermined questions with open discussions. This approach ensures that, while participants respond to set questions, they are still encouraged to elaborate on and engage in a dialogue, allowing for a structured inquiry while also capturing diverse perspectives.

The first 2 focus groups (separate samples, n=8 each) will begin by exploring young employees' experiences with occupational well-being, with a main focus on meta self-efficacy. Discussions will cover four key topics: (1) sources of occupational stress and well-being; (2) distinctions among specific, general, and meta self-efficacy beliefs; (3) behaviors and strategies for leveraging self-efficacy sources; and (4) potential ways to enhance meta self-efficacy and initial requirements for an internet intervention. Subsequently, within the research team, we will discuss the findings and compile a list of the most salient meta self-efficacy strategies, integrating them with proposed activities and the predetermined components of the intervention (see the Meta Self-Efficacy Intervention and Analysis sections). We will prepare an initial version of the intervention based on this. In the third focus group, a new sample of participants (n=8) will review the content and format of the initial version of the meta self-efficacy intervention. Discussions will include (1) occupational well-being, as well as specific, general, and meta self-efficacy to introduce participants to the scope of the intervention; (2) opinions on the psychological content of the activities, with a focus on meta self-efficacy strategies; and (3) technological aspects, such as visuals, user experience, notifications, and others. During the fourth and final focus group, we will present a refined version of the intervention to the same participants. They will be asked to provide areas for potential improvements and remaining concerns regarding both the content of the activities and the intervention format. Figure 1 illustrates the process of collecting qualitative data alongside the iterative refinements made to the meta self-efficacy intervention. The topic guide for the focus groups is provided in Multimedia Appendix 3.

Figure 1. Qualitative data collection and iterative intervention refinements.

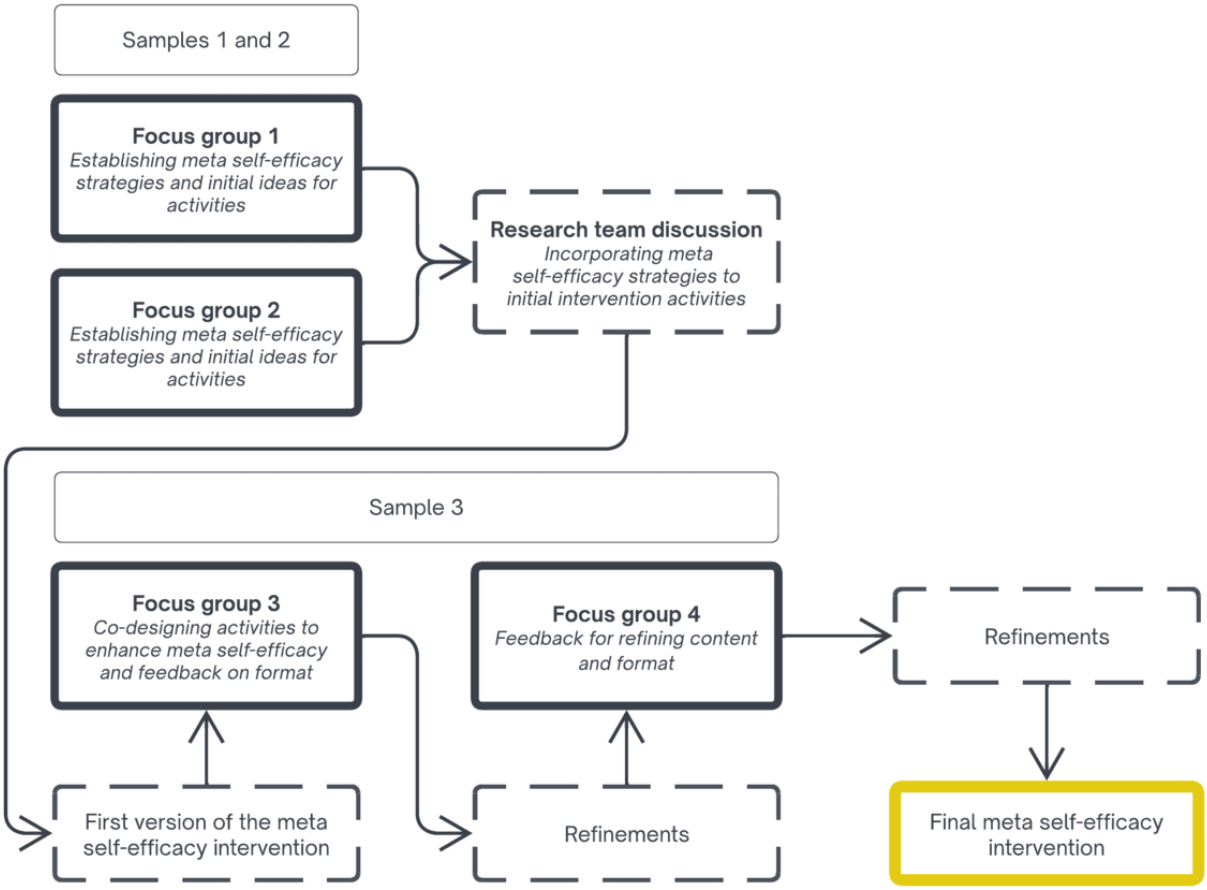

The co-creation phase will be conducted in person and moderated by a psychologist. Focus group discussions will be audio recorded and later transcribed for analysis. Participants' privacy will be respected, and we will inform them about the recordings during recruitment and again before the focus group sessions begin.

Analysis

A preliminary qualitative analysis of each focus group will inform the iterative development of the meta self-efficacy internet intervention (Figure 1). First, transcripts from focus groups 1 and 2 will be assessed to identify user requirements and preferred features, as well as to compile a catalog of meta self-efficacy strategies. Second, the research team will discuss these findings and incorporate the proposed meta self-efficacy strategies into the theoretical model of the intervention (see the

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Meta Self-Efficacy subsection) based on the framework by Bandura [16]. Draft intervention scripts and delivery format screenshots will then be created. Third, this initial version of the intervention will be discussed in focus group 3 to gather participants' opinions, elicit suggestions for improvement, and identify additional meta self-efficacy strategies. Fourth, after further refinement of the intervention contents and technological aspects of the delivery modality, a revised iteration will be presented in focus group 4. Feedback from this session will focus on fine-tuning the content and format of the activities to finalize the intervention before the RCT begins.

After the study is completed, we will conduct an additional analysis to identify the barriers and facilitators that emerged during the iterative intervention development. We will then carry out an in-depth thematic analysis to address the following research question: "What aspects facilitate or hinder uptake and engagement in the meta self-efficacy intervention?" We will analyze all focus groups collectively, tracking what facilitators and barriers emerge throughout the intervention's iterative development. Following the principles of reflective thematic analysis [30], the process will unfold in 6 stages. First, the project's principal investigator will listen to the recordings and review the transcripts to familiarize himself with the data to generate initial codes by identifying transcript sections relevant to the research questions. In the third step, the principal investigator will group codes into themes representing specific meanings. In the 2 subsequent stages, the research team will iteratively review and name the themes. In the final step, we will refine the themes into a coherent narrative and prepare the final write-up.

RCT Phase

Study Design

To evaluate the efficacy of the meta self-efficacy intervention, we will conduct a 2-arm RCT. Participants will be randomly assigned (1:1) to 1 of 2 conditions: an experimental group with access to the meta self-efficacy–enhancing internet intervention or a placebo control group with access to educational content. A placebo comparator in the form of interactive educational content on occupational well-being has been chosen over a waitlist control [31] to avoid a typical expectation bias: participants in the intervention group usually expect improvement, whereas those on the waitlist do not. An active but nontherapeutic comparator delivered through the same modality as the intervention [24] will allow us to isolate the specific effect of the meta self-efficacy intervention while holding expectations similar in both groups. Outcomes will be measured at 4 time points: baseline, posttest, and 3- and 6-month follow-ups.

Sample

The trial will be conducted with a sample of young employees aged 18 to 30 years, representing the early adulthood life stage [2]. To participate in the RCT, individuals must meet the following inclusion criteria: (1) age between 18 and 30 years, (2) professional activity for at least 2 months before trial recruitment (minimum part-time employment or 20 hours per week), and (3) completion of the baseline assessment. Individuals who participated in the co-creation phase focus groups will not be eligible to participate in the RCT phase due to prior exposure to the intervention content and concepts.

Power Analysis

To determine the required sample size, we considered the effect sizes reported for internet interventions aimed at enhancing context-specific self-efficacy. These interventions have shown effect sizes of approximately d=0.5 for various stress-related outcomes [20,32]. However, the effect size for the meta self-efficacy intervention may differ and is likely smaller as it shifts the focus from enhancing self-efficacy in a specific context to bolstering the ability to leverage self-efficacy sources. To account for this, the trial is powered to detect a minimum meaningful effect of d=0.25. We conducted an a priori power analysis for a linear mixed-effects model using the *powerlmm* R package (R Foundation for Statistical Computing) [33]. Given 4 measurement points, an error level of α=.05, and power of $1 - \beta$ of 0.90, the analysis indicates that 600 participants are needed. This calculation factors in a 30% dropout rate based on a previous self-efficacy internet intervention for young adults and a broader review of adherence in mobile interventions [21,34].

Procedure

Participants will be recruited through a hybrid campaign combining traditional media, targeted social media advertisements, and personal contacts. Interested individuals will be directed to a landing page with a brief study description and a link to a detailed study overview and informed consent form. Those who consent to the terms and meet the inclusion criteria will proceed to the baseline assessment (T1). Participants who complete T1 will be randomized in 1:1 blocks to either the intervention or control condition. Participants will be blinded to the allocation. After randomization, they will receive access to their assigned program. Following the intervention period, all participants will be asked to complete a posttest assessment (T2) followed by assessments after 3 (T3) and 6 months (T4). Participant flow is illustrated in Figure 2.

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Figure 2. Study flow.

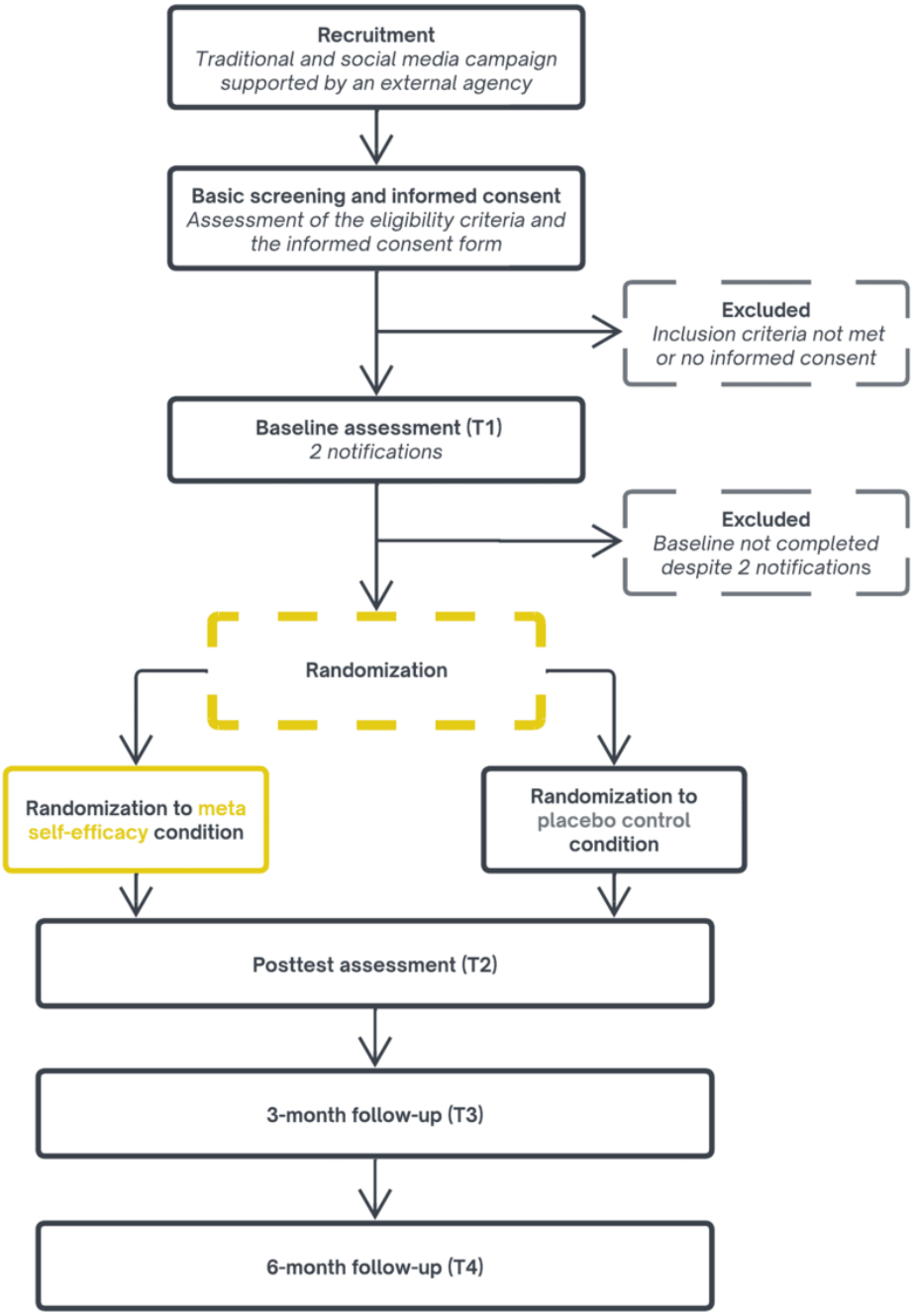

Meta Self-Efficacy Intervention

Following the definition of meta self-efficacy, the intervention will guide participants through understanding the mechanism of self-efficacy, introduce and practice meta self-efficacy strategies (leveraging the 4 sources), and foster the development habits that support the use of these strategies in everyday life. The intervention spans 3 weeks and consists of three components: (1) preparation stage and monitoring of daily challenges and self-efficacy beliefs, (2) learning to leverage self-efficacy sources, and (3) incorporating meta self-efficacy strategies in daily life. The intervention is grounded in the work on self-efficacy sources by Bandura [16]. All activities will be evaluated during the co-creation phase to reflect authentic strategies that individuals use to draw on self-efficacy sources. Crucially, the intervention will be tailored to young employees, ensuring that the activities are relevant to both workplace challenges and the experiences of individuals in early adulthood.

In component 1, participants will engage in monitoring and reflecting on their context-specific self-efficacy levels and describe situations associated with them. They will select and optionally reflect on the sources of their specific beliefs, choosing from the 4 self-efficacy sources. In component 2, participants will learn new meta self-efficacy strategies based on leveraging self-efficacy sources. Activities will guide them through reflecting on potential future challenges and enhancing their self-efficacy through leveraging the sources (ie, using meta self-efficacy strategies). For example, this means identifying a role model similar to oneself, seeking persuasion from someone, or recalling and rephrasing a past successful strategy. This component will be strongly dependent on the results of the

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co-creation phase. Participants will also revisit the challenges they identified in component 1. In this activity, they select a self-efficacy source to target for a specific challenge and plan a strategy for tapping into it, including a backup strategy based on another source. While examples will include actual meta self-efficacy strategies proposed by participants in the co-creation phase, the activities themselves will be subject to refinements resulting from their feedback. Component 3 involves periodic self-efficacy assessments and the application of self-efficacy strategies in real-life situations. High self-efficacy ratings will prompt participants to reflect on the context and sources contributing to a specific type of self-efficacy, whereas low ratings will prompt and lead through applying meta self-efficacy strategies. If necessary, participants will receive contextually relevant examples and boosters of component 2.

The intervention will be self-administered and delivered online [19]. A previous study tested a self-efficacy–based intervention delivered solely using a chatbot on Meta's Messenger [34]. While effective, this format likely reduced deep engagement. To address this, this intervention integrates web- and chatbot-based exercises. All participants will first access the intervention through a link to a chatbot on Meta's Messenger. The chatbot will primarily guide them through low-effort tasks [35], forming the core of the first and third components, which rely on text-based activities and optional voice recordings. For selected, more complex activities, primarily in the second component, the intervention will provide direct links to a web platform that can be accessed directly within the Messenger app. Completion of the full intervention will require engagement with both the chatbot and web-based components. Participants will be able to access the intervention on any device, including desktop and mobile, providing a flexible delivery format. Engagement and adherence will be monitored through back-end logs, including records of the number of completed activities and modules and the total volume of text entered for text-based activities, with the option of including more metrics depending on the results of the co-creation phase.

In the control condition, participants will receive access to educational content on occupational health and well-being. This educational content will be delivered via the same platforms as the intervention in the experimental condition and will be matched in intensity. The educational materials will provide evidence-based information on topics related to the trial outcomes, including aspects of work stress in young employees [5,8], psychological processes associated with coping with stress, and important resources related to occupational well-being [10,27].

Outcome Measures

Overview

All outcome measures will be assessed at all time points via an online survey. The primary outcome is work self-efficacy. Secondary outcomes include 3 dimensions of occupational well-being: job stress, job affective well-being, and work capabilities. Meta self-efficacy will be measured as a manipulation check.

Work Self-Efficacy

The primary outcome is work self-efficacy, measured using the Work Self-Efficacy Scale [36]. Psychometric analyses of the Work Self-Efficacy Scale have revealed a robust bifactor structure—with a global work self-efficacy factor and 4 specific subdimensions—and demonstrated excellent reliability (ω=0.96 for the global factor and 0.67-0.76 for the specific subdimensions), thereby supporting its validity for assessing work-related self-efficacy. The questionnaire consists of 26 items, with responses ranging from 1 ("not at all") to 7 ("completely"). The overall score will be calculated as a mean.

Job Stress

Job stress will be measured using the Perceived Stress Scale [25]. This 4-item questionnaire assesses the frequency of perceiving stress. We will use a version of the tool contextualized to reflect job stress, which has shown high reliability in a previous study (Cronbach α=0.87 to 0.89 [15]). Responses range from 0 ("never") to 4 ("very often"), with the overall score calculated as a mean.

Job Affective Well-Being

Job affective well-being will be measured using the Job-Related Affective Well-Being Scale [26]. We will use a 12-item version that has demonstrated good reliability (Cronbach α=0.64 to 0.79) and a 4-factor structure: high pleasure and low arousal, high pleasure and high arousal, low pleasure and low arousal, and low pleasure and high arousal [37]. Responses range from 0 ("never") to 5 ("extremely often or always"), and scores are averaged across positive and negative emotions.

Work Capabilities

Work capabilities will be measured using the Capability Set for Work Questionnaire [11,27], which is a set of questions assessing capabilities important for sustainable employability. The questionnaire consists of 7 statements and has demonstrated high reliability in a previous analysis (ω=0.77 [38]). Each capability is rated on 3 aspects: importance (whether a certain capability is valued as important), opportunities (whether one has the opportunities related to a certain capability), and success (whether one can succeed in realizing a certain aspect of work). Responses range from 1 ("not at all") to 5 ("very much"). A global score will be calculated as the mean of the 7 items.

Meta Self-Efficacy

In line with the theoretical mechanism of the intervention, meta self-efficacy will be measured as the manipulation check. It will be assessed using a 13-item meta self-efficacy scale [18] encompassing 4 factors that represent leveraging each of the 4 self-efficacy sources: mastery experiences, vicarious experiences, persuasion, and emotional and physiological states. Each item starts with "When I need to, I can..." and is followed by a statement related to 1 of the 4 sources. Example items for each factor are "think about situations where initially I felt I couldn't cope, but eventually managed to" (mastery experiences), "observe someone similar to me who copes despite encountering obstacles" (vicarious experiences), "believe others when they convince me that I will overcome obstacles and manage" (persuasion), and "interpret tension and stress in a difficult situation as a signal that I will manage" (emotional and

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physiological states). Psychometric evaluations have demonstrated high reliability (overall Cronbach α=0.91) and support the 4 theory-informed factors as part of a bifactor scale structure [18]. The general score will be calculated as a mean.

Other Metrics

Other metrics will assess treatment credibility, usage, engagement, and adherence. Treatment credibility will be operationalized as emergent credibility and measured after initial intervention exposure during the first module. We will assess credibility using the Credibility/Expectancy Questionnaire, which has shown high reliability (Cronbach α=0.85) [39]. The questionnaire items will be contextualized to reflect participation in an internet intervention. Use and engagement metrics will include completed components, completed activities, log-ins, activities per log-in, total time spent, and total words written [40]. Adherence will be defined and measured as the percentage of completed intervention activities. Additionally, we will measure subjective adherence using the following question at the posttest time point: "How accurately, in your opinion, have you completed all tasks? For example, did you follow the instructions, reflect on the questions, and respond to them exhaustively?" [22,41].

Statistical Analyses

Preliminary Analyses

We will conduct preliminary analyses, including a randomization check and dropout analysis, using ANOVAs and chi-square tests, as well as examine differential attrition through 2-tailed *t* tests. Dropout will be operationalized as attrition to posttest. Additionally, we will assess intervention-related adherence and engagement metrics (see the Other Metrics subsection).

Intervention Efficacy

The intervention's efficacy will be evaluated for each outcome measure following the intention-to-treat principle, meaning that all randomized participants will be included in the final analysis. The primary efficacy analysis will use a linear mixed-effects model, with a random intercept for participants and fixed effects of time and condition [42]. Although the expected dropout rate is included in our a priori power analysis, we will also examine the actual dropout rate and its characteristics. This examination will determine whether there is a significant difference in dropout percentages between the 2 conditions, a phenomenon known as differential dropout [43]. Subsequently, we will apply an appropriate missing data imputation method and calculate pooled results using linear mixed-effects models (eg, using the *mice* and *mitml* R packages [44]). Sensitivity analyses will be conducted to examine the robustness of the results and compare intervention effect estimates across per-protocol, intention-to-treat, and imputed data analyses. Additionally, we will verify the credibility of the placebo in comparison to the intervention condition.

Predictors of Intervention Effects

Beyond efficacy, we will explore use-related predictors of intervention effects. Research on the dose-response relationship in internet interventions suggests that multiple adherence and engagement metrics may be relevant. For example, one study found that only the number of activities completed per log-in significantly predicted outcomes [40]. However, such relationships may depend on intervention content, delivery modality, and target population. To expand the analysis of intervention efficacy, we will examine which use-related metrics predict the intervention effects using a multiple regression model. The response variable will be the mean residualized change score from the pretest (T1) to posttest (T2) time points in the experimental condition. The predictor variables will include adherence and engagement measures.

Results

As of November 20, 2025, a total of 24 participants have been recruited, with 3 of 4 focus groups conducted and the final one to be completed by the end of 2025. RCT recruitment is scheduled to start in the beginning of 2026, with the last follow-up expected by the end of 2026.

Discussion

In this study protocol, we propose to co-create and evaluate the efficacy of a psychological internet intervention grounded in an established theoretical framework yet introducing a novel psychological construct—meta self-efficacy. Psychological interventions targeting self-efficacy have a long-standing tradition, with examples in many domains: behavior change [14]; education [45]; and psychological well-being, including occupational well-being [15]. However, such interventions target self-efficacy specific to a context [12]. In contrast, with meta self-efficacy, we propose an intervention that promotes tapping into the sources of self-efficacy to provide individuals with the ability develop self-efficacy across relevant contexts. In essence, this approach entails a new level of using self-efficacy, one that takes full advantage of the very mechanism of self-efficacy development, a sort of *self-efficacy of self-efficacy*.

Because meta self-efficacy is context free, it can be applied across populations and contexts, which is its substantial advantage. However, in this project, we begin by tailoring the meta self-efficacy intervention for young employees' well-being to assess its effects in a measurable context. If this initial efficacy is established, future research should verify its applicability to other populations and circumstances. The co-creation approach can be used to adapt the context of the intervention to new populations. In the RCT phase, we will evaluate the meta self-efficacy intervention against a placebo to isolate its core effect. Consequently, our trial will not compare meta self-efficacy enhancement to a traditional context-specific self-efficacy intervention. Even if the effect size is smaller than those reported for context-specific self-efficacy interventions, meta self-efficacy may offer distinct advantages—particularly its potential for more enduring and generalizable benefits as it is hypothesized to function like a tangible skill. If we confirm this fundamental effect of meta self-efficacy, a comparison with a conventional context-specific self-efficacy intervention will become necessary. In the RCT phase, we will additionally examine how adherence and engagement, measured through multiple approaches, relate to intervention effects. While

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correlational, this analysis may shed light on key elements of the meta self-efficacy intervention that drive its effects and offer insight into assessing adherence in internet interventions, a question posed by previous research on the topic [41].

We acknowledge several potential challenges and limitations. First, the co-creation phase may pose certain challenges. Because meta self-efficacy is a high-level psychological construct, discussing it in focus groups may prove difficult. This does not invalidate their use as they will help refine the intervention's technical aspects and the core structure of the meta self-efficacy intervention is pre-established. Nevertheless, input from participants is essential for shaping the content of activities, although the depth generated through co-creation may be limited. Finally, it is important to acknowledge that co-creation alone may not be sufficient to ensure the success of the RCT given the lack of concrete evidence supporting the positive effect of participatory design [46]. Second, there are potential challenges in the RCT phase itself. The sample we need to recruit is quite large, posing the main risk to the project. To mitigate this, we will diversify our recruitment campaign to include several means: targeted social media advertisements, traditional media, and personal contacts. A related risk is the potential dropout in the RCT phase. Prior internet intervention trials have reported moderate to high attrition [21]. While we included the predicted dropout rate in the sample size calculation and will use the co-creation phase as a means to safeguard retention, these efforts may still not be sufficient to overcome the underlying causes of dropout. Should this be the case, we plan to conduct sensitivity analyses that will assess the impact of dropout on our results and, thus, assess the quality of potential inference. Finally, an inevitable limitation is that the RCT phase will not directly test the intervention's underlying mechanism. Mediation analyses in RCTs can be misleading because establishing the causal impact of a mediator on an outcome is inherently methodologically challenging [47]. Therefore, our primary analysis will focus on group differences in all primary and secondary outcomes. We will infer with caution that improvements in outcomes are attributable to meta self-efficacy should the changes in the manipulation check align with these in outcomes and the credibility be equal in both conditions.

This 2-phase study aims to co-create and evaluate a meta self-efficacy–enhancing internet intervention for young employees. By moving beyond the confines of context-specific self-efficacy interventions, we intend to develop a versatile tool capable of safeguarding adaptivity to a wide range of challenges. If effective, this intervention could offer tangible, broad-reaching benefits that extend beyond the initial target population of young employees.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

Conceptualization: JM, RC, and ES
Funding acquisition: JM
Investigation: JM
Methodology: all authors
Supervision: ES
Writing—original draft: JM
Writing—review and editing: all authors

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the Polish National Science Center Grant Review Committee.
[PDF File (Adobe PDF File), 131 KB - resprot_v14i1e85082_app1.pdf]

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Multimedia Appendix 2
SPIRIT checklist.
[DOCX File , 65 KB - resprot_v14i1e85082_app2.docx]

Multimedia Appendix 3
Topic guide for focus groups in the co-creation phase.
[DOCX File , 17 KB - resprot_v14i1e85082_app3.docx]

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Abbreviations

RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Exploring the Influence of a Novel App for Training and Evaluating Walking Aid Skills in Walking Aid Users: Protocol for a Pragmatic Single-Blind Randomized Controlled Trial

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Abstract

Background: More than 12% of the world's population and more than 1 million Canadians use walking aids to support mobility. Unsafe use of walking aids due to a lack of training may lead to injuries and an increased risk of falls. A novel interactive video-based feedback mobile app to train walking aid fitting and safe use, called ICanWALK (Improving Canadians' Walking Aid Skills, Learning, and Knowledge), was recently developed.

Objective: The primary objective of this study is to explore the efficacy of the walking aid skills training app on the balance confidence of walking aid users. The secondary objective is to explore the influence of the mobile app on mobility and knowledge of walking aid users.

Methods: A 2-site single-blind pragmatic randomized controlled trial is proposed. A total of 52 adults who use walking aids will be recruited through clinical and community organizations. Participants will complete measures of balance confidence (Activities-specific Balance Confidence scale; the primary outcome), mobility (6-Minute Walk Test and Timed Up and Go test), walking aid skills (Walking Aids Skills Test, WAST), and knowledge of and confidence in walking aid fit and use (self-reported questionnaire) at baseline (T1). Participants will then be randomly assigned to the experimental (ICanWALK app) or attention-matched control group (breathing activity app) and will complete two 20-minute sessions interacting with the assigned app. Participants will be reassessed 2 to 4 days after the intervention (T2) and again 4 weeks later (T3). Analysis of covariance will be performed for primary and secondary outcomes by using SPSS software.

Results: The study protocols were approved by the institutional review boards of both recruitment sites in 2023 and 2024. A feasibility study was conducted from 2023 to 2024 across the 2 sites. As of November 2025, participant recruitment is ongoing and expected to conclude in December 2026. To date, 26 individuals have been enrolled and have successfully completed all 3 assessment time points: T1, T2, and T3.

Conclusions: Using a video-based feedback training approach, a novel app is hypothesized to improve balance confidence, mobility, and knowledge of and confidence in walking aid fitting and use. This structured educational program for fitting and training of walking aids may improve balance confidence. Better walking aid fitting and use may improve mobility, especially for older adults, thereby increasing independence and social participation. Establishing efficacy is an important first step before exploring how the ICanWALK app may be used by walking aid users and clinicians in clinical and community settings.

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Trial Registration: ClinicalTrials.gov NCT05347875; https://clinicaltrials.gov/study/NCT05347875
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KEYWORDS
walking aids; mobile health; mHealth; balance confidence; mobility; randomized controlled trial

Introduction

Independent personal mobility is associated with physical and psychosocial health benefits, such as reduced risk of chronic diseases, increased participation in meaningful activities, and reduced risk of depression and social isolation [1,2]. Personal mobility, defined as the ability to move oneself (either independently or using assistive devices) within environments [3,4], is a basic human right [3]. According to the Convention on the Rights of People with Disabilities, state parties shall take effective measures to ensure personal mobility with the greatest possible independence [3], which includes facilitating access to quality mobility aids and providing mobility skills training.

The World Health Organization (WHO) and World Bank estimated that 1.3 billion people (representing approximately 15% of the world's population) experience significant disability, with most of them using walking aids, designed to assist ambulation, such as canes, walkers, crutches, and walking sticks [5,6]. In Canada, walking aids support the independent mobility of more than 1 million Canadians (approximately 4.1% of the population), with a 2% prevalence increase from 2004 to 2012 [7]. Walking aid use is particularly prevalent among older adults [7,8], with approximately 24% of adults aged 65 years and older in the United States and Canada using walking aids [7,8]. With life expectancy rising worldwide, the population older than 65 years is expected to continue to increase [9], and, consequently, the need for walking aids will also increase [10].

When used appropriately, walking aids can significantly enhance perceived balance confidence in individuals with mobility challenges, especially older adults and those with neurological conditions [11]. Improved balance confidence has been shown to facilitate motor performance, leading to smoother and more efficient movements [12,13]. Walking aids support postural stability, compensate for muscle weakness or motor deficits, and off-load weight from an injured or postoperative lower limb [12]. Their use is associated with greater feelings of safety, which may contribute to a higher level of physical activity, independence, and reduced risk of fall-related injuries [13,14]. Overall, walking aids support mobility [15], encourage participation [11], and offer both physical and psychosocial benefits [16].

Notwithstanding the numerous benefits of walking aids, inappropriate fit and unsafe use can lead to discomfort, pain, injuries, and even an increased risk of falls. A recent review identified an increased risk of injury when crutches were poorly fitted and used improperly due to a lack of training before use [17]. Inadequate use of walking aids was also found to be associated with a greater risk of falls [15,18]. In US emergency departments, 47,312 fall-related injuries among older adults, which were associated with walking aids (87.3% with walkers, 12.3% with canes, and 0.4% with both), were treated annually between 2001 and 2006 [19]. Furthermore, high rates of walking aid disuse or dissatisfaction were associated with difficult or risky use due to a lack of training before prescription [20]. Although injuries and fall risks could likely be reduced through better education and training, no standardized training program has been documented. A recent study by Best et al [21] that documented the quality of existing online educational resources for mobility device training showed that most walking aid training was in the form of infographics and basic instructions and was not evidence based. Most people obtain walking aids independently from the pharmacies or clinics without receiving instruction or demonstration [20,22]. A standardized and effective approach to training walking aid skills may enhance balance confidence and mobility while reducing the risk of injuries and falls for walking aid users and may be useful for health care professionals (as they are the primary source of care for patients).

The use of mobile apps is increasingly widespread and recognized for improving health outcomes in the general population [23] as well as in individuals with chronic diseases [24]. The COVID-19 pandemic also facilitated the use of mobile health (mHealth) for providing some health services and reducing initial preoccupations about safety, which has increased accessibility to health care services and education while reducing geographic and transportation barriers [24]. While educational mHealth apps have demonstrated potential in enhancing health-related knowledge and promoting behavior change [25-28], their overall effectiveness remains inconsistent. This variability is largely attributable to differences in the integration of key design and theoretical elements, such as behavior change techniques, personalization, user-centered design, social support features, evidence-based content, and technical reliability [29-32]. In the specific context of rehabilitation, some apps incorporate video-based instructional content; however, they typically offer passive viewing experiences and lack interactive features that support active skill acquisition [25,33-35]. Critically, few enable users to engage in guided practice with real-time or postexercise feedback that facilitates the detection and correction of performance errors by comparing their movements to a model [36]. Moreover, the use of video-based feedback, an evidence-informed strategy grounded in observational learning theory, remains notably underused, despite its potential to enhance motor skill acquisition, user engagement, and self-efficacy [37,38]. In addition, no educational app for teaching the fitting and safe use of walking aids exists to date.

The ICanWALK (Improving Canadians' Walking Aid Skills, Learning, and Knowledge) mobile app was developed to address

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critical gaps related to walking aids, including improper fitting, unsafe use, and the widespread lack of structured training [39]. The ICanWALK app is a video-based feedback and interactive tool aiming to serve as a large-scale educational tool [39]. A recent pilot experimental study involving 13 walking aid users reported a high rate of usability (88%) and acceptability of this novel app [40]. Participants found the app simple, useful, and easy to use [40]. This study also showed improvement in balance confidence after two 15-minute sessions using the ICanWALK program [40]. Hence, this study will explore the efficacy of the ICanWALK program on the primary outcome of balance confidence in adult walking aid users. We hypothesize that exposure to the app's content (video-based feedback and interactive learning) will lead to improved balance confidence (main variable), and we expect that if balance confidence improves, mobility and walking aid skills (secondary outcomes) will also improve.

Methods

Study Design

This study will use an assessor-blind, 2-site parallel-group, randomized controlled trial (RCT). This study protocol was registered on ClinicalTrials.gov (NCT05347875). The SPIRIT (Standard Protocol Items Recommendations for Intervention Trials) guidelines [41] and the CONSORT (Consolidated Standards of Reporting Trials) statement [42] will be followed.

Participants and Recruitment

To be included in this study, participants should be aged 18 years or older, should use a walking aid (cane, crutch, or walker) for at least 75% of ambulatory time (self-reported), and should be able to communicate in English or French. Participants will be excluded if they have a progressive condition or injury that may restrict or be worsened by walking aid use (self-reported) or a visual impairment that could limit their ability to interact with a mobile app (self-reported). Reasons for exclusion, declining participation, and dropout will be documented for CONSORT purposes (Figure 1) [33,42].

Participants will be recruited from clinics, community centers, semiprivate assisted living facilities, and via social media and emails distributed to health care practitioners by the study coordinators (FN and RHKM). Recruitment posters will be distributed, and emails will be sent to community associations and organizations, practitioners (kinesiologists, physiotherapists, and occupational therapists) in contact with walking aid users, and all university and research center networks. Active approaches, such as community meetings with presentations and collaboration with community partners in identifying potential participants, will also be used. The study coordinators from the 2 sites (FN for Québec and RHKM for Calgary) will contact interested, eligible participants via email and telephone and send them a consent form at least 24 hours before the first evaluation.

Figure 1. Flow diagram of the progress through the phases of a parallel randomized controlled trial of 2 groups.

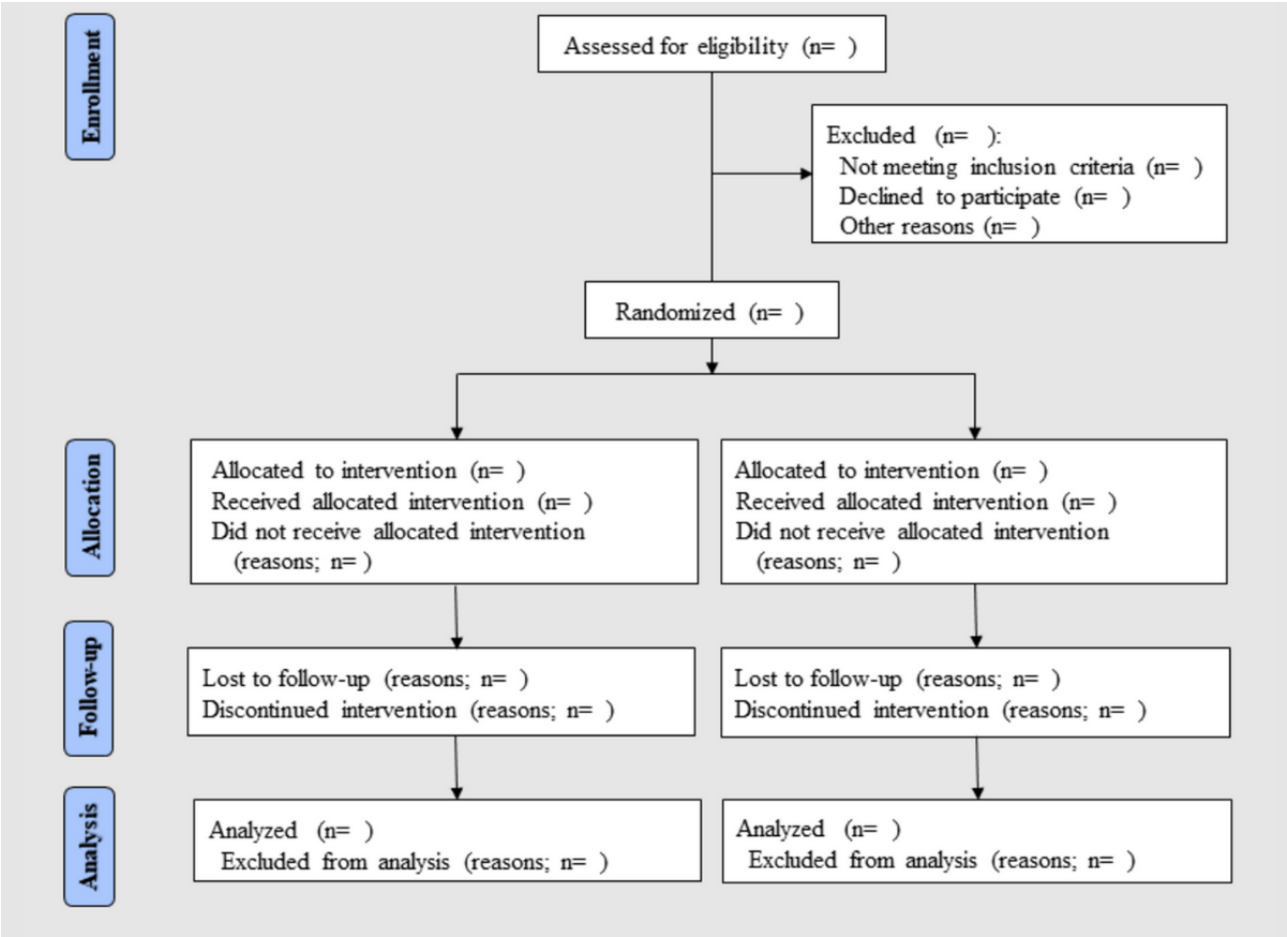

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Sample Size

The sample size calculation was based on the Activities-specific Balance Confidence (ABC) scale questionnaire (primary outcome) [43]. No study has reported the minimum clinically important difference for the ABC scale among walking aid users. However, considering a study on 376 patients with knee osteoarthritis who had undergone surgery (many of whom used a walking aid), ABC scores increased by an average of 9.2% 1 year after total knee arthroplasty (repeated measures model; Cohen d=0.59) [44]. On the basis of the variability reported in the study [44], an estimated correlation of 0.5 between measurements, including ABC scale and 2 potential covariates (type of walking aid and duration of walking aid use), a sample size of 45 would be sufficient to explore a 2-way difference between groups (F tests) in a 2-way repeated measures model (2 groups×2 time points; $1-\beta=.9$; $\alpha=.05$; G*Power [Heinrich Heine University Düsseldorf]) [45]. With a conservative dropout rate estimated at 15% [46], a total sample size of 52 participants is enough to find significant differences between groups for the primary outcome. To minimize participant dropout and ensure high retention rates, several strategies will be implemented. These include clear and transparent informed consent procedures, regular and supportive communication with participants, and flexible scheduling for study visits. Efforts will be taken to maintain a strong and supportive relationship between the research team and participants. All participants will be reassured about the confidentiality of their data and the importance of their contribution to the success of this study.

Randomization and Allocation

Overview

The randomization will be performed by a researcher not directly involved in this study using a computer-generated program. Participants will be randomly assigned to either the experimental group (the ICanWALK group) or the control group (the breathing exercise group) in a 1:1 ratio. Allocation will be performed by the same researcher using opaque envelope assignments.

Experimental Group

The ICanWALK app was recently developed as an educational tool designed to train skills related to fitting and using a walking aid. The experimental group will use the ICanWALK app on an iPad (Apple Inc), available on the MOVE Improve mobile app for both Android and iOS. The MOVE Improve platform is a valid app designed to teach physical movement and improve sports performance [47-49]. The MOVE Improve is a video-based feedback and interactive tool aiming to serve as a large-scale educational tool. The ICanWALK modules [39] follow the MOVE Improve instructional format. Users select a specific skill and then watch an instructional video on that skill with the key skill components highlighted. The user is then videotaped while performing the skill, and that video is shown beside the instructional video. Next, the user is guided through a series of skill performance questions to evaluate their video. At the end of the module, the user receives a summary assessment score from their self-evaluation. The ICanWALK program currently contains 43 modules that teach walking aid-related skills, including fitting, gait patterns, and navigating stairs [39]. Health science students or research assistants will receive 4 hours of training on navigating MOVE Improve, guiding participants in selecting ICanWALK modules, and recording videos. With assistance from a trained health professional student, participants will complete 2 separate 15- to 20-minute sessions within a 1-week period. Using the ICanWALK program, the participant will learn skills for fitting and using a walking aid. Participants will watch an instructional video on each skill, with the key components of appropriate skill execution highlighted (Figure 2). The participant will then perform the task with their walking aid, and the student/research assistant will record the video. The participant will review the video in the app and compare it to the demonstration video to determine whether each component of the skill was performed correctly. A score will be generated at the end. Participants must master the use of the app to be able to independently repeat the tasks of fitting and using their walking aid.

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Figure 2. Screenshot of the main steps in using the ICanWALK (Improving Canadians' Walking Aid Skills, Learning, and Knowledge) app modules.

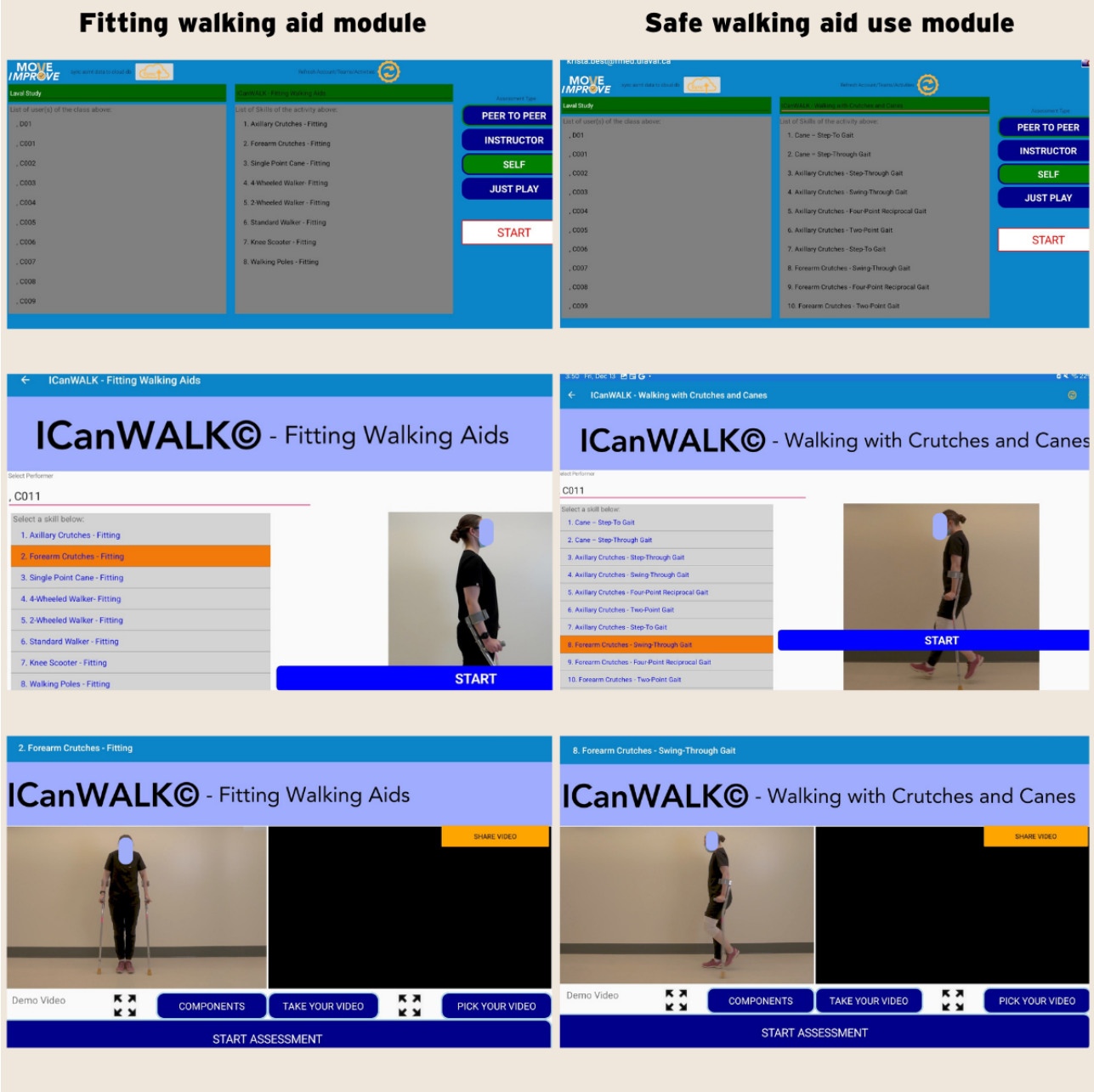

Control Group

The control group will be attention matched to mimic the time, location, and contact with a trainer of the experimental group [50]. Participants will follow the same schedule as the experimental group but will also complete a breathing exercise module available on the MOVE Improve app. The modules are identical in layout, instruction, and self-assessment of videos to the ICanWALK app but differ in content, as no information related to walking aids and mobility is included in this program (Figure 3). With assistance from a trained health professional student or a research assistant, participants in the control group will complete 2 separate 15- to 20-minute sessions within 1 week. Participants will select the breathing exercise module and then choose the specific skill they wish to practice (eg, breathing exercise for reduced stress and breathing exercise for increased lung function), watch the instructional video, and review the performance criteria. A video of the participant performing the selected skill is then recorded and uploaded alongside the model video to allow for side-by-side comparison. The participant will review the video in the app and compare it to the demonstration video to determine whether each component of the skill was performed correctly. A score will be generated at the end.

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Figure 3. Screenshot of the main steps in using the breathing exercises module.

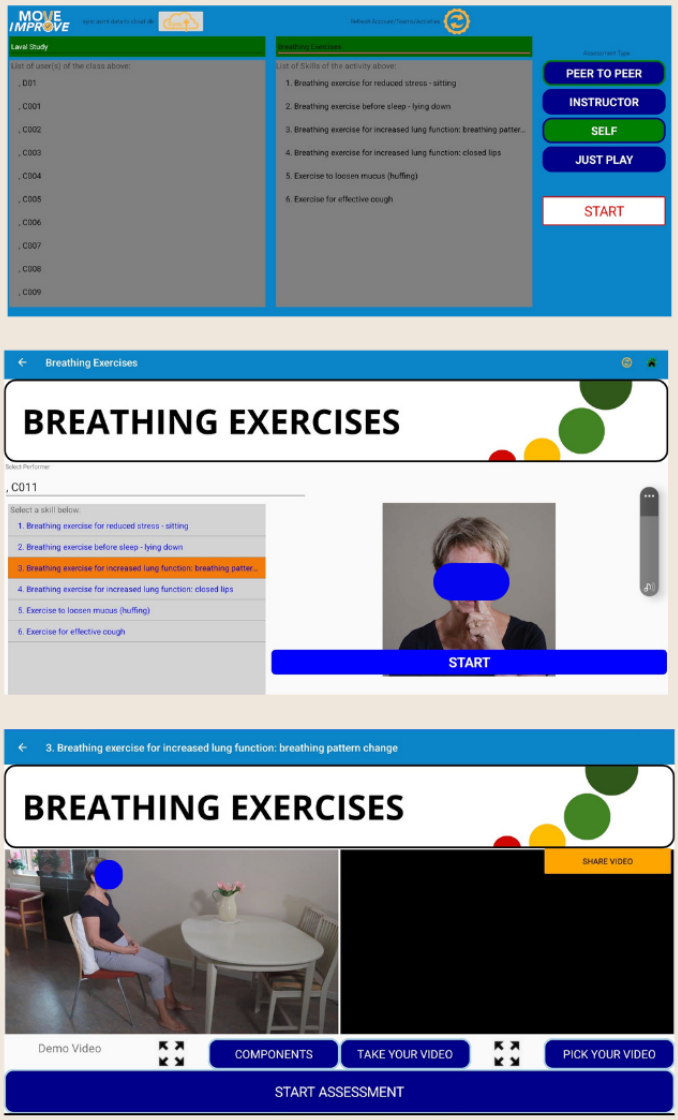

Study Procedure and Data Collection

The study procedures (timeline and measurement tools) are illustrated in the SPIRIT checklist (Table 1). Participants will be assessed at 3 time points: baseline (T1), after intervention (T2), and 4-week follow-up (T3). After signing the consent form, a study coordinator will schedule the first evaluation session (T1). Preintervention questionnaires will include sociodemographic data (eg, age, sex, gender, walking aid type, reasons for using the walking aid, the duration of walking aid use, and previous walking aid experience), the ABC questionnaire, and self-reported knowledge and confidence in fitting and using the walking aid using a tablet or laptop. Participants will then complete the Walking Aids Skills Test (WAST) and mobility tests (6-Minute Walk Test, 6MWT and Timed Up and Go, TUG test).

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Table 1. SPIRIT (Standard Protocol Items Recommendations for Intervention Trials) checklist.

Schedule of activities	Enrollment	Assessment	Allocation	After allocation			Closeout
	Screening	Baseline (T1)		Intervention	After intervention (T2)	4-wk follow-up (T3)	
Enrollment							
Eligibility screen	✓						
Informed consent	✓						
Allocation			✓				
Intervention							
ICanWALK[a] app (experimental intervention)				✓			
Breathing exercises app (control intervention)				✓			
Assessments							
Activities-specific Balance Confidence scale		✓			✓	✓	
Self-reported walking aid knowledge and confidence		✓			✓	✓	
Timed Up and Go test		✓			✓	✓	
6-Minute Walk Test		✓			✓	✓	
Walking Aid Skills Test		✓			✓	✓	

[a]ICanWALK: Improving Canadians' Walking Aid Skills, Learning, and Knowledge.

All data will be collected by an assessor who will be blinded to group allocation. The T1, postintervention (T2), and follow-up (T3) questionnaires will be imported into the LimeSurvey platform to allow for completion during the evaluation while ensuring secure data management. The collected data will be anonymized with a code assigned to each participant and will be stored on the institutional platform. Access to data will be limited to authorized personnel.

Outcomes

Primary Outcome

Given the ICanWALK app's theoretical grounding in self-efficacy, behavior change, and skill acquisition, balance confidence—assessed with the ABC scale—was selected as the primary outcome due to its direct relevance to the intervention's mechanisms of action [32,43]. The ABC scale offers a validated, context-specific measure of individuals' perceived confidence in performing daily mobility tasks with a walking aid, capturing both psychological and functional dimensions of change [43]. As such, it serves as a sensitive and theoretically congruent indicator of the intervention's anticipated impact. The ABC scale is a 15-item self-assessment measure that asks individuals to rate their confidence in balance while performing a series of activities on a scale ranging from 0 (no confidence) to 45 (total confidence) [43]. The raw scores are converted into percentages by dividing the sum of the individual scores by the total score and then scores ranging from 0 (no confidence) to 100% (total confidence). The ABC scale is reliable in individuals using mobility devices [51], healthy older adult community dwellers [52], individuals who have undergone lower limb amputation [51,53], individuals with Parkinson disease [54] or knee osteoarthritis [55], stroke survivors [56], and those with traumatic brain injury [57]. The ABC scale is highly sensitive to fall risk [58]. Previous studies have demonstrated high test-retest reliability (intraclass correlation [ICC]=0.85) and excellent construct validity (r=0.60-0.75) with the Berg Balance Scale, Community Balance and Mobility Scale, and TUG test [52,55,56]. The administration time is 10 to 15 minutes.

Secondary Outcomes

Mobility

Mobility tests will include the 6MWT and the TUG test. The 6MWT assesses walking endurance by objectively measuring the distance covered by an individual during 6 minutes of walking [59,60]. It is a common, valid, and reliable measure of submaximal aerobic capacity in individuals with various conditions that takes about 10 minutes to administer [61]. The TUG test assesses functional mobility and fall risk by recording the time (in seconds) it takes for a participant to stand up, walk 3 m, and sit back down on a chair [62]. Measurement properties of the TUG test have been reported for older adults (test-retest reliability; ICC=0.75) and in patients with hip osteoarthritis

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(interrater reliability; ICC=0.87) [63,64]. The TUG test takes 1 to 2 minutes to administer.

Knowledge and Confidence in Fitting and Using Walking Aids

Subjective self-reported knowledge and confidence in walking aid fitting and using will be documented at T1, T2, and T3 using a 4-level Likert scale ranging from "not at all informed or not at all confident," meaning any knowledge and confidence, to "well informed or very confident," meaning high knowledge or good confidence.

Walking Aid Skills

The WAST test will be used to objectively assess skills of using walking aid when performing daily life activities (eg, walking on flat solid ground, walking on foam surfaces, and going up or down steep or gentle slope or stairs). The WAST is a 15-item objective assessment that measures an individual's ability to use their walking aids in various contexts, such as picking up an object from the ground and walking on various grounds such as gravel or slopes. Using a standardized rating system (videos), the evaluator assigns a score from 0 (the participant does not meet most evaluation criteria, is unsafe, or is unwilling to perform) to 3 (the participant performs the skill very competently or advanced). The total score expressed as a percentage (indicating the individual's performance) is the quotient of the total sum of individual scores over the number of skills performed, ranging from 0% to 100%. The higher the score, the better the performance. Although the psychometric properties of this test have not yet been investigated and published, it has been developed with inspiration from the wheelchair skills program [65,66] but has not yet been validated.

Data Monitoring

The intervention used in this study is an educational, nonpharmacological approach that adheres to the ethical principles of beneficence and nonmaleficence. Given its low-risk nature, it is unlikely to cause adverse effects. Therefore, the establishment of a data monitoring safety board may not be necessary. However, any adverse effects will be monitored informally by the project coordinators.

Statistical Analysis

Responses to questionnaires and test scores will be imported from the LimeSurvey platform and compiled into a Microsoft Excel file. Descriptive statistics (means, SDs, frequencies, and percentages) will be used to summarize sociodemographic data.

An analysis of covariance will be performed to detect postintervention differences between groups for the primary and secondary measures using the respective T1 score as the covariate. Dropout rates and reasons will be reported. Depending on the nature of the missing data (proportion of missing values), appropriate methods will be chosen with careful consideration of the data structure and the underlying assumptions. The significance level will be set at .05, and all statistical tests will be 2-tailed. The scores from the self-reported questionnaires on walking aid knowledge and confidence will be summed and analyzed using an appropriate parametric test (if normally distributed). Retention of balance confidence, mobility, and self-reported score of knowledge in the experimental group will be evaluated using 2-tailed paired *t* tests. Sensitivity analyses will also be conducted based on walking aid type, walking aid use experience, previous training, and the main reason for use. All analyses will be performed in SPSS software (version 27; IBM Corp).

Ethical Considerations

This study protocol has been approved by each of the 2 sites' board committees: the Centre Intégré Universitaire de Santé et des Services Sociaux of the Capitale Nationale Rehabilitation Sectoral Ethics Committee, Québec (approved on June 10, 2024; 2025-3085) and the University of Calgary Conjoint Health Research Ethics Board in Alberta (REB25-1290). Written informed consent will be obtained from the potential participants. Any modification to the protocol will be reviewed and approved by the corresponding ethics boards and will be reported to all investigators during the team's monthly meetings.

During the study, the information about participants will be kept confidential, and signed informed consent will be obtained after the participants agree to participate in this study. The whole procedure will strictly follow the principles of voluntariness, confidentiality, and no harm. Participation is entirely voluntary, and participants may withdraw from the study at any time without providing a reason. Withdrawal will not affect access to health services, medical treatment, or any other rights to which participants are entitled.

To protect participant privacy, all data will be stored on secure, password-protected institutional servers and managed within the institution's Microsoft Teams environment, which provides encrypted, access-controlled data storage. Access to study folders on Microsoft Teams will be restricted to authorized members of the research team who have completed the required institutional privacy and security training. Identifiable information will be stored in a separate, access-restricted location and will not be linked to research data except through encrypted identification codes. All datasets used for analysis will be fully deidentified, and no personally identifying information will appear in any presentations, publications, or knowledge-translation materials. Data storage, retention, and destruction will follow established institutional policies and provincial regulatory requirements.

To minimize participation burden, participants will receive financial compensation of CAD $25 (US $32.50) for each assessment session and will be provided with a parking-lot pass for every in-person visit.

Results

As of November 2025, 26 participants have been recruited and have completed all 3 assessments: T1, T2, and T3. Participant recruitment began in July 2024 and is expected to conclude by the end of December 2026. The study is projected to be completed by June 2027.

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Discussion

Anticipated Findings

Through this single-blind, 2-site RCT, we aim to evaluate the primary hypothesis that an education and training tool for the correct use of walking aids will effectively improve balance confidence and secondarily may influence mobility and walking aid skills. This study protocol should allow us to determine whether the novel video-based feedback educational tool, designed to teach and train fitting and safe use of walking aid, is effective in improving balance confidence, mobility, walking skills, and knowledge. This is an exploratory RCT, given the paucity of literature on the effectiveness of mobile educational apps on short- and long-term walking aid use.

To meet the challenges of the lack of formal training programs for users on the fitting and use of walking aids and the lack of standardized information for health care professionals, mHealth apps may constitute an affordable and scalable digital health intervention to address these growing gaps. The findings from this study will provide valuable insights into the effectiveness of this novel app in improving knowledge of walking aid fitting and safe use as well as improving balance confidence and mobility. Recent evidence suggests that physiotherapy interventions delivered through a smartphone or tablet app were effective in improving mobility outcomes in people with a wide range of health conditions (such as neurological disorders [67,68]). The video-based feedback learning method used by the ICanWALK modules is known for rapidly improving memory recall [69], behavior change [70], and motor skill acquisition [71] and, consequently, should prevent falls while improving functional independence.

The findings of this study may help improve accessibility to health care by reducing the waiting time between the walking aid prescription, purchase, and training with a health care professional. In fact, while some walking aids are owned independently, others are prescribed by health care professionals, with physical therapists being the most common prescribers [72]. Thus, this app would contribute to reducing the waiting time for walking aid prescriptions and training with a health care professional. For instance, more than 10,000 Canadians were reported to be waiting for occupational therapist or physiotherapist services across Ontario [73], and the median waiting time was more than 6 months for 41% of outpatient publicly funded physiotherapy services in Québec [74]. Improving access to mHealth technologies may help address the growing human health care resource challenges in the world [75] and may also enable access to education for people living in remote or rural areas.

Finally, the results obtained from this pragmatic RCT, especially from sensitivity analysis, may help identify specific factors contributing to improved balance confidence, mobility, and knowledge of walking aid users after using an educational tool, such as the type of walking aid, the previous experience using walking aid, and individual factors such as age and diagnosis. This will enable larger-scale studies to be set up by the type of walking aid or the type of condition necessitating the use of a walking aid.

Limitations

This study may have several limitations. First, we will include participants who use various types of walking aid, but we will not stratify them according to type of walking aid, their digital literacy, cognitive level, user experience, or education. This may result in inconsistent responses to the app. However, sensitivity analyses will help to partially address this issue. Furthermore, participants with cognitive impairments or vision or hearing limitations may face barriers to fully engaging with the app. Second, the primary outcome is a self-reported measure, and this may be subject to measurement bias, such as social desirability bias or recall bias. We believe that the study design, methodology, and expected sample size make the expected results plausible. Finally, this study focuses on a short-term follow-up period and may not capture the long-term efficacy of the app. The key strength of this study will be the use of video-based feedback, as it enables the motor learning process and skills acquisition, leading to high memorization, behavioral change, and performance [69,71,76,77].

Comparison With Prior Work

To our knowledge, this study will be the first to investigate the effectiveness of an educational tool that teaches and trains the fitting and use of walking aids.

Acknowledgments

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Data Availability

This is a study protocol; no datasets were generated or analyzed during this study. Upon completion of the study, deidentified data supporting the findings of the study will be made available from the corresponding author upon reasonable request, in accordance with institutional and privacy regulations.

Authors' Contributions

Conceptualization: RHKM and KLB (lead), FR (equal), FN (supporting)
Data curation: FN and RHKM (lead)

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Formal analysis: FN (lead)
Funding acquisition: RHKM, FR, KLB
Investigation: FN and RHKM (lead)
Methodology: FN, KLB, RHKM, FR, WCM
Project administration: FN and RHKM, KLB (supporting)
Resources: RHKM, KLB, FR, WCM
Supervision: RHKM, KLB
Visualization: FN
Writing – original draft: FN
Writing – review & editing: KLB, RHKM, FR, WCM

Conflicts of Interest

RHKM owns the copyright to the Improving Canadians' Walking Aid Skills, Learning, and Knowledge educational modules. The modules are freely available to the public with no commercial income. The modules have been entirely supported through research grants. All other authors declare no conflicts of interest.

Multimedia Appendix 1
SPIRIT checklist.
[PDF File (Adobe PDF File), 121 KB - resprot_v14i1e71060_app1.pdf]

Multimedia Appendix 2
Peer review report by CASEM (Canadian Academy of Sport and Exercise Medicine) Research Committee.
[PDF File (Adobe PDF File), 185 KB - resprot_v14i1e71060_app2.pdf]

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Abbreviations

6MWT: 6-Minute Walk Test
ABC: Activities-specific Balance Confidence
CONSORT: Consolidated Standards of Reporting Trials
ICanWALK: Improving Canadians’ Walking Aid Skills, Learning, and Knowledge
ICC: intraclass correlation

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mHealth: mobile health
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items Recommendations for Intervention Trials
T1: baseline
T2: after intervention
T3: 4-week follow-up
TUG: Timed up and Go
WAST: Walking Aids Skills Test

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Protocol

A Web-Based Contraception Decision Tool for Individuals With Health Conditions in US Outpatient Clinics: Protocol for a Mixed Methods Cluster Randomized Controlled Trial

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Abstract

Background: Choosing contraception is a highly personal, often complex decision. People with acute and chronic health conditions (eg, pulmonary embolism, diabetes, and hypertension) must deliberate additional factors including whether and to what extent a contraceptive method may affect their health conditions or interact with their medications. “My Health My Choice” (web application developed by Alfa Jango) is a web-based decision support tool designed to help patients understand their contraceptive options considering their health conditions, medications, and personal priorities.

Objective: We will evaluate the efficacy of “My Health My Choice” (MHMC) use among people with diverse health conditions who seek contraception in US outpatient clinics.

Methods: This mixed methods cluster randomized controlled trial will compare MHMC and usual contraceptive care (intervention arm) to usual contraceptive care only (control arm). Fourteen clinics that specialize in primary care or obstetrics and gynecology will be enrolled, with 7 clinics in each arm. We will enroll 726 patients (363 in each group) who (1) are 18-49 years old, (2) are able to speak and read English, (3) are seeking contraception for pregnancy prevention, and (4) have at least 1 health condition among 60 eligible health conditions and characteristics (eg, cigarette smoking and postpartum state). Aim 1 (quantitative) is to assess the primary outcome of patient-reported contraceptive nonuse (yes or no) at 3 months. Aim 2 (mixed methods) starts with a quantitative summary of patient-reported contraceptive use by method type (eg, pills and shot) and corresponding Medical Eligibility Risk Category (Category 1, 2, 3, or 4) based on the Centers for Disease Control and Prevention (CDC) US Medical Eligibility Criteria (US MEC) Contraceptive Guidelines. We will conduct exit interviews of a subsample of approximately 30 patients and 30 clinicians to qualitatively understand how MHMC and other contextual factors influenced perceptions about contraceptive risk and contraceptive decisions. Aim 3 (quantitative) is to explore patient-reported contraceptive decisional conflict (measured by the Decisional Conflict Scale) and patient-reported quality of interaction with their contraceptive provider (measured by the Interpersonal Quality of Family Planning Scale) as mediators of the effects of MHMC on the primary outcome. This paper describes the study protocol per the SPIRIT (Standard Protocol Items: Recommendations for Intervention Trials) checklist.

Results: The National Institute of Child Health and Human Development funded this study (R01HD110570, Principal Investigator JPW) in 2023. The study team is collaborating with the DARTNet Institute (Aurora, Colorado) to enroll and prepare health clinics

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for trial launch. Fourteen clinics have enrolled in the trial and are in various stages of study preparation and regulatory approval. We anticipate patient enrollment to run from October 2025 to September 2028.

Conclusions: This is the first mixed methods cluster randomized controlled trial of MHMC, a novel web-based decision support tool for people with health conditions.

Trial Registration: ClinicalTrials.gov NCT07075536; https://clinicaltrials.gov/study/NCT07075536

International Registered Report Identifier (IRRID): DERR1-10.2196/71101

(JMIR Res Protoc 2025;14:e71101) doi:10.2196/71101

KEYWORDS

contraception; decision making; multiple chronic conditions; chronic disease randomized controlled trial; cluster analysis

Introduction

Background and Rationale

Contraceptive care is an essential health service that allows people to achieve their reproductive goals, including the prevention of undesired pregnancy [1]. Selecting contraception is highly personal and, for many, an overwhelming decision due to the sheer number of potential contraceptive methods [2,3]. There are 18 contraceptive methods (hereafter referred to as “methods”) [4] that include nonprescription methods, prescription methods, contraceptive devices, and permanent contraception (tubal surgeries and vasectomy). Contraceptive methods can be short-acting (taken daily or weekly), long-acting (effective for years), or permanent [4]. Each method has a unique benefit and side effect profile (eg, headache and irregular bleeding) that affects the user’s experience and likelihood of method continuation [4]. Contraceptive decision tools help patients understand the full range of methods and weigh their respective pros and cons in the context of their personal values and preferences [5].

People with acute and chronic health conditions, a growing proportion of contraceptive users, face additional and unique information needs [6]. First, they should understand the impact of a specific method on their health conditions; that is, whether a method improves, worsens, or has no impact on disease state or progression. Second, for those who would continue an unplanned pregnancy to childbirth, they should be informed about potential pregnancy-related risks, or lack thereof, in the context of their health conditions. Third, patients should be aware if their medications interact with hormonal contraception [7] or cause birth defects (eg, phenytoin) [8]. Ideally, health care providers should help process this information so that patients can weigh the pros and cons of different methods and select the best method for themselves.

However, studies have shown that people with health conditions inconsistently receive counseling to make informed contraceptive decisions [9-12]. For example, in outpatient settings, 10%-39% of patients report using combined hormonal contraception (CHC) despite having conditions that may preclude the safe use of CHCs [9,11,12]. Patients who cannot use CHCs should be fully informed about non-CHC methods based on their personal needs and preferences.

It is also important to bear in mind that most people with health conditions are medically eligible to use most methods [13]; that is, the proven or theoretical benefits of using a specific method generally outweigh any risks in the majority of cases. However, fear of side effects and health concerns are among the most common reasons cited for not using the most preferred method or not using any method among US contraceptive candidates in a nationally representative survey [14]. Contraceptive nonuse, defined as not using any method despite wanting to prevent pregnancy, is associated with the highest risk of unplanned pregnancy [15]. The use of any method reduces the risk of pregnancy by 70%-99.9%, depending on the method type [15]. Patients should receive accurate and balanced information about contraceptive-related health risks, including cases where there is no known risk, to prevent unnecessary avoidance of otherwise safe methods.

In prior randomized controlled trials (RCTs), contraceptive decision tools have been associated with improved patient contraceptive knowledge [16,17], improved quality of contraceptive care experience [16], reduced contraceptive decisional conflict [16], or increased use of prescription contraception [17,18], while others showed no significant differences in outcomes [19-21]. These trials primarily enrolled healthy young adults or adolescents [16,19,20] and did not address clinician knowledge regarding contraceptive use for patients with health conditions.

However, evidence-based clinical guidelines for contraceptive use by people with health conditions do exist. The Centers for Disease Control and Prevention (CDC) United States Medical Eligibility Criteria (US MEC) summarizes evidence-based and expert-informed recommendations for the safe use of contraceptive methods in the context of more than 60 health conditions and characteristics [13]. To distill the 124-page document for clinical use, the US MEC content is available as a free smartphone app and a downloadable color-coded PDF chart summary [22,23]. However, studies show that the US MEC is underused by clinicians, particularly in primary care [24-27] settings. A decision tool that engages both patients and their clinicians is a novel yet unexplored approach to promote informed contraceptive decision-making and use in the context of health conditions.

To address this unmet need, we designed and piloted a novel, theory-informed web-based tool called “My Health, My Choice” (MHMC) with technical support from Alfa Jango, a software design team [28]. MHMC is an interactive tool with a patient version and a clinician version. The patient version provides contraceptive education specific to a patient’s health history

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and contraceptive priorities; an interactive tool that groups methods by safety (per their reported health conditions and medications) and allows for side-by-side comparisons, and a Birth Control Summary that captures the patient's contraceptive preferences and questions for their clinician. Using the clinician version, clinicians can review the patient's Birth Control Summary and clinical decision support specific to that patient and harmonized with the US MEC Guidelines for individuals with health conditions and relevant characteristics (eg, smoking status and lactation status) [7]. We posit that MHMC will simultaneously address the information needs of patients and clinicians and facilitate interactive discussions, leading to the use of methods that are patient-preferred and safe. This paper details the study protocol for a cluster RCT to evaluate the efficacy of MHMC in 14 outpatient clinics in the United States that provide contraceptive services.

Research Aims and Hypotheses

Quantitative Aims and Hypotheses

The primary aim is to quantitatively assess patient-reported contraceptive nonuse (yes or no) at 3 months (primary outcome).

- Hypothesis 1: Contraceptive nonuse will be less likely in the intervention arm than the control arm at 3 months.

The secondary aim is to quantitatively assess the Medical Eligibility Risk category for patient-reported contraceptive method use per the US MEC schema (Category 1=no risk; Category 2=Advantages generally outweigh theoretical or proven risks; Category 3=Theoretical or proven risks usually outweigh advantages; Category 4=unacceptable health risks) [7]. Clinically translated, Categories 1 and 2 indicate methods that are safe to use, Category 3 indicates methods that should be avoided unless more appropriate methods are not available or acceptable to the patient, and Category 4 indicates methods that should be avoided [7]. We will explore the potential impact of the intervention on contraceptive decisions across US MEC categories using qualitative and mixed methods analysis, with a focus on Category 3 cases.

- Hypothesis 2: Given the need for a careful and informed discussion to weigh the benefits and risks of Category 3 use, we hypothesize that the decision tool will facilitate this process, leading to more Category 3 use cases in the intervention arm than the control arm.

The exploratory aim is to quantitatively explore contraception decisional conflict measured via a modified Decisional Conflict Scale (DCS) [29], and the patient-reported quality of interaction with their contraceptive provider, as measured via the Interpersonal Quality of Family Planning Scale (IQFP) [30], as mediators of the effects of MHMC on the primary outcome.

- Hypothesis 3: The impact of MHMC on contraceptive nonuse will be mediated by lower DCS scores and higher IQFP scores.

Anticipated Qualitative and Mixed Methods Findings

Patients in the intervention arm, particularly those who report Category 3 contraceptive use, will describe a more nuanced understanding of contraceptive risks weighed against the risks of unplanned pregnancy than those in the control arm.

Methods

Trial Design and Rationale: A Cluster RCT With a Mixed Methods Design

This study protocol reflects the SPIRIT (Standard Protocol Items: Recommendations for Intervention Trials) 2025 checklist for reporting RCTs [31]. For this efficacy trial, we will conduct a 2-arm, parallel cluster RCT using mixed methods to compare MHMC and usual care (intervention arm) to usual contraceptive care (control arm) in outpatient primary care or obstetrics and gynecology clinics in the United States. We will randomize at the level of the clinic site (the cluster unit) rather than the individual patient [32]. This group-level randomization approach prevents clinicians from influencing each other's contraceptive practices or changing their contraceptive practices after exposure to MHMC, which then impacts the treatment of subsequent patients [32]. The rationale for incorporating qualitative methods and mixed methods (the integration of quantitative data and qualitative data) in this RCT is to more deeply understand how patients and providers navigate contraceptive decisions in the context of health conditions [33]. In particular, we seek to focus on challenging cases in which there is a method that should be avoided except in special circumstances when there is no appropriate or patient-acceptable alternative. We will use an explanatory sequential design [34], in which qualitative exit interviews will be done after survey data collection to explain our quantitative findings. Figure 1 depicts the mixed methods RCT design and the activities of each data collection and analysis phase.

Figure 1. Mixed methods cluster RCT study design.

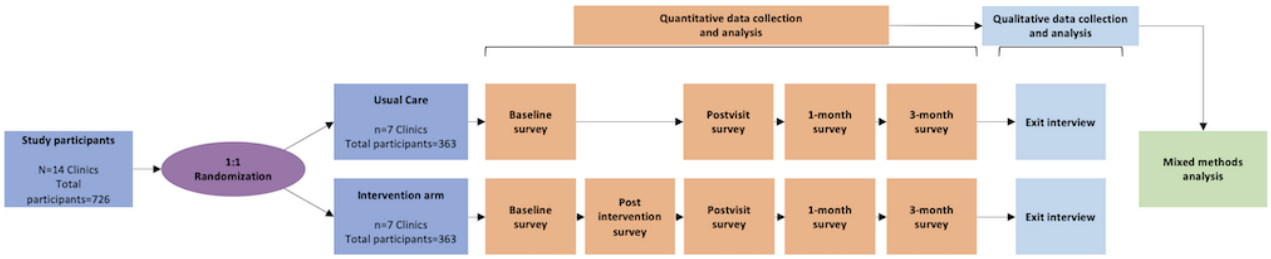

Patients with upcoming clinic visits with their contraceptive provider will be screened on the phone and enrolled in the study. During the screening call, patients must confirm that they are 18-49 years old, potentially fertile, and desire to discuss

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contraception at their upcoming visit (refer to "Methods" section for full eligibility criteria). All patients will complete a baseline survey and attend their clinic visit as scheduled. Patients in the intervention arm will receive a password-protected web login to use MHMC on a smartphone, tablet, or computer prior to their clinic visit. The primary outcome (contraceptive nonuse) will be assessed at 1 month and 3 months to allow time for patients to schedule procedures for contraceptive devices or permanent contraception (eg, tubal surgery and vasectomy). Qualitative exit interviews will be conducted among a subset of 30 patients and 30 clinicians with a focus on US MEC Category 3 cases. These cases represent "gray-zone" situations in which clinicians and patients should carefully weigh the benefits and risks prior to using a specific contraceptive method. Informed by the RE-AIM (Reach, Effectiveness, Adoption, Implementation, Maintenance) framework [35], we will also use quantitative data and qualitative data to assess the potential reach of MHMC to patients outside the trial setting, participant fidelity to the intervention, and factors that may affect widespread and sustained implementation of MHMC in real-world clinical practice.

The Intervention

MHMC is a web-based app that can be viewed on mobile phones, laptops, desktop computers, or tablets. It is not a native app that requires downloading from iOS or Android. Informed by our preliminary data, an explanatory framework informed by the Health Belief Model and the principle of contraceptive autonomy [28], and the Ottawa Decision Support Framework [36], we developed MHMC with a professional software team (Alfa Jango). This process included iterative cognitive interviews with potential end users (people with at least 1 index health condition who want to explore their contraceptive options).

The patient version consists of 3 steps (Figure 2). While using the tool, patients can write down any questions or concerns in a "My Notebook" feature that saves their responses. In Step 1 (All About Me), patients manually indicate if they have any of 60 index health conditions and relevant characteristics, such as smoking status or postpartum status. Most of the index conditions are chronic in nature (eg, migraine headaches, kidney disease, and multiple sclerosis), but they also include acute conditions (eg, recent thromboembolic or cardiovascular event) and past pregnancy-related conditions (eg, gestational diabetes and preeclampsia) that may affect perceived risks and benefits of contraception and unplanned pregnancy. Patients also indicate if they are taking any of the 50 medications associated with fetal defects, interactions with hormonal contraception, or both (Multimedia Appendix 1). To prevent user fatigue and improve readability, similar medications are grouped (eg, statins and neuromodulators) and presented over several screenshots. Patients then receive tailored contraceptive education that uses 6th-8th grade English to explain theoretical or known risks and benefits of different methods in the context of their index health conditions and medications. In Step 2, patients are shown contraceptive methods grouped by a traffic-light color scheme and text to simply translate US MEC medical risk categories for layperson comprehension: (1) Category 1 and 2: "Safe. Use any of these" (green bar); (2) Category 3: "Caution. These methods may be risky for you. Use only if the benefits outweigh the risks to you. Talk to your clinician. (yellow bar)." (3) Category 4: "Stop. Do not use these." (red bar). Patients can click on each method to learn about relevant features (eg, contraceptive effectiveness, impact on periods, and side effects), add a method to their potential "Favorites," and click on methods to compare them side-by-side. In Step 3, the tool generates a "My Birth Control Summary" that displays the individual's health conditions, medications, contraceptive favorites, and questions for their clinician from "My Notebook." No personal identifiers are included in this screenshot (Multimedia Appendix 2).

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Figure 2. My Health, My Choice home screen for patients.

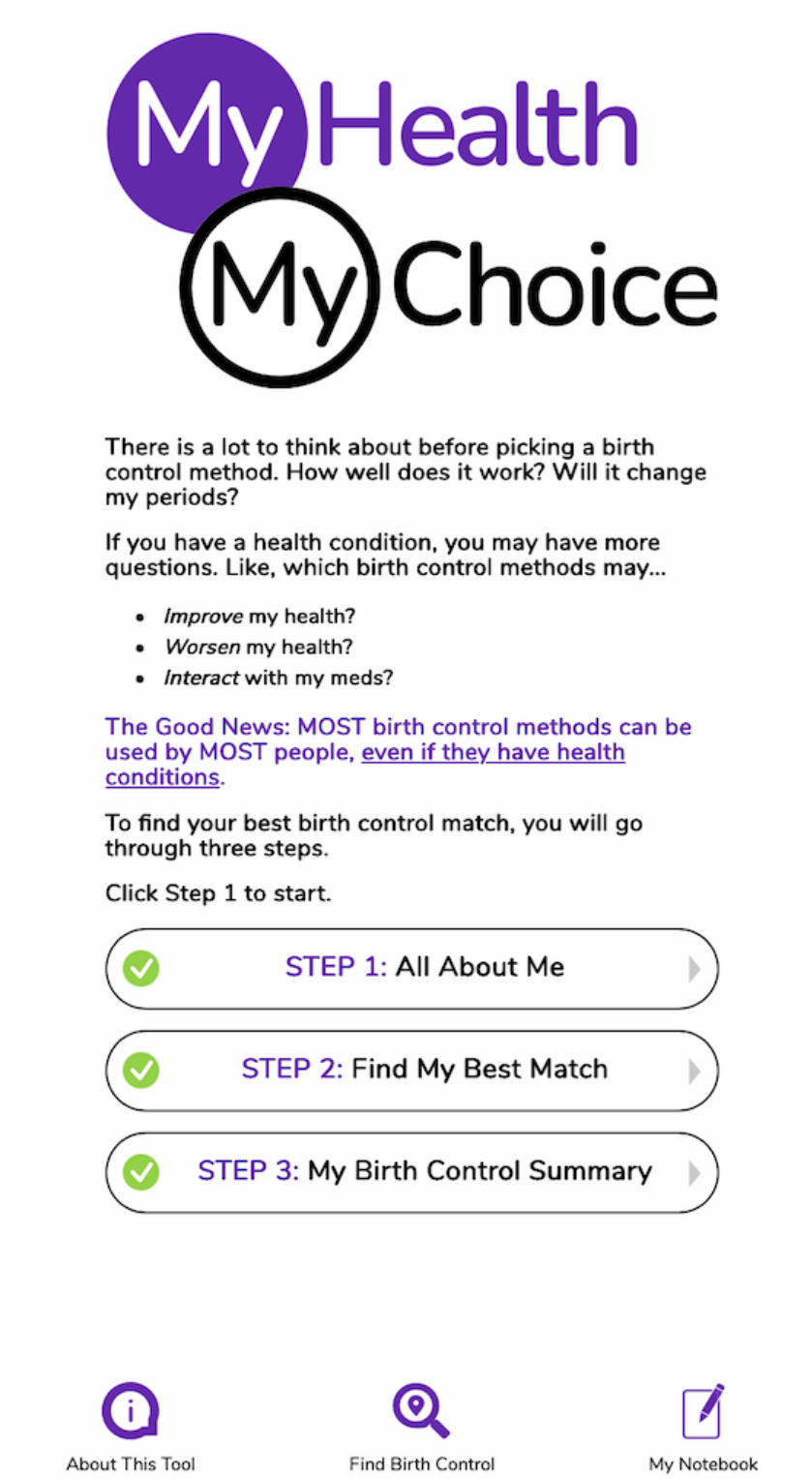

The clinician version (Figure 3) is designed to provide point-of-care support to help clinicians counsel individuals about the safety of different contraceptive methods in the context of their health conditions, medications, and personal concerns. Clinicians are prompted to review each enrolled patient's "My Birth Control Summary" before or during the clinic visit. Clinicians are not required to enter any patient health information. This approach minimizes clinician burden and, more importantly, ensures that the discussion is driven by patient concerns and priorities. Finally, clinicians are provided with curated snapshots and brief text descriptions of sections of the US MEC Chart that highlight conditions and medications relevant to the index patient (Multimedia Appendix 3).

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Figure 3. My Health, My Choice home screen for clinicians.

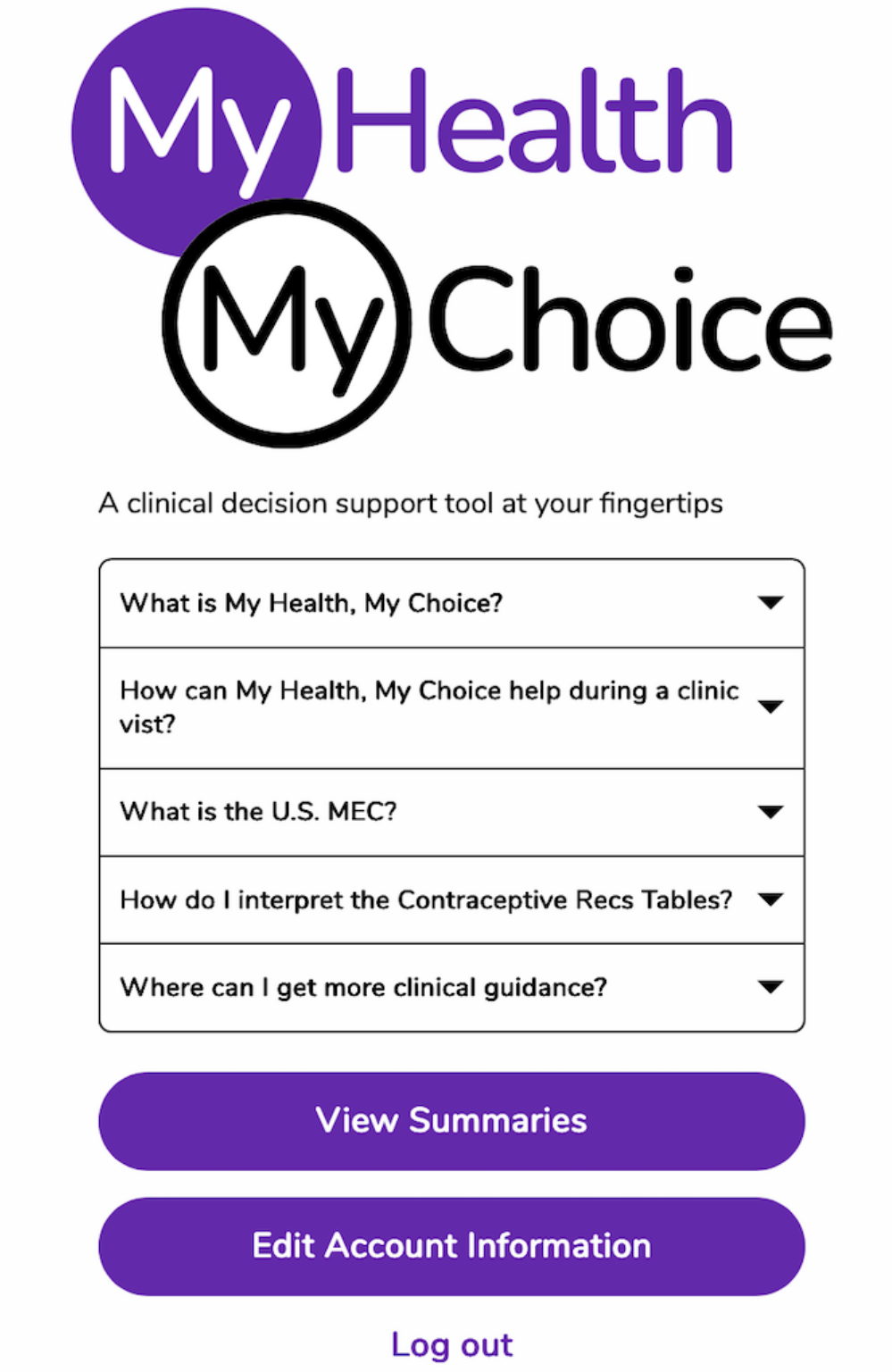

Inclusion and Exclusion Criteria: Clinics, Clinicians, and Patients

Eligible clinics must (1) provide contraceptive counseling and services, including provision of or referral for intrauterine devices (IUDs), implants, and permanent contraception (tubal surgery or vas deferens surgery); (2) identify a clinician to serve as a clinic lead for study activities; (3) agree to be randomized; and 4) cede to oversight by the University of Michigan (UM) Institutional Review Board (IRB) per the National Institutes of Health (NIH) and federal single IRB mandate (US Code of Federal Regulations Part 46.114) [37]. Clinics are not eligible if they share providers or contraceptive quality improvement or educational initiatives with another clinic that is currently enrolled in the trial. Eligible clinics must operate as independent units to avoid the risk of contamination or bias across clinic sites [38].

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Eligible clinicians must (1) be a licensed certified nurse midwife, nurse practitioner, physician assistant, or physician. Resident physicians who have completed 1 year of internship are eligible (interns are excluded) and (2) provide contraceptive services, including provision of or referral for IUDs, implants, and permanent contraception (tubal surgery and vasectomy).

Eligible patients must (1) be aged 18-49 years; (2) be assigned female sex at birth (regardless of gender identity); (3) be able to read in English; (4) have access to a mobile phone, computer, or tablet with internet capabilities; (5) be fertile (have an intact uterus and at least 1 ovary, be premenopausal, have never had permanent contraception surgery, and have no known medical reasons for current infertility, such as use of ovarian suppression medications); (6) have at least 1 index health condition, take an eligible medication, or both (Multimedia Appendix 1; (7) not be currently pregnant; and (8) have a desire to start, switch, or add a contraceptive method for the purpose of preventing pregnancy. Patient exclusion criteria include patients who expect to try getting pregnant in the next 12 months or are presumed infertile for any reason (eg, postmenopausal, hysterectomy, or chemotherapy). During our recruitment process, we explicitly clarify to clinics, clinicians, and patients that transgender patients and postpartum patients are eligible for the trial as long as they meet all other eligibility criteria noted above. Of note, we are developing a Spanish version of the MHMC tool and anticipate expanding eligibility to Spanish-speaking patients in 2026.

Recruitment, Screening, and Enrollment: Clinics, Clinicians, and Patients

To successfully enroll clinics, the study team is partnering with the DARTNet Institute, a national practice-based research network with over 1300 individual primary care physicians and clinician members representing more than 850 clinical practices in all 50 states within the United States. Clinics will be recruited via email, referrals through professional networks, and recruitment activities at professional conferences. If a clinic expresses interest, the DARTNet Institute team will meet with clinic leaders to ensure the clinic meets eligibility criteria prior to enrollment. Each enrolled site will have its own clinic team made up of 2-4 individuals, led by a clinician, who will be responsible for study activities.

Potentially eligible clinicians will have several opportunities to learn about the study through videoconference meetings, study flyers, the study website, direct communications with the clinic team, and customized emails. Clinicians who are interested in participation will complete an electronic informed consent via SignNow (airSlate Inc), a digital platform in compliance with the Health Insurance Portability and Accountability Act (HIPAA) of 1996.

The clinic team will identify potentially eligible patients through electronic medical record (EMR) screening of upcoming patient visits (1-4 weeks in advance to allow time to contact and enroll patients with local adaptations per each site's typical scheduling norms). Visits must be scheduled with a clinician who has enrolled in the study to allow for valid interpretations of the impact of an intervention that targets both patients and clinicians. Eligible visit types include preventive health, gynecologic, postpartum, and follow-up or problem-based visits for any issue, including contraception. Potentially eligible patients will receive a study invitation by email, EMR portal message, text message, or letter, as determined by the clinic team. Study flyers will be posted throughout enrolled clinics to allow potentially interested patients to contact the study team directly. Patients who express interest in the study will undergo eligibility screening over the phone with a study team Research Assistant (RA). If patients meet eligibility, the RA will proceed with informed consent using SignNow.

Patient Study Activities and Quantitative Data Collection

Enrolled patients will complete an electronic baseline survey to report demographics, health history, past and current contraceptive use, contraceptive knowledge, and the secondary and exploratory outcomes (see "Quantitative Outcomes and Analysis" section). To mitigate the risk of differential dropout, recruitment bias, or bias in baseline assessments, we will inform participants of their clinic group assignment after their consent and baseline surveys have been completed [39]. Although this approach entails temporary withholding of information, it is consistent with the Ottawa Statement on the Ethical Design and Conduct of Cluster Randomized Trials [39].

Patients in both the intervention and control arms will receive a web link to a brief video that explains "What to Expect" regarding study activities. Only those in the intervention arm will receive web links to the MHMC tool, a brief video that reviews how to log in and navigate the tool's features, and a posttool survey to report their experience using MHMC.

The study team will encourage all patients to attend their upcoming clinic visit. Immediately after the clinic visit, patients will receive a postvisit survey and be asked to complete this within 5 days. They will be asked to complete surveys 1 month and 3 months after the clinic visit. Patient surveys require 5-15 minutes to complete. The study team will invite approximately 30 patients who complete study participation to do an optional 1-hour qualitative exit interview by phone or videoconference (refer to "Qualitative Data Collection and Sampling Considerations" section). Patients will receive up to US $100 in cash remuneration for completion of study activities (Figure 4).

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Figure 4. Patient Activities Flow Diagram.

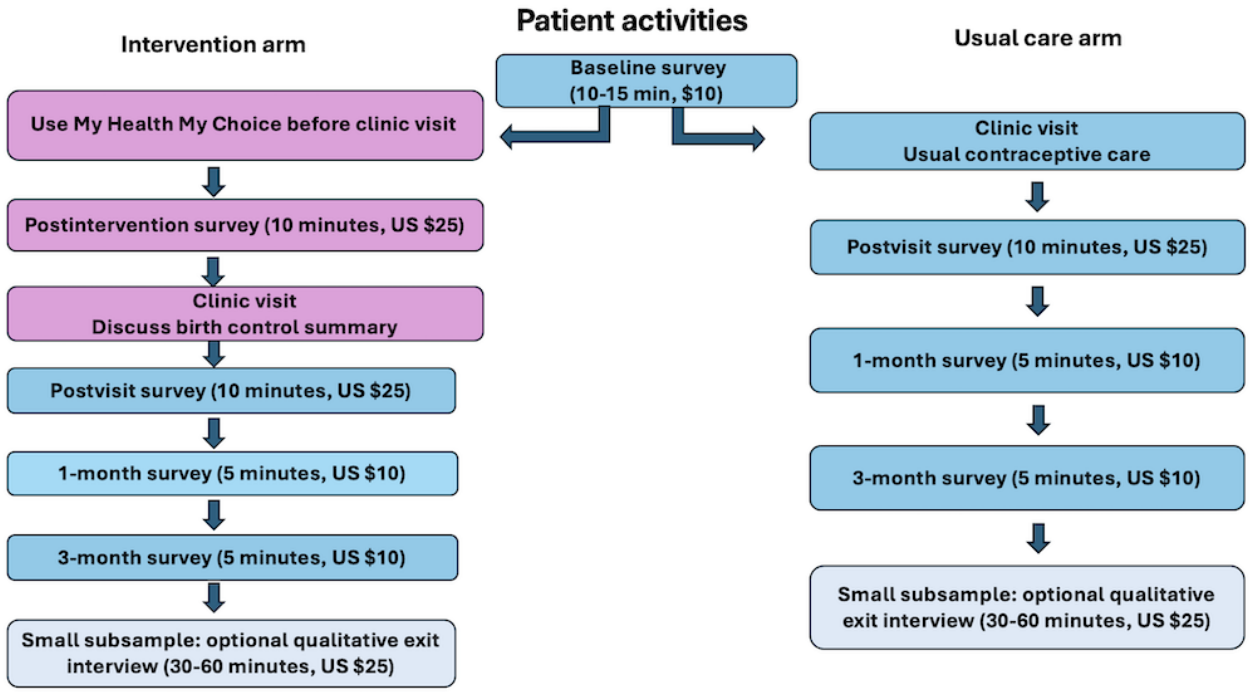

Clinician Study Activities and Quantitative Data Collection

All enrolled clinicians will complete an electronic baseline survey and exit survey about their scope of contraceptive practice and knowledge of contraceptive care in the context of diabetes, hypertension, migraine headaches, and multiple risk factors for cardiovascular disease (common clinical scenarios). Clinicians in both arms will receive a web link to a video that reviews "What to Expect" regarding study activities. Only clinicians in the intervention arm will receive web links to the MHMC tool and a brief video that reviews how to navigate the tool's features. After each clinic visit with an enrolled patient, clinicians will complete a 3-minute postvisit survey. The study team will invite approximately 30 clinicians at the end of the study to do an optional 1-hour qualitative exit interview by phone or videoconference (refer to "Qualitative Data Collection and Sampling Considerations" section). Clinicians will receive up to US $75 in cash remuneration for study activities (Figure 5).

Figure 5. Clinician Activities Flow Diagram.

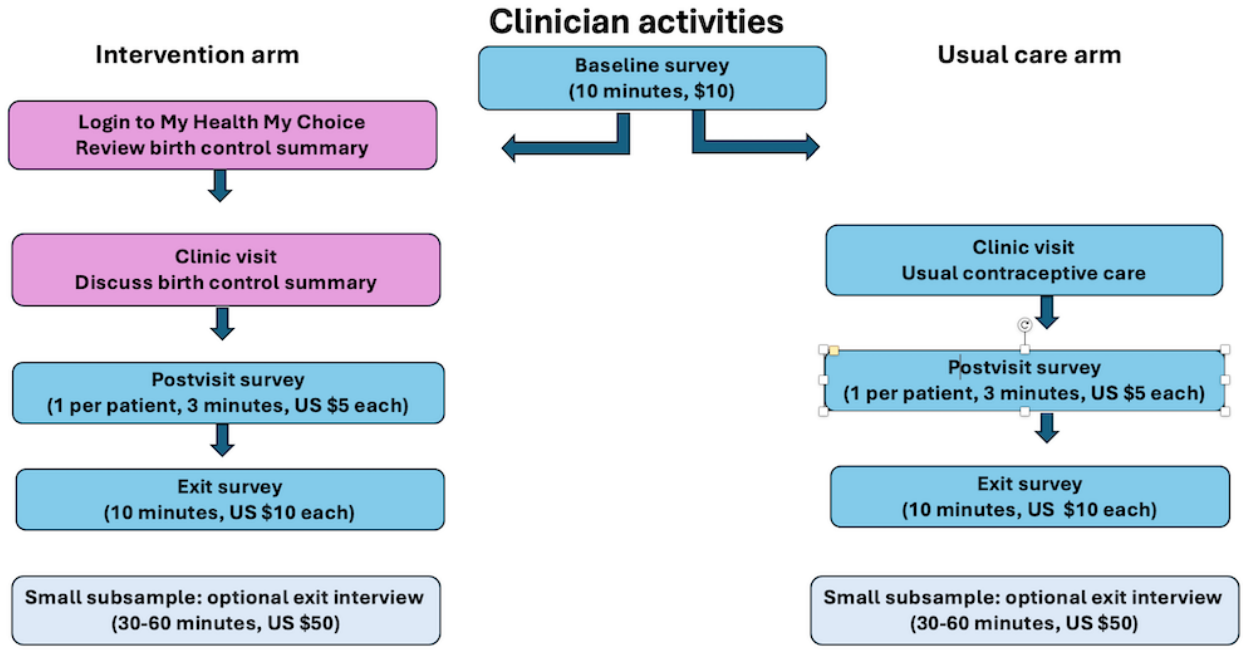

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Clinic Study Activities and Quantitative Data Collection

After patients exit the study, the Clinic Team will conduct an EMR review of each enrolled patient's chart to corroborate 3-month study outcomes, including contraceptive use (contraceptive prescriptions, IUD, or implant insertions) or plans to obtain IUDs, implants, or tubal surgery for themselves or vasectomy for their partners (scheduled visits and referrals).

Qualitative Data Collection and Sampling Considerations

To achieve the qualitative and mixed methods part of Aim 2, we will purposefully sample patients [40] across US MEC Categories 1, 2, 3, and 4). We will oversample patients who report the use of Category 3 to understand factors that led to the use of a method that should be avoided except under special circumstances. As an example, if a patient with well-controlled hypertension reports using a combined hormonal pill (Category 3 use), does this reflect oversight or unawareness of the risks by the patient, the clinician, or both? Or did the patient and clinician carefully review the pros and cons in light of the patient's other comorbidities, age, and tolerance for risk? To what extent, if at all, did use of the intervention contribute to this process? While US MEC Categories will primarily drive qualitative sampling, we will also seek perspectives across a range of chronic conditions (cardiovascular, endocrine, psychiatric, neurologic, and autoimmune) and contraceptive method types whenever feasible, and across both arms. We also aim to purposefully sample clinicians who provided care to the index patients who agree to be interviewed, which will allow for comparison of patient and clinician perspectives on the clinic discussion and decision-making process.

To prevent the risk of affecting participant behavior or survey responses, we will conduct patient interviews right after they exit the study at 3 months and clinician interviews at the end of their clinic's trial participation. A trained qualitative RA will conduct 30- to 60-minute interviews with participants over the phone or via videoconference. All audio and video recordings will be uploaded immediately to a secure cloud server. A professional transcriber will transcribe exit interviews verbatim. Personal identifiers for people and places will be removed and replaced with pseudonyms.

Theoretical saturation refers to the point at which data analysis reveals no further significant findings relevant to the research aims and is commonly used in qualitative research to determine sample sizes [41]. Based on our exit interviews from our pilot study and best practices in qualitative sampling [41,42], we anticipate that interviewing 2 patients and 2 clinicians per clinic (about 60 interviews total, 30 patients and 30 clinicians) will provide high-quality data to achieve theoretical saturation. Upon reaching theoretical saturation, we will stop collecting interview data.

Power and Quantitative Sample Size

The primary outcome is the proportion of participants reporting contraceptive nonuse at 3 months. Based on national estimates [10,11,43,44] and our screening protocol, we anticipate 30% (217/726) of participants at baseline will report contraceptive nonuse. A previous cluster RCT of a contraceptive decision tool in outpatient clinics found a clinic-level intracluster correlation (ICC) of 0.02 [16]. We conservatively estimate an ICC of 0.05. Prior studies have estimated ICCs generally <0.04 for patient-reported outcomes in maternal health and sexual behavior among reproductive-aged women [45-47]. To reduce our estimated ICC, we have taken several precautions. At the design level, we have defined clinic, patient, and clinician eligibility criteria to reduce heterogeneity and variance in estimates [48]. At the analysis level, we will conduct regression adjustment for key covariates [48]. To detect a difference of 20% in the proportion of contraceptive nonuse between the intervention arm and the control arm at 3 months, an effect size consistent with that of prior contraceptive trials [20,49,50], we will need to enroll 14 clinics (7 in each arm) and 45 participants in each clinic. Assuming an attrition rate of 15%, our enrollment goal is 726 patients (363 patients in each arm). We anticipate that we will enroll 5-10 clinicians per clinic, for a maximum total of about 140 clinicians. The allocation ratio will be 1:1 with attention to the balance of obstetrics and gynecology clinics in each arm, which will mitigate the impact of unequal distribution of sites that provide higher volume or scope of contraceptive services.

Randomization Process, Allocation Concealment, and Blinding

To avoid potential contamination across providers and patients, we will randomize by clinic site.

Clinics will be randomized in even-numbered blocks (2,4) to ensure balanced allocation of group conditions. The lead biostatistician (AS) will generate the allocation sequence and assign clinics to the intervention arm or control arm. Due to the cluster-randomized design, allocation concealment is impractical, and it will not be possible to blind patients or clinicians. The study team will remain blinded to the group assignment when evaluating outcomes.

Quantitative Outcomes and Analysis

The primary outcome is contraceptive nonuse at 3 months per patient self-report, consistent with prior contraceptive studies [10,51,52]. Individual contraceptive nonuse will be modeled as a binary outcome. We will use mixed-effects nested logistic regression to assess differences in 3-month outcomes between the study arms. The model will include an arm assignment categorical covariate and will be adjusted using patient-level covariates (baseline contraceptive nonuse, education, race, ethnicity, and parity) and clinician-level covariates (self-reported experience with contraceptive care and specialty type). Random intercepts for the clinic and for clinicians nested within the clinic will account for the clustering. Secondary analyses of contraceptive nonuse will include the same model with 1-month data and a subgroup analysis that only includes patients at risk for pregnancy, that is, those who report penile-vaginal sexual activity at 1 month and 3 months.

The secondary quantitative outcome is patient-reported contraceptive method use as classified by the US MEC. We will summarize US MEC Categories 1, 2, 3, or 4 among patients who report contraceptive use at 1 month and at 3 months with

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descriptive statistics. Chi-square tests will be calculated to compare frequencies between the intervention group and the usual care group.

The exploratory outcomes are hypothesized mediators of the intervention effect on the primary and secondary outcomes. First, contraceptive decisional conflict will be assessed with the DCS, a 16-item validated scale with 4 subscales [29] (0=no conflict; 100=greatest conflict). We slightly modified the wording of DCS items, when appropriate, to reflect contraceptive decisions rather than generic health decisions. Second, we will assess patient-reported quality of interaction with their contraceptive provider via the IQFP [30]. The IQFP contains 11 items that are assigned a score of 1-5 (1=poor, 2=fair, 3=good, 4=very good, and 5=excellent) by the patient to assess their clinician's shared decision-making and interpersonal skills (total scores ranged from 11 to 55). We will conduct a mediation analysis as described by Baron and Kenny [53] with two models: (1) a logistic regression of the mediator (ie, DCS or IQFS, dichotomized) as a function of the primary outcome (contraceptive nonuse at 3 months), with a covariate for intervention versus control group, and (2) a logistic regression of the primary outcome (contraceptive nonuse at 3 months), adjusting for both the mediator (ie, DCS or IQFPS, dichotomized) and intervention versus usual care group.

We will conduct descriptive analyses on other patient, clinician, and clinic-level exploratory measures and statistical comparison tests as appropriate (eg, chi-square, Fisher exact, and *t* tests).

- Patient-level measures: We will categorize patient-reported contraceptive use by method type and method effectiveness (highly effective, moderately effective, and less effective) to enable comparison with other studies. Patients will be asked to assess 6 knowledge questions regarding contraceptive safety (true, false, or I don't know) at baseline, postdecision tool use (for intervention arm only), and postclinic visit. Patients will be instructed to report any pregnancies that occur during the study and at 1 month and 3 months. For any pregnancies reported, patients will be asked to describe their pregnancy intentions at the time of pregnancy using a standardized single item [54]. Patients who are still pregnant at the time of reporting will exit the study and seek follow-up care; they may contribute data up until the point of study exit.
- Clinician-level measures: We will assess clinician knowledge of the US MEC Guidelines at baseline and exit surveys with 5-point Likert-scale items regarding 4 clinical scenarios.
- Clinic-level outcomes: RE-AIM is an evaluation framework to assess an intervention's potential to be translated to real-world settings [35]. We will assess each dimension of RE-AIM with quantitative data, qualitative data, or both:
- Reach: We will collect demographics of participants offered the intervention and those who used the intervention, and these will be compared with those of the usual contraceptive care arm, as well as the general US population at risk for unplanned pregnancy (quantitative).
- Efficacy: We will examine the primary outcome of contraceptive nonuse (quantitative) in the context of patient and clinician perspectives on the intervention's impact (qualitative).
- Adoption: We will report the percentage of patients and clinicians in the intervention arm who used the decision tool intervention.
- Implementation: We will report patient and clinician fidelity to the intervention and what natural adaptations were made (quantitative and qualitative).
- Maintenance: We will summarize patient- and clinician-reported facilitators, barriers, and suggested changes to sustain use of the intervention in clinical practice beyond the clinical trial (qualitative).

Qualitative Analysis

Using qualitative and mixed methods analysis software (MAXQDA, ERBI GmbH) [55], the Principal Investigator (PI;JPW) and a trained qualitative RA will conduct thematic analysis as described by Braun and Clark [56]. Analysis of patient interviews and clinician interviews will be conducted separately. First, we will independently read the first several transcripts and assign codes to text segments. We will iteratively repeat this process with subsequent transcripts and merge and revise codes as needed. The final codes and code definitions will be organized in a consensus codebook. In the second phase of qualitative analysis, the PI and RA will merge codes to advance from descriptive codes to analytic codes and themes. Thematic findings within and across patients, clinicians, and clinics will be compared. Upon reaching theoretical saturation, such that no significant new insights are gained with respect to Aim 2, qualitative data collection will stop. TG will assist as a third analyst to resolve differences in interpretations and help decide when qualitative data collection can stop. We will triangulate thematic findings from the patient interviews and the clinician interviews to explore confirming and disconfirming findings.

Mixed Methods Analysis

Mixed methods in health research involve the integration of quantitative and qualitative data to gain a greater understanding of the phenomenon than can be obtained with either type of data alone [34]. We will integrate the quantitative data findings about US MEC Categories with the qualitative themes to better understand how and why the intervention and other contextual factors may have affected decision-making across US MEC Categories, again, with a focus on Category 3 cases. To do so, we will create a joint display, a mixed methods technique to array quantitative and qualitative findings side-by-side and draw out inferences and generate hypotheses (Figure 6) [34].

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Figure 6. Mock-up example of joint display.

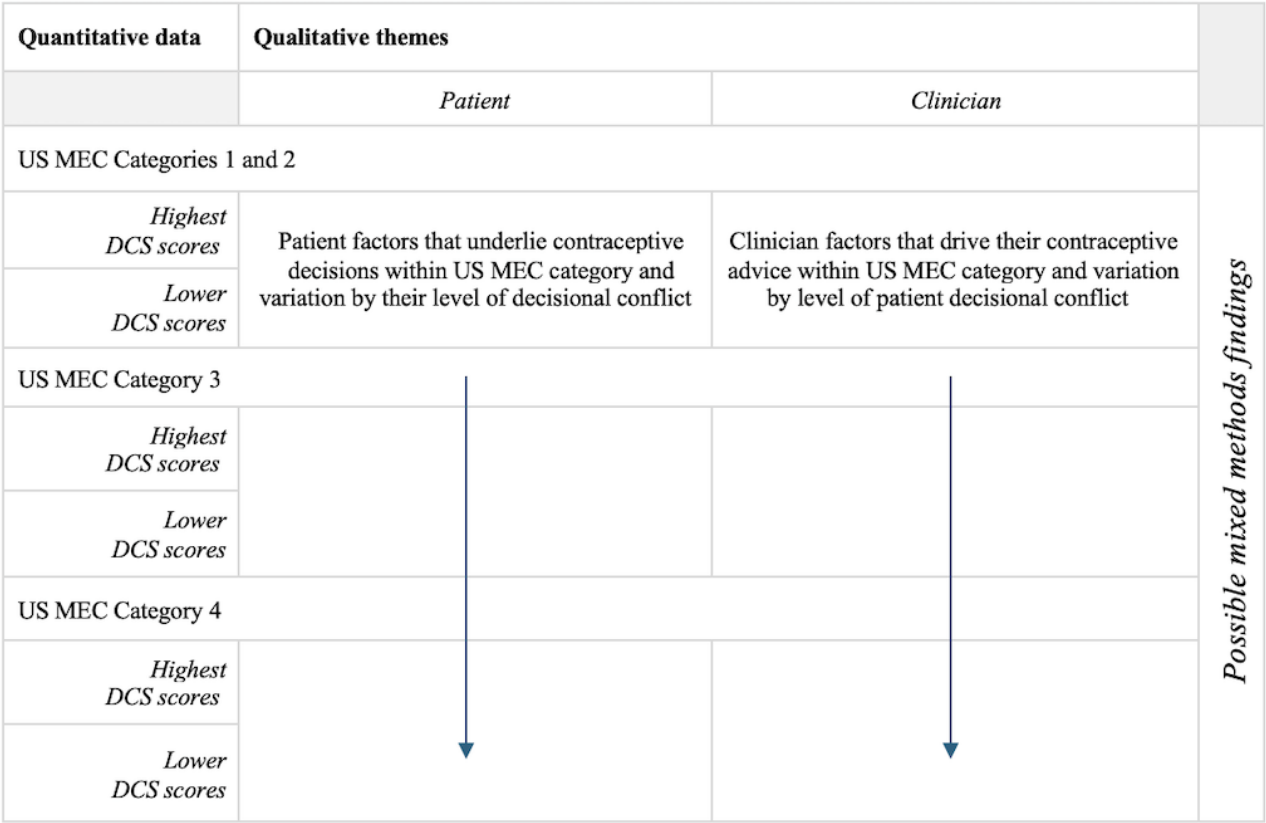

Ethical Considerations

The UM IRB approved the study protocol (HUM00234187). This trial will be conducted in compliance with this protocol, the International Council on Harmonisation Good Clinical Practice, and applicable state, local, and US Code of Federal Regulations (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812), and the National Institute of Child Health and Human Development (NICHD) Terms and Conditions of Award. All personnel involved in the conduct of this study have completed human participants protection and good clinical practices training. All study data will be collected and managed using REDCap (Research Electronic Data Capture; Vanderbilt University) surveys hosted at the UM. REDCap is a secure, web-based software platform designed to support data capture for research studies [57]. Clinician and patient participants receive cash compensation for completion of each study activity (see Figures 4 and 5).

Results

This study was funded in September 2023. We anticipate data collection to start in October 2025 and expect to conclude data collection in October 2028. A Data Safety Monitoring Board of 4 independent experts with combined expertise in biostatistics, maternal and child health, and family planning will assess the trial's progress and monitor participant safety. Our findings will be published in peer-reviewed journals. We anticipate expanding eligibility to Spanish-speaking patients in 2026 after creating a linguistically appropriate Spanish version of the decision tool.

Discussion

Principal Findings

This study aims to evaluate whether a web-based decision tool will decrease contraceptive nonuse by improving patient-reported decisional conflict and the quality of interactions with their contraceptive providers. To our knowledge, this will be the first RCT to focus on the contraception decision support needs of people with health conditions—a group at higher risk of adverse events (albeit low absolute event rates) from hormonal contraception use and pregnancy-related complications than those without health conditions [11,12]. We expect this study to advance our understanding of the impact of contraceptive decision support tools on patients' perceptions of their clinicians' ability to provide comprehensive information, listen to their concerns, respect patient autonomy, and engage in shared decision-making [30]. This study will also generate new knowledge regarding how patients and clinicians deliberate risk-benefit trade-offs of contraceptive use in light of ongoing health considerations.

Study Strengths

A key strength of this study is its cluster RCT design, which is a rigorous approach to mitigate contamination, that is, inadvertent exposure to the intervention among participants in the control arm [39]. Contamination across patients who seek care at the same clinic is possible, though less likely. The greatest risk of contamination from exposure to MHMC is among clinicians who work together at the same clinic; randomization at the clinic level will mitigate this risk. A second strength of the study design is the use of qualitative and mixed

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methods to disentangle the complexities of contraceptive decisions in the context of health considerations that cannot be ascertained via quantitative survey items alone. We anticipate this approach will be most useful for probing Category 3 situations when the use of a method should be avoided unless there is no other appropriate or preferred method available. Finally, this trial will be conducted in real-world clinic settings in diverse geographic regions of the United States, including nonacademic sites, which will improve the generalizability of our findings.

Limitations

The limitations of this study include the heterogeneity of eligible health conditions, which may dilute the overall effect size for the primary outcome (contraceptive nonuse). However, the posited behavioral mechanisms that support this intervention (decreased decisional conflict and improved interactions with clinicians) should, in theory, operate across different health conditions. We acknowledge that including clinicians with a diverse range of expertise in chronic disease management, family planning, and obstetrics and gynecology may introduce performance bias. We will conduct subanalyses to explore this possibility. Finally, a major trial limitation is the exclusion of non–English-speaking patients. Development and piloting of a Spanish version of MHMC is underway, and we anticipate recruiting Spanish-speaking patients in 2027.

Conclusions

In summary, this mixed methods cluster RCT will inform clinical care and best practices to support people's reproductive priorities, reduce contraceptive nonuse, and improve reproductive health outcomes. We will share our study findings with participating clinics and their patients through our study website, newsletters, and national conferences, and with the scientific community through peer-reviewed journals and scientific presentations. This protocol will improve the rigor and reproducibility of future trials of contraceptive decision support tools.

Acknowledgments

The authors would like to thank Sonya Borrero, Hyungjin Myra Kim, Rahmat Olohuntoyin Na'Allah, Ade Olomu, and Lisa Callegari for their feedback regarding study design, and Rania Clark for her technical assistance in preparing the manuscript. No artificial intelligence (AI) or generative language model was used in any portion of manuscript generation.

Funding

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Data Availability

The datasets generated or analyzed during this study will be made available beginning 1 year after publication of trial findings and for an additional 36 months. After this 36-month time period, the quantitative data will be available in the UM's Deep Blue Data Repository, and the qualitative data will be available in the Qualitative Data Repository, but without investigator support other than deposited metadata.

Authors' Contributions

JA, LB, CD, VD, NM, AS, and BZF contributed to conceptualization, methodology, funding acquisition, and writing–review and editing. CL, NM, MVS, and CW handled methodology, project administration, and writing–review and editing. BP was involved in methodology, drafting, visualization, and writing–review and editing. MK was responsible for methodology, visualization, and writing–review and editing. JPW performed conceptualization, funding acquisition, methodology, project administration, supervision, visualization, writing–original draft, and writing–review and editing.

Conflicts of Interest

LRB is the editor-in-chief for JMIR mHealth and uHealth. None of the other authors have conflicts of interest to disclose.

Multimedia Appendix 1
My Health My Choice: List of index health conditions, characteristics, and medications.
[DOCX File , 23 KB - resprot_v14i1e71101_app1.docx]

Multimedia Appendix 2
My Health My Choice: My birth control summary example.
[DOCX File , 188 KB - resprot_v14i1e71101_app2.docx]

Multimedia Appendix 3
My Health My Choice: Clinician point of care US Medical Eligibility Criteria for Contraceptive Use example.

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[DOCX File , 294 KB - resprot_v14i1e71101_app3.docx]

Multimedia Appendix 4
Peer review report from the CMGC - Clinical Management in General Care Settings Study Section, Healthcare Delivery and Methodologies Integrated Review Group (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 163 KB - resprot_v14i1e71101_app4.pdf]

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Abbreviations

CDC: Centers for Disease Control and Prevention
CHC: combined hormonal contraceptives
DCS: Decisional Conflict Scale
EMR: electronic medical record
HIPAA: Health Insurance Portability and Accountability Act of 1996
ICC: intracluster correlation
IRB: Institutional Review Board
IQFP: Interpersonal Quality of Family Planning Scale
IUD: intrauterine device
MHMC: My Health, My Choice
NICHD: National Institute of Child Health and Human Development
NIH: National Institutes of Health
PI: Principal Investigator
RA: Research Assistant
RCT: randomized controlled trial

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RE-AIM: Reach, Effectiveness, Adoption, Implementation, Maintenance
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Intervention Trials
UM: University of Michigan
US MEC: United States Medical Eligibility Criteria for Contraceptive Use

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The Effectiveness of Frontal Plane Adaptability in a Novel Foot Prosthesis: Protocol for a Randomized Crossover Clinical Trial

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Abstract

Background: The primary objective of this study is to investigate whether a novel prosthetic foot with a polycentric ankle, which offers side-to-side adaptability, improves mobility and daily performance in individuals with (1) unilateral above-knee amputation, (2) unilateral below-knee amputation with a lower mobility level (K2) , or (3) bilateral amputation, any level of amputation. Traditional prostheses are primarily designed for forward walking and lack adaptability for navigating uneven terrain, turning, and executing other multidirectional tasks, often resulting in pain, instability, and limited function.

Objective: The objective of this testing protocol is to better understand the functional impact of a novel foot design that offers more inversion/eversion rotation of the polycentric ankle. Although the foot has the potential to address mobility challenges, it is unknown whether people with different amputations and mobility levels respond differently.

Methods: The study includes community-based mobility assessments, standardized questionnaires, and participant feedback. Although side-to-side adaptability prosthetic feet have shown benefits for highly active users, this study aims to evaluate the impact on individuals with more significant mobility limitations.

Results: Results may guide prosthetic prescription, expand access to advanced prosthetic technology, and inform reimbursement policies, particularly benefiting veterans and service members with combat-related amputations. The study began recruiting in October 2023; as of September 2025, there were 66 participants (17 below the knee, 34 above the knee, and 15 bilateral) who completed the protocol. The clinical trial is expected to be completed by March 2027. Dissemination of results is expected to be completed by December 2027.

Conclusions: This procedural study presents a model for evaluating prosthetic feet and other mobility-assistive technologies in real-world contexts, supporting broader efforts to match components to user needs through clinical trials that are grounded in both functional performance and user experience.

Trial Registration: ClinicalTrials.gov NCT06214026; https://www.clinicaltrials.gov/study/NCT06214026

International Registered Report Identifier (IRRID): DERR1-10.2196/84313

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KEYWORDS

prosthetic foot; lower extremity amputation; clinical trial; gait analysis; mixed methods

Introduction

According to 2005 projections, over 1 million adults in the United States live with lower extremity amputation (LEA) [1], with approximately 22,000 people undergoing above-knee amputations annually [2]. Additionally, about 12,000 individuals have bilateral amputations, though precise figures are unavailable [1]. The largest group of individuals seen by prosthetists consists of those with transtibial amputations and limited mobility, classified at Medicare Functional Classification Level (MFCL) K2, accounting for 36% of the lower extremity amputee population [3]. A person with LEA at MFCL K2 can use a prosthesis for transfers and ambulation on level surfaces,

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with the potential to walk in environments with low-level barriers such as curbs, stairs, or uneven surfaces.

Advancements in prosthetic technology have significantly improved the mobility and quality of life for individuals with LEAs. However, the challenge remains in providing tailored prosthetic solutions that optimize both functional outcomes and personal satisfaction for diverse patient populations, especially those with unique needs such as warfighters, veterans, and individuals with bilateral or above-knee amputations. The importance of patient-specific prescriptions cannot be overstated, as prosthetic components must meet the specific biomechanical requirements of each individual to maximize effectiveness.

The need for innovative solutions is particularly pressing for individuals with higher levels of amputation and those experiencing lower levels of mobility. For example, individuals with bilateral amputations face persistent difficulties with balance, cognitive focus during gait, overall mobility, and residual limb pain despite using conventional prosthetic devices. Recent developments in prosthetic ankle technology have shown promising improvements, particularly in enhancing the foot's adaptability to different surfaces, which is crucial for optimizing function in various environments. The META Arc (WillowWood), shown in Figure 1, features 10 degrees of frontal plane motion, which may enhance mobility, balance, and function during activities that benefit from this additional motion, such as turning, side steps, and backward steps.

Figure 1. META Arc (WillowWood).

In our previous study, 21 participants with unilateral below-knee amputation had 16 models of usual prosthetic feet, making comparisons between the usual foot and an investigational foot challenging [4]. Also, comparisons with the usual foot do not isolate the benefits of the unique features of the investigational foot. In the previous study, a locking feature eliminated the mediolateral motion, rendering the foot comparable to a typical energy storage and return foot. This was only completed for gait testing protocols in the laboratory; participants stated they had no opportunity for community testing of the locked version. The current study attempts to overcome some of these limitations.

This paper outlines the procedural approach for a randomized clinical trial designed to evaluate the impact of a novel frontal plane ankle technology on individuals with above-knee or bilateral amputations or those with below-knee amputations classified at an MFCL K2. By using a double crossover design and focusing on person-centered outcomes, this study seeks to improve our understanding of how advanced prosthetic feet can enhance functional mobility, balance, and daily activity

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participation for individuals with complex amputation profiles. A two-period or double crossover research design provides more data per participant, balances potential carryover effects, and improves statistical power and precision by having each participant's response with the usual prosthetic foot, with the novel foot in both the locked and unlocked position, and with the usual prosthetic again. The mixed methods approach used in this study, which incorporates qualitative insights from interviews, daily experiences recorded in logbooks, and surveys, along with objective measures from standard functional tests, provides a comprehensive evaluation of the novel prosthetic foot. This protocol paper can be a model for not only evaluating prosthetic components but other assistive technologies as well.

The findings from this ongoing study are expected to have far-reaching implications for clinical practice, particularly for military service members and veterans who often face unique and severe challenges related to limb loss. With more than 1 million individuals living with LEA in the United States, and a significant portion of these being veterans or military personnel, the outcomes of this research will provide valuable insights into how personalized prosthetic technology can improve long-term mobility and quality of life for this population. This study challenges prosthesis users to move sideways, move backwards, and turn. By completing well-studied clinical assessments on an instrumented walkway, this study allows for biomechanical component analysis, providing more insight into prosthesis use and design.

Methods

Overview

This prospective multisite randomized double crossover clinical trial study will follow an A1-B1-B2-A2 design that includes military veterans and civilians. Three collaborative sites will recruit and enroll participants: (1) University of Washington (Seattle, WA), (2) WillowWood (Mt. Sterling, OH), and (3) University of South Florida (Tampa, FL). Prior to data collection, the principal investigators and main study personnel from each site participated in a study protocol training session to ensure data collection at each site was the same. The study personnel meet every other week to discuss study procedures.

Ethical Considerations

The study received approval (STUDY00017239) from the University of Washington's institutional review board (IRB); the IRBs of the other sites and the US Army's Office of Human Research Oversight reviewed the study protocol. The protocol is listed in the federal clinical trial registry (ClinicalTrials.gov NCT06214026).

All participants will provide informed consent. Study data will be confidential. There will be links between study data and participant identifiers that will be kept in separate secured areas. The link between participant identifiers and the research data will be destroyed after the records retention period required by state and/or federal law. All the information provided by the participants will be confidential.

After the completion of visits 2, 3, and 4, participants will be compensated US $200 per visit for a total of US $600. Parking, mileage, and transportation (within limits) will be paid for study visits.

Participants

The study includes three groups of individuals with amputations: (1) people with a unilateral above-knee amputation, (2) people with bilateral LEAs, and (3) people with a unilateral below-knee amputation who are categorized as having a K2 limited community ambulation level of mobility. All participants must be able to provide written informed consent independently and have the ability to read, write, and comprehend English.

Past research studies of people with amputations have historically underrepresented specific groups. Barriers to participation in clinical trials have been identified. This study targets individuals in these categories, and accommodations have been made. These included flexible payment schedules for participation, free rideshare transportation organized by study staff, free parking for participants who had their own transportation, and an on-call prosthetist. In addition, the study enrollment period was 3 years, enabling participants to delay protocol initiation due to socket changes, skin issues, or personal factors.

Eligibility Criteria

To be eligible for the study, participants must be 16 years or older and reside in an independent living environment within the community. They may use a walking aid but should not primarily rely on wheelchair mobility.

Exclusion Criteria

The weight limit is 165.6 kg (365 lbs). Participants must not have conditions, such as skin wounds, that would preclude the use of a prosthesis. Young children will not be included because they have different functional needs compared to adults. People will be excluded if they have fluctuating conditions that may significantly alter gait mechanics during the 10-week study. Examples include Parkinson disease, alcoholism, brain tumors, and hereditary cerebellar ataxias.

Discontinuation Criteria

Participants will be discontinued from the study if they are unable to use a prosthesis. Examples include surgery or trauma. However, due to the potential for fluctuations in prosthesis use among this population, short-term issues will not disqualify individuals from continued participation.

Procedures

Randomization

Stratified by study site, block randomization will be used to determine the order in which participants receive the locked and unlocked investigational prosthesis. Randomization will be completed and maintained through Research Electronic Data Capture (REDCap), a secure, Health Insurance Portability and Accountability Act–compliant web application for building and managing online surveys and databases.

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Study Procedures

Overview

This study uses a randomized double crossover clinical trial to evaluate a carbon fiber prosthetic foot with a frontal plane–adaptable linkage in two configurations: (1) unlocked, allowing frontal plane motion, and (2) locked, restricting frontal plane motion. When locked, the foot functions comparably to a conventional energy-storing-and-returning carbon fiber foot. A secondary aim is to compare the unlocked configuration to the participant's usual prosthetic foot, representing the current standard of care.

The study follows an A1-B1-B2-A2 crossover design:

- A conditions involve the use of the participant's usual prosthetic foot.
- B conditions involve the study foot with the linkage either locked or unlocked. The order of the B conditions is randomized using block randomization stratified by study site.

A custom-designed pin system is used to lock the linkage and prevent frontal plane motion when required.

A1 (Baseline)

At the initial visit, participants provide demographic information and complete baseline questionnaires and performance assessments. They are then trained on online data entry procedures and fitted with the study prosthesis (either locked or unlocked, depending on randomization) by a licensed prosthetist. Participants with bilateral amputations receive matched prostheses. Once fitted with the study prosthesis, participants start the 2-week accommodation period.

B1 (First Intervention Phase)

Participants use the first randomized configuration of the study foot for two weeks during routine community activities. Throughout this phase, they submit usage data, subjective performance ratings, and qualitative feedback via an online logbook. At the end of B1, standardized questionnaires and performance assessments are administered.

B2 (Second Intervention Phase)

The frontal plane linkage is adjusted to the alternate configuration (locked or unlocked), and participants continue regular use of the study prosthesis for another two weeks. Data collection procedures mirror those in B1. This phase concludes with standardized assessments and a semistructured interview to compare experiences with both foot configurations.

A2 (Postintervention Reflection)

Participants return to using their usual prosthetic foot for two weeks. This phase is intended to facilitate reflection on the differences between the study prosthesis (particularly in its unlocked configuration) and standard care. At the final visit, participants complete additional questionnaires and a concluding semistructured interview.

Outcome Measures

Physical Performance Measures

To determine if the META Arc novel prosthetic foot frontal plane motion improves mobility, participants will be assessed with the 10-meter Walk Test [5], Timed Up and Go (TUG) [5,6], the Three Times Figure-of-Eight Walk Test (3XF8W) [7], and the Four Square Step Test [8]. In addition to the typical timed outcome of these clinically based tests, additional spatiotemporal parameters will be measured with the Zeno electronic walkway (Figure 2). Spatiotemporal parameters of gait are believed to be functionally important and may be correlated with falls [9] and corroborate benefits of increased prosthetic ankle range of motion [10]. These secondary outcomes are hypothesis-generating for this population in relation to any changes in perceived function. These secondary outcomes will include the component TUG test [11] (Figure 3) and an instrumented four square test [12].

Figure 2. Component Timed Up and Go in the lab setting.

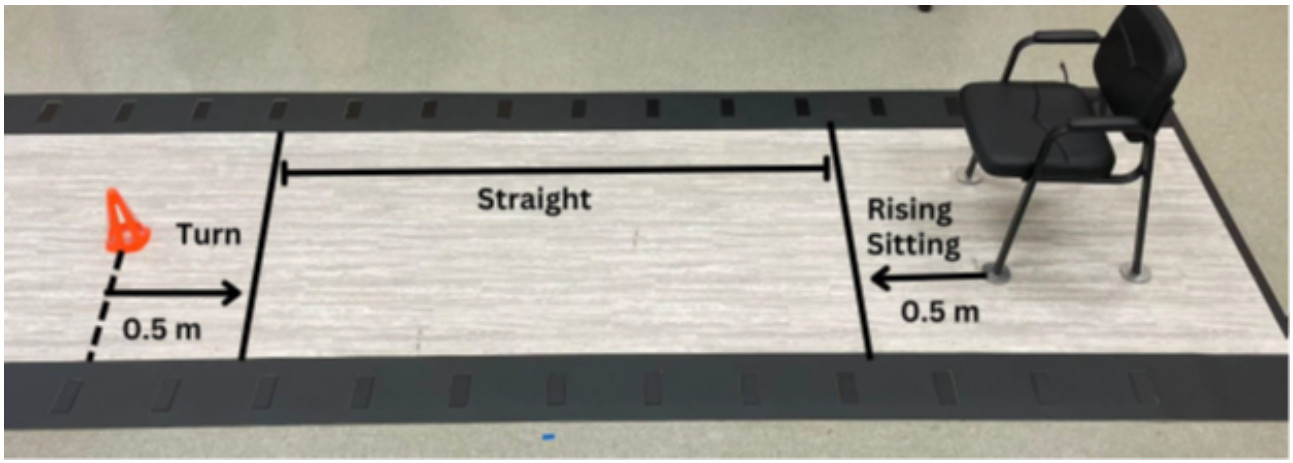

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Figure 3. Timed Up and Go footfall patterns from the ProtoKinectics Movement Analysis Software (Zenometrics LLC).

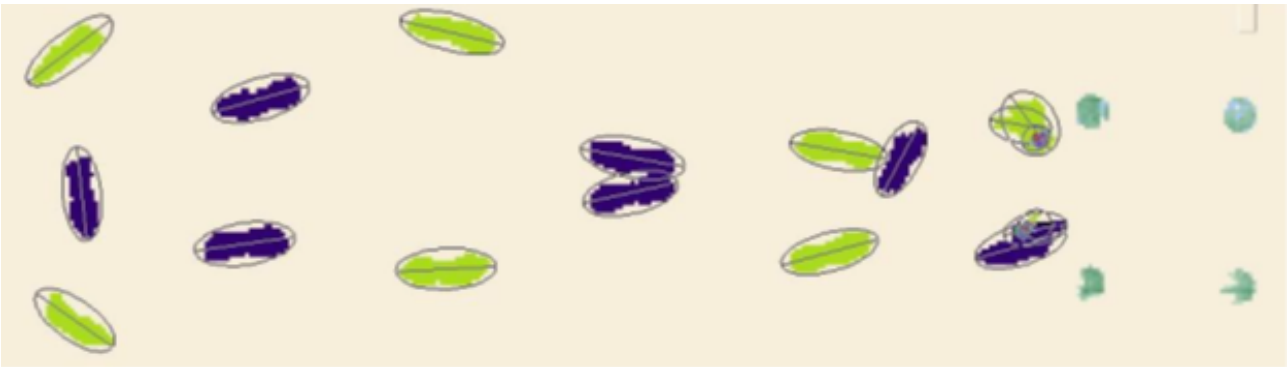

Participant Qualitative Measures

The participant-related outcome measures include a demographic questionnaire and the Prosthetic Limb Users Survey of Mobility (PLUS-M). The PLUS-M is a 12-item questionnaire developed at the University of Washington Center for Outcomes Research in Rehabilitation, which examines typical everyday mobility activities on a 5-point Likert scale. Participants were also asked to fill out a logbook every day during the study. They could complete the logbook on paper or via a digital reminder system sent via email by REDCap.

Semistructured interviews will be completed during research phases B2 (investigational foot) and A2 (usual foot). These interviews will clarify significant events documented in the logbooks. The focus of interviews will be on gathering information about the participants' experience using different prosthetic feet, with an emphasis on identifying activities that are facilitated or hindered by the functioning of the prosthetic foot.

Statistical Analysis

The primary analysis will compare the META Arc foot in locked versus unlocked configurations. Statisticians will remain blinded to condition labels, analyzing outcomes as Condition X versus Y, with knowledge of the order (X→Y or Y→X), but not which corresponds to locked or unlocked.

Descriptive statistics (means and SDs for continuous variables; counts and percentages for categorical variables) will be used to summarize participant characteristics, stratified by amputation group. All analyses will be performed separately for each group.

Primary Outcomes

Primary performance outcomes include the TUG, the 3XF8W, and the Four Square Step Test. Assumptions of normality and homogeneity will be tested. If met, a multivariate analysis of variance (MANOVA) will be used to evaluate the effect of foot configuration at α=.05. A permutational MANOVA will be used if assumptions are violated. If multivariate differences are significant, post hoc paired *t* tests (or Wilcoxon signed-rank tests if nonnormality is present) will be used to assess individual outcomes without correction for multiple comparisons. In order to help control the familywise type I error risk, pairwise comparisons of the primary outcomes will only occur if the multivariate difference comparison from the MANOVA is significant.

Satisfaction Measures

Satisfaction (PLUS-M) will be analyzed using paired *t* tests (or Wilcoxon tests) at α=.025 to maintain a familywise error rate of .05 across satisfaction outcomes.

Power

With n=30 for the above-knee and K2 groups, the study is powered (>80%) to detect a standardized effect size of 0.53. In the bilateral group (n=16), the power is greater than 50% for the same effect size. Preliminary data show larger effects (eg, 0.98 for the 3XF8W), supporting adequate power. Although underpowered to detect a meaningful difference in the bilateral group, 16 subjects is in line with other gait studies that have published data on 10 [13], 15 [14], or 19 [15] subjects with bilateral amputations, a challenging population to recruit and enroll. The study is also powered (81%) to detect a 75% preference for one configuration (vs 50% under the null) using a sign test with n=30. Although no minimal clinically important difference has been established, it is predicted that a standardized effect of at least 0.50 will correspond to an impactful improvement in participants' physical function.

Secondary Outcomes

Secondary outcomes (eg, 3XF8W step count, 10-meter walk, and PLUS-M subscales) will be analyzed using paired *t* tests or Wilcoxon tests at α=.05. Carryover effects will be assessed and, if present, accounted for in sensitivity analyses. As no multiple comparison corrections will be used for secondary analyses, resulting in a higher familywise type I error rate, all secondary results will be considered exploratory and hypothesis generating rather than confirmatory.

Logbook and Walkway Data

Logbook variables (eg, perceived support on challenging surfaces) will be compared using paired *t* tests or Wilcoxon tests. Fall counts will be analyzed with a sign test. Gait variables (eg, step width, double support time) from the Zeno walkway will be analyzed descriptively.

Qualitative Analysis

Interviews will be transcribed via Microsoft Teams or Zoom (Zoom Communications Inc) and analyzed using an inductive thematic approach. Open coding will identify themes, followed by focused coding to group codes into broader categories. Multiple codes may apply to individual responses. Qualitative analysis will follow current standards for rigor and reporting.

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Results

This study protocol, funded by the Department of Defense Orthotics and Prosthetics Outcome Program (OP220033), was approved by the University of Washington's IRB, the University of South Florida's IRB, and the US Army's Office of Human Research Oversight in March of 2023. As of September 2025, a total of 66 subjects have completed the study, including 17 with below-the-knee prostheses, 34 with above-the-knee prostheses, and 15 bilateral prosthesis users. The recruitment and data collection period of the study is expected to be completed by March 2027. Dissemination of results is expected to be completed by December 2027.

It is expected that the side-by-side adaptability of the investigational prosthetic foot will improve community functions such as gait over uneven ground and cross slopes, weight shift during two-legged standing, side-stepping, turning, and precise positioning of the foot at initial stance. Evidence from this study is intended to help clinicians weigh options regarding the use of a prosthetic foot with a passive adaptable ankle in the frontal plane for their patients.

Discussion

Expected Findings

It is expected that the side-to-side adaptability of the META Arc prosthetic foot will help people with above-knee amputations, people with bilateral amputations, and people with lower levels of mobility manage their everyday activities better. It is expected that the results of this study will demonstrate that people with lower levels of mobility can complete non–straight gait tasks such as turning better and will participate in more challenging activities every day.

It is hypothesized that participants with bilateral amputations will report greater satisfaction, mobility, and comfort when using a prosthetic foot with frontal plane adaptability (unlocked condition) than when wearing a prosthetic foot without frontal plane adaptability (locked), as measured by the PLUS-M. It is also expected that participants will demonstrate improved performance during the 3XF8W using a prosthetic foot with frontal plane adaptability compared to a foot without frontal plane adaptability.

A cutoff for the TUG in determining fall risk of ≥8.17 seconds has been previously determined by Sawers and Hafner [16]. However, it is not clear what part of the TUG is causing the increased risk. By completing component analysis, this study will determine what part of the TUG is causing times above this fall risk threshold.

A previous study of the META Arc foot showed that optimal stiffness for walking on flat surfaces is not the same as for turning [17]. Preliminary findings have shown that there are differences in stride length and swing time when comparing turning with the prosthetic foot on the inside or the outside of the turn. This may have some implications in the development of gait training and fall prevention strategies.

During logbook and interview analysis, it is expected that participants will report their perceived changes in person-specific mobility during activities that require frontal plane adaptability. The logbook and interviews will also provide feedback on the investigational foot regarding what aspects the participants did or did not like. This information will be very useful for making improvements for the next version if needed. Preliminary logbook analysis has shown that participants have engaged in walking on uneven terrain and participated in activities such as walking the dog, hiking, and shopping with benefits while wearing the investigational foot.

The study populations are particularly relevant to veterans and service members with amputations resulting from combat-related trauma or disease. Prosthesis users should be challenged to move sideways, move backward, and turn. Biomechanical components are often conflated with typical summary scores, which are typically based on the time it takes to complete a task. By conducting component analysis, mobility challenges, prosthetic design, and training can be addressed to better fit the needs of the users.

There are some limitations to the protocol. The participants have a 2-week accommodation period for each phase of the A1-B1-B2-A2 crossover design. There is no structured training program. Although the order of locked and unlocked use of the study foot will be varied between individuals, participants may continue to become more accustomed to using the foot into the next period, with the possibility of bias in the results.

Conclusion

The study will use a design that allows participants to get used to using two forms of the investigational foot: the locked and unlocked versions. This unique study design feature allows for comparing the investigational foot to a standardized control foot in a randomized order. Accommodation for participants in understudied groups may facilitate recruitment. Findings from this study are expected to generate new knowledge on the functional benefits of frontal plane adaptability, informing prosthetic design and clinical practice.

Funding

The study is funded by the Department of Defense Orthotics and Prosthetics Outcome Program (OP220033). The contents of this manuscript represent the opinions of the authors and not necessarily those of the US Department of Veterans Affairs, the US Department of Defense, the US Department of the Army, or any other health care or academic institution.

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Conflicts of Interest

MMW and JMC are salaried employees of WillowWood Global, which has produced the commercialized version of the investigational foot called the META Arc. MEM is the inventor of the linkage design, and the University of Washington has the following patents for the design: MEM US patent number 9,949,849 and MEM, MMW, Evandro M Ficanha, and JMC US patent number 11,076,970. MEM is an Associate Professor at the University of Washington and has not received anything of value from WillowWood Global.

Conflicts of interest are managed through the University of Washington's Office of Research and the institutional review board's policies and procedures, which are consistent with national guidelines and the training provided to principal investigators. Independent oversight of study procedures also includes the chair of the data and safety monitoring committee, who is external to the study.

Peer Review Report 1

Peer review report by the Fiscal Year 2022 Orthotics and Prosthetics Outcomes Research Program, Clinical Trial Review Committee, U.S. Army Medical Research and Development Command Congressionally Directed Medical Research Programs (Department of Defense, USA).

[PDF File, 116 KB - resprot_v14i1e84313_app1.pdf]

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Abbreviations

3XF8W: Three Times Figure-of-Eight Walk Test
IRB: institutional review board
LEA: lower extremity amputation
MANOVA: multivariate analysis of variance
MFCL: Medicare Functional Classification Level
PLUS-M: Prosthetic Limb Users Survey of Mobility
REDCap: Research Electronic Data Capture
TUG: Timed Up and Go

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Protocol

Multilevel Intervention to Support Tailored and Responsive HIV Pre-Exposure Prophylaxis Care in Rural North Carolina: Protocol for a Randomized Controlled Trial

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Abstract

Background: While access to pre-exposure prophylaxis (PrEP) is an important tool for reducing HIV incidence in the United States, disparities in uptake by race, sex, socioeconomic status, and geography persist. In 2018, the US South accounted for more than half of all new HIV diagnoses but only one-third of PrEP users. PrEP use in North Carolina (NC) similarly lags, with uptake being the lowest among young, sexual and gender minority populations, who account for nearly two-thirds of the state's incident infections. The PrEP-to-need ratio, a metric of PrEP equity that measures PrEP uptake relative to new HIV diagnoses, highlights disparities in PrEP uptake among specific demographic groups such as women and Black, Hispanic, and Southern people, indicating that these groups are underserved relative to their epidemic need. Despite behavioral risk overlap of incident sexually transmitted infections (STIs) and HIV, in NC, PrEP is only offered at a few primarily urban health department–affiliated STI clinics. The lack of robust health care infrastructure in these areas presents challenges for HIV prevention services.

Objective: This protocol describes a randomized controlled trial of a multilevel PrEP intervention recruiting from rural and periurban STI clinics.

Methods: This trial aims to enroll up to 336 participants and randomly assign them 1:1 to either the intervention or control group. The intervention consists of access to a digital health app, linkage to a remote PrEP navigator, and the option of referral to telehealth-based PrEP services. Persons randomly assigned to the control condition will receive an enhanced standard of care, including access to a limited version of the digital health app. All participants will be followed up on quarterly for at least 3 months. The primary outcome is the initiation of PrEP within 3 months of an index STI clinic visit; secondary outcomes evaluate PrEP care engagement and adherence, incident HIV and bacterial STI infections, PrEP stigma, and cost-effectiveness. Binary outcome analyses will estimate the proportion of participants achieving an event (eg, PrEP uptake) in each arm and a probability difference and the corresponding 95% CI to compare the intervention versus control arm at each time point. Continuous end points will use nonparametric Wilcoxon rank sum tests comparing the intervention and control groups.

Results: Enrollment opened on August 31, 2023, at 15 health departments in NC and subsequently expanded to 21 facilities in 20 counties by July 2024. Completion of the enrollment and data collection phases is expected by May 2025. Results will be published thereafter.

Conclusions: This study directly addresses multiple barriers to PrEP use in rural and periurban areas of the Southeastern United States and can inform policy and programming that seek to expand PrEP access and promote use in underserved communities.

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Trial Registration: ClinicalTrials.gov NCT05984030; https://clinicaltrials.gov/study/NCT05984030
International Registered Report Identifier (IRRID): DERR1-10.2196/68085

(JMIR Res Protoc 2025;14:e68085) doi:10.2196/68085

KEYWORDS

pre-exposure prophylaxis navigation; PrEP navigation; digital health app; mobile health; mHealth; telehealth; public health; sexually transmitted infection; HIV prevention; mobile phone

Introduction

Background

To meaningfully reduce HIV incidence, the United States needs integrated, scalable, and cost-effective prevention strategies. Despite the high efficacy of HIV pre-exposure prophylaxis (PrEP), only approximately one-third of PrEP-eligible people nationwide have received a prescription for PrEP; regional and racial disparities have been well characterized and mirror similar disparities in HIV care [1-5]. In 2021, the US South accounted for 52% of new HIV diagnoses but only 38% of PrEP users [6-8]. Coverage of those assigned male sex at birth with PrEP indications was reported by the Centers for Disease Control and Prevention (CDC) as 41% in 2022 but only 12.8% among Black and African American individuals [5]. In North Carolina (NC), the state-level PrEP coverage estimate is 30%, which belies the wide variability from urban to rural areas [9]. Indeed, in NC, where an estimated 1 in 112 residents will acquire HIV in their lifetime [10,11], PrEP use remains below the US average [6,11]. Similar to other states in the Southern region, PrEP uptake is lowest among young, sexual and gender minority men, who account for 76% of new HIV infections in NC [12]. Among the 15 NC counties with the highest rate of HIV diagnoses [13-23], 6 have nonmetropolitan designation, and 8 are small or medium metropolitan areas [12,24]. The lack of a robust health care infrastructure, including scarce HIV care providers, in these areas presents challenges for the sustainable expansion of HIV prevention services.

Similarly to most of the United States, NC's HIV statistics track alongside those of sexually transmitted infections (STIs) [13], with a disproportionately high burden among rural, young, sexual and gender minority men. Previous studies have demonstrated the potential role of STI clinics as effective PrEP linkage sites but have been limited to urban settings [14-23,25]. Despite behavioral risk overlap of incident bacterial STIs and HIV, PrEP is only offered at a few primarily urban health department–affiliated STI clinics in NC [26,27]. STI clinics are a logical entry point for PrEP services, but ineffective integration in rural STI clinics reflects heterogeneity in clinic structure and staffing—PrEP services require additional human resources and longitudinal engagement to be effective [28]. Leveraging STI clinics as an on-ramp to PrEP presents a compelling opportunity to capitalize on STI service encounters and address disparities in PrEP access for rural residents [15-17].

Multilevel impediments to PrEP scale-up in rural NC include provider shortages, intersectional stigmas, and lack of PrEP knowledge among providers and patients [29-33]. These challenges are compounded by poverty and incomplete insurance coverage of PrEP and PrEP services [34,35]. Building on collaborations with state and local partners, we will implement a multilevel intervention in partnership with rural county health departments and health care organizations that links PrEP and STI services to address PrEP use barriers while working within clinic operational limits and competing demands on physical and human resources. This intervention combines multiple evidence-based interventions, including PrEP navigation services [36-38], access to a digital health platform (HealthMpowerment) [39-42] that connects users to tailored social and informational support for PrEP initiation and persistence [43,44], and referral to telehealth PrEP services [45-48].

Research Aims

Our objective is to determine the effectiveness and cost-effectiveness of the proposed PrEP linkage strategy in 2 aims. Our primary effectiveness outcome is PrEP uptake within 3 months of an STI clinic visit, defined as confirmed receipt of PrEP prescription or evidence of detectable tenofovir diphosphate in the blood, evaluated through a randomized controlled trial (RCT). Secondary outcomes evaluate PrEP uptake within 6 months of an STI clinic visit, 3- and 6-month PrEP care engagement and adherence, incident HIV or STI infections, and PrEP stigma.

We will examine implementation outcomes as exploratory outcomes, capturing process indicators, including intervention costs, fidelity, and acceptability, to inform future refinement. We will use decision analytic modeling to determine the cost-effectiveness of the proposed intervention over a range of assumptions and inputs, as well as developing a budget impact analysis. Specifically, intervention effectiveness and prospectively collected cost data will be used to model cost per new PrEP initiation. Budget impact analyses will identify drivers of cost, informing strategy refinement for program staffing and scale-up.

This project is supported via a milestone-based funding mechanism, wherein if predefined effectiveness, implementation, and development milestones are met within the initial phase, we will pursue a second phase, in which we will use intervention mapping to refine the proposed strategy and expand implementation in a nonrandomized fashion with updated cost-effectiveness modeling. The second phase is not described further in this paper as the development and finalization of that protocol are dependent on this trial's outcomes.

This trial has been registered with ClinicalTrials.gov (NCT05984030), which includes reporting of all relevant items

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from the World Health Organization Trial Registration Data Set.

Methods

Protocol Adaptations

We present our methods according to 2 participant recruitment stages: stage I, which focused exclusively on young, sexual and gender minority men seeking STI services from health department–affiliated STI clinics, and stage II, which reflects an amended protocol with modifications made in response to participant enrollment challenges and feedback from collaborating sites. Changes in stage II of protocol implementation include (1) expanding collaborating sites beyond the initially identified 15 health department–affiliated STI clinics, (2) offering a US $5 incentive for completing the brief screening questionnaire, (3) shortening the follow-up period to 3 months for participants enrolled in the final quarter of the study recruitment period, and (4) expanding eligibility criteria to include women assigned female at birth.

Expanding to women more closely aligns with 2021 CDC recommendations, including discussing PrEP with all persons with an STI in the previous 6 months, and reflects the evolving focus on PrEP for women put forth by the CDC, particularly racial minority women in the Southeastern United States. Among new HIV cases in women in the Southern region of the United States, Black women account for 67% of new HIV infections and 72% of new diagnoses among women reporting heterosexual sex [49]. Increasing PrEP use among cisgender women has the potential to significantly impact the spread of HIV in rural and periurban NC and contributes to a broader public health strategy aimed at reducing new HIV infections across various demographics. To explore the potential for our intervention to expand PrEP care to a broader population in NC, we conducted a change in scope that adapted our eligibility criteria to encompass women.

Study Design (Stage 1)

This RCT of a multilevel PrEP intervention strategy will open with recruitment of those assigned male sex at birth seeking sexual health services from rural and periurban NC STI clinics (Figure 1). Participants are randomly assigned 1:1 to the intervention or control condition. All participants regardless of study arm complete study measures and activities at enrollment and the 3- and 6-month follow-up time points, with a subset of participants enrolled in the first 6 months of recruitment also completing a 12-month follow-up assessment (Table 1). The timing of participant follow-up activities mimics the CDC-recommended frequency of testing, which includes screening for bacterial STIs every 3 months among men who have sex with men or among patients with ongoing risk behaviors [50,51]. Therefore, HIV and STI testing will be completed as part of patients' routine care at established STI clinics (not administered through this study). The HealthMpowerment app and study staff will help facilitate participants' return to the STI clinics for HIV and STI testing by providing in-app appointment reminders, SMS text messages, and phone calls as needed. Quarterly surveys will assess participants' adherence to CDC-recommended testing frequency.

Cost data and implementation outcomes are collected throughout study implementation examining organization-level determinants of success via surveys and in-depth interviews with participants, clinic staff, health care providers, and other key stakeholders for PrEP expansion.

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Figure 1. Study schema—aims 1 and 2, years 1 to 3. PrEP: pre-exposure prophylaxis.

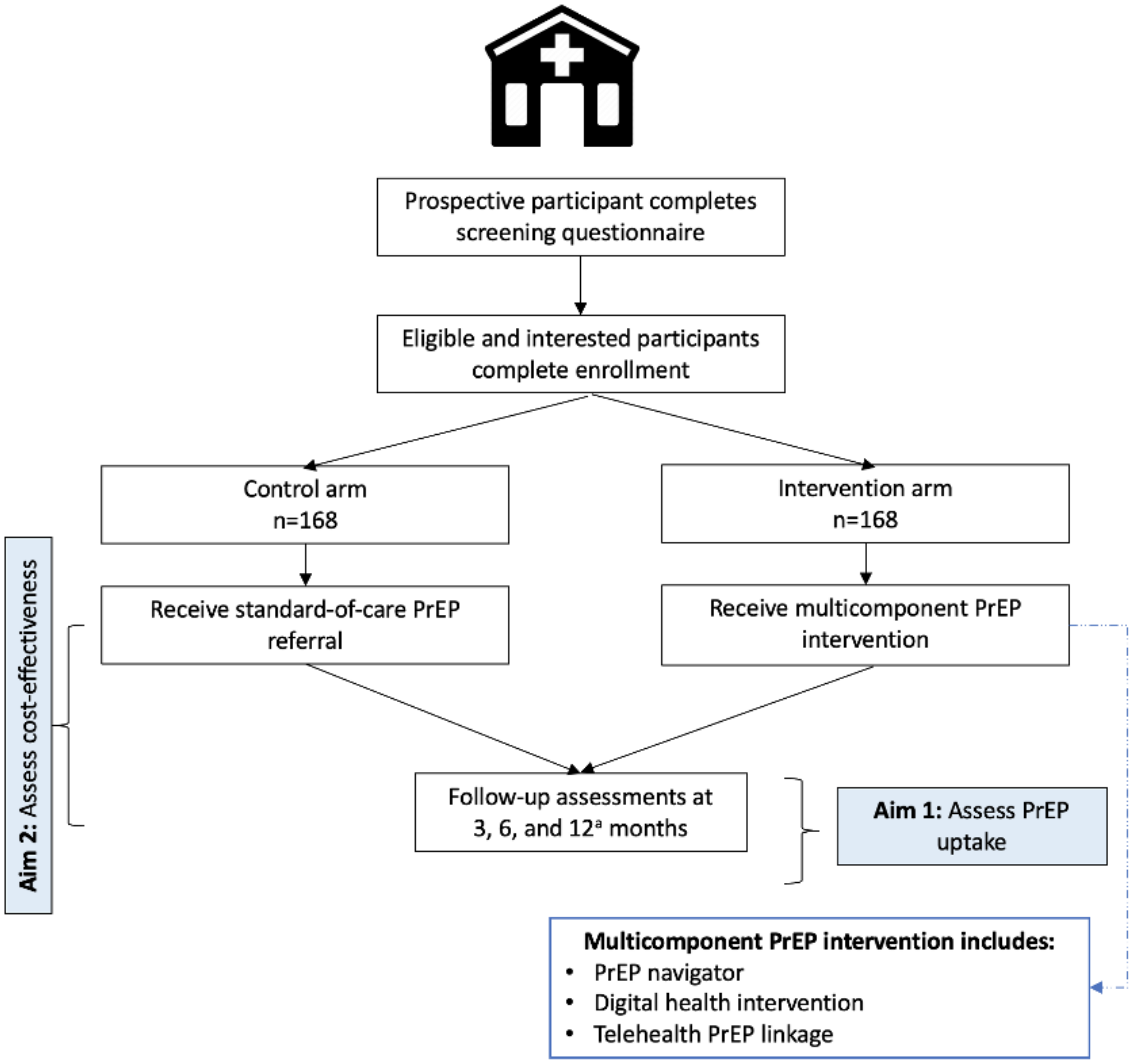

Table 1. Participant assessment timeline.

	Screening	Baseline	3-month follow-up	6-month follow-up	12-month follow-up
Screening questionnaire	✓				
Informed consent		✓			
HIPAA[a] record release authorization		✓			
App onboarding		✓			
Survey assessment (CASI[b])		✓	✓[c]	✓	✓[d]
DBS[e]			✓[c]	✓	
Qualitative exit interview (optional)			✓[f]	✓[f]	

[a]HIPAA: Health Insurance Portability and Accountability Act.
[b]CASI: computer-assisted self-interview.
[c]Participants enrolled in approximately the final quarter of study enrollment will only be followed up on for 3 months.
[d]Only applies to participants who enroll during the first 6 months of study recruitment.
[e]DBS: dried blood spot.
[f]A subset of up to 50 participants will complete an in-depth interview following their 3- or 6-month study visit.

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Study Design (Stage 2)

The updated study design incorporates a shortened follow-up period to extend the enrollment window, allowing for a greater number of participants to contribute to the primary outcome of PrEP uptake assessed at 3 months. Randomization and intervention procedures remain unchanged, and study measure assessments are completed at baseline and 3 months (Table 1).

Eligibility

For stage I, RCT-eligible participants must (1) be assigned male sex at birth, (2) report sexual activity with a male individual in the previous 12 months, (3) report recent HIV testing (within the previous 90 days) and not be known to be HIV positive at screening or enrollment via self-report, (4) be aged 18 to 39 years, (5) have daily smartphone access, (6) be English speaking, and (7) deny recent PrEP use (defined as not having taken oral PrEP or received injectable PrEP within the previous 90 days).

For stage II, the eligibility criteria were updated to reflect the eligibility of persons regardless of sex assigned at birth. All other eligibility criteria from stage I remain unchanged.

We will also conduct qualitative interviews with up to 50 clinic staff members, providers, and other relevant stakeholders for PrEP provision or relevant to the proposed intervention. Interviewees will be purposively sampled to ensure a diversity of clinic roles and responsibilities relevant to STI and sexual health services and referrals, diversity in leadership level, and representation across all participating clinics.

STI Clinic Selection

We initially identified 15 health department–affiliated STI clinics in relatively high–HIV burden, rural, or periurban counties across NC. Counties were selected in coordination with partners in the NC Department of Health and Human Services using county-level 2019 to 2021 HIV and STI data (reported to the State Laboratory of Public Health). Specifically, we examined HIV and STI testing volume and test positivity rates by reported race or ethnicity among men aged <40 years, prioritizing counties with higher rates of HIV and non-HIV STIs ranked by county without a predefined cutoff. We also reviewed the National Center for Health Statistics urban-rural classification scheme focusing on rural counties, as well as those designated as small (<250,000) or medium (<1 million) metropolitan areas [45-47]. We refer to all locations where STI services are offered as *clinics* or *STI clinics*; however, these locations may also include extensions of clinic services, such as mobile testing or service delivery within other outreach events.

Clinics were contacted with information about the study and an invitation to participate. The study team met with clinics who responded; clinics that decided to participate provided signed letters of support indicating commitment to collaborate and outlining expected roles and responsibilities. At the time of study launch, none of the initial 15 participating STI clinics offered PrEP navigation services or had “in-house” providers prescribing PrEP. Only 7% (1/15) of the participating clinics offered referral to a colocated primary care clinic that could prescribe PrEP. Of the remaining 14 initial collaborating clinics that did not offer in-house PrEP services, a minority provided patients with passive referral to services in the community (eg, the clinic shared the name or names of private practice providers that may offer PrEP services). Starting in March 2024, a total of 6 more clinics were added as collaborating sites under protocol version 3.0. None of these clinics offered PrEP navigation services or had “in-house” providers prescribing PrEP.

Sample Size and Statistical Power

On the basis of historical clinic volumes and patient demographics, we expect that >7400 patients will present for care across the sites during the study enrollment period, with 20% to 35% being study eligible. Power calculations were based on the study’s primary outcome (PrEP uptake within 3 months of STI clinic visits). PrEP use among the target population has not been estimated previously as there is currently little to no availability of PrEP in rural NC settings. Assuming that 2.5% of eligible patients start PrEP within 3 months in the control arm, we calculated statistical power to detect a range of small to large effect sizes from 5% to 15% increases in PrEP uptake under a range of possible sample sizes and assuming 10% missing data or attrition at 3 months. At a total sample size of 336 given our design and assumptions, we will have >88% statistical power to detect medium (10%) and large (15%) effect sizes and 80% statistical power to detect a moderate (7.5%) effect size with a 5% type-I error rate (SAS; version 9.4 [SAS Institute]).

Randomization and Enrollment

After providing written informed consent electronically and completing baseline surveys, participants will be randomly assigned 1:1 to the control or intervention condition at enrollment using blocked randomization stratified by county, with randomly ordered blocks of sizes 4 and 6 (Figure 2). There will be no masking to assigned arms. Randomization assignments will be automated through the study database. Arm assignment is then disclosed to participants by study staff during study onboarding. The onboarding session includes orientation to study app features for all participants and, for those randomly assigned to the intervention arm, an introduction to the remote PrEP navigator.

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Figure 2. Participant enrollment flow. (Note: Dependent on their enrollment date, only a subset of participants will be asked to complete 6 and 12-month study activities.) BL: baseline; HIPAA: Health Insurance Portability and Accountability Act; HMP: HealthMpowerment; PrEP: pre-exposure prophylaxis; REDCap: Research Electronic Data Capture.

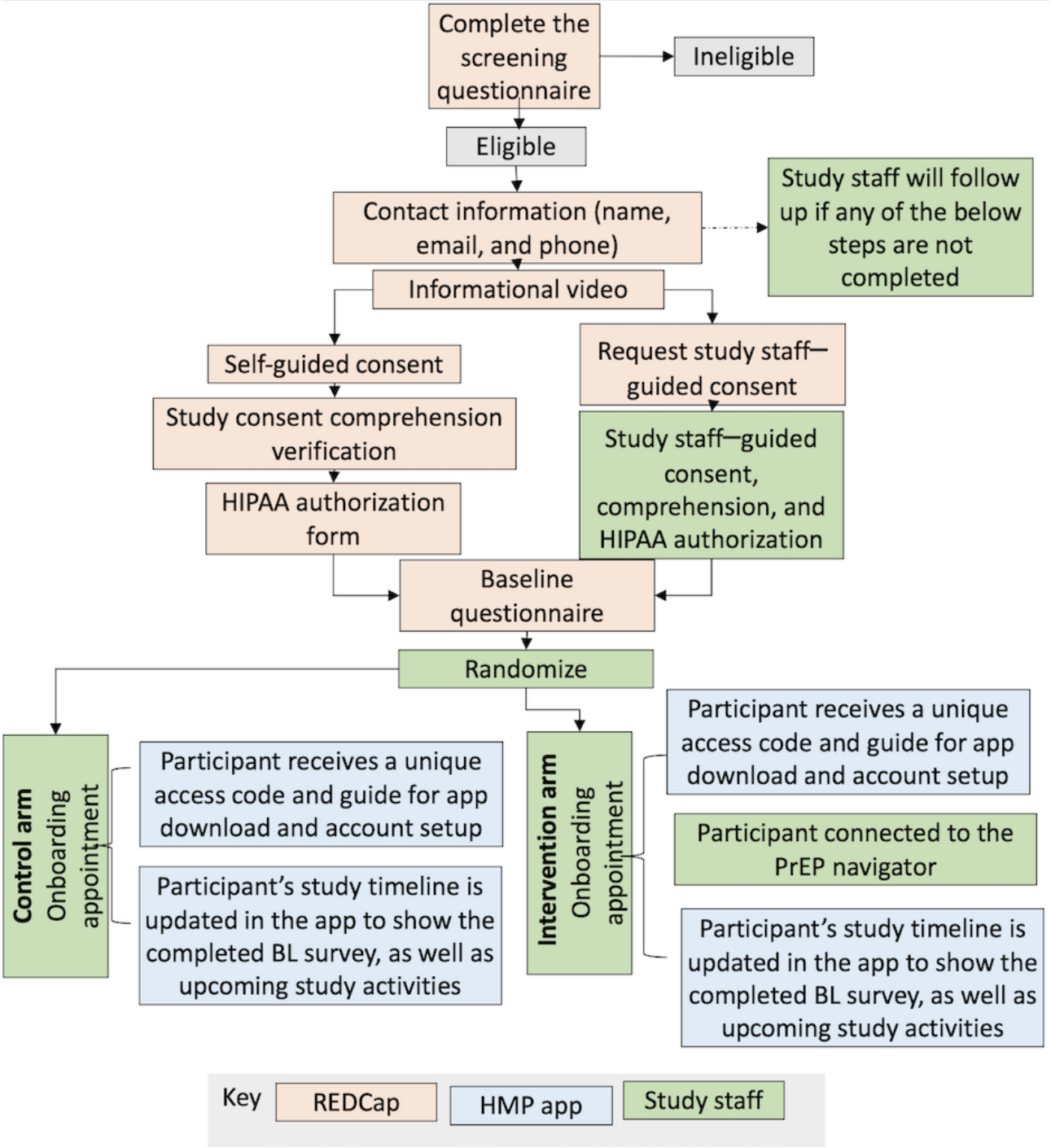

Intervention Arm

Overview

Participants randomly assigned to the intervention arm will receive standard PrEP referral services identical to those available to persons in the control condition (see the following sections), as well as a multilevel intervention with 3 components, all of which they engage with remotely: a PrEP navigator to address potential barriers to PrEP uptake and use and facilitate linkage to PrEP services if interested, referral to telehealth PrEP services as an option for linking to PrEP care, and a Health Insurance Portability and Accountability Act (HIPAA)–compliant web-based digital health intervention app (see additional information regarding app privacy in the *Ethical Considerations* and *Data Quality and Monitoring* sections; Figure 3A).

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Figure 3. Screenshots from the HealthMpowerment app—(A) enhanced version of the HealthMpowerment app for the intervention condition and (B) limited version of the HealthMpowerment app for the control condition. PEP: postexposure prophylaxis; PrEP: pre-exposure prophylaxis.

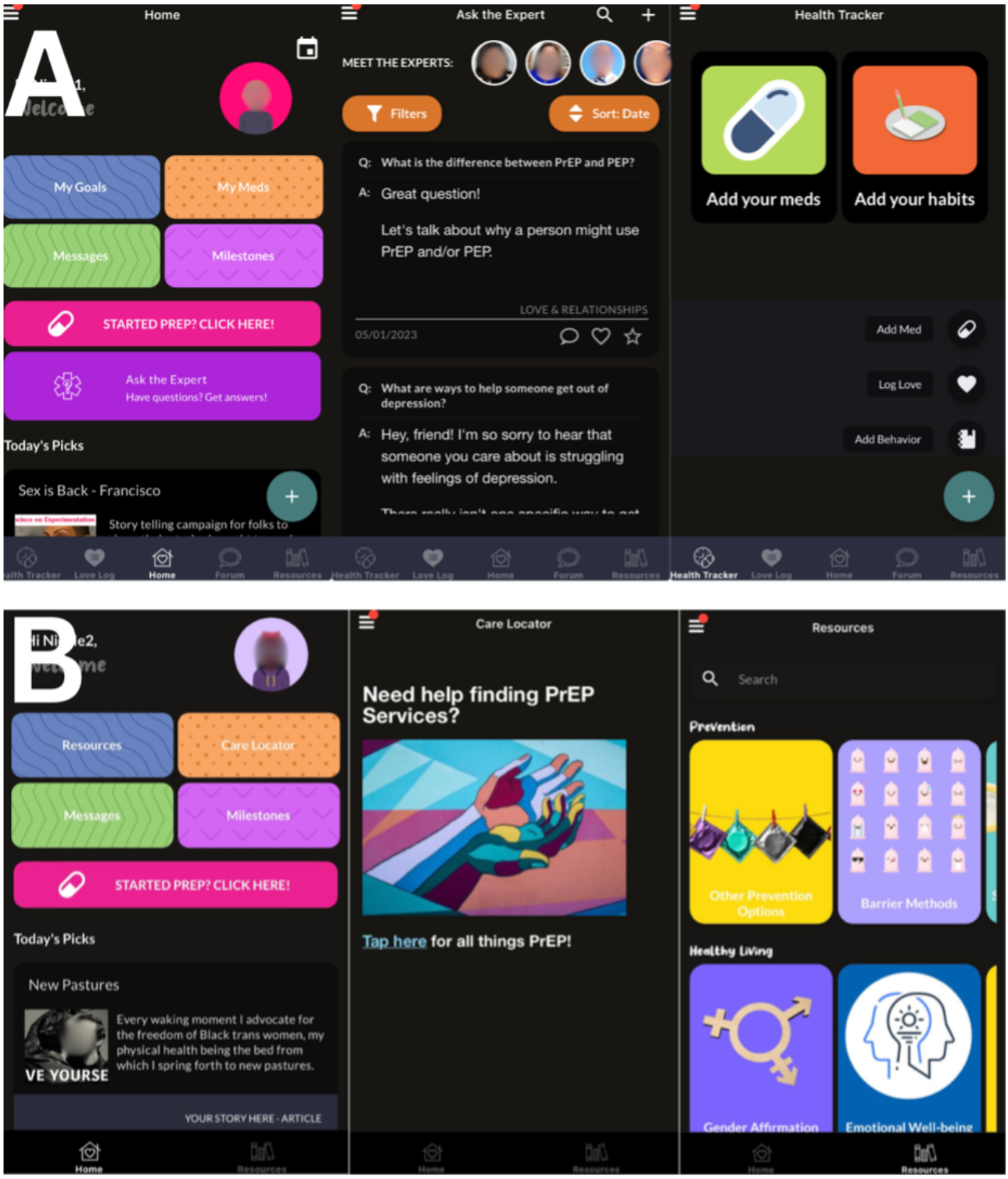

PrEP Navigation

PrEP navigators will connect with participants immediately following app onboarding. Navigator services are available to participants for the first 6 months of participation (active intervention period) and include assessing participant awareness of an interest in PrEP, referral to PrEP care, helping participants engage in PrEP care (including assisting with appointment scheduling, reminders, and other provider access issues), and assisting with completing necessary paperwork for insurance and application for drug assistance programs as needed. PrEP navigators undergo study- and navigator-specific trainings.

PrEP navigators were recruited through relevant recruitment channels and listserves commonly used by professionals in the HIV prevention sector. Preference was given to applicants with experience in sexual health; lesbian, gay, bisexual, transgender, and queer health; health insurance; digital health or telehealth; and patient navigation. In addition, candidates with experience

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collaborating with regulatory bodies and research study teams and in academic-community partnership settings were preferred.

PrEP Linkage

PrEP navigators can link interested participants to preexisting local or telehealth PrEP services, although neither are provided, financed, or staffed by the study. Participants referred to telehealth services will receive these PrEP services via the technology platform or service that the provider typically uses. PrEP clinical eligibility, visit frequency, monitoring of laboratory tests, and all other PrEP management will be at the discretion of the PrEP provider. Before enrollment, all participants will sign a HIPAA authorization form permitting study staff to access their medical records pertaining to PrEP care delivery.

Digital Health Intervention App

HealthMpowerment is an HIV status–neutral, theory-informed, HIPAA-compliant digital health intervention that supports sexual health and risk reduction among young, sexual and gender minority men [52-54]. HealthMpowerment is guided by the Integrated Behavior Model [55], facilitating examination of the individual and structural determinants of health (eg, stigma and discrimination, health literacy, and poverty) and psychological distress (eg, depression, anxiety, and loneliness) that hinder adoption of HIV-preventive behaviors. The app provides a range of resources addressing these social determinants for persons at all stages of readiness to initiate PrEP, as well as ongoing support and resources for those who do initiate PrEP. All information on the app is available to all participants. The app also recommends specific content to individuals based on their voluntary responses to questions and activities within the app. As part of PrEP-monitoring features, participants can indicate how PrEP was prescribed (ie, daily oral, event-driven oral, or injectable), as well as indicate the dates on which PrEP was taken or, in the case of injectable PrEP, received. HealthMpowerment was first found effective in a statewide RCT [42,53] in NC, which found that greater HealthMpowerment engagement was significantly associated with fewer episodes of condomless anal sex; stigma reduction; and greater provider communication, HIV status disclosure to partners, and HIV care outcomes (eg, engagement in care and adherence) [53,56].

The content included in this version of the app was selected from a broader content library developed and used in previous studies involving similar populations. The app's design, interface, and features were developed and user tested by a community advisory board comprising racially and ethnically diverse, young, sexual and gender minority groups. In addition, the app's content is dynamic, with updates made based on user engagement analytics and ongoing developments in the field.

Control Arm

Persons randomly assigned to the control arm will receive an enhanced standard of care, pairing existing referral systems with access to the core educational resources of the HealthMpowerment app. For this study, access to publicly available PrEP locator resources and tailored information on PrEP and HIV prevention will be accessible from within the app (Figure 3B). This comparator condition of an enhanced standard of care control was selected to balance the dual goals of establishing effectiveness and ethical obligations to provide all participants with information regarding available PrEP services and basic PrEP education.

Study Procedures

All study staff will be trained in and follow a detailed study-specific procedure manual and topic-specific standard operating procedures (SOPs) that were informed by the Division of AIDS Site Clinical Operations and Research Essentials Manual [57].

Recruitment

The protocol uses clinic-based recruitment at participating STI clinics. Posters, 1-page flyers, and palm cards with scannable QR codes will be posted throughout the clinic waiting areas, on bulletin boards, and in patient rooms. The study will also be promoted through word of mouth via health professionals, administrative staff, and community outreach personnel associated with each site. Clinic and study staff may also bring recruitment materials to community-based events they attend on behalf of the clinic (eg, health fairs and blood drives) with information about the study.

Scannable QR codes will lead to a web-based screener, which allows potential participants to learn about the study and their eligibility discretely. As of July 17, 2024, prospective participants that complete the screening questionnaire are offered a US $5 e–gift card. Individuals who are not eligible based on screening criteria, duplicate entries, or choosing not to proceed will be thanked and rerouted to a public web page. Prospective participants will be asked to grant permission for study staff to contact them and to provide preferred contact information before they are routed to a brief video describing the research basics and specific study objectives.

Participant Management and Retention

We will collect multiple forms of participant contact information and study-related communication preferences (eg, email and phone or SMS text messaging) as part of study enrollment. The HealthMpowerment app supports participant retention through a timeline that displays upcoming study activities and a 2-way secure messaging feature for participants and study staff. All participants will receive compensation throughout the course of their participation.

Data Sources and Collection Methods

Data sources and collection methods are described in this section and summarized in Table 2. The study will use electronic data capture tools (REDCap [Research Electronic Data Capture; Vanderbilt University]) hosted at Florida State University for all primary data collection and participant management purposes [58,59]. REDCap is a secure, web-based software platform designed to support data capture, audit, monitoring, and export for research studies. Study screeners, assessments, and in-depth interviews will all be completed remotely via secure HIPAA-compliant platforms for survey administration and phone and videoconferencing.

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Table 2. Data sources and collection methods.

Data source and collection method	Primary effectiveness	Cost-effectiveness
CASI[a] surveys—in the clinic or web-based	✓	
Whole blood collection samples—self-collected blood sample	✓	
Qualitative notes and transcripts—interviews and intervention mapping	✓	✓
Digital health intervention paradata—entered into the app by participants, study staff, and PrEP[b] navigators	✓	
Clinic observations—project receipts and personnel salary		✓
Time-and-motion logs		✓
HIV and STI[c] test results—electronic health record and data or Lapcorp or Quest or CELR[d] or participant-provided records	✓	
PrEP care history—electronic health record data or participant-provided records	✓	✓

[a]CASI: computer-assisted self-interview.

[b]PrEP: pre-exposure prophylaxis.

[c]STI: sexually transmitted infection.

[d]CELR: Clinical and Environmental Laboratory Results.

HIV and STI Result Abstraction From Electronic Health Records

Participants will be encouraged to receive HIV and STI testing at intervals consistent with CDC recommendations (quarterly testing for men who have sex with men and annual testing for sexually active women) [50]. HIV and STI testing will be completed as part of participants' routine care at the STI clinic site, not administered through the study or by study staff. Collaborating clinics or PrEP providers will be responsible for specimen collection, processing, and handling of indicated treatment and treatment referral as appropriate. Proof of a nonreactive (negative) HIV assay is required for study enrollment, but no prospective testing is required, nor are participants incentivized to complete these tests. Participants who receive an HIV diagnosis while enrolled in the study will be study stopped. Individuals may choose to keep the digital health app installed on their phone. All test results will be extracted from clinical records. Clinics will either provide study staff with direct access to the participant's HIV and STI results or upload the results to a secure survey via REDCap.

Specimen Collection

Dried blood spot (DBS) specimens will be used to detect the presence of PrEP metabolites in participants' blood and will be administered at months 3 and 6 depending on participants' enrollment date. Participants can choose to have a DBS kit mailed directly to them (at an address of their choice) or opt for the kit to be mailed to their local health department and pick it up in person. Following an illustrated step-by-step instruction card, participants use a single-use lancet to collect blood onto specialized paper cards, and then they return the sample using a preaddressed, prepaid shipping envelope. DBS specimens will be tested for the presence and levels of tenofovir diphosphate and emtricitabine triphosphate to inform PrEP exposure and prevention-effective use as correlated with survey and available medical record data regarding PrEP medication and intended dosing strategy [60,61].

Study Assessments

Computer-assisted self-interview survey assessments from REDCap will be sent to participants via the HealthMpowerment app at baseline and 3 and 6 months, with a 12-month brief assessment for a subset of participants. Participants enrolled in approximately the final quarter of enrollment will only complete the 3-month survey, reflecting the shorter follow-up period for this group. Survey domains include sociodemographic data, sexual behaviors, PrEP use, self-reported STI and HIV testing outcomes, and perceived or experienced PrEP stigma.

Clinic Assessments

Understanding the organizational environment from which participants will be recruited is crucial to interpret outcomes and potential for scale-up and sustainability. We will conduct assessments of all participating clinics to evaluate staffing, patient volume, hours of operation, and available services. These assessments will be conducted using a combination of in-person and remote interactions. We will also ask relevant stakeholders about intervention acceptability and organizational factors that may influence PrEP provision and integration of services, including organizational readiness for change, support climate, and intervention value fit [62-64]. We will also monitor relevant policy changes, such as those pertaining to insurance, PrEP coverage, or recommendations for use that may serve as external influences relevant to our observed outcomes.

Qualitative In-Depth Interviews

Up to 50 participants will complete an in-depth interview following their 3- or 6-month assessment contextualizing their experience with study participation, perceived accessibility of PrEP before and after study enrollment, evaluation of the acceptability of this enhanced PrEP access model (if randomly assigned to the intervention arm), unmet PrEP-related health service needs and barriers, experience initiating PrEP (if relevant), experience using the study-related intervention components (app, PrEP navigator, and telehealth for PrEP), and other topics as raised by participants (Multimedia Appendix 1).

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Participant interviews will be conducted remotely via phone or videoconference platform. Participants will be purposively sampled to ensure diversity in areas such as PrEP initiation status, recruitment clinic, age, and race.

In addition, we will engage up to 50 other stakeholders, including health department–affiliated clinic staff, health care providers, and other stakeholders relevant for PrEP services, for in-depth interviews. Interview topics may include experiences and challenges with being part of a participating clinic for this study, perceived accessibility of PrEP for the target patient population before and after study implementation, perceived strengths and drawbacks of this PrEP access model, suggested changes to this strategy, and unmet PrEP-related health service needs and barriers among the participant population. Stakeholder interviews will be conducted in person or remotely via phone or videoconference platform after consent by trained research staff using a semistructured interview guide (Multimedia Appendix 2). Each interview will be digitally recorded and transcribed for analysis.

Cost-Effectiveness

We will build a decision model to estimate the budget impact and compare the cost-effectiveness and population outcomes of our multilevel PrEP intervention to those of the standard of care.

Specifically, costs will be collected prospectively in 2 ways: microcosting and time-and-motion logs. Microcosting involves "direct enumeration" for consumed inputs [65], an ingredient-based approach. We will further quantify resources associated with the development and implementation of our intervention (eg, costs associated with the adaptation of the HealthMpowerment app and personnel training). Following established methods, we will measure non–research-related costs associated with the intervention and control arms to estimate the incremental cost per additional person starting PrEP. Cost data will be available through contractual information with developers, clinic and project receipts, and NC Department of Health and Human Services supply chain partners. We will also extract data from project expenditure and management records, including purchase logs and human resource records. Time-and-motion assessments record how the involved parties (eg, navigators and providers) divide time among PrEP-related tasks, reliably apportioning effort relevant to implementing the intervention.

Outcomes and Data Analysis

Our primary outcome (PrEP uptake) is assessed through self-reported PrEP use (oral or injection) on a follow-up survey or on the app and verified by at least one of the following: (1) an uploaded photo or image demonstrating a PrEP prescription, (2) any indication of the presence of tenofovir diphosphate or emtricitabine triphosphate in DBS, or (3) staff-abstracted electronic medical record of PrEP prescription issued or prescriber notation of PrEP being initiated (Multimedia Appendix 3).

Outcome Analysis

Analyses will be conducted for all primary and secondary outcomes using the following general procedures. Basic descriptive statistics will be calculated. Frequency tables will be presented for the categorical variables, and means, SDs, and percentiles (25th, 50th, and 75th) will be provided for the continuous variables. For each binary outcome, we will estimate the probability of achieving the event (eg, PrEP uptake) in each arm and a probability difference and the corresponding 95% CI to compare the intervention versus control arms at each time point (3-, 6-, and 12-month follow-ups). For continuous end points, we will use a nonparametric Wilcoxon rank sum test to compare the intervention and control arms. For count data variables (eg, number of unprotected sex acts), we will use small analysis methods for count data (eg, exact Poisson regression).

To address missing data, we will review the frequency of missing and nonmissing values for all variables at baseline and the 3-, 6-, and 12-month follow-ups. We will conduct missing value analyses to determine whether persons with missing values are systematically different from those without missing values and whether the probability of having missing values differs by arm. If this assessment of the frequency and imbalance of missing data suggests that bias may be introduced, we will use inverse probability of observation weights or multiple imputation to address the missing data. If there is chance imbalance in the measured baseline covariates between those randomly assigned to the intervention and control groups, we will conduct sensitivity analyses applying stabilized inverse probability treatment weights.

The primary outcome of PrEP uptake is measured at the 3-month follow-up. The effectiveness of the intervention will be estimated as the difference in probability of starting PrEP within 3 months of an index STI clinic visit comparing patients randomly assigned to the intervention and control groups.

Secondary effectiveness outcomes include PrEP uptake at 6 months, PrEP care engagement, PrEP use, PrEP adherence [66-68], incident STIs, incident HIV, and PrEP stigma [69,70] (all at both 3 and 6 months). All analyses will follow the specifications described previously.

PrEP adherence at 3 and 6 months will be assessed using PrEP metabolite levels and self-reported 30-day adherence as 2 separate outcomes. We will use standard-of-care quarterly STI and HIV testing results to examine differential rates of incident STIs adjusting for testing frequency given potential increased testing frequency among PrEP initiators [71,72].

Exploratory outcomes will report the effectiveness of the intervention (defined previously) as measured using PrEP uptake at the 3-month follow-up stratified by sex assigned at birth.

We will also examine additional exploratory implementation outcomes, including process indicators to inform intervention implementation, optimization, and scale-up. We will measure acceptability of the implementation strategies for providers and clinic directors, feasibility of the intervention, and intervention satisfaction among patients and providers using validated scales [73-76] for outcome assessment, as well as measuring cost-effectiveness.

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To measure the acceptability [73,77,78] of the intervention and explore clinic-level influences on implementation feasibility at each clinic, we will interview providers and clinic directors. We will assess factors such as provider burden of intervention, adequacy and timing of training, supervision or support structure, organizational readiness for change (quantitative scale and qualitative interviews) [62], management support (qualitative interviews), implementation climate (quantitative scale and qualitative interviews) [63], and intervention value fit (quantitative scale and qualitative interviews) [64]. We will use facility audit data, including county population, patient panel size and demographics, number and training level of clinic staff, staff-to-patient ratio, daily patient volume, opening hours, and local access to PrEP to contextualize determinants.

Feasibility measures will assess patient engagement with the intervention, including uptake of elements (ie, linkage to insurance if not durably insured at enrollment, use of telehealth PrEP, and interactions with PrEP navigators). We will examine the percentage of enrolled participants in the intervention arm who are engaged by the PrEP navigator within 2 weeks of enrollment. We will also examine app-specific engagement, including successful app installation, account creation and log-in, total number of log-ins, and time spent on the app.

Measurement of patient satisfaction [74,79,80] with the intervention includes qualitative (in-depth interview data) and quantitative (eg, System Usability Scale [75]) assessments. We will conduct interviews with a subset of patients regarding their experiences with the intervention. This sample will include a mix of persons with variable HealthMpowerment engagement and PrEP uptake. We will ask about satisfaction with clinician interactions as part of STI or PrEP care. As a quantitative assessment, all participants will complete a satisfaction scale at quarterly follow-up visits [81].

Analysis of implementation outcome measures will include qualitative analysis. Transcripts from participants and providers or clinic staff members will be analyzed separately and reviewed for quality. Interview transcripts will be thematically analyzed following a combination of deductive and inductive analytic approaches. An initial codebook will be developed based on a priori concepts driven by the theoretical underpinnings used to develop the interview guide. All textual data will then be read thoroughly to summarize first impressions. Emerging themes will be incorporated into the codebook. Preexisting codes may be modified based on interview transcripts. Transcripts will be coded iteratively using qualitative analysis software. In total, 2 researchers will code the interviews separately to assess intercoder reliability. The codebook will be revised and updated. Analysis of the coded data will include investigation of relationships between codes, coding matrices, and mapping of codes and themes. Data from qualitative interviews will be triangulated with the quantitative data to gain a more complete understanding of the factors underlying implementation. For example, if our survey data show that clinics with lower fidelity tended to score low on the implementation climate scale, we will examine our qualitative data for indications of what aspects of the leadership or climate may have contributed.

Our primary cost-effectiveness outcome is the incremental cost per additional person started on PrEP (the primary study outcome) in the intervention versus control condition.

We will conduct a budget impact analysis of the cost in US dollars of the intervention overall, providing decision makers with estimates of the financial feasibility of the intervention [82,83].

All models will include sensitivity analyses to examine the potential impact of varying cost and effectiveness assumptions, accounting for parameter uncertainty [84] and capturing input uncertainty (eg, PrEP adherence and intervention cost and effectiveness). The upper and lower bounds will be based on trial data, literature, or expert opinion. The results represent an average across simulated model runs with an estimated uncertainty range.

We will report incremental cost-effectiveness ratios. The analyses will take the perspective of the health system and public payers.

Study Monitoring and Adverse Event Reporting

The purpose of study monitoring is to verify that the rights and well-being of human participants are protected; the reported trial data are accurate, complete, and verifiable from source documents; and the trial is conducted in compliance with the currently approved protocol and amendments, with good clinical practice, and with all applicable regulatory requirements. This study will follow a detailed clinical quality monitoring plan that specifies the frequency and types of data that will be reviewed (case report forms, regulatory documents, study staff training records, and medical and laboratory records) to accomplish these monitoring activities. External monitoring for this study will be conducted biannually through the North Carolina Translational and Clinical Sciences Institute monitoring service in accordance with established International Conference of Harmonization Good Clinical Practice Guidelines and Title 21 of the Code of Federal Regulations. This review includes quality assurance (QA) and study monitoring, such as regulatory file review, informed consent review, patient eligibility confirmation, protocol compliance review, assessment of safety reporting requirements, and review of training records.

In addition, a study monitoring committee (SMC) will be constituted before initiation of the study. This committee will include, at a minimum, 2 HIV clinicians or research investigators not directly involved in the study and a community representative. At least one representative from the National Institutes of Health (NIH; study sponsor or funder) will be invited to attend the biannual meetings. SMC members will review cumulative study reports, including reports of adverse events (AEs), social harms, and unanticipated problems. The SMC will assess study conduct, adequacy of the delivery of the intervention package, ascertainment of PrEP uptake outcomes, and other related data to ensure adequate collection of primary and key secondary outcome data.

There are no plans for additional interim analyses beyond standard monitoring and reporting, and there are no explicit, prespecified stopping guidelines for the trial. The study sponsor and funder retain the right to terminate the trial.

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As a behavioral intervention that does not include an investigational product, standard AE reporting will not be undertaken for this study. The study team will monitor for and track serious and nonserious AEs related or possibly related to study procedures or participation in the study. Study participants will be instructed on how to contact the study staff to report any AEs they may experience at any time between enrollment and the follow-up assessments. AEs will also be actively assessed in all follow-up quarterly assessments. Should a participant report experiencing an AE that they perceive to be related to their study participation, research staff will contact the participant to assess the severity and appropriate resolution action.

Ethical Considerations

This study, including the protocol, the informed consent documents, and all participant-facing materials, has been reviewed and approved by the University of North Carolina (UNC) Biomedical Institutional Review Board (IRB; 22-3058), who is responsible for the oversight of the study. Any subsequent modifications will be reviewed and approved by the UNC IRB before implementation. Annual IRB reporting and review is required for the duration of the study.

Eligible participants will have the choice to complete a self-guided electronic informed consent form following the informational video before enrollment or complete a staff-guided electronic informed consent form (via a HIPAA-compliant videoconferencing platform or phone call) before enrollment (Multimedia Appendix 4). All participants will be required to complete comprehension questions to ensure that they adequately understand the research, risks, and benefits and that they can opt out of study participation at any time before providing an electronic signature. All prospective participants who provide informed consent will be required to review and digitally sign a HIPAA release form (Multimedia Appendix 5).

All participants will be assigned a unique participant ID number. Participant-related study information will be identified only through the participant ID on all participant case report forms, audio files, transcripts, and computer-assisted self-interview files. Participant names and other personally identifying information will not be used on any study documents and will be redacted from interview transcripts.

Participants will receive digital cash incentives through the Tango payout platform for completing study visits (surveys, DBS kits, and interviews) as follows: US $60 for enrollment activities (baseline survey and enrollment), US $40 for the 3-month survey, US $50 for the 3-month whole blood self-collection kit, US $40 for the 6-month survey, US $50 for the 6-month whole blood self-collection kit, US $40 for the 12-month survey, and US $50 for the qualitative exit interview. Participants can choose their preferred gift card from a reward catalog.

We will secure study data with all appropriate physical, electronic, and operational protections following our data collection and handling SOP. All data files will have encryption and strong password protection, and files will be stored and managed using HIPAA-compliant, secure servers and cloud-based participant management software. Participant names and their participant IDs will be stored in separate tabs in REDCap accessible only to designated study staff and site monitors. Any files that are not specific to a single participant (eg, laboratory sample manifest) will be stored securely on a university-managed, HIPAA-compliant server. Original source documents for individual participants will be maintained at the UNC study site and will be accessible only to the study staff.

Data Quality and Monitoring

The clinical quality monitoring plan outlines the regular quality control (QC) and QA checks that are completed by the study team and external study monitor. Internal quality management activities ensure that research staff perform the study-required work correctly per the protocol requirements and in real time. Quality management activities also support good clinical practice compliance, human participant protection, and adherence to protocol requirements and site SOPs. Internal QC and QA monitoring and reporting consists of standardized methods and tools for QA and QC checks, as well as mechanisms for summarizing and disseminating the gathered information. Quality management checks will be implemented throughout the data collection process to quickly identify and rectify potential problems. Survey instruments will use skip patterns and built-in checks to minimize discrepant and unrealistic answers. Standard data-cleaning procedures will be used before analyses, including outlier detection and graphical representation of the data.

Data Dissemination

The results of this research will be disseminated via publication in peer-reviewed journals; conference presentations; and direct presentation to other interested stakeholders involved in HIV prevention and STI care provision, programming, and policy generation. The protocol is available for public review at ClinicalTrials.gov (NCT05984030).

Written publication guidelines for authorship eligibility will follow the criteria recommended by the International Committee of Medical Journal Editors (substantial contribution, participation in writing, approval of final version, and accountability) [85].

Lay summaries and infographics of study findings and implications will also be created for a general public audience and distributed via social media channels, as well as to participating clinics. When participants are asked for consent for the study to maintain their preferred contact information, they are informed that this information may be used to inform them of the study results. Thus, primary results and lay summaries will be individually shared back with participants unless they opt out of receiving this communication.

No participant names or other identifying information will be used in any dissemination materials, published or otherwise. The final deidentified dataset will be maintained by the study primary investigators and may be shared with other investigators for the completion of secondary data analysis following the establishment of acceptable data-sharing or data use agreements per the requirements of the US NIH (funder or sponsor) and UNC at Chapel Hill (grantee).

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Results

Enrollment opened on August 31, 2023, at 15 health department–affiliated clinics in NC and subsequently expanded to 21 facilities in 20 counties by July 2024. Completion of the enrollment and data collection phase is expected by May 2025. As of January 2, 2024, a total of 17 persons have been enrolled. We have conducted 13 PrEP trainings, reaching a total of 106 providers and clinic staff members, as well as organizing 15 refresher trainings to promote continued understanding and study engagement among clinics. We have conducted 33 qualitative interviews among study participants, clinicians, and stakeholders. In addition to the customized HealthMpowerment study app, we have developed a PrEP navigation manual that also includes a compiled list of county-specific resources. The conclusion of phase I of this study is expected by May 2025, with results to be published thereafter.

Discussion

Novel Strategies to Address Barriers to PrEP Uptake

This study hypothesizes that leveraging STI clinics as an on-ramp to PrEP will serve as an effective opportunity to capitalize on STI service encounters and address disparities in PrEP access across rural and periurban environments in NC. As infrastructure for providing PrEP in rural NC STI clinics is currently extremely limited, no previous published studies have assessed PrEP uptake in these settings. In some settings, the diverse needs of potential PrEP recipients may exceed what can be reasonably provided by rural STI clinic staff in stand-alone, frequently understaffed clinics. Developing and testing a pathway to PrEP that complements clinic resources and workflow, including linking to remote PrEP navigation and offering high-quality STI testing services or monitoring for PrEP users, is an appealing strategy that could leverage rural STI clinics as a cost-effective on-ramp to sustained PrEP services. We believe that hybridizing components of multiple-effect PrEP uptake strategies, such as access to PrEP navigation and implementation of a virtual PrEP strategy supported by digital health interventions such as HealthMpowerment, may help support PrEP initiation in patient populations that would otherwise face barriers to obtaining and pursuing in-person PrEP service referrals [36,37].

In NC, men assigned male sex at birth who have sex with other men continue to represent a disproportionate majority of new HIV acquisitions. However, as we expanded within rural NC communities and engaged with the rural providers who staff the participating clinics, we recognized the disconnect between this focused recruitment strategy among persons seeking services at STI clinics and the importance of discussing HIV prevention, and PrEP specifically, with all patients. Our expansion to women will offer unique insights into the challenges and opportunities of engaging with this population within rural STI clinics.

Importantly, in this phase of the study, we are screening persons into a research study, not a PrEP referral process or pathway. As such, challenges with the implementation of the study, including recruitment, do not necessarily reflect barriers to linkage to remote navigation and digital health applications that would be implemented were this model to be scaled. Furthermore, although the randomized nature of our approach offers a more robust evaluation of potential efficacy, this design could influence willingness to enroll or engage with study materials. However, the process of referring all persons seeking STI services to PrEP navigation services using a scannable code or offering access to an informational app for those interested, as reflected in the study recruitment process, may indeed be a strategy used in future implementations if our intervention is shown to be effective in improving uptake of PrEP.

Potential Limitations and Future Directions

The external validity of the intervention may be challenging to establish when implemented outside the context of the research study. Participants are provided with a modest monetary incentive for initial engagement, which could influence their motivation to take part initially. In addition, the provision of ongoing incentives for study activities may impact their continued willingness to participate. This potential limitation will be further investigated through qualitative research aimed at exploring the motivation behind participants' decision to engage in the study. Importantly, this study was designed explicitly to address challenges related to PrEP access for persons accessing STI services in rural areas in which PrEP providers and general PrEP services are scarce, and thus, the generalizability, including the acceptability of this approach, may not be immediately relevant to other contexts with more concentrated service delivery options and more widely available, robust PrEP referral and linkage opportunities. The potential expansion or modification of this approach to other similarly resource-constrained settings within and outside the United States will be an important next step but is beyond the scope of this pilot. Incorporating PrEP services into STI clinics presents unique implementation challenges. Barriers at the provider (eg, knowledge and self-efficacy), clinic (eg, budget constraints and understaffing), and structural (eg, limitations in capability for long-term follow-up) levels complicate PrEP scale-up in rural STI clinic settings [86]. However, per CDC recommendations, screening for bacterial STIs should occur at least every 6 months for all sexually active patients and every 3 months among men who have sex with men or persons with ongoing risk behaviors [50,51]. By including budget impact analyses, this study informs program planning and sustainability of the proposed intervention strategy. As public health agencies and providers endeavor to increase PrEP uptake, understanding of the comparative value of alternative strategies, particularly among populations with high HIV incidence and low PrEP use, is urgently needed. Successful implementation and scale-up of the proposed intervention relies on understanding the main drivers of clinic-level costs and demonstrating that an integrated strategy for PrEP and STIs may be more cost-effective than providing these services separately, particularly if optimized models of centralized resources (eg, PrEP navigation and telehealth) and local services (eg, regular HIV and STI testing) can be identified. Ultimately, this study will assess the effectiveness, acceptability, feasibility, and cost-effectiveness of a model to colocate STI services and PrEP access in rural and periurban settings and provide critical information about ways to tailor this service delivery model. A pilot study to assess feasibility

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was not conducted before the full-scale RCT, as the R61 mechanism of the NIH is designed to be informative. This study builds on existing preliminary research that supports the use of PrEP navigators, remote provision of PrEP delivery, and DBS monitoring and draws from extensive literature examining the challenges of HIV care among this population. Further directions of this work will include engaging with state and local stakeholders to refine the PrEP intervention and expanding the refined implementation strategy to all persons who enroll at a participating clinic.

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Data Availability

The datasets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

SER was the principal investigator and contributed to study concept and design, protocol development and writing, manuscript drafting and revision, lead and oversight over all study activities, and lead for telehealth pre-exposure prophylaxis (PrEP) service development and implementation.

EF was the study coordinator and contributed to protocol development and writing, and manuscript revision; served as the lead for the development and coordination of all partnering clinic activities; and the lead for the development and implementation of participant recruitment, enrollment, and retention activities.

OM was the research assistant and contributed to manuscript drafting and revision.

NB was the data manager and contributed to the design, programming, and implementation of data collection tools; ongoing data analytic monitoring reports and data quality control procedures; participant recruitment, enrollment, and follow-up; and manuscript drafting and revision.

JS was the data system designer and served as the lead for the conceptualization and design of fully integrated data systems for participant screening, enrollment, and follow-up; contributed to the design, programming, and implementation of data collection tools; design of integrated data–monitoring reporting tool; and manuscript revision.

AW was the PrEP navigator and served as lead for the development and implementation of PrEP navigation protocols and intervention components, the development and maintenance of tracking procedures for clinic-based PrEP services and referral procedures, and manuscript revision.

VM was the HIV and Sexually Transmitted Disease state medical director and contributed to the study concept and design, ongoing expert consultations to align study-specific procedures with state-level HIV and sexually transmitted infection services and PrEP expansion initiatives, and manuscript revision.

SD was the chief medical officer of North Carolina Medicaid and contributed study concept and design, ongoing expert consultations to align study-specific procedures with state-level HIV and sexually transmitted infection services and PrEP expansion initiatives, and manuscript revision.

JE was a coinvestigator and contributed to the study concept and design; served as lead study statistician and epidemiologist for informing randomization scheme, statistical methodologies, sample size estimation, and scientific rigor; and contributed to protocol development and manuscript revision.

LBH-W was a coinvestigator study concept and design, protocol development, original creation of the HealthMpowerment digital health intervention, and manuscript revision.

CBH was a coinvestigator and contributed to the study concept, design and protocol development; served as lead for the development, implementation, and evaluation of clinic-based PrEP service training and technical support; and contributed to survey design and manuscript revision.

BP was a coinvestigator and contributed to the study concept and design; served as lead for implementation science design and evaluation components; and contributed to manuscript revision.

KEM was the principal investigator and contributed to the study concept and design; served as lead and oversight over all study activities, protocol development and writing; contributed to manuscript drafting and revision; and served as lead for qualitative research methodology components.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
Patient in-depth interview guide.
[PDF File (Adobe PDF File), 258 KB - resprot_v14i1e68085_app1.pdf]

Multimedia Appendix 2
Clinic stakeholder consent form.
[PDF File (Adobe PDF File), 266 KB - resprot_v14i1e68085_app2.pdf]

Multimedia Appendix 3
Primary and secondary study outcomes.
[DOCX File , 27 KB - resprot_v14i1e68085_app3.docx]

Multimedia Appendix 4
Informed consent form.
[PDF File (Adobe PDF File), 266 KB - resprot_v14i1e68085_app4.pdf]

Multimedia Appendix 5
Health Insurance Portability and Accountability Act authorization form.
[PDF File (Adobe PDF File), 432 KB - resprot_v14i1e68085_app5.pdf]

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Abbreviations

AE: adverse event
CDC: Centers for Disease Control and Prevention
DBS: dried blood spot
HIPAA: Health Insurance Portability and Accountability Act
IRB: Institutional Review Board
NC: North Carolina
NIH: National Institutes of Health
PrEP: pre-exposure prophylaxis
QA: quality assurance
QC: quality control
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SMC: study monitoring committee
SOP: standard operating procedure
STI: sexually transmitted infection

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UNC: University of North Carolina

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Protocol

Improving Early Dementia Detection Among Diverse Older Adults With Cognitive Concerns With the 5-Cog Paradigm: Protocol for a Hybrid Effectiveness-Implementation Clinical Trial

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Abstract

Background: The 5-Cog paradigm is a 5-minute brief cognitive assessment coupled with a clinical decision support tool designed to improve clinicians' early detection of cognitive impairment, including dementia, in their diverse older primary care patients. The 5-Cog battery uses picture- and symbol-based assessments and a questionnaire. It is low cost, simple, minimizes literacy bias, and is culturally fair. The decision support component of the paradigm helps nudge appropriate care provider response to an abnormal 5-Cog battery.

Objective: The objective of our study is to evaluate the effectiveness, implementation, and cost of the 5-Cog paradigm.

Methods: We will enroll 6600 older patients with cognitive concerns from 22 primary care clinics in the Bronx, New York, and in multiple locations in Indiana for this hybrid type 1 effectiveness-implementation trial. We will analyze the effectiveness of the 5-Cog paradigm to increase the rate of new diagnoses of mild cognitive impairment syndrome or dementia using a pragmatic, cluster randomized clinical trial design. The secondary outcome is the ordering of new tests, treatments, and referrals for cognitive indications within 90 days after the study visit. The 5-Cog's decision support component will be deployed as an electronic medical record feature. We will analyze the 5-Cog's implementation process, context, and outcomes through the Consolidated Framework

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for Implementation Research using a mixed methods design (surveys and interviews). The study will also examine cost-effectiveness from societal and payer (Medicare) perspectives by estimating the cost per additional dementia diagnosis.

Results: The study is funded by the National Institute of Neurological Disorders and Stroke of the National Institutes of Health (2U01NS105565). The protocol was approved by the Albert Einstein College of Medicine Institutional Review Board in September 2022. A validation study was completed to select cut scores for the 5-Cog battery. Among the 76 patients enrolled, the resulting clinical diagnoses were as follows: dementia in 32 (42%); mild cognitive impairment in 28 (37%); subjective cognitive concerns without objective cognitive impairment in 12 (16%); no cognitive diagnosis assigned in 2 (3%). The mean scores were Picture-Based Memory Impairment Screen 5.8 (SD 2.7), Symbol Match 27.2 (SD 18.2), and Subjective Motoric Cognitive Risk 2.4 (SD 1.7). The cut scores for an abnormal or positive result on the 5-Cog components were as follows: Picture-Based Memory Impairment Screen ≤6 (range 0-8), Symbol Match ≤25 (range 0-65), and Subjective Motoric Cognitive Risk >5 (range 0-7). As of December 2024, a total of 12 clinics had completed the onboarding processes, and 2369 patients had been enrolled.

Conclusions: The findings of this study will facilitate the rapid adaptation and dissemination of this effective and practical clinical tool across diverse primary care clinical settings.

Trial Registration: ClinicalTrials.gov NCT05515224; https://www.clinicaltrials.gov/study/NCT05515224

International Registered Report Identifier (IRRID): DERR1-10.2196/60471

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KEYWORDS

cognitive assessment; cognitive screening; cognitive impairment; mild cognitive impairment; dementia; dissemination and implementation science; clinical trial protocol; randomized controlled trial; hybrid implementation-effectiveness trial

Introduction

Background and Rationale

Problem and Progress

Alzheimer disease and related dementias (ADRD) affect approximately 57 million people globally, a figure projected to rise to 152 million by 2050 [1,2]. Studies have long noted deficiencies and delays in individuals receiving a dementia diagnosis [3-12]. The World Health Organization's Global Action Plan on Dementia includes a focus on the right to a timely dementia diagnosis to enable better planning, treatment, care, support, and quality of life [13]; for example, timely diagnosis can help individuals avoid preventable accidents and injuries leading to care escalation and can reduce distress for patients and caregivers [9,14-16]. In addition, several studies have estimated a potential cost saving of approximately US $10,000 per timely diagnosis because of delayed institutionalization, with the expectation that improved health and quality of life related to early diagnosis could result in even more cost savings [17].

Studies have repeatedly noted that delay and deficiency in diagnosis disproportionately impacts individuals from historically minoritized racial and ethnic groups as well as those from socioeconomically disadvantaged backgrounds [3-12]; for example, a recent nationally representative study found that a higher proportion of non-Hispanic Black and Hispanic individuals had a missed or delayed clinical dementia diagnosis compared to non-Hispanic White individuals (46% and 54% vs 41%; $P<.001$). This is thought to be an underestimate of the impact because the study relied on claims-based data, and non-Hispanic Black and Hispanic individuals may be less likely to access care that generates claims [18].

Experts recommend robust, multifaceted strategies to close these diagnosis gaps [15,17,19-24]; interventions must address implementation ("the actively planned process of putting evidence to use or integrating new interventions within a specific setting." [25]) and dissemination ("the targeted distribution of information and intervention materials to a specific public health or clinical practice audience" [26]) challenges as much as they aim to achieve high clinical accuracy and quality [20,21,27-31]. The Consortium for Detecting Cognitive Impairment, Including Dementia, a collaborative research effort directed and funded by the National Institute of Neurological Disorders and Stroke and the National Institute on Aging of the National Institutes of Health (NIH), has produced promising paradigms to meet this need. As part of this effort, our team at the Albert Einstein College of Medicine and Montefiore Medical Center (hereinafter Montefiore Einstein clinics) in the Bronx, New York, United States, developed the 5-Cog paradigm [32,33]. In a randomized controlled trial (RCT) of 1200 older adults with cognitive concerns at an urban primary care clinic in a primarily Black and Hispanic community, we showed that the 5-Cog paradigm improves dementia care, most notably by increasing the rate of diagnosis of mild cognitive impairment (MCI) and dementia [33]. This detection and diagnosis increases opportunity for primary care providers (PCPs), patients, and patients' families to intervene to potentially slow or prevent progression to dementia or, for individuals who do progress, to prepare in advance to meet the complex caregiving and clinical challenges to come [34].

Hence, our research questions for this cluster randomized trial were as follows:

- Can a brief cognitive assessment paired with a clinical decision tree (5-Cog paradigm) increase the rate of new diagnoses of MCI syndrome or dementia in primary care patients presenting with cognitive concerns in real-world settings, across broad patient groups (hence its categorization as a pragmatic trial [35])?

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- What are the determinants of the 5-Cog's impact in these settings?

Updates to the 5-Cog Paradigm for This Trial

The 5-Cog paradigm (brief cognitive assessment battery and decision support tool) worked well in our initial trial. However, building on implementation reflections from that trial [27] as well as feedback from local primary care stakeholders, we have made 2 refinements to the 5-Cog paradigm to improve clinical utility and aid future dissemination. We substituted the gait speed measurement component of the 5-Cog with a questionnaire that assesses mobility and cognition. In addition, we modified the 5-Cog decision support component to capitalize on electronic medical record (EMR) capabilities and better align the 5-Cog paradigm with existing care provider workflows. All these modifications are described in detail in the following subsection (The 5-Cog Paradigm) and in the Interventions section.

The 5-Cog Paradigm

The 5-Cog paradigm is composed of a 5-minute brief cognitive assessment (the 5-Cog battery) combined with an EMR-embedded clinical decision support tool. The 5-Cog battery was granted US copyright registration effective December 14, 2023.

Clinical decision support provides timely information, usually at the point of care, to inform and improve decisions about a patient's care [36].

The first of the 3 items in the 5-Cog battery is the Picture-Based Memory Impairment Screen (PMIS), created by Verghese et al [37], which uses 4 pictures to test free and cued recall after a delay of at least 2 minutes. Administration and scoring have been previously described [38]. This screener was selected because of ease of use (simple to administer after minimal training and does not require specialized technology), freedom from literacy bias (uses photographs of items instead of words), and cultural fairness (photographs were chosen and validated for consistent recognition by patients in the relevant cultural milieu). In our validation study, PMIS was shown to have high validity for distinguishing older adults with cognitive impairment from those without, regardless of age, sex, education, or presence of depression (sensitivity and specificity >90%) as well as excellent reliability (intraclass correlation 0.91) [37,38].

The second item in the 5-Cog battery is the Symbol Match [39], developed by one of our coinvestigators (EFW). It is an oral timed transcription task created to identify difficulties with divided attention, visual scanning, tracking, and motor speed. It requires individuals to quickly substitute (verbalize) numbers for an array of symbols using a key provided at the top of the page. After a practice run with 7 symbols, individuals are given 90 seconds to correctly name as many items as they can as quickly as they can without making a mistake. The number of correct oral substitutions at the end of 90 seconds is the participant's score. Individuals who complete the task before the time limit receive a ceiling score of 65. Internal validation within our study population suggested 25 as the optimal cutoff score to identify cognitive impairment (refer to the Results section for details). The Symbol Match was chosen because of ease of use (requires no specialized equipment and minimal training to administer) [39]. The 90-second Symbol Match correlates highly with the established Symbol Digit Modalities Task [40,41], which can detect nonmemory impairments and functional changes [42]. This feature allows Symbol Match to detect patients with nonmemory impairments that may not be identified by the PMIS [39].

Finally, the 5-Cog incorporates an assessment of gait. The motoric cognitive risk (MCR) syndrome, first described by Verghese et al [43], and defined as slow gait in the presence of cognitive concerns, has been extensively validated to predict an elevated risk of dementia independent of other cognitive assessments [43-47]. Traditionally, the MCR syndrome assessment involves the measurement of gait speed. Given that gait speed is not routinely tested in current primary care environments and that it may present a barrier for 5-Cog implementation, we modified this assessment. For this study, we will be assessing the Subjective MCR (sMCR) screening tool, developed by Ayers et al [48], which uses the patient's subjective reports of mobility and cognitive concerns via a 5-item questionnaire, rather than having a tester measure gait speed. Responses to these 5 questions are used to derive a weighted score that is used to define sMCR. Administration and scoring have been previously described [48]. We found the sMCR approach to have excellent discriminative validity versus objective MCR (defined using gait speed) and excellent predictive validity for incident dementia; in our validation study, participants who met the sMCR criteria had a >2-fold increased risk of developing dementia [48].

The 5-Cog paradigm's EMR-based decision support tool includes 2 components: documentation of the patient's 5-Cog battery result and recommended next steps that may be appropriate for further diagnosis or management of the patient's cognitive concerns (clinical decision support). This "nudge" supports and supplements the provider's own clinical decision–making process [49,50]. In this study, the decision support tool incorporates 3 additional features that make it resemble other EMR-based decision support systems: first, the 5-Cog result will be listed among other clinical practice advisories that contain information tailored to each patient regarding time-sensitive care needs. Second, providers will receive 5-Cog results through an interruptive alert when they access the patient's chart (as they do in cases of other clinical issues that can impact patient safety). Finally, the decision support tool will include a direct link to orders for the next steps in care. This reduces clinician cognitive load by providing a menu of options (such as appropriate laboratory, imaging, and referral orders) and minimizes clicks by consolidating these options in one place.

Our 5-Cog 1.0 protocol [32] can be referenced for additional detail on the development and design of the 5-Cog paradigm. Figure 1 depicts the 2 components of the 5-Cog paradigm.

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Figure 1. (A) The 5-Cog battery (5-min cognitive assessment). (B) Decision support for a patient with a positive 5-Cog result. (C) Decision support for a patient with a negative 5-Cog result. EMR: electronic medical record.

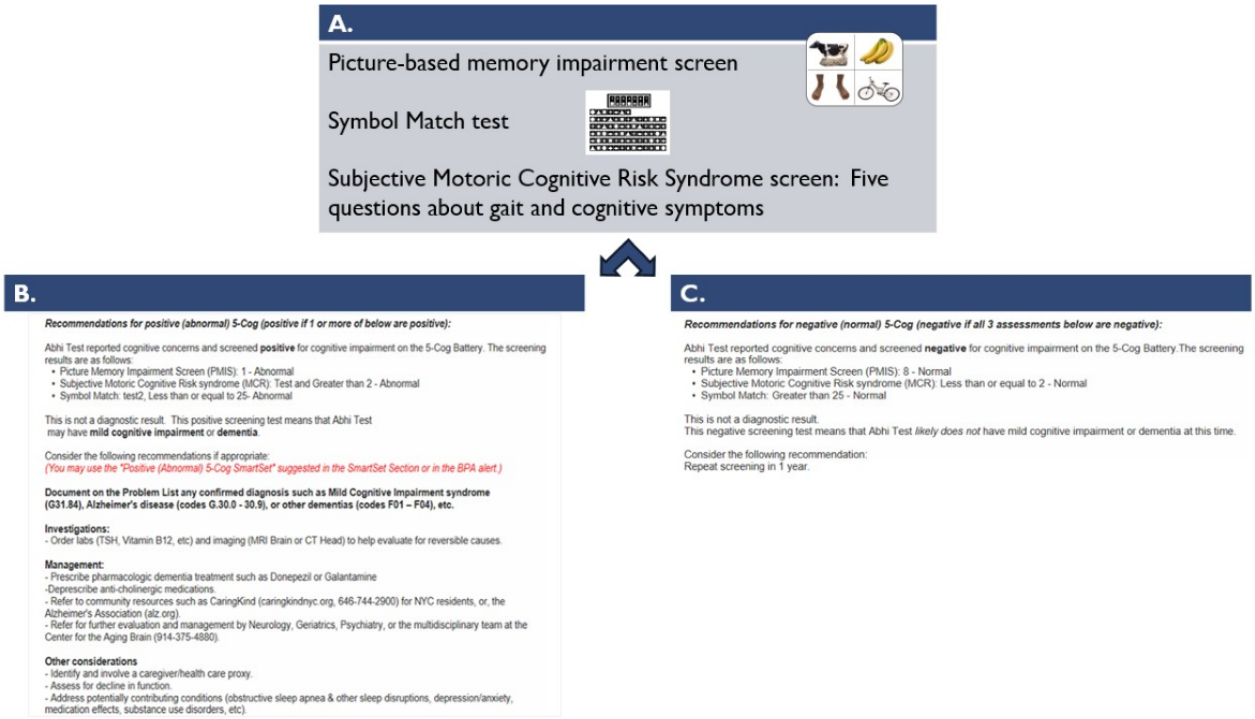

Implementation Study

The United States Institute of Medicine (now the National Academy of Medicine) estimated a 17-year gap from when a clinical innovation is proven effective to when it is routinely implemented in clinical care [51]. Given that cognitive impairment detection paradigms are not adopted widely in primary care, it is important to systematically identify and address potential factors that influence implementation outcomes, that is, implementation determinants [52]. Our implementation measurements for the 5-Cog will be guided by the Consolidated Framework for Implementation Research (CFIR). The CFIR is an established implementation science theoretical framework for identifying implementation determinants [53,54]. We chose the CFIR because it facilitates the identification of implementation determinants that influence implementation outcomes either positively as facilitators or negatively as barriers [55-58]. Each CFIR construct is well defined, has established measures, and can be depicted in rich qualitative detail. The CFIR is practical because it is often used to both explore and subsequently optimize future implementation contexts and processes [59]. As with many implementation science frameworks, the CFIR does not mandate a specific data collection methodology [53]; studies applying the CFIR have used quantitative only, qualitative only, or mixed methods approaches [59]. We have chosen a mixed methods strategy to examine implementation contexts, processes, and outcomes. The study approach is based on the broader epistemology of critical realism [60] and more specifically the realist evaluation framework [61] wherein quantitatively measured implementation outcomes are explained by analyzing the relationships between implementation context and process factors. We will use the CFIR to identify implementation determinants through qualitative processes (interviews). We will use quantitative measures—the Acceptability of Intervention Measure (AIM), the Feasibility of Intervention Measure (FIM), and the Intervention Appropriateness Measure (IAM) [62]—to measure implementation outcomes. We will then analyze all findings using the CFIR as a lens to examine the relationships between these outcomes and implementation context and process factors [54,59].

Cost-Effectiveness Assessment

Currently, Medicare reimburses cognitive impairment assessments for older adults as part of their annual wellness visit (AWV) [22]. However, there is no standardized required form and output for this assessment. For health systems that would like to implement the 5-Cog for the AWV, questions may arise regarding its impact on costs. The 5-Cog battery is a low-cost intervention, requiring simple paper-and-pencil tools that are easily adapted to digital formats and minimal training to administer. For the 5-Cog decision support component, we anticipate programming and workflows to be translatable between EMR systems with a 1-time, upfront customization and without recurring software or staffing costs. Thus, the 5-Cog's direct expenses predominantly include staffing costs (eg, salaries, benefits, and travel expenses for workers administering the 5-Cog). Given the short duration and minimal supplies cost of the 5-Cog, indirect expenses (eg, scheduling, record keeping, facility overhead, and equipment depreciation) and opportunity costs (eg, forgoing other billable care) are anticipated to be minimal. Investigators have previously reported costs associated with both community health workers (CHWs) and practice facilitators throughout Indiana and the Midwest in the United States [63]. There may also be costs associated with dementia care actions resulting from the use of the 5-Cog. However, these follow-up costs may be offset by cost savings resulting from earlier dementia care intervention [64].

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The goal of our budget impact analysis (BIA) [65-67] and cost-effectiveness analysis (CEA) [68] is to understand the cost per cognitive case identified from a societal and payer (eg, Medicare) perspective to facilitate informed dissemination (per the CFIR model). The study design for estimating the financial effects involves addressing several issues, many predetermined by BIA and CEA best practices and the Consolidated Health Economic Evaluation Reporting Standards [65-68]. The BIA will determine financial planning and affordability, and the CEA will determine the effectiveness and value of the 5-Cog compared to enhanced usual care. The BIA can be used to determine financial adoption and scalability for national implementation.

Trial Design

Given the problems of underdiagnosis and undertreatment of dementia, which are expected to worsen with the growing number of aging adults globally [69], we chose a hybrid type 1 effectiveness-implementation design for this trial. In this design, the primary emphasis is on testing the intervention, with a secondary emphasis on exploring implementation-related factors [55]. We chose this design because it would be premature to conduct an implementation-only trial, given that the 5-Cog has previously been studied in 1200 individuals in only 1 urban primary care setting. The hybrid type 1 effectiveness-implementation design allows us to confirm the effectiveness of our intervention, while also hastening its potential to make needed impact in the "real world" through incorporating implementation examination prospectively [55]. The clinical effectiveness (in this case, meaning the degree of beneficial effect [70]) component of the trial will be completed using a pragmatic, cluster randomized design (randomized at the level of the clinic) with intervention clinics receiving the 5-Cog paradigm and control clinics receiving enhanced usual care (cognitive concern information and cognitive impairment detection education provided but no detection approach or clinical decision support tool implemented).

Objectives

This trial's three aims are to (1) test whether the 5-Cog paradigm used in primary care patients with cognitive concerns in diverse urban and rural environments and including individuals from racial and ethnic minority groups and those with socioeconomically disadvantaged backgrounds leads to an increased rate of MCI and dementia diagnoses; (2) explore the implementation context, process, and outcomes of the 5-Cog paradigm in diverse primary care clinics using mixed methods guided by the CFIR; and (3) assess the cost-effectiveness of the 5-Cog paradigm.

We hypothesize that this trial will demonstrate the 5-Cog paradigm's effectiveness in increasing the diagnosis of MCI in dementia and primary care, its cost-effectiveness in achieving this outcome, and the range of factors shaping its successful implementation across diverse primary care settings.

Methods

Participants, Interventions, and Outcomes

Study Setting

The study is being carried out at primary care clinics affiliated with 2 large academic health systems: Montefiore Medical Center and Albert Einstein College of Medicine (hereafter referred to as Montefiore-Einstein) in the Bronx, New York, and Indiana University Health (IUH) in Indiana.

The Montefiore-Einstein clinics serve an urban population primarily composed of individuals from historically minoritized racial and ethnic groups (Hispanic/Latino and Black populations). Of note, these clinics serve Bronx County, which ranks last (62 out of 62) among New York State counties on health-related indicators [71] and has a significant poverty rate, affecting 1 in 4 older adults [72]. The IUH clinics are situated across both urban and rural settings. Within this network, 12 (75%) of the 16 selected clinics are located in regions scoring >60 on the national area deprivation index (score range 0-100; higher scores indicate higher deprivation) [73,74]. Notably, 2 (17%) of these 12 clinics are in areas with an area deprivation index score of >91, underscoring the profound level of need of these communities. Indiana health-related indicators show higher premature death, lower life expectancy, lower PCP and mental health provider availability, and lower median household income than the US average [74].

The study procedures are completed by research assistants (RAs), who are trained as CHWs and embedded in the clinics. This approach was chosen for its pragmatic value, reflecting reality in primary care settings in which CHWs are incorporated into clinical teams and may complete other screening questionnaires with patients [75,76] and because the 5-Cog components have been shown to be practical and feasible for administration by individuals who are not medical professionals and with minimal training [37,44,77]. The RAs at Montefiore-Einstein are bilingual in English and Spanish because of the high proportion of Spanish-speaking participants at this site. All study materials were translated from English into Spanish and back translated to ensure language fidelity.

Eligibility and Screening

Clinics are eligible to participate if they provide primary care (internal medicine or family medicine), not specialty care. Clinics primarily serving as residency teaching sites are excluded.

In keeping with the pragmatic nature of the trial, our individual-level eligibility criteria are designed to ensure that enrolled patients are those who would receive this intervention if it were part of usual care [78-80]. The 5-Cog intervention was designed to improve dementia diagnosis in ambulatory primary care settings. Individuals are excluded if they have a prior diagnosis of dementia or reside in a nursing home. Nursing home residents are excluded because they already have a high prevalence of diagnosed dementia (60%-90%) [81] and largely do not receive primary care from ambulatory clinics because of their mobility and cognitive limitations [82]. To be eligible

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for our 5-Cog effectiveness study, individuals must be aged ≥65 years, have no prior diagnosis of dementia, speak English (Montefiore-Einstein or IUH) or Spanish (Montefiore-Einstein only), have a scheduled primary care office visit, and endorse a cognitive concern via a subjective cognitive concern questionnaire (SCQ) [32,83]. Initial screening is completed by RAs via prospective EMR review of patients scheduled at each clinic and confirmed through screening telephone calls.

Implementation study participants will be recruited from among patients, caregivers, clinicians, clinic staff, clinical leaders, clinical informatics staff, and administrative leaders. The exclusion criteria are the same as those for the effectiveness study.

Textbox 1 lists the complete individual-level inclusion and exclusion criteria, including the SCQ.

Textbox 1. Inclusion and exclusion criteria.

Effectiveness study

- Individual-level inclusion criteria
  - Aged ≥65 years
  - English or Spanish speaking (Albert Einstein College of Medicine and Montefiore Medical Center will enroll English- and Spanish-speaking patients; Indiana University Health will enroll only English-speaking patients)
  - Have a cognitive concern: subjective cognitive concern questionnaire result is positive (≥1 of the following: “Are you concerned about your memory?”—the chosen response is yes; “Are your loved ones concerned about your memory?”—the chosen response is yes; and “Is your mind as clear as it used to be?”—the chosen response is no)
- Individual-level exclusion criteria
  - Prior diagnosis of dementia (as recorded in the electronic medical record or reported by primary care provider; the prior diagnosis of mild cognitive impairment is not an exclusion criterion, but the effectiveness outcome is only counted if a participant previously diagnosed with mild cognitive impairment is assigned a new diagnosis of dementia)
  - Nursing facility resident

Implementation study

- Individual-level inclusion criteria
  - Patients who have undergone the 5-Cog battery, caregivers of these patients, clinicians, clinic staff, clinical leaders, clinical informatics staff, and administrative leaders at each of the randomized primary care practices
  - Ability to provide informed consent
- Individual-level exclusion criteria
  - Prior diagnosis of dementia (as recorded in the electronic medical record or reported by primary care provider; the prior diagnosis of mild cognitive impairment is not an exclusion)
  - Nursing facility resident

Recruitment of Clinics and Patients

The study team actively recruited clinics in the Bronx and Indiana to participate through contacting their administrative leadership to discuss the study. Generally, 1 to 3 meetings were held with clinic leadership and practicing clinicians to introduce the study and secure the clinic’s commitment to participate.

All individual patient recruitment for the effectiveness study is passive. RAs review a clinic’s scheduled patients via the EMR to determine which patients seem to meet the eligibility criteria and contact potentially eligible patients by telephone within 1 week before their scheduled office visit. The patient is informed that the caller is working with the patient’s primary care practice to assess cognitive concerns. The patient is asked to confirm that they plan to keep their upcoming clinic appointment. If they have decided to change the appointment, cognitive concerns are not assessed. If the patient confirms their scheduled appointment, the RA administers the SCQ (Textbox 1). The patient is free to decline to answer, at which point the call is ended. When the patient answers the questions, the results are documented in the EMR. In the clinics randomized to the control arm, patients who have answered the SCQ are considered recruited; and if their SCQ result is positive, they are considered enrolled once they show up to their scheduled clinic appointment. In the clinics randomized to the intervention arm, patients with a positive cognitive concern are invited to undergo additional cognitive screening (the 5-Cog battery) at the clinic on the day of their office visit, just before they see their care provider. Patients who agree are considered recruited, with enrollment confirmed once they complete their scheduled office visit. In both arms, patients who do not show up to their scheduled clinic appointment after a positive SCQ result are not considered enrolled. If these patients have another scheduled clinic appointment during the study period at their clinic, they are eligible to be rerecruited and enrolled at this time (RAs will call and confirm SCQ responses before this visit).

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Implementation study participants will be actively recruited from intervention sites through snowball sampling among different types of key informants mentioned previously. In addition, we will collect quantitative implementation surveys from as many clinicians and staff as possible at the intervention clinics.

Participant Timeline

The 22 participating clinics were randomized in year 1 of the study. These clinics are onboarded in waves throughout the 5-year study period. The time period over which each clinic will experience active study recruitment (with the goal of enrolling 300 patients per clinic) is anticipated to vary from 3 to 12 months, depending on clinic size.

For individual patients in the effectiveness study, the initial screening and recruitment telephone call takes place within 1 week before a patient's scheduled primary care visit and takes 10 to 15 minutes. Patients are then considered enrolled when they complete their scheduled PCP clinic appointment.

At the intervention clinics, participating patients are asked to arrive up to 1 hour early for their scheduled visit to allow sufficient time for undergoing the 5-Cog battery before meeting their care provider. The 5-minute assessment is completed at the clinic before the appointment.

In both intervention and control groups, patients remain enrolled for 90 days. Study outcomes are ascertained at 90 days (primary and secondary end points), at which point the enrolled patients are considered to have completed participation. This time window was selected because >95% of physician actions for dementia care were completed within this period in our initial trial [33].

Implementation study participants are enrolled when they consent to participate in a survey or an interview, and their enrollment is completed at its conclusion. Figure 2 depicts the study flow.

Figure 2. Study flow. EMR: electronic medical record; PCP: primary care provider; RCT: randomized controlled trial; SES: socioeconomic status.

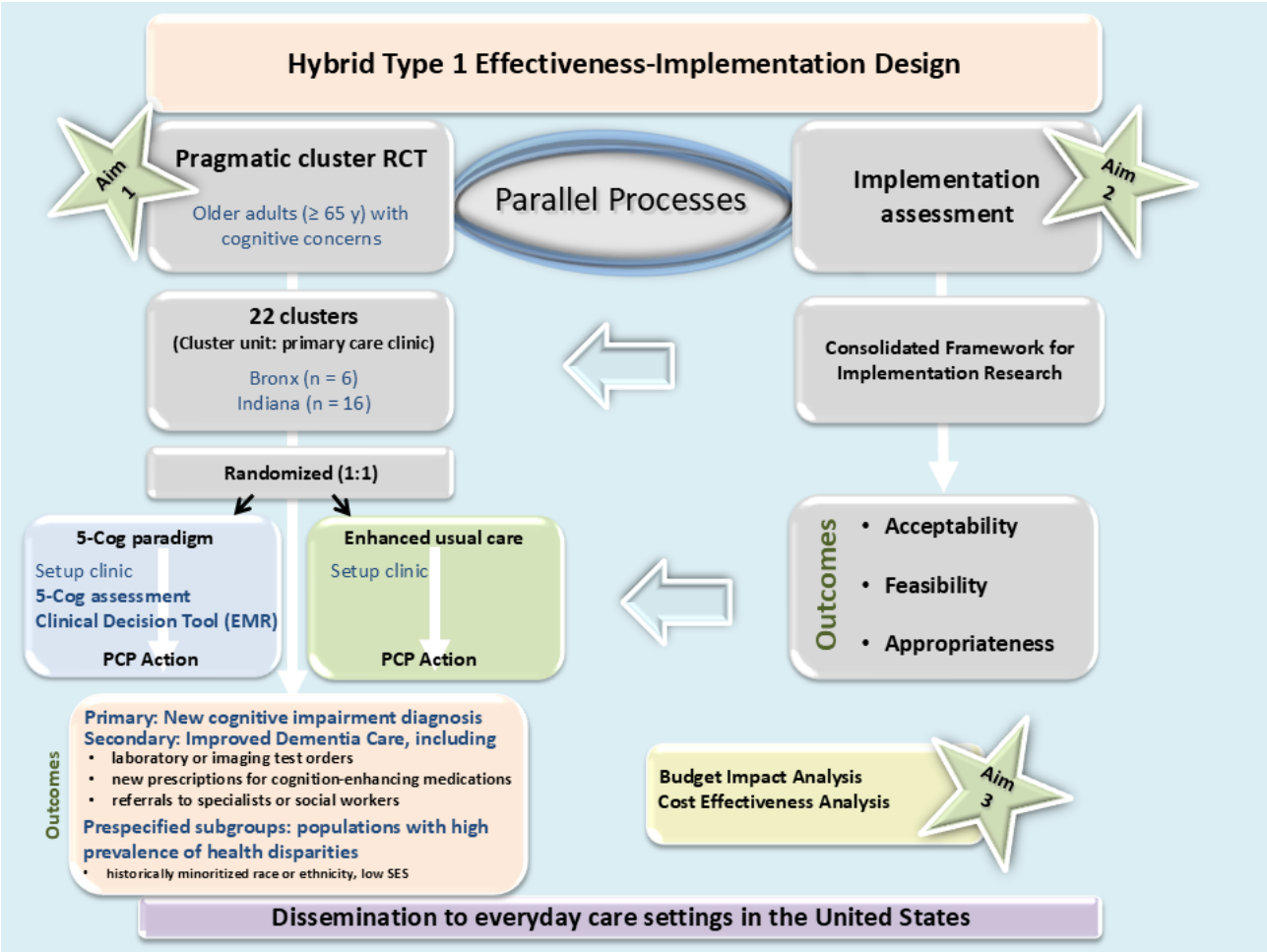

Planned Sample Size

The planned effectiveness study sample size is 6600 enrolled patients, including approximately 300 (4.56%) from each of the 22 participating clinics (Bronx: n=6, 27%; Indiana: n=16, 73%).

For the implementation interviews, we will use snowball sampling to identify the most relevant informants across clinics of different sizes. We anticipate conducting up to 6 implementation interviews per practice for a maximum total sample size of 132 participants or until thematic saturation is reached over the 5-year study period. We will disseminate the quantitative implementation surveys to the clinicians and staff at the intervention clinics.

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Interventions in the Intervention Arm (5-Cog Battery With Decision Support Tool)

On the day of the patient's scheduled clinic visit, an RA meets the patient upon their entry into the clinic waiting area in preparation to complete the 5-Cog with them before their PCP visit. The RA escorts the patient through clinic registration. At the same time, the RA communicates with the clinical team to let them know that the patient will undergo the 5-Cog battery before being ready to see their care provider.

The RA administers the 5-Cog (refer to the Introduction section and Figure 1 for more details on the 5-Cog) in a private space within the clinic and then brings the patient back to the waiting area. Next, the RA informs the clinical team that the patient has completed the 5-Cog battery and is ready to be integrated back into the usual clinical workflow. The RA then completes documentation of the battery results in the EMR (and in the study database). The 5-Cog decision support recommendations are harmonized across sites for a positive 5-Cog result, as they are for a negative 5-Cog result (Figure 1).

Montefiore-Einstein and IUH use 2 different EMR systems: Epic (version 100.2412.0.0) and Cerner (version 2024.3), respectively. Unique features within each EMR are used to capture and house the 5-Cog results, create alerts, and present the results and decision support recommendations to the care providers.

At Montefiore-Einstein, the RA creates a "research note." Here, they input the 5-Cog battery component scores by selecting from a drop-down list for each assessment. They also manually select the appropriate decision support arm (for positive vs negative 5-Cog result) using a quick-text feature. The EMR then responds to the results of the 5-Cog assessments, using structured data elements. Thus, the values that the RA enters for the three 5-Cog battery components trigger a preprogrammed tailored care provider alert, a "best practice advisory" (BPA). If the result of any of the 3 assessments indicates potential cognitive impairment, a "positive 5-Cog" BPA is triggered. If the results do not indicate potential cognitive impairment a "negative 5-Cog" BPA gets triggered. The BPA is "interruptive"; as soon as the care provider accesses the patient's medical record for the current visit in the EMR, they are shown the alert on their screen. The BPA contains the 5-Cog result with a hyperlink to the research note.

At IUH, the RA inputs the 5-Cog battery result into an EMR-based flowsheet through ad hoc documentation. Specifically, these results are entered into the "Results Review - Clinical Assessment" tab. The EMR is programmed to automatically trigger the appropriate decision support content based on the 5-Cog battery result. As at Montefiore-Einstein, a customized, interruptive alert is displayed to the provider. At IUH, the alert itself contains the 5-Cog result, along with all decision support recommendations.

In both IUH and Montefiore-Einstein EMR flows, care providers must respond to the interruptive alert, acknowledging it in some way. The options for this vary by EMR. At both sites, the alert for patients with a positive 5-Cog result also facilitates linking to an order set. This allows the care provider to efficiently and comprehensively select clinical actions that may be relevant to the patient's further cognitive care.

Figure 3 depicts a sample of the Montefiore-Einstein and IUH EMR alerts.

Figure 3. Electronic medical record (EMR)–based provider alerts for the intervention sites at the Albert Einstein College of Medicine and Montefiore Medical Center (Montefiore-Einstein; Epic EMR system) and Indiana University Health (IUH; Cerner EMR system). (A) Montefiore-Einstein: positive 5-Cog result. (B) Montefiore-Einstein: negative 5-Cog result. (C) IUH: positive 5-Cog result. (D) IUH: negative 5-Cog result.

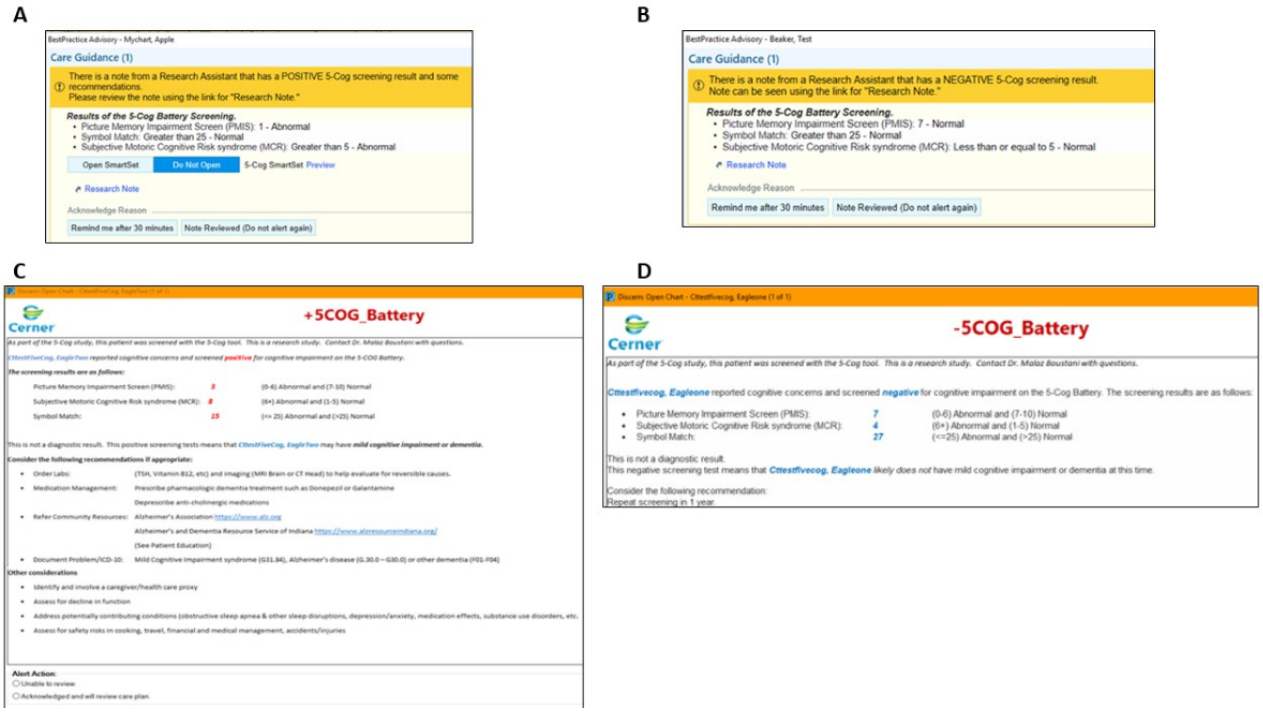

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At both sites, a paper token (Figure 4) is used as an additional feature to help ensure that care providers review the patients' 5-Cog results. Patients are handed this token after they complete the 5-Cog battery and are asked to hand it to their care provider at their scheduled visit, generally within 30 minutes after the 5-Cog battery administration.

Figure 4. Token to alert care provider for patient's 5-Cog participation.

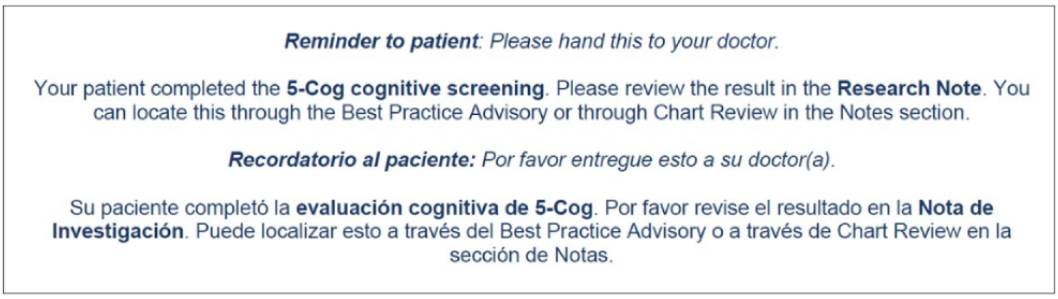

Interventions in the Control Arm (Enhanced Usual Care)

Patients are screened via telephone using the SCQ, as described in the Recruitment of Clinics and Patients subsection. RAs input results into the EMR. Care providers receive positive SCQ results through noninterruptive alerts. Figure 5 presents images of the alerts at Montefiore-Einstein and at IUH. We are calling this arm "enhanced usual care" because care provider are informed about the presence of a cognitive concern in their patient in this group. In addition, as at the intervention sites, care providers at the enhanced usual care sites receive preparatory education (described in the next subsection). The care providers at the control and intervention sites do not overlap.

Figure 5. Electronic medical record (EMR)–based care provider alerts for the control sites at the (A) Albert Einstein College of Medicine and Montefiore Medical Center (Epic EMR system) and (B) Indiana University Health (Cerner EMR system).

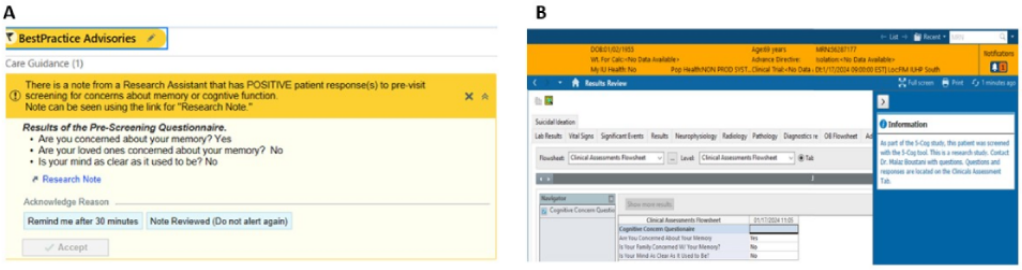

Care Provider Education and Preparation in Both Arms

Care providers at both control and intervention sites receive Microsoft PowerPoint presentations on the 5-Cog study. The presentations review the background to the study and then explain the study interventions that will be carried out at the sites (SCQ and new EMR features at both sites; 5-Cog at intervention sites). The presentations last 10 to 15 minutes at the control sites, and 25 to 30 minutes (to allow education about the 5-Cog battery) at the intervention sites. These presentations are provided 2 to 4 weeks before study start at a regularly scheduled clinic staff meeting. In addition to this education, care providers are given brochures that review cognitive impairment detection, diagnosis, treatment, and billing and invited to contact study staff at any time with questions. Finally, they are given tip sheets summarizing the new EMR features. At the intervention sites, care providers are updated on study progress via a monthly email or an informal in-person check-in by a study leader.

Of note, at both intervention and control sites, members of the interprofessional clinic leadership team (administrative and nursing managers) are provided with education on the study procedures and flow so that they can be prepared to assist and appropriately direct any patients who have questions about the study. At the intervention sites, members of the interprofessional clinic leadership team are also engaged in a session to plan clinic-customized logistical workflows to minimize interruptions to the clinic's operations during the course of the study. These workflows, along with a background to the study, are presented to the full interprofessional clinic staff before study initiation.

Interventions for the Implementation Study

From the intervention sites, a subset of patients (after the completion of study procedures and clinic visit) and providers will be invited to complete interviews to assess implementation issues. We will adapt the semistructured CFIR interview question guide. Interviews will be conducted, recorded, and analyzed by study staff trained in qualitative interviewing. We will aim to include patients with both positive and negative 5-Cog results. PCPs and clinical staff at the intervention sites will be asked to complete quantitative surveys containing 3 standardized 4-item measures: the AIM, FIM, and IAM [62]. The implementation outcomes measures are written at a fifth grade reading level; therefore, no specialized training is needed for administration, scoring, or interpretation. Finally, we will retain and later analyze recordings and field notes from our preimplementation stages (initial conversations with clinics and readiness presentations) through the completion of the project. This analysis will assess the barriers and facilitators to primary care sites' buy-in for study engagement. We will also use

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summary reports to discern trends in care provider responses to the EMR-based alerts.

Interventions for the Cost-Effectiveness Study

Billing and actuarial data will be extracted from the EMR for cost estimation. In parallel fashion to the intervention sites, costs are also collected at the control sites. Standardized cost calculators previously developed by investigators [67,84] will also be used to facilitate microcosting (measuring detailed resource use and unit costs to obtain precise estimates [85]) applicable to the 5-Cog paradigm. We will evaluate the cost of implementing and sustaining the 5-Cog paradigm by accounting for and itemizing specific program characteristics. We will evaluate differences in 5-Cog costs of care on the desired study outcomes compared to enhanced usual care.

Effectiveness Study: Primary Outcomes

The primary outcome is a new diagnosis of MCI or dementia within 90 days after study enrollment. Patients who enter the study with a known diagnosis of MCI will only be counted as meeting the primary outcome if they receive a new diagnosis of dementia. We chose diagnosis as the primary outcome for 2 reasons. First, a new diagnosis was a common outcome in our 5-Cog 1.0 study, and we want to validate this finding [33]. Second, this outcome is highly relevant to patients and PCPs: knowing their cognitive diagnosis has been shown to be important to patients and family members [34,86,87]; moreover, diagnostic clarity facilitates appropriate psychoeducation, resource connections, tailored medical treatment, and caregiver activation [88,89].

Effectiveness Study: Secondary Outcomes

The secondary outcome is a composite: “improved dementia care” within 90 days after study enrollment. “Improved dementia care” is defined by any of the following actions that are relevant to dementia diagnostic assessment and care: orders for dementia-related laboratory or imaging tests; a new prescription for cognition-enhancing medication or the deprescribing of anticholinergic medication; or referrals to a dementia specialist clinician, a nurse navigator, a social worker, or a community-based organization for related supports. We are including this composite outcome because a new diagnosis without subsequent action is less likely to improve patient outcomes. The aforementioned components are highly relevant to both PCPs and patients [90,91]. The actions described are only counted as an outcome if a cognitive indication (eg, memory loss or MCI) is entered as the indication in the EMR. Tests or referrals without indications entered or performed for any other medical reasons are not counted as outcomes. Prescription of dementia medications will always be counted because these medications inherently indicate cognitive impairment. For anticholinergic deprescribing, actions will be counted via a comparison of EMR-extracted medication lists from the 90 days before and after study enrollment. Charts will be reviewed for clinician notation on whether deprescribing (discontinuation or nonrenewal) was due to a cognitive indication [92]. We will consider the medications listed under “Drugs with strong anticholinergic properties” in the American Geriatrics Society Beers Criteria [93].

All primary and secondary outcomes are collected prospectively from the EMR. Textbox 2 presents a summary of the primary and secondary outcomes.

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Textbox 2. Study outcomes.

Primary outcome: new cognitive diagnosis (with associated International Classification of Diseases, Tenth Revision, code [94])

- Vascular dementia with or without modifiers (F01)
- Dementia in other diseases with or without modifiers (F02)
- Unspecified dementia with or without modifiers (F03)
- Mild cognitive impairment or minor neurocognitive disorder (unless patient entered study already having this diagnosis; G31.84)
- Alzheimer's disease with late onset (G30.1)
- Other Alzheimer's disease (G30.8)
- Alzheimer's disease, unspecified (G30.9)
- Frontotemporal dementia (G31.09)
- Lewy body dementia (G31.83)
- Dementia associated with alcoholism (F10.27)
- Unspecified with psychoactive substance–induced persistent dementia (F19.97)
- Variant Creutzfeldt-Jakob disease (A81.01)
- Creutzfeldt-Jakob disease, unspecified (A81.00)
- Other Creutzfeldt-Jakob disease (A81.09)

Composite secondary outcome: "improved dementia care" through relevant actions

- Medications: donepezil, rivastigmine, galantamine, memantine, donepezil-memantine, antiamyloid monoclonal antibody infusions, and any other Food and Drug Administration–approved medications for dementia
- Deprescribing anticholinergic medications: discontinuation or nonrenewal of any of the 41 medications in table 7 ("Drugs with strong anticholinergic properties") of the American Geriatrics Society Beers Criteria [93]
- Laboratory tests (cognitive indication only): thyroid-stimulating hormone, vitamin B12, glycated hemoglobin, complete blood count, basic metabolic panel, liver tests, HIV antigen and antibody combination, and syphilis immunoglobulin G and immunoglobulin M antibody with reflex
- Imaging tests (cognitive indication only): computerized tomography (head without contrast) and magnetic resonance imaging (brain without contrast)
- Specialist referrals for cognitive evaluation: geriatrics, neurology, neuropsychology, psychiatry, geriatric psychiatry, and social work
- Community referrals: Alzheimer's Association or local support organization

Implementation Outcomes

We will begin recruiting implementation study participants after approximately 1 month of patient involvement at each study site, once a "steady state" has been established. We will vary time points for the collection of implementation outcomes throughout our engagement at each clinic in anticipation that informant responses may shift with varied exposure to the 5-Cog. Surveys will assess the implementation outcomes of acceptance, feasibility, and appropriateness, which are considered "leading indicators" of implementation success. These will be measured using the AIM, FIM, and IAM, as noted in the Interventions for the Implementation Study subsection [62,95]. The results of the surveys will be computed using descriptive statistics (central tendency and variability) and, after checking for assumptions (eg, high interclass intraclass correlation), aggregated at the clinic level across all respondents. We will also collect and analyze EMR engagement data (eg, the rates and types of responses to alerts and the use of order sets) to assess the acceptance of EMR tools. In addition, we will collect field notes with observations about the study sites and observations from informal conversations with clinic staff during the study period to better understand the implementation context. Figure 6 summarizes the implementation constructs and the CFIR outcome measurement model for the study.

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Figure 6. Consolidated Framework for Implementation Research (CFIR) Measurement Model.

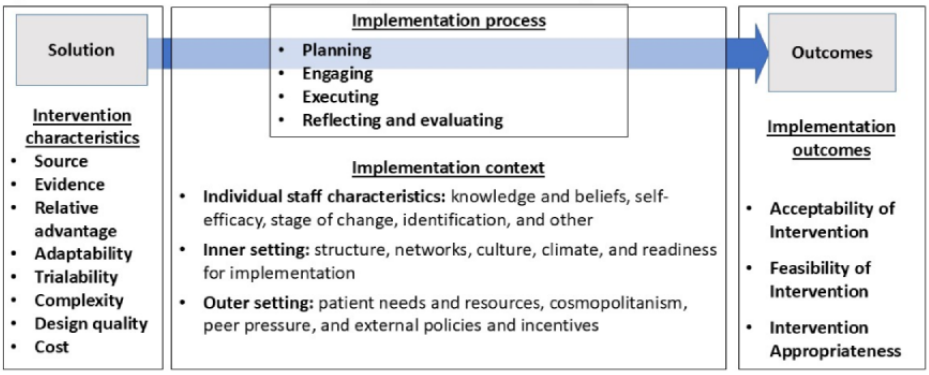

Cost-Effectiveness Outcomes

The cost calculator includes parametric models of cost inputs; cost model outcomes from this study will thus allow scenario analyses [67,84]. The proposed calculator will incorporate both the direct costs of the intervention (test administration, staffing costs, etc) and costs associated with interventions prompted by the 5-Cog (brain imaging, specialist referral, laboratory tests, etc). The cost calculator will thus enable others to determine 5-Cog delivery costs and implementation specifics such as the cost of hiring at future implementation sites. Data collected for the BIA will determine financial planning and affordability, while data collected for the CEA will determine the effectiveness and value of the 5-Cog paradigm compared to enhanced usual care.

Exploratory Outcomes

Medical billing for cognitive impairment detection paradigms may be an important component of sustainability [22] because PCPs often lack sufficient resources to support the effort required to care for patients with complex needs [96]. The 5-Cog may have benefit in enhancing billing opportunities because it incorporates 5 minutes of cognitive testing and may add to the level of medical complexity of a visit. As noted, one of the 5-Cog 2.0 study interventions—implemented at both 5-Cog and control sites—is provider education on billing for cognitive impairment detection, diagnosis, and treatment. Although the 5-Cog study does not include PCP billing interventions as part of its aims, we will monitor and compare the rates of use of “cognitive” billing codes (eg, Medicare AWV and current procedural terminology codes 96136 and 96138 [97]) between the 5-Cog and enhanced usual care sites. At the 5-Cog sites, we will examine whether the use of “cognitive” billing codes is associated with 5-Cog paradigm administration.

Assignment of Interventions

Sequence Generation

As in other pragmatic cluster randomized trials [98], we randomize at the clinic level. Commitment to join the study was sought from clinics. Once an adequate number of clinics (n=22) were identified, they were randomized. Computer-generated randomization assigned primary care practices in a 1:1 ratio within each site (the Bronx and Indiana) to either the 5-Cog paradigm or control arm. Randomization was stratified within each arm by clinic size (number of PCPs).

Allocation Concealment Mechanism

Randomization is central, computer generated, and not vulnerable to researcher influence. The study statisticians are blinded to interventions and other aspects of the trial.

Implementation

The 22 clinic clusters will be phased in gradually for logistical reasons, following a standardized procedure at each clinic: an overview presentation for leadership, a readiness presentation for providers and staff, and then study initiation.

Masking

Blinding of patients or PCPs at 5-Cog sites will not be feasible due to the nature of the intervention. However, the outcome is EMR based, and data abstractors will be blinded to allocation. Standardized checklists will be used for outcome measurement to further minimize bias. Statisticians will not be involved in the intervention delivery.

Data Collection, Management, and Analysis

Data Collection Methods

Data will be collected from 2 sources (refer to the following subsections).

EMR Data

We will collect EMR data on trial-enrolled patients aged ≥65 years receiving care in the participating practices after obtaining consent from the practice leadership and receiving a waiver from the institutional review board (IRB). Outcomes will be extracted and aggregated from the EMR. Deidentified analytic databases will be created and analyzed by investigators.

Feedback From Care Providers, Staff, and Patients

Data on clinician and practice staff perceptions of the intervention and factors that facilitated or impeded implementation and sustainability will be obtained through digital surveys and in-person interviews with key informants. Data on patient perceptions and experiences with the 5-Cog will be obtained through in-person, telephone, and video call platform interviews. Data collection will be the responsibility of the clinical trial staff at the site under the supervision of the site investigators. The investigator will be responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. All source documents will be completed in a neat, legible manner to ensure accurate interpretation of

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data. Hard copies of the study visit worksheets will be provided for use as source document worksheets for recording data for each participant consented and enrolled in the study. Data recorded in the electronic case report form derived from the source documents will be consistent with the data recorded on the source documents. All effectiveness and implementation data will be entered into REDCap (Research Electronic Data Capture; version 14.0.31; Vanderbilt University), a 21 CFR Part 11–compliant data capture system provided by the Albert Einstein College of Medicine through an NIH grant (UM1TR004400). The data system includes password protection and internal quality checks, such as automatic range checks, to identify data that seem inconsistent, incomplete, or inaccurate.

Data Management

Data collected for this study will be analyzed and stored at the Albert Einstein College of Medicine via REDCap. These data will be available through web-based registration to researchers for future analyses after the completion of our pragmatic clinical trial and publication of the main results. For resource-sharing approval, collaborators—both internal and external—will be required to register on the web and submit a resource transfer agreement. Requests can be submitted electronically to expedite research progress. Requests will also be reviewed by the steering committee at regularly scheduled meetings.

Effectiveness Study: Statistical Plan

The baseline characteristics of the clinical sites as well as individual enrolled patients will be examined after the baseline measurement time point at the halfway point of target enrollment. It is possible that baseline differences between the groups or missing data will limit the value of data analysis of measurements. Effects on the power to detect differences in the primary outcome will be evaluated and communicated to the principal investigators (PIs), data safety monitoring board (DSMB), and NIH. Given the monitoring plans outlined in the Monitoring subsection, it is exceedingly unlikely that there will be baseline differences between the groups of a magnitude that could threaten the validity of the study.

We will evaluate the clinical effectiveness of the 5-Cog paradigm on new cognitive impairment detection by comparing the proportion of “new MCI and dementia diagnoses” by PCPs within 90 days after the clinic encounter in the 5-Cog paradigm group versus the enhanced usual care group using generalized linear mixed effects (GLME) models with a logit link to account for clinic-clustered data [99]. Using these models, odds ratios of new MCI and dementia diagnoses between the 5-Cog paradigm and enhanced usual care arms will be calculated and tested. We chose a 90-day cutoff because the majority of PCP actions occurred within the first 30 days in our recent RCT [33]. The 22 clinics are cluster randomized to either the 5-Cog paradigm or enhanced usual care arm, which can result in correlated data due to clustering of patients within clinics. This issue will be handled using random effects in the mixed models. Proportions of new MCI and dementia diagnoses for each treatment group will also be reported. We will perform an intention-to-treat analysis. As a secondary approach, we will also perform a per-protocol analysis. All estimates will be reported together with their 95% CIs. The same method will be used for the secondary outcome (“improved dementia care”).

Stratified analyses across the 22 sites will be performed for groups impacted by health disparities, as designated by the NIH, including those from racial and ethnic minority groups (Black and Hispanic individuals) and individuals from socioeconomically disadvantaged backgrounds. Interactions between race and ethnicity and socioeconomic status (SES) will also be explored by stratified analyses by the combination of the 2 factors and by including the 2 factors and their product as well as interactions with the treatment groups in the GLME model for all enrolled patients. We will compare 5-Cog results by location in sensitivity analyses to detect any health care system–based variations.

All sample size and power calculations were performed using 2-tailed tests with a significance level of α=.05. The within-cluster intraclass correlation in this cluster randomized trial is assumed to be 0.05 based on prior studies [100]. On the basis of our RCT data, the proportions of “new MCI and dementia diagnoses” are expected to be 14% and 2% among the 5-Cog and control arms, respectively. The proportions of “improved dementia care” are expected to be 21% and 7% among the 5-Cog and control arms, respectively. In our total sample (N=6600), we have >99% power to detect the overall effectiveness of the 5-Cog paradigm on “new MCI and dementia diagnoses” and the secondary outcome of “improved dementia care.” Sample size determination was based on the primary outcome among individuals from racial and ethnic minority groups (2112/6600, 32%) and those with low SES (3750/6600, 56.82%). Assuming that 80% (1400/1800) of the participants in the 6 Bronx clinics are from racial and ethnic minority groups, and 75% (1350/1800) have low SES, as well as 14% (672/4800) and 50% (2400/4800), respectively, in the 16 Indiana clinics, 300 patients per cluster (clinic) will enable the detection of the effect of the 5-Cog paradigm on new MCI and dementia diagnoses with 81% power among individuals from racial and ethnic minority groups and 99% power among those with low SES.

Our outcomes are ascertained from the EMR by blinded assessors and do not require repeat in-person assessments. This will minimize missing data issues. We will implement robust EMR-based data management processes to further minimize missing data. Cluster sites are not contiguous, and patients within a cluster are assigned to specific PCPs who do not work across sites. Any intentional or unintentional contamination will be monitored by the data team, including by comparing enrolled patient lists across the sites.

Implementation Study: Statistical Plan

Interview data will undergo content analysis to identify and score implementation barriers or facilitators. Qualitative content analysis will be performed primarily using a deductive approach, starting from a developed theoretical model—the CFIR—and its associated hypotheses and then examining data to disconfirm or confirm these hypotheses [101]. The analysis will also allow for the inductive development of new themes, categories, and relationships as they arise from the data [102]. Deductive data analysis will be guided by the CFIR constructs and their

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definitions such that units of qualitative data (sentences or passages) are assigned to ≥1 codes reflecting the CFIR constructs [102]. We will use NVivo 15 (Lumivero) to manage and code qualitative data. For each implementation interview, there will be an artificial intelligence–generated transcript that will be manually reviewed by study staff before it is moved into NVivo. To guide systematic coding, a codebook will be developed. A multiple-analyst team will be trained and tested on its application. Analysts will code a random subset of interviews together during training and then assigned at a ratio of 2 to 3 per transcript for either all or a subset of transcripts, depending on the original level of coding agreement (ie, interrater reliability) [103,104]. Subsequent coding discussions will be held intermittently for the calibration and discussion of difficult cases and disagreements. Interrater reliability will be computed in NVivo at the start, middle, and end of coding, with retraining and adjustments to the plan depending on the results. Inductively, we will allow for the emergence of new codes and subcodes [104]. We will also use applied thematic analysis [105] to identify patterns within and between codes. As much as possible, data analysis will occur in parallel with data collection, enabling us to adjust data collection procedures to capture emerging and unexpected phenomena, as well as perform member checking with informants willing to complete follow-up interviews to review and validate our coding of their initial interviews. Within each CFIR code, for each implementation context or process element, the assigned analyst will add a rating on a scale ranging from +3 (strong facilitator) to −3 (strong barrier) [54]. Analysts will be trained to use evidence from interviews and not personal opinions to rate each driver [102].

RAs in Indiana and the Bronx will be trained by coinvestigators to reliably collect implementation process data from a combination of documents, field notes, and interviews, with select staff responsible for the implementation process. To capture implementation data monthly, while minimizing staff burden, we will use the Prospectively Reported Implementation Update and Score [106]. The analysts will reconstruct these data into process maps or workflow diagrams depicting key historic moments, process variations, and players [54,59,102].

Linking Implementation to Effectiveness Analysis

Examining how stakeholder-level factors impact and are impacted by the 5-Cog implementation is critical because implementation can be influenced by stakeholders' characteristics, attitudes, intentions, and motivations. Stakeholder-level factors are also shaped by organizational factors [107]. Following the guidance of Damschroder and Hagedorn [58], we will link identified and rated (+3 to −3) context and implementation process drivers to implementation outcomes. Our analytical approach is as follows: we will derive clinic-level mean and variability measures of the AIM, FIM, and IAM scales and examine whether these implementation measures are associated with cognitive impairment detection by using GLME models with a logit link, treating the mean and variability measures of the AIM, FIM, or IAM as independent variables [108]. This analysis will determine how detection rates are associated with the levels or variabilities in implementation acceptance, perceived feasibility, and appropriateness within each clinic. We will explore whether and how context variables account for 5-Cog effects on outcomes by including quantitative context measures and interactions with the intervention group as independent variables in the GLME models from the effectiveness analysis [108]. We will then develop a thematic matrix that includes characteristics derived from stakeholder surveys and emerging themes from our qualitative data for each 5-Cog clinic site and conduct side-by-side comparisons—at system, organizational, and staff levels—of the factors that were identified as facilitating or hindering 5-Cog implementation. We will note common and unique factors for each clinic or location. This will generate a list of relevant system-, organizational-, and staff-level factors and processes organized by level of consensus (ie, identified by >1 source) and operational salience (ie, identified as critical for implementation). We will use this list to generate a heuristic model to inform future implementation strategies [54,55].

CEA and Economic Impact

Using data from the BIA cost-tracking tool, the cost-effectiveness ratio [109,110] "numerator" will account for site personnel and other costs at both intervention and control sites. The denominator will represent the number of cognitive impairment cases identified at the 5-Cog and control sites. In summary, the cost-effectiveness ratio represents the incremental cost of the 5-Cog intervention compared to enhanced usual care to achieve a clinically meaningful change, divided by the difference in effectiveness, to determine the cost per cognitive impairment case identified. This is expressed as follows:

Cost-effectiveness ratio = intervention costs + Δ (health care costs) / Δ health outcomes (5-Cog) – Δ health outcomes (enhanced usual care comparison group)

To assess uncertainty in our analysis, we will follow the recommendations of the International Society for Pharmacoeconomics and Outcomes Research and the Society for Medical Decision Making Modeling Good Research Practices Task Force [63,65-68,111]. Variability of inputs across study sites with differing levels of social determinants of health will be included in analyses [112]. Differences in intervention and health care costs due to secondary procedures will be assessed individually using negative binomial regression and reported with a 95% CI. Only statistically significant differences from the regression analyses will be incorporated into the cost-effectiveness ratio. Differences in health outcomes will be assessed as described in the Effectiveness Study: Statistical Plan subsection, and the estimate of the GLME model, if significant, will be incorporated into the cost-effectiveness ratio. Costs will be discounted at a 3% annual rate for the trial period, as recommended by the Second Panel on Cost-Effectiveness in Health and Medicine [113].

Monitoring

Data Monitoring

Each clinical site will perform internal quality management of study conduct, data collection, documentation, and completion. All sites will follow a common quality management plan. Before we began data collection, the PIs and the DSMB chair reconfirmed that our sites have appropriate safety measures in

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place. The DSMB met with the entire research team to review the study protocols. Particular attention was paid to outcome definition, study design, procedures for recording and reporting adverse events (AEs), informed consent procedures, and documentation. At its initial meeting, the DSMB approved the protocol and formulated its operating procedures (eg, meeting schedule, report deadlines for the study statistician, unblinding policy, and guidelines for releasing interim data to the investigators). At this meeting, the plans for interim monitoring for efficacy and futility were presented to the DSMB to aid in trial oversight. We will train competent staff to conduct the assessments and ensure that they understand the data collection procedures and process as well as AE reporting requirements.

Effectiveness Study: Monitoring for Harms

Patients who receive care at the practices randomized to implement the 5-Cog paradigm may experience minimal risk through their participation. It is possible that patients may feel shame, anxiety, and some emotional discomfort when completing the cognitive assessment; however, this may be the case with the standard of care cognitive assessment as well and may not be specific to the intervention arm. In addition, in our ADRD screening trial that evaluated the potential benefits and harms of ADRD screening, there were no differences between the screened and control groups in quality of life, depressive symptoms, or anxiety [114,115]. That trial also assessed the impact of this early diagnosis on participants' quality of life and care and found no negative impact on quality of life, depression, anxiety, health care use, or independence at home [114,115]. The risk of potential harm such as stigma is not known. However, the early detection of ADRD is considered part of the standard of care, and screening for ADRD is part of the AWV covered by Medicare because of the significant potential benefits.

Implementation Study: Monitoring for Harms

Answering questions on surveys and participation in interviews with trained personnel involve minimal psychological, social, or other risks. We do not expect any AEs during these noninvasive assessments.

Full Study: Monitoring for Harms

Safety oversight will be under the direction of a DSMB composed of individuals with the appropriate expertise. We will set up a data safety monitoring plan, which will be monitored by the PIs and DSMB. The PIs will also conduct data and safety monitoring and will regularly monitor study progress, goal achievement, and overall research direction in consultation with the coinvestigators. Members of the DSMB will be independent from the study conduct and free of conflicts of interest. The DSMB, which will meet at least semiannually to assess safety and efficacy data from each study arm, will operate under the rules of an approved charter that was written and reviewed at its organizational meeting. The DSMB will provide its input to the National Institute of Neurological Disorders and Stroke and NIH staff.

AEs will be monitored on an ongoing basis by the study managers through self-initiated reports from participants or patients, observations of research and clinic staff at the intervention sites, biannual review of acute care use among enrolled patients, and review of EMR data at 90-day outcome collection for any medical records or notes of medical, psychological, or stress symptoms possibly related to the administration of the 5-Cog battery. In addition, a list of hospitalizations and emergency department visits (for any reason) occurring within 90 days after the clinic visit will be generated by the EMR system, which will be reviewed by the PIs and study investigators. All AEs not otherwise precluded per the protocol will be captured on the appropriate case report form. Information to be collected includes event description, time of onset, clinician's assessment of severity, relationship to study procedures (assessed only by those with the training and authority to make a diagnosis), and time of resolution or stabilization. All AEs occurring during the study will be documented appropriately regardless of their relationship to the intervention and followed until adequately resolved. Any preexisting medical or psychiatric conditions at screening will be considered baseline and not reported as an AE. However, any deterioration in a patient's clinical or psychological condition during the assessment will be recorded as an AE. Changes in AE severity will be documented to assess the duration of the event at each severity level. For AEs characterized as intermittent, the onset and duration of each episode will be documented. New diagnoses of MCI or dementia may result in psychological stress for patients that may not be captured in the EMR. Hence, we will also assess these more subtle psychological symptoms during the implementation interviews.

Auditing

Quality control procedures will be implemented. In the implementation study only, regarding informed consent, study staff will review both the documentation of the consenting process and a percentage of the completed consent documents to evaluate compliance with good clinical practice, accuracy, and completeness. Feedback will be provided to the study team to ensure that proper consenting procedures are followed. To assess data accuracy (the level of correctness of stored information [116]), site staff will compare a representative sample of source data against the database, focusing on key data points. The study team will review protocol deviations on an ongoing basis and implement corrective actions if deviations reach a concerning level. Should independent monitoring become necessary, the PIs will provide direct access to all trial-related sites, source data and documents, and reports for monitoring and auditing by the funding agency and inspection by local and regulatory authorities.

Ethical Considerations

The Albert Einstein College of Medicine IRB approved this study (2022-14144) and serves as the IRB of record for both sites under a reliance agreement with the Indiana University IRB. This study will be conducted in accordance with federal publication and data-sharing policies and regulations. Regarding consent for participants, we received a waiver of informed consent from individual patients from the IRB to maintain the pragmatic design of the clinical trial. For the implementation part of the study, consent is obtained from all participants before

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completion of any study measures. Participants who consent for the implementation study receive US $25 in compensation for completed interviews. Outcomes will be extracted and aggregated from the EMR and will be deidentified. After the study is completed, the deidentified, archived data will be transmitted to and stored in a data repository with protections in place for patient confidentiality.

Results

The grant was funded, and the protocol received IRB approval, in September 2022.

Effectiveness Study

A validation cohort of 76 older patients (mean age 76.5, SD 7.72 y; n=50, 66% women) from dementia centers at Montefiore Einstein was evaluated with the 5-Cog battery to determine optimal cut scores. This was completed by July 2023. Among these 76 patients evaluated by the multidisciplinary care provider team at these centers (neuropsychology, neurology, and geriatrics), the resulting clinical diagnoses were as follows: 32 (42%) had a diagnosis of dementia, 28 (37%) MCI, 12 (16%) subjective cognitive concerns without objective cognitive impairment, and 2 (3%) had no cognitive diagnosis assigned. The mean scores on the PMIS were 5.8 (SD 2.7), Symbol Match 27.2 (SD 18.2), and sMCR 2.4 (SD 1.7). We correlated performance on the individual 5-Cog battery tests with the Blessed Information-Memory-Concentration Test scores (range 0-32; higher scores indicate worse performance), an omnibus test of general mental status (mean 10.3, SD 6.8). The PMIS (Pearson $r=-0.76$; $P<.001$) and Symbol Match ($r=-0.69$; $P<.001$) showed excellent correlation with Blessed scores. While the sMCR was not correlated with Blessed scores ($r=0.008$; $P=.95$), it was correlated ($r=-0.34$; $P=.007$) with walking speed (mean 72.3, SD 25.3 cm/s) in this sample. The PMIS was correlated ($r=-0.59$; $P<.001$) with the 5-item memory recall subtest on the Blessed Information-Memory-Concentration Test (mean 2.9, SD 1.84; higher scores indicate worse performance). Symbol Match was correlated ($r=0.88$; $P<.001$) with the Symbol Digit Modalities Task score (mean 21.2, SD 14.6; lower scores indicate worse performance).

As we examined the sensitivity and specificity data to choose cut scores, we chose to favor sensitivity to minimize missing individuals with true disease in this sample of patients considered high risk because of their cognitive concerns. The cut scores for a *positive* result on the 5-Cog components were as follows: PMIS ≤6 (range 0-8), Symbol Match ≤25 (range 0-65), and sMCR >5 (range 0-7). There was a high rate of completion of the PMIS (75/76, 99%), Symbol Match (76/76, 100%), and sMCR (74/76, 97%) tests on the 5-Cog battery, indicating high acceptability and feasibility of administration of the 5-Cog battery in populations with cognitive impairments.

The DSMB met in July 2023, approved the protocol and data safety monitoring plan, and authorized study enrollment. By October 2023, all 22 clinics had agreed to participate and been randomized. By November 2023, decision support tool integration into the EMRs had been finalized. As of December 2024, a total of 12 clinics had completed onboarding processes (refer to the Methods section, Care Provider Education and Preparation subsection), and 2369 patients had been enrolled.

Implementation Study

We have completed 6 implementation interviews and 23 implementation surveys over 12 clinic sites.

Cost-Effectiveness Study

5-Cog 2.0 investigators have already collected procedure and health care cost estimate data for Montefiore-Einstein for a 5-Cog 1.0 CEA. Preliminary results suggest that the 5-Cog paradigm is a cost-effective option compared to “enhanced usual care” for the early detection of cognitive impairment in primary care (H Congivaram, BS, unpublished data, December 2024). Investigators have begun collecting cost estimates for 5-Cog procedures and resulting health care costs in the IUH system, as these were not previously collected.

Discussion

Anticipated Findings

The results of this 5-Cog 2.0 RCT will provide additional evidence that the 5-Cog paradigm is effective in improving dementia diagnosis. At the same time, the implementation portion of this study will provide critical information about the context, facilitators, and barriers to using the 5-Cog successfully, while the cost-effectiveness portion of this study will offer a practical analysis of the cost implications of the paradigm. Taken together, these study outcomes will allow informed, tailored, and rapid adaptation and dissemination of the 5-Cog paradigm to diverse primary care environments.

Meeting the ongoing and anticipated growing need for timely dementia diagnosis and care has been a focus of much study. Despite the availability of high-quality tools for dementia detection [22], significant gaps remain in real-world application, and the rates and timeliness of diagnosis remain unacceptably low [28,117,118]. This translates to clinical “blind spots” for care providers and missed opportunities for patients. These gaps are even more pronounced among individuals from historically minoritized racial and ethnic groups [5,119]. The 5-Cog paradigm is poised to effectively bridge these gaps. The 5-Cog itself is designed for widespread applicability, with characteristics that make it appropriate for individuals from various cultural, linguistic, and literacy backgrounds [32,33]. The 5-Cog’s simple, fast format also makes it easily adaptable in resource-limited environments in contrast to some cognitive assessment tools that require specialized training or equipment to administer [120,121]. Although the evidence for decision support systems to improve clinical practice is mixed [50,122], the 5-Cog paradigm does build on prior evidence of the efficacy of decision supports in dementia detection [123,124].

Strengths and Limitations

This study has several strengths. Its results are anticipated to have improved generalizability compared to prior studies for several reasons: its large sample size; the racially and ethnically diverse patient population being enrolled; and the pragmatic nature (using local CHW staff, colocation in patients’ usual sites of care, and a waiver of written informed consent), which

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may help reduce the hesitancy of individuals from historically marginalized groups to participate in the trial [125]. While the characteristics and specifications of primary care clinic sites will vary, the urban and rural primary care clinic sites in the 5-Cog study are typical of primary care clinics in the United States, especially those that serve underserved individuals from historically minoritized groups. Prior studies of decision supports in dementia were limited by a small sample size and a lack of active control groups [50,122]. The 5-Cog 2.0 study overcomes these limitations. Another strength of this study is that the BIA will form the basis of a tool that can be used to tailor financial adoption and scalability in different practice settings for national implementation. Finally, this study's unique hybrid effectiveness-implementation design will rapidly generate actionable data to advance progress in closing dementia care gaps. This study is anticipated to have a few limitations. Although the inclusion criteria are intentionally liberal in this pragmatic trial, the trial may not address dementia care gaps for the subset of patients who lack insight into their cognitive impairments and deny having them and are therefore not eligible for the trial. Implementation analyses will allow an exploration of whether and how the 5-Cog can support PCPs' clinical approach to this subset of patients who do not recognize their own cognitive decline. A limitation of the CEA is that the time horizon is relatively short, and long-term sustainability will need to be assessed in future studies.

Anticipated Dissemination Strategy

The information gained about the 5-Cog paradigm, including details of the EMR-embedded clinical decision support and incorporation into medical billing systems, in this pragmatic trial will enable future implementation in everyday clinical settings across the United States for routinely detecting cognitive impairment, including dementia. For dissemination, this trial has been registered at ClinicalTrials.gov (NCT05515224), and results information from this trial will be submitted to ClinicalTrials.gov. Every attempt will be made to publish the results in peer-reviewed journals. Final research data will be shared openly and in a timely manner: data from this study may be requested from other researchers 1 year after the completion of the primary end point by contacting Albert Einstein College of Medicine. For dissemination of the 5-Cog paradigm itself, the 5-Cog forms and administration instructions will be made available on a publicly facing website. 5-Cog team members anticipate making presentations at national conferences of clinical, educational, and administrative leaders in dementia care to facilitate the dissemination of the paradigm.

Future Directions

Although there will not be a "one-size-fits-all" solution to detecting cognitive impairment across the country, we anticipate that elements of the 5-Cog battery can be adapted in distinct sites and further studied; for instance, pictures in the PMIS may need to be updated to account for local cultural and ethnic factors. We also anticipate that, as new knowledge regarding MCI and dementia and treatments emerges in the future, we will have to update the 5-Cog decision tree and adapt to other EMR systems. Finally, the results of this study will provide the foundation for further study of the 5-Cog assessment for use in the increasingly common collaborative dementia care models [15,30,126-128], as a screening paradigm for population health models [129,130], and to evaluate the impact of early detection on clinical care and outcomes.

Acknowledgments

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Data Availability

The data that support the findings of this study will not be publicly available due to reasons of confidentiality. On reasonable request to the corresponding author, individual deidentified participant data (including data dictionaries) will be made available via a REDCap (Research Electronic Data Capture) web-based database, after review and approval of a methodologically sound proposal, with a signed data access agreement, in line with ethics committee requirements.

Authors' Contributions

JV and MB were responsible for conceptualization and funding acquisition. EA, DA, AH, and PY were responsible for data curation. CW and HX were responsible for formal analysis. JV, MB, JZ, RBRC, AT, EA, EFW, AA, KF, CW, DA, DDF, JMW, HC, NRF, DS, HX, AH, RJH, MM-V, CN, and PD were responsible for methodology. EA, MM-V, PY, NRF, AH, RBRC, EFW, AA, and CN were responsible for project administration. JV, MB, and AA were responsible for resources. RBRC, DS, and PD were responsible for software. JV, MB, NRF, JZ, EFW, and RJH were responsible for supervision. RBRC, PY, EA, EFW, and DS were responsible for visualization. RBRC, EA, JV, and MB wrote the original draft. EA, JV, MB, NRF, EFW, AT, AA, PY, CW, JZ, KF, DS, RJH, HX, DDF, JMW, HC, MM-V, CN, PD, AH, and DA reviewed and edited the manuscript.

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Conflicts of Interest

JV serves on the editorial boards of the Journal of the American Geriatrics Society and the Journals of Gerontology, Series A: Medical Sciences. He serves as a scientific adviser for Catch U, Inc, and MedRhythms, Inc. JV, EA, and EFW hold a copyright for the 5-Cog battery (TX9340781). MB serves as chief scientific officer and cofounder of Blue Agilis, Inc and chief health officer of DigiCare Realized, Inc. He has equity interest in Blue Agilis, Inc and DigiCare Realized, Inc (he sold his equity in Preferred Population Health Management, LLC and MyShift, Inc [previously known as RestUp, LLC]). He serves as an advisory board member for Eli Lilly and Company, Eisai Inc, Merck & Co, Inc, Biogen, Inc, and Genentech, Inc. MB's conflicts have been reviewed by Indiana University and have been appropriately managed to maintain objectivity. All other authors declare no conflicts of interest.

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Abbreviations

ADRD: Alzheimer disease and related dementias
AE: adverse event
AIM: Acceptability of Intervention Measure
AWV: annual wellness visit
BIA: budget impact analysis
BPA: best practice advisory
CEA: cost-effectiveness analysis
CFIR: Consolidated Framework for Implementation Research
CHW: community health worker
DSMB: data safety monitoring board
EMR: electronic medical record
FIM: Feasibility of Intervention Measure
GLME: generalized linear mixed effects
IAM: Intervention Appropriateness Measure
IRB: institutional review board
IUH: Indiana University Health
MCI: mild cognitive impairment
MCR: motoric cognitive risk
NIH: National Institutes of Health
PCP: primary care provider
PMIS: Picture-Based Memory Impairment Screen
RA: research assistant
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SCQ: subjective cognitive concern questionnaire
SES: socioeconomic status
sMCR: Subjective Motoric Cognitive Risk

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Protocol

Web-Based Human Papillomavirus Education and Professional Skills Intervention for Health Care Providers: Protocol for a Randomized Controlled Trial

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Abstract

Background: The human papillomavirus (HPV) vaccine is an effective way to prevent HPV and its associated cancers. Provider recommendation has been shown to be one of the most successful strategies for increasing the uptake of the HPV vaccine; however, more training and resources are needed to help boost health care providers' confidence and communication skills in recommending the HPV vaccine to their patients, particularly in underserved Hispanic communities where vaccination rates among all ages are lower.

Objective: This study aims to compare HPV educational and professional skills intervention effectiveness on improving provider recommendations and patient communication strategies with health care providers serving the El Paso United States–Mexico border region.

Methods: We will conduct a randomized, blinded, multiple posttest-only controlled behavioral trial using a parallel group design that will examine the effectiveness of a fully automated, web-based, culturally tailored HPV education and professional skills intervention containing unique reading material and video role-play, as compared to a standard Centers for Disease Control and Prevention fact sheet and video about general communication skills. Participants were recruited using a purposive sampling technique, both internet-based and in-person outreach events. Study data are being collected and managed using REDCap (Research Electronic Data Capture; Vanderbilt University) hosted at the University of Texas at El Paso. Chi-square analyses, ANOVA, and other statistical tests will be used with 2-tail α to reject null hypotheses at .05 to analyze the self-assessed outcome data. The Mauchly test of sphericity for each ANOVA and the Huynh-Feldt epsilon test or Greenhouse-Geisser correction to the degrees of freedom of the F-ratio will be reported for each significant effect. We may use multiple imputation procedures to handle the missing data (if applicable). This study is being conducted in the west Texas or southeast New Mexico region of the United States. Chi-square analyses will be used to assess associations between variables reported on the baseline provider knowledge, attitudes, and practice scales. We seek to examine self-assessed changes in provider attitudes and behaviors regarding HPV vaccine recommendation 1 month after receiving our unique multimedia and culturally tailored intervention.

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Results: Research and data collection for this clinical trial began in December 2023. Participant recruitment was closed by May 2024 (N=128), with final data collection expected to be completed by December 2024.

Conclusions: This study team decided to report on the intervention protocol to help ensure transparency in the research process and facilitate the improvement of the research design. Tailored web-based educational programs for health care professionals, designed to address regional and patient population characteristics, may be a promising approach to enhancing the real-world implementation of clinical practice guidelines.

Trial Registration: ClinicalTrials.gov NCT05120869; http://clinicaltrials.gov/ct2/show/NCT05120869

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KEYWORDS

human papillomavirus; randomized controlled trial; HPV knowledge; HPV vaccine; health care provider; provider recommendations; communication strategies; Hispanic

Introduction

Overview

The human papillomavirus (HPV) is a primarily sexually transmitted infection that affects approximately 40 million Americans and is associated with 6 types of cancer [1]. A total of 3 HPV vaccines (nonvalent, quadrivalent, and bivalent) have been developed, licensed, and shown to be effective in preventing high-risk HPV infection. Current immunization guidelines recommend that children aged 11-12 years initiate a 2-dose HPV vaccine series but can begin as early as 9 years of age. Young adults older than the age of 15 years with no previous history of HPV vaccination can start a 3-dose series; the 9-valent HPV vaccine is also approved to protect against 73% of HPV-associated cancers for adults older than 26 years of age [2]. Although national vaccination rates in the United States have steadily increased over the years, vaccination rates for adolescents remain well below the 80% designated target goal set forth by Healthy People 2030 [3]. The need for this vaccine is particularly salient considering the high direct and indirect costs of HPV and associated cancers in the United States; for example, Ong et al [4] found that the average cost of HPV-related cancer and other diseases was approximately US $38,056 per case.

HPV Health Care Provider Recommendation Practices

Recent studies reveal that receiving a recommendation from a health care provider is a crucial factor influencing HPV vaccine uptake among parents of vaccine-eligible children and adults themselves [5-8]. However, in a study currently under review, many health care providers have reported that while they have sufficient knowledge and understanding about HPV and its treatment and prevention, they often lack the confidence to effectively communicate about HPV and recommend the vaccine to their patients. Similarly, some populations, such as adults, men, and sexual minority individuals (members of the LGBTQ+ [lesbian, gay, bisexual, transgender, and queer/questioning] community), are less likely to be encouraged to get vaccinated and tend to have inaccurate perceptions of the importance of vaccination [9]. Due to the need to improve training and resources for health care providers concerning HPV vaccine recommendation (in addition to the recommendation of other salient vaccines such as influenza and meningococcal vaccines [10,11]), researchers have explored the effectiveness of several approaches, theories, and foci when recommending HPV vaccination. The combined use of the presumptive approach (in which the provider assumes parents will vaccinate their child rather than communicating that the HPV vaccine is optional), along with motivational interviewing and a fact sheet for vaccine-hesitant clients, results in higher perceived levels of parental HPV vaccine acceptance [5]. Furthermore, studies [6,7] emphasize the importance of providing recommendations that “announce” the need for the HPV vaccine in a manner that is brief, easy to understand, and focused on cancer prevention.

Beyond the need for improved HPV vaccine recommendations among health care providers’ nationwide, enhancing communication strategies is particularly important for health care providers practicing with racial minority populations, such as predominantly Hispanic populations residing along the United States–Mexico border. Recent literature has identified both barriers and facilitators that exist in trying to increase HPV vaccine uptake in a diverse and predominantly Hispanic community [12]. Similarly, a recent quantitative study revealed that HPV vaccine acceptability in Hispanic young adults is associated with several factors, including the number of HPV informational sources, number of HPV discussions, health care provider recommendations, having a health care provider with similar characteristics, and family vaccine perceptions [12]. Another study found that culture-based factors such as familism and trusted sources of information can predict HPV vaccine acceptance [13]. Additionally, Xu et al [14] demonstrated that patient-provider health communication strategies aimed at enhancing HPV vaccine uptake among racial minority patients must be culturally tailored for the intended population, while including approaches that increase provider self-efficacy, use persistent language, reframing vaccine conversation focus from sex to cancer, and working with the community to culturally sensitize vaccine-related language. All these findings highlight the importance of receiving HPV vaccine recommendations from health care providers in a culturally competent manner, as well as the importance of family in shaping perceptions and behaviors related to vaccinations.

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Web-Based Health Care Professional Educational Interventions

To improve patient care and population health outcomes, health care providers rely on clinical practice guidelines (CPGs) to stay current with evidence-based recommendations [15]. However, the dissemination and implementation of guidelines, such as those for HPV vaccination and screening, vary across health professionals. While traditional print-based delivery methods for CPGs have largely shifted to digital platforms, digitizing guidelines on medical authority websites (eg, the Centers for Disease Control and Prevention [CDC]) have improved the access for health professionals. Despite improved access, time constraints often make it difficult for providers to actively search for and apply these guidelines without additional support. The absence of supportive modules that assist with real-world implementation, such as HPV recommendation practices, creates barriers to addressing gaps in care. Notably, research has shown that web-based medical educational modules can be as effective as in-person training in helping health care providers implement CPGs more efficiently [16].

Intervention Theoretical Framework

Elements of the Health Belief Model have been examined as predictors of HPV vaccine acceptance and uptake among adults in the United States–Mexico border region in a previous study conducted by the researchers [13]. This model demonstrates that a broad range of intersectional factors play a role in an individual's health choices and behaviors, such as perceived benefits (in this case, the belief that the HPV vaccine will prevent infection and cancer) and perceived severity, which have both been associated with HPV vaccine acceptance [13]. Frietze et al [13] also studied perceived safety and perceived harm as predictors of acceptance and uptake. Therefore, the proposed intervention has incorporated 4 tenets of the Health Belief Model (perceived benefits, severity, safety, and harm) into the intervention to increase provider vaccine recommendation practices and strategies. The tailored intervention also builds on educational models including HPV biology, epidemiology, and disease morbidity, coupled with role-played conversations in clinical video vignettes using the "announcement" approach, in which the health care provider works from the presumption that patients or parents will accept the vaccine. The research question is, will health care providers receiving a web-based, culturally tailored, HPV-specific professional skills intervention report stronger HPV prevention recommendation behaviors at 0-3-6 months post intervention, compared to health care providers receiving a web-based intervention using publicly available CDC HPV provider materials and general communication skills modules?

Research Aims and Hypothesis

This study is guided by 2 aims. Aim 1 is to assess the knowledge, practices, and beliefs of emerging and current health care providers in the Paso del Norte Region related to HPV prevention, HPV vaccine, and HPV-associated cancers. Aim 2 is to facilitate the prevention of HPV-associated cancers in the Paso del Norte Region through strengthened recommendation of the HPV vaccine and screening by health care providers.

It is hypothesized that health care providers receiving a web-based, culturally tailored, HPV-specific professional skills intervention will report higher between-group changes in proportions on the HPV health care provider (HCP) practices scale at 0, 3, and 6 months post intervention, compared to health care providers receiving the standard web-based CDC HPV provider materials and communication skills active control intervention.

Methods

Ethical Considerations

This study was approved by the University of Texas at El Paso institutional review board (#1441487). Participation in the study was voluntary and confidential. All potential participants who were screened and met eligibility were invited to join the study and provided informed consent. Informed consent covered primary and secondary data collection procedures and data analysis and dissemination following the completion of the study. Participants consented to relinquish the ownership of anonymous data to the research team for dissemination (primary and secondary analysis). All study data will be deidentified and survey responses will be anonymous. Participants are compensated in the form of a US $30 electronic gift card for the completion of the initial survey and a US $10 electronic gift card for the completion of each of the follow-up surveys (US $50 total throughout the course of the study). The study information sheet made clear to participants that they were free to withdraw from the study at any time with no consequence to them, and withdrawal protocols with contact information were included.

Study Trial Design

We will conduct a mixed (within-between) subjects longitudinal design in which participants are randomly assigned to 1 of the 2 conditions and will be assessed over 3 time points using a parallel group design to examine the effectiveness of a tailored versus a standard HPV education and professional skills intervention. Emerging and current health care providers will be randomly assigned to 1 of the 2 conditions. (1) Treatment condition in which they will receive a tailored Education and Professional Skills Intervention and (2) control condition in which they will receive general, publicly available (ie, CDC) information about HPV and communication skills. Participants will then be followed over 3- and 6-month time frames, and group differences will be assessed. Furthermore, this clinical trial protocol will follow the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) to report the internet-based educational modules (behaviorally based treatment) [17]. The completed itemized checklist instrument is provided in Multimedia Appendix 1.

Study Setting

The intervention is internet based, and participants will complete the survey using personally owned computers, tablets, or cell phones. This study is based on, deployed in, and will reach health care providers primarily in the Paso Del Norte Region, which includes El Paso County, Texas, and Southern New

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Mexico, including Dona Ana County, and the cities of Alamogordo, Hobbs, Artesia, Roswell, and Lovington. The population is predominantly Hispanic, with 82.9% (718,964/867,239) of the population of El Paso County, Texas, identifying as Hispanic or of Latin ancestry, and 50.2% (1,061,413/2,114,371) of the population of the State of New Mexico identifying as Hispanic or of Latin ancestry [18,19].

Community Advisory Board

A community advisory board was formed, as community advisory boards have previously demonstrated to be effective when planning health-related programs and interventions to facilitate meaningful and structured engagement with local community members [20]. Our community advisory board consisted of a formalized collective of community members, research stakeholders, regional clinical partners, and other academics from several institutions, including The University of Texas at El Paso, Texas Tech University Health Sciences Center El Paso, and New Mexico State University. The community advisory board was instrumental in providing insight into the local community while providing insight to develop equitable partnerships with the community. The community advisory board has been involved in all phases of the intervention development, from the reconnaissance phase to the intervention's development, and will remain a vital component of the intervention until the study has concluded and results are evaluated. To date, the community advisory board has met periodically and has been provided with a report of ongoing project-related activities and project progression. All community advisory board feedback and suggestions have been taken into consideration and retro fed back into project-related activities.

Acceptability, Pretest, and Pilot

All components of the clinical trial (survey, control and experimental intervention modules, recruitment plan, and communications) underwent multiple rounds of review and revision by members of the research team. In addition, the intervention and survey were pilot-tested with a small group (n=7) of health care providers in training or in practice, and feedback from those individuals was incorporated into the final products. For example, demographic questions such as participant gender were changed to reflect participant's concerns on gender identity (to include nonbinary and gender nonconforming individuals). For example, "Which of the following best describes your gender identity: male, female, transgender male, transgender female, gender variant/nonconforming, prefer not to answer," and an "other" option which permits text entry. In addition, the pilot test helped to clarify questions regarding previous HPV infections: "How likely do you think it is that you have ever been infected with HPV?" and "How likely do you think it is that your current or recent partner(s) has (have) ever been infected with HPV?" A question was added to elicit the zip code in which the participant primarily practices or trains in, and the amount of time it would take to complete the study was adjusted.

Consolidated Standards of Reporting Trials Flow Diagram

Progress through the phases of this planned randomized trial (ie, enrollment, intervention allocation, follow-up, and data analysis) will be visually represented using the CONSORT (Consolidated Standards of Reporting Trials) flow diagram [17]. A participant is considered to have completed the study if they have completed the initial postintervention assessment and the 3-month and 6-month follow-up assessments.

Intervention Materials

The intervention materials and survey were developed and produced by members of the research team based on, and in alignment with, a health care provider survey and a community needs assessment conducted under the larger parent study [13,21]. HPV knowledge, practices, and beliefs will be assessed, as was done previously in formative research, with additional questions that further assess in-depth provider recommendation behaviors for HPV vaccination that is inclusive of vaccine-eligible age groups and genders. We will also inquire about provider comfort in communicating with patients about sexual health topics, vaccines, and cancer.

Participants will be randomly assigned to 1 of the 2 conditions: (1) the treatment condition, in which they receive the tailored HPV Education and Professional Skills Intervention, and (2) the control condition, in which they receive the General Education and Professional Skills Intervention. An internet-based platform will be developed to deploy the HPV Education and Professional Skills Intervention to emerging or current health care providers. The platform will be comprised of training modules divided into 3 sections paralleled among control and experimental groups—a document to be read, a video to be watched, and an activity to complete. Participants will take 15-30 minutes to complete all 3 sections of the module.

Control Group Materials

The control group (active comparator) will receive the General HPV Education and Communication Skills Intervention materials, which will be comprised of a 3-page PDF document, a web-based video, and 4 rank-order multiple-choice questions to answer. The PDF document will be a standard, publicly available HPV fact sheet from the CDC. The video contains information on improving basic communication skills as would occur in a business or interpersonal setting. The multiple-choice questions will ask the participant to select their preferred mode of communication (ie, email, text, phone call, or face-to-face) in different scenarios.

Experimental Group Materials

The experimental treatment group will receive the tailored HPV Education and Communication Skills Intervention materials, which comprised the same categories of content as in the control intervention. In this case, the 3-page PDF document is modeled after the CDC HPV fact sheet but includes data from the first phase of our program and informs the reader of important and relevant research findings from our region. The video was produced in-house and scripted to focus on improving provider communication with patients, specifically regarding HPV, the HPV vaccine, and addressing vaccine hesitancy. The

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multiple-choice questions are presented as clinical vignettes with response options that address patient concerns, and participants will rank them in terms of their perceived effectiveness.

Thus, the control module will engage participants to improve general communication skills and increase baseline knowledge about HPV, HPV vaccine, and HPV-associated cancers. The experimental intervention module, in contrast, will specifically engage participants to improve patient-provider communication and strengthen HPV vaccine recommendations through (1) identifying critical points of discussion regarding the HPV vaccine and patient health; (2) encouraging discourse on vaccines that are optional (eg, influenza) for patients; (3) sharing best practices for discussing vaccines with patients or parents who are vaccine-hesitant; (4) increasing provider understanding about generalized and region or culture-specific reasons for vaccine hesitancy among patients; and (6) facilitating increased knowledge about HPV, the vaccine, and its cancer relevance.

Surveys are to be delivered 3 and 6 months after the initial intervention, and the survey will again evaluate provider knowledge, practices, and beliefs regarding HPV, HPV vaccine, and cancer and will also specifically assess changes in provider behavior since the intervention. Uptake of the HPV vaccine by the provider or their children, assuming eligibility, will be tracked, as will provider recommendation behaviors and levels of comfort in interacting with patients when issues of sexual health, vaccine hesitancy, or cancer prevention arise.

Study Outcome Measures

Provider Practices

The primary outcome of interest is between-group changes in proportions of provider practices. This will be measured on the 8-item HPV HCP practices scale (HCP vaccine recommendations, HCP screening recommendations, and HCP communication practices) scored on a Likert scale from never (1) to always (5). A composite score is developed that creates an average score for HCP vaccine recommendations, HCP screening recommendations, and HCP communication practices. Postintervention practices of health care providers will determine change in both strength and frequency of recommending the HPV vaccine to patients.

The secondary outcomes of interest include understanding provider beliefs and provider knowledge. These will be measured on previously validated scales adapted from the Vaccine Attitudes and Knowledge Survey (VAKS) [13,21].

Provider Beliefs

Provider beliefs (ie, attitudes toward HPV vaccine) will be measured using the 9-item HPV vaccine attitudes scale (perceived safety, perceived harm, and perceived effectiveness) scored on a Likert scale from strongly disagree (1) to strongly agree (5). A composite score is developed which creates an average score for perceived safety, perceived harm, and perceived effectiveness.

Provider Knowledge

Provider knowledge about HPV and the HPV vaccine will be measured using a previously adapted 14-item HPV knowledge scale scored as true (1) or false (0) [13,21]. A composite score is developed which creates an average score for 14 items and then multiplying by 100 to calculate a percentage.

Participants

Participants will be recruited from the health care provider population in El Paso County, Texas, and Southern New Mexico. Both current (in practice) and emerging (in training) practitioners in the professions of medicine (ie, doctor of medicine, doctor of osteopathic medicine, physician assistant, nurse practitioner, pharmacy, or nursing) are eligible to participate in the study. To qualify, participants must be a current (in practice) or emerging (in training—student, resident, or fellow) health care provider, be between the ages of 18 and 65 years, be working, training, or living in the Paso del Norte Region (ie, El Paso County, TX-Southern New Mexico), have computer or internet literacy and access to an electronic device with internet access (eg, cell phone, tablet, and computer), and have the authorization to recommend the HPV vaccine. Participants will be excluded from the study if they are not affiliated with the El Paso United States–Mexico border region, have not previously participated in phases I or II of the larger parent research project, do not identify as a current or emerging health care provider, decline or are unable to participate in the full intervention and follow-up time points, or are unable to complete participation and activities in the English language.

Recruitment

Recruitment took place over 6 months, from December 2023 to May 2024. No critical secular events fell into this study period. Participants who were eligible and agreed to participate in the study will be active in the project for 7 months post-initial recruitment. This time frame starts at the time of recruitment and ends at the final 6-month follow-up time point. Researchers used a purposive sampling technique to recruit participants through multimedia (ie, print and email) and professional network contacts. The study participants were recruited from (1) the main campus and some regional clinical hubs of the Burrell College of Osteopathic Medicine; (2) the University of Texas at El Paso College of Health Sciences, College of Nursing, and School of Pharmacy; (3) federally qualified health centers in the Paso del Norte Region; (4) private provider clinics; and (5) other health care workers and professional network connections that provide training and services to the Paso del Norte region residents. Special attention will be given to recruit practitioners in the specialties of pediatrics, family medicine, and obstetrics and gynecology due to their increased familiarity with vaccines, HPV, and cancer. All participation is entirely web-based. Once the participant is deemed eligible and agrees to participate, they will be provided with a study information sheet outlining that their participation is voluntary, and they can opt out at any time. Participants will be compensated for their time with a US $30 electronic gift card after completion of the initial training session and surveys (~30 minutes). Participants will receive email reminders to complete each of the 2 follow-up survey sessions at 3 and 6 months after

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completing the initial intervention, as well as an additional US $10 electronic gift card for participating in the follow-up survey sessions (~20 minutes per survey questionnaire).

Randomization, Treatment Allocation, and Concealment

Sequence Generation

After determining eligibility, we will randomize participants on a 1:1 basis to intervention groups (experimental vs control) while controlling for the potential bias introduced by factors of sex, age, and career stage. To achieve this goal, we will use a randomization table within the REDCap (Research Electronic Data Capture; Vanderbilt University) platform to create balanced treatment groups based on these factors and reduce the effect of selection bias [22].

Concealment

This study is double masked (ie, participant and outcomes assessor). Participants will be randomly assigned to treatment and control groups; they will not be made aware of other participants' receipt of treatment or control materials. Participants will be asked not to discuss this project outside of the intervention; delivery of the intervention or other educational materials will be internet-based, limiting the ability of participants to interact with one another during the study. Furthermore, to reduce bias in the implementation and assessment of the clinical trial (eg, outcome assessor), participant information and pre-post survey responses will be maintained separately from the assignment and delivery of the intervention.

Measures

All the survey questionnaire measures or instruments will be made available electronically in English.

Screening Questionnaire

Participants completed a screening questionnaire delivered via the REDCap platform to determine their eligibility to participate in the study or intervention [22]. The questionnaire will assess items such as age, geographical location, and health care provider education status (ie, MD, DO, PA, NP, PharmD, or RN) of the potential participant. The questionnaire will also assess their comfort with auditory and visual content in the English language, and if they had prior participation in the earlier phase of this study. The screening questionnaire requires approximately 3 to 5 minutes to complete. Upon successful completion of the screening questions, participants will read and sign the consent form indicating that they agree to participate in the study.

Demographic and Background Questionnaire

The demographic and background questionnaire via the REDCap platform will gather demographic information (eg, age, gender, ethnicity, and income), as well as information about family composition, HPV vaccination status, trusted sources for medical information, general feelings about vaccines, trust in the government, and experiences with the recent COVID-19 endemic [22]. The demographic survey will only be administered at baseline prior to administering the intervention. The demographics survey requires approximately 5 to 8 minutes to complete.

Postassessment

A post-assessment via the REDCap platform will be administered at baseline (immediately following intervention), 3 months, and 6 months [22]. The post-assessment will include a modified version of the VAKS [13,21] to self-assess factors that influence levels of comfort in discussing HPV-related topics, patient-provider communication about HPV, vaccines, cancer risk, and additional questions designed to evaluate the impact of the interventions and the actual changes in practice in terms of vaccine uptake, patient communication, and vaccine recommendation behavior. Moreover, the outcome variables are included in the post-assessments such as the self-assessment of the proportions of provider practices (as indexed by the HCP practices scale), provider beliefs (as indexed by the HPV vaccine attitudes scale), and provider knowledge (as indexed by the HPV knowledge scale). These will be measured on previously published scales adapted from the VAKS [13,21]. In a previous study that administered the VAKS, Cronbach α ranged from 0.70 to 0.90 for the various scales included in the survey [13]. The post-assessment requires approximately 25-30 minutes to complete.

Data Collection and Management

All study data will be collected using REDCap [22], a password-secured internet-based software application system developed to design and manage web-based databases and surveys, hosted at The University of Texas at El Paso. All data collected will be deidentified. REDCap will be maintained by the College of Science at The University of Texas at El Paso [22]. Data will remain stored for up to 5 years after completion of the study. Only the study team will have access to the data, as the team has received training on maintaining research data confidentiality, responsible conduct of research, and research ethics with human participants. Data will be accessed through password-protected and encrypted computers.

Analytical Methods

All statistical analyses will be conducted using SPSS (version 26.0; IBM Corp) and R (version 4.0.3; R Core Team) and will use 2-tail α to reject null hypotheses at .05. Prior to conducting analyses, data will be screened to ensure that statistical assumptions are met and any transformations or adjustments to the model will be used. We may use multiple imputation procedures to handle missing data. Descriptive statistics will be reported for demographic variables including age, sex, gender, and health professional degree or field. A power analysis estimating repeated measures within-between interaction, assuming a small effect size (f=0.15), determined that approximately 110 total participants are required to provide an 80% chance of detecting an effect between the 2 experimental conditions (tailored intervention vs active control) across 3 time points (0, 3, and 6 months postintervention). To account for an estimated 10%-15% attrition, at least 100 participants needed to be recruited.

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Study Outcomes

The chi-square analyses will be used to assess associations between variables reported on the baseline provider knowledge, attitudes, and practice scales. Repeated measures mixed ANOVA with α set to .05 will examine whether change in our outcome variables (self-assessment of the proportions of provider practices, as indexed by the HCP practices scale), provider beliefs (as indexed by the HPV vaccine attitudes scale), and provider knowledge (as indexed by the HPV knowledge scale) is the result of the interaction between the experimental condition (tailored intervention vs active control) and time (at 3 time points) [23]. If no interaction emerges, we will conduct follow-up tests to determine whether any change in our outcome variables are due to one of the factors (experimental condition or time). We will calculate the Mauchly test of sphericity for each ANOVA, and the Huynh-Feldt epsilon test or Greenhouse-Geisser correction to the degrees of freedom of the *F*-ratio will be reported for each significant effect [23-25]. We may use multiple imputation procedures to handle missing data (if applicable).

Future Directions and Plans for Dissemination

Plans for the dissemination of our findings include publication in peer-reviewed scholarly journals and presentation at scientific conferences, but we are also committed to sharing our data with the community that supports and contributes to this work. For both providers and patients, it is important to base medical decision-making on relevant and up-to-date information. Our findings will also be shared with health care providers in practice and in training at the institutions and locations in which our participants were included. Data will be reported in aggregate form, with no identifying information shared. This data may further be incorporated into the curriculum followed by providers in training in the Paso del Norte region and beyond.

Results

Overview

A larger parent grant (NIH/NIMHD 2U54MD007592) was funded in October 2019. Data collection of this subproject, a provider-focused randomized controlled trial (RCT), began in December 2023, with a total of 128 participants recruited by the closing of recruitment in May 2024. Primary data collection was completed in December 2024. As of March 2025, data analysis is in progress, with publication of results anticipated in winter 2025.

Study Outcomes

Provider Practices

Results of the ANOVA model assessing the primary outcome of between-group changes in proportions of provider practices will be summarized and presented in tables and visuals.

Provider Beliefs and Provider Knowledge

Results of the ANOVA model assessing secondary outcomes of understanding provider beliefs and provider knowledge will be summarized and presented in tables and visuals.

Discussion

Principal Findings

The goal of this RCT was to develop and deploy an educational and professional skills intervention to increase health care provider HPV prevention recommendation scores. This is a critical factor in cancer prevention, and multiple factors contribute to the observation that, while HPV vaccine uptake in our region is higher than in many other regions, it still falls short of national targets. We anticipate finding that health care providers who receive our experimental intervention materials (culturally tailored videos specifically targeting effective HPV vaccine-related communication strategies) will demonstrate improved and more frequent HPV vaccination recommendation practices and behaviors with their patients, as compared to health care provider participants who receive the control materials (standard CDC-issued materials).

Comparison to Prior Work and Strengths

Our approach to intervention with health care providers is not particularly novel, nor is the intention to increase provider vaccine recommendations since it has been well-established that provider recommendation is one of the most critical factors in patient decisions to get vaccinated [26]. What is innovative in our approach, however, is how we engage with and tailor skills-based training for providers in our region. The initial evaluation of provider knowledge, practices, and beliefs about HPV and the HPV vaccine informed us that HPV-related knowledge among providers is high. An intervention that provides additional education on HPV, the vaccine, and cancer was thus likely to have limited benefit and would not be a valuable use of provider time. In contrast, our intervention focuses on supporting the professional development of providers in the domains of modifying their own behavior and improving communication with patients. Increasing provider awareness of biases in vaccine recommendation and delivery, increasing their comfort in discussions about sexual health topics, and supplying them with tools for addressing patient hesitancy associated with vaccination were determined by our group to be more likely to produce the desired results.

A second way in which our research is innovative is to focus on emerging health care providers. Engaging with this group has the potential to produce multiple positive outcomes, including (1) increased vaccine uptake since many individuals in this group are vaccine-eligible but remain unvaccinated, (2) normalization of vaccine-related discussions in patient care if this becomes a consistent component of provider training, and (3) strengthened vaccine recommendations as the providers themselves serve as role models for vaccination to their patients. Third, we are committed to improving vaccine recommendation behavior by providers that serve a binational, majority-Hispanic population that is medically underserved and faces multiple barriers to vaccination. Previous work has shown that Hispanic women have high HPV vaccine acceptability [27], but this may vary based on age and birth origin [28].

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Limitations

This study recruited an internet population of health care providers in the United States–Mexico border region; therefore, findings may not directly translate to other health care provider populations nationally or globally. Furthermore, this intervention did not provide Continuing Medical Education (CME) credit, which would limit uptake outside of an RCT setting. Study participation involved a relatively large time commitment for providers in practice, which worked against recruitment and survey completion. We may, therefore, be somewhat limited in our ability to conduct subanalyses such as comparisons across provider specialties (eg, pediatrics vs family medicine) or other participant characteristics (eg, ethnicity or income level). As we have gathered data from health care providers in medicine, nursing, and pharmacy, different approaches to patient care in these professions may increase variability in the responses obtained. A pretest of HPV and vaccine-associated practices was not done in our study, and the use of solely self-reported data may be incomplete or may contain bias. Our random assignment of participants into control and experimental groups should protect against baseline group differences; however, we will still be able to determine the persistence of any changes in behavior regardless of participant starting point. If any group of providers demonstrates high vaccine recommendation rates at the onset of the study, it will be difficult to determine a statistically significant increase in behavior in response to the intervention. Still, identifying providers with strong recommendation practices will be of benefit to our project. Finally, we anticipate the loss of a limited number of participants through attrition over time for many possible reasons, perhaps reducing the power of our study and our data analysis capabilities at the 3- and 6-month time points.

Conclusions

To improve population health, it is essential to look beyond interventions aimed solely at patient populations. Web-based educational programs for health care professionals are promising tools for enhancing the real-world implementation of CPGs. Tailoring these provider-level interventions to account for regional and patient population characteristics can also improve patient-provider communication as clinical guidelines evolve. Until HPV and other vaccine-preventable infections are eradicated, collaboration between health researchers and providers is critical to delivering accessible and effective professional development interventions. Furthermore, beyond reporting research findings of such studies, reporting specific intervention protocols helps ensure transparency in the research process and facilitates the improvement of population health interventions.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are not publicly available as they are stored in the REDCap (Research Electronic Data Capture) repository maintained by the University of Texas at El Paso and subject to institutional access restrictions but are available from the corresponding author on reasonable request.

Authors' Contributions

EMM, KG, and JIC conceptualized the study with critical input from KLL, MW, and JM. JIC, KLL, MW, and JM wrote the first draft, and EMM, KG, and JIC gave critical input throughout the study development and contributed to the paper revisions. All authors contributed and approved the final study. No artificial intelligence was used in any portion of the paper development.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1253 KB - resprot_v14i1e60790_app1.pdf]

Multimedia Appendix 2

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Peer-review report from the External Advisory Committee for the National Institutes of Health (NIH) Research Centers in Minority Institutions (RCMI) Program - Border Biomedical Research Center at the University of Texas at El Paso (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 171 KB - resprot_v14i1e60790_app2.pdf]

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Abbreviations

CDC: Centers for Disease Control and Prevention
CME: Continuing Medical Education
CONSORT: Consolidated Standards of Reporting Trials
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
CPG: clinical practice guideline
HCP: health care provider
HPV: human papillomavirus
LGBTQ+: lesbian, gay, bisexual, transgender, and queer/questioning
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
VAKS: Vaccine Attitudes and Knowledge Survey

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Protocol

Effects of Using a Smart Bassinet on the Mental Health of Military-Affiliated Pregnant Women: Protocol for a Randomized Controlled Sleep Health and Mood in Newly Expectant Military Mothers (SHINE) Trial

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Abstract

Background: Postpartum mood and anxiety disorders (PMADs) are higher among pregnant military service women (26%) and military spouses (12.2%) compared to the civilian population (10%-15%). This is partly due to military-specific factors, including deployment, which are known to increase risk. Important risk factors for PMADs include sleep disturbances, defined as sleep deprivation, insomnia, or poor sleep quality, which are more are common among military-affiliated pregnant women.

Objective: This study describes a protocol for a new randomized controlled trial that aims to ameliorate the risk for PMADs through improving infant sleep or maternal sleep during the first 6 postdelivery months in a sample of military-affiliated women.

Methods: This study is a 6-month, parallel-arm, randomized controlled trial. Pregnant women (N=342) in the third trimester will be randomized at 1:1 ratio to use a smart bassinet (SB) or a standard commercially available bassinet (HALO BassiNest Swivel Sleeper 3.0; traditional bassinet [TB]) for up to 6 months after delivery. Participants will have their infants sleep in the bassinet, complete monthly web-based questionnaires, and record sleep data with diary and actigraphy for both the participants and their infants for 1 week each postpartum month. Blood samples will also be collected at baseline (late pregnancy) and at 3 months and 6 months post partum to assess immune functioning. The primary outcomes for this study will be postpartum mood (depressive and anxiety symptoms) and infant and maternal sleep. In addition, we are evaluating whether SB has a significant impact on immune functioning—a marker that physiologically connects sleep and mood symptoms.

Results: Recruitment for this study began in January 2025. Six separate mixed 2 (treatment vs control) × 6 (assessment period) multivariate analysis of variance and analysis of variance models will be conducted to test the hypotheses that SB will have a greater impact on infant and maternal sleep than TB, SB will be associated with a greater reduction in postpartum mood symptoms than TB, and immune system function will be less dysregulated in birthing individuals using SB compared to those using TB. Lastly, we will evaluate whether the elevated risk demonstrated by previously identified postpartum depression epigenetic biomarkers in the *TTC9B* and *HP1BP3* genes can be modified with an SB. We hypothesize that the elevated risk will be reduced in SB compared to that in TB.

Conclusions: At the conclusion of this project, we will have gained a thorough understanding of the capability of SB to positively affect infant and maternal sleep compared to the traditional sleep arrangement and its impact on maternal mood through 6 months post partum in military-affiliated women. The promotion of sleep health in both mothers and infants may be an accessible and amenable method to prevent PMADs.

Trial Registration: ClinicalTrials.gov NCT06544941; https://clinicaltrials.gov/study/NCT06544941

International Registered Report Identifier (IRRID): PRR1-10.2196/66439

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(JMIR Res Protoc 2025;14:e66439) doi:10.2196/66439

KEYWORDS

maternal health; postpartum; pregnancy; sleep; infant; depression; anxiety; smart bassinet; intervention; prevention; military

Introduction

Postpartum mood and anxiety disorders (PMADs) are the most common and disabling complications of childbearing. They are often underdiagnosed and undertreated [1]. PMADs are recognized to seriously affect both mother and baby [2,3]. In fact, mental health conditions are a leading contributor to maternal morbidity, with suicide as a major cause of postpartum death. According to the Department of Defense, the number of females in the US military constituted 17.3% of the total force in 2021 [4]. Research indicates that the rate of PMADs in active-duty women can range from 20% to 26% [5-7], with slightly lower rates among military spouses at around 12.2%. Although these rates are similar to that reported in the civilian population (~10%-15%) [8-10], when other factors such as deployment are considered, the rates vary dramatically, reaching as high as 50% [11-16]. Women with spouses who are deployed have more frequent diagnoses of depressive disorders, sleep disorders, anxiety, acute stress reactions, and adjustment disorders compared to women without a deployed spouse. Despite these elevated risks, this segment of our population has been insufficiently evaluated as it pertains to PMAD risk and warrants further attention.

It is well appreciated that sleep disturbance is associated with both new and recurrent depressive and anxiety episodes in all populations, especially perinatal women [17-22]. Sleep disturbance often precedes the development of mood disorders [23,24]. Indeed, sleep issues lasting for at least 2 weeks increase the risk for the future development of mood disorders [25,26] and are a criterion for the diagnosis of depression in the Diagnostic and Statistical Manual of Mental Health Disorders, Fifth Edition, Text Revision (eg, major depressive disorder) [27]. Sleep disturbances, both in prevalence and severity, in military-affiliated women extend beyond what civilian women experience. Active-duty service members and their spouses experience unique stressors that often exacerbate sleep issues [28,29]. Despite this, there are limited empirical data regarding sleep disturbances among military-affiliated women.

Infant sleep problems further contribute to significant maternal sleep issues [30-32] and maternal mental health consequences, regardless of the mothers' depression history [32-34]. Mothers who report poor infant sleep behavior have significantly more depressive symptoms than mothers who report good infant sleep [35-37]. There is some evidence that maternal sleep quality is a mediator of this relationship [35]. Persistent, rather than transient, infant sleep issues contribute to maternal depression, poor sleep, and poor family functioning well into toddlerhood [33,38,39]. We propose that focusing and intervening on infant sleep is a viable pathway to improve maternal sleep and well-being.

Here, we describe the protocol for a randomized controlled trial (RCT; Clinical Trials.gov CT94252410690; Sleep Health and Mood in Newly Expectant Military Mothers [SHINE]) with the following aims.

1. Determine whether the use of a smart bassinet (SB) augments infant sleep and improves maternal sleep during the first 6 months post partum compared to the use of a traditional bassinet (TB). (1) Hypothesis 1a: Infants who sleep in SB will have better sleep (ie, diary and Brief Infant Sleep Questionnaire as maternally reported) [40] than those who sleep in TB. Outcomes will include maternally reported sleep duration, awakenings, as well as objectively assessed (actigraphy) wake after sleep onset and sleep onset latency. (2) Hypothesis 1b: Mothers of infants who sleep in SB will have better subjectively reported (ie, diary and Pittsburgh Sleep Quality Index) and objectively assessed (actigraphy) sleep compared to those of infants who sleep in TB. Outcomes will be the same as those for infants.
2. Determine the effect of SB on maternal postpartum depressive and anxiety symptoms and evaluate the model that the association between SB and postpartum depressive symptoms is mediated by both infant and maternal sleep. (1) Hypothesis 2a: Mothers of infants who sleep in SB will have fewer postpartum depressive symptoms over time (ie, Edinburgh Postnatal Depression Scale) compared to those of infants who sleep in TB. (2) Hypothesis 2b: SB improves infant sleep, which then predicts better maternal sleep, and thereby predicts lower maternal depressive symptoms.
3. Compare the trajectory of immune system function from late pregnancy through post partum between participants with and without PMADs and between SB and TB groups. (1) Hypothesis 3a: Peripheral cytokines, immune cells, and stimulated cytokine profiles of women with PMADs assessed in late pregnancy and at 3 and 6 months post partum will indicate greater innate immune activity compared to those of women without PMADs. (2) Hypothesis 3b: Mothers of infants who sleep in SB will exhibit lesser innate immune dysfunction than mothers of infants who sleep in TB.
4. Exploratory aim: Evaluate whether the elevated risk demonstrated by previously identified PMAD epigenetic biomarkers at the TTC9B and HP1BP3 genes can be modified by using an SB. We hypothesize that the elevated risk will be reduced in the SB group compared to that in the TB group.

Methods

Study Design

This study is a 2-arm, parallel-group RCT. Participants will be randomized at 1:1 ratio to either SB group or TB group. Outcomes are assessed at 7 timepoints (Figure 1): late pregnancy (P3) and in postpartum months 1-6 (M1-M6).

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Figure 1. Flowchart in this study. BISQ: Brief Infant Sleep Questionnaire; EPDS: Edinburgh Postnatal Depression Scale; ESS: Epworth Sleepiness Scale; FFS: Flinders Fatigue Scale; IBQ-R: Infant Behavior Questionnaire-Revised; ISQ: Insomnia Symptom Questionnaire; PSQI: Pittsburgh Sleep Quality Index; SCID: Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-5.

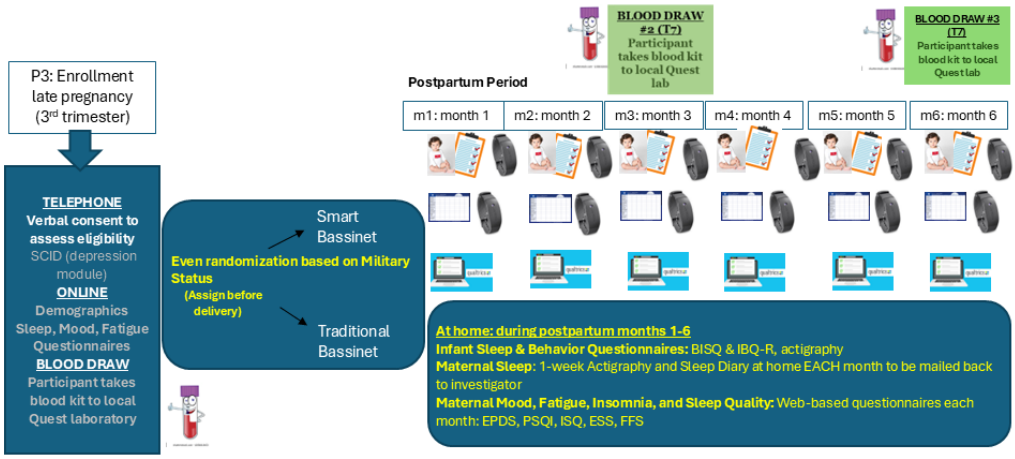

Ethics Approval

This study has been approved by the institutional review board of the University of Colorado Colorado Springs (#2024-071) and the Office of Human Research Oversight (US Army Medical Research and Development Command). The SHINE trial was previously registered with Clinical Trials.gov (CT94252410690). This protocol follows recommendations from CONSORT (Consolidated Standards of Reporting Trials) 2010 statement checklist (Multimedia Appendix 1) and guide [41]. All participants will be required to provide informed written consent prior to enrollment. Participation is completely voluntary, and the participant has the right to withdraw at any time. All participants will be assigned a 6-digit ID number to be used so that all data collected will be deidentified. Participants will be compensated for their time. There are 7 timepoints in this study. At baseline (late pregnancy), participants will be compensated US $100; at postpartum months 1, 2, 4, and 5, they will be compensated US $50 for data collection, and at postpartum months 3 and 6, they will be compensated US $100. At baseline and at postpartum months 3 and 6, they will provide a blood sample.

Participants

At the time of recruitment (P3) (third trimester), participants will complete a screening survey to determine their eligibility. Eligible pregnant women (N=342) will be recruited nationwide. The inclusion criteria were pregnant military-affiliated individuals with a singleton gestation; age 18-45 years; ability to communicate in English during the screening process; access to a computer, smartphone, or tablet with internet service; willing to use the bassinet they are randomized to; and willing to travel to a local Quest Diagnostics (an insert description) for blood draw. The exclusion criteria were presence of a depressive or anxiety disorder assessed over videoconference using the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-5-Clinical Version mood disorders section [42]; current active suicidal ideation, medical or psychiatric instability, or active substance abuse or dependence during the last 90 days; plans to co-sleep with infant; younger than 18 years or older than 45 years; multiple gestations; type 1 diabetes; congenital fetal anomalies; tobacco use (current); self-reported, untreated comorbid sleep disorders, including narcolepsy, periodic leg movement disorder, or obstructive sleep apnea; and current use of psychotropic or sleep medications.

Procedures

Recruitment and Consent

Advertisement for this study will take place primarily online (social media) and through partner advocates (Postpartum Support International and Maternal Mental Health Leadership Alliance). Pregnant military-affiliated individuals who reside in the United States are eligible. Interested participants will contact the study coordinator for additional information and initial eligibility screening, including verification of military status.

Telephone Interview and Screening

Participants who meet initial inclusion criteria and have completed the consent and baseline questionnaires will be contacted for a telephone interview to assess further eligibility. The interview will contain items of the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-5-Clinical Version [42] and the Structured Clinical Interview for Sleep Disorders-Revised [43]. Eligible participants will be randomly assigned to either SB group or TB group. The SB will be shipped to the participants and returned after M6 at no expense to them. TB group participants will be shipped a standard bassinet (HALO BassiNest Swivel Sleeper) to keep. Mother-infant dyads (up to N=342) will be randomly assigned to conditions by using a random number generating program found on a widely used and reputable website [44]. We will perform 1:1 randomization. Variability in the length of bassinet usage may be impacted by size of infant, parental preference, or infant temperament. However, data will be collected through 6 months post partum.

Data Collection

For each assessment (Figure 1), all participants will receive an email with a REDCap (research electronic data capture) link for web-based data collection. All web-based survey data will be published in accordance with the CHERRIES (Checklist for Reporting Results of Internet E-Surveys) checklist. To mitigate

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and minimize the possibility of missing data in the measures, we will program electronic questionnaires to prevent skipping questions. REDCap is a web application and back-end database model designed to support data capture for research studies. REDCap is an open-source tool developed by Vanderbilt University to build and manage web-based forms for data collection. REDCap was developed specifically based on guidance from the Health Insurance Portability and Accountability Act of 1996 security guidelines and contains features such as data encryption. In addition, participants will receive a monthly package containing 2 actigraphs, a baby's day diary, and a prepaid return envelope.

Adverse Events

Adverse events will be monitored monthly via questionnaires and during telephone contact at month 3 and month 6 (phone calls to remind them to get blood drawn). Further, participants will be asked to report to the research team immediately if they experience unwanted adverse effects during participation. These events will be recorded and included in human research ethics reports. The Edinburgh Postpartum Depression Scale [45] has a single item that denotes suicidal ideation. It will be flagged such that if the participant endorses the item, a telephone call from a clinical psychologist (LF) to the participant will be initiated to conduct a risk assessment and assist with triage, as necessary.

Measures and Materials

Table 1 describes the schedule of the study assessments for primary and secondary measures.

Table 1. Assessments and timeline.

Measures	Baseline enrollment	1 month PP[a]	2 months PP	3 months PP	4 months PP	5 months PP	6 months PP
Maternal screening measures							
Consent/inclusion/exclusion	✓						
Demographics	✓						
SCID[b] depression module/sleep SCID	✓						
Infant assessments							
Actigraphy		✓	✓	✓	✓	✓	✓
Brief Infant Sleep Questionnaire		✓	✓	✓	✓	✓	✓
Infant Behavior Questionnaire-Revised		✓	✓	✓	✓	✓	✓
Baby Cry/Fuss chart		✓	✓	✓	✓	✓	✓
Maternal assessments (primary)							
Sleep diary		✓	✓	✓	✓	✓	✓
Actigraphy		✓	✓	✓	✓	✓	✓
Pittsburgh Sleep Quality Index	✓	✓	✓	✓	✓	✓	✓
Edinburgh Postnatal Depression Scale	✓	✓	✓	✓	✓	✓	✓
Generalized Anxiety Scale	✓	✓	✓	✓	✓	✓	✓
Tasso blood collection kit (Epigenetics)	✓						
Blood samples (inflammation)	✓			✓			✓
Maternal assessments (secondary)							
Insomnia Symptom Questionnaire	✓	✓	✓	✓	✓	✓	✓
Epworth Sleepiness Scale	✓	✓	✓	✓	✓	✓	✓
Flinders Fatigue Scale	✓	✓	✓	✓	✓	✓	✓
Treatment expectations	✓			✓			✓
Social support survey	✓	✓	✓	✓	✓	✓	✓
Adherence questionnaire				✓			✓
Delivery information		✓					

[a]PP: post partum.

[b]SCID: Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders-5.

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Primary Infant Assessments

The mother will record infant sleep for 1 week per month in the baby's day diary [46]. Boxes are filled in daily for 1 week with symbols that correspond to when the infant is asleep, awake, awake and fussy, sucking, or feeding. This measure has been widely used and exhibits desirable reliability and validity [47,48]. The Brief Infant Sleep Questionnaire [40] is used to assess the infant's sleep during the past week. The Infant Behavior Questionnaire-Revised [49] will be used to allow mothers to report, on a 7-point scale, the frequency with which infants have enacted specific behaviors in common situations during the past week.

Primary Maternal Assessments

The Consensus Sleep Diary [50] will collect subjective sleep, while actigraphy will be contemporaneously used to derive objective sleep data. The Pittsburgh Sleep Quality Index [51] will measure habitual sleep quality. The Edinburgh Postnatal Depression Scale [52,53] will be used to assess changes in the depressive symptoms over time. The Generalized Anxiety Disorder Scale-7 items [54] and the Perinatal Anxiety Screening Scale [55] will be used to assess anxiety symptoms over time.

Participants will have their blood drawn (up to 20 mL) at enrollment, 3 months post partum, and 6 months post partum at a Quest Diagnostics laboratory near them (Figure 1). Briefly, blood collection kits with ethylenediaminetetraacetic acid tubes will be mailed to participants with a requisition form and a laboratory directive (from Quest) that provides the Quest Diagnostics Patient Service Center instructions on how to collect and process the study kit. Blood samples will be shipped in a temperature-controlled fashion to the Psychoneuroimmunology in Pregnancy & Postpartum (PIPPI) laboratory at Weill Cornell Medical College for analysis. Measurements of circulating cytokines, stimulated cell assays, and flow cytometry analysis will be conducted to evaluate the role of immune dysregulation.

Secondary Maternal Assessments

The Insomnia Symptom Questionnaire [56] is a self-report instrument that identifies a clinically relevant case definition of insomnia consistent with widely used insomnia classification criteria. It has 13 items, which identify sleep symptoms, frequency, duration, and related daytime impairment. Scoring indicates positive or negative for insomnia. The Epworth Sleepiness Scale [57] will assess daytime sleepiness. The Flinders Fatigue Scale [58] will assess daytime fatigue.

Measures in Both Mothers and Infants

Actigraphy watches (Phillips/Respironics and ActiGraph, LLC) will be provided to the dyad each month to collect objective sleep data. Data collection and interpretation will be consistent with previous reports [59-61]. For infants, watches will be placed on the right ankle in accordance with suggested guidelines [61-63].

Epigenetic Biomarker Testing

Blood Draw Collection

Upon enrollment, participants will be sent supplies from TruDiagnostic for blood collection, including a Tasso blood collection kit and a prepaid mailing kit to TruDiagnostic. Blood samples will be processed using the Illumina Human MethylEPIC beadchip. Methylation data for the *TTC9B*, *HP1BP3*, and *MS4A7* genes will be sent to Dr Zach Kaminsky who will use the published algorithm for predicting postpartum depression risk to determine if the participant's epigenetic methylation patterns are consistent with increased risk for postpartum depression. Participants will not be informed of their biomarker status, as we are still determining the clinical value of the biomarkers.

Immune Markers

Blood collection kits with ethylenediaminetetraacetic acid tubes will be mailed to participants with a requisition form and a laboratory directive (from Quest) that provides the Quest Diagnostics Patient Service Center instructions on how to collect and process the study kit. Aliquots of plasma and the second tube of whole blood will be shipped overnight to Weill Cornell Medicine. Peripheral blood mononuclear cell (PBMC) suspensions will be prepared within 24 hours of blood collection by low-density gradient centrifugation via Hermle Z300 (K#55085010) to avoid erythrophagy-related activation of the monocytes. PBMCs will be frozen and stored at –80 °C using 10% dimethylsulfoxide, thereby allowing all samples to be analyzed in parallel. Plasma will also be stored at –80 °C. In our prior studies, we have missing biological data (due to incomplete blood draws) in about 7% of the visits; we anticipate similar rates in this study.

Cytokine Analysis

Cytokine analysis will be performed under Dr Osborne's supervision in the PIPPI laboratory at Weill Cornell Medicine. Plasma cytokines will be measured using the Meso-Scale Discovery Ultrasensitive Proinflammatory Multiplex kit (Meso Scale Diagnostics LLC) according to the manufacturer's protocol in duplicate and read using the MS2400 imager (Meso Scale Diagnostics LLC). We will calculate the coefficient of variation for each woman's replicates when both have concentrations above the limit of detection.

Cell Preparation and Stimulation

Maternal PBMCs will be thawed in Roswell Park Memorial Institute 1640 medium and distributed into three 24-well multiplates (5×10^5 cells/well). Remaining cells will be aliquoted into two 5-mL culture tubes (2×10^6 cells/tube). Cells will be maintained in a humidified atmosphere of 95% air/5% CO_2 at 37 °C. After 24 hours, PBMCs in the 24-well plates will be treated with increasing concentrations of cortisol. Hydrocortisone stock solutions will be prepared by dissolving hydrocortisone in ethanol and then diluting with pyrogen-free sterile saline solution (NaCl 0.9%) to achieve equipotent final culture concentrations of 0.2 µg/mL (physiological plasma cortisol level) and 0.4 µg/mL (plasma cortisol level in high-stress status). PBMCs will be treated with a final cortisol concentration of 0, 0.2, and 0.4 µg /mL. Cells in the 5-mL culture tubes will be stimulated with phorbol myristate acetate (Sigma Aldrich) and ionomycin (Sigma Aldrich) in the presence of GolgiStop (Becton Dickinson) for 4 hours in 37 °C under a 5% CO_2 environment to stimulate T-effector cells. Following the

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incubation periods, the supernatant from cortisol-stimulated cells will be collected and stored at –80 °C until assayed for interleukin (IL)-6, IL-10, IL-8, and IL-4 by using a commercial enzyme-linked immunosorbent assay. Cellular pellets will be resuspended and prepared for flow cytometry to assess the immune cell phenotype.

Flow Cytometry Analysis

Flow cytometry analysis will be performed on the BD LSRII instrument (BD Biosciences, 3 laser, 14 color) within the Cubillos-Ruiz laboratory adjacent to Dr Osborne's PIPPI laboratory. Additional analyses, as necessary, will occur in the Weill Cornell Flow Cytometry Core, which houses a BD AriaII sorter, 5 laser (355, 405, 488, 561, 640) capable of 4-way sorting; a BD Influx sorter, 6 laser (355, 405, 445, 488, 561, 640) capable of 6-way sorting; a BD Fortessa analyzer, 5 laser (355, 405, 488, 561, 640) 20 parameter and a BD FACSCelesta analyzer, and 3 laser (405, 488, 561) 14 parameter. Panel one will include membrane staining markers and will be performed using thawed PBMCs. Stained cells will be analyzed by 8-color flow cytometry (with anti-CD3 BV786, anti-CD4 Pe-Cy7, anti-CD8 BV605, anti-CD14 antigen-presenting cell, anti-CD25 phycoerythrin, anti-CD16 PerCp-Cy5.5, anti-CD56 fluorescein isothiocyanate, and anti-CD19 BV421; Becton Dickinson). We will use a gating method to measure subsets of monocytes, lymphocytes, natural killer cells, T-cells, B-cells, CD4+ T helper cells, and CD8+ cytotoxic T cells. Samples stimulated with phorbol 12-myristate 13-acetate and ionomycin will be stained using a T-cell specific panel and analyzed by 8-color flow cytometry (with anti-CD3 BV786, anti-CD4 Pe-Cy7, anti-CD45RO BV605, anti-IFN-γ antigen-presenting cell, anti-CD25 PE, anti-FoxP3 PerCp-Cy5.5, anti-IL-4 fluorescein isothiocyanate, and anti-IL-17A BV421; Becton Dickinson).

Process Measures

Treatment Expectation Questionnaire

An adapted version of the Treatment Expectation Questionnaire [64] will be administered at month 3 and month 6 to assess the mother's expectations of benefits, satisfaction with condition, and fears. This measure asks about expectations regarding symptom relief, improvement, and benefits from using the specific bassinet. It allows for comparison of the impact of multidimensional expectations across different conditions. Open-ended comment boxes will be provided for mothers to report experiences, adverse events, or other comments.

Patient Adherence

Various items will be collected to determine patient adherence: (1) self-reported adherence assessed using an adapted survey checklist provided by Dr Stremler, (2) self-report data on bassinet usage, (3) pictures of bassinet use by participants, and (4) comment boxes to explain nonadherence.

Additional Factors to Consider and Use as Covariates

These include (1) presence of spouse/partner and other children at home [36,65-67]; (2) type of feeding [68-70]; (3) infant variables such as acid reflux, colic, and gestational age; (4) consistency of bedtime routine [71-73] and when moved to a crib; (5) history of childhood trauma in the mother via the Childhood Trauma Questionnaire [74], as prior trauma is highly correlated with depressive episodes, especially in new mothers [75,76] and negatively affects sleep [77]; and (6) type of delivery, complications, or time spent in neonatal intensive care unit.

Statistical Analysis

Power

Power analyses were performed using $P<.05$ (2-tailed) at .80 power, based on recommended guidelines [78-80]. The power analyses were conducted for each statistical technique to be pursued in aims 1 to 3: mixed (between-subjects and within-subjects) multivariate analysis of variance (MANOVA), mixed (between-subjects and within-subjects) analysis of variance, independent 2-sided t test, dependent 2-sided t test, correlation, and the mediational models involving structural equation modeling (based on the β coefficient). The pilot study collected similar measures from pregnant/postpartum women with a history of major depressive disorder who used SB or HALO TB. Hence, the power analyses were based on pilot sleep and mood data. Calculations revealed an average effect size across all postpartum timepoints (T1 to T6) between the treatment and control groups on the following measures: infant sleep (d=0.39), postpartum sleep quality (d=0.27), and postpartum depression (d=0.33). Based on these effect sizes, a sample size of 208 participants is needed for infant sleep, 434 participants for postpartum sleep quality, and 286 participants for postpartum depression to attain statistical significance. Thus, a final sample size of 393 participants will be targeted (allowing for an attrition rate of 15%).

Randomization

AL generated the random sequence by using a random number generating program found on a widely used and reputable website [44]. We performed 1:1 randomization, stratifying for antidepressant use (actively taking or not). The study coordinator is responsible for the assignment based on the random sequence. This is not a blinded study, as there are distinct differences between the 2 bassinets.

Intention-To-Treat Analyses

Intention-to-treat analyses [81,82] will be conducted to understand the extent to which participants who satisfy the inclusion criteria for enrollment and are therefore randomized to one of the two conditions (intention-to-treat population) are similar to participants who provided complete data across the measurement rounds (actually treated sample). The purpose of intention-to-treat analyses is to scrutinize whether the conclusions drawn from the RCT remain robust even after considering participant attrition across time [81]. We will adhere to the recommended guidelines for performing multiple imputation on clinical research data [83].

Mean Differences

Initial analyses will be performed to verify that the random assignment procedure successfully equalized participants between the treatment and control groups on the preintervention variables. Thus, MANOVA will compare these 2 groups on the entire set of preintervention baseline measures. A chi-square

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test will verify that both groups have the same distribution of infant boys and girls. As participants will be randomized to groups using a random number generator, baseline equivalency of the 2 groups is anticipated.

Six separate mixed 2 (treatment vs control) × 6 (assessment period) MANOVA models will be conducted. Specifically, to assess hypothesis 1a (aim 1), the model (model 1) will be applied to the infant sleep quality outcome measures. To address hypothesis 1b (aim 1), the analysis (model 2) will be applied to maternal postpartum sleep quality outcome measures. To evaluate hypothesis 2a (aim 2), the model (model 3) will be applied to the maternal postpartum depression outcomes. To examine hypothesis 3a (aim 3), the model (model 4) will be estimated on the measures involving peripheral cytokines, immune cells, and stimulated cytokine profiles. To examine hypothesis 3b (aim 3), the model (model 5) will be undertaken on the measures of T-cell dysfunction. Furthermore, to examine the exploratory aim, the model (model 6) will be estimated on the epigenetic biomarkers.

In each of the mixed MANOVA models, several follow-up analyses will be conducted to examine the results. First, a mixed (between-subjects and within-subjects) analysis of variance will be applied on each specific outcome. Second, independent 2-sided *t* tests will assess mean differences between the treatment and control group (at each timepoint) on each outcome. Third, dependent 2-sided *t* tests will permit scrutiny of the temporal change in mean scores between every 2 timepoints on every outcome. Fourth, the longitudinal trajectories across the entire 6-month period for both the treatment and control groups will be graphed using 95% CIs to provide a visual tool to offer insights to understand the effectiveness of the RCT.

Prior to conducting analyses, the normal distribution of all the measures will be inspected. If a variable is evidenced to be nonnormally distributed, then the bootstrapping variant of these statistical techniques instead will be performed to obtain corrected *P* values [84].

Mediational Analyses

Cross-lagged panel designs will be pursued to make inferences about the temporal priority of a set of measures assessed longitudinally [85-87]. Accordingly, cross-lagged panel models permit the opportunity to determine the temporal precedence of antecedents and consequents in the set of constructs [86]: infant sleep quality, maternal sleep quality, and postpartum depression. The depiction of the proposed cross-lagged panel model to be tested is shown in Figure 2.

Figure 2. Cross-lagged panel model. For diagrammatic clarity, not displayed but will be estimated as part of the model are the constructs for postpartum months 3 (T4), 4 (T5), and 5 (T6), the correlations across constructs in every measurement round, and predictive error terms.

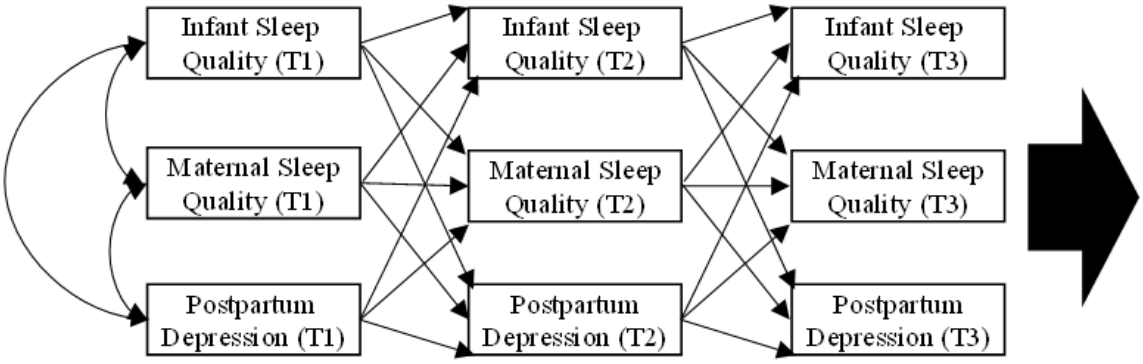

The cross-lagged panel model findings in the above model are expected to help inform how to specify the mediational model for hypothesis 2b. We propose that the cross-lagged panel model will evidence the following significant temporal cross-lagged directions that are consistent with hypothesis 2b: SB versus TB→infant sleep→maternal sleep→postpartum depression. Thus, a longitudinal mediational model, incorporating the intervention factor, will be specified and estimated (Figure 3). This mediational model tests and proposes that following underlying mechanism: SB group (vs the control group) will improve infant sleep quality, which would then predict better maternal sleep quality and finally contribute to lower maternal postpartum depression. All the outcomes of aim 1 are incorporated into the aim 2 mediational model to provide comprehensive and compelling insights that will statistically connect all the psychosocial constructs and understand the underlying process of this RCT.

Figure 3. Mediational model. For diagrammatic clarity, not displayed but will be estimated as part of the model are the predictive error terms. SNOO: smart bassinet.

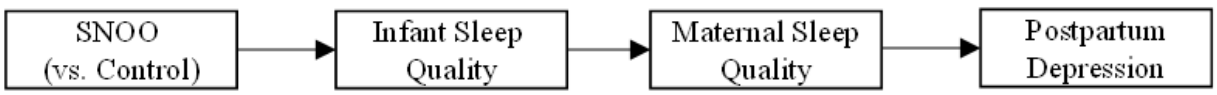

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The cross-lagged panel model and the meditational model each will be estimated with structural equation modeling [88]. The overall adequacy of these structural equation models will be assessed using fit indices [89-91]. A nonsignificant model chi-square test is desired to signify that the model approximates the underlying data, but this index tends to be sensitive to sample size [92]. Thus, additionally interpreted will be the comparative fit index and the Tucker-Lewis index, with higher values, preferably above 0.90, indicative of a good-fitting model [93,94]. The root mean-square error of approximation is sufficiently sensitive in detecting model misspecifications and provides a 90% CI [95]. Values below 0.05 indicate close fit, between 0.05 and 0.08 fair fit, between 0.08 and 0.10 mediocre fit, and above 0.10 poor fit [95].

If the fit indices for a model would be judged satisfactory, then the magnitude of the direct paths and the *P* values of these paths will be interpreted [96]. In the mediational model, the statistical significance of these mediational processes starting from the SB intervention (vs control) to infant sleep quality to maternal sleep quality and finally to postpartum depression with be evaluated in tests of indirect effects to determine whether the mediational process is significant beyond chance [88]. As recommended for structural equation models [96], bootstrapping with bias-corrected CIs will be applied to adjust for potential nonnormality of the variables.

Statistical Analyses for Immune Measurements

The initial statistical approach will include a descriptive cross-sectional analysis at each timepoint, both for quality assurance and to attain a better understanding of the distributions of the immune cell and cytokine profile variables for use in subsequent analyses, including the need for any transformations (ie, logarithmic transformation to symmetrize the residuals). Factor analysis will be employed as a means of data reduction to probe latent cytokine profiles reflected across the manifest indicators (eg, tumor necrosis factor-α, IL-6, IL-1β). We will first compare levels of a combined score of peripheral innate immune cytokines and frequency of maternal immune cells between women who do and do not develop PMADs in separate models to evaluate cross-sectional effects, employing a multivariable linear regression model to adjust for relevant covariates (eg, gestational age, BMI). Similar models will be repeated for maternal cytokines and innate cell recruiting factors as produced by the stimulated cells. Second, we will test whether the magnitude of group difference varies across the study period in a longitudinal analysis. We will fit a generalized linear population-average model estimated using generalized estimating equations with exchangeable working correlation structure to account for within-women correlation of mood measures. The model will include the relevant immune markers identified in the cross-sectional analyses, indicators for visit and group, as well as any relevant interaction terms (immune marker by group or immune marker by visit). The models will adjust for baseline severity of depressive symptoms and psychotropic medication use. Standard model checking will be performed, and the most parsimonious model will be selected based on the Akaike information criterion or quasi-likelihood information criterion for generalized estimating equations models. To test the within-group effects of severity of PMAD symptoms, the dichotomous group variable will be replaced by continuous Edinburgh Postpartum Depression Scale and Generalized Anxiety Disorder Scale-7 item scores in analytic models and restricted to only the subset of women with significant PMAD symptoms.

Missing Data

Attrition in our prior studies has been approximately 15%, and we have accounted for that in our planned sample size. In addition, in our prior studies, we have missing biological data (due to incomplete blood draws) in about 7% of the visits; we anticipate similar rates in this study, which will use the same approach. Given the prospective nature of our study, we will carefully evaluate missingness. If identified, we will employ one of the two strategies to handle missing data. The first approach relies on a technical assumption of missing at random and involves inclusion of covariates related to missingness in all analyses. Full information maximum likelihood performs well under ignorable missing data conditions such as missing at random. A second strategy we will use is multiple imputation. Although this has the potential to yield biased estimates dependent on the nature of missingness [97], we will employ this approach to implement sensitivity analysis under plausible assumption of missing not at random to examine the robustness of our inference [98].

Results

This project was funded in June 2024 and approved by the institutional review board of University of Colorado Colorado Springs (#2024-071) and by the Office of Human Research Oversight in February 2024. Recruitment for this study began in January 2025. We anticipate that the data analysis for the primary and secondary aims will be completed by July 2028. The methodology for the web-based surveys will be reported according to the CHERRIES checklist before the submission of any manuscript. The results from this trial will be used to extend SB efficacy in larger military cohorts and in women experiencing active perinatal mood disorders.

Discussion

Implications of SHINE

At the conclusion of this project, we will have gained a thorough understanding of how SB affects infant and maternal sleep compared to TB and its association with maternal mood through 6 months post partum in military-affiliated women. We will also significantly extend our current knowledge regarding the biological mechanisms associated with PMADs and how they may be modified by behavioral interventions. Future directions will include evaluations of women with current depressive disorders, women with a history of depression but not actively depressed, women with and without a history of trauma, and women who deliver prematurely to determine if SB can mitigate depressive symptomatology over the course of 12 months. This is a primary goal, as PMAD is a serious public health concern.

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Limitations

This study will, however, have important limitations that warrant discussion. The study goal is to determine whether SB can prevent or reduce the reoccurrence of PMADs and not for use as an active treatment. Hence, we chose to exclude participants with active psychopathology at enrollment. We focused on at-risk participants. Those with active psychopathology are not at-risk—they have it. Moreover, we felt that it was a matter of safety. Recruiting participants from across the United States restricts the ability of our team to manage or treat an actively depressed mother. Ethically, we believe that we needed to demonstrate that SB can mitigate or prevent PMADs before evaluating whether it can treat active PMADs. However, if a participant develops PMAD at post partum, they will remain in the study and be referred for treatment. To clarify, we are only excluding women with a positive diagnosis of SCID; women with a history of PMAD or who are effectively treated will be included. This decision comes with some concerns. One is that we may have too small of a magnitude or range of mood symptoms to observe a true positive effect of SB on mood symptoms. In other words, the population will be too mentally normal/healthy. We believe, however, that the diverse sample will provide enough variability in mood symptoms, especially since a greater percentage of active-duty women and military spouses experience mental health conditions and at a higher rate than civilians [99-101]. If we notice that the rate of PMAD symptoms is limited or if we are excluding too many participants due to active psychopathology, we may alter the design to include active psychopathology. Another limitation is that the study requires participants to have access to the internet; therefore, individuals of low socioeconomic status and certain racial/ethnic groups may potentially be excluded from the study [102]. However, low-income Americans have made gains in technology and access to the internet, which is likely to continue in the future. A primary goal of this study is to have a diverse sample of racial and ethnic backgrounds. Recruiting and retaining a broad range of participants, particularly those of low socioeconomic status, has been challenging, with recent calls to enhance representation [103,104]. In order to provide an equitable interpretation of the data, the participants need to be diverse and accurately reflect the population of the United States. Therefore, a major emphasis will be on recruiting a diverse and representative sample of military-affiliated participants. Although attrition has been a minimal issue in our studies, we are cognizant of the duration and expectations of the protocol. Thus, our group will maintain regular contact and troubleshoot, if necessary, to enhance retention.

Conclusions

Pregnant active-duty and military spouses are an underserved population. Data suggest that persistent, rather than transient, infant sleep issues contribute to maternal depression, poor maternal sleep, and poor family functioning. We contend that to achieve the goal of reducing PMADs among new military-affiliated mothers, sufficient and efficient sleep is crucial. Understanding that there are few nonpharmacologic interventions that significantly improve infant or maternal sleep highlights the need for these data. This will be the first study to assess sleep methodically and longitudinally from infants who sleep in an SB and their mothers versus those who sleep in a TB and their mothers and how sleep from both individuals interacts to affect postpartum mood. We hypothesize that this study will indicate that SB may indeed reduce PMADs in military-affiliated mothers.

Acknowledgments

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Data Availability

Data supporting this study will be openly available from the National Sleep Research Resource, which is a National Heart Lung Blood Institute–supported repository for sharing sleep data (polysomnography, actigraphy, and questionnaire-based) collected on tens of thousands of individuals from cohort studies, clinical trials, and other data sources.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT (Consolidated Standards of Reporting Trials) 2010 statement checklist.
[PDF File (Adobe PDF File), 253 KB - resprot_v14i1e66439_app1.pdf]

Multimedia Appendix 2

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Peer review from the Congressionally Directed Medical Research Programs - Fiscal Year 2023 Peer Reviewed Medical Research Program - Lifestyle and Behavioral Health Interventions Research Award - Clinical Trial (Department of Defense, U.S. Army Medical Research and Development Command, USA).
[PDF File (Adobe PDF File), 382 KB - resprot_v14i1e66439_app2.pdf]

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Abbreviations

CHERRIES: Checklist for Reporting Results of Internet E-Surveys
CONSORT: Consolidated Standards of Reporting Trials
IL: interleukin
MANOVA: multivariate analysis of variance
PBMC: peripheral blood mononuclear cell
PIPPI: Psychoneuroimmunology in Pregnancy & Postpartum
PMAD: postpartum mood and anxiety disorder
RCT: randomized controlled trial
REDCap: research electronic data capture
SB: smart bassinet
SHINE: Sleep Health and Mood in Newly Expectant Military Mothers
TB: traditional bassinet

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Protocol

Reducing Heavy Drinking Through the "Sober Curious" Movement in Australia: Protocol for a Mixed Methods Study

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Abstract

Background: Alcohol consumption is a major public health problem. Its socially engrained nature adds complexity to designing successful reduction approaches. Rather than implementing another intervention, we will undertake a natural experiment on the "sober curious" movement, which gained momentum through social media influencers promoting the idea of reducing alcohol consumption for wellness. We focus on ways to reduce alcohol consumption, through sober curiosity, with 4 heavy-drinking population groups: male construction workers; lesbian, gay, or bisexual women; hospitality workers; and tertiary education students.

Objective: Aim 1 analyzes the sober curious movement from the "supply side" using qualitative interviews with sober curious stakeholders and a citizen science study of social media content with the 4 case study groups. We will also undertake citizen science and social media studies with a representative sample of the population. Aim 2 examines the sober curious movement from the "demand side" using qualitative interviews with the 4 case study groups to investigate their knowledge and attitudes toward sober curiosity. We will also undertake a representative national survey and ethnography with a representative sample of the population. For aim 3, we will develop evidence-based interventions leveraging sober curiosity and using citizens' juries, industry symposia, and policy symposia to develop feasible public health measures and options tailored to the needs of the 4 case study groups.

Methods: The project involves 3 stages. Stage 1 will examine the supply side of alcohol-free products. A social media analysis of marketing by alcohol-free producers and distributors will generate an understanding of their techniques and population groups they target. In-depth interviews with producers will create evidence on the intentions behind making alcohol-free products available, their target market, and if and how they balance providing nonalcoholic products alongside alcohol. Stage 2 will be a qualitative study with 4 case study groups with high alcohol consumption: male construction workers; lesbian, gay, or bisexual women; hospitality workers; and tertiary education students. This stage will provide a deep understanding of the reasons for alcohol consumption, potential for alcohol-free product use, and possible interventions to sustainably reduce consumption. Stage 3 will involve deliberative symposia with non-alcoholic beverage producers and distributors, representatives from our case study groups, public health professionals, and policy makers to develop co-designed interventions for alcohol reduction.

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Results: This 3-year research protocol was funded by the Australian National Health and Medical Research Council via their Ideas Grants funding scheme (grant ID GNT2038211). The study will commence in July 2025. Human Research Ethics Committee approval has been granted.

Conclusions: Our study will provide a template for interventions designed to enable reduced drinking within heavy-drinking social worlds with huge potential for scalability of knowledge, expanding the economic, environmental, social, and cultural benefits within and across Australia and internationally.

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KEYWORDS

alcohol reduction; sober curiosity; public health; co-design; abstinence, alcohol; qualitative research

Introduction

The Research Problem and Significance

Alcohol consumption is a major public health problem, contributing to a myriad of health problems such as increased avoidable mortality, chronic illness, and accidents, in addition to social and economic problems (eg, lost days of work, domestic violence) at a cost to the Australian economy of AUD $66.8 billion a year [1]. Australia's National Alcohol Strategy 2019-2028 aims for a 10% reduction in population-level alcohol consumption [2]. This reduction aim is difficult because consuming alcohol is socially acceptable, and heavy-drinking groups sustain population-level harms [3,4]. Indeed, the heaviest drinking 10% of the Australian population accounted for 54% of all alcohol consumed in 2019 [5]. The term "heavy-drinking" refers to levels exceeding the national alcohol guidelines [6] for long-term (>10 standard drinks per week) or single-occasion (>5 standard drinks on one occasion per month) risky drinking. This puts these particular heavy-drinking groups at higher risk of lifetime harm than other people. Urgent action is required to identify socially acceptable alcohol reduction options for heavy-drinking Australians [6].

This project will investigate the untapped potential for public health to leverage the momentum of the "sober curious" (SC) movement toward increasing the social acceptability of nondrinking. Prominent on social media, SC is a social movement that challenges the pervasiveness of alcohol in social contexts, emphasizes the health benefits of reduced alcohol consumption (or abstinence), and provides a series of supports and strategies to help realize these benefits. Our purpose is to ascertain if, how, and why (or why not) the SC movement influences heavy drinkers' openness and ability to reduce alcohol consumption. It explores the leverage potential through two key aspects of the movement: SC programs and communities (eg, Hello Sunday Morning—associate investigator [AI] NL is Chief Executive Officer of this SC organization) and no or low-alcohol (termed NoLos) beverages, producers, and venues. Building on these insights, we will co-design and co-develop new alcohol reduction interventions that have relevance, consonance, and specificity among 4 heavy drinking "case study" groups: (1) male construction workers; (2) hospitality sector workers; (3) lesbian, gay, bisexual, transgender, queer, plus (LGBTQ+) women; and (4) tertiary education students (university and technical and further education [TAFE]) living in regional areas. To the best of our knowledge, this project is a world-first investigation of the diffusion (supply) and uptake (demand) of SC, aimed at reducing drinking among heavy-drinking groups by supporting long-term, sustainable, lower-risk drinking practices.

Although there has been reduced alcohol consumption at a population level, heavy drinking persists in our 4 case study groups:

- Male construction workers: Heavy drinking and "alcohol abuse" has been reported in the male construction industry [7], related to workplace culture and "masculine" group norms [8], where heavy drinking practices are normalized [7]. More than 60% of male construction workers regularly (monthly or more) consume ≥5 drinks in a single session, compared with 40% of men in general [9].
- LGBTQ+ women: Heavy drinking has been found across numerous countries among LGBTQ+ women [10-12] who often participate in alcohol-centric social contexts in order to establish friendships and gain social support [13,14]. They are more likely to drink heavily in these contexts [15]. There is a major gap in knowledge about developing alcohol interventions with and for LGBTQ+ women [11,16].
- Hospitality workers: Heavy drinking is prominent among the hospitality industry. Hospitality workers are 3.5 times more likely than other workers to consume alcohol and are more likely to attend work under the influence of alcohol than other workers [17]. In a recent study of hospitality workers in Victoria, around 75% regularly (monthly or more) consumed alcohol at risky single-session levels [18].
- Tertiary education students in regional areas: Young adults living in regional areas drink (on average) at heavier levels than those in urban areas [19,20]. For example, 62% of young adults in regional areas consumed >5 drinks on a single occasion per month compared with 47% in metropolitan areas [21]. Students are over-represented, indicated by 58% of young people with a certificate or diploma drinking at a risky level and those who finished year 12 drinking more than those who did not [6].

Current alcohol reduction interventions are not working for the 4 case study groups. Our approach differs from existing alcohol reduction approaches focused on individual consumption instead of the social context. It is essential to explore the possibility to use the current groundswell for SC to support urgent alcohol reductions by tailoring SC programs, communities, and NoLo beverages with and to Australia's heaviest drinkers. The

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proposed project is a significant shift away from public health approaches focusing on deficits, which research evidence shows to be limited for reducing alcohol yet persist as a predominant philosophy underpinning current approaches [4,22].

This project represents a novel and time-critical opportunity. It responds to urgent calls to "change our heavy drinking culture" [2], provides an evidence base to support policy changes that increase the accessibility of NoLos, and informs the development of SC programs to meet the needs of heavy-drinking populations. Our research will achieve these outcomes by investigating modifiable group-level alcohol consumption practices, social norms, and identities rather than focusing on individual consumption patterns [16,21]. Our idea represents new territory for public health by focusing on the value and realization of positive nondrinking ways of living.

Key Literature on Alcohol Consumption in Australia

Alcohol consumption in Australia is socially accepted and entwined in what many Australians think makes for pleasurable social engagements [23]. Current data show that 77% of the adult population drank alcohol in 2019 [24] and over 25% of adults exceeded the Australian alcohol guideline thresholds for single-occasion risky drinking in 2020-2021 [25]. Several population groups are at higher risk of harm due to heavy drinking and warrant urgent intervention [26]: male construction workers [7], LGBTQ+ women [11,16], hospitality sector workers [18], and tertiary education students in regional areas [19,27]. Given the persistence and harms of heavy drinking among these groups, urgent action is required to identify socially acceptable alcohol reduction options to reduce population-level harms. The SC approach is one option that is increasingly popular and is a real-world possibility. This project will co-develop and co-design options to use and extend aspects of the movement—programs and communities and NoLos—to support alcohol reduction within heavy-drinking groups. These comprise people who consume alcohol at levels exceeding the national alcohol guidelines for long-term (>10 standard drinks per week) or single-occasion risky drinking (>5 standard drinks on one occasion per month [6]), herein termed "heavy drinking."

There are key shortcomings to current public health responses. Current public health responses to reducing alcohol consumption focus on individual risk messaging and behavior change, stripped from contexts, and the heavy drinking by particular groups persists. These shortcomings necessitate new targeted approaches that address the norms, identities, and practices that operate to sustain drinking.

Our previous work provides in-depth knowledge about the reasons other heavy-drinking groups (midlife women and urban young adults) consume alcohol [28-34] and provides the potential to leverage the SC movement to support alcohol reductions [35]. SC is a social movement encouraging wellness through alcohol reduction, focusing on normalizing nondrinking (or lighter drinking) and increased health consciousness. The SC movement also provides strategies or practices for effectuating and maintaining these transformations (eg, consumption of NoLos, alcohol-free spaces). The movement is prominent on social media, where social media influencers promote drinking in moderation and present it as pleasurable and beneficial [36]. SC represents an important shift away from Australia's "culture of intoxication" [3], which is appropriated by the alcohol industry that profits most from heavy drinking. It emphasizes the health benefits of reducing alcohol consumption and prompts questions about the centrality of alcohol in social life. It fits well with other data suggesting increases in abstinence among young people are part of a broader normalization of nondrinking [37]. Although SC has had success in reaching younger, female, and middle-class groups [24], its potential for reaching and engaging other groups will be explored in the proposed study.

The potential for alcohol reduction in heavy-drinking groups is real. Awareness of the links between alcohol and health harms is growing, and increasing numbers of Australians are open to reducing drinking [38,39], with "health" given as the most common reason for reducing drinking [26,40]. This shift in heavy-drinking social norms demonstrates the potential for leveraging the momentum of the SC movement, whereby moderate or nondrinking is increasingly a plausible and health positive decision—for heavy drinkers specifically. Our proof of concept is our pilot studies [35], which found that the SC movement increased heavy-drinking, midlife women's motivations and attitudes toward reducing alcohol [24].

There has been increasing availability of NoLos. The Australian Institute of Health and Welfare reported that, between 2016 and 2019, the proportion of ex-drinkers increased from 7.6% to 8.9% [41]. Sales of NoLos increased by 83% in the 12 months following Australia's COVID-19 lockdowns in 2020 [35] and were predicted to increase by a further 24% by 2024 [42]. In April 2023, the South Australian Government announced an investment of Aus $2 million in a "No and Low Alcohol Trial Scale Research Facility, as part of its bigger NOLO Alcohol Program" [43]. This is a world-first, trial-scale NoLo facility. This investment recognizes the rapidly growing global NoLo wine market, worth an estimated AUD $1.6 billion in 2020 [43]. This shift in the market represents a huge potential to concurrently change the social contexts that encourage heavy drinking.

Research Aims

Aim 1

Our first aim is to analyze the SC movement from the "supply side" using qualitative interviews with SC stakeholders and a citizen science study of social media content on NoLos and SC with the 4 case study groups to identify the reach and influence of social media and ways to support SC. PhD project 1 will additionally undertake citizen science and social media studies in a representative sample of the population.

Aim 2

Our second aim is to examine the SC movement from the "demand side" using qualitative interviews with the 4 case study groups to investigate their knowledge and attitudes toward SC. PhD project 2 will additionally undertake a representative national survey and ethnography in a representative sample of the population.

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Aim 3

To address aim 3, we will develop evidence-based interventions for leveraging SC using citizens' juries (the 4 case study groups), industry symposia (stakeholders linked to each case study group), and policy symposia to develop feasible public health measures and options tailored to the needs of the 4 case study groups.

Conceptual Framework—Social Practice Theory and "Social Worlds"

The underpinning conceptual framework of the project is social practice theory (SPT) [44,45], which has been used extensively by chief investigators (CIs) PRW and BL [46,47], SM [31], and AL [34] and identified as critically important for examining how alcohol consumption behaviors develop, persist, and can be changed [48-50]. In their previous Australian Research Council (ARC)–funded study, CIs PRW, SM, and AL and AI AP applied SPT to interpret heavy-drinking, midlife women's engagement with SC [35]. CI PRW has another ARC-funded study focusing on SPT around oral health in children [51,52]. Both have methodological and theoretical relevance to our proposed study.

SPT focuses on the shared *social practices*, including materials, meanings, and competencies, that frame and support alcohol consumption [53]. SPT provides a useful approach for examining alcohol practices in heavy-drinking social worlds. It stipulates that change can occur by addressing one or more of the elements that constitute drinking practices or practices that relate to heavy-drinking behavior (eg, work, eating, socializing). For instance, CI MS has shown how the social practices of "after work drinks" can be altered by shifting what it means to socially connect with colleagues and offering different ways of connecting that do not revolve around alcohol [18]. The 4 case study groups are exemplars of what CIs SM and MS, with AI AP, have conceptualized as heavy drinking "social worlds" [54], where drinking alcohol is an important aspect of shared norms, symbolisms, and activities, placing members of the groups at high risk of alcohol-related harm.

Considering how we might change the social practices shaping heavy-drinking social worlds allows greater scale of effect than does a focus on individuals alone, which has proven limited for reducing consumption behavior among heavy drinkers [4]. For example, in the social worlds of men in the *construction industry*, alcohol consumption is a central element of social inclusion, creating a sense of unity ("being one of the boys") [55] and as an "act of friendship" [56], enabling men to support each other. In the social worlds of *LGBTQ+ women*, alcohol plays a key role in identity formation [57] and building relationships, and there are social expectations to drink in LGBTQ+ spaces [58]. Among *hospitality workers*, alcohol contributes to professional identities, cultivating fun atmospheres for patrons, social connection with workmates, and coping with the demands of busy shifts [18]. An SPT study of *tertiary students* showed how university activities and the symbolic aspects of drinking alcohol (eg, a rite of passage) bundle together to reinforce heavy consumption [14]. Overall, SPT provides a powerful framework for understanding how SC can be built into the social worlds of heavy-drinking groups.

Pilot Studies That Informed the Proposed Study

Pilot study 1 included 90 interviews with midlife women (CI PRW's ARC-funded study 2019-2023) to explore their logic and reasons for drinking alcohol and their preparedness for alcohol reduction. We found an openness to SC because it is increasingly popular in the broader community and to moderate drinking by consuming NoLos before or alongside alcohol in social situations [29,30,59,60]. This study focused specifically on midlife women, and the new study will build on it, extending to other groups of heavy drinkers and intersectional forms of oppression.

Pilot study 2 (led by CI BL) investigated factors that support women to be SC (ie, features of programs, forums, and networks) and reduce drinking [35], finding that middle-class women perceived the SC movement as optimistic and a form of empowerment and this enabled alcohol reductions. This study was only undertaken with midlife women, and this new study will build on those findings with new groups of heavy drinkers.

Pilot study 3 is a multicountry, cross-sectional survey (led by CI TH) with LGBTQ+ women in Australia (CIs PRW, SM, and BL), New Zealand (CI AL), Scotland, and the United States (CI TH) to understand barriers and facilitators to SC in this marginalized population group [61]. This pilot study includes cross-sectional surveys that will begin to describe the potential for SC programs to reduce alcohol consumption, but this new study will use novel qualitative methods to gain additional depth of understanding.

Methods

Ethical Considerations

Ethical procedures and approvals for all aspects of our study were sought and provided by Torrens University Human Research Ethics Committee (ID 0467). As with all mixed methods, ethical considerations include informed consent, anonymity, and confidentiality. The topic of alcohol consumption could also be sensitive. Our previous qualitative interview studies with diverse women in midlife (aged 45-64 years) has attuned us to issues pertaining to informed consent including detailing the potential risks and benefits of the study. Our approach in related studies has been to demonstrate empathic neutrality [62] in our style of engagement.

Each participant will have agency to decide the terms of their participation and the information they contribute. Other ethical practices include checking the suitability of the approach with participants before commencing data collection; allowing participants to nominate their preferred pseudonym, modes of contact, and preferred medium for data collection (phone, in-person, or telecommunication software); outlining assurances of confidentiality; and issuing honoraria to recompense their time and resources. Given the success of our previous studies at generating rich understanding and engaging women across long time periods or repeated interviews [47,63-65], we will use similar methods in this study.

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Research Design

The project will occur in 3 interrelated stages (see Figure 1) and follows an experience-based, co-design method [66,67] to investigate the "problems" with consumers (4 case study groups) and stakeholders then use their responses as ideas to devise and test public health "solutions" (programs and policy) that have relevance, consonance, and specificity to them—the intended end user. We will recruit participants for the project from all states and territories across Australia. We will also facilitate 2 PhD projects (funded by Torrens University) to add breadth to the study by examining the potential for SC within a broader cross-section of the Australian population.

The majority of data across all stages of the study will be qualitative, albeit from interviews, social media analysis, ethnographies, and different methods of consensus development. With participants' consent, interviews and consensus groups will be audio-recorded and transcribed verbatim then deidentified and checked for accuracy. Although data analysis will differ slightly between studies, all data will be managed using NVivo v13 [68]. Analysis will follow the 3-step progressive method of precoding and conceptual and theoretical categorization developed by CI PRW and AI SM [69]. For interpretive validity, multiple researchers will independently pre-code samples of transcripts and field notes, social, or media and meet to compare coding and revise the coding frame.

Figure 1. Research design and timeline. NoLo: no or low-alcohol.

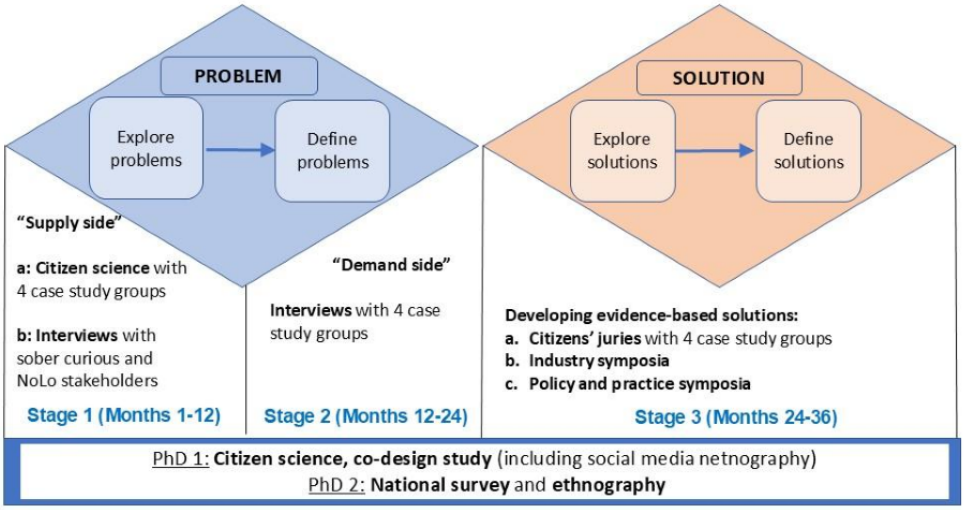

Stage 1a (Months 1 to 9, Led by CIs PRW, MSc, and AL and Linked to Aim 1)

This world-first study will analyze the context and intentions of the SC movement by including the supply side, with the view of leveraging the momentum of the movement to suit the social worlds of our 4 case study groups: male construction and hospitality workers, LGBTQ+ women, and tertiary education students living in regional areas. We will undertake a social media analysis (similar to analysis undertaken by CIs PRW [70] and AL [71]) of promotions of "SC" (advertisements or posts from influencers), producers, and distributors (bars, bottle shops) of NoLos and organizers of alcohol-free spaces, club nights, or events. This will provide knowledge about the techniques that might impact heavy drinkers' motivations and attitudes to reducing alcohol and the acceptability of the approach to our 4 case study groups of heavy drinkers. We will use a citizen science approach successfully used by our research team previously [72,73], whereby researchers work alongside participants from the 4 case study groups who document content about alcohol reduction (eg, SC digital advertising) they see. Participants will interpret how they perceive the content and record its effect on their perceptions, attitudes, and behaviors toward SC using a method developed by CI PRW [72]. These data will be used in stage 3 to inform options that have relevance, consonance, and specificity for each group.

Recruitment strategies will be tailored for each group, although approaches to recruitment previously proven useful [72] will guide our approach, including targeted Facebook campaigns [74]. All participants will be ≥18 years of age. *Male construction workers* will be recruited via Facebook. Given the prior difficulties with recruiting this group experienced by CIs SM and MS and AI AP, we will draw on CI KL's extensive networks within the construction industry to supplement the campaign. *LGBTQ+ women* will be recruited via Facebook, social networks, and snowball sampling. CIs SM and TH and AI AP have extensive experience recruiting LGBTQ+ women in multiple countries and contexts. Similarly, CI MS is experienced with recruiting hospitality workers via social media, snowball sampling, and hospitality training providers. *Tertiary education students living in regional areas* will be recruited through La Trobe University's regional campuses, often co-located with TAFEs, led by CI SM and AI GC. All participants will self-report "heavy" or "moderate" drinking. We will recruit 50 members from each case study group across Australia (total n=200) who will create and upload screenshots (5-10; minimum 5) of social media content that they think relates to NoLos or the SC movement to a study portal. Participants will be asked to take additional photographs of NoLos or SC advertising in their local built environment and upload to the study portal—CIs PRW and BL are experienced in social media analysis. This will enable a meaningful and manageable volume of content for analysis [72]. Participants will be provided with examples

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of content of interest to this study. They will take note of where they saw the image (eg, specific social media platform or location in their local area) and say what they thought of the content by rating it for personal appeal, impact, and intention per the method previously undertaken by CI PRW to understand the impact of alcohol advertising on Australian women [72]. CI MS has also used citizen science to explore digital advertising of alcohol among young adults [73].

Stage 1b (Months 3 to 12, Led by CIs PRW and MS and Linked to Aim 1)

This stage will involve interviews with (1) producers or suppliers of NoLo products and organizers of alcohol-free spaces, club nights, or events (n=30) and (2) representatives of the SC movement, including social media wellness influencers and online SC community organizations (n=30). Interviews will investigate reasons behind their decisions to promote SC (including through NoLos), if the case study groups identified in this proposal are among their intended audiences, how NoLos and SC are (can be) promoted to case study groups, and the ways they think the approach could be shaped to meet the needs of the case study groups. Recruitment will be through cold calling and snowball sampling. We do not anticipate problems with recruitment, given that, in our pilot study [24], NoLo producers and distributors and SC stakeholders and representatives were willing to participate. Despite assumptions that NoLo producers may feel disinclined to disclose or be "truthful," the pilot study by CIs PRW and BL [24] found them to be candid about their motivations and marketing campaigns.

Stage 2 (Months 12-24, Led by CIs PRW, SM, MS, and BL and Linked to Aim 2)

This stage will use qualitative methods to explore heavy drinkers' openness to SC and viable options (programs, forums, supports) for reducing alcohol consumption among the 4 case study groups: male construction workers (led by CI KL), LGBTQ+ women (led by CI TH), tertiary education students living in regional areas (led by CI SM), and hospitality sector workers (led by CI MS). Research assistants will undertake in-depth interviews with approximately 30 participants from each case study group recruited during Stage 1a (total n=120), noting that sampling will continue until saturation is reached [75]. If we are unable to recruit enough participants, we will replicate the original recruitment strategies used in stage 1a. Previous experience suggests this sample size will allow for noticeable patterns within the data for each case study group. Nondrinkers and light drinkers will be excluded. Some moderate drinkers from each group will be recruited alongside heavy drinkers for variability in order to triangulate observations on the social context of drinking within their particular social world [54]. Interviews will be conducted online and will last approximately 1 hour. Interview questions will probe for knowledge, attitudes, beliefs, and practices around reducing drinking and the SC movement specifically, what (if anything) appeals to them about SC, factors and barriers that impact preparedness to reduce consumption (particularly where this behavior is habitual and or social setting or identity-based), what alternatives to drinking alcohol they perceive to be available to them, and what supports are available or suitable. CIs and AIs will meet in person during stage 2 to check for agreement in coding (each co-coding a selection of transcripts) to improve explanatory rigor. Together, they will collate stage 1 and 2 findings for the citizens' juries for deliberation in Stage 3.

Stage 3 (Months 24-36, Led by CIs PRW, AL, and KL and Linked to Aim 3)

Stage 3 will use consensus development methods, including citizens' juries and deliberative symposia, to co-develop and co-design alcohol reduction options that have relevance, consonance, and specificity for the groups (presenting data to stakeholders from stage 1). Two weeks prior to the juries and symposia, materials will be distributed to orient participants to the research findings (from stages 1 and 2). CI PRW has extensive experience using consensus development methods [62-65].

Citizens' juries (n=4) will be conducted with participants from each of the 4 case study groups (a jury of 15 participants per case study group) to deliberate on specific policies, activities, or interventions that might "work" to reduce alcohol consumption for them. Previous research conducted by CI PRW using citizens' juries suggests a group size of 15 will allow for depth and meaningful dialogue [76-78]. Participants (jurors) will be recruited from stage 1b. Citizens' juries will be delivered via Teams (CI PRW successfully ran online citizens' juries in his National Health and Medical Research Council [NHMRC] study [79]). Each jury will meet online over a 2-day period to consider the evidence from stages 1 and 2 and to confer and reach consensus about needed and plausible options for leveraging the SC movement toward alcohol reduction within their social worlds. They will then confer about important factors that shape openness to SC and will put forward recommendations for supporting SC toward alcohol reduction. CIs and AIs will participate in the process to bring in knowledge of the literature and real-world practice (per CI MS's and AI NL's experiences working in the alcohol treatment sector) on what "works" in harm reduction and clinical prevention to ensure approaches developed are evidence-based. Participants will discuss their knowledge of sobriety movements, alcohol-free spaces (venues), and alcohol substitutes (NoLos) and express their preferences. They will also discuss the possible facilitators and barriers to reducing alcohol consumption or "being SC" (including possible social pressures to drink alcohol rather than substitutes) to best support alcohol reduction in the case study group they represent. This enables agency and decision-making within groups, including potential for advocating for policy change.

Industry symposia (n=4) will be conducted with stakeholders linked to each of the 4 case study groups to discuss feasible strategies for supporting SC and increased access to NoLos within their respective social worlds. We will run specific symposia to deliberate about how to support alcohol reduction for male construction workers (eg, construction companies and professional associations, specifically Chartered Institute of Building, Australian Institute of Building, Housing Industry Association, and Centre for NSW Work Health and Safety), LGBTQ+ women (eg, ACON, LGBTIQ+ Health Australia,

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Thorne Harbour), hospitality workers (eg, professional associations and unions, such as HospoVoice; hospitality training providers; hospitality well-being organizations like White Jacket Effect, Go Hospo, and Hospo For Life), and tertiary education students in regional areas (eg, Youth Affairs Council, Local Government Associations, local sporting clubs, universities, and TAFEs). Each symposium will meet for 2 hours to 3 hours via Microsoft Teams and will be identified through our extensive professional networks. For example, CI KL has extensive networks, having undertaken Occupational Health and Safety projects within the building and construction industries. CI BL is an executive member of the Women's Health Research Translation Network with national networks. CI SM and AI GC have extensive youth sector networks and are institutionally connected with La Trobe University, which has regional campuses in Victoria, and CI TH and AI AP have multiple ongoing contacts and affiliations with LGBTQIA+ groups in Australia.

A policy and practice symposium (n=1) will be conducted with SC organizations (eg, Hello Sunday Morning, Sober in the Country) and public health planners or policy makers at local, state, and federal levels (eg, Drug and Alcohol Services SA, VicHealth, Healthway). All CIs and AIs have well-developed networks across government and nongovernmental organizations and will draw on these networks to recruit participants. The half-day symposium will occur online. It will include a presentation of the ideas developed by citizens' juries and deliberative symposia, followed by discussion of feasible policy options for NoLo marketing, regulation, pricing, and visibility and practice options including new SC programs. CI PRW is highly experienced at moderating "policy fora." Policymakers are often willing to spend half a day considering research findings and deliberating about possible policy and practice options. This symposium will develop policy options that harness the popularity of the SC movement for alcohol reduction approaches tailored for each case study group.

PhD project 1 (Torrens University funded) will use citizen science methods to examine how the SC movement is "seen" and acted upon by a cross-section of adults (stratified by age, gender, social class, and drinking levels). Similar methods will be used to those used in stage 1a, but the PhD study will include a larger sample and cross-section of participants with differing levels of consumption, who will collect and co-analyze examples from social media (using approaches from netnography [80]), traditional media, and their local environments (eg, advertising in their neighborhoods) that encourage alcohol reduction, SC, and engagement with the broader wellness industry. Data will be analyzed quantitatively (affect reactions, attitudes, and intentions) and qualitatively (meaning, value, and symbolisms). The PhD will be supervised by CIs PRW, MS, and AL.

PhD project 2 (funded by Torrens University Australia) will support a mixed methods study of SC across the general population (ie, not focused on the 4 case study groups), including a national survey of Australians' attitudes and motivations toward being SC (including their experience with NoLo products, bars, and events and participating in SC alcohol reduction programs). Areas of questioning will cover the SPT domains of meanings (whether there are group-specific ideas or norms about alcohol and sobriety that can be tackled), capabilities (how sociality is enacted in ways that do and do not involve alcohol), and materials (material impediments to taking up SC such as venue options available to group members), which will enable us to identify public health measures in stage 3 (co-design and co-development). In addition, we will conduct an in-depth examination of alcohol-free bars and events, including ethnography and photovoice methods, paying attention to the spatial, affective, and embodied dimensions of SC spaces as well as the experience of being in alcohol events that offer NoLos. This PhD will be supervised by CIs PRW, BL, SM, and TH.

Results

This research protocol was funded by the NHMRC as part of their Ideas Grants funding scheme (grant ID: GNT2038211). The study has been funded for a 3-year period, starting in July 2025. The study was funded for AUD $802,000 (US $518,384). Human Research Ethics Committee approval has been sought and approved by the Torrens University Human Research Ethics Committee (ID 0467).

Discussion

Significance of the Study

The significance of the study is situated in evidence that Australians are open to the idea of needing to reduce alcohol consumption to improve health [38,39]. An openness to SC could make a large and direct impact on reducing population-level alcohol harms by supporting Australia's heaviest drinkers with reductions. The proposed project will use innovative methods known to be well-suited to complex public health policy issues like alcohol reduction, where stakeholder values may differ [4]. A co-designed approach aligns with broad acceptance that, to increase the efficacy of public health efforts, members of the heavy-drinking groups should be active participants in designing reduction approaches.

Expected Outcomes From the Study

There is a global gap in the literature about how to reduce alcohol consumption in heavy-drinking social worlds with persistent high consumption rates, particularly ways that are socially appropriate (ie, suitable, practical, feasible). Our project will provide evidence for targeted disinvestment in approaches that are limited in reducing alcohol harms for heavy-drinking groups. It will provide a template for interventions designed to enable reduced drinking within heavy-drinking social worlds with huge potential for scalability of knowledge, expanding the economic, environmental, social, and cultural benefits within and across Australia and internationally. We will undertake a "natural experiment" on the potential to leverage the SC movement—the various online forums and support programs and networks and proliferation of NoLos—to support alcohol reduction in these groups. Key outcomes are world-first: analysis of the "supply side" of SC and NoLos via social media analysis and industry interviews (stage 1), in-depth investigation of potential ways to support reduction in 4 case study groups (stage

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2), and a set of co-designed and co-developed alcohol reduction options for each of the 4 case study groups.

Major Innovations of the Study

To our best knowledge, this is a world-first attempt to investigate the possibilities of SC and co-design and co-develop new strategies to reduce alcohol consumption that have relevance, consonance, and specificity among 4 groups of heavy drinkers. The success of the SC movement shows how social norms and practices that drive heavy drinking can be reshaped to encourage SC, also harnessing cultural developments such as the increasing focus on health and wellness. This includes considerations such as increased availability of NoLos in off and on-premise venues and messaging that focuses on positives of SC (rather than loss or relinquishment) and resonates with the different case study groups by focusing on values that resonate with the group. Our pilot studies with midlife women showed that features of the philosophy of SC, including security, belonging (to a positive movement in place of drinking), and self-determination, are conducive to reducing drinking. SC also includes programs that improve literacy on alcohol harms and increasing social and emotional supports for reductions—it considers the intricate structural elements that influence alcohol and responds to them with something new. Heavy drinkers could be encouraged to consider why drinking is normalized within their social worlds and if this could be different by reaffirming group social connections through nondrinking. For example, new developments around SC and the growth of sober queer cafes and night clubs provides an important opportunity to explore and change heavy drinking cultures in LGBTQ+ social worlds.

Our study is novel in investigating "social worlds" that encourage heavy drinking and shape people's decisions around alcohol reduction, as previously conceptualized by CIs SM and MS [4,54]. Conventional approaches, which focus on changing individual alcohol behaviors independent of social contexts, have had limited effectiveness for the 4 case study groups [81]. Our conceptual innovation is our focus on alcohol consumption being enmeshed with a series of other social practices and not a discrete standalone behavior—the social nature of alcohol consumption is at the heart of the proposed study. Focusing on the practices of heavy-drinking "social worlds" is effective, albeit underused, and responds to calls to address "Australia's culture of intoxication" [4]. The proposed project responds by focusing on the social practices that shape the "social worlds" of 4 case study groups where group norms influence heavy drinking and unlock new potential for reducing alcohol consumption.

Alcohol reduction techniques targeted at the individual (eg, persuading behavior change through screening for problematic consumption) require that consuming alcohol is recognized by the individual as being a "problem." However, the majority (87%) of Australian drinkers consider themselves "responsible drinkers," even though 68% of Australian drinkers consume ≥11 standard drinks on a "typical occasion" [82]. This leads to alcohol reduction interventions being resisted [83] since the majority of drinkers do not see their behavior as "risky." Our focus on examining the suitability and adaptability of SC programs and communities and the increased availability of NoLos does not need people to see drinking as "problematic," since the SC philosophy is about enabling wellness rather than reducing risk of illness—our focus on co-developing alcohol reduction options regard reduced alcohol as an "asset" to living well and enjoyably.

Rather than implementing yet more individualized interventions with limited efficacy for behavior change (a norm for public health measures around alcohol), we will undertake a world-first "natural experiment" alongside the SC movement to develop socially acceptable and feasible alcohol reduction options. Our multidisciplinary study includes innovative methods such as citizen science, social media analyses, citizens' juries, and deliberative democratic methods, drawing on the expertise of leading international alcohol researchers. These methods have never been used to understand and explore options for alcohol reduction within our 4 case study groups and co-design and co-develop alcohol reduction options.

Potential Limitations of the Study

This is a very complex study with numerous "moving parts." We plan to implement a number of highly innovative methods with different population groups of heavy drinkers. A potential limitation is that we do not recruit enough participants in each of the case study groups, although we have excellent professional networks and prior expertise in working with each group over many years. We also have a plan for recruitment from one stage of the research to the next, with a proportion of participants in stage 1 being recruited into stage 2, then a proportion of those being recruited into stage 3. This increases the feasibility of successful completion and outcomes from the study.

Acknowledgments

We acknowledge the staff at all participating universities that supported us with submitting this research application to the National Health and Medical Research Council (NHMRC).

This research protocol was funded by the NHMRC as part of their Ideas Grants funding scheme (grant ID GNT2038211). The study has been funded for a 3-year period, starting in June 2025. The study was funded for AUD $802,000 (US $518,384).

Data Availability

The anonymized data sets generated or analyzed during this study may be available from the corresponding author on reasonable request (pending appropriate Human Research Ethics Committee approvals).

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Authors' Contributions

All authors were involved in conceptualization, funding acquisition, writing the original grant proposal, and reviewing this protocol for submission to JMIR.

Conflicts of Interest

None declared.

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Abbreviations

AI: associate investigator
ARC: Australian Research Council
CI: chief investigator
LGBTQ+: lesbian, gay, bisexual, transgender, queer, plus
LGBTQIA+: lesbian, gay, bisexual, transgender, queer, asexual, intersex, plus
NHMRC: National Health and Medical Research Council
NoLo: no or low-alcohol
SC: sober curious
SPT: social practice theory
TAFE: technical and further education

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Protocol

Improving HIV Prevention Among Heterosexual Men Seeking Sexually Transmitted Infection Services in Malawi: Protocol for a Type I Effectiveness-Implementation Hybrid Randomized Controlled Trial of Systems Navigator–Delivered Integrated Prevention Package (HPTN 112-NJIRA Study)

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Abstract

Background: Preexposure prophylaxis (PrEP) remains one of the most efficacious interventions for preventing HIV, but its effectiveness is often limited by poor persistence. Although regional efforts have primarily focused on young women and men who have sex with men, heterosexual men in East and Southern Africa represent a crucial group to engage and retain in PrEP care—both to improve health outcomes for men and to interrupt HIV transmission chains. Men seeking sexually transmitted infection (STI) services are particularly vulnerable to HIV acquisition, yet only a few interventions have tested strategies for engaging and retaining these men in PrEP services. Systems navigation, which addresses barriers to health care access and enhances comfort in clinical settings, may offer a promising approach to improving persistent PrEP use among heterosexual men.

Objective: This study will assess the effect of a peer-delivered systems navigator–facilitated HIV prevention package on PrEP persistence at 26 weeks among heterosexual men seeking STI clinical services in Lilongwe, Malawi. It will also evaluate the acceptability of the intervention and barriers to implementation among key stakeholders. Insights will inform the feasibility of a future randomized controlled trial.

Methods: In this single-site pilot type I effectiveness-implementation hybrid randomized controlled trial, 200 heterosexual men seeking STI services and initiated on PrEP in Lilongwe, Malawi, will be randomized (1:2) to standard-of-care PrEP services or

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systems navigator–assisted PrEP care (intervention). Participants will be followed every 13 weeks for at least 26 and up to 52 weeks. PrEP use and engagement in care will be assessed through medical record review and intraerythrocytic tenofovir diphosphate measurement, using objective biomedical analyses via dried blood spot. Primary effectiveness and implementation outcomes include 26-week PrEP persistence (adapted to accommodate daily oral, event-driven oral, or injectable PrEP) and acceptability, respectively. Additional implementation outcomes include feasibility and cost. Exploratory objectives characterize preferences for PrEP modalities, perceived and experienced stigma, and the influence of gender norms on PrEP persistence. All clinical services, including the provision of PrEP and PrEP safety monitoring, are being conducted by the Malawi Ministry of Health.

Results: HPTN (HIV Prevention Trials Network) 112 was funded in November 2023. Study recruitment began in April 2024 and closed in November 2024. As of February 3, 2025, the study has enrolled 199 participants, with follow-up expected through June 2025. No interim analyses were planned; data analysis for primary end points is expected in the summer of 2025.

Conclusions: Improving PrEP use outcomes among heterosexual men in East and Southern Africa is critical to interrupting HIV transmission. This study offers unique insights into a low-resource, potentially scalable intervention, focusing on a group of men at particularly high risk of HIV acquisition—those with recent STIs. The hybrid RCT design addresses clinically relevant effectiveness questions and explores key determinants that will inform future multisite implementation trials.

Trial Registration: ClinicalTrials.gov NCT06200545; https://clinicaltrials.gov/study/NCT06200545

International Registered Report Identifier (IRRID): DERR1-10.2196/72981

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KEYWORDS

hybrid; long-acting injectable; preexposure prophylaxis; peer; heterosexual; HIV prevention; bacterial STI

Introduction

Despite significant reductions in incidence globally, progress toward ending the HIV epidemic has stalled [1]. Biomedical preexposure prophylaxis (PrEP) remains one of the most effective evidence-based interventions for preventing HIV; however, its rollout has been hindered by inconsistent referral, inadequate uptake, poor adherence, and frequent discontinuation [2-7]. In East and Southern Africa, most incident HIV acquisitions occur through heterosexual transmission [8]. Women bear a disproportionate burden of new infections; accordingly, PrEP engagement efforts have historically focused on women. HIV acquisitions among women are frequently driven by male-female age-disparate partnerships and transactional sex, where women may face challenges such as negotiating condom use or adhering to PrEP due to fear of partner disapproval. Engaging heterosexual men in prevention-effective PrEP use—defined as persistent PrEP use before and immediately after potential HIV exposure—is therefore critical to improving HIV prevention outcomes for both men and women.

Despite their relevance in the HIV epidemic, relatively little is known about best practices for effectively engaging and retaining heterosexual men in PrEP care across different global settings. Modifying perceptions of HIV risk and reducing stigma toward PrEP use can improve PrEP persistence among men [9,10]. Longer-acting agents, such as long-acting injectable cabotegravir (CAB-LA), present a promising opportunity to enhance PrEP effectiveness by eliminating barriers associated with daily pill use. Although landmark studies have focused on men and transgender women who have sex with men [11] and on women in high HIV incidence settings [12], CAB-LA is expected to offer similar HIV prevention effectiveness among heterosexual men. Early rollout pilot prevention studies suggest that CAB-LA is a popular choice for men in Africa [13-15]. Despite the promise of newer and longer-acting PrEP agents [16], their effectiveness—and indeed, cost-effectiveness—will only be realized if those most vulnerable to HIV are engaged and remain persistent throughout periods of risk.

In Malawi, men have not historically been the focus of PrEP interventions. Consistent with World Health Organization (WHO) recommendations, individuals with a recent sexually transmitted infection (STI) and those involved in transactional sex are considered priority populations for PrEP in Malawi [17]. Previous research has examined the integration of PrEP and STI services at one of the country's largest urban STI clinics in Lilongwe [18]. STI clinics are a critical yet often underutilized pathway to PrEP services in low- and middle-income countries [19], and may serve as an especially important entry point for men, who may not access health care services as regularly as their female counterparts. Despite declining population-level HIV incidence, our prior work has shown that individuals presenting with STIs continue to have persistently high rates of acute HIV infection [20-22]. Between March and December 2022, 835 individuals initiated PrEP at the STI clinic in Lilongwe, the majority of whom were male (55%) [23]. Nearly two-thirds of all PrEP initiators had a current or recent (within the past 6 months) STI, and nearly one-third reported transactional sex (ie, exchanging sex for goods, money, or favors); these categories were not mutually exclusive. Persistence across the population of all PrEP users was low—estimated at 3.7% at 6 months. Among male PrEP initiators with an STI at the time of PrEP initiation or within the prior 6 months, only 2.4% were persistent (95% CI 1.4-4.1) at 6 months. As with all PrEP outcome evaluations, persistent use must be contextualized by ongoing HIV risk. Among a subgroup of enrolled men initiating PrEP during STI clinic visits, incident infections in the subsequent 6 months were common—55.8 incident *Chlamydia trachomatis*, *Neisseria gonorrhoeae*, or *Treponema pallidum* infections per 100

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person-years [24]. Improving persistent PrEP use among men with current or recent curable STIs may help direct scarce resources to a group in particular need of enhanced PrEP retention efforts.

Systems navigation, including psychosocial support and assistance in maneuvering through sometimes complex or burdensome health care systems, is a promising approach [25,26], though data specific to heterosexual men and PrEP services remain limited. Systems navigation can be conceptualized broadly—encompassing peer-based interventions, psychosocial counseling, and care navigation—generally focuses on addressing barriers to health care access and enhancing comfort and confidence within clinical settings.

. Peer-based models may improve HIV care and outcomes, and the flexibility of this model may be particularly appealing in more resource-poor settings [27]. Promising evidence has emerged from the United States demonstrating that tailored navigation services can help individuals overcome systems-related barriers to PrEP care [28,29], including when integrated into sexual health clinics [30]. Among heterosexual men in South Africa, health care providers and educational materials that encouraged PrEP uptake influenced PrEP use. Increasing individual support, simplifying access to PrEP, and navigator-delivered sexual health and HIV information were identified as effective intervention strategies [31,32]. In Eswatini, male-friendly services were highlighted as key future priorities to improve PrEP use among men, including integrated or community-based PrEP delivery models [9]. Understanding the acceptability, feasibility, and effectiveness of peer-delivered navigation services as a strategy to improve PrEP persistence specifically for heterosexual men can inform HIV prevention programming for a population that has, thus far, rarely taken the spotlight in prevention efforts in East and Southern Africa. This group may face distinct challenges to PrEP persistence related to perceived gender norms, stigma, access to health care services, and the perceived relevance of PrEP within their broader HIV and STI prevention strategies.

NJIRA (Navigated Journey to Improve Reduction of HIV in African Men) translates to “path” or “way” in Chichewa, the national language of Malawi. The name was developed in coordination with our local Community Advisory Board and reflects the study’s objective of examining how best to support men in navigating the complex path toward sustained and effective HIV prevention. The primary objectives of this study are to assess the effect of a systems navigator–facilitated HIV prevention package on PrEP persistence among heterosexual men seeking STI clinical services in Lilongwe, Malawi at 26 weeks, and to evaluate the acceptability of, and barriers to, implementing a systems navigator–delivered HIV prevention package among key clinic stakeholders and heterosexual men initiating PrEP at STI clinics. Implementation outcomes are feasibility, acceptability, and cost. Exploratory objectives aim to characterize men’s preferences for PrEP modalities, perceived and experienced stigma, and the influence of gender norms on PrEP persistence. The overarching hypothesis is that a peer-delivered systems navigation package will improve PrEP persistence at 26 weeks (defined as adherence to any PrEP modality through 26 weeks) among heterosexual men initiating PrEP at an STI clinic, compared with the current standard of care (SOC).

Methods

Study Design

Overview

This study is a single-site, pilot type I effectiveness-implementation hybrid randomized controlled trial (RCT). The overall goal is to evaluate the benefits, acceptability, barriers, and associated costs of integrating systems navigation and brief counseling into STI clinic–based PrEP provision for heterosexual men in Lilongwe, Malawi (Textbox 1).

Two hundred eligible participants will be randomized (1:2) to SOC PrEP services or systems navigator–assisted PrEP care (intervention). Participants will be followed for at least 26 weeks and up to 52 weeks, depending on their enrollment window. All clinical services, including PrEP provision and safety monitoring, are conducted by the Malawi Ministry of Health PrEP nursing staff (Figure 1).

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Textbox 1. Primary, secondary, and exploratory objectives.

1. Primary objectives

- To assess the effect of a systems navigator–facilitated HIV prevention package on preexposure prophylaxis (PrEP) persistence among heterosexual men seeking sexually transmitted infection (STI) clinical services in Lilongwe, Malawi at 26 weeks.
- To assess acceptability and barriers to implementing a systems navigator–delivered HIV prevention package among key stakeholders in the clinic and heterosexual men initiating PrEP at STI clinics.

2. Secondary objective

- To assess the feasibility of a future randomized controlled trial.

3. Exploratory objectives

- To assess prevention-effective PrEP use among heterosexual men initiating PrEP at STI clinics.
- To assess PrEP modality preferences among heterosexual men initiating PrEP at STI clinics.
- To assess the effect of a systems navigator–facilitated HIV prevention package on PrEP persistence among heterosexual men seeking STI clinical services in Lilongwe, Malawi at 39 and 52 weeks.
- To quantify costs and resources necessary to develop and integrate a systems navigator–delivered HIV prevention package into an urban STI clinic, informing future cost-effectiveness model development.
- To perform laboratory assessments that may include evaluation of factors related to HIV acquisition or other STIs; characterization of HIV in participants who acquire HIV; characterization of the host response to antiretroviral drugs; and evaluation of virologic, pharmacologic, or STI-based laboratory assays.
- To evaluate event-driven PrEP drug concentrations in the context of timeline followback–reported PrEP use and sex acts.
- To explore the perceived and experienced PrEP-related stigma and potential influence of perceived gender norms on PrEP persistence among heterosexual men initiating PrEP at the STI clinic.

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Figure 1. HIV seronegative men are randomized after enrollment to either control or intervention conditions, with quarterly follow-up thereafter. Follow-up preexposure prophylaxis (PrEP) care and exposure to systems navigation are separate from study follow-up and proceed according to the PrEP follow-up schedule per Malawi PrEP guidelines. A subset of enrolled participants (approximately 20), along with additional key informants who are not PrEP-initiator participants (approximately 15), will be interviewed to evaluate implementation outcomes of interest. IDI: in-depth interview; MoH: Ministry of Health.

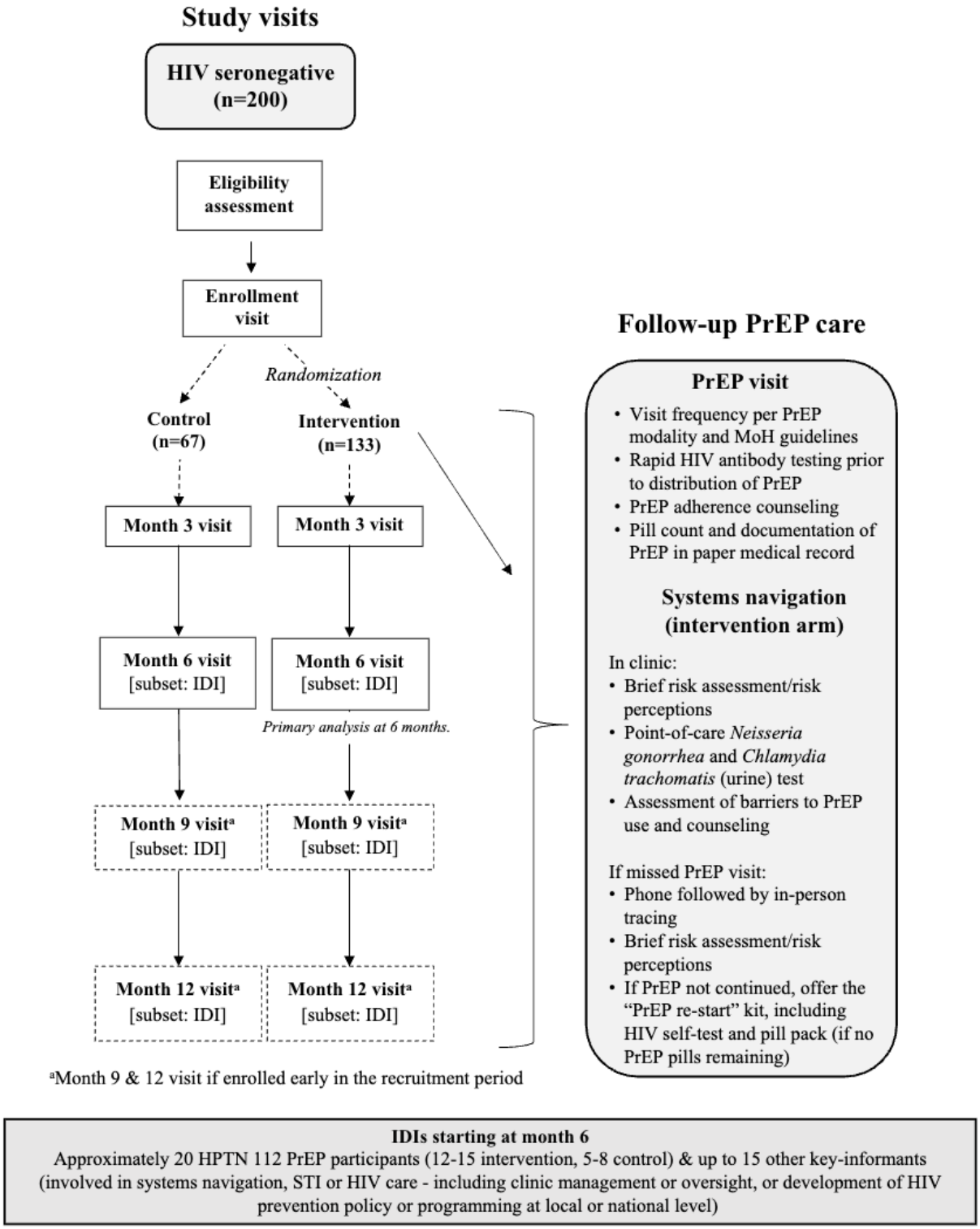

Systems Navigation Intervention

Systems navigation and counseling is a theory-derived, evidence-based intervention that involves identifying persons most likely to benefit from HIV prevention tools and helping them navigate complex, dynamic obstacles to uptake and retention. This intervention draws on a combination of social cognitive theory and social identity theory, the latter helping to explain how individuals conceptualize themselves in relation to social groups, including gender and sexual preferences. In this study, systems navigation uses motivational interviewing to build a person's capacity and confidence to remain engaged

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in PrEP care. The systems navigator manual was adapted from prior intervention studies, namely, HPTN 074 [33] (conducted among persons who inject drugs living with HIV) and HPTN 082 [34] (conducted among adolescent girls and young women not living with HIV), in which peer-adjacent persons were deployed to assist with HIV treatment or HIV prevention service delivery. The navigator manual was adapted to align with the local context and the study-specific objectives of engaging heterosexual men who had initiated PrEP. This manual consists of self-guided content specific to the study, as well as modules and activities that serve as the backbone for all participant sessions (Multimedia Appendix 1).

The systems navigation intervention package includes 3 components as described in Textbox 2.

Textbox 2. Components of the systems navigation intervention package.

1. Access to a systems navigator

Intended to engage with participants at each preexposure prophylaxis (PrEP) visit using a menu of "sessions" that examine items such as risk perception and address barriers to PrEP adherence (Multimedia Appendix 1); provide reminders for upcoming PrEP visits; and trace participants who have missed a scheduled PrEP visit via phone or in person.

2. Point of care sexually transmitted infection testing

Urogenital testing for *Chlamydia trachomatis* and *Neisseria gonorrhea* via urine sample.

3. PrEP reengagement or "restart" kit

Consists of an HIV self-test kit and oral PrEP pills for reinitiation. The "restart" kit is offered to participants who choose to stop PrEP (oral or injectable), alongside counseling regarding safely restarting PrEP as a bridge to reestablish in-person PrEP care at the clinic.

Systems navigators are selected from a cadre of health care workers with some counseling experience but without formal clinical training. Familiarity with HIV testing or prevention services is recommended, though navigators are not required to have personal experience using PrEP. The navigation role provides both behavioral counseling and assistance in navigating the clinical services of the PrEP clinic.

Navigators are men selected from the community with guidance from the Community Advisory Board. They must be knowledgeable about the community's dynamics and reflect the demographics of the target population. Navigators will undergo extensive training, including but not limited to basic knowledge of STIs, HIV, and PrEP; PrEP modalities, including potential benefits and expected challenges; motivational interviewing; psychosocial counseling; techniques for active listening and rapport building; HPTN 112 procedures, including urine specimen collection and handling (for STI testing); and documentation to track participant engagement. As this protocol is still considered research, all navigators will receive training related to the ethical conduct of clinical research (ie, good clinical practice). Navigators are integrated into STI/PrEP clinic procedures but, for this protocol, are hired study staff within the study team.

Although not required, navigators may have been previously or currently prescribed PrEP. They will also be trained on personal safety, discreet tactics for follow-up tracing, and confidentiality. These components and attributes have been developed in coordination with local Community Advisory Board members. All training materials will be prepared in advance of study implementation and compiled into a separate systems navigation manual, which will include a series of didactics, role-playing, and direct observation. Navigators will receive periodic refresher training and regular evaluations. They engage with participants during PrEP visits and in the field to trace participants who have missed a PrEP visit, activities that are intentionally distinguished from study visits.

All navigators participate in regular (eg, weekly) debrief sessions, during which they are encouraged to reflect on recent engagement with participants—considering what worked well and where they encountered challenges. Feedback from these sessions is shared with study leadership to help inform additional training or updates to available tools for participant engagement. Additionally, coordinators review expected PrEP visits and anticipated navigator contact with participants. Gaps in contact attempts or missed outreach (ie, no tracing for missed PrEP visits) are communicated to navigators, and barriers to completing tasks are discussed. This audit-and-feedback [35,36] approach facilitates rapid intervention to address any knowledge or implementation gaps.

Navigators are intended to be integrated within PrEP service delivery at the STI clinic, working alongside Ministry of Health PrEP nurses to engage male participants randomized to receive the intervention. As such, navigation activities occur primarily at the Bwaila STI Clinic, except for tracing, which takes place in the field. Men in the intervention arm of the study will also be exposed to any SOC activities related to PrEP service delivery (Table 1).

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Table 1. Standard of care compared with study intervention components.

Component	Standard of care	Intervention[a]
HIV testing (all PrEP[b] visits)	Serial third-generation rapid antibody	Serial third-generation rapid antibody
STI[c] testing (PrEP follow-up)	Not standard: symptom-based screening	Point-of-care: *Neisseria gonorrhea* and *Chlamydia trachomatis* (urine)
Visit reminders (PrEP follow-up)	Not standard	Per participant preference
Assessment of barriers to PrEP use (all PrEP visits)	PrEP nurse delivered	Systems navigator via motivational interviewing
Adherence counseling (PrEP follow-up)	PrEP nurse delivered	Systems navigator via motivational interviewing
Tracing for missed PrEP visits (PrEP follow-up)	Not standard	Per participant preference (phone or in-person)
PrEP reengagement counseling (PrEP follow-up)	Not standard	PrEP "restart" kit offered

[a]Participants randomized to the intervention condition *also* receive all standard-of-care PrEP services.

[b]PrEP: preexposure prophylaxis.

[c]STI: sexually transmitted infection.

Standard of Care

Men randomized to the SOC condition will receive Malawi's SOC for PrEP services. SOC includes serial third-generation rapid HIV antibody testing before PrEP initiation or refill, an assessment of PrEP need and risk of HIV acquisition, and nurse-provided counseling regarding PrEP adherence and continuation. There is no standard practice for tracing persons who have missed PrEP visits. PrEP counseling is consistent with contemporary guidelines and encourages persons to remain engaged in PrEP care as long as they remain vulnerable to acquiring HIV.

Study Setting

Bwaila STI Clinic

The Bwaila STI Clinic is located within Bwaila District Hospital, a tertiary care hospital in urban Lilongwe, Malawi. PrEP services have been colocated within the STI clinic since November 2021. Per Malawi guidelines, all persons presenting with symptoms of an STI are managed syndromically, and all persons who are not known to be living with HIV are offered HIV testing with serial third-generation rapid antibody tests. Generally, the STI clinic sees about 50 HIV seronegative patients per day, approximately half of whom are men. Per Malawi guidelines, all persons with a recent STI may be eligible for PrEP.

PrEP in Malawi

According to the most recent PrEP guidelines for Malawi, persons are eligible for PrEP if they are HIV seronegative; at substantial risk for HIV, with prioritization of persons who buy or sell sex, are STI clients, or are within sero-different couples, including HIV-negative individuals whose partner living with HIV is not on antiretroviral therapy (ART), has been on ART for less than 6 months, has a high viral load, or is nonadherent to ART; have no concern for acute HIV based on provider screening for signs or symptoms consistent with acute HIV; have expressed willingness to attend scheduled PrEP visits; have no contraindications to PrEP drugs; have a bodyweight ≥30 kg; have no known renal disease; and are not known to have diabetes mellitus.

As of April 2024, Malawi PrEP guidelines included the following biomedical PrEP modalities: daily oral PrEP with tenofovir disoproxil fumarate/lamivudine (TDF/3TC) or TDF/emtricitabine (TDF/FTC) for men and women; event-driven PrEP (TDF/3TC or TDF/FTC) for men only; and injectable PrEP (CAB-LA) for men and women, available under limited-use agreements with implementing partners and external funders. At Bwaila STI Clinic, during the study period, all 3 PrEP modalities are available to men initiating PrEP after presenting with symptoms of an STI.

Study investigators are not providing PrEP services; all PrEP care, including eligibility assessment and clinical monitoring, is conducted by the Malawi Ministry of Health PrEP nurses.

Participant Eligibility

Two populations are eligible to participate in the study: men initiating PrEP after seeking STI services (n=200), and relevant stakeholders involved in the adoption or implementation of PrEP program delivery in Malawi (approximately 15), who will participate in in-depth interviews (Multimedia Appendix 2).

Eligibility criteria for inclusion in this study as a participant initiating PrEP are (1) men; (2) aged 18 years or older, or 15-17 years (with assent and parent/guardian consent); (3) planning to remain in the study area for at least 26 weeks after enrollment; (4) willing to provide a phone number or address to facilitate tracing in the event of a missed study visit; (5) willing to participate in all study activities, including specimen collection (blood and urine) and intervention if randomized to that condition; (6) have sought STI clinic services and initiated PrEP within 7 days of enrollment; (7) self-identify as heterosexual and report at least one female sex partner in the 6 months before enrollment; and (8) able to provide informed consent. Persons who have used PrEP previously are eligible if at least 13 weeks have elapsed since their last PrEP use (pill or injection; Multimedia Appendix 3).

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All participants will have been prescribed PrEP before enrollment. As such, they will have been deemed PrEP-eligible according to contemporary Malawi PrEP guidelines (see above). Key stakeholders relevant to adoption are eligible to participate in in-depth interviews if they are aged 18 years or older; involved in the provision of clinical service navigation, systems navigation, STI or HIV care or prevention (including clinic management or oversight); or involved in the development of HIV prevention policy or programs at the local or national level; and able to provide informed consent.

Participants who appear to have psychological instability or cognitive impairment that would limit their ability to understand study procedures, or any condition that, as determined by the investigators, would make participation unsafe or otherwise interfere with the conduct of the study, will be excluded. For PrEP user participants, current participation in any HIV prevention study or other study considered likely to interfere with the interpretation of study outcomes will also lead to exclusion.

Study Procedures

Data Collection

Data sources and collection methods are described below. The study will utilize electronic data capture tools within the Research Electronic Data Capture (REDCap; Vanderbilt University) database for all primary data collection and participant management purposes. REDCap is a secure, web-based software platform designed to support data capture, auditing, monitoring, and export for research studies. Study-specific assessments will be conducted separately from STI clinic–based PrEP visits. Although study visits and PrEP care can occur on the same day, study visits take place in a separate building. This distinction is intentional, designed to minimize the impact of study-specific compensation, which covers time and transportation expenses, on the primary effectiveness outcome of persistent PrEP use.

Per Malawi PrEP guidelines, persons on daily or event-driven oral PrEP (TDF/3TC or TDF/FTC) have follow-up visits at 1 month, 3 months, and quarterly thereafter. Persons on injectable PrEP (long-acting cabotegravir) have follow-up visits at 1 month, 3 months, and every 2 months thereafter. The study will track how often study visits and PrEP visits occur on the same day. Participants are reminded that remaining on PrEP is not required to stay in the study. Standard pre- and posttest counseling will be provided during HIV testing at each study visit, and all participants will be offered condoms free of charge.

Recruitment

PrEP user participants are recruited from the Bwaila STI Clinic (Figure 2). All individuals seeking STI clinic services receive a group health talk during which the HPTN 112 study is introduced. Ministry of Health PrEP nurses are also briefed about the study and can refer any male initiating PrEP for further enrollment consideration. Palm cards and posters (see Figure 3 [37]) are available for distribution and displayed prominently throughout the STI clinic.

Figure 2. Male sexually transmitted infection (STI) clinic patients proceed through standard clinic procedures, beginning with group counseling and health education talks, which include an introduction to enrolling studies at the clinic. All persons presenting for STI services receive HIV testing and counseling. Individuals who test seronegative on rapid diagnostic tests are referred for further evaluation for preexposure prophylaxis (PrEP) by the Ministry of Health PrEP nurse. Men who accept PrEP are then referred for additional study eligibility assessment. If deemed eligible and interested in participating, they are consented and randomized to 1 of the 2 study arms. Those randomized to the intervention condition will engage with the systems navigator, typically on the same day as enrollment activities.

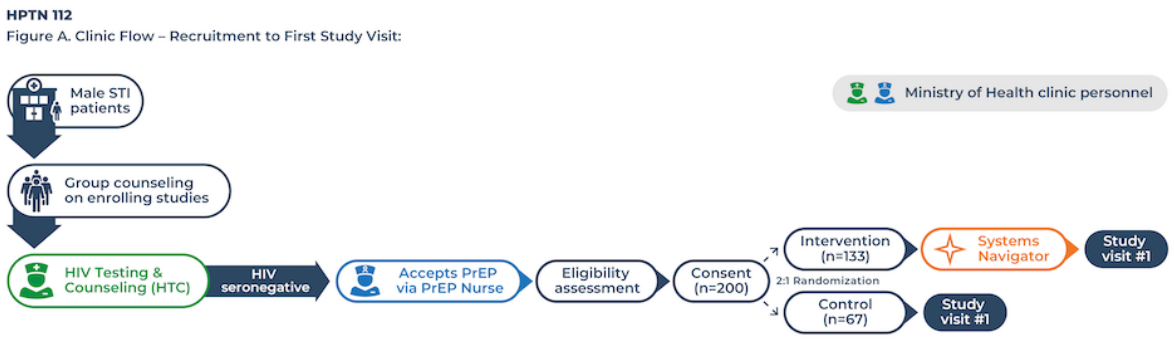

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Figure 3. Potential participants (namely, men seeking sexually transmitted infection services at the recruiting site) may be handed palm cards describing the Navigated Journey to Improve Reduction of HIV in African Men (NJIRA) study. The front of the card features an image of 2 hands meeting, while the back provides basic eligibility information for study participation, including contact details for those interested in learning more, such as a study-dedicated phone number and a study-specific web page. Panel (A) presents this information in English, and (B) in the local language, Chichewa, which is the version that is distributed. The same images and content are also printed on larger-format posters displayed throughout clinic waiting areas and preexposure prophylaxis rooms.

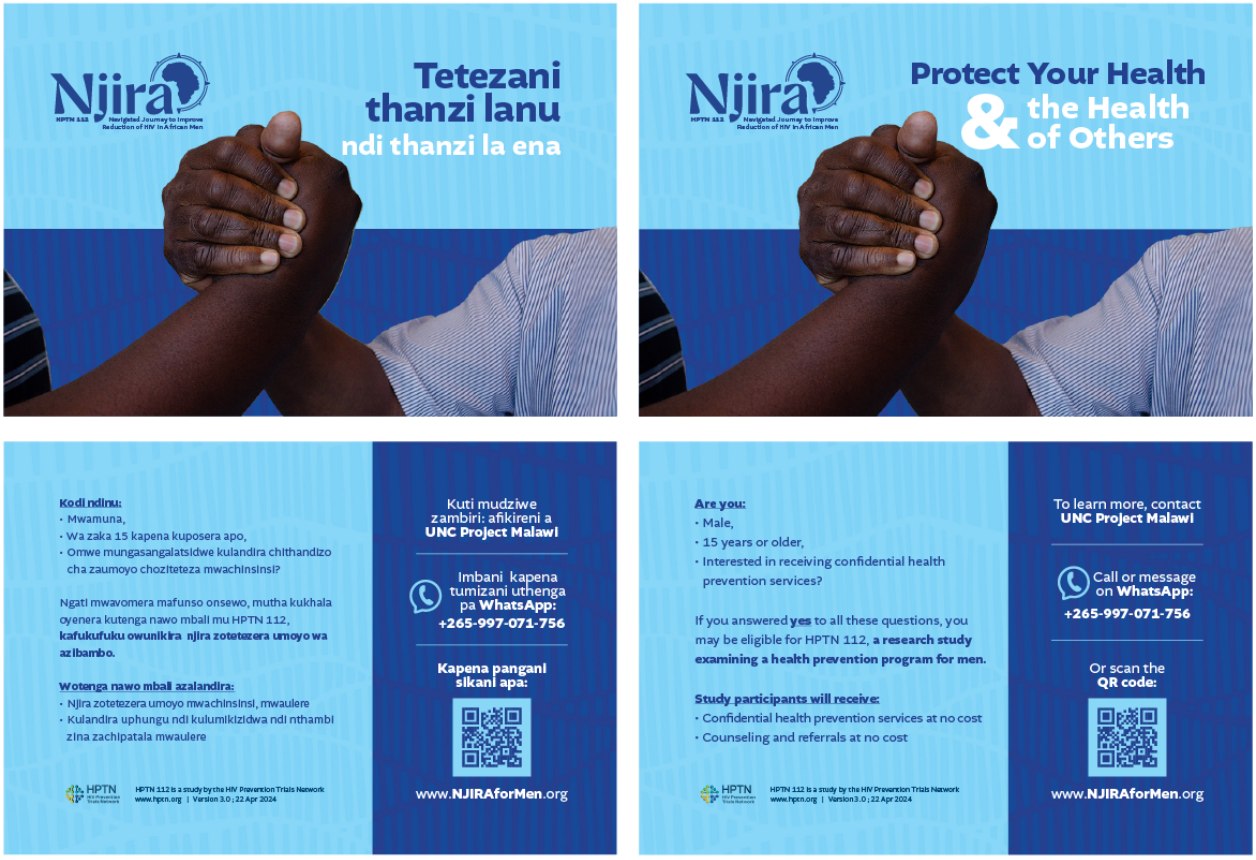

Randomization

Randomization will be stratified by age groups (15-25 and >25 years), using a permuted block design to ensure balanced treatment assignments within each stratum. Age-based stratification was chosen due to anticipated differences in the intervention's effect and expected PrEP persistence between younger and older men [24,38]. A 2:1 randomization ratio is used to facilitate the evaluation of acceptability outcomes, which are assessed only among participants assigned to the intervention arm. Neither participants nor study personnel will be blinded to treatment assignment, as masking is not feasible given the nature of the intervention and the arm-specific data collection procedures.

Enrollment Visit

Participants may enroll up to 7 days after initiating PrEP. Enrollment is completed once all informed consent procedures are finalized, including randomization. All enrolled participants will have undergone HIV antibody testing as part of the local PrEP eligibility assessment; however, specimens for antibody testing will also be collected on the day of enrollment (see Table 2). Additionally, all participants will be screened for acute HIV infection using HIV RNA testing. A detectable HIV RNA result combined with negative or discordant serial HIV antibody tests will be considered indicative of acute HIV infection. Participants with any detectable HIV RNA at enrollment will be promptly linked to appropriate HIV care.

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Table 2. Schedule of evaluations for participants not living with HIV.

Schedule	Eligibility determination	Enrollment	Weeks				Early termination[a]
			13	26	39[b]	52[b]	
Administrative and Behavioral Evaluations/procedures[c]							
Informed consent	N/A[d]	✓	N/A	N/A	N/A	N/A	N/A
Randomization	N/A	✓	N/A	N/A	N/A	N/A	N/A
Demographics	✓	✓	✓	✓	✓	✓	✓
HIV risk factors	✓	✓	✓	✓	✓	✓	✓
Locator information	N/A	✓	✓	✓	✓	✓	N/A
Behavioral risk assessment	N/A	✓	✓	✓	✓	✓	✓
Preexposure prophylaxis use assessment	N/A	✓	✓	✓	✓	✓	✓
Mental health status	N/A	✓	✓	✓	✓	✓	✓
Substance use	N/A	✓	✓	✓	✓	✓	✓
Perceived HIV and preexposure prophylaxis stigma	N/A	✓	✓	✓	✓	✓	✓
Gender norms	N/A	✓	✓	✓	✓	✓	✓
HIV risk reduction counseling	N/A	✓	✓	✓	✓	✓	✓
In-depth interviews[e]	N/A	N/A	N/A	✓	✓	✓	N/A
Clinical evaluations/procedures							
Symptom-driven physical examination	N/A	✓	✓	✓	✓	✓	N/A
Venous blood draw	N/A	✓	✓	✓	✓	✓	✓
Urine collection	N/A	✓	✓	✓	✓	✓	✓
Hair collection	N/A	N/A	✓	✓	✓	✓	✓
Sexually transmitted infection management referral[f]	N/A	✓	✓	✓	✓	✓	✓
Laboratory evaluations/procedures							
Rapid HIV testing	✓[g]	✓[g]	✓	✓	✓	✓	✓
HIV RNA[h]	N/A	✓	N/A	N/A	N/A	N/A	N/A
Sexually transmitted infection testing[i]	N/A	✓	✓	✓	✓	✓	✓
Plasma (storage)	N/A	✓	✓	✓	✓	✓	✓
Dried blood spot (storage)	N/A	✓	✓	✓	✓	✓	✓
Urine (storage)	N/A	✓	✓	✓	✓	✓	✓
Hair (storage)	N/A	N/A	✓	✓	✓	✓	✓

[a]Extent of procedures, including surveys and specimen collection, at early termination visit will be determined depending on reasons for termination and ongoing safety/ability to obtain the consent of the participant.

[b]All participants will be followed at least 26 weeks; persons enrolled in the first 13 weeks will be followed up to 52 weeks.

[c]Systems navigation occurs at the participant's clinic preexposure prophylaxis visits, and not at the study visits for this study. Therefore, systems navigation provided by the study is not included in this schedule of evaluations.

[d]N/A: not applicable.

[e]In-depth interviews will be conducted with a subset of participants at their final visit (week 26, week 39, or week 52).

[f]Referral for management in the event of new or persistent sexually transmitted infection symptoms/complaints.

[g]HIV testing for preexposure prophylaxis eligibility determination will be conducted by Malawi Ministry of Health personnel.

[h]HIV RNA will be tested at the local laboratory at enrollment; HIV RNA testing may be performed on stored plasma collected at follow-up visits at the HPTN Laboratory Center.

[i]Sexually transmitted infection testing, including *Neisseria gonorrhea* nucleic acid amplification test, *Chlamydia trachomatis* (nucleic acid amplification test), and syphilis (rapid plasma reagin) will be collected at study visits *unless* results of these tests are documented within 2 weeks in the review of record. This would occur in the intervention arm only, but there will not be any syphilis testing done by systems navigators (they only collect urine for

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N. gonorrhea and *C. trachomatis*).

All participants will complete study staff-administered surveys using validated scales whenever possible, enabling exploration of predictors of PrEP persistence and informing targeted objectives and strategies to enhance systems navigation and counseling interventions. To gather more detailed information on sexual activity—particularly important for men opting for event-driven oral PrEP—we will use a timeline followback calendar to capture self-reported sexual acts and PrEP use over the preceding 30 days.

After providing informed consent (by signature or fingerprint), all participants are asked to provide locator information to facilitate tracing in the event of a missed study visit. Staff-administered surveys assess sexual behaviors, perceived vulnerability to HIV, and baseline health factors including substance use [39], mental health [40-42], perceived gender norms [43-45], anticipated or experienced HIV [46], and PrEP-related stigma [47].

Participants reporting symptoms of an STI will undergo a symptom-directed physical examination. All participants will provide blood and urine samples for protocol-specified testing, which includes rapid HIV antibody testing, HIV RNA testing, urogenital *C. trachomatis*/*Neisseria gonorrhoeae* testing, and syphilis screening using rapid plasma reagin with reflex *Treponema* pallidum particle agglutination assay if indicated. Plasma, urine, and dried blood spots (DBS) will be collected and stored for batch shipment to a central laboratory for additional testing (see Table 2).

Follow-Up Visits

Participants will be followed quarterly (every 13 weeks) for a minimum of 26 weeks. Those enrolled within the first 13 weeks of recruitment will be followed for 52 weeks, while participants enrolled during the first 26 weeks will be followed for 39 weeks. All other participants will have a total follow-up duration of 26 weeks. The 26-week follow-up period was selected to assess PrEP persistence during the window of presumed indication, specifically reflecting the recommendation that PrEP is appropriate for individuals presenting with STI symptoms or who had an STI in the prior 6 months. This timeline aligns with prior studies evaluating PrEP persistence in the region [34], facilitating comparison with other persistence-focused studies globally, which serve as important benchmarks for clinical outcomes [38]. Following a subset of participants for up to 52 weeks captures anticipated fluctuations in perceived PrEP need and usage, providing valuable insights into PrEP service delivery among individuals with ongoing HIV vulnerability. Each follow-up visit includes a study nurse–administered survey, mirroring the enrollment survey but with additional questions specific to PrEP use during the preceding interval. Participants randomized to the intervention arm will complete additional survey questions focused on their engagement with the systems navigators, including frequency of contact, preferences, and acceptability measures [48-50]. A subset of these participants will be invited to participate in an in-depth interview during their study visits.

As at the enrollment visit, participants will undergo a symptom-directed physical examination and provide blood and urine samples for protocol-specified testing. Per protocol version 2.2 (letter of amendment #2, dated June 28, 2024), participants will also be asked to provide a scalp hair sample at follow-up visits. HIV RNA testing will not be performed routinely at each follow-up but will be reflexively conducted if HIV antibody testing is reactive. Plasma, urine, DBS, and hair specimens will be stored for batch shipment to a central laboratory for further analyses (see Table 2).

Procedures for Participants With Suspected or Confirmed HIV

Any participant with a reactive or positive HIV test during follow-up will undergo additional testing to confirm their HIV status. Confirmation of HIV infection requires positive test results from samples collected on 2 separate occasions. All confirmed cases will be referred to HIV care. Participants confirmed to be living with HIV will remain in the study for up to 26 weeks following seroconversion to allow for further testing and to confirm viral suppression on ART (see Table 3).

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Table 3. Schedule of evaluations for participants who seroconvert/are identified as living with HIV.

Schedule	Weeks after seroconversion[a]		Early termination
	13 weeks	26 weeks	
Administrative and behavioral evaluations/procedures			
Locator information	✓	✓	N/A[b]
Antiretroviral therapy use	✓	✓	✓
Perceived HIV stigma	✓	✓	✓
Clinical evaluations/procedures			
Venous blood draw	✓	✓	✓
HIV management referral[c]	✓	✓	✓
Laboratory evaluations/procedures			
HIV RNA	✓	✓	✓
Plasma (storage)	✓	✓	✓
Dried blood spot (storage)	✓	✓	✓

[a]Persons who are identified as acutely infected (ie, negative HIV rapid antibody test but detectable HIV RNA) at enrollment visit will be followed along the same schedule as those persons who seroconvert during study follow-up.

[b]N/A: not applicable.

[c]HIV management referral will only occur if the participant is not already in care.

Participants with detectable HIV RNA at the enrollment visit (indicating acute HIV infection) will be linked to appropriate HIV care and followed at weeks 13 and 26 to assess viral suppression.

Visit Windows

For each required study visit, an allowable visit window specifies the study days (after enrollment) during which the visit may be completed. These allowable windows are contiguous between visits and do not overlap. Within each allowable visit window, there is a target visit window during which study visits should ideally be conducted. If all visit procedures cannot be completed in a single day, they may be spread across multiple days within the allowable visit window.

Qualitative Data Collection

To assess the acceptability of the intervention, individual semistructured interviews will be conducted with stakeholders involved in PrEP program implementation and scale-up, as well as with enrolled PrEP user participants. Interview guides have been developed to capture key implementation outcomes, using the Consolidated Framework for Implementation Research (CFIR) as a foundation [51,52]. Specifically, the study examines determinants and their relationships to implementation, behavioral, and health outcomes, guided by CFIR domains and selected constructs (Figure 4).

For PrEP users, willingness to participate in in-depth interviews is documented during enrollment via consent forms. We will use a purposive sampling strategy designed to capture a broad range of perspectives related to the phenomenon under study. This approach facilitates careful consideration of range, saturation (redundancy), and stratification within the sampling frame.

Additional key stakeholder participants will be identified based on their roles and responsibilities within PrEP programming at the Bwaila clinic and more broadly across Malawi, as outlined previously (see the discussion on eligibility criteria above).

Semistructured interviews will follow a standardized guide, incorporating probes tailored to the perspectives of stakeholders. These interviews will explore participants' experiences with the intervention, perceived barriers to sustained PrEP engagement among the target population, and potential obstacles or facilitators to scaling and sustaining the intervention. Specifically, they will examine how the intervention addresses barriers or enhances facilitators of PrEP uptake and continued effective use. Conducted by a trained study interviewer, who is a native Chichewa speaker with extensive experience conducting interviews at Bwaila Hospital, each session will last approximately 60 minutes and take place in a setting that ensures participant privacy and confidentiality. During data collection with both key stakeholders and participants, a subset of interview recordings will be translated and transcribed for review by the qualitative analysis team. The team will discuss the transcripts and suggest revisions to the interview guide. This iterative process will continue until a consensus is reached on the guide's structure.

All interviews will be audio-recorded, then translated and transcribed by qualified personnel. Identifiable information will be redacted from transcripts before they are shared for analysis.

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Figure 4. In-depth interview guides are developed using the Consolidated Framework for Implementation Research (CFIR) to examine determinants within the outer setting, inner setting, individual, process, and innovation domains that may influence our implementation, behavioral, and health outcomes of interest. Selected constructs within the CFIR domains are highlighted based on their anticipated relevance for key informant interviews. PrEP: preexposure prophylaxis.

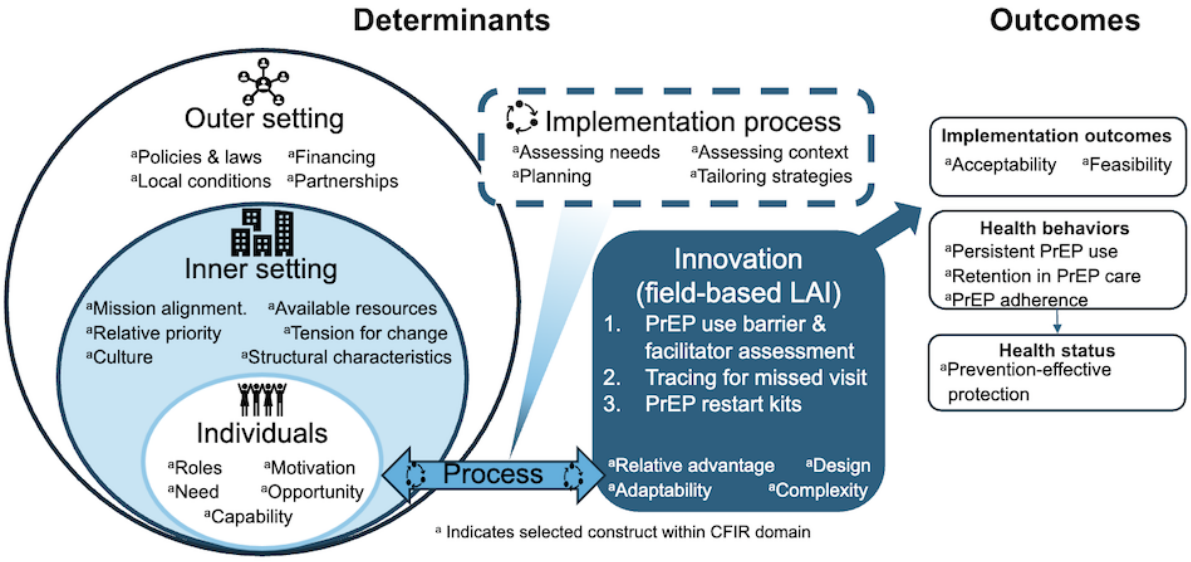

Cost and Resource Data Collection

We will embed empirical costing into the study procedures, collecting cost data prospectively through 2 methods: micro-costing and time-and-motion logs. Micro-costing uses a direct enumeration, ingredients-based approach to quantify all resources consumed in developing and implementing the intervention. Additionally, we will extract data from project expenditure and management records, including purchase logs and human resource documentation. Time-and-motion assessments will capture how navigators allocate their time across navigation-related tasks, such as training, counseling, tracing, and other activities, enabling precise attribution of effort toward the intervention's implementation. No formal economic modeling is planned as part of this protocol.

Statistical Considerations

Sample Size

For the approximately 200 heterosexual men we expect to enroll, we anticipate a 10% loss to follow-up by 26 weeks. As a pilot study, the sample size is selected to provide reasonable precision in assessing the primary end points and to inform future research. We chose a 2:1 randomization ratio favoring the intervention arm over SOC to maximize our ability to evaluate the intervention's acceptability. Based on prior studies, we expect persistent PrEP use under SOC to be approximately 40% at 26 weeks. We aim to detect a difference in persistent PrEP use between the intervention and SOC arms ranging from 15% to 35% at 26 weeks. Our sample size, chosen to enable rapid enrollment and address this important and timely knowledge gap, will be sufficient to detect a minimum regression discontinuity of 0.22 with 80% power at a 5% alpha level, and a regression discontinuity of 0.25 with 90% power at a 5% alpha level.

Statistical Analysis

Effect of Intervention on Persistent PrEP Use

A comparison of persistent PrEP use will be conducted for all enrolled participants during the first 26 weeks of study follow-up. Participants may choose to switch PrEP modalities during follow-up; persistence with each modality will be assessed during the period in which the participant reports using that modality, based on a combination of self-report, measured drug levels (for oral PrEP), and clinic records. Specifically, persistent PrEP use is defined as adherence to any PrEP modality through 26 weeks, with adherence defined as follows: for long-acting injectable PrEP, receiving on-time injections (within 7 days before or after the target injection date for the first injection and within 14 days before or after the target injection date thereafter); for daily oral PrEP, having protective PrEP concentrations detected at designated study follow-up visits, based on intraerythrocytic tenofovir diphosphate (TFV-DP) levels collected via DBS, with TFV-DP concentrations corresponding to 4 or more doses per week classified as adherent; for event-driven PrEP, self-reported adherence to the 2+1+1 dosing regimen in the past 30 days, assessed through self-reports of PrEP use and sex acts at study follow-up visits, along with intraerythrocytic TFV-DP concentrations. Only participants retained in the study at the end of 26 weeks will be considered to have reached the persistence end point. Data will be presented in a 2-by-2 table, classifying each participant as either persistent or nonpersistent to PrEP. A *Z*-test based on asymptotic normality will be used to compare persistent PrEP use between the intervention and SOC arms.

Acceptability and Barriers

For binary end points, frequencies will be tabulated, and proportions will be calculated along with variances estimated under the binomial distribution. For continuous end points, the mean, median, SD, quantiles, and range will be reported.

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Feasibility of Future RCT

Secondary data analysis will tabulate the number of each end point observed during the study. For binary end points, the percentage of total enrolled participants will be calculated, with variance estimated under the binomial distribution. For continuous end points, the mean, median, SD, quantiles, and range will be reported. *Z*-tests will be used to compare end points between study arms.

Qualitative Analysis

After transcription, all qualitative interviews will be translated into English as needed and uploaded into a qualitative data analysis software program. The team will follow a structured process of reading, coding, data display, and data reduction to explore participants' attitudes toward and experiences with the intervention in greater depth. Data coding and analysis will be iterative and interactive, conducted by a team of both US- and Malawi-based qualitative researchers. All US-based team members have lived or worked in Malawi for many years, including conducting trials at the Bwaila STI Clinic. The team will begin by reading all interview transcripts to increase familiarity with the data. Next, they will apply a priori codes and generate emergent codes, using a mixed inductive and deductive approach to coding and analysis. Transcripts will then be reread to develop pattern codes that group related concepts under broader themes. Through iterative discussion and consensus among the qualitative analysis team, consistent patterns in meaning, concepts, and themes across all interviews will be identified to inform the development of the final codebook. A subset of transcripts will be coded by multiple team members to ensure intercoder reliability. Discrepancies will be discussed and resolved through consensus. Detailed memos will support the development of additional codes as needed and guide the construction of data matrices. These matrices will be organized using a combination of parent codes and emergent themes to examine how participants' perceptions converge and diverge with respect to intervention acceptability (eg, ease of use, interactions with systems navigators, perceived efficacy), risk perception (eg, motivations for participation, impact on partners or other social relationships), and interest in the future use of a systems navigation component embedded within the clinic. Efforts will be made to elevate meaning-based, interpretive themes for matrix analysis, consistent with a reflexive thematic analysis approach [53]. Comparative analyses will also be conducted to explore potential differences across participant subgroups. Illustrative quotes will be documented within the data matrix under relevant themes to guide further discussion of response patterns.

Laboratory Procedures

HIV and STI testing will be performed as outlined in the schedule of events (see Tables 1 and 2). HIV antibody and RNA, urogenital *C. trachomatis*/*Neisseria gonorrhea*, and syphilis tests will be conducted locally, with results returned to participants and referrals provided for treatment as appropriate. Blood (plasma and DBS), hair, and urine specimens will be stored and batch-shipped to the HPTN Laboratory Center for additional testing. Stored specimens may be used to measure antiretroviral drugs, characterize HIV in participants who acquire HIV during study follow-up, facilitate additional testing of STI pathogens, and evaluate laboratory assays related to study objectives. Specifically, these tests are conducted to characterize factors associated with HIV and STI infection, as well as virologic, pharmacologic, and immunologic responses among participants initiating PrEP at the Bwaila STI Clinic.

Ethics Considerations

All study materials, including the protocol, informed consent forms (ICFs), and any participant-facing materials or data collection tools, have been reviewed and approved by local institutional review boards (IRBs) and US-based institutional IRBs before study implementation. The protocol, ICFs, participant education and recruitment materials, other required documents, and any subsequent modifications will also be reviewed and approved by the ethical review bodies responsible for oversight of research conducted at the study site. Following initial review and approval, the responsible IRBs/ethics committees will review the protocol at least annually. The investigator will submit safety and progress reports to the IRBs/ethics committees at least once per year and within 3 months of study termination or completion. These reports will include the total number of participants enrolled, the number who completed the study, any changes to the research activity, and all unanticipated problems involving risks to human participants or others.

All study materials have been approved by the University of North Carolina IRB (IRB approval number 433885) and the Malawi National Health Sciences Research Committee (IRB approval number 23/10/4208).

Confidentiality

All study-related information will be stored securely at the study site. Participant information will be kept in locked file cabinets located in areas with access restricted to study staff. All laboratory specimens, reports, study data collection forms, process documents, and administrative records will be identified by coded numbers only, to ensure participant confidentiality. Local databases will be secured with password-protected access. Forms, lists, logbooks, appointment books, and any other documents that link participant ID numbers to identifying information will be stored separately in a locked file in an area with restricted access.

Informed Consent

Written informed consent will be obtained from each study participant by trained study staff. Study ICFs describe the purpose of the study, the procedures to be followed, and the risks and benefits of participation, in accordance with all applicable regulations. ICFs have been translated into the local language, and the accuracy of the translation has been verified through independent back-translation. Literate participants will document their consent by signing the ICF(s). Nonliterate participants will document their informed consent by marking their ICF(s) (eg, with an X, thumbprint, or other mark) in the presence of a literate third-party witness. Participants will be provided with a copy of their ICF if they are willing to receive it.

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All minors (under the age of 18) will be required to provide assent along with parental consent. According to Malawi guidelines, individuals aged 15 years and above may initiate PrEP if they meet other eligibility criteria.

Risks, Benefits, and Compensation

This trial is not expected to expose participants to unreasonable risk. Blood draws may cause discomfort, dizziness, or faintness, and may result in bruising, swelling, or infection. Participants may feel embarrassed, worried, or anxious when completing their HIV risk assessment or receiving risk reduction and PrEP counseling. They may also experience anxiety while awaiting their HIV test results. Trained counselors will be available to support participants in managing these feelings.

Study procedures also address the potential risks associated with field-based tracing for missed study or PrEP visits, conducted by study staff and systems navigators, respectively. All tracing efforts are carried out in accordance with participants' stated preferences and locator information, which is provided and regularly updated by participants or their parents/guardians. Community sensitization and engagement with the Community Advisory Board are key components in ensuring the safety of both participants and those conducting tracing activities. Additional measures to mitigate risk to individuals conducting tracing activities are working in pairs or teams, carrying phones to facilitate communication, using flexible transportation (ie, not relying on public transport availability), and receiving extensive training on the importance of immediate withdrawal if any hostility is perceived. Any such incidents are generally reported back to the community representative.

There may be no direct benefits to participants in this study; however, participants and others may benefit in the future from information gained through this study. Specifically, the information obtained may lead to improved HIV prevention services for heterosexual men. In addition, participants will receive HIV and STI counseling and testing as part of the study process.

Participants will be compensated for their time and effort in this study, to help offset costs related to transportation for study visits and time taken off work. Site-specific reimbursement amounts will be detailed in the study ICFs and approved by all ethical review committees.

Adverse Event Reporting

As this study involves only low-risk activities and does not include any biomedical intervention or clinical care, standard adverse event reporting and monitoring will not be undertaken. No product related to this study is being offered or administered directly by the study staff. All drugs used by participants in this study for the prevention of HIV or management of STIs have regulatory approval for these purposes in Malawi and have well-established safety profiles. All safety monitoring of these approved drugs will be at the discretion of the Malawi Ministry of Health. Confidential HIV and STI surveillance reporting will be conducted in accordance with local regulations.

Monitoring and Clinical Data Review

The study site investigators are responsible for the initial evaluation and reporting of safety information at the participant level, as well as for alerting the protocol team if unexpected concerns arise. Study participants will be provided with a 24-hour telephone number and contact information and will be instructed to contact the study clinician to report any social harm they may experience. For life-threatening events, they will also be instructed to seek immediate emergency care. Where feasible and medically appropriate, participants will be encouraged to seek evaluation at the location where the study clinician is based and to request that the clinician be contacted upon their arrival.

The study will establish a Study Monitoring Committee (SMC), which will meet via conference call approximately every 6 months. More frequent or ad hoc reviews may be conducted by the SMC as needed. The SMC may recommend stopping the trial if warranted; however, given the minimal risk of the study, no predefined stopping criteria will be developed.

Social Impact Reporting

It is possible that participants' involvement in the study could become known to others, potentially resulting in social harm (eg, if participants are perceived as living with HIV or at increased risk of acquiring HIV). For example, they may be treated unfairly or face challenges being accepted by their families or communities. Although self-identification as heterosexual is an inclusion criterion, it is possible that some male participants may disclose having sex with other men or transgender individuals, including naming men as recent partners. Given that homosexuality is illegal in Malawi, extensive care will be taken to preserve the confidentiality and safety of all participants. All staff, including systems navigators, will be informed of the sensitive nature of disclosed sexual activities and trained in the appropriate conduct of clinical research to ensure that all participants are treated fairly and professionally. Reporting of any participant-disclosed homosexual activity is not required in research studies.

Research staff will be trained to recognize, document, and report social impacts, and to provide referrals for counseling and social service support if necessary. Any social harm reported by a participant and judged by the Investigator of Record to be serious or unexpected will be reported to the site's IRBs at least annually, or in accordance with their specific requirements. Participants may also benefit from the study in various ways. Therefore, both social harms and benefits related to study participation will be collected and recorded during study visits. If a participant reports social harm, study staff will make every effort to provide appropriate care and counseling, or refer the participant to suitable resources to ensure their safety. The site will provide such care and counseling in accordance with locally available resources. While maintaining participant confidentiality, study staff may engage the Community Advisory Board to explore the social context surrounding instances of social impact, to help minimize the likelihood of such occurrences.

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Dissemination

The results of the research will be disseminated through publication in peer-reviewed journals, conference presentations, and direct presentations to other interested stakeholders involved in HIV prevention, STI care provision, programming, and policy development. The protocol is available for public review on ClinicalTrials.gov (NCT06200545).

Written publication guidelines for authorship eligibility will follow the criteria recommended by the International Committee of Medical Journal Editors, including substantial contribution, participation in writing, approval of the final version, and accountability.

Lay summaries and infographics of the study findings and their implications will also be created for a general audience, including individuals receiving STI care or HIV prevention services at the recruiting sites. No participant names or other identifying information will be used in any dissemination materials, whether published or otherwise. The final deidentified data set will be maintained by the study's primary investigators and may be shared with other researchers for secondary data analysis, following the establishment of acceptable data sharing and data use agreements, in accordance with the requirements of the US National Institutes of Health (funder/sponsor) and the University of North Carolina at Chapel Hill (grantee).

Results

Enrollment opened on April 2, 2024, and was completed in November 2024. As of February 3, 2025, 199 participants were enrolled: 133 were randomized to the intervention arm and 66 to the standard arm. A total of 4 participants were found to be living with HIV at enrollment (3 with presumed acute HIV infection and 1 with false-negative serologic tests at the time of PrEP initiation). Qualitative interviews are ongoing; as of February 3, 2025, 4 interviews have been conducted with PrEP user participants and 9 with other key stakeholders relevant to HIV prevention programming in Malawi. Data collection and study follow-up are expected to continue through June 2025, with results to be published thereafter. Given the low-risk nature of this study, no interim analyses are planned. The NJIRA study is currently enrolling under protocol version 2.2 (June 28, 2024).

Discussion

Efficiently and effectively addressing barriers to persistent PrEP use is critical to improving HIV prevention outcomes. Although obstacles to PrEP persistence have been extensively studied among certain priority populations, including men who have sex with men globally and young women in East and Southern Africa [38], heterosexual men in East and Southern Africa have been largely excluded from PrEP implementation trials and persistence-focused interventions. The barriers to PrEP use in this population, where health care engagement is often sporadic and health care services may not be perceived as male-centered, are not well understood. In this study, we will test the effects of a peer-delivered systems navigation package, which we hypothesize will improve PrEP persistence at 26 weeks (effectiveness) among heterosexual men initiating PrEP at an STI clinic, compared with the current SOC. We will also evaluate the acceptability of the navigation package among key stakeholders and male PrEP user participants.

Our STI clinic–based recruitment approach leverages the synergistic co-STI/HIV epidemics globally and within the region and population of interest. Prior work demonstrates the importance of engaging persons with STIs in HIV prevention [19], and the WHO identifies persons with STIs as a priority population for PrEP [54]. However, very little is known about how best to engage and retain men seeking STI services who are initiated on PrEP. Our prior work in Malawi suggests this is an important population to retain, given the frequent early discontinuation of PrEP despite persistent HIV vulnerability [24]. Peer and systems navigation emerge as appealing, evidence-based strategies to improve PrEP use in some populations but have not been tested among heterosexual men in East or Southern Africa [25,26,31].

Our single-site pilot RCT responds to the HPTN call for concepts (Fall 2022), which requested proposals focused on understanding prevention opportunities for heterosexual men living in East and Southern Africa, an important gap identified within network research in this region. We have further narrowed the population to men at increased risk of acquiring HIV, specifically those presenting to an STI clinic with symptoms consistent with an STI or recent exposure to a person with an STI.

HPTN 112 will also provide important insights into PrEP choice and persistence in the context of multiple PrEP modality options. Specifically, this study will describe the utilization of CAB-LA among heterosexual men in Malawi and use in-depth interviews to examine patient, provider, and programmer/policy maker perspectives relevant to access to CAB-LA for this population. Although CAB-LA PrEP removes the need for daily dosing, timely injections are necessary to achieve and maintain target drug concentrations. CAB-LA is anticipated to be a desirable option for men in the region [14], but this will be among the first studies to examine the persistent use of event-driven oral PrEP among heterosexual men in the region, a prevention strategy that requires the ability to predict sexual encounters [15,55,56]. Depending on the frequency of sex acts, event-driven PrEP could increase the interval between doses compared with daily oral PrEP. However, data on the use of this strategy have been mixed, and little is known about its acceptability and effective use among heterosexual men [57-62]. By triangulating the timing of self-reported sex acts, self-reported event-driven PrEP use, and PrEP drug concentrations measured via DBS at quarterly intervals (along with an exploratory evaluation of PrEP exposure via hair samples), this study will explore how these measures can be combined to better evaluate prevention-effective event-driven PrEP use among men.

The need for PrEP, whether real or perceived, fluctuates, and our prior work in this context demonstrates frequent PrEP discontinuations within the first 6 months of initiation [23,24]. This study will be the first to evaluate the acceptability and feasibility of a "return-to-PrEP" kit as a potential strategy to mitigate HIV acquisition risk for persons who choose to stop PrEP. Participants who no longer feel they need PrEP are

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encouraged to return to the clinic and are offered this "restart" kit, along with instructions for self-testing and use of the pill pack, to facilitate immediate protection if they are unable to plan ahead to visit the clinic before reengaging in activities that may put them at risk of acquiring HIV. Navigators also serve as a direct entry point to help reengage men in HIV prevention services.

This protocol is among the first studies to test systems navigation as a strategy to improve persistent PrEP use among heterosexual men in the region. The strengths of this study are its focus on an epidemiologically and socially important subpopulation of heterosexual men, who account for approximately half of all persons seeking STI services at the recruitment site but are rarely engaged in PrEP research. We are also uniquely positioned to examine the persistence and acceptability of multiple PrEP modalities, including injectable and event-driven oral PrEP, among heterosexual men. Finally, we have structured our data collection strategy to minimize overlap with PrEP service delivery, that is, study retention is distinct from retention in PrEP services, so compensation for study visits should not affect our assessment of PrEP persistence. However, there are important limitations. For example, due to the limited sample size, short recruitment period, and heterogeneity of determinants of persistent PrEP use across different populations, transgender persons and women are not included in this initial randomized pilot. Based on our experience in Malawi, persons who identify as gender nonbinary typically seek sexual health services at other local drop-in centers rather than at the STI clinic where this study will be conducted. As such, our effectiveness and some acceptability outcomes may not be generalizable to other populations who remain vulnerable to HIV and may also be prioritized for HIV prevention. However, robust implementation outcomes collected through study-specific case report forms and in-depth interviews will provide valuable insights into the determinants of scaling this intervention to other settings and populations.

Study results could inform program development and policies for PrEP delivery in Malawi and elsewhere in the region, with dissemination prioritized to reach key decision makers. Findings could guide a multisite, multicountry implementation science study integrating peer-delivered systems navigation into STI clinics as a strategy to recruit and retain men vulnerable to HIV acquisition in effective HIV prevention tools, including PrEP. Recognizing increasingly cyclical PrEP use patterns, navigators serve as a direct entry point to retain or reengage men in HIV prevention services.

Acknowledgments

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Data Availability

No data are presented herein. The fully approved study protocol is available upon request as well as posted on the HPTN website. The data sets generated during or analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

SER, JSC, YOA, MC, VG, IFH, MCH, MAM, WCM, JP, and M Mukatipa conceptualized the research study and study design. SER, LLK, JSC, IB, EH, MCH, MAM, JP, TY, HMLS, and M Matoga developed the research protocol and data collection tools. YOA, SA, JMF, MAM, and EPM provided expert opinions on laboratory considerations. IB, DH, and TY provided expertise in statistical and data management considerations. All listed authors contributed to, reviewed, and approved the manuscript as submitted.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Intervention manual for systems navigators.
[DOCX File , 1966 KB - resprot_v14i1e72981_app1.docx]

Multimedia Appendix 2
In-depth interview guides.

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[DOCX File , 31 KB - resprot_v14i1e72981_app2.docx]

Multimedia Appendix 3
Informed consent forms for all participants.
[DOCX File , 133 KB - resprot_v14i1e72981_app3.docx]

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Abbreviations

ART: antiretroviral therapy
CAB-LA: long-acting injectable cabotegravir
CFIR: Consolidated Framework for Implementation Research
DBS: dried blood spots
HPTN: HIV Prevention Trials Network
ICF: informed consent form
IRB: institutional review board
NJIRA: Navigated Journey to Improve Reduction of HIV in African Men
PrEP: preexposure prophylaxis
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SMC: Study Monitoring Committee
SOC: standard of care
STI: sexually transmitted infection
TDF/3TC: tenofovir disoproxil fumarate/lamivudine
TFV-DP: tenofovir diphosphate
WHO: World Health Organization

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Protocol

A Customized Neural Transcranial Magnetic Stimulation Target for Functional Disability Among Veterans With Co-Occurring Alcohol Use Disorder and Mild Traumatic Brain Injury: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Alcohol use disorder (AUD) and mild traumatic brain injury (mTBI) commonly co-occur, exacerbating symptoms and negatively impacting function. Co-occurring AUD and mTBI (AUD+mTBI) represents a unique and heterogeneous brain state impacting symptoms and function. Repetitive transcranial magnetic stimulation (rTMS) is a noninvasive neuromodulatory treatment with burgeoning evidence for improving brain function and symptoms for AUD and mTBI each alone. However, there is no consensus on the optimal neural target or treatment site of stimulation for either condition alone or when they co-occur.

Objective: This study aims to (1) test the preliminary efficacy of high-frequency rTMS provided to a customized neural target to treat functional disability among veterans with AUD+mTBI and (2) assess the sustainability of rTMS effects on functional disability among veterans with AUD+mTBI.

Methods: This single-blind randomized controlled trial (RCT) involved treatment-seeking veterans with AUD+mTBI recruited from a Department of Veterans Affairs hospital. Veterans will be randomly assigned to (1) a novel TMS target site using neuronavigation or (2) standard clinical left dorsolateral prefrontal cortex using the Beam F3 method. All participants first receive 10 daily sessions of sham rTMS, followed by 10 daily sessions of active rTMS (10 Hz) provided by a trained TMS administrator. Veterans will complete self-report study questionnaires before and after sham and active rTMS session blocks as well as at 2-week, 1-month, 3-month, and 6-month posttreatment follow-up time points. The primary outcome is the WHO Disability Assessment Schedule 2.0. The secondary outcomes include alcohol use on the Timeline Follow-Back calendar, the Penn Alcohol Craving

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Scale, the Obsessive-Compulsive Drinking Scale, the Alcohol Craving Questionnaire, the Neurobehavioral Symptom Inventory, the PTSD Checklist for *DSM-5*, the Beck Depression Inventory-II, the Beck Anxiety Inventory, and the Mood and Anxiety Symptom Questionnaire.

Results: This study protocol was approved by the institutional review board of the Edward Hines Jr Department of Veterans Affairs Hospital (19-021). This study includes a Food and Drug Administration investigational device exemption (G180292). A 6-year research plan timeline was developed, including cost and no-cost extensions due to the COVID-19 pandemic. As of June 2025, overall, 27 veterans with AUD+mTBI who had been enrolled in the study had completed the neural target identification phase and were awaiting enrollment in the RCT phase. Data collection for the RCT phase will be initiated soon and is expected to be completed by April 2026. We expect the results of this study to be available by May 2027.

Conclusions: We will be able to provide preliminary evidence of the efficacy, safety, and feasibility of a novel TMS target for veterans with AUD+mTBI.

Trial Registration: ClinicalTrials.gov NCT04043442; https://www.clinicaltrials.gov/study/NCT04043442

(JMIR Res Protoc 2025;14:e64909) doi:10.2196/64909

KEYWORDS

transcranial magnetic stimulation; magnetic resonance imaging; alcohol; traumatic brain injury

Introduction

Background

Clinical Problem

Alcohol Use Disorder

Alcohol use disorder (AUD) is defined by the American Psychiatric Association as impaired control over alcohol use characterized by the following symptoms: tolerance, withdrawal, relapse, craving, and impairments in social and occupational functioning [1]. Alcohol-related characteristics (ARCs) are defined for this study per these symptoms as well as AUD-specific outcomes that include but are not limited to alcohol craving, alcohol use, and AUD duration.

Alcohol is the most widely used substance by veterans [2], who have higher AUD rates than American civilians [2]. However, existing AUD treatments remain suboptimal. Although the pharmacotherapies naltrexone and acamprosate are efficacious for AUD, a recent meta-analysis indicates small effects (Hedges g=0.21) compared to placebo [3]. High rates of return to hazardous alcohol consumption after treatment (approximately 60%) [4] necessitate the development of more efficacious primary or adjunct interventions.

Co-Occurrence of AUD With Mild Traumatic Brain Injury

Among veterans with mild traumatic brain injury (mTBI), AUD rates are as high as 35% [5,6]. Both our research and that of others show that co-occurring AUD and mTBI (AUD+mTBI) may exacerbate brain impairment, exacerbate symptoms (eg, alcohol craving and cognitive dysfunction), and negatively impact rehabilitation effectiveness [7-11]. TBI severity is defined by the American Congress of Rehabilitation Medicine [12] as well as the Department of Veterans Affairs (VA) and the Department of Defense [13] based on the presence and duration of loss of consciousness, alteration of consciousness, and posttraumatic amnesia. mTBI is defined as a period of loss of consciousness <30 minutes, alteration of consciousness <24 hours, or posttraumatic amnesia <24 hours, along with a Glasgow Coma Scale score of 13-15 [12,14].

Among veterans with AUD+mTBI, the prevalence rates of co-occurring posttraumatic stress disorder (PTSD) and depression are as high as 44% and 23%, respectively [15,16]. Our work indicates that compared to veterans with AUD alone, veterans with AUD+mTBI and co-occurring mental health conditions self-report higher alcohol craving, a factor associated with relapse [11].

Knowledge Areas to Be Advanced Enabling Customized Treatment Development

Understanding the Relationships Between ARCs and Function

AUD and mTBI each negatively impact multiple domains of functioning. Individuals with AUD report high levels of functional disability in terms of impaired cognition, participation, and work and home life [17]; for example, AUD duration (an ARC) is negatively associated with self-reported global disability [17]. People with mTBI also report high levels of disability [18]. The functional domains of cognition, self-care, relationships, life activities, and participation in society are particularly impacted after mTBI [18].

Among veterans with AUD+mTBI, functional impairments are exacerbated. Co-occurring mTBI and substance use disorders (SUDs) worsen functional disability among veterans [19].

Understanding Unique AUD+mTBI Brain State Relative to Function

AUD and mTBI each affect overlapping and unique neural pathways. Advanced neuroimaging can be used to identify dysfunctional neural networks [20]. Research using resting state functional magnetic resonance imaging (rs-fMRI), for example, demonstrates that most networks supporting task-based function communicate between brain regions via synchronized activity at rest [21]. In addition, rs-fMRI within established networks is associated with biological changes and pathological behavioral outcomes associated with neuropsychiatric conditions [22], suggesting that the condition of rs-fMRI reflects the ability to function. Similarly, white matter integrity assessed through diffusion tensor imaging (DTI) and gray matter volume are substantially low in some neuropsychiatric conditions, indicating

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that these measures are relevant to healthy brain and behavioral function [23,24]. Understanding the unique AUD+mTBI brain state is vital to understanding which neural substrates, when targeted with neuromodulation, are likely to optimize treatment responsiveness, replacing or complementing current pharmacotherapies that, when administered alone, yield suboptimal treatment outcomes.

Neuroimaging Techniques for Customized Transcranial Magnetic Stimulation Target Site Determination

We used multimodal neuroimaging metrics to inform the selection of our repetitive transcranial magnetic stimulation (rTMS) neural target. To understand what is unknown for AUD+mTBI, we examined published neuroimaging literature characterizing the circuitry implicated in AUD and mTBI each alone [8]. While we know that some brain regions and networks implicated in AUD alone overlap with mTBI alone and that others are unique to each condition [8], we do not know how co-occurring mTBI affects the AUD brain state to influence function.

Neurophysiological changes within the whole brain, specific networks, and regions of interest can be assessed using multimodal techniques to derive neuroimaging metrics, including (1) task-based fMRI, (2) rs-fMRI, (3) DTI of white matter integrity, and (4) gray matter density. First, task-based fMRI was used to assess brain activation in response to visual alcohol cues to identify brain regions that have increased or decreased responsiveness compared to veteran controls [25]. This task is clinically relevant because visual cues (eg, pictures of alcohol or people drinking in bars) are related to alcohol craving [25], which is associated with relapse [26]. Second, we used rs-fMRI to examine how brain networks function together at rest [27]. rs-fMRI is free from task-related confounds such as differing attention levels and cognitive abilities [27]. The rs-fMRI metric informed whether connectivity between cortical and subcortical brain regions is pathological in terms of hyper- or hypoconnectivity, which is important because of evidence that rTMS applied to a cortical site can have subcortical effects [20,28,29]. Thus, rs-fMRI data can be used to inform the optimal cortical rTMS target with desired subcortical effects. Third, DTI is an indirect index of the structural integrity and connectivity of white matter tracts comprised in neural networks [30]. DTI can identify structural dysfunction between cortical and subcortical structures, and these tracts can be targeted with neuromodulatory treatment. Finally, metrics of gray matter density and volume measure brain atrophy [31] and complement DTI and rs-fMRI metrics; for example, if there is a common site of atrophy, then this site would not be selected for neuromodulation, but a site that is structurally or functionally connected to the atrophic site may be selected to enable effective neural compensation.

We focused our analysis of multimodal neuroimaging metrics on the following brain networks implicated in both AUD and mTBI [8]: the default mode network, executive control network, the frontoparietal control network, and the salience and ventral attention network. Ongoing data analyses will select the cortical region of interest from these networks as the customized neural target for rTMS, and the results will be published elsewhere (manuscript in preparation). Potential cortical TMS treatment target sites from the default mode network, the salience and ventral attention network, the executive control network, and the frontoparietal control network are summarized in Figures 1- 3, respectively. Target sites were evaluated in a prior phase of the project, and a manuscript is in preparation for publication elsewhere.

Figure 1. Potential cortical default mode network transcranial magnetic stimulation target treatment sites. Regions of interest are derived from the 17-network, 100-parcellation atlas based on the study by Schaefer et al [32,33], and include the default mode network, the salience and ventral attention network, and the frontoparietal control network. Regions of interest that presented surface cortical access were chosen. The numbers in parentheses indicate the Schaeffer atlas parcel number.

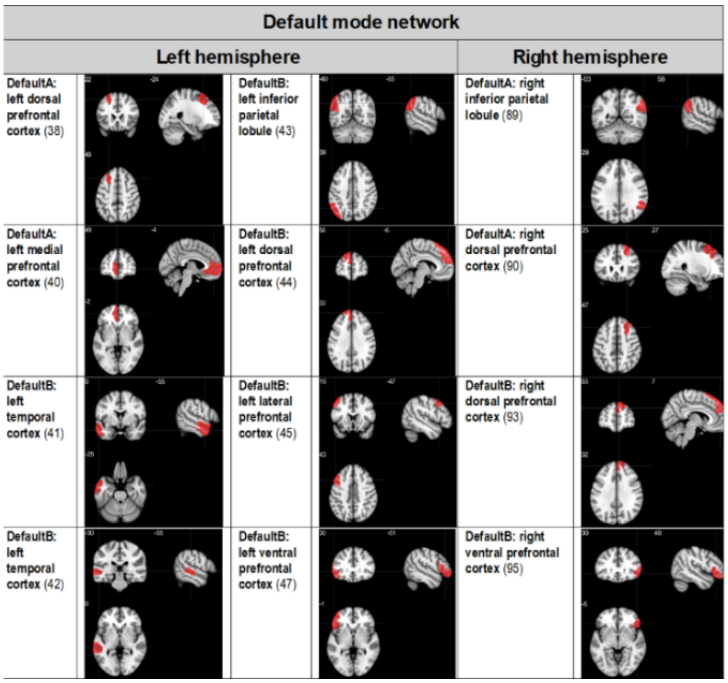

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Figure 2. Potential salience and ventral attention network (SalVentAttn) transcranial magnetic stimulation target treatment sites. Regions of interest are derived from the 17-network, 100-parcellation atlas based on the study by Schaefer et al [32,33]. Regions of interest that presented surface cortical access were chosen. The numbers in parentheses indicate the Schaeffer atlas parcel number.

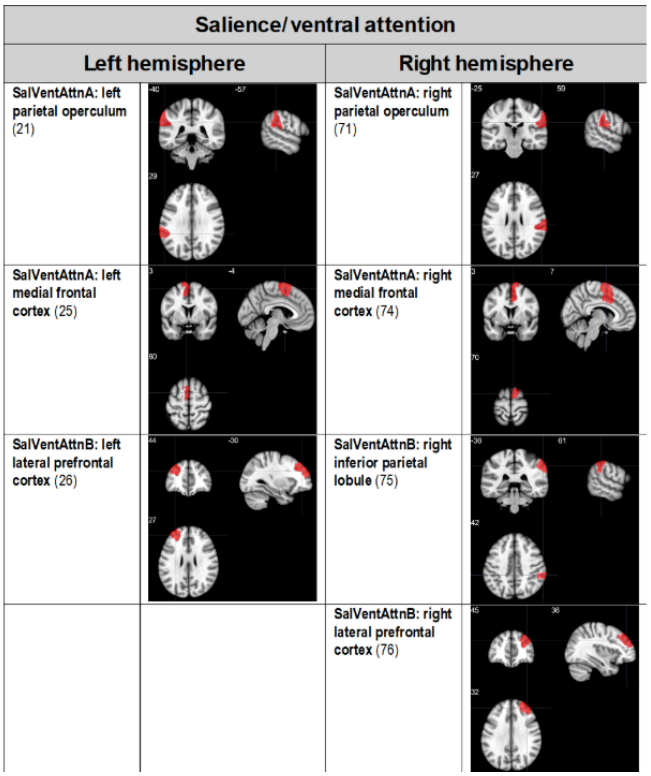

Figure 3. Potential frontoparietal control network (Cont) transcranial magnetic stimulation target treatment sites. Regions of interest are derived from the 17-network 100-parcellation atlas based on the study by Schaefer et al [32,33]. Regions of interest that presented surface cortical access were chosen. The numbers in parentheses indicate the Schaeffer atlas parcel number.

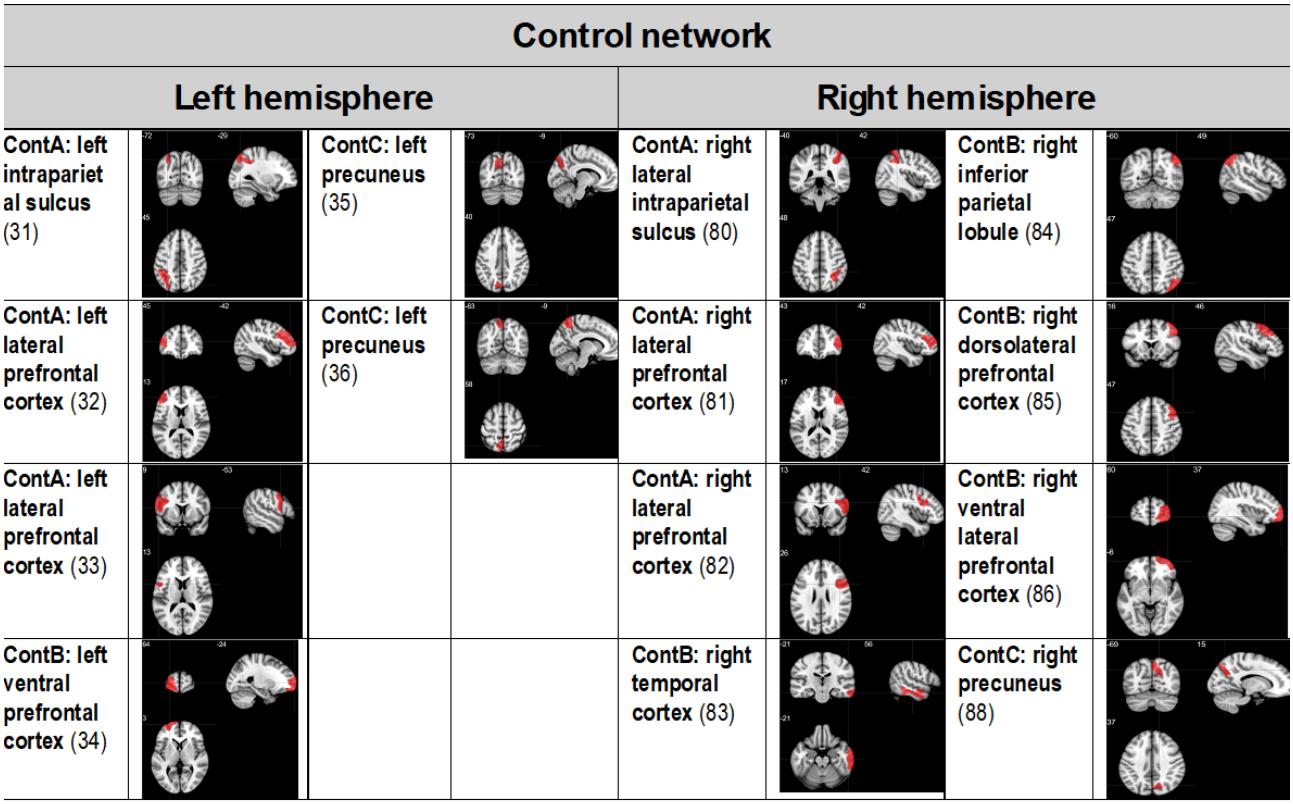

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Rationale: Customized AUD+mTBI Neuromodulation

rTMS may provide a complementary or alternative treatment because it is noninvasive. In addition, neural targets (ie, stimulation sites) and parameters (eg, excitatory or inhibitory) can be customized to unique needs, and preliminary evidence indicates that rTMS attenuates the symptoms and functional compromise of AUD [34-37] and mTBI independently [38-40]. A review of rTMS as a treatment for AUD alone and mTBI alone further supports our contention that rTMS is a strong candidate as an alternative treatment for AUD+mTBI [8]. Published clinical studies examining rTMS for AUD alone indicate that rTMS induces a moderate effect size for reducing alcohol craving (η^2=0.40). The largest and most promising trial used high-frequency (10 Hz), excitatory (110% motor threshold [MT]) rTMS to the right dorsolateral prefrontal cortex (DLPFC) [34]. Notably, the rTMS effect is an improvement on existing pharmacotherapies (Hedges g=0.21) [3]. Furthermore, the same rTMS protocol to the left or right DLPFC significantly (P<.05) reduced alcohol craving for people with AUD alone, with no effect size differences between sites [41]. Among people with AUD, recent findings indicate that an inhibitory patterned type of rTMS, continuous theta burst stimulation (inhibitory), to the left frontal pole in a single session resulted in reduced alcohol cue–induced brain activation within reward circuitry. An effect on alcohol craving was not expected because only a single treatment session was provided, highlighting the need for research on multisession rTMS with AUD+mTBI. In addition, a pilot randomized controlled trial (RCT) examining the utility of intermittent theta burst stimulation (iTBS; excitatory) administered to the left DLPFC for AUD among veterans was recently published. This pilot RCT found that veterans with AUD who received active iTBS were less likely to relapse and experienced greater reductions in anhedonia compared to those who received sham iTBS [42].

There are several case studies on rTMS for TBI [8,43] as well as 8 RCTs of rTMS as a treatment for postconcussive or posttraumatic depression, headache, and chronic central pain among individuals with mTBI, all with modest sample sizes (n≤30) [44]. These trials indicate that high-frequency (10 Hz) and excitatory (100%-120% MT) rTMS is efficacious for mTBI using various stimulation sites, improving mTBI symptoms (left DLPFC) [45], pain and health-related quality of life (individualized motor cortex) [40] as well as headache (although 70% MT) [46], and depression [39] (left DLPFC). However, low-frequency (1 Hz) right DLPFC rTMS was used in 2 RCTs with improved postconcussive depression symptoms as well as working memory and executive function in the study (n=13) by Lee and Kim [47] but without significant improvement in depression symptom outcomes in the study (n=30) by Rao et al [48]. In addition, 2 RCTs provided bilateral rTMS with high frequency (10 Hz) to the left DLPFC and low frequency (1 Hz) to the right DLPFC with improved depression symptoms among the active versus sham rTMS groups in the study (n=15) by Siddiqi et al [49] but without improvement in the study (N=21) by Hoy et al [50]. Of note, the study by Siddiqi et al [49] used individualized rs-fMRI data to inform rTMS targeting and a sham coil, while the study by Hoy et al [50] used a treatment coil angled 45° off the head as the sham condition.

A gap in this literature is that veterans were included in only 1 TMS AUD study [42] and only 1 TMS mTBI study. In addition, most of these rTMS trials used the left or right DLPFC for rTMS provided at 10 Hz (90%-110% MT), which also has demonstrated efficacy with depression [51]. The national VA clinical TMS program recently published findings demonstrating that among its sample of 770 veterans who received TMS for depression, 50.7% reported a prior mTBI (ie, a period of loss of consciousness <30 min and posttraumatic amnesia <24 hours, along with no structural imaging findings). Most patients received 10 Hz rTMS to the left DLPFC (120% MT; 3000 pulses per session for 30 sessions). mTBI status did not predict rTMS-related changes in depression symptom outcomes, and there was no relationship between the number of mTBIs and TMS-related depression remission rates [52]. However, mTBI status was related to a modest rTMS-related improvement in PTSD symptoms [52]. Thus, these naturalistic study results collected among a large sample of veterans provide evidence to support the safety of high-frequency rTMS among veterans with co-occurring mTBI.

However, the use of neuroimaging evidence to select neural targets customized for AUD+mTBI has not been examined. High-frequency stimulation has been efficacious for improving mTBI [38], depression [51], and PTSD symptoms [8]. As we seek to also treat AUD, we will use the parameters demonstrated by Mishra et al [34] as efficacious for reducing alcohol craving (an ARC). Another AUD study by Mishra et al [41] involved the provision of 10 daily sessions (every weekday for 2 wk) of high-frequency (10 Hz) rTMS to the left DLPFC at an intensity of 110% MT. As described previously, patterned types of rTMS, such as TBS, have been examined in PTSD and AUD. A single case study using iTBS as a potential treatment for TBI has been reported [53]. The study details the case of a man aged 25 years with TBI who underwent 3 weeks of cerebellar iTBS combined with rehabilitation. This patient experienced improvements in balance performance, motor recovery, step length, and walking speed after iTBS [53]. Importantly, this report suggests that iTBS can be used among individuals with TBI. However, given the larger body of evidence for high-frequency rTMS for AUD treatment efficacy [8] and the more established safety profile [54], high-frequency (10 Hz) rTMS is a logical first step for treating individuals with AUD+mTBI, a population with elevated risk of seizures associated with potential alcohol withdrawal.

Our hypothesis—that the provision of rTMS to a customized neural target identified using multimodal neuroimaging metrics for AUD+mTBI will optimize rTMS effects on functional disability—is based, in part, on the use of rs-fMRI among healthy controls and people with depression. Previous research demonstrated that it is possible to identify a cortical stimulation site using rs-fMRI to modulate a subcortical target using rTMS [20]. Wang et al [20] found that when rTMS was applied to the posterior parietal cortex, the hippocampus was modulated, and both rs-fMRI and associative memory were strengthened. rs-fMRI was also used to develop neuroimaging metrics for people with depression by depression subtypes [55]. Structural MRI was used to determine that specific rTMS stimulation sites within the left DLPFC (ie, lateral or anterior) were related to

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better depression treatment responsiveness [56]. DTI data were used to define the rTMS treatment site within the injured spinothalamic tract to improve chronic pain among people with mTBI [40].

Objectives

This study aims to (1) test the preliminary efficacy of high-frequency rTMS provided to a customized neural target to treat functional disability among veterans with AUD+mTBI and (2) assess the sustainability of rTMS effects on functional disability among veterans with AUD+mTBI.

Methods

Study Design

This is a single-blind RCT involving veterans with AUD+mTBI randomly assigned to (1) a customized TMS target site of stimulation or (2) standard clinical left DLPFC. The protocol was developed according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement [57].

A 6-year research plan timeline was developed, including cost and no-cost extensions due to the COVID-19 pandemic (Table 1).

Table 1. Research plan timeline.

Tasks	Year 1	Year 2	Year 3	Year 4	Year 5	Year 6
Study start-up	✓					
COVID-19 study administrative hold	✓[a]	✓[a]				
Customized TMS[b] target identification phase: participant procedures		✓	✓	✓	✓	
Neuroimaging processing			✓	✓	✓	
TMS RCT[c] treatment phase procedures					✓	✓
Data analysis				✓	✓	✓
Dissemination						✓

[a]From March 2020 to February 2021.

[b]TMS: transcranial magnetic stimulation.

[c]RCT: randomized controlled trial.

Ethical Considerations

Human Participant Ethics Review Approvals

This study involves human participant research and adheres to appropriate ethics review approvals. This study protocol was approved by the institutional review board (IRB) of the Edward Hines Jr VA Hospital in Hines, Illinois, United States (19-021), on August 7, 2019, and was prospectively registered on ClinicalTrials.gov (NCT04043442). This study includes a Food and Drug Administration (FDA) investigational device exemption (G180292). The research study staff will be responsible for communicating any protocol amendments to the IRB and any investigational device exemption supplements to the FDA, as appropriate. Significant amendments will be submitted to the study sponsor (VA Office of Rehabilitation Research Development and Translation) as a project modification for prior review and approval.

Informed Consent

All study participants will provide informed consent before completing research procedures. Authorized clinical researchers will meet eligible participants at the designated entrance, closest in proximity to a private room where the study visit is to take place. The researcher will provide all documentation, including the study consent form and all assessments that the participant will need to complete.

All participants will be able to make their own decisions regarding research participation. They will be encouraged to discuss study participation with a family member or friend before signing the consent form. The participant will not be openly encouraged to participate in the research or told that there is any expected benefit from the experimental interventions during participation. Participants will be given the option to opt out of consenting or research procedures at any time without loss or penalty. Research participants will have access to research staff to assist with any questions or concerns until understanding is achieved to the judgment of the individual asking the question. If a participant refuses participation, no further contact will be made. If signed informed consent forms are completed, a note will be made in the Edward Hines Jr VA Hospital electronic medical record (EMR), and the original consent form will be kept in a locked cabinet in a locked research office behind swipe-access doors. Copies of the signed consent forms will be provided to the Edward Hines Jr VA Hospital IRB office. In addition, a copy will be provided to the participant.

Privacy and Confidentiality

All hard copies of assessments will include only a unique participant ID number and the date the assessment was completed to maintain deidentification. The only documents containing identifiable information will be the demographics questionnaire and the contact information form. The demographic questionnaire will be kept in a locked filing cabinet within the locked office of the study principal investigator (PI), AAH. Each participant's name and contact information will be linked to the unique study ID number and saved electronically

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on a secure VA server containing the cross-walk file at the Edward Hines Jr VA Hospital. This secure cross-walk file is the only place where identifying information (eg, name, address, telephone number, date of birth, and social security number) is associated with unique participant ID numbers. To further protect participant confidentiality, the PI will have control over which research team members are allowed access to the cross-walk file.

Compensation Details

Participants will receive US $200 for completing all rTMS treatments (sham and active). They will receive up to US $75 for completing all 3 follow-up visits (US $25 per visit). Therefore, at the end of research participation, participants are eligible to receive up to US $275. This compensation is intended to facilitate participation without adding undue influence.

Setting

Treatment-seeking veterans from the Edward Hines Jr VA Hospital will be included. All research procedures will take place at this hospital.

Participants

We will target the enrollment of 46 veterans with AUD+mTBI. Complete study eligibility criteria are presented in Textbox 1. Veterans aged 22 to 70 years without a history of moderate to severe TBI, neurodegenerative disorders, psychotic spectrum disorders, MRI contraindications, intellectual disability (Wechsler Test of Adult Reading predicted full-scale IQ score <70) [58], or the use of illicit substances in the past 30 days (except for cannabis) will be eligible. The lower age limit was set as 22 years because the FDA considers individuals aged ≥22 years as adults. The upper age limit of 70 years was selected to eliminate potential confounds related to neural aging processes and the potential for neurodegenerative disease onset. Veterans will meet *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) [1], criteria for AUD per the Structured Clinical Interview for *DSM-5* [59] and the symptom attribution and classification algorithm (SACA) classification criteria for mTBI. This algorithm, developed by our team [60], is systematic and consistent with the American Congress of Rehabilitation Medicine [12], VA, and Department of Defense mTBI criteria [13].

Textbox 1. Participant eligibility criteria.

Inclusion criteria

- Aged 22 to 70 years
- Can read and speak English
- *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*), criteria for alcohol use disorder symptom attribution and classification algorithm (SACA), criteria for mild traumatic brain injury (mTBI; without requirement of clinical neuropsychological impairment)

Exclusion criteria

- History of moderate to severe TBI
- Within 1 year of mTBI
- History of nontraumatic neuroinjury (eg stroke, neurosurgery, or hemorrhage)
- Neurodegenerative disease (eg, Alzheimer disease, Parkinson disease, or multiple sclerosis)
- Has an active, unstable health condition (ie, decompensated heart failure or recent severe heart attack)
- Within 12 weeks of major surgery
- History of psychosis or current psychosis not attributable to an external cause (eg, illicit drug use)
- Endorses active suicidal ideation with intent and plan (these participants will be brought to the emergency department for emergent psychiatric care)
- Intellectual disability (Wechsler Test of Adult Reading predicted full-scale IQ score <70) [58]
- Is pregnant or nursing
- Use of benzodiazepines, opiates, cocaine, or amphetamines in the past 30 days
- Meets *DSM-5* criteria for moderate to severe cannabis use disorder
- Contraindications to magnetic resonance imaging (eg, claustrophobia, ferromagnetic metal in eyes or face, congestive heart failure, implanted cardiac pacemaker or defibrillator, cochlear implant, or nerve stimulator)
- Contraindications to intermittent theta burst stimulation and transcranial magnetic stimulation (eg, epilepsy or taking medications that elevate the seizure threshold)
- Meets SACA criteria for “questionable validity” of performance effort and symptom reporting

To enhance generalizability, veterans will be included irrespective of combat and deployment status. As cannabis use is prevalent among veterans, including those with AUD, cannabis users and those with mild cannabis use disorder (per *DSM-5*) [1,59] will not be excluded; given that legal cannabis purchase and consumption are likely to increase across the

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United States, the inclusion of cannabis users will increase the generalizability of the findings. As daily cannabis use and cannabis dependence have significant relationships with ARCs, veterans with moderate to severe cannabis use disorder will be excluded. Depression, anxiety, and PTSD commonly co-occur among veterans [61]. As this is the population we seek to generalize our study findings to, participants who meet *DSM-5* [1] criteria for depression, anxiety, or PTSD will not be excluded. To maintain high-quality data, any participant meeting criteria for questionably valid symptom profiles (ie, effort and symptom validity) will be excluded. The forced choice component of the California Verbal Learning Test–Second Edition will be used, with a cutoff score of 15, as a measure of effort performance [62]. The Minnesota Multiphasic Personality Inventory-2–Restructured Form [63] will be used to identify atypical symptom reporting based on the following criteria: infrequency scale T score ≥107, infrequency-psychopathology scale T score ≥85, true response inconsistency scale T score ≥80, and variable response inconsistency scale T score ≥80 [60].

There are no study participation limitations based on gender, race, or ethnicity.

Recruitment

To recruit a study sample representative of veterans with AUD+mTBI, we will target treatment-seeking veterans from the Edward Hines Jr VA Hospital, which houses a residential SUD treatment program, an outpatient SUD treatment program, and a TBI and polytrauma program (ie, a VA polytrauma network site).

We will identify research candidates at this VA hospital using the national inpatient and outpatient files available through the VA Informatics and Computing Infrastructure. We will request access to data housed in the Corporate Data Warehouse, including production domains and vital status files (such as Beneficiary Identification and Record Locator Subsystem), as well as Compensation and Pension Record Interchange (CAPRI) and Veterans Health Information Systems and Technology Architecture (VistA), with real social security number identifiers located in VA Informatics and Computing Infrastructure using the Data Access Request Tracker system. Once this access is approved, we will search the database for the past 10 years using appropriate *International Classification of Diseases, Ninth Revision* and *International Classification of Diseases, Tenth Revision, Clinical Modification* codes reflecting study inclusion criteria. These files will be accessed for the duration of the study.

After identification, veterans' medical records will be reviewed for eligibility, and eligible veterans will be mailed an informational letter. The study team will follow up with a telephone call 1 week after the letter is mailed to inquire whether the veteran is interested, and, if so, screen further for eligibility. The study team will also distribute IRB-approved flyers and present the study at relevant staff meetings for VA providers. VA providers will also be given IRB-approved flyers and encouraged to give them to veterans who may be a good fit for the study. The flyers will contain a study contact telephone number so that veterans can call the study team if they are interested in participating.

The veterans with AUD+mTBI who completed the neural TMS site determination phase will be called to schedule research procedures for the rTMS treatment phase. There will be a gap of 1 month to 4 years between the completion of study phases, and quarterly check-in calls will be completed to maintain study contact with participants.

Data Collection and Measures

Overview

Data collection occurred across multiple study time points, beginning with screening and baseline visits and continuing through posttreatment and follow-up visits. The full study timeline is presented in Figure 4. An overview of the assessments collected at each time point is provided in Table 2.

Figure 4. Study timeline. BL: baseline visit; F1: follow-up time point visit occurring 2 weeks after the last active repetitive transcranial magnetic stimulation (rTMS) session; F2: follow-up time point visit occurring 1 month after the last active rTMS session; F3: follow-up time point visit occurring 3 months after the last active rTMS session; F4: follow-up time point visit occurring 6 months after the last active rTMS session; MT: motor threshold visit; PA: post–active rTMS visit; PS: post–sham rTMS visit; S: screening visit.

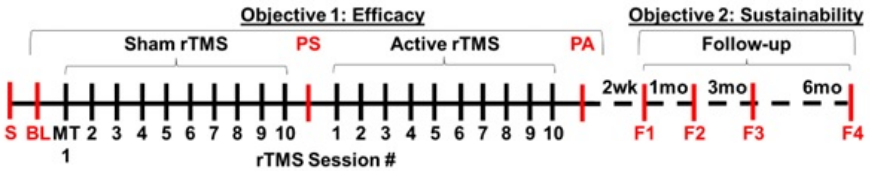

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Table 2. Study assessments, grouped by time point collected.

Time points and assessments administered	Assessment purpose
Telephone screening	
AUDIT-C[a]	Screen for AUD[b]
OSU TBI-ID[c]	Screen for TBI[d]
TMS[e] safety form	Screen for TMS safety
Medication inventory form	Screen for TMS safety
Screening visit	
SCID-5[f] AUD module	Diagnosis and duration of AUD
Structured diagnostic interview [60] with the NSI[g] [64]	mTBI[h] classification and symptoms
CIWA-Ar[i]	Determine acute alcohol withdrawal status
TLFB[j] alcohol calendar, past year	Determine alcohol consumption history
C-SSRS[k]	Determine acute suicidality
Baseline, post–sham repetitive TMS, post–active repetitive TMS, 2-wk, 1-mo, 3-mo, and 6-mo follow-up visits	
WHODAS 2.0[l]	Self-reported functional disability (primary outcome)
PACS[m]	Self-reported alcohol craving (secondary outcome)
OCDS[n]	Self-reported alcohol craving (secondary outcome)
ACQ-NOW[o]	Self-reported alcohol craving (secondary outcome)
NSI	Self-reported mTBI symptoms (secondary outcome)
PCL-5[p]	Self-reported PTSD[q] symptoms (secondary outcome)
BDI-II[r]	Self-reported depression symptoms (secondary outcome)
BAI[s]	Self-reported anxiety symptoms (secondary outcome)
MASQ[t]	Self-reported mood and anxiety symptoms (secondary outcome)
FTND[u]	Self-reported nicotine use symptoms (secondary outcome)
C-SSRS	Determine acute suicidality

[a]AUDIT-C: Alcohol Use Disorder Identification Test–Consumption Questions.
[b]AUD: alcohol use disorder.
[c]OSU TBI-ID: Ohio State University Traumatic Brain Injury Identification Method.
[d]TBI: traumatic brain injury.
[e]TMS: transcranial magnetic stimulation.
[f]SCID-5: Structured Clinical Interview for *DSM-5*.
[g]NSI: Neurobehavioral Symptom Inventory.
[h]mTBI: mild traumatic brain injury.
[i]CIWA-Ar: Clinical Institute Withdrawal Assessment for Alcohol, Revised.
[j]TLFB: Timeline Follow-Back.
[k]C-SSRS: Columbia–Suicide Severity Rating Scale.
[l]WHODAS 2.0: World Health Organization Disability Assessment Schedule.
[m]PACS: Penn Alcohol Craving Scale.
[n]OCDS: Obsessive-Compulsive Drinking Scale.
[o]ACQ-NOW: Alcohol Craving Questionnaire.
[p]PCL-5: PTSD Checklist for *DSM-5*.
[q]PTSD: posttraumatic stress disorder.
[r]BDI-II: Beck Depression Inventory-II.
[s]BAI: Beck Anxiety Inventory.

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[t]MASQ: Mood and Anxiety Symptom Questionnaire.

[u]FTND: Fagerström Test for Nicotine Dependence.

Screening

Veterans identified as research candidates will complete an initial telephone screening for the following: (1) probable AUD, using the Alcohol Use Disorder Identification Test–Consumption Questions (AUDIT-C) [65]; (2) probable mTBI, using the Ohio State University Traumatic Brain Injury Identification Method [66]; (3) TMS safety, using our TMS safety form; and (4) self-reported age as well as the ability to read and speak English. Age will be verified in the EMR (ie, Computerized Patient Record System or Compensation and Pension Record Interchange). The AUDIT-C is a 3-item, self-report measure of alcohol use; scores range from 0 to 12, with a score of ≥4 for men and ≥3 for women indicating hazardous drinking and probable AUD. A list of prescribed and over-the counter medications and the length of time the participant has been on each medication will also be collected over the telephone. Current medications will be cross-referenced with study eligibility criteria and the EMR to identify any antiepileptics as well as any medications known to lower seizure threshold. The EMR will also be reviewed for study eligibility criteria. If review findings indicate possible contraindications to rTMS or MRI related to a metal implant, attempts will be made to identify the model and manufacturer of the implant to determine whether it is safe to expose the implant to a strong magnet. Manufacturer recommendations regarding safety will be followed. If potential participants meet all eligibility criteria, they will be scheduled for the first research visit. They will be mailed a copy of the informed consent form to review, along with a reminder of the appointment date and time.

Veterans meeting the initial screening criteria for the AUD+mTBI group will screen positive for the AUDIT-C and report at least 1 lifetime mTBI on the Ohio State University Traumatic Brain Injury Identification Method.

All veterans aged 22 to 70 years without MRI safety contraindications who can read and speak English will be eligible for enrollment and diagnostic screening as outlined in the following paragraphs. Veterans meeting these criteria will complete behavioral assessments during visit 1 that will be used to confirm study eligibility.

We will complete the Timeline Follow-Back alcohol calendar for the past year, meeting with a study physician to review current medications, recent drinking history, the Columbia–Suicide Severity Rating Scale (C-SSRS), and the Clinical Institute Withdrawal Assessment for Alcohol, Revised.

Abstinence from alcohol and illicit substances will be requested for each in-person visit and will be confirmed with a urine alcohol and urine drug screen and breathalyzer or urine or saliva test for alcohol following evolving hospital COVID-19 guidelines. If veterans opt for an in-person visit 1, the urine drug screen will be completed by a VA clinical laboratory using a manual requisition form with the veteran's unique participant ID number. All subsequent urine drug screens will be conducted by research staff using a urine test kit. The results from the drug and alcohol screens will not be entered into the veteran's medical record; they are for research purposes only. Urine specimens will not be stored. Participants will also complete an acute cannabis intoxication scale [67] that includes four items: (1) increased resting heart rate (>100 beats per min), (2) congestion of the conjunctival blood vessels (red eyes), (3) slowed speech, and (4) giddiness. Any participant testing positive for alcohol, drugs, or cannabis intoxication will be asked to reschedule research procedures, and safe transportation will be arranged (eg, taxi), or participants will be escorted to the emergency department (ED) or mental health intake, as appropriate.

Baseline, Post–Sham rTMS, Post–Active rTMS, 2-Week, 1-Month, 3-Month, and 6-Month Follow-Up Visits

All veterans will complete the primary outcome measure: the WHO Disability Assessment Schedule (WHODAS 2.0), a self-report of functional disability. The following ARCs will also be collected as secondary outcomes: the Penn Alcohol Craving Scale, the Obsessive-Compulsive Drinking Scale, the Timeline Follow-Back (including the number of days between baseline and screening visits), and the Alcohol Craving Questionnaire. The following additional secondary outcomes will also be assessed: the Neurobehavioral Symptom Inventory, the PTSD Checklist for *DSM-5*, the Beck Depression Inventory-II, the Beck Anxiety Inventory, and the Mood and Anxiety Symptom Questionnaire. The C-SSRS will be repeated at baseline, after both sham and active rTMS treatment session 5, and at post–sham rTMS and post–active rTMS visits. We will also assess self-reported smoking status (ie, current, former, or never smoker, with never smoker defined as having smoked <100 cigarettes in a lifetime) and the Fagerström Test for Nicotine Dependence.

Finally, all female participants will complete a urine pregnancy test using a test kit at baseline and post–sham rTMS time points.

We will be using the VA REDCap (Research Electronic Data Capture; Vanderbilt University) secure web application for data collection and data entry. Data will be checked for completeness at the time of assessment and again at the time of data entry. Reasons for missingness will be documented.

rTMS Intervention

Randomization to Stimulation Site Group

Veterans with AUD+mTBI will be randomly assigned to 1 of 2 stimulation site groups: a customized site or left DLPFC. SAS 9.4 (SAS Institute Inc) will be used to develop the randomization protocol for the veterans, ensuring an equal number of participants—assigned sequentially—in each of the 2 groups. An electroencephalography (EEG) cap along with the coordinate Beam F3 method and neuronavigation will be used for each participant to maintain the single-blind design. The randomization scheme will be provided by the biostatistician to a single unblinded administrator (who will not complete any research procedures or analyses). This administrator will inform the rTMS provider of the patient's assigned site (left DLPFC or a customized site) for rTMS treatment.

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The customized site will be one of the sites depicted in Figures 1- 3- as determined by ongoing analyses.

MT and Brain Mapping

Each participant's T1-weighted MRI scan will be loaded into a Localite TMS Navigator system. A MagVenture C-B60 coil will be used to deliver single-pulse TMS to the left motor cortex to identify the abductor pollicis brevis (ie, thumb muscle) coordinates. Resting MT will be guided by adaptive parameter estimation by sequential testing procedures [68] using a web-based tool [69] and defined as the lowest stimulus intensity necessary to produce motor evoked potentials of peak-to-peak amplitude of ≥50 μV in 5 of 10 trials. Motor evoked potentials of the abductor pollicis brevis will be recorded using surface electrodes on the right thumb. MT may be repeated as needed with changes in medication regimens, illness, and so on. The left DLPFC will be mapped using the standard EEG cap and coordinate Beam F3 method [70]. The customized site will be mapped using Montreal Neurological Institute (MNI) atlas coordinates. EEG caps and neural navigation will be used at every rTMS session for blinding purposes. MT procedures will be conducted by a trained TMS administrator.

rTMS Parameters

rTMS will be provided at 10 Hz, 4.9 seconds per train, intertrain interval of 30 seconds, 20 total trains per session, and an intensity of 110% MT [41,51,54]. Each patient will receive 1000 pulses per day. The sham and active rTMS sessions will each be provided daily for 2 weeks (once per d, 5 d per wk; Figure 4). If a date is missed, it will be made up as soon as possible at the end of treatment. The rates of missed sessions and durations between sessions will be recorded and used as potential covariates in analyses. rTMS procedures will be conducted by a trained TMS administrator.

Single-Blind Design

A single-blind design will be maintained. Veterans will know that they will be receiving sham and active rTMS but will not know when they are receiving which treatment. The consent form will specify that they will be blinded to treatment order. The biostatistician will be blinded to group. Researchers will be unblinded to treatment order because all participants receive sham rTMS first and active rTMS second. This is necessary because the "washout" period of rTMS effects is unknown, and objective 2 examines sustainability.

rTMS Device and Blinding Procedures

Sham and active rTMS will be delivered with the MagVenture MagPro X100 with MagOption stimulator and MagVenture Cool B65 A/P (active or placebo [aka sham]) coil, which can be switched to active or placebo. The coil is identical visually for both the sham or placebo and active conditions. During rTMS, veterans and researchers will wear headphones connected to the placebo noise generator so that they hear active TMS for both conditions, thereby maintaining the single-blind design. For sham rTMS, the coil will be switched to placebo or sham where a sensation is produced via surface electrodes placed on the forehead that mimics the sensation produced by the active coil. Thus, the sham rTMS looks, sounds, and feels similar to active rTMS.

Safety Measures

All investigators and research team members who will be providing the experimental treatment will undergo mandatory training on the use of the MagVenture device and the provision of active and sham rTMS.

In addition, to monitor for discomfort or pain, participants will be asked, after each rTMS session, to rate their pain. They will characterize the sensation by describing it as painful, tingling, sharp, piercing, tugging, pinching, or intolerable and rate the degree of the sensation on a scale ranging from 0 100 (100 being the worst pain you have experienced).

The rTMS treatment day safety monitoring plan and log will also be completed for each session. Each item in this log specifies whether it will be completed before, during, or after the rTMS session. The rTMS treatment day safety monitoring plan and log contains a customized severity indicator scale. For each safety variable specified in the rTMS treatment day safety monitoring plan and log, change from baseline is rated according to severity; and for each severity rating, there is a specified medical response to be followed. The ratings are on a scale ranging from 1 to 5, with a higher number indicating more deleterious change. This scale rates changes from baseline in vital signs (temperature, blood pressure, heart rate, and oxygen saturation levels), fatigue, tinnitus, sleep, dizziness, nausea, vomiting, confusion, seizure, syncope (fainting), headache, neck pain, skin integrity of the scalp, substance use, and mental health symptoms. This scale will be completed for each TMS session.

Participants will be clinically monitored for seizure by trained research staff. In the highly unlikely event that a seizure occurs, the following response plan will be followed:

1. A research team member will activate the emergency code for the Edward Hines Jr VA Hospital rapid response team (RRT).
2. Trained research staff will assess the participant's airway, breathing, and circulation.
3. Upon arrival, the RRT will take over; assess; and treat the participant, if needed.
4. The RRT will transport the participant to the Edward Hines Jr VA Hospital ED; for participants treated at a local VA ED, the PI will contact the participant within a week and encourage them to follow up with their primary care physician, in accordance with local VA policy, which recommends that patients treated in the ED should follow up with their primary care physician within 2 weeks.
5. Any seizure will result in stopping treatment and withdrawal from the study.

An adverse event log will also be completed as necessary. In addition, an adverse event tracking log has been developed for this project. Both logs are integrated into the safety monitoring procedures of this study. All serious and nonserious adverse events will be documented in the adverse event tracking log.

All female participants will complete pregnancy tests. If a pregnancy test is positive, the participant will be discontinued from the study.

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To ensure that participant medications remain stable during study participation, participants will be asked before each TMS session whether their medications have changed. In addition, medication lists will be reviewed once per week with the participant to monitor for any changes.

Any C-SSRS score of >3 will prompt a VA comprehensive suicide risk evaluation. If a participant scores >3 on the C-SSRS at any time, the VA suicide prevention team will be alerted, and either a member of the team or a trained member of the research team will complete the comprehensive suicide risk evaluation with the participant, as well as develop a suicide safety plan (if one has not been created by the participant within the past year). This information will be urgently shared with the veteran's current mental health providers, if applicable. If the participant does not have current mental health providers, they will be offered an appointment with the mental health intake team or brought to the ED, as appropriate.

Participants will complete the Beck Depression Inventory-II; item 9 specifically assesses suicidal ideation, plan, and intent on an increasing point value scale (0-3; Table 3). To monitor for changes in suicidality, item 9 from the BDI II will be administered every week in accordance with our data safety monitoring sheet.

Table 3. Beck Depression Inventory-II item 9: suicidal thoughts or wishes.

Scores	Responses
0	I don't have any thoughts of killing myself.
1	I have thoughts of killing myself, but I would not carry them out.
2	I would like to kill myself.
3	I would kill myself if I had the chance.

Participants positively endorsing ≥2 indicators (more than transient ideation with possible plan and intent) will be queried about their response before proceeding with the screening. The assessor will be trained in risk assessment, which will include a review of the frequency and severity of suicidal ideation, a discussion of past and present planning behaviors, and current intent to act on ideation and planning.

A data safety monitoring board was not required by our study sponsor because this is a single-site pilot study.

Research-Related Injuries

Per the Code of Federal Regulations (38 CFR 17.85), the VA will provide necessary medical treatment to research participants if they are injured by participation in this research project approved by the research and development committee and conducted under the supervision of 1 or more VA employees. Except in limited circumstances, this care will be provided at the Edward Hines Jr VA Hospital. This requirement does not apply to treatment for injuries that result from a participant's noncompliance with study procedures. The VA does not normally provide any other form of compensation for injury. The VA has not been released from liability for negligence. Participation in this research may involve risks that are currently unforeseeable.

Statistical Analysis

Sample Size Justification

Our sample size was based on a power calculation for the neural TMS target identification phase of the project using a moderate effect size of 0.65 to achieve 80% power while maintaining the type I error rate at 5%. This effect size is consistent with the WHODAS 2.0 effect sizes reported in a sample of individuals with chronic conditions (0.30-0.70) [71] and a general treatment population (0.44-1.38) [72]. After accounting for an attrition rate of 20%, at least 46 participants with AUD+mTBI will be needed for the study. Thus, we hope to enroll up to 46 participants in this pilot rTMS RCT phase. As the rTMS RCT phase is a pilot study, it is not powered, but data will inform future power calculations for larger-scale studies.

Data Preparation

Deidentified data will be cleaned, and appropriate missing data imputation techniques will be used [73]. Multicollinearity among ARCs will be tested; highly correlated characteristics (except for one) will be removed before the final test.

Covariates

Covariates (eg, age, combat and deployment status, cannabis use, and nicotine dependence) will be used in the model to adjust the effect of the intervention. A bivariate analysis will be performed to test the association between each covariate and the functional disability outcome. Only statistically significant covariates will be included in the regression model.

Confounders

Variables such as depression symptoms, PTSD symptoms, anticraving medication use, and psychotherapy hours, which influence both treatment site (ie, neural target or left DLPFC) and functional disability (WHODAS 2.0), will be considered as confounders. Given a treatment site and confounders, WHODAS 2.0 scores will be calculated. The parameters of the model will be estimated by the weighted regression approach where weights will be determined by the inverse of the probabilities.

Statistical Approach

Objective 1

A within-participant, longitudinal design will be used in which all veterans will first receive sham rTMS followed by active rTMS applied to the customized neural target and the standard FDA-approved treatment site (left DLPFC). Thus, there will be 2 groups. The primary outcome, functional disability (WHODAS 2.0), will be assessed at baseline, after sham rTMS, and after

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active rTMS. A mixed effects model, incorporating within-participant correlation from repeated measures, will be used to compare the difference between difference between sham (Figure 4: PS-BL) and active rTMS (Figure 4: PA-PS) treatments. We will compare the aforementioned difference in sham and active rTMS of the left DLPFC neural target or site of stimulation with the customized neural target group.

Objective 2

A recovery curve will be constructed based on repeated functional disability (WHODAS 2.0) measures at post–active rTMS, 2-week, 1-month, 3-month, and 6-month follow-up time points (Figure 4: PA, F1–F4). A mixed effects model (incorporating within-participant correlation from repeated measures) will be used to examine change (using the slope of the model) in WHODAS 2.0 from post–active rTMS to each follow-up time point for each group. We will examine the change in slope of the left DLPFC group compared to the customized neural target group using WHODAS 2.0 measures from post–active rTMS to each follow-up time point.

Results

As of June 2025, a total of 27 veterans with AUD+mTBI who had been enrolled in the study had completed the neural target identification phase and were awaiting enrollment in the RCT phase. Data collection for the RCT phase will be initiated soon and is expected to be completed by April 2026. We expect the results of this study to be available by May 2026.

Discussion

Hypothesized Principal Findings

For objective 1, addressing preliminary rTMS efficacy, we hypothesize that veterans receiving active rTMS at the customized site will have significantly improved functional disability from before to after active rTMS compared to from before to after sham rTMS and compared to the Beam F3 left DLPFC site. This will be indicated by a significantly lower or improved WHODAS 2.0 total complex score from before to after active rTMS compared to from before to after sham rTMS and compared to the Beam F3 left DLPFC site.

For objective 2, addressing rTMS sustainability, we hypothesize that veterans with AUD+mTBI receiving active rTMS applied to the customized site will sustain improvements in functional disability 2 weeks, 1 month, 3 months, and 6 months after active rTMS and that these improvements will be sustained beyond those sustained with rTMS applied to the Beam F3 left DLPFC site.

Comparison to Prior Work

Research on neuromodulation for a variety of neuropsychiatric conditions is rapidly growing. This study protocol is in line with cutting-edge research that has capitalized on information about functional connectivity and brain state to optimize TMS. Prior work created functional connectivity maps of specific neuropsychiatric symptoms such as PTSD, dysphoria, and anxiety [74,75]. However, to our knowledge, these maps are yet to be tested prospectively as TMS targets in large-scale TMS clinical trials.

Recent research in TMS for SUDs has focused on the salience and ventral attention network, particularly as a potential treatment target [36]. TMS targeting regions that include salience network hubs (eg, the anterior insula and dorsal anterior cingulate cortex) has demonstrated efficacy for smoking cessation [76], leading to the first FDA clearance of TMS for an SUD. There is burgeoning evidence that TMS targeting the salience and ventral attention network could also be promising for AUD [77]. In addition, the frontal pole is another novel potential TMS target for SUDs [78]. As mentioned previously, recent findings indicate that an inhibitory patterned type of rTMS, continuous theta burst stimulation (inhibitory), to the left frontal pole in a single session resulted in reduced alcohol cue–induced brain activation within reward circuitry among people with AUD [79]. Recent results demonstrated improvement for both active and sham TMS groups of frontal pole iTBS groups in reductions in cigarette consumption, cigarette craving, and tobacco withdrawal without between-group effects [80]. Ongoing clinical trials will determine the effects of frontal pole TMS versus left DLPFC TMS for AUD [81]. Thus, this study protocol will contribute to the field and is in line with cutting-edge TMS research.

Strengths of the Study

To our knowledge, our study is the first to test the efficacy of TMS for individuals with AUD+mTBI, a population with few treatment options. Our study will be of particular significance to the neurorehabilitation field because there is still no consensus regarding the appropriate neural TMS target for SUDs or mTBI individually, let alone AUD+mTBI. Furthermore, although much progress has been made in the TMS neuroimaging field in identifying novel targets and circuits, few studies have directly tested these in comparison to the current clinical standard.

Exploring the preliminary efficacy and sustainability of rTMS effects on functioning, according to a customized AUD+mTBI neural target and the commonly used left DLPFC, is a fundamental first step toward developing and optimizing an rTMS treatment for veterans with AUD+mTBI, for whom there are currently limited treatment options.

We will start the process of developing a customized AUD+mTBI rTMS protocol that is clinically implementable. We will do this comparing the preliminary efficacy and sustainability of the empirically derived rTMS neural target used as a treatment site. Future work will validate the customized AUD+mTBI rTMS site in a larger-scale study examining optimal stimulation parameters and dosing. This line of scientific work will lead to more treatment options for attenuating functional disability among veterans with AUD+mTBI.

Limitations of the Study

This study may have 3 limitations. First , the single-blind nature of this study could bias results but is also an important step for developing this novel intervention. Future, larger-scale studies should use a parallel-group design and randomly assign

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participants to sham and active rTMS groups in a double-blinded fashion. Second, the study was powered for the initial TMS target identification phase and not the RCT rTMS treatment phase. In addition, the COVID-19 pandemic significantly affected recruitment. Thus, the RCT rTMS treatment phase could be underpowered. However, the study is intended to provide *preliminary* efficacy data that will serve as foundational work for larger-scale studies. Third, the primary outcome—the WHODAS 2.0—and the secondary outcomes are self-report outcomes that are subjective in nature. However, these measures are standards in the field and encapsulate functional and symptom outcomes that we aim to improve for veterans with AUD+mTBI. Future, larger-scale TMS studies in individuals with AUD+mTBI could add rigor by adding objective measures such as alcohol sensors and clinician-rated functional outcomes that could corroborate patient self-report outcomes.

Future Work and Dissemination Plan

The next step for AUD+mTBI rTMS treatment development will be to validate whether the customized neural target or site results are generalizable in a larger scale, multisite, randomized, placebo-controlled, double-blind clinical trial. Subsequently, future trials using the validated rTMS site can examine rTMS dosing (eg, 10 vs 20 sessions) or treatment parameters (eg, 10 Hz vs 20 Hz). In parallel, the rich data collected in this study and in future trials can be used to explore which neuroimaging metrics and ARCs are most strongly associated with improvements in functional disability after rTMS treatment. Using big data approaches such as machine learning, the markers of treatment candidacy and the predictors of treatment responsiveness can be evaluated. Once the optimal rTMS neural target, dosing, and parameters are defined and validated, a standardized rTMS protocol can be implemented clinically. This protocol would include the generation of a set of optimal MNI brain coordinates to be used as the rTMS treatment site and a complementary international 10-20 EEG electrode placement site that aligns with the MNI coordinates. If clinical sites are equipped with an rTMS neural navigation system, they can input the MNI coordinates onto the averaged structural T1-weighted MRI scan within the navigation system and then register the patient to this average brain. If clinical sites are not equipped with a navigation system, the EEG placement site can be used instead because using a specific EEG placement method (eg, Beam F3) has demonstrated reasonable approximation to MRI-guided scalp sites for the left DLPFC [82].

We plan to submit the trial results to scientific, peer-reviewed journals; there are no publication restrictions. A CONSORT (Consolidated Standards of Reporting Trials) diagram will be included in the publication. We will follow the International Committee of Medical Journal Editors guidelines for authorship, and there is no intention of using professional writers.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study. A deidentified, anonymized dataset will be created and shared. Raw and normalized data will be made available in the form of Microsoft Excel files. Magnetic resonance imaging images will be anonymized and made available through the Northwestern University Research Image Processing System. Final datasets will be made available as per the Edward Hines Jr VA Hospital local policy for long-term storage and access until enterprise-level resources become available. These data will be available on request by researchers and scientists in accordance with federal guidelines and the Edward Hines Jr VA Hospital local policy. The data provided will be sufficient for anyone to perform analogous or supplemental analyses that would permit the validation of the analysis and results. The sharing of data will enable others to evaluate the data and to validate and interpret the data independently. To enable replication and ensure transparency, statistical code complementary to datasets will be made available through the Federal Interagency Traumatic Brain Injury Research Informatics System.

Conflicts of Interest

NSP is a consultant to Motif Neurotech and is on the scientific advisory board of Pulvinar Neuro. In the past 3 years, he has received clinical trial support through Department of Veterans Affairs contracts from Neurolief Inc and Wave Neuro. All other authors declare no conflicts of interest.

Multimedia Appendix 1 [PDF File (Adobe PDF File), 145 KB - resprot_v14i1e64909_app1.pdf]

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Abbreviations

ARC: alcohol-related characteristic
AUD: alcohol use disorder
AUD+mTBI: co-occurring alcohol use disorder and mild traumatic brain injury
AUDIT-C: Alcohol Use Disorder Identification Test–Consumption Questions
C-SSRS: Columbia–Suicide Severity Rating Scale
CAPRI: Compensation and Pension Record Interchange
CONSORT: Consolidated Standards of Reporting Trials
DLPFC: dorsolateral prefrontal cortex
***DSM-5*:** *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*

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DTI: diffusion tensor imaging
ED: emergency department
EEG: electroencephalography
EMR: electronic medical record
FDA: Food and Drug Administration
IRB: institutional review board
iTBS: intermittent theta burst stimulation
MNI: Montreal Neurological Institute
MT: motor threshold
mTBI: mild traumatic brain injury
PI: principal investigator
PTSD: posttraumatic stress disorder
RCT: randomized controlled trial
RRT: rapid response team
rs-fMRI: resting state functional magnetic resonance imaging
rTMS: repetitive transcranial magnetic stimulation
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SUD: substance use disorder
VA: Department of Veterans Affairs
VistA: Veterans Health Information Systems and Technology Architecture
WHODAS 2.0: WHO Disability Assessment Schedule

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Protocol

An Intervention to Support Higher Education Teachers' Teaching Processes and Well-Being: Protocol for an Intervention Study

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Abstract

Background: Higher education (HE) teachers are experiencing numerous pressures in their work, such as increased workload, rising student numbers, and declining job resources, making their well-being a crucial issue. Previous studies indicate that adopting a learning-focused approach to teaching (LFT) correlates positively with HE teachers' self-efficacy beliefs and positive emotions. Moreover, there is growing evidence that mindfulness-based interventions can enhance teachers' well-being and teaching processes.

Objective: This study aims to describe the design of an intervention developed for higher education teachers to support their teaching processes and well-being. The aim of the intervention is to help teachers reflect on their own teaching, offer tools to use learning-focused teaching methods, and increase teachers' ability to define the problem and use learning-focused teaching methods using guided reflection and mindfulness-based practices.

Methods: We developed an intervention in which the teachers participate in 4 group meetings and 2 individual guided reflection sessions (before and after all the group meetings). All group meetings and guided reflection sessions were conducted online via Zoom (Zoom Video Communications). Between the group meetings, the participants independently complete self-study assignments and mindfulness-based exercises available on the Moodle platform. In the guided reflection sessions, the teachers reflect on their previously video-recorded teaching situation together with a researcher. During the video-recorded teaching situation, the teacher wears a Moodmetric smart ring measuring the teacher's arousal level, and episodes with different arousal levels (high, low, and changing) are presented to the participants in the guided reflection sessions. To examine the relations between higher education teachers' teaching processes and well-being, and the intervention's effects, we collect longitudinal data before and after the intervention with various methods (eg, experience sampling, interviews, and surveys).

Results: The recruitment of the intervention participants took place in the fall of 2023 from 9 HE institutions in Finland. Altogether, 56 teachers participated in the first part of the intervention (baseline measurement and guided reflection), and 37 participants completed the intervention in spring 2024 by participating in the second guided reflection session and data collection phase. In addition to these 37 participants, 7 teachers who were not able to record their teaching in the second data collection phase but who had still participated in the group meeting and done mindfulness practices, were interviewed about their experiences. The data collection is still ongoing, and additional data will be collected during the academic year 2024-2025.

Conclusions: This study aims to contribute valuable insights into the relations between higher education teachers' teaching processes and well-being, and how an intervention consisting of guided reflection, group meetings, and mindfulness-based practices may enhance teachers' awareness of how their teaching is related to well-being and ways to influence it.

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KEYWORDS

well-being; higher education; teachers; approaches to teaching; guided reflection; mindfulness; arousal; pedagogical awareness

Introduction

Background

Within higher education (HE), the significance of teacher well-being has been highlighted for various reasons, including increased work intensity, consumer-oriented practices, growing student numbers, and declining job resources and stability [1-5]. Supporting teachers' well-being is important not only for individual teachers' overall health but also for their students' learning [6] and well-being [7], as well as for the teachers' employers from the perspective of teacher attrition and satisfaction [8].

Previous studies on HE teacher well-being have identified several factors that can influence it, such as relationships with colleagues and students, organizational demands and resources, and personal resources. However, considering the characteristics of the teaching profession, it is striking that the role of teachers' pedagogical competence and what kind of teaching processes teachers adopt has been largely neglected in studies exploring HE teachers' well-being. Previous studies suggest that adopting a student-focused approach to teaching correlates positively with HE teachers' self-efficacy beliefs [9,10] and positive emotions [11], indicating its potential relevance for their well-being as well.

Thus, this study aims to describe the design of an intervention developed to support HE teachers in their teaching processes and well-being. The intervention is based on guided reflection, group meetings, and mindfulness-based practices with an aim to increase the teachers' awareness of how their teaching is related to well-being and ways to influence it. To examine the relations between HE teachers' teaching processes and well-being, and the intervention's effects, we collect longitudinal data before and after the intervention.

Approaches to Teaching and Pedagogical Awareness

Approaches to teaching describe what kind of teaching processes teachers adopt, and they mirror the teachers' pedagogical competence [12-14]. In a learning-focused approach to teaching (LFT), teachers pay attention to the amount and quality of teacher-student and student-student interactions and different methods to activate students' previous knowledge and their own thinking, in other words, support constructive learning [15]. They flexibly use a wide range of teaching and assessment methods to engage and activate their students according to the situation and reflect on their own actions in the teaching-learning situation. The use of these LFT methods is crucial also in enabling students' ability to reflect and regulate their learning, relate ideas, and think critically, which in turn have shown to be in relation to students' well-being and positive experiences in the HE context [16-18].

Moreover, LFT is often associated with teachers' ability to reflect on their own teaching, leading to increased pedagogical awareness [13]. Previous research among HE teachers has shown that teachers' awareness of their teaching processes is important for their pedagogical development [13,19]. Reflection is an essential part of teacher development because when thinking deeply about their teaching and experiences, teachers can identify different aspects of the teaching situation and gain greater awareness of their choices [20]. In addition, short pedagogical training has been found to increase HE teachers' ability to use pedagogical awareness in situational teaching practices [21].

Previous self-report-based research suggests that when teachers learn to adopt more LFT, they feel more positive emotions about their teaching tasks [11] and score lower on scales that measure burnout risk [9]. However, contradictory results have also been found during the COVID-19 pandemic as teachers who typically adopted reflective, learning-focused, and interactive teaching approaches in contact teaching have experienced online teaching as challenging, and thus, been the most stressed [22]. Therefore, our research aims to shed further light on the associations between teachers' LFT, pedagogical awareness, and well-being.

Mindfulness to Enhance HE Teachers' Well-Being

In response to teachers' increasing stress and high attentional and emotional demands at work, mindfulness-based training has been proposed as an intervention to support and enhance teachers' well-being and performance as a teacher. Mindfulness is defined as "a kind of nonelaborative, nonjudgmental, present-centered awareness in which each thought, feeling, or sensation that arises in the attentional field is acknowledged and accepted as it is" [23]. Importantly, teachers' emotions have been shown to influence their students' emotions and learning [24,25]. Mindfulness may help teachers to be more proactively aware of their daily emotions, and through this, not only protect and enhance their well-being but create a positive classroom climate that supports students' active learning [26].

The mindfulness-based interventions (MBIs) for teachers primarily focus on enhancing mindfulness, alleviating stress, anxiety, and feelings of burnout, and improving well-being more broadly [27,28]. In support of using MBIs in an educational context, a recent meta-analysis [28] showed that mindfulness-based interventions can increase teachers' feelings of mindfulness, and alleviate stress, anxiety, and feelings of depression and burnout. Besides investigating how MBIs can alleviate negative mental health outcomes, several recent MBI studies have also focused on the positive aspects of well-being, such as positive affect, life satisfaction, and self-compassion (for systematic reviews, [27,29]). Taken together, a growing body of evidence provides evidence that MBIs have the potential to enhance teachers' well-being and teaching processes. Therefore, we adopt mindfulness-based practices in our intervention to support teachers' well-being and ability to use LFT methods in teaching.

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HE Teachers' Well-Being

In previous studies, HE teachers' well-being has been conceptualized broadly and diversely, and no widely accepted definition of the concept exists [30-32]. Previous studies have explored it with a predominant focus on stress, burnout, and psychological well-being [33-37]. For instance, [33] recently conducted a review analyzing burnout syndrome among university educators, identifying stress-related causes (eg, work overload) and associated consequences (eg, health issues), alongside factors contributing to variations in stress levels. Similarly, [34] explored antecedents, correlates, and outcomes of faculty burnout, while [35] delved into factors influencing academic psychological well-being, emphasizing adverse effects such as stress, burnout, and negative emotions.

While acknowledging the significance of stress, burnout, and other adverse elements in HE teachers' well-being, focusing solely on these negative aspects presents a limited view of the phenomenon. Indeed, scholars have advocated for incorporating a positive perspective into the study of well-being to develop a more holistic understanding [36,38]. Thus, in our intervention study, we understand HE teachers' well-being as encompassing negative components, such as stress, burnout, and negative emotions, as well as positive facets like job satisfaction, work engagement, and positive emotions.

Aims and Research Questions

The main aim of this protocol study is to describe the design of an intervention developed to support HE teachers' well-being and teaching processes. We also aim to describe the data collection of longitudinal multi- and mixed methods data that are used to analyze the relationships between HE teachers' teaching processes and well-being, and for intervention evaluation. To evaluate the effects of the intervention, we aim to answer the following research questions in the forthcoming empirical publications:

- RQ1: what are the associations between the LFT (interaction, constructive approach, and pedagogical awareness) and well-being (ie, burnout, teaching satisfaction, emotions, and stress) on a general level?
- RQ2: what is the impact of the intervention on the relations between LFT, physiological arousal, and emotional states in teaching situations?
- RQ3: what is the impact of the intervention over time (and compared to the control group) on (1) approaches to teaching and pedagogical awareness and (2) well-being (ie, burnout, teaching satisfaction, emotions, stress?

Methods

Recruitment and Participants

Participants were recruited from 9 different HE institutions in Finland. The HE institutions were selected based on availability, and the aim was to recruit participants evenly from both the universities and the universities of applied sciences, and from different geographical locations in Finland. The recruitment of HE teachers for the intervention involved advertising through diverse communication channels within participating HE institutions, including intranets, social networking sites, and email lists.

Participants were eligible to participate in the study and the intervention if they were:

- Teaching at a university or university of applied sciences during the academic year 2023-2024.
- Willing and interested in participating in the entire research period carried out during the academic year.
- Willing and interested in participating in group meetings using peer support.
- Able to use the Moodmetric smart ring for 2 weeks during the research period.

The intervention was conducted in Finnish; thus, participating in it required proficiency in the Finnish language. For this reason, participants who were not proficient in Finnish were excluded from participating in the intervention.

Intervention Design

The aim of the intervention is to help teachers reflect on their own teaching, offer tools to use LFT methods, and increase teachers' ability to define the problem and use LFT methods using guided reflection and mindfulness-based practices.

The framework for the intervention was initially developed by the first 3 authors. This development process involved designing 3 distinct elements for the intervention: training in LFT methods, mindfulness-based stress reduction (MBSR), and reflection on teaching practices. For the MBSR component, the initial structure and content were reviewed and consulted with a certified MBSR instructor. Following this consultation, the structure and content were revised accordingly. Subsequently, the focus shifted to training in LFT methods. The pedagogical content of the sessions was tested through a pilot involving a group of HE pedagogy experts. Based on the feedback from these experts, the content was further refined and revised. Lastly, the guided reflection sessions were designed to enhance the participants' reflective practices. This development was a collaborative effort involving all the authors, and it was informed by previous research and theories on guided reflection.

The intervention follows the framework of "Constructivist curriculum" [39] in which participants' reflective learning process is guided by using social interaction, activating previous knowledge, authentic learning experiences, and cooperative dialogue. The learning objectives of the intervention are described as follows: after the training, the participant (1) can teach and guide university students interactively and support their own well-being; (2) recognize the elements of good teaching and guidance and use them in their own teaching, guidance, and teaching development; and (3) become aware of their own pedagogical choices and how to support their own well-being in different teaching situations.

During the intervention, the teachers participate in 4 group meetings and 2 individual guided reflection sessions (before and after all the group meetings). All the group meetings and guided reflection sessions are conducted online via Zoom (Zoom Video Communications). Between the group meetings, the participants independently complete self-study assignments and

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mindfulness-based exercises available on the Moodle platform. The participants have 2 weeks to complete the assignments between the first and second group meetings, and 3 weeks between the following group meetings. The first group meeting lasts for one hour and the following 3 group meetings last for 4 hours (Figure 1).

Figure 1. Intervention design.

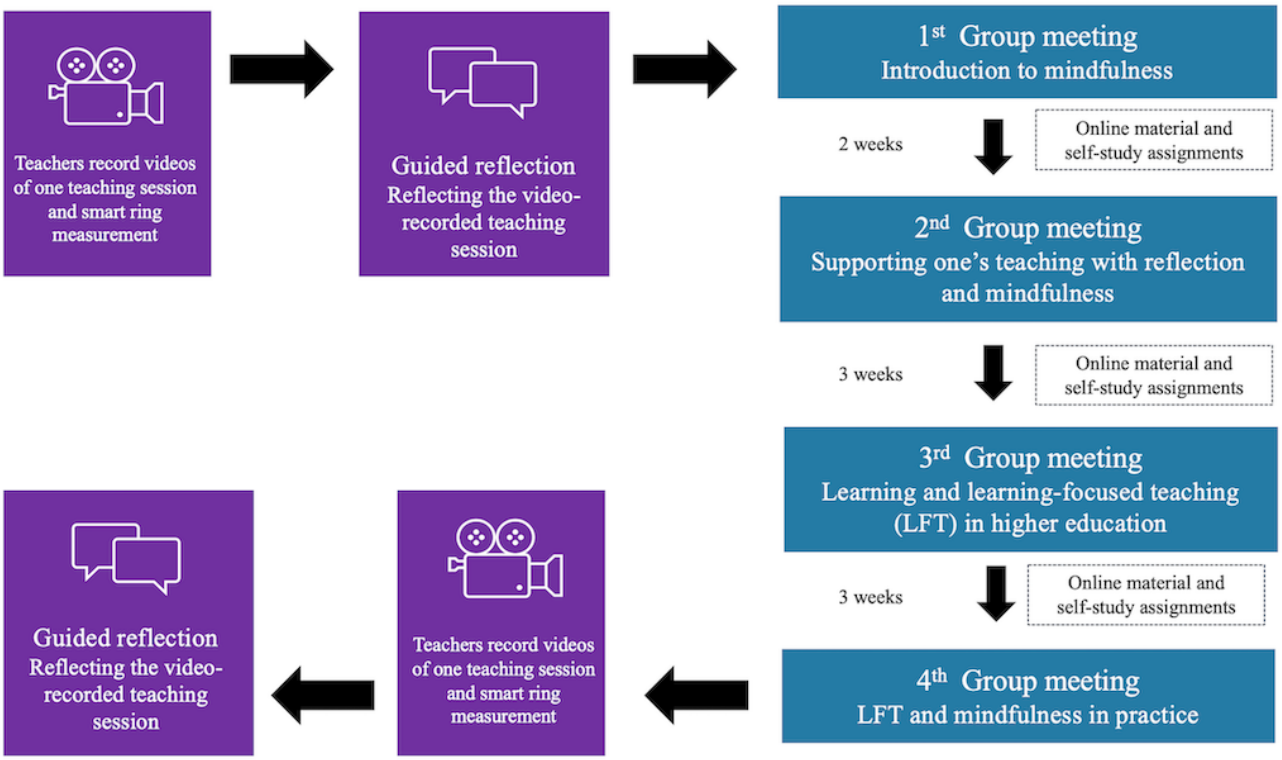

Individual Guided Reflection Session

The intervention starts and ends with a guided reflection session conducted via Zoom. Guided reflection has been found to support, for example, student teachers' ability to implement new methods for improving learning [40] and reflective competencies [20]. It is a process of self-inquiry to enable the practitioner to realize desirable and effective practices with the help of a guide [41,42].

In the guided reflection sessions, the teacher reflects on their previously video-recorded teaching situation together with a researcher. During the video-recorded teaching situation, the teacher wears a smart ring measuring arousal level, and following the critical incident technique [43,44] and stimulated recall interview method, episodes with different arousal levels (high, low, and changing) are presented to the participants in the guided reflection sessions. After watching each episode, the teachers are asked to reflect on what happened during the episodes, what could have influenced their arousal level, and their associated feelings.

Group Meetings

All the group meetings are arranged in Zoom. The group meetings follow the Constructivist curriculum [39] and the following elements are included in every session. Every session starts with a discussion of the previous session's topics, as well as participants' experiences and questions. Group discussions as well as individual reflection are used during the sessions. At the end of every session, the participants are asked to join a learning discussion on the Moodle learning platform in which they reflect on what was important for them after each session. Mindfulness practices are used during the different sessions.

First Group Meeting: Introduction to Mindfulness

During the first group meeting, the teachers are introduced to mindfulness and mindfulness-based practices, and they are given justifications for why mindfulness is selected as a method for the intervention. Mindfulness-based practices have been shown to decrease negative, emotion-focused coping (positive reappraisal and defensive strategies) and increase problem-focused, positive coping strategies (defining the problem, generating alternative solutions, and taking action) [45,46], for example, teachers' ability to generate solutions and use LFT methods in teaching situations.

In this intervention, we adapt elements of the 8-week MBSR program [47]. The participants are instructed to do mindfulness practices 15 minutes per day during the 8-week intervention. Recent reviews on teachers' mindfulness interventions [28,29,48] show that while the length of the intervention varies greatly across interventions, mindfulness interventions for teachers are commonly 8 weeks long. Moreover, interventions designed for teachers that are based on MBSR often encourage teachers to engage in shorter self-practices (ie, 10-30 min instead of 45 min per day [48]). In our intervention, teachers are instructed that if they are not able to commit to such intensive practice, they can adjust the effort to their own life situation and opportunities to do the practices. They are instructed to keep a record of how many practices they do. A mindfulness expert is recruited for the intervention to guide the participants

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throughout the project to do the mindfulness practices. The participants are encouraged to follow mindfulness practices available on the Oiva web page [49] or alternatively, find and complete other mindfulness practices suitable for them. The Oiva web page is a research-based resource that offers over 40 brief mindfulness exercises in the Finnish language that can be easily completed in various settings over the course of a day.

Second Group Meeting: Supporting One's Teaching With Reflection and Mindfulness

The first part of the second session aims to increase teachers' understanding of the importance of pedagogical awareness. Participants develop their reflection skills and learn how to use reflection to promote pedagogical awareness and how to identify what is stressful and empowering in their teaching. The session includes discussions in small groups, where participants reflect on their experiences of the first guided reflection session. The second part of the session aims to increase and deepen participants' understanding of what mindfulness is, encourage them to continue practicing mindfulness and reflect on their experiences with mindfulness so far. Participants are introduced to new mindfulness exercises and instructed to first write down pleasant teaching-related experiences for one week's time and second, unpleasant teaching-related experiences for another week's time.

Third Group Meeting: Learning and Learning-Focused Teaching in HE

The third session focuses on learning and learning-focused teaching in HE. Participants are first introduced to student learning and memorization in HE through interactive learning materials. The participants familiarize themselves with the material first individually and afterward discuss together about the experiences and reflections of the content. Next, the participants will work in small groups to share experiences and thoughts on how to increase students' understanding and reflection and decrease an unreflective approach to learning a fragmented knowledge base [50] in their own teaching. Secondly, the concept of LFT is introduced to participants through a short presentation. Elements of LFT are also introduced in detail. For example, teacher immediacy is introduced as an important component of creating a safe, learning-focused teaching environment. The session also includes mindfulness practice on self-compassion.

Fourth Group Meeting: LFT and Mindfulness in Practice

The focus of the fourth session is teachers' well-being. Teachers are introduced to teaching-related well-being concepts, such as emotions, self-compassion, psychological flexibility, self-efficacy, stress, and burnout risk. Teachers work in small groups where they share their pleasant or unpleasant teaching experiences and reflect on how they could handle and act in similar situations in the future, in real-life situations. It discusses how learning-focused teaching and mindfulness can support teachers' well-being in practice, and the teachers brainstorm in small groups on how they can use mindfulness in their teaching.

Data Collection

To answer the research questions and to evaluate the effect of the intervention, mixed methods data are collected from the participating teachers in 3 phases (Figure 2).

Figure 2. Research design. EDA: electrodermal activity.

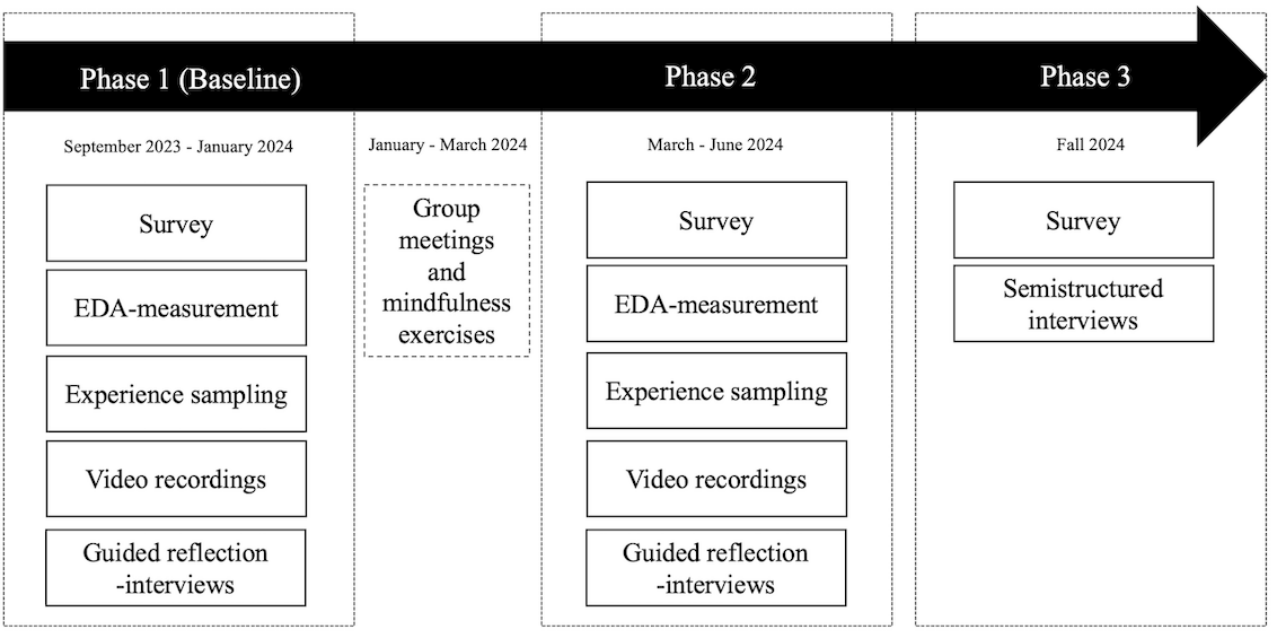

Survey

Teachers will respond to the survey 3 times during the study: once before the group meetings (baseline measurement, phase 1) and twice after the group meetings (phase 2 and 3). The survey is completed in Finnish. The survey contains 78 items from 11 scales as described below. Participants answer the survey items on a 5-point scale ranging from 1=completely disagree to 5=completely agree.

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Approaches to Teaching (HowUTeach)

It [51] is a revised and further-developed version of the Approaches to Teaching Inventory [12]. HowUTeach measures approaches to teaching through 12 items and four dimensions: (1) Interactive approach (3 items, eg, "In my teaching, I create situations where I encourage students to discuss their thoughts and opinions about the topic."); (2) Transmissive approach (3 items, eg, "The most important goal of my teaching is to deliver what I know to the students."); (3) Unreflective approach (3 items, eg, "I have trouble understanding how I can help the students to learn"; and (4) Organized approach (3 items, eg, I spend a lot of time preparing my teaching). In addition to the HowUTeach instrument, a new scale labeled as (5) Constructive approach (4 items, eg, "In my teaching, I help students to integrate the knowledge what they have learned in my course to what they've learned in other courses") is used in the research. The scale is developed from the robust and validated instrument HowULearn which measures students' approaches to learning [17,52]. We modified the scale and items to measure teachers' strategies to support students' deep approach to learning. The student version includes items focusing on students' study strategies such as relating ideas and searching for evidence, and it has been shown to be a reliable scale in previous studies (eg, =.80 in [16]).

Teacher Job Satisfaction Scale

It [53] is a 4-item scale that assesses a teacher's overall job satisfaction (eg, "I enjoy working as a teacher").

Reflection

The 4 items [54] adapted to teaching context (eg, "I sometimes question the way other teachers teach and try to think of a better way").

Mindfulness in Teaching

It [55] was measured with 13 items, 8 items measuring teacher intrapersonal mindfulness (eg, "When I am teaching, I find myself doing things without paying attention"), and 5 interpersonal mindfulness (eg, "I listen carefully to my student's ideas even when I disagree with them").

Stress

It was measured with a single-item measure of stress symptoms [56] both generally and modified to teaching context (2 items):

Stress means a situation in which a person feels tense, restless, nervous, or anxious, or is unable to sleep at night because his or her mind is troubled all the time. Have you felt this kind of stress these days/related to your teaching?

School Burnout Inventory

It [57] was adapted to measure teaching-related burnout through 9 items and 3 dimensions, exhaustion in teaching (eg, "I often sleep badly because of matters related to my teaching"), cynicism toward the meaning of teaching (eg, "I feel that I am losing interest in teaching"), and sense of inadequacy in teaching (eg, "I have often feelings of inadequacy when teaching"). This scale was originally adapted to fit to investigate burnout among HE teachers as part of the HowUTeach project [51], see also the case study by Virtanen and Parpala [10].

Self-Efficacy

It was measured with a 4-item scale from the HowUTeach questionnaire [51]. An example item is "I believe I can cope with my teaching tasks."

Self-Compassion

It was measured with a shortened Self-Compassion Scale [58,59]. The shortened 2-factor scale combines positive aspects of self-compassion (ie, self-kindness, common humanity, and mindfulness) into self-compassion factor (eg, "I try to see my failings as part of the human condition.") and negative aspects (ie, self-judgment, isolation, and overidentification) into self-criticism factor (eg, "I'm disapproving and judgmental about my own flaws and inadequacies.").

Teacher Emotions Scale

This scale [60] measures teachers' positive and negative emotions through 12 items that cover three dimensions: (1) Enjoyment (eg, "I often have reasons to be happy while I teach."), (2) Anger (eg, "I often have reasons to be angry while I teach."), and (3) Anxiety (eg, "I am often worried that my teaching isn't going so well.").

Anxiety

It is measured with a 6-item Sport Anxiety Scale-2 [61] modified for teaching context. The scale consists of two factors: (1) concentration disruption (eg, "I have trouble concentrating when teaching.") and (2) worry (eg, I worry that I will make a mistake when I am teaching.").

Ultrashort Utrecht Work Engagement Scale

The scale [62] was adapted to the teaching context to measure teachers' work engagement. Each dimension of work engagement was measured with one item: (1) Vigor (At my work, I feel bursting with energy"), (2) Dedication ("I am enthusiastic about my teaching job"), and (3) Absorption ("I am immersed in my work as a teacher").

Background Information

In the first survey, participants provide information on their demographics (ie, age and gender) and work background (ie, the type of institution they work at, discipline, work experience in HE, pedagogical training, and qualification). In the second survey, participants are asked if they have (1) completed additional pedagogical training and (2) participated in any other mindfulness training during the ongoing academic year.

Intervention Evaluation

In the postintervention survey (phase 2), participants additionally answered questions about the intervention process. They are asked to evaluate the effectiveness of the reflection sessions, group meetings, and mindfulness exercises on their (1) general well-being, (2) teaching-related well-being, and (3) development as teacher (understanding teaching and learning processes) on a scale from 1 ("not at all useful") to 7 ("extremely useful"). They are also asked to evaluate the level of effort they put into participation in the intervention, how demanding they experienced participating in the intervention to be, and their overall satisfaction with the intervention on a 7-point Likert scale. Finally, participants have an opportunity to leave any

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additional comments about their experience with the intervention.

Weekly Mindfulness Reports

During the intervention period, participants receive 9 weekly reminders to report in Webropol (1) how many times and (2) how many minutes they have completed mindfulness exercises during the previous week.

Electrodermal Activity Measurement

This study will use a nonintrusive method to collect objective data from teaching situations. To capture participants' arousal levels during different teaching-related situations, data will be collected via electrodermal activity (EDA) measurements from the participants during 2 one-week measurement periods (phases 1 and 2). The motivation for measuring arousal with EDA (instead of using, eg, heart variability rate) is based on its connection to unconscious emotional responses [63]. We will use an ambulatory biosensor (Moodmetric smart ring; Vigofere Ltd) to measure EDA from the eccrine sweat glands of palmar skin from the hand [64]. It detects skin conductance from the hand wearing the ring. The ring's algorithm transforms the physiological level of sweat to a within-person standardized value (range 1-100), filtering out bodily movement. Measurement accuracy is close to that of nonambulatory, heavy-duty laboratory equipment [65].

Experience Sampling

Participants will report their teaching-related emotional states [66] using the experience sampling method (ESM) [67] during the two EDA measurement periods (phase 1 and 2). The Learning Tracker (LT) smart device application (iOS and Android) [68] is designed to allow participants to self-report their perceived emotions immediately before and after authentic teaching-related situations. Should the participants experience technical issues with the use of the LT application, they can instead respond via a Webropol survey, which contains the same content as the application. During the analysis phase, this longitudinal, discrete data (user-indicated, teaching-related sequences) will be merged with arousal-level data from the smart ring.

Video Recordings

All the participants will video-record 2 approximately 60-minute-long teaching situations (during phases 1 and 2). Video data are collected to detect positive and negative teaching episodes and to analyze them further in relation to arousal level, emotions, and LFT. The video recordings of the teaching sessions are done through Zoom, Teams, or with a video camera. The teachers themselves can choose which teaching sessions they want to video-record. The sessions can be face-to-face, synchronous online, or hybrid teaching sessions. If face-to-face or hybrid, the teacher is asked to locate the computer's camera so that it can observe the teacher. Permission to video-record and use the recordings for research will also be asked from the students using a Webropol survey [69].

Episodes with high arousal levels are identified by synchronizing participants' EDA level (arousal) data and LT data (emotions) with video data. Episodes are also analyzed through the level of LFT, and how it is manifested in the teaching situations (the use of student-activating methods). Following the coding approach of [70], high arousal episodes are segmented based on LFT and emotional states, and they are analyzed using patterns and temporal order.

Guided Reflection—Interviews and Semistructured Interviews

Teachers' guided reflection sessions will be used as qualitative data. The guided reflection-interviews are semistructured in nature and guided by a list of open-ended questions. In addition to focusing on reflecting on the video-recorded (high, low, and changing) arousal episodes, the teachers are asked general questions related to describing the video-recorded teaching session and their overall teaching experiences. The interview questions are the same in phases 1 and 2, with the exception that in phase 1, the teachers are asked to recall empowering and challenging teaching situations, whereas in phase 2, they are asked to describe themselves as teachers and what they regard as important. In phase 2, the teachers are also asked questions related to intervention evaluation.

Semistructured interviews will also be conducted with voluntary participants in fall 2024 (phase 3) to qualitatively assess the long-term effect of the intervention on their teaching processes and well-being. Before the interviews, participants will receive an individualized summary of their survey results via email. This summary will include their personal results from surveys conducted in phases 1 and 2, focusing on scales measuring approaches to teaching, stress, and teacher job satisfaction. During the interview, teachers will be asked to reflect on their survey answers, including any thoughts the results provoke and, if changes are observed in their answers between phases 1 and 2, what they believe might have contributed to them. In addition, teachers are asked to evaluate the significance of the intervention and discuss more generally the factors they perceive as influencing their well-being as teachers.

Analytical Approaches

Given the risks of both recruiting a sufficient number of participants and the potential for attrition (typical of longitudinal studies), we designed the study so that statistical analyses could be conducted using a within-subject design (without a control group). The required sample size for the within-subject design analyses is 33 participants, based on conventional power levels set to .80 (β=.20) and an α level of .05. However, we also aim to collect a representative control group data and perform analyses using a between-subjects design. In qualitative research, sample size can be flexibly determined based on the richness of the data and saturation [71], one guideline being that 12 interviews are sufficient for thematic saturation [72].

The survey data will be merged with the longitudinal discrete ESM data (user-indicated, teaching-related sequences) from the LT application and continuous EDA data from the smart ring. The resulting panel data will be analyzed using nonlinear and linear mixed-effects methods in the R statistical computing environment [73] using the nlme [74] and brms [75] packages. In the analyses, time-invariant survey data and time-variant

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ESM and EDA data serve as Level 1 indicators, while the clusters (teachers) are at level 2.

All interviews are recorded, pseudonymized, and transcribed for analysis. ATLAS.ti (Lumivero, LLC) software is used to aid the data analysis. The analysis will be conducted in researcher teams, and the data will be analyzed by more than one person. The research team members conducting the analysis will frequently meet to discuss the analysis and solve any discrepancies. The intercoder agreement is calculated when considered suitable. The qualitative interview data will be analyzed with both inductive and deductive qualitative content analysis, taking into account both latent and manifest content [76,77]. The applied approaches of the qualitative analysis will take different forms in the published articles.

Ethical Considerations

The research follows strictly the ethical guidelines formatted by the Finnish National Board on Research Integrity [78]. The research was also ethically reviewed in November 2022 by the Human Sciences Ethics Committee of the Helsinki Region Universities of Applied Sciences with a positive decision (statement number: 20/2022) [79].

Prospective participants were guided to the project website for comprehensive details about the intervention and access to a Webropol survey to sign up for the study. Upon providing their contact information, researchers contacted them to agree on the next steps of participation. Before the intervention, each participant met with a member of the research team either online via Zoom or in-person to sign an informed consent form and receive instructions on how to record one of their teaching sessions, sign up for the experience sampling application, and use the smart ring needed for the measurement period. Participation was voluntary and participants could withdraw at any time. A privacy notice is prepared for research participants to inform them about how their personal and other data will be collected, used, stored, and protected. All participant data are handled and combined using assigned ID codes. Data are maintained accordingly for analysis and verification purposes for 5 years after the project's end. When storing the data, all identifiers will be removed, and the data anonymized (data files containing personal data and participant IDs are erased). Participants did not receive compensation for their involvement; however, they were awarded a certificate of attendance upon completing the intervention upon request.

Results

The data collection is ongoing. The recruitment of the intervention participants took place in the fall of 2023. As of June 2024, the intervention participants completed phase 2 of the data collection. Phase 3 data were collected in autumn 2024. Moreover, to evaluate the effectiveness of the intervention on HE teachers' LFT and well-being - compared to teachers who do not undergo the intervention - we aim to collect survey data from teachers working in the same HE institutions as the intervention participants. These teachers will form a control group. The additional survey data will be collected during the academic year 2024–2025.

Altogether, 68 teachers committed to participating in the baseline data collection in fall 2023. Of these 68 teachers, 64 (94%) answered the first survey, and 61 (90%) provided a video recording of their teaching. As part of the intervention, 56 (82%) teachers participated in the first individual guided reflection session. In spring 2024, after participating in the group meetings and completing mindfulness-based practices, 37 (54%) participants completed the intervention by participating in the second guided reflection session. This also marked the completion of the second data collection phase. In addition, 7 (10%) teachers who were not able to record their teaching but had still participated in the group meetings and done mindfulness practices answered the second survey and were interviewed about their experiences. In phase 3, 43 (63%) participants answered the third survey, and 19 (28%) of them also participated in the semistructured interviews.

Discussion

Overview

Our intervention study is expected to shed light on how a relatively brief intervention for HE teachers may yield positive effects on pedagogical processes and well-being. Recent research shows that even a short pedagogical training may contribute to HE teachers' pedagogical development and adaptation of LFT methods [21]. Especially the social aspect of reflection (ie, peer support and feedback) has been identified as an important component of the professional development of HE teachers [80]. In our intervention, in line with the framework of the constructivist curriculum [39], we use guided reflections and group meetings to stimulate the social aspects of HE teachers' reflection. Moreover, we combine this with 8-week long practice of mindfulness, which is expected to provide teachers a proactive way to become more aware of their present emotions and thoughts, and through this contribute to students' learning and their own well-being [26]. By examining positive well-being outcomes (eg, work engagement and job satisfaction) in addition to deficit-based mental health outcomes (eg, stress and burnout), we also address the call for future MBIs to focus more on positive well-being constructs, such as work engagement [27].

In this intervention study, we combine research on teaching processes and well-being—2 research areas that have previously been explored separately. By doing so, we contribute to a deeper understanding of how pedagogical competence, along with the ability to cope with emotions and stress during teaching, will impact HE teachers' well-being. Moreover, as previous research has largely focused only on schoolteachers' well-being, this study will provide important new knowledge about HE teachers' well-being. Importantly, the intervention study allows for a comparison of the short- and long-term impact of an intervention focusing on increasing LFT on teachers' well-being (both physiological and self-reported). The longitudinal multi- and mixed methods design of the study provides valuable information concerning the effects of a professional development program promoting reflection and mindfulness on teaching processes and well-being.

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There are several limitations that are worth considering when interpreting the design of this intervention study. First, the intervention includes many elements that place a burden on teachers, such as recording their own teaching, learning to use LT and smart ring, responding to a smartphone application, participating in guided reflections, and attending multiple group meetings. Thus, as the participants were self-selected, it can be assumed that the teachers who chose to participate in the intervention were exceptionally motivated and possessed certain personal characteristics, such as an interest in mindfulness and self-development, compared to other teachers. However, considering the benefits gained from the intervention, self-selectors have been found to benefit more from interventions compared to non–self-selected participants [81].

Second, one methodological limitation is the reliance on self-report data. This is particularly problematic from the perspective of social desirability bias, meaning that participants may, for example, overestimate the effects of the intervention or respond to questions in a socially desirable manner. In the video-recorded stimulated recall -interviews the teachers relive the video-recorded teaching session, and this viewing-relieving process can be very stressful, and teachers' insecurity, self-confidence, and personal perceptions can influence what they are willing to mention during the interviews. Thus, to control the teachers' anxiety, a judge-free interview atmosphere is important [82].

Third, this intervention study includes only HE teachers. However, it would have also been useful to include the students' perspectives to retain a more holistic view. Thus, adding student perspectives could be considered when designing similar interventions in the future. Moreover, since discussing one's feelings and well-being is easier in one's native language, only teachers proficient in Finnish were eligible to participate in the intervention. However, there is a need to implement similar interventions in the future for migrant and international teachers who are not fluent in Finnish, considering that they encounter numerous challenges that potentially challenge their well-being, professional identity, and self-efficacy in teaching.

Conclusions

Overall, our study aims to contribute valuable insights into the relations between HE teachers' teaching processes and well-being, and how an intervention consisting of guided reflection, group meetings, and mindfulness-based practices may enhance teachers' awareness of how their teaching is related to well-being and ways to influence it. The implications of this study may contribute to the development of future relatively brief interventions and courses to support HE teachers' pedagogical awareness and well-being.

Acknowledgments

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Conflicts of Interest

None declared.

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Abbreviations

EDA: electrodermal activity
ESM: experience sampling method
HE: higher education
LFT: learning-focused approach to teaching
LT: Learning Tracker
MBI: mindfulness-based intervention
MBSR: mindfulness-based stress reduction

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Protocol

Intervention for Justice-Involved Homeless Veterans With Co-Occurring Substance Use and Mental Health Disorders: Protocol for a Randomized Controlled Hybrid Effectiveness-Implementation Trial

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Abstract

Background: The US Veterans Affairs mental health residential rehabilitation treatment programs (MH RRTPs) provide residential care for veterans experiencing homelessness. However, those with co-occurring mental health and substance use disorders and criminal legal involvement require additional interventions to address risk factors for recidivism.

Objective: We aimed to (1.1) evaluate whether the Maintaining Independence and Sobriety through Systems Integration, Outreach, and Networking Criminal Justice version (MISSION-CJ) intervention lowers criminal recidivism and improves health-related outcomes; (1.2) examine the mechanisms that impact outcomes; and (2) qualitatively assess the implementation of MISSION-CJ.

Methods: Veterans participating in an MH RRTP (N=226) will be randomized to the enhanced usual care (EUC) or MISSION-CJ conditions in a hybrid type 1 randomized controlled trial to test the effectiveness and implementation of MISSION-CJ, a multicomponent intervention for co-occurring disorder. Both conditions will receive 6 months of services beginning within a week of MH RRTP enrollment (duration of stay: 3 months) and continue for 3 months after the MH RRTP in the community. The veterans in the EUC group (113/226, 50%) will receive a peer support curriculum and community outreach and linkage delivered by a peer support specialist. The veterans in the MISSION-CJ group (113/226, 50%) will receive team-based (case manager and peer support specialist) care, including treatment planning, case management using a critical time intervention model to promote referrals and linkages, enhanced dual recovery therapy sessions, and peer support sessions. Assessments, including questions regarding substance use and mental health history, criminal history and recidivism risk, housing, employment, medication adherence, mutual-help group attendance, antisocial attitudes, affiliations with peers, community involvement, and treatment services received, will be conducted at baseline and 6 months and 15 months after baseline. We will use generalized linear mixed effects regression models to evaluate MISSION-CJ based on outcomes (objective 1.1). We will conduct mediation analysis to

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examine mechanisms of action (objective 1.2). For the qualitative evaluation (objective 2), we will use thematic analysis to identify themes.

Results: As of March 2025, 118 veterans (site 1: n=52, 44.1% and site 2: n=66, 55.9%) have been enrolled. Overall, 58 veterans (site 1: n=27, 47% and site 2: n=31, 53%) have been randomized to the MISSION-CJ group, and 60 veterans (site 1: n=25, 42% and site 2: n=35, 58%) have been randomized to the EUC group. Overall, 23 interviews for the qualitative evaluation have been completed with veterans. Veterans are continuing to receive treatment and completing follow-up assessments. The findings from this trial and qualitative evaluation will be available by 2026. The quantitative and qualitative components of this project are intended to work synergistically to reinforce knowledge of MISSION-CJ's effectiveness, implementation, and scalability.

Conclusions: If effective, the implementation of MISSION-CJ alongside the MH RRTPs may be advantageous to address risk factors related to recidivism.

Trial Registration: ClinicalTrials.gov NCT04523337; https://clinicaltrials.gov/study/NCT04523337

International Registered Report Identifier (IRRID): DERR1-10.2196/70750

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KEYWORDS

criminal justice; mental health; substance use; co-occurring disorder; veterans; hybrid trial

Introduction

Background

Each year, 146,000 veterans in the United States are released from correctional settings [1], with estimates being even higher when accounting for veterans who have been diverted from incarceration. Veterans with current or previous involvement in the criminal legal system [2,3] (vs those without such involvement) have higher rates of behavioral health conditions [4], with 60% of them diagnosed with a co-occurring disorder (COD) and mental health and substance use disorder [5]. In addition, veterans with criminal legal involvement and a COD often have other needs associated with behavioral health, such as unemployment and homelessness [6], and consequently, they are at greater risk for criminal recidivism [7-9]. Veterans who are incarcerated are ineligible for Veterans Affairs (VA) services [10], rendering recidivism a critical issue to address, as it disrupts access to VA services that address substance use, mental illness, and other medical comorbidities, all of which are highly prevalent among veterans with criminal legal involvement, thus resulting in long-term health disparities [9,11-13].

The VA mental health residential rehabilitation treatment programs (MH RRTPs) [4] provide an average of 3 months of residential care to veterans experiencing homelessness, many of whom have high rates of COD and criminal legal involvement [14]. While MH RRTPs assist veterans with addressing homelessness, mental health, and substance use, they often do not provide specialized care for those with COD and criminal legal involvement. This is a concern as veterans with COD and criminal legal involvement enrolled in MH RRTPs are particularly vulnerable to poor treatment engagement and adherence [15,16], and have higher rates of being irregularly discharged (ie, leaving treatment prematurely) from MH RRTPs [17]. Retention in MH RRTPs and engagement in continuing care services reduce the likelihood of rehospitalization and other costly acute medical services [18,19]. However, criminal recidivism disrupts the continuity of care and increases costly acute care service use and, in turn, reentry into residential programs [20,21]. Other reports indicate that low engagement among veterans with criminal legal involvement is due to COD; competing behavioral health needs; and practical barriers such as transportation, homelessness, and misunderstanding of VA eligibility [6,16,22-30]. Because of the multifaceted behavioral health needs of this population coupled with poor treatment engagement, veterans with criminal legal involvement may benefit from more comprehensive, wraparound interventions (eg, a community-based intervention that provides a variety of services and treatment to support needs and care transitions) [31] to reduce service fragmentation, criminal recidivism, and improve behavioral health symptoms and functioning [32,33].

The Maintaining Independence and Sobriety through Systems Integration, Outreach and Networking (MISSION) intervention was developed to address the needs of veterans and civilians with a COD experiencing homelessness. MISSION is a multicomponent, evidence-based, wraparound treatment intervention that is delivered by a case manager and peer support specialist team and includes materials to support its implementation (eg, treatment manual and participant workbook). To ensure fidelity [34,35], MISSION integrates three evidence-based core components to address COD: (1) critical time intervention, a time-limited assertive community treatment that addresses situational and motivational barriers to engagement in care [36-38]; (2) dual recovery therapy (DRT), comprising psychoeducational sessions that provide integrated care for mental health and substance use (Ziedonis, DM, unpublished manual, May 2005) [39]; and (3) peer support, a peer curriculum of structured standardized sessions, supporting veterans use of community recovery activities (eg, attending mutual support groups) delivered by a person with lived experience, and facilitating homework assignments to reinforce knowledge discussed in groups [40-42]. While much evidence supports MISSION components individually, when combined, they complement each other in meeting the needs of individuals with CODs [31,43-48]. To address the unique needs of veterans and civilians with COD and criminal legal involvement, an adaptation of MISSION, the criminal justice (MISSION-CJ) version was developed (Pinals, DA, unpublished manual, April 2014 and Smelson, D, unpublished manual, June 2014). MISSION-CJ is guided by the risk-need-responsivity framework

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of offender rehabilitation, which posits that rehabilitation should target "criminogenic needs" (ie, modifiable factors that are robust predictors of recidivism) [49,50]. Thus, MISSION-CJ enhances the DRT curriculum with additional sessions to address antisocial attitudes and behaviors (Gaba, A, unpublished manual, January 2020).

This Study

The MISSION-CJ intervention has been evaluated in other criminal legal settings (ie, reentry support and treatment court settings), and has evidenced reductions in substance use, mental health symptoms, and criminal recidivism [51-54]. However, MISSION-CJ has not been tested in VA MH RRTP settings. Considering the previous effectiveness of MISSION-CJ and the increasing need for comprehensive COD treatment for veterans involved in the criminal legal system, a critical next step is to understand how MISSION-CJ complements MH RRTP treatment to improve the behavioral health outcomes of veterans with criminal legal involvement and COD. Notably, MISSION-CJ provides an opportunity for a paradigm shift in VA care by offering a hybrid treatment and linkage intervention that simultaneously addresses recidivism and behavioral health outcomes and thus could improve care for veterans with criminal legal involvement. Therefore, the study described in this protocol paper will simultaneously test the effectiveness and implementation of MISSION-CJ in MH RRTPs for veterans with criminal legal involvement and COD.

Methods

Study Design

Using a hybrid type 1 effectiveness-implementation design [55], we will test the effectiveness of the MISSION-CJ intervention in a randomized controlled trial (RCT) across 2 large VA health care systems as well as conduct a qualitative evaluation of MISSION-CJ's implementation. Hybrid type 1 designs are beneficial as they allow for simultaneously examining the effectiveness of an intervention (primary aim), mechanism analysis (secondary aim), as well as the intervention's implementation potential (secondary aim) [54]. The *primary aim* of this study is to evaluate whether *MISSION-CJ in addition to the usual MH RRTP care* in comparison to *enhanced usual care (EUC)* lowers criminal recidivism and improves other health-related outcomes (ie, substance use, mental health, housing, and employment) and whether the effects of MISSION-CJ on recidivism and other health-related outcomes are mediated (secondary aim) by reductions in antisocial attitudes; reductions in affiliations with antisocial peers and increases in affiliations with prosocial peers; greater treatment engagement and service use (ie, MH RRTP completion, substance use or mental health continuing care, and mutual support group attendance); and increased community integration measured at 6 months and 15 months after baseline. In addition, the *secondary aim* of this study is to qualitatively evaluate MISSION-CJ using the RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) framework.

Setting: VA MH RRTPs

Veterans will be recruited from VA MH RRTPs at 2 large VA health care systems in the United States. MH RRTPs provide treatment and rehabilitation services to veterans to address their complex behavioral health needs. Services are designed for improving functional status, sustaining treatment and rehabilitation gains, recovery, and community integration. At each VA site, we will recruit from a specific type of MH RRTP for veterans experiencing homelessness, which aims to improve their health and facilitate community reintegration by providing 24/7 care using a structured residential environment. MH RRTPs are comparable across VA sites in terms of program structure and services delivered; program duration (an average of 3 months); individual and group-based clinical approaches, such as cognitive behavioral programming; and staffing (psychiatrists, psychologists, social workers, nurses, addiction therapists, vocational therapists, and homelessness coordinators).

RCT Participants

Overview

Veterans who (1) are entering an MH RRTP, at either of the 2 VA health care systems; (2) were arrested and charged or released from incarceration in the past 12 months; and (3) have a COD diagnosis in their medical record will be eligible for participation. Diagnoses will be confirmed during screening using the Structured Clinical Interview for the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* [56]. The only exclusion criterion is cognitive impairment, which will be assessed using the Montreal Cognitive Assessment's section on Orientation. Veterans who are unable to correctly answer the date and location items will be deemed too cognitively impaired to understand the study's procedures, participate meaningfully in the study, and respond to interviews, and therefore will be ineligible.

Sample Size Determination

To ensure sufficient variability in our outcomes and increase the power to test study hypotheses, power analyses were calculated to determine the sample size needed to obtain a medium-to-large effect size (based on the 3 open pilots with MISSION-CJ) with 80% power [57]. To account for having veterans at 2 sites, power analyses using G*Power were based on having 4 cells (2 conditions per site) [58]. A sample size of 180 (90 in each condition) will provide 91% power to detect a medium-large effect size at an α of .05 (2-tailed test). On the basis of an N of 180 and of .05, we would have 80% power to detect a Cohen f=0.25, a medium size effect [57]. Thus, after accounting for attenuation and 20% attrition [31,59,60], we will recruit 226 veterans (113 per condition). The sample will be stratified by site such that 113 veterans (with rounding) will be recruited separately from each VA site, with 57 veterans (with rounding) entering each condition at each site. The sites were selected because they have MH RRTPs that serve a high volume of veterans with criminal legal involvement and a COD; have criminal legal system outreach specialists, which will maximize recruitment by increasing the pool of veterans that could be referred to the MH RRTPs; and provide geographic variability, which will increase the generalizability of the findings.

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Recruitment for RCT

MH RRTP staff will screen veterans during their admissions process to determine their eligibility. Potentially eligible veterans will be contacted by a research assistant who will explain the purpose of the study, procedures, and risks and benefits of participation. Veterans will be informed that they will be assigned to either an average of 2 hours of additional programming via a peer support group with community outreach care (EUC) or an intervention which provides an average of 2 hours of additional programming weekly, delivered by a MISSION-CJ treatment team. Veterans will be asked to complete an in-person baseline assessment and 2 follow-up assessments (in-person or via phone) 6 months and 15 months (ie, approximately 1 year post-MH RRTP discharge for those not irregularly discharged) later. Veterans will be compensated US $25 for completion of the baseline, US $50 for the 6-month assessments, and US $75 for the 15-month assessments.

Randomization

After completion of the baseline assessment, 226 participants will be randomly assigned to either the EUC or MISSION-CJ condition. Randomization will be done using an SAS macro. Randomization will occur in blocks of 6 to prevent runs that might lead to unequal N's between conditions if the full sample is not obtained. Following the baseline assessment, the research assistant will inform the data manager that a veteran has been enrolled. The data manager will add the veteran to the randomization spreadsheet, notify the veteran of their group assignment, and contact the EUC or MISSION-CJ providers to let them know a veteran has been randomized to their respective condition. The EUC or MISSION-CJ providers will then schedule the first session with the veteran. This process will ensure that the veteran's condition remains blinded to the research assistant conducting assessments.

Study Conditions

Overview

Veterans will be randomized to either MH RRTP care as usual (described in the previous section), with MISSION-CJ or EUC (refer to Table 1 for a comparison of the conditions and Figure 1 for a schematic flow diagram). EUC was chosen to provide an active control that was more ethically and clinically appropriate while still maintaining enough distinction between conditions to adequately test the added value of MISSION-CJ. Both conditions will be rolling entry.

Figure 1. Randomized controlled trial (RCT) flow diagram. CTI: critical time intervention; DRT: dual recovery therapy; EUC: enhanced usual care; MHRRTP: mental health residential rehabilitation treatment program; MISSION-CJ: Maintaining Independence and Sobriety through Systems Integration, Outreach, and Networking Criminal Justice.

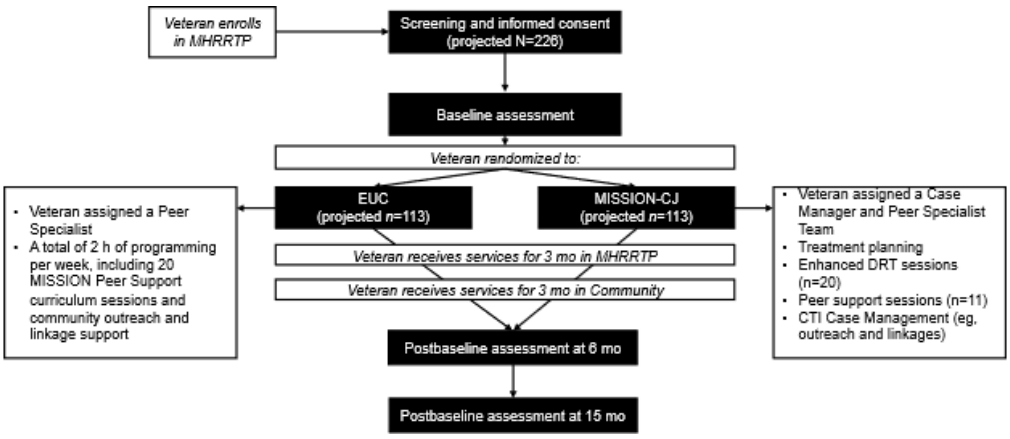

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Table 1. Comparison of the study conditions.

	MISSION-CJ[a]	Enhanced usual care
Treatment duration	• 6 months (begins within a week of the MH RRTP[b] enrollment, duration of stay is 3 months, and continues for 3 months after the MH RRTP in the community) • 2 hours of additional programming per week during months 1 to 3, weekly outreach sessions in month 4 to link veterans to prosocial community supports (eg, drug-free events and probation), biweekly sessions in month 5 (when the veteran is trying linkages), and 1 session in month 6 (MISSION-CJ discharge to transition care to linkages)	• 6 months (begins within a week of the MH RRTP enrollment, duration of stay is 3 months, and continues for 3 months after the MH RRTP in the community) • 2 hours of additional programming per week for 6 months
Treatment services received by veterans	• Risk-need-responsivity–based treatment planning tool • Enhanced DRT[c] (20 sessions) • Peer support curriculum (11 sessions) • Case management using the CTI[d] step-down model to promote linkages to behavioral health and criminal legal services	• MISSION Peer Support curriculum (24 sessions) • Community outreach and linkage support
Treatment condition providers	• Case manager and peer support specialist treatment team	• Peer support specialist

[a]MISSION-CJ: Maintaining Independence and Sobriety through Systems Integration, Outreach, and Networking Criminal Justice version.

[b]MH RRTP: mental health residential rehabilitation treatment program.

[c]DRT: dual recovery therapy.

[d]CTI: critical time intervention.

Training for the MISSION-CJ and the EUC Conditions

At the outset of the study, the case manager and peer support specialist teams delivering MISSION-CJ will receive training on the curriculum, whereas the peer support specialist delivering EUC will receive training on the MISSION Peer Support curriculum as well as how to perform community outreach guidance. The training will be kept separate for each condition but will use the same format. The staff in both groups will first watch a 1.5-hour webinar on the MISSION-CJ or the EUC curriculum. This will be followed by a 1-day comprehensive training on the components of the MISSION-CJ or the EUC curriculum led by the MISSION developers. The MISSION-CJ training will review the components of the intervention, the risk-need-responsivity model, and the implementation materials. The EUC training will cover the MISSION Peer Support curriculum, community outreach, and the implementation materials. Furthermore, staff will have access to implementation materials (ie, the MISSION-CJ Treatment Manual or the MISSION Peer Support Enhanced Service Delivery Manual; Pinals, DA, unpublished manual, April 2014 and Smelson, DA, unpublished manual, August 2019).

Data Collection

Data Collection for the RCT

Trained research assistants will administer a battery of assessments (Table 2) with veterans at 3 time points: baseline and at 6 months and 15 months after baseline. All data are entered and managed in REDCap (Research Electronic Data Capture; Vanderbilt University) [61,62]. Each assessment includes questions regarding substance use and mental health history, criminal history and recidivism risk, housing, employment, medication adherence, mutual help groups attendance, antisocial attitudes, affiliations with antisocial peers and prosocial peers, community involvement, and treatment services received.

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Table 2. Measures for baseline and follow-up assessments for the primary aim.

Domain	Measure	Description	Time points
Substance use[a]	Timeline Follow-back	Retrospective, calendar-based measure; will provide information on quantity and frequency of substance use separately by drug type (ie, percent days of use and percent days abstinent) in the past 90 days [63]	Baseline, 6 months after baseline, and 15 months after baseline
Mental health[a]	Behavior and Symptom Identification Scale-24	Includes a total score and 6 subdomains (eg, depression and functioning, interpersonal relationships, and self-harm); will be used to measure change in mental health functioning [64]	Baseline, 6 months after baseline, and 15 months after baseline
Recidivism, recidivism risk and criminal history[a]	Level of Service Inventory–Revised	Validated and reliable scale consisting of 81 items that measure the dynamic risk factors that are summed to create an overall index of recidivism risk [65]	Baseline, 6 months after baseline, and 15 months after baseline
Housing status[b]	Residential Timeline Follow-back	Retrospective, calendar-based measure; will provide information on duration and frequency (eg, percent of days homeless) in the past 90 days [66-68]	Baseline, 6 months after baseline, and 15 months after baseline
Employment status[b]	Maudsley Addiction Profile (employment subscale)	Measures individuals' employment status (eg, days worked, days absent, and days unemployed) using a 30-day recall period [69-74]	Baseline, 6 months after baseline, and 15 months after baseline
Medication adherence[b]	Medication Adherence Rating Scale	Measures veteran medication adherence behavior and how well the veteran adheres to medication [75-77]	Baseline, 6 months after baseline, and 15 months after baseline
Mutual support groups[c]	Alcoholics Anonymous Involvement	Adapted to measure attendance and involvement in mutual support groups for substance use (lifetime and past 12 months) [78]	Baseline, 6 months after baseline, and 15 months after baseline
Antisocial attitudes and peers[c]	Measures of Criminal Attitudes and Associates	Provides a valid and reliable assessment of an individual's (1) antisocial attitudes (scale A) and (2) antisocial associates (scale B) [79-81]	Baseline, 6 months after baseline, and 15 months after baseline
Prosocial peers[c]	Community Assessment Inventory	Valid and reliable 10-item measure of support in 4 domains: household members, family outside home, friends, and community [75,82]	Baseline, 6 months after baseline, and 15 months after baseline
Community involvement[c]	Community Integration Measure	10-item valid and reliable measure of an individual's integration into their home and community and is used in a broad range of disability research to assess client assimilation, support, productivity (vocational and leisure), and independent living [83-86]	Baseline, 6 months after baseline, and 15 months after baseline

[a]Primary outcomes.
[b]Secondary outcomes.
[c]Mediators.

Health Care Tracking

Health care tracking (mediator) will be conducted weekly and in 2 ways. First, self-reported treatment services received will be tracked via the MISSION Treatment Service Tracking Sheet, which includes detailed logs that quantify the amount and type of services received before and after the MH RRTP and is collected via REDCap. This includes all possible services offered within the MISSION-CJ and the EUC, as well as the community linkages. Regarding linkages, the measure quantifies the number of referrals, referral type, and client engagement. The MISSION-CJ and EUC providers will be prompted weekly to send their logs. The MISSION-CJ services received will be tracked via the MISSION-CJ Fidelity Scale. This scale consists of 27 items (scored yes or no) assessing adherence to the DRT and peer components (Pinals, DA, unpublished manual, April 2014). The fidelity for the MISSION Peer Support curriculum as part of the EUC will consist of a 13-item scale (scored yes or no), which also assesses model delivery adherence (Pinals, DA, unpublished manual, April 2014 and Smelson, DA, unpublished manual, August 2019). Both scales have demonstrated good interrater reliability (Pinals, DA, unpublished manual, April 2014 and Smelson, DA, unpublished manual, August 2019). For MISSION-CJ, we will also use the Critical Time Intervention Fidelity Scale, which includes 20 items rated on a 5-point scale, ranging from "not implemented" to "ideally implemented." Item ratings can be combined to compute an overall fidelity score [87,88]. Second, additional data will be captured from the VA's Corporate Data Warehouse (CDW) [89]. These data include MH RRTP completion status, which will be defined as a regular discharge from the program. Data on substance use and mental health continuing care use from the previous assessment will be defined as the number of sessions in each setting that the clients attend throughout the follow-up period, which will also be captured via the CDW. The CDW data includes both outpatient encounter records and information on inpatient and residential care services used. We will extract all health care encounters from the CDW that occur in a 12-month period before, and ending 15 months after, the study enrollment for all veterans.

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Qualitative Evaluation

For the qualitative evaluation, we will interview 50% (12/24) of the veterans from each site who consented to participate in the study and were randomized to the MISSION-CJ group. Half of these veterans will be drawn from those considered high engagers (ie, completed a full dose, 6 months) of MISSION-CJ, and the other half will be drawn from those considered low engagers (ie, dropped out or completed half or less than the full dose, ≤3 months). The dose of the MISSION-CJ will be determined by the number of sessions attended by the veteran. We will also interview 50% (7/14) of the VA care providers (eg, nurses, psychiatrists, and social workers) from each site.

The RE-AIM Planning Tool will be used to conduct semistructured interviews with the MH RRTP veterans and care providers at each site, using 2 different sets of interview guides [90]. The RE-AIM framework highlights 5 domains to evaluate an intervention's potential for implementation and widespread impact: *reach* (how to reach the target population with the intervention), *effectiveness* (how to know the intervention is effective), *adoption* (organizational support), *implementation* (fidelity of intervention's delivery), and *maintenance* (sustainability) [91]. The RE-AIM Planning Tool asks questions to veterans and VA care providers within each domain regarding issues that should be considered when planning to implement an intervention (refer to Table 3 for sample items). Notably, we will supplement qualitative data with quantitative fidelity data to assess reach and adoption.

Table 3. Sample evaluation items by RE-AIM (reach, effectiveness, adoption, implementation, and maintenance) domain and participant.

RE-AIM domains	Veteran questions	VA care provider questions
Reach	How can we encourage other veterans to participate in MISSION-CJ[a]?	Which type of communication has tended to be most helpful for you to accomplish your MISSION-CJ related activities? To spread the word of the program?
Effectiveness	What changes did you notice in yourself while and/or after participating in MISSION-CJ?	To what extent was MISSION-CJ effective at actually meeting the needs of veterans with COD[b] and criminal legal involvement?
Adoption	What was it like for you to work with the people on your MISSION-CJ team?	To what degree did people involved with MISSION-CJ buy-in to the intervention before it was implemented? Why?
Implementation	Did you receive materials during the MISSION-CJ program? What did you think of these materials? How often did you use them? What do you use the most and why?	How did it work to deliver MISSION-CJ along with your other responsibilities in your role here?
Maintenance	Would you recommend this program to a family member or a friend? Why?	What resources are available to sustain organizational support of MISSION-CJ, such as key decision maker commitments?

[a]MISSION-CJ: Maintaining Independence and Sobriety through Systems Integration, Outreach, and Networking Criminal Justice version.
[b]COD: co-occurring disorder.

Ethics Approval

This study was reviewed and approved by the VA's Central Institutional Review Board (#20-01) on February 25, 2021, and registered with ClinicalTrials.gov (NCT04523337). Consent will be obtained by a research assistant who has been trained in human participants protections and is knowledgeable about the study before participating in any study assessments or procedures. At the time of consent, the study will be explained in depth, and the prospective participant will be given the opportunity to have any questions answered to their satisfaction before being asked to provide informed consent. During this time, prospective participants will be informed that they will be assigned either to the EUC or to the MISSION-CJ (each of which will be described in detail). Prospective participants will be told that enrolling in the study is voluntary, and they may refuse to answer any questions and withdraw at any time; we will assure potential participants that their decision to withdraw it will not impact the standard of care they are receiving (eg, MH RRTP). For the qualitative evaluation, we will ask for verbal consent from both the veterans and the VA care providers (veterans will have provided written consent in the overall study's consent form). In compliance with guidelines and oversight from the Data and Safety Monitoring Board, all collected data will be stored in a format that is identifiable only by an experimentally assigned ID number. The master list that contains identifiable information (eg, name and contact information) will be kept in restricted-access folders behind VA firewalls to which only the research team will have access. In addition the veterans will be compensated US $25 for the completion of the baseline, US $50 for the 6-month assessments, and US $75 for the 15-month assessments.

Data Analysis

RCT Data Analysis

Before any outcome analysis, we will examine whether veterans assigned to the MISSION-CJ and the EUC conditions are comparable on sociodemographics (eg, age, race and ethnicity, marital status, education, and income) and baseline measures of the outcomes and mediators using independent group *t* tests and chi-square tests for continuous and categorical variables, respectively.

To test the effectiveness on the primary (ie, recidivism, risk for recidivism, substance use, and mental health) and secondary (ie, housing, employment status, and medication adherence) outcomes, we will use generalized linear mixed effects regression models to compare the EUC and MISSION-CJ conditions on outcomes. For each outcome, we will estimate a generalized linear mixed effects regression model that specifies

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the appropriate distribution of the outcome variable in the regression model (ie, normal, binomial, or Poisson) and uses the appropriate link and variance functions [92]. All models will include main effects for time (ie, baseline and 6- and 15-month follow-up), treatment (ie, MISSION-CJ vs EUC), and study sites, and will account for clustering of repeated measures over time within individuals using a random effect for veterans. We will assess the effectiveness of the intervention using a treatment x time interaction term, which will estimate the change in the outcome measure of interest across the 3 assessment points for the MISSION-CJ group as compared to the EUC group. All models will also be adjusted for all baseline characteristics to increase the precision of intervention effect estimates. Because the MISSION-CJ and EUC conditions will be standardized and monitored for fidelity, we do not expect variations in outcomes across sites. However, to address the possibility of contamination, we will ask the participants in the EUC group at the 6- and 15-month follow-up assessments whether they observe the MISSION-CJ information being shared in the MH RRTP. The records of the participants in the EUC group who say "yes" will be flagged, and the contamination-adjusted intent-to-treat analyses will be calculated (ie, the effect of treatment assignment on outcomes is adjusted by the percentage of participants assigned to the EUC condition who may have received the treatment) [93].

To minimize missing data, we will train research assistants on the importance of completing each item while respecting the veteran's rights to refuse answers. On the basis of previous studies, we expect less than 5% missing data on each variable at each assessment, in addition to any attrition. We will obtain as high a follow-up rate as possible at each assessment. In contrast to the data on the MH RRTP completion and substance use or mental health continuing care use (which will be collected primarily via the VA administrative data at the 6- and 15-month follow-ups), and the data on recidivism (which will be collected as described previously), the data on recidivism risk and health-related outcomes at the follow-ups will be collected by our study team, and will therefore have more missing data due to expected attrition. The strengths of the generalized linear mixed effects regression model include its ability to use all available data, including data on respondents who have not provided data at each assessment. All the veterans who enter the study will be included in generalized linear mixed effects regression model analyses. However, we will also conduct analyses that include only those veterans who attended at least the first DRT and peer sessions. We will use a model-based multiple imputation procedure and impute missing values using least squares regression imputation [94]. We will select a set of measures associated with the variable at issue and use it in a series of iterated least squares regression models to generate a predicted value for the variable being imputed, and then we will substitute the missing value with the predicted value [95].

We will also examine whether and to what extent, reductions in antisocial attitudes, reductions in affiliations with antisocial peers, increases in affiliations with prosocial peers, MH RRTP completion, substance use or mental health continuing care engagement, mutual help group attendance, and community integration mediate the relationship between treatment group and recidivism, risk of recidivism and health-related outcomes at 6- and 15-month follow-ups [13,96]. To test each mediator, we will estimate a series of regression models that correspond to a hypothesized causal sequence among (1) MISSION-CJ, (2) one of our hypothesized mediators, and (3) better outcomes. In each model, we will control for relevant covariates (eg, baseline values for sociodemographic and the dependent variable). In the first model, we will regress the outcome variable of interest (eg, recidivism and the Level of Service Inventory–Revised [LSI-R] total scores) on the MISSION-CJ treatment condition. In the second model, we will regress the potential mediator of interest on the MISSION-CJ treatment condition. In the third model, we will regress the outcome of interest (eg, recidivism and the LSI-R total scores) on the potential mediator. If the coefficient for the MISSION-CJ treatment condition or a potential mediator is significant in all cases, we will proceed. In the final model, we will regress the outcome of interest (eg, recidivism and the LSI-R total scores) on the MISSION-CJ treatment condition and the potential mediator. If the coefficient for the potential mediator is significant and the coefficient for the MISSION-CJ dummy variable on the outcome is reduced, we will conclude that mediation is supported and will evaluate whether the indirect effect is significant.

Qualitative Evaluation

Deidentified audio files of the veteran and VA care provider interviews will be transcribed using VA Microsoft Teams and analyzed using NVivo (Lumivero) [97]. The research staff will review transcripts of these interviews, taking detailed notes using the RE-AIM Planning Tool structure to guide the analysis. Interviewers will record supplementary observations of initial impressions from the interview. Using an a priori approach informed by AIM combined with thematic analysis, research staff will jointly code several interviews to craft a codebook based on RE-AIM. Coding will involve close engagement with the data, multiple readings, and collaborative iterative defining of the codes [98-101]. We will then organize the codes using RE-AIM into broader themes. We will synthesize the codes into content categories and organize themes for final data interpretation. Drawing on our NVivo database and with team member feedback, we will create tables to summarize and categorize the barriers and facilitators of the MISSION-CJ implementation at the system, treatment care provider, and patient levels, including potential solutions and potential-to-leverage columns that contain evidence-based implementation tools to be considered for more widespread MISSION-CJ use. These analyses will reduce and display the data. With the tables, we will identify a small set of themes within each domain of the RE-AIM framework that signify triangulated findings (eg, factors that would facilitate and maintain use of MISSION-CJ that fit within the clinical and administrative infrastructure of a given facility). We aim to capture in-depth information on the patient, treatment provider, and contextual factors that facilitate or hinder the successful implementation of MISSION-CJ. We will use such factors to inform post hoc interpretation of the findings and guide the development of action plans to be tested in subsequent implementation projects. If hypotheses regarding the effectiveness of MISSION-CJ (vs EUC) are not supported, we

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will use this analytic approach to identify barriers in delivering MISSION-CJ during the RCT and to determine what modifications could be made to maximize effectiveness.

Results

As of March 2025, 118 veterans (site 1: n=52, 44.1% and site 2: n=66, 55.9%) have been enrolled. In total, 58 veterans (site 1: n=27, 47% and site 2: n=31, 53%) have been randomized to the MISSION-CJ intervention and 60 veterans (site 1: n=25, 42% and site 2: n=35, 58%) have been randomized to the EUC group. The veterans are continuing to actively receive treatment and complete follow-up assessments. For the qualitative evaluation, we have completed 23 interviews with veterans. We have started transcribing these data and anticipate analyzing these data in the upcoming months. It is expected that by September 2025, all veterans will have ended the active treatment phase, and then for the following 9 months, we will continue conducting the remaining follow-up assessments. Parallel to this period, the remaining VA care provider interviews for the qualitative evaluation will be conducted, transcribed, and analyzed. We used the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist when writing this protocol (refer to Multimedia Appendix 1) [102]. The findings from this trial and qualitative evaluation should be available by 2026.

Discussion

Anticipated Findings

This study is guided by the logic model depicted in Figure 2. Among justice-involved veterans with COD who are receiving care in an MH RRTP, we hypothesize that those randomized to the MISSION-CJ intervention (vs the EUC group) will have lower rates of criminal recidivism, lower recidivism risk, and improved health-related outcomes (ie, substance use, mental health, housing, and employment). Moreover, we hypothesize that the effects of MISSION-CJ on reduced recidivism and recidivism risk and better health-related outcomes will be mediated by reductions in antisocial attitudes; reductions in affiliations with antisocial peers and increases in affiliations with prosocial peers; greater treatment engagement (ie, MH RRTP completion, substance use or mental health continuing care use, and mutual support group attendance); and increased community integration. We anticipate that the information gained from the qualitative evaluation will provide guidance to our partners in terms of the broader adoption of MISSION-CJ in the MH RRTPs.

Figure 2. Logic model of study hypotheses. LSI-R: Level of Service Inventory-Revised; MHRRTP: mental health residential rehabilitation treatment program; MISSION-CJ: Maintaining Independence and Sobriety through Systems Integration, Outreach, and Networking Criminal Justice version.

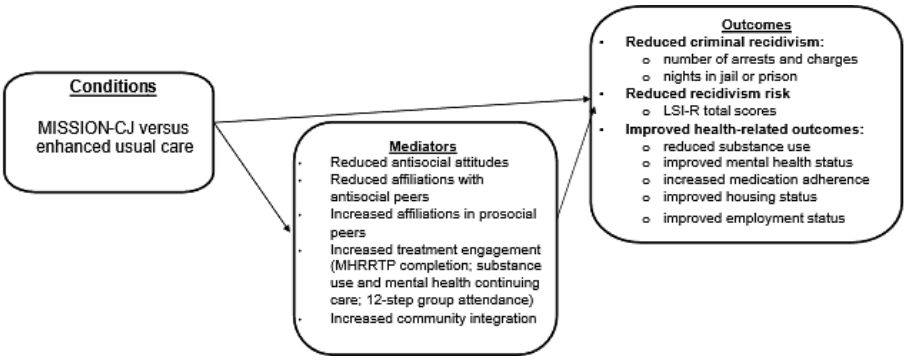

Limitations

This study has several limitations. In particular, while the MH RRTPs were selected with input from key decision makers, this setting poses limitations. First, while veterans enroll in the MH RRTP treatment for 3 months, some veterans may be irregularly discharged due to violating program policies, or veterans may choose to leave the program prematurely. Though both conditions include treatment in the community, leaving the MH RRTP places veterans at risk for disengaging with treatment. Furthermore, leaving the MH RRTPs early disrupts rapport building with case Managers and peer support specialists, which can impact the quality of further treatment and engagement. Second, veterans enrolled in the MH RRTPs are likely to be receiving other individualized treatments, both within and outside of the VA, that may impact their outcomes. Finally, this study is limited to the experiences of veterans within the VA health care system, and therefore, findings may not be generalizable to veterans who are not receiving care in the VA; however, previous MISSION-CJ studies with veterans outside of the VA have found significant improvements [31,47,51,103].

Conclusions

The MISSION-CJ intervention was developed to meet a critical gap by addressing the unique needs of individuals with criminal legal involvement. Having been found effective in other criminal legal contexts, coupled with the service gap in VA care and potential benefits to veterans, an essential next step is to test the effectiveness of MISSION-CJ in the VA MH RRTPs. Thus, this study will test a hybrid linkage and treatment approach currently unavailable in the VA, offering a paradigm shift, supporting care access, emphasizing peer support, and targeting recidivism as a primary outcome. If successful, MISSION-CJ could potentially supplement the MH RRTP care, offering a combined solution to improve behavioral health outcomes among a population of veterans with unique and often unmet needs.

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Acknowledgments

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Data Availability

Analyses for this study will be performed using the Veterans Health Administration (VHA) data. Deidentified data may be provided upon request pending ethics approval and in accordance with VHA guidelines and permissions.

Authors' Contributions

DMB and DS were responsible for funding acquisition. DMB, MAC, and DS were responsible for the conceptualization and supervision of the study. KB, PMS, DMB, MAC, and DS cowrote the original draft of the manuscript. MA and JS were responsible for project administration. TB was responsible for data curation and methodology. All authors assisted in the writing, reviewing, and editing of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT checklist.
[PDF File (Adobe PDF File), 98 KB - resprot_v14i1e70750_app1.pdf]

Multimedia Appendix 2
Peer-Review report from HSR-4 Mental and Behavioral Health, Health Services Research Parent IRG Office of Research & Development (VA Health Systems Research, US Department of Veterans Affairs, USA).
[PDF File (Adobe PDF File), 209 KB - resprot_v14i1e70750_app2.pdf]

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Abbreviations

CDW: Corporate Data Warehouse
COD: co-occurring disorder
DRT: dual recovery therapy
EUC: enhanced usual care

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LSI-R: Level of Service Inventory–Revised
MH RRTP: mental health residential rehabilitation treatment program
MISSION: Maintaining Independence and Sobriety through Systems Integration, Outreach and Networking
MISSION-CJ: Maintaining Independence and Sobriety Through Systems Integration, Outreach and Networking Criminal Justice version
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
RE-AIM: reach, effectiveness, adoption, implementation, and maintenance
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
VA: Veterans Affairs

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Protocol

Sodium Oxybate as a Potential New Treatment for Catatonia in Patients With Depression, Bipolar Disorder, or a Psychotic Disorder: Protocol for a Randomized Controlled Trial

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Abstract

Background: Catatonia is a severe psychomotor syndrome predominantly associated with depressive, bipolar, and psychotic disorders. Untreated catatonia has a 10% mortality rate and may lead to complications such as renal failure, rhabdomyolysis, pneumonia, embolism, and contractures. High doses of the benzodiazepine lorazepam, a gamma-aminobutyric acid (GABA)-A receptor modulator, are the primary pharmacological treatment, enhancing GABA's inhibitory effect, potentially reducing symptoms of catatonia. However, lorazepam is ineffective in about 25% of cases, leaving electroconvulsive therapy (ECT) as the only well-investigated alternative. Although often effective, ECT may have severe side effects and is not easily accepted among patients and caregivers. Therefore, there is an urgent need for novel therapies for catatonia. Sodium oxybate, a GABA precursor and GABA-B receptor agonist, is a promising alternative treatment based on observational data, but its efficacy has never been thoroughly investigated.

Objective: This study aims to evaluate the efficacy and safety of sodium oxybate in treating catatonia unresponsive to lorazepam, while also capturing the natural course and determinants of catatonia through an observational cohort.

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Methods: The Laborit trial consists of a cohort study and an embedded single-blind randomized controlled trial (RCT). Patients with catatonia admitted to a psychiatric ward may join the study's cohort, where their clinical characteristics are recorded. Standard care, including lorazepam up to 24 mg/day, will be administered. On day 4, the Bush Francis Catatonia Rating Scale (BFCRS) will be used to measure symptom response. Patients with ≤50% improvement on the BFCRS, compared to the score at start, will be eligible for the trial. A total of 42 patients will be randomly assigned to either the sodium oxybate group, after a 2-day lorazepam reduction period, or the continuation of lorazepam. The primary endpoint is response, measured by the BFCRS score change after 4 days of treatment. A ≥50% reduction in BFCRS will define a responder, who will continue allocated treatment for an additional 10 days, with a secondary endpoint at 14 days. Data will be analyzed using intention-to-treat and per-protocol methods, with chi-square and logistic regression tests to compare group response and remission rates.

Results: This study was funded by the Dutch Brain Foundation (Hersenstichting) in December 2020. The study protocol was approved by the Amsterdam UMC Ethics Board on May 22, 2023. As of March 2025, the first 4 participants have been included in the cohort, with no trial participants enrolled yet.

Conclusions: If positive, the results of this RCT may pave the way for international catatonia researchers and clinicians to introduce a new pharmacological treatment option for catatonia. Implementation could potentially benefit patients who endure this severe syndrome and present health care professionals with an additional treatment option.

Trial Registration: ISRCTN ISRCTN11236443; https://tinyurl.com/4px5s4aa

International Registered Report Identifier (IRRID): PRR1-10.2196/68356

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KEYWORDS

catatonia; sodium oxybate; GABA; lorazepam; gamma-aminobutyric acid

Introduction

Background

Catatonia was described by Kahlbaum in 1874 as a syndrome accompanied by different psychiatric and somatic symptoms [1,2]. This severe condition has a prevalence of at least 10% in psychiatric hospitals [3,4]. Catatonia is strongly associated with psychiatric disorders, where 30% of cases of catatonia are associated with schizophrenia, and 43% have an underlying bipolar disorder [1]. In addition, catatonia has been linked to other psychiatric disorders such as depressive disorder, obsessive-compulsive disorder, posttraumatic stress disorder, and withdrawal from alcohol or benzodiazepines [1]. There are several somatic underlying disorders to catatonia, such as encephalitis or autoimmune disorders [5]. Even though there are no well-defined risk factors for the development of catatonia, it is known that antipsychotics—especially those with high dopamine receptor affinity—may lead to the development of catatonia [5]. It is hypothesized that catatonia is caused by either a dysfunction of gamma-aminobutyric acid (GABA) receptors or a deficit in GABA [6,7]. Current treatment options target this neurotransmitter imbalance.

Symptoms and Consequences of Catatonia

Catatonia is a clinical syndrome characterized by a distinct constellation of psychomotor disturbances. A total of 2 subtypes have been described: retarded and excited [1,2]. The retarded subtype is characterized by symptoms such as immobility, staring, mutism, rigidity, withdrawal, and refusal to eat or drink, posturing, grimacing, negativism, waxy flexibility, echolalia or echopraxia, stereotypy, verbigeration, and automatic obedience. In contrast, excited catatonia is distinguished by pronounced psychomotor agitation, manifesting in behaviors such as aggression or impulsive behavior or movements, but may also encompass symptoms described earlier. If left untreated, both subtypes of catatonia may lead to increased morbidity and mortality. Complications include dehydration, muscle contractures, pressure ulcers, nutritional deficiencies, severe weight loss, thiamine deficiency, electrolyte disturbance, urinary tract infections, renal failure, rhabdomyolysis, pneumonia, and embolism [1]. Both subtypes may progress into malignant catatonia, a severe condition that may also occur acutely. Malignant catatonia is characterized by autonomic dysfunction and organ failure and may be fatal [8].

Current Treatments

Rapid intervention in catatonia is crucial for achieving the most favorable prognosis [1]. At present, the primary pharmacological treatment involves administering a supratherapeutic dose of benzodiazepines, preferably lorazepam, over 3-7 days [1]. Lorazepam acts as a GABA-A receptor agonist, enhancing the inhibitory effects of GABA [9]. However, approximately 25% of patients do not completely respond to lorazepam treatment [1]. For these patients, electroconvulsive therapy (ECT) remains the only well-established alternative, demonstrating success rates of 80%-100% across various forms of catatonia, even when pharmacotherapy has failed [10]. Despite its efficacy, ECT is perceived as an "intrusive" treatment, compared to pharmacological options [11]. This perception often causes distress among caregivers of patients with catatonia, who may refuse this treatment option. Since communication with patients with catatonia is often challenging due to mutism, we seldom know the patients' preferences about the treatment of catatonia. Concerns about ECT often revolve around potential cognitive side effects associated with ECT. The image of ECT in individual patient stories found on the internet or other media is usually not very positive, and the need for repeated general anesthesia during the typical 2- to 3-week treatment period, which usually involves 9-12 sessions, may cause concern among caregivers [11].

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All parties, patients, caregivers, and health care professionals recognize the necessity of acute treatment for catatonia due to the possible severe consequences of the syndrome when left untreated. If patients and caregivers are unable to consent, and the patient faces serious medical risks, ECT may be administered under local compulsory mental health care acts or medical treatment agreements. However, an additional therapeutic option, such as sodium oxybate, could potentially reduce the need for compulsory treatment, or at least provide an additional option to make an informed decision.

Rationale for Modification of GABA in Patients With Catatonia

Although the pathophysiologic mechanisms underlying catatonia are not fully elucidated, GABA likely plays an important role. Motor symptoms observed in catatonia are strongly linked to a deficient GABAergic state within the central nervous system (CNS) [2,6]. The GABA-model hypothesis of catatonia, supported by findings from several studies, suggests that the syndrome of catatonia is either due to reduced levels of GABA or dysfunction of GABA receptors in the CNS, resulting in decreased inhibitory signaling, which leads to signs of catatonia, such as stupor, catalepsy, mutism, mannerisms, stereotypy, agitation, echolalia, and echopraxia [12].

Functional imaging studies in humans have demonstrated that catatonia is associated with altered activity in the basal ganglia as well as in the orbitofrontal, prefrontal, parietal, and motor regions, suggesting that these cortical structures may also play a role in the pathophysiology of catatonia [13]. Most projection neurons within the basal ganglia are GABAergic, further supporting the role of GABA dysfunction in this condition [14]. This interpretation is further reinforced by observations that GABA-A binding is reduced in the cortical regions of patients with catatonia [6]. Motor and affective symptoms are correlated with these abnormalities in GABA-A binding. Furthermore, cortical abnormalities in patients with catatonia are normalized following exposure to lorazepam [3]. In addition, studies have revealed a decreased density of GABA-A receptors in patients with catatonia, further highlighting the significance of GABAergic mechanisms in the disorder [6].

Current Treatment Options and GABA Modification

Lorazepam, the current primary treatment option for catatonia, binds to benzodiazepine receptors on the GABA-A ligand-gated chloride channel at several sites on neurons within the CNS. It enhances the inhibitory effects of GABA, resulting in an increased influx of chloride ions into the cell. The consequent hyperpolarization stabilizes the neuronal plasma membrane, enhancing cellular inhibition [9,15]. Lorazepam is therapeutically effective in approximately 75% of patients with catatonia [1].

The full working mechanism of ECT is not yet known. Nevertheless, ECT is widely recognized as highly effective in treating catatonia, even in the absence of randomized controlled evidence. A recent study by Breit et al [16] showed a mean reduction in BFCRS score of 82.8% after ECT treatment. An earlier study by Suzuki et al [17] found a recurrence rate of 63.6%, despite continuous pharmacotherapy.

A variety of studies have shown that ECT alters cerebral blood flow and glucose metabolism [18]. In addition, ECT has been found to affect the transmission of nearly all major neurotransmitters in the brain, including GABA [18]. During neurotransmission, ECT acts on various levels, including neurotransmitter synthesis, neurotransmitter release, binding of neurotransmitters to their receptors, as well as their reuptake [18,19]. Recent research shows a regional increase in brain volume post ECT, which is likely related to its neurogenic and synaptogenic effects [20]. Gbyl and Videbech [21] highlight that much remains unknown about the effect of ECT on neurochemical, neuroendocrine, synaptic, and cellular levels. However, it is strongly suggested that the likely deficit in GABA is restored after ECT [22].

Findings From a Large Observational Study on Sodium Oxybate as a Treatment for Catatonia and Animal Studies

To our knowledge, there is only one large observational study that studies the effects of sodium oxybate as a treatment for various psychiatric and neurological disorders. This study included 288 participants diagnosed with conditions such as depression, anxiety, schizophrenia, epilepsy, and catatonia [23]. Sodium oxybate, the pharmacological agent used in this study, acts as a GABA-B receptor agonist and a precursor of GABA [24]. It was administered in doses ranging between 0.01 and 0.1 g/kg, 3 times daily either orally or intravenously (equivalent to 2.4-24 g/d for an 80 kg patient). Among patients with schizophrenia and catatonia, approximately 30 participants, the study showed a reduction of catatonic symptoms ranging from 60% to 70%. Specifically, there were improvements in anxiety, agitation, and restlessness.

Notably, these improvements were observed exclusively in patients with schizophrenia who exhibited catatonic symptoms or patients with disorganized schizophrenia (n=7), but not in patients with other psychiatric disorders (n=252), including those with depressive disorder, anxiety disorder, or schizophrenia of the paranoid type. Importantly, any patients participating in this study reported no adverse respiratory symptoms.

Findings from animal studies also suggest a strong involvement of a lack of GABA in catatonia. In a rat study, symptoms of catatonia such as muscular rigidity, catalepsy, and postural asymmetries could be produced by inhibition of striatonigral GABAergic neurons [25]. Similarly, another study found that the administration of GABA antagonists contributed to muscle rigidity [26]. Finally, animal studies showed that sodium oxybate contributed to an increase in GABA levels in the brain, possibly due to increased GABA-B receptor activity [27].

Hypothesis and Aim

This study aims to provide robust evidence on the efficacy and safety of sodium oxybate for treating catatonia unresponsive to lorazepam, while also capturing the natural course and determinants of catatonia through its observational cohort. We hypothesize that pharmacological therapies, aimed at increasing GABA-B–mediated neurotransmission, could be effective in patients with lorazepam-resistant catatonia. We argue that

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sodium oxybate, the sodium salt of gamma-hydroxybutyric acid, is a viable alternative to lorazepam, which acts as a GABA-A agonist, because it is a precursor of GABA and acts as a GABA-B receptor agonist. Such a pharmacodynamic profile is expected to contribute to increased GABA-mediated neurotransmission [24,28] and could thus be beneficial to patients with catatonia.

If sodium oxybate proves to be an effective novel treatment for catatonia in patients with psychiatric conditions, this could have significant implications for the treatment of this condition. This new approach would expand the therapeutic options available to patients, their caregivers, and their treating physicians.

Methods

Study Design

The Laborit study is a multicenter trial combining an observational cohort study with an embedded randomized controlled trial (RCT). This design enables a comprehensive examination of catatonia symptoms, their progression, and potential determinants while also testing the efficacy of sodium oxybate as a treatment for catatonia in patients with psychiatric conditions unresponsive to a high-dose lorazepam regimen.

The name, Laborit, refers to Henri Laborit (1914-1995), a French surgeon who helped design the first antipsychotic drug, chlorpromazine. In addition, he extensively studied the clinical effects of sodium oxybate, after it was discovered in 1874 by chemist Alexander Zaytsev.

Setting

The study will be conducted across multiple acute psychiatric wards and medical psychiatric units throughout the Netherlands. Study sites include the following hospitals: Leiden University Medical Centre, Amsterdam University Medical Centre, and Antes-Parnassiagroep, as well as mental health care institutions: GGZ inGeest, Arkin, and GGZ Centraal. These settings provide a broad catchment area necessary to recruit the required number of participants.

Characteristics of Participants

The inclusion and exclusion criteria for the clinical trial part of the Laborit study are displayed in Textbox 1. For inclusion, catatonia has to be present, with a minimum score of 3 on the Bush Francis Catatonia Rating Scale as scored by the treating physician or trained nurse.

Exclusion criteria are based mainly on the need for rapid intervention in the treatment of catatonia (in case of malignant catatonia), or factors that cause high risk when taking sodium oxybate (sleep apnea, heart or renal impairment, and concurrent use of certain medications or alcohol). This study focuses on semiacute catatonic episodes caused by either psychotic or affective disorders; hence, chronic catatonia and patients with underlying somatic disorders are excluded. Due to the fact that antipsychotic-induced catatonia may often be treated by discontinuing the antipsychotic medication, patients who are likely to fall into this category are excluded from entering the trial part of the study [5]. They may be included in the observational part of the study.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Age ≥18 years.
- Diagnosis of catatonia associated with unipolar depressive disorder, bipolar disorder, or psychotic disorder.
- Admitted to an acute mental health care ward or medical psychiatric unit.
- Inadequate response to escalating doses of lorazepam up to 24 mg/d over 4 days.

Exclusion criteria

- Chronic catatonia (duration >8 wks).
- Inability to take oral medication, unless hospitalized, where gastric tube administration is available.
- An underlying somatic condition causing catatonia is present or strongly suspected.
- Recent change in antipsychotic medication.
- History of antipsychotic-induced catatonia.
- Heart failure or renal impairment.
- Known sleep apnea.
- Use of specific medications (eg, GABAergic drugs, gamma-hydroxybutyric dehydrogenase inhibitors, and opioids other than tramadol).
- Current alcohol use disorder (alcohol use <7 d before starting the trial).
- Malignant catatonia present at inclusion or the development of malignant catatonia during the study, demanding immediate intervention.

Power Calculation

To detect a clinically significant difference in remission rates (assuming 60% for sodium oxybate vs 15% for continued lorazepam) with a power of 0.80 and alpha of 0.05, 34 participants are needed. Allowing for a 20% dropout rate, 42 participants will be recruited. This sample size ensures sufficient power to test the primary outcome.

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Randomization

Patients will be randomly allocated to sodium oxybate or lorazepam. Patients will be randomized centrally, using random sequences of block sizes of 2, 4, and 6. We opt for this approach due to the low number of patients that will be obtained from each site, which hampers block randomization per site. The research support unit from the Department of Psychiatry, Amsterdam UMC, will be responsible for randomization using Castor Electronic Data Capture (EDC) software. Designated researchers will be responsible for randomization and communication of the allocated treatment with the treatment site. These researchers are not involved in data collection.

Treatment Protocol

When patients are enrolled in the study, the following steps, which are also displayed in Figure 1, will take place:

1. Patients enrolled in the cohort will receive lorazepam, titrated up to a maximum of 24 mg per day or up to the dose that causes sedation.
2. At the end of day 4, catatonia symptoms will be assessed using the Bush Francis Catatonia Rating Scale (BFCRS). If a reduction of less than 50% is achieved, patients may continue to enroll in the clinical trial part of the study.
3. When patients enroll, they will be randomized into two groups: treatment as usual, namely the continuation of high-dose lorazepam for 4 additional days, or a 60% reduction in lorazepam dosage over 2 days, followed by administration of sodium oxybate. Sodium oxybate will be titrated up to 27 g/day (4.5 g every 4 h).
4. If, after 4 days of treatment, patients improve more than 50% on the BFCRS, they may continue sodium oxybate treatment for an additional 10 days. If no response or remission has been achieved, patients will, in general, receive ECT. However, this decision lies outside the scope of this study and is a decision made between the treating professional, the patient, and his or her legal representative, in case of incapability.

Figure 1. Overview of the treatment protocol.

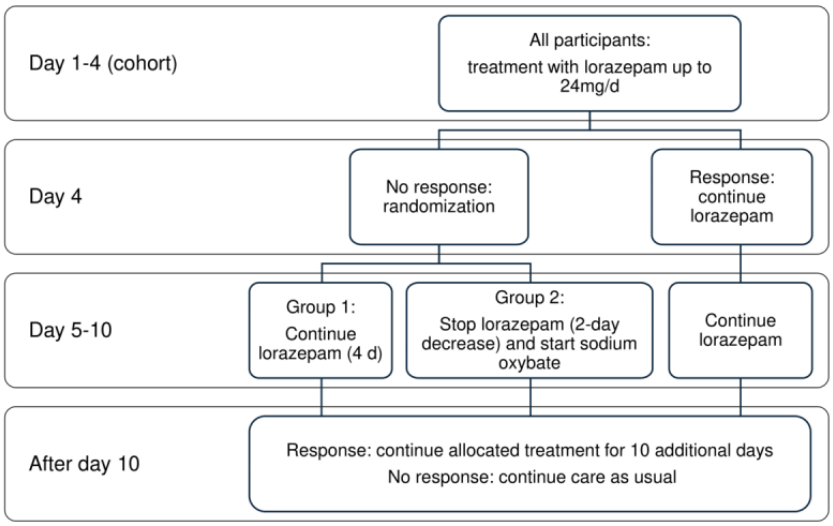

At baseline in the cohort, we will collect descriptive data on the patient characteristics such as sociodemographic, clinical characteristics, somatic and psychiatric history, *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) diagnosis, current and historical medication use, and the Clinical Global Impression (CGI) scale to assess illness severity, together with BFCRS, vital parameters and standard laboratory screening.

To ensure optimal homogeneity in the measurement of symptom severity, we have adjusted the original BFCRS to a new version. The original BFCRS contains 23 items on which between 0 and 3 points may be scored. However, the instructions for these different scores of severities are not well defined. In our adjusted BFCRS, we strive to decrease interrater variability by creating clear guidelines for scoring the severity of symptoms with every item of the list. We have created the adjusted BFCRS in collaboration with psychiatrists and nurses who are familiar with catatonia and use the original BFCRS in daily clinical practice. The adjusted list with the instructions may be found in Multimedia Appendix 1.

In the lorazepam group, patients will receive lorazepam 4 times daily, adhering to the standard treatment regimen for acute catatonia used in the participating wards. In the sodium oxybate group, medication will be administered every 4 hours, totaling 6 doses per day. Medication will be administered orally or through a gastric tube when available in case of admission to a medical psychiatric unit. BFCRS scores will be assessed 3 times a day by trained nurses or physicians on all wards. The research assistant will contact the wards where the participants are admitted 3 times a day. They will then receive information from the nurse or physician on call regarding the symptoms and BFCRS scores of the participant. The research assistant is sufficiently trained to determine if the BFCRS data are collected adequately by the ward staff.

The maximum dosage of sodium oxybate is 27 g per day, which amounts to 4.5 grams every 4 hours. For narcolepsy, for which sodium oxybate is a registered treatment option, the maximum

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dose is 9 grams per night in 2 equal doses 2.5 to 4 hours apart [29]. Opposed to patients with narcolepsy who only need this medication during the night, patients with catatonia need to be treated 24 hours a day. Because of this, we have extended the dosing regimen of narcolepsy, maintaining the same maximum dose every 4 hours. Table 1 shows the scheduled assessments per patient.

First-line laboratory screen: full blood count, C-reactive protein, renal, liver, and thyroid function tests, blood glucose, creatine phosphokinase, and iron measurement, and drug screen of urine. Repeated laboratory screening, as indicated by the treating physician. Tr: trial reduction of lorazepam. T0a: allocated treatment with lorazepam for 4 days. T0b: allocated treatment with sodium oxybate for 4 days after reduction of lorazepam. T1a: allocated treatment with lorazepam for 10 additional days, when lorazepam treatment contributed to an initial response. T1b: allocated treatment with sodium oxybate for 10 additional days.

Table 1. Timeline and schedule of assessments of patients in the Laborit study (based on SPIRIT [Standard Protocol Items: Recommendations for Interventional Trials] figure).

Assessment	Cohort study (Baseline, C1)	Cohort study (after 4 d of lorazepam, C4)	RCT[a] (Tr)	RCT (T0a)	RCT (T0b)	RCT (T1a)	RCT (T1b)	Dropout or end of trial (T2)
Sociodemographics	✓							
Clinical characteristics	✓							
Somatic and psychiatric history	✓							
DSM-5[b] diagnosis by a psychiatrist	✓							
DSM-5 diagnosis through MINI[c]				✓	✓			
Medication use (current)	✓	✓						✓
Medication history	✓							
Clinical Global Impression scale	✓			✓	✓	✓	✓	✓
Bush Francis Catatonia Rating Scale	✓	✓	✓	✓	✓	✓	✓	
Physical + neurological examination	✓							
Blood pressure	✓	✓	✓	✓	✓	✓	✓	
Heart rate	✓	✓	✓	✓	✓	✓	✓	
Temperature	✓	✓	✓	✓	✓	✓	✓	
Oxygen level	✓	✓	✓	✓	✓	✓	✓	
Laboratory screening 1	✓	✓		✓	✓	✓	✓	
Assessment of side effects using SAFTEE[d]				✓	✓	✓	✓	

[a]RCT: randomized controlled trial.

[b]DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition).

[c]MINI: Mini-International Neuropsychiatric Interview.

[d]SAFTEE: Systematic Assessment for Treatment Emergent Effects.

Blinding

This study is single-blind, as patients may be aware of the allocated treatment group they are in. The research assistant responsible for data collection will be unaware of which treatment arm the participant is allocated to. Staff of the participating centers and participants are requested not to disclose whether patients were allocated to the sodium oxybate or lorazepam arm.

Monitoring and Safety

Patients will be closely monitored for side effects, with particular attention to respiratory problems, through the continuous presence of an anesthesia technician for those receiving sodium oxybate in mental health care facilities. In hospitals, nurses will do this, and there will be backup from acute intervention teams from the Intensive Care Units. If patients exhibit side effects such as vomiting, they will be excluded from the trial, and treatment with sodium oxybate will

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be terminated due to the significant risk of aspiration associated with vomiting.

Participants are permitted to refuse the assigned medication once per day. However, if they refuse and subsequently miss more than 1 dose of the assigned drug, they will be excluded from the trial. The data that is gathered up until the moment of exclusion will be used in the intention-to-treat analysis. None of the medications will be administered forcibly under the previously mentioned laws. Given that this medication is an investigational product, individuals unable or unwilling to take the prescribed drug will be excluded from the trial and will receive necessary treatment with local guidelines and practices.

Following the guidelines of the CCMO (Dutch Central Committee on Research Involving Human Subjects), all suspected unexpected serious adverse reactions and serious adverse events (adverse events) will be documented and reported to the medical ethical review committee. In addition, a Data Safety and Monitoring Board (DSMB) has been installed to perform ongoing safety surveillance and to perform interim analyses on the safety data. This committee is an independent committee consisting of a psychiatrist with relevant experience in the treatment of catatonia, a statistician, and a pharmacologist familiar with the pharmacological characteristics of sodium oxybate.

Primary and Secondary Outcomes

For both groups in the RCT, the BFCRS will be measured and documented 3 times daily. The primary outcome measure is the efficacy of sodium oxybate in reducing catatonia symptoms by 50%, as indicated by the BFCRS at the end of the fourth day of the allocated treatment, as compared to the last BFCRS measure before treatment. For the lorazepam group, this will be the BFCRS of the night shift of the last day of the cohort. For the sodium oxybate group, this will be the BFCRS of the night shift of the second day of lorazepam reduction. Secondary outcomes include remission rates (BFCRS <3 or no longer meeting *DSM-5* criteria for catatonia), the side effect profile of sodium oxybate compared to lorazepam, focusing on oxygen levels, blood pressure, heart rate, and vomiting, as well as the acute course of catatonia and its determinants in the observational cohort. Outcome evaluation methods are displayed in Table 2.

Table 2. Primary and secondary outcomes.

Outcome	Evaluation method
Primary outcome	
Response to treatment	Difference in BFCRS[a] between the start of treatment score and the last score after 4 days of treatment
Secondary outcomes	
Remission	No longer meeting *DSM-5*[b] criteria of catatonia or BFCRS <3
Side effect profile	SAFTEE[c]
Acute course of catatonia	Determinants in the observational cohort

[a]BFCRS: Bush Francis Catatonia Rating Scale.

[b]*DSM-5*: *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition).

[c]SAFTEE: Systematic Assessment for Treatment Emergent Effects.

Statistical Analysis

Statistical analyses will be performed on the intention-to-treat as well as the per-protocol sample. For all analyses, corrected *P* values of <.05 will be regarded as statistically significant. Safety data (eg, side effects) will be collected and summarized in the study results. A description of the analyses for the primary, secondary, and exploratory objectives is provided below.

Primary Outcome Measure Analysis

We will use a chi-square test to evaluate the response rate between the 2 groups after 4 days of treatment. Our study requires no adjustment of the type I error, given that it consists of 2 treatment groups and focuses on a single primary variable, response to treatment. The study follows a confirmatory statistical approach with a single, prespecified null hypothesis concerning the primary variable.

Secondary Outcome Measures Analysis

For the secondary outcome measures, we will first determine the remission after 4 days and subsequently after 10 days of treatment using logistic regression. Remission is defined as no longer meeting the *DSM-5* criteria of catatonia. We will also describe the percentage of side effects observed in participants assigned to high-dose lorazepam or sodium oxybate.

Comparative analyses between treatment groups will be conducted using *t* tests or their nonparametric equivalents for continuous variables and chi-square tests for categorical variables. Mixed-effects models will account for repeated measures and clustering within centers.

Second, in the cohort study, we will use standard clinical descriptive measurements from patient records to characterize the acute course of catatonia and its potential determinants, including sociodemographic and clinical characteristics. These characteristics encompass demographic information, additional *DSM-5* diagnoses beyond catatonia, severity and duration of catatonia, type of catatonia, the presence or absence of antipsychotic drugs before the onset of catatonia, and the effects of initial treatment with lorazepam. This analysis aims to identify distinct profiles of catatonia in acute psychiatric wards and their relationship to outcomes. This is particularly important

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given the current lack of studies that may predict which patients will improve from catatonia, with what treatment, and which are at risk of developing it. In addition, we will test the hypothesis that certain risk factors are associated with catatonia and describe their prevalence.

Third, we will test the hypothesis that patients with mild catatonia (eg, BFCRS <8) treated with both lorazepam and antipsychotics will have a higher remission rate compared to those treated with lorazepam alone. It is in line with clinical practice to continue antipsychotics in cases with mild catatonia.

We will use logistic regression to test this hypothesis, with antipsychotic use as a central determinant, and we will adjust for sociodemographic and clinical characteristics.

In addition, we will test the following hypotheses on possible risk factors associated with catatonia:

1. Patients who stop antipsychotics are at risk of developing catatonia. We will describe the prevalence of those with catatonia who stopped antipsychotic medication before the development of catatonia.
2. Patients who change antipsychotics are at risk of developing catatonia. We will describe the prevalence of those with catatonia who changed antipsychotic medication before the development of catatonia.
3. More patients are diagnosed with retarded catatonia than excited catatonia. In addition, we will describe the prevalence of patients with retarded catatonia (ie, characterized by immobility, mutism, staring, and rigidity) and patients with excited catatonia (ie, characterized by prolonged periods of psychomotor agitation).

Finally, we will analyze remission of catatonia in the patients enrolled in the cohort part of the study and treated with lorazepam alone. We will do so using logistic regression, adjusting for sociodemographic and clinical characteristics.

Ethical Considerations

This study protocol was approved by the Institutional Ethics Board of Amsterdam UMC on March 22, 2023. Given the nature of catatonia, most patients will initially be unable to provide informed consent. Therefore, consent will be sought from legal representatives. All participants or their legal representatives, will provide verbal and written informed consent. Representatives will be informed about the trial alongside the information on the observational cohort in order to give them 4 days to consider the decision to participate. Patients regaining competence during the study will be asked to reconsent. Data from those withdrawing after reconsent will be included to minimize bias. Research data will be collected digitally using Castor EDC (a certified online deidentified data collection tool for medical research, password protected). For this study, a specific database has been created in Castor EDC and has been tested by several team members before data entry. At the point of inclusion into this study, a unique project number will be allocated to each subject, with no reference to initials or date of birth. The key to the data file is only available to the research assistants of the Amsterdam UMC and is password protected. Data entry is done by different research assistants for the cohort part and the trial part of the study. All subjects entering the trial part of the study receive a €25 (US $28.50) gift voucher.

Results

This study was funded by the Dutch Brain Foundation (Hersenstichting) in December 2020. Correspondence of peer reviewers of this fund can be found in Multimedia Appendix 3. The study protocol was approved by the Institutional Ethics Board of Amsterdam UMC on 22-05-2023. As of March 2025, we have included the first 4 participants in the cohort part of the study, and we are awaiting the first trial enrollment. Please find the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist in Multimedia Appendix 2.

Discussion

Aim and Hypothesis

This study protocol outlines a multicenter RCT designed to evaluate the efficacy and safety of sodium oxybate for the treatment of catatonia that is unresponsive to lorazepam. In addition, it aims to capture the natural course and determinants of catatonia through an observational cohort. We hypothesize that sodium oxybate, by increasing GABA-B–mediated neurotransmission, could be effective in patients with lorazepam-resistant catatonia.

Challenges

We anticipate possible difficulty with inclusion, as legal representatives of eligible patients may hesitate to enroll their relatives in our RCT due to concerns about the pharmacological product under investigation. Although sodium oxybate is an approved medication for treating narcolepsy, its association with gamma-hydroxybutyrate, a substance misused recreationally, may cause caution and concern.

Another challenge we face is the inability to conduct a double-blind study. Patients receiving sodium oxybate will be aware of their treatment due to the presence of an anesthesia technician assigned to monitor them during the initial 4 days, which will also be apparent to the treating staff on the wards. In addition, sodium oxybate may only be administered as a solution that needs to be taken orally, whereas lorazepam is available in tablets, intramuscular injection, and intravenous administration.

Although extensive exclusion criteria are necessary to ensure the safety of trial participants, they may introduce selection bias by excluding individuals with common comorbidities such as renal impairment. However, this is necessary to protect kidney function due to the high sodium levels in sodium oxybate. The decision to exclude participants with recent changes in antipsychotic drug use, which is known to induce catatonia, is based on the need for prompt intervention and discontinuation of these medications [5]. We expect catatonic symptoms to resolve in patients with antipsychotics–induced catatonia when medication is discontinued during the cohort phase of the study [5]. If participants have discontinued antipsychotic drugs during the observational phase of the study and do not recover from

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the catatonic symptoms, they are still eligible to enroll in the trial. In this way, we hope to minimize selection bias.

Although all teams of the different sites will be adequately trained and informed, the small number of inclusions across a relatively large number of study sites may cause fairly infrequent inclusions per site. However, we expect that the diversity and number of sites are necessary to be able to include enough participants to achieve the calculated statistical power for this study. Adherence to the study and treatment protocol must be well warranted.

Finally, we have based our dosing regimen of sodium oxybate on the current dosage used in the treatment of narcolepsy. However, we know that in the treatment of catatonia, lorazepam is used in supratherapeutic doses. Therefore, a possible challenge may be that our titration protocol for sodium oxybate will not use doses that are high enough to achieve a positive effect on catatonic symptoms, thus finding no effect of this treatment.

Relevance

Catatonia is, in our view, an underexposed and underinvestigated syndrome with potentially serious complications. This may be due to numerous factors, such as lack of funding, inability to obtain informed consent from patients who are not competent during an episode of catatonia, or lack of interest from researchers and sponsors due to the low incidence of the syndrome in the general population. Our research could provide robust evidence of the efficacy of medication targeting GABA-B receptors in the treatment of catatonia.

Conclusion

To conclude, our research, if positive, could provide patients with catatonia, their relatives, and health care professionals with a potential new treatment option in a regimen where current options are limited.

Acknowledgments

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Data Availability

According to European law (General Data Protection Regulation), data containing potentially identifying or sensitive patient information is restricted. However, for academic researchers, data may be available upon request via the Labority study team at laborit@amsterdamumc.nl or through the corresponding author. We aim to publish the results of this study in a scientific journal.

Authors' Contributions

EvE and JvM drafted the original draft proposal and the protocol on which this paper is based. LB then proceeded to draft this manuscript, which was critically reviewed and edited by all authors. EvE is the primary investigator on this project and will supervise the investigation and writing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Bush Francis Catatonia Rating Scale adjusted for the Laborit study.
[PDF File (Adobe PDF File), 220 KB - resprot_v14i1e68356_app1.pdf]

Multimedia Appendix 2
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 80 KB - resprot_v14i1e68356_app2.pdf]

Multimedia Appendix 3
Peer-review report by the Dutch Brain Foundation (Hersenstichting).
[PDF File (Adobe PDF File), 309 KB - resprot_v14i1e68356_app3.pdf]

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Abbreviations

BFCRS: Bush Francis Catatonia Rating Scale
CCMO: Centrale Commissie Mensgebonden Onderzoek
CGI: Clinical Global Impression
CNS: central nervous system
DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)
DSMB: Data Safety and Monitoring Board
EDC: Electronic Data Capture
ECT: electroconvulsive therapy
GABA: gamma-aminobutyric acid
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Exploring Ways to Reduce Heavy Drinking by Increasing Hope Among Midlife Women in Australia: Protocol for a Mixed Methods Study

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Abstract

Background: Alcohol consumption remains a major societal problem, contributing to myriad health conditions. Australian midlife women (aged 45-64 years) consume more alcohol than previous generations of midlife women and more than younger women now. Alcohol poses health risks that are unique to midlife women, including increased risk of breast cancer; 10% of breast cancers result from alcohol consumption and there is no “safe” limit. There is a global gap in knowledge about socially and culturally appropriate interventions for reducing alcohol consumption in these heavy-drinking groups of midlife women.

Objective: The research questions (RQs) driving the study are as follows: RQ1—what are the shared social practices that constitute and connect alcohol consumption in each of the 4 case study groups of midlife women? RQ2—what are the perceptions of women in the case study groups about the “invisible hands” shaping alcohol consumption in their social worlds? RQ3—what are the possible “systems-level” interventions or strategies to counter or oppose the “invisible hands” impacting women’s alcohol consumption? and RQ4—what is the validity, fidelity, and effectiveness of codeveloped critical consciousness interventions on alcohol-related social practices and consumption patterns?

Methods: Our study will identify and implement ways to support the following groups of heavy-drinking midlife women to reduce their alcohol consumption (and their breast cancer risk): (1) women living in regional areas of Australia; (2) lesbian, gay, bisexual, transgender, queer, and other sexual orientation and gender identity women; (3) women living in poverty; and (4) women working in the corporate sector. An expert group of midlife women, termed a women’s thought collective (WTC), will guide all stages of the study. Stage 1 (0-18 months) will collect qualitative data using social media analysis, netnography, photo elicitation, and ethnography to understand the forces oppressing women and shaping their alcohol consumption. We will recruit 50 participants in each of the case study groups. Stage 2 (19-24 months) will involve deliberative dialogue methods with the case study groups (15 participants per group) to identify policy-level changes required to support the reduction in participants’ drinking. Stage 3 (25-36 months) will codevelop alcohol reduction interventions using critical consciousness development and then implement them using a quasi-experimental design. Primary outcomes are readiness to reduce alcohol and actual changes in consumption levels.

Results: This protocol was funded by the Australian Research Council (DP250104494) for 3 years, starting in July 2025. Human research ethics committee approval has been granted (0457).

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Conclusions: Expected outcomes include community actions and policy levers for alcohol reduction, addressing the intersecting sociocultural, political, and commercial factors shaping alcohol use among midlife women. The findings will help inform strategies to counter oppressive forces or transform them into sources of hope, encouraging new practices that challenge social norms.

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KEYWORDS

alcohol; sociology of hope; breast cancer prevention; midlife women

Introduction

Research Problem, Significance, and Timeliness

Alcohol consumption remains a major societal problem in Australia, contributing to myriad health conditions and costing an estimated AUD $66 billion (Aus $1=US $1.53) a year (only AUD $6.5 billion is recouped in alcohol tax revenue) [1]). The National Alcohol Strategy 2019 to 2028 aims for a 10% reduction in population-level alcohol consumption [1]. Australian midlife women (aged 45-64 years) consume more alcohol than previous generations of midlife women; currently, the alcohol consumption in this group of women is more than other age groups of women [2], which was exacerbated during the lockdowns due to the COVID-19 pandemic [3]. While men consume more alcohol than women, midlife women experience specific gendered risks from drinking alcohol, including an increased risk of breast cancer (the most common cancer in women [4]), with 10% of breast cancers caused by alcohol alone in addition to other known risk factors such as genetic, hormonal, and environmental factors [5,6]. Midlife women who drink alcohol face a triple burden: (1) all midlife women (irrespective of alcohol consumption) are at risk of breast cancer due to their age; (2) midlife women who drink alcohol have an increased risk of breast cancer (a dose-response relationship—every drink throughout life accumulates breast cancer risk [7]); and (3) midlife women in specific sociocultural groups (the focus of our project) face structural disadvantages that increase their likelihood of heavy alcohol consumption, further increasing their breast cancer risk.

Recent national evidence suggests that attitudes toward alcohol are shifting [8]. Australians increasingly support action against alcohol harms and are willing to reduce alcohol consumption. This change could be a response to increased drinking during the COVID-19 pandemic, increased availability of no- and low-alcohol products, and increased engagement with the sober curious movement [9]. This evidence of social change adds impetus to the potential for our project to contribute to reduced drinking among midlife women. The project extends our recently completed Australian Research Council (ARC)–funded Discovery Project (DP) study (DP190103434) that highlighted a need for new research into the social practices of different groups of midlife women who engage in heavy drinking. The term "heavy drinking" refers to levels exceeding the national alcohol guidelines [10] for long-term (>10 standard drinks per week) or single-occasion (>5 standard drinks on one occasion per month) risky drinking. Existing public health approaches aimed at reducing alcohol consumption (relying on the exercise of individual willpower) have had limited effectiveness among midlife women. We will use social practice theory (SPT) to support and empower midlife women to reduce their alcohol consumption and the multifarious negative impacts on their lives. The advantage of using SPT is that it works at the levels of meanings, materials, and competencies to reduce the extent to which women are forced to rely on willpower to reduce drinking.

Four Heavy-Drinking Groups of Midlife Women in This Proposed Study

To avoid portraying a homogeneous version of "midlife women," this project will work with midlife women from four different heavy-drinking social worlds: (1) women living in regional centers [11] (towns or small cities outside capital cities); (2) lesbian, bisexual, or queer (LBQ) cisgender women [12]; (3) women living in poverty [13] (earning <AUD $489 per week after tax); and (4) women working in the corporate sector [14] (senior management in large for-profit corporations in male-dominated sectors, such as mining, construction, finance, and IT). We will explore options for reducing alcohol harms with an intersectional lens, considering social class, sexuality, and ethnicity within and across the case study groups.

Innovations in the Context of Recent International Advances in Knowledge

Overview

There is a global gap in knowledge about socially and culturally appropriate interventions for reducing alcohol consumption in heavy-drinking groups of midlife women. Rather than continuing to problematize individual "choices" to drink, there is an urgent need for research that informs solutions addressing the intersecting community and sociopolitical and commercial factors that shape alcohol consumption among different groups of midlife women. For brevity, these multifaceted structural, systemic, sociocultural factors are referred to as "invisible hands" [15,16]. This project will empower groups of midlife women to "see," understand, reflect on, and resist these invisible hands to reduce alcohol consumption. The theory and methodology in both the *Pedagogy of the Oppressed* by Freire [17] and the *Pedagogy of Hope* by Freire [18] identified hidden or unseen "limit situations" (which act like invisible hands), which act as oppressive forces, shaping, blocking, or preventing certain human actions (and hopes) in oppressed groups. Freire [17,18] argues that for currently oppressed people to move from oppression to hope, researchers need to work with them using critical consciousness development; individuals can then become critically conscious of the invisible hands and can then work toward overcoming them to increase their hopes. Within the

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context of the proposed study, we will work with 4 different heavy-drinking groups to identify the invisible hands (or limit situations) acting as oppressive forces to maintain their heavy drinking and prevent reduction in drinking. Once this critical consciousness has been realized, we will co-design interventions to reduce their drinking by overcoming the invisible hands.

Theoretical Innovation: Extending the Pedagogies of Oppression and Hope by Freire

Building on the concept of critical consciousness development by Freire [17,18], we will work with 4 groups of midlife women to identify the invisible hands of oppression linked to heavy drinking and codevelop interventions to reduce their drinking based on a pedagogy of hope. We have a unique opportunity to co-design and codevelop new alcohol consumption reduction interventions that have relevance, consonance, and specificity with groups of women whose social worlds are embedded with heavy-drinking practices that will build our research capacity as world leaders and our reputation globally to innovate alcohol consumption reduction approaches situated within social frames. The co-design of interventions that are situationally specific within 4 different heavy-drinking social worlds is a key innovation and extension of the original work by Freire [17,18].

Conceptual Innovation: Applying SPT and "Social Worlds"

Our project is novel in investigating what chief investigator S MacLean has conceptualized as "social worlds" [19,20] that encourage heavy drinking and shape women's practices related to alcohol consumption reduction. Conventional approaches, focusing on changing individual alcohol behaviors independent of social contexts, have had limited effectiveness for the 4 case study groups [21]. Our conceptual innovation is to focus on alcohol consumption not as a discrete behavior but as one enmeshed within broader social practices; the sociality of alcohol consumption is central to the proposed study. SPT focuses on the materials, meanings, and competencies required within particular social practices [22] and directly extends the previous research conducted by chief investigators PRW and S MacLean. In SPT, materials (eg, types of alcoholic or nonalcoholic products) have active, agentic roles within practices, enabling other practices (eg, self-care and managing stress) and creating meanings attached to alcohol (eg, alcohol as crutch, comfort, or toxic) [23]. SPT elements are all shaped by oppressive and gendered forces in women's lives. Central to SPT is the notion that by changing one or more elements in a practice, the entire social practice can be transformed. For example, participants, through developing critical consciousness of the invisible hands that shape the social practice of drinking, could potentially construct new meanings around the value or relevance of alcohol, choose different material elements (ie, socializing at places where heavy drinking is not facilitated), or develop new competencies (eg, skills to slow down drinking or confidently refuse a drink).

Methodological Innovation

Rather than implementing more interventions with limited efficacy for behavior change (a norm for public health concerns related to alcohol), we will undertake a multidisciplinary study, including innovative social practice methods, such as ethnography, netnography [24], photo elicitation, WTCs [25]), and deliberative democracy and critical consciousness development, drawing on our expertise as leading international researchers in sociology, anthropology, gender studies, psychology, and alcohol policy. Our methodology has never been used to explore and then codevelop options for alcohol consumption reduction within our 4 case study groups.

Policy Innovation

Alcohol consumption reduction techniques that target individuals (eg, persuading behavior change through screening for problematic drinking) require that consuming alcohol be recognized by the individual as a "problem." However, most (87%) of the Australian drinkers consider themselves to be "responsible drinkers," although 68% are risky or heavy drinkers [26], leading to alcohol consumption reduction interventions being resisted (ie, not seeing themselves as problematic drinkers) [27]. Our SPT-codeveloped interventions will provide policy makers with evidence-based, innovative ways to support women in recognizing the invisible hands shaping alcohol consumption within their social worlds and empower them to engage in new or different social practices associated with reduced alcohol consumption rather than requiring drinking to be seen as "problematic" and hence interventions to be resisted.

Key Research Questions

This is a world-first attempt to codevelop interventions examining gendered practices of alcohol consumption (not individual behaviors) as the sites of social analysis and change. Women in 4 different social worlds will be empowered to recognize, through raising their critical consciousness, the invisible hands (oppression) shaping their heavy-drinking practices. Together with women, new interventions will be developed and tested, which aim to either negate the impact of the oppressive forces or change them into forces for hope (raising critical consciousness to adopt new practices that resist norms embedded within social worlds). Participants will be encouraged to consider why drinking practices are normalized within their social worlds and whether or how this could be different by reimagining group social connections through nondrinking or reduced drinking. The research questions (RQs) driving the study are as follows:

- What are the shared social practices that constitute and connect alcohol consumption in each of the 4 case study groups of midlife women? (identification of pedagogies of oppression; RQ1)
- What are the perceptions of women in the case study groups about the invisible hands shaping alcohol consumption in their social worlds? (raising critical consciousness about pedagogies of oppression; RQ2)
- What are the possible "systems level" interventions or strategies to counter or oppose the "invisible hands" impacting women's alcohol consumption? (identification of systems-level possibilities for pedagogies of hope; RQ3)
- What is the validity, fidelity, and effectiveness of codeveloped critical consciousness interventions on alcohol-related social practices and consumption patterns? (impact of intervention aimed at pedagogies of hope; RQ4)

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The project extends a recently completed ARC-funded study (chief investigators PRW, MW, and BL and partner investigator S Meyer) that explored midlife women's reasons for alcohol consumption [28-30]. Our critical learning from that study is that women across different social worlds experience different social, cultural, and economic pressures to drink and have different capacities and resources to contemplate reduced drinking, with variations according to intersecting sources of oppression based on social class, sexuality, and ethnicity. Therefore, midlife women require different interventions to reshape their bespoke social practices, socially and culturally specific logics for consuming alcohol, and levels of critical awareness of heavy-drinking norms. This established the need for the proposed project. A subsequent study led by chief investigator BL investigated factors supporting women in reducing alcohol consumption [9], revealing that women in the corporate sector engage in wellness movements as a form of self-determination and increased agency to express a critical awareness of alcohol-related harms, enabling alcohol consumption reduction. However, this framing may not be readily available to other groups of women, highlighting the need for tailored responses in different heavy-drinking social worlds.

Conceptual Frameworks

We hypothesize that being able to recognize, critique, and counteract the "invisible hands" that shape drinking practices hinges on increasing women's capacities for collective critical realizations about how gender, sociopolitical settings, and regulations (eg, alcohol marketing to women) related to alcohol intersect with heavy-drinking social practices. Our proposed study will draw on and critique the theories and methodologies of Freire [17,18] to understand whether and how women recognize the "invisible hands" (*Pedagogy of Oppression* [17]) that shape their alcohol consumption practices and examine whether and how they can develop a critical consciousness about the "invisible hands" (making them visible) and implement changes within their social worlds to disrupt and reshape drinking practices (*Pedagogy of Hope* [18]). Rather than emphasizing the behaviors of individual women (avoiding blaming or stigma), we will analyze the interconnected gendered social practices (materials, meanings, and competencies) [22] located within "social worlds" [19] that frame heavy drinking in specific social groups and place women at risk of alcohol-related harms. We bring our sociological imagination to extend the work of other scholars [31-33] who also conceptualize "hope" as a sociocultural phenomenon. In a study of residential substance use services, chief investigator S MacLean found that young people's hope was rooted in social relationships and productive discourses and varied according to the external resources available to them, giving them some greater capacity than others to pursue their "hoped-for futures" [34]. This is critically important because it means that women in the 4 case study groups may require different social, cultural, or economic resources to gain a sense of control over the invisible hands and their imagined futures.

Theoretical Framework

We will use SPT [22,35], which has been used extensively by chief investigators PRW, BL [13,36], S MacLean [37], MW [38], and partner investigator AL [39] and identified as critically important for examining how alcohol consumption practices develop, persist, and can be changed [40-42]. Our recent ARC-funded study applied SPT to interpret midlife women's engagement with alcohol consumption reduction [9] (DP190103434), and chief investigator PRW worked on another ARC-funded study (DP210101166) that focused on applying SPT to oral health practices [43,44]. SPT provides a critical approach for examining alcohol practices in heavy-drinking social worlds and focuses on the shared social practices that frame and support heavy drinking [45]. SPT stipulates that change can occur through addressing one or more of the elements that constitute drinking practices or practices that relate to heavy-drinking behavior. For instance, the social practices of "after work drinks" can be altered by shifting what it means to socially connect with colleagues and offering different ways of connecting that do not revolve around alcohol [46]. Overall, SPT provides a powerful framework for understanding how alcohol consumption reduction can be built into the social worlds of heavy-drinking groups.

Methods

Ethical Considerations

Ethical procedures and approvals for all aspects of our study have been approved by Torrens University Human Research Ethics Committee (0457). As with all qualitative research, ethical considerations include obtaining informed consent, ensuring anonymity, and maintaining confidentiality. Alcohol consumption could be a sensitive topic. Our previous qualitative interview studies with diverse midlife women (aged 45-64 y) have attuned us to issues pertaining to informed consent, including detailing the potential risks and benefits of the study. Our approach in related studies has been to demonstrate empathic neutrality in our style of engagement.

Each participant will have an agency to decide the terms of their participation and the information they contribute. Other ethical practices include checking the suitability of the approach with women before commencing data collection; allowing women to choose their preferred pseudonym, mode of contact, and preferred medium for data collection (phone, in person, or telecommunication software); outlining assurances of confidentiality; and issuing honoraria to recompense women's time and resources. Given the success of our previous studies in generating rich understanding and engaging women across long time periods or repeated interviews [13,28,47,48], we will use similar methods in this study.

The online methods involved in our study, including sharing screenshots, digital content, social media analysis, and photo elicitation, entail unique considerations for informed consent and confidentiality. We will use our previous experience designing ethical online or social media–based studies [49], adapting traditional principles of human research ethics (respect, integrity, and beneficence) to guide practice in online research environments. Shared content that includes nonparticipants (eg,

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photos with friends and social media influencer posts) will be kept confidential to the research team, and any shared content that is included in research outputs will be digitally anonymized (eg, through blurring faces, names, and identifiable places or signs).

Ethnographic fieldwork in our study will be conducted in person or offline but also entails particular ethical considerations, as researchers are involved collectively in a social world (to observe the social practices shaping heavy drinking). Informed consent and confidentiality are complicated procedures, involving safeguarding against assumptions made by researchers about participants during the process of understanding women's social worlds. The WTC will be directly involved in the process of gaining access to and developing ethical procedures and field note templates for this aspect of our study.

Research Design

Our 3-year participatory project follows human-centered design thinking [50] (Figure 1). Within the case study groups, we will recruit samples that enable an intersectional analysis (based on social class, ethnicity, and sexuality) of the invisible hands shaping drinking. We are consciously not focusing on First Nations midlife women because this would require a different research team and a decolonized methodology. However, First Nations women will not be excluded from participating in the case study groups.

Figure 1. Research design and timelines. RQ: research question; WP: work package.

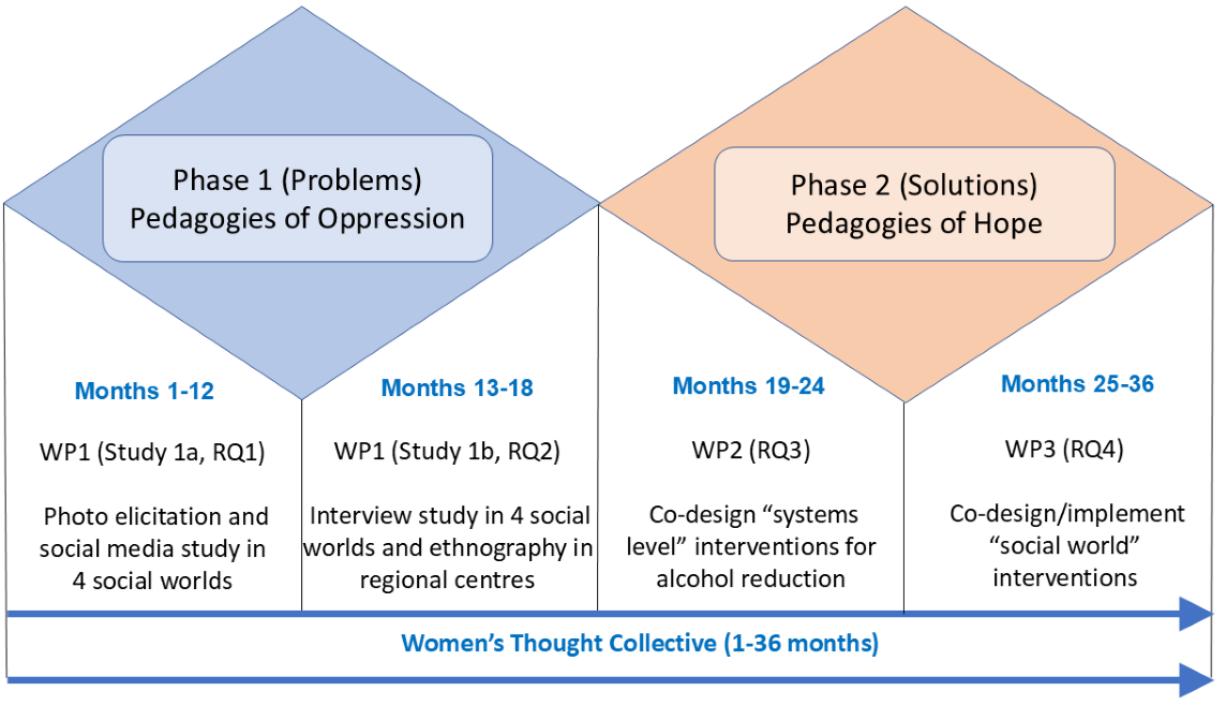

The project will be undertaken in 3 work packages (WPs). WPs 1 and 2 will be led by researchers at Torrens (women in the corporate sector and women in regional areas), Adelaide (women in poverty), and La Trobe (LBQ women) universities. WP3 will be led by Torrens University to maintain the fidelity, validity, and reliability of the interventions.

Project Governance

A project management group (including chief investigators and PIs) will meet monthly to monitor all aspects of the project and identify or manage risks. A stakeholder advisory group (SAG) will be developed to provide ongoing policy advice to the research team, support participant recruitment, and advise on the feasibility of future interventions that may involve their organizations. We will provide early communication of research findings to support their programs (eg, Daybreak app used by Hello Sunday Morning for reducing alcohol consumption). The SAG will meet biannually and include key stakeholders for the case study groups (eg, Chief Executive Women and Hello Sunday Morning for corporate women, Sober in the Country and regional sport assemblies for regional women, Uniting Communities and Women in Poverty Network for women in poverty, and LGBTIQ+ Health Australia and ACON Health for LBQ women) as well as organizations focused on alcohol consumption of individuals and breast cancer support or research (eg, cancer councils and Alcohol and Other Drugs services).

PhD Student 1: Consumer Engagement and Research Translation Strategies

PhD student 1 (scholarship funded by Torrens University) will collect, manage, and coanalyze data, engaging a WTC that is aligned with participatory action research and feminist hermeneutics or methodologies [25]. The WTC will include 5 representatives of each of the 4 case study groups (n=20) to provide their knowledge, expertise, and experience. The members of the WTC will not be participants in other stages of the study. The WTC will meet quarterly as a group and more often as individuals engaging with the PhD student on specific tasks. The PhD student will work with the WTC to develop, prototype, and test different co-design and research translation strategies. The WTC will provide meaningful and sustained co-design of data collection strategies and coanalysis of data

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from WP1 and WP2 (eg, coanalysis of anonymized data from some interviews, netnography, and ethnography). The WTC will also generate "ground truth" data from the dialogue groups and codeveloped interventions (WP3) in terms of feasibility and real-world applicability. We developed and piloted the WTC method with midlife women in our recent ARC DPs, garnering numerous additional insights into recruitment, data collection, data analysis, and real-world interpretation [25].

PhD Student 2: Ethnography in Regional Centers in South Australia

PhD student 2 (scholarship funded by Torrens University) will take responsibility for data collection and analysis for the women living in regional centers for WP1 and WP2. In addition, PhD student 2 will undertake ethnographic data collection in selected regional areas, including wine growing areas in South Australia (eg, Barossa Valley and Clare Valley; local to PhD supervisors and chief investigators PRW, MW, and CP), to understand the invisible hands and situational issues for midlife women in social worlds saturated by alcohol-related industries (eg, viticulture, wineries, distilleries, agricultural suppliers, hospitality, and tourism, etc) and alcohol sponsorship or donations to community sports clubs or associations where alcohol is sold and offered as raffle prizes to raise revenue for club activities and sustainability.

WP1 (RQ1 and RQ2; 0-18 Months)

Overview

Ethnography, netnography, photo elicitation, social media analysis, and qualitative interviews will be used to explore the factors that impact women's possibilities for alcohol consumption reduction within their social worlds. Midlife women will share how, where, and when heavy-drinking practices persist and identify the "invisible hands" that "push" them to drink and "pull" them away from reducing alcohol consumption and how drinking practices embedded in each of their social worlds facilitate heavy drinking. With the view to inform future interventions, they will be asked to describe protective (hope-based) factors that "shield" against "invisible hands" and their ideas on how, why, and where shields improve capacities for alcohol consumption reduction. We will target localized cultures and practices within workplaces, leisure spaces, and communities with the view of identifying new and actionable competencies in relation to alcohol consumption reduction within each social world.

Recruitment strategies will be tailored for each group (based on advice from the SAG and WTC), although we will be guided by previous successful approaches to recruitment, including targeted Facebook campaigns and snowball sampling techniques [51]. The research team will use their long-term relationships with organizations and networks to support recruitment: for women living in poverty through state and national networks (eg, Women in Poverty Network [chief investigator BL is a board director] and National Council for Women); for LBQ women through LGBTIQ+ Health, Thorne Harbour Health, and ACON Health; for women in regional areas through regional sport assemblies and sport or community associations; and for women in the corporate sector through Chief Executive Women and Hello Sunday Morning. All participants will be aged ≥18 years and will self-report "heavy" or "moderate" drinking.

Data Collection for Netnography, Photo Elicitation, and Social Media Analysis (RQ1; Study 1A)

We will recruit 50 participants for each case study group across Australia (n=200) who will create and upload screenshots to a study portal (n=5-10; a minimum of 5) of social media content that they perceive as reinforcing alcohol norms within their social worlds. In addition, participants will be asked to take photographs (and upload to the study portal) of "invisible hands" in their local built environment, community, or workplace that they perceive are social worlds that promote heavy-drinking practices or act as social worlds that promote practices that do not involve alcohol consumption. Participants will be provided with examples of relevant content. chief investigators PRW and BL and partner investigator AL are experienced in netnography and social media analysis [49,52,53], which will enable a meaningful yet manageable volume of content for analysis [54]. Participants will record where and when they saw the image (eg, social media platform or location in their local area, day or night, and day of week) and rate the content in terms of personal appeal, impact, and intention (method undertaken by chief investigator PRW [54]).

Data Collection for Qualitative Interviews (RQ2; Study 1B)

This stage will use qualitative methods to explore heavy drinkers' openness to reducing alcohol consumption among the 4 case study groups. Research assistants and PhD student 2 will conduct in-depth interviews with approximately 30 participants from each case study group (n=120), noting that sampling will continue until saturation is reached [55]. Previous experience suggests this sample size will allow for observable patterns within the data for each case study group. Some moderate drinkers from each group will be recruited alongside heavy drinkers for variability to triangulate observations on the social context of drinking within their particular social world [19]. Interviews will be conducted online and last approximately 1 hour. Interviews will probe for knowledge, attitudes, beliefs, and practices around possibilities for reducing alcohol consumption (particularly where drinking is habitual and tied to social settings, identities, or environments); awareness (critical consciousness) of the invisible hands (social, cultural, economic, and community factors) shaping their drinking; and what alternatives to drinking alcohol they perceive to be available in their social worlds. Data analysis will use NVivo (Lumivero) and follow the well-used 3-step progressive method of precoding and conceptual and theoretical categorization by chief investigator PRW and partner investigator S Meyer [56]. Chief investigators and partner investigators will meet regularly in person during this stage to check for agreement in coding (each cocoding a specific set of transcripts) to improve explanatory rigor. Together, they will collate the data for use in WP2.

WP2 (RQ3; 19-24 Months)

Deliberative dialogue groups (4 groups; 15 participants per group) will be used to identify "systems level" (eg, invisible

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hands not immediately amenable to individual action) drivers of alcohol consumption in the 4 case study groups (note that invisible hands amenable to individual action will be the focus in WP3). Dialogue groups will run separately for each of the 4 case study groups, with each dialogue group comprising midlife women from the case study group (recruited from participants in WP1) along with representatives from relevant stakeholders (upon advice from the SAG and WTC). Chief investigator PRW has extensive experience with deliberative democracy methods [57-59], and a group size of 15 will allow both depth of deliberation and meaningful dialogue. Two weeks before the dialogue groups, materials will be distributed to orient participants to the findings from WP1 (analyzed by the researchers and the WTC). Each dialogue group will meet online over a 2-day period (usually on weekends to increase recruitment and attendance, as in the National Health and Medical Research Council study by chief investigator PRW [60]) to consider the evidence from WP1 and discuss feasible options for "system level" changes for alcohol consumption reduction in the respective social worlds. Deliberations will focus on how to shift meanings, materials, and competencies (elements of SPT) to reduce alcohol consumption. Participants will discuss their understanding of the "systems level" invisible hands shaping their alcohol consumption, which are likely to be different for each case study group. With input from the stakeholders, they will then discuss ways to reduce or negate the impact of the invisible hands. Chief investigators, partner investigators, and stakeholders will participate in the deliberative process to combine empirical knowledge with women's real-world examples of practices on what "works" in harm reduction to ensure the suggested strategies are feasible. Once the invisible hands are identified, the dialogue groups will codevelop policy, practice, or advocacy strategies required to reduce or challenge their oppressive forces and move toward a pedagogy of hope (and reduced alcohol consumption). The outcomes will be codeveloped options for intervention at "systems levels," which could include alcohol policy interventions (eg, reducing price of no or low alcohol products and regulating feminized alcohol marketing) or broader social policy interventions (eg, domestic violence support, advocacy around inclusion, and antidiscrimination).

WP 3 (RQ4; 25-36 Months)

Interventions will be codeveloped and implemented (using a quasi-experimental design), aimed at reducing alcohol consumption (moving from oppression to hope) in each of the 4 case study groups. The key findings and analysis from WP1 and WP2 will form the basis for WP3. We will codevelop, implement, and test 1 intervention per case study group, evaluating the impacts on women's critical consciousness development, their preparedness to question heavy-drinking social norms, their ability to have critical conversations about alcohol, and their readiness to change alcohol consumption patterns and make reductions in drinking. WP3 will be based on the original conception and implementation of critical consciousness presented in the *Pedagogy of the Oppressed* by Freire [17], which has been updated, validated, and tested by chief investigator PRW [61-63]. This will enable women to have critical conversations about alcohol with others in their social worlds (a competency in SPT), which is part of a renewed and less oppressive alcohol-related social practice. The WTC will provide expertise on adjustments required to facilitate new social practices within the case study groups. Participants will be recruited from WP1 and WP2. In line with the previous application of the critical consciousness intervention by chief investigator PRW [61-63], we will recruit 15 participants for each of the case study groups. This sample size enables sufficient variance within each group alongside a manageable number for the co-design and implementation of the intervention. While this sample size will not enable statistical analysis of the efficacy of the interventions, the purpose of this stage is to develop interventions and assess their feasibility, fidelity, and acceptability. Subsequent studies can then implement and test interventions, with sample sizes that are adequately powered for efficacy.

Co-Design of the Critical Consciousness Interventions

The 4 case study groups will meet separately with the research team to identify and prioritize potential interventions within their social worlds. This will occur over 8 fortnightly critical consciousness development sessions, each with its own aims, processes, materials, and outcomes (chief investigator PRW has published details of these 8 sessions [61-63]). Each session builds on the previous session, requiring participants to identify the invisible hands that shape their alcohol consumption (eg, to raise their critical consciousness), reflect on the amenability to change specific invisible hands, and ultimately identify and prioritize (as a group) the invisible hands that, if changed, are most likely to reduce their alcohol consumption. In taking the SPT approach, the co-designed interventions will focus on responding to elements of practice (ie, materials, competencies, and meanings) and their temporal connections. As an example for the "women in the corporate sector," interventions will address social practices of drinking in the corporate social world rather than individual drinking behavior. Interventions will target elements of practice that combine the corporate site (corporate spaces and alcohol products—materials), the know-how required to perform in this environment (gendered expectations in corporate culture—competence), and the significance of shared drinking practices in the corporate sector (managing "nonwork" caring responsibilities alongside "work" after-hours drinking—meaning). Identifying and intervening with the invisible hands that reflect tensions between corporate work cultures, gendered caring responsibilities, and bonding through alcohol consumption provides opportunities for changing social practices of drinking.

Implementation of the Interventions

Within each case study group, one intervention will be identified during the previous stage (critical consciousness development) that could help challenge some of the invisible hands that encourage heavy drinking or discourage reduced drinking. The intervention will then be implemented for 6 months, which is a reasonable time to identify changes (initial and sustained) in alcohol-related practices (reductions in alcohol consumption, substitution with nonalcoholic beverages, and changes in other social practices to sustain reduced drinking). Using participatory action research, participants in each of the case study groups

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(n=15 per group) will implement the intervention within their social world and report on the process and outcomes of the intervention. A process evaluation will be undertaken by collecting qualitative data on the barriers and enablers to implementing the intervention within their social worlds. Throughout the 6 months of the intervention, each case study group will meet monthly to provide feedback to the group and discuss the fidelity, acceptability, and feasibility of the intervention and potentially refine the intervention based on the dynamics of their social world. In addition, individual interviews will be conducted with all participants (before, during, and after the intervention) to understand any context-specific issues in relation to the suitability of the intervention within their social worlds and their level of critical awareness of the factors that impact their drinking, noting issues they perceive as modifiable and more challenging or complex. To measure the effectiveness of the interventions, we will collect quantitative data on both readiness to change alcohol consumption and changes in alcohol consumption (using the validated Alcohol Use Disorders Identification Test) at the study outset, during the intervention development stage, and 6 months after the intervention.

Results

This research protocol was funded by the ARC as part of their DP scheme (grant ID DP250104494). The study has been funded for a 3-year period, starting in July 2025.

Discussion

Enhanced National and International Collaboration

This collaborative study brings together an exceptional multidisciplinary team from Australia and internationally (Auckland, New Zealand; Columbia, United States; York, United Kingdom; and Waterloo, Canada). The research team is a bespoke blend of high-performing, internationally renowned researchers experienced in translating research into policy. We formed a new multidisciplinary (sociology, anthropology, psychology, gender studies, and alcohol studies) and multi-institutional (national and international) team. We are currently undertaking a multicountry cross-sectional survey with LBQ women in Australia (chief investigators PRW, S MacLean, and BL), New Zealand (partner investigator AL), Scotland, and the United States (partner investigator TH) to understand barriers to and facilitators of alcohol consumption reduction, which will feed into the case study group of LBQ women. We have built a team that will develop capacity for the next cadre of exceptional researchers, and we will identify opportunities to build EMCRs research track records and capacity in research translation throughout and beyond the project, with mentoring from senior researchers. Our international research collaborations will enable sister studies to be undertaken in the United States, Canada, New Zealand, and United Kingdom, growing our global profile.

Key Benefits of the Study

At a theoretical level, our innovative synthesis of the "invisible hands," Freire's pedagogies of oppression (1993) and hope (2021) and SPT will advance calls to "curb our culture of intoxication [1]" by pushing past limitations of individual behavior approaches. Our entirely new coupling of pedagogies of oppression and hope with SPT leverages our multidisciplinary expertise across sociology, anthropology, gender studies, psychology, and health promotion and will advance knowledge around "hope" for social change. Benefits will include new applications of critical consciousness, new applications of pedagogy of the oppressed and pedagogy of hope to a contemporary example with real-world health and social implications, comparative data across different social worlds about the invisible hands acting as oppressive forces against midlife women, and comparative understandings of the shared and different social practices in the social worlds of women in the different case study groups.

The proposed study will provide critically important new ways to support alcohol consumption reduction among 4 case study heavy-drinking groups, aligned with the Australian National Alcohol Strategy 2019-28 [1] and the World Health Organization Global Alcohol Strategy [64]. The interventions are more likely to be impactful because women themselves (the case study groups and the WTC) will codevelop them to align with the values and beliefs in their social worlds. A direct and immediate benefit of our empirically driven project is that it draws attention and responds to the "invisible hands" forming alcohol practices among women as points for immediate intervention (a pedagogy of hope).

The interventions will have benefits at 2 levels: community-level actions that are immediately actionable—the results from WP3—and policy or practice levers (results from WP2) readily available for action when "political will" can be harnessed, preparing us to strategically respond to these openings for advocacy.

Potential Limitations of the Study

This is a methodologically complex study, applying numerous sociological theories and implementing multiple qualitative and quantitative research methods. Although our research team has excellent professional networks and extensive experience in undertaking research with each of the case groups, a potential limitation is that we may not recruit enough participants in each of the case study groups. This potential limitation will also be reduced because we will convene a WTC, which will support the recruitment and retention of participants in the study. We also have a plan for recruitment from one stage of the research to the next, with a proportion of participants in stage 1 being recruited into stage 2 and then a proportion of those being recruited into stage 3. This increases the feasibility of successful completion and outcomes from the study. A further potential limitation relates to the implementation of the interventions in stage 3. The actual details of the interventions cannot be known until we have completed stage 2, but the uncertainty of the types of interventions is a potential limitation.

Anticipated Outcomes of the Study

The study will contribute to mobilizing women to develop a more critical attitude toward alcohol consumption within the relationships, contexts, and spaces (eg, their "social worlds") where heavy drinking is enabled. Our focus on community-level

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actions and policy or practice levers for change will contribute to social, economic, and public benefits, extending beyond personal health outcomes to those positively benefiting society. This project will provide evidence for targeted disinvestment in approaches with limited effectiveness in reducing alcohol-related harms for heavy-drinking groups of midlife women. We aim to provide a template for social change toward enabling social practices within heavy-drinking social worlds where reduced drinking becomes easier to imagine and realize. Given our international research team, there will be huge potential for developing sister studies in other heavy-drinking social worlds in the United Kingdom, the United States, New Zealand, and Canada.

Acknowledgments

The authors would like to acknowledge the staff at all participating universities who supported them in submitting this research application to the Australian Research Council. This research protocol was funded by the Australian Research Council as part of their Discovery Project scheme (grant ID DP250104494) The study has been funded for a 3-year period, starting in June 2025. The study received funding of AUD $768,000 (US $504,731).

Data Availability

The anonymized datasets generated or analyzed during this study may be available from the corresponding author on reasonable request (for people to access any of our data, they and authors will need to apply for new ethics committee approvals).

Authors' Contributions

All authors were involved in conceptualization, funding acquisition, writing the original grant proposal, and reviewing this protocol for submission to JMIR.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report by the Australian Research Council (Australian Government).
[PDF File (Adobe PDF File), 4932 KB - resprot_v14i1e72628_app1.pdf]

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Abbreviations

ARC: Australian Research Council
LBQ: lesbian, bisexual, or queer
RQ: research question
SAG: stakeholder advisory group
SPT: social practice theory
WP: work package
WTC: women’s thought collective

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Protocol

Efficacy of Manual Wheelchair Skills Training for Improving Skills and Confidence in People With Hereditary Degenerative Disorders: Protocol for a Sequential Multimethods Study

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Abstract

Background: Mobility impairment and participation restrictions are commonly experienced by individuals with autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) and myotonic dystrophy type 1 (MD1), 2 disorders that are highly prevalent in the province of Quebec, Canada. People with ARSACS and MD1 experience a progressive decline in mobility, which commonly results in the provision of manual or power wheelchairs. While wheelchairs can facilitate mobility and social participation, their provision alone does not guarantee safe and effective use. Wheelchair skills training has been shown to be effective for improving manual skills and confidence among adult users with various diagnoses, which may enhance self-directed mobility and participation and reduce the risk of chronic and acute injuries. However, manual wheelchair skills training for people with ARSACS and MD1 remains understudied.

Objective: The primary aim of this study is to evaluate the efficacy of manual wheelchair skills training for safely improving wheelchair performance in people with ARSACS and MD1. The secondary outcomes include exploring the influence of manual wheelchair skills training on skill capacity, use self-efficacy, mobility, and the retention of outcomes 3 months later. We will also qualitatively explore the manual wheelchair training experiences of people with ARSACS and MD1.

Methods: This study will use a sequential multimethods design, combining a waitlist randomized controlled trial and qualitative interviews. The participants will include adults who have a diagnosis of ARSACS or MD1 who use a manual wheelchair for mobility. Participants will be randomly assigned to the intervention or control group using a 1:1 allocation ratio. The intervention group will receive 5 manual wheelchair skills training sessions (1-2 sessions/week), while the control group will receive no training. Data will be collected at baseline (T1), after the 4-week intervention (or waiting period for the control group; T2), and 3 months after T2 to assess retention (T3). The primary outcome will be manual wheelchair skills performance. Secondary outcomes will include manual wheelchair skills capacity, self-efficacy, and mobility. Semistructured individual interviews will be conducted to explore participants' expectations regarding manual wheelchair use, past manual wheelchair experiences, and perceptions of manual wheelchair skills training. Quantitative data will be analyzed using analysis of covariance (ANCOVA), controlling for baseline scores, and qualitative data will be analyzed using reflexive thematic analysis.

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Results: This study received ethical approval (2025-3100) in July 2024. Recruitment started in January 2025. A graduate student, a research assistant, and a research coordinator have been recruited and trained.

Conclusions: The results of this randomized waitlist-controlled trial will confirm whether manual wheelchair skills training can improve self-directed mobility and related outcomes for people with ARSACS and MD1. The findings may help guide clinical practice toward manual wheelchair skills training for understanding potential influences on manual wheelchair mobility in people living with neuromuscular disorders.

Trial Registration: ClinicalTrials.gov NCT06596850; https://clinicaltrials.gov/study/NCT06596850

International Registered Report Identifier (IRRID): PRR1-10.2196/66974

(JMIR Res Protoc 2025;14:e66974) doi:10.2196/66974

KEYWORDS

ARSACS; myotonic dystrophy type 1; manual wheelchair; wheelchair skills training; mobility; participation; randomized controlled trial

Introduction

Mobility impairment and participation restrictions are commonly experienced by people with neuromuscular and hereditary degenerative disorders [1]. Two highly prevalent disorders in the province of Quebec include autosomal recessive spastic ataxia of Charlevoix-Saguenay (ARSACS) [2,3] and myotonic dystrophy type 1 (MD1) [4,5]. Declining mobility is a hallmark among people with ARSACS and MD1 that can negatively influence physical and psychosocial health outcomes. Approximately 74% of individuals with MD1 have mobility impairments that restrict participation in activities of daily living, leisure activities, and vocation [6-8].

Wheelchairs (manual or power) are prescribed to facilitate mobility for people with ARSACS and MD1 when walking becomes difficult. In the reported literature, approximately 45% of individuals with ARSACS use wheelchairs [9-11], with the average age of wheelchair provision at 38.9 years [10]. Given the varying rate of progression of ARSACS, wheelchairs may be suggested during adolescence or older age (eg, 17 to 59 years of age) [12], but most people (if not all) will eventually need one for mobility. A patient registry of MD1 in the United Kingdom reported that 56% of patients used a wheelchair, with the average age at which wheelchair use began being 34.6 years, ranging from infancy to old age (1 to 72.4 years). Among the wheelchair users in this registry, 22.8% started using it before the age of 10 years and 56.6% began between 30 and 59 years of age [13].

Regardless of diagnosis or type of wheelchair (ie, manual or power), wheelchair provision alone does not guarantee safe and effective use. If not used adequately, wheelchairs could be associated with mobility dependence, restricted participation, reduced social connectedness [14], and reduced quality of life [15]. Moreover, unsafe wheelchair use could lead to accidents that vary in severity from cuts and bruises to life-threatening head injuries [16]. Furthermore, injuries due to wheelchair accidents may increase caregiver burden and strain on the health care system [17].

Learning how to use the wheelchair and developing appropriate wheelchair skills are critical to independent mobility and participation [18]. However, wheelchair mobility for people with ARSACS and MD1 remains understudied. Our team recently demonstrated that adults with ARSACS had lower manual and power wheelchair skills but fewer training goals than adults with other diagnoses (eg, spinal cord injury) [19]. This disparity may be attributed to limited training opportunities and low expectations of wheelchair use for individuals with ARSACS [19]. It may be that the progressive nature of ARSACS and MD1 (and other neuromuscular disorders) and the clinical focus on maintaining functional walking have historically taken clinical precedence over wheelchair mobility outcomes.

The World Health Organization suggests training in wheelchair use and follow-up as important steps in wheelchair service provision [20]. Four meta-analyses demonstrate the effectiveness of wheelchair skills training for improving wheelchair skills, use confidence, and participation [20-23]. However, a survey of 68 Canadian rehabilitation centers demonstrated that >50% of therapists spent 2 hours or less on wheelchair skills training and 18% provided no training at all [24]. Moreover, individuals with ARSACS and MD1 do not typically spend periods of time in rehabilitation centers where most wheelchair skills training occurs. The inherited and progressive nature of ARSACS and MD1 means that people receive wheelchairs when they can no longer walk but do not commonly receive additional assessments, training, or follow-ups related to wheelchair use. Given the evidence on the effect of manual (manual wheelchair) skills training in other progressive conditions (eg, multiple sclerosis, Parkinsonism) [22,23], the association between manual wheelchair mobility and the preservation of upper limb function and strength in ARSACS [19], it is likely that evidence-based training could improve manual wheelchair skills, confidence, and social participation for people with ARSACS, MD1, and other neuromuscular disorders. In a pilot study, 3 individuals with ARSACS improved their manual wheelchair skills (between 18% and 30%) and confidence (between 5% and 15%) after 3 hours or less of manual wheelchair skills training [25].

The overall aim of this study is to evaluate the efficacy of an evidence-based manual wheelchair skills training program for improving safe manual wheelchair mobility in people with ARSACS and MD1. The primary objective is to test the hypothesis that participants who receive manual wheelchair skills training will improve their manual wheelchair performance by at least 20% compared to those in a control group who receive no training. The secondary objectives are to explore the

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influence of manual wheelchair skills training on wheelchair skills capacity, use self-efficacy, and mobility. Finally, the participants' expectations regarding manual wheelchair use and the experiences and perceived impact of manual wheelchair skills training on mobility and quality of life will be explored using a qualitative inquiry.

Methods

Study Design

A sequential multimethods randomized controlled trial (RCT) and qualitative interviews will be used, with the RCT reported according to the CONSORT (Consolidated Standards of Reporting Trials) guidelines [26]. Participants will be randomly assigned to the intervention or control group using a 1:1 allocation ratio. A randomization process with undisclosed block size will be created by a statistician who is not otherwise involved in the project. Given the potential benefits of the intervention already reported in our previous studies [22,23], control group participants will also receive wheelchair skills training following a 4-week control period and postintervention data collection (ie, they will be on a "waitlist" for the wheelchair skills training program and receive no intervention during the study period).

Ethical Considerations

The protocol for this study was approved by the Research Ethics Boards in rehabilitation and social integration of the Centre Intégré Universitaire de Santé et de Services Sociaux de la Capitale-Nationale (CIUSSS-CN; 2025-3100). The study protocol was registered on ClinicalTrials.gov (NCT06596850). Informed consent will be obtained from all participants by a research coordinator (RC). Participants will be made aware that they can withdraw from the study at any moment without facing any consequences. All collected information will remain strictly confidential within the limits established by law. To protect privacy and confidentiality, participants will be identified by a unique code, and their data will be anonymized and securely stored on a password-protected server. Participants will receive financial compensation for data collection activities to acknowledge their time and reduce attrition (CAD $50, equivalent to US $36, after each assessment session).

Participants and Recruitment

Convenience sampling will be used to recruit 20 community-dwelling people with ARSACS or MD1 who use manual wheelchairs. Active recruitment strategies will include recruiting through outpatient services at the local rehabilitation center in Quebec City (CIUSSS-CN). The chief of physiatry (author XR) who has clinical expertise in ARSACS and MD1 will discuss the study with all individuals on his case load who have a diagnosis of ARSACS or MD1 and use manual wheelchairs. In addition, participants from a longitudinal study on ARSACS (completed in 2022) will be contacted and informed of the study. Passive recruitment strategies will include disseminating promotional videos on the social media and websites of Muscular Dystrophy Canada, other collaborators, and community organizations. Participants will be 18 years of age or older; have a diagnosis of ARSACS or MD1; use a manual wheelchair for mobility (≥ 3 times/week for ≥ 8 hours/week); and be able to propel their manual wheelchair at least 10 meters. Individuals will be excluded if they anticipate a health condition or procedure that contraindicates training (eg, surgery) or if they are concurrently receiving or planning to receive other manual wheelchair training during the study.

Sample Size

The sample size was powered to detect a statistically significant difference of 20% between groups using mean change scores from baseline to postintervention in wheelchair skills [27]. A large effect size (Cohen d =1.2) for the wheelchair skills training and a correlation between measures (R^2) of 0.6 was used. With a significance level of α=.05 and 90% power, a sample size of 18 was required for a repeated measures analysis of covariance (ANCOVA) (F tests) with between-group factors, controlling for baseline score (including function and wheelchair experience), as calculated using G*Power [28]. Adjusting for a 10% loss to attrition, a total sample of 20 is required (10 per group).

Study Procedures

Following enrollment, participants will complete baseline measures (T1) and then be assigned to either the experimental or the control group. An RC will then contact the statistician via telephone or email to obtain the group assignment within 48 hours. The participant will be informed of the group assignments, and the trainer will be given the participants' contact information to schedule the training sessions and assign the control group. The training will be scheduled after completing the blinded postintervention data collection (T2). In an effort to minimize bias, a research assistant (RA) will be blinded to group allocation and participants will be instructed not to discuss their program with the RA. The RC will also arrange for the blinded follow-up (retention) data collection for all participants 3 months after postintervention data collection (T3). Qualitative interviews will be conducted by the RC by phone or videoconferencing within 7 days of completing the intervention. Given the self-report nature of the primary outcome, the interdisciplinary experience of 3 study investigators with RCTs who are not located at the data collection site, and the involvement of a citizen partner and Muscular Dystrophy Canada in data collection, analysis, and interpretation, a data monitoring committee was not established. Participants in the intervention and control groups will continue to receive usual care (if any) during the study. The trial design describing coordination, testing, and experimental procedures is depicted in Figure 1.

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Figure 1. Trial design describing coordination, testing, and experimental procedures. WSTP: Wheelchair Skills Training Program.

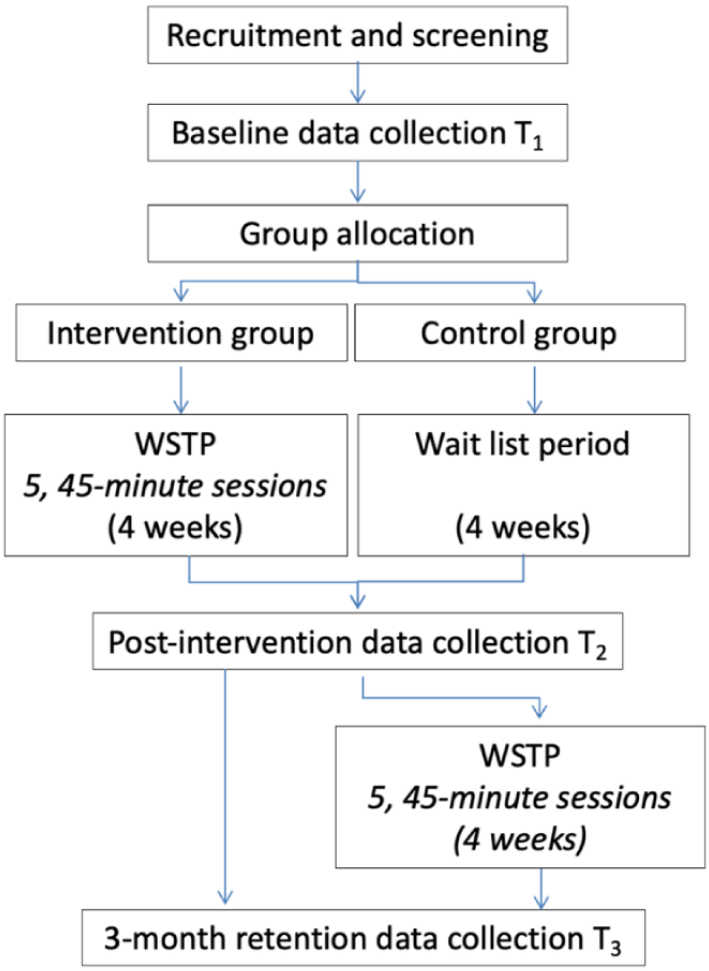

Intervention Details

According to the evidence-based Wheelchair Skills Training Program (WSTP) [29], participants will receive 5 individual 45-minute weekly wheelchair skills training sessions. As previously described by Best et al [26], the training sessions will take place in the community, in and around the participants' homes and neighborhoods (eg, libraries, shopping centers, museums, and parks), and will be customized according to the participants' goals. The WSTP provides suggestions for individualizing the approach based on the learner's impairments (ie, weakness, spasticity, contractures, cognitive impairments, and movement disorders like ataxia, tremor, and chorea). Therefore, specific training considerations can be made regardless of diagnosis. The WSTP sessions will begin with a 5-minute review of goals/progress, followed by a 10-minute warm-up (wheeling activities, random practice of previously learned skills). This will be followed by 20 minutes of attempting new skills, with training on each skill carried over to the next session until the skills are learned or the trainer and participant mutually agree to stop training. The trainer will periodically ask the participant to practice newly learned skills to incorporate variability of practice. Finally, a 10-minute cooldown will take place, during which the participant will practice skills in a self-controlled environment.

The trainer (author EN), a graduate student with training in physiotherapy will receive two 4-hour sessions by experts in manual wheelchair skills training (authors KLB, FR, and RLK), which has been shown to improve knowledge and confidence for training wheelchair skills [30]. The trainer will also complete self-guided learning modules, semistructured practice with trained trainers, and the Wheelchair Skills Program Certification Exam [31]. The fidelity of the WSTP administration will be evaluated by a member of the study team not involved in testing or training who will attend 1 training session per participant (randomly throughout the training period). The trainer will also complete a detailed training log, a checklist of standardized steps to be followed during training, and document adherence to the intervention and any adverse events. Formative assessments with the trainer will ensure fidelity.

Control Group

Participants in the control group will receive the usual care (if any) during a 4-week period. During this time, participants will be considered on a waitlist to receive the WSTP after the completion of the project and may continue or begin any activities provided by therapists or in the community. After completing the T2 evaluations, participants in the control group will complete a target of five 45-minute weekly sessions of the WSTP, delivered by trained personnel as described for the intervention group. While usual care may include some form

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of manual wheelchair skills training, the evidence suggests that the amount of training received during usual care, according to the Wheelchair Skills Program, is limited [24].

Data Collection

The RA, an occupational therapist with 12 years of experience in clinical research, will collect quantitative data and enter them into a secure database. Sociodemographic information will include age, sex, gender, diagnosis, length of time using a wheelchair, previous experience with using a manual wheelchair (where and for which activities), previous wheelchair training, and assistance required for using a manual wheelchair. Assistance will be assessed using the 5-point General Scale for the Extent of Caregiver Assistance scale (5=no assistance/always autonomous, 4=standby assistance only, 3=verbal assistance only, 2=one-person physical assistance, 1=two-person physical assistance, and -0=equipment needed [31]. Additional information will include the propulsion method and wheelchair specifications (frame type, dimensions, tire, and caster size).

Primary Outcome

Manual wheelchair skills performance (ie, what the person does in their daily life) will be assessed using the Wheelchair Skills Test Questionnaire for Manual Wheelchair Users (WST-Q-M version 5.4.2) [32,33]. The WST-Q-M comprises 30 discrete skills required to move around in a manual wheelchair indoors and in the community. Participants will rate their performance for each of the 30 manual wheelchair skills on a 4-point scale. The root performance question asks, “Could you do this (manual wheelchair skill) in your own setting?” Response options include “yes, very well (3),” “yes, but not well (2),” “yes, with help (1),” “no (0),” and “no part” (NP) with the manual wheelchair. The total percentage WST score is calculated as: total percentage WST performance=sum of individual skill scores/([# of possible skills – # of NP scores – # of testing error (TE) scores] 3) × 100%. Participants will be asked whether the skill represents a training goal (yes, no) to assist with defining the training program. The WST-Q-M can be completed in approximately 15 minutes, has strong psychometric properties in English and French [34,35], and has been used extensively in clinical trials [16]. The WST-Q-M has been validated by the study team for ARSACS [36]. A minimally clinically important difference (MCID) of 20% relative improvement in WST scores (T1 to T2) has been suggested for adults [22]. However, a recent invited commentary by Best and Kirby [37] suggests that the potential clinical significance of much smaller improvements should be considered.

Secondary Outcomes

Manual wheelchair skills capacity (ie, what a person can do in a standardized environment) will be assessed using the Wheelchair Skills Test (WST) v5.4 for manual wheelchair users [38,39]. Participants will be asked to execute 30 manual wheelchair skills in a standardized environment. They will be scored on a 4-point scale as “advanced pass (3),” “pass (2),” “partial pass (1),” “fail (0),” “NP,” or “TE.” The total percentage WST score is calculated as: total percentage WST capacity score = sum of individual skill scores/([# of possible skills – # of NP scores – # of TE scores] × 3) × 100%. The WST has been validated in adult populations. An MCID of 20% relative improvement in WST scores (T1 to T2) has been suggested for adults [22].

Manual wheelchair use self-efficacy (ie, belief in one’s ability to accomplish specific tasks while using a manual wheelchair) will be assessed using the Wheelchair Use Confidence Scale for Manual Wheelchair Users Short Form (WheelCon-M) [40]. WheelCon-M comprises 21 statements related to confidence using a manual wheelchair in activities and environments, each rated on a scale from 0 (“not at all confident”) to 10 (“completely confident”), producing a total mean score of 0 to 10 [40,41]. Responses will indicate the current level of perceived confidence in 6 areas (ie, navigate the physical environment in a manual wheelchair, perform activities in a manual wheelchair, problem solve, advocate for needs, and manage social situations and emotions). The WheelCon-M has been validated for ARSACS [36].

Manual wheelchair mobility will be measured using actigraphy, collected with a small, noninvasive, and lightweight accelerometer (Actigraph GT3X; Ametris). The Actigraph GT3X contains a multidirectional accelerometer that integrates information about direction and speed to produce an electrical current with variable magnitude and duration, and the electrical current data are stored as activity counts [42]. The time between sampling units (epochs) will be set at 15 seconds [42].

The participants will receive 2 actigraphs after completing the assessments (T1, T2, and T3); one will be worn on their nondominant arm between the elbow and shoulder, and one will be placed on the rear wheel of their manual wheelchair inside a custom-made waterproof packet that will be installed using tie-wraps. Participants will be asked to wear the actigraphs at all times during a 7-day period, except during sleep, bathing/showering, or swimming. They will also be asked to log the exact time the actigraph was put on and taken off each day [43]. The tester will obtain the actigraphs and logs from the participants at the end of the 7-day period (either in person or by postage-paid envelopes that will be provided to the participants). Actigraphy has been validated for evaluating manual wheelchair mobility in adults [44].

Qualitative Interviews

The participants will complete semistructured individual interviews lasting between 45 and 60 minutes, either in person or online with the RC, after completing the WSTP intervention. The interview guide will be created by the study team using an iterative process following an appropriate framework (eg, International Classification of Functioning, Disability, and Health) [32]. Questions will explore expectations with wheelchair use, previous experiences with using a wheelchair, and perceptions of wheelchair skills training. In addition, we will explore perceptions of the WSTP (dosage, fatigue, training approaches, and usefulness), experiences with manual wheelchair service provision, satisfaction with manual wheelchair use, and social participation. The interview guide will be pilot tested with 1 person with ARSACS and 1 person with MD1. The interviews will be audio recorded.

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Data Analysis

Summary statistics (means, standard deviations, frequencies, and percentages) will be used to describe the sample. Details of adherence and intervention fidelity will be summarized. Assumptions for parametric testing of quantitative data will be verified, and the data will be screened for outliers [45]. An intention-to-treat analysis will be prioritized (with a per-protocol analysis reported depending on adherence and fidelity), and missing data will be addressed using multiple imputation methods for repeated measures of longitudinal data [46].

To address the primary objective, T2 WST performance scores will be compared between the experimental and control groups using ANCOVA or its nonparametric equivalent, with baseline scores used as the covariate. Variance (R^2), statistical significance (95% CI), and effect sizes (partial η^2) will be assessed using sums of squares methods. Secondary objectives will be evaluated using linear mixed-effect models, which are flexible to explore within-participant mixed/random effects [47].

Post-hoc exploratory analyses will investigate the influence of age, gender, diagnoses (ataxia or dystrophy), and manual wheelchair experience on effect size using linear mixed-effect models. Comparisons between WST-Q-M within-participant change scores for the experimental group (T1-T2) and WST-Q-M within-participant change scores after training in the control group (T2-T3) will be explored using *t* tests. Sensitivity analyses will be conducted on demographic variables (eg, age, sex, gender, and diagnoses) to generate hypotheses and inform future investigations.

A reflexive thematic analysis will be used to explore perceptions of the influence of manual wheelchair training on mobility, participation, and quality of life according to an appropriate framework (eg, International Classification of Functioning, Disability, and Health) [48]. Interviews will be transcribed verbatim, and researchers will familiarize themselves with the data by rereading and relistening to interviews. Using NVivo software (version 14; Lumivero), transcripts will be coded line-by-line. Then, the codes will be grouped into similar ideas, and themes will be developed using an inductive approach. Member checking will be performed with participants throughout data analysis, with the citizen partner actively involved in data interpretation and synthesis to enhance confirmability. Final themes and subthemes will be verified with participants and the research team. To further enhance trustworthiness according to Ahmed (2024) [49], the credibility of data interpretation will be strengthened through triangulation with quantitative data. Quantitative and qualitative data will then be integrated using joint display diagrams to merge, compare, and relate findings to better understand how subjective perceptions align with measured improvements [50]. We will also explore why some participants may experience better outcomes or how people deal with challenges. Additionally, we will remain aware of potential personal biases regarding our perception of the effectiveness of the intervention. Finally, findings on the facilitators and barriers to training may be transferable to individuals with other neuromuscular disorders who share similar symptoms and functional characteristics [49].

Results

The study received ethical approval in July 2024 and recruitment started in January 2025. A graduate student, RA, and RC have been recruited and trained. Data collection began in February 2025, and the anticipated completion is February 2026.

Discussion

Overview

The need for improved manual wheelchair skills assessment and training in ARSACS and other neuromuscular disorders was observed and documented by our team. Given the strong documented evidence among heterogenous populations of adults [22,23], we hypothesize that an evidence-based standardized manual wheelchair skills training program will improve manual wheelchair skill performance for people with hereditary degenerative disorders such as ARSACS and MD1. This paper describes the protocol for a randomized waitlist controlled trial to evaluate the efficacy of the WSTP on manual wheelchair performance in adults with ARSACS or MD1 and explore the influence of training manual wheelchair skills capacity, manual wheelchair use self-efficacy, manual wheelchair mobility, and satisfaction with participation.

The United Nations declared mobility a basic human right [51]. For people with neuromuscular and hereditary degenerative disorders such as ARSACS and MD1, manual wheelchairs are commonly provided to facilitate self-directed mobility when walking becomes difficult or not possible. Similar to riding a bike, using a manual wheelchair requires skill development and practice over time in indoor and outdoor environments and during real-life situations. ARSACS and MD1 are highly prevalent in the province of Quebec, Canada. This geographic distribution has positioned our team to explore longitudinal aspects of mobility and participation in these 2 specific disorders, which may be generalized in the future to other neuromuscular disorders (eg, spinal muscle atrophy and muscular dystrophy).

Previous studies have documented the clinical significance of learning just one manual wheelchair skill, which could mean the difference between leaving the house independently to get groceries or relying on another person to complete this instrumental activity of daily living [27]. For example, learning how to do a transient tip (ie, popping the small front caster slightly off the ground to get over a door threshold, may make the difference between being able to leave the home or not). Once in the community, learning various approaches to opening heavy doors, maneuvering within small spaces, and navigating irregular surfaces and curbs may make the difference in being able to go to school independently, use public transit, participate in the workforce, or socialize with friends. Given that people with ARSACS have been shown to have very low manual wheelchair skills compared to other adult manual wheelchair users [16], this study has the potential to have major implications on mobility, participation in social and vocational activities, and quality of life for people with ARSACS and MD1.

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Establishing the effect size in an RCT will position the research team to work with clinical partners to implement manual wheelchair skills training and evaluation into clinical practice. Given the proximity of the researchers and clinicians involved in this study (ie, the research center and rehabilitation center where outpatient services are provided are in the same building), this trial has the potential to catalyze change in manual wheelchair service provision for people with ARSACS and MD1. Implementing manual wheelchair skills training and evaluation into clinical practice would ensure that training starts early, specifically in the fundamental skills (eg, propulsion and maneuvering) and indoor skills that are required for getting around at home, school, and work. The training of various approaches needed for community and advanced skills (eg, ascending curbs and steep ramps) may be customized based on disease progression, manual wheelchair configuration, and personal experiences. This, in turn, could reduce risks of acute (eg, tips and falls) and overuse (eg, repetitive strain due to poor propulsion techniques) injuries [52-54]. Booster sessions may be provided to people on an as-needed basis, such as after accidents or changes in manual wheelchairs (a service covered by the provincial health care system in Quebec every 5 years). Moreover, optimizing manual wheelchair skills may reduce caregiver burden among those who assist with mobility to accomplish activities of daily living and social participation, roles that are commonly filled by parents, spouses, and other family members. Future studies may explore facilitators and barriers to implementing manual wheelchair skills evaluation into practice with clinicians and managers.

Finally, the collaborations with clinicians, a special interest group in neuromuscular disorders (Muscular Dystrophy Canada), and a citizen partner who has lived experiences with ARSACS and manual wheelchair training research will enhance the credibility of the research findings and increase the likelihood of successful future implementation. New research questions may be developed based on the needs identified by these groups.

A multifaceted knowledge translation strategy will be used to increase awareness and knowledge to change practice for manual wheelchair skills training for people with ARSACS and DM1. Targeted materials for health care professionals will include infographics, podcasts, and video capsules that will be launched through the international PROSPAX (Progression Chart of Spastic Ataxias) initiative on recessive ataxias and neuromuscular disorders (Gagnon), including Rare Disease Day. Materials will be shared through clinical and community platforms including websites and social media of Muscular Dystrophy Canada, Groupe de Recherche Interdisciplinaire sur les Maladies Neuromusculaires, and the Wheelchair Skills Program. Lunchtime presentations and manual wheelchair training workshops will be planned with clinicians. Academic dissemination will include a minimum of 2 peer-reviewed articles and 2 national/international conferences. Led by the corresponding author (KLB), all study investigators will have access to the final data set and will be eligible for authorship.

This study has limitations that should be considered. Although the sample size is powered for the primary outcome, we do not have the power to detect changes in secondary outcomes or for subgroup analysis to explore the influence of potentially confounding factors. Considering the population under study, there may be an increased risk of attrition due to fatigue or difficulty in scheduling training/testing sessions within the desired time frame. We hope to mitigate these issues by offering validated questionnaire versions of tests and by providing training in the community to overcome transportation challenges associated with commuting to a research center. Given that wheelchair configuration and positioning are outside the scope of the WSTP, we will not consider wheelchair configuration or positioning in this study. However, these factors may have an impact on manual wheelchair skill performance and capacity, and ultimately on the efficacy of the intervention.

Conclusion

The results of this randomized waitlist-controlled trial will confirm whether manual wheelchair skills training can improve self-directed mobility and related outcomes for people with ARSACS and MD1. The findings may help guide clinical practice toward manual wheelchair skills training for understanding potential influences on manual wheelchair mobility among people living with neuromuscular disorders.

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Data Availability

Deidentified data will be made available to the public upon request to the corresponding author (KLB).

Authors' Contributions

EN contributed to the methodology and original draft writing. FR, CG, RLK, XR, IL, and JL contributed to the conceptualization, methodology, and review and editing of the manuscript. KLB contributed to funding acquisition, conceptualization, methodology, supervision, project administration, original draft writing, and review and editing.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the Muscular Dystrophy Canada.
[PDF File (Adobe PDF File), 145 KB - resprot_v14i1e66974_app1.pdf]

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Abbreviations

ANCOVA: analysis of covariance
ARSACS: autosomal recessive spastic ataxia of Charlevoix-Saguenay
CIUSSS-CN: Centre Intégré Universitaire de Santé et de Services Sociaux de la Capitale-Nationale
CONSORT: Consolidated Standards of Reporting Trials
MCID: minimally clinically important difference
MD1: myotonic dystrophy type 1
NP: no part
PROSPAX: Progression Chart of Spastic Ataxias
RA: research assistant
RC: research coordinator
RCT: randomized controlled trial
TE: testing error
WheelCon-M: Wheelchair Use Confidence Scale for Manual Wheelchair Users Short Form
WST: Wheelchair Skills Test
WST-Q-M: Wheelchair Skills Test Questionnaire for Manual Wheelchair Users (version 5.4.2)
WSTP: Wheelchair Skills Training Program

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Protocol

Investigating the Effects of a High-Load Resistance Training Program on Bone Health in Wheelchair Users (the BoneWheel Study): Protocol for a Randomized Controlled Trial

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Abstract

Background: Low mechanical loading of the bones of wheelchair users leads to low bone mineral density (BMD) and increased risk of bone fractures and associated complications. High-load resistance training of the upper body is one way to achieve mechanical loading of the lumbar spine and the hip bones. In addition, maintaining good nutritional status with key nutrients for bone remodeling, that is, vitamin D and calcium, is important for bone accrual.

Objective: This study aims to investigate the effect of 24 weeks of high-load resistance training combined with nutritional optimization on lumbar spine BMD. Secondary objectives are to investigate the effects of the intervention on (1) bone and physical health parameters, such as bone turnover blood markers, nutritional status, body composition, and maximal muscular strength, as well as (2) exercise motivation and mental health.

Methods: In this randomized controlled trial, we aimed to include 60 wheelchair users with nonprogressive impairments. Participants were randomly allocated to 24 weeks of either (1) high-load resistance training and nutrition optimization or (2) nutrition optimization only, stratified by sex and sport activity status. The training program consisted of 3 weekly sessions comprising 6 exercises periodized in low-, moderate-, and high-load phases. The nutritional optimization aimed to ensure sufficient intake of protein, vitamin D, and calcium. BMD and body composition; maximal muscular strength; and nutritional, physical, and mental health status were assessed at baseline, midpoint, and postintervention visits. Furthermore, follow-up assessments of a subgroup were conducted at 6 to 18 months after the intervention. This protocol was approved by the Regional Committee for Medical and Health Research Ethics South-East, Norway.

Results: Recruitment occurred between November 2022 and 2023. A total of 68 wheelchair users were screened for eligibility, of whom 45 (66%) were enrolled and allocated to one of the study groups (n=24, 53% training group; n=21, 47% control group). At the midpoint and postintervention visits, 36 (n=17, 47% and n=19, 53%, respectively) and 33 (n=14, 42% and n=19, 58%, respectively) participants were assessed, respectively. Analysis of the data collected at the screening visit commenced in spring 2024, while analyses of data collected at the baseline and retest visits began in autumn 2024. Publication of the results of this study is expected by the end of 2025.

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Conclusions: This protocol presents the first randomized controlled trial of a high-load resistance training intervention in wheelchair users, focusing on bone, physical, and mental health. The results will contribute to new knowledge in exercise science for this population and generate novel hypotheses for future studies.

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KEYWORDS

osteopenia; osteoporosis; nonambulatory exercise; adapted physical activity; strength training; spinal cord injury; SCI; cerebral palsy

Introduction

Background

The low mechanical loading of bones of wheelchair users due to nonambulation leads to low bone mineral density (BMD) [1,2]. Low BMD is problematic as it increases the risk of osteoporotic, or low-impact, fractures [2]. In ambulatory people, adding mechanical loading through physical activities, such as running, jumping, and resistance training, is a way of stimulating the bones to prevent bone loss [3-6]. Furthermore, resistance training and impact exercises are explicitly recommended to improve or at least maintain BMD, prevent falls, and thereby reduce the risk of osteoporotic fractures [6]. However, these recommendations are mainly based on studies investigating the effects of a whole-body training programs, which sometimes include jumping, weight-bearing activities, or a combination of resistance training and running [7], that may be inapplicable to nonambulatory wheelchair users.

Most research on bone health in wheelchair users has been performed on individuals with spinal cord injury (SCI). SCI is a risk factor for low BMD due to physiological changes such as reduced neuromuscular activity and changes to systemic hormones that create an unfavorable environment for bone formation, in addition to the acute offloading after injury and the reduction in mechanical stimuli in cases where the paralysis is chronic. Bone loss has been shown to range from 4% to 9% at the hip in the first 6 months after injury, stabilizing at a total loss of approximately 25% around 10 years after injury, when a new steady-state bone mass seems to be reached [8,9]. Throughout life, 25% of individuals with SCI experience at least 1 fracture, of which 70% occur due to a low-impact injury, such as moving from wheelchair to bed [10]. Consequently, interventions to improve BMD or at least slow bone loss are of high value.

In addition to reduced bone loading, low BMD can be related to suboptimal nutrition, such as chronic low energy intakes compared with the energy needs (low energy availability), low vitamin D blood levels, or low dietary calcium intakes [11-13]. In our previous study on Paralympic athletes [14], 25% displayed clinically low vitamin D blood levels (<50 nmol/L) and 75% displayed values below the International Olympic Committee (IOC) recommendations (<80 nmol/L) [12].

Physical activity and sports participation could be of great importance for the bone health of wheelchair users with low mechanical bone load. However, increasing general physical activity per se does not appear to solve the problem of low BMD in wheelchair users. This is evidenced by the finding that reduced bone health is more prevalent in sport-active individuals with a disability compared with the general population. Our group has recently found that 31% to 34% of Dutch and Norwegian Paralympic athletes display clinically low BMD (*z* score <–1.0) at the hip and femoral neck respectively [14]. The low BMD was most prominent in the wheelchair-using athletes, of whom 46% to 55% displayed clinically low BMD at the hip. In addition, 30% of wheelchair-using athletes displayed low BMD at the spine, compared to only 18% among the ambulatory Paralympic athletes [14]. Another study of Norwegian Paralympic athletes found similar results [15]. These findings suggest that the mechanical loading of the hip and spine achieved by physically active wheelchair users may not be adequate for maintaining bone health. In the adapted exercise literature, most interventions aiming to improve BMD are studies in patients with SCI, most commonly during the acute and subacute phases after injury [16]. Therapies such as passive standing [17,18], vibration therapy [19,20], and exercise with functional electrical stimuli [21-23] have shown little to no effect on BMD. However, the effects of high-load resistance training on bone health in wheelchair users are unknown. To our knowledge, no study has yet investigated an upper-body high-load resistance training program for improving the bone health of wheelchair users.

Objectives

Alongside the effects of resistance training on bone health, several positive implications on physical health parameters can be expected, such as increased strength and improved body composition and blood health markers [24-28]. Furthermore, physical activity and participation in sport are major positive contributors to mental health, influencing well-being and quality of life [24]. Therefore, the primary objective of this randomized controlled trial (RCT) is to investigate the effects of upper-body high-load resistance training on the BMD of the lumbar spine and hip in wheelchair users. The secondary objectives are to investigate the effects of the intervention on (1) bone and physical health parameters, such as blood bone turnover markers, nutritional status, body composition, and maximal muscular strength, and (2) motivation for exercise and mental health indicators such as well-being, exhaustion, and vigor.

Methods

Study Design

This protocol describes a multisite, single-blinded, 2-armed RCT comparing a 24-week resistance training intervention combined with nutritional optimization (training) to nutritional optimization only (control).

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Study Setting and Timeline

The study was conducted at 3 sites in Norway: Norwegian School of Sport Sciences (NIH, the main site), Western Norway University of Applied Sciences (HVL) in Bergen, and Norwegian University of Science and Technology (NTNU) in Trondheim.

Participants attended one of the 3 study sites for eligibility screening before being included in the RCT (T0). Those meeting the eligibility criteria were invited for baseline testing (T1), and thereafter intervention midpoint testing (T2, week 12 or 13 approximately), postintervention testing (T3, week 25), and a final follow-up testing (T4, 6-18 months later); overview in Figure 1. All intervention training was conducted at the study site, at a partnering commercial fitness centre local to the participant's home. Within 6 months of completing the study, individual information about the development in BMD, body composition, maximal muscle strength, and nutritional status was provided to each participant in writing, with the option of over-the-phone counseling.

Figure 1. Schematic overview of study timeline per study site and cohort. HVL: Western Norway University of Applied Sciences; NIH: Norwegian School of Sport Sciences; NTNU: Norwegian University of Technology and Science.

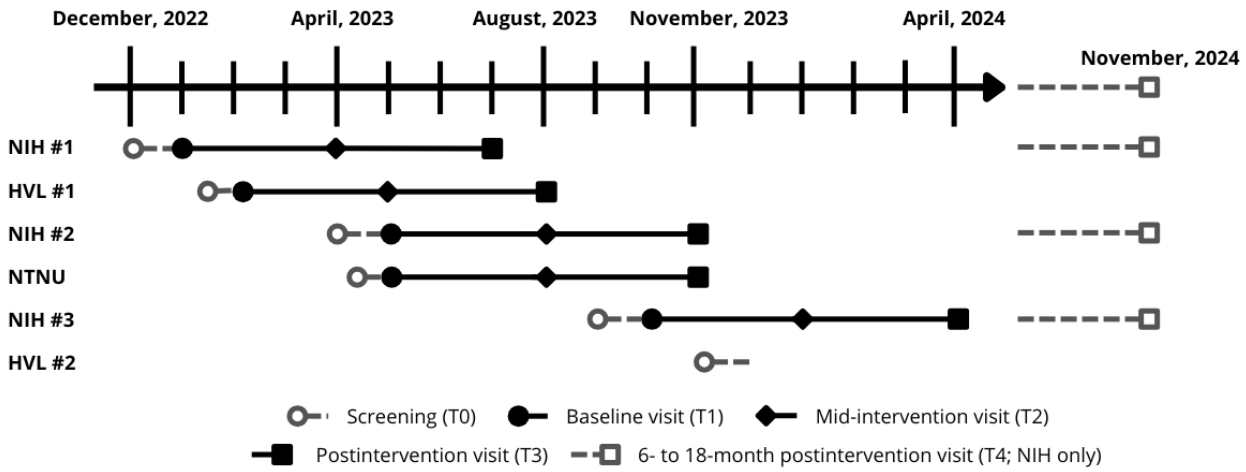

Participants and Recruitment

To be enrolled in the RCT, participants were screened for the following eligibility criteria: (1) BMD *z* score ≤0 SD at the spine, total hip, and femoral neck; (2) mainly nonambulant (using the wheelchair for ≥50% of the time); (3) aged 18 to 60 years; (4) ability to perform key exercises and maximal muscle tests; (5) nonprogressive impairment and, in the case of SCI, ≥2 years since the time of injury; (6) no comorbidities or use of medications that affect bone metabolism, nutritional uptake, or metabolism of vitamin D or calcium or that contraindicate high-load resistance training (eg, heart disorders); (7) not pregnant or menopausal; (8) no medical (eg, bisphosphonates) or physical (eg, functional electrical stimuli) treatment of low BMD; (9) no fractures affecting measured sites or contraindicating strength testing or training; and (10) no language or cognitive barriers interfering with the ability to understand study procedures or perform the training program. In addition, the ability to attend the laboratories and gym at the test site a minimum of 3 times over the study period was necessary for participation. A detailed list of eligibility criteria is provided in Multimedia Appendix 1. The inclusion of participants was authorized by the principal researcher in collaboration with senior researchers on the team and the study medical adviser.

Participants were recruited via Sunnaas Rehabilitation Hospital; the Norwegian Confederation of Sports; Sports cluster of Western Norway (Norwegian: Idrettsklynge Vest); and the Para Sport Centre in Trondheim, Norway, as well as advertisements in local media, the relevant national patient interest groups, and in social media channels. Participants expressed interest via a web-based registration form containing contact details and date of birth.

Sample Size

Power calculation was performed using G*Power (version 3.1; Heinrich-Heine University) [29]. The primary outcome in this study is the change in BMD of the spine. Means and SDs for a relevant difference between the training and control groups are based on 2 previous studies: one validation study in 345 healthy adults [30] and one 24-week bone-strengthening training intervention in a youth cohort with obesity [7]. Using the lowest significant increase in BMD of the spine of 3.5% and SDs from the 2 studies, 14 to 32 (average of 23) persons per group were estimated to achieve 80% power at a significance level of $P \leq .05$. To account for a potential 25% dropout rate, the aim was to include 30 participants in each group. To achieve this, it was estimated that 120 to 150 participants would need to be screened. Of approximately 50,000 wheelchair users in Norway (according to the Norwegian Labour and Welfare Administration [31]), we estimated to have a pool of 1000 possible participants from the 3 main cities in Norway.

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Allocation and Randomization

Eligible participants were randomly allocated to 1 of the 2 groups, the training (training and nutrition, n=30) or the control (nutrition only, n=30) group, directly after completion of baseline test procedures. The randomization list was created by a senior researcher not directly involved in the study procedures, using a web-based randomization tool [32]. The randomization list was stratified by physical activity status (active: high activity categorization in the International Physical Activity Questionnaire [33,34] or actively participating in sports for >6 months at least twice per week or nonactive) and sex (male or female), with a 1:1 allocation using random block sizes of 4, 6, and 8. To ensure that allocation concealment was sequentially numbered, nontransparent and sealed envelopes containing the treatment allocation information were prepared by a person not involved in the study. Blinding is upheld for the main outcome for the main researcher during analyses. The groups were checked for distribution of the number of participants with SCI, age, medication use, degree of injury or disability, and degree of wheelchair use.

Intervention

Piloting and Choice of Exercises

A team of researchers with expertise in resistance exercise and biomechanics with relation to bone loading and practitioners working with wheelchair users defined the exercises for the upper-body resistance training program. The exercises were chosen based on a series of pilot tests. First, wheelchair users from the study reference group tested the feasibility of potential exercises. Second, feasible exercises were then tested in the laboratory while measuring muscle activation with electromyography, focusing specifically on the difference in forces of the back extensors during variations of the same exercise (eg, variation in grip positioning). This confirmed that the exercises were indeed activating the muscles around the lumbar spine, aligning with our biomechanical assumptions on bone loading.

Upper-Body High-Load Resistance Training Program

The exercise intervention comprised a 24-week resistance training program of 3 sessions per week. Each session was completed individually in approximately 60 minutes, depending on the time the participants needed for transitions between the wheelchair and the training apparatuses. The coaches who supervised several of the sessions were trained by the main researcher in all exercises included in the training program, and they had piloted several sessions on wheelchair users. The coaches followed a standard operating procedure for all training sessions. Table 1 presents an outline of the 24-week training program. The program was periodized with six 4-week phases, where the first phase was the familiarization phase wherein all sessions were supervised at the test site (NIH, HVL, or NTNU) by trained coaches (weeks 1-4). This phase had a predetermined coaching focus covering fitness centre familiarization and etiquette including asking for help; exercise techniques such as breathing techniques and independence in setting up, transferring, and performing the exercise; repetitions in reserve; session rating of the perceived exertion (sRPE) with the Borg 11-point scale [35]; and progressing exercise loads.

Table 1. The BoneWheel study training program.

Week	Supervised training	Training program
1 to 4	All	Conservative familiarization (2-3 set, 8-12 repetitions, ≥2-5 RIR[a])
5 to 8	1 session in week 5 and week 8	Moderate intensity (2-4 set, 5-8 repetitions, 2-3 RIR)
9 to 11	None	High intensity (3-5 set, 4-6 repetitions, 1-3 RIR)
12	None	Total deload 1 week before intervention midpoint test
13 to 16	1 session in week 16	Moderate intensity (3-4 set, 5-8 repetitions, 2-3 RIR)
17 to 20	1 session in week 20	High intensity (3-4 set, 4-6 repetitions, 1-3 RIR)
21 to 23	None	High intensity (4-5 set, 3-5 repetitions, 1-3 RIR)
24	None	Deload (approximately 50% volume, maintained intensity from week 21-23) 1 week before postintervention test

[a]RIR: repetitions in reserve.

Subsequent individual supervised sessions (weeks 5, 8, 16, and 20) focused on continued quality in exercise technique and intensity (ie, loading) in addition to resolving any issues that participants reported. From week 5, the participants completed the 3-weekly sessions on their own or with an assistant according to need at a suitable training site (commercial gyms or the study site gym) local to the participants' home. The supervised session in week 5 aimed to help participants transition to their local gym in the cases where they did not continue training at the test site gym, and one of the coaches supervised the session in the new gym setting.

A deload week, 1 week before the intervention midpoint visit, meant that the participants would complete a total of 69 sessions: 15 sessions supervised at the study site and 54 sessions unsupervised, across the 24-week intervention.

The training program consists of 6 main exercises (Figures 2 and 3), 1 warm-up exercise, and 1 optional exercise (Multimedia Appendix 2). Overhead press and incline bench press exercises were performed both dynamically and isometrically on separate days, that is, day 1: dynamic and isometric, and day 2: isometric and dynamic, respectively. The isometric mode of these exercises was introduced in week 3 to allow more contact time for technique training in the dynamic mode. The warm-up

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exercise (Figure S1, top, in Multimedia Appendix 2) was performed passively (with the help of the arms) or actively, depending on the neuromuscular function of the back extensors. The cable rotation exercise (Figure S1, bottom, in Multimedia Appendix 2) was performed by participants with sufficient core stability and function and was introduced in week 4 of the program. All participants, both training and control groups, were allowed to continue their normal sports and training routines. Total training load was discussed between the coach and participants of the training group.

Figure 2. Maximum voluntary isometric contraction test battery: (A) overhead press (OHP), (B) prone row, (C) supine pull, and (D) bench press (BP). All exercises were also training exercises. Grip width and chain length in the OHP and BP were standardized to the position where the forearm was perpendicular and the upper arm parallel to the floor (90° elbow flexion). Photos: Gjermund Erikstein-Midtbø, Norwegian School of Sport Sciences.

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Figure 3. One repetition maximum test battery: (A) overhead press and (B) 30° incline bench press. The top and bottom positions are shown; the bottom position was approved when the elbow flexion was below 90° and the upper arm was below parallel to the floor. Grip width was standardized to the position where the forearm was perpendicular to the floor when in the bottom position. Both exercises were included in the training program. Photos: Gjermund Erikstein-Midtbø, Norwegian School of Sport Sciences.

Any emerging adverse events were dealt with, recorded, and classified by the main researcher and the study medical adviser as per the study's standard operating procedures for adverse events and reported in the dissemination of the results of the study. Events were classified as adverse or serious adverse events and as unrelated, unlikely, possible, probable, or definite causal relationship of the event and the study procedures or intervention.

Nutrition Optimization

To ensure an optimal biochemical environment allowing for bone remodeling, key aspects of nutrition were optimized. For the effects of the resistance training program to be as clear as possible, both the training and control groups received nutritional optimization, as the sample size only allowed for a 2-armed study. Supplementation of vitamin D is frequent in Norway, and the participants were encouraged to adhere to their normal diet. As such, it would have been difficult to investigate the impact of nutritional factors on bone health. Furthermore, nutritional optimization was performed to ensure that nutritional factors of relevance for bone health were as similar as possible between participants in both groups.

First, to ensure stable intakes of key nutrients for optimized bone remodeling conditions, all participants (both training and control groups) received and were asked to consume a mixed powder supplement (FrieslandCampina) consisting of vitamin D (800 IU), calcium (250 mg), and whey protein (30 g) on 3 days of the week throughout the 24-week study period. The supplement could be mixed in water or milk according to preference, and the training group were asked to consume it around the training sessions.

Second, to further ensure optimal intake levels of calcium and vitamin D, supplements were provided to participants (Nycoplus Calcium 500 mg, Nycoplus D_3-vitamin 1600 IE or 3200 IE, Orifarm) using an individual approach considering BMD *z* scores, dietary calcium intake, and S-vitamin D status (Table 2). BMD *z* scores guided the recommended daily intake of calcium, either 800 mg/day as per the Nordic nutrient intake recommendations [36] or 1500 mg/day based on the IOC consensus statement on dietary supplements (*z* score ≤–2.0) [13]. Calcium supplements were to be taken daily until the subsequent test period. Vitamin D_3 supplementation was administered if the participant's serum 25-hydroxyvitamin D (25(OH)D) level was <80 nmol/L as per the IOC consensus statement dietary supplements [13]. The Norwegian clinical reference values for vitamin D_3, that is, 25(OH)D <50 nmol/L is classified as low and <25 nmol/L as clinical deficiency, were used as two further cutoff values for the three doses. The individual dose was prescribed for 4 weeks as it was deemed easier for the participants and important to increase the serum 25(OH)D fast to optimize the biochemical environment for bone remodeling. Dose administered was determined by registered dieticians or nutritionists in the research team or by the medical adviser, following the protocol in Table 2.

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Table 2. Dietary supplement protocol in the BoneWheel study.

Supplement	Dosage	Frequency	Weekly dosage	Duration
Protein (all; alternative A or B)				
A: FrieslandCampina protein				
Protein (g)	30	3 d/wk	90	Continuously[a]
Vitamin D_3 (µg)	20	3 d/wk	60	Continuously
Calcium (mg)	250	3 d/wk	750	Continuously
B: vegan alternative protein				
Protein (g)	30	3 d/wk	90	Continuously
Additional supplements taken with B				
Vitamin D_3	20	3 d/wk	60	Continuously
Calcium carbonate	500	2 d/wk	1000	Continuously
Additional supplementation based on s-D_3[b] and calcium total intake (individual)				
Vitamin D_3 (µg)				
s-D_3 >80 nmol/L	0	__[c]	—	—
s-D_3 <80 nmol/L	80	Daily	560	4 wk
s-D_3 <50 nmol/L	120	Daily	840	4 wk
s-D_3 <25 nmol/L	160	Daily	1120	4 wk
Calcium carbonate (mg)				
Total intake ≥800 mg/d or 1500 mg/d when *z* score <–2.0	0	—	—	—
Total intake <800 mg/d	500 or 1000	Daily	3500 or 7000	Continuously
z score <–2.0 and total intake <1500 mg Ca/d	500, 1000, or 1500	Daily	3500, 7000, or 10,500	Continuously

[a]Continuously indicates until retest dietary recalls are conducted.

[b]s-D_3: serum vitamin D_3 concentration.

[c]Not applicable.

Finally, each participant received individual counseling in written and oral form, based on their nutritional intake (from 24-hour dietary recall interviews) and nutritional biomarkers (from blood samples). The counseling focused on their total daily intakes of calcium and vitamin D, protein, and energy and on related food groups, as well as general nutritional guidelines for fiber, fruit, and vegetable intake [36].

Training and Supplement Monitoring

All participants were asked to log their training and or physical activity in the mobile phone app XPS Network (Sideline Sports). The app was used to provide the intervention training program, and the participants logged their training (exercise loads, completed repetitions, repetitions in reserve, and sRPE). They could also communicate with coaches and nutritionists via the app chat (eg, about scheduling, illness, and issues with or questions about the training program or dietary supplements). It was requested that any training and competition outside of the intervention be logged by all participants including duration, type of training, and sRPE. The app gave weekly prompts to register information about their training or activity, health (illness or injury preventing completing sessions, certain exercises, or dietary supplement protocol), and adherence to the supplement protocol. Any issues arising in their answers were promptly dealt with via the integrated app chat, by phone call, and, if necessary, discussed with the study medical adviser. Participants could be excluded from further participation and referred to their general practitioner or the Norwegian health care system for follow-up in the case of discovery of contraindicating medical, physical, or psychological issues. The participants were offered to extend their length of study to compensate for any missed training (1) if they missed full weeks of training (3 consecutive sessions) or (2) if they had >10 nonconsecutive sessions missing. Compensatory sessions were given in the ratio 1:1 as far as possible, with a maximum of 3 weeks (9 sessions) added to the program. Participants completing ≥80% of the prescribed sessions were deemed compliant with the protocol.

Outcomes

The primary outcome of the study is the change in BMD of the lumbar spine, whereas secondary outcomes are changes in other markers of bone health, such as blood bone turnover markers; parameters of muscular, functional, and psychological dimensions; nutritional status; and other markers of overall health. All outcomes and the corresponding assessment methods

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are provided in Multimedia Appendix 3. Most assessments were conducted by the main researcher. Dual-energy x-ray absorptiometry (DXA) scans at the NIH and Bergen sites were performed by the main researcher, while the DXA scans at the NTNU site were performed by trained hospital staff. DXA scans were performed unblinded, while all DXA scan analyses were performed by the main researcher after blinding to group allocation. Trained bioengineers and researchers collected blood samples, while trained nutritionists or dieticians conducted the 24-hour dietary recalls.

Study Procedures and Data Collection Methods

Overview

At all test day visits, the participants arrived in a fasted state for DXA scanning and blood sampling. Then, a standardized test day meal was provided before strength tests were conducted. The meal consisted of wholegrain bread and spread or oat porridge, water, milk, juice, coffee, and tea ad libitum at the baseline visit, where the meal was recorded and repeated at revisits. The participants recorded their dietary intake on the day before the baseline visit and were asked to replicate the intake before the revisits. Online questionnaires previously sent to the participant by email were checked, and food logs for the previous day were collected. At the midintervention and postintervention visits, supplements that the participant may have left over were collected and weighed to evaluate adherence to the supplement protocol. Subsequent maximal dynamic and isometric muscular strength assessments were conducted.

BMD and Body Composition

Body composition and BMD were assessed in a rested state by DXA with the available scanner at each test site (Lunar iDXA and Prodigy; GE Healthcare; and Horizon A, Hologic) following a minimum of 4 hours of fasting. To account for differences in DXA scanners, cross-calibration equations will be used to standardize the data when compared directly and interindividually. DXA scans were performed at screening (T0), midpoint (T2), and postintervention (T3) testing at the same site using the same equipment for each participant. If the time between screening (T0) and baseline (T1) exceeded 6 weeks, new scans were performed at baseline and used in all analyses. Scans of the lumbar spine, bilateral hip, and whole body were taken as per manufacturer recommendations as far as possible. In cases where standard positioning guidelines were impossible to follow, deviations were noted and standardized at each repeat visit to the best of our ability. Whole and regional body composition and absolute BMD, t scores, and *z* scores were analyzed in a blinded manner using the corresponding DXA software by the main researcher (enCORE version 18; GE Healthcare and APEX version 5.6.1.3; Hologic).

Blood Sampling and Analyses

Biomarkers for bone turnover and nutritional and health status were assessed with fasted venous blood samples. A detailed overview of the biomarkers is presented in Multimedia Appendix 3. Blood sampling was performed by trained bioengineers and researchers and processed by (1) direct centrifuging (EDTA gel tubes for PTH; Vacuette) or (2) waiting a minimum of 30 minutes and a maximum of 2 hours before centrifuging (serum SST gel tubes; Vacuette), both at 1500*g* for 12 minutes at room temperature. Aliquots of 1 mL serum were stored at <–20 °C until shipment for batch analysis of bone-specific markers (Hormone laboratory, Aker, Oslo University Hospital). Direct analyses were performed for all other markers (Fürst Laboratories), and thus, centrifuged vacuette tubes were stored at +4 °C until transport and analysis, maximally 4 days from sampling time point. One aliquot of serum and one of plasma are stored in the project biobank at –80 °C for any further analysis or necessary reanalysis. The project-specific biobank will terminate after project completion, and all biological material will be destroyed.

Maximal Muscle Strength

Overview

Muscle strength was assessed in all main exercises of the intervention training program (Figures 1 and 2), entailing both maximal voluntary isometric contractions and 1-repetition maximum (1 RM). The test battery was preceded by a 5-minute global warm-up on either an arm cycle ergometer (Monark 881E, Monark Sports & Medical) or a ski double poling ergometer (SkiErg, Concept2) at low-moderate intensity (instructed as “to get warm but not fatigued”). All strength tests were performed with 3 exercise-specific warm-up sets at 50%, 75%, and 90% of recorded or estimated maximum from the preceding visit (familiarization session estimated the maximum for baseline tests). A minimum of 3 attempts at achieving a peak value in the isometric tests or volitional failure in the dynamic tests were used. The peak across the attempts in the isometric tests was defined when the third or later attempts showed a <2% increase or a decrease compared to the preceding attempts. Rest periods of 60 and 120 seconds between attempts in the isometric and dynamic tests, respectively, were used. Occasionally, rest periods were slightly longer based on individual needs. Equipment used, grip and seat positioning, as well as any aids (eg, straps or belts) were recorded at baseline and standardized for each participant at subsequent visits.

Maximal Voluntary Isometric Contraction

Maximal voluntary isometric contractions (overhead press, bench press, prone row, and supine pull) were tested in a Gym 2000 isometric bench (Gym 2000 Production AS) with a strain gauge measuring the force applied upon it (U2A tension and compression load cell, 500 kg maximal capacity, D1 accuracy, Hottinger Baldwin Messtechnik). Force exerted over the 5-second contraction was recorded at 1000 Hz and directly smoothed (rolling average) to 100 Hz (MVC, version 2017; LabVIEW, Emerson Electric Company). Recorded data were exported to Excel (version 2407, build 16.0.17830.20210, 64-bit; Microsoft Corporation) for analysis of mean maximal force over 100 to 200 ms around the time of peak contraction force.

1-RM Overview

Maximal dynamic strength was assessed in overhead press and incline bench press using a free barbell (all sites) or a Smith machine (NIH; Gym 2000), with the bench back rest set to 30° and the seat set to as high as needed for the participant to sit in a stable position. During the warm-up, 8, 4, and 1 repetitions were performed with 50%, 75%, and 90% of the preceding or

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estimated 1 RM load, respectively. In the overhead press, the bottom position was achieved when the elbow and shoulder joint angles were visually observed to be <90°. In the incline bench press, the bottom position was achieved when the elbow joint angle was observed to be <90° and the upper arms were below parallel to the floor.

24-Hour Dietary Recalls

Dietary intake assessments were conducted by 3 unannounced 24-hour dietary recalls for preferably 2 weekdays and 1 weekend day, selected randomly within the 2-week period around each test day. Recalls followed the validated 5-step multiple-pass method to increase accuracy [37]. This method consists of 5 steps: (1) the quick list, which is an uninterrupted listing by the participant of foods and beverages consumed; (2) the forgotten foods list, which queries the participant on categories of foods that have been documented as frequently forgotten; (3) a time and occasion at which foods were consumed; (4) the detail cycle, which elicits descriptions of foods and amounts eaten aided by the interactive use of the NORKOST4 food model booklet and measuring guides [38]; and finally, (5) the final probe review. All recalls were checked for completeness and processed with the Norwegian food database KBS (Kostberegningssystem, University of Oslo), preferably by the same nutritionist or dietician at each time point for each participant. All assessors were given the same training in the method.

The dietary recall data will be used to describe the dietary intake of the participants and to document how the participants adhere to the nutrition protocol. Change in energy intake and macronutrients will be analyzed (Multimedia Appendix 3). Nutritional factors of relevance for bone health (ie, intake of energy, protein, calcium, and vitamin D) will be accounted for in the main analyses.

Questionnaires

All questionnaires were provided in Norwegian and were administered, collected, and processed digitally through SurveyXact (Rambøll). The questionnaires with time constructs use a 7-day reference period.

Background Questionnaire

Background, medical, and sports participation history were sought at screening to assess the eligibility of the participants and participant characteristics. The background questions focused on the participants' characteristics (sex, age, height, weight, and socioeconomic status); medical history (impairments and related information, other diagnoses, use of medications, mobility aids, pain, tobacco use, alcohol consumption, and use of dietary supplements); and sports and exercise history. Medication and dietary supplement use were recorded at each visit.

Physical Activity and Functional Health

The validated 7-item International Physical Activity Questionnaire short form, adapted for persons with disabilities, was used to assess physical activity in the past 7 days, both as metabolic equivalents (min) and as categories (low, moderate, or high activity) [33,34]. To assess functional health, the participants completed the 16-item Spinal Cord Independence Measure, which is a validated adaptation of the Functional Independence Measure for patients with SCI [39]. Furthermore, resistance training routine and participation in sports were recorded at each visit.

Risk of Low Energy Availability

To assess the risk of low energy availability, the 25-item Low Energy Availability in Females was filled in by the female participants [40]. The newly developed Low Energy Availability in Males was filled in by the male participants [41]. The use of these questionnaires in Paralympic and adapted sport has been limited; therefore, it is of interest to further investigate the utility of the low energy availability questionnaires in our population.

Motivation for Exercise and Mental Health

Motivation for exercise was measured using the 19-item Behavioural Regulation in Exercise Questionnaire-2 [42]. The 12-item Basic Psychological Needs Satisfaction instrument for exercise (autonomy, competence, and relatedness) was used to measure potential mediators (explanatory factors) of intervention effects on mental health outcomes [43]. A variety of outcome measures was deliberately chosen to capture the multifaceted construct of mental health. Well-being is measured by the widely used World Health Organization's 5-item Well-Being Index [44]. Personal rating of the feeling of physical and emotional exhaustion was measured using a subscale from the Athlete Burnout Questionnaire [45]. Personal rating of feeling of fatigue (8-item) and vigor (7-item) was measured using subscales from the Profile of Mood States [46].

Postintervention Focus Interview

In total, 10 participants from the training intervention group were invited to individual semistructured focus interviews 2 to 3 weeks after the end of the training period. These interviews were audio recorded, and the data were transcribed. The topics of the interview guide were previous exercise experience, their experiences from the training intervention, and potential perceived effects on motivation and mental health. The interviews were conducted by a trained sports psychology researcher with competence in adapted sports. The interviewer and researcher who both collected and analyzed the data had not previously been in contact with the participants earlier in the intervention, and this work was done without any contact with other researchers in the project team. Furthermore, the participants were being ensured that what they shared in the interview would only be shared with the rest of the research team in an anonymous form. This was to enhance the likelihood of the participants' willingness to share their experiences freely and in a less-biased manner.

Ethical Considerations

This study protocol has received ethics approval from the Regional Committee for Medical and Health Research Ethics South-East, Norway (2023/458384). Protocol modifications have been approved in revised versions of ethics approval, and revisions have been communicated to all participants. Multimedia Appendix 4 provides the final approved protocol. In case of any serious adverse events, Norwegian health insurance applied to all participants, and any copayment was to be covered by the responsible institution (NIH).

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All screened participants provided written informed consent before any procedures (including at the screening visit) and before being included in the RCT (Multimedia Appendix 5). Consent can be withdrawn at any time during the study period and until data have been published or have been made unidentifiable. The consent also covers secondary analyses without additional consent. All data were collected and deidentified with a study participant identification number. All participants received NOK 500 (approximately US $45-50) as compensation for participation. Furthermore, they obtained free access to a local fitness centre as part of the intervention period (training group). The control group obtained the opportunity to receive the training program and 4 weeks of supervision at the test site. After study completion, the participants with BMD *z* scores <–2.0 were advised to seek medical support. The study was preregistered in ClinicalTrials.gov (NCT05615402) on November 14, 2022, and in Open Science Framework [47] on January 4, 2023, and reporting follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (Multimedia Appendix 6).

Data Management

A raw data copy was stored before data handling, including range checks and scatter plots to find potential outliers. Any corrections or deletions were saved in working file copies. Invalid data points were removed from the working files but not the raw files, for example, lumbar spine BMD values where the scan contains implants or metal artifacts. Questionnaire data were coded into appropriate categories and scored according to the questionnaire guidelines. Invalid questionnaire responses were sought to be collected again, if possible, either at a subsequent visit or by telephone interview. Data are shared between the collaborating institutions (HVL and NTNU) and the main site (NIH) via shared access to online storage (OneDrive for 365, Microsoft Corporation) for as long as practically necessary. Only key project team members have access to the data. The qualitative data are only available to 2 researchers at NIH.

Statistical Analysis

BMD and participant characteristics at screening will be described and analyzed cross-sectionally, and linear multiple regression models will examine associations between BMD and other baseline data (such as age, sex, diagnosis category, and Spinal Cord Independence Measure mobility subscore) in the analyses of the RCT. The cross-sectional data will be analyzed descriptively, and differences between subgroups as well as explanatory factors of BMD will be analyzed with linear regression analyses. To analyze the group effects over the intervention period, a linear mixed model for repeated measures with an unstructured covariance structure will be used. Random intercept for participants and fixed effects of time, treatment, and their interaction, as well as the dependent variable value at baseline and study site, will be included in the model. The interaction term accommodates different patterns of change over time between intervention and control groups. The mixed model allows all outcome data to be used, regardless of whether an individual has complete data, making these models consistent with an intention-to-treat analysis. Correlation tests between the delta change of main parameters and background variables will also be performed. Data will be analyzed both per protocol and by intention to treat [48]. A P value <.05 will be used to indicate statistical significance. Data will be analyzed using SPSS (IBM Corp) and R studio (Posit PBC). The qualitative data will be analyzed using reflexive thematic analysis [49].

Results

Participants

Between December 2022 and November 2023, a total of 104 interested wheelchair users were prescreened for eligibility before the screening visit (T0), of whom 72 (69.2%) were invited and 66 (63.5%) attended. See the participant flowchart in Figure 4. On the basis of the screening assessments, 52 (50%) eligible participants were invited to take part in the RCT, and ultimately 45 (NIH: n=33, 73%; HVL: n=5, 11%; NTNU: n=7, 15%) were included and underwent a baseline visit (T1). Following this, they were randomly allocated to 1 of the 2 groups: 24 (53%) to training and 21 (47%) to control. At the midpoint visit (T2), 36 (n=17, 47% and n=19, 53%, respectively) participants were reassessed and 33 (n=14, 42% and n=19, 58%, respectively) completed the study (T3). The final postintervention visit was completed in April 2024. Of the 22 participants who completed the study at the NIH test site, 15 (68%) revolunteered to attend a 6- to 18-month postintervention visit (T4) at the end of 2024.

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Figure 4. The BoneWheel study flowchart. Eligible participants progressed to baseline testing and then to the randomized controlled trial (RCT). BMD: bone mineral density; NIH: Norwegian School of Sport Sciences; T0: time point 0; T1: time point 1; T2: time point 2; T3: time point 3; T4: time point 4.

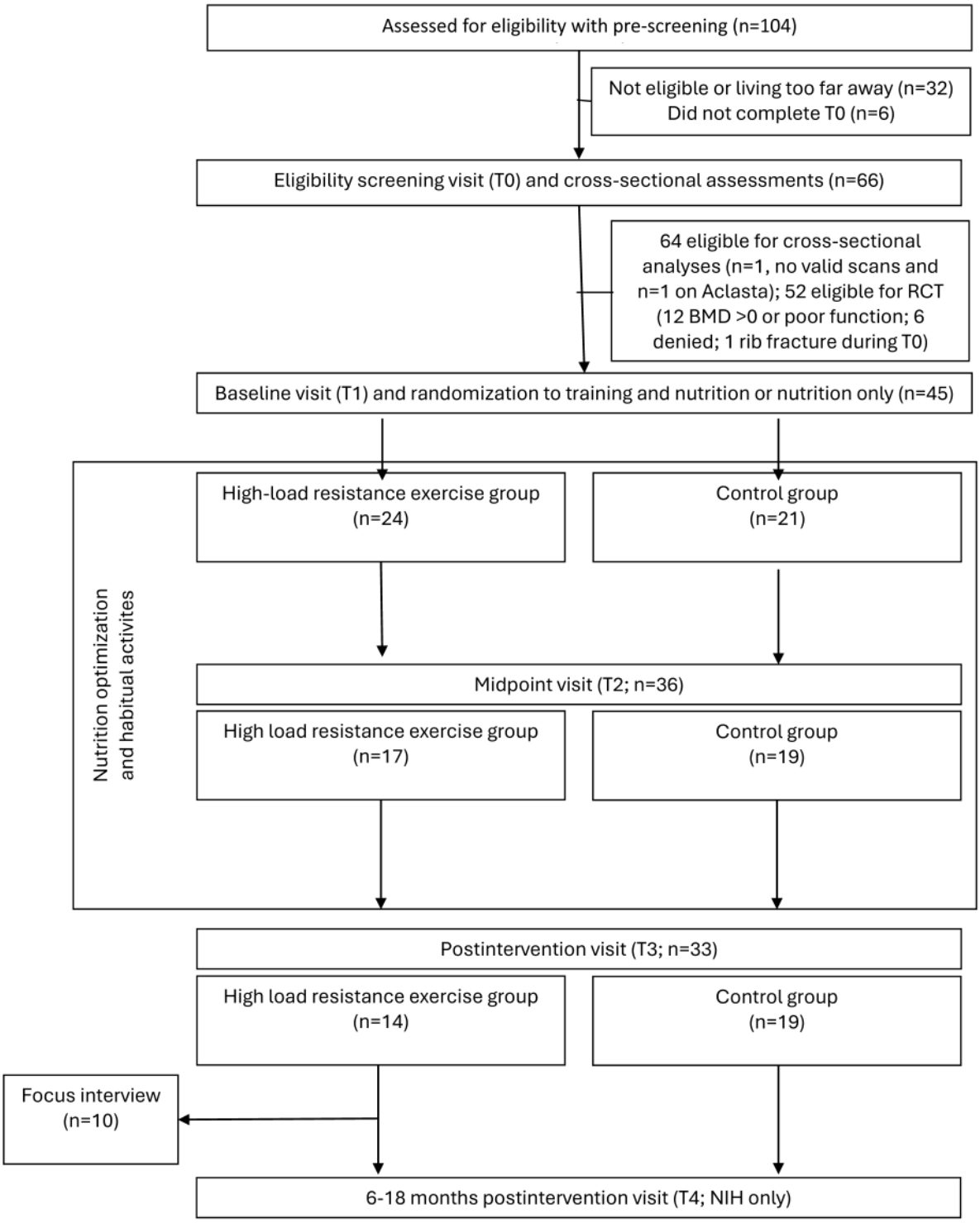

Data Analysis and Dissemination

Data analysis of data collected at the screening visit (T0) commenced in spring 2024, while analysis of data collected at the baseline and retest visits began in autumn 2024. The first results of this study are expected to be disseminated in peer-reviewed journals by the end of 2025.

Discussion

This study aims to investigate the effects of a 24-week high-load resistance training program and nutrition optimization on bone health, muscular strength, body composition, nutritional and health status, and mental health outcomes in wheelchair users.

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Anticipated Findings

The anticipated findings are that those randomized to the high-load resistance training program in combination with nutrition optimization will improve BMD at the spine and hip, and compared to a control group receiving nutrition optimization only.

In addition to the effects on the primary outcome, we further expect that the exercising group will increase both lean mass and muscular strength. Three moderate-high load sessions per week have been suggested to be effective in increasing lean mass and maximal strength [50,51]. As untrained individuals tend to have a greater relative increase in both outcomes, we expect a difference in effectiveness between the untrained and previously trained participants, and little to no effect in the nutrition optimization only group. Finally, we expect positive effects on the participants' physical and mental health in general.

Comparison to Prior Work

This study will give insight into the effects of a novel upper-body high-load resistance training program on BMD at the spine and hip, which we hypothesize will improve after intervention. While there is a knowledge gap regarding how to optimize bone health in wheelchair users nonpharmacologically, existing evidence in ambulatory people allows us to hypothesize that the combination of weight-bearing exercises and optimizing key nutrients for bone formation will be effective for the prevention and treatment of low BMD. Improvements of 2% to 4% over 12 to 24 weeks of resistance training have been shown in ambulatory individuals. In this study cohort of mainly nonambulatory wheelchair users, with far less or no stimuli from standing and walking, we hypothesize the same level of effect despite not including exercises typically performed in other studies (eg, squats or leg press and jumps). We further hypothesize that optimizing nutrition alone is not enough to accrue bone mass in this group, as purported by the mechanostat theory [52].

Strengths and Limitations

A total of 60 adult wheelchair users with nonprogressive impairment and high enough function to perform the exercises in the resistance training program were sought from both sports-active and nonactive environments. Owing to low recruitment in the early stages of the study, the NIH study site conducted several rounds of recruitment and enrollment over almost 12 months. However, we were unable to achieve the target numbers, which need to be accounted for in the dissemination of the results of the study. A more thorough process in estimating the feasibility of recruiting wheelchair users to such an extensive study protocol would have been valuable.

Dissemination Plan

Trial results are provided in an individual report to all participants. The main findings will be published in several open-access publications, following Vancouver guidelines for authorship. We plan to grant public access to the full protocol, participant-level dataset, and statistical code. Furthermore, the results and experiences from the study will be communicated to the scientific community at international conferences and to health care professionals and other relevant groups in workshops and public presentations.

Conclusions

In conclusion, this is the first RCT to implement a long-term high-load resistance training and nutrition program focusing on improving bone health in wheelchair users. Furthermore, including a target group of both sport-active and nonactive participants allow us to compare bone health status at baseline and investigate the effects of the intervention in these subgroups. This study will add valuable scientific and practical information on the effects of targeted training and nutrition for bone health, as well as the coinciding influence on motivation for exercise, along with the general physical and mental health of wheelchair users.

Acknowledgments

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This study is funded by the Dam Foundation, Norway (2022/FO387192, Multimedia Appendix 7 provides the peer review report) and the Taskforce for Applied Research SIA, part of the Netherlands Organization for Scientific Research (RAAK.PRO03.043) through the ParaNut project, where the BoneWheel study is one of the work packages. The funds are assigned to KLJ (principal investigator). The standard nutritional supplement used for participants in both groups was produced and delivered free of charge by FrieslandCampina. Furthermore, any additionally required supplements were sponsored by Orifarm. Local commercial fitness centres sponsored the training intervention group participants' fitness centre memberships for the intervention period to accommodate the unsupervised training (SATS Norway for the NIH and Bergen area and Impulse training for the Trondheim area). When needed, other fitness centres were sought for more rural living participants. None of the sponsors has any authority to impact the study design or results of the study.

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Data Availability

Upon study completion, the results of this study will be submitted as several manuscripts for publication in peer-reviewed scientific journals, regardless of the outcome of this study. Data will be available upon request and shared unidentifiably in the Open Science Framework.

Authors' Contributions

VS, JWvD, TR, and KLJ conceived the original study idea. LCR, VS, JWvD, HMR, ØS, LPVB, JKB, MB, TR, and KLJ designed this study. LCR, VS, JKB, MB, TR, and KLJ will perform data analyses. LCR and KLJ drafted the original manuscript while VS and TR reviewed and edited the manuscript. KLJ and JWvD were responsible for funding acquisition. LCR is defined as the main researcher. All authors approved the final version of this manuscript for publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Study eligibility criteria in detail.
[DOCX File , 18 KB - resprot_v14i1e70125_app1.docx]

Multimedia Appendix 2
Additional exercises in the BoneWheel training program.
[PNG File , 1430 KB - resprot_v14i1e70125_app2.png]

Multimedia Appendix 3
Study outcomes and assessments in the randomized controlled trial.
[PDF File (Adobe PDF File), 176 KB - resprot_v14i1e70125_app3.pdf]

Multimedia Appendix 4
Study protocol approved by the Regional Committee for Medical and Health Research Ethics South-East, Norway (2023/458384).
[PDF File (Adobe PDF File), 662 KB - resprot_v14i1e70125_app4.pdf]

Multimedia Appendix 5
Participant information letter including consent form (in Norwegian).
[PDF File (Adobe PDF File), 223 KB - resprot_v14i1e70125_app5.pdf]

Multimedia Appendix 6
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 checklist.
[PDF File (Adobe PDF File), 126 KB - resprot_v14i1e70125_app6.pdf]

Multimedia Appendix 7
Peer review report by Stiftelsen DAM, Norway.
[PDF File (Adobe PDF File), 16 KB - resprot_v14i1e70125_app7.pdf]

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Abbreviations

1-RM: 1-repetition maximum
25(OH)D: 25-hydroxyvitamin D
BMD: bone mineral density
DXA: dual-energy x-ray absorptiometry
HVL: Western Norway University of Applied Sciences
IOC: International Olympic Committee
NIH: Norwegian School of Sport Sciences
NTNU: Norwegian University of Science and Technology
RCT: randomized controlled trial
SCI: spinal cord injury
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
sRPE: session rating of the perceived exertion

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Protocol

Comparison of 5-Day Multidaily Neuronavigated Theta-Burst Sessions With 6-Week Standard Repetitive Transcranial Magnetic Stimulation (the Dutch Depression Outcome Trial): Protocol for a Randomized Controlled Trial

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Abstract

Background: Novel therapies are crucial for patients with major depressive disorder, as more than 33% of patients do not respond to first-line treatments. A promising novel treatment strategy is an intensive 5-day course of personalized, functional connectivity–guided accelerated intermittent theta-burst stimulation (PAiT), modeled after the Stanford neuromodulation therapy protocol. This new form of repetitive transcranial magnetic stimulation (rTMS) may lead to higher remission rates in patients with treatment-resistant depression (TRD). However, it remains unclear how this accelerated strategy compares to the standard once-daily 10 Hz rTMS at inducing remission of depression.

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Objective: This study aims to compare cost-effectiveness using the PAiT protocol and the standard 10 Hz rTMS in patients with TRD.

Methods: A total of 108 patients will be enrolled in this multicenter randomized controlled trial. Patients will receive stimulation over the left dorsolateral prefrontal cortex using either the PAiT protocol (10 sessions per day over 5 days, resulting in 50 sessions in total and 90,000 pulses) or standard 10 Hz rTMS (once daily for 6 weeks, resulting in 30 sessions in total and 90,000 pulses). Personalized targets will be identified in the accelerated intermittent theta-burst stimulation condition based on negative functional coupling between the subgenual anterior cingulate cortex and the dorsolateral prefrontal cortex. In the rTMS condition, the dorsolateral prefrontal cortex target locations are identified using the standard Beam-F3 method. In both conditions, coil placement is performed with neuronavigation, navigating either to the personalized functional connectivity target or the Beam-F3 location. Patients will undergo pre- and posttreatment functional magnetic resonance imaging scans, including cognitive and emotional tasks. Four follow-up assessments are scheduled at 7, 12, 26, and 31 weeks after baseline. We expect that the PAiT protocol is more cost-effective than the standard 10 Hz rTMS.

Results: Recruitment for this randomized controlled trial started in February 2024. As of December 2024, we had enrolled 31 patients; the last participant is expected to complete their posttreatment assessments in January 2027.

Conclusions: To our knowledge, this study is the first clinical trial to compare the cost- effectiveness of PAiT to standard 10 Hz rTMS as treatment for patients with TRD. The results of our study will offer professionals evidence from a sufficiently powered trial to determine whether the PAiT protocol is more effective than standard high-frequency rTMS. Specifically, it will assess whether PAiT leads to a shorter treatment duration for depression and greater societal or occupational participation among patients with TRD. In addition, this trial will provide further insights into the underlying mechanisms related to treatment effect, the effects of rTMS or accelerated intermittent theta-burst stimulation on cognitive domains such as executive functioning and emotion, possible differences in side effects, long-term effects, and factors contributing to possible relapse.

Trial Registration: ClinicalTrials.gov NCT05900271; https://clinicaltrials.gov/study/NCT05900271

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KEYWORDS

repetitive transcranial magnetic stimulation; rTMS; personalized accelerated intermittent theta-burst stimulation; personalized aiTBS; personalized functional connectivity–guided accelerated intermittent theta-burst stimulation; PAiT; Stanford neuromodulation therapy; SNT; functional magnetic resonance imaging; fMRI; dorsolateral prefrontal cortex; DLPFC; subgenual anterior cingulate cortex; sgACC; treatment-resistant depression

Introduction

Background

Novel therapies for depression are needed because more than 33% of patients with major depressive disorder are treatment resistant, that is, they do not respond sufficiently after treatment with 2 or more evidence‐based pharmacological or psychotherapeutic treatments [1]. Brain stimulation using repetitive transcranial magnetic stimulation (rTMS) or intermittent theta‐burst stimulation (iTBS), an alternative form of rTMS, has been shown effective with remission rates of 20% to 30% [2] in patients with treatment-resistant depression (TRD). rTMS and iTBS are noninvasive procedures, meaning that they do not involve surgery or general anesthesia. While the remission rates of rTMS and iTBS are lower than the 55% remission rate achieved by electroconvulsive therapy (ECT) [3], the most effective treatment for patients with depression, rTMS and iTBS have fewer side effects compared to ECT and antidepressant medication. Therefore, optimization of rTMS and iTBS therapies and their outcomes is a promising scientific goal.

Novel Noninvasive Neuromodulatory Therapies

Transcranial magnetic stimulation (TMS), a noninvasive neuromodulatory therapy, has been added to the treatment arsenal for unipolar depression [4]. TMS is based on the principle of electromagnetic induction by applying magnetic pulses to the brain. This magnetic pulse induces an electrical field in the underlying neurons; when TMS pulses are applied repetitively, this effect outlasts the time of stimulation and leads to enduring effects on cortical excitability [5]. rTMS is recognized as a valuable therapeutic option in TRD [4]. Randomized controlled trials (RCTs) have consistently demonstrated the efficacy and safety of rTMS in TRD, with remission rates of approximately 25% [4,6-8]. In standard Food and Drug Administration–approved 10 Hz rTMS, 3000 pulses are given in 19 minutes; a train of 40 pulses lasting for 4 seconds is given every 15 seconds.

rTMS is not associated with common drug‐associated side effects (eg, nausea, sedation, akathisia, weight gain, and risk of intoxication) or the cognitive side effects often feared with ECT. The risk of developing side effects in response to rTMS is low [4,9]; transient headaches and localized scalp pain are the most common side effects and are self‐limiting or eminently treatable with paracetamol, acetaminophen, or other analgesics.

iTBS is a newer form of rTMS [10]. Magnetic pulses are applied in a certain pattern, called bursts. The basic element of theta-burst stimulation is a 3‐pulse burst at 50 Hz delivered every 200 ms (ie, 5 Hz). In the recently developed Stanford neuromodulation therapy (SNT) protocol, a train of 10 bursts

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lasting for 12 seconds is given every 10 seconds for 60 cycles in iTBS, resulting in a total session duration of 10 minutes. The main advantage of iTBS is that a similar number of pulses can be given in a shorter time frame [11,12]. This shorter time frame facilitates the administration of iTBS multiple times a day, contrary to the 24-hour spacing of standard 10 Hz rTMS [11,12]. Multiple daily iTBS sessions with adequate spacing of 50 minutes is likely to enhance the efficacy, as suggested by animal studies that showed hour - long intervals may be optimal for producing long-term potentiation of neurons [13].

Accelerated iTBS According to the SNT Protocol

There are 2 observational studies and 1 RCT on the SNT protocol (applying accelerated iTBS combined with functional magnetic resonance imaging [fMRI] task-based neuronavigation). The first observational study was a proof-of-principle study involving 6 participants [14]. The second study was a larger observational study [12]. The findings from a subsequent RCT resulted from the planned interim analysis [11]. These 3 studies reported an extremely high overall remission rate, at any point during the 4-week follow-up period, of 79% [15]. Dropout rates were low across all 3 studies; in the study by Williams et al [14], 1 of 5 patients dropped out due to lack of remission by day 4; in the observational study by Cole et al [12], 1 of 22 patients dropped out on day 1 of the trial due to a history of multiple therapeutic intolerances; and no participants dropped out in the RCT by Cole et al [11]. Overall, accelerated intermittent theta-burst stimulation (aiTBS) was well tolerated; reported side effects were similar to standard 10 Hz rTMS, that is, headache and scalp pain. No safety issues were reported. Although promising, it is unclear what the crucial element is of the SNT protocol: the intersession interval (ISI), accelerated delivery, high pulse dose, scalp-cortex correction, individualized targeting, or a combination of these factors.

The 50-minute spacing between sessions is in line with evidence from basic neuroscience research and human physiology data, showing that spaced iTBS sessions have an enhanced effect compared with the same number of single daily sessions [13]. Accelerated sessions, that is, more sessions per day, also contribute to nonlinear improvements in clinical symptoms. ISI of at least 50 minutes may enhance synaptic strengthening [12,13]. Finally, the functional connectivity–guided targeting method used in this study may have contributed to the high remission rate observed. The left dorsolateral prefrontal cortex (DLPFC) is a large brain area that consists of several subregions, some of which are correlated and some anticorrelated with subgenual anterior cingulate cortex (sgACC) activity. Recent studies suggest that these correlated and anticorrelated subregions are part of different affective circuits; stimulating a subregion of the left DLPFC that is anticorrelated with the sgACC reduces melancholic symptoms, resulting in lower depression scores [11,12]. This connection is not necessarily targeted with standard 10 Hz rTMS using the Beam-F3 method [16].

Cost - Effectiveness

No independent international studies exist that assess the cost - effectiveness of SNT (as compared to standard rTMS) in the treatment of TRD. Given the patent restrictions on SNT, we sought to replicate SNT in our own personalized aiTBS protocol (personalized functional connectivity–guided aiTBS [PAiT]) to assess the cost-effectiveness of both treatments. Considering that treatment duration of the PAiT protocol is notably shorter compared to 10 Hz rTMS (1 week vs 6 weeks) and is expected to result in increased remission rates (ie, therefore obtaining more quality-adjusted life year benefits earlier), we will compare the 2 treatments on their cost-effectiveness to evaluate the potential added value of this innovative therapy for a more efficient health care system.

Durability of the Effects of Personalized aiTBS

As of 2024, little was known about the long-term effects of personalized aiTBS. One could argue that the same remission or relapse course can be expected as for ECT, that is, quick antidepressant effects directly after the intensive 5-day treatment in combination with a high chance of relapse in the following weeks. Therefore, our study will have weekly clinical assessments for 7 weeks in both conditions to enable comparisons in treatment efficacy, during treatment, directly after treatment, and 1 week after treatment between rTMS and PAiT, along with follow-up clinical assessments at 6 and 25 weeks after treatment. In addition, we will investigate the (factors contributing to) side effects during the treatment in both conditions using an in-house questionnaire [17].

Contribution to the Field of the Proposed Study

A well-powered and independent RCT is needed to determine the cost-effectiveness and safety of PAiT versus rTMS in patients with TRD.

Methods

Aim

The aim of the Dutch Depression Outcome Trial (D-DOTT) is to determine the cost - effectiveness of PAiT versus standard daily 10 Hz rTMS in patients with TRD, who did not respond to 2 or more evidence - based treatments, using an adequately powered RCT.

Study Design

This multicenter single - blind RCT consists of 2 phases in which participants will be randomly assigned to either standard 10 Hz rTMS (30 daily rTMS sessions in 6 weeks, providing a total of 90,000 magnetic pulses) or PAiT (50 iTBS sessions in 5 days, providing a total of 90,000 pulses) [11,12], with 4 follow - up moments at 7, 12, 26, and 31 weeks after baseline. In either condition, the timing of these measurements translates to clinically relevant time points at 6 and 25 weeks after treatment, as well as aligned postbaseline follow-ups that are important for the cost-effectiveness analysis. As such, the follow-up measurement at 31 weeks after baseline is only used in the rTMS condition (25 weeks after treatment).

Setting of the Study

This multicenter trial will take place within the Dutch specialized mental health care setting. Patients will be recruited from specialized outpatient clinics with ample experience in both the treatment of TRD and treatment with rTMS or iTBS,

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through self - referral, and through the patient organization for depression (refer to the CONSORT [Consolidated Standards of Reporting Trials] flowchart in Figure 1). Participating outpatient clinics are Radboudumc, GGZinGeest, Maastricht University Medical Centre+, and Amsterdam University Medical Centre. The following rTMS machines are used in this trial: MagStim Rapid2 (Amsterdam University Medical Centre, GGZinGeest, and Radboudumc), Neurosoft Neuro-MSX (Radboudumc), MAG and more powerMAG (GGZinGeest), and MagVenture MagPro X-100 (Maastricht University Medical Centre+). All sites use figure-of-8 coils. Localite is used for neuronavigation at all sites. The Neurosoft Neuro-MSX uses a built-in neuronavigation software.

Figure 1. The CONSORT (Consolidated Standards of Reporting Trials) flowchart. UMC: University Medical Centre; MUMC: Maastricht University Medical Centre; rTMS: repetitive transcranial magnetic stimulation; PAiT: personalized functional connectivity–guided accelerated intermittent theta-burst stimulation.

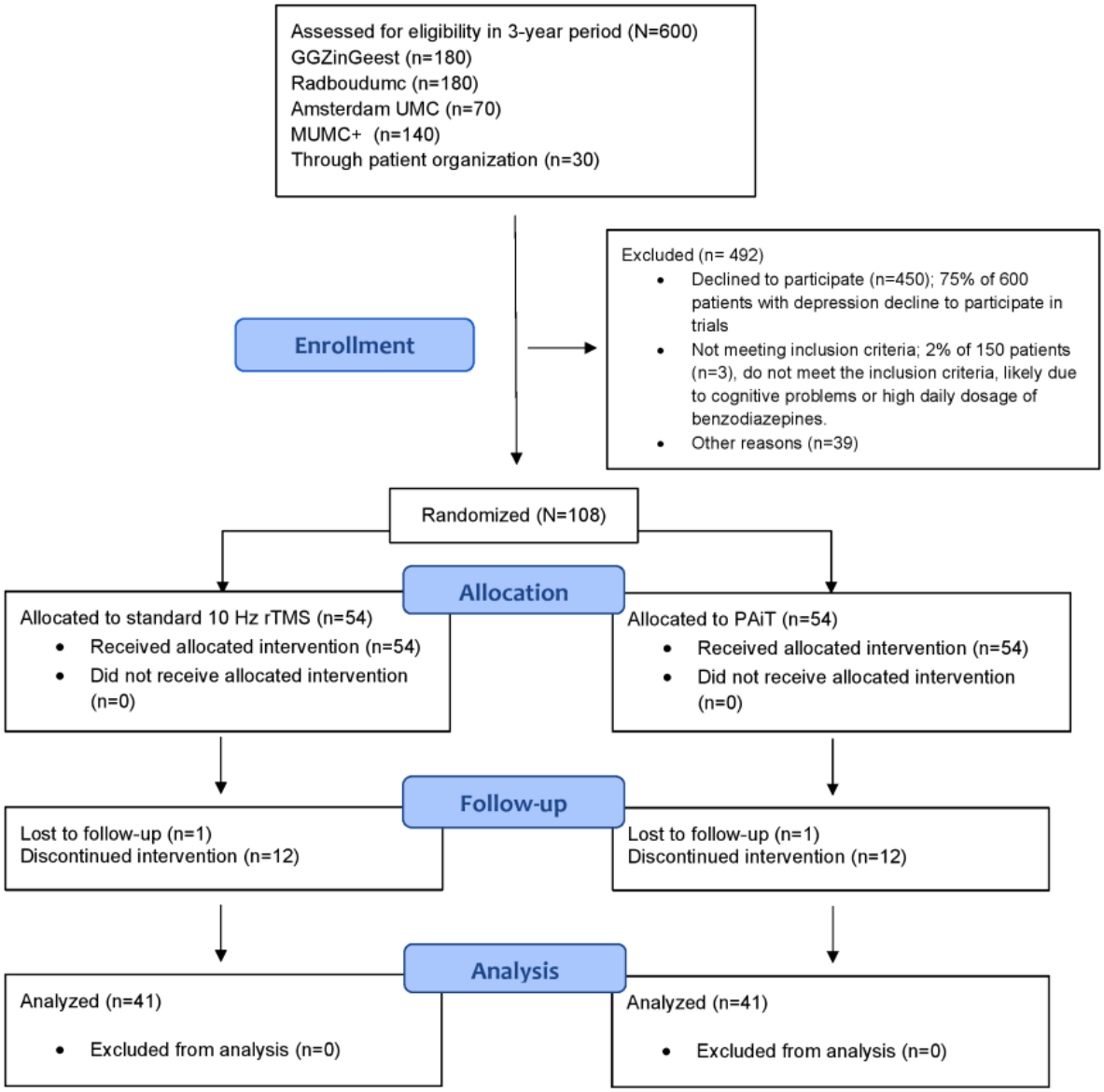

Participants

We aim to include 108 adult patients diagnosed with moderate to severe (Hamilton Depression Rating Scale >16) unipolar major depressive disorder without psychotic symptoms and who have had a failed response to at least 2 treatment trials with adequately dosed antidepressants or evidence-based forms of psychotherapy (interpersonal therapy, cognitive behavioral analysis system of psychotherapy, behavioral therapy, cognitive behavioral therapy, cognitive bibliotherapy, problem - solving therapy, brief psychodynamic therapy, and reminiscence therapy). Exclusion criteria include lifetime diagnosis of bipolar disorder, current psychotic disorder, substance abuse disorder, suspected dementia, active suicidal thoughts with intent to act on them, patients with epilepsy, patients with large or ferromagnetic metal parts in the head (except for a dental wire), implanted cardiac pace maker or neurostimulator, or inability to understand or comply with study requirements.

These exclusion criteria serve 2 purposes: first, to ensure a clinically homogeneous sample of patients with unipolar

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depression, free from comorbid conditions that could affect treatment effectiveness; and second, to comply with safety guidelines related to rTMS, the accelerated iTBS protocol, and the required magnetic resonance imaging (MRI) procedures, as well as general safety standards.

Study Procedures

Study information is provided to eligible participants, and these patients are contacted again after at least 7 days to discuss participation and any remaining questions. If patients choose to participate, they will be invited to a research intake session, during which they will sign the informed consent form and undergo screening for inclusion and exclusion criteria. Participation is voluntary, and individuals may withdraw from the study at any time. Table 1 shows an overview of the study. Participants who were allocated to standard 10 Hz rTMS will be offered PAiT after the end of the study (eg, 25 weeks after the last rTMS session). We will request patients allocated to PAiT to postpone enrolling in standard 10 Hz rTMS for 25 weeks after the last treatment session. This is merely a request as patients are allowed to ask for treatment as usual, including standard 10 Hz rTMS. Our participating treatment centers deem it not ethical to withhold this usual 10 Hz rTMS treatment upon a patient's request. In addition to clinical effectiveness, we will study patient‐reported outcomes, tolerability, and safety. Alongside this RCT, we will also conduct an economic evaluation and evaluate facilitating and hindering factors related to implementation in the group of researchers and health care professionals involved in this study. The funding agency, the Efficiency Studies arm of the Care Research Netherlands and Medical Sciences of the Dutch Research Council, has explicitly requested that the trial be based in care as usual.

Table 1. An overview of the study for both treatment conditions.

	rTMS[a]	PAiT[b]
T0		
Week –2	• Screening: clinicometrics; biobank; MRIc pre+additional tasks; rTMS premeasurements	• Screening: clinicometrics; biobank; MRI pre+additional tasks; PAiT premeasurements
T1		
Week 0	• Baseline	• Baseline
T2		
Week 1	• Treatment • Clinicometrics (weekly)	• Treatment • Clinicometrics (daily)
Week 2	• Biobank	• Follow-up (1 week): clinicometrics (weekly); MRI post+additional tasks; biobank
Week 6	• Clinicometrics	• Clinicometrics
T3		
Week 7	• Follow-up: clinicometrics; MRI post+additional tasks; biobank	• Follow-up: clinicometrics; biobank
T4		
Week 12	• Follow-up: clinicometrics; biobank	• Follow-up: clinicometrics
T5		
Week 26	• Follow-up: clinicometrics	• Follow-up (25 weeks): clinicometrics
T6		
Week 31	• Follow-up (25 weeks): clinicometrics	• Clinicometrics

[a]rTMS: repetitive transcranial magnetic stimulation.

[b]PAiT: personalized functional connectivity–guided accelerated intermittent theta-burst stimulation.

[c]MRI: magnetic resonance imaging.

Randomization

Participants will be randomly assigned to either the rTMS or the PAiT arm. Randomization will be done via Castor EDC and will be stratified for treatment center. We will use block randomization using random sequences of block sizes of 2, 4, and 6. This approach ensures treatment assignment balance within each complete block and minimizes the imbalance of group sizes within clinical centers, thus correcting for confounding from possible differences between treatment sites

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(such as differences in experience with rTMS). In addition, before the start of the trial, we will note patient's preferred treatment, that is, standard 10 Hz rTMS or PAiT. The expected study duration is 48 months, and inclusion of patients started in February 2024.

Intervention

The PAiT protocol, modeled after the SNT protocol [12], consists of 5 days of treatment in which a total of 90,000 magnetic pulses are given over 50 sessions (10 sessions per day, 50 minutes ISI). iTBS at 90% of the resting motor threshold corrected for cortical depth will be administered to the location within the left DLPFC showing the strongest anticorrelation with the sgACC. This is achieved using participant - specific, resting state–fMRI - guided neuronavigation. The coordinates within the DLPFC most anticorrelated with the sgACC are identified using the seedmap- and cluster-based method described by Cash et al [18]. The cluster threshold is set to 2.5%, meaning 2.5% of the most anticorrelated voxels are retained in the DLPFC before clustering. The center of gravity of the largest cluster is defined as the target coordinate. The target coordinate and corresponding stimulation site are located for each individual using neuronavigation software. The resting motor threshold is corrected for cortical depth at the stimulation site using the formula described by Stokes et al [19]. The BrainRuler software [20] is used to determine the cortical distance.

Comparator

The comparator consists of 6 weeks of standard rTMS treatment, following the Dutch depression treatment guidelines [21]. This involves delivering a total of 90,000 magnetic pulses across 30 sessions (1 session per day), using 10 Hz stimulation at 120% of the resting motor threshold. Stimulation is applied to the left DLPFC, localized using the Beam-F3 method [16,22], which identifies the DLPFC based on standardized skull measurements.

Image Acquisition and Preprocessing

Whole brain structural and functional images are acquired within 2 weeks before treatment and within 2 weeks after treatment. Scans will be performed on a 3-T whole-body scanner with standardized and optimized sequences. Sequences included in the pre- and posttreatment scans are described in Textbox 1.

Preprocessing of the functional and structural images is performed using the Freesurfer software suite, fMRIprep, an MRI quality control tool, and the FMRIB software library suite. Functional images are denoised and smoothed for stimulation target identification. Denoising was performed using global signal regression, 6 motion correction parameters, 8 physiological regressors, and spike removal. Smoothing was applied with a 6-mm full width at half maximum kernel.

Textbox 1. Sequences included in the pre- and posttreatment scans.

Pretreatment scans

- T1-weighted structural MRI (5 min): repetition time (TR)=2300 ms, echo time (TE)=2.26 ms, 192 slices, slice thickness=1.0 mm, voxel size=1×1×1 mm, and flip angle=8°
- Resting state–functional MRI (2×10 min): TR=1200 ms, TE=30 ms, 64 slices, slice thickness=2.0 mm, 488 volumes, voxel size=2×2×2 mm, Simultaneous Multi-Slice (SMS) factor=4, and flip angle=66°
- Diffusion tensor imaging (8 min): TR=3100 ms, TE=102 ms, 66 slices, slice thickness=2.0 mm, voxel size=2×2×2 mm, and SMS factor=3
- Tower of London task functional MRI (5.5 min): TR=1200 ms, TE=30 ms, 64 slices, slice thickness=2.0 mm, 488 volumes, voxel size=2×2×2 mm, SMS factor=4, and flip angle=66°
- Hariri Emotion Recognition task functional MRI (5.5 min) [23]: TR=1200 ms, TE=30 ms, 64 slices, slice thickness=2.0 mm, 488 volumes, voxel size=2×2×2 mm, SMS factor=4, and flip angle=66°
- Total scanning time=44 minutes

Posttreatment scans

- T1-weighted structural MRI (5 min): TR=2300 ms, TE=2.26 ms, 192 slices, slice thickness=1.0 mm, voxel size=1×1×1 mm, and flip angle=8°
- Resting state–functional MRI (1×10 min): TR=1200 ms, TE=30 ms, 64 slices, slice thickness=2.0 mm, 488 volumes, voxel size=2×2×2 mm, SMS factor=4, and flip angle=66°
- T2-weighted fluid attenuated inversion recovery structural MRI (6 min): TR=5000 ms, TE=386 ms, inversion time=1650 ms 176 slices, slice thickness=1.0 mm, and voxel size=1×1×1 mm
- Diffusion tensor imaging (8 min): TR=3100 ms, TE=102 ms, 66 slices, slice thickness=2.0 mm, voxel size=2×2×2 mm, and SMS factor=3
- Tower of London task functional MRI (5.5 min): TR=1200 ms, TE=30 ms, 64 slices, slice thickness=2.0 mm, 488 volumes, voxel size=2×2×2 mm, SMS factor=4, and flip angle=66°
- Hariri Emotion Recognition task functional MRI (5.5 min): TR=1200 ms, TE=30 ms, 64 slices, slice thickness=2.0 mm, 488 volumes, voxel size=2×2×2 mm, SMS factor=4, and flip angle=66°
- Total scanning time=40 minutes

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Outcome Measures

Main Study Parameter or End Point

Remission of depression 1 week after the last treatment session was defined as a score of ≤7 on the 17-item Hamilton Depression Rating Scale (HDRS - 17).

Secondary Outcomes

In addition to the primary outcomes, secondary outcomes will be assessed to provide a more comprehensive understanding of the effectiveness and impact of rTMS/PAiT. First, an economic evaluation based on the general principles of a cost - effectiveness (utility) analysis, which will be performed alongside the intervention by comparing patients treated with PAiT with those receiving standard 10 Hz rTMS. In addition, societal costs and health consumption will be assessed for the economic evaluation at baseline and 7, 12, and 26 weeks after baseline. We will use health - related quality of life determined with the EQ - 5D - 5L and health care use or costs, patients' and their family's out - of - pocket costs, and productivity losses owing to absenteeism measured with the Trimbos Institute and Institute for Medical Technology Assessment Cost questionnaire for Psychiatry [24]. Second, patient - reported outcome measures will be recorded, that is, positive mental health, as measured with Mental Health Continuum - Short Form [25] and subjective memory loss. Third, percentage reduction of depressive symptoms will be measured with self - rated 9-item Patient Health Questionnaire (PHQ-9) on each treatment day and the HDRS - 17. Fourth, relapse will be measured at 6 and 25 weeks after treatment. Relapse was defined as an HDRS - 17 total score of ≥15 for 2 consecutive assessments separated by 5 to 15 days or hospitalization for depression. Fifth, we establish tolerability of the treatment and side effects of PAiT and rTMS [9]. Sixth, we will identify health care system–, clinician - , and patient - related factors that influence the implementation of PAiT were identified to inform the development of an implementation plan. Seventh, we will compare patient-reported changes in mood 1 week after treatment (as measured with self-rated PHQ-9) with clinician-reported clinical impression (as measured with Clinical Global Impression [23]).

Exploratory Outcome Measures

In addition, we want to untangle the effects of possible biomarkers and predict treatment outcomes, including cardiovascular risk factors (waist:hip ratio, ankle arm index [a measure to determine peripheral atherosclerosis], c-reactive protein, triglyceride, high-density lipoprotein cholesterol, total cholesterol, and glycated hemoglobin levels); neurophysiological biomarkers, that is, using heart rate reduction, heart brain coupling, and an increase in heart rate variability; magnitude and angle of the electric field induced by rTMS in the cortex; structural and functional brain networks as biomarkers for clinical response; effects of cortical depth; and structural and functional brain network changes induced by 10 Hz rTMS and PAiT (and their relation to treatment outcome), as measured by structural and functional MRI.

We also aim to assess changes in emotional and cognitive task performance (Hariri [26,27] and Tower of London [28]) and task-related brain activation induced by 10 Hz rTMS and PAiT (and their relation to treatment outcome), as measured by task-based functional MRI; assess the changes in Pavlovian bias induced by 10 Hz rTMS and PAiT (and their relation to treatment outcome), as measured by a behavioral controllability task (RobotMadness, refer to Dorfman et al [29] for more information regarding controllability and Pavlovian biases); and to establish a biobank to determine standard 10 Hz rTMS– and PAiT-induced changes, as measured with blood derived biomarkers. Markers of interest include brain-derived neurotrophic factor and epigenetic changes for rTMS-induced plasticity, genotyping for treatment response prediction.

Blinding

Participants and those who will be administering the rTMS or PAiT treatment cannot be blinded. Those carrying out clinical assessments will be blinded. Blind rating will be carried out via video-recorded interviews with participants. Interviewers will not be blinded to the treatment conditions and, therefore, will be thoroughly instructed to carry out the interview in a structured and objective manner. A blinded rater will score the videotaped clinical assessments. To ensure minimal bias effects, 20% (227/1134) of interviews will be randomly assessed on interrater reliability and interview quality. All video footage will be deleted after rating the interviews and after the independent monitor has reviewed and agreed. The clinical ratings will be stored for further analysis.

Sample Size Calculations

Our trial should consist of 108 patients (for a 2 - sided test at α=.05 and with a power=0.80). Remission rates of patients treated with SNT in 2 open - label studies and 1 interim analysis from an RCT were extremely high, that is, 79%. The remission rates in patients treated with ECT, the most well-known and effective treatment for TRD, is approximately 55% (range 48% - 65%). Our sample size calculation is based on the conservative assumption that our PAiT protocol is at maximum as effective as ECT in patients with TRD. For our sample size calculation, we used the 55% remission rate and the known remission rate for standard 10 Hz rTMS, 25%. We will oversample the necessary 82 patients with 32% to adequately handle possible attrition, as the new intervention will be relatively intense compared to standard 10 Hz rTMS treatment, resulting in a required sample size of 108 patients.

Statistical Analyses

Overview

Statistical analyses will be performed on the intention - to - treat as well as the per protocol sample. Missing data will be replaced using the multiple imputation method. For all analyses, corrected *P* values of <.05 will be regarded as statistically significant. Safety data (eg, side effects) will be collected and summarized in the study results. A description of the analyses for the primary, secondary, and exploratory objectives is provided in the following sections.

Primary Study Parameters

For the intention - to - treat analysis, we will use a chi-square test to determine differences in remission 1 week after treatment.

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Secondary Study Parameters

The economic evaluations, that is, cost - utility analysis, will be conducted in accordance with the Dutch guidelines for economic evaluations. The outcome measure for the cost - utility analysis will be quality-adjusted life years, measured using the Dutch tariffs, that is, utility weights of the EQ - 5D - 5L [30-32]. Total costs will be estimated using a bottom - up (or microcosting) approach, where information on each element of service used is multiplied by an appropriate unit cost and summed to provide an overall total cost. We will consider four types of costs: (1) intervention costs, (2) costs stemming from health care uptake, (3) patients' and their family's out - of - pocket costs, and (4) costs stemming from productivity losses due to absenteeism. The recall period for all resource use measurements will be 3 months. A baseline analysis will be performed to examine the comparability of groups at baseline in terms of costs and outcomes. If necessary, the methods will be applied to control for differences in baseline [33]. The incremental cost - effectiveness ratio (ICER) will be computed to obtain the incremental costs per quality-adjusted life years gained. Stochastic uncertainty will be handled using 5000 nonparametric bootstraps and by plotting the simulated ICERs on the ICER plane. The bootstrap replications will be used to calculate the 95% CIs for the costs based on the 2.5th and 97.5th percentiles. For decision-making purposes, the ICER acceptability curve will be plotted for various willingness - to - pay ceilings. Missing data will be handled using single imputations nested in the nonparametric bootstrap samples [34].

For the patient - reported outcome measures, that is, positive mental health, as measured with Mental Health Continuum - Short Form [25]. We will use a linear mixed model on the data of the 3 measurements (baseline, directly after last treatment, and 26 weeks after baseline), comparing differences in the treatment effect. In addition, in order to assess subjective memory complaints, the Subjective assessment of memory impairment (subjective memory) assessment will be done at baseline, after the last treatment, and 26 weeks after baseline.

For the Percentual reduction of depressive symptoms, as measured with self - rated PHQ-9 on each day using the PAiT protocol, compared to weekly reduction of depressive symptoms, as measured with PHQ-9 during standard 10 Hz rTMS we will use linear mixed models. Similarly, we will determine percent reduction of depressive symptoms, as measured with the clinically assessed HDRS - 17 before, during, and after treatment, as well as at the follow-up moments.

Relapse, at 6 and 25 weeks after treatment, defined as (1) sustained remission, that is, HDRS-17≤7, and (2) sustained response, that is, response at end of treatment maintained through week 6 and 25. During treatment phase (T2), we will conduct the HDRS-17 weekly for 6 weeks for both treatment arms. By doing this, using the chi-square test, we can compare the remission rate with PAiT after 6 weeks to 6 weeks of treatment with standard 10 Hz rTMS; this is of interest as patients allocated to PAiT only receive treatment for 1 week.

We will report the prevalence of side effects during and directly after treatment based on international recommendation [17]. We will establish the tolerability and side effects of PAiT and rTMS. We will use qualitative data collected while supporting the implementation of PAiT, to analyze health care system–, patient - , and clinician - related factors that influence the implementation of PAiT in clinical settings. We will use a 1-tailed paired *t* test or an ANOVA to compare patient-reported changes in mood 1 week after treatment (as measured with self-rated PHQ-9) with clinician-reported clinical impression (as measured with the Clinical Global Impression scale).

Ethical Considerations

This clinical trial was approved by the institutional ethics board of Amsterdam University Medical Centre in August 2023 (2023.0437—NL83892.018.023) and was registered at clinicaltrials.gov (NCT05900271) on June 12, 2023. All participants will provide verbal and written informed consent before completion of any study measures. Data will be deidentified and, after completion of data collection, transmitted to a secure repository with safeguards in place to protect patients confidentiality.

Data Monitoring

Each clinical site will manage the internal quality of study conduct, data collection, documentation, and completion. All sites will adhere to a unified quality management plan. Before starting data collection, the principal investigators and the independent monitor confirmed that the necessary safety measures were in place at each site. The principal investigators convened with the full research team to review the study protocols, focusing on the definition of outcomes, study design, procedures for recording and reporting adverse events, informed consent procedures, and documentation. Staff will be trained to conduct assessments, ensuring they understand data collection procedures, processes, and the requirements for reporting adverse events.

Results

Recruitment for this RCT started in February 2024. As of December 2024, we had enrolled 31 patients; the last participant is expected to complete their posttreatment assessments in January 2027. Publication of the study's findings is anticipated around mid-2027.

Discussion

Importance and Broader Impact of the Study

This study protocol describes an adequately powered multicenter RCT investigating the cost-effectiveness of our PAiT protocol compared to standard 10 Hz rTMS in patients with TRD who did not respond to 2 or more evidence - based treatments. Our proposed RCT is important because the limited number of studies using the original personalized aiTBS protocol from the Stanford group (SNT) were performed in relatively small samples. Our trial can provide insight into the clinical effectiveness of the PAiT protocol and its cost - effectiveness. In addition to the clinical trial, primarily aimed at cost-effectiveness, our study also includes a number of exploratory neurophysiological outcome measures, which help

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in elucidating underlying mechanisms of treatment and eventually help in the identification and development of biomarkers that may guide treatment beyond clinical measures.

Principal Findings

It is hypothesized that the PAiT protocol will be more cost-effective than standard 10 Hz rTMS in patients with TRD, achieving a remission rate of 55%, comparable to treatment with ECT. We believe that our PAiT protocol may not be as effective as the original SNT protocol, with an apparent efficacy of 79% [11], due to methodological differences in the primary outcome measurement (remission at 1 week after treatment vs remission at any time point during the 4-week follow-up period) and the anticipated higher treatment resistance rate in our patient population. Remission rates immediately after aiTBS treatment have been seen to vary widely between 10% and 86.4% [15], possibly due to differences in the treatment protocol (sessions per day and amount of treatment days) and patient characteristics. Furthermore, the results of our study will be compared with those of other ongoing trials investigating the efficacy of aiTBS.

Given its notably shorter treatment duration (1 week vs 6 weeks) and the expected increased remission rates, quality-adjusted life years gains will be obtained earlier with similar treatment costs. In addition, PAiT is expected to increase societal or occupational participation of the patients, leading to reduced health care costs and productivity in the long term. Therefore, PAiT is anticipated to be more cost-effective compared to rTMS.

Challenges of the Proposed Trial

We anticipate that patients are drawn toward our trial because the 1-week intensive treatment is appealing to them. However, these patients may not be willing to be randomized. We aim to tackle this by offering PAiT after the end of the study participation (eg, 25 weeks after the last rTMS session) to patients who are randomized to the 6-week rTMS arm. To date, the PAiT protocol, modeled after the SNT protocol for TRD, is only offered in the Netherlands in our trial.

Another challenge is that the PAiT protocol with 10 sessions on 5 consecutive days is intense, and it is anticipated that patients may miss sessions due to various reasons (eg, traffic or oversleeping). In a complete course, participants can miss 20% (10/50) of sessions at maximum. If >20% (10/50) of sessions are missed, it is considered a failed course. In the rTMS condition, depending on feasibility for the patient and the rTMS team, a maximum of 6 missed sessions may be added to the end of the course. In the PAiT condition, in concordance with the Stanford group, missed sessions will not be rescheduled. If optimal adherence to the protocol is not possible for a patient due to limited traveling capacity or due to the distance from the treatment center, we offer admission to the ward.

To further facilitate tolerability of the PAiT condition, separate rooms will be provided for the patients to rest in between sessions.

This clinical trial includes a direct comparison between treatments of varying durations. This poses the challenge of establishing a representative time point for measuring the primary outcome. To capture the clinical effects in more detail and over time, we will perform weekly clinical measurements for 7 weeks following the start of the treatment regardless of the treatment condition. The time point of measuring the primary outcome was set to 7 days following the final treatment session.

Relevance for Practice

PAiT can be applied in various treatment settings and by various health care professionals. If positive, the results of our study will provide Dutch and international professionals with an adequately powered trial answering whether PAiT is an evidence - based therapy for depression. A novel therapy is necessary to overcome TRD in patients who did not respond after 2 or more evidence - based treatments. In addition, this trial will provide further insights into the differences in the side effects, long-term effects, and (factors contributing to) possible relapse between rTMS and PAiT.

Different rTMS equipment will be used at different sites in this trial. Technical and practical differences in the equipment may introduce variability across sites. However, using different machines is important for generalizability of the results because, in daily practice, mental health institutions use different rTMS machines. To minimize variability in the practical application of rTMS, we thoroughly instruct technicians to follow our provided training and standard operating procedures. All treatments will be conducted using neuronavigation systems with a calibration accuracy of less than 3 mm. In addition, we will control for rTMS machine or site to ensure the reliability of our analyses and investigate the impact of different equipment.

Patient and Public Involvement

To contribute to meaningful patient and public involvement in research [35], an individual with lived experience, affiliated with the Dutch Depression Association (Depressie Vereniging), has been actively engaged since the development of the study protocol and the submission of the funding application for the D-DOTT trial. This collaboration serves to ensure that the research remains responsive to, and reflective of, the priorities and perspectives of individuals affected by depression.

Dissemination Plan

The findings from this clinical trial will be disseminated through a peer-reviewed journal article, presentations at academic conferences, and promotion via social media.

Acknowledgments

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has no specific role in the conceptualization, design, data collection, analysis, decision to publish, or preparation of the manuscript or study protocol.

Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

AD and EvE drafted the original grant proposal and this manuscript describing the study protocol that was critically reviewed by all authors. All authors read and approved the final manuscript.

Conflicts of Interest

MA holds equity or stock in Sama Therapeutics and serves as a scientific adviser to Synaeda and Sama Therapeutics. DMB receives research support from Canadian Institutes of Health Research (CIHR), NIMH, Wellcome Trust, Brain Canada, and the Temerty Family through the Centre for Addiction and Mental Health (CAMH) Foundation and the Campbell Family Research Institute. He received research support and in-kind equipment support for an investigator-initiated study from Brainsway Ltd. He was the site principal investigator for 3 sponsor-initiated studies for Brainsway Ltd. He also received in-kind equipment support from MagVenture for 2 investigator-initiated studies. He received medication supplies for an investigator-initiated trial from Indivior. He is a scientific adviser for Sooma Medical. He is the co-chair of the Clinical Standards Committee of the Clinical TMS Society (unpaid). ATS serves as a scientific adviser for PlatoScience Medical and Alpha Brain Technologies and is the director of the International Clinical TMS Certification Course and the Academy of Brain Stimulation. He has received equipment support from MagVenture, Magstim, and Deymed Diagnostics. All other authors declare no other conflicts of interest.

Multimedia Appendix 1
Grant award document from ZonMW (the Netherlands Organisation for Health Research and Development).
[PDF File (Adobe PDF File), 691 KB - resprot_v14i1e70121_app1.pdf]

Multimedia Appendix 2
Peer review comments from DoelmatigheidsOnderzoek, ZonMw program, Netherlands Organisation for Health Research and Development.
[PDF File (Adobe PDF File), 340 KB - resprot_v14i1e70121_app2.pdf]

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Abbreviations

aiTBS: accelerated intermittent theta-burst stimulation
DLPFC: dorsolateral prefrontal cortex
ECT: electroconvulsive therapy
fMRI: functional magnetic resonance imaging
HDRS-17: 17-item Hamilton Depression Rating Scale
ICER: incremental cost - effectiveness ratio
ISI: intersession interval
iTBS: intermittent theta - burst stimulation
MRI: magnetic resonance imaging
PAiT: personalized functional connectivity–guided accelerated intermittent theta-burst stimulation
PHQ-9: 9-item Patient Health Questionnaire
RCT: randomized controlled trial
rTMS: repetitive transcranial magnetic stimulation
sgACC: subgenual anterior cingulate cortex
SMS: Simultaneous Multi-Slice
SNT: Stanford neuromodulation therapy
TE: echo time
TR: repetition time
TRD: treatment-resistant depression

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Protocol

Surveillance of the Genetic Signature in Circulating Tumor DNA for Guiding Adjuvant Chemotherapy in Urothelial Carcinoma: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Urothelial carcinoma is one of the most commonly diagnosed cancers worldwide, with a poor 5-year survival rate. As genomics is the backbone of the precision medicine paradigm, the genetic signature in circulating tumor DNA (ctDNA) is emerging as a pivotal biomarker for detecting early-stage cancer and molecular residual disease (MRD).

Objective: We aim to evaluate the feasibility and preliminary effects of a ctDNA-based sequencing approach for detecting MRD and guiding adjuvant chemotherapy in postoperative urothelial carcinomas.

Methods: We will perform a stratified 2-arm pilot randomized controlled trial in 2 tertiary hospitals in Hong Kong, involving patients with urothelial carcinomas (pT2-4a N0-2 M0) undergoing radical resection. We plan to recruit 20 patients and determine stratification according to their MRD status before randomization. Patients in each stratum (MRD-positive and MRD-negative groups) will be randomly allocated to either a 4-cycle gemcitabine plus cisplatin chemotherapy arm or a standard management arm in a 1:1 ratio. ctDNA MRD will be tested using a personalized next-generation sequencing panel, which is designed based on the individual's whole exome sequencing results from the operation specimen. The primary outcome is the feasibility of this trial (ie, recruitment, retention, adherence, and completeness). The secondary outcome is treatment-related adverse events. Exploratory outcomes include radiographic disease-free survival, cancer-specific survival, overall survival, ctDNA clearance in patients with ctDNA MRD-positive status, quality of life, fear of cancer recurrence, and cost-effectiveness. Benchmarks for feasibility evaluation are set as (1) ≥20% recruitment response rate, (2) ≤20% loss to follow-up or withdrawal, (3) ≥80% intervention adherence, and (4) ≤20% missing value rate. Each benchmark will be assigned one score, and a total score of 4, 2 to 3, and 0 to 1 will be deemed high, medium, and low feasibility, respectively. Safety evaluations will be presented as numbers and proportions of the adverse events. ANOVA and the Kruskal-Wallis test will be used for continuous outcome variables, whereas the chi-square test and the Fisher exact test will be used for categorical outcome variables. Hazard ratios will be calculated to compare the

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preliminary treatment effect of the gemcitabine plus cisplatin arm against the standard management arm on survival within each MRD group.

Results: This project was funded in February 2024. Patient recruitment started on May 2, 2024. Recruitment and data collection for the trial are ongoing. Data analysis will be performed in mid-2025 and the results of this study are expected to be published in late 2025.

Conclusions: Genetic signature in ctDNA is informative for personalized management of postoperative urothelial carcinomas, including personalized treatment and early detection of disease progression.

Trial Registration: ClinicalTrials.gov NCT06257017; https://clinicaltrials.gov/study/NCT06257017

International Registered Report Identifier (IRRID): DERR1-10.2196/72597

(JMIR Res Protoc 2025;14:e72597) doi:10.2196/72597

KEYWORDS

urothelial carcinoma; adjuvant chemotherapy; circulating tumor DNA; sequencing; molecular residual disease; precision medicine; randomized controlled trial

Introduction

Background

Urothelial carcinomas, located in the upper (pyelocaliceal cavities and ureter) or lower (bladder and urethra) urinary tract [1], are one of the most commonly diagnosed cancers worldwide [2]. Although radical resection (ie, cystectomy and nephroureterectomy) is the established therapy for muscle-invasive urothelial carcinoma (MIUC), patients who have undergone surgery still have a poor prognosis with an estimated 5-year disease-specific survival rate of 50% [3]. To improve the overall survival (OS) and reduce the recurrence risk of MIUC, perioperative chemotherapy is recommended as a standard of care [4]. However, it remains a challenge to determine the presence of residual tumor cells. Adjuvant chemotherapy may cause overtreatment and unnecessary toxicity in patients without molecular residual disease (MRD) [5]. In contrast, those with residual disease may miss the potentially beneficial treatment by the time relapse is detected by imaging. Another challenging issue is that, despite clinical guidelines, neoadjuvant chemotherapy (preoperative) and adjuvant chemotherapy (postoperative) are not commonly or regularly provided in Hong Kong (about 6% and 50%, respectively, based on medical records in our center from the past 5 years) due to potential side effect concerns by both physicians and patients. Therefore, it is pivotal to distinguish patients with residual disease from those with early relapse to help physicians prescribe a precise treatment regimen.

As genomics is the backbone of the precision medicine paradigm, the genetic signature in circulating tumor DNA (ctDNA) is emerging as a pivotal biomarker for detecting early-stage cancer and MRD [6]. MRD, a potential indicator of clinical tumor relapse, can be identified by ctDNA in peripheral blood, with a lead time of several months earlier than that of radiological detection [7]. Methods for ctDNA MRD detection can be divided into various categories: (1) those based on techniques, including polymerase chain reaction (PCR) and next-generation sequencing (NGS); (2) those based on assay panel size, including single-locus or multiplexed assays, targeted sequencing, and untargeted sequencing (whole genome or whole exome sequencing [WES]); and (3) those based on previous knowledge of patient-specific tumor mutational profiles, such as tumor-agnostic assays and tumor-informed assays [8-10].

Several clinical validation studies have confirmed that ctDNA is related to recurrence with high sensitivity (>80%) and specificity (>90%) [11]. For instance, 94% of patients with lung cancer and detectable ctDNA in their first posttreatment blood samples were subsequently identified to have recurrence, with an observed lead time of 5.2 months [12]. Similarly, ctDNA detection has been reported to precede radiographic progression in breast, colorectal, pancreatic, and bladder carcinomas by a median of 9.5, 8.7, 4.2, and 2.8 months [13-16]. In addition, ctDNA, with a half-life shorter than 2 hours in the plasma, is an optimal surrogate for real-time relapse monitoring [7]. Thus, ctDNA MRD can possibly serve as a cancer-agnostic surrogate analyte for risk stratification of tumor recurrence [6], thereby guiding individually tailored treatments.

In our preliminary investigation, we used a WES technique to detect the genetic signatures of 3 bladder cancer samples. As shown in Multimedia Appendix 1, a total of 98, 481, and 120 variants with different mutation types were detected in the 3 individuals, respectively. Personalized genetic signatures have been used to design assay panels to dynamically monitor bloodstream ctDNA MRD. We found that ctDNA MRD could precisely reveal the disease severity at baseline, reflect a disease-free status after treatment, and indicate a potential relapse after follow-up for several months (Multimedia Appendix 2). Given the success of our preliminary investigation and the strengths of its noninvasiveness and superior sensitivity, ctDNA MRD can possibly serve as a cancer-agnostic surrogate analyte for risk stratification of tumor recurrence, thereby guiding individually tailored treatments.

Increasing evidence has evaluated the clinical utility of a ctDNA-oriented approach for adjuvant chemotherapy. A multicenter randomized controlled trial (RCT) [17] of a ctDNA-guided approach for postsurgical treatment of colon cancer showed that patients in the ctDNA-guided group received lower adjuvant chemotherapy (15% vs 28%) without compromising disease-free survival (DFS) compared with the standard management (SM) group (2-year DFS absolute difference 1.1%, 95% CI −4.1% to 6.2%). Another randomized trial of a treatment for female breast cancer [18] also indicated

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that a genomically directed therapy could reduce the uptake of capecitabine and was noninferior to an empirical treatment. As to the utility in MIUC, a post hoc analysis from a multicenter randomized trial [19] revealed that in the ctDNA MRD-positive group, patients receiving adjuvant atezolizumab treatment had improved DFS compared with those receiving observation (median DFS 5.9 months vs 4.4 months; median OS 25.8 months vs 15.8 months), whereas in the ctDNA MRD-negative group, there was no difference in clinical outcomes between treatment and observation arms. A biomarker analysis from another clinical trial [20] demonstrated that the dynamic changes in ctDNA during the perioperative period (proportion of ctDNA positive: 63%, 47%, and 14% at baseline, postneoadjuvant, and postcystectomy time points, respectively) could potentially guide clinical monitoring and postsurgical treatment.

However, there is limited evidence from clinical trials on the clinical efficacy of ctDNA MRD detection in guiding treatment regimens for patients who have undergone surgery for urothelial cancer, particularly among the Chinese population. Thus, we propose a pilot RCT, where patients will be stratified by ctDNA results and randomly allocated to receive either 4 cycles of gemcitabine plus cisplatin (GC) chemotherapy or SM regimens in a 1:1 ratio. In this study, we hypothesize that an improved DFS will be observed with GC chemotherapy administration among patients with ctDNA MRD-positive status, whereas there will be no benefit among patients with ctDNA MRD-negative status. In addition, the genetic profile of ctDNA for detecting MRD can provide real-time recurrence monitoring with a significant lead time before radiological relapse.

Objectives

We aim to (1) assess the predictive value of a ctDNA-guided MRD profiling approach for postoperative adjuvant chemotherapy, (2) assess the clinical approach of MRD surveillance by serial ctDNA testing in patients with ≥T2 urothelial cancer who have undergone surgery, and (3) provide preliminary data to assess the feasibility of a definitive trial and perform a more accurate sample size estimation in a future phase 3 clinical trial.

Methods

Study Design, Setting, and Recruitment

A multicenter, open-label pilot RCT is proposed in the Queen Mary Hospital and the Pamela Youde Nethersole Eastern Hospital. Eligible patients with histologically confirmed MIUC will be invited to join the study from February 19, 2024, to February 18, 2025, in the Queen Mary Hospital and the Pamela Youde Nethersole Eastern Hospital in Hong Kong. The study and informed consent process will be explained to all invited patients before they sign the written consent form to participate in this study.

Ethical Considerations

This study has been approved by the Central Institutional Review Board of the Hospital Authority in Hong Kong (CIRB-2023-189-2) on February 28, 2024. Written informed consent will be obtained from all study participants. Participants will be informed of confidentiality and their right to leave the study at any time and without any penalty. Data are deidentified. This study conforms to the principles outlined in the Declaration of Helsinki and is registered on ClinicalTrials.gov (NCT06257017).

Eligibility Criteria

The participants will be recruited based on the predefined inclusion and exclusion criteria, as presented in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Aged 18 to 70 years
- A score of ≤1 for the Eastern Cooperative Oncology Group performance status
- Receiving radical cystectomy (with lymph node dissection) or nephroureterectomy
- Histologically confirmed (surgical specimen) muscle-invasive urothelial carcinoma, and the major histological type should be transitional cell carcinoma
- Classification of tumor, node, and metastasis: pT2-4a N0-2 M0
- Absence of microscopic (ie, positive margin) or gross residual of the tumor (R0 resection) and absence of metastasis, confirmed by a negative computed tomography or magnetic resonance imaging scan of pelvis, abdomen, and chest within 4 weeks before enrollment
- Adequate hematologic and end-organ function

Exclusion criteria

- Receiving any approved anticancer treatment within 3 weeks before study enrollment
- Participation in another clinical trial with therapeutic intent within 28 days before enrollment
- Experiencing malignancies other than urothelial carcinoma within 2 years before study enrollment
- Conditions that contraindicate chemotherapy, such as renal impairment with creatinine clearance rate <50 mL/min, hearing impairment, and inadequate marrow function
- Anaphylactic or hypersensitivity reactions or other contraindication to cisplatin and gemcitabine
- Active or uncontrolled infections, including HIV, hepatitis B virus, hepatitis C virus, or tuberculosis
- Pregnancy or breastfeeding

Sample Size Estimation

Given this is a pilot study intended as a preliminary exploration, the sample size calculation is based on other similar research and a rule of thumb rather than a formal power calculation [21]. As a pilot study, sufficient statistical power is not expected. The preliminary data from this pilot study will help us estimate the sample size in the following phase 3 trial with a scaled-up sample. On the basis of the limited sources of data, assuming a superiority margin of 26% points for the analysis of 1-year DFS in the GC versus SM arms (probability) [19], with a type-I error of 5% (95% confidence) and a randomization ratio of 1:1, a total sample of 20 patients (10 patients with ctDNA MRD-positive status and 10 patients with ctDNA MRD-negative status) will be deemed sufficient to investigate the acceptability, feasibility, and preliminary impact of the GC intervention. According to the medical records from the 2 hospitals, it is feasible for the 2 study sites to recruit 20 participants within the given timeline.

Genetic Profiling

Sample Collection and Processing

Blood samples (10 mL×2 tubes per participant) will be collected in Streck tubes on the day of the operation. The fresh resected tumor tissue (≥50 mg) will be wiped up by gauze or filter paper immediately and then fixed in specimen bottles using 10% formalin (≥60% of the bottle) within 30 minutes. Samples will be stored at 6 to 37 °C for transport to the laboratory within 72 hours for further analysis.

Whole Exome Sequencing

A median of 500 ng of genomic DNA will be used for the WES workflow for the primary tumor tissue and white blood cells, with an average deduplicated on-target read depth of 300× for tumor DNA and 100× for associated matched germline samples. Targeted exome capture, including tumor mutation burden, microsatellite instability, and human leukocyte antigens, will be performed using a capture probe set with high specificity. The sequencing will be implemented by the brPROPHET (Burning Rock Biotech) service [15,22].

Somatic Variant Calling and Bespoke ctDNA Assay Design

Patient-specific somatic variants from the paired primary tumors and matched white blood cell DNA WES profiles (as mentioned previously) will be analyzed for quality control and sample concordance and then processed via a bioinformatics pipeline to identify somatic single-nucleotide variants (SNVs). A total of 50 highly ranked compatible amplicons (whose variant allele frequency is ≥5%) will be selected for the patient-specific panel. Plasma cell-free DNA will be extracted using the QIAamp Circulating Nucleic Acid Kit (Qiagen). No less than 20 ng will be used as the input for library preparation. Finally, a multiplex targeted PCR will be performed to detect ctDNA MRD, followed by amplicon-based sequencing at an average NGS read depth of up to 100,000×, with a target limit of detection as low as 0.004%. A personalized, tumor-informed ctDNA-based NGS assay will be implemented using the brPROPHET service [15,22].

The paired tumor and whole blood samples will be collected on day 0 for WES (operation day). The genetic signature profile

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of ctDNA via a 20-mL blood sample will be performed on day 28 (baseline before chemotherapy) and weeks 12, 24, 36, and 48 after surgery (follow-up at 4 time points).

Randomization and Allocation

Patients will be stratified by their baseline ctDNA MRD results and randomly allocated in a 1:1 ratio to either a 4-cycle GC chemotherapy arm or an SM arm using computer-generated random numbers for simple randomization:

- ctDNA MRD-positive: GC arm (n=5) versus SM arm (n=5)
- ctDNA MRD-negative: GC arm (n=5) versus SM arm (n=5)

A sealed envelope method will be used for group allocation. Specifically, the sequentially numbered envelope containing the allocation sequence will be opened by a research assistant, and the participant will be informed of the allocation.

Blinding is not applicable in this pilot study. However, the treatment group will be deidentified during the data analysis stage, and a collaborator from a third party with no knowledge of the randomization plan will help to review the data analysis.

Interventions

GC Chemotherapy: Intervention Group

GC is the recommended first-line standard therapy for MIUC. Patients will be treated with 1000-mg/m^2 intravenous gemcitabine on day 1 and day 8 plus 80-mg/m^2 intravenous cisplatin on day 1 or day 2 every 3 weeks (1 cycle) for 4 cycles. A reduced dose of GC will be acceptable if the patient is not suitable for a full dose of GC. For instance, patients with a creatinine clearance rate of 50 to 60 mL/min will receive a 75% dosage of GC. A 3-cycle regimen will also be considered upon an oncologist's evaluation.

SM: Control Group

As a standard of care in Hong Kong, regular follow-up will be provided, and deferred chemotherapy will be initiated until radiological progression is confirmed.

Baseline Assessments

Sociodemographic information (eg, age, gender, employment status, educational level, and marital status); baseline quality of life (QoL); and baseline fear of cancer recurrence (FCR) will be collected using a structured questionnaire (Multimedia Appendix 3). The clinical information of each participant will be collected from the Clinical Management System using a case report form (Multimedia Appendix 4). A baseline radiological evaluation (computed tomography scan of the thorax, abdomen, and pelvis) will be implemented on day 28 to confirm the absence of radiological relapse in patients with ctDNA MRD-positive status.

Outcomes and Assessments

The primary outcome is feasibility, which will be evaluated using 4 indicators: recruitment, retention, adherence, and completeness, with the definition and predetermined criteria shown in Table 1.

Table 1. Definition and criteria to assess the feasibility of the trial.

Indicator	Definition	Benchmark
Recruitment	Eligible patients agreeing to participate in the trial	≥20% recruitment response rate
Retention	Completion of the trial and assessments during the follow-up	≤20% loss to follow-up or withdrawal
Adherence	Adherence to the allocated treatment in the gemcitabine plus cisplatin arm	≥80% intervention adherence
Completeness	Completeness and quality of collected data	≤20% missing value rate

The secondary outcome is treatment-related adverse events (AEs). AEs will be reported in accordance with the Common Terminology Criteria for Adverse Events (version 5.0) [23].

Exploratory outcomes include radiographic DFS, cancer-specific survival, OS, ctDNA clearance in patients with ctDNA MRD-positive status, QoL, FCR, and cost-effectiveness. For radiographic DFS, the radiographic assessment is based on the Response Evaluation Criteria in Solid Tumours (version 1.1), refer to the Follow-Up Strategy section. The radiographic DFS time is calculated from the date of randomized allocation to the date of confirmation of cancer recurrence (event time), death, or dropout, or the last date when the patient is still free of disease (censoring time), whichever occurs earlier. The cancer-specific survival time is calculated from the date of death from urothelial cancer. The OS time is calculated from the date of randomized allocation to the date of death. ctDNA clearance is defined as the change from ctDNA positive to ctDNA-negative status after postsurgical treatment. QoL will be assessed by the Functional Assessment of Cancer Therapy—Bladder [24], which is a 39-item questionnaire comprising physical, social, emotional, and functional well-being, and a bladder cancer subscale, with a higher total score indicating a higher QoL level. FCR will be estimated using the Fear of Cancer Recurrence Inventory–Short Form [25], which is a 9-item questionnaire assessing the presence and severity of intrusive thoughts related to FCR, with a higher score reflecting a higher FCR level. Cost-effectiveness will be assessed by the incremental cost-effectiveness ratio, which is calculated by dividing the difference in costs between GC and SM treatment by the difference in effects, where costs are estimated based on a health care perspective and effects consist of radiographic DFS, time to recurrence, and OS. The assessment schedule of the entire study is listed in Multimedia Appendix 5.

Follow-Up Strategy

Patients will be followed up by radiological evaluation (computed tomography scan of the thorax, abdomen, and pelvis) at weeks 12, 24, and 48 after surgery. The genetic signature profiles of ctDNA, treatment-related AEs, QoL, and FCR will be assessed at follow-up at weeks 12, 24, 36, and 48 after surgery. A flowchart of the study design is presented in Figure

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1. A long-term follow-up of every 6 months will continue to be implemented for each participant after the end of this study.

Figure 1. Flowchart of the proposed pilot randomized controlled trial. ctDNA: circulating tumor DNA; CT TAP: computed tomography scan of thorax, abdomen, and pelvis; ECOG: Eastern Cooperative Oncology Group; GC: gemcitabine plus cisplatin; MRD: molecular residual disease.

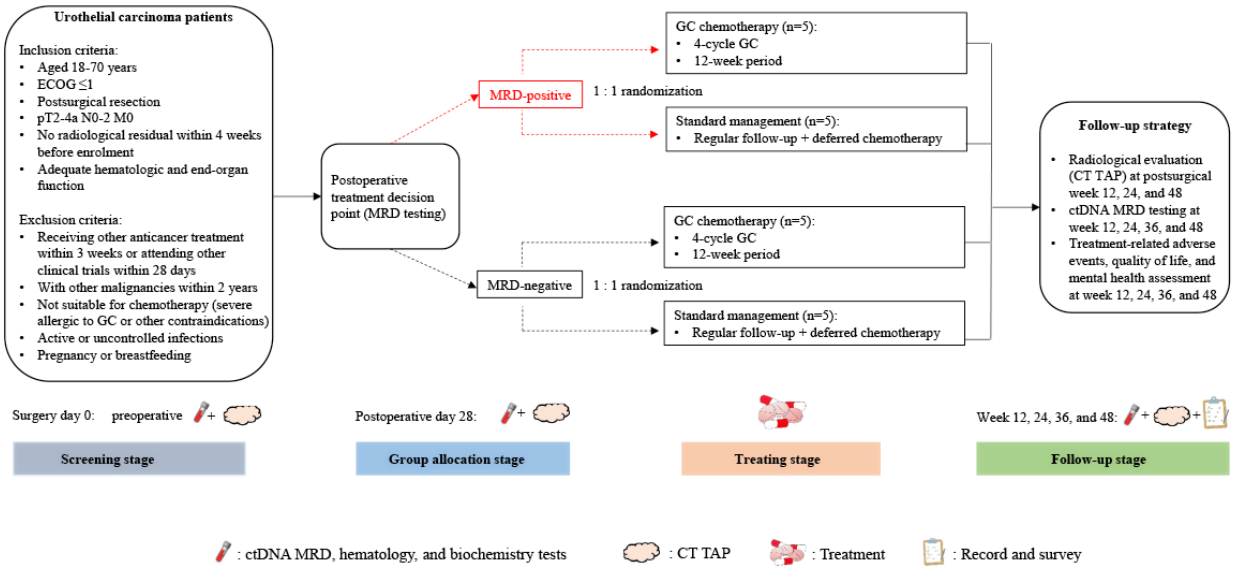

Trial Oversight and Discontinuation or Withdrawal Criteria

Trial Oversight

All research personnel will receive training and comply with the standard operating procedures and the guidelines of the Declaration of Helsinki, the International Council for Harmonisation Good Clinical Practice, and the HKU Health System framework. The study procedure and safety evaluation will be monitored by a research assistant. Participants will be reminded of the scheduled follow-up by a telephone call. Any problems will be addressed by the project coordinator during the course of the study.

Treatment Discontinuation

Treatment discontinuation will be determined after sufficient evaluation by the investigator if participants have any of the following conditions: (1) disease progression during adjuvant chemotherapy; (2) symptom deterioration caused by disease progression, such as uncontrollable pain; (3) unexpected severe AEs from the intervention; (4) receiving other anticancer regimens; and (5) getting pregnant. Discontinuation of the study treatment alone does not constitute a withdrawal from the study.

Participation Withdrawal

Participants can withdraw from any study period at any time without giving reasons and experiencing any disadvantages. Their personal data, along with biospecimens, will be destroyed upon request.

Loss to Follow-Up

Participants will be deemed lost to follow-up if they continuously fail to attend the scheduled visits or continue to be uncontactable or unreachable during the study period. The detailed remedial actions for loss to follow-up are described in the “Contingency Plans” section.

Patient and Public Involvement

Given that GC chemotherapy is the recommended first-line standard therapy for MIUC, patients were not involved in the recruitment and intervention process. However, patients can still benefit from the dynamic MRD monitoring, and the results showing the ctDNA-based MRD trajectory will be sent to every participant at the completion of participation. The side effects of the GC chemotherapy are explained to all participants, who are encouraged to report any symptoms for the duration of the study.

Data Processing and Management

Clinical and Survey Data Processing

The investigator will input the baseline, treatment, follow-up, and outcome data into Microsoft Excel. Survey data entry into Microsoft Excel with preprogrammed check rules will be conducted independently by 2 personnel.

ctDNA Data Transfer and Processing

Patient-specific somatic variants from the WES profile will be analyzed for quality control and sample concordance and then processed via a bioinformatics pipeline to identify somatic SNVs. Bespoke PCR amplicons will be designed based on a prioritized list of the detected SNVs. After plasma cell-free DNA extraction and library preparation, a multiplex targeted PCR will be performed, followed by amplicon-based sequencing. An observation of at least 2 variants within each plasma sample will be defined as ctDNA positive [13,19].

Data Storage

The data storage and processing will comply with the university security code. All clinical and survey data will be kept fully confidential and will be inputted on a dedicated computer with an internet connection and updated antivirus software. The process and reagent or equipment information of the sample processing and genetic profiling will be captured electronically and uploaded to a database with built-in integrity checks. All

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the data will be backed up onto the team server. Files in each follow-up stage will be backed up on an external hard drive for an additional safety purpose

Statistical Analysis

Descriptive Statistics

Numbers with proportions or means with SDs will be calculated to describe the characteristics among the 4 groups (MRD-positive with GC, MRD-positive with SM, MRD-negative with GC, and MRD-negative with SM), including baseline demographics, presurgical examinations, postsurgical examinations, and outcome assessments.

Feasibility Evaluation

Benchmarks for feasibility outcomes are set as (1) ≥20% recruitment response rate, (2) ≤20% loss to follow-up or withdrawal, (3) ≥80% intervention adherence, and (4) ≤20% missing value rate. Each benchmark will be assigned one score, and a total score of 4, 2 to 3, and 0 to 1 will be deemed high, medium, and low feasibility, respectively.

Safety evaluation will be presented as numbers and proportions of the AEs. ANOVA and the Kruskal-Wallis test will be used for continuous outcome variables, whereas the chi-square test and the Fisher exact test will be used for categorical outcome variables.

Efficacy Analysis

Hazard ratios and risk difference will be calculated to compare the treatment effect of the GC arm against the SM arm on survival within each MRD group. As this is a pilot study, we will mainly focus on the magnitude and direction of the preliminary effect sizes, and there will be no anticipation of finding statistically significant differences between the groups.

All process indicators will be presented in accordance with the CONSORT (Consolidated Standards of Reporting Trials) guidelines. Data processing and analyses will mainly be based on the following software: Microsoft Excel, Stata (StataCorp LLC), and R statistics (R Foundation for Statistical Computing).

Contingency Plans

Detailed training will be provided to all research staff, all procedure will be conducted based on the protocol, and all issues will be negotiated and addressed by the same project coordinator in two study sites to ensure site activation in time.

All eligible participants will be documented at the enrolment stage. In case of participant withdrawal, an additional consenting and randomized allocation will be performed from the waiting list as appropriate.

At recruitment stage, contact persons, email address, and mail address should be documented in participants' medical records. If one misses a scheduled visit but can be contactable, a rescheduled visit should be arranged as soon as possible. If one continues to be unreachable during the follow-up, every effort should be made to regain contact with him or her, including telephone call to him or her and his or her contact persons, a reminder sent to his or her email address, a certified letter posted to his or her mailing address, and home visit as appropriate.

Results

The project was funded in February 2024. Patient recruitment started on May 2, 2024 (first patient's first visit). Recruitment and data collection for the trial are ongoing. Data analysis will be performed in mid-2025 and the results of this study are expected to be published in late 2025.

Discussion

Anticipated Findings

To the best of our knowledge, this pilot RCT is the first to frame a contextual ctDNA-guided approach for postoperative adjuvant therapy in patients with urothelial carcinoma. The feasibility and preliminary understanding of effect sizes will be used to inform sample size and refine procedures for a further scale-up and definitive RCT for efficacy and cost-effectiveness estimates.

In this pilot study, the results of the feasibility and safety assessment will help refine the future large-scale trial in terms of inclusion criteria, recruitment procedure, implementation process, and discontinuation and withdrawal criteria. In addition, the magnitude and direction of the preliminary effect sizes calculated in this study will allow for the estimation of the sample size for a larger RCT.

The long-term benefits of this study will mainly stem from the results of the subsequent phase 3 clinical trial. For instance, patient care will be significantly improved; patients with cancer and detected MRD will be timely treated, while those without MRD will be spared from overtreatment and unnecessary toxicity. Hopefully, clinical practice will be improved to a more personalized pattern based on genomics and precision medicine. The future translation and implementation of the research findings and the new technology may also benefit the commercialization of the test and the relevant health care industry.

Limitations

The main limitation of this study is the pilot design with a small sample size, resulting in insufficient statistical power to detect significant differences between groups. Nevertheless, the effect size (ie, hazard ratio and risk difference) will be used to inform a definitive scale-up trial. As this trial is performed within Hong Kong, generalizability is another limitation, and the results of the study may not reflect outcomes representative of the broader population. Finally, given the nature of the intervention, blinding of the participants and the interventionists is impractical.

Conclusions

This study will provide preliminary evidence of personalized management for postoperative urothelial carcinomas, including personalized treatment and early detection of disease progression. This may bring significant benefits to patients and reduce the burden from the potential overtreatment or side effects in the health care system and society.

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Acknowledgments

The authors would like to thank the patients, physicians, technicians, and advisers for their willingness to contribute to the study.

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Data Availability

The trial dataset is not available publicly, and any requests for access should be sent to the corresponding author.

Authors' Contributions

RN was responsible for formulating the overall research questions and for the design, supervision, and funding acquisition of the project. YZ was responsible for the methodological design, manuscript drafting, and setting up of the study. XR, YW, and TTSC were coordinating investigators and involved in study design and implementation. CY, RS, JL, SA, and RM aided in manuscript preparation and critical appraisal. DH, YG, YX, and LC provided technical support and aided in the study implementation. QD, AT-LN, CWBL, and DX provided a critical review of the protocol. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Genetic characteristics of the 3 samples undergoing whole exome sequencing.
[PDF File (Adobe PDF File), 96 KB - resprot_v14i1e72597_app1.pdf]

Multimedia Appendix 2
Circulating tumor DNA surveillance at baseline, treatment, and follow-up.
[PDF File (Adobe PDF File), 113 KB - resprot_v14i1e72597_app2.pdf]

Multimedia Appendix 3
Questionnaire.
[PDF File (Adobe PDF File), 359 KB - resprot_v14i1e72597_app3.pdf]

Multimedia Appendix 4
Case report form.
[PDF File (Adobe PDF File), 3343 KB - resprot_v14i1e72597_app4.pdf]

Multimedia Appendix 5
Assessment schedule of the study.
[PDF File (Adobe PDF File), 166 KB - resprot_v14i1e72597_app5.pdf]

Multimedia Appendix 6
Peer-review report from the Health and Medical Research Fund Research Council Grant Review Board (Hong Kong).
[PDF File (Adobe PDF File), 49 KB - resprot_v14i1e72597_app6.pdf]

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Abbreviations

AE: adverse event
CONSORT: Consolidated Standards of Reporting Trials
ctDNA: circulating tumor DNA
DFS: disease-free survival
FCR: fear of cancer recurrence
GC: gemcitabine plus cisplatin
MIUC: muscle-invasive urothelial carcinoma
MRD: molecular residual disease
NGS: next-generation sequencing
OS: overall survival
PCR: polymerase chain reaction
QoL: quality of life
RCT: randomized controlled trial
SM: standard management
SNV: single-nucleotide variant
WES: whole exome sequencing

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Protocol

Integrated Model of Cancer Control for Early Detection and Treatment in Adolescents and Young Adults Living With HIV: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: Zambia has one of the highest prevalence rates of HIV among adolescents and young adults (AYA) living with HIV in sub-Saharan Africa, which accounts for half of all new HIV cases as of 2023. Compared to their peers who are not living with HIV, AYA living with HIV are more likely to develop cancer. The most frequently diagnosed cancers among AYA living with HIV in Zambia are cervical cancer, Kaposi sarcoma, and non-Hodgkin lymphoma. Premature cancer mortality among AYA living with HIV is driven by late-stage presentation and poor treatment adherence.

Objective: We aim to develop and test an integrated model of cancer control for AYA living with HIV that can be delivered as an embedded component in existing HIV treatment programs in primary care facilities and linked with specialized treatment at cancer centers.

Methods: We propose a cluster randomized controlled trial to compare the AYAHIV Role-Based Responsibilities for Oncology-Focused Workforce (ARROW) program with a one-time education campaign. The ARROW program consists of interventions at the individual, health care provider, and health system levels. Peer counselors will educate AYA living with HIV through one-on-one and group education sessions and offer care coordination and linkages with clinicians. The HIV and oncology workforce will receive collaborative education and training. The ARROW Health Care Collaborative will connect administrators and policy makers to address system-level barriers. The study will recruit AYA living with HIV between the ages of 15 and 39 years who have been on antiretroviral therapy for at least 6 months and are not pregnant; the cancer treatment cohort will enroll AYA living with HIV who have been diagnosed with cervical cancer, Kaposi sarcoma, or non-Hodgkin lymphoma in Lusaka, Zambia. Half of the 18 HIV facilities have been randomly assigned to a one-time educational campaign and the other half to the ARROW intervention. Participants in the cancer treatment cohort will be randomized into 1 of the 2 study arms. We will conduct economic evaluations to assess the cost-effectiveness of the ARROW program. We will use an intent-to-treat approach to test the hypothesis that AYA living with HIV in the ARROW program will have higher uptake of diagnostic services, increased adherence to treatment, and improved outcomes compared to those receiving one-time education.

Results: As of March 2025, early detection cohort recruitment concluded with 3442 participants and cancer treatment cohort enrollment is ongoing, with 105 participants thus far. Results pertaining to the 12-month end points will be available in early 2026.

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Conclusions: If successful, the ARROW program will offer a model to improve cancer prevention, early diagnosis, and treatment through improved integration between HIV and cancer services. Furthermore, ARROW can provide a framework for implementing expanded services, such as survivorship care, for AYA living with HIV.

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KEYWORDS

adolescents and young adults; HIV care; cancer treatment; early detection of cancers

Introduction

Background

Adolescents and young adults (AYA), those aged 15 to 39 years, represent a growing share of people living with HIV worldwide. Zambia has one of the highest prevalence rates of HIV among AYA in sub-Saharan Africa; as of 2023, there are approximately 90,000 AYA between the ages of 10 and 19 years living with HIV, with only half of that population receiving antiretroviral therapy (ART) [1]. The AYA population also accounts for half of all new recorded infections in the country [1]. Compared to their peers who are living without HIV, AYA living with HIV are at an increased risk of developing cancer [2-4]. Cancers most frequently diagnosed among AYA living with HIV in Zambia are Kaposi sarcoma (KS), non-Hodgkin lymphoma (NHL), and cervical cancer (CC) [5-9]. The incidence of these cancers increases with a lower cluster of differentiation 4 cell count (CD4); therefore, adherence to ART is paramount [10]. Unfortunately, AYA living with HIV are among the most vulnerable groups with poor adherence to ART, and there is no large-scale cancer control program to facilitate early diagnosis and completion of guideline-recommended treatments in Zambia [11,12].

A cancer program focused on AYA living with HIV and tailored to the Zambian limited resource setting is needed to reduce premature mortality. Data on malignancies within this group are sparse, but late-stage presentation, unplanned breaks from cancer treatment, and abandonment of treatment have been reported among young patients with cancer in resource-limited settings [13-15]. These factors result in high morbidity and premature mortality among AYA living with HIV and diagnosed with cancer. Late-stage presentation and lack of treatment adherence are key drivers of premature cancer mortality among AYA living with HIV in Zambia.

AYA living with HIV are a vulnerable population who face psychosocial issues, stigma, and comorbidities that affect their health care-seeking behavior [16]. In Zambia, young patients living with both HIV and cancer have unmet needs related to information about health risks, coping strategies for medication side effects, positive peer and family support, and activation of personal agency [17-20]. Furthermore, during the transition from pediatric to adult HIV clinics, many of these individuals are lost to care [21-25]. Health care providers who specialize in HIV care and oncology face barriers, such as time constraints, with regard to treating cancer in AYA living with HIV, which inhibits their ability to deliver optimal care [26,27]. There are also no linkages for collaborative management of cancer in AYA living with HIV by primary care providers specializing in HIV care and cancer specialists. At the health system level, some key barriers include weak referral systems and a lack of standardized protocols to implement AYA-friendly care [28-32].

The Zambian guidelines recommend CC screening for all female AYA living with HIV who are sexually active, regardless of age [33]. However, screening among this population is low, despite the availability of free health care services. According to recent studies [18,34], <40% of AYA living with HIV have undergone screening for CC. There are no screening tests available for KS or NHL, but increasing awareness of the risk factors and symptoms, along with physical examinations, could reduce late presentation [13,29]. In fact, strategies to facilitate early detection of KS have shown promise in other African countries. A recent study in Uganda [35] used education messaging (comic strip and video) to increase KS awareness and knowledge. Furthermore, researchers in Zimbabwe developed a physical examination checklist to identify symptoms of KS [36]. The Cancer Diseases Hospital, which is the main referral center for treatments in Zambia, has adopted the National Comprehensive Cancer Network's (NCCN's) Harmonized Guidelines for sub-Saharan Africa for AYA oncology to optimize treatment. The NCCN guidelines will be most effective when paired in tandem with adequate treatment adherence support for AYA living with HIV.

AYA-focused programs have been successful in other settings, especially in high-income countries. These programs use a variety of models to promote collaboration across multidisciplinary teams and integrate medical and psychosocial care for AYA [37-39]. In sub-Saharan African countries such as Zambia, multiple barriers need to be addressed to facilitate early diagnosis in the primary care setting and to ensure receipt of full treatment course in cancer centers [40].

Objective

We aim to develop and test an integrated model of cancer control for AYA living with HIV that can be delivered as an embedded component in existing HIV treatment programs in primary care facilities and linked with specialized treatment in cancer centers.

Methods

Overview and Conceptual Framework

Overall Approach

We propose a program that embeds cancer control strategies for AYA living with HIV into existing HIV treatment programs in primary care facilities and at cancer centers in Zambia by

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strengthening and supporting the existing clinical teams to optimize cancer care delivery. We used theory-informed multilevel strategies to create the AYAHIV Role-Based Responsibilities for Oncology-Focused Workforce (ARROW) program to increase uptake of services for early diagnosis and improve compliance with cancer treatment for CC, KS, and NHL. ARROW will use an evidence-driven approach to select low-cost, multilevel peer-to-peer support and learning strategies to address identified barriers and delineate roles played by HIV and cancer care providers to deliver guideline-directed care for early diagnosis and cancer treatment. Each of the proposed strategies has been tested in the Zambian and sub-Saharan African context and shown to be feasible [18,41-45].

Our overall approach is based on the evidence-based strategy of peer support for engagement and learning [46-54]. Figure 1 presents the theoretical framework, which is based on the socioecological model [55]. We have created the ARROW program with strategies that focus on barriers at the individual, health care provider, and health system levels. These strategies are guided by the capability, opportunity, motivation, and behavior model, in which capability (eg, knowledge and cancer risk), opportunity (eg, availability of high-quality screening and treatments), and motivation (eg, self-efficacy and care-seeking behavior) interact to facilitate behavior change [55].

Figure 1. Conceptual framework for addressing barriers to reduce cancer mortality. ARROW: AYAHIV Role-Based Responsibilities for Oncology-Focused Workforce; ART: antiretroviral therapy; AYA: adolescents and young adults.

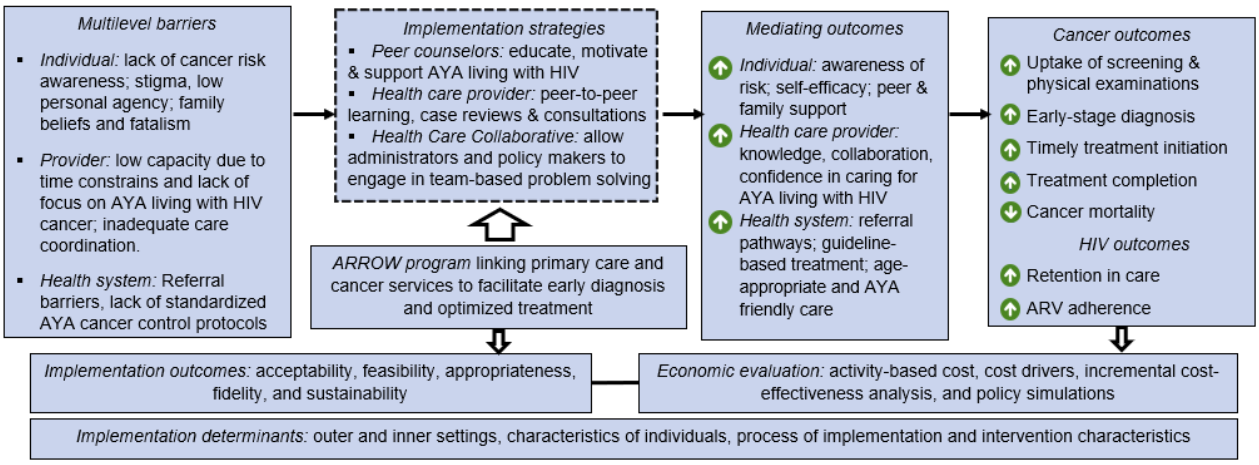

Interventions

The ARROW program is a holistic intervention that is meant to support HIV and cancer care at 3 different levels: individual, health care provider, and health system.

Individual Level

There is growing evidence on the role that peer support can play in addressing individual and interpersonal barriers to improve knowledge and encourage AYA to seek medical care [56-62]. We will place trained peer counselors (PCs) in HIV treatment facilities and at the Cancer Diseases Hospital to educate AYA living with HIV, provide emotional support, and offer care coordination and linkages with the clinical team. PCs will offer support for early diagnosis of cancers, completion of cancer treatment, and ART adherence as required. They will coordinate care with health care providers and serve as an extension of the clinical team by conducting physical examinations to identify signs of KS and NHL and offering coping strategies for ART and chemotherapy side effects.

A total of 21 PCs, 10 (48%) males and 11 (52%) females between the ages of 20 and 39 years, will be recruited. Of the 21 PCs, 18 (86%; 9/18, 50% males and 9/18, 50% females) will receive traning for placement in HIV treatment centers. The remaining 3 PCs (14%; 1/3, 33% male and 2/3, 67% females) will be posted to the Cancer Diseases Hospital. The recruitment of more female PCs is due to the heavy burden that CC places on the health care system. Our existing 3-week training curriculum, from a previous study [18] conducted by the research team, will be tailored for PCs and will include training on appointment tracking systems. The curriculum will include standardized operating procedures for implementing the group education sessions to include additional details on cancer risk, early diagnosis approaches, and optimal treatments. Those assigned to the Cancer Diseases Hospital will receive training on how to help AYA living with HIV manage treatment side effects and assist with their adherence to ART while undergoing cancer treatment. The PCs will conduct site visits of the HIV facilities and the Cancer Diseases Hospital to become familiar with the staff, the layout of the clinics, and the services available.

Table 1 summarizes the 4 core PC roles and their corresponding activities. The PCs will offer 6 group education sessions at each ARROW HIV facility per month (one module each month) for the first 12 months, along with one-on-one education. For the remaining follow-up period, PCs will offer one-on-one education as needed. All other activities will continue throughout the trial.

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Table 1. Key functions of peer counselors (PCs).

Functions	HIV treatment facility	Cancer diseases hospital
HIV and cancer knowledge	Group and one-on-one education on cancer early diagnosis and ART[a] adherence	One-on-one education on cancer treatment and ART adherence; some group sessions
Social and emotional support	Group sessions and individual meetings to discuss coping with stigma, family stressors, and side effects (ART or cancer treatment)	Group sessions and individual meetings to discuss coping with stigma, family stressors, and side effects (ART or cancer treatment)
Care-seeking behavior	Motivational interviews; PCs offer convenient times for physical examinations; reminder phone calls before visits	Documenting treatment plan; tracking of visits to remind AYA[b] living HIV about visits; identifying and addressing barriers
Care coordination	Accompany AYA living with HIV to referral visits; facilitate delivery of results to the HIV care team; inform AYA living HIV about the next steps	Ensure that the cancer care team is aware of any barriers to adherence; facilitate communication with the HIV care team

[a]ART: antiretroviral therapy.

[b]AYA: adolescents and young adults.

Educational materials will be made for the 2 study arms of the randomized controlled trial by adapting existing group and one-on-one educational materials, such as training modules previously tested for KS awareness or the NCCN AYA Guidelines for Patients. These materials will be presented at pretesting workshops. Trained facilitators will present materials to ensure that they are age-appropriate by assessing participants' ability to understand, whether the topics and contents address key issues faced by the age group, and whether AYA living with HIV can embrace and follow the solutions or advice offered. Using the feedback received, we will finalize the modules and brochure. All adapted education materials for AYA living with HIV will be available in English, Bemba, Nyanja, and Tonga. Health care provider guidance documents will be available in English, as in previous projects; all Zambian health care providers are fluent in English.

A treatment plan based on the NCCN treatment and survivorship plans will be developed for study participants at the Cancer Diseases Hospital. The PCs will update treatment plans for AYA living with HIV through the treatment course, which will serve as a comprehensive record that can also be placed in the patient file at the HIV treatment center that the AYA living with HIV will return to after treatment completion.

Health Care Provider Level

Team-based care is critical for optimal oncology care delivery [61,62]. Formalized communication channels, collective learning, and clear team roles are the cornerstone of collaborative care teams [63,64]. The ARROW Provider Network will use a tailored Project Extension for Community Healthcare Outcomes approach to link pediatric and adult health care providers who specialize in HIV care in the primary care facilities with counterparts at the Cancer Diseases Hospital to enable peer-to-peer learning, review of patient cases, and expert consultations [44].

Guidance documents and brochures will be created for health care providers by inviting a mix of pediatric and adult care providers to cocreating workshops. These materials will contain background information, AYA-friendly care delivery, age-appropriate engagement with AYA living with HIV, monitoring of ART adherence, flowcharts with referral pathways for early diagnosis, process steps to implement guideline-recommended cancer treatment for AYA living with HIV, documentation of services provided (eg, in the SmartCare electronic health record, which is used in HIV facilities and capture visit details, medications, and laboratory tests), and a charter with roles and responsibilities for clinical teams in the HIV treatment centers and those at the Cancer Diseases Hospital. Facilitators will use the NCCN sub-Saharan African harmonized guidelines for each cancer, along with the AYA guidelines, and create guidance documents focused on AYA living with HIV that are tailored to the Zambian setting.

Health care providers will also receive in-person training at each of the 9 HIV facilities selected to implement the ARROW program and at the Cancer Diseases Hospital before initiating the implementation trial. These training programs will also include sessions on understanding stigma faced by AYA living with HIV, delivering age-appropriate and AYA-friendly care, and best practices for communication with this population using previous training tools [17]. All HIV care providers (both pediatric and adult) will be encouraged to attend a session. We will hold additional training as needed, including refresher training sessions during the 36-month trial.

We will initiate activities to facilitate collaborative learning and coordination by hosting (1) monthly peer-to-peer web-based sessions with presentations from Zambian and international physicians working to improve AYA cancer care, case reviews for AYA living with HIV, and expert consultation panels to address specific questions from the ARROW Provider Network; (2) an annual in-person meeting in Lusaka to review progress and next steps; and (3) an in-facility biannual seminar with adult and pediatric teams on specific issues related to AYA living with HIV.

Health System Level

We will initiate the ARROW Health Care Collaborative, which will bring together health system administrators and Zambian Ministry of Health policy makers to foster team-based problem solving and implementation of solutions to address system-level barriers (eg, barriers related to referrals). We will also use a user-centered design process to cocreate education materials and guidance documents to implement ARROW.

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We will invite 6 health care administrators from Lusaka province and 4 Ministry of Health policy makers to join the Collaborative to foster team-based problem solving. These individuals will meet quarterly to review implementation challenges related to referral pathways and other system-level barriers to receiving services to facilitate early diagnosis and optimal cancer treatment. Each meeting will end with clear action steps toward resolving the barriers and procedures that will be used to monitor the implementation of the proposed solutions. The first meeting of the Collaborative will take place 6 months before the start of the trials to allow adequate time to identify and address any gaps identified through the readiness assessment. The reduction in barriers will benefit not only the ARROW program participants but also all AYA living HIV in Lusaka province.

Randomized Controlled Trials

Overall Study Design

Overview

We will compare the ARROW program to a one-time education campaign that gives informational brochures to AYA living with HIV and HIV care providers. Given the acute need for cancer control strategies for AYA living with HIV to reduce premature mortality, planning consultations with community stakeholders deemed it unethical to use “usual care” as the comparison arm. We will, therefore, test the hypothesis that the ARROW program will be more effective than a one-time education campaign (education brochures to AYA living with HIV and HIV providers) in increasing care received by AYA living with HIV to facilitate early diagnosis (physical examination for KS and NHL, CC screening, and timely referrals) and in improving adherence to treatment among AYA living with HIV diagnosed with cancer. We will also assess implementation outcomes (based on the Proctor framework), analyze determinants of implementation (based on the Consolidated Framework for Implementation Research), and conduct economic evaluation of the ARROW program [65,66].

Early Detection Cohort

We propose a cluster randomized study to be implemented at 18 HIV treatment facilities in Lusaka province. Three facilities serving each type of regional population (urban, periurban, or rural populations) will be randomly assigned to a study arm: the ARROW program or one-time education. Overall, 9 (50%) facilities will be assigned to each arm of the trial, with data collection at baseline and at 12-, 24-, and 36-month follow-up. At each of the 18 clinics, we will enroll 100 men and 100 females resulting in a total of 3600 participants in the early detection cohort. The 200 AYA living with HIV per facility will be selected by first reviewing the HIV register and identifying those who meet the study inclusion criteria: 15 to 39 years of age, on ART for at least 6 months, not pregnant, and with no pending plans to move from the current residence during the 3-year study duration. For all the 3600 participants, we will collect baseline data and capture information on study end points from the SmartCare system, and the supplemental data will be collected by PCs and trained study data collectors (eg, tracking referrals for all participants and obtaining results of biopsies).

Cancer Treatment Cohort

This will take place entirely at the Cancer Diseases Hospital, with some patients being recruited from the University Teaching Hospital. A total of 500 AYA living with HIV who have been diagnosed with CC, NHL, or KS will be recruited into the study, with 50% (250/500) of the patients in each trial arm (ie, one-time educational campaign vs the ARROW intervention). Patients will be surveyed annually at 12, 24, and 36 months. Trained data collectors will obtain consent and enroll AYA living with HIV, aged 15 to 39 years. We will be aiming for the following targets for each cancer type: 50% (250/500) of the participants with CC, 30% (150/500) of the participants with KS, and 20% (100/500) participants with NHL (with an overall equal number of male and female AYA living with HIV for KS and NHL). While AYA living with HIV who are pregnant will be excluded, as they require specialized care, those who become pregnant during the trial period will remain enrolled in the study; CC screening and physical examinations for KS and NHL will be offered based on Zambian guidelines pertaining to pregnancy.

We hypothesize that, by facilitating peer support to address barriers and gaps at multiple levels, the ARROW program will be more effective than the one-time education campaign, but more expensive as well. As shown in Figure 2, we will simultaneously conduct separate randomized controlled trials at the HIV treatment facilities and at the Cancer Diseases Hospital. The trials will be initiated upon completion of the preimplementation preparation activities. We will then embed PCs into the care teams at the HIV facilities and the Cancer Diseases Hospital and initiate the planned implementation activities of the ARROW Provider Network in the ARROW program arm. The comparison arm will receive the one-time education campaign: health care providers at the HIV facilities (particularly physicians and nurses) will receive a brochure with key guidance for early diagnosis of cancers in AYA living with HIV, and the AYA living with HIV upon recruitment will also receive education brochures at both the HIV facilities and the Cancer Diseases Hospital. The Health Care Collaborative will continue to meet as planned on a quarterly basis.

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Figure 2. Experimental design and sample sizes. ARROW: AYAHIV Role-Based Responsibilities for Oncology-Focused Workforce; AYA: adolescents and young adults.

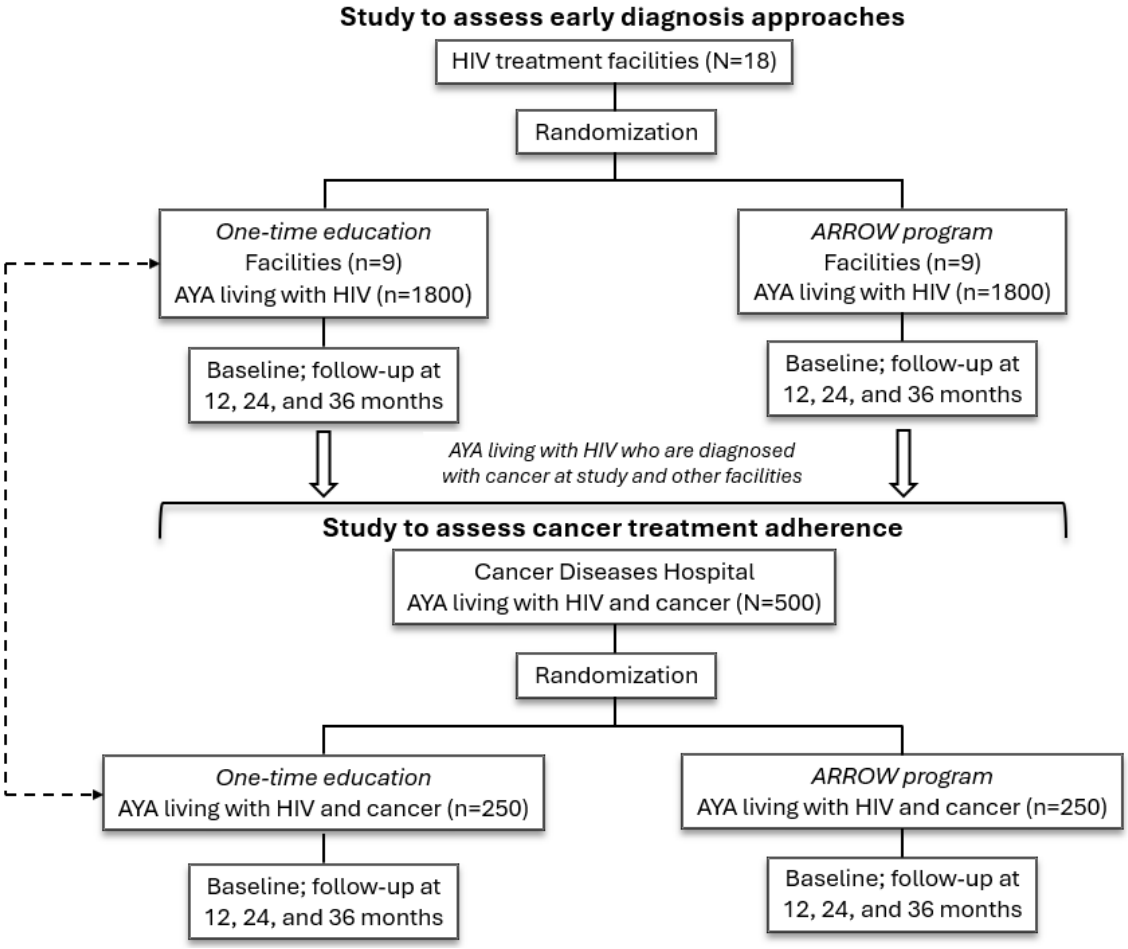

Study End Points

Early Detection Cohort

We will assess effectiveness based on dual primary end points. The first primary end point is the proportion of those who complete a physical examination visit for KS and NHL and the proportion of those who are up to date with CC screening (female participants only) at 12 months. The second primary end point is the proportion of those who complete the recommended follow-up supplemental or diagnostic procedures (within 3 months of receiving follow-up referral), those who initiate cancer treatment (within 3 months of diagnosis), and those who complete additional cancer detection visits over 36 months. The secondary end point, evaluated at 36 months, is the proportion of those diagnosed at an early stage (among those diagnosed with KS, NHL, and CC). We will likely have a few cancer cases in the study facilities. Therefore, these findings will not be conclusive but will offer insights into the potential impact of the ARROW program on facilitating diagnosis at an early stage.

Cancer Treatment Cohort

The primary end point is the proportion of those who are adherent to cancer treatment (complete all treatment modalities as prescribed; 2-week delays will be allowed) at 12 months after diagnosis, the secondary end point is the proportion alive at 12 months after diagnosis, and the tertiary end point is the proportion with recurrence at 24 and 36 months (among those with 24- and 36-month follow-up).

For all the AYA living with HIV, we will report adherence to ART (proportion of those filling prescriptions at least every 3 to 6 months) and viral load at 12, 24, and 36 months. Viral load testing is generally conducted at least annually for AYA living with HIV as part of routine guideline-recommended practice. We will reinforce the need for regular viral load testing as part of health care provider training and have set aside funds to conduct viral load testing for study participants for whom this information is unavailable in the medical record.

Sample Size and Recruitment

Early Detection Cohort

We will use stratified random sampling to select an equal number of male and female participants and a mix of AYA living with HIV with perinatally and behaviorally acquired HIV. In terms of age distribution, 20% (720/3600) of the sample will be aged 15 to 19 years, 20% (720/3600) will be aged 20 to 24 years, and 60% (2160/3600) will be aged 25 to 39 years. We will oversample AYA living with HIV in each stratum to account for AYA living with HIV who may not meet inclusion criteria or who decline to participate. HIV facility staff will contact AYA living with HIV or consenting adults (for those aged 15 to 17 years) to discuss the study, and those interested

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will meet with trained data collectors who will assess eligibility and obtain consent or assent. The sample size was calculated assuming conventional specifications (α=.025 for each end point, 2-sided tests) based on the dual primary end points and allowing for the detection of an absolute 20% point improvement in the primary end points, which is our minimum threshold to consider the ARROW program successful. For the one-time education arm, given the current low level of uptake of early diagnosis services, we estimate uptake of physical examinations to be about 15% (15/100) and CC screening to be about 20% (20/100) at 12 months. With our proposed sample size of 3600, we will be able to detect a 20% difference in uptake of physician examination (35% in the ARROW arm) with over 90% power and CC screening (40% in the ARROW arm) with over 85% power. We can achieve this even after accounting for up to 10% attrition at 12 months (a previous study conducted by the research team achieved this retention rate without the level of active participant contact planned for this study) [67]. We estimate that the interclass correlation coefficient will be in the range of 0.03 to 0.05 because correlation coefficients for binary data are typically quite small, especially when physical examinations and screening uptake are very low [68].

Cancer Treatment Cohort

We will use stratified random assignments to place patients in each arm of the trial. Once we have enrolled 10 patients with each type of cancer, we will randomly assign half to the ARROW program and the other half to the one-time education arm. All patients will have a minimum of 12 months of follow-up, and some will have up to 36 months of follow-up. Data will be collected at baseline and then annually for the 3-year duration of the trial from the AYA living with HIV through surveys and by abstracting information from the Cancer Diseases Hospital records. The sample size (n=500) was calculated using conventional specifications (α=.05; 2-sided tests) based on the primary end point and allowing for an absolute 15% point improvement; the estimated current level of adherence is 75%, which will increase to at least 90% with the ARROW program. With 50% (250/500) of the patients in each arm, we will have more than 90% power to detect this difference.

Ethical Considerations

This study was approved by the institutional review boards at the Population Council (Protocol 1019) and the ERES (Excellence in Research Ethics and Science) Converge (Ref. No. 2022-Dec-003) and has been registered on ClinicalTrials.gov (NCT06004011). For the AYA living with HIV aged <18 years, we will obtain both written parental consent and assent from the minors. The AYA living with HIV aged ≥18 years will be asked to provide written informed consent. Trained data collectors will administer and document informed consent. Data will be collected via a secure data platform, and no identifiable data will be collected in the baseline and annual surveys. The participants will not receive monetary compensation for participation in study education sessions and other activities. The participants will receive ZK 100 (US $4.23) for completing the data collection at baseline and at annual touchpoints. This study also has a data safety monitoring board that provides ongoing evaluation of the study's progress. This board has the authority to review any adverse events and provide guidance for any protocol modifications or termination of the study. The board comprises 5 members from nongovernmental organizations and the Zambian Ministry of Health. Any protocol changes, or other modifications, with be shared with the institutional review boards and the data safety monitoring board.

Data Collection

In the HIV treatment facilities, we will generate electronic data files for the study cohort, and in other settings, such as referral facilities and the Cancer Diseases Hospital, the study team will abstract data from electronic databases or paper files. We will also conduct surveys to collect data from the AYA living with HIV and health care providers. The PCs will document their interaction with the AYA living HIV in the PC tracking tool, and the health care provider participation in the ARROW Provider Network will be captured in the study database. These details will be used to determine the "dose" of the ARROW program. All data will be collected by trained data collectors, who will undergo continual monitoring, and study coordinators, who will confirm fidelity to protocol specifications by random in-person review. Refer to Table 2 for the end point definitions and the biological, self-report, and clinical records data collected at baseline and at 12-, 24-, and 36-month follow-ups.

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Table 2. Data collection at baseline and at 12-, 24-, and 36-month follow-ups.

Constructs and measures	Instrument and specification	Source	Timing
Data elements for primary, secondary, and tertiary end points: HIV and cancer care continuum			
Proportion of participants completing physical examination (KS[a] and NHL[b]) and up to date with CC[c] screening	Confirmation of services will be based on clinical records and PC[d] tracking tool (primary end point at 24 mo)	Biological, imaging, and clinical procedures identified through clinical records and study database	12, 24, and 36 mo
Proportion of participants completing diagnostic tests and initiating treatment in ≤90 d	Measured as days from referral for testing and cancer diagnosis, respectively; based on chart review and study data	Biological, imaging, and clinical procedures identified through clinical records and study database	24 and 36 mo
Proportion of participants completing repeat examinations and screening at the recommended interval	Screening every 2 y for CC and annual examination (especially when CD4[e]<100) based on the Zambian guidelines	Biological, imaging, and clinical procedures identified through clinical records and study database	36 mo
Proportion of participants with early-stage diagnosis[f]	Stage 1 or 2 for NHL and CC; good risk for KS[g]	Biological, imaging, and clinical procedures identified through clinical records and study database	36 mo
Proportion of participants adherent to cancer treatment[f]	Complete cancer treatment modalities as recommended	Biological, imaging, and clinical procedures identified through clinical records and study database	12 mo after diagnosis
Proportion of participants alive at 12 mo after diagnosis[f]	Follow-up conducted by PCs and entered in study database	Biological, imaging, and clinical procedures identified through clinical records and study database	12 mo after diagnosis
Proportion of participants with recurrent disease[f]	AYA[h] living with HIV and cancer who experience cancer recurrence	Biological, imaging, and clinical procedures identified through clinical records and study database	36 mo
Proportion of participants adherent to ART[i] and viral load	Prescription filled every 3 to 6 mo; blood test	Biological, imaging, and clinical procedures identified through clinical records and study database	Annually
HIV status, demographics, mediating outcomes, intervention dose, and clinical services			
HIV status and diagnosis date	Perinatally or behaviorally infected; CD4 count	Clinic record	Baseline
Demographics and socioeconomic status	Research Triangle Institute AYA Zambia survey	Self-report	Baseline
Self-efficacy (AYA living with HIV)	Generalized self-efficacy Scale [69]	Self-report	Baseline and 12, 24, and 36 mo
Social support and mental health (AYA living with HIV)	Brief social support and patient health questionnaires [69,70]	Self-report	Baseline and 12, 24, and 36 mo
HIV and cancer stigma (AYA living with HIV)	Anticipated stigma measures [71,72]	Self-report	Baseline and 12, 24, and 36 mo
Cancer risk (AYA living with HIV)	Updated Research Triangle Institute cancer survey	Self-report	Baseline and 12, 24, and 36 mo
Group education and sessions (AYA living with HIV)	Number and proportion of education sessions attended (dose)	PC tool; study database	12, 24, and 36 mo
One-on-one education (AYA living with HIV)	Number of women receiving each level of strategy (dose)	PC tool; study database	12, 24, and 36 mo
HIV and cancer team training (health care provider)	Proportion who attended initial training sessions (dose)	PC tool; study database	12, 24, and 36 mo
Network meetings (health care provider)	Number and proportion of meetings attended (dose)	PC tool; study database	12, 24, and 36 mo

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Constructs and measures	Instrument and specification	Source	Timing
Clinical team knowledge, confidence in ability, and collaboration (health care providers)	Survey on skills and patient communication; stigma related to AYA living with HIV (modified Nyblade instrument [73]) and peer learning and coordination	Self-report	Baseline and annually
Diagnostic procedures by cancer type	Number of supplemental and diagnostic tests conducted	Clinical record	12, 24, and 36 mo
Treatment modality by cancer type	Chemotherapy sessions; surgery; type of radiation	Clinical record	12, 24, and 36 mo

[a]KS: Kaposi sarcoma.

[b]NHL: non-Hodgkin lymphoma.

[c]CC: cervical cancer.

[d]PC: peer counselor.

[e]CD4: cluster of differentiation 4.

[f]Among AYA living with HIV and diagnosed with cancer.

[g]NHL stage based on the Lugano classification, CC stage based on the International Federation of Gynecology and Obstetrics, and KS stage based on the AIDS Clinical Trial Group system.

[h]AYA: adolescents and young adults.

[i]ART: antiretroviral therapy.

Analysis of Hypotheses

We will use an intent-to-treat approach to test the hypotheses (related to the dual primary and secondary end points) that AYA living HIV in the ARROW program, compared with those receiving one-time education, will have higher uptake of early diagnostic services, increased adherence to treatment, and improved outcomes.

For the facilities assigned to the intervention group in the early detection cohort, we will examine the effects at the individual level across the 2 randomization groups. Given the need to consider the influence of the cluster randomization, we will use generalized estimating equation models to estimate the effect across the trial arms. If the Hausman assumption of correlation between the random and fixed effects is violated, then we will include fixed effects representing cluster identification [74]. For the cancer treatment cohort, we will generate summary statistics for the end points and test statistical significance. We will also conduct logistic regressions to identify key factors that predict adherence.

For both trials, we will adjust for baseline covariates, including sociodemographic factors, should the initial descriptive analyses suggest differences in the distribution of these factors across the study arms. We will also explore the use of propensity scores to control for systematic differences between the AYA living with HIV in the 2 trial arms. In further analyses, we will compare differences in mediating outcomes across the randomized groups and examine the potential moderating roles of key individual behavioral and social factors hypothesized to influence adherence along the cancer care continuum (eg, social support, stigma, and self-efficacy), as shown in Figure 1. We will test the "dose" of the ARROW program received as a covariate in these models. In additional analysis, we will explore differences in the end points by age groups and type of cancer, as appropriate. We will also assess whether knowledge, self-efficacy, social support, and stigma differ by age groups and among AYA living HIV, both with and without cancer.

For measures where we have baseline and 12-, 24-, and 36-month data (eg, self-efficacy and stigma), we will perform difference-in-difference analysis, which will allow for comparisons over time and across the study arms. To understand potential variation across the HIV treatment facilities, we will conduct comparisons to analyze differences in mediating outcomes for the AYA living with HIV and the study end points. Furthermore, to understand ARROW program's impact on health care providers, we will assess dose of the intervention (network session attendance) and change in knowledge, confidence in ability to care for AYA living with HIV, and peer collaboration.

Implementation Outcomes

For assessing the ARROW program, we will collect measures (as outlined in Table 3) from those receiving and implementing ARROW: 250 selected AYA living with HIV with follow-up data collection at the HIV treatment clinics and 250 AYA living with HIV at the Cancer Diseases Hospital, 36 HIV care providers, 12 oncology staff from the Cancer Diseases Hospital, 10 Health Care Collaborative members, and all the PCs. We will collect similar measures focused on the education campaign from those receiving the brochures in the one-time education campaign arm: 250 AYA living with HIV in the early detection cohort, 250 AYA living with HIV in the cancer treatment cohort, and 36 HIV care providers.

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Table 3. Implementation outcomes measurement.

Constructs	Measures	Stakeholder and data	Frequency
Acceptability, feasibility, and appropriateness	AIM[a], FIM[b], and IAM[c] 4-item measures	AYA[d] living with HIV, PCs[e], and health care provider (HIV and cancer) surveys	12-, 24-, and 36-mo follow-up
Fidelity (group and one-on-one education, health care provider meetings, and education campaign)	All content is delivered, or brochures are provided; meetings take place at the frequency and sequence planned	PC tracking tools, the ARROW Provider Network, and the Health Care Collaborative meeting minutes	12, 24, and 36 mo
Sustainability	SMSS[f] subscales specific to strategies	PCs, health care providers, and administrators	12 and 36 mo

[a]AIM: Acceptability of Intervention Measure.

[b]FIM: Feasibility of Intervention Measure.

[c]IAM: Intervention Appropriateness Measure.

[d]AYA: adolescents and young adults.

[e]PC: peer counselor.

[f]SMSS: Sustainment Measurement System Scale.

Our measurement will include the 4-item questions from the Acceptability of Intervention Measure, the Feasibility of Intervention Measure, and the Intervention Appropriateness Measure [75]. Fidelity will be assessed using data collected in the PC tracking tool and Network meeting. The fidelity measures described in Table 3 will be compiled annually, and summary statistics (eg, proportion of sessions in which all content was delivered) will be generated to assess compliance with study protocols. Sustainability will be assessed using subscales of the Sustainment Measurement System Scale [76]. We will review the scores and fidelity measures and compare scores available for both the ARROW and one-time education arms to assess implementation success and draw lessons to improve and optimize the ARROW program.

We plan to conduct interviews and focus groups to identify the underlying moderating factors associated with the successful implementation of strategies, along with facilitators and barriers to inform future scale-up activities. At 12 months, trained data collectors will interview PCs and health care providers as described for the quantitative measures. We will interview this group to seek feedback on their level of preparedness to implement the strategies, their assessment of the quality of the delivery, the level of responsiveness of the AYA living with HIV, whether they felt there were facilitators to deliver the strategies and potential barriers, and suggestions to address the barriers. We will also interview the AYA living with HIV to seek feedback on the ARROW program and one-time education campaign.

At 36 months, at the end of the trials, we will conduct focus groups with PCs, AYA living with HIV, HIV care providers, and oncology care providers. These focus groups (7-10 participants) will explore topics related to the sustainability of the ARROW program and the one-time education campaign, drawing on the findings from the results of the Sustainment Measurement System Scale survey. We will critically discuss interpretations of the data until they reach a consensus on the dominant themes and meanings. The findings will offer insights to improve the ARROW program and understand perceptions of the one-time education campaign.

Cost-Effectiveness and Return-on-Investment Scenarios

We will assess the incremental cost-effectiveness of the ARROW program compared with the one-time education campaign. As shown in Table 4, we will generate the cost of start-up activities to understand the resources required to plan future implementation, the activity-based cost of strategies during the intervention trials, and the estimated cost during scale-up. We will use a previously validated instrument, the Cost Assessment Tool, to collect resource use and cost information [77].

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Table 4. Cost data collection and analysis by phase.

Phase and data category	Purpose	Data elements (examples)
Before implementation		
Start-up costs	To assess the cost of planning to implement strategies	• Formalizing plans for the intervention; hiring staff; conducting training, readiness assessment, and strengthening processes
Intervention implementation (randomized controlled trials)		
Implementation of activity-based cost data	To assess the cost of implementing and maintaining interventions	• Implementation activities: delivering strategies, tracking outcomes, quality assurance, data collection, and evaluation • Patient cost: travel cost and time lost from work
Resource use	To standardize cost	• Labor hours (peer counselors and project staff) and nonlabor resources
Future expansion		
Scale-up cost	To estimate the cost of large-scale implementation	• Fixed versus variable activity-based cost estimates of implementation strategies to project economies of scale

Our main goal is to estimate the implementation cost from the program perspective. We will estimate labor hours by prospectively tracking time spent by each project staff member, including PCs, on a predefined set of activities (individuals will report their time monthly) and use hourly wages to calculate cost. We will capture time spent by health care providers, administrators, and policy makers participating in the ARROW Network and Collaborative using from the meetings. We will also document the expenditures on nonlabor resources to produce education materials, hosting group education sessions, the ARROW Provider Network meetings, and the cost of providing travel support. Using activity-based costing, we will allocate separate costs for supporting early diagnosis services and treatment adherence.

On the basis of these cost estimates and the primary end points from the trial, we will conduct incremental cost-effectiveness analysis by generating the cost per AYA living with HIV undergoing early detection services (physical examinations for KS and NHL and screening for CC) and the cost per AYA living with HIV and cancer completing recommended treatment modalities. Using standard economics methodology, we will explore economies of scale related to the implementation costs that can be achieved during scale-up [77,78]. We will also assess the key drivers of the cost of the ARROW program.

Using the trial data on estimated shift in stage at diagnosis and treatment adherence rates, along with supplemental information on prevalence of KS, NHL, and CC and mortality by stage at diagnosis, we will estimate the projected difference in mortality between ARROW and one-time education for AYA living HIV in Zambia. For CC screening, we will also estimate the incremental change in mortality using a validated microsimulation model, as screening not only will identify CC at an early stage but also can prevent CC by treating precancerous lesions [79,80].

We will derive the cost per life year saved (for all the 3 cancers combined), and our estimates will include both direct and indirect costs (patient time loss). The latter represents the opportunity cost of engaging in health services. We will assess whether the derived costs per life year saved are cost-effective or considered acceptable for implementation based on cost-effectiveness profiles of other strategies or interventions already implemented [81]. The estimated cost and effectiveness will be used to assess return on investment based on resources required to implement the ARROW program and the economic burden that will be reduced by avoiding premature mortality and treatments for adverse events related to KS, NHL, and CC for AYA living with HIV.

Furthermore, we will conduct policy simulations to assess the impact of scaling up ARROW and perform a sensitivity analysis, varying the range of effectiveness and cost estimates, and generate potential best- and worst-case projections. We will create tornado and spider diagrams to display this uncertainty graphically to policy makers. This cost-effectiveness analysis will be complemented by a budget analysis, which will identify the financial outlays that will be required annually to implement the ARROW program at scale.

Results

Recruitment for both the early detection cohort and the cancer treatment cohort began in June 2024. Recruitment for the early detection cohort concluded in February 2025, and we have enrolled a total of 3442 individuals. Of these 3442 participants, 1731 (50.29%) were enrolled in the 9 facilities randomized to the intervention arm and 1711 (49.74%) were enrolled in the 9 facilities in the control arm. The ARROW intervention was launched at all intervention facilities by December 2024. Recruitment for the cancer treatment cohort began in July 2024 and is ongoing; as of March 2025, 105 individuals have been enrolled. Of these 105 participants, 52 (49.5%) are receiving the one-time educational campaign in the usual care arm and 53 (50.5%) are receiving the ARROW intervention. Hypothesis testing analysis, as well as cost-effectiveness and policy implication analysis, will be conducted. The 12-month end point results will be available in early 2026.

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Discussion

Anticipated Findings

The ARROW program is an intervention designed to operate at 3 levels: the individual level, the health care provider level, and the health system level. At the individual level, we hypothesize that, compared to those receiving the one-time educational campaign, participants in the ARROW program will have increased uptake of early detection services and adherence to treatment, and this will, subsequently, improve health outcomes. At the health care provider level, we believe that the ARROW Provider Network will create an environment to link HIV pediatric and adult health care providers with their counterparts at the Cancer Diseases Hospital, which will facilitate peer-to-peer learning. Improved linkages between HIV and oncology care, as well as between pediatric and adult health care providers, will benefit both the health care providers and the AYA living with HIV who move through this health care landscape. At the health system level, the ARROW Health Care Collaborative will bring together health system administrators and Zambian Ministry of Health policy makers and foster an environment for collaborative problem solving. We believe that creating a communal space for health system level barriers will result in the successful implementation of solutions to address obstacles to care that AYA living with HIV experience.

Limitations and Approaches to Minimize Bias

First, although cluster randomization reduces contamination across study arms, it increases the risk that the AYA living with HIV in each arm may differ at baseline. The study sampling frame, based on the HIV registers, will allow us to assess baseline differences before facility randomization and adjust our sampling process with propensity score weights. Second, data could be missing because of nonresponse and study attrition. The PCs will maintain regular contact with the AYA living with HIV, and we will use rigorous field data collection practices, including training data collectors, developing protocols, and monitoring fidelity continually. Furthermore, we will address any missing data by including demographic covariates that will serve as proxies for dropout and conducting sensitivity analyses. Third, we anticipate health care provider turnover at the HIV treatment facilities and will conduct refresher training sessions as needed throughout the trial period.

Impact and Policy Implications

The model tested in Zambia can serve as a blueprint for other sub-Saharan African countries to ensure that AYA living with HIV receive optimal services across the cancer care continuum. We will host consultation and policy forums to share findings and seek feedback on the generalizability of the ARROW program to other sub-Saharan settings. The ARROW program, if shown to be successful, will provide a framework for implementing integrated HIV and cancer services to improve outcomes and reduce mortality among AYA living with HIV.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

SH, NC, ML, LN, MJ, CKM, MM, and SS were responsible for the concept and design of the manuscript. SB, PZ, RM, NC, DM, ML, CKM, MM, and SS were responsible for creating the data collection and analysis plan. SB, SH, and SS were responsible for drafting and revising the manuscript. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 942 KB - resprot_v14i1e68254_app1.pdf]

Multimedia Appendix 2
CONSORT (Consolidated Standards of Reporting Trials) checklist.
[DOC File , 235 KB - resprot_v14i1e68254_app2.doc]

Multimedia Appendix 3

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Peer review report from the ZCA1 SRB-K (M2) - National Cancer Institute Special Emphasis Panel - Cancer Control in People Living with HIV in LMIC, National Cancer Institute (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 139 KB - resprot_v14i1e68254_app3.pdf]

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Abbreviations

ARROW: AYAHIV Role-Based Responsibilities for Oncology-Focused Workforce
ART: antiretroviral therapy
AYA: adolescents and young adults
CC: cervical cancer
KS: Kaposi sarcoma
NCCN: National Comprehensive Cancer Network
NHL: non-Hodgkin lymphoma
PC: peer counselor

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Protocol

An Iteratively Adapted Transdiagnostic Prevention Program for Diverse High School Settings (U-PEACE): Protocol for a Randomized Controlled Trial

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Abstract

Background: Despite many adolescents experiencing mental health concerns, a substantial portion lack access to evidence-based treatments (EBTs) for psychopathology; this issue is magnified for adolescents belonging to communities considered marginalized. One way to ameliorate this is by adapting existent EBTs—typically delivered in research settings—so that they are feasible and scalable in adolescent settings, such as high schools. The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders in Adolescents may be particularly suited for this purpose due to its transdiagnostic, modular approach and its focus on adolescent clients.

Objective: This study aimed to iteratively adapt and implement the Unified Protocol for Transdiagnostic Treatment of Emotional Disorders in Adolescents in 3 Title 1 high schools, with a focus on feasibility and scalability of the intervention in diverse high school settings.

Methods: For initial adaptation, members of participating high school communities will be presented with original, unadapted intervention materials and asked to provide qualitative feedback on how to make the program more appropriate and feasible for their schools (aim 1). After initial adaptations are implemented, an open-trial pilot case series will assess the appropriateness and feasibility of the resulting program: the Unified Protocol for Emotional and Academic Challenges in Education (aim 2). Initial outcome data and qualitative feedback from pilot case series participants will then inform final adaptations for the randomized controlled trial—in which the adapted program will be compared to high schools' mental health services as usual (aim 3). The adapted program's effectiveness will be evaluated by using a mixed methods approach, and feasibility will be preliminarily assessed through cost-effectiveness analyses (aim 4).

Results: Data collection for the study was concluded in May 2025, with primary outcome analyses anticipated to be completed by August 2025.

Conclusions: This protocol may serve as a promising guide for adapting youth EBTs in more accessible, diverse settings, as well as result in a useful prevention program for youth with emotional concerns.

Trial Registration: ClinicalTrials.gov NCT06056674; https://clinicaltrials.gov/study/NCT06056674

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KEYWORDS

adolescent; anxiety; depression; transdiagnostic; prevention; school

Introduction

Adolescent Emotional Disorders: A Public Health Concern in the United States

Adolescent emotional disorders are a serious public health concern in the United States. Rates of adolescent depression rose by 7.7% from 2009 to 2019 [1]. Adolescent anxiety has also increased in prevalence [2], and research suggests that the COVID-19 pandemic exacerbated these trends [2-4]. A report from the Centers for Disease Control and Prevention suggests that nearly all indicators of mental health struggles (eg, persistent feelings of sadness or hopelessness and seriously considered suicide) among high school students steadily increased between 2011 and 2020, and the same report demonstrated that approximately 29% of adolescents endorsed experiencing mental health struggles [5]. Notably, the pandemic has intensified stressors that disproportionately impact adolescents who hold minoritized identities—including, but not limited to, academic challenges (eg, chronic absence and widening achievement gaps in schools) [6-8], financial hardship (eg, job loss and food insecurity) [9], and experiences of racism [10]. Such phenomena underscore the need to deliver mental health care that addresses the needs of diverse adolescents.

Psychologists have created a wide array of evidence-based treatments (EBTs) for adolescent emotional disorders [11,12]. Nonetheless, the National Survey of Children's Health [13] reports low treatment use among youth, especially those who hold minoritized identities. In 2022, only 14% of White children, 11.1% of Black children, 10.3% of Latine children, and 3.4% of Asian children received mental health treatment. Among those not receiving treatment, the percentage of caregivers who believed their child needed care but did not get it was 2.9% for White children, 3.7% for Black children, 2.8% for Latine children, and 1.6% for Asian children [13]. In the same report, 3.7% of families living at or below the federal poverty level reported not receiving mental health care despite needing it, compared to 2.1% to 2.9% of families with an income of 200% or more than the federal poverty level [13]. Barriers to use of EBTs may be practical (eg, financial barriers and transportation) [14,15] and attitudinal (eg, stigma) [16] in nature. The proximity of school environments to adolescents makes high schools a promising setting to overcome these barriers [17], especially given that adolescents' academic performance is often interrelated with their mental health [18].

School-Based Interventions for Youth Anxiety and Depression

Mental health professionals can address these barriers by meeting adolescents where they naturally are and delivering evidence-based mental health services in community settings—such as high schools [17,19-21]. The existing research on school-based interventions for anxiety and depression is primarily focused on increasing access to care, health promotion, and prevention [22-25]. Consequently, school-based interventions have made it possible to deliver mental health care to millions of children who likely would not have received care outside of this setting [26]. Furthermore, school-based services offer the opportunity for mental health professionals to fulfill the mental health needs of children and adolescents through training of school staff [27], increasing prevention efforts [18,24], and reduction of stigma associated with mental health issues [28].

However, while many of these interventions are found to be effective, effect sizes with school-based samples are typically smaller than those with clinic-based samples, and they are often not statistically significant in comparison to clinic-based settings [29-31]. Smaller effect sizes may, in part, be due to the challenges that mental health professionals have faced when adapting and implementing these EBTs into community settings [31-33]. Particularly, there may be school-specific barriers to implementing and sustaining some components of interventions that are more traditionally offered in clinics, such as exposures [33]. These may include financial (eg, purchase materials and pay for staff), attitudinal (eg, support of other school staff), and logistical (eg, competing school priorities) barriers that further compound misalignment between the goals of an EBT and a school's values and focus [34]. Consequently, specific components of EBTs may not be applied with fidelity—or may be deimplemented by stakeholders altogether, given the school-specific barriers—reducing the effectiveness of the interventions [35]. Some of these implementation challenges may be mitigated by using a transdiagnostic intervention that can address a wide range of mental health concerns [36].

Unified Protocol for Transdiagnostic Treatment of Emotional Disorders in Adolescents

Although comorbid psychiatric diagnoses are common in both clinical and school settings, and youth with these presentations often face greater impairments, many EBTs focus on disorder-specific presentations and techniques [20,37]. This problem-focused structure can result in a lower treatment response among adolescents who are most affected by their symptoms, suggesting a need for scalable school-based interventions that can address symptomatology across internalizing diagnoses [38]. Transdiagnostic interventions, such as the Unified Protocols for Transdiagnostic Treatment of Emotional Disorders [39], operate under the premise that internalizing or emotional disorders can be functionally treated as a singular syndrome, with overlapping symptoms and risk factors originating from variances in emotional reactivity and regulation [40,41]. The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders in Adolescents (UP-A) [42] is an evidence-based transdiagnostic treatment that was developed concurrently with the adult Unified Protocol, and it may hold promise in addressing some of the current limitations of school-based anxiety and depression interventions. The UP-A has been found to effectively treat adolescent emotional

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disorders in multiple studies, including randomized controlled trials (RCTs) [43,44].

The UP-A treatment protocol has a modularized, flexible structure that allows mental health providers to address varying and comorbid emotional mental health concerns [42]. This structure reduces required training for community-based mental health providers while simultaneously increasing the number of adolescents and variety of presenting concerns that may benefit from the intervention. The UP-A has also previously been implemented in community-based mental health care settings [45,46] and in more structured, group-based formats.

Inclusion of Community Member Input

The long-standing absence of culturally responsive treatment in diverse settings has contributed to disparities in mental health outcomes in underserved communities [47]. Furthermore, increased awareness of the limited representation of minoritized adolescents in foundational EBT research has prompted efforts to adapt existing treatments to better fit the needs and priorities of diverse adolescents [48,49]. Content adaptations of EBTs are encouraged to prioritize the alignment of diverse youth's values, customs, goals, and traditions, with those incorporated into the intervention [50]. Similarly, cultivating community partnerships through intentional engagement of community leaders (eg, school administrators, students, and caregivers) is a key approach to gaining insights into the unique school environment; this, in turn, may aid researchers in tailoring interventions to better fit the unique needs of this setting [50]. Intervention dissemination and implementation models recommend centering the expertise of individuals who are a part of the target community in the development and implementation of interventions to overcome potential mismatch among lived experiences of diverse adolescents, treatment goals, and school goals [50-52]. Inclusion of community members' input into the development and modification of school-based mental health interventions can help elucidate community perceptions of mental health treatment, identify and modify logistical barriers, and ensure mutual benefit of intervention implementation; this may lead to increased engagement, effectiveness, and sustainability of interventions [53,54]. Previous research has successfully incorporated community members' feedback in the adaptation and implementation of multiple evidence-based mental health interventions for youth, including but not limited to a cognitive behavioral therapy (CBT) intervention for Haitian-American adolescents diagnosed with depression conducted in a middle school [55], digital single-session interventions for youth living in south Texas [56], and mental health treatment engagement interventions conducted in a transition resource center for youth aging out of foster care [57].

This Study

The purpose of this study is to iteratively adapt and implement a school-based, indicated prevention version of the UP-A in Title 1 high schools that cater to minoritized youth and evaluate its efficacy within that setting. The program will be known as the Unified Protocol for Transdiagnostic Treatment of Emotional and Academic Challenges in Education (U-PEACE). First, we anticipate that verbal feedback from community members would suggest that U-PEACE is a good fit for Title 1 high schools, with the inclusion of some suggested modifications. Next, we anticipate that U-PEACE, developed via an iterative feedback process, including 3 phases of evaluation (ie, qualitative interviews of stakeholders, pilot case series, and an RCT), will lead to reductions in anxiety and depression symptoms, as well as improvements in academic domains (eg, grades and attendance). Finally, we anticipate that adoption of U-PEACE will be more cost-effective for high schools than services as usual (SAU) within integrated school health clinics.

Methods

Study Design

Setting and Community Partnership

The University of Miami School Health Initiative clinics provide comprehensive health and mental health services in the 3 Title 1 public high schools where the research protocol will be implemented. These school clinics offer integrated mental health treatment and consultation alongside the provision of no-cost primary and preventive medical care to students attending the schools. The school health clinics have provided these services for >20 years through local grants in collaboration with the high schools. Per the most recent statistics from the National Center for Education Statistics [58], 4249 students attend these schools, of which 66% are Black and 31% are Hispanic. Approximately 66% of students within these schools qualified for free or reduced lunch, indicating high financial need during the 2019 to 2020 school year [58]. Rather than establishing an independent community partnership with local Title 1 high schools, the research team will leverage the existing, long-standing partnership between these clinics and the 3 high schools to carry out this project.

Participants

Participants will be students enrolled at the 3 participating underserved (ie, Title 1) high schools. School staff members (eg school counselors and teachers) and caregivers will also be asked to participate by providing feedback on the mental health and program engagement of the students enrolled in U-PEACE. We anticipate the students enrolled in our study to be demographically representative of the high schools they attend.

Recruitment

High school student participants will be recruited through staff referrals and community outreach. Students will also be able to express interest through QR codes on flyers posted throughout the high school campuses and on high school social media pages. Students can qualify for U-PEACE if they are aged between 13 and 18 years at the time of enrollment into the program and if they self-report clinically significant depressive symptoms (as indicated by scores at or above the clinical cutoff for the Patient Health Questionnaire-9, PHQ-9 [59,60]) or clinically significant anxiety symptoms (as indicated by scores at or above the clinical cutoff for the Generalized Anxiety Disorder-7 [61,62]). To qualify for U-PEACE, students will also need to be enrolled at one of the target high schools, want to voluntarily participate, and have a caregiver who will be available and willing to voluntarily sign their consent forms.

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In addition to students who do not meet inclusion criteria, students will be excluded if their psychological symptomology is considered too severe to be effectively treated with a school-based prevention program, if they have neurological or medical conditions that may impact their ability to effectively participate in the group program, or if they do not speak or understand English or Spanish. During phases 2 and 3 of the study, students will also be excluded if they have a self-reported history of seizures, autism spectrum disorder, substance use disorder, serious mental illness, or other cognitive delay.

Staff members will be recruited to participate as support staff (eg, coach) through recommendations by individuals that participated in the qualitative interviews, clinic staff, or the administrators at participating schools. Staff at the target high schools will be excluded if they are not aged at least 18 years or are not able to speak and understand English fluently.

Ethical Considerations

This study, with the stated methods, is approved by the University of Miami institutional review board (20220700, 20230796). Recruitment and implementation efforts within the participating schools were approved by the school district's Research Review Committee. Informed written consent will be obtained from the caregiver or caregivers of minor adolescent participants and directly from the adolescent participants themselves if they are aged 18 years (for sample consent forms, refer to Multimedia Appendices 1 and 2). Furthermore, informed written assent will be obtained from adolescent participants aged <18 years. To ensure understanding of consent materials, these materials will be provided in English or Spanish and bilingual staff will be available to respond to questions about the study. Students will receive US $50 at each time point for completion of questionnaires and assessments, except at the midpoint when they will receive US $25. Teachers (ie, school staff who complete the Adolescent Academic Problems Checklist [AAPC]) will receive US $5 for each questionnaire completed at each time point. Caregivers will receive US $10 for questionnaires completed at each time point. Coaches will receive US $20 for each student for whom they complete more than 50% of their questionnaires between baseline and midpoint and another US $20 for each student for whom which they complete more than 50% of their questionnaires between midpoint and after treatment.

Study Timeline and Aims

This study has 3 distinct phases to accomplish 4 primary aims using a hybrid-type 1 effectiveness-implementation design [63]. In phase 1, we will interview community members for feedback on (1) mental health needs of adolescents at the target schools and (2) suggestions for delivering transdiagnostic therapeutic services in a high school setting (aim 1). The feedback obtained will be used to inform adaptations for the first iteration (pilot case series) of U-PEACE (school-based UP-A). In phase 2, we will initiate an open-trial pilot case series study with the first iteration of U-PEACE. The pilot case series will be initiated to assess the feasibility of program implementation and identify additional implementation barriers to be remedied in the second iteration (RCT). Feedback from interviews with participants in the pilot case series and support personnel for U-PEACE implementation will be incorporated into U-PEACE's content and delivery (aim 2). In phase 3, we will initiate a randomized, controlled effectiveness trial (RCT) in which the second iteration of U-PEACE will be compared to mental health services as usual in Title 1 high schools (aim 3). In addition, in phase 3, we will analyze U-PEACE implementation (eg, adherence to U-PEACE and session attendance), collect additional feedback through qualitative interviews with study participants who received U-PEACE, and analyze cost-effectiveness (aim 4). For a flowchart of the study timeline and aims, refer to Figure 1.

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Figure 1. Unified Protocol for Transdiagnostic Treatment of Emotional and Academic Challenges in Education (U-PEACE) study design and evaluation flowchart. SAU: service as usual.

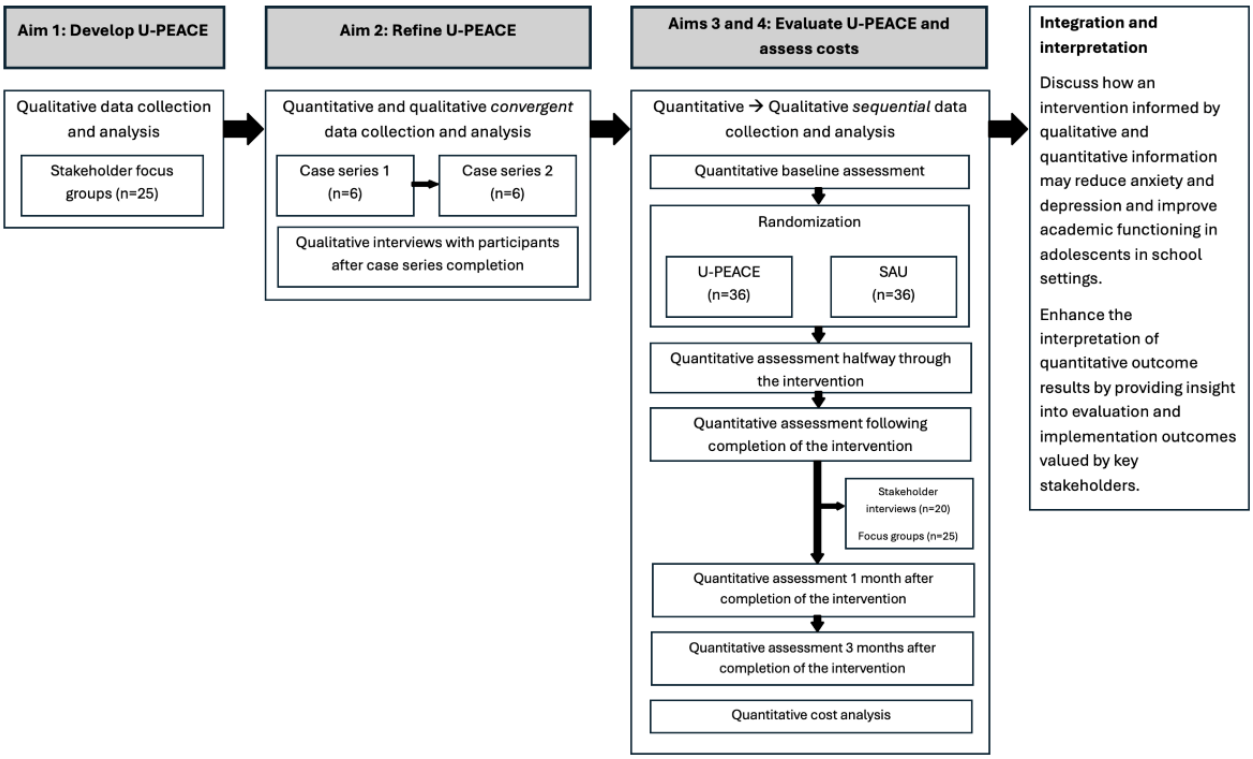

Feedback and Source of Adaptations

The Unified Protocol for Transdiagnostic Treatment of Emotional Disorders in Adolescents

The original UP-A treatment guide follows a CBT framework. However, rather than targeting disorder-specific symptomatology as is the case in traditional CBT protocols, it focuses on higher-order factors that underlie a range of emotional disorders, such as emotion regulation and distress tolerance [42]. The UP-A follows a flexible, modularized structure; when in group format in research clinics, its 8 modules are typically delivered across sixteen 90-minute sessions. For a review of each of the modules in the UP-A, refer to Table 1 [42].

When adolescents are enrolled in the original UP-A treatment, they receive a workbook that consists of both session worksheets (designed to facilitate content learning) and homework worksheets. Adolescents are expected to complete homework practice between each UP-A session to help them apply the skills learned in UP-A outside of the group. While caregivers do not have a regularly scheduled UP-A caregiver group, they are traditionally expected to be engaged and participate within the program. For example, caregivers are provided with session materials and may be given a brief overview by clinicians of content covered within the session. Caregivers are also asked to help their adolescent complete homework between sessions.

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Table 1. Unified Protocol for Transdiagnostic Treatment of Emotional Disorders in Adolescents overview.

Module	Title	Recommended sessions, n	Module content
1	Building and keeping motivation	1 or 2	• Build rapport with your adolescent client • Discuss key problems and set goals • Determine what motivates the adolescent to change
2	Getting to know your emotions and behaviors	2 or 3	• Provide psychoeducation about different emotions • Discuss the purpose of emotions • Introduce the 3 parts of an emotion • Introduce the cycle of avoidance and other emotional behaviors
3	Introduction to emotion-focused behavioral experiments	1 or 2	• Introduce the concepts of opposite action and emotion-focused behavioral experiments • Teach the adolescent how to track emotion and activity levels • Engage the adolescent in emotion-focused behavioral experiments for sadness (and potentially other emotions)
4	Awareness of physical sensations	1 or 2	• Review the connection between physical feelings and strong emotions • Develop the adolescent's awareness of their physical feelings • Conduct sensational exposure exercises to help the adolescent learn to tolerate uncomfortable physical feelings
5	Being flexible in your thinking	2 or 3	• Develop the adolescent's ability to think flexibly about emotional situations. • Introduce common "thinking traps" (ie, cognitive distortions) • Link thoughts to actions by teaching • Detective thinking and problem solving skills
6	Awareness of emotional experiences	1 or 2	• Introduce and practice present-moment awareness • Introduce and practice nonjudgmental awareness • Conduct generalized emotion exposures by asking the adolescent to practice awareness skills when exposed to general emotional triggers
7	Situational emotion exposure	>2	• Review skills the adolescent has learned in treatment so far • Discuss the rationale for situational emotion exposures, introduced to the adolescent as another type of behavioral experiment • Conduct situational emotion exposures in session and assign additional exposures for home learning
8	Reviewing accomplishments and looking ahead	1	• Review skills and progress toward goals • Create a relapse prevention plan
P	Parenting the emotional adolescent	1-3	• Build parent awareness of responding to the adolescent's distress • Introduce 4 common emotional parenting behaviors and their opposite actions (opposite parenting behaviors)

Initial Development of the Unified Protocol for Emotional and Academic Challenges in Education

Program content will be adapted by a team led by the last author, who was the creator of the original UP-A. Adaptations will be focused on using the protocol as an indicated prevention program, improving the cultural acceptability of content, and increasing logistical feasibility of delivery within a dynamic, Title 1 high school setting. Initial adaptations of the UP-A will be informed by semistructured qualitative interviews of members of the school communities conducted within phase 1. These members will include caregivers, students, teachers, administrators, and mental health providers at the schools. We will aim to recruit 5 of each type of school community member, with representatives from each of the high schools participating in the study. The interviews will be conducted as focus groups or individual interviews held online via Zoom (Zoom Communications, Inc) or in person at the schools.

During the interviews, the research team will provide interviewees with examples of the UP-A and ask for feedback on how to make the program better suited for Title 1 high school settings that serve minoritized populations. Interviewees will be asked questions regarding content fit (eg, How can we make U-PEACE more relevant to teens in your school?) and feasibility of delivery (eg, When should we deliver U-PEACE in schools?). The interviews will incorporate an overview of the UP-A, a sample outline of an UP-A session, and a demonstration video for the interviewees' reference. The treatment development team will use the community member feedback to adapt the

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content and delivery of U-PEACE for implementation into the Title 1 high school communities [64].

Iterative Feedback

Throughout phases 2 and 3 of the study, feedback will be iteratively requested from community members through semistructured qualitative interviews and advisory committee meetings.

In addition to obtaining feedback about initial adaptations to the UP-A, feedback will also be requested at the end of phase 2 by individuals who participated in the study. These interviewees may consist of caregivers, students, and mental health care providers. Participants in the U-PEACE pilot case series will be asked to reflect on their experiences in the program and provide feedback on (1) how the program impacted them, (2) how fitting the program was for them and members of their community, and (3) whether the logistics of the program were feasible. On the basis of phase 2 feedback, the research team will adapt the content and delivery of U-PEACE for implementation during the RCT phase of the study. This second iteration of adaptations will again be focused on improving the cultural acceptability of content and increasing logistical feasibility of delivery at the participating Title 1 high schools.

Some participants and their caregivers who are randomized to the U-PEACE group during the RCT phase (phase 3) of the study will be randomly selected to participate in semistructured qualitative interviews at the end of their participation in the program (for a sample interview guide, refer to Multimedia Appendix 3). Participants will consist of an even distribution of responders and nonresponders to the U-PEACE program. Interview questions will mirror questions asked of the pilot case series participants. The third iteration of adaptations will have the same focus as the previous adaptations, with an added focus of making the program scalable and deliverable in similar Title 1 high school settings. The RCT feedback (following completion of phase 3) may also provide guidance on how to further scale the implementation and delivery of U-PEACE in other high school settings.

In addition to qualitative interviews, the research team will also ask the Title 1 high school communities to identify members who are well-known on their campuses and engaged in the community to participate in an advisory committee. Members will ideally include teachers, students, caregivers, school mental health providers, and administrators from each of the high schools. Members will meet at the end of each of the first 3 study aims. During the advisory committee meetings, members will be updated on the study's status and asked to provide feedback. Community members that participate in qualitative feedback interviews or advisory committee meetings will receive US $50 compensation for each time they participate in providing feedback.

Prevention Program Content and Delivery

Content

The resulting U-PEACE indicated prevention program is anticipated to maintain the same overarching intervention principles and flexible modules as the UP-A. Content within existing UP-A modules may be adapted (eg, examples of skills may be more tailored to reflect common adolescent experiences in Title 1 high schools), and modules may be added or removed based on community member feedback. Like the UP-A, each module will have corresponding session materials that facilitate content learning and encourage practice of skills outside of the U-PEACE group. In addition to clinician, adolescent, and caregiver materials; we also anticipate materials to be created for school community members (eg, teachers, school mental health providers, or counselors) who may be involved in facilitating adolescents' practice of skills or homework completion.

Study Intervention

Given that the study was already in phase 3 when this manuscript was submitted for publication, the written protocol for U-PEACE delivery will incorporate community member feedback from phases 1 and 2. For a CONSORT diagram of the RCT, refer to Figure 2.

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Figure 2. Anticipated CONSORT (Consolidated Standards of Reporting Trials) diagram for the Unified Protocol for Transdiagnostic Treatment of Emotional and Academic Challenges in Education (U-PEACE) study. The diagram includes information from the anticipated participant allocation. At the completion of the study, a final CONSORT diagram will be presented with study results that include final data regarding recruitment and retention of participants. SAU: service as usual.

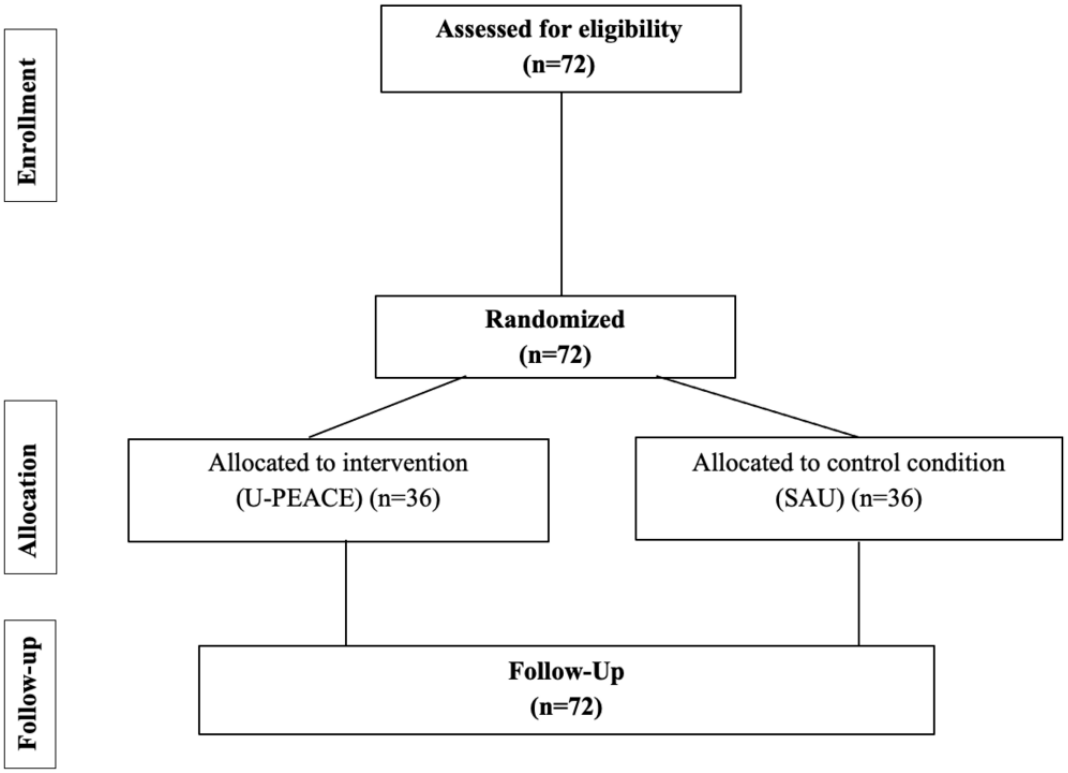

While the research team will be exploring the feasibility of telehealth-delivered U-PEACE, most U-PEACE sessions are expected to be delivered in person, during lunchtime, and in group format. Students who are enrolled in U-PEACE will be permitted to access additional primary, medical, and mental health care services within the school clinics throughout their participation in U-PEACE. The original UP-A typically takes place over 12 to 16 sessions. Thus, it was anticipated that U-PEACE would eventually contain a session count in this range. Each U-PEACE group will ideally have approximately 4 to 8 students enrolled in it at one time, as well as 1 to 2 clinicians in training who serve as program leaders for the group. At the beginning of the U-PEACE group, adolescent participants will receive a binder of U-PEACE session and homework worksheets that they can reference when learning and reviewing the program content. Adolescents will be expected to bring their binders to every U-PEACE session and practice skills learned in the group as homework between program sessions. In addition to U-PEACE binders, adolescents will also be given a caregiver session summary sheet to provide to their caregivers; these summary sheets are intended to keep caregivers informed about skills their adolescents are learning in U-PEACE.

Although initial community member feedback suggested that the research team bring external clinicians into the schools to deliver U-PEACE, the team decided to also incorporate nonclinic school staff into the delivery of U-PEACE by adding coaches to the program. Coaches were typically existent school counselors or school mental health providers at the target schools who are intended to function in U-PEACE in a similar manner to how caregivers function in the UP-A: their primary role is to review and practice skills learned in U-PEACE sessions with adolescents outside of the program (eg, ensuring homework completion). Coaches will try to meet with each assigned student one time per week for approximately 15 minutes. During the meeting, coaches will briefly check in with students regarding whether they have been able to practice the skills they learned in session. They will also provide students with session summary materials if they cannot attend the previous session.

Comparison Condition

Individuals assigned to the comparison condition will have access to any medical, social work, and psychotherapy services available through the school clinic to address emotional and behavioral concerns determined to be needed during the intervention period. The school clinic services are available in person or via telehealth throughout the year. A study staff member will also meet with all SAU adolescents for approximately 10 minutes per week (via telehealth as needed) for 13 weeks to complete weekly study measures, assess and provide linkage to clinic services requested or needed, and monitor for clinical deterioration. If an adolescent seems to be deteriorating in any significant way, additional mental health services or appropriate referrals will be offered after consultation. Data will also be collected from SAU participants 1-month after completion of the 13 weekly meetings. After the 1-month follow-up, SAU participants may be offered participation in the U-PEACE program via telehealth or in person.

SAUs vary in frequency and type based on the availability of the school clinic providers. These services may include weekly

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individual or group CBT, case management, and psychological and psychiatric consultations. These services are often provided by nurses, primary care physicians, master's-level therapists, social workers, psychologists, or psychiatrists. The receipt of these services within the school clinic will be monitored and reported. If a higher level of care is needed than what is typically provided through the school clinic, patients are referred to community resources. Participants will also be asked to report on their access and use of emotional and behavioral health services outside of the school clinic.

Measures

Overview

Each U-PEACE and SAU group will have 4 assessment time points (baseline, midpoint, after completion, and 1-month follow-up) of questionnaire administration. Detailed information regarding questionnaire administration at each time point can be found in Table 2.

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Table 2. List of assessment measures and time points.

Measure name	Every session	Baseline	Midpoint	After completion	1-month follow-up
Demographic survey	N/A[a]	Adolescent and parent or caregiver	N/A	N/A	N/A
DIAMOND-KID[b]–full interview [65]	N/A	Adolescent	N/A	N/A	N/A
DIAMOND-KID–initial interview [65]	N/A	Adolescent[c]	N/A	N/A	N/A
DIAMOND-KID–self-report scanner [65]	N/A	Adolescent[d]	Adolescent[d]	Adolescent[d]	Adolescent[d]
Service Utilization Form	N/A	Adolescent[d]	Adolescent[d]	Adolescent[d]	Adolescent[d]
Generalized Anxiety Disorder 7-item Scale [61]	N/A	Adolescent and parent or caregiver	Adolescent and parent or caregiver	Adolescent and parent or caregiver	Adolescent and parent or caregiver
Child Anxiety Interference Scale–Academic Subscale [66,67]	N/A	Adolescent and parent or caregiver	Adolescent and parent or caregiver	Adolescent and parent or caregiver	Adolescent and parent or caregiver
Patient Health Questionnaire-9 [59]	N/A	Adolescent and parent or caregiver	Adolescent and parent or caregiver	Adolescent and parent or caregiver	Adolescent[e] and parent or caregiver
Affective Reactivity Index [68]	N/A	Adolescent and parent or caregiver	Adolescent and parent or caregiver	Adolescent and parent or caregiver	Adolescent and parent or caregiver
Adolescent Academic Problems Checklist [69]	N/A	Teacher	Teacher	Teacher	Teacher
The Revised Children's Anxiety and Depression Scale–Short-Form [70]	N/A	Adolescent[d]	Adolescent[d]	Adolescent[d]	Adolescent[d]
Behavior and Feelings Survey [71]	N/A	Adolescent[d]	Adolescent[d]	Adolescent[d]	Adolescent[d]
School achievement (as measured by attendance and report card)	N/A	Adolescent[d]	N/A	Adolescent[d]	Adolescent[d]
Everyday Discrimination Scale [72]	N/A	Adolescent	Adolescent	Adolescent	Adolescent
Abbreviated Multidimensional Acculturation Scale [73]	N/A	Adolescent	Adolescent[c]	Adolescent[c]	Adolescent[c]
Distress Tolerance Scale [74]	N/A	Adolescent	Adolescent	Adolescent	Adolescent
Top problems [75]	Adolescent	Adolescent	Adolescent	Adolescent	Adolescent
Participant adherence	Clinician	N/A	N/A	N/A	N/A
Therapeutic Alliance Scale for Children–Revised [76,77]	N/A	N/A	Adolescent	N/A	N/A
Client Satisfaction Questionnaire [78]	N/A	N/A	Adolescent	N/A	N/A

[a]N/A: not applicable.

[b]DIAMOND-KID: Diagnostic Interview for Anxiety, Mood, and OCD-Related Neuropsychiatric Disorders: Child and Adolescent Version—Full Interview.

[c]Not administered at these time points in the randomized controlled trial.

[d]Measure was only administered during the randomized controlled trial.

[e]Patient Health Questionnaire-8 was used at 1 month.

Clinical Presentation and Program Fit

To determine whether students will be a good fit for the U-PEACE program, members of the research team will conduct a modified version of the Diagnostic Interview for Anxiety, Mood, and OCD-Related Neuropsychiatric Disorders: Child and Adolescent Version (DIAMOND-KID) [65] with preliminarily eligible adolescents at baseline. The DIAMOND-KID is a semistructured diagnostic interview and self-report screener assessing clinically significant mental health concerns from the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* [65]. The DIAMOND-KID has demonstrated very good to excellent test-retest reliability and good convergent validity with youth aged between 10 and 17 years [65]. Inter-rater reliability on most diagnoses was found to be good to very good—except for anxiety and depressive

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disorders, in which inter-rater reliability was found to be questionable in youth, possibly due to inconsistent reporting of the specific duration and timing of symptoms by youth [65]. All DIAMOND-KID assessments will take place in person, on school campuses; and each assessment is expected to take about 1 hour.

Demographics and Service Use

Self-reported demographic information of students, caregivers, and coaches will be collected. Demographic characteristics will include contact information, age, race and ethnicity, self-reported gender, and sexual orientation. In addition, students will be asked to report on any past or current psychiatric or psychological services, as well as any past or current psychiatric medications. At each time point following baseline, students will be asked to update previously reported service and medication information. It is anticipated that both English and Spanish speaking students will be included in the RCT.

Academic Progress

Student grade point average for each academic quarter will be calculated by converting all grades to a 5-point scale (4.0=A to 0.0=F). Student grades will not be weighted. School attendance will be collected as measured by the number of days a student was present in school for the academic year. Both student grade point averages and attendance records will be collected in person by having students log into their web-based academic portals and share the pertinent information with study coordinators.

Academic problems will also be measured using the AAPC [69]. The AAPC is a 24-item teacher-report measure that assesses adolescents' concerns in the classroom (eg, behavioral withdrawal and class disruptions). Items are rated on a 4-point Likert-type scale that ranges from "not at all" to "very much," with higher scores suggesting more severe classroom concerns. The AAPC has demonstrated excellent internal consistency (0.92) and strong concurrent validity in assessing behaviors associated with academic functioning [69]. The AAPC will be distributed to teachers chosen by their respective students, with the same teacher completing the form for the same student throughout the study.

Anxiety and Depression Symptoms

Adolescents' anxiety symptoms will be measured using the Generalized Anxiety Disorder 7-item Scale (GAD-7) [61]. The GAD-7 will be used as both a self- and caregiver-report measure; the items in it are rated on a 4-point Likert-type scale that ranges from "not at all" to "nearly every day," with higher scores suggesting more severe anxiety symptoms. While the authors are not aware of published psychometric properties on the parent-report GAD-7, the self-report GAD-7 has demonstrated good reliability in adolescent populations (Cronbach α=0.88) and has demonstrated strict measurement invariance by adolescents' sex and grade, as well as good convergent and discriminant validity [62,79].

Adolescents' depression symptoms will be measured using the PHQ-9 [59]. Items on the PHQ-9 scale are rated on a 4-point Likert-type scale that ranges from "not at all" to "nearly every day," with higher scores suggesting more severe depression symptoms. The PHQ-9 has demonstrated good internal reliability (McDonald Ω=0.87) among adolescents, and confirmatory factor analysis for a 1D model suggested adequate fit [80].

There may be instances in which the research team chooses to administer a modified version of the PHQ-9 to adolescents and their caregivers. For instance, given that this measure may be administered remotely without the presence of a study team member, the Patient Health Questionnaire-8 (PHQ-8) may be used to ensure that any suicide-related concerns are handled immediately and in person by the research team [60]. Research has suggested that omitting the suicide item on the PHQ-9 has minimal impact on scoring [81]. The correlation between the PHQ-9 and PHQ-8 remains high; therefore, the cutoff scores remain unchanged [60,81]. While the authors are not aware of published psychometrics for parent-report PHQ-8, research on the general population suggests good sensitivity and specificity [60].

In addition to the GAD-7 and PHQ-9, adolescents' anxiety and depression symptoms will also be measured by the Revised Children's Anxiety and Depression Scale–Short-Form (RCADS-SF) [70]. The RCADS-SF is only used as a self-report measure in this study. The 25 items in it are rated on a 4-point Likert-type scale that ranges from "never" to "always," with higher scores suggesting more severe symptoms of anxiety and/or depression. The RCADS-SF has demonstrated adequate reliability and acceptable discriminant validity in comparison to the 47-item RCADS [70].

Anxiety-Based Impact on Academic Functioning

The impact of adolescents' anxiety symptoms on their academic functioning will be measured by the Child Anxiety Impact Scale–Academic Subscale (CAIS-AS) [66,67]. The CAIS-AS will be used as a self- and caregiver-report measure. The 10 items in the subscale are rated on a 4-point Likert-type scale that ranges from "not at all" to "very much," with higher scores suggesting more anxiety-based academic impairment. The CAIS-AS child report has demonstrated excellent internal consistency (0.82) and good construct validity. Similarly, the parent report exhibited very good internal consistency (0.85) and good construct validity [67].

Irritability

Adolescents' irritability will be measured using the Affective Reactivity Index (ARI) [68]. The ARI will be used as a self- and caregiver-report measure. The 7 items in it are rated on a 3-point Likert-type scale that ranges from "not true" to "certainly true," with higher scores suggesting more irritability. The ARI has demonstrated good to excellent internal consistency in both the caregiver-report and the youth self-report versions [68].

Internalizing and Externalizing Symptoms

Adolescents' internalizing and externalizing symptoms will be measured using the Behavior and Feelings Survey (BFS) [71]. The BFS is only used as a self-report measure in this study [71]; it is a brief 12-item scale that ranges from "not a problem" to "very big problem," with higher scores suggesting more severe internalizing and/or externalizing symptoms. The BFS has

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demonstrated good internal consistency (0.87) and strong discriminant validity [71].

Distress Tolerance

Adolescents' emotional distress tolerance will be measured using the Distress Tolerance Scale (DTS) [74]. The DTS is only used as a self-report measure in this study. The 15 items in it are rated on a 5-point Likert-type scale that ranges from "strongly disagree" to "strongly agree," with higher scores suggesting lower distress tolerance. The DTS has generally demonstrated adequate to good internal consistency (0.72-0.82) [74], and its factor structure was upheld in a validation study with children and adolescents [82].

Acculturation

Adolescents' acculturative experiences will be documented using the Abbreviated Multidimensional Acculturation Scale (AMAS-ZABB) [73]. The AMAS-ZABB is a 42-item self-report measure that assesses cultural identity, language competence, and cultural competence related to acculturation in the United States and individuals' country of origin (as applicable). Items are rated on a 4-point Likert-type scale that ranges from "strongly disagree" to "strongly agree." While the AMAS-ZABB has been validated in some adult populations, the scale is yet to be validated in adolescents [83]. The AMAS-ZABB will be distributed to all participating students at the 4 major time points during phase 2 and only administered at baseline during phase 3 of the study.

Discrimination

Adolescents' experiences of discrimination will be measured using the Everyday Discrimination Scale (EDS) [72]. In addition to assessing discrimination experiences, the EDS also assesses unfair treatment and perceived reasons for such treatment (eg, race and sexual orientation). The EDS is a 10-item self-report measure and is rated on 6-point Likert-type scale that ranges from "never" to "almost every day," with higher scores suggesting more frequent experiences of discrimination. Although the EDS was not originally created for adolescents, the scale has been used previously in studies with adolescent participants [84].

Treatment Progress

Adolescents will identify 3 problems they want to target during the study using the Top Problems Assessment [75]. The Top Problems Assessment is a personalized change measure used extensively with the UP-A to assess change over time in client-derived reasons for treatment. The Top Problems Assessment has demonstrated criterion validity, test-retest reliability, and sensitivity to change with youth aged between 7 and 13 years [75]. Although the authors are unaware of a validation study of Top Problems with adolescents, Top Problems has been used with adolescent clients receiving the UP-A in prior research [85]. In this study, adolescents will provide a score of 0 to 10, with 10 being the most severe, at all 4 major time points and each program session.

Adherence and Fidelity

U-PEACE adherence will be measured through adolescents' attendance in the program. Session attendance will be recorded through a single item on a clinician-reported or research team member-reported measure. Attendance at individual meetings with the program coach will also be recorded through a single item on coach-reported documentation. Homework completion will be measured through a single item on a clinician-reported measure for each treatment session. Treatment progress, attendance, and homework completion measures will only be completed by students who are randomized to the U-PEACE group. Clinician fidelity to the U-PEACE protocol will be evaluated through audio recordings or live coding by a research associate for assessment of program fidelity, upon obtaining consent from participants.

Therapeutic Alliance and Program Satisfaction

Adolescents' rapport with their program leaders will be measured using the Therapeutic Alliance Scale for Children–Revised (TASC-R) [76,77]. The TASC-R is a 12-item self-report measure of therapeutic alliance. Items are rated on a 4-point Likert-type scale that ranges from "not at all" to "very much," with higher scores suggesting a stronger therapeutic alliance. The TASC-R has been used to assess alliance in various studies, including CBT for anxiety in youth [86].

Adolescents' satisfaction with the U-PEACE program will be measured using the Client Satisfaction Questionnaire (CSQ) [78]. The CSQ is an 8-item self-report measure of client program satisfaction, client self-efficacy, and likelihood of recommending the program to others. Items are rated on a 4-point Likert-type scale, with higher scores suggesting higher client satisfaction. The CSQ demonstrated excellent internal consistency and good convergent validity with other similar measures administered to adolescents [87,88]. Therapeutic alliance and program satisfaction measures will only be completed by students who are randomized to the U-PEACE group.

Data Analytic Plan

Qualitative Analyses

Interviews will be transcribed verbatim, anonymized, and analyzed thematically using rapid qualitative analysis (RQA) [89,90]. RQA is the recommended method to conduct efficient qualitative analysis to address rapidly changing issues, such as modifying interventions to be culturally and contextually relevant in a timely manner [89,91]. The goal of RQA is to rigorously identify actionable data rather than in-depth and theoretical understanding [90]. Individual members of the investigative team summarize key findings and then audit the summaries to assess accuracy and display responses in a matrix. Responses are then discussed in team meetings to identify overlapping and divergent themes. A thorough description of the qualitative methods and findings from the initial qualitative interviews has been published previously by our team [64].

Quantitative Analyses

Quantitative analyses will be conducted to assess (1) within-participant treatment-related changes in emotion regulation and symptoms after participation in U-PEACE and (2) implementation outcomes, including treatment fidelity, acceptability, and implementation costs. We will examine missing data patterns, attrition rates, and distributional properties

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of measures and use transformations when necessary. Depending on patterns of missing data, analyses may use full maximum likelihood estimation, multiple imputation, and inclusion of covariates related to missingness to account for missing data.

Reliable change indices (RCIs) will be calculated by dividing the within-respondent differences in self-report and caregiver scores (ie, anxiety symptoms, depression symptoms, irritability, anxiety-related impairment, and academic problems) from baseline to after treatment by the SE for each measure [92]. RCI has previously yielded reliable estimates of clinically significant change over the course of treatment and can successfully analyze small sample sizes [93]. RCI >1.96 indicates clinically significant change throughout the course of the program—which would provide preliminary support that U-PEACE is impacting theoretical mechanisms and participants' outcomes.

Furthermore, multilevel models will be evaluated to consider nesting of repeated measures (3 or 4 time points, depending on the measure) within participants, who are further nested within study conditions. School and U-PEACE group provider or providers will be included as predictors of intercept and slope to control for environmental differences between the groups. The best-fitting model for change over time will be determined for each dependent variable based on the Akaike Information Criterion and Bayesian Information Criterion. Time will be coded in weeks and will be "centered" alternately at treatment follow-up, such that model intercepts will represent mean scores at these assessments [94]. Treatment condition (ie, U-PEACE or SAU) will be entered as a predictor of the level 2 growth curve parameters (intercepts and slopes). These models will be used to assess group differences in both purported mechanisms of change (ie, emotion regulation measures) and in program outcomes (ie, symptom measures, academic outcomes, and diagnostic measures) as evidenced by slope or mean level differences at different time points.

Growth curve parameters will be used to categorize individual participants' outcomes (as deteriorated, unchanged, improved, or recovered) by comparing them to each outcome measure's clinical cutoffs and RCIs. Categorizations will be used to communicate findings to stakeholders and determine an appropriate range of participants for interviews after the RCT.

Implementation outcomes will be assessed using descriptive data, such as frequency of clinician adherence to U-PEACE components, participant's homework completion, and participant's session attendance. In addition, multilevel models (like those previously described) will be used to compare participants' therapeutic alliance (TASC-R), program satisfaction (CSQ), and use of medication and supplemental services across study conditions.

Mixed Methods Analyses

Qualitative feedback, individual participant response to treatment, and treatment implementation measures from the case series will be interpreted together to elucidate the association between how experiences and perceptions of U-PEACE vary by treatment outcome and implementation. This information will be used to modify U-PEACE before the implementation of the RCT. RQA [89,90,95] will be used to quickly and efficiently summarize qualitative feedback from participants and community members throughout the trial. A joint display analysis will be developed following best practices [96]. The joint display will simultaneously illustrate individual quantitative (eg, emotion regulation, diagnostic symptomatology such as depression and anxiety, and culturally relevant outcomes such as experiences of discrimination) and qualitative (eg, themes and quotes) results reflecting participants' experiences of U-PEACE. Likewise, we will simultaneously examine quantitative (eg, fidelity) and qualitative (eg, themes) implementation data to guide protocol changes before the RCT; these changes will be aimed to increase U-PEACE feasibility and appropriateness.

For the RCT, patterns in the quantitative outcome and implementation data will be examined to generate specific questions for the qualitative interviews after the RCT. Multilevel modeling will be used to elucidate treatment response classifications and will be used to ensure an appropriate representation of adolescent and caregiver participation in the interviews. The resulting joint display will compare representative interview quotes across key domains (eg, intervention acceptability and tolerability) and implementation indicators (eg, U-PEACE fidelity and alliance) between those classified into 2 aggregated clusters: nonresponders, which consists of those identified as falling within the deteriorated or unchanged categories, versus responders, which will include participants whose scores fall within the improved or recovered categories. Inclusion of implementation outcomes (ie, fidelity to treatment, treatment adherence, and acceptability) will provide insight into the sustainability of U-PEACE in diverse high school settings.

Sample Size and Power Analysis

The recommended size for a single focus group is 6 to 8 participants for sufficient diversity of opinions and to encourage discussion [97,98]. Consequently, we will seek to have at least 5 participants included in each adolescent, caregiver, teacher, school administrator, and school mental health provider focus group, for 25 participants at the initial adaptation phase, to gather sufficient data to inform the modifications to the UP-A (aim 1), rather than powering for specific effects. In addition, qualitative feedback will be obtained following the pilot case series and RCT (aims 2 and 3) to inform implementation outcomes (aim 4). All participants in the pilot case series will be invited to participant in the qualitative feedback interviews, and the same recommendation size of 25 participants will be used for the RCT qualitative feedback interviews. Power calculations for the nested multilevel models were conducted using Optimal Design 3.1 [99] to identify the minimum number of participants needed to participate in the RCT across 7 treatment groups with 5 assessment points. We estimated power using intraclass correlation coefficient (ICC) values of 0.01 based on recent effectiveness trials with a similar transdiagnostic intervention [100] and a more conservative estimate of 0.10. With an estimated sample size of 63 adolescents, the sample would have sufficient power (0.80) to detect an effect size of d=0.94 (ICC=0.01) or 1.21 (ICC=0.10), which are smaller effect sizes (d=1.25) than those observed in an UP-A RCT [43].

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Cost Analysis

While the results are expected to be preliminary and descriptive, estimates of the intervention's total cost will be calculated. The total cost of personnel will be calculated by multiplying each personnel's time spent on intervention activities (eg, intervention session delivery, supervision, maintenance of school engagement, and personnel travel) by their respective wages, then summing the resulting products. Administrative records of the project's financial spending will be used to calculate nonpersonnel costs. Total costs for intervention implementation into each school will be calculated, in addition to the average cost of providing each adolescent with services. Implementation costs (cost for starting U-PEACE in schools, such as costs to initially train clinicians) will be analyzed separately from sustainability costs (cost for continuing to deliver U-PEACE in schools, such as the cost of previously trained clinicians continuing to deliver U-PEACE).

Results

This study was funded from July 2022 to July 2025 and is being conducted over the course of 3 years. Participant recruitment and data collection for aim 1 began in September 2022, and qualitative results from aim 1 were published in July 2024 [64]. Participant recruitment and data collection for aim 2 began in January 2023, and we expect the pilot case series results to be published in 2025. The study is currently in the data collection phase for aim 3, and we expect results from the remaining aims of this study to be published in 2026.

Discussion

Anticipated Findings

The goal of this study is to evaluate the effectiveness and feasibility of a school-based, indicated prevention version of the UP-A, which will be branded as the U-PEACE program. U-PEACE will be designed using an iterative approach within Title 1 high schools that primarily serve minoritized youth. To optimize the sustainability of U-PEACE, it will be important to evaluate dissemination and implementation factors throughout the process of designing the intervention [101]. Furthermore, the focus of this study will be to identify and implement warranted modifications within the communities they will ultimately target [102]. Taking this approach will ensure that modifications made are consistent with the community's needs and will use resources native to the Title 1 school context.

Study Strengths and Limitations

This study has multiple strengths. First, the use of a mixed qualitative and quantitative design allows for in-depth understanding of the rationale for potential intervention modifications, as well as contextualization of outcomes as relevant hypotheses are tested [103]. Furthermore, the use of an iterative process ensures integration of school community member feedback into the modifications of an existing evidence-based program. The iterative process increases the likelihood that modifications are consistent with the values, goals, and resources within the Title 1 school context and culturally appropriate for the target audience. Finally, the use of RCIs enhances understanding of the potential clinical relevance of U-PEACE when examining early results from the case series. Potential limitations of the study include an insufficient sample size to conduct mediation analyses, which may lead to a restricted range in relevant treatment outcomes. In addition, Title 1 high schools across the country are comprised of diverse community members; while some of the study participants' experiences may be generalizable to most Title 1 high schools, other identities and experiences (eg, primarily Hispanic or Latine and Afro-Caribbean racial and ethnic identities) may be less generalizable.

Potential Study Implications

Findings from this study may inform adaptation approaches (eg, specific procedural and content modifications to consider) when implementing existent EBTs into Title 1 high school settings. Specifically, qualitative findings may identify themes related to psychoeducational content that need to be included within mental health interventions for minoritized youth. Second, factors associated with successful implementation of school-based mental health interventions—such as potential professionals providing the intervention timing, and support factors—will be identified. Furthermore, the preliminary cost findings can inform mental health professionals and funding sources of requisite resources for the implementation of similar transdiagnostic programs. Finally, the study will provide information about the acceptability and feasibility of implementing a transdiagnostic indicated prevention program into Title 1 high school communities.

Acknowledgments

This program also collaborates with Miami-Dade County Public Schools and the John T MacDonald Foundation School Health Initiative, who are not funders but, instead, community partnerships.

Data Availability

Once data collection and analysis for this study are completed, deidentified data will be available via an open access site.

Authors' Contributions

JE-M, SKD, LG, AJ-D, ERP, and SMSG collaborated on the conceptualization of the Unified Protocol for Transdiagnostic Treatment of Emotional and Academic Challenges in Education (U-PEACE) study, and all authors collaborated on the

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implementation of the U-PEACE study. CVV coauthored the introduction of this manuscript and authored the methods (other than the data analytic plan after qualitative analyses), results, and discussion. MC-P coauthored the introduction and authored the data analytic plan (other than qualitative analyses), as well as provided critical review and edits for the remainder of the manuscript. JMC coauthored the introduction and provided edits for the remainder of the manuscript. JE-M, PMP, CFD, SKD, and ERP provided critical review and edits for the manuscript.

Conflicts of Interest

JE-M is the primary developer and author of the Unified Protocols for Transdiagnostic Treatment of Emotional Disorders in Children and Adolescents manuals or workbooks. She makes a royalty from the sales of these books from the Oxford University Press, and she is paid for clinical training, consultation and implementation support services related to this treatment. Unrelated to data in this manuscript, SKD is a co-investigator on a Merck & Co funded project on "A Qualitative Study to Explore Biomedical HIV Prevention Preferences, Challenges and Facilitators among Diverse At-Risk Women Living in the United States" and has served as a work group consultant on engaging people living with HIV for Gilead Sciences, Inc.

Multimedia Appendix 1
Sample teen interview guide from aim 3 (randomized controlled trial) of the Unified Protocol for Transdiagnostic Treatment of Emotional and Academic Challenges in Education study.
[PDF File (Adobe PDF File), 320 KB - resprot_v14i1e74080_app1.pdf]

Multimedia Appendix 2
Sample informed consent form for caregivers of participants in aim 3 (randomized controlled trial) of the Unified Protocol for Transdiagnostic Treatment of Emotional and Academic Challenges in Education study (English version).
[PDF File (Adobe PDF File), 204 KB - resprot_v14i1e74080_app2.pdf]

Multimedia Appendix 3
Sample informed consent form for caregivers of participants in aim 3 (randomized controlled trial) of the Unified Protocol for Transdiagnostic Treatment of Emotional and Academic Challenges in Education study (Spanish version).
[PDF File (Adobe PDF File), 214 KB - resprot_v14i1e74080_app3.pdf]

Multimedia Appendix 4
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist for the Unified Protocol for Transdiagnostic Treatment of Emotional and Academic Challenges in Education study.
[PDF File (Adobe PDF File), 275 KB - resprot_v14i1e74080_app4.pdf]

Multimedia Appendix 5
Peer review report from the Institute of Education Sciences, United States Department of Education.
[PDF File (Adobe PDF File), 202 KB - resprot_v14i1e74080_app5.pdf]

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Abbreviations

AAPC: Adolescent Academic Problems Checklist
AMAS-ZABB: Abbreviated Multidimensional Acculturation Scale
ARI: Affective Reactivity Index
BFS: Behavior and Feelings Survey
CAIS-AS: Child Anxiety Impact Scale–Academic Subscale
CBT: cognitive behavioral therapy
CSQ: Client Satisfaction Questionnaire
DIAMOND-KID: Diagnostic Interview for Anxiety, Mood, and OCD-Related Neuropsychiatric Disorders: Child and Adolescent Version
DTS: Distress Tolerance Scale
EBT: evidence-based treatment
EDS: Everyday Discrimination Scale
GAD-7: Generalized Anxiety Disorder 7-item Scale
ICC: intraclass correlation coefficient
PHQ-8: Patient Health Questionnaire-8
PHQ-9: Patient Health Questionnaire-9
RCADS-SF: Revised Children's Anxiety and Depression Scale–Short Form
RCI: reliable change index
RCT: randomized controlled trial
RQA: rapid qualitative analysis
SAU: service as usual
TASC-R: Therapeutic Alliance Scale for Children−Revised
UP-A: Unified Protocol for Transdiagnostic Treatment of Emotional Disorders in Adolescents
U-PEACE: Unified Protocol for Transdiagnostic Treatment of Emotional and Academic Challenges in Education

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Protocol

Social Transfers for Exclusive Breastfeeding in Brazil: Protocol for a Randomized Controlled Trial

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Abstract

Background: According to the World Health Organization's infant and young child feeding guidelines, infants should be exclusively breastfed for the first 6 months of life. Despite public health campaigns to increase exclusive breastfeeding (EBF) rates, socioeconomic inequities persist among low-income breastfeeding mothers, especially in countries with large wealth and health gaps, such as Brazil. Social transfer programs are initiatives that provide financial support to individuals or households to improve their well-being and reduce financial burdens. These may be conditional, requiring recipients to meet specific criteria to receive the transfer, or unconditional, in which recipients receive the transfer without prerequisites. Evidence suggests that conditional and unconditional social transfers may help increase EBF rates while addressing the economic challenges breastfeeding mothers face. A randomized controlled trial (RCT) conducted in Vientiane, Lao People's Democratic Republic, found that a social transfer program significantly improved both EBF rates at 6 months and EBF duration. Building on this study, we aim to evaluate the impact of this intervention in a different socioeconomic and cultural context.

Objective: This protocol aims to implement an RCT to assess whether conditional and unconditional social transfers improve EBF rates at 6 months postpartum for mothers in low-income communities in São Paulo, Brazil.

Methods: A prospective RCT will be conducted among 400 mothers who gave birth in the last 72 hours and plan to exclusively breastfeed. Participants will be recruited in São Paulo at the University Hospital of São Paulo and Amparo Maternal. Participants will be randomly assigned to one of the following groups: (1) control group—no social transfer; (2) intervention group 1—an unconditional social transfer at 6 months postpartum; and (3) intervention group 2—a social transfer at 6 months postpartum, conditional upon mothers' EBF. All groups will receive educational materials supporting EBF. The study will have visits at birth, 1 month, 6 months, 1 year, and 2 years and will include a questionnaire and biological collections of breast milk samples, infant fecal samples, and blood samples (finger pricks) from both the mother and infant. The main study outcomes are the prevalence of EBF at 6 months and the duration of EBF across the 3 groups, where we hypothesize higher rates of EBF among mothers in the conditional group.

Results: Recruitment began on March 6, 2024. As of September 2025, we enrolled 204 participants. Our goal is to recruit 400 mother-infant dyads by October 2025, with study visits expected to be completed by October 2027.

Conclusions: We hypothesize that the Social Transfers for Exclusive Breastfeeding in Brazil (STEBB) intervention will positively impact breastfeeding mothers in São Paulo. If successful, the program may inform national policy to enhance Brazil's existing social transfer program for new mothers.

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International Registered Report Identifier (IRRID): DERR1-10.2196/75796

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KEYWORDS
breastfeeding; lactation; human milk; social transfer; child; mother; Brazil; health

Introduction

Background

Breastfeeding is one of the most cost-effective ways to improve health and development outcomes for infants [1]. The World Health Organization (WHO) recommends that infants be exclusively breastfed for the first 6 months of life [2]. Exclusive breastfeeding (EBF) is defined as infants receiving only breast milk, with no other liquids or solids given, with the exception of oral rehydration solution, vitamins, minerals, or medicines [2]. Infants who are exclusively breastfed for a longer duration have strengthened immune systems, lower rates of infectious diseases, improved cognitive development, and overall lower mortality rates [3-9]. Mothers who exclusively breastfeed have improved mental health outcomes and reduced rates of breast and ovarian cancer [10,11]. Although the positive impacts of EBF are recognized internationally, the Global Breastfeeding Collective's goal of an overall EBF rate of 50% by 2025 will be hard to reach [12,13]. Globally, the most commonly documented barriers to EBF are financial constraints, time commitment, insufficient maternity protection, and a lack of breastfeeding support [14-16]. In the last decade, many countries have launched public health campaigns, such as educational awareness programs, to improve rates of EBF. Awareness programs are important but often do not take into account the financial and time constraints associated with breastfeeding and are not always adapted for mothers from lower socioeconomic communities [17-22].

Social transfer programs have been effective in improving health outcomes while also reducing socioeconomic inequalities, especially in low- and middle-income countries [23-25]. Puerto Rico launched a small-scale cash transfer program and found an increase in breastfeeding outcomes for those receiving a financial incentive [26]. In addition, a recent study conducted in Vientiane, Lao People's Democratic Republic (LPDR), demonstrated that a social transfer program significantly improved EBF rates at 6 months postpartum [27]. Mothers who received a conditional social transfer had the highest prevalence of EBF at 6 months, followed by those who received an unconditional social transfer [27].

Brazil has one of the highest levels of economic and health inequalities globally [28]. Most of Brazil's wealth is held by 1% of the population, demonstrating the extreme disparities faced in the country [29,30]. To reduce these prominent wealth and health gaps, Brazil implemented a national conditional cash transfer program called Bolsa Família in 2003, which provides financial incentives to families from low-income communities to help support and improve child health and education [31,32]. Although Bolsa Família has been associated with reductions in poverty and improvements in child health outcomes, disparities continue to persist. These differences are also reflected in breastfeeding practices, where low-income mothers have lower rates of EBF compared to mothers with high income [33,34]. Brazil reports an overall EBF rate of 39% for children aged below 6 months [35,36]. While EBF rates are 46% in high-income communities, they are only 33% in low-income communities [37-39]. To address this, Auxílo Nutriz was introduced within Bolsa Família, offering an additional social transfer of 50 Brazilian Reais (US $10) to support new mothers during the first 6 months postpartum. This program is still in its early stages; therefore, data on outcomes have yet to be evaluated.

This Study

This protocol aims to implement a randomized controlled trial (RCT), the Social Transfers for Exclusive Breastfeeding in Brazil (STEBB) program in São Paulo, to assess the effectiveness of a targeted social transfer intervention in an upper-middle-income country with persistent inequities. Building upon the design of a successful program conducted in LPDR, the STEBB intervention will evaluate the impact of breastfeeding education combined with either no social transfer, an unconditional transfer, or a conditional transfer on EBF outcomes. By leveraging Brazil's existing national social transfer program, this study will explore whether a more focused and enhanced intervention can further promote EBF. The primary outcomes of this study are the prevalence of EBF at 6 months postpartum and the overall duration of EBF. We hypothesize that mothers receiving a conditional social transfer will have the highest rates of EBF at 6 months and, on average, the longest duration of EBF, followed by those receiving an unconditional social transfer and no social transfer.

Methods

Overview

The STEBB study is a prospective, 3-arm RCT conducted in São Paulo, Brazil. Before implementing the intervention, we conducted a qualitative study to identify culturally relevant social transfers and ensure social acceptability of the program.

The qualitative study involved 3 focus group discussions with mothers and fathers as well as key informant interviews with 3 health care workers and 2 representatives from the Ministry of Health and the Ministry of Social Development and Fight Against Hunger. These focus group discussions and key informant interviews assessed behaviors, perceptions, and barriers related to breastfeeding as well as the feasibility of implementing a social transfer program aimed at improving EBF rates. Findings from the qualitative research informed the

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design of a culturally appropriate and acceptable social transfer intervention for participants in Brazil, including options such as diapers, hygiene products, children's clothes, toys, or books.

Recruitment

A total of 400 mother-infant dyads will be recruited at the University Hospital of São Paulo and Amparo Maternal during the postpartum hospitalization period. Recruitment will take place over 8 months, with a target of enrolling 50 dyads per month. Each dyad will be followed for a period of 2 years (Figure 1).

Figure 1. Study timeline.

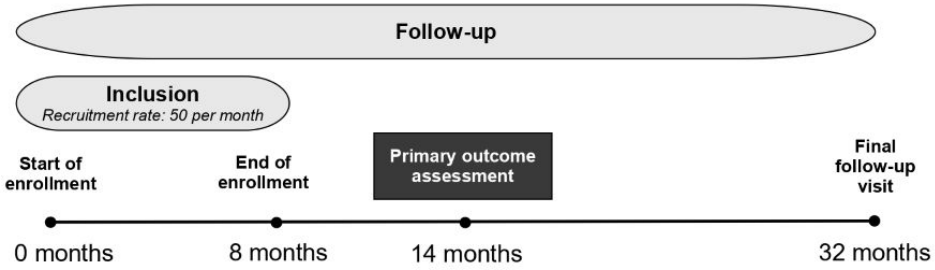

At baseline, mothers will be randomly assigned to one of the three groups (Figure 2): (1) control group—no intervention; (2) intervention arm 1—receipt of a social transfer at the 6-month visit; and (3) intervention arm 2—receipt of a social transfer at the 6-month visit, conditional on EBF status at the 6-month visit. All 3 groups will receive educational material on breastfeeding. The intervention is structured into 3 study arms to enable comparison between the 2 intervention groups and the control group, allowing us to evaluate the effects of conditional versus unconditional programs. Evidence from LPDR has shown that conditional social transfers significantly improved EBF rates [27]. Bolsa Família is another example of a successful conditional social transfer program for child health outcomes [34]. By contrast, our qualitative study found that participants expressed concerns about conditional programs targeting breastfeeding outcomes, particularly due to the pressure placed on mothers and the lack of reliable tools to accurately assess EBF. Given this context, we aim to evaluate both types of interventions to determine their respective impacts and assess which intervention is more effective and feasible for potential large-scale implementation.

Figure 2. Study arms.

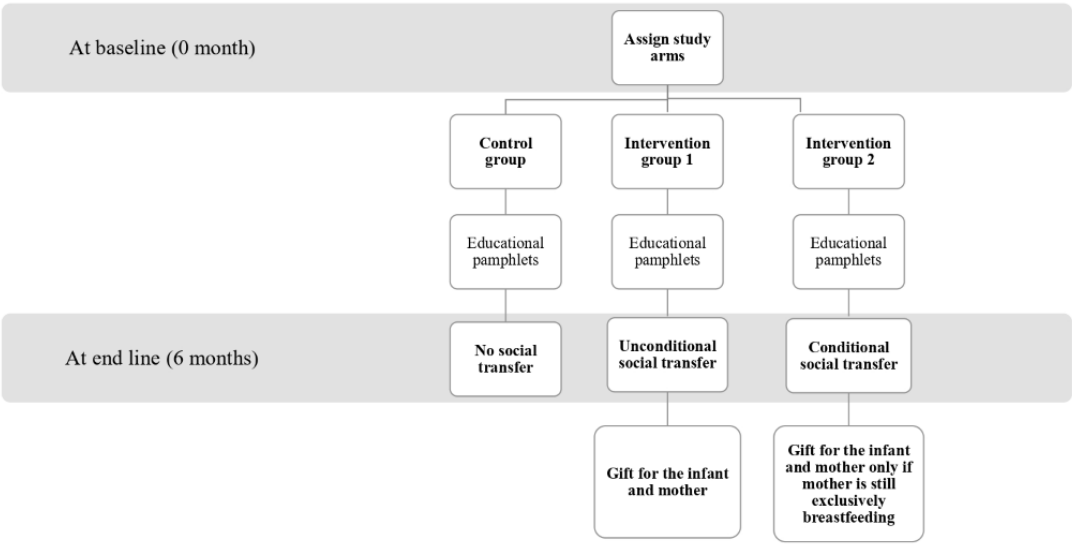

The study participants will be contacted at the hospital after giving birth. New mothers will be eligible to participate in the study if they (1) gave birth in the last 72 hours, (2) are exclusively breastfeeding at the time of recruitment and intend to continue to exclusively breastfeed, (3) are beneficiaries of the Bolsa Família program or part of the eligible population for Bolsa Família registered in the Unified Social Assistance Registry (Cadastro Único), (4) live in São Paulo, (5) have no illnesses that contraindicates breastfeeding, (6) had a healthy singleton infant of 37 weeks or more gestation with a birth weight of at least 2500 g, and (7) agree to participate and sign an informed consent form (ICF). If underage (aged between 12 and 17 years), a legal representative will also have to agree to sign the informed consent.

A team of 2 nurses will be responsible for enrollment and follow-up of participants. The nurses will explain the study to all participants and collect the written ICF. Randomization will be done using a simple random number draw generated by ODK, used to collect data on tablets. The nurses will not have access to the random allocation sequence.

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Sample Size and Power Calculation

We initially planned to only recruit mother-infant dyads at the University Hospital of São Paulo based on the documented average of 200 births per month in 2024. However, after 2 months of recruitment, we observed a lower-than-expected birth rate. To ensure timely enrollment, we expanded our recruitment to include a second recruitment center, Amparo Maternal, which reported an average of 400 births per month in 2024. As a multicenter study, we are confident in reaching our target sample size of 400 dyads by October 2025.

We plan to enroll 200 participants in the control arm and 100 participants in each of the 2 intervention arms. This sample size provides 80% power to detect an increase in EBF from an anticipated 32.5% (65/200) in the control arm to 47% (94/200) in either intervention arm.

Study Design

This study includes 5 visits: at birth (baseline), 1 month, 6 months (end line), 1 year, and 2 years (Figure 3). At baseline, the participants will complete a short questionnaire, and biological samples will be collected from both the mother and infant. At the end of the visit, the nurse will provide detailed information on the intervention depending on the group the mothers are randomly assigned to. If the mothers are assigned to an intervention group, they will be given a gift catalog to choose a social transfer for the visit at 6 months. The catalog will offer gift packages ranging from baby clothes, hygiene products, transportation vouchers, and developmental toys for the child. All 3 groups will receive educational pamphlets explaining the benefits of breastfeeding and providing breastfeeding guidelines.

During the follow-up visits (at 1 month, 6 months, 1 year, and 2 years), data collection will include a questionnaire and biological samples from both the mother and infant. The intervention groups (unconditional and conditional) will receive a social transfer at the 6-month visit. For mothers in the conditional group, assessors will review the maternal feeding reports as well as visually verify milk expression during biological collection.

Figure 3. Study visits and data collection.

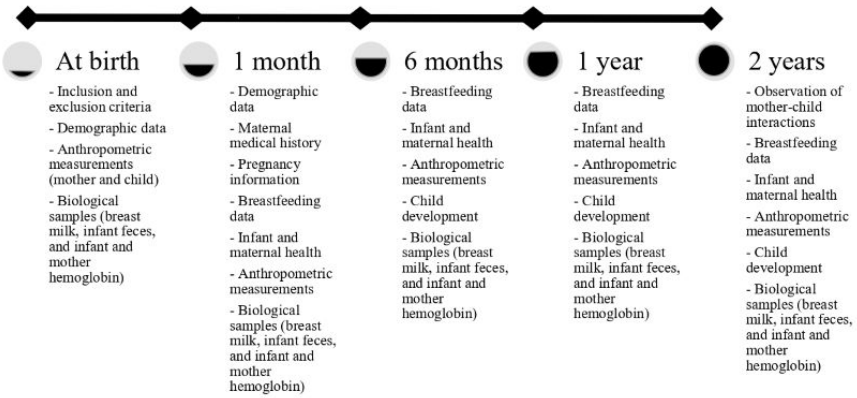

Data Collection Tools

STEBB provides a questionnaire at each visit.

Baseline: At Birth

The baseline questionnaire is given to the mothers during postpartum hospitalization. The questionnaire will consist of the inclusion criteria and basic demographic questions, such as education, employment, and marital status. We will also extract anthropometric measurement data from the child (weight, length, mid and upper arm circumference, abdominal circumference, chest circumference, and head circumference) and mother (blood pressure, height, weight, and heart rate) through medical records. Hemoglobin levels of the mother and infant will be collected and measured using the HemoCue Hb 301. Infant feces and human milk samples will also be collected.

Follow-Up: 1 Month Postpartum

The 1-month questionnaire is given to the mothers at 1 month postpartum during a hospital follow-up visit. The questionnaire includes maternal medical and obstetric history; child health (infectious and chronic illnesses, hospital visits, medication, vitamins, and vaccinations); anthropometric measurements from mother (height and weight) and child (weight, length, mid and upper arm circumference, abdominal circumference, chest circumference, and head circumference); breastfeeding and infant feeding; Resilience Scale-14 [40]; Breastfeeding Self-Efficacy Scale–short form [41]; Perceived Maternal Parenting Self-Efficacy Scale [42]; Iowa Infant Feeding Attitude Scale [43]; Postpartum Specific Anxiety Scale [44]; Edinburgh Postnatal Depression Scale [45]; Growth, Resilience, Integrity, and Tenacity Scale–short form [46]; household assets; family and gender roles; and maternal intimacy and behavioral measurements (diet, tobacco use, and alcohol consumption). This information will be collected during the 1-month visit. Mother and infant hemoglobin levels, along with infant feces and milk samples, will also be collected.

End line: 6 Months Postpartum

The end line questionnaire is given to the mothers at approximately 6 months (1 week earlier or later) postpartum during an at-home visit. The questionnaire includes child health (as done at 1 month), maternal and child anthropometric measurements (as done at 1 month), breastfeeding and infant feeding, Big Five Personality Scale [47], Iowa Infant Feeding Attitude Scale, Perceived Stress Scale [48], Postpartum Specific Anxiety Scale, Edinburgh Postnatal Depression Scale, Caregiver Reported Early Development Instruments–short form [49], and

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maternal intimacy and behavioral measurements (diet, tobacco use, and alcohol consumption). Mother and infant hemoglobin levels, along with infant feces and human milk samples, are also collected.

Follow-Up: 1- and 2- Years Postpartum

Additional follow-up visits will occur at 1 and 2 years postpartum (1 month earlier or later) at the participants' homes. The questionnaire includes maternal and child health and anthropometric measurements (as done at 1 month), breastfeeding and infant feeding, Caregiver Reported Early Development Instruments–long form [49], Me As A Parent Scale [50], Perceived Stress Scale, Brief Infant Sleep Questionnaire–short form [51], maternal intimacy and behavioral measurements (diet, tobacco use, and alcohol consumption), and other questions about daycare, screen time, baby-led weaning, and parenting styles. At 2 years postpartum, child development will also be assessed using the Global Scale for Early Development–long form [52]. Mother and infant hemoglobin levels, along with infant feces and human milk samples, will also be collected.

Outcomes

The primary study outcome is the prevalence of EBF at 6 months postpartum as well as EBF duration. The secondary outcomes will include complementary breastfeeding duration and child development. Bile acids and other human milk components will be evaluated to determine the relationship with infant gut microbiota and infant growth and development.

Statistical Analysis

All participants enrolled in this study will be included in the analysis and will be assessed by intervention group (control, unconditional, and conditional). EBF duration will be analyzed after completion of end line visits using an adjusted Cox proportional hazards model to estimate hazard ratios and 95% CI limits. We will use an adjusted logistic regression model to assess EBF at 6 months in the intervention and control groups. A complete case analysis will be used to address missing data.

Data Management

ODK software will be used to collect and manage the study data. Questionnaires are uploaded onto the ODK platform before data collection, allowing study staff to access the questionnaire offline using a tablet or smartphone. All data collection devices are password protected and stored securely at the hospital when they are not in use. Once the questionnaires are filled out, they are uploaded onto the server and are accessible through a secure web interface, ODK Aggregate. Only authorized personnel who require the data to fulfill their duties within the scope of the research project will be able to access ODK Aggregate.

The collected data will be stored on the secure ODK server and will only be identifiable by a unique participant number. The biological specimen samples will only be identifiable by the same unique participant number. The biological specimens will be stored securely at the University of São Paulo and will only be accessible to authorized personnel. Health-related data will be stored for 15 years, following the University of São Paulo regulations. If participants sign a separate consent form for reusing health data, data and biological samples will be kept for an unspecified amount of time.

Ethical Considerations

This study was submitted and approved by the National Commission for Ethics in Research and the University Hospital of the University of São Paulo in Brazil (6.704.768), and it was submitted for ethical review to the Ethical Commission of Northwestern and Central Switzerland (AO_2024-00015). The study will be carried out in accordance with the Declaration of Helsinki. Any amendments to the protocol, ICF, or any other forms related to the study have to be reviewed by an independent ethics committee.

Eligible participants will be identified by study staff, and an initial visit will occur at the hospital. The nature of the study will be explained to the participants orally before obtaining a written ICF. Once the participants have some time for reflection and to answer any questions, they will be asked to sign an ICF according to their assigned group. For minors (aged <18 years), both the mother and her parents will be required to provide consent. For participants who are illiterate, an additional witness will be required. Participation is voluntary, and participants have the right to withdraw from the study at any given point in time with no further obligations. If the participant decides to withdraw from the study at any time, they may request that their data will be deleted and their biological specimen samples destroyed.

Project data and biological materials will be handled with the utmost discretion and will be accessible only to authorized personnel who require the information to perform their duties within the scope of the research project. Participants will be identified solely by a unique participant number and participants will be assured that all personal information collected during the research study will be kept confidential. Given that the intervention is primarily designed to support mothers, adverse outcomes seem unlikely. Breast milk samples will be collected through hand expression, which should not be painful for participants. For the hemoglobin measurements, blood will be collected through a finger prick, which can lead to a small discomfort for the participants. The risk of inflammation or infection is small if the participants follow proper hygienic procedures. If the participant feels any discomfort, the process will be stopped. Breastfeeding mothers may experience mastitis, which may affect breastfeeding. We will provide information and advice in the educational pamphlets on how to treat the infection without having to stop breastfeeding, as recommended by the WHO.

A social transfer will be provided to participants in the intervention groups. Four gift package options will be given to allow individualized social transfers. If any negative themes arise (eg, stigma), strategies to overcome these will be identified during the qualitative study. In the case that mothers involuntarily stop breastfeeding, a small gift will be provided.

Trial Registration

The RCT was registered on ClinicalTrial.gov on December 6th 2023 (NCT06157697).

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Results

Recruitment for the study began on March 6, 2024. As of September 2025, we have enrolled 204 participants. Our goal is to recruit 400 mother-infant dyads by October 2025, with our primary outcome to be completed by May 2026 and all study visits expected to be completed by October 2027.

Discussion

Anticipated Findings

The STEBB intervention will advance our understanding of the main barriers to breastfeeding in an upper-middle-income country while assessing the effectiveness of a social transfer intervention for increasing EBF rates. The anticipated main finding of this study is that mothers receiving a social transfer, whether conditional or unconditional, will show improved EBF outcomes in São Paulo, Brazil. We believe that providing incentives through a social transfer program targeted at breastfeeding mothers from low-income communities offers a unique opportunity to reduce economic and health inequalities while simultaneously increasing EBF rates.

The STEBB intervention is one of the first social transfer programs implemented in an upper-middle-income country, specifically targeting EBF outcomes. It builds on a social transfer program implemented in LPDR in 2022, which was the first study to demonstrate that both conditional and unconditional social transfers can improve EBF outcomes [27,53]. Capitalizing on the ongoing program in LPDR and insights from our qualitative research, the STEBB intervention was adapted by applying lessons learned from the field and adjusting them to different country contexts.

While other social transfer programs have been implemented in the past, most aim to improve health and educational outcomes. Examples from South America include Bolsa Família in Brazil, Prospera in Mexico, and Más Familias en Acción in Colombia [54]. These programs have been successful in providing financial support to vulnerable populations and improving key development indicators [32,54-56].

If STEBB is successful in improving rates of EBF in São Paulo, we plan to extend the RCT to other parts of Brazil. We also see potential for informing the national social transfer program, the Bolsa Família and Auxílio Nutriz, on possibilities to improve the program outcomes, specifically regarding EBF. For future research, we plan to reproduce the intervention program in other countries and regions, particularly those with low EBF rates and where large health gaps are present.

Our dissemination plan includes sharing and discussing study findings with the local community in São Paulo, including the University Hospital of São Paulo and Amparo Maternal, as well as with policymakers in Brazil. We also plan to present our results at both local and international conferences and through publications in peer-reviewed journals.

Limitations

One limitation for STEBB is that the social transfers provided appear relatively small. Due to ethical regulations in Brazil, we are unable to offer financial compensation for the mothers' work time. Many low-income mothers in São Paulo are considered informal workers and are unable to take paid time off from work or do not have a safe place to pump. Because of the additional barriers low-income mothers face, breastfeeding is difficult, leading to low rates of EBF in these communities. The qualitative study that was conducted before implementation identified ways to overcome these barriers and reduce any additional burdens that these working mothers may face while breastfeeding.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are not publicly available due to ongoing grant analyses that have not been completed but are available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization: SK, JW, AB (equal)
Funding acquisition: JW, JF
Methodology: SK (supporting), JW (lead)
Writing—original draft: SK (lead), JW (supporting)
Writing—review and editing: SK, AB, HB, JF, RF, ACO, SERH, GF, JW

Conflicts of Interest

None declared.

Multimedia Appendix 1

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Peer-review report from the Swiss National Science Foundation.
[PDF File (Adobe PDF File), 272 KB - resprot_v14i1e75796_app1.pdf]

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Abbreviations

EBF: exclusive breastfeeding
ICF: informed consent form
LPDR: Lao People’s Democratic Republic
RCT: randomized controlled trial
STEBB: Social Transfers for Exclusive Breastfeeding in Brazil
WHO: World Health Organization

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Protocol

Culturally Tailored Diabetes Self-Management Education and Support Programs in Black African and Caribbean Adults With Type 2 Diabetes (HEAL-D): Protocol for a Multicenter, Pragmatic Randomized Controlled Trial

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Abstract

Background: People of Black African and Black Caribbean ethnicity experience higher rates and poorer outcomes of type 2 diabetes (T2D) than people of White European ethnicity; these inequalities are compounded by poor healthcare access. Cultural tailoring of diabetes self-management education and support (DSMES) programs has the potential to improve healthcare engagement and clinical outcomes for ethnic minority groups. Healthy Eating & Active Lifestyles for Diabetes (HEAL-D) is a co-designed, culturally tailored group-based DSMES program for adults of Black African and Black Caribbean ethnicity.

Objective: This trial aims to evaluate the clinical and cost effectiveness of the HEAL-D intervention, compared to standard DSMES programs, in Black African and Black Caribbean adults living with T2D.

Methods: A 24-month, multicenter, pragmatic, open-label, 2-arm, parallel-group, individually randomized group treatment trial will be conducted, with primary end point (glycated hemoglobin [HbA_{1c}]) assessment at 12 months. Black African and Black Caribbean adults with T2D (n=300), recruited from 3 to 5 centers in the United Kingdom (including London, West Midlands, and Greater Manchester), will be randomized in a 1:1 ratio to HEAL-D (intervention) or a standard DSMES program (control). HbA_{1c}, blood lipids, anthropometric outcomes, blood pressure, physical activity, and patient-reported outcome measures relating to psychological well-being and self-management support, lifestyle behaviors, and health economics will be collected at baseline

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and follow-up visits (6, 12, and 24 months). Cost-effectiveness will be assessed through a cost-utility analysis conducted from a health and social care perspective. A mixed methods process evaluation will provide a formative evaluation of delivery, intervention fidelity, and implementation of HEAL-D, and an embedded study within a project will assess the impact of multiple long-term conditions on uptake of, and engagement with HEAL-D, and the impact of HEAL-D on multiple long-term conditions. The trial received Research Authority and Research Ethics Council approval on April 22, 2024.

Results: Funding began in August 2023. Site "green light" was received on August 15, 2024, for London; November 29, 2024, for Manchester; and January 31, 2025, for the West Midlands. Recruitment commenced in August 2024 and is due to run for 11 months. As of March 26, 2025, a total of 76 participants have consented. Last patient, last visit is expected in June 2027; primary data analysis is expected to begin in July 2027. Final results are anticipated to be available in September 2027, and publication is expected by the end of 2027.

Conclusions: The HEAL-D trial will address whether a culturally tailored DSMES program, provided in-person or via videoconferencing, is clinically and cost-effective compared to standard DSMES at improving diabetes management in Black African and Black Caribbean adults. If effective, this would provide an evidence-based model of equitable DSMES services and improve the implementation of healthcare programs for ethnic minority groups.

Trial Registration: ISRCTN 1434448; https://www.isrctn.com/ISRCTN14344948

International Registered Report Identifier (IRRID): DERR1-10.2196/71861

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KEYWORDS

type 2 diabetes; education; ethnicity; self-management; clinical trial; protocol

Introduction

Background

Type 2 diabetes (T2D) prevalence has grown steadily over recent decades, now estimated to affect over 6% of the world's population [1,2]. T2D is characterized by elevated blood glucose concentrations and increased risk of macrovascular and microvascular complications [3,4]. Such risks culminate in poorer physical and mental health [5], quality of life (QoL) [6], and earlier death [4], with diabetes consuming around 10% of the annual healthcare budget [7].

The effects of T2D are experienced disproportionally by people of Black African and Black Caribbean ethnicity compared to White European ethnicity [8,9], with 2-4 times greater prevalence [8,9], younger onset [10], poorer outcomes for those who are affected, and greater medication requirements [11-13]. A lack of access to T2D healthcare and reduced effectiveness of current T2D treatment programs in Black African and Black Caribbean populations have been proposed as key causes for these inequalities [13-15]. Therefore, the modification of existing T2D treatment pathways may facilitate better adoption and lower attrition rates in those of Black African and Black Caribbean ethnicity [16,17], who make up the second largest and fastest growing UK ethnic minority group [18].

Optimizing diet and physical activity and promoting self-management are integral parts of T2D management [19], with management guidelines recommending attendance at a diabetes self-management education and support (DSMES) program [19]. In the United Kingdom, quality standards require that DSMES programs have an evidence-based curriculum, delivered by trained and competent educators, usually offering at least 6 hours of education [19]. Several DSMES programs are accredited and commissioned [20,21], mainly using a group-based format and face-to-face (F2F) delivery, although digital programs and digital adaptations of F2F programs have been evaluated or implemented following the COVID-19 pandemic [22,23].

Whilst DSMES programs are effective for improving T2D management and cardiovascular, behavioral, and psychological outcomes, they are substantially less effective in people of Black African and Black Caribbean ethnicity [13,16,17]. Despite recommendations for programs to meet the needs of cultural groups [19], a lack of cultural knowledge and awareness among healthcare practitioners, as well as insensitivity to cultural beliefs and practices, are implicated as key drivers of this inequality [24-26]. Cultural tailoring of DSMES programs to make them sensitive and responsive to health beliefs, practices, and linguistic needs of cultural groups has been shown to enhance improvements in important outcomes, including glycemic control (glycated hemoglobin [HbA_{1c}]), knowledge, and QoL [26-28]. However, few have been evaluated in the United Kingdom [29]. Healthy Eating & Active Lifestyles for Diabetes (HEAL-D) is an evidence-based DSMES program, tailored to the cultural needs of Black African and Black Caribbean adults, which was co-designed with Black African and Black Caribbean people living with T2D, healthcare practitioners and commissioners, and community leaders [29-33]. Patient acceptability of HEAL-D has been demonstrated in a feasibility trial [34], but it is not known if the intervention is clinically and cost-effective.

As the first UK-based clinical trial to evaluate a culturally tailored DSMES program, the HEAL-D trial provides an opportunity to inform the future delivery of T2D care to Black African and Black Caribbean populations that have traditionally been underrepresented in clinical research and underserved by healthcare systems. By doing so, this trial can help to address several healthcare priorities, particularly relating to ethnic inequalities in healthcare outcomes [35-38]. If effective, the HEAL-D intervention could offer healthcare systems equitable DSMES services that meet the needs of some of its most

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vulnerable service users, ultimately reducing the health and economic burden of T2D. Furthermore, the outcomes of this trial could help inform and improve the implementation of healthcare programs for ethnic minority groups more broadly, helping to address health inequalities.

Aims

The primary aim of this trial is to evaluate the effectiveness of the HEAL-D intervention, compared to standard DSMES programs, on glycemic control (assessed via HbA_{1c}) at 12 months in Black African and Black Caribbean adults living with T2D. It is hypothesized that the HEAL-D intervention will improve glycemic control to a greater extent than standard DSMES programs at 12-month follow-up. Secondary aims include testing the effectiveness of HEAL-D, compared to standard DSMES programs, on cardiovascular risk factors; psychological well-being and QoL; T2D knowledge and self-efficacy; and diet and physical activity behaviors at 6, 12, and 24 months, as well as assessing cost-effectiveness. A mixed methods process evaluation aims to assess HEAL-D delivery, intervention fidelity and implementation, and the impact of multiple long-term conditions (MLTC) on recruitment and engagement with the HEAL-D intervention, and the impact of HEAL-D on MLTC.

Methods

Study Design

The trial is a 24-month, multicenter, pragmatic, open-label, 2-arm, parallel-group, individually randomized group treatment trial assessing the clinical and cost effectiveness of the HEAL-D program compared with standard DSMES programs in Black African and Black Caribbean adults living with T2D. A total of 300 Black African and Black Caribbean adults living with T2D will be recruited and randomly allocated to either the HEAL-D program (n=150) or a standard DSMES program (control, n=150). Outcome assessments will be conducted at baseline and 6, 12, and 24 months after randomization (Figure 1). Embedded within the trial are an internal feasibility assessment of recruitment, allocation and intervention engagement; a health economic analysis; a mixed methods process evaluation of intervention delivery, fidelity, implementation and acceptability; and study within a project (SWAP) to assess the impact of MLTC on the uptake of and engagement with HEAL-D, and the impact of the intervention on MLTC.

The trial is funded by the National Institute for Health Research (NIHR) Health Technology Assessment Program (NIHR151372) and is registered with ISRCTN (14344948), which adheres to the World Health Organization (WHO) Trial Registration Dataset. Health Research Authority and Research Ethics Council approval was received on April 22, 2024.

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Figure 1. Trial CONSORT flow diagram. CONSORT: Consolidated Standards of Reporting Trials; DSMES: diabetes self-management education and support; HEAL-D: Healthy Eating and Active Lifestyles for Diabetes; ITT: intention-to-treat.

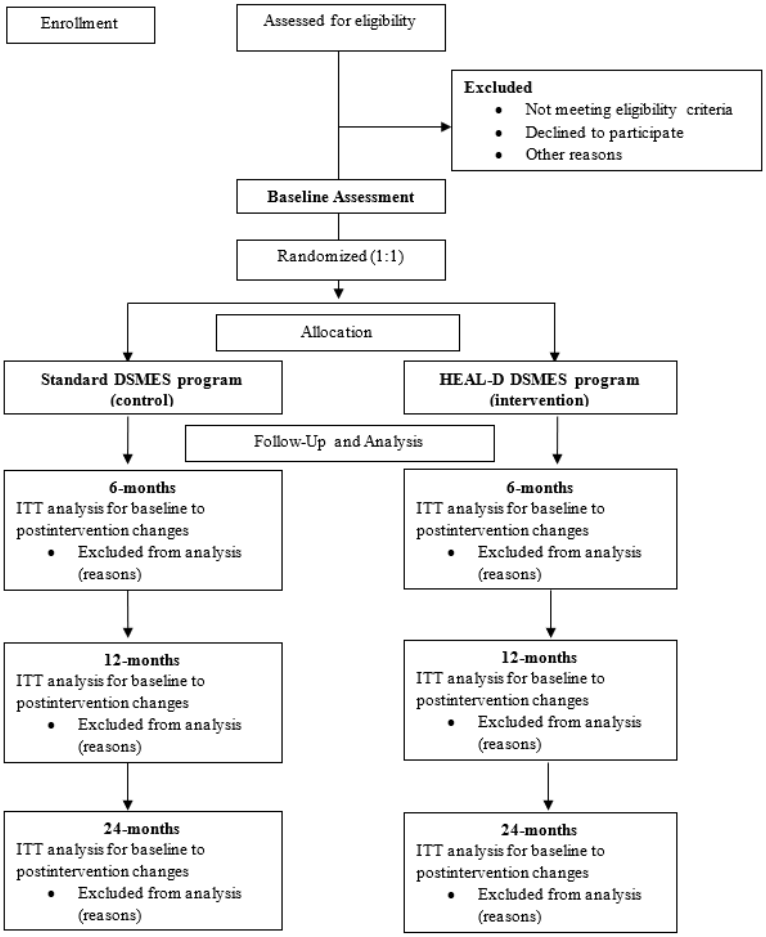

Setting

The trial will be conducted in 3-5 centers in the United Kingdom, including London, West Midlands, and Greater Manchester, which have been selected as areas in the United Kingdom with significant representation of Black African and Black Caribbean adults. The trial will be centrally coordinated by the Diabetes Research Centre (University of Leicester, United Kingdom) and supported by infrastructure provided through the NIHR Research Delivery Network.

Participants

A sample of 300 participants will be recruited. Inclusion criteria are: (1) adult (aged 18 years or older); (2) Black African or Black Caribbean ethnicity (self-declared and classified according to the Census system used within National Health Service (NHS) services: people of “Black African,” “Black Caribbean,” “Black British,” “Black Other,” and “mixed race” with either African or Caribbean ancestry); (3) T2D diagnosis (confirmed by medical history); (4) HbA_{1c}≤100 mmol/mol (or fructosamine <450 µmol for individuals with sickle cell trait or disease); (5) Suitable for group-based training and participation in physical activity (suitability confirmed by a general practitioner or referring healthcare practitioner); (6) willing to undergo randomization; and (7) able to provide informed consent.

Exclusion criteria are (1) current pregnancy; (2) complex medical, lifestyle, or learning needs that require personalized advice or for which group-based training is unsuitable (eg, advanced chronic kidney disease and people with learning disabilities, confirmed by general practitioner or referring healthcare practitioner); (3) need for language translation services (spoken or written); (4) unable or unwilling to provided informed consent; and (5) current participation in competing clinical trial as determined by trial investigator.

The eligibility criteria have been selected pragmatically to align with UK clinical practice, whereby group-based DSMES is a recommended management option for most patients with T2D. However, patients with uncontrolled T2D (ie, high HbA_{1c}) or specific or complex medical, educational, or lifestyle needs would not typically be referred to group-based DSMES programs, but would be managed in services that can provide more individualized advice or care. Similarly, patients needing language translation services would not typically be referred to group-based DSMES programs because of difficulties meeting their language needs.

Recruitment and Screening

The research team will work with healthcare providers and grassroots or community organizations to identify and recruit participants. Several means of recruitment will be used: (1) screening of referrals to DSMES services from primary,

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intermediate or community care, and secondary care clinics; (2) primary care database searches; and (3) self-referral in response to study advertisements and community engagement activities.

Potential participants will be sent a participant information video via SMS text message or a written information leaflet via email or letter, providing a brief explanation of the purpose of the trial and participation requirements. Interested individuals will be invited to contact the research team or a community champion by phone, email, or web form to discuss the trial in detail and schedule a telephone eligibility screening, which will be conducted by the research team. Eligible participants, who confirm their intention to participate, will be invited to attend an in-person visit where written informed consent will be recorded prior to baseline data collection.

Randomization and Blinding

Following the baseline assessment, each participant will be randomly allocated (1:1 ratio) to the intervention or control group using a centralized web-based randomization database (REDCap [Research Electronic Data Capture; Vanderbilt University]). Allocation will use randomly permuted blocks of variable block length and be stratified by center, accounting for the provision of different standard DSMES programs between centers, and baseline HbA_{1c} (48-52, 53-76, and 77-100 mmol/mol). The participants and researchers will not be blinded to group allocation.

Intervention Group

HEAL-D is a culturally tailored DSMES program, consisting of 16 hours (eight 2-h sessions delivered over 6 mo) of group-based T2D self-management education and support, including participatory physical activity classes. The program is delivered by a diabetes specialist dietitian (no specified ethnicity), a community facilitator of Black African and Black Caribbean ethnicity, and exercise instructors (no specified ethnicity), using F2F or remote videoconferencing delivery modes; participants will choose their mode of attendance. HEAL-D aligns with quality standards [19], is underpinned by an evidence-based curriculum [39], and uses evidence-based behavior change techniques, informed by the Behavior Change Wheel and the Capability Opportunity Motivation-Behavior (COM-B) framework [40], to support adoption and long-term maintenance of the following diet and lifestyle goals [39]: (1) achieve 5%-10% weight loss or weight maintenance in those of healthy weight, (2) undertake ≥150 minutes per week of moderate to vigorous intensity aerobic physical activity plus 2 sessions per week of strength training, (3) balance carbohydrate intakes through portion control and promotion of low glycemic index and wholegrain sources, (4) limit saturated fat intake (<10% of energy intake) and replace with mono-unsaturated fats, (5) limit salt intake to no more than 6 g per day, and (6) consume at least 2 portions of oily fish per week.

Culturally tailored resources have been developed and are used to deliver the curriculum, including diet booklets, portion size guides, and participatory games focusing on cultural foods and dishes, and videos including health and motivational messages. Participants will be invited to bring a “significant other” to the program, but this is not compulsory. Sessions 1-7 will be delivered weekly or fortnightly, and Session 8 will be delivered 6 months after the start of the program. F2F delivery will be in community settings, such as faith-based venues and community centers, aiming for 8-12 patients in each group, and remote delivery will be via a videoconferencing platform, aiming for 6-8 patients in a group (remote group sizes will be smaller than F2F to facilitate the development of a supportive group dynamic whilst using a videoconferencing platform).

The HEAL-D intervention was developed in an earlier program of research funded by the NIHR; the intervention development process and findings and evaluation of patient acceptability have been published previously [30-32,34,41-43].

Control Group

Control group participants will be referred to attend the standard NHS-commissioned DSMES course that is delivered in their local area and will be offered the choice of attending F2F or remote delivery, where both delivery methods are available. DSMES courses are a core NHS service with management guidelines recommending that all people with T2D attend a DSMES course [19], and referral is incentivized in primary care [44]. The content and structure of DSMES courses are guided by a quality framework, requiring courses to be group-based, delivering an evidence-based curriculum to support self-management skills, and be delivered by skilled, competent staff [19]. A range of courses are delivered in the NHS, typically providing 6-14 hours of group-based education and support; these courses are typically based on a standardized curriculum that does not include culturally tailored information or advice. HEAL-D has been developed to align with the quality standards for DSMES programs, but it is different from existing NHS courses in several ways. Principally, HEAL-D has been developed through a rigorous co-design process to reflect African and Caribbean cultural health beliefs and practices, providing tailored information, advice, and support through culturally sensitive resources. Furthermore, delivery is led by a combination of healthcare professionals (dietitians), culturally concordant “lay” facilitators, and exercise trainers, and the program includes participatory physical activity classes and practical cooking workshops.

In both trial arms, information on the factors that drove the choice of attendance mode will be collected. Following randomization, participants will attend their allocated DSMES program within 4 weeks, where possible, and the time from randomization to attendance will be recorded.

Data Collection Procedures

As depicted in Figure 1, data will be collected prerandomization (baseline), 6 months, 12 months (primary endpoint), and 24 months post randomization. The primary outcome, secondary and exploratory outcomes, along with their associated timepoints of administration, are listed in Table 1. The measures will be collected during an in-person assessment of approximately 2 hours duration at an NHS research or primary care clinic facility. It is intended that all measures be completed on a single day, but they may occur across a maximum 14-day window. This might include completion of questionnaires via telephone or

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video call, or primary care or home visits for anthropometric or questionnaire measures. All staff will be trained in best practices for data collection and management by the trial manager, who also monitors data quality. Outcome assessors of the primary outcome (HbA_{1c}) and other blood measurements will be blinded to treatment allocation; however, it is not possible to ensure blinding of assessors for the other outcome measures. Trial data will be recorded on a centralized web-based data collection platform (REDCap).

Multiple strategies will be implemented to maximize participant retention and completion of outcome assessments, including offering outcome assessments at different times of the day, remuneration for completion of outcome assessments (£50 [US $68] per assessment visit plus travel costs; there is no remuneration for participation in treatment sessions). Participants will be encouraged to complete outcome assessments, even if they did not attend treatment sessions or missed a previous outcome assessment. Participants will also receive brief study review contacts (via telephone or video calls) from the research team at three monthly intervals where assessment visits are not scheduled, to review ongoing willingness to continue.

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Table 1. Study measures and assessment timepoints.

Outcome measure	Timepoint			
	Baseline	6 months	12 months	24 months
Clinical variables				
Demographic information: age, sex, ethnicity, birthplace and generational status, employment status, education, marital status, socioeconomic status (index of multiple deprivation), all assessed by self-report	✓[a]			
Medical history and medications: medical history (previous or current conditions), type 2 diabetes duration, and medication history, all assessed by self-report	✓			
Primary outcome				
Glycemic control: HbA_{1c}[b] (mmol/mol); nonfasting blood sample	✓		✓	
Secondary outcomes				
Glycemic control: HbA_{1c} (mmol/mol); nonfasting blood sample	✓	✓		✓
Anthropometry and body composition				
Body weight (kg); measured without shoes and removal of heavy clothing	✓	✓	✓	✓
Body mass index (kg/m^2); calculated from weight and height, measured without shoes and removal of heavy clothing	✓	✓	✓	✓
Waist circumference (cm); measured at midpoint between lowest rib and iliac crest, over light clothing	✓	✓	✓	✓
Body fat mass (kg); measured using bioelectrical impedance analysis	✓	✓	✓	✓
Body lean mass (kg); measured using bioelectrical impedance analysis	✓	✓	✓	✓
Cardiovascular risk markers				
Total cholesterol (mol/L); nonfasting blood sample	✓	✓	✓	✓
HDL[c]-cholesterol (mmol/L); nonfasting blood sample	✓	✓	✓	✓
Systolic blood pressure (mm Hg); three seated measurements following 5 minutes rest, record the mean of the last two measures	✓	✓	✓	✓
Diastolic blood pressure (mm Hg); three seated measurements following 5 minutes rest, record the mean of the last two measures	✓	✓	✓	✓
Psychological well-being and quality of life				
EQ-5D-5L quality of life questionnaire	✓	✓	✓	✓
PAID-5[d] questionnaire	✓	✓	✓	✓
PHQ-9[e]	✓	✓	✓	✓
Diabetes knowledge and self-efficacy				
SDKI[f]	✓	✓	✓	✓
DMSES-UK[g] questionnaire	✓	✓	✓	✓
PDDC[h] questionnaire	✓	✓	✓	✓
Lifestyle behaviors				
s-IPAQ[i]	✓	✓	✓	✓
7 to 10-day arm or wrist-worn accelerometry; sleep, inactivity, step count, total physical activity, and moderate to vigorous physical activity	✓		✓	
DQQ[j]	✓	✓	✓	✓
Tertiary or exploratory outcomes				
Blood lipids				
LDL[k]-cholesterol (mmol/L); nonfasting blood sample	✓	✓	✓	✓
Triglyceride (mmol/L); nonfasting blood sample	✓	✓	✓	✓

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Outcome measure	Timepoint			
	Baseline	6 months	12 months	24 months
Body composition: body fat (kg and %); measured using bioelectrical impedance analysis	✓	✓	✓	✓
Lifestyle behaviors: self-reported sleep duration and chronotype	✓	✓	✓	✓
Medication use				
Glucose-lowering therapies use, assessed via self-reported medication history	✓	✓	✓	✓
Blood pressure-lowering therapies use, assessed via self-reported medication history	✓	✓	✓	✓
Multimorbidity status				
Diagnoses or remission or changes in severity of medical conditions, assessed via self-reported medical history	✓	✓	✓	✓
MTBQ[l]	✓	✓	✓	✓
Health economics measures				
Health service use: AD-SUS[m] adapted; self-report log of health service use	✓	✓	✓	✓
Process measures				
Intervention acceptability: quantitative evaluation questionnaire			✓	
Intervention delivery, implementation, and fidelity: session observations and checklists			✓	
Qualitative interview or workshop with participants and intervention delivery staff				

[a]Outcome is assessed at this timepoint only.
[b]HbA_{1c}: hemoglobin A_{1c}.
[c]HDL: high-density lipoprotein.
[d]PAID-5: 5-point Problem Areas In Diabetes.
[e]PHQ-9: Patient Health Questionnaire-9.
[f]SKDI: Short Diabetes Knowledge Instrument.
[g]DMSES-UK: Diabetes Management Self-Efficacy Scale-UK.
[h]PDDC: Perceived Diabetes and Dietary Competence.
[i]s-IPAQ: Short International Physical Activity Questionnaire.
[j]DQQ: Diet Quality Questionnaire.
[k]LDL: low-density lipoprotein.
[l]MTBQ: Multimorbidity Treatment Burden Questionnaire.
[m]AD-SUS: Adult-Service Use Schedule.

Primary Outcome

The primary outcome upon which the trial is powered is the difference between groups in the change in HbA_{1c} from baseline to 12 months. HbA_{1c} was chosen for several reasons: it is the principal clinical measure of diabetes status and glycemic control, and a valuable surrogate measure of holistic engagement with diabetes management and self-care; reduction of HbA_{1c} is associated with reduced risk of micro and macrovascular complications, and in some cases, all-cause mortality [45]; it is also a prominent component of the Core Outcome Measures in Effectiveness Trials initiative core outcomes set for T2D [46]. A 12-month primary endpoint has been chosen to examine the effectiveness of the HEAL-D intervention, as this is a duration long enough to observe a clinically important difference in HbA_{1c}.

Secondary and Exploratory Outcomes

At 6 and 24 months, HbA_{1c} will be measured as a secondary outcome to allow exploration of the time-course of any observed changes and impact of HEAL-D over a longer period. Other secondary outcomes (Table 1), measured at 6, 12, and 24 months, are grouped into holistic health domains and include cardiovascular risk factors, psychological well-being and self-management support, lifestyle behaviors, and health economics.

Tertiary outcomes are low-density lipoprotein-cholesterol, triglycerides, body fat percentage, changes to glucose-lowering and antihypertensive therapies (including addition, removal, or dose adjustment), and changes in MLTC status (including additional diagnoses, remission, or changes in severity).

Measurements

At baseline and all follow-up visits, unless specified otherwise, the following measurements will be conducted.

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HbA_{1c} and Blood Lipids

A 5 mL venous blood sample (nonfasting) will be taken via venepuncture according to local standardized operating procedures for measurement of HbA_{1c} and full lipid profile by the pathology department at the corresponding clinical site. Biological samples taken for the study will be destroyed once analyzed in accordance with the Human Tissue Act 2004.

Blood Pressure

Brachial arterial blood pressure will be measured in the seated position using an automated sphygmomanometer after participants have been resting for ~5 minutes. Three blood pressure measurements will be obtained, and the average of the last two measurements will be used.

Anthropometry

Body weight will be measured using digital scales, with the patient wearing light clothing (without shoes), to the nearest 0.1 kg. Height will be measured to the nearest 0.5 cm, using a stadiometer, without shoes. Waist circumference will be measured using a flexible tape, with the patient wearing only light clothing, using the WHO methodology, which defines the "waist" as the midpoint between the lowest rib and the iliac crest. The mean of three waist circumference measurements will be recorded. Body composition will be measured using Tanita DC-430-MA P bioelectrical impedance scales; body fat (%) and lean mass (kg) will be recorded.

Physical Activity

Physical activity will be measured objectively, using a wrist-worn accelerometer over 7-10 days, measuring sleep, inactivity, step count, total physical activity, and moderate to vigorous physical activity. Accelerometer use will occur at baseline and the 12-month visits only. Self-reported physical activity will be recorded using the short International Physical Activity Questionnaire, which consists of seven questions about the amount of time spent in different levels of physical activity (vigorous, moderate, and low intensity), categorizing overall physical activity levels as low, moderate, or high [47].

Patient Reported Outcome Measures

Several patient-reported outcome measures, including diabetes-specific measures, will be collected:

- QoL will be assessed using EQ-5D-5L [48] and used in the cost-effectiveness evaluation.
- Diabetes-related distress will be assessed using the 5-point Problem Areas in Diabetes (PAID-5) questionnaire [49]; PAID-5 is widely used in diabetes trials as an indicator of diabetes-specific QoL.
- Depressive symptoms will be assessed using the Patient Health Questionnaire-9 (PHQ-9) [50]; PHQ-9 is used widely, including in the NHS, to assess symptoms of depression.
- Diabetes knowledge will be assessed using the Short Diabetes Knowledge Instrument (SDKI) [51].
- Diabetes self-efficacy will be assessed using the Diabetes Management Self-Efficacy Scale [52].
- Diabetes dietary competence will be assessed using the Perceived Diabetes and Dietary Competence (PDDC) [53].
- Multimorbidity treatment burden will be assessed using the Multimorbidity Treatment Burden Questionnaire [54].
- The Diet Quality Questionnaire will be used to assess dietary adequacy, providing a measure of diet diversity and protection against noncommunicable diseases [55].
- Health service resource utilization will be assessed using an adapted Adult Service Use Schedule [56] and will be used to inform the health economic evaluation.
- Self-reported sleep duration and chronotype will each be assessed using an individual question adapted from the Morningness-Eveningness Questionnaire [57].

The EQ-5D-5L, PAID-5, PHQ-9, SDKI, DSMES-UK, and PDDC have evidenced reliability and validity for use in people with T2D [48-53]; none of the questionnaires have been validated specifically in populations of African and Caribbean heritage, although the SDKI and PDDC have been used in studies with African-American populations. The questionnaires will be interviewer-led or self-completed, depending on participant preference or literacy.

Internal Feasibility Assessment

A feasibility assessment will be conducted in the first 6 months of the trial to establish the feasibility of completing the trial within desired timelines, focused on (1) identification of eligible participants, (2) consent and randomization of eligible participants, and (3) engagement with treatment allocation of randomized participants. Recruitment and intervention engagement data will be reviewed by the Trial Steering Committee (TSC) with predefined "stop/go" criteria to determine progression to full trial.

Health Economic Evaluation

The primary aim of the health economic evaluation will be to assess the within-trial incremental cost-effectiveness of both remote and F2F versions of HEAL-D compared to standard DSMES programs. This will be undertaken through a cost-utility analysis with participant outcomes measured in quality-adjusted life years (QALYs) gained. Secondary aims include: (1) whether within-trial cost-effectiveness conclusions are affected by a consideration of long-term cost and QALY outcomes extrapolated from observed clinical end points within the clinical trial, and (2) whether the program is likely to be cost-effective when delivered at scale in routine practice, accounting for costs of implementation, such as facilitator training, and expected population reach or engagement levels.

Inferences regarding the cost-effectiveness of HEAL-D will be made with reference to the incremental cost-effectiveness ratio, applying varying cost-effectiveness thresholds (inclusive of those adopted by The National Institute for Health and Care Excellence) for identifying whether new health programs offer the NHS sufficient value for money [58]. The resource and cost implications of HEAL-D will be evaluated from an NHS or Personal Social Services perspective. All analyses will be undertaken probabilistically to reflect uncertainty in key economic and clinical parameters of relevance.

The short-term costs and benefits of HEAL-D will be quantified using data collected over the trial period, including resource inputs allocated to program delivery and implementation (eg,

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training activity), wider service utilization among trial participants over follow-up (using the self-report Adult Service Use Schedule), and short-term health-related QoL outcomes (based on the EQ-5D-5L instrument). For secondary analysis, long-term resource and QALY impacts will be estimated using the UKPDS Outcomes model [59]. The UKPDS is a microsimulation modeling tool that can be applied to make extrapolations regarding the incidence of complications (micro and macrovascular) and associated costs, QoL, and survival trajectories.

In further secondary analysis, we will draw on data and evidence from the main evaluation of program cost-effectiveness to assess whether it would be cost-effective to deliver alternative versions of HEAL-D at scale within routine service settings within a defined locality and population (South London). We will use existing frameworks and toolkits [60,61] to estimate the potential costs of implementation at scale and will evaluate the cost-effectiveness of scale-up, allowing for implementation costs and population engagement or reach.

Mixed Methods Process Evaluation

An embedded mixed methods process evaluation, combining relevant data gathered within the trial (questionnaires, monitoring data), qualitative interview data, logbook entries, workshops, and observations, will provide a formative evaluation of the intervention's implementation, mechanisms of action, and identification of the contextual factors that influence its implementation and adoption. Implementation will encompass: fidelity (whether training and the intervention sessions were delivered as intended, whether healthcare professionals delivered culturally sensitive behavior change support, and any observed barriers to this), intervention dose (ie, attendance and completion rates), and reach (whether the intended audience encounters the intervention, and how). Mechanisms of action will encompass: satisfaction (with the program), participant and facilitator experience of the intervention, and effective and less effective components of the intervention in engaging participants and producing desired results (eg, increasing physical activity) and potential reasons. The identification of contextual factors that influence the implementation and adoption of HEAL-D includes implications for workforce capacity and for intervention integration within existing care.

Participants who are randomized to the HEAL-D intervention arm and staff involved in HEAL-D delivery will be eligible to participate in the process evaluation. We aim to recruit a total of 48 participants (16 per center) based on sampling for diversity in relation to high versus low intervention engagement, F2F versus remote attendance, and MLTC versus non-MLTC status. Maximum variation in sampling of participants will be guided by age, gender, employment status, and ethnicity (Black African or Black Caribbean). The characteristics of the sample will be continually reviewed to achieve balanced representation, inviting consecutive participants until the target sample and data saturation have been achieved. We aim to recruit up to 27 staff (9 per center), including delivery staff and trainers. Staff must meet the following criteria to participate: clinical and nonclinical staff working at or in partnership with centers participating in the HEAL-D trial, aged 18 years or older, and able to give written informed consent.

Data for the process evaluation will be collected via several means. First, both the training of HEAL-D facilitators and the delivery of HEAL-D sessions by facilitators will be observed. A self-report questionnaire, completed at the 12-month visit, will be used to assess the acceptability of trial procedures by participants. Participants will also be invited to undertake a semistructured interview within 1 month after the 12-month visit. These interviews will be conducted by telephone and provide an open and flexible method for exploring individual experiences in-depth. Participants and staff will also be invited to attend a F2F workshop to explore HEAL-D implementation.

SWAP

The SWAP aims to explore uptake of and engagement with HEAL-D in adults with T2D who also have MLTC, and has the following objectives: (1) to assess the prevalence of MLTC in adults of Black African or Black Caribbean ethnicity participating in the HEAL-D trial and identify and describe common MLTC clusters; (2) to assess the impact of MLTC on uptake, engagement with, and completion of HEAL-D; (3) to assess the impact of the HEAL-D intervention on associated MLTC; and (4) to codevelop dissemination outputs in a workshop with a patient and public involvement and engagement (PPIE) group and other relevant stakeholders, ensuring strong representation of those with MLTC. The SWAP will be conducted in two phases: quantitative data collection, to address objective 1, and qualitative data collection to address objectives 2-4. All participants will be eligible for the SWAP and have quantitative data collected (eg, prevalence and details of MTLC); only participants randomized to the intervention arm will be eligible to participate in the qualitative data phase (ie, semistructured interviews and workshops).

All study participants will complete a questionnaire to elicit background information on the long-term conditions they experience (with MLTC defined as per Guthrie et al [62]). The extent to which these conditions affect their day-to-day living will be assessed using the Multimorbidity Treatment Burden Questionnaire. This questionnaire will be analyzed together with participant demographic data and baseline exercise capacity, QoL, and psychological assessments. A subsample of participants who are randomized to the HEAL-D arm will undertake an interview focusing on: experience of T2D, experience of MLTC, uptake of and engagement with the HEAL-D intervention (both F2F and remote attendance), trial experience, trial completion, and interaction between MLTC and intervention. These interviews will be embedded in the process evaluation and account for 16/48 of the participant interviews. Qualitative data will also be obtained within the three main process evaluation workshops, where additional needs of people with MLTC, the burden of MLTC, and barriers and facilitators to acceptance of HEAL-D will be discussed. For the SWAP, there will also be two additional workshops to deliberate on whether the intervention could be optimized for MLTC and what lessons can be shared with other stakeholders going forward.

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Sample Size Calculation

The trial is based on a minimal clinically important difference in HbA_{1c} of 5 mmol/mol, leading to significant risk reductions for T2D complications [19]. Power was calculated at 90%, with a 5% 2-sided significance level, to detect a standardized effect size of 0.45 (difference in HbA_{1c} of 5 and SD of 11 mmol/mol, determined from the feasibility trial [34] and unpublished primary care data from South London). To allow for correlation of outcomes among group attendees, the sample size, assuming no correlation (103 per arm), is inflated by a design effect (1.09) and then rounded up to ensure divisibility by group size. The F2F intervention is to be delivered in groups of up to 12, while the remote intervention will be delivered in groups of up to 8; for the calculations, an average group size of 10 is assumed. Given the objective outcome, the short duration of treatment, patterns observed in the intracluster correlation coefficient for cluster randomized trials suggest an intracluster correlation coefficient of 0.01 [63]. In the previous feasibility trial, loss to follow-up was 7% at 6 months. Given the pragmatic design, whereby participants are given free choice as to their mode of attendance (F2F or remote) in both the intervention and comparator arms, we do not expect substantial differences in retention between arms. However, with a longer primary outcome follow-up of 12 months, loss to follow-up is estimated to be higher at 15%. For the intervention arm, this is accounted for by increasing the number of clusters. Therefore, we will recruit 150 participants in the control arm and 150 participants in the intervention arm, each across 15 groups of average size 10.

Statistical Analysis

Primary analysis of change in HbA_{1c} at 12 months will be conducted using a mixed effects model with a random effect for the group attended; individuals in the control arm will be treated as groups of size 1 [64]. Treatment arm, center, and baseline HbA_{1c} will be included as fixed effects. The primary analysis will be repeated to include an interaction term between treatment and mode of delivery (F2F or remote) to explore any differential treatment effect among groups. The presence of an interaction will be tested using a likelihood ratio test. The prespecified subgroup analyses of the primary outcome will assess whether the effectiveness of the intervention is dependent on baseline HbA_{1c} or center. This will be assessed by adding interaction terms between group allocation and the potential effect modifiers to the linear regression, one at a time. The analysis exploring the change in treatment effect over time for the secondary outcomes will follow the methodology of the primary analysis, with an additional random effect for the individual to account for within-individual correlation over time, a fixed effect for time, and an interaction between treatment and time effect. Mediation analysis will be conducted using multilevel structural equation modeling [65]. To account for missing data, multiple imputation will be undertaken, provided we have strong predictors of missingness and an appropriate imputation model. Diagnostic checks will be performed to assess this. The missing data mechanism will be assumed to be missing at random. Individual analyses on each imputed dataset will be combined using the Rubin rules. Sensitivity analyses will be conducted to assess the robustness of the primary conclusions to the imputation strategy used.

For data collected during the mixed methods process evaluation, deductive and inductive thematic analysis of interviews, workshops, logs, and observations, using NVivo (QSR International) Framework, will be followed by triangulation of qualitative and quantitative data using a meta-matrix [66]. We will examine divergence and similarity across study groups (eg, remote vs F2F, by center), and within the triangulated data to develop a comprehensive understanding of intervention delivery and fidelity, recruitment and engagement, and mechanisms of impact. Thematic analysis [67] will be undertaken with the interview transcripts, informed by the Theoretical Domains Framework and the COM-B framework, toward identifying barriers and facilitators for engagement and maintenance of behavior change [63]. For the thematic analysis, using NVivo software, two researchers will independently double-code 10% of randomly selected transcripts to develop a coding framework. Further transcripts will be double-coded one by one until interrater reliability is such that the framework is agreed upon. Remaining transcripts will then be single-coded (ie, by one of the two researchers). Themes will be developed through discussion with the wider team. To indicate the frequency with which themes occur, we will use “all” (100%), “almost all” (>85%), “most” (>75%), “the majority” (>50%), “some” (>10%), and “a few” (≥10%). We will use the Consolidated Criteria for Reporting Qualitative Research tool [68]. The health economic evaluation analysis has been described in the relevant section.

Safety Reporting

As the trial is not a clinical trial of an investigational medicinal product, monitoring of pharmacovigilance is not relevant. Adverse events will be recorded and discussed periodically with the TSC as required. Any safety concerns that arise as a result will be reported to the sponsor as soon as possible. Serious adverse events (SAEs) will be reported to the sponsor within 24 hours of becoming aware of the event. The principal investigator or another delegated physician (as agreed by the sponsor) will be responsible for the review and sign-off of the SAE and the assessment of causality (ie, whether an event is related to a study procedure or intervention). Events will be followed up on until the event has been resolved or a final outcome has been reached. In addition to the expedited reporting above, the chief investigator (CI) shall submit, once a year throughout the study or on request, an Annual Report to the Ethics Committee, which lists all SAEs.

Posttrial Care

Provisions will be put in place for posttrial access for all participants who still need an intervention identified as individually beneficial in the trial. This includes referral to local providers of physical activity services and psychosocial support (ie, primary care services).

Ethical Considerations

The trial has been approved by the Health Research Authority (IRAS ID: 326064) and East Midlands—Leicester South Research Ethics Committee (REC reference: 24/EM/0079). The

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trial will be conducted in full conformity with the current revision of the Declaration of Helsinki (last amended October 2000, with additional footnotes added 2002 and 2004), the UK Policy Framework for Health and Social Care Research (2017), and International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice relevant regulations. Potential participants who express an interest in participating in the trial will be provided with an information video or leaflet providing full details of the trial and what is entailed. Participants will be given an opportunity to discuss participation with a trial coordinator. Those who decide to participate will be required to provide written informed consent prior to the collection of research data; consent will be collected by trained research staff at the baseline assessment visit. Participant data will be pseudonymized and treated in confidence and in compliance with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use Good Clinical Practice, the UK Policy Framework for Health and Social Care, and the UK General Data Protection Regulation. All investigators and trial site staff will comply with the requirements of the Data Protection Act or General Data Protection Regulation with regard to the collection, storage, processing, and disclosure of personal information and will uphold the Act's core principles. The CI will have access to the trial documentation and will be the data custodian. Participants will receive £50 (US $68) for each of the assessment visits they attend in compensation for their time commitment and will have their travel costs reimbursed. Individuals who participate in an interview for the process evaluation will receive £20 (US $27) to compensate for their time. Participants will not receive financial reimbursement for attending their allocated treatment.

Study Oversight and Monitoring

This trial is sponsored by The University of Leicester, United Kingdom (reference: 0928). The University of Leicester operates a risk-based monitoring and audit program, to which this study will be subject. The Pragmatic Clinical Trials Unit, Queen Mary University of London, United Kingdom, will provide support regarding data management, statistical analysis, and quality assurance. A TSC, consisting of an independent statistician, health economist, person of Black African and Black Caribbean ethnicity with lived experience of T2D, and other independent subject specialists, has been formed and will offer independent strategic oversight throughout the trial. In line with the European Medicines Agency Guideline on data monitoring committees [69], the sponsor determined that a Data Monitoring and Ethics Committee is not required for the trial.

Protocol Amendments

Amendments will be submitted to the sponsor in the first instance for review and approval. The CI, in agreement with the sponsor, will then submit information to the appropriate body (HRA or REC) for approval. Any amendments will also be approved by the trial funder and communicated to the trial registry.

Results

The trial, funded by the NIHR, will run for 48 months in total (August 1, 2023, to July 31, 2027). Site "green light" was received on August 15, 2024, for London; November 29, 2024, for Manchester; and January 31, 2025, in the West Midlands. Recruitment commenced in August 2024 and is due to run over 11 months. As of March 26, 2025, a total of 76 participants have consented, and 72 participants have been randomized. The "last patient, last visit" is expected in June 2027; primary data analysis is expected to begin in July 2027. Final results are anticipated to be available in September 2027, and publication is expected by the end of 2027.

Discussion

Overview

The HEAL-D trial will evaluate if a culturally tailored DSMES program, provided in person or remotely, via videoconferencing, is clinically and cost-effective, in comparison with standard DSMES programs, at improving glycemic control (HbA_{1c}) at 12-month follow-up in adults of Black African and Black Caribbean ethnicity living with T2D. It is hypothesized that the provision of a DSMES program that is sensitive to the cultural health beliefs and practices of adults of African and Caribbean heritage will promote clinically meaningful improvements in T2D self-management.

Principal Findings

Principally, the trial is designed to evaluate the effectiveness of the HEAL-D intervention, compared to standard DSMES programs, on glycemic control at 12 months. In addition, a range of important clinical and patient-reported outcome measures, including cardiovascular risk factors, psychological well-being and QoL, T2D knowledge and self-efficacy, and diet and physical activity behaviors, will be collected at 6, 12, and 24 months. Importantly, the 24-month endpoint will enable assessment of the longer-term impact of the intervention on the clinical and patient-reported outcomes.

Comparison to Prior Work

To date, in the United Kingdom, there have been no trial evaluations of culturally tailored DSMES programs for T2D self-management in adults of Black African and Black Caribbean ethnicity [29,70]. However, previous trials in the United States have demonstrated significant reductions in HbA_{1c}, as well as improvements in T2D knowledge, which were associated with HbA_{1c} improvements [29].

Strengths and Limitations

The HEAL-D trial builds on a large program of co-design research, which engaged a wide range of stakeholders (people of Black African and Black Caribbean ethnicity living with T2D, healthcare practitioners and commissioners, and community leaders) in the development of the intervention to ensure its relevance to both patients and healthcare service providers [29-33]. Furthermore, the acceptability of the HEAL-D intervention has been rigorously evaluated, and the feasibility of conducting a randomized controlled trial was assessed in

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earlier work [34,41-43,71,72]; the design of this trial has been informed by those evaluations, reflecting the main findings. People with lived experience of T2D continue to inform the delivery of the trial, as well as future dissemination, through involvement in the trial PPIE stakeholder group.

Future Directions

A key concern in clinical practice is the accessibility of educational programs for the population in question. The development of both F2F and remote delivery formats hopefully maximizes the potential for pragmatic use in healthcare, whilst the availability of digital delivery may be particularly beneficial for ethnic minority groups [23]. For example, remote programs can reach those who are unable to attend F2F sessions [73] and can bring together individuals from areas with low population densities of a given ethnic group [23]. Digital interventions may also be more cost-effective, as spotlighted during the COVID-19 pandemic [74]. Furthermore, ongoing PPIE during the development of the HEAL-D intervention has enabled the production of a program and related materials that patients have found both engaging and accessible, as described previously [30-32]. By incorporating assessments of effectiveness, cost-effectiveness, a thorough process evaluation, and SWAP into the trial design, it is ensured that the needs of all stakeholders continue to be accounted for, thus promoting the feasibility of implementing the HEAL-D program within healthcare services.

Dissemination Policy

The trial results will be disseminated via diverse and targeted means. All participants will receive a written plain-language summary of the results of the trial. A PPIE community engagement plan will be developed with our PPIE group, with plans for engagement and dissemination activities using a combination of platforms such as social media or website, radio, and written information via newspapers relevant to Black African and Black Caribbean communities, to ensure communication about the study reaches them. Ongoing review and revision of our dissemination strategy will be undertaken throughout the program, in partnership with PPIE partners, to maximize impact and ensure relevance and accessibility to a wide range of groups.

The trial results will be published in open-access medical journals and at conferences, with the intention of reaching a global audience. The outcome of this multicenter randomized controlled trial has the capacity to change practice and may be implemented in other English-speaking countries with minimal adaptation. It is anticipated that the findings of this study will be incorporated into national and international guidelines. Authorship will be determined in line with the International Committee of Medical Journal Editors guidelines.

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Data Availability

The data that support the findings of this trial will be available from the corresponding author upon reasonable request.

Authors' Contributions

LMG, PB, JD, TH, AH, EH, HJ, TK, C Rivas, C Robinson, JT, ST, MU, and BM conceived and designed the study; DAJ and LMG wrote the manuscript; all authors reviewed the final manuscript.

Conflicts of Interest

BM received a research grant from Novo Nordisk and honoraria as a consultant or speaker for Lilly, Novo Nordisk, Pfizer, Johnson & Johnson, and AstraZeneca. BM is a shareholder of Reset Health.

Multimedia Appendix 1
CONSORT EHEALTH checklist.
[PDF File (Adobe PDF File), 1314 KB - resprot_v14i1e71861_app1.pdf]

Multimedia Appendix 2
Funder peer review reports.
[PDF File (Adobe PDF File), 147 KB - resprot_v14i1e71861_app2.pdf]

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Abbreviations

CI: chief investigator
DSMES: diabetes self-management education and support
F2F: face-to-face
HbA_{1c}: glycated hemoglobin
HEAL-D: Healthy Eating and Active Lifestyles for Diabetes
MLTC: multiple long-term conditions
NHS: National Health Service
NIHR: National Institute for Health and Care Research
PAID-5: 5-point Problem Areas in Diabetes
PDDC: Perceived Diabetes and Dietary Competence
PHQ-9: Patient Health Questionnaire-9
PPIE: patient and public involvement and engagement
QALY: quality-adjusted life year
QoL: quality of life
REDCap: Research Electronic Data Capture
SAE: serious adverse event
SDKI: Short Diabetes Knowledge Instrument
SWAP: study within a project
T2D: type 2 diabetes
TSC: Trial Steering Committee
WHO: World Health Organization

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Protocol

The Effectiveness of the Use of Silver Fluoride and Teledentistry to Manage and Prevent Childhood Caries Among Aboriginal Children in Remote Communities: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: Australian Aboriginal children experience dental decay at more than twice the rate of non-Aboriginal children. The Select Committee into the Provision of and Access to Dental Services in Australia noted that the rate of potentially preventable hospitalizations was the highest among children aged between 5 and 9 years and was higher among Indigenous Australians and those living in remote locations. The application of a silver fluoride (AgF) solution to decayed surfaces has been shown to be effective in stopping the decay process and reducing the occurrence of new decay but has been tested to a limited extent in the Australian context.

Objective: This study aims to evaluate the feasibility of using the skills of an Aboriginal health practitioner to undertake the application of AgF to carious primary molars to arrest the caries progression and prevent the occurrence of new caries among young Aboriginal children in remote communities.

Methods: This study is a cluster-randomized controlled trial with communities randomized and stratified based on caries level and water fluoridation status. The trial will recruit 640 children (aged between 6 months and 7 years) from 30 communities. Informed consent will be obtained. At baseline, each child in the intervention group will be examined by a calibrated examiner and subsequently by an oral health practitioner who will prescribe to an Aboriginal health practitioner the teeth to be treated with AgF. A formulation with 38% AgF will be applied for 1 minute (0.004 mL per tooth). The control group will be provided with standard minimally invasive care. Participants will be followed annually for 2 years to assess caries arrest and prevention by blinded calibrated examiners. Child oral health–related quality of life and dental anxiety will be elicited through validated

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questionnaires. Tests of proportions will be used to evaluate the proportion of lesions arrested and the proportion of surfaces at risk that decayed over the follow-up. Multiple logistic regression with appropriate control for clustering of teeth and communities will be used to evaluate caries arrest, controlling for potential confounding factors.

Results: Community engagement has commenced, and data collection protocols have been prepared. Staff specific to the study (eg, Aboriginal health practitioners or workers) are in the process of recruitment. Participant recruitment will commence in March 2026 and conclude in December 2026. Study outcomes will be reported at 12- and 24-month follow-ups.

Conclusions: This study will test the effectiveness and feasibility of a non-oral health professional applying AgF to achieve caries arrest and prevention and validate clinical findings against digital imagery acquired on site. This pragmatic study will inform the development of suitable and accessible models of care for dental service provision in rural and remote communities in Australia.

Trial Registration: Australian New Zealand Clinical Trials Registry (ANZCTR) ACTRN12624000457549p; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=387518&isReview=true

International Registered Report Identifier (IRRID): PRR1-10.2196/72227

(JMIR Res Protoc 2025;14:e72227) doi:10.2196/72227

KEYWORDS

caries prevention; early childhood caries; Indigenous oral health; minimally invasive dentistry; silver fluoride

Introduction

Background and Rationale

The interim report of the Select Committee into the Provision of and Access to Dental Services in Australia noted that the rate of potentially preventable hospitalizations was the highest among children aged between 5 and 9 years and was higher among Indigenous Australians and those living in remote locations [1]. The higher tooth decay experience of Australian Aboriginal children, in which the majority of the disease remains untreated [2], is believed, partly, to be due to unfavorable visiting patterns to dental care providers, associated with poor accessibility, cost, and the lack of cultural awareness by service providers [3,4]. Australian Aboriginal children experience dental decay at more than twice the rate of non-Aboriginal children. The current models of service delivery are failing to meet the needs, and most decayed teeth remain untreated. The management of dental decay in young children is challenging, and it is commonly undertaken under hospital-based dental general anesthesia.

A recently completed clinical randomized controlled trial (RCT) successfully managed dental treatment of children recommended for dental general anesthesia using minimally invasive dental treatment approaches in a primary care setting (atraumatic restorative treatment [ART] and Hall technique [HT]) [5]. An RCT in remote Aboriginal communities in Western Australia demonstrated improved access to culturally appropriate care with a greater level of dental care provided, with a reduction in the occurrence of new dental decay among preschool-aged children using the ART and HT approach [6]. Although the ART and HT approach improved access to care, it still required an oral health professional team to visit the remote communities and deliver the services. This limits access to services only when the clinical team is in the community and increases the costs of service delivery. The application of a silver fluoride (AgF) solution to decayed surfaces has been shown to be effective in stopping the decay process and reducing the occurrence of new decay but has been tested to a limited extent in the Australian context. The application of the AgF solution is simple, quick, painless, and noninvasive and could be undertaken by an appropriately trained non-oral health professional. A major disadvantage of the use of AgF is the staining of the treated lesion with a dark brown or black color. However, the additional application of potassium iodide (KI) immediately after the application of AgF has been promoted to reduce the staining effects [7,8].

The application of teledentistry and telediagnosis may also offer opportunities to improve service delivery in remote settings by using telecommunication technology to provide oral health care over a distance and diagnoses based on information collected via smartphone technology [9]. Systematic reviews have suggested that diagnostic accuracy in using photographic images for oral diagnosis is comparable to that of traditional clinical examination, and its use may offer opportunities to improve equity and efficiency in service provision in low-income and challenging access settings [10,11].

Objectives

The principal aim of the proposed study is to evaluate the feasibility of using the skills of an appropriately trained Aboriginal health practitioner or worker to undertake the application of AgF to carious primary molars of young Aboriginal children in remote communities and evaluate the effectiveness and acceptability of AgF, using a 2-arm cluster RCT. It will also validate the use of teledentistry to diagnose and prescribe treatment remotely. The outcomes will be compared with those of the alternative care model using the recently tested ART and HT approach, delivered by an oral health professional team, for clinical outcomes, cost-effectiveness, cost utility, child oral health–related quality of life (COHRQoL), and child dental anxiety. The objectives of the project are as follows:

The first objective is to measure the number of teeth and tooth surfaces with arrested carious lesions and restored at baseline and follow-up. The hypothesis is that *the number of arrested*

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carious lesions will be greater in the intervention group at follow-up.

The second objective is to measure the number of teeth and tooth surfaces with dental decay and new decay and the number of teeth with dental infections among study participants at baseline and follow-up. The hypothesis is that *the number of children with newly active decay in their teeth and tooth surfaces and new dental infections in the intervention group will not be greater than the specified difference (risk difference) deemed to be a noninferior outcome.*

The third objective is to measure the extent of discoloration in teeth treated with AgF, with or without KI. The hypothesis is that *the extent of discoloration will be less in the intervention group treated with AgF and KI.*

The fourth objective is to measure the change in COHRQoL and dental anxiety using validated measures. The hypothesis is that *the extent and number of children with improved COHRQoL and dental anxiety in the intervention group will not be any less than the specified difference (risk difference) deemed to be noninferior.*

The fifth objective is to evaluate the cost-effectiveness and cost utility of the interventions. The hypothesis is that *the intervention will be less costly with a noninferior outcome.*

The sixth objective is to evaluate the acceptability of the interventions between the 2 groups of participants through focus group interviews using the "yarning" approach [12].

The seventh objective is to evaluate the reliability and validity of diagnosis and treatment prescription using teledentistry. The hypothesis is that the *sensitivity and specificity will be within the published limits for visual assessment of caries*, that is, 0.86 (95% CI 0.80-0.90) and 0.77 (95% CI 0.72-0.82), respectively.

Methods

Trial Design

This study will use a robust, pragmatic, 2-arm parallel group cluster randomized, active-controlled, noninferiority trial design. This study will be reported according to the CONSORT (Consolidated Standards of Reporting Trials) guidelines on reporting of noninferiority trials [13]. Study communities will be randomized into test or control groups by a central study coordinator through a computer-generated block randomization procedure, stratified by expected decay experience and exposure to community water fluoridation levels based on findings from our earlier work in the Kimberley region [6]. Both arms of the study will be provided with dental care; the control arm will be treated using the ART and HT approach, and the test arm will be treated using AgF. The test group will be further randomized into 2 groups via computer-generated allocation in concealed envelopes at study sites to receive 1 of the 2 AgF formulations. One formulation will have 38% AgF and KI as a staining reducing agent (Riva Star Aqua; SDI Limited); the other formulation will have 40% AgF with stannous fluoride as a reducing agent (Creighton Dental AgF; Whiteley Corporation). The Riva Star Aqua group will be further randomized to receive KI or no KI to evaluate KI's effect on reducing the staining associated with AgF and evaluate its impact on caries arrestment. Moreover, we will evaluate the COHRQoL [14] and child dental anxiety and undertake an economic evaluation of the interventions. Focus group interviews, using the yarning approach, will be conducted to better understand the impact of the dental treatments [12]. We will also test the effectiveness of teledentistry in caries diagnosis and treatment prescription. Participants will have digital images taken of their dentition with a smartphone using standardized procedures [15]. The images will be stored and sent securely to a calibrated assessor at a remote site. The assessor, blinded to group allocation, will evaluate the images and diagnose and prescribe treatment.

Study Setting

The interventions will be undertaken in remote community settings using mobile portable equipment in the Kimberley region of Western Australia. Because of the small population in the participating communities and to ensure confidentiality of participant information, the list of study sites will not be made available. The communities selected for inclusion in the study generally do not have ready access to dental care and may have to travel long distances by road to obtain care because care providers are not usually available in the community.

Eligibility Criteria

Communities that participated in an earlier study will be invited to participate via community consultations with the community chair and community council [6]. Children aged between 6 months and 7 years, with or without dental caries, will be eligible. Children with complex medical conditions or developmental syndromes requiring specialist care or those with a need for urgent dental care will be excluded (those requiring urgent care will be referred to their local service provider).

Ethical Considerations

This study received ethics approval from the Western Australia Aboriginal Health Ethics Committee (1348) and the University of Western Australia Human Research Ethics Office (2024/ET000760). A 2-stage consent process will be used. First, informed community consent will be obtained from the community to participate in the study. After community consent, individual signed informed consent will be obtained. The research team's Aboriginal research assistant will assist parents and guardians by explaining the study to those whose first language is not English. Each participating parent and carer will be provided with a local community store voucher worth Aus $50 (US $32) as compensation for their time. Confidentiality of participant information will be protected by storing information on password-protected computers that are locked in offices accessible only to research personnel. Analysis will be undertaken on deidentified data.

Interventions

Explanation for the Choice of Comparators

The primary comparison group is composed of the children who were provided with the minimally invasive treatment approaches, encompassing the ART [16] and the HT stainless steel crowns [17]. The ART and HT approach has been tested in remote communities and has been found to be an effective

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and feasible approach to delivering dental care in remote communities [6,18]. The secondary comparison is that of teeth treated with AgF with or without KI to evaluate the stain-reducing potential of KI.

Intervention Description

Children allocated to the test group will be provided with AgF, either Riva Star Aqua (38% AgF and KI) or Creighton Dental AgF (40% AgF and stannous fluoride). Only the primary molars will be included. The AgF will be applied by an Aboriginal health practitioner or worker who has been trained in the application of fluoride agents. The agents will be applied once only, after baseline assessment, and repeated at the 12- and 24-month follow-ups. All other treatments required beyond AgF application will be managed by the oral health practitioner team. Interventions for Riva Star Aqua and the Creighton AgF are outlined in Textbox 1.

Textbox 1. Interventions for Riva Star Aqua and the Creighton silver fluoride (AgF).

For Riva Star Aqua

1. Remove food debris and plaque by brushing with a toothbrush (no toothpaste).
2. Isolate teeth to be treated with cotton rolls and gauze and apply petroleum jelly to the gingiva and lips.
3. Dry the affected tooth surfaces and at-risk tooth surfaces to be treated with cotton pledgets.
4. Dispense 0.05 mL AgF; bend the microbrush applicator and dip the tip of the applicator into the agent.
5. Apply the agent with the microbrush onto the decayed surface and rub gently, maintaining contact with the tooth for 60 seconds; apply the agent also to at-risk, non-decayed surfaces for 60 seconds and remove excess from all surfaces with cotton pledgets.
6. For tooth surfaces assigned to receive potassium iodide (KI), dispense 0.1 mL KI; using a new microbrush, dip the brush tip into the agent and apply to the decayed surface until precipitate forms. Then, reapply the agent until no precipitate forms, with 5- to 10-second intervals between reapplications.
7. Place Orabase adhesive (Colgate Oral Pharmaceuticals, Inc) onto AgF-treated decayed surfaces, with or without KI.
8. Advise participant to refrain from eating or drinking for 30 minutes after treatment.

For Creighton Dental AgF

1. Remove food debris and plaque by brushing with a toothbrush (no toothpaste).
2. Isolate teeth to be treated with cotton rolls and gauze and apply petroleum jelly to the gingiva and lips.
3. Dry affected tooth surfaces and at-risk tooth surfaces to be treated with cotton pledgets.
4. Dispense 0.05 mL AgF; bend the microbrush applicator and dip the tip of the applicator into the agent.
5. Apply the agent with the microbrush onto the decayed surface and rub gently, maintaining contact with the tooth for 60 seconds. Apply the agent also to at-risk, nondecayed surfaces for 60 seconds and remove excess from all surfaces with cotton pledgets.
6. Dispense 0.05 mL stannous fluoride. Using a new microbrush, dip the microbrush tip into the stannous fluoride solution and apply it to the decay-treated tooth surfaces.
7. Place Orabase adhesive onto treated decayed surfaces.
8. Advise participant to refrain from eating or drinking for 30 minutes after treatment.

Children allocated to the control group will be provided treatment by the oral health practitioner team (dental therapist and dental clinic assistant). Teeth to be restored using the ART approach will have the decayed tooth surfaces prepared using hand instruments only for caries removal without local anesthesia and teeth restored with a glass ionomer cement. Teeth restored using the HT will have the tooth surface cleaned, but caries will not be removed. The tooth will then be restored with a stainless-steel crown, cemented with a glass ionomer cement. The treating clinician will determine the type of restoration to provide for each control participant.

All the children will be reviewed at 12 and 24 months, and AgF treatments will be reapplied.

Criteria for Discontinuing or Modifying Allocated Interventions

Participants allocated to the test arm (AgF treatment) who request restorative care as per the control arm (ART and HT treatment) will be provided with the requested care. Similarly, control participants who request the test intervention will be provided with the test intervention. The reasons for the request will be noted. All participants will be analyzed on an intention-to-treat and per-protocol basis.

Strategies to Improve Adherence to Interventions

All participants will be provided with information and guidance on oral health care procedures. No specific actions are required from the participants beyond oral hygiene measures to maintain oral health.

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Relevant Concomitant Care Permitted or Prohibited During the Trial

All participants will be able to access and receive regular dental care from their usual dental care provider. Information regarding treatment received during the follow-up interval will be sought from participants at each follow-up.

Provisions for Posttrial Care

All participants will be provided with contact details of the researchers to report any adverse events that may arise after the intervention.

Outcomes

The primary outcome of interest is the number of treated decayed teeth at baseline that became arrested at each follow-up period and the number of sound surfaces treated at baseline that became carious at follow-ups, measured by the count of decayed, missing, and filled tooth surfaces. Secondary outcomes will be changes in COHRQoL and child dental anxiety (Table 1).

Table 1. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) participant timeline.

SPIRIT participant timeline	Enrollment	Allocation	After allocation			Closeout
	–T1[a]		Baseline	12 mo	24 mo	
Enrollment						
Community consent	✓					
Individual informed consent	✓					
List other procedures	✓					
Allocation		✓				
Interventions						
AgF[b]			✓	✓	✓	
AgF and KI[c]			✓	✓	✓	
Assessments						
List baseline variables			✓[d,e,f]	✓[d,e,f]	✓[d,e,f]	
List outcome variables	✓	✓	✓[d,e,f]	✓[d,e,f]	✓[d,e,f]	
List other data variables				✓[g]		

[a]T1: enrollment.
[b]AgF: silver fluoride.
[c]KI: potassium iodide.
[d]DMFS: decayed, missing, and filled tooth surfaces.
[e]COHRQoL: child oral health–related quality of life.
[f]Dental anxiety.
[g]Focus group.

Sample Size

We used the *power* command within Stata (version 15; StataCorp) and data on decay incidence, restorative outcomes, and COHRQoL impacts from the recently completed Kimberley study [6] to estimate the noninferiority sample size. Approximately 61% of the ART restorations were classified as successful (lesion arrestment), and 81% were estimated to be arrested with AgF treatment from published studies [19]; community intracluster correlation was 0.09. Using these parameters at 80% power and an α of .05 and with 30 clusters available (n=15, 50% clusters per treatment arm), the estimated sample size required was 180 in each arm. Allowing for a 25% loss to follow-up each year, the estimated sample size is 320 per arm or 22 children per cluster (rounded up). The sample size will also have 84% power to undertake subgroup analyses to detect a 20% difference in caries arrestment between carious lesions treated with AgF and KI or without KI. A sample size of 40 for the focus group interviews is expected to be sufficient to allow for the elicitation of parent perceptions about the care provided based on our earlier work [20,21].

Recruitment

Strategies used in the recently (successfully) completed study in the Kimberley region will be adopted, with further community engagement undertaken to refine and develop the research protocol with the community leaders. Participant recruitment will commence after obtaining community consent to participate. Participant recruitment and retention strategies will include (but not be limited to) personal contacts by the project coordinator and the Aboriginal research assistant and engagement via the media (radio and television); website; local agencies, such as the community offices, the local school or schools, child care centers, community health and nursing centers; posters and

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flyers at local community stores, and word of mouth via the community and the AAC.

Parents of eligible children expressing an interest in participating will be provided with an information sheet, and the study will be explained by the Aboriginal research assistant. Upon receipt of signed consent, each parent will complete a questionnaire (the Aboriginal research assistant will assist the parent to complete the questionnaire). A calibrated examiner will then undertake the baseline clinical examination and take digital images of the dentition using a developed protocol.

After the baseline examination, each child will be offered treatment as per the protocol for the group allocation. Efforts will be taken to provide comprehensive care, including extractions. From experience, we found that concurrent treatment of the child after the baseline examination offered the best option for care and reduced the likelihood of nonattendance at subsequent appointments. In addition, where extra capacity to deliver dental treatment is available, we will provide dental care to children not enrolled in the study as a community service. The CONSORT participant flowchart is shown in Figure 1.

Figure 1. Participant flowchart. AgF: silver fluoride; KI: potassium iodide.

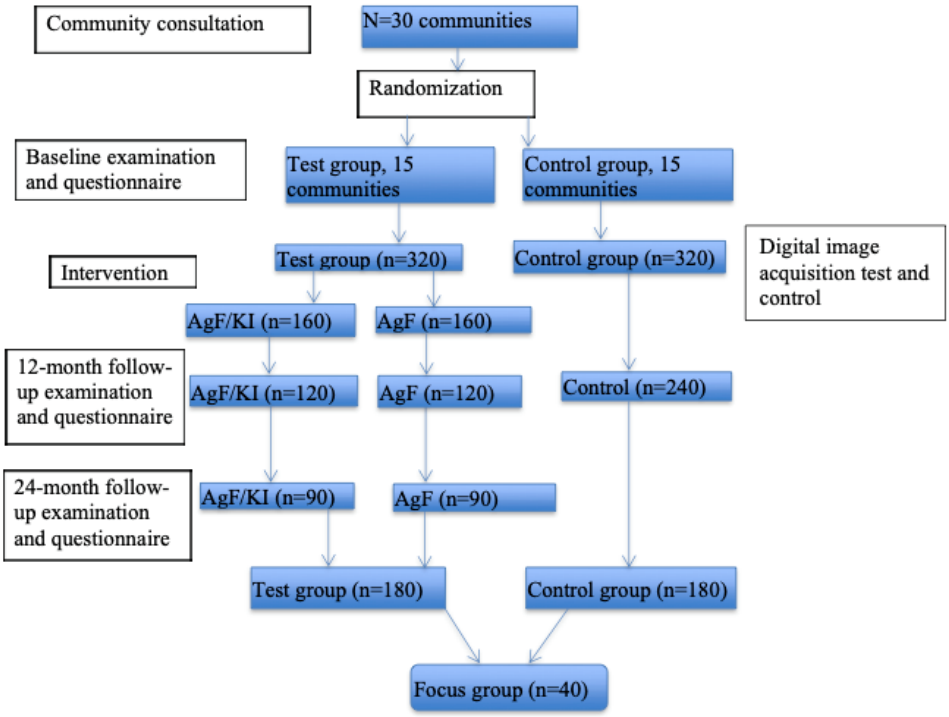

Assignment of Interventions: Allocation

Sequence Generation

Communities will be allocated to intervention or control groups through computer-generated block randomization, stratified based on the estimated caries prevalence and community water fluoridation levels within communities. Communities will be assigned to the intervention or the control group after receiving community consent. Individual children in the intervention group will be further allocated into AgF treatment or AgF and KI treatment via sealed envelopes containing computer-generated block randomization. The envelopes will be opened by the project coordinator at the community study site, and they will assign each child at enrollment.

Concealment Mechanism

The clinical team and the treating clinicians will be aware of the group assignment. Allocation assignment of KI after AgF application will be stored in opaque, sealed envelopes, which will be opened only at the time of treatment by the project coordinator.

Implementation

The allocation will be generated by the project lead off-site, and communities will be allocated into the intervention or control groups. Individual randomization will also be generated off-site and placed in sealed envelopes, which will be opened on-site by the project coordinator and assigned to AgF or AgF and KI treatment groups upon enrollment in the project.

Assignment of Interventions: Blinding (Who Will Be Blinded?)

The nature of the intervention is such that participants, treating clinicians, and assessors will not be blinded to group allocation. The project analyst will be blinded to group allocation.

Data Collection and Management

Plans for Assessment and Collection of Outcomes

Treated teeth with intact, sound fillings will be assumed to have arrested decay. The changes will be evaluated through a count of decayed, missing, filled, and arrested decayed tooth surfaces at baseline and 12- and 24-month follow-ups using the International Caries Detection and Assessment System criteria [22]. The assessment will be undertaken by calibrated

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examiners. Color changes of AgF-treated or AgF- and KI-treated lesions will be evaluated through the classification of the treated lesion into 4 categories according to Pantone color plates. Data will be collected through direct data entry using the REDCap (Research Electronic Data Capture; Vanderbilt University) implementation on iPads (Apple, Inc). The Aboriginal research assistant will assist parents, carers, and children whose primary language is not English in completing the questionnaire.

Parents of the study participants will be invited to take part in focus group interviews at the 12-month follow-up. Consenting parents will be interviewed by the Aboriginal research assistant using a semistructured interview schedule, and the interviews will be digitally recorded. The structured open-ended questions will elicit responses from parents on the care received by their child and follow a yarning approach [12]. The questions will be based on the following:

1. What were some of the positive aspects of dental care experienced by your child?
2. What were some of the negative aspects of the dental care received by your child?
3. Can you give some examples of what you think could have been done and implemented better during your child's treatment?
4. Can you name some aspects of the setting, location, and process that you think could have been improved?
5. Can you identify any changes to your oral health knowledge since the research began?

We will also take digital images of the teeth of selected children who provide consent to have the images of their teeth recorded using a smartphone and a standardized protocol [15]. The images will be sent via email, using a secure protocol used within the Western Australia Health Department, to a remote site where an independent, calibrated assessor will assign scores to the images using the same criteria as the field assessment.

Plans to Promote Participant Retention and Complete Follow-Up

Participant retention will be implemented following the methods adopted in our previous project, which included communication via the project's Facebook account and regular information dissemination to the participating communities through the study community reference group. Direct contact with study participants will also be maintained through email contacts.

Data Management

Data will be collected through the REDCap implementation on an iPad. Data entries will have range checks and data validation. All data entries will be performed via a password-protected iPad, which will be stored in locked cabinets situated within locked offices, accessible only to the research personnel.

Statistical Methods

Statistical Analyses for Primary and Secondary Outcomes

Analyses will be on an intention-to-treat and per-protocol basis. Objectives 1 to 3 will be tested using a test of proportions and logistic regression and negative binomial regression for overdispersed count data, accounting for clustering within individuals and communities. Subgroup objective 4 will be tested using paired tests for pre- and postintervention changes in COHRQol and dental anxiety as well as unpaired tests for between-group differences at baseline and follow-up; multivariable analyses will use generalized estimating equation linear regression to control for teeth and community clustering. Objective 5, economic analyses, will be tested as outlined in the subsequent section. All analyses will be undertaken by analysts who are blinded to group allocation status, and take into account clustering within communities and baseline factors and any baseline intergroup differences. Multiple imputations of missing data will be undertaken to evaluate its impact on the primary and secondary outcomes.

Objective 6 will be evaluated through qualitative analyses of the focus group interviews, with all interviews digitally recorded and independently transcribed. Transcripts will be read, and coding will be undertaken by analysts who are blinded to group allocation status. A thematic analytical approach will be adopted to develop themes and explore the contextual differences among the perceptions, experiences, and beliefs without a strict requirement for a theoretical focus [23,24]. Transcripts will be read multiple times to establish familiarity with the dataset. Two independent reviewers, one of whom will be an Indigenous researcher, will develop a coding scheme of the transcripts and also develop emerging themes. Where disagreement in coding is identified, the differences will be resolved through discussion and consensus. Our approach will broadly follow a reflexive thematic analysis (based on the study by Braun and Clarke [24]), drawing on subjective interpretations of both an Indigenous and a non-Indigenous researcher. The emergent themes will be explored and further refined. Data management will be facilitated using NVivo (version 12; Lumivero). Objective 7 will be evaluated by calculating sensitivity, specificity, predictive values, and receiver operating characteristics, validated against on-site clinical assessment.

Economic Analysis

Costs and outcomes of the interventions will be quantified and analyzed. The costs of the intervention and subsequent dental treatment costs within the trial period will be assessed from the health provider's perspective. The intervention cost will be recorded using a World Health Organization–developed program costing template called CostIt, using a bottom-up approach. Unit costs of the intervention, for example, salary and AgF, will be based on the budget record of the study. The costs of dental treatments required will be determined using the treatment item codes extracted from the participant's dental records and unit costs based on the Child Dental Benefit Schedule. Cost-effectiveness and cost-utility analysis will be undertaken. The incremental cost-effectiveness ratio or the changes in net costs and health outcomes resulting from the intervention compared with the control will be calculated. The incremental cost-effectiveness ratio can be presented as follows:

$$ICER = (Ci - Cc) / (Ei - Ec)$$

where Ci and Ei are the net costs and effectiveness of the intervention and Cc and Ec are those of the control. In the cost-effectiveness analysis, the E component is a clinical

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outcome. For the cost-utility analysis, the outcome is the number of years weighted by the quality-of-life index derived from ECOHIS-4D [25]. A standard World Bank and World Health Organization Choosing Interventions that are Cost-Effective (WHO-CHOICE) discount rate of 3% will be applied to both costs and outcomes that occur after the first year [26]. Uncertainty analysis will be performed.

Plans to Give Access to the Full Protocol, Participant-Level Data, and Statistical Code

Clinical information of the child study participants will be shared with their parents and carers at the examination presentation. The results of this study will be shared widely through publication of the findings in scientific journals and conference presentations.

Oversight and Monitoring

Composition of the Coordinating Center and Trial Steering Committee

All investigators will comprise the trial steering committee and will contribute to overall monitoring of the study and guide its conduct. The committee will meet quarterly, and the lead investigator will report on the progress of the study to date.

Community and Consumer Engagement

At the completion of our earlier work in the Kimberley region, we provided community feedback to the communities that participated in our study through the community council and the local Aboriginal community-controlled health organizations [6]. Because of the community feedback, a proposal was formulated to overcome the sole reliance on visiting dental service providers for primary dental care by using the skills of an Aboriginal health practitioner or worker. The proposal was endorsed by the local Aboriginal community–controlled health organizations, and the resulting project was developed. An Aboriginal advisory committee will also be formed and provide guidance on the research process and ensure cultural safety during the trial. We have also engaged with a community consultant (LP) who read the study proposal and provided input for the study.

Composition of the Data Monitoring Committee, Its Role, and Reporting Structure

An independent data and safety monitoring committee will also be convened, comprising 3 independent senior clinicians, who will review clinical outcomes and, in particular, any reported adverse events to protect and ensure participant welfare.

Adverse Event Reporting and Harms

Participants will be assessed immediately after the treatment for any adverse events, and parents and carers of the child study participant will be provided with contact details of the research team for reporting any adverse events that occur after the treatment. Reporting of any adverse events will be closely monitored and reported to the data and safety monitoring committee on a quarterly basis.

Frequency and Plans for Auditing Trial Conduct

The lead investigator will provide quarterly reports to the steering committee, which will meet quarterly and appraise the trial conduct.

Plans for Communicating Important Protocol Amendments to Relevant Parties (eg, Trial Participants and Ethics Committees)

Any amendments and alterations to the study protocol will be reported to the appropriate institutional ethics committee.

Dissemination Plans

The study findings will be reported back to participating communities in a grouped form, and no individual community or individual will be identifiable. The findings will be further reported in appropriate scientific forums, including conferences and journals. A report will also be prepared and provided to the supporting organizations.

Results

Community engagement has commenced, and we have approached communities that participated in our earlier project for participation in the proposed project. The trial has been registered on the Australian New Zealand Clinical Trials Registry on April 15, 2024 (ACTRN12624000457549p). Recruitment of participants is planned to commence on March 1, 2026, and is expected to be concluded by December 31, 2026.

Data collection tools via REDCap have been prepared. Calibration of clinical examiners is in progress. The study outcomes with respect to oral health will be published after the 12- and 24-month follow-ups have been completed. The qualitative findings will be reported after the focus group discussions have been completed.

Discussion

Anticipated Findings

Access to timely dental care is a challenging issue confronting many people in rural and remote communities in Australia but is particularly acute for the Indigenous population. The remote communities tend to have smaller population sizes, and there are usually no dental services available within the community; the residents of the community will usually have to travel long distances to obtain care or wait for itinerant visits by public dental services or volunteer-based service providers. This then leads either to a delay in getting care or, worse, trying to access care only when in pain, which can sometimes lead to the required care only being able to be provided under general anesthesia. By using the skills of an Aboriginal health worker or practitioner, who would normally reside within a community, to deliver primary dental care, it is expected that the intervention will promote better access to timely dental care, thus mitigating the factors outlined earlier.

The use of AgF to stop caries progression has been tested worldwide and has been shown to be effective in arresting caries. The procedure is relatively simple and painless. The simple and painless application lends itself to use among populations where

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standard care options for the management of dental caries may not be feasible or practical and to test its potential application by an appropriately trained non-oral health practitioner. This study will test the application of AgF by an Aboriginal health worker or practitioner.

This trial will test the feasibility and effectiveness of applying AgF to carious primary molars of young Indigenous children in remote communities. The rate of arrestment will be compared with the rate of arrestment among children in control communities provided with the minimally invasive care using the ART and the HT. We will also test the feasibility of using digital images acquired via a smartphone to validate on-site clinical assessments undertaken by calibrated examiners. The findings have the potential to disrupt a model of care that relies principally on care delivered by an oral health professional team using local anesthesia and the dental drill. Validation of remote clinical assessment for dental conditions will enable the use of teledentistry technology to further improve access to dental care in remote communities by reducing the reliance on care delivered by visiting dental teams.

Conclusions

This trial is set within remote communities in Western Australia and among young children; therefore, the findings may not necessarily be directly applicable to other settings and age groups. However, residents of all ages in remote communities in Australia, in general, confront similar difficulties and challenges in accessing timely dental care, and this study's findings may inform the consideration of policies and practices for service delivery in such settings.

Acknowledgments

The authors thank the communities that have supported the proposed study. They also thank Sergio Chrisopolous for assistance in developing data collection tools. This study is funded by a partnership grant from the Australian National Health and Medical Research Council (grant 2025089), the Western Australia Health Department 2022-23 Major Research Application Support program (Round 4), and the Stan Perron Charitable Foundation Research Programs and Partnership (00007).

Data Availability

The datasets generated or analyzed during this study are not publicly available due to confidentiality, but are available from the corresponding author on reasonable request.

Authors' Contributions

All authors contributed to the conceptualization of the study. PA, LJ, DA, DB, SK, UT, JP, SN, HN, and LA contributed to funding acquisition. PA and SP contributed to data curation. PA drafted the manuscript and all authors reviewed and contributed and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the 2023 Partnership Projects PRC1 (National Health and Medical Research Council, Australian Government).
[PDF File (Adobe PDF File), 135 KB - resprot_v14i1e72227_app1.pdf]

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Abbreviations

AgF: silver fluoride
ART: atraumatic restorative treatment
COHRQoL: child oral health–related quality of life
CONSORT: Consolidated Standards of Reporting Trials
HT: Hall technique
KI: potassium iodide
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
WHO-CHOICE: World Health Organization Choosing Interventions that are Cost-Effective

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Protocol

A Comprehensive and Structured Follow-Up for Persons With Multiple Sclerosis (CoreDISTparticipation) to Optimize Physical Functions, Health, and Employment: Protocol for a Prospective, Single-Blinded Randomized Controlled Trial and Health Economic Evaluation

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Abstract

Background: Multiple sclerosis (MS) is a chronic neurological disease of the central nervous system, primarily affecting young adults. Common challenges in MS include fatigue, physical impairments, and cognitive impairments, associated with low levels of physical activity, unemployment, reduced health-related quality of life (HRQoL), and substantial personal and societal costs. Many leave the workforce or reduce hours even when disability is low and despite a desire to increase work hours if the job is adjusted to their needs. Existing services aiming to optimize physical functions and work participation only initiate retrospectively, and there is a lack of knowledge regarding the possible effect of more proactive services.

Objective: The objective of this study is to investigate the effects of a comprehensive multidisciplinary intervention, CoreDISTparticipation, delivered across health care levels (hospitals and municipalities) and sectors (health and employment/welfare), on barriers to work, physical activity, and physical functions; fatigue; and HRQoL for employed people with multiple sclerosis (pwMS) and to perform a health economic evaluation.

Methods: This prospective, single-blinded randomized controlled trial (RCT) will include 115 pwMS with Expanded Disability Status Scale (EDSS) scores of 0-4 randomly allocated to either a CoreDISTparticipation intervention group or usual care (control group). The CoreDISTparticipation intervention includes (1) information videos, hospital outpatient physiotherapist assessments, and meetings with employment consultants; (2) group-based physiotherapy in municipalities for 60 minutes over 6 weeks, one indoor CoreDIST balance session, one outdoor CoreDIST balance and high-intensity interval session, and tailored work follow-up; and (3) 6 weeks of digitally supported independent training, twice weekly. Assessments will be conducted at baseline, week 9, and week 16. Primary outcomes include Multiple Sclerosis Work Difficulties Questionnaire-23 – Norwegian version (MSWDQ-23NV) and ActiGraph wGT3x-BT monitor scores. Secondary outcomes include Trunk Impairment Scale – modified Norwegian Version (TIS-modNV), Mini Balance Evaluation Systems Test (MiniBESTest), AccuGait Optimized force platform, 6-minute walk test (6MWT), Multiple Sclerosis Walking Scale - 12, Multiple Sclerosis Impact Scale-29 – Norwegian version, EQ-5D-5L, and Fatigue Severity Scale – Norwegian version scores. The study will identify effects of CoreDISTparticipation versus usual care on work barriers, physical activity, balance, walking, fatigue, and quality of life, along with a health economic evaluation. Descriptive statistics and repeated measures mixed models will be performed using IBM SPSS version29.

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Results: We completed the enrolment phase and enrolled and randomized 115 participants in two phases by August 1, 2024. The 15-week retests were completed in December 2024, and data collection is estimated to be completed by September 2025. Results are expected to be published in the first quarter of 2026.

Conclusions: CoreDISTparticipation is an innovative approach proactively addressing physical functions, physical activity, and work participation. If effective, it can offer a low-cost approach that potentially may enhance the quality of life and workforce sustainability and reduce societal costs.

Trial Registration: ClinicalTrials.gov NCT06110468; https://www.clinicaltrials.gov/study/NCT06110468

International Registered Report Identifier (IRRID): DERR1-10.2196/74988

(JMIR Res Protoc 2025;14:e74988) doi:10.2196/74988

KEYWORDS

multiple sclerosis; rehabilitation; physical functioning; physical activity; employment

Introduction

Background

Multiple sclerosis (MS) is a chronic neurological disease of the central nervous system that primarily affects young adults [1]. Approximately 2.9 million people worldwide have MS [2], and Norway is a high-risk area [2] with a prevalence rate of 248/100,000 and an incidence of 10/100,000 [3,4]. Common challenges in MS include fatigue, physical impairments, and cognitive impairments [3], which are associated with low levels of physical activity, unemployment, reduced health-related quality of life (HRQoL), and substantial personal and societal costs [5-7]. In 2022, the socioeconomic costs in Norway related to people with multiple sclerosis (pwMS) amounted to 12 million Norwegian Kroner (NOK), or ~US $120,520, with about one half attributed to loss of productivity and around NOK 900,000 (US $90,390) per person [4]. Given the median survival rate of 48 years postdiagnosis [3], around 30 years of their working life could potentially remain after receiving the diagnosis.

In Norway, most pwMS experience mild-to-moderate disability, as measured with the Expanded Disability Status Scale (EDSS) [3]. Despite low disability, the disease course fluctuates with the accumulation of minor impairments, such as fatigue [7], impaired balance and walking [8,9], and cognitive problems [10]. Physiotherapy and physical activity interventions can reduce fatigue [8,9]; improve balance, walking [10-13], and HRQoL [9,14,15]; and enhance neuromuscular and physical functioning in pwMS [16]. Optimizing physical functions and physical activity when disability is low, and neuroplasticity is optimal [17], can be valuable for maintaining physical activities and work, as less fatigue, mobility-related symptoms, and cognitive disturbances are associated with current employment [18-23].

It is concerning that 40%-70% of pwMS exit the workforce within a few years postdiagnosis [7,24-26], even with minor disability, as measured with the EDSS [4,5,18,19,27]. Nonemployment rates tend to increase with age [28], impacting on identity, self-esteem, self-efficacy, and HRQoL [14,29]. Barriers to work include demographic-, disease-, and workplace-related factors [15,30]. A higher age at onset of MS, a longer disease duration, lower education, fatigue, heavy physical work, depressive symptoms, and high levels of disability are associated with unemployment [18,19,27]. In Norway, 54%-70% of pwMS are outside the workforce [6,18]. Interestingly, our recent pilot feasibility randomized controlled trial (RCT) [31], with 28 participants with an average EDSS score of 1.8 (SD 1), identified a prevalent desire to increase work hours if the jobs were adjusted to their needs. The mean desired employment rate was 72.7% (SD 26.3) for the intervention group and 83.8% (SD 22.6) for the usual care group in contrast to their current mean employment rate of 46.3% (SD 35.6) and 65.4% (SD 39.3) [31], respectively. These findings highlight the potential for pwMS to remain in the workforce for longer with adequate support.

The Norwegian Labour and Welfare Administration (NAV) is responsible for all employment and welfare services. NAV is a result of the merging of three previous public institutions: Employment Services, Social Insurance Administration, and Municipal Social Services. Support from NAV is initiated 26 weeks after a person is prescribed sick leave, with the employer being responsible for initial work adaptation. Communication between pwMS and their managers is essential for sustained employment [17,21]. Employers, however, often lack relevant information about the disease and adequate work adaptations [32], and NAV consultants report challenges, such as limited time, lack of information, and difficulties in understanding people with chronic diseases [33]. At 26 weeks, NAV consultants offer a dialogue meeting to discuss return-to-work options [34], potentially delaying adequate actions for 6 months. This practice, which initiates actions *retrospectively* and is carried out by actors with limited competence regarding MS, needs improvement.

To address these issues, we have developed a comprehensive intervention entitled *CoreDISTparticipation*. This multidisciplinary follow-up is delivered across health care levels (hospitals and municipalities) and sectors (health and employment/welfare). It builds on the GroupCoreDIST exercise intervention [35], which addresses prerequisites for balance, such as dynamic trunk control and coordination within and between proximal (core) and distal bodily areas, delivered in small groups. These exercises emphasize high dose, dual task (D); individualization and new insights (I); somatosensory function optimization (S); and task-oriented training (T). GroupCoreDIST has proven effective for trunk control, balance, and walking in the short and the long term [12,13]; is a valuable

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tool for physiotherapists [36-38]; and enhances pwMS engagement in physical activity [39]. In addition, CoreDISTparticipation incorporates structured support from NAV consultants and employers, as well as digital support, and emphasizes outdoor physical activity. This innovative intervention has been investigated through a feasibility pilot RCT [31], a pretest-posttest feasibility study [32], and interviews [40]. Following minor adjustments, it is ready for a large-scale RCT. Currently, there is a scarcity of evidence regarding proactive comprehensive interventions addressing function, health, and work in pwMS. The trial presented in this protocol will investigate the effectiveness and cost-effectiveness of the new intervention.

Objectives

We pose the overall research question: What are the effects of CoreDISTparticipation on physical functions, health, and employment compared to usual care for pwMS? Subquestions organized in two work packages (WPs 1 and 2) are outlined in Table 1.

Our hypothesis is that CoreDISTparticipation is superior to usual care in terms of addressing barriers to and status of work and improving physical activity, physical functions, fatigue, and HRQoL. It is, however, important to note that the initial phase of the intervention may entail an increase in short-term sick leave costs due to the intensive program that may need to be conducted during working hours.

Table 1. Research questions for work packages WP[a]1 and WP2.

WP	Research questions
WP1	• What are the short- and long-term effects of the CoreDISTparticipation program compared to usual care regarding barriers to work, physical activity, balance, walking, fatigue, and HRQoL[b] in individuals with minor-to-moderate disability due to MS[c]? • What are the distributions of and relationships between barriers to work and physical activity, balance, walking, fatigue, HRQoL, and employment status in individuals with minor-to-moderate disability due to MS?
WP2	• What is the utility of the CoreDISTparticipation program compared to usual care expressed in the unit of QALYs[d] in individuals with MS? • What is the utility of the CoreDISTparticipation program compared to usual care according to long-term employment status and work-related costs in individuals with MS?

[a]WP: work package.

[b]HRQoL: health-related quality of life.

[c]MS: multiple sclerosis.

[d]QALY: quality-adjusted life-year.

Methods

Trial Design

This study consists of two WPs. WP1 is a parallel, two-arm prospective, single-blinded, multicenter RCT with an allocation ratio of 1:1 to investigate whether CoreDISTparticipation is superior to usual care in terms of reducing barriers to work and improving physical activity levels, physical functions, and HRQoL. The study is registered at ClinicalTrials.gov (NCT06110468). WP2 aims to determine the utility of the CoreDISTparticipation intervention in terms of HRQoL and quality-adjusted life-years (QALYs), employment status, and work-related costs when compared to usual care. The trial protocol is reported in line with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist (Multimedia Appendix 1) and the CONSORT statements for reporting RCTs.

Study Setting

The trial will be conducted across levels of health care and institutions, specifically in hospitals and municipalities, in outpatient clinics, in an outdoor setting, and in the participants' home. All testing and initial physiotherapy assessments for the intervention group will be undertaken in a hospital setting. The physiotherapy intervention involves a combination of indoor and outdoor training and will take place in municipality physiotherapy outpatient clinics and appropriate outdoor venues. Work-related meetings will preferably be digital but can be held in the NAV consultants' offices or at the participants' place of work.

Eligibility Criteria

Eligible participants must be diagnosed with MS according to the McDonald criteria [41], have an EDSS score of ≤4, be between 18 and 67 years of age, be employed (10%-100%; may include various degrees of sick leave, disability pension, or Work Assessment Allowance [WAA]), and be living in 1 of the 22 participating municipalities within the regions served by the participating outpatient clinics. Exclusion criteria are pregnancy at enrollment, exacerbation of symptoms (ie, relapse) within 2 weeks prior to enrollment, or other serious acute conditions.

The CoreDISTparticipation Intervention

Choice of Comparators

We have chosen usual care to be the most relevant comparator, even though it is unlikely to be dose-matched, as it represents current practice. These participants will continue with their regular routines and will be encouraged to obtain the national and MS-specific recommendation of 150-300 minutes of moderate physical activity or 75 minutes of high-intensity physical activity per week or a combination of these, stay employed, continue medical treatment, and seek any health care required, including physiotherapy.

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The Intervention

The intervention (Table 2) will consist of information videos on the importance of physical activity and possibilities for work adaptations, individual physiotherapy assessments and indoor and outdoor training in groups, meetings with a NAV consultant to assess the need for work adaptations or support and subsequent follow-up with the participants' leader/manager, digitally supported self-administered home exercises, and a podcast on physical activity.

Table 2. Overview of the CoreDISTparticipation intervention.

Phase and weeks	Description
Phase 1	
Week 1	• The pwMS[a] and their employers watch three short videos. One addresses information regarding MS[b] and another on how NAV[c] can provide support in terms of work adaptations. The third video contains information from both physiotherapists and a user representative regarding the importance of training physical functions and regular physical activity. • A digital work-promoting meeting between the pwMS and a trained NAV consultant following a structured guide (60 minutes): This aims to identify the individual's needs for follow-up regarding work adaptations. The meeting will determine whether the pwMS independently should discuss the work situation with their employer or whether a NAV consultant, a general practitioner, or other professional is needed in the follow-up. • A clinical assessment with a trained MS outpatient physiotherapist (60 minutes): This explores the individuals' movement challenges and explores possibilities for optimalization. Information will be sent digitally to the municipal physiotherapist.
Weeks 2-9	• A clinical assessment with the municipal physiotherapist (90 minutes): This should build on the documentation from the MS outpatient physiotherapist. Focus is on exploring possibilities for change related to their movement problem to enable them to master the principles of the CoreDIST exercises, especially related to core activation in coordination with distal movement, and identify goals for physical functions, physical activity, and work. The goals will be written and evaluated after the 6-week period. The CoreDIST videos [42] and outdoor voiced programs will be introduced, and the pwMS will discuss what physical activity they prefer. Conclusions regarding goal setting will be sent digitally to the general practitioner. • CoreDIST sessions two times per week for 6 weeks (1×60 minutes indoor training in groups of 1-5 participants and 1×60 minutes outdoor training in groups of 1-10 participants). The indoor exercises will focus on optimalization of prerequisites for balance, such as improving somatosensory activation, muscle length, activation of trunk muscles in coordination with distal movement, larger muscle groups and postural control challenges in standing. The outdoor exercises will focus on challenging postural control in standing and moving, as well as physical capacity in high-intensity intervals (4×4minutes) of walking or running or both. A pulse monitor will be worn, and intensity will be individualized. • Self-administered training 1×30 minutes per week, eHealth-supported CoreDIST videos, voiced programs, and a podcast are available. Self-administered training will be registered on a weekly basis through SMS reminders. • A (digital) follow-up meeting regarding work between the pwMS and employers or arranged by NAV with the participants, employers, and professionals relevant for the patients. • Week 9: A physical meeting with the municipal physiotherapist (30 minutes) to evaluate goals and new goal setting for weeks 10-24 regarding physical functions and physical activity. The municipal physiotherapist sends information regarding goals to the general practitioner.
Phase 2	
Weeks 10-15	• Self-administered, digitally supported home training: CoreDIST videos, 3×10 minutes/week • Physical activity and training of own choice, 2×30 minutes/week; for instance, using outdoor training with provided voiced programs. The training should include elements of high intensity and balance. SMS reminder will be sent on a weekly basis from the Nordland Hospital Trust. Participants will register the number of training and physical activity sessions by responding to a digital questionnaire on a weekly basis. • Week 15: Evaluation of work-related goals (30 minutes): The pwMS, employers, and potentially other professionals involved in goal setting/follow-up will evaluate physical activity; the meeting is in consultation with the municipal physiotherapist (30 minutes). The information will be sent to the general practitioner.

[a]pwMS: people with multiple sclerosis.

[b]MS: multiple sclerosis.

[c]NAV: Norwegian Labour and Welfare Administration.

CoreDIST Exercises

Indoor Training

The intervention includes 38 standardized exercises, which will be performed in various positions (Multimedia Appendix 2). These exercises are organized in eight "blocks" according to their objectives, and all are individually named and described (Multimedia Appendix 3). Each exercise includes three to five levels of difficulty to allow for individual tailoring (Figure 1). In the group sessions, all participants perform the same exercise simultaneously, but the level of difficulty may be individually adjusted. The intervention emphasizes performance of exercises with optimal alignment in various body parts to enhance recovery as opposed to compensatory strategies [43]. Dynamical

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proximal stability is enhanced in most exercises by keeping the back, hips, or stomach in dynamic contact with a therapeutic ball (smaller balls may also be used). Trunk muscles are addressed in all exercises, for instance, by keeping the ball still against a wall while moving the arms or legs or by moving the ball while keeping the hands or feet stable. Sensory stimulation of hands and feet to update body schemas is facilitated by using a spiky ball or roller [43,44]. Dual tasks are integrated as variations, for example, by singing, using rhymes, or calculating while exercising. Proprioception and vestibular functions are enhanced by performing exercises with closed eyes. Interacting ball activities, such as bouncing, jumping, and throwing the ball to each other, are included to increase postural control challenge and enhance group dynamics.

Figure 1. Example of exercise description.

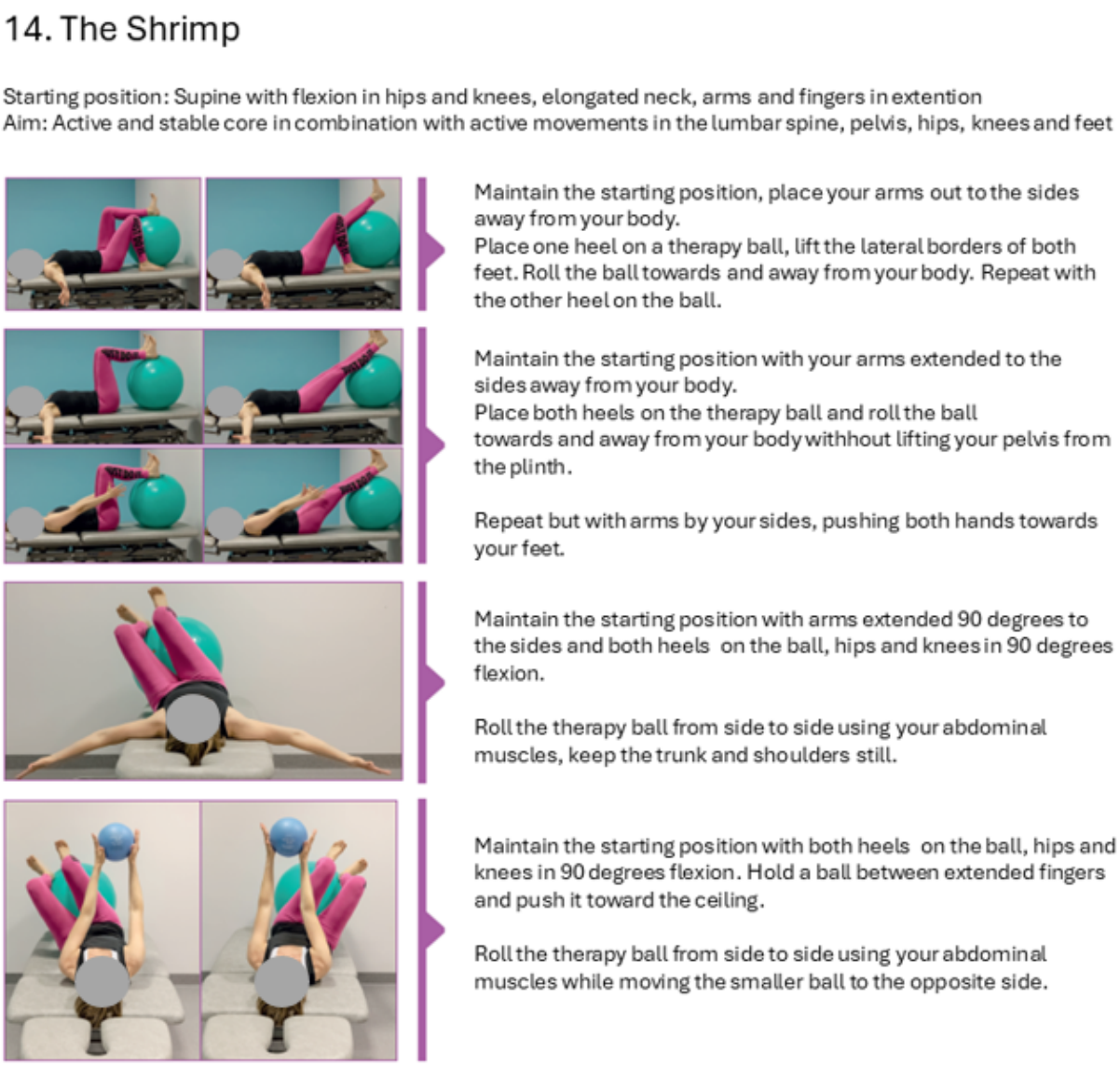

Outdoor Training

The CoreDIST exercises, along with the principles of 4×4-minute intervals form the basis for the outdoor sessions (Multimedia Appendix 2). There is a strong emphasis on high intensity [45] through running or brisk walking or performing exercises when standing with resistance or at a faster pace.

Meeting With the NAV Consultant

A written themed guide for the meetings between participants and NAV consultants have been developed in collaboration with NAV and user representatives (Multimedia Appendix 4).

Participant Timeline

The timeline for participants in the intervention group is outlined in Figure 2. Participants in usual care (control group) will undertake a baseline assessment and retests, along with registrations in weeks 9, 16, and 52.

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Figure 2. Participant timeline. NAV: Norwegian Labour and Welfare Administration.

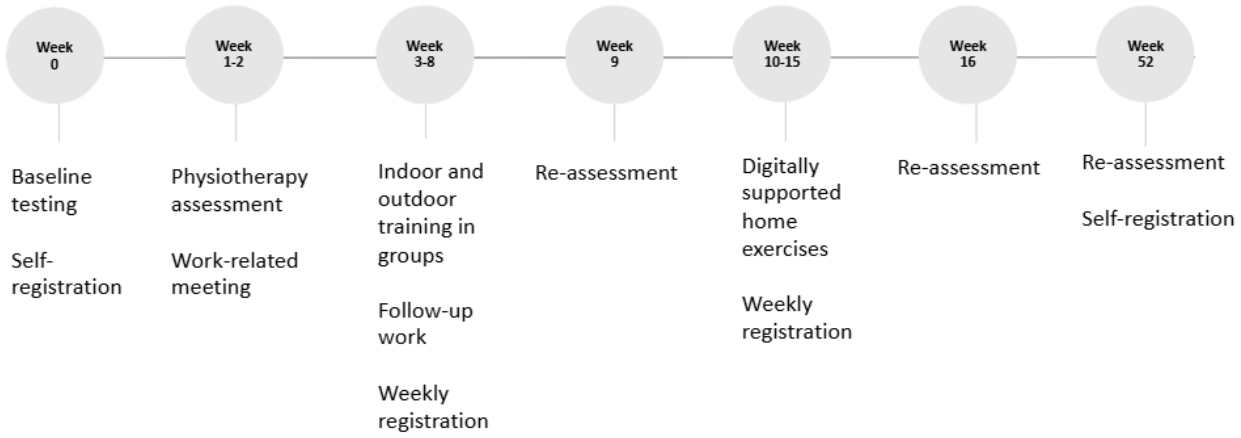

Criteria for Discontinuing or Modifying the Allocated Intervention

All participants may withdraw from the study without providing a reason, and this will not affect their access to care. Participants will not be able to change their group allocation. With the participants' consent, all data collected up to withdrawal will be included in the analysis. Relapses or medication changes will be registered but are not reasons for exclusion, provided the participants are willing and able to continue.

Strategies to Improve Adherence to the Intervention

Several strategies have been developed to improve and monitor adherence. Members of the research team will be available to answer questions or provide support to the participants and physiotherapists during working hours throughout the project period and may be contacted over the phone or via email. NAV consultants and physiotherapists will contact the participants over the phone to set up appointments. To facilitate adherence during the 6-week period of self-administered training, weekly reminders and activity suggestions will be distributed. The participants will perform weekly registrations of the number of sessions and intensity in training. They will also be provided with access to a digital exercise bank. The participants in the intervention group will be provided with fitness watches for the purpose of pulse monitoring and logging during sessions, as well as for setting individual physical activity goals, such as a daily step count.

Strategies to Improve the Fidelity of the Study

All participating physiotherapists will participate in a 3-day training program on the CoreDISTparticipation intervention. The training will focus on the theoretical basis and practical execution of the intervention. The physiotherapists will be provided with a booklet containing images and descriptions of all exercises (see Figure 1), including possibilities for adjusting the level of difficulty in each exercise. They will register all exercises used during each training session. The NAV consultants involved in the delivery of the intervention will participate in an online training course providing basic knowledge of MS. The participants will log their average heart rate and time spent in different pulse zones during the physiotherapy sessions on forms kept by their physiotherapist. This will aid the physiotherapists in achieving sufficient intensity in the sessions.

The participants will be enrolled into the study in two groups, where one group will finish the intervention before the other group starts. Evaluation meetings with the testers, physiotherapists, and NAV consultants will be held before the enrollment of group 2 to address any issues they encounter with group 1.

Relevant Concomitant Care Permitted or Prohibited During the Trial

No restrictions will be imposed on the participants in either group during the study period. The participants will register treatments related to their MS, including rehabilitation treatments.

Provisions for Posttrial Care

All participants may continue to receive routine care from the MS outpatient clinic and multidisciplinary care, as needed. No other arrangements will be made for provision of posttrial care. All participants will be covered by the Norwegian Patient Injury law, providing entitlement to apply for compensation from the Norwegian System of Patient Injury Compensation in the case of any harm while participating in the study.

Outcomes

Work Package 1 (RCT)

An overview of the selected valid and reliable outcome measures that will be used is outlined in Table 3. The primary outcomes will be the Multiple Sclerosis Work Difficulties Questionnaire-23 – Norwegian version (MSWDQ-23NV) scores and physical activity levels measured by ActiGraph wGT3x-BT monitors. We have chosen these primary outcomes as they cover the main parts of the intervention. The secondary outcomes cover factors associated with reduced employment and HRQoL, along with specific insights into gait capacity, balance, and trunk control.

All outcome measurements will be conducted at baseline and weeks 9, 16, and 52 to examine short- and long-term within- and between-group effects, as outlined in Table 4.

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Two trained physiotherapists (research assistants), blinded to group allocation and not involved in the delivery of the intervention, will perform the assessments in the local hospitals near the municipalities where the participants live, and distribute the activity monitors. Questionnaires will be administered digitally through the Research Electronic Data Capture (REDCap) tool. The participants will provide information regarding the type and duration of MS, as well as their age, gender, smoking status, weight, social status, education, current work, employment status, well-being, and motivation for work and physical activity. The patients will also self-report MS attacks, physical activity (type, dose, frequency, intensity), medications, physiotherapy, and work-related meetings.

Table 3. Outline of the primary and secondary outcome measures for WP[a]1.

Outcome and measures	Description
Primary outcomes	
MSWDQ-23NV[b]	This measures how frequently individuals with MS[c] perceive psychological/cognitive (11 items), physical (8 items), and external (4 items) barriers related to work, scored on a 5-point scale (0=best) [46].
Levels of physical activity measured using Acti-Graph wGT3x-BT monitors	The monitors will be worn on a belt around the waist for 7 consecutive days. The average daily percentage of time in mild, moderate, and intensive physical activity and sedative time will be calculated [47].
Secondary outcomes	
6MWT[d]	This measures the distance in meters walked within 6 minutes [48].
ActiGraph wGT3x-BT monitor	This counts the average number of steps taken per day.
EQ-5D-5L + complementary questions	This is the self-perceived HRQoL[e] in five domains and a Visual Analogue Scale (score 0-100) on overall health [49]. Complementary questions will be asked on sleep, well-being, emotions, and social relations (advocated by the Norwegian Health Institute). A higher score indicates better self-perceived health.
Fatigue Severity Scale - Norwegian version	This is a self-report, 9-item scale that measures the physical, social, and cognitive effects of fatigue (score 1-7). A higher score indicates higher levels of fatigue [50].
Multiple Sclerosis Walking Scale-12	This 12-item scale measures the self-reported perception of walking, scored on a 5-point scale. A higher score indicates a higher impact of MS on the individual's walking ability [51].
MiniBESTest[f]	This test involves pro-and reactive balance, dual tasks, and involving sit-to-stand, standing, and walking tests. There are 14 items scored on a 3-point scale. A higher score indicates better performance [52].
TIS-modNV[g]	Trunk control in sitting: This 6 item scale is scored on a 2- or 3-point scale (sum range 0-16 points). A higher score indicates better trunk control [53].
AccuGait Optimized force platform	This measures postural control in standing and one-leg standing: Balance in a quiet stance is expressed through the COP[h] migration and amplitude of postural sway [54].
Multiple Sclerosis Impact Scale-29 – Norwegian version	This measures the self-perceived physical (13 items) and psychological (9 items) impact on HRQoL using a 5-point scale. A higher score indicates an increased impact of MS on the individual's day-to-day life [55].
Patient Global Impression of Change (PGIC) – physical activity and balance	This global index is used to rate the response of a condition to a therapy (transition scale). Higher scores indicate self-perceived improvement [56].

[a]WP: work package.

[b]MSWDQ-23NV: Multiple Sclerosis Work Difficulties Questionnaire-23 – Norwegian version.

[c]MS: multiple sclerosis.

[d]6MWT: 6-minute walk test.

[e]HRQoL: health-related quality of life.

[f]MiniBESTest: Mini Balance Evaluation Systems Test.

[g]TIS-modNV: Trunk Impairment Scale – modified Norwegian version.

[h]COP: center of pressure.

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Table 4. Overview of registrations and assessments.

Registration and assessment	Baseline	Weekly	Week 9	Weekly	Week 16	Monthly	Week 52
Standardized outcome measures	X[a]	—[b]	X	—	X	—	X
Physiotherapy and work-related meetings (baseline and week 52: report the last 3 months)	X	—	X	—	X	—	X
Current work, employment status, well-being	X	—	X	—	X	—	X
Self-reports: MS[c] attacks, physical activity, medications physiotherapy, general practitioner, NAV[d] consultations	X	X	X	X	X	X	X

[a]X: applicable.

[b]Not applicable.

[c]MS: multiple sclerosis.

[d]NAV: Norwegian Labour and Welfare Administration.

Work Package 2 (Utility Study)

The outcomes for WP2 will be the net utility gain, employment status, and cost utility (Table 5). Data related to participation in work will be obtained cross-sectionally at baseline in WP1 and after week 52 through self-registration and linkage to the NAV register. The participants will provide information about the type and number of follow-ups and treatments from the physiotherapist, the general practitioner, the neurologist, and the NAV consultant in digital questionnaires distributed from REDCap. From the NAV registry, data will be obtained for the following variables: work status, sick leave, WAA and disability benefits, family-related leave (ie, maternity leave), pension, social aid, and unemployment benefits.

Table 5. Outline of outcomes for WP[a]2.

Outcome	Description
Net utility gain: QALYs[b]	QALYs will be calculated for both groups using EQ-5D-5L scores from WP1.
Employment status	The status for and changes in employment will be calculated based on self-reports and registry data from NAV[c]. To enable calculation of long-term effects, we will gather data on the aforementioned variables 1 year after the intervention.
Cost utility	Data on treatment costs will be obtained from the tariffs and weights used in municipal and specialist health care.

[a]WP: work package.

[b]QALY: quality-adjusted life-year.

[c]NAV: Norwegian Labour and Welfare Administration.

Sample Size

We calculated the sample size needed to detect a between-group difference, as observed in our pilot study [31], based on the MSWDQ-23NV scores. The mean score change from baseline to posttest was 5.9 for the intervention group and 2.3 for the control group [31]. Considering the observed SDs and covariances and calculating with a power of 0.8 and α=.05, the RCT will need to include 45 individuals in each group. Assuming a dropout rate of 20%, we decided to recruit 115 people with mild-to-moderate disability due to MS into the study.

Recruitment

Participants were recruited from the neurological outpatient clinics in three hospitals in Norway. Based on the prevalence of pwMS and the prospects of being able to recruit sufficient participants to form groups, only municipalities with >4500 inhabitants (n=19) or smaller municipalities (n=3) near an outpatient clinic in a neighboring municipality were invited to participate. Based on patient lists from the participating outpatient clinics, all individuals in the selected municipalities who met the EDSS score criterium received an invitation to participate.

Assignment of Interventions: Allocation

Sequence Generation

Digital randomization to CoreDISTparticipation (intervention group) or usual care (control group) in a 1:1 ratio using block sizes of 4 and 6 with a random variation between the two block sizes was performed. Randomization was stratified based on the participants' region of residence (north or south) to optimize the establishment of exercise groups and avoid geographical bias. Randomization was performed using REDCap hosted by the Clinical Research Department, University Hospital North Norway, a secure web-based app designed to support data capture for research studies, providing (1) an intuitive interface for validated data entry, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for importing data from external sources [57].

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Concealment Mechanism

The allocation sequence was generated outside REDCap and uploaded to the REDCap database prior to enrollment of participants and was not visible to the members of the research group performing the randomization.

Implementation

The allocation sequence was generated by an administrative member of staff at the Research Department at the Northern Norway Regional Health Authority. This member of staff is otherwise not connected to the project and will not reveal the allocation sequence to any member of the research team. A member of the research group not involved in assessment or treatment of the participants or in the generation of the allocation sequence enrolled participants into the REDCap database upon screening them based on the inclusion and exclusion criteria and whether they provided informed consent. Following baseline measurements, digital randomization to the intervention or the control group was performed.

Assignment of Interventions: Blinding

In line with many rehabilitation studies, this will be a single-blinded study. The outcome assessors will be blinded to group allocation. All participants have been instructed not to reveal their group allocation to the outcome assessor. Blinding of participants will not be possible as there is no control group intervention. No procedures for unblinding are planned as this is a single-blinded study.

Data Collection and Management

Plans for Assessment and Collection of Outcomes

Demographic data on age, gender, height, weight, social status, education, medical history (including the type of MS, years since diagnosis, EDSS score and MS-related medications), work status, and physical activity will be collected from each participant digitally through Nettskjema's online forms. All questionnaires will be distributed digitally from the REDCap database, and the participants will be notified via email. The clinical tests will be performed at the patients' local or regional hospital. Two assessors will be trained in all tests to be performed, and training will include calibration of the two assessors. Scores from the clinical tests will be noted on a paper form prior to entry into the REDCap database.

Plans to Promote Participant Retention and Complete Follow-Up

All visits to the hospitals, municipality physiotherapists, and NAV consultants are free of charge, and travel costs will be reimbursed. Trial meetings with the participating physiotherapists and NAV consultants will be held before, during, and after the intervention to address questions. All questionnaires will be distributed digitally, thus allowing the participants to answer them in their own pace and to allow for breaks.

Data Management

Digital consent forms and demographic data collected via online forms will be stored securely at the project database at the Tjenester for Sensitive Data (Services for Sensitive Data; TSD). Data for primary and secondary outcome measures will be collected and managed using REDCap. All patient-reported outcome measures (PROMs) will be distributed digitally from REDCap, and responses will automatically be entered into the REDCap database. Point scores for the Trunk Impairment Scale – modified Norwegian Version (TIS-modNV), the Mini Balance Evaluation Systems Test (MiniBESTest), and the 6-minute walk test (6MWT) will be entered manually into the REDCap database. Paper score sheets for clinical tests will be stored in a locked cabinet. Deidentified data stored at the TSD and in the REDCap database will be exported securely into a secure server at the Nordland Hospital Trust prior to statistical analysis. All data will be coded with the participants' study IDs. A list of participants containing both names and study IDs will be sent to NAV, and NAV will return the registry data for all participants with study IDs but without names. All files will be sent securely as password-encrypted files via email; passwords will be sent separately via text messages. The files will be stored at the Nordland Hospital Trust's secure server for research data. The data management plan is stored in the Trial Master File.

Confidentiality

Lists containing all patients with a diagnosis of MS will be collected from the MS outpatient clinics. These lists will be sent via email as password-encrypted files, and the passwords will be sent separately as text messages. Members of the study group will screen the lists against the inclusion and exclusion criteria through access to the hospital journals. Each participant will be assigned a study ID, and only the study ID will be entered into the study database. A key connecting the study ID to the participant's name will be stored separately in the secure study database and will only be accessible to two members of the study group.

Analysis

First, the study aims to generate new knowledge regarding the short- and long-term effects of the CoreDISTparticipation intervention compared to usual care on barriers to work, physical activity, balance, walking, fatigue, and HRQoL in employed individuals with minor-to-moderate disability due to MS. As the intervention is complex and comprises several elements, the study will investigate the overall effects. The variables examined are well-known barriers to work and quality of life in this population [30]. Understanding the relationships between these and the intervention's potential effects will provide valuable knowledge for further development of follow-up care.

Second, this study will provide objective information about health economic factors related to pwMS with low disability. This includes the utility of the CoreDISTparticipation program compared to usual care, expressed in QALYs, long-term employment status, and work-related costs. Given the high work-related costs associated with pwMS [4,7], this study will offer essential insights to further develop follow-up care and potentially enhance workforce sustainability for this group. Thus, the study addresses the part of the follow-up that represents the highest societal costs for pwMS in Norway [4].

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Data Analysis

Raw data from the ActiGraph wGT3x-BT monitors will be converted into categories of minutes of sedative time, minutes of light and moderate-to-vigorous physical activity, and the number of steps per day using ActiLife software. The raw platform data will be filtered using a fourth-order Butterworth filter at 10 Hz. Center of pressure (COP) data will be calculated using BalanceClinic software and exported to MatLab, where the root mean square (values) representing postural sway amplitude will be calculated. Multiple imputations of missing data in PROMs will be applied, when appropriate. EQ-5D-5L answers will be coded into digits according to the recommendations in the instrument handbook. Value sets representative for the Norwegian population will be used in the calculation of a single summary index value.

Statistical Analysis for Primary and Secondary Outcomes

Work Package 1

Intention-to-treat analysis using descriptive statistics and, when appropriate, mixed models will be used to determine possible between-group differences over repeated measurements. Descriptive statistics including graphical methods, nonparametric tests, correlation, and regression analyses will be performed.

Work Package 2

The EQ-5D-5L (from WP1) is the primary outcome measure used in this analysis, which will be supplemented with generic complementary questions. Responses from the EQ-5D-5L will be used to examine the overall net utility gain from the CoreDISTparticipation program compared to usual care. Cost utility analysis is a form of economic evaluation that uses quality-of-life measurements (eg, from the EQ-5D-5L) to compare the cost-effectiveness of different interventions.

A key indicator used in a cost utility analysis is QALY, a measure that combines the quantity and quality of health to calculate treatment outcomes that influence health. The cost per QALY for the two treatments will be modeled against work barriers to determine the relative costs and health benefits associated with each treatment. We will use the data from the study to develop a model to estimate the total costs and gains of the intervention in a lifetime perspective.

No interim analyses are planned. Subgroup analyses based on age, gender, the EDSS score, physical activity level at baseline, and geographical region will be performed, as appropriate.

Analysis to Handle Protocol Nonadherence and Missing Data

The intention-to-treat principle will be applied to all analyses. Withdrawals from the study, loss to follow-up, and other missing data will be reported, as well as adherence to the intervention as attendance is monitored. In the case of missing data, multiple imputations may be performed, if appropriate.

Oversight and Monitoring

Composition of the Coordinating Center and Trial Steering Committee

The Nordland Hospital Trust is the coordinating center for the trial where the Trial Management Group (TMG) works. The TMG consists of the chief investigator and three study co-investigators who are responsible for the setup of the study, the daily management of the trial, the development of study materials with relevant collaborators, promotion, data management, analysis, and dissemination. The Trial Steering Committee (TSC) consists of neurological consultants with trial experience, statisticians, health economists, quantitative researchers, user representatives, and people with expertise in neurological physiotherapy, cognitive and psychological disabilities in MS, and work adaptations. The TSC will conduct annual meetings to oversee the progress of the trial. Representatives from NAV and four user representatives have been involved in planning and promoting the study, as well as creating materials, such as information videos. The user representatives will take part in discussions throughout the project period, particularly regarding results and implications for practice. The user representatives have participated in both physical and digital meetings and play a central role in delivery of information to members of the MS Association, the MS population, and the general population. Throughout the project, they will find possibilities to impact the project and influence clinical practice within the field.

The study has no data monitoring committee as this is not mandatory for studies not investigating the effects of drugs or medical equipment.

Adverse Event Reporting

Any adverse events or harm to the participants during assessments or the intervention will be registered on a case record form and monitored by the TMG. The TMG will keep a log of any negative feedback from the participants. Any serious study-related adverse events will be reported to the regional ethics committee.

The TSC will monitor the progress of the study and adherence to the protocol.

Plans for Communicating Important Protocol Amendments to Relevant Parties

Any protocol amendments will be discussed in the TMG and will be made by the chief investigator, who will send any proposed amendments to the regional ethics committee and the data protection officer at the involved study sites for approval. ClinicalTrials.gov will be updated in the case of any major protocol changes. All participants will be notified via email in the case of protocol changes affecting their participation.

Ethical Considerations

The study has received ethical approval from the Regional Committee for Medical and Health Research Ethics, North (REK-Nord 608117), and the data protection officers at the Nordland Hospital Trust, the University Hospital of

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North-Norway, the Finnmark Hospital, and the Helgeland Hospital. The study will adhere to the Declaration of Helsinki.

All eligible participants will receive a text message sent to their telephone containing a link to Nettskjema (online form provider) and the TSD's secure solution for storing research data (developed and hosted by the University of Oslo) containing an information letter and the opportunity to provide consent. Participants will fill out a questionnaire with information about their employment status and digitally sign the consent form. At Nettskjema and TSD login, digital consent is interfaced with the governmental ID portal. The digital consent forms will be stored securely in the TSD database. The TSD is designed for storing and postprocessing sensitive data in compliance with the Norwegian Personal Data Act and Health Research Act. All participants and partners in the project will be treated with respect, and anonymity of participants will be undertaken.

All participants will provide consent to the publishing of anonymous results. No identifying images or other personal information of the participants will be presented. The information videos and exercise booklet contain films and images of models. They have consented to the materials being distributed, as described in the protocol, and in publications from the study. In the case of ancillary studies in the future, ethical approval and separate consent will be obtained.

Dissemination will be conducted in accordance with the Vancouver Protocol. At least two scientific papers will be published in peer-reviewed journals, and results will be presented at national and international meetings and conferences, such as the Norwegian Physiotherapy Association Congress, the World Congress for Physical Therapists, multidisciplinary congresses on MS (eg, Rehabilitation in MS); at meetings in Norwegian and local MS Associations; and in newspapers, podcasts, and websites.

Results

The protocol is currently version 5 as of December 5, 2023. We completed the enrollment phase and enrolled and randomized 115 participants in two phases as of August 1, 2024. The 15-week retests were completed in December 2024, and data collection is estimated to be completed in September 2025. Results are expected to be published in the first quarter of 2026. An overview of the flow of participants through the study is presented in Figure 3.

Figure 3. Overview of the flow of participants through the study.

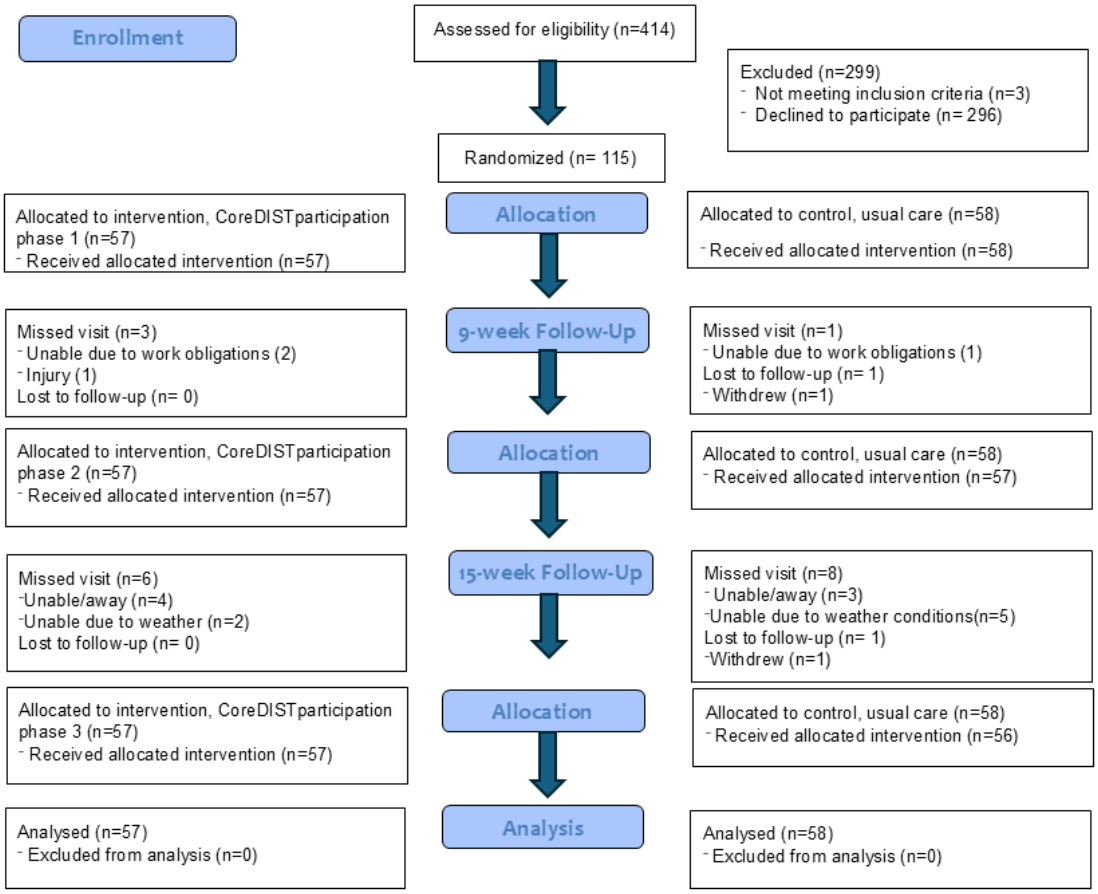

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Discussion

Summary

The study will investigate the effectiveness of CoreDISTparticipation, an innovative comprehensive intervention that is the first to integrate the health and welfare sectors by systematically and proactively addressing physical functions, physical activity, and work adaptations. The study includes employed pwMS with minor-to-moderate disability, a group whose vulnerability in terms of early withdrawal from the workforce is well documented [4,5,18,19,27]. During this stage of MS when disability is minor to moderate, the potential for a significant impact at both individual and societal levels is the greatest [17]. Our hypothesis is that compared to usual care, this comprehensive intervention will positively impact the barriers to work experienced, the levels of physical activity, and balance and dynamic trunk control, as well as HRQoL and health economic aspects, such as utility expressed in QALYs and employment status.

The principal findings of potential short- and long-term reduced work-related barriers and work participation following the CoreDISTparticipation intervention will add new knowledge to meet known challenges regarding early withdrawal from the workforce [4,5,18,19,27]. As CoreDISTparticipation includes information videos about the disease and the possibilities for work-related adaptations for both employers and pwMS, as well as a guide for discussion of such challenges with NAV consultants, these measures can easily be implemented in regular welfare in Norway, as well as adapted to similar health and welfare systems. Thus, this study may meet requests from pwMS for adaptations to increase or maintain their employment status [31], which is essential for HRQoL [5].

Given the positive effects of CoreDISTparticipation on physical activity, this study will add valuable information expanding prior work. So far, it has been difficult to document effects on physical activity [58,59], except for an intervention emphasizing behavioral adaptation [60]. If CoreDISTparticipation proves effective compared to usual care, it will point toward a direction for physiotherapy-led activity highlighting a combination of specific core/balance exercises and high-intensity interval training. Moreover, the study will examine fatigue, balance, postural control, walking, and HRQoL—all well-known barriers to work in this population [30,61]—and will provide a deeper understanding of the relationships between these, which can inform health and welfare services.

Finally, this study will provide objective information about health economic factors related to pwMS with low disability. This includes the utility of the CoreDISTparticipation program compared to usual care, expressed in QALYs, long-term employment status, and work-related costs. Given the high work-related costs associated with pwMS [4,7], this study will offer essential insights to further develop cost-effective models of care and potentially enhance workforce sustainability for this group. Thus, the study addresses the part of the follow-up that represents the highest societal costs for pwMS in Norway [4].

If the novel intervention proves effective compared to usual care, it will offer a low-cost approach to be delivered across sectors and health care levels in both rural and urban settings. CoreDISTparticipation can easily be implemented into routine care as it is integrated into existing health and welfare system structures. Educational materials and training programs for NAV consultants and physiotherapists have been developed, and digital materials to optimize physical functions and physical activity for pwMS are being tested in this trial. The exercise component of the intervention requires low-cost equipment that is typically available in standard physiotherapy practices. Moreover, since the trial involves 4 hospital trusts and 22 municipalities of varying sizes in Norway, the necessary flexibility for implementation in both densely and sparsely populated areas will already be covered. CoreDISTparticpation is the first intervention to introduce a proactive approach to well-known work-related challenges experienced by pwMS. The timing of such support, although in active employment, is so far unexplored within the welfare system.

Additionally, the results from the study may be relevant to inform the follow-up care of other groups of young adults with chronic diseases, particularly in the neurological field. The study will provide the health and welfare sectors with new and highly relevant scientific knowledge that could potentially increase sustained employment and physical activity, which may consequently increase health and HRQoL. Such prospects open for future reduced work-related societal costs and increase in the workforce, which is highly requested by authorities [62].

Limitations

This study is single-blinded as we chose usual care as a comparator and the participants could not be blinded to the treatment they underwent, nor could the physiotherapists who delivered the intervention. The physiotherapists who conducted the testing are, however, blind to allocation.

Although the required number of participants have been recruited successfully, possible issues with implementation fidelity and participant retention may limit the strengths of the study. The physiotherapists involved in the delivery of the intervention have registered attendance and which exercises they have used. These registrations will provide us with insights into whether the intervention has been delivered as intended. In terms of retention, we aim to be as flexible as possible in terms of scheduling of assessments to maintain retention of participants.

Our sample is limited to pwMS who are employed and have an EDSS score of <4. This may limit the ability to make inferences about the feasibility of CoreDISTparticipation for other subgroups of pwMS, such as people who are employed and have an EDDSS score of >4, people who are job seekers, or people who wish to return to the workforce. In addition, the comprehensive nature of the intervention and its focus on physiotherapy and physical activity may attract individuals with an interest in physical activity and may entail fewer participants with more extensive mobility issues or fatigue.

This study will be conducted across a large geographical area, and there is a risk that, for example, the travel distance to test

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sites, particularly during bad weather conditions in winter, may have introduced attrition bias and will require scrutiny of the characteristics of participants lost to follow up.

Acknowledgments

The authors would like to thank the user representatives and all collaborators at the participating hospitals, municipalities, and the Norwegian Labour and Welfare Administration for their contributions in planning this study. This study was funded by the Nordland Hospital Trust, Bodø, Norway, and funded by the Northern Norway Regional Health Authority (grant number HNF1687-23). Neither the study sponsor nor the funder played any role in the study design, collection, analysis, interpretation of the data, and writing and publication.

Data Availability

Key study investigators have access to the final trial dataset. Trial data may be made available to non-study investigators following the approval of a study collaboration request by TSC. There are currently no plans to make the full protocol, participant-level data, and statistical code publicly accessible.

Authors' Contributions

BN is the chief investigator, and ECA and MS are the co–chief investigators. They conceived the study. BN led the proposal and protocol development and wrote the first draft of the protocol. ECA and MS contributed to all parts of the protocol and secured the trial funding. BN, ECA, MS, HF, and ME contributed to development of the intervention. TB and HOM were responsible for statistics and health economic analyses. ME contributed to planning and recruitment. BN and MS drafted the manuscript with the help of ECA and HKF. All authors have reviewed and approved the final manuscript.

Conflicts of Interest

BN and ECA developed the CoreDISTparticipation intervention (Disclosure of Invention/Idea [DOFI] registered) and, piloted and tested it in previous randomized controlled trials (RCTs). Together with MS, HKF, NAV consultants, and user representatives, CoreDISTparticipation was developed, piloted, and included in this RCT. The authors have no financial competing interests.

Multimedia Appendix 1
SPIRIT checklist.
[PDF File (Adobe PDF File), 146 KB - resprot_v14i1e74988_app1.pdf]

Multimedia Appendix 2
Description of starting positions for exercises.
[PDF File (Adobe PDF File), 48 KB - resprot_v14i1e74988_app2.pdf]

Multimedia Appendix 3
Description of all CoreDISTparticipation exercises, objectives, positions, and variations.
[PDF File (Adobe PDF File), 376 KB - resprot_v14i1e74988_app3.pdf]

Multimedia Appendix 4
Conversation guide for the meeting between the participant and the Norwegian Labour and Welfare Administration (NAV) consultant.
[PDF File (Adobe PDF File), 148 KB - resprot_v14i1e74988_app4.pdf]

Multimedia Appendix 5
Peer review reports by the Northern Norway Health Authority Research Program scientific evaluation committee.
[PDF File (Adobe PDF File), 633 KB - resprot_v14i1e74988_app5.pdf]

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Abbreviations

6MWT: 6-minute walk test

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COP: center of pressure
EDSS: Extended Disability Status Scale
HRQoL: health-related quality of life
MiniBESTest: Mini Balance Evaluation Systems Test
MS: multiple sclerosis
MSWDQ-23NV: Multiple Sclerosis Work Difficulties Questionnaire-23 – Norwegian version
NAV: Norwegian Labour and Welfare Administration
PROM: patient-reported outcome measure
pwMS: people with multiple sclerosis
QALY: quality-adjusted life-years
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
TIS-modNV: Trunk Impairment Scale – modified Norwegian version
TMG: Trial Management Group
TSC: Trial Steering Committee
TSD: Tjenester for Sensitive Data (Services for Sensitive Data)
WAA: Work Assessment Allowance
WP: work package

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Protocol

Effects of Aerobic Training Versus Behavioral Intervention to Increase Physical Activity for Disease Control in Patients With Asthma: Protocol for a Randomized Trial

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Abstract

Background: Aerobic training (AT) and behavioral intervention (BI) aimed at increasing physical activity provide numerous benefits to patients with asthma. However, the comparison between the two interventions in the clinical control of this disease is poorly understood.

Objective: This study aims to compare the effects of AT and BI on disease control in people with moderate to severe asthma.

Methods: This is a randomized 2-arm clinical trial with a blinded evaluation. The study will include 56 physically inactive adults with uncontrolled asthma despite optimized medication. Eligible patients will be randomized into either the AT group or the BI group. AT will be performed on a treadmill for 8 weeks (2 sessions per week, 45 minutes each), and the intensity will be determined by the maximum heart rate established in the cardiopulmonary exercise test. BI will be based on social cognitive theory and behavioral change stages that will last 8 weeks (1 session per week, 90 minutes per session). All interventions will last a total of 12 hours. Assessments will be conducted pre- and postintervention and again 16 weeks later and will include physical activity in daily life (PADL; assessed using triaxial accelerometry) level, body composition (measured using octopolar bioimpedance), barriers to PADL (questionnaire), clinical asthma control (Asthma Control Questionnaire), quality of life (Asthma Quality of Life Questionnaire), anxiety and depression levels (Hospital Anxiety and Depression Scale), and number of exacerbations. Time and group interactions will be evaluated using 2-way repeated measures ANOVA. The significance level will be set at $P<.05$.

Results: As of October 2025, 52 participants had been recruited. This study was funded by the São Paulo Research Foundation and the National Council for Scientific and Technological Development. Clinical trial registration was granted in May 2022. Recruitment and data collection for the trial are ongoing, and the results of this study are expected to be available by the end of December 2026.

Conclusions: This is the first study to compare the effects of AT versus BI on increasing physical activity for clinical asthma control. Therefore, the results obtained in the proposed protocol may provide essential information for health care professionals when recommending these approaches to people with asthma.

Trial Registration: ClinicalTrials.gov NCT05364632; https://clinicaltrials.gov/study/NCT05364632

International Registered Report Identifier (IRRID): DERR1-10.2196/78603

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KEYWORDS

asthma; physical activity; physical exercise; sedentarism; quality of life

Introduction

Overview

Asthma is a heterogeneous disease characterized by chronic airway inflammation [1]. It is defined by respiratory symptoms, including shortness of breath, wheezing, chest tightness, and variable expiratory airflow limitation [1]. It is a global problem, and its incidence and prevalence are increasing [2]. Asthma is the second most common chronic respiratory disease and affects approximately 300 million people worldwide [3]. In 2019, 262 million people were diagnosed with asthma, and 461,000 died from the disease [3].

Asthma control strategies include pharmacological and nonpharmacological treatments [1]. A structured and supervised aerobic exercise program, such as aerobic training (AT), is a nonpharmacological behavioral treatment known to improve asthma control [4-7]. Behavioral intervention (BI), aiming to increase physical activity in daily life (PADL), is also part of the nonpharmacological treatment [8]. Both interventions improve the patient's quality of life and asthma symptoms and help minimize exacerbation episodes [7-9].

In 2020, the World Health Organization [10] recommended that adults perform 150 to 300 minutes of moderate-intensity aerobic physical activity weekly to achieve health benefits. People with asthma are less physically active than their healthy counterparts [11]; thus, developing strategies to modify behavior, increase physical activity, and reduce sedentary time among people with asthma is important [12]. Freitas et al [8] applied an 8-week BI to increase PADL and reported improvements in clinical asthma control, PADL, sleep quality, and anxiety symptoms in adults with moderate to severe asthma. Another effective strategy to improve the clinical control of asthma is the AT [13,14]. Furthermore, AT programs have been used as an intervention to reduce the exacerbation of asthma episodes and improve quality of life, making AT a treatment option [9].

Objectives

As previously mentioned, evidence suggests that AT or BI can improve asthma symptoms and reduce comorbidities. However, the comparison between these interventions in improving asthma control remains poorly understood. We hypothesize that these interventions will promote similar benefits in asthma control and quality of life in people with asthma. The main objective of this study is to compare the effects of AT versus BI in increasing physical activity for clinical asthma control. The secondary outcomes will include quality of life, physical activity level, sleep quality, asthma exacerbations, behavioral stages of physical activity, body composition, anthropometric variables, anxiety and depression symptoms, and cardiopulmonary exercise testing (CPET).

Methods

Study Design

This study is a randomized trial with 2 parallel arms and a blinded evaluation. The study will be conducted at a university hospital that offers specialized treatment for moderate to severe asthma. The study protocol was developed in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist guidelines [15], and the trial is registered at ClinicalTrials.gov (NCT05364632). The study flow diagram is presented in Figure 1.

After a regular medical visit, adult outpatients with asthma will be invited to participate in the study, and asthma pharmacotherapy will be maintained during the intervention. Initially, eligible patients will be randomized by a researcher not involved in the study using a computer-generated sequence into 2 groups: the AT group or the BI group. The total duration of each intervention for both groups will be 12 hours (720 minutes). Both groups will be evaluated before and after the interventions and again 16 weeks later. The evaluations will be carried out in a blinded fashion by an evaluator who will not be directly involved in the interventions.

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Figure 1. Study flow diagram of participant recruitment, randomization, interventions, and follow-up assessments. PADL: physical activity in daily life.

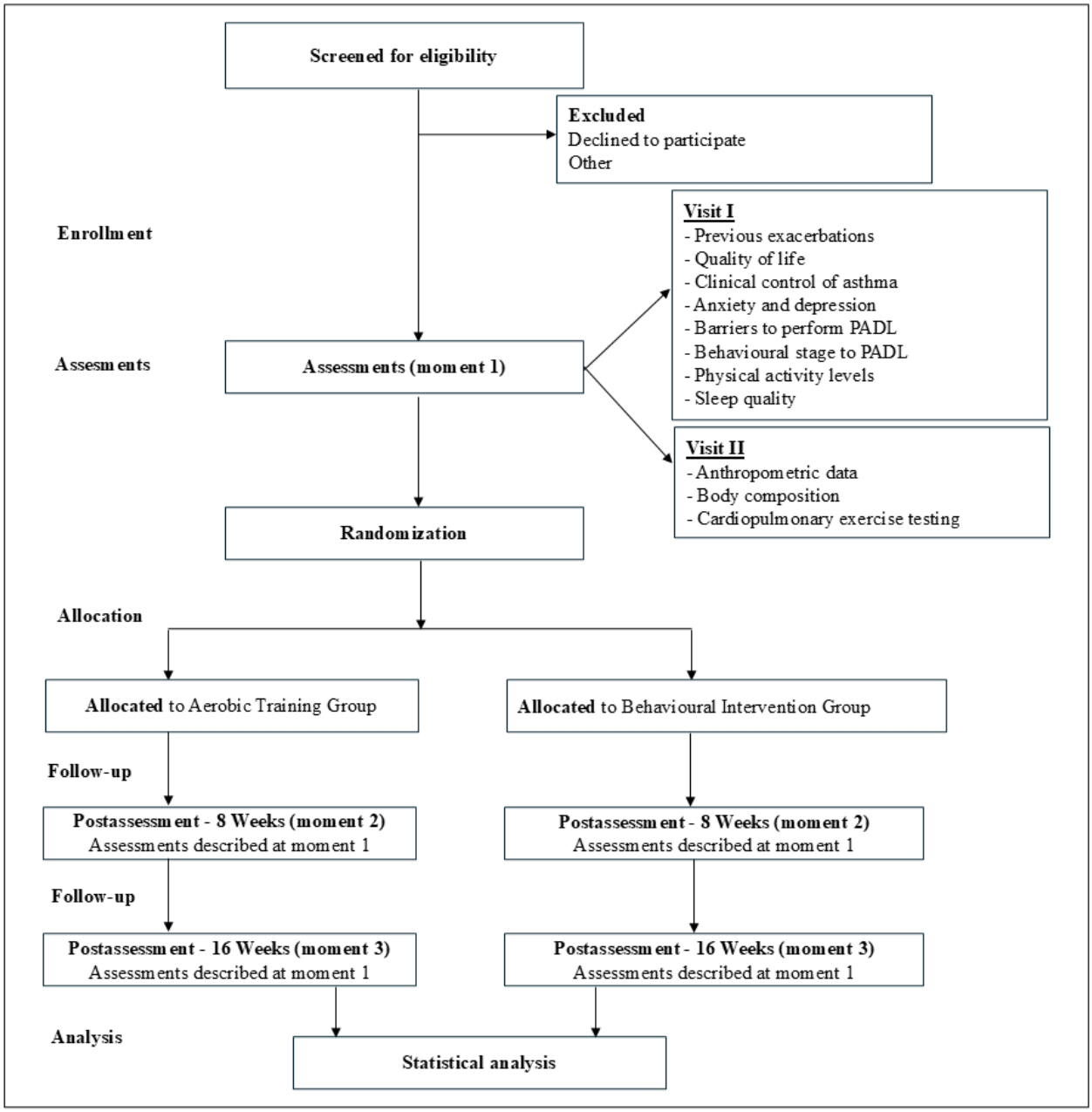

Participants

The study will include adults of both sexes aged 18 to 65 years with moderate to severe asthma [16] who are physically inactive (less than 150 minutes of moderate to vigorous physical activity per week) [17], and patients with uncontrolled asthma (Asthma Control Questionnaire [ACQ]≥1.5) [18]. In addition, the following inclusion criteria will be considered: diagnosis of asthma based on Global Initiative for Asthma recommendations [1], outpatient medical treatment for at least 6 months, and a stable clinical status for at least 30 days (no hospitalizations, visits to emergency services, or medication changes) [19].

Ethical Considerations

Patients will be recruited from the pulmonology outpatient clinic of the Hospital das Clínicas de São Paulo, São Paulo, Brazil. This study will be conducted in accordance with the Declaration of Helsinki. The hospital research ethics committee approved the study (51929221.7.0000.0068). All participants will be informed about the possibility of withdrawing at any time without incurring any loss of treatment at the institution. Participants will receive an identification code upon inclusion in the study. The data will be deidentified by excluding the main identifying elements such as name, address, date of birth, phone number, email, medical record number, institutional identification number, and social security number. In addition, patients will be informed about the voluntary nature of their participation. Financial assistance for transportation will be available. Informed consent will be obtained by researchers from all study participants.

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Randomization

The randomization sequence will be computer-generated via an online platform (Sealed Envelope [20]) and implemented by an independent researcher who will be unaware of the sequence. The researcher will not be involved in recruitment, assessment, or treatment. As described previously, the randomization sequence will be concealed using opaque sequentially numbered envelopes [21]. Each envelope will correspond to one of the 2 study groups, and participants will be sequentially assigned to the envelopes after the initial assessments.

Analysis of the Population

The exclusion criteria will include participation in another study, current smokers or ex-smokers (who stopped smoking less than 1 year ago or had a smoking history of more than 15 pack-years), other associated lung or heart diseases, a diagnosis of cancer in the last 5 years, difficulty understanding any questionnaires, pregnancy, or psychiatric problems that prevent an understanding of the questionnaires. If a patient misses any session, the session will be rescheduled. Attending at least 75% of sessions will be considered the cutoff point to establish patient compliance for both groups [22-24]. An intention-to-treat analysis will be performed using the patient's most recent assessment in case of withdrawal from the study or absence of data [25].

Interventions

Asthma Education Program for Both Groups

All people in both groups will participate in a brief asthma education program of 90 minutes. The educational program will be conducted in a class through group discussions and video presentations. Educational topics will include asthma pathophysiology, medication and peak flowmeter use, self-monitoring of symptoms, environmental hygiene [1,26], and physical activity recommendations and benefits [17].

AT Group

Patients will undergo aerobic physical training on a treadmill twice weekly for 16 sessions, totaling 8 weeks of intervention. Each AT session will last 45 minutes, divided into 5 minutes of warm-up, 35 minutes of aerobic exercise, and 5 minutes of cool-down (2 sessions per week, 45 minutes each). The intensity will be based on the heart rate (HR) corresponding to one third of the difference between the anaerobic threshold and the respiratory compensation point (RCP), and is determined by CPET [27]. After 2 weeks of adaptation, the exercise intensity will be increased to two-thirds of the difference between anaerobic threshold and RCP, obtained via the CPET. If a patient proves capable of sustaining the new training intensity uninterruptedly for 2 consecutive sessions, without presenting respiratory symptoms, the exercise intensity will be increased by 5% of the HR up to a maximum of 85% of the participant's maximum HR [2,3]. Before and after each exercise session, patients will be asked to measure the peak expiratory flow, and if the value is less than 70% of the predicted value or if patients present important symptoms of asthma before or during training, they will be instructed to use 400 µg of salbutamol via aerosol prescribed by their physician [28].

BI Group

The BI will be based on social cognitive theory and the stages of behavior change to increase the practice of physical activity in people with asthma [12,29,30]. Strategies such as motivational interviews, feedback, and guidelines to overcome barriers will be used to make it easier for participants to reach their goals. Individuals will receive a commercially available smartwatch activity monitor (Mi Band 5; Xiaomi) with an alarm that vibrates when the recommended daily number of steps is reached and if the individual remains sedentary for 60 minutes [12]. The main objective of the BI for people with asthma will be to increase PADL at any intensity and reduce sedentary time. The program will be carried out in individual sessions once a week, lasting 90 minutes each, for 8 sessions. At the beginning of the protocol, a motivational interview will identify each participant's behavioral stage for the practice of physical activity through an appropriate questionnaire [31]. In addition, the participants will be asked to complete a daily physical activity diary and sign a contract with their health care professional [12].

Data from each week will be reviewed at every session of the behavioral intervention. Each individual will receive advice based on the smartwatch data. Each session will address different topics related to the practice of physical activity and sedentary behavior. Individuals will be motivated and encouraged to make behavioral changes. In the last session, a final motivational interview will be carried out to identify the change in the patient's behavioral stage, taking stock of the goals reached or not, the benefits acquired with the changes made, the strategies to overcome the most significant barriers, and the establishment of new long-term goals to stay physically active. The schedule and content of each session are detailed in Table 1, which is reproduced from Freitas et al [32]. The Freitas et al [32] protocol will be modified only by changing the activity smartwatch monitor (Mi Band 5; Xiaomi) during the intervention instead of the Fitbit device [32].

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Table 1. Description of the behavioral change intervention sessions.

Number of weeks	Topics covered
Week 1: lifestyle choices	• Motivational interview to establish an educational diagnosis. • Identify the behavior stage regarding physical activity. • Raise awareness of physical activity benefits. • Provide the Mi Band 5 and ask them to wear it for at least 3 d each week.
Week 2: why become physically active?	• Raise awareness of the physical activity international recommendations. • Deepen the knowledge about the physical activity benefits for patients with asthma. • Review Fitbit Flex 2 data of the past week and set one smart weekly goal (number of steps). • Establish the action planning (goal) and sign a contract. • Evaluate the confidence of patients in achieving the goal (self-efficacy). • Explain about the use of the workbook, diary, and vibration alert.
Week 3: sedentary behavior	• Raise awareness of the risks of prolonged uninterrupted periods of sitting. • Ask them to start monitoring their sitting time (diary in a workbook). • Discuss strategies to stand up/break up the sedentary time, according to the Fitbit Flex 2 vibration function. • Review achievement (using the diary and Fitbit Flex 2 data) of the current goal. • Discuss progress of the current goal. • Set one smart weekly goal (number of steps).
Week 4: dealing with barriers	• Dealing with barriers (as part of action and coping planning). • Brainstorm the main barriers and possible solutions or modifications. • Discuss preferred activities. • Invite participants to come up with ideas for walking (progression in duration or intensity). • Congratulate patients on any success (positive reinforcement) and ask them to reflect on any difficulties. • Review achievement (using the diary and Fitbit Flex 2 data) of the current goal. • Progress the current smart goal (number of steps and sedentary behavior).
Week 5: self-control	• Facilitate self-control (how to self-monitor the negative and positive behaviors regarding PA[a]). • Identify the benefits acquired with the lifestyle change and reinforce the commitment to change. • Invite participants to come up with ideas to break up the sedentary time. • Review achievement (using the diary and Fitbit Flex 2 data) of the current goal. • Progress current goals as able or required.
Week 6: setting an additional goal	• Review the initial goal and discuss the progress of this goal (challenges). • Evaluate the confidence about achieving the new goal (self-efficacy). • Reinforce the health benefits of increased participation in PA and of breaking up sedentary time. • Congratulate on any success and reflect on any difficulties. • Review achievement (using the diary and Fitbit Flex 2 data) of the current goal. • Set a new smart goal as able or required.
Week 7: being rewarded	• Identify the behavior stage regarding physical activity. • Discuss the change (or not) that was achieved, as well as the benefits acquired with the new lifestyle. • Discuss positive reinforcement. • Review achievement (using the diary and Fitbit Flex 2 data) of the current goal. • Set a final goal (number of steps).
Week 8: goal balance	• Final motivational interview (goal setting, benefits acquired, and strategies to overcome barriers). • Reinforce the importance of following through with these changes. • Establish a long-term goal to stay physically active.

[a]PA: physical activity.

Participant Timeline

The schedule of enrollment, allocations, interventions, and assessments is outlined in Table 2. The recruitment of the study participants began in August 2022.

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Table 2. Schedule of enrollment, interventions, and assessments.

Study period	Enrollment (t1)	Allocation (0)	Baseline	After allocation (8 wk)	Follow-up (16 wk)
Enrollment					
Eligibility screen	✓				
Informed consent	✓				
Allocation					
Interventions					
Aerobic training		✓	✓		
Behavior intervention		✓	✓		
Assessments					
Lung function			✓		
PADL[a] and sedentary behavior	✓			✓	✓
Asthma clinical control	✓			✓	✓
Asthma exacerbation			✓	✓	✓
Quality of life			✓	✓	✓
Anxiety and depression symptoms			✓	✓	✓
Barriers to performing PADL			✓	✓	✓
Behavioral stage for PADL			✓	✓	✓
Anthropometric data			✓	✓	✓
Body composition			✓	✓	✓
Sleep quality			✓	✓	✓
CPET[b]			✓	✓	✓

[a]PADL: physical activity in daily life.

[b]CPET: cardiopulmonary exercise testing.

Outcome Measures

The primary outcome will be to compare the effects of AT and BI to increase the PADL on clinical asthma control. The secondary outcomes will include quality of life, sleep quality, asthma exacerbations, anxiety and depression levels, barriers that hinder the practice of PADL, body composition, and anthropometric data.

Primary Outcome: Asthma Clinical Control

Clinical asthma control will be assessed using the ACQ, a reliable and validated tool [18,33] that comprises 7 questions [18]. Of those, 5 questions are related to asthma symptoms (waking up at night, activity limitations, shortness of breath, and wheezing), one on rescue medication (short-acting β_2-agonist use), and one on lung function (FEV_1 prebronchodilator, expressed as a percentage of predicted value). The questions are indicated on a 7-point scale ranging from 0 (no limitation) to 6 (maximum limitation), and the total score is the average of the 7 items, ranging from 0 (fully controlled) to 6 (severely uncontrolled). It is considered that values ≥1.5 indicate poorly controlled asthma, 0.75 to 1.5 indicate partially controlled asthma, and ≤0.75 indicate fully controlled asthma [18]. A change of at least 0.5 points in the ACQ score is considered clinically significant [34].

Secondary Outcomes

Physical Activity in Daily Life

PADL will be objectively assessed using an activity monitor (ActiGraph GT9X, ActiGraph), a device that monitors frequency, intensity, and duration [35] in real time and is a sensitive and reliable method [36,37]. This triaxial monitor provides measurements for the amount and intensity of PADL and posture monitoring [35,38] through variations in acceleration. The “counts” obtained during a given period are linearly related to the intensity of the patient’s physical activity in that period [37]. Patients will be instructed to use the accelerometer for 7 consecutive days on the hip secured with an elastic belt. All accelerometers will be initialized to collect data in 60-second “epochs” in the 3 axes via ActiLife software (version 6.9.5; ActiGraph). The data will be analyzed using the same software, including the number of daily steps; the time spent engaging in sedentary behavior; and light, moderate, and vigorous activities. Moderate to vigorous physical activity will also be assessed.

Asthma-Related Quality of Life

Health-related quality of life will be evaluated using the Asthma Quality of Life Questionnaire [39,40]. This questionnaire consists of 32 questions related to the previous 2 weeks and is divided into 4 domains: activity limitation (11 items), symptoms

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(12 items), emotional function (5 items), and environmental stimulus (4 items). The Asthma Quality of Life Questionnaire score ranges from 0 to 7; a higher score will be associated with better quality of life. A difference of 0.5 points is considered clinically significant [41].

Sleep Quality

Sleep quality will be assessed via a monitor (ActiGraph GT9X, ActiGraph) worn on the participant's nondominant wrist. The participants will be instructed to wear the device for 7 consecutive nights. The results for sleep latency (the amount of time required to fall asleep) and sleep efficiency (the number of sleep minutes divided by the total number of minutes the participant was in bed) will be analyzed [8]. The device is valid and reliable for detecting sleep/wake diurnal patterns [42]. In addition, participants will receive a diary for routine analyses covering these 7 nights (time participants went to sleep, time they woke up, and went to sleep on a scale of 0-10).

Asthma Exacerbation

Asthma exacerbation is defined as the patients' need for urgent medical action and a change in pharmacological treatment [43]. During the study, at least one of the following criteria will be used to determine an exacerbation: the use of ≥4 puffs of rescue medication per 24 hours during a 48-hour period; the need for the administration of systemic corticosteroids (pills or injections); or unscheduled medical appointments, visits to the emergency room, or hospitalization [26,32,43].

The Behavioral Stages for Physical Activity

The "readiness for change" assessment will be graded through a questionnaire to assess the following behavioral stages for physical activity: *precontemplation*, *contemplation*, *preparation*, *action*, and *maintenance* [31,44]. Information will be revealed as frequency.

Barriers to Performing Physical Activity

Barriers to the practice of PADL will be assessed via a questionnaire that contains the most common barriers in adults [45,46]. The answer options for each question will include never, rarely, sometimes, almost always, and always, with the score for each item ranging from 0 to 4. Higher scores indicate greater barriers. At the end of the questionnaire, a question regarding the limitations of PADL resulting from the disease will be added, which will receive the same score as the previous questions.

Body Composition and Anthropometric Indexes

Octopolar InBody 720 equipment (Biospace) will be used to measure body weight, fat mass, fat-free mass, visceral adiposity area, and skeletal muscle mass. The InBody 720 uses 8 electrodes to assess body composition according to total body water, protein, mineral, and fat mass. The contact points for the electrode connection will be cleaned with an electrolytic cloth, according to the manufacturer's instructions. At the time of testing, the patient should not be menstruating and will also be instructed not to ingest water for 4 hours and caffeine or alcohol for 12 hours before the test, or to perform physical activity or take a sauna the day before the test, and not to urinate 30 minutes before the test. The data will be electronically imported into Excel via LookingBody 3.0 software (Biospace). Anthropometric data, including height, body weight, abdominal circumference, waist and hip circumference, and waist-to-hip ratio, will be measured according to standardized protocols [47,48]. BMI will be calculated by dividing body weight (in kg) by height (in m^2) [49].

Anxiety and Depression

The Brazilian Portuguese version of the Hospital Anxiety and Depression Scale will be used to assess the symptoms of anxiety and depression [50]. The Hospital Anxiety and Depression Scale consists of 14 questions divided into 2 subscales: anxiety and depression (7 questions each). Each question ranges from 0 to 3 points, with a maximum score of 21 points for each subscale. In this study, a cutoff score (≥9) will be used to classify the presence or absence of anxiety or depression [51].

Cardiopulmonary Exercise Testing

CPET will be performed via an electrical cycle ergometer (Corival; Lode BV Medical Technology) equipped with an electronic system (CPX System; CareFusion) [52]. Peripheral oxygen saturation (SpO_2) and electrocardiography will be continuously monitored during the tests. The following variables will be recorded: work rate, oxygen consumption (VO_2), minute ventilation, carbon dioxide production (VCO_2), respiratory exchange rate, and HR [9]. Blood pressure, leg discomfort, and dyspnea will also be monitored using the Borg scale [53]. The participants will perform the CPET, which is limited by symptoms, consisting of 2 minutes of rest, 2 minutes of warm-up (unloaded pedaling), and a period of work on a ramp (from 5 to 15 W), with increments every minute, according to the participants' daily activity level [9]. AT will be identified as the VO_2 at which the change in the slope of the VCO_2-to-CO_2 ratio occurs. The RCP will be determined by the increased ventilation/VCO_2 values, accentuated tachypnea, and a progressive reduction in end - tidal CO_2 pressure [9]. A 10% correction will be made in the HR at anaerobic threshold and RCP [54,55] because the test will be carried out on a bicycle, and training on a treadmill.

The test interruption criteria will include diastolic blood pressure above 140 mm Hg, sustained drop in systolic blood pressure, systolic blood pressure above 240 mm Hg, motor incoordination, feelings of imbalance, mental confusion, and clinical manifestations of respiratory distress exacerbated by increased workload or associated with electrocardiographic changes in ischemia and severe manifestations of exercise-induced bronchospasm, such as an excessive increase in ventilatory effort, audible wheezing, and signs of respiratory distress [56]. Patients will be instructed to use 400 µg of salbutamol via aerosols if necessary (peak flow, 70% predicted) [6,19,57].

Statistical Analysis Planning

The sample size calculation (n) was established based on the clinical control measured by the ACQ to detect a clinical improvement of 0.5±0.6 points [34]. The required sample size will be 24 patients per group for a total of 48 patients, and a 15% loss will be considered, resulting in a total of 56 patients. The sample power was considered 80% with a significance level of 5%. Before the interventions, clinical, anthropometric,

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physical fitness, PADL, and psychosocial data obtained at baseline will be compared using the 2-tailed *t* test or Mann-Whitney test (depending on data normality) for continuous variables. The chi-square test will be used to compare categorical variables. After the intervention, time and group interactions will be evaluated using a two-way repeated measures ANOVA. The significance level will be adjusted at $P<.05$ for all tests, and the SigmaStat (version 3.5; Systat Software) program will be used for statistical analysis. All the analyses will follow the intention-to-treat principles until 15% of the data are missing. For confidentiality, the participants will be given an anonymous study ID, and only the study investigators will have access to the final trial dataset.

Results

The clinical trial registration was approved in May 2022. Recruitment and data collection for the trial are ongoing, and the results of this study are expected to be completed by the end of December 2026.

Discussion

Potential Relevance and Impact of the Study

This randomized clinical trial, with 2 parallel arms and blinded evaluation, compares the effects of AT and BI on clinical control in individuals with moderate to severe asthma. The effects of physical exercise on people with asthma have been widely discussed in recent years [14], and physical exercise has been proposed as a nondrug therapy for asthma management. AT promotes anti-inflammatory effects in patients with asthma and improves exercise-induced bronchoconstriction [12]. In addition, physical training improves physical conditioning and health-related quality of life, and reduces bronchial hyperresponsiveness, the use of long-term bronchodilators and corticosteroids, and asthma symptoms [5,7,14,27,58,59]. BI, aimed at increasing PADL in people with asthma, also promotes better disease control [8]. Furthermore, recent studies have shown that a higher number of steps per day is associated with better clinical control of moderate to severe asthma [60], and that the minimum clinically significant difference is 1413 steps per day [61]. The results of this study may be highly relevant to clinical practice, as they will enable a similar understanding of how both interventions can improve clinical control of asthma in the short and medium term, regardless of the approach used.

Strengths and Limitations of the Study

This study protocol will be a randomized trial with a 4-month follow-up postintervention. It is essential to determine whether the possible gains will be maintained in the medium term following the intervention. Objective measures of physical activity and sleep quality (ActiGraph GT9X), physical fitness (CPET), and body composition (Octopolar InBody 720) are another strength of this study. One limitation is that assessments using questionnaires are considered subjective measures. However, all tools have been validated and are widely used in interventions for people with asthma. The fact that the study will be conducted in a single hospital center may represent another limitation.

Conclusions

To the best of our knowledge, this will be the first study to compare the effects of AT versus BI on increasing physical activity for clinical asthma control. Therefore, the results obtained in the proposed protocol may provide essential information for health care professionals when recommending these approaches to people with asthma. Additionally, this study may help clarify whether the potential short-term gains following the intervention are maintained in the medium term in people with moderate to severe asthma.

Acknowledgments

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Table 1 was reproduced from from Freitas et al [32], "Effects of a Behaviour Change Intervention Aimed at Increasing Physical Activity on Clinical Control of adults With Asthma: Study Protocol for a Randomised Controlled Trial," which is published under CC-BY License [62]

Data Availability

The datasets generated or analyzed during this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

DHAP, FFdL, and CRFC contributed to the writing of this study protocol. FFdL and DHAP are involved in recruiting and collecting data. DHAP, FFdL, and CRFC will conduct the analyses. ACL, VZC, RAdS, and RMC-P contributed to the review and commented on all versions of this study protocol. All authors approved the final manuscript.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
Peer-review report by FAPESP (São Paulo Research Foundation, Brazil).
[PDF File (Adobe PDF File), 560 KB - resprot_v14i1e78603_app1.pdf]

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Abbreviations

ACQ: Asthma Control Questionnaire
AT: aerobic training
BI: behavioral interventions
CPET: cardiopulmonary exercise testing
HR: heart rate
PADL: physical activity in daily life
RCP: respiratory compensation point
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SpO2: peripheral oxygen saturation
VCO2: carbon dioxide production
VO2: oxygen consumption

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Protocol

Acute Adenosine Receptor Antagonism in Combination With Acute Intermittent Hypoxia to Promote Breathing Plasticity in Amyotrophic Lateral Sclerosis: Protocol for a Randomized, Double-Blinded, Placebo-Controlled Trial

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Abstract

Background: Respiratory impairment is a major concern in amyotrophic lateral sclerosis (ALS), shortening survival and lowering quality of life. One therapy with promise to delay respiratory decline in ALS is acute intermittent hypoxia (AIH), consisting of alternating periods of breathing mildly hypoxic (9%-12% O_2) and normoxic (21% O_2) gas. AIH stimulates spinal, serotonin-dependent neuroplasticity in rodent models, conferring functional benefits in diverse physiological systems without detectable pathology. However, in rodent models, AIH-induced neuroplasticity is constrained by distinct signaling cascades initiated by spinal adenosine.

Objective: We propose to investigate a therapeutic strategy to delay breathing compromise in those living with ALS by combining a selective adenosine 2A (A_2A) receptor inhibitor (istradefylline) with AIH. The fundamental hypothesis guiding this proposal is that a single AIH trial after pretreatment with istradefylline enhances respiratory neuroplasticity versus AIH or sham intervention.

Methods: We propose to evaluate resting breathing, respiratory strength, and participant-reported symptoms in adults living with ALS after combined istradefylline plus AIH. A mixed within- and between-participant study design incorporates 4 test sessions, separated by approximately 2 weeks (±5 days). Testing conditions include single sessions of AIH + istradefylline, AIH + placebo, sham AIH (ie, normoxia) + placebo, and sham AIH + istradefylline. Safety and feasibility will be characterized using the rate of adverse events, changes in vital signs, and participant-reported breathing sensations (Aim 1). Neuroplasticity of breathing and motor function will be evaluated as changes in resting breathing, voluntary respiratory strength, respiratory control, and maximal pinch force (Aim 2).

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Results: As of January 2025, with a target sample of 16 participants in each group, 10 participants with ALS and 5 control participants completed study procedures. Recruiting is ongoing, and the final participant will complete the study by December 2025. Publication of results is expected by the end of 2026.

Conclusions: These aims will provide crucial data regarding the preliminary safety and feasibility of this paired intervention and help optimize therapeutic AIH as a rehabilitation strategy, thereby guiding further research concerning this novel treatment for ALS.

Trial Registration: ClinicalTrials.gov NCT05377424; https://clinicaltrials.gov/study/NCT05377424

International Registered Report Identifier (IRRID): DERR1-10.2196/76105

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KEYWORDS

acute intermittent hypoxia; adenosine A2A receptor; amyotrophic lateral sclerosis; neuronal plasticity; respiration

Introduction

Overview

Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disorder characterized by motor neuron death in the primary motor cortex, brain stem, and spinal cord, leading to muscular weakness and atrophy [1,2]. ALS can lead to progressive, variable weakness of the skeletal muscles involved in swallowing, speaking, coughing, limb movement, trunk control, and breathing. Respiratory muscle denervation causes diaphragm and accessory muscle weakness, hypoventilation, dyspnea, and orthopnea [3,4]. Ineffective airway clearance and aspiration result from bulbar denervation. Respiratory and bulbar dysfunction lead to the need for mechanical ventilation [5], shortened survival, and diminished quality of life [6]. Typical survival is 2-5 years post diagnosis [7]. Treatments that preserve or improve breathing would have a considerable impact on the duration and quality of life.

Acute intermittent hypoxia (AIH) consists of short, repeated exposures to mild or moderate hypoxia (9%-12% O_2), separated by normoxic episodes (21% O_2). Hypoxic episodes activate the carotid body chemoreceptors, sending chemoafferent signals to stimulate medullary respiratory neurons [8] as well as brain stem raphe neurons that contain the neurochemical serotonin. When this neural network is repeatedly stimulated during AIH [9], serotonin release from the raphe neurons triggers cell signaling pathways resulting in new synthesis of brain-derived neurotrophic factor protein. In turn, brain-derived neurotrophic factor strengthens synapses onto respiratory (and nonrespiratory) motor neurons [10-12], increasing respiratory motor output. AIH-induced motor plasticity was first described as a persistent enhancement of phrenic neural activity lasting hours after AIH has ended, an effect known as phrenic long-term facilitation (pLTF); a similar effect occurs in hypoglossal motor neurons [13,14]. pLTF is a form of activity-independent, neuromodulator-induced neuroplasticity that exhibits sensitivity to the pattern of hypoxic episodes and time of day [8,15,16]. Repeated AIH appears to amplify and prolong pLTF without detectable pathology [17-20], Thus, AIH may induce respiratory rehabilitation in ALS as well as other neurological conditions that compromise breathing [21].

Our group recently completed the first clinical trial of AIH administration in patients with ALS compared with unaffected controls. In this study, AIH enhanced tidal volume, minute ventilation, and collective respiratory muscle activation of participants living with ALS versus age- and sex-matched controls. Importantly, AIH was well-tolerated and free of treatment-related adverse effects; the participants typically could not distinguish between AIH versus sham AIH (ie, normoxia) [22].

While the modest AIH used in rehabilitation typically elicits motor facilitation via a serotonin-dependent mechanism (Gq protein–coupled receptor signaling [termed the “Q” pathway]) [8,14,23,24], an alternative AIH-induced signaling pathway results from adenosine (Gs protein–coupled receptor signaling [termed the “S” pathway]) [25-28], acting on adenosine 2A (A_2A) receptors [29]. Serotonin and adenosine signaling oppose one another through powerful cross-talk inhibition; in extreme cases, this “battle” cancels phrenic motor plasticity [28,30-32]. Although both serotonin and adenosine receptors can be activated during mild hypoxia, the serotonergic “Q” pathway predominates. However, multiple personal characteristics, disease states, and treatment factors upregulate the adenosinergic “S” pathway, sufficiently to inhibit plasticity (Figure 1), including aging [33], low estrogen [33-35], inflammation [36], active phase delivery [37], genetic factors [33], and traumatic or neurodegenerative diseases [38].

In rodent models of spinal cord injury, an increased pLTF was observed after the administration of paired AIH and the A_2A receptor inhibitor istradefylline [31]. In a subsequent clinical study, the impact of combined AIH and caffeine, a nonselective adenosine antagonist, found the combined approach further improved walking speed and distance in people with chronic spinal injuries [39]. Thus, combined AIH and A_2A receptor antagonism may amplify respiratory motor plasticity [40]. However, since caffeine is a nonselective adenosine antagonist that also inhibits phosphodiesterase action, off-target effects such as nausea and elevated heart rate (HR) could limit its use in the doses needed to augment AIH plasticity. This study uses istradefylline for its greater affinity for the A_2A receptor and its tolerance in clinical studies of older adults and those with Parkinson disease (PD).

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Figure 1. Competing serotonin- (Q) and adenosine-driven (S) pathways to phrenic motor facilitation. Listed on the right are factors that impact serotonin-dominant plasticity due to increased adenosinergic "S" pathway inhibition. By combining istradefylline with mild acute intermittent hypoxia (AIH), this protocol aims to minimize crosstalk inhibition by reducing S to Q pathway inhibition, allowing full expression of the "Q" pathway.

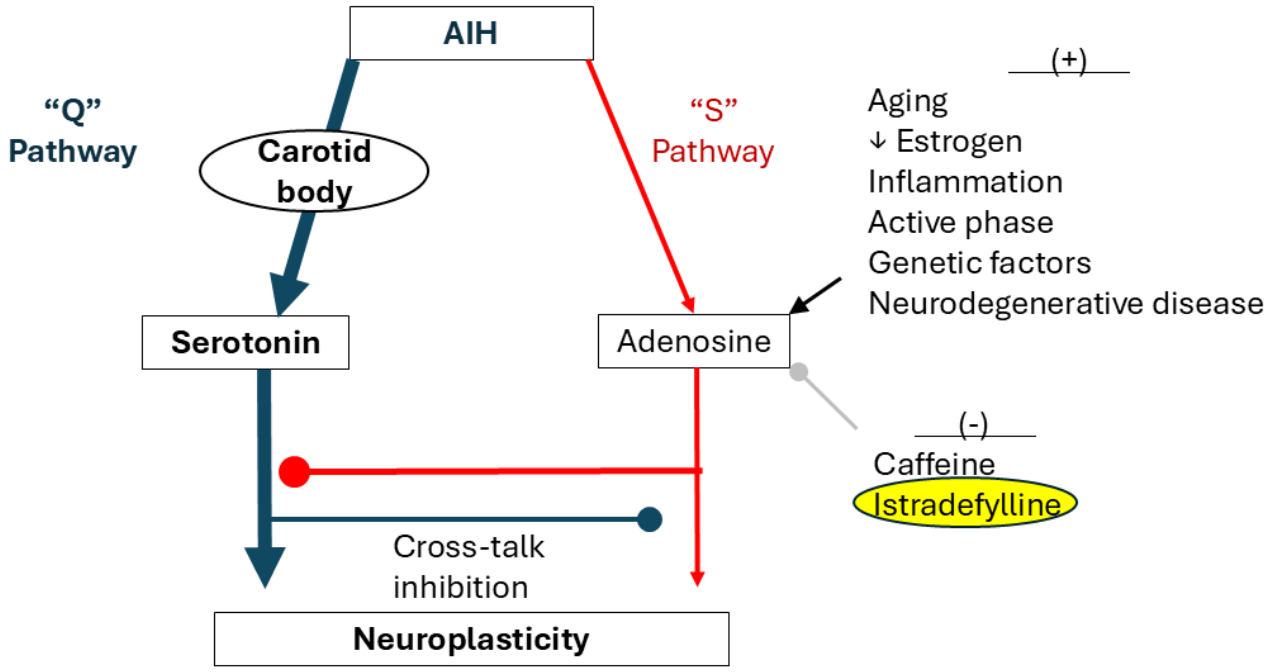

Elevated spinal adenosine is a characteristic of neurodegenerative diseases, such as ALS [41,42]. In the SOD1^{G93A} (copper zinc superoxide dismutase 1) mouse model of ALS, A_2A receptor signaling contributed to motor neuron degeneration, while A_2A receptor antagonism delayed disease progression [42]. A_2A antagonism can also have neuroprotective and anti-inflammatory effects in motor neurons [43]. NOURIANZ (istradefylline) is a highly selective A_2A receptor antagonist currently approved for use in adults with PD to offset inhibitory effects of upregulated A_2A receptors on D2 dopamine receptors of the basal ganglia [44]. Istradefylline reduces daily "off" time in people with PD, improving periods of mobility, and is reported safe and well tolerated [45]. Dyskinesia (5%) and hallucinations (3.4%) were the most common side effects associated with longer-term use [46], but cognition, sedation, or risk of cardiovascular events were not impacted [47]. Considering the demonstrated safety of chronic istradefylline in PD and healthy controls, we hypothesize that this brief, temporary treatment will be safe in ALS.

We further hypothesize that the combination of istradefylline and AIH, in patients with ALS, will elicit greater gains in respiratory and nonrespiratory motor function than either intervention alone, and that will contribute to improvements in breathing and motor function. In a rodent model of phrenic motor neuron death, significant A_2A receptor upregulation preceded motor neuron loss, but the coadministration of istradefylline improved motor neuron survival and maintained diaphragm function [43]. The information gained in this investigation will help us optimize intervention approaches for future studies of repeated, daily AIH as a rehabilitation tool. Thus, this study represents an important step in the iterative process of moving AIH protocols toward clinical practice.

Aims

The objective of this study is to evaluate single and combined effects of selective A_2A receptor antagonism and AIH on respiratory strength, resting breathing, and participant-reported symptoms in adults living with ALS and age-matched unaffected adults. The following two aims are proposed to test the hypotheses:

Aim 1: a single 20 mg istradefylline dose prior to AIH is safe and feasible. Dependent variables will include rate of adverse events (primary outcome), acute changes in vital signs (HR, respiratory rate, blood pressure [BP], etc), patient-reported symptoms (dyskinesias and dizziness), and study completion.

Aim 2: a single 20 mg istradefylline dose prior to AIH improves respiratory motor function when compared to either intervention alone. Dependent variables will include resting tidal volume (primary outcome), breathing rate and minute ventilation, respiratory muscle assessments via multichannel surface electromyography (sEMG), cough force, maximal inspiratory pressure (MIP), and maximal finger pinch force.

Methods

Study Design, Setting, and Recruitment

This is a repeated-measure, double-blinded, placebo-controlled, randomized trial, administered at a single site, the University of Florida (UF). This clinical trial was registered in the United States National Library of Medicine through ClinicalTrials.gov (NCT05377424).

Patients living with ALS will be recruited from the UF ALS clinic, as well as through flyers, word of mouth, and the study registry website. Patients who meet the study criteria will be identified by the study physicians through the UF adult

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neuromuscular clinic. Healthy age-matched controls will be recruited via advertising for the study on ClinicalTrials.gov, StudyConnect, social media for the UF Clinical and Translational Science Institute, and flyers throughout the local community. Additional potential healthy controls will be identified from the Pepper Center Registry maintained by the UF Institute on Aging, and institutional review board (IRB)–approved flyers will be sent to their address. Study interventions will occur at a university-based clinical research center located in Gainesville, FL.

Inclusion Criteria

Eligible participants include nonsmoking adults diagnosed with ALS or age-matched unaffected controls, aged 21-80 years. Eligible participants will have El Escorial diagnostic classification of probable or definite ALS and vital capacity (VC) ≥60% of predicted value; we seek to treat participants before they approach respiratory failure and need for mechanical ventilation, which typically occurs when VC falls below 50% predicted [48]. The ALS Functional Rating Scale-Revised (ALSFRS-R) consists of 12 ordinal items of 5 points (rated 0-4) each, which describe impairments in different systems functionally, where a score of “4” reflects normal function and “0” reflects profound dysfunction [49]. Scores below 2 for respiratory and bulbar items typically reflect severe functional impairment (ie, need for supplemental tube feeding and continuous use of respiratory support). Clinically prescribed ALS medications must be at a stable dose for 30 days.

Exclusion Criteria

Participants (both affected and controls) are ineligible if they are pregnant, have an active respiratory infection, took antibiotics within 4 weeks of recruitment, are diagnosed with another neurodegenerative disease, have symptomatic cardiovascular disease or dysrhythmias, have a BMI of >35 kg/m^2, have a seizure disorder, use respiratory inhalers daily for airway disease, or require external respiratory support while awake and upright. In addition, the following conditions are exclusionary for the use of istradefylline: routine use of CYP3A4 inducers (eg, carbamazepine, rifampin, phenytoin, and St John’s Wort), history of moderate renal impairment or severe hepatic impairment, and history of hallucinations or psychosis.

Rationale for Including Age-Matched Controls

AIH has shown to improve cognitive and exercise performance by improving hemodynamics and work capacity in healthy older adults [50,51]. While effects of AIH and istradefylline have been tested separately in healthy older adults, there is a lack of evidence regarding the additive effects of pairing istradefylline with AIH. Since older adults are the individuals who typically have the greatest need for rehabilitation, we are interested to test whether combined istradefylline and AIH can augment respiratory motor plasticity in healthy older adults.

Healthy older adults have been previously included in clinical trials to evaluate the exposure-response relationship and pharmacokinetic disposition of istradefylline in patients with PD [45,52]. By including healthy older adults in our study, we can determine whether any observed differences with paired AIH and istradefylline among individuals with ALS are specific to ALS or are potentially more generalizable to the older adult population.

Study Procedures

The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) flow chart with all study procedures can be found in Table 1.

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Table 1. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) flow chart with a schedule of enrollment, interventions, and assessments.

Activity	Study period						
	Enrollment	Allocation	Postallocation visits separated by 2 weeks (±5 days), 6-10 weeks total				2-week follow-up
	T–1	T0	T1	T2	T3	T4	T5
Enrollment							
Eligibility screen	✓						
Informed consent	✓						
Allocation		✓					
Interventions							
Istradefylline + AIH[a]			—[b]	—	—	—	
Istradefylline + sham AIH			—	—	—	—	
Placebo + AIH			—	—	—	—	
Placebo + sham AIH			—	—	—	—	
Assessments							
Study completion rate							✓
Adverse events			✓	✓	✓	✓	✓
Vital signs (HR[c]/BP[d])			✓	✓	✓	✓	
Participant-reported symptoms			✓	✓	✓	✓	
Borg dyspnea scale			✓	✓	✓	✓	
Laboratory tests			✓	✓	✓	✓	
Minute ventilation			✓	✓	✓	✓	
MIF[e]			✓	✓	✓	✓	
PCF[f]			✓	✓	✓	✓	
MIP[g]			✓	✓	✓	✓	
SNIP[h]			✓	✓	✓	✓	
Pinch force			✓	✓	✓	✓	

[a]AIH: acute intermittent hypoxia.
[b]Administered at 1 visit, in randomized order.
[c]HR: heart rate.
[d]BP: blood pressure.
[e]MIP: maximal inspiratory pressure.
[f]PCF: peak cough flow.
[g]MIP: maximal inspiratory pressure.
[h]SNIP: sniff nasal inspiratory pressure.

Ethical Considerations

Ethical approval was granted by the UF IRB (IRB 202101568) on May 16, 2022. The US Food and Drug Administration provided clearance for off-label investigational use of istradefylline as described in the protocol (investigational new drug application, approved April 8, 2022; 156267). Informed consent will be obtained in writing from all participants prior to enrollment by study team members. See Multimedia Appendices 1 and 2 for informed consent forms. Participants were informed they would be able to withdraw from the study at any time for any reason. This work is supported by the ALS Association. Outside of the human research protection review, the funding sponsor does not have a direct role in directing the study design; collection, management, analysis, and interpretation of data; writing of the report; or the decision to submit the report for publication.

Health information will be collected, used, and shared with others (ie, clinical and research staff and the UF Research Participant Payment team) to determine if interested individuals are eligible to participate, and then as part of the participation in the study. The following information may be collected, used, and shared with others: medical history, including past

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conditions and surgeries, medications, and information related to diagnosis of ALS; social security number (for reimbursement purposes); demographic information; contact information; and the results of the research tests done for this study. The research team may collect this information from other health care providers, such as laboratories, which are a part of this research, as well as health care providers that are not part of this research (other doctors, hospitals, or clinics). Other professionals at the UF or UF Health Hospital who provide study-related care, and the UF IRB, may also collect health information. Participants will be informed of the collection and protection of health information collected as part of the informed consent process. Health information and study data will be stored in locked filing cabinets or on computer servers with secure passwords or encrypted electronic storage devices, as required by UF policy.

Participants will be compensated US $20 for the screening visit and US $120 for each treatment visit, via prepaid Visa gift cards. Additionally, overnight hotel expenses will be covered by the study for participants traveling from out of town, and lunch will be provided during treatment visits.

Screening

Interested individuals who meet the basic study criteria, agree to participate, and sign the IRB-approved informed consent form will undergo further screening procedures prior to the first interventional visit. Prospective participants will be informed of the eligibility criteria, study procedures, participation risks, privacy and safety precautions in place, alternatives to study participation, and the right to withdraw from the study at any time. The study coordinator will schedule visits and communicate with participants by phone and email. The study coordinator or a designated investigator will complete consenting and screening tests (Figure 2).

Figure 2. Screening procedures. AHI: apnea-hypopnea index; ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; ECG: electrocardiogram; HR: heart rate; VC: vital capacity.

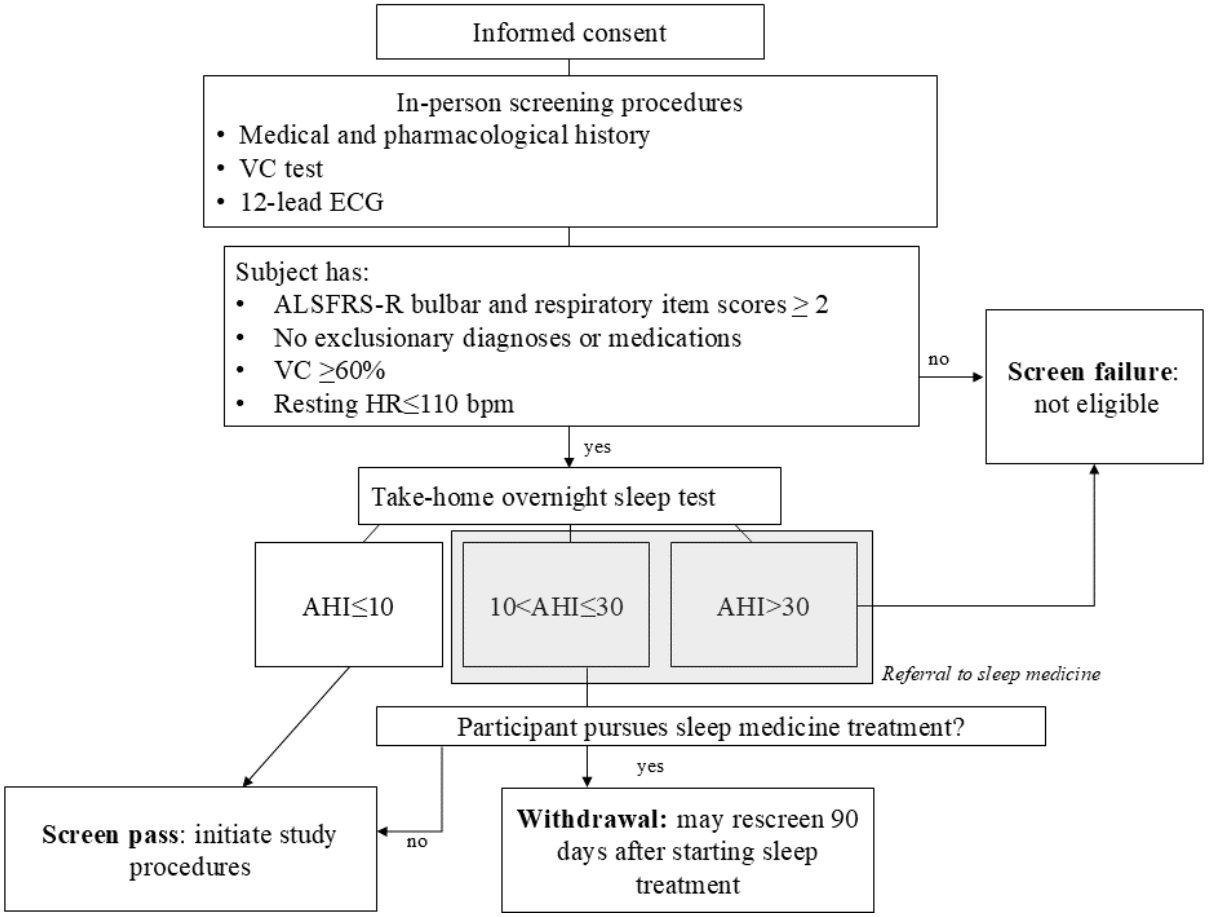

Screening tests shall include:

1. Patient demographic information and medical history: sociodemographic (age and sex), anthropometric (height and weight to calculate the BMI), and general clinical data (medical history, comorbidities, and medications).
2. VC: the maximal volume of gas that can be exhaled, following full inspiration. Upright VC will be administered per American Thoracic Society and European Respiratory Society guidelines [53,54]. Individuals with less than 60% of predicted VC will be ineligible for further participation in this study.
3. 12-lead electrocardiogram: cardiac rate and rhythm will be evaluated. The presence of resting tachycardia (HR >110 bpm), atrial fibrillation, or other dysrhythmias will exclude people from participation.
4. STOP-BANG (Snoring, Tiredness, Observed Apnea, High BP-BMI, Age, Neck Circumference, and Gender) questionnaire: questionnaire to estimate the risk of

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obstructive sleep apnea (OSA) [55]. A meta-analysis found a STOP-BANG score of ≥3 had excellent sensitivity and high discriminatory power to exclude moderate to severe OSA [56].

5. Overnight sleep monitor: participants will wear an overnight sensor that noninvasively monitors arterial oximetry and breathing parameters (Nox T3s; Nox Medical) to estimate the severity of sleep-disordered breathing [57]. If clinically significant OSA (apnea-hypopnea index [AHI] >10 events/hour) is detected, participants will be offered a referral to a clinical sleep specialist for further evaluation. If they choose to pursue clinical treatment for sleep apnea, they will be withdrawn and eligible to rescreen for participation after receiving 3 months of treatment. If they choose not to seek treatment, they will be included in the study. Participants with severe OSA AHI >30 events/hour will be ineligible.

Study Visits

After providing written consent and completing screening, participants will complete 4 individual study visits separated by 2 weeks (±5 days). Visits will include (1) istradefylline + AIH, (2) placebo + AIH, (3) istradefylline + sham AIH, and (4) placebo + sham AIH (Figure 3), in randomized order. Participants will undergo single sessions of each treatment condition. They will be instructed to avoid exercise, caffeine, and nicotine products prior to testing for a minimum of 6 hours and to avoid eating within 1 hour of sessions.

Figure 3. Study design. The gray bars with arrows represent the timing of data collection procedures. AIH: acute intermittent hypoxia; IST: istradefylline.

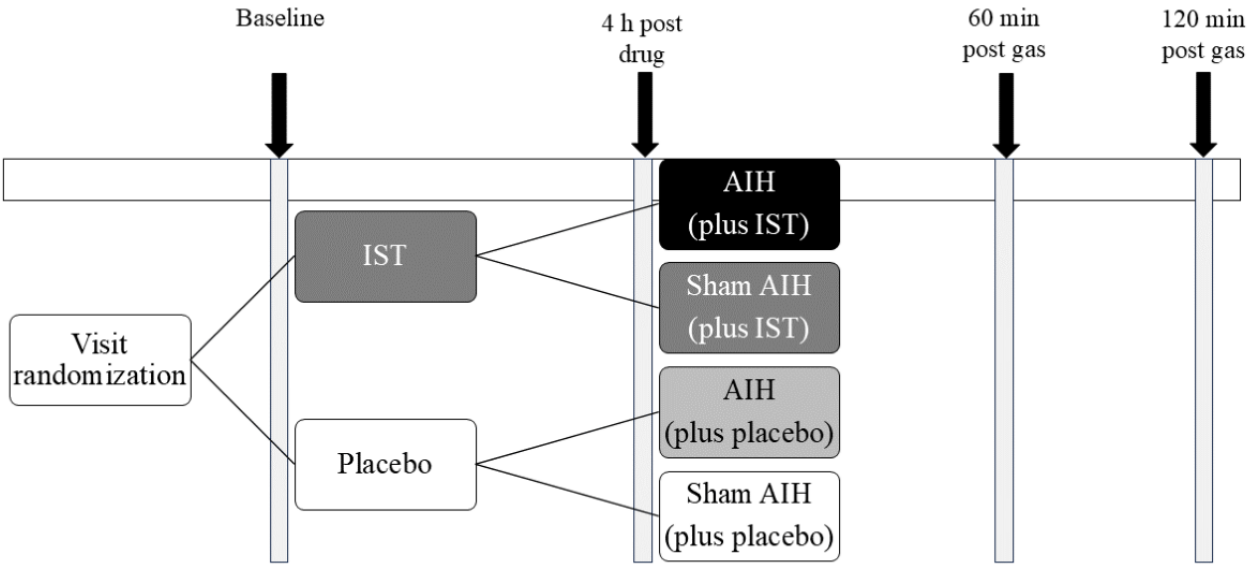

Session order was determined by a random number table generated in advance of the enrollment of the first participant and maintained by the investigational pharmacist. Participants and investigators will remain blinded to istradefylline versus placebo for study administration and data analysis. Participants as well as the investigator collecting test outcomes will be blinded to AIH versus sham AIH. Prior to each study visit, the investigational pharmacist will inform the study coordinator which gas to administer during intervention (ie, hypoxic air for AIH vs normoxic air for sham AIH). Study team members conducting gas treatment cannot be fully blinded to AIH versus sham AIH due to monitoring of pulse oximetry oxygen saturation (SpO_2), which is necessary for safety; thus, the investigator collecting testing outcomes will not be present during gas administration.

Participants will sit upright in a chair with the head and trunk supported while breathing through a sealed face mask. Resting ventilation, respiratory muscle activation, maximal respiratory pressures, maximal pinch force, and blood draws will be completed at the start of each study visit, then participants will receive study medication to be taken orally. After a 4-hour break, all outcome-measure testing will be repeated, followed by gas delivery. Postintervention testing will occur at 60 and 120 minutes following gas delivery. Table 2 delineates outcome measures taken at each time point.

Study visits are expected to last 7-8 hours, including equipment setup, repeated outcome measurements, oral administration of study medication, waiting periods, gas delivery, patient positioning and pressure relief, rest, and snacks or meal breaks.

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Table 2. Timing of variable measurements throughout study visit.

	Baseline	4 h post drug	Gas delivery	60 min post gas	120 min post gas
Adverse events	✓	✓	✓	✓	✓
Vital signs (HR[a]/BP[b])	✓	✓	✓	✓	✓
Participant-reported symptoms	✓	✓		✓	✓
Borg dyspnea scale			✓		
Laboratory tests	✓	✓		✓	
Minute ventilation	✓	✓	✓	✓	✓
MIF[c]	✓	✓		✓	
PCF[d]	✓	✓			✓
MIP[e]	✓	✓		✓	
SNIP[f]	✓	✓			✓
Pinch force	✓	✓			✓

[a]HR: heart rate.
[b]BP: blood pressure.
[c]MIP: maximal inspiratory pressure.
[d]PCF: peak cough flow.
[e]MIP: maximal inspiratory pressure.
[f]SNIP: sniff nasal inspiratory pressure.

Independent Variable—A2A Antagonist Versus Placebo

During each study visit, participants will take a single, 20 mg NOURIANZ pill or an identical-appearing placebo. The study agent will be taken after the completion of baseline breathing tests. Study gas delivery will begin 4 hours later. During the 4-hour waiting period, participants will have a private room with a bed and recliner and access to water, snacks, and a light meal, as well as bathroom facilities. Participants will also be free to move about the research unit.

Independent Variable—AIH Versus Sham AIH

Following the 4-hour break and second round of testing, participants will undergo a 45-minute session of either AIH (up to 1 minute of 9%-10% O_2 with 2 minutes of 21% O_2 for 15 cycles; target SpO_2 nadir 82%-85%) or sham AIH (Figure 4). During sham AIH administration, the 1-minute periods of study gas will use a gas bag containing 21% O_2, with 2-minute room-air periods, so that participants are breathing normoxic air for the entire session. Outcome measures will be repeated 60 and 120 minutes after gas delivery.

A schematic of the respiratory circuit is shown in Figure 5. Participants will sit upright in a chair with the head and trunk supported while breathing through a sealed face mask (Hans Rudolph 7450). The face mask will be connected to a 2-way nonrebreathing valve (Hans Rudolph 2700) that allows the exhaled breath to escape to room air. A pressure transducer (MK1S, GM Instruments) and gas analyzer (Gemini CO_2 & O_2 monitor; CWE Inc) will be connected directly to the face mask connector. A pneumotachograph (Hans Rudolph 4813) will be connected to the inspiratory port of the nonrebreathing valve. Gas bags will be connected to a 3-way stopcock valve (Hans Rudolph 2100), and the direction of the valve will be manually alternated between the study gas (1-minute intervals) and normoxic room air (2-minute intervals). Respiratory data will be recorded during gas delivery, using a data acquisition system (PowerLab 16/35 and PowerLab C; ADInstruments).

Respiratory rate, targeted O_2 value, end-tidal CO_2, HR/rhythm, and SpO_2 will be continuously monitored during the testing sessions. Multichannel sEMG (Trigno Centro; Delsys) will also be recorded from respiratory muscles (bilateral submental, scalene, sternocleidomastoid, second parasternal, and diaphragm) as well as abductor pollicis muscle during testing and captured in real time in LabChart (AD Instruments). At the end of each 1-minute hypoxic (or sham-hypoxic) presentation, participants will report their rating of dyspnea (10-point modified Borg scale). For every fifth presentation, noninvasive BP will be taken. We will establish an individualized communication plan (eg, hand signal, head tilt, call switch, etc) prior to study gas administration to ensure that all participants can alert the investigator of any discomfort, shortness of breath, or requests to remove the face mask.

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Figure 4. Schematic of acute intermittent hypoxia (AIH) and sham AIH interventions. AIH sessions will consist of 1-minute intervals of hypoxia (10% O2) separated by up to 2-minute intervals of normoxic room air (21% O2). Sham AIH will use identical equipment, but the gas bag will contain 21% O2.

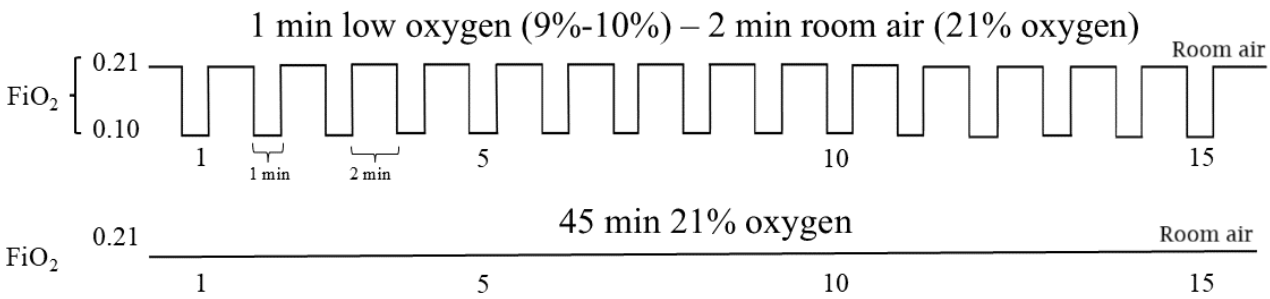

Figure 5. Schematic of the respiratory circuit for gas delivery. AIH: acute intermittent hypoxia; BP: blood pressure; ETCO2: end-tidal CO2; ETO2: end-tidal O2; HR: heart rate; PL: PowerLab; SpO2: pulse oximetry oxygen saturation.

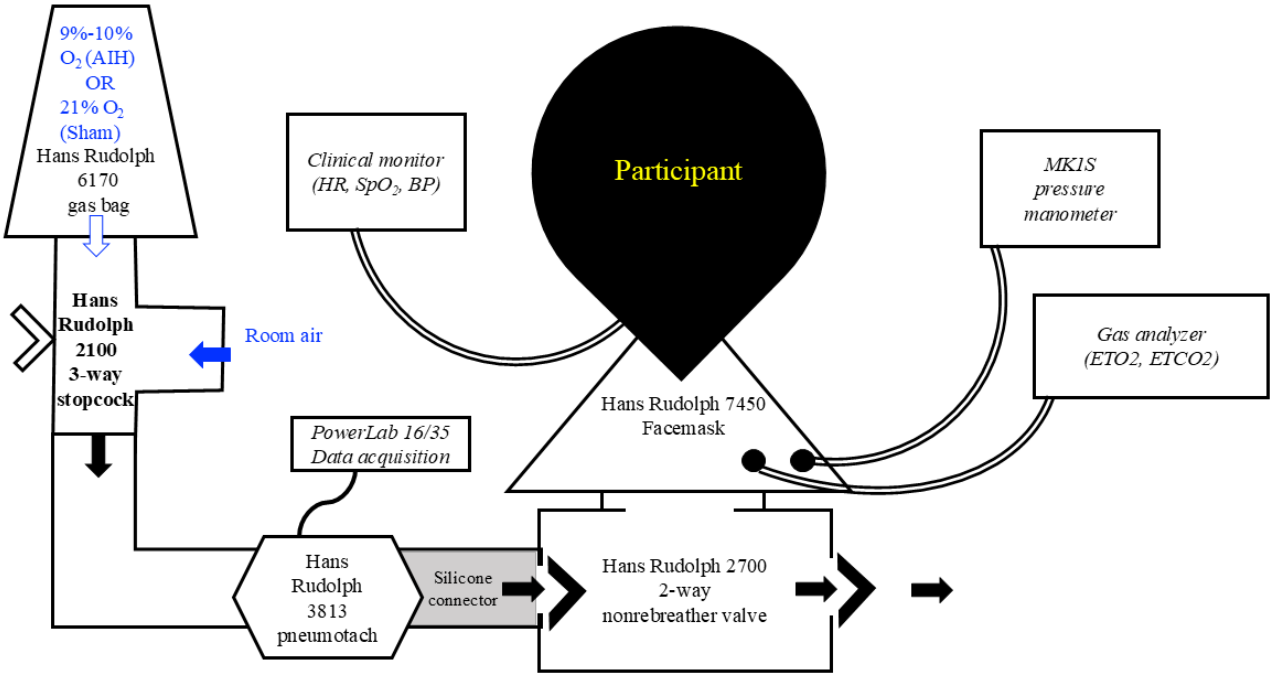

Safety Considerations

The target SpO_2 during AIH is 82%-85% O_2. If the SpO_2 reaches the lower limit of the target range, gas delivery will be switched to the normoxic recovery time. Subsequent hypoxia durations will also be reduced by 5 seconds. AIH will be stopped in the unlikely event the HR increases or decreases >30% from the resting value, or systolic BP changes >30% from the resting value. The expected acute physiological response to hypoxia is a stable or decreased CO_2 due to increased ventilation. However, if end-tidal CO_2 increases >3 mmHg above baseline, we will shorten AIH bouts using the same process described above for SpO_2. Additional stopping criteria include a respiratory rate of >30 that fails to normalize within 1 minute of normoxia, SpO_2 <82% that fails to normalize within 1 minute of normoxia, or SpO_2 <82% occurring within 30 seconds of hypoxia initiation.

In the unlikely event that a participant is injured as a direct result of participation in this study, professional services rendered by any UF Health Science Center health care provider will be provided without charge. These health care providers include physicians, physician assistants, nurse practitioners, dentists, and psychologists. Any other expenses, including UF Health hospital expenses, will be billed to the participant or his or her insurance provider.

Safety oversight will occur internally through the local IRB and a data safety monitoring board (DSMB). The DSMB was convened before enrollment of the first patient, after completion of the first 3 participants, and at least annually thereafter. The DSMB includes 3 members—1 expert in intermittent hypoxia, 1 clinical medicine expert who interprets or prescribes respiratory testing and treatment, and 1 rehabilitation specialist.

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Testing and enrollment of participants will be paused, and DSMB will convene for any of the following events: (1) any clinically significant respiratory event, (2) a clinically significant cardiovascular event, or (3) a serious adverse event as defined by the UF IRB. Should any of the events occur, research staff shall inform the IRB and the DSMB. Any subsequent study activities would only be resumed when cleared or the protocol modified by the IRB and DSMB. As of January 2025, these serious events have not occurred, and the DSMB has only been convened for planned early and annual meetings.

Aim 1 Dependent Variables

1. Adverse events: adverse events will be tracked and recorded per usual IRB requirements and reported as the Aim 1 primary safety outcome. It is hypothesized that there will be no difference in the rates of adverse events among study conditions.
2. Cardiopulmonary responses: vital signs and cardiac rhythm will be monitored throughout administration of each test condition. These measurements will be used in real time to monitor intervention safety, particularly during gas administration, as outlined under "safety considerations." Additionally, 1-minute averages of HR, BP, end-tidal CO2, and SpO2 will be compared at baseline, 60 minutes, and 120 minutes following study gas delivery. It is anticipated that these measurements will remain stable at these time points.
3. Laboratory tests: baseline blood samples will be drawn for each session and include routine clinical laboratory tests (complete blood count, chemistry) and uric acid. Blood samples will be drawn for plasma istradefylline levels at the baseline of each study visit and 4 and 6 hours after ingestion of the study medication. It is anticipated that laboratory test values will remain stable across visits. Participants will be offered an intravenous line to be placed at the start of the visit to avoid multiple venipunctures.
4. Participant-reported symptoms: participants will complete 10-point visual analog scales to rate the intensity of symptoms (of dyspnea, dizziness, weakness, fatigue, nausea, and involuntary movements) at the following time points: baseline, 4 hours after taking the drug or placebo, and 60 and 120 minutes after gas delivery. It is anticipated that symptoms will remain stable across time points and visits.
5. Study completion rate: the primary feasibility outcome will be the proportion of participants who complete all study visits. Additional feasibility metrics will include screening failures, proportions of interested participants who are ineligible, and timeliness of study milestones.

Aim 2 Dependent Variables

1. Quiet breathing assessment: the pneumotachograph and pressure transducer connected to the face mask will record breath-by-breath flow, tidal volume, airway opening pressure, and breathing rate. After achieving a stable tidal volume, minute ventilation will be recorded for 5 minutes. The primary outcome for Aim 2 is an increase in tidal volume from baseline to postintervention 120-minute follow-up. Minute ventilation will be measured at baseline, just prior to study gas delivery, and 60 and 120 minutes post gas intervention.
2. Respiratory muscle assessment: sEMGs of the respiratory muscles and the abductor pollicis muscle (nonrespiratory control muscle) will be recorded as described above to assess effects of intervention on motor control. To identify the muscles active during the quiet breathing assessment, the root mean square of each muscle signal will be averaged. Multimuscle activation will be calculated using a validated, vector-based measure that indexes the magnitude and pattern of composite electromyography activity [58]. The composite respiratory muscle activity from each participant with ALS will be contrasted to the averaged composite magnitude and pattern of the pooled control sample [59]. It is anticipated that composite magnitude will be lower in people with ALS than in controls and increase with intervention, especially with combined AIH + istradefylline.
3. MIPs: inspiratory force generation will be assessed as the maximal voluntary pressure generated by the inspiratory muscles (MIP) against a closed valve, measured at the mouth [60]. Sniff nasal inspiratory pressure measures inspiratory force generation at the nose. These tests will be used as surrogate measures of respiratory strength. Each test will be repeated until 3 measurements are obtained within 10% variability; a minimum 20-second rest will be provided between measurements. A recent systematic review reported a high level of evidence for concurrent validity for MIP; however, interrater reliability was low [61]. To minimize interrater reliability, we standardized instructions given to participants across sessions and used the same rater for each participant. MIP will be measured at baseline, immediately prior to study gas delivery (4 hours after drug administration), and 60 minutes post gas delivery. Sniff nasal inspiratory pressure will be measured at baseline, immediately prior to study gas delivery, and 120 minutes post gas delivery. We hypothesize that these measures will be lower in people with ALS than with controls and will increase with intervention, especially with combined AIH + istradefylline.
4. Maximal airflow testing: peak airflows will be collected with a pneumotachograph attached to the face mask during maximal inspiration (maximum inspiratory flow) and voluntary coughing (peak cough flow). Tests will be repeated for 3-5 trials; at least a 30-second rest will be provided between measurements, but participants may rest as long as needed. Maximum inspiratory flow will be tested at baseline, just prior to study gas delivery, and 60 minutes post intervention. Peak cough flow will be tested at baseline, just prior to study gas delivery, and 120 minutes post intervention. We hypothesize that these measures will be lower in people with ALS than with controls and will increase with intervention, especially with combined AIH + istradefylline.
5. Maximal voluntary pinch force: maximal static voluntary pinch force will be included as a nonrespiratory control. Pinch has been recognized as a sensitive marker of ALS disease severity due to preferential thenar wasting [62]. A recent study found fair to good test-retest reliability for this measure [63]. Pinch force will be evaluated in a seated

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position with the arm at the side in 90-degree elbow flexion and neutral forearm and wrist. The test will be repeated until 3 measurements are obtained with <10% variability, with a minimum 30-second rest between measurements. Pinch force will be measured at baseline, just prior to study gas delivery, and 120 minutes post gas intervention. We hypothesize that these measures will be lower in people with ALS than with controls and will increase with intervention, especially with combined AIH + istradefylline.

Secondary outcome measures will be interpreted as exploratory in nature.

Sample Size, Data Management, and Statistical Analysis

The sample size calculation was based on pilot data from 8 adults with ALS showing ventilation changes in AIH versus a sham condition. The preliminary data showed 10.3% (SD 23%) larger tidal volume and 10% (SD 29%) greater minute ventilation 60 minutes post AIH, as compared to sham. Published work in rodent spinal cord injury models indicates that istradefylline paired with AIH greatly enhances improvement in diaphragm activity versus AIH or drug alone (effect size of combined approach: d=1.92).

Additional preliminary data using caffeine as a nonspecific adenosine receptor antagonist conservatively suggested a capacity for a 10% additional gain in ventilation. With 16 crossover participants, a repeated measures ANOVA comparing 4 conditions across 4 time points, with a pooled SD of 15.3, will be sensitive to detect a difference of power of >0.8 (f=0.31; $F_{3, 36}$=2.86; ρ=0.5; α=.05). A target sample of 24 participants will account for potential attrition. The design includes age-matched unaffected adults as a comparator group.

Descriptive statistics, including frequencies, means, SDs, and medians, will be used when appropriate. Continuous variables will be summarized with descriptive statistics, and categorical variables will be summarized with counts and percentages. Demographics and disease-progression variables will be reported descriptively; while these are not included in a priori analyses of study aims, they may be used in an exploratory manner to interpret findings as appropriate. Change scores and percent change scores will be calculated from baseline for follow-ups at postdrug or placebo administration, 60 and 120 minutes after gas intervention. We will attempt to minimize missing data by planning the study procedures and proper biosignal acquisition, thoroughly documenting the study administration and data collection, and collecting the essential information to complete the study aims. Should missing data points still occur, statistically valid analyses that appropriately address the missing values are maximum likelihood, expectation maximization, and multiple imputation [64]. Any statistical code or algorithms developed to analyze acquired data will be available and shared upon request.

Results

This study received funding from the ALS Association starting in January 2022 and was registered on ClinicalTrials.gov in April 2022 (Multimedia Appendix 3). Recruitment for this study began in June 2022. As of January 2025, a total of 12 people with ALS and 8 age-matched controls have completed informed consent. Of these, 1 person with ALS was withdrawn after the screening visit, and 1 was withdrawn after 2 study visits. A total of 3 of the consented potential control participants were deemed ineligible following the screening visit. Thus, 10 participants with ALS and 5 age-matched controls have completed all study procedures. Recruiting is ongoing, and the final participant will complete the study by December 2025. The publication of results is expected by the end of 2026.

Discussion

This clinical trial will evaluate the effects of istradefylline paired with AIH on breathing function in people with ALS and unaffected age-matched controls. It is anticipated that this combined treatment will be safe and feasible, and that when combined, istradefylline and AIH will result in greater gains in respiratory function (eg, increased tidal volume and increased MIP) than either treatment alone.

Individuals living with ALS face progressive neuromuscular disease that leads to paralysis from motor neuron death. While recently approved ALS drugs offer more options to treat the disease, combinatorial strategies will likely be needed to preserve motor function and independent breathing for as long as possible. To our knowledge, this is the first clinical trial to assess the combined effects of A_2A receptor antagonism and AIH in ALS.

AIH is easy to apply and well-tolerated by most individuals, including people with ALS in a preliminary study conducted by our group [22]. In several studies of humans with chronic spinal cord injury, similar AIH protocols did not lead to adverse events [18,65-70]. We expect AIH will, likewise, be safe and well-tolerated by people with ALS and age-matched controls in this study.

NOURIANZ (istradefylline) has been studied extensively both in participants living with PD and in healthy adult participants. Population pharmacokinetic studies were summarized previously and included both single and repeated daily administration (up to 16 weeks) of istradefylline doses ranging between 10 and 200 mg [52]. Safety was established in participants living with PD and unaffected older participants, with few and minor side effects. In controlled trials, the most common adverse events with repeated daily treatment of istradefylline included dyskinesias, dizziness, hallucinations, and insomnia. These adverse events occurred more frequently after treatment with 40 mg of istradefylline [52]. As this study will use a treatment dose of 20 mg of istradefylline, we anticipate this therapy will be safe and well tolerated by participants with ALS as well as age-matched controls.

Regarding efficacy in people with spinal cord injury, AIH also improved limb function, increased walking speed, and improved ankle strength [12,18,65,67,68,70,71]. AIH combined with task-specific training enhanced hand and walking function [65,68]. However, other studies reported variable responses, indicating that AIH efficacy can be dependent on other factors (ie, time of day, gas composition, sex, age, and genetic mutations

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associated with variable plasticity and rehabilitation responses) [33,72-74]. These variables require further study to optimize rehabilitation strategies for treatment efficacy.

The strengths of this study include the use of a controlled AIH protocol associated with istradefylline use and the comprehensive assessment of variables such as adverse events, vital signs, changes in resting breathing, voluntary respiratory strength, respiratory control, and maximal pinch force. Assessing these variables increases the accuracy of the results, allowing a more complete assessment of changes in response to hypoxia associated with istradefylline. The study design, a randomized, double-blind clinical trial, strengthens the validity of the findings, reducing potential bias. Recruitment of participants with early-stage ALS and random allocation to intervention and control groups ensures that the results are relevant and generalizable to this population.

This study has great importance for scientific advancement, as it investigates the applicability of AIH + istradefylline as a therapeutic intervention for individuals with ALS, a population that faces significant health management challenges. If the results show significant improvements in the studied parameters, this may indicate that AIH + istradefylline is a promising strategy to be integrated into care programs for people with ALS, complementing traditional care approaches, potentially improving the overall health of these individuals and facilitating the care process.

We acknowledge multiple limitations of this study. ALS is a heterogeneous disease, and participants may have variable disease severity, chronicity of illness, limb and bulbar involvement, and requirement of ventilatory support. This limitation will be minimized by clarifying and emphasizing the inclusion and exclusion criteria. Further, there is conflicting evidence from rodent models that A_2A receptor activation may offer some neuroprotection, particularly in presymptomatic ALS, which raises mild concerns about its inhibition [38]. This concern is minimized in this study by the recruitment of participants with symptomatic ALS, close safety monitoring in accordance with Aim 1, and the brevity of the treatment (only 2 active doses of istradefylline). If negative effects of istradefylline are found, this possibility will need to be explored further in the future.

Additional considerations include interinvestigator variability in biosignal acquisition in sEMG and respiratory signals. To address this concern, we will train study staff to follow carefully designed and thorough standard operating procedures throughout data collection. Lastly, this study is not designed to test multiple repeated exposures of the treatment conditions and will not assess any long-term rehabilitative effects of AIH, istradefylline, or combined treatment. Rather, this study intends to inform the design of optimized therapeutic approaches and guide future studies into the rehabilitation of respiratory function in people with ALS.

Acknowledgments

Figures were partly generated using Servier Medical Art, provided by Servier, licensed under a Creative Commons Attribution 3.0 Unported license [75].

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WLO was affiliated with the listed University of Florida departments at the time of protocol development and is currently affiliated with Appalachian State University. PSC was affiliated with the listed University of Florida departments at the time of protocol development and is currently affiliated with the University of Santa Catarina State.

Data Availability

Additional data and materials will be made available upon reasonable request to the corresponding author.

Authors' Contributions

BKS, GSM, NJN, and JPW developed the study protocol and secured funding. BKS and PSC obtained regulatory approvals. BKS, PSC, MSH, WLO, and WSL will complete study-related interventions. JPW will conduct medical oversight. BKS, WLO, GSM, MSH, WSL, and NJN will contribute to data analysis and interpretation. All authors contributed original ideas, read and approved the manuscript, and did not use professional writers or generative AI in the preparation of this manuscript. Additional manuscripts generated by the authors using the data collected by this protocol will not use professional writers.
Conceptualization: BKS, GSM, NJN, and JPW
Data curation: BKS, NJN, WLO, PSC
Formal analysis: BKS, NJN, WLO, PSC
Funding acquisition: BKS, GSM, NJN, and JPW

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Investigation: BKS, PSC, MSH, WLO, AKV, and WSL
Methodology: BKS, GSM, and NJN
Project administration: BKS, PSC, MSH, AKV
Resources: BKS, PSC, WSL
Software: NJN
Supervision: BKS, JPW, MTP, AKV
Validation: BKS, PSC, WSL
Visualization: BKS, PSC, MSH, GSM, AKV
Writing—original draft: PSC (lead), MSH, WLO, BKS (support)
Writing—review & editing: all authors

Conflicts of Interest

None declared.

Multimedia Appendix 1
Informed consent form for participants with amyotrophic lateral sclerosis.
[PDF File (Adobe PDF File), 608 KB - resprot_v14i1e76105_app1.pdf]

Multimedia Appendix 2
Informed consent form for control participants.
[PDF File (Adobe PDF File), 658 KB - resprot_v14i1e76105_app2.pdf]

Multimedia Appendix 3
Trial registration table.
[PDF File (Adobe PDF File), 88 KB - resprot_v14i1e76105_app3.pdf]

Multimedia Appendix 4
Peer review report by 21CTA App Review Committee, ALS Association.
[PDF File (Adobe PDF File), 114 KB - resprot_v14i1e76105_app4.pdf]

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Abbreviations

A2A: adenosine 2A receptor
AHI: apnea-hypopnea index
AIH: acute intermittent hypoxia
ALS: amyotrophic lateral sclerosis
ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised
BP: blood pressure
DSMB: data safety monitoring board
HR: heart rate
IRB: institutional review board
MIP: maximal inspiratory pressure
OSA: obstructive sleep apnea
PD: Parkinson disease
pLTF: phrenic long-term facilitation
sEMG: surface electromyography
SOD1: copper zinc superoxide dismutase 1
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SpO2: pulse oximetry oxygen saturation
STOP-BANG: Snoring, Tiredness, Observed Apnea, High BP-BMI, Age, Neck Circumference, and Gender
UF: University of Florida
VC: vital capacity

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Protocol

Solution-Focused Brief Intervention for Substance Use: Protocol for a Multisite Randomized Controlled Trial

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Abstract

Background: Substance use is a high-impact biopsychosocial problem in Chile, where 21% of adults have experienced a severe alcohol use episode. In the past year, the prevalence rates were 12.5% for marijuana, 0.8% for cocaine, and 0.4% for cocaine base paste. Cannabis prevalence in Chile is higher than the global (4.2%) and South American (3.58%) averages. Cocaine prevalence in Chile is lower than in South America (1.62%) but higher than the global average (0.42%). No international reports are available for cocaine base paste. Mental health and substance use programs in Chilean primary care involve psychologists and social workers. Solution-focused brief interventions (SFBIs) are based on solution-focused brief therapy, a strengths-based and person-centered approach in which practitioners adopt a stance of "not being the expert," respecting clients' needs and perspectives.

Objective: This study aims to determine whether the SFBI implemented by psychosocial teams (psychologists and social workers) for individuals with alcohol and other drug use in primary health care centers leads to better outcomes than usual care.

Methods: We will conduct a randomized controlled clinical trial (ClinicalTrials.gov registration pending) comparing a 3-session SFBI (experimental group) with a single session of brief counselling as usual care (control group) in primary care. Interventions will be delivered in person by a psychologist or social worker. A total of 320 participants are expected to be recruited during preventive routine checkups using the Alcohol, Smoking, and Substance Involvement Screening Test. Participants reporting intermediate- to high-risk substance use on this screening tool will be randomly assigned to each group. Research assistants will administer instruments at baseline and at 3-, 6-, and 9-month follow-ups and will be blinded to the assigned treatments. The primary outcome assessed will be substance use patterns, while secondary outcomes include background information, depressive symptoms, anxiety symptoms, and motivation for treatment. Statistical analyses, including *t* tests, ANOVA, and Fisher exact tests will be conducted depending on variable type and normality. A qualitative component to assess acceptability and pertinence will include focus groups with participants and practitioners, followed by a content analysis.

Results: Funding for this study started in April 2024. As of the submission date of this protocol, 55 practitioners from 9 primary health care centers have been trained in SFBIs. Recruitment began in February 2025, with 73 participants enrolled and 23 who dropped out. Recruitment will continue until December 2026. No analyses have been conducted to date. Findings are expected to be published during the second half of 2028.

Conclusions: This study strengthens primary care by integrating targeted psychosocial interventions for substance use into existing programs, thereby enhancing real-world applicability. If effective, the intervention could be adopted into routine care and inform public policy on mental health and substance use.

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KEYWORDS

brief psychosocial interventions; clinical social work; primary health care; solution-focused brief therapy; substance use

Introduction

Overview

Substance use is a high-impact biopsychosocial problem in Chile. Chile has one of the highest levels of alcohol consumption per capita on the continent, with rates of 15% for men and 3.7% for women [1]. In addition, 21% of the population have experienced a severe alcohol episode, compared with the global average of 18% [1]. These high levels of alcohol consumption are associated with health indicators, including cirrhosis prevalence and alcohol-related causes of death [2]. Furthermore, illicit drug use in Chile showed a prevalence of 12.5% in the past year and 12.7% in the past month for marijuana (18.1% for men and 7.4% for women), 0.76% in the past year and 1% in the past month for cocaine (1.8% for men and 0.3% for women), and 0.4% in the past month for cocaine base paste (0.7% for men and 0.2% for women) [3,4]. The rates of cannabis use in Chile are concerning when compared with the global and South American prevalence. The global prevalence of marijuana is 4.12%, and in South America it is 3.58%. Cocaine prevalence is lower in Chile than in the rest of South America (1.62%) but remains higher than the global prevalence (0.42%) [5]. No international reports are available for cocaine base paste. In terms of age groups, marijuana and cocaine use is more common among individuals aged 19-25 years, whereas cocaine base paste is more prevalent among individuals aged 26-34 years [3]. Drug-related deaths have tripled in the Americas and are among the top 10 causes of disability-adjusted life years [6].

Psychosocial Variables

Alcohol and drug use are associated with various psychosocial indicators, including domestic violence, child abuse, and anxiety-depressive disorders [7-10]. From a social perspective, the highest prevalence of alcohol and substance use disorders, including marijuana, cocaine, and cocaine base paste in Chile, is observed among populations with lower socioeconomic status [2]. In terms of the incidence of alcohol-related crime, 53% of crimes were attributed to alcohol use, and 52.9% of those arrested for drugs, crime, or domestic violence met the criteria for alcohol use disorders. Regarding drug use, a recent study showed that among individuals who have been arrested due to high social connotation crimes, family violence, and drug-related issues, urine tests were applied to 141 individuals (74.7% and 25.3% women); the results showed that 65% has consumed at least one substance, the most common being marijuana (58%), followed by cocaine (30%) [11]. Although, no data were reported regarding cocaine base paste, the same study reported that the prevalence of substance use during the past year was marijuana (48.4%), cocaine (21%), and cocaine base paste (11.4%) [11]. Finally, being a victim of theft, sexual abuse, or any harassment is associated with a higher likelihood of reporting higher quantity and frequency of alcohol consumption [12]. All these dimensions intersect with areas where the intervention of psychosocial teams in primary health care (PHC) centers plays a role in prevention, diagnosis, treatment referral, and follow-up.

Chilean Public Policy for Substance Use

The range of treatment options for substance use in Chile includes various programs to address different patterns of use and diagnoses. In this context, PHC centers play a fundamental role. Within the framework of the National Mental Health Plan (Plan Nacional de Salud Mental) 2017-2025, a series of programs have been established for the benefit of community mental health [13]. These include the Psychosocial Support Program (Programa de Apoyo Psicosocial) in PHC, the Prevention and Treatment Program for Alcohol and Drug Use and/or Dependence (Programa de Prevención y tratamiento del Consumo y/o Dependencia de Alcohol y Drogas) in primary care, as well as the Explicit Health Guarantees Law (Garantías Explicitas en Salud), which since 2007 includes care for individuals under 20 years of age with harmful alcohol and drug use. Additionally, the Detection, Intervention, and Referral Program for Alcohol, Drug, and Tobacco Use (Programa Detección, Intervención, y Referencia de Alcohol, Drogas y Tabaco) is based on brief interventions aimed at reducing substance use and covers 150 communes throughout the country [13].

Brief Interventions

It is worth noting that the duration and intensity of brief intervention programs for substance use and their effectiveness have been widely discussed in scientific literature. The Center for Substance Abuse Treatment from the United States asserts that most individuals in substance use treatment drop out before completing the program and recommends the incorporation of brief therapy techniques when offering treatment [14]. Furthermore, it has been suggested to provide a brief intervention for all individuals seeking treatment before referring them to long-term modalities [14]. In this context, brief interventions are described as a therapeutic relationship in which a professional provides one or more individuals with therapeutic assistance to achieve changes or goals to improve various aspects of the person's life in the short term [15-18]. Interdisciplinary and collaborative work in PHC has shown positive results in addressing substance use. However, such interventions tend to be costly and more intensive than what is typically feasible to provide at this level of care, which may include psychiatrists, nurses, physicians, psychologists, and social workers. Moreover, their outcomes are similar to brief interventions [19]. The psychosocial approach to substance uses in PHC involves understanding that the problem of substance use is related to social determinants of health, as well as internal aspects of the individual, such as self-efficacy, coping strategies, motivation, and commitment [20,21].

In Chile, mental health and substance use programs in primary care involve psychologists and social workers, which often leads to working in pairs and, at times, overlapping daily intervention

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tasks. However, both professions have different focuses in their approach. While psychologists are often trained in the individual's intrapsychic processes, social workers are trained to understand the context, family, and social factors or determinants surrounding the individual. The interdisciplinary approach, which involves collaborative work, mutual learning, and overlapping roles [22], is common in primary care due to the person-centered model promoted by the comprehensive health-care model [23].

A study conducted in Chile found no significant difference in substance use between a single-session brief intervention provided by social workers or psychologists, following the Feedback, Responsibility, Advice, Menu Options, Empathy, and Self-Efficacy approach, and the delivery of a pamphlet [24]. Despite these findings, this type of brief intervention is currently applied in Chilean PHC when individuals are detected with a moderate risk of substance use. In this context, the National Mental Health Plan stated the need to develop more outcome studies that address the needs and particularities of the Chilean health system and population [13].

Solution-Focused Brief Interventions

Solution-focused brief interventions (SFBIs) are based on solution-focused brief therapy: a strengths-based and person-centered approach developed by clinical social workers in the United States that draws from systemic approaches and brief family therapy. Nevertheless, it is applicable to psychologists as well as social workers with clinical training, as it seeks to accompany others in processes of change. One notable aspect of this model is its cultural adaptability, as it approaches individuals participating in an intervention from a stance of "not being the expert" and respects their needs and perspectives [25]. An SFBI considers both individual aspects and interactions with significant others and the context to which individuals belong. Therefore, it is presumed to be more suitable for Latin populations, where close relationships and family ties are highly valued [26,27]. This is different from models such as Motivational Enhancement Therapy (Motivational Interviewing Treatment Context) [28], which focuses on enhancing individuals' intrinsic motivation [29] without considering relational aspects.

In an SFBI, the process of change occurs in conversations about solutions. These conversations aim to co-construct meanings, identify exceptions to the problem, develop a preferred future (based on a miracle or a hypothetical situation where the problem no longer exists), and explore how the person or family has achieved those exceptions in the past to repeat them in the future, thereby, making the desired future possible [25]. A literature review regarding SFBIs with substance users has shown promising results in reducing substance use and psychosocial problems associated with it [30]. Our team has previously developed a linguistic adaptation of SFBIs [31], providing methodological support for its applicability to the Chilean population receiving primary care. After that study, 2 pilot implementations were conducted to examine the feasibility of the model by social workers in primary care [32,33]. The results of the pilot studies showed positive trends in terms of reducing days of abstinence, average use, and maximum number of drinks on a single occasion; decreasing alcohol-related consequences and depressive symptoms, and improving participants' subjective well-being [32,33]. Given that (1) previous research has not shown conclusive evidence of a single-session brief intervention on reducing substance use patterns [24], (2) SFBIs have shown promising results in pilot studies with alcohol use [32,33], (3) there is an urgent need for evidence-based interventions in Chilean public PHC [13], and (4) current usual care in PHC allows for the introduction of a new methodology to be compared, conducting a randomized controlled trial of SFBIs adapted to Chilean culture and language and implemented by psychosocial teams, compared with usual brief interventions, could make a substantial contribution to the available knowledge on brief interventions for substance and the future implementation of public mental health policy addressing substance use in Chilean PHC.

Objectives

The general objective of this study is to determine whether the SFBI implemented by psychosocial teams (psychologists and social workers) in individuals with alcohol and other drug use in PHC leads to better outcomes than usual care. Specifically, the study aims to determine whether the SFBI reduces substance use patterns and the risk level of substance use among participants at the 3-month, 6-month, and 9-month follow-ups post baseline. It also aims to determine whether the intervention reduces the consequences of substance use and improves mental health symptoms at these follow-up points. In addition, the study seeks to determine whether participants receiving the SFBI improve their substance use patterns, substance use risk level, consequences of substance use, and mental health symptoms as compared to those receiving a minimal intervention. Finally, the study explores whether psychosocial professionals implementing the SFBI, as well as the individuals who participated in the intervention group, find the model acceptable and relevant to primary care.

Hypotheses

This study has the following hypotheses. First, participants who receive the SFBI will decrease their substance use patterns and risk-level use of alcohol, marijuana, cocaine, and cocaine base paste. Second, participants receiving the SFBI will report positive changes in the consequences associated with alcohol, marijuana, cocaine, and cocaine base paste use, as well as improvements in mental health symptoms between baseline and follow-ups. Third, when comparing outcomes between the intervention group and the usual care group, it is expected that participants in the intervention group will show greater reductions in substance use, consequences of use, and mental health symptoms than those receiving usual care. Finally, both participants and professionals involved in the intervention group will report experiences indicating that the model is acceptable and relevant for implementation in primary care.

Methods

Ethical Considerations

This protocol has been approved by the Research Ethics Committee of the Pontificia Universidad Católica de Chile (ID

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230619010; May 30, 2024), the Research Ethics Committee of the Local Health Services at the Metropolitan South-East area (September 12, 2024), and the Valparaíso–San Antonio area (N°23/2024; December 11, 2024). This protocol has been registered in ClinicalTrials.gov (registration pending). However, it was previously registered in Open Science Framework Registries (osf.io/875pj) on November 19, 2024. The protocol presented in this study is the second version, approved by the aforementioned committees. All participants (patients and professionals) signed an informed consent document and can choose to stop participating in the study at any time without consequence for their relationship with the primary health clinic or the university.

Confidentiality and privacy of participants will be protected. Psychosocial professionals' information is stored in the database to maintain contact with each of them during this study. This data will not be shared with anyone outside the study. Patients' identifiable information will be stored in a key-protected folder, to which only the research coordinator will have access. An alphanumeric code will be generated automatically once the patient's information is entered into the REDCap (Research Electronic Data Capture; Vanderbilt University) platform, where the instruments are embedded and data from each patient are stored and remain deidentified. Once the data collection phase is complete, the deidentified database will be downloaded and securely stored by the principal investigator in a password-protected digital folder for future research purposes. The deidentified database can be requested from the first author. The research team, professionals, and any research assistants hired to perform data tabulation or analysis tasks related to this study's content will be trained to maintain confidentiality and will sign a confidentiality agreement. They will not possess printed or digital copies of the data.

Psychosocial professionals and patients participating in this study will be recorded on audio during randomly selected sessions within the first 10 months of SFBI implementation (5 sessions per professional). This data and information will be carefully stored and managed by the principal investigator; the names of recordings will be coded, and only an expert in SFBIs will listen to each recording to assess the practitioners' fidelity to the model. The content regarding patients' private lives will not be the focus of these analyses. Recordings of the sessions between psychosocial professionals and patients will be stored for 3 years in a digital folder owned by the principal investigator, protected with a secure password. Participants will be informed through the informed consent that their sessions may be recorded in audio, and they will be reminded of this if their session is recorded.

Patients will receive compensation each time they respond to the questionnaires. The compensation will consist of a grocery store gift card equivalent to US $5 at baseline, US $6 at the 3-month follow-up, US $7 at the 6-month follow-up, and US $8 at the 9-month follow-up. The gift cards are redeemable for food and are intended to compensate participants for the time spent answering the questionnaires.

Study Design

The design of this study corresponds to a superiority randomized controlled clinical trial, conducted in public primary care clinics, to evaluate the effect of an SFBI and compare it with usual care, consisting of brief counseling and an educational brochure. The experimental and control groups will consist of primary care patients who report intermediate- to high-risk substance use and will be randomly assigned to each group. In addition, the acceptability and relevance of the applied intervention will be explored among participants in the experimental group using a qualitative approach, which focuses on a deep understanding of experiences considering the subjectivity and meanings attributed to them by individuals [34], through focus groups and qualitative analysis of their content. This study is guided by the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist (Multimedia Appendix 1).

Sample Size

The necessary sample size was calculated considering the minimum effect size found in evidence-based psychosocial interventions for substance use disorders (Cohen d=0.24 for polysubstance use, equivalent to Cohen f=0.12) [35]. The calculation was performed using the G*Power (Heinrich-Heine-Universität Düsseldorf) statistical software for sample size calculation [36], considering 80% power and a significance level of 5%. For the interaction effect between within-subject and between-subject factors in mixed ANOVA (details available in the Analysis Plan section), a sample size of 96 individuals was obtained, and after considering a 40% attrition rate [24,35] in follow-up, it increases to 160 individuals. The evaluation of the SFBI will be conducted separately by substance type (evaluating its effectiveness separately for at least alcohol, cocaine, and cocaine base paste, considering possible overlaps between them and marijuana). Thus, we plan to recruit 320 participants.

Recruitment

Since in PHC centers the Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) is applied routinely—in preventive check-ups—to individuals aged 20-65 years, the staff members responsible for applying this test at each PHC clinic will invite individuals whose scores are equal to or higher than 11 on the ASSIST for alcohol and 4 for other substances to participate in this study. If they accept, they will be given an appointment with the research coordinator or a research assistant, who will formally invite them to participate.

The inclusion criteria are as follows: participants must have an ASSIST score of 11 or higher for alcohol and a score of 4 or higher for other substances, be able to communicate verbally with others, be willing to participate in the intervention, and be willing to complete the measurement instruments.

The exclusion criteria are as follows: participants with a severe and untreated mental illness such as schizophrenia, those not willing to participate in the intervention, those not willing to complete the measurement instruments, those who have received another brief intervention within the last year, and those currently being treated in another program for substance use will not be eligible to participate.

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Interventions for Control and Experimental Groups

For the control group, the intervention will be 1 brief counseling session and an educational brochure, provided as part of usual care in PHC. Our team has provided the practitioners participating in this study with a guideline to conduct this brief counseling based on the recommendations of the World Health Organization (WHO) [37]. These materials can be requested from the first author.

For the experimental group, the intervention will be a 3-session brief intervention based on solution-focused practices, implemented by trained social workers or psychologists, who will receive 24 hours of training provided by this study. Our team has designed a manual with the goals and structure of each session, main interventions, and examples of application in different situations. The manual can be requested from the first author. The fidelity of this intervention will be monitored through the application of the Fidelity Instrument [38] to 5 audio recordings of sessions per practitioner participating in the program. This adapted instrument, used in a previous study by the research team [32], contains techniques and skills that professionals should implement in SFBIs. It consists of 13 items with binary responses (1=yes and 0=no). In addition, once the recruitment of participants starts, practitioners in this study will participate every 2 weeks in a 1-hour group consultation meeting, where a master's in clinical social work with advanced training in SFBIs will supervise the group in the application of SFBI techniques—focusing on best practices, solving questions, reviewing difficulties, and strengthening adherence of practitioners.

Data Collection

The protocol for participants' invitations begins once the patient is eligible (Figure 1). The practitioner who detects an eligible participant in the PHC will conduct usual care, consisting of a brief counseling intervention of 10-15 minutes, focused on providing advice and an educational brochure with information about the risks of substance use. Following that, the practitioner will invite the potential participant and inform them regarding the implications of participating in this study, including the set instruments to complete, the possibility of receiving 3 SFBI sessions or only the brief counseling already provided, and the voluntary nature of their decision to participate. If the potential participant agrees to participate in the study, both participant and practitioner will read and sign the informed consent form. Neither of them will know which group the participant will be assigned to at this stage.

Figure 1. Research protocol flowchart. ASSIST: Alcohol, Smoking, and Substance Involvement Screening Test; SFBI: solution-focused brief intervention.

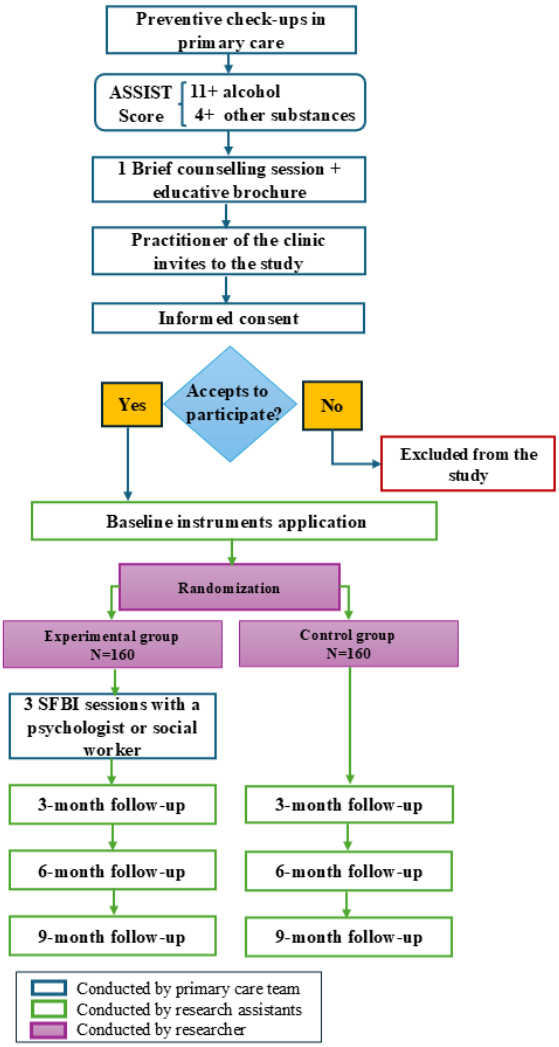

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Once a participant has signed the informed consent form, they will be contacted by the research coordinator to complete a set of measurement instruments 4 times over a total estimated period of 9 months. Even though participants will know which group they were assigned to after completing the baseline forms, research assistants who interact directly with participants will not be aware of the assigned treatments (blinded).

Measurement instruments will be applied to assess baseline, progression, and follow-up for possible changes in outcome variables. The existence of self-selection bias is acknowledged and will be addressed by random allocation of participants to the control or intervention group [39]. The randomization process will be conducted by one of the research members (AV), using a computer-generated randomization sequence with a maximally tolerated imbalance of 3 using the big stick method. Randomization will be stratified so that each center is balanced in terms of participants assigned to each group.

Instruments

Background Information

This includes age, gender, socioeconomic status, education level, employment status, county of residence, and family situation (relationship status, children, and their ages). This information is relevant for documenting and accounting for the heterogeneity or homogeneity of the study's participants and will serve as control variables for data analysis. This instrument will be administered completely at baseline and at the 9-month follow-up and partially (employment status and county of residence) at the 3- and 6-month follow-up, to visualize changes in sociodemographic variables and the identification of protective and change factors during the process.

ASSIST

This 8-item questionnaire developed by the WHO, is used to detect risk in substance use [37]. It predicts low, intermediate, and high risk due to substance use. It is a relatively new instrument, recently validated in Chile and recommended by the WHO for assessing risk in alcohol and substance use. The validation in Chile [40] considers a score equal to or greater than 11 for intermediate to high-risk alcohol consumption and a score equal to or greater than 4 for intermediate to high-risk substance use. It is one of the main dependent variables of the study and will be administered at baseline and follow-ups.

Treatment Outcome Profile

This instrument has been validated in Chile [41] and was originally developed by the National Treatment Agency for Substance Misuse [42]. It is used to obtain comparable data and goals regarding improvements of individuals with substance use after treatment. It consists of 3 sections: substance use in the past 4 weeks, offensive behavior (social norms such as theft, drug dealing, fights, and domestic violence), and physical and psychological health, including quality of life, work, education, and housing. In total, there are 17 questions. It will be administered at baseline and follow-ups.

Patient Health Questionnaire-9

This self-administered 9-item instrument, used in primary care settings, corresponds to the depression module of the Primary Care Evaluation of Mental Disorders, which identifies various mental health disorders [43]. It reflects the 9 symptoms of depression from the *DSM-IV* (*Diagnostic and Statistical Manual of Mental Disorders* [Fourth Edition]). It has high convergent validity (r=0.73; P<.001) with the short version of the Beck Depression Inventory in detecting depression severity [44]. It has been validated in the Chilean population by Baader et al [45]. It will allow the observation of depressive symptoms prevalence in individuals using different types of substances at baseline and follow-ups, as well as exploring the association between them.

Generalized Anxiety Disorder-7 Scale

This is a self-report instrument to assess generalized anxiety disorder (GAD), based on GAD symptoms from DSM-IV. In primary care, its construct validity showed strong correlations between the Generalized Anxiety Disorder-7 (GAD-7) scale's severity scores and worsening function on all 6 Health-Related Quality of Life scales of the Medical Outcomes Study Short-Form General Health Survey, as well as a high internal consistency (Cronbach α=0.92) [46]. This instrument was adapted for the Chilean population by Crokett et al [47]. It consists of 7 items with 4-point ordinal responses, with 0 indicating never and 3 indicating almost every day. This instrument will allow for the observation of the prevalence of anxiety symptoms in individuals who use different types of substances at baseline and follow-ups, as well as the exploration of associations between these factors.

Motivation and Treatment Needs Scale

This scale, developed by Joe et al [48], is part of the Client Evaluation of Self and Treatment, a comprehensive instrument consisting of 147 items grouped into 16 scales. In this study, 2 subscales will be used: Help-seeking Desire and Treatment Readiness [49]. Together, these subscales comprise 14 items with responses on a Likert-type scale, where 1=strongly disagree and 5=strongly agree.

Focus Group Guides

Guidelines for these focus groups, to be conducted with the psychosocial teams and participants from the intervention group, were designed specifically for this study to explore participants' perceptions regarding the implementability of the SFBI model for substance use in PHC contexts (Multimedia Appendix 2).

The quantitative instruments (background information, including demographic data and sociofamilial situation, ASSIST, treatment outcome profile (TOP), Patient Health Questionnaire-9 (PHQ-9), GAD-7, and desire for help and treatment readiness form) will be administered in a private room at the health care center or over the phone (depending on coordination with each patient) by the research coordinator or a research assistant. The estimated time for administering the instruments is 25 minutes per set. The qualitative instruments (focus groups for practitioners and participants) will be implemented after the implementation process has concluded, and conversations will last between 60 and 90 minutes.

Following the informed consent procedures, the instruments will be administered on 4 occasions (Table 1).

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Table 1. Outline for application of instruments per participant.

Instrument	Baseline	3-month follow-up	6-month follow-up	9-month follow-up	After finishing follow-ups
Background information	✔			✔	
TOP[a]	✔	✔	✔	✔	
PHQ-9[b]	✔	✔	✔	✔	
GAD-7[c]	✔	✔	✔	✔	
Desire for help and treatment readiness	✔				
Focus group					✔

[a]TOP: treatment outcome profile.

[b]PHQ-9: Patient Health Questionnaire-9.

[c]GAD-7: Generalized Anxiety Disorder-7.

Safeguarding Mental Health

Regarding mental health well-being, this SFBI focuses on positive aspects and the future, minimizing the risk of causing any harm to mental health. If a patient feels distressed or uncomfortable during an intervention session, professionals trained in SFBIs will also be trained to contain and intervene in crises. This additional training, separate from SFBI training, will consist of a 2-hour training session on psychological first aid, provided by an expert hired for that purpose. Furthermore, the research team will ensure that the health clinic has a mental health protocol in place for its regular care. Additionally, the research coordinator and the principal researcher will be available if required. If, during follow-up procedures or any health assessment, a study participant is identified as being at risk and requiring a different type of clinical intervention, the health care team will notify the research team regarding the participant's continued involvement in the study. In all cases, clinical decisions will take precedence over research participation.

Analysis Plan

For quantitative-specific objective 3, we will use the standard $P<.05$ criterion to make inferences. Tests to detect any potential differences between individuals who received interventions from either social workers or psychologists will be conducted. The analysis approach for each specific objective is described in the following sections.

Specific Objective 1

The first specific objective aims to determine whether the SFBI reduces substance use patterns and risk-level substance use of participants at the 3-month, 6-month, and 9-month follow-ups (post baseline). A descriptive analysis of the recorded variables will be conducted for each participant in the experimental group, pretreatment, and at 3 months, 6 months, and 9 months post baseline. Minimum and maximum values will be reported, and the normality of their distribution will be assessed using frequency histograms and the Shapiro-Wilk normality test. Categorical variables will be described using absolute and percentage frequencies. For individuals participating in the experimental group, the following analyses will be conducted separately at each posttreatment measurement (3 months, 6 months, and 9 months): the change in frequency and quantity of consumption according to the TOP instrument will be calculated for each participant, with the mean change and its corresponding CI estimated, and a paired repeated-measures ANOVA conducted to evaluate whether there is a significant treatment effect on the average weekly consumption; if the normality assumption is not met, the nonparametric Wilcoxon signed-rank test will be used. In addition, the percentage of individuals who decrease their risk category will be calculated, and their respective CIs estimated, and, since the TOP contains categorical items, the McNemar test will be applied to evaluate whether significant changes occurred.

Specific Objective 2

The second specific objective aims to determine whether the SFBI reduces consequences of substance use and improves mental health symptoms of participants at the 3-month, 6-month, and 9-month follow-ups (post baseline). For individuals participating in the experimental group, the following analyses will be conducted for each postbaseline measurement (3 months, 6 months, and 9 months): the scores obtained on the PHQ-9 instrument will be calculated and described using mean, SD, median, minimum, and maximum values, and the distribution normality will be assessed using frequency histograms and the Shapiro-Wilk normality test. The change in the PHQ-9 questionnaire score and the desire for help and treatment-readiness scales will be calculated, the means with their corresponding CIs will be estimated, and a repeated-measures ANOVA will be conducted to evaluate whether there is a significant treatment effect on each score.

Specific Objective 3

The third specific objective aims to determine whether participants receiving the SFBI improve their substance use patterns, substance use risk level, consequences of substance use, and mental health symptoms as compared with those receiving a minimal intervention. A descriptive analysis of the recorded variables will be conducted for each participant in both experimental and control groups at baseline and at 3 months, 6 months, and 9 months post baseline. Quantitative variables will be described using mean, SD, median, minimum, and maximum values, and their distribution normality will be assessed using frequency histograms and the Shapiro-Wilk normality test.

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Categorical variables will be described using absolute and percentage frequencies. For each posttreatment measurement (3 months, 6 months, and 9 months), the following analyses will be conducted: the change in substance use patterns and substance use risk level (TOP) will be calculated for each participant in both experimental and control groups, and the mean with its corresponding CI will be estimated; the change in the PHQ-9 score will be calculated for individuals in both experimental and control groups, and the mean with its corresponding CI will be estimated; the change in the GAD-7 score will be calculated for individuals in both experimental and control groups, and the mean with its corresponding CI will be estimated. Baseline characteristics, including demographic background and sociofamilial situation, of participants in the control and experimental groups will be compared, with *t* tests or Wilcoxon-Mann-Whitney tests used for quantitative variables when the normality assumption is unmet, and the Fisher exact test used for categorical variables. Given that this is a superiority design, 1-tailed tests will be used for the following comparisons. The mean decrease in monthly consumption will be compared between individuals in the experimental and control groups using a mixed ANOVA, with group (experimental and control) as the between-subjects factor and time of measurement (pretreatment, 3 months, 6 months, and 9 months) as the within-subjects factor. Similarly, mean PHQ-9 scores will be compared between the two groups using a mixed ANOVA, with group (experimental and control) as the between-subjects factor and time of measurement (pretreatment, 3 months, 6 months, and 9 months) as the within-subjects factor, with the Friedman-aligned ranks test applied if the variable normality assumption is unmet. Finally, the percentage of individuals who decrease their substance use patterns and risk (TOP) will be compared between the experimental and control groups, using the Fisher exact test.

Specific Objective 4

The fourth specific objective aims to explore whether psychosocial professionals implementing the SFBI and the individuals who participated in the intervention group find that the model is acceptable and relevant to primary care. The transcribed focus groups will be analyzed using content analysis methodology to identify the concepts and themes in the transcribed data. Initially, the concepts appearing in the texts will be recognized and grouped into themes. According to Hsieh and Shannon [50], content analysis can be approached in two ways. The first is a deductive strategy, with predefined thematic categories established by the researchers based on the goals of the analysis or previous theories. The second is an inductive strategy, without predefined categories, as these are constructed based on the findings, maintaining conceptual openness for analysis. In this case, both strategies will be combined, using the predefined categories of acceptability and relevance of the SFBI from the perspective of professionals and individuals, while remaining open to other new categories or concepts emerging in the focus group conversations.

Data Exclusion and Missing Data

Analyses will be conducted including and excluding outliers and differences between these analyses will be reported. Analyses will be performed according to the intention-to-treat principle. Missing data will be handled using multiple imputation.

Data Monitoring

A Data Monitoring Committee has not been included in this protocol because the trial involves psychosocial interventions delivered by trained professionals (social workers and psychologists). These interventions are noninvasive and carry minimal risk to participants. Participants' safety will be ensured through mental health safeguarding procedures and adherence to ethical guidelines throughout the study.

Results

Funding for this study started in April 2024. As of the submission date of this protocol, 9 primary care clinics from 2 regions of Chile are participating in this study; 55 practitioners (30 social workers and 25 psychologists who work in these clinics) have been trained in a 36-hour course on the theory and practice of the SFBI model. The recruitment phase for participants started in February 2025 and will continue until December 31, 2026. To date, a total of 2542 ASSIST assessments have been reported by the clinics. A total of 82 patients have been referred to the study, 73 have been enrolled, and 23 have dropped out, leaving 50 currently enrolled (32% attrition).

Discussion

Study Contributions

This study aims to determine whether a 3-session SFBI demonstrates better outcomes in substance use patterns, risk level, and consequences, as well as mental health symptoms, when compared with usual care. By evaluating the effectiveness of an SFBI, this study aims to expand knowledge on psychosocial interventions, specifically in PHC, by testing a resource-focused model for addressing substance use. In this sense, this study promotes scientific development for the interdisciplinary approach to substance use interventions. A previous study on a single-session brief intervention also trained social workers and psychologists, acknowledging the relevance of brief interventions implemented by practitioners other than physicians [24]. However, studies examining brief interventions by interdisciplinary teams remain scarce.

It is known that previous studies have shown mixed results regarding the effectiveness of brief interventions on substance use in PHC [51,52] and that a previous study conducted in Chile showed no significant results after a single-session brief intervention (17 minutes on average) [24]. The studies referenced did not include a solution-focused model for the intervention; instead, they were based on other models, such as motivational interviewing and cognitive behavioral therapy. On the other hand, recent reviews on solution-focused practices found that research regarding the effects of SFBIs on substance abuse is scarce, and that even though results are promising, either for substance use or psychosocial comorbidities, more randomized controlled trials are needed to strengthen the evidence supporting this trend [30,53].

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A key strength of this study lies in its targeted approach to enhancing outcomes for individuals with substance use in PHC. By integrating this specific intervention methodology within extant programmatic lines and collaborating with the teams expected to implement brief interventions [13], the study aligns closely with real-world practice. If proven effective, this innovation is highly likely to be adopted and embedded in PHC usual care. This work will generate valuable and applicable insights for primary care, influencing public policy frameworks regarding mental health and substance use [13].

This study has some limitations. Since it is a multisite study, the strategies used by the practitioners applying screening, detection, and delivering usual brief interventions might vary widely. To manage this variability, our research team standardized the flowchart, the speech for the usual brief intervention, and the speech for the invitation to the study. Thus, each practitioner participating in the recruitment process received a pack of laminated sheets to keep them visible, so that even though there are more than 50 practitioners involved, all have the same orientations for procedures. The variability of sites and practitioners participating in the implementation of SFBIs also needs to be managed—the training was standardized, each practitioner received a pocket guide of SFBIs, all the practitioners participate in a 1-hour fortnightly meeting for group technical supervision, and their recordings of SFBI sessions receive written feedback to strengthen the fidelity of interventions. Nonetheless, the diversity of sites is a strength; the study is being implemented in the real world, and, as such, insights from the implementation will bring valuable knowledge regarding how primary care works and what the real-world challenges are in implementing innovations and programs in primary care.

Future Directions

The research team systematically documents insights by recording meeting notes, gathering practitioner feedback, and identifying barriers, misinformation, and implementation challenges that inform future research and practices [54]. Good practices are actively disseminated across teams to ensure the transferability of the implementation process. Preliminary findings from this study will be presented at academic and professional conferences. Stakeholders, including clinic directors, supervisory teams within the Health Services, the Division of Primary Health Care at the Ministry of Health, and Treatment and Preventive Divisions at the National Service for Alcohol and Drug Use Prevention and Rehabilitation, are being periodically updated on the study's progress. The results will be disseminated through academic journals, conferences, and seminars. In addition, a dedicated symposium will be organized to present the study's results. This event will bring together primary care practitioners, academic scholars, supervisory teams, and policymakers, fostering dialogue and reflection on the outcomes and broader implications for future research and policy implementation. An audiovisual presentation of the results will be shared through the clinics' social media and other platforms, ensuring study participants interested in the findings have easy access. As most of the research on interventions for substance use has been conducted in high-income countries, and the evidence on the effectiveness of brief interventions is not conclusive [51,55], once findings demonstrate the effectiveness of SFBIs, future research in Chile and Latin American countries could compare the outcomes of several implementation formats, frequencies, and doses of intervention for diverse risk levels. For example, multigroup designs may be used to compare individual, family, group, and online interventions for different risk levels of substance use, including variations in frequencies and doses of intervention, building on previous research and filling current gaps.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization: KGS (lead), RPH (supporting), BDV (supporting)
Methodology: KGS (lead), RPH (supporting), AV (supporting)
Project administration: KGS (lead), BDV (supporting), RPH (supporting)
Supervision: KGS

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Validation: AV
Visualization: KGS (lead), BDV (supporting)
Writing – original draft: KGS (lead), BDV (supporting), AV (supporting), RPH (supporting)
Writing – review & editing: KGS (lead), RPH (supporting), AV (supporting)
Funding acquisition: KGS

Conflicts of Interest

The first author (KGS) is a pro bono member of the Solution-Focused Brief Therapy Association Research Committee; this will not have an impact on either the analysis or the results. The coauthors have no conflicts of interest to declare.

Multimedia Appendix 1
SPIRIT checklist.
[PDF File (Adobe PDF File), 209 KB - resprot_v14i1e75628_app1.pdf]

Multimedia Appendix 2
Focus groups guides.
[PDF File (Adobe PDF File), 116 KB - resprot_v14i1e75628_app2.pdf]

Multimedia Appendix 3
Peer-review report by Agencia Nacional de Investigación y Desarrollo (National Agency of Research and Development; ANID), Ministry of Science, Technology, and Innovation, Government of Chile.
[PDF File (Adobe PDF File), 124 KB - resprot_v14i1e75628_app3.pdf]

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Abbreviations

ASSIST: Alcohol, Smoking, and Substance Involvement Screening Test
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)
GAD: generalized anxiety disorder
GAD-7: Generalized Anxiety Disorder-7
PHC: primary health care
PHQ-9: Patient Health Questionnaire-9
REDCap: Research Electronic Data Capture
SFBI: solution-focused brief intervention
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TOP: treatment outcome profile
WHO: World Health Organization

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Protocol

Short-Term Effects of Nonnutritive Sweetener (Sucralose and Saccharin) Consumption on Glycemic Control and Gut Microbiota in Patients With Type 2 Diabetes: Protocol for a Double-Blind, Randomized, Placebo-Controlled, Crossover Trial

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Abstract

Background: Nonnutritive sweeteners (NNSs) are widely used as sugar substitutes to help individuals with diabetes manage glycemic control. However, emerging evidence suggests that even low doses of NNSs, such as saccharin and sucralose, may adversely affect metabolic health by impairing glycemic regulation, potentially through alterations in the gut microbiota. In Malaysia, where gut microbiome research is still limited, particularly among individuals with type 2 diabetes mellitus (T2DM), further investigation is warranted to inform safe and evidence-based use of NNSs.

Objective: This study aims to evaluate the short-term effects of saccharin and sucralose consumption on glycemic control and gut microbiota composition in adults with T2DM.

Methods: This is a double-blind, randomized, placebo-controlled, crossover trial. A total of 33 adults with T2DM will consume sucralose (5 mg/kg body weight), saccharin (2 mg/kg body weight), or a placebo (calcium carbonate) in capsule form daily for 7 days per intervention arm, with a 4-week washout period. Data collection will include anthropometric measurements, biochemical assessments for glycemic control, dietary records, physical activity levels, and stool samples. The homeostatic model assessment for insulin resistance will be used to assess insulin sensitivity, while 16S rRNA V3-V4 region sequencing will be conducted to profile gut microbiota composition.

Results: Recruitment is planned to begin in January 2026 and is expected to conclude by September 2026, with study completion anticipated by March 2027. As of December 2025, no participants have been enrolled.

Conclusions: This trial will contribute novel insights into the effects of short-term NNS consumption on glycemic control and gut microbiota composition in individuals with T2DM. These findings may support evidence-based recommendations for NNS use in diabetes management and enhance understanding of microbiome-diet interactions in an ethnically diverse Asian population.

Trial Registration: ClinicalTrials.gov NCT07124585; https://clinicaltrials.gov/study/NCT07124585

International Registered Report Identifier (IRRID): PRR1-10.2196/82695

(JMIR Res Protoc 2025;14:e82695) doi:10.2196/82695

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KEYWORDS

saccharin; sucralose; nonnutritive sweetener; artificial sweetener; glycemic control; gut microbiota; type 2 diabetes mellitus

Introduction

Nonnutritive sweeteners (NNSs) are widely used as sugar substitutes to reduce caloric intake and help manage blood glucose levels. Although previously considered metabolically inert, emerging evidence suggests that NNSs may influence host metabolism through their effects on the gut microbiota [1]. A landmark study in 2014 demonstrated that NNS-induced glucose intolerance in mice was mediated by gut microbiota alterations and was transferable to germfree mice via fecal microbiota transplantation [2]. However, subsequent studies have reported inconsistent findings, some indicating that NNSs alter microbial composition and impair glycemic control [3-6], while others have found no significant effects [7-9]. Variability in outcomes likely reflects differences in the type of sweetener, study design, host characteristics, and baseline microbiota composition.

Although all types of NNSs are categorized as sugar substitutes, they differ in their chemical structures, metabolism, and gut accessibility. Therefore, findings from one NNS cannot be generalized to all types of sweeteners. A recent study by Suez et al [3] in 2022 showed that while all tested NNSs altered the gut microbiome, only sucralose and saccharin significantly impaired glycemic responses [3]. These effects were reproduced in germfree mice colonized with microbiota from exposed individuals, strengthening the causal link between NNSs, gut microbiota, and metabolic outcomes. Therefore, this study focuses specifically on sucralose and saccharin.

Observational studies have also raised concerns that long-term consumption of sucralose and saccharin may lead to glycemic dysregulation, increased insulin resistance, or metabolic disturbances [2,3,10-13]. However, these effects have generally been observed at higher doses and with prolonged exposure. In contrast, this study will adopt a short-term, controlled intervention using doses well within the acceptable daily intake recommended by major health authorities, including the US Food and Drug Administration (FDA), the European Food Safety Authority, and the Joint FAO/WHO Expert Committee on Food Additives [14-17]. Both NNSs have been extensively evaluated and are considered safe for human consumption within their established acceptable daily intake limits.

To date, most NNS studies have focused on healthy populations, overlooking the fact that type 2 diabetes mellitus (T2DM) itself is associated with gut dysbiosis and altered metabolic signaling [18,19]. According to the International Diabetes Federation, an estimated 4.75 million adults in Malaysia were living with diabetes in 2024 [20]. The use of NNSs in Malaysia is expected to increase due to growing public awareness of the harmful effects of excessive sugar consumption and the implementation of a sugar tax on sugar-sweetened beverages. Consequently, the food industry has increasingly turned to NNSs for product reformulation.

Given these trends and the limited evidence among individuals with T2DM, this study aims to evaluate the short-term effects of sucralose and saccharin on glycemic control and gut microbiota composition in Malaysian adults with T2DM. Specifically, the primary objective is to assess changes in insulin sensitivity, while the secondary objective is to examine alterations in gut microbiota composition and diversity following exposure to different NNSs.

Methods

Study Design

This study is a double-blind, randomized, placebo-controlled crossover trial. The crossover design allows each participant to serve as their own control across 3 intervention phases. Each participant will complete a 12-week protocol comprising a 1-week run-in period followed by 3 intervention phases, each separated by a 4-week washout period. A total of 6 study visits, comprising 3 preintervention and 3 postintervention assessments, will capture baseline and postintervention data. During the run-in and washout periods, participants will maintain their habitual diet and physical activity. The study will be conducted at a government primary care facility situated in an urban area. Recruitment will be facilitated through clinic listings and physician referrals. Written informed consent will be obtained after participants receive detailed verbal and written explanations of the study procedures, risks, and rights. The study timeline is summarized in Figure 1.

Figure 1. Overview of the study visits.

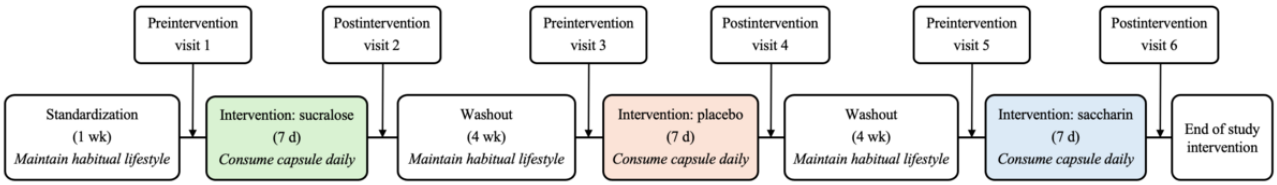

Participants

This study aims to recruit a cohort of clinically stable patients representative of Malaysians with early-phase T2DM. Eligible participants will be males aged 30 to 59 years, with a BMI of 23.0 to 29.9 kg/m², classified as overweight [21]. Participants must have a clinical diagnosis of T2DM for 1 to 10 years, with baseline glycated hemoglobin (HbA_{1c}) below 10%, and be managed with oral antidiabetic medications only. Individuals with stable, nonsevere chronic conditions, such as hypertension

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or dyslipidemia, will be included if they have maintained a consistent oral treatment regimen for at least 6 months before enrollment. All participants must have previously received dietary counseling for diabetes and agree to maintain their habitual diabetes-friendly diet and regular physical activity throughout the study. They must abstain from alcohol consumption during the intervention period and be literate in either English or Bahasa Malaysia to ensure full understanding of the study procedures and informed consent materials.

Exclusion criteria focus on lifestyle or dietary patterns that deviate from typical Malaysian practices or that could substantially alter the gut microbiota. Individuals will be excluded if they currently smoke or consume alcohol, have experienced more than 5% body weight change within the past 3 months, or have acute illness or major comorbidities, such as cardiovascular, psychological, neurological, renal, or endocrine disorders other than T2DM. Those with known intolerance or allergy to the test products, adherence to special diets (eg, vegetarian, ketogenic, or intermittent fasting), or use of medications or supplements (eg, probiotics) that may affect intestinal function or microbiota composition will also be excluded. Participation in another clinical trial within the past 3 months will preclude eligibility. Participants may withdraw voluntarily or be withdrawn for safety reasons, protocol deviation, or the need for antibiotic therapy. Diabetes management will continue as per clinical practice. Adverse events will be monitored and managed by the study physician following institutional protocols.

Intervention

Participants will receive 1 of 3 interventions: sucralose, saccharin, or a placebo, for 7 consecutive days during each intervention phase. Participants will consume the assigned capsule each morning after breakfast with plain water to standardize timing and minimize missed doses. Dosages will be adjusted based on body weight according to national guidelines, with 5 mg/kg for sucralose and 2 mg/kg for saccharin [22]. The placebo, consisting of 500 mg of calcium carbonate, will be administered under identical conditions and is considered physiologically inert at this dose [9].

Randomization and allocation concealment will be conducted by external personnel not involved in recruitment, data collection, or analysis. A computer-generated block randomization sequence will assign participants to 1 of 3 intervention orders (sucralose, saccharin, or placebo) to ensure balanced allocation across participants. All test products will be encapsulated in identical opaque capsules and packaged in indistinguishable small plastic pouches. Labeling will be performed by external personnel according to the intervention sequence, where each package will be marked as “first intervention,” “second intervention,” or “third intervention” to maintain blinding. Both participants and investigators will remain blinded throughout the data collection period. The randomization code will be securely stored and accessible only in the event of a medical emergency.

Outcomes

The primary outcome is the change in insulin sensitivity, assessed using the homeostatic model assessment for insulin resistance (HOMA-IR), derived from fasting glucose and insulin concentrations. The secondary outcome is the change in gut microbiota composition and diversity, analyzed through 16S rRNA gene sequencing. Alpha and beta diversity indexes will be calculated to evaluate within- and between-sample diversity, and differential abundance analysis will be performed to identify microbial taxa associated with each intervention.

Sample Size

The sample size for this crossover trial was estimated based on detecting a medium effect size (Cohen f=0.25), consistent with findings from a recent meta-analysis of soluble fiber supplementation in T2DM, which reported moderate standardized mean differences for HOMA-IR (standardized mean difference −0.58, 95% CI −0.86 to −0.29) [23]. Using G*Power 3.1.9.6, we computed the required sample size for a within-subject repeated-measures ANOVA with 3 conditions (sucralose, saccharin, and placebo), assuming α=.05, and statistical power at 80%, and a moderate correlation (r= 0.5) among repeated measurements [24]. The analysis indicated that a minimum of 28 participants would be required. To account for potential dropout or noncompliance, we will recruit 33 participants.

Ethical Considerations

This study was approved by the Universiti Kebangsaan Malaysia Research Ethics Committee (UKM/PPI/111/8/JEP-2025-322) on July 15, 2025. Procedures follow the Declaration of Helsinki and institutional ethics standards. This study is registered with ClinicalTrials.gov (NCT07124585), first released on August 8, 2025.

Written informed consent will be obtained from all participants before enrolment. Participants will receive a verbal explanation of the study and will be given adequate time to review the participant information sheet. An optional separate consent form will be provided for the storage and future use of deidentified biospecimens in ancillary studies.

Participant privacy and confidentiality will be protected throughout the study. Identifiable information will be collected only as necessary and will be stored separately from research data using unique participant codes. All datasets will be deidentified before analysis, and access to identifiable information will be restricted to authorized study personnel. No identifiable data or images will appear in publications or presentations.

Participants will receive financial compensation for time and transportation. Compensation for harm is not anticipated, as the interventions involve commercially available NNSs administered at doses considered safe. Any adverse events will be documented and managed according to institutional procedures, and medical care will be provided as needed.

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Data Collection

Data and biospecimens will be collected at baseline and after each intervention phase by trained research personnel as outlined in the study visit overview (Table 1).

Table 1. Overview of data and biospecimen collection by study visit.

	Screening	Intervention 1		Intervention 2		Intervention 3	
		Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6
Anthropometry							
Weight	✓	✓	✓	✓	✓	✓	✓
Height	✓						
Waist circumference		✓		✓		✓	
Body composition		✓	✓	✓	✓	✓	✓
Blood pressure		✓	✓	✓	✓	✓	✓
Biological specimens							
Blood		✓	✓	✓	✓	✓	✓
Stool		✓	✓	✓	✓	✓	✓
Questionnaire							
Sociodemographic and medical history	✓						
Medication record	✓	✓		✓		✓	
Dietary record	✓	✓	✓	✓	✓	✓	✓
Physical activity record	✓	✓	✓	✓	✓	✓	✓
Test product compliance record			✓		✓		✓
Adverse effect reports			✓		✓		✓

Anthropometric measurements will be obtained using standardized procedures. Body weight will be measured using a calibrated digital scale with participants wearing light clothing, while height will be measured using a stadiometer, ensuring an upright posture and proper head alignment. The average of 2 readings will be recorded for both weight and height, and BMI will be calculated as weight in kilograms divided by height in meters squared (kg/m²). Waist circumference will be measured at the midpoint between the lowest rib and the iliac crest using a nonstretchable measuring tape [25]. Body composition, including body fat and muscle mass, will be assessed using bioelectrical impedance analysis following standard premeasurement guidelines [26]. Blood pressure will be measured twice after a 5-minute rest using an automated sphygmomanometer, and the mean of both readings will be recorded.

For biological specimens, blood samples of approximately 15 mL will be collected from participants at each study visit by trained nurses after a 30-minute rest period. Analyses will include fasting glucose, fasting insulin, glycated hemoglobin (HbA_{1c}), lipid profile, and kidney function indicators. Insulin resistance will be estimated using the HOMA-IR, derived from fasting glucose and insulin levels [27]. Samples will be transported and processed according to biosafety and quality control procedures to ensure sample integrity for biochemical analysis and future molecular investigations. Stool samples of approximately 1 g will be collected using standardized fecal collection tubes provided to participants. Preintervention samples will be collected a day before each intervention phase, and postintervention samples will be obtained immediately after the final intervention day. Participants will receive detailed written and verbal instructions to ensure correct collection and handling procedures [28].

Sociodemographic and medical history information will be obtained through structured interviews and verified against medical records. Medication use will be reviewed at each study visit. Dietary intake will be assessed using 3-day food records covering 2 weekdays and 1 weekend day. Investigators will review the records during face-to-face sessions using visual aids to ensure completeness and improve portion-size estimation accuracy. Nutrient intake will be analyzed using the Malaysian Food Composition Database [29]. Physical activity will be assessed using the short-form International Physical Activity Questionnaire, available in both English and Malay, which has been validated for the Malaysian population [30,31]. Test product compliance records and adverse event reports will be obtained during each postintervention visit. Any serious adverse event or major complaint will be promptly managed by the study physician and reported to the responsible authorities within 48 hours, with appropriate medical action documented. Leftover blood and stool biospecimens from each visit will be stored at −80 °C in the institutional biobank for future research on disease biomarkers, gene expression, or microbial function, subject to ethics approval and participant consent.

Gut Microbiota Analysis

Gut microbiota profiling will be performed using 16S rRNA gene sequencing targeting the V3-V4 region. DNA will be

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extracted using the Maxwell RSC system (Promega), and library preparation will follow Illumina's 16S Metagenomic Sequencing protocol [32]. Amplicons will be barcoded, pooled equimolarly, and sequenced on the Illumina MiSeq platform (2×250 bp). Raw reads will be demultiplexed, quality-filtered, and denoised using DADA2 in QIIME 2 to generate amplicon sequence variants and remove chimeras [33,34]. Taxonomic classification will be assigned using a pretrained SILVA 138 database classifier [33]. Microbial diversity will be evaluated using α diversity indexes (Shannon, Faith phylogenetic diversity) and beta diversity metrics (Bray-Curtis, UniFrac distances) [35-38]. Differential abundance analysis will be conducted using appropriate statistical frameworks, such as ANCOM-BC or MaAsLin2, with false discovery rate correction [39]. Downstream analyses will be guided by metadata and study endpoints to identify microbial shifts associated with each intervention.

Statistical Analysis

Clinical data will be presented as mean (SD) unless stated otherwise. Statistical analyses will be performed using SPSS Statistics (version 28.0; IBM Corp) [40]. The normality of continuous variables will be assessed using the Shapiro-Wilk test. Participants' baseline characteristics will be summarized using descriptive statistics. Differences in glycemic responses across the 3 study arms will be assessed using either 1-way ANOVA or the Kruskal-Wallis test, depending on data distribution. Changes in clinical variables before and after the intervention will be analyzed using repeated-measures ANOVA, with time (before vs after), group (intervention arm), and the time-by-group interaction as factors. Sociodemographic characteristics, dietary intake, and physical activity levels will be considered as covariates where appropriate. A P value of <.05 will be considered statistically significant. Analyses will be conducted according to the intention-to-treat principle, with per-protocol analyses performed for participants who complete the study without major deviations. Missing data will be handled using appropriate imputation methods, and any exploratory analyses will be clearly identified and interpreted with caution.

Results

Recruitment for this trial is scheduled to commence in January 2026 and is expected to conclude by September 2026. Data collection and analysis will be conducted sequentially after each intervention phase, with overall completion anticipated by March 2027. As of December 2025, no participants have been enrolled.

Discussion

This protocol outlines a trial designed to examine the short-term effects of NNSs, specifically sucralose and saccharin, on glycemic control and gut microbiota composition among patients with T2DM. Glycemic control continues to be a central focus in diabetes management, and growing evidence suggests that the gut microbiota plays a significant role in regulating glucose metabolism [41]. Therefore, investigating these 2 domains concurrently in individuals with T2DM is both timely and clinically relevant. This study addresses a critical knowledge gap, as most prior research has focused on healthy populations, leaving limited evidence regarding metabolic and microbial responses in people with T2DM [2-4,7-13,42]. To date, only 1 study conducted in 2003 has examined the impact of sucralose consumption on glycemic control among individuals with T2DM, reporting no significant effects [43]. Among healthy participants, findings on both glycemic regulation and gut microbiota modulation following sucralose or saccharin intake have been inconsistent. Some studies have reported decreased insulin sensitivity after sucralose or saccharin consumption [2-4,10-13], whereas others have found no meaningful changes in glucose metabolism [7-9,42]. Similarly, evidence regarding gut microbiota alterations remains inconclusive, with several investigations observing significant shifts in microbial composition [2-4], while others have reported no detectable differences [7,9]. These discrepancies likely arise from variations in study design, intervention duration, dosage, sweetener formulation, and participant characteristics. Differences in demographic, dietary, and lifestyle factors also contribute to heterogeneity and make comparisons between studies challenging.

This trial aims to overcome these inconsistencies through a tightly controlled crossover design, enabling each participant to serve as their own control and thereby minimizing interindividual variability. A 1-week intervention period was selected to assess short-term effects while maintaining participant compliance and feasibility, followed by a 4-week washout period to avoid carryover effects. The selected NNS dosages represent the upper acceptable daily intake recommended in medical nutrition therapy guidelines, ensuring both safety and sufficient exposure to detect measurable outcomes [22]. Capsules will contain pure sucralose or saccharin to isolate the effects of the sweeteners themselves, excluding confounding components from commercial formulations. Recruitment through government health care facilities allows for a clinically characterized sample reflective of the local T2DM population. Restricting participation to males within a defined age and BMI range enhances phenotype consistency, while inclusion criteria based on disease duration and treatment regimen further standardize metabolic profiles. Gut microbiota profiling using 16S rRNA sequencing targeting the V3-V4 region will facilitate comparison with established microbiome literature [44].

Several limitations warrant consideration. The relatively short intervention period and modest sample size may not capture longer-term or subtle metabolic and microbial changes. Although participants will be encouraged to maintain their usual diet and physical activity, residual variability in lifestyle behaviors could influence outcomes. These confounders will be monitored using validated dietary and physical activity recall tools to aid interpretation. Furthermore, as limited baseline microbiome data are available for Malaysian individuals with T2DM, observed microbial shifts should be interpreted within the context of population-specific dietary and genetic factors. Nonetheless, the comprehensive baseline characterization and rigorous design of this study are expected to strengthen internal validity and provide a valuable foundation for future investigations.

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In conclusion, this trial will generate novel evidence on short-term metabolic and microbial responses to NNSs in individuals with T2DM. Findings may help refine dietary recommendations and guide policy decisions regarding NNS consumption in Asian populations with T2DM. Beyond clinical implications, the results are expected to inform public and industry perspectives on NNS safety and contribute to the broader understanding of gut microbiome-metabolism interactions, supporting the design of future large-scale and longer-term clinical trials.

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Authors' Contributions

Conceptualization: HKGS, SM, VM, NAJ, SNM
Funding acquisition: HKGS, SM, VM, NAJ, SNM
Methodology: HKGS, SM, VM, NAJ, SNM
Writing—original draft: HKGS
Writing—review and editing: HST, HKGS, SM

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report by The Fundamental Research Grant Scheme (FRGS), Ministry of Higher Education Malaysia.
[PDF File (Adobe PDF File), 2622 KB - resprot_v14i1e82695_app1.pdf]

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Abbreviations

HOMA-IR: homeostatic model assessment for insulin resistance
NNS: nonnutritive sweetener
T2DM: type 2 diabetes mellitus

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Protocol

Effects of Walnuts on Postprandial Cognitive Function in Adults With Subjective Cognitive Impairment: Protocol for a Randomized Crossover Trial

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Abstract

Background: Subjective cognitive impairment (SCI), the earliest sign of cognitive decline, affects 1 in 9 Americans aged older than 45 years. It negatively affects quality of life and is a risk factor for dementia. Healthy eating is a primary preventative strategy to impede cognitive decline. In the short term, cognitive function may be impacted by the consumption of a single meal, suggesting that the meal components, and not solely the metabolic dysregulation resulting from the condition of obesity, can impact cognition. The effect of meals on postprandial cognitive function is influenced by their macronutrient composition. A meal with a low-quality fat composition can acutely impair postprandial cognitive function. Walnuts are a source of high-quality fat as well as polyphenols. Some randomized control trials have shown that walnuts may benefit cognitive function. However, it is not clear whether a single meal high in walnuts can improve cognition in adults with SCI.

Objective: The primary objective of the Essential Fats for Enhancing Cognitive Thinking study is to determine the impact of walnuts on postprandial cognitive function in adults with SCI. Secondary objectives include assessing the impact of daily walnut consumption for 1 week on cognitive function and erythrocyte fatty acids. Exploratory objectives include understanding the effect of walnut consumption on microbiota and intestinal inflammation.

Methods: In this 7-week single-blind randomized crossover design study, 78 adults with SCI consumed 1 study snack per day, consisting of walnuts or a chocolate-style snack for 1 week, with a 4-week washout period between. Before consuming each study snack, participants underwent a meal challenge that included this study's snack. Before randomization, participants completed a 1-week run-in period to become acclimated to consuming 1 study snack per day. A registered dietitian nutritionist counseled participants on incorporating this study's snack into their diet while maintaining their body weight. Participants were blinded to which snack was the treatment and which was the control. Dietary intake and physical activity were measured with 24-hour recalls. Cognitive function was measured using the National Institutes of Health Toolbox for the Assessment of Neurological and Behavioral Function Cognitive Battery, both pre- and postprandially, as well as after 1 week of study snack consumption. Stool samples were collected weekly, except during the washout period, to measure microbiota α-diversity, β-diversity, and butyrate. Additionally, fasting blood samples, weight, and waist circumference were obtained at each study visit.

Results: Recruitment began in February of 2024 and was completed by May 31, 2025.

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Conclusions: Improving cognition through the consumption of walnuts may ultimately prove to be an effective way to mitigate SCI.

Trial Registration: ClinicalTrials.gov NCT06223672; https://clinicaltrials.gov/study/NCT06223672

International Registered Report Identifier (IRRID): DERR1-10.2196/82032

(JMIR Res Protoc 2025;14:e82032) doi:10.2196/82032

KEYWORDS

alpha linolenic acid; cognitive function; dietary fat; linoleic acid; polyphenols; postprandial meal challenge; subjective cognitive impairment; walnuts

Introduction

Background

Cognitive decline ranges from subjective cognitive complaints to mild cognitive impairment to diagnosed dementia. Subjective cognitive impairment (SCI) is the earliest sign of cognitive decline and consists of the experience of worsening or more frequent confusion or memory loss in the absence of observable functional decline [1]. Affecting 1 in 9 Americans aged older than 45 years, SCI is associated with mental distress and poses a risk for dementia [2-4]. Most people with SCI do not progress to a diagnosis of dementia, but some do. In a large US longitudinal cohort study, subjective cognitive decline occurred 4.4 years before mild cognitive impairment, 6.8 years before Alzheimer disease, and 6.9 years before all-cause dementia [5]. Even though the polygenic risk score did not differ between those with subjective cognitive decline and those without it, the former had more than double the risk of developing dementia (hazard ratio 2.14, 1.44-3.18). There are currently no treatments available for dementia; therefore, focusing on prevention strategies at the earliest sign of increased risk—when subjective complaints are present—is important [6].

Healthy eating is a primary preventative strategy for impeding cognitive decline [7,8]. The DASH (Dietary Approaches to Stop Hypertension) diet has been associated with a lower prevalence of subjective cognitive complaints [9]. Additionally, the Mediterranean-style diet and the Mediterranean–Dietary Approaches to Stop Hypertension Intervention for Neurodegenerative Delay diet have been associated with slower cognitive decline in older adults [10-12]. Furthermore, higher Mediterranean diet adherence has been associated with lower odds of having SCI [13,14]. The Mediterranean-style diet features foods rich in unsaturated fats, including sources of the essential fatty acids, α-linolenic acid (ALA) and linoleic acid (LA), as well as polyphenols such as flavonoids and tannins.

Chronic intake of saturated fat, on the other hand, is associated with poorer cognition and the risk for cognitive decline [15-17]. Even in the shorter term, 4 to 7 days, consumption of a high saturated fat diet can affect cognitive function [18-21]. Shorter still, the fat content of a single meal may impact cognitive function [22-28]. In adult males and females, after consuming a meal high in saturated fat, cognitive function is negatively impacted compared to a meal high in unsaturated fats [22,23]. Polyunsaturated fatty acids, on the other hand, may have a beneficial effect on cognitive function [29]. As a rich source of the polyunsaturated fatty acids ALA and LA, consumption of walnuts is associated with a lower risk of cognitive decline [30] and can influence postprandial cognitive function. In healthy, young adults, a high-fat breakfast featuring walnuts improved executive function and initially decreased, but later in the day increased, memory recall compared to a breakfast featuring butter [28]. However, the effect of walnut consumption on postprandial cognition in adults with SCI has not been examined.

The exact mechanism for the potential beneficial effects of walnuts on cognitive function is not known. Potential mechanisms include altering the gut microbiota by increasing β-diversity and shifting relative bacterial populations [31,32], or altering inflammation through metabolism of ellagitannins found in walnuts, which are metabolized to form anti-inflammatory urolithins [33-35]. Additionally, ALA and LA have been shown to reduce endotoxemia and inflammation [36-40]. Conversely, saturated fats promote inflammation, which negatively impacts cognitive function [41,42]. Both saturated and unsaturated fatty acids cross the blood-brain barrier, but this is not always detrimental; in moderation, saturated fatty acids may promote brain health and development [43,44]. Even without crossing the blood-brain barrier, fatty acids can impact the brain via inflammation. Saturated fats, which closely resemble the lipid portion of the endotoxin lipopolysaccharide, stimulate signaling via toll-like receptor-4 [45], an effect that mimics lipopolysaccharide's effect [46]. Activation of toll-like receptor-4 stimulates production of proinflammatory cytokines that cross the blood-brain barrier, which causes neuroinflammation [47]. Saturated fats can also promote inflammation in the gastrointestinal tract, which increases intestinal permeability. A permeable intestine allows bacterial components such as lipopolysaccharide to escape into the bloodstream. Both lipopolysaccharide and saturated fats are powerful provocateurs of the inflammatory response, shifting the microbial composition and leading to a potentially unstable, imbalanced state, which further exacerbates proinflammatory signaling, resulting in a vicious cycle [15]. Additionally, lipopolysaccharide has been negatively associated with cognitive function [15]. Therefore, both chronic and acute dietary fatty acid consumption may influence cognition.

Objectives

The objectives of the Essential Fats for Enhancing Cognitive Thinking (EFFECT) study are to (1) determine the impact of walnuts on postprandial cognitive function, and (2) assess the impact of daily walnut consumption for 1 week on cognitive function, the microbiota, and intestinal inflammation in adults with SCI.

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Methods

Study Design and Setting

The EFFECT study was a 7-week randomized single-blinded placebo-controlled crossover design study. This study consisted of a 1-week run-in period followed by two 1-week intervention periods separated by a 4-week washout period. All participants were asked to consume 1 study snack per day throughout this study, except during the washout period. After completing the run-in period, participants were randomly assigned to the order of snack consumption: control snack followed by walnut snack or walnut snack followed by control snack. All study visits took place at The Ohio State University (OSU).

Recruitment

A total of 78 adults with SCI were planned to be recruited from the central Ohio area. Inclusion and exclusion criteria are reported in Textbox 1. Study flyers were placed around the OSU campus and off-campus sites that include community centers, libraries, restaurants, and coffee shops. Additionally, study flyers were distributed to outpatient medical clinics in the Columbus, Ohio area. Potential participants were sent information about this study through The Ohio State Wexner Medical Center's MyChart, and those who agreed to release their information to the research team were prescreened for eligibility. Radio advertisements were placed to reach potential participants outside of the OSU community. Recruitment for this study included or was carried out via ResearchMatch, a national health volunteer registry that was created by several academic institutions and supported by the US National Institutes of Health as part of the Clinical Translational Science Award program. ResearchMatch has a large population of volunteers who have consented to be contacted by researchers about health studies for which they may be eligible.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Subjective cognitive impairment assessed as a score of ≥4 on either item of the Kohli scale
- Age 40-75 years
- BMI ≥20 kg/m^2

Exclusion criteria

- Montreal Cognitive Assessment score of <23
- Diagnosis of mild cognitive impairment or dementia
- Current diagnosis of or current treatment of cancer other than nonmelanoma skin cancer or chronic stable cancers
- Gastrointestinal or pancreatic diseases or disorders where consumption of this study's snacks would be contraindicated or not tolerated, or nutrient absorption would be impaired
- Bariatric or gastric bypass surgery
- Hyperthyroidism diagnosis
- Food allergy or intolerance or dietary restrictions, or use of supplements or medications, where consuming study snacks is contraindicated
- Use of supplements high in linoleic acid or α-linolenic acid in the 4 weeks before enrolling
- Pregnancy and lactation
- Psychostimulant or nootropic medication use
- Current use of supplements or medications for weight loss or following a weight loss program
- Severe or uncontrolled autoimmune diseases (excluding rheumatoid arthritis, psoriasis, and lupus)
- Current or previous diagnosis of severe kidney failure (glomerular filtration rate <30), liver cirrhosis, and some pulmonary diseases (ie, chronic obstructive pulmonary disease and emphysema)
- Heart disease events (including stroke or heart attack) within the last 3 months before enrollment
- Alcohol or drug abuse

Before providing informed consent, this study's team screened potential participants over the phone using this study's screening questionnaire to confirm that participants were likely eligible for this study. Those who passed the phone screening questionnaire and preferred to enroll in this study provided written informed consent before completing an in-person screen. The in-person screen consisted of measuring height and weight to calculate BMI, and completion of the Montreal Cognitive Assessment. Participants who passed the in-person screen began this study.

Study Timeline

The EFFECT study duration was 7 weeks and consisted of 5 study visits (Figure 1). Participants were asked to fast overnight for at least 12 hours before each study visit. Participants reported to the OSU campus for their in-person screening. Those who passed the in-person screen stayed and completed their first

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study visit (week –1), the start of the run-in period. During their week –1 visit, participants filled out the baseline questionnaire and listed their current medications and supplements. Blood pressure, pulse, temperature, and waist circumference were measured, as well as dominant hand grip strength. A finger stick and venous blood draw were also completed. The run-in period lasted 1 week and concluded with their week 0 study visit.

Figure 1. Study timeline.

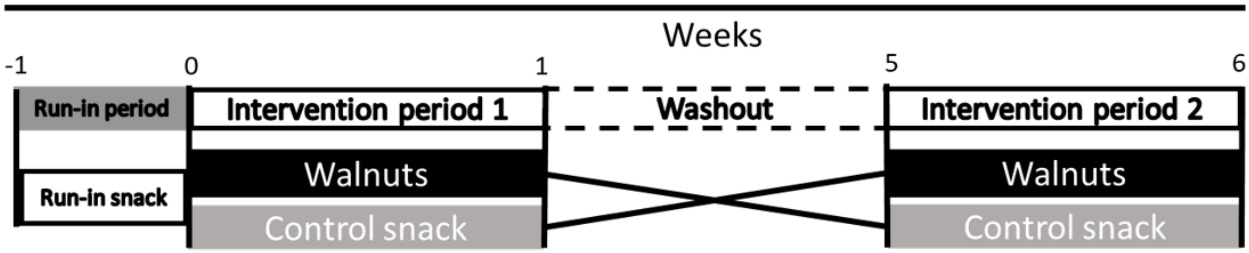

At the beginning of each intervention period (weeks 0 and 5), participants reported to the Clinical Research Center on the OSU campus. At the Clinical Research Center, weight, vitals, and waist circumference were measured, sleep and diet questionnaires were answered, fasting indirect calorimetry was completed, a fasting blood draw was collected, and the meal challenge was administered with subsequent blood draws and indirect calorimetry measurements performed hourly for 5 hours. Additionally, cognitive function was measured both fasting and at 5 hours after the meal challenge, and any updates to medications and supplements were recorded. Each intervention period lasted 1 week and concluded with a study visit (week 1 and week 6). At the week 1 and week 6 visits, weight, vitals, and waist circumference were measured. A fasting blood draw was collected, cognitive function was measured, and updates to medications and supplements were obtained. There was a 4-week washout period between intervention periods. Figure 2 describes the measurements and information collected at each study visit. Participants were supplied with enough study snacks to consume 1 study snack per day until their next study visit. No study snacks were consumed during the washout period. At study visits, this study's team verbally asked participants about adherence to consuming 1 study snack per day, changes to diet or activity, and changes to medications or supplements.

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Figure 2. Study measurement timeline. ACT24: Activities Completed Over Time in 24 Hours; ASA24: Automated Self-Administered 24-Hour; CES-D: Center for Epidemiologic Studies Depression Scale; HbA1c: glycated hemoglobin; MoCA: Montreal Cognitive Assessment; NIHTB-CB: National Institutes of Health Toolbox for the Assessment of Neurological and Behavioral Function Cognitive Battery. *These were not administered at this study's visits. They were given a total of 3 times during the study, which occurred between the week 0 visit and the week 6 visit. The intent is to capture snapshots of diet and activity during the beginning, middle, and end of the study. The "----------" is meant to indicate that the measurement could occur at any time during this range.

	Week –1	Week 0	Week 1	Week 5	Week 6
Baseline Questionnaire	✓				
Diet History Questionnaire	✓				
Grip strength	✓				
HbA_{1c}	✓				
Height	✓				
MoCA	✓				
Blood collection	✓	✓	✓	✓	✓
Blood pressure	✓	✓	✓	✓	✓
Medications and supplements	✓	✓	✓	✓	✓
Pulse and temperature	✓	✓	✓	✓	✓
Waist circumference	✓	✓	✓	✓	✓
Weight	✓	✓	✓	✓	✓
Study snack tracking	✓	✓		✓	
NIHTB-CB		✓	✓	✓	✓
Stool sample		✓	✓	✓	✓
CES-D		✓		✓	
Heart rate		✓		✓	
Indirect calorimetry		✓		✓	
Meal challenge		✓		✓	
Omega-3 Checklist		✓		✓	
Pittsburgh Sleep Quality Index		✓		✓	
ACT24 (physical activity)*		✓----------✓----------✓			
ASA24 (dietary recall)*		✓----------✓----------✓			
Exit Questionnaire			✓		✓

Randomization

Participants were randomly assigned to the order of snack consumption: control followed by walnut or walnut followed by control. A statistician or graduate student studying statistics outside the clinical research team generated the randomization schemes in blocks of 2 and 4. After participants completed the week –1 study visit and before they completed their week 0 visit, the product coordinators assigned participants to the order of intervention from the randomization schemes. The product coordinators also prepared the snacks and meals for distribution to the participants, but had no interaction with the participants.

Interventions

Participants were asked to consume 1 study snack per day throughout this study except during the washout period. Study snacks were portioned at the OSU research kitchen. At weeks –1, 0, and 5, participants were given enough portions of snacks to consume 1 portion per day until their next study visit. Participants were able to choose which time of day and whether to consume the whole portion at once or split it throughout the day. To avoid weight gain, this study's dietitians worked individually with each participant to incorporate this study's snack into their diet by replacing similar foods they were already consuming with this study's snacks. All participants received instructions for incorporating this study's snack into their diets and a list of typical foods to replace with this study's snack.

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During the run-in period (week –1), participants consumed 1 study snack per day consisting of a brownie-style white chocolate snack (Eating Evolved; Table 1). During 1 intervention period, participants consumed a control snack consisting of a white chocolate-style bar (Eating Evolved). During the other intervention period, participants consumed walnuts.

Table 1. Study snack nutrition information[a].

	1 Serving (g)	Energy (kcal)	Fat (g)	Saturated fat (g)	MUFA[b] (g)	PUFA[c] (g)	Carbohydrates (g)	Sugar (g)	Fiber (g)	Protein (g)
Run-in period snack	67	369	34	11	17	4	23	3	10	7
Walnuts	56	366	37	3	5	26	8	1	4	9
White chocolate-style bar	68	366	34	15	15	3	24	2	17	5
Alternate run-in snack	73	364	31	13	—[d]	—	29	3	10	8
Alternate control snack	75	375	35	18	—	—	25	3	7	10

[a]Monounsaturated fatty acid and polyunsaturated fatty acid information was not available for alternate snacks.

[b]MUFA: monounsaturated fatty acids.

[c]PUFA: polyunsaturated fatty acids.

[d]Not available.

Due to unforeseen supply chain issues, which eliminated access to snacks, an alternate run-in period snack consisting of chocolate-covered peanuts (Lakanto, Saraya USA, Inc) and an alternate control snack consisting of dark chocolate peanut butter cups (Lakanto) were used. Alternate snacks were chosen based on matching energy, macronutrients, and saturated fat to the original run-in and control snacks as closely as possible. All study snacks had no added sugar.

The nutrition information of this study's snacks is provided in Table 1. Participants were provided with nutrition information on all snacks during this study.

During this study, participants were asked to maintain their normal physical activity and eating patterns except for replacing a similar habitual food with this study's snack and removing foods high in ellagitannins and replacing them with similar foods low in ellagitannins.

Throughout this study, the study's dietitians were available to help participants avoid weight gain from the study's snacks. The goal was for participants to maintain their weight for the entire study. Weight maintenance was considered at ≤±2 kg over 2 weeks. This study's dietitians discussed with the participant potential reasons for weight change and adjusted counseling as needed. Participants were able to choose which time of day they consumed this study's snack, and whether it was consumed as part of a meal or as a snack. The participants chose whether to consume this study's snack all at once or spread the portion out over the course of the day. The participants were asked to record the study snack they consumed each day and the relative time of day this study's snack was consumed (morning, afternoon, evening, etc). Participants were asked to return uneaten study snacks at their next study visit.

Blinding

The EFFECT study was single-blinded. Participants were not told which snack was the treatment and which was the control. The researchers told participants that 2 snacks were being investigated, but did not disclose the hypothesis of this study to participants. Due to the nature of this study, it was not possible to blind the research team. Once all participants completed this study, they received information about which study snack was the treatment and which study snack was the control. As the snacks were not blinded to the participants or the clinical study team, there was no testing of blinding success.

Outcomes

Cognitive Function

The primary outcome of the EFFECT study is the difference in postprandial cognitive score between control and walnut interventions. Additionally, the difference in change of premeal score at the start and end of the intervention period between the control and walnut interventions will be analyzed. To assess cognitive function, the National Institutes of Health Toolbox for the Assessment of Neurological and Behavioral Function Cognitive Battery (NIHTB-CB) was used, specifically the fluid cognition battery. The tests are fully automated and administered via an iPad (Apple Inc) with consistent program-derived instructions. Minimal practice effects and no floor or ceiling effects are seen with the NIHTB-CB [48-50].

Microbiome

Participants were instructed to collect a stool sample on the 1-2 days before or the morning of week 0, 1, 5, and 6 study visits. An Omnigene Gut fecal collection kit (OMR-200, DNAGenotek) was provided with specific instructions for how to store the sample until delivery to the clinic. Total DNA will be isolated using QIAGEN Power Fecal Pro kits and sequenced to a depth of >25 million reads per sample. Microbe or gene

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abundances will be defined via alignment to reference genomes and de novo assembly.

Anthropometrics

Waist circumference was measured at each study visit using a nonstretch tape measure at the uppermost border of the right iliac crest. Weight and height were measured without shoes using a digital scale and a stadiometer, respectively. Weight was measured to the nearest 1 kg, and height was measured to the nearest 0.1 cm. Weight was measured at each study visit, and height was measured at the first study visit. Height and weight were used to calculate BMI. Grip strength was measured at the first study visit using a Jamar handheld dynamometer and reported in kilograms as previously described [51].

Meal Challenge

At weeks 0 and 5, participants received a high-kilocalorie meal challenge. The meal was approximately 900 kcal with 60 g of fat, 33 g of polyunsaturated fat for the walnut meal and 41 g of saturated fat for the control meal, 60 g of carbohydrates, and 37 g of protein; the meal consisted of a drink and the corresponding intervention period study snack. The macronutrient composition of the meals between the 2 study snacks was equivalent except for the saturated fat, monounsaturated fat, and polyunsaturated fat content. Participants had 20 minutes to consume the entire meal. To measure preprandial and postprandial metabolism, before consuming the meal (fasting) and each hour for 5 hours after consuming the meal, energy expenditure, blood pressure, and heart rate were measured, and venous blood samples and saliva samples were collected.

Energy expenditure was measured using indirect calorimetry (Ultima Series CPX, MGC Diagnostics). For the fasting indirect calorimetry, after arriving for their study visit, participants rested in a quiet, dim room on a hospital bed with the head of the bed at a 30° angle for 30 minutes before assessing energy expenditure over 25 minutes. For postprandial measurements, participants rested for 30 minutes in a hospital bed while being allowed to quietly read, use electronics, or sleep before a 20-minute indirect calorimetry measurement period. A heart rate monitor (FirstbeatTM Bodyguard 3, Firstbeat Technologies) was placed on the participant's chest and abdomen at the start of the first resting period and measured their heart rate throughout this study's visit. Fasting and postprandial blood pressure were measured using a blood pressure cuff.

To reduce variability in postprandial measurements, participants were provided with all meals and snacks for the day before the meal challenge [52]. As described in prior research, the meals and snacks were approximately 30% fat, 20% protein, and 50% complex carbohydrate with low added sugars [53,54] and were prepared by the Ohio State Clinical Research Center. To further reduce variability of postprandial measurements, participants were also instructed to avoid taking blood pressure, glucose-lowering, lipid or cholesterol-lowering, and nonsteroidal anti-inflammatory medications the morning of the meal challenge, to avoid alcohol the day prior, to avoid strenuous exercise 2 days prior, and to abstain from taking dietary supplements and aspirin for 7 days before the meal challenge.

Mitochondrial Measurements

Cardiolipin species will be measured in the peripheral blood mononuclear cell (PBMC) samples. PBMC cardiolipin fatty acyl molecular species mass will be quantified using electrospray ionization-mass spectrometry coupled to high-performance liquid chromatography as previously described [55,56].

Biochemical Markers

Glycated hemoglobin was measured using a finger stick. Erythrocyte and PBMC fatty acids will be analyzed. PBMC lipids will be extracted using methanol and chloroform (1:2 v/v) [57] and methylated using 5% hydrochloric acid in methanol [58] as previously described [59]. Erythrocyte fatty acid methyl esters will be prepared using 14% boron trifluoride in methanol and hexane [60] as previously described [61,62]. Gas chromatography with a 30-m Omegawax TM 320 fused silica capillary column (Supelco) will be used to analyze the fatty acid methyl esters. Standards for fatty acid methyl esters (Matreya, LLC and Nu-Check Prep Inc) will be used to determine retention times of fatty acids in the samples as previously described [63].

From blood collected at fasting and postprandial time points, lipid panels were measured at the OSU Wexner Medical Center Hospital Lab. Glucose will be measured using the Glucose Autokit (FUJIFILM Healthcare Americas Corporation), and insulin levels will be measured using the Meso Scale Diagnostics kit. Fasting glucose and insulin levels will be used to calculate estimated insulin resistance using the homeostatic model assessment of insulin resistance [64]. Markers of inflammation, including fasting and postprandial tumor necrosis factor alpha, tumor necrosis factor receptor 2, C-reactive protein, interleukin-6, and soluble intercellular adhesion molecule-1, will be measured at weeks 0 and 5. Fasting soluble CD14, oxidized low-density lipoprotein, and lipopolysaccharide binding protein will also be measured. Tumor necrosis factor α, tumor necrosis factor receptor 2, soluble intercellular adhesion molecule-1, C-reactive protein, interleukin-6, and lipopolysaccharide binding protein will be measured using a highly sensitive Meso Scale Diagnostics kit, and soluble CD14 and oxidized low-density lipoprotein will be measured by ELISA kits (R&D Systems and Mercodia, respectively). Lipopolysaccharide will be measured using Kinetic-QCL, Kinetic Chromogenic LAL Assay, or ELISA LifeSpan BioSciences. Markers of oxidative stress, 4-hydroxynonenal and malondialdehyde, will also be measured by multiplex methods as previously reported [54,65-68].

Questionnaires and Recalls

At the first study visit, participants were asked to complete the Baseline Questionnaire, a descriptive questionnaire asking about age, gender, sex, race, ethnicity, and health status. At the beginning of each intervention period, participants were asked to complete the Pittsburgh Sleep Quality Index [69] to capture sleep quality and disturbances, an Omega-3 Fatty Acid Checklist to determine omega-3 fat intake [70], and the Center for Epidemiologic Studies Depression Scale to assess depressive symptoms.

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To measure dietary intake before enrollment in this study, participants completed the Diet History Questionnaire III, a food frequency questionnaire developed by the National Cancer Institute staff [71,72]. During this study, participants completed 24-hour dietary recalls, using the Automated Self-Administered 24-Hour Dietary Assessment Tool (version 2022 and 2024), developed by the National Cancer Institute. To assess changes in physical activity, 24-hour recalls were completed using the Activities Completed Over Time in 24 Hours, a web-based physical activity recall tool offered by the National Institutes of Health National Cancer Institute [73-75].

Sample Size

The primary outcome used in sample size calculation was the postprandial cognitive test score from the NIHTB-CB. Based on our previous study [22], we obtained the SD (11.0) of the difference in postprandial cognitive test score between the unsaturated fat meal and the saturated fat meal. We had 80% power with 78 participants to detect a difference of 3.5 in postprandial cognitive test score between the control and the walnut group using a 2-sided paired *t* test with a type I error of 0.05.

Statistical Analysis

Postprandial cognitive test scores will be compared between the control and walnut group using a 2-sided paired *t* test to account for the cross-over design. To further adjust for covariates, a linear mixed effect model with subject-specific random intercept will be fit on postprandial test score with the following covariates: study group, preprandial test score at week 0 and 6, BMI, age, sex, education level, and depression score. The regression coefficient of this study's group will be the adjusted difference in postprandial test score between this study's groups. Potential carryover of treatment effects from the first treatment period to the second period will be assessed by including an interaction between treatment and period in the mixed-effect models. Significant interaction indicates the existence of a carryover effect, in which case we will only use data from the first treatment period to evaluate the treatment effect using a 2-sample *t* test and linear regression models. Analyses for the primary hypothesis will use participants who completed the entire study and will be based on an intention-to-treat principle, regardless of compliance and study group crossover. Sensitivity analyses will be conducted with multiple imputation on missing values for participants who do not complete the entire study. A linear mixed effect model with subject-specific random intercept will be fit on preprandial test score at week 1 and 6 with the following covariates: study group, preprandial test score at day 0 and 35, BMI, age, sex, and education level. The regression coefficient of this study's group will be the adjusted difference in preprandial test score after a 7-day intervention between study groups. A linear mixed effect model with subject-specific random intercept will be fit on postprandial test score at weeks 0 and 5 with the following covariates: change in plasma sum of ALA+LA during 7-day intervention, BMI, age, sex, and education level. The regression coefficient of plasma sum of ALA+LA will measure the adjusted correlation between postprandial test score and change in plasma sum of ALA+LA.

A linear mixed effect model with subject-specific random intercept will be fit on the change of endotoxemia during the 7-day intervention with the following covariates: study group, BMI, age, sex, and education level. The regression coefficient of this study's group will be the adjusted difference in the reduction of endotoxemia between this study's groups. β-diversity of the microbiome community at days 7 and 42 between all pairs of participants will be calculated using the Bray-Curtis dissimilarity measure. Nonmetric multidimensional scaling ordination will be computed, and nonmetric multidimensional scaling plots will be generated to visualize the difference in β-diversity between study groups. Permutation-based ANOVA will be used to compare the β-diversity between study groups. Operational taxonomic units (OTU) abundance will be compared between study groups using paired *t* tests for each OTU, and the *P* values will be adjusted by the Benjamini-Hochberg procedure [76] to control for false discovery rate. A linear mixed effect model with subject-specific random intercept will be fit on postprandial test score with the following covariates: change of endotoxemia during the 7-day intervention, change of OTU abundance during the 7-day intervention, BMI, age, sex, and education level. As the number of OTUs will be very large, exceeding the sample size, a LASSO (Least Absolute Shrinkage and Selection Operator) penalty [77] will be included in the regression model to select significant covariates.

Ethical Considerations

Review and approval for this study and all procedures were obtained from the OSU Institutional Review Board on April 24, 2023 (2023H0111). All interested potential participants were provided verbal and written information about this study, including a copy of the consent form. Potential participants had the opportunity to ask questions and be provided as much time as necessary to review the consent form and consider participating. Informed consent was obtained from all participants. Participants were compensated up to US $200 for participation in this study, where those who discontinued early received a prorated amount. Efforts were made to protect the privacy of this study's participants, such as deidentifying participant information and limiting interactions with participants to essential study team members.

Results

The EFFECT study was funded in May 2023. Recruitment began in February 2024, and the final study visits were projected to be completed in July 2025.

Discussion

Comparison With Prior Work

Studies examining cognitive function after consumption of a meal are limited. Fewer still are reports on the impact dietary fat has on postprandial cognitive function [22-24,28]. Of those investigations, comparisons have been made between a saturated fat meal and an unsaturated fat meal [22,23]. The unsaturated fat meals used dietary oils that were mostly composed of monounsaturated fat. In a population of women, the high

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saturated fat meal had a negative impact on cognitive function compared to the high unsaturated fat meal [22]. In a population of men, the negative impacts of the high saturated fat meal were only observed in men who were obese [23]. In contrast, the EFFECT study did not use dietary oils and instead used walnuts to deliver the unsaturated fat, included both men and women, and included anyone with a BMI over 20.

Delivering unsaturated fats and polyphenols through nuts instead of oil is not novel. A meal supplemented with almonds has also been investigated [24]. This meal was compared to a high-carbohydrate meal, which found that the high-fat almond meal ameliorated declines in cognitive function 2 hours after the meal. Most of the fat in almonds is monounsaturated fat. Differing from almonds, walnuts contain a higher proportion of polyunsaturated fats. Of note are ALA and LA, the 2 essential polyunsaturated fatty acids that cannot be synthesized and therefore must come from the diet. Walnuts are a rich source of both ALA and LA, whereas almonds contain no ALA and only a fraction of the LA that is present in walnuts. The unique fat composition and polyphenols of walnuts may have different effects on postprandial cognitive function compared with the nutrient composition of almonds.

The EFFECT study is not the first to explore a high polyunsaturated fat meal using walnuts in relation to cognitive function. A recent crossover trial investigated the effects of a breakfast containing walnuts on cognitive performance [28]. After consuming the walnut breakfast, improvements to executive function were observed compared to a control meal featuring butter as the primary fat source. The effects on memory were mixed, observing a decrease in recall at 2 hours after the meal, but an increased recall at 6 hours compared to the control. This could be related to the walnuts slowing of gastric emptying, which could result in a delayed response. This design administered cognitive tests at baseline and 2, 4, and 6 hours after breakfast, which differs from the EFFECT study, as postprandial cognitive testing was only completed at hour 5. Furthermore, participants were given a snack before the baseline tests and given a lunch between hours 2 and 4. In the proposed study, participants fasted for baseline cognitive tests and did not consume additional food after the high-calorie breakfast. Additionally, the participants were young, healthy adults, which differs from the older population with SCI in the EFFECT study. Therefore, the proposed study would expand our understanding of postprandial cognitive function.

In addition, walnuts alter the gut microbiota by increasing β-diversity and shifting relative bacterial populations [31,32]. Walnuts are a source of ellagitannins, which are metabolized to form anti-inflammatory urolithins [33-35]. We will look at the relationship between gut microbiota, urolithins, and postprandial cognitive function.

Strengths and Limitations

The EFFECT study uses a randomized, crossover design with a 4-week washout period between interventions. Thus, a strength of this design is that participants served as their own controls. A total of 4 weeks should be sufficient to prevent any carryover effects from the first intervention. Using a run-in period could be considered a limitation, as a study snack used to acclimate participants to consuming 1 study snack per day would be a deviation from their usual diet. However, the fat profile of the run-in period snack is comparable to the typical American diet. An inherent limitation to studying SCI is the subjective nature of the cognitive impairment, as reliance on a self-report of cognitive issues is necessary. Similarly, adherence to the interventions is partially reliant on self-reported consumption. However, changes in fatty acid profiles in erythrocytes were also used as a measure of adherence.

Conclusions

With no current dietary recommendations for managing SCI, discovering a food that improves cognitive function in adults with SCI is important. The dietary interventions in this study are modest and only require substituting a study snack for a food already being consumed. Walnuts can be easily incorporated into an individual's diet, and a total dietary overhaul is not required. Consuming certain fats, or reducing consumption of others, could be an effective, inexpensive way to impact the negative effects of SCI. The EFFECT study will enhance our knowledge of the interplay between cognitive function, dietary fats, and SCI.

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Data Availability

The dataset is not publicly available due to the ongoing nature of the trial. Upon conclusion of the trial, data will be available from the corresponding author upon reasonable request.

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Authors' Contributions

Conceptualization: MAB
Data curation: RMC (lead), MAB (equal), KF (supporting), SZ (supporting)
Formal analysis: AN
Funding acquisition: MAB
Investigation: RMC (lead), DS (supporting), GS (supporting), SZ (supporting)
Methodology: MAB (lead), AM (equal), AN (equal), DS (equal), GS (equal), KF (equal), RMC (equal)
Project administration: MAB (lead), RMC (supporting)
Resources: MAB (lead), RMC (supporting), SZ (supporting)
Supervision: MAB (lead), RMC (supporting)
Validation: MAB
Visualization: SZ (lead), MAB (equal), RMC (equal)
Writing – original draft: SZ
Writing – review & editing: MAB (lead), AM (equal), AN (equal), DS (equal), GS (equal), KF (equal), RMC (equal)

Conflicts of Interest

None declared.

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Abbreviations

ALA: α-linolenic acid
DASH: Dietary Approaches to Stop Hypertension
EFFECT: Essential Fats for Enhancing Cognitive Thinking
LA: linoleic acid
LASSO: Least Absolute Shrinkage and Selection Operator
NIHTB-CB: National Institutes of Health Toolbox for the Assessment of Neurological and Behavioral Function Cognitive Battery
OSU: Ohio State University
OTU: operational taxonomic unit
PBMC: peripheral blood mononuclear cell
SCI: subjective cognitive impairment

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Smartphone App–Based Eating Behavior Monitoring and Feedback Intervention for Glucocorticoid-Induced Appetite Increase in Patients With Systemic Lupus Erythematosus: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Increased appetite and weight gain are common adverse effects of glucocorticoid therapy in patients with systemic lupus erythematosus (SLE). Concerns about appearance-related changes due to weight gain can reduce medication adherence.

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Moreover, the complex interplay among glucocorticoids, mood changes, sleep disturbances, and appetite can influence eating behaviors. Daily data collection using ecological momentary assessment and analysis of interrelations may help clarify these dynamics. Furthermore, real-time feedback based on daily eating behavior may help patients regulate appetite and eating patterns. Accordingly, we developed Mogu!☆Log, a smartphone-based app that enables daily self-reporting of eating behaviors, appetite, and mood and provides graphical feedback on meal frequency and perceived control over eating.

Objective: This paper presents a protocol for a pilot randomized controlled trial designed to evaluate the effects of real-time feedback on eating behaviors using the Mogu!☆Log app among patients with newly diagnosed SLE who had started glucocorticoid therapy.

Methods: This multicenter study recruited Japanese patients with newly diagnosed SLE who had started glucocorticoid therapy across 15 hospitals with rheumatology services. Participants were randomly assigned in a 1:1 ratio to two groups: (1) the immediate feedback group, which receives graphical feedback on meal frequency and perceived control over eating starting from day 1, and (2) the delayed feedback group, which uses the same app without feedback for the first 14 days and begins receiving identical feedback from day 15. Participants enter data daily from day 1 to day 21 after randomization. The primary outcome is the mean number of meals on day 14 after glucocorticoid initiation. Secondary outcomes include the loss-of-control-over-eating score and a 5-item visual analog scale–based appetite score, both recorded on day 14. Between-group mean differences will be analyzed using 2-tailed *t* tests. The target sample size is 60. In an embedded observational "study within a trial," linear mixed models will examine whether glucocorticoid dose influences appetite scores through mood and sleep changes.

Results: We hypothesized that participants receiving immediate feedback will have fewer meals on day 14, reduced loss of control over eating, and better appetite scores. The study received funding in April 2019, April 2022, and April 2024. Recruitment began in October 2024, and 17 participants had been enrolled as of May 2025. Data collection is expected to be completed by March 2027; data analysis has yet to begin. Results will be submitted for publication and reported to the University Hospital Medical Information Network (UMIN) registry in the summer of 2027.

Conclusions: This pilot trial will provide foundational data on the feasibility and efficacy of smartphone-based real-time feedback in managing glucocorticoid-induced appetite increase in patients with SLE. These findings may contribute to the growing body of literature on app-based interventions for medication-related adverse effects.

Trial Registration: UMIN Clinical Trials Registry UMIN000052113; https://center6.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000059479

International Registered Report Identifier (IRRID): DERR1-10.2196/78612

(JMIR Res Protoc 2025;14:e78612) doi:10.2196/78612

KEYWORDS

systemic lupus erythematosus; smartphone app; randomized controlled trial; eating behavior; appetite; glucocorticoid; ecological momentary assessment

Introduction

Clinical Relevance of Glucocorticoid-Related Side Effects in Systemic Lupus Erythematosus

Glucocorticoids are the cornerstone of initial treatment for systemic lupus erythematosus (SLE), a disease that predominantly affects young to middle-aged women [1]. However, prolonged glucocorticoid use is associated with serious medical complications, such as infections and osteoporosis, as well as adverse quality-of-life effects, including increased appetite, weight gain, insomnia, and mood changes [2-4]. More than 30% of glucocorticoid users report experiencing weight gain and insomnia [5]. Furthermore, online patient communities frequently describe appetite increases and weight gain as distressing experiences [1]. Despite their prevalence, these side effects are often underrecognized in clinical practice and underexplored in research, with limited practical guidance available in standard medical literature.

Unclear Mechanisms Underlying Glucocorticoid-Induced Appetite Changes

Prolonged glucocorticoid therapy induces weight gain [1], and patients with Cushing disease—characterized by chronic endogenous glucocorticoid exposure—commonly report increased food cravings rather than hunger [6]. Although exogenous glucocorticoid administration has been shown to increase food intake [7], the specific components of appetite affected by glucocorticoids remain unclear, possibly due to the limited use of validated appetite assessment scales in previous studies. Furthermore, the complex interplay among glucocorticoid use, mood changes, sleep disturbance, and appetite changes is poorly understood. Clinical glucocorticoid use is known to alter mood (eg, depression and irritability) and cognitive function (eg, difficulty with concentration and memory) [8]. Negative emotional states, in turn, can trigger increased food intake in healthy populations [9,10]. Whether similar mechanisms underlie glucocorticoid-induced appetite changes in patients with SLE remains uncertain. Although glucocorticoid-related sleep disturbances, such as insomnia, increased percentage of time spent awake, and increased percentage of time spent in slow-wave sleep, are well

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documented [11], it remains unclear whether these disturbances lead to mood deterioration similar to that observed in healthy individuals or those with mood disorders [12,13].

Potential of Ecological Momentary Assessment and Feedback Interventions

Ecological momentary assessment (EMA) enables real-time monitoring of behavior and symptoms, offering a promising approach to clarify the dynamic interrelationships among appetite, mood, and sleep. In addition, behavioral interventions that incorporate daily feedback may help patients manage their appetite and eating behaviors. Smartphone apps delivering real-time feedback have shown potential in promoting dietary self-regulation among adults with obesity [14].

By using brief questions with simple response options and automated, immediate data processing [15,16], these tools minimize user burden and enhance sustained engagement through real-time feedback [14]. Consequently, such approaches may also benefit patients with SLE who experience appetite increases and weight gain following glucocorticoid therapy.

However, evidence regarding the use of EMA with real-time feedback in patients with glucocorticoid-treated SLE is limited. Although a previous study used an EMA-based smartphone app to assess meal frequency in healthy adults, most studies lack validated appetite measures or control groups [17]. Furthermore, existing EMA studies involving patients with SLE have primarily focused on sleep quality, without assessing appetite or mood [18].

Development of a Smartphone-Based Monitoring and Feedback Tool

To address these gaps, we developed Mogu!☆Log (もぐ！☆ログ), a smartphone app designed to monitor and provide feedback on appetite, mood, and eating behavior. The app allows daily self-reporting and visual feedback and includes a built-in randomization function to assess the impact of feedback on behavior. By integrating clinical and sleep data, this tool facilitates a comprehensive EMA-based analysis of how glucocorticoid therapy influences appetite through mood- and sleep-related pathways.

Objectives

This study aims to (1) evaluate the effect of real-time dietary feedback on meal frequency in patients newly diagnosed with SLE who have started with glucocorticoid therapy and (2) examine how glucocorticoids affect appetite through mood and sleep changes. We will conduct a pilot randomized controlled trial (RCT) to evaluate the feedback intervention, along with an embedded observational cohort study to explore interrelationships using multilevel modeling. This protocol is reported in accordance with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [19] (Checklist 1).

Methods

Study Setting

This study is conducted in the rheumatology departments of 15 general or university hospitals in Japan, each comprising both outpatient and inpatient services. These hospitals were selected based on their established collaborative research relationships with the principal investigators (NK and NY) and their experience managing newly diagnosed patients with SLE.

Eligibility Criteria

Inclusion Criteria

Inclusion criteria include patients who (1) are diagnosed with SLE based on the 1997 American College of Rheumatology classification criteria [20] and (2) have initiated glucocorticoid therapy for the first time, with dosage determined at the discretion of the treating physician. There are no age restrictions; however, as rheumatology departments primarily serve adult populations, the inclusion of minors is expected to be rare. Although SLE predominantly affects women, male patients are also eligible, and sex is not used as an inclusion criterion. Participants must be able to understand Japanese because the mobile app and all study materials are available only in Japanese.

Exclusion Criteria

Exclusion criteria include patients who (1) have neuropsychiatric lupus with seizures, confusion, disorientation, or delusions or (2) are unable to access the Mogu!☆Log app via the LINE platform (LY Corp).

Intervention

Participants use Mogu!☆Log, a smartphone-based app delivered via the LINE platform, to record meal frequency and episodes of loss of control over eating. The intervention group receives real-time graphical feedback immediately after each entry, displaying data from up to the previous 7 days (Figure 1; English translation of the Japanese text displayed in the app is provided in Multimedia Appendix 1).

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Figure 1. Feedback interface of the Mogu!☆Log smartphone app on the LINE social networking platform. (**A**) Graphical feedback showing self-evaluated eating episodes. Data from the past 7 days are plotted, with days on the x-axis and time (midnight to 11 PM) on the y-axis. Label size indicates perceived overeating (larger for episodes rated as overeating), whereas label color reflects perceived loss of control (red for loss of control, green otherwise). (**B**) Graphical feedback showing the frequency of eating episodes. Data from the past 14 days are presented, with dates on the x-axis and the number of episodes on the y-axis.

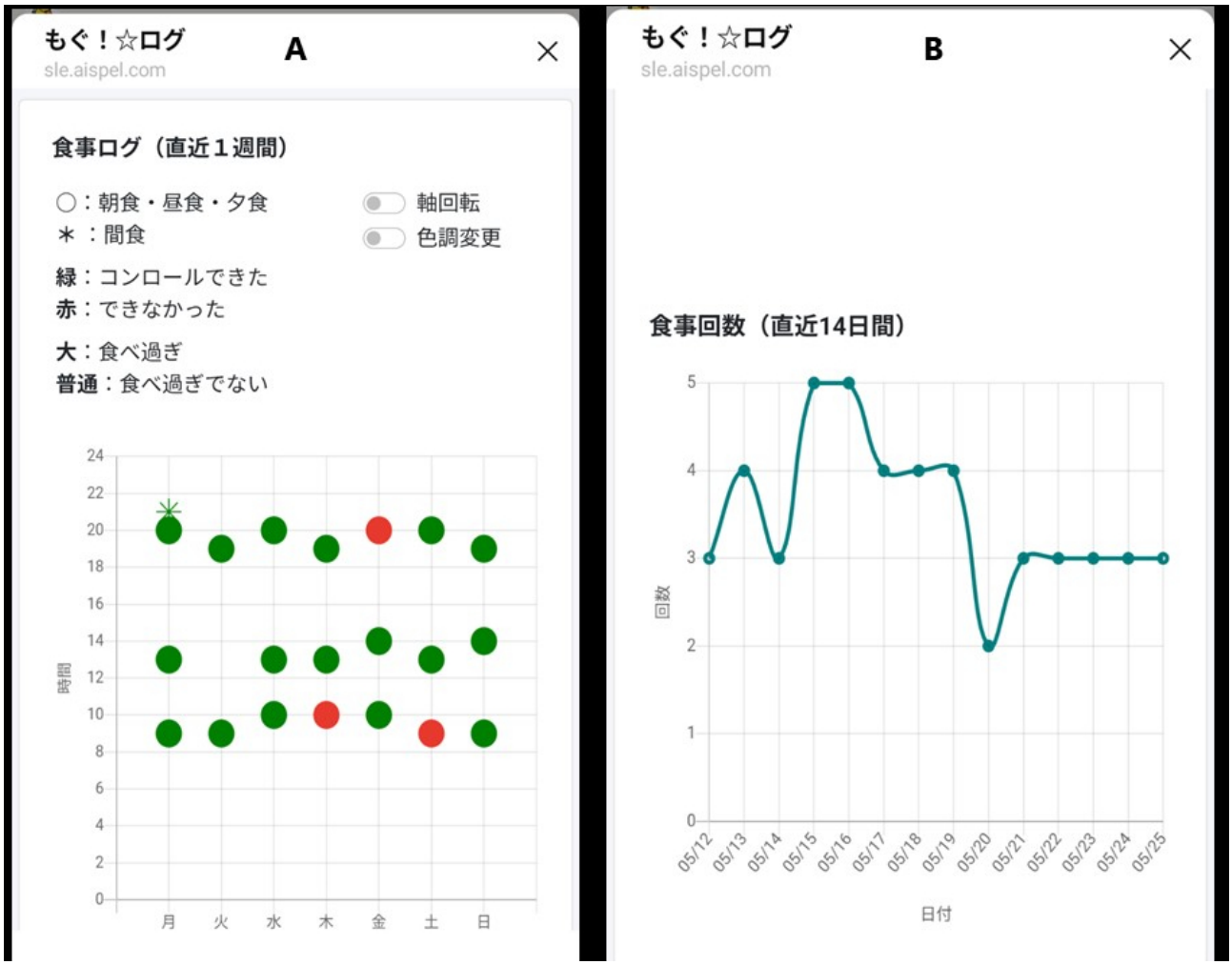

Two types of feedback are provided. The first graph summarizes eating episodes over the past 7 days, indicating whether overeating or loss of control occurred (Figure 1A). The second graph presents daily meal counts over the past 14 days (Figure 1B).

Participants register the day before glucocorticoid initiation and record data from treatment days 1 to 21 (Figure 2; English translation of the Japanese text displayed in the app is provided in Multimedia Appendix 1). Appetite and mood are assessed before and 2 hours after each meal. Overeating and loss of control are recorded immediately after every eating episode, including snacks. Before starting the study, participants received instructions on voluntarily logging entries before and after meals. The app automatically sends reminders for daily reporting. Reminders for postprandial entries (2 hours after a meal) were automatically scheduled based on each participant's self-registered typical meal times (breakfast, lunch, and dinner). Specifically, these reminders were delivered randomly within +30 or −30 minutes of 2 hours after each registered mealtime (eg, if breakfast was set at 8 AM, the reminder was sent randomly between 9:30 and 10:30 AM). In addition, for immediate postmeal entries, if a participant did not submit an entry within 60 minutes after a premeal report, an automated reminder was sent.

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Figure 2. Widget interface of the Mogu!☆Log smartphone app on the LINE social networking platform. (A) Main menu widget: clockwise from the top left—Appetite, Eating Behavior Evaluation, Log Review, User Settings, Morning/Night Entry, and Actigraphy Attachment. (B) Visual analog scale (VAS) input for appetite: users slide bars to rate hunger and satiety. (**C**) VAS input for eating episodes: users rate the degree of perceived overeating and loss of control during meals. (**D**) VAS input for mood: users rate depressed mood and irritation. Values for VAS inputs are automatically calculated based on the ratio of a slider's position (distance from the left) to the full length between labeled end points.

The immediate feedback group receives graphical feedback from day 1, whereas the delayed feedback group does not receive feedback until day 14. After that, participants receive identical real-time feedback as the intervention group. The 14-day delay was determined for the following reasons: (1) at least 7 days of data are required to capture weekly behavioral patterns [15]; (2) a feedback duration longer than 1 week is desirable to detect behavioral change [17]; and (3) the accelerometer device used in the embedded "study within a trial" (SWAT) has a battery life of approximately 21 days, determining the total study duration. Accordingly, data collection spans 21 days, comprising a 14-day intervention or control phase followed by a 7-day delayed feedback phase, ensuring both groups eventually receive feedback exposure.

To encourage adherence, participants receive Amazon e-gift cards at registration and on days 7, 14, and 21 with the amounts corresponding to their logging activities.

Outcome Measures

Primary Outcome

The primary outcome is the mean number of meals on day 14 after glucocorticoid initiation. This measure was selected to assess the impact of graphical feedback on eating behaviors. Meal frequency has previously been used as an index of the effectiveness of app-based feedback interventions [17].

Feasibility outcomes, including the completion rate and SD of the primary outcome, will also be reported to inform sample size estimation and refine the protocol for a future full-scale trial.

Secondary Outcomes

Secondary outcomes include loss of control before meals, loss of control during meals, and appetite, all assessed on day 14. Loss of control is measured using a visual analog scale (VAS) comprising 2 items: before meals, "To what extent do you feel in control of your eating?" (0 - 100 scale); during meals, "During meals, how much did you feel out of control?" (0 - 100 scale). Appetite is measured using a validated 5-item VAS-based scale for EMA [21].

We will also examine the 21-day trajectories of loss of control (ie, before and during meals) and appetite. Given the limited evidence on how glucocorticoid affects appetite over time, these trajectories will be analyzed separately for each feedback group.

Participant Timeline

Patients diagnosed with SLE and scheduled to begin glucocorticoid therapy are recruited 1 to 14 days before treatment initiation (Table 1). From days 1 to 21, all participants use the mobile app to report their mood, appetite, and eating behaviors. Participants also wear an actigraph continuously—except while bathing—to monitor their activity and sleep. Paper-based psychological and behavioral questionnaires are administered on days 1 and 21.

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Table . Participant timeline.

Time point in study timeline	Enrollment (day −14 to day −1)	Randomization (day 0)	Day 1 after randomization	Day 14 after randomization	Day 15 after randomization	Closeout (day 21)
Enrollment						
Eligibility assessment	✓					
Informed consent	✓					
Randomization		✓				
Intervention						
Immediate feedback			✓	✓	✓	✓
Delayed feedback					✓	✓
Assessment						
Baseline variables[a]	✓					
EMA[b]-based mood, appetite, and eating behavior[c]			✓	✓	✓	✓
Medication[d]			✓	✓	✓	✓
Actigraph-based physical activity and sleep data[e]			✓	✓	✓	✓
Paper-based questionnaire[f]			✓			✓

[a]Participant characteristics, including sex, birth date, age, psychiatric/psychosomatic outpatient status, height, weight, and disease activity (systemic lupus erythematosus disease activity index 2000).

[b]EMA: ecological momentary assessment.

[c]Sleep parameters, wake-up time, bedtime, mood (before sleep and before and after meals), appetite (before meals), perceived control over eating (before and after meals), and subjective assessment of meal quantity (after meals).

[d]Including glucocorticoids (prednisone-equivalent dose per day), psychotropic medications (hypnotics, antiepileptics, mood stabilizers, and antidepressants), hydroxychloroquine, and immunosuppressants.

[e]Including activity levels, nocturnal awakenings, wake after sleep onset, sleep onset latency, and sleep efficiency.

[f]A Three-Factor Eating Questionnaire-R18V2, Athens Insomnia Scale, Health-Related Hope Scale, and Short Grit Scale.

Sample Size

The target sample size is 60 participants, taking into account the rarity of newly diagnosed SLE and the constraints of study duration and funding. This pilot trial aims to obtain key data for planning a future trial, ensuring at least 30 participants to estimate parameters for outcome measures (particularly SDs), as recommended in the pilot study design literature [22].

Recruitment

Principal investigators (NK and NY) recruited rheumatologists from 15 hospitals across 5 Japanese regions (Hokkaido, Kanto, Chubu, Kinki, and Chugoku) through professional networks. Despite the rarity of SLE, recruitment was deemed feasible in both outpatient and inpatient hospital settings.

Assignment of Interventions

The procedures for randomization and blinding are as follows:

- Allocation—the app incorporates a simple randomization algorithm for participant assignment.
- Concealment—allocation is centrally randomized and concealed from both patients and physicians at enrollment.
- Implementation—physicians enroll patients, while the app performs group allocation automatically.
- Blinding—participants are blinded, although group inference may be possible based on feedback timing (health care providers remain blinded unless they view the participant's screen; data analysts receive deidentified datasets without group assignment indicators).

Data Collection and Management

Data were collected as follows: meal frequency was recorded electronically through user taps in the app at each eating occasion. VAS scores for loss of control, mood, and appetite were collected via in-app sliders with labeled anchors. Physical activity and sleep parameters, including activity levels, nocturnal

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awakenings, wake after sleep onset, sleep onset latency, and sleep efficiency, were measured using an actigraph (Table 1). These data were analyzed as outcomes or covariates in the SWAT.

Validated paper-based questionnaires included the Three-Factor Eating Questionnaire-R18V2 [23,24], Athens Insomnia Scale [25,26], Health-Related Hope Scale [27], and Short Grit Scale [28].

To promote retention, participants received Amazon e-gift cards on days 7, 14, and 21, with amounts proportional to the number of completed app entries.

Data management was conducted as follows: app data were securely transmitted and stored on an encrypted server. Input options were restricted to predefined ranges to ensure data validity. Paper-based data were double entered and cross-checked to identify discrepancies.

Statistical Analysis

For the primary outcome, meal frequency on day 14 will be compared between groups using a 2-sided Student *t* test with a 5% significance level. For sensitivity analysis, an analysis of covariance will be performed, adjusting for disease activity and glucocorticoid dose.

For the secondary outcomes, between-group comparisons of loss-of-control and appetite scores on day 14 will be conducted using the 2-tailed Student *t* test. Sensitivity analyses with analysis of covariance adjusted for disease activity and glucocorticoid dose will be conducted. Longitudinal changes over the 21-day period will be analyzed using linear mixed-effects models with random intercepts for individual participants and fixed effects for group, time, and group-by-time interactions.

For the observational SWAT, linear mixed-effects models will be used to examine associations between glucocorticoid dose and outcomes such as appetite, snacking behavior, and loss of control. Mood and sleep variables will also be analyzed using the same modeling framework to assess the effect of glucocorticoid dosage. Additionally, linear mixed-effects models will be used to assess whether mood and sleep mediate the relationship between glucocorticoid dose and appetite. All models will incorporate random intercepts for individual participants and fixed effects for group, time, and group-by-time interactions.

Monitoring, Harms, and Auditing

No formal monitoring is planned due to the noninvasive nature of the intervention and the pilot study design. No interim analyses, harm assessments, or audits will be conducted.

Ethical Considerations

Ethics Approval and Consent

This study received centralized ethics approval from the Ethics Review Board of Fukushima Medical University (REC2023-097). Any protocol amendments, including changes in investigators or participating institutions, will be made as required. Eligible participants will receive an approved explanation sheet from collaborating investigators and provide written informed consent before enrollment. Participants will receive compensation in the form of Amazon e-gift cards corresponding to their logging activities, as detailed in the intervention section.

Confidentiality

App-entered data are securely transmitted and stored on a protected server. Paper-based data are mailed to the research office and digitized using double data entry to maintain confidentiality and data accuracy.

Access to Data

The principal investigator (NK) will have access to the final dataset. A deidentified and blinded version will be shared with the biostatistician (HN) for analysis of the pilot trial.

Dissemination Policy

Study results will be disseminated through peer-reviewed publications. Ongoing progress and updates will be reported regularly on the trial registry (UMIN000052113).

Results

This study received funding in April 2019, April 2022, and April 2024. App development was completed in March 2022. The first ethics approval was obtained in September 2023. Participant recruitment began in October 2024. As of May 2025, a total of 17 participants have been enrolled. Data collection is scheduled for completion by March 2027, after which data analysis will be conducted. The study findings will be submitted to peer-reviewed journals and reported on the UMIN trial registry in summer 2027.

Discussion

Overview and Significance of the Study

This study evaluates the feasibility and preliminary effectiveness of real-time, app-based feedback for managing eating behaviors and self-regulation following glucocorticoid therapy. Conducted through a multicenter collaboration across 15 rheumatology centers, this study uses a hybrid design that combines a pilot RCT with an embedded observational SWAT.

The RCT aims to assess the effect of feedback delivered via the Mogu!☆Log smartphone app on meal frequency and perceived appetite control. In parallel, the SWAT uses EMA through the same app to explore the interrelationships among glucocorticoid-induced changes in appetite, mood, physical activity, and sleep.

Advantages and Challenges of Real-Time Graphical Feedback

Advances in mobile health technologies have heightened interest in app-based self-monitoring and feedback interventions. For patients starting glucocorticoid therapy, monitoring appetite and eating behaviors may help mitigate glucocorticoid-induced hyperphagia. However, the burden of frequent data entry may reduce adherence, and interventions lacking validation should be applied with caution. A previous study in the general

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population reported that dietary logging apps reduced meal frequency and prolonged intervals between meals [17]; however, its single-arm, pretest-posttest design limited causal inference. To address this limitation, this study compares immediate and delayed (2-week) graphical feedback, allowing for direct evaluation of the specific impact of real-time feedback on eating behavior. Furthermore, examining changes in eating behavior between days 14 and 21 in the delayed feedback group—after feedback is introduced—may further clarify the behavioral impact of this intervention.

Addressing Appetite Increase and Weight Gain in Glucocorticoid Therapy

Increased appetite and weight gain are among the most common and distressing adverse effects of glucocorticoid therapy in patients with SLE [2-4]. These side effects, specifically appearance-related concerns, negatively impact medication adherence [3,29]. Despite their clinical importance, discrepancies often exist between physicians and patients in how they perceive the significance of glucocorticoid-related adverse effects [30], underscoring the need for patient-centered interventions. This study specifically targets glucocorticoid-induced appetite increase and weight gain—symptoms frequently reported by patients as particularly burdensome. While a previous study in the general population links emotional distress and loss of appetite control to overeating [31], such findings may not be generalizable to individuals undergoing glucocorticoid therapy. This study aims to clarify how neuropsychiatric effects of glucocorticoids influence eating behavior and to inform the development of future smartphone-based interventions that address medication-related side effects.

In medical contexts, the neuropsychiatric effects of glucocorticoid therapy observed during its early stages typically involve mood alterations (eg, depression and irritability) and cognitive changes (eg, difficulty with concentration and memory) [8]. The mood dimension examined in this study primarily reflects valence—including displeasure—within the framework of Russell's circumplex model of affect, which describes affect along the dimensions of valence and arousal [32]. Focusing on valence is reasonable because a study in a nonclinical population demonstrated that transient increases in endogenous glucocorticoid levels were associated with negative affect (low valence), whereas no association with arousal was observed [33].

Importance of an Interdisciplinary Collaborative Framework

This study integrates high-frequency, real-time EMA via a smartphone platform within an interdisciplinary research framework. Experts in rheumatology, EMA, eating behavior, and psychiatry collaborated to ensure appropriate sampling schedules and select validated measurement instruments aligned with the study objectives. Capturing dynamic behavioral changes during glucocorticoid therapy necessitates a research design that balances methodological rigor with participant burden. This interdisciplinary approach strengthens both the scientific quality and clinical relevance of the study, thereby increasing its potential for real-world application.

Limitations and Future Directions

This study has some limitations. First, the small sample size inherent to a pilot study design limits both statistical power and generalizability. Larger-scale trials will be needed to validate these preliminary findings. Second, the requirement to use the LINE app may introduce selection bias by excluding individuals without compatible smartphones or familiarity with the app. However, given that smartphone ownership among Japanese adults in the typical age range for SLE onset (aged 20 to 40 years) is 97% to 100% and LINE use is 84% to 92% [34], this bias is likely minimal. Third, although several app-based measures, such as those for mood and appetite control, were developed with interdisciplinary input to ensure content validity in the context of glucocorticoid therapy, their psychometric properties remain to be further evaluated. Additional validation studies will be necessary to establish their reliability and broader applicability.

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Data Availability

Data sharing is not applicable to this paper as no datasets were generated or analyzed during this study.

Authors' Contributions

Conceptualization: NK (lead), NY (equal), HK (supporting), RS (supporting), HS (supporting)
Data curation: NK (lead), NY (equal), RS (supporting), TY (supporting), NT (supporting), RI (supporting)
Formal analysis: HN (lead), HK (supporting)
Funding acquisition: NK (lead)
Investigation: SF (equal), RW (equal), KO (equal), KK (equal), NS (equal), AO (equal), T Ichikawa (equal), TS (equal), YH (equal), HM (equal), TM (equal), YM (equal), HT (equal), AH (equal)
Methodology: NK (lead), NY (equal), RS (equal), HK (supporting), HS (supporting)
Project administration: NK (lead), NY (equal), TY (supporting), NT (supporting), RI (supporting), RO (supporting), T Isozaki (supporting)
Resources: NK (lead), NY (supporting)
Supervision: NY (lead), HK (supporting), RS (supporting), HS (supporting)
Writing—original draft: TY (lead), NT (equal), RI (equal)
Writing—review and editing: NK (lead), HN (supporting), NY (supporting)

Conflicts of Interest

RS is employed by CureApp, Inc, which develops and sells digital therapeutic apps. He received institutional grants from the Osake-no-Kagaku Foundation and Mental Health Okamoto Memorial Foundation. He holds multiple pending patents (JP2022049590A, US20220084673A1, JP2022178215A, JP2022070086, and JP2023074128A). All these relationships are outside the submitted work. HM received speaker fees from AbbVie, Asahi Kasei, AstraZeneca, Boehringer Ingelheim, Bristol-Myers Squibb, Chugai Pharmaceutical, Eisai, Eli Lilly, GlaxoSmithKline K.K., Sanofi, and Mitsubishi Tanabe Pharma. The Department of Advanced Medicine for Rheumatic Diseases, to which AO belongs, is supported by Nagahama City (Shiga, Japan), Toyooka City (Hyogo, Japan), and 2 pharmaceutical companies (Ayumi Pharmaceutical Co and Asahi Kasei Pharma Corp). These pharmaceutical companies have no role in the study design, data collection, analysis, manuscript preparation, or submission. AO received research grants and speaker fees from Pfizer Inc, Bristol-Myers Squibb, Asahi Kasei Pharma Corp, Chugai Pharmaceutical Co Ltd, Eli Lilly Japan K.K., UCB Japan Co, Mitsubishi Tanabe Pharma Co, Eisai Co Ltd, AbbVie Inc, Taisho Pharmaceutical Co, and Daiichi Sankyo Co Ltd. TM received a research grant from Chugai Pharmaceutical and Asahi Kasei Pharma and speaker fees from Eli Lilly. RW received a research grant from AbbVie and speaker fees from AbbVie, Asahi Kasei, Chugai Pharmaceutical, Eli Lilly, Glaxo SmithKline, and Taisho Pharmaceuticals. All other authors declare no other conflicts of interest.

Multimedia Appendix 1
English translation of the Japanese text displayed in the app.
[PNG File, 95 KB - resprot_v14i1e78612_app1.png]

Multimedia Appendix 2
Prompt used for improving the clarity and grammatical accuracy of the English text.
[DOCX File, 19 KB - resprot_v14i1e78612_app2.docx]

Checklist 1
SPIRIT 2025 checklist of items to address in a randomized trial protocol.
[DOCX File, 35 KB - resprot_v14i1e78612_app3.docx]

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Abbreviations

EMA: ecological momentary assessment
RCT: randomized controlled trial
SLE: systemic lupus erythematosus
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SWAT: study within a trial
VAS: visual analog scale

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Virtual Wound Care in Australian Nursing Homes: Protocol for a Pilot and Feasibility Study

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Abstract

Background: Chronic wounds, those which have not healed in a timely manner, are a significant health and economic burden. Older people, especially those living in nursing homes, are disproportionately affected by chronic wounds, and effective management and prevention is a persistent challenge. Specialized wound care can improve outcomes; however, access is limited by aged care workforce shortages, fragmented care, and lack of local services, especially in rural and nursing home settings. Virtual wound care interventions such as WoundView (Coviu Global Pty Ltd), a novel computer vision–based artificial intelligence wound analysis app embedded in Coviu's existing telehealth platform, offer a potential solution to enhance engagement with specialized wound care services.

Objective: This protocol aims to outline a pilot and feasibility study for WoundView to assess the acceptability and feasibility of the intervention in preparation for a planned implementation study. The pilot and feasibility study will estimate recruitment and retention rates along with protocol adherence and adaptations. Qualitative exploration of the acceptability of recruitment processes, training and education, participant assessments, intervention delivery, and secondary outcome measures will inform the development of an implementation study of WoundView.

Methods: The WoundView pilot and feasibility study is a prospective, nonrandomized study in 2 nursing homes in New South Wales, Australia. The research population will comprise up to 10 nursing home residents, 10 to 30 nursing home staff, and 10 wound care clinicians. All resident participants will receive the intervention, WoundView, as routine clinical care throughout the study period. Virtual care will be conducted with a specialized wound care clinic using WoundView's wound analysis and telehealth features to guide the clinical management of chronic wounds. Wound measures, health-related quality of life, virtual care activity, hospitalization rates, health resource use case studies, and participant satisfaction will be assessed. Nursing home staff and wound care clinicians' satisfaction with WoundView will be collected through brief surveys and in-depth interviews.

Results: The WoundView pilot and feasibility study was approved by the university's ethics committee and registered on the Australian New Zealand Clinical Trial Registry. Recruitment and enrollment for the study began in May 2025. Results are expected in the second half of 2025.

Conclusions: The design and implementation of virtual care interventions in nursing homes is an underinvestigated issue. Outcomes from this study will contribute to the design of an implementation study testing WoundView in a range of nursing homes around Australia. The integration of WoundView is expected to transform the use of virtual care for wound management and lead to earlier intervention and increased access to specialist wound advice services for nursing home residents.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12625000565448; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=389173

International Registered Report Identifier (IRRID): DERR1-10.2196/79652

(JMIR Res Protoc 2025;14:e79652) doi:10.2196/79652

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KEYWORDS

chronic wound; pilot and feasibility study; nursing homes; homes for the aged; telehealth; virtual care

Introduction

Background

Chronic wounds present a major public health challenge with significant health and economic costs [1]. Chronic wounds are those that have not progressed through the normal stages of healing in a timely and organized process [2] and substantially reduce the quality of life of those affected [3]. The most common types are pressure injuries and chronic lower leg wounds, including diabetic, venous, and arterial ulcers [4]. The global burden of skin and subcutaneous diseases has risen rapidly over the last 15 years, but the lack of international prevalence data for chronic wounds limits the ability to estimate true impact [5]. Based on available figures, an estimated 2.5% of Americans are affected by chronic wounds, the majority of whom are older adults [6]. In Australia, the prevalence of chronic wounds is estimated at 1.9% [7] and accounts for Aus $6.6 billion (US $4.29 billion) per year in costs to health and aged care budgets [8]. Between 2013 and 2017, more than two-thirds of people with chronic wounds who were admitted multiple times to public hospitals in the Australian state of New South Wales (NSW) were aged 65 years or older [9].

Older people, with increasing frailty, impaired skin integrity, and comorbidities such as diabetes, obesity, and peripheral vascular disease, are disproportionately affected by chronic wounds [10,11]. Chronic wounds are particularly common among residents of nursing homes, with an estimated prevalence of pressure injuries of up to 26% [12]. Despite being common, less than 1 in 5 of those with pressure injuries had a wound management record documenting every current injury in a 2018 NSW study of 67 nursing homes [12]. Inadequate wound prevention and treatment was also emphasized by the 2021 Australian Royal Commission into Aged Care Quality and Safety as causing pain, distress, and premature death [13]. Aged care staff giving evidence at the commission reported inadequate knowledge and training in managing pressure injuries effectively [13]. Despite the commission's recommendation that wound care training and education be improved, inadequate wound care continues to be one of the most common clinical complaints made to the Australian Aged Care Quality and Safety Commission [14].

Evidence-based wound care can improve clinical outcomes of chronic wounds [15]; however, provision of such care in nursing homes can be challenging. Wound care is a specialized field, and in aged care, there is higher variance in wound management and less specialist wound oversight than in other settings [10]. Chronic workforce shortages, high staff turnover, variable wound care expertise among staff, and fragmented and untimely access to expert wound care also limit the provision of consistent and high-quality wound care [13]. Along with evidence-based care, access to clinicians with expertise in wound management can ensure high-quality care and improve resident outcomes; however, in Australia, specialized wound care clinics are generally confined to major centers, which limits in-person attendance by rural and immobile nursing home residents [16]. This geographic centralization of wound care services creates significant barriers to timely assessment and treatment, contributing to delayed wound healing and avoidable complications [17].

Virtual care, health care delivered remotely using information and communication technology services [18], can address access barriers to ensure personalized and timely health care [19] for those unable to attend in-person wound clinics, such as nursing home residents. While the terms virtual care and telehealth are frequently used interchangeably, virtual care is a broader term encompassing telehealth (video or telephone consultations), remote patient monitoring, store-and-forward communications, and website and mobile apps [20]. Virtual care has demonstrated safety and effectiveness in wound healing and can overcome access gaps in chronic wound care [21,22]. Virtual wound care trials have also shown reductions in wound healing times and wound-related hospitalizations [23]; however, there have been few studies undertaken in nursing homes [24]. Furthermore, while current virtual wound care interventions offer wound analysis and measurement capabilities, they lack seamless integration with video telehealth platforms, restricting their effectiveness in remote care.

The number of Australians living in permanent aged care is growing, with 178,000 people aged 65 years or older residing in aged care in 2022, a 3.1% increase since 2017 [25]. Australia has among the highest proportions of older people living in permanent aged care when compared with other similar countries, including the Netherlands, Japan, and Canada [26]. Despite increasing numbers of nursing home residents, there has been a 5.2% drop in aged care providers, attributed to regulatory and financial pressures [27]. To meet the industry's growing demands and address the imminent implementation of the strengthened Aged Care Quality Standards [28], virtual care innovation, such as artificial intelligence (AI) to assist with wound analysis and remote consultation, is needed to transform the aged care sector, meet the needs of consumers, and improve care outcomes [27]. One such virtual care solution is WoundView, a new AI wound analysis application embedded in an existing telehealth platform, Coviu, which aims to address access barriers to evidence-based and specialized wound care.

WoundView Application

A 5-year, multipartner research project funded by the Australian Government's Medical Research Future Fund has developed the WoundView application (here referred to as WoundView) to improve access to specialized wound care in nursing homes and other remote settings. WoundView uses a computer vision–based AI algorithm that has been developed and validated using more than a thousand wound images. WoundView produces wound bed segmentation and measurements (ie, length, width, and total area), which can be monitored and compared over time. WoundView (Figure 1) is embedded in the existing telehealth platform, Coviu, allowing for real-time video telehealth between nursing home residents and staff and external

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wound clinicians. The Coviu platform enables the video call component of the Australian Government–funded Healthdirect Australia, the national virtual public health information service, enabling telehealth use in Australian nursing homes at no cost.

Figure 1. Visualization of WoundView use (reproduced from Coviu Global Pty Ltd [29] and Unsplash [30]). AI: artificial intelligence.

WoundView uses consumer-grade, hand-held devices, including mobile phones, laptops, and tablet devices to assess chronic wounds. The Coviu platform delivers secure, web-based video telehealth. It does not require the download of an app, and all transmitted call data, including images and documents, are transmitted peer-to-peer (ie, between call participants) and protected with end-to-end encryption [31]. This protocol describes a pilot and feasibility study to assess the acceptability and feasibility of WoundView for residents and staff working in nursing homes and external wound care clinicians in NSW, Australia.

Objectives

The primary objective of the pilot study is to assess the feasibility and acceptability of the proposed approach in preparation for an implementation study on WoundView. Study recruitment and retention and protocol adherence and adaptations will be used to evaluate the primary objective. The secondary objectives are to assess the acceptability of data collection tools for possible inclusion in the implementation study and evaluate collected wound images to verify and update the WoundView AI wound analysis algorithms for future use in nursing homes.

Methods

Study Design

The WoundView pilot and feasibility study is a prospective, nonrandomized trial in which all residents with a chronic wound will be eligible to receive the intervention, WoundView. Use of WoundView will be facilitated by staff working at pilot site nursing homes, and wound care will be provided by the Wound Care Command Centre (WCCC) or usual wound care providers. Nursing home staff, WCCC clinicians, and usual wound care providers who use the intervention will also be invited to participate in the study.

The study will determine the acceptability of WoundView and assess the feasibility of selected outcome measures in preparation for an implementation study. The pilot and feasibility study will be reported using the CONSORT (Consolidated Standards of Reporting Trials) extension to pilot and feasibility trials Checklist 1 [32], SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) statement Checklist 2 and additional guidance on reporting of nonrandomized pilot and feasibility studies by Lancaster and Thabane [33]. A mixed methods approach will be used to assess acceptability and feasibility.

The study will involve 2 phases (Figure 2). During Phase 1, staff working in the pilot site nursing homes will be upskilled in general telehealth and trained to use WoundView. Phase 2 will pilot WoundView and assess the feasibility of the trial design for the planned implementation study.

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Figure 2. Proposed research plan in 2 phases.

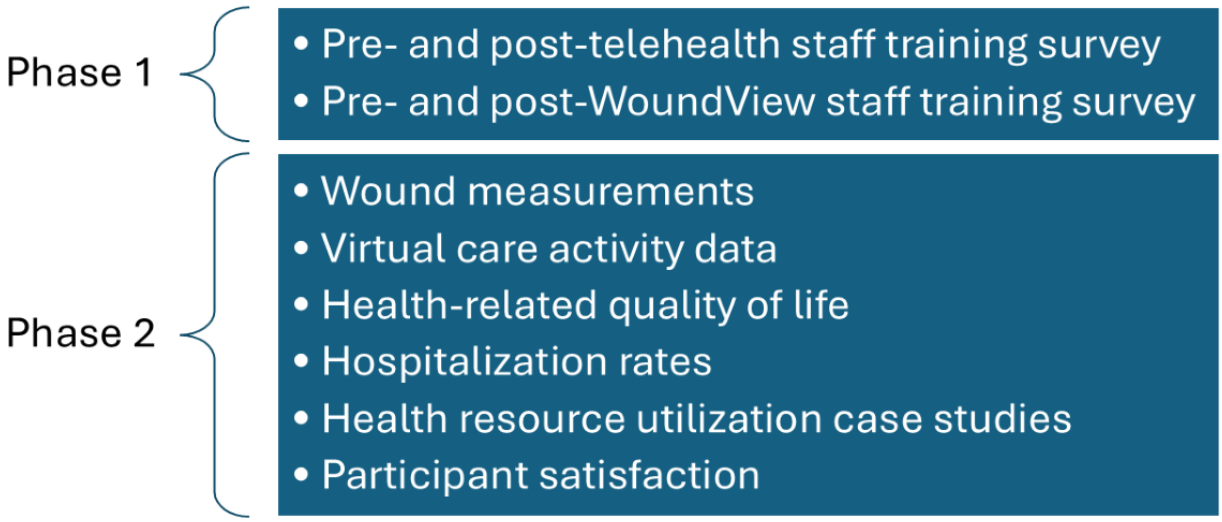

Setting

The study will be conducted in 2 private, not-for-profit nursing homes in NSW, Australia. One site is an 80-bed facility in outer regional NSW, as defined by Australian Statistical Geographical Standard Edition 3 [34]. The second site is a 140-bed facility in Sydney, NSW, a major city [34]. The pilot study nursing home sites will be supported by either the WCCC, a team of specialized nurses at the Royal Prince Alfred Virtual Hospital based in Sydney, Australia, or their usual wound care provider.

Participants

The study will recruit three participant groups: (1) nursing home residents living with chronic wounds, (2) nursing home clinical staff involved in wound care (eg, registered nurses, enrolled nurses, and wound care coordinators), and (3) WCCC clinicians and usual wound care providers, (eg, wound care nurses and general practitioners) who are providing specialized wound care using WoundView.

Residents

All residents living in the nursing home pilot sites who have or develop a chronic wound during the study period, regardless of wound type, will be eligible to participate. It is estimated that the number of participants across both sites will be 6 to 10 residents based on wound burden, number of eligible residents, and the relatively brief intervention period of 4 months.

Recruitment will be undertaken using purposive sampling, where participants who meet the eligibility criteria will be consecutively enrolled into the study. Once enrolled, WoundView will be used to collect and analyze wound images and connect residents to specialized wound management. Resident eligibility criteria are described in Textbox 1 and the participant flow is outlined in Figure 3.

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Textbox 1. Nursing home resident eligibility criteria.

Inclusion criteria

- Adults aged 18 years or older
- Willing and able to give informed consent for participation in the study
- Have a chronic wound at the start or develop a chronic wound during the study period. A chronic wound is defined as a wound that has been present for 3 or more weeks OR is likely to take 3 or more weeks to heal [35] as determined by nursing home staff and managers with clinical experience in wound care
- Wound must be considered suitable for active treatment as per the advice of the nursing home staff

Exclusion criteria

- Cognitive impairment that affects the ability to provide informed consent as determined by the nursing home staff or managers and research team at the point of enrolment
- Sensory, physical, or other health impairment that would preclude data collection participation, as determined by the nursing home staff or managers and research team at the point of enrollment. Other health impairment includes residents who are reliant on medications, for example, participants receiving medication to support end-of-life care or participants with severe mental health conditions where the condition is not adequately controlled by medication at the time of recruitment.
- Have superficial, rapidly healing wounds such as abrasions, blisters, or lacerations.
- Chronic wound located on the genital area
- Not fluent in spoken or written English

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Figure 3. Participant flow diagram.

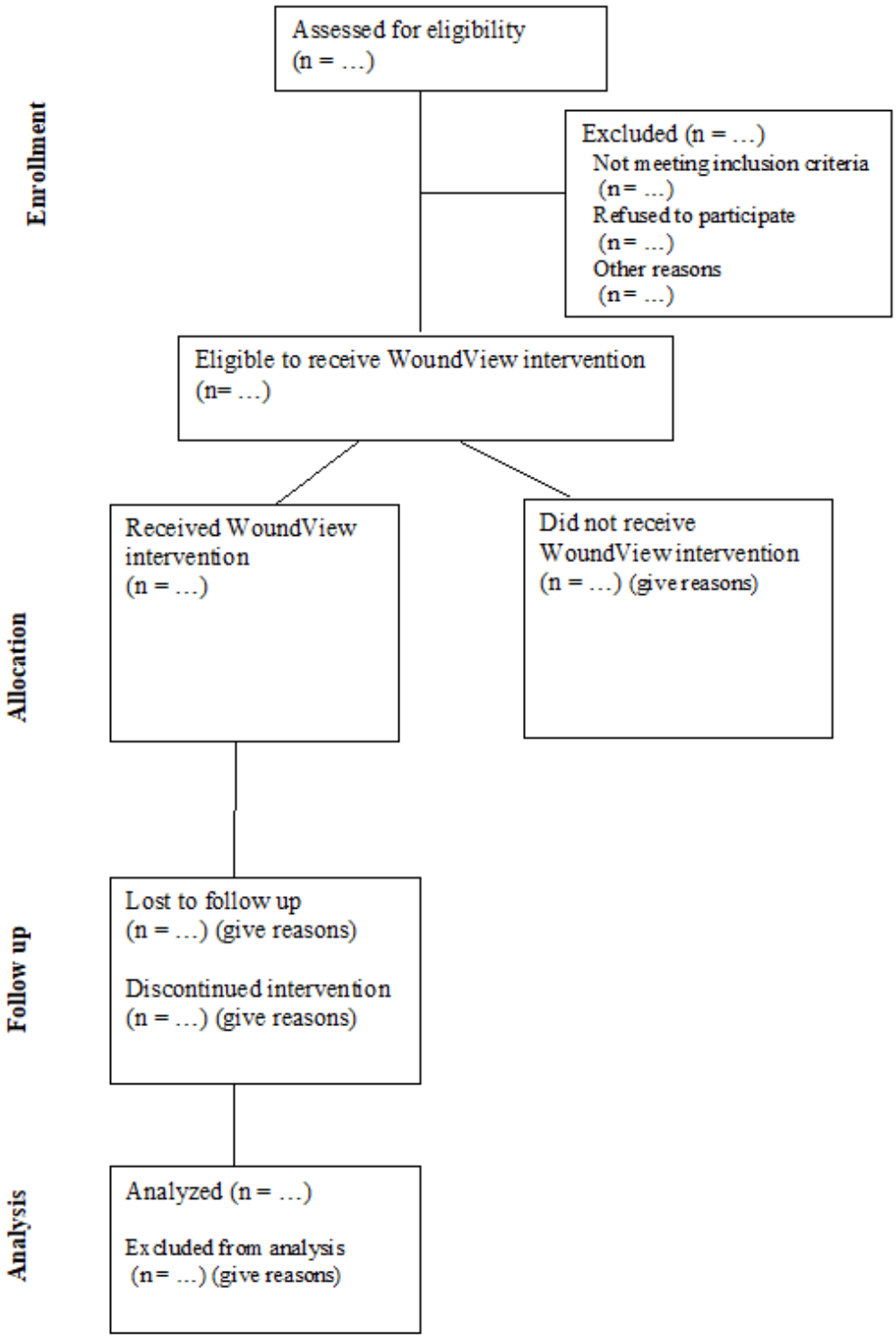

Nursing home staff and managers will be asked to identify residents who meet the study eligibility criteria (Textbox 1). Following the identification of potential participants, the research team will approach the resident to explain the study's nature, purpose, and procedures along with expected duration and potential risks and benefits. Potential participants will be provided with a research information sheet and consent form. Residents will be invited to discuss their potential participation with support people such as next of kin, family, friends, or their enduring guardian. Following a 3-day cooling-off period, the research team will contact the resident to ascertain their preference to be involved in the study. To avoid perceived or actual coercion, recruitment and consent will be undertaken by the research team, who are independent of the nursing home.

Nursing home residents who verbally consent to participate will be invited to provide written consent at the beginning of the study. Throughout the study, WoundView will be used as routine clinical care, and further consent will not be sought for each

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episode of use of WoundView in wound management. At the conclusion of the study, residents will be invited to reconfirm their consent verbally, prior to the final data collection.

Resident participants may withdraw from the research study at any time on request, with assurance that their withdrawal will not affect their relationship with their nursing home or the university. To avoid perceived or actual coercion, written consent of nursing home residents will be undertaken by the research team, who are independent of the nursing home. Participants will not receive any payment or reimbursement for their participation.

Nursing Home and WCCC Clinicians

All clinical staff working at the participating nursing homes, WCCC clinicians, and usual wound care providers are eligible to participate if they are aged 18 years or older and can undertake data collection in English.

During Phase 1, telehealth and WoundView education and training will be conducted with nursing home staff nominated by their organization to participate. Nursing home staff will be provided with access to a curated package of self-directed online telehealth videos [36], which will take approximately 20 to 30 minutes to complete. Following telehealth training, face-to-face WoundView training will be conducted by the research team, lasting 30 to 45 minutes. Training will include how to set up and conduct a WoundView call and optimal wound image capture, such as the use of direct camera angle and adequate lighting to minimize shadow. Nursing home sites will also receive a recording of the training session, quick reference documents, and a site-specific flowchart to integrate WoundView into usual care. A brief training session, including a practice call, will be undertaken with the WCCC staff prior to commencement of the study.

Nursing home staff who participate in training will be invited to undertake a brief, anonymous online evaluation prior to and after the training sessions. The trainer will describe the survey, display a QR code for the survey, and leave the room to allow participants to decide whether to complete the survey. The number of nursing home staff participants is expected to be 10 to 30.

In Phase 2, nursing home staff, WCCC clinicians, and usual wound care providers will be invited to participate in a brief online survey and an in-depth, semistructured interview with a member of the research team lasting approximately 20 to 30 minutes. Nursing home management will be asked to assist by making staff aware of the study through email correspondence or posting advertisements in appropriate locations, such as staffrooms. WCCC clinicians and usual wound care providers will be invited to participate through email correspondence. The survey will be accessible online along with the Participant Information Statement and consent form. Those interested in being interviewed will be able to self-identify at the end of the survey or initiate contact with the research team to arrange an interview. The number of survey participants is expected to be 5 to 10, and interview participants are estimated to be 5.

Participants will not receive any payment or reimbursement for their participation. Participants may withdraw from the research study at any time with assurance that their withdrawal will not affect their relationship with their employer or the university. To avoid perceived or actual coercion, written consent of nursing home staff, WCCC clinicians, and usual wound care providers will be undertaken by the research team, who are independent of the nursing home.

Intervention

The intervention, WoundView, is a novel computer vision–based AI wound analysis application integrated into the Coviu telehealth platform. WoundView is a software component that extends the functionality of the Coviu platform, without requiring changes to its core code. WoundView will link residents with chronic wounds and their clinical care team to specialized wound care clinicians at the WCCC in Sydney, Australia, or their usual wound care providers, who will deliver expert wound care based on clinical data gathered during video telehealth, AI wound analysis, including wound measurements and segmentation, and resident and family preferences.

WoundView requires an initial referral from the participating nursing home to the WCCC or usual care provider for an eligible resident. An appointment is scheduled using the Coviu platform, and the resident, nursing home staff, and wound care clinician attend at the scheduled time. At each use of WoundView, wound image and video data will be gathered by nursing home staff who will take a series of wound photographs prior to or during the WoundView call and submit these for AI wound analysis. The inclusion of an ArUco marker (a marker of known size) in each wound image enables AI wound size analysis using the WoundView AI algorithm. The AI wound analysis provides wound measures such as length, width, and area, along with wound segmentation. Live video stream of the wound will also be available during the call, providing treating clinicians with detailed, close-up vision of the wound, an innovative feature of WoundView. The wound care clinician provides clinical advice about wound management, including cleaning, debridement, dressings, and frequency of dressing change. Further wound review is arranged as advised by the wound care clinician.

Outcomes

The primary outcome will be a narrative description of study feasibility, including participant recruitment and retention, protocol adherence and adaptations, and stakeholder acceptability (Table 1). A traffic light system will guide progression to an implementation study [37], red (stop, main study not feasible), amber (feasible with modifications or close monitoring), and green (continue without modifications) [38]. A recruitment rate of greater than 50% (defined as the percentage of eligible residents recruited) and retention of greater than 75% (proportion of participants who remain in the pilot for its duration) will be considered acceptable to proceed with the implementation study without modification. Protocol adherence, the degree to which the WoundView intervention and research protocol were implemented as intended, greater than 75% will be considered acceptable. Additionally, regular stakeholder input and agreement on the interpretation of pilot findings will be sought [37]. Acceptability will be assessed by measuring participants' satisfaction with study assessment instruments, and the use, delivery, barriers, and enablers to the

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intervention, WoundView. Data collection instruments are described in the section below. Secondary outcomes, including wound measurements, virtual care activity, health-related quality of life (HRQoL), hospitalization rates, health resource use case studies, and patient and staff satisfaction, will be assessed for feasibility of inclusion in a planned implementation study.

Table . Overview of outcomes and methods.

Outcome levels	Methods and approaches
Primary	
Feasibility	
• Recruitment	• Percentage of eligible residents recruited
• Retention	• Proportion of participants who remain in the pilot for its duration
• Adherence	• Degree to which the WoundView intervention and research protocol were implemented as intended (eg, staff training logs and surveys), WoundView use and activity, resident, staff, and clinician-reported WoundView use
• Satisfaction	• Pre- and posttraining staff surveys • Staff satisfaction survey • Short assessment of patient satisfaction • In-depth semistructured interviews (residents, nursing home staff, and wound care clinicians) exploring WoundView acceptability
Secondary	
• User confidence and skills	• Pre- and posttraining staff surveys
• Time to 35% reduction in wound area • Time to complete healing • Percentage area reduction • Gross area reduction	• Wound measurements (eg, width, length, and area)
• WoundView use	• Virtual care activity (eg, call participants, guest, or host), length of call (call, time and date), and AI wound measurements (eg, length, width, and calculated wound area)
• Quality of life	• Wound-QoL-14[a] • EQ-5D-5L[b]
• Care costs	• Hospitalization rates • Emergency department attendance rates • Health resource use case studies
• Adverse events	• Wound recurrence • Adverse events (eg, death, amputation, infection, hospitalization, ED[c] attendance, and allergic reactions).

[a]Wound-QoL-14: Wound Quality of Life-14.

[b]EQ-5D-5L: EuroQoL-5 Dimensions-5 Levels.

[c]ED: emergency department.

Data Collection and Analysis

Phase 1: Pre- and Posttraining Evaluation

Nursing home staff participating in telehealth and WoundView education and training will be invited to rate their pre- and posttraining confidence and skills, along with their satisfaction with the training in a brief, anonymous online survey.

Phase 2: Pilot and Feasibility Study

Phase 2 of the pilot and feasibility study will comprise several components with data collection timepoints at baseline, during the intervention, and at the end of the study. Study outcomes, methods, and data analysis are outlined below.

Feasibility

Recruitment, defined as the percentage of eligible residents recruited, retention, the proportion of participants who remain in the pilot for its duration, and protocol adherence, the degree to which the WoundView intervention and research protocol were implemented as intended, will be assessed. Acceptability will be assessed by measuring participants' satisfaction with study assessment instruments, and the use, delivery, barriers,

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and enablers to the intervention using staff training and satisfaction surveys, patient satisfaction survey, and in-depth semistructured interviews with residents, nursing home staff, and wound care clinicians.

Wound Measurements

At baseline, the research team will record a measurement of the widest dimension of the wound or wounds (length) and the second widest dimension perpendicular to the first widest dimension (width) using a single-use paper tape measure. The wound type, duration, and location will be recorded on the data collection form. For each wound, a series of still photos will be captured using WoundView. The wound images will be assessed using WoundView's AI analysis to determine wound width, length, and total wound area and compared to the manual wound measurements.

At subsequent WoundView use, AI wound data will be used to calculate time to 35% reduction in wound area and time to complete healing, defined as full re-epithelialization or closure [39]. Percentage area reduction and gross area reduction will be calculated from raw data at various intervals (eg, 1 week). If a resident participant withdraws from the pilot, their most recent wound measurements will be analyzed as the final data point.

Virtual Care Activity Data

During the study period, data on all episodes of WoundView use will be extracted from the Coviu platform. Virtual care activity data generated will include call participants (eg, guest or host), length of call, call time and date, and AI wound measurements (length, width, and calculated wound area).

HRQoL

HRQoL will be collected using wound-specific (Wound Quality of Life-14 [Wound-QoL-14]) and general (EuroQoL-5 Dimensions-5 Levels [EQ-5D-5L]) questionnaires at baseline and at the conclusion of the pilot study.

Wound-QoL-14

Wound-QoL-14, a shortened version of the Wound-QoL-17, is a disease-specific, HRQoL measure for patients with chronic wounds [40]. The Wound-QoL-14 asks respondents to rate impairment over the last 7 days in the subscales body (pain, odor, discharge, and sleep), psyche (unhappy, frustrated, worried, and fear of worsening), and everyday life (moving about, everyday activities, leisure activities, activities with others, and depending on help) [41]. A global Wound-QoL-14 score can be calculated if at least 75% of the 14 items have been answered [42]. Wound-QoL-14 has demonstrated high internal consistency (Cronbach α= 0.779 - 0.925), moderate to good test-retest reliability (intraclass correlation coefficient: 0.618 - 0.808), and convergent validity showing highest correlations with global HRQoL rating (r=0.751) and Dermatology Life Quality Index (DLQI) rating (r=0.681) [43]. Wound-QoL-14 has been shown to be valid to assess HRQoL of patients with chronic wounds, acceptable for use in cross-cultural settings [41] and a practical option in time-poor settings [43].

EQ-5D-5L

EQ-5D-5L is a general HRQoL measure which consists of the EQ-5D descriptive system and the EQ visual analog scale [44]. The EQ-5D descriptive system comprises 5 dimensions (mobility, self-care, usual activities, pain and discomfort, and anxiety and depression), each measured at 5 levels (no problems, slight problems, moderate problems, severe problems, and extreme problems) describing the respondent's health state [45]. The EQ visual analog scale records the patient's self-rated health on a vertical visual analog scale where the endpoints are labeled 'the best health you can imagine' and 'the worst health you can imagine' and can be used as a quantitative measure of health outcome that reflects the patient's own judgment [45]. The EQ-5D-5L shows excellent psychometric properties across a range of populations, health conditions, and settings [46].

Hospitalization Rates

At the conclusion of the intervention period, an audit of the electronic medical records (EMRs) of participating residents will be undertaken to capture the frequency and details of transfers to emergency departments (EDs) and hospital admissions for wound-related care. The timeframe of interest will be 12 months prior to the chart audit. The EMR will be audited to capture relevant text entries and discharge summaries associated with wound-related ED visits and hospital admissions.

Health Resource Utilization Case Studies

Health resource utilization associated with the management of chronic wounds in nursing homes will be estimated through a series of wound care episode case studies. An EMR audit and observation of usual wound care will be undertaken with a sample of 3 to 4 consenting residents. The research team will observe the wound dressing change, document the labor and consumables required for wound management, and undertake a chart audit to estimate the number of wound management episodes during the study period. Where possible, more than 1 dressing change for the same resident will be observed, and the total labor and consumables will be averaged.

Adverse Events

An audit of participating residents' EMRs will be undertaken to capture rates of wound recurrence and adverse events (AEs; eg, death, amputation, infection, hospitalization, ED attendance, and allergic reactions) at the completion of the intervention period.

Participant Satisfaction

Nursing Home Residents

Nursing home resident satisfaction will be assessed using a validated instrument, the Short Assessment Patient Satisfaction (SAPS) and through in-depth semistructured interviews with the research team.

SAPS

The SAPS is a brief, validated questionnaire used to assess patient satisfaction across 7 domains, including treatment satisfaction, explanation of treatment results, clinician care, participation in medical decision-making, respect by clinician, time with clinician, and satisfaction with care [47]. The SAPS'

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internal psychometric properties exceed standard psychometric standards (Cronbach α=0.86), and it discriminates at least as well as other longer patient satisfaction measures [48]. SAPS will be administered at the conclusion of the pilot to measure participants' satisfaction with their experience of care in the study.

In-depth Semistructured Interviews

All participating nursing home residents will also be invited to take part in an in-depth, semistructured interview conducted by the research team. Interviews will be undertaken in person in a private room or via Microsoft Teams and last for approximately 20 to 30 minutes. The interviews will explore the acceptability of the recruitment processes, assessments, and intervention delivery. Virtual interviews will be digitally recorded in Microsoft Teams and transcribed using Microsoft Teams or Word. In-person interviews will be recorded using a hand-held digital recorder and transcribed in Microsoft Word by the first author. Participants will be provided with the choice to review a transcribed copy of the interview by checking the appropriate box on the consent form.

Inductive thematic analysis of interview data will be guided by the feasibility objectives of the pilot (Table 1). Qualitative data will be organized and thematically analyzed using NVIVO 15 software (Lumivero). Following familiarization with the data, line-by-line coding will be undertaken to identify initial codes [49]. The research team, consisting of 2 to 3 independent researchers, will undertake reflexive journaling during the coding process to consider the emerging themes [50]. To create a robust codebook, researchers will meet regularly to review candidate themes for distinction and coherence [51]. After a consensus is reached, the codebook will include definitions and examples of each code, and the coding process will continue until data saturation (ie, no new themes are observed) [52]. Thematic analysis will be conducted in accordance with the Reflexive Thematic Analysis Reporting Guidelines [53]. A sample of at least 5 interviews will be undertaken with each target group: nursing home residents, nursing home staff, and wound care clinicians.

Nursing Home and WCCC Clinicians

All nursing home staff, WCCC clinicians, and usual wound care providers who use WoundView during the study period at pilot sites will be invited to rate their satisfaction in a brief anonymous online survey adapted from Barakat-Johnson et al [54] All nursing home staff, WCCC clinicians, and usual wound care providers involved in the study will also be invited to participate in 20 to 30 minute, in-depth, semistructured interviews conducted by the research team. Interviews will be undertaken in person in a private room or via Microsoft Teams for the resident interviews and will explore recruitment, training and education, assessment tools, and the delivery of the intervention. See In-depth semistructured interviews for details on coding and analysis.

Statistical Analysis

ED visits and hospital admission data, including length of stay, reason for admission, diagnosis on discharge, and discharge location, will be recorded and analyzed using descriptive statistics. Descriptive statistics will also be used to illustrate the change in wound size across the intervention period as well as to summarize HRQoL, AEs, and satisfaction survey results. All analyses will be intention-to-treat. An estimate of costs will be derived from the total number of dressing changes and extrapolated as per Wilson et al [55]. The actual and projected treatment costs will be calculated and extrapolated to estimate the overall cost of wound care in the pilot nursing home sites. Estimated costs will be compared with other Australian estimates in nursing home settings [56].

Verification and Update of WoundView AI Wound Analysis Algorithm

Wound images collected during the WoundView pilot and feasibility study will be used as part of the verification and update of the WoundView AI wound analysis algorithm. To verify the quality of the AI wound analysis algorithm, a ground truth mask and an AI-predicted mask will be created and compared for each wound image. Masks are pictorial representations that isolate a specific part of an image, such as the wound bed from the background. To create the ground truth mask used to verify the performance of the AI wound analysis algorithm, wound images collected using WoundView during the pilot will be manually annotated by experienced wound care clinicians using the Computer Vision Annotation Tool (Intel Corporation), a free, open-source, web-based image and video annotation tool. Random checks of the annotation accuracy will be conducted by 3 wound care experts. To verify the performance of the AI model, ground truth annotations will be compared with the AI-predicted mask. Multimedia Appendix 1 outlines data descriptions, study devices, data handling, and storage processes, as well as data retention for the study. Explicit consent will be sought from participating residents for the use of captured wound images in the verification and update of the WoundView AI wound analysis algorithm.

Monitoring

Conduct of the pilot will be overseen by a data monitoring group consisting of members from the research team from the university and Coviu. The Chief Investigator is a member of the data monitoring group and will make the final decision on ceasing or proceeding with the trial. The group will meet regularly to discuss pilot data quality and completeness. The group will review source documents (eg, wound assessments, virtual health activity, health resource use case studies, and HRQoL measures) along with compliance with informed consent and eligibility criteria and monitoring of AEs and endpoints. Additionally, data storage and handling practices, particularly with respect to the transfer of wound images (Multimedia Appendix 1), will be regularly reviewed. If a problem is identified (eg, missing study documents), the team will work to resolve the issue. All parties involved will keep participants' data strictly confidential.

Ethical Considerations

The trial has been registered with the Australian and New Zealand Clinical Trials Registry on June 2, 2025 (ACTRN12625000565448). Ethical approval was received from the University of Sydney Human Research Ethics Committee

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(HREC; 2024/HE001356). Informed written consent will be obtained from all participants. Participants will not receive any payment or reimbursement for their participation. Participants may withdraw from the research study at any time with assurance that their withdrawal will not affect their relationship with the nursing home, employer, or the university. The pilot and feasibility study will collect personal information, which will be reidentifiable and securely stored in HIPAA (Health Insurance Portability and Accountability Act)–compliant REDCap (Research Electronic Data Capture; Vanderbilt University), a secure web application for managing online surveys and databases hosted by the University of Sydney in NSW, Australia. Only approved members of the research team will have access to personal information. All information will be subject to the University's HREC confidentiality policies. Figure 1 uses 2 images of people. These are generic images and are not of research participants. The image of the clinician using the laptop was obtained with permission from Coviu Global Pty Ltd (developer of WoundView) [29]. The image of the older woman and nurse using a mobile device was sourced from Unsplash [30], which grants "irrevocable, nonexclusive, worldwide copyright license to download, copy, modify, distribute, perform, and use images from Unsplash for free, including for commercial purposes, without permission from or attributing the photographer or Unsplash."

Protocol Amendments

Any required changes to the protocol will be submitted as amendments to the University of Sydney's HREC for approval before implementation. In an emergency, deviations from the protocol may be made to protect human subjects' rights, safety, or well-being without the HREC's prior approval. Such deviations will be promptly documented and reported to the HREC.

Dissemination

Results of the study will be included in reports to stakeholders, journal publications, and conference presentations as part of the dissemination of the broader study's outcomes. Findings will be provided in such a way that participants cannot be identified.

Results

Approval for the pilot and feasibility study was granted by the University of Sydney HREC in October 2024 (2024/HREC1356), and the study has been registered with the Australian and New Zealand Clinical Trials Registry. Preliminary work with the 2 pilot nursing homes commenced in January 2025, and telehealth and WoundView training began in March 2025. The first study participants were recruited in May 2025. A timeline of proposed research activities is outlined in Figure 4. Results from the study will be analyzed and presented in tabular, graphical, and narrative formats.

Figure 4. WoundView pilot and feasibility study timeline.

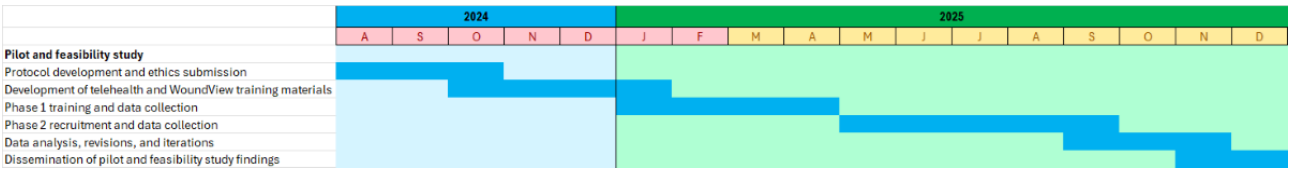

Discussion

Anticipated Findings

Chronic wounds are common among nursing home residents, detrimentally affecting their quality of life and contributing to increased risk of premature death. When compared with other populations, nursing home residents experience significant barriers accessing timely and high-quality wound care. While research in virtual wound care interventions is rapidly expanding, little is known about its use in nursing homes despite the high burden of disease and substantial impact on health outcomes.

The development of a novel computer vision–based AI wound analysis application embedded in an existing telehealth platform is warranted in offering clinicians and residents a "one-stop shop." It is expected that the findings of this study will provide sufficient methodological evidence regarding the design and planning of the intervention to warrant an implementation study. The methodological evidence will include an approach to participant recruitment, retention, and adherence to the intervention. Although this pilot and feasibility study is not powered to detect statistically significant effects, the findings will provide insights to optimize the design of a larger scale implementation study and strengthen the research approach. Results will also inform the implementation and evaluation of new virtual wound care interventions in nursing homes.

Conclusions

The pilot study will assess the acceptability and feasibility of a novel wound care telehealth intervention, WoundView, and will contribute to the design of an implementation study testing WoundView in a range of nursing homes in Australia. The integration of WoundView is expected to transform the use of telehealth for wound management and lead to earlier intervention and better access to specialist wound care services for nursing home residents.

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Acknowledgments

The authors would like to thank our colleagues at Commonwealth Scientific and Industrial Research Organisation's Data 61 for leading the development of the artificial intelligence technology. The research team wishes to thank consumer representative Diane McPhail, PhD, who is actively engaged in the study by reviewing participant information statements and consent forms.

Funding

This 5-year study is funded by the Australian government through the Medical Research Future Fund Rapid Applied Research Translation grant (RARUR000158), Department of Health 2022: Transforming Wound Care through Telehealth in Aged Care. The funder of the study had no role in the protocol design, writing of the paper, or decision to submit for publication.

Data Availability

All data generated or analyzed during this study will be included in a published article and its supplementary information files.

Authors' Contributions

Conceptualization: HR and GL (lead); AB, KS, MB-J, and MM (supporting)
Funding acquisition: GL, MB-J, AB, and MM
Methodology, investigation, and validation: HR and GL (lead); AB, KS, MB-J, and MM (supporting)
Project administration: KS
Software: AB
Supervision: GL, MB-J, and MM supervised HR
Writing – original draft and visualization: HR, GL, AB, MM, and MB-J
Writing – review and editing: HR, GL, AB, KS, MB-J, and MM

Conflicts of Interest

The study, Transforming Wound Care through Telehealth in Aged Care, has been undertaken in partnership with Coviu Global Pty Ltd, who may commercialize WoundView, a novel wound analysis tool embedded in the Coviu telehealth platform. AB is employed by Coviu Global Pty Ltd and has been involved in the development of WoundView.

Multimedia Appendix 1
WoundView pilot and feasibility study data flows and retention.
[DOCX File, 21 KB - resprot_v14i1e79652_app1.docx]

Checklist 1
CONSORT checklist.
[PDF File, 226 KB - resprot_v14i1e79652_app2.pdf]

Checklist 2
SPIRIT 2025 checklist.
[PDF File, 146 KB - resprot_v14i1e79652_app3.pdf]

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Abbreviations

AE: adverse event
AI: artificial intelligence
CONSORT: Consolidated Standards of Reporting Trials

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ED: emergency department
EMR: electronic medical record
EQ-5D-5L: EuroQoL-5 Dimensions-5 Levels
HREC: Human Research Ethics Committee
HRQoL: health-related quality of life
NSW: New South Wales
SAPS: Short Assessment of Patient Satisfaction
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
WCCC: Wound Care Command Centre
Wound-QoL-14: Wound Quality of Life-14

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A Digital Patient Decision Aid to Increase Sexually Transmitted Infection Testing in the Emergency Department: Protocol for a Pilot Randomized Controlled Trial of the STIckER (STI Check in the Emergency Room) Study

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Abstract

Background: Rising rates of sexually transmitted infections (STIs) among adolescents and young adults are concerning. Emergency department (ED) visits offer a unique opportunity to increase STI testing. However, providers in the ED may not have the time or self-efficacy to screen patients, and patients may be unable to initiate discussion on their STI care needs. A patient decision aid may improve the effectiveness and efficiency of the ED encounter for STI testing.

Objective: This study aims to pilot STI Check in the Emergency Room (STIckER) app, a shared decision-making aid for urinary, oral, and rectal gonorrhea and chlamydia testing among adolescents and young adults, and assess STIckER's efficacy and implementation outcomes in an adult and pediatric ED.

Methods: We are conducting a parallel-group, two-arm provider-randomized controlled pilot trial in the adult and pediatric EDs at an urban academic medical center. Fifty providers were randomized 1:1 to intervention (trained on STIckER) or control (standard of care). Adolescents and young adults aged 14 - 24 years, English-speaking, and sexually active within the past 6 months are recruited during eligible shifts and assigned to the study arm of their provider. The standard of care comparator consists of usual provider-initiated STI discussions and testing without access to the decision aid; control participants receive a QR code directing them to a simple landing page encouraging them to ask their provider about STI testing. The planned enrollment target was 44 providers and 140 adolescent and young adult participants. Primary outcome is preliminary efficacy, defined as the proportion of adolescents and young adults receiving gonorrhea and chlamydia testing based on electronic medical record (EMR) review. Secondary outcomes include extragenital testing uptake, STI positivity rates, decisional conflict, and perceived level of shared decision-making. Implementation outcomes include feasibility, acceptability, appropriateness (using acceptability of intervention measure, intervention appropriateness measure, and feasibility of intervention measure), and provider self-efficacy. Data will be analyzed using descriptive statistics and regression models, with mixed-effects models applied if clustering by provider is detected. Exploratory analyses will examine differences by patient age, gender, and sexual identity, and provider characteristics.

Results: Between September 2023 and July 2025, we completed recruitment of 44 providers and 139 adolescent and young adult participants across both adult and pediatric EDs. Enrollment targets were met, with high fidelity to intervention delivery and strong rates of survey completion by both patients and providers. Final data cleaning and analyses are underway, and primary results are expected to be available in late 2025.

Conclusions: This pilot trial will provide critical data on the feasibility, acceptability, and preliminary efficacy of a digital SDM tool to increase STI testing in the ED. Findings will inform the design of a future multisite trial and the potential for scaling STIckER to support equitable, patient-centered STI screening across diverse clinical settings.

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KEYWORDS

adolescent sexual health; emergency department STI testing; sexually transmitted infection; youth; mHealth; mobile apps; digital health; STI

Introduction

Sexually transmitted infections (STIs) pose a significant and growing public health challenge in the United States. In 2022, more than 2.5 million cases of syphilis, gonorrhea, and chlamydia were reported nationally [1]. Gonorrhea and chlamydia require comprehensive screening to detect infections across multiple anatomic sites. Studies have shown that failure to conduct complete screening, including extragenital screening of oropharyngeal and anorectal sites, can lead to underdiagnosis. In fact, research suggests that if only urogenital screening is performed, more than one-third of infections may be missed [2].

Despite this, comprehensive gonorrhea and chlamydia screening, including 3-site screening, remains underused. Less than 5% of emergency department (ED) patients presenting with symptoms suggestive of extragenital infection undergo appropriate screening [3,4]. In outpatient settings, extragenital STIs are also prevalent but often undetected, with studies reporting prevalence rates as high as 77% among females and 22% among heterosexual males [3]. These data underscore the critical need for improved screening strategies that support multisite screening, particularly in settings where vulnerable individuals are likely to present.

The ED represents a vital yet underused venue for STI screening. Each year, over 19 million adolescents and young adults seek care in EDs, many of whom rely on these settings as their primary source of health care [4,5]. However, data suggest that the prevalence of STIs among adolescents and young adults in EDs ranges from 1.8% to 25%, representing substantial unmet need. Despite the potential for EDs to serve as access points for STI care, providers face substantial challenges to routine screening implementation. Time constraints, competing clinical priorities, lack of confidence in sexual history-taking, and discomfort discussing sexual health with patients all limit the integration of STI screening into ED workflows [6-9]. These limitations are especially problematic when caring for adolescent and young adult patients, who may face additional barriers including stigma, concerns around confidentiality, lack of knowledge about STI risks, and discomfort disclosing sensitive information in a high-acuity setting [10].

Novel strategies are needed to increase HIV and syphilis screening in the ED setting. While universal STI genitourinary testing minimizes patient stigma and provider bias, targeted testing recognizes the limited ED resources [11-13]. Furthermore, despite recommendations for universal opt-out HIV testing, fewer than 1% of ED patients are routinely screened. Researchers are currently focusing on clinical decision support (CDS) tools incorporated into the EMR [14]. While CDS tools are promising, they rely on each EMR system, thus leaving a gap in the care provided and missed opportunities for testing.

Shared decision-making (SDM) has been recognized as a valuable strategy for promoting patient-centered care, including for sexual health. However, implementing SDM in the fast-paced ED setting is difficult due to limited visit time, competing priorities, and a lack of standardized tools. Digital decision aids can help address these challenges by delivering tailored health education, collecting patient preferences, and streamlining communication with providers.

While decision aids have shown benefit in improving patient engagement and satisfaction in other ED contexts, including for decisions around chest pain, pain management, and syncope, there is limited work applying this approach to STI care [15-19]. No existing digital tool has been developed to support comprehensive gonorrhea and chlamydia screening, including extragenital screening, in the ED setting using an SDM framework.

To address these gaps, we developed STIckER (STI Check in the Emergency Room), a mobile, web-based decision aid designed to promote SDM between providers and adolescent and young adult patients in the ED. STIckER aims to support 3-site gonorrhea and chlamydia screening through a patient-centered approach grounded in evidence and stakeholder input. The tool guides users through an educational module, a sexual health risk assessment, and tailored screening recommendations, culminating in a provider-facing display that facilitates brief but informed shared decision-making. By front-loading STI education and risk assessment, STIckER reduces the time providers must spend initiating sensitive discussions and provides a standardized way to present testing options. Simultaneously, the app empowers adolescents and young adults by normalizing STI screening, increasing awareness of extragenital testing, and encouraging them to articulate their preferences. These features are designed to foster confidence in requesting testing and to facilitate efficient, values-based shared decision-making during time-limited ED encounters. STIckER was developed through an iterative process involving input from 19 adolescent and young adult patients and 7 ED providers [20]. By targeting known barriers to STI screening and supporting both patients and providers, STIckER aims to improve the delivery of equitable and complete STI care in the ED environment.

Methods

Trial Design

This parallel group, 2-arm, provider-level randomized controlled trial (RCT) was designed as a pilot evaluation to assess the preliminary effectiveness and implementation process of the STIckER app in an adult and pediatric emergency department (ED). The study followed CONSORT-eHEALTH guidelines V1.6 for reporting electronic and mobile health (mHealth) interventions.

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Participants

Provider Eligibility Criteria

A subset of health care providers (HCPs) was invited to participate. Eligible HCPs were attending physicians, residents, or nurse practitioners serving in the adult and pediatric EDs at NewYork-Presbyterian/Columbia University Irving Medical Center (NYP/CUIMC), a larger urban academic medical center in the Northern Manhattan section of New York City.

Patient Eligibility Criteria

Eligible patients were those being seen by an enrolled HCP, between ages 14 and 24 years, sexually active within the past 6 months (per self-report), able to speak English, and assigned a triage level of 3, 4, or 5. These triage levels indicate that the patient was not critically ill. Medical records were reviewed to identify potential subjects. Exclusion criteria include severe illness, cognitive impairment, or inability to speak English.

Providers Recruitment

HCPs were recruited via department meetings, email, and in-person outreach. All HCPs were educated about the study and viewed a recorded presentation on shared decision making and STI testing. HCPs who volunteered for enrollment provided written informed consent.

Participant Recruitment

Patients are recruited during enrollment blocks, which correspond to the ED shifts of enrolled HCPs. After the patient was assessed by an HCP, a research team member approached eligible patients, introduced themselves, and presented the study without the HCP. Not all shifts will be covered, and providers were not informed of which shifts were sampled for enrollment. A research team member confirmed eligibility and obtained written informed consent from each adolescent and young adult and a waiver of parental consent for participants aged 18 years and younger, similar to other sexual health ED-based studies.

Randomization and Allocation

To avoid contamination, 50 HCPs were randomized 1:1 to the intervention (STIckER) or control arm. The allocation sequence was computer-generated by the study epidemiologist using a simple randomization method with stratification by location (adult vs pediatric ED). The randomization sequence was implemented by a study coordinator using a centralized allocation system. The assignment was not concealed from investigators. Randomization health care provider participant (HCP-P) in the intervention arm received 1:1 training with a research assistant on the STIckER app. If a participating provider left the ED before the end of the study period, a new provider randomized to the same study arm was invited to participate.

Intervention

Adolescents and young adults between the ages of 15 and 24 years attending the ED during the time that an HCP trained on STIckER was on service would scan the STIckER app before seeing the provider. patients as study participants (HCP-Ps and adolescent and young adult participants).

Adolescent and young adult participants are assigned to the arm of the provider to whom they are assigned. Adolescent and young adult participants with intervention-arm providers will scan a QR code with their personal mobile device, linking them to the web-based STIckER app. They will interact with the app, completing a sexual health assessment and indicating their personal values and preferences before being led to a final infographic to be shown to the HCP-P. This infographic will alert the provider to both the adolescent and young adult participants' need for oral, rectal, or urinary STI testing and their preference for testing.

Adolescent and young adult participants with control-arm providers will also scan a QR code with their personal mobile device, but it will lead them to a landing page with a prompt informing them they can ask their provider about STI testing. They will not have access to the digital tools and shared decision-making modules within the STIckER app.

All adolescent and young adult participants are followed throughout the ED visit. Adolescent and young adult participants will complete questionnaires at enrollment and upon ED discharge. These questionnaires comprise a comprehensive set of predominantly validated instruments and will capture sociodemographic characteristics, sexual behavior, substance use, perceived HIV risk, patient satisfaction, and decision-making quality. HCP-P will also complete a questionnaire after each adolescent and young adult visit and an end-of-study questionnaire focused on STIckeR implementation.

STIckER Web-Based App

Control Participants

Participants in the control arm will scan a QR code and receive a statement reminding them they can always ask for STI testing.

Intervention Participants

Patient participants in the intervention arm will proceed through the following 5 modules (see Figure 1):

- STI education**:** STIckER starts with a 1:06-minute video describing the importance of STI testing, followed by additional information about STIs and testing for STIs (see Figure 1).
- Sexual health assessment: Participants complete a 13-question assessment to assess their vulnerability to STIs. This assessment categorizes participants into high, medium, or low need for testing and generates recommendations for genitourinary, rectal, and oral gonorrhea and chlamydia testing at the time of ED visit (see Figure 1).
- Decision-making and shared-decision-making modules: Participants are taken through each recommendation with additional education and the option to opt in or opt out of testing (see Figure 1, panel C). Participants who are "intermediate need" for needing testing at that visit are taken to an additional shared decision-making module that accounts for individual values and preferences (see Figure 1).
- Provider display: STIckER ends with a hidden display uncovered when the provider places their finger over the

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STIckER logo to reveal it. This reveals testing recommendations and patient choices for oral, rectal, and urinary testing (see Figure 1).

Figure 1. Overview of the STIckER (STI Check in the Emergency Room) web-based application modules. STIckER is available online, and this version was frozen during the study [21]. Panel A: Educational module with introductory video and supplemental information about sexually transmitted infection (STI) testing. Panel B: Sexual health risk assessment stratifying participants by need for genitourinary, oral, and rectal testing. Panel C: Shared decision-making modules, including values clarification and opt-in/opt-out testing choices. Panel D: Provider-facing infographic summarizing participant testing needs and preferences, revealed by the provider via touch activation.

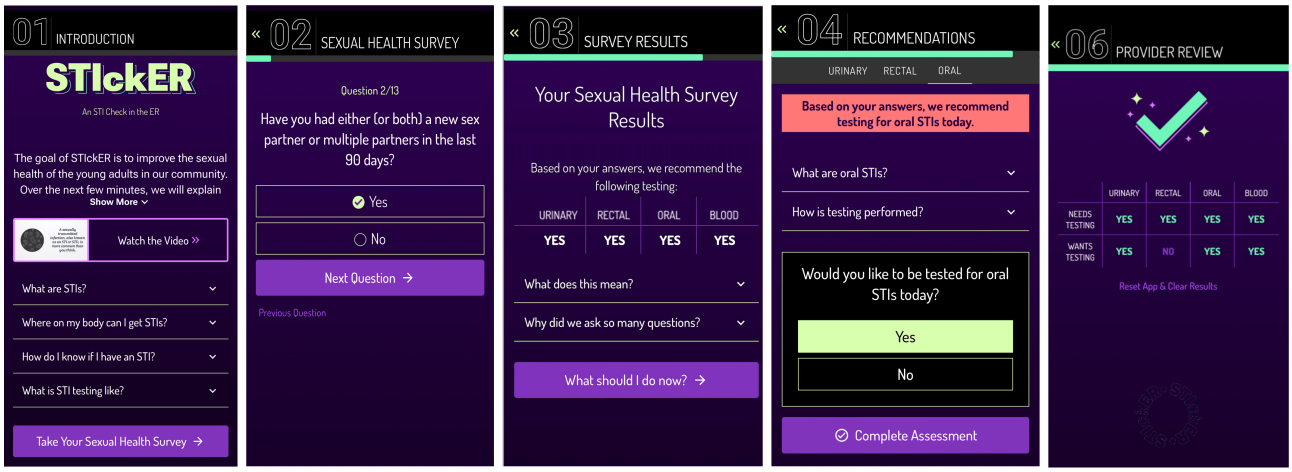

Clinical Setting

This study was conducted in the adult and pediatric emergency departments of NewYork-Presbyterian/Columbia University Irving Medical Center, located in Northern Manhattan. These EDs collectively see more than 150,000 patient visits annually and serve a predominantly Hispanic patient population, with over 25% of patients living below the federal poverty line. The EDs provide safety-net care to many adolescents and young adults who lack consistent access to primary care. The high volume, demographic diversity, and prevalence of structural barriers to care in this setting make it particularly well-suited for piloting an intervention designed to support STI screening among underserved adolescent and young adult populations.

Participants and Recruitment

The target enrollment for this study is 44 HCP-Ps and 140 adolescent and young adult participants.

For HCP-Ps, all ED attending physicians and physician assistants employed in the EDs, who work more than 5 shifts per month, are eligible. ED providers were recruited via a department-wide email request for participants. STIckER research coordinators will explain the study to interested HCPs and obtain written informed consent. HCP-Ps were selected to purposely sample half pediatric and adult ED providers with a range of professional experience.

For adolescents and young adult participants, all patients aged between 14 and 24 years, regardless of chief complaint, are eligible for screening. Adolescents and young adults aged between 14 and 24 years who self-reported sexual activity within the last 6 months and were able to speak English are eligible for enrollment. Participants who were in foster care, wards of the state, or in police custody, as well as those who were cognitively impaired, exhibited aggressive behavior, or were critically ill, as determined by their attending medical provider, were not eligible.

Research coordinators will screen ED patients during clinical hours by the enrolled HCP-Ps. Those times typically consisted of Monday-Friday, 8 AM-10 PM, with limited weekend enrollment. First, information to determine eligibility was gathered from the EMR (ie, age). Next, if a patient was deemed eligible to be assessed further, a research coordinator approached the patient to confirm criteria such as sexual activity and interest in the study. Eligible participants were enrolled with written informed consent. For participants aged between 14 and 17 years, we will obtain a waiver of parental consent and a 2-person verification of agreement to participate, such as the research coordinator and the physician attending the ED. Participants received a US $10 pay card at enrollment.

Study Assessments

HCP-P Study Assessments

At enrollment, enrolled HCP-Ps will complete a basic demographic questionnaire. (age, race, ethnicity, sex at birth, gender identity, years since completing training, and type of clinical training completed).

The exit survey will be conducted immediately after a visit with an adolescent and young adult participant; the HCP-P will complete an exit survey.

HCP-Ps randomized to the control arm get questions on whether STI testing was discussed (“Did you and your patient discuss STI testing”), if the discussion was appropriate (Likert scale of 1 - 5, from “completely appropriate” to “completely inappropriate”), if STI testing was ordered, and if STI testing was ordered what level of shared decision-making involvement occurred using the Control Preferences Scale (Likert scale of 1 to 5, from “I made the decision on my own” to “the patient made the decision on their own”) [22].

HCP-Ps randomized to the intervention will get the same questions on whether STI testing was discussed, if the discussion was appropriate, if STI testing was ordered, and if STI testing

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was ordered, what level of shared decision-making involvement occurred using the control preferences scale. They will also complete validated questions on implementation (acceptability of intervention measure [AIM], intervention appropriate measure [IAM], and feasibility of intervention measure [FIM]) [23].

The postsurvey will be conducted after completing their participation in the STIckER study (a maximum of 6 adolescent and young adult participants or the study completing overall enrollment), HCP-P will complete a postintervention questionnaire.

HCP-Ps, randomized to the control arm, will complete a self-efficacy questionnaire to measure their clinical communication skills [24].

HCP-Ps randomized to the intervention arm will complete the self-efficacy questionnaire measuring their clinical communication skills, a Perceived Characteristics of Intervention Scale (a 20-item assessment measure that covers 9 subconstructs: relative advantage, compatibility, complexity, trialability, observability, potential for reinvention, task issue, nature of knowledge, and technical support), a question on how easy it was To use the screen the participant showed them (Likert scale of 1 to 5, from “Complicated” to “Able to use the app immediately”), and open-ended questions about whether the STIckER app was acceptable and what changes they would like to see made [25].

Adolescent and Young Adult Participants Study Assessments

Enrollment

At enrollment, enrolled adolescent and young adult participants will complete a basic questionnaire to collect data on age, race, ethnicity, sex at birth, gender identity, sexual preferences, the reason for the ED visit, if they had a primary care visit in the past year, and if they had a visit, did they receive an HIV or STI testing.

STIckER

The adolescent and young adult participants, randomized to the intervention, will complete the STIckER web-based app, which includes a 13-question sexual health assessment. This includes a validated 6-question survey of age and STI-related behaviors, as well as locally developed questions about types of sexual activity engaged in the previous 3 months, and if they had received gonorrhea or chlamydia testing in the previous 30 days [26,27].

Exit Survey

Immediately after a visit with an HCP-P, the adolescent and young adult participants will complete an exit survey.

The adolescent and young adult participants randomized to the control arm will complete questions on whether STI testing was discussed (“Did you and your patient discuss STI testing”), if the discussion was appropriate (Likert scale of 1 - 5, from “completely appropriate” to “completely inappropriate”), if STI testing was ordered, and if STI testing was ordered, then what level of shared decision-making involvement occurred using the control preferences scale. The Control Preferences Scale is used to assess the extent to which patients perceived that the decision about STI testing was shared between themselves and their provider. It captures patient-reported involvement in the decision-making process by asking who took the lead in making the decision. While it does not measure specific components, such as depth of discussion or mutual agreement, it is a validated and widely used measure of perceived shared decision-making.

They will also complete 4 questions on the amount of information received, clarity of information received, helpfulness of information received, and if they would recommend that information to others; 9 items from the decisional-conflict scale on uncertainty. They will complete 2 items, providing a rating of the ED (0 to 10) and if they would recommend the ED to family or friends. Finally, they will complete the 13-question sexual health assessment that was included in STIckER.

The adolescent and young adult participants randomized to the intervention will complete questions on whether STI testing was discussed (“Did you and your patient discuss STI testing”), if the discussion was appropriate (Likert scale of 1 - 5, from “completely appropriate” to “completely inappropriate”), if STI testing was ordered, and if STI testing was ordered, then what level of shared decision-making involvement occurred using the control preferences scale. They will also complete 4 questions on the amount of information received, clarity of information received, helpfulness of information received, and if they would recommend that information to others; 9 items from the decisional-conflict scale on uncertainty [28]. They will complete 2 items, providing a rating of the ED (0 to 10) and if they would recommend the ED to family or friends. Finally, they will complete the AIM, IAM, and FIM implementation measures.

Outcomes

Primary Outcome

The primary outcome of preliminary efficacy is the difference in the proportion of sexually active adolescents and young adults tested for Neisseria gonorrhoeae or chlamydia trachomatis between the 2 arms based on the EMR review. We selected preliminary efficacy as the primary outcome because the trial was designed and powered to provide an effect size estimate that would inform the design and sample size calculations for a future multisite trial. While many pilot studies emphasize feasibility and acceptability as primary outcomes, in this single-site trial, we aimed to generate robust preliminary data on testing uptake to guide scale-up and ensure generalizability across diverse ED settings.

Secondary Outcomes

Secondary efficacy outcomes include rates of extragenital Neisseria gonorrhoeae or chlamydia trachomatis testing, overall and site-specific STI positivity rate, decisional conflict, and level of shared decision-making. Secondary implementation outcomes include feasibility (FIM), acceptability (AIM), appropriateness (IAM), and personal traits and attitudes toward STI screening.

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Statistical Analysis

We will summarize efficacy and implementation outcomes using standard descriptive statistics for continuous and categorical variables. We will conduct bivariate analyses to identify balance in the random allocation of the intervention across providers and patient characteristics.

Preliminary Efficacy

An intent-to-treat analysis of all enrolled patients will be conducted according to random assignment of the intervention to estimate the effect of STIckER on STI testing. We will conduct a mixed-effects generalized linear model (GLM) with the logit link function to look at the effect of STIckER on STI testing, if there is a clustering effect by provider, or logistic regression if there is no provider effect. To determine whether there is a provider effect, we will assess the intraclass correlation coefficient (ICC) for the primary outcome using a null (empty) mixed-effects model with provider as a random effect. If the ICC is greater than 0.01, we will proceed with mixed-effects modeling; otherwise, we will use standard logistic regression. For other dichotomous outcomes, we will use the same analytic approach (GLM) with the logit link function if there is a provider effect or logistic regression if there is no provider effect.

Secondary Efficacy and Implementation Outcomes

If there is a provider-level effect, we will use mixed-effect GLM to look at the association of STIckER on the continuous outcomes, such as implementation scales, and linear or logistic regression if there is no provider effect. If needed, we will also conduct sensitivity analyses to explore the effect of spillover, misclassification, missing data, or any other deviation from the study procedures that would affect efficacy or implementation outcomes.

Exploratory and Subanalyses

Additional exploratory analyses will examine differences in the primary and secondary outcomes among adolescent and young adult patients by age (older vs younger), gender, sexual identity, and other covariates of interest. Analyses of providers will include exploring differences by gender, years of professional experience, and other covariates where possible.

Power Analysis

This pilot trial will enroll 44 providers and 140 adolescent and young adult patients over 6 months based on feasibility. Using a simple, parallel randomized design and accounting for providers evaluating more than 1 patient, we estimate the minimum detectable effect size (MDE) of 0.348. MDE is based on the following assumptions: α=.05, a 2-tailed test, with 80% power, and ICC of 0.01, 50% of variance in adolescents and young adults, and 50% of variance in providers explained, and all other covariates of interest (eg, age and gender) were balanced by randomization of STIckER to providers and their adolescent and young adult patients. With our sample size of 140 participants, we have the power to detect a minimum of 35% higher likelihood of being tested for STIs in the intervention arm compared to usual care.

The ICC of 0.01 and the assumption that 50% of the variance would be attributable to provider- versus patient-level factors were based on conservative estimates. These assumptions are intended to ensure sufficient power while accounting for possible provider clustering.

Ethical Considerations

This study was reviewed and approved by the Institutional Review Board (IRB) at Columbia University (Protocol #AAAU7485). Written informed consent was obtained from all adult participants. For participants aged between 14 and 17 years, a waiver of parental consent was granted by the IRB, and assent was obtained using a standardized script and study summary tailored for adolescent comprehension. Agreement to participate was confirmed verbally in the presence of 2 study staff (typically the research coordinator and the physician attending the ED) to ensure understanding and voluntariness. All data are deidentified for analysis to ensure participant confidentiality. Participants received a US $10 pay card as compensation for their time.

Results

Enrollment began in September 2023 and was completed in July 2025, with 44 providers and 139 adolescent and young adult participants enrolled across adult and pediatric EDs. All participants' follow-up and survey data collection are complete. Data cleaning and primary analyses are currently underway, with dissemination of final results anticipated in late 2025.

Discussion

Hypothesis

This protocol outlines an RCT to assess the preliminary efficacy and implementation of the STIckER app, a shared decision-making tool to support gonorrhea and chlamydia testing in adolescents and young adults in EDs. We anticipate that the intervention will lead to a higher proportion of adolescents and young adults receiving comprehensive genitourinary and extragenital STI testing compared to usual care, and that both patients and providers will find the tool acceptable, appropriate, and feasible to implement.

Comparison With Previous Work

Previous studies have highlighted significant gaps in STI testing, particularly for extragenital sites, in both outpatient and ED settings [3,29,30]. While SDM tools have been shown to improve patient engagement and outcomes in other areas of emergency medicine, such as analgesic choice and evaluation of chest pain, few, if any, have focused on sexual health. STIckER addresses this gap by applying the SDM model to STI testing decisions in the ED [15-19,31], a critical access point for many underserved youths [5,32]. By centering the patient's values and preferences, this tool has the potential to both improve care and reduce disparities in STI screening access.

Beyond sexual health, a broader body of work on mHealth in emergency settings demonstrates the feasibility and moderate effectiveness of digital interventions across diverse health domains. For example, randomized trials of text-message interventions have shown reductions in hazardous drinking among young adults [33], while culturally tailored apps and

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SMS programs improved blood pressure control among Black adults with hypertension [34] and increased asthma-related follow-up visits for children [35]. Interventions that were linguistically accessible and rooted in behavioral change theory were most successful, underscoring the potential of ED-based digital tools like STIckER to promote equitable, patient-centered screening.

Strengths and Limitations

This study has several notable strengths. It is designed as an RCT, a robust methodological approach that supports internal validity. The STIckER app was co-developed with input from both AYA patients and ED providers, ensuring relevance and usability for both stakeholder groups [20]. The tool was implemented across both pediatric and adult EDs that serve racially and socioeconomically diverse populations, increasing the relevance of findings for underserved communities. Additionally, the intervention's digital, QR-code-based format is low-cost, scalable, and adaptable to a range of ED workflows.

However, the study also has important limitations. The STIckER app is currently only available in English, which will restrict its accessibility for non-English–speaking patients. The intervention focuses exclusively on gonorrhea and chlamydia and does not address other STIs that require blood-based testing, such as HIV or syphilis. Furthermore, the study is being conducted at a single academic medical center, limiting generalizability to other settings such as community hospitals or urgent care centers.

Given the nature of the intervention, participants and providers could not be blinded, which may have introduced expectation bias. Participants may have been able to infer their assignment based on the version of the app they received, potentially influencing their perception of care or engagement with STI testing discussions. As with many digital health trials, we anticipate variability in user engagement and potential drop-off during app use, which may affect intervention exposure. The inclusion of multiple secondary and implementation outcomes also raises the potential for type I errors. These limitations will be carefully considered during the interpretation of study results.

In a routine clinical setting, providers may not receive individualized training, and research staff would not be available to support app use. The absence of structured onboarding may reduce uptake and effectiveness. Future implementation efforts should explore how STIckER performs in lower-touch models, such as through automated workflows, integration into electronic health record systems, or peer-led education. Additionally, STIckER requires access to a smartphone and internet connection, which may pose challenges for adolescents and young adults from socioeconomically disadvantaged backgrounds. Devices or WiFi were not provided during this pilot, and future implementation efforts will need to consider strategies to improve equitable access.

Finally, although STIckER may influence broader awareness and discussion of STI testing, this pilot is limited to evaluating gonorrhea and chlamydia outcomes. The potential spillover effect on HIV or syphilis testing is not measured in this study but represents an important area for future research.

Future Directions

If the pilot demonstrates feasibility and preliminary efficacy, future studies will focus on scaling the intervention to a larger, multicenter trial. Planned enhancements may include multilingual functionality and expansion of the tool to address additional STIs and linkage to care pathways. The app's SDM framework may also serve as a model for other youth-focused digital health interventions in the ED. If effective, we will also explore partnerships with health care systems and public health organizations to promote adoption and sustainability, including potential integration into EHR systems and staff training modules.

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Generative artificial intelligence (AI) tools were used solely to clarify and improve grammar and sentence structure. No generative AI tools were used to create or generate original content or substantive manuscript text.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization: LC, JZ, MAP, DC
Methodology: LC, JZ, MAP, DC
Protocol development: LC, JZ, MAP, DC, LPT, TA, JDS, CF
Writing – original draft: LC, JZ, MAP, DC
Writing – review & editing: LC, JZ, MAP, DC, LPT, TA, JDS, CF
Project administration: LC, JZ

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Funding acquisition: LC, JZ

Conflicts of Interest

The authors were involved in the design and development of the STIckER app. The app was developed in collaboration with a digital agency under the direction of the study team. No authors hold financial interest or commercial ownership in the tool. None declared by the other authors.

Checklist 1
CONSORT-eHealth V1.6 checklist.
[PDF File, 11072 KB - resprot_v14i1e67103_app1.pdf]

Checklist 2
SPIRIT checklist.
[PDF File, 234 KB - resprot_v14i1e67103_app2.pdf]

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Abbreviations:

AIM: acceptability of intervention measure
CFIR: Consolidated Framework for Implementation Research
ED: emergency department
EMR: electronic medical record
FIM: feasibility of intervention measure
GLM: generalized linear model
HCP: health care provider
HCP-P: health care provider participant
IAM: intervention appropriateness measure
ICC: intraclass correlation coefficient

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RCT: randomized controlled trial
SDM: shared decision-making
STI: sexually transmitted infection
STIckER: STI Check in the Emergency Room

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Assessing the Ability of an Online Education Program to Modify Patient Expectations of Total Knee Arthroplasty Outcomes: Protocol for a Randomized Controlled Trial

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Abstract

Background: Patient satisfaction with total knee arthroplasty (TKA) is strongly influenced by alignment between expectations and outcomes. Despite a satisfaction rate of 80% - 90%, dissatisfaction affects 10% - 20% of patients and is expected to grow with the increasing volume of TKA procedures globally. Misaligned expectations, often driven by unrealistic or overly optimistic recovery views, can lead to unmet goals, dissatisfaction, and unnecessary health care usage. Addressing these gaps through improved presurgical education has the potential for enhancing patient satisfaction, optimizing outcomes, and reducing the burden on the health care system.

Objective: The main objectives of this study are to develop and evaluate a presurgical educational program, which focuses on patient expectations of surgical outcomes and facilitates patients setting realistic postsurgical goals. We will also assess the ability of the program to modify patient expectations, impact expectation fulfillment, improve satisfaction with postsurgical outcomes, and impact patient health literacy.

Methods: A targeted education program will be developed in consultation with key stakeholder groups, including consumer advocates, orthopedic surgeons, health care providers, and physiotherapy and rehabilitation specialists, to address realistic patient expectations of TKA outcomes. Alpha testing with consumers will provide insights into the appropriateness of the program being developed. The ability of the program to modify patient expectation will be assessed in a longitudinal, parallel group, 2-armed randomized controlled trial involving 150 patients identified by their orthopedic surgeon as requiring TKA. Randomly allocated participants will take part in the education program within 5 weeks prior to their scheduled TKA (intervention group) or will be allocated to standard preoperative education (control group). The primary outcome will be a change in the Hospital for Special Surgery Total Knee Replacement Expectations Survey–transformed score measured prior to and following the intervention. At 6 months following TKA, expectation fulfillment and overall satisfaction will be measured. Inferential statistics will be used to test for differences in, or associations between, outcome measures within and between study arms. The methods appropriate to both dependent and independent samples will be used, including nonparametric methods for data in violation of normality and variance assumptions.

Results: The education program will be developed from January to September 2025. The randomized trial will run from October 2025 to March 2027, with data analysis completed by April 2027 and results published in peer-reviewed journals by September 2027.

Conclusions: This study will provide evidence on the effectiveness of a novel presurgical educational program in shaping patient expectations, promoting realistic goal setting, and improving TKA satisfaction. Findings will inform strategies to improve TKA patient care, health literacy, and satisfaction, potentially reducing dissatisfaction and associated burden on health care.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12624001465549; https://anzctr.org.au/Trial/Registration/TrialReview.aspx?id=388664

International Registered Report Identifier (IRRID): PRR1-10.2196/71898

(JMIR Res Protoc 2025;14:e71898) doi:10.2196/71898

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KEYWORDS

health literacy; patient education; expectations; total knee arthroplasty; musculoskeletal

Introduction

Background

Total knee arthroplasty (TKA) is a well-established intervention for end-stage osteoarthritis, offering significant improvements in joint function and pain reduction, with low rates of revision and mortality [1,2]. While these clinical outcomes are critical from a health care provider's perspective, they do not fully encompass the range of outcomes that matter most to patients, particularly those related to functional recovery and goal attainment following TKA [3-5].

Systematic reviews consistently report that 10%‑20% of patients remain dissatisfied with surgical outcomes, often due to persistent pain, limited range of motion, or insufficient improvement in knee function [6-9]. This dissatisfaction persists despite advances in prosthetic design [10], robotic-assisted surgical techniques, and improved implant alignment [11]. Importantly, dissatisfied patients incur up to 57% higher societal costs, including out-of-pocket therapies, lost productivity, and caregiver expenses postsurgery compared to satisfied patients [12].

With the number of TKA procedures projected to rise substantially over the next 2 decades [13,14], improving patient satisfaction is imperative, not only for individual outcomes but also for broader economic and health care system impacts.

Satisfaction with surgical outcomes is a multifaceted construct influenced by various factors [15], including disease severity, preoperative pain, and functional limitations [10,16,17], as well as psychological factors, such as mood and mental health status [18-20]. In addition, fulfillment of TKA patient expectations regarding postsurgical outcomes has been associated with satisfaction levels [7,21-23]. Patient expectations also predict residual pain and functional outcomes, underscoring the importance of goal setting [24,25]. However, unrealistic expectations may lead to discouragement and poor adherence to rehabilitation, while overly modest expectations may reduce motivation [25].

Social, demographic, and cultural factors also influence the nature and scope of patient expectations [26-28]. A comparative study of patients in the United Kingdom, United States, and Australia revealed that while overall satisfaction rates were similar, Australian patients were more likely to expect improved function at 12 months post surgery and placed greater emphasis on recreational activities and unaided mobility [29]. Our recent research in an Australian cohort further demonstrated that the majority of patient expectations centered on high-impact activities, such as golf, cycling, long-distance walking, and gym-based exercise [30].

Despite the importance of patients setting realistic expectations to optimize expectation fulfillment [31-33], this issue is not routinely addressed in clinical practice, partly due to the lack of standardized methods for assessing expectations and their fulfillment. Some studies have focused narrowly on pain reduction and basic functional outcomes, omitting patient-specific goals [21]. Others have used predefined activity lists to gauge importance [34]. However, no gold-standard approach currently exists for characterizing and evaluating patient expectations from TKA.

Despite the lack of a standardized approach, several groups have suggested approaches to assess patient expectations. One approach involves patient-reported surveys that categorize expectations by importance preoperatively and assess fulfillment postoperatively [34,35]. This method allows for structured quantification of expectation levels and categories. A more recent alternative is inductive content analysis, which uses open-ended questions to capture patient-specific expectations without the constraints of predefined categories [36], which enables a more personalized understanding of patient expectations and their fulfillment.

While patient expectations can certainly be assessed, the more critical challenge lies in actively shaping those expectations so that patients are positioned to be highly engaged in their recovery and ultimately satisfied with their outcomes. Achieving this requires more than simple information sharing—it calls for deliberate, structured patient education. However, despite its importance, such education is often underemphasized or even absent in current presurgical discussions. Indeed, preoperative education aimed at modifying expectations has shown promise in enhancing patient satisfaction [35,37]. Such interventions help patients set realistic goals, leading to reduced expectation levels and improved fulfillment at 12 months post surgery [37]. In addition, targeted education has been shown to reduce the number of expectations compared to standard education alone [35]. Collectively, these findings support the integration of expectation management into preoperative care to optimize patient outcomes.

Musculoskeletal health literacy among patients seeking orthopedic care has been found to be lower than general health literacy [38]. While there is a substantial volume of online information regarding TKA, its utility is limited due to poor readability, understandability, and actionability [39]. This is concerning, as low health literacy is associated with patients with musculoskeletal conditions setting lower expectations for surgical outcomes [40-42].

Structured educational interventions have demonstrated efficacy in improving health literacy. Even a single structured session has been shown to enhance health literacy among patients with orthopedic conditions [43]. Furthermore, eHealth education has shown promise in improving both health literacy and self-efficacy in older adults [44]. Despite these encouraging findings, uptake of educational resources related to TKA rehabilitation and recovery remains limited [45].

Clinicians play a critical role in guiding patients toward realistic expectations by providing education on achievable outcomes while also understanding individual patient priorities. This dual approach supports realistic expectation-setting, shared

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decision-making, and a patient-centered model of care. With growing demand from health consumers to actively participate in decisions regarding their health care, there is a clear need for the development of targeted educational models and decision aids. TKA represents a pertinent example, given the high volume of procedures performed and the substantial proportion of patients who report residual dissatisfaction.

Aims and Objectives

In the current project, we will collaboratively develop a novel educational program for patients undergoing TKA with orthopedic care teams, consumer advocates, and key health care provider stakeholders, which will focus on providing information that will inform and encourage patients to set realistic expectations of TKA surgical outcomes. The ability of the program to influence the type of expectations patients set prior to surgery will be assessed by comparing patients' expectations before and after the program and by comparing expectations of those who participate in the program to those who receive "standard clinical care" alone. In addition, the project will determine if education program participation is associated with a higher level of expectation fulfillment, satisfaction with surgical outcomes, and improvement in health literacy. We will apply a number of different methods to define patients' expectations, using both closed- and open-ended questionnaires to evaluate the scope of responses achieved by each approach.

Methods

Study Design

Study Stages

The study will take place over 2 stages. Stage 1 will focus on the collaborative design of an education program intervention to be delivered to patients prior to their TKA, while Stage 2 will involve a randomized controlled trial, which will determine if the developed education intervention is effective in modifying patient expectations regarding TKA outcomes and assess the impact of the intervention on expectation fulfillment and overall satisfaction with surgical outcomes and health literacy 6 months following the TKA.

Stage 1

Overview

The educational materials to be developed will consist of multiple videos that patients will access online. Each video developed will run for no more than 5 minutes and address different aspects of recovery and capacity to undertake a range of different tasks and activities following TKA surgery.

Consultative Process

The content of the videos will be developed through consultancy with key stakeholder groups, including orthopedic teams (local orthopedic surgeons who regularly undertake TKAs and rehabilitation specialists), consumer advocates (people who have undergone a total knee replacement within the last 5 years), and the study steering committee (including members of the research team and collaborating researchers with experience in behavior change methodology and knee replacement rehabilitation). We will approach orthopedic surgeons and rehab physicians from the 3 main private hospitals who undertake TKAs in the greater Newcastle New South Wales area to be involved in our clinical consulting committee. From our recently conducted SuPeR Knee: Support, Predict, Recover study [46], we will send email requests to participants who had consented to be made aware of future research activities being undertaken by our team and ask them to complete an expression of interest form. Interested people will be asked to provide details of their age, sex, date of knee replacement, employment details, and their reasons for wanting to take part. Five advocates will be selected, giving a diverse range of individuals with varied experiences. The key stakeholder groups will be advising on how to present material that can convey to the viewer the importance of setting realistic expectations of outcomes following a TKA. A combination of mixed media styles will be applied, including presentations by rehabilitation specialists and interviews with patients who have lived experience of life following TKA, as well as other graphic tools, such as real-life scenarios and text to clarify key concepts.

Video Design Principles

The design of the educational videos will be guided by social cognitive theory (SCT) [47] and the Information-Motivation-Behavioral Skills model [48], both of which are foundational frameworks for promoting health behavior change. SCT posits that individuals' ability to make choices is shaped by the dynamic interaction of cognitive, behavioral, and environmental factors [47]. It also highlights the importance of observational learning, which can be enhanced by factors such as attention and engagement. To support this, our videos will present relatable content by addressing common themes around expectations identified by individuals preparing for total knee replacement [34]. These themes will reflect variations in medical status, lifestyle, personal priorities, and belief systems. To reinforce the central learning objectives, each video will reiterate key concepts related to expectation-setting and goal-directed behavior. Within SCT, self-efficacy plays a central role in learning and behavior change [47]. Accordingly, the videos will showcase a range of activities and tasks that individuals may aspire to undertake post surgery. These examples are intended to foster viewer engagement and encourage personal reflection on lifestyle, capacity, and realistic goal setting. To enhance relatability, the videos will incorporate plain language, open-ended questions, and visuals of real-world settings, including perspectives from patients with lived experience of TKA. Institutional branding will be used to establish credibility, and narration will be provided by qualified physical therapists and exercise physiologists, offering a trusted and authoritative voice [49].

Content will also be informed by principles from the Science of Learning and the Science of Instruction in Multimedia [50]. Using videos as the media of choice enables the integration of visual and auditory cues aimed at engaging working memory and facilitating the integration of new information with existing beliefs stored in long-term memory. This offers the potential for enhancing the retention of information being conveyed and

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encouraging behavior change, which extends beyond that which could be achieved by providing printed materials.

Using a constructivist learning model, the material presented will go beyond biomedical information to encourage viewers to actively consider their own lifestyle, values, and realistic postsurgical outcomes [51].

Key elements of behavior change incorporated into the information will include enhancing psychological capability and reflective motivation through the provision of knowledge and understanding about recovery following TKA [48,52]. Reflective motivation will be further supported by eliciting positive emotions associated with setting achievable goals, as well as highlighting the potential negative consequences of unrealistic expectations.

Alpha Testing

Our consultative process will involve the development of scripting and storyboards for videos with each of our stakeholder groups. Materials will be reviewed until a consensus regarding the content and format of the educational materials among the consulting groups has been reached. Subsequently, videography and initial editing will then be undertaken, and the first prototype materials generated. Prior to generating the final version of the videos, we will undertake alpha testing by seeking input from an additional consumer group who have undergone a recent total knee replacement. The alpha testing will constitute an evaluation of the understandability (content scope, word choice and style, organization, layout, and design) and actionability of the prototype. The feedback provided will be used to make improvements in the material leading to the generation of the final version.

Initially, we will enroll 5 participants to be involved in the alpha testing. Purposive sampling will be undertaken based on sex and age to maximize the range of viewpoints derived. Participants will be recruited from the cohort who participated in our recently conducted SuPeR Knee: Support, Predict, Recover study [46]. Consequently, they have had prior familiarity with interviewer KR, who was the project manager in this study. Participants will be asked to provide the research team with details regarding their knee replacement history, the highest level of education achieved, information regarding their current health conditions, and the completed 12-item European Health Literacy Survey Questionnaire (HLS-EU-Q12) [53]. A pragmatic, mixed methods approach will be adopted to capture feedback regarding the educational videos and guide further editing. We intend to adopt a qualitative descriptive approach to enable us to gain firsthand knowledge from the patient group regarding the content of our prototype [54,55].

After viewing each video, participant feedback will be provided by completion of the Patient Education Materials Assessment Tool—Audio Visual (PEMAT-A/V) [56,57], which addresses the relevance (content scope), understandability (word choice and style, layout, and design), and actionability (intended actions for the viewer to take) of the materials presented. To provide further insights, qualitative data will also be collected to verify the survey responses.

Participants will be contacted to arrange a time for a one-on-one structured interview with a member of the research team to discuss their responses to the PEMAT-A/V surveys and provide additional feedback regarding the educational program they viewed. To provide credibility to the research data, interviews will be undertaken by members of the research team who have extensive experience in undertaking qualitative research interviews and data analysis (KR, female, PhD, study chief investigator, or LS, female, BComm, BPsych, study research assistant). Interviews will last for approximately 30 minutes, with participants having the option for this to be undertaken as a recorded face-to-face meeting, an online Zoom (Zoom Video Communications) video call, or a phone call. Sessions will be recorded, and transcripts viewed by the participants to verify that they reflect their statements. The following open-ended questions will be used to guide the discussion to elucidate information regarding the participants' experiences with the material they were presented:

1. Can you explain why you gave each score on the PEMAT-AV survey, and are there any changes we need to consider?
2. Do you trust the information that was provided?
3. Do you think that the information provided will influence patients' decisions about what they can expect following a TKA?

The focus of the interviews will be based on the participant's responses to the PEMAT-AV surveys and consequently focus on their narrative, with the interviewer providing additional questions to further expand the participant's views, providing confirmability of the findings. Both researchers undertaking the interviews will also be involved in the development of the education materials, with an overarching aim to develop high-quality educational material in this study. Regarding reflexivity, both researchers will be aware of their own viewpoints regarding the materials being reviewed but keep the narrative of the participant as the focus of the discussion to reduce interviewer biases to influence the topics discussed [58]. To assist with the transferability of the data collected, interviewers will provide a written account for each interview describing additional participant characteristics, including cultural and social features that may have impacted the interview dynamic.

Stage 2

The impact of educational materials generated in stage 1 will be evaluated in a longitudinal, parallel group, 2-armed, block randomization trial with an allocation ratio of 1:1 [59]. Patients undergoing TKA will be enrolled when they have been scheduled for the surgical procedure and will be involved in study assessments for a total of 32 weeks (8 months) from study entry. Referrals of potential study participants will be provided by the participating orthopedic surgeons when their patient has consented to undergo a TKA. The maximum wait time between patient consent and surgery taking place is 6 weeks. Consequently, all presurgery assessments and the study intervention will take place within this 6-week window. Following study consent, baseline assessments will be undertaken at study entry, which is likely to be 5 weeks prior

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to TKA. The intervention (viewing the educational videos+standard care) or control (standard care alone) will be delivered 4 weeks prior to the scheduled TKA. Standard care will encompass any educational materials provided to the patient by their surgeon and health care provider. For the intervention group, participants will be provided online access to the educational videos. They will have the capacity to view the videos several times if they desire and will record the number of times each one is viewed. Postintervention assessments will be conducted 3 weeks prior to TKA, and postsurgical outcome measures will be undertaken at 6 months following the TKA.

Study Setting

The stage 2 randomized trial will be run as a single-center study, centrally managed by the Centre for Rehab Innovations, University of Newcastle, New South Wales. We intend to recruit patients who are scheduled for TKA to take place at private health care facilities within the Greater Hunter Region, New South Wales, Australia and is likely to include, but is not limited to, Lake Macquarie Private Hospital, Gateshead; Maitland Private Hospital, East Maitland; and Lingard Private Hospital, Merewether, New South Wales.

Study Population and Eligibility

Stage 1

We will be sourcing potential study participants from the patient cohort who recently took part in the SuPeR Knee: Support, Predict, Recover study [46]. Study participants who consented to be contacted will be identified and informed about this study. We will recruit 5 patients who have already undergone TKA surgery to assist with alpha testing of the education program being developed in this stage of the study. Patients will need to meet the inclusion and exclusion criteria listed in Textbox 1.

Textbox 1. Inclusion and exclusion criteria for stage 1.

Inclusion criteria

- Have undergone a primary total knee arthroplasty (unilateral or bilateral) within the last 5 years
- Adult patients (>18 years)
- Have the capacity to complete a series of self-reported questionnaires (presented in English)
- Are able to provide informed consent

Exclusion criteria

- Have undergone a recent primary total knee replacement due to acute trauma
- Are unable to provide total knee arthroplasty consent

Stage 2

We will recruit 150 patients who have been identified as requiring a TKA to take part in the randomized controlled trial being undertaken in this stage of the study. Patients will need to meet the inclusion and exclusion criteria listed in Textbox 2.

Textbox 2. Inclusion and exclusion criteria for stage 2.

Inclusion criteria

- Have been identified as requiring a primary total knee arthroplasty (unilateral or bilateral) by their treating orthopedic specialist
- Adult patients (>18 years)
- Have the capacity to complete a series of self-reported questionnaires (presented in English)

Exclusion criteria

- Will be undergoing a primary total knee replacement due to acute trauma
- Have undergone previous knee replacement surgery
- Have had knee surgery within the preceding 6 months, have knee surgery scheduled within the next 6 months or are undergoing a revision for existing joint surgery
- Are unable to provide informed consent

Recruitment and Enrollment Procedures

Eligible participants will be contacted by a member of the research team. This will be a follow-up phone call in stage 1, after information has been posted to them; and in stage 2, after they have received the patient information sheet and study information flyer from their surgeon. For stage 2, participants will be recruited from referrals from orthopedic surgeons who undertake total knee replacement procedures at Lake Macquarie Private Hospital, Gateshead, New South Wales, Australia; Lingard Private Hospital, Merewether, New South Wales, Australia; or Maitland Private Hospital, East Maitland, New South Wales. The surgeon and/or their staff will (1) ensure every eligible patient receives a patient information sheet and a flyer,

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(2) direct patients to contact information for the research team on the patient information sheet/flyer, and (3) share a list of each patient receiving the patient information sheet with the study team. A member of the study team will follow up with each eligible patient via telephone to ensure that they have understood the information they received and to determine if they are interested in participating in the study.

A member of the study team will follow up with each eligible patient via telephone to (1) ensure that they have understood the information they received and (2) determine if they are interested in participating in the study.

Eligible participants can choose not to participate when they receive the patient information sheet and study information flyer. If they do decline to participate, they will not be contacted further. The research team member will ask if the participant has any questions about the study and if they are interested in participating.

If patients opt to have their study questionnaires accessed via the study online platform, they will be provided a copy of the patient information sheet when they access this system via a participant-specific login. Following review of the patient information sheet, they will be asked to acknowledge their consent to participate in the study and provide an electronic consent on the electronic letter of consent. Questionnaire templates will not be accessible to the participants until the consent field on this form has been completed.

If patients opt to have their study questionnaires posted to them, a copy of the patient information sheet and informed consent form will be included in the posted package. Participants will be asked to sign the consent form prior to commencing completion of the questionnaires. The completed consent form and questionnaires will be posted back to the research team.

Participants can decline to participate at any time point during the study, which will not impact their medical care. If patients decide to withdraw from the study, they can specify if their data is to be removed from the study or if they are willing for it to be used as part of the analysis.

Sample Size

Sample Size Estimation and Justification

Stage 1

We will initially involve 5 individuals who have undergone a TKA within the last 5 years to take part in video alpha testing encompassing the understandability and actionability of the prototype of the educational videos. Content analysis will be via an inductive approach [60]. If we find that the issues identified in the prototype videos differ substantially between each participant and saturation of the feedback content is not occurring, we will enroll 5 further individuals to undertake the alpha testing, such that feedback from up to 10 individuals will be included in stage 1. The purposive sampling approach being adopted will enable a diverse group of viewpoints to be derived. Taken together with the collaborative approach between the stakeholder groups involved in the design component of this study, we are confident that the number of participants involved in the alpha testing is sufficient to support the development of education materials to be further evaluated in stage 2 of this study.

Stage 2

A sample of 150 individuals who have been identified as requiring a TKA by their treating orthopedic specialist (2 subgroups of n=75) will be recruited. This will allow for expected dropouts (approximately 22/150, 15%) and ensure a minimum sample size of 64 for each group, which will enable the study to be adequately powered (see calculations below). A screening log will be kept and will collate reasons why any participants were screened but did not take part in the study.

Power Calculation: Sample Size Estimate

The number of participants was selected based on previously published findings using the Hospital for Special Surgery Total Knee Replacement Expectations Survey (HSS-TKR) as our primary outcome measure to demonstrate a clinically meaningful change in the overall patient expectation score [35]. Mancuso et al [35] describe a clinically meaningful change in expectations to be associated with a 6-point change in transformed HSS-TKR total scores. To determine a significant difference between 2 groups of patients, such that α=.05, power 80%, and SD 12, will require 64 patients per group. In this study, we will enroll 75 patients per treatment arm to allow for any potential loss of participation at the follow-up time points.

Randomization Procedures

Block Randomization

To ensure a balance in the sample size for each treatment arm during the participant recruitment phase, we will apply block randomization [59]. For a total of 150 recruited participants, we will generate 38 blocks of 4 participants per block with a 1:1 allocation ratio between the intervention and control arms. The randomization list and block allocation details will be generated using software provided by Sealed Envelope Ltd (2022)[] .

Stratification

We recognize that the level of standard clinical care, with respect to the scope and format of educational materials provided to patients undergoing TKA, may vary significantly between health care providers represented in the recruitment sites involved in the study, and this may influence expectations set by participants. In light of this, we will include “health care provider” as a stratification variable.

Replacements

Replacements will be enlisted if participants need to withdraw prior to their TKA taking place. To maintain the randomization ratio of 1:1, the replacement would be allocated to the same treatment arm of the withdrawn participant.

Data Collection Tools and Procedures

Online Data Collection and Centralized Data Repository

Screening logs

Screening logs will be maintained for all potential candidates being recruited to the study and will contain identifiable patient

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information. The file will be stored online as a password-protected file on the secure University of Newcastle server.

Deidentification of Patient Information

All consented participants will be allocated a study code comprising a patient ID number and their initials. All data collected in the study will be identifiable by the study code and remain deidentified during the data collection and analysis phases of the study.

Data Collection Platform

Study data will be collected and managed using the REDCap (Research Electronic Data Capture; Vanderbilt University) tools hosted at the Hunter Medical Research Institute [61,62]. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for data integration and interoperability with external sources.

REDCap study-specific access will be established, allowing secure access by the research team with all assessment tools formatted as online forms to enable direct data entry by the study participants. Participants will be sent an email from REDCap containing an encrypted link to their forms for completion. If participants request to complete hard copies of forms, these will be generated and posted to the participant by the study team, with the completed form data subsequently entered into the REDCap platform by a member of the study team.

Forms will be disseminated for completion at 3 distinct time points–prior to their TKA at study entry (baseline), following the education intervention, and 6 months following their TKA, as shown in Table 1.

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Table . Assessments to be undertaken in the randomized controlled trial and frequency of collection.

Measure (tools)	Study time points		
	Baseline	Post intervention	6 months post TKA[a]
Clinical and demographic details			
Patient-reported age, sex, highest level of education achieved, employment status, and diagnosis	✓		
Comorbidities			
Charlson Comorbidity Index [63]	✓		✓
Knee symptomology			
12-item short-form for the Knee Injury and Osteoarthritis Outcome Score [64]	✓		✓
Oxford Knee Score [65]	✓		✓
Forgotten Joint Score [66]			✓
Mood status (depression, anxiety, and stress)			
21-item Depression, Anxiety and Stress Scale [67,68]	✓		✓
Quality of life			
EQ-5D-5L [69]	✓		✓
Health literacy			
12-item European Health Literacy Survey Questionnaire [53]	✓		✓
Expectations			
Hospital for Special Surgery Total Knee Replacement Expectations Survey [34]	✓	✓	
Direct Questioning of Objectives Questionnaire Index [70]	✓	✓	
Activity expectations [30]	✓	✓	
Expectation fulfillment			
Hospital for Special Surgery Total Knee Replacement Expectations Survey			✓
Direct Questioning of Objectives Questionnaire			✓
Activity expectation satisfaction			✓
Satisfaction with outcomes			✓

[a]TKA: total knee arthroplasty.

Study Questionnaires

Comorbidities

We will use the Charlson Comorbidity Index, which provides a weighting to concomitant health conditions based on the nature of the condition and age of the individual and is used to predict 1-year mortality. The higher the score, the higher the mortality risk. We will apply the same 10 medical conditions and weightings used by Chaudry et al [63]. Participants will be asked to indicate if they experienced any of the 10 medical conditions provided, at study entry and at 6 months after TKA.

Knee Symptomology and Function

Symptomology of the affected knee that will undergo TKA will be assessed using the 12-item version of the Knee Injury and Osteoarthritis Outcome Score (KOOS-12) [64]. KOOS-12 is a 12-item measure derived from the original 42-item KOOS. KOOS-12 contains 4 KOOS pain items, 4 KOOS function (activities of daily living and sport/recreation) items, and 4 KOOS quality of life. Each item is rated using a 5-point Likert scale from 0 to 4, left to right, with 0 representing no knee problems and 4 representing extreme knee problems [64]. Items with lower scores are indicative of lesser symptoms, and higher scores reflect worse symptomology. Participants will be asked to complete a copy of this questionnaire at study entry and at 6 months after their surgery.

We will also apply the Oxford Knee Score (OKS) [65]. The OKS is a patient-reported outcome measure that consists of 12 questions about an individual's level of function, activities of daily living, and how they have been affected by pain over the preceding 4 weeks, before and after a total knee replacement. Each item is rated using a 5-point Likert scale from 0 to 4, with

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0 representing no knee problems and 4 representing extreme knee problems [65]. Items with lower scores are indicative of lesser symptoms, and higher scores reflect worse symptomology. In this study, the OKS will be applied at study entry and at 6 months after their surgery.

At 6 months following TKA, we will apply the Forgotten Joint Score (FJS) [66]. The FJS is a 12-item questionnaire concerning the participants' awareness of their artificial joint during activities of daily life [66]. For each question, the participant can choose between 6 response options, namely never (0 points), almost never (1 point), seldom (2 points), sometimes (3 points), and mostly (4 points). The summation of the scores is then divided by the number of items responded to. The mean score is multiplied by 25 to give a score from 0 to 100, which is then subtracted from 100. Larger scores are indicative of greater "forgetting" of the artificial joint.

Mood Status

The mood status of our study participants will be assessed using the 21-item Depression Anxiety Stress Scales (DASS-21) [67]. The full DASS and abbreviated DASS-21 have been validated to measure the 3 negative emotional states (ie, depression, anxiety, and stress) in research and clinical settings [68]. Each of the DASS-21 subscales contains 7 items. Participants will be asked to use 4-point severity/frequency scales to rate the extent to which they have experienced each state over the past week. Scores for depression, anxiety, and stress will be calculated by summing the scores for the relevant items. Higher scores are indicative of higher levels of symptoms. All scores derived from the 21-point scale will be multiplied by 2 to enable comparison to the full 42-point DASS and determine clinical cutoffs for symptom severity. In this study, participants will be asked to complete the DASS-21 questionnaire at study entry (prior to their TKA) and at 6 months after their surgery.

Quality of Life

The EQ-5D-5L was developed to describe and value health status across a wide range of disease areas [69]. The tool contains a short descriptive system of the respondent's health status and a visual analog scale to summarize health status (EQ-VAS). The descriptive system contains 5 dimensions, including mobility, self-care, usual activities, pain/discomfort, and anxiety and depression. Participants will choose the most appropriate severity of each dimension on a 5-point scale ranging from "no problems" to "unable to / extreme problems. A summary EQ-5D index score will be derived using dimension weightings from recent value sets described for the Australian population [71]. The EQ-VAS provides an overall current health rating score ranging from 100 (the best health) to 0 (the worst health). In this study, participants will be asked to complete the EQ-5D-5L questionnaire at study entry (prior to their TKA) and at 6 months after their surgery.

Health Literacy

Health literacy is defined as the degree to which individuals can obtain, process, understand, and communicate about health-related information needed to make informed health decisions [72]. In this study, we will assess participants' health literacy using the shortened version of the HLS-EU-Q12 [53]. Participants will be presented with a number of competencies encompassing information relating to health care, disease prevention, and health promotion and covering 4 cognitive domains, including proficiency in accessing, understanding, appraising, and applying health information. Respondents will rate the level of difficulty in undertaking each competency on a 4-point scale ranging from 1 (very difficult) to 4 (very easy), with higher total scores indicative of higher health literacy. In this study, participants will be asked to complete the HLS-EU-Q12 at study entry (prior to their TKA) and at 6 months after their surgery.

Expectations

As there is no current gold standard for characterizing patient expectations of TKA outcomes, we will be adopting a mixed methods approach and using both standardized self-report, closed-response surveys and open-ended questions to quantify patient expectations and changes in these expectations over time. To evaluate the change in expectations, all participants will be asked to complete the following questionnaires at study entry and following the intervention.

Hospital for Special Surgery Total Knee Replacement Expectations Survey

The HSS-TKR [34] is a closed response survey, which enables respondents to provide ratings for the importance of 17 common patient expectations of outcomes following TKA, including pain, physical function, and psychological items. Importance ratings range from 1 (very important) to 5 (does not apply). The survey quantifies the level of importance of common knee replacement patient expectations and has been applied in numerous studies [73].

Direct Questioning of Objectives Questionnaire

Methods comparable to those applied by Karunaratne et al [70], using open-ended questions related to participant expectations, will be applied. Participants will be asked to list at least 1 and up to 5 of their most important expectations of TKA surgical outcomes, and then an assessment will be given for two domains for each expectation on 11-point numerical rating scales: (1) the importance of each expectation and (2) the current ability to achieve the task / item. The reported values for importance and ability will be interpreted as "low" if ≤5, and "high" if ≥8. A Direct Questioning of Objectives Questionnaire Index (DQO Index) will be derived from the product of the score for each domain.

Activity Expectations

We will use an open-ended question to identify participant expectations relating to their most important activities they want to undertake following TKA [30]. Participants will be asked to identify 3 activities important to them to achieve following the TKA by responding to the following question:

> *What activities are you hoping to be able to do after your knee surgery that you cannot do now? (eg this could be an everyday life activity, employment or work activity, social activity, specific movement / motion or exercise etc.)*

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Proceeding With TKA

Following exposure to the education program (intervention arm) or standard care (control arm), all participants will be asked if they will be proceeding with their TKA and, if so, to confirm the date of the procedure.

Expectation Fulfillment

The level of expectation fulfillment or satisfaction to undertake goals identified will be determined at 6 months after TKA for participants who proceeded with surgery.

For the HSS-TKR items, participants will be asked to indicate the extent of fulfillment of the expectations, identified prior to surgery, using a 5-point Likert scale, ranging from 5 (completely) to 1 (not at all).

The DQO Index will be repeated post TKA, and differences with values obtained prior to TKA will be indicative of the ability to achieve the task.

For activity expectations identified in the pre-TKA assessment, participants will be asked to rate how satisfied they were that each activity could be undertaken using a 7-point Likert scale ranging from 1 (completely dissatisfied) to 7 (completely satisfied).

Satisfaction

At 6 months after the TKA, all participants who underwent surgery will be asked to respond to the following:

> *Overall, how would you describe the results of your operation?*

Participants will provide a response on a 5-point Likert scale, ranging from 1 (poor) to 5 (excellent).

Feedback Survey

A study participation evaluation survey will be included at the end of the study to enable participants to provide the research team with feedback regarding the intervention and assessments they were asked to undertake and the overall conduct of the study. It will also give study participants the opportunity to provide ideas for future areas of research they consider important to be addressed in recovery from TKA surgery. For those who did not proceed with undergoing a TKA, information will be collected regarding alternate treatment procedures they have undertaken.

Primary Outcome

The primary outcome of the trial will be a change in patient postsurgical expectation score (within individual patients' scores), derived from the HSS-TKR questionnaire, conducted prior to and following intervention exposure.

Secondary Outcomes

The following secondary outcomes will also be evaluated:

1. The number of participants who decide not to proceed with their TKA.
2. The level of patient expectation fulfillment derived from the HSS-TKR questionnaire, the DQO Index, and activity expectations, conducted 6 months after the TKA
3. The level of patient satisfaction with surgical outcomes assessed at 6 months after the TKA.
4. A change in patient health literacy (within individual patients' scores), derived from the HLS-EU-Q12, conducted at study entry and at 6 months after the TKA

Data Analysis

Stage 1

A Method Triangulation approach will be taken in the alpha testing of the developed educational program, encompassing the participant responses to the PEMAT-A/V survey and content analysis of structured interviews [74]. This will inform editing or adjustments to the prototype videos to enable the final version to be generated and evaluated in stage 2.

PEMAT-AV Tool

Two subscores will be derived from the provided survey ratings, including the understandability and actionability scores. These scores will be provided as the total points (agreement with the statements provided) for each domain, expressed as a percentage of the total possible points. Higher scores will be indicative of good understandability and clarity of the actionability of the information provided in the videos. The scores and responses provided for each statement in the survey will be used to formulate the topics addressed in the subsequent interview between the participant and the researcher.

Content Analysis of Qualitative Data

The interviews will be conducted by either research team member (KR or LS) during a 30-minute, one-to-one session with the research participant. Each interviewer will review the transcript and validate the content, such that it reflects the PEMAT-AV scores for each video. The content concepts will be identified to reflect the acceptability of the prototype videos or potential changes or edits that need to be considered by the research team. To assist with ensuring the dependability of the data, the interviewers will then review the content analysis undertaken by the other interviewer and again undertake their own validation and identification of content concepts for each transcript. Both interviewers will then meet and compare each one's content analysis and discuss until a consensus is reached. Coding will be undertaken such that classifiers will be applied to the common concepts identified across all transcripts. The interviewers will then determine if content saturation has been achieved or if additional participants will need to be recruited for the alpha testing.

Stage 2

Descriptive and inferential statistical analyses will be undertaken to describe the characteristics of the participant cohort and to assess the research hypotheses, respectively. Clinical and demographic characteristics will be described using proportions, measures of central tendency (eg, mean and median), and dispersion (eg, SD, IQR). Inferential statistics will be used to test for differences in, or associations between, outcome measures within and between groups of interest. Methods appropriate to both dependent and independent samples (eg, *t* test, ANOVA, and correlation) will be used, including nonparametric methods for data in violation of normality and

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variance assumptions (eg, Mann-Whitney *U* and Kruskal-Wallis). The threshold for statistical significance will be set at a *P* value of .05.

To determine the impact of the health education program to change expectations, the primary outcome measure (HSS-TKR) will be measured and compared between the 2 treatment arms. The within-patient changes of the open-ended measures of patient expectations between T_0 and T2 will also be compared between the 2 treatment arms to further inform the efficacy of the education platform intervention. We will use data from all participants post surgery to determine the association between expectation fulfillment and overall satisfaction. Activity expectation fulfillment satisfaction and overall procedure satisfaction generate ordinal datasets with associations between the 2 measures undertaken using Spearman rank correlation coefficients.

Ethical Considerations

Human Subject Ethics Review Approval

This research methodology was peer-reviewed by the Hunter Medical Research Institute-nib grant committee and approved by the School of Medicine and Public Health at the University of Newcastle, New South Wales, Australia, in accordance with the Australian Code for the Responsible Conduct of Research. The study will be conducted according to the National Statement on Ethical Conduct in Human Research (2023). Ethical approval was granted by the University of Newcastle Human Research Ethics Committee (approval ID H-2024‑0312) on January 7, 2025.

Informed Consent

All participants taking part in each stage of the study will provide written or electronic consent prior to undertaking any study-related activities. Participant involvement is completely voluntary, and they can choose to withdraw from the study at any time. If they decide to withdraw, they will be asked to notify the research team. The participant will be asked if they consent for any data already collected from them during their study involvement to be used by the research team in their data analysis, or if they prefer that on withdrawal all collected data be destroyed and no longer be accessible for analysis. They will also be asked to provide a reason for their withdrawal, but a response is not mandatory.

Privacy and Confidentiality

To enable participants to be contacted, identifiable contact details will be made available to the research team. All data collected and analyzed in both stages of the study will be deidentified. Patient data will be linked between different time points using a unique study code identifier allocated to each participant at the time of study enrollment. Master participant identification decoding records will be maintained and accessible by the chief investigator.

Compensation Details

All participants will take part in the study on a voluntary basis with no financial compensation provided.

Participant Identification

The deidentified data will be analyzed and presented in publications in scientific journals and at international/national conferences. All data will be presented at a group level, which means that no individual person will be able to be identified in any reports that are generated about the project. Individual participants will not be identifiable in any of the outputs generated from the research project, but individual anonymous responses may be quoted. Nonidentifiable data may be shared with other parties as part of a peer-review process to verify the robustness and integrity of the study or to contribute to further research and public knowledge.

Results

This study was funded by a grant from the Hunter Medical Research Institute provided by nib insurance in December 2024. We forecast enrolling participants to take part in the alpha testing of the education materials developed in stage 1 of the study in October 2025 to enable finalization of the education program in November 2025. Recruitment to the stage 2 randomized trial designed to evaluate the novel educational materials will take place from December 2025 to September 2026. Final results are expected by April 2027.

Discussion

Expected Outcomes

This study responds to the unmet clinical need to address the issue of improving the level of satisfaction experienced by patients following TKA surgery. With the anticipated significant increase in the number of these surgical procedures being performed annually over the next two decades, it is important to consider improving outcomes for a significant number of patients who potentially may experience outcomes that do not meet their expectations following TKA. As the level of satisfaction with surgical outcomes has been shown to be influenced by unmet goals and high expectations of outcomes set prior to surgery, our focus was to enhance the ability for patients to set expectations, which were realistically likely to be met and thereby improve their satisfaction with the outcomes achieved.

We will be engaging in a collaborative consultation process with key stakeholder groups, including consumer advocates and clinical and service provision staff, to support the development of meaningful and accessible education materials that will encourage patients undergoing TKA to set goals that are realistic. The efficacy of the developed educational program will be evaluated in its capacity to impact the expectations of patients undergoing TKA prior to surgery and the capacity to influence postsurgical expectation fulfillment, outcome satisfaction, and level of health literacy. The findings will inform future implementation strategies of the wider application of the educational materials developed.

Comparison With Prior Work

The approach adopted in this protocol builds upon existing research that has demonstrated the impact of unfulfilled

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expectations on patient satisfaction with outcomes following TKA. Previous studies have also indicated that Australian patients undergoing TKA set high expectations regarding TKA outcomes, with goals focused on achieving high physical impact pursuits following surgery [29,30]. While several studies have demonstrated the capacity of presurgical education interventions influencing patient expectations regarding TKA outcomes [35,37,75], widespread use of educational materials focusing on setting realistic expectations regarding surgical outcomes has not been adopted. This may, in part, be due to limitations in accurately characterizing patient expectations due to a lack of gold standards to capture this information. There is also a lack of quality educational materials being developed and distributed to patients undergoing TKA [76,77]. To address these issues, we will be using a multimodal approach to characterize patient expectations and expectation fulfillment by applying closed- and open-ended self-report tools to enhance the accuracy of identifying individual patient expectations and goals. We will also be using quantitative and qualitative methods in the alpha testing of the education materials developed with a TKA consumer cohort, which will enhance the quality of the materials being developed, and we will consider these findings to optimize the suitability of the final educational program to be applied. In our study, we will also be determining if our presurgical videos can impact participant health literacy. In a comparison of the influence of a single video presentation regarding osteoarthritis and recovery following total joint replacement in patients with orthopedic conditions compared to that obtained following a preoperative face-to-face consultation with their clinician [78], not only did the video significantly increase patient health literacy, but the level of knowledge improvement was greater than that achieved by those who underwent a preclinical consultation only.

Potential Impact and Clinical Implementation

If successful, the educational program developed in this study has the potential to impact TKA patient satisfaction with surgical outcomes through improvement of fulfillment of more realistic expectations being set prior to surgery. This will support a more patient-centric classification of surgical “success,” which extends beyond clinical parameters. Improved satisfaction may also reduce usage of health resources postoperatively. The findings will support a broader implementation strategy for a widespread application of the education materials in the clinical setting, which could encompass patients in both the private and public sectors, with the potential to improve patient health literacy and satisfaction with TKA on a large scale. Findings from this study may also influence preoperative processes for other orthopedic surgeries, including total hip replacement and other elective surgical procedures.

Strengths and Limitations

The strength of the design of the educational materials being developed and tested in this study is the collaborative approach we will be adopting through the involvement of key stakeholders including clinical, research, and consumer groups contributing to the content and format to be used. Alpha testing, involving a cohort of patients who have already undertaken TKA, will also ensure the suitability of the education materials for future patients undergoing TKA. The focus of the material will be specifically targeted at enabling patients to make an informed choice of what expectations they would like to be able to achieve following their TKA and that this expectation is realistic and likely to be achieved. While expectations fulfillment has consistently been associated with post-TKA satisfaction, we acknowledge that other factors may also impact patient satisfaction in our study cohort and, as such, are also measuring a number of clinical, demographic, and psychological patient features in our patient group to evaluate the impact of these covariates on satisfaction with postsurgical outcomes.

We have decided to adopt a mixed methods approach to characterize patient expectations and expectation fulfillment; however, for the purposes of powering our randomized controlled study, we have selected the HSS-TKR as our primary outcome measure. This measure was selected as it has been used to assess the efficacy of education interventions in other studies [35]. While the benefit of this approach enables quantification of expectation level and type to be derived from the provision of a closed-question format, it does limit the type of expectations being characterized to those provided in the survey. For this reason, we have also included a number of open-ended questions which enable the participants to define their own expectations and provide a more individualized approach to characterizing expectations.

Our TKA patient cohort is limited to patients in the private health sector, and we acknowledge that there may be differences in the demographics, clinical, and social features and health literacy of this patient group, compared with those in the public health sector, which may limit the translation of findings to a broader clinical group. In light of this, the findings from this study can be considered a pilot phase, which can inform future implementation of the educational materials developed in this study in a wider range of patients undergoing TKA. Moreover, we anticipate that it will be necessary for external validation of the findings for this study to be verified in a cohort of public patients prior to further implementation approaches being considered. In addition to ensuring equitable access to the educational materials developed, implementation strategies will need to consider the capacity for embedding materials into digital platforms accessible to the target patient population. Differences in cultural settings may also limit the generalizability of findings from this study. Previous studies conducted by our team [30] and findings by others [29] have shown that Australian patients undergoing TKA set high expectations and have goals to achieve high-impact physical activities following surgery, which indeed may not be reflected in other countries.

Future Directions

The findings from this study will inform future approaches to accurately characterize patient expectations of postsurgical outcomes following TKA. This will enhance shared decision-making and extend a more patient-centric approach to measures of success following TKA.

Although the findings from this study may be viewed as a part of a pilot phase, they can serve as a foundation for developing

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future implementation strategies to scale the targeted education program across a larger clinical cohort.

Conclusion

In conclusion, this study will develop innovative educational materials co-designed with key stakeholders to help patients undergoing TKA set realistic expectations for their postsurgical outcomes. By aligning expectations with achievable goals, the program aims to improve expectation fulfillment, enhance satisfaction, and empower patients. In addition, study findings will support shared decision-making practices and optimize rehabilitation programs, ensuring that patients receive the right care at the right time to achieve their individual goals.

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Conflicts of Interest

None declared.

Checklist 1
COREQ checklist.
[PDF File, 448 KB - resprot_v14i1e71898_app1.pdf]

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Abbreviations

DASS-21: 21-item Depression, Anxiety Stress Scale
DQO Index: Direct Questioning of Objectives Questionnaire Index
FJS: Forgotten Joint Score
HLS-EU-Q12: 12-item European Health Literacy Survey Questionnaire
HSS-TKR: Hospital for Special Surgery Total Knee Replacement Expectations Survey
KOOS-12: 12-item Knee Injury and Osteoarthritis Outcome Score

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OKS: Oxford Knee Score
PEMAT-A/V: Patient Education Materials Assessment Tool—Audio Visual
REDCap : Research Electronic Data Capture
SCT: social cognitive theory
TKA: total knee arthroplasty

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Protocol

Virtual Reality–Based Psychological Intervention for Young Adults Living With HIV: Protocol for a Randomized Controlled Trial

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Abstract

Background: Young adults (15-24 years old) living with HIV may experience pressure both from HIV infection and social role change problems, resulting in a series of psychological problems such as depression and anxiety. Effective psychological intervention can improve their mental health and quality of life.

Objective: The study aims to explore the effectiveness of VR-based mental intervention on young adults living with HIV. The application and advantages of virtual reality (VR) in children's psychotherapy provide new ideas for psychological intervention for young adults living with HIV.

Methods: We use the qualitative interviews and questionnaire results as well as guided by classical psychotherapy to create a personalized psychological intervention system for young adults living with HIV through VR technology, which is based on the long-term AIDS treatment cohort and infectious diseases cohort of children. We use the mental scales and biochemical indexes as the outcomes, conducting a prospective randomized controlled trial to verify the feasibility and effectiveness of the VR psychological intervention system.

Results: The study began enrollment in September 2023. To date, 160 participants have finished the baseline questionnaires.

Conclusions: The study results might provide a scientific basis for accurate psychological treatment among young adults living with HIV in the future.

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KEYWORDS

HIV; young adults; mental health; virtual reality; VR; psychological intervention; depression; anxiety; living with HIV; privacy; mental health; intervention

Introduction

According to the latest data from the joint United Nations Program on HIV/AIDS (UNAIDS), an average of about 4000 people were newly diagnosed with HIV globally per day in 2021. Young people aged 15-24 years old accounted for 31% of new HIV infections. In the Asia-Pacific region, about 260,000 young people were newly diagnosed with HIV in 2021, accounting for 17.3% of the global increase, second only to Africa [1]. The mental health of people living with HIV/AIDS is an important part of the quality of life, and infection-related stigma makes people living with HIV/AIDS face 2-3 times more anxiety and depression than the general population [2-4]. Young people living with HIV face pressure from social adaptation, such as personal growth and role change, as well as disease pressure caused by the incurability and stigma of HIV infection [5]. Studies on young people aged 10-24 years old living with HIV showed that 21% of them had depression symptoms and 14% had anxiety, and the proportion interval of suicidal ideation was from 4.4% to 24.4%, and those with long-term suicidal ideation ranged from 9.26% to 33.33% [6-9]. So, how to carry out effective psychological intervention for young people living with HIV is very important.

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There are many forms of psychological intervention, and numerous interventions are intended to support mental health, mainly by way of face-to-face and group-based intervention, internet intervention, and mobile remote intervention. Regardless of the form of psychological intervention, it is based on the theoretical framework or theoretical basis. Common theoretical bases include cognitive behavioral therapy (CBT) and dialectical behavior therapy (DBT) [10]. Previous studies proved the effectiveness of CBT or DBT in the way of face-to-face intervention. Synder et al [11] conducted a group-based psychological intervention study on people living with HIV aged between 16 and 24 years of CBT. The results showed that the self-perceived social support of the intervention group was higher than that of the control group, but the difference was not statistically significant (P=.20) [11]. Bedics et al [12] conducted a 1-year DBT treatment on 101 women with borderline personality disorder, which showed that DBT therapy could reduce suicidal behaviors and nonsuicidal self-injury behaviors. Burton et al [13] conducted a psychological intervention with DBT therapy, suggesting that the depression clinical scores had improved of the participants in the intervention group. DBT therapy has achieved some effects in helping improve behavioral problems in children [14] and alcohol problems among college students [15]. However, face-to-face and group-based CBT or DBT needs to be carried out by professionals, and the existing qualified health care providers and infrastructures are limited in meeting the challenge in China.

Studies in developed countries have shown the feasibility and efficacy of using mHealth to provide counseling and services to improve mental health in diverse populations. Mohr et al [16] conducted a self-control psychological intervention in the general population by mobile phone, and the results showed that depression and anxiety decreased over time [16]. The research team conducted a randomized controlled psychological intervention trial on 300 adults living with HIV on the WeChat public platform. At 3 and 6 months after the intervention, the depression level and suicide ideation rate of the experimental group were reduced compared with the control group (P=.02) [17,18]. However, there is no study focusing on mental intervention among young people living with HIV. At the same time, studies showed that compliance with remote Internet or mobile phone intervention is poor, and patients are unable to concentrate during the intervention process, which makes it difficult to ensure the effective implementation of the intervention.

Virtual reality (VR) provides a variety of sensory stimuli to people through the computer-generated virtual environment, enabling people to interact with the virtual environment naturally to achieve a sense of immersion and experience in the real environment [19]. Falconer et al [20] used VR technology to set virtual scenes to treat patients with depression and found that the depression decreased after the intervention, and the improvement effect was still maintained one month after the end of the experiment. Based on the mindfulness-based program (MBP), Modrego-Alarcón et al [21] conducted a study on the stress level of 280 college students through VR equipment. The results showed that the experimental group had increased relaxation and decreased stress levels compared with the control group (P=.006) [21]. Navarro-Haro et al [22] combined DBT therapy with VR to guide mindfulness training. The results showed that the impulse to commit suicide, self-harm, give up treatment, and use drugs in the experimental group was reduced after the intervention [22]. However, most of the existing studies are small-scale pilot studies on general adults or adolescents with adverse psychological conditions, and there is little study on young people living with HIV.

In summary, the proposed study intends to address the issues of prevalent mental health problems in young people living with HIV and to innovatively use VR to provide integrated and culturally appropriate intervention for mental health improvement.

Methods

Goal and Objectives

The objectives of the project are (1) using DBT as the theoretical framework, based on VR technology to carry out the individualized psychological intervention for young people living with HIV; and (2) A 1:1 prospective randomized controlled trial (RCT) will be conducted to verify the effectiveness of VR psychological intervention on reducing depression and anxiety in young people living with HIV.

Intervention Design

Development of A VR Intervention System

Content of the Intervention

The proposed study is guided by DBT and combined with the actual needs and unique characteristics of young people living with HIV to develop a specialized psychological intervention system suitable for the characteristics of this population.

The actual needs of mental health among young people living with HIV were collected based on literature and qualitative interviews with young people living with HIV. The outline of the qualitative interview mainly included (1) basic information and (2) The main source of stress (infection, drug side-effect, income, life expectancy).

Study subjects in the experimental group received 2 modules of psychological intervention. Module 1 was the basic intervention module, mainly the DBT treatment course, which covers 4 parts: mindfulness, distress tolerance, emotional regulation, and interpersonal effectiveness. The second module is a flexible intervention module applicable to the actual needs of young people living with HIV. As shown in Figure 1.

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Figure 1. Psychological intervention content in the experimental group. MOOC: Massive Open Online Courses. DBT: dialectical behavior therapy.

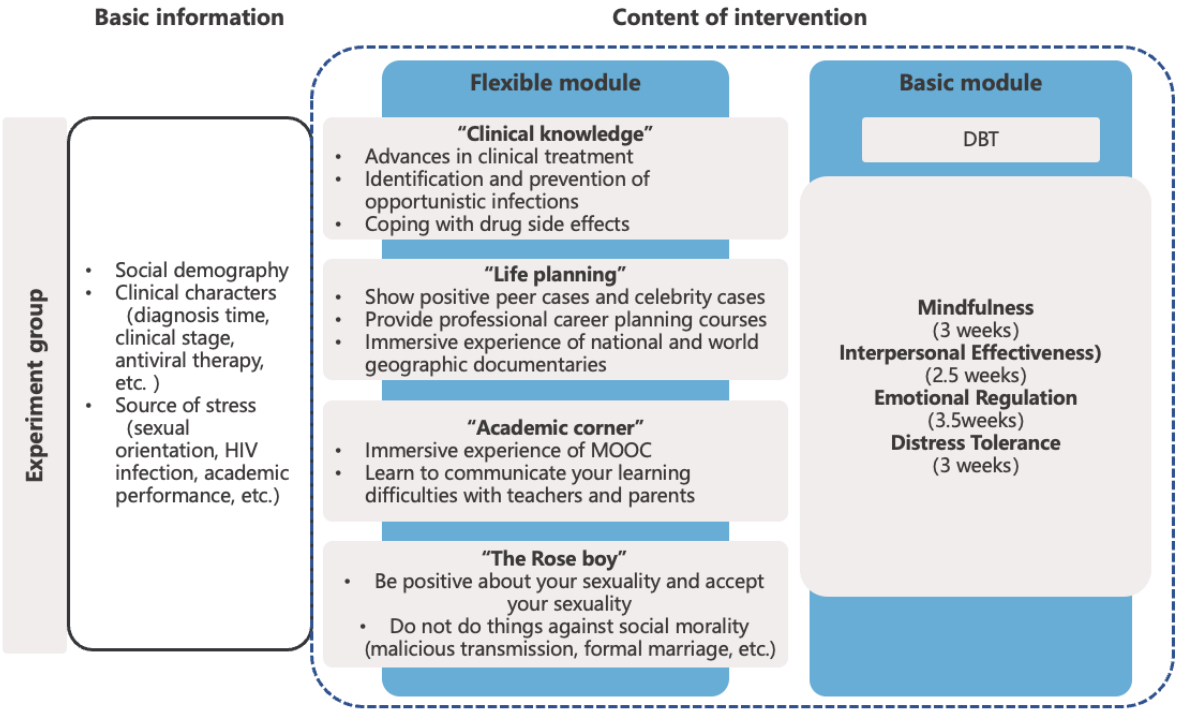

Intervention Delivery

We set up a user management platform as the support for the intervention. The function of the platform included (1) information management: a complete record with a unique number is generated when each research object is enrolled. The researcher is the system administrator and can add and modify the relevant information of the patient, such as fixed number, basic personal information (deprivatized), clinical and therapeutic information, psychological assessment scale, etc. The system is associated with the VR intervention software, which can record and synchronize the completion of the intervention course of the research object, and the administrator can view and export the corresponding data through the number.

(2) Upload and update intervention resources: the intervention content involved in VR software forms a "resource library" in the management system, and the user portrait is generated when the subject is enrolled in the corresponding intervention content. The user portrait is the virtualization of real users and the category of research objects extracted; that is, the entire psychological intervention system is a big picture. Against this background, different types of subjects receive psychological intervention corresponding to their characteristics to achieve personalized customization. In the course of the experiment, the researchers continuously improved and updated the intervention resources.

(3) The intervention goal setting and process supervision: researchers use motivation type interview (motivational interviewing [MI]) to help subjects set up goals, regularly to supervise the completion of the intervention for subjects, and set a message to remind, intervention to ensure compliance.

VR Application Development

VR application development mainly includes 3 stages. First, Scene design is a virtual scene in which the participants experience psychological intervention therapy. This study mainly includes 2 scenes: natural landscape and indoor landscape. The natural landscape was used as the environment for participants to immerse in mindfulness and other skills training. The indoor landscape, including the home environment and the consultation environment, was used for the explanation and learning of psychological intervention courses. Second, regarding interface design, this study follows the principle of consistency of interface structure and style, choosing simple graphical design language and interface style with comfort and color sense. The icon uses a simple 2-dimensional graphic simulation to represent the functional form, which is convenient for the participant to identify and quickly associate the icon function, reducing the possibility of wrong selection. Third, interaction design refers to the use of VR hardware devices such as glasses and gamepads to realize the interaction of subjects in the scene. For example, when the participant enters the "family scene," he or she can move freely and roam in panorama; through the button control of indoor lighting and curtains, choose the bedroom, living room, consulting room, etc, to carry out the study of psychological courses. As shown in Figure 2.

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Figure 2. Virtual reality (VR) system development.

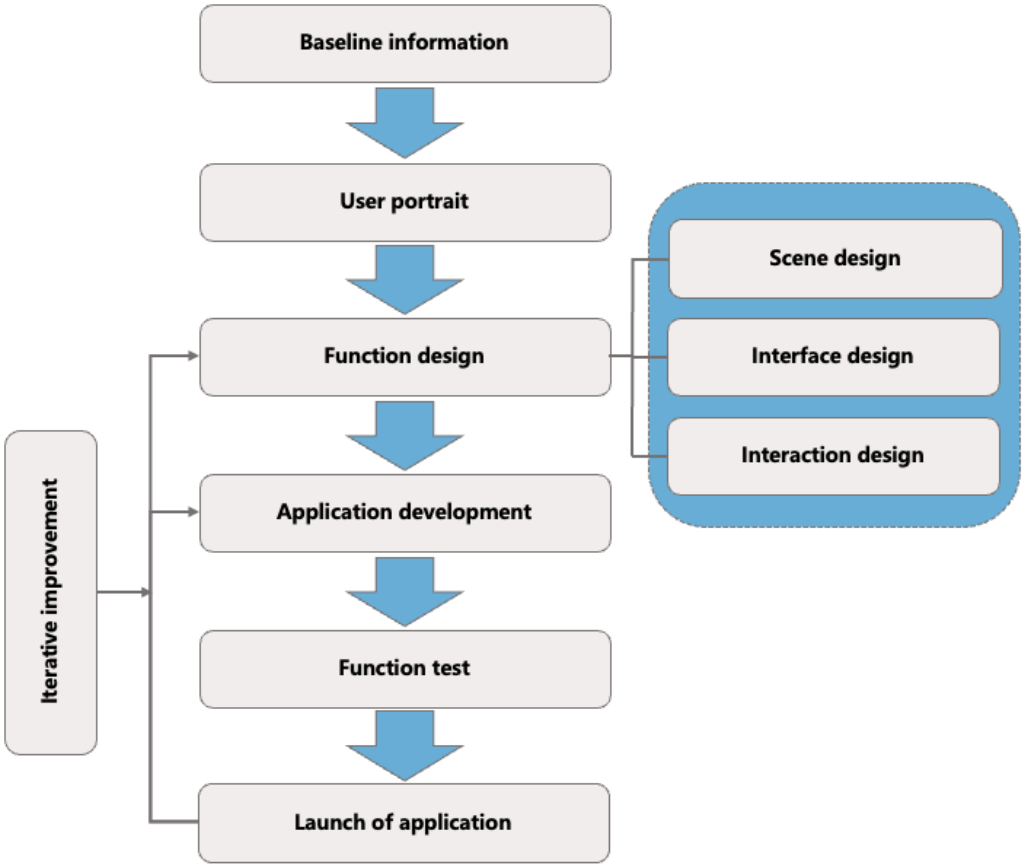

Verify the Effectiveness of VR Psychological Intervention

A 1:1 RCT will be conducted to verify the effectiveness of VR psychological intervention in reducing depression and anxiety in young people living with HIV. The RCT was not possible to blind the participants. The study lasted for 12 months. According to the inclusion and exclusion criteria, the participants are randomly divided into an experimental group and a control group. The experimental group received VR psychological intervention for 3 months, and the control group received non-VR mobile phone intervention for the same period. Data will be collected at 5 time points: baseline, postintervention, 3 months, 6 months, and 9 months after intervention, as shown in Figure 3.

Figure 3. The process of the intervention. PHQ-9: Patient Health Questionnaire-9. VR: virtual reality. DBT: dialectical behavior therapy.

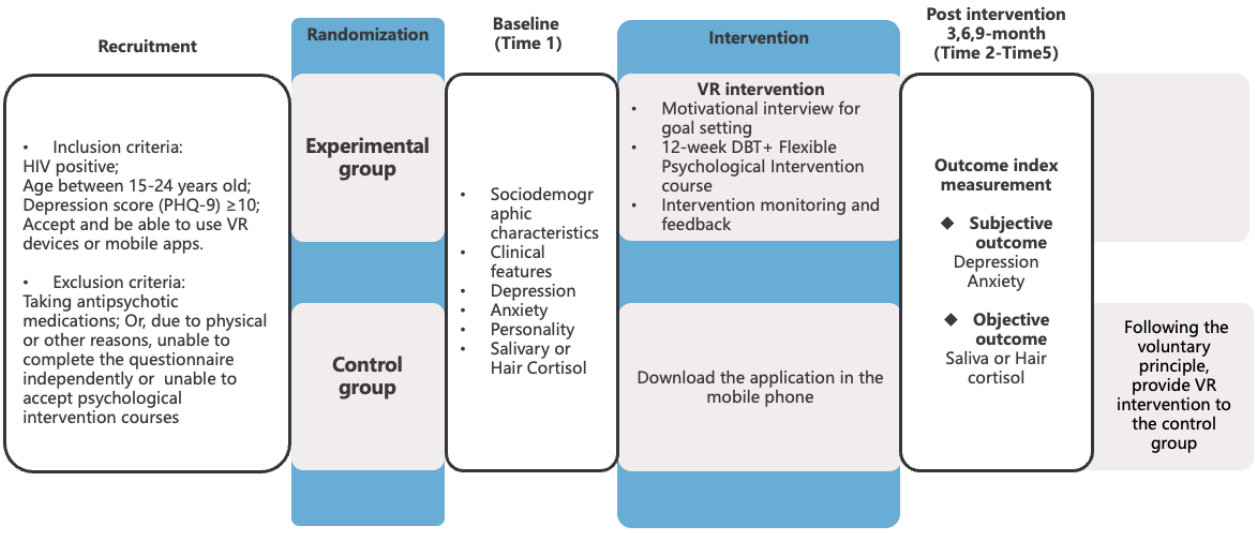

Measurement

Depression score was measured by the Patient Health Questionnaire-9 (PHQ-9). PHQ-9 is shorter but has demonstrated both good reliability and validity in the Chinese populations [23,24]. The scale consists of 9 items, such as "Little interest or pleasure in doing things" and "Feeling down,

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depressed, or hopeless," to measure the depressive status of the participants over the previous 2 weeks. Each item was rated on a 4-point Likert scale ranging from 0 (not at all) to 3 (nearly every day), providing a 0 to 27 total severity score, with higher scores indicating increased depressive symptoms [25].

Anxiety was measured by the Self-rating Anxiety Scale (SAS) that assesses anxiety in the last week with the Chinese version [26,27]. SAS has 20 items with responses of a 4-point Likert scale (1="never or rarely," 2="sometimes," 3="most of the time," 4="almost every day"). The total score ranges from 20-80, with 50 as a cutoff point, 50-59 being considered mild anxiety, 60-69 as moderate anxiety, and ≥70 as severe anxiety.

Study Participants

Inclusion criteria were a positive HIV test, age 15-24 years, depression score (PHQ-9)≥10 (with depressive symptoms), accepting and being able to use VR devices or mobile apps. Exclusion criteria were taking antipsychotic drugs or, for physical or other reasons, being unable to complete surveys or questionnaires independently, or being unable to accept psychological intervention courses.

Recruitment

The recruitment location is mainly based on Beijing Ditan Hospital Capital Medical University, which is treating 11,735 people in 2023. After clinic doctors have completed all the treatment procedures, researchers will distribute research leaflets to them to introduce the research project and invite them to participate. If the young people living with HIV agree to participate, the program's researchers will invite the participants to a separate room to be screened for enrollment conditions.

The staff will present the informed consent form of this study and inform the content of the informed consent form, including the introduction of the project, the benefits and possible risks of participating in this study, and the voluntary principle. The research subjects will be asked to sign the informed consent form after they have fully understood it.

Baseline Information Collection

The collection of baseline information in this study included 2 items: filling out questionnaires and retaining biological samples. A self-designed questionnaire was used to collect baseline information, including sociodemographic characteristics, medication and treatment information, clinical indicators, and mental health scale evaluation. The electronic questionnaire data can be downloaded directly, which is convenient to timely grasp or correct the information of infected people enrolled on the same day, and ensure the quality of data. To facilitate data collection, improve work efficiency, and improve data collection quality, electronic questionnaires were used at baseline and 3 follow-up visits.

Sample Size Calculation and Group Randomization

The sample size was calculated according to depression, the main outcome indicator of this study. Participants with PHQ-9 depression scale score ≥10 were classified as having depressive symptoms. It is expected that after intervention, the proportion of depression in the intervention group will be reduced by 20% compared with that in the control group. A bilateral test with a sample size ratio of the test group and control group as 1:1, test efficacy (1-β) as 0.9, and α as .05 was adopted, and a loss rate of 20% is expected. Through the calculation of PASS software (NCSS), 145 study subjects need to be included, and finally, 160 study subjects are rounded up, including 80 in the experimental group and 80 in the control group.

To ensure the balance between the experimental group and the control group, the block randomization method was adopted, code was written in R (R Foundation for Statistical Computing), random numbers were generated according to random seeds, and randomization was carried out to make the allocation of each treatment group more balanced and meet the research requirements. According to the order in which the subjects were enrolled, each participant was given a random number generated by the above random scheme. According to the group corresponding to the random number, the subjects were randomly assigned to the experimental group and the control group.

Quality Control

To improve the compliance of young people living with HIV, this study conducted regular telephone communication with the permission of the study subjects based on unified management through the user management platform to understand the intervention and treatment of the study subjects and give more humanistic care.

To ensure privacy and reduce reporting bias, this study was conducted anonymously, and the VR intervention was free during the study. The fixed and unique number assigned to each research subject when they were enrolled was used as the basis for information matching. After each collection of questionnaires, data was downloaded and backed up on the same day, and the questionnaire platform data was deleted in time. The downloaded questionnaires were formed into a special database and stored encrypted in an unconnected computer for safekeeping by the project leader. At the same time, the VR intervention software and the intervention program of the control group are regularly maintained, network security is regularly checked, user information is protected in many aspects, and security information is set in the application, such as adding mobile phone number association, email association, secret security issues, and the relevant computer professionals are supervised.

Statistical Analysis

Quantitative data were analyzed using SD or demographic characteristics of composition comparison baseline. The *t* test, ANOVA, or rank sum test were used for hypothesis testing of quantitative data. The chi-square test or Fisher exact probability method was used to test the hypothesis of qualitative data. The effect size would also be calculated. In this study, the intervention effect of the VR psychological intervention system was analyzed using generalized estimating equations (GEE). During the follow-up, the attrition diagram in each group would be plotted over time. In this study, binary classification PHQ-9 is used as the outcome variable, which belongs to longitudinal data, and there is a certain correlation between the data. When conducting statistical analysis of such data, the data correlation should be fully considered. Therefore, GEE was used to analyze

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the intervention effect to correct for the correlation between data caused by repeated measurements at multiple time points.

Study Significance

The clinical cohort supported by this study is a long-term antiviral treatment cohort, which can ensure the sample size and representativeness of the enrolled participants. The research team includes experts and scholars from various disciplines, including epidemiology and health statistics, clinical medicine, psychology, computer science, technology, etc, to provide professional guidance for the design of a psychological intervention department and the implementation of mental health intervention. The case managers in the research team are from Beijing Red Ribbon Home and have rich experience in providing psychological support for people living with HIV. The Home of Red Ribbon was previously known as the Home of Red Ribbon of Beijing Ditan Hospital, which was established in 1999. On January 5, 2005, the Home of Red Ribbon was registered with the Beijing Municipal Civil Affairs Bureau as the first civil society organization in China specializing in comprehensive HIV/AIDS care. It has 6 independent branches focusing on medical support, self-help of HIV-positive people, volunteer service, social assistance, online publicity, and legal aid. Its purpose is to provide comprehensive support and services for people living with HIV by pooling strength from all social strata, carrying out a variety of HIV prevention and control measures, and health awareness campaigns for enhanced public understanding of HIV.

This study innovatively applied modern VR technology to psychological intervention for young people living with HIV, which provides a new idea for our country to carry out psychological treatment. As a special group, people living with HIV are in urgent need of effective psychological guidance and sensitivity for privacy. This study combines VR technology with psychological intervention, uses an immersive 3D virtual environment to overcome the disadvantages of 2D mobile phone intervention, and avoids the privacy exposure that may be caused by offline medical treatment. It can provide data support and a scientific basis for solving the mental health problems of young people living with HIV in the future.

Ethical Considerations

This study was part of a research project that had been approved by the ethics committee of Beijing Ditan Hospital of Capital Medical University (Approval number: 2024-012). All individual participants were provided oral informed consent at the time of enrolment.

Results

This study was funded by the Capital Medical University Research Development Fund (grant PYZ22138) in April 2023. The enrollment started in September 2023. The data analysis is expected to be finished in April 2025.

Discussion

This study innovatively transcends traditional intervention models to conduct a prospective randomized controlled trial of VR-based psychological intervention for young people living with HIV in China. The research results will provide the effectiveness of VR-based mental intervention among young people living with HIV.

This research might provide yields practical data that advocates for the integration of mental health services into the standardized treatment model for HIV, as well as the wider implementation of psychological intervention services within domestic HIV-designated medical institutions and other health care facilities lacking specialized psychological consultation clinics.

The limitation of the study was that the population involved in this study mainly were young people living with HIV, which might cause a selection bias. However, young HIV-positive people were a group with a high proportion of HIV prevalence in China, so the study results still were representative of the effectiveness of the VR intervention and had good prospects of the intervention expanding in China.

The study population needs to be expanded to include people with chronic diseases to achieve effective mental intervention based on VR technology in the future.

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Data Availability

The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

HZ wrote the first draft of the manuscript. YS and JH conducted the field research management and collected field study data. HZ, Zhao H, and FZ critically reviewed and edited the manuscript. The author group was entirely responsible for study design, data collection, and data analysis. We declare that all authors have read and approved the final manuscript.

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Conflicts of Interest

None declared.

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Abbreviations

CBT: cognitive behavioral therapy
DBT: dialectical behavior therapy
GEE: generalized estimating equations
MBP: mindfulness-based program
MI: motivational interviewing
PHQ-9: Patient Health Questionnaire-9
RCT: randomized controlled trial
SAS: Self-rating Anxiety Scale
UNAIDS: United Nations Program on HIV/AIDS
VR: virtual reality

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Protocol

At-Home Immersive Virtual Reality Exergames to Reduce Cardiometabolic Risk Among Office Workers: Protocol for a Randomized Controlled Trial

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Abstract

Background: The worldwide rise in the prevalence of noncommunicable diseases has increased the recognition of the need to identify modifiable risk factors for preventing and managing these diseases. The office worker, as a representative group of physically inactive workers, is exposed to risk factors for metabolic syndrome, which is a primary driver of noncommunicable diseases. The use of virtual reality (VR) exergames may offer a potential solution to the problem of increasing noncommunicable disease prevalence, as it can help individuals increase their physical activity levels while providing a more immersive experience.

Objective: This exploratory study aims to examine the interventional efficacy of at-home immersive VR exergames on metabolic syndrome biomarkers among office workers. Additionally, it seeks to investigate the impacts of at-home immersive VR exergames on the active and sedentary behaviors of office workers.

Methods: A 3-arm, single-blinded pilot randomized controlled trial will be conducted to examine the therapeutic effects of at-home immersive VR exergames. A total of 120 Chinese office workers, engaging in less than 150 minutes per week of moderate to vigorous intensity physical activity, will be recruited via a convenience sampling method. The participants, who will be tested over a 12-week period, will be randomly assigned to one of three groups: (1) the VR exergame intervention group, (2) the regular physical activity control group, and (3) the nonexercise control group. Throughout the 12-week trial, three categories of variables will be collected across the three groups: clinical risk factors associated with metabolic syndrome, active and sedentary behaviors, and demographics. To analyze variance among the groups, a mixed linear model will be applied to assess the efficacy of each group. Differences in metabolic syndrome clinical risk factors among all groups will be used to evaluate the effects of at-home

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immersive VR exergames. Changes in active and sedentary behaviors will also be used to determine the impacts of VR exergames on metabolic syndrome.

Results: The ethics committee of Guangzhou University, China, approved this study on September 25, 2024. Participant recruitment will begin in early 2025 and continue for approximately 3 months. Data will be analyzed after the 12-week trial is completed, with full results expected to be presented in early 2026.

Conclusions: This study explores an emerging topic by applying an at-home immersive VR exergame intervention, potentially contributing to understanding the effects of an exergame program on metabolic syndrome risk among office workers.

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International Registered Report Identifier (IRRID): PRR1-10.2196/64560

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KEYWORDS

metabolic syndrome; noncommunicable diseases; active video game; interactive virtual reality environment; physical activity; workplace health; at-home intervention

Introduction

Noncommunicable diseases, such as cancer, cardiovascular diseases, diabetes, and heart disease, constitute the foremost cause of death internationally [1]. Noncommunicable diseases accounted for 63% or 36 million global deaths in 2008, which increased to 74% in 2019 [2,3]. The increasing prevalence of noncommunicable disease deaths worldwide has increased the need to identify modifiable risks in preventing and managing these diseases.

Metabolic syndrome is a common chronic disease characterized by the co-occurrence of several major biomarkers, including high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), impaired fasting glucose, insulin, triglycerides, blood pressure, waist circumference, and BMI [4,5]. Moreover, as a route to many noncommunicable diseases, such as cancer, cardiovascular diseases, and type 2 diabetes [6-8], metabolic syndrome plays a pivotal role in health status. For example, several systematic reviews have shown that individuals with metabolic syndrome are approximately two to five times more susceptible to developing cardiovascular disease and type 2 diabetes [9-11]. Although metabolic syndrome is one of the threats to a healthy life [12], its prevalence is increasing globally [13]. For example, a study conducted in the United States reported an increase of more than 35% in the prevalence of metabolic syndrome among US adults from 1988-1994 to 2007-2012 [14]. A systematic review reported that approximately 20% of the adult population in most Asian Pacific countries is struggling with a metabolic syndrome epidemic [15]. However, as an effective approach to mitigate the risk and treatment of metabolic syndrome, physical activity is facing a worrisome status across all countries [16,17].

Employed adults, the largest population in the world, spend a large portion of their waking time in the workplace [18,19]. Especially in desk-based workplaces, most of this time is spent sitting [20-22]. For example, in desk-based workplaces, Japanese workers spend approximately 70% of their time sitting with a low level of physical activity [23]. With the ongoing advancement of technology, the worldwide phenomenon of physical inactivity among employed adults has been occurring increasingly in recent decades [24]. An example study conducted in China revealed that the energy expenditure of occupational activity decreased by more than 22% and that the energy expenditure of domestic activity decreased by more than 51% over 9 years [25]. Other studies in the United States reported a steadily increasing trend of low-activity occupations of 76% from 1950 to 2000 [26] and a decreasing occupation-related caloric expenditure of more than 124 calories per day from 1960 to 2008 [27]. Prolonged sitting time adversely affects cardiometabolic health among office workers, an already at-risk population for metabolic syndrome [28]. For example, a study conducted in Central Iran reported that approximately 36% of office workers had metabolic syndrome [29]. Other studies have revealed that approximately one in ten office workers are at risk of metabolic syndrome in Korea [30] and Great Britain [31]. Physical activity promotion interventions have a strong positive impact on people with metabolic syndrome [32]. Nevertheless, several factors, such as the nature of the job and lack of motivation and time [33-35] for exercise, remain key barriers for office workers to adhere to an active lifestyle. Consequently, gym attendance rates are low even among people paying for membership [36], and more than 75% of people fail to keep their health target for more than 3 years [37].

Exergames are defined as video games that require players to be physically engaged in them to play [38,39]. Several systematic and narrative reviews have provided preliminary evidence for the correlations between playing exergames and users' physical activities [40,41]. For example, the contribution of exergames to increasing older adults' health and wellness through physical activity has been validated [41]. Previous studies have demonstrated that exergames can be used as interventions to increase physical activity, particularly among obese individuals [42]. With the ongoing advancement of virtual reality (VR) technology, exergames have become more immersive for users. The concept of immersion is defined as "users' engagement with a VR system that results in being in a flow state" [43]. Owing to the technology limitations of conventional VR, several shortages have been presented to users, such as difficulty in producing dynamic natural environments and interaction deficiencies in human-environment simulations. In contrast, with the development of visualizations and interactions with virtual environments, new immersive VR methods can address these limitations and lead to more accurate

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and efficient virtual environment assessments [44]. Additionally, its new application in exergame areas has already shown potential for promoting the health and well-being of some disabled youth [45]. Nevertheless, research on the health impact of immersive exergames remains rare. A search of the terms "immersive exergame" or "video game," "physical activity" or "exercise," "cardiometabolic" or "metabolic syndrome," and "office worker" produced 0 results in the Scopus database as of May 6, 2024 [46]. Thus, using immersive exergames to promote physical activity in relation to cardiometabolic health is still in its infancy among office workers, with a need for increased knowledge about this topic. Therefore, as the first randomized controlled trial (RCT), to the best of our knowledge, the purpose of this study is to examine the effects of at-home immersive VR exergames on clinical risk factors among office workers, an already at-risk population for metabolic syndrome.

Methods

Study Design

RCTs, a top-level research methodology in the area of evidence-based medicine [47], have played a significant role in evaluating the effects of lifestyle changes on metabolic syndrome [48-50]. This protocol is a longitudinal pilot study that uses a 3-arm parallel-group RCT to examine the interventional efficacy of an at-home immersive VR exergame on several clinical risk factors of metabolic syndrome among office workers. On the basis of prior research on exercise and physical activity interventions [48,51], a 12-week duration was selected for this trial, as it is a commonly used period for evaluating the efficacy of interventions targeting metabolic syndrome. Several clinical risk factors for metabolic syndrome, as well as active and sedentary behavior, will be monitored in three stages during this 12-week trial. Stage 1 will be at the start of the trial, Stage 2 at week 6, and Stage 3 at the end of the trial. The therapeutic effects of the at-home immersive VR exergame intervention for metabolic syndrome will be evaluated by comparing these risk factors among three groups: the VR exergame intervention group, the regular physical activity control group, and the nonexercise control group. The study follows two checklists: the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials Statement for Randomized Controlled Trials of Electronic and Mobile Health Applications and Online TeleHealth) [52] and the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials; Multimedia Appendices 1 and 2) [53,54].

Participant Recruitment

For this exploratory study, a convenience sampling method will be used to recruit 120 office workers from six office-oriented information technology companies in Guangzhou City, Guangdong Province, located in Southern China. This group represents a high proportion of physically inactive individuals [55,56] and is at greater risk of developing metabolic syndrome [56-58]. Recruitment emails will be sent to participants via the Tencent Enterprise Mailbox [59], a platform that allows companies to create email accounts with their corporate domain. This platform serves as a communication and office tool to support enterprises in providing unified notifications to office workers and to support office workers in providing timely and efficient feedback. The inclusion criteria for participants are office workers who are 16-60 years old (based on the standard age of the Labor Law of the People's Republic of China), capable of standing and exercising, and have no history of heart disease, cancer, or dementia. Additionally, participants should be interested in playing with the exergames and willing to adhere to a 12-week intervention exergame treatment because of the nature of the trial.

This research aims to examine the effects of at-home immersive VR exergames on the clinical risk factors for metabolic syndrome. Hence, individuals who are already engaged in more than 150 minutes per week of moderate to vigorous intensity physical activity will be excluded [60]. Additionally, pharmacological treatments, such as metabolic syndrome–related medicines (insulin sensitizers and biguanides, orlistat, sibutramine, etc), some surgeries (bariatric surgery), and traditional Chinese medicine (herbal medicine of ginseng, berberine, bitter melon, etc), are the other exclusion criteria because of their potential to influence cardiometabolic outcomes [61,62].

First, to encourage participation, some basic information related to exercise for health and immersive VR exergames will be introduced to potential participants. After a detailed explanation of what is needed during the trial, a precheck of the inclusion and exclusion criteria will be asked to identify eligible participants. Then, participants who meet the criteria will be instructed to review the information and provide informed consent and assent for this study. Given the nature of the clinical risk factors to be collected, a data collection center will be arranged at a cooperative clinic, and its address will be shared with all the participants for data collection and allocation of experimental equipment and material at the start of the trial.

Intervention and Control Groups

Following RCT guidelines [63,64], participants will be randomized into three equal groups: (1) the at-home immersive VR exergame intervention group, (2) the regular physical activity control group, and (3) the nonexercise control group. Including both the regular physical activity and nonexercise control groups will help determine whether VR exergame intervention offers unique benefits beyond those achieved through traditional exercise or no intervention. This design allows us to isolate the specific effects of immersive VR exergames. The at-home immersive VR exergame intervention includes a 12-week trial of exercise using Meta Quest 2, as shown in Figure 1. The Meta Quest 2 device is a valid tool that has been used in previous studies to support physical activity [65-68]. A VR headset and 2 handheld controllers are contained in the Meta Quest 2 set. Several active aerobic game apps will be installed on headset devices. These apps include the following [69]: Beat Saber (exercise: full-body, aerobic), Synth Riders (exercise: dance, aerobic), OhShape (exercise: dance, aerobic), Ragnarock (exercise: arms, shoulders, aerobic), Dance Central (exercise: dance, aerobic), Until You Fall (exercise: back, shoulders, arms, aerobic), In Death: Unchained (exercise: arms and shoulders, endurance/aerobic), and Space Pirate Trainer (exercise: full-body, aerobic). In these immersive games, the

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users can present their body movements in the game world from a first-person perspective. Moreover, they are all designed to motivate users to participate in physical movements with various categories of motivational affordances. For example, Beat Saber is a rhythm game in which users need to move their bodies to slice blocks at an exact angle. Physical activities such as arm waving, moving, and squatting with an accelerating speed are motivated in the game with affordances of rank, point, and record. The participants in the VR exergame intervention group will be instructed to play one or more of these exergames for at least 150 minutes per week, which is in line with the World Health Organization's physical activity guidelines [60]. They will be requested to record the frequency and duration of their exergaming sessions. Participants in the regular physical activity control group will engage in a physical activity routine similar in duration and intensity to the VR exergame intervention. Participants in the nonexercise control group will not receive any specific exercise instructions. All groups will be advised to maintain regular eating and working habits without making significant changes throughout the 12-week trial. After completing the trial, participants in both control groups will be offered the same procedures as the intervention group, but their data will not be collected.

Figure 1. An example of exercising with aerobic immersive VR exergame using Meta Quest 2 (source: the authors). VR: virtual reality.

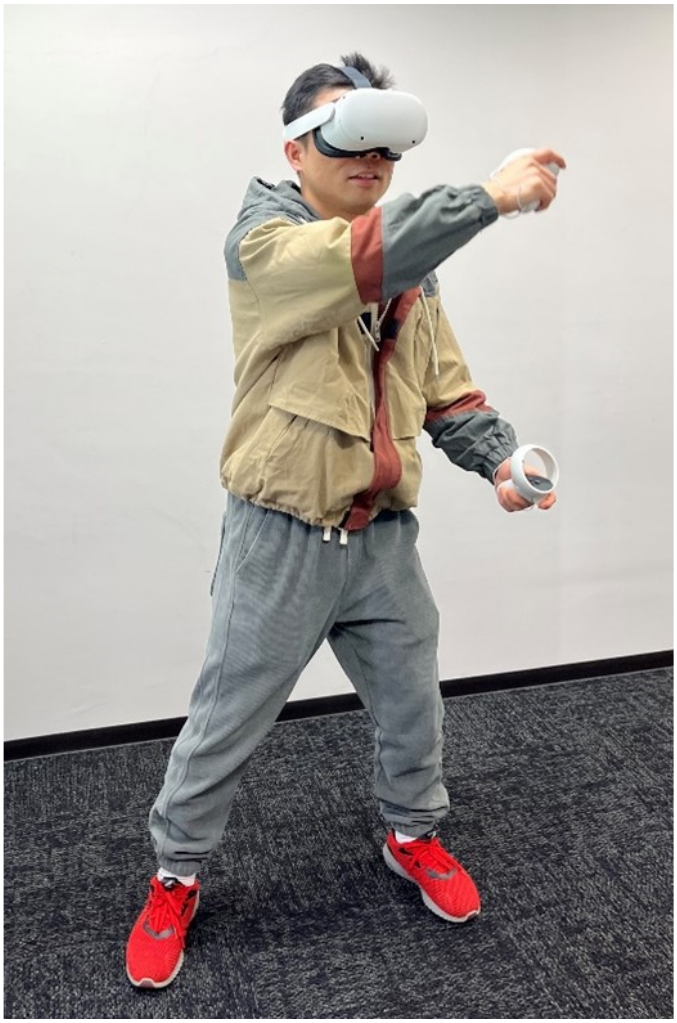

Measures

This exploratory pilot study aims to test the intervention of at-home immersive VR exergame on metabolic syndrome. Two variables, including clinical risk factors for metabolic syndrome and active and sedentary behaviors, will be measured throughout the three stages of the trial. Demographic information will be collected only at stage 1. Major clinical risk factors are objectively measured from participants' blood tests and a sphygmomanometer. The Global Physical Activity Questionnaire (GPAQ) will be used to measure participants' active and sedentary behaviors. A summary of the stages, measures, and indicators is shown in Table 1.

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Table 1. Summary of stages, measures, and indicators.

Measures and indicators	Timeline		
	Stage 1	Stage 2	Stage 3
Demographics			
Age, gender	✓		
Clinical risk factors			
HDL-C[a]	✓	✓	✓
LDL-C[b]	✓	✓	✓
Impaired fasting glucose	✓	✓	✓
Insulin	✓	✓	✓
Triglycerides	✓	✓	✓
Blood pressure	✓	✓	✓
Waist circumference	✓	✓	✓
BMI	✓	✓	✓
Active and sedentary behaviors			
Exercise time (including exergaming time)	✓	✓	✓
Sedentary time	✓	✓	✓

[a]HDL-C: high-density lipoprotein cholesterol.

[b]LDL-C: low-density lipoprotein cholesterol.

To test the therapeutic effect of this intervention, primary clinical risk factors for metabolic syndrome, including blood tests for HDL-C, LDL-C, impaired fasting glucose, insulin, and triglycerides, along with sphygmomanometry of blood pressure, waist circumference, and BMI, will be measured [4,70,71]. Owing to several merits of immersive VR exergames, such as physical engagement [38,39], the nature of immersion, and attractiveness [43], the use of VR exergames may have a significant effect on behaviors, such as exercise and sitting time [72]. Therefore, we use the GPAQ to observe the changes in active and sedentary behaviors produced by immersive VR exergames. Moreover, the validity of the GPAQ has been proven for monitoring physical activity in health promotion research [73]. The whole questionnaire includes 16 items for 3 intensities (light, moderate, and vigorous intensity) of physical activity and sedentary behavior during work, transport, and leisure time [74]. The paper form will be printed and passed to participants to assess the changes in active and sedentary behaviors during the trial.

Study Procedure

Each group in this study will consist of 40 randomly allocated participants (using a simple computer-generated random number sequence managed by JZ), and the trial will be conducted in a single-blinded structure. In this three-arm study, participants will receive the VR exergame intervention, regular physical activity, or no exercise at all. The participants will inherently be aware of their assigned activity. However, they will be blinded to the specific study hypotheses and the detailed objectives regarding comparing the 3 groups. To reduce perceived differences, participants in both control groups will receive VR exergame devices after completing the trial, but no data will be collected from this phase. Additionally, outcome assessors and data analysts will remain blinded to group assignments to prevent bias in data collection and analysis. This single-blind design helps reduce bias in the interpretation of the study results, even though participants are aware of their assigned activity.

The comprehensive framework for this protocol consists of 3 stages over 12 weeks and the allocation of items for each stage is shown in Table 2. In stage 1, when participants arrive at the data collection center, experiment coordinators will distribute and explain the manual booklet to all participants, which includes a description of the procedures, requirements, and address for inquiries. After participants have confirmed the contents and requirements of the manual, the experiment coordinators and clinic nurses will collect demographics, clinical risk factors, and GPAQ from all participants as the baseline data. A Meta Quest 2 set of equipment (entire trial), GPAQ questionnaire (0 to 6 weeks), and a recording sheet of exergaming time (0 to 6 weeks) will be additionally assigned to the VR exergame intervention group. In stage 2, the GPAQ questionnaire (7 to 12 weeks) will be assigned to all 3 groups and a recording sheet of exergaming time (7 to 12 weeks) will be additionally assigned to the VR exergame intervention group. In stage 3, only the Meta Quest 2 set of equipment will be assigned to both control groups. The necessary items for each stage will be passed to participants when they arrive at the data collection center.

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Table 2. Timeline and allocation of items.

	Stage 1[a]	Stage 2[b]	Stage 3[c]
VR[d] exergame intervention group	• Manual booklet • Demographic questionnaire • GPAQ[e] • Meta Quest 2 set • Recording sheet of exergaming time	• GPAQ • Recording sheet of exergaming time	—[f]
Regular physical activity control group	• Manual booklet • Demographic questionnaire • GPAQ	• GPAQ	• Meta Quest 2 set
Nonexercise control group	• Manual booklet • Demographic questionnaire • GPAQ	• GPAQ	• Meta Quest 2 set

[a]Start of the trial.

[b]Week 6 of the trial.

[c]End of the trial.

[d]VR: virtual reality.

[e]GPAQ: Global Physical Activity Questionnaire.

[f]Not applicable.

All participants will be asked to visit the data collection center in three stages for data collection and experimental material allocation. The self-reported GPAQ questionnaire will be completed by all participants at home, as it is a convenient at-home format for exploring impacts on active and sedentary behavior. The VR exergame intervention group will record the frequency and duration of their exergaming sessions, the regular physical activity control group will track their daily exercise routines, and the nonexercise control group will report any physical activities they perform beyond their baseline. Participants will be asked to bring all self-report sheets to the data collection center at stages 2 and 3. Coordinators will collect and summarize all the completed questionnaires and recording sheets for data processing. Major clinical risk factors are objectively measured from participants' metabolic syndrome biomarkers, which are operated by professional nurses at the data collection center (cooperative clinic). Since there is a fasting biomarker for testing metabolic syndrome, all participants are required not to consume any food or drink 12 hours before blood sample collection in the morning. After the major clinical risk factor data from all the participants for the entire trial are collected, the experiment coordinators will visit and obtain the data from the data collection center.

Analyses

After 12 weeks of the trial, 3 categories of data, including demographic, clinical risk factor, and active and sedentary behavior data, will have been collected. Regarding descriptive statistics for each indicator, the changes in clinical risk factors during the first 6 weeks, the last 6 weeks, and the entire 12-week trial will be calculated and presented as the means, SDs, and quartiles to show differences. Active and sedentary behavior will be presented as minutes of weekly light, moderate, and vigorous-intensity physical activity, and sedentary time will be obtained from the self-reported GPAQ items. Demographic variables will be presented as sum values or percentages. Additionally, the diagnosis of metabolic syndrome for all groups of participants will be summarized into sums and percentages at each stage according to the definition from a World Health Organization consultation report (high levels of insulin and impaired fasting glucose, together with at least two of the following items: HDL-C concentration less than 35 mg/dL for men [39 mg/dL for women], triglyceride concentration greater than 150 mg/dL, a waist circumference greater than 37 inches, BMI greater than 30 kg/m^2, systolic blood pressure greater than 140 mm Hg and diastolic blood pressure greater than 90 mm Hg) [4,70].

As it will be adjusted for demographic variables, the linear mixed model, which is recommended in the literature for individually assigned RCTs [75], will be used as an analysis method for determining the effects of the intervention. In cases where participants drop out or are nonadherent, missing data will be handled via multiple imputation techniques. The primary outcome assessed is the change in clinical risk factors for metabolic syndrome, including HDL-C, LDL-C, triglycerides, blood pressure, waist circumference, BMI, impaired fasting glucose, and insulin. The linear mixed model will compare these clinical risk factors across the 3 groups—VR exergame intervention, regular physical activity control, and nonexercise control groups—over three stages. The model will also assess the interaction between groups and time to determine whether the VR exergame intervention has different or additional effects compared with regular physical activity and no physical activity. Adherence to the intervention will be assessed through daily self-report logs for all participants and included as a covariate to account for variations in engagement with the interventions. Additionally, sensitivity analyses will be conducted to examine the potential impact of varying adherence levels on metabolic outcomes. This approach ensures that adherence variations are properly considered when the study's results are interpreted. In this study, the intervention or control groups are fixed factors,

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and demographic factors would be considered as random factors for accommodating variabilities within or between participants. All available data will be imported into Stata (version SE 15.1; Stata Corp) for analysis, and the significance level will be set at $P<.05$. As this is an exploratory pilot study, the primary objective is to assess feasibility and gather preliminary data. Given the lack of prior studies using immersive VR exergames in this context, conducting a power analysis would be speculative. The focus of this pilot is to generate effect size estimates and assess practical considerations, which will inform the design of a future, fully powered RCT. In the larger RCT, a formal power analysis will be conducted using the data generated from this pilot study.

Ethical Considerations

This study was approved by the Institutional Ethics Committee of Guangzhou University, China (2024-112; September 25, 2024). Initially, potential participants will be provided with basic information regarding the benefits of exercise for health and immersive VR exergames. Subsequently, interested individuals will receive a detailed explanation of the study process, and they will be asked to sign the informed consent and assent forms. In addition, some personal information is required during this trial, including name, age, gender, email address, home address, and phone number for the purpose of marking data, sending the results of blood tests and diagnosis of metabolic syndrome, or analyses (eg, as covariates). All participant information will be collected directly by the experiment coordinator (JZ) to ensure the privacy of their personal information. Strict measures will be implemented to manage and store all the collected data. To compensate for participation, participants will be rewarded with RMB 150 (approximately US $21) for completing each stage, whereas participants who complete all the processes of the trial will be rewarded with RMB 500 (approximately US $71). All incentives will be sent via a registered postal cash envelope. For visiting the data collection center at each stage, transportation fees will also be reimbursed.

Results

This study was approved by the ethics committee of Guangzhou University, China, as of September 25, 2024. The completion of participant recruitment and the initiation of the intervention or control trial are anticipated by the middle of 2025. The full processes of this trial, including data analysis and paper writing, are expected to be completed in early 2026.

Discussion

Principal Findings

Our findings will reveal whether the clinical risk factors for metabolic syndrome within the intervention group significantly improved after a 12-week exergaming intervention compared with those in the two control groups. The increase in the time engaged in physical activity (all types of light, moderate, and vigorous intensity) and the decrease in the time spent in sedentary behavior will also be evaluated.

The phenomenon of physical inactivity among employed adults has been occurring increasingly worldwide because of the development of society and technology in recent decades [16,17]. Consequently, the population of employed adults at risk for metabolic syndrome is growing across the globe [14,15]. Several primary factors, such as a lack of motivation, weather restrictions, and busy schedules for work, social lives, and family, have been reported as key barriers to physical activity [34]. Notably, at-home immersive VR exergames can provide several advantages to address these barriers to physical inactivity for employed adults. However, to our knowledge, few studies have explored the health effects of immersive exergames. This study is the first RCT and aims to examine the effectiveness of at-home immersive VR exergame interventions for improving metabolic syndrome. Our hypotheses were based on several advantages of at-home immersive VR exergames. The first benefit to exergames is engagement and enjoyment, as various types of motivational affordances (eg, points, leaderboard, and badges) were found within the gaming process along with several positive psychological effects (eg, joyfulness) [76]. The second advantage is the convenience of at-home exercise, which can mitigate weather restrictions and fit into a flexible schedule. In addition, exergames also have positive impacts on both physical health and cognition [77], which may offer pathways to improve rehabilitation and wellness [41]. Although these positive results have been reported, there is also some evidence that these positive impacts from exergames may be temporary [78].

Strengths and Limitations

This study has several limitations. First, the possibility of VR sickness resulting from individual differences [79] may result in variable exercise time, which can indirectly influence the primary clinical risk factors for metabolic syndrome and bias the efficacy of the intervention. Second, the unsupervised process of self-recorded exercise time and self-reported GPAQ items may produce inexact data about trial results. Third, according to trial length within exercise or physical activity studies, 12 weeks to 1 year is the range for determining interventional efficacy for comprehensive metabolic syndrome risk factors [48,51]. The 12-week trial for this study is consistent with the minimum length threshold, but a longer treatment period may produce more robust and efficacious results. Additionally, our participants will be recruited from Guangzhou, China, where particular life habits and social conventions, such as long work hours [80] and food habits [81], may produce results with limited generalizability. Although these limitations exist, the strengths of this study include its RCT design, the use of clinical measures of risk factors for metabolic syndrome, the novel examination of the impacts of exergames on promoting physical activity and metabolic syndrome, and the improvement of health conditions within the at-risk population of office workers.

Conclusions

The use of at-home immersive VR exergames for improving metabolic syndrome is an emerging topic for promoting physical activity related to cardiometabolic health. The primary aim of this proposed study is to assess the feasibility and preliminary

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effects of an at-home immersive VR exergame intervention on the clinical risk factors for metabolic syndrome. The results of using at-home immersive VR exergames may contribute to promoting office workers' health conditions and help reduce the burden of metabolic syndrome risk among a large and increasingly sedentary population. These results will inform the design and implementation of a larger-scale, fully powered RCT. This exploratory pilot RCT will provide data regarding the intervention's practicality and initial effectiveness, which will guide future research efforts.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1013 KB - resprot_v14i1e64560_app1.pdf]

Multimedia Appendix 2
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 99 KB - resprot_v14i1e64560_app2.pdf]

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Abbreviations

CONSORT-EHEALTH: Consolidated Standards of Reporting Trials Statement for Randomized Controlled Trials of Electronic and Mobile Health Applications and Online TeleHealth
GPAQ: Global Physical Activity Questionnaire
HDL-C: high-density lipoprotein cholesterol
LDL-C: low-density lipoprotein cholesterol
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
VR: virtual reality

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Protocol

Tablet- and Group-Based Multicomponent Cognitive Stimulation for Older Adults With Mild Cognitive Impairment: Single-Group Pilot Study and Protocol for Randomized Controlled Trial

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Abstract

Background: Cognitive stimulation therapy is a group-based psychological treatment for people with dementia as well as those with mild cognitive impairment (MCI) and is shown to improve both cognition and quality of life. Previous studies have indicated the potential to benefit from the use of technological devices in group interventions.

Objective: The pilot study aimed to assess the effectiveness of a tablet- and group-based multicomponent cognitive stimulation therapy (MCST) for enhancing cognitive functions among older adults with MCI. The following study aims to report the protocol for a trial evaluating whether the MCST program is affecting individuals with MCI.

Methods: In the first study, 30 individuals with MCI participated in 10 sessions of the tablet- and group-based MCST group. A subsequent protocol study will compare tablet-based MCST, tablet-based cognitive stimulation therapy, and control groups among 93 individuals with MCI. All participants will be recruited from older adults living in semiurban communities. Intervention groups will be facilitated by trained therapists, nurses, or psychologists. The study will be assessed by a pre- and posttest evaluation, including computer-based neuropsychological tests and electroencephalography assessment. The effects of several indicators, such as cognitive functions, behavioral, and emotional, will be analyzed as being indexed by their neurophysiological data.

Results: The pilot study showed significant cognitive improvement ($P<.001$), reduced depression ($P=.002$), and decreased state anxiety ($P=.001$) post intervention. Quality of life remained unchanged ($P=.18$). The randomized controlled trial study was funded in March 2023. Enrolling began in August 2023 and was completed in December 2023. The data analysis was started, and the results are expected to be published by mid- to late-2025.

Conclusions: The study is the first tablet-group–based MCST for older adults with MCI in middle-income countries. It will provide deeper insight into participants' neuropsychological data, thus identifying specific processes underlying physiologically measured positive outcomes. Furthermore, the project will deliver solid and integrative results to mental health professionals in terms of knowledge and guidance for implementing the tablet- and group-based MCST in people with MCI.

Trial Registration: Thai Clinical Trials Registry TCTR20230829004; https://tinyurl.com/3wuaue3e

International Registered Report Identifier (IRRID): DERR1-10.2196/64465

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KEYWORDS

computerized cognitive stimulation; multisensory integration; cognitive decline; aging; electroencephalography; randomized controlled trial; RCT; protocol; cognitive stimulation; mild cognitive impairment; cognitive; cognition; cognitive simulation therapy; CST; MCI; tablet; effectiveness; pilot study; neuropsychological tests; behavioral; emotional

Introduction

Mild cognitive impairment (MCI) is the stage between normal aging and dementia, including probable Alzheimer disease, characterized by noticeable cognitive deficits that do not impair daily functioning significantly [1-3]. The cognitive domains affected by MCI include learning and memory, language, visuospatial abilities, executive functions, and psychomotor skills. Notably, evident impairment in any of these domains is sufficient for an MCI diagnosis [4]. Furthermore, particular deficits in emotions such as anger, sadness, and fear have been observed in individuals with MCI, with anxiety being more prevalent in clinical samples than in community-based ones [5,6]. In addition, subjective cognitive decline has been linked to anxiety symptoms, independently increasing the risk of MCI or dementia [7]. Depression is also associated with early cognitive impairment, but patients with depression typically do not exhibit the memory deficits observed in MCI or dementia [8,9].

Group-based cognitive stimulation therapy (CST) has been shown to improve both cognitive functions and quality of life in older adults with dementia or MCI [10,11]. The guiding principles of CST were adapted to create 15 fundamental principles of individual-centered CST, including mental stimulation, reminiscence, learning and communication stimulation, and a person-centered approach. The program includes various activity sessions encompassing different areas such as life history, current affairs, creative tasks, games, and cognitive challenges [12,13]. The belief that continuous participation in various mental activities improves cognitive and social functioning underpins cognitive stimulation treatments [14]. Furthermore, Silva and colleagues [15] discovered that in MCI or mild dementia, a cognitive stimulation program could account for the improved cognition response observed. These data reveal that the lower the cognitive damage, the better the neuroplastic capacity and ability to learn, and the greater the potential to induce neurogenesis. Therefore, cognitive interventions should be implemented at the earliest stages of cognitive impairment [15].

Recent studies on tablet-based intervention with cognitive stimulation have focused on the feasibility, acceptability, and cognitive and psychosocial effects of the computerized cognitive stimulation (CCS) and computerized cognitive engagement programs. Both treatments were efficient and acceptable, allowing patients with MCI to improve in several aspects of their cognitive and psychosocial functioning. Still, the effect sizes on cognition, such as free recall and the Trail Making Test part A, were moderate, favoring the CCS group [16]. A further study explored whether CCS induced differential effects in older adults with MCI according to the degree of white matter hyperintensities, were separated into no-to-little and moderate-to-severe groups. Following the session, both groups improved on numerous cognitive tests but not in mood and psychosocial features except for motivation [17]. Previous research suggested that the effectiveness of tablet-based CST on cognition, emotion, or psychosocial outcomes should be investigated [17]. Furthermore, the increased computerization of intervention programs is a step toward treatment uniformity. Computer-based intervention methods are cost-effective, noninvasive, and simple to execute, requiring little human and financial resources [18]. In particular, tablet-based CST should also be further examined in middle-income or developing countries since the expected findings will close the gaps and expand the generalizability of the theories and therapeutic technologies.

In addition, extant research shows that CST is effective in enhancing cognitive functions in people with mild dementia investigated by using the resting-state functional magnetic resonance imaging technique [19] that provided solid evidence of enhancement in the neuronal networks in terms of structures and functionalities by using a group CST. Nonetheless, the previous research came with methodology limitations regarding the small sample sizes and comparison between groups. Furthermore, there is a lack of studies to show the effect of changes in neurobiological features in older adults with MCI. Thus, this study aims to monitor the effectiveness of tablet-based CST using neuroimaging techniques in people with MCI.

The underlying neurobiological factors contributing to MCI involve changes in neurotransmitters, including the noradrenergic, serotonergic, and dopaminergic systems [20]. Notably, the cholinergic system, particularly acetylcholine, plays a crucial role in cognitive function, with its decline correlating with cognitive impairment. Electroencephalography (EEG) measures have revealed alterations in brain activity patterns among individuals with MCI, including increased beta-two power and notable changes in the theta, alpha, and delta frequencies [21]. Atrophy of the hippocampus and the medial temporal lobe regions, along with hypometabolism in specific brain areas, are indicative of MCI [22]. Specifically, electrophysiological recordings and event-related potentials (ERPs) provide valuable insights into cognitive functioning. P300 latency delays have been observed in people living with MCI, and abnormalities in N400 and P600 components are associated with a higher risk of developing Alzheimer disease [23-26]. These EEG and ERP components could potentially serve as biomarkers for monitoring brain change in people with MCI.

Accordingly, the first study aims to evaluate the effects of the tablet- and group-based multicomponent cognitive stimulation therapy (MCST) program on cognition and emotions in older adults with MCI. The program draws on CST principles and multisensory stimulation techniques to create tailored activity

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sessions that target cognitive function and emotions. This study hypothesizes that the intervention positively affects cognition and emotions in older adults with MCI after the intervention.

The following study aims to assess how a tablet-based MCST program, with or without multisensory integration (MSI), affects cognitive functions, emotions, and quality of life in older adults with MCI, comparing experimental and control groups designed as parallel groups. Changes in EEG and ERPs will be examined before and after the intervention. The cognitive domains targeted as primary outcomes for improvement include learning and memory, language, visuospatial abilities, executive functions, and psychomotor skills as well as emotions. Specific brain locations are associated with these domains, and the study aims to enhance the functioning of these regions to counteract the cognitive decline observed in MCI. The protocol study hypothesizes that the intervention will improve cognitive functions, emotions, and behaviors in older adults with MCI, outperforming an active comparator and control group. Expected EEG and ERP changes may reveal brain activity patterns tied to cognitive improvements, focusing on frequency bands and ERPs.

Methods

Overview

The pilot and protocol for a randomized controlled trial (RCT) intervention study have been approved by the Burapha University institutional review board (IRB4-191/2566). The study was conducted according to the Guideline for Good Clinical Practice and the Declaration of Helsinki [27]. Following the gold standard in research on intervention effectiveness—the CONSORT (Consolidated Standards of Reporting Trials; checklist provided in Multimedia Appendix 1), the RCT study design, including the proximal and distal outcomes, has been preregistered in the Thai Clinical Trials Registry (reference TCTR20230829004).

This project consisted of 2 studies. The first study involved a pilot of the MCST intervention and effective assessment of cognitive functions in older adults, which began in August 2023. The next study is the RCT, with recruitment starting in September 2023. The intervention and data collection were done over 14 weeks.

Study 1: Pilot Study

Study Design

This study investigates the efficacy of the tablet- and group-based MCST program, using a 1-group pretest-posttest design. Participants were randomly assigned to 3 subgroups, and dependent variables were measured both before and after the implementation of the program.

Participants

In total, 30 older adults participated as volunteers in the experiment. Participants ranged from 60 to 75 (mean 66.14, SD 4.72 years) years of age with normal or corrected normal vision, no color blindness or weakness, and no history of mental illness or neuropathy. Thai native speakers were capable of reading and comprehending writing. All participants were assessed using the Thai version of the Montreal Cognitive Assessment (MoCA-T) to assess cognitive impairment [28], the subjective memory complaint scale to assess complaints of defective memory [29], the Chula Index Scale and Activities of Daily Living to assess normal activities of daily living [30], and the Clinical Dementia Rating Scale to assess the absence of dementia [31]. These assessments are established screening tools as criteria for detecting MCI [32].

Participant characteristics show that among them, MCI was presented (MoCA-T scores between 17 and 24), 20% (6/30) were male and 80% (24/30) were female. Participants' occupations varied as 43% (13/30) were farmers, 10% (3/30) were freelancers, 10% (3/30) were sellers, 13% (4/30) were retired government officers, and 23% (7/30) were unemployed. Regarding health conditions, 23% (7/30) of participants had diabetes, while 40% (12/30) reported having hypertension. An additional 20% (6/30) reported other diseases. In terms of vision, 57% (17/30) of participants wore glasses and 43% (13/30) did not wear glasses.

Intervention

The MCST interventional program was adapted from group CST for MCI with 10 sessions and once a week over a period of 10 weeks [10]. The intervention is presented in the RCT study and shown in Table 1.

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Table 1. Cognitive stimulation therapy sessions adapted to Thai culture.

Session	Theme	Activities
1	Physical activity	Finger exercise and using a touch screen and learning to navigate the tablet
2	Music and sound	Stimulating auditory and visual senses using old music and sounds from daily life
3	Childhood	Pictures of singers, actors, or celebrities from the past
4	Food and cooking	Different kinds of foods, recipes, and methods of cooking; being creative
5	Travel	Current affairs, places and sounds, well-known destinations and talking about the hometown
6	Occupations	People's jobs, using word games and word association
7	Sports	Sporting events, matching the picture to the word, senses, and sounds
8	Shopping	Using money, prices, and calculation
9	Household	Categorizing objects
10	Team games	Number games

Assessments

The results of the effectiveness of the tablet-based group intervention were evaluated. At the pre-and postintervention assessment, participants were asked to examine the MoCA-T, Thai geriatric depression scale (TGDS), State-Trait Anxiety Inventory (STAI)–state, and Older People's Quality of Life Questionnaire (OPQoL)-Brief (refer to Outcome Measures section for further details).

Data Analysis

Because the sample size in this study was not large enough to permit the assumption of normality on the study variables, the nonparametric test was used. The Wilcoxon signed-rank test was used to examine the effects of the tablet- and group-based MCST on cognition, emotions, and quality of life. The rank-biserial correlation coefficient (r_B) was considered as effect size and is interpreted the same as the r coefficient, such as trivial (<0.10), small (0.10), moderate (0.30), and large (0.50) [33]. The JASP (Jeffreys's Amazing Statistics Program; Version 0.16.2.0; University of Amsterdam), an open-source statistics program, was used for paired samples and effect size analysis [34].

Study 2: RCT

Overview

The RCT aims to assess the effects of the tablet-group–based MCST program on cognitive functions and emotions and quality of life based on the differences between experimental groups with and without MSI compared with a control group, and the changes observed in EEG and ERPs during the pre- and posttest interventions. The study hypothesizes that the intervention affects cognitive functions positively in older adults with MCI after the intervention compared with an active comparator and a control group. Furthermore, it is hypothesized that the intervention improves emotion and behavior in older adults with MCI after the intervention compared with an active comparator and control group. Changes in brain waves are also expected to reveal brain activity patterns associated with cognitive improvement, focusing on frequency bands and ERPs.

Trial Design

This research uses an RCT design with an experimental group, an active comparator group, and a control group. Participants are randomly assigned to 1 of the 3 study conditions. Each participant is randomly allocated 1:1:1 to an intervention or control condition. The study is designed as a randomized, controlled trial with 3 parallel groups. Randomization will be performed by Random Allocation Software (Isfahan University of Medical Sciences) [35].

Participants

Inclusion Criteria

Participants eligible for inclusion must meet the following criteria: (1) language proficiency: participants must be native speakers of the Thai language [32]; (2) age range: the study focuses on individuals aged 60 years or older; (3) objective memory performance: inclusion is based on objective memory impairment assessments [32] using well-established evaluation tools, including the MoCA-T and clinical dementia rating [36]; (4) subjective memory complaints [32]; (5) handedness: participants must be right-handed, as confirmed by the Edinburgh Handedness Inventory; (6) color vision: normal color vision is a requirement, evaluated using the Ishihara Plate Test; (7) health status: individuals with no chronic illnesses, deafness, blindness, or an diagnosed neurological disorder are eligible to participate; (8) cognitive status: eligible participants should not exhibit signs of dementia [32]; (9) reading ability: prospective participants are expected to be capable of reading and comprehending written material; and (10) computer proficiency: participants should be able to use computer devices effectively for the study activities.

Exclusion Criteria

The following criteria will lead to exclusion from participation: (1) a diagnosis of dementia: individuals diagnosed with dementia after participating in the study, irrespective of severity, will not be included in the study; (2) systemic illness: participants with concurrent systemic illnesses that could potentially confound the study outcomes will be excluded; and (3) refusal to participate: individuals who decline to participate or express

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their unwillingness to engage in the study will not be considered for inclusion.

Sample Size

The sample size in the study was estimated using the G*Power program [37]. The required sample size considering an α=.05, a Cohen *d*=0.50 (medium magnitude for the effect size) [17,38], and power=0.95, is 26 or 27 participants in each condition, that is, a total of around 80 participants. Assuming a loss of 15% [17,38,39], in the event, the final sample consists of 93 participants, approximately 31 participants in each condition.

Recruitment

Older adults with MCI will be recruited via communities such as clubs for older adults and elderly schools in the semiurban area of Chonburi province, Thailand. Announcements regarding the study will be disseminated through radio and social media platforms (Line Messenger [Line Corporation], Facebook [Meta], and so on). Individuals who express interest will receive information and undergo a screening test. If they meet the inclusion criteria, they will be enrolled in this study.

Interventions and Control Group

Experiment Intervention

The interventional program was adapted from group CST for MCI with 10 sessions [10], the group CST principle [11,13,40], and adapting CST to other cultures [12,38]. Specifically, the program also adopted audiovisual temporal discrimination training to improve MSI [41], which was included in sessions as shown in Table 1 and Figure 1. Participants will be asked to use a 10-inch tablet with an Android operating system (Google) that has the computerized multicomponent cognitive stimulation app for each session installed so that they can participate in all activities. Intervention groups will be facilitated by trained therapists, nurses, or psychologists. Further details of the MCST intervention and the manual can be found on the website [42].

Figure 1. Screenshots of the computerized multicomponent cognitive stimulation app (screenshots present kinds of foods in different regions of Thailand).

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Active Comparator

The comparator group is similar to the MCST intervention group but excludes MSI training, receiving only tablet-group–based CST. Each session will be like a structured session in the MCST intervention group.

Control Group

The participants in this group will not receive the treatment. They will be measured once at the start and then a second time 2 months later.

Data Collection

The study will take place at the Center of Excellence in Cognitive Science, which is part of the College of Research Methodology and Cognitive Science at Burapha University. Demographic and clinical information about age, gender, education, marital status, occupation, diseases, and physical issues will be self-reported at baseline. The results of the effectiveness of the tablet-based group intervention will be evaluated. The outcomes will be evaluated using measures of cognitive functions and brain waves, including EEG and ERP techniques that are recorded while participants perform the tasks.

At the beginning of the EEG and ERP assessment, participants will be asked to wear the neuro handset to correct the EEG resting-state data which will be measured during eyes-closed and eyes-open sessions at 5 minutes. Afterward, the EEG will be recorded while participants are performing the computerized neuropsychological tasks.

Cognitive functions and MSI tasks will use computer-based tasks to access neuropsychological data using PsychoPy software (Open Science Tools Ltd). Individuals will participate in a different sequence when dealing with order effects and time-related factors, changing the order by using counterbalancing. Furthermore, for each task, participants will rest for around 2 minutes before beginning the next task.

Electroencephalogram recordings on the Emotiv EPOC Flex saline and 10-20 layout 32-channel system will be recorded. The reference electrodes are located at the common-mode sensor (left side) and driven-right-leg (right side) sensor. All signals will be filtered automatically with a high-pass filter of 0.2 Hz and a low-pass filter of 45 Hz using a digital fifth-order sync filter and a sampling rate of 128 Hz, and the electrode impedance will be kept to at least 80% using EMOTIV PRO software to monitor EEG quality before recording and to collect the data [43].

Furthermore, after enrollment, the participants will be informed about the experimentation schedule, and the preconditions of the experiment such as proper sleep, and avoiding drinks like coffee and alcohol. Participants are required to shampoo their hair but avoid applying gel or lotion. Before starting the experiment, the researcher will confirm the participant's preparation before the experiment [44].

Outcomes Measures

Primary Outcomes

Learning, Memory, EEG, and ERP Components

The first running requires participants to learn and recall word pairs. The examination contains a variety of 12 pairs of words, such as related words, unrelated words, and name-word pairings. Participants are told to memorize unrelated word pairings (eg, hospital and lawyer). To test later, they are asked to recall those pairs of words. The total time for the test is approximately 10 minutes. A significant change in the recall numbers, EEG and ERP parameters ($P<.05$) is expected.

Executive Function Scores, EEG, and ERP Components

A standardized form of the Wisconsin Card Sorting Test, Berg Card Sorting Test will be used with the card sorting task using a 64-card deck. Participants are told to press the 1, 2, 3, or 4 keys that they believe match the card at the bottom of the screen. The cards' figures differ in color, number, and shape. The classification rule changes every 5 cards. Participants can complete the Wisconsin Card Sorting Test-64 within 10-15 minutes. The scoring includes percentage errors (%), perseverative responses (%), perseverative errors (%), nonperseverative errors (%), conceptual level responses (%), categories completed, trials to complete the first category, failure to maintain set, and learning to learn [45]. A statistically significant change in the EEG and ERP parameters ($P<.05$) is expected.

Language Scores, EEG, and ERP Components

The verbal fluency test is a short test of verbal functioning. It typically consists of 2 tasks, that is, category and letter fluency. Participants are given 1 minute to produce as many unique words as possible that are within a semantic category (category fluency: animal and fruit) and start with a given letter (letter fluency: words beginning with the letter Koh and letter Aoh in Thai). The participant's score in each task is the number of unique correct words [46]. For example, participants answered for animals such as dogs, cats, and monkeys, scoring 3 points for the category. The total time for the test is approximately 5 minutes. A statistically significant increase in fluency scores and EEG and ERP parameters ($P<.05$) is expected.

Visuospatial, EEG, and ERP Components

In the Corsi block-tapping task, participants were instructed to tap the blocks in the same serial order as presented (2 trials per sequence length ranging from 2 to 9 blocks). Participants receive 2 trials per level, starting from 2 to 9 lengths. Measures are the span (number in the longest correct sequence with the possible number from 2 to 9), the score (number of correctly reproduced sequences with the potential number from 2 to 9), and the product (span×score) [47]. The total time for the test is approximately 2-5 minutes. On the mental rotation task, participants are asked whether 2 objects rotated relative to one another (geometrical forms) are identical or mirror images [48,49]. The task consists of 69 stimuli, and each correct answer is worth 1 point, making a total of 69 points. Participants can complete the test within 5-10 minutes. A statistically significant

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increase in all scores, EEG, and ERP parameters (P<.05) is expected.

Psychomotor, EEG, and ERP Components

In total, 2 reaction time tasks will be used, namely, the Deary-Liewald reaction time task and the number's reaction time box. In the simple reaction time test participants had to press a button or key in response to a single stimulus. The choice reaction time has 4 stimuli, and participants are asked to press the button corresponding to the correct response. The interstimulus interval ranged between 1 and 3 seconds and will be randomized within these boundaries. The task will record each trial's response time and the interstimulus interval for measuring [50]. The total time for the test is approximately 3-5 minutes. A statistically significant decrease in response time and total error, EEG, and ERP parameters (P<.05) is expected.

MSI, EEG, and ERP Components

The audiovisual task consisted of three conditions—2 control conditions (1 beep and 1 flash; 2 beeps and 2 flashes) and the illusion condition (2 beeps and 1 flash; 1 beep and 2 flashes). The auditory and visual stimuli will be presented simultaneously in the control conditions. The visual flash will be delivered simultaneously with the first auditory beep in the illusion condition. In each condition, the stimulus onset asynchronies used are between 150 and 300 milliseconds [51]. For a total of 80 stimuli, participants take approximately 2-3 minutes. Response time and the total error will be assessed. A statistically significant decrease in response time and total error and EEG and ERP parameters (P<.05) is expected.

The MoCA-T

The MoCA-T version 8 is the most frequently used screening test, and it was produced as a quick screening tool for MCI and dementia in its early phases. The visuospatial (5 points), naming (3 points), attention (6 points), language (3 points), abstract (2 points), memory (5 points), and orientation (6 points) abilities are assessed on this examination. When an assessment was completed, all scores were totaled out of a possible overall of 30. Higher scores indicated more significant cognitive function. The internal consistency of the MoCA-T was excellent (Cronbach α=0.91) [28]. It is expected to see a statistically significant increase (P<.05) in global cognition.

The TGDS-15

The TGDS-15 is a structured self-report scale that assesses depression symptoms over the previous week. The scale contains 15 items, with responses chosen as agreeing or disagreeing. The scale has a cutoff point for depression, which is 0-5 for no depression, 6-10 for suggestive of depression, and 11-15 for depression [52,53]. The Cronbach α coefficient of The TGDS-15 was 0.83, which showed high internal consistency [53]. It is expected to see a statistically significant decrease (P<.05) in depressive symptoms.

The STAI

On the State Anxiety Inventory Form Y-I scale, the STAI-state has the 20-item Thai version and has been validated by Thapinta [54]. Participants are asked how often, during the last 2 weeks, they have been bothered by each of the 30 questions of generalized anxiety disorder. Response options are "not at all," "for several days," "more than half the time," and "nearly every day," scored as 0, 1, 2, and 3, respectively. Therefore, the scores range from 0 to 80, with scores of ≥20, ≥40, and ≥60 representing mild, moderate, and severe anxiety symptom levels, respectively. The Cronbach α coefficient of the Thai STAI-state was 0.90, which showed high internal consistency [54]. A statistically significant decrease (P<.05) in the state anxiety symptom is expected.

Secondary Outcomes

The OPQoL-Brief in the Thai version [55] consists of 13 questions that are scored strongly agree=1, agree=2, disagree=4, and strongly disagree=5. The items are added together to get a total OPQoL-Brief score, and then positive items are reverse coded, such that higher scores imply better QoL. The entire sum score varies from 13 to 65. The Cronbach α coefficient of OPQoL-Brief was 0.94, showing that the first and the second questionnaire responses with a 2-week interval were highly stable [55]. A statistically significant increase (P<.05) in the OPQoL-Brief score is expected.

Data Analysis

As part of demographic and behavioral data, the means and SDs will be calculated to explain the general description such as age, gender, education, MoCA-T, TGDS-15, STAI-state, and OPQoL-Brief. Cognitive function scores of the 3 groups will be compared using 1-way analysis of covariance (ANCOVA) to examine differences in posttest scores of various neuropsychological tests controlling for pretest scores. The test involves computing an F-ratio large enough to indicate significant mean differences. Furthermore, ANCOVA is customary to measure the effect size with partial ω^2. In addition, post hoc analyses were performed using the Bonferroni Test.

In total, 4 EEG frequency bands' relative powers will be analyzed, and the latency and amplitude of ERP components will also be assessed. Furthermore, the EEG data collected will be cleaned and manipulated using the EEGLAB toolbox in the MATLAB environment. One-way ANCOVA will be applied to examine differences in the EEG and ERP posttest of various components among intervention groups (MCST, CST, and control) controlling for pretest scores.

Ethical Considerations

The study was approved by the Burapha University institutional review board (approval IRB4-191/2566; issue date: August 11, 2023; valid until date: August 11, 2024). It was also registered with the Thai Clinical Trials Registry (dated August 29, 2023; TCTR20230829004). All participants provided informed consent. All data will be anonymized. The participants were provided travel compensation (US $33 per participant).

Results

Pilot Study

The participants showed significantly improved global cognition as measured by the MoCA-T (P<.001), depression as measured by the TGDS (P=.002), and state anxiety as measured by the STAI-state (P<.001) but not in the quality of life as measured

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by the OPQoL-Brief (*P*=.18). Furthermore, effect sizes among significant measures were large (r_B: 0.85-1.00; Table 2).

Table 2. Assessment results for older adults with mild cognitive impairment who completed both pre- and posttests.

Measure	Pretest (n=30), mean (SD)	Posttest (n=30), mean (SD)	Wilcoxon Signed Ranks Test		Effect sizes[a] (95% CI)
			Z value	*P* value	
MoCA-T[b]	19.50 (2.13)	23.13 (2.71)	4.70	<.001	1.00 (1.00 to 1.00)
TGDS[c]	3.53 (1.89)	2.40 (1.10)	2.99	.002	.85 (0.61 to 0.95)
STAI[d]-state	43.37 (5.40)	37.30 (5.87)	3.96	.001	.87 (0.73 to 0.94)
OPQoL[e]-Brief	52.47 (10.83)	56.00 (5.97)	1.33	.18	.28 (–0.13 to 0.61)

[a]The rank-biserial correlation coefficient (r_B).

[b]MoCA-T: Thai version of the Montreal Cognitive Assessment.

[c]TGDS: Thai geriatric depression scale.

[d]STAI: State-Trait Anxiety Inventory.

[e]OPQoL: Older People's Quality of Life Questionnaire.

The RCT

In the RCT, the project secured funding in March 2023, started in April 2023, and received recommendations and approval from the Burapha University institutional review board in August 2023. Baseline data collection was conducted in September 2023, and the postintervention data collection started in December 2023. From baseline, we have data from 93 older adults with MCI. Results from the study will be available in mid- to late-2025 at the earliest and will be published in peer-reviewed international and national journals, as well as presented at relevant conferences. An overview of the trial flow is presented in Figure 2.

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Figure 2. CONSORT (Consolidated Standards of Reporting Trials) flow diagram. CST: cognitive stimulation therapy; MCST: multicomponent cognitive stimulation therapy; T0: baseline for pretreatment assessment (ie, week 0); T1: the week immediately after the intervention (ie, week 10).

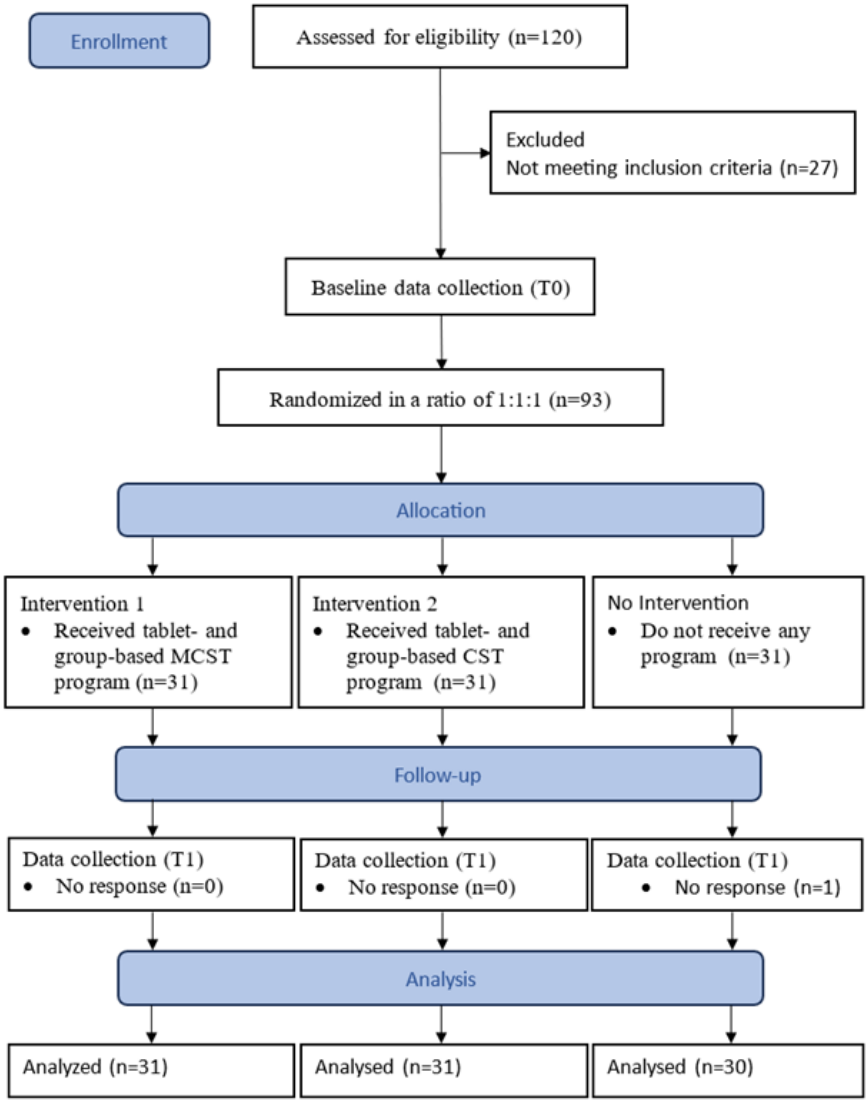

Discussion

Findings From the Pilot Study

The pilot study determined the cognitive function, emotions, and quality of life among older adults with MCI in Thailand. Such improvement was attributed to the tablet- and group-based MCST for 45 minutes per session and once a week over a period of 10 weeks aimed at improving their cognition, emotions, and quality of life. Findings showed that older people with MCI showed improvement in global cognitive function, as proven by scores on MoCA-T. Furthermore, this study also indicated a reduction in depression and anxiety, as demonstrated by scores on TGDS and STAI-state. However, the intervention cannot enhance the quality of life among participants. These findings support that the tablet- and group-based MCST program effectively improves global cognitive function and emotions in older adults with MCI.

The study findings align with previous research regarding CCS using tablet-PCs and social interactions among older adults with MCI [16,17]. A recent study employed the KODRO app (Altera-Group) on Android tablets, incorporating functions like cognitive games, communication tools, and entertainment features to engage various cognitive domains in participants with MCI. The investigation demonstrates that CCS using tablet-PCs enhances cognitive function [16], consistent with meta-analytical findings indicating cognitive training's positive impact on global cognitive function, memory, and working memory in older patients with MCI [56]. Further evaluation of specific cognitive domains will involve neuropsychological assessments and EEG in older adults with MCI.

In terms of emotion, depression and anxiety are common in people with MCI [57-59]. Fascinatingly, emotional symptoms, such as depression and anxiety, decreased following the session. Contrary to the previous study [16], there was unchanged postintervention. Nonetheless, other findings found that not only cognitive functions but also depression and anxiety were improved in people with MCI after they participated in the computerized cognitive training program [60]. The MCST program's social interaction through discussions and games may explain the findings, aligning with research showing that social engagement enhances cognitive interventions. This discovery aligns with previous research, indicating that social

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interaction has the potential to modify the outcome of cognitive intervention programs [61].

In contrast to our hypotheses, this study had no significant effect on the participants' quality of life. Perhaps because all of our participants were aware of their diagnosis and expressed low satisfaction with their cognition and physical well-being, no change in their quality of life was seen after postintervention. It has been shown that patients with MCI who are aware of their diagnosis or have high memory complaints have a poorer quality of life than those who are oblivious to their diagnosis or have low memory complaints [62,63]. However, previous studies showed that reminiscence therapy improved cognitive performance and quality of life, supporting CST's use for cognitive decline [64]. Cognitive stimulation benefits daily activities in MCI [10], while another study reported enhanced social, physical, and mental health [65]. Londos et al [66] noted the quality of life gains from goal-oriented rehabilitation, though self and mood subscales showed no significant change. This suggests that enhancing the quality of life in patients with MCI who are aware of their diagnosis may require more targeted interventions.

Principal Results for the RCT Study

The protocol for the RCT study introduces a comprehensive cognitive intervention program designed to address cognitive functions in older adults with MCI. The proposed program is tailored to target both cognitive domains and MSI. The study hypothesizes that the intervention has a positive effect on cognitive performance in older adults with MCI compared with an active comparator and a control group. In addition, it is anticipated that changes in brainwaves, with a focus on frequency bands and ERPs, are also expected to reveal patterns of brain activity associated with cognitive improvement. This study's contribution lies in its novel approach to combining CST and MSI training to address those cognitive deficits associated with MCI. The inclusion of tablet-based interventions and interactive sessions adds a technological dimension to traditional cognitive interventions, thereby potentially enhancing engagement and outcomes.

The study draws upon established principles from CST and MSI techniques. The cognitive stimulation program is designed based on group-based CST and multisensory stimulation approaches. CST has been shown to improve cognitive function and quality of life in individuals with dementia or MCI [10,11]. Furthermore, the group-based cognitive stimulation program, which involves social support from friends and group activities, is critical for mental health and adherence to health-promoting behaviors. It can reduce feelings of loneliness and isolation, which are common in older adults with MCI. The guiding principles of CST were adapted to create 15 fundamental principles of individual CST, including mental stimulation, reminiscence, learning, and communication stimulation, using a person-centered approach [12,13].

The study uses an RCT design with experimental, active comparator, and control groups. The primary objectives are to evaluate the effects of the computerized multicomponent cognitive stimulation program on cognitive functions in older adults with MCI and to explore the changes in the EEG and ERP components following the interventions. The study's structured design, preregistration, and adherence to ethical standards ensure a robust methodology.

The cognitive domains targeted for improvement encompass learning and memory, language, visuospatial abilities, executive functions, psychomotor skills, and emotions. The study integrates various neuropsychological tasks to assess these domains, evaluating the intervention's impact comprehensively. The expected improvements in these domains align with the program's focus on CST principles and MSI, which have shown promise in enhancing both cognitive functions and quality of life. It is crucial to have a tablet-based intervention that boosts self-confidence and reduces depression and anxiety. This can involve personalized training, support groups, and skill-building activities to manage cognitive stimulation. For example, previous research has demonstrated that the feasibility and acceptability of the CCS program and computerized cognitive engagement programs were efficient and acceptable, allowing patients with MCI to improve in several aspects of cognitive and psychosocial functioning [16,17]. Computerized technology is cost-effective, and simple to execute, requiring little human and financial resources [18]. In addition, implementing this intervention in middle-income countries may face challenges like setup costs and limited digital infrastructure. However, these barriers can be mitigated through local adaptations and partnerships with community organizations that support technology access and training, making tablet-based programs more applicable across diverse socioeconomic settings [67]. Furthermore, CCS is being used more widely as a standard approach for delivering nonpharmacological interventions to older adults, but determining the effectiveness of nonpharmacological therapies can be challenging [68]. They lack an appraisal of brain activities and a neuropsychological evaluation that correlates with the specific cognitive functions in people with MCI.

The study's use of EEG and ERP measures to examine neurobiological correlations of MCI adds welcome depth to the investigation. The alterations in brain activity patterns and the ERP components associated with MCI and cognitive impairment contribute to understanding the underlying mechanisms of the condition and identifying potential biomarkers for assessing and monitoring the relevance of the study to treatment. For instance, previous research shows that the EEG of resting-state conditions and a simple cognitive task are important as likely biomarkers for discriminating between healthy, MCI, and Alzheimer groups [69]. It is consistent with Fauzan and Amran [21], finding that when the EEG resting-state measure of the MCI group was compared with typical healthy aging, the theta and alpha increases were more prevalent, showing symptoms of cognitive impairment in MCI, and a decrease in the delta is associated with cognitive decline. In patients with MCI, P300 latency was delayed significantly [26]. P300 latency was related significantly to disease severity in people with probable Alzheimer disease. P300 latency had the highest correlation coefficients with cognitive measurement [23,24]. Furthermore, the N400 component could be connected to verbal memory and learning. The N400 amplitude correlates negatively with semantic expectancy and is inversely proportional to the

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semantic processing load. P600 has also been linked to memory encoding and retrieval processes [25].

As a result, EEG is a valuable technology for collecting biomedical data from participants pre- and posttest to compare the difference in brain waves after participating in the experiments. However, the limitations of this research are the research design and instrument. The planned follow-up does not take into account that the study may not provide information about the long-term benefits and hazards of medical interventions. Furthermore, EEG data will be collected using the Emotiv Flex which is not capable of native hardware event-marking that can lead to an effect on time-lock stimuli to EEG data [43].

Limitations and Future Implications

The limitations of this study include its short-term focus, which may capture primarily immediate outcomes while potentially overlooking long-term effectiveness. In addition, the results may have limited generalizability, as they are based on a general population sample and may not extend to specific MCI subtypes. The predominance of female or male participants further limits generalizability, highlighting the need for larger studies to explore potential sex-related variations in response.

Further implications will contribute to knowledge, including developing a novel tablet- and group-based MCST program that combines CST with MSI to improve cognitive functions in older adults with MCI. Using EEG and ERP markers to measure cognitive functions and MSI will provide an assessment of the intervention's effectiveness. The EEG-recorded results will give a greater understanding of participants' tablet- and group-based therapeutic data, allowing for the identification of particular mechanisms, such as changes in cognition and emotion, that were found to improve in the pilot study.

Conclusions

To summarize, the pilot study on older adults with MCI in Thailand revealed significant improvements in cognitive function and emotions following a tablet- and group-based MCST program. The intervention, conducted over 10 weeks for 45 minutes per session, notably enhanced global cognitive function while reducing depression and anxiety levels. These findings corroborate previous research on CCS among patients with MCI. However, contrary to expectations, the MCST program did not yield significant improvements in participants' quality of life, likely influenced by their awareness of diagnosis and dissatisfaction with cognition and physical well-being. Nonetheless, the study underscores the importance of cognitive interventions and highlights the need for further exploration into specific cognitive domains among older adults with MCI. Further research employing neuropsychological assessments and EEG may provide deeper insights into the mechanisms underlying cognitive performance enhancement in this population.

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Data Availability

The datasets generated and analyzed during the current study are available from the corresponding author upon reasonable request.

Authors' Contributions

All authors contributed to conceptualization and methodology. Writing – original draft was contributed by KJ. Writing – review and editing was contributed by KJ, PM, PW, and AG. Supervision was handled by PM, PW, and AG. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-EHEALTH V1.6 checklist.
[PDF File (Adobe PDF File), 1231 KB - resprot_v14i1e64465_app1.pdf]

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Abbreviations

ANCOVA: one-way analysis of covariance
CCS: computerized cognitive stimulation
CONSORT: Consolidated Standards of Reporting Trials
CST: cognitive stimulation therapy
EEG: electroencephalography
ERP: an event-related potential
JASP: Jeffreys's Amazing Statistics Program

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MCI: mild cognitive impairment
MCST: multicomponent cognitive stimulation therapy
MoCA-T: Thai version of the Montreal Cognitive Assessment
MSI: multisensory integration
OPQoL: Older People's Quality of Life Questionnaire
RCT: randomized controlled trial
STAI: State-Trait Anxiety Inventory
TGDS: Thai Geriatric Depression Scale

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Protocol

Enhancing Text Message Support With Media Literacy and Financial Incentives for Vaping Cessation in Young Adults: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: The persistent high prevalence of e-cigarette use among young adults remains a significant public health concern, with limited evidence and guidance on effective vaping cessation programs targeting this population.

Objective: This study aims to outline the study design and protocol of a pilot randomized controlled trial aimed at investigating feasibility and assessing whether media literacy education or financial incentives enhance the effectiveness of evidence-based text message support in promoting vaping abstinence among young adult e-cigarette users.

Methods: The pilot study uses a 4-arm (1:1:1:1) randomized controlled trial design to assess the potential impact of different combinations of media literacy education, financial incentives, and text message support on vaping abstinence over a 3-month period. The first month serves as a preparatory phase for quitting, followed by 2 months focused on abstinence. A total of 80 individuals, aged 19-29 years, who have used e-cigarettes within the past 30 days, have internet access, and express interest in quitting vaping within the next 30 days, will be enrolled. Eligible individuals will be randomized into one of the four study groups: (1) Text Message, (2) Media Literacy, (3) Financial Incentive, and (4) Combined. All participants, regardless of group assignment, will receive text message support. Participants will be followed for 12 weeks, with abstinence status assessed at week 12, as well as during remote check-ins at weeks 6, 8, and 10. Feasibility measures include recruitment rate, reach, engagement, and retention. Other outcomes of interest include self-reported 7-day abstinence and changes in nicotine dependence and media literacy scores. Exit interviews will be conducted with those who complete the study to explore facilitators of and barriers to participation and engagement in vaping cessation, which will inform future program refinement and uptake.

Results: Recruitment for the study commenced in December 2023 and concluded in August 2024. A total of 40 participants were randomized into these groups: 9 for Text Message, 11 for Media Literacy, 10 for Financial Incentive, and 10 for the Combined group. The final assessment was completed in November 2024, and analyses are currently ongoing.

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Conclusions: The findings from this trial could provide valuable insights into the design and uptake of vaping cessation strategies among the young adult population.

Trial Registration: ClinicalTrials.gov NCT05586308; https://clinicaltrials.gov/study/NCT05586308

International Registered Report Identifier (IRRID): DERR1-10.2196/60527

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KEYWORDS

contingency management; e-cigarettes; social support; youth; electronic health record; opt-in; recruitment; tobacco marketing; cessation; peer support; young adult; feasibility; public health

Introduction

E-cigarettes have emerged as the most commonly used tobacco product among young individuals [1,2], rapidly becoming a public health concern in the United States, particularly among youth and young adults [3]. Data from the 2021 National Center for Health Statistics reported that e-cigarette use (ie, vaping) was highest among young adults aged 18-24 years, with 11% (approximately 3.4 million people) using e-cigarettes, compared with an overall adult rate of 4.5% [4]. The 2023 National Center for Health Statistics reported an increase in overall adult e-cigarette use to 6.5% [5]. Similarly, another study using the 2021 Behavioral Risk Factor Surveillance System Survey observed a high prevalence of e-cigarette use among US adults (6.9%, 95% CI 6.7%-7.1%), particularly among young adults aged 18-24 years (18%) [6]. The accessibility of vaping products has significantly increased, largely driven by marketing efforts featuring appealing flavors targeted at this population [7]. Moreover, the influence of social media and influencers has contributed to the widespread prevalence of vaping [8,9]. Given the persistently high rates of e-cigarette use, especially among young adults, it is critical to explore the feasibility and effectiveness of targeted cessation programs for this group.

Although marketed as a safer alternative to combustible cigarettes [1,7], evidence suggests that vaping still poses health risks [10,11]. Vaping has been associated with increases in both blood pressure and heart rates [12]. Nicotine, a toxic and highly addictive substance found in e-cigarettes, contributes to these risks, with concentrations varying widely depending on the type of devices, their power, and the brands and models. Notably, nicotine levels in e-cigarettes have increased from 1.7% in 2017 to 5.0% in 2022 [13]. However, critical questions regarding both the short-term and long-term health effects of e-cigarette use remain unanswered [14-16].

Vaping cessation efforts among young adults often yield poor results, with many experiencing failed attempts [17,18]. Data indicate that 53.4% of current young e-cigarette users express an intention to quit, and 67.4% report attempts to do so [19], yet successful cessation rates remain low [20]. Despite a strong desire to quit, many struggle to stop vaping. Evidence-based behavioral vaping cessation programs are scarce compared with pharmacological interventions, such as nicotine replacement therapies [21-23] or vape concentration tapering [24]. Moreover, the implementation and reach of these behavioral programs remain a challenge, particularly among youth and young adult populations [25].

Three recent studies have reported on the effectiveness of behavioral vaping cessation programs using text message support or financial incentives. For example, Raiff et al [26] conducted a pre-post intervention study with 8 college students, finding that all participants quit vaping during the 2-week intervention period, using a remotely delivered program with financial incentives to reinforce abstinence. However, in a feasibility trial involving 27 young adults, Palmer et al [27] found no significant difference in vaping abstinence between the contingency management and monitoring control groups, despite the positive feedback about the intervention program. Another study examined a vaping cessation text message program called This is Quitting [28], which provides social support for quitting. In a randomized clinical trial (RCT) involving 2588 young adults aged 18-24 years, participants in the This is Quitting group were 1.39 times more likely to quit vaping compared with those in the control group [29]. The urgent need for evidence-based behavioral vaping cessation initiatives among this population is critical to addressing this public health concern.

Vaping often appeals to younger populations through marketing campaigns that highlight various flavors and glamorize the practice [7]. Companies also use manipulative strategies like social media influencers and product placement, particularly targeting communities with lower levels of vaping-related media literacy, who tend to be more susceptible to vaping [30]. Although limited evidence exists on the direct impact of media literacy programs on vaping cessation, integrating such programs into vaping cessation initiatives may help promote abstinence by (1) promoting positive behavioral norms (educating people about the true risks of vaping can foster a social environment where quitting is seen as important and achievable [31]); (2) encouraging peer advocacy and mentoring (by understanding marketing tactics and gaining skills to debunk misinformation, individuals can become more effective in supporting their peer to quit vaping [32]); and (3) enhancing self-efficacy against vaping triggers (media literacy can help individuals recognize and avoid triggers that encourage vaping, such as targeted advertising or social media content that normalizes the behaviors [33]). In addition, although media literacy programs are primarily designed for youth for educational and prevention purposes, young adults may also benefit from the content due to the close age proximity between these groups.

Contingency management is a well-established behavioral intervention in which individuals receive reinforcement, such as financial incentives, contingent upon predetermined outcomes [25]. Financial incentives have been shown to be effective in

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promoting healthy behaviors [34] and improving the reach and engagement of evidence-based programs as part of an implementation strategy [35]. Numerous studies have demonstrated the success of financial incentives in encouraging behavior changes [36,37]. Rooted in health promotion economic theory, financial incentives enhance the perceived benefits of abstaining from unhealthy behaviors, thereby bolstering motivation for change [36].

Peer influence plays an important role in vaping behaviors, with family and friend use cited as key reasons for vaping initiation [38]. In addition, vaping for "entertainment" purposes is prevalent among younger populations [39]. Peer support strategies have been shown to be effective [40,41], especially in promoting cigarette smoking cessation in youth and young adults [42,43]. Platforms like SMS text messaging and social media have shown promise as peer support tools [44-46]. Specifically, peer support delivered through text message (eg, This is Quitting) has demonstrated effectiveness in vaping cessation across multiple studies [29,47,48], capitalizing on the widespread use of these communication methods among young adults.

The objective of this paper is to outline the design and methodology of a pilot RCT investigating feasibility and assessing whether media literacy education or financial incentives enhance the effectiveness of evidence-based text message support in promoting vaping abstinence among young adult e-cigarette users.

Methods

Study Design

This pilot study uses a 4-arm RCT design to assess whether media literacy education or financial incentives can enhance vaping abstinence when combined with text message support over a 3-month trial period. The first month involves a preparatory phase for quitting, followed by 2 months focused on maintaining abstinence from vaping. Eligible participants will be randomly assigned to one of four groups in a 1:1:1:1 ratio: (1) Text Message (text message support), (2) Media Literacy (text message support and media literacy education), (3) Financial Incentive (text message support and financial incentives), and (4) Combined (text message support, media literacy education, and financial incentives).

All 4 groups will receive evidence-based text message support (ie, This is Quitting). In addition, to develop and assess the process of conducting biospecimen collection (ie, urine) and analysis, a subsample of 20 participants (5 participants from each study group) will be contacted in order of enrollment until the target is met at baseline. These participants will be asked to provide urine samples both at baseline and at the conclusion of the study. The samples will be shipped to the Division of Laboratory Sciences at the Centers for Disease Control and Prevention for biomarker analyses to evaluate exposures to tobacco-related toxicants from e-cigarette use.

The trial protocol has been reported in accordance with the SPIRIT (Standard Protocol Items Recommendations for Interventional Trials) 2013 checklist [49] (Multimedia Appendix 1).

Participants and Eligibility Criteria

Eligible participants are individuals who: (1) are aged 19-29 years (the minimum age is set at 19 to align with the legal age of majority in Nebraska); (2) have used e-cigarettes within the past 30 days, consistent with previous behavioral vaping cessation trials targeting youth and young adults [29,50]; (3) have access to the internet; and (4) are interested in quitting vaping within the next 30 days. Individuals who self-report as currently pregnant or planning to become pregnant within the next 3 months, or who are currently enrolled in other behavioral or medical vaping cessation programs, will be excluded.

Sample Size Justification

As this pilot RCT aims to assess the feasibility of a future large-scale study, a sample size of 80 (n=20 in each arm) is considered sufficient, following the flat rule of thumb for pilot trials with continuous outcomes of interest (eg, feasibility outcomes), which typically recommend group sizes ranging from 12 to 35 participants [51]. This sample size also takes into account available resources such as time and budget [52].

Recruitment and Sample Selection

We will recruit a total of 80 participants using a population health management approach [53,54], a comprehensive strategy that involves identifying subpopulations of individuals from an existing pool who would benefit from a given evidence-based intervention. This approach includes examining the characteristics of these populations using electronic health record (EHR) data. The potential participant pool will be limited to patients who have opted in to be contacted for research studies in the EHR system at Nebraska Medicine.

Specifically, we will collaborate with EHR Data Access Core at the University of Nebraska Medical Center to first generate a list of potentially eligible participants, filtering for age and using smart text data to determine the vaping or smoking status, as young adults are more likely to engage in multiple tobacco products at the same time [55]. A study invitation email, containing a link to an eligibility screening, will then be sent to individuals on this potential participant list by the study team. In this email, interested individuals will be directed to complete web-based screening questions via Research Electronic Data Capture (REDCap; Vanderbilt University) to assess their eligibility. Eligible participants will then be contacted by research staff members on days 1, 3, 7, 14, and 21 (if no response) after the completion of screening to schedule an in-person baseline visit.

If the recruitment goal of 80 participants is not met after exhausting the initial participant list, the research team will directly contact potential participants via phone calls. In addition, we will implement a social media recruitment strategy by posting study advertisements on platforms such as Facebook (Meta), Instagram (Meta), or X (formerly Twitter). We recognize that there may be differences between participants recruited from various sources (EHR vs social media) and will account

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for these differences in the reporting of trial results and the planning of future large-scale studies.

Interventions

Text Message Support

Grounded in social cognitive theory and designed as a compassionate, nonjudgmental companion, the text message program "This is Quitting" is an evidence-based, cost-free, and personalized initiative by the Truth Initiative, aimed at helping young individuals quit vaping. Most of the support messages are contributed by other users, reinforcing perceived social norms and providing communal encouragement for quitting. A recent RCT involving 2588 young adults aged 18-24 years found that participants receiving text message support were significantly more likely to achieve vaping abstinence compared with the control group (odds ratio [OR] 1.39; 95% CI 1.15-1.68; *P*<.001) at the 7-month follow-up [29]. Participants will retain full access to the text message program even after completing the study.

Participants in this study will receive 1 message per day for the week leading up to their quit date and for 8 weeks following it.

Media Literacy

Media Education for Sensible Evaluation and Nurturing Substance-free Experiences (MediaSense) [56] is an evidence-informed antivaping media literacy education program designed to prevent and reduce vaping among adolescents and young adults. Developed by our research team, the program draws on the social influence framework and incorporates guidance from the Centers for Disease Control and Prevention and Food and Drug Administration tobacco and vaping prevention guides, as well as an extensive review of evidence-based prevention programs and identified vaping risk factors. The MediaSense program consists of 9 web-based modules covering a range of topics, including (1) understanding what e-cigarettes are and how they work; (2) exploring the health impact of e-cigarettes; (3) understanding the role of marketing and advertisement in promoting e-cigarettes; (4) dispelling myths and revealing facts about e-cigarette marketing; and (5) learning how to deconstruct vaping advertisements. These e-learning modules aim to transform participants' knowledge, attitudes, and beliefs regarding e-cigarette use while emphasizing vaping-related media literacy and developing skills to critically deconstruct e-cigarette advertisements.

In our previous study that examined the effect of MediaSense on vaping prevention among middle and high school students (n=384), we observed significant results. Specifically, vaping media literacy scores improved, with mean scores increasing from 2.3 (SD 2.3) to 3.4 (SD 2.4) (*P*<.001). In addition, there was a decrease in the perception of vaping harm (adjusted OR 1.6 95% CI 1.1-1.22) and a reduction in vaping susceptibility (adjusted OR 0.7, 95% CI 0.5-1.0; *P*=.04) [56], indicating a reduced likelihood of students considering vaping.

In this study, participants assigned to Media Literacy or Combined will complete these self-paced modules during the 1-month quitting preparatory phase and will be required to take a short quiz at the end of each module. These quizzes confirm module completion and assess participants' understanding of the education materials. Each module will take approximately 10 minutes to complete.

Financial Incentives

Participants will receive US $3 for each saliva sample submission, regardless of testing results, at week 6, week 8, week 10, and week 12 during the 2-month abstinence phase. In addition, they will earn escalating bonuses for each negative sample. The bonus will start at US $7 and increase by US $5 for each subsequent negative sample, that will be, US $7 for week 6, US $12 for week 8, US $17 for week 10, and US $22 for week 12. However, a reset contingency will be applied, meaning the bonus amount will revert to the initial US $7 if a sample is missing or tests positive for cotinine (refer to Figure 1).

Participants can earn up to $70 in total upon completing all 4 saliva sample submissions. They will be informed of their earnings after completing each scheduled task (ie, immediate reward) and will receive all payments as a 1-time disbursement at the conclusion of the study. The rationale behind the timing and amount of the incentives is to minimize the risk of inhibiting intrinsic motivation [57], as modest incentives (up to US $70) are less likely to undermine intrinsic motivation compared with the larger rewards typically offered in smoking cessation programs (eg, US $1185) [58].

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Figure 1. Financial reward decision flow. Values were negative (-) or positive (+).

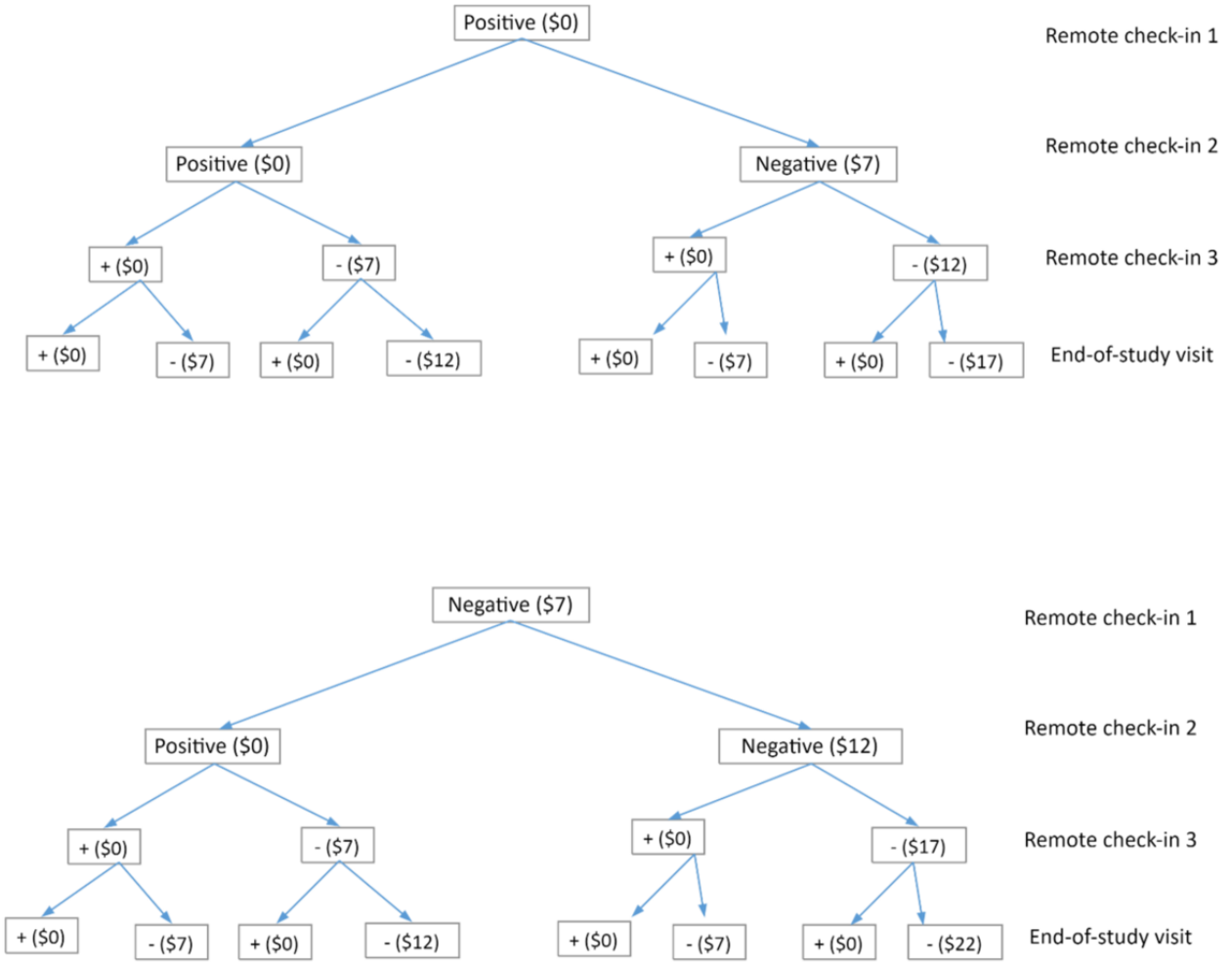

Study Timeline and Data Collection

The study will span a duration of 3 months, consisting of a 1-month quitting preparatory phase (weeks 1-4) and a 2-month abstinence phase (weeks 5-12; Figure 2). Throughout the quitting preparatory phase, participants assigned to the Media Literacy or Combined groups will be directed to complete the web-based media literacy education modules by their quit date, Meanwhile, participants in the Text Message or Financial Incentive groups will be encouraged to prepare for quitting but not to quit before the specified quite date.

Figure 2. Study assessment timepoint.

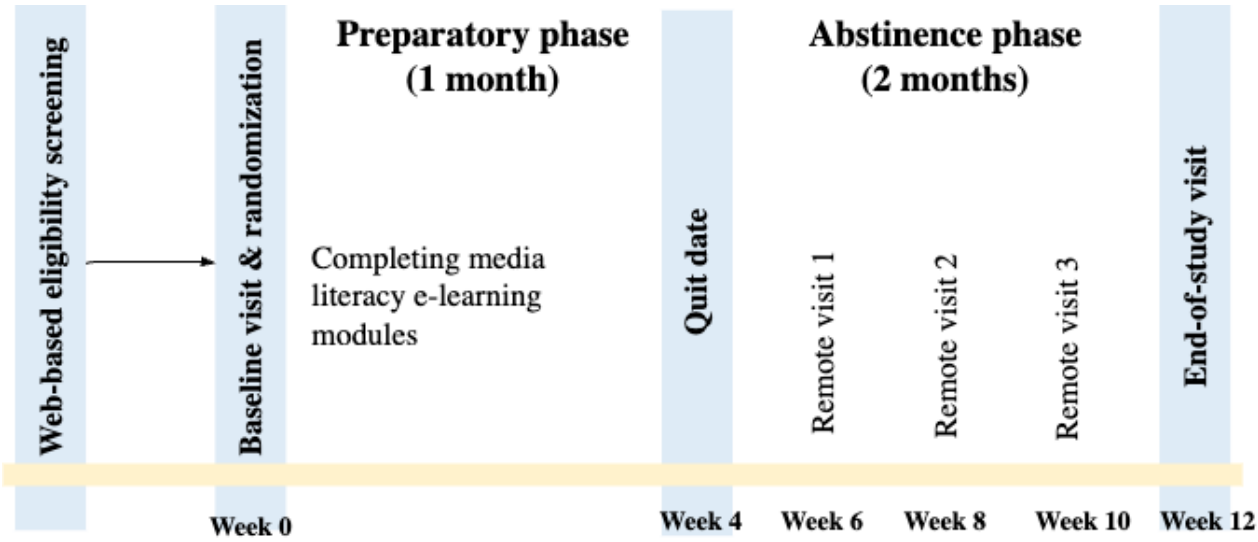

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Baseline Visit

This assessment will include a demonstration and facilitation of the saliva test, which participants will perform themselves at baseline and final study visits, as well as during remote check-ins. Participants will also sign a precommitment pledge (a psychological strategy to help individuals stick with their goals) and complete the baseline survey.

Following these activities, research staff members will conduct randomization using predetermined blocks of 4 and 8, with a computer-generated algorithm, to assign participants to one of the study groups. Participants will also be asked to specify a quit date (no later than 1 month after the baseline visit, which serves as the quitting preparatory phase), register for the text message program, and schedule the 3 remote check-ins for saliva testing.

Remote Check-Ins

During the abstinence phase, participants will engage in a total of 3 video calls, scheduled for week 6, week 8, and week 10. During each live video call, participants will receive instructions on how to complete the saliva sample collection on their own and submit the results. Specifically, they will be directed to open a new test kit and record their participant ID, visit number, date, and time on the kit. Participants will then perform the saliva test, allowing approximately 10 minutes for processing. In addition to verbally providing the test results (positive or negative) to the research staff members, participants will be required to take a picture of the results, including their participant ID, visit number, date, and time, and send it to the research staff members before concluding the call. Each video call will last no longer than 20 minutes. The primary purpose of these remote check-ins is to maintain participants' engagement and monitor their abstinence progress until the final study visit at week 12.

End-of-Study Visit

At the end-of-study visit (week 12), which may be conducted either remotely or in person, participants will provide the results of saliva testing and complete the end-of-study survey. Participants who provided a urine sample at the study baseline will be asked to attend the final visit in person for urine sample collection.

Exit Interview

For quality improvement and future modification and adoption of vaping cessation programs, we will conduct exit interviews with participants (n=8-12; 2-3 participants from each group) who have completed the study via video call. The interview guide will be developed based on the Pragmatic Robust Implementation and Sustainability Framework [59] to identify the barriers and facilitators of participating in a vaping cessation program and achieving abstinence goals.

Measures

Feasibility Outcome

As this is a pilot trial, our primary objective is to assess the feasibility of implementation. Specifically, we will use study records to measure the following: (1) recruitment rate, defined as the proportion of eligible individuals who consent to participate; (2) reach, assessed by the representativeness of sociodemographic characteristics among screened and enrolled individuals; (3) engagement, measured by the proportion of participants completing remote check-ins, and the proportion of participants in the Media Literacy or Combined groups who complete the media literacy e-learning modules; (4) retention, evaluated by the number of participants who withdraw from study, and the completeness of the end-of-study assessment; and (5) the number and proportion of participant providing a urine sample from each group at baseline and the end of study.

Cessation Outcome

The primary cessation outcome for this study is biochemically verified vaping abstinence, determined through the iScreen saliva cotinine test conducted at the end-of-study assessment. A negative cotinine result will be indicated by a cutoff of <30 ng/mL [60].

Additional Outcome

Additional outcomes of interest for this study include: (1) self-reported 7-day abstinence, determined by the question in the end-of-study survey: "Have you used any e-cigarettes, even a puff or pinch, in the last 7 days?" [61]; (2) changes in nicotine dependence, measured by the Penn State E-Cigarette Dependence Index at baseline and end-of-study; and (3) changes in media literacy, assessed using the Vaping Media Literacy Scale [30] at baseline and end-of-study.

Data Analysis Plan

Quantitative Analysis

Descriptive statistics will be used to summarize participants' sociodemographic characteristics, e-cigarette use history, exposure to tobacco marketing and its influence, social support, and self-efficacy at baseline. Bivariate analyses, using either the Chi-squared test for categorical variables or the ANOVA test for continuous variables, will be conducted to identify differences in sociodemographic characteristics and other vaping-related variables at baseline across the study groups.

We will provide a descriptive summary of feasibility outcomes, including the rate of recruitment, reach, engagement, and retention. In addition, we will assume that all covariate data are missing at random, and this assumption will be tested by comparing the missing data patterns with sociodemographic characteristics in the bivariate analyses.

Chi-squared tests will be used to determine differences in proportions of participants with negative saliva test results at the end of the study as well as each remote check-in. Missing end-of-study abstinence outcomes will be coded as vaping (not abstinent) [27]. Similarly, differences in the proportion of participants who self-reported 7-day abstinence across study groups will be evaluated using the Chi-squared test, while the ANOVA test will be used to assess changes in nicotine dependence index and media literacy scores.

Nonparametric methods (eg, Fisher exact test when the sample size is less than 5 in a category or the Kruskal-Wallis test) will be applied when appropriate. All quantitative analyses will be

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conducted in SAS (version 9.4; SAS Institute Inc) with a 2-tailed significance level <.05 if applicable.

Qualitative Analysis

Using a hybrid deductive and inductive qualitative approach, we will analyze data obtained from semistructured interviews to explore the facilitators and barriers to participation and engagement in vaping cessation programs. All interviews will be recorded and transcribed verbatim. Subsequently, 2 trained research staff members will independently code the transcripts into reduced meaning units (sentences or phases with singular meaning). Intercoder reliability will be assessed using Cohen κ, with a threshold of ≥.80. All qualitative data analyses will be conducted using NVivo 14 (Lumivero) or Microsoft Excel.

Ethical Considerations

The study protocol was approved by the institutional review board (0596-22-EP) at the University of Nebraska Medical Center and was registered on ClinicalTrials.gov (NCT05586308).

Informed Consent

Approximately 10 days before the baseline visit, eligible individuals scheduled for the in-person visit will receive an email containing an initial packet with the informed consent form, a letter with instructions for their first visit, and contact information for any questions. During the baseline visit, trained research staff members or study investigators will verbally review the informed consent with participants, covering the data collection procedure and plans for protecting participants and their privacy (ie, data deidentification), address any questions, and obtain written informed consent before proceeding with the baseline assessment.

For participants who opt to provide a urine sample during the baseline visit, verbal consent will be obtained by the research staff members before the sample collection. Participants will be guided through the recommended procedures for urine sample collection according to best practices.

Compensation

All study participants will receive a US $25 gift card each for completing baseline and end-of-study visits. Participants who opt to provide a urine sample will receive an additional US $10 at both baseline and end-of-study visits. As a result, participants in the Text Message or Media Literacy groups can earn up to US $70 in total compensation, while those in the Financial Incentive or Combined groups may earn up to US $140, including additional financial rewards contingent on the submission of 4 saliva samples during remote check-ins or end-of-study visit.

Results

Recruitment for the study commenced in December 2023 and concluded in August 2024. A total of 40 participants were randomized into the following groups: 9 for Text Message, 11 for Media Literacy, 10 for Financial Incentive, and 10 for the Combined group. The final assessment was completed in November 2024, and analyses are currently ongoing.

Discussion

Principal Findings

This study is one of the few to assess the feasibility and potential effects of different vaping cessation program combinations in helping young adults quit vaping. We anticipate that the addition of either media literacy or financial incentives will lead to better preliminary abstinence outcomes (ie, more participants quit vaping) by the end of the study, compared with text message support alone.

Unlike other behavioral trials for vaping cessation, which often use a “doing nothing” approach (ie, assessment-only) for the control condition [28,50], we aim to enhance vaping abstinence outcomes by examining the potential additive effects of various interventions on top of an evidence-based program. This approach accounts for participants’ expectation of receiving some levels of interventions when taking part in research studies [28].

There are currently few published studies on behavioral interventions for young adult vaping cessation [26,27,29]. As of the time of writing, 9 other clinical trial protocols are actively recruiting participants to evaluate behavioral vaping cessation interventions among youth (n=3), young adults (n=4), or a mixed youth and young adult population (n=1). These trials have target sample sizes ranging from 30 to 1715 participants, as listed in their registration records on ClinicalTrials.gov. Given the persistently high prevalence of e-cigarette use among young adults, it is crucial to identify effective cessation programs and the supplementary components that may enhance their success. The study findings will be disseminated through peer-reviewed manuscript publications and presentations at national conferences, as well as shared with relevant stakeholders and communities.

Limitations

This study has several limitations that warrant acknowledgment. First, the exclusion of individuals without access to internet services may inadvertently overlook those most in need of cessation assistance, particularly those of low socioeconomic status or residing in remote areas. However, studies have indicated that approximately 95% of American adults have internet access and 90% own smartphones [62], suggesting that the benefits of using technology-assisted behavioral interventions likely outweigh the drawbacks of this exclusion criterion. Second, our use of a commercially available saliva cotinine test kit, which provides binary positive or negative results, to verify abstinence status may not fully capture the extent to which cotinine levels have fluctuated as a result of cessation efforts. Nonetheless, the saliva test offers cost-efficiency compared with urine testing and may serve as a useful monitoring tool for follow-up assessments during the intervention period. Third, although we apply a population health management approach to identify potential participants from an EHR database, it is likely that we are capturing only individuals who receive health care within a specific system rather than from a broader regional population. In addition, due to institutional policy, we are limited to including only those individuals who have opted in for research participation, which

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may introduce selection bias, as these individuals may be less representative of the broader target population [63]. Furthermore, concerns exist regarding the reliability of using vaping or smoking status as a filter to identify potential participants from the EHR database. To address this, we have incorporated an additional step in the recruitment process, requiring potential participants to complete a screening survey to confirm their eligibility before scheduling the baseline assessment. Finally, while our study targets young adults aged 19-29 years, the text message program (This is Quitting) is tailored for individuals aged 18-24 years. We believe that individuals within the broader age range can still benefit from the support program. To accommodate this, participants aged 25-29 years in the trial will be instructed to adjust their age when registering for the text message program during the baseline visit.

Conclusion

In summary, the findings from this trial will aid in refining the study design, particularly regarding vaping program components, and in planning program implementation. In addition, the results may help identify or develop strategies to enhance participant reach and program uptake among young adult populations.

Acknowledgments

We would like to acknowledge Ms Hayley Jurek and Deb Meyer at the University of Nebraska Medical Center Office of the Vice Chancellor for Research, who have been instrumental in participant recruitment of the pilot trial.

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Data Availability

Data sharing is not applicable to this article, as no datasets were generated or analyzed during this study due to the trial being ongoing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The SPIRIT checklist.
[DOCX File , 38 KB - resprot_v14i1e60527_app1.docx]

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Abbreviations

EHR: electronic health record
MediaSense: Media Education for Sensible Evaluation and Nurturing Substance-free Experiences
OR: odds ratio
RCT: randomized clinical trial
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Examining a Telemedicine-Based Virtual Reality Clinic in Treating Adults With Specific Phobia: Protocol for a Feasibility Randomized Controlled Efficacy Trial

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Abstract

Background: Virtual reality (VR) has strong potential to enhance the effectiveness of telemental health care (TMH) by providing accessible, personalized treatment from home. While there is ample research supporting VR for in-person treatment, there is only preliminary data on the efficacy of telemedicine-based VR. Furthermore, the majority of VR apps used in therapy are not designed for mental health care. VR has the potential to enhance TMH through innovative technology solutions designed specifically for the enhancement of remotely delivered evidence-based practices. This feasibility randomized controlled efficacy trial aims to fill both of these gaps by piloting a novel telemedicine-based VR app (Doxy.me VR) equipped with animal phobia exposure stimuli.

Objective: This is a feasibility randomized controlled efficacy trial comparing exposure therapy via a telemedicine-based VR clinic versus standard TMH with adults with an intense fear of dogs, snakes, or spiders. The primary objective is to assess the feasibility of a fully powered trial. The secondary objective is to conduct a preliminary examination of clinical outcomes (eg, specific phobia symptoms).

Methods: This single-site trial will enroll a minimum of 30 and a maximum of 60 adults with self-reported fear of dogs, snakes, or spiders. Potential participants will be recruited through clinical trial and research recruitment websites and posting flyers. All self-report assessments and homework will be partially automated using REDCap (Research Electronic Data Capture; Vanderbilt University) forms and surveys, but the baseline assessment of phobia symptoms and exposure intervention will be administered by the study therapist.

Results: The feasibility of the proposed trial methodology will be assessed using enrollment, retention, assessment completion, and treatment protocol fidelity benchmarks. Between-group differences in specific phobia, anxiety, and depression symptoms while covarying for pretreatment scores, will be conducted using repeated measures ANOVA along with differences in therapeutic alliance and presence. Data obtained from these analyses will inform power analyses for a fully powered efficacy trial. In total, 54 participants were randomized between October 25, 2023, and July 26, 2024 (Doxy.me VR n=28 and TMH n=26). Data analysis will be completed and submitted by the end of the second quarter of 2025.

Conclusions: This feasibility randomized controlled trial comparing Doxy.me VR versus TMH aims to enhance the delivery of evidence-based treatments via telemedicine and reduce barriers to remotely delivered exposure therapy. This feasibility trial will be followed by a fully powered efficacy trial on telemedicine-based VR for animal phobias.

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KEYWORDS
virtual reality; exposure therapy; phobias; telemedicine; telemental health; tele-VR; immersive simulations

Introduction

Background

Telemental health care (TMH) has revolutionized mental health services by providing accessible, personalized treatment from the comfort and privacy of home [1,2]. TMH is equally to more effective than in-person care, with patients generally reporting higher satisfaction and reduced costs [3-11]. Furthermore, TMH alleviates sociocultural (eg, stigma) and geographic (eg, transportation) barriers to mental health care [12-14]. TMH increased from 41.8% to 62.8% of all telehealth services during 2022, surpassing all other forms of digital clinical care [15]. This trend suggests that clients view TMH as an appropriate substitute for in-person care. As TMH services continue to evolve, there will be a growing need for innovative solutions to enhance the effectiveness of remote care [1,16,17].

Virtual reality (VR) is a promising avenue for advancing TMH. By leveraging immersive simulations, VR can recreate stressors—both physical and psychological—in a safe, controlled environment, which can enhance the effectiveness of remotely delivered evidence-based treatments [18-21]. VR improves treatment compliance and patient retention by offering engaging content for in- and between-session mental health exercises [22]. There is abundant support for on-site VR mental health therapy [23,24]; however, evidence for telemedicine-based VR mental health is limited to a few studies of preliminary efficacy [25-27]. VR has strong potential to drive innovations in TMH [28,29].

The customizable simulations of VR can create new opportunities to personalize TMH. For example, exposure therapy is a gold standard treatment for phobias and other anxiety-related mental health disorders that is efficient and produces durable effects [30,31]. By exposing an individual to fear-related stimuli (eg, a dog) in a controlled setting (eg, the therapist's office), anxiety reduces, and the fear response diminishes over prolonged and repeated exposure (eg, the individual is no longer fearful around dogs). One approach to conducting gradual exposure includes using multimedia stimuli (eg, screen-shared photos or videos), but it can be challenging to standardize exposure formats and assess client affect over conventional telemedicine [32,33]. Another approach is exposing patients to their fears using VR. VR-based exposure therapy (VRET) is a safe, accessible, and engaging alternative to in vivo exposure therapy that can be less stressful and more conducive to treatment success [34-37]. However, most VRET research to date has been conducted in-person, requiring that patients travel to and complete therapy in a clinician's office [38]. Delivering VRET over telemedicine may provide patients with highly engaging and immersive treatment with greater accessibility [39]. Telemedicine-based VR may also address lingering barriers to TMH by expanding the experience of therapeutic alliance and presence. Therapeutic alliance, or working alliance, refers to the extent to which a patient and therapist experience a collaborative and trusting relationship [40,41] and is among the strongest predictors of outcomes in mental health care [42,43]. Presence, also referred to as telepresence, is the extent to which places, activities, and other individuals feel real in a digital environment (eg, VR and videoconferencing) [44].

To explore the potential of telemedicine-based VR therapy, we conducted in-depth interviews with 18 practicing TMH therapists who had delivered exposure therapy via conventional telemedicine [45]. Therapists wanted VR features to build rapport with their patients and the ability to customize VR components for individual patient needs. Therapists needed clinical evidence supporting tele-VR, low costs to adopt VR into their TMH practice, and information on possible side effects for patients. We then surveyed 176 practicing TMH therapists about their perspectives on telemedicine-based VR. We asked therapists to rate the relative importance of tele-VR simulations, features, and implementation factors. Therapists strongly favored tele-VR simulations related to social anxiety, flying, driving, and animals. Therapists rated between-session VR exercises and immersive cooperative activities as some of their most valued tele-VR features. Therapists' highest-rated factors for implementing telemedicine-based VR were HIPAA (Health Insurance Portability and Accountability Act)-compliant, followed by affordability, insurance coverage, and accessibility [46].

Using insights obtained from these studies, we developed Doxy.me VR—an innovative app developed specifically to facilitate immersive TMH. We developed Doxy.me VR with the frequent and direct involvement of key stakeholders. Doxy.me VR is designed for a therapist to meet with a client remotely in a private, comfortable VR clinic that looks and feels like a therapist's office (refer to Figure 1 for screenshots of the clinic). To join the VR session, the therapist provides their unique, persistent 4-digit room code to their client, who enters the code to check in. Once the therapist admits the client, they can interact by speaking and gesturing with each other in immersive VR. Therapists can use a menu to spawn animals such as dogs, snakes, and spiders for use in treating specific phobias. Multiple exemplars are available for each type of animal in varying sizes. For example, there are small dogs (eg, Chihuahua, Corgi, and Jack Russell Terrier), medium dogs (eg, Golden Retriever, Shiba Inu, and Pit Bull), and large dogs (eg, German Shepherd, Doberman, and Husky). Each animal is animated with 4 behavior states, that is, idle (ie, no movement), calm (ie, small, slow movements in a relaxed posture), active

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(ie, fast, frequent movements in a playful posture), and aggressive (ie, fast, attacking movements in a defensive posture). Each behavior state also includes corresponding audio such as a calm dog breathing lightly, an active dog panting and barking playfully, and an aggressive dog snarling and barking loudly. Therapists can select, rotate, and move these animals around the room before making them visible to clients. Once therapists make the animal visible, they can continue to move and rotate the animal or remove the animal entirely. Clients cannot directly manipulate objects; however, clients gain access to all the control features while engaging with Doxy.me VR's homework mode, which is used for between-session practice.

Figure 1. Screenshots from Doxy.me VR. Virtual reality clinic space (top left); client admission menu (top right); phobia stimulus menu (bottom left); and therapist and client interacting with phobic stimulus in virtual reality (lower right).

This Study

We present the protocol for a feasibility randomized controlled efficacy trial comparing exposure therapy delivered via Doxy.me VR versus standard TMH to adults with an intense fear of dogs, snakes, or spiders. The primary aim of this study is to assess the feasibility of and refine our study methodology in preparation for a large, fully powered randomized controlled efficacy trial. The secondary aim is to conduct a preliminary examination of clinical outcomes, including between-group differences in specific phobia symptoms, therapeutic alliance, and presence.

Methods

Enrollment and Randomization

This study will use a feasibility randomized controlled efficacy trial design. This single-site trial will enroll a maximum of 60 adults with self-reported fear of dogs, snakes, or spiders with the goal of completing treatment with 30 adults. Participants will be randomly assigned using the REDCap (Research Electronic Data Capture; Vanderbilt University) [47-49]. Randomization Module on a 1:1 allocation ratio to receive 12 weekly sessions of exposure therapy over the course of three months delivered via standard TMH (n=15) versus Doxy.me VR (n=15). Participants randomized to the Doxy.me group will be provided with Meta Quest 2 VR headsets preloaded with the Doxy.me VR app, to be returned to the study team following completion of the study. All therapy sessions will be conducted via remote videoconferencing, with the Doxy.me VR group transitioning to the Doxy.me VR clinic for the exposure exercise portion of the session, and the standard TMH group using multimedia (ie, photos and videos) shared by the study therapist during video calls. Participants randomized to Doxy.me VR received a Meta Quest 2 headset via mail with the VR clinic already downloaded and were provided a clinic code by their therapist at the beginning of each session.

Study Intervention

This study will follow the treatment protocol developed specifically for VRET by Bouchard et al [50], Côté and Bouchard [51], Michaliszyn et al [52], and St-Jacques et al [53]. Following the baseline assessment session, treatment consists of 12, ≤60-minute therapy sessions, including 1 psychoeducation and treatment planning session (session 1), 10 exposure sessions (sessions 2-11), and 1 relapse prevention session (session 12). During the first therapy session, patients learn about the principles of cognitive behavioral therapy, the etiology of anxiety and specific phobias, and procedures for exposure. They then complete a fear hierarchy (ie, a list of situations ranked from least to most anxiety-provoking) with therapist guidance. Fear hierarchies include a text-based list of various VR situations

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or multimedia situations (ie, static and active states of different types of feared animals) and "in vivo" or live situations (eg, petting a dog and touching a snake at a pet store). Therapy sessions 2-11 begin with a review of homework assigned during the previous week's session, followed by an approximately 35-minute virtual exposure session. Patients report their anxiety level using a 1- to 100-point scale at a 5-minute interval throughout the exposure and remain in the exposure until their self-reported anxiety reaches a 50% reduction from their peak anxiety rating from baseline following the introduction of the stimulus or 35 minutes elapses. That is, participants will spend a maximum of 35 minutes in the exposure and if they have reached a 50% reduction or greater from their peak anxiety rating before the 35 minutes is over, they will move on to the next exposure. Following the exposure, the therapist and patient process thoughts and feelings related to the exposure, reframe appraisals of their feared stimuli through cognitive restructuring, and practice box breathing. The Doxy.me VR group will conduct their in-session exposures in the VR clinic and the TMH group will conduct their in-session exposures using multimedia on the Doxy.me platform by screen-sharing videos and photos. Once patients have progressed through all VR and multimedia situations in their hierarchy and are ready to complete their first in vivo exposure between therapy sessions for homework, weekly therapy sessions will be devoted to processing and planning between-session in vivo exposures.

Homework

All therapy sessions will include the assignment of homework, including reading an informational handout after the psychoeducation and treatment planning session (session 1) and exposure therapy assignments after therapy sessions 2-11. Daily exposure-based homework assignments will require participants to practice exposure exercises similar to those completed during that week's therapy session (ie, using VR or multimedia stimuli) for a minimum of 30 minutes. When the patient states that they are ready, these will include in vivo exposure exercises planned during the therapy session. Participants will receive text or email reminders with links to REDCap surveys with instructions for the homework assignment and the situation to be used in the exposure exercise. The survey will also ask participants to report the date and time of the exposure, their baseline anxiety rating, their peak anxiety level during the exposure, and their anxiety level following completion of the exposure exercise.

Recruitment Strategy

Potential participants will be recruited through Clinical Connection [54], Research Match (retrieved from researchmatch website [55]), Facebook (Meta [56]) advertisements, and flyers distributed on the University of South Florida campus and off-campus community centers. Potential participants will be provided with a URL or QR code directing them to an online prebaseline screening questionnaire administered via REDCap. Those meeting preliminary eligibility criteria will then schedule an initial consent and baseline assessment visit via Microsoft Bookings with text or email reminders 24 hours and 1 hour before the scheduled visit time.

Eligibility Criteria

Eligible participants will (1) be ≥18 years old; (2) have a self-reported fear of dogs, snakes, or spiders; (3) have subthreshold or present specific phobia symptoms as determined by the study therapist via administration of the Diagnostic Assessment Research Tool (DART) Specific Phobia Module [57]; (4) have access to the internet and a computer or smartphone with videoconferencing capabilities; and (5) plan to reside in the state of Florida for the duration of the study.

An individual who endorses any of the following criteria will be excluded from participation in the study: (1) participation in ongoing mental health therapy from a nonstudy therapist; (2) changes to psychotropic medication use within 6 weeks preceding enrollment in the trial; (3) active suicidal or homicidal intent or plan as determined by the study therapist via the DART Risk Assessment Module [57]; (4) active auditory, visual, or tactile hallucinations via the DART Psychosis Module screening question; or (5) a diagnosis of photosensitive epilepsy by a medical doctor or a history of experiencing seizures caused by photosensitivity.

Criteria for Withdrawing Participants

Anticipated circumstances under which participants will be withdrawn without their consent include (1) new participation in mental health therapy from a nonstudy therapist; (2) changes to psychotropic medication use; (3) active suicidal or homicidal intent or plan; (4) onset of auditory, visual, or tactile hallucinations; (5) onset of photosensitive epilepsy or seizures; and (6) moving out of the State of Florida during the study period.

If participants completely withdraw or are administratively withdrawn from the study, staff will attempt to provide them with a referral to a therapist in their area. If participants partially withdraw from the research, study staff will attempt to administer mid- and posttreatment assessments. Participants will be given the option to completely withdraw from the study, including withdrawing previously collected data.

Criteria for Wait-Listing Participants

If potential participants do not meet eligibility criteria due to participating in ongoing mental health therapy from a nonstudy therapist or recent changes to psychotropic medication use within 6 weeks preceding enrollment in the trial, they will be presented with a message on the prescreening survey inviting them to revisit the prescreening questionnaire at a later date if and when those conditions no longer apply.

Consent and Baseline Assessments

The consent and baseline assessment visit will be conducted via videoconferencing platform and will not be audio or video-recorded. During this visit, study staff will (1) confirm the potential participant's responses on the online prescreening questionnaire, (2) provide detailed information about the study and obtain informed consent, (3) assist participants in completing baseline questionnaires via REDCap survey, (4) administer the Specific Phobia and Risk Assessment modules of the DART, and (5) make a final determination on the participant's eligibility. Eligible participants will then be

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randomized using the REDCap Randomization Module and scheduled for their first treatment visit. Neither participants nor study staff will be blinded to the comparator of interest or their group assignment.

Assessment Strategy and Measures

Overview

All assessments were chosen considering several factors including (1) sound psychometric properties, (2) ease of administration, (3) past use in similar clinical trials, and (4) brevity. All assessments will be facilitated remotely by the study therapist and will occur at baseline, each session, midtreatment (ie, after completion of 6 therapy sessions, up to 6 weeks post baseline), and 12 weeks post baseline. Self-report questionnaires will be completed by patients via REDCap survey with the study therapist present to answer any questions. Structured diagnostic interviews will be administered by study therapists and recorded in REDCap.

Specific Phobia Symptoms and Severity

The DART [57] is a modular semistructured interview corresponding with the *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) [58]. Study therapists will administer the DART Specific Phobia Module, which provides designations of absent, subthreshold, and present. While the DART is a new tool, initial validation indicates excellent construct validity, discriminant validity, and convergent validity across modules [57,59].

The Severity Measure for Specific Phobias (SMSP) for adults [60] is a 10-item self-report questionnaire assessing the severity of specific phobia symptoms as they relate to the respondent's feared stimulus. Total scores range from 0 to 4 with higher scores indicating higher phobia severity. The SMSP has excellent internal consistency, criterion, and discriminant validity [61].

Other Mental Health Symptoms

Suicide and Homicide Risk

The DART-Risk Assessment Module [57] will be administered by study therapists to assess risk for suicidal and homicidal ideation, intention, and plans and guides the formation of safety plans where warranted.

Generalized Anxiety

The Generalized Anxiety Disorder-7 Scale (GAD-7) [62] is a 7-item self-report measure of anxiety symptom severity. Scores range from 0 to 15 with higher scores indicating higher anxiety severity. The GAD-7 is widely used and has demonstrated excellent internal consistency reliability and good convergent validity [63].

Depression

The Patient Health Questionnaire-8 (PHQ-8) [64] is an 8-item self-report measure of depression symptom severity. Scores range from 0 to 27 with higher scores indicating higher depression severity. The PHQ-8 has demonstrated excellent internal consistency reliability, good convergent validity, and specificity for depression diagnosis [65].

Treatment-Related Factors

Working Alliance

The Working Alliance Inventory [66] is a 10-item client-rated measure of therapeutic alliance. Total scores range from 1 to 5 with higher scores indicating a better therapeutic alliance. The WAI-SR has demonstrated excellent internal consistency, reliability, and good convergent validity [67].

Presence

The Single Item Presence Questionnaire (SIPQ) [68] is a 1-item self-reported measure of telepresence. Respondents are asked, "To what extent did you feel present in the environment, as if you were really there?" and provide ratings on a scale of 0 "not at all present" to 10 "totally present." The SIPQ has demonstrated good to excellent content, face validity, test-retest, convergent and divergent validity, and sensitivity [68].

Cybersickness

The Cybersickness in Virtual Reality Questionnaire (CSQ-VR) [69] is an 8-item measure of nausea, vestibular, and oculomotor cybersickness experienced in VR. Scores range from 6 to 27 with higher scores indicating higher levels of cybersickness. The CSQ-VR has demonstrated excellent internal consistency and convergent validity [70].

Client Satisfaction With Treatment

The Client Satisfaction Questionnaire-8 (CSQ-8) [71] is an 8-item client-rated measure satisfaction with treatment. Scores range from 8 to 32 with higher scores indicating higher satisfaction. The CSQ-8 has demonstrated good structural validity and internal reliability and is correlated with clinical outcomes and posttreatment functioning [72].

System Usability

The System Usability Scale (SUS) [73] is a 10-item self-report measure of the usability of a particular software system, platform, or app. Scores range from 0 to 100 with higher scores indicating better usability. The SUS has demonstrated good internal consistency reliability and is a useful tool for comparing system usability between 2 and more platforms.

Fidelity to the Treatment Protocol

All treatment sessions will be recorded and 20% (120/600) will be rated by the supervisor (principal investigator) using a treatment fidelity checklist based on the treatment manual. Refer to Table 1 for a summary of study assessments.

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Table 1. Study assessments.

Domain	Measure	Time point				
		Pre	Baseline	Weekly	Mid	Post
Demographics	Demographics Questionnaire		✓			
Specific phobia diagnosis	Diagnostic Assessment Research Tool–Specific Phobia Module (DART-SP)		✓			✓
Specific phobia severity	Severity Measure for Specific Phobia-Adult (SMSP-A)	✓	✓		✓	✓
Risk	Diagnostic Assessment Research Tool–Risk Assessment (DART-RA)		✓			
Anxiety severity	General Anxiety Disorder-7 (GAD-7)		✓		✓	✓
Depression severity	Patient Health Questionnaire-9 (PHQ-9)		✓		✓	✓
Therapeutic alliance	Working Alliance Inventory- Short Revised (WAI-SR)				✓	✓
Presence	Single Item Presence Questionnaire (SIPQ)			✓		
Cybersickness	Cybersickness in Virtual Reality Questionnaire (CSQ-VR)			✓		
Treatment satisfaction	Client Satisfaction Questionnaire (CSQ-8)				✓	✓
Usability	System Usability Scale (SUS)				✓	✓

Partial Automation of Trial Data Collection Using REDCap

All feasibility trial data will be collected via 2 REDCap projects. The first REDCap project will include a survey to collect responses to the online prescreening questionnaire, which will include questions about basic eligibility criteria, the SMSP, and contact information. If potential participants meet the initial study eligibility criteria of the REDCap survey, they will be directed to a Microsoft Bookings page to schedule their baseline assessment, with automated reminders about the appointment 24 and 1 hours before the appointment.

The second, main REDCap project will facilitate all other data collection for the feasibility trial. Participants' online prebaseline screening questionnaire responses will be automatically transferred to the main clinical trial project using the REDCap piping function in preparation for the baseline assessment. After obtaining informed consent, supported by the REDCap e-Consent Framework feature, participants will be automatically directed to baseline questionnaire surveys, for which REDCap auto-calculates the scores. Following completion of the baseline assessment, the participant will be randomized to their respective treatment conduction using the Randomization Module. All therapy session data (ie, session number, date, time, and length), adherence checklist, clinical notes, and in-session exposure ratings will be entered into a REDCap form by the study therapist during each therapy session. Following the completion of each session, participants will receive automated survey invitations to complete homework assignments, which will be delivered on specific days during the following based on the session number, session date, and treatment condition. Weekly postsession questionnaires (ie, SIPQ and CSQ-VR) will be completed via REDCap surveys, displayed conditionally based on treatment condition (eg, the CSQ-VR will only be displayed to those in the Doxy.me VR condition). Specific REDCap automations and features used for each stage of the trial are included in Figure 2.

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Figure 2. REDCap (Research Electronic Data Capture) automation and features. UI: user interface.

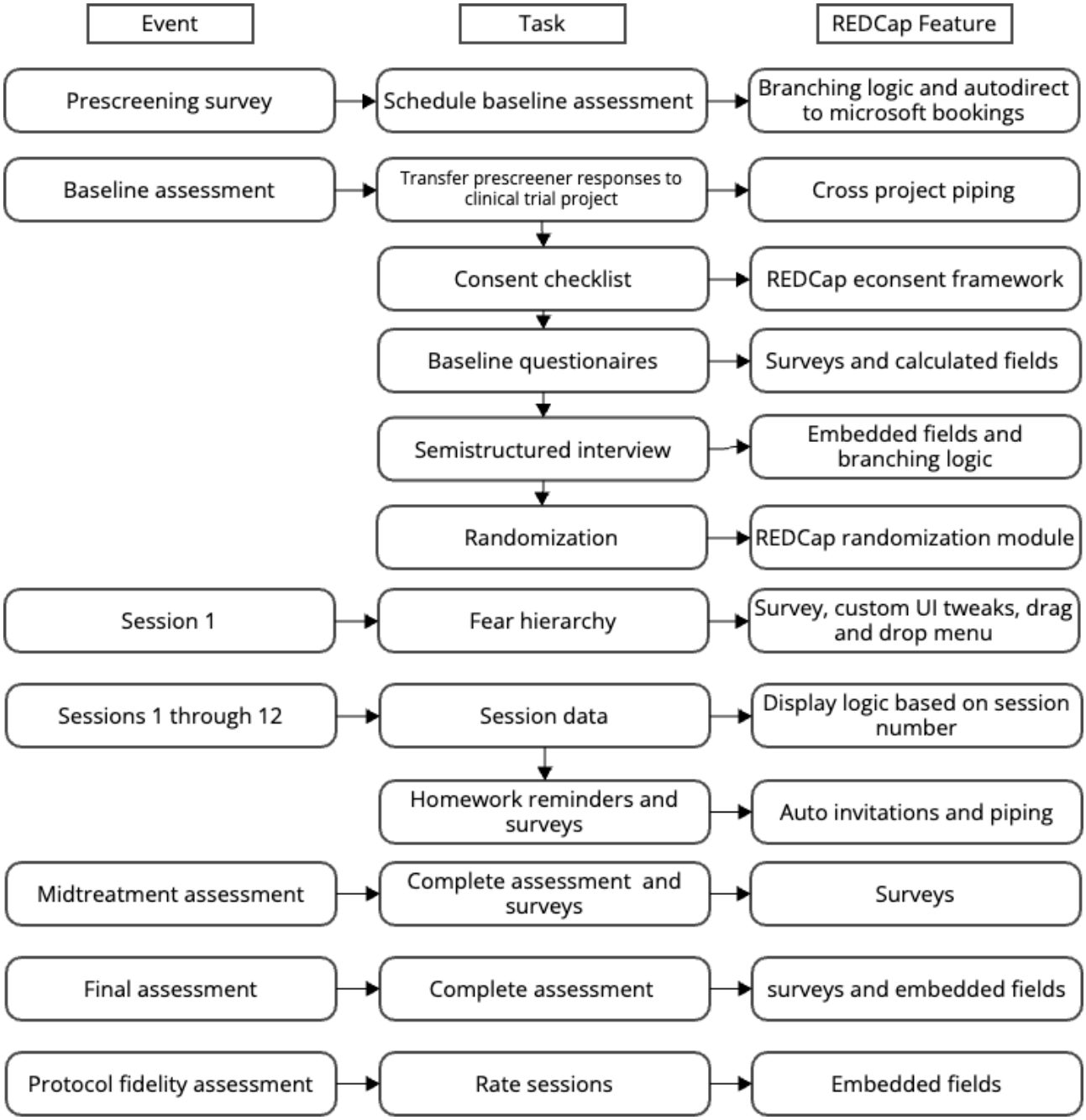

Ethical Considerations

The protocol was approved by the University of South Florida institutional review board (#006215). All participant data will be stored in the University of South Florida REDCap database and only study staff members have access to the REDCap project. All data exported for analysis from REDCap will be anonymized with only participant ID numbers. Participants will be compensated US $50 for completing the baseline, midtreatment assessment, and 3-month post baseline assessment at a total of US $150. Participants will be compensated using Tango e-gift cards.

Procedures to Ensure Participant Safety

Some questions asked during assessments and exposure exercises may cause participants distress, but this distress is expected to be similar to what participants would experience with routine care for specific fears or phobias. The study therapist will ensure that any questions causing distress are discussed with participants and provide them with techniques to reduce distress. A temporary increase in the severity of anxiety is expected at the beginning of exposure therapy, along with a gradual decline in severity over the course of treatment. If participants are distressed and unable to participate in the study following baseline assessments, or at the end of the study, participants feel that they need further treatment, the study therapist will provide a referral to therapists in the participants' local area. Referrals will be provided verbally to participants and the study therapist will follow up in 1 week via telephone to inquire as to the state of the referral and provide further assistance as necessary. If participants endorse suicidality or homicidality at any point during the study, we will follow the

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standard operational procedures of the University of South Florida Department of Psychiatry and Behavioral Neurosciences requiring safety planning with the participant at risk and mandatory reporting responsibilities.

Data Analytic Plan

We will assess the feasibility of the proposed trial methodology using the following benchmarks: (1) 30 participants will be enrolled in months 1-9 of the trial, (2) ≥70% (21/30) of participants will be retained for 3-month follow-up assessments, (3) 70% (420/600) of weekly self-report assessments will be completed, and (4) treatment fidelity we will be ≥80%. The small sample size of this feasibility trial will prevent us from making conclusions about efficacy; however, a repeated measures ANOVA will be used to conduct a preliminary assessment of between-group differences in clinical outcomes while covarying for pretreatment scores. We will also conduct a preliminary examination of associations between study targets (ie, therapeutic alliance and presence) and homework adherence. Data obtained from these analyses will inform power analyses aimed at determining sample size requirements for a fully powered efficacy trial.

Results

The first participant was enrolled on October 25, 2023, and the last therapy session and 3-month post baseline assessment were completed on July 26, 2024. In total, 54 participants were randomized. Refer to Figure 3 for the CONSORT (Consolidated Standards of Reporting Trials) diagram and Multimedia Appendix 1 for the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist. Data analysis for the primary and secondary aims of the clinical trial will be completed and submitted by the end of the second quarter of 2025.

Figure 3. CONSORT diagram.

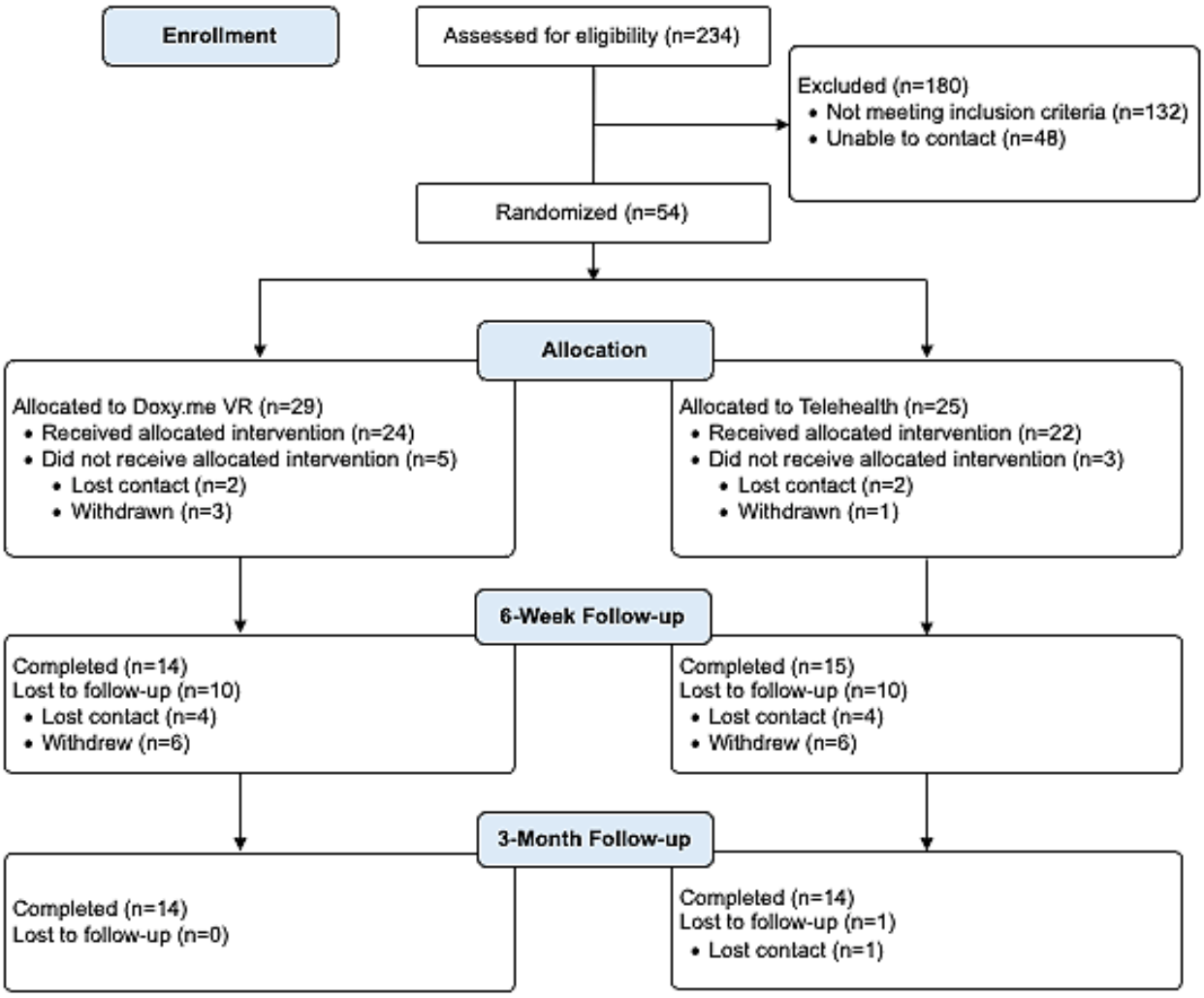

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Discussion

Overview

There will be a growing need for innovative solutions to enhance the effectiveness of remote care as TMH services continue to evolve [1,16,17]. VR has tremendous potential to increase the efficacy of evidence-based practices that were originally designed for in-person treatment but are now delivered via TMH with increased regularity (eg, exposure therapy). This feasibility trial comparing exposure therapy via Doxy.me VR versus TMH for adults with an intense fear of dogs, snakes, or spiders fills an important gap in the nascent research on telemedicine-based VR exposure therapy. Using this protocol, we will assess the feasibility of our proposed study methodology in preparation for a fully powered efficacy trial. We anticipate meeting or exceeding these feasibility criteria, which will provide valuable insights into the feasibility of conducting a large-scale efficacy trial.

Principal Findings

As anticipated, we exceeded our recruitment goal of enrolling 30 or more participants in months 1-9 of the clinical trial by enrolling 54 participants during months 1-7. Data analysis will be completed and submitted by the second quarter of 2025 at which point we will report on the remaining feasibility results.

Comparison With Previous Work

Our study builds upon previous research demonstrating the efficacy of VR exposure to enhance treatment delivery. While there is significant support for in-clinic VR mental health therapy, evidence for telemedicine-based VR mental health is limited. Our study addresses this important gap by evaluating the feasibility and preliminary efficacy of exposure therapy via an innovative telemedicine-based VR clinic (ie, Doxy.me VR), thereby contributing to the nascent research on the use of VR in TMH.

Limitations

The small sample size proposed by this study limits the generalizability of our findings and prevents us from drawing conclusions about treatment efficacy. A large-scale efficacy trial will address this limitation.

Conclusions

This feasibility randomized controlled trial comparing Doxy.me VR versus TMH represents an important step toward leveraging VR technology to enhance the delivery of evidence-based treatments via telemedicine. By evaluating the feasibility and preliminary efficacy of exposure therapy via a telemedicine-based VR clinic, we will contribute a potential solution to common barriers to remotely delivered exposure therapy.

Future Directions

Future research will involve fully powered efficacy trials on telemedicine-based VR and the potential of this technology to improve treatment outcomes for mental health disorders.

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Data Availability

The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

BEB, TO, and BMW are employees of Doxy.me Inc, a commercial telemedicine company. The authors declare no other conflicts of interest.

Multimedia Appendix 1
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1272 KB - resprot_v14i1e65770_app1.pdf]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
CSQ-8: Client Satisfaction Questionnaire-8
CSQ-VR: Cybersickness Questionnaire for Virtual Reality
DART: Diagnostic Assessment Research Tool
DSM-5: Diagnostic and Statistical Manual-Fifth Edition
GAD-7: Generalized Anxiety Disorder-7
HIPAA: Health Insurance Portability and Accountability Act
PHQ-8: Patient Health Questionnaire-8
REDCap: Research Electronic Data Capture
SIPQ: Single Item Presence Questionnaire
SMSP: Severity Measure for Specific Phobias
SUS: System Usability Scale
TMH: Telemental health care
VR: virtual reality
VRET: virtual reality–based exposure therapy

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Protocol

Mobile App–Delivered Motivational Interviewing for Women on Eating Disorder Treatment Waitlists (MI-Coach: ED): Protocol for an App Development and Pilot Evaluation

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Abstract

Background: A significant increase in eating disorder (ED) service waitlists has been observed in the past several years, exacerbating existing barriers to care (eg, long waitlists, scarcity of treatment centers, and positive beliefs surrounding pathology). Given that treatment delays have important clinical correlates (eg, entrenchment of ED pathology), exploring new methods of mental health service delivery for this population is of critical concern. App-based motivational interviewing (MI) delivered prior to the start of treatment has the potential to improve accessibility by simultaneously addressing structural (eg, travel costs) and individual (eg, low motivation) barriers to care. Despite the potential benefits, there remains a lack of empirically validated, ED-specific MI-based mobile apps. Evaluating the feasibility and acceptability of such interventions is a crucial first step before progressing to full-scale efficacy trials.

Objective: This multiphasic mixed methods study aims to develop and assess the feasibility and acceptability of MI-Coach: ED, a novel app designed to increase motivation among women waitlisted for ED treatment. Specifically, this study seeks to determine participant engagement levels, user satisfaction, and perceived usability of the app, as well as to explore preliminary trends in motivation and ED-related symptoms following app use.

Methods: Phase I adapted the content and interface of an existing app based on evidence-based principles (MI-Coach) for an ED population. Phase II pilot tested the app through a pre-post evaluation. Participants (n=30) aged 18 years and older were recruited from ED treatment waitlists in British Columbia, Canada. After completing baseline assessments evaluating demographic and clinical variables (eg, motivation, eating pathology, depression, and anxiety symptoms), participants were provided access to MI-Coach: ED for 1 month. Participants completed postintervention assessments and provided both quantitative and qualitative feedback on the app. Feasibility will be evaluated through the total number of participants recruited, study dropout rates, and engagement indicators (eg, modules completed) within the app. Acceptability will be assessed through self-report measures and semistructured exit interviews, which will explore user experiences, perceived benefits, and barriers to app engagement. Additionally, exploratory analyses will examine changes in motivation and ED symptoms before and after the intervention.

Results: The MI-Coach: ED app has been developed, and recruitment was initiated in November 2022 and terminated in May 2024. Results are being analyzed and will be submitted for publication in May 2025.

Conclusions: This study has the potential to transform ED service delivery and mitigate the impacts of existing treatment barriers for this population. By leveraging a digital MI-based intervention, MI-Coach: ED could serve as a scalable and accessible pretreatment tool, helping to bridge the gap between initial help-seeking and formal ED treatment. Findings from this study will inform the refinement of the intervention and recruitment strategies for future large-scale efficacy trials.

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KEYWORDS

eating disorders; motivational interviewing; treatment barriers; digital interventions; pilot test; protocol; eating disorder; eating; woman; women; female; Canada; Canadian; mobile apps; mobile health; mHealth; app development; app-based; mental health; pilot evaluation; waitlists; mixed methods; feasibility; acceptability; service delivery

Introduction

Eating disorders (EDs) are serious, life-threatening psychological illnesses that involve disturbances surrounding body image, emotion regulation, and eating behaviors [1,2], resulting in a number of deleterious health consequences and high levels of psychiatric comorbidity [3-5]. Despite the severity of these disorders, ED populations are significantly less likely to access mental health services compared to those with other disorders [5,6]. For instance, wait times exceeding 12 months for ED-specific services have been reported in Ontario, Canada, and nonprofit organizations have observed a 2-fold increase in requests for peer-support services following the COVID-19 pandemic [7]. In this regard, several treatment barriers have been identified limiting access to ED treatments and services. As EDs require specialized forms of care, treatment centers are typically few in number, necessitating significant travel time and associated costs (eg, costs related to travel and childcare and loss of income due to sick leave), and often resulting in long waitlist durations [6]. Further, ambivalence regarding treatment is common among ED populations, with motivation for recovery often in conflict with other factors, such as engaging in ED behaviors to cope with difficult emotions or to provide a sense of control [8-10].

Unfortunately, treatment delays are associated with adverse outcomes, such as reductions in pretreatment levels of motivation and poorer long-term prognosis. Early intervention has been associated with improved treatment outcomes following discharge, longer durations between relapses, and improvements in related psychological symptoms such as depression and anxiety [11]. Recent efforts to bridge treatment barriers and improve outcomes for this population include the delivery of brief interventions such as motivational interviewing (MI) prior to the start of formal treatment. Initially developed by Miller and Rollnick [12] to address ambivalence within substance use treatment, MI is a person-centered approach that aims to strengthen the individual's intrinsic motivation to change [13]. A recent systematic review conducted by Denison-Day et al [8] found substantial support for the use of MI interventions for individuals with EDs, with a majority (74%) of the studies reviewed reporting significant and long-term improvements in motivation as a result of MI interventions compared to passive interventions, such as psychoeducation. Broadly, studies report that brief MI interventions lead to improvements in motivation, self-esteem, depressive symptoms, and positive treatment outcomes (eg, greater engagement in treatment), particularly when delivered prior to the start of formal treatment [14-16].

Despite the potential for pretreatment MI interventions to address individual treatment barriers, they are typically conducted through in-person, face-to-face sessions [8,14,16,17]. In-person interventions may not adequately address structural treatment barriers, such as costs and scarcity of treatment providers. In order to address this issue, internet and communications technology (ICT)–based interventions have been proposed as a low-cost and accessible form of delivering ED interventions [5,18-20]. Apps in particular show potential in the delivery of pretreatment MI interventions, as they are easy to use, require low effort, and become habitual over time. Further, unlike other ICT-based interventions, they have high hedonic motivation (ie, they are enjoyable to use), which increases their use and adoption [21,22]. In addition, the digital components embedded within apps (eg, modules, graphic design, and diverse multimedia content) have been shown to significantly improve adherence to interventions and reduce dropout rates [23].

Despite preliminary findings suggesting that apps may be an acceptable means of delivering ED services, there is a paucity of effective, evidence-based apps available for use [24-27]. Most publicly available app interventions are based on CBT and behavioral self-monitoring principles but demonstrate limited efficacy compared to traditional delivery methods [24,28]. However, considering the accessibility of apps and their wide adoption in various health and social contexts [29], they may be an effective mode of delivery for pretreatment MI contexts. Help-seeking individuals waiting for formal services likely do not have access to in-person treatment options, despite their urgent need for services. Further, as they have not yet started formal ED treatment, receiving a pretreatment MI intervention may significantly improve treatment outcomes. For example, such interventions may increase motivation to stay on the waitlist and adhere to treatment once services are received [30]. An app-based MI intervention thus has the potential to simultaneously address structural and individual treatment barriers. Despite the potential benefits, to date, no research has investigated the use of app-based MI pretreatment interventions for EDs.

The proposed study aims to adapt and pilot-test MI-Coach, a widely available app-based MI platform, for individuals on ED treatment waitlists. Created by Resiliens Inc, MI-Coach is an evidence-based self-help app developed in collaboration with a registered clinical psychologist. The app was adapted for use within an ED pretreatment context. Furthermore, this will be the first study to investigate whether an app-based MI pretreatment intervention improves clinical symptoms, motivation for treatment, and openness to change for individuals while they wait for ED treatment.

Methods

Hypotheses

This project is guided by the technology acceptance model (TAM), which theorizes that an ICT's acceptability is determined by its perceived ease of use and usefulness [31]. It is thus hypothesized that greater perceived usefulness and ease of use of the MI-Coach: ED app will lead to greater use and engagement with the app, and subsequently, improved treatment

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outcomes. It is also hypothesized that participants will experience an improvement in their motivation to recover from an ED following use of the app. In addition, the app's acceptability and feasibility will be examined, as well as the possible impacts of other clinical variables (eg, depression, anxiety, BMI, and ED severity) on motivation to recover.

Ethical Considerations

Ethics approvals were granted by the University of British Columbia Okanagan Campus' Behavioral Research Ethics Board (H22-02046) on October 4, 2022, and by the Vancouver Coastal Health Research Institute (V22-02046) on October 10, 2023. All eligible participants provided informed consent electronically through the secure web-based platform Qualtrics prior to enrollment, after receiving detailed information about study procedures, potential risks and benefits, data confidentiality, and voluntary participation. Participants were informed of their right to withdraw from the study at any time without penalty. Participant privacy was maintained by storing data on password-protected university servers accessible only to research personnel. All identifying information was stored separately from the study data. Participants received compensation of up to CAD $40 (≈US $28.41) in the form of digital gift cards. Compensation was clearly outlined in the informed consent form and was structured to avoid influencing participation or app use.

Study Design

The current pilot test evaluation follows a naturalistic pre-post design. A pilot test framework was chosen to assess the initial feasibility and acceptability of the app and to identify any potential issues with the study design and delivery format prior to evaluating the app's efficacy at a larger scale [32]. The MI-Coach: ED app was designed to improve motivation in women-identifying people waiting for formal ED treatment and will be pilot-tested in the province of British Columbia, Canada. Qualitative and descriptive data were collected to determine the acceptability and feasibility of the MI-Coach: ED app.

Study Population

Sample Size Estimation

Given the focus of this study on the acceptability and feasibility, rather than the efficacy, of the MI-Coach: ED app, formal analytic methods were not used to estimate the prehoc sample size. In keeping with previous feasibility studies in the ED field [14,33,34] and pilot study guidelines, which suggest that modest sample sizes based on the pragmatics of recruitment are sufficient when evaluating the processes, feasibility, and preliminary acceptability of novel interventions [32,35], a sample size of 30 participants was selected, recruited while they wait for ED services and treatments in British Columbia, Canada. Additionally, it was determined that qualitative interviews would be conducted with interested participants on a rolling basis until thematic saturation is reached [36].

Participant Recruitment

ED treatment providers and clinicians located in British Columbia were contacted by email and asked to distribute study recruitment flyers providing an overview of the study, incentives, and instructions to contact the study team to indicate their interest to clients on their waitlists (Multimedia Appendix 1). To address existing barriers to ED treatment (eg, logistical challenges and clinician burnout [6,37]) and research [38], a multipronged approach to recruitment has been used in previous studies [15,39], whereby clinician-based referrals are supplemented by web-based recruitment and partnerships with peer support organizations. As such, clinician-based referrals were supplemented by web-based recruitment strategies, including postings on the National Eating Disorder Information Center website and social media, as well as partnerships with peer support organizations. Additionally, a research partnership was established with a local provincial health authority, the Vancouver Coastal Health Eating Disorders Program, which embedded the study flyer as part of an initial resource package provided to patients newly added to their waitlist. Given the findings that recruitment strategies influence sample characteristics and engagement [38], this multipronged approach aimed to maximize the accessibility of the study and diversity within the study sample.

Eligibility Criteria

Eligibility criteria were (1) being on a waitlist to receive services for an ED-specific concern and not for a separate mental disorder in British Columbia, (2) being at least 18 years of age, (3) self-identifying as a woman, (4) fluency in written and spoken English, (5) meeting the criteria for a diagnosis of a threshold or subthreshold ED (ie, BN, AN-R, AN-BP, BED, and OSFED), (6) absence of psychosis or diagnosis of a schizophrenia-spectrum disorder, and (7) absence of cognitive impairments or sensory deficits that may interfere with technology use (eg, hearing impairments and recent traumatic brain injury).

Intervention

MI-Coach is a self-help app created by Resiliens Inc [40] targeting motivation to engage in health behavior change (eg, exercising, smoking cessation, and sleep hygiene), and is widely available on both Apple and Android app stores. Developed in collaboration with a clinical psychologist and MI expert from the University of Queensland (Stan Steindl, PhD), the app features eight modules, consisting of over 35 lessons led by a registered clinical psychologist with accompanying exercises. In addition, the app includes short articles, mood and behavior assessments, mindfulness-based audio tracks, summary screens and analytics, community-based discussion groups, and the ability to communicate directly with a trained mental health professional.

For the purposes of this study, the content of MI-Coach was tailored for an ED population. In line with best practices for developing ED-specific digital interventions [17,30,41], an in-depth review of potentially iatrogenic or triggering content in the existing app was identified. Specifically, content referring to weight loss or health-focused exercise goals was identified, which prior research suggests may inadvertently reinforce disordered eating behaviors [28,30,37,42]. Subsequently, a literature review was conducted to identify MI topics and ED behavior change goals used in previous interventions, such as exploring reasons for and against pursuing treatment, validating

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the difficulties of addressing ED pathology, and identifying values and goals driving ED recovery efforts [11,17,30,41].

Following approaches outlined in previous research [15], the research team then performed iterative content analyses to remove or reframe any references misaligned with ED recovery principles (eg, shifting from weight-centric to motivation-centered goals that explore the individual's reasons for seeking treatment, and the inclusion of topics such as ambivalence and identification of goals and values relevant to recovery). The overall structure and MI principles used in the original app were retained given their demonstrated effectiveness within an ED context [8]. Throughout this process, informal stakeholder consultations were conducted with ED-specialized clinicians involved in the project, who verified the appropriateness of the revised app content. All video lessons were subsequently refilmed using the University of British Columbia Okanagan's recording studio and equipment. The new videos featured a clinical psychologist with ED treatment expertise to reduce discrepancies between the original and adapted app content (eg, clinical expertise and years of training). Examples of the MI-Coach: ED interface are provided in Figure 1.

Once the adaptation of app content was completed, a new section was built into the interface of the existing MI-Coach app by technological partners (Resiliens Inc) to house the adapted content. Several components of the base app (ie, assessments, audio tracks, analytics, discussion groups, and communication with the mental health professional) were removed to reduce the scope of the project and to protect participant confidentiality. The final adapted MI-Coach: ED app consisted of seven modules (Multimedia Appendix 2) targeting motivation to engage in ED recovery behaviors (eg, help-seeking, values exploration, and self-acceptance) covering the following topics sequentially: ambivalence and behavior change, self-acceptance and compassionate motivation, exploring possible behavior change goals, sustain and change talk, commitment language, and relapse prevention.

Figure 1. Screenshots of the MI-Coach: ED interface illustrating (a) the home screen with session modules, (b) example module content, (c) brief videos, (d) examples of exercises available per module, and (e) example exercise content. Each feature targets ED-specific barriers such as ambivalence or low treatment motivation. ED: eating disorder.

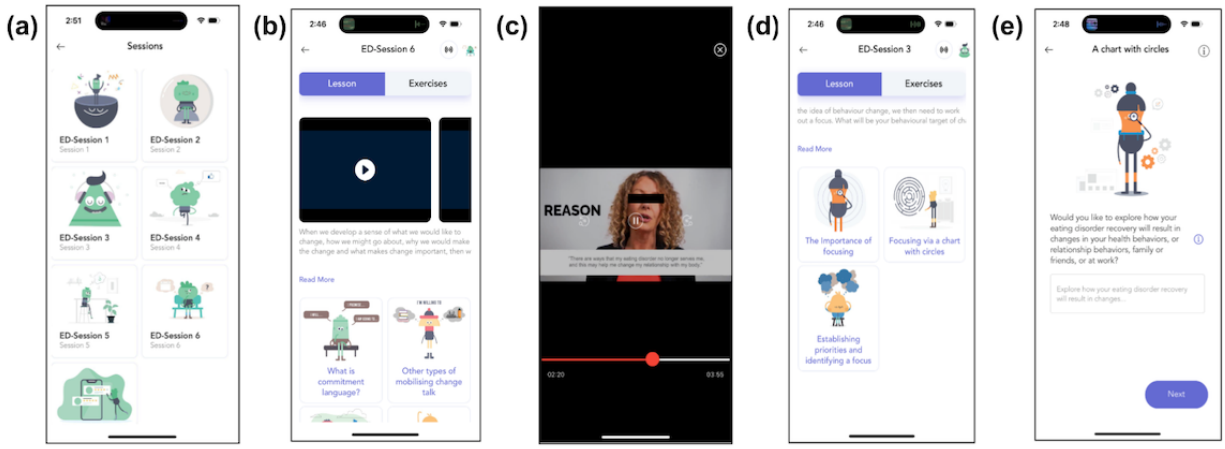

Outcomes and Measures

The primary outcomes that will be evaluated are the overall acceptability and feasibility of the MI-Coach: ED (Multimedia Appendix 3). Feasibility will be assessed through attrition rates throughout the study period, frequency of app use, and module completion. Acceptability will be assessed through qualitative and quantitative feedback from participants through semistructured interviews and self-reports. Additionally, exploratory analyses will be conducted regarding the impacts of the MI-Coach: ED app on motivation and associated clinical characteristics.

Self-reported demographic data, including gender identity, age, level of education, ethnicity, and socioeconomic status were collected using Qualtrics, a web-based and secure data collection platform. Additionally, clinical data (ie, weight and height, history of ED treatment, age of ED onset, presence of cognitive difficulties, sensory deficits, history of traumatic brain injury, other mental health comorbidities, and ED waitlist experiences) was collected. The Sick, Control, One, Fat, and Food questionnaire [43], a brief screener that identifies the presence of common ED symptoms, was used to determine eligibility prior to enrollment. Clinical characteristics (ie, eating pathology, recovery motivation, body dissatisfaction, depression, and anxiety symptoms) were evaluated through several self-report questionnaires administered at baseline and posttest, including the Eating Disorder Examination Questionnaire (EDE-Q) [44], the Readiness and Motivation for Change Questionnaire (RMQ) [45], the Body Shape Questionnaire (BSQ) [46], the Patient Health Questionnaire-9 (PHQ-9) [47], and the 7-item General Anxiety Disorder Scale (GAD-7) [48]. Additionally, technological literacy was evaluated at baseline using the Mobile Device Proficiency Questionnaire [49] and the eHealth Literacy Scale [50].

Quantitative measures of feasibility and acceptability of the MI-Coach: ED app were assessed using an adapted version of the TAM Questionnaire [31] and the user version of the Mobile App Rating Scale (uMARS) [51]. The adapted version of the TAM questionnaire includes changes to each item to better fit the research question and sample characteristics of this study (eg, "Using CHART-MASTER in my job would enable me to

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accomplish tasks more quickly" was modified to "Using MI-Coach: ED allowed me to access mental health services more quickly"). An optional semistructured interview was conducted with interested participants to assess their experiences with the app and to further evaluate the feasibility and acceptability of MI-Coach: ED.

An overview of participant flow is provided in Figure 2. Participants were recruited between November 2022 and April 2024. Clinicians and administrators working in a range of ED treatment settings (eg, provincial health authorities, nonprofit charities, and private practice clinics) were contacted via email and asked to share the recruitment advertisement with clients on their waitlists. Interested participants were asked to communicate with the study team via email to enroll in the study. Once initial contact was established, a 15-minute telephone screener was conducted by the study team to assess participants' eligibility for the study and to provide additional details regarding the study. The Sick, Control, One, Fat, and Food questionnaire was used to evaluate the presence of ED symptoms. Once eligibility was established, consent (Multimedia Appendix 4) and baseline measures were collected through Qualtrics, including a demographics questionnaire, the EDE-Q, the RMQ, the PHQ-9, the GAD-7, and the BSQ. Following this, an onboarding session was conducted through a secure videoconferencing platform (ie, Zoom), during which participants were given a demonstration on downloading and using the app and provided their log-in information.

The subsequent pilot-test portion of the study consisted of a four-week period during which participants used the app in a naturalistic way. Following study completion, participants were compensated CAD $10 (≈US $7.10) for each study portion completed (ie, baseline questionnaire package, onboarding session, posttest questionnaire package, and exit interview), receiving up to CAD $40 (≈US $28.41) through the Tango Card rewards platform. To reduce the impact of possible confounds (eg, financial motivation), participants were informed that their compensation would not be impacted by their app use during the pilot test phase and that there are no minimum requirements for app use. Once the pilot test was completed, a second brief consent form (Multimedia Appendix 5) and posttest questionnaires assessing self-reported clinical features (ie, the EDE-Q, RMQ, PHQ-9, GAD-7, and BSQ) and feedback regarding the app (ie, the adapted TAM-Q and uMARS) were completed. Finally, participants were invited to participate in a videoconferencing-based exit interview to provide additional feedback on their experience with the study author. The semistructured interview guide (Multimedia Appendix 6) was used as an outline to standardize the interview process across participants [52].

Figure 2. Participant flow diagram.

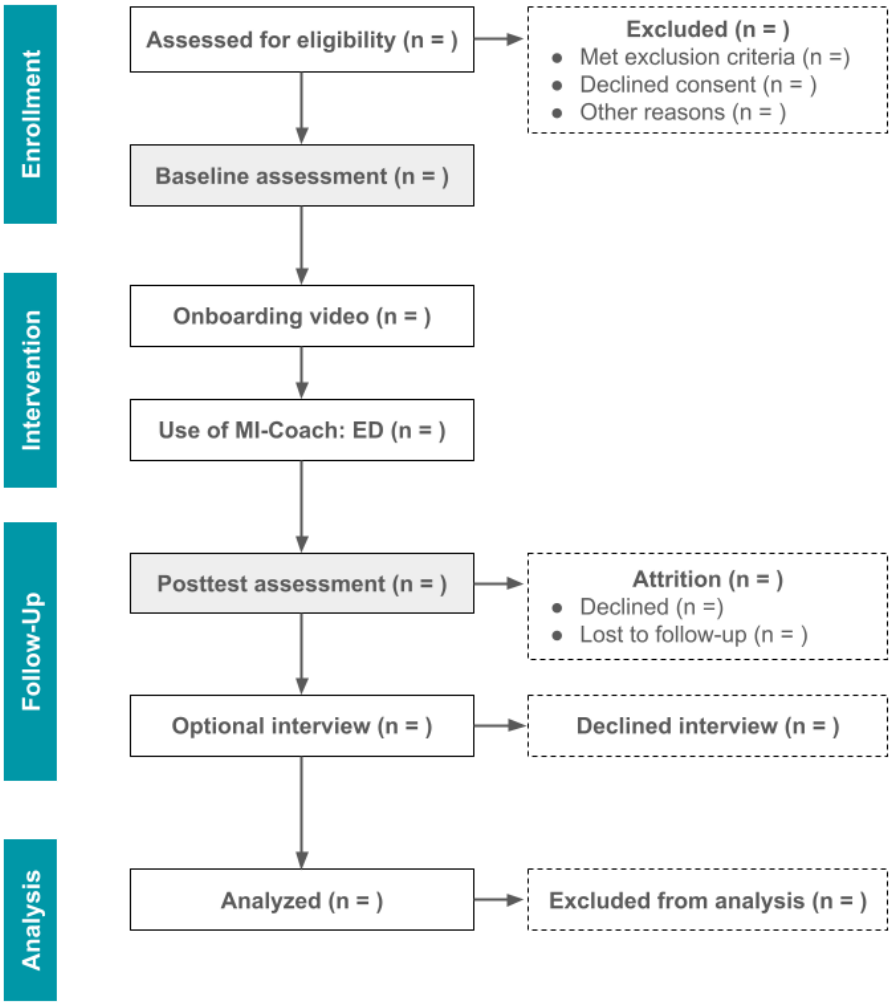

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Statistical Analysis

Prior to analysis, interview audio recordings will be transcribed verbatim by 2 trained research assistants and verified by the primary researcher (AH-A). Qualitative interview transcripts will be analyzed using the NVivo software package (version 12; QSR International), to assess in-depth feedback regarding MI-Coach: ED's feasibility and acceptability. A thematic content analysis will be conducted to analyze the qualitative responses from the open-ended uMARS questionnaire and semistructured interview data using Braun and Clarke's [36] framework. A bottom-up theoretical approach was used, in which the analysis was driven by the data generated through the semistructured interviews [36,53].

Additionally, quantitative analyses will be conducted using the R statistical package (version 4.2.0; R Core Team). Descriptive analyses of posttest feedback questionnaires, attrition data, and sessions completed will be used to determine the feasibility and acceptability of the MI-Coach: ED app. Means, SDs, ranges, and percentages will be calculated for all descriptive variables (ie, age, ethnicity, BMI, height, and weight), and total and mean scores will be calculated for app acceptability measures. Overall app use (ie, number of modules completed, days that the app was used, assessments and exercises completed, and logins) will be calculated using in-app data provided by Resiliens Inc.

Finally, tests of clinical significance [54] will be used to evaluate changes in clinical presentation across time points. The following categorizations will be used to identify whether change is clinically significant: reliably improved, in which there is reliable change and the clinical cutoff is no longer met; reliably deteriorated, in which there is a reliable change in the disordered direction and the individual's score falls within the clinical range; and unchanged, in which neither criteria of the Jacobson-Truax method are met [54,55]. Finally, exploratory growth curve analyses will be used to model individual participants' change trajectories across the 4-week pilot test period [56].

Results

The MI-Coach: ED app has been developed and is available for download and use. Recruitment was initiated in November 2022 and terminated in May 2024. Data analysis is currently underway, and we anticipate reporting results through peer-reviewed academic publications in May 2025.

Discussion

Anticipated Results

This study aimed to evaluate the feasibility and acceptability of MI-Coach: ED, an app designed to support motivation for ED recovery among individuals on treatment waitlists. It is anticipated that the intervention will be feasible to implement, with a high rate of participant engagement with the app, and that MI-Coach: ED would be perceived as an acceptable and useful tool for supporting motivation during the waitlist period. Prior research suggests that digital mental health interventions targeting ED populations are generally acceptable and feasible to users, particularly when they incorporate evidence-based therapeutic principles such as MI [15,28]. Additionally, app-based self-help interventions have demonstrated high engagement rates, which MI-Coach: ED was designed to include [23,27]. Furthermore, we anticipate that exploratory analyses will demonstrate preliminary improvements in motivation and ED-related symptoms following app use, given findings that brief MI-based interventions can enhance motivation for change, improve treatment engagement, and reduce ambivalence in ED populations [8,14,16,17]. As motivation is a key predictor of ED treatment outcomes [11], even small gains during the waitlist period could have meaningful clinical implications.

Conclusions

Individuals with EDs face substantial barriers to accessing appropriate care, despite their urgent need for treatment [37,57,58]. Though both MI and app-based interventions have been suggested as ways to support treatment-seeking ED patients, in isolation, these interventions may not adequately address treatment barriers. For example, in-person MI interventions may be inaccessible to individuals in rural and remote locations, and interventions currently delivered through apps have limited evidence to support their efficacy [24]. As such, this study aims to simultaneously address individual and structural treatment barriers by developing and pilot-testing an MI-based app intervention for women on waitlists for ED treatment.

Providing app-based interventions to individuals who are waiting for ED treatment has the potential to improve treatment outcomes and represents a largely barrier-free, positive-approach method of addressing the growing problem of wait times for mental health care. Although this pilot study focuses on a modest sample, existing intervention frameworks and ED-focused digital interventions demonstrate how pilot studies can be used to guide the adaptation and evaluation of novel interventions through large-scale clinical trials [15,20,28]. For example, collecting and implementing end user feedback prior to formal efficacy testing has been suggested to ensure that the final intervention is used by the targeted population [28]. Furthermore, exploratory analyses on motivation and ED-related symptoms will help identify meaningful clinical outcome measures and establish preliminary effect size estimates to guide the design and power calculations for a full-scale randomized controlled trial. Additionally, by collecting demographic and digital literacy data, this study will provide insights into the app's accessibility across diverse populations and inform potential adaptations to increase inclusivity. Future evaluations will also aim to follow participants into formal psychological treatment to assess the long-term clinical impact of pretreatment MI interventions.

Given that prior research has demonstrated that multimodal recruitment modalities can enhance sample diversity, improve engagement, and ensure the inclusion of individuals with varying levels of symptom severity in digital intervention studies [38], data collected through this pilot study will be particularly valuable in refining future participant engagement strategies. In this regard, feasibility data collected from this study (including recruitment and retention rates, participant engagement with the app, and qualitative user feedback) will directly inform refinements to MI-Coach: ED and recruitment

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methods for subsequent large-scale efficacy evaluations, ensuring that the intervention is optimally structured for broader implementation. For example, future studies may continue to use a multipronged approach, such as the use of social media campaigns to supplement clinician referrals [38], and partnerships with provincial authorities may be expanded to integrate study recruitment directly into clinical workflows given their success in prior research [59]. As such, this pilot study serves as a crucial step in optimizing MI-Coach: ED for large-scale implementation and has the potential to provide tangible psychological support to its participants while contributing to the reconceptualization of ED service delivery.

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Authors' Contributions

AH-A and ML are the primary authors responsible for the development of the underlying research, and all named authors contributed to the drafting of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Study recruitment flyer.
[DOCX File , 428 KB - resprot_v14i1e66298_app1.docx]

Multimedia Appendix 2
Overview of MI-Coach: ED Modules.
[DOCX File , 21 KB - resprot_v14i1e66298_app2.docx]

Multimedia Appendix 3
Study measures and outcome variables.
[DOCX File , 57 KB - resprot_v14i1e66298_app3.docx]

Multimedia Appendix 4
Consent form.
[DOCX File , 327 KB - resprot_v14i1e66298_app4.docx]

Multimedia Appendix 5
Brief consent form.
[DOCX File , 311 KB - resprot_v14i1e66298_app5.docx]

Multimedia Appendix 6
Qualitative interview guide.
[DOCX File , 17 KB - resprot_v14i1e66298_app6.docx]

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Abbreviations

BSQ: Body Shape Questionnaire
ED: eating disorder
EDE-Q: Eating Disorder Examination Questionnaire
GAD-7: 7-item General Anxiety Disorder Scale
ICT: internet and communications technology
MI: motivational interviewing
PHQ-9: Patient Health Questionnaire-9
RMQ: Readiness and Motivation for Change Questionnaire
TAM: Technology Acceptance Model
uMARS: user version of the Mobile App Rating Scale

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Protocol

Efficacy of a Personalized Mobile Health Intervention (BedTime) to Increase Sleep Duration Among Short-Sleeping Patients With Type 2 Diabetes: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: A strong association exists between sleep duration and glycemic control in patients with type 2 diabetes (T2D), yet convincing evidence of a causal link remains lacking. Improving sleep is increasingly emphasized in clinical T2D treatment guidance, highlighting the need for effective, scalable sleep interventions that can affordably serve large populations through mobile health (mHealth).

Objective: This study aims to pilot an intervention that extends sleep duration by modifying bedtime behavior, assessing its efficacy among short-sleeping (≤6 hours per night) patients with T2D, and establishing robust evidence that extending sleep improves glycemic control.

Methods: This randomized, single-blinded, multicenter study targets 70 patients with T2D from 9 institutions in Japan over a 12-week intervention period. The sleep extension intervention, BedTime, is developed using the Theory of Planned Behavior (TPB) and focuses on TPB's constructs of perceived and actual behavioral control (ABC). The pilot intervention combines wearable actigraphy devices with SMS text messaging managed by human operators. Both the intervention and control groups will use an actigraphy device to record bedtime, sleep duration, and step count, while time in bed (TIB) will be assessed via sleep

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diaries. In addition, the intervention group will receive weekly bedtime goals, daily feedback on their bedtime performance relative to those goals, identify personal barriers to an earlier bedtime, and select strategies to overcome these barriers. The 12-week intervention period will be followed by a 12-week observational period to assess the sustainability of the intervention's effects. The primary outcome is the between-group difference in the change in hemoglobin A_{1c} (HbA_{1c}) at 12 weeks. Secondary outcomes include other health measures, sleep metrics (bedtime, TIB, sleep duration, total sleep time, and sleep quality), behavioral changes, and assessments of the intervention's usability. The trial commenced on February 8, 2024, and is expected to conclude in February 2025.

Results: Patient recruitment ended on August 29, 2024, with 70 participants enrolled. The intervention period concluded on December 6, 2024, and the observation period ended on February 26, 2025, with 70 participants completing the observation period. The data analysis is currently underway, and results are expected to be published in July 2025.

Conclusions: This trial will provide important evidence on the causal link between increased sleep duration and improved glycemic control in short-sleeping patients with T2D. It will also evaluate the efficacy of our bedtime behavior change intervention in extending sleep duration, initially piloted with human operators, with the goal of future implementation via an mHealth smartphone app. If proven effective, this intervention could be a key step toward integrating sleep-focused mHealth into the standard treatment for patients with T2D in Japan.

Trial Registration: Japan Registry of Clinical Trials jRCT1030230650; https://jrct.niph.go.jp/latest-detail/jRCT1030230650

International Registered Report Identifier (IRRID): DERR1-10.2196/64023

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KEYWORDS

digital therapeutics; behavior change; Theory of Planned Behavior; sleep duration; type 2 diabetes; randomized controlled trial

Introduction

Worldwide, approximately 537 million people aged 20-79 years have diabetes [1]. Diabetes is a serious public health concern, significantly impacting health care expenditures and human life, causing 4.2 million deaths annually [2,3]. Type 2 diabetes (T2D) is difficult to cure once it develops and, if left untreated, can lead to complications such as cardiovascular disease and microvascular damage [4].

T2D treatment guidelines include both pharmacological and lifestyle modification elements. Traditionally, lifestyle modifications have focused on diet and exercise, but recently, improving sleep in patients with T2D has gained prominence [5,6]. Some patients with T2D suffer from sleep disorders, including obstructive sleep apnea, restless leg syndrome, and insomnia, for which treating the underlying disorder is the appropriate approach [7]. Sleep quality is associated with T2D risk [8], and interventions to improve sleep quality have shown effectiveness [9]. Many patients with T2D do not get sufficient sleep, experiencing what is termed *short sleep*. Definitions of short sleep vary across studies, ranging from 6 or fewer hours per night to less than 4.5 hours per night [10]. This issue is widespread, with data indicating that 39.4% of patients with T2D in Japan sleep fewer than 6.4 hours per night [11].

There is strong evidence that short sleep is associated with an increased risk of T2D and poorer glycemic control. In Japanese patients with T2D, short sleep is linked to higher hemoglobin A_{1c} (HbA_{1c}) levels [11], with a meta-analysis indicating a 0.23% difference in HbA_{1c} due to short sleep [12]. Prospective studies have also shown an increased risk of T2D associated with short sleep [8]. Plausible biological mechanisms support these findings, as sleep extension has been shown to reduce energy intake [13], while sleep restriction worsens insulin sensitivity [14].

Surprisingly, there is a lack of strong evidence for causality—specifically, increasing sleep duration in short-sleeping patients with T2D without sleep disorders leads to improvements in HbA_{1c} levels. Recent meta-analyses [15,16] found limited and conflicting evidence on the effect of sleep interventions on glycemic control. Some studies have investigated interventions for patients with T2D with insomnia [17,18]. One study examined an educational intervention for patients with T2D, including those with short sleep, but results from a published abstract [19] are unclear, and no full paper has been published. Two related studies used cognitive behavioral therapy to improve HbA_{1c} by enhancing sleep quality rather than duration [20,21]. Overall, strong evidence is lacking to support the idea that increasing sleep duration in short-sleeping patients with T2D without sleep disorders leads to improved HbA_{1c} levels.

Numerous studies have successfully increased sleep duration in various populations. A recent meta-analysis of 42 studies found that extending time in bed (TIB) has the greatest potential to modify sleep, with direct interventions (ie, scheduling a longer period in bed) resulting in an average increase of 1 hour and 23 minutes in sleep duration [22].

Mobile health (mHealth) interventions, such as mobile phone apps supporting self-management, have been shown to be effective in increasing physical activity, reducing body weight [23,24], and improving glycemic control [25,26]. However, to our knowledge, no mHealth apps have been designed specifically to improve sleep duration in short-sleeping patients with T2D without sleep disorders. Personalization of intervention components has been shown to enhance patient motivation and engagement with the app [27]. Several studies

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have found that tailored interventions are more effective at changing health behaviors than nontailored ones [28,29]. Moreover, interventions based on behavior change theory have been shown to be more effective than those lacking a theoretical foundation [30], with those based on the Theory of Planned Behavior (TPB) being particularly effective [31]. TPB emphasizes intention and ABC as key determinants of behavior, with perceived behavioral control (PBC)—similar or identical to Bandura's self-efficacy—playing a central role in shaping intention [32,33].

To address the lack of evidence on whether improvements in sleep duration lead to better glycemic control, we developed a pilot study of a personalized mHealth intervention, BedTime, designed to increase sleep duration and assess its impact on glycemic control in short-sleeping patients with T2D. The intervention is based on the TPB framework to promote behavior change toward earlier bedtimes. This trial aims to evaluate the efficacy of the BedTime approach in a 12-week, single-blind, randomized controlled pilot trial. The specific research objectives and hypotheses are as follows:

- Objective 1: To evaluate the efficacy of the BedTime approach in shifting patients to an earlier bedtime, as measured by daily bedtime reporting, and increasing sleep duration, as measured by daily actigraphy.
- We hypothesize that, by the end of the intervention, the intervention group will show statistically significant changes in bedtime and sleep duration compared with the control group.
- Objective 2: To evaluate the efficacy of the BedTime approach in reducing HbA_{1c} levels.
- We hypothesize that, by the end of the intervention, the intervention group will show a statistically significant reduction in HbA_{1c} levels compared with the control group.

Methods

Study Overview

This single-blinded, multicenter pilot study is a 2-arm randomized controlled trial designed to evaluate the efficacy of the BedTime mHealth intervention in promoting earlier bedtime behavior and increasing sleep duration among short-sleeping patients with T2D. The trial will be conducted and reported in accordance with CONSORT (Consolidated Standards of Reporting Trails) guidelines. As outlined in Figure 1, the study begins with recruitment (E0), followed by a baseline measurement period (nominally 2 weeks, but at least 7 days), and then randomized assignment to intervention and control groups (E1). Patients in the intervention group will record their daily bedtime, sleep duration, and step count using an actigraphy device, with TIB assessed via sleep diaries. They will receive weekly bedtime goals, daily feedback on their bedtime performance relative to these goals, and guidance to identify personal barriers to an earlier bedtime along with strategies to overcome them. The control group will also record daily bedtime, sleep duration, and step count using an actigraphy device, with TIB assessed via sleep diaries, but they will receive no feedback and will not be assigned goals. During week 10 of the intervention period (E2), the intervention group will complete a TPB questionnaire. The intervention will last for 12 weeks, followed by end-of-intervention assessments of the primary and secondary outcomes (E3). After the intervention period, there will be an observation phase, nominally 12 weeks in length, but its duration will depend on the date of the final visit (E4), which may occur between 10 and 14 weeks after the intervention ends. The study will be conducted over 1 year, from February 8, 2024, to January 22, 2025.

Figure 1. Overview of the study timeline.

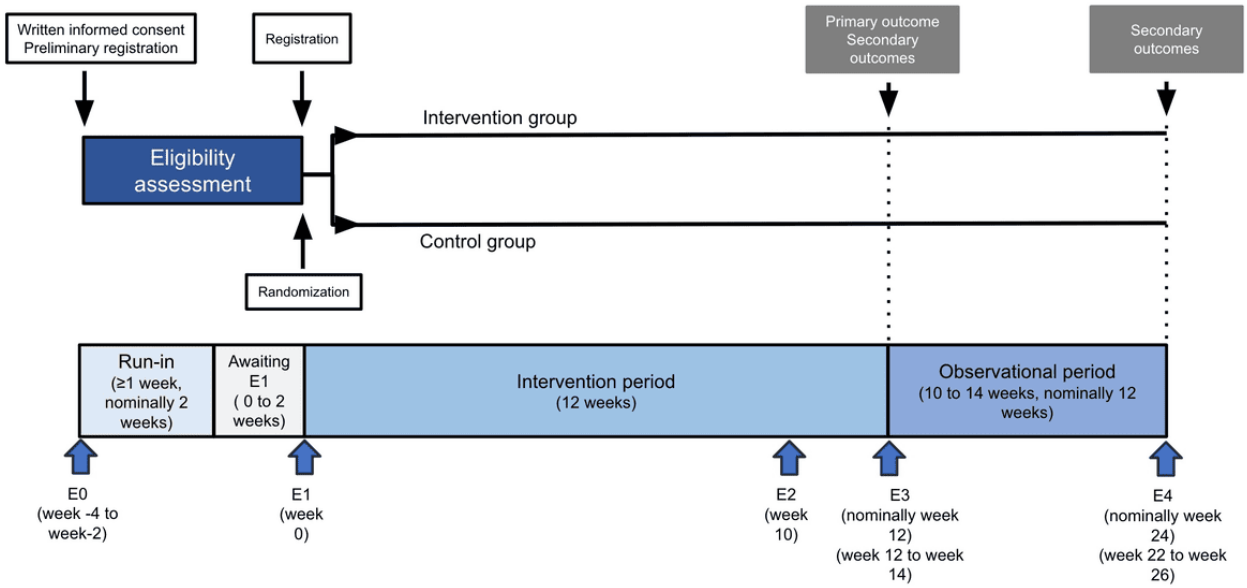

Intervention Design

Some features of the intervention are shared by both the control and intervention groups, while others are unique to the intervention group (Table 1). This mHealth intervention incorporates a physical activity monitoring system (iAide2; Tokai) and a researcher-designed paper diary for patients in both groups. The iAide2 measures activity intensity levels, skin

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temperature, and pulse rate [34,35] to assess step count and sleep, providing minute-by-minute wake/sleep assessments [36,37]. Additionally, the iAide2 enables timely behavioral feedback via a wirelessly connected Event button and near-real-time data access for researchers through an administrative screen. During the 12-week intervention period, patients in both the control and intervention groups wear the iAide2 device at all times except when bathing and press its Event button at bedtime each day. Patients record their bedtime and risetime daily in the paper diary. For the intervention group, the diary includes additional pages implementing specific aspects of the intervention. Bedtime is defined as the time when a patient begins trying to sleep, and risetime as the time when they stop trying to sleep. Diary entries are used to calculate TIB, the duration between bedtime and risetime. The intervention is designed to encourage an earlier bedtime, with the expectation that this will extend TIB and thereby increase sleep duration (ie, the portion of the TIB interval during which the patient is asleep).

Table 1. Intervention features for the intervention and control groups.

Features	Intervention group	Control group
iAide2		
Press the Event button to send bedtime	Yes	Yes
Measure daily sleep and steps (without providing this information to patients)	Yes	Yes
Diary		
Enter bedtime and risetime	Yes	Yes
Define barriers and coping strategies and report the number of coping strategies implemented	Yes	No
TPB[a] questionnaire at E2	Yes	No
SMS text message		
Diary reminder	Yes	Yes
Low battery message	Yes	Yes
Daily feedback and target bedtime	Yes	No
Request for a reply message when patients forget to press the Event button	Yes	No
Surveys and questionnaires		
Screening at E0	Yes	Yes
Sleep and Transtheoretical Model Questionnaire at E0, E3, and E4	Yes	Yes
Feedback survey	Yes	No
TPB questionnaires at E1	Yes	No
Ask if taking any medication that may affect one's sleep at E0, E1, E3, and E4	Yes	Yes
Obtain information about medications, including type 2 diabetes treatments and other drugs, either by asking the patients or by checking their medical records at E0, E1, E3, and E4	Yes	Yes
Measure height at E0, and measure weight and blood pressure at E0, E1, E3, and E4	Yes	Yes
Ask about any adverse events or malfunction in iAide2 at E1, E3, and E4	Yes	Yes
TPB questionnaires at E3 and E4	Yes	Yes

[a]TPB: Theory of Planned Behavior.

For the intervention group, daily and weekly messaging will deliver a TPB-based intervention targeting PBC and ABC (Figure 2). A researcher or clinical research coordinator (CRC), under the supervision of the researcher, will establish a baseline bedtime and set an initial goal for an earlier bedtime. They will also assist patients in identifying barriers to an earlier bedtime and developing coping strategies. Intervention group patients will receive a daily SMS text message assessment of their performance relative to their target bedtime and will record whether they implemented their coping strategies each day. They will also receive weekly assessments of their progress toward the goal, along with an updated target bedtime, via weekly SMS text messages. Additionally, they will determine coping strategies for the upcoming week.

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Figure 2. BedTime's process for implementing Theory of Planned Behavior–based personalization.

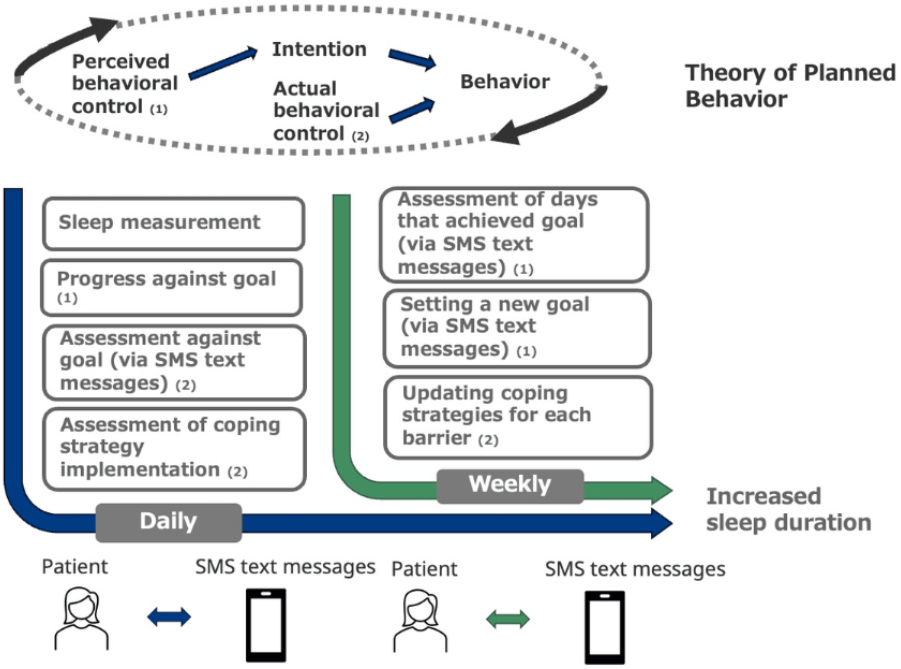

The intervention is based on the TPB framework (Figure 3) [32,33]. According to TPB, behavior is driven by an individual's intention to perform the behavior and their ABC, or ability to do so. A behavior is more likely to occur when both intention and actual ability are high. Intention itself is influenced by 3 factors: personal attitude toward the behavior, subjective norms or the perceived expectations of important others, and PBC, which reflects one's confidence in their ability to perform the behavior. Each of these 3 drivers of intention (attitude toward the behavior, subjective norms, and PBC) is, in turn, influenced by the person's beliefs about them. The stronger the positive behavioral, normative, and control beliefs, the more likely an individual is to intend to perform the behavior. Actually carrying out the behavior depends on both intention and ABC. As ABC is difficult to measure, researchers generally use PBC as a proxy for ABC in predicting behavior [32,38].

Figure 3. Theory of Planned Behavior applied to the BedTime intervention.

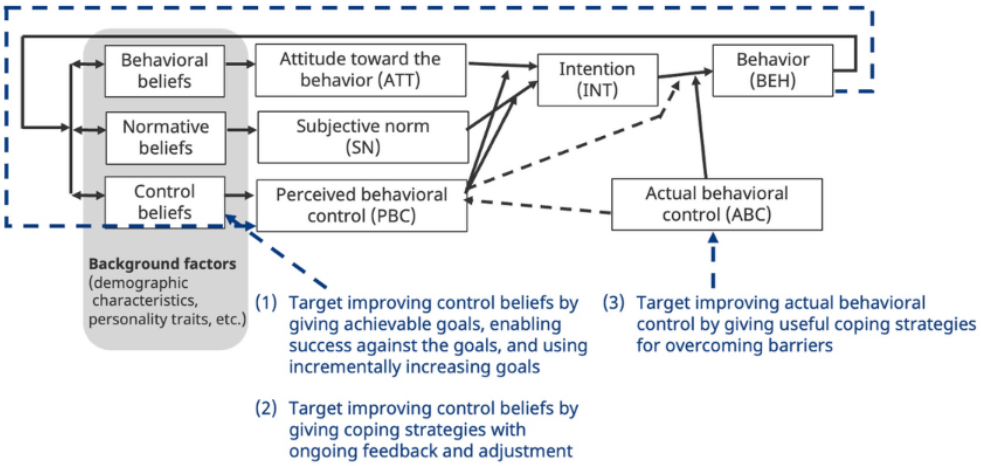

The BedTime intervention is designed to influence PBC by modifying control beliefs. The primary strategy for improving control beliefs—and thus PBC—is to set achievable goals, enabling patients to experience success and build positive self-mastery. We implement progressively challenging but attainable goals using a simple algorithm based on our prior work [39]. This algorithm adjusts the suggested target bedtime each week based on the number of days the user met their goal in the previous week. Adjustments include increases of 5, 10, or 15 minutes and decreases of 5 or 10 minutes, depending on past target bedtime achievement levels.

The secondary mechanism for improving control beliefs involves daily self-reflection on barriers and coping strategies, reinforcing patients' sense of control over their behavior. These mechanisms align with those used to enhance self-efficacy in social cognitive theory [32]. Beyond influencing PBC, the barrier and coping strategy intervention may also improve ABC by providing useful coping strategies. However, its impact on ABC is expected to

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be minor, as the suggested strategies may not be entirely novel or groundbreaking for patients. Each week, participants select or write down 1-3 barriers to achieving their target bedtime and propose a coping strategy for each (Table 2). Participants can select coping strategies from a literature-based list of solutions to common barriers to early bedtime [40-60] or describe their own. At the end of each day, they use the diary to report the number of coping strategies they implemented.

Table 2. Example of personalized coping planning strategy (with English translation).

Japanese		English translation	
Barriers	Coping strategies	Barriers	Coping strategies
遅い時間に夕食を食べて、まだやるべきことがある	就寝時刻の少なくとも2時間前に夕食を終える	I eat dinner late and still have things to do.	Finish dinner at least 2 hours before bedtime.
遅い時間にお風呂に入って、まだやるべきことがある	寝る1～2時間前にぬるめのお風呂に入る	I take a bath late and still have things to do.	Take a lukewarm bath 1-2 hours before going to bed.
就寝前にやるべき仕事がある	もっと睡眠をとるようにという医師の指示を上司に伝え、終業時間を早めるよう交渉する	I have work to do before bed	Tell your boss about your doctor's orders to get more sleep and negotiate an earlier finish time.
仕事から帰ってくるのが遅いため、まだやるべきことがある	もっと睡眠をとるようにという医師の指示を上司に伝え、終業時間を早めるよう交渉する	I'm late coming home from work, so I still have things to do.	Tell your boss about your doctor's orders to get more sleep and negotiate an earlier finish time.
家事など、まだ手をつけていないことがある	就寝1時間前を空けるようにスケジュールを組み立てる	There are things I haven't gotten around to yet, such as housework.	Plan your schedule so that you leave an hour before bedtime.
N/A[a]	やることのリストを作成し、就寝時ではなく翌日にそれをすることに専念する	N/A	Make a to-do list and commit to doing it the next day instead of at bedtime.
N/A	より多くの睡眠をとるようにという医師の指示に基づいて、他の人の助けを借りて家事をする	N/A	Do housework with the help of others based on your doctor's instructions to get more sleep
就寝時に高血糖または低血糖を管理する必要がある	必要な食事療法や投薬治療が就寝時刻までに完了するように、就寝時刻の 30 分～60 分前に血糖値を測定する	I need to manage hyperglycemia or hypoglycemia at bedtime	Measure your blood sugar 30-60 minutes before bedtime to ensure that any necessary dietary or medication therapy is completed by bedtime.
もう少し「自分」の時間が必要だ	「自分」の時間として、日中に10分間の休憩をいくつか取り入れる	I need a little more "me" time.	Incorporate several 10-minute breaks during the day for "me" time.

[a]N/A: not applicable.

The intervention provides daily individualized feedback via an SMS text message (Table 3). These messages, typically sent between 12 PM and 6 PM, inform the patient whether they went to bed earlier or later than their target bedtime the previous night, using an encouraging tone. This timing ensures that participants receive feedback well before their usual bedtime, allowing them sufficient time to adjust their nightly activities accordingly. The exact delivery time of the SMS text messages varies slightly due to the manual nature of the sending process.

At the end of each week, the intervention provides feedback via an SMS text message reporting the number of days the goal was achieved.

Table 3. Example of daily feedback (with English translation).

Situation	SMS text message	English translation
Last night, bedtime was earlier than the target bedtime which is 10 minutes earlier than the baseline bedtime.	昨夜は、「少なくとも 10分早く就寝する」という目標を達成できました。よく頑張りました! 健康を改善するための行動ができています！	Last night you achieved your goal of going to bed at least 10 minutes earlier. Great job! You're taking action to improve your health!
Last night, bedtime was 15 minutes later than the goal bedtime of 30 minutes earlier than the baseline bedtime.	昨夜は15分遅く就寝しましたね。「30分早く就寝する」という目標には達しませんでしたが、今夜は目標就寝時刻の達成に向けてがんばりましょう。 あなたならできます！ お選びになった対処方法を確認して、今夜の就寝時刻を考えてください。 早く寝ると健康増進につながります！	You went to bed 15 minutes later than your goal last night. You didn't reach your goal of going to bed 30 minutes earlier than your baseline bedtime. Try your best to reach your target bedtime tonight. You can do it! Review your chosen coping strategy and think about your bedtime tonight. Sleeping early will improve your health!

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Patient Recruitment

Patients will be recruited from 9 medical institutions in Japan (Textbox 1). Attending physicians will conduct recruitment during patients' regular outpatient consultations. The recruitment period will run from February 8, 2024, to July 30, 2024.

Textbox 1. Participating institutions: 11 medical centers in Japan.

- The University of Tokyo Hospital
- Mitsui Memorial Hospital
- Meiji Yasuda Life Insurance Company Tokyo Hospital
- Kobe University Hospital
- Akita University Hospital
- Tokai University Hospital
- Okayama Saiseikai General Hospital
- Sawaki Internal Medicine and Diabetes Clinic
- Yokota Medical Clinic
- Aikawa Comprehensive Internal Medicine Clinic
- Yokohama Rosai Hospital

To detect a 0.3% difference in the primary outcome (change in HbA_{1c}), assuming an SD of 0.41% (the average observed in 2 prior studies [17,61]), and to achieve a 2-sided significance level of .05 with 80% statistical power, the minimum required sample size is 31 patients per group. Considering an estimated dropout rate of approximately 10%, we aim to recruit a total of 70 patients (35 in the intervention group and 35 in the control group).

All participants will receive a comprehensive written and verbal explanation before providing written informed consent. Eligibility screening will be conducted only after consent is obtained. If any findings related to efficacy or safety arise during the trial that may impact patient consent, we will promptly disclose this information to participants and obtain renewed consent.

We will use survey instruments as part of the inclusion and exclusion criteria (Textbox 2). To recruit patients who are both likely to benefit and capable of participating, we will include only those meeting all inclusion criteria (Textbox 3) while ensuring they do not meet any exclusion criteria (Textbox 4), following the methods of a prior study [62]. We anticipate a roughly equal sex distribution and an average participant age in the late 50s. Women undergoing menopausal transition will be included if they meet the study's criteria.

We will use a Transtheoretical Model (TTM) questionnaire to categorize participants into the contemplation stage (willing to change health behavior within the next 6 months), preparation stage (willing to change health behavior within the next month), or action stage (has already made modifications to health behavior) [63]. In our previous study, patients in the contemplation and preparation stages were more likely to prefer smartphone-based self-management tools than those in the precontemplation stage [64]. Therefore, we will target patients in the contemplation, preparation, or action stage of increasing their sleep duration by 1 hour per day.

Textbox 2. Screening surveys.

- STOP-J (Snoring, Tiredness, Observed Apnea, High Blood Pressure Screen, Japanese version): screening for obstructive sleep apnea [65]
- ISI-J (Insomnia Severity Index, Japanese version): screening for insomnia [66]
- IRLSQ-J version 2.2 (International Restless Legs Syndrome Study Group Rating Scale, Japanese version): screening for restless legs syndrome [67]
- AUDIT-C-J (Alcohol Use Disorders Identification Test—Consumption, Japanese version): screening for alcohol use disorder [68,69]
- PHQ-8-J (Patient Health Questionnaire-8, Japanese version): screening for major depression [70,71]
- TTM (Transtheoretical Model) Sleep Questionnaire: assess the TTM stage [63] relative to sleeping 7 or more hours nightly

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Textbox 3. Study inclusion criteria (selecting patients who are likely to benefit from the intervention and are likely to be capable of participating).

At the time of consent acquisition (E0)

- Diagnosed with type 2 diabetes and attending the hospital/clinic
- Hemoglobin A_{1c} (HbA_{1c}) is 7.5% or higher at the time of obtaining consent
- A patient with short sleep (self-reports an average sleep duration in the prior month of 6 or fewer hours)
- In the contemplation, preparation, or action stage of the Transtheoretical Model (TTM) for the action of sleeping 7 hours or more per day
- Willing and able to wear a wristband-type measuring device on the nondominant wrist during the research period
- Has and uses a mobile phone capable of sending and receiving SMS text messages
- Able to attend consultations at designated times during the research period
- 18 years or older
- Fluent in spoken and written Japanese
- Does not have impaired cognitive function as determined by the investigator or subinvestigator
- Can undergo sleep treatment, as determined by the investigator or subinvestigator
- Fully informed about participation in this study, and has given free and voluntary written consent based on a thorough understanding of the study

Textbox 4. Exclusion criteria, focusing on patients who may not be able to participate safely or whose participation may interfere with the effectiveness of the study.

1. Exclusion criteria at the time of consent acquisition (E0)
   - BMI is greater than 35.0 kg/m^2
   - Age is 76 years or older
   - A shift worker or someone who occasionally deviates from a single main sleep period at night
   - A caregiver (of a child or adult) who needs to wake up during the night
   - At high risk of obstructive sleep apnea (STOP-J [Snoring, Tiredness, Observed Apnea, High Blood Pressure Screen, Japanese version] score of 3 or higher)
   - At high risk of insomnia (ISI [Insomnia Severity Index, Japanese version] score of 15 or higher)
   - Possibility of restless legs syndrome (IRLSQ-J [International Restless Legs Syndrome Study Group Rating Scale, Japanese version] score of 1 or higher)
   - High possibility of depression (PHQ-8 [8-item Patient Health Questionnaire] score of 10 or higher)
   - Taking medications that affect sleep
   - Changed type 2 diabetes medication within the past 8 weeks
   - Currently participating in another clinical research program
   - A heavy user of alcohol (AUDIT-C-J [Alcohol Use Disorders Identification Test—Consumption, Japanese version] score of 4 or higher for females, and 6 or higher for males)
   - Has severe chronic pain (due to cancer, etc)
   - Has a diagnosed clinical sleep disorder
   - Has an uncontrolled psychiatric disorder
   - Pregnant at the time of consent acquisition
   - Any other reason why the patient is classified as unfit for participation by the investigator or subinvestigator
2. Exclusion criteria before allocation (E1)
   - Recorded both bedtime and risetime in a diary for fewer than 7 days during the trial period
   - Recorded the Event button of the iAide2 fewer than 7 days during the trial period
   - Recorded fewer than 7 days of valid iAide2 data showing sleep duration, as judged by the investigator or subinvestigator

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We will provisionally register patients who meet the eligibility criteria at E0. At this stage, each participant will receive an actigraph (iAide2) and will be instructed to wear it 24 hours a day, except when bathing, to press the Event button at bedtime, and to record their bedtimes and risetimes in the diary. Patients who fail to press the Event button for 7 or more days or fail to complete the diary for 7 or more days during the run-in period will be excluded to ensure adequate participation. Data collected during the run-in period will be used to confirm eligibility and establish baseline sleep and step counts. We will randomize eligible participants in a 1:1 ratio to either the intervention or control group using covariate-adaptive randomization by minimization to ensure balance across age (<65 and ≥65 years), sex, HbA_{1c} (<8.5% and ≥8.5%), and institution [72]. Random allocation will be conducted via the Internet Data and Information Center for Medical Research cloud, provided by the University Hospital Medical Information Network, an internet-based central randomization system. A research co-investigator will access the University Hospital Medical Information Network Internet Data and Information Center for Medical Research cloud and input the required baseline information. The system will then securely generate the allocation result immediately before assigning each participant to a group. This process ensures that researchers cannot access or predict allocation results in advance, minimizing potential bias.

Intervention Process

The study (Table 4) consists of 5 events (E0-E4), a 2-week run-in period, a 12-week intervention period, and a 12-week observation period. Initial measurements will be taken at event E0. Questionnaires will be used to assess sleep behavior and gather patient feedback (Textbox 5).

Following randomization, the intervention begins. Before explaining the intervention, the researcher or CRC will administer the TPB Sleep Questionnaire and the Sleep-Related Behavior (SRB) Questionnaire to the intervention group. The researcher or CRC will then provide a diary customized for the intervention group. To establish a baseline bedtime, the researcher or CRC will average bedtimes recorded during the run-in period, considering any exclusions due to unusual circumstances in consultation with the patient. Patients will be informed that their ultimate goal is to shift their bedtime 1 hour earlier than the baseline, with an initial target of going to bed 10 minutes earlier during the first week. The researcher or CRC will help patients identify barriers preventing them from going to bed early and assist them in selecting up to 3 coping strategies tailored to these barriers for the first week. During this process, the researcher or CRC will facilitate discussions using the list in the diary as a reference. Patients may either choose strategies from the list or write their own in the diary. For the control group, the researcher or CRC will provide a diary similar to the one used during the run-in period but covering 12 weeks. Control group patients will be instructed to continue recording their bedtime and risetime as they did during the run-in period. The intervention period lasts 12 weeks, from E1 to E3. We will send reminder SMS text messages to both groups at the end of weeks 1 and 10 to encourage diary use. All equipment, including the diary, will be collected at E3 before the follow-up observation period begins.

For the intervention group, we will provide both daily and weekly feedback. Researchers will monitor the receipt of the Event time, and if it is missing, they will send a reminder asking the patient to report their bedtime via an SMS text message. If no bedtime is reported through either the Event record or SMS text message, the night will be considered a failure to achieve the target bedtime. At E2, 10 weeks after E1, we will send a reminder for participants to complete the TPB Sleep Questionnaire in the diary.

During the study, we will not restrict the use of supplements or drinks that may affect blood glucose and blood pressure. In both the intervention and control groups, T2D treatment—including oral T2D medications, insulin, glucagon-like peptide 1 receptor agonists, and medication dosage—may be adjusted at the discretion of the attending physician. We will collect information on T2D-related medication and medications affecting sleep at E1, E3, and E4.

Discontinuation is defined as a patient expressing a decision to withdraw or failing to record data for a continuous period of 7 or more days. If a participant discontinues during the intervention period, we will attempt to collect E3 measurement items. If discontinuation occurs during the observation period, we will attempt to collect E4 measurement items.

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Table 4. Study events—1 measurement period and 4 visits spanning approximately 26 weeks.

Event	Focus	Time	Key activities
E0	Physical baseline assessments and initial registration	Enrollment: ≥7 days before the beginning of the intervention	• Collect consent • Collect demographic information: age, sex, date of type 2 diabetes diagnosis, smoking and drinking habits, macrovascular disease, diabetic retinopathy, periodontal disease, tinea pedis, diabetic neuropathy, and other medical history • Collect physical data: hemoglobin levels, albumin, uric acid, blood urea nitrogen, estimated glomerular filtration rate, creatinine, fasting blood glucose, HbA_{1c}[a], low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, urine specific gravity, urinary protein, urine albumin-to-creatinine ratio, height, body weight, and blood pressure measurements • Collect medication status • Conduct screening surveys (STOP-J[b], ISI-J[c], IRLSQ-J version 2.2[d], AUDIT-C-J[e], PHQ-8-J[f], and TTM[g] Sleep Questionnaire) • Conduct PSQI-J[h] survey • Distribute actigraph (iAide2) and run-in period diary
Run-in	Baseline	From E0 for 2 weeks	• Patients record daily bedtime and risetime, with automated (blinded) measurements of sleep parameters and step count
E1	Registration, allocation, and beginning of the intervention	Beginning of the intervention	• Verify that run-in diary and iAide recording do not cause exclusion • Finalize registration and allocation • Collect medication status • Intervention only: conduct surveys (TPB[i] Questionnaire, SRB[j] Questionnaire) • Distribute the intervention diary or the control group diary • Check for malfunctions or adverse events during run-in
Intervention period	Ongoing measurement	From E1 for 12 weeks	• Patients record daily bedtime and risetime, with automated (blinded) measurements of sleep parameters and step count • Intervention only: daily feedback, weekly self-set barriers and coping strategies via diary, weekly personalized target bedtime setting via SMS text messages
E2	Ongoing measurement	End of 10 weeks from E1	• Intervention only: conduct TPB Questionnaire via diary
E3	End of the intervention	End of 12 weeks from E1	• Collect physical data: hemoglobin levels, albumin, uric acid, blood urea nitrogen, estimated glomerular filtration rate, creatinine, fasting blood glucose, HbA_{1c}, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, urine specific gravity, urinary protein, urine albumin-to-creatinine ratio, body weight, and blood pressure measurements • Collect medication status • Conduct surveys (TTM Sleep Questionnaire, TPB Questionnaire, SRB Questionnaire, PSQI-J) • Intervention group: conduct survey (feedback survey) • Collect actigraph (iAide2) and intervention period diary • Check for malfunctions or adverse events
E4	End of follow-up	End of 24 weeks from E1	• Collect physical data: hemoglobin levels, albumin, uric acid, blood urea nitrogen, estimated glomerular filtration rate, creatinine, fasting blood glucose, HbA_{1c}, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, triglycerides, urine specific gravity, urinary protein, urine albumin-to-creatinine ratio, body weight, and blood pressure measurements • Collect medication status • Conduct surveys (TTM Sleep Questionnaire, TPB Questionnaire, SRB Questionnaire, PSQI-J)

[a]HbA_{1c}: hemoglobin A_{1c}.

[b]STOP-J: Snoring, Tiredness, Observed Apnea, High Blood Pressure Screen, Japanese version.

[c]ISI-J: Insomnia Severity Index, Japanese version.

[d]IRLSQ-J version 2.2: International Restless Legs Syndrome Study Group Rating Scale, Japanese version.

[e]AUDIT-C-J: Alcohol Use Disorders Identification Test—Consumption, Japanese version.

[f]PHQ-8-J: Patient Health Questionnaire-8, Japanese version.

[g]TTM: Transtheoretical Model.

[h]PSQI-J: Pittsburgh Sleep Quality Index, Japanese version.

[i]TPB: Theory of Planned Behavior

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[j]SRB: Sleep-Related Behavior.

Textbox 5. Assessment questionnaires and surveys.

- TPB (Theory of Planned Behavior) Sleep Questionnaire: assess individual components of TPB [32,33] relative to implementing an earlier bedtime
- SRB (Sleep-Related Behavior) Questionnaire: self-assessment of sleep over the past 2 weeks
- PSQI-J (Pittsburgh Sleep Quality Index, Japanese version): assess sleep quantity and quality [73,74]
- Feedback survey: collect feedback on the intervention

Monitoring, Quality Control, and Data Management

An auditor, independent of the departments involved in the trial, including those responsible for monitoring, will inspect the medical institution and other facilities to ensure the trial is conducted appropriately.

Ethical Approval

This trial will be conducted in compliance with the Declaration of Helsinki, the Pharmaceutical and Medical Device Act, the Ministerial Ordinance on Good Clinical Practice for Medical Devices, and all other relevant guidelines (jRCT1030230650). The study was approved by the Institutional Review Board of the University of Tokyo School of Medicine (approval number 2023336NI). We will obtain written informed consent from all study participants, and all patient data will be pseudonymized. Patients will receive compensation of JPY 30,000 (approximately US $200) at the end of E4.

The participant information materials and informed consent form are available from the corresponding author (KW) upon request. Any amendments to the protocol will be submitted for review and approval by the institutional review board. Study findings will be disseminated through peer-reviewed publications and conference presentations.

Outcome Measures

Primary Outcome

The primary outcome of this study is the between-group difference in the change in HbA_{1c} from baseline (E0) to either the end of the intervention period at week 12 (E3) or, for patients who discontinue before E3, the point of discontinuation. A reduction of 0.3 percentage points in HbA_{1c} is considered clinically significant [75,76].

Secondary Outcomes

Secondary outcomes (Table 5) include health measures, bedtime and sleep measurements, other behavior change assessments, and evaluations of actigraph and diary usage. We will also assess safety outcomes, including hypertension requiring medical assistance (evaluated from system records), subjective hypoglycemia, lower back pain, and pain in the lower extremities (tarsus, thighs, knees, calves, shins, ankles, and feet), as well as any other adverse events (all assessed through patient interviews).

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Table 5. Secondary outcomes investigated in the study.

Measurements	Outcomes
Differences in changes	• Hemoglobin A_{1c} (%) (only after the end of the observation period)[a] • Weight (kg)[a] • BMI (kg/m^2)[a] • Systolic blood pressure/diastolic blood pressure (mmHg)[a] • Estimated glomerular filtration rate (mL/min/1.73 m2)[a] • Fasting blood sugar (mg/dL)[a] • Low-density lipoprotein cholesterol (mg/dL)[a] • High-density lipoprotein cholesterol (mg/dL)[a] • Neutral fat (mg/dL)[a] • Urine albumin-to-creatinine ratio (mg/gCr)[a] • PSQI-J[a,b]
Differences in the measured values	• Survey on past bedtimes[a]
Difference in proportions	• Behavior change questionnaire[a]
Observed data	• Elements of the bedtime questionnaire: attitude, subjective norms, perceived behavioral control, intention[c] • Sleep time calculated from iAide2's sleep data and diary data[d] • Time in bed calculated from bedtime and wake-up time recorded in the diary for each period[d] • Bedtime recorded in the diary for each period and bedtime sent from iAide[d] • Steps recorded by iAide2[d] • Achievement rate of target bedtime[e] • Number of barriers and coping strategies set and implemented in the diary for the intervention period[e] • Percentage of use of each drug[f] • Percentage of new additions for each drug since consent was obtained[g] • Changes in antidiabetic drugs since consent was obtained (strengthened, unchanged, or attenuated)[g]

[a]Evaluate the differences after the end of the intervention period (at 12 weeks) and after the end of the observation period (at 24 weeks) from the time of consent acquisition.

[b]PSQI-J: Pittsburgh Sleep Quality Index, Japanese version.

[c]Evaluate the differences in the measured values for the following items at 10 weeks and after the end of the observation period (24 weeks).

[d]Evaluate the differences in the average change from the trial period in the 2 weeks before the end of the intervention period.

[e]Evaluate the rates weekly during the intervention period, for the intervention group.

[f]Evaluate the differences in percentages at the time of consent acquisition, at the time of actual registration, after the end of the intervention period, and after the end of the observation period.

[g]Evaluate the difference in proportions after the intervention period and after the observation period.

Statistical Analysis

In this study, we define 3 analysis populations: the full analysis set (FAS), the per-protocol set (PPS), and the safety analysis set (SAS). The FAS includes all patients for whom the primary outcome was obtained. Following the intention-to-treat principle, we will analyze data based on the assigned group in the FAS analysis. The PPS consists of the FAS population, excluding patients who violated eligibility criteria after randomization, had 7 or more contiguous days of nonuse of the iAide2, or took medications affecting sleep. The SAS includes all patients who used the iAide2 at least once after randomization. In the safety analysis using the SAS, we will analyze data based on the intervention actually used by patients, regardless of allocation. The FAS will serve as the primary analysis population, while the PPS will provide supportive results. All safety analyses will be conducted using the SAS.

Patient characteristics will be presented as mean, SD, minimum, 25th percentile, median, 75th percentile, and maximum for continuous variables, and as frequency and proportion for categorical variables.

In the primary analysis, we will compare the change in HbA_{1c} from baseline (E0) to week 12 (E3; or the point of discontinuation, if earlier) between groups using analysis of covariance, with baseline HbA_{1c} (ie, HbA_{1c} at E0) included as a covariate in the FAS. For participants who discontinue the study, the most recent HbA_{1c} measurement before E3 will be used.

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We will also conduct 2 subgroup analyses: one based on baseline HbA_{1c} at E0 (<8.5% or ≥8.5%) and the other based on age at initial registration (E0; <65 or ≥65 years). Subgroup analyses of the primary outcome will be performed in each analysis set to assess whether the efficacy of BedTime is consistent across these subgroups.

In the secondary analysis, changes in HbA_{1c} at week 12 (E3) and week 24 (E4) will be analyzed using the same approach as in the primary analysis. The proportion of patients with HbA_{1c} below 7% at E3 and E4 (or at the point of discontinuation, if earlier) will be compared between groups using the Fisher exact test. Changes from baseline in step counts, various laboratory test values, and questionnaire scores at E3 and E4 (or at the point of discontinuation, if earlier) will also be analyzed as key endpoints. Changes in T2D medications, categorized as weakened, unchanged, or strengthened, will be compared between groups using the Cochran-Mantel-Haenszel test. The proportion of newly added medications will be compared between groups using the Fisher exact test. A paired (2-sample) *t* test will be used for within-group comparisons of changes in TPB Questionnaire measurements over weeks 0 (E1), 10 (E2), 12 (E3), and 24 (E4). Changes in TPB Questionnaire and SRB Questionnaire measurements between week 12 (E3) and week 24 (E4) will be compared using a *t* test. A paired *t* test will also be used for within-group comparisons from week 0 (E1) to week 12 (E3) for goal achievement rate, goal increment rate, goal reduction rate, average number of coping strategies implemented per day, and the number of identified barriers.

As an exploratory analysis, we will use linear regression to examine the relationship between the average number of coping strategies implemented per day and improvement in HbA_{1c} within the intervention group. The model will include the average number of coping strategies implemented per day and baseline HbA_{1c} as explanatory variables, with the change in HbA_{1c} as the response variable. Changes from baseline to week 12 (E3) and week 24 (E4) (or the point of discontinuation, if earlier) will be assessed.

We will perform a statistical analysis of safety outcomes by calculating the frequency, number of cases, and percentage of individuals experiencing adverse events during the trial, intervention, and observation periods. For the intervention and observation periods, data will be compiled separately for each group, and the percentages will be compared between groups using the Fisher exact test.

Results

Recruitment began on February 8, 2024, and ended on August 29, 2024. The intervention period concluded on December 6, 2024, and the observation period ended on February 26, 2025, with 70 participants completing the observation period (Figure 4). The analysis is currently underway, and we anticipate publishing the results in July 2025. Before commencing analysis, we will conduct a thorough review of all collected data and data entry.

Figure 4. CONSORT (Consolidated Standards of Reporting Trails) flow diagram depicting enrollment, allocation, follow-up, and analysis phases.

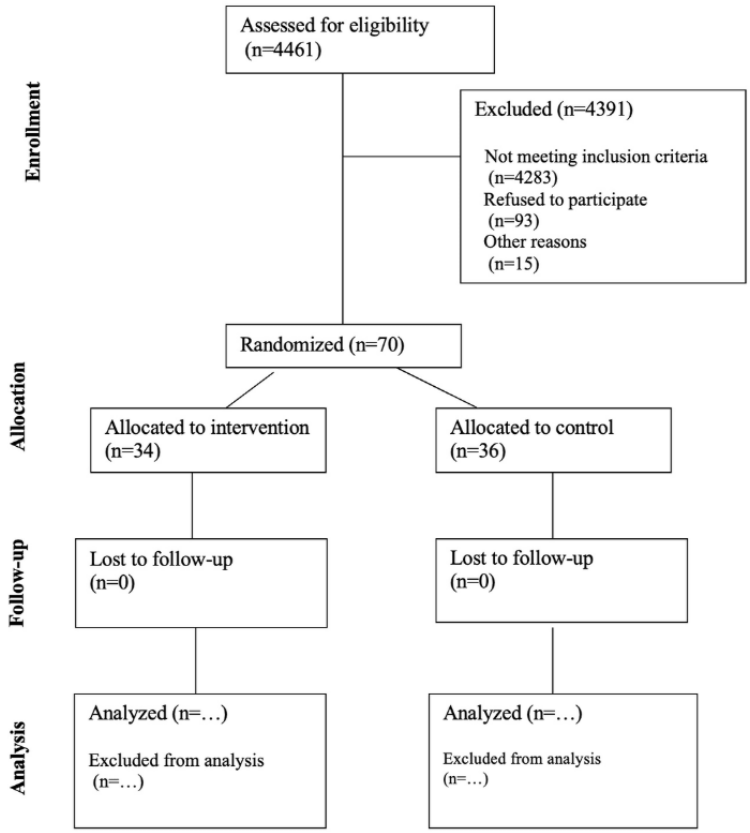

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Discussion

We designed this study based on the foundational concept that it is a behavioral change intervention, despite measuring medical outcomes. The intervention is grounded in a specific theory of behavioral change (TPB) to provide a structured framework, ensure clarity on intervention targets, and maintain focus, avoiding a scattershot approach. We identified a specific, actionable target behavior—going to bed earlier—and developed a measurement and feedback system centered on this behavior. This focused approach provides clarity for both researchers and patients. By maintaining this focus, we can determine whether the intervention effectively changes sleep behavior while also evaluating its impact on sleep patterns and, ultimately, health outcomes. Demonstrating that a behavioral intervention improves HbA_{1c} is not enough, we need to understand the intermediate steps, particularly the behavioral response, to refine the intervention by enhancing effective components and eliminating ineffective ones. This study is designed to generate evidence on these intermediate stages.

Our study utilizes objectively measured data for all primary outcomes and many secondary outcomes. The intervention leverages wireless technology, enabling automatic synchronization of sleep and step count data to the server. These simple, passive features facilitate easy-to-use objective measurements, particularly for older patients.

Participants will be blinded to group assignments to minimize social desirability bias. To achieve this, they will not be informed that the study involves random assignment to 2 groups or that the intervention specifically targets advancing bedtime. Instead, patients will be told that the study examines the relationship between self-management of lifestyle habits (including exercise and sleep) and blood glucose control in individuals with T2D. They will also be informed that various lifestyle factors, including sleep, will be monitored. This approach minimizes the risk of unblinding in the control group by preventing participants from identifying the absence of an intervention. We believe that maintaining blinding offers significant scientific benefits by reducing potential bias and enhancing the validity of the study findings.

We selected the HbA_{1c} level as our primary outcome, as it is recognized as a global standard for assessing glycemic control and an appropriate indicator of T2D treatment effectiveness [77]. According to the Japan Diabetes Society's treatment guidelines, patients with T2D should aim to lower their HbA_{1c} level below 7% to prevent complications [78]. Therefore, in addition to analyzing absolute changes in HbA_{1c} levels, we examined the proportion of patients achieving an HbA_{1c} level below 7%. We acknowledge that T2D duration may influence the primary outcome. Although our recruitment process does not explicitly stratify participants by disease duration, this information is collected at registration and will be incorporated into the analysis to account for its potential impact on study outcomes.

In this study, we have chosen a "formidable" control [79], using the same devices as the intervention group. As an initial proof-of-concept study, our goal is to determine whether our specific behavior change intervention is more effective than simply having patients record their bedtime and risetime. Evidence suggests that providing patients with a pedometer can increase their activity levels [80], raising concerns that bedtime and risetime recording in the control group may similarly trigger behavioral changes, potentially making it more challenging to demonstrate the intervention's superiority statistically. By providing the control group with a diary but withholding the intervention functionality, we have designed the study to offer strong evidence of the intervention's effectiveness—should it indeed be effective.

Many behavior interventions demonstrate solid short-term gains that later fade [39]. This study includes a 12-week observation period following the intervention to assess whether the benefits persist or diminish. Behavior change maintenance is theorized to result from active, ongoing self-regulation, with habit formation emerging after a period of successfully regulating a new behavior [81]. Our goal is to foster sustainable behavior change, ensuring that the new pattern becomes an enduring habit.

A key aspect of our approach is providing patients with a strong introduction to the mechanics of the intervention. Given their busy lives, we strive to make participation clear and manageable. By offering thorough training and ensuring that all intervention messaging remains simple and focused, we maximize the likelihood that patients will engage with the tools as intended.

Another key aspect of our approach is prioritizing the needs of the patients the intervention is designed to serve. Rather than adopting a one-size-fits-all approach, we tailored the intervention for a specific target population, ensuring it aligns with their needs and preferences. Our previous study [39] highlighted the importance of considering cultural background and patient preferences in intervention design. Additionally, we recognize that socioeconomic background may influence sleep patterns. While our recruitment strategy does not explicitly target specific socioeconomic groups, the participating institutions serve patient populations whose demographics are representative of the general community.

Another key aspect of our approach is applying the intervention only to patients who are already motivated to change their behavior. We use the TTM stage as a filter, an approach that has proven highly effective in previous research [39,63]. Our intervention is specifically designed for highly motivated patients who need support in implementing their desired behavior changes, whereas low-motivation patients require a different intervention focused on enhancing motivation. Notably, a large proportion of patients with T2D in Japan exhibit high motivation, with one study indicating that 92% are in the contemplation-through-action stages of TTM for dietary behavior change [82]. There is a substantial pool of patients who could benefit from this targeted intervention. As a multicenter randomized controlled trial, this study enhances the generalizability of our findings to patients with T2D across Japan. Moreover, our techniques are broadly applicable, and there is strong reason to believe that these methods could be

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adapted to increase sleep duration for patients with other conditions and in diverse health care settings worldwide.

This study has several limitations. The findings may be specific to the population studied and may not fully generalize to other groups. Our participants are likely to be older individuals of Japanese ethnicity, and differences in lifestyle and T2D pathophysiology between Japanese and other populations may limit broader applicability. Additionally, the study includes only patients capable of using mobile phones, introducing potential biases related to digital literacy. Furthermore, our baseline sleep measurements rely on actigraphy and sleep diaries provided to participants, which may overestimate true prestudy sleep levels. This effect is mitigated by the 2-arm design and the duration of our trial. However, it may lead to an underestimation of increases in sleep duration, potentially resulting in an overestimation of the per-hour-of-sleep impact on health outcomes.

This trial will provide important evidence on the efficacy of a TPB-based mHealth intervention in improving sleep duration and glycemic control in patients with T2D. If the intervention is proven effective and safe, this study could serve as a key step toward integrating mHealth into standard T2D treatment in Japan.

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Data Availability

The data sets generated during or analyzed during this study can be obtained from the corresponding author on reasonable request.

Authors' Contributions

KW was responsible for conceptualization, methodology, project administration, resources, validation, and funding acquisition. Data curation was carried out by YB and RN, while RN also conducted the formal analysis and visualization. Software development was handled by YB and RN. The investigation was conducted by KW, AI, KM, HW, S Kato, HS, TM, YH, SS, SN, AT, MS, MT, S Kajino, KY, and YT. Supervision was provided by KW, TY, MN, and KO. The original draft was written by YB and KW, while AI, KM, HW, S Kato, HS, TM, YH, SS, SN, AT, MS, MT, S Kajino, KY, YT, KW, TY, MN, and KO contributed to the review and editing.

Conflicts of Interest

None declared.

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Abbreviations

ABC: actual behavioral control
CONSORT: Consolidated Standards of Reporting Trails
CRC: clinical research coordinator
FAS: full analysis set
HbA_{1c}: hemoglobin A_{1c}
mHealth: mobile health
PBC: perceived behavioral control
PPS: per-protocol set
SAS: safety analysis set
SRB: Sleep-Related Behavior
T2D: type 2 diabetes mellitus
TIB: time in bed
TPB: Theory of Planned Behavior
TTM: Transtheoretical Model

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Protocol

Using Music to Promote Hong Kong Young People's Emotion Regulation and Reduce Their Mood Symptoms and Loneliness: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Mental health needs in the community surged during the pandemic, with concerning reports of increased negative mood symptoms among youth. At the same time, preventive psychoeducational interventions were insufficient within frontline youth mental health services in Hong Kong, and research specifically addressing youth loneliness remained limited on an international scale. Given the association between loneliness and other mental health symptoms, psychoeducational programs that empower adolescents to cope with emotions may help address both the research gap and local demand. As such, Tuned In, a previously validated intervention program originally developed in Australia, was introduced to the local context. Cultural adaptations and an added focus on loneliness were incorporated into the project to enhance its acceptability and test its effectiveness.

Objective: This study aims to evaluate an adapted version of the Tuned In music-based psychoeducation program, designed to reduce loneliness, depression, and anxiety symptoms among young people in Hong Kong by enhancing their emotion regulation skills.

Methods: Participants aged 16-19 years will be randomly assigned to either the experimental or control group. The experimental group will receive an online, group-based psychoeducation program focused on emotion recognition and management, delivered weekly over 4 consecutive weeks. The intervention is grounded in Russell's emotion circumplex model and music psychology, and program content included: The 2D model and characteristics of emotions from different quadrants (session 1); happiness and loneliness (session 2); high-arousal and negative-valence emotions, for example, stress and anxiety (sessions 3); and anxiety, perfectionism, and a celebration of achievement (session 4). Both therapist- and participant-selected music will be used in the intervention to provide a rich repertoire for group discussion, psychoeducation, reflection, and the practice of social skills. The main outcome measures will be assessed using the Emotion Regulation Questionnaire, the Difficulties in Emotion Regulation Scale, the Depression Anxiety Stress Scale, and the De Jong Gierveld Loneliness Scale. Feedback on the project arrangement will be gathered through qualitative input. A mixed methods analysis will be conducted following data collection.

Results: The project was successfully funded in February 2023 by the Health and Medical Research Fund in Hong Kong and commenced in August 2023. As of September 16, 2024, a total of 316 completed questionnaires had been received through Qualtrics for screening purposes, with 89 participants deemed eligible for the program. The project is scheduled to conclude in August 2025, with results to be published thereafter.

Conclusions: Participants are expected to show improvements in emotion regulation, along with reductions in mood symptoms and loneliness, following the intervention.

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KEYWORDS
youth; adolescents; adolescence; teens; teenagers; music; moods; mood symptoms; loneliness; emotion regulation; emotions; Hong Kong; mental health; mental illnesses; mental disorders; randomized controlled trial; RCTs; protocol

Introduction

Significance of Study

Youth mental health is a significant concern in Hong Kong. Studies have reported that the prevalence of depression and anxiety among adolescents is approximately 11.3% locally [1]. Loneliness is also widespread among young people in Hong Kong, occurring at a higher rate than that reported for their counterparts in North America [2]. Around 39% of young people in Hong Kong reported feeling lonely—an increase of 55% from 2012 to 2018 [3]. Furthermore, the prevalence of loneliness rose to 47% among adolescents and young adults in 2020 due to the pandemic [4]. A recent survey found that loneliness was associated with symptoms of depression, anxiety, and stress, even after controlling for demographic factors and views on the COVID-19 pandemic [2]. These negative emotional states have also been shown to be linked to other issues, such as substance use [5]. The connection between negative experiences, low mood, and substance use problems may be partly explained by a lack of emotion regulation skills. Emotion regulation involves the ability to manage emotions within a social context, which includes expressing emotions appropriately and with suitable intensity [6]. The Transdiagnostic Emotion Vulnerabilities Model proposes that emotional vulnerability is a core transdiagnostic factor underlying major depression, anxiety, and tobacco smoking [7]. In particular, young people may believe that unhealthy coping mechanisms, such as smoking, help them to relax. Because of this pairing of mental distress and poor health habits, they are likely to engage in—or continue—smoking during times of distress [5]. By contrast, a meta-analysis by Schafer et al [8] found that healthy coping during distress was associated with reduced depressive and anxious symptoms (r ranging from –0.29 to –0.50) among adolescents and young adults.

Given the significant role that emotion regulation plays in promoting youth mental health, it is desirable for preventative interventions to equip young people with age-appropriate, healthy coping strategies that serve as protective factors against long-term emotional difficulties, health problems, addiction, or substance abuse. Unfortunately, few such interventions have been validated by research in Hong Kong [9]. The proposed pilot trial will evaluate the effectiveness of a music-based prevention program in reducing mood problems among young people by enhancing their emotion regulation skills. This project is supported by a seed grant to conduct a small-scale trial in preparation for future large-scale research.

To evaluate the validity and effectiveness of the project in the Hong Kong context, the following hypotheses will be tested:

- The emotion regulation skills of adolescents and young adults will be enhanced following participation in the music-based program (primary outcome).
- The depression and anxiety symptoms of adolescents and young adults will be reduced following participation in the music-based program (secondary outcome).
- The sense of loneliness experienced by adolescents and young adults will be reduced following participation in the music-based program (secondary outcome).

Definition of Terms of Music Interventions

Music, defined by The New Penguin English Dictionary as “any vocal, instrumental or mechanical sounds that have rhythm, melody or harmony” [10], can influence emotions in many ways. As such, music is often perceived as the language of emotion [11]. Distinct from the term song, which refers to a short composition combining both words and music, music is considered a hypernym of song. In other words, music is a broader term that encompasses a range of activities—from listening to background music to engaging in composition and improvisation [12]—whereas song specifically refers to music with lyrics that can be sung [13]. This broader definition of music is adopted by music therapists to allow greater flexibility in the use of music or sound during interventions, enabling them to meet clients where they are in the present moment [14].

Music interventions are broadly classified into 2 types: active and receptive [15]. In active interventions, clients participate in the process of music production. By contrast, receptive interventions involve clients receiving the music experience, with listening focused on the intellectual, emotional, or other aspects of the music [15,16]. Previous studies on group music interventions for young people have not found significant differences in treatment outcomes between the 2 approaches [17].

Music and Emotions

The activation of the limbic system—responsible for processing emotions—when the ears perceive music provides a biological foundation for music’s influence on emotions [18]. The emotions experienced by listeners result from an interplay of multiple factors, including elements of the music itself, the performance, and the surrounding environment. For example, structural features of music such as tempo and melody are known to influence emotional responses. It is widely accepted that tempo can directly affect the pleasantness of emotions and that melodies tend to be higher in pitch in happy music compared with sad music [19]. In addition to musical structural features, song lyrics are often used as a springboard for discussing life events that evoke emotions during interventions [16]. Lyrics play a vital role in eliciting emotions, particularly sadness [20].

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Previous research has also found that engaging with self-selected music can foster a sense of connectedness [21].

Music Interventions, Youth Emotion Regulation, and Tuned In

Listening to music is an effective emotion regulation strategy [22-24], and existing literature supports its use in reducing symptoms of depression and anxiety. One study examining the use of online group music therapy to manage anxiety and stress among university students confirmed the effectiveness of this type of intervention [17].

Tuned In, a preventative program developed by 1 of the coinvestigators to address mild to moderate levels of psychological distress, has demonstrated positive psychological outcomes in both adolescents [25,26] and young adults in Australia [6]. A related intervention, Smoke into Sound, was found to be more effective in reducing cigarette cravings than the gold standard of cognitive behavioral therapy delivered via telephone, as shown in a randomized controlled trial (RCT) [27].

During the COVID-19 pandemic, young adults rated listening to music as the most effective coping mechanism [24]. The Tuned In program is based on Russell's [28] circumplex model of emotion, which categorizes emotions along 2 dimensions: valence and arousal. The theoretical foundation linking music and emotion in the Tuned In program draws from this 2D model [28,29], in which emotions are positioned along an arousal axis (ranging from high to low energy) and a valence axis (ranging from pleasant to unpleasant). It also incorporates the BRECVEMA (brain stem reflexes, rhythmic entrainment, evaluative conditioning, contagion [emotional contagion], visual imagery, episodic memory, musical expectancy, and aesthetic judgment) theory of music and emotion [30], which identifies mechanisms such as lyrical meaning, personal memories associated with music, and imagery evoked by music as key factors influencing emotional responses to listening. Although not explicitly stated in the program materials, this theoretical background is embedded in the content and activities—such as lyric analysis and imagery drawing tasks conducted while listening to music.

Through psychoeducation and experiential activities designed to explore and make meaning of emotions—such as locating emotions in the body, lyric analysis, drawing imagery while listening to music, and group discussions—participants in the program first learn to categorize their emotions in terms of intensity (ie, arousal level) and positivity (ie, valence). They then reflect on and develop a personalized list of songs they relate to, using these songs to increase or decrease the intensity and positivity of their emotions. In other words, participants practice monitoring their emotional states and using music to help modify how they feel.

In addition, music can enhance social connectedness—and potentially foster actual social connections—when shared with others [12]. Therefore, music serves as a universal and comprehensive tool for promoting emotion regulation and reducing feelings of loneliness, as well as depressive and anxious symptoms [24,25,31-33]. Furthermore, emerging local evidence supports the positive role of music listening as a promising strategy for enhancing mental health among adolescents in Hong Kong. In a large-scale cross-sectional survey, Leung and Cheung [34] found that music listening contributed to psychological well-being among young people by enhancing emotional awareness.

Music Interventions, Youth Loneliness, and Tuned In

In addition to depression and anxiety, loneliness is a socioemotional state that has attracted increasing research attention [35]. In 2019, 22% of young Chinese people reported experiencing feelings of loneliness [36]. Recent data also suggest that loneliness is associated with poor health habits—such as smoking—among young Chinese individuals [36].

Although lonely young people may have friends and families, everyday interactions often provide limited opportunities for deep connection and personal sharing within a trusting environment for this age group [37]. This is echoed by recent research findings showing that 76% of lonely adolescents and young adults feel they are not well understood by others—a situation that could potentially be addressed through the empathic effects of music [21,31].

Feelings of empathy or being understood can arise not only through human interactions but also through listening to comforting music, suggesting a promising mechanism for reducing loneliness in young people [21]. Schafer and colleagues [21] found that listening to self-selected music improved participants' self-reported mood following a sad mood induction, regardless of the type of music chosen. They proposed that self-selected (ie, familiar) music acts as a surrogate listener, helping individuals feel that their emotions are being "heard," thereby providing a comforting effect. These soothing effects of music could be leveraged to address a key issue underlying loneliness among young people.

However, there is limited research on interventions aimed at reducing loneliness among young people in Hong Kong. This scarcity is also evident in the broader literature. A recent meta-analysis and systematic review found that certain group-based psychological interventions can be effective in reducing loneliness [38,39].

One psychoeducation group intervention found no significant decrease in loneliness at follow-up [40], while other interventions—such as online dancing and various psychoeducation-based group programs—reported reductions in loneliness [41-43]. These mixed results highlight the need for more promising and effective programs to reduce loneliness, both locally and within the broader research literature.

Nevertheless, there is preliminary evidence that the Tuned In program has positive effects in reducing loneliness among young people. Coinvestigator GD and her team (email communication, February 18, 2025) completed a study applying the original program in a passive control design with 35 English-fluent international students in Australia. They found a significant interaction between time and condition, resulting in a reduction in self-reported loneliness among participants—with a moderate effect size (η^2_p=0.12)—compared with the waitlist group. This

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overall positive effect is attributed to the synergy of the program's core components: psychoeducation, group work, and music. Each serves as an essential therapeutic element, and together they form the comprehensive Tuned In intervention.

Undeniably, adopting an active control would be more ideal. However, due to limited resources and the need to maintain fidelity to the original program, a waitlist control design was chosen for practical reasons. The primary aim of this study is to examine whether this combination of elements can produce desirable outcomes in the Hong Kong context. Investigating the specific role and contribution of each component, as well as comparing the effectiveness of this combination with other types of interventions, represents a valuable direction for future research.

Theoretical Framework for Tuned In

The Tuned In program was developed as an alternative to cognitive behavioral therapy and is grounded in emotion theory and music psychology research on the links between music listening and emotional responses [25-27]. The 4 sessions primarily aim to not only address negative emotions—such as depression, loneliness, anxiety, and anger—but also explore ways to enhance positive emotions or states such as motivation, happiness, and calmness. Each session begins with the facilitator describing the components and functions of emotions (eg, physiological responses and common thoughts), followed by participant sharing and group discussion about songs they currently listen to—or could listen to—that elicit or help regulate those emotions.

As engagement in music does not require participants to have prior knowledge or skills in music [17], a receptive intervention has been chosen for the current project. According to Juslin's BRECVEMA model [30], the meaning of lyrics is one of several mechanisms that link music listening with emotional responses. The model identifies multiple pathways through which a musical event can influence emotions, including brain stem reflex, rhythmic entrainment, evaluative conditioning, emotional contagion, visual imagery, episodic memory, musical expectancy, and aesthetic judgment [30].

Although some experimental evidence suggests that melody has a stronger influence than lyrics on emotional responses to music [44], this effect is highly individualized—some people focus more on melody, while others are more affected by lyrics. Therefore, both instrumental music and songs will be used in this project. In alignment with both the original program and guidelines for receptive music interventions, instrumental music may be used for imaginal and somatic listening, with the flexibility to adjust based on participants' emotional states and feedback. Songs, by contrast, will be used for lyric discussions. Given that the current project is psychoeducational, with music serving as a tool for relationship building and emotional regulation, the inclusion of both songs and instrumental music allows for greater acceptance of diverse musical styles and gives participants the freedom to share and appreciate various kinds of music. Discussions about song components (eg, lyrics) can also deepen participants' understanding of the physiological and cognitive aspects of different emotions. The intention is that, by the end of the program, participants will be able to assess their emotional valence and arousal, and they will have a personalized playlist they can use to enhance or regulate their emotional states. In other words, they will be "tuned in" to their emotions.

Building on the existing evidence, the proposed study aims to establish an effective music-based program to enhance emotion regulation skills among young people in Hong Kong. This approach complements current practices in the region, which often focus on areas such as self-esteem, resilience, social competence, problem-solving, and communication [1,9]. Notably, the proposed study introduces a new session targeting "loneliness"—an addition to the original Tuned In program implemented in Australia [6]. This new component directly addresses the rising prevalence of loneliness among adolescents in Hong Kong [3,4].

The program will be facilitated by a registered music therapist and a research assistant, both under the supervision of the primary investigator. The research assistant will receive training from the coinvestigator and original developer of Tuned In before delivering the groups, along with ongoing supervision from her. This arrangement ensures the standardized delivery of both the music-based activities and the psychoeducational content. Because of previous COVID-19–related restrictions, the program was initially proposed to be conducted online. However, with the loosening of COVID-19 restrictions, the study has incorporated an introductory session where participants can meet each other and the facilitator in person. This session is intended to build rapport and foster a sense of group identity, which is expected to enhance engagement during the subsequent online group sessions while preserving the flexibility of the program format [45,46].

Aims and Objectives

The ultimate aim of this study is to test and validate a music-based program designed to improve emotion regulation among adolescents and young adults in Hong Kong, with the broader goal of reducing symptoms of depression, anxiety, and loneliness.

The objective of the proposed project is to evaluate the effects of a music-based program on young people in Hong Kong. The hypotheses to be tested are listed below.

The primary outcome is as follows:

- The emotion regulation skills of adolescents and young adults will be enhanced following participation in the music-based program.

The secondary outcomes are as follows:

- Symptoms of depression and anxiety among adolescents and young adults will be reduced following the program.
- Feelings of loneliness among adolescents and young adults will be reduced following the program.

Methods

Ethical Considerations

Ethical approval for the study was obtained from The University of Hong Kong (approval number EA230395) and The Hong

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Kong Polytechnic University (approval number HSEARS20221024004). Ethical approval was either exempted or not required by other participating universities for the distribution of advertisement materials.

In adherence to the ethical regulations of the university, signed active parental consent will be obtained for participants under the age of 18 years. All participants are required to sign a physical consent form before participating in the intervention. Participation is entirely voluntary, and all participants have the right to withdraw from the project at any time without any negative consequences.

Study Design

The study adopts a waitlist RCT design. Participants are randomly assigned to either the intervention group, who will receive the program immediately, or the waitlist control group, who will receive the intervention after a 4-week waiting period. The main assessment time points are pre- and postintervention for the intervention group, and baseline and postwaiting period for the control group. Additionally, the control group will be invited to complete an optional postintervention survey following their participation, which will be used for secondary data analysis. The postintervention surveys for both groups will contain identical items to ensure comparability. It is also planned that all participants who complete the intervention will be invited to take part in an optional qualitative interview to gain deeper insights into their experiences using the strategies taught in the program.

Given the project's strong emphasis on psychoeducation, participants' application of the strategies taught serves as an indicator of the program's acceptability. Qualitative inquiry offers valuable insights into the extent to which participants have internalized and consolidated the healthy coping strategies introduced during the intervention. This approach enables exploratory interpretations of the project's outcomes and helps uncover the nuanced, individualized experiences of participants. Therefore, qualitative research is considered appropriate to capture the subjective and personal dimensions of the intervention's impact.

Online delivery was chosen in response to the prevailing pandemic conditions at the time. This decision not only aligned with the original program design but also helped overcome geographical barriers. By eliminating distance as a constraint, the online format significantly enhanced the accessibility of the program. While this mode of delivery presented challenges—such as difficulty in maintaining participants' attention and limited nonverbal communication—it also expanded the potential of digital platforms to support mental health through digital expressive arts and peer support [47]. Moreover, the web-based design increased the mobility and flexibility of the intervention [48]. Previous studies have shown that online group interventions can be effective in reducing mental health symptoms such as depression [43,48], and Draper and Dingle [49] found that virtual groups were effective in addressing psychological needs.

Material and Personnel Preparation

The group sessions are cofacilitated by 2 individuals: a research assistant with a background in a mental health–related discipline and a registered music therapist. The research assistant takes the lead in delivering the psychoeducational content, while the music therapist facilitates the musical experiential activities and supports group discussions. Both facilitators employ techniques such as encouraging participants to be "good group members" to manage group dynamics effectively. For instance, during ice-breaking activities or group discussions led by the research assistant, the music therapist may participate as though they are a group member. This approach helps to foster rapport and strengthen the connection between the facilitators and participants. The same roles and techniques also apply to the research assistant during music activities. Additionally, the research assistant serves as the main point of contact for participants and is responsible for participant follow-up and distribution of reimbursement. The follow-up, limited to the scope of the project, includes administrative liaison (eg, responding to participant inquiries, delivering materials, arranging logistics) and crisis intervention. Crisis intervention involves providing appropriate community crisis support resources and information and making an informed decision regarding the participant's eligibility to continue with the group intervention.

To enhance project fidelity, the English manual from the original program was revised and translated into Chinese. The music selections from the original program were also adapted by the music therapist to better suit the local context. The incorporated music in this project is intended to produce equivalent therapeutic effects while maintaining consistency in music type with the original selections. For instance, Shawn Mendes' *A Little Too Much* [50] from the original program was replaced with Eason Chan's *Today* [51], which is more culturally relevant and relatable for local youth.

The manuals will be printed and distributed to participants and facilitators before the sessions. In cases where distributing hard copies is not feasible, an electronic version will be provided instead. To enhance readability and engagement during session presentations, PowerPoint (Microsoft Corporation) slides aligned with the manual content will also be used.

A session checklist outlining the key components of each session was prepared for facilitators to log the completion of intervention activities. These entries serve as records to support program fidelity and ensure consistency across sessions.

Recruitment

The recruitment process began in August 2023 and will continue until August 2025. Various strategies have been implemented to improve the accessibility of project information across all regions of Hong Kong.

Three main recruitment channels have been used:

- Social Media Platforms: project posters, welcome messages, and links to detailed information were posted on Instagram (Meta Platforms, Inc.), Facebook (Meta Platforms, Inc.), and Social Career (Social Career Limited), which are widely

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used by local youth. Additionally, project details were published on the university website to reach the general public.

- Existing Partnership Networks: Information about the project was shared with 3 local universities, a local integrated children and youth services center, and several secondary schools that either have existing collaborations with the principal investigator (YC) or have expressed partnership interest. These institutions helped disseminate project details to their students or service users (eg, the ELCHK Lutheran Academy).
- Exploratory cold calls and emails: The research assistant reached out to additional secondary schools and integrated children and youth services centers via phone and email. These contacts were selected based on alignment between their service targets, institutional missions, and the goals of the project. Project information and partnership invitations were conveyed either verbally or in writing.

Randomization and Blinding

Participants will be randomly assigned to either the intervention or waitlist control group using a computer-generated randomization procedure. The Random Allocation Software developed by Dr. Mahmood Saghaei [52] will be used to facilitate this process. Block randomization will be implemented to ensure balanced group sizes, with a maximum of 8 participants per group. Randomization will be carried out by an independent researcher who is not part of the current research team or is listed as an author. The principal investigator remains blinded to group assignments to maintain objectivity and reduce potential bias. Outcome measures are managed by a separate research assistant who is not involved in the delivery of the intervention, ensuring independence and reducing potential bias. Once a sufficient number of eligible participants have been recruited, randomization will be conducted, typically 2 weeks before the intervention start date. Participants will then be informed of their group allocation, along with the schedule of their assigned group sessions, by the designated research assistant. In alignment with the ongoing recruitment process and rolling admission, the intervention will be delivered to participants as they are randomized and assigned to groups.

Participants

The target population for this study comprises post–high school students and adolescents aged 16-19 years. This age range aligns with international guidelines, such as those from the World Health Organization, which defines adolescence as ranging from 10 to 19 years, and the United Nations, which considers individuals aged 15-24 years as adolescents and young adults. Recruitment materials for the project will be disseminated to students in their final year of high school as well as recent graduates who maintain connections with their schools. Young adults, primarily those in their first year of undergraduate studies (typically aged 17-19 years in the Hong Kong context), will be recruited through posters displayed on university campuses and word-of-mouth referrals. A snowball sampling method will also be used to expand participant recruitment. Consistent with the approach used by Dingle and Fay [6], this study will include youth who self-report experiencing symptoms of low mood, anxiety, or loneliness.

Inclusion criteria for participation are (1) self-reported difficulties with low mood, anxiety, or loneliness; and (2) a score of 3 or above on the 12-item General Health Questionnaire (GHQ-12), indicating the presence of psychological distress. Exclusion criteria are the presence of severe mental health symptoms, such as self-harm or suicidal ideation, as the Tuned In program has not yet been trialed with individuals experiencing more acute mental health conditions.

Interested participants who do not meet the inclusion criteria will be provided with an information sheet about community counseling services. Eligible participants who confirm their enrollment will be randomized.

Sample Size Calculation

Dingle and Fay [6] found a medium effect size (η^2_p=0.076) for improved emotion regulation after the music intervention with young adults, compared with the control group. Based on this medium effect size, at least 98 participants are needed to detect a significant group × time interaction effect (P<.05). However, based on previous trials, some dropout is expected after the intervention has commenced. The estimated attrition rate is 15%. Besides, considering that partnerships with middle schools have only recently begun to develop, while many university students have already expressed interest in committing to the project, we expect to recruit more university participants. Therefore, we aim to recruit over 100 participants for the randomization stage, including around 50 adolescents and 65 young adults, to account for possible dropouts before the intervention begins.

Contingency Plan

Based on prior trials of Tuned In, we expect a high retention rate among youth [6]. However, some attrition may occur among adolescents [25]. Even with that attrition rate, we anticipate retaining at least 30 adolescents at the postintervention stage, providing sufficient data from this pilot study to inform future large-scale trials. In the event of significant challenges in recruiting adolescents, our backup plan is to recruit additional youth from the university community for this trial.

Because of the online mode of intervention, the study design minimizes potential disruptions arising from any local changes in the COVID-19 pandemic situation. If difficulties or delays in participant recruitment arise, we will place advertisements on social media as an additional recruitment channel.

Considering the risk of potential emotional disturbances, a page listing several 24-hour community crisis support hotlines has been incorporated into the manual to provide participants in need with an additional channel to external resources. Alongside the distribution of these resources, the research assistant will also give instructions on how to use them during the group contracting phase and explicitly encourage participants to seek help and notify the research assistant immediately if they experience emotional distress during the session.

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In situations where psychological distress is identified either by a facilitator or self-reported by a participant, the research assistant will separate the individual from the rest of the group, while the music therapist continues to lead the remaining activities. The research assistant will provide immediate emotional support and conduct a timely risk assessment, and the principal investigator will be informed of the situation. Based on the participant's condition, appropriate referrals will be made as necessary.

The research assistant will follow up with individuals who disclose intentions or actions related to self-harm, suicide, harm to others, or breaches of the law, and will discuss with them the appropriateness of continuing in the project or the available options for discontinuation.

Description of the Intervention

The project consists of 5 weekly sessions: 1 introductory (preassessment) session followed by 4 psychoeducational sessions. Each session lasts approximately 60-90 minutes.

In the introduction session, participants sign the informed consent forms after being informed about the program's content and expectations by the main group facilitator (ie, the research assistant). For participants under 18 years of age, parental consent will also be obtained during the session. Following the signing of consent, the baseline survey will be distributed and collected. Participants' demographic information will be gathered through the survey. This includes, but is not limited to, age, gender, education level, household income, region of residence, living arrangement, and employment status.

Each week, participants will receive WhatsApp (Meta Platforms, Inc.) text message reminders about upcoming sessions and other important announcements.

The psychoeducational sessions differ in theme but follow a similar structure. Session 1 focuses on emotions located in various quadrants of the 2D model, such as high-arousal and negative-valence emotions. Session 2 explores happiness and loneliness, with the new component of loneliness added to this session. Sessions 3 and 4 address high-arousal emotions, such as stress and anxiety. An example session plan is provided in Multimedia Appendix 1 for reference (Table 1).

Table 1. Summary of session content.

Session	Content
Session 1	Emotions located in various quadrants of the 2D model, such as high-arousal and negative-valence emotions
Session 2	Happiness and loneliness
Session 3	High-arousal and negative-valence emotions, such as stress and anxiety
Session 4	High-arousal emotions, such as perfectionism and anxiety (continue) and achievement

For the new loneliness component, in addition to discussing songs that evoke a sense of receiving empathy, psychoeducation will be provided on the positive effects of music sharing in building and strengthening emotional bonds in relationships [12]. The group sessions will offer a safe and pleasant environment where participants can talk about music, using this topic as a channel to foster new connections with fellow group members. In session 2, participants will be guided to discuss how they can apply this skill outside of the program to strengthen existing relationships and build new connections.

Participants are also expected to select music for themselves during the group sessions. These self-selected songs serve to evoke the target emotions for each session and support group discussions and experiential psychoeducation—specifically, increasing awareness of the bodily or physiological changes that accompany each emotion as elicited by music. As music appreciation is used as a tool to support psychoeducation about emotions, rather than being a goal in itself (ie, the program is not intended to enhance musical understanding), we believe that participant-selected songs are more appropriate than those prescribed or suggested by the program facilitators. This is also in line with literature supporting the benefits of using self-selected and familiar music [21]. As such, participants' sharing of their self-selected music is incorporated as a core element in the sessions. The music submitted by participants spans a wide range of styles, reflecting their individual tastes, and includes Cantonese pop songs, classical music, movie soundtracks, and more.

Each session begins with a music check-in led by the music therapist, followed by participants listening to their self-selected music. This music listening and sharing segment takes approximately 15-20 minutes. Once the target emotions are evoked, the research assistant provides psychoeducation on the theme emotion and facilitates a group discussion on coping strategies. Around 10-15 minutes are allocated for this group discussion. Next, the music therapist guides participants through a core music activity designed to support reflection and reconnection with the theme emotion. Selected music activities include body scan, drawing, and lyric analysis. Each activity takes approximately 15 minutes. Each theme emotion is paired with its own specific psychoeducational content and corresponding music activity. The session concludes with a summary and debriefing provided to participants.

By the end of the last session, participants will be invited to complete the postquestionnaire. Individuals who complete both the prequestionnaire and postquestionnaire will receive a reimbursement of HK $200 (US $25.77) in cash. Reimbursement will be provided in person, and participants will be required to sign a receipt for record-keeping purposes. The intervention for the control group will be delivered after the final session of the experimental group and upon completion of the postquestionnaire by its participants. A flowchart outlining the project has been included in Multimedia Appendix 2.

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Outcome Measures

Overview

The following measures of emotion regulation (primary outcome), mood symptoms (secondary outcome), and loneliness (secondary outcome) will be administered pre- and postintervention via Qualtrics (Silver Lake Technology Management, L.L.C.).

Primary Outcome: Emotion Regulation

- The Emotion Regulation Questionnaire is a widely used measure with subscales assessing 2 styles of emotion regulation: cognitive reappraisal and expressive suppression. It has been translated and validated for use in Hong Kong (Cronbach α=0.80-0.83) [53]. A child and adolescent version of the scale has also been translated into Chinese [54]. Given that the primary focus of the Tuned In program is to encourage the outward expression of emotion through music, it is anticipated that changes will be observed in expressive suppression scores, but not necessarily in cognitive reappraisal scores, following the program.
- The Difficulties in Emotion Regulation Scale (DERS) is a more comprehensive measure that assesses emotional awareness, emotional acceptance, impulse control, and emotion regulation strategies among both adolescents and adults. This scale has also been validated for use with Chinese participants (Cronbach α=0.68-0.89) [55]. Given its comprehensive nature, the DERS is considered the primary outcome measure in this study.
- To measure confidence in managing emotions, items from the program evaluation tool used by Dingle and Carter [27], which explicitly asks participants to rate their self-confidence in managing both positive and negative emotions, will also be included.

Secondary Outcomes: Mood Symptoms And Loneliness

- The 21-item Depression Anxiety Stress Scale (DASS-21), which has been used with Chinese participants [56], will be used to measure mood symptoms. Recent research has demonstrated the scale's validity for assessing emotional distress among young people in Hong Kong [57].
- The Hong Kong version of the 6-item De Jong Gierveld Loneliness Scale (Cronbach α=0.76) [58] will be used to assess loneliness.

Additional Measure

We will use the Music USE (MUSE) Questionnaire [59] to assess each participant's typical music listening habits, including whether they play a musical instrument and if they have received formal musical training. This scale was successfully used in a study involving 1318 adolescents in Hong Kong [34], making it a valuable tool for describing participants' engagement with music.

For demographic information such as gender and socioeconomic status collected in the survey, tests will also be conducted across the 2 conditions to examine whether the results differ.

The effect of the intervention on reducing anhedonia will also be explored using the Chinese version of the Snaith-Hamilton Pleasure Scale [60]. Data collected from this scale will be used for future outcome analysis.

The Tuned In program's acceptability among Hong Kong adolescents will be examined using a combination of quantitative and qualitative approaches. Satisfaction ratings will be collected from participants using a 7-point Likert scale. With "strongly disagree" at 1 point and "strongly agree" at 7 points, the ratings will capture the extent to which participants agree with the positive statements. The questions will address the perceived usefulness of the program, the level of interest in the program, the likelihood of recommending the program to other adolescents, and the likelihood of continuing to use music as an emotion regulation strategy in the future [25]. The aforementioned areas of investigation regarding the project's acceptability are framed into 4 separate rating questions, all of which are included in the postintervention survey. The quantitative questions are provided in Multimedia Appendix 3.

In addition, we will include open-ended qualitative questions to gather feedback from participants on their experiences with the program and to collect suggestions for improvements for a future RCT. Written responses are expected from participants. As feasibility indicators, we will also record the recruitment rate and dropout rate for this trial. The qualitative questions are incorporated into the postintervention survey, to be completed by participants at the end of the final session.

To explore participants' continued use of music for emotion regulation after the program, invitations to qualitative interviews will be sent at the 1-month follow-up. All participants who received the intervention will be invited. Open-ended and probing questions will be used to gather descriptive data on participants' views of the program and their music listening habits. Data saturation is expected to be reached by the conclusion of the project. Please refer to Multimedia Appendix 3 for the interview and postintervention survey questions.

Data Analysis

For the main outcome evaluation measures, mixed measures ANOVAs will be performed. The between-participants factor is group (intervention vs control), and the within-participants factor is time (pre- vs postintervention). Before the main analyses, independent samples *t* tests (2-tailed, paired) will be conducted on the baseline demographic variables to identify any significant differences between the 2 groups. Any variables that show statistically significant differences will be included as covariates in the subsequent main analyses. It is expected that the treatment group will demonstrate improved emotion regulation and reduced mood symptoms and loneliness following the music intervention, compared with the control group. A medium effect size is anticipated for the significant group × time interaction effect.

All verbal and written feedback will be analyzed using thematic analysis [61]. The qualitative analysis software NVivo (QSR International) will be used to assist with the process. Content analysis will be conducted following the transcription and coding of the data.

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Results

The successful funding outcome of this project was announced in February 2023. Participant recruitment began in January 2024, and as of September 16, 2024, a total of 316 responses had been received through Qualtrics. Upon submission of the questionnaire, all participants are promptly notified of its receipt. Those deemed eligible receive a basic information sheet, while individuals who are ineligible are provided with a list of supporting resources. Of the responses received, 89 participants were considered eligible for the program. The project is scheduled to conclude in August 2025, with results to be published thereafter.

Discussion

Expected Findings

This proposal focuses on examining the short-term impact of a music-based emotion regulation program for young people in Hong Kong. For this trial, we expect the intervention group to demonstrate improved emotion regulation and reduced mood symptoms and loneliness after completing the Tuned In program, compared with the control group. This expectation is based on previous successful trials of Tuned In conducted in Australia [27]. Furthermore, in line with the Transdiagnostic Emotion Vulnerabilities Model, enhanced emotion regulation may help alleviate a range of mood-related issues [7].

Qualitatively, we expect that participants will describe their reduced loneliness and enhanced mental well-being as being directly and indirectly related to music. For example, they may resonate with the music and experience a sense of being understood [12]. We also anticipate that participants will appreciate the use of self-selected music throughout the program [21]. In the future, we plan to conduct longitudinal studies to examine the medium- to long-term impacts of the intervention.

Strengths

The study demonstrates notable strengths, including the involvement of 2 cofacilitators—a registered music therapist and a trained research assistant with a mental health background—ensuring both clinical expertise and research rigor in program delivery. Additionally, the inclusion of a new session component specifically targeting “loneliness” enhances the intervention by building upon and extending the established “Tuned In” program previously conducted in Australia, thereby addressing an important psychosocial issue with a tailored and evidence-informed approach.

Limitations

As this study is a pilot RCT, the primary focus is on assessing the feasibility and effectiveness of the intervention. The long-term effects can be explored in future, larger-scale trials. It is acknowledged that the outcome measures used are self-reported. This method was chosen to capture participants’ subjective experiences and perceptions. Additionally, the study does not account for individual differences that may influence outcomes. Factors such as the impact of life events or levels of alexithymia may potentially influence the outcomes of the program and should be taken into account in future research. Subsequent studies could incorporate additional forms of assessment, such as physiological measures or reports from family members, to provide a more comprehensive and corroborated evaluation.

As coping through emotions mediates the relationship between resilience and youth well-being [62], equipping young people with adaptive strategies to manage stress and difficult emotions helps consolidate learning and builds greater internal resources and capacity. This, in turn, positively influences both their short- and long-term mental health. Healthy coping also acts as a protective factor for their future emotional well-being.

Although this project does not investigate the medium- to long-term effects of the intervention on youth mental health due to resource constraints, future research could adopt a longitudinal perspective to explore the factors that help sustain the positive outcomes. Future studies could also incorporate an active control design and examine the individual contribution of each component to the overall effectiveness of the program.

Conclusions

This project aims to examine the short-term effects of a music-based emotion regulation program for young people in Hong Kong. We expect positive outcomes from this trial, and the preliminary results will inform the planning of future studies to better understand the underlying mechanisms and longer-term impacts.

From a practical perspective, the project will provide valuable insights into the use of music and psychoeducation in youth mental health work in Hong Kong. From a research and theoretical perspective, it may offer evidence regarding the effectiveness of combining music, psychoeducation, and group work in improving youth mental health. Building on the current project, future studies are encouraged to explore innovative ways to enhance the cost-effectiveness, outcome magnitude, reliability, and sustainability of the intervention.

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Authors' Contributions

YC designed the study, contributed to the intervention design, and was responsible for funding acquisition. DTLS and DHKS contributed to the program evaluation and participant recruitment planning. RT and GD contributed to the intervention design

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and program evaluation planning. YC and DCWL drafted earlier versions of the paper. YS contributed to paper revisions. All authors reviewed and edited the final manuscript before submission.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Tuned In group session plan (session 5).
[DOCX File , 13 KB - resprot_v14i1e67764_app1.docx]

Multimedia Appendix 2
Project flowchart.
[PNG File , 279 KB - resprot_v14i1e67764_app2.png]

Multimedia Appendix 3
Survey and interview questions.
[DOCX File , 17 KB - resprot_v14i1e67764_app3.docx]

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Abbreviations

BRECVEMA: brain stem reflexes, rhythmic entrainment, evaluative conditioning, contagion (emotional contagion), visual imagery, episodic memory, musical expectancy, and aesthetic judgment
DASS-21: 21-item Depression Anxiety Stress Scale
DERS: Difficulties in Emotion Regulation Scale
GHQ-12: 12-item General Health Questionnaire
MUSE: music USE
RCT: randomized controlled trial

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Protocol

Feasibility Testing a Meditation App for Professionals Working With Youth in the Legal System: Protocol for a Hybrid Type 2 Effectiveness-Implementation Pilot Randomized Controlled Trial

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Abstract

Background: Probation officers and other professionals who work with youth in the legal system often experience high chronic workplace stress, which can contribute over time to elevations in anxiety, depression, and workplace burnout. Emotion dysregulation appears to function as a common mechanism underlying these elevations, and growing evidence suggests it can be improved with mindfulness meditation. Implemented successfully, app-based meditation programs could provide professionals with real-time tools for mitigating the effects of chronic workplace stress.

Objective: This paper describes the protocol for a hybrid type 2 effectiveness-implementation pilot randomized controlled trial (RCT) of Bodhi AIM+, a meditation app adapted with and for professionals who work with youth in the legal system. The adaptation process and implementation plan, as well as the pilot RCT design, were guided by theoretically driven implementation science frameworks. The primary outcome of the pilot RCT is app adherence (ie, ongoing app usage per objective analytics data).

Methods: The RCT will be fully remote. Officers and other professionals who work with youth in the legal system (N=50) will be individually randomized to use the meditation app or an active control app matched for time and structure. All participants will be asked to follow a 30-day path of brief audio- or video-guided content and invited to use additional app features as desired. In-app analytics will capture the objective usage of each feature. An adaptive engagement design will be employed to engage nonusers of both apps, whereby analytics data indicating nonuse will trigger additional support (eg, text messages promoting engagement). Mental health outcomes and potential moderators and covariates will be self-reported at baseline, posttest, and 6 months. Participants will also complete 1-week bursts of ecological momentary assessment (EMA) at baseline and over the last week of the intervention to capture the mechanistic target (ie, emotion regulation) in real time. All participants will be invited to complete qualitative posttest interviews. Descriptive statistics will be calculated for quantitative data. Qualitative data will be analyzed using a combined deductive-inductive approach. The quantitative and qualitative data will be incorporated into a mixed methods triangulation design, allowing for the evaluation of app adherence and other implementation outcomes as well as related barriers and facilitators to implementation.

Results: Enrollment into the trial started in December 2024 and is currently underway. Study results are anticipated to be available in 2026.

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Conclusions: Completion of this pilot trial will inform a future, fully powered RCT to formally evaluate the effectiveness and implementation of Bodhi AIM+. Its use of implementation science methods, coupled with digital technology, positions the present study not only to help make meditation tools available to an important workforce at scale but also to inform broader efforts at implementing and evaluating health apps within workplace settings.

Trial Registration: ClincialTrials.gov NCT06555172; https://clinicaltrials.gov/study/NCT06555172

International Registered Report Identifier (IRRID): DERR1-10.2196/71867

(JMIR Res Protoc 2025;14:e71867) doi:10.2196/71867

KEYWORDS

mobile app; mHealth; digital mental health; meditation; mindfulness; juvenile legal system; officers; workplace; ecological momentary assessment (EMA); emotion regulation

Introduction

Juvenile probation officers and other professionals who work with youth in the legal system often experience high levels of chronic workplace stress [1,2]. These stressors can include managing large caseloads, supporting youth through traumatic events, and navigating tense home and court visits [1,3]. Many professionals say these stressors can wear on their mental health, contributing over time to elevations in anxiety, depression, and workplace burnout [2,4,5].

Emotion dysregulation (eg, difficulty up-regulating positive emotions or down-regulating negative emotions) appears to be a common mechanism underlying depression, anxiety, and burnout, and it can be improved through mindfulness meditation [6-9]. Moreover, many professionals who work with young people in the legal system express interest in meditation practice [10]. Yet research in this area is sparse, and the scalability of existing efforts has been limited. For example, an early pilot trial indicated that in-person, group-based meditation was acceptable and generally feasible among officers in the juvenile legal system [10]. However, in-person groups are resource-intensive, face limited instructor availability, and often conflict with the shifting demands of officers' daily schedules. In light of growing evidence that meditation can be effectively delivered via smartphone app [11-13], app-based programs may offer a promising tool for overcoming these barriers. To date, however, no studies of which we are aware have systematically evaluated the effectiveness and implementation of an app-based meditation program with officers and other professionals who support youth in the legal system. This study is a carefully designed first step toward addressing this gap.

It is worth highlighting that individual-level interventions such as meditation do not address the structural and environmental factors that contribute to chronic workplace stress [5,14]. There is thus ultimately a need for programs that intervene directly on these factors. Nonetheless, individual-level interventions can play important roles in providing professionals with tools for more effectively navigating workplace stressors and helping offset potential negative effects such as anxiety, depression, and burnout.

The present study was born out of an earlier project adapting, implementing, and feasibility testing a mindfulness meditation app for youth on probation funded by the National Institute on Drug Abuse (NIDA; grant K99/R00DA047890). The setting for both projects is Cook County, which encompasses Chicago and its surrounding suburbs and houses one of the largest legal systems in the United States. Throughout our pilot trial of the meditation app for youth, officers approached our team requesting their own version of the app both (1) as a stress reduction tool for themselves during the workday, and (2) as a resource to support mindfulness skills–building among youth on their caseloads. In response to these requests, we developed a grant proposal for two main phases of research activity. The grant was funded by the National Center for Complementary and Integrative Health (NCCIH; grant R34AT012078).

During the first phase of the activity, which was conducted in preparation for the pilot trial detailed in this protocol paper (ie, the second phase), we partnered with officers in the juvenile legal system and other stakeholders to guide the adaptation and implementation of an existing meditation app, Bodhi, for use by officers in the workplace. During this process, we received feedback that other professionals working with youth in the legal system, for example in independently contracted probation programming, faced similar workplace stressors and had a shared interest in a workplace meditation app. We thus adapted Bodhi with the intention that it could be used not only by officers but also by other related professionals more broadly.

The original Bodhi app was developed by Tibetan Buddhist meditation teachers to deliver authentic meditation practices in a modern and intuitive interface based on extensive user testing. The meditation practices were derived from the Nyingma lineage, the oldest of the four major schools of Tibetan Buddhism. The original app featured a 30-day program to help users build a daily meditation practice through brief audio-guided meditations, complemented by short videos from scientific experts and everyday meditators. Bodhi also included a menu of To Go integration meditations that users could select to prepare for specific situations (eg, flying on an airplane). Youth from our previous study named their adapted app Bodhi AIM (Action In Mindfulness); officers voted to name the companion version adapted for their use Bodhi AIM+ (called AIM+ for short).

The process of adapting and implementing Bodhi for officers and other professionals was guided by the EPIS (Exploration Preparation Implementation Sustainment) and CFIR (Consolidated Framework for Implementation Research) implementation science frameworks [15-17]. We collaborated with stakeholders to identify key determinants (ie, barriers and

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facilitators) of professionals' adherence to the app and develop corresponding implementation strategies to promote adherence. Adherence (ie, ongoing app usage) was identified as the primary outcome because low adherence to health apps is a pervasive issue and adequate levels are a precondition to achieving health benefits [18]. The implementation strategies that were developed included tailoring the meditation practices for relevance to officers and other professionals during their workday (eg, practices for before a meeting or before court), recording the practices with a guide stakeholders found appealing and trustworthy, and building an automated adaptive engagement design to detect low app adherence based on analytics data and trigger additional support (eg, text messages, as detailed below). All of this was accomplished through an iterative series of qualitative interviews with officers rooted in the EPIS and CFIR frameworks. These formal interviews were supplemented by ongoing feedback from a range of other stakeholders including leadership in the juvenile legal system, youth with experience in the legal system, meditation experts, and the AIM+ Community Advisory Board (CAB). The AIM+ CAB comprised adults with backgrounds relevant to studying AIM+ including working in the juvenile legal system, youth services, meditation instruction, and community mental health.

For the second phase of activity, we will conduct a hybrid type 2 pilot randomized controlled trial (RCT) of AIM+ with officers and other professionals working with youth in the legal system. Hybrid type 2 designs, which address both effectiveness and implementation outcomes, are appropriate when the determinants of implementing an intervention have already been identified and data on corresponding implementation strategies are available [19,20]. In the case of AIM+, we used the first phase of our project activities, described above, to meet these requirements. We selected effectiveness over efficacy testing consistent with the increasing consensus that when the safety concerns for intervention are low, the intervention should be tested in the real-world contexts in which it is meant to be delivered [21]. Compared with efficacy testing, this approach enhances insight into real-world implementation and expedites realization of the intervention's public health impact [21]. The present paper details the protocol for this hybrid type 2 pilot RCT design.

Methods

Overview

We aim to enroll 50 professionals working with youth in the legal system into the pilot RCT. The sample size was selected pragmatically to identify issues related to the feasibility of implementing AIM across both quantitative indicators (eg, objective app adherence) and qualitative feedback (ie, achieving thematic saturation in the interview data). Once enrolled, participants' RCT activities will last approximately 6 months; see Figure 1 for an overview. All study visits will take place remotely via phone or a secure videoconferencing platform. Study data will be collected and managed using REDCap (Research Electronic Data Capture; Vanderbilt University) tools hosted at the University of Illinois Chicago (UIC). REDCap is a secure, web-based software platform designed to support data capture, tracking, storage, integration, and interoperability with external sources [22,23].

Figure 1. Overview of the hybrid type 2 pilot randomized controlled trial procedures. EMA: ecological momentary assessment; min.: minute.

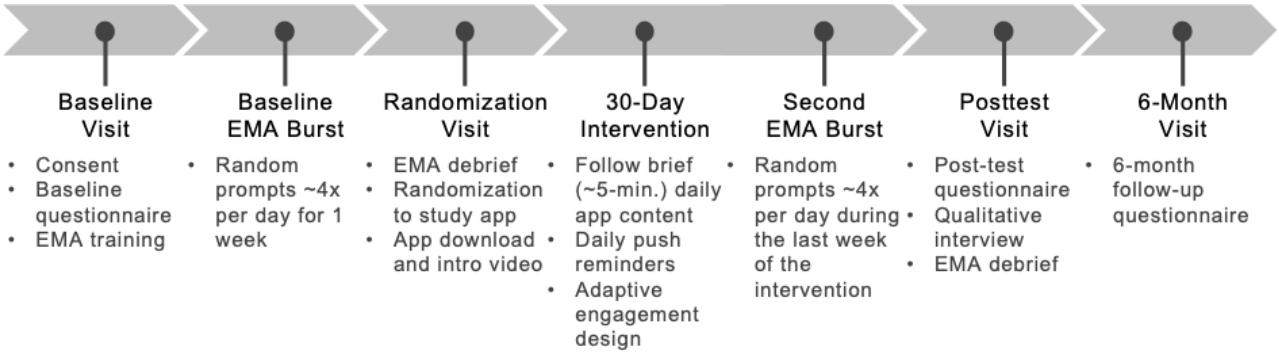

Ethical Considerations

Ethics Approval

The study protocol was approved by an independent monitoring committee (IMC) of scientific experts constituted by the study team to advise the sponsor and study investigators, the AIM+ CAB, and the UIC institutional review board (IRB; protocol # 2023-0363). Details regarding the IMC can be found at nccih.nih.gov. The trial is registered on ClincialTrials.gov (NCT06555172).

Centralized Management of Study Procedures and Data

The data manager developed a robust REDCap infrastructure that will support and automate study procedures including recruitment, enrollment, randomization, retention, assessment, and data management. Informed consent will be obtained electronically by study staff via REDCap; participants' ability to opt out of the study at any point will be emphasized. The REDCap system will also enable secure, remote administration of the study assessments. Processes were programmed into REDCap to validate and check for missing data in real time. Regarding app analytics data, date and time stamps indicating when participants open and close each feature in their study app will be collected and initially stored on a secure server. Other than the app analytics data, the study apps will not access, record, or store any information from participants' phones. Research staff will download coded app analytics data off the server without identifiers; these coded data will be stored on secure UIC servers and imported as relevant into REDCap. Scripts will clean, score, and store coded data separate from

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identifiers. REDCap will track all participant contact and autogenerate a CONSORT (Consolidated Standards of Reporting Trials) map and progress reports including enrollment tables, retention rates, adverse events, quality assurances, and project workflow. This will help ensure that inclusion and exclusion criteria are met, all compliance regulations are met, and the data are collected accurately and completely. Any unanticipated problems, including adverse events, will be documented in REDCap and reported to the IRB, IMC, and sponsor. Trial conduct will be audited at least monthly by the principal investigator, and at least annually by the IRB, IMC, and sponsor. Important protocol modifications are not anticipated but will be reviewed by the IRB, IMC, and sponsor before implementation and will be updated within ClinicalTrials.gov.

Compensation

Participants will be compensated via electronic payment consistent with standards in the field: US $45, US $50, and US $55 for the baseline, posttest, and 6-month follow-up questionnaires, respectively; US $10 for app download and orientation; US $50 for participation in each EMA burst and debrief, with a US $25 bonus at each burst for completion of at least 80% of the EMA reports; and US $30 for the posttest qualitative interview. We anticipate that employment policy will prohibit compensation for some participants; we will carefully document compensation eligibility to enable preliminary examination of its associations with study outcomes. In addition to the monetary incentives for eligible participants, all participants will be offered the option to receive a personalized summary based on their data at the end of the study to encourage ongoing participation.

Participants

Participants will be recruited from Cook County Juvenile Probation and Court Services and related programming for young people in the legal system. All participants must be (1) currently working with youth who are involved in the legal system, (2) English-speaking due to currently available study instruments, (3) able to understand and provide consent, and (4) have an Android or Apple smartphone.

App-Based Interventions

Bodhi AIM+

The AIM+ app—officially named Bodhi AIM+ to recognize its connection to the Bodhi app from which it was adapted—is a meditation app for professionals working with youth in the legal system. It includes 5 main parts: Home, Favorites, To Go, Youth, and Help (see Figure 2 for prototype screenshots). The Home page features a 30-day path of brief (approximately 5- to 10-minute) audio-guided meditations with videos interspersed to promote engagement. Users are encouraged to follow 1 of the practices each day for a month. To unlock the next practice, a user must first play the current practice to completion; once unlocked, users can scroll forward or backward to replay practices as desired. They can also tap a heart icon on any of the daily path practices; these practices will then appear in the Favorites part of their app for easy access. In addition to following the 30-day path, users can select from a menu of To Go audio-guided meditations to prepare for specific situations (eg, attending a meeting). Users also have access to a menu of To Go audio-guided meditations designed with and for youth in the legal system and featured in the original AIM app for young people (eg, meditations for before going to a party or to court). Users are invited to play these practices for any youth who might find them beneficial. Finally, the Help tab in AIM+ serves 2 main functions. First, users can use this part of the app to contact study staff by phone or text for support. Second, the Help tab includes referral buttons for users to share opportunities to participate in clinical trials research of AIM+ and AIM with colleagues and youth, respectively. These buttons auto-populate text messages that provide the recipient with a link to the relevant IRB-approved study flier where they are presented with more information. Users are instructed not to inquire further with peers or youth if they decide to participate to minimize the potential for coercion.

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Figure 2. Screenshots of the Bodhi AIM+ prototype, including the 30-day meditation path (left), meditations to go (center), and meditations to share with youth (right). AIM+: Action In Mindfulness.

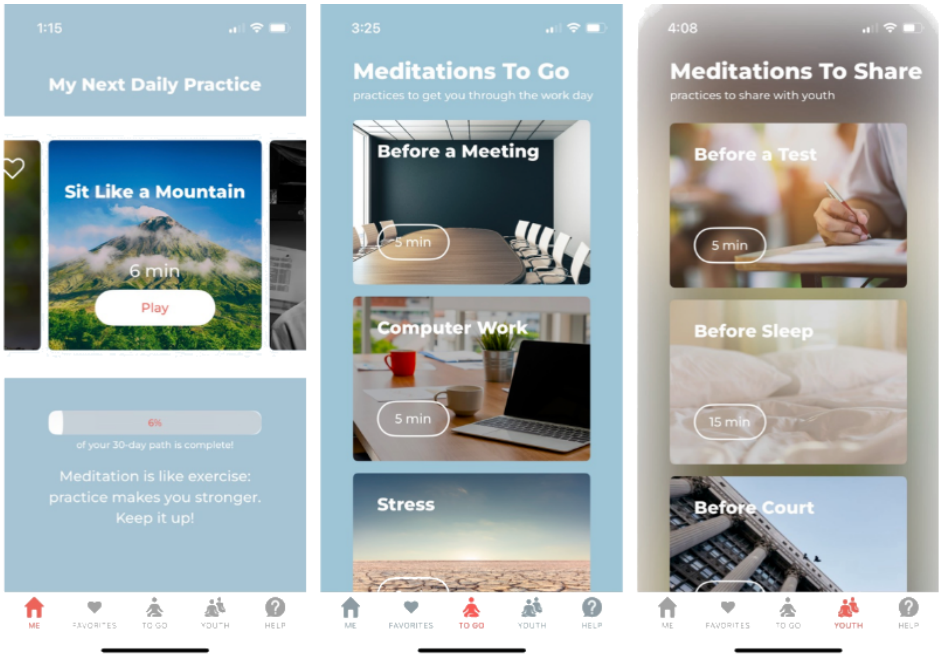

Resource+

The Resource+ app is matched to AIM+ for structure and time. The user interfaces are identical—both made up of Home, Favorites, To Go, Youth, and Help pages—with audio and video files occurring in the same sequence and each lasting approximately the same time across apps. However, whereas AIM+ features meditation practices to improve emotion regulation, Resource+ presents educational overviews of resources for youth to enhance professionals' knowledge of available resources for their clients. Each day of the 30-day path showcases a new resource; popular resources are also presented on the To Go page for easy reference. The Youth page includes overviews of resources intended to be played directly to any young people for whom they might be relevant. The Help page is identical to that in AIM+.

Hybrid Type 2 Pilot RCT

Recruitment

To recruit professionals who work with youth in the legal system into the pilot RCT, 3 main methods may be used: (1) live presentations by study staff, (2) email or flyer distribution, and (3) in-app peer referral. Presentations may be held in-person or virtually and will include an overview of the study along with time for questions. Emails and flyers may be distributed via relevant workplace contacts and will include a brief overview of the study, including a link to a video for learning more. In-app peer referrals will generate a prepopulated text message with a link to the same video for learning about the study. This text message will emphasize that the person sending it will not know if the person who receives it chooses to participate or not. Throughout the recruitment procedures, it will be explicitly stated that participation is voluntary, can be terminated at any time, and will not impact participants' standing within their workplace, UIC, or any related institutions. Interested participants will be invited to submit their contact information via a secure REDCap link. Study staff will follow up to complete an eligibility screener and conduct the baseline visit.

Baseline Visit

Potential participants will be asked to meet remotely via phone or a secure video platform at a time that is convenient for them in a private location. Once consent has been obtained, study staff will send a secure link to complete the baseline questionnaire on the participant's phone or computer. It will probe health outcomes along with potential moderators and covariates, as described below. Staff will remain on the call to answer participants' questions (eg, about the meaning of words) but will not advise on how participants answer or see participants' answers.

After the baseline questionnaire, the study staff member will provide training in ecological momentary assessment (EMA). EMA involves having people report on their experiences in real time throughout their daily lives [24,25], making it ideally suited to capturing emotion regulation (ie, the mechanistic target of the AIM+ app). All participants will be asked to complete EMA reports on their cell phones in response to random prompts approximately 4 times per day over 1 week from 9 AM to 9 PM. Each report will probe current affective states and attentional control as well as objective contexts (ie, if it is during or outside the workday along with current location, activity, and companionship). Participants will be instructed to respond to each prompt as quickly as possible without interfering with their job (eg, while in a meeting), creating safety concerns (eg, while driving), or causing potential embarrassment (eg, while in religious services). Each participant will complete a mock EMA report and go over any questions they have. They will be asked to predict their schedule for the upcoming week; based on this information, staff will guide each participant in anticipating obstacles to reporting and potential solutions.

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Baseline EMA Burst

The baseline EMA burst is intended to begin with completion of the baseline visit and continue for the next week (ie, for a total of 7 consecutive days). Each day, participants will be prompted to complete approximately 4 EMA reports at random intervals between 9 AM and 9 PM. On EMA days 2 and 4, participants will be sent text messages updating them on their progress (eg, percentage of EMA reports completed out of the prompts sent) and inviting them to contact staff with any questions. Staff will remain available over the week during business hours. All EMA reports will be automatically date- and time-stamped and stored on a secure cloud server rather than on participants' local devices.

Randomization Visit

Study staff will meet again virtually with each participant after the baseline EMA burst. Staff will review the total percentage of EMA surveys completed and discuss any issues with compliance, including any potential solutions for the second EMA burst based on their experience. Participants will then be individually randomized via REDCap to the AIM+ or Resource+ app at a 1:1 ratio. The allocation sequence will be generated in advance by the data manager under the supervision of a biostatistician and loaded into REDCap, where it will be fully concealed from the research team. Research staff will use the randomization module in REDCap to assign allocations, but will not be able to see the schedule or view allocations until they are assigned. Both staff and participants will thus be blind to arm through the completion of all baseline assessments. Next, staff will guide participants in downloading their relevant app and playing Day 1 of the 30-day path, which provides a video-guided introduction to the app. Participants will be encouraged to follow the 30-day path by playing a brief path file each day, and invited to use the other app features as desired; for details on the app content, see the AIM+ and Resource+ descriptions above. Participants will be trained not to use their app when doing so could interfere with work, be dangerous, or be embarrassing. Staff will guide participants in planning for when they will be most successful in using the app and then schedule personalized daily in-app push reminders based on those times.

Intervention With an Adaptive Engagement Design

Participants will be asked to use their app daily for 30 days. Adherence to the intervention (ie, ongoing app usage) will be promoted via 2 main methods. First, all participants will receive daily in-app push reminders to use the app as described above. Second, adherence will be automatically monitored, and additional support will be triggered via an adaptive engagement design: after any 2 consecutive days of nonuse, participants will be sent a text message encouraging re-engagement with the app. After approximately 1 week of nonuse, participants will receive a phone call from staff on the closest business day, during which staff will help identify and troubleshoot barriers to adherence. This pattern will repeat for up to approximately 2 weeks, at which point there will be a final phone call attempt before discontinuing texts and calls to reduce the potential for unwanted burden.

Second EMA Burst

In advance of the final intervention week, study staff will contact each participant to provide instructions for completing their second EMA burst, which will be scheduled to coincide as closely as possible with the fourth week of the intervention. Staff will meet virtually with participants to refresh their EMA training, including reviewing any barriers and facilitators to EMA adherence identified after their baseline burst. The second EMA burst is intended to begin immediately after the call and continue for 7 days. It will follow the same procedures as at baseline.

Posttest Visit

Participants will meet virtually with study staff for a posttest visit occurring approximately 1 month after the start of app use (ie, as close as possible to the end of the 30-day app path). This will mirror the baseline visit procedures except that (1) the posttest questionnaire will measure health outcomes and potential covariates since the last assessment and will include an assessment of implementation outcomes, (2) there will be a posttest qualitative interview, and (3) there will be a debrief of the second EMA burst, during which staff solicit feedback on any refinements participants suggest to the procedures.

The posttest qualitative interview will probe 3 main domains: app implementation (eg, determinants of app adherence, acceptability, and penetration), any perceived effects of the app, and suggestions for future refinements. Wherever possible, questions will be worded identically across arms. Staff will be trained to conduct the interviews through didactic instruction, role-playing, and supervised practice, focusing on techniques such as open-ended questions, active listening, and probing for depth while minimizing interviewer bias [26]. Proficiency will be assessed through mock interviews and iterative feedback. The interviews will be audio recorded, securely stored, and transcribed for qualitative coding. At the conclusion of the interview, staff will invite the participant to retain the app on their phone until the 6-month follow-up. All participants will receive automated text messages from the study team once monthly to promote retention.

6-Month Follow-Up Visit

The remote 6-month follow-up visit will be comprised only of the 6-month follow-up questionnaire. The questionnaire will be administered via REDCap using the same procedures as during the baseline and posttest visits. It will measure health outcomes and potential covariates since the last assessment.

Outcomes

Both quantitative and qualitative data will be collected. Table 1 summarizes the primary and secondary quantitative outcomes along with potential moderators and covariates. As described above, qualitative themes that will be probed in posttest interviews to complement and contextualize the quantitative data will include determinants of app implementation, perceived effects of the apps, and suggestions for future refinements.

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Table 1. Quantitative outcomes for the hybrid type 2 pilot randomized controlled trial (RCT).

Outcome	Measure	Time point	Source
Primary outcome			
App adherence	Days of objective app usage	Intervention	App analytics
Secondary implementation outcomes			
Acceptability	Acceptability of Intervention Measure (AIM) [27]	1 month	Questionnaire
Appropriateness	Intervention Appropriateness Measure (IAM) [27]	1 month	Questionnaire
Feasibility	Feasibility of Intervention Measure (FIM) [27]	1 month	Questionnaire
Usability	System Usability Scale (SUS) [28]	1 month	Questionnaire
Satisfaction	Client Satisfaction Questionnaire CSQ-8) [29]	1 month	Questionnaire
Penetration	In-app referral to AIM+ RCT[a]	Intervention	App analytics
Penetration-youth	In-app referral to AIM RCT for youth	Intervention	App analytics
Penetration-youth	Files for youth played in AIM+ or Resource+	Intervention	App analytics
Secondary health outcomes			
Anxiety	PROMIS[b] v1.0 Anxiety (standard computer adaptive test) [30]	Baseline, 1 month, 6 months[c]	Questionnaire
Depression	PROMIS v1.0 Depression (standard computer adaptive test) [30]	Baseline, 1 month, 6 months	Questionnaire
Workplace burnout	Maslach Burnout Inventory–General Survey (MBI-GS) [31]	Baseline, 1 month, 6 months	Questionnaire
Perceived stress	Perceived Stress Scale (PSS) [32]	Baseline, 1 month, 6 months	Questionnaire
Anger	PROMIS Short Form v1.1 Anger [30]	Baseline, 1 month, 6 months	Questionnaire
Sleep disturbance	PROMIS Short Form v1.0 Sleep Disturbance [33]	Baseline, 1 month, 6 months	Questionnaire
Alcohol use	PROMIS v1.0 Alcohol Use [34,35]	Baseline, 1 month, 6 months	Questionnaire
Resilience	Brief Resilience Scale (BRS) [36]	Baseline, 1 month, 6 months	Questionnaire
Mindfulness	Five Facets of Mindfulness Questionnaire (FFMQ-15) [37-39]	Baseline, 1 month, 6 months	Questionnaire
Attentional control	Attentional Control Scale (ACS) [40]	Baseline, 1 month, 6 months	Questionnaire
Emotion regulation	Negative Mood Regulation (NMR) [41]	Baseline, 1 month, 6 months	Questionnaire
Current mood states	International Positive Affect Negative Affect Schedule Short Form (I-PANAS-SF) [42,43]	Baseline, last intervention week	EMA[d]
Current attention	2 items adapted from Chin et al [44]	Baseline, last intervention week	EMA
Moderators and covariates			
Demographics	Gender, age, race and ethnicity, education, household income	Baseline	Questionnaire
Employment	Length of current employment, role	Baseline	Questionnaire
Mental health treatment history	Psychotherapy, hospitalization, psychotropic medication	Baseline, 1 month, 6 months	Questionnaire
Other meditation	Meditation practice frequency and type	Baseline, 1 month, 6 months	Questionnaire

[a]RCT: randomized controlled trial.

[b]PROMIS: Patient-Reported Outcomes Measurement Information System.

[c]1 month and 6 months: 1-month follow-up (ie, posttest) and 6-month follow-up, respectively.

[d]EMA: ecological momentary assessment.

The primary outcome of the pilot RCT will be app adherence per objective analytics data. A total of 2 main operationalizations will be considered. First, following other pilot RCTs of health apps [45], we aim for >60% of participants to open the app on at least 1 day after their randomization visit. Second, we will examine the mean number of content files played over the course of the intervention. Although there is no established dosage for app-based meditation [46], meditation studies have observed

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positive effects on mental health after 2 weeks, including for brief, audio-guided mindfulness practices [47]. Accordingly, we will explore if participants complete an average of 14 daily path files, and if this benchmark appears to be met within some subsets of participants but not others to help contextualize the findings and inform future work.

Secondary implementation outcomes will include acceptability, appropriateness, and feasibility as measured by the Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM) [27], respectively; usability as measured by the System Usability Scale (SUS) [28], satisfaction as measured by the Client Satisfaction Questionnaire (CSQ) [29], and penetration as indicated by objective analytics (ie, in-app referral to our RCTs of AIM+ for professionals and AIM for youth, and files played for youth by professionals using their study app).

All health effects will be treated as secondary outcomes. In accordance with our sponsor guidelines, the purpose of this data collection will be to ensure its feasibility in preparation for a future, fully-powered trial if justified by the present design [48]. That future trial would focus on group differences in anxiety and depression symptoms as measured by the Patient-Reported Outcomes Measurement Information System (PROMIS) v1.0 Anxiety and Depression scales, respectively [30], workplace burnout as measured by the Maslach Burnout Inventory-General Survey (MBI-GS) [31], and perceived stress as measured by the Perceived Stress Scale (PSS) [32]. It will also explore changes in anger, sleep disturbance, and alcohol use as measured by the PROMIS Short Form v1.1 Anger [30], PROMIS Short Form v1.0 Sleep Disturbance [33], and PROMIS v1.0 Alcohol Use [34,35] scales; in resilience as measured by the Brief Resilience Scale (BRS) [36]; in mindfulness as measured by the Five Facets of Mindfulness Questionnaire (FFMQ-15) [37-39]; and in attentional control as measured by the Attentional Control Scale (ACS) [40]. The primary mechanistic target—emotion regulation—will be assessed both retrospectively via the Negative Mood Regulation (NMR) scale [41] and in real time via EMA reports that include a short form of the International Positive Affect Negative Affect Schedule (I-PANAS-SF) [42,43]. A real-time assessment of attentional control will also be included in the EMA reports using 2 items adapted from Chin and colleagues [44]. Data collection will be considered feasible if at least 70% of participants complete the questionnaire measures at 1 and 6 months, and if participants fill out an average of at least 70% of the EMA reports at each burst. EMA reports will be counted if they are completed in full. We will also examine partial EMA completion rates during the pilot RCT and, as relevant, probe barriers to fully completing the EMA reports during the qualitative exit interviews with participants.

Data Analysis

Descriptive statistics will be calculated for the quantitative data (eg, mean number of app files played per objective analytics data, mean total and subscale scores for each self-report measure). We will explore potential biases in missing questionnaires and EMA data (eg, as a function of baseline characteristics). This will be accomplished using chi-square tests for categorical variables and *t* tests or nonparametric Wilcoxon rank-sum tests for continuous variables. Given the relatively small sample size in this pilot study, we will flag potential bias in missing data based in part on the descriptive statistics from these tests, rather than relying only on their significance levels, and use this preliminary information to help inform the interpretation of our results.

Qualitative data will be recorded, transcribed, and analyzed using a combined deductive-inductive approach (ie, use of a priori codes in the early stages, allowing for additional codes to develop from the data [49]). Analytic codes based on a priori categories will correspond to the foci of the interviews and themes that emerge in the data. Coders will follow an iterative procedure of refining, merging, or subdividing codes until a consistent set is developed. The quantitative and qualitative data will be incorporated into a mixed-methods triangulation design following an iterative process based on the recommendations of Turner et al [50], allowing for evaluation of app adherence and other implementation outcomes, as well as related determinants of implementation.

Results

Enrollment into the pilot RCT began in December 2024 and is currently ongoing; study results are anticipated to be available in 2026.

Discussion

This hybrid type 2 effectiveness-implementation pilot RCT of the AIM+ meditation app will integrate quantitative and qualitative data to evaluate app adherence (ie, ongoing app usage) and explore other implementation outcomes, as well as related barriers and facilitators to implementation. It will include an in-depth assessment of health outcomes, including real-time capture of the mechanistic target (ie, emotion regulation), allowing for evaluation of the feasibility of this data collection and setting the stage for a fully-powered RCT if justified by the present pilot findings.

The AIM+ meditation app was built with and for officers and other professionals who work with youth in the legal system to make authentic mindfulness meditation practices available throughout the workday. It is a direct response to requests from stakeholders for such an intervention, created in collaboration with our community partners by adapting an existing meditation app, Bodhi, for use by the target audience. The adaptation process and implementation plan—as well as the pilot RCT detailed in this protocol paper—were guided by the EPIS and CFIR implementation science frameworks [15-17].

Consistent with pilot RCTs of other health apps [45], we expect that >60% of participants will open the app at least 1 day after their randomization visit per objective analytics data, and we will explore the mean total number of content files played over the course of the intervention. We further expect that our longitudinal assessments of health outcomes will be feasible, as evidenced by at least 70% of participants completing the questionnaire measures at each follow-up time point and at least

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70% of the EMA reports being completed within each week-long EMA burst.

Potential limitations to the study warrant consideration, particularly regarding their implications for a fully-powered trial that could build on this design. First, emotion regulation is the primary mechanistic target of AIM+, yet its retrospective assessment is highly subject to recall bias [51]. To address this, we include EMA assessments of mood, which will provide data on emotion regulation in real time and in participants' daily lives. Next, it is not possible to blind participants to arm after randomization has occurred. To partially address this, our control app is matched to AIM+ for time and structure. At the same time, given that common factors are estimated to account for a substantial portion of the effects observed in mental health studies [52], this matching is likely to attenuate our ability in the future to formally detect between-group differences in treatment effects. Finally, the nature of our sample—specifically, professionals who work with youth in the legal system—will necessarily limit the generalizability of the results. However, this group represents a key public health demographic, and findings from these professionals are likely to still have some relevance to implementing health apps with other professionals during the workday.

In summary, this work represents an important public health direction given the high levels of chronic workplace stress that professionals who work with youth in the legal system often face [1,2], the relevance of mindfulness meditation to helping mitigate the negative downstream effects of this stress [6-9], and the interest such professionals have expressed in workplace meditation [10]. Although early studies in this area generally supported acceptability and feasibility [10], these in-person initiatives faced key barriers to scalability, constraining their potential for impact on a national level. The use in the present study of theoretically-driven implementation science methods coupled with scalable, digital technology positions this study not only to help make meditation tools available to an important national workforce at scale but also to inform broader efforts at implementing health apps within workplace settings.

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Data Availability

Data sharing is not applicable to this protocol paper as no finalized data sets have yet been generated.

Conflicts of Interest

None declared.

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Abbreviations

ACS: Attentional Control Scale
AIM: Acceptability of Intervention Measure
AIM+: Action In Mindfulness
BRS: Brief Resilience Scale
CAB: community advisory board
CFIR: Consolidated Framework for Implementation Research
CONSORT: Consolidated Standards of Reporting Trials
CSQ: Client Satisfaction Questionnaire
EMA: ecological momentary assessment
EPIS: Exploration Preparation Implementation Sustainment
FFMQ-15: Five Facets of Mindfulness Questionnaire
FIM: Feasibility of Intervention Measure
IAM: Intervention Appropriateness Measure
IMC: independent monitoring committee
I-PANAS-SF: International Positive and Negative Affect Schedule Short Form
IRB: institutional review board
MBI-GS: Maslach Burnout Inventory-General Survey
NCCIH: National Center for Complementary and Integrative Health
NIDA: National Institute on Drug Abuse
NMR: Negative Mood Regulation
PROMIS: Patient-Reported Outcomes Measurement Information System
PSS: Perceived Stress Scale
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SUS: System Usability Scale
UIC: University of Illinois Chicago

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Protocol

Evaluating the Effectiveness of Community-Delivered Hearing Rehabilitation and Health Education Intervention on Social Isolation and Functioning Among Chinese Adults With Hearing Impairment: Protocol for Randomized Controlled Trial

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Abstract

Background: Hearing impairment (HI) is a common sensory deficit with considerable impacts on social well-being (SWB) in adults. Evidence on the effectiveness of auditory rehabilitation and hearing health education in the social domain of health for individuals with HI is scarce.

Objective: This study aims to test the feasibility and efficacy of providing free hearing aids or a combined offline and online hearing health education intervention on social isolation and functioning among Chinese adults with HI.

Methods: This study is a 3-arm, single-blinded, randomized controlled trial (RCT) with a follow-up at 24 months after the baseline study. A total of 435 participants aged 18 years and older with some degree of HI will be recruited and randomly assigned to 2 intervention groups and 1 control group. Free hearing-aid provision, as well as a hearing health education program that is combined with online and offline lessons, will be implemented in 2 intervention groups, respectively. The control group will not receive any intervention. The primary outcomes include social isolation and functioning in society. The secondary outcomes include social engagement, a sense of mastery, self-efficacy, psychological resilience, chronic diseases, life satisfaction, hearing health literacy, and hearing care usage.

Results: Participants were recruited for hearing tests in September 2022, during which baseline results were collected through in-person interviews. Follow-up interviews were conducted in September 2024. The primary analysis will use ANOVA, linear mixed-effects modeling, structural equation modeling, and cost-effectiveness analysis.

Conclusions: The findings of this study will provide evidence for the impact and cost-effectiveness of a community-based auditory or hearing health education intervention on SWB among Chinese adults with HI, which may contribute to promoting hearing health and reducing adverse health consequences in an aging society.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2200062148; https://www.chictr.org.cn/showproj.html?proj=174741

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(JMIR Res Protoc 2025;14:e64115) doi:10.2196/64115

KEYWORDS

hearing impairment; social isolation; functioning; community-delivered hearing interventions; randomized controlled trial

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Introduction

Background

Hearing impairment (HI) significantly impacts the health and well-being of adults, especially middle-aged and older individuals. Globally, approximately 1.57 billion people had some degree of HI in 2019, with nearly 30% suffering from disabling HI and the majority of whom were aged ≥45 years [1]. HI is associated with various negative consequences, including declines in physical and cognitive functions, increased depression and anxiety, and heightened risks of frailty, hospitalization, and mortality [2-7]. Unaddressed HI often leads to significant withdrawal from the social domain of life and poor performance of functioning in society.

Social well-being (SWB) not only encompasses one's ability to establish healthy relationships and engage meaningfully with social networks but also represents a subjective evaluation of personal life circumstances and functioning in society [8]. The World Health Organization (WHO) identifies SWB as a crucial element for overall health and has prioritized it worldwide to enhance social connections to fight against social isolation, which is often regarded as a common reflection of poor SWB [9]. Social isolation, defined as an objective absence or paucity of contacts and interactions between a person or within a social network [10,11], is associated with HI and is often considered a potential pathway to adverse health outcomes related to HI [12]. Communication difficulties or mental fatigue attributed to HI, as well as the increased cognitive load required to compensate for auditory deficits often discourage social interactions among those with HI [13-15].

Compared to social isolation, functioning in society is a broader and more comprehensive measure for assessing one's capacity to interact with others, contribute to various societal roles, and actively engage in meaningful activities, including but not limited to work, education, family life, and community involvement. The International Classification of Functioning, Disability and Health (ICF), provides a framework for assessing functioning in society across three levels: the body or body part, the whole person, and the whole person in a social context, corresponding to its definition of functioning encompassing all body functions, activities, and participation [16]. Activity limitations and participation restrictions, which measure functions from both individual and societal perspectives, refer to a person's capacity in a standard environment and performance in a normal environment under healthy conditions. The validation of the ICF application for adults with HI and in audiological or rehabilitation research has been examined internationally [17,18], demonstrating a positive association between hearing loss and decline in mobility, self-care, or the ability to get along with others [2,19,20]. Despite evidence supporting HI as a modifiable risk factor for social health, the efficacy of HI interventions in enhancing SWB requires further research [21,22]. Previous studies either have shown mixed results with little consistency in the significance and magnitude of the effectiveness of hearing intervention on social isolation or functioning [13,23-25], or used small sample sizes, and nonrandomized controlled trials to identify the causal relationships between hearing intervention and improvements in SWB [13,26,27]. Furthermore, few interventional studies have further discussed and tested the possible mechanistic pathway through psychosocial or supportive factors, and evidence regarding middle-income countries is scarce.

Conceptual Framework and Interventions

Both the ICF and stress-buffering models provide insights into how adult-onset HI affects SWB and the effectiveness of auditory interventions. The ICF describes the bidirectional association among impairments, activity limitations, and participation restrictions. Besides, functioning can be viewed as the outcome of interactions between health conditions and contextual factors, which include external environmental factors (eg, supportive environment or social attitudes) and internal personal factors (eg, coping style and psychological resources) [16]. The ICF reveals that the ideal interventions should consider a holistic approach combining physical, personal, and environmental factors. The stress-buffering model, derived from the stress process paradigm, posits that social and coping resources can buffer (mediate or moderate) the impacts of stressors such as HI on health and well-being by altering one's appraisal and coping behaviors toward a stressor or threat [28,29]. Empirical studies support the potential psychological resilience to mediate the relationship between functional HI and SWB [14].

Intervention strategies typically focus on individual or environmental approaches. Individual strategies such as audiological training, skill development, and health education aim to use residual hearing through individually tailored intervention and improve communication and coping skills for persons with HI or their communication partners (CPs). Skill development and health education are person-centered approaches that can be widely promoted and implemented at the community level. Either an appropriate use of hearing aids or assistive devices to compensate for auditory loss, the development of self-management skills for HI, or the application of positive communications, are often considered potential effective skill-developing interventions. Educative interventions in the hearing rehabilitation context empower adults with HI and their CPs to adapt to hearing deficits and improve help-seeking behaviors. Hearing health education (HHE) involves the dissemination of knowledge about the nature of hearing and hearing loss, communication strategies, the promotion of hearing devices or assistive technologies use, and the enhancement of psychosocial resources. Environmental strategies center on enhancing support systems within micro and meso environments, such as family and community, by providing information and guidance to the significant others and helping them better understand the challenges faced by adults with HI, as well as fostering active communication skills, awareness, and access for hearing health care.

In response to the WHO's guidelines on integrated person-centered ear and hearing care (IPC-EHC), we initiated the HISEA (Hearing Impairment and Social Outcomes Evaluation in Adults) project to conduct hearing interventions that targeted the social isolation and functioning of HI persons in Guangdong Province, China. This community-delivered

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intervention aligns with the China Disability Action Plan (2021-2025), which emphasizes the importance of raising public awareness of hearing prevention and care through health education as well as treating HI through rehabilitative services.

Figure 1 presents a diagram illustrating how the interventions developed in HISEA align with the ICF and stress-buffering framework.

Figure 1. The theoretical framework of Hearing Impairment and Social Outcomes Evaluation in Adults developed based on the International Classification of Functioning, Disability and Health and stress-buffering model. HI: hearing impairment; ICF: International Classification of Functioning, Disability and Health; KAP: Knowledge, Attitude, and Practice Theory.

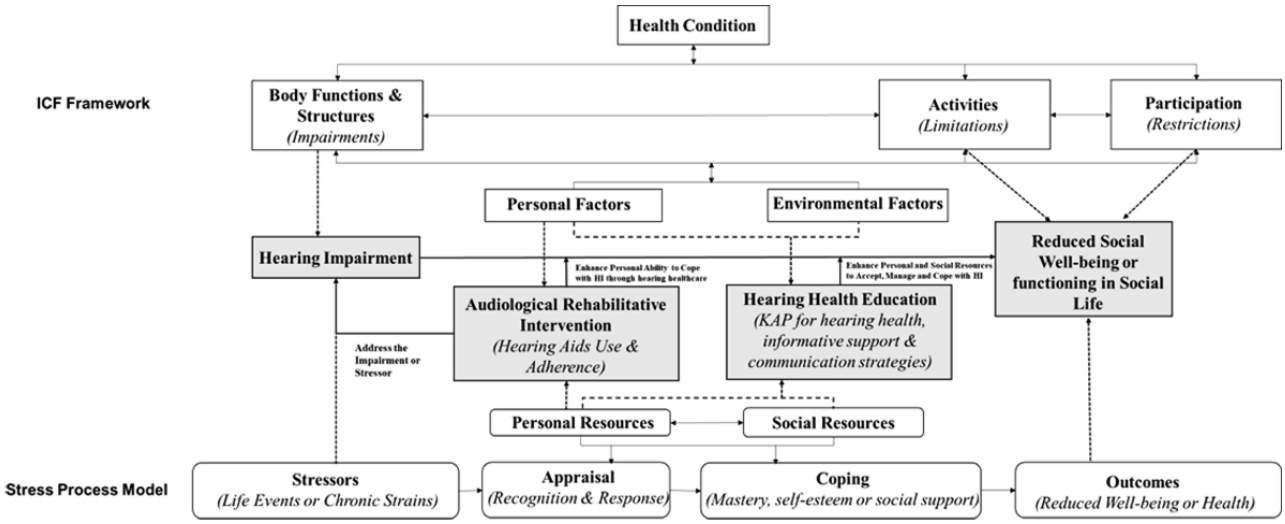

Study Aims and Hypotheses

This full-scale randomized controlled trial (RCT) aims to evaluate the feasibility and efficacy of a community-delivered hearing aid provision and HHE program in improving social health among hearing-impaired adults in China. The key outcomes are social isolation and societal functioning. In addition, it seeks to determine if psychosocial factors and social support buffer the HI-SWB linkage as well as the effects of hearing interventions on social health.

We hypothesize there will be positive effects after the long-term interventions of HAU and HHE on hearing-impaired older adults' social health, and strengthened psychological well-being could be potential pathways.

Methods

Overview

This protocol was developed on the basis of the theoretical framework in Figure 1 and is reported according to the Standard Protocol Items for Interventional Trials (SPIRIT) [30,31]. A peer review report can be found in Multimedia Appendix 1, and a SPIRIT checklist can be found in Multimedia Appendix 1.

Feasibility Study

Before the initiation of the full-scale RCT, a feasibility study was undertaken. This study involved a comprehensive review and evaluation of the overall implementation plan by community social workers and audiologists to ascertain its feasibility from a health care professional perspective. In addition, a cohort of 28 adults with HI was recruited from Zhaoqing City, Guangdong Province, to conduct hearing checks and baseline interviews. During this process, we evaluated the participants' willingness to engage in the study, confirmed their comprehension of the survey questionnaires, and assessed their readiness to participate in health education initiatives or to wear hearing aids over a long period, should they be assigned to the treatment groups. We made some adjustments to the questionnaire based on the feedback from the respondents. The preliminary results validated the feasibility of our intervention study.

Study Design and Setting

A three-arm, single-blinded RCT with a 24-month follow-up period will be conducted. A total of 435 eligible participants were randomly assigned in a 1:1:1 ratio to a control group, a hearing aid use (HAU) group, or an HHE group. The HAU group will receive hearing aids and follow-up instructions. Due to budget constraints, the audiological rehabilitation intervention predominantly used hearing aids provided by the Audiology Department of the Guangdong Provincial Cultural Sports and Rehabilitation Assistive Devices Center for People with Disabilities (GPSRC), which is affiliated with the China Disabled Persons' Federation (CDPF). Individuals diagnosed with disabling HI and classified as persons with hearing disability are eligible to apply for complimentary hearing aids and fitting services from the local CDPF departments. Since the number of adults with HI who were eligible for hearing-aid fitting was limited to one site at the time of the baseline survey and intervention, a total of 139 persons with disabled HI were randomly selected from 4 sites with similar socioeconomic and cultural conditions. The selection was based on the list provided by GPSRC, which maintains records of hearing-disabled persons in Guangdong Province. The HHE group will undergo both offline and online educational interventions, while no interventions are planned for the control group that is similar to a natural setting. A sample of 278 adults diagnosed with some degree of HI was randomly selected and assigned to the HHE group and control group from Hualong County in Guangzhou, Guangdong, based on its roster. For the HAU group, participants were prescribed hearing aids at baseline (T0) and received

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reinstruction on the use of hearing aids 12 months after T0. For the HHE group, participants were required to participate in an offline hearing education at T0, followed by an online educational intervention at 6 months after T0, and an offline information intervention at 12 months after T0. The primary outcomes are social isolation and functioning, assessed at baseline and 24 months.

Participants

Eligible participants are adults aged ≥18 years with adult-onset audiometric HI, without significant cognitive impairments or neurological conditions. Participants are prescreened via telephone and in-person visits conducted by community workers and confirmed with some degree of HI through audiometric assessment by professional audiologists. The eligibility criteria are mentioned in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Age (18 years or older): individuals aged 18 years at the time of recruitment are eligible for the trial. This age range meets the needs of this study by targeting adult-onset hearing impairment (HI). Besides, given that adult-onset HI is more prevalent in middle-aged and older adults, individuals who develop hearing loss after the age of 55 years are preferentially included.
- Residency: community-dwelling within the sites for the duration of the study.
- Audiometric hearing impairment: participants must have adult-onset audiometric HI with a 4-frequency (0.5, 1, 2, and 4 kHz) PTA hearing threshold ≥21 dB hearing level (HL) and ≤90 dB HL in a better hearing ear (ranging from mild, moderate, severe to profound hearing loss according to the World Health Organization (WHO) 2021 grades of hearing loss [32]). These grades of hearing loss indicate the level at which individuals are likely to benefit from the use of hearing aids or other amplified devices.
- No significant diagnosed or self-reported history of dementia or neurological impairments.
- Communication: Fluent in Mandarin or Cantonese with basic word recognition skills.
- Willing to participate, be randomized, and adhere to the protocol: Participants must be willing and able to consent to engage in the study, be willing to participate in the interventions, and commit to adhering to the study protocol until the end of the trial (24 months after the baseline survey).

Exclusion criteria

- Profound, complete, or total hearing loss or deafness: pure tone audiometry (PTA) at 4 frequencies for better ear of >90 dB HL, who are suggested to face challenges in effectively participating in the intervention setting [33].
- Significant ongoing ear-related diseases, medical contraindications to the use of hearing aids, or permanent conductive HI.
- Recent use of hearing aids or other listening devices: to assess the net effect of hearing interventions, participants should not be receiving any treatment for the HI already.
- Previous dementia diagnosis and self-reported mental health problems: self-reported diagnoses of dementia or memory-related diseases, and those who required a proxy to provide informed consent and answer questions due to cognitive problems or other mental health issues are excluded.
- Unwillingness to wear hearing aids regularly.
- Visual impairment: participants who are unable to see well enough (even with correction) to read a brochure or watch an online video are excluded.
- Unable or unwilling to provide written informed consent.

Sample Size Calculation and Recruitment

Sample size calculations are based on the expected effects of the hearing aid intervention on the primary outcome: an individual's functioning in society measured by the World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0), which was developed within the ICF conceptual framework [34]. We estimate that a sample size of 222 (111 participants in each group) provides 85% statistical power with a 5% significance level to detect a standardized effect size of 0.404 for the difference between the HAU group and the control group in the mean change from baseline in the functioning score at the 24-month follow-up [23]. Since there is little evidence evaluating the effects of HAU on social isolation using the Lubben Social Network Scale (LSNS), or the effectiveness of HHE on functioning and social isolation, we will assign the HHE group the same sample size as the HAU group and the control group. To account for a 20% drop-in (uptake of hearing aids in the control group) and dropout (discontinuation of HAU in the hearing intervention group) rate, a total of 435 individuals are included. This comprises 121 individuals in the HAU group, 158 in the HHE group, and 156 in the control group, respectively. Recruitment activities are conducted in communities and villages (n=8) from Guangzhou, Shanwei, Chaozhou, and other areas in Guangdong Province, China. The recruitment of participants commenced on September 1, 2022, and was completed on September 31, 2022. Oral informed consent is obtained through prescreening, and written informed consent is presented by the investigator to the participant before the hearing screening. Hearing screening and assessment will be undertaken by an audiologist following a standardized procedure (Table 1).

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Table 1. Schedule of enrollment, interventions, and assessments.

Time point	Study period														
	Enrollment T_1			Allocation T_0			Postallocation T_1			Postallocation T_2			Close-out T_4		
	–30 to –1 Day			Day 0			6 months			12 months			24 months		
	T[a]	T[b]	C[c]	T	T	C	T	T	C	T	T	C	T	T	C
Enrollment															
Eligibility screen	✓	✓	✓												
Informed consent	✓	✓	✓												
Demographics	✓	✓	✓												
Health history	✓	✓	✓												
Visual status	✓	✓	✓												
Allocation				✓	✓	✓									
Interventions															
Hearing aids provision				✓						✓			✓		
Hearing health education					✓			✓			✓			✓	
Assessments															
Sociodemographics				✓	✓	✓							✓	✓	✓
Hearing outcomes															
Pure-tone audiometry				✓	✓	✓									
HHIA[d] score				✓	✓	✓							✓	✓	✓
Self-reported hearing				✓	✓	✓							✓	✓	✓
IOI-HA[e] score													✓		
Hearing-related health literary				✓	✓	✓							✓	✓	✓
Communication ability					✓	✓							✓	✓	✓
SWB[f] (primary outcome)															
LSNS-6[g] score				✓	✓	✓	✓						✓	✓	✓
WHODAS 2.0[h] score				✓	✓	✓	✓						✓	✓	✓
ISE[i] score				✓	✓	✓	✓						✓	✓	✓
SEAQ[j] score				✓	✓	✓	✓						✓	✓	✓
Secondary outcomes															
GSE[k] score				✓	✓	✓							✓	✓	✓
PMS[l] score				✓	✓	✓							✓	✓	✓
CD-RISC[m] score				✓	✓	✓							✓	✓	✓
EQ-5D-5L score				✓	✓	✓							✓	✓	✓
SWLS[n] score				✓	✓	✓							✓	✓	✓
Covariates				✓	✓	✓							✓	✓	✓
Lifestyle behaviors				✓	✓	✓							✓	✓	✓
Chronic diseases				✓	✓	✓							✓	✓	✓

[a]T: hearing aid intervention group.

[b]T: hearing health education intervention group.

[c]C: control group.

[d]HHIA: Hearing Handicap Inventory Screening Questionnaire for Adults.

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[e]IOI-HA: International Outcome Inventory for Hearing Aids.
[f]SWB: social well-being.
[g]LSNS-6: Lubben Social Network Scale.
[h]WHODAS 2.0: World Health Organization Disability Assessment Schedule 2.0.
[i]ISE: Index of Social Engagement.
[j]SEAQ: Social Engagement and Activities Questionnaire.
[k]GSE: General Self-Efficacy Scale.
[l]PMS: Pearlin Mastery Scale.
[m]CD-RISC: Connor-Davidson Resilience Scale.
[n]SWLS: Satisfaction with Life Scale.

Randomization, Allocation, and Masking

After confirming eligibility and informed consent, participants are randomly stratified by HI severity and the field site to ensure a balanced distribution of participants. Randomization is performed by an independent statistician who is not involved in data collection, management, or analysis using a computer-generated random number sequence to assign participants to either the treatment or control group [35]. Allocated interventions will not be modified unless participants voluntarily withdraw for personal reasons. Due to the nature of the interventions, complete blinding of participants and facilitators is not feasible. However, we minimize the potential biases by blinding participants to the study hypothesis, using standardized protocols for training and tools for measurement, and masking field staff to allocation details.

Study Interventions

The community-delivered interventions are developed based on the conceptual framework of ICF and the stress-buffering model. The HAU group mainly targets addressing HI as a stressor or physical impairment and improving personal resources for managing HI. The HHE group aims to eliminate or minimize the social effects of HI by enhancing awareness, acceptance, adaptation, and support for HI through personal and social resources among adults with HI.

Hearing Rehabilitation Intervention: Hearing Aid Use Group

Participants in the hearing rehabilitation intervention treatment group are fitted with bilateral or unilateral hearing aids. The hearing aids are fitted to participants in accordance with the protocol established by the hearing aid manufacturer and the guidelines launched by CDPF with professional audiologists. Instructions on the usage of hearing aids, the proper insertion of the aids and batteries, and a comprehensive, step-by-step guide on their usage and maintenance, are also provided. Materials for self-management and adaptation strategies are also explained and provided after the fitting services. To improve hearing aid compliance, support is offered after fitting (1 month later) to ensure that each participant is progressing with their hearing aids. In addition, a WeChat (Tencent) group has been established for HAU participants and audiologists to address sporadic needs from hearing aid users, such as battery replacements, cleaning, or proper storage of hearing aids. Unscheduled interim visits are necessary for troubleshooting or repairing malfunctioning hearing aids or addressing other related issues if the problem cannot be resolved through online or telephone communication. Postintervention reinstruction on the use of hearing aids is conducted 12 months after the fitting through telephone communication and the dissemination of digital materials via the WeChat group.

The HHE Intervention

The HHE intervention group is developed based on the Health Education Services Standard of the National Basic Public Health Service Standard (third edition), a national guideline issued by the National Health Commission of the People's Republic of China for guiding health education for community-dwelling residents [36]. It targets participants with HI, their CPs or family members, community residents, and hearing health–related community workers (ie, social workers, local staff of CDPF, and civil affairs). The objectives of HHE include improving awareness, knowledge, and literacy of hearing health among individuals, families, and communities, developing communication strategies and skills for adults with HI and their CPs or family members, as well as creating a supportive family and community environment that promotes social inclusion and accessibility to hearing health care services.

The HHE intervention consists of three parts. Part A is an interactive, face-to-face session consisting of a hearing health lesson and counseling for participants with HHE and community workers. Brochures for participants and their CPs or family members, and posters for community health education boards are provided. The hearing health lesson is taught by the program coordinators with a written lesson plan and prepared with easily accessible teaching materials, such as paper-based visual aids or slides. Part B is an internet-based educational section that aims to reinforce the content covered in Part A through the use of the WeChat public account. It was conducted 6 months after the baseline survey targeted adults with HI and their CPs. Part B consists of a 2-week online information support program delivering knowledge on hearing health and its consequences, positive skills and strategies for interacting with adults with HI, hearing prevention and rehabilitation guidance, and social support for adults with HI through textual, image, and video formats. All interventional-related information is disseminated through the WeChat public account registered by the research team. To ensure the accessibility and reach of online information support, the research team set up a check-in task and regularly reminded the procedure. Part C is an offline information provision that was conducted 12 months after the baseline survey with the purpose of reinforcing content in Part A and Part B. Hearing health educational pamphlets are designed for all the intervention objectives and are delivered to them accordingly.

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The content presented in the lessons, brochures, posters, a WeChat public account, and pamphlets is based on and adapted from the WHO Hearing Report (2021) and other relevant publications [37,38]. During the design phase of the intervention, the HHE intervention settings were discussed and deliberated with experienced audiologists, community workers, and community-dwelling adults with HI who would not participate in the study. It is deemed acceptable for adults with HHE and their CPs in the community.

Control Group

No interventions are provided for the control group considering the current situation of the HI rehabilitation:

Firstly, the prevalence of hearing aid usage in China is notably low, and there is a lack of health care awareness among rural older adults experiencing HI. A population-based survey carried out between 2014 and 2015 across 4 provinces in China, including Guangdong, revealed that the estimated prevalence of hearing aid acquisition among rural older adults with hearing loss is 4.2%. The reasons for not having a hearing aid within this group included “not understanding its function,” “not being able to afford it,” and “not needing it” [39]. According to the China Health and Retirement Longitudinal Study 2018 data, only 3% of older adults in rural areas with subjective hearing loss self-reported experience of using hearing aids [40]. Both sets of data indicate that they resonate with the natural setting for the control group.

Secondly, the policy context in Guangdong Province requires the attainment of a disability status qualification before the application for government-subsidized hearing aids, potentially discouraging older adults with HI from initiating the application process. The government offers subsidized hearing aids at institutions specifically established to provide services related to assistive devices for individuals with hearing disabilities. However, it is essential for these individuals to actively secure an official assessment to obtain a disability certificate, which is a prerequisite for applying for subsidized hearing aids. The process of obtaining disability status may be associated with social stigma, which could inhibit individuals from applying despite the availability of government subsidies. Therefore, the number of disabled individuals seeking these hearing aids remains relatively low.

Considering these 2 points, we have opted not to intervene with the older adults in the control group. Participants who are eligible for the control group are required to engage in both the baseline and follow-up surveys.

Outcome Measures

This study investigates the 24-month impact of HAU and HHE interventions on social isolation, functioning, and engagement among adults with HI and further explores the buffering role of psychosocial factors in these outcomes. The detailed outcomes are listed in Textbox 2.

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Textbox 2. Outcome measures.

Primary outcome measures

- Social isolation, assessed by the abbreviated 6-item Chinese version of the Lubben Social Network Scale (LSNS-6), which has been recognized as a good tool to screen for social isolation among community-dwelling adults by several cross-national and cross-cultural validation studies [41,42]. The LSNS-6 evaluates one's perceived social network or support received from family and friends.
- Functioning, measured by World Health Organization Disability Assessment Schedule 2.0 (WHODAS 2.0), evaluates an individual's health-related functioning and disability across 6 life domains within the International Classification of Functioning, Disability and Health (ICF) framework [34]. WHODAS 2.0 is a cross-culturally valid tool that reflects a person's ability to participate in daily life activities (personal perspective: cognition, mobility, and self-care) and to engage with their environment (social perspective: getting along, life activities, and participation).
- Social engagement, determined through a subjective assessment using the 6-item Index of Social Engagement (ISE), which describes an individual's self-evaluation of both social involvement and autonomy, is used to capture subjective social engagement [43], and objective evaluations via the 10-item Social Engagement and Activities Questionnaire (SEAQ).

Secondary outcomes

- ***Hearing health outcomes***
  - Hearing handicap is measured by the Hearing Handicap Inventory Screening Questionnaire for Adults (HHIA). Participants' self-reported hearing status is also collected to reflect subjective hearing impairment (HI). For the hearing aid use (HAU) group, the International Outcome Inventory for Hearing Aids (IOI-HA) will be used during the follow-up period to verify the treatment effects of HAU.
  - Hearing-related health literacy is measured through a set of 9 questions developed by the research team based on the Knowledge, Attitude, and Practice theory. The 9-item assessment evaluates the respondents' understanding (eg, information on hearing health, preventive measures, and awareness of available hearing health care), attitudes (eg, beliefs and attitudes toward hearing health care, willingness to prioritize and engage in hearing health activities), and behaviors (eg, regular hearing check-ups, protection from loud noises, the use of hearing aids if needed) related to hearing health [44]. The content and validity of the 9-item questionnaire were evaluated by 5 experts in hearing and health education.
  - Communication ability is measured in the follow-up survey using the 10-item Self-Assessment of Communication (SAC), a self-report questionnaire designed to assess the impact of hearing loss and hearing intervention outcomes [45].
- ***Psychosocial and health-related outcomes***
  - Self-efficacy is assessed by the 10-item Chinese version of the General Self-Efficacy Scale (GSE). It has been identified as a good tool for measuring self-efficacy in community-dwelling adults [46].
  - A sense of mastery is measured by the 7-item Chinese version Pearlin Mastery Scale (PMS). In addition to self-efficacy, mastery serves as another psychological resource that may help mitigate the impact of stressors on well-being. PMS has been regarded as a well-validated measure commonly used in studies to examine adults' health and well-being outcomes [47].
  - Psychological resilience in the HHE group is evaluated using the 2-item Connor-Davidson Resilience Scale (CD-RISC). The 2-item CD-RISC has demonstrated good validity and reliability in the elderly or Chinese general population [48].
  - Quality of life includes both a subjective and an objective measure. Health-related quality of life is measured by standard tests such as the EQ-5D-5L, and subjective well-being is measured by the 5-item Chinese version of the Satisfaction with Life Scale (SWLS).

Covariates

Sociodemographic factors (age, sex, residency, marital status, education, income status, and employment), lifestyle behaviors (smoking and drinking), and health conditions (visual status, diagnosed with hypertension, diabetes, or any other cardiovascular diseases, and self-reported health) of the eligible participants are collected during the baseline survey.

Statistical Analysis

The intent-to-treat principle will be used during the impact analysis. The differences between the control and intervention groups in terms of primary and secondary outcomes will be evaluated through ANOVA and linear mixed-effects modeling. Multiple methods such as weighting, matching, and imputation will be used to handle the problem of missing data and sample attrition. In addition, a nonparametric bias-corrected case resampling bootstrap method, structural equation modeling, or interaction analysis will be used to further explore the buffering effect of psychosocial factors. Heterogeneity analysis will be applied to investigate whether the intervention effects are robust across subgroup samples, such as participants with different levels of objective hearing loss.

The cost-effectiveness analysis will be based on the costs of the HAU or HHE interventions and their effects on improving health-related quality of life, as measured by EQ-5D-5L. EQ-5D-5L is designed to measure the generic quality of life in terms of mobility, self-care, usual activities, pain or discomfort, and anxiety or depression [49]. Previous literature has used this multidimensional construct of quality of life to evaluate the effect of hearing interventions [50-53].

Data Collection and Management

Data collection forms and procedures for data management are available upon request. All the data will be collected through a structured paper questionnaire. Trained enumerators will conduct face-to-face interviews with each eligible participant and complete the forms. Double-blind data entry will be performed

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to input the baseline and follow-up data into electronic form for quality assurance purposes. All information collected during the trial will be kept in strict confidence. Participant details will be stored on a secure, password-protected computer disk and mobile hard disk drive. The confidentiality of the intervention objectives during qualitative interviews will be safeguarded by assigning a unique identification code to electronic sound files and transcripts of the interviews. The information will be known only to the qualitative researcher and appropriate members of the research team. The principal investigator (PI) and data analysis personnel will have access to the final trial dataset. According to the Good Clinical Practice guidelines, data will be archived for a period of 10 years after finalizing the study with participants' informed consent. To enhance and protect participant confidentiality, any quotes published will be anonymous. After finalization, the key file containing information linking participants' names and contact details will be destroyed once the project team no longer needs to contact the participants further for study purposes.

Monitoring

Data Monitoring

The study is subject to local regulations. The principal investigator is responsible for developing, implementing, and maintaining the quality assurance and control of all the research. During the period of sample recruitment, an interim analysis will be conducted under strict confidentially, which may include analyses of data from other comparable trials. Through these interim analyses, the PI will determine if the interventions or potential mechanisms have been proven or if they differ from the expectations. The PI will decide whether to modify the trial. Unless this situation occurs, the research staff will remain unknown during the interim analysis.

Adverse Events

Adverse events will be collected and recorded after informed consent and this procedure will continue until the end of the study. For those who report an adverse event after submitting the signed informed consent but before the trial intervention, the event will not be considered as an adverse event related to our intervention. Serious adverse events will be reported to the ethics review committee.

Auditing and Inspecting

The PI will allow study-related audits and inspections by the ethics review committee of the documents pertaining to the research. The PI will guarantee the capability to conduct inspections of applicable study-related facilities.

Ethical Considerations

The study was approved by the Chinese Ethics Committee of Registering Clinical Trials (ChiECRCT, Reference number: ChiECRCT20210561). The trial is registered on ClinicalTrials.gov (registration number: ChiCTR2200062148; date of registration: July 25, 2022). If there are any changes to the protocol, we will report to the ChiECRCT and inform the subjects. A formal amendment to the protocol will be submitted to and approved by the ethics review committee before implementation.

During the enrollment session, participants receive detailed information about the study and are required to provide written informed consent before undergoing the auditory examination. Regardless of their inclusion in subsequent studies, participants received compensation consisting of 30 Yuan (US $4.2) in cash and a gift of daily necessities for their participation in the hearing tests. In the follow-up survey, respondents will also receive 30 yuan (US $4.2) in cash after completing the questionnaire.

Each respondent is assigned a personal identification number, which serves as a unique identifier for correlating the participants' identification details with information related to the trial, thereby safeguarding confidentiality. No further identifiable features will be included in the data analysis process.

Results

Trial Status

The project was funded in July 2019. The current protocol is version 3, dated January 15, 2025. The recruitment of participants and collection of baseline data began on September 1, 2022, and ended on September 30, 2022. A total of 435 participants were recruited and assigned to a random group at baseline. A follow-up survey was conducted after 24 months in September 2024, which included 397 participants. Figure 2 displays the flow diagram of the HISEA trial. Until this version of the protocol, the intervention effects have remained unknown.

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Figure 2. Hearing Impairment and Social Outcomes Evaluation in Adults study flow diagram developed using Standard Protocol Items for Interventional Trials or Consolidated Standards of Reporting Trials.

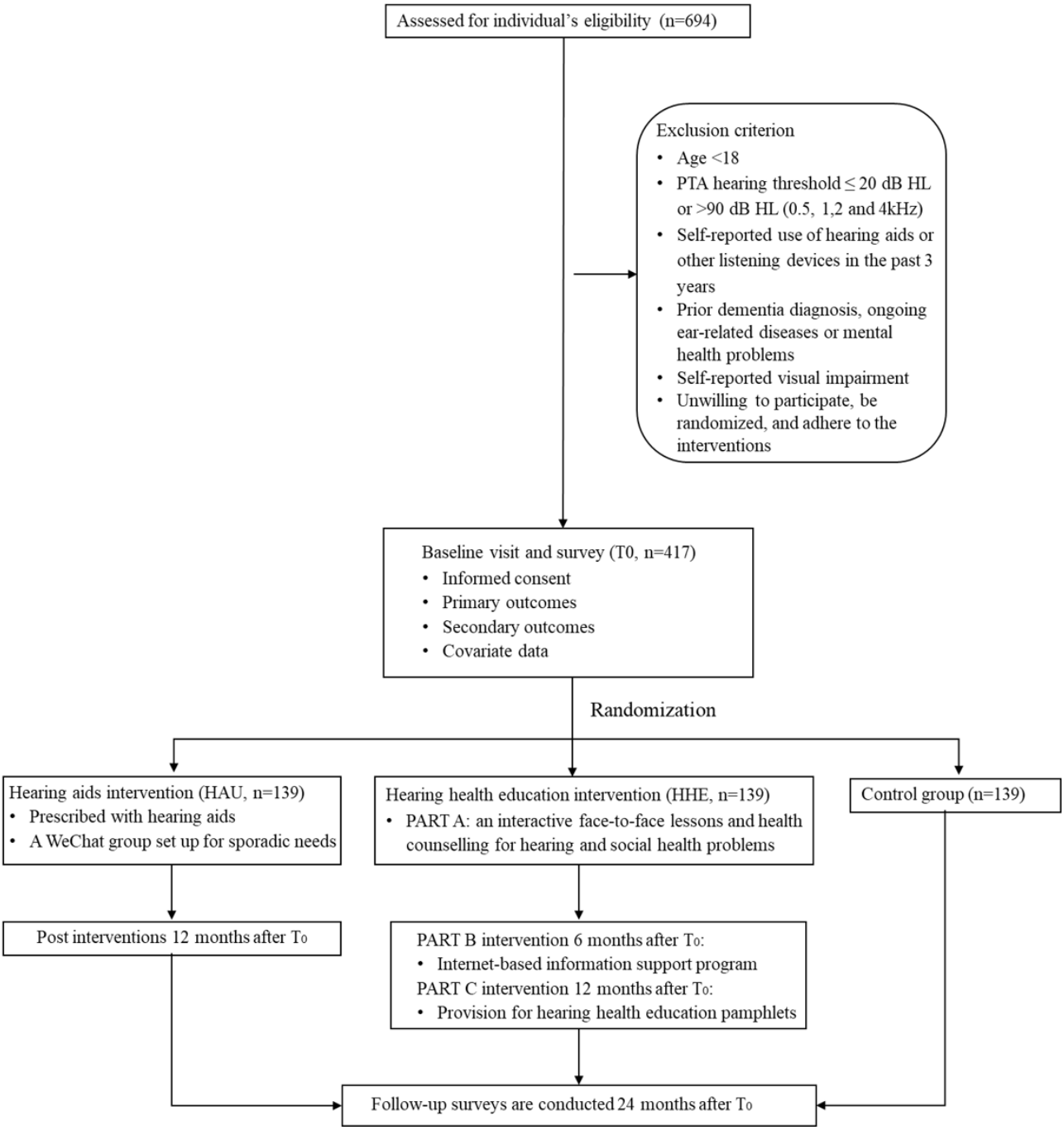

Preliminary Results

Table 2 shows the sociodemographic characteristics of the sample at baseline. The mean (SD) age of the participants in RCT is 71.59 (SD 9.55) years, with 43.09% (187/434) of the sample identifying as female.

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Table 2. Baseline sample characteristics.

Variables	Control group	Hearing health education group	Hearing aid use group	Total
Age (years), mean (SD)	74.82 (9.29)	71.44 (6.51)	67.02 (11.75)	71.59 (9.55)
Sex, n (%)				
Male	56 (35.9)	56 (35.67)	75 (61.98)	247 (56.91)
Female	100 (64.1)	101 (64.33)	46 (38.02)	187 (43.09)
Education, n (%)				
Illiterate	43 (27.74)	27 (17.2)	30 (25.21)	100 (23.2)
Primary school	86 (55.48)	94 (59.87)	61 (51.26)	241 (55.92)
Middle school or higher	26 (16.77)	36 (22.93)	28 (23.53)	90 (20.88)
Marital status, n (%)				
With spouse	116 (75.32)	95 (67.14)	88 (76.52)	298 (72.86)
No spouse	38 (24.68)	46 (32.86)	27 (23.48)	111 (27.14)
Self-rated economic status, n (%)				
Fair	115 (74.68)	109 (70.32)	24 (20)	248 (57.81)
Poor	39 (25.32)	46 (29.68)	96 (80)	181 (42.19)
Self-rated health, n (%)				
Good	76 (48.72)	149 (94.9)	52 (42.98)	277 (63.82)
Fair	65 (41.67)	7 (4.46)	46 (38.02)	118 (27.19)
Poor	15 (9.62)	1 (0.64)	23 (19.01)	39 (8.99)
Chronic disease, n (%)				
No	22 (20)	39 (27.08)	70 (61.4)	131 (35.6)
Yes	88 (80)	105 (72.92)	44 (38.6)	237 (64.4)
Number of observations, n	156	158	121	435

Discussion

Principal Findings

We anticipate a significant positive effect of interventions on reducing social isolation and enhancing functioning outcomes, along with several psychological pathways, which contribute to these main results.

Comparison to Previous Work

This RCT assesses the impact of 2 interventions—the provision of free hearing aids and an HHE program on social connections and functioning among community-dwelling Chinese adults with HI. The design of this RCT is partly similar to the Aging and Cognitive Health Evaluation in Elders (ACHIEVE) RCT conducted in the United States, which commenced in 2017. The ACHIEVE trial implemented a 3-year hearing intervention that included audiological counseling and provision of hearing aids, alongside a control intervention on successful aging health education. A notable distinction in our study's design is the inclusion of a control group that receives no intervention, as well as the specificity of our health education to hearing-related topics. While the ACHIEVE trial primarily targeted cognitive outcomes, it also assessed some mental health and well-being outcomes [54]. In contrast, our study is specifically oriented towards social functioning. Furthermore, secondary analysis of ACHIEVE data indicated no significant association between the 3-year interventions—either hearing aid provision or health education—and health-related quality of life [55]. Our research will help examine the effectiveness of these interventions among older adults with HI within a different sociocultural context. Our use of WHO-DAS II as a generic measure in the hearing-impaired population is similar to another 12-month hearing aid intervention research conducted in the United States [23].

Currently, among the completed RCTs concerning community hearing intervention rehabilitation in China, 2 studies exhibit similarities to our community interventions. One of these studies conducted a 20-month hearing aid intervention [51], while the other implemented a 3-month hearing aid combined with a health education intervention [56]. Both studies used a 2-arm design and assessed a range of outcome variables, with secondary outcomes including quality of life and social isolation. Our intervention design is characterized by a more complex 3-arm intervention design and a larger sample size, which is anticipated to yield more robust evidence regarding the long-term effects of hearing interventions. To our knowledge, this will be the first RCT to evaluate the efficacy of community-delivered hearing rehabilitative and supportive interventions—both hearing aids and health education—on older adults' SWB in the context of Chinese aging society.

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Strengths

This study highlights 2 main strengths. First, the study makes a theoretical contribution by integrating the WHO's ICF and IPC-EHC frameworks in conjunction with the stress process model. The WHO frameworks facilitate a focus on both individual and environmental factors in the design of interventions, emphasizing social isolation and functional outcomes, which distinguishes this research from traditional studies that primarily address quality of life and cognitive functions. Within the context of the stress process model, hearing deterioration is conceptualized as a chronic stressor that can have both direct and indirect effects on psychosocial distress [57]. Thus, the psychological pathway outlined in our hearing intervention aims to provide empirical support for the application of the stress model in the management of chronic diseases such as hearing loss, offering a detailed explanation of the role of stress within the model in relation to different health consequences.

Second, the interventions are community-oriented, which aligns with China's policy setting on hearing rehabilitation and health promotion. Currently, China's Action for Promoting Hearing Health in the Elderly mainly conducts activities based on communities, such as popularizing knowledge about hearing health, screening, and public health initiatives. Besides, both online and offline elements are blended in the interventions, which provides more convenient and efficient support and meets with current digital health trends. The findings of this study may provide valuable insights for health care and social workers to enhance well-being among older adults through auditory interventions.

Limitations

Despite these strengths, the trial faces several limitations. First, the design of a one-time follow-up study presents challenges in evaluating the short-term effects of interventions, as well as their impacts beyond a 24-month period. The duration of intervention and follow-up is selected based on the following considerations: (1) previous research has consistently shown significant findings regarding the short-term effects of hearing aid interventions; however, the medium- to long-term effects remain ambiguous, and adherence to the prolonged use of hearing aids is notably low. Our primary interest lies in investigating these medium- to long-term effects; (2) given that the measurement tools used in both the baseline and follow-up questionnaires are fixed, we intend to extend the interval between the 2 measurements to mitigate potential learning effects; and (3) in addition, the constraints imposed by the project's duration and funding are considered.

Second, there is a lack of subjective measures in our survey questionnaire. To address this gap, we conducted qualitative interviews after the RCT. A subset of older adults with HI from intervention groups were inquired about their satisfaction with the use of hearing aids, their experience in health education activities, and their assessments of the health education materials. In addition, we gathered feedback from CPs.

Third, the provision of free hearing aids may raise concerns regarding the social approval effect. Previous research on hearing aid interventions has typically involved the distribution of free devices [51,58,59]. In instances where there is a financial burden associated with acquiring commercial hearing aids, selection bias may arise, as economically disadvantaged older individuals may find it more challenging to participate in such interventions. The Chinese government has established a range of welfare policies aimed at supporting individuals with disabilities and the elderly, which include not only rehabilitation services, but also living subsidies for disabled individuals, long-term care insurance, and older adult care subsidies. Within this welfare framework, hearing aids do not represent a unique benefit. Therefore, we contend that the social approval effect remains within a manageable scope and is unlikely to compromise the reliability and validity of the RCT. Future research could also compare the intervention effects of paid hearing aids with those of free hearing aids.

Fourth, the interventions are conducted at different sites, which may result in geographical and selection biases. Nevertheless, the comparable socioeconomic and cultural contexts of these sites are expected to alleviate such biases. There was no pilot study due to time and budget constraints; however, given that the social and demographic characteristics of the feasibility study site closely resemble those of the formal trial sites, we believe this limitation does not pose a significant threat to the research design.

Fifth, our reliance on self-reported measures of social isolation and functioning may introduce measurement bias, which we will address through the use of validated tools, cross-validation, and multisource evaluations.

Lastly, although the sample size was determined using standard calculation methods, it remains relatively small, which affects its representativeness and external validity. Randomization in a small sample may not completely eliminate the preexisting differences either. Therefore, we will further use matching techniques or other econometric methods during the statistical analyses.

Dissemination Plan

The results of the study will be disseminated through peer-reviewed publications and national and international conference presentations to publicize and explain the research to key audiences. Dissemination authorship will be fulfilled by the research team's efforts. Information regarding public access can be seen on the Chinese Clinical Trial Registry website.

Future Directions

This trial is poised to provide early insights into the feasibility, acceptability, and effectiveness of community-delivered rehabilitation interventions aimed at mitigating the social impacts of HI. The findings will inform future improvements in hearing health care and community-based health practices.

Conclusions

The findings of this study will evaluate the impact and cost-effectiveness of a community-based auditory or hearing health education intervention on SWB among Chinese adults with HI. It will help promote hearing health in older adults and decrease adverse health risks in an aging society.

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Acknowledgments

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Data Availability

The datasets generated and analyzed during this study are not publicly available due to the confidentiality agreement reached with the participants but are available from the corresponding author on reasonable request.

Authors' Contributions

JG contributed to conceptualization, data curation, funding acquisition, investigation, methodology, project administration, resources, software, supervision, validation, visualization, and writing–original draft. YZ assisted with data curation, formal analysis, investigation, methodology, software, visualization, validation, and writing–review & editing. XJ handled data curation, investigation, methodology, resources, and validation. ZF and HJ contributed to data curation, investigation, and resources.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items for Interventional Trials) checklist.
[DOCX File , 32 KB - resprot_v14i1e64115_app1.docx]

Multimedia Appendix 2
CONSORT-eHEALTH checklist (V1.6.1).
[PDF File (Adobe PDF File), 1028 KB - resprot_v14i1e64115_app2.pdf]

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Abbreviations

ACHIEVE: Aging and Cognitive Health Evaluation in Elders
CDPF: China Disabled Persons' Federation
ChiECRCT: Chinese Ethics Committee of Registering Clinical Trials
CP: communication partner
GPSRC: Guangdong Provincial Cultural Sports and Rehabilitation Assistive Devices Center for People with Disabilities
HAU: hearing aid use
HHE: hearing health education
HI: hearing impairment
HISEA: Hearing Impairment and Social Outcomes Evaluation in Adults
ICF: International Classification of Functioning, Disability and Health
IPC-EHC: integrated person-centered ear and hearing care
LSNS: Lubben Social Network Scale
PI: principal investigator
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items for Interventional Trials
SWB: social well-being
WHO: World Health Organization
WHODAS 2.0: World Health Organization Disability Assessment Schedule 2.0

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Protocol

Optimizing a Personalized Health Approach for Virtually Treating High-Risk Caregivers of Children With Neurogenetic Conditions (Project WellCAST): Protocol for a Randomized Controlled Trial

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This is a corrected version. See correction statement: https://www.researchprotocols.org/2025/1/e80023

Abstract

Background: Even before the COVID-19 pandemic, caregivers of children with rare neurogenetic conditions (NGCs) experienced physical and mental health challenges. These challenges escalated during the COVID-19 pandemic due to crisis-level breakdowns in support services. Tele–mental health and parenting support services expanded rapidly in response to the COVID-19 pandemic and may be well suited to facilitate necessary support interventions for NGC caregivers. However, it remains unclear how to match these evidence-based interventions to individual NGC caregivers' needs.

Objective: Project WellCAST (Supporting Well-Being of Caregivers via Telehealth) is an early-phase clinical trial designed to prospectively test which evidence-based telehealth interventions best meet the needs of NGC caregivers.

Methods: Interested and eligible NGC caregivers are enrolled in a 24-week program with 5 phases, including baseline (2 weeks), support program (12 weeks), and follow-up (2 weeks) periods; a 4-week gap separates the phases. Caregivers participate in 2 randomizations, namely support program assignment via a precision health algorithm versus quasi-random assignment and motivational coaching by another NGC caregiver and project staff member ("peer coaching") versus standard check-ins by a staff member who is not an NGC caregiver ("staff coaching"). Virtual support programs include acceptance and commitment therapy, dialectical and behavioral therapy, culturally informed cognitive behavioral therapy, research units in behavioral intervention, naturalistic communication intervention, Durand sleep intervention, and self-guided resources. A subset of caregivers will participate as waitlist controls before engaging in support programs. We developed and optimized a personalized health decision

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tree algorithm that matches caregivers to telehealth support programs. We then proceeded to test the feasibility and efficacy of algorithm-assigned support programs across 4 waves of data collection, relative to quasi-random assignment and waitlist controls. During each wave, the personalized health algorithm relies on 2 weeks of baseline data collection using clinical tools and innovative smartphone-based ecological momentary assessments. Across waves, we also test the efficacy of a motivational peer-to-peer coaching protocol, deployed by trained NGC caregiver staff, in enhancing support program uptake and clinical outcomes.

Results: Four waves of data collection are scheduled for August 2023 to September 2025. Preregistered analyses will contrast feasibility, efficacy, and acceptability across algorithms and coaching assignments. Multiple waves of data collection will allow us to continually optimize the algorithm and test incremental improvements across project phases. Secondary analyses will probe the feasibility and efficacy of individual evidence-based support programs and peer coaching.

Conclusions: Project WellCAST will test whether a digital personalized health decision tree algorithm and peer coaching protocol can prospectively enhance telehealth support program outcomes among NGC caregivers. This project is relevant to the specific population of NGC caregivers and may also inform how brief digital assessments, precision health tools, and community-academic partnerships can enhance the public health response to mental health crises across other high-need populations.

Trial Registration: ClinicalTrials.gov NCT05999448; https://clinicaltrials.gov/study/NCT05999448 and OSF Registries 10.17605/OSF.IO/8WNDP; https://osf.io/8wndp

International Registered Report Identifier (IRRID): DERR1-10.2196/64360

(JMIR Res Protoc 2025;14:e64360) doi:10.2196/64360

KEYWORDS

caregivers; neurogenetic conditions; telehealth; precision health; community-academic partnerships; ecological momentary assessment; mental health; motivational interviewing; clinical psychology; parent coaching

Introduction

Overview

Although tele–mental health and parent coaching services are increasingly available, it remains unclear which types of support programs are best suited to various populations and how to best deliver these support programs. One population particularly well suited to telehealth support programs is caregivers of children with neurogenetic conditions (NGCs). Here, we defined NGCs as genetic conditions that affect cognitive, psychosocial, and physical development; examples include named conditions, such as Angelman syndrome, Prader-Willi syndrome, and Williams syndrome, as well as rare and ultrarare conditions with lower prevalence rates. These NGC caregivers are vulnerable to elevated stress and mental health challenges due to often extreme caregiving burden; for example, they may experience geographic isolation from specialty support clinics, exhibit elevated levels of parenting stress, and manage complex child behavioral and medical needs with limited structural resources [1-3]. Project WellCAST (Supporting Well-Being of Caregivers via Telehealth) is a National Institutes of Health–funded clinical trial that aims to prospectively develop and test the efficacy of a precision health decision tree algorithm for routing NGC caregivers to evidence-based telehealth supports, based on their unique clinical and lifestyle profiles. Project WellCAST also tests the efficacy of community-engaged peer-to-peer coaching protocol in enhancing the feasibility and efficacy of digital supports. Here, we provide the rationale and protocol for Project WellCAST, including anticipated outcomes and impact within and beyond NGC caregiving communities.

Project Background

Although telehealth support programs have existed for some time, telehealth services expanded rapidly in response to the COVID-19 pandemic [4], providing new opportunities for increased access to mental health programs [5,6]. One population for whom telehealth services offer critical benefits are NGC caregivers. Although the elevated mental health needs of NGC caregivers predated the COVID-19 pandemic [7], the pandemic caused them to face crisis-level breakdowns in support and intervention services that have continued to impact families [8]. These COVID-19 pandemic–related impacts were, in part, driven by social isolation, financial strain, and reductions in face-to-face support programs, which compounded an already fragmented and challenging landscape of care [2,3]. The COVID-19 pandemic–related interruptions required caregivers to take on even more responsibility as they managed urgent educational, vocational, and functional needs of their children [3]. The negative impact on caregivers' health and well-being continues to this day [8]. However, despite their elevated need, caregivers rarely receive support for their own mental health. Any psychological support they do receive is typically disconnected from their child's care plan and delivered by practitioners with little-to-no expertise in the needs of NGC families [9,10]. Consequently, accessible and scalable digital interventions are needed to support the intersectional needs of NGC caregivers and prevent an accelerated breakdown in their mental health, particularly in the wake of the COVID-19 pandemic.

In part due to the rapid and dramatic uptake in telehealth methods during the COVID-19 pandemic, many questions remain regarding the circumstances and populations for which telehealth services are most effective [6], including but not limited to services for NGC caregivers. Although a variety of evidence-based telehealth support programs are available, it is not always clear which programs should be provided to which patients. This issue has long motivated the psychiatry and psychology literature, though many randomized controlled trials

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continue to examine broad treatment effectiveness [11,12] rather than investigating treatment personalization protocols [13]. Precision health literature guides our efforts to move toward support program personalization for NCG caregivers, with promising examples of prognostic models in other populations [14].

One challenge to the effective prospective assignment of patients to treatments is the issue of measurement. Often, mental health providers base selection on limited intake information and through subjective assessment guided by broad symptom checklists or patient-reported symptoms. As an expansion of this approach, precision mental health care aims to optimally match patients to existing evidence-based treatments through the use of demographic, clinical, and dispositional information [14]. Tools such as daily diaries and ecological momentary assessments (EMAs) hold promise for providing temporally dense information about participants' experiences, beyond the contributions of clinical assessments alone. EMAs are brief questionnaires aimed at gathering real-time data on the participants' experiences that reduce the challenges of retrospection [15]. Using EMA data can provide insights into fluctuating daily experiences and momentary affects, as well as information about practical day-to-day constraints within their lives that may affect support program uptake (eg, caregiving burden, health behaviors, and social support). However, to date, tools such as EMA have not been prospectively used to match patients to support programs based on their personal health profiles.

Another consideration for the effective assignment of support programs is the impact of sociocultural and practical issues on a patient's willingness and ability to engage in tele–mental health treatment. For example, several studies have documented that telehealth does not universally improve accessibility and may, in some cases, enhance preexisting disparities by disrupting trust and rapport, distancing communities with poor technology literacy or access, and introducing concerns about data security and privacy [16]. These health care gaps are amplified among Black and other minority families who are less likely to receive mental health care due to discrimination, racism, and historic injustices against Black people in health care settings [17].

One potential solution to the disrupted rapport in telehealth-based programs is to implement community-centered and motivational support programs, such as participation enhancement interventions aimed at addressing barriers to support program participation and enhance motivation and adherence to treatments [18,19]. These support programs may be particularly beneficial for caregivers of children with NGCs due to isolation and disconnection from social support that may accompany their child's complex needs [9,10]. Peer support is known to provide benefits to caregivers [20,21], though to be most useful, perceived need and received support must align [22]. There is also some evidence that peer support may have differential impacts on certain subgroups of parent caregivers (eg, individuals with higher baseline anxiety [23]), though more evidence is needed to determine which participants might benefit most from peer support. Thus, peer support interventions may positively impact willingness and engagement in tele–mental health programs for some caregivers while simultaneously being an extra unneeded hassle for others. Although these programs have demonstrated broad efficacy across several neurodevelopmental populations, they have not been explicitly tested in substantial NGC caregiving samples. Given that coaching programs require extra time and resource commitments from both families and professionals, and many participants effectively engage in intervention without peer support, it is important to determine which participants would benefit from this extra layer of support.

This Study

Project WellCAST (NCT05999448) is an early-phase clinical trial designed to prospectively test which evidence-based telehealth interventions best meet the unique needs of NGC caregivers. We accomplish two specific aims: (1) develop and optimize a personalized health decision tree algorithm to match NGC caregivers to digital health programs using a combination of standard clinical tools and smartphone-based EMA data, and (2) test the efficacy of peer-to-peer coaching, deployed by trained NGC caregivers using an evidence-based motivational interviewing protocol, in enhancing support program uptake and clinical outcomes. Here, we describe the protocol methods and anticipated impact of this project, both for NGC caregivers and the broader field of precision mental health.

Methods

Study Design

Project WellCAST uses a randomized control design with waitlist control to test the effectiveness of both (1) a precision health algorithm and (2) a participation enhancement intervention on improving clinical outcomes for NGC caregivers. It is anticipated that between 500 and 750 caregivers will enroll in WellCAST across waves, with a minimum enrollment of 500 participants, including 50 waitlist controls, to adequately power primary analyses. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) reporting guidelines were used in the preparation of the Project WellCAST protocol [24].

Project WellCAST is deployed across 4 waves. During waves 1 and 2, participants are randomly assigned to be routed to support programs using either a preregistered precision health algorithm (algorithm 1) or quasi-random assignment. During waves 3 and 4, participants are assigned to support programs using optimized algorithms (algorithms 2 and 3, respectively). Across waves 1 to 4, participants are randomized to either a participation enhancement intervention delivered by an NGC caregiver coach (peer coaching) or similarly timed check-ins by non-NGC caregiver staff (staff coaching).

At the time of the initial protocol submission, Project WellCAST has completed waves 1 and 2 (fall 2023 and spring 2024); waves 3 and 4 will be conducted in fall 2024 and summer 2025, respectively. Thus, across waves, 25% of participants are assigned to each algorithm category (quasi-random, algorithm 1, algorithm 2, and algorithm 3), and 50% of participants are assigned to each peer coaching category (peer coaching and staff coaching).

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Ethical Considerations

Overview

Project WellCAST was determined to present no more than a minimal risk of harm to participants. The study was approved by the Purdue University Institutional Review Board (IRB) on March 3, 2023 (2022-1058); collaborating sites deferred oversight to Purdue as the single IRB of record. Participants provide informed consent before engaging in baseline data collection and later provide informed consent specifically for their assigned support program before engaging in sessions.

Compensation

Caregivers are paid US $100 for completing assessments. There are 5 sets of forms total, and the amount of compensation increases over time to maximize response (baseline: US $10; start of programs and mid support programs: US $15 each; end of programs: US $30; and follow-up: US $30). Participants are not compensated for time spent in support programs. Participants who are participating in the waitlist control receive compensation as they would if they participated in a support program. Payment is delivered using Amazon gift cards after participants complete each set of forms, and support programs are delivered free of charge.

Privacy and Confidentiality

Participants provide a variety of personal health information data, including medical and genetic records and psychiatric diagnostic information. We are not subject to the Health Insurance Portability and Accountability Act (HIPAA) guidelines, as we are not a medical entity. However, we use HIPAA-compliant data storage tools and procedures whenever possible. Data are stored on password-protected and encrypted devices, HIPAA-compliant Microsoft Box folders, and the HIPAA-compliant data management system REDCap (Research Electronic Data Capture; Vanderbilt University) [25,26]. Participant data are labeled by identification numbers rather than name, wherever possible. Only key study personnel have access to REDCap, where identification numbers are stored alongside participant information. Otherwise, identification numbers are stored separately from personal information.

Plan for Documenting Potential Protocol Modifications

Potential deviations from protocol and protocol modifications are logged into a protocol deviation log by the research team. Applicable protocol modifications will be submitted to the IRB for review at each instance. The research team will complete a yearly audit of the registered protocol on all platforms.

Trial Registration

Project WellCAST was registered on ClinicalTrials.gov on August 21, 2023, and the first algorithm was registered on Open Science Framework (OSF) Registries on August 30, 2023, before running the first algorithm assignment. The first participant consented to a support program on August 31, 2023, and the first participant started the support program on September 11, 2023. Supplemental analytic plans were preregistered on OSF Registries on October 18, 2023, to further detail the ClinicalTrials.gov registration. Wave 1 participants consented to baseline data collection starting June 28, 2023, and started baseline data collection on August 7, 2023. Baseline data were collected before any participant consented to support programs and were not analyzed or used to route participants until after registration was complete.

Recruitment

Caregivers of children with NGCs are recruited through various sources to maximize the potential participant pool. Recruitment strategies include social media advertisements, sharing materials with genetic clinics and providers, mailers by patient advocacy groups, emails to condition-specific email distribution lists, and recruitment through registries. Inclusion criteria are (1) legal guardian of an individual aged 2 to 35 years with a documented NGC associated with intellectual or developmental disability that is not primarily characterized by neurodegeneration, (2) fluent in English, (3) interacts with the individual with an NGC most of the time, and (4) resides in the United States. Participants are excluded if they either (1) express severe psychiatric illness not indicated for the interventions offered (eg, suicidal, psychotic thoughts, mania, or significant substance use) or (2) are currently in active therapy or receiving support that would conflict with, or be redundant with, the interventions offered.

Screening

Interested participants may scan a QR code on recruitment materials or receive a link via email to a digital prescreening survey via REDCap [25,26]. Once complete, research staff members who are trained in clinical assessments contact interested caregivers by phone to conduct a screening interview and to determine eligibility. The research staff member verifies demographic information and assesses the participant's recent mental health history using the Mini-International Neuropsychiatric Interview [27]. If the participant is determined eligible to participate, the research staff member provides instructions on how to sign electronic consent forms for the baseline phase of the project in REDCap and begins the baseline phase of the study. Participants separately provide consent to their specific support program after being assigned a program arm during the routing phase.

Decision Tree Algorithm Development

Overview

The decision tree algorithm was designed to function as a clinical decision tree. The rules and explanations for the algorithm are coded into an R program, and each output is reviewed by our biostatistics team to ensure that the algorithm is working correctly.

Initial Decision Tree Algorithm

The algorithm, decision nodes, and thresholds are all preregistered on OSF Registries before use to promote transparency, explainability, and interpretability. Support program assignments are based on clinical and lifestyle data provided by participants in the 2-week baseline period. For example, in algorithm 1, participants who report high levels of emotional dysregulation, depression, stress, or anxiety will be eligible for adult-focused mental health programs. Once eligible for adult-focused mental health programs, participants are

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assigned to either individually delivered acceptance and commitment therapy (ACT) or group-based dialectical and behavioral therapy (DBT) based on their initial data. Participants with higher emotional dysregulation scores are routed to DBT, whereas participants with below-threshold levels of emotional dysregulation are routed to ACT. This threshold was determined via multiple data sources. A primary aim of the study is to evaluate and optimize the efficacy of these algorithms, and we anticipate that support program assignment criteria will evolve following preplanned algorithm optimizations, as will be detailed in peer-reviewed manuscripts describing study results. The full descriptions of all decision nodes and thresholds for each iteration of the algorithm are available in algorithm preregistrations on OSF Registries. We also anticipate that further justification for the support program assignment will be discussed in the peer-reviewed manuscripts describing study results after the trial has concluded.

Minimizing Bias

Any algorithm or assessment tool will exhibit bias toward its normative sample. To minimize this, we prospectively implemented several protective measures that are also aligned with guiding principles for addressing algorithm bias [28]. We planned algorithm optimization via a CASCADE (community-engaged approach for scientific collaborations and decisions) panel at 2 preplanned intervals. The CASCADE panel process was intentionally designed to minimize biases. The key pillars of the CASCADE approach include centering community input, minimizing opportunities for cognitive biases in decision-making, and centering diverse experiences and perspectives, particularly of individual patients [29]. CASCADE panels include representation from individuals with lived experience in the trial's target population (eg, rare disorder caregivers) present and engaged in the process. A specific example approach for addressing bias during CASCADE panels includes examining scores and data trends for minoritized populations within our sample to minimize the potential for exacerbated disparities. We anticipate that future applications of our final algorithm will require substantial interrogation for generalizability to any new participant group.

Routing Procedures

Participants are matched to a combination of digital health support programs using a multistep process indicated by the data provided in the baseline phase. First, research staff not involved in participant support programs generate an eligibility panel for each participant that contains feasible and appropriate programs based on broad rule out criteria. For example, participants who do not identify with minority groups will not be eligible for programs focused on race-related trauma. Participants with children aged >8 years are not eligible for certain child-focused programs designed for young children. The preregistered algorithm is then used to generate a sequential list of participants' recommended programs, based on their baseline data.

During waves 1 and 2, the first randomization is to algorithm 1 or quasi-random assignment. Participants randomized to algorithm 1 are assigned their algorithm-indicated support program. If practical issues prevent them from engaging with their top program (eg, lack of availability during group times), they are offered the next indicated support program. Participants randomized to quasi-random assignment are assigned to a support program using a random number sequence generated by a member of the biostatistics team who is not involved in participant management or intervention deployment. Similarly, if practical constraints prevent their first program from being feasible, they are moved to their next program indicated by the random number sequence. Whether the participant received their top assignment is recorded and integrated into statistical analyses. Finally, all participants are randomized to either peer coaching or staff coaching protocols using a random number generator. During waves 3 and 4, participants continue to be randomized to peer coaching or staff coaching. All participants receive algorithm 2 during wave 3 and algorithm 3 during wave 4. Care providers are masked to the status of peer coaching and algorithm assignment. Peer coaches are masked to the status of algorithm assignment. Data managers and statisticians evaluating study outcomes are provided deidentified data and are not involved in support program–related study operations. Research team members evaluating study outcomes are also masked to assignments.

A subset of participants is also assigned to a waitlist control to allow for the evaluation of treatment efficacy and quantify potential attenuation of responses with repeated assessment [30]. Participants assigned to waitlist controls contribute identical data to active participants and receive the same remuneration. They are routed to support programs or resources during the next wave.

Support Programs

Support Program Categories

Overview

Support programs fall into one of four categories: (1) live telehealth intervention focused on caregiver well-being; (2) live telehealth intervention focused on a child's social communication, behavioral, or sleep challenges; (3) self-guided resources; or (4) waitlist control.

Live Telehealth Intervention Focused on Caregiver Well-Being

Participants assigned to receive a live telehealth intervention focused on caregiver well-being are assigned to one of the interventions described in the subsequent sections.

ACT Intervention

Participants who are routed to ACT [31] receive an adapted 12-week version of the treatment containing the 6 major components of ACT. Each session is 60 minutes long and delivered via Zoom (Zoom Communications, Inc). ACT is administered individually between a supervised psychology doctoral student and a participant. In each session, clinicians review new skills and practices in line with the participant's stated goals and review their practice of the skills in their daily life. The sessions are highly structured, while allowing clinicians flexibility with the examples and specifics of session content, so that the content can be most relevant to the participant [31].

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DBT Skills Training

Participants assigned to DBT [32,33] receive an adapted 12-week version of the treatment. DBT is administered as a group therapy, with up to 2 doctoral students and 12 participants who meet once weekly for 90 minutes for 12 weeks. The skills sessions, based on the 4 core modules of DBT, are conducted in a condensed format to suit the 12-week format of DBT. The skills are curated and tailored to the needs of caregivers of children with NGCs. Some skills from the typical set are omitted to fit in with the abbreviated timeline [32,33].

Culturally Informed Cognitive Behavioral Therapy

Participants who identify as Black are eligible to be routed to an individual program or an additional, group version of culturally informed cognitive behavioral therapy [34,35]. This is an evidence-based support program for families affected by traumatic life events and includes psychoeducation, active coping skills, narrative processing, and exposure to traumatic memories [34,35]. The individualized form of this program is administered in once weekly 60-minute-long sessions, over 12 weeks, and delivered via Zoom. The group form is administered in a once weekly 90-minute-long format, with up to 10 participants. The group form is offered to any Black participant, in addition to another support program they were routed to (eg, participants could be in both ACT and this group).

Live Telehealth Intervention Focused on a Child's Social Communication, Behavioral, or Sleep Challenges

Participants assigned to receive a live telehealth intervention focused on parenting techniques are assigned one of the interventions described in the subsequent sections.

Research Units in Behavioral Intervention

Research units in behavioral intervention (RUBI) [36] parent education is an empirically supported intervention that may help prevent and decrease the likelihood of worsening challenging behaviors for children [36]. This manualized program was adapted to a 12-week group-based program and teaches caregivers strategies for preventing and addressing their child's mild to moderate challenging behavior, such as aggression and tantrums, while teaching appropriate caregiver behavior, such as communication and following a daily schedule with support. Each weekly session is 90 minutes long, consists of up to 4 participants and 2 group leaders, and is delivered via Zoom. Participating parents follow a workbook and are asked to complete weekly homework, which is reviewed at the next week's session.

Naturalistic Communication Intervention

Participants assigned to the naturalistic communication intervention [37] receive an empirically supported intervention that helps promote their child's early communication behaviors [37]. It is adapted into a 12-week program and is a 60-minute-long session, conducted individually between an interventionist and the participant. Each session aims to build on the child's interests and preferences and promote communication behavior. This virtual session takes place during daily home and play routines.

Durand Sleep Intervention

Participants assigned to the Durand sleep intervention [38,39] engage in an evidence-based sleep protocol that provides educational content in a 12-week program for telehealth use. This intervention may help prevent or decrease sleep problems for the child. This is an every-other-week group program that offers caregivers resources and skills for identifying, preventing, and addressing their child's sleep problems. On alternate weeks, the clinician checks in individually with the participant to support individual sleep challenges that the participant is facing [38,39]. The group sessions are 2 hours long with up to 7 caregivers, and the individual check-ins are 15 minutes long, alternating across the 12-week program.

Self-Guided Resources

Participants assigned to receive self-guided resources are provided with "The Project WellCAST Journal," which was designed to be an active control condition to the live support program arms. This is a weekly reflections and resource guide for caregivers of children with NGC. During the 12-week guided practice, participants read about basic skills for well-being and mental health. Topics were selected to align with broad concepts that are addressed in many clinical psychology interventions, such as mindfulness, reflective listening, gratitude, breathing exercises, and motivating healthy living. Rare disorder caregivers working as project staff provided input on selected topics, specifically by helping narrow the list of options and suggesting formatting elements that would promote usability. Caregivers also added quotes about how topics relate to their lives as rare disorder caregivers. Each week's entry includes space to reflect on past and current weekly topics, including practical exercises to bring topics to life. Participants do not submit the journal at the end of the study to maintain their privacy; however, they are asked to submit a log of when and for how long they used the journal.

Waitlist Control

Waitlist control participants complete assessment forms and are prompted to provide EMA data, without the presence of a support program. In the next wave, these participants are guaranteed enrollment in a support program.

Support Program Deployment

Overview

Support programs are deployed by trained graduate students and postdoctoral clinicians who are supervised by licensed professionals. Clinicians vary in previous exposure to NGC populations; however, all participate in preprogram, community-led training on NGC caregivers' lived experiences, cofacilitated by NGC caregivers, to learn about community needs.

Participants are also randomly assigned to 1 of the 2 coaching programs as detailed in subsequent sections.

Peer Coaching

Peer coaches, who are NGC caregivers employed by the project, facilitate an evidence-based program for optimizing intervention engagement, grounded in motivational interviewing [18,19]. Sessions with a peer coach take 10 to 30 minutes and involve

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developing a collaborative plan via a "change plan" worksheet. This plan assesses participant-identified goals, identifies paths toward these goals, and proactively addresses barriers to support program attendance, persistence, and home practice. Peer coaches answer questions, troubleshoot barriers, and support accessing follow-up resources, such as connections with patient support organizations. Peer coaches were intentionally recruited to represent a range of NGC and demographic characteristics to align with our anticipated sample. Sessions are deployed via Zoom.

Staff Coaching

A research staff member, who is not an NGC caregiver and has not received training in participant enhancement interventions, conducts brief telephone check-ins at the same intervals as the peer coach to support participants by answering questions about the study or their needs for follow-up resources. Each staff coaching call is designed to take less than 5 minutes.

Study Procedures

Figure 1 depicts the 5 phases of each wave: baseline, routing, support program, gap, and follow-up. Participants only actively participate during the baseline, support program, and follow-up phases, with a 4-week gap during the routing and gap phases.

During the initial 2-week baseline phase, participants complete the first set of clinical assessment questionnaires and EMA surveys. They also complete their preprogram forms and first check-in call. Participants then engage in 12 weeks of their assigned support programs. Throughout their support programs, participants continue completing EMA reports, check-in calls with their coach (peer or staff), and clinical assessment questionnaires, at the timepoints indicated in Figure 1. Support programs are followed by a 4-week gap in study activities. Then, in the final 2 weeks, participants complete their last set of clinical assessment forms and 2 weeks of EMA reports. Participants also complete their last check-in call.

Figure 1. Study timeline. EMA: ecological momentary assessment.

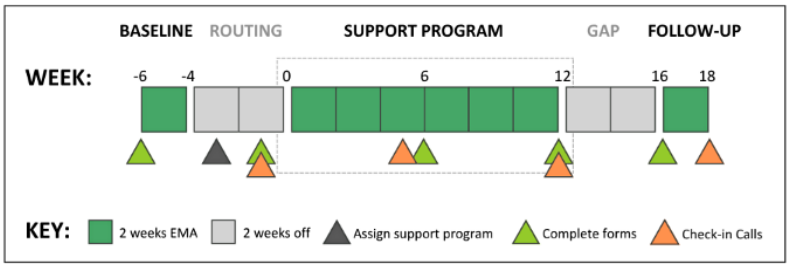

Data Collection

All data collection is deployed and collected using REDCap, a secure, web-based software platform designed to support data capture for research studies, providing an intuitive interface for validated data capture, audit trails for tracking data manipulation and export procedures, automated export procedures for seamless data downloads to common statistical packages, and procedures for data integration and interoperability with external sources [25,26]. Participants complete web-based data collection via personalized links sent via both text and email.

Measures

Information for the questionnaires assessing primary outcomes of interest are presented in detail subsequently. A complete list of measures is presented in Table 1 and Figure 2.

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Table 1. Citations for primary and secondary outcome measures.

Type	Measure	Abbreviation	Study
Primary	Depression, Anxiety, and Stress Scale-21 Items	DASS-21	Lovibond and Lovibond [40]
Primary	Parenting Stress Index, Short Form	PSI-SF	Abidin [41]
Primary	Parenting Sense of Competence Scale	PSOC	Ohan et al [42]
Secondary	Difficulties in Emotion Regulation Scale	DERS	Gratz and Roemer [43]
Secondary	Emotion Efficacy Scale-2	EES-2	McKay and West [44]
Secondary	Zarit Burden Interview, 7-item short form	ZBI-7	Higginson et al [45]
Secondary	Aberrant Behavior Checklist	ABC	Aman et al [46]
Secondary	Child Sleep Habits Questionnaire	CSHQ	Owens et al [47]
Secondary	Daily Life Experiences-Racism	DLE-R	Harrell [48]
Secondary	Multidimensional Inventory of Black Identity	MIBI	Sellers et al [49]
Secondary	Posttraumatic Stress Disorder Checklist for DSM-5	PCL-5	Blevins et al [50]
Secondary	Comprehensive Race Socialization Inventory	CRSI	Lesane-Brown et al [51]
Secondary	Child Behavior Checklist	CBCL	Mazefsky et al [52]
Secondary	MacArthur Communicative Development Inventory	CDI	Dale [53]
Secondary	Albany Sleep Problems Scale	ASPS	Durand [54]
Secondary	Sleep Intervention Questionnaire	SIQ	Durand [55]

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Figure 2. Primary and secondary outcomes. ABC: Aberrant Behavior Checklist; ASPS: Albany Sleep Problems Scale; CBCL: Child Behavior Checklist; CDI: Communicative Development Inventory; CI-CBT: culturally informed cognitive behavioral therapy; CRSI: Comprehensive Race Socialization Inventory; CSHQ: Child Sleep Habits Questionnaire; DASS-21: Depression, Anxiety, and Stress Scales-21 Items; DERS: Difficulties in Emotion Regulation Scale; DLE-R: Daily Life Experiences-Racism; EES-2: Emotion Efficacy Scale-2; IPIP: International Personality Item Pool; MIBI: Multidimensional Inventory of Black Identity; MINI: Mini-International Neuropsychiatric Interview; NCI: Naturalistic Communication Intervention; PCL-5: Posttraumatic Stress Disorder Checklist for Diagnostic and Statistical Manual of Mental Disorders, fifth edition; PSI-4: Parenting Stress Index, fourth edition; PSOC: Parenting Sense of Competency Scale; SIQ: Sleep Intervention Questionnaire; TAAS: Treatment Acceptability/Adherence Scale; ZBI-7: Zarit Burden Interview, 7-item short form.

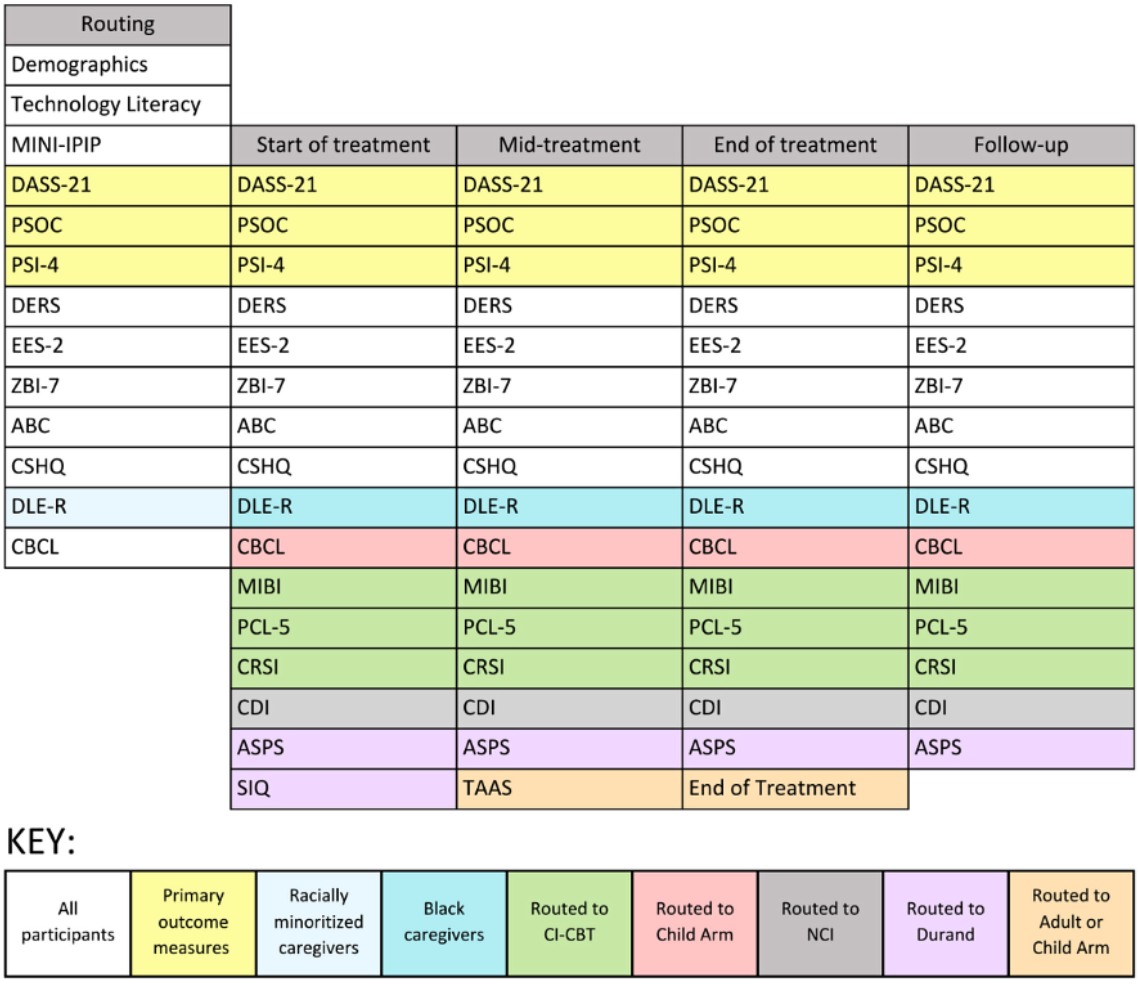

Clinical Assessment Forms: Patient Report

Figure 2 describes clinical measures and deployment schedules, which vary depending on the phase the participant is in, the intervention assigned, and the participant's demographic information. Primary outcomes of patient-reported clinical assessments are detailed in Textbox 1.

Textbox 1. Primary outcomes of patient-reported clinical assessments.

Depression, Anxiety, and Stress Scale-21 Items (DASS-21)

DASS-21 [40] is used to assess psychological symptoms. It evaluates the severity of symptoms of depression (DASS-D), anxiety (DASS-A), and psychological distress (DASS-S) over the past week. Participants respond on a 4-point Likert scale from 0 (did not apply to me at all) to 3 (applied to me very much, or most of the time). In a sample of parents of children with autism, the total scale as well as all 3 subscales were found to have strong internal consistency (DASS-Total: α=.94, DASS-D: α=.88, DASS-A: α=.83, DASS-S: α=.92) [56].

Parenting Sense of Competency Scale (PSOC)

PSOC [42] is a 17-item scale that is used to measure caregiver self-efficacy. The PSOC has 2 subscales to measure a parent's satisfaction and efficacy, which can also be combined to yield a total competence score. Example items include, "A difficult problem in being a parent is not knowing whether you're doing a good job or a bad one." Participants respond on a 6-point Likert scale from 1 (strongly disagree) to 6 (strongly agree). In a sample of parents of children with autism, the PSOC was found to have sufficient internal consistency (α=.79) [57].

Parenting Stress Index-Short Form (PSI-SF)

PSI-SF [58] is a 36-item self-report questionnaire used to assess perceived stress experienced by parents. Subscales include parental distress, parent-child dysfunctional interaction, and difficult child. Participants respond from 1 (strongly agree) to 5 (strongly disagree). The PSI-SF is known to be valid and reliable [41] and was later found to have strong internal consistency in a sample of parents of children with autism (α=.93) [56].

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EMA: Patient Report

EMA surveys are deployed across baseline, support program, and follow-up periods. Participants receive links via text message for 3 EMA surveys per day; these links are sent randomly between 7 AM and 8 AM, 11 AM and 2 PM, and 7 PM and 8 PM, based on the participant's local time. EMA surveys contain measures of sleep, daily activities, social interactions, caregiving responsibilities, stress, and affect. Each participant may contribute up to 336 EMA data points across the study period. Primary outcomes are described in Textbox 2.

Textbox 2. Primary outcomes of ecological momentary assessment (EMA) surveys.

Stress

It is measured by asking participants "How STRESSED are you feeling right now?" Participants rate their stress on a visual analog scale of 0 (not at all) to 100 (extremely).

The Positive and Negative Affect Schedule-Short Form (PANAS-SF)

PANAS-SF [59] is used to measure positive and negative affect. Positive affect is measured by words such as "alert" and negative affect is measured by words such as "upset." Participants are asked to indicate how much they feel each emotion right now, ranging from 1 (never) to 5 (always). Subscales of positive and negative affect have been validated in previous EMA studies (α=.90 and α=.89, respectively) [60].

Clinical Assessment Forms: Informant Reports

Clinicians and peer coaches provide ratings after each session, which summarize attendance, homework completion, and clinical symptoms. Clinicians and peer coaches also provide information on their perception of the participant's support program acceptability at the end of the program. Primary outcomes are described in Textbox 3.

Textbox 3. Primary outcomes of informant-reported clinical assessments.

The Clinical Global Impression Scale (CGI)

It is used to measure clinical impressions of severity (CGI-S) [61] and impressions of overall improvement since the start of support programs (CGI-I). Clinicians respond to a single item for each subscale, ranging from 1 (not at all ill or very much improved) to 7 (among the most extremely ill patients or very much worse since the initiation of treatment). The scale had strong internal consistency when used in a sample of adults with and without psychiatric conditions (CGI-S: α=.99; CGI-I: α=.94) [62].

Support program mismatch

It is assessed by asking clinicians and peer coaches to rate the fit from 1 (poor) to 5 (excellent).

Homework completion

It is assessed by clinicians during the sessions by asking participants if they have completed their homework. Following the session, clinicians report the participant's homework completion rate.

Dropout rates

They are assessed by recording information relevant to participation and can include both passive and active dropouts. "Dropout" is defined as the discontinuation of support programs after consenting to and attending at least 1 session, including active discontinuation and patients lost to follow-up. Both active and passive dropouts are accounted for in data collection, with active dropouts referring to participants who actively express their preference to discontinue participation and passive dropouts referring to participants who passively discontinue engaging in support programs or data collection. Participants who are at risk for passively dropping out are emailed or texted by the study team up to 3 times with reminders and information regarding how to proceed with participation. If a participant wants to drop out, they can alert the clinician during a session or email the study team. The study team then follows up with the participant about their experience and how to alter the study's fit for them. If the participant's final decision is to unenroll, the study team will mark the date and the reason for the participant dropping out.

Data Quality

Researchers review critical data at least biweekly to ensure data quality. When student or staff clinicians are involved in the collection of sensitive data, licensed supervisors will review student or staff data. The biostatistics team runs regular data quality checks to ensure the completeness and correctness of all collected data. Any issues are addressed collaboratively by the biostatistics team and research team.

Patient Monitoring

All study team members can report patient concerns at any time using a centralized form that is immediately reviewed by project leaders. Supervisors are in at least weekly contact with clinicians to ensure ample access for reporting issues of concern; clinicians are also trained to reach out immediately if concerns arise. Clinical meetings with the investigator team and project intervention staff are held monthly, or as needed, to discuss any emerging concerns. Local supervisors meet at least weekly with all trainees involved in active intervention. All intervention leads are licensed mental health professionals and are prepared to make appropriate referrals to community mental health providers, crisis intervention, or safety authorities, as needed. During meetings, clinical staff and supervisors discuss the safety and well-being of participants, progress in intervention, and the fidelity of implementation of the intervention protocol.

Implementation Fidelity

Fidelity is rated offline for each type of participant engagement, including with clinicians, peer coaches, and staff coaches. For each type of fidelity rating, at least 30% of files are coded for

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fidelity, and 20% of these are double coded to ensure interrater reliability. Interrater reliability is computed using Gwet A1C κ. Our predetermined threshold for fidelity is 80% success for program-specific codes across sessions.

Plan for Data Analysis

Preregistered data analytic plans are available for review [63] with complementary information available at the clinical trials registration [64]. Plans for power analysis calculations can be found on OSF Registries [63].

Our primary analyses address specific aims and research questions as detailed in Textbox 4.

Textbox 4. Aims and research questions.

Aim 1

Develop and optimize a personalized health algorithm to match neurogenetic condition (NGC) families to digital health support programs using a combination of standard clinical tools and smartphone-based ecological momentary assessment (EMA) data. Primary research questions include the following:

- Does the personalized health algorithm improve the efficacy of support programs in reducing the secondary health effects of COVID-19?
- How effective is each digital health intervention in reducing the secondary health effects of COVID-19 among NGC caregivers?

Aim 2

Enhance the scalability and sustainability of digital health interventions by training peer-to-peer coaches to meet the needs of diverse NGC families during the COVID-19 pandemic and beyond. Primary research questions include the following:

- Did peer coaches implement the intervention with fidelity and yield high participant satisfaction?
- Does peer-to-peer coaching improve uptake and efficacy of support programs in reducing the secondary health effects of COVID-19?

Specific analytic strategies are detailed in OSF Registries and are aligned with each research question. Analyses will be led by project biostatisticians who are independent of study design, participant engagement, and algorithm development. To promote rigor and reproducibility, all analytic plans are preregistered on OSF Registries.

Interim Data Analysis for Algorithm Optimization

At 2 prespecified intervals, we assess the feasibility, acceptability, and efficacy of the routing algorithm and, broadly, Project WellCAST, in promoting the well-being of caregivers of children with NGCs. Following the CASCADE method for an interdisciplinary “think tank” process, we will use multiple data sources to inform each iteration of the algorithm to optimize and enhance effective triaging for support program implementation [29]. Tables 2-4 detail the metrics of feasibility, acceptability, and efficacy that will be the focus of each think tank, including the desired and undesired outcomes associated with each. Across metrics, we are specifically interested in predicting which individuals will respond suboptimally to the project so that we can proactively minimize these challenges in future versions of the algorithm.

The think tank will be attended by multiple project interest-holders, including NGC caregivers, project staff, clinicians, biostatisticians, and trainees. Before the think tank, biostatisticians will complete preregistered analyses, which will be presented alongside participant feedback and project interest-holder surveys. During the think tank, we will generate a list of hypotheses for how the algorithm can be improved; this list will be narrowed through a systematic process of (1) ensuring each change is supported by more than 2 sources of information (quantitative data, qualitative data, NGC community input, and past literature), (2) evaluating technical feasibility, and (3) ensuring each change is aligned with NGC community priorities. The output of each think tank will be a manuscript submission that justifies specific changes to the algorithm, as well as a preregistration of the resulting optimized algorithm, which will be used to route the subsequent wave of participants to support programs.

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Table 2. Optimal and suboptimal outcome categories across feasibility metrics[a].

Feasibility categories	Desired outcome	Undesired outcome	Outcome coding
Observed feasibility			
Nonattempters	Participants consented and started a support program	Participants consented, but dropped out before starting a support program	Behavior
Noncompleters	Participants started and completed a support program	Participants started a support program, but dropped out before the end of treatment	Behavior
Low general engagement	Participants completed a support program and completed most of the sessions	Participants completed a support program, but did not complete most of the sessions	Behavior
Patient-reported feasibility			
Low general engagement	Participants completed a support program and were highly engaged throughout	Participants completed a support program, but had low engagement throughout	PATT[b] items
Low homework engagement	Participants completed a support program and were highly engaged with homework	Participants completed a support program, but were minimally engaged with homework	Journal log and clinician report

[a]We have retained our original preregistered outcomes but are presenting them via an updated organization.

[b]PATT: Program Acceptability Tool for Telehealth.

Table 3. Optimal and suboptimal outcome categories across acceptability metrics

Acceptability categories	Desired outcome	Undesired outcome	Outcome coding
Patient-reported acceptability			
Low acceptability	Participants completed a support program and found the program fit to be highly acceptable based on their needs	Participants completed a support program, but found the program fit to have low acceptability based on their own needs	PATT[a] total score
Clinician-reported acceptability			
Low acceptability	Participants completed a treatment program, and their clinician rated the treatment program to be a good match based on the participant's needs	Participants completed a treatment program, and their clinician rated the treatment program to be a poor fit based on the participant's needs	Clinician rating
Peer coach-reported acceptability			
Low acceptability	Participants were assigned a peer coach, and their peer coach rated WellCAST to be a good fit based on the participant's needs	Participants were assigned a peer coach, and their peer coach rated WellCAST to be a poor fit based on the participant's needs	Peer coach rating

[a]PATT: Program Acceptability Tool for Telehealth.

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Table 4. Optimal and suboptimal outcome categories across efficacy metrics

Efficacy categories	Desired outcome	Undesired outcome	Outcome coding
Patient-reported efficacy			
Nonresponders	Participants initially demonstrated high needs (per the algorithm), completed a support program, and their needs decreased	Participants initially demonstrated high needs (per the algorithm), completed a support program, and their needs persisted	Algorithm data
Undetected needs	Participants initially demonstrated low needs (per the algorithm), completed a support program, and their needs remained low	Participants initially demonstrated low needs (per the algorithm), completed a support program, and their needs increased	Algorithm data
Clinician-reported efficacy			
Nonresponders	Participants initially demonstrated high needs (per clinician), completed a support program, and their needs decreased	Participants initially demonstrated high needs (per clinician), completed a support program, and their needs persisted	CGI[a]
Undetected needs	Participants initially demonstrated low needs (per clinician), completed a treatment program, and their needs remained low	Participants initially demonstrated low needs (per clinician), completed a support program, and their needs increased	CGI
Peer coach-reported efficacy			
Nonresponders	Participants initially demonstrated high needs (per coach), completed a support program, and their needs decreased	Participants initially demonstrated high needs (per coach), completed a support program, and their needs persisted	CGI
Undetected needs	Participants initially demonstrated low needs (per coach), completed a support program, and their needs remained low	Participants initially demonstrated low needs (per coach), completed a support program, and their needs increased	CGI

[a]CGI: Clinical Global Impression Scale.

Additional information about the think tank and CASCADE method procedures is available on OSF Registries and is being published via separate manuscripts that detail the theoretical impetus, process, and outputs of the think tank process.

Results

The study was approved by the Purdue University IRB on March 3, 2023. The study began its first wave on August 5, 2024, and concluded on January 26, 2024. As of May 31, 2024, 586 participants have completed the virtual prescreening survey. Of those participants, 367 (62.6%) completed screening interviews, and 285 (48.6%) consented to the baseline phase of the study. Figure 3 depicts a CONSORT (Consolidated Standards of Reporting Trials) diagram for additional details regarding initial study enrollment. Data collection is expected to be completed in September 2025, with final study results expected by September 2026; however, the manuscripts will be submitted for publication as data are unmasked across preplanned trial phases.

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Figure 3. CONSORT (Consolidated Standards of Reporting Trials) flowchart for overall study enrollment as of May 31, 2025. LTFU: loss to follow-up.

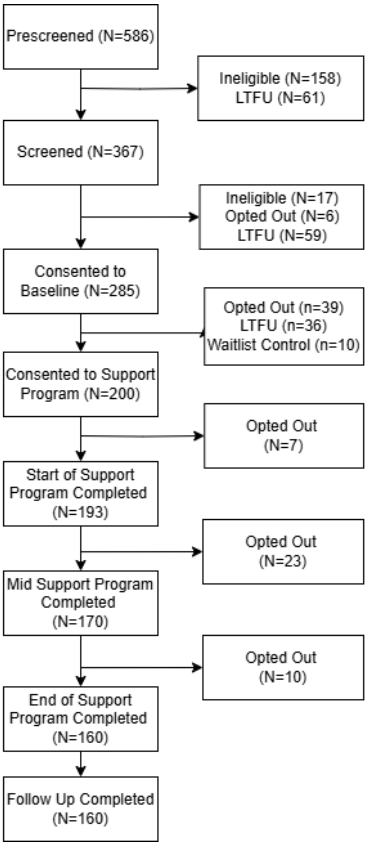

Discussion

Principal Findings

Precision health methods have the potential to improve the feasibility and efficacy of tele–mental health programs for high-need populations, including and beyond NGC caregivers. Project WellCAST tests whether a precision health decision tree algorithm can be developed and used to improve clinical outcomes among NGC caregivers engaging in brief, 12-week, evidence-based support programs. We plan to disseminate trial results through multiple avenues, including publication in peer-reviewed journals, conference presentations, community-based webinars, and other methods as appropriate. It is anticipated that our results will improve understanding of the personal and clinical factors that may predict suboptimal outcomes. If successful, we anticipate Project WellCAST will provide a model for rapidly virtually assessing and triaging populations in need of tele–mental health care, including during future public health emergencies, such as the COVID-19 pandemic.

Several innovations uniquely situate Project WellCAST to contribute to the precision health and psychiatry literatures. First, we use digital health approaches that leverage smartphone-based data to monitor daily fluctuations in symptoms—rather than one-time clinical intake self-report data—providing a more detailed topography of initial patient needs and more sensitive metrics of acute, real-world change over time.

We also leverage community-academic partnerships that provide a scalable, cost-effective model for deploying community-centered interventions while simultaneously training the next generation of mental health providers to deploy digital evidence-based interventions with high-risk populations. To do this, we have aligned multiple digital support programs to a 12-week simultaneous delivery framework, providing a foundation for integrative support programs that can be individualized to families yet delivered with cohesion by trainees.

An additional innovation is that we incorporate extra support elements that we anticipate will boost clinical outcomes for participants who may face further barriers to treatment. For example, we include program options for caregivers experiencing comorbid racial trauma, led by highly qualified experts in the needs of minority families. We leverage community-based partnerships with peer support coaches to deploy evidence-based motivational interviewing protocols to boost program completion and efficacy, while simultaneously maximizing the involvement of patient communities.

These innovations are timely and necessary for NGC caregivers during and after the COVID-19 pandemic; however, this project also has the potential to inform improvements to the long-term landscape for how digital health programs are assigned and deployed far beyond this specific population or public health crisis. Indeed, the high baseline stress and scheduling constraints experienced by NGC caregivers make them an ideal user development group for innovating support program networks that are feasible and acceptable to variety of future users, including those experiencing trauma similar to what was experienced during the pandemic (eg, first responders, teachers, and frontline nurses) or full-time caregivers for other patient

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groups (eg, patients with dementias). In other words, our model, if successful, can be rapidly adapted and scaled to meet the needs of countless special populations as part of both general standard care and crisis response efforts.

Our study may also inform more cost-effective and sustainable clinical trial practices for several reasons. First, the design of the trial is built on community-academic partnerships, where support programs are deployed by graduate student clinicians with appropriate oversight from licensed supervisors. By engaging student-trainees to deploy support programs, we have minimized the overall cost of deploying programs while simultaneously providing high-quality training opportunities, including necessary clinical hours for licensure eligibility, for the next generation of clinicians. More broadly, our study aims to inform how to minimize mismatches between patient needs and provider offerings, which can reduce unnecessary costs associated with ineffective programming and patient attrition. Appropriately matching patients to support programs can save time, money, and frustrations for both the mental health provider and the patient, supporting sustainability and efficiency.

Project WellCAST was also designed to be intentionally *noninnovative* in 1 important way—the support programs being tested are already evidence-based and widely available to the general population. In other words, it is possible that Project WellCAST's 2-week baseline data collection procedure and associated precision health algorithm can improve the field's understanding of how best to route patients to already-available programs in their communities, in line with current directions in precision mental health [14]. For example, our efforts to identify "suboptimal responders" may inform which practical lifestyle factors indicate or counterindicate telehealth-based support programs, which patients may benefit most from additional coaching support, and whether a given patient should be offered mental health support versus parenting coaching. Additional studies on the generalizability of our final decision tree algorithm will be an important interim step toward this goal.

It is important to highlight that we expect Project WellCAST to be a strong match for some participants and a potentially poor match for others. Although telehealth has rapidly expanded in the wake of the COVID-19 pandemic, we and others have continued to caution that telehealth alone will not address the preexisting demographic health disparities that continue to persist across a variety of fields [16]. Our hope is that Project WellCAST can generate the data and results necessary to determine the contexts in which telehealth is most useful [6]. These contributions could be highly clinically relevant for other caregiver groups (eg, other special needs, severe mental illness, and older adults), including those experiencing race-related stress or trauma.

Conclusions

Project WellCAST tests whether a digital personalized health decision tree algorithm and peer coaching protocol can prospectively enhance telehealth program outcomes among NGC caregivers. This project is relevant to the specific population of NGC caregivers and may also inform how brief digital assessments, precision health tools, and community-academic partnerships can enhance public health response to mental health crises across other high-need populations, during and beyond the COVID-19 pandemic.

Acknowledgments

The authors would like to acknowledge the patient communities who funded the initial pilot data for Project WellCAST, including the Angelman Syndrome Foundation, Foundation for Prader-Willi Research, and Williams Syndrome Association. They would also like to thank the families who participated in the iterations of Project WellCAST. Finally, they would like to thank the peer coaches, research assistants, undergraduate and graduate students, community professionals, postdoctoral clinicians, and support staff members who are making Project WellCAST possible. The authors accept full responsibility for activities related to this protocol and trial. Study funders did not participate in any activities. Eligibility for authorship was based on the Authorship Determination Scorecard developed by the American Psychological Association [65].

Data Availability

Deidentified datasets generated during this study are available from the corresponding author on reasonable request. Data access may be requested for eligible studies and qualified researchers for the purpose of addressing specific scientific objectives. A mutually signed data use agreement (nonnegotiable contract for data use and sharing) must be in place before accessing the requested information.

Authors' Contributions

BK was responsible for conceptualization, data curation, formal analysis, funding acquisition, methodology, resources, supervision, writing, reviewing, and editing. KE was responsible for project administration, software, and writing the original draft. LNG was responsible for formal analysis, project administration, writing the original draft, writing, reviewing, and editing. VV was responsible for project administration and supervision. AW was responsible for conceptualization, funding acquisition, and methodology. WF contributed to formal analysis and supervision. DF was responsible for conceptualization, funding acquisition, and supervision. IM contributed to conceptualization, funding acquisition, and supervision. MR was responsible for conceptualization, funding acquisition, and supervision. WM contributed to conceptualization, funding acquisition, and supervision. LM was responsible for conceptualization, funding acquisition, and supervision. SL was responsible for conceptualization and

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funding acquisition. WSN was responsible for data curation. AC contributed to data curation, formal analysis, and software. JB was responsible for conceptualization, funding acquisition, and supervision. LLM was responsible for conceptualization, funding acquisition, and supervision. LB, ES, GD, KP, and EW were responsible for investigation. RN was responsible for investigation and visualization. NH contributed to conceptualization, funding acquisition, and supervision.

Conflicts of Interest

None declared.

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Abbreviations

ACT: acceptance and commitment therapy
CASCADE: community-engaged approach for scientific collaborations and decisions
CONSORT: Consolidated Standards of Reporting Trials
DBT: dialectical and behavioral therapy

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EMA: ecological momentary assessment
HIPAA: Health Insurance Portability and Accountability Act
IRB: institutional review board
NGC: neurogenetic condition
OSF: Open Science Framework
REDCap: Research Electronic Data Capture
RUBI: research units in behavioral intervention
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
WellCAST: Supporting Well-Being of Caregivers via Telehealth

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Protocol

Measuring Stress Reduction in Patients Receiving Multimedia Entertainment During Vascular Surgery Under Regional Anesthesia: Protocol for a Randomized Controlled Study

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Abstract

Background: This study explores the treatment of internal carotid artery stenosis in patients with a high risk for cardiovascular events. The use of regional anesthesia permits ongoing neurological monitoring and enhances patient safety during the procedure. However, the operation can be stressful and lengthy, highlighting the need for strategies to alleviate patient discomfort. This study evaluates audiovisual distractions such as video goggles to potentially improve patient experiences during carotid surgeries, a topic that has not yet been comprehensively researched.

Objective: We aimed to (1) determine whether there is a benefit for patients regarding stress reduction when using video goggles during vascular surgery of the carotid artery and (2) determine whether any parameters can effectively measure such a potential benefit.

Methods: This prospective, randomized study at the University Hospital Augsburg is evaluating the use of HappyMed video goggles by patients undergoing carotid endarterectomy under regional anesthesia. Participants are randomized into either the intervention group, which receives the video goggles, or the control group, which does not. The surgical and anesthetic procedures remain consistent across both groups. Patients are eligible if they meet the surgical criteria, are able to lie supine, and are cooperative. Patients are excluded if they are receiving corticosteroids, have dementia, or have a language barrier. The study uses questionnaires and vital/laboratory parameters, including cortisol levels and heart rate, to assess stress and anxiety. To monitor potential motion sickness, the occurrence of nausea or vomiting is documented. Both patients and surgical staff will evaluate the experience postoperatively to determine the goggles' impact on patient experience and stress management during surgery.

Results: The study has been approved by the local ethics committee and is registered at ClinicalTrials.gov. Patient inclusion started in September 2022 and should be completed within 3 to 4 years. This paper presents a study protocol that was finalized and approved by the local ethics committee in September 2022. At the time of this protocol's final submission for publication, approximately 90% of the recruitment had been completed. Following completion of recruitment and data acquisition, the results are intended to be published within one year.

Conclusions: This study aims to improve patient comfort and perioperative care during vascular surgery. Therefore, our study aims to investigate if the use of video goggles during surgery is feasible and if there are parameters that indicate a benefit for patients. This study is being conducted as a pilot trial to provide a foundation for future research aimed at improving patient comfort during carotid artery surgery under local anesthesia.

Trial Registration: ClinicalTrials.gov NCT06704230; https://clinicaltrials.gov/study/NCT06704230

International Registered Report Identifier (IRRID): DERR1-10.2196/70597

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KEYWORDS

audiovisual distraction; arteriosclerosis; video goggles; vascular surgery; patient comfort

Introduction

Atherosclerosis and macroangiopathy of the internal carotid artery are common conditions in patients with elevated cardiovascular risk. Treatment of internal carotid artery stenosis is often conservative, involving risk factor modification and medication. However, when a certain degree of stenosis is reached or symptoms suggestive of stroke are present, thrombendarteriectomy and revascularization is indicated. Revascularization can be performed either through interventional angiography with stent placement or open surgical endarterectomy [1-3]. The operation is frequently carried out under regional plexus anesthesia, which allows the patient to be awake and enables continuous neuromonitoring. This approach offers the advantage of monitoring for neurological changes during carotid artery clamping, allowing the surgical team to immediately respond, for example, by placing a shunt system to ensure cerebral antegrade perfusion [4]. As a result, regional anesthesia provides a benefit during surgery. However, for patients, the procedure, which can last up to 2 hours or more in some cases, may pose a significant burden. The fixed position, inability to move, sterile drapes over the face, manipulation by the surgical team, and anxiety about potential complications are just a few of the factors that may distress patients during this operation [4]. All in all, studies of operations with local or general anesthesia show that neither technique has any advantage over the other [4]. Both types are carried out frequently. Increased sweating and reports of substantial subjective distress are not uncommon if the procedure is performed under local anesthesia. To the authors' knowledge, there have been no previous attempts to quantify stress parameters or to reduce stress in these patients.

In many medical fields, devices and therapies are now being used to reduce patient stress in the perioperative setting. In procedures performed under local or regional anesthesia, such as in orthopedics or dentistry, efforts are being made to make operations more tolerable and less stressful for patients [5-7]. For example, music and video goggles can be used to entertain and distract patients during the intervention. Several studies have shown that music can significantly reduce patients' anxiety, stress, and perception of pain [6,8]. These applications, however, are often limited to dental or pediatric patients [9,10]. In these patient groups, a need for anxiety reduction is understandable, as many individuals find dental treatment stressful. Nonpharmacological sedation or improving the experience for children is highly justifiable. Newer approaches using video goggles appear in more and more fields, but good systematic randomized studies have not yet been performed. In vascular surgery, particularly carotid surgery, the use of audiovisual distraction during the procedure has not been implemented, to our knowledge, and its potential benefits remain undocumented. Because of the special setting of the surgery and the burden on patients, it is necessary to analyze the use of audiovisual distraction devices in carotid surgery. This study aims to demonstrate the feasibility and potential patient benefit of using video goggles in vascular surgery, particularly during carotid procedures. Additionally, we seek to assess a range of parameters that may be suitable for capturing such effects.

Methods

Trial Design and Study Population

In this prospective, randomized study, the use of the HappyMed video goggles (HappyMed GmbH) will be evaluated in patients undergoing carotid endarterectomy under regional anesthesia. The study is being conducted as a single-center study at the University Hospital Augsburg (Augsburg, Germany) in collaboration with the departments of vascular surgery and anesthesiology. Patient acquisition started in September 2022 and should be completed within three years. All patients scheduled for the abovementioned procedure who meet the inclusion criteria are informed about the study and invited to participate. Upon agreeing to participate, patients are randomized according to a predefined list, assigning them to either the intervention group (with video goggles) or control group (without video goggles). The surgical procedure is identical for both groups, and the study does not influence the operative or anesthetic management of the patients.

Ethical Considerations

Informed consent for the study is obtained during preoperative preparation, separate from the surgical consent process, to ensure that patients clearly distinguish between their participation in the study and the surgical procedure. The study was submitted to the responsible ethics committee (Ethikkommission Ludwig Maximilians Universität München, Germany) for review and has been approved (reference number 21-1199). Both the sponsor (University Hospital Augsburg) and the funder (HappyMed GmbH) have no direct influence on data management or the publication of the study results. All data are fully anonymized and treated confidentially; no data will be shared with third parties. No compensation was provided to participants.

Inclusion Criteria

Patients are included who undergo carotid endarterectomy under regional anesthesia. For anesthesia, a cervical block is used. To qualify for the study, patients must meet the clinical requirements for the surgery, be sufficiently oriented and cooperative, and be able to lie supine for the duration of the procedure.

Exclusion Criteria

Exclusion criteria include current corticosteroid use or medications affecting cortisol levels, as well as patients with insurmountable language barriers that would impair understanding of the questionnaire. Additionally, patients with

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severe dementia or lacking the capacity to provide informed consent are excluded.

Secondary Exclusion Criteria and Adverse Events

Patients who withdraw consent after enrollment will be excluded from the study. If complications arise during surgery requiring conversion to general anesthesia, patients will also be excluded.

Randomization

Patient randomization follows a predefined list based on patient ID, assigning them to either the control or intervention group. The list is followed sequentially, and random assignment to either the intervention or control group is performed using Microsoft Excel. The randomization scheme is constructed to ensure a 1:1 allocation ratio (50-50) upon reaching a total sample size of 100 patients. Due to the nature of the intervention, blinding of participants and investigators is not feasible.

Sample Size Estimation

Due to the exploratory nature of the study, no formal sample size estimation was performed. There are no other studies covering this topic. Therefore, there are no data available on how great a relevant effect should be, nor on how large the sample size should be. The goal is to use this study and its preliminary results as a basis for initiating a confirmatory trial. With a sample size of 100 patients, the sample should be big enough to provide an overview on the possible characteristic values.

Interventions

The intervention group will receive perioperative video goggles with an audio system designed to distract patients from the surgical process and enhance their experience. The video goggles will display various nature scenes accompanied by soft music. Patients can choose from a variety of preloaded content. The device meets the requirements of the Medical Device Directive 93/42/EWG and the Austrian Medical Devices Act. The anesthesiologists, who are primarily responsible for helping the patients use the goggles, received brief online training on how to operate the device. To minimize potential confounding factors, intraoperative management is performed by a small and experienced team of anesthesiologists. Figure 1 shows the timing and parameters that will be measured during surgery.

Figure 1. Timing and measured parameters during surgery. The intervention group uses the goggles during the time indicated by the red line. KAB: Kurzfragebogen zur aktuellen Beanspruchung (German for "short questionnaire for acute stress"); OR: operation room; RASS: Richmond Agitation Sedation Score; STAI: State-Trait Anxiety Inventory.

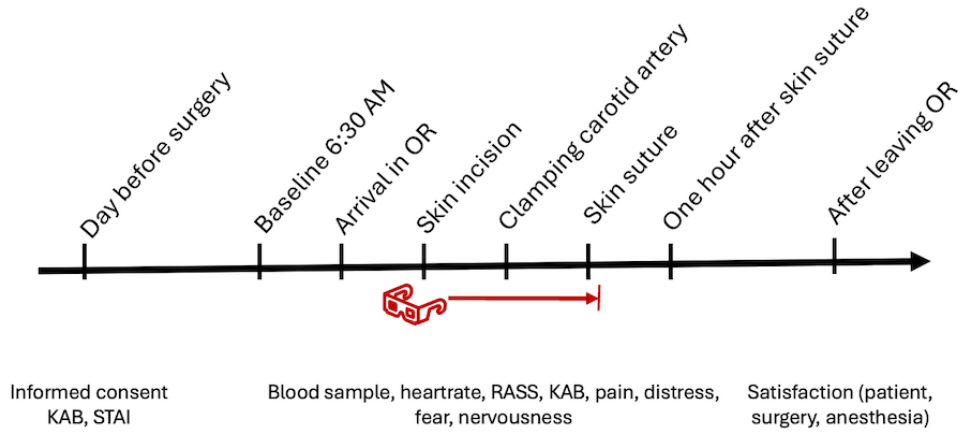

Assessment of Distress

To assess patient stress, questionnaires and vital/laboratory parameters will be used. The day before surgery, after they provide informed consent, the patients will complete initial questionnaires. These include the Spielberger State-Trait Anxiety Inventory (STAI; Hogrefe Verlag), which measures both "trait anxiety" (a general predisposition to anxiety) and "state anxiety" (anxiety related to the current situation, ie, the upcoming surgery) [11]. This questionnaire is often used to measure anxiety and is seen as an indicator of distress. The score is used in many types of analysis, although the trait sections of the STAI are believed to measure negative affectivity rather than trait anxiety per se [12,13]. Additionally, patients will complete the Kurzfragebogen zur aktuellen Beanspruchung (KAB; German for "short questionnaire for acute stress"), which will be repeated perioperatively multiple times to assess changes in response patterns [14]. The focus will be on individual stress trajectories and differences between the control and intervention groups.

For a more objective measurement of stress, the cortisol level in the serum is measured by taking blood samples at multiple times (at baseline, arrival in the operation room, skin incision, clamping the carotid artery, skin suture, and 1 hour after skin suture). Baseline measurements are all taken under consistent conditions: the same time of day before the patient rises from bed. Resting heart rate, KAB score, and the Richmond Agitation-Sedation Scale (RASS) score will be evaluated simultaneously with blood sampling. Cortisol levels are a common tool to measure stress in acute situations [15-17]. The RASS, commonly used in anesthesiology and intensive care, will be used to estimate patients' agitation and provide insight into their stress levels [18]. Heart rate and RASS scores serve as objective measures of patient stress, while the KAB reflects patients' subjective burden across 6 categories. This score is frequently used in psychology to capture current stress levels and is well suited for perioperative use due to its ease of administration. The differences in serum cortisol levels between the groups are considered the primary end point. All other measurements are secondary end points.

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Assessment of Usefulness and Practicality

Postoperatively, the patients and the surgical team (the first surgeon and attending anesthesiologist) will complete a satisfaction survey using a 10-point numerical rating scale (NRS). Surgeons and anesthesiologists will rate the patients' manageability, relaxation, and calmness during surgery. Patients will also rate the satisfaction and anxiety they experienced before and during surgery on a 10-point NRS scale. Patients in the video goggle group will be asked if they would choose to use the goggles again in a potential follow-up operation (as a dichotomic yes/no question). Motion sickness when using the goggles, a significant issue associated with immersion in virtual reality, will be assessed.

Outcomes

Primary Feasibility Outcomes

Patients who meet the inclusion criteria and agree to participate are enrolled in the study. Patients who meet the criteria but decline participation are counted anonymously, with differentiation between those who refuse and those who are excluded for other reasons (eg, language barriers, profound hearing impairment, dementia, or logistical challenges). After the operation is completed and the patient leaves the wake-up room, all data are checked for completeness, and an attempt is made to fill in any missing data. If there any adverse events or remaining missing data, or if the patient withdraws consent to participate in the study, the collected data are excluded from analysis. Because of the very short time from patient inclusion to complete data collection for each patient and because there is no follow-up after the initial inpatient stay, we assume that this method will yield mostly complete records.

Clinical Outcomes

In addition to patient satisfaction, anxiety before and during surgery will be assessed. Comparison of patient satisfaction and anxiety measures between the intervention and control groups will be conducted. Additionally, patients in the intervention group will be asked at the end of the operation day whether they would choose to use the goggles again during potential follow-up surgery. For these patients, the average STAI score will be compared between those who would opt to use the goggles again and those who would not. Furthermore, comparisons of the recorded vital parameters and scores at different time points during surgery will be made between the control and intervention groups.

Data Collection and Management

Missing data are not expected; however, if data are incomplete for a participant, the participant will be excluded from the analysis. Group allocation and reasons for exclusion will be reported transparently to minimize the risk of bias. Due to the pilot nature of the study, no imputation is planned.

Patient-specific data and collected parameters are recorded on paper case report forms and later manually entered into a Microsoft Excel database. The complete dataset will be transferred to an SPSS (version 28, IBM Corporation) database for analysis. Digital data are stored in a folder with restricted access on a protected server of the University Hospital Augsburg. Paper-based data are stored in a locked office at the study office. Final data access is only granted to primary investigators.

Planned Analysis

The analysis will be conducted using SPSS. Due to the study's exploratory nature, descriptive statistics will be applied. Appropriate measures of central tendency and variability will be used depending on the level of measurement. Graphical representations will be made using line graphs or box plots.

Results

The study is registered on the ClinicalTrials.gov platform (NCT06704230). Patient recruitment commenced in September 2022 and should be completed within 3 to 4 years. At the time of this protocol's final submission for publication, approximately 90% of the recruitment had been completed. After the including the 100th patient, the acquired data will be analyzed and the results will be published in a peer-reviewed journal within one year.

Discussion

Summary

To our knowledge, this is the first study to investigate the perioperative use of video goggles in patients undergoing carotid surgery under local anesthesia. Audiovisual distraction is commonly used in surgical procedures performed under local or regional anesthesia to reduce patient stress and discomfort [8,19,20]. This, in turn, may lead to reduced use of analgesics and sedatives, thereby minimizing the risk of complications and overdose [21]. In addition, such interventions can facilitate outpatient procedures, allowing patients to be discharged shortly after treatment without the need for extended postoperative monitoring because of sedation.

In vascular surgery—particularly carotid endarterectomy performed under local anesthesia—continuous monitoring of the patient is essential to detect signs of cerebral hypoperfusion when the carotid artery is clamped. Local or regional anesthesia thus provides an advantage [22]. However, for the patient, undergoing surgery in the neck region can be physically and psychologically challenging, as they must remain in a fixed position on the operating table for approximately 2 hours while being covered by a sterile drape, which is placed closely over the patient's face and cannot be repositioned without risking a breach of sterility. Patient stress during procedures under local anesthesia can also pose a challenge for the clinical team and affect surgical outcomes. The current literature does not indicate a significant overall benefit of one anesthetic technique over the other in carotid endarterectomy; thus, the decision should be individualized [4]. This study aims to assess the feasibility of using video goggles during such procedures and to evaluate their potential in reducing patient-reported stress levels. Furthermore, there is currently no tool to predict which patients may benefit from the use of video goggles and which may not.

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Strengths, Limitations, and Dissemination

To evaluate patient stress, we use a multimodal approach that includes objective and subjective parameters. Serum cortisol levels serve as the primary objective marker, complemented by heart rate monitoring and the RASS. Additionally, the KAB questionnaire was used to assess patient-perceived stress. All parameters were recorded at multiple time points before, during, and after the operation, enabling a comparative analysis comparing the intervention and control groups.

Drug administration was meticulously documented, as medications could potentially confound the measured parameters. Although the sample size is limited, which may preclude statistically significant findings, and this is a single-center study, which means that just one device in one specific procedure is evaluated, the study primarily aims to assess the feasibility and acceptance of video goggles by patients, anesthesiologists, and surgeons, as well as to identify robust parameters for future research. By publishing our findings in a peer-reviewed journal, we hope to provide a basis for further research in this field and to promote enhanced approaches to perioperative stress reduction in patients undergoing carotid surgery under local anesthesia. In future work, a potential third group using music as a distraction tool could be explored.

Conclusions

This pilot study explores the implementation of video goggles during carotid surgery under conscious sedation and aims to identify suitable outcome parameters for evaluating this interventin's potential benefits in reducing perioperative stress.

Acknowledgments

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Authors' Contributions

TPM, KG, AH-D, and HK contributed equally to generate this protocol. HK drafted the manuscript. TPM, KG, and AH-D critically revised the manuscript for important intellectual content. Final approval of the version to be published was given by all authors. Parts of this manuscript were translated with the help of artificial intelligence and revised by the authors.

Conflicts of Interest

None declared.

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Abbreviations

KAB: Kurzfragebogen zur aktuellen Beanspruchung; German for “short questionnaire for acute stress”
NRS: numeric rating scale
RASS: Richmond Agitation-Sedation Scale
STAI: Spielberger State-Trait Anxiety Inventory

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Protocol

A Personalized, Texting-Based Conversational Agent to Address Sleep Disturbance in Individuals Who Have Survived Breast Cancer: Protocol for a Pilot Waitlist Randomized Controlled Trial

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Abstract

Background: Sleep disturbance is one of the most common health concerns reported by individuals who have survived breast cancer (BC) and is associated with poor quality of life (QoL) and greater mortality after treatment. Cognitive behavioral therapy for insomnia (CBTi) has shown efficacy for improving sleep and QoL for this population. Considered the gold standard for insomnia treatment, CBTi can be delivered remotely, including via digital intervention. Despite the potential for wider dissemination of CBTi via digital means, these modalities have unique challenges, including technology barriers and poor adherence. We developed a conversational agent (CA) to deliver CBTi via a SMS text messaging intervention, supported by mobile-ready web content. Named "Cecebot," this CA delivers sleep education, implements sleep compression, provides just-in-time interventions for sleep-disrupting behaviors, and includes enhanced support for physical activity (PA) beyond what is typically included in CBTi. This represents a novel modality for a CBTi and PA intervention among individuals who have survived BC.

Objective: We aim to examine the safety and acceptability of the Cecebot intervention, developed by an academic partnership between Dr Reding's research team and Moby Inc, for individuals who have survived BC and experience symptoms of insomnia, and to explore its efficacy.

Methods: This trial will recruit 60 individuals who have survived BC and are experiencing moderate to severe sleep disturbance. Participants will be assigned to the Cecebot intervention or waitlist control group at a 1:1 ratio. The treatment group will receive the Cecebot intervention during weeks 1-6 of the study, while the waitlist control condition will receive the Cecebot intervention during weeks 6-12. The Cecebot intervention uses SMS text messaging technology paired with a Fitbit. Participants will be assessed at baseline, week 6, and week 12. Measurements will include feasibility and acceptability and will explore the effect of the Cecebot intervention. Feasibility will be assessed through recruitment, enrollment, and retention rates. Acceptability will be evaluated using a satisfaction survey and open-ended responses. Quantitative analysis, such as *t* test, Fisher exact tests, and generalized linear models, will be used to assess feasibility, baseline group differences, and the outcomes of the intervention.

Results: Recruitment of participants began in Fall 2024. The completion of data collection is anticipated to be by Fall 2025.

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Conclusions: The study results will give insight into the potential for an SMS text messaging–based CA to improve sleep in individuals who have survived BC and experience sleep disturbances.

Trial Registration: ClinicalTrials.gov NCT06392789; https://clinicaltrials.gov/study/NCT06392789

International Registered Report Identifier (IRRID): DERR1-10.2196/62712

(JMIR Res Protoc 2025;14:e62712) doi:10.2196/62712

KEYWORDS

breast cancer; conversational agent; sleep disturbance; randomized controlled trial; cognitive behavioral therapy for insomnia; physical activity

Introduction

Background

More than 4 million women with a history of breast cancer (BC), often termed individuals who have survived BC [1], are estimated to be living in the United States today [2]. Though improved BC treatments are contributing to increased survival rates, one-third of these individuals endure long-lasting side effects, such as fatigue and depression [3]. Sleep disturbance is one of the most common effects, with more than 50% of people who have survived BC experiencing sleep disturbances after treatment [4-6]. Lower sleep quality is associated with worse psychosocial outcomes, more severe symptoms of fatigue and pain, and a greater need for supportive care [4].

Cognitive behavioral therapy for insomnia (CBTi) is recommended as a first-line treatment for insomnia symptoms since it is safe and effective, exhibiting robust and persistent reduction in symptoms of insomnia and quality of life (QoL) improvements for individuals who have survived BC in well-designed clinical trials [7-9]. However, the need for treatment exceeds the availability of trained CBTi providers [10], and implementation at a large scale is relatively expensive. Patient burden is a critical concern, as poor sleep and fatigue may interact with practical and motivational barriers to limit engagement with standard CBTi, particularly after BC and treatment [11]. Digital health modalities may offer less burdensome and more scalable intervention opportunities, which may be particularly useful for people with barriers to traditional health care. However, intervening via remote telemedicine has limitations. Technological barriers (eg, incompatible hardware, software, connectivity, or scheduling) can prevent access to the intervention, and remote digital modalities generally entail a more self-directed experience than one with a live therapist or coach [12].

We developed a CBTi intervention delivered via SMS text messaging that is supported by mobile-ready web content. Named Cecebot, the 6-week intervention takes the form of a rule-based conversational agent (CA) and integrates passive data collection from Fitbit and active collection from participants. CAs offer the opportunity for more accessible and personalized digital health tools, which may promote participant retention and intervention effectiveness while remaining scalable and cost-efficient [13].

Study Objectives

The objectives of this pilot randomized trial are (1) to examine the acceptability of the Cecebot intervention and the feasibility of the clinical trial for individuals who have survived BC with chronic moderate-to-severe insomnia and (2) to explore the efficacy of Cecebot for reducing insomnia symptoms, improving QoL, increasing physical activity (PA) frequency, reducing symptoms of depression, and decreasing fatigue.

Methods

Study Overview

The study is a fully remote, 12-week, 2-arm pilot randomized controlled trial (RCT; N=60) for women with early-stage BC who have completed BC treatment and are experiencing moderate sleep disturbance (refer to Figure 1 for the study schema). Preliminary acceptability, feasibility, and efficacy of the 6-week Cecebot intervention will be assessed in comparison to a passive waitlist control group with 1:1 assignment of intervention to control.

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Figure 1. Flow diagram of Cecebot trial design. QoL: quality of life.

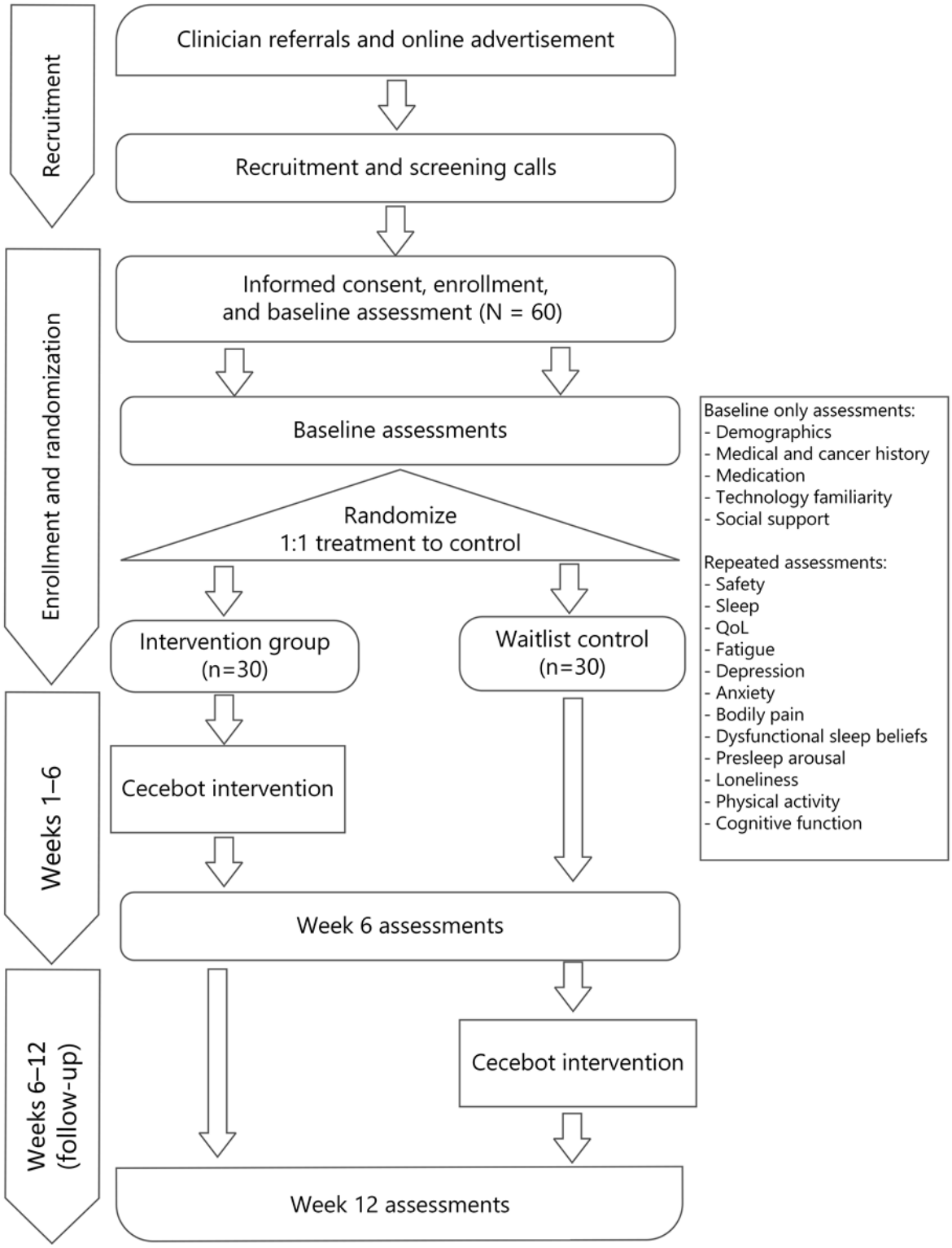

All participants will receive the full intervention. The treatment condition will use Cecebot from weeks 1-6, and the waitlist control condition will receive the intervention during weeks 7-12. All participants will complete outcome measures remotely via a secure web form at baseline, 6 weeks, and 12 weeks. This protocol follows the CONSORT‐EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) (refer to Multimedia Appendix 1 for the checklist) and SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (refer to Multimedia Appendix 2) [14,15].

Study Population and Recruitment

This study will recruit 60 participants through a multipronged approach. The primary methods will be via provider referral from oncology clinics, recontact of previous study participants in unrelated BC research projects, medical record invitation, and web-based advertising. Candidate participants will initially

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complete a secure web-based screening survey to assess basic eligibility criteria. Those who are eligible after the first pass will be asked further screening questions by phone with trained staff to assess more sensitive eligibility, such as psychiatric comorbidities. All eligibility criteria will be self-reported, with some assessed via validated clinical assessment (eg, current insomnia) and others with self-report of past or current diagnosis (eg, noninsomnia sleep disorder). The inclusion and exclusion criteria are listed in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Age ≥18 years.
- Diagnosis of stage I-III invasive breast cancer in the previous 5 years.
- Female gender.
- Clinically significant insomnia symptoms, defined as a T-score ≥55 on the Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance 8a.
- Self-report of insomnia symptoms lasting ≥3 months.
- Eastern Cooperative Oncology Group (ECOG) performance status of 0-2, indicating the ability to perform activities of daily living.
- Owns a smartphone with internet connectivity.
- Proficiency with written and spoken English.
- Willing and able to complete the intervention with their smartphone.

Exclusion criteria

- Self-report of a prior diagnosis of restless leg syndrome, periodic leg movement disorder, narcolepsy, or rapid eye movement behavior disorder.
- Current high risk for sleep apnea, assessed with modified STOP (Snoring, Tiredness, Observed apnea, and high blood Pressure) criteria.
- Current shiftwork or regular environmental disturbance (eg, infant child).
- Actively receiving chemotherapy or radiation (endocrine therapy permitted) or plans to receive chemotherapy, radiation, or surgery in the next 6 months.
- Contraindications to cognitive behavior therapy for insomnia include self-report of active psychosis, uncontrolled bipolar disorder, active suicidality, active substance use disorder (moderate or greater severity, as identified by the Tobacco, Alcohol, Prescription medication, and other Substance), or severe depression defined as the 8-item Patient Health Questionnaire (PHQ-8) depression scale ≥20.
- Use of prescribed sleep medication >3 times per week.
- Previously received cognitive behavior therapy for insomnia with a professional therapist.
- Previously participated in user testing of Cecebot.
- Unwilling or unable to complete study procedures.

Because Cecebot is a self-directed, text-based digital intervention, we expect that both reading skills and resource access are important facilitating factors for benefiting from the intervention. These factors are influenced, at least in part, by education, but most digital health versions of CBTi have been tested in highly educated populations. To investigate the feasibility and acceptability for people with less education, we aim to enroll a sufficient proportion of participants (50%) who do not have a bachelor's degree.

All eligible participants will provide informed consent before the collection of baseline data. Following baseline data collection, participants will be randomly assigned to the intervention or the waitlist control group at a 1:1 ratio. Permuted block randomization will be used, stratified by whether participants are older than 55 years and whether they have a bachelor's degree. The random allocation procedure will be conducted using the randomization module in Research Electronic Data Capture (REDCap), developed by Paul A Harris at Vanderbilt University, by qualified and trained research staff.

Intervention Overview

The 6-week Cecebot intervention is based on the core content of CBTi and uses Go! To Sleep, a 6-week self-directed web version of CBTi [16] previously developed by Dr Michelle Drerup that has enrolled over 1500 patients with insomnia. Cecebot was developed with an iterative design process that involved recruiting individuals who have survived BC and conducting multiple rounds of interviews and user testing to tailor the intervention for this population. Preferences for format, features, and content were solicited in focus groups (n=13, 3 groups) and individual interviews (n=3) to inform the initial design, after which a 1-week prototype version was developed and subsequently tested by individuals who have survived BC to elicit feedback. This feedback was synthesized and used to develop the full 6-week intervention.

Cecebot interacts with participants via SMS and is supported by mobile-ready web content. There are four core components: (1) tailored CBTi education delivered through SMS conversations and supporting web content (refer to Figure 2),

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(2) implementation of a sleep compression protocol based on web-based daily sleep diaries, (3) passive PA tracking via a consumer-grade activity tracker worn 24/7 during the intervention, and (4) accountability for sleep and PA behavior change using individually tailored messages. Cecebot is written in English, and the language is designed to be conversational, uncomplicated (approximately seventh-grade reading level), and empathic to facilitate accessibility by a broad audience and to minimize the cognitive burden of engaging in the intervention.

Figure 2. Example message of Cecebot.

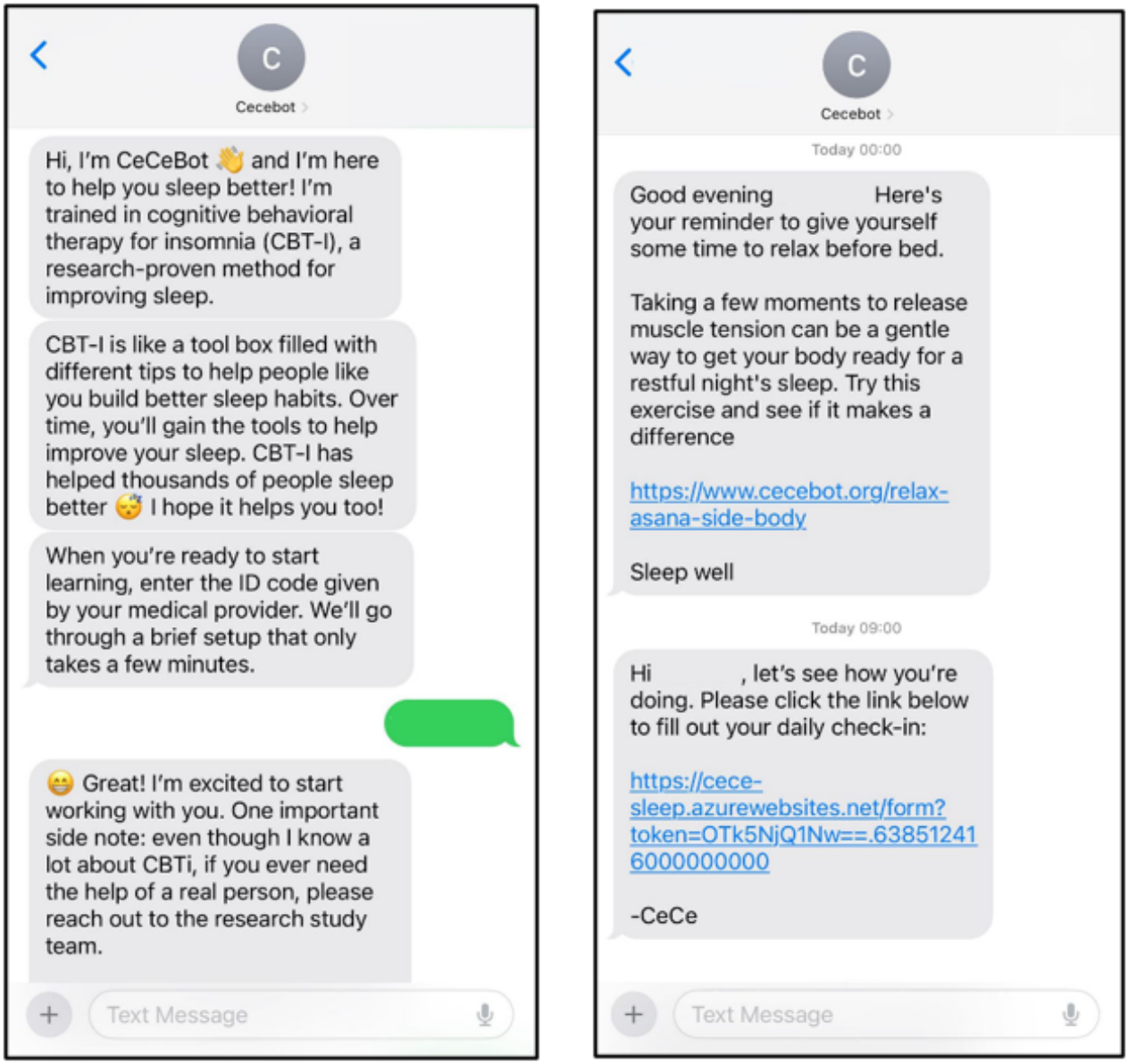

The education component focuses on core CBTi concepts (eg, the 3P model, stimulus control, sleep hygiene, sleep-related cognitions, and relaxation) delivered via SMS modules 2-4 times a week. Each educational component is designed to be completed in approximately 10 minutes (Table 1 and Figure 3 [17]). In total, there are 20 modules delivered over 6 weeks (42 days). These modules are pseudo-conversations, where Cecebot presents information in a conversational tone and often asks the participant a reflective question, which can be answered with a free response. Cecebot gives the same response regardless of participant input. Web content is provided as a link within most conversations and offers additional details for the concepts presented via text. All supporting web content is designed to be accessed on a mobile device. Over 25% of the education modules that present new information have a tailored component. These modules provide additional content based on participant answers provided during an "intake" conversation completed with Cecebot at the beginning of the intervention. For example, participants are asked about common dysfunctional sleep beliefs, such as "When I feel tired, have no energy, or just seem not to function well during the day, it is because I did not sleep well the night before." Endorsing a specific dysfunctional belief tailors a later education conversation to specifically address that belief. Sleep compression, a less intensive version of the sleep restriction therapy that is part of CBTi, is algorithmically implemented in once-per-week SMS conversations based on sleep efficiency and sleep need over the past week, which are calculated from sleep diaries submitted

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daily by each participant [18]. Cecebot tracks items on the 4-item Sleep Need Questionnaire over each 7 days so that sleep needs can be used for the algorithm [19,20]. If a participant's sleep efficiency is less than 85%, Cecebot recommends reducing time in bed by 30 minutes. If a participant's sleep efficiency is greater than 85% but they have high sleep needs, Cecebot suggests increasing time in bed by 30 minutes. Sleep compression is considered low risk with minimal side effects, making it a better fit for an unsupervised digital intervention than sleep restriction.

Table 1. Cecebot education module schedule and conceptual areas addressed.

Conceptual area and module title	Timing of the module within the intervention	
	Week	Day
Insomnia basics in the context of cancer		
"The Insomnia Cycle" (3P model)[a]	1	1
Sleep drive	1	2
Stimulus control	1	3
Sleep compression	1	6
Sleep hygiene and physical activity		
Take a time-out	2	2
Sleep and physical activity	2	3
Sleep or wake clock	2	5
Sleep hygiene	2	7
Review		
Review week 1	3	2
Managing barriers		
Managing sleep barriers[a]	3	4
Physical activity barriers[a]	3	6
Cancer-related barriers[a]	4	2
Addressing anxiety and restructuring cognitive		
Helpful worry time	4	3
Changing thought patterns[a]	4	5
Gratitude and sleep	4	7
Physical activity and sleep	5	2
Review		
Review week 1	5	5
Review week 3 and 4 content	6	2
A postintervention action plan		
Physical activity action plan	6	4
Sleep action plan	6	7

[a]Indicates a tailored module.

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Figure 3. Conceptual model of insomnia in breast cancer and the intervention effects of Cecebot (adapted from Levenson et al [17]).

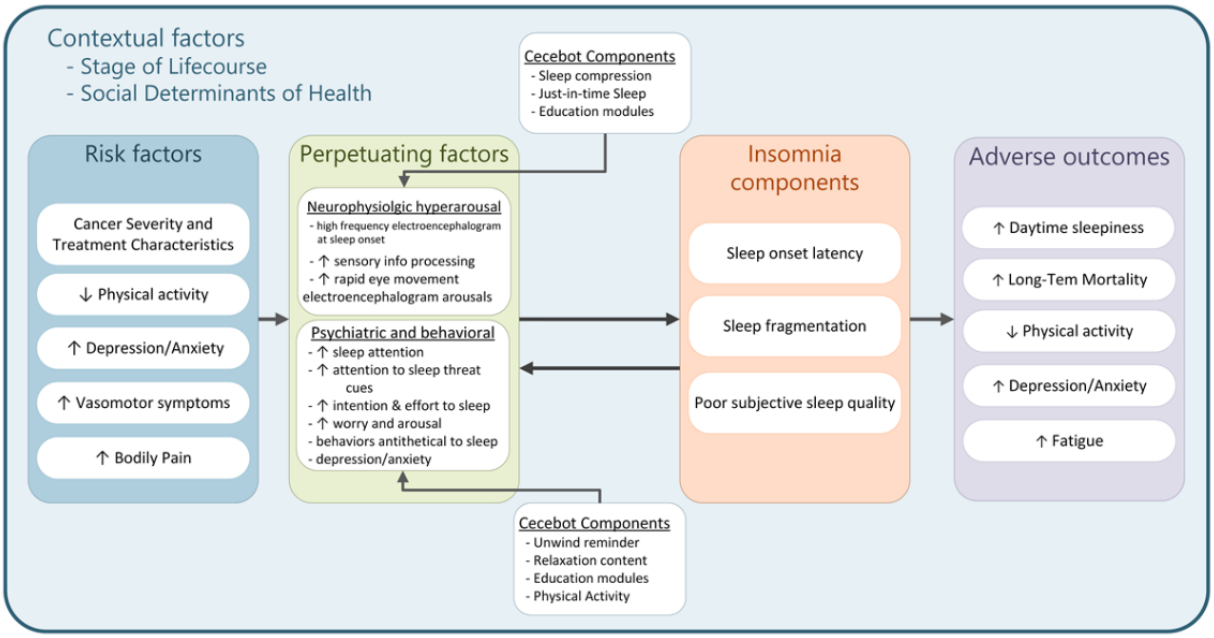

In addition to 4 tailored sleep modules, one tailored module addresses barriers to PA experienced by the participant. This module supports the PA content and motivation offered in Cecebot, which is augmented beyond what is typically provided in standard CBTi. Though a causal link between increased PA and improved sleep is not firmly established, interventional evidence from individuals who have survived BC suggests PA interventions can reinforce improved sleep quality [21]. This evidence, along with the benefits of PA on fatigue and fitness for this population, justifies increased attention on PA within the intervention.

The enhanced PA focus of Cecebot is supported by integration with a Fitbit consumer activity tracker (Fitbit Inc). Cecebot uses the Fitbit application programming interface to collect participant step count, heart rate, and sleep data regularly. Participants can request a summary of their previous week's step count at any time and receive a summary at each weekly check-in. Passive activity tracking also supports Cecebot's just-in-time (JIT) functionality. JIT behavior interventions aim to provide microinterventions with temporal relevance to the behavior being changed or initiated [22]. Cecebot checks PA levels every 4 days and sends unique messages based on the mean 4-day step count observed—a low step count (<2000/d) prompts a message suggesting initiation of brief activity, while a high step count (>8000/d) prompts congratulations, and a middle-range step count (>6000/d) prompts a message nudging the participant toward increased PA. The PA JIT messages pair with weekly PA feedback and with PA education. The Cecebot website, maintained by the study, contains videos of workout routines tailored for individuals who have survived BC, led by a trained instructor.

Cecebot also provides sleep-specific JIT messages on a 4-day cycle. Participants endorse sleep-related behaviors from the previous day as part of each web-based daily sleep diary. The behaviors that can be tracked include sleep-promoting behaviors such as relaxation or a prebed routine, as well as sleep-disrupting behaviors such as late afternoon caffeine or nighttime alcohol. If a participant endorses a sleep-disrupting behavior on 2 or more days in 4 days, Cecebot sends a message aimed at intervening on the behavior. If more than one behavior is endorsed 2 or more times in the 4 days, the intervening message is tailored to the separate behaviors endorsed. These messages are drawn randomly from individual pools of messages that correspond to the behavior targeted for intervention (eg, a pool of caffeine messages).

Cecebot includes an optional prebed relaxation feature. If enabled, Cecebot sends a message 1 hour before the participant's established bedtime to prompt them to begin unwinding and preparing for bed. Each message includes a web link to relaxation content created specifically for the intervention. The content is in audio format, based on feedback garnered from individuals who have survived BC during early rounds of design, which highlighted the potentially sleep-disrupting impact of video before bed. There are over 25 recordings that focus on either mindful meditation, breathing, progressive muscle relaxation, or light stretching.

Measures

Baseline Measures

Following informed consent, enrolled participants will remotely complete surveys via REDCap, a secure data collection portal. Surveys completed only at baseline will collect basic demographics, medical and cancer history, current perceived social support, and familiarity with technology (Table 2). Perceived social support will be assessed with the 19-item Medical Outcomes Study Social Support Survey (MOS-SSS) questionnaire [23]. Technology familiarity will be measured using a short questionnaire developed by the research team. In addition to these assessments, the measures described below will be evaluated at baseline.

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Table 2. Schedule of baseline and outcome measurements.

Outcome	Measure	Week 0 (baseline)	Week 6	Week 12
Baseline only measures				
Demographics	Survey	✓		
Medical history	Survey	✓		
Technology literacy		✓		
Social support	MOS-SSS[a]	✓		
Outcome measures				
Feasibility	Multiple		✓	✓
Acceptability	Multiple		✓	✓
Safety	Interview		✓	✓
Insomnia	ISI[b]	✓	✓	✓
Sleep beliefs	DBAS-16[c]	✓	✓	✓
Presleep arousal	PSAS[d]	✓	✓	✓
Quality of life	SF-36[e]	✓	✓	✓
Fatigue	FACIT-F[f]	✓	✓	✓
Depression	PHQ-8[g]	✓	✓	✓
Anxiety	GAD-7[h]	✓	✓	✓
Bodily pain	PROMIS Interference[i]	✓	✓	✓
Bodily pain	PROMIS Intensity[j]	✓	✓	✓
Cognitive function	FACT-Cog[k]	✓	✓	✓
Physical activity	IPAQ-SF[l]	✓	✓	✓

[a]MOS-SSS: Medical Outcomes Study Social Support Survey.
[b]ISI: insomnia severity index.
[c]DBAS-16: 16-item Dysfunctional Beliefs and Attitudes About Sleep Scale.
[d]PSAS: Pre-sleep Arousal Survey.
[e]SF-36: 36-item Short Form Survey.
[f]FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue.
[g]PHQ-8: Patient Health Questionnaire-8.
[h]GAD-7: Generalized Anxiety Disorder 7-item.
[i]PROMIS-Interference: Patient-Reported Outcomes Measurement Information System Pain Interference.
[j]PROMIS-Intensity: Patient-Reported Outcomes Measurement Information System Pain Intensity.
[k]FACT-Cog: Functional Assessment of Cancer Therapy-Cognition Function.
[l]IPAQ-SF: International Physical Activity Questionnaire-Short Form.

Outcomes

Several hypothesized treatment effects of the intervention will be assessed at each time point to determine the effect of Cecebot on health outcomes. These include insomnia, QoL, PA, depression, anxiety, and cognitive function. In addition, putative treatment mechanisms will be assessed, including dysfunctional sleep cognitions, presleep arousal, and knowledge of CBTi concepts and principles.

Insomnia and sleep quality will be assessed with the insomnia severity index [24] and secondarily with daily web-based sleep diaries delivered through the intervention. The insomnia severity index (ISI) has 7 items (score range: 0-28), with higher scores reflecting more severe insomnia symptoms [25]. To measure treatment mechanisms that may partially mediate the effects of Cecebot, sleep cognitions will be assessed with the 16-item Dysfunctional Beliefs and Attitudes About Sleep Scale (DBAS-16) [26] presleep experience with the 16-item Pre-sleep Arousal Survey (PSAS) [27], and knowledge of CBTi concepts with a 13-item true or false questionnaire designed by the research team.

Quality of life will be assessed with the 36-item Short Form Survey (SF-36) [28], comprised of eight domains covering physical and mental health. Fatigue will be measured using the

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Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) [29], a 13-item survey with scores ranging from 0 to 52, where higher scores indicate greater functional impact of fatigue. Depression will be assessed with the PHQ-8 (8-item Patient Health Questionnaire) depression scale, and anxiety with the Generalized Anxiety Disorder 7-item (GAD-7) scale [30,31]. Higher scores indicate a higher level of depression or anxiety symptoms on these scales. The PROMIS (Patient-Reported Outcomes Measurement Information System)-Pain Interference [32] and PROMIS-Intensity will be used to measure the severity of pain and the influence of pain on their lives. Cognitive function will be measured using the 20-item perceived cognitive impairments subscale of the Functional Assessment of Cancer Therapy-Cognitive Function (FACT-Cog) questionnaire [33]. To assess the safety profile of Cecebot, adverse events will be collected at the 6- and 12-week timepoints with a brief structured interview administered by research staff. Participants will be instructed to report any severe adverse events to the research team during the interim between study visits.

Physical activity duration and intensity over the previous week will be assessed with the International Physical Activity Questionnaire-Short Form (IPAQ-SF) [34] survey. Wrist-worn consumer-grade actigraphy (Fitbit Charge 4, Fitbit Inc) will secondarily be used to assess PA by recording step count and movement pattern. The Fitbit measurement will collect daily reports from participants, and Fitbit metrics will be analyzed for quality control. Only days with greater than 7 hours of wear time will be considered valid.

To assess intervention acceptability and potential areas for improvement, participants will answer survey questions about their satisfaction with Cecebot with a survey developed by the research team, including 11 multiple-choice items and 4 open-ended questions. Since both the intervention and outcome measures are noninvasive, the risk of harm to participants is minimal. If a participant encounters discomfort and requests to withdraw, the research team will record their reason for withdrawal and conduct a safety assessment.

Statistical Analysis

Primary Endpoint and Secondary Endpoints

The acceptability of the Cecebot intervention will be assessed in several ways. The daily sleep diaries will be used as a primary measure of adherence (the proportion of sleep diaries submitted) and treatment discontinuation, which will be defined as no sleep diary submission for 7 consecutive days or logging out of Cecebot. An all-cause discontinuation rate of 40% will be considered a threshold for acceptability. Treatment adherence will secondarily be assessed by comparing participant bedtimes and wake times to recommendations offered by Cecebot and by calculating (1) the proportions of weekly goal-setting conversations completed and (2) reflective prompts replied to within education modules. Qualitative satisfaction will be measured with a structured survey of participant opinions, including Likert scale assessments of satisfaction and opinions about Cecebot, along with open-ended questions allowing free text responses. Free text responses will be coded for themes. The adverse event rate will be another key indicator of acceptability. The number of participants experiencing an adverse event attributable to study procedures will be compared after the first 6 weeks to identify if any detectable differences are present between the treatment group and waitlist control group.

Trial feasibility will be assessed by calculating recruitment rates (proportion of participants enrolled of those approached), enrollment rate (proportion who enroll among those eligible), and loss to follow-up (proportion who do not complete the final study visit).

To determine if group differences are present after randomization, descriptive statistics of baseline characteristics (eg, age, cancer severity, and time since treatment) will be generated, and the treatment and control groups will be compared with *t* tests for continuous variables and chi-square tests for categorical variables. The Fisher exact test will be used for expected cell counts <5.

Exploratory Endpoints

We will conduct an exploratory analysis to investigate the effect of the Cecebot intervention on insomnia and other QoL outcomes. The analysis will analyze the following secondary outcomes: QoL, fatigue, depression, pain, and anxiety. Using generalized linear models to model difference scores, this study will examine the differences between intervention and waitlist control participants. The outcomes will be modeled as continuous variables using the measures described above. These analyses will be performed according to the intent-to-treat principle, where outcomes are analyzed by the intervention assigned, regardless of the level of adherence. The study will examine whether the intervention and control arms differ at baseline on pertinent variables using chi-square tests (for categorical variables) and *t* tests (for continuous variables). All analyses will use α=.05. A secondary per-protocol analysis accounting for adherence differences will be conducted. These results will be reported and interpreted along with the intent-to-treat analysis.

The study is powered to detect a crude effect size (Cohen f^2) [35] of 0.16, which represents a moderate effect [36]. Controlling for baseline confounders (eg, age, race, cancer severity, endocrine or anti-human epidermal growth factor receptor 2 therapy, social support, and technology familiarity) increases the minimum detectable effect size to 0.30, a moderate-to-strong effect. Data analysis will be conducted using R version 4.5.1 (R Foundation for Statistical Computing). Missing data will be addressed using multiple imputations.

Ethical Considerations

The protocol has been approved by the University of Washington institutional review board (19874) and is registered on ClinicalTrials.gov (NCT06392789). All participants are required to complete the informed consent form before participating in the study. The research team will ensure they are fully informed about the objectives and process of the study. All the collected data are securely stored in REDCap, and only authorized research team members have access to the data. Participants will receive a US $25 gift card for each completed study visit (baseline, 6 weeks, and 12 weeks), with a total

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possible reimbursement of US $75 in gift cards. Any significant modifications to the trial protocol will be documented in an amended protocol and submitted to the institutional review board for approval before implementation. Revised protocols will also be submitted to ClinicalTrials.gov. The research team will communicate with participants if applicable.

Results

The final version of the protocol is version 6.0, dated January 31, 2025. Recruitment of participants to the pilot RCT commenced at the University of Washington and Fred Hutchinson Cancer Center in Fall 2024. As of February 25, 2025, this pilot RCT has recruited a total of 20 participants, with 11 participants in the intervention group and 9 participants in the waitlist control group. The completion of recruitment is planned to be completed by fall 2025. The research findings will be disseminated through peer-reviewed journal publications and presentations at academic conferences.

Discussion

Principal Findings

We hypothesize that the Cecebot intervention will improve sleep among individuals who have survived BC without causing any adverse effects, and we anticipate that the research process will be feasible and acceptable. We also expect to receive feedback on improvements and refinements from users. This study will provide useful information regarding the feasibility and acceptability of the Cecebot intervention for this population with sleep disturbance. The results will help define the potential value of an SMS-based CA for individuals who have survived BC. In addition, the data from the baseline, week 6, and week 12 follow-up timepoints will assist in exploring whether the intervention improves sleep quality in this population.

Previous studies have demonstrated that digital CBTi, such as mobile apps, may be beneficial in improving sleep [37,38]. Another randomized controlled trial using internet-delivered CBTi reported a reduction in the severity of insomnia and improved sleep quality among individuals who have survived BC [9]. However, limited studies are using an SMS-based CA in this population with insomnia. Furthermore, most studies of self-directed insomnia have included highly educated populations. Thus, evaluating the feasibility and effectiveness of this intervention, especially among those with less education, is a useful contribution to the area of sleep management during postcancer treatment survivorship. If the Cecebot intervention is proven to be feasible and effective in a future fully powered trial, it holds great potential for dissemination, which could lead to improved sleep quality and QoL for individuals who have survived BC.

Strengths and Limitations

Cecebot is a tailored and SMS-based CA. Compared with traditional and face-to-face CBTi and PA interventions, it requires low resources and is inexpensive to execute. Therefore, this individualized intervention has the potential to be disseminated to a wider population, especially to marginalized groups. A limitation of the intervention is that, with its design as an SMS-based CA, the project cannot directly track how participants interact with Cecebot, as would be more feasible with an app-based solution. Instead, their behavior must be inferred from indicators such as which links were clicked and when. Another limitation is that Cecebot is a self-directed experience, which may be difficult to benefit from for participants with severe insomnia burden, a high burden of other cancer-related symptoms, or limited resource access.

Conclusions

Cecebot is an intervention that overcomes resource-based barriers for marginalized groups via an SMS-based program that can be accessed at any time and place with minimal technological requirements and without the need to see a sleep specialist. This intervention has a high potential for future development, testing, and ultimately dissemination. The current study will evaluate the feasibility and acceptability of the intervention and explore the efficacy of an SMS-based conversational agent in individuals who have survived BC with sleep disturbances.

Acknowledgments

The authors would like to thank the pilot study participants and student groups involved in this research project. Funding for this study was supported by the SWOG-Hope Foundation Impact Award and the Center for Innovation in Sleep Self-Management at the University of Washington School of Nursing. No generative artificial intelligence tools were used for this protocol.

Authors' Contributions

CT contributed to the methodology, original draft writing, review and editing, and visualization. WS was responsible for conceptualization, methodology, project administration, original draft writing, review and editing, and visualization. MD contributed to conceptualization, methodology, investigation, original draft writing, and review and editing. JL, AV, HG, and JH were involved in conceptualization, methodology, and review and editing. RY contributed to the review and editing. KR contributed to conceptualization, methodology, supervision, and review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1

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CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1036 KB - resprot_v14i1e62712_app1.pdf]

Multimedia Appendix 2
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 184 KB - resprot_v14i1e62712_app2.pdf]

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Abbreviations

BC: breast cancer
CA: conversational agent
CBTi: cognitive behavior therapy for insomnia
CONSORT‐EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
DBAS-16: 16-item Dysfunctional Beliefs and Attitudes About Sleep
FACIT-F: Functional Assessment of Chronic Illness Therapy-Fatigue
FACT-Cog: Functional Assessment of Cancer Therapy-Cognitive Function
GAD-7: Generalized Anxiety Disorder 7
IPAQ-SF: International Physical Activity Questionnaire-Short Form
ISI: insomnia severity index
JIT: just-in-time
MOS-SSS: Medical Outcomes Study Social Support Survey

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PA: physical activity
PHQ-8: 8-item Patient Health Questionnaire
PROMIS: Patient-Reported Outcomes Measurement Information System
PSAS: Pre-sleep Arousal Survey
QoL: quality of life
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SF-36: 36-item Short Form Health Survey
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Mobile Health Technology for Personalized Tobacco Cessation Support Among Cancer Survivors and Caregivers in Laos (Project SurvLaos): Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Tobacco use remains a major cause of preventable deaths and evidence suggests that smoking cessation offers considerable benefits for patients with and survivors of cancer. In the Lao People's Democratic Republic (Lao PDR), approximately 60% of male patients and 15% of female patients with cancer smoke cigarettes. Nevertheless, there is no tobacco treatment program for this population.

Objective: This pilot randomized controlled trial (RCT) aims to evaluate the feasibility and preliminary efficacy of our mobile health–based automated treatment (AT) program to help Lao cancer survivors and caregivers quit smoking cigarettes.

Methods: We used an intervention mixed methods research design, which included a pilot 2-group interventional RCT and an embedded qualitative component to explain RCT outcomes. In the pilot RCT, cancer survivors or caregivers (n=80, no dyads) who smoked were recruited from national hospitals in Vientiane. Recruited participants were randomized to 1 of 2 treatment groups: standard care (SC) or AT. SC consisted of brief advice to quit smoking delivered by research staff, self-help written materials, and a 2-week supply of nicotine replacement therapy (transdermal patches). AT consisted of all SC components plus our fully automated, interactive, smartphone-based behavioral treatment program personalized and tailored to cancer survivors or caregivers and delivered by our Insight app. Feasibility outcomes of interest include the percentages of intervention messages delivered and viewed, and participant retention at the 3-month follow-up. The preliminary efficacy outcome is biochemically confirmed self-reported 7-day point prevalence abstinence at 3 months post study enrollment. During the interventional RCT and

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after the 3-month follow-up assessment, we used additional open-ended questions to explore why and how the participants did or did not successfully quit smoking and stay abstinent.

Results: Data collection occurred from April 2022 to May 2023. Outcome analyses are ongoing, and results are expected to be published in 2025.

Conclusions: Our course of research will address the critical need of having a scalable and sustainable tobacco cessation treatment program for patients with cancer and their caregivers in Lao PDR. The preliminary data from this pilot project will lay a foundation for a subsequent fully powered RCT to evaluate the actual efficacy of our mobile health–based AT program. Ultimately, our course of research will contribute to reducing tobacco-related complications in cancer treatments, comorbidities, tobacco-related cancer recurrence, and mortality rates in Lao PDR.

Trial Registration: ClinicalTrials.gov NCT05253573; https://clinicaltrials.gov/study/NCT05253573

International Registered Report Identifier (IRRID): DERR1-10.2196/66517

(JMIR Res Protoc 2025;14:e66517) doi:10.2196/66517

KEYWORDS

smoking cessation; tobacco cessation; tobacco dependence; cancer survivorship; mHealth; Lao People's Democratic Republic

Introduction

Globally, tobacco is responsible for around 6 million deaths annually; 80% of these occur in low- and middle-income countries (LMICs) [1,2]. Tobacco use is the primary modifiable risk factor for cancer prevention and remains a leading cause of preventable deaths [1]. Cigarette smoking prevention and cessation stand out as the most impactful and cost-effective interventions among various evidence-based preventive health services [3]. Despite this critical need, smoking cessation treatments in LMICs are frequently unavailable or unaffordable for the majority of the population [1].

A report of cancer incidence and mortality estimates in 2022 indicated that the Lao People's Democratic Republic (Lao PDR) has the largest age-standardized cancer mortality rate per 100,000 person-years in Southeast Asia [4]. The same report also showed that more than 50% of the new cancer cases (n=9101) in Lao PDR resulted in mortality (6215 cancer deaths). Tobacco smoking prevalence among patients with cancer in Lao PDR is high: 60% in men and 15% in women in our preliminary analysis of data from the Lao National Cancer Center (LNCC) medical records, and up to 87% in patients with lung cancer [5]. Data regarding smoking prevalence among caregivers of Lao patients with cancer are lacking. However, the most recent national survey of the general Lao population indicated that 51% of adult men and 7% of adult women smoke tobacco [4,5], suggesting a potentially equivalent smoking prevalence among caregivers.

Evidence from high-income countries suggests that smoking cessation offers considerable benefits for cancer survivors, including improving cancer treatment outcomes, reducing recurrence rates, reducing second primary tumor development, and reducing overall cancer mortality rates [6,7]. Thus, developing and evaluating a scalable and sustainable tobacco cessation treatment program is essential to improve cancer treatment and survivor outcomes. In addition, for caregivers who smoke, seeing their family members, relatives, or friends combating tobacco-induced cancer and mortality is a teachable moment for the caregivers to quit smoking to protect their own health. When caregivers quit, the likelihood that patients with or survivors of cancer are exposed to second-hand smoking and craving triggers is also reduced; therefore, the journey to quitting smoking among patients with cancer will be more likely to succeed. Despite this need, no widely accessible tobacco treatment programs are available in major (public) hospitals in Lao PDR, including cancer hospitals or related institutions, as confirmed in our discussions with leaders of the LNCC and the National Tobacco Control Committee (NTCC) of Lao PDR. A quit line offering telephone counseling was piloted at the national Mahosot Hospital; however, funding limitations hinder the NTCC's ability to train and retain more counselors for nationwide implementation. Therefore, there is a critical need for an evidence-based and highly scalable tobacco cessation treatment in Lao PDR to prevent smoking-related morbidity and mortality, especially among cancer survivors and caregivers.

The World Health Organization (WHO) acknowledges that mobile health (mHealth) could transform the face of health service delivery across the globe, including delivery in the lowest-income countries [8]. Data from the Lao government's Statistics Bureau show that 96% of Laos' population subscribed to a mobile phone plan in 2022 [9]. Although Laos is among the lowest-income countries [10], 100% of the Lao urban districts and 96% of the rural villages are covered by a mobile-cellular network [9]. These provide an ideal yet largely untapped mechanism to deliver smoking cessation treatment in Lao PDR. A small but growing body of research indicates that mHealth interventions are feasible in Lao PDR [11-13]. The Lao Ministry of Health's (MOH's) receptiveness and support of mHealth solutions in these studies increase the potential for sustainability and widespread adoption of our proposed mHealth intervention approach. The effectiveness of smoking cessation interventions using text messaging, traditionally delivered via SMS, is shown in both randomized controlled trials (RCT) and a recent Cochrane review [14,15]. Mobile phone–delivered text messaging has been identified as one of the most affordable interventions [16] and has been endorsed and used by several international organizations, including the WHO, in their global tobacco control efforts [17,18]. Many agencies, such as the US National Cancer Institute (NCI) have made scientifically supported apps available for public use [19].

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We previously developed a theoretically and empirically based mHealth smoking cessation intervention and pilot-tested it with 50 Cambodian people with HIV who smoked cigarettes [20]. Our results have shown that our proposed mHealth approach is highly feasible, appropriate, and potentially scalable for LMIC settings. This mHealth automated treatment (AT) program includes a fully automated, interactive, personalized, smartphone-based intervention for behavioral treatment, delivered through our Insight platform. In the parent project of this study (R21CA253600), we have adapted and validated the AT content to the sociocultural context, language, and communication styles of Lao people in the general population.

Herein, we describe the design, methods, and analysis plans for a supplemental pilot project that focuses on patients with and survivors of cancer, funded by an Administrative Supplement grant (3R21CA253600-02S1) from the US NCI. This pilot project aims to adapt and evaluate the feasibility and preliminary efficacy of our mHealth-based AT intervention to help Lao patients with and survivors of cancer and their caregivers quit smoking cigarettes. We used an intervention mixed methods research design, which included a 2-group interventional RCT and an embedded qualitative component to explain RCT outcomes. Findings from this pilot RCT will provide useful information for larger, fully powered RCTs to assess the efficacy and effectiveness of mHealth-based smoking cessation treatments and ultimately to reduce tobacco-related morbidities and mortalities in Lao PDR.

Methods

Ethical Considerations

The study was approved by the institutional review boards (IRBs) of the Lao MOH–National Ethics Committee for Health Research (NECHR; IRB00006227) and of The University of Oklahoma Health Sciences Center (OUHSC; IRB#: 14125). Our collaborative hospitals (where the study took place)—Setthathirath Hospital (SH) and LNCC—are public hospitals under the management of the Lao MOH and have assurances relying upon the NECHR IRB. All participants underwent an informed consent process and provided written informed consent to participate. Participants were informed of the nature of the investigation, the steps that they would complete, and the types of interventions involved. Specifically, for the RCT, potential participants were made aware that (1) they would be participating in a research study, (2) they would be asked to complete assessments according to research protocols, (3) they would have a chance of being randomized to either treatment arm of the study, and (4) their study data, without any identifiers, will be posted on ClinicalTrials.gov. Participants received explanations about the potential risks of participation, measures to protect against risks, and the alternative option of not participating. The whole informed consent process was conducted in Lao language by local research staff. Participant privacy and confidentiality have been carefully maintained. All study paper records with personal identifiers were maintained in locked offices and locked file cabinets at the participating institutions. Electronic files and data are stored on secure OUHSC servers, following information security standards required by the OUHSC Information Technology Department and IRB. Only research staff have access to these paper records or electronic data. All data will be analyzed and reported in aggregate form, and individual participants will not be identified in any public reports or documents. All study staff completed human participants protection training. Participants were compensated an amount in Laotian kip equivalent to US $15 after completing each of the 2 primary assessments—at baseline and at the 12-week follow-up.

Overall Study Design

We used an intervention mixed methods research design, which included a pilot 2-group interventional RCT and an embedded qualitative component to explain RCT outcomes (Figure 1). In the pilot RCT, cancer survivors (n=30) or caregivers (n=50) of both sexes who smoked were recruited from SH and LNCC in Vientiane (the capital of Lao PDR). Recruited participants were randomized to 1 of 2 treatment groups: standard care (SC) or mHealth-based AT, delivered by our Insight app. Participants in both groups were asked to complete assessments delivered by REDCap (Research Electronic Data Capture; Vanderbilt University) at baseline and at the 12-week follow-up. All participants were also asked to complete brief weekly assessments (ecological momentary assessments) via the Insight app. SC consisted of brief advice to quit smoking delivered by research staff, self-help written materials, and a 2-week supply of nicotine replacement therapy (transdermal patches). AT consisted of all SC components plus our fully automated interactive smartphone-based treatment program, personalized and tailored to cancer survivors or caregivers, and delivered by our Insight app. Feasibility outcomes of interest include the percentages of intervention messages delivered and viewed (documented as digital stamps in our Insight app), usability, and participant retention at the 3-month follow-up. The preliminary efficacy outcome is biochemically confirmed self-reported 7-day point prevalence abstinence at 3 months post study enrollment. During the interventional RCT and at the 3-month follow-up assessment, we used additional open-ended questions to explore why and how the participants did or did not successfully quit smoking and stay abstinent.

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Figure 1. Study schema.

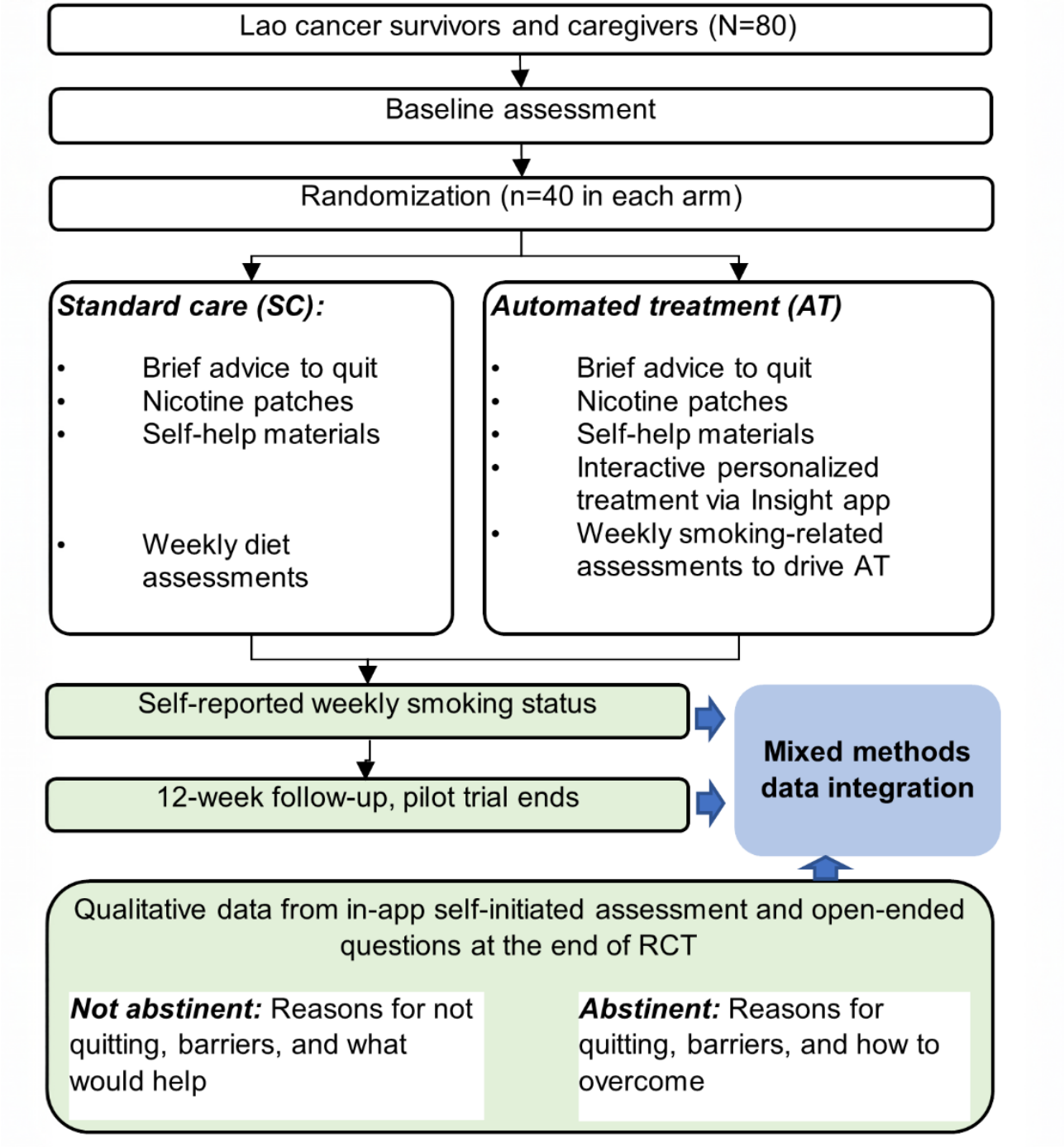

Conceptual Framework for AT

Our AT intervention was based on the Phase-Based Model (PBM), a theoretical framework that is specific to smoking cessation [21,22]. PBM partitions the cessation process into 4 phases: motivation, preparation (precessation), cessation (quit date to 4 weeks post quit), and maintenance (up to 6 months post quit); this RCT focuses on the latter 3 phases. PBM helps identify challenges/opportunities that smokers face at each phase, explains underlying phase-specific mechanisms, and facilitates selection of intervention components and measures. Using data from weekly assessments, our AT intervention dynamically targets several putative mechanisms, mainly those that are relevant across phases and have been reliably associated with long-term abstinence in previous studies: withdrawal/craving, motivation to quit, positive/negative affect, coping with stress and urges, and self-efficacy [22-26].

Participants and Eligibility

Overview

At SH, the Department of Oncology and Department of Breast and Gynecologic Cancer serve >200 patients with cancer each year. LNCC serves >400 new patients with various types of cancer each year [27]. Research staff reviewed medical records of patients with cancer receiving care at the 2 hospitals in the past 2 years, screened for their smoking status documented in the records, and contacted those who smoked for further screening. To recruit caregivers, research staff contacted random

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patients with cancer who did not smoke and asked if they had a caregiver and if the caregiver smoked. Given the pilot nature of this study, we proposed to recruit independent groups of cancer survivors and caregivers who smoked, that is, no dyads of smokers, to avoid potential interpersonal interactions. Participants who agreed to further screening were asked to complete a brief survey to determine their eligibility (Figure 2). REDCap was used to collect and manage information for most procedures, including screening eligible participants.

Figure 2. CONSORT flow diagram. CONSORT: Consolidated Standards of Reporting Trials; NRT: nicotine replacement therapy.

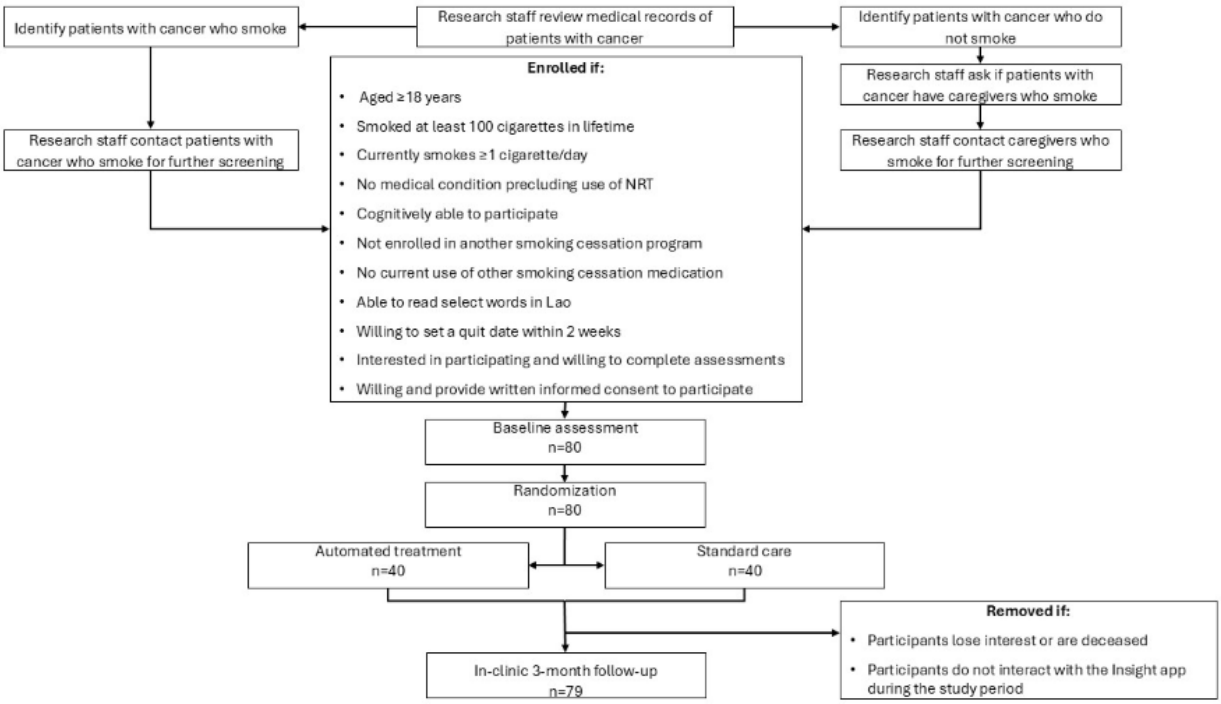

Inclusion Criteria

The pilot RCT included those who were (1) aged ≥18 years, (2) self-reported current combustible cigarette smokers (smoked at least 100 cigarettes in lifetime and currently smoke ≥1 cigarette/day), (3) willing to set a quit date within 2 weeks of study enrollment, (4) able to provide written informed consent to participate, and (5) able to read Lao (score of ≥4 points on the Rapid Estimate of Adult Literacy in Medicine—Short Form [28]).

Exclusion Criteria

Exclusion criteria were (1) history of a medical condition that precludes the use of nicotine patches, (2) ineligibility to participate based on medical or psychiatric conditions diagnosed by a physician/clinician, and (3) enrollment in another cessation program or current use of other cessation medications.

Baseline Assessment and Randomization

Eligible individuals interested in participating completed an informed consent process and were enrolled in the study. Baseline assessments were conducted in person at the clinic. Enrolled participants completed a 45-minute baseline self-interview on tablets using the REDCap Mobile App. If a participant did not know how to use a tablet or preferred the questions to be read to them, research staff assisted them or conducted the interview. After the interview, research staff also assessed expired carbon monoxide (CO) with a CO monitor to verify smoking status, and collected additional data from participants' medical records for AT personalization (eg, comorbidities or recent/current diagnosed health conditions). The tablets that contain the REDCap app were password-protected, encrypted, and could be remotely wiped if lost [29,30].

Participants were randomly assigned to SC or AT by the REDCap randomization module (simple, 1:1) and were blinded to their study group. Smartphones were loaned to participants as needed. All participants completed a brief training session on smartphone use that included downloading and navigating the Insight app. The Insight app also included a help button for instructions on how to use each feature, which participants could review at any time.

Intervention Conditions

SC Intervention

SC consisted of brief advice to quit smoking delivered by research staff, self-help written materials (based on the WHO's "A guide for tobacco users to quit" [31] that we translated to and validated in Lao), and a 2-week supply of nicotine patches. As mentioned above, there is no evidence-based smoking cessation support program implemented in Lao PDR to be used as standard care for our study. Thus, our SC treatment approach was based on a US guideline, which indicates that the use of nicotine replacement therapy doubles quit rates and should be considered the minimal standard care [32], together with the translated WHO's behavioral guide.

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AT Intervention

AT consisted of all SC components plus a fully automated smartphone-based treatment program that involved proactive, interactive, and personalized messages in Lao, along with some images. AT content was adapted from our previous efforts and was designed to target theoretical constructs of the PBM. That is, AT content was designed to increase motivation, self-efficacy, and the use of coping skills and reduce nicotine withdrawal symptoms and stress. In the R21 phase of the parent project in 2021-2022, we had culturally adapted the AT intervention content to Lao using the cultural adaptation of evidence-based interventions approach [33,34], as well as the International Quality of Life Assessment– and WHO-recommended methodology [35,36]. Briefly, major steps in the adaption and validation process included qualitative interviews with Lao health care providers and smokers to identify additional local factors that help smokers to quit, modifying the original English intervention content, forward translation, rating the quality of the translated materials on 5 dimensions (conceptual equivalence, clarity in meaning, comprehensibility, use of common simple language, and cultural appropriateness), conducting 4 focus groups with Lao smokers to evaluate the updated materials' comprehensibility and cultural appropriateness, and backward translation for checking conceptual equivalence (particularly for PBM-based aspects). For this SurvLaos project, we further modified and validated the Lao intervention content with 10 patients with and survivors of cancer.

AT began immediately after enrollment and continued for 12 weeks (about 2-4 messages or images per day, delivered by our Insight app at participants' preferred time). Quit date was set at day 14 post enrollment for both AT and SC participants. All daily messages were delivered as push notifications, and all necessary information and images were also available in the app for on-demand viewing. AT content was personalized and tailored to each participant's baseline information (eg, sex, cancer types, caregiver status, and current health conditions), current PBM phase [21], and responses to the brief weekly assessments that drive AT. Insight enables complex built-in algorithms and branching logic, allowing us to create and deliver dynamically and individually tailored treatment content, using near-real-time input data from the weekly assessments. For example, there were different bins of messages for different cessation phases to ensure that the AT intervention targets critical mechanisms of each phase. Participants were asked to complete brief Insight-delivered assessments during each week of the AT treatment course, with questions about their smoking status in the past week, coping skills, and current levels of motivation and self-efficacy. Depending on participants' responses to these questions (eg, quit or smoked, or low self-efficacy), different messages from different bins were delivered to the participants. Our AT only targeted cigarette smoking because it is the most common type of tobacco used by Lao smokers (95%) [37].

Measures

In-Person Assessments at Baseline and at 12-Week Follow-Up

These were the primary assessments that collected 3 types of data: self-reported data collected by REDCap, expired air CO (assessed with Vitalograph BreathCO) to verify smoking status biochemically, and medical record data (for AT personalization).

Brief Weekly Smartphone Assessments

Participants in both groups were asked to complete brief weekly assessments via the Insight app on smartphones. AT participants received 6 PBM-based smoking-related questions; responses to these questions drove the tailored AT content (eg, tips to increase self-efficacy if participants indicated a low self-efficacy). To balance the effects of these weekly contacts between the RCT groups, we also asked SC participants to complete a weekly 6-item assessment; however, these questions were about diet. All participants were provided a prepaid 3-month unlimited data plan.

Outcomes

Feasibility outcomes of interest included Insight app use and adherence, usability, and participant retention at the 3-month follow-up. Measures of Insight app use and adherence, documented as digital stamps in our Insight app, included numbers of messages or images opened and viewed, weekly assessments opened and completed, and other activity logs documented in our Insight platform. Participants answered questions regarding Insight app usability and their satisfaction with the intervention at the 12-week follow-up assessment. Retention was documented by research staff.

The preliminary efficacy outcome was smoking status at 12 weeks post enrollment. Abstinence was defined as biochemically confirmed self-reported 7-day point prevalence abstinence with expired CO below 6 ppm. Secondary outcomes included continuous and sustained abstinence, number of quit attempts, and length of abstinence. There was also an in-app, participant-initiated qualitative assessment, with an app home screen button labeled "Share with us anything on your mind" and an open-text field for responses, to capture the participant's thoughts, feelings, and behaviors.

Additional Open-Ended Questions

After the structured assessment for the RCT at the 3-month follow-up, we asked additional open-ended questions (Multimedia Appendix 1) to explore why and how the participants did or did not successfully quit smoking and stay abstinent. Specifically, for participants who were biochemically confirmed abstinent, the questions focused on what motivated them to quit and how they overcame challenges or barriers to stay abstinent. For participants who were not abstinent, the questions focused on why they did not or could not quit, what they underwent, what challenges or barriers they had, and what would help them quit in the future.

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Data Analysis Plan

RCT Outcome Analysis

Regarding the feasibility of AT, we hypothesize that ≥75% of AT content will be viewed/opened as indicated by digital date/time stamp in the Insight app. The 75% threshold is anticipated based on the observed rates in our similar pilot RCT in Cambodia, which showed that 81% of all delivered messages and assessments were opened and resulted in a statistically significant preliminary efficacy [20]. Descriptive statistics will be used to assess the feasibility outcomes of AT.

Regarding the preliminary efficacy of AT, we hypothesize that at the 12-week follow-up, 7-day point prevalence abstinence will be higher in the AT (vs SC) group. We will use log-binomial regression with an intent-to-treat approach (ie, missing=smoking) to compare the effect of the treatment on the dichotomous abstinence outcome at 12 weeks post enrollment, controlling for selected covariates such as sex, education level, and/or baseline stress level. Secondary outcomes will be examined using appropriate linear and generalized linear mixed models, with log binomial and linear regression for binary and continuous variables, respectively. Given the preliminary nature of the RCT, we do not expect to have sufficient power for full hypothesis testing. However, from our previous work, we anticipate that the abstinence at the 12-week follow-up will be 8% in the SC group [20]. With 40 participants in each treatment group, we will have 80% power to detect a difference as small as 20% in smoking abstinence rates between groups (α=.05, 1-tailed, unadjusted).

Mixed Methods Data Analysis

Two research team members will perform qualitative data coding with the aid of the R-QDA [38]. Discrepancies will be discussed to achieve intercoder agreement. Codes and quotations will be arranged into focused themes (ie, thematic content analysis) to develop the mixed methods data inventory [39]. Codes and themes will be based on the purpose of this component (ie, explaining the RCT preliminary efficacy outcome) and on theoretical constructs of the PBM. Next, we will examine quantitative (RCT) and qualitative data jointly, using the integration strategy of explaining with the intent to explore why participants could or could not quit and stay abstinent [39,40]. Mixed methods–linked data, results, and meta-inferences will be presented in visual joint displays [40], similar to our previous publication [20].

Results

Participant enrollment started in April 2022 and ended in February 2023 (ClinicalTrials.gov ID: NCT05253573) with a final sample of 80 participants. Follow-ups were completed in May 2023, with a loss to follow-up due to the death of a patient with cancer. Implementation data in Insight and REDCap platforms were frequently analyzed to monitor research protocol fidelity. Outcome analyses are ongoing, and results are expected to be published in 2025.

Discussion

Anticipated Findings

In Lao PDR, tobacco smoking prevalence among patients with cancer is high, ultimately affecting cancer treatment outcomes. Nevertheless, there are no tobacco treatment programs in cancer hospitals or institutions in Lao PDR. Our study is the first effort that uses scalable and sustainable mHealth technology to provide tobacco cessation treatment to patients with or survivors of cancer and their caregivers in Lao PDR. The study adapted an evidence-based cancer survivorship care service (ie, smartphone-based smoking cessation treatment) in the United States to serve similar Lao populations. The results of this study will inform the feasibility, acceptability, and preliminary efficacy of AT in offering tobacco cessation support to Lao cancer survivors and caregivers. We hypothesize that the AT approach will be highly feasible and acceptable, as found in our previous studies. For example, in a previous pilot study with 50 Cambodian smokers, we found that most participants agreed that our mHealth-based treatment program was helpful in supporting smoking cessation (92%) and would recommend it to other smokers (88%) [20]. In another pilot study with 50 Lao patients with respiratory disorders, AT was highly acceptable: 91.6% agreed or strongly agreed that our app was easy to use, 100% of AT participants agreed or strongly agreed that the message content was easy to understand, and 95.8% felt comfortable with opening messages in public places [41]. For this SurvLaos project, one available result of the feasibility—the retention of participants through the 3-month study period—has been shown to be very promising (all surviving participants completed the 3-month follow-up). We also anticipate that the AT, compared to the SC, will demonstrate a higher preliminary efficacy as in our pilot study in Cambodia [20]. By demonstrating these critical metrics, this SurvLaos project will lay a foundation for a subsequent fully powered RCT to evaluate the actual efficacy of our mHealth-based AT program. Ultimately, the projects have the potential to improve cancer care and cancer survivorship research in Lao PDR and in other LMICs. In addition, their results will suggest the potential of a cancer care delivery model beyond health care settings (ie, an mHealth approach) that can be applicable to other behavioral interventions/treatments targeting cancer survivors and caregivers.

This course of research is conducted by a uniquely qualified multidisciplinary research team with extensive experience in conducting health promotion research in international settings and in mixed methods studies. US coinvestigators provide their valuable expertise in behavioral sciences, mHealth tobacco cessation research for low-income and other underserved populations, tobacco health risk communication, mHealth methodology, and biostatistics. This project has been implemented by the National Center for Laboratory and Epidemiology, a core unit of the Lao MOH that is responsible for a wide range of public health issues. Thus, our project can use several local expertise and resources for the successful implementation of the interventions in Lao PDR. In addition, the project is built on a strong partnership with stakeholders at other national institutions in Lao PDR, including SH, the LNCC,

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the NTCC, and the MOH. This partnership will enhance the intervention's sustainability in the future.

Our proposed mHealth intervention approach is novel in many aspects. Our Insight platform enables ecological momentary assessments and just-in-time adaptive intervention for various health behaviors or issues. The use of Insight allows our AT to function autonomously and minimizes human involvement, making the approach affordable for large-scale implementation in LMICs. Using the friendly, intuitive Insight platform's interface, Lao researchers can directly manage AT as they wish without knowledge of programming languages. Thus, in the subsequent implementation phase of AT or in future cancer survivorship research projects, Lao researchers can modify the AT content in Insight to target other behavioral, physical, and psychosocial survivorship outcomes (eg, monitoring cancer treatment compliance, fatigue, and complications; providing timely personalized screening recommendations to detect recurrence early; or improving retention in care).

This study has some limitations. First, this proposal was submitted to a small supplementary funding opportunity that supported pilot studies, and the data collection is expected to be completed within 1 year. Given the pilot nature of the project and the limited resources and time, a larger sample size or a longer follow-up period was not feasible. Second, the small sample size may not provide sufficient statistical power to evaluate fully the intervention's efficacy or to perform subgroup analyses (eg, by sex, cancer types, or cancer stages). Thus, a future large-scale fully powered RCT is needed for these purposes. Finally, the use of mHealth and smartphone approaches may exclude some patients who do not own a smartphone or do not know how to use a smartphone. However, as we explained above, the trend in smartphone ownership in Lao PDR over the past decade has grown substantially, which clearly indicates that smartphone ownership will be nearly ubiquitous in the near future.

Conclusion

Developing and evaluating a scalable and sustainable tobacco cessation treatment program for patients with and survivors of cancer and their caregivers in Lao PDR is a pressing need to improve cancer treatment and survivor outcomes. Our course of research aims to address this critical need. The preliminary data from this pilot project will lay a foundation for a subsequent fully powered RCT to evaluate the actual efficacy of our mHealth-based AT program. Ultimately, our course of research will contribute to reducing tobacco-related complications in cancer treatments, comorbidities, tobacco-related cancer recurrence, and mortality rates in Lao PDR.

Acknowledgments

We would like to thank staff of the Ministry of Health of the Lao People's Democratic Republic (Lao PDR), National Center for Laboratory and Epidemiology of Lao PDR, Setthathirath Hospital, and Lao National Cancer Center for supporting data collection. This study was supported by an Administrative Supplement grant (3R21CA253600-02S1) from the US National Cancer Institute (NCI), National Institutes of Health. This award was supplemental to the parent award (R21CA253600/R33CA253600) and used some of the parent project's resources. SK, MSB, SGF, and TCB are also supported in part by the US NCI Cancer Center Support Grant (P30CA225520) awarded to the University of Oklahoma Stephenson Cancer Center (SCC), and a grant from the Oklahoma Tobacco Settlement Endowment Trust (R23-02). SK is also supported in part by the Presbyterian Health Foundation's 2024 Research Support Grant Program. mHealth programming and technological support was provided through the Mobile Health Shared Resource of the SCC via the NCI Cancer Center Support Grant (P30CA225520). The content is solely the responsibility of the authors and does not necessarily represent the official views of the funding agencies. No artificial intelligence program was used to generate any portion of this manuscript.

Data Availability

Data generated during this study will be available upon request to the corresponding author, following the NIH's, OUHSC's, and Lao Ministry of Health's data sharing requirements.

Authors' Contributions

Conceptualization: PK, PX, DV, and TB
Data curation: SK
Formal analysis: SGF-P and SK
Funding acquisition: PK, PX, DV, and TB
Investigation: CS, DX, and CV
Methodology: PX, KP, LS, VD, and PA
Project administration: CS, DX, and CV
Resources: MB
Software: MB
Supervision (clinical content): JV
Supervision: PX, KP, LS, VD, and PA
Validation: JV

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Visualization: SGF-P and SK
Writing—original draft: PK, PX, DV, and TB
Writing—review and editing: CS, CV, DV, DX, JV, KP, LS, MB, PA, PK, PX, SGF-P, SK, TCB, and VD

Conflicts of Interest

MB, DV, and JV disclose that they are coinventors of the Insight mobile health platform that is used in this study. Intellectual property rights are held by The University of Oklahoma Health Sciences. They have no additional/external interests in the platform. However, they receive their inventor percentage for the scientific usage of the platform. All other authors declare no conflict of interest.

Multimedia Appendix 1
Open-ended questions for the qualitative component.
[DOCX File , 33 KB - resprot_v14i1e66517_app1.docx]

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Abbreviations

AT: automated treatment
CO: carbon monoxide
IRB: institutional review board
Lao PDR: Lao People's Democratic Republic
LMIC: low- and middle-income country
LNCC: Lao National Cancer Center
mHealth: mobile health
MOH: Ministry of Health
NCI: National Cancer Institute
NECHR: National Ethics Committee for Health Research
NTCC: National Tobacco Control Committee
OUHSC: University of Oklahoma Health Sciences Center
PBM: Phase-Based Model
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SC: standard care
SH: Setthathirath Hospital
WHO: World Health Organization

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Protocol

Gamification of Incentive Spirometry in Trauma Patients: Protocol for a Prospective, Observational Feasibility Study

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Abstract

Background: Thoracic trauma accounts for 10% to 15% of trauma-related hospital admissions and contributes significantly to morbidity and mortality. Rib fractures, the most common thoracic injury, often result in pulmonary complications such as pneumonia and atelectasis due to impaired respiratory mechanics. Incentive spirometry (IS) is a widely used noninvasive technique aimed at improving pulmonary function after injury, yet patient compliance remains a challenge. Gamification of respiratory therapy has emerged as a promising approach to enhance engagement and adherence.

Objective: This paper presents the protocol for a study to evaluate the feasibility and safety of using gamified IS through the OmniFlow Breathing Therapy BioFeedback System in trauma patients. While preliminary observations related to potential clinical efficacy (eg, respiratory function and adherence) are of interest, structured clinical or physiological end points are not included in this protocol for a pilot study and are planned for future trials.

Methods: This protocol is for a single-center, prospective, observational phase 2 pilot study to be conducted at Wake Forest Baptist Medical Center. Adult patients (aged ≥18 years) admitted to the trauma intensive care unit with rib fractures and a Glasgow Coma Scale score of 15 are eligible for inclusion if their first intervention session can occur within 48 hours of admission. Patients requiring mechanical ventilation, those with baseline lung disease, and those with contraindications to IS are excluded. Enrolled patients participate in at least one gamified respiratory therapy session daily, lasting 15 to 20 minutes, with the possibility of additional sessions based on patient preference and tolerance. Primary end points include the feasibility of enrolling 20 patients and their participation in at least one session. Secondary end points evaluate patient adherence, number of completed sessions, and session interruptions due to predefined safety criteria (eg, pain score >8/10, oxygen desaturation <92%, new cardiac arrhythmia, or respiratory distress). If 5 consecutive patients fail to complete a session due to adverse events, the intervention is deemed unsafe.

Results: The study was approved by the institutional review board and registered on ClinicalTrials.gov. Due to an unexpected delay in the initiation of the project, no patients were enrolled.

Conclusions: OmniFlow offers a promising, much-needed solution for promoting adherence to breathing exercises among patients with thoracic trauma. This study protocol is designed to evaluate its safety and feasibility in patients with thoracic trauma

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and rib fractures. Looking ahead, incorporating multiplayer games into the platform could further enhance its effectiveness, allowing patients to engage in group activities while working toward their individual therapeutic goals.

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KEYWORDS

incentive spirometry; thoracic trauma; patient adherence; engagement; gamification

Introduction

Thoracic trauma is encountered in 10% to 15% of all trauma-related hospital admissions and has been cited as causing 35% of all trauma-related deaths in the United States. Between 2010 and 2016, over 500,000 trauma patients were diagnosed with at least one rib fracture in the United States [1]. Traumatic rib fractures are the most common thoracic trauma and are associated with significant morbidity, mortality, and decreased long-term quality of life. Fractured ribs are present in approximately 20% of patients admitted to trauma centers with blunt chest trauma [2]. Thoracic trauma causes increased splinting of the chest muscles due to pain, causing increasing incidence of pulmonary complications like pneumonia, atelectasis, and acute respiratory failure. Rib fracture pain and disability can be a serious impediment to returning to work. Mortality rates of up to 33% have been reported for flail chest injury [3].

The mortality rate associated with chest trauma involving rib fractures is estimated to be approximately 10%, with the risk increasing with the number of fractured ribs, reaching nearly 40% in patients with more than 6 fractures [4]. Pulmonary complications remain a leading cause of death in these cases. Numerous strategies have been used to reduce pulmonary complications following chest trauma, such as surgical stabilization of rib fractures and multimodal analgesia, including epidural anesthesia. However, these techniques are invasive and may not be practical in all cases [5]. Physiotherapy has been considered a critical component in the postoperative recovery of these patients. Specifically, airway clearance techniques, including instruction on breathing exercises aimed at reducing the effects of atelectasis, have been demonstrated to significantly lower the incidence of postoperative pulmonary complications. Incentive spirometry (IS) is a method that enables patients to perform deep breathing exercises autonomously, providing visual feedback on inspiratory effort. This technique is believed to enhance the precision of deep breathing exercises and to motivate patients to engage consistently in these exercises [6]. While it reduces pulmonary complications [7], low patient compliance has prompted the need for innovative strategies to increase patient engagement and motivate patients to engage in breathing exercises while offering quantitative measurements of their progress and adherence.

Emerging efforts have focused on gamification of pulmonary rehabilitation through game-based IS in patients with chest trauma to prevent pulmonary complications. Previously, a game was developed to enhance breathing exercises in which users control an airplane with their breath and guide a bird through scenic landscapes, accompanied by calming music. The game was tested on healthy individuals and received positive feedback [8]. A virtual IS application for smartphones called QUT Inspire has also been developed as an HTML5 web application [9]. This app uses the smartphone's built-in microphone to detect inspiratory sounds, which in turn sustains a responsive animated graphic display as long as the breath sound is detected. A postresearch questionnaire showed that the majority of participants preferred the new virtual app for visualizing their inspirations. Despite promising preliminary results, these studies have enrolled either healthy volunteers or patients with specific lung pathologies, and there is a paucity of data regarding the gamification of respiratory therapy involving patients with trauma, specifically trauma to the thoracic cavity; nevertheless, such therapy has significant potential to benefit these patients by enabling increased respiratory therapy.

We designed this study to assess the safety and feasibility of a respiratory intervention in trauma patients with rib fractures using a gamification platform. Herein, we describe the study protocol for this study. While preliminary observations related to potential clinical efficacy (eg, respiratory function and adherence) are of interest, structured clinical or physiological end points were not included in this protocol and are planned for future trials.

Methods

This investigation entails a single-center, prospective, observational, pilot phase 2 study focusing on the primary objective of feasibility and safety of gamified respiratory therapy interventions among thoracic trauma patients. The study leverages the OmniFlow Breathing Therapy BioFeedback System as an evaluative tool for gauging the efficacy of gamified respiratory therapy interventions in thoracic trauma patients. The OmniFlow Breathing Therapy BioFeedback System uses a virtual environment (the OmniFlow system), a US Food and Drug Administration–approved health care gaming system that uses biofeedback mechanisms to assess and encourage thoracic trauma patients to achieve optimal breathing patterns essential for pulmonary recovery.

Participant Recruitment and Enrollment

In the study described by this protocol, all adult patients aged ≥18 years admitted for rib fractures to the trauma intensive care unit (ICU) at Wake Forest Baptist Medical Center are screened for the study and included if they have a Glasgow Coma Scale (GCS) score of 15, are willing to participate, and the first session of intervention can occur within 48 hours of admission. This feasibility study is designed to include a total of 20 consenting patients. Patients are excluded if they (1) require mechanical ventilation or bilevel positive airway pressure, (2) have a GCS

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score <15, (3) have facial fractures, (4) have baseline lung disease or use home oxygen, (5) have a physical disability or trauma impairing the use of IS, (6) are expected to be transferred or discharged within 24 hours of expected enrollment, as per the treating physicians' judgment, (7) are transitioning to palliative care or are anticipated to die within the next 48 hours, (8) are unable to provide self-consent, and (9) are unable to use the mouthpiece of the OmniFlow System due to visual or hearing impairments.

The sample size of 20 participants was chosen based on feasibility study conventions, which recommend 12 to 30 participants to assess logistical and safety outcomes in early-phase research. We defined a successful outcome for feasibility as the ability to enroll 20 patients within the study timeframe and for at least 75% of these patients to complete one full session without interruption due to safety-related criteria.

Ethical Considerations

Eligible patients are approached by the investigators and study coordinators for detailed discussion of the study. Informed consent is sought to initiate the first session of the OmniFlow Breathing Therapy Biofeedback System within 48 hours of admission. The care team is consulted prior to deploying each session of the OmniFlow system to ensure that it is safe and does not interference with the patient's care. Comprehensive information about the study, including session initiation timing, session frequency, game details, potential benefits, and risks associated with the OmniFlow Breathing Therapy BioFeedback System are communicated to the patients before obtaining consent. The protocol has been approved by the Atrium Health Wake Forest Baptist Medical Center institutional review board (IRB00097144) and registered at ClinicalTrials.gov (NCT06090279).

Privacy and Confidentiality

Participants' privacy and confidentiality were carefully protected throughout the study. All data were de-identified and securely stored on password-protected systems accessible only to the research team. Personal identifiers were replaced with unique participant codes to ensure anonymity. No identifying information was included in any publications or shared datasets. All research personnel followed strict confidentiality protocols and HIPAA-compliant practices.

Compensation

No compensation was provided to participants. Their voluntary participation was based solely on willingness to contribute to the study without financial or material incentive.

Data Collection and Confidentiality Measures

Upon obtaining consent, patient-specific information such as name, medical record number, age, gender, weight, height, medical history, and current respiratory status and care are collected. Strict confidentiality measures are implemented, collecting only essential information for assessing study outcomes, minimizing identifiable data, and securely storing all study-related information. Unique study identifiers are used on data collection forms, with a separate, secure linkage file maintaining any patient-identifying information. Access to the linkage file is restricted to designated study personnel, and data access is granted solely to team members educated in Health Insurance Portability and Accountability Act practices. Physical and electronic records are secured, and participant descriptions in reports, presentations, or publications omit personal health identifiers, ensuring participant anonymity.

All instances of missed sessions, dropouts, or early discontinuation are recorded in the Research Electronic Data Capture (REDCap; Vanderbilt University) system with documentation of the underlying reason, including patient-reported barriers, clinical contraindications, or scheduling and logistical constraints. Partial adherence (eg, completing fewer than the recommended number of sessions) is also tracked. These data will be descriptively analyzed and categorized into thematic groups (eg, clinical deterioration, lack of interest, and device discomfort) to better understand patient engagement and barriers to full participation.

Given the exploratory nature of this pilot study and the limitations in anticipated enrollment, structured clinical or physiological efficacy end points (eg, pulmonary function, respiratory rate trends, or serial pain scores) were not predefined. These will be incorporated into future, larger-scale trials aimed at assessing the therapeutic impact of gamified IS more comprehensively.

Intervention

Patients commence the intervention with a regimen of at least two daily sessions, each anticipated to last 15 to 20 minutes. Should patients exhibit favorable tolerance and express a desire for additional sessions, an optimal dosage may involve an increase in the frequency of daily sessions. Conversely, if patients do not demonstrate a preference for the intervention, it may be inferred that gamified therapy is not the optimal therapeutic modality for them.

The session will be ended if one or more of the following termination criteria is met:

- Sustained pain score exceeding 8/10
- Elevated oxygen requirements surpassing an increment of 2 L/min from before the intervention or a decline in oxygen saturation below 92% during the intervention, necessitating the escalation of an oxygen supplementation device
- Sustained heart rate surpassing 110 beats per minute, accompanied by either a new cardiac arrhythmia or a respiratory rate exceeding 30 per minute
- Manifestation of cyanosis, pallor, or the onset of new confusion

All sessions are conducted at the bedside under the direct supervision of a trained study coordinator who monitors the patient's vital signs and tolerance in real time using the hospital's standard ICU monitoring systems (including pulse oximetry and telemetry). The session is immediately ended if there is any indication of distress or a breach of the predefined termination criteria. A bedside ICU nurse is notified prior to each session, and the clinical care team remains on standby to respond if needed. All adverse events or session interruptions are recorded in a REDCap database with detailed documentation

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of observed symptoms, vital sign trends, criteria met, time of termination, and any follow-up clinical actions.

Data Collected as Part of the Study

The primary end point of the study is the enrollment of 20 patients who consent to the study and participate in at least one session. The secondary end points of the study are the number of patients who do not complete any therapy sessions after initiation, and the number of sessions interrupted due to the above criteria. The safety end point of the study is if 5 consecutive patients do not complete a therapy session due to any of the above criteria.

In addition to the primary feasibility end point of 20 enrolled patients participating in at least one session, we also collect data on session adherence (total number of sessions completed per patient), tolerance (interruption of sessions due to predefined clinical criteria), and engagement (patient requests for additional sessions). These secondary indicators will provide a more comprehensive understanding of the intervention's feasibility and acceptability.

Results

The study was approved by the institutional review board and registered on ClinicalTrials.gov. Due to an unexpected delay in the initiation of the project, no patients were enrolled.

Discussion

Overview

Much of a thoracic trauma patient's hospitalization is focused on adverse outcome risk reduction through aggressive pulmonary therapies. Internal fixation of rib fractures and multimodal analgesia, including epidural anesthesia, have been found to be effective in preventing pulmonary complications. However, these techniques are invasive and may not be practical in all cases [10]. Breathing exercises and physiotherapy serve as noninvasive alternatives, with IS being one of the most commonly used modalities. IS was developed in the 1970s to encourage patients to repeatedly and gradually increase inspiratory volumes in an effort to avoid alveolar atelectasis [11]. It serves as a simple, easy-to-teach modality that promotes deep inhalation and mucous clearance (9). For alert and motivated patients, IS can be self-driven and used frequently, and it has been shown to improve lower airway patency, lung compliance, oxygenation, and maximal inhalation capacity. IS forces patients to take long, deep breaths and hold them for a few seconds to facilitate the clearing of secretions by reducing breathing effort, minimizing the use of accessory muscles, and opening the alveoli.

Multiple studies have demonstrated the benefits of IS use. For example, in a study involving 50 patients with traumatic rib fractures, participants were divided into 2 groups: a study group of 24 patients who used IS (with the flow-oriented Triflo device, which uses 3 floating balls to indicate inspiratory flows of 600, 900, and 1200 ml/s) and a control group of 26 patients who did not use IS. The study group demonstrated an improvement of 18.65% (SD 17.77%) in percentage of forced vital capacity, compared to a decrease of 4.86% (SD 10.92%) in the control group, adding evidence for the clear positive effect of IS use [7]. However, this study was limited by its small sample size, which may not have fully represented all patients with rib fracture, especially those who are not hospitalized but still experience complications. Additionally, pulmonary function was only tested within a week of injury, so the long-term effects remain unclear.

Despite its benefits, IS is often perceived as monotonous, which may reduce compliance. Gamification has emerged as a promising strategy to address this challenge by enhancing user engagement and motivation. For example, recent research on the development and testing of a mobile app–connected lung rehabilitation device (Pulmo) demonstrated that gamified breathing interventions can achieve high levels of user satisfaction and feasibility in respiratory training contexts [12]. In that study, participants rated both the game design and device responsiveness highly, with overall feasibility scores averaging 4.4 out of 5. These findings reinforce the growing evidence that interactive, game-based respiratory tools can effectively engage users in consistent lung exercise, even outside traditional clinical populations. Although the Pulmo study focused on healthy adults, its findings support the value of integrating game-based elements into respiratory training.

Similarly, the UBICU system is a gamified respiratory incentive spirometer that combines real-time biofeedback with interactive breathing games [13]. In a clinical trial, UBICU outperformed the conventional Triflo device by producing greater lung volume improvements, as measured by electrical impedance tomography, and achieving higher patient engagement and usability scores. The success of UBICU further underscores the potential of game-based platforms like OmniFlow to enhance respiratory therapy adherence and outcomes.

Evidence from other clinical populations also supports this approach. During hospitalizations for cystic fibrosis exacerbations at the University of Vermont, investigators conducted a trial involving 10 inpatients who used a digital spirometer paired with a breath biofeedback game. Patients completed at least five 15-minute sessions in which they were challenged to track a moving target using their breath. Overall, participants responded positively to the intervention, and the game was determined to be safe [14].

Patients with stroke who participated in game-based breathing exercises for 25 minutes 3 times a week over 5 weeks showed significant improvement in forced vital capacity, forced expiratory volume in 1 second, and maximum voluntary ventilation compared to those who did not. The game-based breathing exercises involved a game application installed on a laptop, paired with a headset equipped with a sensor that detects the patient's breathing. Once activated, the game begins based on the patient's respiratory pressure and rhythm. The application features 14 different games, each designed to guide inhalation and exhalation, while also accommodating patient preferences. Stroke patients who used game-based breathing exercises showed significant improvements in pulmonary function parameters such as forced vital capacity and forced expiratory volume in 1 second [15]. In patients with spinal cord injuries,

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a study developed 7 different breathing exercise devices incorporating 10 game-based exercises. Two participants engaged in a respiratory rehabilitation program twice weekly for 60-minute sessions over 8 weeks. The intervention led to improved maximum inspiratory and expiratory pressures. Participants reported that the competitive, game-like nature of the exercises enhanced their motivation, enjoyment, and adherence. Beyond respiratory benefits, the gamified exercises positively influenced psychological well-being and social engagement [16]. Furthermore, an interdisciplinary team of physical therapists, game designers, engineers, and computer scientists developed 6 prototype games to encourage patients undergoing abdominal and cardiac surgery—who are at risk for postoperative pulmonary complications—to engage in their breathing exercises. These games were found to improve the patients' adherence to the exercises and enhance pulmonary function [8]. There have been no studies on patients with chest trauma [8].

Given these findings, our proposal introduces the OmniFlow Breathing Therapy Biofeedback System, which is designed to assist patients with breathing difficulties by offering interactive exercises through visual biofeedback in a virtual environment. This approach encourages the desired breathing response, targeting the patient's specific impairments or conditions. The device's airflow sensor measures the air passing through the spirette tube, allowing for the setting of inspiratory and expiratory flow and volume thresholds to guide exercise progression and optimize outcomes. Research supports the effectiveness of combining virtual reality–augmented biofeedback with traditional respiratory therapy techniques, as patients tend to perform more repetitions when motivated by positive feedback

The OmniFlow system consists of several key components, including a Microsoft Windows laptop that features on/off functionality, password protection, and a keyboard cover, while also running respiratory biofeedback software. Additionally, the system incorporates an airflow sensor for precise measurement during exercises. Disposable elements include the NDD Spirette (ndd Medical Technologies) bacterial and viral filter, an inline filter, and a barrier film to ensure hygiene and safety during use.

Games Included in the System

Overview

The OmniFlow system includes 5 interactive games, each designed to target specific breathing exercises. Each game is easy to understand, with clear instructions displayed on the OmniFlow screen, making them accessible to patients of all ages and educational backgrounds. Parameters such as inspiratory and expiratory volume and flow targets can be adjusted based on patient performance. The competitive nature of the games motivates patients to continue playing and achieve their therapeutic goals. In our study, the research team will monitor patients during their use of the OmniFlow system and discontinue the exercises if the patient ask to stop or if any of the termination criteria listed above are met.

Diamond Mine (Deep Inhalation)

This game focuses on strengthening inspiratory muscles and improving inspiratory vital capacity, which enhances diaphragmatic breathing, lung elasticity, and volume. Figure 1 illustrates the deep inhalation exercise in the Diamond Mine game. This exercise increases the muscle endurance necessary for functional activities such as self-care, respiratory-swallowing coordination, and sustained speech production. As the patient inhales a preset air volume in one breath, the game displays a vacuum collecting coins and jewels, with a large diamond awarded for reaching the target volume.

Figure 1. Diamond Mine: deep inhalation.

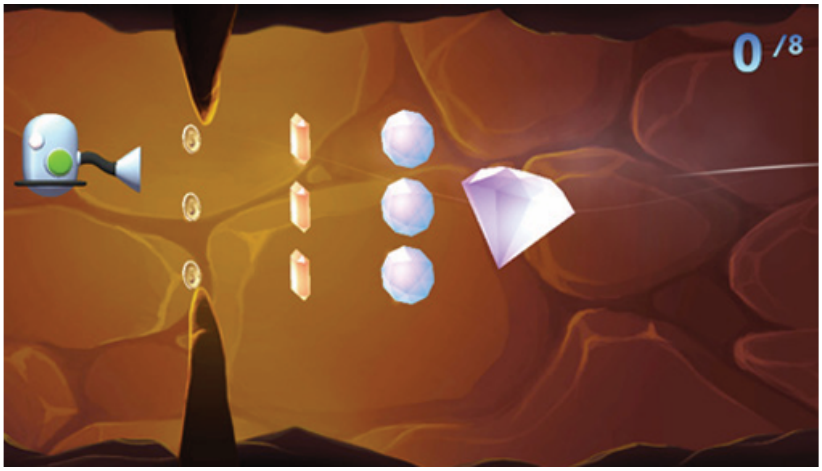

Prehistoric Contest (Forced Expiration)

This game aims to strengthen expiratory muscles, preparing patients for functional forced expiration activities such as airway protection during swallowing, coughing, and achieving adequate intensity during phonation. The patient's exhalation is represented as a javelin throw, with the force of the exhalation determining the distance the javelin travels. The reward increases with the target volume, culminating in a mammoth for exceeding the preset value. Figures 2 and 3 illustrate the forced expiration in the Prehistoric Contest game.

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Figure 2. Prehistoric Contest: forced expiration.

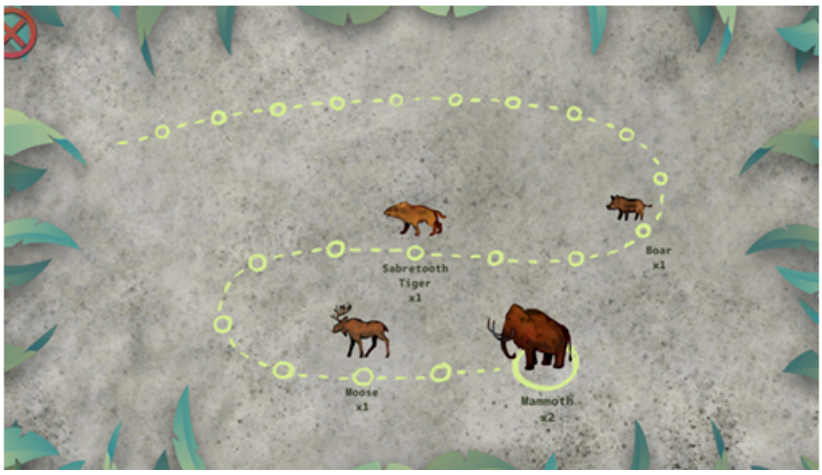

Figure 3. Prehistoric Contest: javelin throw.

Sail Away (Controlled Expiration)

Designed to regulate expiratory volume and flow, this game helps expel carbon dioxide, reduce dyspnea, and promote calmness. It improves diaphragm control to slow breathing, aiding sustained phonation, voice intensity, and speech intelligibility. Patients are instructed to inhale through the nose and exhale steadily through the mouth, with the exhalation moving a sailboat forward. Reaching 100% of the target volume brings the boat to a grassy island. Figure 4 illustrates the Sail Away exercise.

Figure 4. Sail Away exercise.

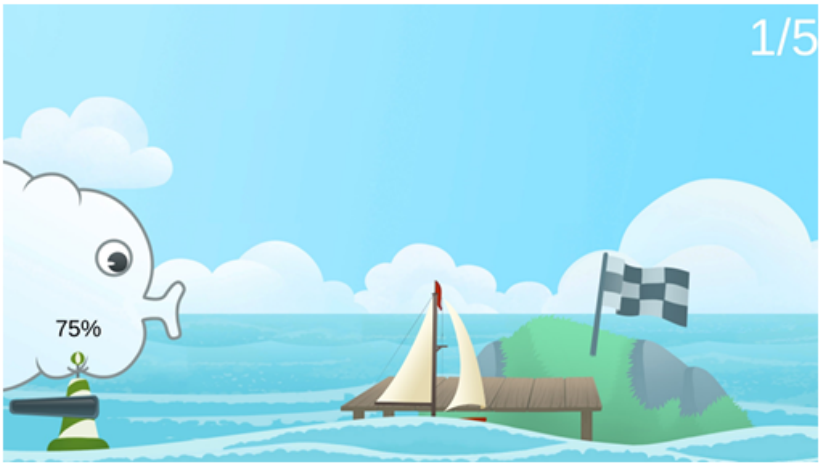

Starry Road (Rhythmical Breathing)

This game trains patients in rhythmic breathing, normalizing the inhalation-exhalation ratio and addressing irregular breathing due to pain, anxiety, or stress. Proper respiratory patterns are reinforced, improving respiratory-swallow coordination, sustained phonation, voice intensity, and speech intelligibility. Patients guide a floating figure along a starry pathway by adjusting their breathing, collecting stars along the way. Figure 5 illustrates the rhythmical breathing in the Starry Road game.

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Figure 5. Starry Road: rhythmical breathing.

Dandelion (Active Cycle of Breathing Technique/Huff Technique)

This game teaches the active cycle of breathing, or huff, technique to mobilize and expel secretions with minimal energy expenditure. The game has 3 phases. In phase 1, breathing control, patients breathe gently to make a dandelion sway, relaxing the airways. In phase 2, thoracic expansion, patients take deep breaths and hold them to move mucus away from the lung walls, causing the dandelion to sway further. In phase 3, the huff technique, patients exhale forcefully to expel mucus, blowing dandelion seeds away as they exceed the set expiratory threshold. This technique promotes airway clearance, improving aerobic capacity and muscle endurance for functional activities and respiratory-swallow coordination. Figure 6 illustrates the Dandelion game.

Figure 6. Dandelion exercise.

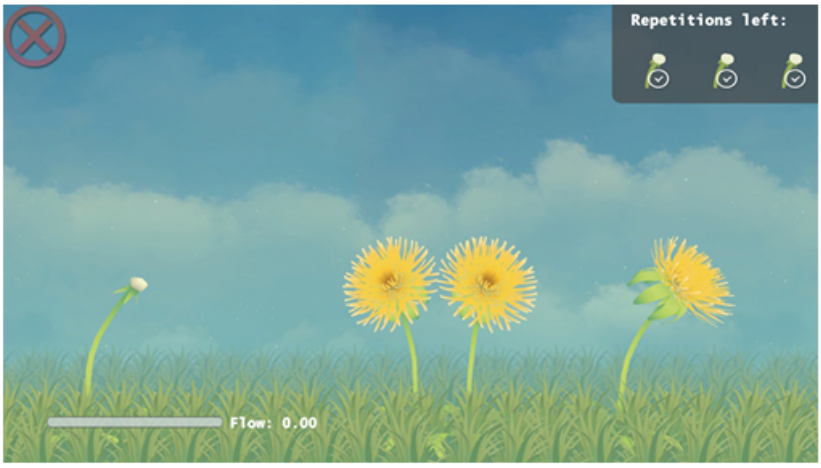

Study Goals

OmniFlow is expected to significantly improve compliance with breathing exercises in patients with thoracic trauma, as it allows them to engage in game-based exercises effortlessly, independently, and as often as desired from the comfort of their own rooms, without needing assistance from medical staff. The device is user-friendly, with simple instructions that are easy to follow. The games are safe and pose no risk of harmful effects, while offering numerous benefits, including a reduction in pulmonary complications. The competitive aspect of the games provides strong motivation for patients to continue playing, helping them achieve their respiratory therapy goals through enjoyable and effective exercises.

One key aim of this feasibility study was to better understand factors influencing patient adherence and engagement. In addition to tracking the proportion of participants who completed sessions, we systematically documented reasons for missed sessions or dropouts. These insights will help refine future study designs, including session scheduling, and support strategies to improve participation.

Limitations

We acknowledge that defining feasibility by participation in only one session is limited. Therefore, we incorporated broader process metrics—including session completion rates, interruptions, and patient interest in continuing therapy—as indicators of adherence and tolerance. While this pilot design does not include qualitative feedback such as satisfaction or perceived benefit, future trials will include structured, patient-reported usability and engagement measures to assess acceptability more comprehensively.

Another limitation of this study is the absence of predefined clinical or physiological efficacy metrics, such as spirometric measurements, serial pain scores, or respiratory rate trends. These metrics are essential for evaluating the therapeutic value

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of any respiratory intervention. Our current focus was to assess feasibility and safety in a complex trauma ICU environment as a foundational step. Future studies will incorporate structured efficacy end points to quantify improvements in pulmonary function, oxygenation, and symptom relief, thereby enabling a more comprehensive evaluation of clinical benefit.

Finally, the reliance on a single proprietary device (the OmniFlow Breathing Therapy Biofeedback System) may limit generalizability. Institutions without access to this technology might find replication difficult. Nevertheless, the fundamental components of the intervention—gamified breathing exercises, real-time feedback, and session-based monitoring—can be adapted to similar platforms, such as QUT Inspire (Queensland University of Technology) or other virtual spirometry tools. Future work should explore cross-platform compatibility to support broader dissemination.

Conclusion

OmniFlow offers a promising, much-needed solution for promoting adherence to breathing exercises in patients with thoracic trauma. Our study protocol is designed to evaluate its safety and feasibility in patients with thoracic trauma and rib fractures. Looking ahead, incorporating multiplayer games into the platform could further enhance its effectiveness, allowing patients to engage in group activities while working toward their individual therapeutic goals. Although the sample size is limited to 20 participants, this aligns with established recommendations for feasibility studies and is intended to inform the design of future larger-scale trials. We acknowledge that generalizability is constrained by sample size and setting, and that feasibility thresholds—such as a ≥75% session completion rate—are preliminary benchmarks to be refined in subsequent research.

Acknowledgments

We thank the OmniFlow team for their support in this project.

Data Availability

All data generated or analyzed during this study are included in this published article.

Authors' Contributions

AA-D: conceptualization, formal analysis, methodology, and writing (original draft). AG: conceptualization, formal analysis, and writing (review and editing). CG: writing (review and editing). PS: supervision and writing (review and editing). SM: supervision and writing (review and editing). AS: supervision and writing (review and editing).

Conflicts of Interest

None declared.

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Abbreviations

GCS: Glasgow Coma Scale
ICU: intensive care unit
IS: incentive spirometry
REDCap: Research Electronic Data Capture

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Protocol

A Work-Based, Fully Remote, and Peer-Supported Exercise Snack Behavior Change Intervention (MOV'D): Protocol for a Randomized Controlled Pilot Trial

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Abstract

Background: Prolonged sitting and lack of moderate to vigorous physical activity represent 2 independent risk factors for myriad poor health outcomes. The negative effects of prolonged sitting can be ameliorated with as little as 2 minutes of large muscle movement. Further, cardiovascular benefits from moderate to vigorous activity can be accumulated throughout the day in short bouts rather than require continuous long bouts. Taken together, "exercise snacks" provide a way to both interrupt prolonged sitting and accumulate moderate to vigorous physical activity during a sedentary workday.

Objective: This protocol describes the feasibility and acceptability pilot of MOV'D (Move Often Every Day)—a fully remote, peer-supported behavioral intervention to interrupt prolonged bouts of sitting at work with exercise snack breaks.

Methods: The MOV'D pilot study aims to recruit approximately 60-80 participants who work full-time in a sedentary occupation. Participants were randomly assigned either to the Fitbit Control or the MOV'D experimental group in a randomized 2-group design. The pilot study had a 4-week active intervention and a 4-week follow-up with assessments at baseline, 4 weeks, and 8 weeks. The Fitbit control group received a Fitbit to self-monitor their physical activity prior to receiving the intervention material at the end of the study. In addition to Fitbit, the MOV'D intervention features included a private social support group chat seeded with daily experimenter prompts, weekly 5-minute behavior change technique videos, daily self-monitoring, and daily exercise snack suggestion videos.

Results: Study enrollment began in March 2022 and concluded in June 2022. Data collection concluded in October 2022. We enrolled 70 participants, and 68 participants completed all the study assessments.

Conclusions: This protocol integrates findings from education, behavioral sciences, sedentary behavior, and exercise physiology to promote building an exercise snack habit at work: taking short intense exercise breaks to break up prolonged sitting. The results from this pilot study will show the feasibility and acceptability of the MOV'D intervention.

Trial Registration: ClinicalTrials.gov CT05360485; https://clinicaltrials.gov/study/NCT05360485

(JMIR Res Protoc 2025;14:e64455) doi:10.2196/64455

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KEYWORDS

physical activity; sedentary behavior; eHealth; intervention; behavior change theory; exercise snacks; social support; exercise; behavior change; behavior; peer support; feasibility; acceptability; pilot study; Fitbit; self-monitor; sedentary

Introduction

Background

Cardiovascular disease (CVD) is the leading cause of death in the United States [1,2]. One major risk factor for CVD is uninterrupted bouts of sitting, which can decrease lipoprotein lipase activity, heart rate variability, glucose management, and vascular function, and increase resting blood pressure and back pain [3-11]. Another CVD risk factor is inadequate levels of moderate to vigorous physical activity (MVPA), with 77% of the US adults failing to meet MVPA guidelines [12]. A growing body of evidence highlights how even short bouts of MVPA or "exercise snacks" can provide significant health benefits [13]. Conceptually, one can address both CVD risk factors at once by interrupting prolonged sitting with MVPA bouts to accrue MVPA minutes. To date, only a few interventions interrupt prolonged sitting at work with exercise snacks. Further, few studies have investigated how to utilize behavior change strategies to motivate these exercise snacks in the workplace, resulting in a lasting habit. We first cover a brief background on exercise snacks and then describe some behavior change techniques (BCTs) and social support features incorporated into this protocol.

Exercise Snacks and Other Breaks in Sitting

Exercise snacks or brief bouts of MVPA (1-5 minutes) performed periodically throughout the day [14] can simultaneously interrupt prolonged sitting and increase accumulated MVPA minutes [15]. With 80% of the jobs in the United States being predominantly sedentary, exercise snacks can serve as an accessible way to increase workers' levels of activity while still at work [16]. Although exercise snacks have only appeared in a few studies to date, adopting the behavior of exercise snacks into one's daily routine has proven to be a more sustainable way to increase daily activity [17,18]. Exercise snacks have physical health benefits. One study showed similar significant improvements in maximal oxygen consumption (VO_2 max) and cycling time trial after 6 weeks of either 3×20-second cycle sprints spread throughout the day to the same volume or 3×20-second bouts all within a single training session [16]. Compared to a time-matched long bout of MVPA, multiple shorter bouts exhibit similar cardiorespiratory fitness [19-21], glycemic control [7,22,23], exercise adherence [24], and weight loss [19,25].

Similarly, disruptions in prolonged sitting through stretching, walking, or standing can also confer psychological and cognitive benefits during a workday. A recent meta-analysis concluded that short breaks (cognitive, physical, and relaxation) of less than 10 minutes can improve participants' well-being [26]. Specifically in worksite interventions, breaks involving movement were shown to successfully increase overall levels of physical activity, maintain productivity or work performance, and reduce muscle and joint pain and fatigue [27-29]. Sutherland et al's [30] review of sedentary behavior interventions exemplified the need for high-quality research across different settings in this field. One worksite intervention showed a significant improvement in individuals' exercise enjoyment, self-efficacy, and physical activity levels when people integrated exercise snacks at work [30]. Stork et al [29] compared 3 times/day single staircase sprints (sprint snacks) to a single bout of 3 staircase sprints (single session) within participants and found a more positive valence with a lower perceived effort in the sprint snacks, and 10 of the 14 participants preferred sprint snacks. Additionally, workers are more productive on days they engage in exercise at work compared to days when they do not [31].

Finally, exercise snacks are a behaviorally accessible way to increase MVPA minutes at work. Exercise snacks are more flexible compared to a singular longer bout of MVPA. With minimal time and space requirements, exercise snacks are not only easy to integrate into most workplaces and workdays but also adaptable and accessible, as the intensity, duration, and time occurrence of these bouts can be self-determined. Although existing workplace exercise snack interventions exhibit mostly positive outcomes, more research is needed to elucidate the best behavioral science support to encourage people to adopt exercise snacks at work as a long-term lifestyle habit.

BCTs

Although we know exercise snacks can be beneficial, initiating and sustaining this habit is difficult [32]. BCTs are evidence-based strategies based in various behavior change theories. Michie et al [15] developed a taxonomy of 93 BCTs linked to sustainable behavior change in 2013 [29,33-50]. Studies that intentionally incorporate behavioral theories of change are more effective than those that do not [51]. This pilot study incorporated several BCTs such as self-monitoring, social support, social cognitive theory, and implementation intentions to enhance the effectiveness of outcomes by addressing and modifying individuals' behaviors [29,33-50]. Further, in addition to building BCTs, we explicitly *teach* participants BCTs via short (4-5 minutes) educational, interactive videos, to add to their own behavior change toolkit.

Social Support

Behavior change interventions that capitalize on existing social support or create a study-based social support system are more effective at changing and improving health behaviors [52]. Social media platforms can be an effective tool for encouraging social support in remote studies. Social media stands out for its capacity to disseminate health information widely and enables users to engage with others, contribute to content, and offer social support [13,20,22,23,53-55].

These positive effects of social support can also be seen in a previous study [45], Tweet2Quit, which was a Twitter-delivered intervention for smoking cessation. That study utilized a hybrid social media–based support group where participants were given a Twitter account and additionally paired with a buddy to both

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support and receive support for sustained abstinence from smoking [45,56-58]. As a result, Tweet2Quit exhibited 2 times more sustained abstinence for smoking cessation compared to other standard care control methods [45,56-58]. Further, Tweet4Wellness, a walking-break intervention based on Tweet2Quit, identified engagement in social support correlated with an increase in active hours and walking breaks [59]. Here, we are utilizing Tweet2Quit's buddy pairing within a larger social support group to enhance learning and behavior change in increasing exercise snacks at work.

MOV'D (Move Often Every Day) Intervention

This protocol for MOV'D (Move Often Every Day) is a fully remote, peer-supported, behavior change intervention that delivers BCT videos and exercise snack videos (2-5 minutes of moderate to vigorous activity) to a private social media support group of participants with the goal of interrupting prolonged sitting at work with MVPA. Common moves used in exercise snacks include running upstairs, squat variations, jumping movements, and other high-intensity exercises that require little to no equipment. In this pilot, the term "snacktivity" was utilized in participant-facing materials in place of exercise snacks. The study builds off the original pilot Tweet4Wellness [59], which tested the feasibility, acceptability, and preliminary efficacy of a novel Twitter-based walking break intervention with daily behavior change strategies and prompts for social support, combined with a Fitbit compared to a Fitbit-wearing only control group. The Tweet4Wellness study found that (1) social media engagement correlated with improvements in active hours and daily steps; however, engagement dropped off halfway through the study period; (2) poststudy interviews (Multimedia Appendix 1) and survey questions indicated the acceptability of the study but a desire for social support that was similar in socioeconomic status or baseline activity levels; (3) at follow-up, the improvement in the ratio of moving to sitting time was maintained. These findings led to modifications seen in the MOV'D design (eg, added a matched peer motivation coach; incorporated a learning-by-teaching element to improve uptake of the BCTs taught to participants; changing the walk breaks to exercise snacks to also tackle the problem of inadequate MVPA in those who due to time or resource constraints are unable to achieve adequate MVPA).

Here, we describe the protocol for the feasibility and acceptability pilot trial of MOV'D—a fully remote, peer-supported behavioral intervention to interrupt prolonged bouts of sitting at work with exercise snack breaks.

Methods

Overview

This was a randomized controlled pilot testing feasibility and acceptability of the MOV'D intervention compared to Fitbit-only control. Data were collected in 3 waves or cohorts, allowing for an iterative design. The self-monitor only "Fitbit control" group established dropout rates as feasibility for a fully-powered trial. For the MOV'D intervention only, we will assess the average snacktivities reported for the 4-week intervention period. Both groups took part in a 4-week fully remote intervention with assessments at baseline, postintervention, and 4-week follow-up. An overview of the study design and timeline can be seen in Figure 1.

Figure 1. Study overview and timeline. MOV'D: Move Often Every Day.

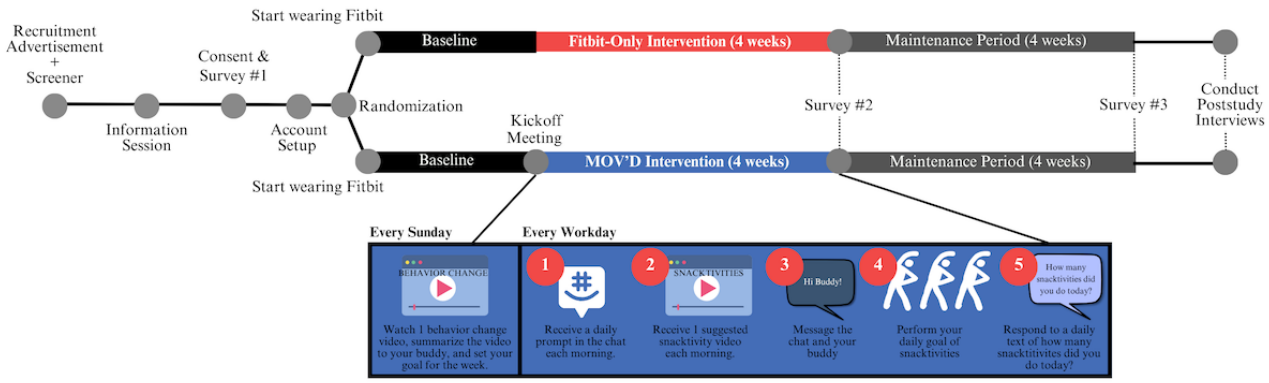

Ethical Considerations

All procedures were registered at Clinicaltrials.gov (NCT05360485) and approved by Stanford University's institutional review board (approval 60388) before beginning recruitment. All participants provided written electronic consent for study participation. Participants received US $10 e-gift cards for the completion of each follow-up survey (up to US $20) and their Fitbit device as study incentives. Data for this study were deidentified to ensure participants' privacy.

Participant Recruitment

Participants were recruited through a health care facility at a university; a staff email listserv; and a third party research service, ResearchMatch, a nonprofit program helping connect people interested in research studies with researchers [60]. Study advertisements included information about the study, critical inclusion criteria, and a link to our screener questionnaire. If interested, individuals would respond to our screener questionnaire to confirm eligibility.

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Inclusion and Exclusion Criteria

The inclusion criteria included being 25-75 years old, being sedentary for the majority of the workday, using social media and text messaging regularly, having a smartphone with unlimited texting, working full-time, being fluent in English, and demonstrating an interest in the study. Individuals were excluded if they had any medical conditions that would prevent them from increasing their physical activity, as determined by the Physical Activity Readiness Questionnaire [61]. Additionally, individuals were required to provide adequate contact information, could not have participated in Tweet4Wellness, and could not be currently enrolled in another physical activity or sedentary behavior study.

Study Procedures

Information Session

After screening eligible, interested individuals were invited to a Zoom-based information session. This session overviewed the study procedures, timeline, and general research principles. Based on motivational interviewing principles, the session also covered randomization, the importance of hearing from participants especially if the study is not working for them, and the pros and cons of participating. This structure has been shown to improve participant trust, sense of partnership, and retention rates [62]. Participants could ask consent and study questions and could consent within 2 days of the information session. Participants were not blinded to the group assignments due to the nature of the study.

Buddy Pairs and Randomization

All participants were assigned a within-study buddy pair during randomization. We block randomized in 3 waves to ensure sufficient numbers for stratification. After 20 eligible participants consented, they were randomized to treatment by using statistical software [63], stratified by self-reported baseline physical activity levels using a block-4 design. Physical activity levels were measured using the International Physical Activity Questionnaire and calculated by summing up the metabolic equivalent of task minutes [64]. First, we stratified into groups of 4 by participants' metabolic equivalent of task minutes. Second, we randomly assigned buddy pairs within each group of 4. Third, prior to randomizing pairs into treatment groups, adjustments were made to 4 buddy pairs to address strong mismatches in work environment or age while maintaining as close a match as possible on baseline physical activity levels. Next, the buddy pairs were randomized to treatment with equal probability by using statistical software. A group of 4 was used to account for the within-group buddy pairings. The second and third waves were randomized in a similar manner but accounting for uneven groups (groups not divisible by 4). Buddy pairs randomized to control were never informed of their buddy pair, while treatment buddy pairs were introduced via Zoom and encouraged to interact directly within the group chat. RA and MB generated the randomization scheme, while JM and MO enrolled the participants and allocated group assignments to the participants after randomization.

Account Setup Calls

Following randomization, participants had a Zoom visit with study staff for the study-provided account setup (both conditions: Fitbit accounts; MOV'D participants only: Twitter [cohort 1], GroupMe [cohorts 2-3]) and app downloads (both conditions: Fitbit; MOV'D participants only: Twitter [cohort 1], GroupMe [cohorts 2-3], EdPuzzle [all cohorts]). For MOV'D participants, Twitter or GroupMe was utilized for social support, and EdPuzzle was used to deliver the video materials (BCT videos and exercise snack suggestion videos). Due to updates at Twitter, our team switched social media platforms for cohorts 2-3. Additionally, study staff informed participants that they were to open their app daily to synchronize their data. Reminder messages were sent to participants on weekdays if they had not synchronized their data for 48 hours.

Intervention

Both MOV'D and Fitbit-only participants were instructed to wear their Fitbit device (Inspire 2) throughout the study, minimizing nonwear time. Participants in the Fitbit-only control groups were given Fitbit accounts with the reminders to move turned off. Participants in the MOV'D intervention group were given Fitbit accounts with the reminder to move turned on. Study staff monitored participants' Fitbit accounts to ensure that reminders to move were not altered.

MOV'D participants received the following components (detailed in Table 1): (1) weekly BCT educational videos, (2) weekday daily reinforcement prompts sent in the group chat (Twitter or GroupMe) to reinforce the BCT content and increase within-group engagement, (3) weekday exercise snack video suggestion demonstrating 2-5 minutes of activity that the participants could do as their exercise snack break, (3) group support via access to a group of peers who are also in the study and attempting to incorporate exercise snack breaks into their daily work routine, and (4) nightly behavior tracking to collect data on the participants' exercise snack breaks for that day and serve as an avenue of self-monitoring. Each week, MOV'D participants were sent their weekly BCT educational video content via a group chat message encouraging them to watch at least one of the provided videos each Sunday. There were 3-5 videos provided each week. MOV'D participants were asked to perform daily exercise snack breaks and actively participate in the group chat. On Sunday, participants set a daily goal of the number of exercise snack breaks for each workday for the upcoming week. Monday through Friday participants receive 2 messages each morning—1 message provided the encouraging daily reinforcement prompt and 1 message provided the suggested exercise snack video for that day. Participants were encouraged to engage in a group chat each day.

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Table 1. Details of the MOV'D (Move Often Every Day) study components.

Study component	Delivery method	Delivery frequency	Description	Examples
Behavior change technique educational videos	Hyperlinked group chat message	Weekly (Sunday) in the evening	Short (4-5 minutes) videos that briefly describe a behavior change technique and how one can incorporate it into their daily life	Avoiding the "What the Hell" Effect: how to stop a slip up from becoming a dive bomb; Fix Faulty Thinking: how shifting your thoughts can help change your behavior
Daily reinforcement prompts	Group chat message	Daily (weekdays) in the morning	1-2 sentences that reinforce the ideas presented in the weekly behavior change technique videos and encourage engagement in the group chat	A situation plan for this week: add something to your workplace that makes it easier to do your snacktivities. What can you ADD to make snacktivities easier?
Exercise snack video suggestion	Hyperlinked group chat message	Daily (weekdays) in the morning	Short (2-5 minutes) follow-along exercise snacks video suggestions	4 min* Jump squat & Mountain climbers, Hip Hop Movement Break
Group support	Twitter (cohort 1); GroupMe (cohorts 2-3)	Daily (weekdays and weekends) throughout day	Cohort-size group (10-xx) chat, with buddy pairs within; encouraged to message every day	How did things go yesterday? It was a tough go for me, but I was still able to get 3 snacktivities
Exercise snack breaks (behavior)	Performed at work or at home	Participant-selected (1-5 times per day)	Weekly goal set on Sunday of how many exercise breaks they hoped to take each workday. They would utilize our videos or come up with their own exercise snacks	Walking briskly up and down the stairs for 3 minutes, YouTube video of the participant's choosing, any of our exercise snack video suggestions
Behavior tracking	Text message	Daily (weekdays and weekends) in the evening	Daily autogenerated text messages prompt daily exercise snack tracking	How many snacktivities did you perform today?

Measures

Assessments included 3 web-based surveys (conducted at baseline, 4 weeks [end of the intervention], and 8 weeks). Surveys assessed exercise self-efficacy, exercise mindset, self-reported physical activity, sleep, and other psychological variables across time points. Demographic information was collected at baseline. Study component acceptability was collected at 4 weeks.

Feasibility and Acceptability

The measures for feasibility and acceptability are detailed in Table 2, including the predetermined cut point for success or target. Feasibility was tracked throughout the study with various methods of measurement. Acceptability metrics included qualitative acceptability data from poststudy interviews and responses to survey questions. Semistructured poststudy qualitative interviews were conducted with a subset of Fitbit-only control and MOV'D intervention participants.

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Table 2. Definitions, methods, and targets of the feasibility and acceptability measures.

Outcome category, measure name	Method of measurement	Measure definition	Target
Feasibility			
Recruitment rate	Recruitment data	The ratio of retained participants to interested individuals	>25%
Recruitment of racial and ethnic minority individuals[a]	Recruitment data	The percentage of retained participants who were racial and ethnic minority individuals	>50%
Retention rate	Surveys, Fitbit data	The ratio of retained participants to randomized participants	>80%
Fitbit valid wear	Fitbit data	The percentage of participants with at least 80% of study days with valid Fitbit data	>80%
Behavior change technique video adherence	Views of behavior change technique videos	The percentage of participants who watched at least 4 behavior change technique videos	100%
Group support engagement	Chat logs from the group support group chat	The percentage of participants who chatted at least half (50%) of the study days	>80%
Exercise snack video usage	Views of exercise snack videos	The percentage of participants who watched at least 4 exercise snack videos	100%
Behavior tracking response rate	Message replies	The ratio of the replied messages to the sum of all the sent tracking messages	>90%
Acceptability			
Qualitative acceptability	Semistructured interviews with participants	Interviews with participants at the end of the study asking about their experience with the intervention	N/A[b]
Quantitative acceptability	Surveys	Survey questions asking about the acceptability of various study components on a 5-point Likert scale	>70% for all study components

[a]An individual who identified as African American, American Indian or Alaska Native, Chinese, Filipino, Indian, Japanese, Korean, Latinx or Hispanic, Pacific Islander or Native Hawaiian, Vietnamese, Other Asian, or other.

[b]N/A: not applicable.

Exercise Snack Behavior Description

Exercise snacks are measured via self-report daily text messages for each workday. Participants were asked "How many snacktivities did you perform today?" Participants were instructed to reply with the number of completed exercise snacks or "NW" for any nonworking day.

Other Measures

The Pittsburgh Sleep Quality Index [65] was utilized to assess sleep, the International Physical Activity Questionnaire [64] was adapted to measure physical activity levels, 2 questions were taken from the Rapid Assessment Disuse Index [66] to capture sedentary behavior, the Perceived Stress Scale [67] was used to assess stress levels, and the Need for Recovery Scale [68] was utilized as a proxy for workplace well-being. Additionally, self-reported height and weight were collected before and after the intervention. Demographic variables such as age, gender, racial and ethnic group, educational attainment, and questions about their work environment were collected at baseline.

Analysis Plan

Feasibility and Acceptability Analysis

Qualitative acceptability interview data generated themes, discussed by the study team, and will be used to refine the intervention as needed. Interviews were transcribed and analyzed using an iterative approach based on reflective thematic analysis [69]. Consistent with the recommendations for behavioral pilot studies, we have set a priori standards for this pilot's acceptability and feasibility metrics (see Table 2). Descriptive statistics for all feasibility and acceptability metrics were conducted using RStudio. As a pre-efficacy pilot trial (ORBIT model) [70], the primary objective is feasibility and acceptability. If successful, these data will inform the development of and provide estimates needed for the implementation of a phase III efficacy trial [70].

Exercise Snack Behavior Analysis

We will graph the average number of reported exercise snacks throughout the 4-week study and describe the average, standard deviation, and range of exercise snacks that are self-reported. As an exploratory measure, we will also examine the changes in the overall MVPA within participants.

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Results

Study enrollment began in March 2022 and concluded in June 2022. Data collection concluded in October 2022. As of July 2025, the data for this pilot study have been analyzed, and results are expected to be reported in late 2025. The MOV'D study has been updated, and an iterative version, MOV'D 2.0, began recruiting participants in 2024. Figure 2 shows the CONSORT (Consolidated Standards of Reporting Trials) diagram for this study (Multimedia Appendix 2).

Figure 2. CONSORT (Consolidated Standards of Reporting Trials) flow diagram for the MOV'D study. MOV'D: Move Often Every Day.

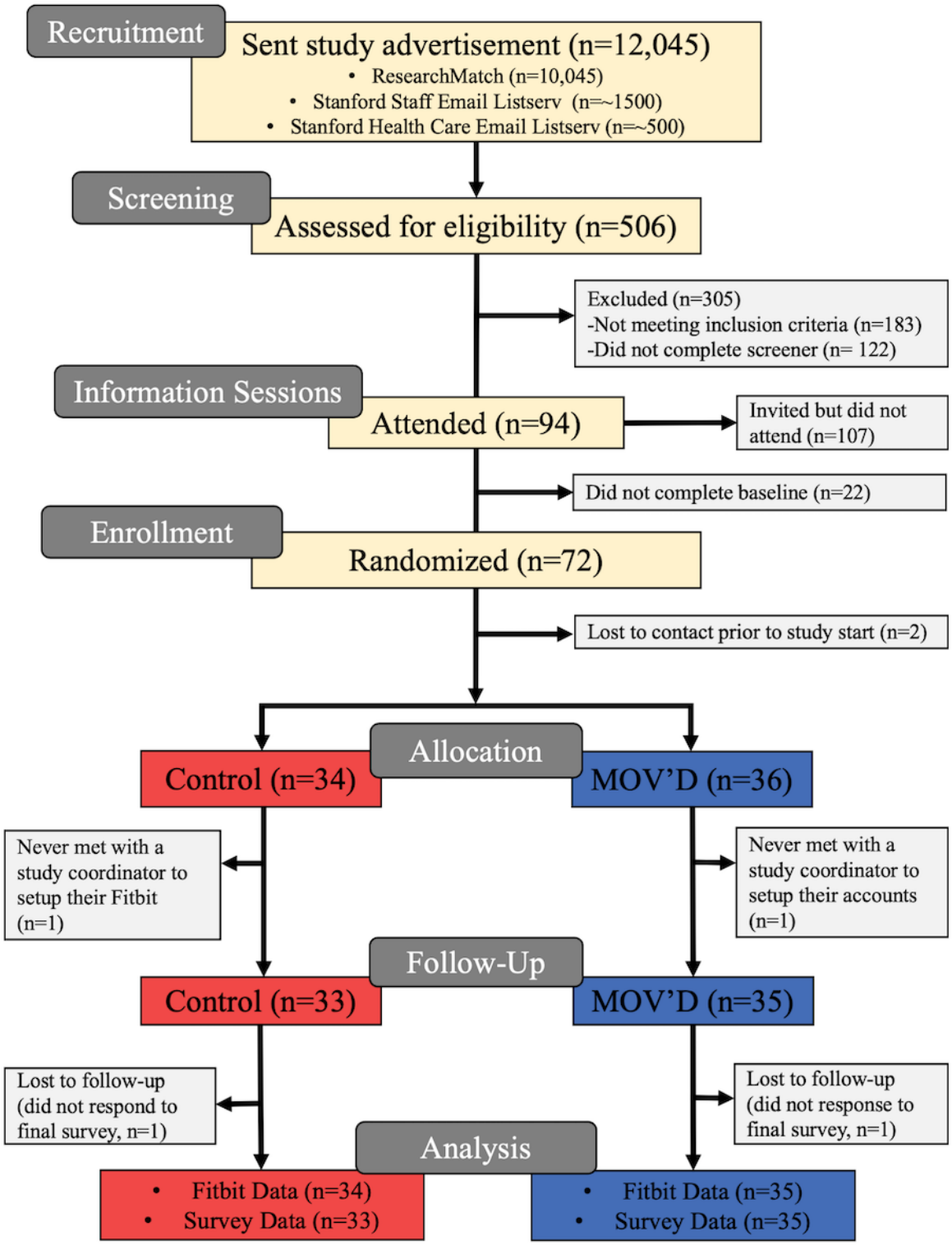

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Discussion

This protocol paper describes a multicomponent, remotely delivered, and peer-supported behavioral intervention to increase exercise snacks at work. This intervention integrates findings from education, behavioral sciences, sedentary behavior, and exercise physiology to promote a habit of taking short intense exercise breaks to break up prolonged sitting. The study results will either inform an iteration to run another feasibility and acceptability pilot phase IIb study or inform a fully powered phase III efficacy trial.

The novel features of this intervention are augmented versions of previously established behavior change principles. First, exercise buddies have been shown in pilot trials to improve exercise adherence [71,72]. In MOV'D, buddy pairs are peer coaches. They not only provide accountability but teach each other behavior change strategies they learn each week. This increases the learning of each participant (eg, they watch 1 video but learn 2 strategies) and increases the likelihood of the coach remembering the strategy (eg, teaching another increases learning and application of concepts) [52,73]. Second, group support has been shown to increase the informational and emotional support for behavior change [74,75]. MOV'D augments this feature by integrating experimenter-seeded prompts to increase and guide engagement and reinforce behavior change practices. Third, exercise videos can provide guidance, aid in exercise completion, and provide role model behavior. MOV'D filmed diverse bodied and aged models in work attire and office settings to demonstrate the ability to do exercise snacks in atypical settings, modeling that a gym, equipment, or clothing are not requirements to integrate moderate to vigorous exercise bouts into one's workday. This is based on the principles of the social learning theory [76] using role modeling and vicarious learning [77]. Finally, interventions based on the behavioral science theory are more effective than those that are not [51]. Typically, these evidence-based strategies are built into the intervention itself, such as reward incentives [78], study-provided reminders [79], or growth mindset modules [80]. The MOV'D intervention instead explicitly taught evidence-BCTs to participants to utilize themselves.

The ORBIT model of optimizing behavioral intervention development recommends iteration and pilot testing of feasibility and acceptability (ORBIT phase IIb, aim 2). This protocol and feasibility pilot will position the MOV'D intervention to either be further iterated or tested in an ORBIT phase III efficacy trial. The MOV'D intervention combines learning science, behavioral science practices, and social support in a fully remote, peer-supported workday activity intervention. The ultimate goal is to test a potential intervention addressing 2 independent and major risk factors for CVD: prolonged sitting and inadequate physical activity.

We expect this study to add to the literature on exercise snack workplace interventions. Stork et al [29] demonstrated preference for short exercise snacks. We add a measurement-only maintenance period after the intervention to investigate if the preference extends to behavior change without intervention scaffolds. We also add a nonintervention control group to test for differential dropouts.

A limitation of this study protocol is the inability to objectively measure heart rate and minutes of exercise snacks taken at work. Although pilot testing indicated the Fitbit may detect these, most consumer-grade wearables are inaccurate at higher heart rates with arm movements. Further, many of the exercise snack movements are done in place (therefore will not accrue steps on the wearable). Finally, Fitbit's proprietary algorithms that smooth data may overwrite the short bursts of heart rates, detecting it as an anomaly. Another limitation is the potential between-group variability of group interaction and support. Groups can look different from each other in terms of the support offered, chattiness, and energy [81].

Acknowledgments

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Data Availability

The datasets generated and analyzed during this study will be available upon reasonable request from the corresponding author.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Poststudy interview guide.
[DOCX File , 19 KB - resprot_v14i1e64455_app1.docx]

Multimedia Appendix 2
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1073 KB - resprot_v14i1e64455_app2.pdf]

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Abbreviations

BCT: behavior change technique
CONSORT: Consolidated Standards of Reporting Trials
CVD: cardiovascular disease
MOV'D: Move Often Every Day
MVPA: moderate to vigorous physical activity

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Protocol

Comparison of Telehealth and Onsite Supervised Maintenance Exercise Programs for Adults With Chronic Lung Disease: Protocol for a Pilot Randomized Feasibility Trial

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Abstract

Background: Chronic lung diseases (CLDs) such as chronic obstructive pulmonary disease, interstitial lung disease, and chronic asthma contribute significantly to the global burden of disease. Pulmonary rehabilitation (PR) is an effective intervention for improving the exercise capacity, increasing the quality of life, and reducing hospitalizations in individuals with CLD. However, benefits from PR quickly decline following discharge from traditional programs. Telerehabilitation (tele-rehab) has emerged as a potential solution for extending the benefits of PR; yet, few studies have compared its efficacy with conventional onsite maintenance rehabilitation.

Objective: This pilot protocol aims to assess the effectiveness of an 8-week supervised maintenance rehabilitation program delivered onsite or remotely via tele-rehab in patients with CLD.

Methods: This randomized, assessor-blinded feasibility pilot trial will enroll 30 participants who have completed outpatient PR. Participants will be randomized into 2 groups: (1) tele-rehab, involving remotely supervised sessions conducted via videoconferencing or (2) onsite maintenance rehabilitation with in-person sessions. Both groups will receive weekly supervised sessions for 8 weeks facilitated by licensed physical therapists. Assessments will be conducted onsite at baseline, after the 8-week intervention, and at 1-month follow-up by a blinded assessor. The feasibility of the intervention and the study methods will be assessed by the log-in into the number of sessions attended after randomization, the ease of using the equipment and procedures, optimal session length, and adherence to the intervention protocol. Clinical outcomes will include dyspnea and perceived exertion, respiratory muscle strength, physical function, 6-minute walk distance, physical activity, and quality of life. Descriptive statistics with means and standard deviations for continuous and frequency distributions for categorical data will be utilized to report individual and group characteristics. Feasibility outcomes will be compared using independent 2-sided *t* tests. Between-group comparisons will use mixed analysis of variance, and within-group comparisons will be analyzed with a repeated measures analysis of variance.

Results: Recruitment for this institutional review board—approved study (approval date: July 25, 2023) began in January 2024, with 11 (37%) of the 30 participants enrolled to date. This study will generate data comparing tele-rehab and onsite rehabilitation in terms of the primary and secondary outcomes. Use data such as program adherence and attrition will also be reported. The results will inform the feasibility, adherence, and effectiveness of tele-rehab as a sustainable alternative to onsite maintenance rehabilitation. The study is anticipated to be completed by April 2026.

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Conclusions: This study hypothesizes that both tele-rehab and onsite programs will significantly improve clinical outcomes, with tele-rehab yielding comparable benefits to onsite maintenance. Findings will provide evidence supporting accessible and sustainable maintenance rehabilitation options for patients with CLD and guide future large-scale efficacy trials.

Trial Registration: ClinicalTrials.gov NCT06304207; https://clinicaltrials.gov/study/NCT06304207

International Registered Report Identifier (IRRID): DERR1-10.2196/71039

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KEYWORDS

chronic lung disease; pulmonary rehabilitation; telerehabilitation; exercise capacity; quality of life; health care utilization

Introduction

Chronic lung disease (CLD), an umbrella term for persistent lung conditions, including chronic obstructive pulmonary disease (COPD), interstitial lung disease, bronchiectasis, and chronic asthma, is a major contributor to the global burden of disease [1,2]. Patients with CLD are often trapped in the downward spiral of mobility, where symptoms such as dyspnea and fatigue limit physical activity [3,4]. Reduced activity levels further accelerate disease progression, leading to declines in muscle strength, deconditioning, and worsening of symptoms [3,4]. Consequently, patients experience increased respiratory exacerbations, resulting in frequent hospitalizations and readmissions, impacting the quality of life and health care costs [5-9].

Pulmonary rehabilitation (PR) has been reported as one of the most evidence-based, cost-effective, and efficient interventions to improve health outcomes in CLD [5-9]. The American Thoracic Society/European Respiratory Society statement defines PR as “a comprehensive intervention based on a thorough patient assessment followed by patient-tailored therapies, which include, but are not limited to, exercise training, education, and behavior change, designed to improve the physical and emotional condition of people with chronic respiratory disease and to promote the long-term adherence of health-enhancing behaviors” [5]. Compared to medical management alone, strong evidence supports PR to improve lung function, exercise capacity, physical function, self-efficacy, quality of life, and physical activity while also delaying disease progression and reducing the risk of hospitalization and mortality [5-9].

Despite strong evidence demonstrating PR effectiveness, reported benefits rapidly decline after discharge in the absence of supervised maintenance as adherence to health-enhancing behaviors and physical activity levels wane over time [10,11]. To promote long-term adherence, patients may need a continuum of care with tapered supervision beyond formal PR. Supervised maintenance programs involve ongoing supervised exercise at a lower frequency than PR programs. Although an abundance of literature supports the benefits of PR, studies examining maintenance programs are scarce and demonstrate mixed results. Limited studies using community-based supervised maintenance following PR have demonstrated a strong potential of these programs in maintaining a variety of outcomes, including physical activity level, quality of life, 6-minute walk distance, and dyspnea scores [12], but other studies on maintenance have failed to demonstrate these benefits [13,14]. Overall, the certainty of evidence on the benefits of maintenance programs is deemed low, particularly due to inconsistent performance on outcome measures, high risk of bias, lack of rigorous methodologies, attrition, and small sample sizes [15]. Ongoing improvements in outcomes are believed to result from enhanced function, exercise tolerance, and symptom control with structured maintenance programs [6,7,15]. However, access barriers and adherence challenges persist, highlighting the need for feasible, scalable models like telehealth [16]. These limitations underscore the need for well-designed studies to evaluate the feasibility and effectiveness of supervised maintenance programs, particularly those delivered via telehealth.

One method to improve adherence in maintenance programs is telerehabilitation (tele-rehab), which is a way of participating in medical appointments via a technology device [17]. Tele-rehab is a viable alternative rehabilitation approach for patients with CLD and holds potential as an effective tool for increasing positive behavioral changes, including long-term adherence and a more physically active lifestyle [18-21]. Few studies [18,22-24] have compared the benefits of tele-rehab versus onsite PR on health outcomes in people living with CLD, and even fewer studies have compared supervised maintenance programs delivered via tele-rehab with onsite maintenance, leaving many gaps in the literature [25]. Furthermore, most studies are limited to people with COPD, with only a small number investigating the effects of tele-rehab on other CLDs [26,27].

Given these limitations, there is a clear need for well-designed feasibility studies to evaluate the effectiveness and practicality of supervised maintenance programs, particularly those delivered via telehealth. The purpose of this pilot feasibility trial is to (1) assess the feasibility of delivering an 8-week supervised maintenance program remotely via tele-rehab in comparison to onsite delivery and (2) compare the effectiveness of these interventions on clinical outcomes in patients with CLD. We hypothesize that tele-rehab will be feasible to implement, with acceptable adherence, and will yield comparable improvements in clinical outcomes to onsite rehabilitation.

Methods

Ethical Considerations

The study protocol has been reviewed and approved by the institutional review board at Massachusetts Brigham (approval 2023P000708). The study protocol is registered on

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Clinicaltrials.gov (NCT06304207). Any changes to the protocol will be reported to the institutional review board by the principal investigator. Participants will provide verbal consent during a phone call after being prescreened for eligibility. A signed consent form will then be obtained either in person during their baseline assessment or electronically through Research Electronic Data Capture (REDCap) [28]. Institutional affiliations (eg, Massachusetts Brigham and the MGH Institute of Health Professions) will be transparently presented to the participants during recruitment to ensure trust and informed decision-making. In order to protect the participant's privacy, all recorded data will be deidentified and stored in a password-protected computer. This information will then be destroyed at the end of the study. All study team members underwent training on protecting data privacy. To reduce the barriers to participation and to encourage enrollment, we will provide free parking for onsite visits; an iPad will be loaned for the study duration if needed for tele-rehab, and a US $50 gift card will be provided upon study completion.

Study Design

This study follows the CONSORT (Consolidated Standards of Reporting Trials; Multimedia Appendix 1) and SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials; Multimedia Appendix 2) guidelines. The study will be a randomized, assessor-blinded, pilot feasibility trial. Participants will be randomly assigned in a 1:1 allocation ratio to either (1) a tele-rehab group with remotely supervised intervention or (2) an onsite group with in-person supervision. Figure 1 outlines the study design and recruitment process. The anticipated study period is from September 1, 2023, to April 1, 2026.

Figure 1. Participant Recruitment and Allocation.

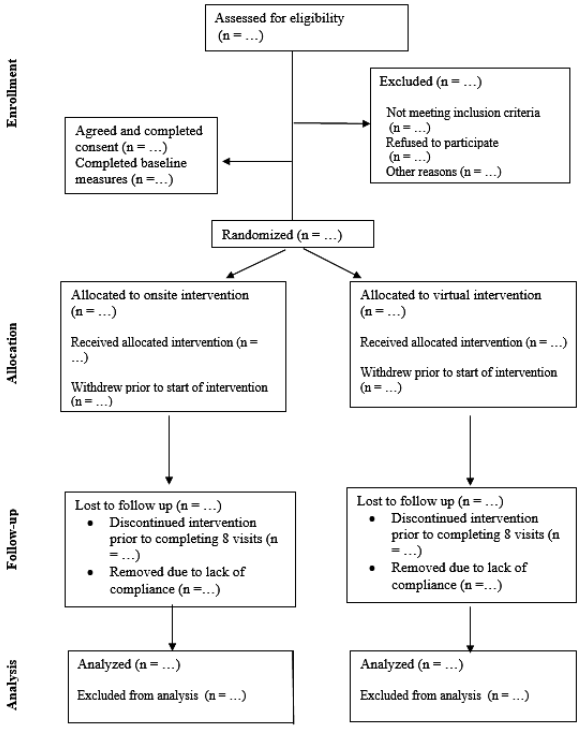

Given the higher prevalence of CLD in late adulthood [29-31], individuals aged 40 years and older with a physician-confirmed diagnosis of CLD will be recruited for this study. Inclusion criteria include the ability to understand English instructions, walk independently with or without the use of mobility devices, complete a 6-minute walk test (6MWT) while maintaining oxygen saturation of at least 85% with or without supplemental oxygen, a history of onsite rehabilitation completion, and internet access, which will be verified by accessing email for communication. Exclusion criteria include medical conditions causing significant mobility limitations such as stroke, Parkinson disease, multiple sclerosis, or severe degenerative joint disease. Participants will also be excluded if they are unable to maintain oxygen saturation of at least 85% during 6MWT, have baseline hemodynamic instability (eg, unstable angina, recent myocardial infarction within 3 months, uncontrolled atrial fibrillation), advanced heart failure (New York Heart Association Class IV), or require mechanical circulatory support such as ventricular assist devices.

Participant Enrollment

Eligible participants will be recruited through clinical settings, offline outreach, and direct contact by study team members. During recruitment, participants will receive detailed verbal information about the study, including the randomization process, assessments, and intervention details.

Study Procedures

Onsite Initial Evaluation

After providing informed consent, all participants will complete a baseline assessment at Dr Charles and Ann Saunders IMPACT Practice Center at MGH Institute of Health Professions. This initial visit, conducted by an assessor blinded to group allocation, will serve as the index date, referred to as time point 0 (time0). Since recruitment will occur on a rolling basis, time0

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will vary for each participant. During the baseline visit, the assessor will review the self-monitoring of vitals and symptom provocation with participants. Education on monitoring oxygen saturation by using pulse oximetry, rate of perceived exertion, and heart rate will be provided in detail. Additionally, participants will receive a pulse oximeter and a Threshold Inspiratory Muscle Trainer Respironics positive expiratory pressure device during the baseline visit to use throughout the study.

Random Assignment

Following the baseline assessment, a separate research team member will contact each participant via phone to communicate the randomized group assignment. Participants will be randomly assigned to one of the 2 groups: (1) tele-rehab, where the participants receive supervised intervention remotely at home or (2) onsite outpatient rehabilitation. A web-based randomization service [32] will be used to generate random assignments to eliminate allocation bias.

Outcome Assessments

Outcomes will be recorded in-person at 3 time points: at baseline before the intervention (time0), at the end of the 8-week intervention (time1), and at 1-month post intervention during follow-up (time2). A blinded study team member will conduct all outcome assessments at each time point (Table 1), with reminder emails sent to participants during the week the assessment is scheduled. Feasibility outcomes will include the number of sessions attended post randomization, the ease of using equipment and procedures, optimal session length, and adherence as measured by the daily activity log. Clinical outcomes will include baseline vitals such as heart rate, respiratory rate, oxygen saturation measured with a pulse oximeter, Borg rating of perceived exertion [33], and modified Medical Research Council dyspnea scale [34,35]. Respiratory muscle strength will be evaluated using maximal inspiratory pressure, while physical function will be assessed with the 30-second chair rise test [36] and the 10-meter walk test [37]. Functional capacity will be measured through 6MWT [38,39] and the 10-meter incremental shuttle walk test [40]. Physical activity will be assessed using the International Physical Activity Questionnaire [41], and the quality of life will be evaluated with the Patient-Reported Outcomes Measurement Information System Global Health Questionnaire [42] and the COPD Assessment Test [43]. Secondary outcomes will include planned or unplanned physician visits, emergency room visits, falls, and injuries.

Table 1. Interventions provided for tele-rehab[a] and onsite rehab[b] groups.

Goal (duration)	Tele-rehab group and onsite rehab group
Check-in and education (5 min)	• Review of activities during the week at home • Symptom changes during the week • Education on self-management of airway clearance • Education on the importance of maintaining regular physical activity
Breathing retraining (5 min)	• Inspiratory muscle training using a Threshold Inspiratory Muscle Trainer at 30%-50% of maximal inspiratory pressure
Warm-up (5 min)	• Spot marching • Stretching large group muscles
Aerobic exercise (25 min)	• Treadmill/cycle ergometer/NuStep/walking/stair climbing[c] • Treadmill walking: initial walking speed at 60%-85% of peak VO2[d] estimated from 6MWT[e] and/or rate of perceived exertion of 13-16 (somewhat hard to hard) corresponding to 60%-85% of peak VO2 • Cycle ergometer and NuStep intensity at rate of perceived exertion of 13-16 or a resistance corresponding to 60%-85% of peak VO2 derived from published equations • Overground walking or stairs at rate of perceived exertion of 13-16 (somewhat hard to hard) corresponding to 60%-85% of peak VO2
Functional strengthening (15 min)	• Partial squats, sit-to-stand exercise, lunges, and step-ups/downs • 3 sets of 10 repetitions each
Cool down (5 min)	• Spot marching • Stretching of large group muscles

[a]Tele-rehab: telerehabilitation group. This group receives remotely supervised sessions conducted via videoconferencing.

[b]Onsite-rehab: onsite maintenance rehabilitation. This group receives onsite maintenance rehabilitation with in-person sessions.

[c]No stair climbing in the onsite rehabilitation group.

[d]VO_2: oxygen consumption.

[e]6MWT: 6-minute walk test.

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Intervention

Participants will begin the 8-week intervention for the PR maintenance program in either the onsite or remote group depending on their group allocation, with supervised visits occurring once a week for both groups and regular reminders for the meetings sent to participants. At the initial treatment session, each participant will receive printed educational materials from the COPD Foundation [44] and the Pulmonary Fibrosis Foundation [45]. These resources will cover topics such as living well with CLD, the impact of smoking, and creating a CLD action plan, including disaster preparedness. Both groups will participate in a weekly 60-minute supervised session. Supervised sessions will be delivered in-person for the onsite group and remotely via video conferencing for the tele-rehab group. The intervention intensity will be determined by the distance covered in 6MWT conducted at baseline. Licensed physical therapists from the study team who have expertise in managing chronic conditions will deliver all the interventions. These therapists will receive specific training on the study protocol to ensure consistency in intervention delivery. All interventions will adhere to the research protocol outlined in Table 1.

Onsite Group

The supervised 60-minute session for onsite participants will include multiple components. The session will begin with a brief check-in to review the participant's weekly activities at home and any changes in symptoms, followed by education on self-management strategies for airway clearance and the importance of maintaining regular physical activity. Breathing retraining will involve inspiratory muscle training using the Threshold Inspiratory Muscle Trainer Respironics PEP at 30% to 50% of maximal inspiratory pressure. After the breathing exercises, participants will complete a 25-minute aerobic exercise training session, preceded by a short warm-up. Aerobic training will be performed using available equipment such as a NuStep, treadmill, cycle ergometer, or through overground activities, including walking or stair climbing. The training intensity will be prescribed based on the baseline 6MWT results. Peak oxygen consumption (VO_2) will be estimated using published regression equations [46]. Training will be conducted at 60%-85% of VO_2 reserve and converted to walking distance and speed using the American College of Sports Medicine walking equations for treadmill and overground walking [47]. For nonwalking activities such as cycling or stair climbing, a corresponding rate of perceived exertion of 13-16 will be used. Aerobic training may be completed as a continuous 25-minute session or divided into intervals (eg, 2 × 12.5 minutes or 3 × 8.3 minutes) if symptoms limit continuous exercise.

Following aerobic training, functional strength exercises focusing on lower extremity muscles, including partial squats, sit-to-stand exercises, lunges, and step-ups/step-downs, will be performed. Each session will conclude with a short cool-down period. The details of the intervention sessions are outlined in Table 1. Participants will also be asked to maintain a daily physical activity log and report any planned or unplanned physician visits, emergency room visits, falls, or injuries. The attendance for each session will be recorded.

Tele-Rehab Group

Participants in the tele-rehab group will follow the same intervention protocol as the onsite group described above, with the mode of aerobic exercise adjusted based on available equipment (see Table 1). Each tele-rehab participant will receive a respiratory muscle training inspiratory muscle trainer device for home use. The intervention will be delivered remotely via established tele-rehabilitation models using a tablet computer. iPads will be loaned to participants as needed for the duration of the study. Videoconferencing will be conducted via research-grade Zoom teleconferencing [48], which will enable participants to see and speak to the supervising physical therapist. To ensure the safety of participants and proper understanding of equipment use and the exercise program, we will conduct the initial training session and home exercise program setup during the initial onsite visit. The fidelity of the exercise intervention for both groups will be maintained through regular staff training, audits of exercise prescription and progression, and monitoring of participant engagement.

Statistical Analysis

Since a large 2-group comparative study has not yet been published, this pilot study will generate an estimate of variance and the percentage of change in outcomes needed to determine the power and sample size for a larger study. Therefore, estimation rather than statistical testing is the main objective of this study. Given the possibility of attrition from dropouts, we will recruit 40 participants with a goal to have 30 participants complete the study (15 in each group). Descriptive statistics will be used to summarize the demographic and clinical characteristics and outcomes for all the participants. Feasibility will be assessed using frequency distributions of session adherence and use of activity logs. Comparisons between groups on all outcomes at preintervention and postintervention will be conducted with the intention to treat using a mixed analysis of variance. Within-group comparisons at all 3 time points will be conducted via a repeated measures analysis of variance. Adherence to the program between groups will be compared using independent 2-sided *t* tests. Finally, descriptive statistics with frequency distributions of adverse events, planned and unplanned physician visits, and frequency of use of daily activity log will be reported.

Results

This study received institutional review board approval from Massachusetts Brigham (approval 2023P000708) on July 25, 2023.The recruitment for the first wave began in January 2024. To date, we have enrolled 11 (37%) out of 30 participants, as projected. The final wave of recruitment will end by December 2025, and the final participant will complete the study by March 30, 2026. Descriptive data revealed that 1 participant in the virtual group who completed the study had better 6MWT scores than the participant in the onsite group. We will start analyzing the complete responses by April 30, 2026, and the publication of results is expected at the end of 2026.

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Discussion

Overview

We describe a protocol for a pilot randomized feasibility clinical trial to examine the effectiveness of virtually delivered supervised maintenance for patients with CLD. This proposed intervention breaks down barriers to equitably ensure sustained benefit and improved self-efficacy for all, regardless of their ability to physically reach an onsite location. Despite level 1 evidence from high-quality clinical trials supporting the effectiveness of PR in improving health outcomes, barriers to accessing physical locations have historically limited the utilization of these services. More importantly, even for those who complete the onsite rehabilitation, the benefits from rehabilitation do not last following discharge. As finding ways to improve self-efficacy and long-term adherence are key to preventing adverse outcomes, examining maintenance programs is crucial. This pilot trial will provide information on the feasibility of the intervention in a remote setting and will pave the way for large-scale clinical trials.

Limitations

There are several limitations that we would like to acknowledge. Although we anticipate achieving a feasible, acceptable, and high-fidelity protocol, it is possible that some challenges remain. Given a feasibility pilot, we anticipate being underpowered to assess intervention efficacy. Despite the randomized design, allocation concealment is not possible. The risk of participants dropping out after learning their allocation assignment cannot be ruled out. We have taken measures to minimize this risk by having trained research staff instead of staff manage action planning and SMS text messaging procedures to avoid any accidental information exchange about other participants. Although steps are taken to improve access to all potential individuals, limiting inclusion to participants who speak English may limit the reach to participants who have limited English proficiency.

Conclusions

This pilot randomized feasibility trial aims to address critical gaps in the long-term management of CLD by comparing onsite and tele-rehab supervised maintenance programs. The study emphasizes the importance of overcoming traditional barriers to PR, such as transportation challenges and limited facility availability while promoting equitable access to care. By focusing on improving self-efficacy and adherence to health-enhancing behaviors, this intervention has the potential to sustain the benefits of PR beyond discharge and reduce adverse health outcomes. The trial will provide valuable data on feasibility, adherence, and clinical outcomes for tele-rehab and onsite programs, providing insights for the development of larger-scale trials. Additionally, this study addresses the growing need for innovative care models that incorporate technology to enhance patient outcomes and reduce health care disparities. Despite the acknowledged limitations such as the small sample size, language restrictions, and the potential for dropout, the findings will contribute valuable information to guide future efficacy trials. This trial has the potential to inform future standards of care for patients with CLD by demonstrating the feasibility of accessible and effective tele-rehabilitation maintenance programs to sustain long-term health benefits.

Acknowledgments

We are grateful to Dr Daniel Kelleher and Dr Monica Warren for their assistance with the recruitment phase. This study was supported by the MGH Institute of Health Professions.

Data Availability

The datasets generated or analyzed during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization: SG (lead), MS (supporting)
Investigation, methodology, data curation, and validation: SG (lead) JB (supporting), RK (supporting), LS (supporting), RP (supporting), LM (supporting)
Data curation, software, visualization, and formal analysis: SG (lead), HJK (supporting)
Writing – original draft: SG (lead), all authors (supporting)

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 2666 KB - resprot_v14i1e71039_app1.pdf]

Multimedia Appendix 2
SPIRIT checklist for reporting the protocol.
[PDF File (Adobe PDF File), 1082 KB - resprot_v14i1e71039_app2.pdf]

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Abbreviations

6MWT: 6-minute walk test
CLD: chronic lung disease
CONSORT: Consolidated Standards of Reporting Trials
COPD: chronic obstructive pulmonary disease
PR: pulmonary rehabilitation
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
Tele-rehab: telerehabilitation
VO2: oxygen consumption

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Protocol

Development of a Social Communication Intervention Mobile App for Adolescents With Autism Spectrum Disorder and Social Communication Disorder: Protocol for a Pilot Randomized Clinical Trial

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Abstract

Background: Autism spectrum disorder (ASD) and social communication disorder (SCD) are neurodevelopmental disorders characterized by deficits in social communication that hinder social adaptation, with limited pharmacological options for therapy owing to the absence of identified biomarkers. Individuals with ASD or SCD require lifelong interventions tailored to their development stages. However, most existing interventions primarily focus on early childhood, leaving adolescents relatively underserved. Moreover, timely access to interventions is often limited by geographic and economic barriers as specialized clinics and therapists tend to be concentrated in major urban areas.

Objective: This pilot randomized clinical trial aimed to evaluate the initial safety and efficacy of NDTx-01, a digital therapeutic (DTx) for adolescents with ASD or SCD. NDTx-01 was designed to overcome the accessibility limitations by integrating cognitive behavioral therapy principles, story-based interventions, and gamification elements.

Methods: We introduce a protocol for a multicenter, prospective, assessor-blinded pilot randomized clinical trial involving children and adolescents aged 10 to 18 years diagnosed with ASD or SCD. Participant enrollment was conducted at 3 major medical hospitals. Enrolled participants were randomly assigned to either the intervention group (NDTx-01 and treatment as usual [TAU]) or the control group (TAU only). TAU included medications and therapeutic services. Participants were instructed to use the app approximately 10 minutes per day, 5 days a week. To evaluate the efficacy of NDTx-01, standardized tools were administered, including the Korean version of the Vineland Adaptive Behavior Scales, Second Edition (K-VABS-II); the Social Responsiveness Scale, Second Edition; Clinical Global Impressions–Severity (CGI-S); Clinical Global Impressions–Improvement (CGI-I); the Social Communication Questionnaire; and the Korean version of the Stress Index for Parents of Adolescents. Assessments were conducted in weeks 0, 1, 2, 4, and 6, except for K-VABS-II, CGI-S, and CGI-I, which were administered only in weeks 0, 4, and 6. Statistical analyses were conducted using the SAS software. Between-group differences were assessed using independent 2-tailed 2-sample *t* tests or Wilcoxon rank sum tests. Within-group changes were evaluated using paired *t* tests or Wilcoxon signed rank tests.

Results: From August 2024 to December 2024, a total of 42 individuals were screened, 39 (93%) participants who met the inclusion criteria were enrolled, and 1 participant withdrew consent; the remaining participants completed the study. The pilot

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randomized clinical trial was successfully completed, and the results were published in April 2025. As of 2025, we are conducting a confirmatory clinical trial at 5 major hospitals across South Korea.

Conclusions: The results of this pilot clinical trial provided important insights into the initial safety and efficacy of DTx as interventions for adolescents with ASD and SCD. Both groups demonstrated statistically significant improvements in adaptive skills and socialization.

Trial Registration: Clinical Research Information Service KCT0009140; https://cris.nih.go.kr/cris/search/detailSearch.do?seq=26713

International Registered Report Identifier (IRRID): DERR1-10.2196/66419

(JMIR Res Protoc 2025;14:e66419) doi:10.2196/66419

KEYWORDS

autism spectrum disorder; social communication disorder; digital therapeutics; adolescents; clinical trial; social communication

Introduction

Background

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by deficits in social communication, repetitive behavior, and restricted interests [1]. Deficits in social communication result in difficulties in engaging in reciprocal interactions. These challenges manifest in various situations, such as maintaining dialogue, comprehending humor and idioms, and understanding others' emotions. These impediments play a critical role in the complexity of social adaptation.

Social communication disorder (SCD) is a new diagnosis included in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* [1]. While individuals with SCD share the primary impairment of deficits in social communication with those with ASD, they can be differentiated from those with ASD in that people with SCD do not manifest restricted interests and repetitive behaviors [1-4]. As science develops and social awareness increases, there has been an observed increase in the diagnostic rates and prevalence of both SCD and ASD. The Centers for Disease Control and Prevention [5] reported that 1 in 44 people have ASD in the United States. According to Kim et al [6,7], the prevalence of ASD in South Korea is estimated to be 2.64% (95% CI 1.91%-3.37%), which translates to 1 out of 38 people, and Russell et al [8] state that the diagnosis rate of ASD in the United Kingdom increased by 787% in the last 2 decades. The prevalence of SCD is difficult to determine because of inconsistent or ambiguous definitions [9]. However, Ellis Weismer et al [4] reported that the prevalence of SCD in developmental disorders was 7% to 11% from 1491 samples in phases 1 and 2 of the Study to Explore Early Development.

To date, there is no specific medication licensed for the treatment of the core symptoms of ASD and SCD as biomarkers have not been fully identified. Face-to-face interventions are recommended by various clinical guidelines, such as *Post-diagnostic Management and Follow-up Care for Autism Spectrum Disorder* [10] and specific interventions for the core features of ASD [11] and SCD [9].

Individuals with ASD and SCD require lifelong care involving various treatments, such as social skill training, speech therapy, applied behavior analysis, and special education. Research shows that approximately 50% of children with ASD have used at least one medication in the past year [12-16], and they are currently undergoing an average of 6 to 8 treatments [17]. Given the critical importance of early intensive intervention for later developmental outcomes [18,19], early diagnosis and adequate treatment are crucial. However, the concentration of medical institutions and treatment services in urban areas poses a significant barrier for individuals living in rural areas seeking proper care [20-22].

The high costs associated with treatment can also pose a burden on individuals, families, and society, potentially impeding continuous interventions [6,7,23]. In the United States, Leigh and Du [24] estimated the total national economic burden of ASD to be US $268 billion in 2015, a figure projected to increase to US $461 billion by 2025. This estimate includes direct medical costs, direct nonmedical costs, and productivity losses. MacKay et al [25] reported an annual cost of £2.3 billion (US $3.1 million) in Scotland. However, it is crucial to recognize that these figures may not fully capture the entire economic burden both within and outside medical institutions and that many treatments fall outside the scope of health insurance coverage.

In several studies, technology-based interventions have proven effective in teaching and developing social skills in patients with ASD and other developmental disorders. Gamification—applying game elements and game design techniques in nongaming contexts [26]—enhances the sense of engagement, immediate feedback, and success in overcoming challenges [27]. This can significantly increase the effectiveness of technology-based interventions. Repetitive learning and training in a safe environment, such as using smart devices at home, can reduce anxiety and distraction in adolescents in need [28-30]. Furthermore, technology-based interventions can lessen the physical, temporal, and economic burdens on caregivers.

The prevalence of chronic diseases and the high cost of face-to-face medical treatments underscore the need for digital therapeutics. According to Statista [31], the digital therapeutics market will increase from US $1.67 billion in 2016 to US $8.94 billion in 2025. The number of DTx users is projected to grow to 652.4 million by 2025 from 44 million in 2021. The global market value of digital therapeutics was US $4.2 billion in 2021 and is estimated to reach US $17.3 billion by 2030 following the impact of the COVID-19 pandemic.

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Objectives

The development of digital therapeutics for social skill training holds significant potential but is still in its early stages. Consequently, there is limited guidance on how to evaluate the efficacy and safety of newly developed digital social skill training programs, especially for ASD and SCD. Therefore, we developed a digital therapeutic agent, NDTx-01, and designed a pilot clinical trial to validate its initial safety and efficacy. This pilot clinical trial was conducted in accordance with protocol ND-01 (version 7.1; December 6, 2023). Thus, the research objectives of this study were to design and develop a simulation game–based digital therapy aimed at enhancing social communication and interaction skills for adolescents with ASD and SCD and to develop a pilot clinical trial protocol for assessing the clinical effectiveness of the simulation game–based digital therapy.

Methods

Study Design

To improve the social abilities of adolescents with ASD and SCD, we developed a digital therapeutic named NDTx-01. To evaluate the initial efficacy and safety of NDTx-01, a multicenter, prospective, randomized, and assessor-blinded pilot study was conducted.

Participants were instructed to maintain their usual care, such as medication, other face-to-face interventions, and special education, from 4 weeks before the start of the clinical trial to its conclusion. Any changes in their usual care led to participant exclusion from the trial. However, all data collected up to the point of exclusion were preserved in the electronic data capture system for analysis.

The flowchart of the pilot clinical trial is presented in Figure 1. The intervention group was provided with NDTx-01, which contained stories with questions about social situations commonly experienced in school settings. Questions regarding verbal or nonverbal expressions, appropriate communication responses, and social cognition of the situations they observed were presented, all guided by instructions. At the end of each story, summaries, additional questions, and behavioral tasks were presented. Each session lasted approximately 10 minutes, and the participants used NDTx-01 a total of 5 days a week for 6 weeks. In addition, usual care was maintained for the intervention group participants throughout these 6 weeks. The control group maintained their usual care, or treatment as usual, for 6 weeks, with the option to use NDTx-01 after the end of the clinical trial. Treatment as usual included ongoing care such as pharmacological treatment, speech therapy, psychiatric consultations, or school-based counseling. These interventions needed to be initiated at least 4 weeks before screening and were required to be maintained throughout the study period. The type and frequency of interventions varied based on individual clinical needs and were not standardized by the study protocol.

Assessments were conducted in weeks 0, 1, 2, 4, and 6 or weeks 0, 4, 6 (with a margin of −3 days to +3 days for each) to evaluate the effectiveness of NDTx-01.

Figure 1. Flowchart of the pilot clinical trial. CGI-I: Clinical Global Impressions–Improvement; CGI-S: Clinical Global Impressions–Severity; K-SIPA: Korean version of the Stress Index for Parents of Adolescents; K-SSRS: Korean version of the Social Skills Rating System; K-VABS-II: Korean version of the Vineland Adaptive Behavior Scales, Second Edition; RCMAS-2: Revised Children's Manifest Anxiety Scale, Second Edition; SCQ–Current Form: Social Communication Questionnaire–Current Form; SRS-2: Social Responsiveness Scale, Second Edition.

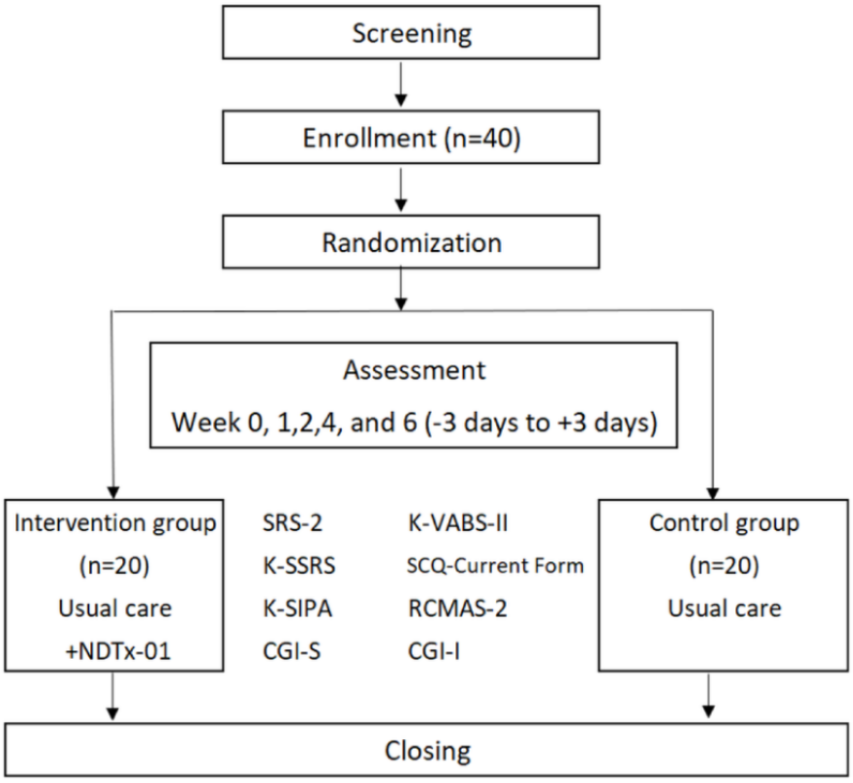

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Ethical Considerations

This study underwent thorough ethical review and was approved by the institutional review boards of several medical institutions: Samsung Medical Center (SMC2023-05-070-011), the Catholic University of Korea Seoul St. Mary's Hospital (KC23DIDS0453), Daegu Catholic University Medical Center (MDCR-23-008-L), and Dankook University Hospital (DKUH 2022-11-012-002). All procedures were conducted in accordance with the relevant guidelines and regulations.

Written informed consent was obtained from all participants by investigators before enrollment. For children and adolescents aged 10 to 12 years, age-appropriate explanations regarding the clinical trial were provided, after which they signed a child-specific informed consent form. Their legal guardian also received detailed information about the clinical trial and signed the standard informed consent form to authorize their child's participation. Participants aged 13 to 18 years provided assent and signed the informed consent form alongside their guardians in accordance with institutional review board guidelines. Any secondary analyses using existing data for future research purposes will not require additional consent.

All data collected during the clinical trial were securely stored as paper documents and electronic records. To ensure the privacy and confidentiality of participants, data were anonymized and deidentified to prevent personal identification. Data were used solely for clinical trial purposes. Access to source data was restricted to regulatory authorities or for the purpose of the device approval process for NDTx-01; even in such cases, all personally identifiable information remained protected through deidentification protocols. No images were collected, and individual participants cannot be identified from the data obtained.

To compensate for the time and effort required for participation, each participant received KRW 50,000 (approximately US $35) per in-person visit. Compensation was not provided for televisits.

Study Participants

Participant recruitment took place at the Samsung Medical Center, the Catholic University of Korea Seoul St. Mary's Hospital, and Daegu Catholic University Medical Center. A total of 40 participants were expected to be enrolled in the study.

As this clinical trial was a pilot study, a formal sample size calculation was not mandatory. However, to inform the design of a confirmatory randomized clinical trial, we aimed to provide preliminary evidence regarding sample estimation. A power of 90% was set for reference purposes [32], and relevant previous studies were reviewed to ensure that the protocol was as evidence based as possible [33-36]. On the basis of these considerations, a total sample size of 40 participants was determined to be appropriate for this pilot randomized clinical trial.

Inclusion criteria were as follows: children and adolescents in the age range of 10 to 18 years diagnosed with ASD or SCD by psychiatrists based on the *Diagnostic and Statistical Manual of Mental Disorders* criteria and assessed using the Autism Diagnostic Interview–Revised (ADI-R) [37], Korean version of the Wechsler Intelligence Scale for Children–Fourth Edition (K-WISC-IV) or Fifth Edition (K-WISC-V) [38,39], and clinical evaluation; adolescents who could use NDTx-01 independently or with caregiver assistance; adolescents who could continue using NDTx-01 for the recommended period; adolescents who agreed not to initiate new additional interventions, including applied behavior analysis or social, educational, or rehabilitation programs from 4 weeks before the start of the clinical trial to its completion; adolescents and their parents who voluntarily agreed to participate in the pilot clinical trial; and adolescents and their parents who could adhere to the clinical protocol.

Exclusion criteria were as follows: adolescents with clinically significant behavioral problems, emotion control problems, psychotic symptoms, or probability of harm (including self-harm); adolescents with serious acute or chronic medical or psychiatric diseases; adolescents who had had serious physical injury or surgery within the previous month; adolescents with serious neurological disorders (ie, brain lesions and mental illnesses); adolescents who were participating in other clinical trials or had done so within the previous 30 days; adolescents who had changes in use or dosage of medications or alterations in participation in therapeutic, educational, or rehabilitation programs that could significantly influence social abilities within 4 weeks before the clinical trial; and adolescents whom the examiner judged inappropriate for the clinical trial owing to ethical concerns or the potential of factors that would influence the trial results. In the event of trial-related harm, participants were entitled to appropriate medical treatment and financial compensation in accordance with the insurance coverage arranged by the sponsor.

Diagnosis Standardization Education

The ADI-R served as one of the diagnostic assessment tools for participant inclusion. The ADI-R is a semistructured, standardized interview designed to assess ASD symptoms through caregiver reports. While its semistructured format provides flexibility in how questions are explored, it requires administration by a well-trained and experienced assessor. The reliability and consistency of the ADI-R depends not only on its structured framework but also on the assessor's ability to elicit detailed and developmentally relevant information from caregivers. To maintain the interreliability of the ADI-R assessment, ADI-R training by an internationally certified trainer was conducted, including theoretical lectures, clinical practice, and scoring practice.

To ensure the accuracy and consistency of SCD diagnosis, we convened an SCD diagnosis standardization consensus meeting. The participants included principal investigators and pediatric psychiatrists from all the medical hospitals involved in the pilot clinical trial. During the meeting, specialists shared their clinical diagnostic interpretations.

Randomization and Assessor-Blinded Approach

For random assignment in this clinical trial, an interactive web response system was used to allocate participants to either the intervention or control group. A stratified block randomization method was applied at each medical center with an allocation

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ratio of 1:1. A qualified statistician determined the block size, set at 4, and selected seed numbers for the randomization process. This method was chosen to maintain the integrity of the randomization and minimize potential biases in participant allocation.

An assessor-blinded approach was used to ensure the objectivity of assessment during the clinical trial. The assessors responsible for conducting the validation assessments were kept unaware of the group allocation of each participant. To maintain the integrity of this blinding, direct interaction between the assessors and participants, as well as their caregivers, was restricted throughout the assessment process. Instead, clinical research coordinators acted as intermediaries.

Intervention

The digital therapeutic, NDTx-01, as an intervention tool integrated social skill training and cognitive behavioral therapy methodologies and techniques. Its framework encompassed stages from assessment and reconceptualization to skill acquisition, skill consolidation, and application training to generalization, cognitive processing, and modeling. The social situations presented in NDTx-01 were constructed based on well-verified social skill training programs such as the Program for the Education and Enrichment of Relational Skills (PEERS) and Social Stories [3,33,40-45]. However, existing programs often target different age groups, such as early childhood or early adulthood, which limited their applicability to our intended population. This gap led us to conduct a focus group interview (FGI). A total of 10 individuals participated in the FGI, including 4 (40%) individuals with ASD (n=3, 75% male and n=1, 25% female), 2 (20%) mothers of adolescents with ASD, 1 (10%) special education teacher, 1 (10%) middle school teacher, and 2 (20%) therapists.

Through this FGI, we identified common situations that children and adolescents with ASD find most challenging or distressing in daily school lives or peer relationships. It also provided insights into which social skills were perceived as most critical for social functioning and the underlying reasons for these priorities as expressed by parents, teachers, and therapists.

On the basis of both the literature review and FGI findings, we constructed scenarios and items that reflected social skills applicable to the real lives of children and adolescents with ASD or SCD.

NDTx-01 is a story-based intervention centered on a main player character and 6 nonplayer peers. To design visually relatable and appealing characters, a preference survey was conducted among prospective users. The most favored styles and imagery were then handed to a designer to create the characters, backgrounds, and props. The gamified app was developed using Unity (Unity Technologies) by a developer with expertise in mobile and computer game development. At each developmental stage, detailed discussions were held to ensure the appropriateness of the social scenarios, dialogue content, level of difficulty, and user engagement.

A pilot version of the app underwent usability testing, which evaluated the clarity of the storylines, playability, and overall appeal. The test involved individuals with ASD, their parents, and therapists. The feedback collected from these assessments was used to refine and improve NDTx-01.

A key feature of NDTx-01 was its emphasis on generalization, facilitated by the user's engagement with diverse situations and scenarios assisted and prompted by direct and sometimes indirect therapeutic interventions in school settings. This construction was particularly relevant because most user groups were affiliated with schools.

To aid in the understanding and interpretation of social cues and situations, NDTx-01 provided a broad spectrum of social scenarios and narratives within a school setting, such as making new friends at the start of a new semester and expanding relationships with schoolmates. These scenarios, presented as a Daily Story in the main menu of NDTx-01, run for 10 minutes per day, 5 days a week over 6 weeks (Figure 2). The stories were presented from a third-person perspective to enhance users' comprehension and perspective-taking abilities. NDTx-01 also featured a supportive fairy and friends who assisted the main character both verbally and nonverbally. This multifaceted intervention not only aided in social skill development but also enhanced user engagement and practical applications in real-world situations. The specific contents and goals of each NDTx-01 session are outlined in Table 1.

Figure 2. Main menu of NDTx-01. The Daily Story presents 30 stories to last for 6 weeks, 5 days a week.

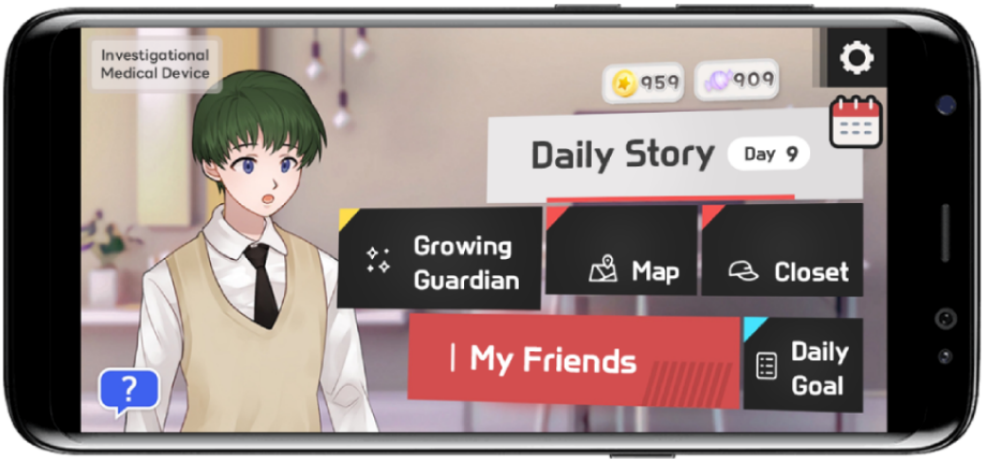

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Table 1. Contents and goals of each session within NDTx-01.

Week and session number	Contents	Goal of the session
Week 1		
1	Day before starting a new grade	Preparing for a new grade emotionally and cognitively
2	First day in the classroom	Greetings and a short conversation with a new classmate
3	Lunchtime at the school cafeteria	Appropriate topics to talk about with a classmate
4	Meeting new classmates in the art room	Expressing interest properly
5	One-on-one meeting with the teacher	Appropriate topics to talk about with a teacher
Week 2		
6	Accidentally hurting a classmate in gym class	How to talk and behave in an embarrassing situation
7	Small talk about K-pop stars	Sharing one's interests with others
8	Cleaning time after class	Solving a conflict
9	April Fool's day happening in class	Joining a group activity
10	Watching a classical performance	Etiquette to keep at the art theater
Week 3		
11	Exchanging defective goods at a shop	How to talk and behave when exchanging goods
12	Meeting the sister of a friend	How to talk to and behave with an acquaintance of a friend
13	Going to the library	Etiquette to keep at the library
14	Preparing a birthday present	How to prepare a present for someone
15	White lies	Situations that need white lies
Week 4		
16	Shopping with friends	How to give advice nicely
17	A psychological test	Using metaphors to explain a person's character
18	Too much desire to win	Behaviors that can make others uncomfortable
19	A presentation	Dealing with social anxiety
20	A musical performance	Dealing with performance anxiety
Week 5		
21	Sharing lunch	Dining etiquette
22	Working as a team	Cooperating with others
23	Deep down inside one's mind	Understanding discordance between situations and thoughts
24	Language class	Understanding proverbs and idioms
25	Unexpected incident	Controlling bad feelings and accepting advice
Week 6		
26	Helping a friend with shopping	How to express gratitude
27	Situations that need to be rejected	How to reject nicely
28	Going to the movies	Movie etiquette
29	Interviewing others	How to ask questions and respond properly
30	Closing	Closing

Assessment

Assessment Tools for Screening

Korean Version of the ADI-R

The ADI-R is a standardized, semistructured tool designed to gather comprehensive information for the assessment of ASD. A skilled clinician conducts in-depth interviews with a guardian familiar with the participant's developmental history and current daily functioning, such as the mother, grandmother, or other primary caregiver. This approach ensures a detailed understanding of the participant's developmental milestones and current adaptive functioning, which is critical for accurate ASD assessment. The type of variable is continuous, and a

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higher score means more symptoms of ASD. The ADI-R was used once to facilitate the selection of participants.

K-WISC-IV and K-WISC-V Tools

The K-WISC-IV and K-WISC-V are standardized intelligence tests that measure the intellectual abilities of children and adolescents in the age range of 6 years, 0 months to 16 years, 11 months. The K-WISC-IV analyzes intelligence in full-scale intelligence quantity (FSIQ) and 4 domains, whereas the K-WISC-V presents FSIQ and 5 domains. The type of variable is continuous, and a higher FSIQ score indicates better intellectual ability. The K-WISC-IV or K-WISC-V was used once to facilitate the selection of participants.

Assessment Tools for Efficacy and Safety

Overview

To identify appropriate assessment tools for evaluating the efficacy and safety of treatments for ASD and SCD, we reviewed clinical guidelines and comparable study designs. Scales recommended by the European Medicines Agency, the National Institute for Health and Care Excellence of Great Britain, and the Canadian Paediatric Society were reviewed. An extensive review of clinical trial designs was conducted in November 2022. A search on ClinicalTrials.gov using keywords such as “social skill training,” “intervention,” “ASD,” “Asperger’s syndrome,” “pervasive developmental disorder,” and “mental retardation” yielded 28% (214/763) of trials that met our specified criteria (Figure 3).

Figure 3. Flow description of the selection process for the literature review. ASD: autism spectrum disorder; PDD: pervasive developmental disorder.

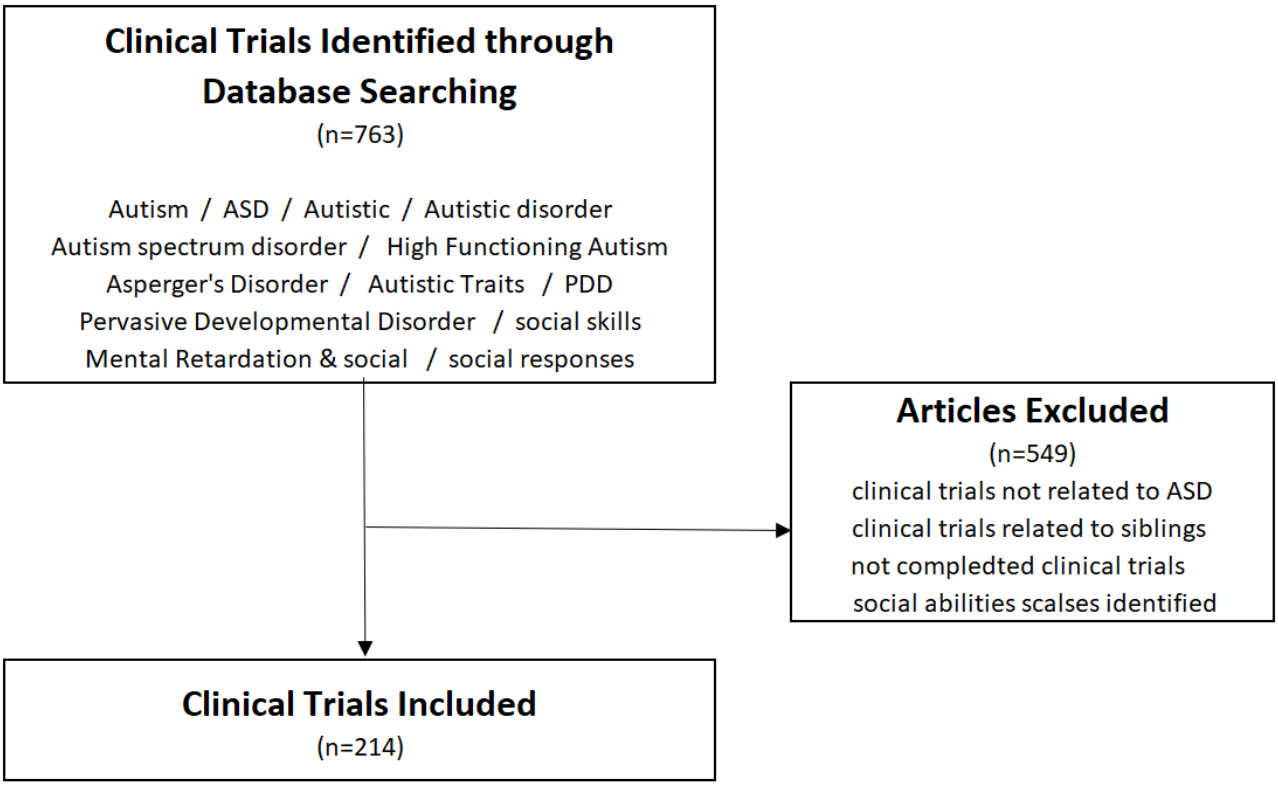

As shown in Table 2, among the 214 clinical trials, the Social Responsiveness Scale was used in 108 (50.5%) cases, constituting the highest rate. The Vineland Adaptive Behavior Scales (VABS) was used in 28% (60/214) of cases, and the Social Skills Rating System was used in 5.1% (11/214) of cases. As previously mentioned, the European Medicines Agency recommends the Childhood Autism Rating Scale; Social Responsiveness Scale, Second Edition (SRS-2); VABS, Second Edition; Children’s Yale-Brown Obsessive Compulsive Scale for children with ASD; and Clinical Global Impressions–Improvement (CGI-I). On the basis of the study results, the following assessment tools were selected (Table 3): the SRS-2; the Korean version of the VABS, Second Edition (K-VABS-II); the Korean version of the Social Skills Rating System (K-SSRS); the Social Communication Questionnaire–Current Form (SCQ–Current Form); and the CGI-I. In addition, the Revised Children’s Manifest Anxiety Scale, Second Edition (RCMAS-2), was incorporated to measure anxiety levels among the participants. The Korean version of the Stress Index for Parents of Adolescents (K-SIPA) was used to assess anxiety levels in the parents of the participants. The Clinical Global Impressions–Severity (CGI-S) was also included to assess the clinicians’ brief impressions of the severity of the illness.

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Table 2. Use rate of the scales among the clinical trials from our literature search (N=214).

Scale	Studies, n (%)
SRS[a] [46]	108 (50.5)
VABS[b] [47]	60 (28)
SSRS[c] [48]	11 (5.1)
SCQ[d] [49]	8 (3.7)
CCC[e] [50]	5 (2.3)
ESCS[f] [51]	5 (2.3)
BOSCC[g] [52]	4 (1.9)
TSSK[h] [53]	3 (1.4)
GSOM[i] [54]	2 (0.9)
SSiS[j] [55]	2 (0.9)
Others	6 (2.8)

[a]SRS: Social Responsiveness Scale.
[b]VABS: Vineland Adaptive Behavior Scales.
[c]SSRS: Social Skills Rating System.
[d]SCQ: Social Communication Questionnaire.
[e]CCC: Children's Communication Checklist.
[f]ESCS: Early Social Communication Scales.
[g]BOSCC: Brief Observation of Social Communication Change.
[h]TSSK: Test of Social Skills Knowledge.
[i]GSOM: General Social Outcome Measure.
[j]SSiS: Social Skills Improvement System.

Table 3. Assessment schedule.

Outcome measures	Visit 1[a] (screening)—−4 wk approximately	Visit 2[a] (baseline)—day 0	Visit 3 (tele-visit 1)—day 7 (–3 d to +3 d)	Visit 4 (tele-visit 2)—day 14 (–3 d to +3 d)	Visit 5—day 28 (–3 d to +3 d)	Visit 6 (final visit)—day 42 (–3 d to +3 d)
K-VABS-II[b]		✓			✓	✓
SRS-2[c]		✓	✓	✓	✓	✓
K-SSRS[d]		✓	✓	✓	✓	✓
RCMAS-2[e]		✓	✓	✓	✓	✓
K-SCQ[f]		✓	✓	✓	✓	✓
K-SIPA[g]		✓	✓	✓	✓	✓
CGI-S[h]		✓			✓	✓
CGI-I[i]					✓	✓

[a]Visits 1 and 2 can be conducted on the same day.
[b]K-VABS-II: Korean version of the Vineland Adaptive Behavior Scales, Second Edition.
[c]SRS-2: Social Responsiveness Scale, Second Edition.
[d]K-SSRS: Korean version of the Social Skills Rating System.
[e]RCMAS-2: Revised Children's Manifest Anxiety Scale, Second Edition.
[f]K-SCQ: Korean version of the Social Communication Questionnaire.
[g]K-SIPA: Korean version of the Stress Index for Parents of Adolescents.
[h]CGI-S: Clinical Global Impressions–Severity.
[i]CGI-I: Clinical Global Impressions–Improvement.

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SRS-2 Instrument

The SRS-2 is a quantitative measure of symptoms associated with ASD. It comprises 5 distinct subscales: social awareness, social cognition, social communication, social motivation, and restricted interests and repetitive behavior. The scale consists of 65 items, with each item rated on a 4-point scale to reflect symptom severity. The scores for each subdomain and the total score were aggregated and converted into T scores using a standardized scoring method. Higher scores indicate more serious symptoms of ASD. The SRS-2 was administered in weeks 0, 1, 2, 4, and 6 (−3 days to +3 days for each).

K-VABS-II Instrument

The K-VABS-II [56] measures adaptive behavior levels across 4 domains (communication, daily living skills, socialization, and motor skills) and provides an adaptive behavior composite score. Higher standard scores signify more adaptive behavior. The K-VABS-II was administered in weeks 0, 4, and 6 (−3 days to +3 days for each).

K-SSRS Secondary Level, Student Form

The K-SSRS [57] is an assessment tool designed to evaluate adolescents' social skills. It comprises 39 items organized to assess proficiency in 4 subdomains: empathy, assertion, self-control, and cooperation. Higher average scores on the 4 domains and total scale indicate greater proficiency in social skills. The K-SSRS was administered in weeks 0, 1, 2, 4, and 6 (−3 days to +3 days for each).

SCQ–Current Form

The Korean version of the SCQ–Current Form [58] is a parent-reported assessment tool designed to screen for ASD and its associated symptoms. This tool comprises 40 items extracted from the ADI-R. Caregivers answer *yes* or *no* to each item based on the observed behaviors of the patient over the previous 3 months. A higher score indicates a higher probability of ASD. The SCQ–Current Form was administered in weeks 0, 1, 2, 4, and 6 (−3 days to +3 days for each).

RCMAS-2 Instrument

The Korean version of the RCMAS-2 [59] is a self-report tool designed to evaluate the level and characteristics of anxiety experienced by children and adolescents. It comprises 49 items, each requiring a simple *yes* or *no* response.

The tool includes an inconsistent response index and defensiveness scale, which function as validity scales. When the scores on these validity scales fall within the normal range, the resulting measures of total anxiety, physical anxiety, worry, and social anxiety are deemed credible and reflective of the respondents' anxiety levels. Higher scores mean higher anxiety levels. The RCMAS-2 was administered in weeks 0, 1, 2, 4, and 6 (−3 days to +3 days for each).

K-SIPA Instrument

The K-SIPA [60] is a comprehensive assessment tool designed to measure parental stress associated with raising adolescents. It comprises 112 items that respondents are required to answer on 5-point and 2-point Likert scales. It evaluates parental stress across 5 domains: adolescent domain, parent domain, adolescent-parent relationship domain, life stress domain, and an index of total parenting stress. Both the adolescent and parent domains are divided into 4 subdomains. Higher scores on the K-SIPA indicate greater levels of parental stress. The K-SIPA was administered in weeks 0, 1, 2, 4, and 6 (−3 days to +3 days for each).

CGI-S and CGI-I Instruments

The Clinical Global Impressions provides a brief assessment of a clinician's perspective on a patient's global functioning. The CGI-S assesses the severity of a patient's illness, whereas the CGI-I assesses the degree of improvement of symptoms. Higher scores indicate worse conditions. The CGI-S was administered in weeks 0, 4, and 6 (−3 days to +3 days for each). The CGI-I was administered in weeks 4 and 6 (−3 days to +3 days for each).

Statistical Analysis

The data collected in the pilot clinical trial were analyzed using the SAS statistics program (SAS Institute Inc). Initially, descriptive analysis was applied to the entire dataset. A frequency analysis was conducted on demographic data. Outcome measures were analyzed based on the full analysis set.

For within-group comparisons, the analytical approach was contingent on the distribution of the data. If the data were normally distributed, a paired *t* test was used to compare mean values. For data that were not normally distributed, the Wilcoxon signed rank test was used. If the bilateral significance probability was <.05, within-group changes were considered statistically significant.

For between-group comparisons, when the data were normally distributed, an independent 2-sample *t* test was applied to analyze the differences in means. Otherwise, the Wilcoxon rank sum test was conducted. If the bilateral significance probability was <.05, it was considered statistically significant. Missing data were imputed using the last observation carried forward method.

Results

This clinical trial was registered with the Clinical Research Information Service, which is part of the World Health Organization International Clinical Trials Registry Platform, under the number KCT0009140 on July 7, 2023. The Korean Food and Drug Administration approved this clinical protocol in February 2023. A total of 42 participants were screened, and 39 were enrolled in the study. As of August 2024, this clinical trial was completed, and the clinical study report was submitted to the Ministry of Food and Drug Safety in April, 2024 The findings and outcomes of this pilot randomized clinical trial were published in April 2025 [61].

Discussion

Expected Findings

The NDTx-01 is a newly developed digital therapeutic tool designed to improve social communication and interaction abilities in adolescents with ASD and SCD. On the basis of

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cognitive behavioral therapy principles, social skill training, story-based interventions, and gamification elements, NDTx-01 aims to deliver comprehensive therapeutic stimuli and interventions to achieve these therapeutic objectives. To evaluate its efficacy, we planned to conduct a pilot randomized clinical trial using a stringent protocol. The goal was to substantiate the effectiveness of NDTx-01 in improving the social skills and adaptability of adolescents with ASD and SCD.

From a therapeutic perspective, NDTx-01 was anticipated to serve as an effective stand-alone intervention for enhancing social communication and cognitive abilities in adolescents with ASD and SCD [61]. In addition, its potential as a supplementary tool to traditional face-to-face interventions was also noteworthy. The diverse situational simulations and story-based formats of NDTx-01 were designed to foster broader generalization of learned skills, offering a multifaceted approach to treatment.

From a socioeconomic perspective, NDTx-01 is expected to serve as a viable alternative to conventional clinical interventions for individuals with ASD and SCD, particularly in terms of accessibility. This digital therapy aims to bridge the gap in access to high-quality medical treatments, potentially democratizing the availability of effective therapies for these populations [62-65].

However, this study has some limitations. Our methodology involved reviewing clinical trials from ClinicalTrials.gov focusing on the assessment tools used for ASD and related developmental disorders in adolescents and targeting their social cognition ability. We selected the K-VABS-II, SRS-2, K-SSRS, RCMAS-2, SCQ–Current Form, K-SIPA, CGI-S, and CGI-I to evaluate the effectiveness of NDTx-01. While these tools are widely accepted, it is important to note that none are officially designated as diagnostic assessments for ASD or SCD. In addition, the SRS-2 and K-SSRS have not been standardized for the Korean population. Despite this, we included them in the pilot clinical trial as their validity has been supported by many studies and trials, as shown in Table 2.

We designated the control group in the clinical trial as a waitlist control group because it is considered unethical to withhold interventions from adolescents with ASD and SCD who require continuous treatment. Participants in both the intervention and control groups continued receiving their usual care from 4 weeks before the start of screening to study conclusion.

The sample size for this study was determined by reviewing previous research with similar participant diagnoses or intervention methodologies [33-36]. We constructed the protocol with a sample size of 40. However, as this was a pilot randomized clinical trial, we had no previous data for statistical calculation. The absence of statistical analytical justification for the sample size is a limitation of this study.

The frequency and duration of NDTx-01 use require further evidence to establish their optimal configuration. While intensive treatments have shown efficacy in various studies [66-68], the daily use of NDTx-01 may be perceived as burdensome, potentially affecting user compliance. We developed NDTx-01 as a 6-week intervention based on references from several studies and trials ranging from 4 to 12 weeks [34,35,69-73]. To sustain the effectiveness of NDTx-01, follow-up interventions are necessary. These concerns must be addressed in a confirmatory randomized clinical trial.

Conclusions

Herein, we presented a clinical trial protocol to assess the efficacy and safety of a digital therapeutic, a new treatment designed to improve social cognition and communication in adolescents diagnosed with ASD and SCD. By analyzing the data, we intended to identify the primary outcome measure for assessing improvements in social cognition and communication skills, which would be crucial for a subsequent confirmatory clinical trial. Ultimately, this study laid the groundwork for the application of digital therapeutics in treating adolescents facing challenges in social communication and interaction.

Acknowledgments

This study was funded by the Korea Health Industry Development Institute (grant RS-2023-00265178); Daegu Gyeongbuk Medical Innovation Foundation (KMEDIhub; grant B0081112000610); National Center for Mental Health (grant MHER25C02); and Korea Health Technology Research and Development Project through the Korea Health Industry Development Institute funded by the Ministry of Health and Welfare, Republic of Korea (grant HR21C0885). The funders had no role in the design of the study; collection, analysis, or interpretation of the data; writing of the manuscript; or decision to publish the results.

Authors' Contributions

YSJ and SJC conceptualized the study by outlining the clinical goals of NDTx-01. TYC and JHY designed the methodology to ensure both scientific rigor and clinical applicability, and also conducted validation. HJK developed the software and created visualizations to illustrate the system architecture. EYL and RJ carried out the investigation, including implementation and data collection. JHY provided the technical and clinical resources necessary for the project. EYL curated and managed the data for analysis and prepared the initial draft of the manuscript as the first author. YSJ, SJC, TYC, and JHY reviewed and revised the manuscript. YSJ and SJC supervised the entire project and coordinated its administration. SJC acquired funding to support the development and evaluation of the digital therapeutic. All authors have read and agreed to the published version of the manuscript.

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Conflicts of Interest

SJC is the chief executive officer of Neudive Inc. EYL, HJK, and RJ are employees of Neudive Inc. All other authors declare no other conflicts of interest.

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Abbreviations

ADI-R: Autism Diagnostic Interview–Revised
ASD: autism spectrum disorder
CGI-I: Clinical Global Impressions–Improvement
CGI-S: Clinical Global Impressions–Severity
FGI: focus group interview
FSIQ: full-scale intelligence quantity
K-SIPA: Korean version of the Stress Index for Parents of Adolescents
K-SSRS: Korean version of the Social Skills Rating System
K-VABS-II: Korean version of the Vineland Adaptive Behavior Scales, Second Edition
K-WISC-IV: Korean version of the Wechsler Intelligence Scale for Children–Fourth Edition
K-WISC-V: Korean version of the Wechsler Intelligence Scale for Children–Fifth Edition
PEERS: Program for the Education and Enrichment of Relational Skills
RCMAS-2: Revised Children's Manifest Anxiety Scale, Second Edition
SCD: social communication disorder
SCQ–Current Form: Social Communication Questionnaire–Current Form
SRS-2: Social Responsiveness Scale, Second Edition
VABS: Vineland Adaptive Behavior Scales

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Protocol

An mHealth App–Based Social Capital Intervention (PrEP US NoW) to Improve Sexual Health and Uptake of Pre-Exposure Prophylaxis Among Young, Black, Sexual Minority Men: Protocol for Intervention Development and a Pilot Randomized Controlled Trial

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Abstract

Background: Black Americans are disproportionately impacted by HIV. This disparity is more profound in the Southern United States, with the highest rates being among young, Black, sexual minority men, who are also less likely to receive state-of-the-art interventions such as pre-exposure prophylaxis (PrEP). Individual-level interventions to increase PrEP uptake do not often capitalize on the opportunity to leverage the significant effects of this group's social networks, including Black women, on attitudes, beliefs, and behaviors around HIV prevention.

Objective: To increase PrEP use, an intervention, PrEP US NoW, was designed to engage young, Black, sexual minority men's social networks in discussions with supportive Black female facilitators and ultimately enhance their social capital.

Methods: First, qualitative information on core health-promoting elements of social capital bonds was captured among young, Black, sexual minority men and Black women in extant social support networks. This information was then applied to adapt an existing, evidence-based mobile health app to create the PrEP US NoW pilot through an unblinded randomized controlled trial. Six social network groups (5 young, Black, sexual minority men + 1 Black woman) will participate in the intervention arm. These will be recruited through a network-based approach and will undergo tailored training (mobile-based and face-to-face) for app usage. At baseline, men will undergo HIV testing and both men and women will complete a sociodemographic survey. The groups in the intervention arm will engage in four 60-minute discussions led by Black women through the modified mobile health app. After the intervention, young, Black, sexual minority men will complete surveys electronically at 1 and 3 months (accompanied by HIV testing) on additional factors such as experiences of discrimination and PrEP stigma. The Black women will complete an electronic survey at 1 month, measuring feasibility and acceptability, and will participate in web-based qualitative interviews at 3 months to gain more knowledge on the PrEP US NoW facilitation process. Participants in the control arm will not engage in Black women–facilitated group discussions and will use a control version of the app. The baseline and follow-up surveys and HIV testing will be documented similarly to the intervention arm.

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Results: Phase 1 (development) of PrEP US NoW research activities lasted from November 2019 to June 2024. Data collection for the phase 2 randomized controlled trial began in August 2024 and is expected to be completed in December 2025. The findings will capture the intervention's feasibility and acceptability and changes in PrEP uptake among young, Black, sexual minority men.

Conclusions: The development and pilot implementation trial of the PrEP US NoW intervention is thought to leverage essential social capital among young, Black, sexual minority men, which may promote engagement in PrEP care, thus decreasing the overall number of HIV diagnoses.

Trial Registration: ClinicalTrials.gov NCT07024745; https://clinicaltrials.gov/study/NCT07024745

International Registered Report Identifier (IRRID): DERR1-10.2196/66326

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KEYWORDS

young; Black; sexual minority men; the South; pre-exposure prophylaxis

Introduction

Black Americans, who constitute 14% of the total US population, account for 37% of new HIV diagnoses [1]. Among Black Americans, sexual minority men account for 35% of the total new HIV diagnoses nationally, ranking as the second largest impacted group after Hispanic or Latino sexual minority men [2]. These racial disparities are more severe in the Southern United States, where nearly half of new HIV diagnoses occur [3]. In Alabama, Black Americans constitute only 27% of the total population but account for 70% of the new HIV diagnoses, with young (ages 15-29 years) Black, sexual minority men being most heavily impacted [4]. Further, Jefferson County in Alabama (which includes the Birmingham-Hoover metropolitan service areas) accounts for the highest number of new HIV diagnoses in the state, and over half of the new cases occur in young, Black, sexual minority men [5].

US federal agencies are working toward the Ending the HIV Epidemic (EHE) initiative by focusing on geographic hotspots in addition to populations that face HIV disparities [6]. The EHE initiative targets disparate populations, like young, Black, sexual minority men, in promoting the use of HIV prevention tools such as pre-exposure prophylaxis (PrEP) to reduce the number of HIV diagnoses [7-10]. Where a higher PrEP-to-need ratio indicates better PrEP coverage for those in need, recent data have suggested that Black people have the lowest PrEP-to-need ratio in the United States, 8 times lower as compared with White people [11]. These racial disparities are often a result of disparities in various crucial components of the social construct, such as racial discrimination and marginalization or homonegativity in health care settings, removing a relationship of trust, thus discouraging this population from seeking medical attention for important preventive measures, such as PrEP [12]. Recent data have suggested that people residing in the Southern United States and those aged 13-24 years are among the groups with the lowest PrEP-to-need ratio [11]. Where higher PrEP uptake has shown to reduce HIV diagnoses, poor engagement in PrEP care remains an issue, which is even more profound among young, Black, sexual minority men living in the Deep South [13,14]. This highlights the critical need for increasing PrEP engagement to decrease new HIV diagnoses among this population.

PrEP engagement can be described in terms of discrete stages constituting a PrEP Care Continuum, which includes gaining PrEP awareness, PrEP uptake (linkage to PrEP and PrEP prescription), and PrEP retention (PrEP adherence and PrEP persistence) [15,16]. Previous studies among young, Black, sexual minority men have shown that low perceived risk of HIV acquisition, poor education on sexual health, lack of information on accessing local PrEP services, concerns around PrEP-related costs or insurance, and stigma related to HIV and sexuality act as barriers to PrEP awareness and uptake [17-20]. Additionally, in populations where PrEP uptake is high, barriers to PrEP persistence remain a challenge, including stigma, low perceived HIV risk, PrEP-related side effects, PrEP-related cost, difficulty with adherence to daily medication, and attending regular PrEP-related medical visits requiring routine adjustments and availability of reliable transportation [21-23]. These persisting barriers highlight the need for additional interventions to improve PrEP care engagement.

Much work has been done around targeting social network–level factors in improving PrEP engagement [24,25]. The disproportionate burden of HIV on the young, Black, sexual minority men community in the South has been connected to intersectional stigma, a concept that elucidates how multiple stigmas occurring simultaneously worsen marginalization [26,27]. One social network-level factor that is gaining increased attention is social capital, which refers to "the sum of an individual's resource-containing, reciprocal, and trustworthy social network connections" [28]. The social capital derived from a social network can be directly influenced by a multitude of factors, including the size and diversity of the social network, as well as knowledge and material resources owned by network members [29,30]. In other words, social networks yield social capital by providing informational, emotional, social, and instrumental support, and are thought to have beneficial effects on health behaviors, such as PrEP use [31].

Existing research has shown that Black women within young, Black, sexual minority men's social networks have the potential to enhance PrEP uptake and adherence [32,33]. For example, a randomized controlled trial conducted in Chicago leveraged young, Black, sexual minority men's social networks to improve sexual health engagement and help with PrEP uptake [34]. This study found that PrEP use among young sexual minority men

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was strongly associated with network-level factors [34]. Specifically, this work highlighted the impact of ties within a social network to help with introducing new ideas, such as information on PrEP [34]. A detailed network analysis of the Chicago study also discovered that Black women were identified as the primary support figures for over half of young, Black, sexual minority men participants [34]. Our prior work exploring social networks that supported and facilitated acceptance of sexual identity among young, Black, sexual minority men participants found that both young, Black, sexual minority men and Black women functioned as main support systems [35]. Another qualitative study exploring young, Black, sexual minority men's social networks and social capital found Black women, such as mothers and female friends, to play a major role in young, Black, sexual minority men's social capital [36]. Together, these findings suggest the importance of Black women in providing a unique, underused health-promoting social capital for young, Black, sexual minority men. Although social network–level PrEP interventions have shown promising findings, these interventions for PrEP have been relatively underused, especially in the Southern United States.

Boosted with the fast adoption of smartphones featuring various networking apps, social networks have rapidly advanced in their ability to communicate quickly and be more interactive. While providing an excellent medium for networking, mobile apps have also shown to be an acceptable and effective method for reaching youth, including young, Black, sexual minority men, to participate in HIV testing and other HIV prevention strategies [37,38]. This suggests that mobile apps can be a useful platform for improving PrEP use among young, Black, sexual minority men and, potentially, their social networks.

Keeping in mind (1) the disproportionate impact of HIV on young, Black, sexual minority men with simultaneous underuse of PrEP in this population, (2) evidence that social networks yielding social capital can be helpful in improving PrEP use among young, Black, sexual minority men, (3) evidence that Black women play a vital role within young, Black, sexual minority men's social networks, and (4) the success of mobile apps in improving the uptake of HIV prevention strategies, an intervention, PrEP US NoW (Pre-Exposure Prophylaxis Utilization Through Increasing Social Capital Among Young, Black, sexual minority Men Networks With Women), was designed. This intervention aims to improve PrEP uptake among young, Black, sexual minority men by engaging Black women facilitators to conduct semistructured conversations with groups of young, Black, sexual minority men around HIV prevention, sexual health, intersectional stigma, and PrEP access using a mobile health (mHealth) platform. Since the aim is to assess if social network discussions conducted within the mHealth platform would improve the social capital, beyond the existing app features, such as in-app messaging, which may also contribute, we did not add any content-based approaches to the app. The goal of this intervention is to leverage heterogeneous bonds in diverse social networks between young, Black, sexual minority men and Black women to address intersectional stigma and enhance social capital toward PrEP use.

This paper describes the PrEP US NoW protocol. Using qualitative methods, core health-promoting elements of social capital bonds between young, Black, sexual minority men and Black women in existing social networks were evaluated. This information was then applied to adapt an existing, evidence-based mHealth app to create PrEP US NoW. The intervention, piloted as a randomized controlled trial, is currently ongoing, in which the feasibility and acceptability of PrEP US NoW will be evaluated along with preliminary efficacy to increase PrEP uptake among young, Black, sexual minority men.

Methods

Conceptual Framework

This protocol paper has followed the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) reporting guidelines (Multimedia Appendix 1) [39]. The theoretical foundation (Figure 1) for this study is an adaptation of the situated Information, Motivation, and Behavioral Skills (sIMB) model, which posits that information (information regarding PrEP use), motivation (personal and social attitudes and beliefs regarding sexual identity that facilitate PrEP use), and behavioral skills (objective and perceived skills, including self-efficacy, in accessing PrEP care) within the cultural and situational context in which they occur are necessary for behavioral change [40-42]. The adapted sIMB model is aimed at increasing PrEP use among young, Black, sexual minority men by increasing social capital within young, Black, sexual minority men's social networks, by strengthening the bonds between young, Black, sexual minority men networks, and by gaining and having structured discussions around key topics known to influence PrEP use among this group (specifically, intersectional stigma, PrEP knowledge, and sexual health empowerment). We hypothesize that through these structured discussions, social network members will be able to gain key instrumental and emotional gains in social capital. Social networks yield social capital, which has health-promoting effects for individuals living with and at-risk for HIV. For this study, social capital was defined similar to Pierre [28], as the sum of an individual's resource-containing, reciprocal, and trustworthy social network connections.

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Figure 1. Adapted sIMB conceptual framework mapped to the PrEP US NoW intervention. Items in boxes are constructs of the Anderson Behavioral Model and sIMB, with arrows relating their interactions. mHealth: mobile health; PrEP: pre-exposure prophylaxis; PrEP US NoW: Pre-Exposure Prophylaxis Utilization Through Increasing Social Capital Among Young, Black, Sexual Minority Men Networks With Women; sIMB: situated Information, Motivation, and Behavioral skills.

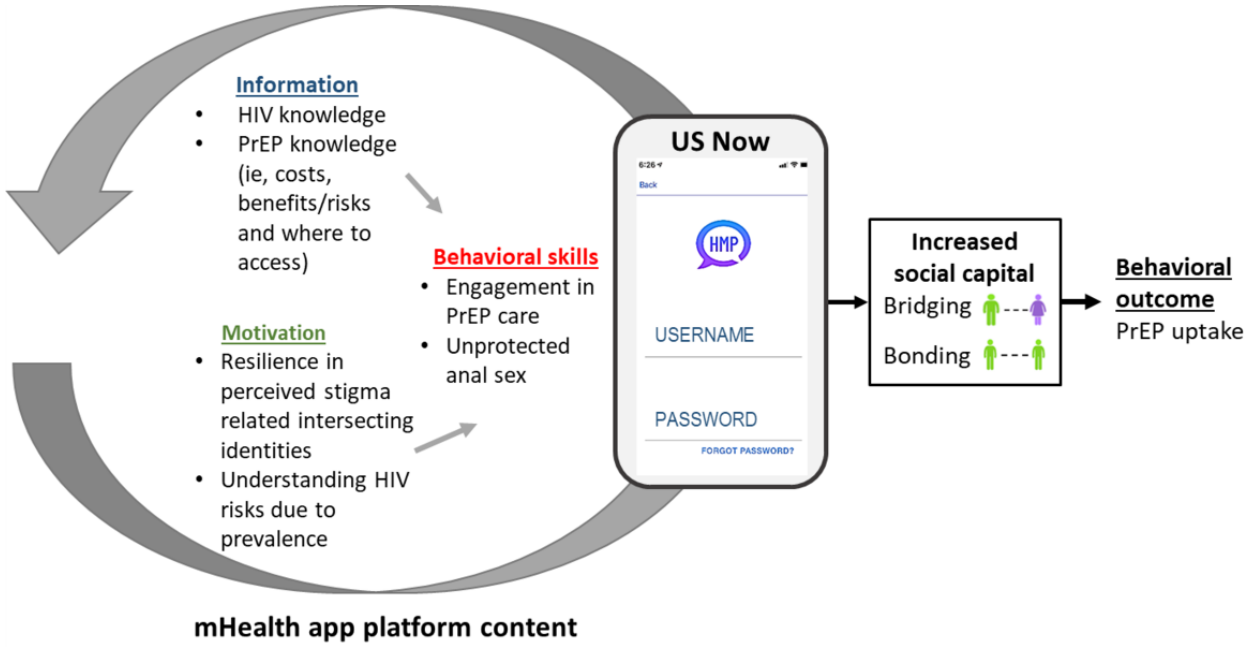

Figure 2 provides various pathways that are thought to impact the social capital within an individual, here young, Black, sexual minority men. For example, factors such as age (individual characteristic) can be considered as "investments in social capital," which have a direct impact on the "access to social capital," such as network size, which then builds a foundation for the "mobilization of social capital," such as resources for instrumental gains, leading to "return of social capital," such as power or status. Previously, sIMB has been used to improve PrEP adherence (iPrEx study), for studying engagement in HIV care, adherence to antiretroviral therapy, and HIV risk behavior change in adolescents [42-44]. However, to our knowledge, sIMB has never been applied to an intervention aimed at improving PrEP engagement by increasing social capital.

Figure 2. Potential factors and pathways for building social capital.

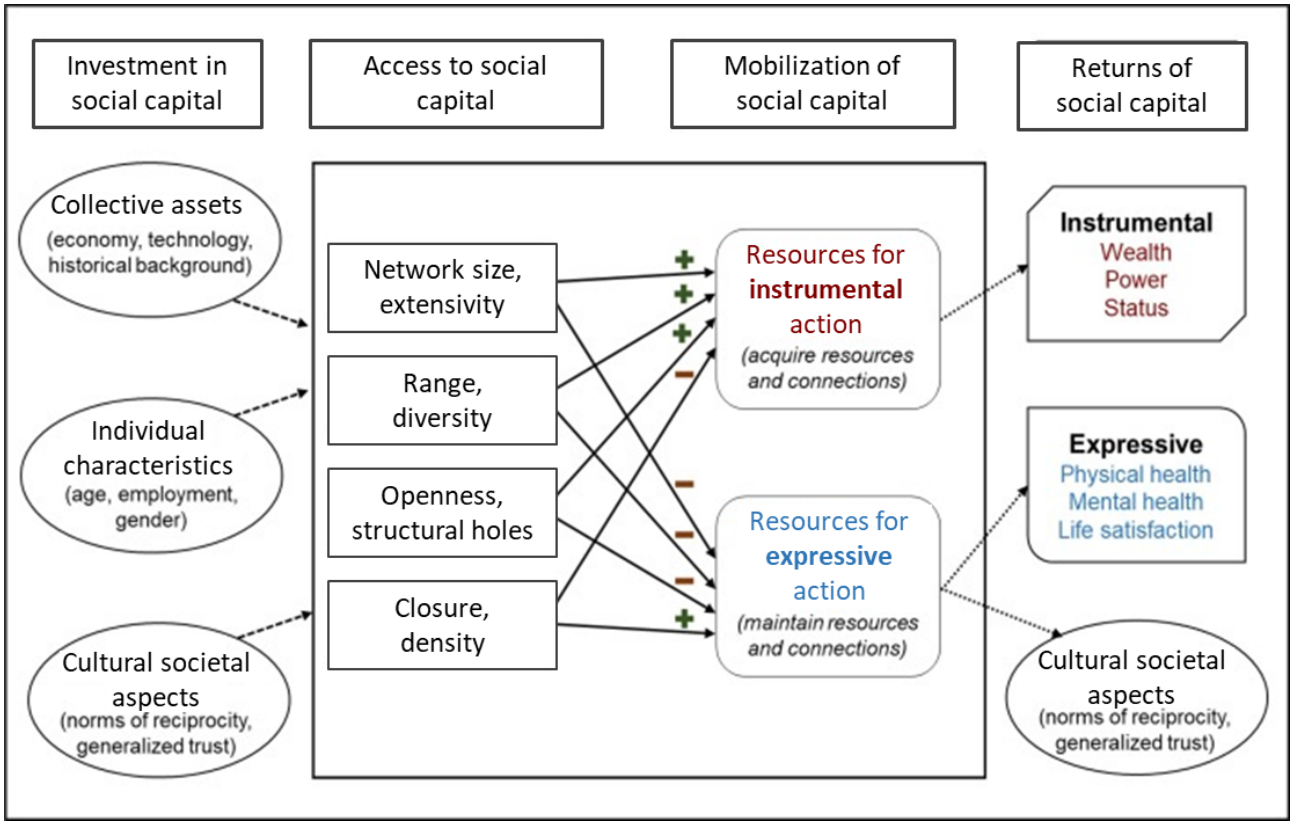

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Community Advisory Board

Initially, 2 community advisory boards (CABs), each consisting of 6 to 8 individuals, were proposed: one CAB composed of young, Black, sexual minority men and the other of Black women. The principle for the development of CABs was cocreation based on the principles of community-based participatory research [45]. However, based on feedback from potential CAB members, one combined group was created instead to mirror the goal of the study, allowing for social connectedness among Black, sexual minority men (BSMM; n=3) and Black women (n=5). The CAB members meet remotely and in-person at least monthly for 1 hour, and 1 Black female and 1 Black, sexual minority man serve as coleads. Depending on agenda topics, some meetings have included the principal investigators and some have been exclusive to CAB members, depending on whether topics discussed were felt to be sensitive. The CAB coleads were tasked with leading discussions on meeting agenda topics and facilitating direct communication with the investigative team for meetings where they were not present. Topics for the study reviewed with the CAB included study design, intervention content, app features, intervention beta testing, and recruitment procedures. Additionally, the CAB provided feedback on initial qualitative results and will provide feedback on the results from the pilot trial, which will assist with the dissemination of study findings.

Designing the PrEP US NoW Intervention

Overview

In addition to regular discussions with the CAB, qualitative in-depth interviews were conducted with young, Black, sexual minority men and Black women. Through the interviews, a more granular understanding was gained of (1) young, Black, sexual minority men's perceptions on the content needed to motivate engagement in the PrEP care continuum, (2) specific attributes of Black women that allow them to facilitate creation of a safe space, and (3) Black women's perceptions of educational materials around safer sex promotion strategies that will be critical to enhance their abilities to be conduits of support when leading discussions for young, Black, sexual minority men's social networks.

Recruitment and Sampling

Recruitment of young, Black, sexual minority men occurred in Birmingham, AL, through established connections of the principal investigators (LE in the Birmingham, AL, area and SH in Atlanta, GA); LE and SH have previous experience with recruiting young, Black, sexual minority men for other research studies. When young, Black, sexual minority men were screened in prior studies, respondents were able to indicate if they would like to be contacted for future studies, creating a contact list of HIV-negative young, Black, sexual minority men who are interested in being involved in research. In addition to contacting prior participants, flyers were posted to listservs and physical locations where young, Black, sexual minority men are known to socialize or seek medical care. In addition, the team recruited participants working with Black, sexual minority men study recruiters with large social followings and influence in the community. The eligibility criteria for young, Black, sexual minority men participants were (1) age 18-29 years, (2) cisgender men (based on gender and sex at birth), (3) self-reported past sex with other men (in the past 6 months), (4) Black race, and (5) English speaking. Of note, young, Black, sexual minority men already on PrEP were not excluded. A purposive sampling scheme was used to ensure representation of diverse perspectives of young, Black, sexual minority men. To include both younger and older young, Black, sexual minority men, half of the participants were 18-24 years old, and the other half were 25-29 years old.

Black women for in-depth interviews were recruited by direct referral by young, Black, sexual minority men or CAB members, or from prior studies. This was thought to ensure enrollment of Black women with close connections to young, Black, sexual minority men. Eligibility criteria for Black female participants included (1) Black race, (2) female (cisgender or transgender women), (3) having at least one close connection to a young, Black, sexual minority man, (4) age ≥18 years, and (5) English speaking. Since the aim of these interviews was to explore if certain traits, for example, age, made Black women more suited to lead the discussions, a specific age group within the Black women was not targeted.

In-Depth Interviews

Potential participants (young, Black, sexual minority men and Black women) were asked to complete a web-based screening tool to determine their eligibility. Once an individual was deemed eligible, they were contacted by the study staff via phone to schedule an in-depth interview. When in-person interviews were not possible, phone-based interviews were conducted. A semistructured interview guide was created with help from the CAB and refined through repeated pilot testing and revision. The interview guide (Table 1) consisted of a mixture of descriptive or narrative questions and questions structured around the domains of the adapted sIMB model, which, in addition to exploring participants' experiences, also allowed for novel concepts and ideas to emerge. In-depth interviews were conducted in a private and quiet space mutually convenient for the interviewer (research coordinator or graduate research assistant) and the interviewee. During the interviews, interviewers documented field notes. All interviews were digitally audio recorded, deidentified, transcribed verbatim, and uploaded to an encrypted password-protected computer for the purpose of qualitative analysis.

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Table 1. Interview guide associated with the PrEP US NoW[a] study.

Topics	Operationalized topics
Young, Black, sexual minority men (n=15)	
Information	• Social support networks (types of relationships with young, Black, sexual minority men and Black women) • Intersectional stigma (discussion of coping with discrimination, poverty, and sexual identity) addressed within social support networks
Motivation	• Archetypical Black women who provide support • Current social norms • Types of interpersonal relationships that support HIV prevention uptake
Behavioral skills	• Skills related to self-efficacy in navigating PrEPb care and condom use
Black women (n=20)	
Information	• Information topics necessary to support young, Black, sexual minority men in sexual health • Current attitudes and beliefs regarding young, Black, sexual minority men
Motivation	• What would support Black women being engaged in young, Black, sexual minority men's social support networks
Behavioral skills	• Skills required to counsel young, Black, sexual minority men on sexual health and HIV prevention

[a]PrEP US NoW: Pre-Exposure Prophylaxis Utilization Through Increasing Social Capital Among Young, Black, sexual minority Men Networks With Women.

[b]PrEP: pre-exposure prophylaxis.

Qualitative Data Analysis

The coding and analysis of the transcripts were conducted using the NVivo qualitative data management software (QSR International). A preliminary codebook was developed, which consisted of (1) predetermined deductive codes related to sIMB domains of interest, (2) inductive codes emerging from the data, and (3) pattern codes connecting concepts to one another. The coding team applied these codes to a subset of transcripts, comparing coding strategies and adjusting code definitions until adequate intercoder reliability was achieved. During this process, the team also developed analytic memos regularly, reflecting dimensions and characteristics of each code, as well as noting major themes. Additionally, data matrices were created to visually represent relationships between key concepts and elicit patterns in the data. Throughout this process, the qualitative team held weekly analysis meetings (via Zoom) to facilitate collaboration between team members. Once the analysis was completed, findings were reviewed with the CAB as a form of member checking.

Translation of Qualitative Findings to Design the PrEP US NoW Intervention

Working with the CAB, the intervention mapping techniques [46] guided translation of nascent literature regarding barriers to PrEP use among young, Black, sexual minority men into an intervention protocol for subsequent piloting. Intervention mapping highlights the importance of incorporating data to map out the problem (ie, PrEP underuse by young, Black, sexual minority men), its determinants, and potential solutions. The planning team (CAB and study team) worked closely to describe the content for the web-based discussions by identifying the influences on PrEP uptake. Next, the team focused on the objectives, smaller goals, and the overarching larger goals for improving the PrEP care continuum. Moving forward, an intervention protocol was laid out, which informed the development of study materials, such as in-app discussion topics, training materials for female facilitators, etc, in a way that addressed the problems identified earlier. Next, the team worked to develop specific content, mapped to the sIMB conceptual framework, to facilitate web-based discussions around identified topics of importance. The team also worked with a technology partner to modify the app accordingly.

For this study, the existing HealthMpowerment (HMP) app was adapted, which would support online communities in discussions around stigma and sexual health [47-49]. The HMP app allows anonymity, which protects unintentional disclosure of HIV status and sexual identity and may help those facing HIV and sexual orientation stigma. This app also provides a virtual location for network members from different geographic locations, enabling them to discuss sensitive topics with shared access to information about HIV prevention strategies, like PrEP. Previous testing of the HMP app has shown that greater app engagement was significantly associated with stronger primary intervention effects (eg, condomless anal sex) and secondary effects such as HIV-related communication (eg, provider communication, HIV status disclosure to partners) and HIV care outcomes (eg, perceived barriers, engagement in care, self-reported adherence) [49-51].

The current participant forum in the HMP app was expanded to add a space where the intervention content will be delivered in real time through semistructured discussions led by Black female facilitators with the young, Black, sexual minority men network. Only Black women who possess the qualities identified in the qualitative findings associated with trust and nonstigmatizing support will lead the discussion topics. Black female facilitators and young, Black, sexual minority men

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network members will have the option of using an avatar to maintain confidentiality. At this time, the intervention mapping process with our CAB has led to the app name being changed to “US NoW.”

Each week, discussions ranging from 30 to 60 minutes will be conducted at a mutually agreed-upon time. Prior to each session, topic-specific scholarly articles suitable for the lay audience and activities will be provided in the HMP app that map the conceptual framework (see Figure 3). Young, Black, sexual minority men's social networks will be asked to view content and engage in discussions during these sessions. The young, Black, sexual minority men participants will be able to communicate and post privately as well as publicly with each other. If Black female leads are contacted ad hoc by a group member (between discussions or 1 week following the last discussion), they will be expected to reciprocate communication or request information within a 24-hour timeframe.

Figure 3. Community advisory board–informed topics, content, and structure for the intervention. Forum topics track the adapted sIMB conceptual framework. PrEP: pre-exposure prophylaxis; sIMB: situated Information, Motivation, and Behavioral skills; STI: sexually transmitted infection.

Forum topic	Forum structure	Forum content	
HIV prevention	**Chat-room networks:**	**Articles:** Information: common condom mistakes Motivation: HIV self-testing Behavioral skills: getting real about STI prevention	**Activities** Information: how to use a condom – in steps Motivation: get tested for HIV Behavioral skills: reduce your risk of getting HIV
Sexual health		**Articles:** Information: the 411 on safe(r) sex Motivation: good enough video series Behavioral skills: how to say no to sex	**Activities** Information: safer sex Motivation: better sexual health, better sex. Behavioral skills: slide baby, slide
Intersectional stigma	**4 topics:** - Discussed in 60-minute forum each week - Associated articles and activities mapped to the sIMB framework weekly - Predesignated times, after traditional work hours	**Articles:** Information: stigma: defined Motivation: three reasons to come out to your provider Behavioral skills: ways to build resilience	**Activities** Information: connect with the LGBTQ+ community! Motivation: born this way! Behavioral skills: just breathe
Engagement in PrEP care		**Articles:** Information: are you ready for PrEP? Motivation: being on PrEP Behavioral skills: navigating the PrEP conversation with a provider	**Activities** Information: what is PrEP? Motivation: PrEP motivation Behavioral skills: talking to others about PrEP

Beta testing of the app and intervention was carried out with the CAB to get a sense for how the features will work in the subsequent pilot trial. The CABs were oriented to the app and were asked to use it for a month. During the beta testing, 4 semistructured discussions were convened that mimicked how anticipated sessions will occur during the actual trial. The CAB members reconvened with the study team to provide feedback on their experiences, which was used to make the necessary final changes to the intervention prior to the randomized controlled trial.

Piloting and Evaluating the PrEP US NoW Intervention

The primary outcomes from the trial will include feasibility and acceptability, improvement in social capital, and reduction in internalized homonegativity. Secondary outcomes will include estimates of intervention efficacy in increasing PrEP uptake and decreasing condomless anal sex acts. Figure 4 outlines the study design for the pilot intervention.

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Figure 4. PrEP US NoW study design. One-to-one randomization will be done prior to this, with control arm indexes (n=10) to refer 8-10 young, Black, sexual minority men from their social network. These network referrals will be screened for eligibility, undergo sociograms, and then have access to the HealthMpowerment app alone, with surveys at T0, T1 (at 1 month), and T3 (at 3 months). mHealth: mobile health; PrEP: pre-exposure prophylaxis; PrEP US NoW: Pre-Exposure Prophylaxis Utilization Through Increasing Social Capital Among Young, Black, Sexual Minority Men Networks With Women.

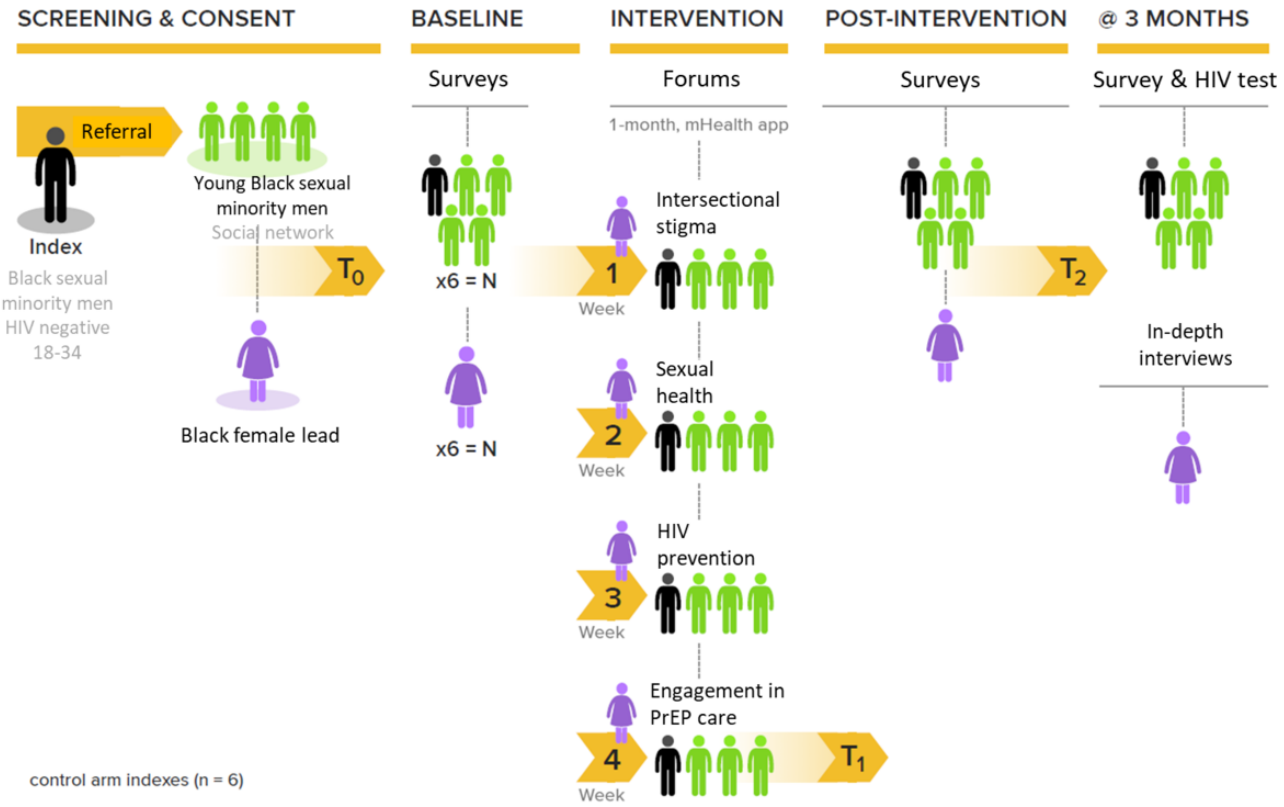

Recruitment, Screening, and Consent

A network-based approach was used to identify social network members of the index young, Black, sexual minority men participants by following a sociogram protocol [52], that is, graphic plotting of the young, Black, sexual minority men's social network members. The recruitment for young, Black, sexual minority men is still ongoing, whereas recruitment for Black female group facilitators has been completed. For each index young, Black, sexual minority man in the intervention arm, a Black female social network member, referred by the CAB and external to the young, Black, sexual minority men's network, was screened. The inclusion criteria for the Black women facilitators included (1) self-identified Black race and female gender, (2) age >18 years, and (3) fluency in written and spoken English. The goal was to have at least one eligible Black female member per 6 eligible young, Black, sexual minority men, serving as a facilitator in each group. The ultimate Black female facilitator selection only consisted of cisgender women and was made by the CAB based on a structured interview to assess stigmatizing beliefs and cultural humility. As this was an egocentric network analysis, the investigators assumed networks were independent of one another; however, the first name and last initial of participants were collected to evaluate for overlaps across networks in the analyses.

To recruit networks of young, Black, sexual minority men, index young, Black, sexual minority men participants will be recruited first, who will subsequently recruit up to 8 young, Black, sexual minority men members of their own social networks. Similar resources and strategies used earlier will be used to recruit index young, Black, sexual minority men participants. Inclusion criteria for young, Black, sexual minority men index participants are (1) age 18-29 years, (2) HIV negative (based on self-performed HIV OraQuick test), (3) Black cisgender men (based on gender and sex at birth), (4) self-reported past sex with other men (past 6 months), (5) English speaking, and (6) able to identify 6-8 young, Black, sexual minority men in their personal social network. The exclusion criterion is cognitive impairment resulting in the inability to provide consent. Potential index participants will complete a web-based screening survey to determine eligibility. Once an individual is considered eligible, they will be contacted (via phone or in person) to provide more details about the study and will be asked to complete an informed consent. Enrolled index young, Black, sexual minority men participants (n=12) will be randomized (2:1) to the intervention arm (n=30, 6 indices with 5 network members per index) or the control arm (n=30, 6 indices with 5 network members per index). The allocation sequence is generated and assigned by REDCap (Research Electronic Data Capture), and participants are enrolled by our research coordinator. The allocation is computer-generated for randomization by our REDCap. Allocation concealment is provided by the REDCap system. Participants' IDs are provided to our data manager, who enters this information into REDCap. They then inform our research coordinator of the randomization arm for the participant. Both the intervention and control arms will be unblinded. At recruitment, the participants will be

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educated on the protocol and goal of the study, understanding how support systems can improve access to HIV prevention strategies like PrEP. The randomized controlled trial was registered within ClinicalTrials.gov (NCT07024745).

Intervention Arm

A total of 6 young, Black, sexual minority men's social networks, each including 5 young, Black, sexual minority men (including index participants) and 1 Black female facilitator, will participate in the intervention arm. Before the trainings, the Black female facilitators completed a baseline survey electronically, which measured sociodemographics, HIV knowledge, PrEP knowledge, HIV-related stigma [53], homophobia [54], and PrEP stigma. Black female facilitators have completed their training on app usage. In addition, Black females also completed an (web-based or face-to-face) intensive training covering (1 day) cultural competence and humility when working with sexual and gender minority populations; experiences of stigma among young, Black, sexual minority men in the South; LGBTQ-focused sexual health topics; and basic information about HIV treatment and prevention, including the use of PrEP and steps required to engage in PrEP care.

All young, Black, sexual minority men in the intervention arm will also receive a training (web-based or face-to-face), including a tour of the downloadable US NoW app, a brief demonstration of how to join and participate in the web-based discussion, and practice on posting content publicly and privately. Once trained, young, Black, sexual minority men will complete HIV testing using OraQuick rapid HIV test (remote participants will be asked to text a picture of the test result via a secure server) and an electronic baseline survey prior to study commencement capturing information on sociodemographics, stigma related to race or ethnicity and sexual practices or orientation [55,56], HIV, poverty, PrEP use [57], PrEP knowledge [57], sexual history and practices [58], alcohol [59] and substance abuse [60], and depression [61] and anxiety [62], using appropriate validated measures. In the event an individual tests positive on an HIV test, they will be referred to the linkage team at the study site's university-affiliated clinic for counseling, access to confirmatory testing, and linkage to care, if necessary.

Following enrollment of young, Black, sexual minority men and Black women facilitators, 4 predesignated 60-minute discussions with the network and the Black woman facilitator will commence. Activities of Black female facilitators will include leading discussions and answering any questions or comments posted by young, Black, sexual minority men. Young, Black, sexual minority men participants will be instructed how to use the app throughout the 4-week period. The importance of attendance at the discussions will be emphasized and incentivized through app badges given by other members within the network and by Black female facilitators. Additionally, a reminder, through phone texts, will be sent to young, Black, sexual minority men participants about discussion times.

The data collection began in August 2024 and is expected to be completed in December 2025. Once the intervention ends, young, Black, sexual minority men participants will receive follow-up surveys electronically at T_1 (1-month postintervention) and T_3 (3-month postintervention), capturing the primary and secondary outcomes (explained in detail later). Young, Black, sexual minority men will also be asked to perform a rapid HIV OraQuick test at T_3, remotely. Similarly, Black female facilitators will also complete a follow-up electronic survey at T_1, which will measure feasibility and acceptability, as well as any changes in stigma and PrEP knowledge or attitudes from baseline. In addition to surveys, Black female facilitators will also participate in web-based qualitative interviews at T_3, which will evaluate PrEP knowledge, intersectional stigma, and change in attitudes following the intervention and gain descriptive information about the process (ie, feasibility and acceptability) of PrEP US NoW facilitation. Additionally, experiences and comfort around delivering the intervention will also be assessed.

Control Arm

The control arm will be similar to the intervention arm in terms of HIV testing, baseline and follow-up surveys, and incentives. However, there will be no Black female facilitators, and instead of the modified intervention HMP app, these participants will use a control version of the HMP app without any discussions or scheduled check-ins with study staff. These participants will, however, be provided with the opportunity to contact the study team in case of technical difficulties or any other issues.

Survey Measures

Independent Variables

Using validated measures, the following will be assessed: sociodemographics (age, income, employment, education, insurance, and housing); stigma related to race or ethnicity, sexual practices or orientation, HIV, poverty, and PrEP; PrEP knowledge; sexual history and practices; alcohol and substance abuse; and depression and anxiety.

Primary Outcomes

Four primary outcomes—feasibility, acceptability, social capital, and homophobia—will be measured. *Feasibility* and *acceptability* will be measured using responses from T_3 surveys. Validated scales will include the Acceptability of Intervention Measure, Intervention Appropriateness Measure, and Feasibility of Intervention Measure [63]. These scales include straightforward questions such as "[PrEP US NoW] is appealing to me," to which participants respond on a 5-point Likert scale. Feasibility will also be measured by monitoring in-app usage characterized by the completion of 15-minute discussions, the number of posts, and the total time spent in virtual discussions. Moreover, intervention fidelity will be monitored by documenting the completion of 15-minute discussions and the response rate for questions posted, and by reviewing the accuracy of information shared. *Social capital* will be measured using a modified version of Chen's Personal Social Capital, the Modified Social Capital Scale [64], adapted for young, Black, sexual minority men use. This scale measures bonding (resources accessed within similar sociodemographic social groups) and bridging (resources derived from cross-identity connections) social capital with sources and types of support (eg, emotional, instrumental, and informational). *Homophobia* will be measured using the Internalized Homophobia Scale [65].

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Secondary Outcomes

The secondary outcomes will include *connectedness to one's own ethnic community*, measured using an adapted version of the Social Connectedness in the Ethnic Community Scale [66], *condomless anal intercourse in the past 3 months* (ordinal measures), and *PrEP uptake* (yes or no).

Sample Size Justification

For this pilot study, the importance of sample size lies in establishing feasibility and the precision of estimated changes, which will inform the design of future studies. Twelve index participants will be recruited, and each index will provide information to recruit 4 others, yielding a total sample size of 60. Six indexes will be randomized to PrEP US NoW and 6 to the control group. The clustering of participants within the index (specifically the PrEP US NoW group) may result in a reduced effective sample size. Assuming no correlation within indices for all participants, a rate of advancement of 50% for PrEP US NoW, the bootstrap 95% CI would have a margin of error of ±12%. On the other hand, assuming a large correlation, 0.9, the margin of error becomes ±25%. With an anticipated 15% PrEP uptake, the 95% CI margin of error is ±9% for no correlation and ±18% for a correlation of 0.9.

Data Analysis

The data will be stored in a secure server housed in the health system at the University of Alabama at Birmingham and will only be viewed on designated encrypted devices by the principal investigator and study team. Descriptive statistics will be calculated to characterize acceptability and feasibility measures. Stratifying young, Black, sexual minority men by age ranges, 18-21 and 22-29 years, all outcomes will be described by independent variables using frequencies (percentages). Generalized estimated equations will be used to perform logistic regression with empirical standard errors using an exchangeable working correlation, based on the reasonable assumption of equal correlation among members within each index. Other structures will be examined. These models will be used to estimate the rate of PrEP uptake to determine the difference in odds of PrEP uptake, controlling for within-index correlation to determine the difference in the odds of uptake between the two groups (intervention and control). Separate models will be fitted directly after the intervention (T_1) and 3 months following the intervention (T_3). For each model, independent predictor variables (sociodemographic factors, variables related to stigma, knowledge, sexual history and practices, alcohol and substance abuse, and depression and anxiety) will be included as covariates. All categorical outcomes (advancement, change in social capital, connectedness, and condomless anal intercourse in the past 3 months) will be treated similarly. Lastly, if there are overlaps in social networks between index cases, we will perform a network analysis to determine closeness, betweenness, and degree to determine if there will be potential for treatment interference.

Data Management

Results of remotely conducted HIV tests will be shared via a secure server hosted in the university's health system. The results will only be viewed by the study staff on encrypted mobile devices. All electronic surveys will be entered into a secure, web-based application, REDCap. For quality control purposes, REDCap has data visualization tools to assist in data cleaning and evaluation. The Data Export Tool includes methods for data deidentification. The REDCap database is hosted at the UAB Department of Medicine's secure data center, which will be used as a central location for data storage, processing, and management. The servers are protected by an aggressive firewall and a log monitoring system. All web communications are protected via SSL encryption. Only institutional review board (IRB)–approved research team members will have access to the REDCap. Access is granted according to "the principle of least privilege." Each team member will be granted access to the REDCap data system through a secure log-in. The data will be deidentified for analysis, and findings will be disseminated in an aggregate form. All digital files will be deleted, and all physical files will be shredded after 5 years in line with the University of Alabama at Birmingham's policy.

Ethical Considerations

This study was approved by the University of Alabama at Birmingham's institutional review board (IRB-300007813) on October 18, 2021. Informed consent was collected and documented from all young, Black, sexual minority men and Black female participants (Multimedia Appendices 2 and 3). The qualitative and quantitative data used for this study were covered under the study's IRB. The consent forms were documented electronically. All data were deidentified before being analyzed. All CAB members were compensated with US $50 per meeting. Black women in the intervention arm underwent a training and received US $400 after training completion. In addition, young, Black, sexual minority men and Black women will complete 3 surveys (baseline, T_1, and T_3) and will be incentivized with US $50 per survey.

Results

For informing the PrEP US NoW intervention, 52 individuals (young, Black, sexual minority men: 33; Black women: 19) completed a web-based screening, which lasted between May 2022 and June 2024. Of these, a total of 30 were selected for semistructured interviews (young, Black, sexual minority men: 15; Black women: 15). The interviews were conducted between May 2022 and June 2024. The findings from the interviews indicated that young, Black, sexual minority men value emotional support the most and that Black women provide both emotional and tangible support (manuscript in the process of submission). These findings were then applied in designing the app for the intervention. The intervention is currently in the initial phases of recruitment. The intervention arm will have 6 social network groups, each comprising 5 young, Black, sexual minority men and 1 Black female facilitator. The control arm is expected to have 30 young, Black, sexual minority men participants. The baseline surveys with young, Black, sexual minority men began in August 2024 and are still ongoing. The baseline surveys with Black females were completed between July and August 2024. The young, Black, sexual minority men's follow-up surveys at T_1 and T_3, along with Black women's surveys at T_1 and qualitative interviews at T_3, are expected to

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be completed by the end of 2025. The analysis of findings from young, Black, sexual minority men and Black women in the intervention arm and young, Black, sexual minority men in the control arm will be helpful in assessing the effectiveness of the PrEP US NoW intervention in improving PrEP uptake among young, Black, sexual minority men. If the study shows promising findings, a subsequent grant application will be submitted, which will help develop a fully powered randomized controlled trial that can test the efficacy of the intervention at multiple sites across the US South. In case the findings are not as anticipated, the knowledge gained on young, Black, sexual minority men's social networks, social capital, and the role of Black women facilitators will still provide novel insights to inform future HIV prevention research among this highly impacted group.

Discussion

Anticipated Findings

This paper describes a novel research protocol that will develop and pilot an mHealth intervention, PrEP US NoW, which aims to improve engagement in PrEP care among young, Black, sexual minority men in Birmingham, AL, by leveraging and supporting the social capital within their social networks. This intervention is anticipated to increase social capital in accessing sexual health services, like PrEP, among young, Black, sexual minority men. The pathways by which this is thought to occur are related to increasing knowledge around sexual health well-being, specifically PrEP. In addition, by focusing on motivating participants in engaging in the sexual health system, self-efficacy in accessing sexual health services as an empowered self-advocate will also increase. With a high HIV incidence rate among young, Black, sexual minority men in the Southern United States, coupled with a low PrEP-to-need ratio among this population [20], the PrEP US NoW intervention is timely in that it addresses this disparity effectively among young, Black, sexual minority men, a group at significant risk for HIV, by evaluating strategies to increase uptake of PrEP, a highly efficacious HIV prevention tool. The PrEP US NoW intervention hence aligns with the national priorities outlined by the EHE initiative.

Previously, a study used social networks to improve PrEP uptake among young, Black, sexual minority men [36]. In this study, each young, Black, sexual minority men participant was asked to identify and recruit a social confidant in the study. As a part of the intervention, the young, Black, sexual minority men and their social confidant met with the social worker 4 times to develop a retention in care plan. The goal of these meetings was to improve HIV-care knowledge and to activate the dyadic social support in order to improve PrEP uptake. With the control group receiving the usual treatment without a social confidant, the participants in the intervention group showed significantly better retention in care outcomes than the controls, particularly kept-visits. Similarly, another study enrolled 5 HIV-negative Black, sexual minority men, who then involved members of their social networks, who were predominantly Black [24]. These social groups then engaged in weekly group sessions and booster sessions led by the project's staff. The topics discussed in these sessions involved improving knowledge on PrEP, its importance in HIV prevention, and the process of initiating and maintaining PrEP use. This study showed an increase in PrEP knowledge, PrEP use willingness, and PrEP use prevalence after the intervention. While these studies showed positive PrEP uptake outcomes, they mainly engaged network members with similar sociodemographics to the index participant, for example, young, Black, sexual minority men getting help from young, Black, sexual minority men peers. Additionally, while one of these studies also identified Black women as trusted members of young, Black, sexual minority men's social networks [36], there is a dearth of research evaluating the role of Black women within social networks for young, Black, sexual minority men or leveraging these bonds to improve health outcomes. Keeping these gaps in mind, an innovative approach was designed, which will use a network-based approach by involving both young, Black, sexual minority men and Black women (considered trustworthy by young, Black, sexual minority men) to engage in discussions on intersectional stigma, sexual health, HIV or sexually transmitted infection prevention, and PrEP, which are expected to improve their social capital and subsequently PrEP uptake. Regardless of the intervention outcomes, the results from this intervention would enrich the current literature on the role of Black women figures in young, Black, sexual minority men's social networks in HIV prevention.

While the intervention is expected to be completed within the described timeline, in case young, Black, sexual minority men's networks are not reliably attending the web-based discussions, the intervention may get extended for 5-6 weeks. Although best practices were adopted to design and implement this intervention, there may be a few limitations. For example, there is a potential for selection bias, where young, Black, sexual minority men who are interested in participating in this study may have less internalized stigma than the general population of young, Black, sexual minority men. To avoid this, necessary efforts were made to recruit using web-based approaches and to recruit in rural settings where there was more stigma, leading to fear of unintentional disclosure of sexual orientation through participation in the intervention. Additionally, some young, Black, sexual minority men may be unstably housed or have other disruptions to research participation. To address this, multiple contact methods (email, phone, and social media) will be obtained, and this information will be updated every 3 months.

Conclusions

The young, Black, sexual minority men living in the Southern United States are disproportionately impacted by the HIV epidemic. This population has a high incidence rate of HIV coupled with a low PrEP-to-need ratio. This intervention aims to increase social capital among young, Black, sexual minority men in gaining self-efficacy on their sexual health and navigating structural barriers to access PrEP services in Alabama (1 of the 11 non-Medicaid expansion states), ultimately leading to increased PrEP uptake among this population.

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Data Availability

The datasets generated during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

LE conceptualized the study and acquired funding for this project. SH, SDS, MM, JS, LH-W, JT, and ML advised on the project investigation and methodology. BJ performed activities associated with administration. MS wrote the manuscript. All authors provided feedback on the manuscript.

Conflicts of Interest

LE serves as an investigator on a Merck Pharmaceuticals research grant. We attest that generative AI was not used for the generation of any portion of this manuscript.

Multimedia Appendix 1
SPIRIT checklist.
[DOCX File , 36 KB - resprot_v14i1e66326_app1.docx]

Multimedia Appendix 2
Informed consent form: Black female participants.
[PDF File (Adobe PDF File), 76 KB - resprot_v14i1e66326_app2.pdf]

Multimedia Appendix 3
Informed consent form: young, Black, sexual minority men participants.
[PDF File (Adobe PDF File), 88 KB - resprot_v14i1e66326_app3.pdf]

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Abbreviations

CAB: community advisory board
EHE: Ending the HIV Epidemic
HMP: HealthMpowerment
IRB: institutional review board
mHealth: mobile health
PrEP: pre-exposure prophylaxis
PrEP US NoW: Pre-Exposure Prophylaxis Utilization Through Increasing Social Capital Among Young, Black, sexual minority Men Networks With Women
REDCap: Research Electronic Data Capture
sIMB: situated Information, Motivation, and Behavioral skills
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Advancing Knowledge of Values-Clarification Processes During Complex Decision-Making Among Older Adults With Advanced Cancer: Protocol for a Pilot Randomized Trial Using Simulated Patient-Clinician Encounters

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Abstract

Background: Older adults represent the majority of individuals diagnosed with cancer in the United States and often face complex treatment decisions that require balancing survival benefits with quality-of-life considerations. Despite the emphasis on shared decision-making (SDM), many patients report that clinical guidance does not reflect their personal values. Values-clarification tools have shown slight improvements in aligning care with patient values; however, the factors by which these tools influence decision-making are less studied.

Objective: This pilot study aims to estimate the quality of values-clarification and SDM processes that occur during simulated diagnosis encounters for advanced cancer among participants who do and do not receive a values-clarification tool.

Methods: Pilot randomized study using simulated patient-clinician encounters to assess how values are elicited, processed, and integrated into treatment decisions. Participants aged 60 years and older with an advanced cancer diagnosis will be randomized to receive either a digital values-clarification instrument codeveloped through stakeholder engagement, referred to as Values and Outcomes to Improve Cancer Experiences (VOICE), or a general communication guide from the American Cancer Society (ACS). Each participant will engage in 2 simulated encounters (values-based and nonvalues-based), conducted by trained medical students portraying oncologists. The simulations are structured using a situational awareness framework. A novel rating scale, referred to as VECTORS (Values Elicitation and Clarification of Treatment Options Rating Scale), will measure the quality of rapport building, clinician engagement, and patient engagement through observation. Additional validated instruments will be used to quantify observed (OPTION-5) and patient-reported (CollaboRATE) SDM behaviors and patients' perceived usefulness of either VOICE or the ACS guide (PrepDM [Preparation for Decision-Making]). Qualitative interviews will be used to better understand participants' experiences during encounters and perceptions of VOICE or the ACS guide.

Results: The study was conducted between September 2024 and December 2024, with a total of 44 participants, and is ready for data analysis.

Conclusions: This pilot study will provide preliminary evidence into the quality of values-clarification processes occurring during patient-clinician encounters among older adults making treatment decisions for advanced cancer.

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KEYWORDS

human factors; oncology; values-clarification; shared decision-making; communication; simulations

Introduction

In 2025, over 2 million people in the United States are expected to be diagnosed with cancer [1], with older adults (aged ≥60 years) comprising the majority of these diagnoses [2]. While cancer is the leading cause of death for older adults [1], their survival rates are improving, making up 78% of the more than 18 million people living with cancer [3]. These advances are positive, but also introduce greater complexity into decision-making [4], as older adults must weigh the benefits of survival to the risks to their quality of life [5]. For those with advanced cancers [6], particularly older adults with comorbidities, treatment pathways can vary and are often influenced by personal values [6,7].

Many older adults report that the guidance they receive from their clinicians does not align with their values when making a treatment decision [8-14]. Patient "values" are the unique preferences, concerns, and expectations a patient brings to a clinical encounter, which should be integrated into clinical decisions for effective patient care [12]. When patients do not engage in values-based communication with their clinicians, it can lead to decisions that negatively impact their quality of life [15], including undergoing aggressive treatments due to patients' unrealistic expectations of a cure [12,16,17].

Shared decision-making (SDM) guidelines advocate for aligning treatment plans with patient values [14,18-22], and values-clarification tools have shown slight improvements in values-discordance [20]. Research has often focused on decision-making outcomes rather than the process itself, leaving the values-clarification processes that occur during clinical encounters understudied [23,24]. Therefore, to advance knowledge of how patients' values are discussed, understood, and incorporated into the treatment decision, we applied a situational awareness framework. Situational awareness characterizes an individual's ability to gather information, comprehend information, and anticipate what will occur after making a decision based on that information [25]. Situational awareness can be assessed using simulations and has been used in health care to identify communication gaps and training opportunities [26-29]. Therefore, applying the situational awareness framework to values-clarification and SDM provides a structured approach to evaluate engagement quality, highlight missed communication opportunities, and conceptualize values-discordance as a potential safety risk given its link to higher treatment burden [21] and more aggressive care [18,22].

This protocol describes a pilot study to estimate the quality of values-clarification and SDM processes during simulated diagnosis encounters for older adults (aged ≥60 years) with advanced cancer, among participants who do and do not receive a values-clarification tool. Using a situational awareness framework, we aim to evaluate how these processes unfold, where they can be strengthened, and how a values-clarification tool may influence engagement. These aims guide the following primary research questions: (1) Do participants in the intervention group experience higher quality values-clarification processes compared to the control group, as measured by a standardized rating scale? (2) Does participant use of the intervention tool influence clinician engagement in values-clarification processes, as measured by a standardized rating scale? (3) Are participants in the intervention group more likely than the control group to initiate discussions about their values during simulated encounters? (4) Does participant initiation of values (compared to clinician initiation) have an impact on the quality of values-clarification processes, as measured by a standardized rating scale?

These aims also guide the following secondary research questions: (1) Does the intervention improve both observed and patient-reported SDM experiences and perceived preparedness for decision-making, compared to the control group? (2) What themes emerge from qualitative data regarding patients' experiences of value-clarification and decision-making processes during simulated encounters?

Methods

Prior Work

We previously developed the Values and Outcomes to Improve Cancer Experiences (VOICE) tool, a digital values-clarification instrument intended to support SDM in oncology settings. To inform the development of VOICE, we conducted a stakeholder-driven concept mapping study involving 7 older adults with advanced cancer, 2 caregivers, and 12 oncology specialists [30,31]. VOICE uses best-worst scaling (BWS) to elicit and prioritize treatment values (ie, what patients value most when making treatment decisions). VOICE also generates a tailored summary report that includes question prompt lists aligned with each patient's top-ranked treatment values [30,31]. The tailored summary report was designed to prompt patients to discuss their values, ask questions, and express in their own words how the treatment options may affect what matters most to them.

Study Design

We will conduct a double-blinded randomized pilot study using 2 types of simulated patient-clinician encounters (values-based [VB] and nonvalues-based [NVB]) between an intervention group that will receive VOICE and a control group that will receive an American Cancer Society (ACS) communication guide. Participants randomized to VOICE will complete a series of 7 BWS questions, then receive a tailored summary report based on their values, within Qualtrics. Completing VOICE typically takes up to 8 minutes. See Multimedia Appendix 1 for

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an example of the BWS instrument and tailored summary report. For this study, we selected the ACS guide as the control condition. Participants randomized to the control group will receive the ACS guide in Qualtrics and typically takes up to 5 minutes to review. The ACS guide was developed as a tool to improve patient-clinician communication and includes a general list of cancer-related question prompts. By comparing VOICE to the ACS guide, we aim to isolate whether tailored summary reports that are aligned with patient values better prepare patients to engage in values-based discussions with their clinicians. Therefore, if VOICE effectively prepares patients, it may prompt clinicians to engage in values-based discussions, subsequently influencing clinician behavior. This conditional structure is embedded in the nonvalues-based simulation script design (see the Simulation Scripts section). The study design schema is described and depicted in Figure 1.

Figure 1. Randomized pilot testing study schema. (A) Participants will complete informed consent in REDCap (Research Electronic Data Capture) and participant characteristics in Qualtrics remotely before scheduling to engage in simulations. (B) To ensure balanced participation across the 4 potential pathways, a systematic alternating method in Qualtrics will be used to assign participants to the intervention (VOICE) or control (ACS) groups. (C) After participants complete and review VOICE or the ACS guide, they are prompted to contact the research team to schedule the patient-clinician simulated encounters. Patients are reminded they are preparing for a simulated patient-clinician encounter in which they will be asked to discuss and make a decision regarding a "mock" secondary cancer diagnosis. (D) The order of encounter type (VB vs NVB) will be random using a random number generator in Microsoft Excel. (E) All participants will engage in two (20- to 30-minute) simulated encounters (VB and NVB) in random order, both occurring on the same day. Clinicians (ie, medical students portraying oncologists) will only be blinded as to whether the participants received VOICE or the ACS guide prior to the interaction. Clinicians will be informed of the encounter type to ensure they follow appropriate scripts. Simulated encounters will be held at a single site in the Simulation, Experiential Learning, and Training (SET) Center located at the University of North Carolina at Chapel Hill School of Medicine. Simulated patient-clinician encounters will be audio-video recorded. (F) Participants will complete surveys (CollaboRATE and PrepDM [Preparation for Decision-Making]) and engage in semistructured interviews immediately following each simulation. Our research team will complete observed ratings of encounters (VECTORS and OPTION-5) after simulations have concluded by reviewing the audio-recorded simulations. ACS: American Cancer Society; VECTORS: Values Elicitation and Clarification of Treatment Options Rating Scale; VOICE: Values and Outcomes to Improve Cancer Experiences.

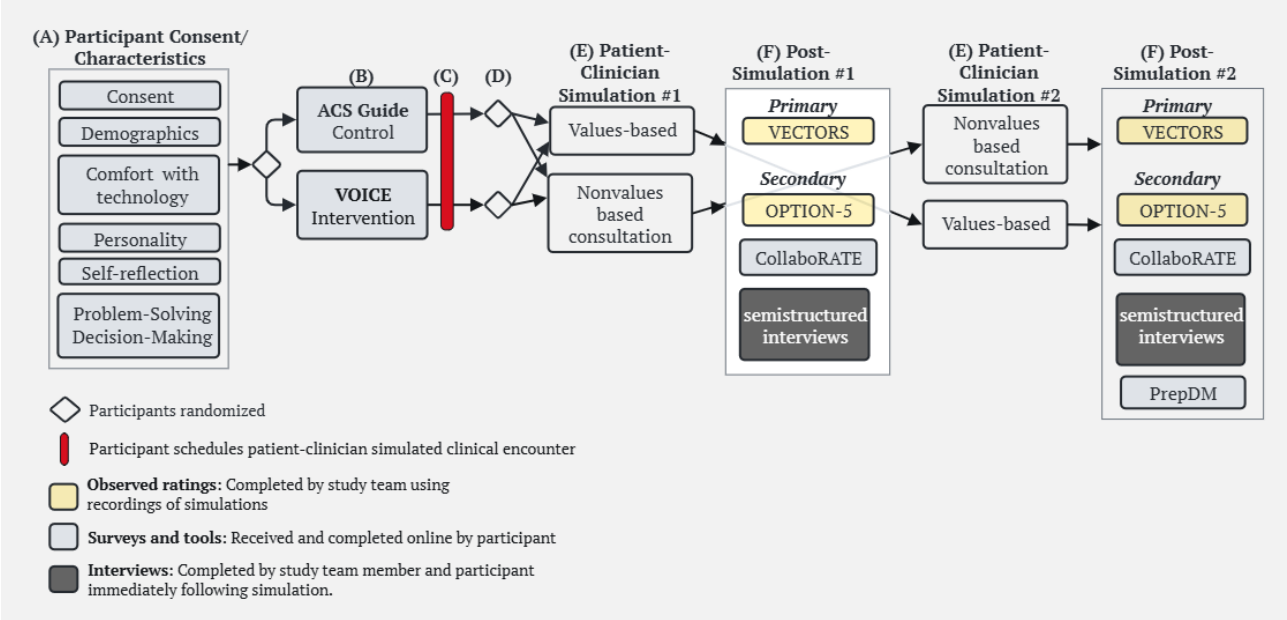

Study Participants

We will identify potential participants by reviewing inpatient census and clinic schedules within Epic and contacting them by phone and email. Participants' recruitment eligibility includes (1) confirmed cancer diagnosis at an advanced stage, not limited by cancer site, (2) being able to read and understand English, (3) being age ≥60 years, and (4) being willing to provide consent. Participants with dementia, altered mental status, or psychiatric conditions that would prohibit the understanding of informed consent or participation in a simulated encounter are not eligible to enroll in the study. With a study team member, participants will review and complete informed consent in person or by phone before enrollment and review it again upon arrival for the simulations.

Ethical Considerations

This study was reviewed and approved by the University of North Carolina at Chapel Hill (approval number 24-1566). Participant consent will be obtained electronically through REDCap (Research Electronic Data Capture; Vanderbilt University). Participants will receive US $100 for their participation. Survey data will be recorded in REDCap, a secure web application. Survey data, as well as recordings from mock consultations and interviews, will be deidentified and stored on a secure HIPAA (Health Insurance Portability and Accountability Act)-compliant location managed by the University of North Carolina School of Medicine. Protections will be taken to ensure that confidentiality is maintained, ensuring that all personnel are trained on HIPAA regulations, and restricting data access to study personnel.

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Simulation Preparation

To conduct the simulated encounters, we (1) developed disease briefs, (2) trained medical students, (3) developed 2 simulation scripts, and (4) used a modified situational awareness rating scale to estimate the quality of values-clarification processes.

Disease Briefs

Textbox 1 describes 2 disease briefs developed and reviewed by 3 clinical oncologists. Disease briefs included a mock cancer diagnosis and treatment options (delivery, side effects, and efficacy).

Textbox 1. Disease briefs for simulated patient-clinician encounters.

Disease brief 1

Cancer diagnosis: "Leukocythemia"—aggressive blood cancer

- **Treatment option 1 (standard option):** Combination chemotherapy
  - Delivery: Infusions 7 days in a row at the infusion center every month plus a chemo pill
  - Side effects: Fatigue, risk of hospitalization, weakness; 95% of patients are admitted for complication of treatment at some point in time
  - Efficacy: Median survival of 12 months
- **Treatment option 2 (medically inferior option):** Oral chemotherapy
  - Delivery: Oral pill taken every day
  - Side effects: None
  - Efficacy: Median survival of 8 months

Disease brief 2

Cancer diagnosis: "Encephaloid tumor"—lung cancer

- **Treatment option 1 (standard option):** IV chemotherapy
  - Delivery: IV chemo weekly
  - Side effects: Low blood counts, infection risk, weakness (100% of patients)
  - Efficacy: Median survival of 4-5 years
- **Treatment option 2 (medically inferior option):** Oral chemotherapy
  - Delivery: Oral chemo every day
  - Side effects: Constipation (50%), muscle pain (50%), joint pain (50%), weakness (100%)
  - Efficacy: Median survival of 4-5 years

Medical Student Training

Five students from the University of North Carolina School of Medicine were recruited and trained to portray oncologists in the simulated patient-clinician encounters. A member of the research team served as a standardized patient during training. The training process included 2 hours of simulation script review with our research team, 1 hour of observation of an oncologist conducting both VB and NVB simulated encounters, and 6 hours of in-person practice, during which students practiced both types of simulations. To ensure consistency throughout the study, students will be debriefed after each simulated encounter to reinforce standardized engagement with participants.

Simulation Scripts

We developed 2 simulation scripts (values-based and nonvalues-based), with guidance from a simulation expert and 3 clinical oncologists.

Values-Based Simulation Script

A review of literature was performed to assess the best practices in communication and SDM during clinical encounters [21,32-37]. The resulting VB script was designed to model a "high-quality" encounter in which clinicians focus on discussing and incorporating patients' values into treatment decisions. The quality of the encounter was structured using three levels of situational awareness [38], modified for clinician and patient engagement.

- **Level 1—Gathering Information:** Identifying what matters most to the patient when making a treatment decision.
- **Level 2—Processing Information:** Exploring how the patient's values are impacted by treatment options.
- **Level 3—Projecting Information:** Anticipating what will occur after making a decision based on that information.

This script was developed to ensure the oncologist addressed all 3 levels during the encounter, supporting a values-aligned decision-making process.

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Nonvalues-Based Simulation Script

The NVB simulation script was designed to model a "lower quality" encounter in which the oncologist focuses on treatment decisions without explicitly addressing the patient's values. In these encounters, any shift toward values-based discussion must be initiated by the patient, referred to as "patient agency."

For example, if a participant mentions caring for their grandkids and expresses concern about how treatment may affect that role, the clinician is prompted to transition to level 2 of the VB framework (processing information about how the patient's values are impacted). This may also prompt the clinician to go to level 1 (gathering information about what the patient values most). After addressing the patient's concern, the clinician returns to the NVB script to inquire if the patient is then ready to make a treatment decision. During NVB encounters, clinicians are instructed not to advance through the values-based levels unless explicitly prompted by the patient. This structure ensures that values-based engagement in NVB encounters occurs only in response to patient-initiated cues.

See Figure 2 for the simulation script schema. This schema was used to support both the development of simulation scripts and medical student training for conducting VB and NVB encounters.

Figure 2. Simulation script schema.

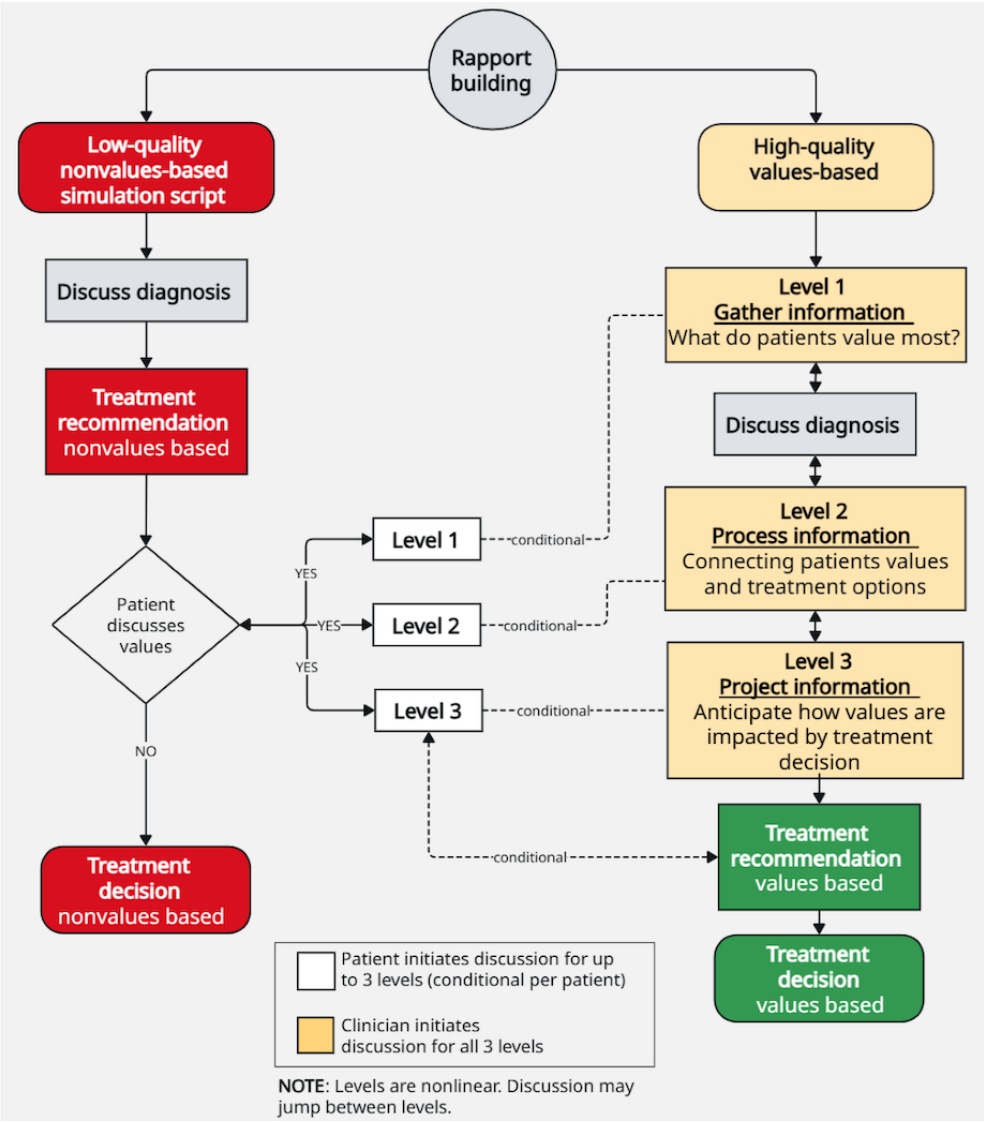

Values Elicitation and Clarification of Treatment Options Rating Scale

We developed a novel rating scale called the Values Elicitation and Clarification of Treatment Options Rating Scale (VECTORS). VECTORS is a 7-item rating scale that includes 3 domains: rapport building (1 item), clinician engagement (3 items), and patient engagement (3 items). VECTORS uses a Likert-type scale with 3 response options representing a 10-point scale (0=no effort observed, 5=moderate effort was observed, and 10=exemplary effort was observed). Higher scores reflect higher quality of values-clarification processes.

Table 1 displays the rating score criteria for each of the 7 items in VECTORS. VECTORS was established following the same situational awareness framework and review of literature as described under the simulation script development to rate the quality of values-clarification processes that occurred during patient-clinician encounters.

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Table 1. Values Elicitation and Clarification of Treatment Options Rating Scale (VECTORS).

Rating score	Scoring criteria	Rating example
Rapport building (clinicians and patients engaged in rapport building)		
0	Patients and clinicians did not engage in rapport building.	N/A[a]
5	Patients and clinicians engaged in rapport building moderately well, but only surface-level discussion.	*Clinician*: *"How are you doing today?, How was your drive in?, etc."Patient*: *"I'm doing okay, it's a nice day outside, and the drive in wasn't too bad."*
10	Patients and clinicians engaged in rapport building extremely well. Patients and clinicians engage in a dialogue to learn more about one another.	*Clinician*: *"Tell me about yourself, what are some of things that you enjoy doing."* *Patient*: *"I'm 62 years old, married and have 2 kids. I enjoy going for walks with my dog, playing the violin and going out to restaurants with my friends."* *Clinician*: *"That sounds very enjoyable. I appreciate you sharing that with me. I hope to learn more about you as we go through this journey together. I'd like to tell you more about myself, and the role that I will have in your cancer care."*
Clinician engagement		
Level 1: Gather information (clinicians discussed what their patients value most)		
0	Patients' values not discussed, no reference or acknowledgment.	N/A
5	Discussed moderately well. Clinician initiates discussion to understand how the patients' values might inform a treatment decision but does not follow up with questions to learn more about what that means to the patient. Additional conversation does not ensue to understand how their values would be applied to making a treatment decision.	*Clinician: "I would like to talk about what you value most when thinking about treatment options as this can help us decide on the treatment pathway that is best for you. Patient: [responds]. Clinician: "Thank you for letting me know, that's important for us to think about when making a treatment decision."*
10	Discussed extremely well. Clinician initiates a discussion to understand how their patients' values might inform a treatment decision. Follows up with questions to learn more about what that means to the patient.	*Clinician: "I would like to talk about what you value most when thinking about treatment options as this can help us decide on the treatment pathway that is best for you. Would that be okay if we talked about that?" Patient: [responds]. Clinician: "Can you tell me what maintaining your day to day activities mean to you. What concerns do you have about this?"*
Level 2: Process information (clinicians discussed how treatment options may impact what patients value most)		
0	Not discussed, presented treatment options, but did not mention how the patients' values may be impacted.	N/A
5	Discussed moderately well.	Treatment options were presented, but the conversation only addressed how the clinician's recommended option might affect what the patient values.
10	Discussed extremely well.	Treatment options are presented, and the conversation addressed how each option might affect what the patient values.
Level 3: Project information (clinicians confirmed their patient understood how treatment options may impact what they value most)		
0	Not discussed, no reference or acknowledgment.	N/A
5	Discussed moderately well. Clinician asks a simple question confirming understanding of the treatment the clinician recommended.	*Clinician: "Do you have questions about this treatment?"*
10	Discussed extremely well. Clinician confirms the patient understood or helps clarify any misunderstandings.	*Clinician:* "How would you describe both treatment options to your family?", or "In your own words, how will each treatment impact the values we previously discussed?" or "In your own words, what does choosing this treatment mean to you?"
Patient engagement		
Level 1: Gather information (patients discussed what they value most)		
0	Patients' values not discussed, no reference or acknowledgment.	N/A
5	Discussed moderately well. Patient initiates discussion to discuss what they value most. Patient does not explain why this is important to them. Additional conversation does not ensue to clarify why this is important to them.	*Patient: "Maintaining my day-to-day activities is important to me." Clinician: [responds]. Note: Clinicians' response varies based on their engagement level.*

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Rating score	Scoring criteria	Rating example
10	Discussed extremely well. Patient initiates discussion to discuss what they value most. Patient provides examples of why this is important to them. Additional conversation ensues to clarify why this is important to them.	*Patient: "Maintaining my day-to-day activities is important to me because I want to..." Clinician: [responds]. Note: Clinicians' response varies based on their engagement level.*
Level 2: Process information (patients discussed how treatment options may impact what they value most or asks questions to clarify how their values could be integrated into treatment decisions)		
0	Not discussed, no reference or acknowledgment.	N/A
5	Discussed moderately well. Patient discusses or asks questions about how *what they value* may be impacted by treatment options.	*Patient: "I have some questions about how this will..." Clinician: [responds].***Note:** Patient asked questions but the responses and follow-up conversation do not help to clarify how their values can be applied to making a treatment decision. Patient does not ask additional clarifying questions or engage in additional dialogue.
10	Discussed extremely well. Patient discusses or asks questions about how *what they value* may be impacted by both treatment options.	*Patient: "I have some questions about how this will..." Clinician: [responds].***Note:** Patient asked clarifying questions or engaged in additional dialogue to ensure the clinician explains how their values can be applied to making a treatment decision.
Level 3: Project information (patients confirmed they understood how treatments may impact what they value most)		
0	Not discussed, no reference or acknowledgment.	N/A
5	Moderately well. Patient provides a simple confirmation, either in response to the clinician or by initiating the confirmation themselves.	*Patient: "Yes, I understand how each treatment option may impact what I value most."*
10	Extremely well. Patient provides examples of how each treatment option may impact what they value most, either in response to the clinician or initiated confirmation themselves.	*Patient: "I understand that if I choose treatment x, I may have to rely on a caregiver to help me get dressed, take a bath, etc."*

Data Collection

All data will be collected electronically, deidentified, and stored on a secure HIPAA-compliant drive. Only study team members will have access to these data to maintain confidentiality of study participants. Missing or incomplete data will not be imputed or otherwise adjusted; analyses will be conducted using available data only.

Participant Characteristics

Characteristic information will include participants' age, sex, race, ethnicity, cancer diagnosis, education level, household income, employment status, comfort level with technology, self-reflection and insight, and preferred role in problem-solving and decision-making (PSDM).

Self-reflection and insight will be assessed subjectively using the validated Self-Reflection and Insight Scale (SRIS) [39]. The SRIS is a 12-item assessment that measures participants' (1) engagement in self-reflection, (2) need for self-reflection, and (3) insight into self-reflection using a 5-point Likert-type scale. Higher scores indicate higher self-reflection and insight. The SRIS is an appropriate measure to assess participants' perceptions on whether the information in either the VOICE report or the ACS guide was useful for treatment decision-making.

To determine participants' preferred role in PSDM, mean scores will be calculated for both problem-solving (PS) and decision-making measures for each participant, then placed into 1 of 3 classifications: hand over (mean score <3), share (mean score between 3 and 3.99), or keep (mean score ≥ 4) [40]. Participants who "hand over" both PS and decision-making are categorized as "passive." Patients categorized as "shared," either "hand over" or "share" PS, but "share" or "keep" decision-making. Four subcategories exist for patients categorized as "shared": (1) leaning passive, (2) shared equally, (3) leaning autonomous, and (4) divide and share. Patients categorized as "autonomous" want to retain control of both PS and decision-making (ie, PS equals "keep," and decision-making equals "share" or "keep"). Two subcategories exist for patients categorized as "autonomous": (1) leaning shared and (2) consumerist. It is considered theoretically implausible for an individual to assume control for PS, but not for decision-making. Categorization of PSMD roles is displayed in Table 2.

Table 2. Participant categorization of problem-solving and decision-making (PSDM) roles.

Decision-making	Problem-solving (PS)		
	Hand over (mean <3)	Share (between 3 and 3.99)	Keep (mean ≥3)
Hand over (mean <3)	Passive	Theoretically implausible	Theoretically implausible
Share (between 3 and 3.99)	Shared (leaning passive)	Shared (equally)	Autonomous (leaning shared)
Keep (mean ≥3)	Shared (divide and share)	Shared (leaning autonomous)	Autonomous (consumerist)

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Primary Measure—Quantitative

The primary outcome is the quality of values-clarification processes during simulated treatment decision encounters for advanced cancer, assessed using VECTORS to compare intervention (VOICE) and control (ACS) groups, as well as VB and NVB encounters.

Two independent raters will review the recorded simulations and use VECTORS to estimate the quality of values-clarification observed during each encounter. Rater 1 will assist with recordings; therefore, it will not be blinded. Rater 2 will be blinded, as the recorded simulations will not indicate whether simulations were VB or NVB, or whether participants were in the intervention or control groups. We will calculate the Cohen κ coefficient to evaluate interrater reliability. We will conduct a sensitivity analysis by performing data analysis on the dataset that includes ratings from rater 1, then perform the same data analysis using the dataset that includes ratings from rater 2. We will compare the data analysis results to look for differences.

Secondary Measures—Quantitative

Data from secondary measures will either be collected through observed ratings by study team members (VECTORS and OPTION-5), participant surveys (CollaboRATE and PrepDM), or interviews, as described below and depicted in Figure 1.

SDM communication behaviors will be subjectively assessed using the OPTION-5 scale [36,37]. OPTION-5 is a validated scale used to assess the extent to which SDM communication behaviors occur during an initial diagnosis encounter. OPTION-5 is a 5-item validated survey that has been used to measure the extent to which clinicians involve patients in treatment decisions, including oncology patients, and is therefore an appropriate assessment for this study [37,41-44]. Five aspects of the clinicians' behavior during the simulated encounters will be evaluated and rated using a 5-point Likert scale, ranging from "0=no effort observed" to "4=exemplary effort is observed" [37]. The five aspects include the extent to which the clinician (1) draws attention to or confirms alternate treatment options exist, (2) supports the patient to become informed or deliberate about treatment options, (3) gives information or checks understanding about the options available, (4) elicits the patients' preferences about the options available, and (5) makes an effort to integrate the patients' preferences into the treatment decision [36,37]. Two independent raters will use the OPTION-5 scale to assess the level of SDM observed during each simulated patient-clinician encounter, as described for VECTORS. Interrater reliability and sensitivity analyses will be performed, as described for VECTORS.

The level of SDM that occurs in the simulated encounters from the patient's perspective will be subjectively assessed immediately following simulations using the 3-item validated CollaboRATE scale [35]. CollaboRATE is a patient-reported assessment that measures patients' perceived effort of clinicians to (1) understand patients' health issues, (2) listen to what matters most about their health issues, and (3) include what matters most when choosing a treatment [35].

Usefulness in preparing participants to engage in SDM will be measured immediately following the final simulation using the PrepDM scale. PrepDM scale [45], a validated 10-item scale, will be used to assess participants' perceived usefulness of the tool in preparing them to communicate with oncologists during the simulated encounter.

Performance actions of participants will be assessed after encounters, including (1) whether participants brought either the tailored digital summary report from VOICE or the ACS guide to the encounter and (2) whether participants informed the clinician they completed and reviewed VOICE or the ACS guide.

Secondary Measures—Qualitative

All participants will engage in 2 semistructured interviews immediately following each simulation to assess (1) situational awareness (ie, ability to gather, process, and project information) [38] during the simulated encounter and (2) perceptions of whether VOICE or the ACS guide prepared them for the encounter. Qualitative data from postsimulation interviews will be summarized and grouped into themes, which will be used to understand the impacts of using VOICE or the ACS guide prior to an encounter.

Data Analysis

Quantitative analyses will be performed in RStudio, and qualitative analyses will be performed in MAXQDA.

Sample Size and Power

This pilot study was not powered, as its primary objective was to gather preliminary data necessary to inform the design and power calculations of a future, larger-scale study. We aimed to estimate the quality of values-clarification processes during simulated encounters (as measured by VECTORS, ranging from 0 to 100) for intervention and control groups in 2 different simulated encounters (VB and NVB). We will attempt to enroll 11 participants in each pathway to gather preliminary data, for a total of 44 participants.

The preliminary data gathered from this pilot study, as well as other study outcome measures, will inform future work using VECTORS in real-world and simulated encounters.

Participant Characteristics

Descriptive statistics will be used to summarize participants' demographic characteristics, comfort level with technology, personality (BFI-2-XS [Big Five Inventory-2 Extra-Short Form]) [46], self-reflection and insight (SRIS) [39,47], and preferred role in PSDM [40].

Primary Outcome—Quantitative

Simulated encounters will be quantified using VECTORS to assess the estimated quality of values-clarification processes that occur between intervention and control groups during both VB and NVB encounters. Interrater reliability for VECTORS will be assessed by calculating the Cohen κ weighted coefficient and discrepancies in ratings. Kappa statistics between 0.61 and 0.80 indicate substantial agreement between raters, and 0.81 to 1.00 indicate almost perfect agreement between raters [48]. Analyses of the 3 domains in VECTORS include the raw scores (rapport building: 0-10; clinician engagement: 0-30; patient engagement: 0-30). Analyses of VECTORS overall scores

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involve taking the sum of all 3 domains, producing a raw score of 0-70, then rescaling to a score of 0-100.

Descriptive statistics will be used to report the mean and SD for VECTORS overall and by each domain. Mean and SD will be reported as cross-tabulations for all encounters, and by intervention and control for VB and NVB encounters, and for whether clinicians transitioned from NVB to VB encounters due to patient agency (ie, patients initiated a discussion pertaining to their values).

Linear regression models using generalized estimating equation methods will be fit using all patient data from both encounter types (VB vs NVB) to account for repeated measures per patient. These models will objectively estimate differences by group and by encounter type and test for potential interactions to show if the intervention works better in one scenario compared to the other.

Secondary Outcome—Quantitative

Simulated encounters will be subjectively analyzed using the OPTION-5 instrument to assess the extent to which SDM communication behaviors occurred during the simulation. The OPTION-5 scores from each simulation will be summed, producing a score from 0 to 20, then rescaled to a scale of 0-100. Interrater reliability for OPTION-5 will be assessed as described in the primary outcome for VECTORS.

Patient self-reported scores from the CollaboRATE assessment will be summed, then rescaled to a scale of 0-100. CollaboRATE scores will also be dichotomized (perfect score vs nonperfect score) to allow the use of logistic regression. CollaboRATE often shows ceiling effects; therefore, dichotomizing responses improves the variation among participant scores [49,50].

The PrepDM total mean scores will be quantified by averaging 10 subscales. Items will be summed, then divided by 10 to provide a mean score. Scores will be rescaled to a 0-100 scale by subtracting 1 from the summed score and multiplying by 25, with higher scores representing higher perceived levels of preparation in decision-making [45].

Descriptive statistics will be used to report the mean and SD by intervention and control groups for secondary outcome measures: OPTION-5, CollaboRATE, and PrepDM. Mean and SD will also be reported by VB and NVB encounters for OPTION-5 and CollaboRATE, and by whether participants brought the tool (VOICE or ACS guide) for PrepDM scores.

Descriptive statistics will also be used to summarize the number of participants who (1) brought either the tailored digital summary report from VOICE or the ACS guide to the encounter or (2) informed the clinician they completed and reviewed VOICE or the ACS guide.

Kruskal-Wallis tests will be performed to objectively evaluate differences in distributions in OPTION-5, CollaboRATE, and PrepDM scores.

Linear regression models will be performed for OPTION-5, as described in the primary measure for VECTORS. Log-binomial regression models will be performed with all binary patient data from both types (VB vs NVB) to account for repeated measures per patient. These models will objectively estimate differences by group and by encounter type and test for potential interactions to show if the intervention works better in one scenario compared to the other.

Secondary Outcome—Qualitative

Qualitative data from the simulated patient-clinician encounters and postsimulation interviews will be analyzed by 3 members of our research team. The blinded rater responsible for scoring VECTORS and OPTION-5 will not be involved in coding interviews to maintain independence between assessments. The qualitative analysis will follow a hybrid approach with 3 phases [51]. In phase 1, data from interviews will be categorized by a priori themes from the interview guide. In phase 2, a posteriori codes will be created and summaries from participant responses developed, looking for meanings and patterns in the interviews. Discrepancies will be collectively addressed to ensure consensus on codes. In phase 3, the a priori and a posteriori codes will be combined into family codes to structure the findings from the interviews [51]. All codes will undergo a comprehensive review and will be grouped into themes through discussion of the research team.

Results

The study was conducted between September 2024 and December 2024, with a total of 44 participants, and is ready for data analysis.

Discussion

Anticipated Findings

This study addresses a critical gap in understanding how to evaluate the quality of values-clarification processes, specifically how patients' values are discussed, understood, and incorporated into the treatment decisions. By simulating initial diagnosis encounters and using a situational awareness framework, we will evaluate how these processes unfold and where they can be strengthened, when patients do and do not receive values-clarification tools. This approach will also provide empirical evidence to better understand how a values-clarification tool may influence the quality of values-clarification and SDM processes.

Strengths and Limitations

This study may be limited by not fully capturing the emotional and contextual complexity of real-world interactions. This study also focuses on short-term outcomes and is unable to provide evidence for the long-term impacts of values-clarification processes on patients' quality of life or satisfaction with treatment decisions. While there is potential for the Hawthorne effect, where participants alter their behavior due to awareness of being observed, our use of standardized simulations and both observed and patient-reported measures will help mitigate its impact by ensuring consistency and capturing multiple perspectives.

The strengths of this study protocol are its integration of patient-reported measures, observer ratings, and the development of simulations using standardized methodologies. This mixed

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methods approach provides a more comprehensive understanding, allowing for identification of both alignment and gaps between patients' expressed values and treatment decisions. Combining evaluations of participant characteristics and secondary measures alongside VECTORS (primary measure) helps provide a more comprehensive understanding of the study participants and will contribute to improvements in values-clarification and SDM processes. Assessing participants' behaviors and interactions during simulated encounters through VECTORS and a validated assessment (OPTION-5) will lead to a better understanding of what factors may influence participants' engagement in values-clarification and SDM processes. Personality (BFI-2-XS), self-reflection and insight (SRIS), and preferred role in PSDM measures provide benefit to this research, serving as complementary measures. The SRIS is effective for assessing the differences in an individual's self-awareness and gives insight into an individual's behavior around decision-making [39]. PSDM serves as a complementary measure to better understand relationships between patients' perceptions of who should make health care decisions and the actual decisions they make, as observed during the simulated encounters.

By simulating patient-clinician encounters, we control for potential confounding variables, including clinicians' values-clarification and SDM behaviors, and randomization of information (VOICE vs ACS guide). As current SDM measures alone may not provide evidence on whether patients are actively engaged in SDM [52], simulations of patient-clinician encounters provide the opportunity to evaluate deviations from a "high-quality" SDM encounter.

Conclusions

This study protocol outlines a structured, simulation-based approach to estimating the quality of values-clarification processes in clinical decision-making. By capturing how patients and clinicians engage in values-clarification processes, this study will provide a replicable framework for studying values-based communication and evaluation of values-clarification tools. Findings from this study may inform clinical practice by identifying communication and intervention strategies that improve how older adults with advanced cancers and clinicians elicit and integrate patients' values during treatment decision-making. Although this study is conducted in a simulated setting, the framework and insights may be generalizable to clinical contexts and will guide future research and clinical practice aimed at improving SDM.

Authors' Contributions

Conceptualization: ACC (lead), LM (equal), DRR (equal)
Data curation: ACC (lead)
Formal analysis: ACC (lead), AMD (equal)
Funding acquisition: ACC (lead)
Investigation: ACC (lead)
Methodology: ACC (lead)
Project administration: ACC (lead)
Resources: LM (lead)
Supervision: LM (lead), DRR (equal)
Writing – original draft: ACC (lead)
Writing – review & editing: ACC (lead), AMD (supporting), AMS (supporting), FY (supporting), LV (supporting), AJK (supporting), LM (supporting), DRR (supporting)

Conflicts of Interest

None declared.

Multimedia Appendix 1
Example of best-worst scaling (BWS) survey and tailored summary report.
[PDF File (Adobe PDF File), 131 KB - resprot_v14i1e80531_app1.pdf]

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Abbreviations

ACS: American Cancer Society
BFI-2-XS: Big Five Inventory-2 Extra-Short Form
BWS: best-worst scaling
HIPAA: Health Insurance Portability and Accountability Act
NVB: nonvalues-based
PrepDM: Preparation for Decision-Making
PS: problem-solving measures
PSDM: problem-solving and decision-making measures
REDCap: Research Electronic Data Capture
SDM: shared decision-making
SRIS: Self-Reflection and Insight Scale
VB: values-based
VECTORS: Values Elicitation and Clarification of Treatment Options Rating Scale
VOICE: Values and Outcomes to Improve Cancer Experiences

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Original Paper

High-Intensity Interval Training for Individuals With Isolated Impaired Fasting Glucose: Protocol for a Proof-of-Concept Randomized Controlled Trial

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Abstract

Background: Standard lifestyle interventions have shown limited efficacy in preventing type 2 diabetes among individuals with isolated impaired fasting glucose (i-IFG). Hence, tailored intervention approaches are necessary for this high-risk group.

Objective: This study aims to (1) assess the feasibility of conducting a high-intensity interval training (HIIT) study and the intervention acceptability among individuals with i-IFG, and (2) investigate the preliminary efficacy of HIIT in reducing fasting plasma glucose levels and addressing the underlying pathophysiology of i-IFG.

Methods: This study is a 1:1 proof-of-concept randomized controlled trial involving 34 physically inactive individuals (aged 35-65 years) who are overweight or obese and have i-IFG. Individuals will undergo a 3-step screening procedure to determine their eligibility: step 1 involves obtaining clinical information from electronic health records, step 2 consists of completing questionnaires, and step 3 includes blood tests. All participants will be fitted with continuous glucose monitoring devices for approximately 80 days, including 10 days prior to the intervention, the 8-week intervention period, and 10 days following the

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intervention. Intervention participants will engage in supervised HIIT sessions using stationary "spin" cycle ergometers in groups of 5 or fewer. The intervention will take place 3 times a week for 8 weeks at the Aerobic Exercise Laboratory in the Rehabilitation Hospital at Emory University. Control participants will be instructed to refrain from engaging in intense physical activities during the study period. All participants will receive instructions to maintain a eucaloric diet throughout the study. Baseline and 8-week assessments will include measurements of weight, blood pressure, body composition, waist and hip circumferences, as well as levels of fasting plasma glucose, 2-hour plasma glucose, and fasting insulin. Primary outcomes include feasibility parameters, intervention acceptability, and participants' experiences, perceptions, and satisfaction with the HIIT intervention, as well as facilitators and barriers to participation. Secondary outcomes comprise between-group differences in changes in clinical measures and continuous glucose monitoring metrics from baseline to 8 weeks. Quantitative data analysis will include descriptive statistics, correlation, and regression analyses. Qualitative data will be analyzed using framework-driven and thematic analyses.

Results: Recruitment for the study is scheduled to begin in February 2025, with follow-up expected to be completed by the end of September 2025. We plan to publish the study findings by the end of 2025.

Conclusions: The study findings are expected to guide the design and execution of an adequately powered randomized controlled trial for evaluating HIIT efficacy in preventing type 2 diabetes among individuals with i-IFG.

Trial Registration: Clinicaltrials.gov NCT06143345; https://clinicaltrials.gov/study/NCT06143345

International Registered Report Identifier (IRRID): PRR1-10.2196/59842

(JMIR Res Protoc 2025;14:e59842) doi:10.2196/59842

KEYWORDS

isolated impaired fasting glucose; prediabetes; high-intensity interval training; fasting hyperglycemia; diabetes incidence; fasting glucose; glucose; diabetes; proof of concept; interval training; type 2 diabetes; hyperglycemia; overweight; obese; weight; insulin; feasibility

Introduction

The prevalence of type 2 diabetes is increasing globally [1-3], driven predominantly by a rising number of individuals with prediabetes [2]. Globally, an estimated 860 million (8.4%) adults are living with prediabetes, a condition that increases the risk of developing type 2 diabetes [2], micro- and macrovascular complications, and mortality [4].

Prediabetes is not a singular entity but rather a heterogeneous group of metabolic defects that often precede type 2 diabetes [5-7]. Prediabetes phenotypes include isolated impaired fasting glucose (i-IFG), isolated impaired glucose tolerance (i-IGT), and IFG + IGT. Each prediabetes phenotype exhibits distinct pathophysiological abnormalities [5-7]. i-IFG is marked by impaired early-phase insulin secretion and hepatic insulin resistance. Conversely, i-IGT involves impairments in both early- and late-phase insulin secretion and skeletal muscle insulin resistance [5,7]. IFG + IGT presents a combination of defects observed in both i-IFG and i-IGT [5,7]. i-IFG accounts for a substantial portion of the global prediabetes population, ranging from 43.9% to 58% among Caucasian individuals and 29.2% to 48.1% among Asian individuals, depending on the diagnostic criteria [8]. Individuals with i-IFG exhibit a 4 to 5.5 times higher rate of progression to type 2 diabetes, depending on the diagnostic criteria, compared to those with normoglycemia [9].

Individuals with prediabetes are typically advised to adopt standard lifestyle interventions that emphasize improving diet quality with a modest calorie restriction and increasing moderate-intensity physical activity to reduce the risk of developing type 2 diabetes [10,11]. However, recent research highlights the varied effectiveness of these interventions among different prediabetes phenotypes. While these approaches prove highly effective for individuals with i-IGT and IFG plus IGT, their efficacy is notably limited for those with i-IFG [6,12,13]. Thus, there arises a necessity for alternative lifestyle intervention strategies tailored specifically to individuals with i-IFG.

One of the promising approaches is high-intensity interval training (HIIT), recognized as a time-efficient exercise option with significant benefits for metabolic health [14]. HIIT entails alternating short bursts of high-intensity exercise with periods of less active or passive recovery [15]. It is noteworthy that HIIT represents a more intensive exercise regimen compared to the current physical activity recommendations for individuals with prediabetes [10,11].

HIIT has been shown to effectively reduce hepatic insulin resistance and improve early-phase insulin secretion in individuals with type 2 diabetes [16-20], leading to significant reductions in fasting plasma glucose (FPG) levels [17,21-25]. Given that i-IFG shares these same pathophysiological defects [5-7], it is reasonable to hypothesize that HIIT could also be effective in individuals with i-IFG, as depicted in Figure 1. However, this hypothesis has yet to be tested in a randomized controlled trial (RCT). This is a critical investigation, as reducing fasting hyperglycemia is key to preventing the progression of type 2 diabetes in those with i-IFG [6,26]. To inform the design and implementation of this RCT, we propose conducting a proof-of-concept study among individuals with i-IFG, with the following objectives.

- Primary objectives (feasibility and acceptability): (1) assess the feasibility of recruiting and retaining participants and executing study procedures; (2) examine the feasibility, acceptability, and appropriateness of the HIIT intervention for participants; and (3) investigate participants' experiences, perceptions, and satisfaction with the HIIT

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intervention, and identify facilitators and barriers to participation.

- Secondary objective (preliminary efficacy): Investigate the preliminary efficacy of HIIT in reducing FPG levels and addressing the underlying pathophysiology of i-IFG.

Figure 1. Potential pathways through which high-intensity interval training sessions may address the pathophysiological abnormalities and fasting hyperglycemia in individuals with isolated impaired fasting glucose. VLDL: very low-density lipoprotein.

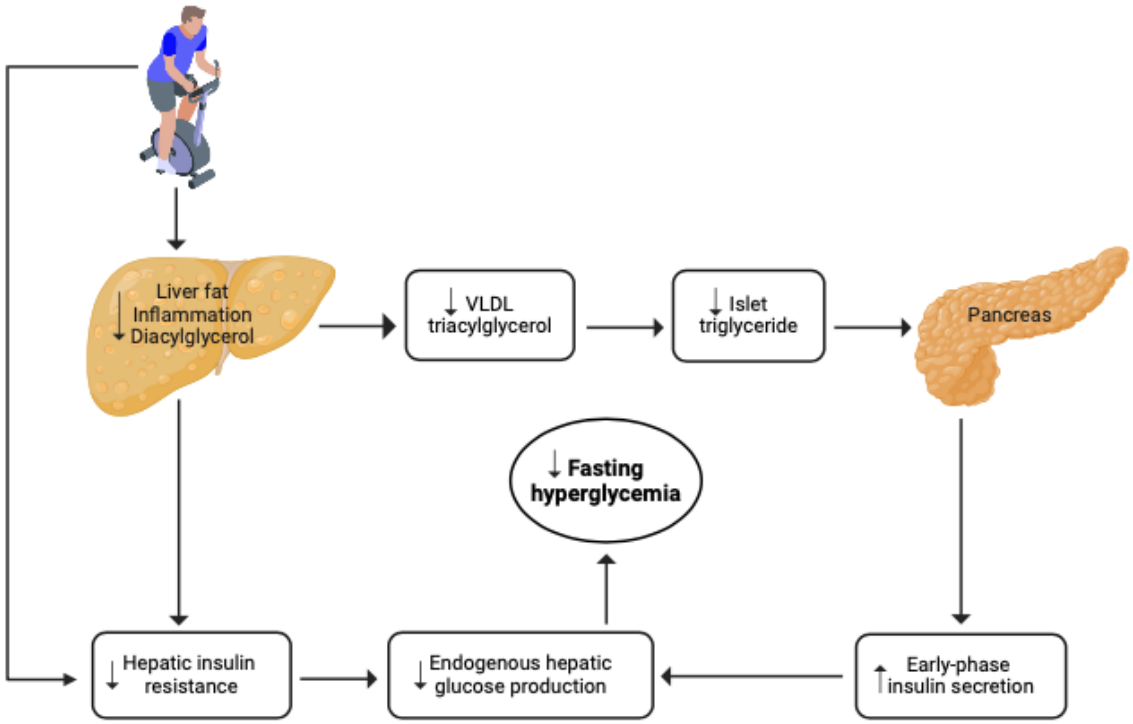

Methods

Study Design, Study Setting, and Participants

The study will be reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) guidelines for randomized pilot and feasibility trials [27]. This is a "proof-of-concept" 1:1 parallel-group RCT involving 34 physically inactive individuals aged 35-65 years who are overweight or obese and have i-IFG. Figure 2 presents the study's CONSORT diagram. The Georgia Clinical Research Center (GCRC) at Emory University Hospital will serve as the site for participant recruitment and conducting study procedures. A highly trained and experienced study coordinator will recruit participants through a comprehensive 3-step screening procedure.

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Figure 2. CONSORT (Consolidated Standards of Reporting Trials) flow diagram. CGM: continuous glucose monitoring; HIIT: high-intensity interval training; i-IFG: isolated impaired fasting glucose; OGTT: oral glucose tolerance test; REDCap: Research Electronic Data Capture.

Step 1: Screening (via Electronic Health Records)

Potential participants will be identified using Emory's electronic health care records system, known as "MyChart." Queries within this database will target individuals aged 35-65 years with a BMI≥25 kg/m^2 (≥23 kg/m^2 if Asian descent) [28], who have been diagnosed with prediabetes (hemoglobin A_{1c} [HbA_{1c}] 5.7%-6.4%) [29] within the last 12 months, have no diagnosis of diabetes (FPG≥126 mg/dL or 2-hour plasma glucose ≥200 mg/dL or HbA_{1c}≥6.5% or currently taking antidiabetic drugs) [29], not currently taking weight-loss medications, not currently taking drugs known to influence glucose tolerance (steroids and antipsychotics), not currently taking beta-blockers and calcium channel blockers (individuals taking these drugs will not reach heart rate (HR) targets for the HIIT sessions), did not undergo bariatric surgery, no anemia (anemia may limit the exercising capacity), and have no chronic illnesses (cardiovascular disease, stroke, cancers, chronic respiratory diseases, and mental health disorders). Individuals meeting these criteria will receive an invitation through the MyChart platform to participate in the second screening step.

Step 2: Screening (via Phone Calls)

Those expressing interest in participating in the study through MyChart will be contacted via phone. During these calls, individuals will receive a comprehensive explanation of the study and have any questions addressed. They will then be asked to sign an electronic consent form via Emory's REDCap (Research Electronic Data Capture; Vanderbilt University) platform [30]. Following consent, potential participants will complete a questionnaire to assess their eligibility for step 3 screening based on the following criteria.

- Physically inactive (less than 150 minutes per week of moderate-intensity physical activity, less than 75 minutes per week of vigorous-intensity physical activity, and <600 metabolic equivalent task–minutes per week) [31] assessed by the International Physical Activity Questionnaire (IPAQ) [32].
- Available to participate in the HIIT group sessions.
- No history of smoking (smoking is associated with reduced insulin secretion and increased insulin resistance) [33].
- Not enrolled in weight loss programs in the past 6 months.

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- Not enrolled in any regular exercise programs in the past 6 months.
- Not currently following a specific diet (eg, ketogenic and Mediterranean).
- No plans to undergo bariatric surgery during the study period.
- No plans to relocate outside the study area during the study period.
- Not pregnant.
- Not breastfeeding.

Step 3: Screening (via In-Person Clinic Visits)

Individuals meeting the step 2 criteria will be invited to visit the GCRC at Emory University Hospital after fasting overnight for a minimum of 8 hours [29]. During the visit, participants will complete standard questionnaires to collect sociodemographic information (education, occupation, and marital status) [34,35] and details on alcohol consumption [34,35] and dietary intake [36]. Additionally, physical measurements will be conducted using standardized instruments in accordance with the World Health Organization's STEPwise approach to noncommunicable disease risk factor surveillance (STEPS) protocol [37]. Following these assessments, individuals will undergo an oral glucose tolerance test (OGTT) and provide blood samples for insulin. Individuals diagnosed with i-IFG, defined by the American Diabetes Association criteria as FPG between 100-125 mg/dL and 2-hour plasma glucose<140 mg/dL [29], will be deemed eligible to participate in the study. Individuals without i-IFG will be excluded from further participation in the study. They will receive a summary report of their test results and general healthy lifestyle advice and will be referred to their general practitioner if they have IGT or undiagnosed diabetes for further management.

Randomization and Blinding

Participants will be equally randomized into either the intervention or control group after completing baseline assessments and being found eligible, using a computer-generated randomization sequence by a statistician not involved in the trial. Given the nature of the study, only specific personnel such as nursing staff, laboratory personnel, and the data analyst will be blinded to participant allocation to the study groups. Participants, the study coordinator, the HIIT intervention instructor, and the principal investigator will not be blinded to participation allocation.

Intervention

Following the recommendation of the American College of Sports Medicine [38], participants in the intervention group will be required to obtain medical clearance from their general practitioner before starting the HIIT sessions. These sessions, led by a qualified exercise physiologist (the instructor) and adhering to standard protocols [39,40], will take place in the Aerobic Exercise Laboratory at Emory University's Rehabilitation Hospital. Using "spin cycle ergometers" (Schwinn), sessions will be conducted in small groups of 5 or fewer participants at specified times on Mondays, Wednesdays, and Fridays, spanning 8 weeks. Each participant will undergo a maximum of 24 HIIT sessions. Each session will consist of a 5-minute warm-up, followed by an interval-based workout phase with steady up-tempo cadences, sprints, climbs, and interspersed recovery periods. A 5-minute cooldown will conclude each session. The workout sessions will initially last 20 minutes and will progressively increase in time based on participants' tolerance and instructor recommendations. Each session will include "active rest" periods where resistance is reduced to lower HR, alternating with high-intensity intervals featuring sprints or climbs to elevate HR. The duration of active rest versus high-intensity intervals will be adjusted according to individual responses and target HR. To monitor and maintain intensity within the target HR range, participants will wear Polar H10 chest strap HR sensors [41]. The target HR will be calculated using the Karvonen method [42]. Exercise intensity will begin at 75% of the estimated maximum HR reserve (HRR) and will increase by 5% every week, as tolerated or deemed necessary by the instructor, over the 8-week intervention period. During the workout phase, the target HRR reserve will be maintained by averaging increases and decreases in intensity or HR with a target to maintain within a 10% offset from the HRR goal [39,40]. Participants will need to adhere to within-session HR targets at an 80% rate (or greater) for a session to be counted as attended and participants will need to attend 19 out of 24 sessions to be included as a "completer" in the final data analysis. To date, our interventions have yielded a within-session adherence rate to the prescribed intervention of 91% (as measured by HR) and a retention rate of 85% [40,43-45]. Participants' weight and body composition will be measured weekly.

To ensure high compliance in session attendance, the instructor will hold weekly one-on-one meetings with participants to provide personalized feedback and encouragement. Participants' HR data will also be reviewed during these meetings. Additionally, the study coordinator will remind participants of their scheduled sessions 1 day in advance through phone calls or texts. Attendance in sessions will be closely monitored, and records of attended exercise sessions will be maintained. Participants who miss sessions will be contacted via phone calls to encourage attendance.

Any adverse events occurring during or after HIIT sessions will be documented, with medical advice sought if necessary. Both intervention and control participants will receive instructions to maintain a eucaloric diet throughout the study. Dietary adherence will be monitored biweekly by a registered dietitian using the Automated Self-Administered 24-Hour Dietary Assessment Tool (National Cancer Institute) [36]. This tool will be administered via phone calls 3 times a week, covering 2 weekdays and 1 weekend day. Additionally, control participants will be instructed to refrain from engaging in intense physical activities during the study period. Physical activity adherence will be assessed biweekly using the short form of IPAQ, also administered via phone calls [32].

Procedures

The details about the measurements, study tools, and timelines are outlined in Table 1.

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Table 1. Measurements, study tools, and study timeline.

Variables	Components	Study tools	Baseline	8 weeks
Study feasibility	Response rate, screening yield, enrollment rate, time to enrollment, intervention compliance, resource use, and retention rate	REDCap[a] database	✓	✓
Intervention feasibility	Qualitative and quantitative research	Feasibility of Intervention Measure [46]	✓	✓
Intervention feasibility	Qualitative and quantitative research	In-depth interviews	✓	✓
Intervention acceptability	Qualitative and quantitative research	Theoretical Framework of Acceptability questionnaire [47]	✓	✓
Intervention acceptability	Qualitative and quantitative research	In-depth interviews	✓	✓
Intervention appropriateness	Qualitative and quantitative research	Intervention Appropriate Measure [46]	✓	✓
Intervention appropriateness	Qualitative and quantitative research	In-depth interviews	✓	✓
Participants' expectations of and experiences with the intervention	Qualitative research	In-depth interviews	✓	✓
Sociodemographics	Age, sex, marital status, education, and occupation	WHO STEPS[b] [34] and NHANES[c] questionnaires [35]	✓	x[c]
Eligibility criteria	Inclusion and exclusion criteria[e]	Short-form IPAQ[f] [32]	✓	x
Behavioral measures	Dietary habits	ASA24[g] dietary assessment tool [36]	✓[h]	✓[h]
Behavioral measures	Physical activity	Short-form IPAQ [32]	✓[i]	✓[i]
Behavioral measures	Smoking	WHO STEPS [34] and NHANES questionnaires [35]	✓	✓
Behavioral measures	Alcohol consumption	WHO STEPS [34] and NHANES questionnaires [35]	✓	✓
Physical measures	Height	Stadiometer	✓	x
Physical measures	Weight	Digital weighing scale	✓	✓
Physical measures	Waist circumference	Inelastic measuring tape	✓	✓
Physical measures	Hip circumference	Inelastic measuring tape	✓	✓
Physical measures	BP[j]	DINAMAP BP apparatus	✓	✓
Physical measures	Body composition	Bioimpedance analysis	✓	✓
Biochemical measures	OGTT[k] (0, 30, and 120 minutes)	Enzymatic assays	✓	✓
Biochemical measures	Insulin levels at 0 and 30 minutes	Immunoassays	✓	✓
CGM[k]	Proportion of time and mean time spent in nocturnal (00:00-06:00) normoglycemia (60 to <100 mg/dl) [48]	Dexcom G6 Pro (DexCom, Inc)	✓[l]	✓[l]

[a]REDCap: Research Electronic Data Capture.

[b]WHO STEPS: World Health Organization STEPwise approach to noncommunicable disease risk factor surveillance.

[c]NHANES: National Health and Nutrition Examination Survey.

[d]x: the particular variable will not be collected during that particular timepoint.

[e]Inclusion criteria: aged 35-65 years, overweight or obese (body mass index ≥25 kg/m² [≥23 kg/m² if Asian descent]), physically inactive (less than 150 minutes per week of moderate-intensity physical activity and less than 75 minutes per week of vigorous-intensity physical activity and <600 metabolic equivalent task–minutes per week), and a diagnosis of isolated impaired fasting glucose (fasting plasma glucose 100-125 mg/dL and 2-hour plasma glucose<140 mg/dL). Exclusion criteria: diagnosis of diabetes, diagnosis of other chronic illnesses (eg, cardiovascular disease, stroke), current smoker, history of anemia, currently enrolled in weight loss programs, currently enrolled in any regular exercise programs, currently following a specific diet (eg, ketogenic diet, Mediterranean diet), currently taking weight-loss medications or drugs known to influence glucose tolerance (steroids and antipsychotics), currently taking beta-blockers or calcium channel blockers, underwent bariatric surgery or plans to undergo the surgery during the study period, plans to relocate outside the study area during the study period, pregnant, or breastfeeding.

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[f]IPAQ: International Physical Activity Questionnaire.

[g]ASA24: Automated Self-Administered 24-Hour Dietary Assessment Tool.

[h]Dietary habits will be assessed biweekly throughout the study duration.

[i]Physical activity of control participants will be assessed biweekly throughout the study duration.

[j]BP: blood pressure.

[k]OGTT: oral glucose tolerance test.

[l]All participants will be fitted with the continuous glucose monitoring device 10 days before the intervention, and they will be trained to replace the device every 10 days until 10 days post intervention.

Study Feasibility

Table 2 shows the study feasibility metrics. Continuous data collection on feasibility parameters, such as response rate, screening yield, enrollment rate, time to enrollment, intervention compliance, resource use (cost and staff time), and retention rate, will be conducted throughout the study.

Table 2. Study feasibility metrics.

Parameters	Calculations
Response rate	• Number of individuals responded to the invitation/number of individuals invited
Screening yield	• Number of individuals diagnosed with i-IFGa/number of individuals screened
Enrollment rate	• Number of individuals enrolled/number of individuals diagnosed with i-IFG
Time to enrollment	• Average time taken from sending the invitation to enrolling one participant in the trial
Intervention compliance	• Number of HIITb sessions attended/Total number of HIIT sessions
Resource use	• Program costs: Includes screening cost, cost of procedures, intervention cost, participant incentives, and other costs. • Staff time: Time spent screening and recruiting participants, time spent delivering the intervention, time spent making phone calls to participants, time spent implementing the study procedures, and time spent on baseline and follow-up assessments.
Retention rate	• Number of participants attended follow-up visits/number of participants enrolled

[a]i-IFG: isolated impaired fasting glucose.

[b]HIIT: high-intensity interval training.

Intervention, Feasibility, Acceptability, and Appropriateness

The Feasibility of Intervention Measure (FIM) will evaluate the feasibility of the intervention, encompassing questions regarding its implementability, possibility, doability, and ease of use [46]. The acceptability of the intervention will be assessed through the Theoretical Framework of Acceptability (TFA) questionnaire, which explores affective attitude, burden, ethicality, perceived effectiveness, intervention coherence, self-efficacy, opportunity costs, and general acceptability [47]. The Intervention Appropriate Measure (IAM) will evaluate the appropriateness of the intervention, including questions about its fittingness, suitability, applicability, and alignment with participants' needs [46]. Responses to the questions in all 3 questionnaires will be recorded on a Likert scale of 1 to 5. The mean total score for each of these scales will be calculated by combining the individual Likert points of each scale. Higher scores on the FIM, TFA, and IAM scales indicate greater feasibility, acceptability, and appropriateness, respectively, among participants.

Continuous Glucose Monitoring

By providing 288 glucose measurements per day throughout the 8-week intervention and 10-day follow-up, continuous glucose monitoring (CGM) can track the dynamic changes in fasting glucose levels induced by HIIT [48]. This can help identify when the effects of HIIT on fasting glucose levels become evident and whether these effects are sustained after the intervention, which may not be captured by a single blood glucose measurement taken after 8 weeks. All participants, regardless of their assigned treatment, will be fitted with a CGM device on their abdominal area upon enrollment. The CGM device, Dexcom G6 Pro CGM system (DexCom, Inc), will be used in blinded mode to minimize bias and ensure that it does not influence the study outcomes. Participants will be instructed to eat their last meal by 10 PM daily after the CGM fitting. They will wear CGM devices for approximately 80 days, including 10 days prior to the intervention, the 8-week intervention period, and 10 days following the intervention. Participants will be trained on how to replace the device every 10 days, using the instructions provided in the manual [49], during the first study visit. The adequacy of CGM data will be evaluated using the following criteria: a minimum of 80% of the potential 288

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glucose values per day should be present for any 7 consecutive days, commencing from the day following sensor insertion [50].

Clinical Measures

Data on health behaviors, physical measurements, and biochemical measurements will be collected at both baseline and 8 weeks.

Health Behaviors

Physical activity levels will be assessed using the short form of IPAQ [32] and dietary intake with the Automated Self-Administered 24-Hour Dietary Assessment Tool questionnaire [36]. Data on smoking and alcohol use will be obtained using questions adapted from the WHO STEPS [34] and the National Health and Nutrition Examination Survey questionnaires [35].

Physical Measures

Physical measurements will be taken following standard protocols [37,51]. Height will be measured using a stadiometer (Welch Ally—Scale-Tronix) with an accuracy of 0.1 cm. Weight will be assessed using a digital weighing scale (Welch Ally—Scale-Tronix) with precision to the nearest 0.1 kg. Waist and hip circumferences will be measured using an inelastic measuring tape (BaumGartens) with a precision of 0.1 cm. Blood pressure will be measured using the DINAMAP automatic blood pressure apparatus (GE HealthCare). Body composition measures, including fat mass, muscle mass, fat-free mass, visceral adipose tissue mass, and fat percent, will be obtained using the bioimpedance analysis.

Biochemical Measures

Participants will undergo an OGTT following standard protocols [52,53]. The test will be conducted after an overnight fast of at least 10 hours, with the session scheduled between 7 and 9 AM. Venous blood samples will be collected at 0, 30, and 120 minutes after ingesting a 75-g oral glucose load dissolved in 250-300 mL of water, consumed over 5 minutes. Additionally, blood samples for insulin will be obtained at 0 and 30 minutes after glucose load ingestion. Blood samples will be processed and analyzed at the Emory Medical Laboratory (EML). EML is a fully accredited and licensed clinical laboratory, actively participating in the College of American Pathologists Laboratory Accreditation Program. Additionally, it holds Clinical Laboratory Improvement Amendments certification through the Centers for Medicare and Medicaid Services. EML is also duly licensed by the state of Georgia. Glucose levels will be assessed through enzymatic assays and insulin levels via immunoassays based on the EML protocol [53]. All these analyses will use kits provided by Beckman Coulter Inc and will be performed on a Beckman Coulter analyzer.

Indices of ß Cell Function and Insulin Resistance

Table 3 provides details on the indices of ß Cell function and insulin resistance derived from glucose and insulin levels. Early-phase insulin secretion will be assessed using the insulinogenic index [54], while total ß cell function with be evaluated with the oral disposition index [55] and homeostatic model assessment of ß cell function [56]. Whole-body insulin resistance will be determined using the Matsuda index [57] and homeostatic model assessment of insulin resistance [56], while tissue-specific insulin resistance will be assessed with the hepatic insulin resistance index [58] and muscle insulin sensitivity index [58].

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Table 3. Indices of ß-cell function and insulin resistance.

ß cell function or IR[a] and components	Indices	Formula
ß cell function		
Early-phase insulin secretion:	IGI[b] [54]	$(I_{30}^{c}–I_0^{d})/(G_{30}^{e}–G_0^{f})$
ß cell function	DI_O[g] [55]	$([I_{0-30}/G_{0-30}]\times[1/I_0])$ • I0 in µU/l • G0 in mmol/l
ß cell function	HOMA-B[h] [56]	$(20\times I_0)/(G_0–3.5)$ • I0 in µU/l • G0 in mmol/l
Insulin resistance		
Whole-body insulin sensitivity	Matsuda index [57]	$10{,}000/\sqrt{((G_0\times I_0)\times(G_{mean}^{i}\times I_{mean}^{j}))}$
Insulin resistance	HOMA-IR[k] [56]	$(I_0\times G_0)/22.5$ • I0 in µU/L • G0 in mmol/l
Hepatic insulin resistance	HIRI[l] [58]	$(G_0–G_{30}[AUC^{m}]\times I_{0-30}[AUC])$ • G0 in mg/dl • I0 in µU/ml
Muscle insulin resistance	MISI[n] [58]	$(dG/dt^{o})/\bar{I}^{p}$

[a]IR: insulin resistance.
[b]IGI: insulinogenic index.
[c]I_{30}: mean insulin at 30 minutes during the oral glucose tolerance test.
[d]I_0: mean insulin at 0 minutes during the oral glucose tolerance test.
[e]G_{30}: mean glucose at 30 minutes during the oral glucose tolerance test.
[f]G_0: mean glucose at 0 minutes during the oral glucose tolerance test.
[g]DI_O: oral disposition index.
[h]HOMA-B: homeostatic model assessment of ß cell function.
[i]G_{mean}: mean glucose during the 2-hour oral glucose tolerance test.
[j]I_{mean}: mean insulin during the 2-hour oral glucose tolerance test.
[k]HOMA-IR: homeostatic model assessment of insulin resistance.
[l]HIRI: hepatic insulin resistance index.
[m]AUC: area under the curve during the first 30 minutes of the oral glucose tolerance test.
[n]MISI: muscle insulin sensitivity index.
[o]dG/dt: slope of the regression line from the peak of the plasma glucose curve to its nadir (mmol/L/min).
[p]$\bar{I}$: mean insulin concentration over the 2-hour duration of the oral glucose tolerance test (pmol/L).

Qualitative Research

Participants assigned to the intervention group will be invited to take part in in-depth interviews both before and after the HIIT intervention. Trained interviewers will administer these interviews either in person during scheduled study visits or via Zoom within 1 week of the visits if participants are unable to attend in person. The interviews will be guided by interview guides specifically developed for the study and piloted with members of the study team. Preintervention interviews will delve into participants' prediabetes history, physical activity and dietary habits, perceptions of body size and image, as well as their comfort levels, perceived difficulty, confidence, and expectations regarding the HIIT intervention. Post-intervention interviews will focus on participants' experiences with the intervention. Every effort will be made to interview both dropouts and active participants to ensure a comprehensive understanding of program acceptability and to identify barriers and facilitators to adherence. All interviews will be audio recorded, transcribed verbatim, and deidentified for analysis.

Outcomes

Primary Outcomes

- Quantitative measures: (1) feasibility metrics and (2) mean FIM, TFA, and IAM scores.

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Qualitative measures: participants' experiences, perceptions, and satisfaction with the HIIT intervention, and facilitators and barriers to participation.

Secondary Outcomes

- Between-group differences in changes in the following parameters from baseline to 8 weeks: (1) mean FPG and insulin levels, (2) indices of β cell function and insulin resistance, and (3) weight, body composition, waist and hip circumferences, and blood pressure.
- CGM metrics: (1) between-group differences in the proportion of time and mean time spent in nocturnal (12 to 6 AM) [50] normoglycemia (60 to <100 mg/dL) during the 8-week intervention period and the 10 days following the intervention, and (2) within-participant differences in the proportion of time and mean time spent in nocturnal (12 and 6 AM) normoglycemia (60 to <100 mg/dL) between exercise and non-exercise days during the 8-week intervention period.

Data Management

The study coordinator will enter questionnaire data, as well as physical and biochemical measurements directly into Emory University's REDCap database [30]. This database will feature validation checks to ensure data accuracy, along with skip patterns facilitated by branching logic functions. The principal investigator (ST) will constantly review the data for any errors, promptly flagging any errors for correction by the study coordinator. Upon completion of data entry and cleaning, a master copy of the data set will be generated and securely stored within the REDCap database. CGM raw data (in CSV file format per participant) will be downloaded from the DexCom Clarity software and uploaded to REDCap. Access to these datasets will be limited to the study coordinator and the principal investigator for confidentiality and data security purposes.

Sample Size Calculation

Assuming a Cohen *d* of 0.3 to <0.7 (medium standardized effect size) [25,59] for FPG in the planned main trial, with an alpha of 5% and a power of 90%, a sample size of 15 participants per treatment group is deemed necessary for this pilot study. Factoring in a 10% loss to follow-up in each group, the total sample size was estimated to be 34 participants (17 per group).

Statistical Analysis

Quantitative Research

Objective 1

Continuous variables will be summarized using either mean (SD) or median (IQR), depending on their distribution, which will be visually assessed through histograms. Categorical variables will be presented as counts (n) and percentages (%).

Objective 2

The analyses will adhere to the "intention-to-treat" principle. Between-group differences in changes in continuous variables from baseline to 8 weeks will be analyzed using mixed-effects linear regression models, while categorical variables will be assessed with log-binomial models. Skewed variables will be log-transformed prior to analysis. Fixed effects will include the study group (intervention vs control), timepoint (follow-up vs baseline), and the interaction between the study group and timepoint. Random effects will be specified for participants to account for the correlation between repeated measurements on the same individual. The *P* value for the study group-by-timepoint interaction will be used to evaluate the difference in changes between the study groups. The correlation between changes in fasting glucose levels and the indices from baseline to 8 weeks will be assessed using either Pearson or Spearman correlation coefficients, depending on the nature of the data distribution. Mixed-effects linear regression models will be used to compare CGM metrics between study groups, adjusting for baseline values. These models will also examine within-participant differences in CGM metrics between exercise and non-exercise days. Statistical significance will be considered with a 2-sided *P* value<.05 with no adjustments for the multiplicity of comparisons. All analyses will be conducted using Stata (version 18.0; StataCorp LLC).

Qualitative Research

In-depth interviews will be conducted with intervention group participants and dropouts. All interviews will be audio recorded and transcribed verbatim for analysis. The qualitative analysis plan involves 2 main components: a framework-driven analysis of intervention acceptability data and a thematic analysis focusing on participant expectations, experiences, barriers, and facilitators in undergoing the HIIT intervention. For the framework-driven analysis, a deductive codebook containing the TFA dimensions will be applied to both baseline and postintervention interview data. This approach aims to provide a comprehensive and longitudinal understanding of HIIT acceptability among program users, comparing results across timepoints and between those who remained in the program and study dropouts. Additionally, an inductive approach will be used to create a codebook of inductive codes around other aspects of acceptability, program barriers, facilitators, experiences, and sustainability through a close reading of the transcripts. Once the data is coded, thick descriptions of individual codes will be developed, including structured comparisons such as between baseline and postintervention interviews, program adherents and dropouts, men and women, and older and younger participants. These comparisons will guide data reporting and program adaptation for further trials, providing insights into the diverse experiences and perspectives of participants.

Challenges and Mitigation Strategies

The potential challenges that could be encountered at various stages of the study and the corresponding mitigation strategies are outlined in Table 4.

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Table 4. Potential challenges and proposed mitigation strategies.

Study stage	Challenges	Mitigation strategies
Identifying potential participants	Insufficient number of potentially eligible individuals	• We will use physician referrals as an additional recruitment strategy.
Screening	Low yield of screening	• The 3-step screening procedure was carefully designed, drawing upon insights from our previous research and existing literature, to target individuals who are likely to have i-IFG[a].
Intervention	Low HIIT[b] compliance	• The study coordinator will remind participants of their scheduled exercise sessions through phone calls. Additionally, the coordinator will regularly review the attendance log, providing motivation and support to participants with low attendance levels. • The exercise instructor will hold weekly one-on-one meetings with participants to review their progress and provide motivation, specifically targeting those with low attendance levels.
Procedures	Periodic data gaps with CGM[c] whenever the receiver is located more than 5 feet	• The CGM data will be assessed for adequacy based on the following criteria: Data points must be present for at least 80% of the possible 288 glucose values per day for any 7 consecutive days, starting on the day after sensor insertion.
Follow-up	Low retention rate	• Compensation for time and parking: (1) participants will receive a US $50 gift card upon completion of the study and (2) parking fees at study sites will be covered. • Building rapport: study staff will create a warm and supportive environment during study visits, fostering a sense of trust and comfort. • Ongoing support: the study coordinator will provide continuous support through regular phone calls. This proactive approach ensures that participants feel connected to the study outside of scheduled visits. The study coordinator will address any concerns, answer queries, and offer encouragement, reinforcing a sense of partnership between participants and the research team.

[a]i-IFG: isolated impaired fasting glucose.

[b]HIIT: high-intensity interval training.

[c]CGM: continuous glucose monitoring.

Ethical Considerations

The study protocol was approved by the institutional review board of Emory University, Atlanta, USA (MOD001-STUDY00005855). All participants will provide written informed consent prior to study participation. Participant identifiers will be kept strictly confidential in a secure REDCap database, accessible only by the principal investigator and study coordinator. Data will be deidentified before analysis. Participants will receive a US $50 gift card as compensation for their participation.

Results

Table 5 shows the study timeline. Recruitment for the study is scheduled to begin in February 2025, with follow-up expected to be completed by the end of September 2025. We plan to publish the study findings by the end of 2025.

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Table 5. Study timeline[a].

	2023		2024				2025			
	May	July-December	January-March	April-June	July-September	October-December	January-March	April-June	July-September	October-December
Received funding	✓									
Finalizing the study protocol and study tools		✓								
Clinical trial registration		✓								
Obtaining approvals: NIH[b], NCATS[c], and IRB[d]			✓	✓	✓					
REDCap database setup						✓				
Screening and recruitment							✓	✓		
Baseline assessments							✓	✓		
Baseline in-depth interviews							✓	✓		
HIIT[e] intervention							✓	✓		
8-week assessments									✓	
In-depth interviews at 8 weeks									✓	
Data entry							✓	✓	✓	
Data analysis									✓	✓
Study report and publications										✓
Conferences and scientific meetings										✓

[a]The cells colored in gray showing the timeline for various activities.

[b]NIH: National Institutes of Health.

[c]NCATS: National Center for Advancing Translational Sciences.

[d]IRB: institutional review board.

[e]HIIT: high-intensity interval training.

Discussion

Expected Findings

This proof-of-concept study will generate data on the feasibility and acceptability of the HIIT intervention, as well as participants' experiences and satisfaction levels. Additionally, the study will offer preliminary estimates on the efficacy of HIIT in reducing FPG levels and addressing the pathophysiology of i-IFG.

Strengths and Limitations

To our knowledge, this study will be the first to assess the feasibility and acceptability of a HIIT intervention exclusively among individuals with i-IFG. Additionally, we adhered to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) statement [60] when reporting the details of this study protocol. However, there are some limitations. We will assess the pathophysiological abnormalities in i-IFG using indices derived from the OGTT and fasting insulin levels instead of gold-standard methods like the intravenous glucose tolerance test and glycemic clamps [61-63]. However, these indices have demonstrated strong correlations with estimates obtained from the gold-standard methods [61-63]. Additionally, our reliance on a single OGTT may be subject to day-to-day variability in glucose tolerance status. Nevertheless, strict adherence to standardized protocols for conducting the OGTT [52,53] should help minimize this variability to a significant extent.

Conclusions

The results of this study are expected to guide the design and implementation of an RCT to assess the efficacy of HIIT intervention in reducing diabetes incidence and achieving remission in individuals with i-IFG.

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Acknowledgments

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Authors' Contributions

ST, LS, FL, MLMS, MDS, FJP, and JRN conceived the idea; ST received funding; ST, TRZ, MBW, LS, FL, MLMS, MDS, FJP, and JRN designed the study methodology; ST wrote the first draft of the manuscript; TRZ, MBW, LS, FL, MLMS, MDS, AV, RB, FEF, MP, SK, RJT, JES, FJP, and JRN reviewed the manuscript draft and provided critical comments. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

FP received research support from Dexcom, Ideal Medical Technologies, Tandem Diabetes Care, and Novo Nordisk, and consulting fees from Dexcom and Insulet (paid to his institution). None of these entities were involved in the development of this manuscript, and none had editorial oversight.

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Abbreviations

CGM: continuous glucose monitoring
CONSORT: Consolidated Standards of Reporting Trials
EML: Emory Medical Laboratory
FIM: Feasibility of Intervention Measure
FPG: fasting plasma glucose
GCRC: Georgia Clinical Research Center
HbA1c: hemoglobin A1c
HIIT: high-intensity interval training
HR: heart rate
HRR: heart rate reserve
i-IFG: isolated impaired fasting glucose
i-IGT: isolated impaired glucose tolerance
IAM: Intervention Appropriate Measure
IPAQ: International Physical Activity Questionnaire
OGTT: oral glucose tolerance test
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
STEPS: STEPwise approach to noncommunicable disease risk factor surveillance
TFA: Theoretical Framework of Acceptability

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Protocol

Weighted Blankets for Agitation in Hospitalized Patients with Dementia: Protocol for a Randomized Controlled Trial

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Abstract

Background: There are limited therapies approved for the treatment of aggression and agitation in patients with dementia. While antipsychotics and benzodiazepines are commonly used, these medications have been associated with significant side effects and US Food and Drug Administration (FDA) boxed warnings. Weighted blankets have been associated with decreased anxiety and improved sleep. Weighted blankets are potentially a nonpharmacologic option to reduce agitation in hospitalized patients with dementia.

Objective: The aim of this study is to investigate the effect of weighted blankets on aggression and agitation in hospitalized patients with dementia.

Methods: A pilot study will be conducted on a total of 30 hospitalized patients with a documented clinical diagnosis of dementia and ongoing agitated behaviors admitted to a medicine or psychiatry service. Patients will be randomly allocated to receive either a weighted blanket for 3 nights or continued usual care. The primary outcome is the change in the observational version of the Cohen-Mansfield Agitation Inventory (CMAI-O) over the course of the 3-night study period. The secondary outcomes are changes in Edmonton Symptom Assessment System Revised (ESAS-r) and Clinical Global Impression (CGI) scores, hours of sleep, use of antipsychotics and benzodiazepines, and incidence of delirium. Identical study assessments will be completed for both the usual care and the weighted blanket study groups. At 5 study time points (baseline, postnight 1, postnight 2, postnight 3, and a final assessment 48-72 h after the last use of the weighted blanket), patients will be assessed with the CMAI-O, ESAS-r, and CGI tools. All assessments will be completed by the bedside nurse or patient care assistant caring for the patient each day. Within 2 to 4 weeks post discharge from the hospital, study coordinators will contact the patient's legally authorized representative (LAR) to assess for continued use of the weighted blanket.

Results: Enrollment of participants began on April 23, 2023. As of November 2024, a total of 24 participants have been enrolled in the study. Baseline characteristics of enrolled participants will be analyzed and reported upon completion of enrollment. We anticipate completing data collection by March 2026.

Conclusions: The study will determine the effect of weighted blankets on agitation in hospitalized patients with dementia. Insights into the effect of weighted blankets on sleep will also be gained. The results of this study will be relevant in the setting of increasing numbers of older adults with dementia exhibiting agitation, leading to increased hospitalizations, caregiver burden, and health care costs.

Trial Registration: ClinicalTrials.gov NCT03643991; http://clinicaltrials.gov/ct2/show/NCT03643991

International Registered Report Identifier (IRRID): DERR1-10.2196/57264

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KEYWORDS

dementia; hospitalized dementia patients; agitation; aggression; behaviors; sleep; weighted blankets; nonpharmacologic strategy; pilot study; inpatients; occupational therapy

Introduction

Background

Many patients with dementia develop neuropsychiatric symptoms and somewhere between 40% and 76% of patients demonstrate agitation and aggression [1,2]. Agitated behaviors are often disruptive and difficult to manage, and are associated with increased caregiver burden and burnout, increased hospitalizations, and elevated health care costs [1,3]. Agitation includes a range of behaviors, including restlessness, pacing, physical aggression, and verbal agitation [4].

Nonpharmacologic strategies are the first line in the prevention and treatment of neuropsychiatric symptoms of dementia, including agitation. Limited pharmacologic options exist in this setting. In fact, no pharmacologic therapies were approved by the Food and Drug Administration (FDA) for this indication until the recent approval of the atypical antipsychotic brexpiprazole for the treatment of agitation associated with dementia due to Alzheimer disease [5]. Other antipsychotics are commonly used, particularly in emergency and acute care settings when agitated or aggressive behaviors threaten either patient or caregiver [6]. These medications, however, are associated with significant serious long- and short-term side effects including akathisia and restlessness [7], and carry an FDA-boxed warning for increased risk of mortality [8]. The 2016 American Psychiatric Association practice guidelines recommend that antipsychotic medications be reserved for severe, dangerous, or significantly distressing symptoms and used at the lowest effective dose due to concern for side effects [9]. The management of agitated and aggressive symptoms without primary reliance on antipsychotics remains a challenge. Benzodiazepines are typically avoided due to the risk of cognitive impairment, falls, and respiratory depression [10].

Weighted blankets are filled with plastic pellets or beads and are commercially available in weights ranging from 5 to 30 pounds. Weighted blankets have been used in occupational therapy as a form of noninvasive deep-pressure stimulation, which appears to increase parasympathetic arousal and decrease anxiety [11-13]. Weighted blankets have been studied in patients with psychiatric diagnoses in both the inpatient and outpatient settings, and they appear to be associated with decreased anxiety and improved sleep [14,15]. Weighted blankets have also been associated with improved chronic pain and reduced anger scores [16,17]. Currently, however, there are no studies investigating the use of weighted blankets to address agitation in hospitalized patients with dementia.

Objectives

The aim of this study is to investigate the effect of weighted blankets on aggression and agitation in hospitalized patients with dementia. We hypothesize that compared to controls, patients with agitation in the setting of dementia will show reduced agitation, reduced anxiety, and potentially improved sleep while hospitalized when provided with a weighted blanket.

Methods

Design and Randomization

To address this question, we designed a pilot study (ClinicalTrials.gov NCT03643991) with 1:1 randomization of hospitalized patients with dementia and evidence of agitated behaviors to receive either a weighted blanket for 3 nights or continued usual care.

Study Population and Recruitment

Patients will be recruited from a single large tertiary care hospital. Participants are eligible for inclusion if they are 60 years or older, have a documented clinical diagnosis of dementia, and are currently admitted to either a medicine or psychiatry primary service. All participants are required to have ongoing agitated behaviors at the time of enrollment as demonstrated by an elevated CMAI-O with a score of 2, 3, or 4 on at least one aggression-related item (items 1-11 or 22-24) [18]. Patients will be excluded if they have severe pain likely to be exacerbated by the use of the weighted blanket, have significant burns or wounds for which weighted blanket use could potentially be detrimental, or are admitted on a 72-hour involuntary hold. Participants can be enrolled at any point during their hospitalization. Hospitalizations will not be prolonged for the purpose of the study. To reflect real-world conditions, all other usual medical care will be continued at the discretion of the primary medical or psychiatric team.

Intervention

Participants will be randomized 1:1 to either the usual care group or the weighted blanket group. The weighted blankets used are commercially available and purchased for the study. Patients randomized to the weighted blanket group will be provided with either a 10 lb, 15 lb, or 20 lb weighted blanket, ensuring that the weight is not more than 10% of the participant's body weight. Participants will be withdrawn from the study if they refuse the blanket or are unable to tolerate it for more than 2 hours on the first night after enrollment. Participants can also be withdrawn from the study at any time if the primary team feels that further participation will jeopardize patient safety. Enrolled participants will use the blanket for a total of 3 consecutive nights, or until the time of discharge if that occurs sooner. Following participation in the study, participants will be allowed to keep the weighted blanket for future personal use. To reduce potential bias, the data analysis team will remain blinded to group assignment during statistical analyses, although investigators administering the questionnaires will not be blinded due to the nature of the intervention.

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Primary Outcome

The primary end point will be the change in CMAI-O over the course of the 3-night study period. The CMAI-O is a validated scale published in 2020 by Griffith et al [18] to quantify neuropsychiatric behavior in patients with dementia. Observers rank the frequency of 29 behaviors grouped into categories: physical aggressive behaviors (questions 1-11), physical nonaggressive behaviors (questions 12-21), verbal aggressive behaviors (questions 22-24), and verbal nonaggressive behaviors (questions 25-29). The frequency of each behavior is ranked as 1 (never), 2 (less than once per h), 3 (once per h), and 4 (several times per hour).

Secondary Outcomes

Secondary end points will include change in Edmonton Symptom Assessment System Revised (ESAS-r) score and change in Clinical Global Impression (CGI) score as well as hours of sleep, use of antipsychotics and benzodiazepines, and incidence of delirium.

The ESAS-r was originally designed as a self-report tool in which patients rate the severity of 9 symptoms on a scale from 0 to 10 (10 being the most severe) [19]. The tool assesses the following nine symptoms: pain, tiredness, drowsiness, nausea lack of appetite, shortness of breath, depression, anxiety, and well-being. This assessment tool has been commonly used in palliative medicine and oncology settings, translated into several languages, and is well received by patients and nursing staff [19]. The ESAS-r captures the pattern of a patient's severity of symptoms at a point in time and may be repeated to track changes over time. Since patients with a diagnosis of dementia vary significantly in their ability to report symptoms, we have standardized the protocol by using caregiver (nurse or patient care assistant) input to complete the ESAS-r assessment tool [19].

The CGI scale is a brief, independent assessment initially designed to summarize a caregiver's view of a patient's global functioning before and after initiating an intervention [20]. The CGI consists of 2 one-item measures that evaluate the severity of psychopathology and change from the initiation of treatment on a 7-point scale. The CGI may be used to track clinical progress over time [20].

Further clinical data will be extracted from the medical record. Caregiver staff will estimate hours of sleep. Use of antipsychotics and benzodiazepines will be recorded based on the medical administration records. The incidence of delirium will be estimated based on documentation of a newly positive Brief Confusion Assessment Model (bCAM) assessment [21]. Delirium Triage Screen and bCAM assessments are performed to screen for delirium every 12 hours (once per nursing shift) in the hospital where this study will be conducted.

Study Timeline and Follow-Up

Identical study assessments will be completed by the patient's caregiver (either registered nurse or patient care assistant) for both the usual care group and the weighted blanket study group. Cohen-Mansfield Agitation Inventory (CMAI-O), ESAS-r, and CGI scores will be collected at 5 study time points (baseline, postnight 1, postnight 2, postnight 3, and a final assessment 48-72 hours after the last use of the weighted blanket). A total of 3 nights were determined to be sufficient for assessing trends in agitation, anxiety, and sleep, while also testing the feasibility of the intervention in a real-world clinical environment. Within 2-4 weeks following hospital discharge, study coordinators will contact the patient's legally authorized representative (LAR) to assess for continued use of the blanket. Refer to the patient timeline (Table 1).

Table 1. Patient timeline.

Assessment	Baseline (enrollment)	WB[a] day 1	WB day 2	WB day 3	Final within 72 hours of last use of WB (cohort 1) or no WB (cohort 2)	Within 2-4 weeks post discharge
CMAI-O[b]	✓	✓	✓	✓	✓	
ESAS-r[c]	✓	✓	✓	✓	✓	
CGI[d]	✓	✓	✓	✓	✓	
Posthospitalization phone call to assess continued weighted blanket use						✓

[a]WB: weighted blanket.

[b]CMAI-O: Cohen-Mansfield Agitation Inventory.

[c]ESAS-r: Edmonton Symptom Assessment System Revised.

[d]CGI: Clinical Global Impression.

Sample Size

We will target an enrollment of 30 participants in this pilot study. This sample size was chosen to balance the need for gathering preliminary data with the constraints of patient availability, time, and resources within our hospital setting. The sample size of 30 is sufficient to provide preliminary insights into the effects of weighted blankets on agitation, allowing us to explore trends and estimate effect sizes for future studies. Recruitment will be facilitated by daily review of hospital-wide behavior emergency response team activations and patient referrals from inpatient medicine and psychiatry primary services.

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Data Collection, Management, and Confidentiality

Participants will be randomized 1:1 to the treatment and usual care groups via computer-generated sequence which will be concealed until after each patient's enrollment. Given the nature of the study, blinding of caregivers and study coordinators to treatment groups is not feasible.

Data will be collected by study personnel in a manner consistent with patient confidentiality. For patients withdrawn from the study, no further data will be collected but existing study data to the point of withdrawal will be included in the final analysis which will be performed based on intention to treat.

All data obtained will be entered into REDCap (Research Electronic Data Capture), a secure electronic database that is password-protected and accessible only to the study team. Each participant will be assigned a unique identification code to protect their identity, and only the code will be used for forms, reports, and data analysis. Paper records containing protected health information will be maintained in locked file cabinets in a secure room accessible only to research personnel. All patient information will be kept confidential and managed according to the Health Insurance Portability and Accountability Act of 1996 requirements.

Data Analysis

A per-protocol analysis will be used. Baseline characteristics of participants will be reported using percentages for categorical variables and mean with SD for continuous variables. Differences between the 2 treatment groups for the descriptive variables will be compared using chi-square tests for categorical variables and Kruskal-Wallis tests for continuous variables. The medications and dosages taken during the study will also be reported. The primary outcome of the CMAI-O score will be described at each of the 5 time points (baseline, day 1, day 2, day 3, and day 72 follow-up). A linear mixed effects model with time as a random effect will be used to analyze changes in the CMAI-O score over time. Both the unadjusted and an adjusted model with age, sex, and unit type as covariates will be reported. Age and sex were included as covariates as they are standard demographic factors that can influence behavioral outcomes. Unit type (medicine vs psychiatry) was included as it may impact patient management practices and potentially influence study outcomes. This model also allows for missing data which occurs in the dataset when a patient was discharged before the end of the study period. Secondary outcomes of ESAS-r and CGI scores will be analyzed in a comparable way with a linear mixed model. The end-of-study survey results will be described for each question. A per-protocol analysis will evaluate only the enrolled patients who followed protocol.

Monitoring

The principal investigator will conduct weekly meetings with the study coordinator and research team to review the status of the study, recruitment and enrollment of participants, protocol adherence, safety issues, and overall conduct of the study. The principal investigator will monitor, track, and report any adverse events, protocol deviations, and progress reports or continuing reviews to the institutional review board (IRB) with research regulations.

Ethical Considerations

This study follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines for reporting (see Multimedia Appendix 1). The study protocol was approved by the Mayo Clinic IRB (IRB 17-009951) and was registered with ClinicalTrials.gov (NCT03643991). Amendments to the protocol will be submitted to the Mayo Clinic IRB for approval before implementation. Written informed consent approved by the IRB will be obtained from the participant's LAR, who will be provided sufficient information regarding the risks and benefits of the study to make an informed decision about the participation of their loved ones in the study. The LARs will be fully informed about their right to withdraw participation at any time. No compensation is being provided to participants, although individuals randomized to the weighted blanket group are permitted to keep the weighted blanket. Study investigators will have access to the final dataset, which will include deidentified participant information only as outlined above in the "Data Collection, Management, and Confidentiality" section. Results will be submitted to a peer-reviewed journal and scientific conferences for the advancement of clinical care.

Results

Enrollment of participants began on April 23, 2023. As of November 2024, 24 participants have been enrolled in the study. Baseline characteristics of enrolled participants will be analyzed and reported upon completion of enrollment. We anticipate completing data collection by March 2026. The study results will be reported in a peer-reviewed journal upon completion.

Discussion

Primary and Secondary Outcomes

We hypothesize the use of a weighted blanket will reduce patients' behaviors and agitation; therefore, patients' CMAI-O scores will decrease. In addition, we anticipate patients' ESAS-r and CGI scores will decrease with the use of a weighted blanket. We hope with reduced behaviors and agitation that patients will have reduced antipsychotic and benzodiazepine administrations and decreased incidence of delirium.

Strengths and Limitations

There are several strengths of this study. This study is a randomized controlled trial being performed in both medical and psychiatric inpatient settings at an academic medical center. The study's intervention is a nonpharmacologic option that has minimal potential side effects. The study is a pilot study that can offer opportunities for further research studies. A couple of the study's limitations are the small sample size and performed at a single organization. In addition, the investigators are nonblinded and could lead to a potential bias. It is unclear if the results will be generalizable to all patients with agitation and dementia, other health care organizations, and outpatient settings.

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Conclusions

This study addresses the important clinical issue of agitation in hospitalized patients with dementia. This study will contribute to the growing body of knowledge on nonpharmacological management of behavioral symptoms in older adults with dementia. This is important as the management of agitated and aggressive symptoms without primary reliance on antipsychotics and benzodiazepines remains a challenge. We anticipate that these study results will be used to inform health care professionals, caregivers, and family members regarding the potential usefulness of weighted blankets as a nonpharmacologic method to decrease agitation and distress in hospitalized older adults with dementia.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

HAS, AKP, NBS, DKL, KMF, MIL, and RED contributed to conceptualization. DKL, KMF, MIL, and RED performed data curation. KMF, MIL, and RED were involved in formal analysis. MIL was responsible for funding acquisition. HAS, AKP, NBS, DKL, MIL, and RED participated in the investigation. HAS, AKP, NBS, DKL, KMF, MIL, and RED performed the methodology. HAS, AKP, NBS, DKL, MIL, and RED handled project administration. HAS, AKP, NBS, DKL, KMF, MIL, and RED were involved in writing–original draft, review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT Outcomes 2022 checklist.
[PDF File (Adobe PDF File), 265 KB - resprot_v14i1e57264_app1.pdf]

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Abbreviations

bCAM: Brief Confusion Assessment Model
CGI: Clinical Global Impression
CMAI-O: Cohen-Mansfield Agitation Inventory
ESAS-r: Edmonton Symptom Assessment System Revised
FDA: US Food and Drug Administration
IRB: institutional review board
LAR: legally authorized representative
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Combination of Electroacupuncture and Medication for Patients With Tinnitus Associated With Idiopathic Sudden Sensorineural Hearing Loss: Protocol for a Prospective Randomized Controlled Trial

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Abstract

Background: Tinnitus, a common and troublesome symptom of idiopathic sudden sensorineural hearing loss (ISSNHL), is the perception of sound without any external or internal sound source. The etiology of ISSNHL accompanied by tinnitus remains unclear. Tinnitus often occurs alongside or before hearing loss and can severely impact patients' quality of life, leading to psychological stress and emotional distress. Current treatments primarily focus on improving hearing loss while neglecting tinnitus treatment. Electroacupuncture (EA), a technique widely applied in China for tinnitus management, may become a promising intervention by addressing both auditory and psychological symptoms.

Objective: This study aims to conduct a double-center, assessor-blinded, prospective randomized pilot clinical trial to explore the potential effects and feasibility of EA combined with medication for patients with ISSNHL accompanied by tinnitus, and to generate preliminary data to inform future large-scale trials of EA as an adjunctive therapy for this condition.

Methods: In this double-center, assessor-blinded, randomized controlled trial, 60 patients with ISSNHL accompanied by tinnitus will be randomly allocated to either the EA group, receiving EA combined with medication, or the control group, receiving standard medication treatment, for a total treatment duration of 4 weeks. Follow-up assessments will be conducted at weeks 2 and 4, and at 1, 2, and 3 months after treatment. The feasibility primary outcomes are recruitment rate, adherence rate, data completeness, and safety outcomes. The primary outcome measures will include pure tone audiometry, tinnitus matching, and the Tinnitus Handicap Inventory, while the secondary outcome measures will comprise speech-recognition thresholds in noise, the Self-Rating Anxiety Scale, and the 36-item Short Form Health Survey Questionnaire.

Results: This study began recruitment on July 15, 2024, and is scheduled to conclude on August 31, 2025. To date, 42 participants have been enrolled, with 35 having completed the intervention and posttreatment assessments (control group: n=21; EA group: n=14). Following protocol publication, data compilation and analysis will be conducted, with results anticipated to be published in a relevant journal in 2026.

Conclusions: This pilot trial is expected to provide critical insights into the feasibility of integrating EA with standard medication for managing ISSNHL with tinnitus. By generating preliminary evidence on its practicality and potential benefits, this study aims to inform the design and sample size estimation of future multicenter trials, potentially advancing nonpharmacological treatment options for this challenging condition.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2400086802; https://tinyurl.com/mtxthpzj

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International Registered Report Identifier (IRRID): DERR1-10.2196/69163

(JMIR Res Protoc 2025;14:e69163) doi:10.2196/69163

KEYWORDS

idiopathic sudden sensorineural hearing loss; tinnitus; acupuncture; study protocol; electroacupuncture; adjunctive therapy

Introduction

Idiopathic sudden sensorineural hearing loss (ISSNHL) is characterized by a rapid, unexplained sensorineural hearing loss of at least 30 dB over 3 contiguous frequencies within 72 hours, typically occurring unilaterally [1]. The incidence of ISSNHL is estimated to range from 5 to 20 cases per 100,000 individuals annually. However, some studies suggest that this figure may be underestimated, as those who recover swiftly often do not seek medical care [2]. The tinnitus associated with ISSNHL lacks a precise definition. Clinically, it is typically described as tinnitus that arises simultaneously with, or within hours to days after, the onset of ISSNHL. In some cases, tinnitus may even precede the hearing loss by a few hours to several days. However, patients often pay more attention to symptoms such as tinnitus, aural fullness, or dizziness, which may lead them to overlook the initial onset of ISSNHL. Previous clinical studies have reported a tinnitus incidence ranging from 69.8% to 93.3%. A multicenter study in China found that, among 1024 patients with ISSNHL, 90.1% experienced tinnitus—a prevalence notably higher than that of vestibular symptoms, aural fullness, or dizziness [3,4]. Patients with tinnitus frequently endure considerable psychological stress, mood disturbances, and sleep disorders, all of which can impair their performance at work or in their studies. In more severe cases, these individuals may also develop anxiety and depression [2,5]. The alleviation of tinnitus symptoms typically progresses more slowly than the recovery of hearing. Even after hearing is restored, some patients may continue to experience persistent tinnitus, which can significantly diminish their quality of life. Consequently, clinicians should prioritize addressing tinnitus in tandem with treating hearing loss [6,7].

The pathogenesis of ISSNHL with tinnitus remains unclear [8]. It is generally believed that the onset and progression of tinnitus are related not only to peripheral hearing impairment but also to abnormal brain activity [9], including disrupted intra- and internetwork connectivity, psychological factors, and stress hormones [10,11]. Currently, treatment for ISSNHL accompanied by tinnitus primarily aims to address the underlying hearing loss [6,12]. Restoring auditory function can help disrupt the mechanisms that induce tinnitus, reestablish central auditory input, and prevent its progression [13,14]. The standard treatment approach involves corticosteroid administration, either systemically or through intratympanic injection [1]. The American clinical practice guideline for ISSNHL [1] does not provide specific recommendations for the treatment of comorbid tinnitus, but it highlights its prevalence, refractoriness, and the potential economic and psychological burdens associated with the condition.

The Chinese guideline for the diagnosis and treatment of sudden hearing loss [15] classifies ISSNHL into 4 types based on audiometric patterns: low-frequency descending, high-frequency descending, flat, and total. Different audiometric patterns may suggest distinct pathogenic mechanisms for ISSNHL. For example, the low-frequency descending type is associated with endolymphatic hydrops, the high-frequency descending type with hair cell damage, and the flat type may reflect a broader inner ear injury mechanism, such as stria vascularis dysfunction or inner ear vascular spasm [16]. These differences may influence treatment responses and prognosis [17].

Acupuncture, a therapy that involves the insertion of fine needles into the body followed by manipulation techniques such as lifting, thrusting, and twisting, was described as a treatment for tinnitus as early as the 5th century BCE in China [18]. Although the clinical practice guideline developed by Tunkel et al [19] does not mention acupuncture for the treatment of persistent tinnitus due to the lack of high-quality randomized controlled trials (RCTs), the expert panel acknowledged that many patients with persistent or bothersome tinnitus seek acupuncture therapy. Additionally, a European epidemiological study showed that the average annual out-of-pocket expenditure for European patients with tinnitus was €565 (US $640), with €183 (US $207) spent on acupuncture, homeopathy, and osteopathy. These patients were willing to pay 1.6-7 times their monthly income for complete tinnitus relief [20]. Furthermore, emerging evidence suggests that acupuncture, including electroacupuncture (EA), may modulate functional connectivity within brain networks, such as those involving the insula and frontal regions, potentially contributing to its therapeutic effects on tinnitus and possibly extending to cases associated with ISSNHL [21-24]. EA is a safe and effective intervention that is easier to standardize and more controllable than manual acupuncture, providing prolonged stimulation, precise intensity control, and enhanced acupuncture sensation [25,26].

This study aims to investigate the feasibility and potential effects of EA combined with medication on hearing and tinnitus outcomes in patients with ISSNHL and tinnitus, generating preliminary data to support future research on EA as an adjunctive treatment for ISSNHL.

Methods

Design and Setting

The study is designed as a prospective, single-blinded RCT. It will take place in the clinics of Beijing Tongren Hospital, Capital Medical University, and the Acupuncture and Moxibustion Hospital, China Academy of Chinese Medical Sciences (CACMS). Eligible participants will be randomized in a 1:1 ratio to either the EA group (EA plus medication) or the control group (standard medication alone). This pilot trial will apply a longitudinal follow-up design, with a baseline assessment before enrollment (t–1), allocation and intervention initiation at t0,

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on-treatment follow-ups at week 2 (t1), week 4 (t2), and posttreatment follow-ups at 1 month (t3), 2 months (t4), and 3 months (t5) after intervention completion, barring loss to follow-up. This trial will be reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials)-EHEALTH (see Multimedia Appendix 1) statement, which defines standard reporting items for RCTs [27]. Participant recruitment began on July 15, 2024, with the study scheduled to continue until December 2025. The flowchart is illustrated in Figure 1, and the overall procedure is presented in Table 1.

Figure 1. The enrollment process of the trial. EA: electroacupuncture.

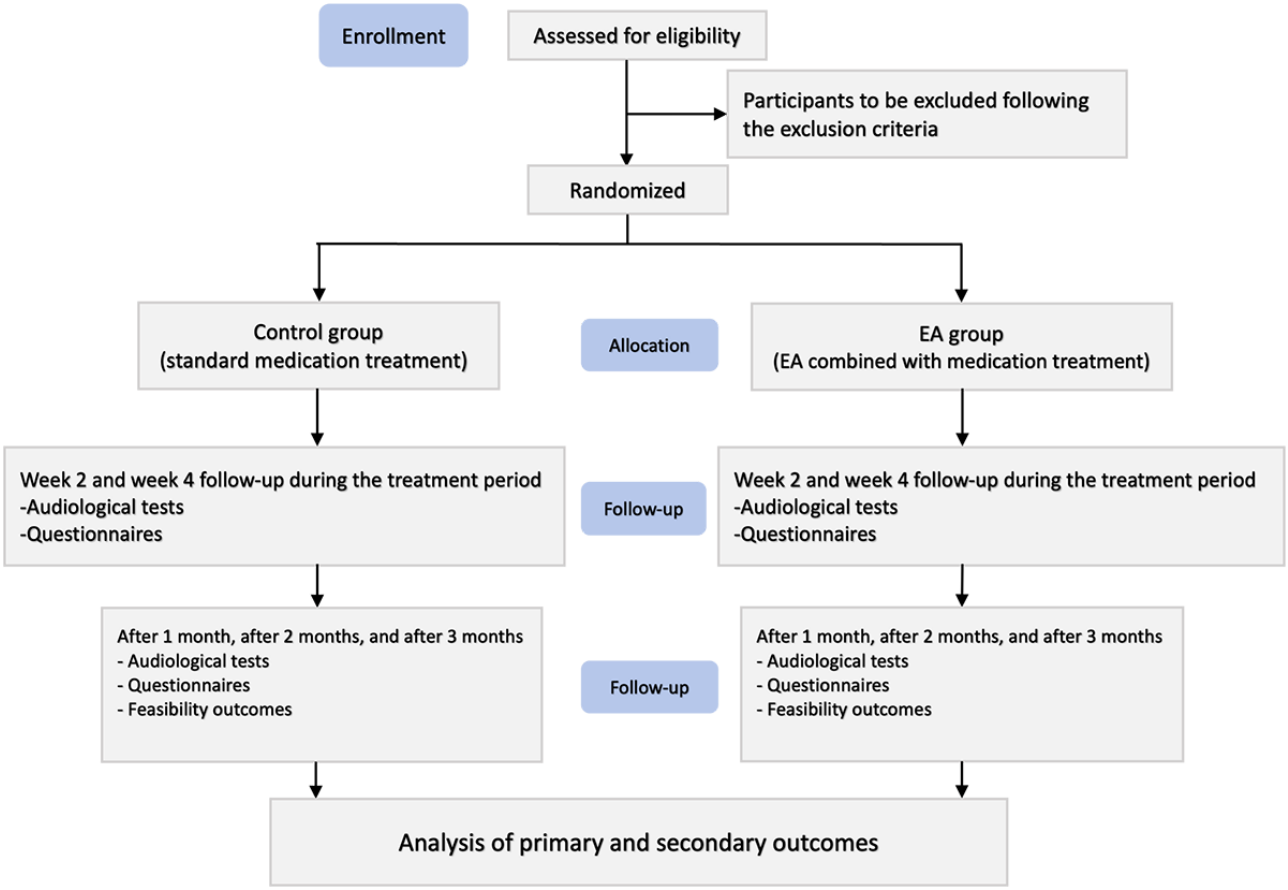

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Table 1. Overall procedure of this study.

Stages	Enrollment	Allocation	On-treatment follow-up		Posttreatment follow-up		
Time point	$-t_1$	t_0	t_1	t_2	t_3	t_4	t_5
Enrollment							
Eligibility screening	✓	N/A[a]	N/A	N/A	N/A	N/A	N/A
Informed consent	✓	N/A	N/A	N/A	N/A	N/A	N/A
Allocation	N/A	✓	N/A	N/A	N/A	N/A	N/A
Interventions							
Control group	N/A	N/A	✓	✓	N/A	N/A	N/A
Electroacupuncture group	N/A	N/A	✓	✓	N/A	N/A	N/A
Assessments							
Feasibility outcomes							
Recruitment rate	N/A	N/A	N/A	N/A	✓	N/A	N/A
Adherence rate	N/A	N/A	N/A	N/A	✓	N/A	N/A
Data completeness	N/A	N/A	N/A	N/A	✓	N/A	N/A
Adverse events	N/A	N/A	✓	✓	✓	✓	✓
Exploratory outcomes							
Pure tone audiometry	N/A	✓	✓	✓	✓	✓	✓
Tinnitus matching	N/A	✓	✓	✓	✓	✓	✓
Tinnitus Handicap Inventory	N/A	✓	✓	✓	✓	✓	✓
Secondary outcomes							
Speech-recognition thresholds in noise	N/A	✓	✓	✓	✓	✓	✓
Self-Rating Anxiety Scale	N/A	✓	✓	✓	✓	✓	✓
36-item Short Form Health Survey Questionnaire	N/A	✓	✓	✓	✓	✓	✓

[a]N/A: not applicable.

Eligibility Criteria

Inclusion criteria included the following: a diagnosis of ISSNHL [15], defined as sudden hearing loss (≥30 dB) within 72 hours affecting 3 consecutive frequencies, and accompanied by tinnitus; between 18 and 65 years of age at the time of recruitment; pure tone audiometry (PTA) results showing a flat drop audiogram; onset of hearing loss within 1 week before randomization; clear consciousness, normal cognition, and unaffected basic communication.

Exclusion criteria were hearing loss from other causes (eg, congenital deafness, conductive deafness, presbycusis, large vestibular aqueduct syndrome, Meniere disease, tumors, or deafness due to systemic genetic diseases); having received medication or acupuncture treatment within the past 6 months, or having an allergy to the treatment medication; pregnancy or lactation in females; presence of severe systemic diseases or psychiatric disorders; and participation in other trials.

Ethical Considerations

Ethics approval was obtained from the Ethics Committee of Beijing Tongren Hospital, Capital Medical University (approval number TREC2024-KY060). Before the trial begins, researchers must provide participants with detailed information about the clinical trial, including its purpose, procedures, potential benefits and risks, alternative treatment options, and the rights and responsibilities of the participants. Participants will also be informed that they are free to withdraw consent at any time during the study. They must fully understand this information and provide their consent by signing an "informed consent form" before the clinical trial can commence.

Enrollment, Randomization, and Blinding

Recruitment will be conducted through WeChat (Tencent Holdings Limited) public account notifications, roll-up banners at clinic entrances, and collaboration with community committees for promotion.

Stratified block randomization will be performed according to the study center. Both groups will be assigned in a 1:1 ratio to the EA and control groups using a block size of 4. Weijuan Gang, a statistician from the Evidence-Based Medicine Center at CACMS, will serve as the randomization coordinator and will be responsible for generating the stratified block randomization sequence using SAS 9.3 software (SAS Institute). She will not participate in the trial's implementation or data analysis. After obtaining informed consent and before initiating

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treatment, the treating physician at each center will contact the randomization coordinator by phone to receive the randomization number and group assignment.

Because of the nature of acupuncture, it is not possible to blind the acupuncturists or participants. However, steps will be taken to minimize bias from single blinding as much as possible. Acupuncturists will receive specialized training before participating in the study and will be instructed not to discuss treatment procedures or outcomes. They will also be excluded from evaluating the results. Patients will be treated separately to prevent contact between participants. The randomization staff and acupuncturists will have access to the assignment information, but the outcome evaluators and statisticians will remain blinded throughout the entire clinical trial. Statisticians will speculate on the group allocation before data analysis to assess the efficacy of blinding, and unblinding will only occur after the completion of data analysis.

Sample Size

As previous RCTs have not investigated EA as a combination intervention in patients with ISSNHL with tinnitus, it is challenging to determine the optimal sample size through power calculation. Therefore, rather than performing a formal sample size estimation, this trial will adopt a preliminary exploratory clinical pilot design to estimate the appropriate sample size [28]. However, to preliminarily assess the feasibility of the proposed intervention, we will ensure an adequate number of participants in our experimental design by adhering to the established guideline of a minimum of 12 participants per group for pilot studies [29]. A previous study suggested that each group should have a sample size ranging from 20 to 25 cases for exploratory clinical trials assessing the effectiveness of intervention measures [30]. Therefore, in this study, each group will consist of 25 patients, resulting in a total of 50 cases across the 2 groups. To account for a potential dropout rate of 20%, we will recruit a total of 60 patients (30 per group). The results of this study will provide effect size data for calculating sample sizes in future large-scale RCTs.

Interventions

The control group intervention protocol was designed in accordance with the 2015 Chinese Guidelines for the Diagnosis and Treatment of Sudden Deafness [15]. These guidelines were developed based on extensive RCT data from multicenter clinical studies on sudden deafness in China, incorporating updates from the latest American and German clinical guidelines as well as recent research advancements, ensuring alignment with clinical practice in China [1,4,16]. The treatment regimen for the control group was designed to comprehensively address the inflammation and microcirculatory disturbances associated with ISSNHL through a combination of prednisone, Ginkgo biloba extract, and batroxobin injection. The specific pharmacological interventions are detailed in Table 2.

Table 2. Standard treatment regimen for the control group.

Period	Drug	Dosage and administration	Duration
Weeks 1-2 after onset	Prednisone (glucocorticoid)	1 mg/kg/day (maximum 60 mg), oral, once daily in the morning	5 days
Weeks 1-2 after onset	Ginkgo biloba extract	87.5 mg in 250 mL 5% glucose, intravenous infusion, once daily	2 weeks
Weeks 1-2 after onset	Batroxobin injection	5 batroxobin units in 250 mL 5% glucose, intravenous infusion, every other day[a]	2 weeks
Weeks 3-4 after onset	Ginkgo biloba tablets	9.6 mg × 2 tablets, oral, 3 times daily	2 weeks

[a]Before the administration of batroxobin, blood tests are required to confirm fibrinogen levels (>1.5 g/L) and normal coagulation parameters (eg, prothrombin time or activated partial thromboplastin time). Fibrinogen and coagulation function are monitored 24 hours after the first dose and periodically thereafter.

Patients in the EA group will receive the same treatment as the control group, in addition to EA, which will not interfere with their medication treatment.

The EA group received acupuncture using disposable sterile needles (Hwato Needles; Suzhou Medical Appliance Factory) at acupoints previously identified in studies as functionally related to ISSNHL and tinnitus, including Tinggong (SI19), Tinghui (GB2), Yifeng (SJ17), Yunting area, Anmian, Waiguan (SJ5), Zhongzhu (SJ3), Taichong (LR3), and Taixi (KI3). For limb acupoints, 30-gauge needles (0.25 mm in diameter, 40 mm long) will be inserted to a depth of 10-15 mm. For head acupoints, 32-gauge needles (0.25 mm in diameter, 25 mm long) will be inserted to a depth of 3 mm. A specialized acupuncture technique will be used when needling the Tinggong point (SI19) on the impacted side. The patient will be instructed to slightly open their mouth, and a needle (0.25 mm in diameter, 40 mm long) will be inserted to a depth of approximately 15-25 mm. The assistant will pinch the patient's nostrils, prompting the patient to take a deep breath, close their mouth, and hold their breath to push air through the Eustachian tube into both ears. During this procedure, the acupuncturist will gently twist the needle until the patient feels a local sensation of soreness or distension. Afterward, the patient will exhale through the mouth, and the acupuncturist will withdraw the needle by approximately 10 mm and leave it in place. Additionally, the Tinghui (GB2) and Yifeng (SJ17) points on the impacted side will be needled and connected to an EA device (KWD-808I type; Great Wall, Yingdi). A sparse wave with a frequency of 2-15 Hz will be applied at an intensity that induces muscle contraction and is tolerable for the patient. The needles will be retained for 30 minutes. Figure 2 provides an operational illustration of the acupuncture technique at the Tinggong (SI19) point, while Figure 3 shows the acupuncture point selection diagram. EA treatment will last for a total of 4 weeks, with 4 sessions per week during the first 2 weeks and 3 sessions per week during the last 2 weeks, conducted every other day.

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Figure 2. The operational illustration of acupuncture technique at SI19.

Figure 3. The acupuncture point selection diagram.

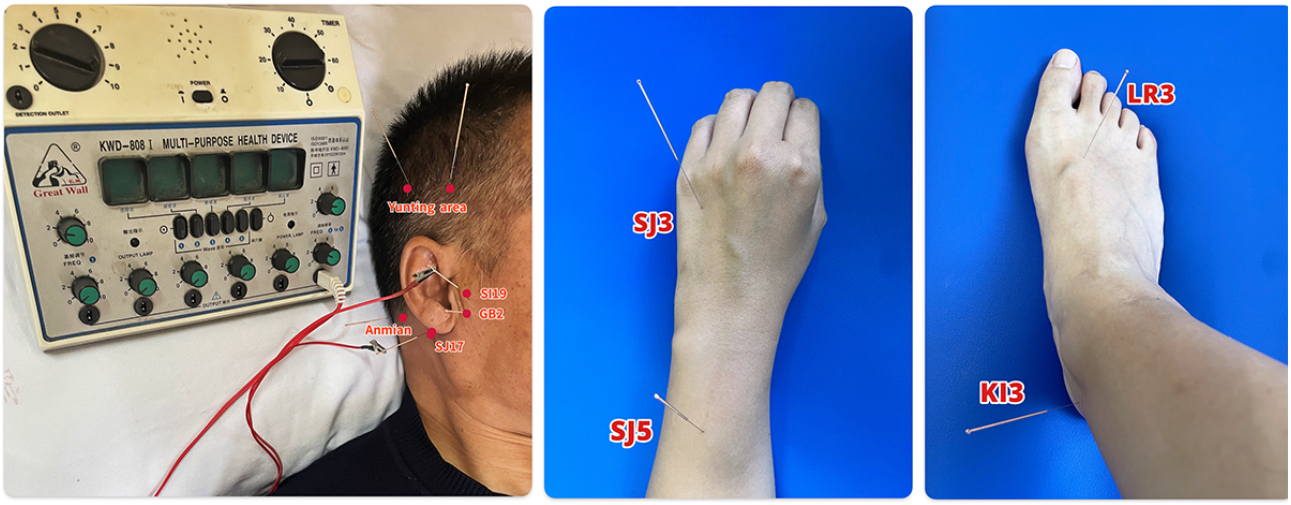

Outcome Measures

Feasibility Primary Outcomes

The feasibility primary outcomes are recruitment rate, defined as the proportion of enrolled participants relative to the target sample size; adherence rate, measured as the proportion of participants completing at least 80% of the prescribed EA sessions over 4 weeks, as extracted from treatment logs; data completeness, assessed as the proportion of participants with fully collected baseline and follow-up data for key measures such as PTA and Tinnitus Handicap Inventory (THI); and safety outcomes, recorded as the incidence of adverse events during the treatment period, based on session-by-session reports [31,32].

Exploratory Primary Outcomes

Overview

PTA threshold tests will be performed using an audiometer (Otometrics Conera, Natus Medical Incorporated/GN Otometrics A/S) in a standard soundproof room with background noise less than 30 dB(A) to minimize the influence of human factors on the test results. The patient will be presented with sounds at frequencies ranging from 0.25 to 8 kHz [33,34]. An audiologist will use the audiometer to measure both air conduction and bone conduction hearing thresholds. A shift of more than 30 dB between adjacent frequencies indicates hearing loss. Following these measurements, the audiogram configuration is obtained simultaneously. Hearing loss across all frequencies, represented by a horizontal line with threshold differences of less than 20 dB between frequencies, is classified as a “flat” audiogram type [35].

Tinnitus matching is currently the most objective means of detecting tinnitus. It mainly includes 2 parts [36], as described in Textbox 1.

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Textbox 1. Parts of tinnitus matching.

- **Tinnitus frequency matching**

Tinnitus frequency matching is performed using an audiometer (Otometrics Conera). A pure tone with an intensity similar to the tinnitus sound is presented to the ear opposite to the tinnitus-impacted ear or the more severe side, with the frequency adjusted between 0.25 and 8 kHz. This adjustment continues until the presented pure tone frequency matches or closely resembles the patient's perceived tinnitus frequency, which is then defined as the tinnitus pitch. For patients who cannot match a pure tone, a narrowband noise frequency is used, and the center frequency of this narrowband noise is defined as the tinnitus pitch. Tinnitus frequencies are categorized as low (<1 kHz), medium (1-4 kHz), and high (≥4 kHz).

- **Tinnitus loudness matching**

After determining the tinnitus pitch, the audiologist matches the loudness at this frequency. Starting from the hearing threshold at the tinnitus pitch, the intensity of the test tone is gradually increased in 1-dB increments until it just masks the tinnitus sound. The difference between the measured sound intensity and the corresponding hearing threshold at this frequency is recorded as the tinnitus loudness [37]. Tinnitus loudness is classified into 5 levels based on the World Health Organization hearing loss grading: ≤25 dB, 26-40 dB, 41-60 dB, 61-80 dB, and ≥81 dB [38].

Tinnitus Handicap Inventory

This scale consists of 25 questions and assesses the severity of tinnitus from various aspects, including psychological, social, occupational, physiological functions, and emotional issues such as anger [39]. Responses are scored as follows: "Yes"=4 points, "Sometimes"=2 points, and "No"=0 points, with a maximum possible score of 100 points. Based on the THI score, tinnitus is classified into 5 levels: 1-16 points as grade I (mild tinnitus), 18-36 points as grade II (mild tinnitus), 38-56 points as grade III (moderate tinnitus), 58-76 points as grade IV (severe tinnitus), and 78-100 points as grade V (catastrophic tinnitus) [40]. In this proposed study, the validated Chinese version of the THI, which has high test-retest reliability (r=0.98) and internal consistency (Cronbach α=0.93), will be used [41].

Secondary Outcomes

Speech-Recognition Thresholds in Noise

Speech audiometry in background noise effectively simulates real-life conditions, providing a more accurate representation of a participant's hearing ability in everyday social interactions [42]. The test will be conducted using the HOPE automated software (ADDI Medical AB), following the speech-recognition thresholds in noise (SRT) testing guidelines recommended by the American Speech-Language-Hearing Association. The SRT calculation will be as follows: SRT = initial test level – number of correctly repeated words + 5 dB (correction factor) [43].

Self-Rating Anxiety Scale

The Self-Rating Anxiety Scale (SAS) [44] consists of 20 items and uses a self-report format to assess anxiety symptoms that may have occurred in the past week, covering emotional, physical, and behavioral aspects. After calculating the original total score, it is multiplied by 1.25 to obtain a standard score (range 25-100). Higher scores indicate more severe anxiety symptoms.

36-Item Short Form Health Survey Questionnaire

The 36-Item Short Form Survey Questionnaire (SF-36) [45] is a self-reported questionnaire that assesses health-related quality of life over the past 2 weeks to 1 month across 36 items, covering 8 health dimensions. For each dimension, the final score is calculated by converting the raw score using the formula: final score = (actual score – minimum possible score)/(maximum possible score – minimum possible score) × 100. Each dimension is scored on a scale from 0 to 100, with higher scores indicating better quality of life in that domain.

Program Safety and Feasibility

Study Oversight and Standardization of Clinical Procedures

The trial protocol has undergone rigorous review by a multidisciplinary team, including acupuncturists, otolaryngologists, audiologists, and statistical experts. Investigators will be selected following a qualification assessment and will remain consistent throughout the study. All team members—including acupuncturists, otolaryngologists, and audiologists—will receive standardized prestudy training to ensure uniform implementation of the protocol. To monitor study progress, address emerging issues, and ensure protocol adherence, regular meetings will be held twice a month. Hearing assessments will be conducted in accordance with standardized operating procedures. Any sudden changes in hearing or adverse reactions to acupuncture during the study will be promptly managed. All acupuncture treatments will be administered exclusively by practitioners with over 2 years of clinical experience, and no other techniques, such as acupressure or intradermal needle application, will be used. Senior physicians will supervise the entire process, providing guidance and resolving any issues to ensure the smooth and consistent delivery of treatment.

Management of Adverse Drug Reactions

If a drug-related allergic reaction occurs, the offending medication will be immediately discontinued. Patients will be advised to increase fluid intake to facilitate drug excretion. Antihistamines such as loratadine or cetirizine will be administered as needed, and calamine lotion may be applied topically to relieve localized symptoms.

Management of Acupuncture-Related Adverse Events

Needle Fainting

In the event of needle fainting, all acupuncture needles will be promptly removed. The patient will be assisted into a supine position in a well-ventilated area, with the legs elevated and the head positioned lower, without a pillow. The patient will be allowed to rest quietly and will be offered warm sugar water or hot tea to aid recovery.

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Stuck Needle

If a needle becomes stuck, especially in anxious patients, the retention time may be extended while gently massaging the area around the acupuncture point to promote relaxation. If the needle remains immobile, a secondary needle may be inserted near the original point to help release tension. In cases where the needle is stuck due to unidirectional rotation, it should be twisted gently in the opposite direction. Additional techniques, such as scraping or flicking the needle handle, may be applied to release entrapped muscle fibers and facilitate safe needle removal. For bleeding around the acupuncture site, a cold compress or pressure will be applied as needed. Participants may choose to withdraw from the intervention or study at any time and for any reason. They will be informed about the permission, consent, and assent forms and may discontinue participation at any point without any consequences.

Given the disease characteristics of hearing loss and the professional level of the hospitals conducting the study in China, participant compliance is expected to be high. To further support compliance, we will provide regular hearing assessments, offer health education, and provide a compensation of 200 RMB for transportation and time costs.

Oversight and Monitoring

The principal investigators (JH and XH) will oversee the trial and report any serious adverse events to the Tongren Hospital Ethics Committee. Detailed records of adverse events—including their timing, severity, and treatment—will be maintained. In the event of an adverse reaction, a senior acupuncturist and otolaryngologist will evaluate whether the patient should be excluded from the study, and the clinical supervisor will be informed accordingly. Researchers will document the event details in the case report form (CRF; Multimedia Appendix 2) and ensure follow-up care until the patient stabilizes, with a summary report sent to the relevant authorities. Audiologists, acupuncturists, and nurses will conduct weekly follow-up calls to monitor symptoms and manage potential adverse reactions.

Data Collection and Management

This RCT will adhere to the principles outlined in the Declaration of Helsinki [46]. Written informed consent will be obtained from all participants, with personal data and consent forms securely stored in a locked unit in the ENT (ear, nose, and throat) outpatient department at Tongren Hospital. Each participant will be assigned a unique ID to maintain anonymity, and all data collected in the computer system will be identified only by this ID number. Documentation files (including ID numbers and participant identifiers) will be stored separately from study information files and consent forms. Only the principal investigators and designated team members will have access to the participant ID list and associated information. Clinical data will be collected and recorded by trained research evaluators in our outpatient clinic, initially entered on CRFs, and then into the EpiData system (EpiData Association). Each CRF will undergo double entry by 2 staff members, followed by a consistency check to generate a validation report. Any discrepancies will be investigated and corrected. All paper records will be stored securely in a controlled room with appropriate temperature, humidity, and fire safety measures. Digital files will be securely stored on a computer or external hard drive to prevent data loss. If issues arise during the study, database variables, particularly primary ones, may undergo full or sampled manual checks and be cross-referenced with the CRFs for accuracy.

Statistical Analysis

All efficacy analyses will follow the intention-to-treat principle, including all randomized participants. Statistical analyses will be performed using SPSS version 22.0 (IBM Corp). Continuous variables, including PTA, THI, SAS, and SF-36, will be reported as means (SDs) for normally distributed data, or as medians (IQRs) for nonnormally distributed data. Tinnitus matching (frequency and loudness) will be treated as a categorical variable and summarized as proportions or percentages.

Baseline PTA distributions for both groups will be reported as means (SD) or medians (IQRs). Differences in baseline hearing loss severity will be assessed using the 2-tailed (unpaired) independent samples *t* test (for normally distributed data) or the Mann-Whitney *U* test (for nonnormally distributed data). If significant differences are identified, group comparisons will be adjusted for hearing loss severity using analysis of covariance to ensure comparability.

Changes in PTA, THI, SAS, and SF-36 across 6 time points (t0, t1, t2, t3, t4, and t5) will be evaluated using repeated measures analysis of variance for normally distributed data, or the Friedman test for nonnormally distributed data. Changes in tinnitus matching across the 6 time points will be assessed using the Cochran *Q* test to detect overall differences. If significant, pairwise comparisons will be conducted using the McNemar test with a Bonferroni correction for multiple comparisons.

Group differences in PTA, THI, SAS, and SF-36 at each time point will be analyzed using the independent samples *t* test (for normally distributed data) or the Mann-Whitney *U* test (for nonnormally distributed data). If baseline hearing loss severity differs significantly, analysis of covariance will be applied to adjust for this covariate. Differences in tinnitus matching at each time point will be evaluated using the chi-square test or Fisher exact test, as appropriate. Statistical significance will be set at α=.05 (2-sided).

As a pilot study, the primary feasibility outcomes include the proportion of enrolled participants relative to the target sample size (recruitment rate, reported as a percentage), the proportion of participants completing at least 80% of prescribed EA sessions over 4 weeks (adherence rate, extracted from treatment logs and reported as a percentage), the proportion of participants with complete baseline and follow-up data for key measures such as PTA and THI (data completeness, reported as a percentage, with the proportion of missing data reported as a complementary indicator), and the incidence of adverse events during the treatment period (safety outcomes, recorded from session-by-session reports and summarized as total events and incidence rate per 100 person-sessions). These feasibility outcomes will be presented using descriptive statistics, without hypothesis testing.

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Results

This study began recruitment on July 15, 2024, and is scheduled to conclude on August 31, 2025. To date, 42 participants have been enrolled, with 35 having completed the intervention and posttreatment assessments (control group: n=21; EA group: n=14). Following protocol publication, data compilation and analysis will be conducted, with results anticipated to be published in a relevant journal in 2026.

Discussion

Overview

The treatment guidelines for ISSNHL have been clearly established. However, the treatment protocol for tinnitus, a common comorbid symptom of ISSNHL, remains uncertain [1,47]. This study aims to investigate the potential efficacy and feasibility of EA combined with medication for patients with ISSNHL accompanied by tinnitus. Currently, only a limited number of studies have focused on the treatment of tinnitus, with therapeutic approaches including sound therapy and psychological therapy [48]. Because of the varied nature of tinnitus symptom maintenance, a single treatment modality may not be suitable for all patients [49]. Acupuncture, as one of the most widely accepted complementary and alternative therapies in China, has been explored in prior research for its potential in managing ISSNHL and tinnitus. For instance, Zhou and Jin [50] conducted a retrospective study comparing EA with traditional acupuncture and found that EA was more effective in reducing hearing thresholds and alleviating tinnitus over a 3-month treatment period. Similarly, Zhang et al [51] performed a systematic review and meta-analysis of 12 RCTs, demonstrating that manual acupuncture or EA combined with medication outperformed medication alone in improving hearing outcomes, with some evidence suggesting that EA alone was superior to medication. Additionally, Chen and Jing [52] reported 2 refractory cases where EA alone (12 sessions over 4 weeks) led to complete recovery of unilateral sensorineural hearing loss. However, these findings are limited by low evidence quality and the rare use of tinnitus-specific outcomes (eg, tinnitus matching or THI) as primary end points.

The selection of acupuncture points is primarily based on the following rationale. A study by Huang et al [53] revealed that, through data mining analysis of 112 studies containing 221 prescriptions, the 4 most frequently used acupuncture points were SI19, GB2, SJ17, and SJ3. The SI19-GB2-SJ17 point combination was identified as the core acupoint cluster according to association rule analysis. These peri-auricular acupoints may alleviate tinnitus by stimulating auditory-related nerves and improving blood circulation in the ear region [24,54]. Additionally, scalp acupuncture may exert its effects through the trigeminal nerve and blood circulation regulation, contributing to the improvement of auditory processing and neural activity [55,56].

Most studies currently agree that the earlier patients with ISSNHL receive treatment, the better their prognosis. The study by Byl [57] indicated that patients who received medical attention within 7 days of onset had an approximately 56% recovery rate, whereas those who presented after 30 days had a recovery rate of only 27% (also see [58]). The study by Diao et al [59] also demonstrated that the number of days from onset to treatment was an independent prognostic factor, with shorter time intervals correlating with better outcomes. Therefore, all patients selected for this study were within 7 days of onset. The medication treatment protocol for ISSNHL with tinnitus is the same as that for ISSNHL. The inclusion of multiple variables (ie, multiple drugs) in the standard treatment is driven by the complex pathophysiology of ISSNHL. Research indicates that inflammation is likely a key contributing factor, and corticosteroids such as prednisone are used to reduce inner ear inflammation and edema, thereby improving hearing outcomes [60]. Ginkgo biloba extract, known for its circulation-enhancing and antioxidant properties, may help restore cochlear microcirculation [61]. Batroxobin, a snake venom–derived enzyme with fibrinolytic activity, may improve inner ear blood flow by reducing blood viscosity [62]. This combination of drugs is designed to simultaneously target distinct pathological mechanisms, thereby enhancing overall therapeutic efficacy. The rationale for this combined approach is supported by evidence from studies conducted in China. A retrospective study involving 342 patients with total deafness-type ISSNHL found that adding batroxobin to a treatment regimen of Ginaton and glucocorticoids significantly improved hearing recovery outcomes and maintained plasma fibrinogen levels within a safe and prognostically favorable range [63]. This improvement was particularly notable in terms of hemorheological parameters and peripheral blood T-cell subset reactivity. Additionally, a 2023 meta-analysis further corroborated the efficacy of Ginkgo biloba extract as an adjuvant therapy, suggesting it may outperform corticosteroid monotherapy [64]. These findings support the decision to incorporate multiple pharmacological agents into the standard treatment protocol, aligning with the goal of addressing the multifaceted nature of ISSNHL.

Innovations and Limitations

This study innovatively investigates EA for flat-type ISSNHL, integrating traditional Chinese medicine with modern clinical needs to explore a potential nonpharmacological treatment option. However, there are several limitations to this study. First, due to the inability to implement blinding in the intervention measures, there may be some degree of bias, particularly regarding placebo effects and patient expectations, which could interfere with subjective evaluations of treatment outcomes. Moreover, this study does not include a sham acupuncture control, which further increases the potential for bias, as the lack of a placebo control for acupuncture makes it difficult to rule out nonspecific treatment effects. Second, this study only included patients with flat-type ISSNHL, excluding the other 3 types of hearing curves, which may limit the generalizability of the results to a broader population of patients with ISSNHL with tinnitus.

Conclusions

This pilot study evaluates the feasibility of combining EA with medication for flat-type ISSNHL, integrating both subjective and objective outcomes across multiple follow-up time points to assess potential benefits in hearing, tinnitus, anxiety, and

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quality of life. Using rigorous stratified randomization and high-quality data management, this study generates preliminary evidence on EA's viability as a complementary therapy, laying the groundwork for the design and sample size estimation of future large-scale multicenter RCTs to advance nonpharmacological treatment options for ISSNHL.

Acknowledgments

This work is supported by the Basic Scientific Research Business Foundation of the Institute of Acupuncture and Moxibustion, CACMS (grant ZZ-2023013 covered costs related to resources and equipment, and journal open access costs). However, the funder had no role in the study design, data collection and analysis, decision to publish, or preparation of the manuscript. We thank Director Weijuan Gang from the Evidence-Based Medicine Center at the Institute of Acupuncture and Moxibustion, CACMS, for her assistance.

Data Availability

No data sets were generated or analyzed during this study. All relevant data from this study will be made available upon study completion and can be obtained by contacting the corresponding author.

Authors' Contributions

JH and XH defined the study design and method. SD and CL performed the data acquisition. TW and MZ conducted the acupuncture operation. TW also drafted the initial manuscript. LQ interpreted the data. BC performed the listening assessment. JC and PL handled participant recruitment and registration. XZ monitored adverse reactions. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 1253 KB - resprot_v14i1e69163_app1.pdf]

Multimedia Appendix 2
Case report form.
[PDF File (Adobe PDF File), 473 KB - resprot_v14i1e69163_app2.pdf]

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Abbreviations

CACMS: China Academy of Chinese Medical Sciences
CONSORT: Consolidated Standards of Reporting Trials
CRF: case report form
EA: electroacupuncture
ENT: ear, nose, and throat
ISSNHL: idiopathic sudden sensorineural hearing loss
PTA: pure tone audiometry
RCT: randomized controlled trial
SAS: Self-Rating Anxiety Scale
SF-36: 36-Item Short Form Survey Questionnaire
SRT: speech-recognition thresholds in noise

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Protocol

Development and Pilot Testing of an Addiction Clinic–Based Pre-Exposure Prophylaxis Uptake and Adherence Intervention for Women with Substance Use Disorders: Protocol for a Pilot Randomized Trial

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Abstract

Background: Black and Hispanic women in the United States continue to bear disproportionate incidence of HIV related to sexual transmission and injection drug use. Specifically, women with substance use disorders (SUDs) are more likely to engage in vaginal or anal condomless sex associated with HIV transmission. Pre-exposure prophylaxis (PrEP) is a highly effective HIV prevention tool but is not widely used by racial or ethnic minority women. Effective interventions for engaging women with SUDs in HIV prevention interventions that are culturally appropriate and, therefore, more appealing to racial or ethnic minority women with SUDs are critically needed.

Objective: This 3-phased study, including a pilot randomized controlled trial (RCT), will assess the initial efficacy, feasibility, and acceptability of an addiction clinic–based behavioral and PrEP services intervention to increase the uptake and adherence to PrEP among racial or ethnic minority women.

Methods: A 3-phased mixed methods research design will involve formative qualitative methods using thematic analysis to design the intervention (phase 1), theatre testing to adapt and refine the intervention (phase 2), and RCT methods to pilot test the intervention for efficacy, feasibility, and acceptability (phase 3). The pilot RCT will enroll and randomize 60 women to either the standard SUD treatment program or SUD treatment integrated with PrEP services. The addiction clinic–based behavioral intervention will include 4 motivational counseling sessions guided by the Information-Motivation-Behavioral Skills Model to increase the uptake of PrEP. A mobile health app will be used to engage participants with the intention of motivating PrEP initiation and supporting adherence to PrEP. Following phase 3, generalized linear modeling will be used to model effects of the proportion of participants who fill their prescription and take at least 1 dose as a function of the intervention group.

Results: Findings from individual qualitative interviews informed the development of the addiction clinic–based behavioral intervention. Study recruitment for the randomized pilot (phase 3) launched in May 2024. Additional statistical analyses will be performed upon completion of the study.

Conclusions: This addiction clinic–based behavioral intervention aims to increase PrEP uptake and adherence among racial or ethnic minority women who engage in sexual and substance use behaviors associated with increased susceptibility to HIV transmission. The addiction clinic–based behavioral intervention has the potential to reduce HIV-related disparities among Black

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and Hispanic women with SUDs. Findings from this study will provide a foundation for future HIV prevention interventions for racial or ethnic minority women with SUDs.

Trial Registration: ClinicalTrials.gov NCT06158607; https://clinicaltrials.gov/study/NCT06158607?term=NCT06158607&rank=1

International Registered Report Identifier (IRRID): DERR1-10.2196/64961

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KEYWORDS

HIV prevention; Pre-Exposure Prophylaxis; substance use disorder; clinic-based intervention; harm reduction

Introduction

Background

In the United States, women with a lower socioeconomic status and women from racial or ethnic minority backgrounds continue to bear a disproportionate HIV burden [1]. According to the Centers for Disease Control and Prevention (CDC), women made up 18% of the new HIV diagnoses in 2022, with 83% of those cases representing transmission through heterosexual contact and 16% representing transmission through injection drug use. The HIV diagnosis rates for Black and Hispanic women are 10 and 3 times, respectively, the rates for White women [1]. Women with substance use disorders (SUDs) are particularly vulnerable to HIV transmission due to the greater likelihood of engaging in vaginal or anal sex without using a condom, concurrent sexual relationships, sex in exchange for drugs, money, or other items, and sexual coercion from experiencing sexual abuse or assault by intimate partners [2-6]. Inequities experienced by women, including relationship power and control differentials and physical or sexual violence, further influence women's engagement in both the risk behaviors that increase their likelihood of contracting HIV as well as the potential preventive measures. To adequately address the syndemic effect of substance use, HIV, and trauma [7], interventions must be specifically developed for the unique needs of this population.

Pre-exposure prophylaxis (PrEP) is a medication with demonstrated efficacy in reducing HIV transmission, including among heterosexual women [8]. PrEP removes the barrier of partner consent, thus empowering women to engage in their own HIV prevention strategies. This is an important factor among women who have difficulty negotiating safer sex practices with their partners due to relationship power imbalances [9-11]. Despite the effectiveness of PrEP, uptake has been slow among women, and the reasons for this, particularly among women with SUDs, are not completely understood [12].

According to the CDC, in 2019, approximately 1.2 million adults had PrEP indications. Yet, there are disparities among those with PrEP indications, with males more likely to have been prescribed PrEP than females [13]. HIV prevention research has overwhelmingly focused on men who have sex with men, with few studies designed specifically to study PrEP uptake in women [14,15]. Evidence suggests that low perceived risk and concerns about side effects (most commonly nausea and vomiting) are barriers to PrEP use [16]. Some women perceive themselves to be at low risk for HIV despite engaging in condomless sex and sex while using substances [17-19]. In contrast, studies examining PrEP knowledge and attitudes have found low rates of initial knowledge with high levels of interest among women once they are informed of the benefits of PrEP for HIV prevention [14,15]. This interest, however, does not always result in PrEP uptake.

Social and structural factors such as poverty, race or ethnicity, inequities, discrimination, and lack of empowerment combine as barriers to HIV prevention for women with SUDs [9-11,20-25]. Extending availability and access to effective HIV prevention strategies, such as PrEP, may help overcome these intersecting barriers and is consistent with the nation's "Ending the HIV Epidemic" plan by "preventing new HIV transmissions by using effective interventions which include PrEP" [26]. In addition to the individual barriers to PrEP use mentioned above, there are also social and structural barriers to PrEP uptake. These include, but are not limited to, perceived stigma, lack of access to knowledgeable providers, and mistrust of health care providers and health care systems [12,14,15,27]. Lack of access to PrEP services and provider reluctance to prescribe PrEP are also significant barriers, given that women have reported a preference for conversations about HIV prevention to be initiated by medical providers [17]. Expanding PrEP uptake to women is a vital component of the nation's plan [28]. However, research on PrEP initiation among women is limited [29].

A few studies have found daily oral PrEP to be effective for reducing HIV acquisition in heterosexual women [8,30]. However, 2 major trials specifically examining PrEP in women were unable to demonstrate the efficacy of oral PrEP because of low adherence [31,32]. The few published research studies on PrEP uptake among women have taken place in a variety of US and international settings where available resources and barriers to uptake and adherence may vary considerably, thus making it difficult to ascertain the potential for PrEP to reduce HIV acquisition among heterosexual women. The notable absence of published findings on effective interventions to increase PrEP uptake and adherence among women represents a significant gap in the research literature [33]. A recent review of best practices for increasing PrEP uptake and persistence in the United States identified 9 interventions meeting the criteria for best practice, with only 1 of the 9 including women as participants [34]. The 1 study included in the review, which included women, reported only 6 of the 198 participants identified as women [35]. One promising intervention using motivational interviewing with women was not included as meeting best practice guidelines due to low participant

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enrollment [36]. Additional research on interventions designed to increase PrEP uptake and adherence among women is needed [15]. A meta-analysis of oral PrEP use among women found only a 61% reduction in HIV acquisition risk among women who reported 75% adherence to a daily PrEP regimen [37]. Researchers have called for greater attention to both PrEP uptake and adherence among women and future studies that focus on developing and evaluating methods to enhance adherence and greater reliance on laboratory-based versus self-reported adherence measures [38].

Integrating HIV prevention into environments where individuals are already engaged in other services helps to increase access to care. In a previous study, researchers found that offering HIV testing and prevention counseling within SUD treatment programs resulted in increased rates of receiving these preventive services [39]. This is an example of work at an individual level to increase HIV testing behavior and at a structural level to remove barriers to care by increasing the SUD treatment program's capacity to provide HIV prevention services [40]. It has been recommended that SUD treatment programs routinely offer HIV testing to all participants and linkage to primary medical care for individuals who test positive for HIV as a means of increasing access to HIV care [41]. However, despite the well-known associations among substance use, HIV, and sexual risk, it is estimated that only about half of SUD treatment programs offer HIV prevention services [42,43].

The addiction treatment clinic setting is ideally situated to provide additional services for HIV prevention. In recognition of the important role that addiction providers can play in the adoption and delivery of PrEP services and to identify potential barriers to implementing PrEP, researchers have explored providers' perspectives on including PrEP as part of addiction treatment [44]. To our knowledge, PrEP and HIV prevention services have not been optimally integrated into the addiction treatment clinic environment; thus, the study team proposed to develop an addiction clinic–based behavioral intervention designed to increase PrEP uptake for racial or ethnic minority women.

Theoretical Framework

This project is guided by the Information-Motivation-Behavioral Skills (IMB) [45] model, shown in Figure 1. The IMB model of health behavior change posits that information, motivation, and behavioral skills are key determinants of engaging in health behaviors. This model has been applied to various health promotion behaviors, including HIV treatment and prevention [40-43]. Specific to HIV prevention, the 3 fundamental determinants of HIV risk reduction include information regarding how HIV is transmitted and methods for preventing HIV infection; motivation to change risky behaviors; and training in behavioral skills necessary for engaging in specific preventive acts [46]. In HIV research, the IMB model has been used to inform interventions for medication adherence in persons living with HIV [47] and has some preliminary evidence for utility with PrEP uptake and adherence interventions [48-50]. The IMB model has also been used to guide the development of interventions to increase PrEP uptake and adherence using mobile health (ie, text messaging, appointment reminders, and medication reminders using mobile devices) [51,52]. Previous research supports the use of mobile technologies as a cost-effective and convenient method for increasing health-promoting behaviors [53].

Figure 1. The Information-Motivation-Behavioral Skills model of pre-exposure prophylaxis uptake (adapted from Fisher et al [47]). PrEP: pre-exposure prophylaxis.

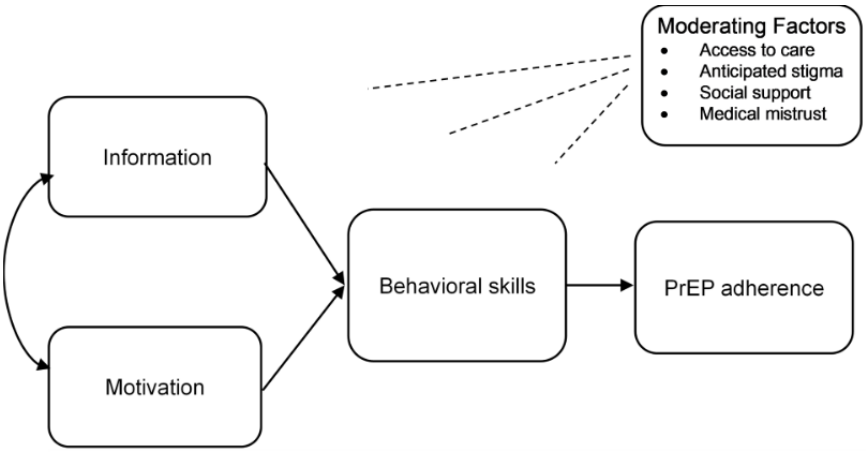

Research supports the IMB model in the development of interventions aimed at increasing willingness to use PrEP in people who use drugs with high HIV risk [54]. Guided by the IMB model, our addiction clinic–based PrEP uptake and adherence intervention provides knowledge of PrEP effectiveness and side effects and offers motivational incentives for increasing PrEP uptake using an innovative remote-delivery monetary incentive application (Scene mobile app; formerly Emocha [55,56]) that provides the behavioral skills necessary to effectively use PrEP (eg, adherence and side effect management) including video directly observed therapy to monitor medication taking. Video directly observed therapy allows participants to upload videos of themselves taking their medication through a video-enabled device such as a smartphone so that their treatment teams can verify that medication has been taken. In addition, the Scene Health mobile app includes videos showing behavioral skills, a library of motivational messages, and frequently asked questions to address barriers to PrEP use.

Within the context of the IMB model, the research team anticipates that the addiction clinic–based behavioral

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intervention will improve PrEP uptake and adherence among racial or ethnic minority women engaged in SUD treatment. By co-locating services within the addiction clinic, the intervention will address moderating factors (access to care and adherence support) that have been barriers to successful PrEP uptake and adherence.

Objectives and Study Design

This study aims to develop an addiction clinic–based behavioral intervention for increasing PrEP uptake and adherence among racial or ethnic minority women who engage in sexual and substance use behaviors associated with HIV transmission. To accomplish this, investigative team proposes a 3-phase study, as illustrated in Figure 2, to address 3 specific aims: (1) to elicit information on knowledge and attitudes about PrEP use and obtain feedback about the design of an addiction clinic–based behavioral intervention for racial or ethnic minority women with sexual and substance use behaviors associated with HIV transmission; (2) to develop an addiction clinic–based behavioral intervention to promote PrEP uptake and adherence in women undergoing treatment for SUD who are susceptible to HIV infection; and (3) to assess initial efficacy, feasibility, and acceptability of the addiction clinic–based behavioral intervention.

Figure 2. Overall study design. Development and pilot testing of an addiction clinic–based prep adherence intervention for women with substances use disorders. CAB: community advisory board; IMB: Information-Motivation-Behavioral Skills: PrEP: pre-exposure prophylaxis.

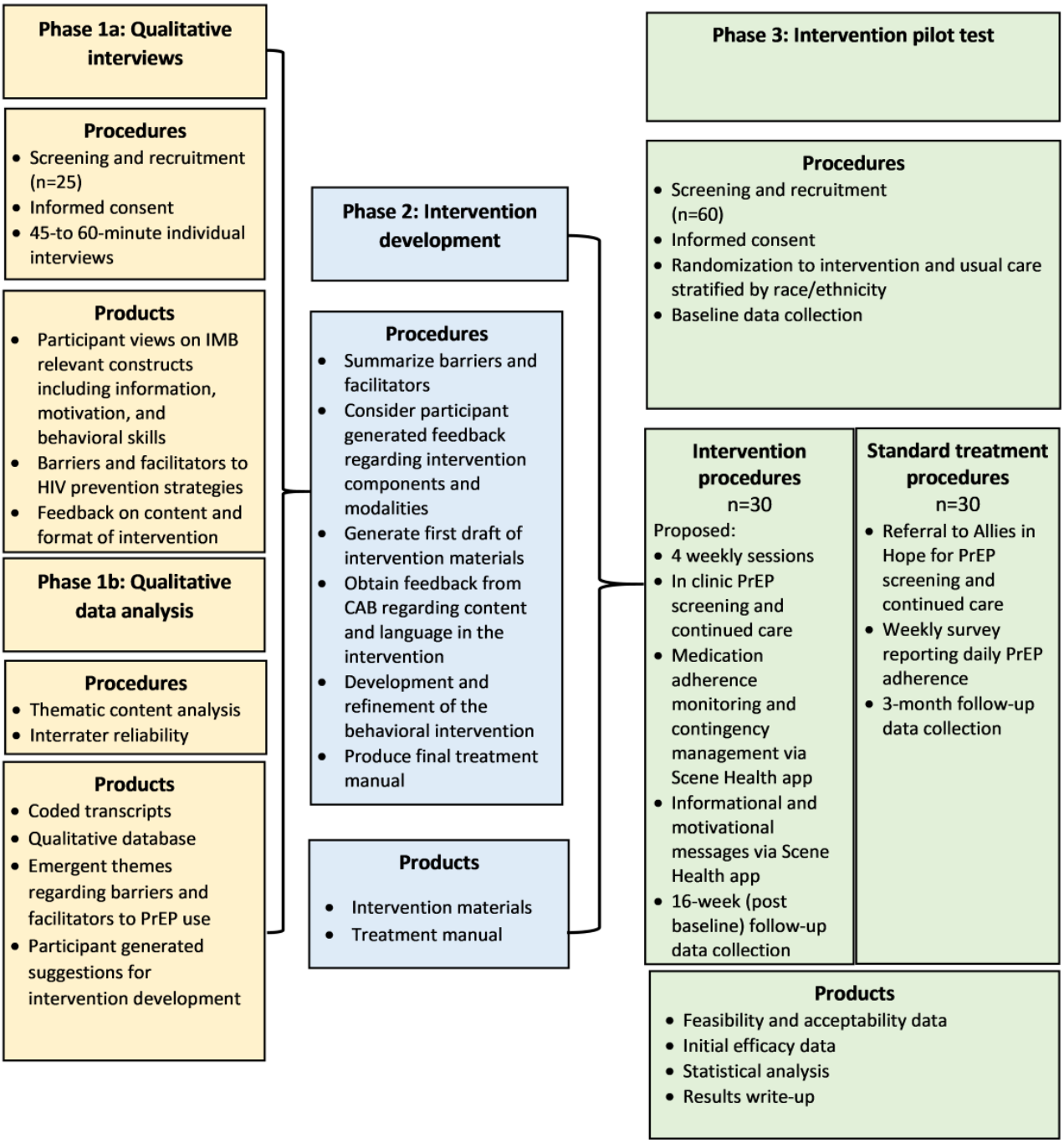

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Methods

Study Setting

The primary study setting will be the outpatient treatment research clinic of the Center for Neurobehavioral Research on Addiction (CNRA), a university-supported center of excellence within the Louis A Faillace, MD Department of Psychiatry and Behavioral Sciences at UTHealth Houston. Allies in Hope (formerly AIDS Foundation Houston), established in 1982, is a community-based organization providing HIV prevention, HIV treatment, counseling, and case management to Houston residents. Allies in Hope will be the referral site for the control group (ie, standard-of-care treatment condition) in the phase 3 pilot randomized controlled trial.

Study Population and Eligibility

Participants are eligible to participate in all phases of the study if they are self-identified as Black/African American and Hispanic/Latina women, aged 18 years or older, diagnosed with an SUD per *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) criteria [57], HIV-negative, sexually active (ie, vaginal or anal sex) with a male within the past 6 months, not using PrEP for HIV prevention at the time of screening, fluent in English, and own or have regular access to a smartphone.

Participation in the current study is limited to English-speaking individuals because intervention materials have not yet been translated into Spanish. Future research will use instruments translated into Spanish and include interview and data collection materials in Spanish to address the unique needs of individuals whose primary or preferred language is Spanish.

Phase 1: Formative Research

Phase 1a: In-Depth Qualitative Interviews

This phase of the study was conducted between June 2022 and February 2023. We recruited 25 women to complete in-depth qualitative interviews to provide their personal and detailed perspectives about PrEP and our proposed addiction clinic–based behavioral intervention. Recruited women were currently enrolled in treatment for SUD. The interviews lasted between 45 to 60 minutes, and participants were compensated US $25 for their participation.

The interview guide was developed based on the IMB model, focusing on the following areas:

1. Information: participants' knowledge and awareness of PrEP, including their understanding of its effectiveness, who it is recommended for, the importance of taking it consistently, potential side effects, and possible drug interactions.
2. Motivation: participants' attitudes toward HIV prevention and PrEP, perceived barriers to using PrEP such as beliefs about its outcomes, experiences or concerns related to stigma, and the level of social support from partners, family, and friends.
3. Behavioral skills: participants' confidence in their ability to prevent HIV, strategies for retaining HIV prevention information, maintaining medication adherence (eg, setting reminders), attending follow-up medical appointments, and managing side effects.

The interviews also gathered insight about barriers and facilitators of the proposed integration of HIV prevention services within standard SUD treatment, specifically (1) preferences for in-person versus remote delivery of motivational enhancement interventions to improve PrEP adherence, (2) frequency and duration of sessions; (3) frequency of motivational messages, and (4) content of motivational messages. Interviewers also introduced the Scene Health app and obtained feedback on the appointment reminder, video uploads for medication adherence, and notification of the app's awards (ie, monetary incentives) features.

A community advisory board (CAB) consisting of 6 members from local community-based organizations who are representative of the populations of interest for the current study was created. Members of the CAB provided feedback on surveys, interview guides, advertising, and other study materials. CAB member feedback on the motivational messaging included in the intervention was also elicited.

Phase 1b: Data Analysis

Qualitative data were analyzed using MAXQDA. Our analysis used a thematic analysis approach, which involves identifying themes through an iterative process comprised of multiple stages of data collection, theme refinement, and data categorization. The investigators used the IMB framework to organize emergent themes based on participants' interviews. The team used the results from the qualitative data analysis to inform the development of the addiction clinic–based behavioral intervention. Future manuscripts will present findings from phase 1 of the study.

Phase 2: Development and Theater Testing of the Cultivating HeAlth Resilience Growth & Empowerment (Take CHARGE) Intervention: Addiction Clinic–Based Behavioral Intervention

Based on information obtained in phase 1 and the IMB model, the study team developed an addiction clinic–based behavioral intervention, Theater Testing of the Cultivating HeAlth Resilience Growth & Empowerment (Take CHARGE), that provides PrEP-related information, motivational messaging, and behavioral skills necessary to use PrEP effectively. The intervention will include a PrEP service component to be delivered in the addiction treatment clinic by a nurse practitioner, leveraging the existing SUD treatment and HIV prevention infrastructure and removing accessibility barriers. This intervention will be provided alongside standard SUD treatment which consists of participation in individually delivered, evidenced-based intervention (eg, cognitive behavioral therapy) focused on quitting or reducing substance use delivered by a master's-level counselor, psychologist, or psychology intern under the supervision of a licensed psychologist.

The intervention will consist of 4 weekly sessions that can be delivered through a HIPAA (Health Insurance Portability and Accountability Act)-compliant videoconferencing platform. Sessions will be approximately 30 minutes in length and are

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intended to increase knowledge of PrEP, increase positive attitudes toward PrEP, and decrease behaviors that place individuals at risk for HIV infection with a goal of increasing PrEP uptake and PrEP adherence.

The IMB Framework

The study team used the IMB domains to develop the addiction clinic–based behavioral intervention. Specifics on how each domain informed the development of the intervention are outlined below.

The Information Domain

The information component involved providing basic information about PrEP, including how it works, who is eligible, safety and efficacy, and the importance of adherence. The information component also provided information about the benefits of individually controlled HIV prevention methods (eg, not relying on men to wear condoms, racial or ethnic minority women maximizing their power and decision-making abilities for their sexual health) [50]. Based on findings in Phase 1, the study team tailored the intervention to address gaps in knowledge and misconceptions about HIV and PrEP.

The Motivation Domain

The motivational enhancement component included motivational counseling and monetary incentives for achieving desired behaviors. To address low perceptions of HIV risk as a barrier, the intervention will individually address perceived versus actual personal risk for HIV infection. The motivational therapy will address attitudes about the potential advantages of using PrEP and potential outcomes of not using PrEP. To address the social aspects of motivation, sessions will explore stigma and social support concerns. Monetary incentive-based motivation will be embedded into video-based directly observed therapy using the Scene Health mobile app and is a CDC-endorsed model of care to ensure medication adherence while capturing adverse events [51,52]. The platform will be customized to provide appointment reminders and immediate delivery of monetary incentives (refer to the Monetary Incentives subsection under Intervention Arm and Control Arm subsection) upon confirmation of engagement in the target behavior (ie, attendance and medication taking).

The Behavioral Skills Domain

The behavioral skills development component will provide specific skills to increase self-efficacy. This included helping the participant identify ways to remind themselves to take their medication, communicating a need for social support, managing side effects, and identifying supportive others. This component leverages the SUD treatment clinic's current HIV prevention infrastructure to deliver PrEP services including initial screening, prescription, side effect monitoring, and follow-up to women engaged in SUD treatment. The study team proposes to fully integrate PrEP services into the addiction clinic setting. All services, including laboratory tests, monitoring, and follow-up, will be delivered within the clinic setting for those in the intervention arm. Individuals in the control arm of the study will be referred to Allies in Hope for standard-of-care PrEP services. They will be provided with an appointment and transportation assistance. Participants in both conditions will continue receiving their addiction treatment services.

Motivational Messages

The study team also created a library of approximately 200 motivational messages to be delivered between sessions. These will include text-based messages and brief videos created by research staff, adapted from the UCARE4LIFE study [58], and supplemented with the CDC's #ShesWell: PrEP for Women campaign to promote the uptake of PrEP among women of color. A sample of these messages were provided to phase 1 and phase 2 participants who provided their feedback on the language and acceptability of the messages. The messages are intended to motivate participants to attend their appointments with the nurse practitioner, take PrEP daily as prescribed for those on daily oral PrEP, continue their SUD treatment, speak with the nurse practitioner regarding side effects or questions, and decrease sexual behaviors that may increase their susceptibility to HIV infection.

Theater Testing

The investigators invited 5 participants who had completed the qualitative interviews in phase 1 to a theater testing session to provide feedback on the developed intervention, including the motivational messages that had been created. The investigators conducted theater testing from February 19 to February 28, 2024. Participants were compensated US $25 for their time. During the theater test, participants completed a 45-minute sample session, which included elements from the 4 planned sessions of the full intervention. Following the theater test, each participant completed a feedback form with open and closed-ended questions and participated in a 15-minute interview to obtain their reactions to the proposed intervention [59]. The research team used this feedback to tailor the specific content of the sessions further to be more appealing to women engaged in treatment for SUD who have increased susceptibility to acquiring HIV.

Phase 3: Intervention Pilot Test—Study Design

The investigative team will rigorously pilot test the degree to which the addiction clinic–based behavioral intervention promotes increased PrEP adherence compared with standard linkage to PrEP. The investigative team will randomly assign 60 women to 1 of the 2 conditions. Participants in both the intervention and control groups will continue to receive evidence-based behavioral therapy for SUDs (ie, cognitive behavioral therapy with licensed counselors).

Participants and Recruitment

The investigators will recruit 60 BlackBlack or Hispanic women to participate in the study. The investigators will invite individuals who are engaged in or initially enrolling in treatment for SUDs at the CNRA. The research assistant will describe the study by informing participants that this is an HIV prevention study focusing on women engaged in treatment for SUD and will not directly impact their regular SUD treatment. Potential participants will be screened over the phone by the research assistant and informed of the purpose of the study. Those meeting inclusion criteria and agreeing to participate will sign an informed consent form and receive a copy. After completing the informed consent process, participants will be randomized to the intervention or control group.

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The study team will recruit eligible participants by posting flyers, through word of mouth (through addiction treatment staff referral), and advertising in local print sources (newspapers and magazines). Recruitment and enrollment began in May 2024 and will continue through March 2025.

Intervention Arm

Weekly Counseling Sessions

Participants randomized to the addiction clinic–based behavioral intervention will receive 4 motivational counseling sessions (~30 minutes each) related to HIV prevention, PrEP, and partner communication information delivered by a trained study counselor with expertise in HIV prevention among substance using populations. The study counselor will assist the participant with downloading the Scene app and completing a profile. The incentive scheme and expectations for treatment will be explained at the time of the baseline assessment.

In-Clinic PrEP Screening

After completion of the four motivational sessions, the participant will be scheduled for their initial visit with the nurse practitioner in the CNRA, who will conduct a clinical assessment which will include fourth-generation HIV screening (ie, tests that detect both HIV antibodies and p24 antigens), screening for sexually transmitted infections, a basic metabolic panel to include serum creatinine, and hepatitis B and C screening. The nurse practitioner will review laboratory results. If there is no contraindication for PrEP, the participant will be provided a prescription for PrEP. The decision to prescribe daily oral PrEP or long-acting injectable (LAI) PrEP will be based on a collaborative decision-making process between the patient and nurse practitioner, considering clinical appropriateness, patient choice, and medication availability. Participants on daily oral PrEP will be instructed to take the medication daily and to follow up for laboratory tests in 12 weeks while participating in the intervention. Participants enrolled in LAI-PrEP will be provided with a prescription for a 4-week supply of oral cabotegravir per local clinic protocol of prescribing lead-in medication to monitor side effects before initiating LAI-PrEP. Participants are then instructed to follow up with the nurse practitioner in 4 weeks for their first injection while participating in the intervention. All participants who receive a PrEP prescription from the on-site nurse practitioner will meet with the risk reduction specialist, who will assist those without prescription insurance with enrollment for an appropriate patient assistance program to access medication free of charge through the Advancing Access Program or the Health and Human Services ready, set, PrEP program.

Medication Adherence Monitoring

Participants will be instructed to provide proof that they are in receipt of the prescribed PrEP medication (video message within the Scene app) and to begin daily video uploads of adherence to medication regimen. Participants who do not fill their PrEP prescription within 2 weeks will be scheduled for a follow-up visit with the nurse practitioner, who will address any concerns and questions related to starting the medication. Participants who are prescribed daily oral PrEP will be asked to upload daily adherence videos (ie, video of the participant taking the medication) for 12 weeks after initiating PrEP.

Motivational Messaging

Participants will receive motivational messages through text for the entire 12 weeks to promote medication uptake (for participants who, after the motivational counseling sessions, have not chosen to start PrEP and agree to continue receiving the informational messages) or reminders and motivational messages to support adherence to PrEP (for participants who initiate PrEP). All participants will be given the option of choosing how often they receive the messages and can opt out of messaging at any time through the app.

Monetary Incentives

Participants will receive monetary incentives for completing project-related tasks and engaging in desirable health-promoting behaviors. Each participant will receive US $25 for the baseline data collection, US $10 per session for attending 4 weekly motivational counseling sessions, US $25 for the initial nurse visit with laboratory tests, US $10 for providing proof of the initial prescription fill, US $1/day for uploading daily adherence videos during weeks 5-16 (those on LAI-PrEP will receive US $1/day for weeks 4-8 and US $60 for proof of injection for weeks 9-16), US $25 each for data collection at 4-weeks and 1-weeks post baseline, US $25 for the 90-day follow-up visit with the nurse practitioner, and US $50 for completing the follow-up data collection at week 16 (US $309 possible for the entire intervention).

Control Arm

Participants randomized to the control arm will receive standard of care PrEP information along with a referral and a scheduled appointment with Allies in Hope. Transportation assistance for appointment attendance will be provided. In this agency, if there is no contraindication for PrEP, the participant will be provided a prescription for daily oral PrEP or long-acting injectable PrEP and follow up with the community-based partner per normal procedures at that facility. Allies in Hope will provide the research team with information regarding appointment attendance and whether a prescription was provided to the participant, with consent from the participant. Participants in standard treatment will continue to receive their regular SUD treatment services.

Monetary Incentives

Participants in the control arm will receive the same incentives, except for the weekly session amounts, for a possible total of US $269 for the entire study. Standard treatment participants will not have access to the Scene Health app and will be asked to respond to a daily yes or no question regarding medication adherence through REDCap (Research Electronic Data Capture; Vanderbilt University) with the same US $1/response incentive.

Data Collection

Participants in both arms will complete baseline surveys and follow-up surveys administered at 4 weeks, 10 weeks, and 16 weeks post baseline. Data sources to examine efficacy will include a computer-assisted self-interview (self-report

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measures), pharmacy records, Scene Health app data, and medical records.

Master's-prepared clinicians (eg, mental health counselors and psychologists) will conduct a comprehensive diagnostic interview using the Mini International Neuropsychiatric Interview (MINI) [60] and the National Institute on Drug Abuse Modified Assist [61]. This will be used to determine a diagnosis and severity of SUD and any co-occurring mental health disorders. Other data collection will include baseline assessment of outcome variables and potential moderators. These self-report questionnaires will be delivered through a REDCap survey. The link will be emailed or texted to the participant based on their preference. Refer to Table 1 for a description of measures and outcomes of interest.

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Table 1. Overview of phase-wide data collection methods and measures-Harris County, Texas (2021-2025).

Construct	Measure	Study week	Source
Eligibility			
SUD[a]	• Substance use and co-occurring mental health diagnoses (Mini International Neuropsychiatric Interview)	0	SUD intake records
PrEP knowledge and attitudes (based on barriers identified in aim 1)			
PrEP[b] knowledge	• PrEP knowledge questionnaire [62]	0, 4, 10, 16	REDCap[c] survey
PrEP attitudes	• PrEP Attitudes Measure [63]	0, 4, 10, 16	REDCap survey
PrEP stigma	• PrEP Anticipated Stigma Scale (PASS) [64]	0, 4, 10, 16	REDCap survey
PrEP adherence self-efficacy	• Adherence Starts with Knowledge (ASK-20) [65]	0, 4, 10, 16	REDCap survey
HIV risk behaviors	• Risk Assessment Battery [66]	0, 4, 10, 16	REDCap survey
HIV risk perceptions	• Perceived Risk of HIV Scale [67]	0, 4, 10, 16	REDCap survey
Initial efficacy (aim 3)			
PrEP eligibility	• HIV screening, viral hepatitis screening, pregnancy screening, screening for sexually transmitted diseases, and behavioral risk factors	4, 16, 4	Laboratory results Nurse interview
PrEP uptake (primary outcome)	• PrEP prescription filled and self-reported initial dose of PrEP taken	10, 16	Self-report
PrEP adherence (behavioral)	• Video-confirmed dose (intervention, daily oral PrEP) • Video-confirmed dose (intervention, long-acting injectable [LAI] PrEP, and initial oral cabotegravir) • Follow-up injection (intervention LAI) • Self-reported dose daily oral PrEP (intervention and standard treatment)	5-16 n/a and 5-16	Scene health reports, study records, study records, and weekly online survey
PrEP adherence (laboratory-confirmed)	• Tenofovir concentrations (>1000 ng/mL)	16	Laboratory results
Feasibility measures (aim 3)			
Enrollment rate	• Proportion screened who are eligible • Proportion eligible who consent	—[d]	Study records
Session attendance	• Proportion of motivational enhancement sessions attended	—	Study records
Use of Scene Health app	• Proportion of medication adherence videos uploaded	—	Scene Health reports
Study retention	• Proportion of participants who remain in the study at 12-week follow-up	—	Study records
Acceptability measures (aim 3)			
Client satisfaction	• Client satisfaction questionnaire	4, 16	REDCap survey
Other covariates			
Substance use severity	• NIDA-Modified Alcohol, Smoking, and Substance Involvement Screening Test [68]	0, 4, 10, 16	REDCap survey
Alcohol	• Alcohol Use Disorders Identification Test [69]	0, 4, 10, 16	REDCap survey
Health literacy	• Calgary Charter on Health Literacy Scale [70]	0	REDCap survey
Medical mistrust	• Group Based Medical Mistrust Scale [71]	0, 4, 10, 16	REDCap survey

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Construct	Measure	Study week	Source
Trauma	• Life Events Checklist/PTSD[e] Checklist for *DSM-5*[f] [72,73]	0, 4, 10, 16	REDCap survey
Depression	• Patient Health Questionnaire-9 [74]	0, 4, 10, 16	REDCap survey
SUD treatment attendance	• Number of substance use disorder therapy sessions attended	16	Study records

[a]SUD: Substance use disorder.
[b]PrEP: pre-exposure prophylaxis.
[c]REDCap: Research Electronic Data Capture.
[d]Not applicable.
[e]PTSD: posttraumatic stress disorder.
[f]*DSM-5: Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition).

Primary Outcome

The primary outcome of interest is PrEP uptake defined as filling the PrEP prescription and taking at least 1 dose of the medication by 2 weeks following their visit with the PrEP provider. The primary outcome will be measured at 12 weeks post completion of the 4-week motivational sessions.

Secondary Outcome

The secondary outcome of interest is daily PrEP adherence as measured by the proportion of videos uploaded showing medication being taken (intervention group only), the proportion of self-reported daily adherence (intervention and control group), levels of tenofovir (TFV) urine concentrations (>1000 ng/mL) [75] detected in urine measured at 12-weeks post-PrEP initiation (both groups). According to previous research, urine concentrations of TFV at >1000 ng/mL is indicative of use of oral PrEP in the previous 3 days (high adherence), detectable levels of TFV but <1000 ng/mL are indicative of low adherence and undetectable levels of TFV suggesting nonadherence [75]. Studies have also shown that directly observed therapy is useful for interpreting PrEP adherence. This provides an additional layer of certainty regarding this method of measuring this important secondary outcome [76]. Medication adherence for long-acting injectable PrEP will be determined by examining medical records for the timing of the dose.

Other Outcomes

Other outcomes of interest include intervention feasibility (enrollment rate, session attendance, use of Scene Health, and study retention), and intervention acceptability (client satisfaction scores).

Safety Considerations

A data safety monitoring board affiliated with the CNRA will provide oversight for this study including the possibility of loss of confidentiality. The Scene Health mobile app is HIPAA-compliant and allows for secure messaging and encrypted videos, Access to the app requires a participant to log in with credentials. Videos submitted to the app are not available in the device gallery and videos are deleted from the device once received by Scene Health's secure server. Only approved project staff will have access to the participant data via the "Backstage" by Scene Health web portal.

Statistical Analysis

Generalized linear modeling will model effects of the proportion of participants who fill their prescription and take at least one dose as a function of intervention group. In unique models, generalized linear modeling will evaluate 2 secondary outcomes as a function of intervention group: (1) dichotomous verification of adherence based on urine TFV levels >1000 ng/mL (no vs yes), and (2) TFV levels >1000 ng/mL indicating recent adherence, detectable levels of TFV but <1000 ng/mL indicating low adherence and undetectable levels of TFV suggesting nonadherence [75].

Where necessary, generalized linear mixed modeling will account for correlated observations by including random effects (eg, random intercepts or slopes for participant ID in longitudinal analyses of adherence over time). Survival analysis (ie, Kaplan-Meier estimation; Cox proportional hazards regression) will evaluate PrEP retention. Additional analyses will evaluate descriptive statistics about the enrollment rate, study retention, session attendance, and participant satisfaction. Analyses will be performed in R (R Foundation for Statistical Computing) [77]. Statistical significance will be measured at an α of <.05 for all a priori hypothesis tests. Hypothesis 3a: (primary outcome) compared with standard treatment, the intervention will result in a greater proportion of participants who fill their first PrEP prescription. Hypothesis 3b: compared to standard treatment, the intervention will result in greater adherence to PrEP in those who filled their prescriptions (self-report and laboratory verified urine tenofovir concentrations). Hypothesis 3c: the intervention will be feasible and acceptable by women as demonstrated by enrollment rate, study retention, session attendance, and participant satisfaction scores.

Ethical Considerations

This study is approved by the University of Texas Health Science Center at Houston Committee on the Protection of Human Subjects (HSC-MS-21-0451). This study is registered on ClinicalTrials.gov (NCT06158607).

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Results

A total of 25 participants were recruited to complete phase 1, qualitative interviews that informed the final intervention. Findings from phase 1 will be reported in a future manuscript. In October 2023, the investigators received institutional review board approval to conduct theater testing of the intervention (phase 2). Theatre testing has been completed with 5 participants, resulting in final refinements to the intervention. Phase 3 started in May 2024, with preliminary results anticipated by January 2025. The study team plans to publish all findings in future manuscripts and disseminate findings at future conferences and to all community partners. Refer to Figure 2 for the overall study design.

Discussion

Principal Findings

The investigators anticipate that the addiction clinic–based behavioral intervention will address the structural and social barriers often cited for their associations with a lack of PrEP uptake and adherence among racial or ethnic minority women. This intervention is innovative in its integration of PrEP services co-located with SUD treatment setting and using mobile health technology to support adherence to PrEP. Although the focus of the intervention is primarily on individual level factors (knowledge, motivation, and skills), there are some aspects of the intervention that help address interpersonal and structural level barriers. The availability of PrEP services within a familiar treatment setting removes a barrier of access for women with substance use disorder. The intervention's added focus on communication and strategies for seeking social support and knowing when and when not to disclose about PrEP use addresses interpersonal barriers. Through this intervention, the goal is that women will be empowered to engage in their own HIV prevention strategies, promote PrEP as a low-barrier and safe tool for HIV prevention, and remove potential concerns (eg, side effects, confidence in PrEP adherence, stigma from providers, family, and friends) [78,79], to reduce HIV-related disparities in Black and Hispanic women.

Limitation and Strengths

The current study is primarily limited by scale, given that this is a pilot study of HIV-negative Black and Hispanic women living in Houston, Texas, United States, findings may not be generalizable to areas with divergent demographic characteristics. In addition, participants in the control group will provide self-reported data, which may be subject to recall bias. Due to the limited nature of this pilot study mechanism, it is not possible to follow participants for a longer term as would be necessary to draw conclusions about medication adherence. This will be accomplished through a future larger-scale trial of the intervention. In addition, to test the feasibility and acceptability of the Scene Health app components, we required that participants have regular access to a smartphone. The study team's experience with this population indicates that the vast majority of participants have access to smartphones. However, this can change on an individual bases as participants have difficulties with paying bills, lose phones, etc. The study team will monitor participants' access as 1 of the aspects of feasibility for this type of intervention to be further explored in a future implementation study. Finally, participants must speak English to meet eligibility requirements, thus potentially limiting the generalizability of findings for Hispanic women who may only speak Spanish.

Despite these limitations, this study has several strengths. First, there are limited studies specifically focused on developing effective behavioral interventions for women with SUD. Second, tailoring the intervention with the use of videos and content representative of women of color has the potential to engage this population more effectively in care than existing interventions. Third, the intervention uses an app that can help support PrEP adherence by providing information, motivation, and behavioral skills necessary to increase the likelihood of starting and staying on PrEP.

Conclusions

The addiction clinic–based behavioral intervention aims to increase PrEP uptake and adherence among racial or ethnic minority women who engage in sexual, and substance use behaviors associated with HIV transmission. This addiction clinic–based behavioral intervention has the potential to reduce HIV-related disparities among Black and Hispanic women with SUDs. Findings from this study can also serve as a framework for future culturally appropriate HIV prevention interventions for women.

Acknowledgments

This work was supported, in part, by the Centers for Disease Control and Prevention of the US Department of Health and Human Services (award U01PS005209). The authors would like to acknowledge the leadership and staff of Allies in Hope, who served as advisors during the formative phase of the project. The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention.

Data Availability

The datasets generated and analyzed during this study will be available from the corresponding author upon reasonable request.

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Authors' Contributions

AH contributed to conceptualization, funding acquisition, and project administration. RS and CD managed quantitative formal analysis and methodology. AH, KE, and ZG conducted qualitative formal analysis. AH and MH conducted investigation. AH and KE managed writing-original draft. AH, DS, JS, MH, LY, and ZG managed writing—review and editing.

Conflicts of Interest

None declared.

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Abbreviations

CAB: community advisory board
CDC: Centers for Disease Control and Prevention
CNRA: Center for Neurobehavioral Research on Addiction
***DSM-5*:** *Diagnostic and Statistical Manual of Mental Disorders* (Fifth Edition)
HIPAA: Health Insurance Portability and Accountability Act
IMB: Information-Motivation-Behavioral Skills
LAI: long-acting injectable
MINI: Mini International Neuropsychiatric Interview
PrEP: pre-exposure prophylaxis
RCT: randomized controlled trial

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REDCap: Research Electronic Data Capture
SUD: substance use disorder
Take CHARGE: Theater Testing of the Cultivating HeAlth Resilience Growth & Empowerment
TFV: tenofovir

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Original Paper

Associations Among Minority Stress, Allostatic Load, and Drug and Alcohol Use in Sexual Minorities: Protocol for the Queer Health Study—a Longitudinal Feasibility Evaluation

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Abstract

Background: Substance use rates among sexual minorities are disproportionately greater than that of their heterosexual counterparts. Minority stress theory posits that one explanation for disproportionate substance use in sexual minority populations is a result of increased social stress associated with holding a minoritized identity. This minority stress has been linked to a myriad of negative mental health outcomes, including alcohol and drug use. In addition, emerging research has begun to demonstrate links between minority stress and stress physiology dysregulation. While animal and human models have demonstrated links between stress physiology dysregulation and substance use outcomes, to date, no studies have examined the role that stress physiology plays within a minority stress framework in predicting substance use among sexual minorities. The Queer Health Study was designed to explore the longitudinal links among minority stress, stress physiology (specifically, allostatic load, the cumulative "wear and tear" on the body and brain as a result of chronic stress), and substance use.

Objective: This study aims to assess the feasibility of collecting longitudinal data to explore the temporal links between minority stress processes, allostatic load, and drug and alcohol use, as well as to obtain estimates of effect size to determine the appropriate sample size necessary to conduct a fully powered longitudinal study.

Methods: This feasibility study is a 3-wave longitudinal design consisting of a self-report survey, researcher-assisted Timeline Followback to assess for drug and alcohol use, and blood and anthropometric data collection to measure allostatic load at each of the time points. A total of 40 ethnically and racially diverse sexual minority adult participants (aged 18-60 years) will be enrolled.

Results: The study received University of Houston institutional review board approval on July 31, 2023 (STUDY00004277). Recruitment began in June 2024. As of February 2025, the initial sample of 46 participants completed the time 1 visit, and time 2 visits are ongoing. We estimate that all study activities will be completed by July 2025.

Conclusions: Results can inform the development of targeted prevention and treatment interventions. In addition, this research will provide an innovative framework for exploring diverse risk and resilience factors impacting addiction in this at-risk population. Ultimately, results have important implications for public health and have the potential to reduce the many dire economic and health consequences of drug use and addiction.

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KEYWORDS

sexual and gender minorities; allostatic load; substance use; minority stress; biomarkers; LGBTQ+; health disparity

Introduction

Background

Sexual minority (SM) adults disproportionally use drugs and are at greater risk for substance use disorders (SUDs) than their heterosexual counterparts. National data revealed that SM adults were more than twice as likely as heterosexuals (39.1% vs 17.1%) to have used drugs in the past year [1]. Likewise, SM women (60.8% vs 24.3%) and SM men (65% vs 49.9%) are more likely to have a lifetime SUD compared to their heterosexual counterparts [2]. Drug use is estimated to cost society over US $193 billion annually [3,4]. Given the documented disparity in drug use and SUDs among SM adults, it is critical to understand the factors that mediate risk and resilience for drug use and abuse.

One explanation for high rates of drug use and SUDs among SMs is that increased stress related to being an SM confers risk for drug use. This social stress has been termed minority stress [5,6] and has been linked, primarily in cross-sectional research, to a variety of negative mental health outcomes [7] and alcohol and drug use [8,9].

Nascent research has begun to demonstrate that minority stress is related to stress physiology dysregulation [10]. This research demonstrated that SMs who had disclosed their sexual orientation had lower concentrations of the stress hormone cortisol than those who had not disclosed [10]. Related, Doyle and Molix [11] found that gay men who experienced more discrimination had higher levels of the inflammatory cytokine interleukin (IL)-6. Another study found that SM young adults who were raised in highly stigmatizing environments demonstrated a blunted cortisol response to a social stressor [12].

In addition to limited studies linking minority stress processes to individual markers of stress physiology, research has revealed that SMs, compared to heterosexuals, demonstrate different stress physiology patterns. For example, Juster et al [13] showed that SM men had a lower allostatic load (AL) than heterosexual men. Also, SM women displayed higher cortisol reactivity than heterosexual women; SM men, on the other hand, showed lower cortisol reactivity than heterosexual men. Mays et al [14] found that bisexual men had significantly higher AL than heterosexual men but gay men had lower AL than heterosexual men.

Currently, only a handful of studies exist that examine minority stress constructs in the context of stress physiology. However, no studies to date have examined the link between stress physiology and drug use in SM samples. Research in other populations suggests that stress physiology dysregulation, specifically, the concept of AL, may be a promising avenue for understanding drug use vulnerability and trajectory.

AL refers to the cumulative “wear and tear” on the body and brain due to repeated activation of allostatic responses resulting from chronic stress [15]. Prolonged secretion of stress hormones, through the hypothalamic-pituitary-adrenal (HPA) axis and sympathetic-adrenal-medullary axis, results in strain on interdependent systems and subsequent physiological dysregulation. Moreover, AL confers risk for accelerated aging, worsened disease trajectories, and all-cause mortality [16]. In both animal and human research, chronic stress, subsequent HPA axis dysregulation, and allostatic states, including AL, are linked to both the initiation of and trajectories of drug use [17] and addiction [18]. Indeed, stress and addiction neurocircuitry are intertwined [19].

At a theoretical level, drug addiction fits within an allostatic model in that it challenges the brain circuits involved in emotional regulation to exacerbate addiction cycles of binge and intoxication, withdrawal and negative affect, and preoccupation and anticipation [18]. Under conditions of chronic drug abuse and relapse, reward and stress pathways become dysregulated and contribute to allostatic states and AL via the HPA axis and downstream effects [20]. For example, Wand et al [21] found that stress-induced cortisol was positively correlated with both amphetamine-induced mesolimbic dopamine and the subjective positive effects of amphetamine, both risk factors for drug use initiation and addiction. Moreover, AL has been implicated in the transition from drug use to addiction, and the AL framework helps to explain the biological mechanisms undergirding both initial use and subsequent addiction [22,23].

No published research to date has explored the link between AL and drug use in SM adults. Given that SM adults face unique, chronic stressors, which are linked to AL, and are more likely than their heterosexual counterparts to use drugs and be diagnosed with SUDs, there is an urgent need to explore the mechanisms underlying drug use outcomes in this at-risk population. In addition, limited research has measured AL repeatedly over time (in any population) to explore the link between AL change and subsequent health outcomes. The limited data suggest that AL variability over time may be an important predictor of health [24]. Thus, more research is needed to understand the longitudinal links between changes in AL and health outcomes.

The Current Research

To date, no studies have comprehensively measured minority stress (ie, discrimination, internalized homonegativity, concealment, and expected rejection [5]) in research examining SM biomarkers. Moreover, most research examines single markers of stress physiology. Next, the majority of research is cross-sectional. Thus, there is a need to fully explore the impact of minority stressors on a comprehensive measure of stress physiology dysregulation using longitudinal methods. Finally, no research exists to examine the links between stress physiology and drug use in SM adults, a population with demonstrated drug use and SUD disparities. Thus, this study

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proposes that minority stressors resulting from minority sexual orientation lead to allostatic states and increased AL, which, in turn, confers risk for drug use. Figure 1 (adapted from Juster et al [25]) provides an overview of our conceptual model.

Figure 1. Conceptual model.

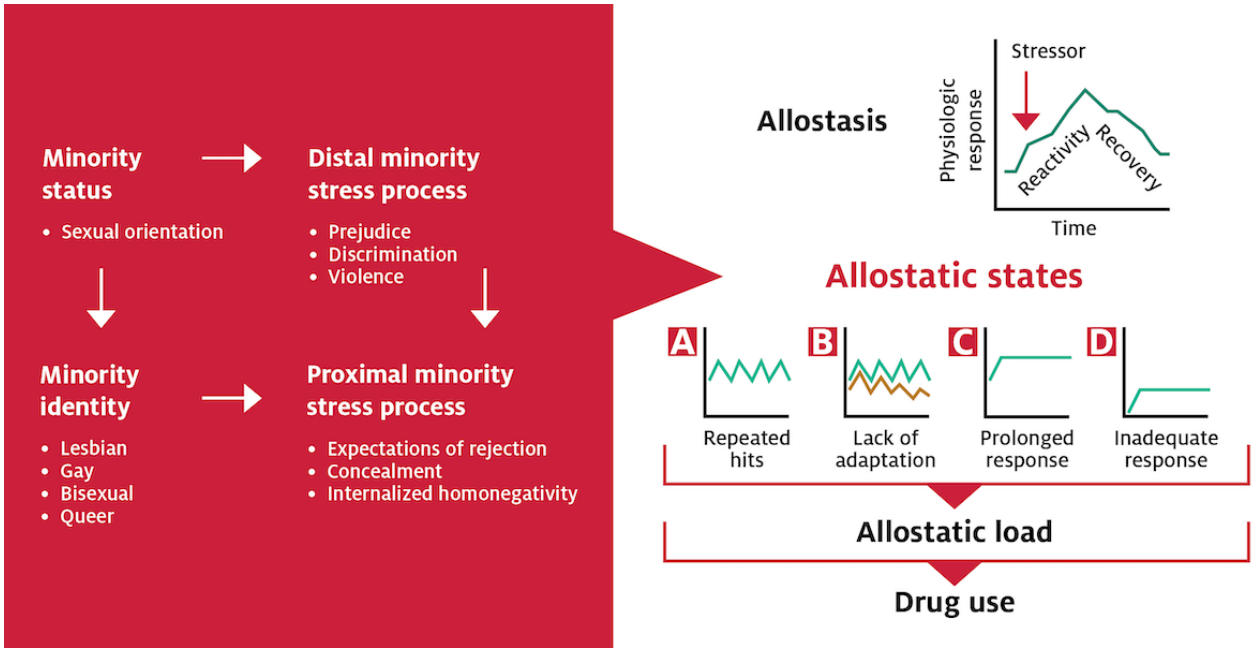

Objective

This study aims to examine the feasibility of collecting longitudinal data to examine the relationships between minority stress, AL, and drug use, following a sample of SM adults over the course of 1 year. This innovative study will be the first to explore the links between AL and drug use in this population, which has demonstrated drug-use health disparities.

This protocol proposes 3 aims:

1. Assess the feasibility of collecting longitudinal data to explore the links among minority stress processes, AL, and drug use. It is hypothesized that participants will find the study procedures acceptable, there will be minimal attrition over time, there will be minimal missing data, and the target sample size will be successfully recruited.
2. Obtain estimates of effect size. Pilot data will be used to obtain estimates of effect sizes between minority stress and AL, AL and drug use, and minority stress and drug use over 3 repeated-measures time points. These effect sizes will be used to determine the necessary sample size to conduct a fully-powered longitudinal study over a longer time period (eg, 6 time points over 2 years).
3. Explore the temporal links between minority stress, AL, and drug use. Because physiological dysregulation has been linked to the initiation of drug use, and drug use has been linked to subsequent physiological dysregulation, an exploratory aim (given the limited sample size) of this research is to test 2 competing models: (1) minority stress→AL→drug use versus and (2) minority stress→drug use→AL.

Methods

Ethical Considerations

The study received University of Houston institutional review board approval on July 31, 2023 (IRB ID: STUDY00004277).

Background

In order to test the proof of concept and feasibility, we will conduct a prospective longitudinal design with 3 time points over the course of 1 year (ie, every 4 months). These 3 time points were chosen to reduce participant burden while maximizing our ability to examine change over time. Moreover, prior research has shown statistically significant changes in AL over a 4-month period, with those who abstained from alcohol being more likely to evidence decreases in AL over 4 months [26].

A total of 40 ethnically and racially diverse SM adult participants (aged 18-60 years) will be targeted. A sample of 40 participants is consistent with sample size recommendations for pilot feasibility studies [27,28]. To address potential attrition, the first time point will over enroll by approximately 20% (approximately 48 participants to be enrolled at time 1). Participants will be limited to the age range of 18-60 years because of the impact of natural aging on AL [16]. This age range was chosen because AL steadily increases from the age of 25 years to 60 years and then plateaus [29]. Limiting to adults aged <61 years will allow us to target the age group that shows the greatest shifts in AL, maximizing chances of detecting meaningful change.

We expect to have equal proportions of female-assigned-at-birth and male-assigned-at-birth participants. Transgender individuals who also identify as SMs will be included. The racial and ethnic makeup of the sample is expected to mirror that of Houston,

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which includes non-Hispanic White (24.4%), Black or African American (22.6%), Asian or Asian American (6.8%), and Latin or Hispanic individuals (45.0%) [30].

Participants will be recruited in the metropolitan Houston, Texas, area through advertisements and events in community venues. Advertisements will include flyers in SM-inclusive bars, restaurants, and retail shops; in print/electronic advertisements (eg, Facebook, Instagram, and Grindr); and at SM community events, such as the annual Houston pride celebration (700,000 attendees annually).

Inclusion and exclusion criteria include (1) self-identification as lesbian, gay, bisexual, queer, or other nonheterosexual identity; (2) age of 18-60 years; (3) willingness to complete study tasks; (4) valid email address (for maintaining contact, such as sending appointment reminders); and (5) proficiency in English. Failure to meet any inclusion criterion will result in study exclusion.

Design

This study involves a prospective longitudinal design with 3 time points over the course of 1 year (ie, every 4 months). Participants come to the laboratory every 4 months over the course of 1 year to provide biomarkers and self-report data. At each visit, participants will complete computer-administered (Qualtrics) self-report measures and a researcher-assisted Timeline Followback to assess for drug and alcohol use. Participants will provide blood samples to assess biomarkers and have anthropometric data collected to assess for adiposity and blood pressure.

Participants will be compensated in retail gift cards (ie, Tango) for the completion of specific portions of the study. They will receive US $50 for completing each of 3 in-person assessment visits (US $150 total) and an additional US $50 for the completion of all 3 in-person assessments. In total, a participant can receive up to US $200 in retail gift cards for participating in the study.

Interested participants will complete an initial phone screening to assess for inclusion criteria. Those meeting all inclusion criteria will be given a scheduled time to come to the laboratory. Eligible participants will then complete blood draw, anthropometric measurements, and self-report measures.

Measures

At each of 3 time points, participants will complete self-report questionnaires (via Qualtrics), containing a demographic questionnaire and the measures below. All measures have good reliability and validity, and have been used with SM samples. Demographics will assess sexual orientation, sex assigned at birth, current gender identity, race and ethnicity, age, income, education, employment, occupation, relationship status, and current medications. Internalized homonegativity will be measured using the Internalized Homophobia Scale of Theodore et al [31] with edits to be inclusive of all genders, per Edwards et al [32]. Discrimination will be measured using Szymanski's [33] Heterosexist Harassment, Rejection, and Discrimination Scale. Anticipated discrimination will be measured using the Gay-Related Rejection Sensitivity Scale of Pachankis et al [34] with edits to be inclusive of all genders, per Feinstein et al [35]. Sexual orientation concealment will be measured using Jackson and Mohr's [36] Sexual Orientation Concealment Scale [36]. Intersectional stress will be measured by the Everyday Identity Stress Scale of Mereish et al [37].

Participant acceptability will be measured using quantitative and qualitative questions from the Theoretical Framework of Acceptability [38,39].

Study feasibility will be assessed via participant recruitment, enrollment, and attrition, which will be tracked following CONSORT (Consolidated Standards of Reporting Trials) guidelines [40].

In addition, we will track how long it takes to recruit the sample and calculate the proportion of missing data, usable biomarker data, participants eligible after screening, participants consented, and participants retained at each time point.

Drug and alcohol abuse consequences will be assessed via the Drug Abuse Screening Test (DAST-10) [41] and the Alcohol Use Disorders Identification Test (AUDIT) [42]. Depression will be measured by the Center for Epidemiological Studies Depression Scale [43]. Anxiety will be measured by the Generalized Anxiety Disorder-7 Scale [44]. Sleep quality will be measured using the Pittsburgh Sleep Quality Index [45]. Belongingness will be measured using the General Belongingness Scale [46]. Drug and alcohol use frequency will be assessed using 120-day Timeline Followback [47] for the following substances: alcohol, cannabis, cocaine, phencyclidine, opiates, methamphetamine (including 3,4-methylenedioxymethamphetamine and ecstasy), hallucinogens, methadone, heroin, amphetamines, barbiturates, benzodiazepines, inhalants, and synthetic cannabinoids.

Smoking will be measured using standard questions from the National Health Interview Survey [48]. Vaping will be measured by the Penn State Electronic Cigarette Dependence Index [49].

Physiologic and Anthropometric Measures

Biomarkers will include immune functioning indicators (IL-1β, -6, and -8, tumor necrosis factor-alpha, C-reactive protein, serum amyloid A, vascular cell adhesion molecule 1, and intercellular cell adhesion molecule 1), metabolic functioning indicators (glycosylated hemoglobin, high-density lipoprotein, and low-density lipoprotein cholesterol, and triglycerides), adiposity (BMI, body fat percent, and waist-to-hip ratio), and blood pressure.

Blood Collection and Assaying

A total of 10 mL of blood will be collected via venipuncture at the University of Houston by a certified phlebotomist. Samples will be centrifuged, and plasma will be extracted and aliquoted into cryovials for storage at –80 °C until assaying. All samples will be tested in duplicate; samples from the same participant will be assayed on the same plate within the same run. Validated V-PLEX Viral Panel 1 kits (ie, IL-1β, IL-6, IL-8, and tumor necrosis factor-α) and Vascular Injury Panel 2 kits (ie, C-reactive protein, serum amyloid A, vascular cell adhesion molecule 1, and intercellular cell adhesion molecule 1) from Meso Scale Discovery will be used to assay these biomarkers

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using the MESO QuickPlex SQ 120. Glycosylated hemoglobin will be measured using a Siemens DCA Vantage Analyzer. High-density lipoprotein and low-density lipoprotein cholesterol and triglycerides will be measured using CardioChek Plus, a standard point-of-care device.

Adiposity

Weight, percent body fat, muscle mass, bone mass, and percent body water will be measured using a Tanita DC-430U dual-frequency total body composition analyzer. Height will be measured using a Seca (model 217) stadiometer. BMI will be calculated using the standard formula. Body fat percentage will be calculated using sex-specific formulas (for trans participants, the average of the male and female ranges will be used). The waist-to-hip ratio will be measured with an ergonomic Seca (model 201) measuring tape, measured in cm, dividing the waist by hip circumference.

Blood Pressure

Blood pressure will be measured using an electronic sphygmomanometer (Omron model BP785N). The average of 3 systolic and 3 diastolic resting readings, taken while sitting, will be computed.

Allostatic Load

AL will be calculated using an established count-based approach [10,50,51]: for each measure, a clinical cutoff will be used such that those falling above the cutoff will score 1, while those falling below will score 0; scores will be summed to calculate AL index. This approach to AL index calculation has been used in previous studies of SM adults [10]. As an alternative to the most commonly used count-based AL index, we also will calculate a *z* score AL index that represents the sum of an individual's obtained *z* scores for each biomarker based on the sample's distribution of biomarker values, allowing the relative weight of each biomarker to be different depending on its deviation from the sample's mean [16]. We will annotate the sample collection date and time so that time can be controlled for analyses. Likewise, we will assess for current medications at each time point and control in analyses.

Participant Retention Plan

Because the research aims to follow participants over three time points, we will implement several efforts to reduce attrition [52,53]. First, regular communication from the research team will be sent to participants (with opt-in consent), such as health information communication, to continue to engage participants. We will use a graphics designer to develop a "project identity" [54] so that all paper and electronic materials have a consistent look and feel, which has been shown to increase participant identification with research projects and minimize the possibility that communication will be discarded or overlooked. Next, participant tracking procedures will be followed and will include sending reminders of upcoming appointments using participants' preferred contact methods (phone call, social media direct messaging, or email), and following up with participants who miss appointments. We will offer appointments both during the day and evenings, to help accommodate participant work schedules. Next, participants who complete all 3 assessments will be given an additional US $50 gift card. Finally, participant tracking will be integrated with research staff training; as well, participant tracking strategies and success or lack thereof will be regularly evaluated and addressed in research team meetings.

Data Analytical Plan

To address aim 1, we will track how long it takes to recruit the sample and calculate the proportion of missing data, useable biomarker data, participants eligible after screening, participants consented, and participants retained at each time point. Measures of central tendency and dispersion will be calculated for acceptability measures. Qualitative acceptability data will be analyzed via content analysis and any recommendations from participants regarding adaptation of study procedures will be evaluated for refinement of future large-scale implementation of the protocol.

To address aim 2 and exploratory aim 3, we will first examine the missing data pattern and apply imputation procedures for the missing responses following dropout, such as multiple imputation, in which each missing value is replaced with several plausible values [55]. Next, field and range checks will be conducted. Distributional characteristics will be assessed and outliers will be checked. Prior to inferential procedures, extensive descriptive statistical analyses of the outcome and predictor variables will be conducted. Standard descriptive statistics including means, SDs, ranges, box plots, histograms, and frequencies will be calculated. Normalizing transformations will be explored as appropriate. For aim 2, estimates of effect size will be calculated via Pearson correlations (or Spearman correlations, depending on distribution).

For exploratory aim 3, a longitudinal path modeling using a fully cross-lagged design [56] will be used to explore whether (1) minority stress impacts AL, which in turn impacts drug use or (2) minority stress impacts drug use, which in turn impacts AL. Because minority stress and AL will be measured at the same time, the casual directions between them cannot be established. Therefore, we will use a cross-lagged design, a special case of structural equation modeling [57], to estimate autoregressive and cross-lagged paths, allowing us to address the reciprocal influences of minority stress and AL simultaneously. Because of the longitudinal model, the autoregressive effects are modeled as lags where baseline measures are predictors of post-1 measures and post-1 measures are predictors of post-2 measures; thus, the temporal order is preserved. Given the small sample size and exploratory nature of aim 3, the model will be underpowered and at risk for increased likelihood of type II errors. As such, the results of inferential statistics will need to be interpreted with caution. Nonetheless, we will be able to observe trends and calculate descriptive statistics in the exploratory data. All analyses will be conducted using SAS (version 9.4) [58] and Mplus (version 8.4) [59].

Results

Funding for the study was approved by the National Institute of Minority Health and Health Disparities on August 1, 2023. Recruitment began in June 2024. As of February 2025, an initial sample of 46 participants completed the time 1 visit. Time 1

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was oversampled to account for anticipated attrition with the goal of achieving a total sample size of 40 that completes all time points. Approximately half of the initial sample has completed the time 2 visit, and assessments are ongoing. We estimate that all study activities will be completed by July 2025.

Discussion

It is expected that the protocol will be feasible with high participant satisfaction. The results will also provide estimates of effect size, which we will use to develop a fully powered study to be conducted over a longer time period (eg, 6 visits over 2 years). With a fully powered and larger sample size, we will be able to minimize the likelihood that the model falsely leads to a type II error. More importantly, the results will provide novel insights into the mechanisms and trajectories of drug addiction in an at-risk population and provide a useful framework for examining the role of stress physiology dysregulation in other populations at-risk for drug use disparities.

This innovative protocol is the first to propose a longitudinal study of sexual minority biopsychosocial determinants of substance use. As the only research to date that explores the interplay of neurobiological and psychosocial risk factors in drug use outcomes among SM adults, a population with demonstrated disparities in drug use and SUDs, the current research will provide an innovative framework for future research to explore diverse risk and resilience factors impacting addiction in this at-risk population. As such, this research addresses a critical health disparity.

Moreover, the outcomes of this research will provide important insights into the potential mechanisms of action for substance use trajectory and addiction, as well as offer implications for the development of interventions to reduce and prevent substance use. If results support the longitudinal links between minority stress and substance use through stress physiology dysregulation, researchers will be provided with novel insights into the mechanisms driving substance use in this population.

In addition, such results will provide clear direction for intervention development. For example, the results can influence the development of tailored interventions to directly target AL among SMs. Indeed, reducing AL has been demonstrated to be beneficial. Research in older adults has revealed that reductions over time in AL are protective against all-cause mortality, with a mortality rate of 15% for those whose AL increased over 2.5 years but only 5% for those whose AL decreased over the same time period [24]. In addition, research has revealed that behavioral interventions can reduce AL. For example, stress-reduction interventions such as transcendental meditation and yoga have demonstrated effects on reductions in AL-related variables such as blood pressure [60] and cortisol [61]. Interventions targeting minority stress in SM adults also have been developed and show promise for addressing substance use problems (eg, [62,63]). Thus, interventions that target both minority stress factors and AL may have the potential to move the needle on SM substance use outcomes. Results from this study will offer unique insights that can be used to develop tailored, interdisciplinary interventions that target multiple, modifiable risk factors for addiction.

Next, the methodological framework developed and tested in the research has the potential to serve as a model for exploring factors influencing addiction in other underrepresented populations with health disparities (see, for example, research on links between physiological dysregulation and drug use in African American young adults [64]). As noted, the results can also be used to develop innovative prevention, early detection, and treatment efforts to reduce drug use and addiction (in this and other populations) based on understanding how the interactions of biological and psychosocial factors influence drug use trajectories.

There are some limitations of the protocol to note. Participants are required to complete multiple assessments, including psychological, behavioral, and physiological measures over multiple time points. The battery has the potential to increase participant burden and impact dropout. We will review responses to our qualitative acceptability questions to determine if participants noted fatigue or viewed the protocol as burdensome and use such data to refine future studies. We will also explore attrition rates. Of note, we previously enrolled SM adults in Houston, Texas, in another study that included in-person data collection with lengthy surveys and multiple anthropometric and physiological measures. Though we did not assess for acceptability, we did not receive any unsolicited feedback regarding participant fatigue and we had minimal missing data. Moreover, the study aims were found to be feasible [65]. As noted previously, the small sample size runs the risk of type II errors, so quantitative results will be interpreted cautiously. Despite these limitations, this innovative study will provide valuable feasibility and acceptability data that will form the basis of a subsequent fully-powered study and will offer unique insights into drivers of SM substance use.

Ultimately, the research described in this protocol has the potential to reduce the many dire economic and health consequences of drug use and addiction. Moreover, the research represents a critical step in eliminating health disparities that reduce quantity and quality of life and increase health care costs.

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Authors' Contributions

NGS contributed to conceptualization, investigation, funding acquisition, methodology, project administration, supervision, and writing—original draft. TAC contributed to formal analysis and writing—original draft. RPJ contributed to methodology and writing—review & editing. EMO contributed to methodology, resources, and writing—review & editing. JSC contributed to investigation, project administration, and writing—original draft.

Conflicts of Interest

EMO is the founder and sole owner of HEALTH Equity Empowerment, LLC.

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Abbreviations

AL: allostatic load
AUDIT: Alcohol Use Disorders Identification Test
CONSORT: Consolidated Standards of Reporting Trials
DAST-10: Drug Abuse Screening Test
HPA: hypothalamic-pituitary-adrenal
IL: interleukin
SM: sexual minority
SUD: substance use disorder

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Protocol

Rationale for the Use of Acupuncture to Stabilize Blood Pressure Fluctuations During Total Laparoscopic Hysterectomy: Protocol for a Pilot Parallel-Group Randomized Clinical Trial

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Abstract

Background: Reducing blood pressure fluctuations during surgery is a key objective in improving patient outcomes. Although acupuncture has been suggested as a potential noninvasive intervention for blood pressure modulation, its effectiveness in reducing intraoperative fluctuations remains unclear.

Objective: This study aims to investigate whether acupuncture can help stabilize blood pressure during surgery, particularly in women undergoing laparoscopic hysterectomy, a procedure known to cause marked hemodynamic changes during the early intraoperative phase.

Methods: This is a prospective, single-center, randomized controlled clinical trial with a parallel-group design. Forty-eight adult patients scheduled to undergo a total laparoscopic hysterectomy are eligible for this study. Participants who provide consent will be randomly assigned in a 1:1 ratio to the acupuncture or placebo groups. They will be followed up for at least 14 days to assess the safety of the intervention, general anesthesia, and surgery. Researchers will compare the difference between the highest and lowest mean blood pressures from anesthesia induction to the postincision period as the primary endpoint. As secondary outcomes, systolic, diastolic, and mean blood pressures will be compared at each predetermined timepoint. The incidences of hypotension, hypertension, tachycardia, and bradycardia will be determined separately. The use of remifentanil at the early stage of surgery, rate of surgical discontinuation, and length of hospital stay will be assessed as surrogate indicators of stable general anesthesia and surgical procedures. For patient-reported outcomes, the Spielberger State-Trait Anxiety Inventory and EQ-5D-5L will be used to evaluate changes in anxiety and overall quality of life. This study may support the use of acupuncture as a complementary intervention to help maintain hemodynamic stability during laparoscopic hysterectomy. The study will be conducted in accordance with the Declaration of Helsinki and has been approved by the Institutional Review Board of CHA Ilsan Medical Center (ICHA 2022-11-010; date of approval: January 03, 2023).

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Results: Recruitment began in October 2023 and is expected to continue until December 2025. The intervention and data collection procedures are proceeding without major difficulties, with a dropout rate of 11.4%. As of June 2025, a total of 35 participants have been successfully recruited and randomized. Final data analysis is scheduled for completion by March 2026, and the study results are expected to be published in December 2026.

Conclusions: This trial will provide valuable evidence on the efficacy of acupuncture for stabilizing intraoperative blood pressure and supporting hemodynamic control during laparoscopic hysterectomy.

Trial Registration: ClinicalTrials.gov NCT05720884; https://clinicaltrials.gov/study/NCT05720884

International Registered Report Identifier (IRRID): DERR1-10.2196/77009

(JMIR Res Protoc 2025;14:e77009) doi:10.2196/77009

KEYWORDS

general anesthesia; blood pressure; hemodynamic; acupuncture; hysterectomy; laparoscopy; leiomyoma

Introduction

Various factors, such as the use of agents that induce anesthesia, surgery-induced stress, and hemorrhage, contribute to blood pressure fluctuations during surgery. Because blood pressure values lower or higher than the normal range can affect a patient's prognosis, reducing blood pressure fluctuations during surgery is an important goal for anesthesiologists [1,2]. A previous study reported that both hypotension and hypertension increased the oxygen demand in peripheral organs, postoperative complications, and mortality [3].

Blood pressure fluctuations that occur during anesthesia induction, tracheal intubation, and the early stages of surgery can develop rapidly within a short time due to the dynamic balance between anesthetic administration and noxious surgical stimuli. Hypotension may result from excessive analgesic or anesthetic dosing, while hypertension may arise from insufficient depth of anesthesia or sudden intense stimulation. Therefore, it is essential to anticipate the timing and intensity of such stimuli and preemptively titrate the concentration of analgesic agents to maintain hemodynamic stability. To minimize these abrupt hemodynamic changes, anesthesiologists and surgeons must perform thorough preoperative evaluations and develop individualized anesthetic plans tailored to the surgical context and patient condition [4-6].

Acupuncture is an established adjunctive therapy in anesthetic practice. Numerous studies have demonstrated that it can reduce the required doses of anesthetic and opioid agents, and alleviate postoperative symptoms such as pain, ileus, nausea, and vomiting [7]. These effects are thought to be mediated through modulation of the autonomic nervous system and nociceptive pathways, ultimately contributing to greater physiological stability throughout the perioperative period. However, despite these established effects, the role of acupuncture in directly modulating intraoperative blood pressure remains unexplored. The few available studies have primarily addressed either essential hypertension or the prevention of anesthesia-related hypotension as isolated conditions [8,9].

Notably, acupuncture has demonstrated bidirectional regulatory potential, with the capability of lowering elevated blood pressure and elevating suppressed blood pressure depending on the physiological context [10-13]. This dual effect suggests that acupuncture may serve as a stabilizing intervention for both extremes of hemodynamic instability under general anesthesia.

To investigate this, the study group designed a randomized controlled clinical trial to assess the impact of acupuncture on blood pressure fluctuations in patients undergoing total laparoscopic hysterectomy, a gynecological procedure known to cause significant hemodynamic shifts during the early intraoperative phase [14,15]. The study group hypothesized that acupuncture may contribute to overall blood pressure stability by attenuating both hypertensive and hypotensive responses in this highly dynamic setting.

Methods

Study Design

This is a prospective, single-center, randomized controlled clinical trial with a parallel-group design for blood pressure fluctuations during general anesthesia. Forty-eight adult patients scheduled to undergo a total laparoscopic hysterectomy will be included in this study. Participants who voluntarily consent to participate in the clinical trial will be randomly assigned in a 1:1 ratio to the acupuncture or placebo group. Eligible participants will be followed up for at least 14 days to assess the safety of the intervention, general anesthesia, and surgery.

The study protocol adheres to both the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (Multimedia Appendix 1) and STRICTA (Standards for Reporting Interventions in Clinical Trials of Acupuncture) guidelines (Multimedia Appendix 2). All study procedures will be performed in accordance with the Declaration of Helsinki and Korean Good Clinical Practice Guidelines. The study protocol has been registered and updated at ClinicalTrials.gov (NCT05720884), the Clinical Research Information Service, and the South Korean registration service for clinical trials (KCT0009149). This article describes the study based on protocol version 1.4 (dated November 13, 2024). The latest protocol will be updated in a timely manner for both registration sites.

Ethical Considerations

The study protocol has been approved by the Institutional Review Board of CHA Ilsan Medical Center (ICHA 2022-11-010; date of approval: January 03, 2023). Written

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informed consent will be obtained from all participants after a thorough explanation of the study's purpose and procedures, and after confirming their voluntary willingness to participate. To protect personal information, all data will be anonymized and stored using initials. Participants will receive a total compensation of 60,000 KRW (approximately US $45) for their time and involvement. Their participation may contribute to reducing perioperative blood pressure fluctuations for the broader public benefit.

This clinical study involves a data and safety monitoring board (DSMB) consisting of at least one medical clinician and a statistician. The composition and operation of the DSMB will be in accordance with the standard operating procedures of the trial. Study monitoring is scheduled to be conducted once a year. If a protocol modification is recommended, an appropriate amendment or response will be provided. If a suspected unexpected serious adverse reaction case occurs or the DSMB suspects a significant harmful association with the intervention and requests unblinding, the intervention researcher will unblind the allocation to other researchers and the committee, and submit the unblinded interim results.

Eligibility

Participants scheduled to undergo surgical removal of the uterus for uterine fibroids and those who have an expected date of total laparoscopic hysterectomy by a gynecologist are eligible. The specific inclusion criteria are as follows: (1) age between 19 and 69 years, (2) American Society of Anesthesiologists (ASA) class I or II, (3) requirement for surgical removal of the uterus by a gynecology specialist, and (4) scheduled to undergo total laparoscopic hysterectomy in advance. All participants will be required to understand and agree with the study protocol. A delegated researcher or research coordinator will obtain written informed consent from all participants.

Participants under the following conditions or situations are ineligible: (1) survival expectancy of less than 3 months; (2) emergency operation, which was not scheduled in advance; (3) hypertension or hypotension that can significantly interfere with the study result; (4) diagnosis of arrhythmia, such as atrial fibrillation and frequent ventricular or supraventricular premature beats; (5) diagnosis of heart failure or valvular disease; (6) anemia with hemoglobin level <12 g/dL; (7) incapable of surgery due to hemodynamic or medical reasons other than stated above; (8) incapable of receiving acupuncture treatment on the determined location; (9) current use of gonadotropin-releasing hormone receptor agonists; (10) current use of drugs that may interfere with the result, including steroids, immunosuppressants, and drugs for psychiatric disorders; (11) significant comorbidities that may interfere with the interpretation of intervention efficacy or results, such as stroke, myocardial infarction, kidney disease, dementia, or epilepsy; (12) pregnant, planning to be pregnant within the study period, or breastfeeding; (13) previous participation in any other clinical trial within 1 month of participation, planning to participate in another clinical trial within 6 months after the enrollment date, or planning to participate in another clinical trial in the follow-up period; (14) failure to complete the informed consent form voluntarily; and (15) being deemed to be unsuitable for participation.

Randomization and Allocation

Eligible participants who sign the informed consent form will be randomly assigned to the acupuncture or placebo group in a 1:1 ratio. Random sequences will be generated by permuted block randomization of block size 2 or 4 using the random allocation tool in R software 4.1 (R Foundation for Statistical Computing). Random sequence generation will be performed, and random sequences will be determined by an independent statistician prior to enrollment. Only the statistician who generates the random sequence will be aware of the full randomization sequence.

Each random sequence will be sealed in an opaque envelope and stored in a double-locked cabinet. The delegated researcher or research coordinator will explain the trial process to the candidate, obtain written informed consent, open the randomization envelope for each participant, and assign them to an appropriate group.

Intervention researchers will perform acupuncture or placebo acupuncture according to their assigned group. The intervention researchers will stay unblinded because the researchers will perform different interventions according to the group. However, the researchers will separate the person and location to maintain anonymization as robustly as possible. The participant, assessor, and statistician will be blinded, and the location where the intervention is performed will be separate from the location where the assessment will be performed. Interventions will be performed in the ward, and assessments will be performed in the operating room.

Intervention

Acupuncture will be performed with a disposable, sterilized, stainless steel needle measuring 0.20 × 30 mm (Dongbang Medical) in both groups. Ten acupoints (PC6, PC5, SP3, KI3, and ST36) will be chosen bilaterally for the intervention group (acupuncture group). The depth of acupuncture varies (1 to 1.5 cm) among the participants. After acupuncture needles are inserted, they will be manually manipulated to obtain a predetermined sensation, De Qi. Acupoints PC6 and PC5 will be inserted with depth adjustment to reach the anatomical plane right above the median nerve, thereby facilitating a more prominent sensation. Acupuncture will continue for 20 minutes. Ten other points that are not official acupoints and are not on the median or peroneal nerve will be chosen for the placebo group. An acupuncture needle depth of 0.5 cm will be used.

Acupuncture or placebo will be administered 2 times during the first and second visits. Administration will be done by a qualified acupuncturist who is a physician in Korean medicine with 10 years of clinical experience, independent of the anesthesia team.

Study Process

After a sufficient explanation of the purpose and methods of this clinical study by a researcher, subjects who voluntarily decide to participate and sign a written consent form will be evaluated for eligibility at the screening visit. Eligible subjects

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will be randomly assigned to the acupuncture or placebo control group according to randomization. Acupuncture treatment will be performed twice, one day before surgery (V1) and on the day of surgery (V2).

All intraoperative management and outcome assessments will be independently performed by anesthesiologists who are not involved in the acupuncture procedure. All participants will fast for 6-8 hours prior to surgery. After entering the operating room (V3), electrocardiography, pulse oximetry, and monitoring of the partial pressure of end-tidal carbon dioxide (IntelliVue MX550; Phillips North America Corporation) will be performed continuously. Automated oscillometric measurements of blood pressure at 2.5-minute intervals and "train of four" (TOF) (ToFscan; Drager Technologies) assessments will also be performed. Throughout the surgery, these data will be downloaded to personal computers using RS232C cables.

After checking the initial vital signs (heart rate, blood pressure, and oxygen saturation) (P1), anesthesia will be induced intravenously with propofol (1-2.5 mg/kg) and remifentanyl (0.01-0.1 ng/kg/min). Mask ventilation (P2) with desflurane will be performed after the administration of rocuronium (0.6-1 mg/kg). Once the TOF ratio reaches <2, the anesthesiologist will perform tracheal intubation (P3). The lungs of the subjects will then be ventilated with desflurane and oxygen in air (FiO2=0.5), and the tidal volume and ventilation rate will be adjusted to maintain the partial pressure of end-tidal carbon dioxide between 35 and 45 mmHg. An additional venous tube will then be secured (P4).

With the patient in the lithotomy position and under general anesthesia, the abdomen will be prepared, painted, and draped in the usual manner (P5). The uterine elevator will be inserted. A skin incision will be made (P6), and a trocar will be inserted. CO_2 gas will be infused to create a pneumoperitoneum at a pressure of 12 mmHg (P7). After entering the abdominal cavity, the patient's position will be changed to the Trendelenburg position. The pelvic cavity and the entire abdomen will then be examined. The bilateral pelvic sidewall triangles will be opened parallel to the infundibulopelvic ligament, and ureteral dissection will be performed. The ureteral course will be identified, and the right round and ovarian ligaments will be coagulated with a bipolar endocoagulator and cut with endoscissors. The left uterine ligament will be manipulated using the method described above. The bladder flap will be pushed, and the posterior broad ligament will be mobilized. The bilateral uterine vessels will be skeletonized, coagulated, and cut. Circumferential colpotomy will be performed by using unipolar scissors. The uterus will be removed transvaginally, and the vaginal cuff will be closed using continuous intracorporeal sutures. Hemostasis and ureteral peristalsis will be ensured, and the abdominal cavity will be irrigated with normal saline. The subcutaneous tissue and skin will be closed layer by layer.

During the procedure, the infusion rate of remifentanil and the concentration of desflurane (6.0-7.0 vol%) will be adjusted to maintain stable hemodynamic values (systolic blood pressure >80 mmHg; heart rate >45 beats/min) and an appropriate depth of anesthesia (>1 minimal alveolar concentration). If necessary, ephedrine or atropine will be administered to maintain stable hemodynamic values. All decisions will be made by a qualified anesthesiologist with at least 10 years of clinical experience.

The neuromuscular blockade will be reversed by administering sugammadex (2-5 mg/kg) at the end of the surgery, and the patient will be confirmed to be fully awake (TOF >0.9) and transferred to the postanesthetic care unit (P8).

By participating in this clinical study, the study participants will not be restricted from receiving rescue medicine required in the surgical process. If rescue medicine or rescue treatment is administered, the researcher will record the combination of therapy and rescue medicine in a case report form.

Since the intervention will be conducted over a short period, strategies for study adherence have been deemed unnecessary. However, to improve adherence, follow-up surveys will be conducted both online and offline. The online platform data are only accessible to the principal investigator and the delegated research coordinator. Other data will be electronically locked or stored in a document archive accessible only to researchers for the duration of the study and for 3 years after its completion.

Outcome Measures

To investigate the efficacy of acupuncture on initial blood pressure fluctuations during laparoscopic hysterectomy, we will compare the difference between the highest and lowest mean blood pressures from the induction of anesthesia to the postincision period as the primary endpoint. As secondary outcomes, systolic, diastolic, and mean blood pressures will be compared at each predetermined timepoint. The incidence of hypotension (systolic blood pressure <90 mmHg or 80% of the baseline), hypertension (systolic blood pressure >160 mmHg or 120% of the baseline), tachycardia, and bradycardia will be recorded. The total use of remifentanil, surgical discontinuation, and length of hospital stay will be assessed as surrogate indicators of stable general anesthesia and surgical procedures.

For patient-reported outcomes, the Spielberger State-Trait Anxiety Inventory (STAI) and EQ-5D-5L will be used to evaluate changes in anxiety and the overall quality of life. The STAI was first validated in 1996 [16,17]. The STAI consists of 40 questions divided into 2 categories: 20 items assessing state anxiety and 20 items assessing trait anxiety. State anxiety refers to experiencing anxiety at the moment, while trait anxiety refers to the type and characteristics of anxiety.

The EQ-5D-5L will be used to assess the effects on the patient's quality of life. The questionnaire consists of questions in 5 areas: mobility, self-care, usual activities, pain, and anxiety/depression. The EQ-5D-5L assesses the patient's current state of health. Responses will be provided on a 5-point Likert scale [18].

The study process and timepoints are presented in Figure 1.

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Figure 1. Timetable and outcome measurements. NRS: numeric rating scale; STAI: State-Trait Anxiety Inventory. *After the intervention, preoperative, and prior to anesthesia induction.

	Study period					
	Screening	Allocation		Follow-up		
Timepoint	V0 (outpatient department)	V1 (D1)	V2 (D2, ward)	V3 (D2, operation room)	V4 (recovery unit)	V5 (D16)
Enrollment						
Written informed consent	✓					
Eligibility screening	✓					
Vital signs	✓	✓	✓			
Sociodemographic characteristics	✓					
Medical history	✓	✓				
Randomized allocation		✓				
Interventions						
Acupuncture/placebo		←	→			
Compliance to intervention				✓		
Assessments						
Blood pressure (peripheral)			✓	✓	✓	
NRS					✓	
Incidence of hypertension/hypotension					✓	
Heart rate			✓	✓	✓	
Total remifentanil					✓	
STAI		✓		✓*		
EQ-5D		✓		✓*		
Credibility and expectancy	✓	✓				
Drug consumption		✓	✓	✓	✓	
Adverse events		✓	✓	✓	✓	✓
Length of hospital stay						✓

Concomitant Care

The participants are not restricted from concomitant care, similar to the conditions in an actual clinical environment. They can choose any type of combination therapy and any necessary salvage treatment throughout the hospitalization period. Researchers will document these therapies in the case report form. Documentation of these therapies will include the type, dosage, route of administration, frequency, and purpose.

Safety

Safety will be evaluated by grading the severity of the symptoms or medical conditions. Adverse events will be defined according to MedDRA 24.0, and causality will be assessed according to the World Health Organization-Uppsala Monitoring Centre (WHO-UMC) Causality Assessment. The severity of subjective and objective symptoms will be evaluated according to the Common Terminology Criteria of Adverse Events version 5.0.

The clinical study is covered by liability insurance to compensate for any foreseeable or unforeseeable harm that may occur during the research process.

Sample Size

No prior clinical trial has examined the effect of acupuncture on intraoperative blood pressure fluctuations. As acupuncture

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is applied as an adjunct to propofol-based general anesthesia in this study, sample size estimation is based on a study comparing mean arterial pressure (MAP) variability between remimazolam and propofol anesthesia [19], which reported MAP fluctuations of 26.7 (SD 9.1) mmHg and 19.5 (SD 7.5) mmHg, respectively. Although the interventions differ, this dataset was considered the best available proxy for estimating between-group differences in MAP variability under general anesthesia.

Using these values, 21 participants per group would be required to achieve 80% power with a 2-sided α of .05 when employing the *t*-test modules, considering that this study is a pilot trial. Assuming a 10% dropout rate due to the short follow-up period, the final sample size has been set at 24 participants per group, totaling 48. All calculations are performed using G*Power version 3.1.9.7 (Heinrich-Heine-University Düsseldorf).

Statistical Analysis

Both intention-to-treat and per-protocol analyses will be performed, with intention-to-treat being the primary analysis. For per-protocol analysis, the study participants who successfully complete the surgery will be analyzed separately. Successful completion of the surgery is defined as the completion of the scheduled total laparoscopic hysterectomy under general anesthesia without protocol violations, conversion to open surgery, early termination due to intraoperative complications, or major deviations from the anesthetic protocol, such as changes in the anesthetic agents beyond the predefined regimen. For handling missing data, multiple imputations will be performed to obtain estimates and standard errors by setting 10 imputation sets.

The primary endpoint of this clinical trial is the difference between the highest and lowest mean blood pressure measured from anesthesia induction to the postincision period. The Student *t* test will be used to test whether the difference between the 2 groups in the primary endpoint is statistically significant. To account for potential confounding factors affecting the primary outcome, a multivariable linear regression analysis will be conducted. Covariates will include the placebo credibility score (at V1 and V2), anxiety levels (as measured by the STAI and EQ-5D), baseline ward blood pressure (V2), and preoperative blood pressure measured in the holding area prior to operating room entry (V3).

In addition to the primary outcome, secondary outcomes will include hemodynamic stabilization time, incidence of hypotension and hypertension, comparison of drug use, and other efficacy endpoints, including STAI scores. Differences between the 2 groups will be compared using the Student *t* test or Wilcoxon rank sum test, unless otherwise specified. The 2 groups will also be compared by estimating the ratio between the blood pressure measured at each timepoint and that measured at V2, using the blood pressure at V2 as the baseline. Because blood pressure is measured repeatedly, it is not possible to assume independence between measurements; thus, generalized estimating equations will be used. To estimate this ratio, measurements will be log-transformed and included in the model. The 2 groups will be compared using the same method for the pulse rate measured at V2 and the pulse rate at each timepoint. To quantify the length of hospitalization in both groups, we will use Kaplan-Meier estimation to estimate the time until 50% of the participants are discharged. The log-rank test will be used to determine differences in the distribution of discharge times between the 2 groups.

The significance level for all analyses is set at .05. All statistical analyses will be performed using SAS 9.4 (SAS Institute, Inc) or R software 4.1 (R Foundation for Statistical Computing).

Results

Recruitment for the study commenced in October 2023 and is ongoing, with enrollment expected to continue through December 2025. The flow diagram of the trial is shown in Figure 2. As of June 2025, a total of 35 participants have been successfully recruited and randomized. Although the intervention and data collection procedures have been proceeding without major difficulties, the overall pace of recruitment has been slower than anticipated. This is primarily due to fluctuations in surgical scheduling and staffing capacity caused by medical strikes in the Republic of Korea [20].

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Figure 2. Flow diagram of the trial.

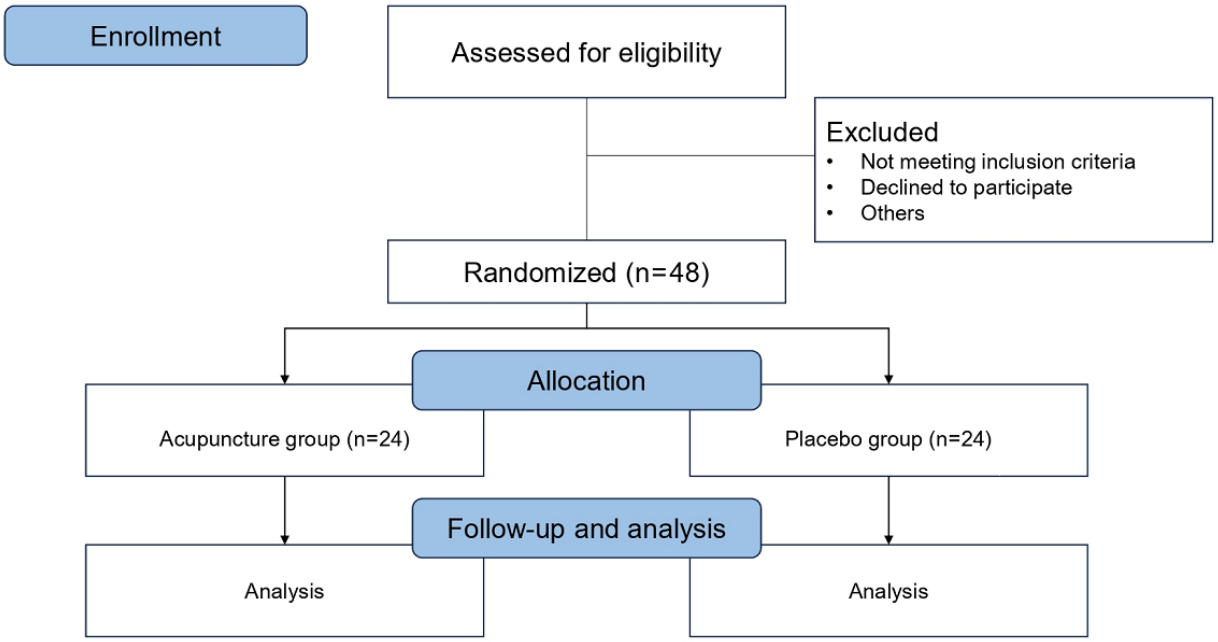

All participants enrolled thus far are female, reflecting the eligibility condition of requiring total laparoscopic hysterectomy. The mean age of the enrolled participants is 48.3 years. The current dropout rate is 11.4%, and up to the time of this protocol description, all reported adverse events have been mild and unrelated to the intervention.

Final data collection is projected to be completed by December 2025, which will be followed by data cleaning and statistical analysis through March 2026. Publication of the main study results is expected in the latter half of 2026.

Discussion

The primary role of anesthesiologists during surgery extends beyond maintaining unconsciousness to actively minimizing the physical stress induced by intraoperative stimuli. These stimuli include not only surgical manipulation but also the administration of anesthetics and analgesics, which, while essential, can disrupt homeostasis and result in intraoperative hypotension. Factors, such as surgical bleeding and patient positioning, may exacerbate this effect. Even in patients without comorbidities, sustained hypotension has been associated with poor postoperative outcomes [21,22], and hypertensive episodes during surgery, often a sign of inadequate analgesia, are similarly linked to increased risks of major adverse cardiovascular events [3]. Thus, maintaining blood pressure within a target range is an important goal of anesthetic management.

Laparoscopic hysterectomy is a procedure often associated with significant hemodynamic fluctuations, particularly in the early intraoperative period. Pneumoperitoneum and Trendelenburg positioning may stimulate sympathetic activation or trigger vasovagal reflexes, resulting in rapid changes in blood pressure [15,23,24]. Anesthesiologists must anticipate nociceptive stimuli, such as tracheal intubation and skin incision, and preemptively adjust opioid administration to ensure hemodynamic stability [25,26]. However, due to interindividual variability and the pharmacokinetics of agents like remifentanil, achieving consistent control is challenging [27,28]. Although remifentanil's rapid onset and offset allow precise titration, excessive dosing has been linked to adverse effects such as delayed emergence, postoperative nausea and vomiting, and opioid-induced hyperalgesia [29]. Because of these dose-related risks and the challenge of achieving consistent hemodynamic control, minimizing remifentanil use without compromising analgesia is a meaningful anesthetic goal. Reflecting this, the amount of remifentanil administered during the early surgical phase has been included as a secondary outcome in our study, aligning with the broader goal of minimizing opioid use while preserving analgesic efficacy [30,31]

Acupuncture has been proposed as a supportive technique to anesthesia, with studies reporting its potential to reduce anesthetic requirements, alleviate perioperative anxiety, and improve postoperative recovery [32,33]. Given its low invasiveness and favorable safety profile (characterized by mostly minor local reactions and rare treatment-requiring events), acupuncture remains a feasible adjunct in the perioperative setting [34]. Although its role in intraoperative blood pressure regulation remains under investigation, emerging evidence points to its influence on autonomic nervous system modulation. Functional magnetic resonance imaging studies have demonstrated that acupuncture alters hypothalamic connectivity, a key brain region involved in cardiovascular control [13]. Additionally, acupuncture has been shown to attenuate hemorrhage-induced hypotension in animal models and lower systemic blood pressure in patients with hypertension [10,35,36].

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Outside the perioperative setting, acupuncture has shown clinically meaningful effects in reducing blood pressure among patients with essential hypertension. For example, studies by Flachskampf et al [35] and Yin et al [36] reported significant reductions in systolic and diastolic blood pressure after 6 to 8 weeks of repeated acupuncture sessions [10], whereas studies with shorter durations (15-25 days) failed to demonstrate such benefits [37]. Overall, although the long-term use of acupuncture therapy has blood pressure–lowering effects of 4-10 mmHg in patients with uncontrolled hypertension, the effects of short-term acupuncture therapy on blood pressure fluctuations have not yet been clearly established.

One important limitation in previous studies assessing acupuncture as an anesthetic adjunct is the timing and duration of stimulation [38]. Acupuncture requires adequate time to induce physiological effects, with analgesic effects typically emerging 20 minutes after needle insertion and lasting for just several hours. Therefore, acupuncture initiation only shortly before or during anesthesia may have different physiological potential, particularly because volatile anesthetics can suppress neural pathways responsive to acupuncture.

In this context, the selection of acupoints in the treatment group was based on previous studies demonstrating their physiological relevance in autonomic modulation and cardiovascular regulation. Specifically, PC5, PC6, and KI3 have been widely associated with reductions in perioperative anxiety and stabilization of heart rate variability, while ST36 is well-documented for its influence on vagal activation and blood pressure regulation. SP3 has been included for its role in supporting systemic homeostasis. For the selection of placebo acupoints, the following 3-fold strategy has been considered to minimize specific physiological stimulation: (1) if possible, a sham needle is preferable; (2) points should avoid all recognized World Health Organization acupoints and should not be situated along any known meridian pathways; and (3) anatomical regions are restricted to outside the limbs, where the treatment acupoints are applied. Since the use of nonpenetrating sham needles is not possible due to product discontinuation, the other 2 strategies have been used for the placebo group.

Our study protocol was designed to optimize the timing of acupuncture application, administering stimulation at 2 timepoints, once on the day before surgery and again on the morning of the surgery, which would allow a sufficient lead time before anesthesia induction. This schedule was chosen based on both clinical feasibility and physiological rationale. As patients are routinely admitted the day before laparoscopic hysterectomy, it is practical to deliver acupuncture during the hospital stay without requiring additional outpatient visits. Moreover, this repeated, preoperative approach provides a longer stimulation window than the approach in most prior studies evaluating acupuncture as an anesthetic adjunct, which typically applied stimulation only shortly before or during anesthesia. While the duration remains shorter than long-term outpatient regimens used for chronic hypertension, it represents a balanced and realistic timeframe to allow acupuncture's physiological effects to manifest before the influence of general anesthetics begins, potentially enhancing its effectiveness in modulating intraoperative hemodynamics.

Another strength of our design is the inclusion of psychological covariates to explore individual variability in response. Although not a primary or secondary endpoint, researchers have incorporated validated tools, such as the Spielberger STAI and EQ-5D-5L, to assess baseline anxiety and quality of life. These tools enable exploratory analysis of whether the psychological state moderates the physiological effects of acupuncture, helping to distinguish autonomically mediated responses from those influenced by psychological factors. This addresses a common limitation of prior acupuncture trials, which often did not account for patient-level psychological differences.

For our primary outcome, researchers chose absolute thresholds of MAP, rather than relative changes, due to inconsistencies in baseline blood pressure definitions in perioperative settings. Establishing a reliable baseline for relative changes is challenging, as preinduction blood pressure often differs from values obtained during preoperative evaluation [38], and normal blood pressure levels can vary depending on individual conditions and circadian rhythms [39]. Given these limitations, researchers have adopted standardized MAP thresholds: values below 65 mmHg are associated with impaired organ perfusion, while sustained elevations above 80 mmHg may increase the risk of major adverse cardiovascular events [40]. These thresholds align with intraoperative blood pressure management goals, providing a clear rationale for selecting them as our primary outcome measure. This standardization, along with the use of 2.5-minute noninvasive blood pressure monitoring, enables close tracking of blood pressure changes during the highly dynamic early intraoperative phase [41].

Despite its strengths, our study protocol has several limitations. First, as with most acupuncture trials, blinding of the practitioner is not feasible. In this study, however, acupuncture is administered preoperatively by a certified traditional medicine physician in the ward, while intraoperative management and outcome assessments are independently performed by anesthesiologists in the operating room. This structural separation minimizes the risk of performance and detection bias. Additionally, outcome assessors remain blinded to group allocation throughout the trial. Second, this is a single-center exploratory study, which may limit the generalizability of the findings. Nevertheless, the trial's methodological strengths, including the timing and repetition of acupuncture, the incorporation of psychological covariates, and the focused monitoring of intraoperative blood pressure, enhance its internal validity and potential clinical relevance.

In summary, this randomized controlled trial is designed to evaluate whether preoperative acupuncture, applied at 2 timepoints, can help stabilize intraoperative blood pressure during laparoscopic hysterectomy. By addressing both physiological mechanisms and psychological factors, the study aims to clarify the short-term effects of acupuncture on hemodynamic stability in a controlled surgical setting. The results may provide useful evidence on the feasibility and potential benefits of incorporating acupuncture into perioperative care to reduce blood pressure fluctuations and minimize opioid requirements.

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Data Availability

Publication is scheduled for December 2026. The data will not be publicly available but can be requested from the corresponding author.

Authors' Contributions

Conceptualization: JL and JWR; methodology: KHH and JL; writing – original draft preparation: KHH, JYL, and JL; writing – review and editing: BSY, YJN, and JL; visualization: JYL; supervision: JWR; project administration: YJN and MJK; funding acquisition: JYL. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 52 KB - resprot_v14i1e77009_app1.pdf]

Multimedia Appendix 2
STRICTA (Standards for Reporting Interventions in Clinical Trials of Acupuncture) checklist.
[PDF File (Adobe PDF File), 30 KB - resprot_v14i1e77009_app2.pdf]

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Abbreviations

DSMB: data and safety monitoring board
MAP: mean arterial pressure
STAI: State-Trait Anxiety Inventory
TOF: train of four

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Protocol

A Recovery-Oriented Suicide Prevention Program Led by Peer Specialists for Veterans With Serious Mental Illness: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Veterans with serious mental illness (SMI) have significantly elevated suicide risk compared to those without SMI. This group may also experience cognitive and functional impairments that complicate suicide prevention care.

Objective: We detail a pilot randomized controlled trial protocol evaluating a novel peer specialist–delivered suicide prevention intervention tailored to SMI called Suicide Prevention by Peers Offering Recovery Tactics (SUPPORT). In SUPPORT, peer specialists are trained in foundational suicide prevention information and intervention delivery. Once a week for 50 minutes, a peer specialist meets with a veteran via telehealth or in person to deliver the 4 SUPPORT modules that focus on recovery and suicide prevention. The peer specialist conducts 2 check-in calls at 2 and 4 weeks after the final module to reinforce the intervention material and offer additional resources. Aim 1 will evaluate the feasibility and acceptability of SUPPORT. Aim 2 will determine the preliminary impact of SUPPORT versus enhanced standard care on personal recovery and suicide ideation severity (primary outcomes), as well as domains of veteran functioning (secondary outcomes). Standard care is enhanced such that all veterans receive additional suicide risk assessment, which may result in additional clinical interaction.

Methods: A pilot randomized controlled trial with 50 veterans randomized into 2 groups will be conducted. Participants will be recruited from the Veterans Affairs San Diego Healthcare System. Veterans with SMI and past-1-month active suicide thoughts or past-3-month suicide behavior as defined by the Columbia–Suicide Severity Rating Scale will be included. Enrolled veterans will be randomized to receive SUPPORT or enhanced standard care. All veteran participants will be assessed at baseline and the 1-, 2-, and 3-month follow-up assessments. Feasibility is defined as attainment of recruitment goals and a ≥70% retention rate. Acceptability for veterans is measured using the Client Satisfaction Questionnaire–8. Acceptability for peer specialists is measured using a satisfaction question rated on a 5-point Likert scale. Primary outcomes are measured using the Recovery Assessment Scale–41 (personal recovery), as well as the Beck Scale for Suicide Ideation and the Columbia–Suicide Severity Rating Scale (suicide ideation severity). Secondary outcomes are measured using the Specific Level of Functioning Scale (functioning), the brief version of the World Health Organization Quality of Life Scale (quality of life), and a laboratory-developed self-knowledge task (suicide prevention strategy recall). Outcomes will be tested using mixed-effects models. Safety procedures for all participants are discussed.

Results: This trial was funded in November 2022. Community-engaged intervention and protocol refinement were completed in January 2025. Data collection for the randomized controlled trial began in January 2025.

Conclusions: By combining training for peer specialists with a novel recovery-oriented suicide prevention intervention, SUPPORT helps establish a role for peer specialists in suicide prevention and addressing suicide in veterans with SMI.

Trial Registration: ClinicalTrials.gov NCT05537376; https://clinicaltrials.gov/study/NCT05537376

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KEYWORDS

peers; peer support; recovery; suicide prevention; veterans; serious mental illness

Introduction

Background

Among the veteran population, those with a serious mental illness (SMI), particularly veterans with bipolar disorder or schizophrenia spectrum disorders, are at markedly elevated suicide risk compared to veterans without SMI and nonveterans with SMI [1]. Making suicide prevention care challenging, people with SMI are often excluded from suicide-related treatment options [2,3]. There are also different means of suicide used, such as self-stabbing [4], as well as functional and cognitive impairments that may alter uptake of suicide prevention strategies in this group [5,6]. To address these unmet needs, we provide the rationale, design, and clinical pilot randomized controlled trial protocol for a novel augmentative peer-delivered, recovery-oriented suicide prevention intervention for veterans with SMI.

Several psychosocial rehabilitation initiatives in the Veterans Health Administration (VHA) have included individuals with lived experience ("peers," now known as "peer specialists") to support veterans with a wide range of mental health experiences [7]. In the context of VHA mental health care, peer specialists are defined as veterans with lived experience in recovery [8] from mental illness who are specifically trained, certified, and employed [9] to share their recovery story to support other veterans also experiencing mental illness [10,11]. Numbering approximately 1400 in VHA in 2024, peer specialists play an adjunctive yet integral role in VHA health care [7,12]. However, there is a dearth of existing interventions that use peer support services in suicide prevention initiatives [13-15] Reviews of this literature have concluded that the use of peer specialists for suicide prevention is feasible [13,14]. VHA peer specialist administrative data show that 8% are already working directly with veterans at high risk of suicide [16]. Moreover, peer support has been shown to be a positive adjunct to VHA suicide prevention initiatives by filling an existing gap [17]. Although there is limited suicide prevention training for peer specialists, VHA peer specialists report interest in receiving such specific training [11,18]. Thus, there is a tremendous opportunity to involve peer specialists in VHA suicide prevention initiatives.

Objectives

The Suicide Prevention by Peers Offering Recovery Tactics (SUPPORT) program was co-developed by peer specialists and veterans with SMI along with scientific experts in the field [18]. The SUPPORT program includes training tailored to a peer's scope of practice in suicide prevention (SUPPORT 101) and a recovery-oriented suicide prevention intervention (SUPPORT intervention) that was designed for and tailored to the unique experiences of veterans with SMI. This paper describes a protocol for a pilot randomized controlled trial aiming to preliminarily evaluate this peer specialist-delivered suicide prevention intervention program for veterans with SMI. The specific aims of this pilot study are as follows:

1. To evaluate the feasibility and acceptability of SUPPORT versus enhanced standard care. We hypothesize that SUPPORT will be feasible to deliver, as measured through attainment of recruitment goals and retention rates of ≥70%, with high satisfaction ratings.
2. To determine the preliminary impact of SUPPORT compared to enhanced standard care on personal recovery, suicide ideation severity, and domains of veteran functioning to determine whether a larger trial is warranted. We hypothesize that SUPPORT compared to enhanced standard care will yield greater enhancement of personal recovery and reduction in suicide ideation severity (primary outcomes), as well as enhanced psychosocial functioning, quality of life, and suicide prevention strategy recall.

Methods

Setting

This pilot randomized controlled trial is taking place in the Veterans Affairs (VA) San Diego Healthcare System. Recruitment sites are the medical center and the community-based outpatient clinics providing behavioral health care services.

Ethical Considerations

The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) reporting guidelines for clinical trials were used [19]. The trial was registered on ClinicalTrials.gov (NCT05537376; see Multimedia Appendix 1). This protocol was approved by the VA San Diego Healthcare System institutional review board (H210132). The institutional review board requires regular updates on the status of the project, including the number of participants enrolled, adverse events or unanticipated problems, number of withdrawals from the project, complaints about the research, and any protocol changes. The institutional review board also audits the consent forms quarterly and ensures that appropriate HIPAA (Health Insurance Portability and Accountability Act) information is included, with full regulatory audits taking place every 3 years. Taken together, the use of these methods allows for adequate evaluation of and response to the data and safety monitoring of both potential enrollees and actual participants.

All participants will provide written informed consent, as detailed in the Recruitment, Screening, and Enrollment Procedures section. It is clear in the consent form that SUPPORT is the experimental condition that is being added to the standard care that a veteran would receive. As part of informed consent, participants are told that they may withdraw from the study at

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any point without penalty, VHA will cover any care if harm occurs as part of their participation, and veteran participants randomized to SUPPORT may drop out of the intervention and continue with research assessments. Data collected are stored separately from protected health information, including electronic data that are only stored on the VHA network and are password protected, whereas hard copy data remain on VHA property behind 2 locks. Data are only accessible by those approved on the institutional review board protocol. Veteran participants are compensated with up to US $260 for completing all research assessments. Peer specialist participants are not eligible for monetary compensation due to their VHA employment and the federal funding mechanism; they are delivering the intervention as part of their regular tour of duty. Due to the nature of peer services being augmentative, all veteran participants are encouraged to maintain their other ongoing behavioral health care.

Participants

Peer Specialist Participants

All VA San Diego Healthcare System–employed certified peer specialists are potentially eligible to be recruited into the study. All local peer specialists will be invited to the SUPPORT training as a service to the medical center per conversations with local leadership, although they must meet inclusion criteria to deliver the SUPPORT intervention. All VHA employees are required to maintain basic competencies in suicide prevention screening and referral procedures [20]. Thus, study inclusion criteria are (1) a minimum of 2 years of experience after certification as a peer specialist and (2) provision of verbal or written consent by the peer specialist for research staff to discuss their ability to participate with their direct clinical supervisor. The peer specialist's direct clinical supervisor must agree to allow the peer specialist time as part of their current scope of practice to (1) participate in the 8-hour SUPPORT training, (2) participate in the study's biweekly group supervision, and (3) take on at least one SUPPORT veteran participant at a given time.

Veteran Participants

The inclusion criteria are purposefully broad and include veterans who report active suicide ideation in the previous month (ie, Columbia–Suicide Severity Rating Scale, C-SSRS [21], score of ≥2) or suicide behavior in the previous 3 months. Additional inclusion criteria are (1) current SMI diagnosis (ie, "a mental, behavioral, or emotional disorder resulting in serious functional impairment, which substantially interferes with or limits one or more major life activities" [22]) and (2) capability to provide informed consent (via the University of California, San Diego, Brief Assessment of Capacity to Consent [23]). Prioritized SMI diagnoses include those with psychosis or bipolar symptoms. Veterans with a diagnosis that falls under the broad VHA definition of SMI, which includes the following—major depressive disorder, schizophrenia spectrum and other psychotic disorders, bipolar disorders, obsessive-compulsive disorder, panic disorder, posttraumatic stress disorder, and borderline personality disorder [24]—are eligible. To prioritize those with psychosis and bipolar symptomology, recruitment will be expanded to the broad SMI diagnoses if no veterans meet the criteria for psychosis-related or bipolar disorders, with a guideline that 4 out of every 5 veterans recruited should experience psychosis or bipolar symptoms.

The following are the exclusion criteria: (1) inability to complete the assessment battery, (2) current intoxication requiring immediate detoxification or an outpatient plan directed specifically to residential substance use disorder (not mental health) services, and (3) imminent psychiatric hospitalization. We will include participants with an active substance use disorder if they do not require acute detoxification or residential treatment, and they can participate after acute detoxification. Participants can be engaged in other forms of treatment, including psychotherapy, as SUPPORT is meant to augment existing treatment as is standard of peer services. Veterans who participated in the previous open pilot trial will not be eligible to participate in the pilot randomized controlled trial to allow for the intervention to reach a broad range of veterans.

Recruitment, Screening, and Enrollment Procedures

Peer Specialist Participants

Research staff presented to the local peer specialists during their monthly team meeting to introduce the study. Peer specialists who met eligibility criteria were invited to follow up with research staff if they were interested in participating and instructed to provide verbal or written consent for research staff to contact their direct clinical supervisor. Next, the research staff contacted the peer specialists' direct clinical supervisors to discuss inclusion criteria. If eligibility was determined, they were consented and enrolled in the study. If they were not eligible, they were informed and still invited to participate in the SUPPORT trainings.

Veteran Participants

The veteran recruitment processes were designed to produce minimal impact to usual care. The primary recruitment locations for this study include VHA inpatient and outpatient behavioral health clinics, emergency services, and specialty services (eg, suicide prevention coordinators) across the VA San Diego Healthcare System. Potential veteran participants are recruited via three primary avenues: (1) veterans accessing same-day services, (2) veterans with recent documented suicide ideation or behavior, and (3) VHA clinician referrals. Veterans may also self-refer. Usual care for any veteran accessing same-day services involves a diagnostic interview with a triage provider and a psychiatric evaluation, which includes the VHA system-wide standardized Comprehensive Suicide Risk Evaluation (CSRE) and, as indicated, referrals to outpatient mental health services following evaluation. VHA clinicians are required to screen veterans yearly for suicide risk via the C-SSRS screener [21,25] and document this in the veteran's electronic health record. The C-SSRS screener is also used by VHA clinicians as clinically indicated and is required upon transitions of care (eg, discharge from inpatient psychiatry).

Research screening is used to confirm eligibility. Research staff will be available on the same day to accept a "warm handoff" for screening as needed. For all veterans contacted for screening, a CSRE will be conducted subsequently by the on-call

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psychologist if their risk level has changed since their last documented CSRE. If the veteran is deemed to be at moderate or high risk, a suicide safety plan will be completed or reviewed and updated. If the veteran is eligible, they will be invited to participate in a separate informed consent meeting and then subsequently enrolled in the study. Following enrollment, veteran participants will complete a diagnostic and baseline assessment and then randomized to SUPPORT or enhanced standard care. Those randomized to the SUPPORT condition will be matched with a peer specialist participant based on the peers' and veteran's availability. Randomized matching and veteran preference were considered but deemed not to be feasible given the nature of the pilot design. As feasible, veteran preference for identity characteristics such as gender as well as shared lived experience will be considered in matching as is standard practice for VHA peer services. Veterans not eligible at any stage will receive standard mental health care referrals and a study-designed resource packet.

Specific to allocation of conditions, a computer-generated 50-participant randomization table for this study was created and will be maintained by the project's biostatistician. The table includes no matching on baseline characteristics, 1 follow-up assessment as the minimum number of follow-up assessments needed to be considered as intention to treat, and completion of a minimum of 1 module of the intervention to be considered as intention to treat for those in the SUPPORT condition. After enrollment, the study coordinator emails the veteran participant's unique identification number to the biostatistician, who then provides the study coordinator with the allocation. There is no masking due to the pilot feasibility and acceptability design. See Figure 1 for the veteran participant timeline flow.

Figure 1. Veteran participant timeline. SUPPORT: Suicide Prevention by Peers Offering Recovery Tactics.

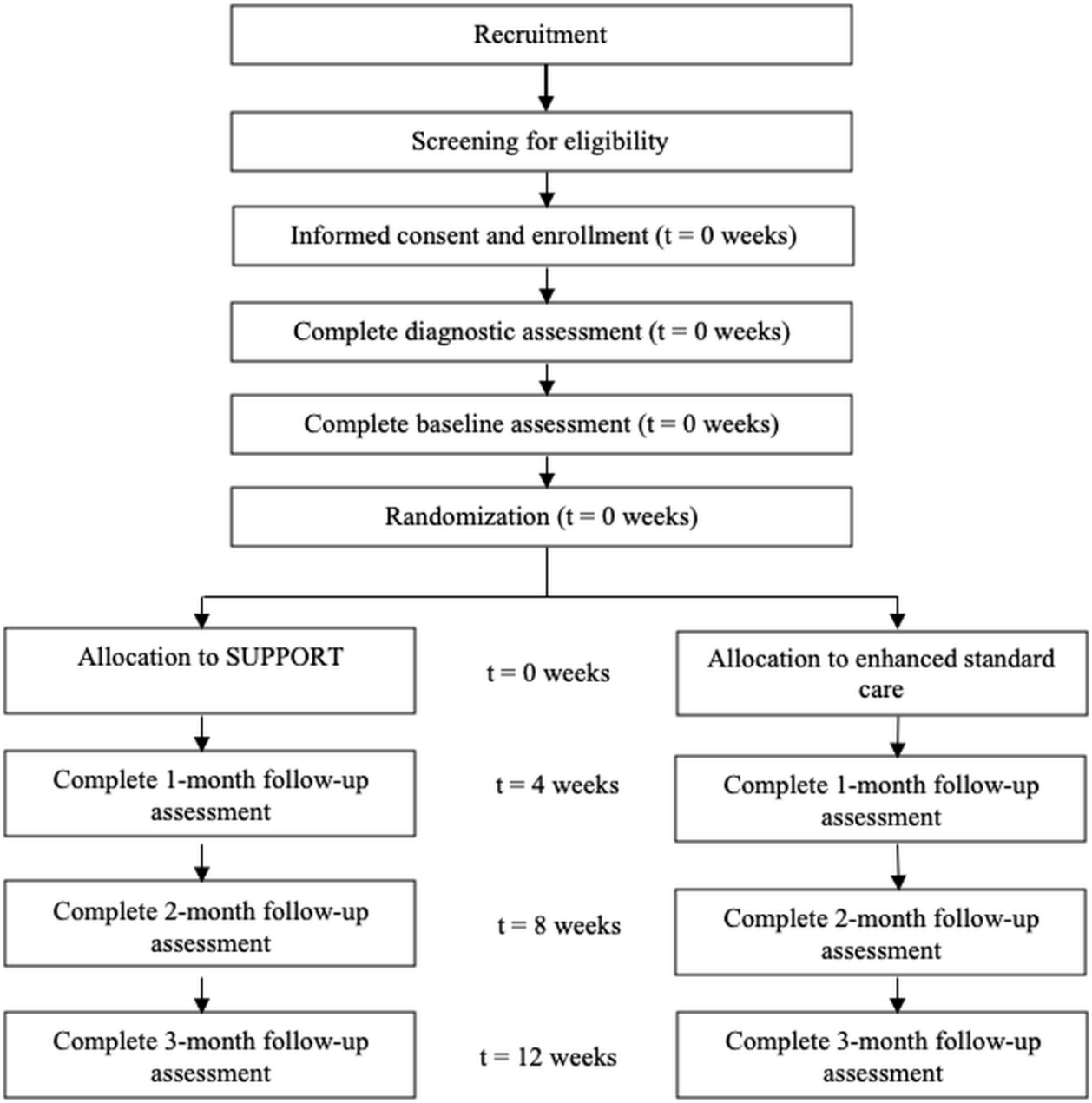

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Safety Procedures

Overview

At least one member of the on-call team of 3 licensed psychologists, who are part of the research team and employed at the VA San Diego Healthcare System, is available during all participant interactions. The on-call team is available for suicide risk assessments and appropriate triage as well as support to the research staff and peer specialists. The local suicide prevention coordinator team is also available on call during business hours for additional consultation.

Peer Specialist Participants

Peer specialist participants conduct a posttreatment assessment after completing SUPPORT with each veteran participant. To assess potential iatrogenic effects of delivering the intervention, peer specialist participants will complete the Negative Effects Questionnaire [26,27] (See peer specialist participant measure section below) as part of their posttreatment assessment. If the peer specialist participant reports that a negative effect occurred due to delivering the intervention and rate it as "very" or "extremely" impactful, research staff will notify the on-call psychologist to follow up with the peer specialist participant to determine whether additional support, such as referral to the employee assistance program, is needed. Described in more detail in the SUPPORT training section (subsection: Peer Specialist Training), peer specialists also receive ongoing support as part of the study supervision group and can request to meet individually with the principal investigator at any time.

Veteran Participants

Veteran participants referred to the study are gauged by a licensed VHA clinician as not needing immediate psychiatric hospitalization; however, as risk can change, veteran participants are assessed for suicide risk at multiple stages of the study. Peer specialists are trained in the SUPPORT safety protocol to directly screen for increasing veteran suicide risk at each SUPPORT appointment [18,28]. This protocol trains the peer specialists to contact the on-call psychologist during the appointment if suicide ideation is reported to be more severe since the last licensed VHA clinician's assessment and if there is intent to act before the next meeting with a licensed VHA clinician. If suicide ideation is current but reported not to be more severe and it is not likely the veteran will act on their suicide thoughts, peer specialists are to review the veteran's suicide safety plan and alert the on-call psychologist after the appointment concludes. A detailed procedure for this safety protocol is described in the work by Chalker et al [18].

All veteran participants will also be screened for suicide risk at screening, baseline, and all follow-up assessments by the research staff. Research staff are trained in an adapted version of the University of Washington Risk Assessment Protocol [29,30] to fit VHA protocols. Specifically, research staff are trained to alert the on-call psychologist while still with the participant if they report current active suicide ideation, a plan for suicide, access to lethal means, and intent to act on their plan in the following 48 hours—all of which are questions asked in the baseline and follow-up assessment batteries. If any of the previous criteria or any suicide behavior is reported during baseline and follow-up assessments, research staff are trained to alert the on-call psychologist to review the participant data, and the on-call psychologist will determine the appropriate next steps, for example, contacting the veteran for additional suicide risk assessment. Veterans are informed of limits to confidentiality such that, if they report increases in their acute suicide risk to research staff or peer specialists, their treatment team may be informed by the principal investigator to support continuity of care.

If a veteran participant is psychiatrically hospitalized at the local medical center, research staff and their assigned peer specialist as applicable will coordinate with the veteran's broader treatment team to determine appropriate ongoing engagement. As part of their role, peer specialists can and do provide services in inpatient psychiatry settings.

Peer Specialist Training

The SUPPORT training includes two 4-hour workshops tailored to the scope of a peer: SUPPORT 101 (a stand-alone general suicide prevention training) and the SUPPORT intervention training (a training for veteran peer specialists in how to provide the recovery-oriented, evidence-informed intervention for veterans with SMI at increased suicide risk). Training in the SUPPORT safety protocol is also provided. Chalker et al [18] provide a detailed description of the full training.

After the SUPPORT training, a study supervision group is held biweekly. This supervision is led by the principal investigator, who is a licensed clinical psychologist and trained as a peer specialist supervisor in the state of California [31]. Study supervision serves as a dedicated time to discuss immediate concerns; receive feedback on SUPPORT appointments; discuss and process general concerns, fears, and questions; receive support; and discuss implementation or other administrative topics. Peer specialist participants will continue to attend the regular supervision that they receive outside of the study that includes monthly group supervision with all local peer specialists and individual supervision with their direct clinical supervisor.

SUPPORT Intervention Curriculum

Overview

The SUPPORT intervention was co-developed by veterans with lived experience and inspired by 4 evidence-based interventions: suicide safety planning [32,33], Whole Health [34], Wellness Recovery Action Plan [35], and compensatory cognitive training [36,37]. Therefore, the SUPPORT intervention integrates elements of value-based living, recovery and action planning, and compensatory cognitive strategies (called "learning strategies" in SUPPORT). The role of learning strategies is to enhance recall and engagement in plans for adaptive coping during high-risk situations, as well as to enhance recovery plans to work toward meaningful goals [38]. After learning strategies are introduced, the progress of using them is reviewed and updated as needed in subsequent appointments. The content is formatted into 4 modules (Table 1) that are delivered in weekly one-on-one via telehealth or in-person appointments for approximately 50 minutes, each in the usual clinic in which the peer specialists work. The peer specialist conducts brief check-in

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calls at 2 and 4 weeks after the final module to reinforce the intervention material and offer additional resources as needed. Following the SUPPORT safety protocol, if a veteran is screened to be at increased suicide risk and the on-call psychologist is required to join the appointment, the peer specialist and veteran may reschedule that module's content to a separate appointment. A SUPPORT intervention note template is provided for peer specialists to document their encounters in the veteran's electronic health record following their standard clinic procedures.

Table 1. Peer-led Suicide Prevention by Peers Offering Recovery Tactics intervention curriculum.

Module number	Theme	Psychoeducation topics	Activities
1	Reasons for living	Recovery, values, and reasons for living	Identifying reasons for living by recognizing strengths and values
2	Hope	Wellness tools and hope kit	Developing wellness tools to feel well, stay well, and live the way they want to; developing a hope kit (a collection of reminders of one's values, positive memories, and reasons for staying alive)
3	Recovery goal	Recovery goals, action steps, and goal planning	Creating a long-term recovery goal as well as short-, mid-, and longer-term action steps to work toward recovery goals, particularly when suicidal
4	Social connections	Social support and crisis support	Building and maintaining social support, how supports contribute to recovery and suicide prevention, identifying who to call in a suicide crisis, addressing barriers to contacting supports, and reinforcing alternative tools

A workbook is provided to all veterans, which they are encouraged to complete with their peer specialist as well as in between appointments. The prompts in the workbook encourage a conversation focused on recovery and suicide prevention, including building a SUPPORT plan. By the end of SUPPORT, veterans will have a completed SUPPORT plan with 4 reminders for living that map to each module. All SUPPORT appointments also have four objectives for the peer specialist to meet: (1) ask directly about suicide, (2) work on the SUPPORT plan, (3) build learning strategies, and (4) share relevant experiences.

Fidelity

All SUPPORT appointments are recorded, and adherence is coded using the SUPPORT fidelity measure—developed with input from both advisory boards who co-developed SUPPORT [18] and based on previous peer specialist fidelity work [39]. Adherence is evaluated at the appointment level. An adherent SUPPORT appointment is defined as meeting all 4 objectives. Given the pilot nature of the trial and development stage of the intervention, all recorded appointments will be coded for adherence by at least one coder to provide feedback to the peer specialist. Adherence ratings are shared weekly with peer specialists and discussed in the study supervision group; peer specialists can meet individually with fidelity coders or the principal investigator as needed. A total of 15% of all SUPPORT appointments will be randomly selected and rated by 2 coders to determine fidelity. If the 2 coders disagree about whether an appointment has reached adherence, a third coder will rate the appointment, and a consensus meeting will be held among the 3 coders.

Enhanced Standard Care

SUPPORT will be compared to an enhanced standard of care delivered at the VA San Diego Healthcare System that contains the following elements: (1) suicide risk assessment, (2) VHA safety planning intervention, and (3) timely referral to VHA mental health outpatient care. Standard care is said to be enhanced as veterans randomized to this condition will also be assessed for suicide risk at baseline and follow-up assessments, which may result in additional clinical interactions.

Data Collection and Management

Overview

To become an approved assessor, training includes live training by the principal investigator and online training as provided by certain measures such as the C-SSRS [40]. Assessors then sequentially conduct role-plays with approved assessors, shadow an approved assessor, and are finally observed and approved by a previously approved assessor. Data are collected by approved assessors and stored in a VHA-approved secure web application for building and managing online surveys and databases called REDCap (Research Electronic Data Capture; Vanderbilt University) [41,42]. REDCap has validity checks for individual variables (eg, whether the data are in the appropriate range) included in the project design. Once data are entered into REDCap, they are also checked by a separate research staff member. Laboratory meetings are held weekly to discuss data collection and management questions.

Feasibility and Acceptability Data

Feasibility is defined as attainment of recruitment goals (n=50 veterans; n=2 peer specialists) and a ≥70% retention rate for veterans at the end of the intervention. Acceptability for veterans is measured using the Client Satisfaction Questionnaire–8 [43]. While direct suicide prevention interventions have been only shown to be helpful [44,45] and our advisory boards did not anticipate any negative effects for veterans, we do ask 1 open-ended question after intervention completion or dropout to determine whether veterans found the intervention to be harmful. After each veteran participant completes or drops out of the intervention, the following acceptability item is asked of the peer specialist to rate on a 5-point Likert scale (1=not at all, 2=a little bit, 3=somewhat, 4=quite a bit, and 5=very much): "Overall, how satisfied are you with delivering the SUPPORT Intervention?" High satisfaction for peer specialists is defined as "quite a bit" or "very much" satisfied.

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Peer Specialist Participant Measure

To track potentially negative effects for peer specialists, a revised and shortened version of the Negative Effects Questionnaire [26,27] is administered after each veteran participant completes or drops out of the intervention. The Negative Effects Questionnaire was revised from "receiving" to "delivering" an intervention and includes 8 yes or no items related to possible negative effects one might experience because of delivering the intervention. If any item is endorsed positively, two follow-up questions are asked: (1) "Indicate the severity of your experience (how negative the experience was for you)" (response scale: 0=not at all, 1=slightly, 2=moderately, 3=very, and 4=extremely) and (2) "Do you believe your experience was caused by the intervention you delivered or other circumstances that occurred during the same period as this intervention?" Traditional scoring may not be useful, so the Negative Effects Questionnaire results will be reported as (1) a total score of endorsed negative effects (range 0-8), (2) a total score of severity across all endorsed items (range 0-32), and (3) a total score of the negative effects being caused by the intervention (range 0-8).

Veteran Participant Measures

Veteran assessments are conducted at baseline and the 1-, 2-, and 3-month follow-ups. Table 2 shows the veteran participant measures. The measures included assess a range of standard outcomes important in the prevention of suicide, as well as including 2 laboratory-developed measures to explore SUPPORT's potential unique impact on suicide prevention.

The primary outcome of personal recovery is measured using the 41-item Recovery Assessment Scale, a self-report measure of personal recovery with 5 domains: personal confidence and hope, willingness to ask for help, goal and success orientation, reliance on others, and no domination by symptoms [46]. The other primary outcome is assessed using interviewer -administered assessments of the 19-item Beck Scale for Suicide Ideation [47] for past-week suicide ideation severity and the C-SSRS [21,25] for past-month suicide ideation severity.

Table 2. Veteran participant measures at all time points.

Timing and domain	Measure	Outcome type
All time points		
Personal recovery	Recovery Assessment Scale–41	Primary
Suicide ideation severity	Beck Scale for Suicide Ideation; C-SSRS[a]	Primary
Psychosocial functioning	Specific Level of Functioning Scale	Secondary
Quality of life	Brief version of the World Health Organization Quality of Life Scale	Secondary
Cognitive strategy use	Cognitive Problems and Strategies Assessment	Exploratory
Perceived burdensomeness and thwarted belongingness	Interpersonal Needs Questionnaire–15	Exploratory
Hopelessness	Beck Hopelessness Scale	Exploratory
Suicide behaviors	C-SSRS	Exploratory
Suicide crisis service use	Chart review	Exploratory
2-month follow-up only		
Peer impact	Laboratory-developed measure	Exploratory
2- and 3-month follow-ups		
Suicide prevention strategy recall (SUPPORT[b] plan and suicide safety plan)	Laboratory-developed measure	Secondary

[a]C-SSRS: Columbia–Suicide Severity Rating Scale.

[b]SUPPORT: Suicide Prevention by Peers Offering Recovery Tactics.

Secondary outcomes of psychosocial functioning and quality of life are measured using the Specific Level of Functioning Scale and the brief version of the World Health Organization Quality of Life Scale, respectively. The Specific Level of Functioning Scale is a 43-item self-report questionnaire assessing functioning on 4 domains (interpersonal, social acceptance, activities, and work) and has been determined to be the best measure of functioning for adults with schizophrenia to assess real-world functioning in 1 scale [48]. The brief version of the World Health Organization Quality of Life Scale is a 26-item self-report instrument assessing 4 domains of quality of life: physical health, psychological health, social relationships, and environment [49]. Collected only at the 2- and 3-month follow-up assessments, suicide prevention strategy recall (secondary outcome) is measured using laboratory-developed self-knowledge tasks in which veterans are given 10 minutes to say what they remember from each section of their SUPPORT plan (SUPPORT condition only) and suicide safety plan [50]. Each plan is scored based on standard safety planning scoring practices [51,52], with SUPPORT plan scores ranging from 0 to 4 and safety plan scores ranging from 0 to 18.

The exploratory outcomes are cognitive problems and strategy use, burdensomeness and belongingness, hopelessness, suicide

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behavior, service use, and peer impact. Cognitive strategy use is measured using 30 self-report items on memory and thinking strategies that have been successfully used with a population with SMI and designed to capture changes in the use of compensatory cognitive training skills [37], referred to as "learning strategies" in SUPPORT. Burdensomeness and belongingness, which, when they converge, according to the interpersonal theory of suicide [53], create suicide desire [54], are captured using a 15-item self-report measure. The Beck Hopelessness Scale is a 20-item true-or-false self-report measure that has been shown to be predictive of eventual suicide in psychiatric inpatients [55]. Suicide behavior is measured using the C-SSRS behavior section, and service use (ie, suicide-related emergency department visits and inpatient psychiatry stays, Veteran Crisis Line contacts, and outpatient visits) is captured via chart review. Finally, based on theories related to peer support [56-63] and the Peer Specialist Fidelity Measure–Veteran Version (previously used to establish fidelity in traditional VHA peer support programs [39]), we co-developed with our advisory boards a measure collected posttreatment to evaluate the peer impact of veterans receiving SUPPORT. This measure includes 17 Likert scale–rated items and 14 open-ended questions. Likert scale items are rated from 1 (not at all) to 5 (very much). These items will be summed to obtain a total score; a higher score indicates a higher impact of the peer specialist. Sample Likert scale items include the following: "How much did your peer specialist encourage you to be hopeful?" and "How much did you feel connected with your peer specialist?" Open-ended items are asked to better understand the Likert scale–rated items (eg, "What did you have in common with your peer specialist that helped you connect?").

Veteran Participant Sample Size Determination

The sample size for the pilot randomized controlled trial was estimated using a previous method provided by Hedeker et al [64] and the Repeated Measures and Sample Size software. This minimum power estimation is based on a 5% attrition rate per time point, correlation of 0.5% of repeated measures, and medium to large effect sizes. A total sample size of 44 will yield a minimum of 80% power to detect a large effect size, defined as a between-group difference increasing linearly from 0 at baseline to 0.7 SD units at the last time point. A large effect size was chosen as this is a pilot feasibility study and is not intended to be powered to detect a small or medium effect [65].

Analysis of Outcomes

Overview

The primary goal of the pilot randomized controlled trial is to evaluate feasibility and acceptability for a potential efficacy study using recruitment and retention rates and the Client Satisfaction Questionnaire–8. In addition to the primary goal, this study will also assess several primary, secondary, and exploratory outcomes. We are aware that we may be underpowered for the following analyses.

Primary and Secondary Outcomes

Primary and secondary outcomes will be tested using mixed-effects models [64,66]. This method allows for the inclusion of participants with missing data and those who dropped out without relying on data imputation. It provides an estimate of the individual variability around the population trend and the variability of the individual intercepts (baseline values) and slopes (changes across time and the correlation between them). A fully saturated treatment by visit model will be used for inference. Covariate structure will be chosen based on the Akaike information criterion. Data will be analyzed for all participants who were randomized for whom we have a baseline assessment and at least one follow-up assessment. We expect the dropout rate to be <10% after the baseline assessment (this dropout rate is considered in our power analysis estimation).

Exploratory Outcomes

Due to focus on feasibility, recovery, suicide ideation, and functioning, as well as the low anticipated base rates of suicide behaviors and crisis service use and overall sample size, these analyses are exploratory. The pilot randomized controlled trial exploratory analyses are twofold: (1) to compare SUPPORT to enhanced standard care on cognitive strategy use, thwarted belonginess, perceived burdensomeness, hopelessness, rate of suicide behavior, and rate of crisis service use; and (2) to compare SUPPORT to enhanced standard care on the mediational effect of personal recovery on suicide ideation severity. Peer impact will be reported descriptively for those who received SUPPORT, including a deductive analytic approach [67] of open-ended responses to determine themes.

First, mixed-effects models will be conducted as described for the primary and secondary outcomes. Next, given our small sample size, mediators will be tested in separate models [68,69]. We define treatment mediators as mechanisms through which a treatment might achieve its effects. We will test the products of (1) the *a* path (the independent variable [condition] to the mediator [eg, 2-month follow-up personal recovery]) and (2) the *b* path (the mediator to the dependent variable [3-month follow-up suicide ideation severity]). This procedure is a variation of the Sobel test [70] that accounts for the nonnormal distribution of the *a*-*b* path through bootstrapping procedures. Significant mediation effects are indicated when the 95% CI of the indirect path (*a*-*b*) does not overlap with 0. We will test a full mediation model, with changes in the mediator (assessed at the 2-month follow-up) preceding changes in the outcome variable (assessed at the 3-month follow-up).

Results

This trial was funded in November 2022. Community-engaged intervention and protocol refinement were completed in January 2025. Data collection for the pilot randomized controlled trial began in January 2025 and is projected to continue until May 2027.

Discussion

Anticipated Findings

This study's primary aims are to evaluate the feasibility, acceptability, and preliminary impact of a novel peer specialist–led suicide prevention program for veterans with SMI at risk of suicide. We hypothesize that SUPPORT will be feasible to deliver, with high satisfaction ratings. It is further

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hypothesized that SUPPORT, compared to enhanced standard care, will yield greater enhancement of personal recovery and reduction in suicide ideation severity (primary outcomes), as well as enhanced psychosocial functioning, quality of life, and suicide prevention strategy recall. Combining suicide prevention training for VHA peer specialists with the creation of a recovery-oriented suicide prevention intervention curriculum, SUPPORT was designed to meet the unique needs of veterans with SMI. Key considerations for this study include adequate training and ongoing supervision for peer specialists, exploring the impact of the peer-delivered component to further add to the nascent peer-based suicide prevention literature, and determining the impact of peer specialists on recovery outcomes for veterans with SMI at increased suicide risk. As this is the first study to our knowledge examining a VHA peer specialist–led suicide prevention program for veterans with SMI, it will be critical to consider feedback from veteran and peer specialist participants alike to best serve the needs of this population and contribute to the growing body of research.

Limitations and Future Directions

This study is not without limitations. First, the ongoing implementation of SUPPORT in usual care while determining preliminary feasibility, acceptability, and impact lends itself to unique challenges such as staffing turnover, although this enhances the real-world effectiveness of the program. Second, as described in the work by Chalker et al [18], peer specialists are participants instead of only members of the research team, which proves to have advantages and disadvantages. Advantages include the ability to collect crucial data on what it is like for them to deliver a suicide prevention intervention; however, disadvantages include ongoing stigma of peer specialists resulting in the need to be monitored in their intervention delivery work and inability to monetarily compensate them as participants as they are also VHA employees. Various types of compensation or other incentives should be considered in future peer-related research. In addition, it is not clear whether naturalistic changes through the course of treatment will be distinct from those caused by the augmentation. Future research should explore accommodation for these factors in comparing SUPPORT to treatment as usual inclusive of existing suicide prevention initiatives. Other limitations common in pilot studies include a lack of study power and no time-matched comparison not focused on suicide, such as with the Wellness Recovery Action Plan [35], 2 aspects that could be addressed in a future larger randomized trial.

Conclusions

Overall, this study presents an important opportunity to learn from a group of peer specialists and veteran participants. Pending outcomes of a larger trial, a goal is to implement SUPPORT in a broader capacity across VHA. By incorporating a curriculum to meet the unique social and cognitive needs of veterans with SMI, this study will fill existing gaps in care in terms of both available recovery-oriented interventions within VHA and within the breadth of existing suicide prevention research initiatives.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are not publicly available due to data use agreements in place by the Department of Veterans Affairs. A summary of group findings will be published.

Authors' Contributions

All authors were involved in the conceptualization and review and editing of the manuscript. SC and JC wrote the original draft. SC received funding to support this trial. CD and MC provided supervision and resources.

Conflicts of Interest

None declared.

Multimedia Appendix 1
World Health Organization trial registration dataset.
[DOCX File , 24 KB - resprot_v14i1e66182_app1.docx]

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Abbreviations

CSRE: Comprehensive Suicide Risk Evaluation
C-SSRS: Columbia–Suicide Severity Rating Scale
HIPAA: Health Insurance Portability and Accountability Act
REDCap: Research Electronic Data Capture
SMI: serious mental illness

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SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SUPPORT: Suicide Prevention by Peers Offering Recovery Tactics
VA: Veterans Affairs
VHA: Veterans Health Administration

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Protocol

Mindful Movement Programs in Community and University Preschools: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Chronic stress and emotional and cognitive regulation difficulties during early childhood are associated with risky behaviors and negative outcomes later in life. As preschoolers are at a developmental stage where their emotional and cognitive regulation skills are still emerging, they often rely on external support to manage their emotions and behaviors. Intervening early promotes healthy development and preventing adverse outcomes. Mindful movement practices (MMPs)—which incorporate physical activities, breathwork, and reflective exercises—show the potential to enhance emotional and behavioral skill regulation. However, the impact of MMPs on cognitive and social-emotional development in young children has not been thoroughly researched, and the underlying mechanisms remain unclear.

Objective: This pilot randomized controlled trial aims to assess the feasibility and acceptability of implementing MMPs in preschool classrooms and explore their effects on preschoolers' social-emotional, cognitive, and physiological development. The study also focuses on enhancing prosocial behaviors and reducing problem behaviors. This protocol paper outlines the research procedures, sample demographics, and survey data psychometric properties.

Methods: The study was conducted in 3 preschool classrooms (2 intervention and 1 waitlist control). Data were collected among 32 children and 8 teachers. Before the study began, 8 formative focus groups were facilitated with 5 administrators and 33 teachers in total to inform modifications to the program and research design. The intervention group participated in a 16-week program that included neural-based drills, aerobic activities, breathwork, and "feelings circle" exercises, along with classroom and home kits. The waitlist control group received a shortened 8-week program after the intervention groups completed their sessions. Data were collected before the intervention, at the midway point of the intervention, and after the intervention and again 2 months after the intervention. Measures included behavioral tasks, biomarkers (heart rate variability via wearable sensors and hormonal substrates in hair), and surveys from parents and teachers. Implementation fidelity was assessed using quantitative logs, qualitative field notes, and video observations. Postintervention interviews and focus groups were conducted with teachers, parents, and administrators.

Results: Formative focus groups were conducted with 33 teachers and 5 administrators. Behavioral task, biomarker, and survey data were collected from 40 participants, including 32 preschoolers aged 3 to 5 (mean 4.4, SD 0.64) years and 8 teachers with a mean age of 37.9 (SD 11.47) years. Postintervention interviews and focus groups were completed with 7 teachers, 4 administrators, and 8 parents.

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Conclusions: This paper describes study procedures. Future publications will present primary outcome findings and evaluate the feasibility and acceptability of this MMP and research design in community-based and university-based preschool settings. Future papers will explore the data to provide preliminary evidence for the program's effectiveness, mechanisms of effects, and the need for larger randomized controlled trials to optimize early childhood mindfulness interventions.

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KEYWORDS

mindfulness; mindful movement practices; mindfulness-based intervention; preschool children; early childhood; emotional regulation; stress response; randomized controlled trial; social-emotional learning

Introduction

Background

Chronic stress is an increasing public health concern that often originates in early childhood, especially among vulnerable populations [1,2]. Chronic stress in early childhood—often referred to as early life stress or childhood adversity—is typically measured by adverse experiences such as abuse, neglect, or lack of resources (eg, Smith and Pollak [3]). Persistent stress during early childhood can lead to emotional and cognitive dysregulation, which may later result in risky behaviors during adolescence, including substance abuse, violence, delinquency, and unsafe sexual practices [4-6]. Such outcomes contribute to substantial social and economic burdens in adulthood, manifesting as increased interactions with the criminal justice system, addiction, unemployment, and various health issues [7-9]. Early childhood is a crucial period to develop positive coping strategies via the implementation of evidence-based interventions designed to foster positive trajectories in life.

Preschool years are a pivotal period for the maturation of brain regions associated with motor function, self-regulation, cognition, language, and social competencies [10]. The developmental changes occurring in early childhood present an optimal opportunity for intervention, with preschool environments serving as ideal settings for such initiatives. The traditional social-emotional learning (SEL) programs, such as the well-known Business As Usual program, are standardized programs that have been embedded in the daily routine and classroom curriculum (eg, literacy, math, and circle time), especially focusing on regulating classroom environments and instructional practices [11]. Such a program has been critiqued for limiting responses to individual developmental needs and impeding the integration of comprehensive and inclusive models [12].

Mindful movement practices (MMPs) extend beyond traditional SEL programs by adopting a more developmental and sensitive approach tailored to the unique needs of children. MMPs incorporate movement patterns, attention-focused exercises, breathwork, and static postures, providing effective self-regulation strategies for young children [13-15]. These practices leverage sensory motor systems, cognitive control, and emotional regulation skills to assist children in managing stress and emotional responses [16,17]. Furthermore, the SEL components inherent in MMPs foster positive emotional and behavioral development in children. There are several facets that make this MMP unique from other SEL programs. First, the MMP used in this study adopted a train-the-trainer approach, whereby teachers were trained by program implementers on how to implement the MMP outside of the planned programming schedule. This approach builds teachers' capacity to implement the program independently. Furthermore, teachers were given calm corner kits to use in the classroom and parents received kits for children to use at home. Using this approach facilitated the reinforcement of learned mindfulness strategies and ensured the consistency of school-home environments to support children's behavior. By training the teachers and providing calm corner kits, children have more opportunities across settings for SEL.

While most school-based mindfulness research has focused on adolescents, findings show limited effects on externalizing behaviors (eg, aggression) and modest impacts on internalizing behaviors (eg, anxiety) [18-20]. Randomized controlled trials (RCTs) are now emerging that investigate the effects of mindfulness in preschool-aged children [21-24] and the implementation of MMPs in early elementary settings [25]. These studies have shown improvements in self-control, motor function, behavior, executive function, and social-emotional competencies. In addition, MMPs have demonstrated feasibility in urban elementary settings, yielding enhancements in self-control, motor skills, and behavior [25]. Mindfulness practices tailored for preschoolers have also indicated positive outcomes in motor control and social-emotional functioning [21]. These published RCTs show the benefits of mindfulness among preschoolers and school-aged children, but they have not examined which children are most responsive to specific components of MMPs nor have they explored the underlying mechanisms that contribute to the observed changes. Further research is needed to understand the physiological and social-emotional mechanisms underlying MMP effectiveness including identifying which elements of MMPs are most effective for children from diverse racial, sociodemographic, and neurodiverse backgrounds.

Many studies have highlighted the positive impacts of mindfulness-based interventions in children, and there is a growing body of evidence that demonstrates benefits for teachers who participate in mindfulness-based educator training [26-29]. These include minimized teacher burnout, enhanced well-being and social-emotional competencies, cultivation of classroom climates more conducive to learning, teacher-student relationships, classroom management, and self-efficacy [26].

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These findings are consistent with the prosocial classroom model, which suggests that teachers' social-emotional skills and well-being have a positive impact on their relationship with children and classroom management [30]. To our knowledge, no study has examined the effects of mindfulness-based classroom interventions on teacher outcomes. For example, changes in children as a result of mindfulness-based interventions may lead to improved teacher outcomes as mentioned earlier, student-teacher relationships, and attunement in physiological responses.

In response to these gaps, we conducted a pilot RCT to evaluate the hypothesis that MMPs could alter preschoolers' behavioral difficulties by impacting physiological, social-emotional, and cognitive factors, which, in turn, could affect teacher outcomes. This preliminary evidence will provide support for using these assessments in a future full-scale RCT.

Objectives

This pilot study was designed to lay the groundwork for a larger RCT using the MMP and building an evidence base to support broader dissemination of an effective, low-cost, highly scalable program. This pilot study has 3 primary aims.

Feasibility

This aim focused on assessing the practicality and reception of the intervention and research procedures among preschoolers, teachers, parents, and administrators, including evaluation of the acceptability of data collection methods, such as physiological, behavioral, qualitative, and survey measures. In this study, we draw from the work of Bowen et al [31] and Teresi et al [32], who outline facets of feasibility studies, including factors such as acceptability, implementation, and practicality (among others). These factors may be assessed by consenting to be part of a study, retention, satisfaction, and participation in activities.

Effects on Mechanisms and Outcomes

This aim focused on investigating how the implementation of the MMP influences self-regulatory capacities, SEL skills, problem behaviors, and prosocial behaviors, as well as identifying underlying physiological mechanisms of program effects at the midpoint, postintervention time point, and 2-month follow-up. Physiological data were collected after each MMP component, allowing for the evaluation of the effects of sequential implementation on physiological responses.

Teacher Effects

This aim focused on evaluating how exposure to MMPs affects teachers' stress responses due to physiological attunement with children and classroom dynamics, which may subsequently enhance child outcomes.

Methods

Setting

Two sites, including 1 community-based site (2 classrooms) and 1 university-based site (1 classroom), participated in the study. These sites were chosen because they serve families from the local community, creating a more heterogeneous sample of children as opposed to focusing on disadvantaged or advantaged populations. Site 1 (community-based preschool program Head Start) had 8 active preschool classrooms, and site 2 (university-based preschool) had 3 active preschool classrooms. Site 1 receives federal funding to provide early childhood education for children from families living below federal poverty guidelines or facing other stressors such as homelessness or disability. Of the enrolled families, 90% were low-income families and 14% received public assistance [33]. Enrollment was determined by need. According to a county-level report for all Head Start sites in the broader study area, approximately 11% of children faced homelessness; 14% were referred for developmental disability or special education; and 32% received Supplemental Nutrition Assistance Program benefits. By comparison, an estimated 13% of the United States receives these benefits (Economic Research Service [34]). Site 2 uses an enrollment model that provides a diverse group of children and families. Using a stratified enrollment model, 25% of enrolled children were children of faculty members, support staff, university students (both undergraduate and graduate), and community families. Approximately 20% to 30% of the children enrolled came from low-income homes (supported by Child Care Assistance Program subsidy vouchers, a grant supporting childcare needs of low-income undergraduate student parents, and a sliding fee scale).

Participants

A total of 40 participants were enrolled in the RCT part of the study. Participants included 32 preschool children aged 3 to 5 (mean 4.4, SD 0.64) years: 17 (53%) female, 11 (34%) Black, and 4 (12%) Hispanic. Demographics of children were based on parent reports unless those data were missing (n=3, 9%), in which case teacher-reported values were used. In total, 69% (22/32) of the children received the intervention immediately, and 31% (10/32) were assigned to the waitlist control group. Of the 40 participants enrolled across the 3 classrooms, 8 were female teachers with a mean age of 37.9 (SD 11.47) years: 3 (38%) were Black and 4 (50%) were White. A total of 29 parents with a mean age of 33.6 (SD 6.75) years completed the demographic questions: 23 (79%) female, 12 (41%) Black, and 2 (7%) Hispanic. Baseline demographics by intervention group for children and parents are presented in Tables 1 and 2.

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Table 1. Demographic characteristics of children (N=32).

Characteristics	Full sample	Intervention (n=22)	Control (n=10)
Age (y), mean (SD)	4.4 (0.64)	4.6 (0.50)	3.9 (0.72)
Sex n (%)			
Male	12 (55)	__[a]	—
Female	17 (53)	10 (45)	7 (70)
Ethnicity, n (%)			
Hispanic or Latinx	—	—	—
Not Hispanic or Latinx	28 (88)	21 (95)	7 (70)
Race, n (%)			
Asian, Native Hawaiian, or Other Pacific Islander	6 (19)	5 (23)	—
Black or African American	11 (34)	6 (27)	5 (50)
White	15 (47)	11 (50)	4 (40)
Language, n (%)			
Native English speaker	20 (62)	13 (59)	7 (70)
Disability, n (%)			
None	27 (84)	17 (77)	10 (100)
One or more disabilities	5 (16)	5 (23)	0 (0)

[a]Samples sizes of <5 participants.

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Table 2. Demographic characteristics of parents (N=29).

Characteristics	Full sample	Intervention (n=19)	Control (n=10)
Age (y), mean (SD)	33.6 (6.75)	34.8 (5.64)	30.9 (8.36)
Number of children, mean (SD)	2.1 (1.11)	2.0 (0.77)	2.4 (1.57)
Sex, n (%)			
Male	6 (21)	6 (32)	—[a]
Female	23 (79)	13 (68)	10 (100)
Ethnicity, n (%)			
Hispanic or Latinx	—	—	—
Not Hispanic or Latinx	27 (93)	19 (100)	8 (80)
Race, n (%)			
Asian, Native Hawaiian, Other Pacific Islander	—	—	—
Black or African American	12 (41)	5 (26)	7 (70)
White	13 (45)	10 (53)	—
Education level, n (%)			
High school degree or GED[b]	9 (31)	5 (26)	—
Some college but no degree	6 (21)	—	—
Associate or bachelor degree	7 (24)	—	—
Graduate degree	7 (24)	7 (37)	—
Marital status, n (%)			
Single, living alone	6 (21)	—	—
Living with a romantic partner	—	—	—
Married	16 (55)	14 (74)	—
Separated or divorced	—	—	—
Employment status, n (%)			
Employed for wages or self-employed	23 (79)	13 (68)	10 (100)
Unemployed	6 (21)	6 (32)	—
Income range (US $), n (%)			
≤$26,000	8 (28)	6 (32)	—
$27,000 to $49,000	12 (41)	5 (26)	7 (70)
≥$50,000	7 (24)	7 (37)	—

[a]Samples sizes of <5 participants, except for reported missingness.

[b]GED: General Educational Development.

Procedures

This pilot study consisted of 8 formative focus groups with administrators and teachers who aimed to inform modifications to the study design before data collection and implementation. The RCT took place from January 2024 through August 2024 and consisted of multiple components (detailed below).

Formative Interviews and Focus Groups

In fall 2023, 6 focus groups were conducted with 33 teachers and 2 focus groups were conducted with 5 administrators. These formative focus groups were conducted at 3 Head Start locations and the university preschool to gauge teacher and administrator interest in participating in research studies and a proposed intervention study. All 33 teachers expressed positive sentiments about the program being implemented in classrooms; however, because this was a pilot study, we could only implement the program in 3 classrooms across 2 sites. Classrooms were selected based on the children served (those aged 3 to 5 years), teacher buy-in, and administrator feedback on the feasibility of implementation (eg, full-day classrooms vs half-day classrooms). The future full-scale RCT will randomize classrooms to conditions. The research team followed up with teachers in 3 identified classrooms and confirmed their willingness to participate in the research study before classroom selection was finalized.

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Randomization Procedures

At site 1, a total of 2 classrooms were randomly assigned to receive the 16-week intervention or serve as the waitlist control group. Because randomization was only needed for 2 classrooms at site 1, we used a manual procedure by writing classroom numbers on pieces of paper, which were then folded and mixed, and one was drawn to assign the intervention group. The one classroom at site 2 was assigned to receive the 16-week intervention. A 2:1 ratio between the intervention and control groups was chosen to maximize the number of children receiving the intervention while maintaining a comparison group for evaluating the effectiveness of the program.

The Mindful Movement Program

The MMP combined movement practices (Mission2Move [35]) and positive behavioral intervention and supports (PBIS; Calm Caterpillar [36]) into one progressive program, referred to as M2M-CC (Mission2Move and Calm Caterpillar) for short. M2M-CC integrated evidence-based movement (Z-Health [37]) and meditation (Mindful Schools [38,39]) strategies. It was an SEL program that provided a mindful movement curriculum and tools to support classrooms and child development. M2M-CC practices included (1) neural-based drills, (2) aerobic activity, (3) breathwork and guided meditation, and (4) "feelings circle" or reflective practices. Positive behavioral intervention occurred with the use of visual and tactile aids, and support was provided through classroom or home kits that children, parents, and teachers could use in times when children needed assistance in regulating their emotions and behaviors. The movement (neural-based drills and aerobic activity) and mindfulness (breathwork and guided meditation, as well as reflective practices and "feelings circle") practices worked in conjunction with each other to teach children how physical health is tied to social-emotional well-being and goal attainment [40]. Teachers and parents received a calm corner kit (classroom or home kits) near the end of the program to help children practice self-regulation techniques at home and in the classroom when direct instruction was not occurring.

Program Implementation

For the study, the program was delivered twice per week in classrooms receiving the intervention. One weekly session was a 15-minute mindful movement class and the other session was a 5- to 7-minute refresher or booster class. These classes were taught over 16 weeks (immediate intervention group) and 8 weeks (waitlist control). Study implementers were trained and supported by the MMP developer, one person led the implementation of the program to create consistency across sites, and an established curriculum was used to maintain standardization of the program. Before programming began, teachers received professional development training. During programming, teachers were present for direct instruction by study implementers so that they could learn the MMPs for use outside of planned programming and booster sessions each week and for future classroom implementation.

A 4-part sequence of program components was administered over time. First, children warmed up with "neural-based drills." Drills used specific movements to train the nervous system in how body parts were supposed to move. These increased children's body awareness in movement, location, and action (ie, proprioception). Neural drills included movements such as hip circles or ankle tilts. In addition to neural drills, children were led in aerobic movement–focused activities (eg, dance and running in place). Second, children learned a variety of "simple breathing practices" that used different techniques for varied benefits. For example, children learned hand breathing—inhaling and tracing up a finger, then exhaling and tracing down a finger—to support self-calming. Third, children engaged in a reflective practice known as "feeling circles," where they talked about the meaning of different feelings and shared when they experienced the feeling. We used a "talking stick" approach whereby each child had the opportunity to share and be heard when they held the stick. Finally, classrooms and parents were provided a kit of tools for creating a calming corner as another component of PBIS to reinforce skills taught in the program.

As presented in Table 3 (based on a 15-minute mindful movement class), mindfulness program components were sequentially introduced every 4 weeks after the first component. For example, during a 16-week implementation, components were added every 4 weeks (weeks 1-4, 5-8, 9-12, and 13-16). In an 8-week-long administration, program components were added every 2 weeks. Movement was first introduced, followed by breathwork and meditation, then feeling circles or reflection, and finally the calm corner (PBIS). This allowed for assessing program component effects on physiological (ie, respiratory sinus arrhythmia and vagal efficiency) and SEL mechanisms.

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Table 3. Programming component description, impact, and implementation details.

Component	Description	Hypothesized impact	Timing	Weeks	Modality	Location	Method
Neural drills	Activate the brain through specific body movements (eg, hip and arm circles)	Learn body awareness and inhibitory control	5 min	1-16	Movement	School	Direct instruction
Aerobic activities	Elevate heart rate via different activities and movement sequences	Reduce overall stress and cortisol	10 min	1-16	Movement	School	Direct instruction
Breathwork and meditation	Practice breathing techniques (eg, hand, belly, lion's breath, and body scan meditation)	Practice control over emotions	2-3 min	5-16	Mindfulness	School	Direct instruction
Feelings circles	Label feelings and share personal examples with the circle and emotion recognition	Practice reflection and learn empathy and interpersonal connection	2-3 min	9-16	Mindful	School	Direct instruction
Calming corner	Down-regulation strategies for children included a classroom kit and a home kit for parents, a quiet space with reduced stimuli, visual aids for self-calming, and tactile weighted toy for soothing and counting	Practice self-calming skills; removed from environmental stimuli (eg, sounds, people)	Varies	13 to ≥16	Positive behavioral intervention and supports	School and home	Child and adult self-guided

Waitlist Control Procedures

For consistency of exposure to research team personnel, both the immediate intervention and waitlist classrooms were visited by the implementation team twice weekly for 20 minutes per week. For the waitlist classroom, implementers interacted with children during typical classroom activities (eg, reading and playing with sensory tables).

Following the 16 weeks of programming and postassessment time point, the waitlist group received 8 weeks of the MMP with each program component sequentially added every 2 weeks. This condition allowed for testing of shorter program dosage effects than longer ones.

Data Collection Timeline

Data were collected at 4 time points: baseline (preintervention; all classrooms), midintervention time point (8 weeks into programming; all classrooms), postintervention time point (immediately following the 16-week intervention or waitlist period; all classrooms), and 2-month follow-up (2 months after the intervention; 1 intervention classroom). In the waitlist control group, the postintervention time point also served as their second baseline and the 2-month follow-up served as their postintervention time point (immediately after the 8-week intervention). The data collection time points are illustrated in Figure 1 for the intervention (black) and waitlist control (gray) groups. At each time point, survey data were collected electronically (in person or online) or via paper and pencil, whichever was feasible and preferred by participants. Behavioral assessments were administered at all time points except for the midintervention time point.

Figure 1. Overview of data collection time points for the experimental group.

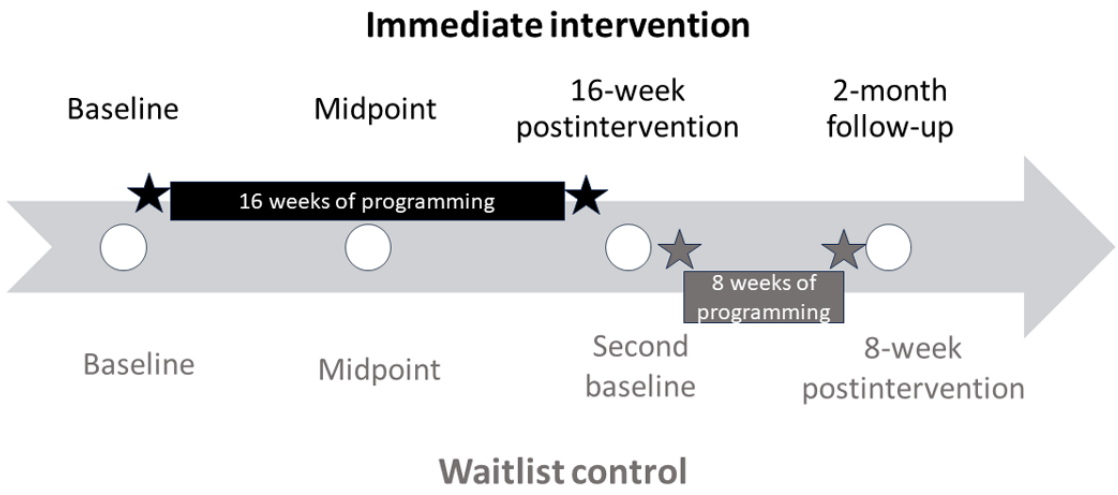

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Outcome Measures

Behavioral Assessments

The pencil tapping task assessed working memory and inhibitory control [41,42]. In this task, both the evaluator and the child held a pencil in their dominant hand. The child was instructed to tap the pencil twice when the evaluator tapped once and to tap once when the evaluator tapped twice. This required the child to hold the rules in working memory while inhibiting the natural tendency to mirror the evaluator's tapping pattern. Up to 6 practice trials were used before the official assessment began. During the practice trials, the evaluator provided feedback on correct and missed trials to ensure understanding of the task. Following the practice trials, 16 scored trials were administered without feedback. The total number of correct responses ranges from 0 to 16.

The gift delay task assessed self-regulation [43]. In this study, it also served as a stress task to assess child coping and stress response (eg, behavioral and physiological response via heart rate variability [HRV], respiratory sinus arrhythmia, and vagal efficiency). During this task, the child sat at a table while the experimenter presented a gift bag containing a prize, explaining that the bag needed a bow before the child could open it. The experimenter placed the bag in the center of the table and instructed the child to remain seated and not touch the bag until she returned. After a 3-minute delay, the experimenter returned, placed the bow on the bag, and gave the child the gift, regardless of whether they followed the instructions. Scoring was based on the child's ability to resist the temptation to touch the gift bag during the waiting period. Children were given a score of 1 if they took the gift from the bag, 2 if they put their hand in the bag, 3 if they peeked in the bag, 4 if they touched the bag, and 5 if they followed all instructions. Scores ranged from 1 to 5. Time spent out of the seat was also calculated and categorized into 4 distinct levels: 1 for <30 seconds in the seat to 4 for >2 minutes in the seat. A final seat score was computed by assigning an additional half point for each minute a child spent out of the seat within arm's reach of the table for those with scores of 1 or 2. The task was video recorded using a discreet camera for later review and double scoring by a second researcher.

The tower task assessed turn-taking and inhibition [43]. During this task, the child sat at a table with the experimenter seated across from them. The child was given a practice trial where they were instructed that they would be building a tower together by taking turns. First, the experimenter placed a block on the table and instructed the child to place the next block on top. The practice trial ended after the tower was 6 blocks tall. During the practice trial, they were reminded to take turns if they were not taking turns. The actual trial consisted of 12 blocks and the experimenter told the child that they would build a really tall tower together and the child could go first. Children were scored on 2 characteristics. First, on turn-taking: 0 for no turns (children built the tower by themselves), 1 for partial turn-taking, or 2 for full turn-taking. A second turn-taking score was calculated based on the proportion of blocks placed by the experimenter (multiplied by 10) relative to the total number of blocks placed. The child received the highest score if they alternated placing blocks equally with the experimenter. A penalty of 5 points was applied if the child knocked the tower over, while an additional 5 points were awarded if the child gently removed blocks from the tower during cleanup. Children were given 2 minutes to clean up the tower and were scored 2 if they cleaned up the towers on the first try, 1 if they needed follow-up after 1 minute, or 0 if they did not clean up the tower.

The go/no-go task assessed inhibitory control in young children [44-48]. In our study, we used an app-based version of the go/no-go task on an Apple iPad. Children were tasked with catching fish (go trials) and avoiding sharks (no-go trials) as they moved across the screen [49]. To enhance the dominant response and increase the difficulty of inhibiting responses during the "no-go" trials, 80% (n=60) of the trials were "go" trials and 20% (n=15) were "no-go" trials. Before starting, children received instructions on both trial types and practiced 5 trials of each. This was followed by a mixed block of 10 practice trials (with 80% being "go" trials). A brief review of the instructions was provided before the task began. The main task consisted of 75 test stimuli evenly distributed across 3 blocks. The stimuli were presented in pseudorandom order, ensuring that no block began with a "no-go" trial and that no more than 2 consecutive "no-go" trials occurred. A 1000-millisecond interval was maintained between stimuli. Scores were calculated by first excluding trials with response times <300 millisecond, as these were considered non–task related. Next, blocks were removed if the child demonstrated nonresponsiveness (ie, go trials with <20% accuracy or no-go trials with >80% accuracy) or indiscriminate responding (ie, go trials with >20% accuracy and no-go trials with <20%). The impulse control score, which reflects the ability to withhold a response in the presence of a strong, automatic tendency to respond, was calculated by multiplying the percentage of correct "go" responses by the percentage of correct "no-go" responses.

Biomarkers

Overview

Data were collected to assess potential physiological mechanisms driving the intervention effects. These mechanisms were evaluated across several biological systems: the autonomic nervous system, the hypothalamic-pituitary-adrenal (HPA) axis, and the hypothalamic-pituitary-gonadal (HPG) axis. These systems were chosen because they play key roles in self-regulation and the body's response to stress and challenge or threat [50].

HRV Measurement

HRV assesses acute stress response and reflects the balance between the sympathetic nervous system and parasympathetic nervous system, both of which are integral to maintaining homeostasis [51]. HRV is a well-established biomarker of an individual's ability to regulate and recover from stress [52].

For teachers and children who opted into this component of data collection, HRV data were collected at multiple time points: before the intervention, every 4 weeks during implementation (with each new module), and at postintervention and 2-month follow-up assessments. To collect HRV data, trained research assistants attached Firstbeat Body Guard sensors (Firstbeat

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Technologies Ltd [53]) to the participants—both children and teachers—by placing them beneath the right collarbone and connecting the sensor cable to the rib cage on the opposite side [54]. If a participant had sensitivities to its placement on the front of the body, electrodes were placed in these equivalent locations on the back. The sensors were removed once data collection was complete.

HRV Collected During Implementation

For children, the baseline HRV was measured while they were sitting still or engaged in low-physical movement during class activities for approximately 3 to 5 minutes. During each program module, HRV was measured in both the active and recovery states, with sensors worn for around 20 minutes during the program implementation days. Teachers wore the sensors at the same time points as the children, both before and after the program, during normal classroom activities, and for the same amount of time as the children during the program.

HRV Collected During Behavioral Tasks

Children wore Firstbeat sensors while completing all the tasks, especially the gift delay task that was designed to induce moderate psychological stress. This task, commonly used in research to provoke a physiological stress response [55,56], was assessed via data collected at preintervention, postintervention, and 2-month follow-up time points. The task sequence involved 3 phases. First, there was a 3-minute baseline phase, where children colored quietly to establish a baseline HRV measurement. This was followed by a 3-minute gift delay task, which was intended to evoke the stress response. Finally, there was a 3-minute recovery phase, where children had time to recover after the stressor. Throughout the paradigm, heart rate and pulse wave activity were continuously monitored to assess changes in vagal tone, allowing for the measurement of both reactivity (the body's immediate response to stress) and recovery (how well the body returns to baseline following stress). This procedure of baseline, task, and recover was followed for the pencil tapping, tower building, and go/no-go task as well, even though they were not hypothesized to elicit the same stress response as the gift delay task.

Hormone Measurements

Hair was collected to measure cortisol, testosterone, and dehydroepiandrosterone (DHEA) levels to capture chronic stress and threat-challenge exposure. Cortisol, a hormone secreted by the HPA axis, is known to rise in response to stress [57]. Testosterone, produced by the HPG axis, also increases in response to challenging situations [58,59]. DHEA is closely linked to both cortisol and testosterone and is needed to tease out the unique coupling effect. DHEA is produced adrenally in both the gonads and the brain. DHEA and its sulfated analog are the most abundant hormones in the body, and as an adrenal androgen, DHEA operates as an end-product of both HPA and HPG axes [60]. By examining the coupling of HPA and HPG axes activity, both independently and together, we can better predict the risk of negative health outcomes related to stress [61]. In addition, exploring HPA and HPG coupling broadens the understanding of stress from the traditional "fight-or-flight" response to a more nuanced "threat-challenge" framework, which can apply to a wider range of real-world stressors [58,62].

Hair samples were collected from both children and teachers who consented to participate in this component of the study. These samples were used to assess cortisol, DHEA, and testosterone levels, as hair is highly sensitive to hormonal changes. Hair sampling is more feasible than saliva collection in preschool-aged children, and hormone measurement is more reliable in hair than fingernail clippings. Hair samples were collected at 3 time points: preintervention, postintervention, and 2-month follow-up time points. A 1-cm section of hair reflects approximately 1 month of growth. Therefore, with hair lengths of several centimeters, we were able to assess the change of time in hormonal activity, with the closest hair to the scalp representing the most recent hormone accumulation [63,64].

Trained research assistants cut a small section of hair, containing around 50 to 100 strands, from the posterior vertex of the participant's scalp following standardized hair sampling procedures [63]. If necessary, multiple small samples from the same region were collected to ensure that there was sufficient hair for analysis. The samples were preserved in foil and envelopes and labeled with the date and participant ID. Family members were also given the option to provide hair samples on site or follow instructions to cut them at home. The research team made efforts to accommodate different preferences for hair sample collection.

Surveys

Overview

Surveys containing standardized questionnaires were completed by parents and teachers either via paper and pencil or electronically via Qualtrics (Qualtrics International Inc), depending on preference and availability. Lead and assistant teachers completed surveys about themselves (self-report), and lead teachers completed surveys about each child in their classroom. Parents completed surveys about their children and a self-report survey about their perceived stress. Table 4 provides the list of survey questionnaires and scales collected at each time point and by respondents. Published scoring guidelines were used for all standard scales and questionnaires.

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Table 4. List of survey assessments and time points collected during the study.

Report type and category	Measure	Respondent	Time point
Report on children			
Sociodemographic	• Age, sex, race or ethnicity, disabilities, home language, and language proficiency	Parent and teacher	Before intervention
Adversity	• Adverse Childhood Experiences Questionnaire	Parent	Before intervention
Social-emotional behavior	• Children's Behavior Questionnaire– very short form • Strengths and Difficulties Questionnaire • Open-ended questions[a]	Parent and teacher	Before intervention, after intervention, and follow-up
Relationship and implicit bias	• Student-Teacher Relationship Scale–short form • Preschool expulsion risk measure • Open-ended questionsa	Teacher	Before intervention, after intervention, and follow-up
Self-report			
Sociodemographic	• Age, sex, race or ethnicity, highest level of education achieved, household income, marital status, employment status, number of kids, and teachers' role[b]	Parent and teacher	Before intervention
Stress level	• Perceived Stress Scale	Parent and teacher	Before intervention, after intervention, and follow-up
Teachers' changes	• Teacher SEL[c] Beliefs Scale • Mindfulness in Teaching Scale	Teacher	Before intervention, after intervention, and follow-up

[a]These were also administered at the midintervention time point.

[b]Data collected only from teachers at follow-up.

[c]SEL: social-emotional learning.

Teacher Reports on the Children

Children who had parental consent were rated by lead teachers on preschool expulsion risk, student-teacher relationship quality, behaviors, and strengths and difficulties.

The Preschool Expulsion Risk Measure was used to measure implicit bias [65]. This 12-item scale included 4 subscales with 3 items each: classroom disruption, fear of accountability, hopelessness, and teacher stress. Items were rated on a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree), and mean scores were calculated. Higher scores represented a greater risk of expulsion.

The Student-Teacher Relationship Scale–short form was used to assess teachers' perceived relationship quality with individual students [66]. This 15-item scale included 2 subscales: closeness (8 items) and conflict (7 items). Items were scored on a 5-point Likert scale ranging from 1 (definitely does not apply) to 5 (definitely applies). Mean scores were calculated with higher scores indicating more quality.

Open-ended questions were included in surveys at each time point. The teacher surveys included questions regarding expectations for each child in the MMP, what makes the job of teaching the child more or less enjoyable, and changes in the child's behavior or typical behavior at school in general and during stressful situations over the course of the intervention. The teacher self-report surveys included questions related to feedback on having the research team visit their classrooms. Teachers were given the opportunity to comment about additional information they liked to share at the end of each survey.

Teacher and Parent Reports on the Children

The Children's Behavior Questionnaire–very short form was administered to evaluate child temperament [67,68]. This 36-item questionnaire contained 3 subscales: surgency or extraversion, negative affectivity, and effortful control. The surgency or extraversion subscale included 12 items about a child's sociability and activity level. Negative affectivity was a 12-item subscale that assessed the frequency of negative emotions, such as frustration. Effortful control was a 12-item subscale that focused on a child's ability to regulate attention and manage impulses. Respondents were asked to read each statement and indicate the child's reaction to that situation. Items were rated on a 7-point Likert scale ranging from 1 (extremely untrue) to 7 (extremely true). If a respondent had not observed the child in the situation, the response was left blank. Mean scores for each subscale were calculated with higher scores representing poor temperament.

The Strengths and Difficulties Questionnaire was a 25-item scale used to measure behavioral and emotional strengths and difficulties in children and young people [69]. This scale was divided into 5 subscales of 5 items each: hyperactivity, emotional symptoms, conduct problems, peer problems, and prosocial behavior. Each item was scored on a 3-point Likert scale ranging from 0 (not true) to 2 (certainly true). Sum scores were calculated for each of the 5 scales. A composite total difficulties score was generated by summing the scores for

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hyperactivity, emotional symptoms, conduct problems, and peer problems. Higher scores for hyperactivity, emotional symptoms, conduct problems, peer problems, and total difficulties denoted worse behavior, whereas higher prosocial scores represented better behavior.

Parent Reports on the Children

The Adverse Childhood Experiences Questionnaire was a 10-item measure used to identify traumatic events experienced during childhood, specifically involving abuse, neglect, and household dysfunction [70]. Each item prompted respondents to indicate whether specific events occurred in their child's life, with answers scored as 1 (yes) and 0 (no). A total Adverse Childhood Experiences Questionnaire score was generated by summing the responses across all items. For this study, only 8 items were used; items regarding reportable events were removed. The minimum score was 0 and the maximum was 8, with a higher score indicating greater exposure to adverse childhood experiences.

The parent surveys about their child included open-ended questions regarding what makes parenting them more or less enjoyable and changes in the child's behavior or typical behavior at home in general and during stressful situations that occurred over the course of the intervention. In the middle of programming, parents with children in the intervention group were asked whether their child shared anything with them about the program. At the end of classroom programming, parents were asked questions about using the calming corner kit at home. Parents were given the opportunity to comment about additional information they liked to share at the end of each survey.

Teacher and Parent Self-Reports

The Perceived Stress Scale was used to assess how different situations affect feelings and perceived stress over the past month in both teachers and parents [71]. This scale includes 10 items rated on a 5-point Likert scale ranging from 0 (never) to 4 (very often). Scores range from 0 to 40 with higher scores representing greater perceived stress.

The Mindfulness in Teaching Scale was used to assess teachers in the context of their teacher activities [72]. This 16-item scale is divided into 2 subscales: 8-item Intrapersonal Teacher Mindfulness and 8-item Interpersonal Teacher Mindfulness. Items are rated using a 5-point Likert scale, from 1 (never true) to 5 (always true). A total of 8 items were reverse coded such that subscales and total mindfulness score calculated sums had higher scores, indicating a greater level of mindful teaching.

The Teacher Social-Emotional Learning Beliefs Scale was a 12-item scale that assessed teachers' beliefs about SEL [73,74]. This measure was divided into 3 subscales, each with 4 items: comfort with teaching SEL, commitment to learning about SEL, and school culture surrounding SEL. Respondents were asked to read each item and rate their agreement with each item for the past 4 weeks on a 5-point Likert scale from 1 (strongly disagree) to 5 (strongly agree). Composite scores for each subscale were generated by summing each item's scores, with scores ranging from 4 to 20.

Postintervention Interviews and Focus Groups

Between June and August 2024, qualitative data were collected through interviews and focus groups with teachers, parents, and administrators. These interviews and focus groups gathered insights into teachers' and parents' perceptions of the program's effectiveness, challenges encountered, and suggestions for improving the program. In the intervention group, 5 teachers completed interviews, 4 parents participated in 2 focus groups and 1 parent completed an interview. A total of 4 interviews were conducted with administrators. In the control group, there were 2 interviews with teachers and 3 with parents after the intervention.

The protocols for the qualitative data collection were adapted from protocols used in other qualitative studies of mindfulness programs [75,76]. Modifications were made by the project team to capture a wide range of insights. The protocols for each set of reporters began with questions or probes about experiences with the program (eg, "Describe your experiences working with implementers."); perceived changes in participants (eg, "Since the program began, what changes, if any, have you observed?"); and experiences with research components (eg, What was your experience with these data collection components?). The wording was modified based on whether the interviewee was a parent, teacher, or administrator. Protocol questions were informed by team members' foundations in implementation science, addressing broad constructs such as barriers and facilitators of implementation, as well as implementation outcomes such as acceptability or sustainability, more specifically [77,78]. For example, 1 question was, "Thinking about the next academic year, what are your hopes for the programming to continue in your school? What supports will help it continue?"

Program Implementation Measures

Several strategies were used to assess implementation fidelity, acceptability, feasibility, and sustainability. In addition to the qualitative interviews, focus groups, and open-ended survey questions about program components (described in the Surveys section and the Postintervention Interviews and Focus Groups section), implementation was documented through (1) implementer-reported fidelity assessment forms, (2) teacher-reported activity logs, (3) attendance and engagement logs, (4) videos, and (5) field notes. Fidelity forms were modified from a previous school-based mindfulness study [76] and included fidelity to curriculum components and core process quality (eg, the day's planned activities, maintaining engagement, and overall quality). Teacher activity logs documented instances when teachers implemented program activities outside the designated implementation period, including details on which activities were used (eg, weekly primary and booster sessions), how often they were implemented, the duration, and the context in which they occurred. Attendance and engagement logs tracked attendance of children and teachers, as well as engagement, disruptiveness, and open-ended notes per session. Finally, field notes were written per session to document the contextual factors (eg, special considerations for child life events, school disruptions, and technology difficulties).

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Data Analysis

Qualitative, quantitative, and mixed methods analyses will be used. Scale and subscale reliability was assessed using Cronbach α values. Quantitative data will be analyzed using descriptive and inferential statistics. Standard descriptive statistics are conducted to understand variable distributions (eg, sociodemographic characteristics). Inferential parametric and nonparametric statistics (mean comparisons via 1-tailed *t* tests and linear regression) will be used to answer research questions about program and implementation effects for objectives 2 and 3. Content and thematic analysis approaches will be used to analyze qualitative data (interviews, focus groups, and open-ended survey responses) for objective 1. Qualitative and quantitative findings will be integrated, where appropriate.

Ethical Considerations

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the University of Illinois Urbana-Champaign Institutional Review Board (IRB23-0310). All data have been deidentified with unique numeric study IDs created for each participant. Digital copies of data are stored on university-maintained secure servers and password-protected computers. Hard copies of data are stored in locked file cabinets in a secure office. Pseudonyms will be used for qualitative data reporting. Audio files, video files, and photos will be destroyed at the end of the study.

Informed consent for children was obtained from legal guardians, and teachers provided consent for their own participation. Participants had the option to provide consent in person or electronically via the Qualtrics survey platform.

Participants were compensated US $5 for each survey they completed. Those who consented to hair collection and wearable sensors received US $10 for each sample. Parents who consented to provide existing school and observational data received US $10. A bonus of US $15 was given to teachers and parents who provided all data at each time point. Participants who completed interviews or focus groups received US $15. The maximum total for parents and teachers was US $100. Teachers who completed the entire study received a US $150 account transfer to purchase supplies for their classrooms.

Results

Demographics and Study Flow of Participants

The intervention and data collection have been completed. Currently, data are being processed for analysis. To determine whether there were group differences in demographic variables between the intervention and waitlist control groups, we conducted *t* tests for continuous variables and chi-square tests (Fisher exact test) for categorical variables. The intervention group was significantly older than the control group ($t_{30}=-2.97$; $P=.006$). There were no other statistical differences in any demographic characteristics.

Overall, there was limited attrition across the study. The study flow and sample sizes for each component are illustrated in Figure 2.

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Figure 2. Diagram of the flow of participants through each stage of the study. GNG: go/no-go task.

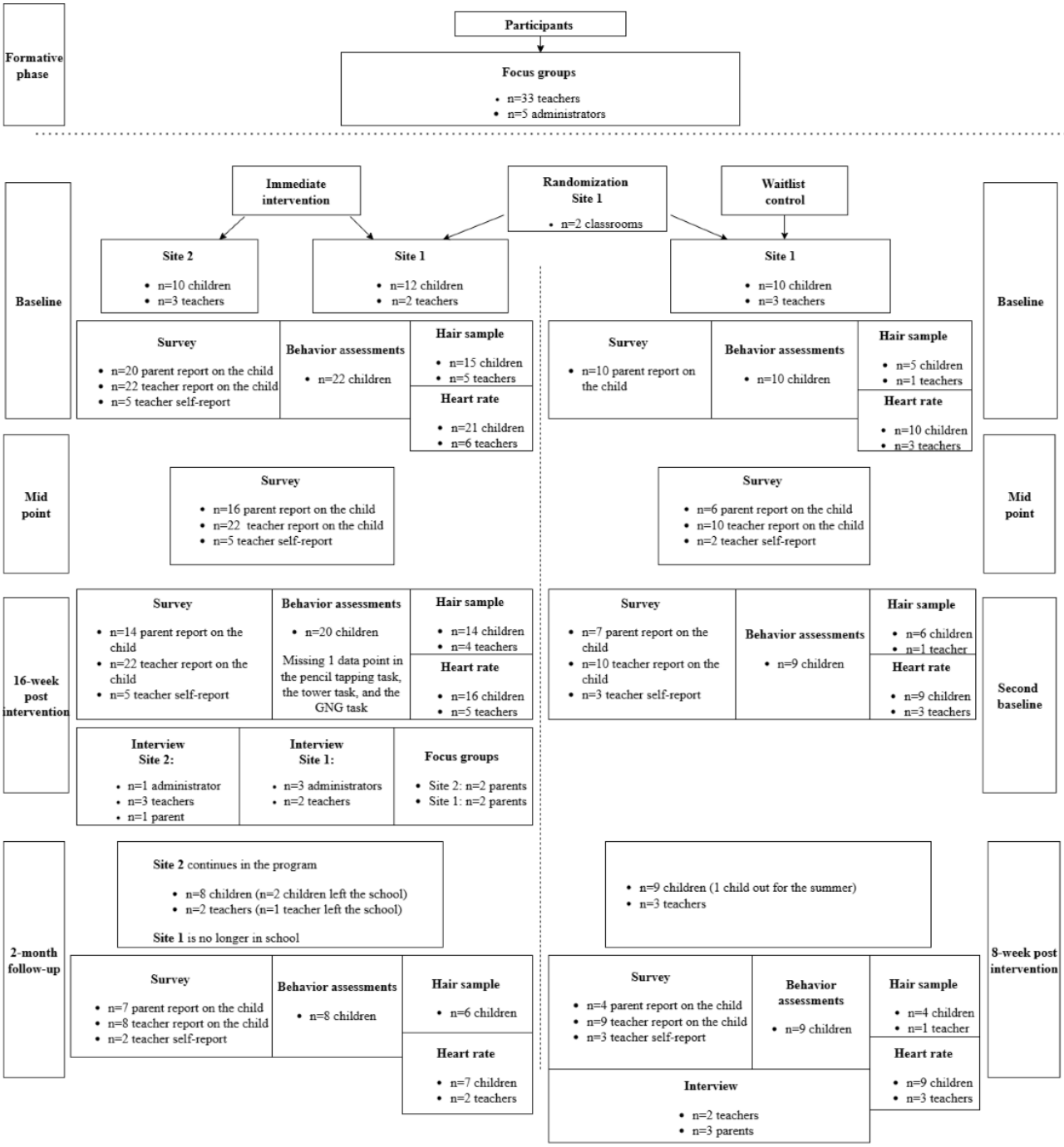

Feasibility and Acceptability

Although benchmarks or thresholds of success are not agreed upon for pilot studies, we aimed for 75% parent consent for all data collection components. This threshold was achieved for children who consented to wear sensors at >95% and nearly achieved for all research components and hair at >65%. This is consistent with recommendations by Teresi et al [32]. All participating teachers consented to all parts of the research study. Focus groups and interviews revealed acceptability among teachers and administrators who reported that a mindfulness-based intervention in the classroom would be welcome, with a few teachers noting that physiological data collection would require intentional communication with parents who may have reservations; those recommendations were incorporated into recruitment and consenting procedures, although direct quantification remains challenging.

Scale and Subscale Reliability

Reliability was calculated for each scale and subscale. Cronbach α values for all scales and subscales are presented in Table 5. In total, 26 scales and subscales had Cronbach α values of ≥0.70, 2 scales had values between 0.60 and 0.69, and 5 scales had a value at 0.60. A cutoff value of 0.60 is considered acceptable for reliability [79]. For the 5 subscales with reliability <0.60, we assessed whether removing any items would improve the reliability and found that it increased to >0.60 for 4 of them (Table 5).

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Table 5. Reliability values for survey measurements.

Measures	Cronbach α[a]	Items, n	Improvement	Items deleted
Teacher report on child				
Preschool Expulsion Risk Measure				
Full scale	0.96	12	__[b]	—
Classroom disruption	0.96	3	—	—
Fear of accountability	0.83	3	—	—
Hopelessness	0.89	3	—	—
Teacher stress	0.97	3	—	—
Student-Teacher Relationship Scale				
Closeness	0.84	8	—	—
Conflict	0.86	7	—	—
Children's Behavior Questionnaire				
Surgency	0.82	12	—	—
Negative affect	0.57	12	0.61	26[c]
Effort control	0.70	12	—	—
Strengths and Difficulties Questionnaire				
Hyperactivity	0.89	5	—	—
Emotional symptoms	0.68	5	—	—
Conduct problems	0.70	5	—	—
Peer problems	0.48	5	0.64	23
Prosocial behavior	0.90	5	—	—
Total difficulties	0.87	20	—	—
Teacher report on self				
Perceived Stress Scale				
Short	0.70	4	—	—
Sum	0.89	10	—	—
Mindfulness in Teaching Scale				
Intrapersonal teacher mindfulness	0.59	9	0.71	4[c]
Interpersonal teacher mindfulness	0.60	5	—	—
Teacher Social-Emotional Learning Beliefs Scale				
Comfort	0.82	4	—	—
Commitment	0.94	4	—	—
Culture	0.41	4	0.67	12
Parent report on child				
Children's Behavior Questionnaire				
Surgency	0.77	12	—	—
Negative affect	0.80	12	—	—
Effort control	0.75	12	—	—
Strengths and Difficulties Questionnaire				
Hyperactivity	0.742	5	—	—
Emotional symptoms	0.49	5	0.53	16
Conduct problems	0.70	5	—	—

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Measures	Cronbach α[a]	Items, n	Improvement	Items deleted
Peer problems	0.63	5	—	—
Prosocial behavior	0.84	5	—	—
Total difficulties	0.81	20	—	—
Parent report on self				
Perceived Stress Scale				
Short	0.79	4	—	—
Sum	0.93	10	—	—

[a]Cronbach α values reported for the preintervention time point only.

[b]Not applicable.

[c]Reverse-coded items.

Discussion

Program Outcomes

The study investigates the effect of an MMP on preschool children's social-emotional, behavioral, and cognitive outcomes, including effects on acute and chronic stress. A mixed methods approach was used, integrating quantitative, qualitative, and physiological data. The study addresses several notable gaps in the literature, including determining MMP effects on a sociodemographically diverse population of preschoolers, identifying differential responses by program component (eg, movement alone and movement plus breathing), and exploring underlying physiological and social-emotional mechanisms of intervention responsivity. Taking this approach will further enrich our understanding of the potential mechanisms and efficacy of mindfulness-based interventions.

Feasibility and Acceptability of the MMP

Unique to this study is the collection of formative qualitative data used to improve the feasibility and acceptability of programming and the design of the research protocol. Results from this pilot study will inform the scaling of the MMP across multiple sites and settings. This MMP will be improved through our evaluation of program feasibility, including whether the program was implemented with fidelity or adaptations at each site by the program implementers and teachers. Qualitative findings related to program implementation; expectations; and outcomes from parents, teachers, and school administrators will guide modifications. We will use observed engagement levels among children, teachers, and parents to identify any additional improvements to the MMP. Furthermore, the study will determine the feasibility of collecting diverse forms of data in preschool settings, including physiological (heart rate sensor data and hair samples), behavioral, and survey data.

Strengths

Strengths of the study include its focus on the crucial early childhood period for emotion regulation and behavioral intervention, the investigation of physiological and behavioral mechanisms undergirding the effects of mindfulness on outcomes, and the exploration of program implementation feasibility and acceptability among diverse early childhood populations. The study uses multiple reporters and data sources to triangulate findings and uses a whole-person approach. Moreover, it examines short-term and sustained effects of programming on teacher and child outcomes. It captures potential dose effects by administering 16 weeks of programming to the intervention group and 8 weeks of programming to the waitlist control group. Finally, it incorporates a train-the-teacher model of implementation that can be tested with follow-up, even for 2 months, to inform the need and frequency for boosters and technical assistance.

Limitations

Limitations include the small sample size of 32 children and 8 teachers and the relatively short follow-up period of only 2 months, leaving the sustained effects uncertain. Teacher effects may affect findings. The use of multiple reporters and data sources (eg, parents, observations, and behavioral tasks) helps reduce potential bias. Finally, some items on subscales had to be deleted to achieve a Cohen κ of at least 0.6, which reduces the number of items.

Conclusions

Results from this study will enrich our understanding of mindfulness-based interventions on preschool children. Findings from this pilot study will also guide the scaling of this RCT across additional diverse preschool populations. An adequately powered full-scale RCT will provide a better understanding of mechanisms of change and child responsiveness to different MMP components, helping to inform the tailoring of future programs to determine what works best for whom and under which circumstances.

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Data Availability

The datasets generated or analyzed during this study are not publicly available due to privacy or ethical restrictions.

Authors' Contributions

JKD conceptualized the study, secured funding, and led the investigation. DAE led project and data management and served as co–first author of this manuscript. JKD, RJ-G, and HL collected data. JKD, DAE, HL, RJ-G, KNW, and CX formally analyzed and verified the data and wrote, reviewed, and edited the original and later drafts of this paper.

Conflicts of Interest

None declared.

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Abbreviations

DHEA: dehydroepiandrosterone
HPA: hypothalamic-pituitary-adrenal
HPG: hypothalamic-pituitary-gonadal
HRV: heart rate variability
MMP: mindful movement practices
M2M-CC: Mission2Move and Calm Caterpillar
SEL: social-emotional learning
RCT: randomized controlled trial
PBIS: positive behavioral intervention and supports

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Protocol

Community-Engaged Approach to Increase Physical Activity Among Black Individuals With Colorectal Cancer: Protocol for a Feasibility Randomized Controlled Trial of the Physical Activity Centers Empowerment Study

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Abstract

Background: Black individuals are more likely to die from colorectal cancer (CRC) and experience more treatment-related side effects compared to White individuals. Physical activity (PA) has been associated with decreased side effects, improved CRC treatment completion rates and responses, and survival. However, Black survivors of CRC are 60% less likely to engage in PA than White survivors. The Physical Activity Centers Empowerment (PACE) study is testing an intervention specifically designed to increase PA among Black individuals diagnosed with CRC.

Objective: This study outlines the protocol for a randomized controlled trial. The study aims to test the feasibility of PACE and will use the reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) framework.

Methods: The PACE study was developed in partnership with a community advisory board consisting of Black cancer advocates and survivors of cancer. The study aims to recruit 72 participants aged >18 years from North Carolina who have been diagnosed with CRC. These participants will be randomized in a 1:1 ratio to an intervention or control group. During the 12-week intervention, all participants will receive a wearable activity tracker and informational materials from the American College of Sports Medicine's "Moving through Cancer" program. The intervention group will also receive additional PACE theory–guided intervention

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components, including personalized daily adaptive step goals, access to the PACE video library, and optional video chat meetings for PA support. Data will be collected at 3 time points: baseline, after the intervention (3 months), and 6 months after the intervention (9 months). Using the RE-AIM framework, the study aims to evaluate the intervention's reach, effectiveness, acceptability, implementation, and maintenance.

Results: The National Institute on Minority Health and Health Disparities funded this study in 2021. Study enrollment began in August 2024 and is anticipated to conclude in December 2024.

Conclusions: This study will advance our understanding of effective behavioral strategies to increase PA and help advance the use of PA as a form of complementary cancer treatment, with the aim of improving health outcomes for Black survivors of CRC.

Trial Registration: ClinicalTrials.gov NCT06411756; https://clinicaltrials.gov/study/NCT06411756

International Registered Report Identifier (IRRID): DERR1-10.2196/65804

(JMIR Res Protoc 2025;14:e65804) doi:10.2196/65804

KEYWORDS

African American; community-based participatory research; physical activity; colorectal cancer; disparities

Introduction

Background

Colorectal cancer (CRC) has a disproportionate impact on Black individuals, who experience higher incidence rates and CRC-related mortality compared to White individuals [1]. Black Americans also experience a higher CRC symptom burden compared to White individuals, including treatment-related side effects, such as pain, fatigue, depression, and bowel dysfunction, which affect their quality of life [2]. Physical activity (PA) has been shown to help manage these side effects, improve treatment completion rates and responses, and improve survival [3]. Despite the safety and benefits of PA during CRC treatment [4,5], Black survivors are 60% less likely to engage in PA compared to White survivors [6]. This disparity underscores the urgent need for targeted, culturally relevant interventions that promote PA during CRC treatment in Black populations. However, few interventions have been designed specifically with and for this population, and even fewer have been evaluated for feasibility before scale-up.

The Physical Activity Centers Empowerment (PACE) study tests a PA intervention designed with and for Black survivors of CRC. Grounded in the National Institute for Minority Health and Health Disparities (NIMHD) Research Framework [7] and the affective-reflective theory (ART) of physical inactivity and exercise [8], the intervention was developed through qualitative research with Black survivors of cancer and oncology nurses, identifying key barriers and facilitators to PA engagement. This foundational work informed both the structure and content of the PACE intervention, ensuring alignment with community needs and evidence-based behavior change strategies. This study aims to assess the feasibility of the PACE intervention. Measurement of feasibility will be based on applying the reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) planning and evaluation framework to the intervention [9].

A feasibility study is a critical and appropriate next step before launching a fully powered trial. It allows the evaluation of core implementation outcomes, including recruitment, retention, intervention delivery, and participant engagement, each of which is essential to understanding whether the intervention is acceptable, practical, and sustainable in real-world settings. This is particularly important when working with populations considered historically underserved, such as Black survivors of CRC, where community engagement and contextual fit must be rigorously assessed before moving to effectiveness trials.

The PACE study was created and is being implemented and disseminated in collaboration with the members (PD, DFL, JLM, and KC) of Stiving to Hold Accountability in Research Equity (SHARE)—a community advisory board whose mission is to work with researchers to identify community needs and promote evidence-based interventions to reduce cancer disparities that impact Black and African American communities [10]. The PACE study protocol is detailed in the study, with our reporting guided by the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist—a guide for reporting clinical trial protocols. (Multimedia Appendix 1). Recruitment of participants began in August 2024 following version 1 of the study protocol.

Objectives

The objective of this study is to describe the design, rationale, and protocol of the PACE feasibility trial. The PACE trial will evaluate the feasibility of delivering a culturally tailored, theory-based PA intervention among Black survivors of CRC and will generate preliminary data on implementation and potential intervention impact. The findings from this study will inform future efficacy and dissemination efforts.

Methods

Study Design

The PACE feasibility study is a community-based 9-month 2-arm parallel group randomized controlled trial. A total of 72 participants will be enrolled and randomized 1:1 to either an intervention group or a control group. All participants will receive a wearable activity tracker (Fitbit Inspire, Fitbit, Inc) and the American College of Sports Medicine's "Moving Through Cancer" materials [11]; intervention arm participants will receive the 12-week PACE intervention. Participants will complete study measures at baseline, immediately after the intervention (3 months after baseline), and 6 months after the intervention. Participation will be discontinued if a participant

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dies or requests to withdraw from the study. Figure 1 shows an overview of the study flow.

Figure 1. Overview of the study flow for the Physical Activity Centers Empowerment (PACE) study.

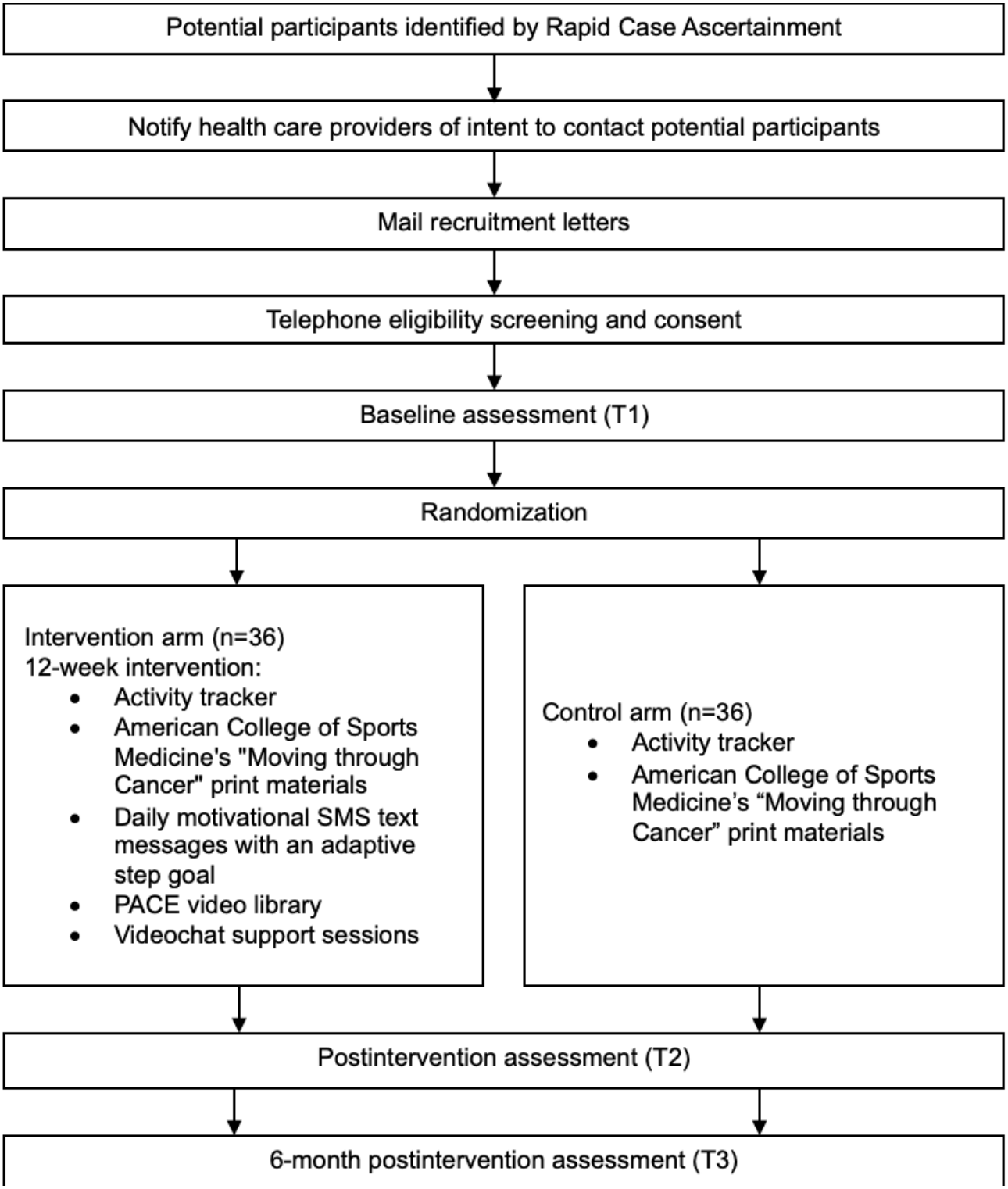

Ethical Considerations

This study was approved by the University of North Carolina (UNC) Lineberger Comprehensive Cancer Center Protocol Review Committee and the UNC Chapel Hill Institutional Review Board (IRB; 21-0881). The PACE feasibility trial is registered with ClinicalTrials.gov (NCT06411756).

Conceptual Framework

The conceptual framework guiding PACE (Figure 2) follows the NIMHD research framework's 5 domains of health influence (ie, built and physical environment, sociocultural environment, health care system, behavioral outcomes, and biological outcomes) [7]. To develop the PACE framework, the aforementioned qualitative study [12] was conducted with Black survivors of cancer to identify PA barriers and facilitators related

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to the physical and built and sociocultural environment domains. In addition, a survey was conducted with oncology nurses to evaluate the feasibility of delivering the intervention within the health care system. Findings showed that while nurses recognized the benefits of PA interventions for patients, implementation in clinical practice was challenging because of competing demands and limited resources [13]. These findings align with a systematic review on nurse recommendations for PA during CRC treatment, which concluded that while providing PA recommendations is feasible for nurses, integrating a full PA intervention into clinical practice is not [14]. Findings from these formative studies with Black survivors of cancer and oncology nurses were applied to develop the PACE intervention, which aims to improve PA and related outcomes in the behavioral domain, which, in turn, are hypothesized to improve outcomes in the biological domain, including inflammatory biomarkers, symptoms, and side effects.

Figure 2. Physical Activity Centers Empowerment guiding framework. Text in gray boxes indicates the National Institute for Minority Health and Health Disparities domains and how they structure the study. Text in red outlines the study's theoretical framework. Text in blue indicates the outcome variables measured. IL: interleukin; TNFα: tumor necrosis factor α.

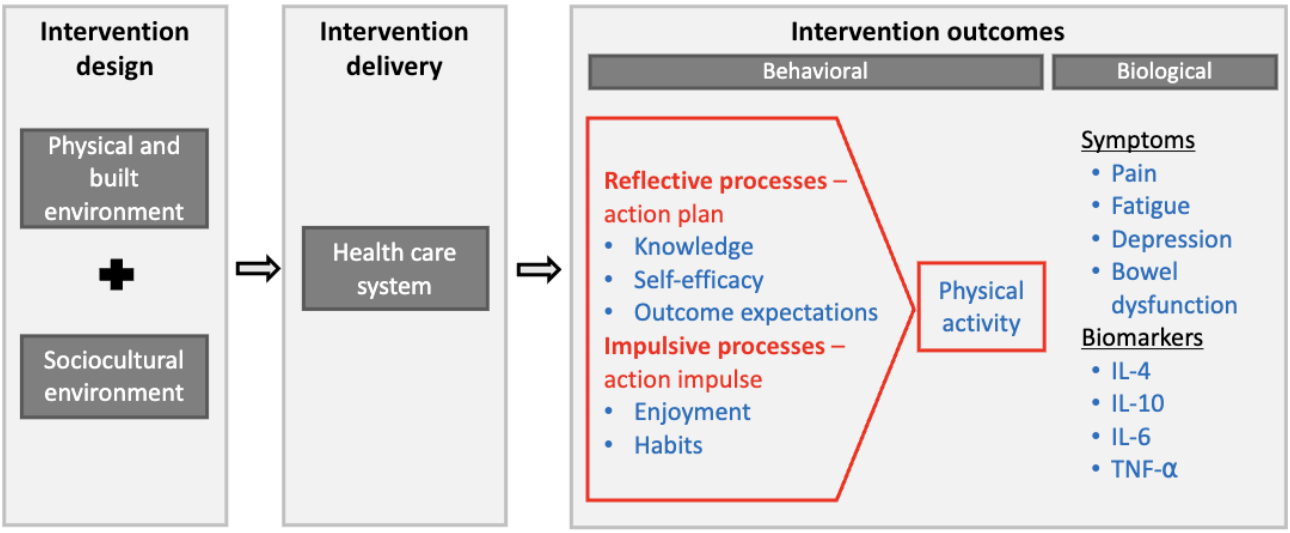

Intervention Overview

The PACE intervention was informed by qualitative research conducted with SHARE, which highlighted the need for a PA intervention for Black individuals undergoing cancer treatment to address physical and psychological challenges; incorporate support from faith, family, other survivors, and the Black community; emphasize psychological benefits of PA; and include realistic, flexible goals [13]. On the basis of these insights, potential intervention components were drafted and refined through qualitative interviews with 9 Black survivors of CRC. The study team and SHARE members reviewed the findings to finalize the intervention. The key design elements determined from these interviews include Fitbit use, SMS text messages emphasizing PA's mental health benefits, individualized step goals, personal story videos, PA resources, side effect management strategies, and print materials.

The PACE intervention is guided by the ART of physical inactivity and exercise, which accounts for both reflective processes and impulsive processes that influence PA behavior [8]. In contrast, most behavioral theories commonly used in PA interventions focus solely on reflective processes, predicting PA intentions but having limited impact on PA behavior. Thus, the PACE intervention targets theoretical constructs that relate to reflective (ie, knowledge, self-efficacy, and outcome expectations) and impulsive processes (ie, enjoyment and habit). Structured around these constructs, behavior change techniques (BCTs) [15] are applied in the intervention to increase PA. Multimedia Appendix 2 provides an overview of intervention components, theoretical constructs targeted, and BCTs used in each component.

Community Engagement

PACE recruitment methods were created in collaboration with the Angelic Warrior Foundation (AWF). The AWF is a nonprofit organization based in North Carolina focused on raising CRC awareness and supporting patients with CRC and their families (Angelic Warrior Foundation, Inc. 2020). The PACE researchers and AWF work closely on research and community CRC awareness and support initiatives, with the AWF president (PD) serving as a SHARE member (ie, the community advisory board for PACE) and the PACE principal investigator (RH) serving on the AWF board of directors. AWF played a key role in shaping recruitment strategies by drafting study introduction letters, codeveloping all materials included in recruitment packages, and collaborating on the timing and frequency of participant outreach via mail and telephone.

Recruitment

Potential study participants will be identified through the Rapid Case Ascertainment (RCA) program. The RCA program is a collaboration between the North Carolina Central Cancer Registry and the Lineberger Comprehensive Cancer Center at UNC Chapel Hill, designed to rapidly identify newly diagnosed cancer cases and facilitate timely recruitment for research studies. Individuals diagnosed with CRC in the past year will be identified through the RCA program, which will provide the PACE team with the contact information for both the individuals

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and the physicians who diagnosed their cancer. Following RCA protocols, the PACE team will first contact each provider for permission before mailing study information to the potential participants.

Eligibility Criteria and Screening

One week after the recruitment package is mailed, study staff will call potentially eligible participants to assess their interest in study participation and confirm eligibility among those interested. Inclusion and exclusion criteria are listed in Textbox 1. The Physical Activity Readiness Questionnaire (PAR-Q) [16] will be used to assess participant safety for engaging in PA. Per PAR-Q guidelines, individuals who endorse items 1 to 4 (having a diagnosed heart condition requiring doctor-recommended PA, experiencing chest pain during PA, recent chest pain, or episodes of dizziness or loss of consciousness) will be ineligible to participate. Individuals endorsing items 5 to 7 (bone or joint problems aggravated by PA, use of prescription medications for blood pressure or heart conditions, or other medical concerns) will be eligible if they obtain provider approval. In addition, we acknowledge the availability of the updated PAR-Q for Everyone and will consider its use in future studies. Potential participants confirmed to meet the eligibility criteria will complete verbal informed consent and a demographic survey over the telephone. Consenting participants will be mailed a data collection package that includes materials for blood self-collection, a prepaid return package to return blood samples, and the wearable activity tracker with setup instructions. Participants will be sent video instructions on setting up and using the activity tracker (Fitbit Inspire) and completing self-collection blood samples. Participants will be provided a link to video instructions for blood collection. Consenting participants will also receive a unique URL to complete baseline survey measures on the web through a secure web-based data capture program called REDCap (Research Electronic Data Capture; Vanderbilt University) [17]. Participants will be emailed an authentication web link to authorize the study team to access data from their activity tracker. Within a week of the activity tracker being mailed, study staff will assess whether the participant's data from the device are accessible. If a participant's data are not accessible, staff will contact the participant and follow up daily for 7 days, as needed, to troubleshoot the activity tracker setup process.

Textbox 1. Inclusion and exclusion criteria for participants in the Physical Activity Centers Empowerment (PACE) study.

Inclusion criteria

- Self-identify as African American or Black
- Histological diagnosis of adenocarcinoma, goblet cell, adenosquamous, or medullary carcinoma of the colon or rectum
- Aged >18 years

Exclusion criteria

- Endorsing items 1 to 4 on the Physical Activity Readiness Questionnaire (PAR-Q; ie, being told by a doctor that you have a heart condition and should only do physical activity [PA] recommended by a doctor, experiencing chest pain when doing PA, chest pain within the last month, or loss of balance because of dizziness or losing consciousness)
- Endorsing items 5 to 7 on the PAR-Q (ie, bone or joint problems that could be worsened by PA, currently taking prescription drugs for blood pressure or a heart condition, or other known reasons you should not do PA) and failure to obtain provider consent for participation
- Plans for a major surgery other than colorectal cancer–related surgery within the next 6 months (eg, knee replacement)
- Current participation in another PA research study
- Pregnant or planning to become pregnant
- Does not own a smartphone with active data plan (required for synchronizing with the wearable activity tracker)
- No internet access (required for viewing PACE videos)
- Not willing to be randomly assigned
- Not willing to use the wearable activity tracker throughout the study

Randomization

After confirmation that baseline surveys have been completed, a research assistant will enroll participants using a random number list generated in REDCap tools to assign participants to the intervention or control group in a 1:1 ratio. The tool conceals the sequence until the research assistant clicks the button to complete the randomization. Participants will not be aware of their randomization results. However, participants will be able to self-identify whether they receive the PA intervention. Study arm assignments will be revealed only to research assistants responsible for mailing study materials to ensure the correct materials are mailed. In addition, those who lead monthly video chat meetings will identify that the meeting participants are assigned to the intervention arm.

Interventions

Control Arm

Control arm participants will receive an activity tracker and the American College of Sports Medicine's Moving through Cancer" booklet. These components were selected to create a control condition that provides widely available and commonly used activity trackers and publicly available PA recommendations. The control condition will facilitate the

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examination of the effects of the theory-guided PACE intervention components.

Intervention Arm

In addition to the activity tracker and booklet, intervention arm participants will also receive (1) a daily adaptive step goal via an SMS text message with a short positive message, (2) access to the PACE video library, and (3) optional monthly video chat (Zoom) meetings for PA support.

Daily Adaptive Step Goal Sent With a Short Positive Text Message

Participants will be asked to wear their PACE-issued activity tracker daily throughout the PACE intervention. The tracker will display the number of steps a participant takes throughout a given day. The study team will collect daily steps from participants' accounts associated with the tracker, which will be used to generate a tailored goal for each participant that is responsive to their changing PA levels as they navigate cancer and treatment side effects. Using a previously developed rank order algorithm [18,19], daily step goals will be set at the 60th percentile of participants' daily step counts from the past 7 days. Daily step goals will be texted to participants each morning with a short positive message; Figure 3 shows an example SMS text message.

Figure 3. Example of a daily SMS text message.

PACE Video Library

Throughout the 12-week intervention, web links for each of the 22 PACE videos will be sent to participants via SMS text messaging and email. Once a video is released, participants can view it as many times as they wish for the duration of the study. Each video was created through an interactive process between PACE researchers and SHARE members. Researchers created a first draft for each video topic that included references to exercise oncology and behavior change–related evidence. The topics were selected based on a literature review of PA relevant for survivors of cancer, combined with topics identified in our formative qualitative work and input from SHARE members. Messages within each video address ART constructs (ie, knowledge, self-efficacy, outcome expectations, habits, and enjoyment) and include BCTs [15], as detailed in Multimedia Appendix 2. According to the narrative theory [20], information is processed more deeply, believed, and acted upon when messages are from individuals with whom one identifies. Thus, SHARE members, who are Black survivors of cancer and caregivers, narrated the videos. The respective narrator edited each video script to include their personal experiences and voice. Next, a draft of each script was read, reviewed, and edited in real time during an in-person or virtual meeting between a researcher and SHARE members. The researchers then reviewed, edited, and coded the scripts for BCT content. Finally, the respective narrator for each script provided a final review and edits to ensure the messaging felt like it was in their voice before recording.

Optional Monthly Video Chat Meetings for PA Support

The virtual PA support meetings will be delivered via Zoom video conferencing software [21] and facilitated by a researcher following the focus group methodology [22]. One member of the SHARE community advisory board will attend each session. Each meeting will begin with a confidentiality review, during which all members will be asked to ensure they are in a private place where others cannot hear or see the meeting. All members will verbally state that they commit to keeping the identities and experiences of other group members confidential. The SHARE member will begin with a welcome and group introduction, and then, the researcher will ask questions to guide conversations about each of the theoretical constructs of the PACE study (ie, knowledge, self-efficacy, outcome expectations, habits, and enjoyment). The SHARE member will provide a closing and thank participants for attending the meeting. Meetings will not be recorded; however, the researcher will take notes to capture the main themes of the conversation. The researcher will also document the attendance of participants in a secure university-sponsored and IRB-approved digital folder.

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Data Collection

All outcomes will be measured at baseline, immediately after the intervention (3 months after baseline), and 6 months after the intervention (9 months after baseline). For each assessment point, survey links will be sent via email and SMS text messaging; up to 4 reminders to complete surveys will be sent. Participants may begin the surveys and return to complete them later using a link provided by email upon request. Participants will be sent blood self-collection kits and a prepaid return package at each time point. The collection materials will be labeled with a biosample identifier number unique from their study identifier. The return package will be preaddressed and will contain the return address of the PACE research study to protect against the risk of samples being misplaced or participants being identified during the mailing process. No identifying information beyond the blood samples will be included in the blood return package. If the research team does not receive blood kit return packages within 2 weeks of being mailed, study staff will call and email participants for a maximum of 3 attempts to support participants in completing blood sample collections. If a participant's daily step count is <200 for 4 consecutive days, an automated email will remind them to wear their activity tracker. Study staff will contact participants via telephone and email for a maximum of 3 attempts to troubleshoot their activity tracker use. Participants in the intervention arm will complete a 15-minute telephone interview after the intervention that includes three questions: (1) What aspects of the PACE intervention did you find most beneficial? (2) Were there any challenges or difficulties you faced while participating in the intervention? (3) Do you have any suggestions for improving the PACE intervention?

Outcome Measures

Feasibility

The primary study outcome, feasibility, will be determined using the RE-AIM framework [11], with each of the 5 key RE-AIM elements assessed independently and through specific criteria. Rather than a simple "yes or no" determination or a composite score, feasibility will be evaluated based on thresholds for each element. Specifically, reach will be tested by measuring the number of participants contacted, found eligible, recruited, and retained for the duration of the study. On the basis of enrollment in other similar studies [16,23] involving Black participants and patients with CRC, we determined that feasibility would be achieved if 72 participants are enrolled within 18 months and the total attrition rate is <20%. Intervention effectiveness will be tested by measuring intervention effects on selected behavioral, psychosocial, and health-related outcomes, as well as inflammation biomarkers, as detailed subsequently. We anticipated that, compared to the control group, the intervention group will have higher scores on behavioral, psychosocial, and health-related outcomes, as well as on anti-inflammatory biomarkers, and lower scores on proinflammatory biomarkers. Adoption will be measured as the percentage of providers who agree or grant consent for their patients to participate. Implementation fidelity will be assessed as the extent to which the intervention is delivered as intended. This will be measured by the percentage of intervention days that participants wear their Fitbits, the percentage of eligible intervention arm participants attending support sessions, and the percentage of videos viewed relative to the total number of available videos across all participants. While limited published guidance exists on a priori feasibility thresholds [24,25], we have set the feasibility threshold at 60%. This decision is based on recommendations for pilot studies, which suggest selecting a threshold that allows identifying areas where adaptations and improvements can be made in a subsequent efficacy trial [26]. Intervention uptake will be assessed through participant interviews. Intervention arm participants will complete a 15-minute interview via Zoom after the intervention. Using a semistructured format, participants will be asked about their experiences participating in the PACE intervention. Maintenance will be assessed by measuring intervention effects on selected behavioral, psychosocial, health-related outcomes, and inflammation biomarkers 6 months after the intervention. We anticipated that compared to the control group, the intervention group will have higher scores on behavioral, psychosocial, and health-related outcomes, as well as on anti-inflammatory biomarkers, and lower scores on proinflammatory biomarkers.

PA Measures

PA will be measured with wearable activity trackers (ie, Fitbit Inspire), which will capture daily minutes of vigorous, moderate, and light exercises; sedentary time; and the number of daily steps. The data will be used to calculate weekly steps; weekly minutes of light-, moderate-, and vigorous-intensity PA; active days per week; and weekly sedentary minutes. The wearable activity trackers used in this study have demonstrated satisfactory validity on step counts measured by metabolic equivalents [27]. PA will be measured subjectively using an adapted Godin Leisure-Time Exercise Questionnaire [28,29], which asks participants to self-report their weekly minutes of strenuous, moderate, and mild or light exercise. The Godin Leisure-Time Exercise Questionnaire demonstrates good reliability and validity compared to other self-report PA measures [30,31] and has a test-retest reliability coefficient of 0.94, 0.46, and 0.48 for self-reported strenuous, moderate, and light exercises, respectively [32]. Fitbit data will serve as the primary measure of PA. Objective and subjective PA measures will be analyzed in parallel and compared. Where discrepancies arise, descriptive analyses and sensitivity tests will be conducted to explore sources of variation.

This feasibility pilot study is not powered to detect statistical significance. On the basis of prior longitudinal PA intervention studies for survivors of cancer [33-35], conservatively, we anticipate 17% total attrition. Therefore, we will enroll 72 participants to obtain a final sample of 60 (30 in each group). With 30 participants per group, we will have 80% power to detect a standardized mean difference of d=0.74 at 9 months, which is a large effect for a PA intervention.

Sedentary Behaviors

Sedentary behaviors will be measured using the Sedentary Behavior Questionnaire [36], which includes 9 common sedentary behaviors and measures the number of hours per day participants spend doing sedentary behaviors. The questionnaire has shown moderate to excellent intraclass correlation

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coefficients (0.48-0.93) for the time spent on each sedentary behavior and the total sedentary time and acceptable validity for measuring sitting and inactivity minutes [36].

Psychosocial Constructs

Psychosocial constructs will be measured using previously validated scales. PA knowledge will be measured using a behavioral capacity measure primarily developed by Short et al [37]. This measure is a 5-point Likert scale assessing participants' knowledge about the types, intensity, frequency, and skills of doing PA [37]. Self-efficacy will be measured using a 9-item barrier self-efficacy scale and a 4-item task self-efficacy scale, which assess participants' confidence in overcoming barriers to PA and their ability to engage in PA. The 2 self-efficacy scales have Cronbach α values of 0.96 and 0.89, respectively, among patients with cancer [38]. Outcome expectations will be measured using the 19-item Multidimensional Outcome Expectations for Exercise Scale, which has an internal consistency of 0.82, 0.84, and 0.81 for physical, self-evaluative, and social outcome expectations, respectively [39]. PA habits will be measured using a 6-point bipolar scale that assesses the 4 indicators of habit strength:: negative consequences if not done, patterned action, stimulus-response solid bonds, and automaticity [40]. The scale has Cronbach α values ranging from 0.77 to 0.85 for the 4 PA habit indicators [40]. Finally, the 4-item short version of the Physical Activity Enjoyment Scale will measure the enjoyment of doing PA [41]. This scale has internal consistency values ranging from 0.82 to 0.87 among diverse populations.

Patient-Reported Outcomes

Patient-reported health outcomes—commonly observed among patients with CRC and known to be positively influenced by PA—will be measured [42]. These include pain, fatigue, depression, bowel dysfunction (ie, diarrhea and constipation), quality of life, and sleep. These outcomes will be measured using the Patient-Reported Outcomes Measurement Information System (PROMIS) tools [43]. The PROMIS pain, fatigue, depression, and sleep measures have reliability coefficients of 0.96, 0.94, 0.91, and 0.88, respectively, with excellent validity among survivors of cancer [44,45]. The diarrhea and constipation scales also have internal reliability values of 0.88 and 0.89, respectively [46]. Neurotoxicity will be measured using the Functional Assessment of Cancer Therapy/Gynecologic Oncology Group–Neurotoxicity 4 scale. The internal consistency of this scale ranges from 0.73 to 0.91 at different assessment cycles among patients with cancer [47]. Quality of life will be measured using the 36-item Short Form Health Survey [48], which is a widely used survey for assessing respondents' general physical and mental health status to determine their quality of life among survivors of CRC [49], with an acceptable to high internal consistency (>0.07) and validity observed among survivors of cancer [50,51].

Inflammation Biomarkers

Inflammation biomarkers that are thought to mediate the effects of PA on cancer mortality will be measured [52,53]. These include interleukin (IL)-4, IL-10, IL-6, and tumor necrosis factor α and will be measured using serum samples collected with a dried blood spot (DBS) card kit [54]. DBS cards are widely used to assess biomarkers, such as antibodies [55]. The validity of using the DBS card to measure these inflammation biomarkers in this sample will be evaluated with a comparison to whole blood samples collected using a Tasso+ kit [56]. Although DBS cards have been validated in previous studies, we will also validate them with this sample. Because the purpose of this testing is to assess the validity of DBS cards in accurately measuring the biomarkers of interest, a convenience sample is appropriate. Therefore, we will recruit the first 10 consenting participants to ensure we collect the necessary samples. Participation in this part of the study is optional and will not impact study inclusion.

Retention

To support participants' adherence to the study and build their understanding of the importance and value of their participation in the PACE study, we include the PACE logo (Figure 4) in all study documents to help create a sense of identity and the PACE study community. Participants will receive monthly PACE study update cards with a message thanking them for their time; a statement about what the study team hopes to learn from their participation; plans for community and scientific dissemination of findings; and a positive affirmation note from the AWF, our community partner organization described earlier. Participants will receive a US $30 gift card for completing the baseline assessment, a US $40 gift card for completing the 3-month assessment, and a US $50 gift card for completing the 9-month assessment. Intervention arm participants who complete interviews will receive an additional US $15 gift card. The 10 participants who complete the Tasso blood collections will receive an additional US $10 gift card.

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Figure 4. Physical Activity Centers Empowerment (PACE) logo.

Safety and Monitoring

At weekly PACE research team meetings, all issues relevant to study progress, including but not limited to enrollment, safety, regulatory, and data collection, will be reviewed. Unanticipated adverse events will be reported to the IRB within 1 week. Study documents will be made available for inspection when requested by any of the regulatory bodies charged with the safety of human participants and the integrity of data, including, but not limited to, the Office of Human Research Ethics IRB, the Oncology Protocol Review Committee, and the North Carolina Translational and Clinical Sciences Institute Data and Safety Monitoring Board.

Potential participants' information from RCA, including identifiable information (eg, names, phone numbers, and physical addresses), will be stored on a secure university server and will only be available to members of the research team. Identifiable information for potential participants who do not enroll in the study will be removed when the RCA recruitment is completed. For those who enroll, identifiable information will be removed at the study's completion unless participants have agreed to be contacted by the research team for future studies.

Statistical Data Analysis Plans

Reach

Descriptive statistics will be used to calculate the number of participants contacted and the percentage eligible, recruited, and retained for the duration of the study.

Adoption

Descriptive statistics will be used to calculate the percentage of providers who agree to have their patients contacted about the study out of the total number approached, as well as the percentage of providers who grant consent for their patients to participate in PACE out of the total number asked for consent based on the PAR-Q screener.

Implementation Fidelity

Descriptive statistics will be used to calculate the percentage of days that participants wear the study-issued activity tracker, the percentage of participants who participate in the optional PA video chat support meetings, the percentage of videos viewed by participants, and the percentage of days that daily step goals are achieved.

Intervention Uptake

Thematic qualitative analysis [57] will be applied to participant exit interview data to identify barriers and facilitators to participants' uptake of PACE intervention components.

Intervention Effects and Maintenance

Activity tracker data will be used to calculate average steps per week. To explore the intervention effects on outcomes (ie, average weekly steps) from baseline to 3 and 9 months after baseline (6 months after intervention), an intent-to-treat analysis scheme will be adopted, and a mixed-effects model will be fitted to estimate the intervention effect on each outcome. Fixed effects terms will include time point (categorical), intervention group, and intervention × time point, and the model will control for the baseline level of the outcome in addition to age and time

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since diagnosis. A random intercept will be included to account for within-participant correlation. The estimates and tests of the interaction term will be used to assess the preliminary efficacy of the intervention at each time point. Subgroup analysis by sex will be conducted to explore the difference. Missing data will be carefully imputed using mean or median imputation for continuous variables and mode imputation for categorical variables.

Dissemination

Study findings will be shared with the research and medical community via conference presentations and peer-reviewed publications. Participants will receive a lay summary of the study findings. At the conclusion of the study, the PACE video library will be made available to the public via the UNC Lineberger Cancer Network video library [58]. The continuation of virtual support sessions will be explored through collaboration with AWF.

Results

NIMHD funded this study in 2021; NIMHD is not involved in conducting this research. Study enrollment began in August 2024 and is anticipated to conclude in December 2024. As of June 26, 2025, 16 participants have been enrolled.

Discussion

Anticipated Findings

The PACE intervention addresses a critical gap in cancer care by focusing on a population that does not engage in recommended levels of PA and that experiences significant disparities in mortality and quality of life—Black survivors of CRC. The PACE study will provide an understanding of how theory-guided intervention components promote PA in this population beyond what is achieved through publicly and widely available trackers and information. Insights on engaging community advisory board members in implementing PA trials will also be provided. The PACE study will evaluate the feasibility of collecting blood samples using an innovative blood spot collection method. This approach has the potential to significantly enhance the feasibility of conducting biomarker research, particularly among hardly reached populations. It eliminates the barriers of participants needing to travel long distances and finding time for laboratory appointments. The findings from the PACE study on blood spot data collection could greatly impact the volume and generalizability of mechanistic exercise oncology research.

The PACE study tests an intervention that was co-designed with African American survivors of cancer. This study will expand our understanding of how co-designed interventions can improve PA and how scientists can better approach designing and implementing future interventions with hardly reached populations. The use of adaptive step goals is responsive to each individual's circumstances and the evolving needs experienced during cancer treatment. Simultaneously, the PACE intervention is conducive to large-scale implementation, with minimal need for additional interventionist resources. This not only aligns with the increasing role of technology in health care but also provides a scalable and cost-effective method for delivery.

Limitations and Strengths

Limitations noted in the design of the PACE intervention include the use of self-report measures and the potential for social desirability bias. In addition, depending on how long it takes to obtain consent for participation and set up the activity tracker, participants may begin the PACE intervention at different times after receiving their cancer diagnosis. This may lead to variation in the nature and intensity of side effects participants experience and how effects impact their activity levels. However, the use of a control group, as well as daily step goals that are adaptive to individual participants' activity levels, will minimize this study's limitation and allow for the enrollment of participants earlier in the treatment trajectory, as well as an inclusion of a broader range of CRC diagnoses (ie, from early-stage participants undergoing surgery only to those with metastatic disease receiving palliative treatments), all of whom can benefit from PA substantially. Finally, although this study uses previously validated measures, the validity testing for these measures has often been conducted outside the United States, where race and ethnicity are often not reported in study demographics, and much of the research has been conducted with primarily White participants. The PACE study focuses solely on developing and testing an intervention for Black patients because of their historical underrepresentation in prior research. Our study will provide much-needed information on the feasibility of intervention methods and explore intervention effects for this population, including pilot validity data for the exploratory measures used. A further strength of the PACE design is the collaboration with Black survivors of cancer and caregivers in all aspects of this research, from formative research to method development and active engagement in creating and delivering the PACE intervention. Finally, through the use of BCT coding, findings will identify which components of the PACE intervention are most effective and may inform a broad range of future PA interventions for individuals diagnosed with cancer.

Conclusions

Overall, this research has broad implications for addressing cancer disparities, advancing the understanding of PA's impact on cancer outcomes, and innovating intervention strategies for populations considered underserved that can be adapted to benefit additional populations.

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Authors' Contributions

RH, PD, DFL, JLM, KC Jr, ALB, HKS, TT, BZ, JL, SBW, CLB, and CGV contributed to the conceptualization of this study. RH, JX, NW, PD, DFL, JLM, KC Jr, NRB, and RLH directly contributed to the intervention development and data collection methodology. PD, DFL, JLM, and KC Jr served as community consultants for this work and ALB, HKS, TT, BZ, JL, SBW, CLB, and CGV served as research consultants for this work. BZ specifically provided guidance on data analysis methodology. RH, JX, NW, and RLH wrote the first draft of this manuscript. All authors have reviewed and approved the submission and publication of this manuscript.

Conflicts of Interest

None declared

Multimedia Appendix 1
SPIRIT checklist.
[DOCX File , 61 KB - resprot_v14i1e65804_app1.docx]

Multimedia Appendix 2
Physical Activity Centers Empowerment intervention components, theoretical constructs targeted, and behavior change techniques used in each component.
[DOCX File , 82 KB - resprot_v14i1e65804_app2.docx]

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Abbreviations

ART: affective-reflective theory
AWF: Angelic Warrior Foundation
BCT: behavior change technique
CRC: colorectal cancer
DBS: dried blood spot
IL: interleukin
IRB: institutional review board
NIMHD: National Institute for Minority Health and Health Disparities
PA: physical activity
PACE: Physical Activity Centers Empowerment
PAR-Q: Physical Activity Readiness Questionnaire
PROMIS: Patient-Reported Outcomes Measurement Information System
RCA: Rapid Case Ascertainment
RE-AIM: reach, effectiveness, adoption, implementation, and maintenance
REDCap: Research Electronic Data Capture
SHARE: Stiving to Hold Accountability in Research Equity
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
UNC: University of North Carolina at Chapel Hill

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Protocol

Healthy Body and Mind Program to Improve Health Outcomes and Reduce Dementia Risk in People With Osteoarthritis: Protocol for a Feasibility and Acceptability Pilot Randomized Controlled Trial

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Abstract

Background: Globally, approximately 55 million people are living with dementia. Osteoarthritis occurs in half of all older adults and is associated with pain, depression, and increased dementia risk. Currently, no program exists for people with osteoarthritis and cognitive decline that addresses modifiable risk factors, such as physical inactivity and lifestyle behaviors.

Objective: This study aims to examine the feasibility, acceptability, and health outcomes following the 12-week Healthy Body and Mind Program, designed for people with osteoarthritis who are experiencing cognitive decline. The findings will inform the designs of larger trials.

Methods: In total, 20 consenting participants aged 45 years or older with osteoarthritis and cognitive decline will be randomly allocated to the 12-week program or a waitlist control group. Feasibility and acceptability will be assessed based on retention and adherence rates to the program, the number of people who provide consent to take part in the study, and evaluation questions following completion of the program. Health outcomes will include quality of life, cognition (global, attention, learning, and memory), pain, psychological health (stress, anxiety, and depression), and physical health.

Results: This study has been reviewed and approved by the University of New South Wales Human Research Ethics Committee (HC230506). This project will be carried out according to the National Statement on Ethical Conduct in Human Research (2007). As of October 2025, we have enrolled 18 participants and completed their data collection. Results are expected to be published in peer-reviewed journals during the first quarter of 2026. Participant confidentiality will be maintained in line with ethical considerations.

Conclusions: This protocol reports methods to determine feasibility, acceptability, and preliminary health outcome data of the Healthy Body and Mind Program informed by individuals with lived experience of dementia and osteoarthritis.

Trial Registration: ClinicalTrials.gov NCT06070818; clinicaltrials.gov/study/NCT06070818

International Registered Report Identifier (IRRID): DERR1-10.2196/75816

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KEYWORDS

healthy aging; osteoarthritis; pilot randomized controlled trial; dementia; lifestyle; physical activity

Introduction

Background

Globally, approximately 55 million people are living with dementia [1]. Osteoarthritis is experienced by approximately 528 million people worldwide [2] and is associated with a 20% to 25% increase in dementia risk [3,4]. The prevalence of osteoarthritis has been reported in almost half of people living with dementia [5,6]. Both dementia and osteoarthritis are associated with increased pain and depression [7-9] and reduced quality of life (QoL) [8,10]. Comorbid conditions, such as osteoarthritis, depression, and dementia, exacerbate symptoms of a disease; for example, a higher number of comorbidities (ie, multimorbidity) correlates with more severe pain and depression [1].

Depression, anxiety, and reduced QoL are common in dementia [9,11] and osteoarthritis [12], in addition to pain [7]. Furthermore, osteoarthritis has been associated with a 1.2- to 1.5-fold increase in dementia risk [13] and rises to 5.7-fold when experienced with an additional chronic condition [14]. However, most older adults, including people experiencing cognitive decline, are living with comorbid conditions such as osteoarthritis [15,16]. Depression and anxiety are also commonly found as comorbid conditions along with cognitive decline [17] and osteoarthritis, and depression has also been linked with increased dementia risk [18].

Nonpharmacological lifestyle approaches involving physical activity (PA) have been shown to improve health outcomes for 26 different chronic conditions [19], including dementia [20] and osteoarthritis [7]. Osteoarthritis and other chronic conditions are associated with increased dementia risk [20,21], and PA and other nonpharmacological approaches improve health outcomes in older adults while reducing dementia risk [20]. PA interventions improve cognition in people living with dementia [22] as well as reduce dementia risk in older adults [20]. Studies have shown that PA and lifestyle approaches reduce dementia risk [14,20,23] and improve cognition and QoL for people already experiencing cognitive decline [24-26]. Furthermore, nonpharmacological approaches have been shown to be cost-effective [27] and preferable to pharmacological approaches for people living with dementia and their families and care partners [28].

Systematic reviews have shown that PA has a positive effect on cognition [29], depression, and QoL [30]. However, findings are inconsistent regarding the most effective type of PA. Multimodal and mind- and body-focused approaches tend to outperform singular or unimodal approaches [30]. Interventions shown to be effective in reducing pain in osteoarthritis include aerobic and strengthening exercises and multimodal approaches that incorporate lifestyle education specific to osteoarthritis, such as pain coping skills training [31]. Multimodal approaches have been shown to be more effective than unimodal approaches in reducing pain [7] and improving depressive symptoms. PA has positive effects on mental health [32] and improves outcomes for older adults living with anxiety and depression. Meta-analyses have shown that nonpharmacological approaches reduce symptoms of depression in people with cognitive decline [9] and osteoarthritis [7]. Nonpharmacological approaches include care staff education and reminiscence therapy for people living with dementia and multimodal exercise approaches (eg, combined strength, balance, aerobic, and mind-focused approaches such as tai chi and yoga) for people with osteoarthritis.

Despite this evidence, there is a lack of accessible, implementable, and scalable lifestyle programs for people living with comorbid conditions, such as cognitive decline and osteoarthritis. This gap reflects a major opportunity for improving health outcomes and reducing dementia risk. Guidelines for multidisciplinary approaches that include PA have been developed for people living with cognitive decline [33,34], but effective interventions are specifically needed to target people living with comorbidity [15,35] and reduce dementia risk. It is vital to consider associations between conditions and how symptoms may be exacerbated (eg, symptoms of depression resulting from limitations in completing usual daily activities due to osteoarthritis-related pain and cognitive difficulties).

Objectives

We will pilot the evidence-based Healthy Body and Mind Program (HBMP), which includes PA, nutrition, lifestyle, and behavior change education on health outcomes in people living with cognitive decline and osteoarthritis. The evidence base for development of the program is outlined in Figure 1. The primary aims of this pilot randomized controlled trial (RCT) are to determine (1) the feasibility (ie, recruitment, retention, and adherence) of the HBMP for people living with osteoarthritis and cognitive decline in a community clinic and the University of New South Wales (UNSW) Medicine and Health Lifestyle Clinic, Sydney, Australia, and (2) the acceptability of the program to people living with osteoarthritis and experiencing cognitive decline. The secondary aim is to obtain pilot data on health outcomes in people with osteoarthritis and cognitive decline, following the program when compared to usual care. Health outcomes are QoL, cognition, pain, psychological health (depression, anxiety, and stress), and physical health (weight, waist circumference, blood pressure, cardiorespiratory fitness, strength, mobility, and balance). We hypothesize that individuals who complete the program will have better health outcomes when compared to the baseline and the control groups.

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Figure 1. Evidence-based conceptualization illustrating how the Healthy Body and Mind Program will improve health outcomes for people with osteoarthritis and cognitive decline in community settings.

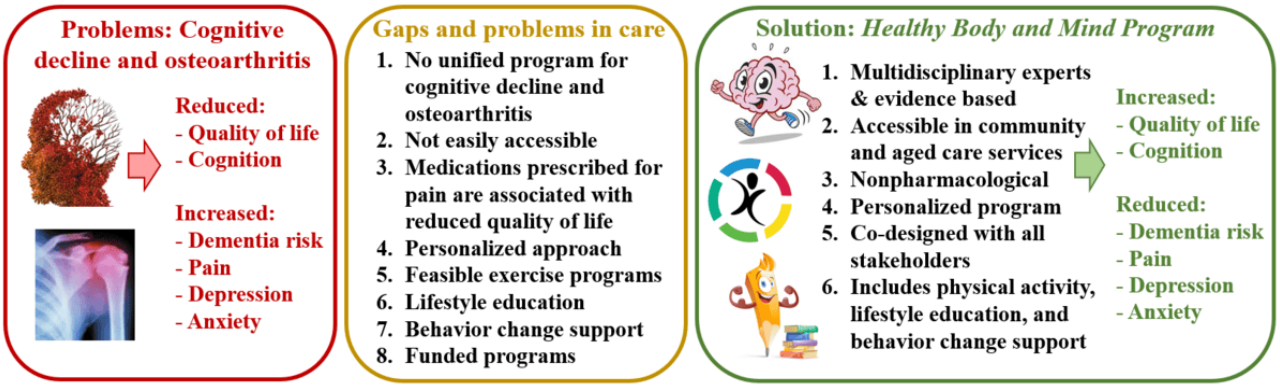

Methods

Ethical Considerations

All data will be deidentified and participants will be allocated a unique identification number. Personal identifying information will be stored separately from research data in a password-protected file accessible only to the research team. Deidentified research data will be stored securely for a minimum of 7 years as per institutional requirements, after which it will be destroyed. Only deidentified data will be used in publications and presentations. All participants will provide written informed consent before participation, after reading the participant information sheet and having the opportunity to ask a researcher any questions. Participation is entirely voluntary and participants may withdraw at any time without penalty or impact on their access to services. Participants who withdraw can request that their data be destroyed, provided the data has not yet been deidentified and aggregated. All participants will receive a lifestyle program provided by accredited exercise professionals and psychologists free of charge (valued at approximately US $2000). Participants who additionally take part in the focus group will receive a voucher worth US $50 to compensate for the extra time commitment involved in this component of the study. All electronic data will be stored on password-protected, encrypted devices and secure university servers. Hard copy materials will be stored in locked cabinets in a secure research office. Only named members of the research team will have access to identifiable data. Ethics approval for this study has been obtained from the UNSW Human Research Ethics Committee (HC230506). This is the third version of the protocol and aligns with approved ethics amendments (most recently approved on June 14, 2024; first approval on September 18, 2023). Changes from the first version pertained to the inclusion criteria, where “Montreal Cognitive Assessment (MoCA) [36] score 18-25 indicating mild cognitive impairment or mild dementia” was removed, and the age requirement was reduced to people aged 45 years or older. These changes were made due to recruitment challenges, although they do not change the overall aims of the study. Other amendments included changes to the terminology used in study materials (“dementia,” “cognitive decline,” and “thinking difficulties” to improve recruitment) and updates to the list of staff members. All team members received email correspondence regarding submitted changes and were requested to review amended documentation where appropriate. The clinical trial has been prospectively registered on ClinicalTrials.gov (NCT06070818). This protocol has been prepared in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Intervention Trials) guidelines (Multimedia Appendix 1) [37].

Study Design

This 12-week pilot RCT of the HBMP with a waitlist control group will use quantitative and qualitative research methodologies. Data collection will comprise the following: (1) clinical observations routinely completed as part of standard care (eg, clinical interviewing, physical assessment, and exercise monitoring), (2) validated patient-reported outcome measures (including QoL, cognition, pain, and psychological health), and (3) focus group or interviews (Table 1). Clinical observations and questionnaires will be completed at baseline (0 wk) and after intervention (12 wk). Initial community and stakeholder engagement has assisted in developing the group program and ensuring it is feasible and acceptable to participants. The study team includes accredited exercise physiologists (AEPs), accredited practicing dietitians, a health psychologist, and research assistants (RAs). All study activities will take place within the UNSW Medicine and Health Lifestyle Community Clinic facilities.

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Table 1. Data collection methods and outcome measures.

Measure or tool	Procedure (tools or guidelines)
Clinical assessments (resting cardiovascular and anthropometry measures)	
Resting blood pressure and heart rate	• Blood pressure will be measured using a validated automated sphygmomanometer. • Participants will be seated and rested for at least 10 minutes before the blood pressure assessment [38]. • Participants will place their forearm on a table with the elbow at an approximate 90° angle, and the cuff will be placed on the upper arm according to the manufacturer's instructions. • Three separate measurements will be taken on both right and left arms, with the average of the 3 measurements used in subsequent analyses.
Waist circumference, height, weight, and BMI	• Weight will be measured using a digital scale (SECA 813 model) with the participant unfasted, barefoot, and dressed in light clothing. • Height will be measured barefoot using a wall-mounted stadiometer (SECA 216 stadiometer). • Waist circumference will be measured according to the International Diabetes Federation guidelines [39].
Handgrip strength	• Handgrip strength will be measured using a manual dynamometer.
Functional fitness	• Functional fitness will be assessed using the submaximal 6-minute walk test [40]. • The participant will be instructed to cover as much distance walking on flat ground in a laboratory setting until they have completed 6 minutes or they choose to stop walking. • Risk of falls will be minimized by the AEP[a] or RA[b] following the participant closely to enable spotting and assistance should they lose balance. • They will also monitor the participant throughout the test for safety (including heart rate and RPE[c]).
Lower extremity function and mobility	• Lower extremity function and mobility will be measured using the Short Physical Performance Battery [41], which involves timing the duration of 5 sit-to-stand repetitions from a chair, feet together, semitandem and full tandem stance, and a 2.44-m walk.
Balance	• Balance will be evaluated using the single-leg balance test. • The participant will be instructed to stand on 1 foot for as long as possible without assistance up to a maximum of 60 seconds. • To minimize the risk of falls, they will be supported by an AEP or RA, and there will be a wall or sturdy chair in front of them that they can hold onto if needed.
Questionnaires	
APSS[d]	• The APSS developed by Exercise and Sports Science Australia will be used to screen exercise readiness [42].
Atherosclerotic Cardiovascular Disease Risk Estimator Plus	• Cardiovascular disease risk will be estimated using the American College of Cardiology calculator [43].
Active Australia Survey	• Physical activity levels will be measured using the Active Australia Survey following the guide and manual for implementation, analysis, and reporting by the Australian Institute of Health and Welfare.
Cognition (global, executive, learning, memory, and visuospatial ability)	• Cognition will be assessed using the MoCA[e] [36] and the Cambridge Neuropsychological Test Automated Battery (attention, memory, and learning tasks).
Pain, physical health, and stiffness	• Pain and stiffness will be evaluated using the WOMAC[f] [44].
Depression, anxiety, and stress	• Psychological health will be assessed using the DASS-21[g] [45].
Quality of life	• Quality of life will be measured using the SF-36[h] (version 2) survey [46].
Qualitative methods	
Participant feedback and recommendations	• Participant feedback and recommendations will be obtained through focus groups or interviews using semistructured questions [47].
Individual or stakeholder feedback and recommendations	• Individual and stakeholder perspectives will be gathered through stakeholder meetings or workshops using a semistructured format.

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Measure or tool	Procedure (tools or guidelines)
Adverse events	• Adverse events will be monitored and reported in accordance with CONSORT[i] guidelines [48].

[a]AEP: accredited exercise physiologist.
[b]RA: research assistant.
[c]RPE: rating of perceived exertion.
[d]APSS: Adult Pre-Exercise Screening System.
[e]MoCA: Montreal Cognitive Assessment.
[f]WOMAC: Western Ontario and McMaster Universities Osteoarthritis Index.
[g]DASS-21: Depression, Anxiety, and Stress Scale-21.
[h]SF-36: Short Form Health Survey-36.
[i]CONSORT: Consolidated Standards of Reporting Trials.

Sample Size Calculation

For pilot trials, using a 90% 1-sided CI, it is estimated that a sample size should be at least 9% of that calculated for a fully powered RCT [49]. Given a minimal clinically important difference of 0.5 SD (medium effect size), QoL measured using the Short Form Health Survey-36 [50], α of .05 (with Holm-Šídák correction), and power of 90% (β=.20) for a 2-group comparison, the required sample size would be approximately 85 participants per group (170 total). Accounting for potential dropout or attrition (15%-20%), 102 participants per group (N=204 total) would need to be recruited for a fully powered trial, and 16 participants would be required for a pilot trial. This study aims to recruit 20 participants.

Eligibility Criteria

Eligibility criteria will be as follows: (1) aged 45 years or older, (2) living with osteoarthritis diagnosed by a health care professional, (3) living with cognitive concerns or dementia, (4) able to safely undertake study assessments and complete exercise without assistance, and (5) have appropriate medical clearance to take part. Exclusion criteria will be as follows: (1) MoCA score of less than 18; (2) unwilling or unable to provide written informed consent and comply with study requirements; (3) inability to speak and understand English unless a translator is available; and (4) contraindications to exercise in accordance with American College of Sports Medicine (ACSM) guidelines (Multimedia Appendix 2) [51], such as symptomatic hernias, proliferative retinopathy, uncontrolled arrhythmias, or rapidly progressing or terminal illness. Consent will be obtained by the lead researcher (CVB).

Recruitment

A total of 20 participants with osteoarthritis and cognitive decline will be recruited through the UNSW Medicine and Health Lifestyle Clinic, StepUp for Dementia Research, and general practitioner and health district referrals. Study advertisements will also be displayed electronically via online social media platforms (eg, X, formerly known as Twitter [X Corp]; Facebook [Meta Platforms, Inc]; and LinkedIn [LinkedIn Corporation]). Initial contact will be made by potential participants emailing the study investigators through the study email or the StepUp team or by referral from a health professional. A member of the research team will then contact potential participants. Participants will be screened in person, online, or over the telephone to confirm their eligibility. The lead investigator will review participant screening data and confirm participant eligibility before providing the participant information sheet and consent form (Multimedia Appendix 3). If eligible and after written consent has been obtained, potential participants will be invited to an in-person screening visit. Demographic information, chronic disease history, lifestyle behaviors, and medication use will be documented. Potential participants will complete the Adult Pre-Exercise Screening System and Exercise and Sports Science Australia [42] screening questionnaires for exercise-induced symptoms (eg, chest pain and musculoskeletal pain; Multimedia Appendix 4). To ensure safety, only people cleared through the screening will be enrolled and randomized. Once deemed eligible, participants will complete written informed consent, and baseline testing will commence. Participants will be assigned a unique ID number to ensure personal details are not linked to collected data.

Due to ethical considerations where many potential participants may not be aware of cognitive decline, the term “thinking difficulties” will be used throughout study advertisements and participant information sheets. An ethically approved protocol is in place for advising people of their health assessment results (eg, cognition and depression) and referring them to their general practitioner where appropriate. Eligible participants will have mild cognitive impairment; therefore, they will have the capacity to provide informed consent.

Following successful screening, the participant will be allocated a unique ID number using the generated list. The RA who performs the randomization will advise the data collectors of the participants’ IDs by referring to the password-protected spreadsheet of participant names and allocated ID numbers. After completion of baseline testing, participants will be randomly assigned to the intervention (n=10) or waitlist control groups (n=10) using a computer-generated randomization list produced by a researcher external to the study group. In total, 20 participants will complete the program. After completing a 12-week period of usual care, those in the waitlist control group will then complete the 12-week HBMP. A 12-week follow-up will be performed to examine sustainability. Participants are allowed to withdraw from the trial at any time they wish and are assured that doing so would not alter their care or relationship with the university or the community clinic.

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Data Collection and Outcome Measures

Feasibility and Acceptability

The feasibility of the program will be determined by the number of eligible participants who provide consent and retention and adherence to the program (ie, number of exercise and education sessions attended, completed, and engaged with). Retention will be determined by the percentage of participants who provide consent and complete the program. Adherence will be determined by the percentage of program sessions attended by participants who enter the program. Adherence will be recorded using attendance records (recorded by the AEP and health psychologist facilitating the sessions). The acceptability of the program will be assessed by postprogram evaluation questionnaires after the program is completed.

Health Outcomes

Baseline and postintervention assessment visits will take between 90 and 120 minutes, including the health interview, physical assessment, and questionnaire completion. The RA completing assessments will be blinded to the condition (intervention or waitlist control groups). The RA will be trained and supervised by an AEP.

Secondary outcome measures will be completed before randomization at baseline and 12 weeks after intervention. The outcome measures (questionnaires outlined in the subsequent section) will be completed by an RA and a member of the research team who is blinded to the group allocation. Health outcome measures will include QoL (measured using the Short Form Health Survey-36) [46]; cognition (MoCA [36] and the Cambridge Neuropsychological Test Automated Battery attention, learning, and memory tasks); pain (Western Ontario and McMaster Universities Osteoarthritis Index) [44,52]; psychological health (Depression, Anxiety, and Stress Scale-21) [45]); and physical health (weight, waist circumference, blood pressure, functional fitness, strength, mobility, and balance). Balance exercises will be simple easy to perform movements that take place in a purposefully designed environment that minimizes the risk of falls (ie, they will be beside a wall, with an AEP closely monitoring them and simple exercises will be completed first, enabling the AEP to continually assess whether it is safe for the participant to continue to the slightly more challenging balance exercises).

The questionnaires (Table 1) will assess the participants' health relevant to the outcome measures (eg, cognition, QoL, and psychological health). The data collection process will be administered using UNSW Qualtrics, except for the cognition measures, as these require the participant to draw on the printed tool (ie, pen and paper questionnaire). Participants will be asked questions by an experienced health psychologist and RA who has experience interviewing people with cognitive decline. They will enter the data directly onto a tablet or paper for the MoCA (with no identifying information, just a participant ID). The MoCA data will then be entered electronically. The health psychologist has received appropriate training to administer the MoCA [36] and a license (obtained in July 2022) and permission to train other staff and students to administer the tool. Participants will be invited to bring a support person with them if they wish, given that variability in level of independence is expected in this population (people with osteoarthritis and cognitive decline). All questionnaires have been validated and used extensively in the literature and with clinical populations, including people with osteoarthritis and cognitive decline.

Data Management

The questionnaires will be completed within the UNSW Medicine and Health Lifestyle Clinic facilities. The data captured on Qualtrics and the Cambridge Neuropsychological Test Automated Battery software using a computer or tablet will be exported to Microsoft Excel and SPSS Statistics (IBM Corp) for data analysis and stored on a secure OneDrive (Microsoft Corporation) database hosted by UNSW, Sydney. The data will be entered, checked, and cleaned by 2 members of the research team. Only members of the research team will have access to the data. All recruited participants will be assigned a unique study ID number, ensuring no personal details, such as their names, are stored alongside data.

Adverse Events

PA may cause concern in older adults and people living with chronic conditions. Adverse events may occur (eg, a fall), despite the safety protocols we have put in place (eg, AEP or RA closely monitoring participants during exercise in a purposefully designed clinic or laboratory setting with handrails). Throughout the trial and follow-up, adverse events will be documented, and risk will be continually assessed by appropriately trained professionals (ie, AEP). Reported adverse events will include details about the type of event, date, time, and duration; severity (mild to severe); whether it could have been avoided; outcome (solved to fatal); and whether it was related to the study (certainly, probably, possibly, unlikely, or cannot say). The relevant ethics committee and participant's general practitioner will be informed about any serious event (eg, requiring hospitalization) that takes place during the study. Adverse events will be reported transparently alongside study outcomes. In accordance with the CONSORT (Consolidated Standards of Reporting Trials) statement [48] and similar to other studies [53], data from participants who are suspended from the trial due to an adverse event will be entered into the analysis by their allocated treatment group. The lead researcher will continue to communicate and support the participant and signpost them to relevant support services where appropriate. An independent safety monitoring process has been established (the data safety monitoring board) to oversee participant safety and review this trial. These arrangements have been documented in a safety monitoring plan, reviewed and approved by the human research ethics committee. All research staff involved in this trial have completed training and certification in Good Clinical Practice guidelines.

Intervention

Overview

The HBMP has been designed in line with the strongest evidence for dementia risk reduction [20,21] and treatment for osteoarthritis [7,31,54]. Furthermore, the exercise component was designed according to international guidelines for prescribing exercise in older adults from the ACSM [51]. Health

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behavior theories that informed the intervention were the health belief model [55] and behavior change techniques [56]. The health belief model focuses on how individuals perceive health threats (eg, aging, pain, dementia, and decreased mobility) and the likelihood that actions taken toward their goals will lead to success. Behavior change techniques include shaping knowledge, providing information on the health consequences of behavior, action planning, self-monitoring of behavior, graded tasks, and social support. Participants will focus on goals, barriers, and enablers using the specific, measurable, achievable, relevant, and time-bound goals approach [57]. Taken together, the program aims to promote participants' health behavior changes. Measures of behavior change, such as knowledge and self-efficacy, are not being included in this pilot feasibility trial, although following successful completion of the pilot, they will be incorporated into a fully powered RCT.

The program will be delivered within the UNSW Medicine and Health Lifestyle Clinic facilities by AEPs and health or clinical psychologists. The 12-week program sessions will take place twice per week (24 sessions in total) and will be 60 to 90 minutes long, including exercise, lifestyle, and behavior change education. Both weekly sessions will comprise 45 minutes of supervised exercise. The first weekly session will be followed by 45 minutes of education (including pain self-management, nutrition, sleep, and reducing smoking and alcohol consumption). Participants will be assigned to time slots suitable for them at the beginning of the program to help reduce the number of missed sessions. Catch-up sessions will be available for participants who are unable to attend their allocated slot. Four groups (2-8 participants per group) will complete the HBMP for 6 months (2 groups in a waitlist control group for the first 3 months). Participants can choose the days and times that suit them and will repeat those for the full 12-week program.

Exercise Component

The exercise component will be evidence based and delivered using a variety of exercise equipment available within the UNSW Medicine and Health Lifestyle Clinic facilities as well as through independent exercise sessions completed at home. Exercises will be modified for each individual based on ability and fitness. A combination of aerobic, resistance, balance, and flexibility exercises will be prescribed to suit the needs of the individual participants.

The ACSM guidelines state that older adults should aim to complete "resistance training twice a week and aerobic exercise of moderate intensity for 150-300 minutes a week, or vigorous intensity for 75-150 minutes per week" [51,58]. Therefore, the exercise prescription guidelines presented in Table 2 will be followed. Participants will complete resistance training twice weekly at the clinic in addition to 60 minutes of aerobic activity and 90 minutes or more of independent or home-based aerobic activity. Independent activity will be recorded each week on a printed record sheet and returned to the AEP upon completion. This will total the ACSM's recommended 150 minutes per week of aerobic activity and 2 strength-based sessions that older adults should engage in for health benefits (Table 2) [51,58]. The prescriptive elements of all exercises performed will be recorded in program training sheets for each session to ensure all necessary details are captured. The education sessions will provide information on how participants can complete PA independently (Table 3).

Table 2. Healthy Body and Mind Program—clinic-based exercise component.

	Aerobic exercise	Resistance exercise
Frequency	Twice weekly (clinic based)	Twice weekly (clinic based)
Duration	30 minutes	30 minutes
Intensity	Light to vigorous (light: RPE[a] 8-10; moderate: RPE 11-13; vigorous: RPE 14-16) [59]	Light to vigorous (light: 30%-49% 1 RM[b]; RPE 9-11; moderate: 50%-69% 1 RM; RPE 12-13; vigorous: 70%-84% 1 RM; RPE 14-17)
Type	Major muscle groups: cycling (upright or recumbent), walking (treadmill), rowing, and stepping	Pin-loaded weight plate machines (eg, leg press, leg extension, leg curl, seated row, chest press, and latissimus [or "lat"] pull down), body weight, free weights, and resistance bands
Volume	Frequency×intensity×time	Sets×repetitions×days; 1 to 3 sets and 8 to 12 repetitions
Pattern	One continuous bout or multiple bouts (eg, 30 min or 3×10 min)	Rest between sets and exercises
Progression	Commence first exercise session in week 1 at low to moderate intensity (50%-60% HRmax[c]; RPE 9-13) and progress gradually as tolerated by the individual	Increased weights to ensure participants' RPE remains within the required range

[a]RPE: rating of perceived exertion [59].

[b]RM: repetition maximum.

[c]HRmax: maximum heart rate (beats per min).

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Table 3. Healthy Body and Mind Program—lifestyle and behavior change education component in accordance with leading organizations.

Session topic[a]	Resource (fact sheets or guidelines) and organizations
Personalized goals and action plans	Behavior change techniques, action planning, and SMART[b] goals
Nonpharmacological approaches	Osteoarthritis (Arthritis Australia); mild cognitive impairment (Dementia Australia)
Physical activity	Osteoarthritis fact sheet (Exercise is Medicine Australia); physical exercise and dementia (Dementia Australia)
Pain neuroscience education	UNSW[c] Medicine and Health; Arthritis NSW[d]; Exercise is Medicine Australia; Musculoskeletal Australia
Nutrition	Healthy eating and arthritis (Arthritis Australia); food diary
Psychological health	Arthritis and emotional well-being (Arthritis Australia); depression and dementia fact sheet (Dementia Australia)
Social connections	Social connectedness in older adults (Centre for Healthy Brain Ageing, UNSW); American Association of Retired Persons
Sleep	Arthritis Foundation; Sleep Foundation; Musculoskeletal Australia
Alcohol and smoking	Arthritis Foundation; Australian Government Department of Health; American Heart Association
Participant's choice	Participants allowed to choose areas they would like to focus on

[a]Each session was facilitated by educational slides developed by CVB.

[b]SMART: specific, measurable, achievable, relevant, and time bound.

[c]UNSW: University of New South Wales.

[d]NSW: New South Wales.

The AEP and health psychologist will receive training from 2 of the study investigators (CVB and BJP) to deliver the exercise and education components. Exercise monitoring observations will take place to record and assess the participants' compliance with the prescribed exercise program relevant to the secondary outcome measures. This data collection will be undertaken face-to-face during group exercise sessions. The AEP will conduct the clinical assessment and group exercise sessions. Each session's data will be collected using program sheets already used in the clinic to capture descriptive details of specific exercises. Measurements of heart rate, blood pressure, and rating of perceived exertion (Borg Rating of Perceived Exertion [59]) will be recorded during the group sessions. These data will be analyzed to provide information on the overall intensity of exercise achieved in each group session.

Lifestyle and Behavior Change Education Component

The education component will also take place at the UNSW Medicine and Health Lifestyle Clinic and involve group discussions developed by a health psychologist and delivered by a health and clinical psychologist. The education topics and resources are presented in Table 3. In summary, they include information about living with osteoarthritis and cognitive decline, PA, nutritional advice, psychological health, social connections, developing individual goals and action plans, and final sessions determined by individual or group preferences. Educational materials are presented in the resources column of Table 3 and have been developed by organizations, including Dementia Australia, Arthritis New South Wales, Alzheimer's Association, and the Australian Government Department of Health. Printed and electronic copies will be provided to participants and used to guide discussions.

Statistical Analysis and Clinical Interpretation

Feasibility, acceptability, and preliminary efficacy of the program will be analyzed. Feasibility will be examined by assessing group session attendance, quantified as total sessions attended out of a maximum possible and reported as a percentage. Feasibility will be quantified as session compliance with criteria for success, requiring performance of at least 10 minutes of aerobic training and 5 progressive resistance training exercises per session. Participant attendance, exercise programming, and adverse events will be recorded. Reasons for nonattendance will be collected and reported. Adverse events will be recorded, and ongoing monitoring and reporting will be completed in accordance with CONSORT guidelines [48]. Acceptability will be determined by participants' perspectives and experiences of the program based on final participant feedback (focus groups or interviews). Acceptability will encompass what participants liked most and least about the program and their suggestions for the content and format of the sessions. Preliminary efficacy of the program will involve analysis of health outcomes (QoL, cognition, and psychological health). Quantitative data will be analyzed using SPSS Statistics (version 30.0.0.0, 172), with normality checks and descriptive statistics for frequencies and distributions. Baseline data will be compared between control and intervention groups to ensure there are no significant differences between groups at baseline. Health outcomes will be compared pre- and postprogram completion and between the intervention and control groups using 1-tailed *t* tests and repeated measures ANOVAs. Statistical significance will be set to $P<.05$. Effect sizes will be calculated using Cohen *d* for *t* tests and ηp^2 for ANOVAs. Results will be reported comparing the intervention versus the waitlist control group and before versus after the 12-week program. Qualitative data will be analyzed using thematic content analysis [47].

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Dissemination

The project findings will be submitted to national and international conference presentations and scientific journal publications. Findings will also be prepared appropriately for other stakeholder groups (eg, lay summaries for people with lived experience of chronic conditions, families, and the public and reports for health care, government, and industry partners). When participants provide consent, they will be invited to indicate whether they would be interested in receiving study findings. Preliminary findings from this project have been presented at national and international conferences (eg, the Australian Dementia Research Forum and the Alzheimer's Association International Conference). The outcomes will be published in high-quality peer-reviewed scientific journals.

Patient and Public Involvement

The design of the program was informed by meetings with people living with osteoarthritis and dementia. WY is a study investigator and is a dedicated professional in the dementia and health care community. They currently serve as a living experience associate consultant at HammondCare, are a member of the Alzheimer's Disease International (ADI) Global Review Panel for Accreditation, the Public Involvement Panel for StepUp for Dementia Research, and the Sleep, Lifestyle, Engagement, and Activity Program (SLEAP). They have been a member of the Dementia Australia Advocacy Program since 2020. In addition, they hold the role of vice chair at Dementia Alliance International and are part of the Forward with Dementia co-design group. Their professional engagement includes participation in numerous international and national conferences, such as the ADI Global Conferences in Krakow and London; the ADI Asia-Pacific Conference in Taiwan; and various Australian conferences, including the International Dementia Conference and Australian Dementia Research Forum. They have also established their own website, awakeningyourpositivity.com, to further share their insights and expertise.

WY is a lead investigator on this project and has been involved in all stages of developing this research. Prestudy consultation identified specific considerations for people living with osteoarthritis and experiencing cognitive decline and highlighted different experiences and expectations of a program such as the HBMP. In summary, feedback included practical considerations, such as transport and accessibility to take part in the program (eg, building and environmental considerations, ease of access, and lighting), the option of having a support person while participating in the program, ensuring the program included multiple components though considering that individuals may differ in how much support they would like to receive from each component (eg, nutritional advice sought by some and considered less important by others), including a social component to the program or considering social factors, and ensuring a tailored approach is adopted to suit participants' unique needs. We have set up a community lived experience group of 30 people within our clinic who were invited to provide feedback on this study at the beginning of the project development. Participants and support persons will be invited to take part in a focus group or interview at the end of the pilot RCT to provide their feedback and share their experiences. These meetings and focus groups will inform the interpretation and dissemination of findings and guide future large-scale implementation.

Results

As of October 2025, we have enrolled 18 participants and completed their data collection. Results are expected to be published during the first quarter of 2026.

Discussion

Anticipated Findings

This is a pilot RCT with complementary quantitative and qualitative components that aims to determine the feasibility and acceptability of a 12-week HBMP. Furthermore, we will examine whether the program improves QoL, cognition, and other health outcomes (pain, depression, and physical health) in people with osteoarthritis and cognitive decline. Currently, there is no program available to meet the specific needs of this population, despite the prevalence of dementia rapidly increasing and the fact that half of older adults globally are living with chronic pain, often attributable to osteoarthritis. The program has been developed in partnership with people with lived experience of dementia and osteoarthritis, AEPs, clinical researchers, chronic disease specialists, and accredited practicing dietitians. The program will continue to be codeveloped, ensuring it is feasible in a real-world setting and easily scalable.

The anticipated findings of this study are that the 12-week program will be feasible and acceptable for people living with osteoarthritis and thinking concerns. Participant feedback will be valuable in informing a larger clinical trial. Regarding secondary outcome measures, we hypothesize that improvements will be observed for pain, QoL, physical function, and cognition in those who complete the program, though these may not be significant given the small sample size.

Implications and Comparisons to Prior Work

This is the first program that has been developed to target osteoarthritis and thinking concerns, both of which are specific risk factors associated with dementia. Currently, people are not aware that they can reduce their dementia risk [60], and societal awareness of dementia is lacking [61] even among health care professionals. The World Alzheimer Report [60] found that 62% of the health care professionals and 70% of the general population surveyed (across 155 countries) think dementia is a part of normal aging. Alarmingly, 25% believe that nothing can be done to prevent dementia [60]. This is particularly concerning given the overwhelming evidence demonstrating that approximately 45% of dementia cases could be prevented or delayed if modifiable risk factors, such as those that form the focus of this program (ie, physical inactivity and obesity), were eliminated [20], highlighting an opportunity for universal dementia prevention. With regard to interventions for osteoarthritis, medicines can have serious adverse side effects and have been associated with increases in addiction, morbidity, and mortality [62]. Many studies have demonstrated positive effects on pain, QoL, and depression following PA [7,63],

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dietary interventions [64], pain education [65], and other lifestyle behaviors. However, none have combined effective PA and lifestyle education into a single program as we have done here, nor have the effects on outcomes associated with dementia, such as cognition, been investigated in this higher-risk group.

Strengths and Limitations of This Study

The first stage of the study involved conducting interviews with people with lived experience of osteoarthritis and dementia to inform the design of the HBMP. Their recommendations were incorporated into the final design of the program**.** In the second stage, participants have been recruited to complete a pilot RCT. Feasibility and acceptability will be examined. Health outcomes, including QoL, pain, cognition, psychological and physical health, will be compared before and after intervention and between program and control groups. Following the program, participants will take part in interviews or focus groups to determine the acceptability of the program and investigate the views of participants, including their recommendations for future programs. In the third stage, stakeholder workshops with individuals, health care providers, and policymakers will take place to discuss future implementation of similar programs at a larger scale with broader outreach. Recruitment and feasibility challenges may impact the success of the trial. Mitigation strategies include considering the language used in recruitment materials, advertising the trial widely using multiple recruitment platforms and health care contacts, and ensuring smooth communication processes between researchers and participants.

Strengths of this study are the range of health outcomes being investigated (eg, QoL, pain, cognition, and psychological measures), allowing for in-depth inquiry into multiple factors associated with comorbidity and dementia risk. The qualitative component will provide feedback from experts living with osteoarthritis and cognitive decline regarding whether the program was enjoyable and feasible and met their needs as well as providing an opportunity to gather recommendations to improve the program and deliver it on a larger scale to benefit more people.

A multicomponent, evidence-based program that has been informed by diverse experts, including those with lived experience, may improve health outcomes for older adults with osteoarthritis and cognitive decline and reduce dementia risk. This is timely, given the substantial increases in dementia cases predicted globally.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

CVB, BJP, NB, MDJ, and KAM contributed to conceptualization. CVB contributed to funding acquisition and writing the original draft. WY, KAM, HB, and BJP contributed to methodology. CVB, BJP, NB, MDJ, KAM, and HB contributed to reviewing and editing the manuscript.

Conflicts of Interest

HB is or has been an advisory board member or consultant to Biogen, Eisai, Eli Lilly, Medicines Australia, Roche, NovoNordisk, and Skin2Neuron. He is a medical and clinical advisory board member for Montefiore Homes and Cranbrook Care. All other authors declare no conflict of interest.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Intervention Trials) checklist.
[PDF File (Adobe PDF File), 1147 KB - resprot_v14i1e75816_app1.pdf]

Multimedia Appendix 2
Contraindications to exercise.
[PDF File (Adobe PDF File), 20 KB - resprot_v14i1e75816_app2.pdf]

Multimedia Appendix 3
Participant information sheet and consent form.
[PDF File (Adobe PDF File), 263 KB - resprot_v14i1e75816_app3.pdf]

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Multimedia Appendix 4
Pre-exercise screening questionnaires.
[PDF File (Adobe PDF File), 584 KB - resprot_v14i1e75816_app4.pdf]

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Abbreviations

ACSM: American College of Sports Medicine
ADI: Alzheimer's Disease International
AEP: accredited exercise physiologist
CONSORT: Consolidated Standards of Reporting Trials
HBMP: Healthy Body and Mind Program
MoCA: Montreal Cognitive Assessment
PA: physical activity
QoL: quality of life
RA: research assistant
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Intervention Trials
UNSW: University of New South Wales

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Protocol

The Effects of a Modified Mediterranean Diet on Gut Microbiota and Chemotherapy Side Effects in Patients With Metastatic Colorectal Cancer Undergoing First-Line Chemotherapy With or Without Either Antiepidermal Growth Factor Receptor or Antivascular Endothelial Growth Factor Agent: Protocol for a Randomized Pilot Study in Italy

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Abstract

Background: The gut microbiota is attracting increasing interest as a factor possibly impacting colorectal cancer risk, therapy toxicity, and, as a consequence, patient's quality of life. It has been observed that microbial imbalance in the gut and in cancer tissue is facilitated by a Western type of diet, rich in meat, sugars, and refined grains, while a Mediterranean diet, rich in low saturated fat and fibers, promotes gut eubiosis, and results in reduced risk of developing colorectal cancer. Specifically, a high fiber content diet has been associated with a reduced incidence of therapy related adverse events in patients with malignant melanoma.

Objective: This study aimed to analyze and compare the gut microbiota of patients with metastatic colorectal cancer undergoing first-line chemotherapy with or without a biological agent (antiepidermal growth factor receptor or antivascular endothelial growth factor), and receiving either a free standard Western diet, or a modified Mediterranean diet, and the impact of microbiota on chemotherapy toxicity.

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Methods: This is a pilot nondrug, interventional prospective, randomized, controlled, single-center (Italian), open-label trial. Patients (n=40) living in Italy, and with a local style of life, will be randomized 1:1 to either a modified Mediterranean diet or a free Western-type diet. Blood and fecal samples will be collected at baseline and control visits, for metagenomic and metabolomic analysis. The primary endpoint is the Firmicutes:Bacteroidetes ratio after completion of the third cycle of first-line chemotherapy (time T1). Secondary endpoints are (1) the percentage of patients experiencing gastrointestinal side effects at T1, (2) the percentage of patients experiencing grade 3/4 gastrointestinal side effects at T1, and (3) changes in the Firmicutes:Bacteroidetes ratio, overall microbiome composition, and metabolome at T1, and after the sixth chemotherapy cycle (T2) versus baseline.

Results: This pilot trial received ethics approval on July 24, 2024. By July 2025, a total of 17 participants have been recruited. The study will conclude with the visit at T2 for the last enrolled patient. Results are expected to be published in October 2028.

Conclusions: This study has the potential to provide critical insights into the role of diet in modifying the gut microbiota, diminishing chemotherapy-related side effects, and possibly enhancing the therapeutic efficacy in metastatic colorectal cancer by improving tolerability. In addition, data may pave the way for future research in immunotherapy, potentially influencing both clinical practice and public health strategies.

Trial Registration: Clinicaltrial.gov NCT06794931; https://clinicaltrials.gov/search?term=NCT06794931

International Registered Report Identifier (IRRID): DERR1-10.2196/72950

(JMIR Res Protoc 2025;14:e72950) doi:10.2196/72950

KEYWORDS

colorectal cancer; modified mediterranean diet; gut microbiota; metagenomics; metabolome; pilot study

Introduction

Colorectal cancer (CRC) is one of the most frequent and deadly malignant tumors, globally [1]. The overall incidence and mortality rates are increasing, probably due to population aging, and increasing incidence of CRC risk factors associated with socioeconomic development [1]. In addition, a relevant rise in early-onset CRC diagnosis was observed in the last three decades [2].

Among the risk factors for CRC, some are unmodifiable, such as age, sex, inflammatory bowel disease, and genetic predisposition [3,4], while others are controllable, such as overweight or obese body weight, smoking, sedentary habits, and unhealthy diet [4,5]. Several of these determinants interact with the gut microbiota (GM), which represents the collection of microorganisms (ie, bacteria, viruses, fungi, and archaea) colonizing the gastrointestinal tract. Therefore, GM attracts increasing interest as an initiator of CRC [6].

The main representatives of the GM are the Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria phyla, with variable prevalence along the oxygen gradient in the lumen of the gastrointestinal tract [7]. These microorganisms, when in equilibrium (a condition mentioned as eubiosis), are beneficial to the host by many activities including fermenting complex carbohydrates to short chain fatty acids (SCFAs), that are used as energy source by gastrointestinal epithelial cells [8]. In addition, the eubiotic GM contributes to the synthesis of vitamins [9], protection from pathogen colonization [10], and maintaining mucosal integrity [11]. When the microbial balance is perturbed by any cause (a condition referred to as dysbiosis), the gut barrier is disrupted, microbial invasiveness increases, and commensal bacteria may turn to pathogens, resulting in inflammation and activation of tumorigenic pathways [11].

Specific changes in the GM have been associated with steps in CRC progression, suggesting that dysbiosis may contribute to such disease states [12]. The lumen- or mucosa-associated GM in CRC patients has higher proportions of *Fusobacterium nucleatum*, *Bacteroides fragilis*, and *Escherichia coli* species, compared to the GM of healthy individuals [13-15].

It is known that the GM has a role as a modulator of the efficacy and toxicity of conventional chemotherapeutic agents used for CRC treatment [16]; the presence of certain bacterial species can exacerbate chemotherapy-induced side effects and pharmacological therapy toxicity, but conversely, microbiota can also enhance treatment efficacy [17].

The microorganisms act on tumor microenvironment through many mechanisms, including genotoxin and free radical production, modification of signaling pathways in host cells, immune modulation, interaction with drug metabolism, and synthesis of small molecules, lipids, proteins, sugars, terpenoids, and organic acids, which may contribute to the pathogenesis of cancer [12,18].

Not only the GM affect the metabolism in the gut, but also compounds and metabolites may influence the GM contributing to the development of a dysbiotic state. It has been repeatedly observed that the presence of *F. nucleatum* in the gut and in CRC tissue is facilitated by a Western type of diet, rich in meat, sugars, and refined grains [14,19], generating intestinal microbial imbalance. On the contrary, the Mediterranean diet, rich in low saturated fat and fibers, promotes eubiosis, and results in reduced risk of developing CRC [20-23]. Epidemiological data show that a healthy diet and eubiosis contribute to reduced risk of CRC [23], while an unhealthy diet is associated with enhanced risk, recurrence, and mortality of CRC [21,23,24]. However, the exact mechanisms through which diet affects CRC are still incompletely understood.

Consuming fiber- and phytochemical-rich foods promotes an increase of beneficial bacterial populations capable of preventing mucus layer damage, reducing inflammation, and lowering CRC risk [14]. It has been observed that in *F. nucleatum*-positive

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patients, a Mediterranean-type diet, rich in fibers and whole-grains, referred to as a "prudent diet," can reduce CRC onset [14].

Overall, current evidence suggests that acting on GM composition by a dietary intervention may be a suitable strategy to prevent CRC risk, can improve outcomes of therapy, and reduce toxicity in CRC patients. GM biodiversity can be improved by the introduction of microbiota-accessible carbohydrates, which are nondigestible by the host, but fermentable by gut bacteria [25]. Microbiota-accessible carbohydrates, classified as prebiotics, are selectively used by microorganisms as substrates to produce SCFAs, such as acetate, propionate, and butyrate [26,27]. Thus, they provide energy for colonocytes, regulate mucin (MUC2) expression, which is critical for intestinal barrier formation, and support immune function. Common prebiotics such as galacto-oligosaccharides and fructo-oligosaccharides, stimulate the growth of beneficial Bifidobacteria and Lactobacilli, modulate cytokine activity, and suppress proinflammatory markers, while promoting apoptosis, and protecting the mucosal barrier [28,29]. Additionally, postbiotics, metabolites produced during bacterial fermentation of nondigestible compounds, mediate the GM-host interaction and facilitate the synthesis and regulation of mucin [30].

Relevant to the ideation of this study, recent data from the Diet study on patients with metastatic melanoma, suggest that a high fiber content diet is associated with a reduction in therapy associated adverse events [31].

Firmicutes are the main producers of butyrate, the preferred metabolic substrate for colon epithelial cells, while acetate and propionate, which contribute to barrier protection, are predominantly derived from Bacteroidetes [32]. In vitro, butyrate administration enhances mucin protein content, supporting probiotic adhesion and inhibiting *E. coli* pathogenicity [32]. Butyrate also regulates mucin expression and epithelial tight junction proteins, strengthening the intestinal barrier [33].

Another beneficial compound acquired through the diet is tryptophan, an essential amino acid that maintains mucosal homeostasis via bacterial metabolism. A protein-rich diet with tryptophan may enhance intestinal defenses [34].

Overall, nutritional interventions, including the use of prebiotics and probiotics, appear capable of modulating the GM, promoting eubiosis, stimulating the production of SCFAs, resulting in enhanced mucus layer, barrier function and prevention of chronic inflammation. Possibly, changes in the GM could result in reduced side effects of chemotherapy, and improved quality of life. Based on this evidence, and investigating these hypotheses, a pilot study was designed to determine and compare the GM of patients with metastatic CRC undergoing first-line chemotherapy with or without a biological agent (antiepidermal growth factor receptor [EGFR] or antivascular endothelial growth factor [VEGF]), and receiving, based on random allocation, either a free choice Standard Western Diet (SWD), or a Modified Mediterranean Diet (MMD).

Methods

Ethical Considerations

This pilot trial has received ethics approval from the Ethics Committee Lombardia 2, Milan, Italy (reference n. R1926/24 – L2-130). All participants will provide full written informed consent before enrolling in the study. The processing of personal data collected during the study complies with the General Data Protection Regulation (GDPR), according to legislative decree. 196/2003, and any Italian laws governing personal data protection. The data of the enrolled participants will be kept strictly confidential and will be pseudo-anonymized. The trial will be conducted in conformity with the Declaration of Helsinki and Good Clinical Practice guidelines.

Study Design

This is a pilot nondrug interventional clinical study, involving biological sampling, designed as a prospective, randomized, and controlled, single-center, Italian, open-label trial with a 1:1 allocation ratio (Clinicaltrial.gov NCT06794931). Figure 1 shows the workflow of MIC-1. The study will be conducted in Vimercate Hospital, Azienda socio sanitaria territoriale (social and health territorial unit) della Brianza, 20871 Vimercate, Italy. The randomization lists will follow a block design generated by dedicated software and maintained by an independent data manager. Stratification is based on gender. Recruitment of participants began in October 2024, and it is expected to be completed in October 2027.

Given the relevance to study results of patients' diet habits, only subjects living in Italy, and with a local style of life (as assessed by a free interview during the first visit) will be enrolled, to reduce variability in the control group. In addition, homogeneous performance status was necessary in the patients' sample. The nutritional state will be assessed before enrollment to exclude patients with malnutrition.

The inclusion criteria are listed in Textbox 1.

Malnutrition Universal Screening Tool is a five-step screening tool planned to identify adults, who are malnourished, at risk of malnutrition (undernutrition), or obese, and including also management guidelines for a care plan [35].

Participants will not be eligible if they meet any of the exclusion criteria (Textbox 2)

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Figure 1. Study timepoints.

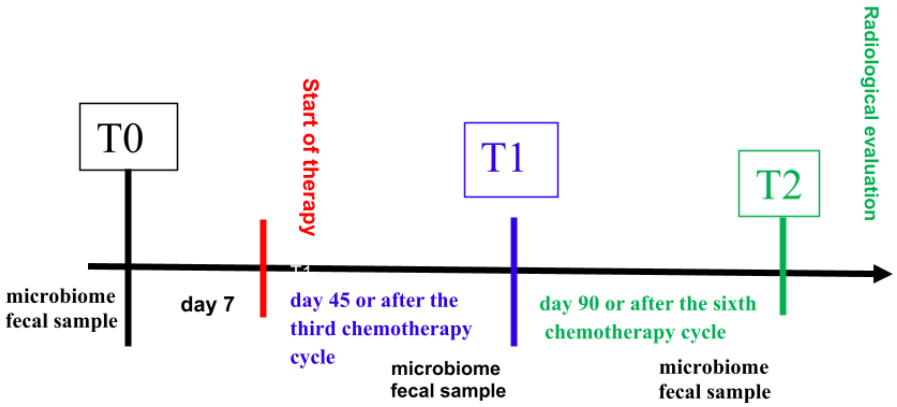

Textbox 1. Inclusion criteria.

Inclusion criteria.

- Italian residence and habits;
- Eastern Cooperative Oncology Group performance status: 0 or 1;
- age at diagnosis should be 18 years or older;
- histologically and radiologically confirmed diagnosis of metastatic CRC based on Response Evaluation Criteria in Solid Tumors 1.1 criteria;
- first-line chemotherapy with or without a biological agent (anti-EGFR or anti-VEGF);
- Malnutrition Universal Screening Tool score: 0-1;
- written informed consent.

Textbox 2. Exclusion criteria.

Exclusion criteria

- living outside Italy;
- age<18 years;
- previous oncological medical treatments;
- indication for parenteral and/or enteral nutrition;
- Malnutrition Universal Screening Tool Score: ≥2.

Intervention

Study Arms: Arm A: MMD; Arm B: SWD (designed according to patient's habits)

Patients will be randomly included in one arm according to a block diagram generated by dedicated software and stored by a study independent data manager.

Diet

The authors planned the present diet on the bas`is of their previous experience [36]. An exemplary diet is presented in Table 1. To develop a nutritional plan favoring bacterial biodiversity, we are mainly focusing on foods containing high-quality prebiotic fibers, reducing the total amount of the fiber content compared to standard guidelines (Livelli di Assunzione di Riferimento di Nutrienti [Nutrient Intake Levels]-Italian Dietary Reference Intakes) to limit the gastrointestinal side effects associated with chemotherapy. To this aim, foods containing resistant starch are preferred. Evidence indicates that such starch promotes changes in bacterial abundance, specifically increasing Firmicutes and particularly *Faecalibacterium prausnitzii*, and the production of butyrate, a SCFA essential for intestinal health [37,38].

Moreover, the dietary plan incorporates foods rich in polyphenols such as brown rice, extra virgin olive oil, and green tea, which have been shown to positively influence cellular aging, blood cholesterol levels, and apoptosis [39]. Polyphenols have been demonstrated to increase protective bacteria (Bifidobacteria and Lactobacilli) and butyrate-producing bacteria (*Faecalibacterium prausnitzii*). Furthermore, polyphenols are known to reduce pathogenic bacteria, including Proteobacteria like *E coli* [37,38].Beta-glucans, indigestible polysaccharides found in barley, oats, and mushrooms, are included in the MMD since GM bacteria metabolize these compounds to produce SCFAs, which are crucial for the nutrition and integrity of intestinal mucosal cells.

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Table 1. Exemplary MMD; changes may be planned according to patient's requests. Each lunch and each dinner must be represented in a week, but the sequence within the 7 days may be adjusted by the patient. Each meal may be added with 3 spoons of extra virgin olive oil (evoo). Admitted vegetables: steamed zucchini, carrots, fennels, asparagus, artichokes, chard, spinach, cauliflower; raw or baked Belgian endive; pan fried mushrooms; salads; tomato sauce. Admitted fish: cod, sole, hake, sea bass, bream. Drink at least 2 l water per day.

	Breakfast	Snacks	Lunch	Dinner
Monday	Either: Black coffee or tea with stevia or mannitol; 50 g rye bread; 50 g lactose free ricotta or 2 teaspoons of evoo, Or: 125 g lactose free yogurt with 3 spoons of oat bran	Either: one fresh fruit without peel, Or: 150 g kefir, Or: 10-12 olives, Or: 30 g crackers	80 g whole rice, 100 g fish, 200 g of admitted vegetables	3 fried egg whites with 200 g mushrooms and Parmigiano cheese; 80 g hard wheat bread
Tuesday	As Monday	As Monday	Vegetable soup with 100 g beans + 50 g pearl barley + 2spoons of Parmigiano cheese	200 g of baked or steamed admitted fish or 160 g chicken fillet, 200 g of admitted vegetables, 80 g toasted hard wheat bread
Wednesday	As Monday	As Monday	80 g basmati rice, 80 g Emmenthal cheese, 200 g of admitted vegetables	2 boiled eggs, 200g admitted vegetables, 80 g of hard wheat bread
Thursday	As Monday	As Monday	90 g (weighted before cooking) lentils, 200 g of admitted vegetables, 40 g of toasted hard wheat bread	200 g roasted, baked, or steamed admitted fish, 200 g admitted vegetables, 80 g toasted hard wheat bread
Friday	As Monday	As Monday	3 fried egg whites with 200 g steamed zucchini and evoo (or one egg and 2 egg whites with mushrooms), and 80 g of toasted hard wheat bread	Chickpeas or beans (90 g) cream, 200 g admitted vegetables, 40 g toasted hard wheat bread
Saturday	As Monday	As Monday	80 g semolina pasta with 150 g artichokes and 50 lactose free ricotta; Or: 60 g semolina pasta with 150 g cooked beans, and 150 g salad	Cream with 100g topinambur, vegetable broth, 1 potato, and evoo + 20 g hard wheat bread + 150 baked blue fish and 150 g admitted vegetables
Sunday	As Monday	As Monday	80 g semolina pasta with tomato sauce, 50 Parmigiano cheese, 200 g admitted vegetables	150 g roasted salmon or 180 g trout; 200 g admitted vegetables; 80 g of toasted hard wheat bread

Fermented products with low lactose content, such as kefir, are incorporated due to the proven effects on enhancing GM biodiversity, and on modulating immune function by supporting specific beneficial bacterial populations [40].

Highly antioxidant foods, such as fruits, vegetables, whole grains, and legumes, are useful to increase the abundance of *Akkermansia Muciniphila*, a key bacterium associated with maintaining a healthy intestinal barrier, and reducing inflammation mediated by lipopolysaccharides [41].

The plan also incorporates high-quality protein sources that also exhibit prebiotic properties, such as ricotta cheese (from cow, sheep, or goat milk, lactose-free if necessary). These proteins have been shown to support symbiotic bacteria and promote intestinal health [42].

The inclusion of salmon and other fish (eg, mackerel and sardines) rich in omega-3 fatty acids aims to enhance the growth of butyrate-producing bacteria, and reduce inflammation, supporting the gut's overall health [43].

Study Workflow

During a routine control visit, eligible patients are informed about the study and, upon signing the written informed consent, undergo nutritional screening containing the components shown in Textbox 3, Table 2, and Figure 1.

Finally, patients are provided with a container for collecting baseline fecal samples.

After the nutritional assessment confirms eligibility, patients will attend baseline visit (time T0) to be randomized into study arms.

Follow-up visits will align with the patient's chemotherapy schedule. Visits will occur after the third chemotherapy cycle (approximately at day 45 – time T1), and the sixth chemotherapy cycle (approximately at day 90 – time T2).

At each visit (T0, T1, T2), patients will return a fecal sample and receive a container for further sampling. In addition, they will be administered the 30-item European Organization for Research and Treatment of Cancer quality of life questionnaire. At T1 and T2, patients will undergo the activities listed in Textbox 4.

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Textbox 3. Components of the nutritional screening.

- A detailed nutritional assessment using a dedicated chart,
- Routine blood tests,
- Assessment of serum carcinoembryonic antigen and carbohydrate antigen 19-9 levels,
- Serum sampling for nutritional markers (C reactive protein, prealbumin, albumin, interleukin [IL]-6, transferrin),
- Assessment of lifestyle factors (ie, sleep quality, smoking habits),
- Recording of a 24-hour dietary recall (food diary of the past 24 hours),
- Anthropometric measurements (body weight, height, BMI, and bioimpedance analysis),
- Calculation of caloric-protein needs,
- Malnutrition Universal Screening Tool score.

Table 2. Study workflow.

	T0: baseline visit	T1: day 45 or after the third chemotherapy cycle	T2: day 90 or after the sixth chemotherapy cycle
Clinical interventions	• Informed consent • Recording of lifestyle • Nutritional assessment • Blood tests • CEA[a] and CA19.9[b] • Food diary • Anthropometric measurements • Caloric protein needs are calculated • MUST[c] score • EORTC QLQ-C30[d] test • Fecal sample container is received	• Nutritional assessment • Gastrointestinal events report • Blood tests • CEA and CA19.9 • Oncologic visit • EORTC QLQ-C30 test • Fecal sample is given and a new container is received • KIDMED[e] test	• Nutritional assessment • Gastrointestinal events report • Blood tests • CEA and CA19.9 • Oncologic visit • EORTC QLQ-C30 test • Fecal sample is given • KIDMED test • Routine radiological evaluation
Metagenomic and metabolomic analysis	—[f]	On frozen fecal sample	On frozen fecal sample
Firmicutes:Bacteroidetes ratio	—	Assessed from OTU[g] tables	Assessed from OTU tables

[a]CEA: carcinoembryonic antigen.
[b]CA19.9: carbohydrate antigen 19-9.
[c]MUST: malnutrition universal screening tool.
[d]EORTC QLQ-C30: European Organization for Research and Treatment of Cancer quality of life questionnaire.
[e]KIDMED: Mediterranean diet quality index for children and adolescents.
[f]Not applicable.
[g]OTU: operational taxonomic unit.

Textbox 4. Activities at T1 and T2.

- Nutritional assessment to evaluate compliance with the assigned diet,
- Routine blood tests,
- Assessment of carcinoembryonic antigen and carbohydrate antigen 19-9,
- Serum analysis for nutritional markers (C reactive protein, prealbumin, albumin, IL-6, transferrin),
- Clinical examinations as required by the oncological treatment plan,
- A modified adherence questionnaire derived from the Mediterranean Diet Quality Index for Children and Adolescents (KIDMED) test to assess dietary compliance [44,45],
- Recording of reported gastrointestinal events

At T2, a radiological evaluation as per routine clinical practice is also planned.

To assess chemotherapy side effects, gastrointestinal events will be considered and the proportions of subjects with

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gastrointestinal events (diarrhea, nausea, and vomit) and with sever gastrointestinal events will be compared in the 2 groups of patients 45 days after beginning chemotherapy with or without the biologic agent. Events will be scored by the National Institutes of Health or National Cancer Institute Common Terminology Criteria for Adverse Events criteria, version 5.0 [46].

Adherence to the Diet

The KIDMED (Mediterranean Diet Quality Index for Children and Adolescents) test is designed to evaluate the adherence to the Mediterranean diet of children and young people [44]. As the diet included in this study introduces several changes to the Mediterranean diet and excludes dairy foods to limit the risk of diarrhea, the KIDMED test will be changed accordingly, based on previously published experience [36,45].

Metagenomic and Metabolomic Analysis

Frozen fecal samples will be sent to the Institute of Biomedical Technologies, National Research Council (Segrate, Milan, Italy) for metagenomic and metabolomic analysis.

Endpoints

The primary objective of this pilot study is to evaluate the impact of the MMD compared to the SWD, on GM biodiversity, in patients with metastatic CRC undergoing first-line chemotherapy with or without a biological agent (anti-EGFR or anti-VEGF).

To this aim, the primary endpoint is the Firmicutes:Bacteroidetes ratio after completion of the third cycle (T1) of first-line chemotherapy, which will be compared between the 2 randomized arms.

Secondary objectives are to assess the impact of the MMD versus the SWD on tolerability of chemotherapy.

To these goals, secondary endpoints are: (1) the percentage of patients experiencing gastrointestinal side effects (diarrhea, nausea, and vomiting) at T1; (2) the percentage of patients experiencing severe gastrointestinal side effects (Grade 3/4 diarrhea, nausea, or vomiting, according to Common Terminology Criteria for Adverse Events criteria) at T1; (3) changes in the Firmicutes:Bacteroidetes ratio, overall microbiome composition through alpha-diversity (Shannon index) and beta-diversity (Weighted Unifrac) calculation to obtain information about richness, evenness, phylogenetic relationships, and relative abundance and metabolome at T1 and T2 versus baseline.

Exploratory objective is to assess the impact of the MMD versus the SWD on the quality of life.

Screening Methodology for Metagenomic and Metabolomic Analysis

DNA Extraction Techniques, 16S rRNA Gene Metabarcoding Library Preparation, and Ultramassive Sequencing

Fecal samples, collected from study patients, are stored at –-80°C until DNA extraction, carried out by Institute of Biomedical Technologies, National Research Council. Automated bacterial DNA isolation will be performed by Maxwell RSC Fecal Microbiome DNA Kit (Promega, Milan, Italy) and DNA quality will be assessed using the TapeStation 4200 system (Agilent Technologies). Only samples with a DNA integrity number ≥ 4 will proceed to further analyses. Samples with DNA integrity number <4 at T1 will result in the patient's exclusion from the study, and previously collected data will not be used. Metabarcoding libraries will be prepared following the "16S Metagenomic Sequencing Library Preparation" protocol, which includes amplification of the V3 and V4 hypervariable regions of the 16S rRNA gene and indexing with DNA or RNA UD Indexes (Illumina).

Libraries will be quantified using the Qubit 4 fluorometer (Invitrogen) and pooled at equimolar concentrations. Sequencing will be performed on an Illumina MiSeq or NextSeq1000 platform, by paired-end 2×300 bp runs.

Bioinformatics Analysis of Sequencing Data

Raw reads derived from sequencing will be processed using a custom bioinformatics pipeline. Overlapping paired reads will be assembled into a single fragment using PandaSeq software (publicly available) [47]. Taxonomic units will be generated using the zero-radius operational taxonomic unit (OTU) method and classification. Classification will use the QIIME suite [48], unoise3 algorithm [49], RDP Classifier [50], and the SILVA 16S rRNA database [51].

Alpha-diversity will be calculated using metrics such as Chao1, Shannon Index, Observed Species, Good's Coverage, and Faith's Phylogenetic Distance. Beta-diversity will be assessed with weighted and unweighted UniFrac metrics, coupled with Principal Coordinate Analysis. Genus-specific reads will be further classified to species level via Basic Local Alignment Search Tool realignment against a custom database derived from NIH-NCBI sequences [52]. Metabolic pathways will be inferred using Phylogenetic Investigation of Communities by Reconstruction of Unobserved States software and the Kyoto Encyclopedia of Genes and Genomes pathway database.

Shannon Diversity Calculation

The Shannon diversity index will be calculated from OTU tables containing absolute counts at the species level using the vegan R package (v2.5-6). Species with an average relative abundance of < 0.1% across all samples will be excluded. OTU counts will be normalized via rarefaction analysis before diversity calculations.

Firmicutes:Bacteroidetes Ratio Evaluation

The Firmicutes/Bacteroidetes ratio will be derived from OTU tables grouped at the phylum level. Phyla with an average relative abundance of <0.1% across all samples will be excluded.

Metabolomic Analysis

Metabolites will be extracted by preparing aqueous fecal extracts by TissueLyser II homogenizer (Qiagen, Hilden, Germany). Samples will be subsequently derivatized with pentafluorobenzyl bromide in acetone, and SCFAs (acetate, propionate, butyrate) will be isolated into the organic phase using hexane (all chemicals sourced from Sigma-Aldrich, St. Louis, MO, USA). Samples will be analyzed by a 5977B single-quadrupole mass spectrometer coupled to an Intuvo 9000 gas chromatograph

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(Agilent Technologies, Santa Clara, CA, USA). Chromatographic separation will be conducted using a DB-FATWAX UI column (30 m × 0.25 mm × 0.25 µm; Agilent Technologies), and detection will be achieved via single ion monitoring for enhanced sensitivity. Absolute quantification of SCFAs (acetate, propionate, butyrate) will be achieved using calibration curves from standard solutions. Obtained data will be analyzed using MassHunter Quantitative software (version 10.2, Agilent Technologies). Furthermore, metabolite concentrations will be correlated with bacterial composition by calculating Spearman correlation coefficients between metabolites and bacterial genera present at ≥ 1% in at least one sample. Only correlations with $P<.05$ will be considered statistically significant.

Rationale for the MMD Plan for Arm A Patients

The diet assigned to each patient will be strictly personalized, considering sex, food preferences, anthropometric characteristics, underlying oncological condition, clinical characteristics (eg, comorbidities), and pharmacological treatment plan.

Daily caloric needs will be calculated by multiplying the basal metabolic rate (determined using the Harris and Benedict formula) by 1.3, assuming moderate physical activity.

Sample Size and Statistical Analysis

The enrollment of 16 patients per arm is required to show a relative reduction of 35% in the Firmicutes:Bacteroidetes ratio from 40% (SD 13) in arm SWD (control arm) to 26% in Arm DMM at time T1, with a significance level of the Mann-Whitney test of 5% (two-sided) and a power of 80%. To consider the possibility of approximately 20% dropouts, 20 patients per arm will be randomized.

The primary comparison of the Firmicutes:Bacteroidetes ratio in Arm DMM vs SWD at T1, will be done with the Mann-Whitney test; an additional analysis adjusting for potential confounding variables (eg, age, comorbidities, chemotherapy type) will be done using quantile regression with these factors as covariates.

For secondary endpoints involving the comparison of the percentage of patients with gastrointestinal effects between the 2 arms, the chi-Square test will be applied.

To adjust for potential confounding factors, an additional analysis will be performed with a logistic regression model.

The analysis of secondary endpoints on changes in the Firmicutes:Bacteroidetes ratio at T1 and T2 versus baseline will be done with the Wilcoxon Signed-Rank test.

The primary and secondary endpoint analyses will follow the Intention-to-Treat principle.

After describing the KIDMED score distribution, expressing the level of adherence to the MMD, an additional per-protocol analysis will be performed excluding patients with a poor adherence, defined as KIDMED test score ≤3 [45].

The sample size is underpowered to draw definitive conclusions on response rates, toxicity, or quality of life differences; clinical outcomes are exploratory and meant to generate hypotheses for future properly powered studies.

Subgroup analyses within different chemotherapy regimens will be performed for exploratory purposes only, due to the relatively limited number of patients, with the aim of having indications on the possible different efficacy and safety of the MMD vs SWD and of proposing additional in-depth studies.

The significance level for all tests is set at 5% (2-tailed).

Results

This pilot trial has received ethics approval from the Ethics Committee Lombardia 2, Milan, Italy (reference R1926/24 – L2-130), on July 24, 2025. Recruitment started in October 2024 and will be completed in 36 months. Data collection commenced in October 2024, with the enrollment of the first patient. By July 2025, a total of 17 participants have been recruited. The study will conclude with the visit at T2 for the last enrolled patient. Results are expected to be published in January 2028.

Discussion

Expected Findings and Perspectives

The main finding expected from this pilot study on patients with metastatic CRC undergoing first-line chemotherapy with or without anti-EGFR or anti-VEGF agents would be a significant difference in GM between patients following a predominantly plant-based MMD, and those following a free Western diet. To this purpose, our research project aims to compare the effects of the Mediterranean diet, characterized by the exclusion of sucralose, red meats, and processed meats (experimental arm), to those of a Western-type free diet (control arm).

Secondarily, a reduction in gastrointestinal events related to chemotherapy is expected by the introduction of the MMD. As far as we know, this will be the first evaluation of the impact of the diet on chemotherapy side effects in patients with CRC, in a precision nutrition trial. We expect that improvements in therapy tolerability may also have implications in terms of treatment efficacy, by reducing dose delay, nutritional decay following gastrointestinal events, and therapy discontinuation. Our exploration of possibly impacting clinical outcomes by improving chemotherapy tolerability with an appropriate diet may generate hypotheses for future proper powered studies.

Metagenomic and metabolomic analyses will provide the identification of the metabolites produced by the GM in response to either the Mediterranean diet or the free Western diet. This knowledge could be the basis for further studies aiming at identifying the optimized diet for patients with metastatic CRC when undergoing chemotherapy.

Novel insights are expected in mechanisms and pathways linking the GM to CRC progression, and response to therapy. By investigating the impact of the Mediterranean diet on chemotherapy side effects, this study paves the way for future research on the relationship between diet-induced GM changes and therapeutic outcomes, immunotherapy responses, in patients with CRC, highlighting dietary interventions that could enhance adherence to treatment, and thus resulting in improved clinical

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outcomes. Specifically, the control of gastrointestinal toxicity by the targeted dietary intervention might reduce the risk of treatment delay, interruption, or dose reduction.

As highlighted in a recent review published in Science, one of the most striking findings distinguishing responders from non-responders to anti–PD-1 therapy is the differential composition of the gut microbiota, particularly the ratio of beneficial to detrimental bacterial species [53]. This was further substantiated by a prospective study by Gopalakrishnan et al. conducted in 112 patients with metastatic melanoma. Using 16S rRNA gene sequencing and whole-genome shotgun metagenomics of fecal and oral samples collected before and during anti–PD-1 therapy, the authors demonstrated that the gut microbiome profoundly influences treatment efficacy. Specifically, patients with a "favorable" gut microbiota—characterized by higher diversity and an abundance of Ruminococcaceae and Faecalibacterium—showed enhanced antitumor immunity, driven by improved antigen presentation and effector T cell activity both peripherally and within the tumor microenvironment. Conversely, those with an "unfavorable" microbiome, dominated by Bacteroidales, had a blunted systemic and intratumoral immune response with impaired lymphoid and myeloid infiltration and decreased antigen presentation [54].

This concept of microbial influence on treatment efficacy extends beyond immunotherapy. In a recent exploratory, prospective, cross-sectional study of 14 breast cancer patients treated with CDK4/6 inhibitors, specific fecal microbiota profiles were also associated with response to therapy. Bifidobacterium longum and Ruminococcus callidus were enriched in responders, while non-responders showed higher abundance of Clostridium innocuum and Schaalia odontolytica. Importantly, patients harboring favorable bacterial species also experienced better overall survival outcomes [55].

Beyond microbial taxonomy, the role of bacterial metabolites—particularly SCFAs such as butyrate, acetate, and propionate—has been well documented. SCFAs not only promote colonic regulatory T cell (Treg) induction and interleukin-10 production to maintain intestinal barrier integrity, but also act systemically. Butyrate, for instance, directly enhances the antitumor function of CD8+ T cells, contributing to improved responses to checkpoint inhibitors such as anti–PD-1/PD-L1 and anti–CTLA-4 therapies. Crucially, SCFAs are produced through microbial fermentation of dietary fibers, underscoring the importance of diet in shaping the metabolic output of the microbiota [56].

A recently randomized phase 2 clinical trial—the "DIET Study," presented at ASCO 2025—provides compelling support for this concept. Among 43 patients with metastatic melanoma receiving immunotherapy, those randomized to a high-fiber diet experienced significantly improved objective response rates and a marked reduction in immune-related adverse events (especially grade ≥3), compared to those on a low-fiber diet [13].

These data collectively support the rationale behind our current study. In our experimental dietary arm (Mediterranean Microbiota Diet, MMD), we have designed a fiber-focused intervention that includes foods rich in high-quality prebiotic fibers and resistant starches, while moderately reducing total fiber content compared to Livelli di Assunzione di Riferimento di Nutrienti guidelines to mitigate gastrointestinal side effects of chemotherapy. Resistant starch has been shown to enhance the abundance of Firmicutes, particularly Faecalibacterium prausnitzii, a known butyrate producer essential for maintaining intestinal health. Moreover, our dietary strategy incorporates foods rich in antioxidants (fruits, vegetables, whole grains, and legumes) to promote the growth of Akkermansia muciniphila, a key species involved in preserving the mucosal barrier and reducing lipopolysaccharide-mediated inflammation.

Therefore, our metabolomic analysis is expected to identify distinct SCFA profiles and other microbial-derived metabolites that differentiate the two dietary arms, thereby helping to determine which dietary pattern best supports antitumor immunity.

An important goal in the course of our study will be to raise awareness among patients about the importance of adhering strictly to the dietary plan as part of their therapy. To facilitate compliance, study participants are provided with flexible substitution options (eg, replacing fish with white meat) for foods they find unpalatable, and adjustments designed to maintain the therapeutic rationale of the diet.

Our group is committed to the dissemination of our research products in the field of nutritional intervention in oncologic patients. We reported findings of previous research to the medical audience in international published articles, congress posters and presentations. As well, we plan to publish the results of our pilot study. In addition, we cooperate with the "Oncologia e Cucina" Association, which supports dissemination of scientific information to lay readers by an online blog. Usable information will be communicated as soon as possible to patients and caregivers, through the Association blog, with a plain language summary of published results.

Conclusions

In conclusion, the MIC-1 study, the first precision nutrition trial of our knowledge, may provide novel insights into the role of diet in modulating the gut microbiota and metabolome, highlighting the potential of dietary interventions to reduce chemotherapy-related toxicities and enhance the efficacy of immunotherapy through SCFA-mediated immune mechanisms in solid tumors. These findings could lay the groundwork for personalized nutritional strategies in oncology based on microbiome–metabolome–host interactions

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Data Availability

Data are presented in the main manuscript.

Authors' Contributions

SA is the principal investigator, ideated the project, and designed the study protocol. MGV and GC are trial statisticians. CC and CC are responsible for metagenomic and metabolomic analyses and elaborate the study protocol. FA is responsible for nutritional programs and developed the diet protocol with SB. All the authors contributed to manuscript drafting and revision; the final version was read and approved by all authors.

Conflicts of Interest

None declared

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Abbreviations

CRC: colorectal cancer
EGFR: epidermal growth factor receptor
GDPR: General Data Protection Regulation
GM: gut microbiota
KIDMED: Mediterranean diet quality index for children and adolescents
MMD: modified Mediterranean diet
OTU: operational taxonomic unit
SCFA: short-chain fatty acids
SWD: Standard Western Diet
VEGF: vascular endothelial growth factor

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The Effectiveness of Social Support–Based Interventions for Dietary and Physical Activity in Adults Living With Overweight and Obesity: Protocol for a Systematic Review

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Abstract

Background: Obesity is a global public health concern, affecting roughly 1 in 3 individuals. Social support has been identified as a key factor in promoting healthy behaviors, including dietary improvements and increased physical activity. While previous reviews have focused primarily on weight loss outcomes, there is limited evidence on how social support–based interventions specifically influence diet and physical activity behaviors.

Objective: This study aims to evaluate (1) the effectiveness of social support–based interventions in improving dietary and physical activity behaviors among adults living with overweight and obesity (plus weight changes and psychosocial factors as secondary outcomes) and (2) identify which types of social support are most effective in facilitating positive behavioral changes.

Methods: A comprehensive search will be conducted across 7 databases and registers (MEDLINE, Embase, PsycINFO, CINAHL, Web of Science, Cochrane Library, and ClinicalTrials.gov) and gray literature sources (Google Scholar, ProQuest, and PsyArXiv), in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Two independent reviewers will screen randomized controlled trials and quasi-experimental studies involving adults living with overweight or obesity who have participated in social support–based interventions targeting diet and physical activity. The revised Joanna Briggs Institute critical appraisal tools will be used to assess the risk of bias. Findings will be reported qualitatively, and where appropriate, meta-analyses will be performed to generate pooled effect estimates for the primary outcomes. Secondary outcomes will also be reported qualitatively.

Results: A pilot database search was conducted on November 29, 2024, to refine the search syntax. The screening, data extraction, quality assessment, and analysis will be conducted, with completion expected by March 2026.

Conclusions: This review will synthesize current evidence on the effectiveness of social support–based interventions for improving diet and physical activity among adults living with overweight and obesity. The findings will help inform the development of future interventions and contribute to public health strategies.

Trial Registration: PROSPERO CRD42024598335; https://www.crd.york.ac.uk/PROSPERO/view/CRD42024598335

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KEYWORDS

protocol; systematic review; meta-analysis; overweight; obesity; social support; intervention; diet; physical activity; PRISMA

Introduction

Obesity is a chronic, complex disease characterized by disproportionate fat accumulation that worsens health. It is a worldwide public health concern. Over 43% of adults aged 18 years and older are overweight, and 16 % live with obesity [1]. At least 2.8 million people die each year as a consequence of being overweight or obese worldwide [1].

Excessive dietary energy intakes and insufficient physical activity are among the primary drivers of overweight and obesity [2]. Managing obesity requires a multisectoral approach that extends beyond individual responsibility, encompassing interpersonal support, community engagement, environmental modifications, and policy interventions [3]. Social support comprises efforts to aid individuals and to foster their sense of connection to meaningful social groups [4]. Social support

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covers multiple dimensions, including emotional, instrumental or tangible, informational, and appraisal support [5].

Social support is important for achieving positive changes in a range of risk factors for chronic diseases, such as overweight and obesity [6,7]. A longitudinal study highlighted that social support from friends and coworkers for healthy eating, and from family for physical activity, was associated with weight reduction, whereas family social undermining of healthy eating predicted weight gain among employed adults [8]. A recent systematic review identified 24 social support–based weight loss interventions lasting between 6 weeks and 18 months (median 3.5 mo) [9]. Meta-analyses indicated that these interventions resulted in uncertain effects when assessed during the intervention period, but significant benefits at longer-term follow-ups, particularly at the end of treatment and at 3- and 6-month postintervention assessments [9]. Another meta-analysis revealed that in 20 articles reporting on 15 online, group-based social support interventions for adults with severe obesity lasting between 3 and 18 months (median 6 mo), participants achieved significant weight loss immediately after treatment [10]. These reviews primarily assessed weight loss outcomes [9,10]. However, intervention effects on dietary and physical activity behaviors were inconsistently assessed, indicating a need for more comprehensive evaluation [10].

Systematic reviews of social support–related interventions for individuals with obesity and overweight have focused primarily on weight loss outcomes [9,10]. However, we were unable to identify a systematic review of evidence on the effectiveness of such interventions on improving dietary and physical activity behaviors in this population. Although weight is a key parameter for assessing obesity, these behaviors are the primary drivers of overweight and obesity [2]. Focusing on these behaviors provides a better understanding of how social support facilitates sustainable lifestyle change, which may contribute to weight management [11]. Therefore, we aim to conduct a systematic review of the effectiveness of social support–based interventions for improving diet and physical activity among adults living with overweight and obesity. Review questions include the following: (1) How effective are social support–based interventions in improving diet among adults living with overweight and obesity? (2) How effective are social support–based interventions in increasing physical activity among adults living with overweight and obesity? and (3) Which types of social support are most effective in promoting dietary and physical activity behavior change among adults living with overweight and obesity?

Methods

To maintain project integrity, the review protocol was registered with PROSPERO (CRD42024598335) on November 22, 2024 [12], and the review will adhere to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines for its conduct and reporting [13].

Inclusion and Exclusion Criteria

Inclusion and exclusion criteria were developed based on the PICOS (population, intervention, comparison, outcome, and study design) framework, as shown in Table 1. Only randomized controlled trials (RCTs) and quasi-experimental (QE) studies will be included to ensure methodological rigor and allow a more reliable assessment of intervention effects. Nonrandomized and before-and-after studies will be excluded, as the absence of control groups and randomization limits the ability to draw causal inferences about intervention effectiveness.

Operational criteria for screening will be applied to differentiate social support–based interventions from general lifestyle interventions as follows:

- Structured facilitation: the social support mechanism must be structured and facilitated by the intervention design. This includes interventions that provide specific platforms, schedules, or mechanisms for interaction (eg, assigned peer buddies, facilitated group discussions, or mandatory family attendance at sessions).
- Distinct component: social support must be identifiable as a distinct and active intervention component (eg, labeled as social support, peer-led, or family-based). To ensure clear operational boundaries and interrater reliability, we will classify types of social support based on the primary source of the support. We define these categories as family-based, peer-based, community-based, and mixed source. Details are included in Multimedia Appendix 1.

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Table . Inclusion and exclusion criteria developed using the PICOS (population, intervention, comparison, outcome, and study design) framework.

	Inclusion criteria	Exclusion criteria
Population	• Adults (aged >18 y) living with overweight or obesity	• Adolescents (aged <18 y)

Intervention	• Interventions based on type of social support [5,14]:
	  • Family-based support
	  • Community-based support
	  • Peer-based support
	  • Mixed source
	• Intervention focus:
	  • Interventions focused on promoting healthy dietary behavior changes
	  • Interventions that aim to increase physical activity
		• Nonsocial support interventions:
		  • Studies focusing solely on individual-based interventions without any social support component
		  • Interventions providing only professional guidance or education

Comparator	• Studies with any type of control condition will be included	• Studies without comparator
Outcomes	• Primary outcomes include measurement of any component of diet or physical activity, such as total calorie intake, daily fruit and vegetable intake, total walking score, or total energy expenditure • Secondary outcomes may include changes in psychological variables, such as perceived social support, quality of life, or overall well-being, with corresponding measures of effect assessed similarly • Interventions that clearly state duration and a measurable follow-up period to assess behavior change	• Studies without a clear measure of diet or physical activity
Study design	• Randomized controlled trials • Quasi-experimental studies	• Other study designs

Searching and Screening

Electronic Searches

The search will be restricted to the following databases and registers: MEDLINE (Ovid), Embase (Ovid), PsycINFO (Ovid), CINAHL (EBSCO), Web of Science (Core Collection), Cochrane Library (Wiley), and ClinicalTrials.gov. Additionally, gray literature sources (Google Scholar, ProQuest, and PsyArXiv) will be searched. Only studies published in English, regardless of publication date, will be included. Retracted studies will be excluded.

Search Strategy

Search strategies were developed based on the PICO (population, intervention, comparison, and outcome) framework [15], as outlined in Table 2. The proposed search strategies for all databases are detailed in Multimedia Appendix 2.

Table . Search strategies.

Element	Terms
P (population)	obesity OR overweight OR “body mass index” OR BMI
I (intervention)	“social support” OR “peer support” OR family-based OR community-based
C (comparison)	usual care OR control OR “no intervention”
O (outcome)	diet* OR nutrition* OR “physical activity” OR exercise

Study Selection

Following the database search, duplicate records will be identified and removed. Two independent authors (PM and DC) will screen all titles and abstracts to assess studies for potential inclusion based on the predefined eligibility criteria. For studies deemed potentially relevant, full-text articles will be retrieved and independently assessed by the same reviewers to determine final eligibility.

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Reasons for exclusion will be documented at the full-text stage, such as lack of dietary or physical activity outcomes, baseline-only studies without follow-up, feasibility studies, or protocol registrations.

Any disagreements between the 2 reviewers will be resolved through discussion. If consensus could not be reached, a third reviewer (RC) will be consulted.

The study selection process will be documented in sufficient detail to complete a PRISMA flow diagram.

Rayyan (Rayyan Systems, Inc) will be used to organize, screen, and manage all identified records from the database searches [16].

Data Extraction and Management

A data extraction form will be created by PM in Microsoft Excel to capture study characteristics, intervention details, and outcome data. Data entry will be double-checked by comparing the extracted table with the original article reports. Information will be extracted from each included study, with categories provided in Multimedia Appendix 3.

If any data are unclear or missing, the corresponding author of the study will be contacted, with 1 follow-up email, to request additional information. If no response is received within 4 weeks, the specific data or outcome will be excluded from the analysis, with the reason for exclusion documented in the review. Where feasible, sensitivity analyses will be conducted to assess the potential impact of missing data on the overall findings.

Quality Assessment

Two independent reviewers (PM and DC) will assess the risk of bias of each study using the Joanna Briggs Institute (JBI) critical appraisal tools, selected according to study design. These include the revised JBI tool for RCTs and QE studies. The revised JBI tool for RCTs evaluates 5 domains: bias related to selection and allocation; administration of the intervention and exposure; assessment, detection, and measurement of outcomes; participant retention; and statistical conclusion validity. The revised JBI tool for QE studies evaluates 7 domains: temporal precedence; selection and allocation; confounding factors; administration of the intervention and exposure; assessment, detection, and measurement of outcomes; participant retention; and statistical conclusion validity [17,18]. Each item will be rated as yes, no, unclear, or not applicable. An overall risk of bias judgment will be made for each study using the grading scale adapted from a previous systematic review, where studies with 3 or fewer “no” responses were classified as low risk, those with 4 to 6 “no” responses as moderate risk, and those with more than 6 “no” responses as high risk [19]. This approach was used since the original JBI tool does not provide explicit thresholds for determining the overall risk of bias. The Grading of Recommendations Assessment, Development, and Evaluation approach will not be applied, as this review does not aim to produce certainty of evidence ratings or guideline recommendations; instead, the focus is on evaluating methodological quality and synthesizing findings across study designs. Publication bias will be examined qualitatively when fewer than 10 studies are included and, where 10 or more studies are available, assessed formally using funnel plots and Egger regression test [20].

Data Analysis and Statistical Analyses

Study characteristics, intervention details, and outcome data will be summarized in tabular form, accompanied by a narrative synthesis. Where data are qualitative or not suitable for statistical analysis, descriptive summaries will be provided. Functional dimensions of the support, including emotional, instrumental, informational, and appraisal, will be discussed qualitatively. If at least 5 studies provide comparable outcome data, a meta-analysis will be conducted to evaluate differences between intervention and control groups. This threshold was chosen to ensure stable estimation of between-study variance and to maintain adequate power for detecting heterogeneity, as recommended in previous methodological research [20,21]. For continuous outcomes, pooled results will be expressed as mean differences or standardized mean differences when measurements differ with 95% CIs, while dichotomous outcomes will be reported using relative risks with 95% CIs.

To address heterogeneity in the measurement of diet and physical activity, outcomes will be harmonized prior to meta-analysis. We will mathematically convert reported units to uniform metrics where feasible (eg, kcal to kJ, daily to weekly amounts, etc). However, incompatible outcomes will be kept as distinct domains (eg, separating total energy intake from diet quality scores). Where possible, the standardized mean difference will be used to pool effects within specific domains.

Heterogeneity will be assessed to examine the differences between studies using Cochran Q and the I^2 statistic, and results will be interpreted cautiously when fewer than 10 studies are available, as heterogeneity estimates and small-study effects are less reliable in small meta-analyses [22]. If substantial heterogeneity is detected (I^2>50%), subgroup analyses will be conducted, or meta-regression analyses will be performed for continuous variables. A random-effects model will be applied throughout [23]. Sensitivity analyses will be carried out to assess the robustness of pooled results.

Meta-analysis and statistical analyses will be conducted using JASP (version 0.95.4).

Results

The project was funded in August 2024. A pilot database search was conducted on November 29, 2024, to refine the search syntax and confirm the suitability of selected keywords and indexing terms. This preliminary step informed the final search strategy that will be used for the full systematic review. This review will adhere to the PRISMA guidelines for its conduct and reporting as shown in Figure 1 [13].

No formal screening, data extraction, or analysis has yet been undertaken. The full systematic search and screening will be conducted in December 2025, with data extraction and synthesis expected to be completed by March 2026.

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Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram template.

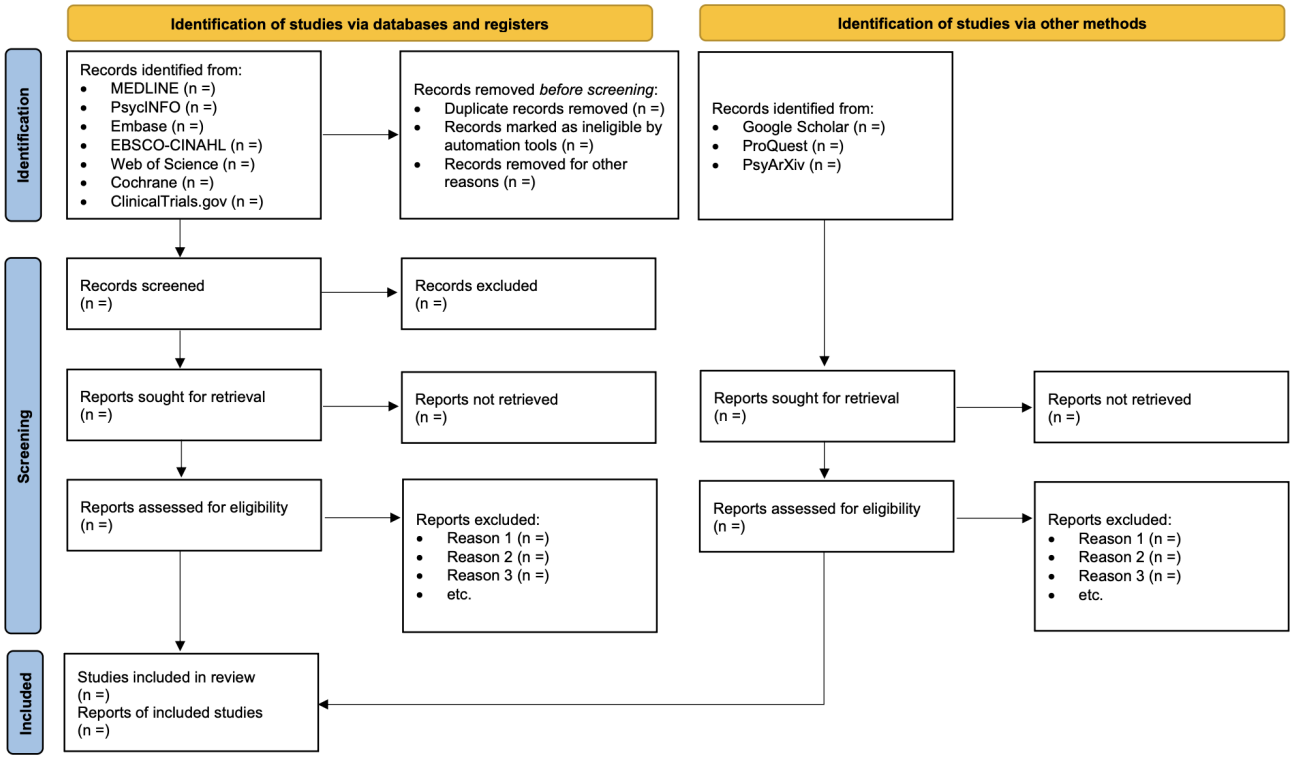

Discussion

Anticipated Findings

This review is a part of a broader study aimed at developing a social support–based intervention prototype focused on improving diet and physical activity among adults living with overweight and obesity. Subsequent stages of the project will involve patient and public involvement to shape the research direction, including qualitative interviews to explore the needs of the target population and co-design workshops to develop the intervention. Therefore, it is essential to review existing literature to identify effective interventions that incorporate social support elements for behavior change.

The findings from this review will enhance understanding of current evidence on social support–based interventions for overweight and obesity and help identify key research gaps to inform future development work. With obesity rates rising globally and dietary and physical activity behaviors remaining the major drivers of excess weight, evidence on effective support strategies is needed. This review will inform the creation of scalable, adaptable interventions that can promote behavior change worldwide.

Strengths and Limitations

This review protocol has notable strengths. It adheres to rigorous methodological standards, including registration with PROSPERO and compliance with PRISMA guidelines, which ensures transparency and reproducibility. The comprehensive search strategy spans 6 major databases, 1 register, and 3 gray literature sources, increasing the likelihood of capturing a broad range of relevant studies. The inclusion criteria are clearly defined, focusing on structured social support interventions targeting both dietary and physical activity behaviors. The use of validated tools for risk of bias assessment, such as the revised JBI critical appraisal instruments, enhances the reliability of quality evaluations. Additionally, the dual-reviewer approach for screening and data extraction, with a third reviewer available to resolve disagreements, further strengthens the methodological rigor.

However, this review also has some limitations. First, the inclusion of only English language publications may introduce language bias and limit the comprehensiveness of the evidence base. Second, the variability in outcome measures, particularly in how diet and physical activity are assessed, may affect the consistency and interpretability of the results. Therefore, outcomes will be harmonized before meta-analysis. Finally, it is not possible to assess the intensity of the social support component of interventions (eg, percentage of contact time). However, preliminary exploration of the data found that this was not usually reported and was deemed an inappropriate indicator of intervention quality.

Conclusions

This protocol will systematically review social support–based interventions for diet and physical activity among adults living with overweight and obesity to identify the most effective support mechanisms and key intervention characteristics. By integrating quantitative and qualitative evidence, it will uncover research gaps and inform the development of tailored, evidence-based public health strategies to reduce the global obesity burden. As previous reviews have not fully examined how different forms of social support affect dietary and activity outcomes in this population, our work will fill this gap and guide the design of more effective, socially informed interventions.

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Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization: PM, AF, AB, DC, and RC
Methodology: PM, AF, AB, and RC
Registration (PROSPERO): PM, AF, AB, DC, and RC
Screening and quality assessment: PM and DC
Writing—original draft: PM and DC
Writing—review and editing: PM, AF, AB, DC, and RC
Supervision: RC, AF, and AB
Project Administration: PM

Conflicts of Interest

None declared.

Multimedia Appendix 1
Operational definitions for social support types.
[DOCX File, 17 KB - resprot_v14i1e81735_app1.docx]

Multimedia Appendix 2
Proposed search strategies.
[DOCX File, 20 KB - resprot_v14i1e81735_app2.docx]

Multimedia Appendix 3
Data extraction categories.
[DOCX File, 15 KB - resprot_v14i1e81735_app3.docx]

Checklist 1
PRISMA-P checklist.
[DOCX File, 32 KB - resprot_v14i1e81735_app4.docx]

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Abbreviations

JBI: Joanna Briggs Institute
PICO: population, intervention, comparison, and outcome
PICOS: population, intervention, comparison, outcome, and study design
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Register of Systematic Reviews
QE: quasi-experimental
RCT: randomized controlled trial

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Electroacupuncture for the Prevention of Perioperative Neurocognitive Disorder in Older Patients Undergoing General Anesthesia: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Perioperative neurocognitive disorder (PND) is a prevalent complication among older patients undergoing general anesthesia, imposing significant burdens on individuals, health care systems, and society. While electroacupuncture shows promise for PND prevention, current evidence remains inconclusive.

Objective: This study aims to critically evaluate the effectiveness and safety of perioperative electroacupuncture for PND prevention in older patients undergoing surgery under general anesthesia.

Methods: A comprehensive literature search will be conducted in 8 electronic databases (PubMed, Embase, Web of Science, Cochrane Library, China National Knowledge Infrastructure, Chongqing VIP Chinese Science and Technology Periodical Database, Wan Fang Database, and China Biomedical Literature Database) and 3 clinical trial registries from inception to March 16, 2025. The search strategy aims to identify all relevant randomized controlled trials evaluating perioperative electroacupuncture for PND prevention in older patients (aged ≥60 years) undergoing general anesthesia. The primary outcome will be the incidence of PND. Secondary outcomes will include (1) neuropsychological assessment scores (Mini-Mental State Examination and Montreal Cognitive Assessment), (2) serum inflammatory biomarker levels (interleukin-1β, interleukin-6, and tumor necrosis factor-α), (3) serum neurological damage marker levels (neuron-specific enolase and S100 calcium-binding protein β), and (4) safety outcomes (incidence of adverse events). Two independent reviewers will perform study selection, data extraction, and methodological quality assessment using the revised Cochrane risk of bias tool for randomized trials. All statistical analyses will be conducted in RevMan 5.4 using suitable meta-analysis models based on heterogeneity testing. The certainty of evidence will be evaluated using Grading of Recommendations Assessment, Development and Evaluation (GRADE).

Results: The study selection process will be presented through a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram, detailing the number of records identified, screened, and included. Characteristics of eligible studies will be summarized in evidence tables, including study designs and populations, intervention protocols, and outcome measures. The results will be visualized through a risk of bias graph, forest plots displaying pooled effect estimates with 95% CIs, and funnel plots for publication bias evaluation (when ≥10 studies are available). This protocol is currently in the active phase. The literature search has been completed as of April 2025, with an updated search planned until December 31, 2025. Data extraction is scheduled to commence on January 15, 2026, followed by data analysis starting February 1, 2026. Results are expected to be submitted for publication in March 2026.

Conclusions: The effectiveness and safety of perioperative electroacupuncture for PND prevention in older patients undergoing general anesthesia remain uncertain. This systematic review will provide an evidence-based evaluation of perioperative electroacupuncture's effectiveness in preventing PND, offer practical recommendations for optimizing surgical care for older adults, and identify knowledge gaps to inform future research.

Trial Registration: PROSPERO CRD420251035172; https://www.crd.york.ac.uk/PROSPERO/view/CRD420251035172

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KEYWORDS

electroacupuncture; perioperative neurocognitive disorder; postoperative cognitive dysfunction; postoperative delirium; older adults; meta-analysis; Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PRISMA

Introduction

Perioperative neurocognitive disorder (PND), the revised diagnostic terminology replacing postoperative cognitive dysfunction (POCD), is a common surgical complication characterized by impairment and decline across multiple cognitive domains, including perception, executive function, memory, orientation, language, and attention [1]. According to the 2018 International Nomenclature Consensus [2], PND encompasses 3 components: preexisting cognitive impairment, POCD, and postoperative delirium (POD), meaning postoperative PND specifically refers to both POCD and POD. PND arises from an interplay of multiple risk factors, with older patients undergoing major surgeries under deep anesthesia being particularly vulnerable [1,3,4]. Epidemiological data reveal that PND affects 12% to 25.8% of patients older than 60 years undergoing general surgery [1]. However, in those undergoing major surgeries, such as certain orthopedic and noncardiac procedures, the incidence can rise to as high as 50% [1,3], underscoring the profound impact of surgical invasiveness and trauma. The cognitive impairment may persist for extended periods or become permanent [1,3], leading to serious consequences such as prolonged hospitalization, increased medical expenses, frequent readmissions, diminished quality of life, and elevated risks of dementia and mortality [5-8].

Despite dexmedetomidine showing some therapeutic promise, its use remains limited to severely agitated or distressed cases due to unavoidable side effects [1,3], while other pharmacological approaches lack convincing evidence for preventing or slowing PND progression [9]. These limitations have increased the emphasis on nondrug preventive measures [1,3,9,10]. Electroacupuncture, as an alternative therapy, has emerged as a leading candidate for PND due to its safety, convenience, and high efficacy [11], with clinical trials [12-16] demonstrating perioperative electroacupuncture's effectiveness in reducing PND incidence and improving postoperative cognitive recovery in older patients undergoing major surgeries (knee replacement, total hip arthroplasty, subtotal gastrectomy, and spine procedures) and mechanistic studies [17-21] elucidating its multimodal neuroprotective effects, including neuroinflammation attenuation, synaptic plasticity remodeling, microglial activation suppression, oxidative stress mitigation, and cerebral perfusion enhancement.

Nevertheless, current evidence regarding perioperative electroacupuncture for PND prevention in older adults undergoing surgery under general anesthesia remains inconclusive, primarily owing to significant clinical heterogeneity (eg, age, surgical types, anesthesia methods, and electroacupuncture stimulus parameters), methodological heterogeneity (eg, diagnostic criteria, assessment tools, and outcome assessment time points), potential methodological biases (high risk of performance and detection bias induced by inadequate blinding), and inadequate statistical power (small sample sizes) in existing studies [12-16,22]. Previous systematic reviews and meta-analyses [23-28] have primarily focused on investigating the effects of transcutaneous electrical acupoint stimulation on isolated outcomes (eg, POCD or POD alone), failing to address PND as a unified clinical entity or leverage interconnected pathophysiological insights. Only 2 studies [16,22] have investigated the effects of electroacupuncture on PND. One study [16] specifically observed older patients but included both general anesthesia and spinal-epidural anesthesia; the other [22] enrolled participants aged 18 years and above, failing to meet the criteria for an older adult population.

Given this, we plan to conduct a comprehensive systematic review and meta-analysis of randomized controlled trials (RCTs) investigating perioperative electroacupuncture for PND prevention in older patients (≥60 years) undergoing general anesthesia. This systematic review and meta-analysis is specifically designed to address the abovementioned challenges by rigorously assessing the risk of bias, investigating heterogeneity through prespecified subgroup analyses, and applying standardized outcome definitions, thereby providing a more nuanced and reliable estimate of electroacupuncture's true effect. The objectives are threefold: (1) to quantify electroacupuncture's effectiveness in preventing PND and improving cognitive recovery, (2) to quantitatively analyze electroacupuncture's modulatory effects on serum inflammatory markers (interleukin-1β [IL-1β], interleukin-6 [IL-6], and tumor necrosis factor-α [TNF-α]) and neurological injury biomarkers (neuron-specific enolase [NSE] and S100 calcium-binding protein β [S100β]), and (3) to objectively examine methodological limitations in existing RCTs. We anticipate that our findings will provide a comprehensive evidence base regarding electroacupuncture's efficacy and safety. This evidence is poised to inform the optimization of postoperative neurocognitive protection strategies and may offer a compelling, nonpharmacological intervention for integration into Enhanced Recovery After Surgery (ERAS) protocols, particularly for the vulnerable older adults. Furthermore, this review will provide crucial guidance for the design of future high-quality RCTs in this field.

Methods

Study Registration

Registration has been completed in the PROSPERO database before data extraction (CRD420251035172). The protocol is reported in compliance with PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) [29], and the completed PRISMA-P checklist is provided in Checklist 1. The study will be conducted strictly in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [30] and will adhere to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines [31] to ensure transparent and complete reporting.

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Study Design

We intend to incorporate RCTs that meet predefined eligibility criteria to evaluate the effectiveness and safety of electroacupuncture in preventing PND among older patients undergoing general anesthesia.

Eligibility Criteria

Studies will be selected according to the criteria outlined in the following sections.

Type of Studies

We will include all parallel-group RCTs. Non-RCTs (eg, cohort studies, case reports, and reviews) will be excluded, regardless of their sample size.

Type of Participants

Participants must be older patients (age ≥60 years) undergoing elective surgery under general anesthesia, with no preoperative cognitive impairment, as confirmed by the Mini-Mental State Examination (MMSE) or Montreal Cognitive Assessment (MoCA). There are no restrictions on gender, type of surgery, or educational level. Patients with preexisting cognitive disorders according to the MMSE or MoCA or those with cognitive decline caused by neurodegenerative diseases such as Alzheimer disease, mild cognitive impairment, vascular dementia, mental illness, cranial brain trauma, stroke, and other psychiatric conditions before surgery will be excluded.

Type of Intervention

The intervention must be perioperative electroacupuncture (preoperative, intraoperative, postoperative, or combined multiphase), with no restrictions on acupoint selection, waveform, frequency, stimulus intensity, or duration.

Types of Comparisons

The comparators will receive sham electroacupuncture (nonpenetrating or nonacupoint stimulation), no intervention, or standard care. Studies using electroacupuncture in the control group to compare technical parameters (eg, waveform, frequency, or intensity) will be excluded, as these investigations primarily aim to optimize stimulation protocols rather than evaluate clinical efficacy against blank, routine, or sham controls.

Types of Outcome Measures

The primary outcome will be the incidence of PND (POCD or POD). POD is explicitly defined as an acute and fluctuating disturbance in attention and awareness occurring within the first 7 days postoperatively or until discharge [2]. Diagnosis is based on either the Confusion Assessment Method or the Nursing Delirium Screening Scale. POCD is defined as an objective decline in cognitive function, assessed by a battery of neuropsychological tests from preoperative baseline to a postoperative time point (1-7 days, 14 days, 1 month, and 3 months) [2]. A postoperative decline in the MMSE score of ≥1 SD from the preoperative baseline [2] or an absolute postoperative MMSE score of <27 [32] is defined as POCD. Secondary outcomes will include cognitive function scores (assessed by MMSE or MoCA), serum inflammatory biomarker levels (IL-1β, IL-6, and TNF-α), serum neurological damage marker levels (NSE and S100β), and the incidence of adverse events. Studies demonstrating clearly erroneous outcomes or ambiguous diagnostic criteria will be excluded.

Other Criteria

Eligible studies may be from any region but must be published in English or Chinese. Studies without preoperative cognitive assessment will be excluded to ensure baseline comparability of cognitive function.

Information Sources and Search Strategy

A comprehensive search will be conducted in 8 electronic databases, including PubMed, Embase, Cochrane Central Register of Controlled Trials, Web of Science, China National Knowledge Infrastructure, Chongqing VIP Chinese Science and Technology Periodical Database, Wan Fang, and China Biomedical Literature Database, from inception to March 16, 2025. The literature search will be updated to include all studies available up to just before the manuscript's final submission to capture the most recent evidence. To maximize the scope of review, the ClinicalTrials.gov, Chinese Clinical Trial Registry, International Traditional Medicine Clinical Trial Registry, and gray literature (eg, dissertations) will be additionally searched to identify eligible trials. Furthermore, the reference lists of included studies will be manually screened to supplement relevant literature.

The search strategy will integrate both Medical Subject Headings (MeSH) and free-text terms across four critical domains: (1) population—"aged," "elderly," "geriatric," "perioperative neurocognitive disorder," "postoperative cognitive dysfunction," "delirium," and "cognitive decline"; (2) intervention—"electroacupuncture," "acupuncture," and "EA"; (3) context—"general anesthesia," "surgery," and "postoperative period"; and (4) study design—"randomized controlled trial" and "RCT." Boolean operators (AND, OR, NOT) and truncation symbols (*) will be used to ensure optimal balance between search sensitivity and specificity. The detailed search strategy for PubMed is provided in Table 1. The complete, reproducible search strategies for all other databases and clinical trial registries are provided in Multimedia Appendix 1, ensuring full reproducibility as per PRISMA-P guidelines.

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Table . The search strategy for PubMed.

Order	Strategy
#1	(cognition) OR (neurocognitive disorders) OR (cognitive dysfunction) OR (cognition disorders) OR (delirium) [MeSH[a] Terms]
#2	(cognitive disorders) OR (cognitive impairment) OR (cognitive decline) OR (cognition dysfunction) OR (cognition impairment) OR (cognition decline) OR (cognit*[b]) [Title/Abstract]
#3	#1 OR #2
#4	(postoperative period) OR (anesthesia recovery period) OR (postop*) OR (postoperative*) OR (postoperative) OR (postsurgical*) OR (post anesthesia) OR (after surgery) OR (post-surgery) [Title/Abstract]
#5	#3 AND #4
#6	(postoperative cognitive complications) [MeSH Terms]
#7	(delayed neurocognitive recovery) OR (perioperative neurocognitive disorder) OR (perioperative cognitive disorder) OR (POCD[c]) OR (POD[d]) OR (PND[e]) [Title/Abstract]
#8	#5 OR #6 OR #7
#9	(acupuncture) OR (electroacupuncture) OR (acupuncture therapy) [MeSH Terms]
#10	(aged) [MeSH Terms]
#11	(elderly) OR (older) OR (geriatric) [Title/Abstract]
#12	#10 OR #11
#13	(randomized controlled trial) OR (controlled clinical trial) OR (random*) OR (randomization) OR (randomly) [Title/Abstract]
#14	#8 AND #9 AND #12 AND #13

[a]MeSH: Medical Subject Headings.

[b]Asterisks denote the special character that represents zero or more characters in wildcard searching.

[c]POCD: postoperative cognitive dysfunction.

[d]POD: postoperative delirium.

[e]PND: perioperative neurocognitive disorder.

Study Selection

All identified records will be imported into EndNote (version X20; Clarivate Analytics) for reference management and deduplication. Two independent reviewers (CW and XW) will perform screening based on title, abstract, and full-text assessment. Discrepancies will be discussed and adjudicated by a third reviewer (KW).

Data Extraction

Two independent researchers (CW and XW) will perform data extraction using a standardized template developed in accordance with the Cochrane Handbook [33], with disagreements resolved by KW. Researchers will extract (1) study characteristics (first author, publication year, nationality, etc), (2) participant demographics (age, sex ratio, sample size, surgical type, etc), (3) intervention details (acupoints, stimulation parameters [waveform, frequency, and intensity], electroacupuncture intervention timing [preoperative, intraoperative, and postoperative], sessions, duration, etc), and (4) outcomes (evaluation indicators [POCD and POD], assessment time points, measurement tools, diagnostic criteria for outcome events, etc). For all biomarker outcomes from each included study, we will systematically extract detailed methodology including the specific assay technique (eg, enzyme-linked immunosorbent assay or chemiluminescence immunoassay), sampling time points, biomarker reference ranges, and units of measurement. Missing data will be retrieved from corresponding authors via email. Studies with irretrievable critical data will be excluded from quantitative synthesis. For duplicate publication of outcome data, we will retain only the most comprehensive or recent publication to avoid data overlap.

Risk of Bias Assessment

Two investigators (CW and XW) will independently assess the methodological quality of included studies using the revised Cochrane risk of bias tool for randomized trials (RoB 2) [34]. The evaluation will cover 7 domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. Searching for and comparing preregistered trial protocols will be an integral part of identifying selective reporting. Each domain will be judged as “low risk,” “high risk,” or “unclear risk,” with discrepancies arbitrated by KW.

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Data Synthesis and Analysis

All meta-analyses will be performed using RevMan (version 5.4; Cochrane Collaboration). Mean differences and 95% CI will be used to calculate the effect size for continuous variables, and relative risk estimates with 95% CI will be used for dichotomous variables. When the units of continuous variables are not standardized, the standardized mean differences with 95% CI will be used. Heterogeneity will be assessed via I^2 statistic and Q test. If $I^2 \leq 50\%$ and $P \geq .1$, indicating acceptable heterogeneity, a fixed-effect model will be used; if $I^2 > 50\%$ or $P < .1$, suggesting substantial heterogeneity, a random-effects model will be selected [35]. Forest plots will be generated to visually present the meta-analysis results, with $P < .05$ considered statistically significant (2-tailed). Where feasible, independent analyses for POD and POCD will be performed to investigate the potential differential effects of electroacupuncture. For biomarker outcomes, quantitative synthesis will be attempted only for studies with comparable methodologies and sampling time points (eg, enzyme-linked immunosorbent assay results from samples taken 24 hours postoperatively). Where quantitative synthesis is precluded by clinical or methodological heterogeneity (eg, vast differences in timing and methods or too few studies per group), we will perform a systematic narrative synthesis and summarize key findings in structured evidence tables.

Subgroup Analyses and Sensitivity Analyses

Given the anticipated clinical heterogeneity in electroacupuncture interventions, we will use the following strategies: (1) detailed description of electroacupuncture parameters (eg, acupoints, stimulation parameters, and timing) for all included studies; (2) prespecified subgroup analyses to explore the impact of key sources of heterogeneity, including acupoint selection (eg, scalp vs body acupoints and standardized vs individualized prescriptions), stimulation frequency (eg, 2 Hz vs >20 Hz), the number of electroacupuncture sessions (multiple sessions [≥2] vs single session), and electroacupuncture intervention timing (preoperative, intraoperative, postoperative, or multiphase perioperative intervention); and (3) if a sufficient number of studies are available (eg, ≥10 studies), meta-regression will be conducted to assess the contribution of continuous variables (eg, the total number of electroacupuncture sessions) to the observed heterogeneity. The results of these analyses will be integral to the interpretation of the pooled findings. Additionally, procedure-stratified and evaluation time–stratified subgroup analyses will also be conducted to reveal differential effect sizes contributed by surgical trauma intensity and outcome assessment time points. Sensitivity analyses will be performed by sequentially excluding each low-quality study with high overall risk of bias, aiming to evaluate the robustness of the findings and determine whether potential methodological bias exists in these studies.

Evaluation of Publication Bias

When more than 10 studies are included for a specific outcome, we will assess publication bias through funnel plot asymmetry test and Egger linear regression test, with a statistical significance threshold of $P < .05$ indicating potential publication bias [36].

Evidence Certainty Assessment

Two reviewers (CW and XW) will independently grade the evidence certainty for each critical outcome using the Grading of Recommendations Assessments, Developments and Evaluations (GRADE) approach [37], yielding classifications of “high,” “moderate,” “low,” or “very low” confidence. Disagreements will be resolved through discussion or third-party (KW) adjudication. The GRADE assessment will evaluate 5 domains: risk of bias, inconsistency, indirectness, imprecision, and other considerations. The assessment of “risk of bias” will be informed by the overall RoB 2 judgment. The certainty of evidence will be downgraded for risk of bias if a substantial proportion of the contributing studies are judged to be at high risk in key domains. The certainty of evidence will be downgraded for imprecision if the included studies have limited sample sizes that fail to meet the optimal information size criterion. If the included studies are found to have potential publication bias, the certainty of evidence will be downgraded within the “other considerations” domain.

Patient and Public Involvement

Patients and the public will not be involved in the design, conduct, data analysis, interpretation of results, reporting, and dissemination plans of this study.

Ethical Considerations

This study does not involve the direct participation of patients and the public, so ethics approval and informed consent are not applicable and required. Because the systematic review relies on previously published data, no original data will be collected.

Validity, Reliability, and Rigor

The study will be rigorously conducted following the Cochrane Handbook for Systematic Reviews of Interventions [30] and will comply with the PRISMA 2020 guidelines [31] to guarantee transparency and comprehensive reporting.

Amendments

The protocol for this systematic review will be amended when necessary, and the revisions will be documented in PROSPERO.

Results

The study selection process will be detailed using a PRISMA [31] flow diagram (Figure 1), which will document the number of records identified through database searching and the number of studies screened, assessed for eligibility, and ultimately included in the review, along with reasons for exclusions at each stage. Characteristics (design, populations, intervention protocols [eg, specific acupoints, waveform, frequency, intensity, duration per session, total number of sessions, and electroacupuncture intervention timing], comparisons, outcome measures, etc) of included RCTs will be tabulated. Methodological quality will be assessed by the RoB 2 tool and visualized graphically. All eligible studies will be included regardless of their risk of bias to avoid introducing selection bias. Data will be synthesized and analyzed using appropriate

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meta-analytic models where feasible, with forest plots for presentation (reporting relative risk, mean difference, or standardized mean difference with 95% CI). The results of subgroup analyses, sensitivity analyses, and evidence quality will be displayed in tables, while funnel plots will be used to evaluate publication bias. Should substantial heterogeneity preclude a meaningful meta-analysis for any outcome, the results will be synthesized narratively and presented in structured summary tables.

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of study selection process. CBM: China Biomedical Literature Database; CNKI: China National Knowledge Infrastructure; CQVIP: Chongqing VIP Chinese Science and Technology Periodical Database.

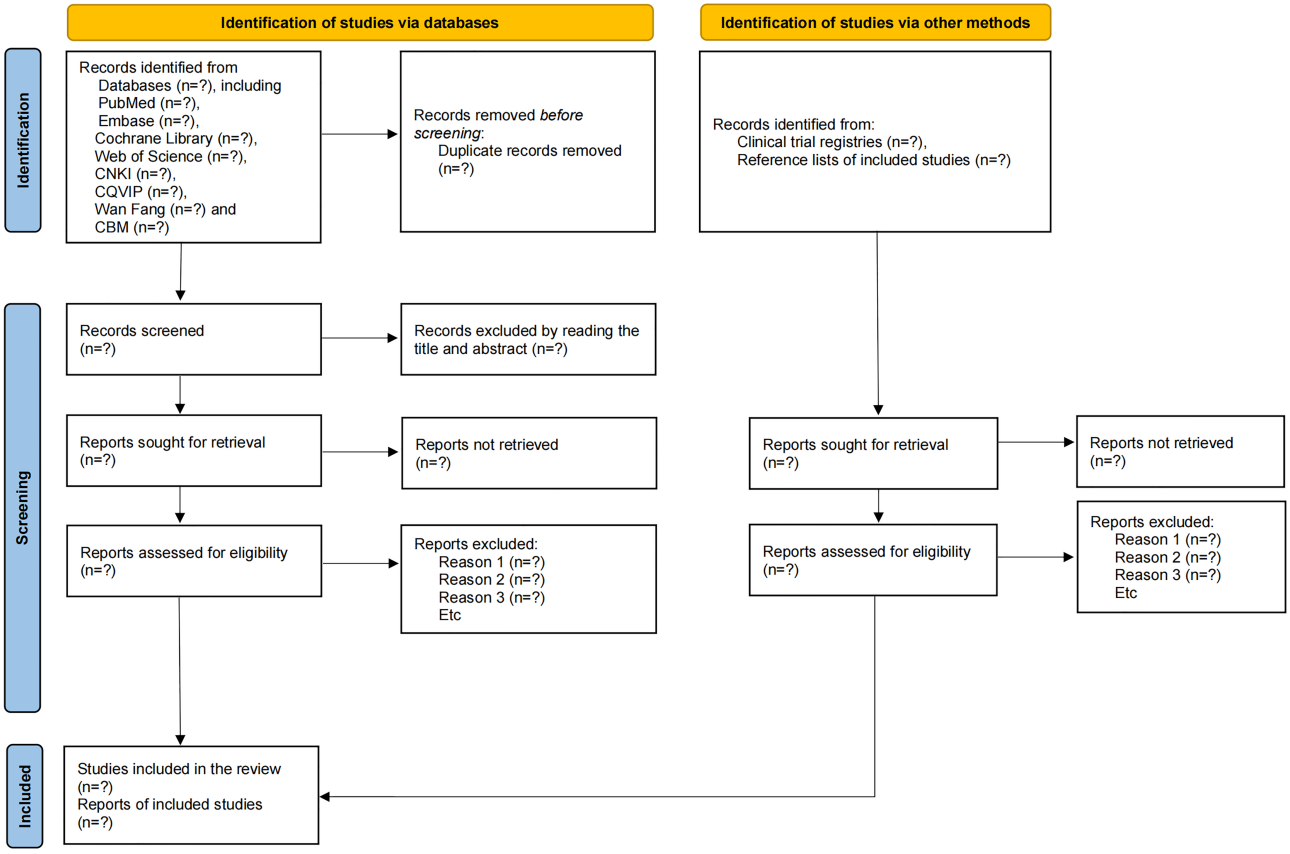

The findings of this study will be submitted for publication in a peer-reviewed journal. To keep the review up to date, we will conduct quarterly updates of all database searches (including gray literature sources) and incorporate any newly available evidence through a standardized living systematic review approach, with protocol revisions documented in PROSPERO.

The protocol was funded in March 2025. The literature search has been completed as of April 2025; an updated search will be conducted through December 31, 2025. Data extraction is projected to start on January 15, 2026, and end on January 31, 2026. Data analysis is planned to begin on February 1, 2026. Results are expected to be submitted for publication in March 2026.

Discussion

Clinical Dilemma of PND

Advanced age (≥60 years, particularly ≥70 years) and general anesthesia are established independent risk factors for PND [1,3]. Epidemiological data demonstrate a marked age-dependent increase in PND incidence, with patients aged 70 years and older experiencing twice the risk compared with those aged 60 to 69 years [38]. The confluence of population aging and rising surgical volumes has rendered PND a critical public health challenge, adversely affecting both short-term recovery trajectories and long-term quality of life, while compounding societal health care burdens [1,39]. To date, no effective treatment exists for PND, underscoring the critical importance of exploring a novel preventive strategy.

Potential Impact of Electroacupuncture on PND

Accumulating evidence supports acupuncture's neuroprotective potential, with studies reporting significant cognitive improvements across multiple disorders including Alzheimer disease [18], mild cognitive impairment [40], vascular dementia [20], vascular cognitive impairment [41], poststroke cognitive impairment [42], schizophrenia [43], and cognitive dysfunction following acute myocardial ischemia-reperfusion injury [17]. Clinical studies [12,13,16] have confirmed electroacupuncture's potential to reduce PND incidence and improve cognitive recovery in older patients receiving general anesthesia. Electroacupuncture may exert neuroprotective effects through multifaceted mechanisms such as (1) attenuation of neuroinflammation and systemic inflammatory responses [18,44], potentially mediated via the vagal-adrenal axis activation [44]; (2) remodeling of synaptic structural and functional plasticity [18]; (3) upregulation of brain-derived

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neurotrophic factor related to neuronal survival and synaptic plasticity [45,46]; (4) modulation of gut microbiota homeostasis [19]; (5) inhibition of microglial activation [17,19]; (6) prevention of neuronal apoptosis [17]; (7) mitigation of oxidative stress [21]; and (8) enhancement of cerebral perfusion [20]. Neuroimaging evidence indicates that acupuncture can activate and enhance neural activity in cognition-related brain regions (eg, prefrontal cortex and hypothalamus) [18,40], while strengthening functional connectivity to modulate brain networks [47]. This suggests that the molecular effects of electroacupuncture ultimately translate into enhanced neural efficiency and network integration, providing a plausible substrate for observed cognitive benefits. Furthermore, acupuncture provides complementary perioperative benefits [48,49] such as preoperative anxiety relief, intraoperative anesthetic requirement reduction, attenuation of surgical stress responses, and postoperative complication decrease, collectively contributing to PND prevention [1]. In addition, electroacupuncture demonstrates unique integrative advantages by combining acupoint specificity, electrical stimulation, and needling effects. Its favorable safety profile, minimal invasiveness, and lower cost-effectiveness render it particularly suitable for perioperative application.

Evidence Gaps in Existing Research

Current evidence remains fragmented and insufficient due to clinical heterogeneity, methodological heterogeneity, and limited sample sizes in existing studies [12-16,22], which consequently restricts the widespread perioperative application of electroacupuncture. While previous systematic reviews and meta-analyses [23-28] have primarily focused on transcutaneous electrical acupoint stimulation for PND, there remains an evidence gap regarding electroacupuncture's potential for PND prevention in older patients (≥60 years) undergoing general anesthesia. Therefore, we propose this review to objectively evaluate the effectiveness and safety of perioperative electroacupuncture for PND prevention in this high-risk population, with the ultimate goal of providing updated evidence-based recommendations for clinical practice.

Rationale for Outcome Selection

The incidence of PND will serve as the primary outcome, providing direct evidence on whether electroacupuncture reduces the risk of PND. The MMSE scores are selected as a secondary outcome due to its well-established sensitivity and specificity in assessing global cognitive function [32], thereby comprehensively capturing electroacupuncture's potential benefits on postoperative cognitive recovery. Neuroinflammation represents one of the most critical pathological mechanisms underlying PND [50]. Specifically, the systemic inflammatory response syndrome triggered by surgical trauma and stress exacerbates central nervous system inflammation through multiple pathways: (1) increased blood-brain barrier permeability, (2) activation of microglia and astrocytes, and (3) subsequent release of proinflammatory cytokines (eg, IL-1β, IL-6, and TNF-α) into the central nervous system. These processes collectively contribute to synaptic dysfunction, neuronal injury or death, impaired hippocampal neurogenesis, and loss of synaptic plasticity, ultimately leading to PND. Neuronal damage is further reflected by elevated levels of brain injury biomarkers (NSE and S100β). These proteins enter systemic circulation via a compromised blood-brain barrier. Clinical studies have consistently demonstrated significantly increased serum concentrations of NSE and S100β in patients with PND following coronary artery bypass grafting [51], abdominal surgery [52], and orthopedic procedures [53]. Therefore, this study selects serum levels of IL-1β, IL-6, TNF-α, NSE, and S100β as secondary outcome measures to evaluate whether electroacupuncture exerts neuroprotective effects by mitigating peripheral inflammatory responses and reducing brain injury severity. These outcomes will help establish an "intervention-effectiveness-mechanism" framework, providing critical insights into electroacupuncture's perioperative neuroprotection.

Strengths, Anticipated Results, and Clinical Implications

This study will address a critical evidence gap by specifically investigating electroacupuncture's effectiveness for PND prevention in older patients (≥60 years) undergoing elective general anesthesia—a previously unexamined yet clinically significant population. Through prespecified subgroup and sensitivity analyses, we will determine how key covariates influence intervention effects and verify the robustness of results. Furthermore, the evaluation of methodological rigor in existing RCTs will identify crucial knowledge gaps to inform the design of future high-quality clinical trials.

Should meta-analysis confirm electroacupuncture's effectiveness and safety for PND prevention among older patients undergoing surgery, the GRADE-assessed evidence from this review will (1) qualify electroacupuncture as a candidate intervention for inclusion in clinical guidelines, (2) offer a novel nonpharmacological strategy to optimize perioperative care protocols for older adults, and (3) potentially mitigate the cascade of adverse outcomes associated with PND through enhanced cognitive recovery in high-risk populations. Such confirmation would represent a significant advancement in clinical practice, particularly for anesthesia and surgical teams managing older patients.

Limitations

This study has several inherent limitations: First, clinical heterogeneity is anticipated due to variations across studies in both demographic factors (anesthesia regimens and surgical types) and electroacupuncture intervention protocols (eg, acupuncture prescription, intervention timing, sessions, and stimulation parameters), which may preclude pooled quantitative analysis for certain outcomes. Second, methodological limitations in the included studies may compromise the strength of the evidence. Third, the generalizability of findings may be restricted to older patients undergoing elective surgery under general anesthesia, excluding those requiring emergency procedures. Future research should (1) conduct multicenter RCTs with standardized electroacupuncture protocols (including optimal acupoint selection, waveform, frequency, and intervention timing) and improved methodology (eg, standardized outcome assessment protocols), (2) elucidate electroacupuncture's mechanisms of action by correlating

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biomarkers with multimodal neuroimaging data, and (3) develop risk stratification tools to identify patients most likely to benefit from electroacupuncture intervention.

Conclusions

This systematic review will provide a comprehensive, GRADE-assessed evidence synthesis specifically focused on the efficacy and safety of electroacupuncture for PND prevention in older patients undergoing general anesthesia. The findings are expected to either support electroacupuncture's integration into ERAS protocols if effectiveness is demonstrated or identify critical knowledge gaps requiring further RCTs if evidence remains inconclusive.

Acknowledgments

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during this study.

Authors' Contributions

All authors directly participated in this study. Conceptualization, methodology, and writing—review and editing were performed by KW and JZ. Funding acquisition, project administration, and resources were provided by JZ. Supervision and validation were provided by KW. CW and XW contributed to investigation, data curation, formal analysis, visualization, and writing—original draft. All authors reviewed and approved the final protocol. KW is a co-corresponding author and can be reached via email at wangke8430@163.com.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategies.
[DOCX File, 67 KB - resprot_v14i1e84010_app1.docx]

Checklist 1
PRISMA-P checklist.
[DOCX File, 33 KB - resprot_v14i1e84010_app2.docx]

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Abbreviations

ERAS: Enhanced Recovery After Surgery
GRADE: Grading of Recommendations Assessments, Developments and Evaluations

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IL-1β: interleukin-1β
IL-6: interleukin-6
MeSH: Medical Subject Headings
MMSE: Mini-Mental State Examination
MoCA: Montreal Cognitive Assessment
NSE: neuron-specific enolase
PND: perioperative neurocognitive disorder
POCD: postoperative cognitive dysfunction
POD: postoperative delirium
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
PROSPERO: International Prospective Register of Systematic Reviews
RCT: randomized controlled trial
RoB 2: revised Cochrane Risk of Bias tool for randomized trials
S100β: S100 calcium-binding protein β
TNF-α: tumor necrosis factor-α

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Renal Resistive Index and Cardiovascular Events, Cardiovascular Mortality, and All-Cause Mortality: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: The renal resistive index (RRI) is a noninvasive indicator of renal vascular resistance and systemic hemodynamic status. Elevated RRI values have been consistently associated with subclinical vascular damage and target organ injury. Observational studies within the past decade have suggested that RRI may also serve as a prognostic marker for adverse cardiovascular outcomes and mortality. However, the evidence remains scattered and heterogeneous, and no systematic review has yet synthesized this body of literature.

Objective: This systematic review aims to evaluate the association between elevated RRI and the risk of cardiovascular events, cardiovascular mortality, and all-cause mortality in adult populations.

Methods: This protocol has been developed in accordance with the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) guidelines. We will include observational studies (prospective and retrospective cohort studies and nested case-control studies) involving adults (≥18 years) with RRI measurements obtained through Doppler ultrasound. Studies focused on pediatric populations, pregnant women, and patients undergoing dialysis will be excluded. The primary exposure will be elevated RRI, typically defined as RRI of ≥0.70, compared to lower or normal values. The primary outcomes are cardiovascular events, cardiovascular mortality, and all-cause mortality with a minimum follow-up of 6 months. A comprehensive search will be conducted in PubMed, Embase, Web of Science, and Scopus, as well as in gray literature sources. Two independent reviewers will screen articles, extract data, and assess risk of bias using Version 2 of the Cochrane revised risk-of-bias tool for randomized controlled trials and the Risk of Bias in Nonrandomized Studies of Interventions and Risk of Bias in Nonrandomized Studies of Exposure tools for nonrandomized studies of interventions and exposure, respectively. Meta-analyses will be conducted if at least 3 studies report comparable data, and effect estimates will be calculated using raw data whenever possible. Subgroup and meta-regression analyses will be used to explore heterogeneity, whereas sensitivity analyses will be conducted to assess the robustness of the observed results. The Grading of Recommendations Assessment, Development, and Evaluation framework will be applied to evaluate the overall quality of evidence.

Results: A preliminary exploratory search has been conducted to map the existing literature and confirm the absence of prior systematic reviews on this topic. The formal study selection and data extraction are expected to begin upon protocol acceptance with review completion anticipated by December 2026.

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Conclusions: By systematically synthesizing the available literature, this review will provide a comprehensive overview of the prognostic value of RRI in predicting cardiovascular outcomes and mortality. The findings may inform clinical decision-making, enhance cardiovascular risk stratification, and identify research gaps for future studies focused on standardizing RRI assessment and its clinical applications.

Trial Registration: PROSPERO CRD420251071996; https://www.crd.york.ac.uk/PROSPERO/view/CRD420251071996

International Registered Report Identifier (IRRID): PRR1-10.2196/79071

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KEYWORDS

all-cause mortality; cardiovascular outcomes; meta-analysis; renal resistive index; systematic review; PRISMA

Introduction

Background

The renal resistive index (RRI) is a noninvasive Doppler-derived hemodynamic parameter first introduced in the 1980s to evaluate intrarenal vascular resistance. Since then, its applications have progressively expanded from nephrology to cardiology and critical care. RRI is calculated as (peak systolic velocity – end-diastolic velocity)/peak systolic velocity and reflects both renal vascular resistance and vascular compliance. This measurement captures the dynamics of renal blood flow and is influenced by intrarenal and systemic factors, including arterial stiffness, vascular tone, and parenchymal compliance. In healthy individuals, typical RRI values range from 0.60 to 0.70, whereas higher values indicate increased vascular stiffness and reduced renal compliance [1]. Over the past 2 decades, RRI has emerged as a potential marker of subclinical vascular dysfunction and organ damage, particularly in patients with arterial hypertension, chronic kidney disease, and diabetes [2-4].

Elevated RRI values—typically defined as ≥0.70—have been consistently associated with early signs of end-organ damage, such as carotid intima-media thickness, carotid atherosclerosis, aortic stiffness, left ventricular hypertrophy, and albuminuria. These markers are well-established predictors of adverse cardiovascular outcomes and mortality in diverse clinical settings [4-11]. More recently, the literature has highlighted that RRI reflects not only renal vascular resistance but also systemic cardiovascular properties such as arterial stiffness and pulse pressure. In this regard, higher RRI values have been linked to increased cardiovascular morbidity and mortality in older adults followed for 7 years [12]. Similarly, in patients with primary hypertension and no prior cardiovascular disease, RRI emerged as an independent predictor of both renal and cardiovascular events over a mean follow-up of 3.1 years, particularly when combined with reduced glomerular filtration rate [4,13].

These findings collectively highlight the potential utility of RRI as a prognostic tool in cardiovascular risk stratification. However, the existing literature remains fragmented, with variations in study populations, RRI thresholds, outcome definitions, and follow-up durations. As a result, the strength and consistency of the association between elevated RRI and major clinical outcomes—including cardiovascular events, cardiovascular mortality, and all-cause mortality—remain unclear.

To date, no systematic review has comprehensively evaluated this association across different populations and clinical settings. Therefore, a structured synthesis of the available evidence is warranted to clarify the prognostic value of RRI and inform its potential application in clinical practice.

Study Objectives

The aim of this systematic review is to evaluate the impact of elevated RRI on the risk of cardiovascular events, cardiovascular mortality, and all-cause mortality in adult populations. By synthesizing current evidence, this review will clarify the prognostic utility of RRI and help inform its potential role in clinical risk stratification.

Methods

This systematic review protocol follows the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) guidelines [14]. The protocol for this review has been registered in the PROSPERO database under the number CRD420251071996.

Eligibility Criteria

Type of Participants

This review will include studies involving adult participants (aged ≥18 years) in whom the RRI was measured using Doppler ultrasound. Participants may come from various clinical settings, including the general population and outpatient clinics, and may have conditions such as hypertension, kidney disease, or heart failure (HF). We will exclude studies involving children or adolescents, as well as those focused on pregnant women due to physiological changes during pregnancy that can affect pathophysiological pathways and RRI values. Importantly, eligible participants must have undergone RRI assessment in nonhospitalized, stable conditions. Patients who experienced prior hospitalizations (eg, for HF decompensation, myocardial infarction, or other acute events) will still be eligible provided that the baseline RRI measurement was performed in an ambulatory setting and at least 3 months after the last hospitalization. This criterion is intended to ensure that the RRI reflects a patient's chronic hemodynamic status rather than transient alterations related to acute illness or hospitalization. In this way, the review will specifically assess the role of RRI in long-term cardiovascular risk stratification rather than in the acute setting. Studies exclusively including acute unstable hospital inpatients, as well as patients receiving maintenance dialysis (hemodialysis or peritoneal dialysis), will be excluded

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as RRI in these settings is influenced by specific hemodynamic factors that differ from those in nonhospitalized or nondialysis populations; this may introduce confounding, limit clinical interpretability, and inflate effect sizes due to their high-risk status [4].

Type of Exposure and Comparators

The exposure of interest in this review is an elevated RRI as measured via Doppler ultrasound. RRI will be analyzed both as a continuous measure and by categorical thresholds. In the latter case, we will consider studies that define elevated RRI using a threshold value—commonly RRI of ≥0.70—or other cutoff points as specified in the individual studies. Participants with elevated RRI will be compared to those with normal or lower RRI values, typically defined as RRI of <0.70. We will include all studies that clearly categorize participants into groups based on higher versus lower RRI values, regardless of the exact threshold used, if the definitions are clearly reported.

Type of Outcomes

The primary outcomes of interest in this review are cardiovascular events, cardiovascular mortality, and all-cause mortality. In particular, cardiovascular outcomes will be prespecified into the following categories: (1) major adverse cardiovascular events (myocardial infarction, stroke, and cardiovascular death), (2) HF outcomes (eg, hospitalization for HF), and (3) other cardiovascular outcomes (eg, arrhythmias, revascularization, or composite outcomes as reported). When studies use heterogeneous or composite definitions, outcomes will be harmonized into these categories, and sensitivity analyses will assess the impact of different definitions on pooled estimates.

Cardiovascular mortality refers to death specifically caused by cardiovascular diseases, whereas all-cause mortality includes death from any cause. If available, we will also consider secondary outcomes such as individual cardiovascular end points or composite outcomes that combine multiple clinical events. We will include studies that report at least one of these outcomes in relation to RRI values and that have a minimum follow-up period of 6 months to ensure sufficient time for outcome development and capture meaningful prognostic associations.

Type of Studies

This review will include observational studies, such as prospective cohort studies, retrospective cohort studies, and nested case-control studies, that examine the association between RRI and the outcomes of interest. Randomized controlled trials (RCTs) reporting relevant data on RRI will also be included. We will exclude case reports, case series, letters, editorials, conference abstracts, and review articles as these do not provide primary data suitable for quantitative or qualitative synthesis.

Search Strategy

Published studies will be identified through a comprehensive search of major international databases: PubMed, Embase, Web of Science, and Scopus. A detailed search strategy for each database will be reported in the appendix or supplementary materials (Multimedia Appendix 1). To ensure a comprehensive capture of relevant evidence, we will complement database searches with a structured gray literature search, including OpenGrey, ClinicalTrials.gov, and the World Health Organization International Clinical Trials Registry Platform. The reference lists of the included studies and relevant reviews will also be manually screened. The search will cover all literature available up to the date of the final search, with no restrictions on publication language, publication year, or geographic location.

The literature search will be performed using a combination of MeSH (Medical Subject Headings; in PubMed only), keywords, and free-text terms related to “renal resistive index,” “RRI,” “renal Doppler,” “cardiovascular events,” “mortality,” and “outcomes.” The search strategy will be tailored to the specific syntax and indexing of each database to ensure comprehensive retrieval of relevant studies.

Study Selection

All records identified through the database searches will be imported into a reference management software, where duplicate entries will be automatically removed. The study selection process will be carried out independently by 2 reviewers in 2 stages. First, titles and abstracts will be screened to identify potentially relevant studies. Full-text articles of selected records will then be retrieved and assessed for eligibility based on the predefined inclusion criteria. Any disagreements between reviewers will be resolved through discussion or consultation with a third member of the review team. Studies deemed eligible after full-text screening will be included in the systematic review and, where appropriate, in the meta-analysis. The overall selection process, along with reasons for exclusion at the full-text stage, will be documented and presented in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram [14].

Data Extraction

Data will be extracted independently by 2 reviewers using a standardized and piloted extraction form. To ensure accuracy and completeness, all extracted data will be cross-verified against the original full-text articles by a third reviewer. Any disagreements or uncertainties will be resolved through discussion among the study team. If key information is missing or unclear, the corresponding authors of the included studies will be contacted via email, with up to 3 attempts made over a 3-month period, to obtain the necessary data.

The data extracted will be directly aligned with the research questions of this review. Specifically, the following information will be collected from each included study: general information (ie, first author, year of publication, and country of study), study characteristics (study design, study period, and duration of follow-up), participant characteristics (sample size, mean or median age, sex distribution, and relevant comorbidities), exposure details (RRI values, cutoff points used to define elevated RRI, and methodology for RRI assessment), and outcomes (cardiovascular events and mortality, including definitions and tools or criteria used to assess outcomes).

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Risk-of-Bias Assessment

The risk of bias for each included study will be assessed independently by 2 reviewers. For RCTs, we will use version 2 of the Cochrane risk-of-bias tool for randomized trials. For nonrandomized studies, we will apply the Risk of Bias in Nonrandomized Studies of Interventions (ROBINS-I) and Risk of Bias in Nonrandomized Studies of Exposure (ROBINS-E) tools to assess risk of bias in studies of interventions and exposure, respectively [15]. Any disagreements between the reviewers will be resolved through discussion and, if necessary, consultation with a third reviewer. To facilitate clear presentation of the findings, we will use the *robvis* tool to generate graphical summaries of the risk-of-bias assessments [16].

Data Synthesis and Analysis

Data synthesis will be conducted using statistical software commonly used for systematic reviews and meta-analyses, including Review Manager (version 5.4.1; The Cochrane Collaboration) and the R software (version 4.2.3; R Foundation for Statistical Computing).

Meta-analyses will be performed for each outcome if at least 3 studies provide sufficient and comparable data. Pooled effect estimates (and 95% CIs) will be calculated using either a fixed-effects or random-effects model depending on the degree of heterogeneity across studies. The primary analysis will assess the association between RRI and the outcomes of interest. Whenever possible, we will analyze RRI as a continuous variable to minimize the impact of arbitrary cutoffs. In addition, categorical analyses will be performed using study-defined thresholds, with results presented according to commonly used definitions (eg, ≥0.70). The primary effect measures will be risk ratios, hazard ratios, or odds ratios depending on the type of study design. When possible, effect estimates will be calculated directly from the raw data in line with Cochrane Handbook for Systematic Reviews of Interventions guidance [15]. If raw data are not available, separate meta-analyses will be conducted by effect measure, and narrative synthesis will be used to summarize findings. Separate meta-analyses will be also conducted for observational studies and RCTs to ensure methodological consistency [17,18]. Subgroup analyses will be conducted only when at least 3 studies provide data for the subgroup of interest to ensure sufficient robustness and interpretability. In particular, we will conduct subgroup analyses stratified by cutoff values to explore whether different thresholds explain the heterogeneity in effect estimates. Other subgroups may include variables such as age, sex, presence of arterial hypertension, and different RRI thresholds. Sensitivity analyses will be conducted using a leave-one-out approach in which each study is sequentially removed to assess the influence of individual studies on the overall effect estimate. Differences between the recalculated and original pooled estimates will be compared to evaluate the robustness of the results.

Heterogeneity will be assessed using the chi-square test and the I^2 statistic. A P value of <.10 in the chi-square test or an I^2 value of >50% will be considered indicative of significant heterogeneity. Conversely, a P value of ≥.1 and I^2 of ≤50% will be interpreted as evidence of low or no significant heterogeneity. If heterogeneity exceeds 75%, potential sources will be explored using subgroup analyses and meta-regression. In particular, if 10 or more studies are available for a given outcome, meta-regression analyses will be performed to further investigate sources of heterogeneity and determine whether specific study-level variables explain variations in effect estimates—to either reconcile conflicting findings or reinforce consistent associations [18]. Moderating variables (ie, the extracted studies' characteristics) will be initially assessed separately in univariable models before being examined together in a single model.

For outcomes for which meta-analysis is not feasible, a narrative synthesis will be provided, summarizing study characteristics, populations, exposure definitions, and key findings.

Assessment of the Certainty of the Evidence

The overall quality of evidence for each primary outcome will be assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. The certainty of the evidence will be rated as high, moderate, low, or very low based on 5 key domains: study design, risk of bias, inconsistency, indirectness, and imprecision. In applying the GRADE approach, we anticipate that the domains of risk of bias and indirectness will be most critical in nonrandomized studies of RRI. Risk of bias will be evaluated using the ROBINS-I and ROBINS-E tools, as mentioned previously. Indirectness will be assessed in relation to variability in RRI thresholds, study populations, and outcome definitions. These factors will be explicitly reported in a summary of findings table to clearly present the quality of evidence and the key results for each outcome included in the review [19].

Results

As of June 2025, a preliminary scoping search has been conducted to assess the type and volume of available evidence and ensure that no prior systematic reviews or meta-analyses have addressed this specific research question. The formal literature search will begin upon acceptance of this protocol, with study selection and data extraction expected to be completed within 6 months and data synthesis and final manuscript preparation expected to be completed by December 2026, ensuring the timely completion of the review. Clinicians (nephrologists and cardiologists) will contribute to the interpretation of findings, whereas input from patient advocacy groups will be sought to guide dissemination strategies and ensure that results are aligned with patient needs and perspectives.

Discussion

Expected Principal Findings

This systematic review is expected to demonstrate that elevated RRI is associated with an increased risk of cardiovascular events, cardiovascular mortality, and all-cause mortality across diverse adult populations. By considering both continuous and categorical definitions of RRI, the review will provide insights into the consistency and magnitude of this association and clarify whether different thresholds meaningfully influence prognostic

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value. Furthermore, the planned subgroup, sensitivity, and meta-regression analyses will allow us to explore whether population characteristics (eg, hypertension, chronic kidney disease, and age) or methodological heterogeneity explain differences across studies.

Comparison to Prior Work

Although multiple observational studies have reported an association between elevated RRI and adverse cardiovascular outcomes [4,20,21], the evidence base remains fragmented and heterogeneous. Previous studies have used varying thresholds for RRI and have reported on diverse cardiovascular end points, often without harmonization across outcomes [22-24]. To date, no systematic review or meta-analysis has comprehensively synthesized these findings. By consolidating the available evidence, our review will build on individual studies and provide the first quantitative estimate of the prognostic value of RRI in predicting cardiovascular and mortality outcomes. In addition, our approach aligns with recent systematic review protocols in the field while offering unique contributions through broader inclusion criteria, structured outcome classification, and sensitivity analyses addressing high-risk groups. Importantly, this systematic review does not overlap with other recently registered or published protocols in similar domains and will provide a distinct and nonduplicative contribution to the literature.

Strengths and Limitations

A major strength of this review is the comprehensive search strategy, which includes multiple databases, structured gray literature sources, and preprint servers, thereby reducing the risk of publication bias. The use of version 2 of the Cochrane risk-of-bias tool for randomized trials and the ROBINS-I and ROBINS-E tools for nonrandomized studies, together with the GRADE framework, will ensure rigorous evaluation of evidence quality. The inclusion of subgroup and meta-regression analyses will enhance the interpretability of the findings.

Nevertheless, certain limitations are anticipated. Variability in RRI thresholds and outcome definitions may also introduce heterogeneity; however, these issues will be explicitly addressed through prespecified outcome groupings and methodological strategies. Finally, the observational nature of most eligible studies may result in residual confounding that cannot be fully eliminated.

Future Directions

If elevated RRI is confirmed to be a robust predictor of cardiovascular and mortality outcomes, this parameter could be incorporated into cardiovascular risk stratification models and support clinical decision-making for high-risk patients [25]. Future research should prioritize the standardization of RRI measurement protocols; the definition of clinically meaningful thresholds; and the validation of its prognostic role in prospective cohorts across diverse populations, including patients undergoing dialysis and inpatients who are acutely ill. This direction is consistent with recent recommendations from the critical care field that emphasize the need for standardized RRI assessment to enhance reliability and facilitate clinical translation. Furthermore, cost-effectiveness analyses may be warranted to determine the potential health care impact of integrating RRI into routine practice.

Dissemination Plan

The results of this systematic review will be disseminated through publication in a peer-reviewed journal and presentations at relevant scientific conferences in nephrology, cardiology, and internal medicine. Summaries of the findings will be shared with professional societies and patient advocacy groups to facilitate translation into clinical practice. In line with JMIR guidance, dissemination will also include digital platforms and stakeholder engagement to maximize accessibility and impact for clinicians, researchers, and patients.

Conclusions

In summary, this systematic review will provide the first comprehensive synthesis of the evidence regarding the prognostic role of RRI in predicting cardiovascular and mortality outcomes. By systematically addressing methodological heterogeneity and assessing evidence quality, the review aims to clarify the clinical utility of RRI, inform risk prediction strategies, and highlight priorities for future research.

Funding

This research received a grant from the Department of Clinical and Experimental Medicine, University of Catania (grant 6C725202048/2024).

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during this study.

Authors' Contributions

GG contributed to the conceptualization and drafting of the protocol. VC developed the statistical methodology. GRMLR contributed to methodological design and critically revised the manuscript. GC, LLV, and NS were responsible for database management and study coordination. RP secured funding and provided overall supervision. PF, AS, CC, GM, and JG contributed to the supervision of the review process and manuscript editing. All authors read and approved the final version of the manuscript.

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Conflicts of Interest

JG has received funding from numerous charities and the pharmaceutical industry. However, he has no conflicts of interest with regard to the contents of this protocol. RP is a full-tenure professor of internal medicine at the University of Catania (Italy) and medical director of the Institute for Internal Medicine and Clinical Immunology at the same university. He has received grants from Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes and Airway Disease–Predicting Outcomes Through Patient-Specific Computational Modelling; the Integral Rheumatology and Immunology Specialists network; Global Action to End Smoking (previously known as Foundation for a Smoke-Free World); Pfizer; GSK; CV Therapeutics; NeuroSearch A/S; Sandoz; Merck Sharp and Dohme; Boehringer Ingelheim; Novartis; Arbi Group; Duska Therapeutics; Forest Laboratories; and the Italian Ministry of University and Research Competition PNRR 3277/2021 (CUP E63C22000900006) and 341/2022 (CUP E63C22002080006) funded by NextGenerationEU, the European Union economic recovery package. He is the founder of the Center for Tobacco Prevention and Treatment at the University of Catania and of the Center of Excellence for the Acceleration of Harm Reduction at the same university. He receives consultancy fees from Pfizer, Boehringer Ingelheim, Duska Therapeutics, Forest Laboratories, CV Therapeutics, and Sermo. He is being paid textbook royalties from Elsevier. He is also involved in a patent application for ECLAT Srl. He is a pro bono scientific advisor for the Italian Anti-Smoking League and the International Network of Nicotine Consumers Organisations, and he is chair of the European Technical Committee for Standardization on Requirements and Test Methods for Emissions of Electronic Cigarettes (CEN/TC 437; WG4). The declared conflicts of interest are unrelated to the objectives of this protocol and will not affect its content, the conduct of the review, or the dissemination of its findings. All other authors declare no other conflicts of interest.

Multimedia Appendix 1
Search strategy for each database.
[DOCX File, 15 KB - resprot_v14i1e79071_app1.docx]

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Abbreviations

GRADE: Grading of Recommendations Assessment, Development, and Evaluation
HF: heart failure
MeSH: Medical Subject Headings
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
RCT: randomized controlled trial
ROBINS-E: Risk of Bias in Nonrandomized Studies of Exposure
ROBINS-I: Risk of Bias in Nonrandomized Studies of Interventions
RRI: renal resistive index

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Effects of Aromatherapy on Chemotherapy-Induced Gastrointestinal Toxicity in Patients With Cancer: Protocol for a Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: Chemotherapy-induced gastrointestinal toxicity (CIGT) is a common and distressing adverse effect in cancer care, manifesting as nausea, vomiting, appetite loss, oral mucositis, constipation, and diarrhea. These symptoms severely impair patients' quality of life, reduce treatment adherence, and may lead to premature therapy discontinuation. Aromatherapy, a complementary therapy using plant-derived essential oils, has shown potential benefits for alleviating CIGT symptoms; however, most existing systematic reviews focus solely on nausea and vomiting, leaving its effects on other CIGT symptoms under-studied. Moreover, the influence of essential oil types, intervention forms, and intervention durations on therapeutic outcomes remains unclear.

Objective: This systematic review and meta-analysis aims to comprehensively evaluate the efficacy and safety of aromatherapy for the full spectrum of CIGT symptoms in patients with cancer and to clarify how essential oil types, intervention forms, and intervention durations influence treatment outcomes.

Methods: Nine databases (PubMed, Cochrane Library, Web of Science, Embase, Cumulative Index to Nursing and Allied Health Literature, Chinese National Knowledge Infrastructure, Wanfang, Chinese Science and Technology Journal Database, and SinoMed); the World Health Organization (WHO) Trials Portal; and the Chinese Clinical Trial Registry will be searched from inception to August 2025 to identify randomized controlled trials focusing on aromatherapy for CIGT management in patients with cancer. Data on participant characteristics, interventions, comparisons, outcomes, and adverse effects will be extracted from included studies. Continuous outcomes will be synthesized using standardized mean differences with 95% CIs, and categorical outcomes will be summarized as odds ratios with 95% CIs. All analyses will adopt a random-effects model to account for expected clinical and methodological heterogeneity. Subgroup and meta-regression analyses will be conducted to examine differences across essential oil types, intervention forms, and intervention durations. The Hartung-Knapp-Sidik-Jonkman method will be used for random-effects estimation, and prediction intervals will be calculated where applicable to reflect real-world variation. Risk of bias will be assessed using the Cochrane Risk of Bias 2 tool, and evidence certainty will be graded using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.

Results: This study was funded in February 2024. As of August 2025, the literature search and study selection have been completed, and 20 eligible randomized controlled trials have been identified. Data extraction and quantitative synthesis are expected to be completed in December 2025, and the final results are anticipated to be submitted for publication in March 2026.

Conclusions: The anticipated findings will address key evidence gaps by evaluating aromatherapy's therapeutic potential for CIGT beyond nausea and vomiting and clarifying parameter-specific effects on CIGT management. These findings will support the development of evidence-based, standardized aromatherapy interventions, guide future mechanism-based research, and inform clinical decision-making in supportive cancer care.

Trial Registration: PROSPERO CRD42024578888; https://www.crd.york.ac.uk/PROSPERO/view/CRD42024578888

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International Registered Report Identifier (IRRID): DERR1-10.2196/76350

(JMIR Res Protoc 2025;14:e76350) doi:10.2196/76350

KEYWORDS

aromatherapy; chemotherapy; gastrointestinal toxicity; cancer; protocol; systematic review and meta-analysis

Introduction

Background

Cancer remains a major contributor to global morbidity and mortality, with an estimated 19.3 million new cases and nearly 10 million deaths reported in 2020 [1,2]. Chemotherapy is the primary treatment for cancer [3] and plays a crucial role in improving patient survival. However, it can induce a wide range of side effects, including myelosuppression, nephrotoxicity, neurotoxicity, gastrointestinal toxicity, alopecia, fatigue, and other systemic reactions [4,5]. Chemotherapy-induced gastrointestinal toxicity (CIGT) is the most commonly reported adverse effect [6]. It refers to the adverse effects on the gastrointestinal tract caused by chemotherapy drugs, manifesting as nausea, vomiting, appetite loss, oral mucositis, constipation, and diarrhea [7-9]. Previous studies have reported that nausea and vomiting affect 70% to 80% of patients [10], oral mucositis affects 40% to 75% [11], and diarrhea affects up to 80% of patients receiving chemotherapy [12]. These CIGT symptoms significantly compromise the quality of life of patients with cancer, increasing the risk of treatment nonadherence or discontinuation and even leading to death in case of severe gastrointestinal toxicity [13,14].

The current management of CIGT primarily relies on pharmacological interventions, which alleviate symptoms [5] but are hindered by their cost and often modest long-term efficacy, limiting their widespread clinical application. In recent years, complementary and alternative therapies have attracted increasing attention due to their efficacy in managing CIGT [5,15]. Aromatherapy, a type of complementary and alternative therapy, uses essential oils and other aromatic compounds derived from plants to enhance health and well-being [16]. It has empirical support for alleviating nausea, vomiting [17], oral mucositis, and constipation [18], which are key symptoms of CIGT.

Existing systematic reviews and meta-analyses have predominantly focused on aromatherapy's effects on nausea and vomiting [17,18]. Notably, no systematic reviews have yet addressed aromatherapy's role in managing other common CIGT symptoms, including appetite loss, oral mucositis, constipation, and diarrhea. These under-studied symptoms not only exhibit high incidence rates (comparable to nausea and vomiting in some patient cohorts [19,20]) but also share pathophysiological links with nausea and vomiting, and this co-occurrence often exacerbates patient distress and impairs treatment adherence [5]. Furthermore, critical gaps remain in understanding how aromatherapy parameters influence CIGT outcomes: variations in essential oil types (eg, peppermint, ginger, and lavender); intervention forms (eg, inhalation vs topical massage); and intervention durations (short term: <2 weeks; long term: ≥2 weeks) have not been systematically compared to determine their relative efficacy for CIGT. This lack of granularity limits the translation of existing evidence into standardized clinical practice.

Thus, this protocol aims to address these identified gaps in existing evidence: by systematically evaluating the efficacy of aromatherapy for the full spectrum of CIGT symptoms in patients with cancer and clarifying the effects of key aromatherapy parameters (essential oil types, intervention forms, and intervention durations) via subgroup analyses. By synthesizing comprehensive evidence on CIGT symptoms management and parameter-specific effects, this study will provide a foundation for developing evidence-based aromatherapy interventions and optimizing CIGT management strategies, ultimately supporting improved patient quality of life and treatment tolerance.

Objectives

The primary objective of this systematic review and meta-analysis is to address the identified gaps in existing evidence regarding aromatherapy for CIGT in patients with cancer. Specifically, the study aims to achieve two core goals: (1) Systematically evaluate the efficacy of aromatherapy in alleviating the full spectrum of CIGT symptoms, including nausea, vomiting, appetite loss, oral mucositis, constipation, and diarrhea in patients with cancer, rather than focusing solely on nausea and vomiting, and (2) quantify the effects of key aromatherapy variables on CIGT outcomes through subgroup analyses, with a focus on 3 critical parameters: essential oil types (eg, peppermint, ginger, and lavender); intervention forms (eg, inhalation and topical massage); and intervention durations (eg, short term and long term). These goals will collectively clarify the clinical utility of aromatherapy for CIGT and provide parameter-specific references for clinical practice.

Methods

Registration

This study will follow the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) guidelines [21] (Checklist 1). The protocol was officially registered in PROSPERO on August 28, 2024 (CRD42024578888).

Design

This systematic review includes comprehensive meta-analyses based on aggregated data.

Ethical Considerations

Ethics approval was not required for this study because it is a systematic review and meta-analysis that uses only aggregated data from previously published randomized controlled trials and does not involve the recruitment of human participants or

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access to identifiable individual-level data. According to our institutional ethics policies, secondary research based solely on published and fully deidentified data is exempt from research ethics board review.

Eligibility Criteria

Types of Studies

This review will consider randomized controlled trials and include articles published in both English and Chinese, with no limitations on the year of publication. Studies with data that cannot be extracted or transformed, as well as duplicate publications, conference abstracts, reviews, editorials, letters, and protocols, will be excluded. The inclusion criteria were determined according to the participants, interventions, comparisons, outcomes, and study (PICOS) framework and guided by the Cochrane Handbook for Systematic Reviews of Interventions [22].

Types of Participants

Studies involving adult patients (>18 years) with a confirmed cancer diagnosis who were receiving chemotherapy will be included. There will be no restrictions on the type or stage of cancer or chemotherapy regimens.

Types of Interventions

The interventions to be assessed in this review will encompass all forms of aromatherapy regardless of dosage, method, or route of administration.

Comparisons and Controls

Studies comparing aromatherapy with various control conditions, including blank controls, waitlist controls, placebos, usual care, and standard treatments, will be considered.

Types of Outcome Measures

The outcomes will include the following: (1) nausea, (2) vomiting, (3) diarrhea, (4) appetite loss, (5) constipation, (6) oral mucositis, (7) quality of life, (8) sleep quality, (9) anxiety, (10) depression, and (11) adverse events. Detailed assessment methods for each outcome are summarized in Table 1.

Table . Outcome assessment methods.

Outcomes	Assessment methods
Primary outcomes	
Nausea	Visual Analog Scale; Rhodes Index of Nausea, Vomiting and Retching; and various measures of intensity, duration, or other scales
Vomiting	Rhodes Index of Nausea, Vomiting and Retching, frequency measures, or other scales
Diarrhea	Severity grading scales or other validated tools
Appetite loss	Visual analog scale, changes in dietary intake, or other scales
Constipation	Constipation Assessment Scale or other scales
Oral mucositis	World Health Organization oral mucositis grading scale, Common Terminology Criteria for Adverse Events, or other scales
Secondary outcomes	
Quality of life	European Organization for Research and Treatment of Cancer, Quality of Life Questionnaire-Core 30, the Quality of Life Questionnaire-Lung Cancer 13, or other scales
Sleep quality	Pittsburgh Sleep Quality Index or other scales
Depression and anxiety	State-Trait Anxiety Inventory, Hospital Anxiety, and Depression Scale or other scales
Adverse events	Self-reported physical distress (eg, rash, malaise, dizziness, headache, or sneezing)

Searching Methods for the Identification of Studies

A comprehensive literature search will be conducted in PubMed, Cochrane Library, Web of Science, Embase, Cumulative Index to Nursing and Allied Health Literature, Chinese National Knowledge Infrastructure, Wanfang Database, Chinese Science and Technology Journal Database, and Chinese Biomedical Literature Service System from inception to August 2025. Additionally, the World Health Organization (WHO) trial portal, Chinese Clinical Trial Registry, gray literature, and reference lists of included studies will also be searched.

The search will be performed using Medical Subject Heading terms and free-text words related to cancer, aromatherapy, chemotherapy, and gastrointestinal toxicity. The detailed PubMed search strategy is presented in Table 2.

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Table . PubMed search strategy.

Search no	MeSH terms and keywords	Items found
1	((((((neoplasms[MeSH Terms]) OR (tumor*[Title/Abstract])) OR (tumour*[Title/Abstract])) OR (neoplas*[Title/Abstract])) OR (cancer*[Title/Abstract])) OR (carcinoma*[Title/Abstract])) OR (malignan*[Title/Abstract])	5,334,288
2	((((((((drug therapy[MeSH Terms]) OR (Chemoradiotherapy[MeSH Terms])) OR (Chemotherapy, Adjuvant[MeSH Terms])) OR (chemotherapy[Title/Abstract])) OR (pharmacotherapy[Title/Abstract])) OR (chemo*[Title/Abstract])) OR (chemical[Title/Abstract])) OR (chemotherapeutic[Title/Abstract])) OR (chemotherapeutant[Title/Abstract])) OR (chemical therapy[Title/Abstract])	2,960,959
3	((((((((((((((aromatherapy[MeSH Terms]) OR (aroma*[Title/Abstract])) OR (essential oil*[Title/Abstract])) OR (fragrance[Title/Abstract])) OR (oils, volatile[MeSH Terms])) OR (volatile oil*[Title/Abstract])) OR (aroma therap*[Title/Abstract])) OR (aromatic massage[Title/Abstract])) OR (inhalational aroma[Title/Abstract])) OR (inhalation aromatherapy[Title/Abstract])) OR (massage aromatherapy[Title/Abstract])) OR (incense therap*[Title/Abstract])) OR (natural medicine[Title/Abstract])) OR (Medicine, Traditional[MeSH Terms])) OR (phytotherapy[MeSH Terms])) OR (plants, medicinal[MeSH Terms])	331,508
4	((((((((((randomized controlled trial[MeSH Terms]) OR (Double-blind method[MeSH Terms])) OR (Single-blind method[MeSH Terms])) OR (controlled clinical trial[Publication Type])) OR (Clinical Trial[Publication Type])) OR (RCT[Title/Abstract])) OR (random*[Title/Abstract])) OR (Random Allocation[MeSH Terms])) OR (alloc*[Title/Abstract])) OR (assign*[Title/Abstract])) OR (placebo[Title/Abstract])) OR (trial[Title/Abstract])	2,535,445
5	#1 AND #2 AND #3 AND #4	1855

Data Collection

Selection of Studies

All references retrieved from the 9 databases and 2 trial registries will be imported into Endnote X9 (Clarivate), and duplicate entries will be eliminated. Two reviewers will independently screen the titles and abstracts to identify studies eligible for inclusion. Secondary screening will involve a detailed examination of the full texts to determine eligibility according to the selection criteria. Any disagreements between the reviewers will be resolved by consensus. If the 2 reviewers are unable to reach a consensus, a third reviewer will be sought to make a final decision.

Data Extraction and Management

Two reviewers will perform independent data extraction from the eligible studies, and the data will be entered into Microsoft Excel 2016. The data will include study characteristics (first author, country, and publication year), characteristics of participants (sample size, age, sex, cancer type, and chemotherapy regimens), details of the intervention and comparison (dose and route of administration), outcomes, adverse effects, and conclusions. To minimize reporting bias, we will request missing data, including unreported outcomes or adverse events, from corresponding authors of published trials or investigators identified through trial registries via email once any missingness is identified during data extraction. Data will be extracted by 2 independent reviewers and any differences will be promptly resolved by consensus.

Assessment of Risk of Bias

The quality of the studies will be independently evaluated by 2 reviewers using the Cochrane tool for assessing the risk of bias in randomized trials version 2 (RoB2) [23]. The RoB2 encompasses 5 domains and 22 items, with response categories including “yes,” “probably yes,” “probably no,” “no,” and “no information.” Each item is assessed as “low risk of bias,” “some concerns,” or “high risk of bias.” A consensus will be reached through a meeting between the 2 reviewers. If disagreements remain between the two initial reviewers after discussion, a third reviewer will be consulted; if consensus is still not reached,

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final decisions will be made through discussion within the review team.

Data Analysis

The meta-analysis will be performed using RevMan software (version 5.2; The Cochrane Collaboration). Continuous data will be synthesized using standardized mean differences and 95% CIs to account for differences in measurement tools across studies, whereas categorical data will be evaluated using odds ratios and 95% CIs to quantify associations between aromatherapy and CIGT outcomes. All meta-analyses will be conducted using a random-effects model to account for potential clinical and methodological heterogeneity across studies [24]. The heterogeneity of the studies will be evaluated using the Q test and the I^2 statistic, and 95% prediction intervals, where applicable, will be calculated to indicate the range of true effects across studies. The Hartung-Knapp-Sidik-Jonkman [25] method will be applied for random-effects estimation to improve the precision and robustness of pooled effect sizes. Potential outliers will be graphically assessed using forest plots. Subgroup analyses will be prespecified to assess potential sources of clinical heterogeneity, including essential oil types (eg, ginger, peppermint, and lavender); intervention forms (eg, inhalation and topical massage); and intervention durations (eg, short term and long term). If sufficient studies are available, meta-regression analysis will be performed to further explore potential sources of heterogeneity. Sensitivity analyses will be conducted to assess the stability and reliability of the pooled estimates. Additionally, when substantial heterogeneity remains unexplained, results will be supplemented with a narrative synthesis.

Publication Bias Assessment

Small-study effects will be evaluated as an indirect approach to explore potential publication bias. Funnel plots will be visually inspected, and the Egger test ($P<.05$) will be performed if ≥10 studies are included in the meta-analysis. If substantial small-study effects are detected, the trim-and-fill method will be applied to assess the potential impact on the robustness of pooled results. Funnel plot asymmetry tests will not be performed if the SEs of intervention effect estimates are similar (ie, studies are of comparable size), as such tests lack statistical power in this context.

Grading the Quality of Evidence

The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology [26] will be used to assess the quality of evidence for all outcomes. The quality of evidence will be graded as “high,” “moderate,” “low,” and “very low,” based on domains including risk of bias, inconsistency, indirectness, imprecision, and publication bias. Inconsistency will be judged according to the degree of heterogeneity (I^2 statistic and overlap of CIs), while imprecision will be evaluated based on the width of CIs and the total sample size relative to the optimal information size. Two reviewers will perform the GRADE assessment independently. If disagreements remain after discussion, a third reviewer will be consulted; if consensus is still not reached, final decisions will be made through discussion within the review team.

Dissemination

The findings will be disseminated via publication in peer-reviewed journals and presentations at academic conferences.

Results

The literature search was completed in August 2025, identifying 6833 records from 9 databases and 2 trial registries and an additional 10 records from other sources (websites, n=7; citation searching, n=3), for a total of 6843 records. Among the records from databases and trial registries, 1054 duplicate entries (15.4%) were removed, leaving 5779 records for title and abstract screening. In total, 184 full-text articles (2.7% of all identified records), including 182 records from databases and trial registries and 2 from other sources, were assessed for eligibility. Ultimately, 20 randomized controlled trials (0.3%) met the predefined eligibility criteria (Figure 1). Quality assessment and data synthesis are currently underway and are expected to be completed by December 2025. The final results of the review are anticipated to be available in March 2026. Given that this review synthesizes data from existing published studies, no direct participant recruitment is required.

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Figure 1. Study flow diagram. ChiCTR: Chinese Clinical Trial Registry; CINAHL: Cumulative Index to Nursing and Allied Health Literature; CNKI: Chinese National Knowledge Infrastructure; ICTRP: International Clinical Trials Registry Platform; RCT: randomized controlled trial; VIP: Chinese Science and Technology Journal Database.

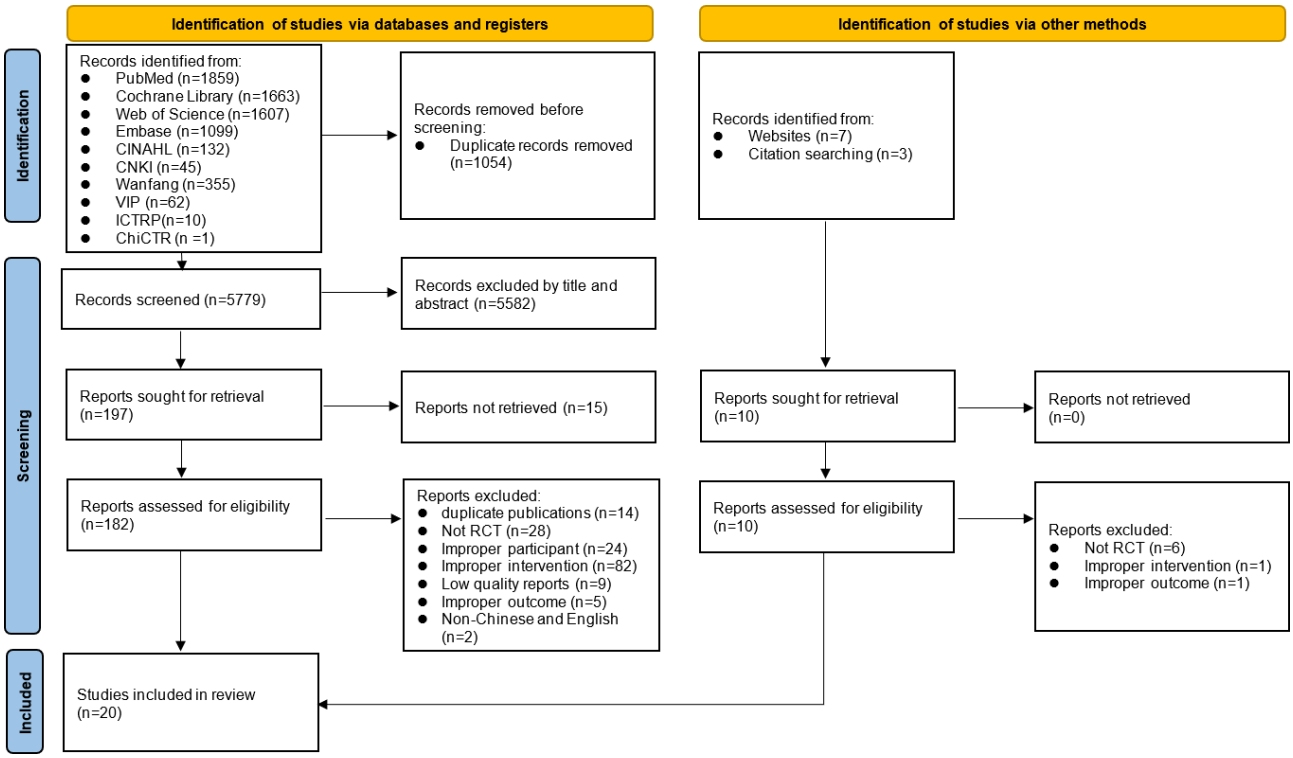

Discussion

Anticipated Findings

This systematic review and meta-analysis aims to summarize current evidence on aromatherapy for CIGT and specifically fill key gaps in existing research, by clarifying aromatherapy's effects on the full spectrum of CIGT symptoms (ie, nausea, vomiting, appetite loss, constipation, diarrhea, and oral mucositis) rather than focusing solely on nausea and vomiting. All analytical procedures will adhere to PRISMA and Cochrane Collaboration standards to ensure methodological rigor, transparency, and reproducibility. The methodological quality of included studies will be independently assessed by 2 reviewers using the RoB2 tool, and the certainty of evidence will be appraised via the GRADE approach.

To explore differential therapeutic effects, we will systematically analyze differences in essential oil types, intervention forms, and durations. Subgroup analyses will be conducted to examine potential variations associated with essential oil types (eg, ginger, peppermint, and lavender); intervention forms (eg, inhalation and topical massage); and intervention durations (eg, short term: <2 weeks; long term: ≥2 weeks) based on clinical practice. These analyses are expected to clarify how intervention parameter differences influence outcomes, addressing the lack of granularity in parameter-related evidence.

By conducting a rigorous literature search, structured data extraction, and the aforementioned quality appraisal, this review will deliver a comprehensive synthesis of existing evidence. Specifically, it will clarify aromatherapy's overall effectiveness in managing CIGT, the consistency of its effects across different symptoms, and the clinical applicability of specific aromatherapy regimens.

Ultimately, the findings may lay 3 key foundations: first, to inform the development of evidence-based aromatherapy interventions for CIGT, thereby addressing the limitation of "nonstandardized practice" in existing research; second, to optimize supportive care for patients with cancer by reducing CIGT-related distress, improving quality of life, and enhancing treatment adherence, which directly addresses the clinical harms of CIGT highlighted in the Introduction; and third, to guide future research exploring the underlying mechanisms by which aromatherapy alleviates CIGT, thus promoting the development of mechanism-driven, more targeted interventions.

Strengths and Limitations

This systematic review has several methodological strengths: it adheres to PRISMA-P and Cochrane Collaboration standards to ensure rigor and transparency; 2 reviewers will independently conduct literature selection, data extraction, and bias assessment, with discrepancies resolved by consulting a third reviewer; the RoB2 tool and GRADE approach will be used to enhance the reliability of results; and subgroup analyses will explore heterogeneity related to essential oil types, intervention forms, and intervention durations.

Nonetheless, certain limitations should be acknowledged: restricting the search to English and Chinese studies may introduce language bias; heterogeneity in aromatherapy interventions (eg, oil concentration and dosage regimens) could impact pooled results; unpublished negative studies may lead to publication bias; and high methodological heterogeneity

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among included studies may weaken the credibility of conclusions.

Despite these limitations, the findings are expected to serve as a scientific foundation for developing standardized clinical guidelines, which will ensure the safe, effective, and evidence-based integration of aromatherapy into oncology care. Ultimately, this will enable health care professionals to select appropriate essential oils, determine optimal dosages, and apply suitable administration methods, thus improving patient outcomes and promoting high-quality, patient-centered supportive care [27]. The findings will also be disseminated through peer-reviewed publications and academic conference presentations to facilitate the translation of evidence into clinical oncology practice.

Conclusions

This protocol outlines a comprehensive systematic review and meta-analysis aimed at evaluating the efficacy and safety of aromatherapy for CIGT in patients with cancer. Evidence from randomized controlled trials will be synthesized to clarify the therapeutic value of aromatherapy; identify effective essential oil types, intervention forms, and intervention durations; and resolve inconsistencies in existing evidence. The anticipated results will provide an evidence-based foundation for the safe and standardized integration of aromatherapy into supportive cancer care, while guiding future research on mechanistic exploration, optimized intervention protocols, and long-term clinical evaluations.

Acknowledgments

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Disclaimer

If protocol modifications are needed, the rationale for each adjustment will be documented and the respective dates will be carefully recorded.

Authors' Contributions

HS: conceptualization, funding acquisition, supervision, writing–original draft, writing–review and editing. XC: conceptualization, funding acquisition, supervision, writing–original draft, writing–review and editing. XXF: formal analysis, methodology, investigation, writing–review and editing. MQL: project administration, methodology, investigation, writing–review and editing. WP: supervision, funding acquisition, writing–review and editing. WZ: supervision, funding acquisition, writing–review and editing.

Conflicts of Interest

None declared.

Checklist 1
PRISMA-P checklist.
[PDF File, 127 KB - resprot_v14i1e76350_app1.pdf]

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Abbreviations

CIGT: chemotherapy-induced gastrointestinal toxicity
GRADE: Grading of Recommendations Assessment, Development, and Evaluation
PICOS: participants, interventions, comparisons, outcomes, and study
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
RoB2: Risk of Bias 2
WHO: World Health Organization

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Psychological Factors Influencing Pain Perception and Experience in Women Undergoing Mammography: Protocol for a Systematic Review

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Abstract

Background: Breast cancer is the most frequently diagnosed cancer among women worldwide and a leading cause of cancer-related mortality. Mammographic screening significantly improves the early detection and survival rates. However, the pain and discomfort experienced during mammography, primarily due to breast compression, can serve as major deterrents to participation in routine screening programs. Psychological factors such as anxiety, fear, and pain catastrophizing have been shown to influence pain perception and experience during mammography. These factors may affect women's decisions to participate in or avoid screening, undermining public health efforts for early detection.

Objective: This study aims to synthesize the scientific literature on the psychological factors influencing pain perception and experience in women undergoing mammography.

Methods: This systematic review protocol is in accordance with the 2015 PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) guidelines. Eligible studies will include randomized controlled trials and observational designs that examine psychological factors—such as anxiety, catastrophizing, and related constructs—in relation to pain perception and experience among women undergoing screening or diagnostic mammography. The primary outcome is women's perception and experience of pain during mammography, and the role of psychological factors may influence it, while secondary outcomes include pain intensity and pain-related distress, measured with validated pain scales or self-reported questionnaires. There will be no restriction on publication year, but only peer-reviewed, full-text articles in English will be included. Gray literature will be excluded. A systematic search will be conducted in PubMed, Scopus, and PsycINFO using database-specific strategies with keywords and Boolean operators; reference lists of included studies will also be screened. Study selection and data extraction will be performed independently by two reviewers. Risk of bias will be assessed using the Joanna Briggs Institute critical appraisal tools. Data will be synthesized narratively, with thematic grouping of psychological factors and tabulation of study characteristics. Due to anticipated heterogeneity across populations, study designs, and outcome measures, a meta-analysis will not be feasible; instead, greater interpretive weight will be given to findings from studies judged to have a lower risk of bias.

Results: The database search has been completed in September 2025. Data extraction and organization into summary tables are scheduled to be finished by December 2025, followed by a narrative synthesis of findings. The systematic review manuscript is planned for submission to a peer-reviewed journal in January 2026.

Conclusions: This protocol outlines the first systematic review to comprehensively investigate women's perception and experience of pain during mammography and the psychological factors, such as anxiety, depression, fear, and coping strategies, that may influence it. The review aims to generate evidence-based insights that will inform clinical practice and guide the development of targeted interventions designed to reduce discomfort, improve screening experiences, and increase participation in breast cancer screening programs. The authors also plan to disseminate the findings through publication in a peer-reviewed journal.

Trial Registration: PROSPERO CRD420251117801; https://www.crd.york.ac.uk/PROSPERO/view/CRD420251117801

International Registered Report Identifier (IRRID): PRR1-10.2196/77118

(JMIR Res Protoc 2025;14:e77118) doi:10.2196/77118

KEYWORDS

screening mammography; breast cancer screening; psychological factor; anxiety; pain catastrophizing; pain

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Introduction

Background

Breast cancer remains a significant global public health issue and is the most common malignancy among women. It ranks among the top three most prevalent cancers worldwide, alongside lung and colorectal cancer [1,2]. In 2022, approximately 2.3 million women were diagnosed with breast cancer, resulting in 670,000 deaths globally [3]. The annual incidence continues to rise by 0.5%, and projections suggest that cases will surpass 3 million by 2040. While mortality has significantly declined since the 1980s due to advances in early detection and treatment, this decline has slowed in recent years. Breast cancer remains the leading cause of cancer-related death in women. African American women show disproportionately high mortality rates, and countries such as China are witnessing a sharp increase in incidence [4].

Screening programs are designed to detect the disease at an early stage and ultimately reduce breast cancer-related morbidity and mortality [5-7]. Population-based screening has substantially decreased breast cancer mortality rates in high-income countries. However, such programs require robust health system infrastructure, significant resource investment, and equitable service delivery. These prerequisites often present barriers in low- and middle-income countries, where healthcare systems may be fragmented, under-resourced, and understaffed, making quality screening and follow-up services difficult. Consequently, many low- and middle-income countries lack effective population-based breast cancer screening programs or fail to achieve the desired public health impact [8]. In countries such as India and those across Sub-Saharan Africa, implementation is often hindered by limited financial and logistical resources [9,10].

Mammographic screening is widely available and is regarded as one of the most effective methods for the early detection and prevention of breast cancer before the onset of clinical symptoms [6,11]. This has led many European countries, including the United Kingdom, Spain, and Germany, to establish population-based mammography screening programs [12]. For women at average risk, most guidelines recommend screening between the ages of 40 and 74 years, with the 50 - 69 age group typically considered the optimal target for preventive screening [13].

Mammography utilizes X-rays to detect early signs of breast cancer. The standard protocol includes two views: craniocaudal and mediolateral oblique, which involve pulling and separating the breast tissue from the chest wall. During the procedure, the breast is compressed between two plates to immobilize the tissue and reduce its thickness, thereby minimizing radiation exposure and improving image quality [14,15].

Pain during medical procedures is widely recognized as a complex experience influenced not only by physiological factors but also by psychological, emotional, and cognitive elements [16]. Research across various clinical settings, such as gynecological examinations, colonoscopies, and dental work, has shown that psychological factors—particularly anxiety, fear, past experiences/expectations, and maladaptive coping strategies—can heighten pain perception and reduce adherence to preventive screenings [17-19]. In breast imaging, these psychological aspects are essential, as mammography requires repeated participation to meet public health goals.

While some women experience only mild discomfort during mammography, others describe the procedure as painful or distressing. Compression of the breast can cause pain during and after the examination, which has been shown to deter women from attending subsequent screening appointments, despite the known benefits of early detection [15,20]. A systematic review reported that between 25% and 46% of women cited pain during compression as the primary reason for avoiding future mammography [21].

Psychological factors such as situational anxiety and fear of pain play a significant role in pain perception during mammography [22,23]. Anxiety is the most reported emotional reaction to mammography, and fear may act as a barrier to participation [24]. General cancer-related anxiety may facilitate screening adherence, particularly when women believe in the effectiveness of mammography and have the necessary resources to access it [25]. However, anticipatory anxiety specifically related to the procedure itself may reduce compliance, as women seek to avoid the examination to alleviate their distress [26-28].

Numerous studies have demonstrated that pain catastrophizing—exaggerated negative thoughts and feelings about pain—contributes to higher pain intensity, emotional distress, and avoidance behavior [29,30]. Catastrophic thoughts regarding mammographic pain (eg, “the pain will be overwhelming”) can significantly affect screening adherence, particularly among breast cancer survivors. The cognitive-behavioral model of anxiety highlights how such thoughts can fuel avoidance of anxiety-provoking situations [31,32].

In the context of breast cancer, catastrophizing has been studied regarding screening adherence [33], persistent breast pain and mammography-related pain among survivors [34,35], and cancer worry among first-degree relatives of survivors [36]. Although limited, evidence from studies [37] suggests that healthy women with higher levels of catastrophizing and self-reassurance tendencies report greater pain during mammography.

However, the available findings are not entirely consistent. While several studies report significant associations between psychological factors—such as anxiety, catastrophizing, or depression—and mammography-related pain, others describe weaker or non-significant relationships [37-40]. This inconsistency may be due to differences in study design, the populations studied, and the variables evaluated.

Despite these insights, the available evidence remains fragmented and partly contradictory, as most studies have focused on individual psychological factors or specific subgroups. To date, no systematic review has synthesized the literature on psychological determinants of pain perception during mammography. This represents a significant knowledge gap, as a comprehensive synthesis could clarify the extent to which psychological factors contribute to mammography-related

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pain and influence women's adherence to screening. Addressing this gap is essential for designing targeted interventions aimed at reducing discomfort, improving women's experiences, and enhancing participation in breast cancer screening programs.

Objective

This study aims to synthesize the scientific literature on the psychological factors influencing pain perception and experience in women undergoing mammography.

Review Questions

The primary question was, "Is there an association between underlying psychological factors in women undergoing mammography and the experience of pain?" The secondary question was, "What is the intensity of pain experienced by women during mammography, as assessed through validated questionnaires?"

Methods

Overview

This protocol follows the 2015 PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis for Protocols) checklist, and it is intended that this systematic review will contain the items of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, 2020 version. This systematic review is registered with PROSPERO (ID: CRD420251117801). This protocol does not amend a previously completed or published protocol. Any necessary amendments made during the review process will be documented in the final report and transparently reported in the published manuscript.

Eligibility Criteria

The selection of studies is based on the eligibility criteria given below.

Population

We will include studies involving women undergoing screening or diagnostic mammography. Studies that include patients with breast augmentation or breast reconstruction following mastectomy will also be eligible. All races and ethnicities of women reported in the included studies will be considered for inclusion. No exclusion criteria will be applied based on prior cancer history or comorbidities.

Exposure of Interest

Studies will be included if they examine psychological factors such as anxiety, fear of pain, and pain catastrophizing, or any combination of these exposures. Any additional or emerging psychological constructs related to pain perception during mammography identified in the literature will also be considered eligible for inclusion.

Outcomes of Interest

The primary outcome of interest is the perception and experience of pain among women undergoing mammography. Specifically, the review will assess whether psychological factors influence how pain is perceived and experienced during the procedure.

Secondary outcomes will include the level of pain experienced during or after mammography, assessed through validated pain scales or self-reported questionnaires, and whether this pain level is associated with specific psychological factors.

Type of Studies

All randomized control trials and comparative observational studies, including prospective and retrospective cohort studies, case-control studies, and cross-sectional studies, will be eligible. Reviews, including narrative and systematic reviews, conference abstracts, case series, case reports, editorials, and commentaries, will be excluded.

Language and Publication Status

We will include publications in the English language, and we will consist of studies reported as full text.

Years Considered

There will be no publication date restrictions.

Information Sources

A systematic literature search will be performed in the PubMed, Scopus, and PsycINFO databases using text words related to psychological factors and perception of pain undergoing mammography. Based on the references of the included studies, we will identify further relevant studies. Gray literature (eg, dissertations, conference abstracts, unpublished reports) will be excluded to ensure that only peer-reviewed studies of established methodological quality, with sufficient methodological and statistical details, are included in the synthesis.

Search Strategy

The project team will develop the search strategy. We will perform a preliminary search in the PubMed database to identify the first set of publications suitable for inclusion. We will identify additional keywords to build a final search strategy. This final search strategy will be reused for the PubMed database and adapted for the abovementioned further databases. The database searches will use keywords and subject terms connected by Boolean operators (OR and AND) to create specific search strategies for each database. In Textbox 1, the complete search strategy for the PubMed (MEDLINE) database is presented. From their inception, we will search all databases, restricting our search to English-language publications or publication status. We will check the reference lists of all included studies and any relevant systematic reviews identified for additional references to trials.

Textbox 1. Search strategy for PubMed.

((mammograph* OR "screening mammograph*" OR mammogram* OR "breast cancer screening" OR "mammographic screening")) AND (("Psychological factor*" OR anxiety OR stress OR fear OR "fear of pain" OR pain OR catastrophizing OR "pain catastrophization" OR depression OR "coping strateg*" OR neuroticism OR extraversion))) AND ((pain OR soreness OR tenderness).)

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Data Management

Literature search results will be stored in Mendeley Reference Manager for duplicate removal and reference organization.

Selection Process

After removing duplicates, two independent reviewers will independently assess titles and abstracts of all publications from the databases. Studies that do not meet the inclusion criteria are excluded from further consideration. Any inconsistency between the researchers will be solved by discussion, and the reasons for each excluded study will be recorded. A third reviewer will be consulted to make the final decision if consensus cannot be reached. Full texts of the remaining studies will be treated in the same way. The selection procedure will be documented in a PRISMA flow diagram.

Data Collection Process

The review team will use a standardized data charting form to extract the data from the included studies. The template will be piloted on a subsample of three studies by two reviewers before use to ensure consistency, where any adaptations or refinements made will be reported. All extracted data will be verified for accuracy by a second reviewer. Any disagreements will be resolved by consensus or, where necessary, a third reviewer.

Data Items

From each included study, the following data will be extracted in a table: study details (eg, authors, year of publication, country of study, study design, and sample size), participants characteristics (eg, age, menopausal status, clinical characteristics, history of mammography, other relevant demographics), psychological factors and assessment tools (eg, anxiety, depression such as State-Trait Anxiety Inventory, Hospital Anxiety and Depression Scale, or other scales), pain outcome measures (eg, visual analog scale, or other validated tools), and main outcomes (eg, associations between psychological factors and pain during mammography, proportion of women reporting pain). This list is not exhaustive and may be refined further during the review process. Any discrepancies during data extraction will be resolved by discussion between the reviewers.

Risk of Bias in Individual Studies

The quality assessment of the included studies will be conducted using the Joanna Briggs Institute (JBI) checklist [41]. These tools offer checklists for various study designs. The assessment will address potential sources of bias in each study, such as participant selection, reliability of outcome measurements, appropriateness of the statistical analysis, and potential selective reporting of results. Responses to the questions are categorized as “yes,” “no,” “unclear,” and “not applicable.” A study is considered “unclear” if it does not provide explicit information for a specific question. If a question is irrelevant to the study’s context, it is marked as “not applicable.” Two reviewers will perform this process independently. Subsequently, the agreement between reviewers will be evaluated, and in cases of disagreement, consensus will be reached. No studies will be excluded based on quality; however, the appraisal results will be reported to allow readers to assess the credibility of the findings. Instead, the findings will inform the synthesis, with results from studies at higher risk of bias receiving less interpretative weight in the narrative synthesis. We will present stratified summaries of evidence according to risk of bias level (low, moderate, and high). The results of this quality assessment will be displayed in tabular form in the systematic review.

Data Synthesis

In this review, the search is expected to reveal heterogeneous studies in the population, outcome measures, psychological constructs, and study designs. This diversity prevents meaningful pooling or meta-analysis of results, as combining heterogeneous effect estimates would obscure rather than clarify relationships. Therefore, the meta-analysis of study findings is not an objective of this review. Nevertheless, whenever possible, descriptive quantitative data (such as mean pain scores, prevalence of moderate-to-severe pain, or correlation coefficients) will be tabulated to provide a quantitative overview; however, the interpretation will mainly remain narrative. Data synthesis will take the form of a structured narrative synthesis of the included studies. The synthesis will be conducted in line with the framework proposed by Popay et al [42], which provides a systematic, transparent, and reproducible approach for narrative synthesis in systematic reviews. The defining characteristic of this approach is that it adopts a textual and thematic method to summarize and interpret findings in a structured manner. The synthesis will be organized around two main themes: (1) findings on the association between psychological factors and the experience of pain during mammography will be synthesized; (2) findings on the intensity of pain experienced by women during mammography will be collated from all studies. After findings on the association between psychological factors and the experience of pain during mammography will be synthesized, the extracted quantitative results (eg, correlation coefficients, *P* values, regression outcomes, or categorical findings such as “significant association” or “no association”) will first be categorized by the direction and strength of the association (positive, negative, or non-significant). These quantitative findings will then be qualitatively coded into broader thematic statements (eg, “anxiety amplifies pain perception,” “adaptive coping mitigates pain,” or “previous painful experience predicts greater pain”). This process will enable the integration of diverse statistical results into clear thematic patterns across studies. (2) Findings on the intensity of pain experienced by women during mammography will be collated from all studies. Reported pain outcomes (eg, visual analog scale scores, categorical pain levels, or prevalence rates) will be grouped according to each study’s measurement scale and reporting format. Descriptive summaries will be presented where available, and narrative patterns will be identified (eg, “higher intensity of pain among women, greater anxiety’’). The synthesis will highlight similarities and differences in reported pain intensity across studies. The results of the JBI quality appraisal will be integrated into the synthesis to aid interpretation, with greater weight given to findings from studies assessed as higher quality. Any discrepancies or variations across studies will be explicitly reported, and areas of consistency will be highlighted to provide a comprehensive overview of the evidence.

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Ethical Considerations

Ethical clearance is not applicable as the present review will include only published articles from different databases, and no human participants will be involved.

Results

As of September 2025, the database search has been completed, and the organization of extracted data into summary tables is currently in progress. A narrative synthesis of the findings will follow, along with drafting the systematic review manuscript. Data extraction and synthesis are expected to be finalized by December 2025, and we plan to submit the manuscript for peer-reviewed publication by January 2026.

Discussion

Principal Findings

Studies have demonstrated associations between psychological factors and pain perception across various medical procedures [43,44]. Research in the field of mammography has indicated that anxiety and catastrophizing may exacerbate the experience of pain, whereas adaptive coping strategies, such as ignoring pain sensations, can mitigate pain intensity [37,40]. However, to date, no systematic review has synthesized the available evidence to provide an in-depth understanding of how psychological factors specifically influence women's pain experience during mammography.

Therefore, it is hypothesized that the results of the selected studies will confirm the significant impact of psychological factors on pain experience. Women with higher levels of anxiety or catastrophizing are expected to report greater pain intensity compared to those with lower levels of anxiety or more effective coping strategies. Additionally, the review will address a secondary research question: the extent to which women report the intensity of pain experienced during mammography, as measured by validated questionnaires. Although supplementary, this question is expected to provide a more objective assessment of the pain experience.

Strengths and Limitations

One of the strengths of this review is its rigorous methodology, adherence to the PRISMA-P guidelines, and the use of JBI tools to assess risk of bias, which improve the validity of the findings. Additionally, the review will offer an updated, specialized, and detailed overview of how psychological factors directly influence the pain experienced by women undergoing mammography, highlighting the importance of including psychological interventions in clinical practice and helping policymakers develop patient-centered strategies. However, some limitations should also be recognized, such as the heterogeneity of studies and measurement tools for psychological parameters, which may introduce bias, along with the restriction to English-language studies. Moreover, because of this heterogeneity, conducting a meta-analysis will not be feasible. Finally, the exclusion of gray literature, although intended to ensure methodological rigor and the inclusion of peer-reviewed studies, may have introduced publication bias and limited the comprehensiveness of the evidence base.

Future Directions

For future research, it would be useful to explore the effectiveness of psychological interventions that could be integrated into mammography clinical practice, aiming to reduce pain perception and enhance women's overall experience. Additionally, the present review will identify existing knowledge gaps, encouraging further studies to address them and thereby deepen the overall understanding of the topic, ultimately leading to improvements in clinical practice.

Dissemination Plan

The findings of this review will be shared through publication in a peer-reviewed journal and presentations at international radiology and public health conferences. Additionally, patient-focused educational materials may be created to enhance awareness and participation in screening programs. Dissemination will also include professional societies, clinical guidelines, and training programs for radiologic technologists, ensuring that the results influence both practice and policy.

Conclusions

To our knowledge, this will be the first systematic review to thoroughly examine the impact of psychological factors, such as anxiety, depression, fear, coping strategies, and others, on how women perceive and experience pain during mammography. The expected findings aim to provide evidence-based insights that inform clinical practice, support the development of targeted interventions, and reduce psychological barriers to screening participation. Ultimately, this knowledge could promote patient-centered care, increase adherence to breast cancer screening, and contribute to earlier detection and better health outcomes.

Acknowledgments

We thank our academic mentor, Eleni Jelastopulu, for providing feedback and for assistance with proofreading during protocol development.

Data Availability

No data are associated with this article, and the results of this study have not yet been generated. This protocol reflects the planned methodology and objectives at the time of submission.

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Authors' Contributions

IN and EJ designed this study. IN was a major contributor to the writing of this paper. All authors read, edited, and approved the final paper. IN was the guarantor of the review.

Conflicts of Interest

None declared.

Checklist 1
PRISMA-P checklist.
[DOCX File, 35 KB - resprot_v14i1e77118_app1.docx]

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Abbreviations

JBI: Joanna Briggs Institute
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: Prospective Register of Systematic Reviews

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Methodological Approach for Dengue Viral Load Quantification in Wastewater: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: In recent years, the rapid emergence and global spread of dengue has become a public health burden. Clinical surveillance alone has limited capacity, with delayed detection of upcoming outbreaks. Hence, the potential use of wastewater-based surveillance (WBS) for early detection of incoming surges of dengue cases could complement proactive public health action. However, there are still substantial gaps in the standard approach for sampling and detection methods in dengue WBS.

Objective: This review aims to determine the current methodological approach for the detection of dengue virus (DENV) in wastewater across geographical areas.

Methods: The review will be conducted systematically following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. In the initial stage, peer-reviewed publications from PubMed, Embase, Scopus, and Web of Science will be searched using predefined terms such as “Dengue” and “WBS.” Keywords will be adjusted to suit each database to identify studies related to DENV WBS from inception until June 2025. Subsequently, the references from relevant articles will be screened for eligibility. All data will be extracted from full-text articles highlighting the characteristics and methodological context of the investigated DENV WBS using a standardized form. The ROBINS-I (Risk of Bias in Non-randomized Studies - of Interventions) tool and the GRADE (Grading of Recommendations Assessment, Development, and Evaluations) system will be used to assess study bias and the quality of the evidence. Further descriptive analysis and meta-analysis will be applied to evaluate the methodologies for DENV WBS.

Results: The data on DENV detection in wastewater will be synthesized by analyzing sampling techniques, viral detection method, study sites, geographic locations and dengue serotype. A meta-analysis will be conducted using a random-effects model if data are heterogeneous, with pooled estimates reported as 95% CIs. Heterogeneity will be assessed using I^2 and chi-square tests, with subgroup and sensitivity analyses conducted as needed. Findings will be reported in accordance with PRISMA 2020. As of October 2025, records have been identified from the databases and data analysis is expected to be completed by the first quarter of 2026.

Conclusions: This protocol outlines a systematic approach to identifying and evaluating existing methods for detecting DENV in wastewater. This research aims to provide valuable insights into best practices for dengue surveillance and offer guidance for future research by highlighting current strengths and limitations in the field.

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KEYWORDS

Dengue virus; wastewater surveillance; viral concentration; serotypes; sampling methodology

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Introduction

Over the past decade, the persistent threat of dengue virus (DENV) has emerged as a significant global health concern, despite the decline in the incidence of other infectious diseases [1,2]. The increasing spread of dengue, an arthropod-borne viral infection, has led to endemic and epidemic transmission cycles in many regions globally. DENV, an arbovirus belonging to the genus *Flavivirus*, has four serotypes ranging from DENV-1 to DENV-4 [2]. The disease is exacerbated by increasing urbanization, increased population density, inadequate housing, improper waste management, scarce water supplies, and climate change [3]. Moreover, the shift and expansion of vector distribution areas and pathogen suitability zones has led to an increase in arboviruses such as DENV [4,5].

Southeast Asia and the Western Pacific region are the hyperendemic hot spots for DENV infections, contributing to nearly 75% of the global dengue burden [6]. The highest number of dengue cases was recorded in 2023, affecting over 80 countries in all World Health Organization regions [6]. Sustained transmission combined with an unexpected rise in dengue infection led to more than 6.5 million cases with more than 7300 dengue-related deaths worldwide [6]. This underscores the critical role of vector-borne disease surveillance, which is an essential part of the dengue control program in many endemic countries [7].

Furthermore, the number of asymptomatic infections was estimated to be higher than those with clinical manifestations, posing a great challenge to public health, considering the former are about 80% as infectious as their symptomatic counterparts [8,9]. The asymptomatic infections may account for 84% of all dengue transmissions, with only 1% attributable to people with clinical manifestations and a positive diagnostic test [9]. Hence, the limitations of clinical and vector surveillance in detecting these subclinical cases may hamper the progress in containing the spread of dengue [10]. Moreover, shifts in circulating DENV serotypes have been associated with the emergence of outbreaks and severe dengue cases, leading to increased morbidity and mortality [11]. This underscores the need for a comprehensive, population-based surveillance system to support timely public health responses and preparedness efforts.

Considering the existing limitations of current dengue surveillance, wastewater-based surveillance (WBS) has been proposed as a promising tool for population-level surveillance [10,12-14]. In addition, DENV RNA has been detected in the urine, rectal swabs, and bodily fluids of infected persons, thereby confirming its presence in the sewage system and reinforcing the applicability of WBS for dengue monitoring [15-17]. Even in areas with low case prevalence and lower shedding, DENV RNA has been successfully detected in wastewater in several studies [10,14]. Additionally, several arbovirus WBS reviews offer valuable insights with focuses on technical feasibility and methods [18,19], highlighting real-world challenges, especially for vector-borne diseases in tropical settings [20]. This review aims to consolidate dengue-specific knowledge.

Despite its potential, the relative importance of dengue WBS has not yet been comprehensively studied. The use of WBS to detect DENV in low-prevalence areas depends heavily on the sensitivity of viral RNA detection in sewage. Accuracy is influenced by factors like population shedding, sewer network characteristics, sampling methods, and analysis techniques. Variability in methodology including sampling strategies, RNA stability, and detection tools (eg, quantitative polymerase chain reaction, sequencing) limits data comparability. The lack of standardized protocols and uneven lab capacity further hinders consistent reporting [21]. A comprehensive evaluation of optimal methods is still lacking, and addressing these gaps is key to improving the reliability and impact of dengue WBS.

Therefore, this review will focus on the methodologies and findings and will highlight the gaps that need to be addressed. Hence, the objectives of this review are to (1) describe methodologies for sampling, detection, and serotype analysis of DENV in wastewater across geographical areas, (2) determine the dengue viral load in different sampling and detection methodologies, and (3) identify potential use of dengue WBS for public health action.

Methods

Ethical Considerations

This systematic review has been registered with the National Medical Research Register, Ministry of Health Malaysia, and the protocol has been registered with PROSPERO (International Prospective Register of Systematic Reviews; CRD42024574930). The findings will be disseminated to relevant stakeholders involved in policymaking and program management for dengue surveillance. These results will also help in our future research on dengue wastewater surveillance to choose the best sampling and analysis methods. This review involves data extracted from previously published, publicly available sources and does not directly involve participants or the use of any identifiable personal data. Therefore, formal ethics approval was not required.

This protocol was prepared based on the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist (Checklist 1). This review is still ongoing and the procedures outlined in this section will be applied during the review process. The systematic review and meta-analysis will be reported in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [22].

Population

This review will include sewage samples from wastewater treatment plants serving population-based communities or public/private institutions.

Intervention

We will include studies conducting WBS involving different sampling methodologies (sample type, sampling techniques, frequency, location), detection and serotype analysis.

Comparator

There is no restriction of the included articles with or without a comparator.

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Outcomes

The outcomes that will be included are viral load (gene copies, Ct value). The outcomes will be compared based on different contexts, which are sampling methodologies and detection methods (polymerase chain reaction–based, enzyme-linked immunosorbent assay) and geographical area.

In addition, we will include studies reporting serotype analysis, positivity rate (%), epidemiological trends (above or below the limits; stagnation, increase, or decrease in the number of cases), and molecular characterization of DENV.

Patient and Public Involvement

There is no involvement of patients and the public in this review.

Eligibility Criteria

The eligibility criteria are as described in Textbox 1.

Textbox 1. Study inclusion and exclusion criteria.

Inclusion criteria

- Preprints and peer-reviewed studies that are descriptive, experimental, cohort, cross-sectional, or case-control, which determine the amount of dengue RNA in wastewater
- Articles published in the English language

Exclusion criteria

- Nonoriginal or nonresearch publications (eg, review papers, case reports, technical reports, conference proceedings, books, book chapters, non–full text articles)
- Non-English articles

Information Source

A comprehensive search will be performed using 4 databases (PubMed, Scopus, Web of Science, and Embase) by two authors independently based on the eligibility criteria. The search strategy will include a combination of predefined keywords that are Medical Subject Headings (MeSH) terms and free-text terms related to dengue WBS. Boolean operators such as OR and AND will be used to combine these keywords and refine the search findings in the titles and abstracts of databases. The search strategy to be used is presented in Checklist 1. Additionally, a manual screening of references from articles will be performed. The time frame for the inclusion of studies will be from inception until June 2025.

Data Management

Articles retrieved from the electronic searches will be imported into Zotero software (version 6.0.37; Corporation for Digital Scholarship) to check for and remove duplicates. Subsequently, the records will be exported to a CSV file format. Unique identifiers will be given to the records and the data will subsequently be managed through Microsoft Excel (Microsoft Corp).

Selection of Studies

Preliminary title and abstract screening of the remaining articles will be done independently by two authors to retrieve relevant articles based on the predetermined criteria of the study population, intervention, comparator, and outcomes. Subsequently, full-text articles will be reviewed by two reviewers to assess their eligibility based on the exclusion and inclusion criteria using an eligibility form. If discordance to accept or reject an article arises, a third reviewer will be sought to come to a decision. Reasons for exclusion of articles will also be recorded and discussed. Two independent authors will identify articles to be included in the meta-analysis. The flow of the strategy used for the selection of the included articles will be summarized in a PRISMA diagram as a figure.

Data Extraction

Comprehensive data extraction will be performed using a standardized form to systematically gather information from each study. This will include study characteristics (author details, publication year, country, study design), sampling methodology (sample type, sampling techniques, frequency, location), method of detection, and serotype analysis. To ensure the reliability of the data, two independent reviewers will perform the extraction, with any discrepancies resolved through discussion or consultation with a third reviewer. This will facilitate a thorough analysis of the evidence, emphasize significant findings, identify research gaps, and establish a basis for future studies in the field.

Quality Assessment and Risk of Bias

Quality and risk of bias will be appraised with design-specific instruments. The Risk of Bias in Non-randomized Studies – of Interventions (ROBINS-I V2) tool will be used to assess the quality of included studies. This tool evaluates the risk of bias across seven domains: (1) bias due to confounding, (2) bias in the classification of interventions, (3) bias in the selection of participants into the study (or into the analysis), (4) bias due to deviations from intended interventions, (5) bias due to missing data, (6) bias arising from measurement of the outcome, and (7) bias in the selection of the reported result [23]. Each domain will be rated as having a low, moderate, serious, or critical risk of bias [24]. Two independent reviewers will assess each study across these domains, and any discrepancies will be resolved by involving a third reviewer. The overall risk of bias for each study will be determined based on the "worst-score rule," meaning that the final judgment reflects the highest level of bias identified in any single domain.

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In addition to ROBINS-I, other tools may be considered based on study design. For cohort and case-control studies, the Newcastle-Ottawa Scale may be used, which judges study selection, comparability, outcome and exposure domains via a star system, and classifies overall quality (good/fair/poor) using established thresholds [25]. Diagnostic accuracy or method-comparison studies (eg, assay sensitivity and specificity against a reference standard) will be appraised with QUADAS-2 (Quality Assessment of Diagnostic Accuracy Studies tool), covering the case selection, index test, reference standard, and flow/timing that led to domain-level ratings (low, high, or unclear) and an overall judgment [26]. For analytical validation without a case-level reference, we will apply adapted QUADAS-2 signaling questions focused on sample handling, analyst blinding, repeatability, and selective reporting. In studies with overlapping designs or mixed components such as those reporting both exposure-outcome associations and diagnostic accuracy, we will apply more than one appraisal tool as appropriate to each component. In such cases, we will present risk-of-bias ratings separately for each tool and component. If this yields differing overall judgments, we will prioritize the tool corresponding to the study's primary aim or default to the higher risk rating for synthesis purposes. The rationale for tool selection and integration will be documented. However, it should be noted that these alternative tools are generally less comprehensive than the ROBINS-I tool, particularly when adapted for assessing bias in exposure studies. A quality summary will be presented in a table or figure.

Two independent reviewers will complete domain-level ratings using prespecified guidance and standardized forms; disagreements will be resolved by discussion and, if necessary, a third reviewer, defaulting to the more high-risk rating when consensus is not achievable. We will document rationales for each judgment and present domain- and study-level summaries in tables or traffic-light plots.

Statistical Analysis

Statistical analysis will be performed using Review Manager (RevMan; version 5.4; The Cochrane Collaboration). A meta-analysis will be conducted if at least two comparable studies with similar outcome measures are available. Meta-analyses will be conducted for viral load quantifications from included articles to determine overall effect sizes. Effect sizes will be calculated as risk ratios or odds ratios for categorical outcomes (eg, detection of DENV in wastewater) and as mean differences or standardized mean differences for continuous outcomes (eg, viral load or concentrations of dengue markers) [27]. Heterogeneity will be assessed using the I^2 statistic and Q test. The I^2 statistic will be used to quantify the proportion of total variation across studies attributable to heterogeneity rather than chance, with thresholds of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively [28]. The Q test, which will apply a χ^2 test, will be used to statistically evaluate heterogeneity among the studies. Pooled analyses that use fixed-effects models for low heterogeneity (I^2<50%) and random-effects models for moderate to high heterogeneity (I^2≥50%), accounting for variability across studies, will be performed [29]. Subgroup analyses will be performed based on factors such as sampling techniques, detection methods, dengue serotypes, sampling sites, geographic location, and seasonality. Sensitivity analyses will be conducted to assess the robustness of the overall findings by excluding studies with high risk of bias or outlying results [30]. Cumulative meta-analysis will track trends in effect sizes over time [31]. Studies meeting inclusion criteria but lacking data for meta-analysis will be summarized narratively and compared with the meta-analysis findings.

Certainty of Evidence

The certainty of evidence will be systematically evaluated using the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) framework [32,33]. This evaluation will address (1) study limitations, considering potential biases in selection, performance, detection, and reporting that may affect the reliability of the results; (2) inconsistency, where variations in findings across studies may undermine confidence in the estimated effect size; (3) indirectness, which will assess the applicability of the evidence to the research question by examining differences in populations, interventions, and outcomes across studies; (4) imprecision, which will evaluate the certainty of the effect estimates, with wide confidence intervals reflecting uncertainty in the findings; and (5) publication bias [33]. Each of these domains will be rated to determine the overall quality of the evidence as high, moderate, low, or very low.

Assessment of Reporting Biases

Publication bias will be assessed using a funnel plot by visualizing the effect sizes of different studies, particularly between small and large study sizes. Further tests including the Egger regression test significance at P<.05 [34] will be suggested if bias is suspected, given the number of articles included will be more than 10 [30].

Results

A PRISMA 2020 flow diagram will be presented to illustrate the process of study identification, screening, and final inclusion for this systematic review and meta-analysis (Figure 1) [35]. Results will be charted and tabulated to provide a detailed summary of methodologies and outcomes. The study characteristics and key outcomes including dengue WBS methods, detection rates of the DENV, viral load, and the accuracy of these methods in terms of sensitivity and specificity will be presented. The meta-analysis of viral load quantification and subgroup analysis will be visualized using forest plots. As of October 2025, records have been identified from the databases and data analysis is expected to be completed by the first quarter of 2026.

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Figure 1. PRISMA flow diagram. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

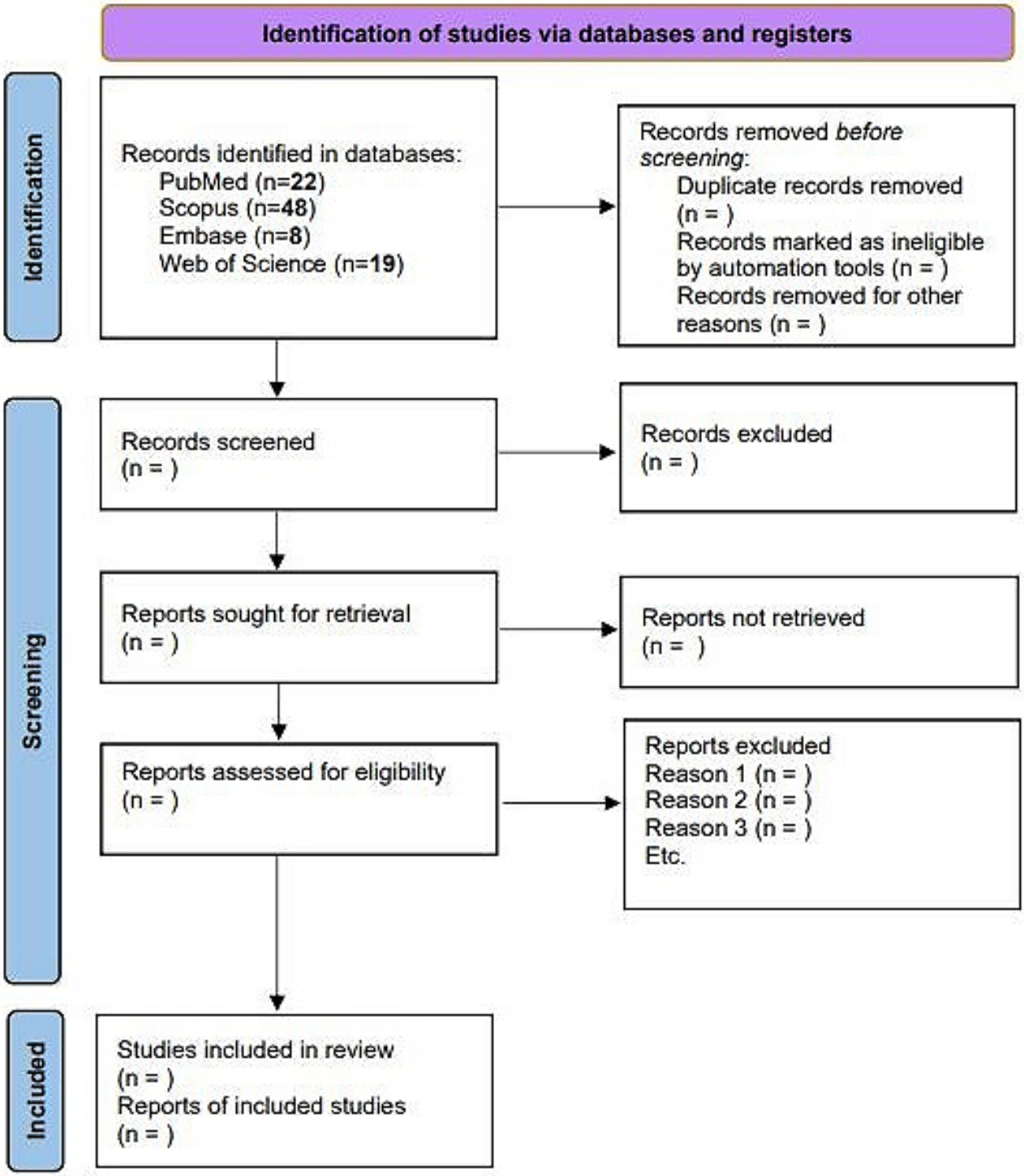

Discussion

Expected Outcomes

This systematic review and meta-analysis will describe and synthesize the current evidence of dengue WBS in terms of the available methodologies and their correlation with viral concentration. The reviewed studies are expected to demonstrate the detection and quantification of DENV in population-based WBS and dengue-spiked experimental setups. Importantly, these studies will inform the selection of critical methodologies for conducting dengue WBS, including sampling strategies, sample types, concentration methods, nucleic acid extraction, and detection techniques. Additionally, they will offer insights into the feasibility and practical challenges of implementing WBS for dengue surveillance.

Strengths and Limitations

This will be the first comprehensive review on the global application of this surveillance method for dengue. WBS has been increasingly recognized as a cost effective and non-invasive tool to monitor infectious diseases in the community setting and its application has great potential to enhance public health measures and improve disease outcomes

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[36]. The data from the WBS could complement clinical surveillance to predict possible dengue outbreaks and provide an early warning through the detection of asymptomatic cases. This review will also guide the selection of key methodologies in performing dengue WBS and identify the gaps and limitations of different sampling and detection methods.

Given the emerging status of this field, we anticipate a limited number of studies will be available, which could limit the comparability and meta-analysis of the sampling and detection methods. There is also a possibility of reporting biases, with a higher frequency of positive results being published than negative findings.

Acknowledgments

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Authors' Contributions

Conceptualization: NAKH, SR, SAR, NFS; methodology: NAKH, SR, SAR; writing—original draft: NAKH, SR, SAR; writing—review and editing: NAN, NFS, TTYC, JCSW; supervision: NAN, NFS; guarantor: SAR. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Conflicts of Interest

None declared.

Checklist 1
PRISMA-P checklist.
[DOCX File, 24 KB - resprot_v14i1e71635_app1.docx]

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Abbreviations

DENV: dengue virus
GRADE: Grading of Recommendations Assessment, Development, and Evaluation

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MeSH: Medical Subject Headings
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PROSPERO: International Prospective Register of Systematic Reviews
QUADAS: Quality Assessment of Diagnostic Accuracy Studies
WBS: wastewater-based surveillance

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Factors Associated With Body Image Distress in Patients With Head and Neck Cancer: Protocol for a Systematic Review

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Abstract

Background: Body image distress (BID) is a significant psychological issue for patients with head and neck cancer (HNC) and arises from the visible disfigurements and functional impairments often associated with the disease and its treatment. Understanding the factors contributing to BID in this population is crucial for developing effective interventions and support mechanisms.

Objective: This systematic review outlines methods for identifying, evaluating, and synthesizing the available evidence on factors associated with BID among patients with HNC. This review intends to explore both clinical and psychosocial variables that may influence body image perceptions and the resulting psychological impact.

Methods: This review will follow the Joanna Briggs Institute (JBI) Reviewer's Manual for Systematic Reviews Concerning Etiology and Risk Factors. PsycINFO, MEDLINE, EBSCOhost CINAHL, Web of Science, Cochrane Library, and Embase were searched for relevant studies from inception to December 2024. All in-depth quantitative analyses, descriptive observational studies, experimental studies, and quasi-experiments published in English or Chinese were analyzed and described. Studies examining factors associated with BID in patients with HNC were included. The population, exposure, comparison, and outcome (PECO) format was used to develop the search strategy. For different databases, search terms will be combined using Boolean operators. The JBI Risk of Bias Tool was used to evaluate bias risk in the included studies. The extracted data will include basic study information, research design, sample characteristics, BID measurement tools, primary outcomes, statistical analysis methods, and quality assessment results. Subgroup and meta-regression analyses will be performed on different therapies, treatment stages, genders, ages, cultural backgrounds, etc. I^2 statistics will be used to evaluate heterogeneity, and funnel plots will address publication bias. If we detect significant heterogeneity, the findings will be reported as a systematic review without a meta-analysis.

Results: The database search will be conducted in October 2025. It is anticipated that the study findings will be submitted for publication in a peer-reviewed journal by the end of March 2026.

Conclusions: This study will summarize the factors that can help identify and evaluate the factors associated with BID in patients with HNC, providing up-to-date evidence to inform the management of body image in this patient population.

Trial Registration: PROSPERO CRD42023424006; https://www.crd.york.ac.uk/PROSPERO/view/CRD42023424006

International Registered Report Identifier (IRRID): PRR1-10.2196/69213

(JMIR Res Protoc 2025;14:e69213) doi:10.2196/69213

KEYWORDS

body image distress; head and neck cancer; systematic review; psychosocial factors; quality of life

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Introduction

Background

Head and neck cancer (HNC), a diverse group of malignancies affecting the oral cavity, pharynx, larynx, and more, ranks as the sixth most common cancer type worldwide, leading to more than 600,000 new cases annually [1]. Survival rates are approximately 40%‑50%, and early detection and comprehensive treatment strategies, including surgery, radiation therapy, and chemotherapy, are crucial. However, surgery and radiation therapy, despite their effectiveness, can lead to severe side effects. The most common acute side effect is mucositis, which can cause significant pain and impact a patient's ability to eat and speak [2]. Other acute side effects include xerostomia (dry mouth), dysphagia (difficulty swallowing), and odynophagia (painful swallowing). Long-term side effects can include fibrosis, lymphedema, and osteoradionecrosis. Among these, skin reactions are prevalent and can be particularly distressing for patients because they are often visible and disfiguring [3]. These skin reactions can range from mild erythema to severe ulceration and necrosis, leading to significant body image distress (BID) [4].

BID is defined as a negative self-perception of one's body arising from a discrepancy between one's actual physical appearance and ideal body image [5]. It encompasses a range of emotional, cognitive, and behavioral disturbances that can affect an individual's self-esteem, mood, and social functioning. For patients with HNC, the impact of BID can be profound. Given the visible changes in appearance and function and their impact on daily social interactions, it is not surprising that 75% of HNC survivors express concerns about their body image [6], with up to 28% experiencing clinically significant BID [7,8]. The visible disfigurements and functional impairments resulting from the cancer itself, as well as from treatments such as surgery and radiation therapy, can lead to significant distress. Patients may experience feelings of self-consciousness, shame, and social isolation as a result of changes in their appearance and abilities [9-11]. These psychosocial challenges can exacerbate the physical difficulties faced during treatment and recovery, potentially leading to depression, anxiety, and a diminished quality of life [12,13].

The literature on factors influencing BID in patients with HNC is expanding, with numerous studies examining a variety of potential contributors. These factors can be broadly categorized into clinical variables, such as tumor location, stage, and treatment side effects, and demographic variables, such as age, sex, and cultural background [12,14]. Research has also begun to explore the role of psychosocial variables, including social support, coping strategies, and preexisting mental health conditions, in influencing the experience of BID [15]. However, most evidence comes from small, single-center cross-sectional surveys that use heterogeneous instruments and lack multivariable adjustment. Consequently, the magnitude and interplay of these putative determinants remain poorly quantified, and no integrated framework currently exists. To address this gap, we conducted the first systematic review and meta-analysis to quantitatively appraise and synthesise the clinical, demographic, and psychosocial factors associated with BID in HNC survivors.

Exploring the factors influencing BID in patients with HNC is crucial and indispensable for developing targeted psychosocial interventions. Existing research on HNC-related BID has predominantly used a cross-sectional design, yielding heterogeneous results that reflect the complexity of body image issues in this patient population. For instance, Fingeret et al [16] found that individuals with higher levels of education may experience lower levels of BID. Conversely, Jiayan et al [17] reported that higher educational levels are associated with more severe BID, possibly due to the higher social and economic status of these patients and their greater demands for self-image. This discrepancy underscores the need for more longitudinal and comprehensive studies to better understand the multifaceted nature of BID in the context of HNC. Moreover, the psychological aspects of body image, which are multifactorial and encompass elements such as self-esteem, depression, and social support, are also critical to address, as highlighted by Patterson et al [18]. These studies indicate the complexity of the factors at play and the need for a more nuanced understanding of the psychosocial needs of patients with HNC.

The purpose of this systematic review was to summarize the literature on the factors associated with BID in patients with HNC. By identifying these factors, this review aims to inform health care professionals and researchers about the key areas targeted for psychosocial support and intervention. Furthermore, this study seeks to identify gaps in the current research, providing a roadmap for future studies to enhance our understanding of BID in patients with HNC and to improve their overall care and quality of life.

Research Questions

This review seeks to answer the following two research questions: What is the level of BID in patients with HNC? How do the individual characteristics of patients with HNC (including age, sex, social support status, and mental health status) affect the level of BID?

Methods

Standards

The methodological framework for this systematic review is grounded in the guidelines outlined in the Joanna Briggs Institute (JBI) Reviewer's Manual for Systematic Reviews Concerning Etiology and Risk Factors [19]. Additionally, the methodology is informed by the processes described by Dekkers et al [20]. This review protocol strictly conforms to the guidelines set forth by the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) statement [21]. Furthermore, the final systematic review will comply with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [22]. To ensure transparency and reproducibility, this protocol has been proactively registered in PROSPERO (unique registration number CRD42023424006).

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The Eligibility Criteria

English- and Chinese-language reports published in peer-reviewed sources were included.

Types of Studies

These studies include original observational studies, such as case-control, cohort, and cross-sectional studies, demonstrating a quantitative relationship between at least one associated factor and HNC-related BID. Experimental studies and quasi-experiments will also be included, although these are less likely to assess factors associated with BID. We excluded conference abstracts, qualitative articles, commentaries, letters to the editor, books, systematic reviews, meta-analyses, and case reports. There will be no restrictions based on the type of setting. Studies published in English or Chinese are considered. There will be no restrictions on the year of publication.

Types of Participants

Studies involving patients with HNC diagnosed regardless of sex, race, or educational background will be included. Studies included individuals with a confirmed HNC diagnosis, as evidenced by medical records, histopathological confirmation, and diagnostic criteria, as specified in the study. All studies must be inclusive of any gender identities. Studies exclusively focusing on one gender, unless providing a justified scientific rationale, will be excluded to ensure a diverse and comprehensive understanding of BID across the population. Studies should include adult patients (aged 18 years and older) with HNC. If age-specific factors related to BID are of interest, age subgroups (eg, young adults, middle-aged, and older adults) should be specified in the protocol.

Conditions

BID, as the variable of interest in our systematic review protocol, refers to the psychological discomfort or distress that a patient with HNC experiences due to changes or perceived changes in their appearance. To be included in our review, studies had to measure BID either as a primary or secondary outcome. BID will be quantified using validated psychometric tools specifically designed to assess body image concerns in patients with cancer, such as the Derriford Appearance Scale (DAS-24), the Inventory to Measure and Assess imaGe disturbance-Head and Neck (IMAGE-HN), the Body Image Scale (BIS), and the McGill Body Image Concerns Scale-Head and Neck Cancer (MBIS-HNC). Studies included in the review will provide clear information on the threshold used to define clinically significant BID, ensuring that only patients who meet or exceed this threshold are considered. Our systematic review will, therefore, encompass articles that quantify BID using these standardized tools, allowing us to synthesize data on how frequently this distress occurs and identify factors associated with increased BID.

Context

We will include studies that evaluate factors associated with HNC-related BID, covering a range of demographic, clinical, and psychosocial variables such as age, sex, type and extent of surgery, level of education, stage of cancer, presence of anxiety or depression, availability and quality of social support, and coping styles. Additionally, we will consider the role of treatment modalities (eg, chemotherapy and radiation therapy), physical side effects (eg, disfigurement and functional impairment), and patient-reported outcomes related to quality of life. Studies that provide a comprehensive analysis of the relationships between these variables and BID—using quantitative, qualitative, or mixed methods approaches—will be included.

Information Sources

PsycINFO, MEDLINE, EBSCOhost CINAHL, Web of Science, Cochrane Library, and Embase will be comprehensively searched from inception to October 2025. The preliminary search process is shown in Figure 1. An initial search using this filter yielded several authors (WX, LX, SW, MZ, and YZ). Additionally, we will contact the authors of the articles identified for inclusion in our systematic review and possible meta-analyses regarding the details of the completed but unpublished research. We will locate ongoing clinical trials by searching prospective clinical trial registries (national and international).

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Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of the screening process.

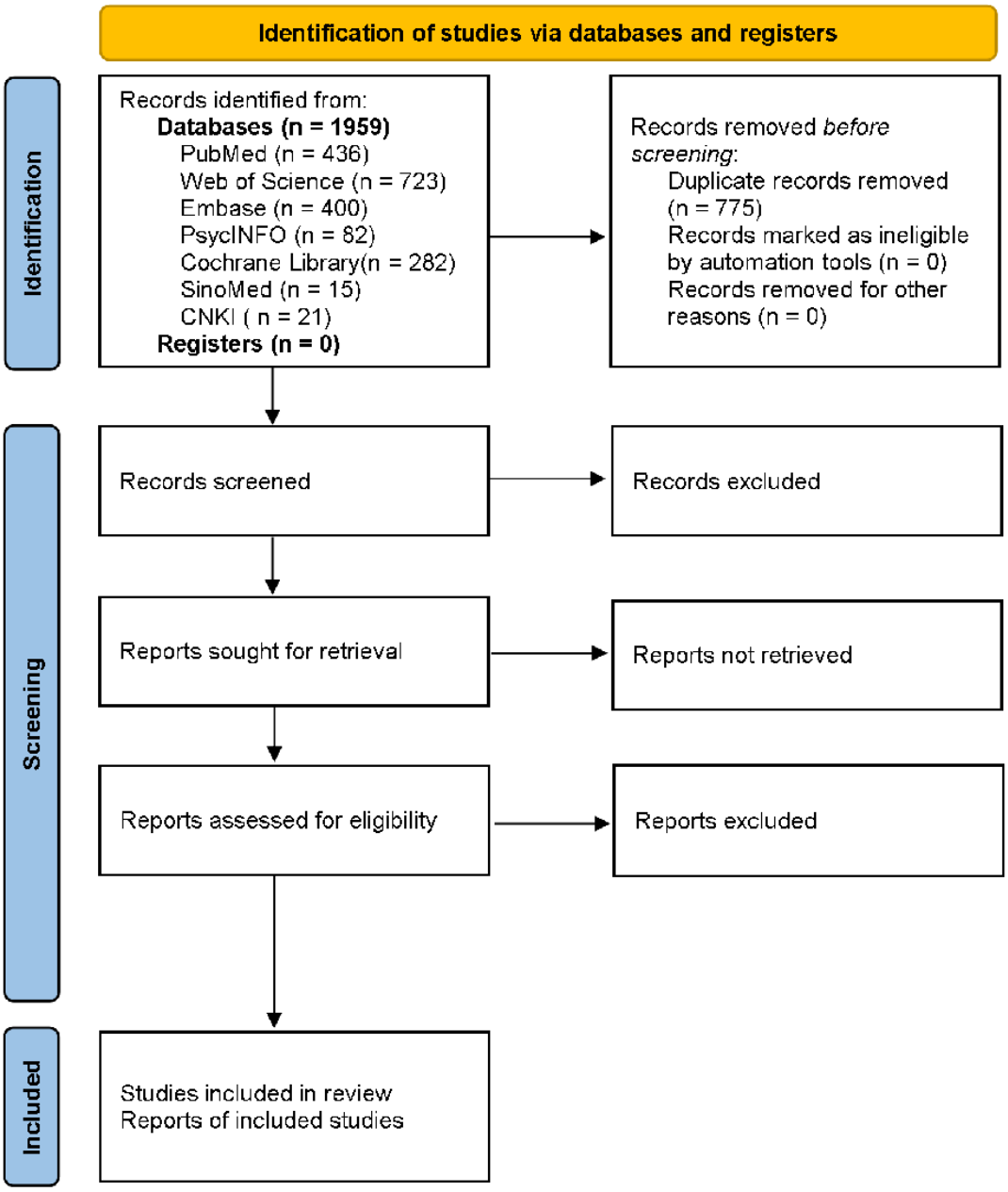

Search Strategy

The population, exposure, comparison, and outcome (PECO) format was used to develop the search strategy. The most important keywords for each PECO component are as follows.

Comparison

The search strategies were developed using a combination of keywords and standardized index terms. The literature search will be limited to articles written in English or Chinese and involving human participants. To ensure comprehensive coverage, we scanned the reference lists of the included studies and relevant reviews identified through the search. Additionally, we will search the authors' files to ensure that all relevant material has been included. Finally, the systematic review team will circulate a bibliography of the included articles. There will be no time restrictions for the search.

Population

Patients with HNC who are older than 18 years; have no serious heart, brain, kidney, or other functional failure diseases; have no consciousness disorders; and have not received psychological treatment will comprise the study population.

Exposure

The factors considered include personal factors (such as sociodemographic and psychological factors), disease-related factors, and sociocultural background factors.

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Outcome

BID and stress related to body image are the outcomes of interest.

A preliminary literature search was conducted by a health sciences librarian specializing in systematic reviews, with input from the study investigators. The draft MEDLINE search strategy can be found in Multimedia Appendix 1. Once the MEDLINE strategy is finalized, it will be adapted to match the syntax and subject headings of the other databases. As relevant studies are identified, reviewers will also search for additional relevant articles that have been cited or those cited by the identified studies. Additionally, the search will be updated toward the end of the review to ensure that the PubMed strategy retrieves a high proportion of eligible studies found through any means but indexed in PubMed.

Assessment of Methodological Quality

The systematic review protocol will specify the criteria used to determine the methodological quality of the papers included in the review. In line with these requirements, the JBI critical appraisal tool will be used preferentially for assessing the quality of studies [23]. These tools are chosen for their comprehensive nature and their ability to evaluate a wide range of study designs and methodologies.

Criteria for Methodological Quality

The criteria for assessing methodological quality will include, but will not be limited to, the following: study design appropriateness, clarity of objectives, use of valid and reliable measures, adequacy of sample size, handling of data and analysis, consideration of confounders, and robustness of the findings. These criteria ensure that only studies with sufficient methodological rigor are included in the review.

Use of JBI Tools

For each type of study design identified in the search process, the corresponding JBI critical appraisal checklist will be used. The JBI Checklist for Analytical Cross-Sectional Studies will be used for observational studies [24].

Critical Appraisal for Prevalence Studies

Given the possibility of prevalence data emerging from various study designs, including RCTs, a specific critical appraisal checklist for prevalence studies has been developed by JBI. This checklist will be used to ensure a consistent and targeted approach to appraising studies reporting prevalence data.

Independent Review Process

Two independent reviewers (WX and SW) will critically appraise each study. The reviewers will use the designated JBI critical appraisal tools to systematically assess and document the methodological quality of the studies. They will work independently to minimize bias and enhance the reliability of the appraisal process.

Consensus and Dispute Resolution

Upon completion of the independent appraisals, the reviewers will convene to discuss their findings and reach a consensus on the final appraisal for each study. This collaborative approach fosters transparency and agreement in the assessment of methodological quality. When 2 reviewers cannot reach a consensus through discussion, a third reviewer will be called to provide an independent evaluation to resolve the disagreement.

By meticulously detailing the criteria and process for methodological quality assessment, this protocol ensures that the systematic review will be based on rigorously appraised evidence. The independent and collaborative approach to critical appraisal enhances the validity of the review findings and supports the integrity of the review process.

Data Extraction

The authors (WX and SW) independently screened the titles and abstracts against the inclusion criteria. Reviewers will submit a detailed report if there is any uncertainty or if a title appears to meet the inclusion criteria. Reviewers will then screen the full-text reports to determine if they comply with the inclusion criteria. If an article meets the inclusion criteria but is not available through our institution's library access, the authors of the article will be contacted via email to obtain the full text. Reviewers will record the reasons for excluding trials. The review authors will not be blinded to the journal titles, study authors, or institutions.

After the final number of studies included in the systematic review is determined, the data will be extracted. The data extraction tool will be developed specifically for this review, and a data collection form will be created using Microsoft Excel 2020. The tool will be tested on 2 - 4 articles and modified as needed before being used. WX and SW will independently extract data from each study. We will extract the following information from each study: study design, sample size, inclusion/exclusion criteria, evaluated risk factors, and outcome measures (ie, BID assessment tool, presence/absence of BID, the overall frequency of BID, raw numbers of actors associated with patients with and those without HNC related-BID, and results from univariate and multivariate analyses). To extract effect measures (both ratio and difference measures), we will follow the recommendations of the JBI. Both unadjusted and adjusted estimates will be extracted. In the analysis of factors associated with BID, confounding factors will be considered, and the list of confounders will be collected for each study. We will contact the authors via email if the necessary data are not included in the published manuscript.

Data Synthesis

To investigate the associations between factors and the burden of BID in patients with HNC, we intend to conduct a meta-analysis. This analysis will commence after evaluating the data availability and extent of heterogeneity across the included studies. If the studies demonstrate sufficient homogeneity, we will compute pooled odds ratios for each factor by using a fixed/random effects meta-analysis model. The choice to use a fixed/random-effects model will be based on the level of heterogeneity both within and across the studies. We will measure statistical heterogeneity and inconsistency by estimating the I^2 index. The analysis will be conducted using RevMan (version 5.3; The Cochrane collaboration) and MetaXL software

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(EpiGear International Pty Ltd), and we will derive meta-analytic estimates for both unadjusted and adjusted data separately.

Ethical Considerations

Ethics approval will not be necessary because the publications included in our study did not involve patient privacy. The main data will be extracted from published literature. This systematic review will be published in a peer-reviewed journal with significant visibility in the field of psychosocial oncology.

To discern potential confounding factors, we will compare both adjusted and unadjusted estimates. A meta-analysis of factors associated with BID may present challenges due to considerable methodological heterogeneity among the studies. As an alternative approach to synthesizing data on factors associated with BID, we will use harvest plots, which are especially advantageous for addressing broader research questions.

We also provide a methodology for synthesizing results when studies report only the direction of an association or when there is inconsistency in the measured effects across studies. Subgroup analyses will be conducted to explore differences between patients with and without BID, to examine study design factors such as retrospective versus prospective observational studies, and to evaluate study quality, specifically the risk of bias ranging from low to high.

Synthesizing Evidence

We will apply the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach to grade the quality of evidence, considering factors such as imprecision, inconsistency, indirectness, and publication bias. The most robust evidence for prognostic factors or those related to the topic may initially be assigned high certainty ratings [25]. Additionally, we will consider other domains, including the magnitude of the effect and the potential impact of residual confounding [26]. For example, a substantial effect estimate (ie, relative effect size over 2.0) may warrant an upgrade in the certainty level. Depending on the concerns related to these domains, evidence certainty will ultimately be classified as high, moderate, low, or very low [25]. To create evidence summaries, we will use GRADEpro software via the GRADEpro GDT website. We will assess the evidence quality (certainty in estimates) for each factor associated with HNC-related BID. In cases where significant heterogeneity across studies prevents us from conducting a meta-analysis, we will adhere to the framework proposed by Murad et al [27] for determining evidence certainty without a single effect estimate.

Results

At the time of writing, the literature search had been completed by the medical librarian, and the screening of titles and abstracts is in progress. The database search will be conducted in October 2025. We anticipate completing the screening process by December 2025 and submitting the manuscript for peer review by the end of March 2026. The research findings will be submitted to journals specializing in head and neck tumors or body image, presented at relevant conferences, and shared with stakeholders, including nongovernmental organizations, educational and health care institutions, assistive technology developers, and policy makers.

Discussion

In conclusion, this systematic review protocol outlined a structured approach to identify and evaluate the factors associated with BID in patients with HNC. By conducting a comprehensive meta-analysis, we aim to synthesize existing data to better understand the extent to which various demographic, clinical, and psychosocial factors contribute to BID in this population. The use of both adjusted and unadjusted meta-analytic estimates will allow for a nuanced examination of potential confounding variables.

The anticipated challenges in comparing factors across studies due to methodological heterogeneity will be addressed by using alternative methods, such as harvest plots for data synthesis. Subgroup analyses will further refine our understanding by comparing different patient groups, study designs, and levels of study quality. Although publication bias remains a concern, our commitment to analyzing only those estimates supported by a sufficient number of studies should mitigate this issue.

The possible strengths and limitations of this study are as follows. The main strength of this systematic review is its novelty. This study will help identify iatrogenic risk factors for HNC-related BID, which may be helpful in developing future interventions. The findings of this study will inform researchers of the future development of clinical prediction rules when identifying patients with HNC at risk for BID. Some studies might need a more well-defined differentiation of BID. The significant heterogeneity across studies may prevent us from performing meta-analyses. The quality of the included studies is expected to be low, resulting in a low level of certainty regarding the associations between certain factors and HNC-related BID. The types of studies included were mostly cross-sectional, and more high-quality longitudinal studies analyzing the factors influencing BID in patients with HNC are needed. Additionally, the review is limited to English- and Chinese-language publications, potentially excluding relevant evidence in other languages, and qualitative studies that could offer deeper insights into patient experiences are omitted.

Acknowledgments

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Data Availability

This protocol has also been registered in PROSPERO (registration number CRD42023424006).

Authors' Contributions

Conceptualization: WX and LX
Writing—original draft: WX and LX
Formal analysis: SW, MZ, and YZ
Writing—review and editing: WX, LX, SW, MZ, RG, YZ, and HW

Conflicts of Interest

None declared.

Multimedia Appendix 1
Draft of the MEDLINE search query.
[DOCX File, 11 KB - resprot_v14i1e69213_app1.docx]

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Abbreviations

BID: body image distress
BIS: Body Image Scale
DAS-24: Derriford Appearance Scale
GRADE: Grading of Recommendations, Assessment, Development, and Evaluations
HNC: head and neck cancer
IMAGE-HN: Inventory to Measure and Assess imaGe disturbance-Head and Neck
JBI: Joanna Briggs Institute
MBIS-HNC: McGill Body Image Concerns Scale-Head and Neck Cancer
PECO: population, exposure, comparison, and outcome
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Rpeorting Items for Systematic Reviews and Meta-Analyses Protocols

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Effectiveness of Transcutaneous Spinal Cord Stimulation for Lower Limb Rehabilitation in Spinal Cord Injury: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Spinal cord injury (SCI) affects millions of people worldwide and often results in impaired lower limb function and reduced mobility. Transcutaneous spinal cord stimulation (tSCS) has emerged as a promising neuromodulation technique for enhancing motor recovery and walking ability in individuals with SCI.

Objective: This systematic review and meta-analysis will determine the effectiveness of tSCS, compared with sham stimulation, no intervention, or other active interventions, for improving lower limb motor function in individuals with SCI. Secondary objectives are to evaluate tSCS effects on walking ability, spasticity, quality of life, and safety outcomes.

Methods: This systematic review will be conducted according to the Cochrane Handbook for Systematic Reviews of Interventions and reported following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 statement. We will search electronic databases (PubMed, Web of Science, Embase, CINAHL, MEDLINE, Cochrane Library, Physiotherapy Evidence Database, and Scopus) from inception to August 2025, along with gray literature, trial registries, and hand-searching of key journals. We will include randomized controlled trials (RCTs), quasi-RCTs, and nonrandomized studies (case series with ≥5 participants) that evaluate the effects of tSCS applied over the spinal region on lower limb rehabilitation outcomes in adults with traumatic or nontraumatic SCI. The primary outcome will be lower limb motor function assessed by validated measures such as the Lower Extremity Motor Score. Secondary outcomes will include walking ability, balance, functional independence, spasticity, quality of life, and adverse events. Two reviewers will independently screen studies, extract data, and assess risk of bias using version 2 of the Cochrane Risk of Bias tool for RCTs and Risk of Bias in Non-randomized Studies of Interventions tool. Data will be synthesized using random-effects meta-analysis if appropriate, with subgroup analyses examining injury level, completeness, stimulation site, and cointervention effects, and sensitivity analyses. Evidence certainty will be evaluated using the Grading of Recommendations Assessment, Development, and Evaluation approach.

Results: This protocol paper presents strategy development and protocol registration, with results expected by October 2025.

Conclusions: This comprehensive systematic review and meta-analysis will address an important evidence gap, providing the first focused evaluation of tSCS effectiveness for lower limb rehabilitation in SCI. Results will inform clinical practice guidelines and guide future research directions.

Trial Registration: PROSPERO CRD420250652270; https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD420250652270

International Registered Report Identifier (IRRID): PRR1-10.2196/80995

(JMIR Res Protoc 2025;14:e80995) doi:10.2196/80995

KEYWORDS

spinal cord injury; transcutaneous spinal cord stimulation; tSCS; lower limb rehabilitation; motor function; walking ability; spasticity; neuromodulation

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Introduction

Background

Spinal cord injury (SCI) is a devastating condition that affects millions of people worldwide. The global incidence of SCI in 2019 was estimated at 0.9 million new cases [1]. SCI often results from traumatic causes such as road traffic accidents, falls, and violence, but can also be due to nontraumatic etiologies like spinal tumors, infections, and vascular disorders [2]. Depending on the level and severity of the lesion, SCI can lead to a range of impairments, including paralysis, sensory loss, spasticity, pain, autonomic dysfunction, and bowel or bladder dysfunction, which significantly impact functional independence and quality of life [3].

Restoring walking ability is a top priority for many individuals with SCI [4]. Despite significant advancements in rehabilitative therapy, recovery of independent walking remains a major issue for most SCI patients. Reduced physical inactivity and marked deconditioning are highly prevalent among persons with SCI [5]. Physical inactivity is an independent risk factor for cardiovascular disease and premature mortality [6]. Thus, it is imperative to explore various means to increase the physical activity in this group of patients. There is a pressing need for novel interventions that can enhance neuroplasticity and improve functional outcomes in this population.

While various neuromodulation approaches exist for SCI rehabilitation, tSCS represents a unique intervention that specifically targets spinal networks through noninvasive transcutaneous delivery. Unlike broader neuromodulation reviews that encompass diverse techniques with different mechanisms and targets, tSCS requires focused evaluation given its distinct mechanism of activating proprioceptive and cutaneous afferent fibers to modulate spinal cord excitability. The specificity of tSCS for lower limb rehabilitation warrants dedicated examination, as the intervention's effectiveness may vary significantly based on stimulation site, parameters, and the specific neural pathways involved in lower extremity motor control.

Transcutaneous spinal cord stimulation (tSCS) has emerged as a promising neuromodulation technique for SCI rehabilitation. tSCS involves delivering electrical currents to the spinal cord via surface electrodes placed over the neck or back vertebrae. The stimulation parameters, such as frequency, intensity, and pulse width, can be adjusted to optimize the motor response. The mechanisms of action of tSCS are not fully understood, but computational simulations of cervical tSCS suggest that groups of dorsal root proprioceptive Aα and cutaneous Aβ fibers are coactivated with tSCS at low stimulating intensities [7]. It remains unclear whether similar mechanisms apply to thoracic tSCS protocols. The postulated mechanism by which tSCS affects functional recovery is through the activation of proprioceptive fibers during stimulation, contributing to spinal cord neuromodulation [8,9].

Several studies have investigated the effects of tSCS on lower limb motor function and walking ability in individuals with SCI. Gerasimenko et al [10] first demonstrated that tSCS could enable voluntary leg movements and standing in individuals with motor-complete paraplegia. Subsequent studies have reported improvements in Lower Extremity Motor Scores (LEMS), walking speed, step length, and spasticity with tSCS training in individuals with both complete and incomplete SCI [11-14]. For example, Samejima et al [15] found that a 2-month multisite tSCS program targeting both cervical and lumbosacral regions, combined with intensive locomotor training, increased 6-Minute Walk Test distance threefold compared with locomotor training alone in 2 participants with chronic motor-incomplete tetraplegia. In addition, both participants demonstrated improvements in balance, bowel function, and sensory recovery, with 1 participant eliminating the need for intermittent catheterization following the intervention.

Despite these promising findings, the evidence on tSCS for SCI rehabilitation remains limited by small sample sizes, heterogeneous protocols, and a lack of long-term follow-up data. It is unclear which subgroups of individuals with SCI may benefit most from tSCS, what the optimal stimulation parameters and training regimens are, and whether the effects are maintained over time. A comprehensive synthesis of the current literature is needed to inform clinical practice guidelines and guide future research directions. Recent methodological reviews have highlighted the importance of standardized approaches to tSCS research [16,17], while emerging evidence continues to expand our understanding of optimal stimulation protocols and patient selection criteria.

To date, there has been no systematic review specifically focused on evaluating the effectiveness of tSCS for lower limb rehabilitation in people with SCI. While several reviews have examined neuromodulation techniques in SCI, they have either been broader in scope or focused on different aspects. García et al [18] analyzed tSCS across 13 studies but covered both upper and lower extremities, without a specific focus on lower limb outcomes. Most recently, García-Alén et al [19] performed a systematic review and meta-analysis specifically examining noninvasive electromagnetic neuromodulation for upper limb motor strength and functionality in cervical SCI, further highlighting the gap in systematic evaluation of tSCS specifically for lower limb rehabilitation. Barss et al [20] examined tSCS effects on lumbar networks, but this work focused on physiological mechanisms rather than providing a comprehensive literature review of rehabilitation outcomes.

Most recently, Hernandez-Navarro et al [21] conducted a systematic review examining both noninvasive brain and spinal cord stimulation for motor and gait recovery in incomplete SCI. Their review was restricted to randomized controlled trials (RCTs) scoring above 5 on the Physiotherapy Evidence Database (PEDro) scale and only included 1 tSCS study [22], indicating a need for more comprehensive evaluation of tSCS evidence. Our systematic review addresses this specific gap by focusing exclusively on tSCS, using broader inclusion criteria for study designs (including nonrandomized studies and case series with ≥5 participants), and analyzing a wider range of clinical outcomes including spasticity and quality of life. This approach provides a more comprehensive assessment of the emerging evidence for tSCS in SCI rehabilitation by capturing studies that were excluded from previous reviews due to

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methodological constraints. In addition, our review will include newer studies published since the search period for Hernandez-Navarro et al [21] ended in March 2024, incorporating the latest evidence until March 2025.

Furthermore, our systematic review methodology uses a more comprehensive search strategy across multiple databases including PubMed, Web of Science, Embase, CINAHL, Cochrane Library, PEDro, and Scopus, compared with the 3 databases used by Hernandez-Navarro et al [21]. Our review extends the scope of outcome measures to include important functional outcomes, such as Spinal Cord Independence Measure and quality of life assessments (EuroQol-5 Dimension [EQ-5D]), providing a more holistic evaluation that addresses meaningful patient-centered outcomes. Our planned subgroup analyses examining injury type, stimulation parameters, and stimulation site will allow for more nuanced conclusions about optimal tSCS protocols for different SCI populations. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach for evidence evaluation will provide clearer clinical guidance, while our inclusion of safety and adverse event reporting will address an important gap in understanding the risk-benefit profile of tSCS interventions across different SCI populations.

Given the limitations of previous reviews and the growing body of research on tSCS for SCI, a comprehensive and up-to-date systematic review with meta-analysis is warranted. This will help to determine the overall efficacy and safety of tSCS as a lower limb rehabilitation strategy for SCI, identify factors that may influence treatment response, and guide the design of future clinical trials.

Objectives

This systematic review and meta-analysis aims to determine the effectiveness of tSCS compared with sham stimulation, no intervention, or other active interventions for improving lower limb motor function, as measured by validated assessments such as the LEMS, in individuals with SCI. Secondary objectives include evaluating tSCS effects on walking ability (speed, distance, and independence), spasticity, quality of life, and safety outcomes. The review will also examine potential treatment effect moderators, including injury characteristics (level, severity, and chronicity), stimulation parameters (frequency, intensity, and site), and co-interventions to guide optimal tSCS implementation protocols.

Methods

Overview

This systematic review will be conducted in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [23] and reported following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 statement [24]. Any amendments to this registered protocol will be documented and reported transparently, including the date, rationale, and description of changes. Major amendments that could affect study conclusions will be highlighted in the final review publication to ensure protocol transparency and adherence monitoring. The PRISMA flow diagram will visually summarize the study selection process, including the number of records identified, included, and excluded, and the reasons for exclusions at each stage.

This systematic review is in the planning and protocol development phase. The search strategy has been developed and the protocol has been registered with PROSPERO, but formal screening of records has not yet begun. We anticipate completing the record screening by June 2025, followed by data extraction by August 2025. Analysis, synthesis, and results are expected to be available by October 2025. We confirm that our systematic review is prospective in nature, with data collection and analysis planned but not yet executed. This protocol describes the methodology that will be used to conduct the review once all preliminary steps are completed.

The Population, Intervention, Comparator, and Outcome (PICO) framework was used to design this systematic review protocol. The PICO framework is a widely used tool for formulating research questions and eligibility criteria in systematic reviews of interventions [25]. It helps to ensure that the review is focused, clinically relevant, and captures all key aspects of the topic.

In this protocol, the PICO elements were defined as (1) population: adults with SCI of any level, severity, or chronicity; (2) intervention: active tSCS; (3) comparator: sham tSCS, no intervention, conventional rehabilitation, or other active interventions; and (4) outcomes: primary—lower limb motor function, and secondary—walking ability, spasticity, quality of life, and adverse events.

Using the PICO framework, we developed a clearly defined review question: “What is the effectiveness of tSCS compared with sham stimulation, no intervention, or other active interventions for improving lower limb motor function, walking ability, spasticity, and quality of life in adults with spinal cord injury?” This question guided the selection of eligibility criteria, search terms, and data extraction variables.

Eligibility Criteria

Study Designs

We will include RCTs, quasi-RCTs, and nonrandomized studies (cohort studies, case-control studies, and case series with ≥5 participants) that evaluate the effects of tSCS on lower limb rehabilitation outcomes in individuals with SCI. To manage the anticipated heterogeneity from diverse study designs, we will implement a hierarchical synthesis approach. RCTs will be analyzed separately from nonrandomized studies, with primary conclusions drawn from RCT evidence where available. Nonrandomized studies will be used to supplement RCT findings and explore treatment effects in populations or contexts not adequately represented in controlled trials. Meta-analysis will only be attempted when studies demonstrate sufficient clinical and methodological homogeneity, with narrative synthesis used when heterogeneity precludes quantitative pooling. Crossover trials will be included if data from the first treatment period can be obtained. Conference abstracts, case reports, qualitative studies, narrative reviews, editorials, and expert opinions will be excluded.

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To address concerns about methodological heterogeneity from including diverse study designs, we have established strict criteria for synthesis. Only studies with sufficient clinical and methodological homogeneity will be included in meta-analyses, with a minimum threshold of I^2 <75% for pooling. When heterogeneity exceeds this threshold, we will conduct narrative synthesis only. Furthermore, we will weight evidence hierarchically, with RCTs forming the primary evidence base and nonrandomized studies serving as supplementary evidence to explore treatment effects in populations or contexts not represented in controlled trials. Case series will be analyzed separately and used primarily to assess safety outcomes and identify potential treatment responders, rather than contributing to efficacy estimates.

Participants

Studies involving adults (≥18 y old) with traumatic or nontraumatic SCI, regardless of level of injury, severity (American Spinal Injury Association Impairment Scale [AIS] grades A-D), or chronicity (acute, subacute, and chronic) of injury will be included. Studies with mixed populations (eg, SCI and stroke) will be included only if SCI-specific data can be extracted. Studies involving children (<18 y old) or individuals with other neurological conditions without SCI will be excluded.

Interventions

The intervention of interest is tSCS applied over the neck or back using surface electrodes, with or without simultaneous physical training, for the purpose of improving lower limb motor function and walking ability. Studies must report the stimulation parameters used, including frequency, intensity, pulse width, and duration of application. tSCS can be delivered alone or in combination with other interventions. Studies using other types of electrical stimulation (eg, functional electrical stimulation and epidural stimulation) without tSCS will be excluded.

Comparators

Eligible comparators include (1) sham tSCS (using identical procedures but with no actual stimulation), (2) no intervention, (3) conventional rehabilitation (eg, physical therapy and overground walking training), and (4) other active interventions (eg, robotic gait training, exoskeletons, and bodyweight-supported treadmill training).

Studies comparing different tSCS parameters or combined interventions will also be included. We will not pool data from different comparator groups (sham stimulation, no intervention, and other active interventions) in our primary analyses. Instead, we will conduct separate meta-analyses for each comparison type and perform subgroup analyses to examine differential effects across comparator categories. This approach will preserve the distinct mechanisms and expected effect sizes associated with different control conditions.

Outcomes

The primary outcome will be lower limb motor function, as measured by a validated assessment tool such as the LEMS [26] and International Standards for Neurological Classification of Spinal Cord Injury (ISNCSCI) [27]. The LEMS represents a subset of the total ISNCSCI motor score, focusing specifically on lower extremity muscle groups. When studies report only total ISNCSCI motor scores, we will contact authors to obtain LEMS-specific data. If multiple measures are reported, LEMS will be prioritized as it is the most widely used outcome in SCI clinical trials. To address the breadth of outcomes, we will establish a clear hierarchy for interpretation and clinical recommendations. The primary outcome (LEMS) will be the main focus for drawing conclusions about tSCS effectiveness. For secondary outcomes, we will prioritize patient-important functional outcomes in the following order: (1) walking independence (Walking Index for Spinal Cord Injury), (2) walking speed and distance, (3) functional independence (Spinal Cord Independence Measure), and (4) quality of life measures. Motor impairment measures will be considered surrogate outcomes, with clinical recommendations based primarily on functional outcomes when both are available. This prioritization will be applied consistently in the results synthesis and clinical interpretation.

Secondary outcomes will include (1) walking speed (eg, 10-Meter Walk Test), (2) walking distance (eg, 6-min Walk Test), (3) walking independence (eg, Walking Index for Spinal Cord Injury), (4) spasticity (eg, Modified Ashworth Scale), (5) balance (eg, Berg Balance Scale), (6) functional independence (eg, Spinal Cord Independence Measure), (7) quality of life (eg, EQ-5D and Spinal Cord Injury Quality of Life [SCI-QoL]; we will consider including the SCI-QoL measure in addition to or instead of the EQ-5D, given concerns about the relevance and fairness of EQ-5D questions for the SCI population, and (8) adverse events (eg, pain, skin irritation, and autonomic dysreflexia).

Outcome measures at all time points (eg, preintervention, postintervention, and follow-up) will be extracted. For studies with multiple follow-up assessments, we will prioritize consistency in timepoints across studies for meta-analysis. The selection of follow-up time points will be determined after data collection to optimize homogeneity across included studies.

To clearly define the scope of this systematic review, the inclusion and exclusion criteria are summarized in Table 1 below:

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Table . Inclusion and exclusion criteria.

Variables	Inclusion criteria	Exclusion criteria
Population	Adults (≥18 y old) with traumatic or nontraumatic spinal cord injury of any level, severity, or chronicity	Adults aged <18 y old; neurological conditions other than spinal cord injury
Interventions	tSCS[a] alone or combined with other interventions	Other types of electrical stimulation without tSCS (eg, functional electrical stimulation and epidural stimulation)
Comparators	Sham tSCS, no intervention, conventional rehabilitation, or other active interventions	None
Outcomes	Primary: lower limb motor function; and secondary: walking ability, spasticity, quality of life, and adverse events	Nonmotor outcomes (eg, cardiorespiratory function, pain, and bowel or bladder function)
Study designs	RCTs[b], quasi-RCTs, cohort studies, case-control studies, case series (≥5 participants)	Case reports, cross-sectional studies, qualitative studies, reviews, editorials, commentaries, animal studies

[a]tSCS: transcutaneous spinal cord stimulation.

[b]RCT: randomized controlled trial.

Information Sources and Search Strategy

We will conduct a comprehensive literature search of the following electronic databases from their inception to August 2025: PubMed (MEDLINE), Web of Science, Embase, CINAHL, The Cochrane Library (CENTRAL), PEDro, and Scopus. The search strategy will be developed in consultation with experts and include a combination of keywords and controlled vocabulary terms (eg, Medical Subject Headings) related to SCI, tSCS, and lower limb rehabilitation outcomes. No language or publication date filters will be applied. The search will be adapted for each database and peer-reviewed using the Peer Review of Electronic Search Strategies checklist [28].

A draft search strategy for PubMed is provided below:

((spinal cord injur*[Title/Abstract] OR SCI[Title/Abstract] OR paraplegi*[Title/Abstract] OR quadriplegi*[Title/Abstract] OR tetraplegi*[Title/Abstract]) AND (transcutaneous spinal cord stimulat*[Title/Abstract] OR trans-cutaneous spinal cord stimulat*[Title/Abstract] OR tSCS[Title/Abstract] OR “transcutaneous electrical spinal stimulation”[Title/Abstract] OR “non-invasive spinal cord stimulation”[Title/Abstract] OR “noninvasive spinal cord stimulation”[Title/Abstract]) AND (lower limb[Title/Abstract] OR lower extremit*[Title/Abstract] OR leg[Title/Abstract] OR gait[Title/Abstract] OR locomotion[Title/Abstract] OR walk*[Title/Abstract] OR motor function*[Title/Abstract]))

In addition to electronic databases, we will search the following sources to identify potentially relevant studies:

- ClinicalTrials website
- World Health Organization International Clinical Trials Registry Platform
- OpenGrey (for gray literature)
- Reference lists of included studies and pertinent reviews
- Hand-search of key journals (eg, Spinal Cord, Journal of Neurotrauma, and Journal of Neuroengineering and Rehabilitation)

We will also contact experts in the field, including authors of included studies, to inquire about ongoing or unpublished trials.

Study Selection

The results of the literature search will be uploaded to Covidence, a web-based systematic review management platform. After removal of duplicates, 2 reviewers will independently screen titles and abstracts against the eligibility criteria. Studies that clearly do not meet the inclusion criteria will be excluded. The full-text articles of the remaining studies will be retrieved and assessed for eligibility by the 2 reviewers independently. Any disagreements will be resolved through discussion or consultation with a third reviewer. Reasons for exclusion at the full-text stage will be recorded and reported in a PRISMA flow diagram. The study selection process will be pilot-tested on a sample of articles to ensure consistency between reviewers.

Data Extraction

Data from included studies will be extracted independently by 2 reviewers using a standardized form in Covidence. The form will be piloted on a subset of studies and refined as necessary. Disagreements will be resolved through consensus or adjudication by a third reviewer. Two reviewers will independently extract data using a comprehensive framework that captures multiple domains of information. This systematic approach will ensure thorough data collection across all included studies while maintaining consistency and reliability in the extraction process.

A detailed data extraction framework has been developed to capture key information from each study, encompassing study characteristics, methodological approaches, participant demographics, intervention specifics, comparison groups, outcome measurements, and study quality indicators. This structured approach ensures standardized data collection that will facilitate subsequent analysis and synthesis of the evidence.

The complete data extraction framework is detailed in Multimedia Appendix 1, which provides a comprehensive

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outline of all data fields to be extracted. These include study details (authorship, publication information, and funding), methodological aspects (study design, setting, and recruitment), participant characteristics (demographic and clinical data), intervention and comparator specifications (parameters, protocols, and schedules), outcome measures (primary and secondary end points, measurement tools, and time points), and study limitations (potential biases, data gaps, and methodological concerns). This detailed extraction protocol will enable robust analysis and synthesis of the evidence while maintaining consistency between reviewers.

If data are missing or unclear, we will attempt to contact the study authors for clarification. Studies will be excluded if key data cannot be obtained after 3 attempts. We will also contact authors of included studies to request access to individual participant data when published aggregate data are insufficient for planned subgroup analyses. This approach will enable more detailed examination of treatment effects across different injury characteristics and stimulation parameters.

Risk of Bias Assessment

Risk of bias in individual studies will be assessed independently by 2 reviewers using version 2 of the Cochrane Risk of Bias tool (RoB 2) [29] for RCTs and the Risk of Bias in Non-randomized Studies of Interventions (ROBINS-I) tool [30] for nonrandomized studies. RoB 2 evaluates 5 domains of bias: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain is judged as low risk, some concerns, or high risk. ROBINS-I assesses 7 domains: confounding, selection of participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of reported results. The overall risk of bias is categorized as low, moderate, serious, or critical.

Disagreements between reviewers will be resolved through discussion or referral to a third reviewer. The risk of bias judgments for each study will be presented in a “traffic light” plot and summarized in a risk of bias table. The results will be used to guide the interpretation of the review findings and assess the certainty of the evidence.

Data Synthesis

If 2 or more studies report the same outcome, we will conduct a meta-analysis using a random-effects model in RevMan 5.4 software (Cochrane). Continuous outcomes will be pooled using mean differences or standardized mean differences with 95% CIs, depending on whether the same or different measurement scales are used across studies. Dichotomous outcomes will be combined using risk ratios with 95% CI. If data are missing or cannot be converted to the required format, we will use alternative methods such as the generic inverse variance or contact study authors for additional information.

Statistical heterogeneity will be assessed using the I^2 statistic and chi-square test. I^2 values of 25%, 50%, and 75% represent low, moderate, and high heterogeneity, respectively [31]. If substantial heterogeneity is present (I^2>50% or P<.10), we will explore possible sources through subgroup and sensitivity analyses. If a meta-analysis is not appropriate due to clinical or methodological heterogeneity, we will provide a narrative synthesis of the findings, including tables and figures to aid in data presentation.

Subgroup and Sensitivity Analyses

If sufficient data are available, we will perform subgroup analyses to investigate potential effect modifiers and sources of heterogeneity. The following subgroups will be considered:

- Level of injury: cervical versus thoracic versus lumbosacral
- Severity of injury: complete (AIS A) versus incomplete (AIS B-D)
- Type of injury: traumatic versus atraumatic
- Time since injury: acute (<1 mo) versus subacute (1 - 6 mo) versus chronic (>6 mo)
- Site of stimulation: cervical versus thoracic versus lumbosacral
- tSCS frequency: low (<50 Hz) versus high (≥50 Hz) tSCS waveform: monophasic versus biphasic versus both tSCS intensity: different intensity parameters as defined in individual studies
- Cointerventions: tSCS alone versus tSCS+physical or functional training
- Carrier frequency: studies using kilohertz (kHz) carrier frequencies versus conventional frequencies, given ongoing debate in the field regarding optimal stimulation parameters

We will use the test for subgroup differences in RevMan to determine whether the effect of tSCS differs significantly between subgroups.

Given the anticipated limited number of studies, we will prioritize subgroup analyses based on clinical importance and statistical feasibility. We will only conduct subgroup analyses when there are at least 3 studies per subgroup and a minimum of 10 total studies for the outcome. The primary subgroup analyses will focus on injury completeness (AIS A vs B-D) and cointerventions (tSCS alone vs combined), as these are most likely to be clinically meaningful and adequately powered. Secondary subgroup analyses will only be performed if sufficient studies are available, and results will be interpreted cautiously with clear acknowledgment of limited power.

Sensitivity analyses will be conducted to assess the robustness of the meta-analysis results. We will repeat the analysis excluding studies at high risk of bias, studies with missing data, and outliers (studies with effect estimates that are substantially different from the pooled estimate). If the results remain largely unchanged, we will consider the findings to be stable. If the results change substantially, we will explore potential reasons and interpret the results with caution.

Meta-Biases

To assess publication bias, we will create funnel plots for each outcome if there are at least 10 studies in the meta-analysis. Asymmetry in the funnel plot may indicate the presence of publication bias or small-study effects. We will also use the test by Egger et al [32] to quantitatively assess funnel plot asymmetry. If evidence of publication bias is found, we will

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use the trim-and-fill method [33] to estimate the impact on the pooled effect estimate.

Confidence in Cumulative Evidence

The strength of the body of evidence for each outcome will be assessed using the GRADE approach [34]. In interpreting results, patient-important functional outcomes (walking independence and quality of life measures) will be prioritized over surrogate motor assessments when drawing clinical conclusions. Evidence from RCTs will be weighted more heavily than nonrandomized studies, with separate synthesis and interpretation strategies used for different evidence levels to prevent dilution of high-quality findings. Two reviewers will independently evaluate the evidence for limitations in study design, inconsistency, indirectness, imprecision, and publication bias. The quality of evidence will be rated as high, moderate, low, or very low for each outcome. Disagreements will be resolved through discussion or input from a third reviewer. The GRADE assessments will be presented in a summary of findings table.

Results

The study selection process will be documented using a PRISMA flow diagram, which will detail the number of records identified, screened, excluded, and included at each stage of the review process (Figure 1). This systematic review protocol was funded and registered with PROSPERO in February 2025. The comprehensive search strategy has been finalized and peer-reviewed. Systematic database searching is scheduled to begin in March 2025, followed by title and abstract screening through May 2025. Full-text review and data extraction are projected for June-August 2025, with meta-analysis and manuscript preparation planned for September-October 2025. Results publication is expected in the first quarter of 2026. No recruitment is applicable as this is a systematic review of published literature.

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

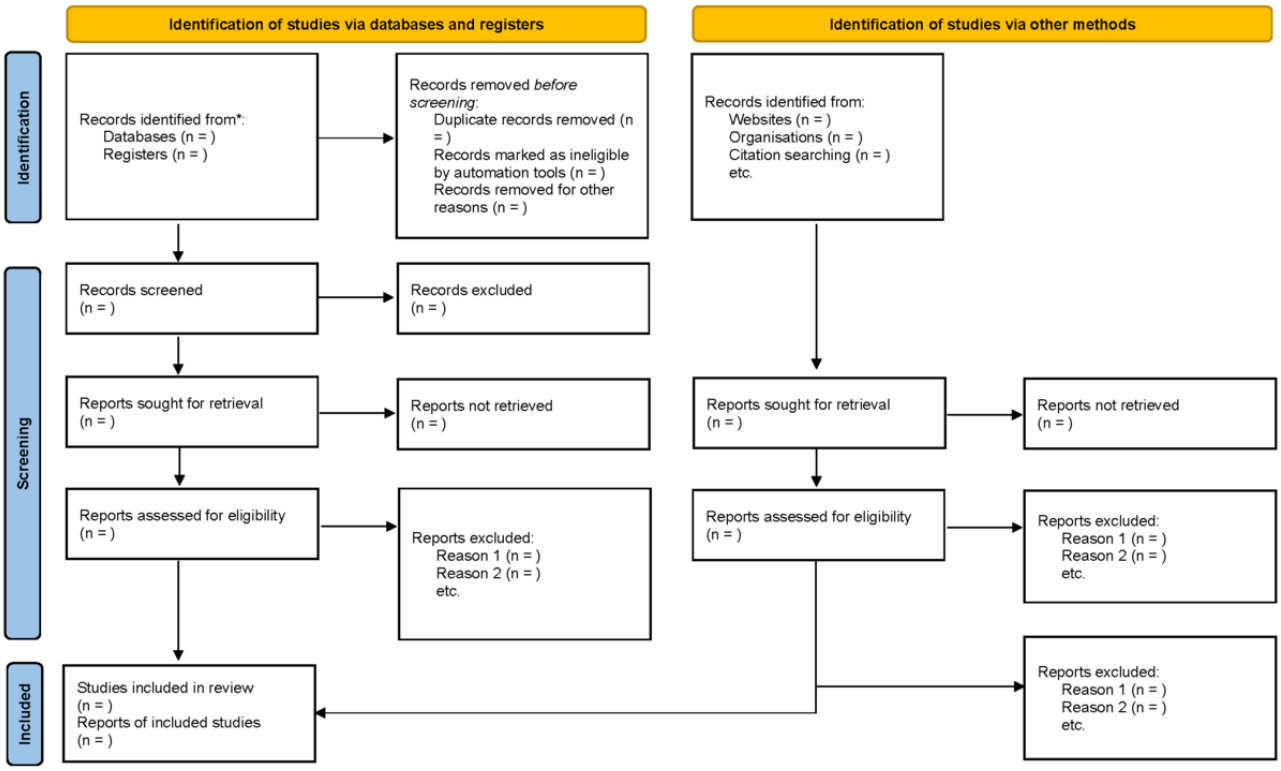

Discussion

Anticipated Principal Findings

This systematic review is expected to reveal heterogeneous effects of tSCS across different SCI populations and stimulation protocols. Based on existing literature suggesting variable responses to neuromodulation interventions, we anticipate finding that individuals with incomplete injuries (AIS B-D) will demonstrate significantly greater improvements in lower limb motor function compared with those with complete injuries (AIS A). We expect effect sizes to be moderate for incomplete injuries (standardized mean difference 0.5 - 0.8) and minimal for complete injuries. In addition, we anticipate that combined tSCS and physical training protocols will show superior outcomes compared with tSCS alone, with combined interventions potentially doubling the treatment effect size, supporting the concept of activity-dependent neuroplasticity.

Comparison With Previous Work

This review will provide the first comprehensive meta-analytic synthesis specifically focused on tSCS for lower limb rehabilitation in SCI, addressing a critical gap identified in previous broader reviews. Unlike the review by Comino-Suárez et al [35], which covered both upper and lower extremities without a specific focus, and Hernandez-Navarro et al [21] which had a restrictive inclusion of only high-quality RCTs, our approach balances methodological rigor with the practical

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reality of the emerging tSCS evidence base. Our findings will either support or challenge preliminary conclusions from individual studies and smaller reviews, potentially revealing whether early promising results from case series translate to meaningful effects in controlled trials.

Methodological Strengths and Limitations

This protocol incorporates several methodological strengths including prospective PROSPERO registration, comprehensive search across 8 databases, and rigorous quality assessment using validated tools (RoB 2 and ROBINS-I). The hierarchical synthesis approach acknowledges the current research landscape while maintaining scientific rigor. However, important limitations must be acknowledged. The inclusion of diverse study designs, while comprehensive, may introduce substantial heterogeneity that could limit meta-analysis feasibility. The emerging nature of tSCS research suggests many included studies may have small sample sizes and limited follow-up, potentially affecting evidence quality and our ability to detect clinically meaningful effects. The broad range of outcome measures, while providing comprehensive coverage, may dilute focus and complicate identification of the most clinically relevant treatment effects.

Clinical Implications and Future Directions

The results will directly inform clinical decision-making by identifying optimal tSCS protocols, appropriate patient populations, and realistic expectations for functional improvement. If our hypotheses are confirmed, clinical guidelines should prioritize tSCS for individuals with incomplete SCI and emphasize combined stimulation-training protocols. The review will also identify critical research gaps, potentially revealing needs for standardized outcome measures, longer follow-up studies, and adequately powered trials in specific populations. Future research should focus on dose-response relationships, maintenance protocols, and cost-effectiveness analyses to support health care implementation decisions.

Dissemination Plan

Results will be disseminated through multiple channels to maximize clinical impact. Primary dissemination will include publication in a high-impact rehabilitation or neurology journal, presentation at major SCI conferences (International Spinal Cord Society and American Congress of Rehabilitation Medicine), and development of clinical practice recommendations. We will create accessible summaries for patient organizations and rehabilitation professionals and work with clinical guideline developers to incorporate evidence-based recommendations. Social media and professional networks will be leveraged to reach practicing clinicians globally, ensuring research findings translate to improved patient care.

Conclusions

This systematic review protocol establishes a methodologically rigorous framework for evaluating tSCS effectiveness in SCI rehabilitation while acknowledging the challenges inherent in synthesizing evidence from an emerging intervention field. The hierarchical synthesis approach and outcome prioritization strategy will ensure that clinical recommendations are based on the highest quality evidence available while capturing the full scope of current research. Anticipated findings of heterogeneous treatment effects across injury types and stimulation protocols will provide crucial guidance for clinical implementation and future research priorities. By October 2025, this review will deliver evidence-based recommendations for tSCS use in SCI rehabilitation, informing both clinical practice guidelines and research funding priorities as this promising neuromodulation technique continues to evolve.

Acknowledgments

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No generative artificial intelligence tools were used in the writing or editing of this manuscript. All content was authored directly by the named contributors.

Authors' Contributions

Conceptualization: RS, WWKS, GC
Methodology: RS, WWKS, GC
Project Administration: RS
Supervision: RS, GC
Writing – Original Draft: RS
Writing – Review & Editing: WWKS, GC

Conflicts of Interest

None declared.

Multimedia Appendix 1
Data extraction form.
[DOCX File, 22 KB - resprot_v14i1e80995_app1.docx]

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Abbreviations

AIS: Association Impairment Scale
EQ-5D: EuroQol-5 Dimension
GRADE: Grading of Recommendations Assessment, Development and Evaluation
ISNCSCI: International Standards for Neurological Classification of Spinal Cord Injury
LEMS: Lower Extremity Motor Score
PEDro: Physiotherapy Evidence Database
PICO: Population, Intervention, Comparator, and Outcome
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT: randomized controlled trial
RoB 2: version 2 of the Cochrane Risk of Bias
ROBINS-I: Risk of Bias in Non-randomized Studies of Interventions
SCI: spinal cord injury
SCI-QoL: Spinal Cord Injury Quality of Life
tSCS: transcutaneous spinal cord stimulation

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Exclusive Effects of Moxibustion on Gut Microbiota: Protocol for a Focused Systematic Review and Meta-Analysis

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Abstract

Background: The gut microbiota (GM) plays a critical role in systemic health, influencing immune, metabolic, and neurological functions. There is emerging evidence suggesting that moxibustion, a traditional thermal therapy, may modulate the GM to restore microbial homeostasis, yet its exclusive effects remain undifferentiated from those of combined therapies such as acupuncture. Previous meta-analyses lack mechanistic specificity, necessitating a focused evaluation of moxibustion's impact on microbial ecology.

Objective: This systematic review and meta-analysis aims to quantify moxibustion-induced changes in GM diversity, taxonomic composition, and functional metabolites (eg, short-chain fatty acids).

Methods: We will systematically search the PubMed, Web of Science, Cochrane Library, China National Knowledge Infrastructure, Wanfang, and VIP databases from inception to December 31, 2024, using keywords such as "moxibustion," "gut microbiota," and "intestinal flora." Eligible preclinical (animal) and clinical (human) studies evaluating stand-alone moxibustion interventions on the GM will be included. Primary outcomes include microbial α diversity indexes (Shannon and Simpson) and relative abundance of key taxa (eg, *Firmicutes* and *Bacteroidetes*). Risk of bias will be assessed using the Systematic Review Center for Laboratory Animal Experimentation risk-of-bias tool for animal studies and the modified Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies criteria for human trials. Pooled effect estimates for continuous outcomes (eg, diversity indexes and taxa ratios) will be calculated using the ratio of means with 95% CIs. Statistical analyses will be conducted in RevMan (version 5.4) and R (*metafor* package), with data archived on Figshare for reproducibility.

Results: As of March 2025, the literature search and screening have been completed, and 31 studies meeting the inclusion criteria have been identified. The comprehensive analysis is scheduled to be completed by October 2025, with results anticipated to be published in late 2025. On the basis of previous work, an anticipated result is that moxibustion may reduce pathogenic genera such as *Ruminococcus* while enhancing beneficial genera, effects that are expected to be associated with improved intestinal barrier integrity and anti-inflammatory responses.

Conclusions: This protocol provides a rigorous framework to evaluate moxibustion's unique role in GM modulation, bridging traditional medicine with microbiome science. The results will inform optimized, nonpharmacological strategies for managing microbiome-associated chronic diseases and guide future research priorities.

Trial Registration: PROSPERO CRD42025639714; https://www.crd.york.ac.uk/PROSPERO/view/CRD42025639714

International Registered Report Identifier (IRRID): PRR1-10.2196/73317

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KEYWORDS

moxibustion; gut microbiota; systematic review; meta-analysis; traditional medicine; microbiome

Introduction

The gut microbiota (GM) constitutes a diverse and dynamic microbial ecosystem in the gastrointestinal tract, comprising bacteria, archaea, fungi, viruses, and protozoa [1,2]. It is closely linked to host physiology, influencing immune modulation, metabolic homeostasis, and disease progression [1,3,4]. Recent advances in high-throughput sequencing and metagenomics have enabled precise mapping of microbial composition and function [5], confirming that the GM not only participates in nutrient metabolism and pathogen defense [6,7] but also sustains intestinal barrier integrity by regulating epithelial renewal and differentiation [8,9]. Particularly noteworthy is the gut-brain axis, a bidirectional neuroendocrine-immune network that illustrates how microbial communities shape neurological conditions and systemic health outcomes through cross-organ

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communication [10]. These multilayered interactions demonstrate the GM's regulatory role beyond the gut, whereas microbial metabolites such as short-chain fatty acids (SCFAs) further contribute to host adaptation by maintaining barrier function, modulating immune pathways, and influencing gene expression [1,3].

Emerging evidence indicates that microbial dysbiosis, characterized by reduced commensal abundance, proliferation of pathogenic taxa, and loss of ecological stability, exhibits significant associations with diverse public health challenges [1]. These encompass digestive disorders such as inflammatory bowel disease (IBD) [11-14] and functional bowel disorders [15,16]; systemic autoimmune conditions, including rheumatoid arthritis [17,18]; metabolic disturbances such as obesity [19] and glucose intolerance [20]; neurodegenerative pathologies such as Alzheimer disease [21] and Parkinson disease [22,23]; circadian rhythm disruption [24]; carcinogenic processes [25,26]; and neuropsychiatric manifestations, including mood disorders [10,27]. Mechanistic studies suggest that dysbiosis contributes to systemic pathology via endotoxemia, barrier dysfunction, and chronic inflammation. For instance, increased lipopolysaccharide exposure, impaired tight junctions, and nuclear factor kappa-light-chain-enhancer of activated B cells activation potentiate inflammation [28,29], whereas translocation of microbial products can induce apoptosis, oxidative stress, and systemic immune responses [30,31]. Recognition of microbial patterns by innate immune receptors further activates cytokine cascades, some of which cross the blood-brain barrier, potentially explaining microbe-driven neuropathology [10]. These mechanisms highlight the microbiome as both regulator and driver of systemic disease and support microbiota modulation as a promising preventive and therapeutic strategy [1,19,25].

Complementary and alternative therapies based on traditional Chinese medicine have increasingly been investigated for their capacity to reshape the GM [32,33]. Moxibustion, a thermal therapy using burning Artemisia argyi at acupoints along meridians, has shown potential to restore microbial balance and reduce inflammation. Compared with acupuncture, it requires minimal operator training, can be implemented by nurses at the bedside, and is well accepted by patients due to its noninvasive nature, making it cost-effective and feasible in resource-limited settings.

Preclinical and clinical evidence indicates that moxibustion can modulate microbial composition and diversity across multiple conditions. In a polycystic ovary syndrome rat model, moxibustion increased *Lactobacillus* abundance; reduced harmful taxa; and elevated SCFAs such as acetate, propionate, and butyrate, thereby improving the intestinal microenvironment [34]. In osteoarthritis models, treatment shifted microbiota profiles closer to those of healthy controls, significantly reducing *Ruminococcus* and *Proteobacteria* [35]. In ulcerative colitis, moxibustion alleviated dysbiosis and attenuated inflammation by downregulating NLRP3 inflammasome signaling [36,37]. Similarly, in colorectal cancer liver metastasis models, moxibustion reshaped disrupted microbiota and reduced metastatic progression [38]. Aging models further suggest that moxibustion enhances probiotic abundance and SCFA levels while suppressing proinflammatory mediators such as tumor necrosis factor (TNF) and interleukin-6 (IL-6) [39]. Collectively, these findings indicate that moxibustion may help restore microbial balance, improve barrier function, and reduce systemic inflammation.

Despite these promising observations, most reviews and meta-analyses have grouped acupuncture and moxibustion as a single intervention, limiting the ability to identify moxibustion's unique contribution. A meta-analysis in 2024 [40] reported significant microbial shifts with combined "acupuncture-moxibustion," including changes in *Firmicutes*, *Bacteroidetes*, and *Lactobacillus*, but did not distinguish each intervention's distinct mechanisms. More recent studies have underscored that acupuncture and moxibustion differ substantially: acupuncture relies on mechanical needling and neural regulation, whereas moxibustion exerts effects capable of driving microbial remodeling via heat-dependent signaling pathways [41]. Importantly, acupuncture is frequently declined by patients due to needle-associated pain or anxiety and requires specialized medical training beyond the scope of nursing practice, whereas moxibustion has been formalized as a standardized traditional Chinese medicine nursing procedure [42]. Therefore, clarifying the exclusive effects of moxibustion on the GM is crucial for accurate mechanistic interpretation and for generating evidence-based recommendations in nursing and integrative medicine. This systematic review will synthesize clinical and preclinical evidence to evaluate moxibustion's effects on microbial diversity, taxonomic composition, and functional metabolites and explore links between thermal dose parameters and microbiota-dependent outcomes.

By establishing standardized efficacy evaluation metrics and mechanistic frameworks, this study will advance the epistemological foundations of traditional medicine while generating tiered evidentiary support for policy implementation. The derived data will elucidate optimized protocols for microbiota-targeted therapies, facilitating their integration into multinational health care systems addressing microbiome-associated chronic diseases.

Methods

Study Registration

This protocol follows the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015 checklist [43]. Before commencement, the full methodological details were cataloged in the PROSPERO registry of planned systematic reviews (CRD42025639714).

Ethical Considerations

The use of secondary data sources in this analytical study exempted it from institutional review board approval requirements. The finalized findings will be communicated to the scientific community through established academic channels, including journal manuscript submissions and international conference proceedings.

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Inclusion Criteria

Study Designs

This review will include clinical and preclinical studies assessing the effects of moxibustion on the GM. Observational studies, reviews, and case reports will be excluded. Only peer-reviewed articles will be considered, with a preference for studies demonstrating a low or moderate risk of bias to ensure the reliability and validity of the findings.

Study Types

Eligible studies must involve human participants or validated animal models evaluating GM outcomes, with a control group receiving no treatment, a placebo, or standard therapy.

In human studies, sham moxibustion may be used as a form of placebo control, defined as a procedure mimicking treatment without producing therapeutic effects (eg, nonacupoint application at ≥1.5 cm from recognized acupoints such as ST25, nonignited moxa sticks, or insulated devices). Standardized protocols are required, including consistent reporting of moxa type and stimulation duration, frequency, and distance. Eligible participants must have clinically confirmed GM-related disorders (eg, irritable bowel syndrome [IBS] via the Rome IV criteria; IBD through endoscopy; obesity via BMI≥30; or depression diagnosed via the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition*, with Hamilton Depression Rating Scale scores of ≥17). Studies with patients with major comorbidities or recent antibiotic use will be excluded.

For animal studies, eligible experiments must use validated disease models (eg, dextran sulfate sodium [DSS]–induced colitis, high-fat diet–induced obesity, or chronic unpredictable mild stress–induced depression). Acceptable controls include no treatment, standard care, or sham procedures using nonignited moxa or equivalent thermal-neutral conditions under standardized dietary and housing conditions.

Interventions

This review will focus exclusively on moxibustion therapy, including direct, indirect, mild, or thunder-fire moxibustion, administered either as a stand-alone intervention or in combination with adjunctive treatments. Where combination therapies are applied (eg, moxibustion plus mesalamine for IBD), the same adjunctive regimen must be provided to both the intervention and control groups. To ensure comparability, details such as drug type, dosage, treatment duration, and adherence should be reported; studies lacking such information will be flagged and considered in sensitivity analyses. Studies involving probiotics or unmatched cointerventions will be excluded.

Exclusion Criteria

Studies will be excluded if they meet any of the following criteria:

1. Nonvalidated in vitro or ex vivo studies: in vitro (eg, cell culture) or ex vivo experiments lacking in vivo validation (animal models or human trials) to confirm GM outcomes
2. Nonprimary research: reviews, meta-analyses, case reports, conference abstracts, editorials, or expert opinions (due to inability to extract original data)
3. Noninterventional designs: case studies, surveys, or purely computational (in silico) analyses without experimental validation
4. Irrelevant outcomes: studies lacking quantitative GM metrics (eg, 16S ribosomal RNA [rRNA] sequencing, metagenomic analysis, α or β diversity, or taxa abundance changes)
5. Data deficiencies: duplicate publications (the most comprehensive dataset will be retained; preprints will be excluded if peer-reviewed versions exist) or insufficient data for meta-analysis (eg, missing mean or SD, sample size, or statistical comparability between groups)

Primary Outcome

The primary outcomes will be changes in GM diversity (Shannon index and Simpson index) and relative abundance of major bacterial phyla (*Firmicutes* and *Bacteroidetes*) and beneficial genera (*Lactobacillus* and *Bifidobacterium*).

Secondary Outcomes

The secondary outcomes will be levels of SCFAs, inflammatory markers (eg, IL-6 and TNF), and clinical symptom improvement scores.

Search Strategy

A comprehensive literature search will be conducted across the PubMed, Web of Science, Cochrane Library, China National Knowledge Infrastructure, Wanfang, and VIP databases from inception to December 31, 2024. The search will use a combination of MeSH (Medical Subject Heading) terms and free-text keywords pertinent to moxibustion and the GM, including terms such as “moxibustion,” “moxa therapy,” “gut microbiota,” and “intestinal flora.” The strategy will follow PRISMA-S (PRISMA literature search extension) guidelines. In addition, the reference lists of relevant studies and systematic reviews will be manually screened to identify any further eligible studies. No language restrictions will be applied during the initial search. Studies published in Chinese will be included if they meet the eligibility criteria, with independent translation and data extraction performed by 2 bilingual reviewers. Discrepancies will be resolved through consensus or adjudication by a third reviewer. Non–English-language studies will be screened at the title or abstract level and, if potentially eligible, translated using professional services or validated translation software to ensure accurate data extraction. A detailed description of the search strategy is provided in Multimedia Appendix 1.

Study Selection

A blinded evaluation system will be implemented where 2 researchers will independently analyze bibliographic records through the NoteExpress digital workflow management software. Initial screening of metadata will progress to full-text appraisal, with interrater inconsistencies addressed through consensus-building dialogues or adjudication. The study selection process will be visually mapped using established PRISMA diagrammatic conventions.

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Data Extraction

Two independent reviewers will extract data using a standardized, pilot-tested form (Multimedia Appendix 2). For human studies, details will include participant demographics (age and gender), diagnostic criteria (eg, Rome IV for IBS), and clinical settings; for animal studies, species and strain, disease induction protocols (eg, 5% DSS for colitis), and environmental controls (diet and housing) will be recorded. Moxibustion parameters (type [direct, indirect, or mild], acupoints using World Health Organization nomenclature [eg, ST25 or "Tianshu"], and session duration and frequency) and microbiome sequencing details (platform: Illumina NovaSeq; 16S rRNA region: V3-V4; bioinformatics pipeline: QIIME 2 with SILVA version 138) will be systematically extracted. To minimize heterogeneity, sequencing parameters (platform, primer region, reference database, and pipeline version) will be recorded in detail, and subgroup analyses will be conducted based on these factors. GM outcomes include α diversity indexes (Shannon, Simpson, and Chao1) and β diversity metrics (Bray-Curtis permutational multivariate ANOVA) alongside taxonomic abundances (phylum and genus level). Where raw or normalized abundance data are reported, potential batch effects will be noted; if feasible, batch correction strategies (eg, ComBat and remove unwanted variation) will be documented during extraction. Missing data will be retrieved via WebPlotDigitizer (version 4.6) or author correspondence (2 email attempts, 14-day interval). Multiple treatment arms will be analyzed separately. Data will be standardized (relative abundance conversion and log transformation) and archived in formats compliant with the findability, accessibility, interoperability, and reusability principles (CSV and Microsoft Excel) on Figshare (Digital Science). Interreviewer consistency will be validated using the Cohen κ (threshold of ≥0.8), with discrepancies resolved by a third reviewer.

Assessment of Risk of Bias

The risk of bias will be evaluated using a modified version of the Systematic Review Center for Laboratory Animal Experimentation risk-of-bias tool [44] and the Collaborative Approach to Meta-Analysis and Review of Animal Data from Experimental Studies checklist [40,45]. The assessment will cover the following domains: (1) adequacy of random sequence generation, (2) baseline comparability between groups or adjustment for confounding variables, (3) allocation concealment, (4) random housing of animals during the experiment (for animal studies only), (5) blinding of caregivers and researchers, (6) random selection of participants for outcome assessment, (7) blinding of outcome assessors, (8) handling of incomplete outcome data, (9) selective outcome reporting, and (10) presence of other potential sources of bias. The same checklist will be applied for human studies except for domain 4, which is not applicable for these studies.

Each item will be rated as having a low, high, or unclear risk of bias. Although complete blinding of moxibustion interventions is challenging, outcome assessment blinding will still be evaluated. Any disagreements in bias assessment will be resolved through discussion or consultation with a third reviewer.

Data Synthesis

Meta-analyses will be conducted when ≥5 studies report comparable GM outcomes (eg, α diversity and Firmicutes-to-Bacteroidetes ratio) to ensure statistical power following PRISMA-P (PRISMA-Protocols) guidelines. For continuous variables such as Shannon or Simpson indexes and *Firmicutes/Bacteroidetes* ratios, values will be pooled using the ratio of means with 95% CIs, calculated by dividing the treatment group mean by the control group mean [40,46]. To address skewed distributions common in microbiome data (eg, relative abundance), arcsine square root transformation will stabilize the variance by reducing the disproportionate influence of extreme proportions, whereas log transformation will normalize metrics such as SCFA concentrations to approximate Gaussian distribution and enable valid parametric comparisons. Zero-inflated distributions of low-abundance taxa will be addressed by applying centered log ratio transformation, aggregating rare taxa to higher taxonomic levels (family and phylum), and excluding features present in <10% of the samples in sensitivity analyses. A random-effects model (DerSimonian-Laird estimator) will prioritize heterogeneity adjustments arising from variations in study designs (eg, randomized controlled trials vs animal models), sequencing platforms (eg, Illumina vs Ion Torrent), primer regions (eg, V3-V4 vs V4-V5), bioinformatics pipelines (eg, QIIME 2 vs Mothur), and intervention protocols (eg, direct vs indirect moxibustion).

Heterogeneity will be quantified using the Cochran Q test (α=.10) and the I^2 statistic (I^2≥75% indicating substantial heterogeneity). For secondary outcomes (SCFAs and inflammatory markers), standardized mean differences will harmonize heterogeneous units (eg, mmol/L vs μg/g). Both clinical and preclinical studies will be included in the primary meta-analysis to maximize statistical power and identify overall patterns. To further address heterogeneity, subgroup analyses will be conducted by study type (clinical vs animal), disease category (IBD, IBS, and obesity), model type (eg, DSS-induced colitis vs chronic unpredictable mild stress–induced depression), and sequencing platform. In addition, protocol-related variables will be explored: subgroup analyses will be conducted by moxibustion type (direct, indirect, mild, and thunder-fire), treatment duration (≤4 weeks vs >4 weeks), and session frequency (≤3 vs >3 sessions per week). Where substantial heterogeneity persists, narrative synthesis will complement quantitative findings. Sensitivity analyses will exclude studies with high risk of bias or nonstandardized methodologies (eg, quantitative polymerase chain reaction–only data or incomplete sequencing metadata). Batch effect correction will be attempted in sensitivity analyses when raw abundance data are available. All analyses will be conducted in RevMan (version 5.4; The Cochrane Collaboration) and validated using R (*metafor* package; R Foundation for Statistical Computing), with scripts and datasets archived on Figshare to ensure reproducibility. P<.05 will be considered statistically significant for the overall effect.

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Publication Bias and Evidence Quality

If ≥10 studies are included, contour-enhanced funnel plots and the Egger test (P<.05) [47] will assess publication bias. The Grading of Recommendations Assessment, Development, and Evaluation system [48] will evaluate evidence quality, downgrading for risk of bias, inconsistency (I^2>50%), indirectness (eg, animal-to-human extrapolation), and imprecision (wide CIs).

Results

The protocol was funded by the 2024 Nanjing University of Chinese Medicine Natural Science Foundation (grant XZR2024009) in March 2024. We identified 1327 records across 6 databases, of which 470 duplicates were removed (470/1327, 35.4%). After screening 857 titles and abstracts, 146 full texts were reviewed (146/857, 17.0%), and 31 studies met the eligibility criteria (31/857, 3.6%) for inclusion (Figure 1). The review is progressing through quality assessment and data synthesis, with final analyses expected by October 2025. Final results are anticipated by late 2025.

Figure 1. Study flow diagram. CNKI: China National Knowledge Infrastructure; RCT: randomized controlled trial.

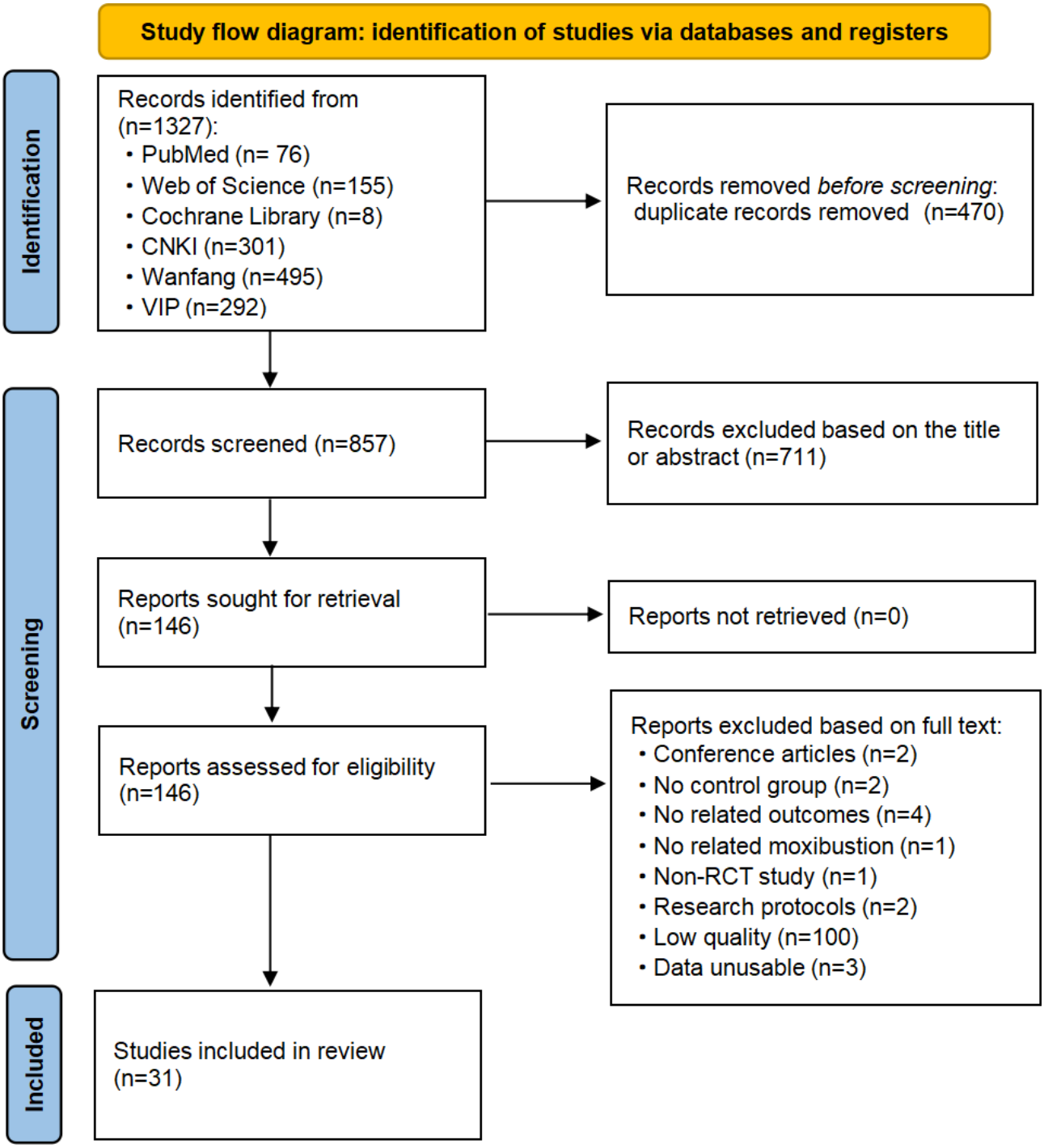

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Discussion

The GM constitutes an indispensable microbial community within the human physiological system. Research on the gut-brain axis confirms that the GM mediates bidirectional interactions among neural, metabolic, and immune systems, extending its influence beyond gastrointestinal functions [49]. Studies have demonstrated that microbial community stability exhibits sensitivity to host-intrinsic variables (genetic predisposition, gestational changes, and aging) and environmental modulators (dietary patterns, antibiotic exposure, and behavioral factors) [50]. Pathological alterations in microbiota composition (dysbiosis) show close associations with aberrant adaptive immune activation, sustaining chronic inflammatory states that may constitute the pathological basis for various diseases, including degenerative joint cartilage lesions [51] and IBD [52]. Current therapeutic paradigms increasingly recognize microbial ecosystem engineering as a viable intervention strategy, with microbiota-targeted therapies demonstrating clinical translational potential. The mechanistic foundation of such interventions lies in restoring microbial diversity and functional redundancy, thereby re-establishing host-microbe symbiosis that is critical for physiological equilibrium.

Moxibustion, a therapeutic modality rooted in traditional medicine, regulates homeostatic processes through thermal stimulation generated by burning *Artemisia argyi* at specific acupoints or meridian pathways. This intervention has gained recognition for its immunomodulatory properties and capacity to regulate inflammatory pathways, with emerging evidence suggesting its potential to exert broader systemic effects via gut microbiome modulation. Contemporary research demonstrates that moxibustion's therapeutic spectrum extends beyond analgesia and immune system optimization to encompass gut microbial community restructuring. Notably, experimental models reveal its ability to enhance commensal microbiota while suppressing pathogenic genera, thereby promoting intestinal ecological equilibrium and mitigating inflammatory cascades [34]. This multimodal therapeutic profile positions moxibustion as a viable treatment option for patients with pharmacotherapy contraindications or preferences for noninvasive interventions. While preliminary data suggest that microbiota-mediated mechanisms may contribute to moxibustion's clinical effects, its precise biomolecular pathways and long-term therapeutic outcomes require systematic exploration. Current knowledge gaps underscore the necessity for rigorously designed clinical trials coupled with mechanistic studies integrating multiomics analyses. Such investigations could elucidate the intervention's pleiotropic actions while establishing evidence-based protocols to facilitate its integration into modern therapeutic paradigms.

This systematic review protocol provides a framework to evaluate the exclusive effects of moxibustion on GM modulation. By focusing on microbial diversity, taxonomic shifts, and metabolites (eg, SCFAs), this study bridges traditional medicine with modern microbiome science. The protocol's emphasis on sham-controlled trials, standardized moxibustion parameters (eg, acupoint localization and session duration), and consistent handling of combination therapies enhances methodological rigor and comparability. Preclinical studies [35] provide preliminary evidence that moxibustion may reduce pathogenic taxa (*Ruminococcus* and *Proteobacteria*) and increase beneficial microbes (*Lactobacillus* and *Bifidobacterium*), correlating with improved barrier integrity and reduced inflammatory markers (TNF and IL-6). These findings align with data linking GM regulation to outcomes in osteoarthritis and IBD, where cyclic adenosine monophosphate signaling pathways may mediate anti-inflammatory effects.

Nevertheless, the causal direction of these associations remains uncertain. Moxibustion may act directly on host physiology—through immune regulation, neuroendocrine signaling, or circulatory changes—with secondary effects on the GM, or primary microbiota shifts may instead drive systemic improvements. A bidirectional relationship is also plausible, consistent with the gut-brain and gut-immune axes. These possibilities will be examined in this review. Although causality cannot be established, this review will identify consistent patterns and propose mechanistic hypotheses to guide future longitudinal and interventional microbiome studies. By integrating clinical and preclinical models, this review will clarify whether moxibustion-induced GM changes are consistent across species and pathologies, supporting its potential as a scalable, nonpharmacological intervention for microbiome-associated disorders.

Despite its strengths, several limitations warrant consideration. First, variability in moxibustion protocols (eg, direct vs indirect methods, acupoint selection, and treatment duration) and microbiome profiling techniques (eg, 16S rRNA variable regions, sequencing platforms, and bioinformatics pipelines) may complicate cross-study comparisons. Although random-effects models and subgroup analyses will be applied, residual confounding from unmeasured factors such as host genetics or dietary habits may persist. Second, publication bias remains possible as negative findings in traditional medicine research are often underreported. Funnel plots and Egger tests will be used to evaluate this risk. Third, achieving complete blinding is inherently difficult for moxibustion in clinical settings. Even with sham devices, participants may perceive differences in heat intensity or treatment location, introducing expectation bias. Although this will be addressed by assessing blinding quality and conducting sensitivity analyses, residual performance bias cannot be entirely ruled out. Finally, this review made the decision to pool both clinical and preclinical studies in the primary analysis. While this approach increases statistical power and enables broader pattern recognition, it introduces potential cross-species heterogeneity because animal models may not fully replicate human physiology or microbiota composition. Although subgroup analyses by study type and disease or model category will be conducted to explore sources of heterogeneity, residual differences between clinical and preclinical evidence may limit the direct generalizability of pooled results to patient populations. These factors will be explicitly acknowledged when interpreting the findings.

Thus, future studies should prioritize dose-response optimization to define thermal parameters (intensity, duration, and frequency) that maximize GM modulation while minimizing adverse effects. Furthermore, exploring synergistic therapies combining

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moxibustion with probiotics or dietary interventions could amplify SCFA-driven barrier restoration.

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during the current study.

Authors' Contributions

The systematic review framework was initially developed through collaborative design by XZ and YL, who established the methodological architecture during preparatory phases. XZ and YG will implement the multistage evidence synthesis protocol, encompassing database searching, citation screening, and relevance verification. Subsequent phases involving data curation and methodological rigor assessment (including bias evaluation) will be jointly administered by XZ, YG, and YL. Scholarly interpretation of synthesized evidence and manuscript preparation will be conducted through iterative coauthor deliberations. In the revised manuscript, JS and QZ contributed to data verification, language editing, and refinement of the Introduction and Discussion sections. Final editorial ratification and content validation will require unanimous approval from all contributing researchers.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy for the systematic review of the exclusive effects of moxibustion on gut microbiota.
[DOCX File, 18 KB - resprot_v14i1e73317_app1.docx]

Multimedia Appendix 2
Data extraction framework for studies on the exclusive effects of moxibustion on gut microbiota.
[DOCX File, 23 KB - resprot_v14i1e73317_app2.docx]

Checklist 1
PRISMA-P checklist.
[PDF File, 81 KB - resprot_v14i1e73317_app3.pdf]

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Abbreviations

DSS: dextran sulfate sodium

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GM: gut microbiota
IBD: inflammatory bowel disease
IBS: irritable bowel syndrome
IL-6: interleukin-6
MeSH: Medical Subject Heading
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses–Protocols
PRISMA-S: Preferred Reporting Items for Systematic Reviews and Meta-Analyses literature search extension
rRNA: ribosomal ribonucleic acid
SCFA: short-chain fatty acid
TNF: tumor necrosis factor

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Evaluating Diversity in Open Photoplethysmography Datasets: Protocol for a Systematic Review

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Abstract

Background: Photoplethysmography (PPG) is an optical method for measuring blood volume changes in microcirculation through noninvasive photodetection. It has become a widespread and essential clinical tool, used in pulse oximeters and wearable devices. However, technical aspects of PPG make it susceptible to intrinsic bias, with the potential to adversely affect particular patient and consumer populations. Developments in PPG technology, increasingly driven by openly accessible datasets as opposed to de novo experimentation, have the potential to help monitor an array of physiological variables. However, some populations may be underrepresented in PPG datasets. We describe a protocol for a systematic review to assess the biases within open access PPG datasets.

Objective: This review aims to evaluate the underlying reporting patterns and structure of openly accessible PPG datasets. We will provide insight into the measured biosignals and demographic variables included in the datasets in the hope of shedding light on what PPG data parameters are being used to develop medical devices. Therefore, we can elucidate current gaps and areas for improvement to reduce bias in medical device development.

Methods: This review will be reported in accordance with the standard PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. We will include primary studies that mention PPG and specifically reference openly accessible datasets since 2000. The datasets must contain physiological parameters such as heart rate, blood pressure, or respiratory rate, as well as the PPG waveform data, collected from humans. Searches will be conducted in literature databases and data repositories, including MedLine OVID, IEEE Xplore, Scopus, and PhysioNet. Studies will be evaluated in accordance with the Standing Together Initiative recommendations, which are urging for health care technologies supported by representative data. Biosignal and demographic variables will be extracted from the PPG datasets, with steps taken to harmonize and store this information. Statistical analysis will be performed, including descriptive statistics and the chi-square test for comparisons. Additional statistical analyses will be performed after data extraction is completed and the level of heterogeneity is characterized.

Results: We will analyze the dataset diversity and the structural basis of PPG datasets. This includes statistically analyzing the demographic and biosignal variables in the datasets. By using statistical test fit for nominal variable comparisons, we will evaluate the frequencies of characteristics like the devices used, biosignals collected, clinical parameters, demographic characteristics, and geographic information. This systematic review is expected to be completed by September 2025. The screening and review of the articles is currently being conducted.

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Conclusions: This review will provide insight into the potential gaps of existing open access PPG datasets. It will inform future data collection and design of openly available PPG datasets for training medical devices, including wearables, to avoid perpetuating biases, allowing for application in diverse clinical settings.

Trial Registration: PROSPERO CRD42024564759; https://www.crd.york.ac.uk/PROSPERO/view/CRD42024564759

International Registered Report Identifier (IRRID): PRR1-10.2196/73040

(JMIR Res Protoc 2025;14:e73040) doi:10.2196/73040

KEYWORDS

photoplethysmography; PPG; open data; diversity; skin tone; bias; equity; fairness

Introduction

Photoplethysmography (PPG) is an optical method for measuring blood volume changes in microcirculation, through noninvasive photodetection. It has become a widespread and essential tool, providing the sensing technology for pulse oximeters in clinical use and being widely used in consumer wearables such as smartwatches for heart rate monitoring. However, technical aspects of PPG make it susceptible to intrinsic bias, with the potential to adversely affect particular patient and consumer populations. Developments in PPG technology, increasingly driven by existing datasets as opposed to de novo experimentation, have the potential to help monitor an array of physiological variables with both clinical and wellness applications. However, these may disenfranchise those populations who are underrepresented in the existing training datasets.

PPG waveforms depict blood volume changes due to changes in absorption and reflection patterns detected by the photodetector [1]. PPG measurements are usually obtained by placing the device on the extremities of the body where the vascular bed is shallow and widespread [2]. These locations can include the wrist, fingers, toes, and ears. Through signal processing, and in some cases the use of different wavelengths of light, PPG can provide information on respiratory rate, blood pressure, sleep patterns, arterial stiffness, and blood oxygen saturation [3]. In addition, the periodicity of electrocardiogram and PPG waves can be correlated in terms of heart rate variability and arrhythmias, as the waveforms correlate to specific points within the cardiac cycle [4].

The 2 primary components of a PPG waveform consist of the pulsatile and the lower frequency portions. The pulsatile component directly correlates to the volumetric changes associated with the heart rate [5]. The lower frequency component, on the other hand, consists of the light absorbed by the tissue, veins, and blood, which correlates to volume capacity [5]. The optical measurements are usually taken at red or near-infrared wavelengths (625 nm-750 nm and 750 nm-1400 nm) or green wavelengths (500 - 565 nm) [6]. These are commonly used because the red or near-infrared wavelengths penetrate up to 2 cm beyond the skin surface whereas the green penetrates up to 0.3 mm and allows for the differentiation between oxyhemoglobin and deoxyhemoglobin [7-9]. However, some PPG methods include the use of multiple wavelengths, including blue, green, and yellow light to improve the signal-to-noise ratio [10,11].

PPG, along with pulse oximetry, has limitations attributed to motion, ambient light, sensor contact, pulse pressure reduction, and disturbances in contact between the sensor and the skin. One key limitation that has recently been highlighted is that of inaccuracy across different skin tones [7,12,13]. Sjoding et al recently reported that black patients had almost 3 times the frequency of occult hypoxia–falsely elevated oxygen saturation levels–compared to their white counterparts [14]. Occult hypoxia can lead to higher risk of mortality and organ failure for darker-skinned patients and has been shown to reduce the provision of life-saving treatment modalities like supplemental oxygen and medications. This is clearly of concern, both due to the limitations of clinical devices but also the biases inherent in commercial health technology which systematically underserve select populations. The reduced performance of PPG-based technology on darker-skin-toned and obese patients necessitates further inclusion of demographic characteristics like skin tone, race or ethnicity, and even BMI in PPG datasets used to train medical devices, like pulse oximeters. Furthermore, as continuous clinical monitoring and the availability of wearable technology increases globally without correctional strategies, these biases will only worsen the performance of medical devices on diverse populations.

While the original experiments in pulse oximetry involved permissive hypoxia of test subjects, a number of current PPG developments are largely driven by training on available datasets. However, the biases within openly available datasets have not been described. This makes it difficult to understand their possible impact on both clinical and consumer technology. We describe a protocol for the first systematic review of which we are aware designed to assess the biases within currently open access PPG datasets. This has immediate value for those seeking to derive physiological data from PPG technology using training datasets. By focusing on openly accessible datasets and repositories, we will provide insight into the demographic characteristics of the data that is commonly used for a majority of existing PPG technology including wearables.

This review aims to evaluate the underlying reporting patterns and structure of openly accessible PPG datasets. We will provide insight into the measured biosignal and demographic variables included in datasets in hopes of shedding light on what PPG data parameters are being used to develop medical devices.

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Methods

Overview

This review will be reported in accordance with the standard PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. The study has been registered with PROSPERO (CRD42024564759) [15] before the initial literature search [16]. The full planned search strategy is provided in the Supplementary Material in Multimedia Appendix 1, which has been developed in close concordance with a medical librarian (IK and EE). This search strategy includes the databases and data repositories: MedLine OVID, IEEE, SCOPUS, Physionet, National Sleep Research Resource, UC Irvine Machine Learning Repository, and Borealis.

Eligibility Criteria

We will include any peer-reviewed primary studies—observational and nonobservational—which use PPG datasets. This includes PPG datasets in published randomized controlled trials, nonrandomized trials, cross-sectional studies, cohort studies, and algorithmic models.

We will include studies published since 2000 to ensure the datasets are relevant to current technology developments. The year of 2000 was defined as the lower bound to ensure the datasets selected for analysis are aligned with contemporary medical device design, especially since there has been a rise in usage of PPG datasets to train wearable health technologies in the last 2 decades. In the early 2000s, significant global health milestones like the Millennium Development Goals were established, marking a period in time when critical frameworks and health care initiatives for promoting greater equity and diversity were implemented. We plan to include studies that mention PPG and specifically reference openly accessible datasets. Therefore, accounts will be created to access datasets as needed; however, any datasets that require a fee or monetary incentive to access the datasets will be deemed as not openly accessible. The datasets must contain physiological parameters such as heart rate, blood pressure, or respiratory rate as well as data describing the waveform, such as pulse wave or slope transit time. These terms have been chosen as they are indicators of parameters routinely collected in PPG datasets. The inclusion and exclusion criteria are outlined in Textbox 1. Included studies will be evaluated for the extent to which they include demographic characteristics and consider these characteristics.

Textbox 1. Summary of inclusion and exclusion criteria.

Inclusion criteria

- Openly accessible datasets
- Literature containing datasets years 2000-present
- Must contain photoplethysmography (PPG) signal and physiological parameters such as heart rate, blood pressure, or respiratory rate
- Human studies
- English and non-English articles, provided the non-English articles have datasets with English translation

Exclusion criteria

- Animal studies
- Lack of PPG signals
- Primary literature without reference to datasets
- Conference papers and abstracts

Datasets meeting the eligibility criteria will be included for analysis of demographic characteristics. Articles mentioning openly accessible datasets may be used to provide contextual information on the datasets, but only the datasets will be analyzed to ensure the primary objective of this review is focused on the reporting quality of openly accessible PPG datasets.

Data Analysis

Following the initial literature search, all studies will be reviewed independently by two authors using systematic review software, Rayyan.ai [17,18]. Studies will initially be screened by title and abstract. The full-text articles will then undergo screening. Disagreements will be discussed with and resolved by a third author, a senior author with expertise in the topic. At each step, studies will be retrieved only if they meet the eligibility criteria.

Information Sources

Databases including Medline OVID, IEEE Xplore, and Scopus have been searched for articles including relevant datasets or mentionings of dataset repositories. The latest search was completed in December 2024. Following this literature search, specific dataset repositories including Physionet and GitHub will be searched to provide any additional openly accessible datasets relevant to the eligibility criteria and aim of the systematic review.

Risk of Bias

The studies will be assessed using the STANDING Together Initiative guidelines as a framework for evaluating the datasets, as there are no widely accepted tools for assessing the risk of bias of datasets [19-21]. The STANDING Together Initiative provides guidelines that address dataset diversity and inclusion to improve the transparency of dataset reporting [19]. Though

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these recommendations do not make up a definitive risk of bias tool, they provide content areas for analyzing the datasets, as they promote greater transparency in the reporting of datasets used for training and developing medical devices.

Synthesis of Results

After dataset extraction, a systematic analysis and summary of all included studies and datasets will be provided by describing their dataset characteristics and study outcomes. Due to the heterogeneity of the datasets included, the statistical analysis and summary will provide an overview of the current state of openly accessible PPG datasets and repositories. Details such as the devices, biosignals collected, clinical parameters (sample size), demographic characteristics (age, sex, race or ethnicity, skin tone, and BMI), and geographical information (country, health care setting, and dates) will provide insight into the dataset characteristics. We expect the need for stepwise data harmonization where variables included in the datasets will be extracted, compared, and stored in a CSV file format with standardized labeling. The analysis of the biosignal and demographic variables will be analyzed in R to allow for the creation of data visualizations and provide statistical comparisons of the variables included across the datasets. Quantitative analysis will allow this review to focus on the frequencies and counts of the measured biosignal and demographic data variables. This information will provide insight into the reporting quality of the datasets; however, the specific values or information collected within the dataset for each biosignal and demographic variable will not be analyzed, to ensure a broader understanding of dataset documentation.

Summary statistics will be provided based on the characteristics of the datasets. These will include descriptive statistics such as means, SD, and data visualizations depicting the distribution of demographic and geographical characteristics. Statistical analysis will be performed on the dataset characteristics, such as age, sex, race, ethnicity, skin tone, BMI, and other relevant parameters, including analysis on the frequency of the variables and other quantitative aspects extracted from the studies [21]. Raw counts of the characteristics will be visualized as percentages or proportions to depict the array of demographic variables reported in the PPG datasets. These characteristics will also be analyzed using statistical tests such as chi-square for frequency and independence [14]. These tests will provide insight into the differences in both the frequencies and the co-occurrence of demographic characteristics, respectively. Further analysis of the literature will contextualize why such differences may or may not be statistically significant. Visualizations such as histograms will include information on the mean ages, dataset sizes, and number of waveform characteristics reported. This analysis will provide insight into how datasets are structured and the amount of information reported in them to qualify potential reasons for statistically significant differences in dataset reporting. Additional statistical tests will be used, and information such as geographical or socioeconomic data will be displayed cartographically or in a heatmap to depict the geographical sources of PPG studies and datasets.

Limitations and Implications

We predict that there will be heterogeneity in the data reporting quality and the terminology used to signify specific variables; therefore, it is important to use broad inclusion criteria to capture relevant articles.

We also anticipate significant heterogeneity of demographic characteristics. Jiang et al [19] reported that less than seven percent of physiological datasets, specifically those available on PhysioNet, include all 4 key demographic variables—age, sex, race, and ethnicity. Consequently, it is important to not include these variables in our inclusion or exclusion criteria to truly understand the level to which PPG datasets consider demographic aspects including variables such as age, sex, race, ethnicity, and other relevant parameters like skin tone or BMI. Understanding the extent to which demographic parameters are collected in PPG datasets will therefore shed light on what information is used in informing the development and deployment of healthcare technology. By collecting information on the structural aspects of the PPG datasets, we will provide a critical comprehension of the reporting quality of openly accessible datasets.

Results

After the protocol was registered, the literature search was run in the databases IEEE, Scopus, and MedLine OVID in December 2024. The search yielded 1198 articles for initial screening. The openly accessible PPG datasets extracted from these repositories will be included in the analysis of demographic and biosignal data. The abstract screening phase has yielded 464 articles. The full-text screening is projected to be completed by July 2025. After which data analysis, detailed below, will be projected to be completed by September 2025.

Discussion

Principal Findings

Understanding the reporting quality of datasets used to develop health care technology is becoming increasingly important as the use of algorithmic models and processing to train medical devices grows. By analyzing openly accessible PPG datasets, we aim to provide a more comprehensive view of standard of data collection and usage for medical devices. Because of PPG's long-standing usage in medical devices since the 1970 s and the wide range of biosignals that can be extracted from PPG data, it is vital to increase transparency in the demographic information collected in tangent to the biosignal data. The principal finding from this review will be to extract the different demographic and biosignal characteristics listed in openly accessible PPG datasets. We will provide summary statistics including frequencies, proportions, and distributions of the number and types of dataset characteristics. These summary statistics will be visualized in diagrams like histograms and box-whisker plots as well as tables. Any additional information related to characteristics such as the geographical location of the data collection or socioeconomic status will be portrayed in heatmaps to provide a general overview of additional social variables.

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Comparison to Previous Work

Wearables including smartwatches are commonly used to track personal health measures such as heart rate, sleep, and blood pressure. These commercially available medical devices often use PPG to take physiological measurements. However, PPG data collected by wearables have been observed to be affected by skin tone and higher adipose tissue due to obesity [12]. In combination, differences of up to 61% in signal intensity have been observed [12]. The Fitzpatrick scale is commonly used to assess for differences in skin tone, and while it provides an insight into the physiological signal values caused by greater melanin levels, it is subjective and treats skin tone as a categorical, rather than a continuous, variable [22]. This has limitations when considering the many underlying factors that result in the chromatic appearance of an individual's skin tone, particularly if complicated by clinical conditions such as jaundice or hypoxia. Exploring the extent to which variables such as this are captured within existing datasets may be instructive in understanding their inherent ability to account for overall skin coloration.

Clearly, this same need to account for diversity in skin tone and clinical condition applies to clinical PPG studies and their resultant datasets. In a clinical setting, having erroneous oxygen saturation values or heart rate measurements can result in poorer clinical outcomes. There is evidence that the obese and those with greater melanin content in their skin endure worse health outcomes, with inaccurate monitoring a clear potential contributor [22]. Obesity can be attributed to physiological changes such as the reduction in trans-epidermal water loss and an increase in skin thickness due to adipose tissue can influence the light scattering patterns needed to obtain a PPG reading [22]. In addition to melanin content and obesity, other factors influencing perfusion and skin temperature can all affect PPG. When expanding PPG technology to low-resource settings, there is a need to account for diverse populations not only in terms of melanation but also factors such as obesity and conditions altering perfusion. Moreover, they may have a greater diversity of endemic clinical conditions including anemia, parasitemia, and malnutrition—whose effects on PPG have not been clearly described. Effective clinical PPG monitoring in these patients mandates an interpretation based on data from representative populations.

This understanding of demographic and biosignal variables is critical to presenting the current standard of reporting quality across openly accessible PPG datasets. In a recent review of PhysioNet datasets, a data repository with biosignal datasets, information regarding demographic and geographical information was presented to highlight the disparities and demographic gaps present in biosignal datasets [19]. This marks the analysis of openly accessible PPG datasets relevant and important for promoting transparency and equity in medical device development, as PPG is a widely accepted technology growing in popularity in health care. The aims of this systematic review mirror those of the review by Jiang et al [19], but take a broader look at openly accessible PPG datasets across multiple databases and repositories.

Strengths and Limitations

Providing a detailed summary of the demographic and biosignal variables in openly available datasets, we aim to promote a more comprehensive understanding of reporting standards in existing PPG datasets. This review will provide a structured overview of the current gaps and sources of bias in developing PPG-based medical devices. Transparency in dataset reporting will highlight the need for greater diversity and promote an increased range of demographic characteristics collected in openly available PPG datasets. However, we do expect limitations such as heterogeneity in the datasets, especially as it comes to which characteristics are collected and included in the datasets. We also anticipate challenges in gaining access to certain datasets as we will likely have to go through repositories or databases that require account creation or multiple steps in gaining access to the PPG databases. These limitations will be mitigated by maintaining clear documentation of the characteristics extracted from the datasets being analyzed and data harmonization. Also, accounts will be created as needed to ensure adequate access is gained to review the dataset characteristics.

Future Directions

In this systematic review, we will analyze the structural basis of PPG datasets and critically evaluate the different variables included in the datasets. This analysis will highlight the reporting quality of openly accessible PPG datasets. By critically appraising the dataset diversity and reporting quality, we can highlight the gaps present in current PPG data to inform future collection and design of medical devices including wearables to be more inclusive to avoid perpetuating biases. In addition, by looking at the structure of PPG datasets and their representativeness, we can also provide insight into the gaps that may be present in the context of PPG applications in low-resource settings. The findings can promote awareness of sources of bias in openly accessible PPG datasets, informing future data collection and modulation when training PPG-based medical technology. With the synthesis of this information and data analysis, we hope that medical device developers would consider dataset level biases and their implications on human health. We hope that these considerations would push toward greater transparency in PPG data collection and extraction of demographic and biosignal characteristics to ensure users are informed of the design and development of medical devices and avenues for promoting fairness. This review, therefore, aims to address disparities in openly available PPG datasets, the downstream effects of these disparities, and potential avenues for greater equity in PPG dataset creation and usage.

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Data Availability

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Authors' Contributions

Conceptualization: VP (lead), LR (equal), PHC (equal), TB (equal)
Data curation: VP (lead), LR (equal)
Formal analysis: VP (lead), LR (equal), PHC (supporting), TB (supporting)
Funding acquisition: No specific funding has been sourced for this work
Investigation: VP (lead), LR (equal)
Methodology: VP (lead), LR (equal), PHC (equal), TB (equal)
Project administration: TB (lead), PHC (equal)
Resources: VP (lead), LR (equal), PHC (equal), TB (equal)
Supervision: TB (lead), PHC (equal), LR (equal)
Validation: VP (lead), LR (equal), PHC (equal), TB (equal),
Visualization: VP (lead), LR (equal), BGS (supporting), SN (supporting), PHC (supporting), TB (supporting)
Writing–original draft: VP (lead), LR (equal), PHC (supporting), TB (supporting)
Writing–review & editing: VP (lead), LR (equal), PHC (supporting), TB (supporting), BGS (supporting), SN (supporting), OM (supporting), TE (supporting), LH (supporting)

Conflicts of Interest

PHC is employed by Nokia Bell Labs. He has performed consultancy work for Cambridge University Technical Services, has received travel funds from VascAgeNet, and has received honoraria from IOP Publishing and Emory University (the latter not received personally).

Multimedia Appendix 1
Search strategy.
[DOCX File, 14 KB - resprot_v14i1e73040_app1.docx]

Checklist 1
PRISMA-P checklist.
[PDF File, 220 KB - resprot_v14i1e73040_app2.pdf]

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Abbreviations

PPG: Photoplethysmography
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Effect of Physiotherapy Intervention on Improvement of Respiratory Function and Degree of Respiratory Distress Reduction in Neonates With Respiratory Distress Syndrome: Protocol for a Systematic Review

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Abstract

Background: Neonatal respiratory distress syndrome (NRDS), a common and serious illness in preterm infants, is characterized by lung immaturity and inadequate surfactant production. Even though improvements in neonatal care have increased survival rates, optimizing supportive therapies such as physiotherapy is still essential to improve respiratory outcomes and overall recovery.

Objective: This study aims to evaluate the effectiveness of physiotherapy therapies in enhancing respiratory function and clinical outcomes in neonates with NRDS.

Methods: PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) guidelines will be followed for conducting a systematic review. Studies assessing the effects of physiotherapy therapies on newborns with NRDS, such as respiratory exercises, manual chest compressions, percussion, vibration, and postural drainage, high-frequency oscillation of the chest wall, cough stimulation, or suctioning will be included. A comprehensive search of electronic databases, including PubMed, Embase, CINAHL, and the Cochrane Library, to find pertinent observational studies, experimental studies, and randomized controlled trials, will be conducted. Important outcomes will be respiratory function metrics, oxygen saturation levels, length of mechanical ventilation, occurrence of problems, and overall newborn outcomes.

Results: Exact numbers are not accessible at this time, as the review is hypothetical and has not yet been conducted. In order to inform clinical procedures and future studies, the results will contain data on respiratory improvement, intervention kinds, safety profiles, and the best times and frequencies for physical therapy in neonates with respiratory distress syndrome.

Conclusions: This review will provide a comprehensive understanding of the role of physiotherapy in managing NRDS and its impact on clinical outcomes in neonates. The findings may guide clinical practice and inform future research on noninvasive strategies for improving neonatal respiratory care.

Trial Registration: PROSPERO CRD42025635782; https://www.crd.york.ac.uk/PROSPERO/view/CRD42025635782

International Registered Report Identifier (IRRID): PRR1-10.2196/71854

(JMIR Res Protoc 2025;14:e71854) doi:10.2196/71854

KEYWORDS

NRDS; chest physiotherapy; respiration; pulmonary rehabilitation; new born; non-invasive interventions; neonatal intensive care; neonatal respiratory distress syndrome

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Introduction

Rationale

Neonatal respiratory distress syndrome (NRDS) is a leading cause of morbidity and mortality among preterm infants. It primarily results from insufficient pulmonary surfactant production, which compromises alveolar stability and gas exchange. The incidence of NRDS is inversely proportional to gestational age, affecting approximately 40% - 60% of neonates born before 28 weeks of gestation and 15% - 30% of those born between 32 and 36 weeks [1]. NRDS presents significant clinical challenges, necessitating early diagnosis and prompt intervention to improve survival and reduce complications.

A portion of newborns still suffer from chronic respiratory compromise in spite of improvements in neonatal care, such as the use of prenatal corticosteroids, exogenous surfactant administration, and respiratory support techniques, such as mechanical ventilation or continuous positive airway pressure (CPAP) [2-4]. In order to maximize lung function and clinical recovery, this has led to research into supplementary therapies including physical therapy.

In the neonatal intensive care unit, physical therapy includes a variety of therapies aimed at promoting respiratory function, including positioning, vibration, chest percussion, and expiratory flow increase exercises. In newborns experiencing respiratory distress, these methods seek to improve ventilation-perfusion matching, facilitate secretion clearance, and increase oxygenation [5]. Theoretically, physiotherapy has several advantages; however, there are conflicting data regarding its effectiveness and safety in treating NRDS. According to a number of studies, physiotherapy may help newborns experiencing respiratory distress achieve better clinical outcomes, including lower oxygen requirements, improved arterial blood gases (ABGs), and shorter hospital stays. Other publications, however, express concerns about possible negative consequences, such as hypoxemia and reactions associated with stress [6]. These discrepancies could result from differences in timing, therapeutic strategies, and therapist skill.

Furthermore, the scope and methods of earlier evidence syntheses on newborn physiotherapy have been constrained, frequently concentrating on a small number of therapies or merging diverse populations without sufficient stratification. The impact of physiotherapy in newborns with NRDS especially has to be thoroughly assessed, and the relevant data must be consolidated. The purpose of this systematic review is to evaluate the safety and efficacy of physiotherapy techniques as NRDS adjunctive treatments. This review will give a thorough grasp of the available data, point out knowledge gaps, and guide future clinical guidelines for infant respiratory treatment by combining findings from observational and interventional studies.

The findings of earlier systematic reviews that looked at physiotherapy in neonates were not as applicable to neonates with NRDS since they frequently encompassed diverse populations, such as newborns with bronchiolitis, pneumonia, or postsurgical disorders. A majority of these reviews combined different respiratory conditions without classifying the results according to gestational age or diagnosis, 2 important factors in the treatment of NRDS [7,8]. Furthermore, current syntheses usually place more emphasis on short-term physiological metrics such as respiratory rate or oxygen saturation rather than clinically significant outcomes such as mortality, hospital stay, or length of respiratory support. In addition, few evaluations have addressed how to manage heterogeneity in interventions, demographics, and end measures, or examined the efficacy of various physiotherapy modalities in a systematic manner. These gaps highlight the necessity of a targeted, diagnosis-specific review of the literature regarding physiotherapy for newborns with NRDS [9].

Objective

Assessing the effectiveness of physiotherapy therapies in improving respiratory function and lowering distress in infants with respiratory distress syndrome (RDS) is the goal of this systematic review methodology. Analyzing the decrease in respiratory support requirements, classifying the different forms and protocols of physiotherapy, and assessing the improvement in clinical respiratory scores are among the goals. The review will also look into the physiological mechanisms, safety, and viability of physiotherapy in this population, as well as the best times and frequencies of interventions to optimize therapeutic results. This thorough investigation will help to improve neonatal care for patients with RDS and refine clinical procedures.

Methods

Overview

This review aims to guide future research in neonatal respiratory care and enhance clinical practice by identifying potential dangers and successful interventions.

Eligibility Criteria

The eligibility criteria was assessed by PICO (Population, Intervention, Comparison, and Outcome) framework.

For the Population component, we will only accept studies that involve human neonates (≤28 days old) who have been diagnosed with NRDS either clinically or radiographically.

For the Intervention component, infants who have had physical therapy treatments will be included. (1) The interventions will be grouped as active techniques (eg, expiratory flow increase, percussion, and vibration) versus passive or supportive strategies (eg, positioning). Techniques used in chest physical therapy include manual chest compressions, percussion, vibration, and postural drainage. (2) Methods for clearing the airways will include high-frequency oscillation of the chest wall, cough stimulation, or suctioning. (3) Breathing exercises will include methods to enhance lung expansion, include inspiratory training or mild inflation therapy. (4) Positioning therapy will include methods to improve respiratory mechanics and oxygenation, such as lateral tilt or prone positioning. (5) Other treatment will include an expiratory flow increase technique, which is a thoracoadominal movement performed manually by the physiotherapist to clear airway obstructions [6,10].

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For the Comparison (C) component, the inclusion of a control group without treatment is necessary in studies, and this group may consist of participants receiving a placebo.. Normal treatment without physiotherapy will include standard medical care for neonates with NRDS, including surfactant replacement therapy. Mechanical ventilation, such as invasive ventilation or CPAP, will be given. Supportive treatment, such as controlling body temperature and fluid intake, will be provided. Different approaches to intervention include other nonphysiotherapy therapies, such as medication or surgery, that target respiratory function will be administered to neonates with NRDS.

In terms of outcome measures, oxygen saturation levels (SpO_2), ABG analysis (eg, PaO_2, $PaCO_2$, and pH), respiratory rate (breaths per minute), and lung compliance (static or dynamic) will all be used to quantify respiratory function. Validated scoring methods, such as the Downes or Silverman-Andersen scores, will be used to assess the degree of respiratory distress reduction. Length of hospital stay will be monitored. The length of respiratory support, including mechanical ventilation, CPAP, or oxygen therapy, will be documented from the start of the intervention to the end of respiratory support.

For study design, both observational studies (prospective and retrospective cohort studies and case-control studies) and randomized controlled trials (RCTs) that assess the impact of physiotherapy therapies in neonates with NRDS will be included in this review. Regarding language, only English-language research or studies with available translations will be deemed eligible for this study due to translation restrictions (due to resource constraints for translation). Studies published from 2000 to 2025 will be considered for inclusion. Both published article and gray literature will be considered as eligible publication types.

Information Sources

To find papers that are pertinent to our study issue, we will use both manual and electronic searches. A total of 4 databases—PubMed, Embase, CINAHL, and the Cochrane Library—will be searched electronically (from 2000 to 2024 December). Although it is acknowledged as a search engine rather than a formal database, Google Scholar will be used to supplement the search. Depending on the needs of each database, our search algorithms will blend free texts and MeSH (Medical Subject Headings). Due to the low quality of the evidence, individual case reports, case series, and expert views will not be included in the data extraction process. Papers that are not published or in full text will also not be included.

Search Strategy

The Cochrane Library, PubMed, Embase, and CINAHL will be thoroughly searched. Physiotherapy will be used, along with MeSH and pertinent keywords such as “Infantile Respiratory Distress Syndrome,” “Neonatal Respiratory Distress Syndrome,” “Respiratory Distress Syndrome, Infant,” “Respiratory Distress Syndrome,” “physiotherapy,” “respiratory function,” “neonates,” “respiratory distress syndrome,” and “New-born” combined with Boolean operators AND/OR. To make sure the most recent research is included, searches will be conducted again prior to the final analysis. In addition, trial registers, investigator contacts, and conference proceedings will be searched for unpublished studies. ProQuest Dissertations & Theses Global and Google Scholar will be used to consult the gray literature. Medline and the Cochrane Library will use MeSH phrases to help find other relevant publications. For different suffixes, truncation (*) and Boolean operators (OR, AND) are used (S1 supplementary file).

Selection and Data Collection Processes

SH and IQ are 2 calibrated and independent reviewers and will conduct the study in 2 stages. The first stage involves screening abstracts and titles for alignment with the inclusion criteria and research question. To decide on the final inclusion, the full texts of possibly pertinent research are examined in the second stage. This procedure will be guided by the inclusion and exclusion criteria. In phase 1, the titles and abstracts of the chosen papers will be read by the 2 reviewers, SH and IQ. The entire texts of the previously included papers will be read by the same reviewers (SH and IQ) in phase 2. The selection criteria will be the same as those from the first round. A dual-reviewer approach will be used, and any disagreements will be resolved through consensus discussions or by involving a third independent reviewer (HP). A summary of the study selection procedure is given in Figure 1. This process is now explicitly detailed to ensure consistency and transparency during study selection.

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Figure 1. PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) flowchart.

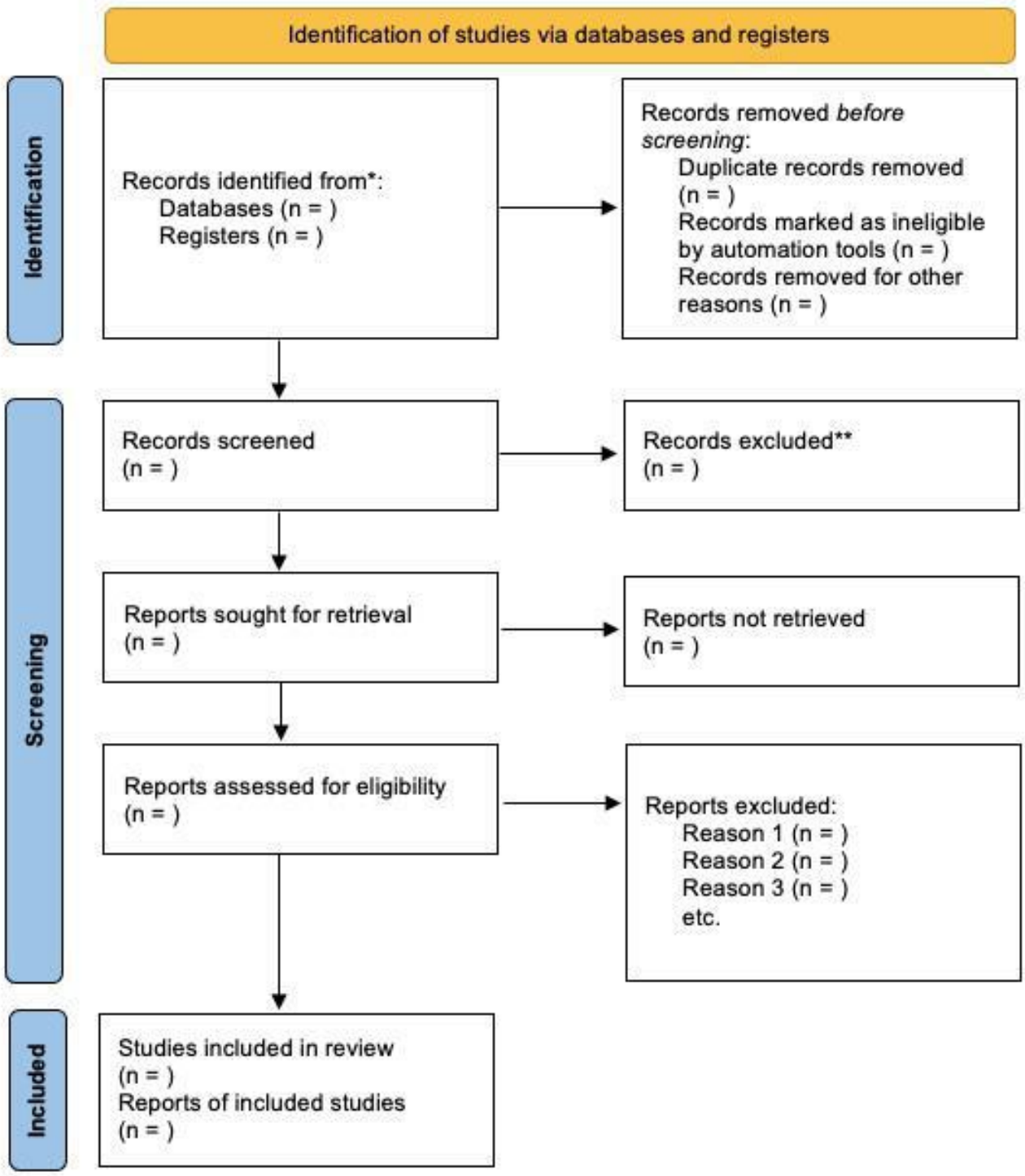

Data Items

Participant characteristics will include baseline characteristics such as gestational age (mean age and age range), gender distribution, and inclusion and exclusion criteria, respiratory function, and degree of respiratory distress reduction among other pertinent demographic or clinical data. Details of the intervention will include the type of physiotherapy intervention (eg, chest physiotherapy and positioning), its duration, frequency, intensity, and mode of delivery. Information about the sort of control or comparative interventions (such as a placebo, standard care, or no intervention), as well as its length, frequency, and intensity, will be gathered for comparators. Respiratory function will be the main focus of outcome measures. Downes or Silverman-Andersen scores, respiratory rate (breaths per minute), lung compliance (static or dynamic), SpO_2, and ABG analysis (eg, PaO_2, $PaCO_2$, and pH) will be used to evaluate the extent of respiratory distress reduction and any adverse effects reported. The study design (such as an observational study or RCT), sample size, funding sources to evaluate potential bias, and any conflicts of interest disclosed by the study authors are all examples of study features. To

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ensure consistent and accurate data extraction and analysis across all included research, preplanned data assumptions and simplifications will be used when needed [11,12].

Outcomes

Improvements in respiratory function and a decrease in the intensity of respiratory distress are the main goals of this review. SpO_2, ABG analysis (eg, PaO_2, $PaCO_2$, and pH), respiratory rate (breaths per minute), and lung compliance (static or dynamic) will all be used to quantify respiratory function. These measures will be evaluated using pulmonary function tests or ventilator settings. Data will be collected at preintervention (baseline), postintervention, and at follow-up periods (eg, 24-72 hours and 1 week). Validated scoring methods, such as the Downes or Silverman-Andersen scores, will be used to assess the degree of respiratory distress reduction. The length of hospital stay and the duration of respiratory assistance are examples of secondary outcomes. The length of respiratory support, including mechanical ventilation, CPAP, or oxygen therapy, will be documented from the start of the intervention to the end of respiratory support. This duration will be expressed in hours or days. The number of days from admission to discharge or transfer, recorded at the time of discharge, will be used to calculate the length of hospital stay. These results will be useful in evaluating the immediate and long-term effects of physical therapy treatments on newborns with NRDS.

Assessment of Risk of Bias in Included Studies

Using proven instruments based on study design, 2 reviewers, SH and IQ will independently evaluate the risk of bias. We will use the Cochrane Risk of Bias 2.0 tool for RCTs and the Risk Of Bias in Non-randomized Studies-of Interventions (ROBINS-I) tool for observational studies. Any disagreements will be settled by consensus with a third reviewer (RR). The weighting of the evidence during synthesis and interpretation will be influenced by the quality assessment's findings. The authors will discuss the tool and establish the settings for its assessment before applying it. A calibration exercise among the evaluators will also be conducted. Each tool's suggested presentation of the results will be used. The Robvis website will be used to make figures [13]. If there are enough studies (typically more than 10) to address publication bias, a funnel plot will be used. We will use either Egger or Begg test to statistically analyze the funnel plot's asymmetry [11,12]. We will perform subgroup and sensitivity analyses, and outline procedures for assessing interrater reliability during bias evaluation. These additions further strengthen our methodological framework.

Data Synthesis

During synthesis, a hierarchical strategy will be used. Priority will be given to RCT evidence when analyzing and interpreting results. In order to address areas where RCT data are scarce or unavailable, highlight new patterns, or offer supporting evidence, observational studies will be used. When applicable, findings will be categorized by study design to differentiate between data from higher and lower quality sources. Standardized mean differences or relative risks with 95% CIs will be used to measure the effectiveness of treatment for NRDS in order to assess primary outcomes such as respiratory function and a reduction in the severity of respiratory distress. A narrative approach will be the main method used for data synthesis due to the expected heterogeneity among research. Key outcomes, types of interventions, and their reported benefits on respiratory function and the degree of respiratory distress reduction will be highlighted in a descriptive summary of the findings from the included studies. To improve clarity, pictorial representations will be added to a narrative summary. To evaluate variations in the effects of the intervention across participant demographics or intervention attributes, subgroup analyses will be carried out. We will perform subgroup analyses based on intervention type, gestational age, or setting (eg, neonatal intensive care unit vs step-down units), apply random-effects models for meta-analyses, and conduct narrative synthesis when heterogeneity will be too high for pooling [10,11].

Confidence in Cumulative Evidence

This systematic review will be assessed using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) method. In the management of neonates with RDS, the GRADE approach may facilitate a comprehensive evaluation of the evidence supporting the efficacy of physiotherapy treatments.

Ethical Considerations

This study is a protocol for a systematic review and does not involve the collection of primary data from human participants or animals. Therefore, ethical approval and informed consent were not required. All data to be analyzed will be obtained from previously published studies that had already received ethical approval and informed consent from their respective authors and institutions.

Results

The time frame for completing this investigation is January 2025-December 2027. The 2 reviewers will be blinded at each step of the process. Regular team meetings will be held to settle disputes or conflicts between the reviewers. This will contribute to increasing the transparency of the evaluation process. Every discussion will be recorded. As soon as the systematic review is complete, it will be submitted for publication. The intended review will be conducted in accordance with guidelines mentioned in the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) checklist. This study has been registered with PROSPERO (CRD42025635782)and PRISMA-P flowchart has been elicited in Figure 1.

Discussion

Anticipated Findings

In order to improve respiratory function and decrease respiratory distress in newborns with RDS, this systematic review methodology attempts to thoroughly assess physiotherapy therapies. Numerous physiotherapy strategies, such as posture interventions, respiratory muscle training, airway clearance techniques, and chest physiotherapy, will be methodically

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examined in this study. Clinical recovery parameters, oxygen saturation levels, mechanical ventilation time, and respiratory function indicators will be the main emphasis of the outcome measures. The methodology includes conducting a thorough literature search, defining precise inclusion and exclusion criteria, evaluating the caliber of studies, and, when appropriate, performing a meta-analysis. The lack of high-quality neonatal physiotherapy studies, possible diversity in therapeutic protocols, ethical research limitations, and the requirement for standardized evaluation techniques are some of the difficulties that researchers foresee. The ultimate objective of the protocol is to offer evidence-based perspectives on the efficacy of physiotherapeutic methods for treating respiratory distress.

Strengths and Limitations

The Meta-Analyses and Systematic Reviews of Observational Studies (MOOSE) standards and the PRISMA-P were used in the design of this study. The 2 independent reviewers will choose the studies, and a third reviewer will facilitate any disputes over data extraction and study inclusion. The literature will only contain English-only texts due to translation restrictions, which will decrease the total amount of data that may be extracted. In addition to outlining any knowledge gaps, the study will serve as a direction for future research into these areas if there was not enough data available for extraction and analysis. Although there may be a significant chance of bias due to the inclusion of nonrandomized studies, this will be addressed as a restriction in our systematic review and provide valuable information for future work. This systematic review is expected to demonstrate that physiotherapy interventions, including respiratory muscle training, chest physiotherapy, airway clearance techniques, and positioning, improve respiratory function and lessen respiratory distress in neonates with RDS. Our hypothesis is that these interventions will be linked to better overall respiratory outcomes, higher oxygen saturation levels, shorter periods of mechanical ventilation, and superior clinical recovery measures. Depending on data availability and homogeneity, this may involve a meta-analysis in addition to a comprehensive literature search, well-defined inclusion and exclusion criteria, and a quality assessment of chosen studies.

Conclusions and Direction for Dissemination

In neonates with RDS, the systematic review may offer important new information about the safety and effectiveness of physical therapy therapies for enhancing respiratory function and lowering discomfort. The results could help update neonatal care guidelines and best practices, making sure that therapies are safe and effective for this susceptible group. The findings of this review will be essential for sharing with medical professionals via peer-reviewed journals, clinical conference presentations, and incorporation into university curricula. Furthermore, presenting the results in easily comprehensible formats such as policy briefs, infographics, and webinars can involve a wider range of stakeholders, such as advocacy organizations and health care policy makers. This comprehensive strategy will guarantee that the information reaches every segment of the health care system, impacting clinical practice as well.

Dissemination Plan

The dissemination plan is listed as follows:

1. Academic dissemination: This study will be presented at conferences for physiotherapy and newborn care and also be published in high-impact journals. Creating policies or suggestions for newborn health care professionals is known as clinical implementation.
2. Public and policy engagement: working together with health care groups to make sure that results influence policy choices pertaining to neonatal care.
3. Open access and media outreach: to increase the systematic review's reach, make it publicly available and use press releases or social media sites.

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Authors' Contributions

Conceptualization: SH, IQ.
Data curation: SH, SD.
Funding acquisition: SH, RR.
Investigation: SH, IQ, PW.
Methodology: SH, IQ, SD.
Project administration: SH, RR.
Software: SH, NB.
Supervision: IQ, RR.
Validation: SH, IQ, RR.
Visualization: SH, IQ, RR.
Writing – original draft: SH.
Writing – review & editing: SH.

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Conflicts of Interest

None declared.

Checklist 1
PRISMA-P checklist.
[PDF File, 144 KB - resprot_v14i1e71854_app1.pdf]

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Abbreviations

ABG: arterial blood gas
CPAP: continuous positive airway pressure
GRADE: Grading of Recommendations, Assessment, Development, and Evaluation
MeSH: Medical Subject Headings
MOOSE: Meta-Analyses and Systematic Reviews of Observational Studies
NRDS: neonatal respiratory distress syndrome
$PaCO_2$: partial pressure of carbon dioxide
PaO_2: partial pressure of oxygen
PICO: Population, Intervention, Comparison, Outcome
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
RCT: randomized controlled trial
RDS: respiratory distress syndrome

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ROBINS-I: Risk Of Bias in Non-randomized Studies-of Interventions
SpO_2 : oxygen saturation levels

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Protocol

Research Participants' Engagement and Retention in Digital Health Interventions Research: Protocol for Mixed Methods Systematic Review

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Abstract

Background: Digital health interventions have become increasingly popular in recent years, expanding the possibilities for treatment for various patient groups. In clinical research, while the design of the intervention receives close attention, challenges with research participant engagement and retention persist. This may be partially due to the use of digital health platforms, which may lack adequacy for participants.

Objective: This systematic literature review aims to investigate the relationship between digital health platforms and participant engagement and retention in clinical research. It will map and analyze key definitions of engagement and retention, as well as identify design characteristics that influence them.

Methods: We will carry out a mixed methods systematic literature review, analyzing qualitative and quantitative studies. The search strategy includes the electronic databases PubMed, IEEE Xplore, CINAHL, Scopus, Web of Science, APA PsycINFO, and the ACM Digital Library. The review will encompass studies published between January 2018 and June 2024. Criteria for inclusion will be the presence of digital health care interventions conducted through digital health platforms like websites, web and mobile apps used by patients, and informal caregivers as research participants. The main outcome will be a narrative analysis with key findings on the definitions of participant engagement and retention and critical factors that affect them. Quality assessment and appraisal will be done through the Mixed-Methods Assessment Tool. Data analysis and synthesis will follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 flow diagram. Quantitative data will be qualified and integrated into qualitative data, which will be analyzed using thematic analysis and synthesis.

Results: The study expects to map and summarize critical definitions of participant engagement and retention, and the characteristics of digital health platforms that influence them. The systematic review is expected to be completed in June 2025.

Conclusions: This systematic review will contribute to the growing discussion on how the design of digital health intervention platforms can promote participant engagement and retention in clinical research.

Trial Registration: PROSPERO CRD42024561650; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=561650

International Registered Report Identifier (IRRID): PRR1-10.2196/65099

(JMIR Res Protoc 2025;14:e65099) doi:10.2196/65099

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KEYWORDS

clinical research informatics; participant engagement; participant retention; clinical research; mobile application; digital platforms; mobile phone

Introduction

In 2022, over 100,000 health care mobile apps were available in Apple and Google app stores combined [1]. Digital health care has transformed care delivery through a diverse fleet of technologies, from mobile apps and wearable devices to biosensors and the Internet of Things [2]. It offers a myriad of innovative ways to provide treatments, monitor health conditions, assist, and empower patients with diverse needs to be more in charge of their health, and enable health care professionals to deliver better service [3]. Following the expansion of the digital health care range, digital health (DH) interventions have also increased exponentially (Textbox 1). DH interventions are interventions delivered through digital technology for the treatment or management of physical or mental conditions [4].

Textbox 1. Key concepts.

Digital health intervention

- Interventions are delivered through digital technologies such as smartphones, websites, wearables, video games, or text messaging [2,5,6]. A digital health intervention offers guidance, information, and support for a diversity of physical or mental health conditions through a digital platform. Also commonly referred to as health informatics or eHealth interventions [7]; they are designed to help people avoid, recover from, or cope with disease and disability or to improve the quality and safety of health care [8], for example, as self-help or self-guided eHealth interventions [9,10].

Digital health platforms

- Websites, web-based or mobile apps used to access digital health interventions.

Digital clinical research

- Clinical research is conducted through digital health platforms. It may include digital health interventions, digital data collection, and electronic Case Report Forms, among other resources. Only digital clinical research encompassing digital health interventions will be considered for this study.

Research participant

- Recipients of intervention; for example, patients or informal caregivers.

Participant engagement

- Length and depth of participant's involvement with the digital health intervention.

Participant retention

- Duration and continuity of the participant's involvement with the digital health intervention.

Through online treatments, DH interventions promise to improve health care, enhancing accessibility, effectiveness, and personalization [2,11]. DH interventions are available in commercial applications, as easily accessible health care, and as part of clinical research (Figure 1). When conducted as part of clinical research, they share the same benefits as general digital health care. DH interventions also allow for the development of effective treatments for more patients [11], are more community-inclusive [12], decrease health disparities [13], and improve study generalizability and validity [14,15]. Successful clinical research generates evidence that, in turn, promotes health care improvements [16].

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Figure 1. Digital health interventions are part of general digital health care and clinical research. The latter can be delivered through clinical research informatics or commercial health platforms and software.

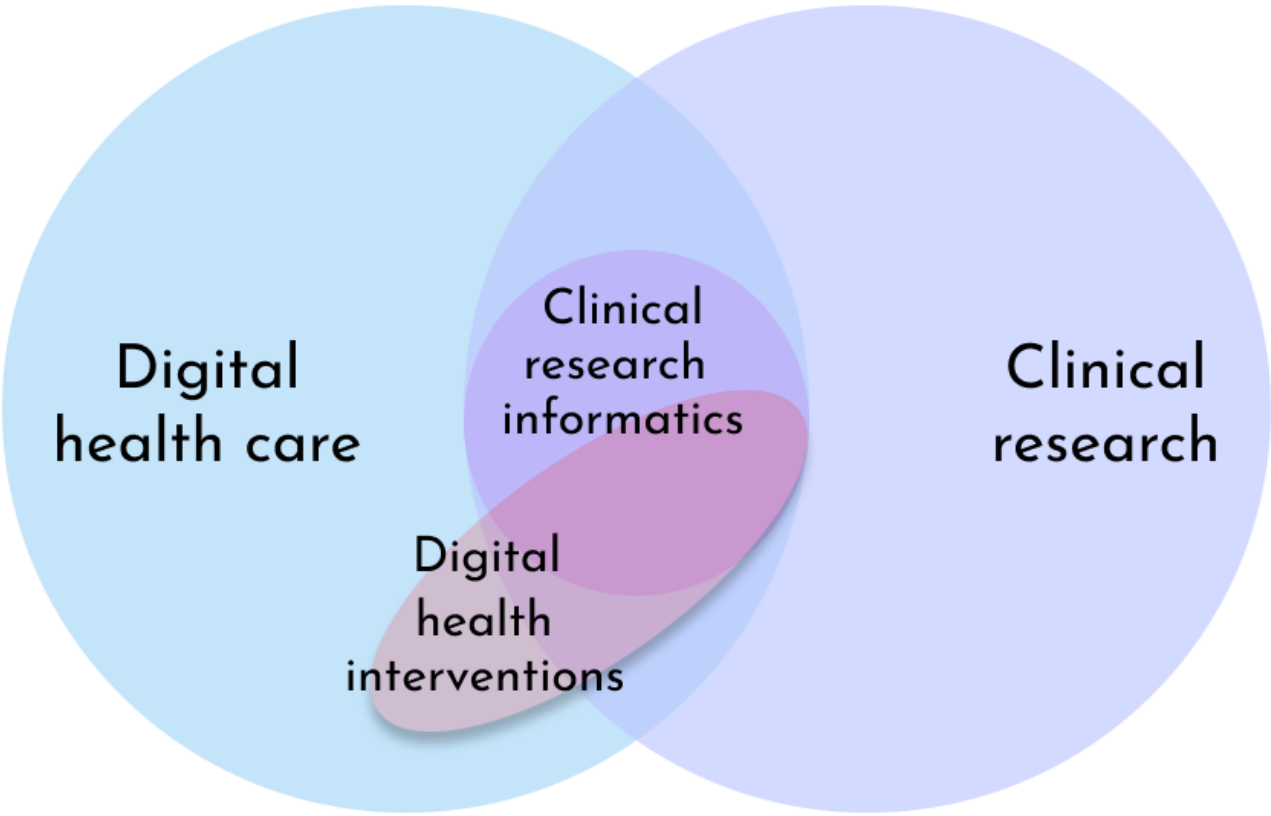

In clinical research, DH interventions are designed following the principles of clinical research informatics (CRI) [4]. CRI is the use of informatics principles and techniques to conduct clinical research [4]. DH interventions have the potential to accelerate the process from initial research to "real world" outcomes, contributing to increasing scale and distribution, cost and resource optimization, and facilitating financial auditing processes [12,16-18]. These principles could also be applied to DH interventions.

Both engagement and retention of clinical research participants are crucial intervention research outcomes, but the concepts have varying definitions. Frequently, different terms for engagement are used interchangeably, like involvement, participation, acceptability, and completion rates, among others. Engagement can be described as the extent and manner in which people actively use a resource [19]. Perski et al [20] define engagement as two main concepts: (1) a subjective experience, meaning a state of focus and interest with a temporal dissociation, and (2) a behavior, described as usage over time. It is often connected to concepts like adherence, duration, and frequency that can be quantified through concrete measurements like opening or using a mobile app, frequency of times, or the duration of the use [21]. Participant retention, in turn, refers to the proportion of recruited participants who remained in the study until its end and at an optimal proportion that does not compromise the study's validity [22,23].

In DH intervention research, both engagement and retention can vary considerably. Intervention dropout from internet-based treatment for psychological disorders, for example, fluctuates between 30% and 50% [24]. While poor engagement or retention may be due to the intervention quality or outside factors, an often-overlooked component is the design of DH platforms. Appraising the DH platforms' design choices and how they impact participant engagement and retention could help make DH interventions better. In this context, there is an untapped opportunity to explore the practical factors that affect intervention success. This systematic literature review will focus on DH platforms' design choices concerning engagement and retention and their relationship with research participants' behavior.

The relationship between DH platforms and research participants is receiving growing interest, as evidenced by the increase in research. Studies have examined participant engagement and retention across various settings, for example, mHealth or web-based platforms [21,25], focusing on particular patient groups, for example, older adults with dementia or digital mental health interventions [26-29].

Still, a comprehensive literature review on the relationship between DH interventions and participant engagement and retention in digital clinical research has yet to be conducted. This review aims to fill the gap by studying DH platforms that have been used in digital clinical research. We will map the various definitions that capture the engagement and retention of research participants in DH interventions. We will further identify platform design factors and features that hinder or promote participants' engagement and retention. The key concepts relevant to the review are defined in Textbox 1.

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Methods

This systematic review was submitted for registration with the International Prospective Register of Systematic Reviews (PROSPERO) on June 8, 2024 (CRD42024561650), to avoid bias in conducting and reporting findings. According to the study's progress, amendments will be made if necessary [30].

Review Question

The review question was elaborated using the Population-Exposure-Outcome (PEO) statement, as outlined in Textbox 2. We chose to apply the PEO as it is regarded as the more appropriate approach for qualitative inquiries [31]. It is also more suitable for the definition of associations between particular exposures and factors and related outcomes [32]. The overall review question is: What factors and aspects promote research participants' engagement with and retention in DH interventions in digital clinical research? This was further broken down into 2 specific research questions:

Research question 1: How are engagement and retention of research participants defined in DH interventions conducted for clinical research?

Research question 2: What user interface elements, interaction design, and platform characteristics influence research participants' engagement and retention in DH interventions?

Textbox 2. Population-exposure-outcome structure.

Population-exposure-outcome element and description
Population
Research participants who are patients, informal or family caregivers.
Exposure
User interface, interaction elements, and platform characteristics of digital health interventions conducted in clinical research.
Outcomes
Engagement and retention of research participants.

Methodology Choice Rationale

The choice to perform a mixed methods systematic literature review is due to the number of individual studies that have already been conducted in digital health care and DH interventions, providing substantial evidence for the review.

The methodology selected for this systematic literature review is the mixed methods systematic review (MMSR) [33]. It is a standard approach that allows to systematically combine qualitative and quantitative data [34]. By integrating the findings of effectiveness (quantitative data) with findings on participants' experiences (qualitative data), MMSR offers a comprehensive evaluation with balanced data insights [35].

We plan to carry out the MMSR as we expect both data types to be prevalent in the reviewed studies. By including both data types, we will adopt a holistic approach to defining engagement and retention. For instance, qualitative data can shed light on the context, patient and informal caregivers' experiences, and barriers to engagement and retention, which quantitative data alone may not fully capture.

Search Strategy

We will analyze studies that (1) offered a DH intervention; (2) used a DH platform component, such as a mobile app, website, or text-messaging process; (3) collected engagement and retention-related measurements–quantitative, qualitative, or both; and (4) presented a digital interface to the research participants—patients, and informal caregivers—to interact with the DH intervention. The DH platforms can be designed specifically for clinical research or not. Commercially available health applications will be considered if they are used for clinical research purposes.

The search strategy for this systematic literature review was developed in collaboration with Görel Sundström, a librarian from Uppsala University, and the researchers involved in this study, LT, AK, MH, and MIM.

The PEO statement was used to construct the search strategy (Table 1). The keywords refinement process involved different approaches: tests conducted by the librarian, consultation of referenced articles to analyze the keywords they used, and expert reviews conducted by the research team. The keywords selection process was performed to ensure the search would capture studies using various terminologies to address the same research questions (Multimedia Appendix 1).

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Table 1. Preliminary Web of Science search strategy (to be adapted for the other databases).

Search number	Database search algorithm
User engagement, user retention, and metrics	
1	(“active user*” OR Attrition OR “Click rate” OR “Completion rate*” OR “Frequency of use” OR “Follow up” OR Login OR “log in” OR “Returning user*” OR “Session duration” OR “Sign in” OR “Study complet*” OR “Time spent” OR usage OR “User actions” OR “Use Rate*” OR “User metric*” OR “user session*”)
2	((Caregiver* OR “Healthy Volunteer*” OR “Research Subject*” OR participant* OR patient* OR subject* OR user*) NEAR/3 (accept* OR activit* OR adher* OR attitude* OR barrier* OR challeng* OR complian* OR discontinu* OR Disengagement* OR Dropout* OR Efficien* OR Effectiveness OR engag* OR evalutation* OR experience* OR Finish* OR involvement* OR interaction* OR obstacle* OR participation* OR perception* OR perspective* OR retention* OR satisf* OR visit* OR view*))
3	1 OR 2
Clinical research informatics and digital care	
4	(“Clinical informat*” OR “Clinical research informat*” OR “Clinical trials informatic*” OR CRI OR “digital care” OR eHealth OR e-health OR etherap* OR “e-Mental health” OR “Health informati*” OR iCBT OR “Internet Cognitive Behavioral Treatment*” OR “medical informatics*” OR mHealth OR m-health OR mtherap* OR m-therap* OR “Online Clinical Trial*” OR telerehabilitation)
5	((“clinical research” OR “clinical trial*” OR “medical research” OR health OR intervention* OR psychotherap* OR therap* OR “self-help program*” OR treatment*) NEAR/3 (Computer* OR cyber OR Digital OR electronic OR informatics OR Internet OR Mobile OR Online OR Smartphone OR “Technology Based” OR “Web based”))
6	4 OR 5
Design and aspects of software or digital platform	
7	(“Interaction design*” OR Interface OR Usability OR “User centered design*” OR “Visual design*”)
Combining all topics	
8	3 AND 6 AND 7

The search will be conducted across a range of electronic databases: PubMed, IEEE Xplore, CINAHL, Scopus, Web of Science, APA PsycINFO, and the ACM Digital Library. These databases are chosen based on their relevance to the research topic and their widespread use in academic and research communities.

In addition to the electronic database searches, the research team will use additional search methods to identify potential studies that may not be captured through the database searches. It includes hand search, which involves manually scanning relevant journals; back-forward citation tracking, where we examine the references of identified articles; and reference checking to ensure no valuable sources are overlooked during the review process.

This systematic literature review will not involve collecting sensitive personal data.

Study Selection Criteria

The PEO statement was used to outline the eligibility criteria for study inclusion and exclusion, delineating them by population, exposure, and outcomes (Table 2).

Table 2. Population-exposure-outcome inclusion and exclusion criteria.

PEO[a]	Inclusion criteria	Exclusion criteria
Population	Research participants, study participants, patients, informal caregivers, carers, caregivers, and users. No exclusion based on age or gender.	Researchers, physicians, doctors, nurses, social care workers, social workers, dentists, and health care professionals.
Exposure or environment	User interface and interaction design of DH platforms.	Engagement and experience related to the intervention or treatment itself. Experience with content quality (text and multimedia content).
Outcomes	Engagement and retention to the study.	Efficacy of the treatment, efficacy related to the intervention or treatment itself.
Study methods	Qualitative methods, quantitative methods, mixed methods.	Reviews (systematic, scoping, meta-analysis, etc)
Publication types	Formally published peer-reviewed journal articles, conference papers.	Grey literature, opinion pieces, protocols, reviews
Geographical considerations	Initially not limited to any geographical area.	

[a]PEO: Population-exposure-outcome.

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Types of Studies

Qualitative Studies

Qualitative interviews, focus group discussions, usability studies, participatory research, participatory design, case studies, grounded theory research, thematic and content analysis of textual data, phenomenological studies, narrative research, and ethnographic observations.

Quantitative Studies

Randomized controlled trials, cohort studies, longitudinal studies, experimental studies, case-control studies, cross-sectional studies, and observational studies.

Mixed Methods Studies

Studies integrating qualitative and quantitative data collection and analysis methods within a single research design, encompassing but not restricted to convergent design, sequential explanatory design, and sequential exploratory design.

In the case of studies addressing the same DH intervention and cohort of individuals, only the study with more detailed data regarding engagement and retention-based measurements will be considered, unless the studies present different aspects of the 2 mentioned subjects.

Studies such as gray literature, editorials, letters, opinion papers, and theses and dissertations will be excluded.

Time Period

The study will consider articles published from January 2018 to June 2024. This 7-year publication window was chosen because of the rapid evolution in the technology and health informatics domain. The timeframe also covers DH intervention platforms developed before and after the COVID-19 pandemic [36].

Language

Due to resource constraints, the study will exclusively include articles published in English. The research team acknowledges that this approach limits the inclusion of studies performed in different parts of the world and published in other languages.

Study Screening

First, a search conducted by an independent librarian will identify potentially eligible studies based on predefined keywords that consider the inclusion and exclusion criteria. The results from this initial search will undergo deduplication: Duplicates will be identified and removed using EndNote (version 21; Clarivate), using the Bramer et al [37] guidelines. The remaining studies will then be imported into Covidence [38]. There, data will be screened in two steps: (1) title and abstract screening, and (2) full-text screening. During the first step, at least 2 reviewers will independently review the titles and abstracts, blinded to the authors' names, and each other's review decisions (ie, double-blinded) [38]. After, the potential articles will have their full text screened, filtered, and categorized according to the predefined inclusion and exclusion criteria. In the event of disagreements between the 2 reviewers, at either stage of the review process, a third reviewer (LT) will be consulted to reach a consensus.

Data Extraction

The data extraction will use a standardized data extraction form elaborated by the research team. The form is designed to capture study information such as (1) identification: study ID, authors, year, country, publication type, and analysis type (qualitative, quantitative, and mixed-methods); (2) characteristics: research participants' characteristics, age, sample size, intervention description, digital platform or software, and the medium used; (3) results: engagement and completion measurements, results and findings presented in qualitative and quantitative data, and measurement tools.

Other information may be added as the research team considers it relevant to the analysis. One reviewer will independently extract the data, and a second reviewer will check it for accuracy and completion. The extracted information will be organized in a previously formatted table in Microsoft Excel. Qualitative data regarding results and findings will also be collected. The qualitative data will be analyzed using NVivo (version 14; Lumivero) afterward.

Quality Assessment and Appraisal

The study plans to use the mixed-methods assessment tool (MMAT) for quality assessment and critical appraisal [39]. MMAT provides a systematic approach to assessing quality criteria on a variety of study designs, such as qualitative studies, quantitative randomized controlled trials, quantitative nonrandomized, quantitative descriptive, and mixed-methods studies [40]. Using MMAT, we will evaluate the studies' clarity of the research question, appropriateness of the study design, data collection methods, data analysis, and interpretation of results.

Data Analysis and Synthesis

The study selection procedure will be visualized through the PRISMA 2020 flow diagram, as seen in Figure 2 [41].

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Figure 2. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

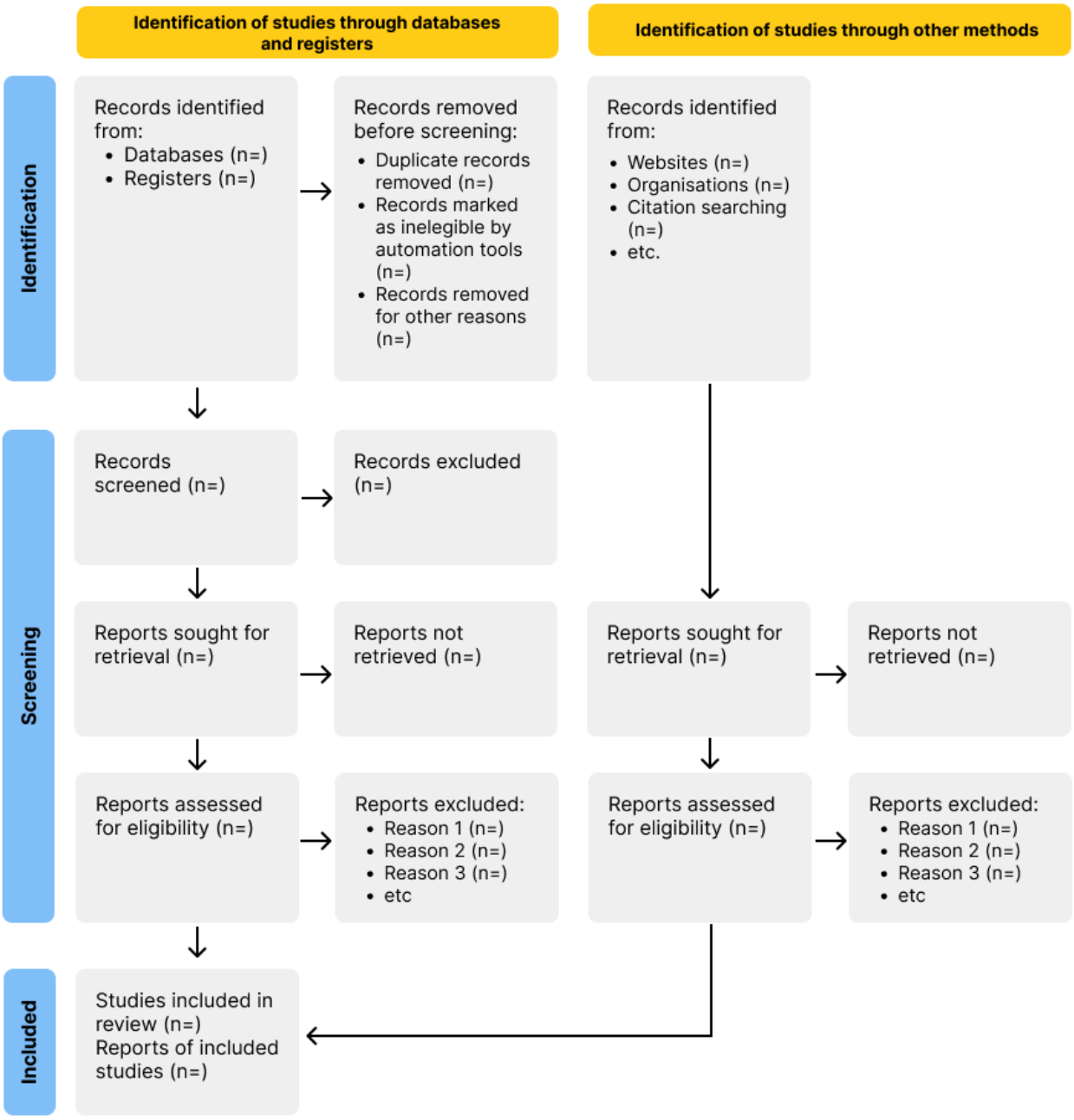

Data related to the identification of a given study and its characteristics will be organized in summary tables. As the review question stipulates the inclusion of a wide range of research designs, including qualitative and quantitative designs, the main results from our investigation will be organized into major themes and subthemes, and key findings on terms will also be presented. If significant differences and patterns arise, such as those related to health conditions, age, or digital literacy, thematic clusters for analysis will be delineated. Since the data will potentially arise from diverse study designs, quantitative data will be submitted to a data transformation process to be qualitized to be converted into qualitative data in the form of themes and categories and afterward summarized in a narrative synthesis to allow further integration with qualitative data [35,42,43]. Once qualitative and quantitative data are integrated, they will be compiled through a thematic analysis in order to identify the main concepts regarding engagement and retention. The codes for this investigation will be developed by one of the reviewers and checked by at least 1 member of the research team. The codes will be built using the Persuasive System Design framework developed by Oinas-Kukkonen and Harjumaa as a basis [44]. Kelders et al [25] have already applied this framework in the digital health area. A total of 2 independent reviewers will conduct the coding, and discrepancies and new codes will be discussed between the 2 reviewers. If no agreement is reached, a third reviewer will be consulted to reach a consensus. Afterward, the major themes and subthemes will be summarized in a narrative synthesis. One of the authors will compose the narrative synthesis, and a second author will assess and provide appraisal.

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Dissemination Strategy

The results of this study will be disseminated as a scientific publication in a peer-reviewed journal and presented at conferences. Plain-language summaries will also be produced to share in various channels, such as social media, ResearchGate, and technology and health care websites.

Ethical Considerations

According to the Ethical Review Data (2003:460) by the Swedish Ethical Review Authority, ethical approval will not be required for this research.

Results

As of June 2024, the literature review has conducted 2 pilot searches to test and refine keywords and verify the initial quality of results. The results are expected to be published as a systematic literature review and submitted for publication in June 2025.

Discussion

Principal Findings

In light of the potential benefits of technology in clinical research, DH intervention design demands further investigation, to mediate the relationship between research participants and the technology. As highlighted by Johnson [45], connected technologies have provided many new opportunities in clinical research in recent years, such as increasing research awareness, recruitment options, and delivering interventions and treatments. Achieving a high rate of participation required to ensure the quality of an investigation is still a challenge. To meet these opportunities, CRI researchers and developers becoming more aware of the importance of developing adequate software for research participants to expand intervention. Although a "user-centric" approach has increased through participant-centered initiatives, digital clinical research is still on the journey to find ways to reduce the time and labor requirements that hinder participant involvement [14,46]. Offering a proper setting to a plurality of participants is fundamental to guaranteeing clinical research quality; otherwise, CRI risks increasing health care inequalities and disparities. DH interventions that do not consider socioeconomic factors such as financial situation, race, ethnicity, age, education, and digital literacy present higher chances of producing intervention-generated inequalities, increasing the digital divide, and may only benefit the already more advantaged populations [6,9,47].

Intervention researchers have long experimented with strategies for engagement and retention. Intervention factors like acceptability and feasibility of devices and technology, system usability, visual design, content, and adaption to literacy levels have been found to affect participant behaviors. These factors commonly influence access conditions by minimizing attrition but do not necessarily guarantee engagement, retention, and adherence. Importantly, engagement and retention may be promoted by factors that pertain to the particular characteristics of the digital platforms and software. Here are included platform usability and design, but also and others are research-based strategies, such as compensation, incentives, or rewards [21]. Interaction features can also incentivize participant's engagement and retention. These could be in the form of (1) gamification, (2) reminders or notifications, (3) social support provided within the DH intervention, (4) personalization, and (5) content tailored to participants' physical and cognitive abilities [21,25,26]. Understanding how platform design choices interact with participant behavior in DH interventions has become a crucial consideration for intervention research.

Limitations

Summarizing the key DH platform factors that affect participant engagement and retention given the variability of intervention designs, target participant groups and DH platform mediums may be challenging. Given the heterogeneity of the reviewed studies, we may have to focus only on some participant populations or DH platforms or include only broad trends in the narrative synthesis. Preliminary research, however, showed that concepts like personalization and fit to participants' conditions and needs are commonly important design factors, as discussed in previous literature [11].

Implications

We foresee that this review will serve as a useful resource to those developing DH interventions, but may not be versed in DH platform design. By summarizing key platform design characteristics that affect participant behavior on the platform and, by proxy, the intervention, the review will be particularly relevant to intervention researchers.

Conclusions

Systematic reviews are considered one of the most informative sources of research evidence and have supported decision-making in health care in recent decades [40,48]. Acknowledging the relevance of this resource, this review aims to contribute to the growing field of digital clinical research and patient-centered design, providing a comprehensive reference for developing more engaging and effective digital platforms and software for clinical research.

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during this study.

Authors' Contributions

LT, AK, and MH contributed to the idea conception. LT wrote the initial manuscript draft. Manuscript revision was performed by LT, AK, MH, and MIM, Visualization was done by LT. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
String searches.
[PDF File (Adobe PDF File), 135 KB - resprot_v14i1e65099_app1.pdf]

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Abbreviations

CRI: clinical research informatics
DH: digital health
MMAT: mixed-methods assessment tool
MMSR: mixed-methods systematic review
PEO: population-exposure-outcomes
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: Prospective Register of Systematic Reviews

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Protocol

Value Cocreation and Codestruction in Digital Health Services: Protocol for a Systematic Review

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Abstract

Background: To successfully design, develop, implement, and deliver digital health services that provide value, they should be cocreated with patients. However, occasionally, the value may also be codestructed. In the field of health care, the concepts of value cocreation and codestruction still need to be better established within emerging digital health services. Studying these concepts is essential for developing effective and sustainable patient-centered care.

Objective: The aim of the study is (1) to understand the antecedents, decisions, and outcomes of value cocreation and codestruction in digital health services, (2) to define the dynamics between value cocreation and codestruction, and (3) to map future research areas of value cocreation and codestruction within digital health services.

Methods: The systematic review will be conducted in accordance with the Joanna Briggs Institute methodology for mixed method systematic reviews and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement. The review considers scientific qualitative, quantitative, or mixed method studies published in English, Finnish, or Swedish that concern either value cocreation or codestruction in digital health services. Studies focusing on physical robotics and online health communities, as well as non–peer-reviewed and nonscientific papers, will be excluded. The searches were conducted using Scopus and MEDLINE during this protocol creation. Critical appraisal will be done using suitable checklists for qualitative, quantitative, and mixed method studies. The review will adhere to a convergent integrated approach as outlined in the Joanna Briggs Institute methodology for mixed methods systematic reviews.

Results: The searches resulted in a total of 837 records. The antecedents, decisions, and outcomes of value cocreation and codestruction in the context of digital health services will be described in a finalized systematic review. In the outcomes, our main interest is the effect on patient outcomes and experiences and professional experiences.

Conclusions: Since our study involves diverse scientific fields, there is a risk that our search does not capture all relevant papers. To mitigate this risk, we used 2 large databases for the searches. In addition, the value cocreation or codestruction terms may not have been used in all studies focusing on the collaborative roles of patients and providers, especially in the medical field, and that may be difficult to capture. The review reveals the current understanding of value cocreation and codestruction in digital

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health services and shapes the research agenda for these phenomena. Value cocreation can be used to both design and efficiently use digital health services trying to maximize the value for patients.

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KEYWORDS

value cocreation; value codestruction; telemedicine; eHealth; systematic review

Introduction

Value cocreation and customers' interactive roles in the service exchange have been essential to understanding how value is created in services [1]. Rapid technological advances and digital transformation are transforming the context in which value is created [2]. Health care services had a significant transformation as digital health services rapidly expanded during the COVID-19 pandemic [3,4]. Digital health services can be defined as the use of information and communication technologies in health care products, services, and processes [5]. Digital services, including telemedicine interventions, mobile health apps, and remote monitoring devices, have been suggested as a potential solution to tackle issues related to accessibility, availability, and health care costs [6,7]. In addition to the technical development, it also changes the way of thinking and how services are provided and perceived [4].

Cocreation, a burgeoning paradigm within management literature, facilitates the joint creation of value by enterprises and consumers through interactive processes [8]. Since the onset of the 21st century, the concept of cocreation has proliferated extensively, evidenced in scholarly discourse and empirical inquiries, thereby challenging established tenets of capitalist economies. In such economies, value traditionally tends to be predetermined prior to market transactions [8,9]. Health care is a complex service where defining and operationalizing value presents significant challenges [10,11]. Since Porter [12] introduced the idea of measuring health care value as patient-relevant outcomes per costs associated with the health problem, the concept has been widely discussed for its potential to unify the objectives of various stakeholders [11]. In the context of digital health services, value may be more closely related to outcomes and experiences, with costs being more pertinent at the system level.

From the standpoint of cocreation, suppliers and customers are no longer perceived as adversaries but rather as collaborators engaging with each other to foster the emergence of novel business prospects [13]. During the last decade, Yi and Gong [14] established the significance of value cocreation behavior, which provides a multidimensional framework encompassing diverse value cocreation activities, such as information seeking, information sharing, responsible behavior, and personal interaction, that help explain how customers and firms, or patients and health care providers in this case, interact and collaborate.

Additionally, the digitalization of services within health care ecosystems is altering how value is created, delivered, experienced, and evaluated [15,16]. Understanding value cocreation and the interactive roles of customers in the service exchange is crucial for comprehending how value is created in services [1], with value cocreation being conceptualized as a joint problem-solving process [17]. For instance, value cocreation in digital health services can be depicted through customer engagement, encompassing emotional, active, and cognitive dimensions [18].

However, value is not always cocreated. Value codestruction signifies that not all interactions and relationships yield positive or value-creating results; occasionally, these engagements may even lead to adverse outcomes [19,20]. Value codestruction refers to an interactive process between service systems that leads to a reduction in the well-being of at least 1 of the systems, which can affect either individuals or organizations depending on the nature of the service system [20]. For example, value codestruction may manifest in the inability to search for, understand, and use health information gathered on the web [21]. Additionally, the assumption that telemedicine can negatively impact doctor-patient relationships inevitably leads to value-in-use destruction [21].

As digital services differ significantly from traditional services, there is a need to understand how to enhance value cocreation between a service provider and its users in digital services [22,23]. Tuunanen et al [23] identified 5 mechanisms to support value cocreation in the design of digital services, namely social use, customer orientation and decision-making, service experience, service use context, and customer values and goals.

In response to evolving population needs, it is evident that the role of patients within digital health services and health care at large has transitioned toward a collaborative partnership between professionals and patients [24,25]. According to Huber et al [26], the definition of health is also changing from "complete mental, physical, and social well-being" toward "the ability to self-manage and adapt." According to van Druten et al [27], a similar multifaceted approach to Huber's concept of positive health was shared by many perspectives. Nevertheless, upon closer examination, it was observed that the core elements of positive health, namely "the ability to adapt and to self-manage," were also acknowledged in other health concepts, regardless of perspective. These health concepts described "the ability to adapt" as, for instance, adjusting to changing physical conditions like aging, illness, or disability, maintaining emotional balance, and viewing health as a dynamic state requiring adaptation to circumstances. "The ability to self-manage" was often described as autonomy or independence. Through the value cocreation process, professionals and patients can make a significant contribution to health outcomes as partners [28]. For example, patients can provide perspectives on areas of the care process

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that are invisible to health care professionals [29,30]. Previous literature has discussed many consequences of value cocreation related to health outcomes, service experience, perceived service quality, and service engagement [31].

While value cocreation has also been studied in health care, less attention has been given to the investigation of value codestruction [29,32]. As the field of health care is constantly becoming more digitalized, examining value cocreation and value codestruction in digital services would provide valuable insights into developing such services. Peng et al [31] conducted a systematic review of value cocreation in health care and digital services before the COVID-19 pandemic. They also encouraged researchers to explore further opportunities for value cocreation in both web-based and hybrid environments. Even so, the review by Peng et al [31] did not address value codestruction, which, in conjunction with value cocreation, could aid in enhancing the efficiency of digital health services. Several authors have highlighted the necessity of gaining a more comprehensive understanding of value codestruction and integrating it with the research on value cocreation [33,34]. Considering the pandemic's impact on digital service expansion [3,4], increasing resource constraints due to rising chronic illnesses, and aging populations [35,36], conducting a new systematic literature review could provide a contemporary perspective on value cocreation in health care. Furthermore, this review aims to provide a more comprehensive understanding of value codestruction.

So as to gain a more current understanding of both value cocreation and value codestruction in digital health services, this review seeks to identify scientific studies published between 2020 and 2024, using the Joanna Briggs Institute's (JBI) guidance for mixed method systematic reviews [37] and adhering to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist for reporting systematic reviews [38] The objectives of the review will be (1) to understand the antecedents, decisions, and outcomes (ADO) of value cocreation and value codestruction, (2) to define the dynamics between value cocreation and value codestruction in digital health services, and (3) to map future research areas of value cocreation and value codestruction within digital health services. To answer the first research question, this review uses a systematic literature review framework, namely, the ADO framework by Paul and Benito [39]. The ADO framework aims to identify the known aspect of any phenomenon, which in the case of this review is value cocreation and value codestruction in the context of digital health services. Our research questions are (1) What are the ADO of value cocreation and value codestruction in digital health services? (2) What are the dynamics between value cocreation and value codestruction in digital health services? (3) What are the most promising future research areas in value cocreation and value codestruction within digital health services?

Methods

Overview

The systematic review will be conducted in accordance with the JBI methodology for mixed method systematic review [37] and the PRISMA statement [38,40] (Multimedia Appendix 1). This protocol has been registered in PROSPERO (International Prospective Register of Systematic Reviews; 549303). During this review protocol, the searches have been conducted, but the screening, quality assessment, and analysis will be carried out in the finalized systematic review.

Search Strategy

Using the search strategy developed by Peng et al [31] as a foundation, adjustments were made to include value codestruction. The search strategy aimed to identify peer-reviewed scientific studies and was conducted in 3 steps. First, to ensure an optimal search strategy for both value cocreation and value codestruction, an initial limited search of MEDLINE and Scopus was conducted on May 21, 2024, which resulted in 48 and 247 papers, respectively. MEDLINE and Scopus were selected since they collectively provide extensive coverage of publications on digital health services, value cocreation, and value codestruction. Second, relevant papers were identified through title, abstract, and index term analysis. An information specialist was consulted during the development of the final search strategy. Keywords were truncated as necessary, and index terms such as MeSH were used in MEDLINE (Multimedia Appendix 2). Additionally, the reference lists of all included studies will be screened to identify additional relevant studies.

Eligibility Criteria

This study will include studies that investigate either value cocreation, value codestruction, or both in digital health services. This review will consider scientific qualitative, quantitative, or mixed method studies. Papers published in English, Finnish, and Swedish will be eligible for inclusion. Only papers published between January 1, 2020, and the present (June 2024) concerning value cocreation were considered, as an earlier review covered the period from 2008 to 2019 [31]. Regarding value codestruction, the limitation period extends from January 1, 2008, to December 31, 2008, since the earlier review did not address value codestruction. Studies focusing on physical robotics, as well as non–peer-reviewed and nonscientific papers, will be excluded.

Study Selection

The results of the search are presented in a PRISMA flow diagram [38]. All citations identified through the described search strategy were compiled and uploaded into Rayyan (Al Rayyan Company), which was also used to remove duplicate entries. Titles and abstracts will then undergo independent screening by 2 team members (NH and JP) using predefined inclusion and exclusion criteria. For papers lacking abstracts, the full text will be obtained. Following the title and abstract screening, potentially relevant studies will be retrieved in full. Two independent reviewers (NH and JP) will thoroughly assess these studies and determine their suitability based on the inclusion criteria. Exclusion reasons will be documented for studies that do not meet the inclusion criteria. Any discrepancies during the study selection or any other process will be resolved through discussion or by consulting a third team member (EL

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and PT). All search methods, strategies, and sources will be detailed or named in the final report, ensuring replicability.

Assessment of Methodological Quality

Before being included in the review, papers will undergo evaluation by 2 separate reviewers (EL and M Vanhanen) to ensure methodological soundness. We will use the JBI checklists for qualitative and quantitative studies and the Mixed Methods Appraisal Tool for mixed method studies [41]. In cases where necessary, authors of papers will be contacted to request missing or additional data to ensure clarity. The outcomes of critical appraisal will be presented both in narrative form and in a table format. Data extraction and synthesis will be conducted for all studies, irrespective of their methodological quality assessment outcomes, whenever feasible.

Data Extraction and Synthesis

Two independent reviewers (EL and M Vanhanen) will extract both quantitative and qualitative data from the studies included in the review. The extracted data will encompass specific details about populations, study methods, phenomena of interest, context, and outcomes relevant to the review questions. Quantitative data will include outcomes derived from descriptive and inferential statistical tests. Additionally, qualitative data will comprise verbatim themes or subthemes accompanied by corresponding illustrations and will be assigned a level of credibility. Authors of papers will be contacted up to a maximum of 2 times to request missing or additional data, as necessary.

Data Transformation

The quantitative data will undergo a process of “qualitization,” which entails transforming it into textual descriptions or narrative interpretations that directly address the review questions.

Data Synthesis and Integration

This review will adhere to a convergent integrated approach as outlined in the JBI methodology for mixed methods systematic reviews. This approach involves integrating the qualitized data with the qualitative data. The assembled data will be categorized and pooled based on similarity in meaning, ultimately generating a set of integrated findings presented as the line of action statements. We will classify the data using the ADO framework [39]. Additionally, we will synthesize the current knowledge of each dimension and formulate a future research agenda based on the findings.

Ethical Considerations

Since concept analyses solely rely on secondary publicly available data sourced from primary research studies, there is no requirement for research ethics approval.

Validity and Rigor

The following activities will be performed to enhance the review’s validity and rigor:

1. Method: The systematic review will be conducted following the JBI guidelines [37] and following the PRISMA statement [38].
2. Search: To increase the reliability of the review, an information specialist with expertise in health care, value cocreation, and value codestruction will be consulted. Additionally, several database sources will be included in the final search to ensure the richness of the data to be analyzed.
3. Screening, data extraction, and synthesis: Each of the previously mentioned phases will be conducted independently by at least 2 independent team members (NH and JP), which will enhance the reliability of the review.
4. Process: The research team members (EL, TT, M Vanhanen, NH, JP, MJ, M Vesinurm, and PT) will continuously review the paper during ongoing meetings throughout the process.

Results

The review started in May 2024 and will be completed in a time frame of 8 months. This time phase includes the following phases: screening, data extraction, quality assessment, and data synthesis. The literature search was conducted entirely during the review protocol process and reported in the PRISMA diagram. The final search in MEDLINE and Scopus on June 6, 2024, resulted in 58 and 770 papers, respectively (Figure 1). As Peng et al [31] omitted value codestruction in their search, a supplementary search focusing exclusively on value codestruction was conducted on September 19, 2024, covering the years 2008 to 2019. This search yielded 9 papers from Scopus and none from MEDLINE. In total, 837 records were detected. The systematic review is anticipated to be ready for submission by December 2024.

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Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

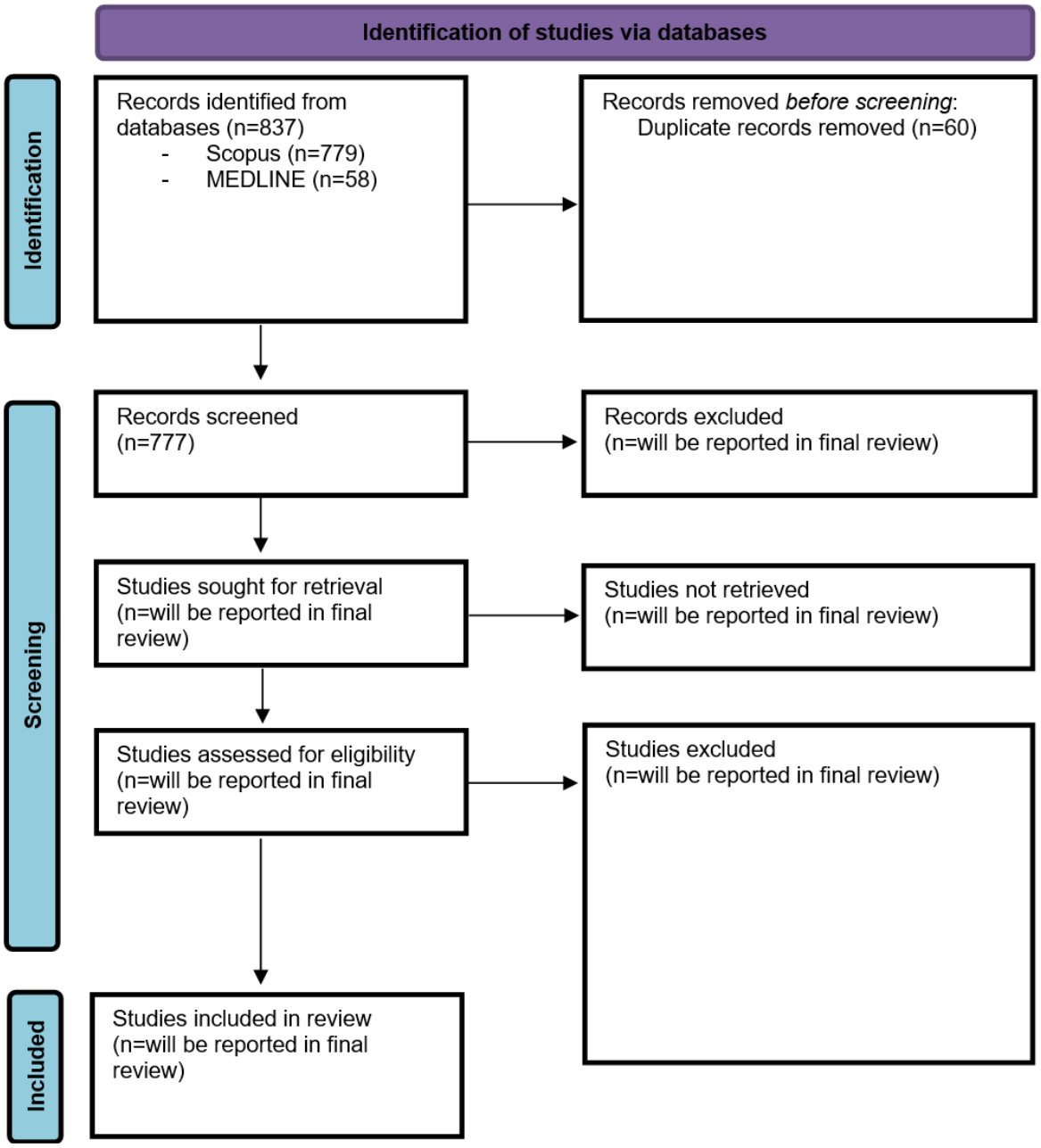

Discussion

Principal Findings

Our review will reveal the current understanding of value cocreation and codestruction in digital health services and shape the research agenda for these phenomena. In their review, Peng et al [31] focused on studies published prior to the COVID-19 pandemic, a period after which the number of digital health services has significantly increased. Consequently, our review will provide the most recent insights into value cocreation and value codestruction within digital health services. The ADO framework [39] assists in producing a knowledge map outlining the associations between ADO of value cocreation and codestruction in the context of digital health services. The ADO of value cocreation and codestruction will be described. In the outcomes, our main interest is the effect on patient outcomes and experiences and professional experiences. The more detailed results will be determined based on the finalized review.

Value cocreation can be used in both designing as well as the efficient use of digital health services trying to maximize value for patients. In other digital services, value cocreation and codestruction have been studied more thoroughly, as most of the services nowadays are digital, and the world has already been described as digital-first [42].

As the field of health care is constantly more digitalized, examining value cocreation and codestruction in digital services would provide valuable insights into developing such services. To support the cost-effectiveness of the services and try to minimize the effects of digital exclusivity, it is crucial to understand value cocreation and codestruction better in digital health services.

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Strengths and Limitations

Since our study is crossing the scientific fields, there is a risk that our search does not capture all relevant papers. To mitigate this risk, we include multiple databases for the searches. However, only peer-reviewed studies will be included in this review, which excludes gray literature [43]. In addition, the value cocreation or codestruction terms may not have been used in all studies focusing on the collaborative roles of patients and providers, especially in the medical field, and that may be difficult to capture.

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Data Availability

The datasets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

The review protocol was conceived and supervised by EL and PT. EL, TT, MJ, M Vanhanen, NH, JP, M Vesinurm, and PT planned the review and formed the aim and research question. PT, NH, and JP developed the search strategy and conducted the search. EL, NH, JP, and PT screened papers. EL and PT drafted the main text. All authors contributed revisions.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-S (Preferred Reporting Items for Systematic reviews and Meta-Analyses Literature Search Extension) checklist.
[DOC File , 159 KB - resprot_v14i1e63015_app1.doc]

Multimedia Appendix 2
Search strategy.
[DOC File , 164 KB - resprot_v14i1e63015_app2.doc]

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Abbreviations

ADO: antecedents, decisions, and outcomes
JBI: Joanna Briggs Institute
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Register of Systematic Reviews

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Protocol

Evaluating Online and Offline Health Information With the Patient Education Materials Assessment Tool: Protocol for a Systematic Review

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Abstract

Background: The Patient Education Materials Assessment Tool (PEMAT) is a reliable and validated instrument for assessing the understandability and actionability of patient education materials. It has been applied across diverse cultural and linguistic contexts, enabling cross-field and cross-national material quality comparisons. Accumulated evidence from studies using the PEMAT over the past decade underscores its potential impact on patient and public action.

Objective: This systematic review aims to investigate how the quality of patient education materials has been assessed using the PEMAT.

Methods: This review protocol follows PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) guidelines. PubMed, MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), APA PsycInfo, and Web of Science Core Collection will be searched systematically for articles published since September 2014. Two independent reviewers will conduct the search to yield a list of relevant studies based on the inclusion and exclusion criteria. Rayyan QCRI software will be used for screening and data extraction.

Results: The results will be included in the full systematic review, which is expected to start in September 2024 and be completed to be submitted for publication by early 2025.

Conclusions: The findings are expected to identify the quality of materials evaluated by the PEMAT and the areas under evaluation. This review can also highlight gaps that exist in research and practice for improving the understandability and actionability of the materials, offering deeper insights into how existing materials can facilitate patient and public action.

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KEYWORDS

patient education; health communication; health information; behavior change; understandability; actionability Patient Education Materials Assessment Tool; PEMAT; medical information; health literacy; patient education materials

Introduction

Patient education materials, such as brochures, websites, videos, and apps that provide health and medical information to patients and the general public, are used in various clinical and public health areas. Given the known relationship between health literacy and health outcomes [1], assessing the quality and usefulness of the materials to patients or general public is

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worthwhile. Particularly, Healthy People 2030 emphasized organizational health literacy [2], which represents organizational competencies that enable people to access, understand, appraise, and use health information and services [3].

Therefore, medical institutions, companies, and government agencies providing health care information need to produce higher quality materials to support the health behaviors of patients and the general public.

A range of tools have been designed to assess the effectiveness of patient education materials. Garner et al [4] outlined a three-step process that characterizes the audience's interaction with such materials: (1) reading to the end, (2) constructing a coherent understanding, and (3) responding to the content. In response to these processes, they introduced an evaluation framework of readability, comprehensibility, and communicative effectiveness [4]. Among these 3 factors, readability formulas, which focus on the aspect of "reading to the end," have been used since the 1930s. Later, following the establishment of the concept of health literacy, comprehensibility indicators were developed to assess whether materials align with audience's health literacy demands. These indicators consider not only the wording of the material but also its structure and style; notable examples include suitability assessment of materials [5] and the CDC (Centers for Disease Control and Prevention) Clear Communication Index [6]. However, understanding the material alone is insufficient; a separate evaluation is necessary to determine whether audience can translate the material's content into actionable behavior.

The Patient Education Materials Assessment Tool (PEMAT) is a reliable and validated tool to evaluate and compare the understandability and actionability of patient education materials [7,8]. Understandability refers to the likelihood that the reader or viewer will be able to understand and explain the material's key messages. Actionability refers to the likelihood that the reader or viewer will know how to act on the information presented in the material. The PEMAT calculates a material's understandability and actionability scores as a percentage. There are 2 types of PEMAT: PEMAT-P for printable materials and PEMAT-A/V for audiovisual materials. The PEMAT consists of 26 items in total. For PEMAT-P, items 1-12 and 15-19 assess understandability, while items 20-26 evaluate actionability. For PEMAT-A/V, understandability is assessed using items 1, 3-5, 8-14, and 18-19, while actionability is evaluated with items 20-22 and 25. On the practical side, the PEMAT visualizes the challenges of materials to find the most understandable and actionable materials among the many available. It also supports experts in improving their materials. The original version of the PEMAT was developed in 2013 [7], and as of 2024, Brazilian Portuguese [9], Bahasa-Malay [10,11], Japanese [12], Chinese [13], and Turkish [14] versions are available. The PEMAT has been used to analyze materials for patients of various cultural and linguistic backgrounds, allowing quality comparisons of materials across clinical fields and nations. For example, our study on internet-based materials for Japanese patients with chronic kidney disease found that, unlike trends in English-speaking countries, materials published by for-profit companies were easier to understand and act upon than those published by public organizations [15].

Despite the large number of PEMAT analyses, to date, previous studies have not systematically integrated and compared the findings obtained by the PEMAT. In addition, scoping reviews have comprehensively introduced indicators for assessing the quality of health care information [16-18]; however, no systematic reviews have assessed the understandability and actionability of patient education materials using the PEMAT. This study reviews how the quality of materials has been assessed using the PEMAT in previous patient education materials. We pose the following research questions: "in which areas (eg, clinical areas, types of media, and target populations) have patient-education material quality assessment studies been conducted using the PEMAT?" "what is the degree of understandability and actionability of materials based on the PEMAT in previous studies?" and "what gaps in research and practice should be filled in the future? (eg, in which areas should understandability and actionability of materials be examined and in which areas should understandability and actionability be improved?).

Methods

Study Design and Registration

We designed the study protocol following the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) guidelines [19]. A PRISMA-P checklist is available as Multimedia Appendix 1. Once this protocol is accepted for publication in a peer-reviewed journal and fixed, it will be registered with the International Prospective Register of Systematic Reviews (PROSPERO). We plan to begin the literature search on September 1, 2024, and complete the analysis by late 2024.

Literature Search

We will search the following databases: PubMed, MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), APA PsycInfo, and Web of Science Core Collection. We will search abstracts and titles using a combination of keywords related to previous studies: (PEMAT) OR (Patient Education Materials Assessment Tool) OR (understandability) OR (actionability) OR (comprehensibility). Since the development study of the original version of the PEMAT was published in September 2014, the inclusion period will be limited to September 2014 through September 2024. Details of search queries in each database are shown in Table 1. We will import all search results into Rayyan QCRI software to ensure a systematic literature selection process [20]. We will include all publications covered from the time the database search is initiated to the time of the final search. We will search the reference lists of identified eligible studies to supplement the database searches and identify any additional potentially eligible literature.

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Table 1. List of search queries.

Database	Interface	Search queries
PubMed	NLM	(“PEMAT”[All fields] OR “patient education materials assessment tool”[Title/Abstract] OR “understandability”[Title/Abstract] OR “actionability”[Title/Abstract] OR “comprehensibility”[Title/Abstract]) AND (2014/9/1:2024/6/30[pdat])
MEDLINE	Web of Science	(pemat) OR (AB patient education materials assessment tool) OR (AB understandability) OR (AB actionability) OR (AB comprehensibility) Limit - Publication date: 20140901-20240631
Web of Science	Web of Science	(ALL= (PEMAT))) OR AB=(patient education materials assessment tool)) OR AB=(understandability)) OR AB=(actionability)) OR AB=(comprehensibility)) Timespan: 2014-09-01 to 2024-06-30
CINAHL	EBSCOhost	(pemat) OR (AB patient education materials assessment tool) OR (AB understandability) OR (AB actionability) OR (AB comprehensibility) Limit - Publication date:20140901-20240631
APA PsycInfo	EBSCOhost	(pemat) OR (AB patient education materials assessment tool) OR (AB understandability) OR (AB actionability) OR (AB comprehensibility) Limit - Publication date:20140901-20240631

Inclusion and Exclusion Criteria

This proposed systematic review covers studies that analyzed health and medical information by the PEMAT. The inclusion and exclusion criteria are as follows (Textbox 1):

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

Evaluating patient education materials or decision aids (brochures, website, videos, apps, social networking posts, and artificial intelligence tool responses).

Using the Patient Education Materials Assessment Tool (PEMAT) as an evaluation tool.

Published in peer-reviewed scientific journals.

Exclusion criteria

Intervention studies using PEMAT or brush up on existing educational materials by PEMAT.

Articles on the development of original and translated versions of PEMAT.

Systematic review or meta-analysis.

Patient education material itself.

Non-English articles.

Not published in full text.

Screening of Studies

We will conduct study selection using Rayyan QCRI software [20]. Two independent reviewers [EF and ML] will screen the titles and abstracts of all studies initially identified according to the eligibility criteria. Disagreements will be resolved by consensus; the opinion of a third reviewer [HO] will be sought when necessary. A PRISMA-P flow diagram will outline the number of included and excluded studies in each stage of the study (Figure 1 [19]).

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Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of the studies.

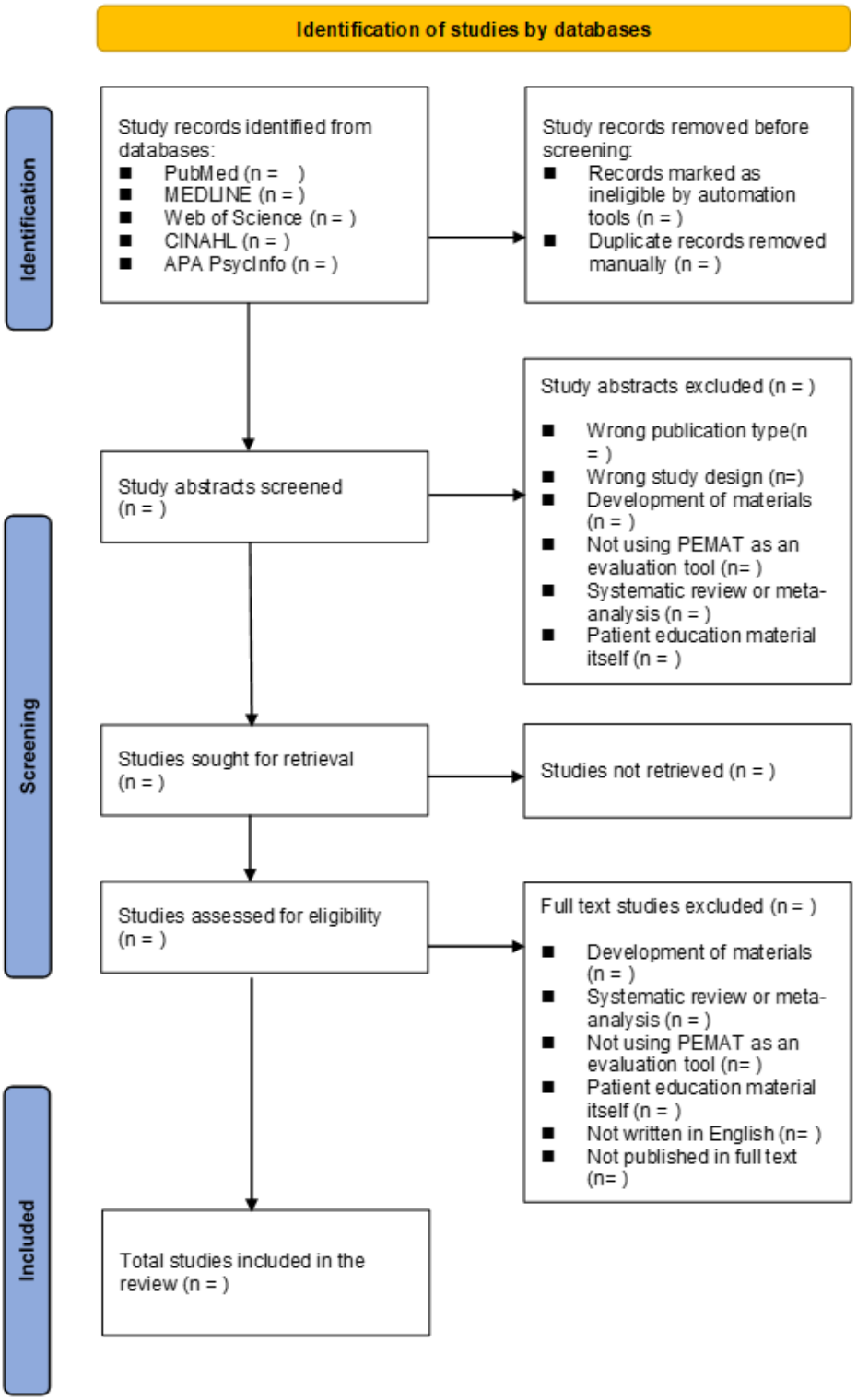

Data Extraction

The extracted data will include study characteristics (eg, author, year of publication, country, type of publication, and study design), material characteristics (eg, intended audience, language, number, media [eg, text, audio, and video], clinical field, and type of source), evaluation methods (eg, evaluation tools or indicators alongside the PEMAT, the evaluators' expertise, and material evaluation by the audience [if any]), and main results of the evaluation (eg, PEMAT scores, scores of other tools or indicators, quantitative or qualitative material evaluation by audience [if any]), and a summary of the characteristics of contributing studies will be tabulated in the above order.

Data Synthesis

The numerical summary will describe the characteristics of the included studies. We will summarize the findings in tables and

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synthesize them in a descriptive, narrative review, using the framework to answer the research questions. We will use descriptive statistics (means, SDs, and proportions) to summarize the characteristics of the retrieved studies. PEMAT scores are expressed as 0%-100% and therefore, considered continuous variables. We will express the estimate of the PEMAT score as the mean difference with 95% CI.

We will conduct subgroup analyses based on material type, clinical field, and type of source as these group comparisons are essential to explore the determinants of material quality. We perform a test of normality when integrating the data. When data are normally distributed, we will use ANOVA for subgroup analysis. If significant differences are found, we will use Tukey multiple comparisons. When data are not normally distributed, we will use the Kruskal-Wallis test. For a post hoc comparison, a 2-arm comparison using the Mann-Whitney U test will be performed with Bonferroni adjustment. We will conduct all statistical analysis using R software (version 4.4.0; R Foundation for Statistical Computing).

For each study, we will assess heterogeneity using a tool for assessing Risk Of Bias due to Missing Evidence in a synthesis (ROB-ME) [21]. ROB-ME provides a systematic method for evaluating the risk of bias when particular methods or results within studies are missing from a meta-analysis due to the *P* value, magnitude, or direction of the study results. Although the studies included in this view are not systematic reviews in a strict sense, their authors have included multiple materials and conducted “reviews” based on certain indicators. The ROB-ME can be used to evaluate the appropriateness of the inclusion criteria and consistency of the description of the results in the included studies. The risk of bias will then be integrated with ROBVIS, a risk-of-bias assessment summary table [22].

Ethical Considerations

This study will be exempted from the Research Ethics Committee of The University of Tokyo Graduate School of Medicine and Faculty of Medicine as the studies under review are publicly accessible and do not involve patient records.

Results

The results will be included in the full systematic review, which started in December 2024 and be completed to be submitted for publication by early 2025.

Discussion

Principal Findings

Since the development of the PEMAT a decade ago, evidence of studies that have evaluated materials using the PEMAT has accumulated. This review is the first to systematically evaluate and analyze studies that have reviewed materials with the PEMAT, providing deeper insight into the potential of existing materials to support action for patients and the general public.

Limitations

This systematic review has several potential limitations. First, the limitations of the PEMAT itself include the fact that it is based on expert evaluation and therefore does not fully reflect the patient’s perspective. Second, the studies used different methods for measuring materials, with differences observed in the assessment approaches used alongside the PEMAT and in the methods for group comparisons. As such, they may have a high degree of heterogeneity. In addition, comprehensiveness may not be fully ensured as we exclude studies written in languages other than English. Despite these limitations, this review will present implications for improving the quality of health information targeted at patients and the general public.

Conclusions

We will carry out a systematic review to examine how the understandability and actionability of existing materials have been assessed using the PEMAT.

Acknowledgments

This work is supported by the Japan Society for the Promotion of Science KAKENHI (grant number 24K23676). We used generative AI, Grammarly, in a limited way, to clarify topic sentences and improve grammar, punctuation, and concision. We have reviewed each suggestion before adopting it. For additional quality control, we discussed professional proofreaders in Forte [23].

Data Availability

The datasets generated during and analyzed during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

EF contributed to conceptualization, methodology, investigation, writing – original draft, and funding acquisition. TO handled methodology, writing – original draft, and writing – review and editing. ML managed investigation and writing – review and editing. HO performed investigation and writing – review and editing. TK contributed to writing – review and editing, resources, and supervision. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) checklist.
[DOCX File , 35 KB - resprot_v14i1e63489_app1.docx]

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Abbreviations

CDC: Centers for Disease Control and Prevention
CINAHL: Cumulative Index to Nursing and Allied Health Literature
PEMAT: The Patient Education Materials Assessment Tool
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
PROSPERO: International Prospective Register of Systematic Reviews
ROB-ME: Risk Of Bias due to Missing Evidence in a synthesis

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Protocol

Interventions to Maintain HIV/AIDS, Tuberculosis, and Malaria Service Delivery During Public Health Emergencies in Low- and Middle-Income Countries: Protocol for a Systematic Review

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Abstract

Background: Although existing disease preparedness and response frameworks provide guidance about strengthening emergency response capacity, little attention is paid to health service continuity during emergency responses. During the 2014 Ebola outbreak, there were 11,325 reported deaths due to the Ebola virus and yet disruption in access to care caused more than 10,000 additional deaths due to measles, HIV/AIDS, tuberculosis, and malaria. Low- and middle-income countries account for the largest disease burden due to HIV, tuberculosis, and malaria and yet previous responses to health emergencies showed that HIV, tuberculosis, and malaria service delivery can be significantly disrupted. To date, there has not been a systematic synthesis of interventions implemented to maintain the delivery of these services during emergencies.

Objective: This study aimed to synthesize the interventions implemented to maintain HIV/AIDS, tuberculosis, and malaria services during public health emergencies in low- and middle-income countries.

Methods: The systematic review was registered in the international register for prospective systematic reviews. It will include activities undertaken to improve human health either through preventing the occurrence of HIV, tuberculosis, or malaria, reducing the severity among patients, or promoting the restoration of functioning lost as a result of experiencing HIV, tuberculosis, or malaria during health emergencies. These will include policy-level (eg, development of guidelines), health facility–level (eg, service rescheduling), and community-level interventions (eg, community drug distribution). Service delivery will be in terms of improving access, availability, use, and coverage. We will report on any interventions to maintain services along the care cascade for HIV, tuberculosis, or malaria. Peer-reviewed study databases including MEDLINE, Web of Science, Embase, Cochrane, and Global Index Medicus will be searched. Reference lists from global reports on HIV/AIDS, tuberculosis, or malaria will also be searched. We will use the GRADE-CERQual (Grading of Recommendations Assessment, Development, and Evaluation—Confidence in Evidence from Reviews of Qualitative Research) approach to report on the quality of evidence in each paper. The information from the studies will be synthesized at the disease or condition level (HIV/AIDS, tuberculosis, and malaria), implementation level (policy, health facility, and community), and outcomes (improving access, availability, use, or coverage). We will use the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist to report findings and discuss implications for strengthening preparedness and response, as well as strengthening health systems in low- and middle-income countries.

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Results: The initial search for published literature was conducted between January 2023 and March 2023 and yielded 8119 studies. At the time of publication, synthesis and interpretation of results were being concluded. Final results will be published in 2025.

Conclusions: The findings will inform the development of national and global guidance to minimize disruption of services for patients with HIV/AIDS, tuberculosis, and malaria during public health emergencies.

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KEYWORDS

service availability; emergencies; tuberculosis; malaria; systematic reviews; health services; emergencies; HIV; AIDS; public health emergency; low- and middle-income countries; qualitative reviews; qualitative; policies; communities; health facilities; emergency; implement; implementation

Introduction

Background

The effective management of disasters requires deliberate investment across the phases of the disaster management cycle including mitigation or prevention, preparedness, response, and recovery [1]. In public health disaster management, several frameworks have been developed to provide a blueprint for investments to improve capacities for preparedness, response, and control of public health emergencies. The most widely applied framework is the World Health Organization (WHO) Joint External Evaluation of the International Health Regulations core capacities [2]. Others include the Global Health Security Index [3], the Health System Resilience Index [4], and the Epidemic Preparedness Index [5]. Taken together, the frameworks are comprehensive insofar as prescribing the mechanics or the hardware of a country's capacity to respond to and control health emergencies. For example, investment in building diagnostic capacity, establishing emergency operations centers, investing in health workers, and having a coordination structure are all critical for both preparedness and response to emergencies. However, little attention is paid to issues such as leadership and trust [6], gender and equity [7], and continuity of other services [8]. Health service maintenance during public health emergencies is critical to minimize preventable disease mortality and morbidity. During the 2014 Ebola outbreak in West Africa, there were 11,325 reported deaths due to the Ebola virus [9] and yet the disruption in access to care also caused more than 10,000 additional preventable deaths due to measles, HIV/AIDS, tuberculosis, and malaria [10]. The 2009 H1N1 pandemic increased the risk of adverse neonatal outcomes among pregnant women [11] and increased emergency department visits [12]. The COVID-19 pandemic also reduced overall health care use across 20 countries by about a third [13]. Furthermore, a systematic review of the effects of the COVID-19 pandemic on service delivery and treatment outcomes of people living with HIV [14] noted that there were challenges in accessing services in health facilities, loss of adherence to drugs, and increase in mortality due to COVID-19–related complications. And yet, several modeling studies [15,16] predicted that even brief interruptions to services such as antiretroviral therapy (ART) and condoms could increase HIV/AIDS–related morbidity and mortality in both the short and long term. Previous researchers have described this failure as the "tyranny of the urgent" [7,17] where the response to the public health emergency is prioritized over other health system functions like routine service delivery. In fact, prior to the COVID-19 pandemic, service continuity was not part of the standard operations of an emergency response [18], and the WHO monitoring and evaluation framework for assessing the effectiveness of a response did not have indicators for monitoring continuity of delivery of other services [19]. Our aim is not to contend that services are delivered during the emergency in the exact same way as in normal settings but to recognize the need for modifications and adaptations to service delivery to maintain demand for and continued access to services. Since the WHO International Health Regulations (2005) governing framework for global health security was established [20], the events that have been declared public health emergencies of international concern include the H1N1 pandemic influenza of 2009, Ebola outbreak in West Africa (2013-2015), Ebola outbreak in the Democratic Republic of Congo (2018-2020), Zika virus outbreak (2016), poliomyelitis (2014 to present), the COVID-19 pandemic [21], and the monkeypox outbreak (2022-2023). Previous studies have consistently shown the impact these public health emergencies have on access to HIV, tuberculosis, and malaria services [22-26]; in addition to the already high mortality and morbidity due to these diseases in low- and middle-income countries [27]. To date, there has not, to our knowledge, been a systematic synthesis of the interventions implemented to maintain the demand for and delivery of HIV, tuberculosis, and malaria services during emergencies. Recent reviews have primarily focused on the challenges [28] or the interventions [29] for the delivery of maternal and child health services during emergencies. The findings from this review will inform the development of national and global guidance on the maintenance of services for HIV/AIDS, tuberculosis, and malaria during public health emergencies.

Review Question

What interventions have been implemented to maintain the delivery of HIV/AIDS, tuberculosis, and malaria services during public health emergencies in low- and middle-income countries?

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Objective

This study aims to identify strategies and interventions used to maintain the delivery of and access to HIV/AIDS, tuberculosis, and malaria services during public health emergencies of international concern including H1N1 2009, Ebola 2014, Zika 2015, and the COVID-19 pandemic in low- and middle-income countries to inform efforts for incorporating essential health services maintenance as a key preparedness and response strategy.

Methods

Study Design

The proposed systematic review will be conducted following the guidance given by the Cochrane Handbook for Systematic Reviews of Interventions [30]. The systematic review has been registered in the International Register for Prospective Systematic Reviews (PROSPERO Registration #CRD42023408967).

Inclusion Criteria

Concept

For purposes of this systematic review, we will define interventions as any strategies or activities undertaken to improve human health either through preventing the occurrence of HIV, tuberculosis, or malaria, reducing the severity of HIV, tuberculosis, or malaria among patients, or promoting the restoration of functioning lost as a result of experiencing HIV, tuberculosis, or malaria [31]. The interventions for the continuity of HIV/AIDS, tuberculosis, and malaria services will include policy-level interventions (eg, development of guidelines), health facility–level interventions (eg, service rescheduling), and community-level interventions (eg, community drug distribution). We will define service delivery in terms of improving access (physical and economic ability to use services), availability (physical presence of services), use (quantity of services used), and coverage (proportion of people who access a needed service) [32].

We will report on any interventions to maintain services along the stages of the HIV care cascade including improving testing, linkage to care, retention in care, ART adherence, and viral suppression [33]. Similarly, we will report any interventions implemented to maintain services along any of the stages of the tuberculosis care cascade including tuberculosis testing, linkage to treatment, retention in treatment, posttreatment survival, and achieving durable cure [34]. For malaria, we will include interventions aimed at prevention (eg, vector control), diagnosis, or treatment according to the WHO malaria guidelines [35]. We will include studies reporting any quantitative assessment of service delivery processes (screening, testing, linkage to care, retention in care, and ART adherence) or outcomes (viral suppression, cure, and case counts).

Context

This systematic review will include studies conducted to maintain delivery of and access to HIV, tuberculosis, and malaria services during public health emergencies of international concern in low- and middle-income countries according to the World Bank classification of countries by income level [36].

Types of Sources

This systematic review will consider both quantitative and qualitative studies that use cross-sectional, case-control, randomized and nonrandomized control trials, or cohort study designs. Other designs such as before and after, interrupted time series, and analytical observational studies will be considered for inclusion. Global disease-specific reports published by the Joint United Nations Programme on HIV/AIDS, WHO, or any other global bodies will be considered for inclusion. Editorials, preprints, abstracts, study protocols, commentaries, webinar papers, or opinion pieces will not be eligible for inclusion in the study. Studies conducted among animals or studies assessing the direct effects of emergencies will also be excluded as the review focuses on the maintenance of services for HIV/AIDS, tuberculosis, and malaria.

Search Strategy

A test search was conducted in PubMed to identify published papers on the maintenance of HIV, tuberculosis, and malaria services during public health emergencies. Thereafter, we developed a full search using words in the titles and abstracts of the papers we identified to be relevant (Multimedia Appendix 1). The search strategy will be used to identify relevant papers in each of the other databases. We will include only studies published in English. In addition, we will restrict the search to studies published between 2009 (when the H1N1 pandemic happened) and the end of March 2023.

Peer-reviewed study databases including MEDLINE, Web of Science, Embase, Cochrane, and Global Index Medicus will be searched. Two experienced librarians at Karolinska Institutet's University Library provided guidance about the choice of article databases that would provide the most relevant studies related to the research question. In addition, we will review reference lists of eligible studies, specific journals, and Google Scholar for relevant studies. Reference lists from Global Reports for HIV/AIDS, tuberculosis, or malaria will also be searched for relevant papers. The search will be guided by 2 experienced librarians from Karolinska Institutet's University Library. We anticipate that this search will be completed by the end of May 2023.

After the search is completed, the citations of all identified studies will be exported to Endnote X7 (Clarivate) and screened to remove any duplicates. Thereafter, the search will then be exported to Rayyan [37]—a web-based software that was developed by the Qatar Computing Research Institute and uses semiautomation to expedite the process of screening studies. Two reviewers will independently apply the inclusion and exclusion criteria and select studies based on the title and abstract. Disagreements between the individual judgments of the reviewers will be resolved through a discussion. After consensus building on studies based on titles and abstracts, additional studies may be excluded at full-text review.

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Data Extraction

A data abstraction form will be used to obtain information from each of the relevant studies (Multimedia Appendix 2). The data to be extracted from each paper includes the year of publication, first author, year of study, journal or other publication source, country or countries, title, study design, target population, circumstance or outbreak, disease category (HIV/AIDS, tuberculosis, malaria, or a combination of these), list of measures implemented to maintain services, and limitations and strengths. The other information to be extracted about the interventions include the implementer (facility health workers and community health workers), the level at which the intervention is implemented (facility and community), the measure of assessment of the intervention (eg, number of people initiated on ART, number of people tested, and viral load coverage), and the type of indicator (process: number receiving drugs or outcome: number virally suppressed). The number of variables and the order in which they are presented will be adjusted depending on the amount of relevant information we find in the identified studies.

Risk of Bias or Quality Assessment

We will use several strategies to ensure the quality of studies included in the systematic review. First, we will involve 2 reviewers to screen the studies that will be included in the review. The reviewers will have experience in research related to HIV/AIDS, tuberculosis, and malaria service delivery as well as response and control of public health emergencies. In addition, since we do not anticipate quantitatively combining the relevant studies, we will use the GRADE-CERQual (Grading of Recommendations Assessment, Development, and Evaluation—Confidence in Evidence from Reviews of Qualitative Research) approach [38] to assess the quality of each paper. Each study will be assessed for quality in terms of the methodological quality, coherence, adequacy, and quality of the data collected and the relevance of results in line with the review question. The overall assessment of the quality of each study will be graded as either high, moderate, low, or very low.

Data Synthesis and Presentation

Findings from the systematic review will be presented using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analyses) checklist and flow diagram [39]. The data extracted for the review studies will be summarized and presented in tabular or graphic form as appropriate. The synthesis of the data will be conducted at various levels. These will include at disease or condition level (HIV/AIDS, tuberculosis, malaria, or a combination of these), at the implementation level (policy, health facility, and community), and outcomes (improving access, availability, use, or coverage of services)

Results

The initial search for published literature yielded 8119 studies from web-based databases. This search was conducted between January 2023 and March 2023. At the time of publication, synthesis and interpretation of results were being concluded. Final results will be published in 2025.

Discussion

Expected Findings

We will discuss the findings and their implications for strengthening both preparedness and response, as well as strengthening health systems in low- and middle-income countries. Specifically, we will discuss interventions that are common to the 3 disease programs and how such interventions can support the response to a public health emergency but also be scaled up to strengthen service delivery beyond the emergency. We will also discuss how the interventions have been assessed by comparing process indicators (such as number of people tested) and outcome indicators (such as number of people with viral suppression).

Previous literature has tried to synthesize the challenges [28] and interventions [29] for the delivery of specific service delivery programs like delivery of maternal and child health services during emergencies. However, the scope of essential health services is broad and includes services for noncommunicable diseases like diabetes and hypertension, services for older adults as well as health promotion and referral services. This protocol will provide a structure and framework for the synthesis of the literature for the continuity of essential health services more broadly beyond HIV/AIDS, tuberculosis, and malaria.

Limitations

The main limitation of the review will be the exclusion of studies conducted in languages other than English. In addition, the review will include only studies publishing information about interventions implemented during public health emergencies of international concern. However, a public health emergency need not be declared to be of international concern to cause disruption of access and delivery of HIV, tuberculosis, and malaria services. Nonetheless, the identified interventions will be transferrable to contexts in which an emergency is local and does not pose a threat to the international community. In addition, the development of the protocol followed the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) checklist (Multimedia Appendix 3).

Conclusions

The findings will inform the development of national and global guidance to minimize disruption of services for patients with HIV/AIDS, tuberculosis, and malaria during public health emergencies. The protocol will also inform studies conducted to synthesize interventions to maintain other health programs beyond HIV/AIDS, tuberculosis, and malaria.

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Acknowledgments

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Authors' Contributions

SNK, RKW, and TA were involved in idea conceptualization. RKW, HL, NR, JMS, and TA were involved in the review of technical content and supervision. SNK wrote the first draft of the manuscript. All authors reviewed and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[PDF File (Adobe PDF File), 209 KB - resprot_v14i1e64316_app1.pdf]

Multimedia Appendix 2
Data Abstraction Form.
[DOCX File , 31 KB - resprot_v14i1e64316_app2.docx]

Multimedia Appendix 3
Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) checklist.
[PDF File (Adobe PDF File), 131 KB - resprot_v14i1e64316_app3.pdf]

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Abbreviations

ART: antiretroviral therapy
CERQual: Confidence in Evidence from Reviews of Qualitative Research
GRADE: Grading of Recommendations Assessment, Development, and Evaluation
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols
PROSPERO: International Register for Prospective Systematic Reviews
WHO: World Health Organization

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Protocol

Strategies to Improve Health Care Provider Prescription of and Patient Adherence to Guideline-Recommended Cardiovascular Medications for Atherosclerotic Occlusive Disease: Protocol for Two Systematic Reviews and Meta-Analyses of Randomized Controlled Trials

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Abstract

Background: In patients with atherosclerotic occlusive diseases, systematic reviews and meta-analyses of randomized controlled trials (RCTs) report that antiplatelets, statins, and antihypertensives reduce the risk of major adverse cardiac events, need for revascularization procedures, mortality, and health care resource use. However, evidence suggests that these patients are not prescribed these medications adequately or do not adhere to them once prescribed.

Objective: We aim to systematically review and meta-analyze RCTs examining the effectiveness of implementation or adherence-supporting strategies for improving health care provider prescription of, or patient adherence to, guideline-recommended cardiovascular medications in patients with atherosclerotic occlusive disease.

Methods: We designed and reported the protocol according to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis-Protocols) statement. We will search MEDLINE, Embase, The Cochrane Central Register of Controlled Trials, PsycINFO, and CINAHL from their inception. RCTs examining implementation or adherence-supporting strategies for improving prescription of, or adherence to, guideline-recommended cardiovascular medications in adults with cerebrovascular disease, coronary artery disease, peripheral artery disease, or polyvascular disease (>1 of these diseases) will be included. Two investigators will independently review identified titles/abstracts and full-text studies, extract data, assess the risk of bias (using the Cochrane tool), and classify implementation or adherence-supporting strategies using the refined Cochrane Effective Practice and Organization of Care (EPOC) taxonomy (for strategies aimed at improving prescription) and Behavior Change Wheel (BCW; for adherence-supporting strategies). We will narratively synthesize data describing which implementation or adherence-supporting strategies have been evaluated across RCTs, and their reported effectiveness at improving prescription of, or adherence to, guideline-recommended cardiovascular medications (primary outcomes) and patient-important outcomes and health care resource use (secondary outcomes) within refined EPOC taxonomy levels and BCW interventions and policies. Where limited clinical

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heterogeneity exists between RCTs, estimates describing the effectiveness of implementation or adherence-supporting strategies within different refined EPOC taxonomy levels and BCW interventions and policies will be pooled using random-effects models. Stratified meta-analyses and meta-regressions will assess if strategy effectiveness varies by recruited patient populations, prescriber types, clinical practice settings, and study design characteristics. GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) will be used to communicate evidence certainty.

Results: The search was completed on June 6, 2023. Database searches and the PubMed "related articles" feature identified 4319 unique citations for title/abstract screening. We are currently screening titles/abstracts.

Conclusions: These studies will identify which implementation and adherence-supporting strategies are being used (and in which combinations) across RCTs for improving the prescription of, or adherence to, guideline-recommended cardiovascular medications in adults with atherosclerotic occlusive diseases. They will also determine the effectiveness of currently trialed implementation and adherence-supporting strategies, and whether effectiveness varies by patient, prescriber, or clinical practice setting traits.

Trial Registration: PROSPERO CRD42023461317; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=461317; PROSPERO CRD42023461299; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=461299

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KEYWORDS

coronary artery disease; cerebrovascular disease; peripheral artery disease; polyvascular disease; underprescription; nonadherence; implementation strategy; adherence-supporting strategy; statins; antiplatelets; antihypertensives; guideline-recommended medications; implementation; atherosclerosis; patient adherence; RCT; randomized controlled trials; PRISMA

Introduction

Background

Atherosclerotic occlusive disease is common worldwide, increasing in global prevalence, and characterized by arterial stenosis (narrowing) and occlusion secondary to the buildup of lipid-rich plaque within arterial walls [1]. This disease may be further categorized by anatomic location, with atherosclerotic plaque buildup within the arteries of the extracranial and intracranial circulation, heart, and peripheral arteries being referred to as cerebrovascular disease (CVD), coronary artery disease (CAD), and peripheral artery disease (PAD), respectively [1]. An estimated 101 million [2], 197 million [3], and 113 million [4] individuals have CVD, CAD, and PAD worldwide, respectively. CVD, CAD, and PAD are associated with a significantly increased risk of hospitalization; need for coronary, carotid, or lower limb revascularization; major adverse cardiac events (MACEs) and major adverse limb events (MALEs); stroke; and cardiovascular and all-cause mortality [5,6].

International, evidence-based clinical practice guidelines strongly and consistently recommend that adults with CVD, CAD, PAD, and polyvascular disease be prescribed and take antiplatelets and statins (ie, hydroxymethylglutaryl-CoA reductase inhibitors) [7-11]. They also recommend antihypertensives for those patients with concurrent hypertension [7-11]. These recommendations are based on high-quality data from randomized controlled trials (RCTs) and systematic reviews and meta-analyses of RCTs that reported a significantly lower risk of MACE; MALE; need for coronary, carotid, and lower limb revascularization procedures; cardiovascular and all-cause mortality; and health care resource use when these patients are prescribed these medications [12-14].

Despite this, evidence suggests that many patients with atherosclerotic occlusive disease are not prescribed these medications adequately or do not adhere to them after prescription [15-18]. More specifically, only approximately 40% to 90% of patients with any form of atherosclerotic occlusive disease are prescribed any antiplatelet, 30% to 60% any statin, 40% to 60% any antihypertensive, and 10% to 40% all three guideline-recommended cardiovascular medications [15,16]. Studies also report that patient adherence percentages to these medications range from ~70% to 80% for antiplatelets, ~50% to 60% for statins, ~40% to 70% for antihypertensives, and ~20% to 40% for all three guideline-recommended cardiovascular medications [17,18]. Those with PAD are also significantly less likely to be prescribed these medications and adhere to them compared to those with CVD and CAD [19]. The increased frequency at which patients with PAD are underprescribed and nonadherent to guideline-recommended cardiovascular medications may partially explain why studies demonstrate persistently higher risks of cardiovascular-related hospitalization (eg, for atherothrombotic events), MACE, stroke, and cardiovascular mortality in patients with PAD compared to those with CVD or CAD [20].

To improve the use of guideline-recommended cardiovascular medications among patients with atherosclerotic occlusive disease, RCTs [21-48] have evaluated implementation strategies (interventions directed at the health system and health care providers) and adherence-supporting strategies (interventions aimed at patients directly) [49] to improve health care provider prescription of and patient adherence to guideline-recommended cardiovascular medications, respectively. However, the design [21-24], length of follow-up [24,27,31], setting [21,24-26], and implementation or adherence-supporting strategies examined [21,26,27,30-32,36,40-48] varies considerably across published trials. Existing RCTs have also examined implementation and adherence-supporting strategies aimed at improving prescription of or adherence to different medication classes (antiplatelets [25,28,29], statins [27-29], antihypertensives [25,28,42], or all guideline-recommended medications [27,29,43,44]) among patients with different diagnoses (CVD [31-33], CAD

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[24,26,27], PAD [34,35], and polyvascular disease [36,37]). Further, the implementation and adherence-supporting strategies examined within published trials target different types of health care providers (ie, cardiovascular specialists [38,39] or noncardiovascular specialists [21,23]) and health care provider behaviors [31,33,38,40]. Given this interstudy heterogeneity, evidence-synthesis efforts are needed to interpret the results of the above RCTs collectively.

Rationale

Two updated, comprehensive, and methodologically rigorous systematic reviews and meta-analyses are needed to determine the effectiveness of implementation and adherence-supporting strategies for improving health care provider prescription of, and patient adherence to, guideline-recommended cardiovascular medications for atherosclerotic occlusive diseases. All forms of atherosclerotic occlusive disease (CVD, CAD, PAD, and polyvascular disease) will be examined within both systematic reviews as the underlying pathophysiology [50-52], and guideline-recommended cardiovascular medications for medical management of these diseases [7-11] are nearly identical. Further, patients with these atherosclerotic occlusive diseases tend to have similar demographics (ie, frequently past or current smokers, often male, and typically over 65 years of age) and comorbidities [53-55]. Finally, these diseases often coexist together [56,57], and similar prescribers are involved in their medical management [58-60]. The results of these systematic reviews will help identify promising implementation and adherence-supporting strategies for each and all classes of cardiovascular medications recommended for patients with atherosclerotic occlusive diseases. The systematic reviews will facilitate an effective comparison of implementation and adherence-supporting strategies by classifying them according to established taxonomies [61,62].

Objectives

The primary objectives of the two systematic reviews are to synthesize the effectiveness of implementation and adherence-supporting strategies for improving health care provider prescription of, and patient adherence to, guideline-recommended cardiovascular medications among patients with atherosclerotic occlusive disease, including CVD, CAD, PAD, or polyvascular disease. We conceptualized the desired behavior changes for our primary objectives and key actors involved in bringing about these desired behavior changes using the Action, Actor, Context, Target, Time (AACTT) framework [63] (see Table 1 for the underprescription systematic review AACTT framework and Table 2 for the nonadherence systematic review AACTT framework).

Table 1. AACTT[a] behavior specification framework [63] for the systematic review of implementation strategies for improving health care provider prescription of guideline-recommended cardiovascular medications to adults with atherosclerotic occlusive disease.

AACTT domains	Examples among the systematic review of implementation strategies for improving health care provider prescription of cardiovascular medications
Action	Prescription of guideline-recommended cardiovascular medications (antiplatelets, statins, or antihypertensives)
Actor	Health care providers responsible for managing patients with atherosclerotic occlusive disease
Context	Any setting where prescribers are responsible for prescribing medication to patients with atherosclerotic occlusive diseases (eg, primary care practices, tertiary academic hospitals, or pharmacies)
Target	Patients with an atherosclerotic occlusive disease (cerebrovascular disease, coronary artery disease, peripheral artery disease, or polyvascular disease) in whom one or more guideline-recommended cardiovascular medications is indicated
Time	During encounters between prescribers and patients with atherosclerotic occlusive disease

[a]AACTT: Action, Actor, Context, Target, Time.

Table 2. AACTT[a] behavior specification framework [63] for the systematic review of adherence-supporting strategies for improving patient adherence to guideline-recommended cardiovascular medications in adults with atherosclerotic occlusive disease.

AACTT domains	Examples among the systematic review of adherence-supporting strategies for improving patient adherence to cardiovascular medications
Action	Adherence to guideline-recommended cardiovascular medications for atherosclerotic occlusive disease (antiplatelets, statins, or antihypertensives)
Actor	Patients with a diagnosed atherosclerotic occlusive disease (cerebrovascular disease, coronary artery disease, peripheral artery disease, or polyvascular disease)
Context	Any setting in which patients (or their caregivers) are responsible for managing their own medications
Target	Patients who have been prescribed one or more guideline-recommended cardiovascular medications for management of their atherosclerotic occlusive disease by a health care professional
Time	Following prescription of guideline-recommended cardiovascular medications by a health care professional

[a]AACTT: Action, Actor, Context, Target, Time.

The AACTT framework [63] was developed to describe the action (ie, the behavior to change), actor (ie, who is involved in performing the behavior), context (ie, the physical, social, or emotional settings where the behavior is performed), target (ie, the person or people for or with whom the behavior is performed), and time (ie, when the behavior is performed) of

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behaviors targeted for change in clinical practice. Describing desired behavior changes using the five elements of the AACTT framework [63] provides a concise overview of which individuals at what organizational levels need to do what differently to ensure the effective implementation of desired best practices. Secondary objectives are to determine whether (1) the effectiveness of implementation or adherence-supporting strategies at improving health care provider prescription of or increasing patient adherence to guideline-recommended cardiovascular medications for atherosclerotic occlusive disease varies by patient characteristics, prescriber traits, medication classes, atherosclerotic occlusive disease diagnoses, or clinical settings; and (2) improved health care provider prescription of or patient adherence to guideline-recommended cardiovascular medications improves patient outcomes and reduces health care resource use.

Methods

Registration and Reporting

This protocol was created following recommendations from the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) statement [64] (a completed PRISMA-P checklist is provided in Multimedia Appendix 1). The protocols for the systematic reviews of implementation and adherence-supporting strategies for improving health care provider prescription and patient adherence were registered separately on PROSPERO (underprescription systematic review: CRD42023461317; nonadherence systematic review: CRD42023461299). We chose to create a single protocol paper describing the methods of the two planned systematic reviews and meta-analyses as we felt that their background, rationale, and methods overlap significantly. However, as scout searches suggested that one systematic review may include over 100 RCTs, we plan to report their results separately to summarize the results of these evidence syntheses in sufficient detail.

Eligibility Criteria

Eligibility criteria for the two systematic reviews were created according to the Population, Intervention, Comparison, Outcome, and Design framework [65]. Their specific inclusion and exclusion criteria are presented in Table 3 (underprescription systematic review) and Table 4 (nonadherence systematic review).

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Table 3. Inclusion and exclusion criteria for systematic review examining implementation strategies for improving health care provider prescription of guideline-recommended cardiovascular medications to patients with atherosclerotic occlusive disease.

PICOD[a] framework domain	Inclusion criteria[b]	Exclusion criteria[c]
Population	• Prescribers (ie, physicians, nurse practitioners, or pharmacists) involved in the management of adults (≥18 years of age) with atherosclerotic occlusive disease (defined as cerebrovascular disease, coronary artery disease, peripheral artery disease, or polyvascular disease).	• >20% of the patient population had nonatherosclerotic cardiovascular disease (eg, aneurysmal disease). This 20% threshold was selected based on prior literature [66]. • Studies examining the prescription of nonguideline-recommended medications. • Prescribers involved in the management of people exclusively <18 years of age.
Intervention	• Any implementation strategy aimed at increasing health care provider prescription of guideline-recommended cardiovascular medications to patients with atherosclerotic occlusive disease. An implementation strategy will be defined as any "method or technique to enhance the adoption, implementation, and sustainability of a clinical program or practice" [49].	• Studies examining implementation strategies directed exclusively at patients.
Comparison	• Health care providers prescribing guideline-recommended cardiovascular medications to patients with atherosclerotic occlusive disease without the use of an implementation strategy, patients receiving the same implementation strategy at a lower intensity or shorter duration than the intervention group, or patients receiving a different implementation strategy than the intervention group.	• Studies examining implementation strategies directed exclusively at patients.
Outcomes	• Primary[d]: Effect estimates (or data required to calculate) describing differences in health care provider prescription between implementation strategy and control arms of each (ie, antiplatelets, statins, or antihypertensives) or all classes of guideline-recommended cardiovascular medications. • Secondary[d]: Effect estimates (or data required to calculate these) describing differences between patients in the implementation strategy and control arms regarding adverse clinical outcomes (eg, major adverse cardiac events, revascularization procedures, amputations, cardiovascular mortality, or all-cause mortality) and health care resource use outcomes (eg, emergency department visits, hospital admission or readmission, or length of hospitalization).	• Studies not reporting effect estimates (or data required to calculate) describing differences in guideline-recommended cardiovascular medication prescription between prescribers in the implementation strategy and control arms.
Design	• Study designs will include RCTs[e] and cluster-RCTs.	• Nonrandomized studies (eg, prospective cohort studies). • Studies published in abstract form only and unpublished studies (ie, gray literature).

[a]PICOD: Population, Intervention, Comparison, Outcome, and Design.

[b]Inclusion criteria formulated according to the Population, Intervention, Comparison, Outcome, and Design framework for posing clinical questions [65].

[c]Studies meeting one or more of the following criteria will be excluded.

[d]Effect estimates (and measures of variation, such as 95% CIs) will be extracted as reported and may include weighted mean differences or standardized mean differences for continuous outcomes; odds ratios, relative risks, and risk differences for binary outcomes; and hazard ratios for time-to-event data.

[e]RCT: randomized controlled trial.

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Table 4. Inclusion and exclusion criteria for systematic review examining adherence-supporting strategies for improving patient adherence to guideline-recommended cardiovascular medications in patients with atherosclerotic occlusive disease.

PICOD[a] framework domain	Inclusion criteria[b]	Exclusion criteria[c]
Population	• Adults (≥18 years of age) with atherosclerotic occlusive disease (cerebrovascular disease, coronary artery disease, peripheral artery disease, or polyvascular disease) prescribed one or more guideline-recommended cardiovascular medications (eg, statins, antihypertensives, or antiplatelets).	• >20% of patients had nonatherosclerotic cardiovascular disease (eg, aneurysmal disease). This threshold was selected based on prior literature [66]. • Studies where ≥20% of patients were pediatrics (<18 years of age). • Studies examining adherence to medications not recommended within relevant clinical practice guidelines.
Intervention	• Any adherence-supporting strategy aimed at increasing adherence to guideline-recommended cardiovascular medication in patients with atherosclerotic occlusive disease. An adherence-supporting strategy will be defined as any "method or technique to enhance the adoption, implementation, and sustainability of a clinical program or practice" [49].	• Studies examining adherence-supporting strategies directed at health care providers or the health care system without components directed toward patients.
Comparison	• Patients taking guideline-recommended cardiovascular medications for atherosclerotic occlusive disease management without a concurrent adherence-supporting strategy, patients receiving a different adherence-supporting strategy than the intervention group, or patients receiving the same adherence-supporting strategy at a lower intensity or shorter duration than the intervention group.	• Studies examining adherence-supporting strategies directed at health care providers or the health care system without components directed toward patients.
Outcomes	• Primary[d]: Effect estimates (or data required to calculate) describing differences in medication adherence between adherence-supporting strategy and control arms of each (eg, antiplatelets, statins, or antihypertensives) or all classes of guideline-recommended cardiovascular medications. • Secondary[d]: Effect estimates (or data required to calculate these) describing differences between patients in the adherence-supporting strategy and control arms regarding adverse clinical outcomes (eg, major adverse cardiac events, revascularization procedures, amputations, cardiovascular mortality, or all-cause mortality) and health care resource use outcomes (eg, emergency department visits, hospital admission or readmission, or length of hospitalization).	• Studies not reporting effect estimates (or data required to calculate) describing differences in medication adherence between patients in the intervention and control arms.
Design	• RCTs[e] and cluster-RCTs.	• Nonrandomized studies (eg, case-control studies). • Unpublished studies (ie, gray literature) and studies published in abstract form only.

[a]PICOD: Population, Intervention, Comparison, Outcome, and Design.

[b]Inclusion criteria formulated according to the Population, Intervention, Comparison, Outcome, and Design framework for posing clinical questions [65].

[c]Studies meeting one or more of the following criteria will be excluded.

[d]Effect estimates (and measures of variation, such as 95% CIs) will be extracted as reported and may include weighted mean differences or standardized mean differences for continuous outcomes; odds ratios, relative risks, and risk differences for binary outcomes; and hazard ratios for time-to-event data.

[e]RCT: randomized controlled trial.

Guideline-recommended cardiovascular medications will be defined as any medications recommended within evidence-based clinical practice guidelines cited within the included studies. In studies where evidence-based clinical practice guidelines are not cited, guideline-recommended cardiovascular medications will be defined as antiplatelets (eg, aspirin or clopidogrel), statins, and antihypertensives (eg, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, β-blockers, calcium-channel blockers, or thiazide diuretics), as these medications are consistently recommended for individuals with CVD, CAD, PAD, and polyvascular disease across multiple evidence-based clinical practice guidelines [7-11].

Clinical Questions

Primary Clinical Questions

The primary clinical questions are as follows:

1. What is the effectiveness of different implementation strategies for improving health care provider prescription of guideline-recommended cardiovascular medications to

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adults (≥18 years of age) with atherosclerotic occlusive disease, including CVD, CAD, PAD, or polyvascular disease?

2. What is the effectiveness of adherence-supporting strategies for increasing adherence to guideline-recommended cardiovascular medications among adults with atherosclerotic occlusive disease?

Secondary Clinical Questions

The secondary clinical questions are as follows:

1. Does the effectiveness of implementation and adherence-supporting strategies for improving health care provider prescription of and patient adherence to guideline-recommended cardiovascular medications to adults with atherosclerotic occlusive diseases vary by study design, prescriber characteristics, patient characteristics, atherosclerotic occlusive disease diagnosis, or clinical practice setting?
2. Does the use of implementation or adherence-supporting strategies aimed at improving health care provider prescription of or patient adherence to guideline-recommended cardiovascular medications to adults with atherosclerotic occlusive disease improve patient outcomes or reduce health care resource use?

Information Sources

We will search MEDLINE, Embase, The Cochrane Central Register of Controlled Trials, PsycINFO, and CINAHL from their inception. We will also use the PubMed "related articles" feature and manually search reference lists of included studies and relevant reviews identified during the search.

Search Strategy

Our electronic search strategy was designed in consultation with an information scientist. Using combinations of Medical Subject Headings (National Library of Medicine) or Emtree (Elsevier) terms and keywords, we constructed search filters covering the themes "atherosclerotic occlusive disease" and "medication prescription or adherence." These search filters were then combined with a validated RCT search filter from the Cochrane Handbook for Systematic Reviews of Interventions [67]. The search strategy was subsequently piloted and refined by adding additional thesaurus or indexing terms to the nonsearch filter themes when new, relevant citations were located during iterative pilot searches. The penultimate search strategies were peer-reviewed by another medical librarian in accordance with the Peer Review of Electronic Search Strategies framework [68] (see Multimedia Appendix 2 for final search strategies).

Study Selection and Management

Titles and abstracts of identified citations will be reviewed by two independent reviewers using Rayyan Systematic Review Software [69]. Citations deemed potentially relevant by either reviewer during title/abstract screening will be subject to independent full-text review using relevant inclusion and exclusion criteria (see Tables 3 and 4). Disagreements regarding study inclusion will be resolved by consensus.

Outcomes

The primary outcome for the underprescription systematic review will be the health care provider's prescription of each (eg, antiplatelets, statins, or antihypertensives) or all classes of guideline-recommended cardiovascular medications between the implementation strategy and control arms. The primary outcome of the nonadherence systematic review will be the patient adherence to each (eg, antiplatelets, statins, or antihypertensives) or all classes of guideline-recommended cardiovascular medications between the adherence-supporting strategy and control arms. Secondary outcomes for both systematic reviews will be differences in patient outcomes and health care resource use between the implementation or adherence-supporting strategy and control arms. Patient outcomes will include MACE [70] (defined as nonfatal myocardial infarction, stroke, or cardiovascular mortality), MALE [70] (defined as limb ischemia requiring revascularization or above-ankle lower limb amputation), stroke, revascularization procedures, amputations, patient-reported outcome measures, cardiovascular mortality, all-cause mortality, and any other patient-important outcomes reported by study authors. Health care resource use outcomes will include emergency department visits, hospital admission or readmission, length of hospitalization, and any other health care resource use outcomes reported by study authors.

Data Items and Selection Process

Two investigators will independently extract data using a predesigned electronic data extraction spreadsheet (see Tables 5 and 6 for data items to be extracted from the underprescription and nonadherence systematic reviews, respectively).

When potentially relevant articles published in languages other than English are identified, translators will be recruited to review the full texts and extract data if identified studies meet inclusion criteria. Effect estimates and their 95% CIs (or data required to calculate these measures) describing associations between implementation or adherence-supporting strategy use and primary and secondary outcomes will be extracted as reported in studies and may include weighted mean differences or standardized mean differences for continuous outcomes; odds ratios (ORs), relative risks (RRs), and risk differences for binary outcomes; and hazard ratios (HRs) for time-to-event data. Where studies do not provide effect estimates and their 95% CIs (or data required to calculate these measures) within the text or summary tables but summarize this information within figures, data will be extracted independently by two investigators using ImageJ software (National Institutes of Health) [72] and then their results will be averaged across investigators. Where data are not provided in the text, summary tables, or figures, these data will be sought from the supplementary materials of included trials or from trial registration repositories. In cases where data cannot be found using the above methods, study authors will be contacted in a final attempt to obtain all relevant study data. Discrepancies between investigators regarding data extraction will be resolved by consensus.

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Table 5. Data items to be extracted from included studies when reported for systematic review examining implementation strategies for improving health care provider prescription of guideline-recommended cardiovascular medications to adults with atherosclerotic occlusive disease.

Data item theme	Items to be extracted
Study design	• Country of origin • Recruitment period • Study design (eg, RCT[a] or cluster-RCT) • Setting (eg, primary, secondary, or tertiary) • Number of health care providers, patients, or clusters • Follow-up duration • Clinical practice guidelines followed (eg, 2016 American College of Cardiology/American Heart Association PAD[b] guidelines [7])
Prescriber characteristics	• Health care provider specialty (cardiovascular specialist or noncardiovascular specialist) • Health care provider subspecialty (eg, family medicine, general internal medicine, cardiology, or vascular surgery) • Number of female health care providers • Mean years of health care provider practice
Patient characteristics	• Number of patients with different atherosclerotic occlusive diseases (cerebrovascular disease, coronary artery disease, PAD, or polyvascular disease) • Mean or median patient age • Mean or median patient BMI • Number of female patients • Number of non-White patients • Number of patients with low socioeconomic status[c] • Number of past or current smokers • Whether patients were inpatients, outpatients, or long-term care residents • Number of patients who are overweight[d] or obese[e] • Number of patients residing in rural areas • Number of patients with specific comorbidities (dyslipidemia, diabetes mellitus, hypertension, congestive heart failure, chronic kidney disease, or chronic obstructive pulmonary disease)
Guideline-recommended medications	• Classes of guideline-recommended medications examined (antiplatelets, statins, antihypertensives, or all medications) • Types of guideline-recommended medications examined (eg, clopidogrel, simvastatin, or β-blockers)
Implementation strategies	• Implementation strategy classification according to refined Effective Practice and Organization of Care taxonomy [61]
Effect measures	• Effect measures (eg, weighted mean differences, standardized mean differences, odds ratios, relative risks, risk differences, or hazard ratios) and measures of variability (eg, 95% CIs) describing the effect of implementation strategies on primary and secondary outcomes
Risk of bias	• Risk of bias for the 7 domains of the Cochrane risk of bias tool [71]

[a]RCT: randomized controlled trial.

[b]PAD: peripheral artery disease.

[c]As defined by study authors.

[d]Defined as a BMI ≥25 kg/m^2.

[e]Defined as a BMI ≥30 kg/m^2.

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Table 6. Data items to be extracted from included studies when reported for systematic review examining adherence-supporting strategies for improving patient adherence to guideline-recommended cardiovascular medications in adults with atherosclerotic occlusive disease.

Data item theme	Items to be extracted
Study design	• Country of origin • Study design (eg, RCT[a] or cluster-RCT) • Setting (eg, primary, secondary, or tertiary) • Recruitment period • Number of patients, prescribers, or clusters • Clinical practice guidelines followed (eg, 2022 Canadian Cardiovascular Society PAD[b] guidelines [9]) • Duration of follow-up
Patient characteristics	• Atherosclerotic occlusive disease diagnoses (cerebrovascular disease, coronary artery disease, PAD, or polyvascular disease) • Whether patients were inpatients, outpatients, or long-term care residents • Mean or median age • Mean or median BMI • Number of patients with low socioeconomic status[c] • Number of female patients • Number of non-White patients • Number of past or current smokers • Number of patients who are overweight[d] or obese[e] • Number of patients residing in rural areas • Number of patients with specific medical comorbidities (dyslipidemia, diabetes mellitus, hypertension, congestive heart failure, chronic kidney disease, or chronic obstructive pulmonary disease)
Prescriber characteristics	• Specialty of health care providers (cardiovascular specialist or noncardiovascular specialist) • Subspecialty of health care providers (eg, family medicine, general internal medicine, cardiology, or vascular surgery) • Mean or median years of health care provider practice • Number of female health care providers
Guideline-recommended medications	• Classes of guideline-recommended medications examined (statins, antiplatelets, antihypertensives, or all guideline-recommended medications) • Types of guideline-recommended medications examined (eg, aspirin, rosuvastatin, or angiotensin-converting enzyme inhibitors)
Adherence-supporting strategies	• Adherence-supporting strategy classification according to the Behavior Change Wheel [62]
Effect measures	• Effect measures (eg, weighted mean differences, standardized mean differences, odds ratios, relative risks, risk differences, or hazard ratios) and applicable variation measures (eg, 95% CIs) describing the effect of adherence-supporting strategies on primary and secondary outcomes
Risk of bias	• Risk of bias for 7 domains of the Cochrane risk of bias tool [71]

[a]RCT: randomized controlled trial.

[b]PAD: peripheral artery disease.

[c]As defined by study authors.

[d]Defined as a BMI ≥25 kg/m^2.

[e]Defined as a BMI ≥30 kg/m^2.

Risk of Bias

Two independent investigators will assess the risk of bias for all included trials using the Cochrane risk of bias tool [71]. Discrepancies between investigators regarding risk of bias assessment will be resolved by consensus.

Data Synthesis

Qualitative

Before considering meta-analyses, we will first perform thematic clustering [73] of all included studies. We will classify implementation or adherence-supporting strategies used within both the intervention and comparator arms of identified trials based on (1) the levels and categories of the refined Effective Practice and Organization of Care (EPOC) taxonomy [61] (for implementation strategies for improving health care provider prescription); or (2) the nine intervention functions (education, persuasion, incentivization, coercion, training, restriction, environmental restructuring, modelling, and enablement) and seven policy categories (communication or marketing, guidelines, fiscal, regulation, legislation, environmental or social planning, and service provision) of the Behavior Change Wheel (BCW) [62] (for adherence-supporting strategies for improving patient adherence). The refined EPOC taxonomy was selected

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because it was designed to assist reviewers in selecting papers for inclusion in systematic reviews of implementation strategies [61]. It has also been used in systematic reviews examining RCTs of implementation strategies for patients with other chronic conditions [74,75] and allows for an adequate description of complex and multiple implementation strategies [61]. The BCW was selected because it was constructed by behavior change experts through systematic analysis and synthesis of 19 previously existing adherence-supporting strategy classification frameworks [62]. The BCW also satisfies three usefulness criteria not completely satisfied by any of the 19 individual frameworks on which it is built (comprehensiveness, coherence, and links to an overarching model of behavior) and can classify every adherence-supporting strategy that has been developed [62]. Further, linkage to an overarching model of behavior (the capability, opportunity, and motivation model) may allow for the selection of adherence-supporting strategies more likely to achieve the desired behavior change [62]. The BCW has also been shown to be reliable for classifying adherence-supporting strategies across a wide range of clinical contexts [62]. Implementation and adherence-supporting strategies will be classified by 2 independent investigators. Disagreements regarding implementation or adherence-supporting strategy classification will be resolved through consultation with a health psychologist.

Following implementation and adherence-supporting strategy classification, we will tabulate studies [73] based on the implementation strategies contained within their intervention and comparator arms. This will allow us to narratively summarize [73] how the implementation or adherence-supporting strategies used within the intervention and comparator arms of included studies differ regarding (1) the type and number of implementation or adherence-supporting strategies used; or (2) the intensity and duration of implementation or adherence-supporting strategy use. It will also allow us to describe which and how frequently specific implementation or adherence-supporting strategies are used in combination (ie, how frequently they co-occur together in complex implementation or adherence-supporting strategies). Studies will also be tabulated [73] by the classes of guideline-recommended cardiovascular medications that their implementation or adherence-supporting strategies are designed to improve the prescription of or adherence to, the predominant diagnoses of the patients included in this study (CVD, CAD, PAD, and polyvascular disease), and whether their implementation strategy was aimed at cardiovascular or noncardiovascular specialists (for implementation strategies for improving health care provider prescription).

Quantitative

Descriptive data will be summarized using weighted means and SDs, medians and IQRs, or counts and percentages where appropriate. Where minimal clinical interstudy heterogeneity exists [76], DerSimonian and Laird [77] random effects models will be used to pool effect estimates whenever two or more studies report on the effect of implementation or adherence-supporting strategies of the same type (according to the refined EPOC taxonomy [61] [underprescription systematic review] or the BCW [62] [nonadherence systematic review]) on similar outcomes. We will preferentially summarize the pooled effects of implementation or adherence-supporting strategies on the primary and secondary outcomes using RRs for dichotomous outcomes, weighted mean differences for continuous outcomes, and HRs for time-to-event outcomes (along with their 95% CIs). Where substantial interstudy clinical heterogeneity exists [76], we will summarize the results of included studies narratively [73] by reporting effect estimates (along with their 95% CIs) describing the effectiveness of implementation or adherence-supporting strategies at improving primary or secondary outcomes.

Where studies report effect measures other than RRs (ie, ORs or HRs), we will use corresponding raw data describing the cumulative incidence of underprescription or nonadherence or secondary outcomes to calculate RRs from ORs or HRs using validated methods [78,79] as has been done previously [80,81].

For included cluster-RCTs, we will calculate a design effect (DE) for each study using an established formula ($DE = 1 + [n - 1] \times \rho$) [82,83]. This DE will then be used to reduce the total sample size to an "effective sample size" (*effective sample size* = *n/DE*) to account for clustering effects [82]. If an interclass correlation coefficient (ICC; ρ) is not reported in one or more of the included studies, a single conservative ICC value will be used [84]. The value of this single conservative ICC will be based on ICCs from similar studies [84] and will be imputed separately for RCTs examining provider-level or health care system-level strategies (ie, those targeting underprescription) and patient-level strategies (ie, those targeting nonadherence) [85].

Interstudy heterogeneity will be assessed by inspecting forest plots and calculating I^2 statistics [86]. We will consider I^2 statistics >25%, >50%, and >75% to represent low, moderate, and high degrees of heterogeneity, respectively [86]. We will also conduct stratified meta-analyses and meta-regressions using several prespecified risk factors for underprescription and nonadherence selected based on the findings of related systematic reviews [87-92] and methodological considerations [15,16,93-103]. The following risk factors will be used within these analyses to determine whether they may be effect modifiers: (1) whether the predominant atherosclerotic occlusive disease was CAD or another atherosclerotic occlusive disease (CVD, PAD, or polyvascular disease) [15,16]; (2) whether most prescribers were cardiovascular specialists (eg, cardiologists or vascular surgeons) or noncardiovascular specialists (eg, family physicians, general internal medicine physicians, pharmacists, or nurse practitioners) [96-98]; (3) whether studies originated from high or low-middle income countries [99,100] (according to the list provided by the World Bank in 2023) [93]; (4) the proportion of female [101-103], non-White [101-103], and low socioeconomic status [101-103] patients; (5) whether the mean age of patients was ≥65 years of age instead of <65 years of age (or whether ≥50% of the population was aged ≥65 years versus <50% of the population was aged ≥65 years) [101-103]; (6) study setting (primary care versus tertiary care) [101-103]; (7) whether participants were predominantly inpatients, outpatients, or long-term care residents (nonadherence systematic review only) [101,102]; (8) whether there was a high or unclear versus lower risk of bias related to random sequence generation,

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allocation concealment, and blinding of outcome assessors [73]; and (9) whether information regarding medication adherence was obtained using objective methods (eg, biochemical assays [94,95], electronic pill bottle openings [94,95]) or participant self-report [94] (eg, Morisky Medication Adherence Scale [104], Medication Adherence Report Scale [105] [nonadherence systematic review only]).

Publication Bias and Small-Study Effects

The presence of publication bias will be evaluated using the Egger test and by visually inspected produced funnel plots from primary outcomes [106].

Statistical Software

All analyses will be conducted using Stata Standard Edition (version 17.0; Stata Corp). Risk-of-bias graphics will be generated using Review Manager Systematic Review Software (version 5.4; The Cochrane Collaboration).

Certainty in the Cumulative Evidence

We will use the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) [107] to rate certainty in outcome estimates. First, we will assess the risk of bias, imprecision, inconsistency, indirectness, and publication bias in outcome estimates [107]. The overall certainty in these estimates will then be judged as high ("further research is very unlikely to change our certainty in the estimate"), moderate ("further research is likely to have an important impact on our certainty in the estimate and may change the estimate"), or low ("further research is very likely to have an important impact on our certainty in the estimate and is likely to change the estimate") [107].

Ethical Considerations

These systematic reviews will examine previously published data and are therefore exempt from ethics approval at our institution.

Results

We conducted the database and PubMed "related articles" search on June 6, 2023. Database searches identified 4353 total citations (n=996 from MEDLINE; n=1316 from Embase; n=1245 from Cochrane Central; n=275 from PsycINFO; and n=521 from CINAHL). The PubMed "related articles" feature identified another 34 citations. After removing duplicates, 4319 unique citations remain for title/abstract screening (see Figure 1 for our PRISMA [Preferred Reporting Items for Systematic Review and Meta-Analysis] flow diagram). We are currently in the process of performing title/abstract screening. We hope to complete analyses for the two systematic reviews by mid-2025.

Figure 1. PRISMA flow diagram describing the flow of articles through the systematic reviews. PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

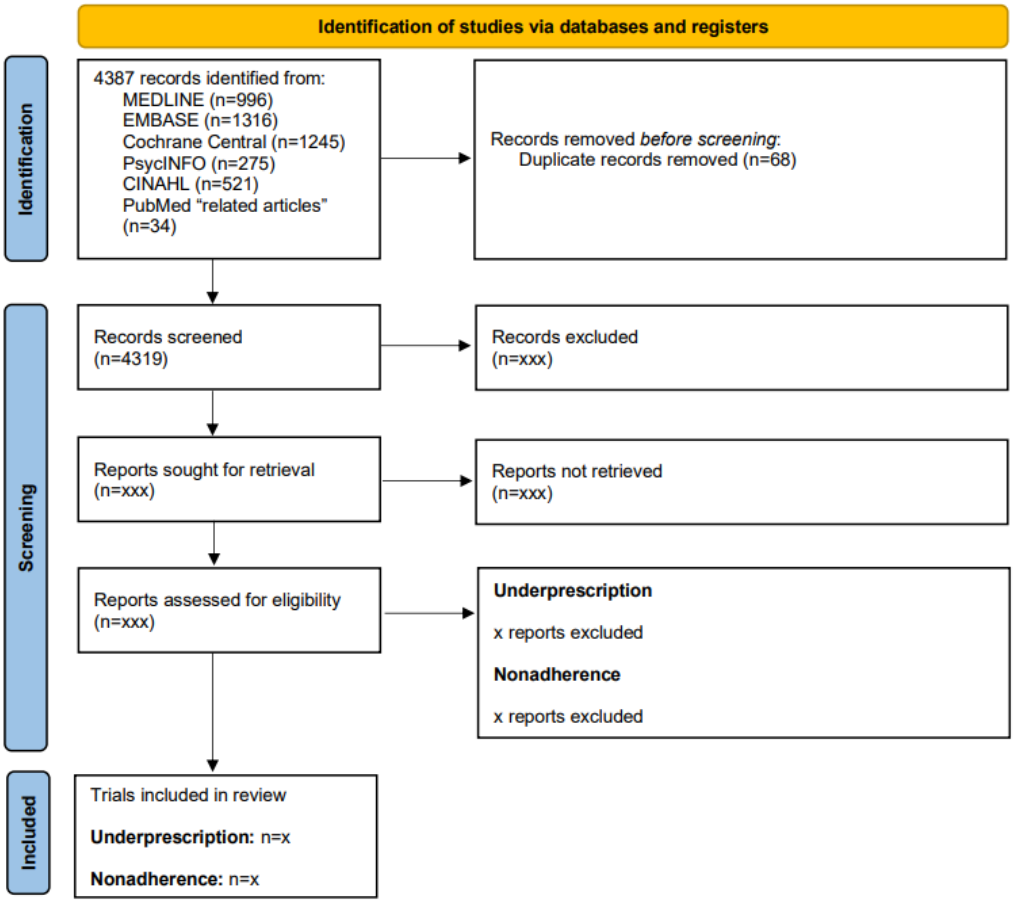

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Discussion

Future Directions and Anticipated Principal Results

Our systematic reviews will assess all RCTs examining the effectiveness of implementation and adherence-supporting strategies for improving health care provider prescription of, and patient adherence to, guideline-recommended cardiovascular medications among adults with atherosclerotic occlusive diseases. We also aim to determine the effectiveness of implementation strategies at improving medication prescription across different classes of health care providers working across different clinical practice settings. We anticipate that clinician education may be a particularly effective strategy for improving prescription among those working in primary care settings, given that these types of practitioners may have relatively reduced awareness of guideline recommendations for the management of patients with atherosclerotic occlusive disease relative to cardiovascular specialists [108]. As patients treated at tertiary medical centers tend to have complex electronic medical records [109], we anticipate that a facilitated relay of information to clinicians may be particularly effective for improving medication prescription among cardiovascular specialists and clinicians working in tertiary academic centers. Strategies anticipated to be promising for improving guideline-recommended cardiovascular medication prescription across different health care provider types and clinical practice settings include audit and feedback, provider reminder systems, and organizational changes given the promise these interventions have demonstrated for improving medication prescription among patients with varied cardiovascular diseases [87,88].

We will also examine whether the effectiveness of adherence-supporting strategies varies across patients with different types of atherosclerotic occlusive diseases (CVD, CAD, PAD, and polyvascular disease). In particular, identifying promising adherence-supporting strategies for improving medication adherence among patients with PAD is of crucial importance given that research has shown that those with PAD are less likely to be prescribed guideline-recommended medications compared to those with CVD or CAD [19]. As patients with PAD tend to have worse awareness of their condition and relevant secondary medical prevention options compared to those with other atherosclerotic occlusive diseases [110], we anticipate that patient education may be a particularly promising strategy for improving medication adherence among patients with PAD. Adherence-supporting strategies involving fiscal components (eg, medication copayment) may also be a particularly promising strategy for improving medication adherence among patients with PAD given the high costs of guideline-recommended cardiovascular medications [111]. Further, as patients with atherosclerotic occlusive disease tend to be older [53-55], strategies that remind patients to take their prescribed medications may serve as promising adherence-supporting strategies across patients with atherosclerotic occlusive disease in general.

Comparison With Previous Work

Although systematic reviews have examined the effectiveness of implementation and adherence-supporting strategies for improving health care provider prescription of [87,88], and patient adherence to [89-92], guideline-recommended cardiovascular medications for atherosclerotic occlusive diseases, they have important limitations. One systematic review of implementation strategies for improving health care provider prescription [87] characterized its implementation strategies according to the EPOC taxonomy [112], which was developed to help authors classify implementation strategies in systematic reviews. However, it aggregated implementation strategies together to assess whether they collectively increased health care provider prescription of guideline-recommended medications instead of examining whether strategy effectiveness varied within different EPOC taxonomy [112] levels (ie, professional, organizational, financial, and regulatory). This systematic review [87] also only examined patients with CAD. Although a second systematic review [88] on the effectiveness of implementation strategies for improving health care provider prescription also characterized implementation strategies using the EPOC taxonomy [112], it examined the effectiveness of improving physician adherence to "guideline-recommended care" (eg, use of cardiovascular risk assessment tools or following guidelines for cardiovascular disease screening) in addition to medication prescription [88]. It also included patients with nonatherosclerotic cardiovascular diseases. Limitations of the existing systematic reviews of adherence-supporting strategies for improving patient adherence is that many include patients "at risk" of developing an atherosclerotic occlusive disease or with nonatherosclerotic cardiovascular diseases (eg, hypertension or congestive heart failure) [91,92]. Further, many only examine specific adherence-supporting strategies (eg, polypills, text-message reminders, or patient education) [89,90,92] or adherence to specific cardiovascular medications among patients with CVD or CAD [89-92]. Many also did not categorize their adherence-supporting strategies according to an established taxonomy [91]. Finally, many relevant RCTs have been completed since the publication of prior underprescription [87,88] and nonadherence [89-92] systematic reviews.

Strengths and Limitations

Our proposed systematic review has potential limitations. First, we anticipate that it may be difficult to pool the results of some studies due to interstudy heterogeneity [113]. We anticipate that many relevant RCTs [21-48] may have reported different primary and secondary outcomes at different time points and using different outcome measurement scales. Should we be unable to pool our quantitative results, we will summarize our results narratively instead of using the methods outlined above [73]. Second, it may be argued that including patients with all forms of atherosclerotic occlusive disease in our study population may introduce clinical heterogeneity due to small differences in underlying disease pathophysiology [50-52] and epidemiology [53-55]. Nevertheless, the patient populations in our proposed systematic reviews are more similar regarding disease pathology, epidemiology, and medication requirements than others in previously published systematic reviews [87-92]. Further, these conditions commonly coexist within patients [56,57] and similar prescribers are involved in their medical management [58-60]. Finally, although the use of self-reported

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data to quantify medication adherence introduces the possibility of outcome misclassification bias [94], we plan on performing stratified meta-analysis and meta-regression to determine whether observed differences in medication adherence vary by whether studies quantified medication adherence using objective methods versus participant self-report.

Conclusions

In conclusion, we will perform systematic reviews and meta-analyses of RCTs examining implementation and adherence-supporting strategies designed to improve health care provider prescription of, and patient adherence to, guideline-recommended cardiovascular medications among patients with atherosclerotic occlusive diseases. These systematic reviews will also determine the effect of these interventions on patient-important outcomes and health care resource use. Finally, they will determine whether effectiveness varies by patient characteristics, prescriber traits, and clinical practice setting.

Acknowledgments

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Data Availability

Data from the systematic review will be provided by study authors upon reasonable request.

Authors' Contributions

AMK and DJR conceived this study, and AMK, DJR, DAF, JP, and DIM developed this study. AMK, RS, and DJR designed the search strategy and the qualitative and quantitative data synthesis plan, which DAF, JP, and DIM further refined. AMK wrote the initial draft of the protocol, which was critically reviewed by DAF, JP, DIM, and DJR. AMK submitted the protocol to PROSPERO. All of this study's authors have critically read and approved the final version of this protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-*P* 2015 checklist. PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols.
[DOCX File , 24 KB - resprot_v14i1e60326_app1.docx]

Multimedia Appendix 2
Database search strategies (June 6, 2023). MeSH: Medical Subject Heading.
[DOCX File , 17 KB - resprot_v14i1e60326_app2.docx]

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Abbreviations

AACTT: action, actor, context, target, time
BCW: Behavior Change Wheel
CAD: coronary artery disease
CVD: cerebrovascular disease
DE: design effect
EPOC: Effective Practice and Organization of Care
GRADE: Grading of Recommendations, Assessment, Development, and Evaluation
HR: hazard ratio
ICC: interclass correlation coefficient
MACE: major adverse cardiac event
MALE: major adverse limb event
OR: odds ratio
PAD: peripheral artery disease
PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
RCT: randomized controlled trial
RR: relative risk

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Protocol

Applications of Natural Language Processing and Large Language Models for Social Determinants of Health: Protocol for a Systematic Review

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Abstract

Background: In recent years, the intersection of natural language processing (NLP) and public health has opened innovative pathways for investigating social determinants of health (SDOH) in textual datasets. Despite the promise of NLP in the SDOH domain, the literature is dispersed across various disciplines, and there is a need to consolidate existing knowledge, identify knowledge gaps in the literature, and inform future research directions in this emerging field.

Objective: This research protocol describes a systematic review to identify and highlight NLP techniques, including large language models, used for SDOH-related studies.

Methods: A search strategy will be executed across PubMed, Web of Science, IEEE Xplore, Scopus, PsycINFO, HealthSource: Academic Nursing, and ACL Anthology to find studies published in English between 2014 and 2024. Three reviewers (SR, ZZ, and YC) will independently screen the studies to avoid voting bias, and two (AS and YX) additional reviewers will resolve any conflicts during the screening process. We will further screen studies that cited the included studies (forward search). Following the title abstract and full-text screening, the characteristics and main findings of the included studies and resources will be tabulated, visualized, and summarized.

Results: The search strategy was formulated and run across the 7 databases in August 2024. We expect the results to be submitted for peer review publication in early 2025. As of December 2024, the title and abstract screening was underway.

Conclusions: This systematic review aims to provide a comprehensive study of existing research on the application of NLP for various SDOH tasks across multiple textual datasets. By rigorously evaluating the methodologies, tools, and outcomes of eligible studies, the review will identify gaps in current knowledge and suggest directions for future research in the form of specific research questions. The findings will be instrumental in developing more effective NLP models for SDOH, ultimately contributing to improved health outcomes and a better understanding of social determinants in diverse populations.

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KEYWORDS

social determinants of health; SDOH; natural language processing; NLP; systematic review protocol; large language models; LLM

Introduction

Rationale

Social Determinants of Health

Social determinants of health (SDOH) are the nonmedical conditions in which people are born, grow, live, work, and age [1]. These circumstances are shaped by the distribution of money, power, and resources at global, national, and local levels, and are primarily responsible for health inequities—the unfair and avoidable differences in health status seen within and between countries. As a result, one of Healthy People 2030's five overarching goals is specifically related to SDOH: "Create social, physical, and economic environments that promote attaining the full potential for health and well-being for all" [2]. Studies have shown that SDOH has powerful influences on health [3] and well-being at the individual and population levels [4]; therefore, it is important to capture them. Such information is valuable to a range of stakeholders including patients, health care providers, policymakers, and insurance companies. For instance, clinicians might modify a patient's medication regimen if they learn that the patient has difficulty affording their prescriptions or lacks reliable transportation to the pharmacy. It is important to note here that SDOH concepts are often described using a variety of synonyms, paraphrases, or language variations [5], which makes it difficult for simple keyword-based methods to capture all relevant instances. Moreover, many SDOH indicators are not directly stated but implied through context.

Natural Language Processing

Natural language processing (NLP) is a subfield of artificial intelligence and computer science that enables computers to understand, interpret, and generate human language in a way that is both meaningful and useful. NLP encompasses a wide range of tasks, including but not limited to language translation, sentiment analysis, speech recognition, text summarization, and information extraction. NLP offers a promising tool to systematically analyze vast amounts of unstructured text data, including electronic health records (EHRs), social media, public health reports, and others [6]. Such tools and techniques can, therefore, be used to extract socioeconomic factors, environmental conditions, and personal lifestyles that significantly impact an individual's health outcomes. NLP models trained on labeled datasets can learn to recognize these patterns, which can improve extraction accuracy. SDOH information is often embedded within patient narratives or longer descriptions. NLP can assist in parsing and understanding context, coreferences, and the relationships between text parts. Unlike a manual review (time-consuming, labor-intensive, and prone to human error), NLP enables the rapid and scalable analysis of large datasets with greater accuracy and consistency [7,8].

NLP for SDOH

Multiple studies exist that showcase the application of NLP to various SDOH-related tasks in addressing health disparities. One key application is the identification and extraction of SDOH factors from EHRs, where NLP techniques have been used to classify and analyze clinical notes for social needs, behavioral factors, and other determinants that influence patient outcomes [9-12]. In the context of public health, NLP has been used to explore the impact of external events (eg, the COVID-19 pandemic) on marginalized communities by analyzing social media data [13]. Additionally, NLP has been leveraged to identify SDOH in specific populations, such as pediatric patients [14,15], patients living with Alzheimer disease [11], and individuals with lower back pain [16]. Advanced models such as the recent GPT and transformer-based models have further refined the extraction of SDOH from patient records and contributed to more precise and scalable analyses [17,18]. Moreover, NLP has been used to find out the underlying social factors in clinical social work notes [19] and emergency medical services records [20] that further enhance the understanding of how social determinants influence health care delivery.

Despite the promise of NLP in the SDOH domain, the literature is dispersed across various disciplines. Hence, a systematic review is necessary to consolidate existing knowledge, identify knowledge gaps in the literature, and inform future research directions in this emerging field. Our systematic review will focus on studies from 2014 onwards which is well-supported by the significant advancements in NLP techniques and the conceptual evolution of SDOH research that have occurred during this period. The development and introduction of Word2Vec [21] and the subsequent introduction of transformer models [22] marked a point of great improvement in NLP research. In addition, the rise in popularity of large language models (LLMs) such as BERT [23] and GPT [24] has driven substantial progress in the field of NLP. By limiting the review to this decade, the systematic review will capture the evolution of NLP approaches and their application in SDOH tasks, thereby providing a comprehensive and up-to-date study of the literature.

Objectives

This systematic review has two major objectives. First, to identify and highlight distinct NLP techniques, including LLMs (commercial, as well as open-sourced), which are used for tasks including but not limited to augmentation, organization, annotation, prediction, trend analysis, detection, identification, extraction, or classification of SDOH in a given dataset. The NLP model can be used in conjunction with other techniques, but at minimum, the NLP element should be there. The second objective is to report the effectiveness of such techniques or models, identify potential knowledge gaps, and design research questions for future studies.

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Methods

Protocol and Registration

The study has been registered in PROSPERO (CRD42024578082) and will be carried out under PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [25]. This protocol was developed using the 2015 PRISMA-P recommended checklist (Multimedia Appendix 1) for systematic review protocols [26]. However, we omit items 16 (meta-biases) and 17 (confidence in cumulative evidence), given we will not synthesize the outcomes of studies. The review team is composed of researchers across disciplines with diverse backgrounds.

Eligibility Criteria

The eligible publications for this review are restricted to peer-reviewed published literature (observational studies, algorithm validation studies, computational model evaluations, experimental, and qualitative), including journal studies and full conference papers such as ACL anthology. The study must be written in English, although the language of the textual dataset used can vary. The publication period of the included studies was restricted to the last decade, that is, from 2014 to 2024. To be included, a study should answer a research question on the design, development, and application of NLP in health data analysis for SDOH and have used (1) a dataset containing health care data including but not limited to EHRs, social media posts, and clinical notes or narratives, and (2) NLP techniques or models or LLMs (commercial, as well as open source) for tasks including but not limited to augmentation, organization, annotation, prediction, trend analysis, detection, identification, extraction, or classification of SDOH in a given dataset. The NLP model can be used in conjunction with other techniques, but at least the NLP element should be there. Comparisons will be performed against studies included in the review.

For this review, we focused primarily on peer-reviewed literature to ensure the reliability of quantitative information. However, as part of the final systematic review, we will incorporate relevant preprints published between the last search query and up to one month before publication. This approach balances the inclusion of recent advancements while maintaining methodological rigor.

Information Sources

We conducted a systematic search of the following databases from January 1, 2014, to August 9, 2024, across 7 databases: PubMed, Scopus, Health Source: Nursing/Academic, PsycINFO, Web of Science, ACL Anthology, and IEEE EXPLORE. Preprints (arXiv/bioRxiv), forewords, prefaces, table of contents, programs, schedules, indexes, call for papers or participation, lists of reviewers, lists of tutorial abstracts, invited talks, appendices, session information, obituaries, book reviews, newsletters, lists of proceedings, lifetime achievement awards, erratum, systematic reviews, scoping reviews, and notes will be excluded. We will screen relevant review studies based on eligibility criteria. We will further screen studies that cited the included studies (forward search). We will perform hand searches.

Search Strategy

The database search strategies were developed by a health sciences librarian (HR) with expertise in literature searches. Known relevant studies collected by the authors were analyzed to select keywords for the search query. The initial search strategy in PubMed was then iteratively developed by adding or removing additional keywords until all known relevant studies were retrieved by the search query. Textbox 1 shows a draft of the search strategy to be used for the PubMed database, including planned limits. The full search strategies for all information sources are provided in Multimedia Appendix 2.

Textbox 1. Search strategy on PubMed.

Query

(“Natural Language Processing”[Mesh] OR “natural language”[tw] OR NLP[tw] OR “large LM*”[tw] OR LLM[tw] OR LLMs[tw] OR “large language model*”[tw] or ChatGPT*[tw] OR “Chat GPT*”[tw] OR GPT4*[tw] OR GPT-4*[tw] OR GPT3*[tw] OR GPR-3*[tw] OR “Generative Pre-trained Transformer*”[tw] OR LLAMA[tw] OR “Claude 3”[tw] OR Mistral[tw] OR MedPaLM*[tw] OR Med-PaLM*[tw] OR “text mining”[tw] OR “text process*”[tw] OR “information retrieval”[tw] OR “information extract*”[tw])

AND

(“Social Determinants of Health”[Mesh] OR SDOH[tw] OR SDH[tw] OR SBDH*[tw] OR “determinants of health”[tw] OR “health determina*”[tw] OR “life events”[tw] OR “social determinant*”[tw] OR “socioeconomic determinant*”[tw] OR “socioeconomic factor*”[tw] OR “social determinate*”[tw] OR “social factor*”[tw] OR “social need*”[tw] OR “social prescribing”[tw] OR “social determining factor*”[tw] OR “social risk*”[tw])

Filters

- Manuscript language: English
- Publication years: 2014-2024
- Other: exclude preprints

In addition, a refreshed search strategy will be implemented to ensure that the systematic review includes the most up-to-date and relevant studies. If a significant amount of time has elapsed between the initial literature search and the subsequent stages of citation screening or paper preparation, a secondary search will be conducted. This refreshed search will follow the same search strategy as the initial one, using the same databases, search terms, and inclusion or exclusion criteria. Any newly

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identified studies will undergo the same rigorous screening process as those identified in the original search to ensure their relevance and quality before inclusion in the final analysis.

Study Records

Data Management

Potentially relevant citations will first be imported into EndNote (Clarivate) and then exported as an XML file to Covidence (Veritas Health Innovation Ltd), which will identify and remove duplicate records.

Selection Process

Three reviewers (SR, ZZ, and YC) will independently screen each study for eligibility by marking it as a "yes" (for inclusion), "no" (for exclusion), or "maybe" (in case of uncertainty about relevance) in the Covidence platform. Two senior reviewers (AS and YX) will resolve potential discrepancies during any screening step. All voting is blinded, meaning the colleagues cannot see votes until they have cast their own, and vice versa. In the first stage, the reviewers will screen the titles and abstracts of each study as identified in the databases by our search strategies. In the second stage of screening, the team will obtain and screen the full-text papers as per the eligibility criteria. Studies that do not meet the eligibility criteria will be moved to an exclusion folder. The final corpus of selected studies will be then approved by the consensus of all reviewers involved in this study and sent to an expert consultant for potential suggestions. The selection process will be displayed in a PRISMA flowchart.

Data Collection Process

Two independent researchers (SR and ZZ) will extract data from the final included full texts. Before formal data extraction, one reviewer (SR) will pilot the data extraction form with a sample of five papers to identify and address any issues in the form to ensure it is comprehensive. The data extraction will then be conducted independently by both reviewers using the finalized form. Any disagreements between the two reviewers will be discussed and resolved through consensus. If consensus cannot be reached, a third reviewer will mediate. In cases where data is incomplete or unclear, the original study authors may be contacted to request additional information or clarification. All data will be managed using Covidence or via a shared Excel (Microsoft Corp) sheet to ensure consistency throughout the process.

Data Items

Figure 1 outlines a preliminary list of variables for which data will be collected, including study identifications (eg, year of publication and type), dataset details (eg, sample size and type), intervention specifics (eg, type of NLP technique and SDOH task), and outcomes (eg, accuracy and precision). Each variable is defined to ensure consistency across studies. During the data extraction process, any assumptions made (such as imputing missing values or converting data into a common format) will be documented and justified. If necessary, modifications to the list of variables will be made during the review, and these changes will be detailed in the final systematic review report.

Figure 1. The data to be extracted. EHR: electronic health record; EMR: emergency medical services; NLP: natural language processing; SDOH: social determinants of health.

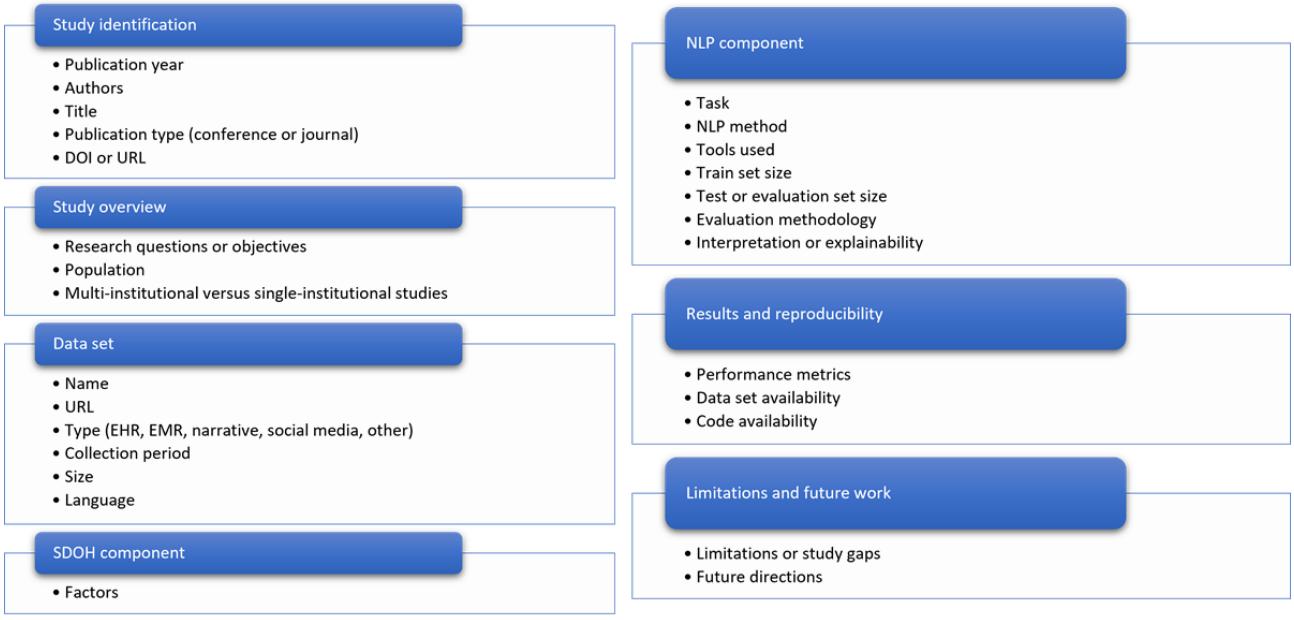

Outcomes and Prioritization

We will focus on evaluating the effectiveness and accuracy of various NLP techniques and models applied to SDOH tasks. The primary outcomes of interest will include key performance metrics such as precision, recall, F_1-score, and others, as these are critical indicators of the success of NLP models. Secondary outcomes will involve assessing the integration of NLP techniques with other computational models, such as machine learning and deep learning approaches, to determine their combined impact on model performance. In cases where metrics are not reported, the review will include a qualitative assessment of the study's findings, focusing on the reported outcomes and their relevance to the SDOH task.

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Risk of Bias Assessment

We anticipate that the studies included in the review may vary significantly. For instance, some may use complex NLP algorithms while others rely on rule-based systems. Hence, it is challenging to name one specific tool for assessing bias at this stage. We will prioritize assessing key factors that could introduce bias, such as the quality of the datasets, the transparency in reporting the models' performance, and the robustness of the evaluation metrics such as precision and recall.

In addition to assessing general risks of bias, this review will evaluate potential algorithmic bias across individual studies. Algorithmic bias can arise from imbalanced datasets, where certain populations or social determinants are underrepresented, leading to biased predictions. We will examine whether studies report efforts to mitigate such biases.

Data Synthesis

For this systematic review, a narrative synthesis approach will be used. Data from the included studies will be analyzed by two reviewers, with any disagreements resolved through discussion or consultation with a third reviewer if necessary. Given the diverse methods used in the selected studies, the synthesis will focus on identifying and describing common patterns, trends, and knowledge gaps. The analysis will be divided into the following parts:

- Characteristics of the studies (such as the number of studies, types of datasets, NLP techniques, outcomes, and potential biases).
- Contributions of these studies to the development and application of NLP models for SDOH. As this review is intended to be qualitative, no (or minimum) statistical tools will be applied.

Ethical Considerations

No ethical approval is required for this protocol and proposed systematic review, as we will only use data from previously published papers that have received ethics clearance and used proper informed consent procedures. The systematic review's results will be disseminated through publication in a peer-reviewed journal and shared on a publicly accessible GitHub repository [27].

Results

As of December 2024, the systematic review is in progress (SR, ZZ, and YC started screening studies) and is expected to be finished by March 2025. Our final paper is expected to be submitted to peer-reviewed journals by spring 2025.

Discussion

Anticipated Principal Findings

This systematic review is expected to reveal valuable insights into the current state of NLP applications in SDOH tasks. We anticipate identifying the most effective NLP techniques and models across various types of health care data, as well as the common challenges and limitations associated with these approaches. Specifically, we expect to find that the integration of NLP with other computational models, such as machine learning and deep learning, often enhances performance and results in more robust outcomes. We also anticipate that the review will reveal significant variability in model performance based on the type of data used (eg, EHRs vs social media posts) and the specific SDOH being targeted (eg, socioeconomic status vs housing stability). It is important to investigate these factors separately because the challenges in data processing and model effectiveness can vary significantly across different contexts. Investigating these subgroups will provide insights into which NLP techniques are most effective for specific types of data and SDOH, which will enable a more targeted approach in future model development and application. We anticipate that the GitHub repository will offer a platform where researchers can contribute new studies and insights, facilitating ongoing dialogue and collaboration in the field of NLP for SDOH.

Limitations

One limitation of this study is the selection of studies published between 2014 and 2024. Although this timeframe is chosen to focus on recent advancements, it may limit the historical context. We focus on peer-reviewed papers to ensure the inclusion of high-quality and rigorously evaluated studies. While this approach emphasizes established research, it may mean that some recent studies (such as preprints) will not be captured. By prioritizing peer-reviewed literature, we base our findings on research that has undergone thorough scrutiny.

Acknowledgments

We are grateful to the anonymous reviewers at JMIR Research Protocols for their helpful feedback. YX is supported by the National Institute of Mental Health (RF1MH134649), the American Foundation for Suicide Prevention (YIG-2-133-22), the Mental Health Research Network, Google, and the National Institutes of Health (1OT2OD032581-02-259). AS is supported by the National Institute on Drug Abuse (R01DA057599).

Data Availability

All data generated or analyzed during this study will be included in the final systematic review publication and its supplementary information files.

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Authors' Contributions

SR developed the study concept and methodology, conducted the investigation, wrote the original manuscript, and created Figure 1. ZZ reviewed the papers, did a literature review, and wrote the manuscript. YC reviewed the papers and wrote the manuscript. HR provided data for Textbox 1 and handled search query curation. AS and YX conceptualized the study, resolved study review conflicts, and provided overall supervision and project administration. All authors reviewed the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P 2015 checklist: recommended items to address in a systematic review protocol.
[PDF File (Adobe PDF File), 132 KB - resprot_v14i1e66094_app1.pdf]

Multimedia Appendix 2
Search strategies and the number of results.
[PDF File (Adobe PDF File), 1643 KB - resprot_v14i1e66094_app2.pdf]

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Abbreviations

EHR: electronic health record
LLM: large language model
NLP: natural language processing
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses—Protocols
SDOH: social determinants of health

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Protocol

Sign Language Recognition System for Deaf Patients: Protocol for a Systematic Review

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Abstract

Background: Individuals with hearing impairments may face hindrances in health care assistance, which may significantly impact the prognosis and the incidence of complications and iatrogenic events. Therefore, the development of automatic communication systems to assist the interaction between this population and health care workers is paramount.

Objective: This study aims to systematically review the evidence on communication systems using human-computer interaction techniques developed for deaf people who communicate through sign language that are already in use or proposed for use in health care contexts and have been tested with human users or videos of human users.

Methods: A systematic review will be performed based on a literature search in MEDLINE, Web of Science, ACM, and IEEE Xplore as well as top-tiered conferences in the area to identify relevant studies. The inclusion criteria are the description of the development of a sign language recognition system in a health care context and the testing with human users. Independent investigators (LFRO, LRV, and LMMSR) will screen eligible studies, and disagreements will be solved by a senior researcher (MSM). The included papers will undergo full-text screening. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flow diagram will be presented to visually summarize the screening process, ensuring clarity and transparency in presenting the results. Additionally, a comprehensive chart table will be constructed to consolidate essential data related to the key variables extracted from the studies. These results will be meticulously analyzed and presented descriptively, offering insightful interpretations of the information encapsulated within the table.

Results: A preliminary search was performed in April 2024. Researchers concluded the study selection by July 2024. Data extraction, synthesis, report, and recommendations are expected to be finished by February 2025.

Conclusions: This systematic review will identify human-machine systems that enable communication in health services involving deaf patients, presenting the framework that includes usability and application in human contexts. We will present a comprehensive panel of findings, highlighting systems used to tackle communication barriers and offer a narrative comparison of current implementation practices.

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(JMIR Res Protoc 2025;14:e55427) doi:10.2196/55427

KEYWORDS

computer neural networks; artificial intelligence; biomedical technology; communication aids for disabled; computer vision; sign language; hearing loss; deaf people; communication barriers; gestures

Introduction

The term "disabling hearing loss" refers to any type of hearing problem that is considered to be at least moderate (greater than 40 dB), including deafness, and that requires some type of health device to allow adequate communication with the individual [1]. According to the World Health Organization, approximately 430 million people, which accounts for over 5% of the world's population, have some disabling hearing loss [2]. It is estimated that by 2050, over 700 million people will have some hearing impairment [2].

The scientific literature highlights numerous inequalities faced by the deaf community regarding access to health care services [3-5]. A qualitative study involving 93 deaf adults primarily communicating in American Sign Language revealed that most participants struggled with understanding medical instructions due to communication challenges [6]. Despite often being accompanied by family members during medical appointments, participants expressed dissatisfaction with their effectiveness as communication facilitators. They reported feeling excluded from conversations and expressed privacy concerns when using interpreters [6], a pertinent issue regarding the confidentiality of medical interactions.

In this context, it becomes evident that individuals with hearing impairment are more likely to experience preventable health issues, including adverse problems in acute care and chronic diseases, such as obesity, hypertension, cardiovascular disease, diabetes, smoking, and alcoholism [7,8]. A scoping review of 2022 revealed a gap in the interpretation of sign language for health care and showed that this area is underresearched [9]. Thus, several studies have been committed to the development of assistive technologies, using artificial intelligence techniques, aiming to mitigate the inequalities related to health accessibility experienced by the deaf community. Among these technologies, it is important to highlight that the creation of communication systems that allow translation between sign language and written text, has shown to be very promising [10]. However, despite all the progress attained, the current literature has also shown a huge gap regarding the use of these strategies with deaf people, especially in health care contexts. For this reason, it seems obvious that the creation and implementation of communication systems to enable better interaction between the deaf population and health care workers are paramount. This study aims to systematically review the evidence on communication systems using human-computer interaction techniques developed for deaf individuals who communicate through sign language that are already in use or proposed for use in health care contexts and have been tested with human users or videos of human users.

Methods

Study Design

This is a systematic review protocol. The study design is a systematic search of the medical and other technical literature followed by a narrative synthesis of the results. The research protocol was registered in the Open Science Framework (OSF) [11]. It followed guidance from the Cochrane Guidelines and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) statement [12]. The PRISMA-P (PRISMA Protocols) checklist can be seen in Multimedia Appendix 1.

A multidisciplinary team comprising researchers from health and computing domains, along with linguistic specialists in sign language, will collaboratively conduct the systematic review. Two members (ELAB and RAAC) of the team are linguistic specialists and sign language researchers, of whom one is deaf (RAAC). Both of them revised the terminology used in this review and revised the methodology critically to ensure that the needs of deaf people have been taken into account.

Strategy for Preparing the Research

Phases of this review are as follows: (0) identification of the need for a review, (1) preparation of a proposal for a review, (2) development of a review protocol, (3) protocol registration in OSF, (4) identification of research, (5) selection of studies, (6) study quality assessment, (7) data extraction, (8) data synthesis, and (9) report and recommendations.

Research Question

The primary research question is as follows: What technologies have been developed and tested in real-world settings to translate sign and oral languages, facilitating communication between deaf patients who primarily use sign language and health care workers?

The specific questions are as follows:

- Question 1: In which context of health care have these technologies been used?
- Question 2: Which languages (sign and oral) can these technologies translate?
- Question 3: Which technologies are required in loco for it to be used?
- Question 4: How were they developed?
- Question 5: How were they deployed and tested?
- Question 6: How has the communication between health care workers and deaf people been improved by using these technologies?
- Question 7: How was the efficacy of these technologies evaluated?
- Question 8: Is the system or technology "bidirectional"?

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Search Strategy

The search process will commence following registration on the OSF [10]. Independent reviewers will meticulously search the following databases: Web of Science, MEDLINE, IEEE Xplore, ACM, and Google Scholar.

A draft of the search strategy was developed by 5 of the authors (MSM, LFRO, LRV, ROP, and ZSNR), using Medical Subject Headings (MeSH), and text words related to the topic of interest were defined. The proposed search strategy is shown in Multimedia Appendix 2.

Studies published from the inception of the database onward will be inclusively considered, without imposing restrictions on the time frame or publication date, as well as language. Searches will be rerun before the final analysis to ensure comprehensiveness. Additionally, in the event of unpublished studies, authors will be contacted. Reference lists of eligible studies will be thoroughly explored to identify additional eligible studies.

Detailed search data for the identified studies and information for each phase will be presented in a flowchart, accessible in Multimedia Appendix 3, following the guidelines outlined in the PRISMA method [12].

Eligibility Criteria

To be included in the systematic review protocol, a study must be prospective, retrospective, or descriptive; describe the development of communication systems applied to deaf people who communicate through sign language in a health care encounter context; and include testing with human users or videos of human users. The human users of the identified technologies should encompass individuals of any age who are deaf and primarily communicate through sign language.

Correspondences, short communications, and conference abstracts will also be included. Studies that do not align with the research questions specified earlier, fail to report use within health care encounters, do not involve testing with human users, or lack videos of human users will be excluded from the review.

Outcome Definition

The primary anticipated outcome will consist of a compilation of reports detailing technologies using human-computer approaches aimed at facilitating communication for deaf patients during health care encounters. Secondary outcomes will involve conducting a narrative comparison of the identified technologies.

Study Selection

In the screening phase, studies will be selected based on the predetermined inclusion and exclusion criteria after reviewing their titles, abstracts, and full texts. Researchers will independently screen titles and abstracts, with full-text review conducted if uncertainty arises from the abstract. Papers deemed potentially eligible based on title and abstract will undergo full-text screening for final eligibility determination. Eligible papers will be included in the study. Any disagreements regarding eligibility will be resolved by a senior member (MSM) of the team (MSM). The study selection process is represented using the PRISMA flow diagram, which can be found in Multimedia Appendix 3. Included studies will subsequently be selected for qualitative and quantitative analysis during the inclusion phase.

Risk of Bias and Methodological Quality Analysis

The review will conduct a descriptive analysis. There is no specific risk of bias tool for the type of study we expect to find. If applicable, we use the mobile health evidence reporting and assessment checklist in the individual studies [13].

Data Extraction and Data Synthesis

Independent reviewers (LFRO, LRV, and LMMSR) will extract data from the full text of eligible manuscripts using a predefined model. Any uncertainties or divergences will be resolved by a senior researcher (MSM). The following data items will be extracted from each publication: first author, journal and year of publication, country, the aim of the study, whether it was a multidisciplinary study team, corpus of terms used to develop the communication system, corpus examples, communication system development, intervention and testing, languages involved (oral and sign), evaluation or use in a real context, sample size (number of users), preconditions to use the technology and technology needed (hardware or software), development technology (artificial intelligence, imaging processing, etc), which health context (eg, general, emergency, and teleconsultation), technology readiness level (development and testing or if it is being marketed), testing: human users or video of human users, accuracy measures, metrics for evaluating communication effectiveness and parameters to assess to what extent innovation is addressing the communication needs of deaf persons, and ethical and software security issues. These data are detailed in Multimedia Appendix 4. Whenever possible, we will also seek to infer systems' characteristics of flexibility and scalability in various health care settings. Additionally, the research team will email researchers from all individual studies included in the systematic review to update the current status of their systems and to ensure the accuracy and relevance of the information presented in the systematic review. A qualitative analysis of the usability results will be performed for the review.

Results will be presented in a PRISMA flow diagram and a descriptive format (using tables and diagrams, if necessary) aligned with the objective and scope of the review. Results will be presented to carry out a descriptive analysis of the information in the table. For each variable extracted, a narrative summary will be provided, describing how the results relate to the review's objective.

Data Management

The abstracts and full text of manuscripts identified from the search will be uploaded to Rayyan software from Qatar Computing the Research Institute, a software developed specifically to expedite the screening of titles, abstracts, and manuscripts using a process of semiautomation [14]. After uploading the search results, duplicates will be removed in the Rayyan environment [15]. A data extraction form will be developed in Microsoft Excel and piloted before use.

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Description of Statistical Methods and Software Used

If feasible, we intend to conduct statistical analysis to aggregate accuracy measures. However, we anticipate that this approach may not be sufficient. In such instances, the systematic review will proceed with a narrative review of the evidence, providing a qualitative synthesis of the findings.

Ethical Considerations

The systematic review does not require ethics approval, as all data used will be provided from published documents. The authors are committed to reporting any outcomes, even the unexpected ones, to ensure transparency and responsibility.

Results

A preliminary search was performed in April 2024. Researchers concluded the study selection by July 2024. Data extraction, synthesis, report, and recommendations are expected to be finished by February 2025. The review timeline is shown in Multimedia Appendix 5.

Discussion

Expected Findings

Communication barriers persist for deaf individuals in health care, urging solutions. In this context, this review aims to summarize the current literature on communication systems using human-computer interaction techniques for sign language users, in a health care context. As the main finding, we aim to reveal the current state of communication systems dedicated to improving health care interactions with deaf people and using a variety of advanced models to enhance accuracy and usability. Additionally, we seek to identify existing gaps in the development of these systems. We anticipate that the predominant focus on technical aspects or innovations may lead to a scarcity of manuscripts addressing communication outcomes, which should ideally be the primary focus, as it determines the effectiveness of communication.

Strengths

Sign language recognition is often considered less advanced compared to other recognition systems like facial or speech recognition. Several characteristics are important to enhance communication with deaf people using systems and devices, such as adequate screens, stable internet connection, qualified and trained professionals, interoperability of the system, safety for the patient and professional, and extensive testing [9]. Research in this field must focus on models that improve the accuracy of recognition systems and, more importantly, communication. To investigate these factors, a multidisciplinary staff including health, linguistic, and technology teams will participate in the search process, conducting and validating its progress. This would strengthen the results, as it broadens the results landscape. Another important strength to highlight is that the systems assessed in this review will not depend on a translator, as is the case for video remote interpretation. We believe that, if proven effective, these systems could enhance the autonomy of deaf individuals in managing their health care. Furthermore, these systems have the potential to surmount barriers related to patient privacy concerns and communication challenges. With the escalating integration of artificial intelligence techniques in health care, there is growing recognition that capturing signs or gestures and converting them into audio or written language, and vice versa, can significantly enhance accessibility to health care services, ranging from primary care facilities to emergency departments. Identifying information regarding the availability, usability, and implementation specifics of such systems stands as a crucial outcome to be unearthed.

In response to this urgent demand, our research group is diligently conducting a comprehensive and high-caliber systematic review. While the ultimate goal must consider context and innovation, it is paramount to prioritize meeting the needs of the ultimate end users: individuals who are deaf.

To identify and delineate these systems, along with associated contextual possibilities, use methods, required equipment, and technological development and testing, we will present a comprehensive findings panel and conduct a narrative comparison. This approach aims to facilitate a comprehensive overview and deeper understanding of the current state of the art. Our results are poised to offer valuable insights into the landscape of systems and the evolution of human-computer–assistive technologies used in aiding deaf patients.

In emergency care units, timely access to information is crucial for defining patient routes, conducting necessary examinations, and providing critical interventions and advice. Previous studies have shown that preventable adverse events are more likely to occur in cases with communication problems, particularly in emergency situations [7]. Despite the pressing need for studies in this area, testing interventions in emergency contexts is more complex, leading us to anticipate fewer analyses in this critical domain.

Limitations and Future Directions

This systematic review, while intended to be comprehensive, may encounter limitations impacting its conclusions. First, the diversity of sign language dialects, and the specificity of their use, might limit the generalizability of the findings across different cultural contexts. Additionally, the rapid evolution of technology in the field of sign language recognition systems may also mean that some of the reviewed technologies quickly become outdated.

With the results of this review, we expect to advocate future directions for the creation of more adaptive and inclusive communication systems, capable of learning from a broader spectrum of sign language dialects and styles. However, it specifically targets individuals who use sign language. This approach may not represent the entire deaf community, as some individuals may prefer lip reading, writing, or other forms of communication due to unfamiliarity with or reluctance to use sign language. Further studies should explore technologies aimed at enhancing communication for individuals with varying degrees of hearing impairment and differing abilities in sign language proficiency. Expanding research in this direction can

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contribute significantly to addressing the diverse communication needs within the deaf and hard-of-hearing community.

Our team plans to disseminate the protocol and findings of this research in forums with public authorities, academies, and the population to present solutions for improving effective communication in health services, especially involving the most vulnerable populations. In addition, as social media has a relevant impact on our society, all the results will be posted on social media as well to be available to the population.

Acknowledgments

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Data Availability

All data generated or analyzed during this study are included in this published paper and its supplementary information files.

Authors' Contributions

MSM, LFRO, LRV, ROP, and ZSNR developed a draft of the literature search, which was executed by LFRO and LRV. MSM, ROP, ZSNR, TBCS, and MFMC guided the construction of the protocol, and MSM is a guarantor of the review. MSM, LFRO, LRV, and LMMSR drafted the manuscript; all the other authors performed critical revisions. ELAB is a linguistic professor who is a specialist in sign language. She has revised the whole manuscript to ensure that language complies with disability and deaf literature. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist.
[DOCX File , 38 KB - resprot_v14i1e55427_app1.docx]

Multimedia Appendix 2
Search strategy.
[DOCX File , 14 KB - resprot_v14i1e55427_app2.docx]

Multimedia Appendix 3
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) flowchart.
[DOCX File , 65 KB - resprot_v14i1e55427_app3.docx]

Multimedia Appendix 4
The variables analyzed in the systematic review.
[DOCX File , 196 KB - resprot_v14i1e55427_app4.docx]

Multimedia Appendix 5
Gantt chart for the project timetable.
[DOCX File , 20 KB - resprot_v14i1e55427_app5.docx]

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Abbreviations

OSF: Open Science Framework
MeSH: Medical Subject Headings
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols

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Protocol

Role of Injectable Platelet-Rich Fibrin in the Management of Soft and Hard Tissue Periodontal Regeneration in Dentistry: Protocol for a Systematic Review

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Abstract

Background: Injectable platelet-rich fibrin (i-PRF) has the capacity to release great amounts of several growth factors, as well as to stimulate increased fibroblast migration and the expression of collagen, transforming growth factor β, and platelet-derived growth factor. Consequently, i-PRF can be used as a bioactive agent to promote periodontal tissue regeneration.

Objective: We aim to compare and evaluate the effectiveness of i-PRF in periodontal tissue regeneration.

Methods: We will conduct an electronic search in the following databases: PubMed, Cochrane Library, Google Scholar, Semantic Scholar, Scopus, and Web of Science. Papers will be restricted to those in English and to those that are randomized controlled trials comparing PRF or any other biomaterial with i-PRF for periodontal regeneration during dental treatment. The included papers in this review and the reference lists of pertinent reviews will be manually searched. The selection of studies, data extraction, and assessment will be carried out separately by 2 reviewers using the Risk of Bias 2 tool for the included research.

Results: The success of i-PRF will be evaluated by comparing the mean difference in periodontal regeneration of soft and hard tissues in terms of gingival recession, probing pocket depth, clinical attachment level, bone gain, and gingival width. The combined effect size measurements and the associated 95% CIs will be estimated using a random-effects model. The synthesis or work for this systematic review started in October 2023 and will last until December 2025.

Conclusions: i-PRF may play a role in dentistry and could enhance soft and hard tissue regeneration.

Trial Registration: PROSPERO CRD42023464250; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=464250

International Registered Report Identifier (IRRID): PRR1-10.2196/65137

(JMIR Res Protoc 2025;14:e65137) doi:10.2196/65137

KEYWORDS

injectable platelet-rich fibrin; pulp regeneration; periodontal regeneration; periodontium; tissue engineering

Introduction

Rationale

A leucocyte-enriched platelet-rich concentrate called injectable platelet-rich fibrin (i-PRF) has recently been researched and developed to help in wound healing and increase the success of periodontal tissue regeneration [1,2]. The objective of developing an i-PRF formulation is to provide specialists with a platelet concentration in liquid form that is simple to administer and may be mixed with various biomaterials or used alone [3-6]. By adopting slower and shorter centrifugation rates, i-PRF yields significantly more regenerated cells and higher concentrations of growth factors than prior PRF formulations that used faster centrifugation speeds [7]. i-PRF has been shown

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to produce more fibroblast migration and have higher levels of growth factor production, as well as superior antibacterial adhesive action against a range of periodontal disease pathogens [8].

i-PRF is a novel platelet-rich concentrate that enhances periodontal tissue regeneration due to its "supraphysiological" growth factors and cell concentrations [1]. The slow release of growth factors is possible due to the dynamic fibrin liquid gel that i-PRF delivers, which embeds platelets rich in leucocytes, collagen type I, osteocalcin, and growth factors even in their liquid phase. i-PRF can improve intrinsic tissue regeneration by generating human mesenchymal stem cells (MSCs) and starting osteogenic differentiation in MSCs [9]. By allowing the inclusion of grafts without the need for additives or anticoagulants, i-PRF creates a well-agglutinated "sticky bone graft" [1].

The applicability of i-PRF as a promising regenerative adjuvant in periodontal tissue regeneration has been validated by clinical research [2]. Liquid PRF permits other alterations, like incorporating different biomaterials, in an injectable form [10]. One of the components that makes up i-PRF is fibronectin, which is an extracellular glycoprotein with a high molecular weight (approximately 440 kDa) [4,6,11]. It has been demonstrated that i-PRF centrifugation at a horizontal angle is far more effective than traditional fixed-angle centrifugation at accumulating more cells and growth factors. The physician can construct customized clotted PRF membranes (biografts) by manipulating i-PRF before clotting, which can then be combined with different regenerating agents [9].

Objective

This systematic review will determine the effect of i-PRF in the management of soft and hard tissue periodontal defects in the context of periodontal tissue regeneration. The review will highlight the use of i-PRF as a bioactive agent capable of stimulating periodontal tissue regeneration.

Methods

Overview

We aim to ascertain whether i-PRF is effective in soft and hard tissue regeneration in periodontics by conducting a systematic review of the literature.

Eligibility Criteria

We will examine eligible studies and describe how i-PRF is used for the treatment of pulp and periodontal tissue regeneration. The publications that qualify will be limited to those published in English. There will be no restrictions on publication date. We will search the identified publications' reference lists for more papers that might meet the eligibility requirements. This review will cover the research designs of clinical randomized controlled trials (RCTs).

Information Sources

We will search the following electronic databases for papers that fit the review's eligibility requirements: PubMed, Cochrane Library, Google Scholar, Semantic Scholar, Scopus, and Web of Science.

Search Strategy

First, a restricted search of MEDLINE was carried out to find applicable papers. A comprehensive search method was developed using words found in the titles, abstracts, and keywords.

Study Selection, Data Management, and Data Collection Process

When choosing which studies to include, the 3 reviewers (US, PB, and MW) will refer to the eligibility criteria. Records management and duplicate removal will be facilitated by the recording of selections. Blind screening of studies will be used, and differences will be settled through discussion. Two researchers will load the retrieved studies and perform title and abstract screening. Two authors will conduct a full-text review, and any disagreements will be settled by discussion or, if necessary, a third reviewer. A summary of the study selection procedure is given in Figure 1.

Reviewers will be guided by a data extraction tool applied to the included articles. Systemically healthy patients and patients receiving periodontal or pulp regenerative therapy will be included in the RCTs. Patients with a history of systemic illness, as well as pregnant women, will be excluded. A narrative summary of the results from the included research will be provided. We will assess methodological, statistical, and clinical heterogeneity. If there is enough homogeneity among the included studies, a quantitative synthesis, or meta-analysis, will be carried out.

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Figure 1. Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) flowchart.

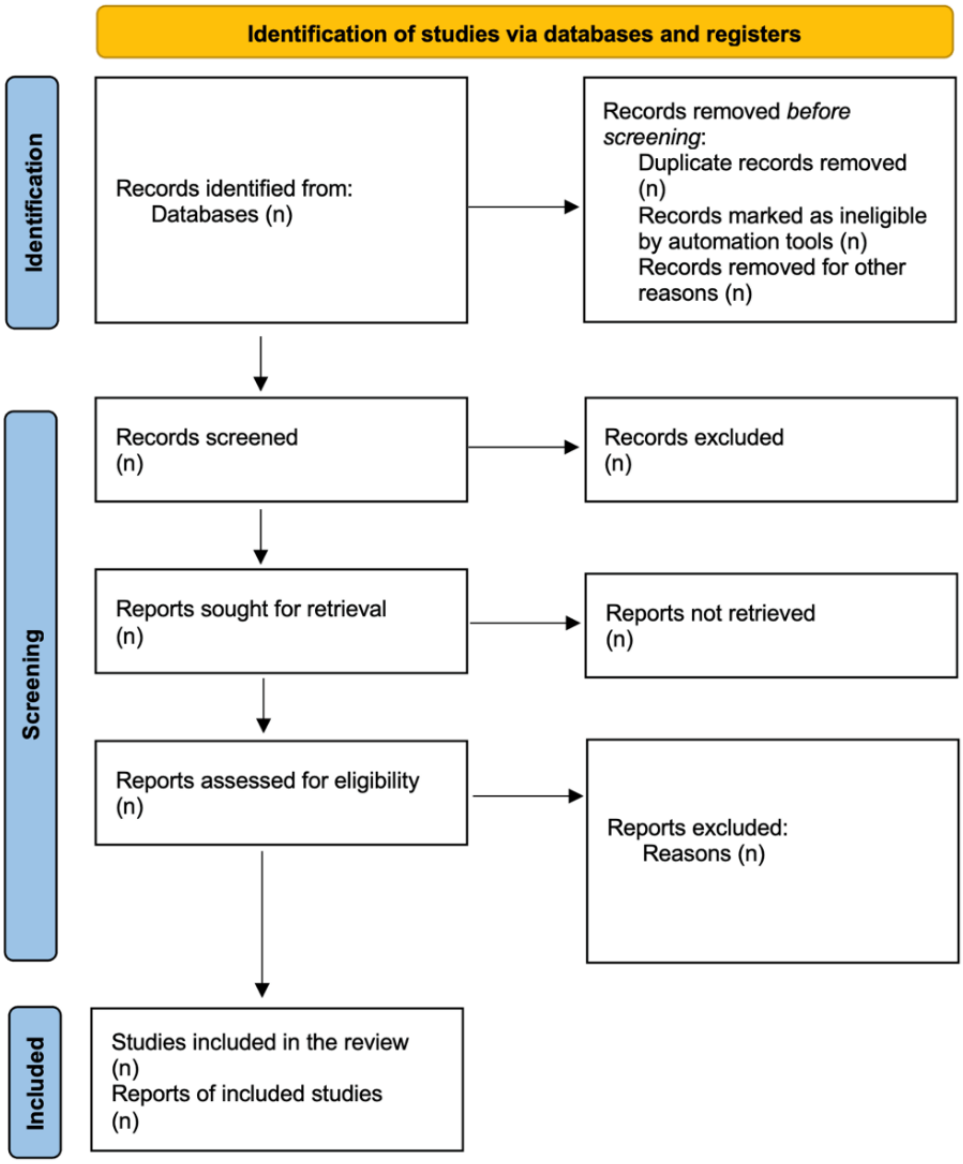

Data Items

Two separate, blinded reviewers (US and PB) will each record the extracted data in duplicate. The extracted data, which will include publication details, the research study's setting, the regeneration agent, adjunctive treatment, and the defect type, will be entered into a Microsoft Excel spreadsheet. Clinical determinants will include periodontal clinical parameters, osseous defect fill, and soft tissue parameters.

Outcomes and Prioritization

The primary outcome is to determine the role of i-PRF in soft and hard periodontal tissue regeneration in dentistry. The secondary outcomes will be whether i-PRF improves probing pocket depth reduction, gain in clinical attachment loss, and osseous fill in periodontal osseous defects.

Risk of Bias

The Risk of Bias 2 (RoB 2) tool will be used to evaluate the risk of bias in included studies and to verify the methodological quality of the reviews. The assessments will be completed by 2 different reviewers (US and MW), with the 2 other reviewers (PB and MP) acting as arbiters to settle any disputes. The entire process will be concealed from the reviewers.

Data Synthesis and Assessment of Heterogeneity

Statistical heterogeneity will be assessed with a random-effects model. If there is enough homogeneity among the included studies, a quantitative synthesis, or meta-analysis, will be carried out. The goal is, if at all feasible, to carry out a subgroup analysis based on the effects of various i-PRF preparation protocols on the regeneration of hard and soft tissues by varying centrifugation force, revolutions per minute, and time. Using statistical software, the results will be aggregated and computed according to the statistical guidelines cited in the most recent edition of the *Cochrane Handbook for Systematic Reviews of Interventions*.

Results

This study is to be completed from October 2023 to December 2025. Each stage of the procedure will involve the blinding of

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2 reviewers. To resolve disagreements or conflicts between the reviewers, regular team meetings will be convened. This will help to improve the review process's transparency. Every conversation will be documented. The systematic review will be submitted for publication as soon as it is finished. The planned review has been registered with PROSPERO (CRD42023464250) and will be carried out in compliance with the guidelines provided in the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist.

Discussion

Anticipated Findings

i-PRF in the periodontal regenerative process offers hope for improved patient outcomes and enhanced therapeutic interventions [12,13]. It might help to provide improved healing and periodontal tissue reconstitution in the context of improvement in osseous fill or bone gain, as well as soft tissue fill, by reducing probing pocket depth and increasing clinical attachment loss. i-PRF might potentially act as a bioactive agent capable of inducing tissue regeneration. Wang et al [14] contrasted i-PRF to conventional platelet-rich plasma (PRP) and examined the osteoblast behavior of a unique therapeutic i-PRF that was 100% natural and additive-free. They found a noticeable increase in the messenger RNA levels of osteocalcin, Runx2, alkaline phosphatase, and immunofluorescent staining of osteocalcin when comparing an i-PRF group to a PRP group. The results of that study favored the use of naturally formulated i-PRF in conjunction with anticoagulants over PRP [14].

Varela et al [15] investigated the blood cell composition, morphological characteristics, type I collagen gene expression, and growth factor release of i-PRF. Blood samples from 15 people were used to create i-PRF samples. The study found that i-PRF was a potentially effective treatment option for the healing of soft and mineralized tissues because it promoted the development of a 3D fibrin network comprising platelets, leukocytes, type I collagen, osteocalcin, and growth factors. Indeed, given its flowable mixing capabilities with other biomaterials and simplified procedures, i-PRF may be used in various dental applications [15]. Iozon et al [4] investigated how human gingiva–derived mesenchymal stem cells (MSCs) proliferated and underwent osteo-differentiation in response to i-PRF; they concluded that gingiva-derived MSC proliferation was promoted by 5% i-PRF, but that an overabundance of i-PRF may hamper osteogenic induction [4].

Strengths and Limitations

To the best of our knowledge, this is the first systematic review to focus on whether i-PRF aids in tissue regeneration. The integration of qualitative as well as quantitative data synthesis in this study will help in promoting oral and periodontal health.

Limitations of this systematic review may include variations in the study design, sample size, and methodological quality of the included studies, as well as potential bias in reporting outcomes related to the use of i-PRF for periodontal tissue regeneration. Additionally, heterogeneity in treatment protocols, variations in PRF preparation methods, and differences in follow-up duration may influence the generalizability of findings. Publication bias and the exclusion of non–English language studies could further affect the comprehensiveness of the review.

Conclusion and Directions for Dissemination

This study aims to assess whether i-PRF has the potential for regeneration of periodontal structures. If we find that the intervention has an effect, the results will aid in tissue engineering, maintaining and promoting osseous defect gain by osseous fill, and hastening healing. Results from this study will be published in national and international academic journals. This protocol follows the PRISMA-P guidelines (Multimedia Appendix 1).

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

All authors contributed to the drafting and writing of the manuscript. US and PB conceptualized and registered the work. MW and MP worked on drafting the initial manuscript and on study design. Final study design and manuscript writing were done by US. All authors checked and finalized the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1

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Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) checklist.
[DOCX File , 33 KB - resprot_v14i1e65137_app1.docx]

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Abbreviations

i-PRF: injectable platelet-rich fibrin
MSC: mesenchymal stem cell
PDGF: platelet-derived growth factor
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PRP: platelet-rich plasma
RCT: randomized controlled trial
RoB 2: Risk of Bias 2

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Protocol

Effectiveness of Gastric Cancer Endoscopic Screening in Intermediate-Risk Countries: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Gastric cancer (GC) is the fifth most prevalent neoplasm worldwide and the fourth with the highest mortality, and its geographical distribution is not homogeneous with high-risk, intermediate-risk (IR), and low-risk areas. Advanced stages at diagnosis are related to high mortality, but early detection greatly increases the chances of survival. Upper endoscopy with biopsy is the gold standard for GC diagnosis. Several studies have investigated the relevance of endoscopic screening and how to implemente it in IR countries. However, most Western societies recommend screening only in selected populations with high-risk factors for GC. No systematic reviews on GC endoscopic screening in IR countries exist.

Objective: We aimed to determine the effectiveness of endoscopic GC screening in IR countries.

Methods: We will include randomized and nonrandomized controlled trials, cohort studies, case-control studies, cross-sectional studies, and economic studies focusing on endoscopic screening of GC in the asymptomatic population of IR countries. The search will be conducted in MEDLINE, SCOPUS, Embase, and Web of Science. Other gray literature sources will be additionally searched. Studies published in English, Portuguese, or Spanish until September 2024 will be included. Two independent reviewers will screen the titles and abstracts of all search results. The selected studies will then be fully analyzed, and the data will be collected and coded in a database. To minimize the risk of bias, the included studies will undergo a quality analysis according to Cochrane risk of bias tools, RoB 2 of randomized trials and ROBINS-I for nonrandomized trials; Newcastle-Ottawa Quality Assessment Scale for case-control and cohort studies; and National Heart, Lung and Blood Institute study quality assessment tools for cross-sectional studies. The data collected will be cataloged in 2 categories: efficacy or effectiveness data and economic data, and separate meta-analyses will be performed for each category if appropriate.

Results: This study is expected to provide results on the efficacy, effectiveness, and cost-effectiveness of endoscopic screening in an IR population. To date, 969 studies were screened for title and abstract, 75 were selected for full-text screening, and 44 were retained for data analysis. Additionally, 2 studies were selected from our manual search. Currently, the study is in the early stages of data extraction and risk of bias assessment and is expected to be published in the first quarter of 2025.

Conclusions: To our knowledge, this review will be the first to provide evidence on the effectiveness of endoscopic GC screening in IR countries. In doing so, we believe we will help guide future research, inform health care decisions and assist policy makers in this area, and support future decisions to implement GC screening programs in this type of population.

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Trial Registration: PROSPERO CRD42024502174; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=502174
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KEYWORDS

gastric cancers; endoscopic screening; intermediate-risk countries; neoplasia; early detection; diagnosis; cancer screening; survival; meta-analysis; gastrointestinal cancers

Introduction

Gastric adenocarcinoma, also known as gastric cancer (GC), is a malignant neoplasm resulting from anarchic growth of gastric mucosal gland cells [1]. It is a heterogeneous disease with multiple clinical, histological, and molecular variables that influence its presentation [1,2].

According to data from The Global Cancer Observatory 2022, GC is the fifth most common and the fifth most lethal neoplasm worldwide [3]. Its geographical distribution is not homogeneous: there are high-risk areas with incidence 20 and more (age-standardized rate measured per 100,000 people-year; eg, Japan, South Korea, or Mongolia); intermediate-risk (IR) areas with age-standardized rate 10 and more and less than 20 (eg, Portugal or China); and low-risk areas with age-standardized rate 10 or less (United States, United Kingdom, Switzerland, or Germany) [2,3].

Diagnosis at an advanced stage and the aggressiveness of the disease result in a 5-year survival rate of between 20% and 40% [4]. In contrast, early-stage GC has an excellent prognosis, with a 5-year survival rate of greater than 90%, and can often be treated with minimally invasive and organ-sparing techniques such as endoscopic resection [5]. Therefore, early detection of cancer greatly increases the chances of successful treatment. The 2 components of cancer screening are early diagnosis and screening. The former focuses on detecting symptomatic patients as early as possible, while the latter involves testing healthy individuals to identify those with the disease before symptoms occur [6]. The symptoms of stomach cancer are nonspecific and usually develop late, meaning that detection based on symptoms would not detect the disease in its early stages. On the other hand, screening programs should be implemented when: their effectiveness has been demonstrated; the resources needed to implement them are sufficient to cover the target population; there are facilities to confirm the diagnosis, treatment, and follow-up of those with positive results; and the prevalence of the disease is high enough to justify the effort and cost of the screening program [6]. Therefore, the decision to implement the screening program requires that these conditions are met. Several methods have been proposed to screen for GC, namely serological markers, biomarkers, molecular or genetic tests, or more invasive techniques such as upper gastrointestinal endoscopy [7]. The latter, which allows direct visualization of the gastric mucosa and collection of biopsies for histological examination, is considered the gold standard technique for definitive diagnosis of GC [8].

In some high-risk countries, such as Japan and South Korea, GC screening programs have been in place for several years and have been shown to reduce mortality and increase early detection and 5-year survival rates [9-11]. The same has been demonstrated in screening programs developed in China [12,13].

In Western IR countries, several studies have been developed to determine the relevance of screening and how it might be developed. Of particular importance was the study developed by Areia et al [14], which showed that endoscopic screening for GC in IR countries can be cost-effective when combined with endoscopic screening for colorectal cancer. This has been included in the recommendations of the United European Gastroenterology and the European Society of Gastrointestinal Endoscopy [14-16]. Despite this evidence and the recommendations, most Western Societies continue to recommend screening only in selected populations with high-risk factors for GC [16,17]. Furthermore, and to the best of our knowledge, there are no systematic reviews on GC endoscopic screening in IR countries. With this systematic literature review, we aim to analyze the scientific evidence published until September 2024 on the cost-effectiveness of endoscopic screening for GC in IR countries.

This study aims to determine the effectiveness and economic viability of endoscopic GC screening in IR countries**,** which will answer the research question, “What is the effectiveness of endoscopic screening for GC in IR countries?”

These objectives are defined according to the Population, Intervention, Comparison, Outcome and Study Design (PICOS) framework (Textbox 1).

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Textbox 1. Population, Intervention, Comparison, Outcome and Study Design (PICOS) framework for the systematic review and meta-analysis.

PICOS question: What is the effectiveness of endoscopic screening for gastric cancer (GC) in intermediate-risk countries?

- Population:

  Asymptomatic population of intermediated-risk countries (countries with incidence age-standardized rate 10-20 per 100.000 person/years: Tajikistan, Iran, Azerbaijan, Kyrgyzstan, Bhutan, Belarus, Peru, Mali, Chile, Costa Rica, Democratic People Republic of Korea, China, Kazakhstan, Russian Federation, Viet Nam, Estonia, Colombia, Portugal, Ecuador, Albania, Guadeloupe [France], Guatemala, Latvia, Armenia, Turkmenistan, Myanmar, Samoa, Turkey, Lithuania, Lao People's Democratic Republic, Sao Tome and Principe, Afghanistan, Martinique [France], Brunei Darussalam, Zimbabwe, and Uzbekistan), between 40 and 80 years of age, without diagnostic of GC or precancerous lesions.
- Intervention: Endoscopic screening for GC.
- Comparison: No screening for GC.
- Outcome: The effectiveness of endoscopic screening of GC is defined as the detection rate of Helicobacter pylori; detection rate of precancer lesions; detection rate of GC; detection rate of early GC; stage at diagnosis; mortality rate of GC of screened versus nonscreened patients; 5-year survival rate of GC screened; and costs of screening program.
- Study designs: Randomized controlled trials, nonrandomized controlled trials, cohort studies, case-control studies, cross-sectional studies, and cost-effectiveness studies.

Methods

This study will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [18] and PICOS criteria for comprehensive assessment.

Eligibility Criteria

The inclusion criteria include studies published as free full papers in English, Portuguese, or Spanish until September 2024, from countries with an IR for GC (countries with incidence age-standardized rate 10-20 per 100,000 person/years: Tajikistan, Iran, Azerbaijan, Kyrgyzstan, Bhutan, Belarus, Peru, Mali, Chile, Costa Rica, Democratic People Republic of Korea, China, Kazakhstan, Russian Federation, Viet Nam, Estonia, Colombia, Portugal, Ecuador, Albania, Guadeloupe [France], Guatemala, Latvia, Armenia, Turkmenistan, Myanmar, Samoa, Turkey, Lithuania, Lao People's Democratic Republic, Sao Tome and Principe, Afghanistan, Martinique [France], Brunei Darussalam, Zimbabwe, Uzbekistan); eligible study designs are randomized controlled trials, nonrandomized controlled trials, cohort studies, case-control studies, cross-sectional studies, and cost-effectiveness studies; and no filters or restrictions related to year of publication or publication status, will be applied.

The exclusion criteria include systematic reviews and other types of reviews, meta-analyses, case series, case reports, and other publication types such as editorials, commentaries, notes, letters, and opinions.

Information Sources

The information sources for this systematic review are electronic databases (MEDLINE, SCOPUS, Embase, and Web of Science). To capture additional studies (gray literature), manual searches will include published abstracts from the most relevant international gastroenterology and endoscopy conferences, clinical trial registries for ongoing studies, reference lists of included studies or other published reviews or meta-analyses. Authors of unpublished studies or published studies in which data are missing will be contacted to confirm eligibility.

Search Strategy

The search strategy follows the Peer Review of Electronic Search Strategies (PRESS) guidelines [19]. The search will be conducted in MEDLINE, SCOPUS, Embase, and Web of Science and the search strategy will be tailored to each database using database-specific search terms (Multimedia Appendix 1).

Selection Process

The references, including the abstract of studies retrieved after searching each database, will be imported to Rayyan (Rayyan Systems, Inc), an open-source software that allows several reviewers to blindly access the inclusion or exclusion of studies in literature reviews registering the entire process. This software will analyze and merge the potential duplicates, under operator validation. The initial selection process will be carried out by 2 independent reviewers (MBM and NP) based on the title and abstract. Studies will be classified as "included," "excluded," or "maybe." The selection process will be blinded and supervised by 2 other independent authors (FT and ABP). Conflicts and "maybe" assessments will be resolved between the 2 reviewers with the support of 2 authors (FT and ABP). After the final list of included studies is obtained, the full texts are retrieved. The full text of each study will be analyzed by 3 independent reviewers (MBM, NP, and ABP), and a decision taken on inclusion or exclusion. The list of items included is exported to a Microsoft Excel database where the data to be analyzed are entered.

The agreement rate will be calculated using Cohen κ, Egger regression, and Begg regression and will be reported at all stages of the selection process (title screening, abstract screening, and full-text screening).

Data Collection Process

Data from included studies will be collected by 2 reviewers (MBM and NP) and inserted into a Microsoft Excel database with data coding. The data collected will be cataloged in 2 categories: efficacy or effectiveness data and economic data, and separate meta-analyses will be performed for each of these categories.

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For the statistical analyses and meta-analysis of the data collected, the authors will use SPSS (version 29.0.2.0; IBM Corp) and Jamovi (version 2.5; The jamovi Project). Bibliographic references will be managed in Zotero (Corporation for Digital Scholarship) software. Artificial intelligence tools may be used to extract and analyze data.

Data Items

The data collection form will include the items or variables defined in outcomes (Table 1) and other variables (Table 2).

Table 1. Variables related to outcomes of screening and cost-efficiency.

Variable	Definition or domain
Endoscopic screening	Number of individuals screened by endoscopy.
Frequency of screening	Frequency of endoscopic screening in years.
Age range covered by screening	Age at start and end of screening.
Screening adherence rate	Percentage of invited individuals that did the screening.
Number of biopsies	Total number of biopsies performed in the study.
Helicobacter pylori diagnosis rate	Percentage of individual screened that were diagnosed with *Helicobacter pylori*.
Detection rate of premalignant lesions	Number of premalignant lesions (atrophic gastritis, intestinal metaplasia and low-grade intraepithelial neoplasia, formerly low-grade dysplasia) / total number of upper endoscopies performed.
Gastric cancer detection rate	Number of gastric cancers diagnosed by screening endoscopy / total number of screening upper endoscopies performed.
Early gastric cancer detection rate	Number of early gastric cancers (high-grade intraepithelial neoplasia and mucosal adenocarcinoma) detected by endoscopic screening / total number of gastric cancers detected by endoscopic screening.
Lethality rate	Number of people who died from gastric cancer diagnosed by endoscopic screening / population at risk during the study period.
5-year survival rate in patients diagnosed with gastric cancer at screening	Percentage of patients diagnosed with stomach cancer at screening who live at least 5 years after diagnosis.
Incremental cost-effectiveness ratio	Value (in euro) of implementing the upper endoscopy screening program (or adding it to other existing screening programs, eg, endoscopic screening for colorectal cancer).

Table 2. Other variables

Variable	Domain
Study Bibliographic Reference	• Reference
Country or countries of origin of the study	• Country
Study design	• Randomized controlled trial • Nonrandomized controlled trial • Cohort • Case-control • Cross-sectional • Cost-effectiveness
Population or sample	• Base population potentially to be screened by upper endoscopy
Participants	• Age • Sex distribution

Risk of Bias in Individual Studies

To minimize the risk of bias, the included studies will undergo a quality analysis according to Cochrane risk of bias tools, RoB 2 of randomized trials and ROBINS-I, for nonrandomized trials; Newcastle-Ottawa Quality Assessment Scale [20] for case-control and cohort studies; and National Heart, Lung and Blood Institute study quality assessment tools [21] for cross-sectional studies. The Consensus on Health Economic Criteria (CHEC) list [22] will be used for the assessment of the methodological quality of cost-effectiveness studies.

Studies with low quality or high risk of bias will be reported and not be used for meta-analysis.

Data Synthesis

If it is possible to collect quantitative data from the selected studies, we will perform 2 separate meta-analysis: one to report the effect size of 5 outcomes in studies reporting efficacy or

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effectiveness of endoscopic screening for GC (detection rate of premalignant lesions, detection rate of GC, detection rate of early GC, and 5-year survival rate and mortality of GC diagnosed in screening programs); other to report the effect size of cost-effectiveness of endoscopic screening for GC in IR countries.

If appropriate (at least 2 studies per outcome) [23], pooled rates and odds ratio along with 95% CIs will be calculated for GC detection, early GC detection, adherence to the screening program, and GC mortality using random-effects model, using SPSS, Jamovi, and Meta-Essentials for Microsoft Excel (Erasmus Research Institute of Management). The I^2 homogeneity will also be performed to check the need for subgroup analysis (moderation analysis).

If it is not possible to carry out a meta-analysis due to insufficient data, an executive summary is prepared that summarizes the data from the studies included in the systematic review.

Meta-Bias(es)

After evaluating the biases of individual studies and ensuring that all studies that may be of interest for their conclusions are integrated into the review, a summary of the risks of bias in the meta-analysis or meta-synthesis will be presented.

Confidence in Cumulative Evidence

The strength of the body of evidence will be assessed with Grading of Recommendations, Assessment, Development and Evaluation (GRADE) [24].

Results

Our initial search of the 4 electronic databases, using descriptors adapted for each database, identified 1615 studies of potential interest (Figure 1). After excluding duplicates, 969 studies were screened for title and abstract. Of these, 75 were selected for full-text screening. We retained 44 studies for data analysis and the remaining 31 studies were excluded for the following reasons: wrong population (n=2), same population as another study (n=2), wrong screening method (n=6), wrong outcome (n=18), wrong study design (n=2), and wrong publication type (n=1). In addition, our manual search identified 23 publications of potential interest, of which 2 were selected for the data extraction phase. Currently, the study is in the early stages of data extraction and risk of bias assessment and is expected to be published in the first quarter of 2025.

Figure 1. Flowchart of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses). NA: not applicable.

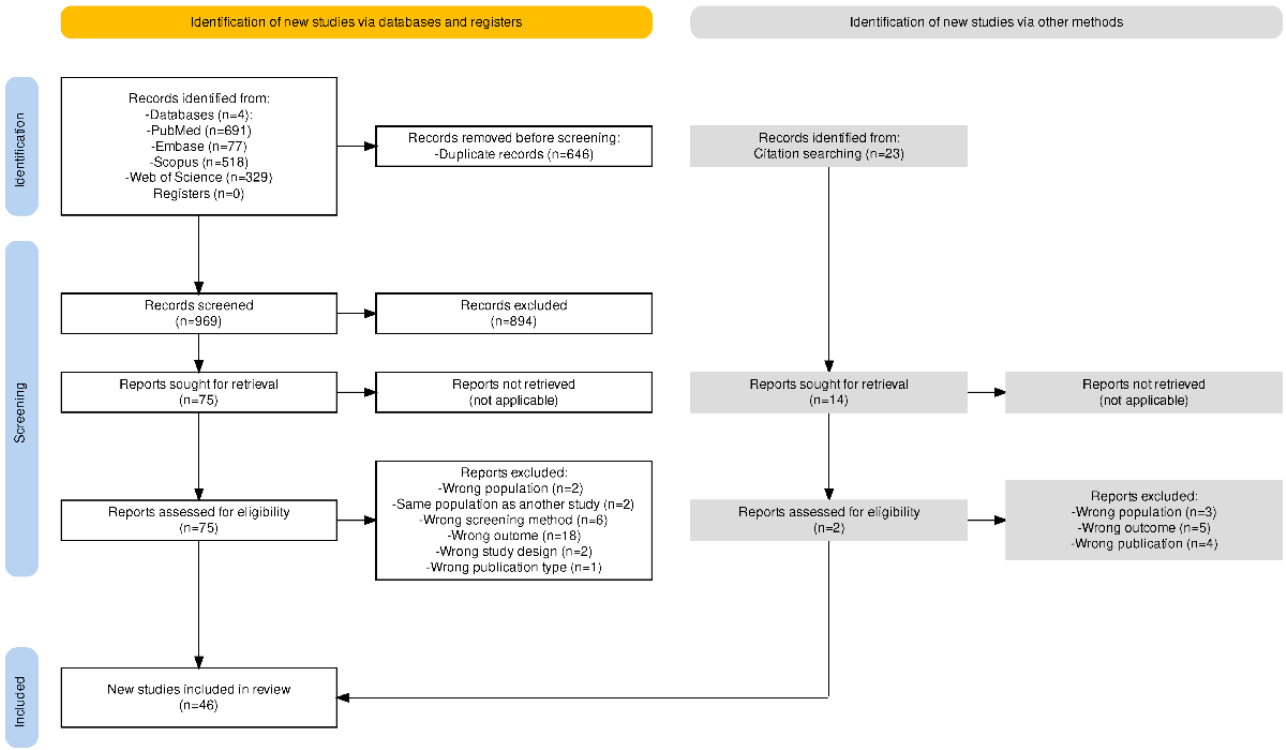

Discussion

This protocol outlines the methods for a systematic literature review and meta-analysis of published primary scientific studies on the effectiveness of endoscopic GC screening in IR countries.

This study will provide results on the following outcomes: frequency of screening, age range covered by screening, screening adherence rate, number of biopsies, *Helicobacter pylori* diagnosis rate, detection rate of premalignant lesions, GC detection rate, early GC detection rate, lethality rate, 5-year survival rate in patients diagnosed with GC at screening, and incremental cost-effectiveness ratio.

To the best of our knowledge, this is the first systematic review of the effectiveness of endoscopic screening for GC in IR countries and it is expected that the presentation of these results will shed light on the relevance of endoscopic GC screening in these populations. The benefit of performing screening upper endoscopy for asymptomatic individuals for GC remains

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controversial [25]. Due to the high burden of GC, countries in East Asia such as Japan and Korea have implemented nationwide population-based GC screening strategies to reduce incidence and mortality [9,26]. Other studies have shown that endoscopic screening for GC is cost-effective in the IR to high-risk population [14,27]. However, to date, we have not found a systematic review that synthesizes the results of all studies conducted in IR countries, and for this reason, our systematic review is of particular interest to inform health policy makers in IR countries about the effectiveness of endoscopic screening for GC in this type of population.

An extensive search of databases and gray literature will be conducted to identify all relevant studies. However, this review may have some important limitations. First, it is important to bear in mind that the majority of IR countries, especially Western countries, do not yet have population-based screening for this pathology, which may make it difficult to obtain primary studies on this topic from these countries. Second, although China is an IR country with endoscopic screening for GC, some studies reporting the results of these screening programs are written in Chinese and cannot be included in our review. Nevertheless, we will conduct an intensive search of the databases to ensure that we obtain studies written in English, Portuguese, or Spanish that report the results of these screening programs. Third, on the other hand, the Chinese territory is so large that risk varies greatly between different areas of the country, which may introduce a significant bias if some included studies are based only on results of high-risk areas, as this type of population may have different characteristics from those observed in other areas of China or other IR countries. These limitations will be reported in the final paper of the systematic review so that our results can be interpreted rigorously and truthfully. The final paper of the systematic review and meta-analysis will be published in the first quarter of 2025.

With this systematic review and meta-analysis, we hope to contribute to the design of GC screening strategies in IR countries, with the primary goal of reducing mortality from this disease. In the future, it may be necessary to update this systematic review as a new consortium. Towards Gastric Cancer Screening Implementation in the European Union [28] has recently been established in Europe to study and implement GC screening in this area.

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Data Availability

All data generated or analyzed during this study are included in this published article (and its supplementary information files).

Authors' Contributions

MBM was responsible for designing and writing the protocol. NP provided assistance with protocol design and writing. AB was responsible for reviewing the writing of the manuscript. FT provided assistance with protocol design. RC was responsible for designing the search expression in the various databases. IF and MA were involved in protocol design and manuscript review. RD was responsible for the revision of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[PDF File (Adobe PDF File), 27 KB - resprot_v14i1e56791_app1.pdf]

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Abbreviations

CHEC: Consensus on Health Economic Criteria
GC: gastric cancer
GRADE: Grading of Recommendations, Assessment, Development and Evaluation
IR: intermediate-risk
PICOS: Population, Intervention, Comparison, Outcome and Study Design
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRESS: Peer Review of Electronic Search Strategies

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Protocol

Mesenchymal Stem Cell Therapy for Acute Myocardial Infarction: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Medical therapy and interventional approaches have improved outcomes in patients with acute myocardial infarction (MI). However, these strategies are inadequate for replacing cells lost during tissue ischemia, thereby leaving behind noncontractile scar tissue. The anti-inflammatory and immune modulating properties of mesenchymal stem cells (MSCs) may prove useful in inducing functional cardiac regeneration following acute MI.

Objective: This is a protocol for systematic review and meta-analysis that will aggregate and synthesize high-level clinical data on the effects of MSC therapy for acute MI. The findings of this study may serve as evidence for clinicians and researchers in guiding the use of MSC therapy as an adjunct to reperfusion and optimal medical therapy in patients with acute MI.

Methods: The proposed systematic review is registered with PROSPERO (International Prospective Register of Systematic Reviews). A systematic search of bibliographical databases, including Embase, PubMed, and Cochrane was conducted from inception to June 2023 to identify English-language human studies with adult patients receiving MSC therapy and optimal medical therapy for acute MI in comparison with respective controls. Article screening was performed using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Data on functional cardiac outcomes and major adverse cardiac events were extracted and analyzed as primary outcomes.

Results: Literature search and article screening commenced in June 2023. Data extraction and analysis will be completed by October 2024. The findings will be synthesized and reported by the end of November 2024.

Conclusions: This systematic review and meta-analysis will summarize the best available updated evidence from published randomized controlled trials on the effects of MSC therapy for the treatment of acute MI. The findings of this systematic review and meta-analysis may shed light on the efficacy of MSC therapy in improving cardiac functional and structural parameters and reducing adverse cardiac events following acute MI.

Trial Registration: PROSPERO CRD42024522398; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=522398

International Registered Report Identifier (IRRID): DERR1-10.2196/60591

(JMIR Res Protoc 2025;14:e60591) doi:10.2196/60591

KEYWORDS

mesenchymal stem cells; mesenchymal stromal cells; progenitor cells; acute myocardial infarction; outcomes; stem cell; myocardial; protocol; systematic review; meta-analysis; medical therapy; therapy; cardiac; efficacy

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Introduction

Background

Acute myocardial infarction (MI) remains a significant cause of morbidity and mortality globally, with nearly 3 million people experiencing an acute MI annually worldwide [1]. During acute MI, blood flow to the myocardium is reduced, resulting in tissue hypoxia, ischemia, and eventual cell death, which in turn, may result in adverse consequences, including left ventricular (LV) dysfunction, heart failure, arrhythmias, cardiogenic shock, and death. Myocardial reperfusion with percutaneous coronary intervention is a standard treatment for acute MI. Time to reperfusion is directly correlated with prognosis; therefore, prompt revascularization should be pursued [2]. After reperfusion, patients receive optimal medical therapy, which has significantly improved outcomes since its advent [3]. However, reperfusion and medications are unable to replenish necrotic cardiac myocytes, and many patients still experience significant morbidity and mortality following acute MI [4]. Following significant tissue infarction, large areas of the myocardium are scarred and rendered nonfunctional, leading to the adoption of regenerative therapies as a possible solution.

Accordingly, regenerative therapies that aim to restore functional cardiac tissue continue to be a topic of clinical research interest. Recent evidence suggests that stem cells may be useful as a method of repairing damaged myocardial tissue [5,6]. In animal models, studies have shown the potential of Mesenchymal stem cells (MSCs) to differentiate into cardiac myocytes, to participate in regenerative signaling through immunomodulation, and paracrine actions [7-9]. So far, human clinical trials have yielded mixed results. Several randomized control trials (RCTs) in patients with acute MI have demonstrated improvement in LV ejection fraction (LVEF), remodeling, myocardial viability, and reduction in hospitalization rates following treatment with MSCs [10-13]. Conversely, other RCTs have shown no difference in LVEF between MSC-treated patients and the standard-of-care [14,15]. Concerns for safety has arisen with the novelty of regenerative therapy, and the evaluation of major adverse cardiac events (MACE) has been the hallmark for safety [10-15]. Particularly, mortality rates (periprocedurally and long-term), malignant arrhythmias, recurrent MI, cerebral vascular accident, and revascularization are among the most common evaluated adverse events [10-15]. Although with no significant difference was noted in previous RCTs, our meta-analysis aims to evaluate the safety of MSC therapy through the evaluation of MACE. There may be added benefit to decreasing MACE outcomes through the use of MSC therapy, which will also be evaluated.

While many clinical trials have examined the efficacy of MSCs in acute MI treatment, the data collection methods, timing of MSC administration, route of MSC administration, and evaluated end points have been heterogeneous. Several articles representing long-term follow-up of original studies have recently been published, which collectively provide additional insights. Aggregation and analysis of the updated data are needed to gain a better understanding of the effects of MSC administration in patients with acute MI.

Objectives

Several previous meta-analyses have been published on the outcomes of stem cell therapy for acute MI, however, these were based on studies with a heterogeneous mixture of stem cells, not exclusively MSCs. In addition, the existing meta-analyses included only original RCTs without the follow-up studies, thereby obscuring insights related to longer-term outcomes. The current systematic review aims to provide the most comprehensive and updated evidence regarding MSC transplantation solely for the treatment of acute MI, along with a meta-analysis focused specifically on RCTs, including follow-up RCTs to evaluate long-term outcomes of MSC therapy. The meta-analysis will compare the effects of MSC injection and standard therapy on LVEF, LV end-systolic volume (LVESV), LV end-diastolic volume (LVEDV), and MACE as primary end points. Secondary end points will include, but not limited to, myocardial viability, myocardial perfusion defect, and stroke volume.

Methods

Review Question

This study aimed to answer the following question: “What are the short-term and long-term effects of MSC therapy in patients with acute MI?”

Eligibility Criteria

Inclusion and exclusion criteria were initially determined using the PECOS (Population, Exposure, Comparator, Outcome, Study Design) framework. Detailed PECOS criteria for the meta-analysis are denoted in Multimedia Appendix 1.

The initial systematic review included RCTs, single-arm studies, and case series. The meta-analysis included RCTs and secondary reports based on the original studies. English-only original articles published before June 15, 2023, were included; case reports, abstract-only articles, systematic reviews, meta-analyses, animal studies, commentaries, position papers, opinions, and editorials were excluded from the meta-analysis. Studies enrolling adult patients aged 18 years and older with acute MI who received MSC therapy within 1 month of MI were included. Studies using MSCs, mesenchymal stromal cells, and mesenchymal progenitor cells as therapeutic substrates were included. Studies that included patients with recurrent MI in their study were excluded. Studies with other types of stem cells or combinatorial cellular mixtures were excluded. Studies that did not report the outcomes of interest were excluded.

Information Sources and Search Strategy

Bibliographic databases, including PubMed, Cochrane, and Embase were queried from inception to June 2023. The search strategy was guided by 2 librarian experts in medical sciences and was reviewed and devised in accordance with the Peer-Reviewed Electronic Search Strategy guidelines [16].

The original search strategy was formulated for PubMed and used PubMed syntax. Additional searches were modified and optimized for subsequent databases. Given the specificity of the question at hand, the search strategy used key search terms without the use of MeSH (Medical Subject Headings).

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The full search strategy, including the development of the final search terms, can be found in Table S1 in the Multimedia Appendix 2. Keywords in the final search strategy included the following: mesenchymal stem cell, progenitor cell, mesenchymal stromal cell, ST-elevation MI, ST-elevation myocardial infarction, and acute MI.

Selection Process

All retrieved articles were reviewed by 2 independent investigators to check for inclusion and exclusion criteria in a stepwise process to include title screening, abstract screening, and full-text screening. Reasons for the exclusion of articles will be addressed in greater detail in the final publication.

Study Records

Data Collection Process and Management

Data extraction from the eligible full-text articles was performed by 2 investigators who independently extracted the data elements of interest to ensure accuracy and completeness. Extracted data and records are maintained in separate Microsoft Excel sheets by the 2 investigators, as well as a combined Microsoft Excel sheet after consensus.

Incongruencies in data extraction were resolved through discussion with a third senior investigator to achieve consensus.

Data Items/Elements

Data extraction elements for both systematic review and meta-analysis are outlined in Table S2, which can be found in Multimedia Appendix 3.

Information that required further clarification and/or required additional data were attempted to be resolved by contacting the corresponding authors of the respective articles; queries that yielded no response were not included in the data extraction or analysis.

Outcomes

The primary outcomes of the meta-analysis included (1) effects of transplantation on LVEF, (2) LVESV, (3) LVEDV, and (4) MACE.

The secondary outcomes that included (1) myocardial viability, (2) myocardial perfusion defect index, (3) coronary flow reserve, (4) adenosine-induced minimal vascular resistance index, and (5) stroke volume.

Quality Analysis

Overview

Quality assessments for strength of the body of evidence of all included studies will be performed using the National Heart, Lung, and Blood Institute (NHLBI) quality assessment tool. A total of 2 investigators will independently screen full texts for quality. Scoring will be performed independently. All essential components of original research studies will be evaluated using the NHLBI scoring checklist (Multimedia Appendix 4). Study quality will model the scoring protocol performed by Elks et al [17].

Risk of Bias Assessment

Within the quality assessment, articles selected for analysis underwent assessment for risk of bias. Bias was assessed by examining randomization and adequacy of randomization, blinding, and attrition. Specific questions are outlined in Figure 1 below. Meta-biases will be assessed as appropriate.

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Figure 1. The PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram modified for the current study selection process.

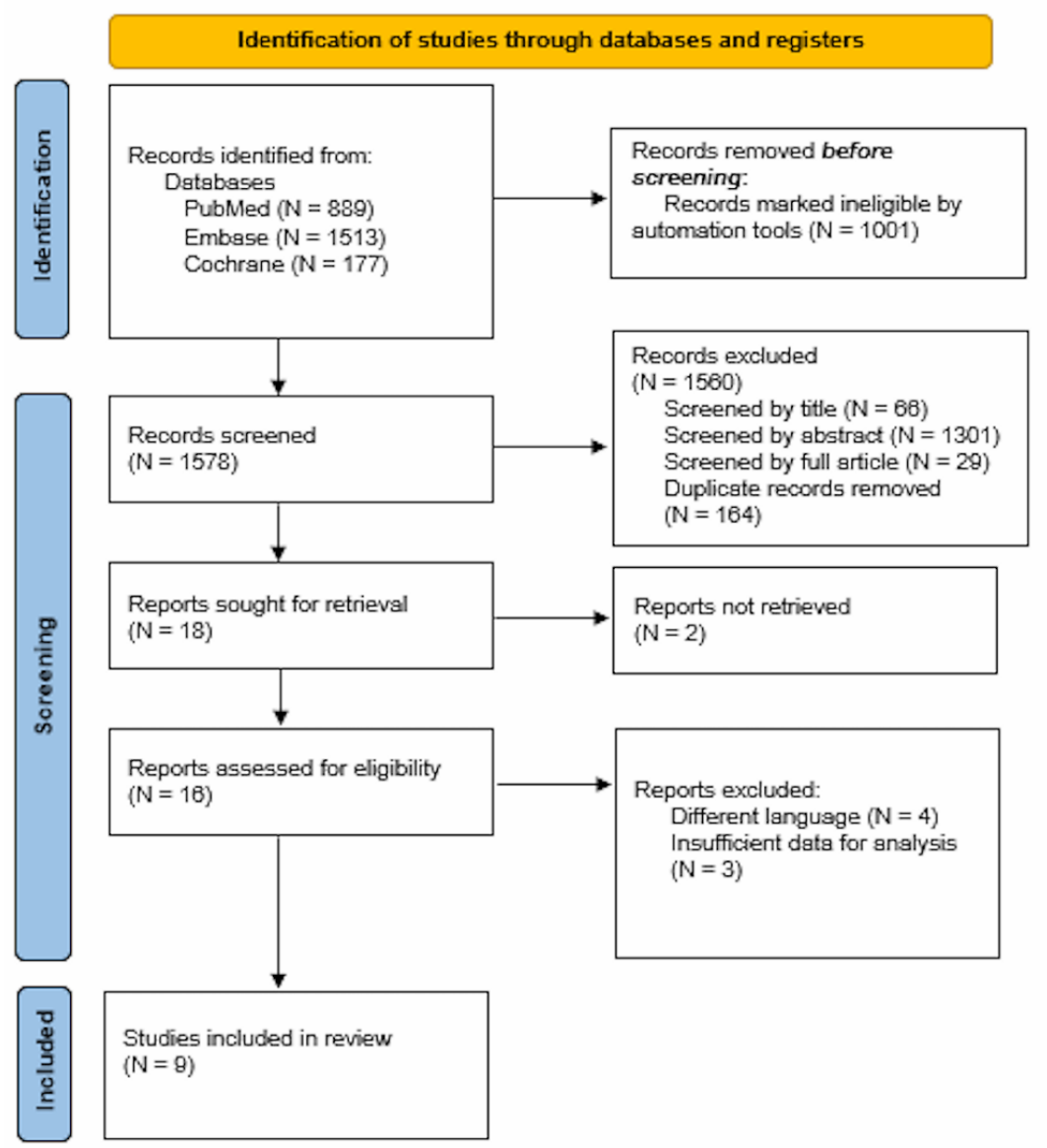

Data Synthesis

First results of all finally included studies will be described succinctly in the form of a summary table. A random-effects model will be used to calculate pooled estimates as this is a more robust estimate regardless of heterogeneity [18]. Cochran Q and I^2 statistics will be used as indicators of heterogeneity. The pooled estimates of the primary end points (eg, LVEF, LVESV, and LVEDV) will be calculated as the weighted mean differences with 95% CIs using the Comprehensive Meta-analysis Package (CMA version 3.0). For dichotomous outcomes, Peto odds ratios will be used as this allows the inclusion of the continuity correction of 0.5 to all 0 cells outcomes and accounts for the expected rarity of events. Sensitivity analysis will be conducted to identify studies that may severely affect the pooled estimates. The Exploratory subgroup analyses by different moderator variables (eg, MSC source, MSC route of administration, location of MI, and duration of follow-up, etc) will also be conducted to examine sources of heterogeneity. A funnel plot and Egger linear regression test will be used to assess publication bias [19]. The significant level will be set as 2-sided and $P<.05$. Forest plots will be used to present the data.

Data Analysis and Presentation

Data will be presented in a tabular form and as a conclusive summary of our analysis. A data extraction form will be developed and agreed upon by all investigators before article analysis occurs. Selected articles will be present in the rows of the table, and variables will be present in the columns of the table. Quantitative analysis of all extracted variables will be performed.

Ethical Considerations

IRB or institutional review was not needed in this systematic review and meta-analysis since this design relies only on the findings from the previously published data and did not involve direct interaction with human participants. However, to adhere to a strict methodology, the protocol of this systematic review

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and meta-analysis was registered with PROSPERO (International Prospective Register of Systematic Reviews) registration number CRD42024522398. PROSPERO is an international database of prospectively registered systematic reviews, which provides a unique permanent registration number to the protocol that prevents duplication, thereby reducing reporting bias. In addition, PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) checklist was completed during the process to ensure comprehensive and quality results (Figure 2).

Figure 2. PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist completed for the current study.

Section and topic	Item No	Checklist item	Completed? (Y or N)
ADMINISTRATIVE INFORMATION			
Title:			
Identification	1a	Identify the report as a protocol of a systematic review	Y
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	N/A
Registration	2	If registered, provide the name of the registry (such as PROSPERO) and registration number	Y
Authors:			
Contact	3a	Provide name, institutional affiliation, e-mail address of all protocol authors; provide physical mailing address of corresponding author	Y
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	Y
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	N/A
Support:			
Sources	5a	Indicate sources of financial or other support for the review	N/A
Sponsor	5b	Provide name for the review funder and/or sponsor	N/A
Role of sponsor or funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	N/A
INTRODUCTION			
Rationale	6	Describe the rationale for the review in the context of what is already known	Y
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	Y
METHODS			
Eligibility criteria	8	Specify the study characteristics (such as PICO, study design, setting, time frame) and report characteristics (such as years considered, language, publication status) to be used as criteria for eligibility for the review	Y
Information sources	9	Describe all intended information sources (such as electronic databases, contact with study authors, trial registers or other grey literature sources) with planned dates of coverage	Y
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	Y
Study records:			
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	Y
Selection process	11b	State the process that will be used for selecting studies (such as two independent reviewers) through each phase of the review (that is, screening, eligibility and inclusion in meta-analysis)	Y
Data collection process	11c	Describe planned method of extracting data from reports (such as piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	Y
Data items	12	List and define all variables for which data will be sought (such as PICO items, funding sources), any pre-planned data assumptions and simplifications	Y
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	Y
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	Y
Data synthesis	15a	Describe criteria under which study data will be quantitatively synthesised	Y
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data and methods of combining data from studies, including any planned exploration of consistency (such as I^2, Kendall's τ)	Y
	15c	Describe any proposed additional analyses (such as sensitivity or subgroup analyses, meta-regression)	Y
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	Y
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (such as publication bias across studies, selective reporting within studies)	Y
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (such as GRADE)	Y

Results

The development of the search strategy for this systematic review and meta-analysis began in June 2023. The search strategy underwent peer-reviewed electronic search strategy review with 2 academic librarians in June 2023. The final search strategy was agreed upon by all investigators in July 2023. Databases were queried and articles were screened between September 2023 and October 2023. Data extraction took place between November 2023 and February 2024. Data analysis is currently taking place as of March 2024 with the final analysis anticipated to be completed in October 2024. It is anticipated that findings will be synthesized and reported by the end of November 2024. Findings will be organized, summarized, and submitted for publication in a peer-reviewed journal. The goal of this work is to provide a comprehensive analysis and enhance the understanding of the safety and effectiveness of MSC therapy in acute MI. A timeline is provided in Table 1.

Preliminary searches performed in PubMed, Embase, and Cochrane databases yielded 1578 articles after appropriate filters were applied. A total of 889 articles were returned from PubMed, of which 521 were human studies. A total of 1,513 articles were returned from Embase, of which 880 were human studies. A total of 177 articles were returned from the Cochrane

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database, which were all reviews of human studies (Figure 1). A detailed step-by-step outline of our search strategy, including search terms, limit criteria, and results is provided in Table S1 of the Multimedia Appendix 2 (adapted from Page et al [20]).

Table 1. Timeline of project task completion.

Task	Jun 2023	Jul 2023	Aug 2023	Sep 2023	Oct 2023	Nov 2023	Dec 2023	Jan 2024	Feb 2024	Mar 2024	Apr 2024	May 2024	Jun 2024	Jul 2024	Aug 2024	Sep 2024	Oct 2024	Nov 2024
Design search strategy	✔	✔																
Title screening			✔															
Abstract screening				✔														
Full-text screening				✔	✔													
Data extraction						✔	✔	✔	✔									
Synthesis and risk of bias assessment										✔	✔							
Data analysis										✔	✔	✔	✔	✔	✔	✔	✔	
Abstract and manuscript drafting												✔	✔	✔	✔	✔	✔	✔
Data dissemination																		✔

Discussion

Overview

This systematic review and meta-analysis will be a comprehensive review and analysis of the existing relevant literature pertaining to the efficacy of MSC therapy in patients enduring from acute MI. We anticipate that the current findings will be congruent with the previous observations regarding the outcomes and safety of MSC therapy. We also aim to glean insights with regard to changes in LVEF, LVESV, and LVEDV as a result of MSC therapy. In addition, we will examine the pooled event ratio estimates of MACE, including death, recurrent MI, need for revascularization, and stroke, compared with control, to draw conclusions on the safety of MSC therapy.

In an attempt to ensure the comprehensiveness of the assessment of relevant data, a narrative synthesis of studies that lie at relatively lower levels of hierarchical evidence as compared with the gold standard (RCTs) was also performed. These additional qualitative findings allow us to gain a complete understanding of several factors, including timing and route of administration, source of cells, and other variables that may impact the outcomes of MSC therapy.

Significance

We anticipate that our results, by virtue of including data from recently published RCTs, will significantly advance the existing evidence regarding the safety and efficacy of MSC therapy. Previous meta-analyses examining the effects of MSC therapy in ischemic heart diseases often combined with chronic and acute ischemic heart diseases [21,22], whereas we plan to focus on acute MI therapy alone. In addition, previous meta-analyses reviewed a variety of regenerative cells [6] for the treatment of acute MI, whereas our focus specifically on mesenchymal stem and progenitor cells will allow us to comment on the efficacy of a specific cell type in the management of acute MI. Finally, while our meta-analysis examines primary RCTs, we have also included secondary/follow-up RCTs of original studies in our analysis, which will provide additional information regarding the longer-term and additional end points for subgroup analysis.

Limitations

This meta-analysis will have several limitations. First, there will be inherent heterogeneity among included studies due to the variability of research methodologies undertaken by each unique study. We anticipate heterogeneity in several variables, including the timing and route of MSC administration, the tissue source of MSCs, the methods used to measure primary and secondary end points (for example, echocardiogram vs angiography vs cardiac magnetic resonance imaging), and the follow-up period after MSC transplantation. Second, there is a risk that relevant literature will be missed because studies with insignificant findings or low sample size are seldom published, thus leading to publication bias. Finally, there will be inherent reviewer bias when selecting articles during the screening process, which will be mitigated by using an individualized screening process with 2 independent reviewers, along with a

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third senior reviewer to resolve disagreements on article selection.

Dissemination Plan

The findings of this systematic review and meta-analysis will be submitted as a manuscript to a peer-reviewed journal by the end of 2024. Derivations of this work will be submitted as abstracts to academic conferences.

Conclusions

This systematic review and meta-analysis will provide a comprehensive review of the safety and efficacy of MSC therapy in patients with acute MI. It will include an analysis of data on clinically relevant primary end points pertaining to functional cardiac parameters, such as LVEF, LVESV, and LVEDV. It will also examine specific safety outcomes by performing a subgroup analysis on MACE. This review will also provide qualitative synthesis of evidence related to MSC therapy, which will generate additional insights toward its potential future clinical applications in a broader spectrum of cardiovascular pathologies.

Acknowledgments

The authors would like to acknowledge the Ana Coral and Aidybert Weeks at the University of Nevada, Las Vegas Library for their assistance with developing the search strategy and for conducting the PRESS (Peer-Reviewed Electronic Search Strategy) review. The authors did not use AI for any portion of manuscript generation.

Data Availability

The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization was undertaken by MD, BY, and BD. Methodology and project administration was performed by MD, BY, KB, and BD. Formal analysis was handled by KB. Investigation, resources, and data curation was conducted by MD and BY. Writing-original draft preparation was performed by MD, BY, and KB. Writing-review and editing and visualization was conducted by MD, BY, KB, and BD. Supervision was handled by KB and BD.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The PECOS (P-Population; E/I-Exposure/Intervention; C-Comparator; O-Outcome; S-Study design) framework for the eligibility criteria.
[PNG File , 208 KB - resprot_v14i1e60591_app1.png]

Multimedia Appendix 2
Full search strategy for utilized databases.
[DOCX File , 19 KB - resprot_v14i1e60591_app2.docx]

Multimedia Appendix 3
Elements included in data extraction for meta-analysis purposes.
[DOCX File , 18 KB - resprot_v14i1e60591_app3.docx]

Multimedia Appendix 4
National Heart, Lung, and Blood Institute scoring checklist.
[DOCX File , 16 KB - resprot_v14i1e60591_app4.docx]

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Abbreviations

LV: left ventricle
LVEDV: left ventricular end-diastolic volume
LVEF: left ventricular ejection fraction

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LVESV: left ventricular end-systolic volume
MACE: major adverse cardiac events
MeSH: Medical Subject Headings
MI: myocardial infarction
MSC: mesenchymal stem cells
NHLBI: National Heart, Lung, and Blood Institute
PECOS: Population, Exposure, Comparator, Outcome, Study Design
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
PROSPERO: International Prospective Register of Systematic Reviews
RCT: randomized control trial

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Protocol

Just-In-Time Adaptive Interventions to Promote Behavioral Health: Protocol for a Systematic Review

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Abstract

Background: The goal of just-in-time adaptive interventions (JITAIs) is to use mobile, digital tools to provide individuals with personalized interventions at the optimal time and in the optimal context. Accordingly, JITAIs are promising for advancing accessible, equitable, and evidence-based treatment for behavioral health. To guide future inquiry in this space, a review of the literature is needed to describe the state of research on JITAIs for behavioral health.

Objective: This study aims to systematically review the literature to describe the landscape of existing JITAIs for behavioral health at any stage of intervention development. In addition, conditional upon a sufficiently homogeneous literature, we will conduct meta-analyses to investigate the effectiveness of JITAIs for promoting distal outcomes (here, aspects of behavioral health) and proximal outcomes (eg, emotion regulation).

Methods: This systematic review is being conducted in accordance with the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols). We developed our search strategy and executed the literature search in collaboration with biomedical librarians; 5 databases (PubMed, Embase, Cochrane Library, Web of Science: Core Collection, and APA PsycINFO) were searched, and results were managed using EndNote 20 (Clarivate). We are screening (title, abstract, and full text) all records in duplicate in Covidence according to eligibility criteria. Data items will be extracted, and risk of bias will be assessed in duplicate from the included articles in Covidence. We will summarize JITAI characteristics in tables and text. We will conduct meta-analyses for the distal and proximal outcomes conditional upon sufficient homogeneity in subgroups. Moderation (conditional upon sufficient heterogeneity of outcomes) and mediation (ie, whether changes in proximal outcomes mediate the relation between JITAIs and distal outcomes) will be conducted as appropriate. We will investigate publication bias and use the Grading of Recommendations Assessment, Development and Evaluation to characterize the quality of evidence of our estimates.

Results: The search strategy was developed between July 2023 and November 2023. The literature search was executed between November 2023 and December 2023. Title and abstract screening began in December 2023, and full-text screening began in May 2024. Data extraction and analyses have not begun.

Conclusions: Here, we propose a systematic review to assess the state of the literature on JITAIs for behavioral health. The insights derived from this study will describe the literature on JITAIs in promoting behavioral health, reinforce JITAI definitions, clarify JITAI elements, and inform the next steps in JITAI research.

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KEYWORDS

just-in-time adaptive interventions; JITAI; behavioral health; systematic review; behavior change; health outcomes; accessibility; digital treatment delivery; mobile phone

Introduction

Background

Mental illness has devastating consequences for individuals, their families, and society. Those in need of treatment are woefully underserved, with a dearth of professionals relative to patients [1]. Race and ethnicity, geography, and socioeconomic status influence who can and who cannot access care [2]. For the subset of individuals who receive treatment, lack of evidence-based care [3] and issues with dropout [4] and nonresponse [5,6] limit recovery. New solutions are critical for reaching and equitably and effectively treating people suffering from mental illness. Technological advances may provide a pathway to more equitable evidence-based care at scale. While structural barriers (eg, cost and transportation) impede access to in-person health care, mobile devices are plentiful and may allow for greater population coverage [7,8]. Furthermore, while treatment may be perceived as stigmatizing, further reducing service use [9,10], research provides preliminary support for willingness to initiate and maintain engagement with digital interventions (even in severe mental illness) [11]. Beyond accessibility and acceptability, treatment delivered through technology allows for the provision of therapeutic support when and where it is most needed—outside of the clinic and within patients' daily lives [12,13]. After a prescribed treatment is delivered, technological solutions can be seamlessly integrated and accessed again to boost skills and maintain treatment gains [12,13].

Just-In-Time Adaptive Interventions

Despite the potential benefits of digital treatment delivery, evidence for the effectiveness of intervening using standalone mobile applications is limited [14]. Still, just-in-time adaptive interventions (JITAIs) are promising [15-18]. The goal of JITAIs is to target mechanisms for therapeutic change at the time and in the context that is optimal for the individual [19,20]. JITAIs have the potential to capitalize on states of vulnerability and opportunity [20]. That is, JITAIs can intervene when individuals are susceptible to negative or positive change. For example, capitalizing on a state of opportunity might be prompting an adult with social anxiety disorder to approach others while in a public place. JITAIs may be able to intervene when individuals are maximally receptive or most likely (willing and able) to accept a specific intervention [20]. To do so, JITAIs leverage real-time data collected passively or actively from smartphones, including or excluding paired wearable devices in combination with personalized algorithms [19-21].

JITAIs are defined by six elements: (1) distal outcome (long-term goal of the JITAI), (2) proximal outcome (short-term goal of the JITAI, which may be a mediator of the distal outcome), (3) tailoring variable (baseline or time-varying information on the individual that informs which interventions to deploy at which decision points), (4) decision point (time frame when an intervention option is, or is not, deployed), (5) decision rule (operationalization of which intervention option should be used, when, and for whom), and (6) intervention options (set of potential components that may be deployed toward behavior change at a given decision point). JITAIs are being developed for a variety of problems, including substance use [18,22], affective disorders [23], and stress management [24]. The potential impact of an intervention (here, a JITAI) is dependent on the potency of its mechanistic target. Some, but not all, JITAIs that aim to augment behavioral health outcomes describe doing so through purported proximal outcomes [23]. Importantly, to increase the likelihood that JITAIs will be effective, their development must be informed by well-established findings from psychiatric research. For example, deficits in emotion regulation, or efforts to modify the intensity or duration of an emotion, are a transdiagnostic pathway in the development and maintenance of psychopathology [25,26]. Importantly, emotion regulation is malleable in that it can be augmented with intervention [27]. As such, emotion regulation is a key exemplar candidate transdiagnostic treatment target for behavioral health. Emotion regulation skills are aspects of empirically supported treatments for psychopathology [28,29] and have been shown to mediate and moderate the effects of interventions on outcomes [27]. Increasingly, emotion regulation skills have been incorporated into digital health interventions [30-33].

There are 2 major gaps in understanding the potential use of JITAIs in behavioral health care [34]. Henceforth, we use the term "behavioral health" to refer to psychological disorders and symptoms (including substance use disorders), as well as physical symptoms related to life stressors and crises. First, little research has summarized the effectiveness of JITAIs for behavioral health conditions. Intervention development is a multistage process that involves iteratively tailoring a program through repeated evaluation and from accumulating evidence [35-37]. For example, the National Institutes of Health's Obesity-Related Behavioral Intervention Trials (ORBIT) model provides a framework for intervention development that starts with establishing a significant clinical question and progresses through design (ie, defining, refining), preliminary testing (eg, proof-of-concept, feasibility pilots), efficacy trials, and finally effectiveness research. At any stage, in the case of a suboptimal outcome, the model would dictate that the investigator returns to an earlier phase for intervention refinement. All considered, the development of an intervention can take over 10 years before the program settles into its finalized form. What's more, by design, a finalized form of an intervention may never be achieved. Interventions must be optimized to strike a strategic balance between effectiveness, affordability, scalability, and efficiency. That strategic balance may vary across time and context [36]. Frameworks like multiphase optimization strategy (MOST) can be used to guide these optimization efforts. Experimental designs should be matched to the research question and stage of development (eg, microrandomized trial [38] or sequential multiple assignment randomized trial [SMART] [39]

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during optimization, randomized controlled trial during evaluation [35]). JITAIs as intervention frameworks were conceptualized 10 years ago [19]. Considering the intervention development process, the majority of published JITAIs likely either do not exist in their finalized form or are constantly evolving through optimization. Still, systematic reviews and meta-analyses exist that have examined the impact of JITAIs on the promotion of physical health, providing some early support for JITAIs as a digital health tool [15,16]. The extant systematic reviews relevant to behavioral health have evaluated JITAIs either within a larger health promotion framework or for a specific psychiatric disorder. In their meta-analysis of JITAIs for physical and mental health (eg, healthy diet, weight loss, diabetic management, addiction, bipolar disorder, and anxiety), Wang and Miller [17] found a large effect of JITAIs relative to a waitlist control (Hedges' g=1.653). In their systematic review of JITAIs for substance use, Perski et al [18] found mixed results. Second, few systematic reviews [23] have described JITAI proximal outcomes despite the important role that proximal outcomes play in elucidating intervention mechanisms of action [40]. Here, we propose a systematic review (and meta-analysis, as appropriate) of JITAIs targeting proximal outcomes (eg, emotion regulation) to improve behavioral health outcomes.

Objective

The objective of this review is to describe the state of the literature on JITAIs for behavioral health outcomes. Given that JITAIs originated in the past 10 years, our primary methodological approach for addressing our objective will be qualitative. That is, through a systematic review of the literature, we will extract, report, and describe the 6 elements (ie, distal outcome, proximal outcome, tailoring variable, decision point, decision rule, and intervention options) for each JITAI, regardless of the stage of intervention development (eg, preliminary testing, feasibility, clinical trial). In doing so, we will reinforce the existing JITAI framework [19,20] and provide a roadmap for the development of future JITAIs to improve behavioral health. Our secondary methodological approach for addressing our objective will be quantitative. That is, if it is determined that our included studies are sufficiently homogeneous, we will conduct meta-analyses to examine the effectiveness of JITAIs in promoting (1) aspects of behavioral health as distal outcomes and (2) proximal outcomes. We will examine moderators (eg, sociodemographic variables, symptom severity) conditional upon sufficient heterogeneity in outcomes. Given the importance of developing JITAIs incorporating empirically supported intervention targets, we will focus our discussion on emotion regulation as one proximal outcome of interest.

Methods

Overview

We used the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) checklist to write this systematic review protocol [41]. Multimedia Appendix 1 shows the PRISMA-P checklist.

Eligibility Criteria

Textbox 1 shows the inclusion and exclusion criteria. After examining a subset of records, it became clear that we were unable to determine with certainty if interventions were JITAIs (ie, just-in-time and adaptive) and if behavioral health outcomes were reported by examining article titles and abstracts. As such, to prevent excluding relevant articles during title and abstract screening, we retained a subset of our inclusion and exclusion criteria for this stage. That is, we focused on identifying articles using digital methods and proposing specific interventions and articles of the correct format (eg, excluding reviews and case reports). The full eligibility criteria are being used for full-text screening.

Textbox 1. Eligibility criteria for systematic review.

Inclusion criteria:

- Population: All individuals, regardless of age, sex and gender, race and ethnicity, socioeconomic status, geographic location, and other aspects of identity.
- Intervention design: Just-in-time adaptive interventions (JITAIs), that is:
  - Just-in-time: deployed when the individual needs it.
  - Adaptive: incorporates time-varying or contextual or both types of information for individualization, leveraged through passively or actively collected data from smartphones or wearable devices.
  - Intervention: activities intended to modify behavior, thoughts, or emotions.
- Outcome: Behavioral health.
- Article format: All languages; empirical research studies; publication in a peer-reviewed journal.

Exclusion criteria:

- Population: None.
- Intervention design: No JITAI.
- Outcome: Physical health and wellness outcomes that do not directly focus on behavioral health.
- Article format: Reviews, meta-analyses, case reports, dissertations, theses, and conference abstracts.

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Information Sources

A total of 5 databases were searched by a biomedical librarian (NT): PubMed/MEDLINE (US National Library of Medicine), Embase (Elsevier), Cochrane Library (John Wiley & Sons), Web of Science: Core Collection (Clarivate), APA PsycINFO (Dialog and Clarivate). To identify relevant articles missed by the search strategy, reviewers (LMH, MB-T, CEH, CNR, ET) will scan the bibliographies of included studies and relevant review articles. Protocols, feasibility studies, and acceptability studies were flagged during screening, and reviewers will revisit these records to determine if clinical outcomes were published. The final list of included studies, and additional, relevant studies, will be evaluated by the entire review team, along with relevant unaffiliated collaborators. Articles identified through these supplemental methods will proceed through the full screening process.

Search Strategy

A biomedical librarian (NT) with expertise in systematic review searches developed the search strategy in collaboration with the other members of the study team. A second librarian (Alicia A. Livinski, MPH, MLS) not otherwise affiliated with the project peer-reviewed the search strategy. The review team provided feedback on the search strategy. The search strategy incorporated keywords and controlled vocabulary terms (ie, EMTREE [Embase], MeSH [PubMed], Thesaurus of Psychological Index Terms [PsycNet]) for each concept of interest. The search strategy syntax was adapted for each database searched. Multimedia Appendix 2 shows the PubMed search strategy.

Study Records

Data Management

We used EndNote 20 (Clarivate) to collect and manage the results of the literature search and identify unique records. We used Covidence (Veritas Health Innovations), an internet-based tool for systematic review data management, for selection and data collection. Before selection and data collection, reviewers (LMH, MB-T, CEH, CNR, and ET) were trained in using Covidence.

Selection Process

Before each stage of screening (title and abstract, full text), a 20-article trial was conducted with all reviewers to pilot and refine the eligibility criteria to increase reliability. All reviewers are conducting screening using the stated eligibility criteria. For title and abstract screening, articles with missing abstracts automatically advanced to full-text screening. Following the title and abstract screening, the PDFs of the articles that were included were obtained and uploaded into Covidence for full-text screening. All articles are being double-coded for each stage of screening; that is, each record is independently screened by 2 reviewers. Screening discrepancies are being resolved during a group consensus meeting. Interrater reliability is being recorded in Covidence and will be documented in the final report.

Data Collection Process

Before data collection, a 15-article trial will be conducted with all reviewers (LMH, MB-T, CEH, CNR, and ET) to increase reliability. All reviewers (LMH, MB-T, CEH, CNR, and ET) will independently extract data items from records included after full-text screening. Each data item from each study record will be extracted in duplicate. Coding discrepancies will be discussed and resolved through dyadic consensus meetings, including the two relevant reviewers for each article. Discrepancies that cannot be resolved during dyadic consensus meetings will be resolved at a group consensus meeting. Data extraction forms will be published.

Data Items

Table 1 shows the data items that will be collected.

Table 1. Data items for systematic review

Category	Criteria
Article	Authors, title, journal, year.
Sample demographics	Where the study took place, sample size, age, gender, sex, race, and ethnicity.
JITAI[a] elements	Tailoring variable, decision points, decision rules (including static or adaptive status), intervention options, proximal outcomes (eg, emotion regulation), distal outcomes (eg, depression).
Study	Intervention development framework (eg, National Institutes of Health's ORBIT[b] model, MOST[c]), experimental design (eg, MRT[d], SMART[e]), where the JITAI was developed (eg, university, industry), was the JITAI delivered alongside other support (eg, in-person intervention), was the JITAI delivered alongside sensors or ambulatory devices, types of sensors used, JITAI delivery service (eg, iPhone, personal device), number of intervention days, payment structure (eg, flat fee), user engagement, user compliance (eg, response to prompts or frequency of JITAI use, or both), usability.

[a]JITAI: just-in-time adaptive intervention.

[b]ORBIT: obesity-related behavioral intervention trials.

[c]MOST: multiphase optimization strategy.

[d]MRT: microrandomized trial.

[e]SMART: sequential multiple assignment randomized trial.

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Outcomes and Prioritizations

Our primary outcome of interest is the distal outcome of the JITAI. Here, we focus on JITAIs that target behavioral health outcomes. Examples of potential distal outcomes include affective, substance use, disruptive behavior, eating, trauma-related, personality, psychotic, and neurodevelopmental disorders; psychological symptoms (ie, not meeting criteria for a disorder); pain; and well-being. Multimedia Appendix 2 shows the full list of search terms related to behavioral health. Our secondary outcome of interest is the proximal outcome of the JITAI. All proximal outcomes will be collected. We will calculate effect sizes for both the distal and proximal outcomes.

Risk of Bias in Individual Studies

Tools appropriate to the study design of individual records will be used to determine risk of bias. For example, Version 2 of the Cochrane risk-of-bias (RoB 2) tool for randomized controlled trials will be used for randomized controlled trials, including SMARTs [42]; Risk Of Bias In Non-Randomized Studies - of Interventions (ROBINS-I) will be used for nonrandomized studies comparing the effects of two or more interventions [43]; and Risk Of Bias In Non-randomized Studies - of Exposure (ROBINS-E) will be used for observational studies [44]. Risk of bias will be evaluated by 2 reviewers for each study. Disputes will be resolved during dyadic consensus meetings, and discrepancies that cannot be resolved during dyadic consensus meetings will be resolved during group consensus meetings.

RoB 2 includes 5 domains: bias due to the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, and bias in the selection of the reported result [42]. Each domain will be classified as low risk of bias, some concerns, or high risk of bias. ROBINS-I includes 7 domains: bias due to confounding, bias in the selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in the measurement of the outcome, and bias in the selection of the reported result [43]. Each domain will be classified as low, moderate, serious, or critical risk of bias or no information. ROBINS-E includes 7 domains: risk of bias due to confounding, risk of bias arising from the measurement of exposure, risk of bias in the selection of participants into the study, risk of bias due to post-exposure interventions, risk of bias due to missing data, risk of bias arising from the measurement of outcome, and risk of bias in the selection of the reported result [44]. Each domain will be classified as low risk of bias, some concerns, high risk of bias, or very high risk of bias.

Data Synthesis

Elements (eg, tailoring variables and decision points) of each JITAI will be presented in tables and summarized in the text. Data synthesis will be explored based on outcomes, and a summary of findings table will be presented, as appropriate.

We will categorize studies by design type (eg, randomized controlled trial, observational). If studies in each subgroup are sufficiently homogeneous, meta-analyses will be conducted for the distal and proximal outcomes. Features of the studies collected will inform the selection of the measure of effect size (eg, Cohen's d and Hedges' g). Subgroup analyses will be considered based on characteristics, including age, gender, type of psychopathology, and type of JITAI. In addition, sensitivity analysis will be carried out, excluding studies of low methodological quality, if necessary.

I^2 statistic will be used to quantify heterogeneity across effect sizes, and Q statistic will be used to test heterogeneity reduction through the inclusion of moderators. To address potential heterogeneity, meta-regression will be used to assess clinical characteristics (eg, the severity of symptoms), individual JITAI features (eg, type of emotional regulation strategies used in the intervention), study quality, and demographic characteristics (eg, age, gender, race, and ethnicity) that might influence the effect sizes.

If appropriate, mediation analyses will be considered to investigate whether changes in proximal outcomes mediate the relation between JITAIs and distal outcomes.

Meta-Biases

Publication bias, resulting from selective publication or reporting, will be investigated through visual inspection of funnel plots. Statistical tests for assessing symmetry (eg, Egger's test) will be explored if 10 or more studies have evaluated the same outcome. Trim and fill analyses will be conducted as necessary.

Confidence in Cumulative Evidence

The quality of evidence of estimates will be rated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework [45]. GRADE characterizes the quality of evidence according to publication bias, study limitations, inconsistency, imprecision, and indirectness [17]. Evidence of effectiveness outcomes will be rated from high to low quality by 2 reviewers. Disputes will be resolved during dyadic consensus meetings, and discrepancies that cannot be resolved during dyadic consensus meetings will be resolved during group consensus meetings. Results from GRADE ratings will be included in the summary of findings table.

Results

The search strategy was developed between July 2023 and November 2023, and the literature search was executed between November 2023 and December 2023. We retrieved 1243 records from our literature search. We excluded 91 duplicate records, leaving 1152 records for the selection process. Of note is that we performed a preliminary literature search for systematic reviews related to this topic and found no review identical to the one proposed. Title and abstract screening began in December 2023, and full-text screening began in May 2024. Data extraction and analyses have not begun.

Discussion

Principal Findings

In our systemic review, our objective is to describe the state of the literature on JITAIs for behavioral health outcomes. We

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expect that there will be sufficient data available to take a qualitative approach, including describing the aforementioned 6 elements for each JITAI. Conditional upon sufficient homogeneity of the included studies, we will also take a quantitative approach to examine the effectiveness of JITAIs in promoting (1) aspects of behavioral health as distal outcomes and (2) proximal outcomes.

Strengths and Limitations

Our systematic review has numerous strengths, including a comprehensive search strategy, double coding in each stage of screening and data extraction by trained reviewers, assessment of risk of bias of the included studies by reputed tools, evaluation of publication bias, and ratings of quality of evidence of estimates derived from the review.

There are also potential limitations of our work. Primarily, some ambiguity exists in the use of the term "JITAI;" the definition of JITAI has evolved since it was coined in 2015 [19]; the term has been used inconsistently (eg, an intervention with all the characteristics of a JITAI being characterized as a "momentary intervention" or related term) and imprecisely (eg, an intervention labeled as a JITAI despite the lack of an adaptive element); and there is overlap in the definitions of JITAIs and similar intervention frameworks (eg, ecological momentary interventions). As such, we have developed a robust search strategy, including not only the term JITAI but also related terms (eg, ecological momentary intervention, real-time intervention; more details in Multimedia Appendix 2). Furthermore, we developed and implemented detailed eligibility criteria for screening. We also clearly describe the 6 elements that constitute a JITAI in this protocol and will describe each element for each included JITAI in the final report. Accordingly, this systematic review may provide the field with further clarity on the definition and elements of JITAIs. Another limitation is that due to the iterative design process that characterizes JITAIs (and interventions, in general), JITAIs included in this report may not reflect their finalized form. Future scholarship will be needed to capture further JITAI innovations and evaluations. Finally, although we did not limit our search to English language articles, most of our articles are written in English, so the samples and populations represented may be similarly homogeneous. Additional work may be needed to increase the representation of studies published in languages other than English in JITAI effectiveness research.

Comparison With Previous Work

Previous research has typically evaluated JITAIs as digital health tools for the promotion of physical health [15,16]. While a select few reviews have examined JITAIs for specific psychiatric disorders [13], research has yet to robustly summarize the impact of JITAIs on behavioral health conditions.

Conclusions

This systematic review will summarize the evidence on the effectiveness of JITAIs in improving distal (ie, behavioral health) and proximal (eg, emotion regulation) outcomes. Results will provide clarity on JITAI definitions and elements, describe the effectiveness of JITAIs for behavioral health, elucidate targeted proximal outcomes, and inform the development of future JITAIs.

Acknowledgments

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Data Availability

The datasets generated during or analyzed during this study will be available in the OSF repository [46].

Authors' Contributions

LMH, MB-T, CEH, CNR, ET, NT, MK, OM, MAB, and SLG contributed to conceptualization, methodology, writing–original draft, and writing–review, and editing. LMH, MB-T, CEH, CNR, ET, and NT performed the investigation. LMH and MB-T handled project administration. NT, MAB, and SLG handled resources and funding acquisition. MAB and SLG performed supervision.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 checklist.
[DOCX File , 32 KB - resprot_v14i1e58917_app1.docx]

Multimedia Appendix 2
Search Strategy.
[DOCX File , 79 KB - resprot_v14i1e58917_app2.docx]

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Abbreviations

GRADE: Grading of Recommendations Assessment, Development and Evaluation
JITAI: just-in-time adaptive intervention
MOST: multiphase optimization strategy
ORBIT: Obesity-Related Behavioral Intervention Trials
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta Analyses Protocols
RoB 2: Version 2 of the Cochrane risk-of-bias tool for randomized controlled trials
ROBINS-E: Risk Of Bias In Non-Randomized Studies - of Exposure
ROBINS-I: Risk Of Bias In Non-Randomized Studies - of Interventions
SMART: sequential multiple assignment randomized trial

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Protocol

Posttraumatic Growth Among Suicide-Loss Survivors: Protocol for an Updated Systematic Review and Meta-Analysis

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Abstract

Background: Losing a loved one to suicide is an event that can have strong and potentially traumatic impacts on the lives of the bereaved survivors, especially regarding their grief, which can be complicated. These bereaved individuals are also less likely to receive social support following their bereavement. However, besides these adverse impacts, growing evidence supports the concept of posttraumatic growth following suicide bereavement. Posttraumatic growth is the personal improvement that occurs as a consequence of experiencing a traumatic or extremely challenging event or crisis. Only 1 systematic review and meta-analysis on posttraumatic growth following suicide bereavement has been conducted; this protocol is for the planned systematic review and meta-analysis update of the original systematic review and meta-analysis, as the original review collected its data in 2018.

Objective: This review aims to investigate demographic characteristics, correlational relationships, and facilitative factors of posttraumatic growth in individuals bereaved by suicide. In addition, as this is an update of a previous systematic review and meta-analysis, we aim to compare our findings with the original review and to identify any similarities or differences.

Methods: This protocol outlines the planned procedures of the updated systematic review and meta-analysis. MEDLINE, PsycINFO, Embase, CINAHL, Scopus, and Web of Science (Core Collection) were examined, and the search results were imported to Covidence, where title and abstract screenings and full-text screenings occurred. The inclusion and exclusion criteria for this updated review match those in the original review: (1) the study population must contain participants bereaved by suicide, (2) the study data must be quantitative, and (3) the study must report data on posttraumatic or stress-related growth. The original review conducted its search before 2019; thus, this updated review searched databases for the timeframe of January 2019 to January 2024. The updated meta-analysis will synthesize data from both the original and updated reviews to examine trends over time. The Newcastle-Ottawa Scale (NOS) will be used to assess publication quality. Random-effects meta-analyses will be conducted using RStudio (R Foundation for Statistical Computing).

Results: The review was funded in October 2023 and is currently in progress. Results are expected to be finalized in October 2024. There are 21 articles that have been included in the review and are being analyzed at this time. We aim to submit the full article for publication in December 2024.

Conclusions: The results of this updated systematic review and meta-analysis will be used to examine key relationships and findings regarding posttraumatic growth in individuals bereaved by suicide. The discussion will also investigate the findings of this updated review in comparison to the findings of the original review. Any differences would be highlighted. Limitations of the current review will be discussed, such as the quality of the articles included.

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Trial Registration: PROSPERO CRD42024485421; https://tinyurl.com/3hzpnzr3
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KEYWORDS

posttraumatic growth; suicide-loss survivors; trauma; systematic review; meta-analysis; posttraumatic; suicidal; systematic review; meta-analysis protocol; traumatic impacts; bereaved survivor; social support; bereavement; data collection; sociodemographic; psychological; databases

Introduction

When someone dies by suicide, those who lose this individual in their lives often face significant stress. These feelings can be inundating and are often accompanied by a sense of complicated grief and, at times, depression [1]. It is a tragic event that can generate negative emotions as well as many questions that may be left unanswered in the minds of these surviving individuals. In addition, this population of people bereaved by suicide is at an increased risk of suicidal behavior themselves [2]. Based on data that over 700,000 people die by suicide each year globally [3], and that for each suicide, there are from 6 family members to 135 community members considered to be bereaved or exposed, respectively [4,5], up to 94.5 million can be affected by suicide annually. Thus, many people affected by suicide loss each year are subsequently at increased risk of dying by suicide themselves.

There are commonalities between bereavement of suicide and other forms of death; however, some features of suicide bereavement are more pronounced, such as feelings of guilt, blame on self or others, or a longing for answers [6,7]. While all bereaved people may experience feelings of grief, loss, and depression, people bereaved by suicide specifically can begin to develop symptoms of posttraumatic stress disorder (PTSD) [8,9]. However, some individuals show signs of posttraumatic growth (PTG) more so than symptoms of PTSD. PTG is the personal improvement that occurs as a consequence of experiencing a traumatic or extremely challenging event or crisis. Literature has begun to show that, on average, PTG occurs more often than the development of pathological disorders following exposure to a traumatic event [10,11]. This is, of course, not to say that PTG is always the result of trauma, but rather, psychological suffering allows the opportunity for a person to grow and for new meaning to flourish in the face of trauma. An inverted U-shaped curve best describes the relationship between the developments of PTG—both too much and too little suffering are detrimental to the development of PTG [12,13]. This concept of PTG following a traumatic event [14] has since been applied to learning more about the bereavement experiences of individuals bereaved by suicide. Some authors have also used the phrase “personal growth” [15] or “stress-related growth” [16] in place of PTG. This study will use the terminology of PTG rather than personal growth or stress-related growth.

Determining a metric for PTG can be difficult as it is seen as both an ongoing process and a final result. However, the Posttraumatic Growth Inventory (PTGI) has been developed and shown to capture and highlight well many of the defining characteristics of PTG [10]. These characteristics are broken down into 5 domains: “greater appreciation of life and changed sense of priorities; warmer, more intimate relationships with others; a greater sense of personal strength; recognition of new possibilities or paths for one’s life; and spiritual development” [14]. It does not, however, fully account for all idiosyncratic differences that occur over time; in this regard, a more longitudinal approach for the measurement of such a complex construct (ie, PTG) could provide valuable insight [17].

For those who lose someone to suicide, there can be variables that affect their desire or willingness to seek both formal and informal help and work towards the development of PTG. Each of these variables can influence how well someone bereaved by suicide copes with and grows following their loss. For example, some individuals who have experienced suicide bereavement have reported that their primary support came from nonprofessional sources and that they were disappointed by their family and friends’ responses to their bereavement [18]. Suicide and the survivors’ grieving process can also be seen from a variety of perspectives depending on the culture from which someone comes, such as being seen as stigmatized, taboo, and isolating [19,20]. Along with these responses, some individuals have reported generally negative attitudes toward professional support systems, such as tactlessness and being unaligned in the grieving process [21]. Unfortunately, these detrimental experiences can be an additional stressor on top of what can already be a tragic and intense time of grieving. These factors could contribute to why up to 25% of people bereaved by suicide receive neither informal nor formal support [22]. Each of these variables (ie, poor support, stigmatization, tactless professional help, etc) can hinder PTG development.

This systematic review and meta-analysis is an update of a previous systematic review and meta-analysis conducted by Levi-Belz et al [23]. Our searches have found that the latter is the only one to ever be conducted on this topic. As their original review gathered data from literature before 2019, this review will include data found from searches between January 2019 and January 2024. This updated meta-analysis will synthesize data from both the original and updated reviews to search for any new or consistent trends. As some authors and databases call for a systematic review to be updated every 2 years [24], and with the paucity of understanding that exists on this subject, examining new literature, in conjunction with the previous review, could allow for a more in-depth understanding of which factors facilitate PTG in people bereaved by suicide. The aforementioned evidence suggests that PTG can and does occur following suicide bereavement; therefore, investigating further

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which factors might facilitate, as well as detract from, PTG development could greatly benefit people bereaved by suicide.

We have three primary aims with this review: (1) to investigate whether PTG can occur in the aftermath of a suicide loss, (2) to examine the sociodemographic and psychological correlates of PTG among people bereaved by suicide, and (3) to observe which factors facilitate PTG in the aftermath of suicide bereavement.

Methods

Overview

This systematic review will locate and summarize applicable data from the peer-reviewed literature [25]. The findings will be reported using PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [26] formatting and follow the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) checklist [27]. A meta-analysis will be conducted using the data extracted from this update as well as the data from the original review.

Inclusion Criteria

Population

Study populations must include individuals bereaved by suicide. No limitations on age will be implemented.

Study Design

In accordance with the original review, only quantitative studies that report data on PTG will be included. While qualitative studies could offer a more comprehensive perspective on the topic, this update excluded them in order to follow the criteria of the original review. Gray literature and dissertations will be excluded such that peer-reviewed studies will be the only data involved. This was also done to follow the parameters set by the previous review.

Concept

Studies must report data on PTG in individuals bereaved by suicide. Studies that report data on PTG following various forms of bereavement but which do not separate the effects of suicide bereavement from other forms of bereavement will be excluded.

Context and Date of Publication

This systematic review and meta-analysis is an update of a previous systematic review and meta-analysis that gathered data before January 01, 2019. This update reviews literature published on or after January 01, 2019, and uses the same inclusion criteria as the first study. This updated meta-analysis will include the data from the 2019-2024 range as well as the initial study's findings so as to paint a full picture.

Language and Location

There are no restrictions on language or location.

Search Strategy and String

As this review is an update of a previous systematic review, the inclusion criterion for the date range is publication on or after January 01, 2019. The initial systematic review, upon which this update is based, included all dates up to December 31, 2018, in its search. Databases searched include MEDLINE (through Ovid Platform), PsycINFO, Embase, CINAHL, Scopus, and Web of Science (Core Collection). We used the MeSH (Medical Subject Headings) terms "Posttraumatic Growth, Psychological," and "Suicide" in databases that allowed for them (ie, MEDLINE [through Ovid Platform] and [PsycINFO])—the rest of the search string was free text and was used for each of the 6 databases mentioned. Multimedia Appendix 1 shows the search included in each database.

Data Extraction

Using Covidence [28], a title and abstract screening was conducted by 2 reviewers (SW and BM) to exclude studies outside the criteria as well as to remove duplicate search results. A further full-text screening was performed in Covidence by the same 2 reviewers (SW and BM), and studies deemed inapplicable were excluded; reasons for exclusion of these studies were recorded. Any disagreements on the inclusion or exclusion of an article by the 2 reviewers were brought to the review team for further opinion to resolve the dispute. Data extracted included author's name, year, location (country), study design, sample size, participants' age and sex distribution, participants' time since onset of bereavement, participants' relationship to the deceased, outcome measures, names of the instruments used, and primary findings of the study. To allow for the analysis of subgroups, we also extracted information related to demographic factors, loss-related factors, intrapersonal factors, and interpersonal factors (see the *Analysis of Subgroups or Subsets* subsection). The authors of the original review shared their data from the first review; it will be used for the meta-analysis portion of this update.

Risk of Bias (Quality) Assessment

The risk of bias will be assessed using 2 adapted versions of the Newcastle-Ottawa Scale (NOS) [29]. One adapted version will be for cross-sectional studies (7 questions), and the other for longitudinal studies (8 questions). This tool allows for the overall quality of a study to be assessed by the summation of "stars," which each question can provide based on quality. Questions are broken into categories of "selection" (4 questions), "comparability" (1 question), and "outcome" (2 questions for cross-sectional and 3 questions for longitudinal). The highest grade a study can receive is 8 stars for cross-sectional studies and 9 stars for longitudinal studies. The total number of stars is then used to determine a quality ranking for each study, where quality levels range from poor (<5 stars), fair (5-6 stars), and good (6-8 stars) in cross-sectional studies and poor (<5 stars), fair (5-6 stars), and good (7-9 stars) in longitudinal studies. Studies from all quality levels will be included as there is a paucity of literature on this topic; however, the inclusion of any "poor quality" articles will be addressed in the limitations of this updated systematic review and meta-analysis.

Strategy for Data Synthesis

The analysis will be conducted in RStudio (R Foundation for Statistical Computing) [30]. When studies did not report *r* coefficients, raw effects will be converted to *r* coefficients using the R package *effectsize* (version 0.8.3) [31]. Before conducting the analysis, we will apply a Fisher's *r*-to-*z* transformation to

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the extracted effect sizes. Sampling variances and standard errors for the effect sizes will be calculated using the R package *esc* (version 0.5.1) [32].

Random-effects meta-analyses will be conducted using the R package *metafor* (version 4.4.0) [33]. This approach posits that individual study effects deviate not solely due to sampling error but also stem from another source of variance [34]. Heterogeneity will be assessed by Cochran Q, I^2 statistics, τ^2, and prediction intervals as recommended by Borenstein [35]. Publication bias will be assessed visually through a contour-enhanced funnel plot [36] and also by Egger regression test. To identify and assess the impact of potential outliers on the pooled effect and heterogeneity, influential analysis will be conducted using the R package *dmetar* (version 0.1.0) [37], using the leave-one-out method and the Baujat plot.

Analysis of Subgroups or Subsets

In line with the original review, moderating factors will be categorized into 4 categories, with effect sizes calculated for each subsequent variable. The following examples are from the original review:

1. Demographic factors (eg, age, gender, race, religious affiliation, educational level, marital status, and voting or civil involvement).
2. Loss-related factors (eg, grief experience, time since loss, and closeness to and type of relationship with the deceased).
3. Intrapersonal factors (eg, resilience, coping, rumination, personality, optimism, and emotional experience).
4. Interpersonal factors (eg, self-disclosure, social support, help-seeking, suicide stigma and secrecy, interpersonal burdensomeness, lack of belonging, and attachment style).

Results

This updated systematic review and meta-analysis was funded in October 2023 and is currently underway. It is expected to have results in October 2024. A total of 21 studies are included in this review; this will be reported by a PRISMA flow diagram (Figure 1). These 21 studies are currently being analyzed. All data produced in this review is included in Multimedia Appendix 2. A meta-analysis will be conducted using the data from both the studies of this updated search as well as the studies from the original review's search. Doing so will allow for any varying or static trends to be revealed. Moderating factors will be examined to determine which variables may influence PTG development in people bereaved by suicide. We aim to submit the full paper for publication in December 2024. The PRISMA-P checklist will be abided by to ensure a higher quality of research practices are followed (see Multimedia Appendix 3).

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. PTG: posttraumatic growth.

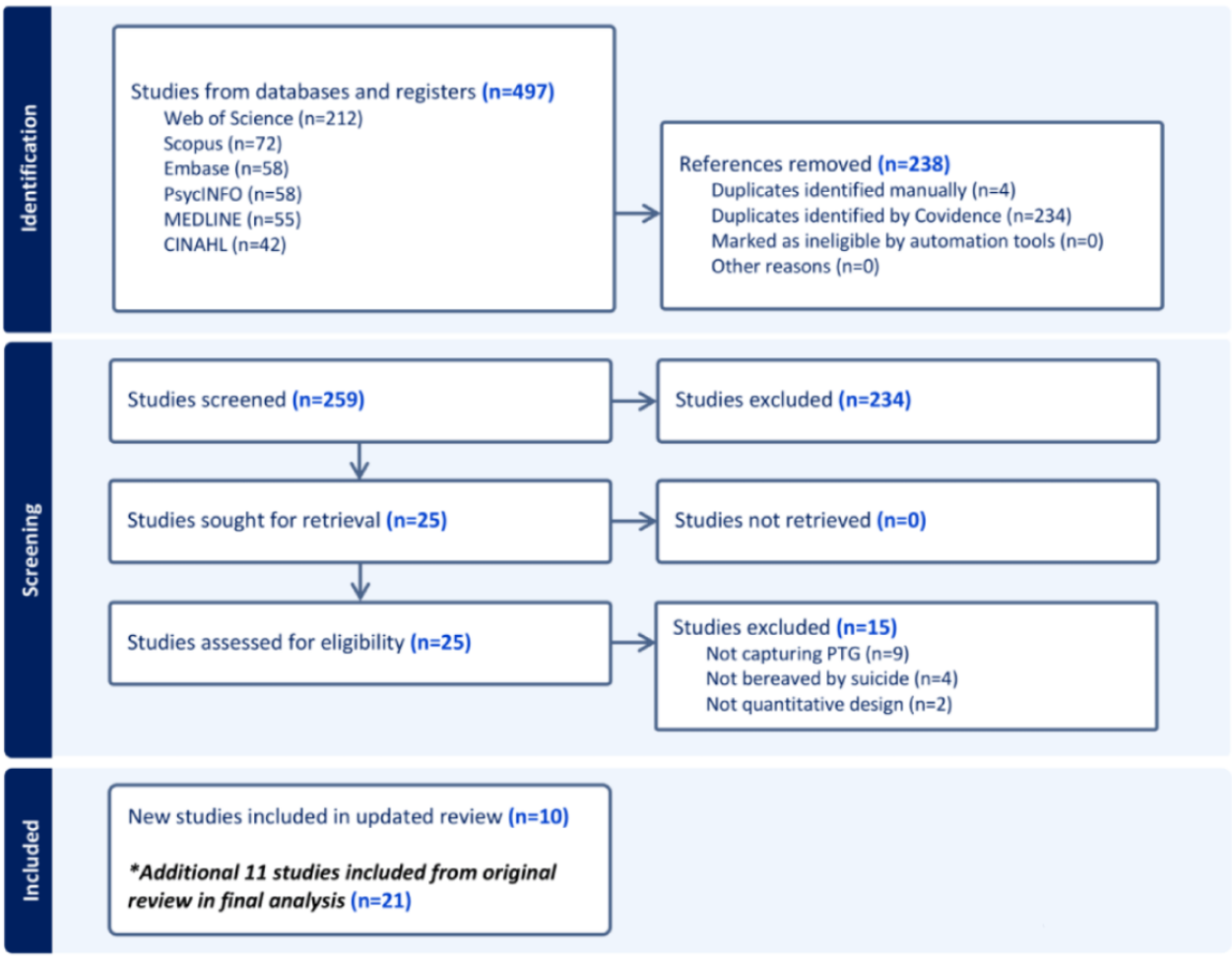

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Discussion

We hypothesize that interpersonal variables of self-disclosure and social support, as well as the loss-related factor of time since loss and the intrapersonal variable of resilience, will have a positive influence on PTG. A full discussion will further examine these key relationships and general findings identified in the Results section. These findings will then be discussed in relation to 3 research aims identified in this review. The discussion will also investigate the findings of this updated review in comparison with the findings of the original review. Any differences would be highlighted and expounded upon to discover which factors have changed. Overall, we anticipate that the moderating variables will have varying effects on PTG and will deliberate on any potential correlational relationships, as this could emphasize which specific factors are correlated to greater PTG facilitation.

Implications and strengths, future work, and subsequent research, which could build upon the findings of this updated review will be discussed. The limitations of this review will be considered as well, such as the quality of the journal articles included in this review. Similarly, we will discuss how this systematic review has chosen to exclude qualitative articles as well as gray literature and dissertations and the strengths and limitations that follow this decision. We will also examine the impact of using solely the NOS for quality assessment of studies. While the NOS is a widely recognized tool for assessing the risk of bias, it may not fully capture the complexities associated with PTG. PTG involves multidimensional psychological, social, and emotional processes, which may be influenced by a variety of factors not entirely accounted for by the NOS. As such, relying solely on the NOS may limit the ability to assess the nuanced methodological challenges present in studies of PTG. Future research may benefit from supplementing the NOS with other bias assessment tools or qualitative methodologies to provide a more comprehensive assessment of study quality and the contextual factors influencing PTG outcomes. This paper will be submitted for peer-reviewed publication. It will also be part of a thesis submitted to the University of Strathclyde.

Acknowledgments

This PhD studentship is being funded by the University of Strathclyde's Global Research Award.

Data Availability

All data generated or analyzed during this study are included in this published article and Multimedia Appendices 1-3.

Authors' Contributions

This review is being completed as part of a PhD thesis by SW with the University of Strathclyde and is being supervised by SR, NC, and DT. The 3 authors of the original review—YL-B (Ruppin Academic Center), KK (University of Melbourne), and KA (University of Melbourne)—have joined this updated review as coauthors and team members. The meta-analysis is also under specific supervision by VS. BM is assisting in the screening, extraction of data, and writing of this article.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[PNG File , 119 KB - resprot_v14i1e64615_app1.png]

Multimedia Appendix 2
Systematic review and meta-analysis data extraction form.
[XLSX File (Microsoft Excel File), 77 KB - resprot_v14i1e64615_app2.xlsx]

Multimedia Appendix 3
PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist.
[DOC File , 89 KB - resprot_v14i1e64615_app3.doc]

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Abbreviations

MeSH: Medical Subject Headings
NOS: Newcastle-Ottawa Scale
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
PTG: posttraumatic growth
PTGI: Posttraumatic Growth Inventory
PTSD: posttraumatic stress disorder

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Protocol

Acceptance Factors and Barriers to the Implementation of a Digital Intervention With Older Adults With Dementia or Caregivers: Protocol for an Umbrella Review

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Abstract

Background: The increase in average life expectancy, aging, and the rise in the number of people living with dementia contribute to growing interest from the scientific community. As the disease progresses, people with dementia may need help with most daily activities and need to be supervised by their carer to ensure their safety. With the help of technology, health care provides new means of self-managing health that support active aging, allowing older people and people with dementia to live independently in their homes for a longer period of time. Although some systematic reviews have revealed some of the impacts of using digital interventions in this area, a broad systematic review that examines the overall results of the effect of this intervention type is mandatory.

Objective: The aim of this review is to further investigate and understand the acceptability and barriers to using technology to monitor and manage health conditions of people living with dementia and their caregivers.

Methods: A review of systematic reviews on acceptability factors and barriers for people with dementia and caregivers was carried out. Interventions that assessed acceptability factors and barriers to the use of technology by people with dementia or their carers were included. Each potentially relevant systematic review was assessed in full text by a member of a team of external experts.

Results: The analysis of the results will be presented in the form of a detailed table of the characteristics of the reviews included. It will also describe the technologies used and factors of acceptability and barriers to their use. The search and preliminary analysis were carried out between May 5, 2023, and August 1, 2024.

Conclusions: This review will play an important role as a comprehensive, evidence-based summary of the barriers and facilitators to the use of digital interventions. This review may help to establish effective policy and clinical guideline recommendations.

(JMIR Res Protoc 2025;14:e56584) doi:10.2196/56584

KEYWORDS

dementia; aging; telemedicine; implementation; digital intervention; older people; elderly; geriatrics; mobile applications; barriers; adherence; caregivers; self-management; acceptability

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Introduction

The increase in average life expectancy and aging population give rise to numerous health problems, including a decline in physical performance; changes in sensory, cognitive, and psychological abilities; and changes in social interactions [1]. Decreased physical and cognitive function is associated with a high risk of falls, increased memory loss, and difficulty completing daily tasks such as eating, dressing, medication management, and shopping [1]. Deterioration in cognition may be important, resulting in interference with occupational, domestic, or social functioning [2], making it difficult to communicate and manage activities of daily living [3,4].

The number of people with dementia worldwide is expected to increase from 46.8 million today to approximately 131.5 million by 2050 [5-7]. According to the Global Dementia Observatory and World Health Organization (WHO), dementia is the seventh leading cause of death worldwide [8]. The impact of dementia on society is well known, so early detection, timely intervention, and prevention are extremely important [9]. This issue is attracting increasing interest from the scientific community [10] and WHO, and many policies [11] are being developed worldwide.

With advances in medicine and the aging population, there is a growing number of older adults with cognitive, motor, and sensory limitations who need support to continue to be at home and maintain some degree of autonomy. For these individuals, the alternative is to live in a residential structure for older adults, where (in theory) they will have more specialized support, free from the problem of managing a home or daily activities. However, the type of care provided is usually depersonalized, often not directed toward the disease and the patient, and often too basic and not specific to individual needs. Growing economic difficulties also imply greater difficulties in this solution. Therefore, many people choose to stay at home, being cared for by other people—family members or friends—who become informal caregivers [12].

It is increasingly important to realize how we can promote the independent living and safety of people with dementia. As the disease progresses, people with dementia may need help with most daily activities, and there is a need for caregiver supervision to ensure their safety [13,14]. However, in the face of rising demand and scarce resources, the ability of health care systems and caregivers to provide equitable, responsive, and timely postdiagnostic support on a sustainable basis is a growing concern [15].

The physical, psychological, social, and economic impacts on not only people with dementia but also their caregivers, families, and society in general are another point of alarm [12,16-18]. The characteristics and complexities of dementia give rise to concerns such as frustration, risk of psychological stress, depression, reduced quality of life (QoL), and poor health on the part of the caregiver, leaving them with a great deal of responsibility and less free time to look after themselves [13,16,17,19-21]. Individuals with dementia and their carers have a range of educational and support needs that vary throughout the different stages of dementia. Information resources, caregiver training or skills development, support groups, counseling, respite care, care coordination programs, transportation services, grocery and meal delivery, personal care, and care planning are essential to help and support caregivers and patients [14].

The COVID-19 pandemic highlighted the relevance of innovative technologies in guiding the interventions of professionals and carers and supporting frail older people. It seems essential to use technologies as a means of supporting and analyzing individual behaviors, identifying the need for and barriers to specific interventions by caregivers, and maintaining the QoL of people living with dementia and their caregivers and supporting active aging for people with dementia.

The use of the internet and digital technologies is increasing rapidly around the world, including among older adults [7,22]. Digital technology encompasses a range of interconnected innovations, including the Internet of Things with next-generation telecommunication networks (eg, 5G); big data analytics; artificial intelligence using deep learning; and blockchain technology [23]. These technologies play a crucial role in active aging, as digital interventions [10] and monitoring systems [11] have been reported to be important for enabling older people and individuals with dementia to live autonomously in their own homes for a longer period of time [10]. The complexity of behavior and context in which the most diverse situations occur makes measuring this effect challenging [11]. However, the importance of 24-hour monitoring of older people has been emphasized [11]. Technology is increasingly being used in health care, such as the provision of services, home monitoring, interactive communication (eg, between patient and doctor), the transfer of health information, and peer support [24]. The benefits of telehealth or information and communication technologies to support family carers at home are increasingly being studied [7]. In this way, digital interventions can offer several advantages, including the promotion of autonomy and self-management of health and allowing patients to maintain a certain degree of independence [12-14]. These types of digital tools can provide advantages and disadvantages of residential care by providing quick access to medical information and remote support for health care professionals, as well as reducing the need for in-person visits to doctors' offices and hospitals, resulting in transportation and other associated costs [12-14]. However, these interventions may also present limitations, such as technical barriers due to a lack of technical knowledge among older adults and caregivers, concerns about the privacy and security of personal and medical data, and accessibility and adaptation challenges, as all older adults neither have access to nor are adapted to the use of digital technologies, especially individuals with severe sensory or cognitive disabilities [12-14].

Considering the complexity of this issue, it is extremely important to understand what problems occur at this stage of life and how the use of technology can help people with dementia maintain their independent living and QoL, improve their health, and prevent possible emergencies [11]. However, the use of this type of technology to assist and monitor people with dementia and their carers should not be accepted uncritically. Older people are often referred to as reluctant users

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or opponents of technological change [10], and the use of technology by carers reportedly increases their burden [15,16].

This knowledge is crucial for developing more effective and personalized strategies that can improve QoL for patients and their caregivers [13,17,19,25]. In this way, by better understanding the specific challenges faced by this population, both formal and informal caregivers can adapt technological interventions to ensure greater adherence and effectiveness, thereby promoting more integrated and patient-centered care [6,7,9,13,22].

With this umbrella review, we set out to gather the data available in the literature in detail, which will allow research teams and policymakers to identify the technologies that have been successful and the objections to their use in supporting active aging and carers. The main aim of this review is to investigate, understand, and summarize the acceptability and barriers to using technology to monitor and manage health conditions in people with dementia and their carers, using more recent data. Another aim is to contribute to a theoretical debate and offer suggestions for future research in this area of work, as well as categorize the barriers and motivations for using technology. This scientific evidence will help with clinical guideline development and support political orientations.

To the best of our knowledge, this is the first general review that specifically addresses issues related to acceptability factors and barriers to the use of digital technology in people with dementia and their caregivers. We will be able to summarize the effectiveness of digital technology to support people with dementia and their carers, which is a challenge that requires an umbrella review approach.

Several research questions will be addressed: (1) What are the barriers to implementing digital interventions for people with dementia and/or caregivers? (2) What are the facilitators in implementing digital interventions for people with dementia or caregivers? (3) What digital interventions have been proposed for people with dementia or caregivers? (4) How effective were these digital interventions in alleviating the targeted problems?

Methods

Study Design

With the increase in the number of publications and reviews on the use of technology by older people and people with dementia in recent years, we aimed to use an umbrella review to examine whether the evidence for our research question is consistent or contradictory. Umbrella reviews focus on research questions or clinical practice for which there is a rich, high-quality evidence base. By reviewing all the existing literature on our research questions, we will be able to provide an overview of the main research findings.

To implement this umbrella review, we used the Preferred Reporting Items for Overviews of Review (PRIOR) statement protocol [26]. We selected and analyzed the studies according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. We used the Cochrane PICOS framework (population, intervention, comparison, outcomes, and study design; Table 1). The methods used in all stages of screening, selection and extraction, quality assessment, overlap management, analysis, and synthesis were referenced to ensure that our analysis can be replicated.

Table 1. Eligibility criteria for the inclusion of systematic reviews and meta-analyses.

Category	Specific criteria
Inclusion criteria	
Publication type, date, and language	Systematic reviews (or meta-analyses) published in a peer-reviewed journal
Study design	Systematic reviews and meta-analyses
Population	Male or female individuals with dementia (age ≥60 years) or their caregivers
Intervention	Interventions based on the evaluation of the acceptability and barriers to implement digital interventions for people with dementia or their caregivers
Outcomes	Outcomes will be extracted from systematic reviews that include these aspects. Reviews including effectiveness of implementing digital interventions for people with dementia or their caregivers (eg, Results from the Unified Theory of Acceptance and Use of Technology Questionnaire, Telehealth Satisfaction Questionnaire) and among them, if available, strategies impacting the implementation process (eg, results from the Mini-Mental State Examination, Zarit Burden Interview, Impact of Caregiving Scale, Caregiver Strain Instrument)
Exclusion criteria	
Study design	Articles that were not systematic reviews and meta-analyses were not included.
Time period	Reviews that used studies carried out during the COVID-19 pandemic
Intervention	Reviews using articles with robot intervention

Target Population

We included systematic reviews with or without a meta-analysis focusing on acceptability factors and barriers to the use of technology by people with dementia or carers. The inclusion and exclusion criteria for this umbrella review are presented in Table 1.

Our population includes adults aged 60 years and older with dementia who had been included in studies using technologies.

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We did not limit the place (eg, home, clinics, academic centers, nursing home, rural populations) of intervention or the type of intervention carried out. We excluded analyses measuring acceptability factors and barriers of studies performed during the COVID-19 pandemic. The reason for this exclusion was to reduce the influence of compulsion or technology being the only way to access the intervention, which could influence the wanted results.

Intervention, Comparators, and Outcomes

We included all systematic literature reviews that present results on the factors that can limit or enhance the use of technology by older people with dementia and carers. Among these, we focused on factors of acceptability and barriers to use and implementation using technologies. This umbrella review focuses on dementia interventions that are delivered using digital technology. For the purpose of this review, digital technology is defined as technology interventions that use smartphone apps, wearable technology, or mobile text messaging to deliver health care. These digital technologies are developed to support the independence of older people living in the community, alleviating or preventing functional or cognitive impairment, thus limiting the impact of dementia on older people and their caregivers.

The following comparisons were analyzed: technology versus control (no technology), intervention environments, type of technology used, and intervention by carers. Where possible, the intervention of caregivers will be divided into formal and informal caregivers, including factors of acceptability and barriers to the use of technology. The outcomes will be divided into outcomes of people with dementia and outcomes of caregivers. Outcomes of people with dementia include the sociodemographic characteristics of the patients, cost efficiency of using the intervention, changes in health outcomes after using the intervention (eg, Mini-Mental State Examination), patients' adherence to and engagement with the intervention, adverse events, and barriers to using the intervention (eg, The Unified Theory of Acceptance and Use of Technology Questionnaire, Telehealth Satisfaction Questionnaire). Outcomes of caregivers include the quality and reliability of the interventions (eg, Zarit Burden Interview, Impact of Caregiving Scale, Caregiver Strain Instrument), patients' follow-up with health care services after using the intervention, caregivers' adherence to and engagement with the intervention, adverse events, and barriers to using the intervention (eg, Telehealth Satisfaction Questionnaire).

Publication Type, Date, and Language

Reviews published in peer-reviewed journals were included, without any date limitations.

Data Sources and Search Strategy

The search for this umbrella review aimed to identify all systematic reviews of the literature on our research question. ISI Web of Science, Scopus, and PubMed databases were used to search for scientific articles for the development of this umbrella review. In this search, articles were identified using keywords and MeSH words (for PubMed search), individually and/or in combination. The research strategy used in PubMed included the following: (((((Elderly) OR (“Older population”)) OR (“Older people”)) OR (“Geriatrics”[Mesh])) OR (“Aged”[Mesh])) OR (“Aging”[Mesh])((((“Telemedicine”[Mesh]) OR (“Mobile Applications”[Mesh])) OR (“health informatics”)) OR (“healthcare technology”)((((implementation) OR (Barriers)) OR (Acceptance)) OR (Adherence)) OR (Restriction)((((“Dementia”[Mesh]) OR (“Cognition Disorders”[Mesh])) OR (“mental deterioration*”)) OR (“cognitive impairment*”)) OR (“mild cognitive impairment*”)((((((((Elderly) OR (“Older population”)) OR (“Older people”)) OR (“Geriatrics”[Mesh])) OR (“Aged”[Mesh])) OR (“Aging”[Mesh])) AND ((((“Telemedicine”[Mesh]) OR (“Mobile Applications”[Mesh])) OR (“health informatics”)) OR (“healthcare technology”))) AND (((((implementation) OR (Barriers)) OR (Acceptance)) OR (Adherence)) OR (Restriction))) AND (((((“Dementia”[Mesh]) OR (“Cognition Disorders”[Mesh])) OR (“mental deterioration*”)) OR (“cognitive impairment*”)) OR (“mild cognitive impairment*”)).

The research strategy used in Web of Science and Scopus included ((((((((Elderly) OR (“Older population”)) OR (“Older people”)) OR (“Geriatrics”)) OR (“Aged”)) OR (“Aging”)) AND ((((“Telemedicine”) OR (“Mobile Applications”)) OR (“health informatics”)) OR (“healthcare technology”))) AND (((((implementation) OR (Barriers)) OR (Acceptance)) OR (Adherence)) OR (Restriction))) AND (((((“Dementia”) OR (“Cognition Disorders”)) OR (“mental deterioration*”)) OR (“cognitive impairment*”)) OR (“mild cognitive impairment*”)).

Data Exclusion

Data from the included studies were analyzed by 2 independent reviewers (MVP and RM) and extracted into Microsoft Excel according to the acceptability and barriers of new technologies, reported by people with dementia or their caregivers. Discrepancies will be resolved through discussion with a third author (NP).

Data Synthesis

Results analysis will aim to present the technology used and the factors of acceptability and barriers to its use to support people with mild cognitive impairment or dementia and their carers. It will describe in detail each of the studies analyzed, presenting the study population, site of the intervention, time of the intervention, technology used and its category, evaluation instruments, and site. It will also describe the intervention that was carried out, reasons for acceptability and barriers, impact of the intervention, and limitations or future research with people with dementia and their carers. If possible, we will use the Consolidated Framework for Implementation Research (CFIR) to organize and analyze the factors of acceptance, barriers, and impact of support technologies for people with mild cognitive impairment or dementia and their caregivers. The CFIR tool provides a comprehensive theoretical framework that will help categorize and interpret the results, promoting a deeper understanding of the factors that influence the acceptance of and challenges with implementing technologies for people with mild cognitive impairment and dementia as well as their caregivers.

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Methodological Quality and Risk of Bias Assessment

The methodological quality of all the included studies was assessed using the AMSTAR-2 (A Measurement Tool to Assess Systematic Reviews) checklist [27]. The tool helps categorize the quality of reviews according to 7 critical areas and 9 noncritical areas. The assessment will be grouped into low, moderate, and high critical quality categories.

Patient and Public Involvement

No patients nor members of the public were involved in the development of this comprehensive review. However, the scope and methods of this review were based on the literature and discussed with experts.

Ethical Considerations and Dissemination

The proposed comprehensive review was based exclusively on published data from secondary sources and therefore did not involve any interactions with human beings.

The results of the umbrella review will be presented at international conferences in the fields of, for example, gerontology and geriatrics, health informatics, primary care, public health, and social sciences and will be published in a journal aimed at a wide audience. When the results are published, we will make the data generated by our research openly and publicly available. The team also intends to use social networks and the institutional websites of its research centers to disseminate its findings through websites, social media, and newsletters.

Results

We expect to find information on the facilitators and barriers to the implementation of digital interventions for people with dementia or their caregivers. We expect to provide information for politics and practice and to extract guidance for future research.

The search and preliminary analysis were carried out between May 5, 2023, and August 1, 2024. A total of 612 studies were identified across 3 databases. After the removal of duplicates, 400 articles remained. Title and abstract screening further reduced this number to 20 articles for full-text analysis. Ultimately, 5 studies met the inclusion criteria, focusing on the acceptability and barriers to technology use among individuals with dementia or their caregivers. Results were analyzed between August 2024 and October 2024, and the results are expected to be published later in 2025.

Discussion

Overview

As far as we know, this will be the first umbrella review addressing acceptance factors and barriers to the implementation of digital interventions in older people with dementia and their caregivers. Providing information on the facilitators and barriers to the implementation of digital interventions in people with dementia and their caregivers is extremely relevant from a clinical perspective [6,7,9,13,17,19,22,25]. This debate, present in the literature, encompasses several key issues: the effectiveness of digital interventions, the acceptability and usability of these technologies by older adults with dementia, and the various barriers to successful implementation, such as technological complexity and lack of digital literacy [12-14]. Additionally, there is concern about the potential for digital technologies to increase the burden on caregivers, who must learn and manage new technologies while providing care [12-14]. Discussions also focus on how digital technologies can improve QoL and health outcomes for people with dementia and their caregivers, including assessing clinical effectiveness and the impact on daily living and well-being [13,25]. Furthermore, the economic feasibility and broader social implications of implementing digital technologies in dementia care have been debated, including considerations of cost-effectiveness and potential health care cost reductions [6,7,25]. By systematically reviewing and synthesizing the available literature, this review seeks to provide a clearer understanding of these issues, thereby contributing to the theoretical debate and offering insights for future research and policy development.

Our umbrella review can significantly contribute in several ways, as noted in the following paragraphs.

It can identify barriers and facilitators. By synthesizing the results of various systematic reviews and meta-analyses, this review identifies common barriers and facilitators for implementing digital technologies in dementia care. This includes technical, financial, social, and psychological aspects that influence the accessibility and effectiveness of these interventions [12-14].

It can provide information for policies and practices. Insights obtained from this review can inform the formulation of policies and clinical practices, helping to shape guidelines that encourage the adoption of effective and sustainable technologies in dementia care [6,7,25].

Guidance for future research will be obtained. By highlighting gaps in the existing literature, this review can point to areas that need further investigation. This includes the need for studies exploring new technologies as well as studies examining diverse populations and different care contexts [12-14].

The review will also highlight research gaps in the field, pointing to associations and issues that have not been adequately explored. For example, there may be a lack of studies evaluating the impact of emerging technologies or considering the cultural and socioeconomic variability among different groups of patients and caregivers. Additionally, there may be a need for investigations into the long-term effects of using digital technologies in dementia care [12-14].

Overall, this umbrella review will contribute to the current debate on the value of a technological approach in dementia care. By providing a holistic view of the facilitators and barriers, this review can promote a more informed discussion on how to better integrate technology into geriatric care, potentially leading to better support for the autonomy and QoL of patients and their caregivers.

In summary, this review offers a unique opportunity to consolidate and critically evaluate the existing evidence on the

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acceptance and barriers to digital interventions in dementia care. Its findings can influence both clinical practice and future research, contributing to a better understanding and implementation of these technologies in a context that continues to grow in importance due to the aging global population.

Limitations

To the best of our knowledge, this is the first general review that specifically addresses issues related to acceptability factors and barriers to the use of digital technology in people with dementia and caregivers. However, we expect to find difficulties: We expect to find systematic reviews with different protocols and different populations with different objectives. That will make the possibility of reaching final conclusions more difficult and, in certain cases, unobtainable.

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Data Availability

The data sets generated or analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

RM, DE, NP, AV, and MVP conceived or designed the review, performed the analysis, interpreted the data, drafted the work or revised it critically for important intellectual content, provided final approval of the version to be published, and agree to be accountable for all aspects of the protocol in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.
All authors read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AMSTAR: A Measurement Tool to Assess Systematic Reviews
CFIR: Consolidated Framework for Implementation Research
PICOS: population, intervention, comparison, outcomes, and study design
PRIOR: Preferred Reporting Items for Overviews of Review
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
QoL: quality of life
WHO: World Health Organization

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Protocol

Use of Educational Technology in Inclusive Primary Education: Protocol for a Systematic Review

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Abstract

Background: Educational technology (EdTech) has been instrumental in the last few decades in promoting inclusive education by overcoming various learning barriers and offering tools and opportunities to all students, including those with special educational needs and disabilities (SEND). However, there is limited understanding of current classroom practices and policies and of the effects of the COVID-19 pandemic on EdTech use in the inclusive classroom.

Objective: This systematic review aims to outline the current knowledge on the use of EdTech to support the learning of students with SEND in inclusive primary schools in high-income countries.

Methods: We followed the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) and the Generalized Systematic Review Registration Form in reporting the details of this protocol. The inclusion criteria for the systematic review require that studies focus on students with SEND who are attending the primary stage of school in high-income countries. The studies can be qualitative or quantitative and should explore the design and use of EdTech with these students. Eligible studies must be published between 2016 and 2024, be peer-reviewed, and be available in English. We systematically searched the ACM, Directory of Open Access Journals, British Educational Index, ERIC, Google Scholar (first 100 records), IEEE, PsycINFO, Scopus, and Web of Science databases. The titles and abstracts of all records will be screened for relevance according to the inclusion criteria. Following this, the full text of the articles will be screened. To ensure the reliability of the screening process, an independent reviewer will screen a percentage of the records for the first screening round. The data extraction process for this systematic review will start with a pilot stage to validate and eventually update the list of entities to be extracted. Following the pilot stage, the final data extraction will be undertaken. An independent reviewer will extract data from a subsample of the records to ensure the reliability of the data extraction process.

Results: The database search was conducted in July 2024. The database search identified a total of 547 records. It is anticipated that the study findings will be submitted for publication in a peer-reviewed journal by the end of January 2025.

Conclusions: This study will provide up-to-date evidence of the use of EdTech in inclusive primary school settings in high-income countries and will describe the impact of the COVID-19 pandemic on the use of EdTech with students with SEND.

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KEYWORDS

special education needs; disabilities; primary education; inclusive education; education technology; assistive technology; high-income countries; systematic review

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Introduction

Background

Educational Technology (EdTech) usually includes a number of broad definitions across disciplines. For the purposes of this systematic review, this term includes any use of information and communication technology and assistive technology. Information and communication technology refers to the technologies used for accessing, processing, and communicating information and encompasses a wide range of technologies, including (1) computers and software applications, (2) internet and network systems, (3) mobile phones and other handheld devices, (4) digital broadcasting technologies (radio and TV), and (5) email and other communication tools [1]. Assistive technology includes any item or piece of equipment that helps a person with a disability to increase, maintain, or improve their functional capabilities as a learner and any related assistive technology service [1].

EdTech has transformed education and learning in the last few decades by offering multiple means to represent information, express knowledge, and engage in learning [2]. Moreover, EdTech has played a crucial role in supporting inclusive education by addressing multiple barriers to learning and by providing tools and opportunities to all students, including students with special educational needs and disabilities (SEND). For instance, EdTech has supported fair and optimized access to the curriculum while developing students' independence, agency, and social inclusion [2]. In addition, it has facilitated personalized learning, enhanced communication, and interaction among peers and teachers, and strengthened social skills [2]. However, as noted in the UNESCO (United Nations Educational, Scientific and Cultural Organization) report [2], the overall benefits and drawbacks of the implementation of EdTech are still not fully understood. Several factors contribute to this lack of understanding. First, the effectiveness of EdTech tools varies by the socioeconomic level of the students and by the income level of the country. It also depends on teacher willingness to adopt these tools and their readiness to use them as well as on the education stage. In fact, students at different stages show distinct behavior habits in terms of web-based learning experiences [3]. Third, the costs associated with implementing and maintaining EdTech, both in the short term and in the long term, may be higher than initially anticipated, posing affordability challenges, especially in poorer countries. These costs include the cost of the EdTech tools as well as the cost of training teaching staff members, which is necessary for the effective use and the appropriate selection of technologies for specific students. Finally, not all technologies are suitable for students with different types of SEND. To be effective, these technologies must be tailored to each student's specific learning needs.

With such numerous factors affecting the effectiveness of EdTech and the wide range of software applications, devices, and other technologies available on the market, teachers and policy makers can easily feel overwhelmed. Therefore, systematic reviews are needed to understand the available options and to help them make informed decisions for effective and manageable employment of EdTech in education to facilitate the inclusion of students with SEND. In recent years, a few systematic reviews have examined the use of EdTech for students with SEND [1,4-6]. Despite the importance of these studies, some are limited in their scope and in the variety of EdTech tools examined, while others encompass all educational levels, preventing a focused analysis of EdTech effectiveness for specific educational stages. In addition, only one study included research published after the COVID-19 pandemic.

The systematic review by [4] investigated the technology practices in special education contexts and included 126 studies published between 2014 and 2018. The results revealed that the most examined technology was games, and the most studied outcome was the improvement of learners' cognitive abilities. The majority of the studies included precollege students with learning disabilities and focused on natural sciences. Interventions were primarily conducted in formal educational environments and were mainly implemented over 5-10 weeks. Based on their results, the authors recommended providing a greater level of detail in reporting research findings and placing more emphasis on promoting life, job, and social skills.

The study by [5] investigated the impact of using augmented reality in the education of students with SEND. The review included 18 studies published between 2016 and 2021. The authors noted a decrease in studies from 2020 onwards, which they attributed to the COVID-19 pandemic and to the consequent closure of educational centers. The majority of the included studies used quantitative methodologies. Most of these studies focused on primary and secondary school students, with very few examining early childhood education or higher education. The experiences were primarily conducted with students with intellectual disabilities, followed by students with autism, learning difficulties, and hearing impairments. The use of augmented reality showed positive results in the learning of students with SEND. Improvements were observed in academic performance, motivation, communication, social interaction, and level of autonomy. However, the authors identified several limitations to the use of augmented reality in the education of SEND. These included low levels of teacher training, limited availability of augmented reality technology, lack of support from educational institutions, and technical and accessibility issues.

The study by [6] presented a systematic review investigating technology-enhanced and game-based learning activities used with children with SEND. The authors included 18 studies published between 2009 and 2019. They reported that about one-third of the studies involved participants with intellectual disabilities, another third included autistic participants, and the remaining studies involved participants with Down syndrome, motor impairments, visual impairments, and hearing impairments. The primary goal of the game-based activities was to support students' cognitive skills. These activities covered a wide range of academic areas, including mathematics, functional skills, and communication. The results of the included studies were mixed, with some interventions improving the learning of participants and others promoting their motivation.

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Finally, the systematic review by [1] investigated the use of assistive technology among primary school students with disabilities in low- and middle-income countries. The study included 51 studies published between 2007 and 2020. The findings showed little evidence of the efficacy of educational interventions, with learning outcomes often considered secondary to the technological aspects of the studies. The authors reported a considerable variation in the number of studies addressing different types of impairments, with two-thirds of the studies involving students with sensory impairments. In addition, teachers and parents were often excluded from the process of using and evaluating EdTech. A consistent theme reported in the included studies was the reluctance of teachers to adopt EdTech solutions in their everyday teaching practices. Most of the studies were case studies or small-sample multiple baseline studies and rarely included control groups.

The current systematic review aims to summarize the current understanding of how EdTech supports the learning of students with SEND in inclusive primary schools in high-income countries. Moreover, this study will allow the investigation of the effects of the COVID-19 pandemic on the use of EdTech in this specific setting.

Review Questions

This systematic review seeks to answer the following questions:

1. How can EdTech support students with SEND in primary school settings in high-income countries?
2. What EdTech interventions are used to support students with SEND in high-income countries?
3. What are the gaps in the literature, and what is the potential for further development in this field?
4. How has the COVID-19 pandemic impacted the use of EdTech in primary inclusive classrooms?

Methods

Study Registration

The protocol for this systematic review follows the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist [7,8] and the Generalized Systematic Review Registration Form [9]. The PRISMA-P checklist used for the development of this systematic review protocol is provided in Multimedia Appendix 1. The systematic review protocol was preregistered before the analysis of the data in the Open Science Framework in July 2024 and was last updated in December 2024 [10].

Inclusion Criteria

To be included in the systematic review, studies must meet the following criteria.

Population

- Students with SEND.
- Attending primary school.

Setting

We will include studies conducted in high-income countries, as classified by the World Bank [11] and based on the World Bank's Gross National Income per capita thresholds for the 2024-2025 fiscal year.

Study Design

We will include qualitative and quantitative studies exploring the design and the use of EdTech tools with students with SEND. We will exclude reviews of the literature.

Publication Date

We will include studies published between 2016 and 2024. This timeframe encompasses 4 years before the COVID-19 pandemic, which provides a baseline, and 4 years after, allowing us to assess the immediate and evolving effects of the pandemic. Moreover, focusing on this timeframe complements existing literature, which already covers earlier years, and provides a comprehensive and up-to-date perspective on the subject.

Publication Type

We will include peer-reviewed journal articles and peer-reviewed conference proceedings. While we originally considered including gray literature, such as reports from nongovernmental organizations, we realized that these sources would require a different approach to data extraction and synthesis, demanding additional time and resources that are not available to our research team. Similarly, Master and PhD theses will be excluded. Although these documents can be valuable resources, they may not be subjected to the same level of scrutiny as peer-reviewed articles, depending on the country in which they are conducted. Their length and the challenge of assessing them raise concerns about data extraction and synthesis of the findings for the systematic review. Moreover, their limited accessibility and dissemination could complicate replicability and comprehensive data extraction. Finally, we assumed that high quality studies are typically published in a peer-reviewed journal, supporting our decision to exclude these sources.

Language

We will include only studies available in the English language.

Exclusion Criteria

Studies that do not involve participants with SEND will be excluded.

In addition, studies focusing on individuals outside the primary school age range (5 years to 11 years) will not be considered. This exclusion criterion will be based on the mean age of the sample of students with SEND, which has to fall within this range.

Research conducted in countries other than high-income nations, as classified by the World Bank [11], will also be excluded.

Studies conducted in contexts other than the classroom settings, such as hospitals, clinical settings, or participants' homes will be excluded.

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Furthermore, non–peer-reviewed studies and gray literature will be excluded. Previous reviews of literature will also be excluded.

Finally, studies not available in English will be excluded.

Search Strategy

Literature search strategies were developed using keywords from previous relevant systematic reviews, with guidance from a specialist librarian at UCL. The librarian provided recommendations on both the keyword list and database selection. The databases searched include ACM, Directory of Open Access Journals, British Educational Index, ERIC, Google Scholar (first 100 records), IEEE, PsycINFO, Scopus, and Web of Science. To ensure comprehensive coverage, the electronic database search will be supplemented by scanning the reference lists of studies that meet the inclusion criteria.

Starting from the list of keywords used by [1], the list of keywords was optimized by including synonyms and relevant terms derived from the research questions. The search strategy underwent several iterations to refine the terms and optimize the query string. The desirability of reducing the number of keywords or adding new terms to the query was evaluated based on the effect on the number of hits [12]. The terms evaluated were not considered necessary and hence deleted if the number of hits increased greatly and included a high ratio of nonrelevant references. To further validate the search results, we ran the search using alternative search terms to confirm that the search string captured the relevant studies. Search terms were limited to the title, the abstract, and the keywords of the papers, when possible. Alternatively, they were limited to the abstract of the paper only. When possible, the search was restricted to specific subject areas (such as “psychology” or “education”) or educational levels (such as “primary school”). The search strategy was conducted on July 26, 2024, by ER. Table 1 displays the search strategy for each database.

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Table 1. Search strategy formulated for each database included in the study.

Database	Search string
PsycINFO[a]	(blind or deaf* or autis* or neurodiver* or “intellectual dis*” or “learning dis*” or “mental* retard*”).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] AND (tech* or assistive or smartphone or tablet or laptop).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] AND (“primary school” or “elementary school” or “junior school” or “middle school”).mp. [mp=title, abstract, heading word, table of contents, key concepts, original title, tests & measures, mesh word] Filters applied: limit to (english language and abstracts and 180 school age <age 6 to 12 yrs> and journal article and yr=“2016 - 2024”)
Web of Science	(((TS=(blind OR deaf* OR autis* OR neurodiver* OR “intellectual dis*” OR “learning dis*” OR “mental* retard*”)) AND TS=(tech* OR assistive OR smartphone OR tablet OR laptop)) AND TS=(“primary school” OR “elementary school” OR ”junior school“ OR ”middle school“)) AND (DT==(”ARTICLE“) AND TASCA==(”EDUCATION SPECIAL“ OR ”PSYCHOLOGY EDUCATIONAL“ OR ”EDUCATION EDUCATIONAL RESEARCH“) AND LA==(”ENGLISH“) AND PY=2016-2024)
Scopus	(TITLE-ABS-KEY (blind OR deaf* OR autis* OR neurodiver* OR ”intellectual dis*“ OR ”learning dis*“ OR ”mental* retard*“) AND PUBYEAR > 2015) AND (TITLE-ABS-KEY (tech* OR assistive OR smartphone OR tablet OR laptop) AND PUBYEAR > 2015) AND (TITLE-ABS-KEY (”primary school“ OR ”elementary school“ OR ”junior school“ OR ”middle school“) AND PUBYEAR > 2015) AND LANGUAGE (english) AND SUBJAREA (psyc OR soci-edu OR comp-csa OR comp-hci) AND (LIMIT-TO (DOCTYPE,”ar“) OR LIMIT-TO (DOCTYPE,”cp“))
ERIC[b]	Noft(blind OR deaf* OR autis* OR neurodiver* OR ”intellectual dis*“ OR ”learning dis*“ OR ”mental* retard*“) AND noft(tech* OR assistive OR smartphone OR tablet OR laptop) AND noft(”primary school“ OR ”elementary school“ OR ”junior school“ OR ”middle school“) AND rtype.Exact(”Article“) AND la.Exact(”English“) AND lv(”primary education“ OR ”elementary education“ OR ”middle schools“) AND PEER(yes) AND PEER(yes) AND pd(20160101-20240630) Filters applied: Document type: Article; Language: English; Education level: Elementary education, Middle schools, Primary education
British Education Index	AB (blind OR deaf* OR autis* OR neurodiver* OR “intellectual dis*” OR “learning dis*” OR “mental* retard*”) AND AB (tech* OR assistive OR smartphone OR tablet OR laptop) AND AB (”primary school“ OR ”elementary school“ OR ”junior school“ OR ”middle school“) Limiters: Peer Reviewed; Publication Date: 20160101-20241231; Publication Type: Academic Journal; Language: English Expanders: Apply equivalent subjects Search modes: Proximity
Directory of Open Access Journals	blind OR deaf* OR autis* OR neurodiver* OR intellectual dis* OR learning dis* OR mental* retard* AND tech* OR assistive OR smartphone OR tablet OR laptop Filters applied: 2016-2024
ACM[c] Digital Library	[[Abstract: blind] OR [Abstract: deaf*] OR [Abstract: autis*] OR [Abstract: neurodiver*] OR [Abstract: ”intellectual dis*“] OR [Abstract: ”learning dis*“] OR [Abstract: ”mental* retard*“]] AND [[Abstract: tech*] OR [Abstract: assistive] OR [Abstract: smartphone] OR [Abstract: tablet] OR [Abstract: laptop]] AND [[Abstract: ”primary school“] OR [Abstract: ”elementary school“] OR [Abstract: ”junior school“] OR [Abstract: ”middle school“]] AND [E Publication Date: (01/01/2016 TO 30/06/2024)]
IEEE[d] Xplore	(“Abstract”: blind OR “Abstract”: deaf* OR “Abstract”: autis* OR “Abstract”: neurodiver* OR “Abstract”: “intellectual dis*” OR “Abstract”: “learning dis*” OR “Abstract”: “mental retard*”) AND (“Abstract”: tech* OR “Abstract”: assistive OR “Abstract”: smartphone OR “Abstract”: tablet OR “Abstract”: laptop) AND (OR “Abstract”: “primary school” OR “Abstract”: “elementary school” OR “Abstract”: “junior school” OR “Abstract”: “middle school”). Filters applied: 2016-2024 & Journals & Conferences
Google Scholar	(blind OR deaf* OR autis* OR neurodiver* OR “intellectual dis*” OR “learning dis*” OR “mental* retard*”) AND (tech* OR assistive OR smartphone OR tablet OR laptop) AND (”primary school“ OR ”elementary school“ OR ”junior school“ OR ”middle school“) Filters applied: 2016-2024

[a]PsycINFO: American Psychological Association.

[b]ERIC: educational resources information center.

[c]ACM: association computing machinery.

[d]IEEE: Institute of Electrical and Electronics Engineers.

Screening

Rayyan [13], a web-based literature review software, will be used to remove the duplicates and to assist with the screening process. The titles and abstracts of all the records will be screened for relevance against the inclusion criteria by ER. Following this, the same reviewer will evaluate the full text of the articles deemed eligible. The reference list of all the studies that ultimately will meet inclusion criteria from the database search will be screened for any additional records that may have been missed.

An independent reviewer will screen a subsample of all records to establish the reliability of the screening process. The percentage of records to be independently screened will be

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determined based on the total number of records, according to the following rule: if there are more than 201 records, 5% will be screened; if there are between 100 and 200 records, 10% will be screened; and if there are 100 or fewer records, 20% will be screened. Disagreements will be discussed and resolved during agreement meetings through consensus or by consulting a third reviewer. The rationale for excluding records that do not meet the eligibility criteria will be documented.

Data Extraction

The data extraction process will begin with a pilot stage, during which ER and MB will independently extract data from a randomly selected sample of the included studies. The sample size will be determined based on the total number of studies included at this stage of the review, following the same criteria used for the screening process. The purpose of the pilot phase is to ensure adherence to standardized procedures and to validate and, if necessary, update the data extraction criteria. After the pilot stage, ER will complete the final data extraction for all included studies, using Microsoft Excel to collect and organize the information.

The provisional list provided in Textbox 1 outlines the data to be extracted. Based on the pilot stage, this list and the corresponding coding rules will be finalized. If significant updates are made to the list of entities to be extracted, MB will independently review the data extraction to ensure the reliability of the final data extraction process. The sample size will be determined based on the total number of studies included at this stage of the review, following the same criteria used for the screening process.

The study's characteristics include the authors, publication year, and the country of data collection. It also includes the study design (cross-sectional or longitudinal) and type of study based on the category used in the Mixed Methods Appraisal Tool (MMAT) [14]. For interventions and single-case research, information about the length and framing of the intervention will also be extracted. The intervention's framing will be coded based on the Multi-Tiered System of Support model, which operationalizes how teachers implement the Universal Design for Learning model and includes three categories: (1) core classroom instruction, (2) targeted small group instruction, or (3) intensive individual intervention [15].

The SEND sample characteristics cover sample size, participant age, sex, socioeconomic status, and the diagnosis or disability categorization.

EdTech characteristics include the terminology used to refer to the tool described in the study (eg, "information and communication technology" or "assistive technology"), cost, level of technology (low-tech or high-tech), and the type of EdTech tools used, categorized according to the World Bank [16], as shown in Textbox 2.

Textbox 1. Provisional list of data to be extracted

Characteristics of the study

- Authors
- Year of publication
- Country where the data was collected
- Study design
- Type of study
- Length and framing of the intervention (limited to intervention studies and single-case research)

Characteristics of the sample with SEND

- Sample size
- Chronological age of participants
- Sex of participants
- Socioeconomic status
- Diagnosis or disability categorisation

Characteristics of Educational Technology (EdTech)

- Use of EdTech terminology
- Overall cost of the EdTech tool
- Level of technology of the EdTech tool
- Type of EdTech employed

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Textbox 2. Type of education technology (EdTech).

Type of EdTech

- Augmentative and alternative communication
- Accessible textbooks
- Assistive hearing and listening technology
- Braille reading and writing equipment
- Mainstream accessible software and applications
- Mobility technology
- Personal electronic devices
- Platforms and applications for learning support
- Technology for teaching support
- Technology for vision enhancement
- Text-to-speech technology

Outcomes

The primary outcome of this systematic review will be the overall effectiveness of EdTech tools used in the inclusive classroom, defined as their impact on a range of factors including academic achievement, student engagement, social inclusion, accessibility, and other relevant outcomes that contribute to an inclusive learning environment.

Assessment of Risk of Bias in the Included Studies

To assess the risk of bias in the studies included in this systematic review, we will use the MMAT [14]. The MMAT is a generic critical appraisal tool that was developed for the appraisal of multiple types of studies including qualitative studies, quantitative randomized controlled trials, quantitative nonrandomized studies, quantitative descriptive studies, and mixed methods studies. As the present systematic review includes studies using a range of methodologies, the MMAT was deemed the most suitable approach for ensuring quality and consistency in the evaluation of the risk of bias. The assessment consists of 2 screening questions and 5 category-specific items. Each item can be rated as “yes” if the criterion is met, “no” if it is not met, or “can’t tell” if the study provides insufficient information to score the criterion as met or not met. The MMAT has been applied in previous research, such as in systematic reviews to assess the methodological quality of the included studies investigating the use of EdTech for health and social care practitioners and the use of gamification in education [17,18].

All included studies will be evaluated for quality by one reviewer of the research team. In addition, an independent reviewer will reassess 20% of those studies to ensure consistency and reliability in the evaluation process. Disagreements will be resolved through discussion, and if consensus cannot be reached, a third reviewer will be consulted.

Data Synthesis

We will present the collated results in a structured format, aligned with the research questions of the systematic review. This review will use a mixed methods analysis, incorporating both quantitative and qualitative approaches to analyze the results from the included studies.

For the interventions, we will assess the primary outcome by comparing pre- and posttest scores of students with SEND using specific EdTech tools. Tables will be created to describe the characteristics of the studies, populations, and EdTech tools used.

Qualitative data will be analyzed using content analysis to synthesize and interpret key issues and themes related to Review Question 1 across the studies. If a sufficient number of comparable studies are included, a subgroup analysis will be conducted. Potential subgroups may be based on the type of EdTech used, the population involved, or the country where the study was conducted.

Assessment of Meta-Biases

We anticipate that assessing publication bias may not be feasible due to the heterogeneous nature of the included studies. Similarly, assessing outcome reporting bias may be challenging because of the potential lack of registered protocols for these studies. However, we will provide a narrative discussion on the potential for publication bias, focusing on whether negative results were excluded or difficult to identify, and we will highlight any inconsistencies in outcome reporting where possible.

Results

As shown in Figure 1, a database search was conducted in July 2024, identifying 547 records. We expect to complete the screening process by November 2024 and submit the manuscript for peer review by the end of January 2025. The results of the completed study will be submitted to a journal relevant to the SEND population, and findings will be presented at relevant conferences and shared with stakeholders, such as nongovernmental organizations, education and health care organizations, assistive technology developers, and policy makers.

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Figure 1. Flow diagram of the search process PsycINFO: American psychological association; ERIC: educational resources information center; ACM: association computing machinery; IEEE: Institute of Electrical and Electronics Engineers.

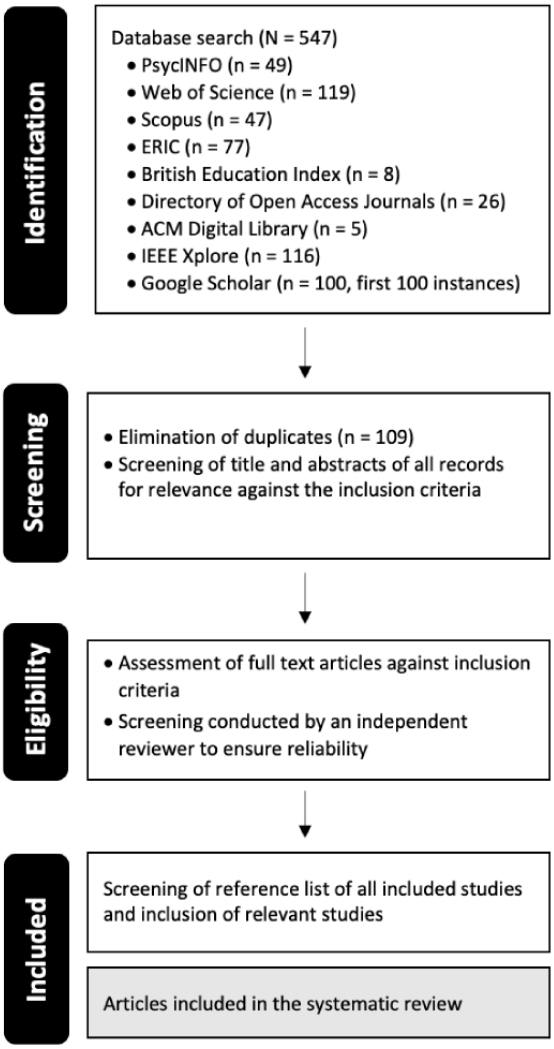

Discussion

Principal Findings

Many reviews have already been conducted on the use of EdTech with students with SEND. However, these reviews are limited by their focus on specific tools, such as augmented reality or educational game-based activities. In addition, some reviews encompass all educational levels, which prevents a detailed examination of the effectiveness of these tools for specific educational stages (such as primary, secondary, or higher education). These limitations reduce their usefulness for making targeted decisions about EdTech implementation. Furthermore, some reviews have a narrow scope regarding publication years, covering studies only up to 2021. It is essential to have current insights into classroom practices, as technology and devices used just 5 years ago may now be outdated or unavailable, and new EdTech devices may have been introduced and evaluated. To fill this gap, our systematic review will collect and analyze data on the use of EdTech in inclusive primary school settings in high-income countries and will also discuss findings in comparison with previous reviews of literature in this field. Finally, this study will describe the impact of the COVID-19 pandemic on the use of EdTech in the field of research education. We anticipate that the review will reveal an increase in the use of EdTech in the inclusive classroom following the COVID-19 pandemic. These findings are expected to inform the use and the design of inclusive EdTech and assistive technology tools to support students with SEND in the primary classroom and to establish best practices for the seamless integration of EdTech, ultimately producing positive outcomes for these students.

In addition, one of the outcomes of our systematic review will be the creation of an updated database that catalogs all studies investigating the use of EdTech in inclusive primary schools in high-income countries. This database will offer accessible, current evidence on how EdTech supports students with SEND in this setting. The final database, which will be published in the Open Science Framework platform and as supplementary material following the publication of the systematic review, aims to facilitate evidence-based decision-making, support the development of guidelines, interventions, and policies, and identify gaps in the current research landscape. It is expected to serve as a valuable resource for researchers, educators, assistive technology developers, policy makers, and other stakeholders.

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Limitations

While we will use a comprehensive search strategy, it is possible that relevant studies could be overlooked. In addition, our search is restricted to English-language and peer-reviewed publications, potentially excluding studies in other languages and unaudited studies and thereby limiting the comprehensiveness of the evidence available. Finally, a limitation of this systematic review is that it may not be feasible to meta-biases. As a result, the confidence in the conclusions drawn from this review may be somewhat limited, and this limitation should be considered when interpreting the findings.

Conclusions

To our knowledge, this will be the first systematic review to describe the impact of the COVID-19 pandemic on the use of a wide range of EdTech to support the learning and inclusion of primary school students with SEND in high-income countries. This review aims to facilitate evidence-based decision-making and contribute to the future improvement of guidelines for the effective use of EdTech to support inclusion in primary school settings. Such knowledge is crucial for promoting educational equity, enhancing learning outcomes, and supporting the diverse needs of all students.

Acknowledgments

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Data Availability

The dataset generated during this study is available in the OSF repository [10] and will be published as supplementary material alongside the main systematic review paper.

Authors' Contributions

MB and ER contributed to conceptualization, methodology, and writing–original draft, and editing. ER handled data curation. CH and MB handled funding acquisition. MB performed project administration. CH handled supervision, writing–review, and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) checklist.
[DOCX File , 41 KB - resprot_v14i1e65045_app1.docx]

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Abbreviations

EdTech: educational technology
MMAT: Mixed Methods appraisal Tool
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
SEND: special educational needs and disabilities
UNESCO: United Nations Educational, Scientific and Cultural Organization

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Protocol

Efficacy and Safety of Acupuncture for Post–COVID-19 Insomnia: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: The COVID-19 pandemic has had a profound global impact, leading to a range of persistent sequelae referred to as post–COVID-19 condition or "long COVID" that continue to affect patients worldwide. Among these sequelae, post–COVID-19 insomnia (PCI) has emerged as a significant issue. Conventional treatments, including cognitive behavioral therapy and pharmacological interventions, face limitations such as variable efficacy, potential side effects, and substantial costs. Recently, acupuncture has gained traction due to its efficacy, cost-effectiveness, and safety profile.

Objective: This study aims to conduct a meta-analysis and systematic review evaluating the efficacy and safety of acupuncture for the treatment of PCI to delineate the optimal modality, intervention frequency, and duration for achieving the most beneficial outcomes, thereby providing a comprehensive understanding of acupuncture's role in managing PCI, contributing to evidence-based clinical practice, and informing clinical decision-making.

Methods: Electronic searches will be performed in 12 databases from inception to October 2024 without language restrictions. This includes both English databases (PubMed, Cochrane Library, Web of Science, Embase, OVID and Scopus), as well as Chinese databases (China National Knowledge Infrastructure, Wan-Fang Data, Chinese Biomedical Literature Database, Chinese Scientific Journal Database, Duxiu Database and the Chinese Clinical Trial Registry Center). Randomized controlled trials on acupuncture for PCI will be included. Primary outcomes will include the response rate and insomnia severity; secondary outcomes will include the Traditional Chinese Medicine Symptom Scale (TCMSS) and adverse event rates. Data synthesis will use risk ratios for dichotomous data and mean differences for continuous data. Study selection, data extraction, and quality assessment will be conducted independently by 2 reviewers. Methodological quality of eligible studies will be evaluated following the *Cochrane Handbook for Systematic Reviews of Interventions* (version 6.3). Meta-analysis will be performed with RevMan 5.3.

Results: Based on the data on response rate, insomnia severity, TCMSS score, and adverse event rates, this study will provide an evidence-based review of the efficacy and safety of acupuncture for PCI treatment.

Conclusions: This systematic review will present the current evidence for acupuncture for PCI, aiming to inform clinical practices and decision-making and to enhance the understanding of acupuncture's role in managing PCI. Furthermore, it will identify research gaps and suggest potential areas for future investigation.

Trial Registration: PROSPERO CRD42024499284; https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=499284

International Registered Report Identifier (IRRID): DERR1-10.2196/69417

(JMIR Res Protoc 2025;14:e69417) doi:10.2196/69417

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KEYWORDS

acupuncture; traditional Chinese medicine; post–COVID-19 condition; long COVID-19; insomnia; sleep disorder; depression; complementary and alternative medicine; treatment; public health; study protocol; systematic review

Introduction

Background

The COVID-19 pandemic caused by the SARS-CoV-2 virus has emerged as one of the most significant public health challenges in recent years [1], with over 770 million cases and approximately 6.9 million deaths worldwide [2,3]. Despite the World Health Organization having declared the end of the global public health emergency in May 2023, evolving virus variants continue to impact the world, exacerbating the global effects of the pandemic [4]. Nearly 90% of hospitalized patients with COVID-19 develop post–COVID-19 condition [5,6], commonly referred to as "long COVID" according to the National Institute for Health and Care Excellence, which includes a range of signs and symptoms that continue or develop after the acute phase of the illness [7]. These symptoms include sleep disturbances, depression, fatigue, tinnitus, and anxiety [8,9].

Studies indicate that insomnia has a high prevalence, impacting roughly 20% to 35% of the general population [10-13], and this rate is even higher among health care workers and patients with COVID-19, reaching up to 75% [8]. Substantial evidence indicates that post–COVID-19 insomnia (PCI) frequently persists over the long term [14-17], leading to serious health issues such as increased depression, prolonged work absences, and a heightened risk of hypertension [15,18,19]. Insomnia poses a significant threat to public health, not only by impairing physical, emotional, and social well-being but also by reducing quality of life [20]. It can degrade psychological functioning and decision-making, compromise the immune system, raise the risk of accidents, and cause mood alterations, all while boosting medical expenditures [21,22]. Moreover, the interaction between sleep deprivation and SARS-CoV-2 infection could potentially raise the risk of developing neurodegenerative diseases like dementia [16]. Consequently, PCI has become widely acknowledged as a critical and pressing issue affecting the entire world. The emergence of SARS-CoV-2 subvariants in the postpandemic COVID-19 era, particularly the highly mutable Omicron lineage and its numerous subvariants, presents new challenges to public health interventions [23].

Current standard treatments for PCI include cognitive behavioral therapy for insomnia (CBT-i) and pharmacotherapy [24,25]. Although these methods have demonstrated efficacy, they are not without limitations. For instance, the 2017 clinical practice guidelines of the American Academy of Sleep Medicine indicate that CBT-i alone may not be beneficial for all people with insomnia due to issues like noncompliance, treatment unresponsiveness, access barriers, and financial constraints [25]. Pharmacological therapies for insomnia comprise benzodiazepines, nonbenzodiazepines, antidepressants, melatonin receptor agonists, and other sedatives [24,26]. While these medications can offer short-term relief, their long-term, routine use is not recommended due to the risks of developing tolerance, dependency, and withdrawal issues [20,26-28]. Moreover, these medications can lead to rebound insomnia, residual daytime sedation, cognitive and memory impairments, and motor incoordination, particularly increasing the risk of falls among older people [20,26-29]. Given these concerns, there is a pressing need to find alternative therapeutic approaches that are both efficacious and safe for treating PCI.

In recent years, complementary and alternative medicine (CAM) has become widely used to address insomnia in various countries, including the United States, Australia, and numerous Asian nations [30-32]. Acupuncture, recognized as one of the most popular and safest CAM therapies [28,33], has a long-standing history of treating sleep disorders dating back to ancient times [26]. Based on traditional Chinese medicine, acupuncture works by inserting fine needles into acupoints throughout the body. It seeks to reestablish the equilibrium between yin and yang, thereby facilitating the body's return to a state of physiological homeostasis [34-36]. A multitude of studies indicate that acupuncture is highly effective in improving both sleep quantity and quality [37-42]. The underlying mechanisms include regulating neurotransmitters such as gamma-aminobutyric acid [43-46] and serotonin [47-50], increasing melatonin levels [51-53], and modulating the hypothalamic-pituitary-adrenal axis and the expression of corticotropin-releasing hormone and adrenocorticotropic hormone [54-57], thereby improving sleep quality. Furthermore, acupuncture can also regulate inflammatory cytokines such as interleukin-1, interleukin-6, and tumor necrosis factor-α [58-62], and it can influence the gut microbiota to regulate sleep-wake behavior [63,64].

Much of the research supporting the use of acupuncture for insomnia is constrained by the limitations of low- or moderate-quality evidence and inconsistent reports regarding its clinical efficacy and safety. Furthermore, the effects of acupuncture on PCI remain largely unknown. Through an extensive literature review, we identified a notable absence of systematic reviews specifically addressing the efficacy of acupuncture for PCI. In light of this gap, we will conduct a meta-analysis and systematic review to assess and synthesize the available evidence on the efficacy and safety of acupuncture for PCI. This review aims to establish a robust theoretical foundation for clinical practice, thereby providing credible evidence on the therapeutic potential of acupuncture for PCI.

Objectives

This review has 3 objectives: (1) to evaluate the efficacy and safety of acupuncture for the treatment of PCI in comparison to comfort therapy (such as placebo, sham acupuncture, or a blank control) or other therapies (such as Western medicine or nondrug therapies); the results will provide a comprehensive understanding of acupuncture's role in managing PCI, thereby contributing to evidence-based clinical practice and informing clinical decision-making in practice; (2) to assess the methodological quality and the strength of the evidence supporting the use of acupuncture for PCI, offering a thorough

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appraisal of the existing literature; and (3) to delineate the optimal modality, intervention frequency, and duration to achieve the most beneficial outcomes.

Methods

Overview

This study will be conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA) statement [65]. This protocol has been prepared in accordance with the Cochrane recommendations and registered on PROSPERO (CRD42024499284).

Study Eligibility Criteria

The inclusion and exclusion criteria for this review are detailed in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Types of studies
  - All randomized controlled trials (RCTs) focusing on the treatment of insomnia after COVID-19 using acupuncture therapy
  - Studies involving single acupuncture therapy, as well as those comparing acupuncture with other interventions
  - Studies published in English or Chinese
  - Studies published from the inception of the database up to October 2024
  - No restrictions on publication status or type
- Types of participants
  - Participants who developed insomnia following COVID-19 infection without a prior history of insomnia who were subsequently enrolled in an RCT; this will include patients with confirmed COVID19 or asymptomatic SARSCoV-2 infections based on the results from nucleic acid testing, antigen testing, and clinical criteria
  - Participants meeting the diagnostic criteria for insomnia, including the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* [66], *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition* [67], *International Classification of Sleep Disorders, Third Edition)* [68], and *Chinese Classification and Diagnostic Criteria of Mental Disorders, Third Edition* [69] or equivalent standard diagnostic criteria
  - No restrictions on gender, age, race, onset time, or source of cases
- Types of intervention
  - Simple acupuncture therapy
  - Trials where acupuncture is used as an adjunct to other interventions (eg, behavior therapy, psychotherapy, or pharmacotherapy) only included if the control groups receive the same additional interventions
  - No specific restrictions on acupoints or course of treatment; the selection of acupoints and acupuncture methods should be derived from traditional Chinese medicine
  - The specific length, thickness, and model of the acupuncture needle will not be considered in this review
- Types of comparisons
  - Comfort therapy (placebo, sham acupuncture, or blank control)
  - Other therapies (Western medicine or nondrug therapy)
- Types of outcome measures
  - The primary outcomes will include response rate and insomnia severity as measured by validated instruments (eg, the Insomnia Severity Index, Pittsburgh Sleep Quality Index, or Athens Insomnia Scale)
  - The secondary outcomes will include the Traditional Chinese Medicine Syndrome Score Scale score and adverse events

Exclusion criteria

- Non-RCTs, such as reviews, animal experiments, commentary articles, letters, and case reports
- Participants with primary insomnia or a serious underlying disease that makes them unsuitable for acupuncture treatment
- Studies that explored interventions using nontraditional acupoints, such as ear acupuncture, scalp acupuncture, and other methods
- Duplicate publications
- Studies found in gray literature
- Studies with incomplete data

Electronic Searches

A search strategy will be designed and conducted following the guidelines outlined in the *Cochrane Handbook*. The meta-analysis will be reported based on the PRISMA guidelines.

Electronic searches will be carried out by 2 independent researchers (YL and JZ) from initiation until October 2024. English databases (PubMed, Cochrane Library, Web of Science, Embase, OVID, Scopus) and Chinese databases (China National Knowledge Infrastructure, Wan-Fang Data, Chinese Biomedical Literature Database, Chinese Scientific Journal Database, and Duxiu Database) will be included in the search. The Chinese Clinical Trial Registry Center will also be searched for ongoing

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trials. There will be no restrictions on countries or publication types.

The search will use keywords such as *COVID-19*, *2019-nCoV infection*, *SARS-CoV-2 infection*, *acupuncture therapy*, *acupuncture treatment*, *pharmacoacupuncture treatment*, *sleep initiation and maintenance disorders*, *sleeplessness*, and *insomnia disorder*. To ensure a comprehensive search, a combination of subject headings (Medical Subject Headings) and free words will be used, regardless of the language or type of publication. The search will be conducted across all databases to identify all relevant articles. An example search strategy for the PubMed database is provided in Multimedia Appendix 1.

Similar search strategies will be used for the other databases. Additionally, in the case of studies for which the full text is not available, efforts will be made to contact the first author or corresponding author to obtain the necessary full text.

Study Selection and Data Collection

Selection of Studies

All reviewers have undergone training to ensure a fundamental comprehension of the context and purpose of the review. In this step, EndNote X9 (Clarivate) will be used to screen the search results. Two reviewers (YL and JZ) will independently conduct the screening process and cross-check the results. Based on the predefined inclusion and exclusion criteria, relevant studies will be selected after reviewing their titles, abstracts, or full texts. In instances of duplicate publications, the original publication will be selected. Should there be any incomplete data or ambiguous details, efforts will be made to contact the first author or corresponding author for clarification. In cases where disagreements arise, a third reviewer (KS) will be consulted, and a final decision will be reached through discussion. A comprehensive overview of the selection process will be depicted with a PRISMA flow chart (Figure 1).

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) flow chart. RCT: randomized controlled trial.

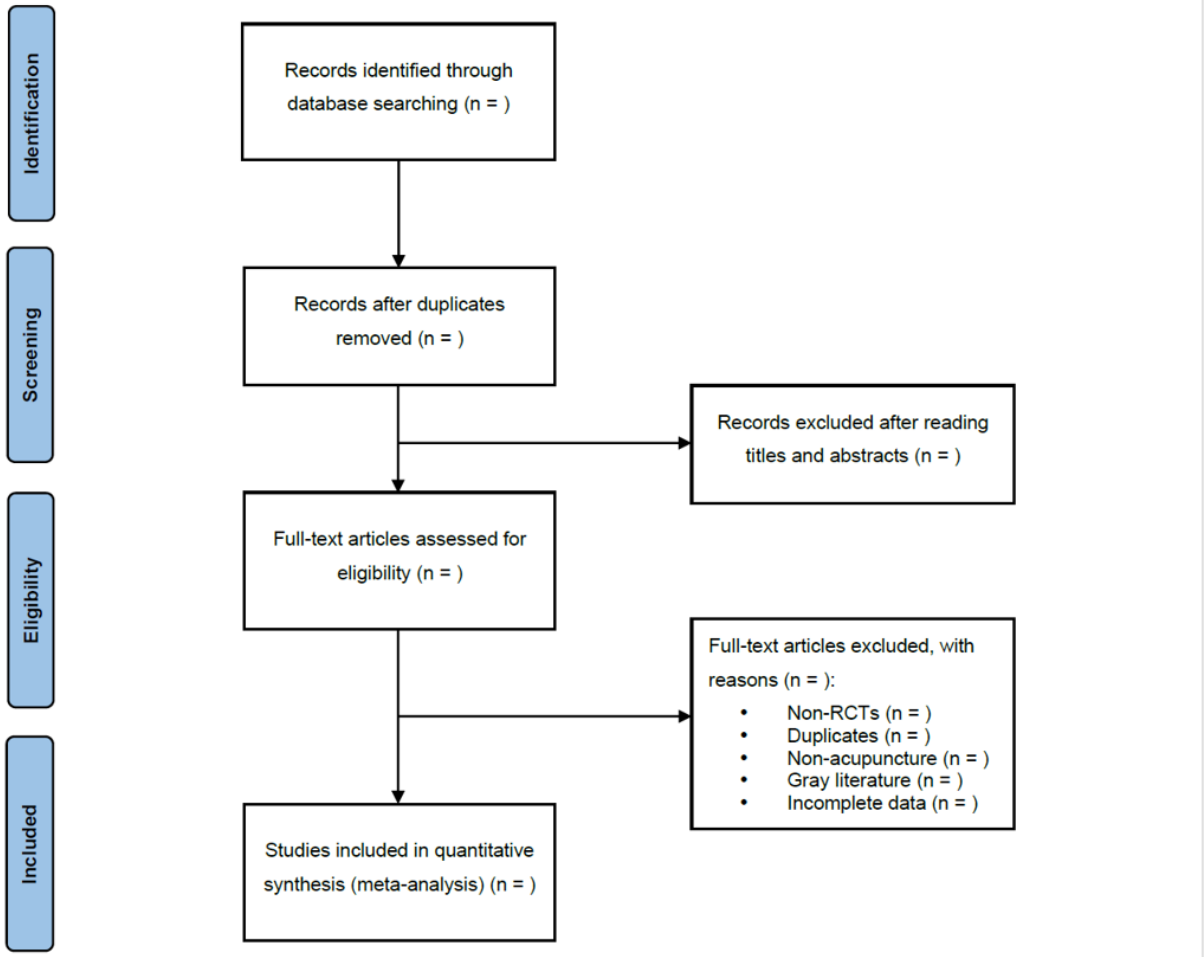

Data Extraction and Management

Two reviewers (ZW and LL) will independently perform data extraction using the provided data extraction form (Multimedia Appendix 2). Any disagreements that emerge during the process will be addressed through discussion between the 2 reviewers. If a resolution cannot be achieved, the input of a third reviewer (HX) will be sought. The following information will be recorded using a standardized data extraction form: (1) basic information on the study (first author, year, and country of publication); (2) study characteristics (study inclusion criteria, sample size, and participants' details, including age, gender, complications, severity, and course of insomnia); (3) details of the study intervention and control intervention, including modality, frequency, and treated acupoints; (4) a risk of bias assessment; and (5) outcome data, adverse effects, and drop-out rate.

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EndNote will be used by the reviewers to facilitate data management and to identify duplicate publications. In cases where 2 or more reports describe the same trial, only one of these publications will be considered for inclusion in the analysis.

Assessing Risk of Bias in Included Studies

The methodological quality of selected studies will be assessed using the Cochrane Risk of Bias 2.0 tool. Two reviewers (HX and CL) will independently assess the risk of bias for each included randomized controlled trial according to the guidelines provided in the *Cochrane Handbook for Systematic Reviews of Interventions* (version 6.3). The assessment will cover the following domains: (1) bias arising from the randomization process, (2) bias due to deviations from the intended intervention, (3) bias due to missing outcome data, (4) bias in measurement of the outcome, and (5) bias in selection of the reported results.

Each study will be classified as "low risk," "high risk," or "some concerns" based on the evaluation. Should any disagreements arise, a third reviewer (GL) will be engaged to facilitate consensus.

Measures of Treatment Effect

Statistical analysis will be conducted using RevMan (version 5.3; Cochrane Collaboration), with forest plots being used to visually represent the comparative efficacy of the treatments. For continuous variables, the mean difference (MD) will be used to express the treatment effect, whereas for dichotomous data, the risk ratio (RR) will be used. For each treatment effect, the estimated value and 95% CIs will be determined and reported within the analysis.

Dealing With Missing Data

For studies with missing or ambiguous data, efforts will be made to contact the first author or corresponding author for assistance. Should the missing data remain unobtainable despite attempts to contact the authors, the study will be excluded from the analysis.

For studies with missing data, the intention-to-treat analysis will be used to conduct statistical and omission analysis. Intention-to-treat analysis helps maintain the integrity of the original randomized allocation of participants, even in cases where some data may be missing. This approach guarantees that participants are evaluated based on their original randomized groups, irrespective of any missing data.

Assessment of Reporting Biases

Should more than 10 studies report on the same outcome measure, a funnel plot and an Egger regression test will be applied to assess the potential for reporting bias.

Data Analysis

RevMan will be used for the calculation of the RR for dichotomous data and the MD for continuous variables. For each effect, the estimated values and the 95% CIs will be determined.

The RR is calculated as follows:

where a and b are the number of events and nonevents in the intervention group, and c and d are the number of events and nonevents in the control group.

The MD is calculated as follows:

where and are the means of the intervention and control groups, respectively.

Heterogeneity will be assessed using the I^2 statistic, calculated as follows:

where Q is the Cochrane Q statistic and k is the number of studies.

If the research results exhibit low heterogeneity (I^2<50%), a fixed-effect model will be applied for the meta-analysis. On the other hand, in case of significant heterogeneity (I^2>50%), a random-effects model will be used for the meta-analysis, after which, further analysis will be conducted to ascertain the sources of heterogeneity.

When the data are not amenable to quantitative synthesis, a narrative summary will be provided to elucidate the findings of the included studies.

For trials that report only pre- and postintervention values, the mean change will be derived by computing the difference between post- and preintervention measurements. Consequently, the SD for these changes will be estimated.

Subgroup Analysis

When significant heterogeneity is observed, a subgroup analysis will be performed to investigate the possible sources of this variability. The following factors will be examined as potential subgroup variables: age, gender, duration of COVID-19 infection, severity of insomnia, the type of acupuncture intervention, treatment frequency and duration, and other relevant parameters.

When sufficient data are available for each subgroup, a quantitative subgroup analysis will be performed to assess the influence of these factors on the treatment effects. Nonetheless, if the data for subgroup analysis are inadequate, a qualitative synthesis will be conducted. In this approach, the results from individual studies will be summarized and compared without a formal quantitative synthesis.

Sensitivity Analysis

If significant heterogeneity persists even after the subgroup analysis, a sensitivity examination will be implemented. This process involves reconducting the meta-analysis after discarding studies of low quality or those with possible biased sources.

The comparison of the meta-analysis results before and after sensitivity analysis allows for a thorough assessment of the

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findings' stability and reliability. This approach aids in understanding the impact of individual studies on the total results, offering a more in-depth insight into the meta-analysis outcomes.

Grading the Quality of Evidence

Researchers will assess the quality of evidence using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach. The quality of evidence will be classified into 4 levels: very low, low, moderate, or high.

The GRADE methodology facilitates a systematic and transparent assessment of the certainty and strength of the evidence, thereby enabling researchers to present a comprehensive and reliable summary of the evidence in a distinct and dependable way.

Ethical Considerations

Ethics approval is not required since this protocol is solely for a systematic review and does not involve private data.

Dissemination

The results will be disseminated electronically through publication in a peer-reviewed journal or presented at a relevant conference.

Results

The study will be conducted following the methodology in the *Cochrane Handbook for Systematic Review of Interventions*. Two independent researchers will perform comprehensive searches across 12 databases, encompassing English databases (PubMed, Cochrane Library, Web of Science, Embase, OVID, and Scopus) and Chinese databases (China National Knowledge Infrastructure, Wan-Fang Data, the Chinese Biomedical Literature Database, the Chinese Scientific Journal Database, the Duxiu Database, and the Chinese Clinical Trial Registry Center). Focusing on the outcomes such as response rate, insomnia severity, TCMSS score, and adverse event rates, this study will deliver an evidence-based review of the efficacy and safety of acupuncture for PCI treatment.

Discussion

Overview

The COVID-19 pandemic has become one of the most formidable public health crises in recent years. As the persistence of post–COVID-19 condition continues, a considerable number of individuals have been grappling with PCI. This issue is escalating and poses a critical challenge to public health, placing a substantial economic burden on society. Not only does PCI negatively impact physical and mental well-being, but it also contributes to a decline in social functioning and a lower quality of life [20]. PCI is often accompanied by other symptoms, such as anxiety and depression [70]. Although CBT-i and pharmacological interventions are widely used in clinical settings, they face certain constraints, such as variable efficacy, adverse effects, and high costs. These limitations have sparked a surge of interest in CAM therapies.

As a significant component of CAM therapies, acupuncture has gained increasing recognition for its effectiveness, affordability, and favorable safety profile. It is rooted in the basic theory of traditional Chinese medicine, which emphasizes the interconnectedness of nature and humanity, viewing the body, mind, and spirit as a unified whole [71,72]. Considering that PCI affects both physical and mental health, acupuncture's natural, potent, and low-risk attributes, along with its holistic approach, make it a compelling alternative for individuals with PCI. However, given that PCI is a relatively novel condition, it is imperative to conduct a thorough analysis of acupuncture's therapeutic efficacy and safety as a treatment option.

This paper presents the protocol for a systematic review that constitutes the first quantitative analysis of the efficacy and safety of acupuncture for PCI. Through a meticulous evaluation of evidence gleaned from published randomized controlled trials, we aim to provide a comprehensive appraisal of acupuncture's impact on PCI. Furthermore, the study endeavors to delineate the optimal modality, frequency of intervention, and duration of treatment to achieve the most favorable outcomes. The findings from this meta-analysis and systematic review are expected to offer valuable insights to clinical practitioners, establishing a robust theoretical foundation and essential reference for the application of CAM therapies in PCI treatment. This evidence may significantly enhance the quality of informed clinical decision-making, particularly in the selection of therapeutic strategies for patients with PCI.

All amendments to this protocol will be meticulously recorded, including the amendment date, a description of the changes, and the corresponding rationale.

Limitations

Due to language barriers, some relevant electronic databases might not be included, potentially limiting the comprehensiveness of the findings.

Conclusion

This review will offer a thorough synthesis of the literature on acupuncture as a treatment for PCI, thereby enriching the current scientific discourse on this subject. By examining the evidence base, the review will deliver significant insights aimed at optimizing clinical practices in practical health care environments. It will also present health care professionals with a novel viewpoint on the use of complementary and alternative medicine in addressing PCI, facilitating more informed clinical decision-making.

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Authors' Contributions

Conceptualization: YL, JZ, ZW and KS
Data collection, data analysis and interpretation: YL, JZ, ZW, LL, HX, CL, GL, WL, YX and XW
Writing: YL, JZ, ZW, LL, HX, and KS
Critical revision: YL, JZ, ZW, LL and KS

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy in PubMed database.
[DOCX File , 16 KB - resprot_v14i1e69417_app1.docx]

Multimedia Appendix 2
Data extraction tool.
[DOCX File , 16 KB - resprot_v14i1e69417_app2.docx]

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Abbreviations

CAM: complementary and alternative medicine
CBT-i: cognitive-behavioral therapy for insomnia
GRADE: Grading of Recommendations, Assessment, Development, and Evaluation
MD: mean difference
PCI: post–COVID-19 insomnia
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RR: risk ratio
TCMSS: Traditional Chinese Medicine Symptom Scale

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Protocol

Epidemiological Characteristics of Intestinal Protozoal Infections and Their Risk Factors in Malaysia: Systematic Review and Meta-Analysis Protocol

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Abstract

Background: Intestinal protozoal infections caused by *Entamoeba histolytica*, *Giardia lamblia*, and *Cryptosporidium parvum* are prevalent in Malaysia. They cause severe diarrheal diseases with symptoms such as bloody stools, abdominal pain, stomach discomfort, and bloating. These infection outbreaks have been reported in diverse socioeconomic backgrounds and geographical regions usually during the rainy season or in areas with poor sanitation. Despite the importance of these infections, data on its overall prevalence, risk factors, and diagnostic methods remain limited.

Objective: The aim of this study is to systematically review and synthesize evidence on the risk factors, prevalence, and detection methods for intestinal protozoal infections in Malaysia, offering insights that are applicable to other tropical and low-income regions.

Methods: Studies on intestinal protozoal infections among Malaysian patients published after January 2010 up to November 2024 will be eligible for inclusion. The eligibility criteria include studies investigating infections caused by *E. histolytica*, *G. lamblia*, and *C. parvum* using validated diagnostic methods such as microscopy, molecular techniques, or immunoassays. Case reports, reviews, and studies without original data will be excluded. Comprehensive database searches will be conducted in PubMed/MEDLINE, Scopus, ProQuest, Web of Science, Google Scholar, and the Cochrane Library. The reference lists of selected papers are also checked. A standardized data extraction form will be used to record study characteristics, outcomes, and associated variables. Risk of bias will be assessed using the Joanna Briggs Institute tools and Newcastle-Ottawa Scale approach. Data synthesis will utilize a random effects model to estimate pooled prevalence and identify risk factors associated with these infections. Subgroup analyses will examine variations by geographic region and diagnostic method. Statistical heterogeneity will be assessed using I^2 statistic and meta-regression. Publication bias will be assessed using Egger and Begg funnel plot test. The results are reported in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Results: This systematic review was funded in June 2024. Database searches were started in July 2024, and we identified 1652 papers as of December 2024 for screening. Completion of study screening is anticipated by May 2025, with data extraction and analysis expected to conclude by December 2025.

Conclusions: Our study will address critical knowledge gaps in the epidemiology and risk factors of intestinal protozoal infections in Malaysia. Study limitations include potential bias in study selection, heterogeneity in diagnostic methods, and differences in the reporting quality of the included studies. Our findings will provide valuable insights into the prevalence of these infections,

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the associated risk factors, and the diagnostic techniques employed, which should strengthen public health measures, improve diagnostic procedures, and guide future research to reduce the prevalence of intestinal protozoal infections in Malaysia.

Trial Registration: PROSPERO (International Prospective Registry of Systematic Reviews) registration CRD42023456199; https://www.crd.york.ac.uk/PROSPERO/view/CRD42023456199

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KEYWORDS

intestinal protozoa; infection; gastroenteritis; epidemiology; parasite; risk factor; Malaysia; contamination; diarrhea; outbreak; socioeconomic; sanitation; systematic review; meta-analysis; protocol; observational; PRISMA

Introduction

Intestinal protozoal infections are the most common parasitic infections and are a serious global health concern. An estimated 3.5 billion people are affected, with approximately 450 million individuals currently experiencing intestinal protozoal infections [1]. The typical intestinal protozoal infection cases are reported from *Entamoeba histolytica*, *Giardia lamblia*, and *Cryptosporidium parvum*. The transmission of these protozoa occurs via the oral-fecal route, which involves either indirect or direct contact with the infection. This includes various modes of transmission such as human-to-human, zoonotic, waterborne, and foodborne transmission [2,3]. The most common symptoms of an intestinal protozoal infection include nausea and watery diarrhea, which are caused by the release of enterotoxins, and are often accompanied by inflammation in the stomach, small intestine, and large intestine [3]. Individuals infected with *E. histolytica*, the causative agent of amoebiasis, show characteristic symptoms such as abdominal pain, bloody diarrhea, fever, and in severe cases, liver abscesses. *G. lamblia* causes giardiasis, which is characterized by watery diarrhea, abdominal pain, flatulence, and weight loss. Similarly, *C. parvum*, which is responsible for cryptosporidiosis, primarily manifests with watery diarrhea accompanied by stomach cramps, nausea, vomiting, and fever, with an increased risk in immunocompromised individuals. These different clinical signs emphasize the importance of targeted diagnostic approaches and tailored therapeutic interventions, with the severity of the disease depending on the immune status of the affected individuals [4,5]. The causes can be difficult to determine because the majority of enteric pathogens cause similar symptoms. There can be multiple infectious agents that can cause acute gastroenteritis, and contamination may come from food, water, the environment, or animals. Therefore, it is difficult to make accurate and fast reports via epidemiological analysis [6,7].

The primary method for detecting intestinal protozoa is the microscopic analysis of stool samples, which is laborious and requires specialized personnel. Molecular approaches such as real-time polymerase chain reaction offer increased sensitivity and efficiency and require only 1 sample for testing. Immunodiagnostic approaches targeting parasite antigens or host antibodies improve sensitivity and specificity. Despite advances, there is no one-size-fits-all strategy for diagnosis, which requires careful evaluation of aspects such as the suspected parasite, the nature of the sample, and the resources available [8]. A comprehensive approach may involve a combination of microscopic, molecular, and immunodiagnostic approaches to ensure accurate detection and treatment of intestinal protozoal infections.

Currently, intestinal protozoa, including *E. histolytica*, infect nearly 50 million individuals annually, leading to 100,000 deaths. Moreover, *Entamoeba* infection affects 50% of the global population, notably in Central and South America, Africa, and Asia, with rates up to 25% in certain limited-income and heavily indebted poor countries [9]. Giardiasis, caused by *G. lamblia*, is prevalent in the United States, the United Kingdom, Africa, Asia, and Latin America, and affects approximately 200 million people annually. In temperate countries such as Spain, the United Kingdom, and France, the prevalence in children is approximately 1.1%-2.1% [10,11]. *Cryptosporidium spp.* infection is widespread in the United States and tropical countries, with rates as high as 13% in India and 7.3% in Thailand [12,13]. These infections impose a significant burden, especially in heavily indebted poor tropical nations and parts of Central/South America, Africa, and Asia. Addressing sanitation and hygiene is crucial in prevention efforts.

In Malaysia, helminths and protozoa are the most common types of parasites causing diarrheal diseases. Diarrheal diseases are the leading cause of death in children younger than 5 years, with a mortality rate of 0.8% in 2019 [14]. The occurrence and wide distribution of intestinal protozoal infections in Malaysia represent significant events in the epidemiology of infectious diseases. Unfortunately, only limited data are currently available on the epidemiology and the risk factors associated with these diseases. Moreover, overall data on the diagnostic approach used to detect intestinal protozoal infections in Malaysia are lacking [15]. To address this knowledge gap, we will conduct a comprehensive systematic review with meta-analysis, aiming to synthesize the available data and overcome the limitations of individual studies. This study will be conducted to gain a better understanding of the prevalence and distribution of different intestinal protozoal infections, risk factors associated with intestinal protozoal infections among patients, and update on the diagnostic methods primarily used to detect intestinal protozoal infections, with a specific focus on the Malaysian population. Although this study focusses on Malaysia, the outcomes are also relevant for other tropical regions with similar socioeconomic, environmental, and health challenges. These findings can guide strategies to manage intestinal protozoal infections in regions such as Southeast Asia and beyond.

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Methods

Patient and Public Involvement Statement

This protocol was not developed with the involvement of patients.

Study Design

The systematic review and meta-analysis will be reported in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement, which was considered in the development of this protocol (Multimedia Appendix 1) [16]. This protocol is registered with PROSPERO (International Prospective Registry of Systematic Reviews; registration CRD42023456199). The methodology chosen for this study is designed to be replicable in different settings. Although the focus is on Malaysia, the search strategy and data extraction can also be applied to other regions to gain comparable insights.

Study Area

We will include studies published on intestinal protozoal infections among patients in Malaysia, except for case reports, reviews, and studies without original data, and the studies will be divided according to region. Malaysia is an ideal case study for the study of protozoal infections due to the unique intersection of tropical climate, diverse population, and varied socioeconomic conditions. These factors combined with the limited epidemiological data underscore the urgent need for comprehensive research in this context.

Types of Participants

We will include primary studies that investigate patients without age restrictions that provide estimates of any symptoms of intestinal protozoal infection (eg, amoebiasis, giardiasis, cryptosporidiosis). We will include studies that explicitly describe the detection methods and definitions of intestinal protozoal parasites. Studies on intestinal protozoal infections in which at least one of the 3 protozoa were detected will be included. We will exclude case reports, reviews, and studies without original data. If we find multiple studies with the same data, then we will use the study with the largest sample size. The results will be presented in tables and figures.

Types of Outcome Measures

This meta-analysis will have 2 main outcomes. The primary outcome will be the prevalence of intestinal protozoal parasites in Malaysia. The second aim is to investigate the risk factors associated with the diseases and the update on the primarily used detection methods for intestinal protozoa, that is, *C. parvum*, *E. histolytica*, and *G. lamblia*.

Information Sources

The following electronic databases of scientific literature that have been peer-reviewed, as recommended by Siddaway et al [17], will be carefully searched without language restrictions and limited to human research only: PubMed/MEDLINE, Scopus, ProQuest, Web of Science, Science Direct, Google Scholar, and Cochrane Library databases. A manual search of reference lists of identified papers will be added to the electronic searches. The authors of the research will be contacted for explanation or to provide any additional crucial missing metadata when necessary. Google Scholar will be used meticulously to search for relevant literature, including grey literature and unpublished data, to compile a thorough understanding of the prevalence rates, socioeconomic impact, and various diagnostic techniques employed for these infections within the Malaysian population. Studies completed after January 1, 2010, with no language constraints will be considered.

Search Strategy

The proposed search term for the first theme will be developed in MEDLINE by using medical subject headings (MeSH) combined with free-text terms around the 3 search components for intestinal protozoal infection, that is, giardiasis, cryptosporidiosis, and amoebiasis. The second theme will be prevalence, including epidemiology, incidence, epidemiological studies, and observational studies. The third theme will be risk factors and detection methods of intestinal protozoal infection and other similar names used (see detailed list in Multimedia Appendix 2) and then adapted for use in the other databases. The search, the evaluation of the titles and abstracts, and the review of the complete texts will be performed independently by an author. After removing duplicates and irrelevant entries, the reference lists of the studies received were checked for further studies that were not found in the database search.

Eligibility Criteria

The selection or exclusion of studies is based on the criteria proposed in Table 1. Studies published after January 2010 up to November 2024 will be eligible for inclusion. The literature search is limited to papers published after 2010, highlighting the significant change in the diagnostic process when molecular techniques began to replace traditional microscopic methods for detecting intestinal protozoal infections. This time frame allows for studies that include both the transition period and the continuous use of microscopy, including the more recent implementation of molecular techniques. This methodology allows for a full assessment of the evolution of diagnostic methods across time. We will not apply any language restrictions as part of the eligibility criteria. The PICO (Population, Intervention, Comparison, Outcome) classification technique is a popular method for creating search methods and describing meta-analyses.

The study population includes individuals with intestinal protozoal infections identified through positive laboratory test results, physician diagnoses, self-reported infection status, treatment registries, or other medical records. Both asymptomatic and symptomatic cases will be included, with no restrictions on age, gender, ethnicity, or geographical location within Malaysia. Eligible populations encompass mixed communities, outpatients, inpatients, and residential settings, spanning diverse socioeconomic backgrounds. This inclusion criterion ensures a representative sample of intestinal protozoal infections across Malaysia.

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Table 1. Criteria for inclusion and exclusion.

Category	Included	Excluded
Population	Both asymptomatic and symptomatic cases from diverse socioeconomic backgrounds, including all ages, genders, ethnicities, and geographical locations in Malaysia (including non-Malaysians) will be considered, with identification based on laboratory tests, physician diagnoses, or medical records	Both asymptomatic and symptomatic cases conducted outside Malaysia or non-Malaysian settings will be excluded, including cases from mixed communities, outpatient, inpatient, and residential settings, regardless of age, gender, ethnicity, or non-Malaysians
Intervention/exposure	Studies conducted on the 3 common intestinal protozoal parasites (*Entamoeba histolytica*, *Giardia lamblia*, and *Cryptosporidium parvum*) and using any of these methods: microscopic examination, immunoassay technique, and molecular methods	Studies excluding these 3 intestinal protozoa (*E. histolytica*, *G. lamblia*, and *C. parvum*) and other intestinal protozoa parasites unrelated to this study or using other detection methods as mentioned
Study design	Quantitative studies, cross-sectional studies, cohort, and case controls will be included	Case reports, reviews, and studies without original data will be excluded
Outcome	Diarrhea and presence of intestinal protozoa	Nonenteric infection and studies without detection method mentioned

The primary outcome measure is self-reported diarrhea, which is commonly defined as the occurrence of 3 or more watery stools or bloody diarrhea within a 24-hour period. This information is reported by the patient's family or caretaker and covers a 2-week period preceding the assessment. Additionally, laboratory confirmation of diarrheal illness involves the identification of specific pathogens in the patient's stool. This confirmation can be achieved through microscopic examination or culture techniques. Furthermore, the presence of intestinal parasites is confirmed through laboratory procedures, including microscopy, serological tests, or molecular methods.

This study will focus on the prevalence of intestinal protozoal infections in Malaysia, exploring the epidemiology, diagnostic methods, and contributing factors to these infections. This research aims to investigate the extent to which individuals in Malaysia are affected by these parasitic infections and the various factors contributing to their occurrence, shedding light on their epidemiology and diagnostic methods. We will consider both randomized and nonrandomized controlled trials, along with observational studies that have examined the connection between the exposure and outcome of interest. We will collect data on the measures of association. However, we will put a lower priority on unadjusted measures (please refer to the "Risk of bias assessment for eligible studies" section for details).

Screening and Selection Procedure

In the research methodology, citations retrieved from diverse search engines will be imported into EndNote and subjected to a deduplication process to eliminate redundant entries. The exclusion criteria are usually unrelated, duplicate, unavailable full texts, or pure abstracts. These exclusions should be stated in advance to prevent any biases. The inclusion criteria would be studies with the target patients, interventions studied, or the comparison between the 2 interventions studied. These are publications that contain information relevant to our study subject. The most critical aspect is that the information provided is clear and adequate to answer the problem, whether positive or negative. Then, the required data will be meticulously extracted by the primary researcher (NSM). To ensure accuracy and reliability, the extracted information from all papers will undergo a thorough cross-checking process conducted independently by 2 other researchers (HA-T and SMW). The goal of this review is to confirm the consistency of the data, identify and mitigate potential biases, and correct minimal errors. The validated studies will be organized and stored in a structured spreadsheet program specifically designed for systematic data extraction. Following this, the collected data will undergo a series of rigorous assessments to evaluate the adequacy of the studies, ensuring a solid and reliable basis for subsequent analysis and interpretation. We will record the selection process in sufficient detail to complete a PRISMA flow diagram shown in Figure 1 [18,19].

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Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for systematic review and meta-analysis. *Reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). **Indicate how many records were excluded by a human and how many were excluded by automation tools.

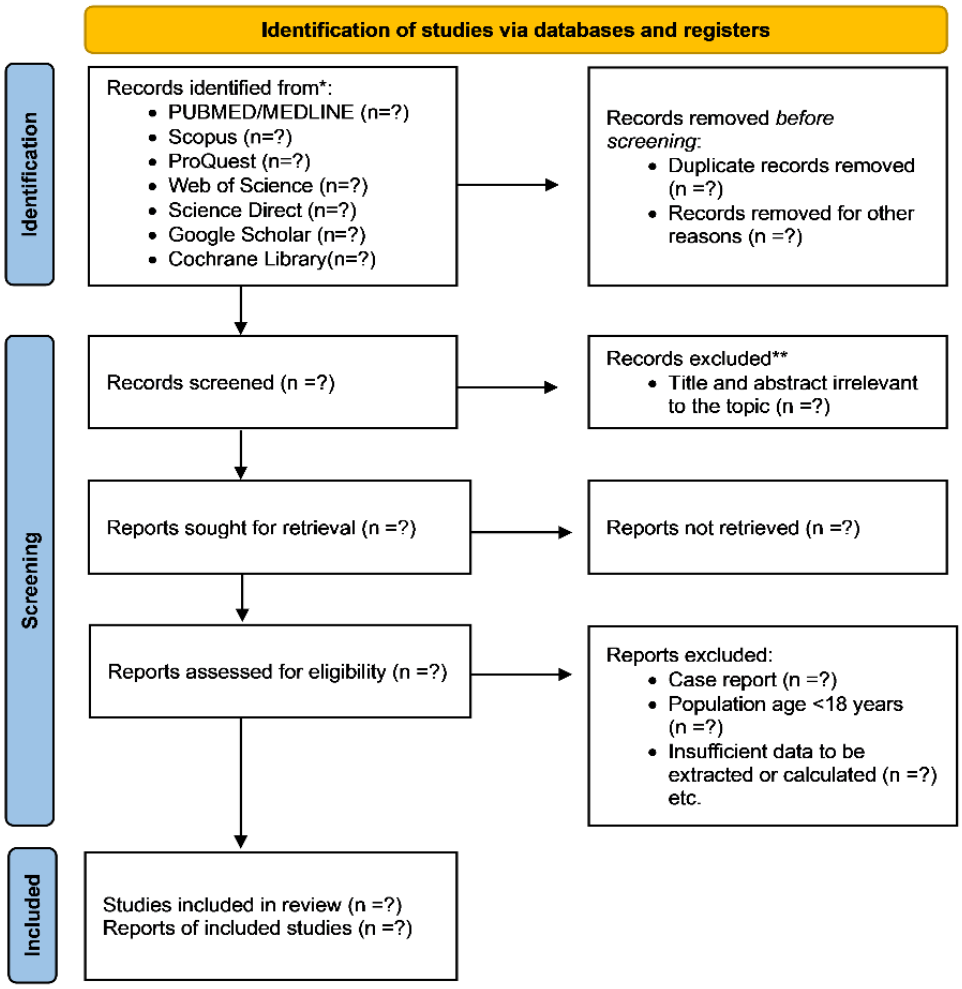

Data Extraction

We will use a standardized data extraction created in the online Microsoft Excel spreadsheet for study characteristics and outcome data. The data capture sheet will consist of a screening checklist consisting of study details (author, year of publication, period of study, place the study was performed), study characteristics (sample size, mean age, and age range of participants), risk factor analysis (socioeconomic status, population characteristics, geographical area), and outcome (presence of intestinal protozoa status; odds ratios, prevalence ratios, relative risks or hazard ratios [95% CI] with their related variability [SD or SE]). Please see "Eligibility criteria" section and Table 1 for the list and definitions of the aforementioned exposures and outcomes. Any significant limitations of the study will be identified, and any further relevant information will be requested from the corresponding author if necessary.

Data Synthesis

The data will be analyzed using STATA software (version 17.0; William Gould) and REVMAN software (The Cochrane Collaboration). To accurately report the content of each paper under consideration and to explore the relationships between outcomes and risk factors, the data will be summarized in a tabular form and the main findings of each paper will be presented, including descriptive analysis of gender, age, region, and others. We will also calculate the overall prevalence of intestinal protozoal infections among patients by using a random effects model to allow heterogeneity across the included studies and later divide the studies into regions. This study will include a qualitative or narrative analysis to summarize the key features and overall quality of the publications. In addition, a comprehensive assessment of potential bias will be performed for each paper (see the "Assessment of Risk of Bias for Eligible Studies" section). All meta-analyses will be conducted using the random effects model because of the expected epidemiologic and clinical heterogeneity. Because the underlying effects of the different studies are assumed to be normal, we will use random effects modelling to account for variation within and between studies.

Risk of Bias Assessment for Eligible Studies

Risk of bias (quality assessment) will be performed using the Joanna Briggs Institute critical appraisal tools [20]. The primary author and 2 independent reviewers will evaluate each study individually at both the outcome and study levels to provide an

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overall assessment of the risk of bias. Each reviewer will examine each study as yes, no, unclear, or not applicable for bias (Multimedia Appendix 3). The quality of the included studies will be assessed using the Newcastle-Ottawa Scale, which is specifically designed to evaluate observational and cohort studies [21]. This tool will ensure a consistent and balanced evaluation of the methodological quality of all studies included in the review, accommodating the variability between experimental and observational study designs (Multimedia Appendix 4).

Assessment of Heterogeneity

We will visually inspect the forest plots for any evidence of heterogeneity. The pooled estimates will be visually assessed using forest plots to determine the degree of heterogeneity between studies. We will also measure statistical heterogeneity by using the I^2 statistic to estimate the difference between studies [22]. The I^2 statistic quantifies the proportion of variability observed in the prevalence estimates that can be explained as genuine variations in treatment effects rather than random sampling error. The I^2 statistic is bounded in the scientific literature by a range of 0% to 100%. Values between 0% and 25% indicate low heterogeneity, while values between 75% and 100% indicate substantial heterogeneity [23]. We will investigate potential sources of heterogeneity by using subgroup analyses and meta-regression. The possible causes will be explored and evaluated in terms of their methodological characteristics to determine whether the degree of heterogeneity can be explained by differences in these characteristics and whether meta-analysis is appropriate. The overall prevalence and 95% CIs estimate of the outcome (presence of intestinal protozoa status; odds ratios, prevalence ratios, relative risks or hazard ratios), with their related variability (SD or SE) will be presented in forest plots. If the selected studies are acceptable for quantitative synthesis, the data will be pooled in a meta-analysis to combine the primary exposures across studies and to provide a summary of effects according to study design/measurement of effects. Where possible, we will also conduct subgroup analyses by age group, detection methods (microscopy, immunoassays, and molecular techniques), study design (ie, cross-sectional or prevalence studies), and geographical region (Peninsular Malaysia and East Malaysia) to assess differences between the strength of association by geographical location and the potential impact of contextual confounders, which may vary by region.

Meta-Biases

To assess the possibility of publication bias, we plan to use funnel plots [24], a widely used graphical tool in meta-analyses, to visually check the symmetry of the data distribution. In addition, we will apply statistical tests such as Egger and Begg funnel plot test [25], which are specifically designed to detect asymmetries in funnel plots and provide quantitative measures of publication bias. In addition, we intend to perform a comparative analysis between the outcomes derived from the fixed effects model and the random effects model. This comparative evaluation will allow us to assess the possible presence of small sample bias in the published literature. Specifically, we aim to determine whether the effects of the studied exposure appear to be more pronounced in studies with smaller sample sizes, indicating a possible bias in favor of smaller studies in the existing literature. By applying these comprehensive analyses, we aim to ensure the robustness and reliability of our results and to rule out potential biases that could affect the interpretation of the results.

Ethical Considerations

No primary data will be collected; thus, no formal ethical approval is required. The results will be disseminated though a peer-reviewed publication and conference presentation.

Results

This systematic review was funded in June 2024. Database searches were started in July 2024 using specific databases such as PubMed, Scopus, ProQuest, Web of Science, Science Direct, Google Scholar, and Cochrane Library databases. As of December 2024, 1652 studies have been identified for title and abstract screening. The screening phase is expected to be completed by May 2025. Data extraction and synthesis will be performed. Data analysis is expected to be completed by December 2025. The results will be published in peer-reviewed journals and presented at conferences in early 2026.

Discussion

Currently, there are few epidemiological data on the prevalence of intestinal protozoal infections in the Malaysian population. A comprehensive study of the prevalence and distribution of intestinal protozoal infections is critical to understanding their public health impact and implementing effective control measures. Given the lack of available data, it is important that Malaysia conduct detailed epidemiological studies that will allow a more thorough assessment of the prevalence, risk factors, and distribution of these intestinal protozoa. Such studies would not only make an important contribution to the scientific knowledge base but also facilitate the development of targeted interventions and public health strategies to reduce the burden of these infections in the region. The results of this study will show that local data are consistent with global data, indicating that socioeconomic factors and diagnostic limitations are key barriers to the treatment of intestinal protozoal infections. For example, the diagnostic challenges in Malaysia mirror those observed in other tropical regions such as sub-Saharan Africa and South Asia. By addressing these gaps, this study provides a framework that can be transferred to other regions with similar public health problems.

The theory under study is that several factors, particularly in vulnerable populations such as low-income societies with poor sanitation and immunocompromised patients, may increase the risk of infection with intestinal protozoa and that differences in the validity of different diagnostic techniques may lead to different rates of detection of intestinal protozoa, that is, false positive or false negative results. The above hypothesis proposes that the combination of various contextual risk factors may jointly contribute to an increase in the overall prevalence of intestinal protozoal infections in the studied population.

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In our study, we will conduct a thorough and systematic review, including a meta-analysis, to integrate the available data and address the limitations of individual studies. Our main objective is to better understand the prevalence and geographic distribution of intestinal protozoal disease. In addition, we will investigate the factor analysis that contributes to this infection and its relationship with its detection method. Our work, by synthesizing this extensive information, will provide a more nuanced and comprehensive view of intestinal protozoal infections and add significantly to the current body of knowledge in the field of infectious diseases and public health. No changes to the current protocol are envisioned. If critical changes prove necessary, they will be documented in the published review. Our findings will be published in a peer-reviewed scientific journal. In addition, they will be disseminated to relevant health care organizations.

A limitation of this study is that data on symptoms of intestinal protozoal infections are currently extracted from medical records, which may lead to underreporting due to gaps in documentation. Although documented medical records are often used as the main source of data, this approach has limitations. This method is consistent with real-life situations where diagnostic assessment often depends on accessible clinical data. Implementing a model that requires additional prospective assessments of patients beyond conventional clinical care procedures may be impractical, particularly in a health care setting where such assessments are often not mandatory. It is crucial to understand that the proposed model is preliminary and should not be used in clinical practice without additional validation. Another striking feature of our research design is the possibility of selection bias due to differences in duration of symptoms or time since exposure to protozoal infections at the time of study entry. By excluding individuals with recent protozoal infections who may have different clinical characteristics or outcomes, we aim to create a model that applies only to those who may have overcome the acute phase of infection.

In addition, future research should investigate the serial examination of clinical symptoms and use dynamic modelling techniques to enable the application of the model across different stages of infection. A comparison of the performance of the model we developed with established diagnostic algorithms or clinical guidelines in similar patient populations would also be crucial for validation. However, it should be noted that certain diagnostic indicators required for established algorithms may not be routinely assessed during standard clinical care, necessitating additional assessments beyond the scope of our study.

Even after further validation, predictive models for intestinal protozoal infections are primarily ambiguous, and the goal is to provide guidance to health care providers regarding potential infection outcomes and not to replace clinical assessment. Once the models are externally validated, a clinical decision aid should be available to better identify individuals at high risk for protozoal infections, thereby improving patient care and regulating appropriate diagnostic techniques. The future development of such a decision aid would require collaboration with health care professionals and researchers to ensure its effectiveness and appropriateness in clinical practice.

Acknowledgments

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Disclaimer

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Authors' Contributions

Conceptualization: HA-T (lead), NSM (equal)
Data curation: NSM
Formal analysis: HA-T (lead), SMW (supporting)
Funding acquisition: HA-T
Investigation: NSM
Methodology: NSM and HA-T
Project administration: HA-T (lead), NSM (equal), SMW (supporting)
Resources: NSM
Supervision: HA-T, SMW
Validation: NSM, HA-T, SMW
Visualization: HA-T (lead), NSM (supporting)
Writing the original draft: HA-T (lead), NSM (supporting)
Writing – review and editing: HA-T (lead), NSM (supporting), SMW (supporting)

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Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Review Protocols) 2015 checklist.
[DOCX File , 37 KB - resprot_v14i1e66350_app1.docx]

Multimedia Appendix 2
MEDLINE search strategy.
[DOCX File , 17 KB - resprot_v14i1e66350_app2.docx]

Multimedia Appendix 3
Joanna Briggs Institute's critical appraisal checklist.
[DOCX File , 17 KB - resprot_v14i1e66350_app3.docx]

Multimedia Appendix 4
Newcastle-Ottawa quality assessment scale.
[DOCX File , 18 KB - resprot_v14i1e66350_app4.docx]

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Abbreviations

MeSH: medical subject headings
PICO: Population, Intervention, Comparison, Outcome
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Registry of Systematic Reviews

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Protocol

Mental Health Apps Available in App Stores for Indian Users: Protocol for a Systematic Review

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Abstract

Background: There has been a surge in mental health apps over the past few years. While these have great potential to address the unmet mental health needs of the population, the recent proliferation of mental health apps in the commercial marketplace has raised several concerns, such as privacy, evidence-based, and quality. Although there is mounting research on the effectiveness of mental health apps, the majority of these are not accessible to the public and most of those available have not been researched. Despite the rapid growth of the digital health market in India, there are no comprehensive reviews of publicly available mental health apps for Indian users. Hence it becomes important to review mental health apps freely available to potential end users in terms of their scope, functions, and quality.

Objective: This study aims to systematically evaluate mental health apps available to Indian users in app stores.

Methods: This systematic review of mental health apps will be performed following the Target user, Evaluation focus, Connectedness and Health domain approach and the PASSR (Protocol for App Store Systematic Reviews) checklist. Fifteen key search terms covering various mental health conditions and therapies will be used on the Android and iOS stores. The identified apps will be further screened and reviewed based on the inclusion and exclusion criteria. The pool of eligible apps will be downloaded for detailed review. The following steps will be adopted to streamline the review process and interrater consistency. Six apps will be randomly selected from the downloaded apps, for joint discussion and review by a team of 4 primary reviewers and 2 mentors. Following this, a new set of 6 randomly selected apps will be rated independently by the primary reviewers and the differences in ratings will be jointly discussed for generating consensus. Subsequently, the primary reviewers will individually review the remaining apps in the list. Data will be extracted based on predecided parameters such as privacy policy, basic purpose, type of developer, nature of intervention strategies, and guided versus unguided nature. Additionally, the apps will be reviewed for quality using the Mobile Application Rating Scale. The data analysis and synthesis strategy will incorporate descriptive statistics based on quality evaluation using the Mobile Application Rating Scale and examining the content of the apps for generating descriptive information.

Results: The initial screening of mental health apps available for Indian users on the Google Play Store and Apple App Store was initiated in October 2024. We expect to complete the detailed systematic review by April 2025.

Conclusions: This study will offer a comprehensive review of mental health apps available in digital marketplaces for Indian users and has implications for end users, policy makers, developers, and mental health professionals.

Trial Registration: International Platform of Registered Systematic Review and Meta-analysis Protocols INPLASY2024100035; https://inplasy.com/inplasy-2024-10-0035/

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(JMIR Res Protoc 2025;14:e71071) doi:10.2196/71071

KEYWORDS

mental health apps; mHealth; review of apps; smartphone apps; MHApps for Indian users; India; mobile phones

Introduction

Background

According to the National Mental Health Survey (2017-2018), approximately 10% of Indian adults experience a diagnosable mental health condition, and the treatment gap for most such conditions exceeds 60% [1]. For example, the treatment gap for depression in India is 85.2%. Factors contributing to this gap include the stigma surrounding mental health issues and their treatment, the uneven distribution of mental health services, affordability challenges, and the scarcity of trained mental health professionals [2]. Some of these same factors have also become the drivers of the growth of digital mental health solutions in India.

There has been an increasing popularization of telehealth and digital mental health services in India [3,4]. This has been fueled by several factors such as the rapid proliferation of smartphone users, increasing internet penetration, the emergent needs and familiarity with digital services during the COVID pandemic, government initiatives promoting digital literacy, digital health, and specifically telemental health, rising number of startups in the mental health space apart from improved awareness about mental health and felt needs for convenient and accessible solutions [4-8].

India's smartphone penetration rate was 71% in 2023 [9]. Mental health apps have seen a 30% increase in downloads, with over 200,000 new users in the year 2023 alone. India's digital mental health market is projected to grow at a compound annual growth rate of 28.16% and is expected to reach a projected revenue of US $62.86 million by 2032 [10].

The last few years have seen a mushrooming of mental health apps, several of which have been developed with peripheral involvement or lack of involvement of mental health professionals, and this can raise significant concerns about the validity and appropriateness of suggestions, messages, and recommendations contained in the apps [11]. Inadequately customized recommendations can delay seeking professional help and extend the period of reliance on self-help alone even when the nature and severity of the problem warrants professional help.

Globally, the last decade has also seen a plethora of scoping reviews, systematic reviews, and meta-analyses of effectiveness and efficacy studies, including a few from India on mental health apps. 1009 psychosocial wellness and stress management apps with varied content were reviewed by Lau et al [12]. Almost all were designed as purely self-help apps, with less than 2% meant to serve as a supplement to in-person therapy or involving therapy via a web-based platform. It was noted that only 4.66% of apps targeted individuals with psychiatric disorders. This review also highlighted that only 2% of the apps in app stores were supported by original research publications. Another review aimed to document the proportion of mental health apps offering comprehensive therapeutic treatments for anxiety and depression available in the app stores and developed using evidence-based frameworks. The authors found that out of the 293 apps shortlisted as offering a therapeutic treatment for anxiety and/or depression, 55.3% mentioned an evidence-based framework in their app store descriptions. However, only 6.2% had published evidence of their efficacy [13].

Alqahtani and Orji [14] examined more than 13,000 user reviews of 106 publicly available mental health apps in app stores. Their review highlighted the value placed by end users on the user interface, user-friendliness, and adaptive functionalities. Lack of variety of content, low scope for personalization, lack of customer service, trust, and privacy issues were cited as some of the pitfalls [14]. In another review, 104 mental health apps on Google Play and App Store were examined through sentiment analysis of 88,125 user reviews, using machine learning and thematic analysis. The emergent negative themes spanned usability, content, ethics, customer support, and billing issues. The positive themes included appealing interface, app stability, customizability, high-quality and diversity of content, personalization, privacy and security, and low subscription cost [15].

Some of the recent research papers on mental health apps continue to use App Store star ratings as a proxy for quality and satisfaction, although there are growing concerns with this metric. Despite the potential clinical applications and benefits, the app marketplace, with an estimated 3,00,000 health apps and 10,000 focused on mental health, poses enormous challenges to users who wish to explore and find apps that may suit their needs [16]. Insufficient regulation of health apps in the commercial marketplace can result in several apps making unsubstantiated claims, offering inaccurate and potentially dangerous information, or posing threats to user privacy. Recent research has shown that the measures that are currently used in the app marketplace for the purpose of evaluating apps (eg, app downloads or star ratings) do not provide adequate representation of apps in terms of important metrics such as security, engagement, or effectiveness [17,18].

Studies on mental health apps and reviews from India have been scarce. An overview of smartphone apps aimed at suicide prevention available for Indian users on Google Play Store found that only 11.62% of 43 apps reviewed provided information about a formal evaluation process or study [19]. It was also noted that only about 16% of the apps intended for direct use by people at suicidal risk had an initial screening aspect. Only 4 of these 43 apps were developed in India. In a review of free apps for depression available for Android phone users in India, 278 apps were identified in the first step and information on coping with depression and stand-alone screening

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tools formed the 2 largest types of free apps. Features of interactive self-care apps (N=33) were reviewed further, and this exercise showed that less than 10% of the apps incorporated explicit delineation of their scope or initial screening for suitability. Slightly more than one-third of these apps included content aimed at encouraging professional help-seeking when needed or an explicit mention of their theoretical or empirical basis. Challenges for potential users were highlighted [20].

A recent survey of smartphone users in India highlighted that most of them (69%) were not aware of any mental health apps [21]. In another study involving persons with severe mental illness seeking treatment in a tertiary care setting in India and their caregivers, it was noted that health app use was low, with costs, lack of familiarity, and language being significant barriers to use [22]. An Indian study examined mental health apps in the Google Play Store between 2016 and 2020 by extracting data using various software programs. The keywords used for the search included: “mental health,” “mental illness,” “mental disorders,” “cure of mental disorder,” and “healing of mental illnesses.” As per the content analysis of the apps, the apps targeted various mental health concerns ranging from depression, anxiety, stress, posttraumatic stress, sleep, obsessive compulsive disorder, substance use, and panic symptoms to schizophrenia. This review examined basic content, number of downloads, mention of interactivity, and pricing and ratings of apps. It was observed that most app users did not leave their opinions or share their experiences, and thus, 70% of app ratings were based on a small number of users (100 or fewer users). The intervention approaches mentioned in this review ranged from relaxation, stress management, symptom tracking, calming audio, keeping a diary, interpersonal support meditation, and mood tracking. Connecting to mental health professionals as a strategy was mentioned in less than 2% of the instances. This study did not focus on examining the quality and appropriateness of content, usability, or empirical evidence-based [23].

The need for mental health app libraries independent of commercial biases has been advocated [24-26]. Lagan et al [17] systematically evaluated 278 mental health apps using the Mhealth Index and Navigation Database framework, which comprises 105 questions across 6 categories, namely, app origin or accessibility, privacy or security, inputs or outputs, clinical foundation or evidence base, features or engagements, and interoperability. The most common features offered by the 278 apps were mood tracking and journaling, with much fewer ones offering comprehensive therapeutic interventions that may be useful for addressing the diversity of user needs. Less than 25% of apps were supported by a feasibility or efficacy study [17].

From end users’ perspectives, when selecting apps, they rely mainly on ratings and reviews in app stores or on advice given through social media or word of mouth [27]. However, the lack of involvement of mental health experts in app development and insufficient attention to evidence-based development are factors that can limit the effectiveness of the apps or even pose a risk for harm due to unscientific suggestions or lack of information on limitations of app-based interventions and need for direct professional consultations.

It has been observed that many apps in commercial app stores, including low-quality ones, make it difficult for users to identify a suitable app for various mental health conditions, and evidence-based is often lacking, even for top-rated apps in app stores [28,29].

Rationale for the Review

Studies have highlighted that most well-researched apps are not easily accessible to the public, while a bulk of apps available in app stores are not backed by research evidence or do not involve qualified mental health professionals in their conceptualization, development, or validation [30]. In contrast to the reviews on research studies on the efficacy or effectiveness of mental health apps, there have been fewer studies that have directly reviewed mental health apps themselves, which are available for end users in app stores.

Apart from the lacuna mentioned earlier, data security and privacy concerns are some of the factors that restrict the potential of this field, as mental health apps use sensitive information pertaining to personal concerns, thoughts and moods, and sleep patterns. High attrition rates and inconsistent or infrequent usage of apps are challenges noted across the globe that reduce the potential effectiveness of the apps for users, and this is particularly true of mental health apps that are completely unguided as these do not involve any human interface or assistance for use. The other challenges surrounding mental health apps in India include the diversity of languages spoken across the country and the sociocultural factors that can make it difficult to develop apps that cater to the population's diverse needs.

There is a dearth of systematic reviews of mental health apps available in app stores for Indian users. Reviews that rely on the number of downloads, user ratings, or merely app store descriptions are unlikely to be helpful in guiding the consumers of mental health apps in making informed decisions. This study is designed to address these gaps by conducting a systematic review of mental health apps accessible to Indian users, using a standardized framework for assessment. This systematic review is expected to help in the creation of a user-friendly platform to guide consumers of mental health apps in India. This is especially important as the commercial marketplace offers a confusing array of options with a plethora of apps, a diverse range of content, a lack of clarity on scope or indications for the use of specific apps, and a lack of noncommercial platforms providing detailed information that can assist users in choosing apps that serve their needs.

Hence, we aim to conduct a comprehensive and systematic review of smartphone-based mental health apps available in app stores that are accessible to Indian end users in order to (1) describe these apps in terms of characteristics such as purpose, nature of the intervention, mental health conditions focused upon, involvement of mental health professionals in development, mention of empirical basis, nudges to seek professional help as well as (2) evaluate and document the quality of these apps.

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Methods

Ethical Considerations

The systematic review has been registered on the International Platform of Registered Systematic Review and Meta-analysis Protocols (INPLASY2024100035). An exemption from the Institute Ethics Committee (Behavioural Science Division), NIMHANS (No. NIMHANS/EC/[BEH.SC.DIV.] MEETING/2024) was sought and obtained for this review.

App Review Approach

An approach called Target user, Evaluation focus, Connectedness and Health domain (TECH) has been developed to formulate research questions and determine eligibility criteria for systematic reviews of commercially available health apps. This is because formats such as Population, Intervention, Comparison, and Outcome (PICO) and Sample, Phenomenon of Interest, Design, Evaluation, Research (SPIDER) are appropriate primarily for a systematic review of studies examining the effectiveness of interventions and for systematic qualitative review, respectively [31]. Here TECH refers to (1) target user (the specific population in question); (2) evaluation focus (eg, app characteristics, quality, usability, techniques, or components); (3) connectedness (whether the app connects with other apps or services); and (4) health domain (eg, specific health condition or concern being focused). This approach is aimed at helping in the development of the research question and for guiding eligibility criteria for the review of apps. Applying the TECH approach in this study context, the target population broadly consists of Indian adults interested in exploring or using apps to understand or manage mental health concerns. The evaluation focus is kept intentionally broad to include descriptive information on app characteristics, content, and quality. The review intends to include stand-alone apps as well as those that may connect to services but apps that connect to wearables or other apps would fall beyond the purview of this review. The health domain focused upon in the review is broad and includes various mental health concerns and conditions, The eligibility criteria mentioned subsequently drew upon these elements of the TECH approach.

Since this is proposed to be a review of mental health apps and not a systematic review of research studies on mental health apps, the Protocol for App Store Systematic Reviews (PASSR) checklist will be used (see flow diagram in Figure 1) [13]. It is a combination and adaptation of the items from A Measurement Tool to Assess systematic Reviews (AMSTAR) and Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) checklists that can be applied to the systematic search of app stores for any category of apps [32,33].

Figure 1. Flow diagram depicting the exclusion of apps at different stages of the review.

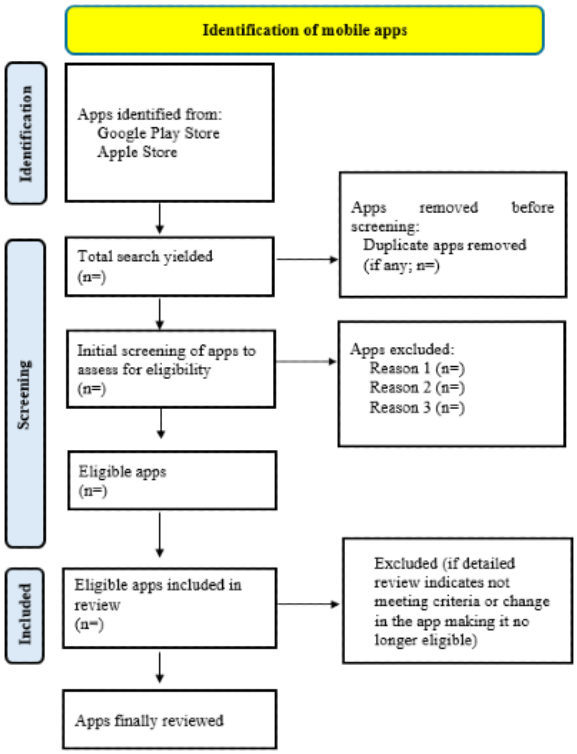

Inclusion and Exclusion Criteria

The inclusion criteria for the review of apps are as follows:

- Apps available in Google Play Store or Apple App Store for Indian adults.
- The store description of the app indicates they are offering guidance on mental health problems or therapy, information, self-help, or support and are thus relevant for the review.
- Apps available in English.
- Free apps and partially free apps (for those involving in-app purchases, what is freely available will be reviewed).

It should be noted that the number of apps that are available in any Indian language that do not have an English version will also be documented but not included in the detailed review.

The exclusion criteria for the review of apps are as follows:

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- Mental health apps that are fully paid and do not have a free trial period.
- Apps available solely in a non-English language.
- Apps meant for exclusive use by health professionals (eg, for training or education).
- Apps that require any additional wearable devices or sensors.
- Apps that are solely focused on enhancing wellness without the context of mental health concerns (eg, improving time management, improving productivity, managing relationships).
- Apps available only for research participants of a given study.

The keyword-driven search was carried out during October 2024 and November 2024. Apps that are no longer available to download in January 2025 for a detailed review will be excluded.

The aforementioned search criteria have been set in order to ensure that the research objectives can be adequately addressed while also taking into account feasibility considerations for this comprehensive review. The search will be carried out on Google Play stores and Apple iOS stores as these together comprise about 99% of the Indian market share [34]. Most of the mental health apps for Indian users are in English language. Any app in an Indian language that has an English version will be included for review. India is a multilingual country with 121 languages [35]. Apps available only in a non-English language will be documented but excluded from detailed review as that would require expertise in the given language. There is a very huge and broad range of apps that are on themes related to well-being and these deserve a separate review exercise. The review is restricted to apps that focus on one or more mental health conditions to ensure a focus and enhance the feasibility of the study. Apps that require additional wearable devices are not included in this review as they can have accessibility or affordability issues. These are also likely to be vulnerable to cyberattacks and may require smart intrusion detection systems [36]. Also, apps directed at health professionals would be excluded as the purpose of the review is to evaluate apps for the public.

App Search Strategy

The keywords used in this study are “Mental health,” “Depression,” “OCD,” “Addiction,” “Schizophrenia,” “Anxiety,” “PTSD,” “Bipolar,” “BPAD,” “CBT,” “ACT,” “DBT,” “Cognitive Behaviour Therapy,” “Acceptance and Commitment Therapy, and “Dialectical Behaviour Therapy.”

The selection of these 15 keywords was guided by the purpose of this study which was to cover a broad range of common and prevalent mental health concerns, common psychotherapy interventions as well and their commonly used acronyms. Further, a broad scan of review studies in the last 5 years on mental health apps, as well as an initial scanning of the apps in the app stores helped in finalizing the keywords.

The following search strategy will be adopted:

- Searches will be conducted in each store (marketplace) with each of the aforementioned keywords.
- Will use a clean or reset device to search the data store with a new Gmail or iOS ID.
- Details of the search dates will be recorded.
- The entire search process will be screen-recorded for reference while ensuring slow scrolling from the top to the end of the screen. To avoid missing any apps, scrolling will continue past any advertisements until all content is thoroughly recorded.
- Before the second key term search, the Play Store or Apple App Store history from settings will be cleared and reset.
- All the listed apps in the screen recordings will be carefully entered on a Microsoft Excel sheet.
- If an app is available both on the Google Play Store and Apple Stores Android and iOS phones, the version on the Google Play Store will be reviewed, and the app will be counted only once.
- Four mobile devices (2 Apple and 2 Android devices) will be used for the search.

Initial Screening

After lists of apps on the 2 stores are generated, duplicates will be removed, and the remaining apps will be screened for eligibility using the selection criteria. This screening task will be divided among 4 members of the review team. Any doubts regarding inclusion will be resolved through joint discussions.

The apps meeting the inclusion criteria will be downloaded for detailed review. At this stage too, if any apps are found to be nonrelevant or not meeting any of the inclusion criteria will be excluded from further review.

From the final pool of apps, 6 apps will be randomly selected for joint discussion and review by a team consisting of 4 primary reviewers along with 2 clinical psychology faculty serving as mentors (with more than 10 years of overall experience and familiarity with app review processes). Following this, a new set of 6 randomly selected apps from the remaining ones will be rated independently by the primary review team and the differences in review ratings, if any, will be discussed with all the team members, including the mentors, to arrive at a consensus. This process is adopted to streamline the review process and increase interrater consistency in review and ratings through training and the use of a panel of primary reviewers and mentors. In the last step, the primary reviewers will individually review the remaining apps in the list. In addition, 2% of all the apps, (depending on the number of finally selected eligible apps) will be randomly selected and reviewed collectively by the mentor team in order to note the concordance with the ratings by the primary reviewers.

Data Extraction

The detailed review of downloaded apps will involve documenting the following aspects in Table 1.

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Table 1. Information of apps planned to be extracted.

Serial number	Information parameter	Coding format
1	• Privacy-related: • Privacy policy accessible to users • Privacy terms clearly explained • Mention of data-sharing policy with third parties • Mention of data retention duration • Mention of provision for deletion of user account	• Yes or no
2	• Payment requirements	• Completely free to use • Fully paid • Involves in-app purchases
3	• Nature of developer	• Company • Not-for-profit organizations • Academic bodies • Government agency • Insufficient information available
4	• Country of origin	• Mentioned name of the country • Insufficient information available
5	• Release	• Date of first release • Insufficient information available
6	• Update	• Date of last update • Insufficient information available
7	• Downloads	• Number of downloads
8	• Rating	• Number of reviews • Average review rating
9	• Log-in requirements	• Yes or no
10	• Language	• English • Non-English • If in any Indian language
11	• Mental health professionals' involvement in development of the app	• Clearly specified • Generally mentioned • Not mentioned
12	• Empirical research on the app mentioned	• Yes or no
13	• Target users: • Specified minimum age (if any) • Any special group (eg, veterans)	• Yes or no
14	• Basic purpose of the app (as ascertained from the content and features)	• Free text (eg, providing information, psychoeducation, screening, self-help, synchronous or asynchronous chat-based support, therapy or counseling support, artificial intelligence–based counseling, peer-support, symptom monitoring, tracking)
15	• Mental health condition	• Single mental health condition focused • Multiple mental health conditions focused • Not mentioned
16	• Type of intervention: • Type of therapy mentioned • Guided or unguided	• Free text (like CBT[a], DBT[b], and mindfulness) • Yes or no

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Serial number	Information parameter	Coding format
17	• Components of the intervention	• Single component or multiple components
18	• Empirical basis of the intervention	• Mentioned or not mentioned
19	• Nature of the intervention • Attempts to dispel common myths related to mental health and illness	• Yes or no
20	• Crisis management • Mentioned helpline, emergency service details, or directories • Basic crisis support strategies	• Yes or no
21	• Sociocultural appropriateness of examples used (case study)	• Yes, no, or could not be ascertained
22	• Inclusion of pointers on when to seek professional help	• Yes or no
23	• Inclusion of nudges to seek professional help when needed	• Yes or no
24	• Any special feature	• Yes (a brief description of the feature) or no

[a]CBT: cognitive behavior therapy.

[b]DBT: dialectical behavior therapy.

Some modifications and refinements in the data extraction parameters and process may be considered if required depending on the review of the initial 15 apps by the primary reviewers.

Evaluation of Quality of Apps Using Ratings From the Mobile Application Rating Scale

In addition to documentation on the earlier aspects, primarily related to the content, the apps will also be evaluated using the Mobile Application Rating Scale (MARS). This scale consists of 19 items across 4 domains, that is, engagement, functionality, aesthetics, and information quality [37]. Each item is rated on a 5-point Likert scale: (1) inadequate, (2) poor, (3) acceptable, (4) good, and (5) excellent. The total score and the 4 objective domains have high internal consistency. An additional 4-item subjective quality scale is also available, though it is not counted toward the total. MARS has been one of the most widely used tools across nations for the evaluation of the quality of mobile health (mHealth) apps, including mental health apps [38-40]. A recent study documented the validity of MARS by using pooled MARS data from 15 international reviews assessing the quality and content of mHealth apps in various health conditions [41].

Strategy for Data Analysis and Synthesis

The analysis will involve the use of descriptive statistics such as frequencies, percentages, mean, and SDs. This would be in addition to the qualitative analysis of the apps as mentioned earlier through the use of MARS ratings. In addition to the overall findings, an attempt will be made to synthesize and present subgroup-wise findings based on apps with a different focus in terms of the nature of mental health conditions (eg, severe vs common mental health conditions) and those with single versus multicomponent interventions, provided there is a sufficient number of apps to form such subgroups. This study is focused on reviewing apps themselves rather than reviewing studies about apps and hence the traditional methods for assessing the risk of bias are not applicable. There is a scarcity of guidelines to assess the risk of bias in studies evaluating apps on app stores. An attempt will be made to describe the potential risk of bias at the stage of inclusion of apps for review, their detailed review by independent reviewers, and the handling of missing data while reporting findings. The risk of bias will also be documented by mentioning whether any apps being reviewed have been examined by any member of the research team for effectiveness or efficacy [13].

Results

The search for mental health apps in virtual stores has been completed. The initial screening has been completed. The initial search yielded 5827 apps, comprising 3708 apps on the Android Play Store and 2119 apps on the Apple App Store. We expect to complete the detailed systematic review by April 2025.

Discussion

Significance of the Systematic Review of Mental Health Apps

In the background of a huge treatment gap, mental health apps can contribute in numerous ways to strengthen mental health care systems, empower communities with low-intensity, affordable, and accessible options for self-care for milder problems as well as enhance mental health literacy and reduce barriers to seeking mainstream mental health services; provided that the challenges related to quality, security, congruency to user needs, and user engagement are appropriately addressed [42-44]. As pointed out earlier, the current regulatory frameworks for mental health apps are still evolving and there is a plethora of apps in the commercial marketplace with little information available on their evidence or use of evidence-based content [18,20]. Hence, a review like the present one can be a stepping stone to exploring the nature of apps and subsequently

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coming up with suggestions and recommendations to improve the safety and quality of apps [45]. The review is not focused on outcome research on apps; instead, it delves into examining apps in terms of the nature of content, their scope, and quality. As previous research indicates, the popularity of apps and user experience do not necessarily predict sustained engagement and hence the need for systematic evaluation of apps on a comprehensive set of parameters including sociocultural appropriateness, as planned in this review [29,46,47]. It is important to highlight that the potential impact of the review is not to come up with a list of apps that are "flagged as not useful," instead it attempts to draw the attention of the public, developers, and mental health professionals to make informed decisions for choosing, using, designing, and studying mental health apps judiciously to maximize their potential for serving the mental health needs of the population.

Future Plans

Following the systematic review of the mental health apps in app stores, an attempt will be made to categorize them based on various parameters that may be relevant for potential end users as well as professionals who search for relevant apps on stores for specific purposes (eg, target group, main purposes, level of interactivity, functions, and scope and limits of the app). The outcome of this process will be made available to the public and professionals in a web-based portal in an easy-to-use search or filter format.

Strengths and Limitations

This would be one of the first systematic reviews of mental health apps available in app stores for Indian users, using a comprehensive set of keywords related to mental health conditions and therapies. Also, this review would go beyond app store descriptions and indices such as user reviews and number of downloads and would entail examining the actual content, functionalities, and features of the apps through engaging a panel of raters, including mental health professionals. Unlike literature searches, searching apps in app stores have some limitations. The search can be challenging as the order in which the search results are displayed can be variable and the usual filter functions like those when reviewing research are not available. Moreover, the initial screening would be guided by the app store descriptions that may not always provide clear information being sought by the reviewers and hence may result in the exclusion of some relevant apps, although an attempt will be made to err on the side of overinclusiveness, during the initial round of screening.

Conclusions

The review will provide a comprehensive and critical review of the smartphone apps on mental health that are available for Indian end users. The review findings are likely to have implications for end users, policy makers, developers, and researchers in the field of mental health apps.

Acknowledgments

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Authors' Contributions

SM conceptualized and designed the protocol, contributed to the development of selection criteria, supervised the drafting, revising of the manuscript, and finalized the same; RT conceptualized and designed the protocol, contributed to the development of selection criteria, supervised the drafting and helped in the editing of the same; P Sengupta and AK contributed to the drafting of the manuscript and also revised the same along with planning for data analysis. AF and P Sharma reviewed the literature and were also involved in the process of data collection and analysis and contributed to writing up portions of the manuscript; P Sudhir and GNR supervised the analysis plan, writing of the manuscript, and its revision; TKS was involved in the review and write up of technological aspects, contributed to revisions of the manuscript while RS provided supervisory support and helped in finalization of the manuscript. All authors reviewed the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AMSTAR: A Measurement Tool to Assess systematic Reviews
MARS: Mobile Application Rating Scale
mHealth: mobile health
PASSR: Protocol for App Store Systematic Reviews
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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TECH: Target user, Evaluation focus, Connectedness and Health domain

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Protocol

The Impact of Long-Chain Omega-3 Polyunsaturated Fatty Acid Supplementation in Pregnant Women Toward the Intelligence Status of Early Childhood: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Long-chain omega-3 polyunsaturated fatty acids (LCPUFAs) are essential fatty acids that protect cellular structures and provide energy, particularly for fetal growth and development. The maternal supplementations of omega-3 LCPUFA may affect the rate of intelligence in early childhood development.

Objective: This systematic review aims to synthesize available evidence on the impact of omega-3 LCPUFA supplementation during pregnancy toward intelligence in early childhood development by analyzing the outcomes specifying the aspects of intelligence such as neurodevelopment, social-emotional, language, attention, behavior, cognition, vision, hearing, and motor skills.

Methods: We will only include randomized controlled trials on pregnant women supplemented with omega-3 LCPUFA interventions and the outcome measured is the children's intelligence. Based on the World Health Organization's definition of early childhood, we will include children aged 8 years or younger. Children's intelligence can be indicated using several tools measuring their intelligence index, such as neurodevelopment, social-emotional, language, attention, behavior, cognition, vision, hearing, and motor skills. Irrelevant and unavailable studies will be excluded. A systematic search will be conducted in 3 electronic databases, namely PubMed, Scopus, and Cochrane using relevant and synonymous terms. Study screening and selection will be conducted by the authors based on eligibility criteria. Upon encountering conflicting decisions, a discussion will be held to reach a consensus. The screening and selection process will be recorded using a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart. The included studies will be subjected to bias and quality assessment in accordance with the Critical Appraisal Skills Programme (CASP) and Grading of Recommendations Assessment, Development, and Evaluation (GRADE) assessment tool for randomized controlled trials.

Results: An initial search was conducted on November 1, 2023, which returned 1998 studies for screening. The extracted data will be classified into groups and subgroups according to the indicator of intelligence measured in the study. Next, the extracted data will be summarized using tables of evidence. Whenever possible, a meta-analysis of homogeneous groups of studies will be conducted using statistical software such as RevMan (version 5.4; Cochrane Collaboration). Studies with significant heterogeneity will be discussed narratively. The systematic review is estimated to be published in November 2025.

Conclusions: This systematic review will systematically pool the evidence on the potential use of omega-3 LCPUFA supplementation to improve children's intelligence status. This review is also important in addressing any existing knowledge gaps on this topic. Finally, a deeper understanding of the association between the consumption of omega-3 LCPUFA

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supplementation during pregnancy and children's intelligence will aid policy makers, health care practitioners, and mothers with more informed evidence-based decisions.

Trial Registration: PROSPERO CRD42023463910; https://www.crd.york.ac.uk/PROSPERO/view/CRD42023463910

International Registered Report Identifier (IRRID): DERR1-10.2196/60417

(JMIR Res Protoc 2025;14:e60417) doi:10.2196/60417

KEYWORDS

antenatal; long-chain omega-3 polyunsaturated fatty acids supplementation; pregnant women; systematic reviews; pregnant; pregnancy; maternal; maternity; infant; babies; nutrition; fish oil; docosahexaenoic acid; eicosapentaenoic acid; supplements; cognition; attention; motor skills; languages; behaviors; vision; neurodevelopment

Introduction

Long-chain omega-3 polyunsaturated fatty acids (LCPUFA), also known as omega-3 fatty acids are a part of polyunsaturated fatty acids (PUFA). It is characterized by multiple double bonds (C=C), with the first double bond located on the third carbon chain counting from the terminal methyl group (omega carbon). The 3 forms of this type of PUFA include alpha-linolenic acid (ALA), docosahexaenoic acid (DHA), and eicosapentaenoic acid (EPA). As the body lacks the necessary enzymes to synthesize ALA, it must be acquired through food or supplements, making it an essential fatty acid. Although ALA can be converted to DHA and EPA, the efficiency of its conversion is rather low, hence it is recommended to consume foods that are rich in DHA and EPA [1,2]. The primary source of ALA is plant oils such as canola oils, soybeans, and flaxseed while DHA and EPA are mainly found in fatty oil–enriched fish, which includes sardines, mackerel, and salmon [3,4].

In addition to being essential for the structural integrity of cell membranes, omega-3 LCPUFA also operates as a source of energy and bioactive lipid mediators [5,6]. These functions are critically essential for fetal growth and development, particularly for DHA as DHA plays a key role as part of the cell membrane components in the fetal brain and retina [7]. Placental transfer is the primary source of DHA accumulation in utero, which is involved in neurotransmitter metabolism, neural, and visual functions [8]. Thus, the consumption of omega-3 LCPUFA, in general, is essential to promote optimal fetal growth and maturation for several vital organs, notably the brain and eyes [9]. According to Khalid et al [10], the fetal brain and eyes that were developed in a systematic fashion in response to an adequate intake of omega-3 LCPUFA have some influence on optimal cognitive and visual acuity development in early childhood [10]. DHA prevents cognitive aging by reducing brain apoptosis through upregulating the expression of antiapoptotic proteins or downregulating the apoptotic proteins, thus enhancing early memory and learning ability related to intelligence [11].

According to the World Health Organization, the definition of early childhood corresponds to the period from prenatal development to 8 years of age [12]. While the key factors that determine intelligence in these age groups are hotly debated and vastly described, some genetic and modifiable environmental and nutritional factors contributed to the high intelligence quotient in early childhood [13,14]. Consumption of daily omega-3 LCPUFA during pregnancy as part of maternal nutritional benefits, has been linked to increased early childhood intelligence, according to multiple clinical studies [15-17]. However, as opposed to other clinical studies, randomized controlled trials (RCT) have shown that the most promising outcomes as the confounding factors will be removed in the early phase of the trial to obtain a solid causality that influences the development of early childhood intelligence.

Throughout the years, RCTs related to the consumption of omega-3 LCPUFA have reported varying degrees of results, and several systematic reviews have made an effort to assess the corpus of literature as a whole. The recent Cochrane-based systematic review of omega-3 LCPUFA conducted by Middleton et al [18] has concluded the necessity of conducting a series of follow-ups for completed RCTs for both mothers and children to understand the growth, metabolic, and neurodevelopmental pathways as the RCT outcomes varied by different types of omega-3 LCPUFA, along with the timing, doses, and characteristics of women [18]. This is also supported by a previous systematic review conducted by Gould et al [19]. However, the evidence from these reviews does not conclusively show that the consumption of omega-3 LCPUFA during pregnancy influences the improvement of cognitive and visual development in childhood. This systematic review aims to synthesize available evidence on the impact of omega-3 LCPUFA supplementation during pregnancy toward intelligence in early childhood development as compared to placebo by using a similar approach with added keywords based on the previous systematic review by Gould et al [19] and Middleton et al [18]. The outcome of children's intelligence can be assessed using various tools that measure factors like cognition, attention, motor skills, language, behavior, vision, hearing, social-emotional, and neurodevelopment.

Methods

Overview

We will conduct a systematic review in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [20]. We will ensure adherence to the PRISMA 2020 guidelines throughout the review process by following their checklist (Multimedia Appendix 1) and flow diagram (Figure 1). All processes will be recorded systematically, precisely, and transparently. The systematic review flow diagram will be divided into three processes: (1) identification, (2) screening, and (3) inclusion. The identification

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of studies will be categorized into 2 sections, via databases, registers, and other methods. Records identified from each section will be documented accordingly. The final selection process will display the total number of studies that are eligible to be included in the review. To avoid the potential confounding factors that may affect the relationship between omega-3 LCPUFA supplementation and childhood intelligence, such as socioeconomic status, maternal education, and prenatal care, several review strategies will be used in the methodology phase. First, several effect models, such as fixed effects and random effects models will be reviewed in all studies to account for unmeasured individual-level confounding that might vary over time to help in estimating the causal effects of omega-3 LCPUFA supplementation. Second, during the screening phase, only studies where the participants are randomly assigned to either the treatment group (omega-3 LCPUFA supplementation) or the placebo group will be accepted. This randomization ensures that confounders are evenly distributed between the groups, thereby reducing their potential influence on the study results.

Figure 1. PRISMA flow diagram.

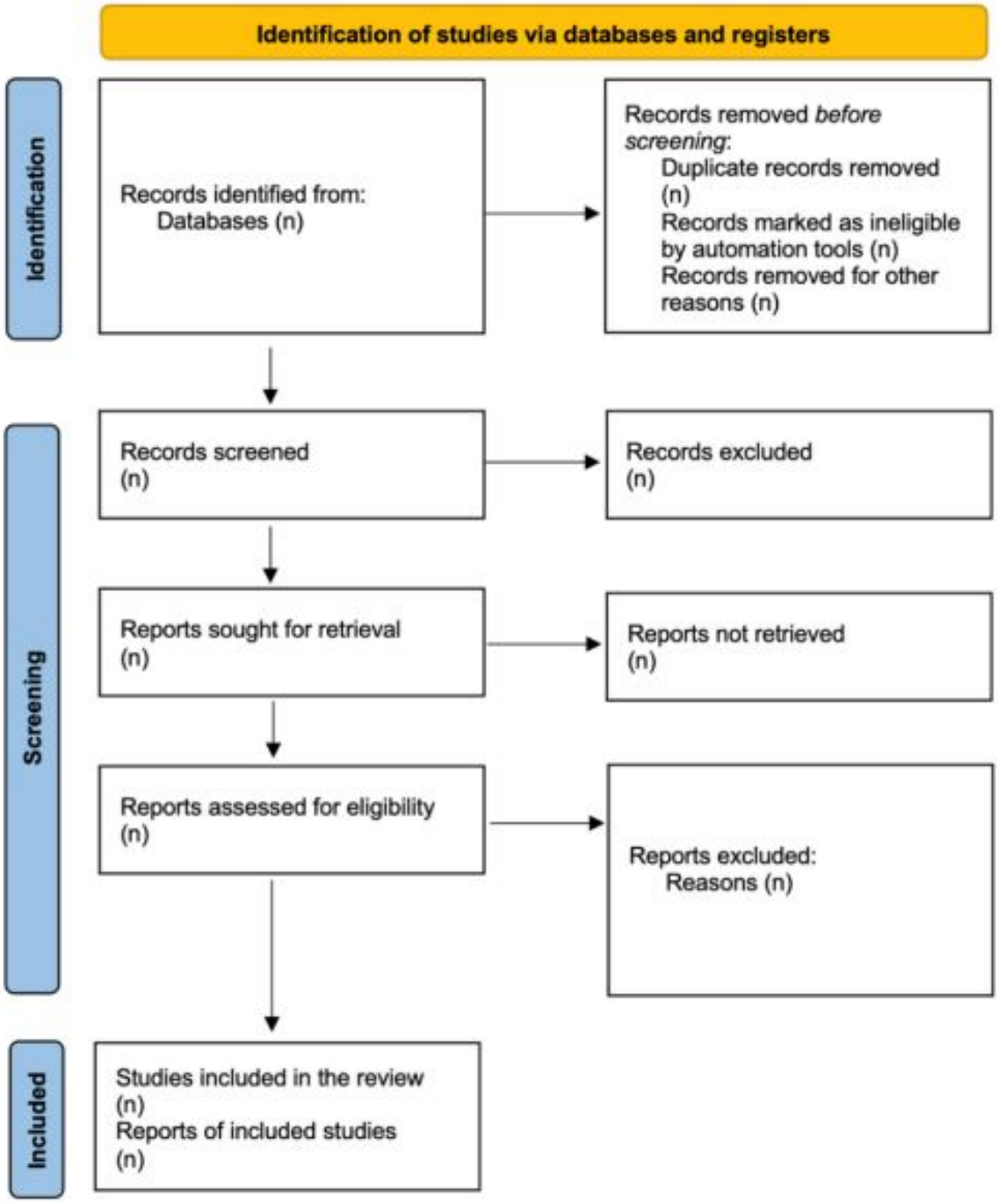

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Eligibility Criteria

We will use the Participant, Intervention, Control, Outcomes (PICO) model in constructing eligibility criteria for study inclusion in the review.

Study Selection

We will include individual and clustered RCTs that studied the children's intelligence status between the supplementation of omega-3 LCPUFA during pregnancy compared to placebo or other supplemented intervention or standard perinatal care. Other types of study designs such as unpublished studies, gray literature, reviews, letters, short communications, conference papers, conference abstracts, abstracts, in vitro or in vivo, prospective or retrospective cohort, case-control, quasiexperimental and nonrandomized clinical trials will be excluded. We will include studies published in English. For studies in other languages, we will seek translations, if available.

Population

Our systematic review will focus on studies involving healthy pregnant women who received omega-3 LCPUFA supplementation. These pregnant women must be free from major confounding factors that are not representative of the general population of pregnant women. Additionally, we will consider the outcomes for their children who are aged 8 years or younger, assessing the impact of omega-3 LCPUFA supplementation on the children's intelligence using validated tools. The studies selected will exclusively involve mothers without chronic health conditions as well as children who have not been diagnosed with congenital anomalies, gastrointestinal issues, or metabolic disorders.

Intervention

In the review, we will evaluate the omega-3 LCPUFA supplementation in pregnant women as the intervention. We will not put a restriction on the dose. We will follow the study authors on the dose of omega-3 LCPUFA supplementation. Any RCTs that involve the supplementation before pregnancy or during the postnatal period will be excluded.

Comparison

We will include studies that compare the intervention with pregnant women receiving placebo or other supplement interventions.

Outcomes

We will include studies that measured the intelligence status of children using validated inventory or tools, for example, but not limited to, The Bayley Scales of Infant and Toddler Development, Third Edition, and Kaufman Assessment Battery for Children, Second Edition. The intelligence status may be based on several indicators such as cognition, attention, motor skills, language, behavior, vision, hearing, social-emotional, and neurodevelopment. The children included in the outcome group must be aged 8 years or younger. Studies that did not measure the intelligence status of the children, or studies that used children older than 8 years as an outcome group will also be excluded.

Data Sources, Search Terms, and Search Strategy

The authors have agreed to use 3 prominent journal databases as sources. The selected databases are PubMed, Scopus, and Cochrane Library. These databases were selected since they can fulfill every performance criterion as a search system [21]. All authors participated in a discussion to determine relevant terms and keywords that will be used in database searching. MeSH (Medical Subject Headings) terms will also be used in the search. Advanced search in each database will be performed using Boolean operators such as "AND" and "OR" to build search strings. Databases will be searched from inception to the most recent study publication. Any unpublished studies upon the final search date will not be included. No search filters will be used during the database search. The query search string will be adjusted following the interface provided by the databases (Multimedia Appendix 2).

Data or Reference Management

All studies identified in the final hit will be downloaded using NLM or RIS format. A reference manager software, EndNote (Clarivate) will be used to combine studies identified in the 3 databases. In-apps feature using the reference manager will be used to identify and remove duplicates.

Study Screening

Study screening will commence once database searches have been fully accomplished. A data selection form will be developed using Microsoft Excel and a systematic review tool. We will use Rayyan software (Qatar Computing Research Institute) to streamline the screening process, as it is a widely recognized tool designed for systematic reviews. All identified studies will be uploaded to the Rayyan review panel. Any duplicates identified by Rayyan will be removed. Before the process of selection, at least 5 randomly chosen studies will be pilot-tested to ensure all reviewers are familiar with the software. The references can be filtered by category, which makes the extraction process a lot easier. Collaborators or other reviewers will be invited to join the page and blind will be turned on in collaboration reviews to remove the risk of bias. References can be included by clicking "Include," excluded by clicking "Exclude," or "Maybe," if not sure. The label and reason box can be used to include labels and reasons for exclusion. The probability of the references (included, excluded, or undecisive) will be calculated by Rayyan. Undecided references will have a rating from 1 to 5, where 5 is most likely to be incorporated.

The screening process will be conducted in two phases: (1) title and abstract screening, and (2) full-text screening. Two reviewers (IHAS and MAMF) will be assigned to screen the titles and abstracts based on the eligibility criteria. Following that, the other 2 reviewers (SM and WASM) will conduct the second screening process by evaluating the full-text studies to be included in the review. If both reviewers have different opinions or judgments, a third reviewer (HYL) will be called upon to unravel the disagreements.

Data Extraction

A data extraction form will be constructed in an Excel (Microsoft Corp) sheet and the following information will be gathered from the relevant selected studies such as title, last

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name of the first author, year of publication, duration of intervention, study design, single or multicenter, country, source of funding, aims, population (inclusion and exclusion criteria), intervention, indicator, index test, comparison, reference standard, primary and secondary outcomes (including tools and period of measurement), and results. Two reviewers (IHAS and MAMF) will extract the data of eligible studies independently. The other 2 reviewers (SM and WASM) will recheck the data extracted. Any discrepancies will be resolved by discussion to achieve a consensus. Any missing data, incomplete information, or variation in results will be obtained by contacting the corresponding author of the study.

Risk of Bias and Quality Assessment

Assessment of risk of bias will be conducted by 2 independent reviewers (IHAS and MAMF). A third reviewer (HYL) will be the referee for any uncertainties or disagreements in the discussion. All included RCTs will be assessed for study quality and potential biases using the Critical Appraisal Skills Programme (CASP) checklist for RCT. CASP is a checklist widely used for RCT evaluation, chosen for its simplicity, structured approach, and focus on key domains of study quality. This tool considers the following four domains of biases: (1) arising from the validity of the study design for RCT; (2) the soundness of the methodology applied; (3) measurement of the outcome; and (4) whether the results will provide any benefit to the targeted population. Each domain will be judged as "yes," "no," or "can't tell." If necessary, the authors will be contacted to obtain or clarify any information needed. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) tool will be used to assess the quality and certainty of the evidence for the outcomes analyzed in the meta-analysis. A summary of the risk of bias will be compiled into a table along with the justification for each judgement.

Data Synthesis

Meta-analysis will be performed when there are at least 2 studies reporting on the same outcome of interest between the omega-3 supplementation (intervention) and placebo (control), otherwise, a narrative summary approach will be presented. In the case of RCT with more than 2 arms, each arm will be treated separately. Data extracted from each study will be pooled and analyzed using the RevMan (version 5.4; Cochran Collaboration) software. For outcomes of interest measured in continuous or scale, sample size, means, and corresponding SDs will be used in pooling the effect size of the outcomes across the included studies. The pooled effect estimates for continuous outcomes will be expressed as mean differences with 95% CIs for studies using a similar outcome assessment tool, meanwhile, standardized mean differences with 95% CIs will be expressed for studies using different outcome assessment tools. For outcomes of interest measured in dichotomous or binary, the number of events and total sample size will be used in pooling the effect size of the outcomes across the included studies. The pooled effect estimates for dichotomous outcomes will be expressed in odds ratio with 95% CI. In cases where the data reported in the included studies are not usable (ie, cannot be pooled with other data), the corresponding author of the study will be contacted for access to data or revised statistics. If the corresponding author is uncontactable, or the data are unavailable, we will retain the study as eligible but restricted for meta-analysis. In view of inconsistencies between results in the existing literature highlighted by Gould et al [19] and Middleton et al [18], meta-analysis will later identify patterns of agreement and disagreement, thus offering insights into the reasons behind conflicting results.

The overall effect estimates that have a P value less than .05 will be interpreted as statistically significant. Heterogeneity will be assessed using the I^2 statistic, which represents the percentage of the total variation present between studies included. The I^2 statistic values of over 50% will be considered substantial heterogeneity. To address the variability of dosage, duration, and types of PUFA supplementation, random effects models will be used during analysis to manage heterogeneity. This will ensure a robust analysis of our findings. Sensitivity analysis will be performed when heterogeneity is high to address potential confounding factors and strengthen the study's robustness. We will group the outcomes according to the same assessment tools. Subgroup analyses for outcomes will be conducted when 2 or more studies are available per subgroup of interest. The following prespecified subgroups will be considered: maternal age, duration of intervention, presence of co-interventions (by itself or combined with complementary interventions), baseline nutritional status in mothers, sex of infant, country or geographic region, and risk of bias (low, high, or some concerns). If the dosage of the supplementation varies significantly, we will also do a subgroup analysis based on the dose group if we can pool studies with the same outcome.

Funnel plots will be conducted for the detection of publication bias if there are 10 or more studies available for an outcome. Publication bias is unlikely if data forms a symmetric inverted funnel shape around the mean effect estimate. As the funnel plots will be presented graphically, subjective judgments are required, which might differ from one person to another in interpreting the result. In addition, the Egger test will be conducted to determine funnel plot asymmetry. The presence of publication bias will be considered if the P value of the Egger test is less than .05.

For outcomes with insufficient data or extreme heterogeneity that cannot be analyzed by meta-analysis, a narrative synthesis will be provided.

Registration and Reporting

This systematic review and meta-analysis protocol has been registered on the International Prospective Register of Systematic Reviews (PROSPERO, CRD42023463910) and in the National Medical Research Register Malaysia (03507-WSF). In the event of protocol amendments, the date of each amendment will be accompanied by a description of each change and the rationale on PROSPERO. In preparing this protocol, we followed the PRISMA 2020 checklist (Multimedia Appendix 1). This systematic review will be reported in accordance with the Cochrane Handbook for Systematic Reviews of Interventions [22] as well as the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) guidelines (Multimedia Appendix 3) [23].

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Ethical Considerations

As this systematic review and meta-analysis uses secondary data, ethical approval is not required, and an exemption letter for ethical approval is obtained as per requirement by the Ministry of Health, Malaysia.

Results

After discussing and finalizing the search keywords and search strategy, 1 author conducted the initial search. The first keyword search was run on November 1, 2023. The first database, which is PubMed, yielded 530 hits whereas the second database from Cochrane found 306 hits. The most hits were from Scopus with 1162 hits. In total, our first database search yielded 1998 hits. All references were then imported into a reference manager specified in the search strategy section. All hits will be pooled and screened for duplicates using automation tools. Then, the titles and abstracts will be extracted for the first screening by the authors. We aim to finish extracting and analyzing data from chosen studies and prepare the report by November 2025.

Discussion

Principal Findings

In our planned systematic review, we intend to investigate the existing body of literature concerning the effects of maternal omega-3 LCPUFA supplementation on the cognitive development, specifically the IQ, of children in early childhood. The justification for maternal omega-3 LCPUFA supplementation, often promoted as a means to enhance a child's cognitive development, remains a topic of ongoing debate. Given the extensive systematic review conducted in 2018, this systematic review aims to provide a more rigorous analysis of the available evidence [18]. While previous findings suggest a positive association between omega-3 LCPUFA supplementation during pregnancy and children's IQ, it is important to note that the existing evidence is characterized by relatively low quality due to limitations such as small sample size. Hence, our objective is to enhance the quality of evidence through this review. A consistent body of research indicates a significant link between maternal omega-3 LCPUFA supplementation during pregnancy and a substantial enhancement in the IQ of the children [24,25]. Despite the overall indication of support for the beneficial effects of maternal omega-3 LCPUFA supplementation, it is important to acknowledge the presence of factors that can influence the outcomes [26,27]. Therefore, in our systematic review, we will also look at the variations in indicators of the intelligence status of the children based on several indicators such as cognition, attention, motor, language, behavior, vision, hearing, social-emotional, and neurodevelopment, which may contribute to heterogeneity in the results. The systematic review will adhere strictly to the protocol, and any deviations will be documented and reported in the published manuscript.

The implications of these findings for public health are significant. A more tailored approach to prenatal nutritional guidance, as suggested by Cetin et al [28], may be warranted to ensure optimal cognitive development in early childhood [28]. This, in turn, could have long-term cost-saving benefits for health care systems by potentially reducing the societal burden of cognitive impairments.

Comparison With Prior Work

Previous systematic reviews were published more than 5 years ago and the findings were varied [18,19]. Given the potential impact of maternal omega-3 LCPUFA supplementation on child IQ, there is a strong case for revisiting and possibly refining dietary recommendations for pregnant women. Thus, this review builds on these works by incorporating updated evidence and conducting subgroup analyses to address key factors, such as timing, dosage, and source of supplementation.

Limitations

We will thoroughly examine the limitations and potential sources of bias in the included studies. Despite our review's rigorous evaluation of evidence quality, there may still be sources of bias, such as publication bias or unaccounted confounders, that influence the overall results. To address potential publication bias, we will include a funnel plot analysis to visually assess the presence of asymmetry. Furthermore, the quality and design of the individual studies may vary. It is important for researchers and policymakers to recognize these limitations when interpreting the findings and consider them when making recommendations.

Future Research

This systematic review will address the necessity for further research in this area. It will also help future studies to address the identified limitations and clarify the optimal timing, dosage, and duration of maternal omega-3 LCPUFA supplementation to maximize the potential benefits on child IQ. Additionally, the long-term effects of maternal supplementation in children beyond the age of 8 years warrant exploration. This will not only deepen our understanding of this complex relationship but also help refine practical recommendations for expectant mothers, contributing to the well-being of future generations.

Conclusions

In conclusion, the systematic review will provide valuable insights into the potential impact of maternal omega-3 LCPUFA supplementation on children's IQ. If the evidence suggests a positive association, further research is needed to address limitations, confirm findings, and refine recommendations. The results will be disseminated by publishing the review, presenting at conferences, and sharing with stakeholders such as policy makers, nutritionists, and doctors, following PRISMA guidelines for transparent reporting. The implications for public health are substantial, and addressing these gaps can lead to a more comprehensive exploration of the impact of omega-3 LCPUFA supplementation during pregnancy on children's intelligence. Thus, this systematic review can provide a thorough understanding of the topic and offer valuable insights for future research and practice.

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Acknowledgments

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Data Availability

All data generated and analyzed in this systematic review are available upon request from the corresponding author.

Authors' Contributions

HYL, MAMF, SM, IHAS, and WASM designed the systematic review and wrote the original draft; HYL and WASM designed the systematic review and approved the final manuscript. All authors are researchers involved in clinical nutrition research, with several years of experience in nutrient analysis and clinical nutrition at the Institute for Medical Research, Malaysia.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA 2020 checklist.
[DOCX File , 606 KB - resprot_v14i1e60417_app1.docx]

Multimedia Appendix 2
The protocol search strategy.
[DOCX File , 21 KB - resprot_v14i1e60417_app2.docx]

Multimedia Appendix 3
PRISMA-P 2015 checklist.
[DOCX File , 22 KB - resprot_v14i1e60417_app3.docx]

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Abbreviations

ALA: alpha-linolenic acid
CASP: Critical Appraisal Skills Programme
DHA: docosahexaenoic acid
EPA: eicosapentaenoic acid
GRADE: Grading of Recommendations Assessment, Development, and Evaluation
LCPUFA: long-chain omega-3 polyunsaturated fatty acid
MeSH: Medical Subject Headings
PICO: Participant, Intervention, Control, Outcomes
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis

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PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols
PUFA: polyunsaturated fatty acid
RCT: randomized controlled trial

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Protocol

Paving the Road for More Ethical and Equitable Policies and Practices in Telerehabilitation in Psychology and Neuropsychology: Protocol for a Rapid Review

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Abstract

Background: Virtual rehabilitation, or telerehabilitation (TR), has exponentially evolved in the last few years, gaining particular momentum since the COVID-19 pandemic. In response to a new reality of strict restrictions of physical contact necessitating the shift from in-person health services to tele-health visits, TR has seen widespread adoption. In this context, ensuring ethical and equitable TR services is crucial for establishing sustainable TR models for psychology and neuropsychology into health care systems. This requires complete and consistent guidance for clinicians and patients involved.

Objective: The objective of this study is to synthesize existing evidence to provide timely insights on potential ethical and equitable benefits and pitfalls associated with the use of TR in a psychological and neuropsychological framework.

Methods: A rapid review of TR practices will be conducted specifically within the context of neuropsychology and psychology rehabilitation. We will include review articles published between 2010 and 2020 as well as original articles published between 2020 and 2023, all addressing TR issues with a main focus on neuropsychological and/or psychological rehabilitation activities. This research protocol describes the methodology, including search strategy, screening process, data extraction, and analysis methods.

Results: Guided by an experienced librarian, the search strategy was designed and performed in 3 relevant databases. Articles were screened in accordance with the inclusion and exclusion criteria, and data were collected by 2 independent reviewers. Data extraction is underway, and we expect to complete the rapid review in January 2025.

Conclusions: This study is part of a broader cross-Canadian initiative aimed at informing policy development and clinical practices in TR. By evaluating the ethical and equitable considerations specific to psychology and neuropsychology, this review aims to contribute to help shape future TR practices to ensure access to high-quality, accessible TR services supporting diverse patient needs in psychology and neuropsychology.

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KEYWORDS

telerehabilitation; psychology; neuropsychology; equity; ethics; virtual rehabilitation; database; rapid review; Canada; telemedicine

Introduction

In previous years, the use of telerehabilitation (TR), also known as virtual rehabilitation, has rapidly increased [1-3]. TR is the branch of telehealth whose purpose is to remotely assess, monitor, or provide rehabilitation that best meets the patient's needs [4]. In the context of the COVID-19 pandemic, the public health system has been compelled to adjust its services in response to the emerging health crisis, which included making necessary changes in care delivery methods [4,5]. To comply with strict distancing regulations and protect vulnerable populations such as older adults and individuals with disabilities and chronic illnesses, TR has been suggested as a promising and viable alternative to traditional in-person health services while ensuring the continued delivery of essential rehabilitation services [6].

TR in neuropsychology and psychology can facilitate the assessment and treatment of psychological symptoms and disorders (eg, anxiety and depression), cognitive functions and impairments (eg, memory and attention), and interventions for psychological and cognitive problems (eg, psychotherapy and cognitive rehabilitation). TR approaches have been shown to be as effective as in-person care and has additionally been suggested as a means to enhance accessibility to health care services [3,7,8]. Indeed, systematic reviews have shown that virtual rehabilitation can be as effective as traditional services for patients with different conditions across their lifespan [9-16]. Furthermore, TR can improve access to care for rural populations, those with mobility challenges and individuals facing demanding work or caregiving responsibilities [7].

Despite its benefits, TR is a care model that is still in development, and as such, inconsistent and incomplete guidance can potentially affect the quality of care provided, especially for vulnerable populations such as individuals from lower socioeconomic backgrounds, those with low digital literacy, and rural populations. Ethical considerations in TR encompass fundamental principles such as integrity, accountability, independence and impartiality, respect for dignity, worth, equality, diversity, and privacy, and professional conduct [17]. In neuropsychology and psychology, these concerns manifest through challenges such as privacy threats due to the presence of family members during interventions, risks in security of sensitive data, or changes in the clinician-patient relationship [18]. Equity is another key concern in telehealth, defined as the absence of unfair, avoidable, or remediable differences between groups [19]. TR risks unintentionally exacerbating social and cultural disparities by requiring patients to have access to private electronic device supporting video consultation, stable high-speed internet, and a private space to conduct the intervention—resources that may be less accessible to underserved populations such as individuals from lower socioeconomic populations and those living in rural areas [20].

Neuropsychology and psychology clinicians, decision makers, and managers must navigate complex considerations associated with the implementation of TR in the COVID-19 and post–COVID-19 environment [21], while individuals with disabilities need support and resources to adapt to this new rehabilitation services model. Although existing research has explored the implementation of telehealth in neuropsychology and psychology, highlighting its feasibility, potential benefits and challenges, significant gaps remain in addressing the ethical and equity-related challenges specific to neuropsychological and psychological interventions within physical telerehabilitation. To harness the potential benefits of TR, it is essential to develop and apply robust guidance and tools addressing concerns related to inadequate and inequitable practices. This includes the need to address significant ethical issues for both clinicians and patients, such as proactively identifying and addressing potential inequities adversely affecting certain populations [22]. This review aims to fill this gap by focusing on the virtual delivery of care in the specific context of neuropsychology and psychology interventions in physical rehabilitation. This focus will provide more in-depth insights into these issues and more appropriately adapted solutions for this field of rehabilitation. By identifying existing barriers and proposing appropriate solutions, we aim to contribute to the development of equitable, evidence-based TR practices in these fields.

The proposed rapid review is one of a series of rapid reviews that are part of a larger cross-Canada study aimed at guiding policy-making and clinical practice to provide ethically sound and equitable virtual rehabilitation care. In order to better inform recommendations, a series of rapid reviews, conducted by field of TR, including in neuropsychology and psychology, are being conducted. Findings from the individual reviews will be combined to inform subsequent steps of the pan-Canadian study (surveys, interviews, and focus groups).

Methods

Study Design

A rapid review approach was chosen as the first step of this study. While systematic reviews offer the most comprehensive and rigorous evidence synthesis, they require significant time and resources and can quickly become outdated, particularly in a fast-evolving field such as TR [23]. A rapid review is more suitable for efficiently synthesizing and summarizing evidence in a timely manner [24], providing actionable results for an emerging topic. Given the dynamic nature of TR and the urgency of addressing its ethical and equity considerations, a rapid review ensures that findings remain current and readily available for informed decision-making. This study will provide up-to-date and contextualized scientific and ethical guidance to ensure that TR continues to be integrated into clinical practices and contribute to improve health equity and access to care in Canada.

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Search Strategy

This rapid review is conducted in two main phases: (1) a review of existing reviews on TR in the fields of neuropsychology and psychology and (2) a review of recent original articles in the field. Guided by an experienced health science librarian, an web-based search strategy was designed based on the PICOTSS (Population, Intervention, Comparison, Outcome, Timeframe, Study Design, and Setting) framework. Studies will be included in this review if they meet the following general inclusion criteria: (1) review articles published between 2010 and 2020 or original studies published between 2020 and 2023, (2) articles written in French or English, and (3) articles addressing TR and related terms with their main focus on neuropsychological and/or psychological evaluation and intervention rehabilitation activities conducted with patients with physical disabilities. Only peer-reviewed literature will be included, while gray literature and preprints will be excluded, given their extensive amount deemed unsuitable for the purpose and timeline of this rapid review. The search strategy will be designed for articles related to virtual care using specific keywords related to TR (eg, "telehealth," "e-health," "digital health," "m-health," and other synonymous terms), neuropsychology, and psychology. Three databases were selected (MEDLINE, CINAHL, and Embase) for their broad scope in medical literature, allowing a comprehensive overview of relevant TR reviews and studies. Reference lists of the included articles were not screened for additional studies, given the time-sensitive nature of this rapid review. The search strategy was designed to comprehensively capture relevant peer-reviewed literature, reducing the necessity of supplementary screening through reference lists. The full search strategy, including the exact syntax and search terms for all databases, is provided in Multimedia Appendix 1.

Eligibility Criteria

This rapid review follows the PICOTSS framework to ensure a structured study selection based on the research questions identified by the research team (see Table 1). To be included in the rapid review, studies needed to involve human individuals of diverse age groups receiving TR interventions in any setting with neuropsychological and/or psychological services aiming to supplement or replace in-person care. This includes both synchronous and asynchronous approaches, such as videoconferencing, phone calls, recorded videos, links to exercises, or educational materials. Studies needed to report outcomes related to ethical and equity components, efficacy of the intervention, engagement, acceptance, feasibility, and satisfaction, among others. Review articles (including systematic reviews, rapid reviews, narrative reviews, etc) were included from 2010 to 2020, while original study articles (within any design) were included if they were published between 2020 and 2023. These criteria were chosen to balance comprehensiveness and relevance. TR began to gain traction around 2010, with notable technological advancements and increased integration into health care systems shaping its evolution. Considering the scale of virtual rehabilitation literature, exclusively reviews published between 2010 and 2020 will be included to provide a broad and synthesized overview of key developments in the field during this period. This choice ensures that critical findings from earlier studies are incorporated while prioritizing synthesis of evidence and a manageable scope. The inclusion of original articles between 2020 and 2023, including those having been conducted during the COVID-19 pandemic, allow capturing of the most up-to-date advancements in technology, emerging ethical and equity concerns in response to rapid digital transformation, and changes in clinical practice. As information and communication technologies have evolved rapidly and become more readily available in the last few years [25], recent studies are essential to understanding current practices and challenges in TR implementation.

Table 1. Criteria for inclusion and exclusion of studies.

PICOTSS[a] criteria	Inclusion	Exclusion
Population	Human patients of all ages who receive telerehabilitation services with a neuropsychology or psychology intervention.	Animal studies.
Intervention	Telerehabilitation with a neuropsychology or psychology intervention intended to supplement or replace in-person care, including both synchronous and asynchronous interventions.	Studies with no direct interaction with a psychology or neuropsychology health care professional (eg, self-guided interventions without follow-up).
Comparison	Not applicable.	Not applicable.
Outcomes	Any outcome related to ethical and equity components, efficacy, engagement, acceptance, feasibility, and patient satisfaction, among others.	Outcomes not relevant to the review questions.
Timeframe	Studies conducted from January 2010 to March 2023.	Studies conducted before January 2010 and after March 2023.
Setting	All telerehabilitation settings (eg, outpatient, inpatient, home, nursing home, and hospital).	No exclusion.

[a]PICOTSS: Population, Intervention, Comparison, Outcome, Timeframe, Study Design, and Setting.

Data Collection

Data collection and extraction will take place using the screening and extraction software Covidence (Veritas Health Innovation). After identifying reviews and articles using the keywords, the data collection will follow 3 main steps. First, the reviews and articles will be screened based on their title and abstract. Second, the reviews and articles included in the first step will be

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examined by the reviewers based on the full text. Third, the data will be extracted from the included reviews and articles in data extraction tables and analyzed with team members for emerging and overarching themes. At each step, an independent verification of the data was performed by a second author on a random sample of 10% of the articles, following established recommendations for rapid reviews [26]. In the rare cases where consensus was not initially reached on inclusion or exclusion, discrepancies were resolved through discussion among all authors until full agreement was reached. Studies included in this review were critically appraised following the methodological guidance from the Cochrane Rapid Reviews—Interim Guidance from the Cochrane Rapid Reviews Method Group [26,27]. Moreover, the Equity-Based Framework for Implementation Research [28], the Quadripartite Ethical Tool [29], and the Consolidated Framework for Implementation Research [30] were used to guide the data collection and analysis. These guidelines provide structured recommendations to maintain rigor and reliability for analyzing barriers and facilitators to health care implementation. In fact, these frameworks provide a comprehensive approach to assess how ethical and equity issues manifest in TR implementation, ensuring that findings were contextualized within broader health care considerations. In accordance with Cochrane's rapid review guidelines, risk of bias assessment was limited to primary outcomes to optimize the feasibility of the rapid review process. Particular attention was paid to risk of biases in the methods and outcomes that could impact the ethical and equity aspects being examined in this study. By prioritizing risk of bias assessments for these outcomes, this approach ensures a focused evaluation of the most critical evidence while maintaining efficiency in the review process. Risk of bias was assessed by one reviewer and discussed with a second team member. Where discrepancies occurred, they were further discussed with the other team members. For example, the studies' inclusion and exclusion criteria for articles (for review articles) and study participants (for original articles) were examined for their risk of introducing bias. Lastly, studies were reviewed for potential missing data on key variables. Methodological gaps were noted and considered as part of the risk of bias assessment and reported in the synthesis.

Data will be extracted using a customized data extraction spreadsheet developed by one of the authors based on the study frameworks and adapted to the needs of psychological and neuropsychological fields by two of the authors. Characteristics of interest include (1) the field of therapy, (2) the clinical features (eg, patient population, technology used, outcome measures and tools used, and frequency of intervention), (3) study objectives and findings, (4) limitations (eg, ethical limitations), (5) the quality assessment and risk of bias, and (6) equity considerations.

Results

This review adhered to PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines (see PRISMA checklist in Multimedia Appendix 2). The search strategy was designed and performed in the 3 identified databases. Initial electronic database searches have retrieved 566 reviews and 2751 original articles meeting the search criteria. Articles have been exported to Covidence and were screened in accordance with the inclusion and exclusion criteria by 2 independent reviewers. Ultimately, 17 reviews and 82 original articles meeting the eligibility criteria were included for data extraction. Preliminary results from data extraction identified key concern dimensions with a focus on ethical and equitable aspects of TR. Ethical concerns centered on privacy, confidentiality, burden of care, and patient-clinician relationship quality and accessibility issues. Equity-related concerns focused on access to care, digital literacy, and socioeconomic disparities issues.

Discussion

Anticipated Findings

This paper describes the procedure of the first phase of our study: a rapid review that aims to synthesize evidence on the ethical and equity-related challenges associated with TR in neuropsychology and psychology in the context of physical rehabilitation. Through identification, analysis, and extraction of relevant data, this study will contribute to a more comprehensive understanding of current TR practices and challenges. The findings will serve as a foundation for informing subsequent steps in order to provide guidance to ensure ethically sound and equitable virtual rehabilitation practices. Particularly given the current rapid expansion of TR, it is essential to assess both its benefits and limitations in the context of neuropsychology and psychology. Research has demonstrated the feasibility and effectiveness of web-based neuropsychological and psychological interventions; yet, concerns persist regarding ethical and equity considerations. This study addresses an important need in the field of rehabilitation by contributing to filling a gap in the literature by identifying current challenges and emerging needs based on real-world implementation. Our review identified key ethical and equity-related barriers and facilitators associated with TR. Ethical concerns centered on privacy, confidentiality, the clinician-patient relationship, and potential burden of care. These concerns align with those reported in existing literature, which emphasizes that web-based neuropsychology and psychology interventions must address heightened risks related to data security, professional conduct, and patient privacy [31]. Equity-related issues were also a central theme, particularly regarding digital literacy, socioeconomic disparities, and access to technology. While TR has the potential to expand care to underserved populations, it may simultaneously exacerbate disparities: rural populations, older adults, and individuals from lower socioeconomic backgrounds are particularly vulnerable to being excluded from TR services due to technological and geographic barriers, among others. These findings reinforce concerns that TR must be implemented with an equity-driven approach to avoid widening health care access gaps [32].

Additionally, as part of a series of rapid reviews across rehabilitation fields, this study contributes to exploring TR in a multidisciplinary context. Understanding interdisciplinary collaboration in TR is crucial to fully understand the reality of TR and better inform practice, as rehabilitation often involves

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professionals from diverse fields working together to address complex patient needs. Such collaborative efforts have been shown to improve patient outcomes, enhance service efficiency, and patient satisfaction in rehabilitation [33]. Finally, the use of rapid reviews ensures a timely synthesis of a large body of evidence and current TR practices, enabling researchers to provide actionable results more efficiently.

To ensure the practical impact of this review, our findings will be summarized in targeted formats for different stakeholders, and a structured approach will be used to translate key themes identified in the review into actionable guidance. For example, recommendations for clinicians will be focused on ethical guidelines and best practices for patient engagement, while emphasis will be placed on organizational factors such as implementation strategies, costs, and training requirements for health care administrators. These tailored outputs will support decision-making at various levels, ensuring that TR implementation in neuropsychology and psychology is both effective and equitable.

Limitations

Despite its strengths, this work has some limitations worth acknowledging. First, the exclusion of gray literature restricts the scope of this rapid review. Information generated outside of traditional scientific peer-reviewed publications, such as government reports, policy briefs, and clinical guidelines, may offer additional insights into the real-world implementation of TR. However, given the substantial amount of scientific literature that is rapidly emerging and the methodological constraints of a rapid review, gray literature was excluded to maintain a rigorous and manageable scope. As a result, some findings may not be fully captured in our synthesis, impacting the applicability of recommendations, particularly in settings where institutional policies and practice-based knowledge play a significant role in shaping TR implementation. Future research could incorporate gray literature to supplement our findings. Moreover, in the context of this rapid review, we are not including telehealth practices in neuropsychology and psychology that are not in the field of rehabilitation (eg, mental health web-based services), although certain learnings from more general telehealth practices could inform TR practices. However, this restriction ensures that our findings are directly applicable to rehabilitation settings, and future studies comparing TR and general telehealth applications could help refine recommendations and make them more adaptable across health care settings. Additionally, the timeframe for included studies was chosen to balance historical perspectives with emerging evidence, particularly given the urgency of generating guidance for TR practices. However, some relevant original research published before 2020 and reviews published after 2020 may have contained relevant information for this review. It is possible that findings regarding ethical and equity considerations outside of these timeframes, such as evolving regulatory frameworks, engagement strategies, or new digital health tools, may not be fully reflected in our findings. This could affect the long-term relevance or our recommendations, reinforcing the need for continuous updates to TR guidelines. Finally, the rapid evolution of digital health technologies and telehealth policies means that TR practices will likely continue to change. As a result, some of the recommendations derived from this review may need adaptation over time.

Conclusions

In conclusion, the rapid expansion of TR use has presented not only new opportunities but also concerns about quality of care and equitable access to care in the context of neuropsychology and psychology interventions. This study thus aims, through this rapid review, to identify the impact of virtual care in psychology and neuropsychology on equity of access, patients' and caregivers' experiences, appropriate use, and the impact of TR on health care. Data emerging from this rapid review will be useful to better understand the issue at stake, namely TR practices in the context of neuropsychology and psychology practices, and along with the next steps of our study, contribute to better TR practices and improved rehabilitation care. Practical, evidence-based recommendations will be developed to guide the appropriate implementation of TR in neuropsychology and psychology. The findings from this study will allow us to cocreate impactful evidence-informed and practice-based recommendations and tools to guide clinical practice and policy and inform both clinical practice and broader health care decision-making. Ultimately, these will support the continued use of TR, inform policy and regulations, and ultimately optimize the health and well-being of people with disabilities.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Full search strategy.
[DOCX File , 23 KB - resprot_v14i1e66639_app1.docx]

Multimedia Appendix 2
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist.
[PDF File (Adobe PDF File), 797 KB - resprot_v14i1e66639_app2.pdf]

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Abbreviations

PICOTSS: Population, Intervention, Comparison, Outcome, Timeframe, Study Design, and Setting
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
TR: telerehabilitation

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Protocol

Telesimulation in Medical Education for High-Acuity Low-Occurrence Procedures and Clinical Encounters for Physicians and Medical Trainees in Emergency Medicine: Protocol for a Systematic Review

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Abstract

Background: Proficiency in high-acuity low-occurrence (HALO) procedures and clinical encounters is crucial for physicians and medical trainees in emergency medicine. Simulation-based medical education (SBME) provides valuable learning opportunities for these skills. However, accessing SBME can be challenging. Remotely delivered SBME, known as telesimulation, can enhance access to such training, especially in remote locations.

Objective: Based on this review, the research team aims to evaluate the effectiveness of telesimulation in enhancing learning outcomes of HALO procedures and clinical encounters in emergency medicine.

Methods: A systematic review will be conducted using the electronic databases PubMed, CINAHL, Embase, and Cochrane, focusing on studies published in English from 2011 to the present. The inclusion criteria are emergency physicians and medical trainees as learners; telesimulation sessions where the adequate performance of the procedure or clinical encounter, retention of information, or user feedback after implementing telesimulation were assessed; and original research in the form of a randomized controlled trial or nonrandomized experiments with an intervention and control group and pre- and posttest design. The exclusion criterion is defined as any study that does not fully meet the inclusion criteria. The primary outcome is the effectiveness of telesimulation in enhancing learning outcomes for HALO procedures and clinical encounters for physicians and medical trainees in emergency medicine. The secondary outcomes are the effectiveness of telesimulation for these procedures and clinical encounters delivered asynchronously and synchronously for physicians and medical trainees in emergency medicine. At least two reviewers will conduct data extraction and quality assessment. The primary and secondary outcomes will be analyzed through a systematic narrative synthesis. The methodological quality of comparative studies will be assessed using the Downs and Black checklist. The interrater reliability among the authors will be analyzed with Cohen κ.

Results: This project was funded in the summers of 2022 and 2023 by two Summer Undergraduate Research Awards from the Memorial University of Newfoundland Faculty of Medicine. The literature search and screening will begin in April 2025, and the results of the systematic review will be available in the summer of 2026.

Conclusions: The results of the systematic review could inform the development of research on telesimulation for HALO procedures in emergency medicine. By investigating this topic, more effective telesimulation sessions can be designed in the future, potentially enhancing the skills of physicians and medical trainees.

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KEYWORDS

assessment; task performance; medical education; emergency medicine; telesimulation; synchronous; asynchronous; medical education; simulation-based; physicians; medical trainees; emergency medicine; systematic review; proficiency; high-acuity low-occurrence; HALO

Introduction

Background

On-the-job experience is not always adequate in providing emergency physicians with the skills necessary for high-acuity low-occurrence (HALO) procedures and clinical encounters. This is because HALO procedures and clinical encounters may present in an intermittent and episodic nature to emergency departments, making it hard to plan for them. Exacerbated by the fact that these skills are particularly susceptible to degradation over time [1], frequent follow-up training is needed. Increasingly, educators are turning to simulation-based medical education (SBME) to provide physicians and medical trainees with learning opportunities for HALO procedures and clinical encounters [2-4]. SBME has been defined as any educational activity that uses simulative aids to replicate clinical scenarios [5]. SBME provides a learning environment where physicians and medical trainees can learn skills without compromising patient safety [6], and it has also been found to reduce health care costs by improving medical providers' competencies [5]. However, accessing SBME can be challenging for individuals working in rural or remote locations due to financial, geographical, and time constraints [7,8].

Some of these challenges have been overcome by using technology to remotely deliver this SBME; this is known as telesimulation [9-18]. Telesimulation is a type of SBME that has been defined as the use of telecommunication and simulation resources to provide education, training, assessment, and debriefing to learners at an off-site location [19]. The role of telesimulation is an active area of research in procedural task training, debriefing, and instruction delivery in critical care fields such as emergency medicine [19]. Using telesimulation, the instructor does not need to travel to the learners and vice versa. Other benefits of telesimulation include eliminating time barriers to educational content delivery, allowing for interinstitutional networking/collaboration, and providing a means for rapid dissemination of new content in medical education [19]. Additionally, the resources necessary for telesimulation have been described as free or low-cost [19].

Telesimulation in SBME is typically categorized as either asynchronous or synchronous. Asynchronous instruction involves using prerecorded video demonstrations to teach procedures or manage clinical scenarios and has been shown to be an effective teaching method [9,11]. Synchronous instructions, on the other hand, are delivered live to learners and have been shown to be just as effective as traditional methods [12-18].

Review Aims

The primary outcome of this study is to determine the effectiveness of telesimulation of HALO procedures and clinical encounters in enhancing learning outcomes for physicians and medical trainees in emergency medicine. Evaluating the effectiveness of telesimulation is important to ensure emergency physicians and medical trainees receive appropriate training for HALO procedures and clinical encounters. This includes, but is not limited to, procedures such as chest tube insertion and surgical airway management, and clinical scenarios such as managing anaphylaxis, ST-elevated myocardial infarction, and cardiac arrest. A systematic review was published in 2012 to evaluate the effectiveness of instruction design features of simulation-based training interventions [20]. Given the advances in technology over the last decade and ongoing research in telesimulation, further investigation is warranted. This is also supported by the ongoing shift to e-learning methods in emergency medicine established by the COVID-19 pandemic [21].

The secondary outcome of our study is to assess the effectiveness of telesimulation of HALO procedures and clinical encounters delivered asynchronously versus synchronously in enhancing learning outcomes for physicians and medical trainees in emergency medicine. One recommendation from the 2012 review was to investigate what simulation characteristics were effective for specific populations under certain conditions [20]. It also suggested focusing on comparing different types of simulations to assess effective design features [20]. Comparing asynchronous with synchronous instructions will explore these recommendations. Additionally, our study will investigate which methods are most effective for emergency medicine, a topic not well studied in the literature.

Our review will serve as a means of updating the literature on the use of telesimulation in emergency medicine since the review by Cook et al [20] over a decade ago. An updated understanding of telesimulation of HALO procedures and clinical encounters in emergency settings will allow for more effective planning of telesimulation to reach physicians and medical trainees in rural and remote areas where access to in-person SBME is limited.

Research Question

Primary Research Question

How does telesimulation for HALO procedures and clinical encounters impact the learning outcomes of emergency physicians and medical trainees?

Secondary Research Question

How does telesimulation for HALO procedures and clinical encounters delivered asynchronously versus synchronously impact the learning outcomes of emergency physicians and medical trainees?

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Methods

Systematic Review Design

We will include articles that focus on the delivery of telesimulation to teach or enhance the skills necessary for HALO procedures and clinical encounters in emergency medicine. Textbox 1 outlines the framework for the systematic review using a Population, Exposure, Comparator, Outcomes (PECO) structure, which is being registered on PROSPERO. It should be noted that "no instructions provided" refers to studies where learners did not receive instructions before participating in the telesimulation.

Textbox 1. Systematic review framework.

Population

- Emergency physicians or medical trainees as learners

Exposure

- Use of telesimulation for high-acuity low-occurrence (HALO) procedures and clinical encounters in emergency medicine

Comparator

- Use of in-person methods for HALO procedures and clinical encounters in emergency medicine

Outcomes

- Primary: ability to meet learning objectives such as performance of the procedure or clinical encounter
- Secondary: ability to retain information and user feedback on the learning experience

Primary

- Effectiveness of telesimulation in enhancing learning outcomes of HALO procedures and clinical encounters for physicians and medical trainees in emergency medicine

Secondary

- Effectiveness of telesimulation delivered asynchronously versus synchronously in enhancing learning outcomes of HALO procedures and clinical encounters for physicians and medical trainees in emergency medicine

Design (study)

- Eligible studies will include randomized controlled trials and nonrandomized experiments with intervention and control groups with a pre- and posttest design

Time range

- 2011 to present day

Search Strategy

The online databases to be used for the systematic review include CINAHL, Cochrane, Embase, and PubMed. MEDLINE will not be searched given it shares the same material as PubMed. The search strategy was developed by the project team and peer-reviewed by two medical education librarians with expertise in systematic reviews. Literature search strategies will use Medical Subject Headings (MeSH) and key concepts related to simulation-based training for emergency physicians and medical students. This includes "telesimulation," "medical education," "task performance," "assessment," and "emergency medicine." Common synonyms and alternative spellings of these concepts will be included in the search strategy.

The search will be limited to the English language. To ensure literature saturation, two researchers will review the cited references of all included articles. PROSPERO will be searched for ongoing or recently completed systematic reviews. As studies relevant to our project are identified, reviewers will assess for additional relevant cited and citing articles. Additionally, key studies identified by the team will be searched for in the results to ensure the validity of the search strategy.

An example of the search strategy for PubMed is demonstrated in Table 1. A similar strategy will be used for each database (Multimedia Appendix 1).

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Table 1. PubMed search strategy.

Search number	Query
1	((((“Simulation Training”[Mesh] OR “High Fidelity Simulation Training”[Mesh]) OR “Patient Simulation”[Mesh]) OR “Computer Simulation”[Mesh]) OR “Computer-Assisted Instruction”[Mesh]) OR “Educational Technology”[Mesh]
2[a]	simulation OR telesimulation
3	#1 OR #2
4	((“Education, Continuing”[Mesh]) OR “Education, Medical”[Mesh]) OR “Health Personnel/education”[Mesh:NoExp]
5[a]	“medical education” OR “continuing education” OR “virtual learning” OR “distance learning”
6	#4 OR #5
7	“Task Performance and Analysis”[Mesh]
8[a]	“technical skills” OR “technical skill” OR “task performance” OR ((procedure OR procedural OR procedures) AND train*) OR resuscitat*
9	#7 OR #8
10	(((“Educational Measurement”[Mesh:NoExp]) OR “Professional Competence”[Mesh]) OR “Comparative Effectiveness Research”[Mesh]) OR “Program Evaluation”[Mesh]
11[a]	assessment OR feedback OR evaluation OR measurement
12	#10 OR #11
13[a]	(“Emergency Medicine”[Mesh]) OR “Critical Care”[Mesh] OR “emergency medicine” OR “critical Care” OR emergen*
14	#3 AND #6 AND #9 AND #12 AND #13

[a]All fields searched.

Identification of Studies

The systematic review will follow the standard PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guideline study identification process [22]. This 2-stage process will start with a review of abstracts identified by the search strategy. At least two reviewers will independently screen titles and abstracts filtered by the inclusion criteria of the search. Any disagreement will be resolved through discussion, and the reasons for excluding literature will be documented. In the case that consensus is unable to be reached via discussion, a third researcher on the project team will review the study to make a final decision.

Literature search results will be uploaded to Covidence software. This software will be used to facilitate collaboration among reviewers throughout the study selection process. All team members involved with the review will receive training with the Covidence software before the start of the review.

Abstract Review

The initial review will examine the abstracts of the articles returned in the searches. To be relevant, an abstract must identify the use of some telesimulation component and involve HALO procedures and clinical encounters relevant to the field of emergency medicine.

Researchers will err on the side of inclusion. If an abstract does not clearly meet a requirement but seems related to the theme, it will be selected for full-text review. If a literature review (eg, narrative, scoping, or systematic) is identified by the search that seems applicable to the research question, the researchers will read the review to determine if any cited studies are relevant to include.

After relevant abstracts are identified, a full-text review will be completed to identify which studies meet all inclusion criteria. Researchers will use a standardized screening tool, based on the tool from Elzinga et al [23], to determine the inclusion eligibility of every study. The tool consists of four questions, each addressing a specific inclusion/exclusion criterion. The first question addresses the population and whether the study involves emergency physicians and medical trainees as learners. The second question focuses on the outcome studied. This includes whether the SBME session in the study evaluated adequate performance of the procedure or clinical encounter, retention of information, or user feedback after implementing telesimulation. Questions three and four focus on the methodology of the paper, which must be original research that is either a randomized controlled trial or nonrandomized experiment with an intervention and control group and pre- and posttest design. This screening tool is illustrated in Figure 1 [23].

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Figure 1. Full-text inclusion screening tool (adapted from Elzinga et al [23]). EMT: emergency medical technician; HALO: high-acuity low-occurrence.

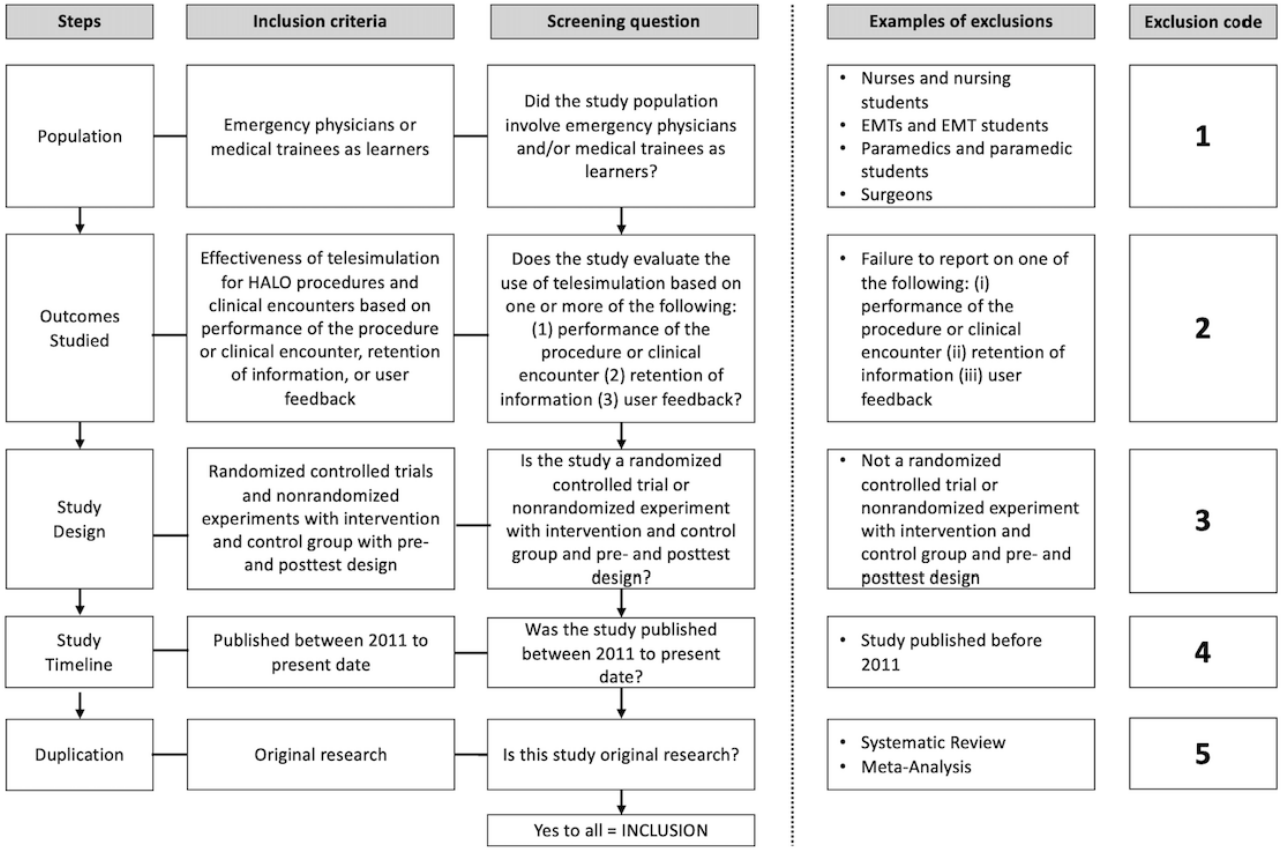

Data Extraction and Synthesis

Data extraction and quality assessment will be completed by at least two reviewers. Both reviewers will perform these tasks independently and then compare results, and any disagreements will be resolved through discussion. In the case that consensus is not met through discussion, a third researcher on the project team will review the article to make a final decision.

Review authors will use standardized data collection forms to ensure consistency while extracting data from reports. Data will be extracted into Microsoft Excel (version 16.96). This is included in Multimedia Appendix 2. The data extracted will include four themes (study characteristics, population characteristics, outcomes, and quality). Textbox 2 summarizes the themes within each.

Textbox 2. Data extraction variables.

Study characteristics

- Publication date, publication author, publication journal, study methodology, study geographic location, study time frame

Population characteristics

- Sample size, education level (medical student, resident, or staff physician), preexisting knowledge/skill level of high-acuity low-occurrence procedure or clinical encounter

Outcomes

- Primary: performance of the procedure or clinical encounter, retention of information, user feedback
- Secondary: comparison of primary outcomes for asynchronous versus synchronous telesimulation

Quality

- Downs and Black [24] checklist

Quality Assessment

The Downs and Black [24] checklist will be used to assess the methodological quality of the comparative studies. The checklist is comprised of 27 items addressing reporting, external validity, internal validity, and power. Recent systematic reviews have used the following cut points to categorize studies by quality: excellent (26-28), good (20-25), fair (15-19), and poor (≤14) [25,26].

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A standardized process will be implemented to ensure consistent understanding among authors on how to proceed with the abstract review, full-text review, data extraction, risk of bias, and Downs and Black [24] checklist. First, all authors will receive training on how to complete each step of the study. Then, authors will complete 10-20 papers and compare results. The interrater reliability will be analyzed with Cohen κ. Authors may proceed with the rest of the papers independently once very good agreement is achieved, defined by κ>0.80 [27]. If this is not achieved, the authors will go through retraining, and a new Fleiss κ will be measured. A final Cohen κ value will be calculated for author agreement at the abstract review, full-text review, data extraction, risk of bias, and Downs and Black [24] checklist stages. This value will be reported in the study results.

Data Analysis

The primary and secondary outcomes will be analyzed using a systematic narrative synthesis. The narrative synthesis will summarize and explain findings from studies filtered by the inclusion criteria. It will compare reports on the performance of the procedure or clinical encounter as well as the retention of information and user feedback within and between the included studies.

Results

This project was funded in the summers of 2022 and 2023 from two Summer Undergraduate Research Awards by Memorial University of Newfoundland's Faculty of Medicine, supporting preliminary literature search and the development of the research proposal and protocol. Additional funding was awarded in March 2025 through the Medical Education Research Fund Award from Memorial University of Newfoundland to support the systematic review.

The literature search and screening process is expected to begin in July 2025. An initial search conducted in July 2023 across four databases identified 3346 studies that met the search criteria. After exporting the citations to Covidence, a systematic review platform, 572 duplicates were removed, leaving 2759 articles for screening. Before screening, an additional search will be conducted to update the identified articles and ensure they are the most current. Title and abstract screening is scheduled to begin in July 2025, with two independent reviewers (KWT and QJ). Abstract screening and full-text review are expected to be completed by the end of October 2025. Data analysis will take place once the full texts have been approved by two independent reviewers (KWT and QJ). The two reviewers will extract all relevant data and key findings, and any discrepancies will be resolved with the principal investigator of the study (MHP). Results of this systematic review are expected to be available by the winter of 2026, aiming to complete the final paper by the summer of 2026.

Discussion

Expected Findings

SBME equips emergency physicians and medical trainees with the necessary skills to handle HALO procedures and clinical encounters [2-4]. Without SBME, these skills may be inadequately developed and maintained [1]. However, accessing SBME can be challenging due to financial, geographical, and time constraints [7,8], especially for those based in rural or remote areas [7,8]. Telesimulation has been shown to address these challenges and is as effective as traditional methods [9-18]. We anticipate that telesimulation for teaching HALO procedures and clinical encounters will be just as effective as other SBME methods. We also anticipate that synchronous telesimulation will be demonstrated as more effective than asynchronous telesimulation.

The method of delivering instructions in SBME has been widely studied [19]. Telesimulation is a popular approach using either synchronous or asynchronous instructions [9-18]. Given the advances in technology and the recent shift to internet-based learning due to the COVID-19 pandemic, further investigation into the effectiveness of telesimulation is warranted.

Limitations

Although many established HALO procedures and clinical encounters exist, their definition appears unclear [28]. Therefore, the selection of specific procedures and clinical encounters for inclusion or exclusion will be guided by those essential for training emergency physicians in Canada and further refined based on the search results. Additionally, other medical specialties beyond emergency medicine have published studies on using telesimulation in SBME for HALO procedures and clinical encounters. Therefore, this report may draw on studies conducted by specialists in other fields involving medical trainees as learners, provided they are relevant and applicable to emergency medicine, particularly if the search does not yield a sufficient number of studies for a comprehensive review.

This protocol serves as a guide for developing the scoping review but may not capture all relevant literature. Studies indexed in databases not included in the searches could be missed. Additionally, restricting the study's inclusion criteria to publications in English may exclude some relevant works. Despite these limitations, the review will provide key findings in the field and effectively address the proposed objectives.

Conclusion

This report describes the systematic review protocol that will be used to evaluate the effectiveness of telesimulation to enhance learning outcomes associated with HALO procedures and clinical encounters in emergency medicine. The timeline of this review will include studies published from 2011 to the present. The findings of our review can lead to the design and planning of more effective telesimulation sessions in the future, potentially enhancing the skills of practitioners and medical trainees.

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Acknowledgments

Two Summer Undergraduate Research Awards were awarded for completion of this protocol by Memorial University of Newfoundland's Faculty of Medicine. The first was a 4-week research grant awarded to KWT in the summer of 2022 valued at CAN $1600 (US $1236). The second was a 4-week research grant awarded to KWT in the summer of 2023 valued at CAN $1600 (US $1236).

Authors' Contributions

Methodology: KWT, JJ, QJ, MHP
Investigation: KWT
Writing – original draft: KWT
Writing – review and editing: KWT, JJ, QJ, MHP
Conceptualization: JJ, RM, MHP
Project administration: JJ, MHP
Funding acquisition: MHP
Supervision: MHP

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategies for databases.
[PDF File (Adobe PDF File), 1266 KB - resprot_v14i1e53565_app1.pdf]

Multimedia Appendix 2
Data extraction tool.
[XLSX File (Microsoft Excel File), 9 KB - resprot_v14i1e53565_app2.xlsx]

Multimedia Appendix 3
PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015 checklist.
[DOCX File , 27 KB - resprot_v14i1e53565_app3.docx]

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Abbreviations

HALO: high-acuity low-occurrence
MeSH: Medical Subject Headings
PECO: Population, Exposure, Comparator, Outcomes
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SBME: simulation-based medical education

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Protocol

The Prevalence of Hypertension Among Children and Antihypertensive Use: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Early-onset hypertension (HT) presents compounded risks for cardiovascular, renal, and other systemic complications. Childhood HT is associated with HT during adulthood and detrimental lifelong cardiovascular disease events. However, most of the cases are not detectable as HT measurement in children is complicated and unstable. The global prevalence of HT among children is rapidly increasing. A previous study (2019) reported that the pooled global HT prevalence is 4.0% and the number is believed to be elevated. However, prevalence estimates of childhood HT have rarely been synthesized globally.

Objective: This study aims to systematically pool all evidence from published articles and synthesize the evidence on the global prevalence of childhood HT and antihypertensive (anti-HT) use among children and its effects.

Methods: This systematic review of observational and experimental studies will investigate the overall prevalence of HT and anti-HT use among children. We will search articles from 4 web-based databases: PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, and Scopus using the specific keywords across the databases. During the article search conducted until October 2024, we retrieved 14,575 articles. Articles published in the English language with full text and are peer-reviewed journals included children aged between 0 and 18 years, confirmed with HT or high blood pressure (BP) on at least 3 separate occasions, and stated the definition of HT will be included in this protocol. Study selection and reporting will follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and the Meta-Analysis of Observational Studies in Epidemiology guidelines and Cochrane Risk of bias tool (ACROBAT) for experimental studies. Data will be extracted using a standardized data extraction form using Microsoft Excel software and the studies' quality will be assessed using the Joanna Briggs Institute's guideline according to the study design. We will use STATA software (version 17.0; StataCorp LLC) to calculate the global pooled prevalence and RevMan software (version 5.4; StataCorp LLC) to observe the effect of anti-HT use and BP among children. The risk of bias will be assessed using a funnel plot.

Results: We retrieved 14,575 articles from 4 databases in October 2024. We will report the current global overall or pooled prevalence of HT as well as by region, risk factors, anti-HT use, and the anti-HT BP-lowering effect among the general children population. The findings will be presented in summary table findings and forest plot. This review is expected to be completed in the middle of 2025.

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Conclusions: This review will provide a comprehensive synthesis of the overall prevalence of HT among children—a public health issue of growing concern with long-term impact. This review will also provide important information to inform practice in developing effective strategies for preventing and managing childhood HT.

Trial Registration: PROSPERO CRD42024500248; https://www.crd.york.ac.uk/PROSPERO/view/CRD42024500248

International Registered Report Identifier (IRRID): PRR1-10.2196/65807

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KEYWORDS

children hypertension; protocol; systematic review; meta-analysis; hypertension; children; anti-hypertensive; prevalence; childhood hypertension; risk factor; teenager; HPN; high blood pressure; blood pressure

Introduction

Overview

Hypertension (HT) occurs when the blood pressure (BP) is elevated above the normal range. It is a major risk factor for cardiovascular diseases (CVD), chronic kidney disease, and a major cause of death [1]. Studies have suggested HT in childhood to be associated with essential HT in adulthood [2,3]. However, childhood HT is less commonly studied and reported than adult HT [4] and receives less attention in public health [5]. Globally, confirmed HT is prevalent in 2%-4% of children [6]—as also demonstrated in the United States (2.2%-3.9%) [7]. Whereas in the African and Asian continents, the pooled prevalence of HT among children is 5.5% (Africa) [8], 18.4% (China) [9], and 29.8% (India) [10].

Evidence from pathophysiological and epidemiological studies suggests that essential HT and precursors of CVDs (atherosclerosis, stroke, left ventricular hypertrophy, and decreased cognitive function) [11], begin in childhood but often go unnoticed unless specifically monitored [3]. Genetics and lifestyle factors are associated with HT [12-14]. For example, high salt intake increases the risk of HT in young people [15] and high BMI during adolescence is associated with an increased risk of developing HT or CVD in adulthood [16].

Early intervention is important to reduce the burden and future complications of HT [1]. The effects of antihypertensive (anti-HT) from the classes of diuretics, beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, calcium channel blockers, and vasodilators on children have been investigated [17-19]. However, there is scarce evidence on the association between anti-HT and the decrease of BP in children. Therefore, we will conduct a systematic review and meta-analysis to synthesize the evidence on the current global overall or pooled prevalence of HT, risk factors, anti-HT use, and the anti-HT BP-lowering effect among the general children population.

Review Questions

1. What is the estimated pooled prevalence for children globally, and by regions (Asia, Africa, Europe, Oceania, North and South America)?
2. What is (are) the type of anti-HT medication(s) taken by children and the estimated decrease of the mean systolic BP and diastolic BP?
3. What are the risk factors associated with HT among children?

Methods

Overview

This protocol is registered with the International Prospective Register of Systematic Review (PROSPERO) and the review will be conducted and reported following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-analysis) protocol [20].

Study Design

We will include all empirical study designs including observational (eg, case control, cohort, and cross-sectional) and experimental studies (randomized controlled trial [RCT], non-RCT, and cluster RCT) to capture all desired outcomes. No restriction will be imposed on the date of publication and sample size.

Study Area

We will include all published studies with information on HT among children globally and divide the studies according to the regions.

Type of the Participants

We will include primary studies that investigated children (0 to 18 years old) that provide estimates of any stage of systemic HT, prehypertension, or systolic or diastolic HT. If we find studies that were conducted for both adults and children, we will separate the prevalence data of HT for children (0-9 years) or adolescents (10-18 years) following the World Health Organization classification [21]. If the data is not amenable to the World Health Organization classification, we will contact the author to obtain clarification/data in studies.

We will include studies that explicitly describe the methods of measuring BP, definitions of HT, initial systolic BP and diastolic BP, posttreatment systolic BP and diastolic BP, anti-HT medication used, duration of treatment, dosage, sample size, number of individuals with HT, prevalence of HT, and others. Studies with BP measurements with a minimum of 3 separate readings are also eligible to be included. We will exclude studies on the adult population (aged 19 years and older), or any population with abnormal groups or conditions such as obese and disabled children or children with specific diseases. We will also exclude articles that do not explain the definition of

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HT, include at least 3 BP measurements, are not in English, or whose full text is unattainable. Editorials, review articles, letters to the editor, abstracts and poster presentations will also be excluded from this review. If we find multiple articles with the same data, then we will use the study with the largest sample size. Findings will be presented in tables and figures.

Type of Outcome Measures

The primary outcome will be the pool prevalence of HT among children. We will measure the pool prevalence according to different age groups such as younger than 7 years, between 7 and 12 years, and older than 12 years to 18 years, if the data are available. Secondary outcomes will be HT associated with morbidity such as stroke, coronary heart disease, diabetes, or end-stage renal disease; types of anti-HT intake; the decrease of systolic BP and diastolic BP number after anti-HT intake; and the effect of anti-HT on the BP.

Searching Methods for Identification of Studies

Electronic Search

We will search using 4 databases—PubMed, Cochrane Central Register of Controlled Trials (CENTRAL), Embase, and Scopus—to identify eligible studies. There is no restriction on the publication date, however, the language will be restricted to English. The search will be performed up to October 2024.

Search Strategy

The proposed search term for the first theme will be "hypertension"—which includes high BP or HT or HTN or HBP. The second theme is "children" including adolescents (aged 10-18 years) or neonates. The third theme is "antihypertensive medication," which includes all classes of anti-HT medication, and the other similar name used. The PICO (Population, Intervention, Comparison, and Outcomes) framework will be used during the article search; "P (population)" refers to children, and "O (outcome)" refers to risk factors, anti-HT medications taken to estimate the decrease of the mean systolic BP and diastolic BP. Both "I (Intervention)" and C "(comparisons)" aspect is not included in this review. Table 1 lists the search strategy using PICO framework. The exploded versions of MeSH (Medical Subject Headings) will be used for the first theme. All themes will be searched for using "AND" in combination. The details for the proposed search terms for all the databases are listed in Textbox 1.

Table 1. Search strategy using the PICO (Population, Intervention, Comparison, and Outcomes) frameworks.

PICO elements	Keywords
Population	Children aged 0-18 years with hypertension
Intervention	N/A[a]
Comparison	N/A
Outcomes	Prevalence, risk factor, anti-HT[b], and the decrease of BP[c]

[a]Not applicable.

[b]anti-HT: antihypertensive.

[c]BP: blood pressure.

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Textbox 1. Proposed search terms.

PubMed

Search: Hypertension OR HTN OR HT [MeSH Terms]

AND

Child*[Title/Abstract]) OR (Adolescent*[Title/Abstract] OR (Neonate*[Title/Abstract] OR (Teenager*[Title/Abstract] OR (Toddler*[Title/Abstract] OR (Newborn*[Title/Abstract] OR (Infant*[Title/Abstract] OR (Youth*[Title/Abstract] OR (Boy [Title/Abstract] OR (Boys[Title/Abstract] OR (Girl*[Title/Abstract] OR (Youngster*[Title/Abstract]

AND

Hypertension [Title/Abstract] OR (High blood pressure [Title/Abstract] OR (Elevated blood pressure [Title/Abstract]) OR (HT[Title/Abstract] OR (HBP[Title/Abstract] OR (HTN[Title/Abstract]

AND

Prevalence [Title/Abstract] OR (Epidemiology [Title/Abstract] OR (Population [Title/Abstract] OR (Blood pressure [Title/Abstract]

AND

Antihypertensive medication[Title/Abstract] OR (Antihypertensive drug[Title/Abstract] OR (Anti-HTN[Title/Abstract] OR (Anti-HT[Title/Abstract] OR (Diuretics[Title/Abstract]) OR (Thiazide[Title/Abstract]OR (Hydrochlorothiazide[Title/Abstract] OR (Bendroflumethiazide[Title/Abstract] OR (Loop[Title/Abstract]) OR (Furosemide[Title/Abstract] OR (Bumetanide[Title/Abstract] OR (Torsemide[Title/Abstract] OR (Potassium sparing[Title/Abstract] OR (Distal, potassium retaining[Title/Abstract] OR (Spironolactone[Title/Abstract] OR (Eplerenone[Title/Abstract] OR (Combination diuretics[Title/Abstract] OR (Spironolactone + hydrochlorothiazide[Title/Abstract] OR (Spironolactone and hydrochlorothiazide[Title/Abstract] OR [Beta-blockers[Title/Abstract]) OR (Propranolol[Title/Abstract] OR (Inderal[Title/Abstract] OR (Atenolol[Title/Abstract] OR (Metoprolol tartrate[Title/Abstract] OR (Metoprolol succinate[Title/Abstract] OR (Labetalol[Title/Abstract] OR (Bisoprolol[Title/Abstract] OR (Carvedilol phosphate[Title/Abstract] OR (Combination beta-blocker/diuretic[Title/Abstract] OR (Combination beta-blocker and diuretic[Title/Abstract] OR (Hydrochlorothiazide[Title/Abstract] and bisoprolol[Title/Abstract] OR (Hydrochlorothiazide + bisoprolol[Title/Abstract] OR ACE inhibitors[Title/Abstract] OR (Angiotensin Converting Enzyme Inhibitors[Title/Abstract] OR (ACEI[Title/Abstract] OR (Benazepril[Title/Abstract] OR (Captopril[Title/Abstract] OR (Enalapril[Title/Abstract] OR (Fosinopril [Title/Abstract] OR (Lisinopril[Title/Abstract] OR (Moexipril[Title/Abstract] OR (Quinapril[Title/Abstract] OR (Ramipril[Title/Abstract] OR (Perindopril[Title/Abstract] OR (ARB[Title/Abstract] OR (Angiotensin receptor blockers[Title/Abstract] OR (Angiotensin II receptor blockers[Title/Abstract] OR (Candesartan[Title/Abstract] OR (Irbesartan[Title/Abstract] OR (losartan[Title/Abstract] OR (Olmesartan[Title/Abstract] OR (Telmisartan[Title/Abstract] OR (Valsartan[Title/Abstract]OR (Calcium channel blockers (CCB[Title/Abstract]OR (Calcium channel blockers[Title/Abstract] OR (Calcium channel antagonists[Title/Abstract])OR (Dihydropyridine group[Title/Abstract] OR (Amlodipine[Title/Abstract] OR (Felodipine[Title/Abstract])) OR (Nifedipine[Title/Abstract] OR (Nifedipine LA[Title/Abstract] OR (Nicardipine[Title/Abstract] OR (Isradipine[Title/Abstract] OR (Clonidine[Title/Abstract] OR ((Nondihydropyridine group[Title/Abstract] OR (Verapamil[Title/Abstract] OR (Alpha blockers[Title/Abstract] OR (Doxazosin[Title/Abstract]OR (Prazosin[Title/Abstract] OR (Terazosin hydrochloride[Title/Abstract] OR (Alpha-2 receptor agonists[Title/Abstract] OR (Methyldopa[Title/Abstract] OR (Guanfacine[Title/Abstract] OR (Vasodilators[Title/Abstract] OR (Hydralazine[Title/Abstract]OR (Minoxidil[Title/Abstract]

Scopus

TITLE-ABS-KEY (Child*OR Adolescent* OR Neonate*OR Teenager* OR Toddler*OR Newborn* OR Infant*OR Youth* OR Boy OR Boys OR Girl* OR Youngster*)

AND

TITLE-ABS-KEY (Hypertension OR “High blood pressure” OR “Elevated blood pressure” OR HT OR HBP OR HTN)

AND

TITLE-ABS-KEY (“Antihypertensive medication” OR “Antihypertensive drug” OR “Anti-HTN” OR “Anti-HT” OR Diuretics OR Thiazide OR Hydrochlorothiazide OR Bendroflumethiazide OR Loop OR Furosemide OR Bumetanide OR Torsemide OR “Potassium sparing” OR Distal OR “potassium retaining” OR Spironolactone OR Eplerenone OR “Combination diuretics” OR “Spironolactone + hydrochlorothiazide” OR “Spironolactone and hydrochlorothiazide” OR “Beta-blockers” OR Propranolol OR Inderal OR Atenolol OR “Metoprolol tartrate” OR “Metoprolol succinate” OR Labetalol OR Bisoprolol OR “Carvedilol phosphate” OR “Combination beta-blocker/diuretic” OR “Combination beta-blocker and diuretic” OR “Hydrochlorothiazide and bisoprolol” OR “Hydrochlorothiazide + bisoprolol” OR “ACE inhibitors” OR “Angiotensin Converting Enzyme Inhibitors” OR ACEI OR Benazepril OR Captopril OR Enalapril OR Fosinopril OR Lisinopril OR Moexipril OR Quinapril OR Ramipril OR Perindopril OR “Angiotensin receptor blockers” OR ARB OR “Angiotensin II receptor blockers” OR Candesartan OR Irbesartan OR losartan OR Olmesartan OR Telmisartan OR Valsartan OR “Calcium channel blockers” OR CCB OR “Calcium channel antagonists” OR “Dihydropyridine group” OR Amlodipine OR Felodipine OR Nifedipine OR “Nifedipine LA”OR Nicardipine OR Isradipine OR Clonidine OR “Nondihydropyridine group” OR Verapamil OR “Alpha blockers” OR Doxazosin OR Prazosin OR “Terazosin hydrochloride” OR “Alpha-2 receptor agonists” OR Methyldopa OR Guanfacine OR Vasodilators OR Hydralazine OR Minoxidil

CENTRAL (Cochrane Central Register of Controlled Trials)

MeSH descriptor: [Hypertension OR HTN OR HT] explode all trees

AND

Search: Hypertension OR HTN OR HT [MeSH Terms]

AND

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Child*[Title/Abstract]) OR (Adolescent*[Title/Abstract])) OR (Neonate*[Title/Abstract])) OR (Teenager*[Title/Abstract])) OR (Toddler*[Title/Abstract])) OR (Newborn*[Title/Abstract])) OR (Infant*[Title/Abstract])) OR (Youth*[Title/Abstract])) OR (Boy[Title/Abstract])) OR (Boys[Title/Abstract])) OR (Girl*[Title/Abstract])) OR (Youngster*[Title/Abstract]))

AND

Hypertension [Title/Abstract] OR (High blood pressure [Title/Abstract] OR (Elevated blood pressure [Title/Abstract]) OR (HT[Title/Abstract] OR (HBP[Title/Abstract] OR (HTN[Title/Abstract]

AND

Prevalence [Title/Abstract] OR (Epidemiology [Title/Abstract] OR (Population [Title/Abstract] OR (Blood pressure [Title/Abstract]

AND

Antihypertensive medication[Title/Abstract] OR (Antihypertensive drug[Title/Abstract] OR (Anti-HTN[Title/Abstract] OR (Anti-HT[Title/Abstract] OR (Diuretics[Title/Abstract]) OR (Thiazide[Title/Abstract]OR (Hydrochlorothiazide[Title/Abstract] OR (Bendroflumethiazide[Title/Abstract] OR (Loop[Title/Abstract]) OR (Furosemide[Title/Abstract] OR (Bumetanide[Title/Abstract] OR (Torsemide[Title/Abstract] OR (Potassium sparing[Title/Abstract] OR (Distal, potassium retaining[Title/Abstract] OR (Spironolactone[Title/Abstract] OR (Eplerenone[Title/Abstract] OR (Combination diuretics[Title/Abstract] OR (Spironolactone + hydrochlorothiazide[Title/Abstract] OR (Spironolactone[Title/Abstract] and hydrochlorothiazide[Title/Abstract] OR [Beta-blockers[Title/Abstract]) OR (Propranolol[Title/Abstract] OR (Inderal[Title/Abstract] OR (Atenolol[Title/Abstract] OR (Metoprolol tartrate[Title/Abstract] OR (Metoprolol succinate[Title/Abstract] OR (Labetalol[Title/Abstract] OR (Bisoprolol[Title/Abstract] OR (Carvedilol phosphate[Title/Abstract] OR (Combination beta-blocker/diuretic[Title/Abstract] OR (Combination beta-blocker[Title/Abstract] and diuretic[Title/Abstract] OR (Hydrochlorothiazide[Title/Abstract] and bisoprolol[Title/Abstract] OR (Hydrochlorothiazide + bisoprolol[Title/Abstract] OR ACE inhibitors[Title/Abstract] OR (Angiotensin Converting Enzyme Inhibitors[Title/Abstract] OR (ACEI[Title/Abstract] OR (Benazepril[Title/Abstract] OR (Captopril[Title/Abstract] OR (Enalapril[Title/Abstract] OR (Fosinopril[Title/Abstract] OR (Lisinopril[Title/Abstract] OR (Moexipril[Title/Abstract] OR (Quinapril[Title/Abstract] OR (Ramipril[Title/Abstract] OR (Perindopril[Title/Abstract] OR (ARB [Title/Abstract] OR (Angiotensin receptor blockers[Title/Abstract] OR (Angiotensin II receptor blockers[Title/Abstract] OR (Candesartan[Title/Abstract] OR (Irbesartan[Title/Abstract] OR (losartan[Title/Abstract] OR (Olmesartan[Title/Abstract] OR (Telmisartan[Title/Abstract] OR (Valsartan[Title/Abstract]OR (Calcium channel blockers (CCB[Title/Abstract]OR (Calcium channel blockers[Title/Abstract] OR (Calcium channel antagonists[Title/Abstract])OR (Dihydropyridine group[Title/Abstract] OR (Amlodipine[Title/Abstract] OR (Felodipine[Title/Abstract])) OR (Nifedipine[Title/Abstract] OR (Nifedipine LA[Title/Abstract] OR (Nicardipine[Title/Abstract] OR (Isradipine[Title/Abstract] OR (Clonidine[Title/Abstract] OR ((Nondihydropyridine group[Title/Abstract] OR (Verapamil[Title/Abstract] OR (Alpha blockers[Title/Abstract] OR (Doxazosin[Title/Abstract]OR (Prazosin[Title/Abstract] OR (Terazosin hydrochloride[Title/Abstract] OR (Alpha-2 receptor agonists[Title/Abstract] OR (Methyldopa[Title/Abstract] OR (Guanfacine[Title/Abstract] OR (Vasodilators[Title/Abstract] OR (Hydralazine[Title/Abstract]OR (Minoxidil[Title/Abstract]

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AND

(Child*[Title/Abstract] OR (Adolescent*[Title/Abstract] OR (Neonate*[Title/Abstract] OR (Teenager*[Title/Abstract] OR (Toddler*[Title/Abstract] OR (Newborn*[Title/Abstract] OR (Infant*[Title/Abstract] OR (Youth*[Title/Abstract] OR (Boy*[Title/Abstract] OR (Girl*[Title/Abstract] OR (Youngster*[Title/Abstract]

AND

(Hypertension[Title/Abstract] OR (High blood pressure[Title/Abstract] OR (Elevated blood pressure[Title/Abstract OR (HTN[Title/Abstract]] OR (HT[Title/Abstract] OR (HBP[Title/Abstract]

AND

(Prevalence [Title/Abstract] OR (Blood pressure [Title/Abstract] OR (Risk factor*[Title/Abstract]

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Data Collection and Analysis

Selection of Studies

Two review authors (NAZZ and NLMN) will independently screen for titles and abstracts to identify the potential studies to be included. The studies will be identified and coded as "retrieve" (studies to be included, with potential to be included, or unclear) or "do not retrieve" (studies to be excluded). We will also identify and exclude duplicate studies. Two authors (KM and SZSAY) will retrieve the full text and review them against the inclusion and exclusion criteria along with the justifications. We will resolve any disagreement between the 2 reviewers via discussion or rechecking the full text. If a consensus cannot be reached, a third author (NHM) will deliberate.

We will record the selection process in sufficient detail to complete a PRISMA flow diagram [20,22] as shown in Figure 1. This review will use The Mendeley Reference Management Software [23] to store, arrange, and manage all articles identified from the databases.

Figure 1. PRISMA flow chart.

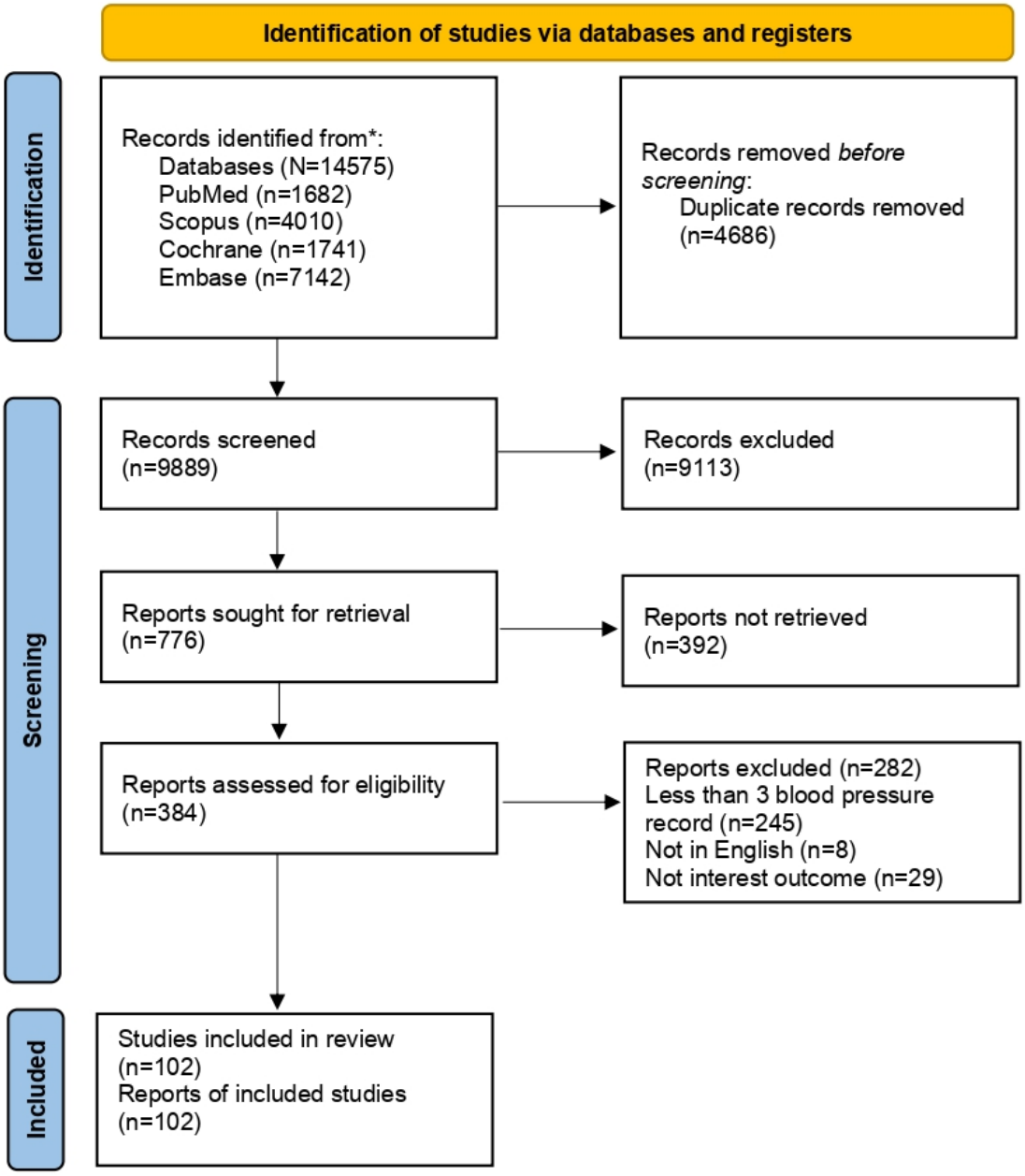

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Data Extraction and Management

We will use a standardized data extraction created in the Online Microsoft Excel Spreadsheet for study characteristics and outcome data to capture comprehensive information pertinent to the research question. Two review authors (KM and SZSAY) will independently extract the data from the included studies. If there is any disagreement on the data extraction, both authors will discuss and consult with 2 other authors (NAM and LLM). We will extract the following study characteristics from the included studies:

- Authors, year, title, country, region
- Participants: Total participants, HT individuals, age, sex, BMI, wrist and waist circumference, and risk factor for HT (such as family history or disease)
- Methods: Study design
- Analysis: Method used to measure BP reading, how many BP reading is repeated (measure at least 3 separate occasions), type of anti-HT used, the SBP and DBP reading after consumption of anti-HT, whether the patient also had another disease or comorbidities.

If there is any unclear data from the studies, we will validate it by contacting the corresponding author to provide any unclear, missing, or additional details.

Quality Assessment

The study's quality will be evaluated using the Joanna Briggs Institute's checklist by 3 review authors (NHM, NAZZ, and NLMN) independently. Any discrepancies in the assessment will be addressed through discussion among reviewers until a consensus is reached. Numerous Joanna Briggs Institute scales will be used in this review based on the type of study design (either cross-sectional, case-control, or cohort study). If we find experimental studies, we will use the ACROBAT NSI or Cochrane risk of bias tool to judge the study quality. The overall appraisal of the articles which are the potential to be included will be defined as either to include, exclude, or seek further info [24].

Statistical Analysis

Data will be analyzed using STATA (version 17.0; StataCorp LLC) and RevMan software (StataCorp LLC). Statistical analysis will be divided into regions, age (preschool [less than 6 years old], elementary [7-12 years], and adolescent [13-18 years old]), device, and BMI. We will perform descriptive analysis and calculate the overall pool prevalence of HT among children using a random effect model to allow heterogeneity across the included studies and later divide the studies into regions. Freeman-Turkey transformation (arcsine square root transformation) will be applied to overcome the limitation of meta-analysis in prevalence studies as some of the included articles will have very low or very high prevalence. Having a wide range of prevalence values can result in disproportionately high weight due to the significant decrease in their inferred variance towards 0 [25]. The Freeman-Turkey transformation will be used for pooling to obtain a synthesized point estimate of prevalence with a 95% CI [26].

In addition to reporting the use of anti-HT medication, dosage, and duration of taking anti-HT, we will also document any other comorbidities or complications experienced by the patients. The mean and SD of BP readings (systolic BP and diastolic BP) before and after taking anti-HT medication will be recorded and analyzed in the RevMan software. We will also perform a meta-analysis to identify the risks and measure the effect of the intervention. A forest plot will be created for each pool estimate, and the distribution will be presented graphically. We plan to create a funnel plot if 10 or more studies are available to pool in a meta-analysis to assess reporting biases. We will assess funnel plot asymmetry visually. We will use a linear regression test to analyze the degree of publication bias with a P value of <.10 indicating significance for this test [27,28]. If the funnel plot is asymmetrical, (caused by a relationship between the effect size and sample size, or by publication bias), we will examine any observed effect for clinical heterogeneity [29]. Besides the funnel plot, we will also apply the Egger test to assess potential publication bias in meta-analysis [30].

We will conduct a meta-analysis by pooling the appropriate data using Cochrane's statistical software, considering studies to be sufficiently similar in terms of population category, intervention, comparison, and outcome [31]. We will use a random effect model for pooled data. We will consider not pooling data if we encounter considerable heterogeneity (I^2 of 75% or more) across studies. We will follow the strategies in the Cochrane Handbook for Systematic Reviews of Interventions for data management [27,28]. For multiple-arm studies, we will adjust the data following the methods described in the Cochrane Handbook for Systematic Reviews of Interventions [27,28]. For 2 arms that are relevant, we will include the relevant arms. If there are more than 2 relevant arms (eg, A vs control), we will set up separate pair-wise comparisons.

Assessment of Heterogeneity

We will visually inspect the forest plots for any evidence of heterogeneity. We will assess heterogeneity using both Q test and I^2 statistics. The I^2 statistic will be used to quantify the impact of heterogeneity while Q test will be used to identify whether there is a significant heterogeneity occurring in the included studies. We will set the significance level for the Q test at 0.01 [32] while the I^2 level of 75% indicates a substantial degree of heterogeneity. We will adopt a higher threshold of I^2 in this due to heterogeneity inherent in the possible included article.

If the I^2 of the overall studies is below 75%, the random effect model will be applied in the meta-analysis to overcome the inherent heterogeneity that might be highly present among different prevalent studies [33]. If significant heterogeneity is detected using the I^2 index (>75%), we will investigate potential sources of heterogeneity using subgroup analyses and meta-regression. Subgroup analysis will be performed for the different study designs, gender, age, region, and specific risk factors using STATA software (version 17.0). Meta-regression will be performed using the same software. The possible causes will be explored and evaluated for their methodological characteristics to determine whether the degree of heterogeneity

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can be explained by differences in those characteristics and if a meta-analysis is appropriate. The overall prevalence and 95% CI estimate of individual studies will be presented in forest plots [4,34].

Dissemination

This review will target a specific scientific publication targeting children as the population in their journals such as *The Journal of Pediatrics*, *Pediatrics*, *Journal of Child Health Care*, *Clinical Pediatrics*, and others. We also plan to publish in a high-impact journal that is suitable for our topic such as BMJ, PLOS, and JMIR. Few findings will be presented in the conferences both local and international as well as in any pediatric conference event. The preliminary findings will be presented to the Pediatric Clinical Practice, Ministry of Health Malaysia. This review will also help the clinicians to decide the best treatment for the patients and might be used as a reference during making documents for clinical practice guidelines for HT in children. We will also produce plain language summaries that will be shared with the public such as social media and health care websites.

Ethical Considerations

We have registered this systematic review with the National Medical Research Register, Ministry of Health Malaysia (National Medical Research Register ID-24-00078-A7A). Since this review will only include published articles, ethical approval is not needed. This protocol has been registered with PROSPERO (CRD42024500248).

Results

Article search will be performed in October 2024 and any articles published from inception until October 2024 will be included in this study before abstract and title screening. A total of 14,575 articles were retrieved from the 4 databases and the remaining 9889 articles were remaining for the title and abstract screening. About 776 articles are sought for retrieval and 384 articles will be screened for data extraction and eligibility (Figure 1). The findings will be visually presented in a summary of findings and a forest plot. The review is expected to be complete and published by the middle of 2025. Results on the global overall or pooled prevalence of HT, risk factors, anti-HT use, and the anti-HT BP-lowering effect among the general children population will be presented in this manuscript. Analysis for observational studies such as cohort, case-control, and cross-sectional and experimental studies will be analyzed separately.

Discussion

Principal Findings

The increased prevalence of HT among children between 2% and 5% contributed to significant challenges to public health and the economy [35]. Additionally, a previous review conducted in 2019 reported a global prevalence of HT in children at 4.0% [34], while the most recent study on BP and anti-HT was reported in 2018 [36,37]. It shows that the prevalence of HT among children is increasing yearly. Additionally, to the best of our knowledge, there is no available review on the prevalence, anti-HT, and decrease of the BP and risk factors among children were discussed in one paper. The strength of this review is rooted in the broad scope undertaken in HT among children. Therefore, the aim of this review is to highlight the updated overall prevalence of HT among children globally, drug therapy prescribed to manage HT, the reduction of BP following anti-HT regimens, and associated risk factors for HT among children. Additionally, among recent reviews, diagnostic criteria and therapeutic options are indicated for different medical conditions and comorbidities [38]. This review will conduct a qualitative analysis that may offer a deeper understanding of aspects that quantitative data alone may not capture [39]. Other studies also highlighted the necessity to revise current guidelines, to include the management of children with HT [40]. Despite evidence of HT prevalence in the general pediatric population [34], as stated previously, there is currently no updated systematic review and meta-analysis that simultaneously investigates the prevalence of HT and the effectiveness of anti-HT medication in decreasing BP in children.

This review will discuss the risk factors contributing to HT, such as BMI and family history. An increase in BMI in children has been associated with a higher risk of developing HT [41]. In China, the incidence of HT is higher in overweight and obese children compared with those with normal weight, with rates of 24.3% and 18.5% versus 11.1%, respectively [42]. Additionally, children with consistently high BMI trajectories are at greater risk for developing HT in later life [43].

While rapid weight gain during early childhood may predict higher BP, it may also increase the risk for cardiovascular risks during adulthood [44]. Similar findings have been reported in preterm births and low birth weight babies [45]. Children with asthma may also have an increased risk of HT [46] due to the interplay between asthma and HT likely involving inflammatory pathways. Furthermore, changes in vascular and asthma medications have been associated with increased BP, potentially contributing to HT [47].

Having a family history of HT also significantly influences the risk of HT among children, as there is a hereditary component to BP regulation [48]. Interestingly, exclusive breastfeeding has been linked to a decreased risk of HT in children. A study in China revealed that children who were exclusively breastfed had a reduction of 0.07 mm Hg in systolic BP and 0.05 mm Hg in diastolic BP [49].

We believe that our review will benefit both clinicians and researchers, especially in controlling BP among children as HT in childhood is a predictor of HT in adulthood that leads to elevated heart disease morbidity [50]. As the current cost of HT treatment is quite expensive, this review will also benefit in cost-effectiveness for HT treatment among children in the future. Thus, the findings from this review will inform clinical practice, particularly in prescribing anti-HT medications, and explore the most effective anti-HT treatment that can be applied to treat HT among children. This review will also be useful for both the local governments and policy makers to improve public

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awareness of HT among children, especially for the benefit of parents and caretakers.

Potential Limitations of Review Methods

This review may have possible limitations due to the language restriction to include studies in English. This review will focus on the anti-HT among children and therefore, nonpharmacological interventions or prevention strategies will be excluded. The article search will be conducted using electronic databases and we will exclude the unpublished literatures which may potentially result in the oversight of some studies. Some resources may complicate the systematic retrieval as it potentially affects the overall reliability.

Conclusions

This review will provide a comprehensive synthesis of the overall prevalence of HT among children a public health issue of growing concern with long-term impact. This review will also provide important information to inform practice in developing effective strategies for preventing and managing childhood HT.

Acknowledgments

We would like to thank the Director General of Health Malaysia for his permission to publish this protocol. We also would like to thank Dr Aimi Nadiah for her guidance. No specific funding was received for this protocol, nor will be received for the systematic review planned.

Data Availability

The datasets generated or analyzed during this study are available upon request from the corresponding author.

Authors' Contributions

NHM, NAM, and LNM were responsible for conceptualization. Investigation and methodology were conducted by NHM, NAZZ, NLMN, KM, and SZSAY. Project administration was handled by NHM and KM, while supervision was provided by NAM and LNM. Validation was performed by NHM, NAZZ, and NLMN. NHM also contributed to visualization and wrote the original draft. The manuscript was reviewed and edited by NHM, NAM, and LNM.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis-Protocols) checklist.
[PDF File (Adobe PDF File), 220 KB - resprot_v14i1e65807_app1.pdf]

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Abbreviations

anti-HT: antihypertensive
BP: blood pressure
CENTRAL: Cochrane Central Register of Controlled Trials
CVD: cardiovascular disease
HT: hypertension

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MeSH: Medical Subject Headings
PICO: Population, Intervention, Comparison, and Outcomes
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Register of Systematic Review
RCT: randomized controlled trial

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Protocol

Identification of Compounds With Potential Dual Inhibitory Activity Against Drug Efflux Pumps in Resistant Cancer Cells and Bacteria: Protocol for a Systematic Review

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Abstract

Background: Drug efflux mediated by transporter proteins is one of the major mechanisms conferring multidrug resistance (MDR) to antimicrobial agents in bacteria and to chemotherapeutics in cancer cells. Therefore, the development or identification of efflux modulators represents a promising strategy to overcome the resistant phenotype. Various chemical compounds have been tested in experimental studies as reversal agents either in combination with antimicrobial or anticancer drugs and have shown sensitizing activity in resistant bacteria or cancer cell lines. Owing to the common resistance mechanisms exhibited by bacteria and cancer cells, the identification of chemical agents with dual reversal activity offers a strategy to simultaneously combat antibacterial and cancer multidrug resistance.

Objective: This study aims to conduct a systematic review to identify compounds that have shown activity in reversing antibacterial as well as cancer MDR mediated by drug efflux pumps and to summarize their structural and biological parameters responsible for the interactions with drug efflux pumps.

Methods: The protocol has been developed in accordance with PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) guidelines. We searched PubMed and Scopus databases for abstracts of full-text peer-reviewed journal papers in English language published between January 2012 and September 2024. Only studies from in vitro experiments were considered if they used methods to detect changes in antibiotic sensitivity of resistant bacteria and chemosensitivity of resistant cancer cells upon treatment with efflux pump inhibitors. A total of 763 unique records were identified. Of them, 246 were selected for full-text review based on the eligibility criteria. Abstract screening was performed by 2 independent reviewers. As of March 1, 2025, the systematic review is at the stage of completed abstract screening. The next steps of the full-text review, study selection, data extraction, and risk of bias assessment will be performed by 2 independent reviewers as well. Main data elements will include a structural identifier of the tested inhibitor, bacterial strain, cancer cell line, methods proving reversal activity, half maximal inhibitory concentration, and other relevant quantitative estimates of reversal activity. Data synthesis will be performed as a narrative summary and the content will be curated in tabular and graphical form.

Results: We anticipate that results from this study will outline the potential of various compounds to act as dual chemosensitizers and reverse both antimicrobial and cancer MDR.

Conclusions: Our review will highlight the overlap between efflux pumps' inhibition as a strategy to combat MDR in both bacterial and cancer cells and it will provide structured data for rational drug design of dual efflux pump inhibitors.

Trial Registration: PROSPERO CRD42024548350; https://www.crd.york.ac.uk/PROSPERO/view/CRD42024548350

International Registered Report Identifier (IRRID): PRR1-10.2196/66197

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(JMIR Res Protoc 2025;14:e66197) doi:10.2196/66197

KEYWORDS

drug resistance; bacterial; neoplasm; reversing agents; efflux pump inhibitors; cancer cells; bacteria; protocols; systematic reviews; antimicrobial; PRISMA-P

Introduction

Drug resistance defined as the loss or diminution of pharmacological drug effects represents an important impediment to the success of medical treatments. Cancer and infection are the 2 medical contexts where the emergence of drug resistance is of utmost clinical importance as it may significantly compromise treatment outcomes. Both pathogenic microorganisms and human cancer cells have developed protective mechanisms to evade cytotoxicity triggered by pharmacological agents and one of the commonest multidrug resistance (MDR) mechanisms shared by both is the drug efflux mediated by transmembrane transport molecules [1].

Antimicrobial resistance (AMR) has been recognized by the World Health Organization (WHO) as a global public health threat and economic burden [2]. According to a report on the global burden of AMR, there were an estimated 4.95 million deaths worldwide associated with AMR in 2019 [3]. When compared with all underlying causes of death in the Global Burden of Disease 2019 AMR would have been the third leading cause of death after ischemic heart disease and stroke on the basis of the counterfactual scenario of no infection.

Cancer cells can also exhibit resistant phenotypes to the antineoplastic agents they have been exposed to in the course of anticancer drug treatment. Induced resistance to chemotherapy is responsible for nearly 90% of cancer deaths [4].

Drug efflux mediated by the overexpression of transport proteins recognizing and extruding a wide range of drugs, thus acting as efflux pumps, is one of the major mechanisms conferring resistance to antimicrobial agents in bacteria and to structurally unrelated chemotherapeutic agents in cancer cells (classical MDR phenotype) [5]. By extruding xenobiotics (cytotoxic agents and antibiotics) out of the cell, the efflux pumps decrease the intracellular concentration of drugs, thereby obviating their cytotoxic effects. Efflux pump inhibitors (EPIs), also called MDR modulators, are chemical compounds, either of natural or synthetic origin, that bind to the efflux pump and block the extrusion of other ligands, that is inhibit their efflux. In several studies, it has been demonstrated that the sensitivity of bacteria or cancer cells to antimicrobials or cytotoxic agents is reinstated when these are coadministered with an EPI. This ability to reverse MDR (MDR reversal) represents a possible strategy to overcome the MDR phenotype. Despite their differing origin, some bacterial and mammalian efflux pumps share the same or structurally similar ligands [6]. Owing to the common resistance mechanisms exhibited by bacteria and cancer cells, the development or identification of chemical agents that act as dual efflux pump inhibitors or modulators offers a promising avenue to tackle the problem of rising cancer and antimicrobial drug resistance.

In addition, a range of other applications might be considered. In some instances, dual inhibition is undesirable; thus, identifying dual inhibitors can prevent their misuse. For example, the inhibition of the *Staphylococcus aureus* efflux pump NorA, belonging to the Major Facilitator Superfamily (MFS) superfamily, by EPIs helps restore the effectiveness of antibiotics against resistant strains. However, many of these inhibitors also bind to P-glycoprotein, one of the most studied ABC transporters associated with MDR in cancer cells when overexpressed [7,8]. Under physiological conditions, P-glycoprotein inhibition is considered harmful as it can adversely affect the metabolism, distribution, and elimination of drugs. Therefore, identifying dual NorA and P-glycoprotein inhibitors can aid in characterizing selective NorA inhibitors [9]. Conversely, the identified inhibitors may be seen as bioavailability enhancers for P-glycoprotein substrate drugs proving beneficial for antibiotics with bioavailability challenges [10].

The primary objectives of this systematic review are (1) to gather information from recent scientific literature on compounds that have shown activity in reversing antimicrobial as well as cancer MDR mediated by drug efflux pumps, that is exhibit dual reversal activity; (2) to identify, systematize, analyze, and summarize their structural and biological parameters responsible for the inhibitory effect toward efflux pumps; and (3) to provide insights on potential mechanisms of interaction between EPI and drug efflux pumps.

Methods

Approach

The methodology of a systematic review has been implemented as it is suitable to identify in an exhaustive manner compounds from literature with evidence of dual reversing activity and to explore the intersection between antimicrobial and cancer MDR. The protocol has been developed in alignment with the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) [11]. The PRISMA-P checklist can be found in Multimedia Appendix 1.

We have identified the research question within the Problem-Intervention-Comparator-Outcome (PICO) framework: what compounds that have been tested as efflux pump inhibitors have shown activity in reversing antimicrobial resistance in bacteria and multidrug resistance in cancer cells (Table 1) [12]?

In accordance with PRISMA-P, the protocol was registered in the PROSPERO (International Prospective Register for Systematic Reviews) on December 24, 2024 (registration number CRD42024548350).

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Table 1. Concepts according to Population Intervention Comparator Outcome framework.

Population (P)	Bacteria resistant to antimicrobials and chemotherapy-resistant cancer cells
Intervention (I)	Efflux pump inhibitors and MDR[a] modulators
Comparator (C)	No efflux pump inhibitors and MDR modulators
Outcome (O)	Reversal of resistance by binding to the efflux pump and reinstatement of antimicrobial sensitivity in bacteria and chemosensitivity in cancer cells

[a]MDR: multidrug resistance

Ethical Considerations

Ethics approval was not applied due to the *in silico* nature of the study being a systematic review of already peer-reviewed and published studies according to the local institutional review board policy of Biomed.

Eligibility Criteria

Eligibility criteria for the study selection are specified in Textbox 1. Studies are considered eligible if all inclusion and none of the exclusion criteria are met.

Textbox 1. Study characteristics to be used as criteria for eligibility for the review.

Inclusion criteria

- Studies reporting data from in vitro experiments on multidrug-resistant bacteria or cancer cell lines.
- Studied populations are bacteria resistant to antimicrobials and chemotherapy-resistant cancer cells (including bacterial isolates from clinical specimens and cancer cells from resistant tumors).
- Studied resistance mechanism is the classical multidrug resistance phenotype, that is resistance induced by overexpression or activity of drug efflux pumps.
- Study design includes treatment of resistant bacteria or cancer cells with an efflux pump inhibitor (EPI) in the presence of antimicrobials or chemotherapy drugs.
- Used EPI is a chemical compound that interacts with the membrane transport protein.
- Reported outcome is the reversal of resistance, that is an increase in sensitivity towards antimicrobials or chemotherapeutics is detected in resistant bacteria or chemotherapy-resistant cancer cells upon the addition of an EPI to the treatment. As a measure of resistance reversal upon the addition of the EPI at least a half-maximal inhibitory concentration of the antibacterial or chemotherapy drug should be reported.
- Studies in the English language reporting original research data.

Exclusion criteria

- *In vivo* animal studies, clinical studies, or *in silico* studies without an *in vitro* validation experiment.
- Studies on populations other than that of interest: fungi, parasites, viruses, noncancerous cells or tissues, chemosensitive cancer cells or susceptible bacteria without a resistant counterpart, precancerous conditions, carcinoma in situ.
- Multidrug resistance phenotype is induced by other mechanisms, for example, mismatch repair system or alterations in the signal-transduction pathways.
- Study design does not use cotreatment with an EPI.
- Studies that test a reversal mechanism other than an EPI interacting with the transport protein, for example, inhibition of transport protein expression or inhibition of transporter activity by an autoantibody.
- Change in the sensitivity of resistant bacteria or cancer cells is not detected by a quantitative measure.
- Review articles, conference proceedings, posters, abstracts without full text, systematic reviews, doctoral theses, patents, preprints, and technical reports. Articles not in the English language.

Data Sources

Published articles were collected from the electronic scientific abstract and citation databases PubMed and Scopus. We have decided on the use of the 2 databases as they provide wide coverage, are considered sources for reliable and reproducible experimental data, and provide optimal tools for electronic search of biomedical literature [13]. The search was time-limited to looking for papers published in the time span between January 1, 2012, and August 31, 2024. We have focused on studies published after 2011 because we identified a review by Amaral et al [5], published in 2012, that very comprehensively summarizes previous data on EPIs with activity on both bacterial and cancer cell efflux pumps.

Search Strategy

The search strategy, exemplified but not exhaustive, is demonstrated in Textbox 2.

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Textbox 2. Search strategies.

A. Search strategy for PubMed database

1. (“Drug resistance” [tw] OR “Multidrug resistance” [tw] OR “Antimicrobial resistance” [tw] OR MDR [tw] OR AMR [tw] OR “Antibiotic drug resistance” [tw] OR “Drug-resistance” [tw] OR “Xenobiotic resistance” [tw] OR “Tumor multidrug resistance” [tw] OR “Tumour multidrug resistance” [tw]) AND (“Drug efflux pump*” [tw] OR

ABC [tw] OR “ATP-binding cassette transporter*” [tw] OR “P-glycoprotein-mediated drug resistance” [tw] OR “Efflux of antimicrobial agent*” [tw] OR “Efflux of anticancer agent*” [tw])

2. (“Drug resistance, multiple” [mh] OR “Drug resistance, bacterial” [mh] OR “Drug resistance, microbial” [mh] OR “Drug resistance, neoplasm” [mh] OR “Drug tolerance” [mh]) AND (“Multidrug resistance-associated protein*” [mh] OR “Multidrug resistance protein*” [mh] OR

“ATP-Binding Cassette Transporter*”)

3. #1 OR #2

4. “Multidrug resistance modulat*” [tw] OR “Multidrug-resistance revers* agent” [tw] OR Modulat* [tw] OR “Revers* multidrug resistance” [tw] OR Modifier [tw] OR Modulat* [tw] OR “Overcom* multidrug resistance” [tw] OR “Clinical modulat*” [tw] OR “Resistance-overcoming activity” [tw] OR Bind* [tw] OR Substrate [tw] OR Sensitize* [tw]

5. #3 AND #4

6. (Neoplas*[tw] OR cancer [tw] OR tumor [tw] OR tumour [tw] OR malignancy [tw]) AND (Microb* [tw] OR bact* [tw] OR microorganism* [tw])

7. Neoplasms [mh] AND (Bacteria [mh] OR “Bacterial infections” [mh])

8. #6 OR #7

9. #5 AND #8

10. Filters applied: from 2012/1/1 - 2024/8/31 to #9

11. Limitation: English language

B. Search strategy for Scopus database

(TITLE-ABS-KEY ((inhibit* OR substrate* OR bind* OR ligand OR modulat*) AND (efflux AND pump OR efflux AND transport* OR efflux OR p-glycoprotein OR nora) AND (bacter* OR antibacter*) AND (cancer* OR anticanc* OR carcin* OR tumor* OR antitumor* OR antitumour* OR tumour* OR mammal*)) AND PUBYEAR > 2011 AND PUBYEAR < 2025 AND NOT PUBDATETXT (“September 2024” OR “October 2024” OR “November 2024” OR “December 2024”)) OR (TITLE-ABS-KEY (resistance AND (“efflux pump*” OR abc-transporter* OR mfs OR p-glycoprotein OR nora) AND (inhibit* OR modulat* OR bind* OR substrate OR “efflux pump inhibitor*” OR “pump inhibitor*”) AND (cancer OR tumor) AND bacteria*) AND PUBYEAR > 2011 AND PUBYEAR < 2025 AND NOT PUBDATETXT (“September 2024” OR “October 2024” OR “November 2024” OR “December 2024”)) AND (LIMIT-TO (DOCTYPE , “ar”)) AND (LIMIT-TO (LANGUAGE , “English”))

Selection Process

After applying the search strategy retrieved records were independently screened by 2 reviewers (AD and EB) by title and abstract based on the eligibility criteria. The discrepancy in results from studies selection after this initial stage was resolved by discussion with supervisors (IT and IP). Studies that have been selected for full-text review will undergo a second round of independent review by AD and EB and disagreements, again, will be resolved by the supervisors. Reviewers are blinded to each other’s decisions during the review process. For organizing, screening, conflict resolution, extracting, and archiving the results of the systematic review, we use Systematic Review Data Repository Plus (SRDR+) [14].

Outcomes for Which Data Were Sought

Outcomes of interest are broadly categorized in Textbox 3.

Textbox 3. Outcomes.

- Overcoming multidrug resistance in bacteria and cancer:
- Compounds that reverse resistance to antimicrobials in bacteria;
- Compounds that reverse resistance to chemotherapeutics in cancer cells;
- Knowledge about the mechanism of interaction between efflux pump inhibitors and a drug efflux pump
- Exploring the intersection between antimicrobial and cancer multidrug resistance

Data Management, Extraction, and Main Data Elements

The authors will review selected studies to extract parameters of interest. Data to be extracted include (1) study title; (2) study author; (3) year; (4) International Union of Pure and Applied Chemistry name of EPI, Chemical Abstracts Service number; (5) structural identifier of EPI: Simplified Molecular-Input Line-Entry System, International Chemical Identifier; (6) cancer cell line; (7) bacterial strain; (8) drug efflux pump subjected to inhibition; (9) methods for proving reversal activity of inhibitor; (10) IC_{50} (half-maximal inhibitory concentration); (11) measures

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of MDR, for example, MDR reversal ratio; (12) intracellular drug accumulation; (13) percentage cell survival; (14) affinity constant; (15) drug-induced apoptosis; (16) effect of adenosine triphosphatase activity; (17) methods used for in silico analysis; and (18) protein-ligand interactions. In the data extraction process, one reviewer will extract data and another one will check the extracted data. Disagreements between reviewers will be resolved by supervisors. In case a chemical identifier is missing, such will be generated provided a chemical structure is given in the source. Alternatively, and for any other ambiguities, authors will be contacted.

Risk-of-Bias Assessment

For the assessment of risk of bias a domain-based tool-ToxRTool (toxicological data reliability assessment tool) developed to evaluate the reliability of toxicological data, will be used [15]. ToxRTool addresses 5 specific criteria groups relevant to toxicological and pharmacological properties of compounds tested in in vitro experiments: (1) test substance identification, (2) test system characterization, (3) study design description, (4) study results documentation, and (5) plausibility of study design and results. Application of the tool leads to the assignment of each item to one of the four reliability categories by Klimisch: “reliable without restriction,” “reliable with restriction,” “not reliable,” and “not assignable” [16]. Two reviewers will independently apply the tool for each included item, record the numerical result leading to a reliability category, and justify the evaluation. Any discrepancies will be resolved through discussion with the supervisors. For quality assessment across studies, a development of GRADE (Grading of Recommendations Assessment, Development, and Evaluation) for preclinical studies will be used [17].

Data Synthesis

Data synthesis will be performed as a narrative summary. Qualitative and quantitative content will be analyzed and presented as tables and figures. Data will be organized around the compounds tested as EPI both in bacteria and cancer cells. No meta-analysis is being planned due to the essence of the review question.

Results

The protocol for this systematic review was developed in June 2024 and few pilot searches were performed. Initially time limitation was set between January 1, 2012, and June 30, 2024. Since there were differing views on the optimal search strategy, it took several rounds of discussion to reach a consensus. After a consensus was reached among the team members on the final combination of search strategies to use, the protocol was amended to expand the search up to September 2024. PubMed was searched on October 28, 2024, and Scopus was searched on February 12, 2025. Results from the searches were downloaded as csv files. A txt file containing a list with PMIDs from the PubMed search results and a csv file containing DOIs of the Scopus search results were fed into SRDR+ to fetch citations. SRDR+ was used to perform the abstract screening and to select records for further full-text screening. The results from the search and the abstract screening are presented in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart (Figure 1). In total, 1003 records were identified through database search. After the removal of duplicates, 763 unique records were screened by title and abstract by AD and EB. Each reviewer was blinded. Any screening conflicts that arose at this stage were resolved by the supervisors, IT and IP. During abstract screening, 517 records were excluded, and 246 records were accepted for the next step of full-text screening. Given the time requirements to perform full-text screening and data extraction, we envision this next step as compassable to execute by the end of August 2025. Data analysis will be performed by November 2025, and preparation of manuscript containing a report on the results from the systematic review and manuscript submission will be completed by February 2026.

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Figure 1. PRISMA flowchart of the selection and review process.

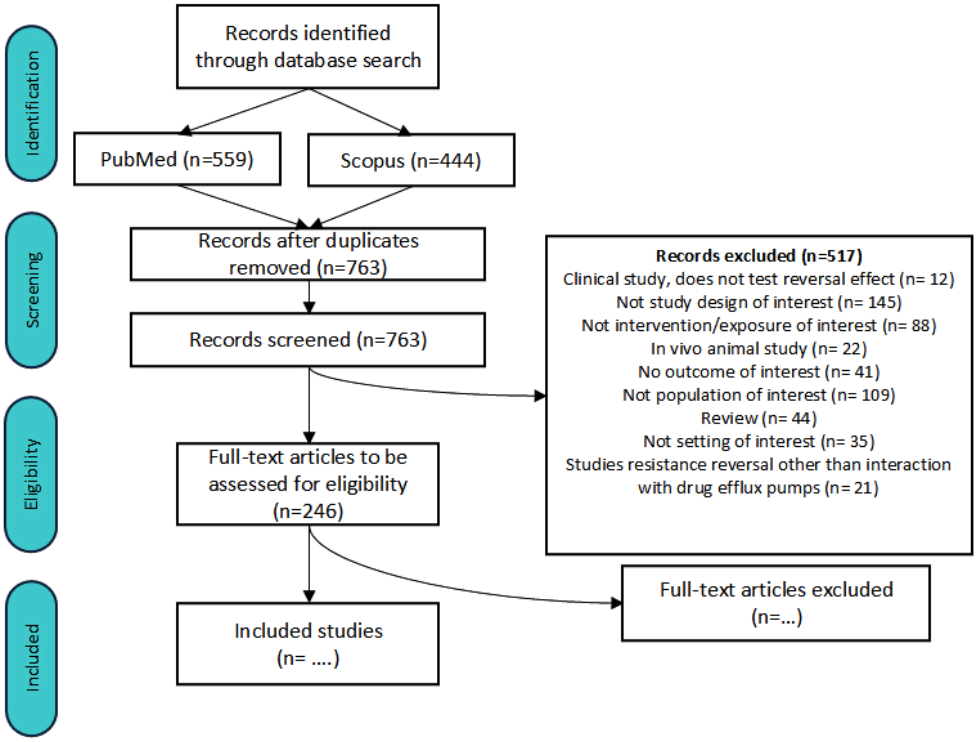

Discussion

Overview

While efflux pumps of the ATP-binding cassette (ABC) superfamily are known to play a role in cancer resistance pathways, 6 bacterial efflux pump families have been identified. These include the ABC superfamily, as well as MFS, multidrug and toxic compound extrusion family, resistance nodulation cell division family, small multidrug resistance family, and proteobacterial antimicrobial compound efflux family [18,19]. Depending on the source of energy they use to pump out the substrates, the efflux pumps are categorized into primary transport proteins, which hydrolyze ATP for energy (ABC superfamily), and secondary transport proteins, which use the proton or ions gradient (proton motive force) as their energy source [20].

Principal Findings

Exploration of the intersection between bacterial and cancer multidrug resistance has been identified as an interesting research topic since the findings that the extrusion of xenobiotic compounds by efflux pumps represents a shared resistance mechanism for both bacteria and cancer cells [1]. The proposed systematic review will critically analyze the scientific literature in the last 15 years to identify chemical compounds that have shown activity as EPIs in both resistant bacteria and resistant cancer cells. We expect that results from this study will demonstrate the potential of various compounds to act as dual chemosensitizers and reverse both antimicrobial and cancer multidrug resistance. The anticipated main finding of this systematic review would be the summary of data on chemical compounds with the ability to decrease resistance toward antimicrobial and antineoplastic agents. Our findings will be systematically summarized as a database to outline the available structural and biological parameters of the identified compounds relevant to their reversing activity. In addition, as another principal finding we expect to present an overview of the proposed mechanisms of interaction between drug efflux pumps and EPIs. Findings from in silico studies modeling the interactions between the small molecules and efflux pumps, when supported by in vitro studies, have not been systematically reviewed.

Comparison With Previous Work

Even though numerous studies have evaluated chemical compounds of natural and synthetic origin as MDR reversal agents, in their majority they have focused either on resistance reversal in bacteria or in cancer [21-25]. Few studies have reported results from testing a compound simultaneously on bacteria and cancer cells in the same experimental setting [26-29]. Moreover, studies differ in the targeted efflux pump, in the population of interest (bacterial strain or type of cancer cells) as well as in the tested EPIs. Other reviews have already discussed compounds with the potential to dually inhibit efflux pumps in bacteria and cancer, albeit not in a systematic manner. However, some of those reviews focus on a single drug class and discuss efflux inhibition among a myriad of other cell-directed effects of the class [30,31]. Therefore, we felt the need to summarize available data on compounds with EPI activity from either separate or simultaneous experiments in bacteria and cancer cells along with aggregation of data on their structural and biochemical properties that might be effectively used for in silico drug design.

Strengths

By attempting to summarize the results from experiments on various bacteria and cancer cells differing in terms of EPIs our

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review will highlight the overlap between efflux pump inhibition in bacterial and cancer cells as a strategy to combat MDR in both settings. Further, it will provide structured data for rational drug design of dual (bacterial and cancer) EPIs such as, but not limited to, pharmacophore generation, Quantitative Structure-Activity Relationship models, and molecular dynamics simulations.

Limitations

The systematic review will have limitations. We envision heterogeneity between studies as the most significant limitation. We expect certain variability between studies with respect to the methodology used for proving reversal activity, experimental setting, bacterial strains, cell lines, and outcome measurements, all of which may render the comparison across studies difficult. There is also the risk of inherent reviewer bias which will be mitigated by independent blinded review and solicited input from experts on the subject. In addition, we will implement a standardized tool for assessing the risk of bias for each study. There is a chance that only a few compounds will be identified as dual ABC pump inhibitors after this review. Nevertheless, the review will screen the literature and provide comprehension of whether the topic of the intersection between bacterial and cancer MDR is plausible for exploration with further research endeavors.

Future Directions

By providing curated data on dual EPIs we hope that this review will subsequently aid in the discovery of new compounds with EPI activity or guide the repurposing of already approved compounds into their clinical use as EPIs in conjunction with antibacterials or chemotherapeutics. Furthermore, the outcomes of this review may support the concept of using bacteria as a tool to screen and evaluate EPIs that could potentially be used to overcome MDR in cancer cells. Finally, the results from this review will generate perspectives for future research efforts in tackling drug resistance with potential implications in the clinical setting.

Dissemination Plan

The findings of this peer review will be disseminated through a peer-reviewed journal article.

Conclusion

This systematic review will provide a comprehensive analysis of EPIs that have been tested as reversal agents in resistant bacteria and cancer cells. Ultimately, it will identify those compounds that intersect as dual resistance sensitizers. This research will hopefully provide the basis for the development of protocols for in silico investigations of efflux pump inhibitors.

Acknowledgments

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Data Availability

The dataset generated or analyzed during this study will be made available in the SRDR+ repository.

Authors' Contributions

AD, EB, and IT contributed to conceptualization. AD, EB, IT, and IP assisted with data curation and formal analysis. IT handled funding acquisition. AD, EB, IT, and IP contributed to investigation. AD, EB, and IT assisted with methodology. IT and IP handled project administration. IP and IT contributed to resources. IT and IP assisted with supervision. AD, EB, IT, and IP handled validation. EB contributed to visualization. EB and IT assisted with writing–original draft. AD, EB, IT, and IP handled writing–review & editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P checklist.
[PDF File (Adobe PDF File), 198 KB - resprot_v14i1e66197_app1.pdf]

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Abbreviations

ABC: ATP-binding cassette
AMR: antimicrobial resistance
EPI: efflux pump inhibitor
GRADE: Grading of Recommendations Assessment, Development, and Evaluation
IC50: half-maximal inhibitory concentration
MDR: multidrug resistance
MFS: major facilitator superfamily
PICO: Problem Intervention Comparator Outcome
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analysis
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis-Protocols
PROSPERO: International Prospective Register for Systematic Reviews
SRDR+: Systematic Review Data Repository Plus
ToxRTool: toxicological data reliability assessment tool
WHO: World Health Organization

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Protocol

Prediction Models for Postoperative Delirium of Cardiovascular Surgery (PODOCVS): Protocol for a Systematic Review

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Abstract

Background: Postoperative delirium of cardiovascular surgery (PODOCVS) is an acute brain dysfunction characterized by inattention, impaired consciousness, and cognitive disorders, and the severity and presence of these symptoms fluctuate over time. PODOCVS occurs during the early postoperative period and is associated with adverse outcomes, including prolonged mechanical ventilation, premature mortality, and so on. Advances in its early diagnosis and treatment have mitigated some of the initial adverse effects of PODOCVS, but models for predicting risk in patients who have already developed PODOCVS remain inadequate for effective secondary prevention. Developing multivariable prediction models for stratifying PODOCVS risk would enable early, personalized interventions.

Objective: This study aims to systematically review and critically evaluate the development, performance, and applicability of existing prediction models for PODOCVS.

Methods: An extensive systematic search will be performed across multiple databases, including Embase, PubMed, the Web of Science, and so on, to identify studies related to multivariate predictive models for PODOCVS. A manual search of the included studies' reference lists will also be conducted to identify any additional relevant publications. This systematic review will include studies that meet the following criteria: (1) studies with subject populations comprising adult cardiovascular surgery patients aged ≥18 years, (2) studies involving the development and internal or external validation of predictive models for PODOCVS via multivariate analysis, and (3) studies with outcome measures focused on postoperative delirium. Two researchers (ZXL and WYK) will independently extract the data and assess the included studies' model quality using the Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies (CHARMS) checklist and the Predictive Model Bias Risk Assessment Tool (PROBAST). Since this study will not involve patient data, ethics approval is not required. Our findings will be published in a peer-reviewed scientific journal and the dataset will be made freely available.

Results: Literature searches were conducted from the inception of the database to May 20, 2024 (updated up to January 31, 2025), and data extraction and analysis are expected to be complete by the end of May 2025. We currently have a preliminary plan to publish the complete study results by August 2025, subject to any unforeseen delays or changes in the research timeline.

Conclusions: We present a protocol for the systematic review of prediction models for postoperative delirium in cardiac surgery patients. Aiming to identify, summarize, and critically appraise existing risk models globally, this review seeks to provide an up-to-date reference for stakeholders involved in patients with cardiac surgery care, policy making, and research. In addition, we aim to investigate whether machine learning models for PODOCVS offer more accurate predictions than traditional statistical models.

Trial Registration: PROSPERO CRD42024578957; https://www.crd.york.ac.uk/PROSPERO/view/CRD42024578957

International Registered Report Identifier (IRRID): DERR1-10.2196/75368

(JMIR Res Protoc 2025;14:e75368) doi:10.2196/75368

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KEYWORDS

prediction models; postoperative delirium; cardiovascular surgery; acute brain dysfunction; machine learning; systematic review

Introduction

Background

Postoperative delirium of cardiovascular surgery (PODOCVS) is an acute brain dysfunction characterized by inattention, impaired consciousness, and cognitive impairment that fluctuates in presence and severity across time [1].

Studies show that PODOCVS affects approximately 26% to 52% of patients with cardiovascular surgery [2]. As a common complication of cardiovascular surgery, PODOCVS worsens patient outcomes [3] and consumes enormous financial resources in excess of US $164 billion per year [4]. PODOCVS is independently associated with major surgical trauma, advanced age, cardiopulmonary bypass, compromised brain health, and transfer to the cardiovascular intensive care unit post surgery [2,5,6]. PODOCVS occurs during the early postoperative period and is associated with adverse outcomes including prolonged mechanical ventilation times and hospital stays, long-term nursing needs, worsening of pre-existing cognitive impairment, new dementia, increased anxiety and depression, and premature mortality [7]. In terms of pharmacological therapies, ramelteon and suvorexant can reportedly reduce delirium, but premedication to prevent delirium is not recommended for all patients [8]. However, due to the lack of specific treatments, strategies for managing delirium currently focus only on its prevention and early detection [9,10]. Therefore, identifying populations at high risk of developing delirium and providing targeted and effective interventions are crucial [9,11]. Risk stratification and identification of vulnerable patients offer an extremely efficient method of protecting them from the initial adverse outcomes of PODOCVS. The pathogenesis of PODOCVS is multifactorial and, as such, multivariable prediction models for stratifying PODOCVS risk may enable early personalized treatment interventions [12-14]. This would significantly reduce the incidence of delirium, shorten hospital stays, cut medical costs, and reduce the incidence of postoperative complications and mortality risk [4].

At present, there are many PODOCVS prediction models used in clinical practice. These can be divided into traditional statistical models and machine learning (ML) models. Although statistical models (eg, logistic regression) are favorable in terms of model interpretability, Choi et al [15] indicate that ML is preferred for predictive accuracy. The predictive power of traditional statistics-based models (eg, the E-PRE-DELIRIC [Early Prediction Model for Delirium in the intensive care unit] model) varies greatly across regional cohorts with an area under the curve (AUC) of 0.54, which is below the receiver operating characteristic curve of 0.75 [16,17]. Mufti et al [18] and Xue et al [19] have shown that the predictive accuracy of ML algorithms was superior to that of conventional statistical models in the area of PODOCVS [20]. ML models can handle complex, multidimensional data without the limitations of traditional statistical methods. Although there is an expanding body of published literature on the use of ML models in cardiovascular health care, whether their performance in predicting PODOCVS is superior to that of traditional statistical models remains to be verified [21].

The accuracy of predictive models for patients at risk of developing delirium has been reported to be insufficient when applied to patients with cardiac surgery [17]. Hence, predictive models for delirium risk should be constructed for patients with cardiac surgery specifically [22]. In recent years, an increasing number of studies have focused on developing or validating predictive models to estimate PODOCVS risk. However, health care professionals are uncertain as to which model to use for patients undergoing cardiac surgery in specific patterns, settings, and populations. Hence, the quality of existing models and their applicability remain unclear. Therefore, it is critical to thoroughly evaluate the predictive performance, applicability, and quality of existing PODOCVS risk prediction models [23]. To this end, this study presents a protocol for the systematic review and critical assessment of the quality, performance, and applicability of current predictive models for PODOCVS risk.

Objectives

The systematic review aims to thoroughly evaluate the predictive performance, applicability, and quality of existing PODOCVS risk prediction models. To provide a robust scientific foundation for health care professionals to select appropriate delirium prediction models tailored to patients with cardiac surgery in specific clinical environments. The objectives of this project are listed in Textbox 1.

Textbox 1. Research aims.

- The construction methodology and model validation approach of the existing postoperative delirium of cardiovascular surgery risk prediction model were thoroughly analyzed, and the predictors were ranked based on the prevalence and strength of the predictors.
- Comprehensively assess the predictive performance, applicability, and quality of existing postoperative delirium of cardiovascular surgery risk prediction models.
- Inform stakeholders, such as policy makers and health care workers directly involved in the treatment of patients with cardiac surgery, on the available delirium prediction models and their setting-specific clinical utility, strengths, and limitations.
- Determine whether postoperative delirium of cardiovascular surgery machine learning models can provide more accurate predictions as compared with postoperative delirium of cardiovascular surgery traditional statistical models.

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Methods

Study Design and Data Source

This protocol was developed according to the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) guidelines (Multimedia Appendix 1) [24].

A systematic review will be conducted according to the recommended methods for systematic reviews and meta-analyses of prediction models [24] and will adhere to the CHARMS (Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modeling Studies) checklist [25]. The results of this review will be reported as per the updated PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 checklist [26]. The review will be registered in the International PROSPERO (International Prospective Register of Systematic Reviews). Any modifications to the protocol will be amended accordingly.

Eligibility Criteria

This review follows the PICOTS (Population, Intervention model, Comparator, Outcomes, Timing, and Setting) approach to frame the review question and determine the inclusion criteria (Table 1) [25,26].

This systematic review will include studies with a subject population of patients with cardiac surgery aged 18 years and older, and studies using developed and internally or externally validated predictive models for PODOCVS risk based on multivariate analysis. The outcome metric is postoperative delirium. Studies will not be excluded based on their publication status and language. The exclusion criteria are as follows: (1) studies focused solely on the external validation of existing models; (2) studies that construct predictive models without conducting internal/external verification; (3) studies for which data are unavailable through the accessible channels; (4) studies lacking evidence of mode performance in derivation or validation cohorts; (4) studies that only analyze predictive risk factors without constructing predictive models; and (5) various types of publications such as conference abstracts, reviews, comments, research protocols, animal model studies, and textbook materials.

Table 1. Eligibility criteria are based on the Population, Intervention model, Comparator, Outcomes, Timing, and Setting.

	Criteria
Population	The population of interest comprises patients with cardiac surgery aged 18 years and older.
Index model	This review will include studies involving the development and concurrent internal or external validation of predictive models for postoperative delirium of cardiovascular surgery risk. Studies that focus exclusively on the external validation of existing models and studies that construct predictive models without conducting internal/external validation will be excluded from consideration.
Comparator	Not applicable.
Outcome	The outcome is defined as postoperative delirium.
Timing	Outcomes will be predicted using either preoperative, intraoperative, or postoperative conditions.
Setting	Predictive models are intended to perform risk stratification for the development of delirium, enabling the implementation of preventive measures and early intervention.

Search Strategy

Once this protocol is published, the search will be performed in the following databases: Embase, PubMed, the Web of Science Core Collection, the China National Knowledge Infrastructure (CNKI), Wan Fang, and Wei Pu (VIP). The following search terms will be used: “cardiac surgical procedure,” “cardiac surgery,” “cardiovascular surgery,” “heart surgery,” “coronary artery bypass grafting,” “Coronary Artery Bypass Grafting (CABG),” “extracorporeal circulation,” “type A aortic dissection,” “type B aortic dissection,” “subacute delirium,” “delirium,” “postoperative delirium,” “delirium of mixed origin,” “deliri*,” “psychosis,” “intensive care delirium,” “neurological complications,” “risk prediction,” “model,” “risk score,” and “risk assessment”. The retrieval time limit will range from each corresponding database’s inception until May 20, 2024 (updated until January 31, 2025). The search will be performed by 2 authors (WYK and ZXL). We will perform both forward and backward citation searches for the included studies and relevant previous systematic reviews. The complete search strings are presented in Multimedia Appendix 2.

Selection Process

EndNote’s “Delete duplicates” function will be used, followed by the manual deletion of any remaining duplicates. Subsequently, the authors (ZXL and WYK) will evaluate the acceptability of the titles and abstracts. In case of an eventual disagreement between the authors who analyze the eligibility of the documents, the opinion of a third author (LLJ) will be considered. Any inconsistencies will be resolved through discussion to arrive at a consensus. Thereafter, the selected full texts will finally be included in the review.

Data Extraction and Management

The following information will be identified from each selected study and summarized in tables for qualitative analysis: author name, country, the aim of the study, model development sample size, external validation sample size, internal validation sample size, participants, follow-up, study design (prospective study or retrospective study), events per variable, the main outcome, predictors in the final model, modeling methodology, number of models, model characteristics (ie, modeling methods, model validation methods, and candidate predictors) and model

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performances (ie, discrimination, calibration, and classification measures; Table 2). Data will be extracted independently by 2 authors (ZXL and WYK), who will enter the data into different Microsoft Excel spreadsheets. A third author will verify their agreement and resolve disagreements by reanalyzing the data (LLJ). A further limitation of the planned review is that we will not contact study authors to request unreported information, as we will explicitly document instances where information is missing.

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Table 2. Information for data extraction and subsequent summary and appraisal. Adapted from Checklist for Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies and Prediction model Risk Of Bias Assessment Tool.

Domain	Key items
Source of data	• Source of data (eg, cohort, case-control, randomized trial participants, registry data, etc).
Participants	• Participant eligibility and recruitment method (eg, location, number of centers, setting, and inclusion and exclusion criteria). • Participant description (age, sex, Types of cardiovascular surgery, and postoperative follow-up time). • Details of undergoing cardiovascular surgery. • How delirium diagnosis is defined (whether consistent for all participants, clinical history and physical signs, etc). • Study dates.
Outcomes to be predicted	• Type of outcome (eg, single or combined endpoints). • Definition and method for measurement of outcome (delirium and subtypes of delirium). • Was the same outcome definition (and measurement method) used in all patients? • Time of outcome occurrence or summary of duration of follow-up. • Was the outcome assessed without knowledge of the candidate predictors (ie, blinded)?
Candidate predictors	• Number and type of predictors (eg, demographics, patient history, physical examination, laboratory parameters, etc). • Definition and method for measurement of candidate predictors (including whether defined and measured in a similar way for all participants). • Timing of predictor measurement (eg, at patient presentation, at diagnosis, at treatment initiation, or otherwise). • Handling of predictors in the modeling (eg, continuous, linear, nonlinear transformations or categorized).
Sample size	• Number of participants and number of outcomes. • Events per candidate predictor. • Whether the authors describe a sample size calculation.
Missing data	• Number of participants with any missing value (including predictors and outcomes). • Number of participants with missing data for each predictor. • Handling of missing data (eg, complete-case analysis, imputation, or other methods).
Model development	• Modeling method (eg, logistics, survival, or other). • Modeling assumptions satisfied. • Description of participants that were excluded from the analysis with justification. • Method for selection of predictors for inclusion in multivariable modeling (eg, all candidate predictors, preselection based on unadjusted association with the outcome). • Method for selection of predictors during multivariable modeling (eg, full model approach, backward or forward selection) and criteria used (eg, *P* value, Akaike information criterion). • Shrinkage of predictor weights or regression coefficients (eg, no shrinkage, uniform shrinkage, penalized estimation).
Model performance	• Calibration (calibration plot, calibration slope, Hosmer-Lemeshow test), discrimination (C-statistic, D-statistic, and log-rank), and overall performance measures with CIs. • Classification measures (eg, sensitivity, specificity, predictive values, and net reclassification improvement) and whether a priori cutoff points were used.
Model evaluation	• Method used for testing model performance: development dataset only (apparent performance, a random split of data, resampling methods, for example, bootstrap or cross-validation or none) or separate external validation. • For external validations; data source and participants to be described as per “source of data” and “participants” domains. Definitions and distributions (including missing data) of outcome and candidate predictors.
Traditional prediction model	• Traditional algorithm-based prediction models refer to those that use classical statistical methods for forecasting future events or values, for example, linear regression, and logistic regression.
Machine learning prediction model	• Machine learning–based prediction models are capable of processing and analyzing extensive historical datasets, extracting underlying patterns and rules, and leveraging the acquired knowledge to forecast future scenarios, for example, extreme gradient boosting, support vector machine, adaptive boosting, multilayer perceptron, neural network, naive Bayes, and gradient boosting machine. • In case of poor external validation, whether the model was updated or extended (eg, intercept recalibrated, predictor effects adjusted, or new predictors added).
Results	• Final and other multivariable models presented, including predictor weights or regression coefficients, intercept, baseline survival, and model performance measures (with standard errors or CIs). • Any alternative presentation of the final prediction models, for example, sum score, nomogram, score chart, and predictions for specific risk subgroups with performance. • Comparison of the definition and distribution of predictors (including missing data) for development and validation datasets.

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Domain	Key items
Interpretation and discussion	• Study authors' interpretation of presented models (intended use and clinical utility, etc). • Study authors' reported strengths and limitations.

Risk of Bias in Individual Studies

Two authors (ZXL and WYK) will independently use the CHARMS checklist [25] to extract the relevant key information. Candidate studies with uncertain model characteristics (ie, modeling methods, model validation methods, and candidate predictors) and model performances (ie, discrimination, calibration, and classification measures) will be discussed with a third author (LLJ) before inclusion.

We will use the Prediction Model Risk of Bias Assessment Tool (PROBAST) to evaluate the quality of the candidate studies, as evaluated independently by 2 authors (ZXL and WYK). Similarly, uncertain cases will be discussed with a third author (LLJ) before inclusion. PROBAST [27] comprises 4 domains, namely, participants, predictors, outcome, and analysis. Each domain includes 20 signaling questions used to evaluate the risk of bias and applicability. These signaling questions rely on factual information and are categorized as either "Yes" or "Probably yes" (Y), "No" or "Probably no" (N), or "No information" (NI). After evaluating each domain using signaling questions specific to that domain, they will be categorized as either "High," "Low," or "Unclear." By synthesizing the results obtained from each dimension, an overall assessment will be made regarding the predictive models' risk of bias and applicability.

Assessing the Models' Predictive Performance and Accuracy

The evaluation of the predictive models' performance will be based on an assessment of their discrimination and calibration [28]. "Discrimination" refers to a model's ability to distinguish between individuals with different outcomes or conditions. It assesses how well the model correctly ranks individuals based on their risk of experiencing a certain event or condition. Common methods for evaluating discrimination include the c-statistic (also referred to as the area under the receiver operating characteristic curve) and the concordance index [28]. "Calibration" refers to the conformity between a model's predicted probabilities or risk evaluations and the observed actual outcomes. Calibration is often assessed by comparing the predicted and observed event rates among different risk groups, or by using calibration plots [20,28].

Ethical Considerations

Ethics approval is not required for this systematic review, as it does not require primary data collection. The protocol will be registered with the PROSPERO. The results of this systematic review will be disseminated through publication in an academic journal and scientific conferences.

Results

Literature searches were conducted from the inception of the database to May 20, 2024 (updated up to January 31, 2025), and data extraction and analysis are expected to be complete by the end of May 2025. We currently have a preliminary plan to publish the complete study results by August 2025, subject to any unforeseen delays or changes in the research timeline. The findings will be used to inform stakeholders, including policy makers and health care professionals directly involved in the treatment of patients with cardiac surgery, about the existing delirium prediction models, their setting-specific clinical utility, strengths, and limitations. In addition, it serves as a reference for selecting between traditional statistical models and ML models in future research.

Discussion

Expected Results and Practical Implications

This protocol aims to provide a detailed description of the process for conducting a systematic review of existing global predictive models for PODOCVS, focusing on their predictive performance, applicability, and quality. Due to differences in the basic characteristics of study populations, protocols, surgical methods, and evaluation methods and frequency, the reported incidence of PODOCVS varies greatly [29-31]. PODOCVS can cause serious adverse outcomes [32], and prevention is the most effective strategy for minimizing its occurrence and poor prognosis [2]. Accurate risk estimation for surgical patients using predictive models can aid clinical decision-making and inform policy, thereby guiding the optimal allocation of often-limited resources. By identifying, summarizing, and evaluating published PODOCVS prediction models, this systematic review will serve as a comprehensive resource for PODOCVS stakeholders, including health care workers, policy makers, and researchers. Although numerous PODOCVS prediction models exist, most of them have not been developed, validated, and assessed according to established guidelines for predictive research. This has given rise to significant biases in PODOCVS risk estimation, deficiencies in the statistical methods used, and a lack of internal and external validation.

While the clinical outcomes of PODOCVS are heterogeneous, many predictors of poor clinical outcomes have been identified. These include age (≥60 years old), sex (male), education level, history of living alone, frailty, BMI (>30 kg/m^2), high EuroSCORE (≥14), disease severity, changes in lifestyle patterns before and after admission, personality traits (high irritability), and history of smoking and alcohol consumption [33-35]. These interrelated factors' relative influence on patient outcomes can be described through multivariable modeling and subsequently used to construct a predictive model to estimate patients with cardiac surgery risk of developing postoperative delirium [36]. Therefore, to ensure the validity of the included predictive models, we will only select models that are internally or externally validated during development. Studies focused solely on the external validation of existing models or otherwise unvalidated predictive models will be excluded since several

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existing externally validated models have exhibited significant variability in their predictive accuracy across different populations. The reason for this may be that postoperative delirium in patients with cardiac surgery is closely related to the type of surgery that patients receive [2,37]. The planned systematic review will concisely summarize key information presented across all identified predictive model studies. Patients with cardiac surgery health care providers and policy makers can then use this information to assess a model's applicability to the patients with cardiac surgery population in different scenarios.

In recent years, ML-based predictive models have shown great success [38]. ML models can process vast quantities of multidimensional and unstructured data to reveal the roles and relationships between multiple variables, providing an effective means for accurately predicting delirium risk in patients with cardiac surgery [9,39,40]. Although ML-based predictive models exhibit good predictive performance, research has shown that they lack explanatory power. The reason for this may be that patients' clinical data are not uniform and standardized, and key data are often omitted [41]. Which of the 2 model types (ie, ML-based or statistical models) exhibits superior discrimination and calibration in the prediction of PODOCVS risk has not been demonstrated. To some extent, this affects the selection and use of predictive models by clinical medical staff. Therefore, this review will also analyze whether ML models can provide more accurate predictions as compared with traditional statistical models.

Strengths of this study include its strict adherence to the updated PRISMA 2020 checklist and its planned adherence to the CHARMS checklist. The use of a consensus-based analytical approach fosters collective accountability in interpretative decisions, thereby strengthening the robustness and credibility of the findings.

Limitations

Some limitations of the study warrant consideration. We will only conduct qualitative descriptions and not perform a meta-analysis. We anticipate that inconsistencies in the predictors included in the models, follow-up duration, clinical settings in which the models were developed, types of cardiovascular surgery, and geographic distribution of the study populations may pose challenges to conducting a meta-analysis. Even if each predictive model we included has undergone internal or external validation, its limited clinical application necessitates further evaluation of its generalizability to ensure both applicability and scientific rigor. Although the study uses a comprehensive methodology, one limitation is the omission of a search for grey literature, which could potentially result in the exclusion of studies reported in nontraditional publications. Another limitation of the planned review is that we will not contact study authors to request unreported data, although missing information will be explicitly documented.

Conclusion

We present a protocol for the systematic review of prediction models of postoperative delirium for patients with cardiac surgery. With the aim of identifying, summarizing, and appraising the available risk models, we hope to provide a current reference to stakeholders engaged in patients with cardiac surgery care, policy, and research. In addition, we also hope to explore whether PODOCVS ML models can provide more accurate predictions as compared with PODOCVS traditional statistical models.

Authors' Contributions

ZXL and WYK contributed conceptualization, writing-original draft preparation, and review and editing. ZXL, WYK, and LLJ handled methodology. LMJ and HXD conducted supervision.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P checklist.
[DOCX File , 22 KB - resprot_v14i1e75368_app1.docx]

Multimedia Appendix 2
Search strategies.
[DOCX File , 20 KB - resprot_v14i1e75368_app2.docx]

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Abbreviations

AUC: area under the curve
CHARMS: Critical Appraisal and Data Extraction for Systematic Reviews of Prediction Modelling Studies
CNKI: China National Knowledge Infrastructure
E-PRE-DELIRIC: Early Prediction Model for Delirium in the intensive care unit
ML: machine learning
PICOTS: Population, Intervention model, Comparator, Outcomes, Timing, and Setting
PODOCVS: postoperative delirium of cardiovascular surgery
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols)
PROBAST: Predictive Model Bias Risk Assessment Tool
PROSPERO: International Prospective Register of Systematic Reviews

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Protocol

Single Herbal Medicine for Insulin Resistance: Protocol for a Systematic Review and Meta-Analysis of Randomized Clinical Trials

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Abstract

Background: Insulin resistance (IR) is a central factor in the pathogenesis and progression of metabolic disorders, such as type 2 diabetes mellitus and obesity. Chinese herbal medicine (CHM) has been investigated as a potential therapy to enhance insulin sensitivity. Compared to multiherb formula therapy, single-herb therapy provides a clearer understanding of its pharmacological effects and mechanisms of action. A systematic review of the available evidence is needed to elucidate the potential effectiveness and harm of single CHMs for IR.

Objective: This study aims to conduct a systematic review and meta-analysis to evaluate the potential effectiveness and harm of single herbs for the treatment of IR, thereby providing a clearer understanding of the efficacy and safety profiles of single CHMs.

Methods: A systematic review and meta-analysis, in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020, will be conducted to evaluate the efficacy and safety of single herbs for IR. Various databases, such as Cochrane Central Register of Controlled Trials, MEDLINE, Embase, Allied and Complementary Medicine Database, China National Knowledge Infrastructure, Chinese BioMedical Literature Database, and the Wanfang Database, will be searched. Randomized controlled trials comparing single herbs or extracts originated from single herbs with a placebo or no treatment for adults diagnosed with IR-related diseases (eg, type 2 diabetes mellitus and obesity) will be included. A total of 2 researchers will independently perform study selection, data extraction, and quality assessment. The risk of bias (RoB) tool will be used to assess the quality of included studies. The overall certainty of evidence will be assessed using Grading of Recommendations Assessment, Development, and Evaluation (GRADE). The primary outcome will include measurements that assess IR, such as the hyperinsulinemic-euglycemic clamp, homeostatic model assessment, insulin sensitivity index, and oral glucose tolerance test. Secondary outcomes will include adverse events. Meta-analysis will be performed with RevMan (version 5.4; The Cochrane Collaboration). The heterogeneity of the synthetic data will be assessed using the chi-square test and the I^2 statistic.

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Results: Based on the data on IR-associated outcomes (eg, hyperinsulinemic-euglycemic clamp, homeostatic model assessment, insulin sensitivity index, and oral glucose tolerance test) and adverse event rates, this study will provide an evidence-based review and high-quality synthesis regarding the efficacy and safety of single CHMs for IR.

Conclusions: This systematic review and meta-analysis will rigorously synthesize existing evidence to clarify the efficacy and safety of single CHMs in ameliorating IR, offering critical insights for their integration into evidence-based therapies for metabolic disorders. By focusing on single-herb therapy, the findings may promote the application of CHM for IR, bridge the gap between traditional applications and evidence-based practice, and ultimately optimize the role of CHM in integrative metabolic health management.

Trial Registration: PROSPERO CRD42024589362; https://www.crd.york.ac.uk/PROSPERO/view/CRD42024589362

International Registered Report Identifier (IRRID): PRR1-10.2196/68915

(JMIR Res Protoc 2025;14:e68915) doi:10.2196/68915

KEYWORDS

insulin resistance; single herbal medicine; systematic review; homeostatic model assessment for insulin resistance; oral glucose tolerance test

Introduction

Insulin resistance (IR), defined as an impaired biological response to insulin stimulation of target tissues, primarily involves liver, muscle, and adipose tissue [1-3]. IR is the consequence of the inhibition of the insulin signaling pathway that may result from mutations or posttranslational modification of the insulin receptor or the downstream effector molecules [4]. Consequently, insulin action is disrupted in insulin-sensitive tissues, leading to abnormal glucose metabolism and dysfunction in insulin secretion [5]. IR is present in one-quarter of the general population, predisposing these people to a wide range of diseases [6]. IR is a central component of type 2 diabetes mellitus (T2DM) and is associated with various pathological states, such as metabolic syndrome, obesity, polycystic ovary syndrome, nonalcohol fatty liver diseases, hypertension, and cardiovascular diseases (CVDs) [7-9]. The rising incidence of IR and its associated complications pose a significant medical and socioeconomic burden [10]. Improving insulin sensitivity may provide a therapeutic strategy for controlling T2DM and IR-associated diseases.

Lifestyle modifications (eg, physical exercise and dietary adjustments), medications, and complementary and alternative medicine are commonly used for managing IR [11,12]. Chinese herbal medicine (CHM), a crucial element of complementary and alternative medicine, has been investigated as a potential therapy to enhance insulin sensitivity [13]. CHM encompasses a wide range of applications, including single herbs, herbal active components, and herbal formulas [14]. While herbal formulas combine multiple herbs, single herbal medicine uses a single herb (or its extract), offering a clearer understanding of its pharmacological effects and mechanisms of action. Randomized clinical trials have demonstrated that CHM prescriptions exhibit comparable efficacy to metformin in reducing homeostatic model assessment for insulin resistance (HOMA-IR) among patients with T2DM [15,16]. A systematic review of 14 studies (n=1255) found that berberine significantly reduced HOMA-IR in individuals with T2DM compared to control, with a reduction of 0.71 (95% CI –1.03 to –0.39) [17]. Given the increasingly widespread use of CHM for treating IR-associated diseases, concerns about its effectiveness and safety are increasing. A systematic review of the available evidence is needed to elucidate the potential effectiveness and harm of single CHMs for IR. Due to the large number of mixed Chinese herbal prescriptions presenting a great challenge to the evaluations, this systematic review and meta-analysis focuses on single CHMs and aims to evaluate the efficacy and safety of managing IR.

Methods

Study Registration

The protocol of this meta-analysis has been registered in PROSPERO (International Prospective Register of Systematic Reviews) with the registration number CRD42024589362. This review will be conducted and reported in line with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 statement [18].

Eligibility Criteria

Study Types

The included studies must be randomized controlled trials regardless of blinding method and publication status. Nonrandomized trials, quasi-experimental studies, animal experiments, editorials, letters, commentaries, study protocols, reviews, case reports, and conference abstracts will be excluded.

Participants

The included studies enrolled adults (18 years old) diagnosed with IR-related diseases, such as T2DM, obesity, polycystic ovary syndrome, hyperlipidemia, metabolic syndrome, and CVDs [19].

Interventions and Controls

Interventions will include single herbs or extracts originating from any single herb regardless of their compositions or administration route. Eligible single herb is based on traditional Chinese medicine theory and its form of use must have been listed in the latest version of the Chinese Pharmacopoeia (2020) or the National Essential Drug List (2018) of the People's Republic of China. The comparators include placebo or no

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treatment and allow cointerventions administrated in both intervention and control groups.

Outcomes

Studies will be included if they reported one of the following predefined outcomes: hyperinsulinemic-euglycemic clamp (HEC), insulin suppression test (IST), insulin tolerance test (ITT), intravenous glucose tolerance test (IVGTT), oral glucose tolerance test (OGTT), oral glucose insulin sensitivity index (OGSI), continuous infusion of glucose with model assessment (CIGMA), minimal modeling, fasting insulin (FINS), HOMA-IR, quantitative insulin-sensitivity check index (QUICKI), insulin sensitivity index, homeostasis model assessment-β (HOMA-β), 2-hour insulin, acute insulin response (AIR), disposition index, C-peptide level, insulin-to-glucose ratio, triglyceride glucose index (TyG index), triglyceride/high-density lipoprotein cholesterol (TG/HDL-C) ratio, TyG-BMI, metabolic score for insulin resistance (METS-IR), McAuley index, and glycated hemoglobin [20-23]. Secondary outcomes will include adverse events.

Database and Search Strategies

The following electronic databases will be searched: Cochrane Central Register of Controlled Trials (CENTRAL, Ovid), MEDLINE (Ovid, from 1946 to present), Embase (Ovid, from 1974 to present), Allied and Complementary Medicine Database (Ovid, from 1985 to present), China National Knowledge Infrastructure (from 1949 to present), Chinese BioMedical Literature Database (from 1949 to present), and Wanfang Database (from 1985 to present). Search terms include (traditional medicine OR oriental medicine OR medicinal plants OR phytotherapy OR Chinese herbal drugs OR plant extracts OR herbal medicine) and (insulin resistance OR insulin sensitivity OR glucose intolerance OR glucose tolerance OR impaired glucose OR impaired glycaemia OR metabolic syndrome OR prediabetic state). The search strategy will be developed and modified for different databases (Table S1 in Multimedia Appendix 1). We will apply the Cochrane sensitivity-maximizing randomized controlled trial filter with adaptations [24]. There will be no restriction on the language. Gray literature will be searched with Google. We will also use the ClinicalTrials.gov and World Health Organization International Clinical Trials Registry Platform (ICTRP) Search Portal to identify ongoing or unpublished trials. In order to gather missing information and details of ongoing trials, we will reach out to the authors for clarification. We will further review the reference lists of included studies and any relevant systematic reviews to identify additional references. The screening process of the searched studies will be conducted according to the PRISMA flow diagram (for checklist, see Multimedia Appendix 2) [25].

Study Selection

Literature retrieved citations will be managed by EndNote (version 20; Clarivate) software. Eligibility evaluation will be done by title and abstract reviews and when abstracts do not provide enough information, the full text of the paper will be retrieved for evaluation. This will be performed independently by 2 reviewers. Discrepancies will be resolved by consensus and arbitration by a third reviewer when necessary.

Data Extraction and Management

A data extraction form will be constructed and include general information (author, year, title, journal, language, and country), participant characteristics, and study design (sample size, age, gender, IR-related diseases, diagnosis criteria, group assignment, and blinding), treatment regimen (dosage, form, administration route, duration, and frequency), clinical outcomes, adverse events, and assessments of risk of bias. Before implementing it for all included studies, we will conduct a pilot test using at least 1 study from the review. A total of 2 review authors will independently extract study characteristics from the included studies.

Quality Assessment

The risk of bias (RoB) of the included studies will be adopted by 2 reviewers independently using the Cochrane revised tool for randomized trials (RoB 2) [24]. Each trial will be scored as either high, low risk, or some concerns for 5 items: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. When there are disagreements, a third reviewer will be consulted.

The overall certainty of evidence will be assessed by 2 assessors using Grading of Recommendations Assessment, Development, and Evaluation (GRADE), as outlined by the GRADE Working Group [26]. The 5 items will be investigated, including limitations in study design, inconsistency, imprecision, indirectness, and publication bias. The certainty of evidence will be summarized in 4 categories: high, moderate, low, and very low certainty.

Data Synthesis and Analysis

We will perform statistical analysis using the RevMan (version 5.4; The Cochrane Collaboration) software. We will calculate the mean difference or risk ratio with 95% CI, separately, for continuous and dichotomous outcomes. Data heterogeneity will be assessed using the chi-square test and the I^2 statistic. A fixed-effects model will be used to analyze pooled effects when heterogeneity is not significant ($P \geq .10$ or $I^2 \leq 50\%$); a random-effects model will be used when heterogeneity is statistically significant ($I^2 > 50\%$ or $P < .10$). We plan to conduct the following subgroup analyses: single herbal medicine versus placebo, single herbal medicine versus no treatment, and single herbal medicine combined with cointervention versus cointervention alone. Sensitivity analysis will be conducted by excluding trials with a high RoB in more than 2 domains or with a dropout rate exceeding 20%. Egger regression test and funnel plot (if more than 10 trials are included) will be performed to assess the publication bias of the included studies.

Missing or ambiguous data will be addressed by contacting the first or corresponding authors via email twice (at 2-wk intervals) to request additional information. In cases where data remain unavailable despite repeated correspondence attempts, the affected studies will be excluded from quantitative synthesis.

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For included studies with partial missing data, intention-to-treat analysis data will be used.

Results

The study will be conducted following the methodology outlined in the Cochrane Handbook for Systematic Reviews of Interventions. A total of 2 researchers will independently perform the study selection, data extraction, and quality assessment. By focusing on IR-associated outcomes (eg, HEC, IST, ITT, and OGTT) and adverse events, this study aims to provide an evidence-based review and high-quality synthesis regarding the efficacy and safety of single herbs for IR.

Discussion

Overview

IR is a central factor in the pathogenesis and progression of metabolic disorders, including T2DM, obesity, and hypertension [27]. Furthermore, a strong association has been established between IR and an increased risk of developing cardiovascular diseases [28]. The intricate mechanisms underlying IR may involve complex interplay among inflammation, endoplasmic reticulum stress, oxidative stress, and mitochondrial dysfunction [29-32]. CHM has emerged as a potential therapeutic modality for enhancing insulin sensitivity [13,33]. Numerous CHMs have demonstrated therapeutic effects in improving insulin sensitivity in peripheral tissues, enhancing glucose-stimulated insulin secretion, promoting browning of white adipose tissue, and lowering glucose and lipid levels [34-37]. The growing use of CHM for improving insulin sensitivity underscores the urgent need for a thorough assessment of its effectiveness and safety.

Anticipated Principal Findings

This systematic review and meta-analysis will synthesize existing evidence to comprehensively evaluate the therapeutic efficacy and safety profiles of single CHMs for insulin IR. Subgroup analyses will compare single herbs against placebo or no treatment and assess efficacy variations across IR-associated conditions (eg, T2DM and obesity), providing important insights into context-specific therapeutic potential. In addition, critical appraisal of the study and reporting quality in included trials will identify methodological limitations in current research, informing recommendations for future trial design and transparency.

Outcome Selection

While the HEC remains the gold standard for quantifying IR due to its direct measurement of insulin-mediated glucose uptake [38-40], its clinical utility is limited by technical complexity and invasiveness [41]. Consequently, multiple validated markers, such as fasting-based (eg, HOMA-IR and QUICKI), dynamic tests (eg, OGTT and IVGTT), and composite indices (eg, TyG index and METS-IR), are widely adopted in clinical research [20-23], Among these, HOMA-IR is prioritized in observational and interventional studies due to its simplicity and reproducibility [38]. To ensure methodological inclusivity, this review will incorporate all IR-associated outcomes.

Strengths and Limitations

This represents the first systematic evaluation of all single herbs and herbal extracts for IR, addressing a critical gap left by prior reviews focused on multiherb formulas [42,43] or isolated compounds [44,45]. While single-herb analyses deviate from traditional multiherb clinical practice, they provide clarity in therapeutic efficacy essential for evidence-based integration into IR management protocols. However, heterogeneity in treatment details (eg, administration routes and treatment duration) and the potential inclusion of low-quality studies may limit the generalizability of findings.

Future Directions

This study may inform the potential of single CHMs as alternative therapies for IR, bridging traditional knowledge with clinical needs. Identified high-priority herbs should undergo rigorous preclinical validation (eg, pharmacokinetic studies, in vivo mechanistic models) followed by confirmatory clinical trials with rigorous design. Concurrently, the quality assessment framework established here may guide future trial designs to minimize bias and enhance reproducibility.

Conclusion

This systematic review and meta-analysis will rigorously synthesize existing evidence to clarify the efficacy and safety of single CHMs in ameliorating IR, offering critical insights for their integration into evidence-based therapies for metabolic disorders. By focusing on single-herb therapy, the findings may promote the application of CHM for IR, bridge the gap between traditional applications and evidence-based practice, and ultimately optimize the role of CHM in integrative metabolic health management.

Dissemination

Results will be disseminated through peer-reviewed journals and presentations at international conferences focused on metabolic disorders, ensuring accessibility to clinicians, researchers, and policy makers.

Acknowledgments

We would like to express our gratitude to all authors for their contributions to this paper, as well as to the editors and reviewers for their valuable criticisms and corrections. This work is supported by the Vincent and Lily Woo Foundation. The funder has no role in the design of the study, in the collection, analysis, and interpretation of data, nor in the writing of the manuscript.

Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

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Authors' Contributions

ZB and JZ conceived and designed the study. JL, ZZ, and HW developed the search strategy and drafted the protocol. All authors contributed to the research, and read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Literature search strategy.
[DOCX File , 24 KB - resprot_v14i1e68915_app1.docx]

Multimedia Appendix 2
PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) 2015 checklist.
[DOCX File , 21 KB - resprot_v14i1e68915_app2.docx]

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Abbreviations

AIR: acute insulin response
CHM: Chinese herbal medicine
CIGMA: continuous infusion of glucose with model assessment
CVD: cardiovascular disease
FINS: fasting insulin
GRADE: Grading of Recommendations Assessment, Development, and Evaluation
HEC: hyperinsulinemic-euglycemic clamp
HOMA-β: homeostasis model assessment-β
HOMA-IR: homeostatic model assessment for insulin resistance
ICTRP: International Clinical Trials Registry Platform
IR: insulin resistance
IST: insulin sensitivity index
ITT: insulin tolerance test
IVGTT: intravenous glucose tolerance test
METS-IR: metabolic score for insulin resistance
OGSI: oral glucose insulin sensitivity index
OGTT: oral glucose tolerance test
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Register of Systematic Reviews
QUICKI: quantitative insulin-sensitivity check index
RoB: risk of bias
T2DM: type 2 diabetes mellitus
TG/HDL-C: triglyceride/high-density lipoprotein cholesterol
TyG index: triglyceride glucose index

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Protocol

Comparing Clearances of Polymethylmethacrylate and Polysulfone Dialyzer Membranes for Postdilution Hemodiafiltration in Patients With Kidney Failure: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Kidney replacement therapy (KRT) is needed by patients with kidney failure to eliminate metabolic waste. When kidney transplantation is not feasible, hemodialysis (HD) is performed. Hemodiafiltration (HDF) provides a better solute clearance than conventional HD due to its higher convective dose. The clearance performances of HDF also depend on the type of dialysis membrane used. Polysulfone (PS) membranes have been used since 1965 due to their excellent resistance and biocompatibility. However, the newer generation of polymethylmethacrylate (PMMA) membranes offers comparable convective capacity with reduced albumin loss.

Objective: The forthcoming study aims to compare the solute clearance of postdilution HDF using PMMA versus PS dialyzer membranes in patients with kidney failure requiring long-term HD.

Methods: The literature search will use databases including PubMed, Scopus, Web of Science, Embase, and Cochrane. Two independent reviewers will select studies and assess their quality. Pooled estimates of relevant factors will be computed via a random-effects model using Stata/BE 18 (StataCorp) software. The reporting of findings will adhere to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.

Results: The search and screening for the systematic literature review are expected to be completed in May 2026. Data extraction, quality appraisal, and subsequent data synthesis will begin in June 2026. The review should be completed by October 2026, and the study results will be published in 2027.

Conclusions: Dialyzer membrane clearance determines HD quality. Nevertheless, many middle uremic molecules are poorly cleared with conventional HD. Consequently, HDF was invented to improve their clearance. Among the most widely used dialyzer membranes, PS and PMMA are used in the newer generation of HDF. Nevertheless, no available systematic reviews have compared the efficacy of the 2 dialyzer membrane materials. Although no ideal dialyzer can efficiently remove all types of uremic toxins

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while retaining essential elements, improving solute clearance should benefit patients. This information could help clinicians determine which membrane to use in HDF.

Trial Registration: PROSPERO CRD42024603277; https://www.crd.york.ac.uk/PROSPERO/view/CRD42024603277

International Registered Report Identifier (IRRID): PRR1-10.2196/71943

(JMIR Res Protoc 2025;14:e71943) doi:10.2196/71943

KEYWORDS

albumin; beta 2-microglobulin; creatinine; dialysis; end stage kidney disease; polymethyl methacrylate; polysulfone

Introduction

In patients with chronic kidney disease (CKD), signs and symptoms typically develop gradually [1-3]. As kidney function declines progressively, the condition may eventually lead to kidney failure. At this stage, the kidneys can no longer effectively eliminate metabolic waste, resulting in the accumulation of toxins and disturbances in electrolyte balance [4]. The definitive treatment for kidney failure is kidney replacement therapy (KRT) through a kidney transplant. Still, this option is not always feasible or successful, necessitating other KRT modalities, namely hemodialysis (HD) or peritoneal dialysis [5-9]. HD can be divided into conventional HD, hemodiafiltration (HDF), and expanded HD [10].

Conventional HD uses solute diffusion and limited ultrafiltration, using a high-flux membrane inserted in a hollow-fiber dialyzer. Conventional HD is linked to “residual risk” resulting from the accumulation of inadequately removed medium-sized compounds. Meanwhile, HDF uses convection and diffusion to eliminate small- and medium-sized molecules. A significant distinction between HDF and conventional HD is the total ultrafiltered volume per session (dialytic convective dose). HDF can achieve a significantly higher convective dose (10- to 15-fold), leading to a 2-fold increase in middle-molecular-weight solute clearance [11,12].

HDF was initially introduced in the United States by Lee Henderson in 1973 [13]. On-line generation of substitution fluid for HDF was then implemented in the mid-1980s [14]. HDF has since undergone substantial development. See et al (2019) [15] found that HDF was associated with a significantly lower risk of all-cause mortality (adjusted hazard ratio [HR] of 0.79 and 0.88 for patients in Australia and New Zealand, respectively). An association was also found between HDF and reduced cardiovascular mortality, with an adjusted HR of 0.78 in Australian patients. Using the French Renal Epidemiology and Information Network Registry, Mercadal et al (2016) [16] found that the HRs for all-cause and cardiovascular mortality in patients treated exclusively with HDF were 0.77 and 0.66, respectively.

HDF can be conducted with dialysis membranes comprising different raw materials, including cellulose, polysulfone (PS), polyamide, polymethylmethacrylate (PMMA), and polycarbonate [17]. Clinicians must consider several factors to determine which dialyzer membrane is most suitable for dialysis: performance, biocompatibility, cytotoxicity, sterilization, and endotoxin retention [18]. This systematic review and meta-analysis will focus on the efficacy of PMMA dialyzers compared to that of PS in postdilution HDF in patients with kidney failure requiring long-term HD. A PS membrane has an asymmetric structure where the pore size enlarges from inside to outside and a thin skin layer with very small pore sizes to control solute separations. Conversely, a PMMA membrane has a uniform pore size structure, and the entire membrane controls solute separations. Therefore, the separation characteristics of PMMA are broader than those of PS membranes. Furthermore, PS membranes remove uremic toxins from the blood via diffusion and filtration, while PMMA membranes also use adsorption in addition to diffusion and filtration [19-21]. However, PMMA membranes have lower permeability than PS membranes, increasing the risk of fouling and platelet-induced membrane coagulation [22].

A dialyzer’s efficacy is assessed based on the clearance of solutes, including urea, creatinine, phosphate, uric acid, albumin, α1-microglobulin, ß2-microglobulin, myoglobin, prolactin, and κ and λ free light chains [23,24]. Our review aims to answer the following question: in patients with kidney failure requiring long-term HD, does the PMMA dialyzer membrane demonstrate a higher efficacy than the PS dialyzer membrane? The PICO (Population, Intervention, Comparison, and Outcomes) framework will be used during the article search; “P (population)” refers to patients with kidney failure requiring long-term HD, “I (intervention)” refers to HDF using PMMA dialyzer membrane, “C (comparison)” refers to HDF using the PS dialyzer membrane, and “O (outcome)” refers to the efficacy of solute clearance.

Methods

Overview

This review will be conducted and reported following the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) guidelines (Multimedia Appendix 1) [25,26]. We will also integrate this review with the Meta-analysis of Observational Studies in Epidemiology guidelines, since the outcome will be a meta-analysis of selected observational studies [27].

Eligibility Criteria

We will include all original articles in English based on the following criteria:

1. Studies involving adult patients diagnosed with kidney failure and requiring long-term HD.
2. Studies investigating postdilution HDF using PMMA and/or PS as dialyzer membranes.

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3. Studies reporting dialysis efficacy as the primary or secondary outcome.
4. Peer-reviewed original articles, including randomized controlled trials (RCTs) and observational studies (cohort, case-control, and cross-sectional studies).

The exclusion criteria are as follows:

1. Studies involving patients with acute kidney injury, from which long-term dialysis patients' group data cannot be extracted.
2. Studies using dialyzer membranes other than PMMA or PS and using mixed or combined membrane types, from which PMMA or PS group data cannot be extracted.
3. Studies investigating dialysis modalities other than HDF (eg, high-flux and low-flux HD, expanded HDF).
4. Any review, case study, commentary, qualitative study, or editorial.

Outcome Measures

The review outcomes are efficacy based on solute clearance of urea, creatinine, phosphate, uric acid, α1-microglobulin, β2-microglobulin, myoglobin, albumin, and prolactin. The efficacy will be assessed based on the solutes' reduction ratio (RR) measured before and after the HDF session. Quantitative data will be reported as mean (SD) values.

Information Sources

Electronic Search

We will systematically conduct a comprehensive literature search using various literature databases, including MEDLINE (PubMed), Web of Science, Scopus, Embase, and the Cochrane Central Register of Controlled Trials (CENTRAL) to identify eligible studies. Secondary searches will be conducted on Google Scholar and other websites, and the reference section of the included studies will also be hand-searched for additional relevant studies. Studies will be restricted to the English language. The search will be performed from selected electronic databases up to October 2025.

Search Strategy

The proposed search term for the first theme will be "long-term hemodialysis." The second theme is "polymethylmethacrylate" and "polysulfone." The third theme is "efficacy." The exploded versions of the MeSH (Medical Subject Headings) browser for each theme will be included. All 3 search themes will be combined using the Boolean operators "OR" and "AND." Multimedia Appendix 2 presents the detailed search terms for each database.

Study Selection

We will identify and remove duplicates and collate multiple reports. Two review authors (AKK and NN) will independently screen all the titles and abstracts to examine the potential studies for inclusion and exclude evidently irrelevant studies. We will identify studies from databases and remove duplicate records. We will then perform an initial screening based on the title and abstract of the articles to identify those that are irrelevant or meet the inclusion criteria. Articles deemed irrelevant based on the title and abstract will be excluded from further consideration. For the included study, we will retrieve the full-text study reports and publications, and the review authors will independently screen the full text to identify studies for inclusion and exclusion to determine their eligibility. The reasons for excluding articles, such as having an in vitro design and having different interventions, HD modalities, patient groupings, outcomes, or measurements, will be documented. Articles that meet all inclusion criteria and are not excluded will be included in the review.

We will resolve any disagreement through discussion. If no consensus is reached, the other 2 authors will act as arbiters. We will record the selection process in sufficient detail to complete a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram and construct a table describing the characteristics of the excluded studies [25,26]. Rayyan (Qatar Computing Research Institute) will be used to store, organize, and manage all the articles identified from databases.

Data Extraction and Management

We will use a standardized data extraction form created by the Microsoft Excel Spreadsheet software for study characteristics and outcome data. Two review authors (CGA and NN) will independently extract outcome data from the included studies. Discrepancies in determining data usability will be resolved by discussion or by involving the other 2 review authors. The usability of outcome data will be documented in the characteristics of included studies. Data will be considered unusable if any of the following apply: (1) a nonstandard formula or procedure is used to calculate the RR; (2) RR is reported as median (IQR), and conversion to mean (SD) is not feasible; (3) results are presented only in graphical form without sufficient resolution or accompanying numerical data; (4) inconsistent or incomplete reporting of outcome data across comparison groups; (5) the HDF procedure is not adequately described, particularly concerning the dialysis modality (eg, postdilution vs predilution), membrane type, and dialysis settings; (6) the type of membrane used is not reported or is ambiguous; and (7) key demographic or baseline characteristics of participants (eg, age, sex, and dialysis duration) are not reported. Studies meeting the eligibility criteria but excluded due to unusable data will be listed in the final review along with specific reasons for exclusion, to ensure transparency and minimize selective reporting bias.

We will recheck that data are entered correctly by comparing the systematic review data with the study reports. The following study characteristics from the included studies will be extracted:

- Title, first author, study country based on the study setting, region, and publication year.
- Methods: study design, data source, total study duration, and analysis method.
- Participants: number of patients, mean and/or median age, age range, and sex.
- Outcome: efficacy based on solute clearance, which is the measurement of RR of each solute such as urea, creatinine, phosphate, uric acid, α1-microglobulin, β2-microglobulin, myoglobin, albumin, and prolactin, which were measured before and after HDF.

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- Exposures or risks: CKD etiology, dialysis vintage, and comorbidity. However, whenever data are applicable, we will extract the data on other exposure risks or modifiable factors, control conditions, and adjustment variables.

If there is any unclear or missing data for extraction, we will contact the corresponding author of the original studies to request clarification or check whether additional data can be made available upon request. If there is no response from the corresponding author within a reasonable time frame, the study will be excluded from the analysis, with the reason for exclusion documented in the review. We will also assess the potential impact of missing data on the overall findings through sensitivity analysis, where feasible. We will also consider the risk of bias due to incomplete data in the overall quality assessment.

Quality Assessment

Two review authors will independently assess the risk of bias depending on the study design (AKK and AW). For RCTs, we will use the Cochrane Risk of Bias 2 (RoB 2) tool, which evaluates five domains: (1) bias due to the randomization process, (2) deviation from intended intervention, (3) missing outcome data, (4) measurement of outcomes, and (5) selection of the reported result. Each domain will be rated as "low risk," "some concerns," or "high risk," and an overall risk of bias judgment will be assigned [28].

For nonrandomized intervention studies, we will use the Risk Of Bias In Non-randomized Studies of Interventions (ROBINS-I) tool. The risk of bias will be assessed across several domains: (1) bias due to confounding, (2) bias in participant selection, (3) bias in classification of the intervention, (4) bias from deviations in the intended interventions, (5) bias due to missing outcome data, (6) bias in outcome measurement, and (7) bias in the selection of reported results. The risk of bias for each domain will be rated as low, moderate, serious, or critical. An overall risk of bias judgment will also be made [29]. In the sensitivity analysis, we will exclude trials assessed as high risk of bias with the RoB 2 tool and those rated as serious or critical risk of bias with the ROBINS-I tool. This will allow us to assess whether the inclusion of these studies significantly influences the pooled effect estimates.

Statistical Analysis

Data Analysis and Statistical Analysis

The primary outcome of our study is the efficacy, which will be based on solute clearance, based on the RR of each solute. RR will be determined using laboratory parameters, which include serum concentrations of urea, creatinine, phosphate, uric acid, α1-microglobulin, β2-microglobulin, myoglobin, albumin, and prolactin, measured before and after HDF. Quantitative data will be reported as mean (SD) values. Since RRs are measured using the same scale across all included studies, we will use the mean difference as the effect measure. For parametric comparisons, paired Student *t* tests followed by Bonferroni post hoc tests will be used. A P value of <.05 will be considered statistically significant.

Although both RCTs and nonrandomized studies will be included in this systematic review, a meta-analysis will be conducted separately for each study design to account for their inherent methodological differences. Meta-analyses will be conducted using a random-effects model to account for potential variability and heterogeneity among studies. Given the inclusion of nonrandomized studies, we acknowledge the potential for confounding and selection bias. To address this, we will prioritize adjusted effect estimates (eg, those derived from multivariable regression models or propensity score analyses) where available. Additionally, we will conduct subgroup or sensitivity analyses by excluding studies judged to be at overall high risk of bias. If 10 or more studies are included, we will consider performing meta-regression to explore potential effect modifiers. A narrative synthesis will be provided for outcomes not amenable to quantitative synthesis.

Heterogeneity Assessment

Assessing heterogeneity is critical in a meta-analysis, as it enables the evaluation of the degree of inconsistency or variability among the results of individual studies. This review will evaluate heterogeneity using the I^2 and Q statistics. The I^2 statistic will be used to quantify the impact of heterogeneity, with percentages of around 25%, 50%, and 75% representing a low, moderate, and high degree of heterogeneity, respectively [30]. The statistical Q test determines whether significant heterogeneity exists among the studies. The significance level for the Q test is set at 0.01 in this review [31]. If significant heterogeneity is detected using the Q test or I^2 index (>50%), we will explore potential heterogeneity sources using subgroup analyses and meta-regression. We will also explore possible causes (for example, differences in study quality, participants, or outcome assessments) and evaluate the studies based on their methodological characteristics to determine whether differences in these characteristics can explain the degree of heterogeneity and whether a meta-analysis is appropriate.

Assessment of Publication Bias

We will create and examine a funnel plot to explore possible small study biases if we can pool over 10 studies in 1 meta-analysis. The number of studies missing from the funnel plot will be estimated. The effect size after inputting these missing studies will be estimated using the trim-and-fill method. This simple estimation approach proposed by Duval and Tweedie [32] involves trimming off the asymmetric outlying part of the funnel, using the symmetric remainder to estimate the true funnel center, and replacing the trimmed studies and their counterparts around the center. Other methods to assess the publication bias will include the Begg rank correlation and the Egger weighted regression method test [33,34].

Ethical Considerations

We registered this systematic review in PROSPERO (systematic review registration: CRD42024603277). Since this review will use published data, the need for ethical approval is waived in accordance with local guidelines. The systematic review will focus on determining whether the PMMA or the PS dialyzer membrane has a higher efficacy in patients with kidney failure requiring long-term HD.

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Results

The search and screening for the systematic literature review is expected to conclude in May 2026. Data extraction, quality appraisal, and subsequent data synthesis will begin in June 2026. The review should be completed by October 2026, and the study results will be published in 2027.

Discussion

PS is an amorphous polymer with excellent thermal and chemical stability [35]. The PS membrane is asymmetric, implying that for a membrane thickness of 30 microns, a 1-micron layer controls the separation process, while the remainder has structural functions. Conversely, the PMMA membrane is symmetric, with the whole thickness involved in the separation process [21]. The PMMA membrane adds adsorption to the existing HD diffusion and convection processes. While diffusion and convection remove small and medium-sized molecules, adsorption enables the removal of medium- and high-molecular-weight molecules [22].

The removal of toxins and waste products from the patient's blood defines the adequacy of HD. Adequate dialysis can improve patient survival and quality of life [36-39]. Kt/V calculation is the most widely used method to assess dialysis adequacy, where K is the effective dialyzer solute clearance, t is the duration of the dialysis session, and V is the solute distribution volume [40]. Currently, small solute clearance is regarded as the best measure of HD adequacy. Kt/V urea, also known as fractional urea clearance, is a widely used tool to assess dialysis efficacy in daily clinical practice [41].

The use of urea as the sole representation of dialysis adequacy tends to oversimplify this concept. In this context, urea does not represent the kinetic behavior of other solutes, including inorganic solutes such as phosphate, middle molecules such as β2-microglobulin, and protein-bound uremic toxins such as p-cresyl sulfate, whose detrimental effects are linked with inflammation, oxidative stress, and cardiovascular disease [42-47]. Hence, the concept of adequacy is evolving to include nonurea parameters [48].

HD adequacy is partly determined by dialyzer membrane clearance [49]. Moreover, membrane properties, including pore size, wall thickness, and surface area, determine solute clearance. The uremic toxins HD removes are divided into four categories: (1) small water-soluble compounds (eg, urea) with a size of <500 Da, (2) a middle-molecular-weight of 500-15,000 Da, (3) large molecules with a size of >15,000 Da, and (4) protein-bound molecules (eg, p-cresol of 108 Da). However, when describing the in vitro performance of dialyzers, many studies only considered the results obtained with small solutes and middle-molecular-weight molecules [50].

Middle-molecular-weight molecules include several cytokines, adipokines, growth factors, and other signaling proteins significantly elevated in dialysis patients compared to that in people with normal kidney function. The serum levels of interleukin (IL)-1β, IL-6, and IL-18, and κ and λ free light chains are also elevated in patients with advanced CKD [51]. These molecules play key roles in the inflammation-cardiovascular disease pathway and are linked with chronic inflammation, atherosclerosis, structural cardiac disease, and protein-energy wasting [52,53].

While conventional HD can effectively remove small uremic molecules (<0.5 kDa), including urea, it poorly removes middle-molecular-weight molecules in the 0.5-60 kDa range. Thus, HDF was invented to improve the clearance of middle-molecular-weight molecules [54]. The clinical application of on-line generation of replacement fluid HDF has been limited in the United States and has predominantly advanced in Europe. Increasing numbers of patients in Japan and other Asian countries have recently opted for HDF treatment [55,56].

The HDF removal efficiency is mainly determined by the replacement fluid volume, while the removal characteristic is affected by the dilution method. Postdilution HDF, when combined with a protein-nonleakage hemodiafilter, is superior in removing small to middle-molecular-weight molecules. Conversely, predilution HDF with a protein-leakage–type hemodiafilter is preferred for removing middle- to high-molecular weight molecules [57]. Predilution HDF efficiently removes middle-molecular-weight molecules of up to α1-microglobulin (26-30 kDa). However, the biological activity of α1-microglobulin is unclear, and the uremic toxins in its vicinity are also unknown. Meanwhile, postdilution HDF increases the removal efficiency for molecular weights up to those of β2-microglobulin (11-12 kDa), which has been established as a uremic toxin [57].

Views differ on the impact of dialyzer characteristics on patient outcomes and the characteristics that the clinician should prioritize. The impact also relies on the dialyzer's application, where convective therapies such as HDF outperform diffusive therapies such as HD [58]. Although no ideal dialyzer can efficiently remove all types of uremic toxins while retaining vitamins and other essential elements, expanding the range of uremic toxin clearance should benefit patients. Nevertheless, further research is required to demonstrate the superiority of these new dialyzers [59].

Our study will include stable patients with kidney failure undergoing thrice weekly HD sessions. We recognize that the duration of each dialysis session (in minutes) might differ between studies. Therefore, we will only include studies with similar dialysis prescriptions and the same modality, postdilution HDF, to limit bias. To our knowledge, this study will be the first to conduct a systematic review and meta-analysis of the available evidence regarding comparing clearance between PMMA and PS dialyzer membranes for postdilution HDF in patients with kidney failure.

Our study may have several limitations. Even if the studies used the same membrane material (PS or PMMA), if they used dialyzers from different manufacturers or the same manufacturer but different versions (type, design, or specification), bias could result from different clearance capacities. Second, clearance is subject to methodological heterogeneity, as the time point for each blood sampling collection might differ between studies.

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We will not specify time points as inclusion criteria due to the risk of eliminating potentially relevant studies.

Third, our study will not assess some aspects potentially affecting the fluid removal rate. We will not evaluate the patients' primary kidney disease or other health problems potentially affecting the blood protein level (albumin). Moreover, we will not assess the quality of blood vessels or HD lumen catheters used for dialysis, which potentially affect dialysis efficiency through resistance and subsequently influence the fluid removal rate.

In summary, our systematic review and meta-analysis may help compare the solute clearance of PMMA and PS dialyzer membranes for postdilution HDF in people with kidney failure. The results may help clinicians determine the most suitable membrane for HDF for their routine HD practice. The data may also provide a starting point for further research on the impacts of various dialyzer membranes on the HDF solute removal rate.

Authors' Contributions

Conceptualization: CGA and NN
Data curation: CGA and NN
Formal analysis: CGA and NN
Investigation: CGA, AKK, and NN
Methodology: CGA and NN
Project administration: CGA and NN
Resources: CGA
Supervision: CGA, AKK, and AW
Validation: CGA, AKK, and AW
Visualization: CGA and NN
Writing—original draft: CGA and NN
Writing—review and editing: CGA, AKK, AW, and NN

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P checklist.
[DOCX File , 29 KB - resprot_v14i1e71943_app1.docx]

Multimedia Appendix 2
Search terms.
[DOCX File , 18 KB - resprot_v14i1e71943_app2.docx]

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Abbreviations

CKD: chronic kidney disease
HD: hemodialysis
HDF: hemodiafiltration
HR: hazard ratio
IL: interleukin
KRT: kidney replacement therapy
MeSH: Medical Subject Headings
PICO: Population, Intervention, Comparison, and Outcomes
PMMA: polymethylmethacrylate
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
PS: polysulfone
RCT: randomized controlled trial
RoB 2: Cochrane Risk of Bias 2
ROBINS-I: Risk Of Bias In Non-randomized Studies of Interventions
RR: reduction ratio

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Protocol

The Effectiveness of Virtual Reality–Based Mindfulness Interventions for Managing Stress, Anxiety, and Depression: Protocol for a Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Abstract

Background: While traditional mindfulness-based interventions demonstrate effectiveness in improving mental health outcomes, their delivery methods face significant challenges related to accessibility and engagement. Geographic barriers to trained facilitators, time constraints for in-person sessions, and participant dropout rates of 15% to 30% due to perceived monotony limit intervention reach and effectiveness. Virtual reality (VR) technology offers innovative solutions through multisensory immersion that creates presence, the subjective feeling of "being there," enhancing attention regulation and reducing external distractions. Meta-analyses demonstrate that VR interventions achieve higher engagement rates and lower dropout compared to traditional delivery methods; however, systematic evaluation of VR-based mindfulness interventions remains limited.

Objective: Following the population, intervention, comparison, and outcome framework, this systematic review protocol aims to evaluate whether VR-based mindfulness interventions (intervention), compared to traditional face-to-face mindfulness interventions, digital mindfulness apps, active nonmindfulness controls, and waitlist or no-treatment groups (comparisons), effectively reduce stress, anxiety, and depression while improving mindfulness and well-being (outcomes) in adults aged 18 to 65 years from both general and clinical populations with diagnosed mental health conditions (population).

Methods: We will conduct comprehensive searches across 8 databases (PubMed, Web of Science, Embase, CINAHL, MEDLINE, the Cochrane Library, PsycINFO, and Scopus) from inception to June 2025, including gray literature and unpublished trials. Eligible studies include randomized controlled trials evaluating VR-based mindfulness interventions using immersive technology (head-mounted displays and cave environments) with explicit mindfulness content in adult populations. Primary outcomes include stress, anxiety, and depression; secondary outcomes encompass mindfulness levels, well-being, and user experience. Two independent reviewers will screen studies, extract data, and assess risk of bias using the Cochrane Risk of Bias 2 tool with standardized criteria. Meta-analysis will use random effects models with inverse variance weighting, calculating standardized mean differences with 95% CIs. Preplanned subgroup analyses will examine intervention duration (<2 wk, 2-8 wk, and >8 wk), VR technology type (head-mounted displays vs cave environments), population characteristics (clinical vs nonclinical samples), and mindfulness technique type, with heterogeneity quantification using prespecified I^2 thresholds.

Results: Database searches will commence in June 2025, with data extraction planned for August 2025 to September 2025 and systematic review completion planned by December 2025. Expected results include pooled effect sizes for primary outcomes, forest plots displaying individual and combined study effects with comprehensive subgroup analyses, and heterogeneity statistics with Grading of Recommendations Assessment, Development, and Evaluation evidence quality assessments.

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Conclusions: The review will provide definitive evidence regarding VR-based mindfulness interventions' effectiveness for mental health outcomes. The findings will inform clinical practice guidelines for integrating VR-based mindfulness, guide technology development specifications, and establish evidence-based recommendations for health care policy regarding therapeutic VR reimbursement and regulatory frameworks.

Trial Registration: PROSPERO CRD42024585899; https://tinyurl.com/288evyku

International Registered Report Identifier (IRRID): PRR1-10.2196/68231

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KEYWORDS

virtual reality; mindfulness; mental health; digital health interventions; systematic review; meta-analysis

Introduction

Background

Mindfulness, defined as the practice of purposefully paying attention to the present moment without judgment, has emerged as a popular and effective approach to promoting mental well-being and reducing symptoms of various psychological disorders [1]. Rooted in ancient Buddhist traditions, mindfulness has been adapted and integrated into various therapeutic interventions, such as mindfulness-based stress reduction (MBSR) and mindfulness-based cognitive therapy [2]. A growing body of research has demonstrated the effectiveness of mindfulness-based interventions in reducing stress, anxiety, and depression as well as improving overall well-being and quality of life [3].

The core principles of mindfulness involve cultivating a nonjudgmental awareness of one's thoughts, feelings, and sensations in the present moment [1]. This heightened awareness is thought to promote emotional regulation, cognitive flexibility, and a more adaptive response to stress [4]. Mindfulness-based interventions typically involve a structured training program, which includes various meditation practices, such as focused attention, open monitoring, loving-kindness meditation, as well as psychoeducation and group discussions [2].

While traditional mindfulness-based interventions have shown promise in improving mental health outcomes, they may face certain limitations in terms of accessibility, adherence, and engagement. For example, some individuals may find it challenging to attend regular in-person sessions due to time constraints, geographical barriers, or personal preferences [5]. Moreover, the traditional format of mindfulness training, which often involves sitting meditation and verbal guidance, may not be appealing or engaging for all individuals, particularly those who prefer more interactive and immersive experiences [6].

Empirical evidence supports these accessibility and engagement challenges. Dropout rates in traditional 8-week MBSR programs range from 15% to 30% [3], with common reasons including scheduling difficulties (reported by 42% of the individuals who dropped out); perceived boredom with practice formats (37%); and geographical barriers to qualified instructors, particularly in rural or underserved areas (25%). In addition, practice adherence in traditional mindfulness interventions averages only 64% of recommended home practice time, with a significant decline over the course of interventions [7]. These quantified barriers disproportionately affect certain populations, including younger adults, those with attention difficulties, individuals with demanding work schedules, and those in regions with limited access to trained mindfulness facilitators.

Recent evidence further supports these accessibility challenges across diverse populations. Research from Iran demonstrates similar barriers in Middle Eastern contexts, where traditional mindfulness interventions face cultural adaptation challenges and limited trained instructor availability [8]. Cross-cultural studies indicate that technology-mediated interventions may overcome geographic and cultural barriers while maintaining intervention fidelity across diverse populations [9]. In addition, comparative effectiveness research suggests that virtual reality (VR)–based approaches show particular promise for populations with attention-related difficulties who struggle with traditional mindfulness intervention formats [10], while behavioral intervention studies confirm enhanced engagement through immersive technologies [11].

In recent years, rapid advancements in VR technology have opened new avenues for the delivery of mindfulness interventions. VR, which involves the use of computer-generated simulations to create immersive and interactive environments, has shown promise as a tool for enhancing the effectiveness and accessibility of various therapeutic interventions [12]. By providing a sense of presence and embodiment, VR has the potential to facilitate deeper engagement and immersion in mindfulness practices, potentially leading to enhanced outcomes [6].

VR offers distinct advantages over other digital mindfulness alternatives, such as smartphone apps or online programs. While mindfulness apps provide accessibility similar to VR, they lack the multisensory immersion that creates presence, which is a key mechanism for deepening practice. Comparative studies show that VR mindfulness demonstrates significantly higher user engagement metrics (average session duration 22 mins vs 7.5 min for apps), stronger attentional focus (measured by fewer reported mind-wandering episodes), and greater physiological indicators of relaxation response (larger decreases in heart rate variability and skin conductance) compared to identical content delivered via smartphone [6]. In addition, VR uniquely provides real-time biofeedback opportunities through integration with physiological monitoring, dynamic environment adaptation based on user states, and embodied interaction that traditional digital formats cannot replicate.

Several theoretical frameworks have been proposed to explain the potential mechanisms underlying the effectiveness of

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VR-based mindfulness interventions. One such framework is the presence-attention-compassion (PAC) model, which suggests that VR technology can enhance mindfulness training by promoting a sense of presence (ie, the feeling of being in the virtual environment), attention (ie, focused awareness on the present moment), and compassion (ie, a nonjudgmental and kind attitude toward oneself and others) [6]. According to this model, the immersive nature of VR can help individuals disengage from distracting thoughts and external stimuli, allowing them to focus more fully on the present moment experience. The PAC model specifically proposes that VR enhances mindfulness through three mechanistic pathways: (1) presence—the subjective feeling of "being there" in the virtual environment increases absorption and reduces external distractions through multisensory immersion; (2) attention—interactive elements guide focus to relevant stimuli while filtering extraneous information, effectively training sustained attention networks; and (3) compassion—emotional engagement with virtual environments facilitates self-compassion through embodied perspective taking. These mechanisms directly address cognitive and emotional processes underlying mindfulness practice that traditional delivery methods may struggle to engage consistently. Recent neuroimaging studies support this model, showing that VR mindfulness activates similar neural networks as traditional practices but with heightened engagement in attention-related brain regions. Moreover, the sense of embodiment facilitated by VR can promote a more visceral and emotionally engaging experience of mindfulness, potentially enhancing its therapeutic effects [6].

Another theoretical framework that may help to explain the potential benefits of VR-based mindfulness interventions is the embodied cognition theory [13]. This theory posits that cognition is not solely a mental process but is deeply rooted in the body's interactions with the environment. In the context of VR-based mindfulness interventions, the embodied cognition theory suggests that the immersive and interactive nature of VR can facilitate a more embodied and experiential form of mindfulness training, which may be more effective than traditional approaches that rely primarily on verbal guidance and mental imagery [6].

Several studies have explored the feasibility and effectiveness of VR-based mindfulness interventions in various populations and settings. For example, Nararro-Haro et al [14] conducted a randomized controlled trial (RCT) comparing a VR-based mindfulness intervention to a traditional mindfulness intervention in a sample of healthy adults. The VR intervention featured a virtual beach environment where participants were guided through various mindfulness exercises, including focused attention on the breath and body scan meditation. The results showed that both interventions led to significant improvements in mindfulness, stress, and affect, with the VR group showing greater reductions in stress compared to the traditional mindfulness group.

Similarly, Chandrasiri et al [15] reviewed the literature on VR-based mindfulness interventions for pain management, concluding that VR mindfulness shows promise as a complementary approach to pain management, with the potential to enhance the effectiveness of traditional mindfulness practices. The authors highlighted several advantages of VR-based mindfulness interventions, such as the ability to create personalized and engaging environments, the potential for greater adherence and motivation, and the opportunity for more precise measurement and feedback.

Other studies have explored the use of VR-based mindfulness interventions in clinical populations, such as individuals with anxiety disorders [6], depression [16], and substance use disorders [17]. These studies have generally shown promising results, with VR-based mindfulness interventions leading to significant improvements in clinical outcomes, such as reduced anxiety and depressive symptoms, increased mindfulness skills, and enhanced emotion regulation.

However, the existing literature demonstrates considerable methodological heterogeneity. A critical analysis revealed persistent limitations, including small sample sizes (typically n<50), short intervention durations (often single-session designs), reliance on convenience samples with limited demographic diversity, and inconsistent measurement approaches. For example, the finding of superior stress reduction in the VR condition by Navarro-Haro et al [6] was based on a sample of only 28 participants with no long-term follow-up. Similarly, while Chandrasiri et al [15] highlighted VR's potential for pain management, they acknowledged significant variability in hardware specifications and software design across studies, which limited generalizability. These methodological weaknesses underscore the need for a systematic evaluation that critically examines intervention quality and research rigor.

Despite the growing interest in VR-based mindfulness interventions, there is a lack of comprehensive and systematic reviews examining their effectiveness across different populations and outcomes. A recent systematic review by Ma et al [16] investigated the effectiveness of immersive VR-based mindfulness training in improving mental health in adults. While their review provided valuable insights, our planned systematic review differs in several key aspects. First, we will focus specifically on RCTs, which are considered the gold standard for evaluating the effectiveness of interventions. Second, we will include a meta-analysis to quantitatively synthesize the results of the included studies, providing a more precise estimate of the effect sizes. Finally, our review will include studies published up to September 2024, ensuring that the most up-to-date evidence is considered. By addressing these gaps, our systematic review will provide a comprehensive and rigorous evaluation of the effectiveness of VR-based mindfulness interventions, complementing and extending the findings of the existing reviews.

Our review acknowledges important scope limitations inherent in focusing exclusively on RCTs and English-language studies. While this approach ensures the highest level of evidence quality for effectiveness evaluation, it may exclude valuable insights from nonrandomized implementation studies and non–English-language research, particularly from countries with advanced VR technology development. This methodological decision reflects a deliberate trade-off

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prioritizing internal validity and evidence certainty over broader inclusivity of study designs and global perspectives.

Following the population, intervention, comparison, and outcome framework, our systematic review aims to evaluate whether VR-based mindfulness interventions (intervention), compared to traditional mindfulness, digital alternatives, active controls, or no treatment (comparisons), effectively reduce stress, anxiety, and depression while improving mindfulness and well-being (outcomes) in adults aged 18 to 65 years from general and clinical populations (population). Our hypothesis predicts that VR interventions will demonstrate at least equivalent effectiveness to traditional approaches, with potentially superior outcomes in engagement-related metrics and specific subpopulations. We hypothesize that VR-based mindfulness interventions will demonstrate at least comparable effectiveness to traditional approaches, with potentially superior outcomes for specific populations or contexts due to enhanced engagement and immersion.

Objectives

The primary objective of the systematic review is to evaluate the effectiveness of VR-based mindfulness interventions in improving mental health outcomes, such as reducing stress, anxiety, and depression and enhancing overall well-being. The specific objectives are as follows:

1. To evaluate the effectiveness of VR-based mindfulness interventions in improving primary mental health outcomes (stress, anxiety, and depression) and secondary outcomes (mindfulness, well-being, and user experience) compared to traditional mindfulness practices, other interventions, or no intervention
2. To analyze potential moderators of intervention effectiveness, including participant characteristics, intervention duration, and VR technology used
3. To assess the quality of existing research on VR-based mindfulness interventions, identify gaps in the literature, and provide recommendations for future studies

Methods

Protocol and Registration

The systematic review will be conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [18]. This protocol has been registered with the PROSPERO (registration number CRD42024585899).

Eligibility Criteria

Overview

The population, intervention, comparison, and outcome framework is used to guide the eligibility criteria for the systematic review.

Our inclusion criteria were developed through preliminary scoping searches and expert consultation to ensure comprehensive but targeted study identification. The specific criteria that will be applied during the screening process are discussed in the subsequent subsections.

Population

Adults aged 18 to 65 years will be included. We will include both healthy individuals and those with diagnosed mental health conditions (eg, anxiety disorders, depressive disorders, and stress-related disorders). Studies focusing exclusively on older adults (aged >65 y) with cognitive impairments will be excluded to maintain population homogeneity as will studies targeting children or adolescents.

Intervention

VR-based mindfulness interventions must include (1) immersive VR technology using specified hardware platforms including Oculus Rift, HTC Vive, PlayStation VR, Samsung Gear VR, or comparable head-mounted displays with a minimum 90° field of view, or cave automatic virtual environments with 3D projection mapping (desktop VR, smartphone-based viewers, and 2D screen-based applications will be excluded); (2) interactive software elements enabling user agency within virtual environments such as gaze-based navigation, hand tracking, or controller-based interaction; (3) explicit mindfulness content including guided meditation, body scan, breath awareness, or other evidence-based mindfulness techniques; and (4) minimum one session of at least 10 minutes duration. We will record and analyze variations in delivery format, including guided versus self-directed, session frequency, total intervention duration, and specific hardware or software platforms.

Comparison

Eligible comparators include (1) traditional face-to-face mindfulness interventions (eg, MBSR or mindfulness-based cognitive therapy), (2) non-VR digital mindfulness interventions (eg, apps and audio recordings), (3) active nonmindfulness interventions (eg, relaxation training, and psychoeducation), or (4) no-treatment controls or waitlist groups. Studies without a comparison group will be excluded.

Outcomes

The primary outcomes of interest will be measures of stress, anxiety, and depression, assessed using validated self-report questionnaires or clinician-administered scales. Examples of commonly used measures include the Perceived Stress Scale, the State-Trait Anxiety Inventory, and the Beck Depression Inventory.

Secondary outcomes will include measures of mindfulness, well-being, and user experience. Mindfulness outcomes may be assessed using validated questionnaires, such as the Five Facet Mindfulness Questionnaire or the Mindful Attention Awareness Scale. Well-being outcomes may be evaluated using measures such as the Warwick-Edinburgh Mental Well-being Scale or the Satisfaction with Life Scale. User experience outcomes may include measures of presence, immersion, and usability, such as the Presence Questionnaire or the System Usability Scale.

In addition to the primary and secondary outcomes, we will extract data on reported adverse events or side effects associated with VR-based mindfulness interventions, such as cybersickness, visual discomfort, disorientation, or psychological distress. This information is crucial for evaluating the safety, feasibility, and

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acceptability of VR-based mindfulness interventions in real-world settings. Studies that do not explicitly report adverse events will be noted as having incomplete safety data.

Study Design

The review will include RCTs that compare VR-based mindfulness interventions to traditional mindfulness interventions, other active interventions, or no intervention. Nonrandomized studies, case studies, and qualitative studies will be excluded.

Language and Publication Status

Only studies published in the English language will be included. This language restriction is justified by a feasibility analysis showing that <5% of relevant studies identified in preliminary searches were published in non-English languages, balanced against resource constraints for professional translation. While this introduces potential language bias, the pragmatic decision enables comprehensive analysis of the predominantly English-language VR mindfulness literature while maintaining methodological rigor within available resources. Both published and unpublished studies (eg, conference abstracts and dissertations) will be considered for inclusion.

Information Sources and Search Strategy

A comprehensive search strategy will be developed in consultation with a librarian experienced in systematic reviews. The following electronic databases will be searched from inception to June 2025: PubMed, Web of Science, Embase, CINAHL, MEDLINE, the Cochrane Library, PsycINFO, and Scopus. The search strategy will combine terms related to VR, mindfulness, and RCTs, using a combination of keywords and controlled vocabulary (eg, Medical Subject Headings [MeSH] terms). An example search strategy for MEDLINE (via PubMed) is provided in Multimedia Appendix 1.

Search strategy development followed a systematic five-phase process: (1) initial keyword identification through preliminary literature review and expert consultation; (2) iterative refinement using a validation set of 20 known relevant articles to ensure 100% retrieval sensitivity; (3) medical librarian consultation to optimize MeSH terms, subheadings, and Boolean operators; (4) cross-database syntax adaptation while maintaining conceptual consistency; and (5) final validation through retesting against the reference article set. This rigorous development process ensures comprehensive capture of relevant literature while minimizing search bias.

In addition to the electronic database searches, the reference lists of included studies and relevant systematic reviews will be hand searched to identify any additional eligible studies. Experts in the field will also be contacted to inquire about any ongoing or unpublished studies that may be relevant to the review.

Study Selection

The study selection process will be conducted in 2 stages. First, 2 reviewers will independently screen the titles and abstracts of all records identified through the search strategy against the eligibility criteria. Studies that clearly do not meet the inclusion criteria will be excluded at this stage. Second, the full-text articles of the remaining studies will be retrieved and independently assessed for eligibility by 2 reviewers. Any disagreements between the reviewers will be resolved through discussion or by consulting a third reviewer if necessary. The reasons for excluding studies at the full-text stage will be documented. The study selection process will be reported using a PRISMA flow diagram [18] (Figure 1).

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

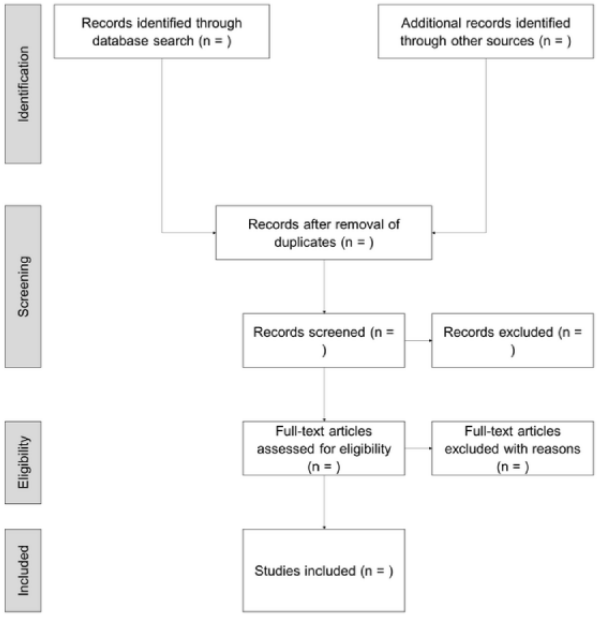

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Data Extraction

A standardized data extraction form will be developed and piloted on a sample of included studies to ensure its adequacy and consistency. Two reviewers will independently extract data from the included studies, with any discrepancies resolved through discussion or by consulting a third reviewer, if necessary. Data extraction will encompass study characteristics (author, publication year, country, design, sample size, and funding), participant details (age, gender, population, and inclusion and exclusion criteria), intervention specifics (VR technology, session duration or frequency, mindfulness techniques, and cointerventions), comparator information (type, duration or frequency, and cointerventions), outcomes (primary or secondary, measurement tools, and assessment time points), results (means, SDs, sample sizes, effect sizes, and *P* values), and risk of bias assessment for each study. This comprehensive data collection will enable thorough analysis of VR-based mindfulness interventions' effectiveness and contextual factors (Multimedia Appendix 2).

Quality Assessment

The methodological quality of the included studies will be assessed using the Cochrane Risk of Bias 2 (RoB 2) tool for randomized trials [19]. Two reviewers will independently assess the risk of bias for each included study across the following domains: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Each domain will be judged as having a low risk of bias, some concerns, or a high risk of bias, and an overall risk of bias judgment will be made for each study. Any disagreements between the reviewers will be resolved through discussion or by consulting a third reviewer, if necessary.

Data Synthesis

If the included studies are sufficiently homogeneous in terms of participants, interventions, comparators, and outcomes, a meta-analysis will be conducted using a random-effects model. The effect sizes for each outcome will be calculated as standardized mean differences with 95% CIs. Heterogeneity will be assessed using the I^2 statistic, with values of 25%, 50%, and 75% representing low, moderate, and high heterogeneity, respectively [20].

If a meta-analysis is not feasible due to substantial heterogeneity or a limited number of studies, a narrative synthesis will be conducted. The narrative synthesis will involve a qualitative summary of the included studies, focusing on the characteristics of the interventions, the outcomes assessed, and the main findings. Subgroup analyses or meta-regression may be performed to explore potential moderators of the effectiveness of VR-based mindfulness interventions, such as participant characteristics, intervention duration, and VR technology used, depending on the availability of data.

To address potential heterogeneity in VR technology and mindfulness techniques, we will conduct detailed subgroup analyses based on the following: (1) type of VR technology used (eg, head-mounted displays vs cave automatic virtual environments), (2) specific mindfulness techniques used (eg, focused attention vs open monitoring), (3) duration and frequency of intervention, and (4) population characteristics (eg, healthy vs clinical samples). If substantial heterogeneity is identified (I^2>75%), we will explore meta-regression to examine the impact of these variables on intervention effectiveness. In addition, sensitivity analyses will be conducted to assess the robustness of findings by excluding studies with a high risk of bias or extreme effect sizes. This stratified analytical approach will help account for intervention heterogeneity and provide more nuanced insights into the effectiveness of different VR-based mindfulness approaches.

Publication Bias

If a sufficient number of studies (n≥10) are included in the meta-analysis, publication bias will be assessed visually using a funnel plot and statistically using the Egger test [21]. If publication bias is suspected, the trim-and-fill method will be applied to estimate the effect of potential missing studies on the overall effect size [22].

Confidence in Cumulative Evidence

The strength of the evidence for each outcome will be assessed using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach [23]. The GRADE approach considers several factors such as study design, risk of bias, inconsistency, indirectness, imprecision, and publication bias, to determine the overall quality of evidence for each outcome. The quality of evidence will be rated as high, moderate, low, or very low, reflecting confidence in the estimated effect size.

Results

This protocol has been registered with PROSPERO (registration number CRD42024585899). The comprehensive search will commence in June 2025, followed by screening and selection of eligible studies in July 2025. Data extraction and quality assessment are planned from August to September 2025. Data synthesis and manuscript preparation will be conducted from October to November 2025, with completion of the systematic review expected by December 2025. Publication of results is anticipated in early 2026. Contingency planning addresses potential challenges: if >1000 records require screening, the timeline extends by 2 weeks with additional reviewer recruitment; high heterogeneity preventing meta-analysis triggers structured narrative synthesis protocols; and reviewer disagreements exceeding 20% invoke third reviewer arbitration with structured consensus procedures. Project management includes weekly progress monitoring, monthly team meetings, and quarterly milestone assessments to ensure timeline adherence while maintaining quality standards.

The completion timeline is realistic given our comprehensive project management plan; database searches will require approximately 4 weeks (June 2025), followed by 6 weeks for dual-reviewer screening (July 2025 to mid-August 2025), 6 weeks for data extraction and quality assessment (mid-August 2025 to September 2025), 4 weeks for meta-analysis (October 2025), and 8 weeks for manuscript preparation and internal review (November 2025 to December 2025). This timeline may

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be adjusted based on the volume of studies identified during the search process and the feasibility of meta-analysis.

Discussion

Anticipated Findings

The systematic review will provide a comprehensive evaluation of the effectiveness of VR-based mindfulness interventions in improving mental health outcomes, such as reducing stress, anxiety, and depression, and enhancing overall well-being. By synthesizing the available evidence from RCTs, the review will offer valuable insights into the potential of VR technology as a complementary or alternative approach to traditional mindfulness practices.

The findings of the review may have important implications for clinical practice and future research. If VR-based mindfulness interventions are found to be effective, they may be considered as a viable option for individuals who may have difficulty accessing or engaging with traditional mindfulness practices. VR technology may also offer unique advantages, such as the ability to create immersive and personalized environments that facilitate deeper engagement and skill acquisition [6]. Moreover, VR-based interventions may be particularly appealing to certain populations, such as younger individuals or those with a preference for technology-based approaches [5].

The results of the systematic review may also inform the development and refinement of VR-based mindfulness interventions as well as the design of future research studies. By identifying the key features and components of effective interventions, the review can guide the optimization of VR-based mindfulness programs to maximize their therapeutic potential. In addition, the review may highlight important considerations for the implementation and dissemination of VR-based mindfulness interventions in various settings, such as clinical practices, community centers, or educational institutions.

Beyond clinical applications, our findings will have implications for technology policy, health care economics, and educational practices. From a policy perspective, results showing significant benefits could support reimbursement models for VR-based mental health interventions and drive standards for clinical VR applications. Economic analyses derived from our effectiveness data could inform cost-benefit evaluations for health care systems considering VR implementation, particularly examining whether increased initial costs might be offset by improved engagement, reduced dropout rates, and potentially stronger clinical outcomes. Policy implications extend beyond clinical practice to health care funding models. Our effectiveness data will inform evidence-based arguments for VR mindfulness reimbursement, particularly relevant as health care systems globally adopt digital therapeutics frameworks. Cost-benefit analyses suggest VR interventions' higher initial costs (US $500-$2000 per headset) may be offset by reduced therapist time requirements, improved scalability, and enhanced patient engagement, leading to better outcomes and reduced rereferral rates. Regulatory implications include informing the Food and Drug Administration digital therapeutics pathways and international medical device classifications for therapeutic VR applications. In addition, our findings may guide the development of VR mindfulness training protocols for health care providers and educators, potentially influencing the curriculum design for mindfulness instructor certification programs to include technological competencies alongside traditional facilitation skills.

For technology developers, our detailed examination of VR hardware characteristics and software design elements associated with superior outcomes will provide evidence-based guidelines for future intervention development. Specifically, our subgroup analyses examining the comparative effectiveness of different VR platforms, environment designs, interaction methods, and guidance approaches will identify the technical specifications most strongly correlated with positive outcomes.

Strengths and Limitations

The systematic review offers several unique contributions distinguishing it from previous reviews: (1) exclusive focus on RCTs providing the highest evidence level, unlike previous reviews including diverse study designs; (2) multidisciplinary team expertise spanning mindfulness research, VR technology, and clinical psychology enabling comprehensive technical and therapeutic evaluation; (3) comprehensive GRADE evidence assessment providing transparent reliability ratings for each outcome; (4) prespecified subgroup analyses examining VR-specific moderators (hardware type and software features) absent from general mindfulness reviews; and (5) systematic adverse event assessment addressing VR-specific safety concerns such as cybersickness. The results will be structured according to the PRISMA guidelines, with distinct sections addressing the following: (1) study selection process with PRISMA flow diagram detailing the number of records identified, screened, eligible, and included with reasons for exclusions; (2) study characteristics presented in comprehensive evidence tables categorized by population type (clinical vs nonclinical), intervention characteristics, and outcome measures; (3) risk of bias assessment with traffic light plots visualizing quality ratings across domains for each study; (4) primary outcome analyses with forest plots displaying standardized mean differences by outcome type (stress, anxiety, and depression) and subgroup analyses by intervention duration (<2 wk, 2-8 wk, and >8 wk) and VR technology type; (5) secondary outcome analyses examining mindfulness levels, well-being metrics, and user experience measures; and (6) exploratory analyses investigating potential moderators of effectiveness, including participant characteristics, intervention features, and contextual factors.

The review will use a thorough search strategy, encompassing multiple electronic databases and supplementary search methods, to ensure the identification of all relevant studies. The use of a standardized data extraction form and the independent assessment of study eligibility, data extraction, and quality by 2 reviewers will minimize the risk of bias and enhance the reliability of the findings.

Another strength of the review is its focus on RCTs, which are considered the gold standard for evaluating the effectiveness of interventions. By including only RCTs, the review will provide the highest level of evidence regarding the efficacy of VR-based

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mindfulness interventions in improving mental health outcomes. Furthermore, the review will assess the quality of the included studies using the Cochrane RoB 2 tool, enabling a critical appraisal of the strength of the evidence and the identification of potential sources of bias.

The review also benefits from a broad scope, encompassing adult participants from any population, including both healthy individuals and those with specific mental health conditions. This approach allows a comprehensive assessment of the effectiveness of VR-based mindfulness interventions across diverse populations and facilitates the identification of potential moderators of treatment efficacy.

Despite its strengths, the systematic review may have some limitations. One potential limitation is the heterogeneity of the included studies in terms of participant characteristics, intervention details, and outcome measures. This heterogeneity may make it challenging to directly compare the results across studies and may limit the feasibility of conducting a meta-analysis. To address this issue, the review will use appropriate statistical methods, such as subgroup analyses or meta-regression, to explore potential sources of heterogeneity and to account for differences between studies.

The search strategy development process included (1) initial identification of keywords through preliminary literature review, (2) consultation with a medical librarian specializing in systematic reviews, (3) testing and refinement of search strings using a sample of known relevant articles to ensure 100% retrieval, (4) validation of MeSH terms and subheadings to maximize sensitivity, and (5) incorporation of recommended Boolean operators and truncation symbols. We will adapt the search strategy for each database's specific syntax requirements while maintaining consistent conceptual blocks. The decision to exclude non–English-language studies was made after preliminary searches identified that <5% of the potentially relevant studies were published in other languages, balancing comprehensive coverage with feasibility constraints.

Another limitation is the potential for publication bias, which may lead to an overestimation of the effectiveness of VR-based mindfulness interventions. Studies with positive or significant results are more likely to be published than those with negative or nonsignificant findings, which can skew the overall evidence base. To mitigate this risk, the review will include both published and unpublished studies and will assess publication bias using funnel plots and statistical tests when appropriate.

In addition, our review is limited to studies published in English, which introduces potential language bias. This restriction may lead to the exclusion of relevant studies from non-English speaking countries where VR technology and mindfulness research may be advancing significantly. Future reviews should consider including studies in multiple languages to provide a more globally representative assessment of VR-based mindfulness interventions.

Furthermore, the primary outcomes of interest (stress, anxiety, and depression) are predominantly assessed through self-report measures, which are susceptible to response bias, social desirability bias, and demand characteristics. The lack of physiological or behavioral outcome measures limits the objective evaluation of intervention effectiveness. Future research should incorporate multimodal assessment approaches, including physiological markers (eg, cortisol levels and heart rate variability) and behavioral indicators to complement self-report measures and provide a more comprehensive evaluation of VR-based mindfulness interventions.

Finally, the review may be limited by the quality and reporting of the included studies. Poor methodological quality or insufficient reporting of study details can make it difficult to accurately assess the risk of bias and to draw firm conclusions about the effectiveness of the interventions. To address this issue, the review will use the Cochrane RoB 2 tool to critically appraise the quality of the included studies and consider the potential impact of study quality when interpreting the results.

A significant strength of our review is its focus exclusively on RCTs, which represent the gold standard design for evaluating intervention effectiveness. This methodological rigor distinguishes our work from previous reviews that included diverse study designs with varying levels of evidence quality. In addition, our comprehensive application of the GRADE approach for evaluating certainty of evidence, considering study limitations, inconsistency, indirectness, imprecision, and publication bias, will provide transparent assessments of the reliability of our conclusions for each outcome. The preregistration of our protocol on PROSPERO further enhances transparency and reduces the risk of reporting bias in our final review.

Our review also benefits from a multidisciplinary team with expertise in mindfulness research, VR technology, systematic review methodology, and clinical psychology. This diverse expertise ensures thorough evaluation of both technical aspects of VR interventions and their psychological mechanisms, providing a unique contribution to the literature that bridges technological innovation with evidence-based mental health practice.

On the basis of anticipated findings, we propose a forward-looking research agenda focusing on three priority areas: (1) long-term effectiveness studies with minimum 6-month follow-up periods to assess maintenance of gains and continued practice engagement, (2) mechanism-focused trials using physiological biomarkers and neuroimaging to validate proposed theoretical frameworks such as the PAC model, and (3) implementation science research examining factors affecting successful integration of VR mindfulness in diverse health care and community settings. We propose a specific research agenda with clear rationales: (1) multiarm RCTs (n>200) comparing VR mindfulness to both traditional and digital alternatives with 6-month follow-up to establish sustained effectiveness and comparative advantage; (2) longitudinal biomarker studies incorporating cortisol, inflammatory markers, and neuroimaging to validate proposed mechanisms such as the PAC model; (3) implementation science trials examining VR integration barriers in health care settings, including health care provider training requirements, technical infrastructure needs, and patient acceptance factors; (4) cost-effectiveness analyses using standard health economic frameworks (quality-adjusted life

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year and incremental cost-effectiveness ratio) to inform reimbursement decisions; and (5) personalization research identifying patient characteristics predicting optimal VR versus traditional mindfulness response.

From a clinical perspective, our findings may inform the development of evidence-based guidelines for integrating VR mindfulness into existing treatment protocols, particularly for populations demonstrating suboptimal engagement with traditional mindfulness approaches. Mental health practitioners, mindfulness instructors, and health care administrators will gain valuable insights into which specific VR mindfulness approaches show the strongest evidence for particular outcomes and populations, enabling more targeted and effective implementation.

Conclusions

This systematic review protocol establishes a comprehensive framework for evaluating VR-based mindfulness interventions' effectiveness in improving mental health outcomes. The review's anticipated contributions include (1) definitive effectiveness evidence across multiple mental health outcomes using gold standard RCT methodology; (2) evidence-based guidance for clinical adoption through systematic examination of intervention components, optimal populations, and implementation considerations; (3) technology development insights identifying VR specifications most strongly associated with positive outcomes; and (4) health care policy implications for reimbursement and regulatory decisions regarding therapeutic VR applications.

Specific recommendations emerging from the review will include (1) evidence-based protocols for VR mindfulness integration into existing mental health care pathways, (2) training curricula for health care providers implementing VR-based interventions, (3) technical specifications for health care–grade VR mindfulness systems, (4) patient selection criteria optimizing VR versus traditional mindfulness matching, and (5) quality standards for therapeutic VR applications ensuring safety and efficacy.

The review addresses a critical gap in the digital mental health evidence, bridging technological innovation with rigorous clinical evaluation. By providing comprehensive effectiveness evidence, our findings will accelerate evidence-based adoption of VR mindfulness interventions while identifying priority areas for future research, ultimately advancing accessible, engaging mental health interventions for diverse populations.

Acknowledgments

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Authors' Contributions

RS was involved in conceptualization, methodology, writing the original draft, supervision, project administration, and funding acquisition. AB was involved in reviewing and editing the manuscript and visualization. AM was involved in reviewing and editing the manuscript and supervision. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy for PubMed (search conducted in September 2024).
[DOCX File , 14 KB - resprot_v14i1e68231_app1.docx]

Multimedia Appendix 2
Data extraction form.
[DOCX File , 14 KB - resprot_v14i1e68231_app2.docx]

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Abbreviations

GRADE: Grading of Recommendations Assessment, Development, and Evaluation
MBSR: mindfulness-based stress reduction
MeSH: Medical Subject Headings
PAC: presence-attention-compassion
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT: randomized controlled trial

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RoB 2: Risk of Bias 2
VR: virtual reality

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Protocol

Activity-Based Interventions to Increase Independence After Stroke In the Hospital Setting: Protocol for a Systematic Review

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Abstract

Background: Stroke is a leading cause of disability, commonly resulting in difficulty completing basic and instrumental activities of daily living. Rehabilitation is recommended to improve functional performance; however, it remains unknown whether early (hospital-based) intervention is effective; nor is it known what intervention components should be delivered.

Objective: We propose a systematic review to summarize the evidence for the effectiveness of activity-based interventions, led by occupational therapists, for improving performance of basic activities of daily living (b-ADL) or simple cognitive instrumental activities of daily living (C-IADL) among adults with stroke. Reviewing simple C-IADLs as opposed to instrumental activities of daily living will allow us to review interventions for activities with similar executive functioning demands. By identifying effective interventions, we aim to improve outcomes for stroke survivors by maximizing independence during hospitalization.

Methods: Searches will be conducted in MEDLINE, CINAHL, EMBASE, and Cochrane Central Register of Controlled Trials. We will include randomized controlled trials and quasi-randomized controlled trials that include adult stroke survivors and tested interventions (delivered in the hospital setting) aiming to improve or promote independence in b-ADLs or C-IADLs. Two reviewers will independently screen full-text articles, and one reviewer will extract data, with a second reviewer providing confirmation. The Physiotherapy Evidence Database (PEDro) scale will be used to assess the methodological quality of studies. The Cochrane *Q* test will assess heterogeneity among studies, and where appropriate, meta-analysis will then be performed. Measures of outcomes may include global ratings of function (such as the Functional Independence Measure) or specific task performance assessments (such as the Nottingham Dressing Assessment).

Results: Results will be presented based on subgroup analyses where possible, including activity type (activity or occupation level), time after stroke (within or after 1 week), and delivery of intervention (group or individualized).

Conclusions: This systematic review will address the current gap in the literature regarding activity-based interventions for stroke survivors in the inpatient setting and provide clinical guidance on the most effective methods, if any, for improving independence early after stroke.

Trial Registration: PROSPERO CRD42024562195; https://www.crd.york.ac.uk/PROSPERO/view/CRD42024562195

International Registered Report Identifier (IRRID): DERR1-10.2196/73133

(JMIR Res Protoc 2025;14:e73133) doi:10.2196/73133

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KEYWORDS

stroke; rehabilitation; activities of daily living; occupational therapy; stroke rehabilitation; hemiplegia

Introduction

Stroke is a leading cause of adult disability [1]; despite advances in acute treatments, the need for neurorehabilitation continues [2,3]. Stroke-related impairments can lead to difficulties in performing meaningful activities, such as showering or preparing a meal, and problems in participating more broadly in life, such as maintaining a home. Previous studies have shown that around two-thirds of all survivors of stroke experience a disability that impacts their ability to complete activities of daily living (ADLs) [4]. ADLs are the everyday tasks completed by an individual and are often divided in multiple domains, including basic activities of daily living (b-ADLs) and simple and complex cognitive instrumental activities of daily living (C-IADLs). Basic ADLs "rely heavily on physical abilities and procedural memory" [5], such as self-feeding, dressing, grooming, and showering, whereas simple C-IADLs are tasks that "are more familiar, contain fewer steps and require less planning or problem solving" [5], such as preparing a hot drink, preparing a simple meal, or folding clothing. Complex C-IADLs are "more novel, less predictable, and place greater demands on multitasking, planning, decision making, and problem-solving capacities" [5], such as organizing and managing medications, planning an event, or creating a budget for an extended period of time.

Effective rehabilitation enables stroke survivors to achieve optimal functional outcomes across all areas of their life [4]. Occupational therapists assess and deliver rehabilitation for stroke survivors who have experienced changes to their ability to engage in meaningful everyday activities as a result of their stroke impairments [6]. Occupational therapy interventions often target ADLs to improve functional performance [7].

Stroke survivors should receive intensive rehabilitation throughout their inpatient stay to support a meaningful recovery [4] and promote neuroplasticity [3]. Neuroplasticity is the theory that neural pathways are able to adapt and regenerate to improve function [8]. Neuroplasticity is time sensitive, and research has shown that early rehabilitation is linked to improved functional recovery [9,10]. Previous research has explored the effectiveness of occupational therapy rehabilitation among stroke survivors for ADLs in a community setting [11]. The results highlighted that stroke survivors who received ADL-targeting occupational therapy in the community had increased levels of ADL independence [11]. There were limitations inherent in this systematic review; in particular, only a third of previous trials used appropriate randomization and allocation concealment methods [11]. Overall, research on the effects of activity-based interventions alone in the inpatient setting has been limited [12]. Examining the available evidence, a recent systematic review found that occupational therapy–specific interventions in the inpatient setting did not have a significant effect on improving quality of life and activity performance of stroke survivors [13]. These results should be interpreted cautiously given the substantial heterogeneity of the IADL performance analysis (I^2 of 70.69) and that both the control and experimental groups were provided occupation-specific interventions, which does not allow the reader to discern the effectiveness of activity-based interventions from this systematic review [13]. Additional evidence from an observational study suggests that intensive hospital rehabilitation correlates with improved ADL performance on discharge. However, the specific type of rehabilitation completed in this study was unclear [12]. The literature on the effectiveness of occupational therapy specifically for stroke survivors in the hospital setting is limited, and studies to date have recommended further research to determine the specific rehabilitation interventions and intensity required [12,14].

Therefore, this systematic review will synthesize activity-based intervention studies that aim to improve performance of b-ADLs and/or simple C-IADLs in the hospital setting among stroke survivors. Complex C-IADLs were excluded from this review as the demands of these tasks were identified as being significantly different from b-ADLs and simple C-IADLs. The guiding research question developed was as follows: Do occupational therapy–led, activity-based interventions designed to target b-ADLs and/or simple C-IADLs in the hospital setting increase functional independence in stroke survivors?

Methods

Study Design

The protocol was developed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Protocols statement [15]; the PRISMA statement will guide reporting of the completed systematic review. The protocol has been registered in the International Prospective Register of Systematic Reviews (PROSPERO; CRD42024562195).

Eligibility Criteria

The primary objective of this review is to synthesize effectiveness research on rehabilitation interventions delivered in the hospital setting to improve independence after stroke. We will include publications from any date in our search.

Types of Studies

Studies will be included if they are full publications of randomized controlled trials (RCTs) and quasi-RCTs.

Population and Setting

Studies that include adults (aged ≥18 years) diagnosed with stroke who are inpatients in the hospital setting will be included. Studies involving mixed diagnoses will be included where the data from those with a diagnosis of stroke are able to be extracted, or where ≥75% of the participants have a diagnosis of stroke. Studies involving mixed age groups will be included where the data from those aged ≥18 years are able to be extracted, or where ≥75% of the participants are aged ≥18 years. Studies will be excluded if they were performed with people

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who reside in the community setting, including care-based facilities (eg, residential aged care).

Intervention

Studies that provide an activity-based intervention completed in the hospital setting and that fit within the scope of occupational therapy will be reviewed. Retraining interventions specific to b-ADLs and simple C-IADLs will be included in our systematic review. Both compensatory and remedial rehabilitation strategies will be included. We will exclude community-based interventions and computer-based or virtual reality interventions given the focus of the systematic review on the effects of real-life training in the hospital environment. For studies that include a combination of activity-based interventions alongside other interventions, studies will be included where the effects can be isolated (ie, the only difference between the experimental group and the comparator group is the activity-based intervention).

Comparison Interventions

Included studies may have either an inactive comparison (where the control group received no occupational therapy input) or an active comparison, such as those where participants received an occupational therapy intervention that was not specific to activity-based retraining for ADLs or where a nondescriptive intervention was used in the control group. Examples of this include impairment-based treatments, such as upper limb treatment or visual scanning retraining.

Outcomes

We will record the outcome measures that the included studies used to report outcomes related to b-ADLs and simple C-IADLs to determine the effectiveness of activity-based interventions on stroke survivors' functional independence. All clinical measures used to evaluate the effectiveness of activity-based interventions will be considered. Outcome measures may be reported as a global measure of function, such as the Functional Independence Measure, or specific evaluations of b-ADLs or simple C-IADLs, such as the Nottingham Dressing Assessment or Barthel index.

Textbox 1 provides a summary of the eligibility criteria that will shape the search terms and identify relevant studies.

Textbox 1. Eligibility criteria.

Inclusion criteria

- Participants: at least 75% aged 18 years or older with a diagnosis of stroke
- Intervention: activity-based retraining (basic activities of daily living [b-ADLs] or simple cognitive instrumental activities of daily living [c-IADLs]); intervention delivered in inpatient setting
- Comparison: no occupational therapy input, no allied health, occupational therapy not specific to activity-based retraining for activities of daily living, or intervention not defined in the control group
- Outcomes: (1) determine the effectiveness of activity-specific interventions (b-ADLs and/or simple C-IADLs) on stroke survivors' functional independence; (2) identify and describe the assessments and occupational therapy interventions designed to target b-ADLs and simple C-IADLs currently being used with adult stroke survivors in the hospital setting
- Study design: randomized controlled trials and quasi-randomized controlled trials

Exclusion criteria

- Intervention: computer-based or virtual reality retraining; community-based interventions

Search Strategy

Electronic searches will be conducted in CINAHL, EMBASE (via Ovid) and MEDLINE. The search strategy will be developed with senior researchers. The search strategy will include key terms such as *stroke*, *hemiplegia*, *activities of daily living*, *activity-based interventions*, and *hospital*. During screening of titles and abstracts, only English-language articles will be included due to no access to translation.

Procedures

All studies identified by the search strategy will be uploaded to Covidence (Veritas Health Innovation Ltd), and duplicates will be removed. All articles will be screened at the title and abstract stage by one reviewer, in line with the exclusion and inclusion criteria. Duplicate studies (ie, those with the same authors, setting, location, and interventions) will be removed. All articles excluded at the title and abstract screening stage will be reviewed by a senior researcher to ensure no articles were inadvertently excluded. Full-text articles will then be reviewed by 2 research team members. If there are conflicts in decision-making, a third research team member will be consulted for a third review. Authors of studies may be contacted if there is missing information or further details are required to ensure articles are not inadvertently excluded or included. Details of the data screening will be presented in a PRISMA study flow chart.

One reviewer (TG) will extract data using a predetermined form; all data extraction will be confirmed by the senior author (NAL). If discrepancies occur, these will be resolved by discussion between the authors. If the discrepancies are not resolved, a third author will independently extract the data. The data extraction form will extract variables necessary for describing the study and conducting data analysis, including the following: the title of the paper, the authors' names, the year the study was completed, the study design (eg, RCT or quasi-RCT), the country where the study was completed, participant age and sex, time after stroke of participants, primary and secondary assessments used, intervention and comparison details

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(according to the Template for Intervention Description and Replication [TIDieR] checklist items [16]), and the outcomes and results (eg, number of participants in analysis; summary data for each intervention group; estimate of effect, along with measure of variability, eg, mean difference; and 95% CI around the estimate).

The Physiotherapy Evidence Database (PEDro) scale will be used to critically appraise the studies to determine any risk of bias [17]. The PEDro scale scores the methodological quality of clinical trials [18]. It is an 11-point scale exploring the internal and external validity of studies and is known to be reliable for use in systematic reviews [17]. The OTseeker database will be used, if available; however, if not available online, PEDro will be completed by 2 reviewers separately. If there are disagreements regarding the results, the 2 reviewers will first attempt to resolve them between themselves; if they are unable to reach a consensus, a third reviewer who is a senior researcher in the research team will review and make the final decision.

Statistical Analysis

A meta-analysis will be completed to compare effects between treatment and control groups. RevMan will be used to conduct a statistical analysis to calculate effect measures. The treatment effect measure will be determined by the data located. For instance, continuous data may be calculated using the standard mean difference and 95% CI when studies measure the same concept but have used a different measurement scale. The mean difference and 95% CI may be used when the results are expressed using the same measurement scale. The impact of heterogeneity will be reviewed. If results are too dissimilar, a sensitivity analysis will be considered and a narrative synthesis will be considered as an alternative.

Results

Results will be discussed based on subgroup analyses where possible, including activity type (activity or occupation level), time after stroke (within or after one week), and delivery of intervention (group or individualized). Data extraction and analysis were completed in February 2025, and the results of the study and the submission of a manuscript for peer review are expected in July 2025.

Discussion

Overview

The findings from this systematic review will aim to address the gap in the literature regarding activity-based interventions for stroke survivors in the inpatient setting. Clinicians will be able to use the results to make evidence-informed decisions regarding activity-based interventions and rehabilitation for reducing long-term disability.

Limitations

This review will only search for and synthesize studies published in English; this limitation will be acknowledged in the systematic review when it is published. We acknowledge that the heterogeneity of the intervention types and of the clinical measures used to evaluate independence may not permit direct comparisons between studies. These limitations are not uncommon in systematic reviews of complex interventions.

Comparison With Prior Work

Prior reviews [13] did not systematically synthesize intervention effects from only those studies that delivered activity-based interventions with the goal of increasing independence. Findings will therefore allow reliable conclusions regarding such interventions to be determined. Consistent with the prior work, we will use a validated tool (PEDro) to assess the quality of evidence.

Conclusion

This systematic review will provide a detailed summary of the current evidence for the effectiveness of activity-based interventions on functional independence for stroke survivors. The findings of this review will guide clinicians in their selection of rehabilitation interventions and enable researchers to determine future evidence needs. Synthesis of published effectiveness trials will not only support evidence-based practice from an occupational therapy perspective, but will also guide future trial design, given the limited overall research available to date in the inpatient setting.

Acknowledgments

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Data Availability

The data generated and analyzed during this study will include content extracted from published, peer-reviewed journal articles. Additional data generated and analyzed during the study will be available from the corresponding author upon reasonable request.

Authors' Contributions

Conceptualization: TG, LJ, NAL (equal)
Investigation: TG (lead); LJ, NAL (supporting)
Methodology: TG, LJ, KW, NAL (equal); ES, AED (supporting)

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Project administration: TG (lead)
Writing—original draft: TG (lead); LJ, KW, NAL (supporting)
Writing—review and editing: TG (lead); LJ, KW, ES, AED, NAL (supporting)

Conflicts of Interest

None declared.

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Abbreviations

ADL: activity of daily living
b-ADL: basic activity of daily living
C-IADL: cognitive instrumental activity of daily living
PEDro: Physiotherapy Evidence Database

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PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Register of Systematic Reviews
RCT: randomized controlled trial
TIDieR: Template for Intervention Description and Replication

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Protocol

Digital Health Applications (DiGA) for Treating Depression and Generalized Anxiety Disorder: Protocol for a Systematic Health App Review and Systematic Review of Published Evidence

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Abstract

Background: Depression and generalized anxiety disorder (GAD) are widespread mental health diseases with significant individual and societal consequences. Psychotherapy, particularly cognitive behavioral therapy (CBT), is a common treatment approach, but its application is limited due to costs and staff shortages. Germany has been the first country to integrate and reimburse digital health applications (DiGAs) as an easily accessible treatment option since 2020. Despite regulatory processes, skepticism among physicians regarding clinical relevance and evidence persists.

Objective: This protocol aims to describe the methodology of the planned systematic review. Using expert ratings, the app review will assess the guideline conformity, functions, and usability of German DiGAs for depression and GAD listed at the Federal Institute for Drugs and Medical Devices (BfArM). The additional systematic review will synthesize the effectiveness and quality of these DiGAs based on randomized controlled trials.

Methods: The study protocol follows the 2015 PRISMA (Preferred Reporting Items for Systematic Reviews) guideline and was registered in the international Prospective Register of Systematic Reviews (PROSPERO). The review consists of 2 parts: (1) a systematic health app review of DiGAs addressing depression or GAD and (2) a systematic review of published evidence on these DiGAs. The systematic health app review comprises a summary of the DiGA features including the Institute for Healthcare Informatics (IMS) App Functionality Scoring System, a guideline conformity check, and the Mobile Application Rating Scale (MARS) assessment. The systematic review of published evidence is based on a systematic literature search in electronic databases (MEDLINE via PubMed, Cochrane Central Register of Controlled Trials [CENTRAL], Web of Science), as well as relevant websites. The approach includes an effectiveness evaluation, a risk of bias assessment using the Cochrane tool, Risk of Bias 2 (RoB2), and an overall quality evaluation using the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) method.

Results: The systematic literature search was conducted in July 2024 and August 2024, and an updated search is planned for November 2025. Data extraction, narrative synthesis, and evaluation of DiGA and corresponding studies are expected to be completed in spring 2026. The results will be presented using a PRISMA flow diagram and tables to display general information, risk of bias, and overall quality.

Conclusions: The review will influence both the actual use and future developments of DiGAs. Good quality characteristics will enhance transparency and trust among physicians, while quality deficits provide options for improvement by manufacturers and governing institutions. Consequently, patients' care with DiGAs may improve.

Trial Registration: PROSPERO CRD42024557629; crd.york.ac.uk/PROSPERO/display_record.php?RecordID=557629

International Registered Report Identifier (IRRID): PRR1-10.2196/63380

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(JMIR Res Protoc 2025;14:e63380) doi:10.2196/63380

KEYWORDS

digital therapeutics; mental illness; mental distress; psychological well-being; evidence synthesis; mental health; mHealth; digitalization; mobile health

Introduction

Prevalence and Consequences of Depression and Generalized Anxiety Disorder

Depression and generalized anxiety disorder (GAD) are common disorders worldwide [1-5]. Approximately 15% to 20% of individuals experience depression at least once in their lifetime. Similar to other western nations, the 12-month prevalence of depression in Germany in 2015 was 9.7% for women and 6.3% for men, while the prevalence of GAD in Germany was 1.2% for men and 2.8% for women [6,7]. A significant proportion of patients have both diseases. Patients with GAD exhibited a 12-month prevalence rate of comorbid depression of 78.9% [8]. High prevalence rates of depression lead to significant individual and systemic consequences, including reduced quality of life, increased morbidity with a rise in chronic diseases, higher service utilization, and more sick leave days, as well as reduced work performance and early retirement [9-11].

The common therapeutic approach for depression and GAD is psychotherapy, especially cognitive behavioral therapy (CBT), which takes up a lot of manpower [12-14]. CBT "utilizes behavioral and cognitive strategies, particularly exposure, cognitive restructuring, changes in behavior, and development of coping skills, to address learned and conditioned behaviors, thoughts and emotional and psychophysiological reactions" [15]. Due to a shortage of professionals, long waiting times are prevalent in Germany. Digital health applications (DiGAs) were introduced in 2020 in the German health care system. DiGAs can bridge the waiting time for therapy or even replace human-guided face-to-face therapy by using CBT strategies [15,16].

Internet-based CBT (iCBT), as provided by DiGAs, can be divided into unguided and guided iCBT [17]. An international systematic review of applications using unguided and guided iCBT demonstrated their effectiveness [18]. "Unguided iCBT has considerable potential for improving long-term results of interventions with constrained economic and workforce resources" [18]. However, the intervention content differs between apps, and research is needed to identify the intervention components that are most effective [17,19].

DiGAs in Germany

Germany was the first country to introduce an institutionally regulated approval procedure for mobile health apps, known as DiGAs [20]. DiGAs are "based on digital technologies" [21] and used by patients (with or without supervision by a health care provider) to support "the recognition, monitoring, treatment or alleviation of diseases or the recognition, treatment or alleviation or compensation of injuries or disabilities" [21] but not to prevent diseases. These DiGAs must provide scientific evidence of their effectiveness, distinguishing them from conventional apps available in app stores, which do not undergo regulatory review nor require proof of efficacy.

DiGAs are part of the digital transformation of the German health care system and regulated by legal provisions such as the Social Code – Book V – Statutory Health Insurance (SGB V) including the Digital Care Act and the Digital Act [21-23]. They are intended to enable evidence-based, low-threshold, and personalized health care and complement existing treatment services.

To be an official reimbursable DiGA, the device must be listed in the DiGA directory of the Federal Institute for Drugs and Medical Devices (BfArM) [21,24]. The BfArM holds regulatory authority and is responsible for the scientific evaluation of the efficacy and health care benefits of DiGAs. Manufacturers must apply to the institute for DiGA listing. A fundamental prerequisite for a DiGA listing is its classification as a registered medical device of risk class I, IIa, or IIb according to the Medical Device Regulation [23,25]. In order to be listed as an official DiGA, the BfArM has stipulated several requirements, including security, functionality, quality, data security, and data protection, that must be fulfilled according to Section 139e of the SGB V [21]. A key aspect of the approval process is the demonstration of medical benefits or patient-relevant structural and procedural improvements through clinical trials or other validated scientific methods. Economic indicators or reductions in health care personnel workload alone are not sufficient to justify approval [21].

To ensure rapid access to digital health care solutions, a fast-track procedure has been implemented, ensuring a listing decision within 3 months [26]. Depending on the available evidence, listing in the BfArM DiGA directory can be either permanent or provisional. Provisional admission to the directory is linked to a trial phase in which a positive therapeutic effect must be demonstrated within 12 months to obtain permanent approval [21]. After successful evaluation, DiGAs become reimbursable, both in permanent and temporary status. Physicians and psychotherapists can prescribe DiGAs nationally, at the expense of statutory health insurance or private insurance companies, similar to pharmacological agents. Patients can also apply to their health insurance company to use a DiGA. For this, patients need a qualifying diagnosis that entitles them to use it. Currently, 59 DiGAs are listed, including 19 provisionally and 40 permanently approved applications. Additionally, 10 DiGAs have been removed from the list due to insufficient evidence or voluntary withdrawal by manufacturers (as of March 2025) [24].

Despite the requirements, physicians criticize the process and question the effectiveness of DiGAs, especially in treating depression [12,27]. In a 2022 online survey with approximately 2600 physicians, 27.7% considered DiGAs for depression to be ineffective or contraindicated [27]. Additionally, a lack of

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information regarding DiGA content and effectiveness was noted. Strong evidence is considered a factor that facilitates physicians' readiness to prescribe DiGAs; however, this is frequently lacking [27,28]. Critics particularly highlight the absence of study and analysis plans, which are required to be submitted to the BfArM but are not mandated for publication. In terms of methodology, the high dropout rates and lack of blinding in the studies are criticized. The criticism also extends to the selection of end points, with calls for a greater emphasis on patient-centered structural and procedural end points that align more closely with real-world evidence. This warrants the evaluation of DiGAs using patient-reported outcome measures and patient-reported experience measures [29-32].

Rationale for Performing This Systematic Review

Only a few studies have systematically evaluated DiGAs, focusing on various aspects. Kolominsky-Rabas et al [31] analyzed the methodological quality of studies related to DiGAs for mental health and the nervous system and concluded that not all studies fulfill good scientific practice criteria. Lantzsch et al [29] examined clinical trials on DiGAs and reported a high risk of bias, especially regarding the reporting quality. A scoping review of DiGAs for treating mental illnesses by Schreiter et al [32] focused solely on summarizing clinical evidence but did not address care guidelines, usability items, or a risk-of-bias evaluation. Haaf et al [33] performed a systematic review and meta-analysis "to estimate the immediate effects and the long-term effects" of freely available applications and DiGAs for treating depression. They performed sensitivity and subgroup analyses but no content analysis nor usability evaluation [33]. The international Prospective Register of Systematic Reviews (PROSPERO) lists 2 systematic review protocols about DiGAs. Nevertheless, there is no overlap because the authors focused either on DiGAs for overweight and obesity or solely on the risk of bias of all DiGAs [34,35]. The review approach described in this protocol is designed to be more comprehensive by including all available evidence, current literature, a comparison with guideline-recommended content, and usability testing.

Review Objective and Question

The anticipated systematic review aims to synthesize, through a structured methodological approach, the best available evidence concerning the quality of randomized controlled trials (RCTs) of DiGAs designed to support patients with depression or GAD. Specifically, the review seeks to examine the effectiveness of DiGAs on psychological well-being in comparison with control conditions, as well as to assess the risk of bias in the included RCTs. Additionally, the review aims to analyze the intervention strategies used by DiGAs in relation to national guidelines for the treatment of depression and GAD and to evaluate their usability and functional quality based on expert assessments.

Methods

Overview

The systematic review is structured in 2 parts: (1) systematic health app review evaluating the selected DiGAs and (2) systematic literature review evaluating effectiveness studies of the DiGAs. Both parts evaluate the DiGAs identified in Part 1. The review process is illustrated in Figure 1. This review addresses guideline conformity, quality, and functions of the DiGAs as well as the published evidence regarding DiGAs' effectiveness. The systematic review will be conducted and reported in accordance with the 2020 PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) checklist [36]. The systematic review protocol is registered in PROSPERO (CRD42024557629). If unforeseen changes are needed, we will document them by adding an amendment to the registry.

Figure 1. Review Process.

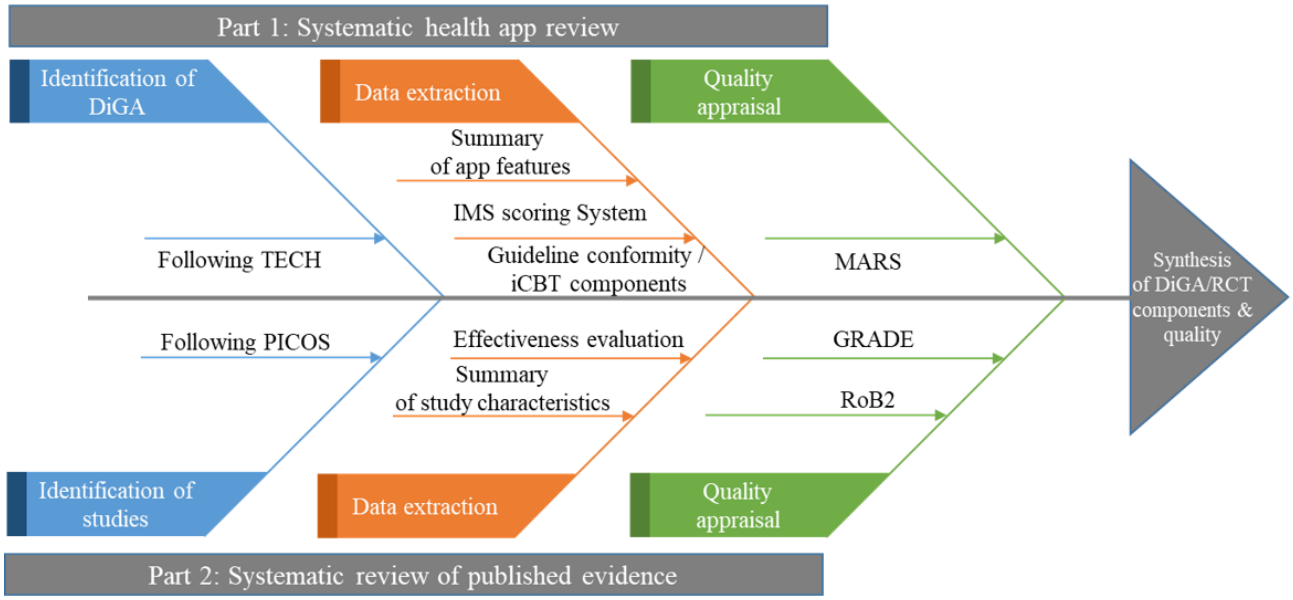

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Part 1: Systematic Health App Review

Identifying Apps

The planned systematic health app review will be conducted and reported in accordance with the methodological considerations of Gasteiger et al [37]. This involves a 2-stage approach: The first stage entails screening the app's title and description on the app store, and the second stage involves downloading the app and assessing its eligibility.

Adaptations in the search strategy are required, because the review's focus is on reimbursable DiGA not on freely available apps in the common app stores. Thus, DiGA will be identified via the DiGA directory not in app stores.

The BfArM DiGA directory is the primary and only source used to identify DiGAs, as it contains the complete list of DiGAs. The BfArM directory was filtered using the category "mental health" and the status "permanently listed" [24]. Listing status is important because only permanently listed DiGAs are obliged to have published evidence. The search was conducted in July 2024, and DiGAs identified stem from 2020 (earliest DiGA inclusion possible at the BfArM) through 2024. An updated search will be conducted shortly before the review is published (approximately in November 2025). After this initial selection, the 2-step approach was used.

Two reviewers performed and documented the screening process. The inclusion criteria were selected in accordance with the TECH (Target user groups, Evaluation focus, Connectedness, Health domain) framework (Textbox 1) [37]. The app search and screening process will be displayed as a flow diagram. Given that access to DiGAs is regulated via a doctor's prescription or a health insurance application, the authors will contact the DiGA manufacturers to request access to DiGAs.

Textbox 1. Inclusion and exclusion criteria following the TECH (Target user groups, Evaluation focus, Connectedness, Health domain) framework [37].

Target user groups

- The app must address adults aged 18 years and older.
- Target users must currently have depression or generalized anxiety disorder (GAD).
- There are no criteria for gender, age, nor ethnicity.
- Apps not specifically designed for adults (≥18 years) or those that do not target individuals currently with depression or GAD will be excluded.

Evaluation focus

- The evaluation centers on app characteristics, particularly the psychotherapeutic approach.
- The quality and usability of the app will be evaluated.
- The app needs to meet standards to support individuals with depression or GAD.
- Apps that do not use a psychotherapeutic approach or fail to meet the defined standards of quality and usability will not be considered.

Connectedness

- Standalone applications that operate independently from other technologies are considered.
- However, apps that provide the option to connect with other technologies are not excluded.
- Apps that cannot function independently are excluded.

Health domain

- Apps need to support patients with at least one of the following International Classification of Diseases (ICD) indications: F32.0; F32.1; F32.2; F33.0; F33.1; F33.2; F34.1; F41.1.
- Digital health applications (DiGAs) are excluded if they address mainly other mental disorders, such as agoraphobia, panic disorder, nonorganic vaginism and dyspareunia, nonorganic insomnia and sleep disturbance, and mental and behavioral disorders caused by alcohol, tobacco, or other drugs.

Data Extraction

The DiGAs will be evaluated using 4 different strategies including frameworks and guidelines: (1) a tabular summary of the features as suggested by Arnhold et al [38], (2) the Institute for Healthcare Informatics (IMS) App Functionality Scoring System [39], (3) a comparison of the DiGA content with professional guidelines for both diseases and disease-specific iCBT components published in the literature [12,14,40-43], and (4) a quality appraisal using the Mobile Application Rating Scale (MARS) [44].

Tabular Summary

Arnhold et al [38] developed a summarizing checklist for their study on mobile apps for weight loss. Modifications were implemented to align with DiGAs for mental well-being. The form includes details regarding general information, operating system, acquisition costs, and data storage. Range of functions is excluded because a functionality assessment for consumer

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health care apps is used. Two reviewers are responsible for extracting data from the included DiGAs using this form and resolving any disparities through discussions with a third reviewer.

Functionality Assessment

Based on the recommendations of Gasteiger et al [37], the IMS App Functionality Scoring System is used to assess the functionality of the DiGAs [39]. The assessment comprises 7 functionality criteria and 4 subcriteria (Table 1). The focus is on the availability of the functions, thus the reviewer rate the functionality using a binomial 0 for not available or 1 for available. A visual representation of the findings in the form of a radar graph is planned. Interrater reliability is calculated using the Cohen kappa statistic [37,39].

Table 1. Institute for Healthcare Informatics Functionality Scoring System [39].

Functionality scoring system[a]	Description
1. Inform	Provides information in a variety of formats (text, photo, video)
2. Instruct	Provides instructions to the user
3. Record	Captures user-entered data
3a. Collect data	Able to enter and store health data on individual phone
3b. Share data	Able to transmit health data
3c. Evaluate data	Able to evaluate the health data entered by patient and provider, provider and administrator, or patient and caregiver
3d. Intervene	Able to send alerts based on the data collected or propose behavioral intervention or changes
4. Display	Graphically displays user-entered data and output user-entered data
5. Guide	Provides guidance based on user-entered information, may further offer a diagnosis, or recommend a consultation with a physician or a course of treatment
6. Remind or alert	Provides reminders to the user
7. Communicate	Provides communication between health care professionals and patients or provides links to social networks

[a]Total score (0-11): 1 point is assigned to each functionality that is present.

Comparison With Guidelines

To evaluate the guideline conformity of the DiGAs, 2 checklists were prepared from the National Care Guidelines for Depression and the German S3 Guideline for Anxiety Disorders [12,14]. These checklists summarize the recommended therapy approaches. In addition, iCBT components for depression and GAD were extracted from the literature and compiled in a checklist [40-43]. iCBTs that were not applicable were excluded (eg, waiting component, conventional drug treatment, placebo effect). During the review, reviewers will mark all DiGA content modules as “yes” (1), “no” (0), or “to be discussed.” In addition, free text options are offered (see Multimedia Appendix 1). The compiled findings will be used to generate an overview of the DiGAs’ content.

To ensure a high level of objectivity, 6 patient cases based on the literature will be used for all raters involved, namely 3 cases of depression and 3 cases of GAD (see Multimedia Appendix 2) [40-44]. The patients presented differ in severity, age, and prognosis. All checklists were piloted by 2 physicians and a health care scientist using a web-based application for depression. The form was then discussed with a psychiatrist treating patients with depression and GAD.

Quality Appraisal

The 2 reviewers will evaluate the app quality using the MARS tool. MARS is a reliable and valid tool for appraising mobile health interventions, with 19 items evaluating 4 dimensions: engagement, functionality, aesthetics, and information. Interrater reliability will be analyzed using the intraclass correlation coefficient [37,44].

Part 2: Systematic Review of Published Evidence

This protocol is reported in line with the 2015 PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist, and the completed PRISMA-P checklist is provided in Multimedia Appendix 3 [45]. During the review process, 2 reviewers performed the literature search and will extract and evaluate the data. In case of disagreement, a more experienced reviewer will lead discussions until a consensus is reached. Cohen kappa is used to calculate the agreement coefficient [46].

Identifying Studies

After identifying the DiGAs, a systematic literature search was conducted in July 2024 and August 2024. An updated search is planned shortly before the review is published (approximately in November 2025). This process was divided into 3 steps. First, a systematic literature search was conducted in the electronic bibliographic databases MEDLINE via PubMed, the Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science. Only studies in German or English were considered. All citations identified by the search strategy were managed using Rayyan, which was used to remove duplicate records and

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further screen the results. There were no restrictions regarding the publication year. Although DiGAs were implemented in the German health care system in 2020, studies of these might have been carried out earlier.

A separate search using the original DiGA name was conducted for each identified DiGA. Search queries must be customized to suit the specific requirements of various databases and electronic libraries using Boolean logic and Medical Subject Headings (MeSH) terms. The search terms focused on 3 key areas: DiGA name, impact evaluation, and research design. To ensure a comprehensive literature search on the effectiveness of the selected DiGAs, we used a detailed and structured search string. For instance, the search string for one DiGA in PubMed is listed in Table 2.

Table 2. Search string for study identification.

Number	Field of interest	Search string
1	DiGA[a] name	Deprexis
2	Impact evaluation: studies that focus on the effects or effectiveness of the intervention	(“effect”[All Fields] OR “effecting”[All Fields] OR “effective”[All Fields] OR “effectively”[All Fields] OR “effectiveness”[All Fields] OR “effectivenesses”[All Fields] OR “effectives”[All Fields] OR “effectivities”[All Fields] OR “effectivity”[All Fields] OR “effects”[All Fields] OR “effectiv*”[All Fields])
3	Impact evaluation: Studies that focus on the safety of the intervention	(“patient safety”[MeSH Terms] OR (“patient”[All Fields] AND “safety”[All Fields]) OR “patient safety”[All Fields] OR (“patient harm”[MeSH Terms] OR (“patient”[All Fields] AND “harm”[All Fields]) OR “patient harm”[All Fields]) OR “safety management”[MeSH Terms])
4	Impact evaluation: Studies that focus on equity regarding the intervention	(“equities”[All Fields] OR “equity”[All Fields] OR “disparit*”[All Fields] OR “inequit*”[All Fields] OR “inequalit*”[All Fields])
5	Research design	(“studies”[All Fields] OR “study”[All Fields] OR “study s”[All Fields] OR “studying”[All Fields] OR “studys”[All Fields] OR (“research personnel”[MeSH Terms] OR (“research”[All Fields] AND “personnel”[All Fields]) OR “research personnel”[All Fields] OR “researcher”[All Fields] OR “researchers”[All Fields] OR “research”[MeSH Terms] OR “research”[All Fields] OR “research s”[All Fields] OR “researchable”[All Fields] OR “researche”[All Fields] OR “researched”[All Fields] OR “researcher s”[All Fields] OR “researches”[All Fields] OR “researching”[All Fields] OR “researchs”[All Fields]) OR (“clinical trial”[Publication Type] OR “clinical trials as topic”[MeSH Terms] OR “clinical trial”[All Fields]) OR (“randomized controlled trial”[Publication Type] OR “randomized controlled trials as topic”[MeSH Terms] OR “randomized controlled trial”[All Fields] OR “randomised controlled trial”[All Fields]))
6	Combined string	#1 AND #5 AND (#2 OR #3 OR #4)

[a]DiGA: digital health applications.

Second, a gray literature search was conducted in the BfArM directory, corresponding websites, and manufacturers’ websites. Third, the snowball method was used to identify further studies that evaluate the DiGAs of interest. This includes a search for studies of the DiGAs published under a different name.

All identified titles and abstracts were independently screened by 2 reviewers. Disagreements were documented and discussed between the reviewers until a joint decision was made. In the next step, the full texts of the eligible studies will be screened and rated following the processes described. The complete process will be displayed in a PRISMA flow diagram.

The Eligibility Criteria

The criteria shown in Textbox 2 were used to identify eligible studies. The eligibility criteria are based on the population, intervention, comparison, outcomes, and study design (PICOS) scheme [47].

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Textbox 2. Eligibility criteria in the population, intervention, comparison, outcomes, and study design (PICOS) scheme.

Population

- The examined participants must not meet any criteria in terms of gender, age, or ethnicity.
- Symptoms of depression or generalized anxiety disorder (GAD) must be present for the participants.
- To identify a broad range of studies examining digital health applications (DiGAs), all countries are included.
- Excluded are studies focusing on participants who do not present psychological symptoms.

Intervention

- The study must examine at least one of the predefined DiGAs.

Comparison

- The comparison group must receive either the standard therapy, no therapy, or therapy with another DiGA, based on the specifications of the Federal Institute for Drugs and Medical Devices (BfArM).
- The comparison group must be as close as possible to treatment as usual.

Outcomes

- Included types of outcome measurements are any objective measurements of health that are directly linked to the patient (eg, depressive symptom severity, activities of daily life, cognitive outcomes relating knowledge, and others).
- Excluded are outcomes that focus solely on the physician or the economy.

Types of studies

- Studies must be conducted as a randomized controlled trial to ensure a rigorous assessment of DiGA effectiveness under controlled conditions.

Data Extraction From RCTs

Data extraction will be performed using prepiloted forms. Missing data will be requested from the study authors or DiGA manufacturers. Two reviewers will independently extract the data. Similar to the screening process, an experienced reviewer will discuss any disagreements.

All included studies will be summarized in a table. Table items include DiGA name, author, year, title, inclusion criteria, exclusion criteria, indication, recruitment, treatment, gender and age distribution of the study population, intervention and control, outcomes and operationalization, study design, randomization, blinding, sample size calculation and sample size, dropouts, results, observation period, observation times, place of study, time of study, strengths, and limitations.

Effectiveness

We will evaluate the effectiveness of the DiGAs by calculating risk ratios for dichotomous data or standard mean differences for continuous data, utilizing data extracted from published studies or data obtained directly from study authors. Heterogeneity among the studies will be assessed using the I^2 test, which is known for its robustness to sample size variations. To ensure the robustness of our findings, sensitivity analyses will be conducted to examine the impact of different assumptions or methodological choices on our results.

Furthermore, we will address potential publication bias by generating funnel plots and conducting additional analyses using the Egger test. This multifaceted approach will provide a comprehensive evaluation of the intervention's effectiveness while accounting for potential sources of bias and variability across the included studies [47].

Quality Appraisal

Risk of bias will be assessed independently by 2 reviewers using the Cochrane tool to assess the risk of bias in randomized trials (Risk of Bias 2 [RoB2]) [48]. The RCTs are rated in the following categories: randomization sequence generation, treatment allocation concealment, blinding, completeness of outcome data, selective outcome reporting, and other sources of bias. Again, a third reviewer will lead any discussions about disagreements. The level of the risk of bias will be presented in the final review.

The overall quality of evidence will be assed using the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) method [49]. This method helps rate the quality of the evidence. The rating process will be conducted in the same manner as the risk of bias assessment.

Results

Status

The systematic literature search was conducted in July 2024 and August 2024. The process involved searching the electronic bibliographic databases MEDLINE via PubMed, CENTRAL, and Web of Science. Only studies published in German or English were considered. All citations identified with the search strategy were managed using Rayyan, where duplicate records were removed and initial screening was performed. An updated search is planned in November 2025 to capture any new evidence before the review is submitted.

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The subsequent steps, including data extraction, narrative synthesis, evaluation of DiGAs, and corresponding studies, as well as the final writing of the systematic review and meta-analysis are expected to be completed in spring 2026.

Results of Systematic Health App Review

In a scoping process, 26 DiGAs for mental health were identified, 17 of which are permanently listed [24]. The permanent inclusion in the DiGA directory of the BfArM requires publication of the positive therapeutic effect of a DiGA.

For the DiGA evaluation, tables will be generated to present general information and intervention components, along with quality ratings for each DiGA. Interrater reliability calculations will be presented. These results will provide a comprehensive comparison of DiGAs for depression and GAD focusing on content and quality.

Results of Systematic Review of Published Evidence

A PRISMA flow diagram will be used to illustrate the inclusion process. The results of the study evaluation will be presented in tables to show general information, risk of bias, and overall quality. Interrater reliability calculations will be presented.

Integrated Data Synthesis Across Both Review Components

Both components of the review are anticipated to yield valuable insights into DiGAs. To complement this, a combined synthesis through subgroup analyses is planned to assess how specific qualitative and content-related features relate to intervention effectiveness within the meta-analytic findings.

Discussion

Overview

In contrast to systematic literature reviews, there is no gold standard for conducting or reporting systematic health app reviews yet. As more apps are brought to market and depression rates rise, there is a need for such a standard to ensure high-quality care. Despite the evident benefits of DiGAs, several issues persist. Methodological flaws in efficacy studies, including inadequate participant screening, reliance on self-reported outcomes, and the use of generalized content approaches undermine their reliability [12,29,32,33,50]. Addressing these concerns through rigorous content, quality, and evidence-based investigations is crucial for advancing the evidence of digital health interventions.

Since the integration of DiGAs into the German health care system in 2020, patients have been able to access these digital tools easily, receiving support for a variety of medical conditions. The majority of DiGA activations have been in the field of psychological and behavioral disorders. The use of digital mental health interventions has the potential to alleviate strain on the health care system, particularly in light of the growing shortage of skilled therapists [51]. However, concerns regarding the high costs associated with DiGAs persist [52].

During the trial phase, manufacturers independently determine the price of a DiGA, which is subsequently reimbursed by health insurance providers. Once a DiGA receives permanent listing status, its price is negotiated and set by an arbitration board. For instance, the cost of Velibra, a DiGA designed for anxiety disorders, was reduced by 51.70% following the trial phase—from €476 to €230 [52]. As price reductions are effective after the trial period, health insurance funds face substantial financial burdens in the initial phase. Conversely, manufacturers experience financial constraints when prices are reduced after permanent listing.

DiGAs have become well integrated into the German health care system, which is currently undergoing a digital transformation. Plans are in place to improve interoperability with other digital systems. The electronic patient record is currently being implemented, and interfaces with DiGAs are expected to be established. As a result, DiGAs must already comply with the necessary technical requirements. Despite these technical advancements, real-world implementation remains challenging. Physicians, for instance, face barriers to prescribing DiGAs, such as limited information and a lack of trust in their effectiveness. A current discussion revolves around the introduction of an application-accompanying success measurement [53]. Such an approach could, on the one hand, allow reimbursement to be based on measurable outcomes, thereby potentially reducing costs. On the other hand, it could provide physicians with better insights into the effectiveness of DiGAs for their patients, ensuring greater transparency in digital health care.

In general, it is likely that individuals with greater technological proficiency experience fewer difficulties with using these applications than those who are less tech-savvy. However, health literacy and patients' self-management skills are crucial factors in successful DiGA adoption [54]. Therefore, in addition to the systematic evaluation of the evidence, further studies are needed to investigate DiGAs and, above all, the users.

Limitations

The detailed analytic approach comprising an app review in addition to a systematic review addressing the content, functionality, and quality of DiGAs is one of the strengths of this review. However, it includes apps available only in Germany, which may limit the generalizability of the findings. The available evidence may restrict the effectiveness of the analyses in the review.

Conclusions

Given the increasing availability and use of DiGAs for mental health, the anticipated multifaceted review will provide important insights into their current potential and quality for depression and GAD: The more is known about the quality of a DiGA, the better its actual benefit can be valued by physicians. High quality leads to greater trust and better utilization. Accordingly, indications of low quality would lead to specific recommendations for action. Ultimately, the quality of patient care is improved as DiGAs either gain more trust or targeted recommendations for improvement are made.

The review's results will be considered in various contexts to generate actionable improvement suggestions. If additional evidence gaps are identified, proposals for further research will be made. The DiGA development process will be evaluated,

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particularly regarding content, with clinical perspectives included to validate or challenge physicians' assumptions about DiGA effectiveness. The political dimension will assess the spread of DiGAs and potential future challenges. Finally, the results will be compared with international and national findings in this research area to contextualize insights and contribute to the development of therapies and access options for patients with depression and GAD.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated nor analyzed during this study. All data of the planned review generated or analyzed during the study will be included in the published article and its supplementary information files.

Authors' Contributions

AS, SF, AK, ALN, and BW conceptualized the review protocol. AS and SF developed the methodology. AK, ALN, and BW supervised the project, while AS and BW administrated the project. AS, LK and JK validated the checklists. AS visualized and prepared the original draft. LK, JK, SF, AK, ALN, and BW revised it. All authors reviewed and approved the final manuscript.

Conflicts of Interest

ALN is funded by the National Institute for Health and Care Research (NIHR) Applied Research Collaboration Northwest London (ARC NWL) and NIHR Patient Safety Research Collaboration, with infrastructure support from Imperial NIHR Biomedical Research Centre. All remaining authors declare no conflict of interest.

Multimedia Appendix 1
Checklists for DiGA treating depression or GAD.
[PDF File (Adobe PDF File), 859 KB - resprot_v14i1e63380_app1.pdf]

Multimedia Appendix 2
Cases for DiGA evaluation.
[PDF File (Adobe PDF File), 646 KB - resprot_v14i1e63380_app2.pdf]

Multimedia Appendix 3
PRISMA-P checklist.
[PDF File (Adobe PDF File), 375 KB - resprot_v14i1e63380_app3.pdf]

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Abbreviations

BfArM: Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte)
CBT: cognitive behavioral therapy
CENTRAL: Cochrane Central Register of Controlled Trials
DiGA: Digital health applications (Digitale Gesundheitsanwendung)
GAD: generalized anxiety disorder
GRADE: Grading of Recommendations, Assessment, Development and Evaluation
iCBT: internet-based cognitive behavioral therapy
IMS: Institute for Healthcare Informatics
MARS: Mobile Application Rating Scale
MeSH: Medical Subject Headings
PICOS: population, intervention, comparison, outcomes, and study design
PRISMA: Preferred Reporting Items for Systematic Reviews
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PROSPERO: Prospective Register of Systematic Reviews
RCT: randomized controlled trial
RoB2: Risk of bias tool 2
SGB V: Social Code – Book V (Fünftes Buch Sozialgesetzbuch)
TECH: Target user groups, Evaluation focus, Connectedness, Health domain

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Protocol

A Higher-Than-Standard-Intensity International Normalized Ratio Goal for Patients Undergoing Mechanical Aortic Valve Replacement With Additional Thrombotic Risk Factors: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Lifelong anticoagulation therapy with vitamin K antagonists is recommended following mechanical aortic valve replacement (MAVR) to prevent valve thrombosis. Current guidelines recommend a standard international normalized ratio (INR) of 2.5 for patients with MAVR without additional thromboembolic risk factors, and a higher INR goal of 3.0 for those with conditions such as atrial fibrillation, prior thromboembolism, or left ventricular dysfunction. However, limited clinical evidence exists to guide anticoagulation intensity in this high-risk subgroup, necessitating a systematic review.

Objective: We aimed to assess the safety and efficacy of higher-intensity INR goals (>3.0) compared to standard-intensity goals (approximately 2.5) in patients with MAVR with additional thromboembolic risk factors.

Methods: This protocol describes a systematic review and meta-analysis following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 guidelines. A comprehensive literature search will be conducted across PubMed, Embase, and the Cochrane Library for studies published before December 18, 2024. Eligible studies include randomized controlled trials (RCTs), cohort studies, and follow-up studies involving adult patients with MAVR on warfarin therapy, stratified by the presence of additional thromboembolic risk factors. Non–English-language studies, case reports, editorials, and animal studies will be excluded.

Results: The review will synthesize existing data to compare the risks and benefits of intensified anticoagulation in patients with MAVR with additional thromboembolic risk factors. Data analysis and manuscript preparation are scheduled for July-August 2025.

Conclusions: This study will provide critical evidence on INR management in high-risk patients with MAVR, potentially informing future updates to clinical guidelines and optimizing the balance between thromboembolic prevention and bleeding risk.

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KEYWORDS

mechanical aortic valve replacement; MAVR; thromboembolic risk factors; thromboembolism; anticoagulation; international normalized ratio; warfarin; Coumadin; vitamin K antagonist

Introduction

Severe aortic valvular disease, if left untreated, carries a mortality rate exceeding 90% and often necessitates surgical intervention through mechanical aortic valve replacement (MAVR) [1-3]. After surgery, patients require lifelong anticoagulation therapy with vitamin K antagonists, such as warfarin, to prevent prosthetic valve thrombosis.

Current guidelines differ on the target international normalized ratio (INR) for patients with MAVR, especially those with additional thromboembolic risk factors. While the 2020 American College of Cardiology/American Heart Association (ACC/AHA) guidelines recommend an INR goal of 3.0 for high-risk patients, the 2012 American College of Chest Physicians (ACCP) guidelines continue to advise a standard INR of 2.5 [4]. These inconsistencies highlight the ongoing debate regarding optimal anticoagulation intensity in this subgroup.

The majority of MAVR candidates already exhibit structural cardiac changes, such as left ventricular hypertrophy, chamber dilation, or atrial fibrillation due to longstanding pressure overload [5,6]. These features inherently increase the risk of thromboembolism, suggesting that many MAVR recipients may require more intensive anticoagulation [7]. However, balancing thrombotic protection with bleeding risk is critical, and existing evidence is insufficient to guide personalized INR targets.

To date, only one multicenter retrospective study has evaluated anticoagulation strategies in patients with MAVR with thromboembolic risk factors, reporting fewer bleeding and thromboembolic events with standard-intensity therapy compared to higher-intensity regimens [8]. Despite its important insights, this single study is not sufficient to inform clinical guidelines.

Notably, there is currently no systematic review or meta-analysis specifically focused on patients with MAVR with additional thromboembolic risk factors. While prior studies have explored INR goals in broader MAVR populations, they have often failed to stratify outcomes by thromboembolic risk status [9-13]. Therefore, a targeted synthesis of existing evidence is needed to evaluate whether higher INR goals provide additional benefit or pose increased harm for this population.

Our systematic review aims to fill this gap by examining the safety and efficacy of intensified anticoagulation in patients with MAVR with elevated thromboembolic risk. These findings have the potential to inform future guideline updates and guide individualized management strategies for this high-risk group.

Methods

Ethical Considerations and Protocol Registration

Institutional review board approval was not required for this systematic review, as it did not involve patient interaction and was conducted using publicly available, published data. To maintain project integrity, it was registered with PROSPERO (registration CRD42025639037, registered on January 27, 2025). PROSPERO is an international database where systematic reviews across various fields, including health care, can be registered to prevent duplication and minimize reporting bias by comparing the protocol with the final review.

Review Questions

Guided by the population, exposure, comparison, outcome, and study design (PECOS) framework [14], this study was developed to answer the following question: Does a higher than standard-intensity INR goal benefit patients with MAVR and additional thrombotic risk factors?

Inclusion and Exclusion Criteria

The systematic review will include case studies, randomized controlled trials (RCTs), and single-arm studies, while the meta-analysis will primarily consist of RCTs and follow-up studies. Only English-language articles published before December 18, 2024, will be included. Single-patient case reports, abstract-only articles, animal studies, commentaries, position papers, opinions, and editorials will be excluded, as will other meta-analyses and systematic reviews.

The study populations will comprise patients older than 18 years with a prior MAVR who are receiving warfarin therapy. A specific INR goal was not defined in order to expand the inclusion criteria, thereby maximizing the sample size and statistical power. Patients younger than 18 years or not receiving warfarin therapy will be excluded. Additionally, patients with bioprosthetic aortic valve replacement (AVR) will be excluded, as they do not require warfarin therapy. Non-bileaflet mechanical valves will also excluded due to the higher thromboembolic risks associated with single-leaflet AVRs compared to bileaflet prostheses [15,16]. Only studies with a patient population meeting the above criteria will be included in the systematic review. Among these, we will include patients with and without additional thromboembolic risk factors. Specifically, the control group will include adult patients (aged ≥18 years) with MAVR who receive warfarin therapy and do not exhibit any of the following predefined thromboembolic risk factors: atrial fibrillation, prior venous thromboembolism, hypercoagulable states (eg, antiphospholipid syndrome or inherited thrombophilias), severe left ventricular systolic dysfunction (ejection fraction <40%), left atrial dimension >50 mm, spontaneous echocardiographic contrast in the left atrium, significant vascular disease, or current estrogen replacement

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therapy. Older-generation prostheses or non-bileaflet devices will be excluded due to practical concerns. This definition ensures a consistent comparator population across studies and enhances the reproducibility and interpretability of the systematic review and meta-analysis. Textbox 1 summarizes the inclusion and exclusion criteria.

Textbox 1. Inclusion and exclusion criteria guided by the population, exposure, comparison, outcome, and study design (PECOS) framework.

Inclusion criteria

Population: age ≥18 years; mechanical aortic valve replacement (MAVR); presence of ≥1 thromboembolic risk factor (eg, atrial fibrillation, venous thromboembolism, hypercoagulability, ejection fraction <40%)

Exposure: warfarin-based anticoagulation with international normalized ratio goal defined or reported

Comparison: patients with MAVR receiving warfarin without thromboembolic risk factors: no atrial fibrillation, no venous thromboembolism, no hypercoagulability, ejection fraction ≥40%, left atrial dimension ≤50 mm, no spontaneous echo contrast, no significant vascular disease, not receiving estrogen therapy

Outcomes: primary outcomes include major or minor thromboembolic and bleeding events; secondary outcomes include all-cause mortality, prosthetic endocarditis, valve reoperation, and hemolytic anemia

Study design: randomized controlled trials, observational studies, single-arm studies in English

Exclusion criteria

Population: age <18 years; not receiving warfarin therapy; bioprosthetic aortic valve replacement; non-bileaflet mechanical valve

Outcomes: studies lacking extractable clinical outcome data

Study design: case reports, editorials, commentaries, conference abstracts, prior systematic reviews or meta-analyses, non–English-language articles

Informational Sources and Search Strategy

Bibliographic databases, including PubMed, Cochrane, and Embase, were searched from the initial development through December 18, 2024. The search strategy was developed by an expert medical librarian and adheres to the guidelines outlined by the Peer-Reviewed Electronic Search Strategy (PRESS). Initially, the search strategy was designed for the PubMed database using search criteria specific to that platform. It was then adapted for use with other databases. The detailed search strategy is provided in Table 1.

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Table 1. The search strategy. All databases were searched from inception to December 18, 2024.

Database and query number	Query	Results, n
PubMed		
#1	INR	20,246
#2	International Normalized Ratio	13,833
#3	Warfarin	35,162
#4	Coumadin	35,662
#5	Vitamin k antagonist	11,315
#6	#1 OR #2 OR #3 OR #4 OR #5	56,899
#7	Mechanical aortic valve replacement	4375
#8	MAVR	55
#9	#7 OR #8	4405
#10	#6 AND #9	341
Embase		
#1	INR	61,976
#2	International Normalized Ratio	55,005
#3	Warfarin	117,951
#4	Coumadin	5260
#5	Vitamin k antagonist	9682
#6	#1 OR #2 OR #3 OR #4 OR #5	167,310
#7	Mechanical aortic valve replacement	7589
#8	MAVR	82
#9	#7 OR #8	7626
#10	#6 AND #9	1114
Cochrane Library[a]		
#1	INR	4847
#2	International Normalized Ratio	3434
#3	Warfarin	5802
#4	Coumadin	234
#5	Vitamin k antagonist	909
#6	#1 OR #2 OR #3 OR #4 OR #5	10,974
#7	Mechanical aortic valve replacement	261
#8	MAVR	3
#9	#7 OR #8	262
#10	#6 AND #9	61

[a]The search for the Cochrane Library was limited to “all text.”

Screening and Data Management

Each article identified through the search strategy described above will be reviewed by 4 independent researchers to ensure it meets the inclusion criteria. This process will be carried out step-by-step, including review of the title, abstract, and full text. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram (Figure 1 [17]) will be included in the final review to further illustrate the screening process. Prior to initiating the formal screening process, all reviewers will undergo a training session and participate in a piloting exercise involving a random sample of articles. This calibration step is designed to ensure consistent interpretation of the inclusion and exclusion criteria and improve interreviewer reliability. Any discrepancies identified during piloting will be discussed and used to refine reviewer alignment before full screening begins. The screening and selection process will be managed using Rayyan, a web-based platform for systematic reviews. Rayyan will enable independent, blinded screening of titles and abstracts by at least two reviewers. Full-text screening

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will follow the same process. Disagreements will be resolved through consensus discussions, and if necessary, a third reviewer will adjudicate. This workflow will enhance transparency, minimize bias, and ensure a structured review process.

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram describing the study selection process (reproduced from Page et al [17]. This figure details the number of records identified, screened, assessed for eligibility, and included in the final analysis. It begins with the total number of articles retrieved through database searches (PubMed, Embase, and Cochrane Library), followed by the number of duplicates removed. Records are then screened by title and abstract, with exclusions noted. Full-text articles are reviewed for eligibility, with specific reasons for exclusion documented. The final number of studies included in the qualitative and quantitative synthesis is displayed at the bottom. This structured approach, based on PRISMA 2020 guidelines, ensures transparency and reproducibility in the literature selection process.

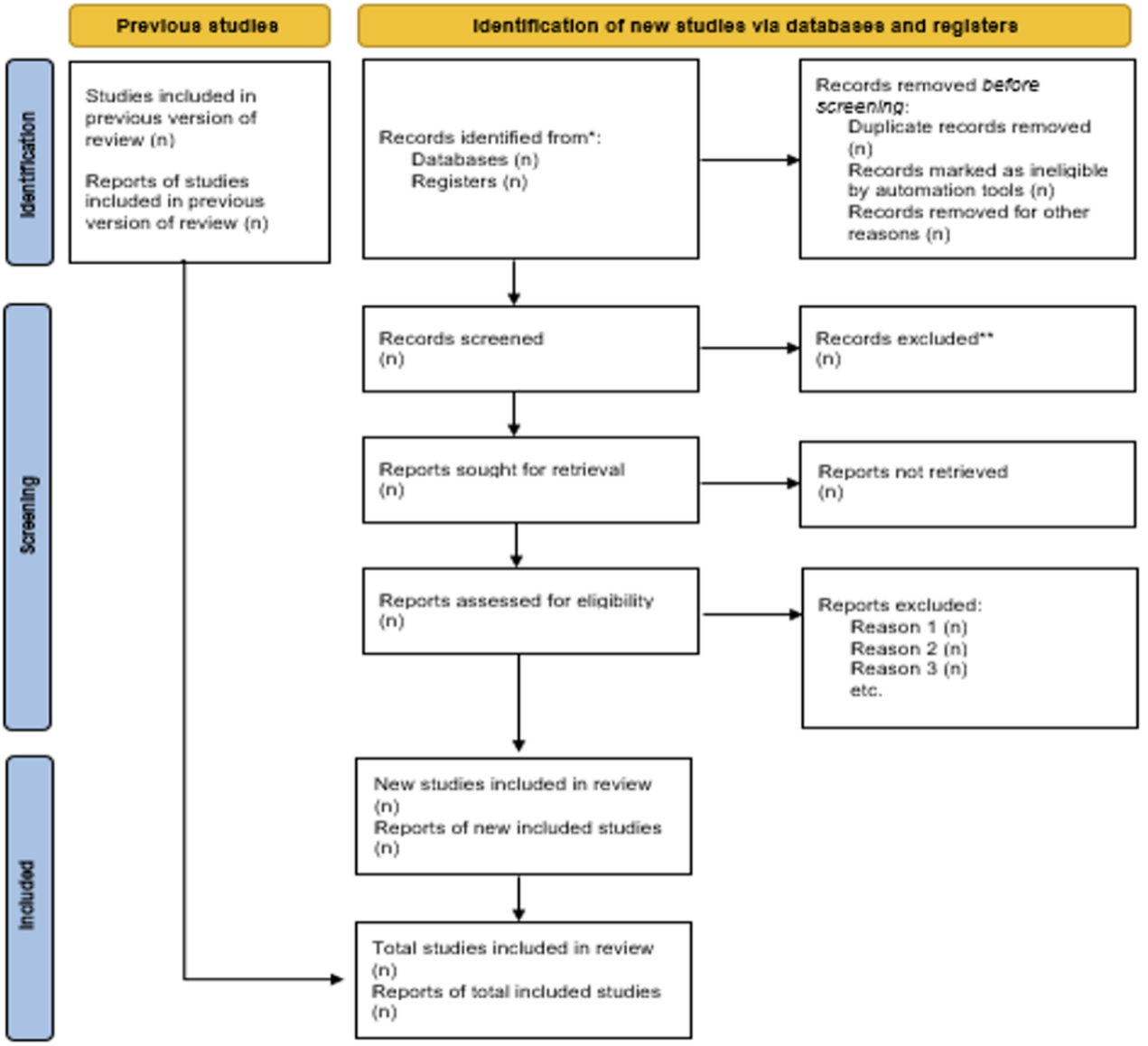

Data Extraction and Main Data Elements

Four research team members will independently extract data from the articles accepted through the screening process to ensure a thorough and accurate review. Any discrepancies in the findings after data extraction will be discussed among authors and another independent team member to determine their relevance to the systematic review. The outcomes of the meta-analysis and systematic review will include the following: (1) occurrence of thromboembolic events during warfarin therapy, (2) occurrence of bleeding events during warfarin therapy, (3) all-cause mortality, (4) prosthetic endocarditis, (5) preoperative aortic valve replacement or repair, and 6) hemolytic anemia.

Quality or Risk of Bias Assessment

All studies included in the final publication that meet the original inclusion criteria will be assessed using the National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool [18]. Randomized controlled trials will be assessed using the NHLBI Quality Assessment Tool for Controlled Intervention Studies, while noninterventional studies (eg, cohort and cross-sectional designs) will be evaluated using the NHLBI Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies. The evaluation will be conducted

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according to the NHLBI criteria outlined in Textbox 2. The scoring protocol follow the model previously developed by Elks et al [19]. Two independent reviewers will evaluate each study, and discrepancies will be resolved through discussion or consultation with a third reviewer. To assess consistency between reviewers, the Cohen κ statistic will be calculated to quantify interrater agreement for each domain of the quality assessment. A κ value ≥0.75 will be considered excellent agreement, 0.40-0.74 moderate to good agreement, and <0.40 poor agreement. This additional layer of statistical validation will enhance the transparency and rigor of our bias assessment process.

Textbox 2. National Heart, Lung, and Blood Institute (NHLBI) Quality Assessment Tool used to evaluate risk of bias in included studies. This checklist includes multiple domains assessing internal validity, including participant selection, exposure and outcome measurement, confounding control, statistical analysis, and reporting clarity. Each item is rated as "yes," "no," "cannot determine," or "not applicable" according to standardized NHLBI criteria. Two independent reviewers applied the tool to all included studies. Discrepancies were resolved by consensus or a third reviewer.

Quality Assessment of Controlled Intervention Studies: Criteria

1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?
2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?
3. Was the treatment allocation concealed (so that assignments could not be predicted)?
4. Were study participants and providers blinded to treatment group assignment?
5. Were the people assessing the outcomes blinded to the participants' group assignments?
6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?
7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?
8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?
9. Was there high adherence to the intervention protocols for each treatment group?
10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?
11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?
12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?
13. Were outcomes reported or subgroups analyzed prespecified (i.e., identified before analyses were conducted)?
14. Were all randomized participants analyzed in the group to which they were originally assigned, i.e., did they use an intention-to-treat analysis?

Strategy for Meta-Analysis

The statistical analysis for this meta-analysis will involve several key steps to assess the practical benefits of higher-intensity warfarin therapy for patients with MAVR and additional thromboembolic risk factors. First, data will be pooled using a random-effects model, as this approach accounts for potential variability between studies [20]. For continuous outcomes, such as INR level or left atrial dimension >50 mm, mean differences or standardized mean differences will be calculated. For dichotomous outcomes, such as bleeding or thromboembolic events, all-cause mortality, prosthetic endocarditis, preoperative aortic valve replacement or repair, and hemolytic anemia, we will compute risk ratios or odds ratios with 95% CIs. In addition to dichotomous outcomes, we will also extract time-to-event outcomes when reported, such as cumulative incidence rates at specific follow-up intervals or hazard ratios derived from survival analyses. If sufficient studies report comparable timeframes and event definitions, we will explore the feasibility of conducting a meta-analysis of time-to-event data using appropriate statistical models (eg, pooled hazard ratios). When heterogeneity in reporting precludes quantitative pooling, a narrative synthesis of time-to-event results will be included to provide additional context.

Subgroup analyses will explore potential differences based on factors such as additional thromboembolic risk factors (eg, atrial fibrillation, prior thromboembolism, hypercoagulable states, or severe left ventricular dysfunction), spontaneous echocardiographic contrast in the left atrium, significant vascular disease, and estrogen replacement therapy, as well as age, sex, and study design (randomized controlled trials vs observational studies). Sensitivity analyses will be conducted by excluding studies with a high risk of bias or small sample sizes to evaluate the robustness of the results. The heterogeneity of the results will be assessed using the I^2 statistic, and if significant heterogeneity is detected, meta-regression and subgroup analyses will be performed to explore its sources. Publication bias will be assessed using funnel plots and the Egger test [21]. Statistical significance will be defined as a 2-sided P value of less than .05. The Comprehensive Meta-Analysis Package (version 4.0; Biostat Inc) will be used for data analysis.

Data Analysis and Presentation

Assuming sufficient data are extracted, the data will be presented in a detailed table, accompanied by a final summary discussing the analysis performed. A data extraction form will be created and reviewed by all investigators before analysis. The articles included in the publication will be listed as horizontal rows in the table, and the variables agreed upon by the team will serve as columns. Quantitative analysis will be conducted on all variables extracted from the available data.

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Results

A PRESS review of the search strategy with an academic librarian was conducted in December 2024. The development of the search strategy began in December, and the final strategy was completed by the team of investigators in January 2025. Database queries and title screenings will begin in February 2025, with abstract screenings scheduled for February and March 2025. Full-text retrieval will occur from March to May 2025. Data extraction, synthesis, and risk of bias assessment will be carried out in May and June 2025. Data analysis and manuscript drafting will take place during July and August 2025. The findings will be summarized, organized, and submitted to a peer-reviewed journal by September 2025. The primary goals of this effort are to assess the utility of higher INR goals in patients with MAVR with additional thromboembolic risk factors, balancing the benefits and risks of harm, and to inform the development of future guidelines for medical practice. A timeline is presented in Table 2.

Table 2. Project milestones and timelines.

Tasks	December 2024	January 2025	February 2025	March 2025	April 2025	May 2025	June 2025	July 2025	August 2025	September 2025
1. Protocol development	✓									
2. Design of search strategy	✓	✓								
3. Title screening			✓							
4. Abstract screening			✓	✓						
5. Full-text screening				✓	✓	✓				
6. Data extraction						✓	✓			
7. Synthesis and risk of bias assessment						✓	✓			
8. Data analysis								✓	✓	
9. Manuscript drafting								✓	✓	
10. Submission and peer review										✓

Discussion

Overview

Our systematic review will be a comprehensive analysis of the relevant literature to synthesize the need for higher-intensity anticoagulation therapy in patients with MAVR and additional thromboembolic risk factors. We anticipate that the results of our analysis will align with current guidelines, recommending higher INR goals (3.0-3.5) for this group compared to the standard INR goals (2.5-3.0) for patients without additional risk factors. We will analyze each thromboembolic risk factor, such as atrial fibrillation, history of thromboembolism, hypercoagulable states, and left ventricular systolic dysfunction, to evaluate their individual contributions to thromboembolic events in this population. In addition to the thromboembolic risk factors highlighted in the 2020 ACC/AHA and 2012 ACCP guidelines, we will also explore other potential risk factors, including left atrial dimension >50 mm, spontaneous echocardiographic contrast in the left atrium, significant vascular disease, and concurrent estrogen replacement therapy. In addition to major and minor thromboembolic and bleeding events as primary end points, we will examine all-cause mortality, prosthetic endocarditis, preoperative aortic valve replacement or repair, and hemolytic anemia as secondary end points to assess both the positive and negative outcomes of higher-intensity anticoagulation therapy in this group.

Significance

Although studies have examined the optimal INR goals for patients with MAVR, no previous systematic review or meta-analysis has specifically addressed the group with additional thromboembolic risks. As our study will be the first to focus on thromboembolic risk factors in patients with MAVR related to anticoagulation therapy, it may help validate the current guidelines, establish new ones, and guide future research in this patient population. In addition to primary RCTs, our systematic review will include secondary or follow-up RCTs of the original studies. This broader inclusion criterion will enhance subgroup analyses and provide a more comprehensive understanding of the safety profile of anticoagulation therapy in patients with additional thromboembolic risk factors. This study will balance the benefits of thromboembolic prevention against the harms of bleeding associated with higher-intensity warfarin therapy in this group. Since the majority of MAVR candidates already have significant cardiac conditions, such as atrial fibrillation or left ventricular systolic dysfunction due to chronic severe aortic valvular disease, most patients with MAVR are naturally at high thromboembolic risk. Given the lack of supporting data, many physicians and institutions continue to follow standard anticoagulation therapy guidelines despite the presence of additional thromboembolic risk factors. We anticipate that our study will benefit the majority of patients with MAVR, as most are at high thromboembolic risk for the reasons outlined above.

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Limitations

Our study will have several limitations. First, the selected articles were conducted in different settings, with varying demographics, primary and secondary end points, time periods, follow-up periods for INR checks, and INR goals. This variability in methodologies will introduce inherent heterogeneity. Additionally, there is a potential for reviewer bias during article selection. To mitigate this, we will implement the following strategies: (1) an individualized filtering process with 4 independent reviewers, with the first author overseeing the entire screening process to resolve any disagreements; (2) full transparency of methods, with subject matter experts providing input at each step of the systematic review; and (3) a standardized risk of bias assessment for every article. There is also a risk of publication bias in the article selection process, as studies with small sample sizes or insignificant results are less likely to be published, potentially causing relevant work to be overlooked. An additional limitation of our review is the restriction to English-language articles. This decision was made due to resource constraints and to ensure accuracy in data extraction and analysis, as our review team does not have access to certified medical translators. While this may introduce language bias and potentially exclude relevant studies published in other languages, previous meta-epidemiological studies have shown that excluding non-English articles often has a limited effect on the overall conclusions in many clinical domains [22]. Nonetheless, this language restriction may impact the comprehensiveness and global applicability of our findings, and we acknowledge it as a potential source of bias. Finally, given the variable study methodologies, we may encounter diverse outcomes of interest. While we hope our study will provide valuable insights and future directions on this topic, the possibility remains that the results may not reach statistical significance.

Dissemination Plan

Our systematic review will be submitted as a manuscript to a peer-reviewed journal by September 2025. Abstracts based on this study will be created, submitted, and presented at academic conferences.

Relevance to Practice and Policy

This systematic review protocol was developed by a multidisciplinary team of clinician-researchers specializing in cardiovascular medicine, internal medicine, and health outcomes research. Their clinical experience managing patients with MAVR directly informed the formulation of the research question and outcome selection, ensuring alignment with frontline clinical challenges.

To further enhance the applicability of the findings, we plan to engage a broader group of end users during the dissemination phase. This includes clinicians, patient advocacy groups, and policymakers. Presentations at cardiology and health services conferences, along with institutional and policy-focused briefings, will serve as platforms to gather feedback and support translation of findings into practice. We also aim to develop accessible summaries of the results tailored to patients and decision-makers to maximize the impact of this review on future guideline development and individualized care strategies.

Conclusions

This systematic review will provide a comprehensive evaluation of the safety of high-intensity anticoagulation therapy in patients with MAVR and additional thromboembolic risk factors, including atrial fibrillation, previous thromboembolism, a hypercoagulable state, or severe left ventricular dysfunction, as outlined in the 2020 ACC/AHA guidelines. We will also broaden the scope to include other thromboembolic risk factors, such as left atrial dimension >50 mm, spontaneous echocardiographic contrast in the left atrium, significant vascular disease, and estrogen replacement therapy. The primary end points will include major or minor thromboembolic and bleeding events, while secondary end points will include all-cause mortality, prosthetic endocarditis, preoperative aortic valve replacement or repair, and hemolytic anemia. Our study will also generate a qualitative synthesis of evidence regarding the risks of thromboembolism and bleeding across different INR goals in this patient population. Ultimately, our findings may guide future research and either support or modify current guidelines.

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Conflicts of Interest

None declared.

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Abbreviations

ACC: American College of Cardiology
ACCP: American College of Chest Physicians
AHA: American Heart Association
AVR: aortic valve replacement
INR: international normalized ratio
MAVR: mechanical aortic valve replacement
NHLBI: National Heart, Lung, and Blood Institute
PECOS: population, exposure, comparison, outcome, and study design
PRESS: Peer-Reviewed Electronic Search Strategy
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT: randomized controlled trial

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Protocol

Anti-Inflammatory Versus Antifibrotic Therapies for the Management of Rheumatoid Arthritis–Associated Interstitial Lung Disease: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease that affects approximately 0.5% to 1% of the population in the United States and Northern Europe. Interstitial lung disease (ILD) is the most common and severe pulmonary manifestation of RA, collectively referred to as RA-associated ILD (RA-ILD). RA-ILD contributes significantly to morbidity and mortality and often presents with a variable clinical course. Although corticosteroids and disease-modifying antirheumatic drugs (DMARDs) remain the cornerstone of RA management, their role in RA-ILD is less clearly defined. In contrast, antifibrotic therapies such as pirfenidone and nintedanib, initially developed for idiopathic pulmonary fibrosis, are now being explored for their potential in treating fibrosing variants of RA-ILD. Despite increasing clinical use, no systematic review has comprehensively compared the safety and efficacy of antifibrotic versus anti-inflammatory therapies in chronic RA-ILD.

Objective: This study aims to compare the impact of antifibrotic and anti-inflammatory therapies on lung function, radiologic progression, clinical outcomes, and safety in patients with chronic RA-ILD.

Methods: This study will follow PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and is registered with PROSPERO (CRD42024583847). A comprehensive search of PubMed, Embase, and the Cochrane Library will be conducted for studies published between January 1991 and August 2024. Eligible studies will include adult patients (aged ≥18 years) with a diagnosis of RA and confirmed ILD based on radiological or histopathological findings who have been treated with either antifibrotic or anti-inflammatory therapies. The PECOS (Population, Exposure, Comparator, Outcome, Study Design) framework will be used to define inclusion criteria. The primary outcomes assessed in this review will include the following pulmonary function parameters: forced vital capacity, forced expiratory volume in 1 second, and diffusing capacity of the lungs for carbon monoxide. Anti-inflammatory therapies will be stratified into corticosteroids, conventional synthetic DMARDs, and biologic DMARDs to account for heterogeneity. The Cochrane Risk of Bias 2 (RoB 2) and Risk of Bias in Non-randomized Studies - of Interventions (ROBINS-I) tools will be used for quality assessment, and GRADE (Grading of Recommendations Assessment, Development, and Evaluation) methodology will be used to evaluate the certainty of evidence.

Results: The literature search and screening commenced in August 2024, and data extraction is underway. The final results are expected by December 2025.

Conclusions: This systematic review and meta-analysis will provide a comprehensive comparison of antifibrotic and anti-inflammatory therapies in the treatment of chronic RA-ILD. The findings will help inform clinical decision-making, support evidence-based treatment selection, and identify gaps in current research. By addressing both efficacy and safety, this review aims to guide future studies and improve patient outcomes for this complex and debilitating condition.

Trial Registration: PROSPERO CRD42024583847; https://www.crd.york.ac.uk/PROSPERO/view/CRD42024583847

International Registered Report Identifier (IRRID): DERR1-10.2196/73219

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KEYWORDS

Rheumatoid arthritis; interstitial lung disease; anti-inflammatory; antifibrotic; autoimmune; pulmonary fibrosis

Introduction

Rheumatoid arthritis (RA) is a prevalent autoimmune inflammatory condition affecting approximately 0.5% to 1% of the population in the United States and Northern Europe [1]. Interstitial lung disease (ILD) is the most common respiratory manifestation of RA and can lead to significant morbidity and increased mortality in some patients with RA-associated ILD (RA-ILD). The prevalence of RA-ILD among individuals with RA ranges from 2% to 8% [2]. RA-ILD often follows a clinically unpredictable course, with recent studies reporting an increasing prevalence of RA-ILD ranging from 27% to 67%, a notable proportion of which includes asymptomatic patients [3].

RA-ILD is believed to result from persistent immune activation and inflammation, which leads to excessive fibroproliferation in the lung tissue of individuals with a genetic predisposition [4]. In some cases, the clinical symptoms of ILD may appear before the onset of articular symptoms in patients with RA. One study found that approximately 14% of patients with RA-ILD were diagnosed with ILD 1 to 5 years prior to being diagnosed with RA [5]. Several risk factors for the development of ILD in patients with RA have been identified, including older age, male sex, cigarette smoking, and the presence of positive anticyclic citrullinated peptide antibodies or immunoglobulin M rheumatoid factor [6-9].

RA-ILD can be classified into acute, subacute, and chronic forms based on the clinical presentation. In patients with acute RA-ILD, characterized by diffuse alveolar damage, high-dose corticosteroids are typically the first-line treatment. About half of patients with RA develop ILD either before or within 5 years of the RA diagnosis [10]. In contrast, the management of chronic RA-ILD focuses on controlling the underlying disease to prevent further progression of ILD. Disease-modifying antirheumatic drugs (DMARDs) have traditionally been used to manage RA-associated symptoms. For RA-ILD specifically, therapies such as corticosteroids, mycophenolate, azathioprine, rituximab, and TNF-α inhibitors are commonly used. Antifibrotic therapies, including pirfenidone and nintedanib, have been approved by the United States Food and Drug Administration for idiopathic pulmonary fibrosis and are now being explored for RA-ILD [11].

Several clinical trials have demonstrated the safety and efficacy of antifibrotic agents in the treatment of ILD [12-14]. However, a comprehensive review comparing the safety and efficacy of antifibrotic versus anti-inflammatory therapies in patients with chronic RA-ILD remains lacking. In this systematic review and meta-analysis, we aim to compare the safety and efficacy of these 2 therapeutic approaches in the management of chronic RA-ILD. By examining the comparative benefits and limitations of these treatment strategies, this study aims to provide valuable insights to guide clinical decision-making and improve the management of patients with chronic RA-ILD.

Methods

Ethical Considerations and Guidelines

As this study does not include the direct involvement of human participants, an institutional ethical review will not be warranted. However, to adhere to a strict methodology, the protocol of this systematic review was registered on PROSPERO (CRD42024583847) [15]. PROSPERO is an international database of prospectively registered systematic reviews, which provides a unique permanent registration number to the protocol that prevents duplication, thereby reducing reporting bias. We followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines in conducting and reporting this systematic review to ensure a comprehensive and transparent approach to the evaluation of the available evidence (Multimedia Appendix 1) [16].

Review Interest

The study will analyze the effectiveness of antifibrotic and anti-inflammatory therapies in improving or stabilizing lung function and clinical outcomes in adult patients with RA-ILD.

Inclusion and Exclusion Criteria

The inclusion criteria for this systematic review were developed using the PECOS (Population, Exposure, Comparator, Outcome, Study Design) framework to ensure that only studies directly relevant to the research question are included (Table 1) [17]. Eligible studies will include adult patients (aged ≥18 years) with a diagnosis of RA and confirmed ILD based on radiological or histopathological findings who have been treated with either antifibrotic or anti-inflammatory therapies. The primary outcomes assessed in this review will include the following pulmonary function parameters: forced vital capacity (FVC), forced expiratory volume in one second (FEV1), and diffusing capacity of the lungs for carbon monoxide (DLCO). Secondary outcomes may include radiological changes in high-resolution computed tomography (HRCT), clinical end points (eg, overall survival), and safety and tolerability of treatment. We will include randomized and nonrandomized clinical trials, case-control studies, and prospective or retrospective cohort studies. Only studies involving human patients and adult populations and published in English between January 1, 1991, and August 1, 2024, will be considered, regardless of geographic location. Exclusion criteria include studies involving nonhuman subjects, pediatric populations, or other ILD subtypes not specifically related to RA. Studies that do not evaluate antifibrotic or anti-inflammatory therapies or that fail to report quantitative data on lung function or clinical outcomes will be excluded. Additionally, case reports, abstract-only publications, review articles, editorials, short communications, and opinion pieces will be excluded. The decision to limit inclusion to

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English-language publications was made due to resource constraints and the lack of access to reliable translation services, which may impact the feasibility and consistency of non-English data extraction and interpretation. Furthermore, gray literature such as conference abstracts, dissertations, and preprints were not included in this review due to concerns about inconsistent reporting quality and the inability to assess methodological rigor or extract full datasets. In case of missing data, we will assess the potential impact through sensitivity analyses and report the extent of missing data in our results.

Table 1. PECOS (Population, Exposure, Comparator, Outcome, Study Design) criteria for the systematic review of rheumatoid arthritis-associated interstitial lung disease therapies.

PECOS criteria	Details
Population	Adult patients (aged ≥18 years) diagnosed with rheumatoid arthritis (RA) and confirmed interstitial lung disease (ILD) via radiological or histopathological findings.
Exposure	Antifibrotic therapy for the treatment of RA-associated ILD.
Comparator	Anti-inflammatory therapy for the treatment of RA-associated ILD.
Outcomes	Change in lung function parameters (eg, forced vital capacity, forced expiratory volume in 1 second, and diffusing capacity for carbon monoxide), and changes observed on high-resolution computed tomography.
Study design	Included: Studies that compare the efficacy of antifibrotic versus anti-inflammatory therapies, including randomized controlled trials, cohort studies, and observational studies.
	Excluded: Case studies, case reports, abstract-only studies, reviews, editorials, short communication, and opinion articles.

Informational Sources and Search Strategy

A comprehensive search strategy was developed by the study investigators, with guidance from a librarian, to identify relevant articles across multiple databases, including PubMed, Embase, and Cochrane Library. The search was designed to capture studies related to RA-ILD and treatment options involving antifibrotic or anti-inflammatory therapies. The search strategy was refined through preliminary searches in Embase, with additional terms introduced as new concepts were identified. Keywords included combinations of terms such as “rheumatoid arthritis,” “interstitial lung disease,” “antifibrotic therapy,” “anti-inflammatory therapy,” “pirfenidone,” “nintedanib,” “disease-modifying anti-rheumatic drugs (DMARDs),” and “high-resolution computed tomography (HRCT).” These terms were selected to ensure comprehensive coverage of studies addressing the relevant interventions and outcomes in RA-ILD. The search strategy in detail is highlighted in detail in Multimedia Appendix 2.

Screening

All articles will be imported into an intelligent systematic review tool, Rayyan (Rayyan Systems Inc), for screening. After deduplication, the records will be independently reviewed by 2 reviewers to evaluate eligibility based on predefined inclusion and exclusion criteria. Screening will be conducted systematically and sequentially, starting with titles, followed by abstracts, and then full-text assessments. Reasons for excluding studies will be documented at each step of the screening process to ensure transparency. The study selection process will be visually represented using a PRISMA flow diagram.

Data Extraction and Main Data Elements

Two reviewers will independently extract the relevant data elements from the eligible full texts of the articles and will record these variables in a standardized code book. A double extraction method will be used to ensure accuracy and completeness. After data extraction, disparities will be resolved by consensus and discussion with the third reviewer or a “tiebreaker.” Attempts to contact the corresponding authors of the included articles will be made if more information about the individual study data is needed. The following data elements will be extracted: study title, authors, year of publication, study design, quality score, total sample size, sex distribution (percentage of male to female patients), mean age and SD, duration of RA diagnosis (mean or median and SD), duration of ILD (mean or median and SD), geographic location (country and region if applicable), data on comorbidities (eg, cardiovascular disease, diabetes, and smoking history), baseline lung function parameters (eg, FVC, FEV1, and DLCO with units and baseline values), names of the antifibrotic drugs used (eg, nintedanib and pirfenidone), names of the anti-inflammatory drugs used (eg, methotrexate and TNF inhibitors), dosage regimen, treatment duration, adverse events related to therapies (eg, side effects of antifibrotic or anti-inflammatory treatments), qualitative changes in fibrosis patterns (eg, ground-glass opacities and honeycombing), effect sizes for outcomes (eg, mean differences, hazard ratios, and odds ratios), CIs and *P* values, clinical endpoints (overall survival and progression-free survival), and the type of anti-inflammatory treatment. To improve comparability across studies and reduce heterogeneity, anti-inflammatory therapies will be categorized into subgroups based on pharmacologic class, including systemic corticosteroids, conventional synthetic DMARDs (eg, methotrexate and azathioprine), and biologic DMARDs (eg, TNF inhibitors and rituximab). These subgroups will be analyzed separately where the data permit, in accordance with classifications used in prior RA-ILD studies.

The primary outcomes of this study will focus on pulmonary function parameters to evaluate the impact of interventions on lung function. These include FVC, FEV1, and DLCO. For each parameter, both absolute values and percentages of predicted normal will be assessed, alongside changes from baseline to follow-up.

The secondary outcomes will focus on radiological changes evaluated using qualitative changes in high-resolution computed

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tomography (HRCT) to assess fibrosis patterns, including ground-glass opacities and honeycombing, and to determine the progression, stabilization, or regression of fibrosis. Additionally, clinical end points such as overall survival, measured as the time from baseline to death from any cause, will be studied. Lastly, safety and tolerability will be assessed by monitoring adverse events related to the therapies used in the study. The key primary and secondary outcomes of the study are highlighted in Table 2. For outcomes such as disease progression, regression on HRCT, and exacerbations, we will use the definitions as provided by each individual study. No single standardized definition will be applied across studies, but variations in definitions will be documented and considered in the interpretation of the results. Where feasible, subgroup or sensitivity analyses will be conducted to account for heterogeneity in outcome definitions.

Table 2. Key primary and secondary outcomes of the study.

Outcome	Description
Primary outcomes	
Pulmonary function parameters	Forced vital capacity, forced expiratory volume in 1 second, and diffusing capacity for carbon monoxide
Secondary outcomes	
Radiological changes	Fibrosis regression, stabilization, or progression evaluated through high-resolution computed tomography scans
Clinical end points	Disease progression rates, frequency of exacerbations, overall survival, and quality of life measures
Safety and tolerability	Adverse events related to the therapies

Quality or Risk of Bias Assessment

Risk of bias for each included study will be independently assessed by 2 reviewers. For randomized controlled trials, we will use both the Cochrane Risk of Bias 2 (RoB 2) tool and the National Heart, Lung, and Blood Institute quality assessment tool [18,19]. Two independent reviewers will evaluate the full texts and score them separately. Inter-rater agreement will be measured using κ statistics. The National Heart, Lung, and Blood Institute tool consists of 14 checklist items that cover all key components of original research studies. Based on the tool's guidelines, the quality will be rated as poor (0-4 out of 14), fair (5-10 out of 14), or good (11-14 out of 14).

For nonrandomized studies, we will use the Risk Of Bias In Non-randomized Studies – of Interventions (ROBINS-I) tool, which assesses bias across domains such as confounding, selection of participants, classification of interventions, and measurement of outcomes [20]. Discrepancies in assessments will be resolved through discussion or consultation with a third reviewer. All risk of bias evaluations will inform the interpretation of the results and contribute to the GRADE (Grading of Recommendations Assessment, Development, and Evaluation) assessment of the overall quality of evidence.

Statistical Plan

The initial results of all the studies ultimately included in the analysis will be summarized in a concise table. The pooled effect estimates, along with their 95% CIs, will be calculated using Comprehensive Meta-Analysis software (version 3.0; Biostat). Given the expected heterogeneity across the included studies, a random-effects model will be used to compute the pooled estimates, as it provides a more robust approach by accounting for variability between studies.

To assess the overall quality and strength of the body of evidence for each key outcome, we will apply the GRADE approach. The quality of evidence will be rated as high, moderate, low, or very low based on factors such as study limitations, inconsistency, indirectness, imprecision, and publication bias. GRADE assessments will be performed independently by 2 reviewers, with discrepancies resolved through consensus or consultation with a third reviewer.

Furthermore, to evaluate heterogeneity, both the Cochran Q test and the I^2 statistic will be applied. These measures will help determine the extent of variability that is due to true differences across studies, rather than being attributable to random chance. The Cochran Q test will assess the overall heterogeneity, while the I^2 statistic will quantify the proportion of total variation across studies that is due to differences in study outcomes.

If a sufficient number of studies are available, subgroup analyses will be performed to examine the influence of moderator variables, such as sociodemographic factors, country, and types of interventions, on the outcomes. Additionally, sensitivity analyses will be conducted to determine if any individual studies have an outsized effect on the pooled estimates.

To assess publication bias, a funnel plot will be created, and an Egger linear regression test will be conducted. The significance level for all tests will be set at a 2-sided P value of <.05. In the meta-analysis, effect sizes will be presented using standardized mean differences for continuous outcomes and risk ratios for dichotomous outcomes. Standardized mean differences will allow for the comparison of effect sizes across studies with different measurement scales, while risk ratios will quantify the likelihood of an outcome occurring in the treatment group relative to the control group. Forest plots will be used to visually represent the effect estimates and their associated CIs, providing a clear depiction of the pooled results.

Results

The literature search and screening commenced in August 2024 and are projected to be completed by August 2025. We are currently in the data extraction phase of this systematic review and meta-analysis. A detailed overview of the project timeline and key milestones is shown in Table 3. No external funding

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was obtained for this project. The final results are anticipated to be submitted for publication by December 2025.

Table 3. Timeline for systematic review and meta-analysis tasks.

Tasks	Aug 2024	Sep 2024	Oct 2024	Nov 2024	Dec 2024	Jan 2025	Feb 2025	Mar 2025	Apr 2025	May 2025	Jun 2025	Jul 2025	Aug 2025
Initial design and searches	✓	✓											
Screening of duplicates and titles			✓	✓									
Screening of abstracts					✓	✓							
Screening of full-text articles							✓	✓					
Search references of included studies									✓				
Data extraction										✓	✓		
Synthesis and risk of bias assessment											✓	✓	
Analysis												✓	
Abstract and manuscript drafting													✓
Submission to conferences and peer-reviewed journals													✓

Discussion

Overview

RA-ILD represents a complex and challenging aspect of managing patients with RA. This systematic review and meta-analysis aims to comprehensively assess the efficacy of antifibrotic and anti-inflammatory therapies in patients with chronic RA-ILD, highlighting the comparative benefits and limitations of these therapeutic strategies. The prevalence of RA-ILD is significant, and its clinical presentation varies widely. Given the complexity and heterogeneity of RA-ILD, it is imperative to tailor treatment strategies based on the underlying pathophysiology and patient characteristics.

Diagnostic Imaging in RA-ILD

RA-ILD can be diagnosed based on histopathologic and imaging features. The most common subtype of RA-ILD is usual interstitial pneumonia (UIP), which is characterized by fibrosis and is associated with poor prognosis. There is growing evidence to support differentiating UIP from non-UIP patterns in patients with RA-ILD due to differences in clinical outcomes [21,22]. The prognosis of patients with RA-ILD with UIP patterns is poorer than that of patients with non-UIP patterns [23]. Patients with RA-ILD with UIP tend to be older individuals and seem to be less responsive to conventional treatment compared to patients without UIP [24,25]. HRCT serves as a reliable tool for accurate identification of the histopathologic UIP pattern, with a positive predictive value of 95% (19 out of 20 cases) [26]. The presence of definite HRCT UIP patterns characterized by basal and subpleural interstitial reticulations, fibrosis, traction bronchiectasis, and honeycombing exhibits a specificity of 96% (26 out of 27 cases) and a sensitivity of 45% (19 out of 42 cases) in relation to histopathologic UIP patterns [26]. Nonspecific interstitial pneumonia is also common in some patients with RA-ILD. Nonspecific interstitial pneumonia is characterized by parenchymal inflammation and has a better prognosis compared to UIP. Other less common RA-ILD subtypes include lymphocytic interstitial pneumonia, acute interstitial pneumonia, organizing pneumonia, desquamative interstitial pneumonia, and respiratory bronchiolitis ILD [27]. In most cases, radiographic imaging in the form of HRCT is sufficient to identify the underlying fibrosis pattern, and surgical biopsy is reserved only for patients in whom radiographic imaging is not diagnostic [28].

Strengths and Limitations

This systematic review has several strengths, including a comprehensive evaluation of the literature and rigorous methods to assess study quality and minimize biases. However, limitations exist. One major challenge is the heterogeneity among the studies, stemming from differences in methodologies, settings, interventions, diets, and outcome measures, which may impact the consistency of the findings. Reviewer bias is another concern, but we will address this by using standardized risk of bias tools for each study and conducting sensitivity analyses to assess the impact of low-quality studies on the overall results. To further ensure objectivity, we will seek input from subject matter experts and maintain transparency throughout the process. Furthermore, anti-inflammatory agents are often prescribed primarily for articular RA control rather than for the treatment of RA-ILD itself, whereas antifibrotic drugs are typically initiated specifically for ILD. This potential misclassification of therapeutic intent could confound comparative-effectiveness results.

Another limitation is the potential for missing relevant studies despite a broad search strategy developed with the help of a medical librarian. This risk could affect the completeness of the review. Additionally, publication bias may skew the results, as studies with positive outcomes are more likely to be published.

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To address this, we will assess publication bias through funnel plots and Egger regression tests, helping to ensure a balanced and accurate interpretation of the evidence.

Dissemination Plan

The findings from this systematic review will be disseminated through a peer-reviewed journal article and presentations at academic conferences.

Conclusions

This study will provide a comprehensive review comparing antifibrotic and anti-inflammatory therapies in the management of chronic RA-ILD. This study will include data on treatment efficacy, patient outcomes, radiologic progression, symptom burden, and quality of life for patients with RA-ILD following antifibrotic and anti-inflammatory therapies, thereby offering insights for the management of chronic RA-ILD.

Acknowledgments

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Data Availability

The data analyzed in the study will be available upon request from the corresponding author.

Authors' Contributions

Conceptualization: SS
Data curation: SS (lead), AJ (supporting), NJ (supporting)
Formal analysis: KB
Methodology: SS, KB
Project administration: SS
Software: KB
Supervision: KB
Validation: KB
Writing – original draft: SS (lead), AJ (supporting), NJ (supporting)
Writing – review & editing: KB

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) checklist.
[DOCX File , 19 KB - resprot_v14i1e73219_app1.docx]

Multimedia Appendix 2
Research query for database search.
[DOCX File , 138 KB - resprot_v14i1e73219_app2.docx]

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Abbreviations

DMARD: disease-modifying antirheumatic drug
DLCO: diffusing capacity of the lungs for carbon monoxide
FEV1: forced expiratory volume in 1 second
FVC: forced vital capacity
GRADE: Grading of Recommendations Assessment, Development, and Evaluation
HRCT: high-resolution computed tomography
ILD: interstitial lung disease
PECOS: Population, Exposure, Comparator, Outcome, Study Design
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Register of Systematic Reviews
RA: rheumatoid arthritis
RA-ILD: rheumatoid arthritis-associated interstitial lung disease
UIP: usual interstitial pneumonia

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Protocol

Defining and Measuring Engagement and Adherence in Digital Mental Health Interventions: Protocol for an Umbrella Review

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Abstract

Background: Digital mental health interventions (DMHIs) offer scalable solutions to address mental health needs, particularly among marginalized populations. However, engagement and adherence rates in DMHIs are often suboptimal, limiting their potential impact. Despite the growing body of literature on DMHI engagement, there is no consensus on how engagement and adherence are defined and measured across studies. Understanding these variations is crucial to improving DMHI design, evaluation, and outcomes.

Objective: Using the population, concept, context framework to frame the objectives, this umbrella review aims to synthesize existing systematic reviews, meta-analyses, and scoping reviews to identify how engagement and adherence are defined and measured in DMHIs. Additionally, this review seeks to explore factors that may influence DMHI engagement and adherence.

Methods: A systematic search of peer-reviewed literature will be conducted across major electronic databases following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Eligible studies will include systematic reviews, meta-analyses, and scoping reviews published in English in the past 10 years that examine engagement and/or adherence in DMHIs. Data will be extracted and synthesized to identify definitions, measurement methods, and influencing factors. Risk of bias will be assessed using the Joanna Briggs Institute (JBI) critical appraisal checklist for systematic reviews and research syntheses. Findings will be presented using a mixed methods convergent integrated approach, identifying and synthesizing themes across the included quantitative and qualitative study results.

Results: This study is expected to be conducted over a 6-month period. The search, conducted in early March 2025, initially identified 5087 papers. An additional 35 papers were found through manual handsearching of BMC Digital Health. These totals were recorded prior to the removal of duplicates. This umbrella review is expected to be conducted with screening, quality assessment, and data extraction streamlined through the Covidence platform. The screening and selection of studies will be performed in month 1, followed by data extraction and quality appraisal in months 2 and 3. Data synthesis and integration will take place in months 4 and 5, and writing conclusions and preparing the manuscript will occur in month 6. This review will provide a comprehensive summary of how engagement and adherence are operationalized across existing literature. It will highlight commonalities, inconsistencies, and gaps in definitions and measurement methods. Additionally, this review will outline the key factors that influence engagement and adherence, including individual, technological, and contextual elements.

Conclusions: This umbrella review will contribute to a more nuanced understanding of engagement and adherence in DMHIs, informing future intervention design and evaluation. The findings will support the development of standardized definitions and measurement frameworks, ultimately enhancing the effectiveness and inclusivity of DMHIs.

Trial Registration: PROSPERO CRD42025637603; https://www.crd.york.ac.uk/PROSPERO/view/CRD42025637603

International Registered Report Identifier (IRRID): PRR1-10.2196/73438

(JMIR Res Protoc 2025;14:e73438) doi:10.2196/73438

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KEYWORDS

engagement; adherence; user retention; digital mental health interventions; umbrella review; systematic review; mHealth; eHealth

Introduction

Digital mental health interventions (DMHIs) are technology-enabled tools that deliver psychological information, support, or therapy through platforms such as mobile apps, websites, and telehealth services. These interventions aim to promote mental well-being and help users manage mental health conditions [1,2]. By offering flexibility, cost-effectiveness, and accessibility, DMHIs provide important alternatives to traditional face-to-face services, particularly for individuals who encounter barriers to in-person care [3,4]. As the demand for scalable mental health solutions grows globally, DMHIs have become central to contemporary public health strategies. However, despite their promise, DMHIs frequently suffer from low engagement and poor adherence, which limit their long-term effectiveness and scalability [5,6]. Many users discontinue use prematurely or do not engage with the content in a sustained or meaningful way. A major barrier to resolving these challenges is the lack of agreement on how engagement and adherence are defined and measured in the literature.

Some studies focus on narrow behavioral metrics such as login frequency or total time spent [7], while others consider broader outcomes such as initial uptake, continued use, or program completion rates [6]. In some cases, superficial indicators such as app downloads are mistakenly equated with meaningful engagement, despite offering little insight into user experience or therapeutic benefit [8]. Recent studies have advocated for a more comprehensive understanding of engagement that includes cognitive (eg, attention, comprehension) and emotional (eg, motivation, satisfaction) dimensions alongside behavioral indicators. This broader perspective emphasizes the quality of user interaction with DMHIs, rather than solely the quantity [9-11].

Current definitions and measurement approaches remain highly inconsistent. This heterogeneity poses significant challenges to the comparability of findings, the development of standardized evaluation frameworks, and the creation of effective, evidence-based strategies for improving user engagement and retention. Addressing this issue is essential for advancing the design, implementation, and evaluation of DMHIs. Without conceptual and methodological clarity, it is difficult to determine which interventions are effective, under what conditions, and for whom.

This umbrella review aims to synthesize existing systematic reviews, meta-analyses, and scoping reviews to provide a comprehensive understanding of the definitions, measurement approaches, and factors that influence engagement and adherence in DMHIs. To frame the review's objectives, the population, concept, context framework recommended by Joanna Briggs Institute (JBI) is applied, as outlined in Table 1. This umbrella review aims to examine how engagement and adherence is defined and measured in systematic reviews, meta-analyses, and scoping reviews of DMHIs. This review also investigates whether there are other factors that influence DMHI engagement and adherence.

Table 1. Objectives of the umbrella review.

JBI[a] framework	Measurements
Population	All populations (no restrictions)
Concept	Definition and measurement of engagement and adherence
Context	Digital mental health interventions

[a]JBI: Joanna Briggs Institute.

Methods

Database Selection

No ethics approval will be required, as this review is based on already published and publicly available data. The databases utilized for this umbrella review include Web of Science, CINAHL via EBSCO, MEDLINE via Ovid, PsycINFO via Ovid, Cochrane via EBM Reviews, and ProQuest Complete. Full access to these databases is provided by the Ulster University library. An additional handsearching of the BMC Digital Health journal will also be conducted. These databases were selected for their comprehensive coverage of peer-reviewed literature in relevant subject matters of psychology, health care, and digital health interventions [12,13].

From the set of key publications identified by the authors, there was one paper [7] from BMC Digital Health. As this journal is relatively new and has not yet been indexed in major databases, there was a risk of missing additional relevant studies. After discussion with the review team and to ensure the comprehensiveness of the search, it was decided to include BMC Digital Health through handsearching, a method where journals are manually browsed to identify potentially relevant studies that may not be captured through database searches [14].

In addition to this, CINAHL and Cochrane did not yield the expected relevant studies from this set of key publications. Therefore, precision testing and unique hits testing were conducted on CINAHL to assess the database's contribution to the overall search strategy [15]. The results indicated that CINAHL contributed a small number of unique relevant records not identified in other databases, thereby justifying its inclusion for comprehensiveness. Cochrane, on the other hand, was retained due to its established role as a specialized database for high-quality systematic reviews and evidence syntheses, particularly within health and clinical research [16].

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Search Strategy

Database searches, with search strategies developed in assistance with the subject librarian, will include the following concepts: engagement, adherence, digital (web-based, smartphone, app, computer), mental health (well-being, emotional health, anxiety, stress), and interventions (promotion, prevention, treatment). The search will focus on identifying systematic reviews, meta-analyses, and scoping reviews that were peer-reviewed and published between 2015 and 2025 in English (Multimedia Appendix 1).

A combination of keyword searching and subject heading searching will be employed using the appropriate Boolean operators. Keyword searching identifies studies based on specific words appearing in titles, abstracts, or full texts, while subject heading searching uses controlled vocabulary to capture relevant studies, regardless of terminology variations. Combining both approaches enhances search sensitivity and specificity. Gray literature will be excluded, but supplementary searching using forward citation-chaining using the citation chaser tool will be utilized to ensure that the reviews included are up to date [17]. To ensure comprehensiveness and accuracy, searches will be rerun prior to the analysis stage.

Efforts were made to validate the search strategy. Following guidance from the Cochrane Handbook [18], the team tested whether the search strategy could retrieve key publications with which they were already familiar. To mitigate bias, preliminary citation chaining was also conducted to identify additional relevant studies that may not have been known in advance. Matters regarding databases are discussed above.

Eligibility Criteria

Search criteria already structure studies that are eligible for inclusion. Within the search results, the Population, Intervention, Comparator, Outcome, and Study Design framework is applied to guide the inclusion and exclusion of studies. This will be added on the Covidence platform for reference when examining eligibility. This is elaborated in Table 2. The included studies focus on DMHIs that define or measure engagement and/or adherence. Eligible study designs include systematic reviews, meta-analyses, and scoping reviews that examine engagement and adherence in DMHIs. Studies will be excluded if they evaluate digital interventions without a mental health outcome, focus on non-DMHIs, or discuss digital mental health without an intervention component. Additionally, reviews that do not sufficiently define or measure engagement and adherence as well as noneligible study designs such as integrative reviews, narrative reviews, primary studies, or research protocols will be excluded. No restrictions are applied to comparators or populations.

Table 2. Inclusion and exclusion criteria.

	Inclusion criteria	Exclusion criteria
Population	No restrictions applied	• No restrictions applied
Intervention	Digital mental health interventions	• Digital interventions without mental health outcomes • Mental health interventions delivered nondigitally • Digital mental health papers without interventions
Comparator	Not applicable	• Not applicable
Outcome	Definition or measurement of engagement; definition or measurement of adherence	• No sufficient details on definition or measurement of engagement or adherence
Study design	Systematic reviews, meta-analysis, and scoping reviews	• Any other type of review (including but not limited to integrative reviews, narrative reviews), independent studies, or research protocols

Screening and Selection

The primary reviewer and a subject librarian will comprehensively search the relevant databases. After removing duplicates, the references will be imported into the Covidence platform for screening. Two independent reviewers will assess the titles and abstracts against the eligibility criteria, resolving disagreements through discussion. If necessary, a third reviewer will be consulted to achieve consensus. Full-text articles of potentially eligible studies will then be extracted, where possible, and reviewed independently by 2 reviewers for relevance and eligibility, with disagreements addressed in consultation with the project team. The reasons for study exclusion at both the abstract and full-text stages will be documented. Each step of the process will be tracked and reported using a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart (Multimedia Appendix 2).

Data Extraction

Once the citations to be included in the umbrella review are identified, data extraction will be conducted using Covidence's Extraction 2 tool to ensure a structured and standardized approach. The following data will be extracted: references (authors, year of publication), study design (systematic review, meta-analysis, or scoping review), research aims, data synthesis approach, type and number of studies included, demographic information, description of DMHIs, outcome variables, and main findings. To assess the quality of their primary data, their overall critical appraisal scores and quality assessment indicators will also be extracted. This information will be organized into data extraction tables on review characteristics, included study

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characteristics, participant characteristics, and study results. Covidence will facilitate consistency across reviewers and minimize data entry errors. For missing or unreported data, if deemed necessary, the original authors of the study will be contacted. All findings will be reported following the PRISMA 2020 guidelines and its extension for umbrella reviews.

Quality Assessment

The methodological quality of the included systematic reviews, meta-analyses, and scoping reviews will be evaluated using the JBI critical appraisal checklist for systematic reviews and research syntheses. Utilizing the Covidence platform, 2 reviewers will independently assess the selected studies, resolving any disagreements through detailed discussions. If required, a third reviewer will be involved to reach a consensus.

Evaluating overlap is critical, as it can lead to the disproportionate weighting of certain primary studies within the analysis. Given that no widely accepted method currently exists for handling overlap in umbrella reviews [19], this study will consider the approach of similar reviews, the scope of the review question, and the breadth and complexity of the final set of the included studies when considering how best to manage overlap. A dedicated section in the discussion will address how duplication of primary studies was handled in the overall analysis.

Data Synthesis

Due to the presumed heterogeneity of the data, the data synthesis will follow a mixed methods convergent integrated approach. Quantitative data on engagement and adherence metrics (eg, usage frequency, completion rates, adherence duration) will be synthesized descriptively. Concurrently, qualitative data such as narrative definitions, thematic insights, and contextual factors influencing engagement and adherence will undergo thematic analysis to identify patterns and broader themes. Both data types will be synthesized and reported side by side, ensuring that the insights from each complement and enhance the understanding of how engagement and adherence are defined, measured, and influenced in DMHIs. Study conclusions will also draw on the study's implications for coproduction, patterns of engagement, and inclusivity in DMHIs.

Results

The search, conducted in early March 2025, initially identified 5087 papers. An additional 35 papers were found through manual handsearching of BMC Digital Health. These totals were recorded prior to the removal of duplicates. This umbrella review is expected to be conducted over a 6-month period, with screening, quality assessment, and data extraction streamlined through the Covidence platform. The screening and selection of studies will be performed in month 1, followed by data extraction and quality appraisal in months 2 and 3. Data synthesis and integration will take place in months 4 and 5, and writing conclusions and preparing the manuscript will occur in month 6. Regular weekly meetings among the whole review team will be conducted to monitor progress and ensure timely completion of each phase.

The results will be presented in terms of the definitions of "engagement" and "adherence" within the context of digital health, along with the qualitative and quantitative methods and tools used to measure these concepts in DMHIs. Additionally, the review will outline key factors that influence engagement and adherence, including individual elements such as age, gender, mental health status, and digital literacy; technological factors such as intervention design features, usability, and personalization; and contextual aspects such as social support, accessibility, and the broader health care environment. The exploration of these factors will provide a comprehensive understanding of the complex and dynamic nature of engagement and adherence in DMHIs.

Discussion

Principal Findings

Given the inconsistencies in how engagement and adherence are defined and measured in DMHIs, this umbrella review is crucial in providing clarity and enabling meaningful comparisons across studies. The definitions of these constructs are often heavily influenced by the parameters of individual studies, and it is anticipated that they may differ depending on whether they are applied at the intervention level or the treatment level. For instance, engagement might be measured by the number of sessions attended within a study protocol versus actual participation in the intervention program itself. Additionally, related constructs such as attrition, dropout, adoption, and retention are often used interchangeably or inconsistently, further complicating synthesis efforts.

This review also highlights the potential importance of distinguishing between the quantity and quality of engagement, recognizing that engagement is not merely a behavioral metric but also involves emotional and cognitive investment. These conceptual nuances have significant implications for the design and reporting of DMHI studies. By addressing the use of umbrella terms and the tendency of existing reviews to focus solely on individual-level data, this study aims to promote more precise terminology and improve the interpretability and utility of DMHI studies. This review will outline future research priorities and needs for effectively understanding engagement and retention, as these are fundamental to the successful design, monitoring, and evaluation of DMHIs.

Comparison With Prior Work

Although a select few reviews [5,7] have explored engagement and retention in digital interventions, many of these lack methodological rigor, often relying solely on narrative reviews, limited systematic searches, or qualitative studies. Additionally, much of the existing literature focuses on digital health applications more broadly, rather than digital mental health specifically, which presents unique challenges and nuances [5,7]. Several studies have emphasized the importance of further investigating engagement as a complex and multifaceted phenomenon within digital mental health contexts [12,13]. Given the rapid evolution of technology and the increasing integration of artificial intelligence in digital interventions, there is a pressing need for a timely and methodologically robust

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review to synthesize current evidence and guide future research and practice.

Limitations

Given the expected heterogeneity of findings, the authors anticipate challenges in consolidating the data not only due to variations in definitions and measurements but also because of the wide range of existing interventions and the diverse mental health concerns they address. This underscores the need for a robust and systematic approach to data extraction and categorization. Furthermore, considering the rapid pace at which research in this field evolves, it will be essential to strike a balance between comprehensive analysis and timeliness. We also acknowledge that due to our focus on peer-reviewed reviews with methodological rigor, some potentially relevant studies may have been excluded as a result of omitting gray literature.

Implications and Conclusion

This review's findings have important implications for both research and practice. For researchers, the synthesis will offer a foundational understanding of how engagement and adherence are conceptualized, informing future study designs and methodological approaches. For practitioners and app developers, this review will highlight key factors that promote sustained engagement, supporting the development of more user-centered interventions. These insights will ultimately aid in enhancing user retention, improving mental health outcomes, and contributing to the overall quality of DMHI research.

Dissemination Plan

To maximize this review's impact, the findings will be disseminated through publication in a peer-reviewed journal and presentation at high-level international conferences involving key stakeholders in digital health and mental health research. Any deviations from this protocol will be recorded and justified in the final version of the study.

Acknowledgments

We are grateful to Joan Atkinson, subject librarian for the Life and Health Sciences at Ulster University, for her assistance in drafting the search strategy.

Conflicts of Interest

This study is conducted as part of LKY's PhD thesis. LKY is under a PhD studentship financed by Ulster University's Vice-Chancellor Research Scholarship.

Multimedia Appendix 1
Search strategy.
[DOCX File , 20 KB - resprot_v14i1e73438_app1.docx]

Multimedia Appendix 2
PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) checklist.
[DOCX File , 33 KB - resprot_v14i1e73438_app2.docx]

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Abbreviations

DMHI: digital mental health intervention
JBI: Joanna Briggs Institute
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

Remote Digital Health Interventions to Support the Physical, Functional, or Psychological Rehabilitation of Adult Patients With Major Traumatic Injuries: Protocol for a Systematic Review of Randomized Controlled Trials

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Abstract

Background: The use of digital health (DH) interventions has increased over the past 2 decades, providing patients with alternative remote pathways for receiving health care services. Patients with major trauma frequently require long-term access to health care services to support their mental and physical health and their overall quality of life. DH interventions can help patients stay connected to rehabilitation services, thereby enhancing their health condition and helping them regain their independence, which will enable them to return to the workplace or regain a role in society. There is a need to explore existing evidence on the effectiveness of DH interventions for improving health-related outcomes in patients with major trauma.

Objective: This review aims to identify DH interventions that support the physical, functional, or psychological rehabilitation of patients who have experienced major physical trauma.

Methods: This review targets randomized controlled trials. Studies investigating DH interventions in adult patients with major traumatic physical injuries (end users of the interventions) are considered eligible for inclusion. Digital interventions that are delivered remotely and studies that report the impact of DH interventions on patients' health-related outcomes will be included. The search will be limited to publications since 2000 and peer-reviewed journals. No language restrictions will be applied, and articles not written in English will be translated. The search will be conducted in MEDLINE, Embase, AMED, CINAHL Plus, and PsycInfo. Grey literature and bibliographies of included studies and relevant reviews will also be searched for potentially relevant articles. A minimum of two reviewers will independently screen retrieved references. Data extraction will be conducted by 1 reviewer and independently checked by another reviewer. Quality assessment of the included studies will be conducted using the Cochrane Risk of Bias 2 tool. Any disagreements arising at any stage of the review will be resolved through discussion or by consulting a third reviewer, if required. A meta-analysis will be performed where possible, and a descriptive analysis of the included studies will be reported.

Results: As of January 2025, the systematic review is in the data extraction stage. Seven studies have been identified as eligible for inclusion. The findings are expected to be published in a peer-reviewed journal by December 2025.

Conclusions: The review findings will help identify existing evidence regarding DH interventions used to support the physical, functional, or psychological rehabilitation needs of patients with major trauma. This would help guide practitioners and policy

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makers to implement effective interventions to better support patient outcomes. The evidence synthesized from this review will also identify existing gaps and direct future research.

Trial Registration: PROSPERO CRD42023485748; https://www.crd.york.ac.uk/PROSPERO/view/CRD42023485748

International Registered Report Identifier (IRRID): DERR1-10.2196/67675

(JMIR Res Protoc 2025;14:e67675) doi:10.2196/67675

KEYWORDS

digital health; mHealth; mobile health app; telemedicine; rehabilitation; physical trauma; major trauma; major injury

Introduction

Background

The last 2 decades witnessed a significant development in information technology to the point that it has become widely available in almost all aspects of modern life [1]. This has been greatly influenced by the innovative development of devices, the widespread implementation of various performing networks (eg, Microsoft Teams), and more recently, the rising need for remote delivery associated with the COVID-19 pandemic [2,3]. This has strongly contributed to driving improvements in the use of technology in health care and introducing new concepts in health care delivery through the use of digital health (DH) [1,4,5].

DH plays a significant role in health care, and it can be seen in many medical specialties [6,7]. Several definitions exist for DH [5], often with different terms used interchangeably, including DH care [1,4], telehealth [1,5,8], telemedicine [6,8-10], or telecare [11]. However, DH is the umbrella term that encompasses all other terms [12-14].

DH tools can be delivered anywhere. They can be delivered in different health care settings, with both the health care professional (HCP) and patient present in these settings, or at the patient's own residence, where the patient can use a digital tool to track, document, and monitor their health and can have an opportunity to communicate with the HCP [6]. Thus, DH provides a wider scope of care and interventions that aim to reduce associated pressures on health care systems [8].

Traumatic injuries represent a significant cause of early death and morbidity, especially among the working population [15,16]. Globally, traumatic injuries are reported to cause around 5 to 6 million deaths each year [16,17], with around 40 million people left with permanent impairments and 100 million left with transient impairments [18-21], and there is a rising need for prolonged rehabilitation care to adjust to postinjury life. Rehabilitation is described as "a process of assessment, treatment, and management with ongoing evaluation by which the individual (and their family/carers) are supported to achieve their maximum potential for physical, cognitive, social, and psychological function, participation in society and quality of living" [22]. While there has been a recognition that more lives are being saved, rehabilitation following trauma is greatly behind, with global estimates of at least one in every 3 people needing rehabilitation services at some point throughout their injury [23]. Many people who have had major trauma are left with disability, medical dependency, family disruption, and ongoing psychosocial issues [16,24]. There is additionally a financial burden associated with supporting the rehabilitation needs of patients after major trauma [25,26].

A traumatic injury is defined as any injury that requires admission to a hospital at the time of injury [15]. According to the National Institute for Health and Care Excellence (NICE), a major trauma or injury is also defined as an injury or a combination of injuries that are life-threatening or life-changing and that could result in long-term disability [27,28]. This includes musculoskeletal injuries, traumatic brain injuries (TBIs), spinal cord injuries (SCIs), multiple fractures, and traumatic amputation [29].

Traumatic injuries have negative consequences, both physically and mentally [15]. SCIs, for example, hinder the patient's ability to access health care, affecting their mobility and transportation [30,31] and thus disrupting the patient's quality of life [32,33]. On the other hand, TBIs affect memory, executive functions, and cognitive skills associated with planning and decision making [34,35], leading to long-lasting activity-limiting impairment [36], disability [37,38], and changed health care needs [39]. These injuries are usually associated with psychological consequences that require equal attention [29].

Mild injuries are usually treated at home with minimal time spent in the hospital when needed [29]. However, major injuries usually require more intensive or specialized care to properly manage the patient's condition [29]. Following traumatic injuries, patients still need rehabilitation support to help them regain their optimum function and independence [15]. However, several challenges are encountered with providing continuous services in the health care setting, including a lack of available beds in rehabilitation facilities, a dwindling number of workers in these facilities, the location of rehabilitation facilities far from a person's home and from family members (eg, people living in rural areas), and the difficulty for people with different injuries to travel to rehabilitation facilities to receive rehabilitation support [40-43]. There is therefore a need to continue delivering services using alternative and remote pathways to keep patients connected to rehabilitation and health care services [41]. DH is a cost-effective solution that is increasingly being used to support people with different traumatic injuries [44-47].

Similar results were reported for services delivered face-to-face and those delivered in a virtual remote environment [48]. Over the past decade, the advancement and wide availability of information and communication technologies have been associated with an increase and expansion of the use of remote approaches to deliver medical and rehabilitation services [35,49,50]. Several DH interventions have been designed in the

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past decades to support people with different types of traumatic injuries.

Aims and Objectives

This review aims to (1) identify DH interventions that support the physical, functional, or psychological rehabilitation of adult patients who have experienced major high-impact physical traumatic injuries and (2) assess the impact of these interventions on health-related outcomes.

The review attempts to answer the following questions:

1. What types of DH interventions are being used?
2. Which health care conditions are currently supported by DH interventions?
3. What is the impact of DH interventions on patient health-related outcomes?

Methods

Criteria for Considering Studies for This Review

Types of Studies

For this systematic review, randomized controlled trials (RCTs) with associated patient-reported health-related outcome measures will be considered eligible for inclusion. Completed studies that are published in peer-reviewed journals will be included. Other study designs, such as case reports, case studies, qualitative studies, and reviews, will be excluded. All languages will be considered, and studies that are written in a language other than English, which are eligible for inclusion, will be translated using the Online Doc Translator website [51] to confirm their eligibility. Furthermore, corresponding authors will be contacted to confirm the accuracy of the data extracted from the translated studies that will be included in the review.

Participants

The review will target studies that are conducted with adult patients (aged 18 years or older) who report having experienced major physical high-impact trauma or injury, who have had a period of inpatient hospitalization due to their injury, and who have received remote rehabilitation support through a DH tool. This review will focus on high-impact injuries that are usually treated in major trauma units or services (eg, TBIs, SCIs, and road traffic accidents) [52-54]. Other types of traumas will not be included as they follow a different treatment pathway to high-impact injuries (eg, fractured neck of the femur linked to fragility or injuries that can be the result of low-velocity trauma, such as a fall from standing as opposed to a fall from a high-speed motor vehicle collision). The level of severity of the traumatic injury will depend on how it is described by the included studies, which may include the injury severity score or other measures [55].

Interventions

Studies involving DH interventions that are used to improve physical, functional, or psychological rehabilitation and are remotely delivered or utilized by patients will be considered for inclusion. Rehabilitation interventions include interventions involving treating, assessing, managing, or evaluating individuals for the purpose of improving their health-related outcomes [22]. DH interventions that are only delivered in the health care setting (eg, hospital or clinic) will not be included in this review. Additionally, DH interventions that are directed to HCPs, students, family members, parents, or carers, and blended interventions where the impact of the targeted DH intervention on patients cannot be identified or distinguished will be excluded. No restriction will be imposed on the type of control group to be included in this review.

Outcomes Measured

This review will only include studies that report patient health-related outcomes associated with the use of DH interventions. This will help in identifying the impact of DH interventions on these outcomes and therefore allow drawing conclusions on their potential usefulness in supporting the care of patients with major traumatic injuries. Based on the focus of this review, reported outcomes will primarily focus on physical patient outcomes (eg, improving activity, movement, or physical function) or psychological patient outcomes (eg, improving cognition, reducing depression, or improving mental function). Studies that only report outcomes that are not related to health (eg, intervention satisfaction or acceptability, or feasibility of delivering the intervention) will not be included. The review will also mention the tools used in measuring the reported outcomes, if any.

Search Methods for the Identification of Studies

Electronic Searches

A search will be conducted systematically by the main researcher using the following electronic databases: MEDLINE, Embase, AMED (via Ovid), CINAHL Plus, and PsycInfo (via Ebsco). Preliminary searches will be initially conducted using these databases to identify relevant keywords, and the final search strategy will then be developed in consultation with an information specialist with expertise in developing search strategies for systematic reviews in order to identify published relevant studies focusing on DH interventions, rehabilitation, and major trauma.

Table 1 provides the keywords that will be used to search the databases for eligible studies. The search will be limited to studies published since 2000, as this time period is associated with a wide range of technological innovations that allow patients and service users to gain easier access to the world of medicine [56-58]. An example of the full search strategy is provided in Multimedia Appendix 1.

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Table 1. Search keywords.

Keyword heading	Keywords[a]
Digital health	telemedicine or “e?health” or “electronic health” or “m?health” or “mobile health” or “e?medicine” or e?therapy or “health technolog?” or “information technolog*” or “communication technolog*” or “mobile technolog*” or tele?care or tele?communication or tele?monitoring or “remote monitor*” or “remote consult*” or telephone or phone or smart?phone or wearable or smart?watch or internet or web?based or e?mail or “electronic mail” or online or wireless or “mobile app*” or app* or “digital health” or “digital health?care” or tele?health or “remote health*” or internet?based or computer?based or e?learning or electronic?health or electronic?learning or video?gam* or gaming or “game-based” or gamification or “Virtual Reality” or “augmented reality” or “artificial intelligence” or “Internet of Things” or technology or virtual or teletherapy or “medical technology” or “mobile application” or teleconsultation or “virtual medicine” or “video consultation” or telepsychiatry or telepsychology or telerehabilitation or tele?therapy
Rehabilitation	Rehabilitation or “Exercise Therapy” or “exercise rehabilitation” or physiotherapy or “physical therapy” or “physical rehabilitation” or “cognitive rehabilitation” or “cognitive therapy” or “psychological rehabilitation” or “psychological therapy” or “mental rehabilitation” or “mental therapy” or “musculoskeletal rehabilitation” or “physical therapy modalities” or “occupational therapy” or “post?trauma rehabilitation” or “occupational rehabilitation” or “post?traumatic rehabilitation” or “rehabilitation exercise” or “vocational rehabilitation” or kinesiotherapy or “neurologic rehabilitation” or “neurological therapy” or “recreation therapy” or “recreation rehabilitation”
Trauma or injury	“traumatic injur*” or “musculoskeletal trauma*” or “complex fracture” or fracture* or “traumatic brain injur*” or “spinal cord injur*” or “traumatic amputation” or “major trauma” or “brain injur*” or “brain trauma*” or “musculoskeletal injury” or “posttraumatic stress disorder” or “PTSD” or “acquired brain injur*” or “physical injur*” or “physical trauma*” or injur* or trauma* or “multiple trauma” or “multiple injur*” or “soft tissue injur*” or “soft tissue trauma*” or “nervous system injur*” or “nervous system trauma*” or “athletic injur*” or “athletic trauma*”

[a]The keywords of different headings are combined using “AND.”

Searching Other Resources

Reference Search

The reference lists of all studies included for final analysis and of relevant reviews will be inspected to identify previously conducted studies that might be relevant to this review.

Author Contact

Authors will be contacted for any missing data. Studies will not be included if there is ambiguity and if the authors cannot be contacted for clarification.

Grey Literature Search

A grey literature search will be conducted using the same search strategy to identify additional studies that might be useful for this review. This will be conducted using the OpenGrey website [59].

Inclusion and Exclusion Criteria

The study inclusion criteria are as follows: (1) research that is focused on a DH intervention to support the physical, functional, or psychological rehabilitation of patients with major physical trauma; (2) primary end user of the DH intervention is an adult patient (aged 18 years or older); (3) DH intervention with potential for direct interaction with a HCP; (4) any form of digital-based intervention or treatment delivered by any digital means (eg, website or app) over any time frame; (5) intervention delivered remotely at the patient’s own residence (no need to be in an office, clinic, or health care setting); (6) research that reports patient health-related outcomes (any reported health care outcome); (7) RCT with a comparison or control group; and (8) original research (article or journal article).

Studies that do not meet one or more of the above criteria or that meet any of the following exclusion criteria will be excluded from the review: (1) DH intervention that is not focused on the physical, functional, or psychological rehabilitation of patients; (2) research that includes patients with minor or low-impact trauma or injury; (3) research focused on healthy people or public members; (4) DH intervention that is only delivered at a hospital or health care setting; (5) study where the researcher or HCP needs to perform home visits to deliver the intervention; (6) DH intervention end user is a patient carer or caregiver, family member, HCP, or student (eg, medical or nursing student); (7) research that includes caregivers or family members with reported outcomes that cannot be distinguished from patient-reported outcomes; (8) research with no reported outcomes or that only reports outcomes that are not related to health (eg, feasibility, acceptability, satisfaction, or economic evaluation); (9) research that includes mixed patient cohorts with several underlying conditions having no specific links to reported outcomes; (10) research where the underlying cause of injury is mixed (eg, traumatic and nontraumatic SCIs); (11) research that focuses on stroke or poststroke, burns, concussion, or stress after intensive care unit discharge; (12) research that focuses on psychological health rehabilitation that is not secondary to physical traumatic injury; (13) research that predicts the occurrence of an outcome or where the digital intervention is used as a screening tool; (14) digital intervention validation research; and (15) study design that is not considered an RCT (eg, quasiexperimental design, pretest/posttest cohort study, qualitative research, observational study, cross-sectional study, and review).

Data Collection and Analysis

Study Selection

Search results obtained from all databases will be exported into the reference manager EndNote 9.3.3 for reference management and removal of duplicates. A double review process by 2 reviewers will be independently carried out at all screening stages to check the eligibility of all retrieved records against the inclusion criteria. Screening will be conducted using

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Covidence software [60]. Any arising discrepancies will be resolved by discussion between the reviewers, and a third reviewer will be consulted, if necessary. Interrater agreement will be measured using the Cohen kappa coefficient.

The search results and final findings will be presented in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart, including summaries of the number of studies included or removed throughout the screening process, with reasons for exclusion provided for the full-text screening.

Data Extraction

A data extraction template using an Excel sheet (Microsoft Corp) will be designed to extract relevant data from each eligible study, where possible. Table 2 displays the data that will be extracted from the included studies.

Table 2. Data to be extracted from the included studies.

Data category	Details to be extracted
General characteristics	Study title, authors, publication year, study design, and country
Characteristics of included participants	Sample size of patient participants, demographics of recruited patient participants, type of traumatic injury under investigation, and people involved in delivering the digital health intervention (eg, health care professionals)
Characteristics of the digital health intervention	Type of digital health intervention, duration and mode of intervention delivery, control group, outcomes, outcome measures, and impact or effect

Data from each eligible study will be independently extracted by 1 reviewer and checked by a second reviewer to verify the accuracy and completeness of all data extracted. Disagreements will be resolved by discussion and consensus or by consulting a third reviewer, if necessary.

Assessment of Risk of Bias in the Included Studies

The need for quality assessment of the identified studies will be determined once data extraction begins. Two reviewers will independently assess the risk of bias in the included studies using the Risk of Bias 2 (RoB 2) tool [61,62]. This tool assesses the risk of bias in 5 domains in RCTs: randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome, and selection of the reported result. Any arising disagreement will be resolved by discussion or by consulting a third reviewer, if needed.

Strategy for Data Synthesis

The results of the search from all databases will be fully reported in the final document and presented in a PRISMA flowchart. A description of all included studies will be provided in tables to summarize extracted data. Study participant characteristics and intervention specifications will be presented, as reported in the original articles, to enable comparisons across studies. The quality ratings of the included studies will also be presented.

We will undertake a meta-analysis if the participants, interventions, comparisons, and outcomes are judged to be sufficiently similar to be combined in order to arrive at an answer that is clinically meaningful. Results will be pooled from the trials using fixed effects or random effects models, considering the issue of trial methodological and clinical heterogeneity, and will be reported diagrammatically using forest plots. Where the issue of trial methodological and clinical heterogeneity appears to exist, we will also consider strategies, including not pooling data and conducting subgroup analyses or sensitivity analyses. Where data cannot be pooled due to high heterogeneity, we will still provide descriptive analysis of trial results and report them in the text of the review.

Where meta-analyses are possible, for continuous outcomes, we will use the inverse variance method for fixed effects models and the DerSimonian and Laird variant of the inverse variance method for random effects models. For dichotomous outcomes, we will use the Mantel-Haenszel method for fixed effects models and the DerSimonian and Laird method for random effects models. A 0.5 zero-cell correction will be applied in the event of zero frequencies.

For studies with multiple treatment groups, we will aim to combine treatment groups to facilitate a single pairwise comparison following the methods recommended by Cochrane [63].

We will base our analyses on change scores where all necessary data, including baseline and follow-up scores and correlations, are provided; otherwise, we will use follow-up scores. Where not provided directly, we will calculate SDs from reported standard errors or CIs, or estimate from other statistics, such as IQR, or graphical representations. We will conduct sensitivity analyses to assess the influence of individual studies and represent the findings on influence plots. We will consider representing small-scale effects using funnel plots following the methods recommended by Cochrane [63] and subject to a minimum of 10 included studies.

We will use Stata statistical software (StataCorp) for all meta-analyses and use SPSS (IBM Corp).

Subgroup Analysis and Investigation of Heterogeneity

We have not planned for subgroup analysis and investigation of heterogeneity.

Ethical Considerations

No ethical approval is deemed necessary for this review, as the review will be conducted by searching available evidence that does not report any personal information about individual participants.

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Results

As of January 2025, the systematic review is in the data extraction stage. Seven studies have been identified as eligible for inclusion in this review, focusing on people with TBIs and SCIs, and describing the use of different DH remote interventions. Following the completion of data extraction and assessment of risk of bias, the findings are expected to be published in a peer-reviewed journal by December 2025. The review is registered on PROSPERO (registration number: CRD42023485748).

Discussion

Principal Findings

This review is designed to identify published RCTs that investigate the use of remotely delivered DH interventions and their impact on supporting the physical, functional, or psychological rehabilitation of adult patients with major physical high-impact traumatic injuries. Identifying this would add more information to current knowledge on the use of DH interventions in rehabilitation care and would establish the extent of the use of these interventions and their potential impact for improving patient outcomes.

Major traumatic injuries can drive problems with the patient's mobility and access to health care services, and depending on the type of injury, other associated symptoms may include changes in breathing, swallowing, drinking, and cognitive functioning, and may cause depression and anxiety [15]. Major trauma thus puts patients at risk for chronic health conditions that can become life-threatening if not adequately managed [64]. Major trauma is a common cause of death in adults younger than 40 years. Various traumatic injuries demand different rehabilitation support [15]. Therefore, it is important to address the rehabilitation care needs of individual patients. Patients discharged home following acute inpatient care for their major traumatic injuries are usually still in need of continuous long-term rehabilitation support. Effective DH interventions that will be identified in this review are expected to benefit these patients by supporting their needs and improving their health-related outcomes and overall independence.

Comparison With Prior Work

DH has undergone great development in terms of its application, growth, and reach. The number of DH interventions is increasing worldwide, as evidenced by the growing number of scientific publications, which has been greatly influenced by the COVID-19 pandemic [1]. There is additionally growing development of DH interventions for managing patients with traumatic injuries [65-68]. A wide range of DH tools have been described by previous studies in rehabilitation services, including the use of remote communication pathways such as emails, text messages, and video conferencing [69,70]. Positive outcomes were also reported by previous studies on the impact of telerehabilitation in improving patient outcomes [71,72]. Therefore, there are promising expectations for the use and impact of DH interventions in patients with major trauma.

Strengths and Limitations

This review has several strengths. To the best of the authors' knowledge, this is the first review to investigate the use of DH interventions in supporting people with major traumatic injuries. The findings of the review are expected to address, inform, and minimize gaps in DH rehabilitation specific to this patient population. The review will adhere to the PRISMA guidelines related to conducting systematic reviews [73] and will use a rigorous strategy, including searching related databases and checking the bibliography of the included studies and relevant reviews to identify additional relevant studies. Furthermore, no language restriction will be used in the search strategy to reduce the risk of missing studies that might be relevant to this review. Moreover, to reduce the risk of selection bias, the screening of retrieved studies and the quality assessment of included studies will be conducted by 2 reviewers, and data extraction will be checked by another reviewer, with disagreements resolved via discussion or by consulting a third reviewer, where appropriate.

The review has some limitations. The review will only focus on studies that include patients with major traumatic injuries; thus, studies with a mixed cohort of patients with various degrees of injury severity will be rejected. This may lead to missing the identification of useful interventions. However, if a distinction is made regarding the impact of the DH intervention on the various injury levels in the included cohort sample, the study will be included. Another limitation is that the review does not investigate a specific DH intervention or outcome measure. This approach might identify studies with a wide range of different DH interventions and outcomes, reducing the possibility of conducting a meta-analysis of the included studies. Upon completion of this review, further strengths and limitations might be identified and summarized.

Future Directions

DH interventions provide an avenue to support the rehabilitation needs of patients, especially using remote pathways, when challenges exist in providing face-to-face support. The findings of this review will help identify the interventions currently available to support patients with major traumatic injuries, the types of major injuries being targeted by DH interventions, the impacts these interventions have on patient health-related outcomes, and the prioritization of resources toward rehabilitation interventions that are most effective or have the largest evidence base. Additionally, by identifying existing evidence, this review could support drawing conclusions to inform policy makers and guide HCPs to implement effective interventions in practice to better support patient outcomes.

Dissemination Plan

The findings of this systematic review will be disseminated through various channels to share the results with the wider academic, professional, and research communities. The findings will be published in a peer-reviewed journal, and the work will be presented at relevant scientific conferences. Additionally, links to conference presentations or posters and published peer-reviewed work will be shared on professional social media platforms such as LinkedIn.

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Conclusions

The findings of this review will highlight the available evidence on DH interventions to support physical, functional, or psychological rehabilitation in patients with major trauma, and the associated impact on patient health-related outcomes. The review results will provide directions on the available interventions that could be implemented in practice. The findings will also help identify existing gaps that warrant further research and investigation.

Acknowledgments

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Data Availability

Data sharing is not applicable at this stage, as no data have been generated and presented in this protocol.

Authors' Contributions

HA, ES, EH, JS, and TH participated in conceptualization and designing of the protocol. HA-J drafted the manuscript. All authors reviewed and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy using the Ovid MEDLINE database.
[DOCX File , 21 KB - resprot_v14i1e67675_app1.docx]

Multimedia Appendix 2
PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist.
[DOCX File , 33 KB - resprot_v14i1e67675_app2.docx]

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Abbreviations

DH: digital health
HCP: health care professional
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT: randomized controlled trial
SCI: spinal cord injury
TBI: traumatic brain injury

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Protocol

Centenarian Mortality Rate During COVID-19: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Marked by high mortality rates on a global scale, with disease mortality being notably focused among older adults, the COVID-19 pandemic has become a significant health crisis. Despite the numerous publications on COVID-19 mortality among older adults, there is still a gap in knowledge when considering centenarians, as there is no systematic review and meta-analysis that summarizes COVID-19 mortality in centenarians globally.

Objective: This study aims to systematically review and synthesize global evidence on COVID-19 mortality rates among centenarians and the population of older adults worldwide, whether residing in long-term health facilities, hospitals, or their homes.

Methods: An automated search was conducted on the following databases: PubMed, Scopus, and Web of Science. Observational studies, both cohort and case-control, were selected. Quality assessment of the selected studies was based on the Joanna Briggs Institute critical appraisal tool for observational cohort and case-control studies. Three independent authors conducted the searches, and any possible disagreements were resolved by consensus. A meta-analysis of mortality proportions will be conducted to calculate the raw, logit, and arcsine proportions for all studies included in our meta-analyses. Heterogeneity between studies with a significance of P=.05 will be assessed by calculating the I^2 value using the DerSimonian and Laird method for random effects. Odds ratios and 95% CIs for dichotomous data and weighted mean risk differences and 95% CIs for continuous variables will be calculated. Further subgroup analyses will be attempted to explore heterogeneity among over 6.7 million older adults. Leave-one-out sensitivity tests will be conducted to assess the robustness of our results. The meta-analysis will be conducted using R software version 4.4.2 (R Foundation for Statistical Computing).

Results: A total of 4 studies were included in our systematic review and meta-analysis. Of the included studies, 3 are retrospective cohort studies and 1 is an observational, retrospective case-control study. As for study group size, 1 cohort study was conducted on a population of less than 1000 participants, 2 studies (1 cohort and 1 case-control) involved more than 10,000 participants, and 1 cohort study included more than 6 million participants.

Conclusions: This study has significant potential. Given the consensus that older adults, let alone centenarians, are the most vulnerable demographic to serious outcomes and deaths during pandemics. Addressing these gaps is crucial for the informed development of public policies, enabling countries to minimize the impacts on this population, particularly during health crises such as the COVID-19 pandemic.

Trial Registration: PROSPERO CRD42025645150; https://www.crd.york.ac.uk/PROSPERO/view/CRD42025645150

International Registered Report Identifier (IRRID): DERR1-10.2196/74068

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KEYWORDS

coronavirus; pandemic; mortality; COVID-19; older adults; centenarians; systematic review; meta-analysis

Introduction

Overview

Novel coronavirus cases were first detected in China in December 2019, with the virus spreading rapidly to other countries worldwide. This led the World Health Organization to declare a public health emergency of international concern on January 30, 2020, and to mark the outbreak as a pandemic on March 11, 2020 [1,2]. The aim of this study is to conduct a systematic review and meta-analysis of studies published between December 2019 and December 2024 on the rate of COVID-19 mortality in centenarians (ie, individuals aged 100 years and older) versus older adults aged 60-99 years (hereafter referred to simply as other older adults) [3]. Since the beginning of the pandemic, more than 777 million people have contracted the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) globally, and over 7.1 million people have lost their lives due to COVID-19 to date [4]. Mortality from COVID-19 increases with age, with children being the least susceptible to death [5,6]. Italy was the first European country to be affected by COVID-19 [7]. The biggest cluster of cases occurred in Lombardy, the most populous Italian region, and older adults were hit in the hardest way [8]. In this population, Marcon et al [8] questioned if the COVID-19 mortality in centenarians was lower than that in other older adults and whether sex differences exist in mortality among different age classes. Comparisons were made using total mortality (ie, not only confirmed COVID-19 cases) at the peak of infection (March 2020) against March's total mortality of previous years. They did not find reduced mortality in centenarians relative to other older adults but highlighted a difference between sexes across different age classes. While mortality in those aged 60-99 years was much higher in men than in women, the rate at which the risk increased by age was slower in men than in women, such that centenarian women had a higher mortality rate. They suggested that the proinflammatory status of older adults, referred to as inflammageing, could explain such age-related vulnerability. Despite the observations of multiple studies measuring the mortality rate in older adults, studies concerning mortality in centenarian patients with COVID-19 remain very scarce [9,10]. Addressing this gap is essential to reinforce our understanding of the unique challenges faced by centenarians and enable more effective health planning. This, in turn, facilitates the development of targeted treatment approaches with proper interventions tailored to the specific health needs of this demographic, particularly in situations of health crises like the COVID-19 pandemic [11-13]. In view of the foregoing, the aim of this study is to investigate the mortality rates in centenarians worldwide due to COVID-19.

Objective

The aim of this study is to conduct a systematic review and meta-analysis of studies published between December 2019 and December 2024 on the rate of COVID-19 mortality in centenarians versus other older adults.

Methods

Study Protocol and Meta-Analysis Strategy

The protocol for our systematic review and meta-analysis was conducted following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [14]. Our meta-analysis study will be conducted in compliance with the guidelines detailed in the Cochrane handbook for systematic reviews of interventions [15].

Eligibility Criteria

Inclusion Criteria

The PICOS (population, intervention, comparison, outcomes, and study) design for eligibility criteria [16] was adopted in this study (Figure 1). The population of interest will be individuals aged 100 years and older. The intervention will be testing positive for COVID-19. The comparison group will be individuals aged 60-99 years. The outcome of interest will be mortality rates in both populations from COVID-19. The studies included will comprise only peer-reviewed, longitudinal observational cohort and case-control studies published from December 2019 until December 2024 in English.

Figure 1. PICOS (population, intervention, comparison, outcomes, and study) design for eligibility criteria.

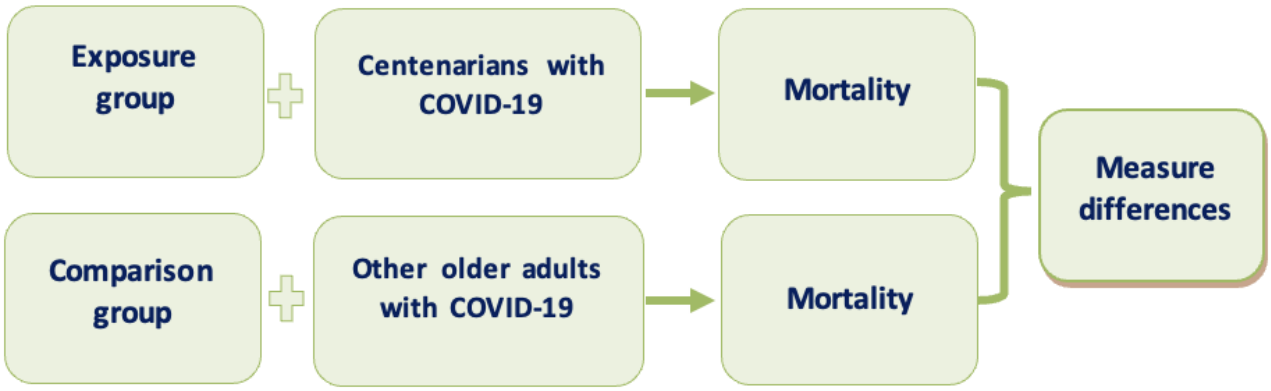

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Exclusion Criteria

The following studies will be excluded from the meta-analysis: (1) studies that do not include centenarians, (2) mortality studies during the COVID-19 pandemic that include deaths not due to COVID-19, (3) studies that do not include individuals younger than 100 years, (4) studies that do not present mortality rates as their effect measure, and (5) studies that do not fit or address our research question. Systematic reviews, scoping reviews, and book records will also be excluded, as well as research papers not available in English. The restriction regarding publication time (December 2019 to December 2024) is meant to reflect the temporality of the COVID-19 pandemic and at the same time widen our search window to include studies that were published after the pandemic was declared over in May 2023 [17].

Information Sources, Search Strategy, and Study Selection

The PubMed, Scopus, and Web of Science electronic search databases were consulted by 2 researchers on January 7, 2025, to search for studies published between December 2019 and December 2024 to identify any cohort and case-control studies that investigated the relationship between COVID-19 diagnosis and mortality in centenarians versus other older adults. The main keywords used were “centenarians” and “covid” in addition to their variations (Table 1). In the search strategy, keywords were systematically combined using the Boolean operators “AND” and “OR” to refine and expand the retrieval of relevant literature. The references of the studies included in the full-text evaluation phase were reviewed independently by the 2 researchers to identify potentially relevant studies that were not considered in earlier search phases. The studies were screened against the eligibility criteria in 2 phases: title and abstract screening followed by full-text screening. In cases of disagreement between the 2 reviewers at any stage, a consensus process was undertaken. If a resolution was not reached, a third reviewer was consulted for resolution. If data are missing or unclear, attempts will be made to contact the study authors for clarification. If contact cannot be established, the study will be excluded from our analysis, and this will be addressed in the discussion section. Science reviews, systematic reviews, and meta-analyses found in the automated search were excluded from our study.

The data to be extracted from the selected studies will include (1) author and year of publication, (2) name of the journal, (3) study design, (4) country of origin of the study, (5) study objective, (6) sample size, (7) period of data collection, (8) statistical test used, (9) age of participants, (10) sociodemographic details (ie, living alone or in a long-term health facility), (11) COVID-19 status (ie, positive or negative), and (12) measured outcome. A spreadsheet in Microsoft Excel will be used to record the necessary data for running the meta-analysis. Data will be presented in tables and charts, and their interpretation will be discussed.

Table 1. Search strategy.

Database	Query	Number of studies
PubMed	(“centenarians”[MeSH Terms] OR “centenarians”[All Fields] OR “centenarian”[All Fields]) AND (“sars cov 2”[MeSH Terms] OR “sars cov 2”[All Fields] OR “covid”[All Fields] OR “covid 19”[MeSH Terms] OR “covid 19”[All Fields])	34
Scopus	(TITLE-ABS-KEY (centenarian AND covid)) OR (TITLE-ABS-KEY (*supercentenarian* OR semi*supercentenarian) AND ORIG-LOAD-DATE AFT 20240314) AND (LIMIT-TO (DOCTYPE , “ar”) OR LIMIT-TO (DOCTYPE , “no”) OR LIMIT-TO (DOCTYPE , “cp”) OR LIMIT-TO (DOCTYPE , “sh”) OR LIMIT-TO (DOCTYPE , “le”) OR LIMIT-TO (DOCTYPE , “ed”))	29
Web of Science	(ALL=(centenarian)) AND ALL=(covid)	38

Risk of Bias and Study Quality Assessment

Funnel plots will be structured to visually assess publication bias in our meta-analysis [18]. They will be structured as scatter plots, with study effect sizes on the x-axis and a measure of study precision (standard error) on the y-axis. Because visual inspection can be subjective, statistical Egger regression tests will supplement visual assessment for more robust conclusions. In addition, trim-and-fill analysis [19] will be considered to assess publication bias and display the heterogeneity of the studies included in the systematic review. The Joanna Briggs Institute critical appraisal tool will be used to evaluate the quality of observational cohort and case-control studies [20]. The quality assessment for the selected literature will be evaluated independently by all authors (Multimedia Appendix 1).

Synthesis of Results

Our preliminary search in the 3 databases resulted in a total of 101 research papers. An additional paper was found in Google scholar, totaling 102 papers. A third researcher was consulted for help with screening the 102 articles, reviewing their respective abstracts and removing duplicates. This resulted in 54 articles remaining. The 54 articles were downloaded and fully reviewed to check their eligibility for our study. Data will be extracted from the chosen studies into tables and charts, and their interpretation will be discussed. Overall mortality proportions will be compared among studies to calculate pooled raw, logit, and arcsine proportions for all studies included in our meta-analysis. A random effects model for meta-analyses will be calculated using the DerSimonian and Laird method. This model acknowledges that studies included in the analysis may have different underlying effect sizes, rather than assuming a single true effect size across all studies, as in the fixed-effect model [21]. This means that, in addition to the within-study variability, there is also between-study heterogeneity that needs to be accounted for. The random effects model estimates both the within-study (I^2) and between-study (τ^2) variances. Heterogeneity will be evaluated with a significance

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level of P=.05. An assessment of heterogeneity with I^2 values will be presented. Heterogeneity of around 25% will be considered low, around 50% moderate, and around 75% high. The arcsine transformation of proportions will be primarily considered in our meta-analyses because it stabilizes the variance of proportion data, especially when proportions are close to 0 or 1 (ie, when studies report very low or very high proportions and variance instability is most pronounced) [22]. Arcsine transformation makes the data more suitable for standard meta-analytic analysis techniques that assume normality and homogeneity of variance. Weighted mean risk differences and 95% CIs will be calculated for continuous variables. Odds ratios and 95% CIs for each dichotomous data outcome will also be determined [23]. Individual study results will be visually summarized using forest plots to display both individual study estimates and the pooled estimate from the meta-analysis [15]. Meta-analyses will be conducted using R software version 4.2.2 (R Foundation for Statistical Computing).

Subgroup Analysis and Sensitivity Test

Further subgroup analyses will be conducted considering other factors such as country, age brackets, and long-term care facility versus community dwelling to explore the heterogeneity among the 6.7 million older adults included in our study [24]. This is to help explain whether there is a variation in effect sizes across studies. Leave-one-out sensitivity tests will illustrate how far the calculated pooled effect estimate shifts when each study is excluded one at a time and recalculating the pooled effect size [25]. This will help identify whether any single study disproportionately influences our overall findings and ensure that our conclusions are not unduly influenced by any single study, thereby enhancing the credibility of our synthesized evidence.

Ethical Considerations

Ethical approval is not required for this protocol as it is a systematic review that includes secondary data from published studies. In this study, participants are not actively recruited, and data are not collected directly from them. The findings of the systematic review and meta-analysis will be disseminated through peer-reviewed publications.

Results

Included Studies

A total of 19 qualitative and 4 quantitative studies were found relevant and were considered in our systematic review and meta-analysis (Figure 2). The qualitative studies were particularly valuable in guiding the methodology of our meta-analysis, informing our interpretation of the results, and shaping our conclusions. Additionally, they played a crucial role in constructing the literature review and establishing the background for our hypothesis by highlighting existing gaps in the literature. Of the 4 included quantitative studies, 3 are retrospective cohort studies and 1 is an observational, retrospective, case-control study. As for study group size, 1 cohort study was conducted on a population of less than 1000 participants [26], 2 studies (1 cohort [27] and 1 case-control [28]) involved more than 10,000 participants, and 1 cohort study included more than 6 million participants [29].

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Figure 2. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart.

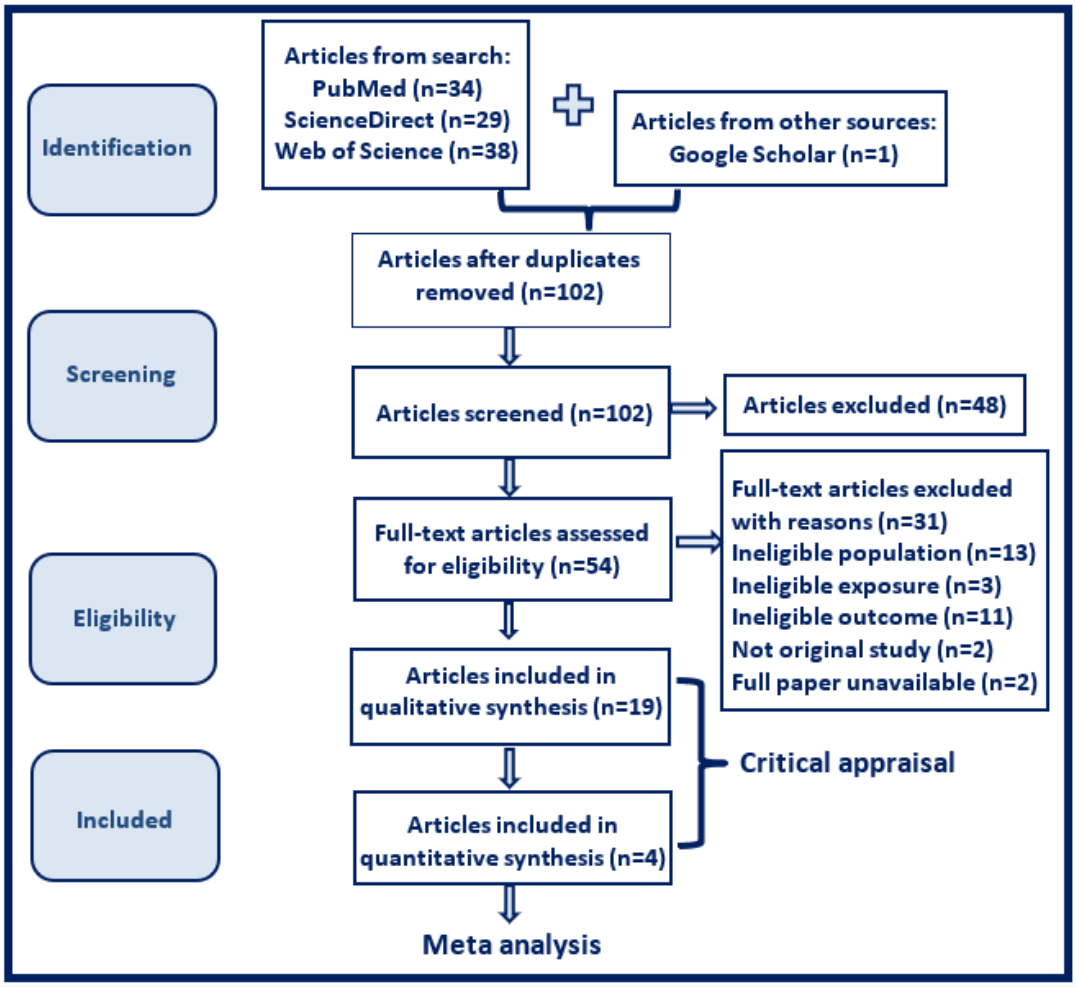

Synthesis of Results

Our hypothesis being that overall centenarian mortality during COVID-19 is insignificant, we anticipate our synthesis of results from the meta-analysis pooled odds ratio and risk difference will reveal and support our hypothesis. We will also synthesize further evidence by running several subgroup analyses considering other variables in an attempt to reveal whether any differences in our outcome exist. For example, differences in outcome might be due to geographic location, age group, or type of residence.

Discussion

Interpretation

While extensive literature examines COVID-19 mortality in older adults [30,31], no systematic review has comprehensively synthesized global evidence specific to centenarians, a population with distinct biological resilience and vulnerability profiles. This study bridges this critical gap through a meta-analysis of mortality rates in SARS-CoV-2–positive centenarians and other older adults (≥60 years) across different care settings (long-term care facilities, hospitals, and home-based care). Using multiple estimators (raw-, logit-, and arcsine-transformed proportions; risk differences; and odds ratios) to quantify differential outcomes, our findings will help inform public health policies for older populations, integrate risk-stratified treatment protocols during future pandemics, and disseminate gerontological frameworks for protecting centenarian cohorts.

Strengths Compared With Prior Work

Our study is different from the meta-analysis studies published regarding mortality in centenarians and other older adults. For example, a study highlighted that older individuals with dementia diagnosed with COVID-19 face a higher risk of mortality compared to those without dementia [32]. Another study found that, overall, frailty among older adults was linked to higher rates of COVID-19–related mortality compared with less frail counterparts [33]. A third study concluded that comorbidities contribute to increased COVID-19 mortality among older adults; however, this study relied on a single database [34]. Unlike the previous studies, our study looks at centenarian patients diagnosed with COVID-19 during the period from December 2019 to December 2024 and investigates their rate of mortality due to COVID-19 illness and not due to other or combined variables.

Limitations, Implications for Practice, and Future Research

A key limitation was our narrow focus on mortality rates, omitting assessment of contributing factors—such as

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comorbidities, care settings, socioeconomic status, or health care access—which were rarely reported in the predominantly retrospective studies. Scant centenarian-specific data on these variables further precluded meaningful subgroup analyses. Future studies should adopt prospective designs with standardized risk factor assessments to identify predictors and predisposing factors of severe COVID-19.

Future studies should prioritize larger, more representative samples for this growing demographic to ensure adequate statistical power for complex analyses, including multivariable regression modeling of independent risk factors, confounder-adjusted effect estimation, and clinically meaningful subgroup stratification.

Future research should prioritize multicenter and international collaborations to assemble larger, more diverse cohorts of centenarians. This approach will enable pooled databases with enhanced statistical power, geographically representative sampling, and robust assessment of context-specific risk factors.

To address data sparsity and retrospective biases, we recommend prospective longitudinal cohorts capturing real-time clinical and social variables and stratified data collection disaggregating centenarians by age strata (eg, 100-105 years, 106-109 years, ≥110 years) and gender-specific responses for discovering mechanisms of resilience observed in some centenarians. International consortia (eg, Istituto di Ricovero e Cura a Carattere Scientifico-Istituto Nazionale di Ricovero e Cura per Anziani [IRCCS INRCA]) could operationalize this while ensuring standardization of data collection, definitions for symptoms, comorbidities, treatments, and outcomes, which maintain adequate power for minimizing risk of bias, data collection inconsistency, and imprecision.

Conclusion

Considering centenarians, there is a notable absence of systematic reviews or meta-analysis studies consolidating knowledge about individuals in this demographic who succumbed to SARS-CoV-2 infection, even when considering available global data. Given the consensus that the centenarian population is a continuously growing demographic and is the most vulnerable to serious outcomes and consequences during pandemics, addressing this research gap is crucial for the informed development of public policies enabling countries to minimize the impacts on this population, particularly during health crises such as the COVID-19 pandemic. Filling this gap will contribute valuable insights to the field of gerontology and public health.

This meta-analysis provides the first comprehensive synthesis of COVID-19 mortality in centenarians, demonstrating that while rates are elevated, the difference from other older adults is modest and often not statistically significant. These findings challenge assumptions of inevitable poor outcomes in the oldest population and support the development of nuanced, evidence-based care frameworks for such populations.

Acknowledgments

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Data Availability

Data sharing is not available for this study yet as no data sets or analyses were generated at the time of submitting this protocol.

Authors' Contributions

Conceptualization: SI, WAEK-M, OMA, SC
Data curation: SI, WAEK-M, OMA
Formal analysis: SI, SC
Data investigation: SI, WAEK-M, OMA
Methodology: SI, WAEK-M, OMA, SC
Supervision: WAEK-M, SC
Writing – original draft: SI.
Writing – review & editing: SI, WAEK-M, OMA, SC

Conflicts of Interest

None declared.

Multimedia Appendix 1
COVID-19 protocol supplementary file.
[DOCX File , 47 KB - resprot_v14i1e74068_app1.docx]

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Abbreviations

PICOS: population, intervention, comparison, outcomes, and study
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SARS-CoV-2: severe acute respiratory syndrome coronavirus-2

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Protocol

Single-Stage Versus 2-Stage Facial Reanimation With a Free Functional Muscle Flap: Protocol for a Systematic Review

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Abstract

Background: Facial paralysis is a condition that has several etiologies and is associated with significant physical and psychosocial complications. Classically, 2-stage facial reanimation was used to treat patients with unilateral facial paralysis; however, single-stage facial reanimation has seen an increase in use. Studies comparing both techniques are limited, and to the best of our knowledge, no systematic reviews have compared these techniques.

Objective: We aim to perform a systematic review that explores how the outcomes of single-stage facial reanimation with a free functional muscle flap compare against those of 2-stage facial reanimation.

Methods: This systematic review protocol has been written according to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) and NICE (National Institute for Health and Care Excellence) guidelines. The search strategy will involve 3 stages: electronic databases (MEDLINE, Embase, and Web of Science Core Collection), trial registers (ClinicalTrials.gov), and snowballing. Studies published from 1995 to 2025 will be screened using inclusion and exclusion criteria. Data will be extracted into a standardized spreadsheet, and the risk of bias and quality of evidence will be assessed. Two reviewers will screen, extract, and assess the included studies. Discrepancies will be discussed and rectified with a third reviewer, if needed. A narrative synthesis of the findings will be performed and presented with descriptive and statistical analyses, where possible, using GraphPad Prism (GraphPad Software).

Results: The review formally began in February 2025 and will be performed and reported according to this protocol and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A PRISMA flow diagram and checklist have been used to summarize the current search and study selection. A narrative synthesis and tables will be used to summarize the results of the included studies. Where possible, statistical analyses will be presented using graphs and figures. The final systematic review is expected to be published in December 2025.

Conclusions: This systematic review will aim to summarize the outcomes of the single-stage and 2-stage facial reanimation techniques and explore the differences between these surgical techniques, if any. The results will provide updated information for patients and clinicians. Moreover, the review may help identify potential areas for further research and policy development.

Trial Registration: PROSPERO CRD42024556255; https://www.crd.york.ac.uk/PROSPERO/view/CRD42024556255

International Registered Report Identifier (IRRID): PRR1-10.2196/64009

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KEYWORDS

facial palsy; facial reanimation; plastic surgery; single-stage technique; 2-stage technique

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Introduction

The loss of function associated with facial muscle movement is termed facial paralysis or facial nerve palsy. Facial nerve damage arising from various etiologies can cause facial paralysis. The most common cause of facial paralysis is Bell's palsy, an acute idiopathic unilateral lower motor facial nerve lesion [1]. Other common causes of facial paralysis are cerebrovascular events, facial trauma, viral infections (notably herpes zoster), bacterial infections, neoplasms, and congenital causes, including birth trauma and syndromic conditions such as Moebius syndrome. Bilateral facial paralysis is rare, often caused by systemic manifestations of a disease, and it occurs in up to 2% of all cases [2]. Facial paralysis is associated with a poor quality of life, likely because of physical and psychosocial sequelae. Altered facial appearance, difficulty with swallowing and speech, and ophthalmic complications may occur [3-6]. Patients with facial paralysis may experience altered self-perception, social anxiety, and depression [7]. The etiology and onset of facial paralysis determine the treatment. In acute-onset Bell's palsy, the urgent administration of high-dose corticosteroids is indicated [8]. Other medical adjuncts for acute facial palsy include antivirals, such as acyclovir, especially if the facial palsy is associated with herpes zoster infection (Ramsay Hunt syndrome). Surgical intervention is indicated if medical therapy is unsuccessful or facial paralysis has been present for many months [9]. Within a year of onset, nerve reconstruction to stimulate native muscles may be effective for patients. In facial palsy lasting over a year, there is irreversible fibrosis of the neuromuscular junction, and therefore, nerve reconstructive surgery is unlikely to lead to improved facial nerve function [10].

Facial reanimation surgery using free functional muscle flaps, such as the gracilis muscle flap, provides smile potential in facial paralysis. These free muscle flaps have been reported to provide effective long-term outcomes even in long-standing facial paralysis [11-13]. Since its conception in the 1970s, 2-stage facial reanimation using free muscle flaps has been widely accepted in the surgical management of long-standing unilateral facial palsy [14,15]. The first stage of this approach involves establishing a cross-facial nerve graft (CFNG) by connecting the sural nerve to the proximal facial nerve on the unaffected (contralateral) side. The second stage involves a separate operation for free muscle transfer and coaptation to the CFNG [16]. This is the single innervation technique. In the dual innervation technique, a CFNG and nerve to the masseter are used to restore facial muscle function. The immediate drawbacks of 2-stage facial reanimation are the need for 2 separate operations and the risk of complications secondary to nerve grafting, such as paraesthesia.

Single-stage facial reanimation was developed in 1998, with researchers reporting faster reinnervation times and impressive cosmetic outcomes [17,18]. In single-stage facial reanimation, the nerve of the free muscle flap may be connected to the contralateral facial nerve using a CFNG, connected to the ipsilateral nerve to the masseter (a branch of the trigeminal facial nerve), or connected to both (dual innervation) within a single operation. This avoids multiple operations, and if a CFNG is not used, this approach avoids nerve grafting. Recent studies have shown the key benefits of single-stage facial reanimation, namely stronger smile excursion and faster muscle neurotization and recovery [18-20]. Textbox 1 summarizes the benefits and risks of the single-stage and 2-stage facial reanimation techniques according to the current literature.

Textbox 1. Benefits and risks of single-stage and 2-stage facial reanimation using a free functional muscle flap.

Single-stage facial reanimation

Benefits

- Single recovery
- Lower anesthetic risk

Risks

- Increased complexity
- Further operations may still be needed

Two-stage facial reanimation

Benefits

- More planned approach
- More predictable outcome

Risks

- Increased surgical or anesthetic time
- Increased recovery time

There are limited randomized controlled trials and systematic reviews reporting on facial reanimation surgery [21-35]. Most studies discuss the optimal types of free muscle flaps, nerve reconstructive techniques, or patient-reported outcome measures (PROMs). There is a paucity in the literature of comparisons between the single-stage and 2-stage reanimation techniques,

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with only 1 systematic review published a few years ago [30]. Understanding the broad outcomes and patient experiences of these surgical techniques is important to provide patients with up-to-date and accurate information when consenting to facial reanimation. Moreover, it is vital for clinicians to better understand the indications, effectiveness, and complications of the single-stage and 2-stage facial reanimation techniques. Consequently, this proposed systematic review aims to explore how the outcomes of single-stage facial reanimation compare against those of 2-stage facial reanimation. Ideally, the results of this review will further inform clinical practice and provide collated evidence for future research and guidelines.

Methods

Protocol Registration

This systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO), a database produced by the Centre of Reviews and Dissemination and funded by the National Institute for Health Research (NIHR). The registration information is as follows: PROSPERO 2024 CRD42024556255 [36]. This review protocol has been reported with guidance from the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) and NICE (National Institute for Health and Care Excellence) checklists [37,38]. The systematic review, once completed, will be reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [39].

Study Question

This study will explore how the outcomes of single-stage facial reanimation with a free functional muscle flap compare against those of 2-stage facial reanimation. This will be in the context of patients with unilateral facial palsy undergoing surgical facial reanimation to correct their condition.

Search Strategy

A qualified librarian (JG) has devised the search strategy with support from the lead author (OA) as a subject specialist. The question has been broken into concepts using PICO (population, intervention, comparison, and outcomes) (Table 1) and not according to outcome because this review strategy has been suggested to introduce additional biases, such as outcome reporting bias [40]. The strategy has been peer reviewed by librarian colleagues at a tertiary National Health Service hospital trust and approved by the lead author before being adapted individually to each database and trial registry.

Table 1. PICO (population, intervention, comparison, and outcomes) framework.

Characteristic	Information
Patient	• Patients who underwent facial reanimation surgery for unilateral facial palsy
Intervention	• Single-stage facial reanimation using a free functional muscle flap
Comparison	• Two-stage facial reanimation using a free functional muscle flap
Main outcome	• Clinician-reported outcomes of facial symmetry
Additional outcomes	• Patient-reported outcome measures • Adverse outcomes

The main outcomes include clinician-reported outcomes of facial symmetry, such as smile excursion, recovery time for facial movements, and nerve regeneration rate. The first additional outcome subcategory includes PROMs such as the FACE-Q instrument [41,42]. The second additional outcome subcategory includes adverse outcomes such as operative complications.

The search will be carried out in 3 stages. The first stage will investigate published studies in the listed electronic bibliography databases. MEDLINE, Embase, and Web of Science Core Collection will be searched because of their medical and surgical content. The second stage will investigate trial registers, such as ClinicalTrials.gov (via Cochrane Library), to identify ongoing or recently completed trials to screen for eligible studies with published data that may be included. The third and final stage will involve searching the reference lists of eligible primary studies (“backward snowballing”) as well as studies that have cited these primary studies (“forward snowballing”) [43]. Example search strategies for the first search stage (MEDLINE via Ovid) and the second search stage (ClinicalTrials.gov via Cochrane Library) are displayed in Multimedia Appendices 1 and 2, respectively.

Only human studies written in the English language and published between 1995 and 2025 will be included. The search will not be limited by country of origin; however, studies published in languages other than English will be excluded. Studies including animals will also be excluded. Unpublished studies, dissertations, conference proceedings, and grey literature identified during the search will be excluded.

The search strategy will be rerun before the final analysis to identify further eligible studies so that the most contemporary literature will be presented in the review. We will aim to include the full search strategies for all databases in the published systematic review.

Study Selection and Data Extraction

Study screening and selection will be performed according to the PICO framework and exclusion criteria. The exclusion criteria for this review will be studies involving patients with facial palsy due to trauma alone and patients with bilateral facial

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palsy. Traumatic facial palsy often differs in outcomes because of associated injuries to the head, neck, and other regions of the body [44]. Moreover, additional management options for facial nerve palsy, such as facial nerve decompression, may affect the use of free functional muscle flaps [45]. Bilateral facial palsy was excluded mainly due to the surgical approach. Often, there are preferred muscle flaps or nerves used in bilateral facial palsy, which may affect patient recovery and outcomes compared with unilateral palsy [10,46-49].

Studies that include single-stage or 2-stage facial reanimation or compare both will be included. Textbox 2 displays the types of studies that will be included and excluded in the review. Quasirandomized trials are trials that have the same approach as randomized controlled trials but use a method of allocation that is not truly random [50].

Textbox 2. Types of studies included and excluded.

Types of studies included

- Randomized controlled trials or quasirandomized trials
- Cohort studies
- Case series (with at least 10 patients included)
- Mixed methods studies (quantitative and qualitative methods used)

Types of studies excluded

- Reviews (literature or systematic review, with or without meta-analysis)
- Case-control studies
- Case reports and case series (with less than 10 patients included)
- Qualitative-only studies

Rayyan software will be used to screen and select eligible studies [51]. Initially, 1 reviewer (OA) will screen the titles and abstracts of all studies identified by the search strategy against the eligibility criteria. The full text of studies that pass the initial stage of screening will be retrieved and independently screened once more by the same reviewer. Afterwards, a second reviewer (MK) will independently examine the screening process. Disagreements will be settled by discussion between the 2 reviewers; however, if deemed necessary, a third reviewer (FA) will be involved.

Data will be extracted from the included studies using the Systematic Review Repository Plus software and stored in a secure, standardized database [52]. Textbox 3 displays which data will be extracted in the review.

One reviewer will independently extract data (OA), and a second reviewer will evaluate the extracted data (MK). Disagreements will be settled by discussion between the 2 reviewers; however, if deemed necessary, a third reviewer (FA) will be involved. Missing data from the included studies will be requested from the authors via email. Missing data will be extracted and analyzed using the same methodology as that used for the previously gathered datasets.

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Textbox 3. Data extraction strategy.

Study setting

- Full citation
- Year
- Country
- Study design
- Methodology
- Study duration
- Length of follow-up

Patient demographics

- Number of patients
- Age
- Sex
- Etiology of facial palsy
- Baseline clinical status including severity
- Side of facial palsy

Intervention details

- Surgical intervention or technique
- Operating time
- Details of the free flap
- Donor site morbidity
- Innervation details
- Recovery time

Comparator details

- Presence of a comparator group
- Surgical intervention or technique
- Operating time
- Details of the free flap
- Donor site morbidity
- Innervation details
- Recovery time

Outcome measures

- Clinician-reported outcomes of facial symmetry
- Patient-reported outcome measures
- Adverse outcomes

Risk of Bias and Quality of Evidence

The risk of bias of the included studies will be assessed with consideration of the criteria recommended by the International Cochrane Collaboration [53]. This includes randomization sequence generation (only valid for true and quasirandomized controlled trials), treatment allocation concealment, blinding, completeness of outcome data, selective outcome reporting, and other sources of bias. The ROBINS-I (Risk of Bias in Nonrandomized Studies-of Interventions) tool will be used to assess the risk of bias in nonrandomized studies included in this review, such as quasirandomized trials and cohort studies [54]. The RoB 2 (revised risk of bias tool for randomized trials) tool will be used to assess the risk of bias in randomized controlled trials [55]. The included studies will also be assessed for quality of evidence using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) framework [56,57].

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Each study will be graded from very low to high (GRADE certainty ratings) on each of the GRADE domains, and the study's overall quality will be based on the lowest scoring domain. Two reviewers (OA and JG) will independently assess the risk of bias and quality of evidence of the included studies. Disagreements will be settled by discussion between the 2 reviewers; however, if deemed necessary, a third reviewer (MK or FA) will be involved. Tables will be used to display the risk of bias and quality of evidence of the included studies.

Data Synthesis

A narrative synthesis of the findings from the included studies will be carried out using descriptive analysis. Our data synthesis will describe the data extracted, including patient demographics, intervention and comparator details, and outcomes. Where possible, statistical analysis will be employed to explore differences in preoperative and postoperative outcomes (clinician-reported outcomes, PROMs, and adverse outcomes) between single-stage and 2-stage facial reanimations in individual studies. The risk of bias and quality of evidence of the included studies will also be discussed in the context of the research question and the wider literature of facial reanimation. Discussion points may be drawn from such analyses. GraphPad Prism (version 10.0.0; GraphPad Software) will be used for any statistical analysis undertaken in the review. The heterogeneity of clinician-reported outcomes and PROMs used in facial palsy indicates that there is limited scope for a high-quality meta-analysis, and thus, a meta-analysis will not be carried out. Subgroup or subset analysis is unlikely to be useful for examining the sufficiently specific original review question.

Results

This systematic review formally began in February 2025, although it has been planned since July 2024. The final systematic review will be performed and reported according to this protocol and the PRISMA guidelines [37,39]. A PRISMA flow diagram and checklist have been included to summarize the search and selection strategy up to this date (Multimedia Appendices 3 and 4). Initially, the search returned 2120 records, and 56 records are currently being screened for eligibility. Data from the final included studies will be extracted, collated, and analyzed. The risk of bias and the quality of evidence will be ascertained. A narrative synthesis will be used to summarize the results of the systematic review. Where possible, statistical analyses will be presented using graphs and figures. The final systematic review is expected to be published in December 2025.

Discussion

The authors hypothesize that the included studies, particularly those that are more recent, will show that patients who undergo single-stage facial reanimation using free functional muscle flaps have quicker reinnervation and recovery times than patients who undergo 2-stage facial reanimation. As mentioned, there is an expected heterogeneity in the outcomes used by studies, which may mean that the hypothesis is difficult to objectively display. For example, it is unlikely that the data extracted and analyzed from the included studies will allow for a forest plot that would summarize the results of this review's outcomes. This systematic review, however, will still be clinically useful as the most up-to-date review comparing the single-stage and 2-stage facial reanimation techniques. The information collated and discussed in this review may be used to aid clinicians and patients in shared decision-making. Moreover, future research questions may be raised, allowing for the conception of further studies on this topic.

To the best of our knowledge, Natghian et al [30] published the only systematic review comparing single-stage and 2-stage facial reanimation using free functional muscle flaps. The study specifically examined smile excursion as an outcome and concluded that single-stage facial reanimation may produce superior smile excursion and symmetry when compared with the 2-stage technique; however, the study lacked data on the spontaneity of smiling after surgery, which is a key indicator of smile quality. Previous research has shown that 2-stage facial reanimation produces a greater spontaneous smile [11]. Since the study by Natghian et al [30], further articles discussing facial reanimation with free functional flaps have been published; however, a contemporary systematic review that discusses the most recent literature is yet to be performed. The proposed systematic review will be a necessary addition to the current literature because it will provide an updated comparison of the single-stage and 2-stage facial reanimation techniques using a broader range of outcomes than that in the study by Natghian et al [30], such as recovery time, nerve regeneration, and smile spontaneity. Therefore, the authors argue that this proposed systematic review's strengths are its recency and wide scope.

A limitation of the proposed review is the heterogeneity of the outcomes used in the topic, which limits the scope for statistical analyses such as meta-analysis. There are likely to be differences even within the single-stage and 2-stage techniques, such as different free functional muscle flaps and different innervations. While the proposed review will extract these data where possible, the scope for subgroup analysis is likely limited due to the limited number of studies. Many included studies will be prone to selection bias because clinicians may prefer one technique due to psychosocial factors, such as appearance, and clinical characteristics, such as comorbidities, which may impact recovery [58,59]. Therefore, the findings may be undermined. Hence, tools, such as ROBINS-I and GRADE, will be used to provide the risk of bias and quality of evidence of each included study for transparency. To disseminate the results, the authors will aim to present this review at a relevant conference and to publish it in a relevant journal.

Authors' Contributions

Conceptualization: MK and FA.
Data curation: OA and JG.

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Formal analysis: OA, JG, and MAD.
Funding acquisition: MAD and MK.
Investigation: OA and JG.
Methodology: OA and JG.Project administration: OA, MK, and MAD.
Resources: MK and MAD.
Supervision: MK and FA.
Validation: MK and MAD.
Visualization: OA.
Writing – original draft: OA and JG.
Writing – review & editing: OA, JG, MAD, FA, and MK.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Example search strategy for MEDLINE via Ovid.
[DOCX File , 24 KB - resprot_v14i1e64009_app1.docx]

Multimedia Appendix 2
Example search strategy for ClinicalTrials.gov via Cochrane Library.
[DOCX File , 24 KB - resprot_v14i1e64009_app2.docx]

Multimedia Appendix 3
Up-to-date PRISMA flow diagram.
[PDF File (Adobe PDF File), 166 KB - resprot_v14i1e64009_app3.pdf]

Multimedia Appendix 4
Up-to-date PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist.
[DOC File , 83 KB - resprot_v14i1e64009_app4.doc]

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Abbreviations

CFNG: cross-facial nerve graft
GRADE: Grading of Recommendations, Assessment, Development, and Evaluations
PICO: population, intervention, comparison, and outcomes
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROMs: patient-reported outcome measures
ROBINS-I: Risk of Bias in Nonrandomized Studies-of Interventions

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Protocol

Development of the Double-Blind, Randomized Trials of Effects of Antihypertensive Medicines (DREAM) Database and Characteristics of the Included Trials: Protocol for an Umbrella Review and Meta-Analyses

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Abstract

Background: A comprehensive evaluation of short-term effects of antihypertensive medicines is important for informing guidelines and clinical practice.

Objective: We aimed to develop the Double-blind Randomized trials of Effects of Antihypertensive Medicines (DREAM) database to facilitate a series of meta-analyses evaluating the short-term effects of antihypertensive medicines.

Methods: We searched the Cochrane Central Register of Controlled Trials, MEDLINE, and Epistemonikos from inception until December 2022 to identify relevant randomized clinical trials (RCTs). We included RCTs in the DREAM database if they were double-blind, enrolled adult participants, evaluated the 5 major classes of antihypertensive medicines over a duration of 2 to 26 weeks, and were published in the English language. Screening of records for inclusion and data collection were both conducted in duplicate. The planned meta-analyses using the DREAM database will follow standard methods as recommended by the Cochrane Handbook for Systematic Reviews. The general methods for these meta-analyses are outlined.

Results: The DREAM database includes 1623 RCTs (4359 comparisons), of which 44% (707/1623) were placebo-controlled, 70% (1141/1623) had parallel-group allocation, and 37% (607/1623) had 3 or more randomized groups. A total of 304,253 participants (mean age 54 years; 509/1623, 46% female) were included, 86% (1391/1623) of RCTs had participants with hypertension, and 11% (175/1623) of RCTs had participants with cardiovascular disease at baseline. RCTs with at least 1 group

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randomized to combination therapy accounted for 23%(371/1623). The median duration of treatment was 8 weeks. Most (93%, 1509/1623) RCTs reported data on effects on blood pressure.

Conclusions: The first series of meta-analyses using the DREAM database will assess the effects of antihypertensive medicines on blood pressure and safety outcomes, including effects on headache, and cardiovascular events. The findings of these meta-analyses will inform clinical practice guidelines and help identify priorities for future research.

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KEYWORDS

double-blind; randomized controlled trials; blood pressure; anti-hypertensive medicines; systematic review; hypertension; cardiovascular disease; antihypertensive medicines; meta-analyses

Introduction

High blood pressure (BP) is the leading cause of disease burden globally [1], and antihypertensive medicines are among the most prescribed medicines worldwide to prevent cardiovascular disease events and death. Antihypertensive medicines are also used for the management of other health conditions, including renal disease and migraine. Use of medicines should be guided by comprehensive, up-to-date, and reliable evidence of their safety and efficacy. There is an established collaboration that conducts meta-analyses of individual participant data from randomized controlled trials (RCTs) for long-term effects of antihypertensive medicines [2], and there are many trial-level meta-analyses of the effects of antihypertensive medicines on cardiovascular disease events. However, for short-term efficacy and safety of antihypertensive medicine, the last comprehensive systematic review and meta-analysis was reported 20 years ago [3]. The short-term effects of antihypertensive medicines are important for several reasons. First, guidelines recommend achieving BP control within a few months [4]. Second, maximum BP-lowering effects of antihypertensive drugs accrue within 4 weeks [5] and there is consensus that the extent of BP lowering accounts for most or all cardiovascular event reduction [6,7]. Finally, changes to the antihypertensive medicine regimens are usually done within the first few months [8] of initiation, based on BP levels achieved or adverse events experienced. We, therefore, aimed to develop a database of Double-blind Randomized trials of Effects of Antihypertensive Medicines (DREAM), to facilitate conduct a series of meta-analyses on short-term effects of antihypertensive medicines. The findings of these meta-analyses will inform guidelines, clinical practice, and future research priorities. In this manuscript, we report the methods of development of the DREAM database, present characteristics of RCTs included, and outline the general methods for the planned meta-analyses.

Methods

Database Development and Eligibility Criteria for Including RCTs

RCTs were included in the DREAM database if they were randomized, double-blind; enrolled adult participants (age ≥18 years or as defined in individual RCTs); and compared antihypertensive medicines or their combinations with each other or placebo, for a duration of 2 to 26 weeks; reported data to assess the difference in reduction in BP or headache incidence between the groups, given BP lowering efficacy and headache reduction were 2 key areas of interest. Antihypertensive medicines had to be from the 5 major classes of antihypertensive medicines, namely angiotensin-converting enzyme inhibitors, angiotensin II receptor blockers, beta-blockers, calcium channel blockers, and diuretics, and must have been approved by regulatory agencies for hypertension. RCT groups that involved conditional or optional change in therapy (eg, based on BP or adverse effects) such that different participants within a group received different medicines or doses were not included. RCTs among participants with significant health conditions that could alter or interfere with the assessment of the effects of antihypertensive medicines were not included. Also not included were trials published in a non-English language. Detailed inclusion and exclusion criteria, along with the rationale are reported in Table S1 in Multimedia Appendix 1. Additional inclusion and exclusion criteria for the planned individual meta-analyses will be reported in the respective subsequent manuscripts.

Identification and Selection of RCTs

The following databases were searched using a systematic search strategy (Tables S2, S3, and S4) comprising relevant keywords and MeSH (Medical Subject Headings) terms: Cochrane Central Register of Controlled Trials (until December 2022) for RCTs; and MEDLINE (from 1946 to December 2022), and Epistemonikos (inception to December 2022) for systematic reviews of RCTs. Bibliographies of systematic reviews were reviewed to identify eligible RCTs. In addition, drug approval packages available on the website of the United States Food and Drug Administration were reviewed until December 2022 for unpublished RCTs.

After removing duplicates, 2 reviewers independently assessed in duplicate the title and abstract, and subsequently the full text of each record for assessing eligibility against the eligibility criteria in DistillerSR [9]. Disagreements between the reviewers were resolved by discussion or by adjudication by a third senior reviewer.

Data Collection

A data collection form was developed to collect characteristics of the RCTs, participants, interventions, and outcomes data, considering the planned analyses. A full list of variables is reported in Table S5 in Multimedia Appendix 1. A data

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collection guidance document was developed which provided information on where to find the data in the manuscript or report, what data to collect, and if necessary, how to make data conversions. The data collection form and the guidance document were piloted before commencing data collection. For RCTs with more than 1 treatment period, data for all treatment periods were collected. If BP data were reported for more than 1 position in which BP was measured, we collected data for all positions: seated, standing, and supine. Similarly, for the time of BP measurement, data were collected if it was trough or peak. The BP data reported in graphs were extracted in duplicate by 2 reviewers independently using webPlotDigitizer [10] a web-based tool to extract data from images. Reviewers were provided training on data collection. Data from each included RCT were collected in electronic forms using DistillerSR [9]. Conflicts in data collection were resolved by discussion between the reviewers or by adjudication by a third reviewer.

Planned Meta-Analyses

In the first series of planned meta-analyses, we aim to assess the effects of antihypertensive medicines and their combinations on BP, including evolution or time course of BP-lowering effects, effects on BP variability, safety, effects on headache, cardiovascular events, and death. Where feasible and appropriate, effects will be assessed by medicine class, individual medicines, dose, and participant characteristics at baseline (eg, age, gender, ethnicity, BP, and comorbid conditions). The following are the primary objectives of the first series of planned meta-analyses:

1. To evaluate, among adults, BP-lowering medicines and their combinations compared with placebo for BP-lowering efficacy.
2. To evaluate, among adults, BP-lowering medicines and their combinations compared with placebo for safety.
3. To evaluate, among adults with hypertension (systolic BP [SBP] ≥140 mm Hg, diastolic BP [DBP] ≥90 mm Hg), combinations of BP-lowering medicines as initial therapy compared with placebo, monotherapy, and combinations of other BP-lowering medicines for BP-lowering efficacy and safety.
4. To evaluate, among adults with hypertension (SBP ≥140 mm Hg, DBP ≥90 mm Hg), the time interval at which intensification of BP-lowering medicines is required, if desired BP control is not achieved following initiation or modification of BP-lowering medicines.
5. To evaluate, among adults with hypertension (SBP ≥140 mm Hg, DBP ≥90 mm Hg), BP-lowering medicines and their combinations compared with placebo for effects on cardiovascular events and death.
6. To evaluate, among adults, BP-lowering medicines and their combinations compared with placebo, other BP-lowering medicines, and their combinations for effects on headache.
7. To evaluate, among adults, BP-lowering medicines and their combinations compared with placebo for effects on BP variability.

Risk of Bias in Included RCTs

For individual meta-analyses, risk of bias in the included RCTs will be assessed using the Cochrane Risk of Bias Tool, or a similar standard tool. Where appropriate, we will use the results of the risk of bias assessment for sensitivity analysis.

Governance and Data Management Policies

The database is hosted by The George Institute for Global Health. The core team plans to periodically update the database, plan and conduct meta-analyses and disseminate the findings. Other than the planned meta-analyses listed in this manuscript as initial outputs, colleagues, collaborators, and external stakeholder might suggest additional meta-analyses to the DREAM database core team. If appropriate, after approval by the core team, the proposers can work with the core team to develop the protocol, conduct the meta-analyses, and disseminate findings.

Patient and Public Involvement

This manuscript describes the development of a database for the purpose of a systematic review and outlines secondary analyses, such as evidence generation from published data. Patients were not involved in conceptualizing the DREAM database. For the planned and future meta-analyses, relevant stakeholders will be involved at appropriate stages of the conduct of the meta-analysis to ensure that the results produced are relevant and meaningful to patients affected by the health condition under study, and to those who use evidence to inform guidelines and practice.

Statistical Analysis

For each planned meta-analysis, a separate protocol will be written, eligible RCTs will be retrieved from the DREAM database, and included in the meta-analysis. Below, we provide an overview of the general methods for the planned meta-analyses.

Measures of Treatment Effect

For continuous outcomes, such as change in BP, creatinine, the treatment effect (TE) will be the difference in mean change or difference in standardized mean change (when different scales were used to assess the same outcome values) from baseline to follow-up between the treatment groups. If baseline values are not available, then the difference between mean follow-up values will be used to calculate the TE. When relevant, raw TE will be standardized to the mean values at baseline to adjust for baseline differences between the treatment groups. For dichotomous outcomes (eg, incidence of adverse events), TE will be odds ratios, relative risks, or risk differences between the comparison groups.

Unit of Analysis Issues

Treatment groups with same medicine but different doses will be treated as separate groups for analyses of the dose-response effect. Treatment groups with the same medicine, same dose, but different formulations (eg, sustained release) will be combined. When dealing with RCTs involving more than 2 groups and contributing multiple comparisons to the same analysis, the sample size for continuous outcomes and the

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sample size, as well as the number of patients with the outcome of interest for binary outcomes, in the shared group across contributing comparisons, will be divided by the number of times a group is used to prevent unit of analysis error. Outcome data from multiple follow up time points from the same RCT will not be combined in the same analysis. In a previous large meta-analysis of efficacy of antihypertensive medicines on BP [3], parallel and crossover RCTs yielded similar results and hence will be combined in our analyses, unless they yield significantly different results.

Definition of Standard Dose of Antihypertensive Medicines

To facilitate comparisons across medicines, we used an updated standard dose method [3]. The standard dose is defined as the average maintenance dose per day based on the World Health Organization daily defined dose and regulatory approved strengths (Table S6 in Multimedia Appendix 1).

Dealing With Missing Data

Data will be assumed to be missing at random. As most RCTs were completed over a decade ago, contacting authors or sponsors to obtain missing data was not feasible. All analyses will be on an intention-to-treat basis, that is, based on the number of participants randomized. If this information is not available, the number of participants who completed the treatment or were included in the analysis will be used. If the sample size for a treatment group is missing, it will be calculated from the overall RCT sample size, splitting it evenly among all groups for parallel RCTs with 1:1 randomization. For cross-over RCTs, the sample size for each group will be the same as that of the overall RCT.

Missing SDs will be calculated using established methods [11]. If it is not possible to calculate, SDs will be imputed as per the following hierarchy based on the available data, for SD of the mean change, SD of the last follow-up mean, SD of the baseline mean, mean SD of the mean change from other RCTs of same medicine or class. For dichotomous outcomes, when 2×2 tables are not reported to derive odds ratio and associated variance, we will impute these based on available data following the method suggested by Elbourne et al [12]. For cross-over RCTs, correlation coefficients are important for both continuous and binary outcomes. If they cannot be calculated from the available data, they will be imputed based on data from other RCTs in the DREAM database [11].

Meta-Analysis

Principally, the 3 approaches to analyses will be pairwise meta-analysis, network meta-analysis (NMA), and meta-regression modeling, depending on the research question, objectives and availability of data. A narrative overview of RCTs included in the meta-analysis will provide insights regarding the degree of clinical and methodologic homogeneity among included RCTs, thereby helping to explore the assumptions of homogeneity and similarity for pairwise meta-analysis and NMA.

Pairwise Meta-Analysis

Where at least 2 RCTs are available, and if appropriate, we will perform pairwise meta-analysis. Fixed-effect model using inverse variance weighting will be used for meta-analysis of both continuous and binary outcomes. However, where appropriate, a random-effects model may be used. Where relevant, both the models will be used with 1 of the 2 used to assess robustness of results as part of sensitivity analysis.

Network Meta-Analysis

The DREAM database has 84 antihypertensive medicines, and 120 unique combinations of from the 5 major classes. In the proposed meta-analyses, where feasible and appropriate, a comparison of 2 or more medicines, classes, or doses will be conducted. NMA is a useful approach for providing a multiway comparison of treatment effects. NMA uses both direct and indirect comparisons to compare multiple (3 or more) treatments simultaneously while maintaining internal randomization in an RCT. It facilitates the ranking of treatments based on parameters of efficacy and safety [13]. NMA will be considered if there is limited direct evidence of comparative effects of pairs of interventions from RCTs, and ranking of interventions for efficacy or safety has important implication for clinical practice and policy. It will be ensured that RCTs contributing to each network are not substantially heterogeneous and there is an absence of important intransitivity, NMA relies heavily on transitivity to draw valid conclusions from indirect comparisons. NMA will be undertaken using either a frequentist or Bayesian framework based on the objectives of the analysis and availability of data. Approaches such as mean rank, median rank, and cumulative ranking probabilities will be used where relative ranking to identify the best of the interventions for a particular outcome is sought. Disagreement between direct and indirect evidence (inconsistencies/incoherence) in a network of interventions will be explored.

Meta-Regression

Meta-regression will be conducted, where appropriate, to assess the effects of continuous as well as categorial explanatory variables on the outcome variable. Relatively common outcomes such as BP-lowering will be analyzed with a linear, nonlinear or log-binomial model depending on the type of variable (continuous or categorical). Uncommon events such as rare adverse effects or those occurring over variable periods of time will be studied with a Poisson model. For example, the meta-analysis of time-course of BP-lowering of effect, will be modeled using meta-regression, with medicine classes and monotherapy versus combination therapy as covariates. Bubble plots with 95% confidence bands will be used to visualize the meta-regression plots. Both unadjusted and adjusted analyses will be conducted. Initially, pooled effect estimates with 95% CI will be obtained using unadjusted meta-regression analysis, weighted for RCT sample size. The analysis may be repeated using a multivariate meta-regression model, with adjustment for other covariates including RCT design (parallel or crossover), duration (weeks), baseline mean (mm Hg), and medicine dose.

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Assessment of Statistical Heterogeneity

In evidence synthesis, assessing statistical heterogeneity is essential for ensuring validity, reliability, and interpretability of the generated evidence. The basic way of assessing statistical heterogeneity in results across RCTs included in a meta-analysis would be reviewing the overlap of CIs in a forest plot, with poor overlap suggesting heterogeneity. Heterogeneity, which is due to variability in true effect sizes across trials, will be expressed using 95% predication intervals for the summary effects when there are more than ten RCTs in the meta-analysis. The I^2 statistic, which represents percentage of total heterogeneity across included RCTs that is true heterogeneity and not due to sampling error (chance) will also be assessed. I^2 values will be interpreted as unimportant (0% to 40%), moderate (30% to 60%), substantial (50% to 90%), and considerable (75% to 100%) heterogeneity [14].

Assessment of Nonreporting (Publication Bias)

When there are at least 10 RCTs included in a meta-analysis, an assessment of nonreporting bias will be performed using funnel plots and statistical tests (eg, the Egger test) [15], and imbalance and asymmetry distance statistics, where appropriate [16]. In network meta-analyses, the presence of small-study effects will be assessed by drawing comparison-adjusted funnel plot that accounts for the fact that different RCTs compare different sets of interventions [18.19]. These assessments will be interpreted in combination with the results of heterogeneity and effect measures being used for the meta-analysis [17,18].

Subgroup Analysis

Where appropriate and possible, subgroup analysis will be prespecified and performed. Subgroups will be based on important characteristics that modify the effects of antihypertensive medicines, such as class of medicine, treatment duration, baseline BP, and participant characteristics. These subgroups will be used to explore heterogeneity in results across included RCTs. Statistical testing will be used to compare results across subgroups if there are enough RCTs in each subgroup. If appropriate, an I^2 statistic (percentage of variation in effect estimates across subgroups that is due to real subgroup differences) will be computed for subgroup differences.

Sensitivity Analyses

Where necessary, sensitivity analyses will be performed to assess robustness of results according to assumptions, imputed data, RCTs with a high risk of bias, and different statistical models. The results of sensitivity analyses will be reported in a summary table for easy comparison. As much as possible, sensitivity analyses will be prespecified.

Assessment of the Certainty of Evidence

The assessment of certainty of evidence will be conducted following GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach [19]. When applicable, a summary table will be generated using the GRADEpro GDT software. Since all RCTs included in the DREAM database have randomized double-blind design, initially, the certainty of evidence will be graded as high. However, if there are limitations, the certainty of evidence will be appropriately downgraded based on the risk of bias, consistency across studies, directness of evidence, precision of estimates, and potential publication bias, to moderate, low or very low. The approach suggested by Salanti et al [20] and Adriani Nikolakopoulou et al [21] using the CiNeMA tool will be used to assess confidence in the evidence from network meta-analyses.

Ethical Considerations

This research involves analysis of secondary data from previously published RCTs; therefore, ethical approval was not required. Individual meta-analyses protocols will be registered on registries such as PROSPERO (International Prospective Register of Systematic Reviews) [22] or INPLASY (International Platform of Registered Systematic Review and Meta-analysis Protocols) [23]. The results of the planned meta-analyses will be published with reference to this prespecified protocol. We will share and present findings of meta-analyses at various scientific meetings and through the collaboration's networks and memberships across professional societies. For reporting individual meta-analysis results, the PRISMA (Preferred Reporting items for Systematic Reviews and Meta-Analyses) statement's recommendations will be followed [24].

Results

The PRISMA flow chart (Figure 1) presents the identification and inclusion of RCTs in the DREAM database. A summary of characteristics of included RCT is reported in Table 1. Overall, 1623 RCTs were eligible and included, from which 4359 groups were included in the DREAM database. Most (1096/1623, 68%) RCTs were published before the year 2000. A total of 707 (44%) were placebo-controlled, 482 (30%) were cross-over, and the mean and median duration of intervention were 9 (SD 6) weeks and 8 (IQR 4-12) weeks, respectively.

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Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart for identification and inclusion of the randomized controlled trials in the Double-blind Randomized trials of Effects of Antihypertensive Medicines database. DREAM: Double-blind Randomized trials of Effects of Antihypertensive Medicines; FDA: Food and Drug Administration; RCT: randomized controlled trial; SR: systematic review.

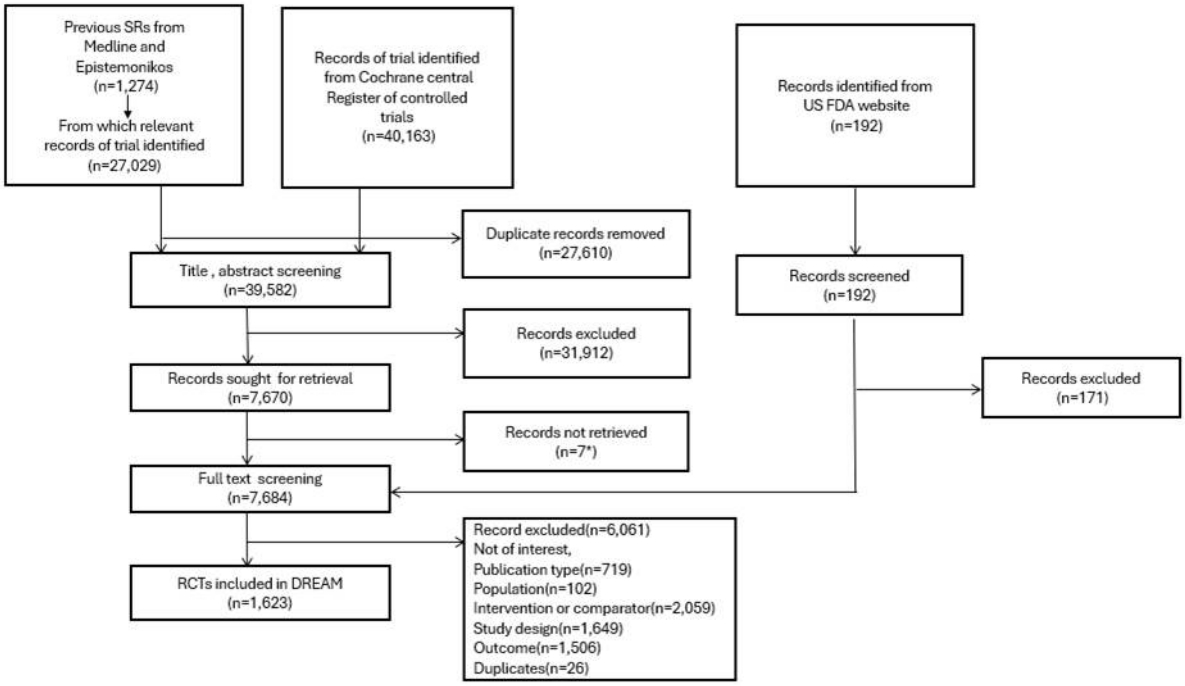

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Table 1. Summary of characteristics of randomized controlled trials (N=1623) included in the Double-blind Randomized trials of Effects of Antihypertensive Medicines database.

Characteristics	Randomized controlled trials, n (%)
Year of publication	
Before 1990	473 (29)
1990 to 1999	623 (38)
2000 to 2009	338 (21)
After 2009	189 (12)
Design	
Double-blind	1623 (100)
Placebo-controlled	707 (44)
Parallel allocation	1141 (70)
2 groups	1016 (63)
≥3 groups	607 (37)
Duration (weeks)	
2	63 (4)
2.1-4	336 (21)
4.1-8	634 (39)
>8	590 (36)
Funding	
Industry	543 (33)
Academia, government, nonprofit, or charity	147 (9)
Mixed	48 (3)
None	4 (0.3)
Not reported	881 (54)
Sex	
Female participants ≥50%[a]	509 (31)
Mean age (years)	
<50	271 (17)
50 to 59	956 (59)
60 to 69	185 (11)
70 to 79	61 (4)
≥80	3 (0.2)
Not reported	147 (9)
Mean systolic blood pressure at baseline (mm Hg)	
110-119	12 (0.8)
120-129	48 (3)
130-139	91 (6)
140-149	169 (10)
150-159	484 (30)
160-169	416 (26)
170-179	168 (10)
≥180	51 (3)
Not reported	184 (11)

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Characteristics	Randomized controlled trials, n (%)
Condition s of interest at baseline	
Hypertension[b]	1391 (86)
Cardiovascular disease	175 (11)
Endocrine conditions	97 (6)
Chronic kidney disease	18 (1)
Intervention: randomization to at least 1 group	
Monotherapy	1545 (95)
Angiotensin-converting enzyme inhibitor	432 (27)
Angiotensin II receptor blocker	292 (18)
Beta-blocker	434 (27)
Calcium channel blocker	574 (35)
Diuretic	324 (20)
Dual combination	354 (22)
Triple combination	16 (1)
Quadruple combination	1 (0.1)
Treatment periods	
1	1425 (88)
2	150 (9)
3	48 (3)
Outcomes data available	
Systolic or diastolic blood pressure	1509 (93)
Adverse events data available[c]	809 (50)

[a]Number of trials in which there were at least 50% female participants.

[b]All participants had hypertension as defined in the individual randomized controlled trials, or trial eligibility clinic systolic BP (SBP) of ≥140 or diastolic BP (DBP) of ≥90 mm Hg or 24-hour ambulatory SBP of ≥130 mm Hg or DBP of ≥80 mm Hg or home SBP of ≥135 mm Hg or DBP of ≥85 mm Hg.

[c]Adverse events data reported: at least 2 groups in a trial reported at least 1 of the following—any adverse events, any serious adverse event, treatment-related adverse event, treatment related serious adverse event, or withdrawals due to adverse event.

Overall, 304,253 participants were included: mean age was 54 years, and in 74% (1205/1623) of RCTs, the participants' mean age was ≥50 years. Overall, the mean proportion of female participants was 46% (139,182/304,253), and 31% (509/1623) of RCTs had ≥50% female participants. Most RCTs (1391/1623, 86%) had participants with hypertension, and 11% (175/1623) of RCTs had participants with cardiovascular disease. Most common randomization to an antihypertensive medicine class was to calcium channel blockers (at least one group in 574/1623, 35% RCTs randomized to calcium channel blockers), and in 23% (371/1623) of RCTs, at least 1 group was randomized to a combination of 2 or more antihypertensive medicines. Most (1509/1623; 93%) RCTs reported data on effects on systolic or diastolic BP and data for incidence of adverse events were available from 50% (809/1623) of RCTs.

Discussion

Principal Findings

The DREAM database is a comprehensive resource of double-blind RCTs, developed to enable a series of meta-analyses on the short-term effects of antihypertensive medicines. These analyses will offer novel insights into the impact of antihypertensive treatments on BP, including its trajectory and variability.

In addition, the database will support evaluations of the safety profiles of these medicines, focusing on their effects on headache and cardiovascular outcomes. Findings will be stratified by drug class, dosage, and key patient characteristics, addressing critical gaps in the current evidence. This comprehensive evidence base will facilitate the development of tools to predict the efficacy of antihypertensive regimens, enabling health care providers to optimize patient care. Ultimately, the findings will contribute to refining clinical practice guidelines, improving treatment strategies, and

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identifying priorities for future research in the pharmacological management of hypertension and related conditions.

Comparison With Previous Work

Our work builds on the foundational study by Law et al [3] in 2003, which synthesized 354 randomized double-blind, placebo-controlled trials to evaluate the effects of antihypertensive medicines, including combination therapies. Unlike the analyses by Law et al [3], now over 2 decades old, the DREAM database includes over 1600 double-blind trials published up to 2022, also incorporating active-controlled trials. The work also complements Cochrane Collaboration reviews, which are restricted to specific drug classes. This comprehensive database enables network meta-analyses to assess the relative efficacy and safety of antihypertensive medicines and their combinations, providing updated and robust evidence for clinical decision-making.

This project focuses on short-term (<6 months) effects of these drugs during which most change regimens is usually undertaken, and as such complements meta-analysis of longer-term outcomes. In particular, our work also complements the contributions of the Blood Pressure Lowering Treatment Trialists' Collaboration [2], which conducts individual patient-level meta-analyses of over 300,000 participants from 100 long-term randomized trials. Blood Pressure Lowering Treatment Trialists' Collaboration focuses on stratified effects of BP-lowering on major vascular events, all-cause mortality, safety outcomes (eg, renal failure, diabetes, and fractures), and extended effects on conditions such as atrial fibrillation and dementia. Other similar collaborations include the Blood Pressure in Acute Stroke Collaboration and the Beta-Blockers in Heart Failure Collaborative Group, which synthesize evidence to improve cardiovascular outcomes [25]. Together, these efforts strengthen the evidence base for the pharmacological management of hypertension and related conditions, advancing and optimizing cardiovascular care.

Strengths and Limitations

Our work has several notable strengths. It represents the most comprehensive resource of double-blind randomized trials on antihypertensive medicines to date. The database facilitates stratified meta-analyses by medicine class, dose, and patient characteristics and allows regular updates to enable living systematic reviews providing up-to-date evidence for health care decision-making. However, there are some limitations. Exclusion of trial published in non-English languages and nonavailability of full text of some possibly included RCTs (n=7) despite extensive procurement efforts is a limitation we acknowledge. However, given the small number of these trials, the impact on findings of meta-analyses is likely minimal. The review also includes data abstracted from publication figures, and imputation of data for missing or implausible variability data using standard methods. The lack of individual participant data means we did not have an opportunity to assess in-depth effects across important subgroups of patients based on age, gender, race, and concomitant conditions. Also, given the large number of trials in many countries and a long time frame, safety data were often reported in different ways, hence making overall synthesis more challenging.

Acknowledgments

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Data Availability

The datasets that will be generated during the analysis will be available from the corresponding author on reasonable request.

Authors' Contributions

AS contributed to the conception, data acquisition, data interpretation, and drafting of the manuscript. RD was involved in data acquisition, data interpretation, and drafting the manuscript. VK, PK, ST, HP, FH, RK, RT, RB, and KC contributed to data acquisition, while RP and AK were responsible for data analysis and interpretation. SB,NW, and SG contributed to data interpretation. AR contributed to the conception and data interpretation. All authors critically reviewed the manuscript and approved it for publication.

Conflicts of Interest

AR is employed by The George Institute for Global Health (TGI) and Imperial College London. TGI has submitted patent applications for low-dose combination products for hypertension and AR is listed as an inventor. George Medicines Pt Ltd (GM) is a subsidiary of TGI, holds a license for these patents and has received investment to develop these combination therapies. AR is seconded part-time to GM. AR and other TGI staff have no financial interest in these patents or in GM.

Multimedia Appendix 1
Additional material.
[DOCX File , 51 KB - resprot_v14i1e65205_app1.docx]

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Abbreviations

BP: blood pressure
DBP: diastolic blood pressure
DREAM: Double-blind Randomized trials of Effects of Antihypertensive Medicines
GRADE: Grading of Recommendations, Assessment, Development, and Evaluation
INPLASY: International Platform of Registered Systematic Review and Meta-analysis Protocols
MeSH: Medical Subject Headings
NMA: network meta-analysis
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PROSPERO: International Prospective Register of Systematic Reviews
RCT: randomized controlled trial
SBP: systolic blood pressure
TE: treatment effect

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Protocol

Domains of Access for Interventions Addressing Intimate Partner Violence Among Latina Immigrants: Protocol for a Systematic Review

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Abstract

Background: Latina immigrants in the United States face barriers to accessing information and support for intimate partner violence (IPV) due to language and cultural differences, a lack of legal awareness, social isolation, and financial issues. Despite numerous interventions, research lacks insight into how these programs address access barriers and target IPV-related risk and protective factors.

Objective: This systematic review aims to (1) identify intervention studies conducted with Latina immigrants in reducing IPV outcomes (ie, sexual and physical violence and gender-based violence–related knowledge and attitudes), (2) evaluate the extent to which the implementation of these IPV interventions aligns with the access to care framework, and (3) establish whether the extent of IPV intervention alignment with the access to care framework has any significant impact on effectiveness.

Methods: A systematic review will be conducted using the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-analysis Protocols) checklist. The research will proceed iteratively among authors. The team, including a librarian, developed a search strategy and searched 7 databases, namely, APA PsycInfo, CINAHL Plus with Full Text, PubMed, Scopus, Social Work Abstracts, GenderWatch, and Sociological Abstracts, from inception to June 9, 2025. Two reviewers independently conducted a double selection of titles, abstracts, and full texts. Disagreements were resolved by a third reviewer. Data extraction will be performed by 2 reviewers and validated by a senior researcher. We will develop an intervention characteristics form for data extraction and analyze the study quality using the modified Methodological Quality Rating Scale. To assess alignment with access implementation standards, we will operationalize the access to care framework by creating the Domains of IPV Service Access Rating Scale to evaluate how interventions address access barriers and determine whether addressing these barriers increases intervention effectiveness.

Results: The search strategy and literature review were finalized in June 2025. A total of 943 references were identified after duplicates were removed, of which 182 will be reviewed in full text. A follow up search will be performed prior to submission. The publication is anticipated for October 2025.

Conclusions: This review will provide a comprehensive synthesis of strategies to address access barriers in IPV interventions for Latina immigrants, informing future practice and research to enhance equitable access to support and resources.

Trial Registration: PROSPERO 42024622171; https://www.crd.york.ac.uk/PROSPERO/view/CRD42024622171

International Registered Report Identifier (IRRID): DERR1-10.2196/76996

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KEYWORDS

interventions; intimate partner violence; Latina; access to care; systematic review protocol

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Introduction

Background

Intimate partner violence (IPV) constitutes a significant public health crisis, disproportionately impacting women in the United States and globally. IPV encompasses physical, sexual, or psychological harm, including stalking and coercive tactics, inflicted by a current or former intimate partner [1]. It is estimated that 1 in 3 women experience IPV [2]. The repercussions of IPV are severe, resulting in an elevated risk of homicide, physical injuries, chronic pain, reproductive health issues, adverse pregnancy outcomes, substance use disorders, and mental health conditions such as posttraumatic stress disorder, depression, and suicidality [3-6]. Within the United States, Latino populations, the largest immigrant group, encounter unique sociocultural and structural challenges that exacerbate their vulnerability to IPV and restrict their access to support [7]. Latinas who have experienced IPV report higher levels of poor physical health and psychological distress than non-Latina women with similar experiences [8,9]. They also face a distinct set of risk factors and barriers when seeking assistance after IPV, including limited legal protection, cultural stigma, and fear of authorities or deportation [10-12]. This underscores an urgent need for evidence-based interdisciplinary responses to guide organizations and service systems in identifying and overcoming barriers to accessing resources and support that are specifically tailored for Latino immigrant populations.

Ensuring access to essential health, mental health, social, and legal services is vital for the recovery and well-being of IPV survivors. However, Latina immigrants face numerous intersecting barriers such as structural challenges (eg, service availability), logistical concerns (eg, transportation and operating hours), financial constraints (eg, costs and insurance), and sociocultural factors (eg, acceptability and language compatibility) that impede their ability to obtain timely, culturally appropriate, and effective assistance [13-15]. Latina survivors use formal services, including health and social services, at significantly lower rates than other IPV survivors [16,17], and Latinas with undocumented status sought formal support services at even lower rates [11]. Research studies have consistently identified factors deterring Latina immigrants from disclosing abuse, including fear of separation from their children, limited information about their legal rights, limited knowledge about community resources, lack of English proficiency, social isolation, and limited access to health care [18,19]. Similarly, in a qualitative metasynthesis of 47 articles over 20 years, Hulley et al [20] found that immigrant women face challenges arising from institutional barriers, immigration status, cultural differences, and insufficient diversity among service providers who speak the language and understand the lived experiences of those they serve.

To better address these challenges, the Domains of Access framework, encompassing availability, accessibility, accommodation, affordability, and acceptability, offers a useful lens for analyzing Latina immigrants' interactions with service systems in the United States. [21]. Within the context of IPV, availability refers to the presence of services and providers capable of addressing the concerns of Latina immigrant women. Yet, many communities, especially rural or underserved areas, experience ongoing shortages of providers, a lack of bilingual staff, and limited cultural understanding of how to address this issue [15,20,22,23]. The accommodation domain involves flexibility around service delivery to meet individual needs, including hours of operation, walk-in hours, literacy levels, and linguistic requirements. Immigrants often work in sectors with limited flexibility for scheduling appointments with providers or advocates [24,25]. Once a survivor receives services, linguistic and cultural alignment with providers facilitates abuse disclosure and improves resource access for immigrant women [26,27]. The affordability domain includes access to health insurance and costs such as transportation and childcare [13,24]. A California study found that immigrant Latinos had poorer health care access than US-born Latinos, with undocumented immigrants accessing fewer resources due to costs or qualification barriers [18]. This results in fewer preventive care visits and missed opportunities for IPV screening. The acceptability domain concerns the relationship between organizations providing support and participants' comfort in discussing IPV. For instance, in a systematic review investigating effective interventions to address IPV among Latinas, Alvarez et al [28] found that the most effective interventions were gender-specific, culturally tailored, delivered in a group format, and developed collaboratively with the participants. Lastly, accessibility refers to the survivor's ability to reach and understand the nature of services being offered. Limited public transportation, lack of language and information delivery that accommodate various literacy levels, geographic isolation, and abuser restrictions further constrain immigrant survivors' ability to access resources and support [25,29,30]. Given these layered barriers, research that identifies and evaluates effective strategies to reduce access gaps is urgently needed.

While the Domains of Access framework provides a valuable lens for understanding the multilevel barriers Latina immigrants face in seeking IPV services, no systematic review has yet applied this model to the issue of violence and service access in this population. This gap has resulted in a fragmented evidence base, limiting the ability of practitioners and policymakers to design interventions that fully account for the complexities of access. Nonetheless, there is growing recognition of the unique needs of Latina immigrants, and targeted multicomponent interventions have begun to emerge addressing information and language requirements, financial constraints, and contextual factors that impede engagement [31]. Although individual interventions have demonstrated promise in supporting immigrant IPV survivors [32-35], this proposed study will be the first to synthesize the evidence on interventions that explicitly address access barriers for Latina immigrants within a comprehensive theoretical framework.

Objectives

This protocol outlines the methodology for a systematic review to map and synthesize evidence on interventions for IPV among Latina immigrants in the United States and their service access using the Domain of Access framework. The objectives include

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(1) identifying intervention studies conducted with Latina immigrants to reduce IPV outcomes (ie, sexual and physical violence and gender-based violence–related knowledge and attitudes), (2) evaluating the extent to which the implementation of these IPV interventions aligns with the Domains of IPV Service Access, and (3) establishing whether the extent of IPV intervention alignment with the Domains of IPV Service Access has any significant impact in terms of effectiveness. The review outcomes will inform the development of equitable interventions, practices, and policies for Latina immigrant women experiencing violence.

Methods

Reporting Standards

A systematic review will be conducted by a research team in accordance with the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-analysis Protocols) checklist [36].

Search Strategy

The research strategy was developed by a research team in collaboration with a health sciences librarian. The research was conducted in the following databases from their inception until the final search date of June 9, 2025: APA PsycInfo (EBSCOhost), CINAHL Plus with Full Text (EBSCOhost), PubMed, Scopus, Social Work Abstracts (EBSCOhost), Sociological Abstracts (ProQuest), and GenderWatch (ProQuest). The search terms based on a combination of 4 key concepts: ethnic identity, migration, relationship context, and violence and abuse. The complete and reproducible search strategy for all databases is provided in the appendix. The search results were imported into EndNote X9, where duplicates were removed. All unique references were imported into Covidence (Veritas Health Innovation). Two reviewers then proceeded individually and independently to conduct a double selection of the titles, abstracts, and full texts. A third reviewer resolved any disagreements between the reviewers. Data extraction will be performed by a reviewer and validated by a senior researcher.

Eligibility Criteria

The eligibility criteria will be based on the PICOS (population, intervention, comparison, outcomes, and study design) model [37] and are presented in Table 1. To be included in the review, studies should target Latino immigrant adults and youth in the United States. In addition, all studies on interventions related to IPV, domestic violence, or related forms of violence (eg, dating violence) will be included in the review. Studies with or without a control group will be included in this review. As for the types of studies, we included those with a quantitative component that included measures of targeted outcomes to determine effectiveness (ie, surveys and assessments). This systematic review will consider only studies published in English or Spanish. In addition, studies must have been published as peer-reviewed empirical studies; therefore, reviews, conference proceedings, study protocols, and editorials were excluded. We excluded non-Latina immigrant samples to highlight programs that aimed to address the complexities of immigrant status and IPV, including legal status, social isolation, language, and culture.

Table 1. Eligibility criteria based on the PICOS (population, intervention, comparison, outcomes, and study design) model.

PICOS	Criteria
Population (P)	Latina or Hispanic immigrant women in the United States who have experienced IPV[a].
Intervention (I)	IPV prevention or intervention programs, including culturally tailored, trauma-informed, or community-based approaches.
Comparative (C)	Standard IPV services without cultural tailoring, alternative programs, or no intervention.

Outcomes (O)	The following elements will be examined:
	• Categories:
	  • Level of intervention: individual, group, or mixed.
	  • Mode of design: theory, empirical evidence, or none.
	  • Targeted outcomes: primary and secondary outcomes, operational definitions, and measurement tools (ie, mental health, awareness about IPV and resources, and changes in self-esteem).
	• Characteristics of interventions: intervention name, setting, and target population,
	• Results and success factors of interventions: acceptability of services (ie, retention) and mitigation of access barriers.

Study design (S)	All quantitative empirical or mixed method studies without or without a control group will be included.

[a]IPV: intimate partner violence.

Study Selection and Extraction

The studies will be selected using Covidence [38]. Reviewers from the research team will independently assess the titles and abstracts, followed by the full texts of the relevant studies. Figure 1 presents a flowchart depicting the search and screening process. After study selection, data will be gathered by a reviewer and verified by a senior team member using an extraction grid created and tested by the research team. A third reviewer will resolve any conflicts or disagreements that arise. We will assess interrater reliability using Cohen κ to measure agreement prior to reconciliation. For quantitative data, reconciliation will include a comparison of the extracted values with the original source to verify accuracy.

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Figure 1. PRISMA flow diagram.

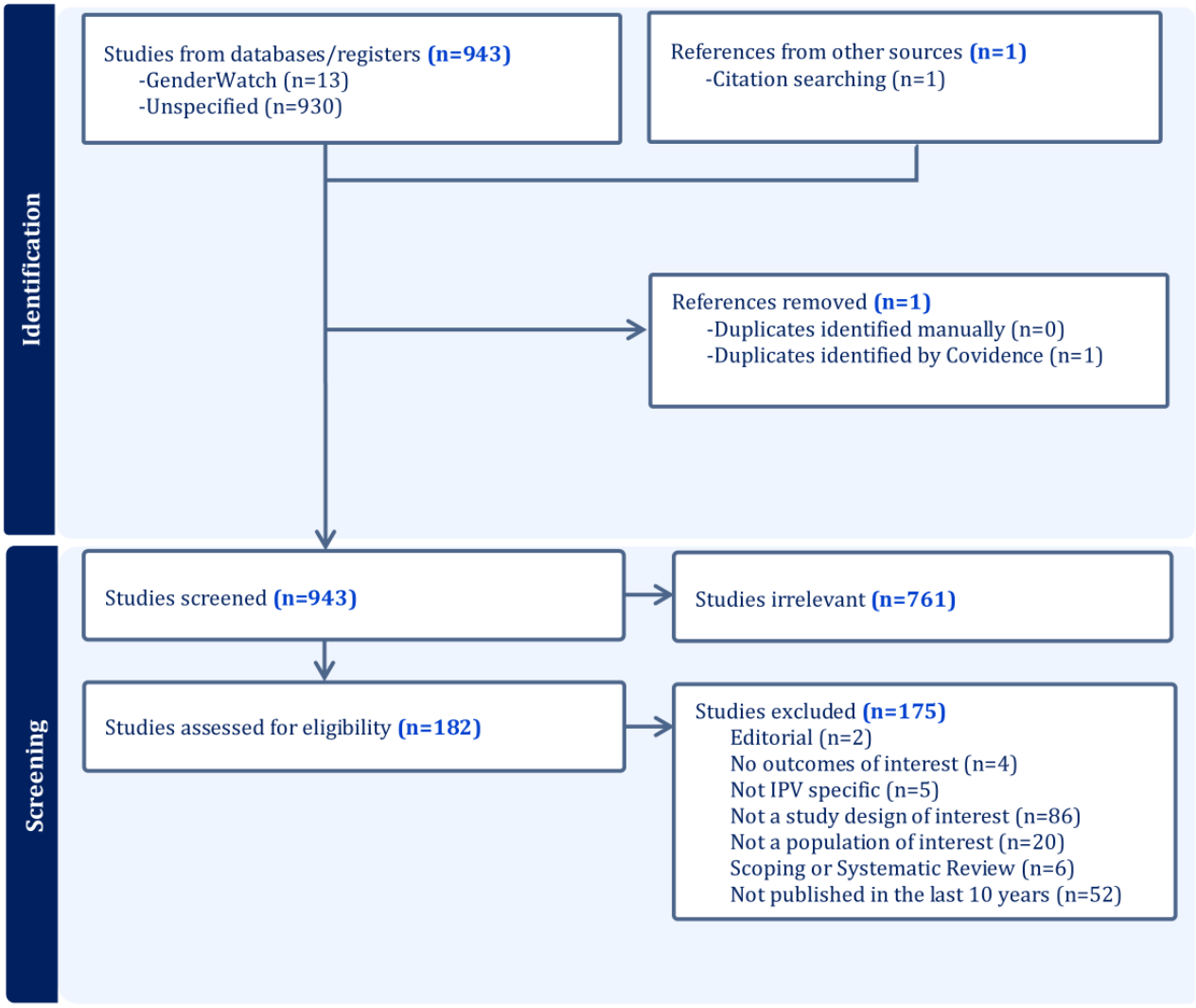

Data Synthesis and Analysis

We will use narrative synthesis to synthesize the data. We will provide a descriptive synthesis of the results of all included studies. A narrative summary of the main results will be produced to gather comprehensive information from each included study systematically. The extracted data will encompass key characteristics of the intervention (eg, intervention name, setting, delivery format, target population, and sample size), study design and methodological features (eg, design type, theoretical framework, intervention duration, and follow-up period), intervention components (eg, targeted risk and protective factors and cultural or contextual adaptations), and outcomes (primary and secondary outcomes, operational definitions, and measurement tools). Additionally, we will present the results related to the identification and mitigation of access barriers. Two reviewers will independently extract the data, with any discrepancies resolved through discussion or consultation with a third reviewer if necessary. All extracted data will be organized into structured tables to facilitate detailed comparisons and syntheses across the studies. The analysis will involve the tabulation and systematic review of variables pertinent to the study objectives, ensuring the consistency, transparency, and reproducibility of the review process.

Methodological Quality Assessment

Two reviewers will assess the methodological rigor using a modified version of Miller et al's [39] Methodological Quality Rating Scale, as described by Nyoni et al [40] (Table 2). This adaptation extends the original 14-item Methodological Quality Rating Scale by adding 3 items (theoretical basis, intervention intensity, and multiple outcome measures), removing 2 items (contact and collaterals), merging dropout and attrition into 1 item, and expanding scoring for study design and multisite assessment. The revised scale allows a maximum score of 24, ensuring a systematic evaluation of methodological rigor across the included studies. Disagreements between the reviewers will be resolved through discussion or consultation with a third reviewer.

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Table 2. A Methodological Quality Rating Scale.

Methodological criteria	Rating (points)
Study design	3 – Longitudinal randomized control trial
	2 – Mixed methods
	1 – Open pilot trial
	0 – Single group (pretest or posttest)
Theoretical foundations	1 – Intervention theory reported
	0 – Intervention theory not reported
Quality control	2 – Standardized by manual procedures, specific training, and quality control measures
	1 – Standardized by manual procedure or specific training
	0 – No standardization reported
Follow-up rate	2 – Equal or greater than the intervention phase
	1 – 70% to 99% of the intervention phase
	0 – Less than 70% of the intervention phase
Follow-up length	2 – 12 months or longer
	1 – 6 to 11 months
	0 – Less than 6 months
Measures	1 – Reliability and validity measures reported
	0 – Reliability and validity measures not reported
Multimethod measures	3 – Four or more IPV and associated risk or protective factors
	2 – Three measures of IPV and risk or protective factors
	1 – Any two of the measures
	0 – One measure
Objective verification	1 – Objective verification reported
	0 – Objective verification not reported
Intervention intensity	2 – Treatment group receives three or more components
	1 – Treatment group receives two components
	0 – Treatment group receives one component
Dropouts and attrition	1 – Dropouts enumerated or discussed
	0 – Dropouts not enumerated or discussed
Blind follow-up	1 – Follow-up by a person blind to participants' condition
	0 – Nonblinded or no follow-up
Analysis	1 – Appropriate statistical analysis (between-group differences, control for baseline differences)
	0 – No statistical analysis conducted
Multisite	3 – Parallel replications within the United States
	2 – Within the state
	1 – Within the same community
	0 – No replication
Generalizability	1 – Generalizability discussed (eg, sample characteristics, site, and curriculum)
	0 – Not discussed

Assessment of Study Compliance With Domains of IPV Service Access

To evaluate how IPV intervention studies among Latina immigrants in the United States address access barriers, we will develop a Domains of IPV Service Access Rating Scale (DISARS). This 5-item scale will assess the extent to which interventions incorporate (1) availability, (2) accommodation, (3) affordability, (4) acceptability, and (5) accessibility. In developing DISARS, we will draw upon prior empirical conceptualizations [40] (refer to Table 3). For each intervention, we will rate performance across the items and calculate a composite DISARS score to quantify adherence to access-oriented implementation standards. The DISARS will also allow us to explore whether greater alignment with the Domains of IPV Service Access is associated with enhanced intervention effectiveness.

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Table 3. The operationalization of the concepts used for intervention study appraisal.

Domain	Definition	Operationalization of the concept
Availability	The presence of services to address IPV[a] in rural or urban areas with a large concentration of Latinos.	• Services or resources to screen and support participants are present in clinics or community centers. • Public transportation services are present in the area.
Accommodation	The presence of sensitivity around issues of immigration status and other elements that may impact women's ability to access interventions or other forms of support.	• Information and resources are delivered in the languages spoken by Latina immigrants. • The hours of operation account for work schedules with little flexibility. • Immigration status–related concerns were addressed.
Affordability	The relationship between the cost of accessing the intervention and the women's ability to pay for it.	• Interventions and services were made available for participants regardless of health insurance. • Transportation is provided and childcare is offered. • Information about discounted or free phones and internet was made available.
Acceptability	The relationships between the approach to delivering the intervention that address IPV and the participants' attitudes toward and comfort with the content.	• The mode of delivery is acceptable for this population (ie, group format). • Community health workers provide input into the design and mode of delivery. • The curriculum is delivered alongside other culturally relevant activities.
Accessibility	Information about IPV and related resources is made available and can be understood by the participants	• Information is available to different literacy levels. • Linkage to legal or other social services is provided as part of the intervention. • The intervention is situated in a location familiar to the participants and accessible within walking distance.

[a]IPV: intimate partner violence.

Ethical Considerations

Ethical approval is not necessary because this is a protocol for a systematic review. The results will be shared through publications in peer-reviewed journals and presentations at conferences.

Results

The search strategy and literature review were finalized in June 2025. A total of 943 references were identified after duplicates were removed, of which 18 will be reviewed in full text. The publication of this systematic review is scheduled for September 2025.

Discussion

The Main Contributions of This Systematic Review

This systematic review protocol is designed to address a critical gap in the literature on how interventions for Latina immigrants experiencing IPV address barriers to service access across the Domains of Access framework. While previous reviews have examined IPV prevalence among Latinas [41], key components of effective interventions [28], the effectiveness of culturally tailored interventions [42], the effectiveness of group-format programs [43], and the intersection of IPV and immigration status [44], there remains a limited insight into how interventions explicitly operationalize and address access barriers, particularly in the domains of availability, acceptability, accessibility, affordability, and accommodation. Applying the Domains of Access model enables a comprehensive exploration of barriers and facilitators that extend beyond individual or cultural determinants. This theoretically informed approach has the potential of revealing the structural, organizational, and interpersonal dynamics that often intersect to either enable or hinder service access, especially among marginalized and vulnerable populations such as Latina immigrants. Additionally, this review's focus on Latina immigrants in the US addresses an important but underserved area where cultural, linguistic, legal, and sociostructural complexities are frequently overlooked in mainstream discourses and research on violence and service access [31]. Taken together, the findings of this review may be critical for developing more targeted multicomponent interventions that respond to the specific needs of individuals facing one or more of these challenges.

Potential Impact and Future Directions

This systematic review will influence violence prevention and service accessibility for Latina immigrants in the United States. Using the Domains of Access framework, it analyzes barriers and facilitators affecting survivors' experiences, providing practitioners, policymakers, and researchers with insights into strategies that have shown promise in improving service access for Latina immigrants experiencing IPV. Prior research suggests that culturally and linguistically tailored group-format programs developed collaboratively with the target population can enhance service acceptability and engagement [28,42,43]. Building on these insights, this review not only synthesizes existing strategies

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but also highlights critical gaps, including the limited availability of interventions addressing social and linguistic isolation [32], cultural factors [45-47], and financial burdens extending beyond health insurance and transportation [31]. By applying a domains-based approach, this review also establishes standards for future systematic reviews in migration, violence, and public health research, fostering methodological innovation and enhancing transparency.

Identifying the key elements that facilitate broader access to IPV-related resources and support contributes to the development of effective and innovative interventions that meet the needs of this population. The literature shows significant variability in the design, integration of culturally specific elements, and focus on prevention versus response among interventions targeting Latinas, along with a need for research that emphasizes cultural strengths as well as structural barriers [48]. The wide variability in intervention design could be explained by the variety of measurement tools, recruitment strategies, integration of mental health services, and geographic settings. These elements could also explain why some interventions are more effective than others in achieving their goals. Therefore, there is a need to comprehensively understand and highlight effective interventions that engage Latina immigrant survivors of IPV and the factors that these interventions address to promote more equitable access.

Although this review aims to provide a thorough overview, it is important to acknowledge several methodological limitations. First, the search was restricted to studies published in English and Spanish, which may have excluded relevant research in other languages. Second, relying mainly on major academic databases might overlook studies indexed in regional or less conventional sources, limiting comprehensiveness. Finally, since the focus is on Latina immigrant women, the findings may not fully reflect the experiences of Latino men, nonbinary individuals, or other underrepresented groups. Recognizing these limitations promotes transparency, situates the findings within their proper context, and emphasizes that this review should be understood as part of an expanding and evolving evidence base.

Conclusions

The outcomes of this systematic review will provide a comprehensive overview of effective interventions that mitigate access barriers among Latina immigrants. They will elucidate the characteristics of intervention studies that focus on IPV-related risk and protective factors while enhancing access to information and support. The findings will constitute a valuable repository of knowledge and evidence, illustrating effective strategies for rigorous and methodologically diverse interventions, particularly in light of a rapidly evolving immigration landscape.

Acknowledgments

The authors acknowledge all individuals who were consulted or involved in this study.

Data Availability

Data related to the search strategy for this review are provided in Multimedia Appendix 1. All data generated or analyzed, including the PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analyses) flowchart, will be provided as multimedia appendices. The databases compiled during data extraction are available upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy report.
[DOCX File , 43 KB - resprot_v14i1e76996_app1.docx]

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Abbreviations

DISARS: Domains of IPV Service Access Rating Scale
IPV: intimate partner violence
PICOS: population, intervention, comparison, outcomes, and study design
PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analyses Protocol

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Protocol

Effectiveness and Safety of Tuina Therapy Combined With Yijinjing Exercise for Neck Pain: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Neck pain with high incidence and recurrence rates significantly impairs patients' quality of life and imposes a considerable economic burden. Traditional Chinese medicine therapies such as Yijinjing exercise and Tuina have shown promising efficacy in alleviating the local symptoms of neck pain. However, there is currently insufficient high-level evidence to robustly support these findings.

Objective: This study aims to evaluate the efficacy and safety of combining Yijinjing exercise with Tuina for the treatment of neck pain.

Methods: PubMed, Cochrane Library, Embase, Web of Science, China National Knowledge Infrastructure, Chinese Biomedical Database, VIP Chinese Science and Technology Periodicals Full-Text database, and Wanfang database will be systematically searched for all relevant randomized controlled trials (RCTs) from their inception to September 2025, without language or publication status restrictions. The Cochrane Risk of Bias 2 assessment tool will be used to evaluate the risk of bias in the included studies, and the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) system will be employed to grade the quality of evidence. Heterogeneity will be evaluated through I^2 statistics and Cochran's Q test: a fixed-effect model will be used when $I^2<50\%$ and $P\geq.01$. If $I^2\geq50\%$ or $P<.01$, subgroup analysis will be conducted. When heterogeneity still exists, sensitivity analysis or exploratory subgroup analysis will be performed. If it cannot be explained ultimately, the random-effects model will be adopted and the GRADE evidence level will be reduced.

Results: As of June 2025, we have completed the preliminary screening of titles and abstracts for 573 studies. The full-text screening is expected to be completed by September 2025, and data analysis is planned to be completed by December 2025. About two-thirds of the studies were published after 2015. Geographically, the samples in the studies were highly concentrated in Asia. The results were comprehensively developed around the core outcomes. The primary outcome was presented by changes in the visual analog scale. The secondary outcomes were evaluated by the neck disability index, self-rating anxiety scale score, mean vertebral artery blood flow velocity, and Cobb angle.

Conclusions: If the results of this study confirm the effectiveness of massage combined with Yijinjing, it can provide a direction for the nonpharmaceutical treatment of neck pain. However, some studies have risks of bias such as insufficient standardization of massage operations and difficulty in implementing blinding methods. The expected heterogeneity is significant due to differences in intervention plans and patients' cultural backgrounds, and the original RCTs are few and regionally concentrated, with limited extrapolation of conclusions. In the future, it is necessary to optimize the plan and supplement data through high-quality multicenter research to enhance reliability.

Trial Registration: PROSPERO CRD420251026508; https://www.crd.york.ac.uk/PROSPERO/view/CRD420251026508

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International Registered Report Identifier (IRRID): DERR1-10.2196/77864

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KEYWORDS

massage; traditional Chinese exercise; cervical spondylosis; systematic review; meta-analysis

Introduction

Neck pain is the fourth leading cause of disability, with an annual prevalence of over 30% [1-3]. By 2050, the number of neck pain cases is projected to reach 269 million worldwide due to population growth and aging [4]. After the early acute neck pain ends, about half of the patients still have recurrent frequent pain [5]. The etiology and pathogenesis of neck pain are multifactorial, primarily associated with muscle strain, soft tissue injury, cervical facet joint disorders, and cervical disc degeneration [6,7]. The clinical symptoms and signs of neck pain are complex; therefore, its therapy often involves comprehensive intervention of multiple disciplines, but there is no complete unified treatment method [8,9]. Combination therapy is commonly used in the clinical treatment of neck pain, including medication, acupressure, cervical region exercises, psychological counseling, acupuncture, laser therapy, or traction [10]. Moreover, clinical treatment combined with functional exercise is absolutely necessary for neck pain [11,12].

Tuina, a form of manipulative therapy, is widely utilized in China for neck pain management due to its efficacy, cost-effectiveness, and noninvasiveness [13,14]. Tuina for the treatment of soft tissue injury and spinal degeneration has a wide range of effects such as reducing inflammation and swelling, separating adhesions, enhancing microcirculation, relieving spasm, alleviating pain, correcting small joint disorders, and improving the subhealth state [15,16]. Yijinjing is a traditional Chinese exercise that enhances the motor function and flexibility of the limbs through breathing and slow movements, reduces pain caused by joint pathology and stress [17,18], and helps in the later stages of recovery from several illnesses such as cardiovascular, psychiatric, and respiratory disorders [19,20]. For patients with neck pain, Yijinjing can regulate the muscle groups and improve skeletal muscle contraction and ligament strength, thus promoting blood circulation and achieving pain improvement. Following the completion of Tuina, instructing patients to perform Yijinjing exercise at home may enhance the therapeutic efficacy for neck pain and alleviate psychological issues such as anxiety and depression associated with prolonged pain [21,22]. Additionally, active participation in rehabilitation exercises can help patients build confidence in managing their condition, fostering a more positive attitude toward coping with neck pain [23,24].

At present, the combination of massage and Yijinjing exercise for the treatment of neck pain has been widely applied in clinical practice. Multiple clinical observations suggest that it has potential in relieving pain and improving cervical spine function [25]. However, the existing evidence system has obvious deficiencies. A search of the Cochrane Library, PubMed, and Chinese databases revealed that systematic reviews on neck pain mostly focused on single therapies and did not cover the abovementioned combination regimens [13,26]. To the best of our knowledge, to date, there is no systematic review or meta-analysis on the combination of massage and Yijinjing, and there is a lack of high-quality clinical research to support its safety and efficacy [27]. This evidence gap makes it difficult to fully verify its clinical value and limits its standardized application in clinical practice. To this end, this study intends to strictly screen the literature (only including randomized controlled trials [RCTs]), use the Cochrane Risk of Bias (RoB2) tool to evaluate the quality of the study, and apply the GRADE (Grades of Recommendation, Assessment, Development, and Evaluation) system to grade the strength of evidence, aiming to comprehensively and objectively integrate the clinical efficacy and safety of this combination therapy. We also aim to make up for the deficiencies of the existing studies [5,28] in the evaluation of combination regimens, methodological rigor, and evidence integration and to provide reliable evidence-based basis for clinical decision-making.

Methods

Study Registration

This systematic review protocol was developed following the guidelines of PRISMA-P (Preferred Reporting Items For Systematic Reviews and Meta-Analyses Protocols) (Multimedia Appendix 1). It has been registered in the PROSPERO database (registration CRD 420251026508). This protocol provides detailed descriptions focusing on research criteria, database selection, data collection, and bias assessment to ensure that the systematic review is objective, fair, transparent, and reproducible. The protocol will be updated on the PROSPERO database in the event of any methodological changes.

Ethics and Dissemination

The required data will be obtained from published studies rather than from patients; therefore, ethical approval is not required for this study. The results of this systematic review will elucidate the efficacy and safety of Tuina combined with Yijinjing for the treatment of neck pain, which facilitates clinicians to make treatment decisions.

Inclusion Criteria

The inclusion criteria will be determined using the PICOS (Population, Intervention, Comparison, Outcomes, and Study design) framework.

Population

The individual participants are aged between 20 and 70 years, with a visual analog scale (VAS) score over 3 points, a neck disability index (NDI) score over 10 points, and with no history of shoulder or neck surgery. The inclusion criteria were set at an age range of 20 to 70 years, as the cervical vertebrae of those

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younger than 20 years are still developing, and the causes of pain are different from those of middle-aged and older adults. People older than 70 years often have underlying diseases, which can easily interfere with the assessment. A VAS score greater than 3 indicates that pain significantly affects function and quality of life and can be used as a basis for evaluating treatment effects and clinical intervention. An NDI score greater than 10 indicates that the patient's daily activities are restricted, which is in line with the core objective of the research to assess the impact of neck pain on life status. Having no history of shoulder and neck surgery can avoid the anatomical and physiological changes caused by surgery and the interference of complex pain mechanisms, thereby accurately determining the relationship between intervention measures and primary neck pain.

Intervention

Patients in the experimental group performed Tuina therapy combined with Yijinjing exercise at least once a week.

Comparison

Patients in the control group only received Tuina therapy.

Outcome

The primary outcome was the change in the VAS score after the intervention. Secondary outcomes encompassed the NDI score, self-rating anxiety scale score, average vertebral artery flow velocity, and Cobb angle. The Cobb angle, defined as the angle formed between the vertical lines of the lower endplates of C2 and C7 on the lateral cervical radiograph, serves as the standard for quantifying and monitoring scoliosis progression.

Study Design

The design of the study was an RCT of Tuina combined with Yijinjing for neck pain, regardless of sample size, publication status, or language.

Exclusion Criteria

Non-RCTs, including reviews, case reports, observational studies, conference papers, and duplicate reports, are excluded. Patients with specific cervical spine conditions such as nerve root injury or spinal cord injury, pregnant or breastfeeding women, those who experienced major trauma or tumor-related major diseases, those unable to communicate verbally, those who develop adverse reactions to Tuina and Yijinjing, those who are unable to cooperate with the treatment, or those who refuse to self-exercise are excluded.

Search Strategy

According to the inclusion criteria, PubMed, Cochrane Library, Embase, Web of Science, China National Knowledge Infrastructure, China Biomedicine database, VIP Chinese Science and Technology Periodicals Full-Text database, and Wanfang Data Knowledge Service Platform will be searched for RCTs published from database inception to September 2025. The search strategy combines P + I + S blocks by using medical subject headings (MeSH) and text words, with "OR" logic for broader scope and "AND" logic for precision. To obtain the latest evidence, the research team will reconduct the search at 1 month before submission and extend the timeline to include studies published before this date. PubMed search terms are provided in Table 1.

Table 1. PubMed search terms.

Search block	Search items
Participants	"Neck pain [MeSH[a] Terms]" OR "Nonspecific neck pain [Title/Abstract]" OR "Neck pain [Title/Abstract]"
Intervention	"Yijinjing [MeSH Terms]" OR "Yijinjing [Title/Abstract]" OR "Chinese medicine exercise [Title/Abstract]" OR "Tuina [Title/Abstract]" OR "Massage [Title/Abstract]" OR "Chinese massage [Title/Abstract]"
Study design	"Randomized controlled trial [Title/Abstract]" OR "Controlled clinical trial [Title/Abstract]" OR "Clinical trial as topic [MeSH Terms]" OR "Randomized [Title/Abstract]" OR "Randomly [Title/Abstract]" OR "Trial [Title/Abstract]"

[a]MeSH: medical subject headings.

Study Selection and Data Extraction

Study Selection

Two researchers (JS and JL) will independently screen studies, removing duplicates and ineligible studies based on titles and abstracts. The screening of differences is resolved through the following process. First, JS and JL negotiate and reach a consensus by comparing the inclusion and exclusion criteria with the original text. If the negotiation fails, the case will be submitted to a senior supervisor (YZ) with over 10 years of experience in traditional medical research. The arbitration will be based on the consensus in the field and the research design. The basis for the arbitration needs to be recorded and archived. If there are still disputes, the research team will be organized to hold a special meeting, collectively discuss and determine the plan, and form meeting minutes for retention. The PRISMA flow diagram illustrates the selection process (Figure 1).

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Figure 1. PRISMA (Preferred Reporting Items For Systematic Reviews and Meta-Analyses) flow diagram of this study. CBM: Chinese Biomedical Database; CNKI: China National Knowledge Infrastructure; VIP: VIP Chinese Science and Technology Periodicals Full-Text database.

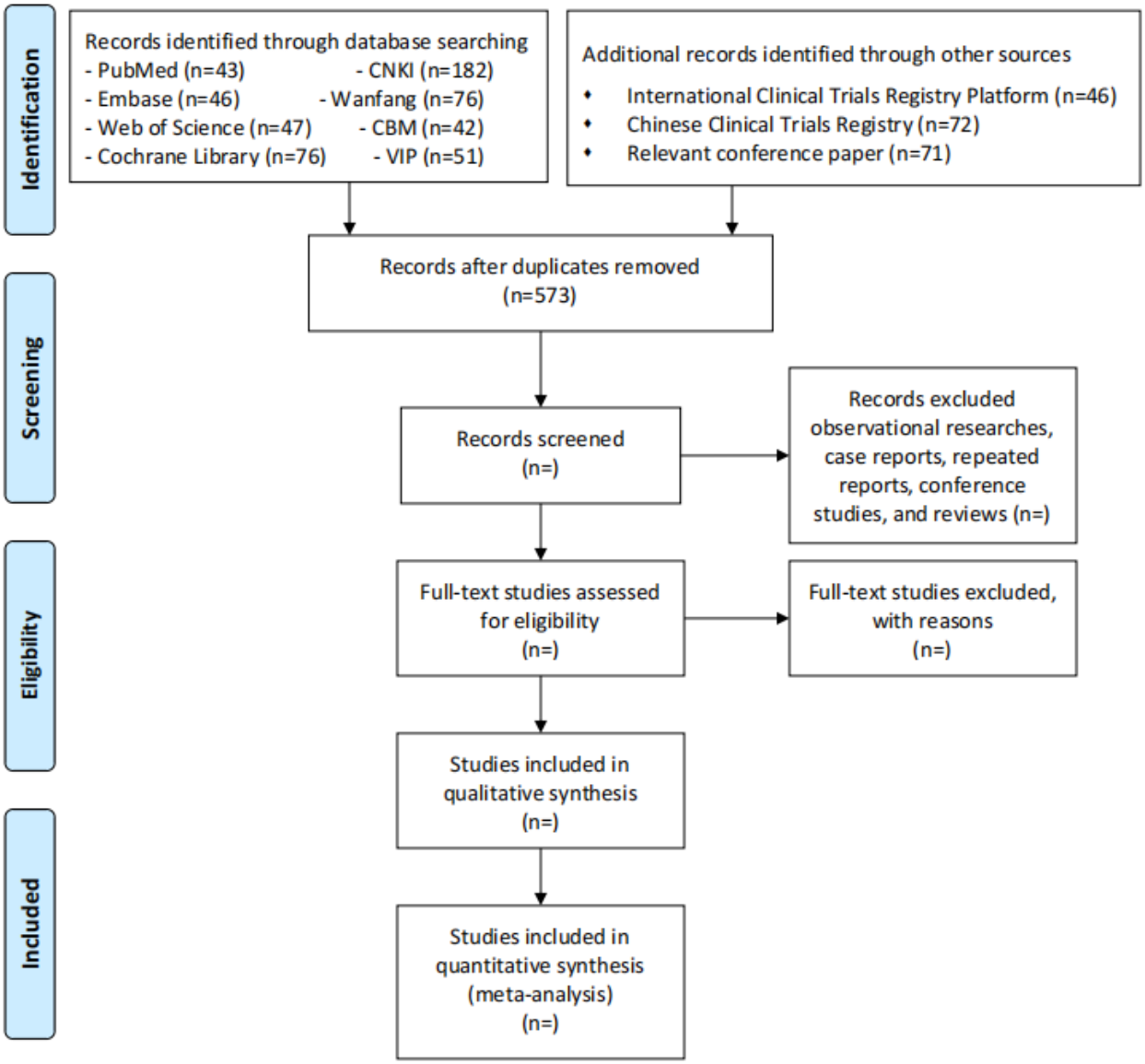

Data Extraction

During the data extraction stage, we will use a structured table system to collect key information that may cause methodological differences across studies. Massage techniques need to record item by item the type of technique (rolling method, pressing method, etc), application site (cervical pinch muscle, Fengchi point, etc), force level (light, moderate, heavy), operation frequency (times per day or times per week), and the duration of each session (minutes). The Yijinjing plan covers core movement combinations (such as Weituo Presenting the Pestle and Zhaixing Changing the Dou), practice time, frequency, and guidance form (professional guidance or self-study) and uniformly adopts classification by continuous or grade coding to achieve standardized recording. Data will be extracted using NoteExpress and Excel by 2 independent researchers (YL and HS) and stored in a spreadsheet. Extracted data include authors, publication year, patient demographics, study population, interventions, and outcomes. In case of any disagreement during the execution process, the 2 execution personnel will first negotiate together. If no agreement is reached through negotiation, it will be submitted to a senior supervisor (YZ) with over 10 years of experience in traditional medical research. The supervisor will arbitrate based on the consensus in the field or the requirements of the research design, clarify the arbitration basis, and file it. If there are still disputes after arbitration, the research team will be organized to hold a special meeting, determine the final plan through collective discussion, and form meeting minutes for retention.

Risk of Bias Assessment

Two reviewers (SY and QY) will use Cochrane RoB2 to assess the risk of study bias and conduct a 3-level determination of low risk, partial risk, and high risk referring to the tool manual in 5 areas: randomization process, deviation from expected intervention, missing outcome data, outcome measurement, and selective reporting of results. The GRADE system was applied to grade the quality of evidence. Before the evaluation, 3

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literature pretrials were conducted for calibration (target κ≥0.80). During the evaluation, factors such as the risk of bias, consistency, accuracy, and publication bias were independently and blindly evaluated. The quality of evidence was classified into 4 levels: high, medium, low, and very low. In case of disagreement, third-party arbitration was conducted.

In certain circumstances such as a large effect size, a clear dose-response relationship, or a scenario where all plausible biases would attenuate the effect estimates, the quality of evidence may be upgraded. For instance, if several included studies demonstrate a very large effect size or if an increase in the frequency or intensity of Yijinjing practice is associated with an increase in pain relief, these scenarios may support an upgrade in the quality of evidence. The quality of evidence is often downgraded due to factors such as research limitations, inconsistent results, circumstantial evidence, and publication bias. The quality of the evidence will also be downgraded if more than half of the studies have a high risk of bias in the Cochrane RoB2 assessment; if heterogeneity remains significant after subgroup analysis (I^2≥50% and Cochran's Q test P<.01) and cannot be explained by clinical factors; if there are large differences in study populations, interventions, and the target question; or if obvious publication bias (eg, asymmetric funnel plots or failure to report negative results) is present.

Disagreements are resolved through discussion or third-party adjudication (JW). Before the formal evaluation, some randomly selected studies will be pre-evaluated to unify the evaluation criteria. The data from the included studies will be used for subsequent meta-analysis or bias risk analysis. Further, the bias risk assessment results of all the included studies will be presented in the form of tables or charts.

Statistical Analysis

Data analyses will be performed using Review Manager (RevMan) 5.4. For continuous outcome measures (such as VAS score and NDI score), the mean difference and 95% CI are calculated. Heterogeneity is evaluated using the I^2 statistic and Cochran's Q test. If I^2<50% and Cochran's Q test P≥.01, it indicates that heterogeneity can be ignored, and the fixed-effect model is used to combine the effect size. If I^2≥50% or Cochran's Q test P<.01, indicating substantial heterogeneity, stratified analysis will be conducted according to the preset subgroups. Subgroups include (1) characteristics of intervention implementation, such as the frequency of Yijinjing training (≥2 times/week vs <2 times/week) and massage treatment courses (<4 weeks vs ≥4 weeks); (2) population characteristics such as disease duration (<3 months vs ≥3 months), age (20-40 years vs 41-70 years), and NDI baseline score (10-20 points vs >20 points); and (3) study methodological characteristics such as blinding quality (double-blind/single-blind vs nonblind) and sample size (<100 cases vs ≥100 cases). The fixed-effect model was preferred within the subgroups. If in a subgroup I^2<50% and Q≥0.1 but the clinical or methodological differences remain significant, a sensitivity analysis with item-by-item exclusion should be conducted first. After discovering new sources of heterogeneity, exploratory subgroups are established and labeled as post-hoc analyses. If heterogeneity still cannot be explained, a random-effects model will be adopted, and the evidence level will be downgraded according to GRADE.

Multiple Test Correction

To control the risk of type I errors caused by multiple tests, in this study, the Bonferroni correction strategy is adopted for the intergroup difference analysis of 5 secondary outcome indicators (NDI score, self-rating anxiety scale score, average vertebral artery flow velocity, and Cobb angle). If the interaction effect test is included in the subgroup analysis, the same correction method must also be applied based on the actual number of tests.

Suppose significant heterogeneity still exists after subgroup analysis (I^2≥50% and Cochran's Q test P<.01), sensitivity analysis will be conducted. The stability of the results will be evaluated by eliminating low-quality studies (determined as high-risk bias based on the Cochrane RoB tool), excluding small sample studies (sample size <50 cases) or using the leave-one-out method to eliminate individual studies one by one, recalculating the combined effect size. If heterogeneity remains unresolved after sensitivity analysis, a metaregression will be conducted using the metareg command in Stata software to explore the contribution of the continuous variables (such as the average age of patients, disease duration, and intervention frequency) to heterogeneity. The significance of the covariates is determined by P<.05.

Publication Bias

If fewer than 10 RCTs are included, publication bias will be assessed using funnel plots. If more than 10 RCTs are included, Egger regression test will be used for the quantitative analysis.

Results

This systematic review was funded in August 2024. Starting from December 2024, specific databases were used for study retrieval: PubMed, Cochrane Library, Embase, Web of Science, China National Knowledge Infrastructure, Chinese Biomedical Database, VIP Chinese Science and Technology Periodicals Full-Text database, and Wanfang database. As of June 2025, after the initial search and deduplication, a total of 573 studies have entered the title and abstract screening stage. The full-text screening is expected to be completed by September 2025. Subsequently, rigorous data extraction and quality evaluation will be conducted. Data analysis is planned to be completed in December 2025. RevMan will be used in combination with the GRADE system and the RoB 2.0 tool to complete the quantitative synthesis of outcome measures and the grading of evidence quality.

A preliminary review of 573 search records revealed that previous research mainly focused on nonpharmaceutical interventions: approximately 45%-50% explored massage only, about 5%-8% used Yijinjing only, and less than 5 RCTs focused on the combination of massage and Yijinjing. Rest of the studies include acupuncture and exercise therapy. In terms of the time trend, approximately two-thirds of the studies were published after 2015. At the geographical level, about two-thirds of the studies were from Asia (especially China), <30% of the studies

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were from Europe and America, while there were relatively scarce number of studies from Africa and South America. The above distribution indicates that the original RCTs of this combined intervention are scarce and regionally concentrated, further supporting the necessity of this systematic review.

Discussion

Neck pain is a globally prevalent chronic pain condition with high prevalence and recurrence rates that significantly impair patients' quality of life. Currently, various therapeutic approaches are used to treat neck pain; yet, no standardized therapy has been established [29]. Common treatments include pharmacotherapy, physiotherapy, massage, acupuncture, and exercise [30]. In modern clinical medicine, nonsteroidal anti-inflammatory drugs combined with physical therapy are usually used to treat neck pain through analgesic and anti-inflammatory effects. However, long-term administration of nonsteroidal anti-inflammatory drugs may cause gastrointestinal discomfort and other adverse reactions. Additionally, this approach demonstrates definite therapeutic efficacy for acute neck pain conditions such as trauma or acute sprain. As for chronic neck pain and cases with complex symptoms, clinical practice often employs multimodal nonpharmacological therapies, including acupressure, psychological counseling, acupuncture, laser therapy, or traction [31]. Notably, traditional Chinese medicine therapies are widely used to treat neck pain because of their noninvasiveness, low toxicity, minimal side effects, and significant clinical efficacy [28,32].

Although there are several therapies available for neck pain, the treatment of neck pain still presents significant challenges. Due to the large individual differences of various treatment methods among patients with neck pain, the improvement of cervical pain symptoms in some patients is limited [33,34]. Tuina fully implements the traditional Chinese medicine concept of "blockage causes pain, while patency relieves pain" through the manipulation of soft tissue release and joint reduction. Its primary advantage resides in the capacity for immediate physical intervention, which directly releases local tissue adhesion and addresses mechanical disorders through manipulation, thereby rapidly alleviating pain symptoms. However, a few manipulation therapies in Tuina have inherent risks, for instance, cervical manipulation may worsen neck pain or cause damage to the vertebral arteries [35]. In addition, current treatment programs often overemphasize physician-led interventions and overlook the importance of patients' self-exercise and timely feedback on treatment effects [36,37]. Therefore, effective therapies such as Tuina combined with self-exercise may provide better results for patients with neck pain. Different from modern self-exercise, traditional Chinese Yijinjing exercise with simplicity and wide applicability is suitable for patients of all ages with neck pain and will not be limited by environment and equipment [38,39]. As a representative of traditional Chinese dynamic exercises, the Yijinjing exercise has achieved continuous functional reshaping through a 3-in-1 intervention model of regulating the body, breath, and mind. This exercise method can effectively optimize the biomechanical state of the cervical vertebrae and play a regulatory role in neural regulatory function. Previous studies have proved that the combination of deep breathing and Yijinjing exercise can relieve neck muscle tension, promote blood circulation, and greatly improve patients' negative emotions [40,41]. In addition, Yijinjing exercise combined with Tuina treatment can accelerate rehabilitation and improve the outcomes of patients with neck pain through a synergistic effect.

This study may encounter significant cross-trial heterogeneity, especially at the level of operational standardization of traditional therapies. The variations in massage techniques, force, body parts, and treatment courses can be as high as over 30%, and such operational differences may directly lead to systematic deviations in the evaluation of therapeutic effects. There are also significant differences in the guidance intensity, practice frequency, and compliance monitoring of Yijinjing, which may dilute or exaggerate the aggregated effect size. More crucially, the operator-dependent characteristics of traditional therapies are not limited to technical differences: the clinical experience of massage therapists and their ability to dynamically adjust to individual patient differences are both difficult to fully control through existing standardized means. This operational variability may lead to an increase in the amplitude of effect size fluctuations among studies (the expected I^2 value may exceed 50%), and even with subgroup analysis or sensitivity analysis, it may still be impossible to completely eliminate its interference with the pooled results. Furthermore, this heterogeneity will directly limit the generalizability of the research conclusions. The intervention programs implemented by highly skilled massage therapists may have significantly higher effects than those in community medical institutions. Moreover, the differences in patients' acceptance of traditional therapies from different cultural backgrounds (for instance, Asian patients may have a higher compliance with massage than those in Europe and America) further increase the difficulty of extrapolating the results. All these factors suggest that the meta-analysis results of this study should be interpreted with caution. The pooled effect size is more suitable as a theoretical reference value rather than a uniform clinical practice standard.

Acknowledgments

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Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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Authors' Contributions

Conceptualization: SY, JW, YL
Data curation: JS, JL
Formal analysis: HS, QY
Resources: JW, JS
Software: SY, JW
Writing – original draft: SY, QY
Writing – review & editing: GW, YL, YZ

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P checklist.
[DOCX File , 30 KB - resprot_v14i1e77864_app1.docx]

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Abbreviations

GRADE: Grades of Recommendation, Assessment, Development, and Evaluation
MeSH: medical subject headings
NDI: neck disability index
PICOS: Population, Intervention, Comparison, Outcomes, and Study design
PRISMA-P: Preferred Reporting Items For Systematic Reviews and Meta-Analyses Protocols
RCT: randomized controlled trial
RoB 2: Risk of Bias 2
VAS: visual analog scale

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Protocol

Prevalence and Associated Risk Factors of Self-Harm Among Health Care Workers: Protocol for Systematic Review and Meta-Analysis

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Abstract

Background: Self-harm is a major public health concern, with prevalence increasing worldwide, particularly after the COVID-19 pandemic and associated lockdown restrictions. Health care workers (HCWs) face various challenges, such as pressures of social and familial responsibilities, a lack of integration within the profession, heavier workload, bullying at the workplace, and limited support in the workplace, that impact their mental health and often lead to self-harm.

Objective: We aim to synthesize the evidence on the pooled prevalence of self-harm worldwide and identify risk factors for self-harm among HCWs.

Methods: We will conduct a systematic review of observational and experimental studies that investigated the overall prevalence of self-harm among HCWs. We will search the PubMed, PsycINFO, Embase, and CINAHL databases for eligible articles from inception until March 2025 using specific search terms developed using the population, exposure, comparison, and outcome framework. Study selection and reporting will follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and the Meta-Analysis of Observational Studies in Epidemiology guidelines. We will contact the corresponding author via email if the required data are not available in the article. After completing the article search, duplicate records will be removed. Titles and abstracts will then be screened according to the inclusion and exclusion criteria, followed by retrieval of the full texts for detailed screening. All the required data for the review, such as names of authors, publication year, prevalence of self-harm, type of profession, associated risk factors to self-harm, and others, will be extracted using a standardized data extraction form. The quality of the studies will be assessed using the Joanna Briggs Institute guidelines based on the study design. Random-effects meta-analysis will be used to derive the pooled prevalence using Stata (version 17.0) software. We will conduct a subgroup meta-analysis on sex, regions, and the type of profession (physicians or nurses). We will also examine the association of risk factors of self-harm with sociodemographic factors to observe their relationship. Both analyses will be performed using RevMan software. Publication bias will be examined using the funnel plot and Egger test.

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Results: Data analysis is expected to be completed by August 2025, and manuscript preparation is expected to be completed by October 2025. This review is expected to be completed and published by January 2026.

Conclusions: We will provide a comprehensive synthesis of the overall prevalence of self-harm among HCWs. We will also provide important information to develop effective strategies for preventing and managing self-harm among HCWs.

Trial Registration: PROSPERO CRD42024581791; https://www.crd.york.ac.uk/PROSPERO/view/CRD42024581791

International Registered Report Identifier (IRRID): PRR1-10.2196/67059

(JMIR Res Protoc 2025;14:e67059) doi:10.2196/67059

KEYWORDS

self-harm; health care workers; protocol; systematic review; meta-analysis

Introduction

Background

Self-harm refers to the deliberate initiation of behaviors, for example, self-cutting, with the intention of causing harm to oneself [1]. It is also reported as an early manifestation of suicide [2] or a short-term risk factor for future attempted and completed suicide [3]. Self-harm tends to be underreported, although this issue affects countries and societies worldwide [4]. It had been reported that in 2015, approximately 575,000 people attended a hospital for injuries due to self-harm in the United States [5]. During the COVID-19 pandemic in 2021, an increase in psychiatric illness cases [6] was observed, where the cases were different based on the working categories. This was due to the loss of jobs and struggle for income among the low socioeconomic group [7]. This led to an increase in depression; anxiety; insomnia; substance abuse; and fear of contagion, losing loved ones, and transmitting infection to loved ones. These factors have contributed to an increased chance of self-harm [8].

Medical and health professionals or health care workers (HCWs) are often required to work for an extended time, which may contribute to long-term stressful work conditions, affecting both physical and mental health. In addition, moral injury was reported to be significantly associated with the risk of self-harm among HCWs, manifesting as symptoms of self-guilt, self-denial, self-blame, sadness, and anger [9]. Besides that, an unprecedented workload, tension in physician-patient relationships, and moral distress led to a higher risk of burnout and moral injury to HCWs. Therefore, addressing the high level of psychological impact and self-harm ideation in this population is crucial and has become an important public health concern that affects all sectors of society [9]. Before the pandemic, HCWs were reported to have higher rates of depression, anxiety, traumatic stress conditions, suicidal ideation, and self-harm compared to the general population, and the prevalence increased during the COVID-19 pandemic [10]. For example, the prevalence of self-harm among HCWs during the COVID-19 pandemic was 46.9% in Australia [7], 38% in China [9], and 13% in the United Kingdom [11]. The prevalence of self-harm among HCWs was reported to be 5.3% before the pandemic compared to 9.3% after the pandemic [12,13].

This shows that the issue of HCWs and self-harm has become an important public health concern that affects all sectors of society [14]. Although a few reviews have reported on self-harm among HCWs, no single systematic review has reported on this issue during, before, and after the COVID-19 pandemic. This comparison is needed as it was previously stated in a few articles [7,9,11] that the increase in prevalence of self-harm among HCWs after the impact of the COVID-19 pandemic is a growing concern for suicide risk among HCWs.

This Study

Therefore, we will conduct a systematic review and meta-analysis to synthesize the evidence on the global overall or pooled prevalence of self-harm and risk factors associated with HCWs. We will also perform subgroup analyses based on professional groups, geographic regions (Asia, Africa, Europe, Oceania, and North and South America), and settings (urban vs rural). Furthermore, we seek to identify the associated risk factors of self-harm among HCWs. The findings will be used to identify further research and prevention efforts.

Methods

Study Design

This protocol is registered with PROSPERO (CRD42024581791). The review will be conducted and reported following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analysis) protocol [15] and Observational Studies in Epidemiology guideline.

We will include all empirical study designs, including observational, for example, case-control, cohort, and cross-sectional, to capture all desired outcomes. No restrictions will be imposed on the date of publication and sample size.

Study Area

We will include all published studies with information on self-harm among HCWs globally and later divide the studies according to the regions and ages. The period before the COVID-19 pandemic is defined as the period before March 2020. We will examine the methodology section to determine when the data collection occurred. Conversely, the period after the COVID-19 pandemic refers to the period following March 2020.

Type of Participants

We will include primary studies that investigated self-harm or nonsuicidal injury (or other synonyms) among HCWs aged 18 years and above. In addition, if the required data are not

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available in the article, we will contact the corresponding author to obtain clarification and data from that article.

We will exclude studies that do not involve HCWs and include participants aged less than 18 years. If a study includes medical students, their data will also be excluded from this study due to different work responsibilities. If we find multiple articles with the same data, then we will use the study with the largest sample size. The findings will be presented in tables and figures.

Type of Outcome Measures

The primary outcome will be the pooled prevalence of self-harm among HCWs before and after the COVID-19 pandemic. The secondary outcomes will be the risk factors associated with self-harm based on the 3 domains: psychological factors, work-related factors, and personal factors.

Searching Methods for the Identification of Studies

We will search the articles in 4 different databases: PubMed, PsycINFO, Embase, and CINAHL for any eligible articles from inception until July 2025. There is no restriction on the publication date; however, the language will be restricted to English. We will include primary studies and exclude conference proceedings, abstracts, editorials, and comments. We will include studies discussing self-harm among HCWs only.

Search Strategy

The population, exposure, comparison, and outcome framework will be used during the article search. “Population” refers to HCWs (physicians and nurses), “exposure” refers to self-harm or nonsuicidal self-injury, and “outcome” refers to the prevalence and risk factors associated with self-harm among HCWs. The “comparisons” aspect is not included in this review. “OR” will be used to widen the keyword search and “AND” to narrow the search. The details of the proposed search terms for all the databases are listed in Table 1 and Multimedia Appendix 1.

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Table 1. Detailed proposed search terms for all databases.

Number	Search terms
#1	Health care worker*
#2	Health care staff*
#3	Health care professional*
#4	Health care provider*
#5	Health care personnel*
#6	HCW
#7	Nurse*
#8	Doctor*
#9	Physician*
#10	Surgeon*
#11	Therapist*
#12	Houseman
#13	House officer
#14	Medical officer
#15	nurs*
#16	midwi*
#17	registered nurse
#18	RN
#19	licensed practical nurse
#20	LPN
#21	Medical assistant*
#22	Paramedic*
#23	Pharmacist*
#24	hospital staff*
#25	General practitioner*
#26	GP
#27	Frontlin*
#28	Employer*
#29	Employee*
#30	Medical personnel*
#31	Medical professional*
#32	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31
#33	self overdos*
#34	Deliberate self harm
#35	DSH
#36	Self inflict*
#37	Self harm*
#38	Self mutilat*
#39	Self poison*
#40	Self injur*
#41	automutilat*

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Number	Search terms
#42	ligature strangulate*
#43	self hurt*
#44	self lacerat*
#45	self strang*
#46	self hang*
#47	self neglect*
#48	self destruct*
#49	self immolat*
#50	self violen*
#51	Self-Injurious Behav*
#52	#33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51
#53	Prevalen*
#54	incidence
#55	Number of cases
#56	Risk factor*
#57	Associated factor*
#58	Predisposing factor*
#59	Factor*
#60	Predictor*
#61	Financial problem
#62	Marital status
#63	Family crisis
#64	Family problem
#65	Mental health problem
#66	Work related problem
#67	Physical health problem
#68	Substance use problem
#69	Alcohol problem
#70	Drug problem
#71	Poor support system
#72	#53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67 OR #68 OR #69 OR #70 OR #71
#73	#32 AND #52 AND #72

Data Collection and Analysis

Selection of Studies

Three review authors (NAM, TPNTBS, and NHJ) will independently screen for titles and abstracts to identify the potential studies to be included. The studies will be identified and coded as “retrieve” (studies to be included, with potential to be included, or unclear) or “do not retrieve” (studies to be excluded). We will also identify and exclude duplicate studies. If there is an overlap in the included studies, the authors will read the methods section of the article. If the methods or included participants are different, the study will be included in this review. However, if the studies include similar populations, 1 study will be excluded after discussing among the authors. Three authors (NHM, NAFNA, and FNL) will retrieve the full texts and review them against the inclusion and exclusion criteria, along with the justifications. We will resolve any disagreement between the 2 reviewers via discussion or rechecking the full text. If a consensus is not reached, a third author (NAM) will deliberate.

We will record the selection process in sufficient detail to complete a PRISMA flowchart [15,16], as shown in Figure 1.

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This review will use the Mendeley reference management software (Elsevier) [17] to store, arrange, and manage all articles identified from the databases.

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart.

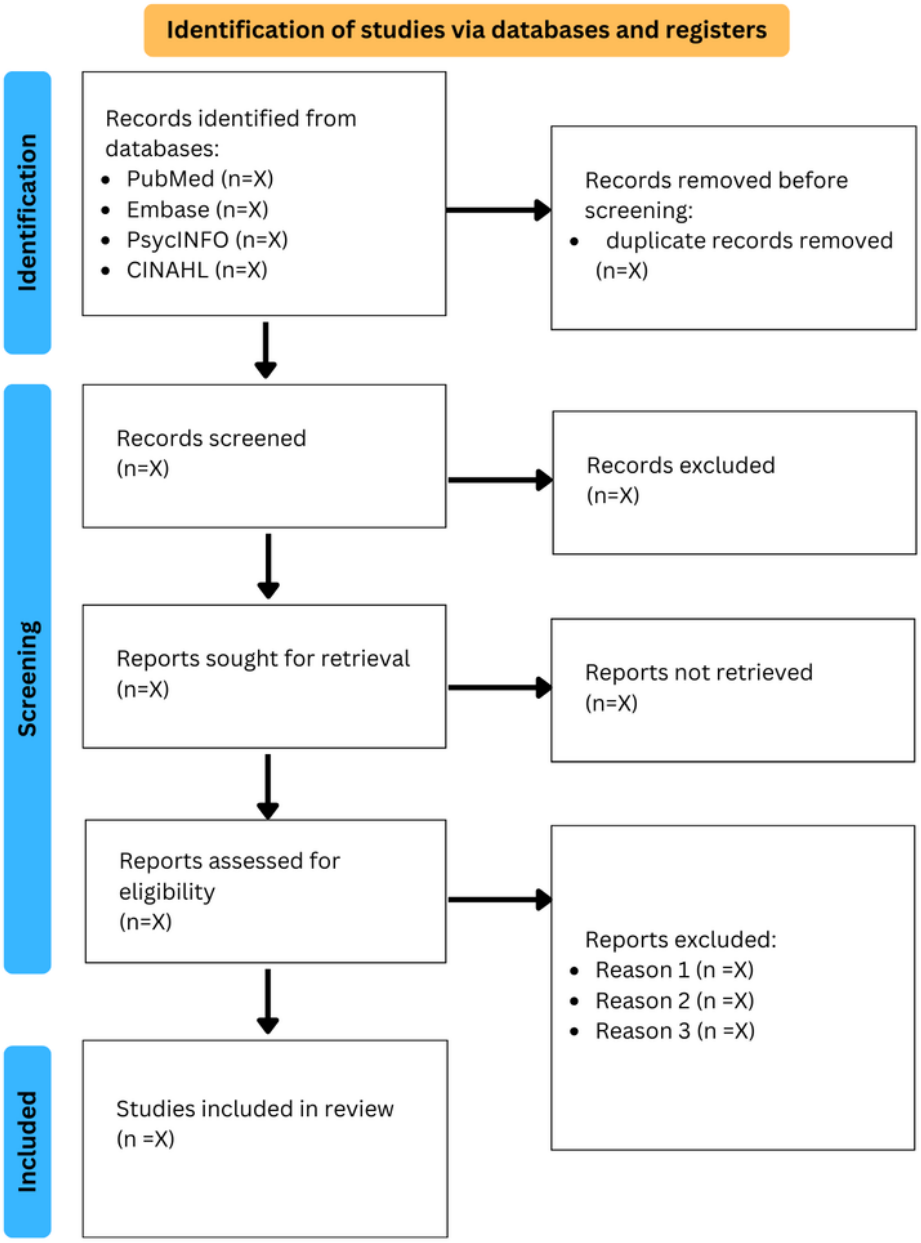

Data Extraction and Management

We will use a standardized data extraction form created in an online Microsoft Excel spreadsheet for study characteristics and outcome data. Two review authors (IAR and FNL) will independently extract the data from the included studies. If there is any disagreement on the data extraction, both authors will discuss and consult with another author (NAM). We will extract the following study characteristics from the included studies:

1. Article information: authors, year, title, country, and region.
2. Participants: total number of participants, age, sex, and history of psychiatric and any other morbidity disease.
3. Methods: study design and health care settings (primary care, hospital, or community).
4. Analysis: score from the questionnaire will be used to identify self-harm among respondents, prevalence will be reported, and factors associated with self-harm among HCWs will be discussed.

Quality Assessment

The study's quality will be evaluated using the Joanna Briggs Institute's (JBI's) checklist by 3 review authors (NHM, TPNTBS, and NHJ) independently. If a consensus is not reached after discussion and reading back the article together, a third author (NAM) will deliberate. Multiple JBI scales will be used, as numerous types of observational studies will be included in this review, such as cross-sectional, case-control, and cohort studies. The overall appraisal of articles with the potential to be included will be defined either to include, exclude, or seek further information [18] based on the average answer evaluated

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by the 3 review authors. Each criterion with the answer "yes" will be accorded 1 point, and the cut-off point for being included, excluded, and seeking further information will be discussed among all authors. Articles with poor scores will be excluded from this review. The findings will be summarized in a table format. The details of this assessment, based on the criteria of the JBI checklist, will be listed in a Multimedia Appendix 1.

Statistical Analysis

Data will be analyzed using Stata (version 17.0; StataCorp) and RevMan (Cochrane) softwares. If there are missing data, the review author will contact the corresponding author to obtain the data. The study will be divided into 3 groups: overall, before, and after the COVID-19 pandemic, as we assume that there might be a difference in terms of overall prevalence as well as the risk factors associated with self-harm among HCWs.

We will segregate the data based on profession, such as physicians, nurses, and others. If the article does not mention the HCWs' profession, the included sample will be referred to as "HCWs." If the included articles mix the analysis for the professions, the term "HCW" will also be used. We will also perform a separate analysis based on the health settings (primary care, hospital, or community care). We will perform descriptive analysis, for example, sex, age, regions, and others. The risk factors associated with self-harm will be divided into a few domains: psychological factors (depression, anxiety, stress, and others), work-related factors (burnout, working hour or shift, satisfaction, engagement, workload, organizational conflict or culture, bullying, harassment, resources, service duration, profession, and others), and personal factors (age, relationship or marital status, income, support, health status, gender, self-conflict, life events, and others).

The overall pool prevalence of self-harm among HCWs will be calculated using a random effect model to allow heterogeneity across the included studies, and later divide the studies into regions. Freeman-Turkey transformation (arcsine square root transformation) will be applied to overcome the limitation of meta-analysis in prevalence studies, as some of the included articles will have very low or very high prevalence. This will possibly occur as we will collect articles from all types of study designs in this review. Having a wide range of prevalence values can result in disproportionately high weights due to the significant decrease in their inferred variance toward 0 [19]. Therefore, the Freeman-Turkey transformation will be used for pooling to obtain a synthesized point estimate of prevalence with a 95% CI [20].

A forest plot will be created for each pool estimate, and the distribution will be presented graphically. We will create a funnel plot if there are 10 or more studies available in 1 analysis to assess biases. We will assess funnel plot asymmetry visually and perform the Egger test to detect publication bias [21-23]. If the funnel plot is asymmetrical and the Egger test has a $P<.05$, it may suggest the presence of publication bias [23]. However, a symmetrical plot indicates the absence of publication bias in the included articles.

We will also conduct a meta-analysis by pooling the appropriate data using Cochrane's statistical software, considering studies to be sufficiently similar in terms of population category, intervention, comparison, and outcome to observe the association between self-harm and the risk factors among HCWs. We will use a random effect model for pooled data. We will follow the strategies in the Cochrane Handbook for Systematic Reviews of Interventions for data management [21,22]. For multiple-arm studies, we will adjust the data following the methods described in the Cochrane Handbook for Systematic Reviews of Interventions [21,22]. Data analysis is expected to be completed by August 2025.

Assessment of Heterogeneity

We will visually inspect the forest plots for any evidence of heterogeneity. We will assess heterogeneity using both the Q test and I^2 statistics. The I^2 statistic will be used to quantify the impact of heterogeneity, while the Q test will be used to identify whether there is a significant heterogeneity of the included studies. We will set the significance level for the Q test at 0.01 [24] while the I^2 level of 75% indicates a substantial degree of heterogeneity. We will adopt a higher threshold of I^2 in this study due to the inherent heterogeneity in the included articles. If the I^2 of the overall studies is less than 75%, the random effect model will be applied in the meta-analysis to overcome the inherent heterogeneity that might be highly present among different prevalent studies [25]. If significant heterogeneity is detected using the I^2 index (>75%), we will investigate the potential sources of heterogeneity using subgroup analyses and meta-regression. The possible causes will be explored and evaluated for their methodological characteristics to determine whether the degree of heterogeneity can be explained by differences in those characteristics and if a meta-analysis is appropriate. The overall prevalence and 95% CI estimates of individual studies will be presented in forest plots. Forest plot with a $P<.05$ will be reported as statistically significant for the analysis [26].

Dissemination

We will disseminate findings through flyers on the internet website. We will publish this review in an international open-access journal to have more citations and engagement regarding this issue. The findings will also be presented at conferences in both local and international settings to share our results. The preliminary findings will be presented to the clinicians, medical officers, and the Ministry of Health, Malaysia, through engagement, meetings, and forums. We will also produce plain language summaries that will be shared with the public through social media and health care websites. This review is expected to be completed and published by January 2026.

Ethical Considerations

Because this review will only include published articles, ethics approval is not needed. All findings will be shared and disseminated at a local or international conference. The preliminary findings will be presented to psychiatrists or clinical practitioners of the Ministry of Health, Malaysia.

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Results

The article search will be performed in March 2025, and any articles published from inception until March 2025 will be included in this study before abstract and title screening. Data analysis is expected to be completed by June 2025, and the manuscript preparation is expected to be completed by July 2025. This review is expected to be completed and published by August 2025. Results on the global overall or pooled prevalence of self-harm among HCWs and the risk factors associated with it will be presented in this paper.

Discussion

Anticipated Findings

This review will highlight the updated overall prevalence of and factors associated with self-harm for better recognition of predisposing, precipitating, perpetuating, and protective factors for thoughts of suicide and self-harm among HCWs [26]. We believe that our review will be important for both clinicians and researchers, especially in controlling distress and potential harm among HCWs. The findings will note the differences between the conditions before and during the COVID-19 pandemic. Therefore, it will help clinical practices to advocate for safer workplaces, perhaps a different approach to treatment or intervention and strengthen the support for HCWs who are at risk of self-harm [27]. Furthermore, we will also observe how self-harm affects HCWs in different health care settings (primary care, hospital, and community), as the burden of work might be associated with self-harm among them. This issue will also influence the patient experience during their visit to different health care facilities [28]. The risk factors listed under the workplace-factor domain might also be associated with self-harm in different health care settings, for example, bullying [29] and long shift hours [26], among others. Therefore, we will perform a separate analysis for each health care setting, in addition to considering regions and types of professions.

This review will also be useful for institutions where HCWs work, such as hospitals, clinics, and local governments organizations, to improve public awareness of self-harm among HCWs. Such efforts are important for the benefit of patients and health services, as self-harm is a strong predictor of suicide [30], which has become a global health and social concern. Furthermore, programs such as counseling services and institutional interventions are needed to address this issue. Providing exercise facilities or aerobic exercise in the health care setting might help to decrease self-harm, as exercise has been shown to decrease depression [31]. A previous study reported the significant association between higher physical activity levels and reduced risk of depression (odds ratio [OR] 0.77, 95% CI 0.72-0.82) among HCWs. Interestingly, the association was also consistent in other subgroup analyses, such as age groups, gender, and regions. Furthermore, both low- and moderate-intensity physical activity showed the most significant protective effects against depression (low-intensity: OR 0.81, 95% CI 0.75-0.56; moderate-intensity: OR 0.79, 95% CI 0.72-0.87) [32]. In short, by understanding the protective mechanisms, spanning emotional, social, and environmental domains, it may help prevent or reduce the risk of self-harm and increase resilience among HCWs [33-35].

These important review findings will be shared publicly, and disseminated in publications and presented at conferences through poster or oral presentations. Furthermore, findings might be translated into practical recommendations for different health care settings to decrease the burden and self-harm cases among HCWs. The results of this study will delineate the differences by profession type, health care setting, and other relevant factors.

Strengths and Limitations

A bias may have been introduced by limiting the language of the included articles to English due to resource constraints, such as a translational resource. To overcome this issue, we included 3 different databases during the article search to increase the number of articles retrieved. The most common study design included in this review was a cross-sectional study; therefore, it cannot demonstrate a causal relationship for self-harm among HCWs.

Conclusions

Self-harm among HCWs is increasing annually, and multiple risk factors are associated with it. Therefore, this review will provide a comprehensive synthesis of the overall prevalence and describe the associated risk factors of self-harm among HCWs worldwide. It will also provide important information to inform practice in developing effective strategies for preventing and managing self-harm among HCWs. It will also provide useful information on the psychological support, create better clinical environments, and protect their mental health.

Acknowledgments

The authors thank the Director General of Health, Malaysia, for his permission to publish this protocol. No specific funding was received for this protocol, nor will it be received for the systematic review planned.

Authors' Contributions

NAM, SH, FY, and LSL contributed to conceptualization. NHM, TPNTBS, NHJ, FNL, NAFNA, and IAR contributed to the investigation and methodology. NHM, TPNTBS, NHJ, FNL, and NAFNA contributed to project administration. NAM contributed to supervision. IAR, NHM, and TPNTBS contributed to validation and visualization. NHM and NAM contributed to writing, reviewing, and editing the paper.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Proposed search terms for all the databases.
[DOCX File , 14 KB - resprot_v14i1e67059_app1.docx]

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Abbreviations

HCW: health care worker
JBI: Joanna Briggs Institute
OR: odds ratio
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

The Health Sector Response to Gender-Based Violence and Sexual Reproductive Health Programs in the Commonwealth and Selected African Countries: Protocol for a Mixed Methods Systematic Review and Meta-Analysis

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Abstract

Background: The intertwining nature of gender-based violence (GBV) and violence perpetrated against women and girls (VAWG), as well as sexual and reproductive health rights (SRHR), underlines the urgent need for the health sector to enhance the coordination of services to improve health outcomes. Importantly, GBV and VAWG are intricately linked to a spectrum of SRHR challenges, ranging from unintended pregnancies to severe maternal, gynecological, and mental health outcomes. Cumulative GBV had a more significant effect on abortion risk than associated variables. Recognizing the interplay between GBV, VAWG, and SRHR highlights the necessity for a comprehensive health sector response. A systematic review of the health sector response to GBV, VAWG, and SRHR will be conducted to understand the extent and array of health facility–based coordinated responses to GBV, VAWG, and SRHR; lessons learned; and successes and challenges in the Commonwealth and selected African countries.

Objective: We aim to understand the context of GBV, VAWG, and SRHR by conducting a comprehensive review of health sector responses in different national, cultural, and socioeconomic contexts, and we aim to share best practices, experiences, and lessons learned.

Methods: A mixed methods systematic review will be conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) guidelines. The population, intervention, comparison, and outcome framework will be applied to screen and select relevant sources guided by the inclusion and exclusion criteria. The review will include relevant research papers published in the last 15 years and conducted in the 24 Commonwealth and 7 selected African countries. Electronic databases to be searched will include PubMed, Google Scholar, Science Direct, EBSCOhost, Web of Science, Embase, PsycINFO, Cochrane, CINAHL, Index Medicus for the Eastern Mediterranean Region, and POPline.

Results: Ethics approval will be waived as the study will use data in the public domain. The project has been commissioned by the Commonwealth Secretariat (2022-2025). The database search, data screening, and data extraction process for the review will

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be completed by September 2025. A manuscript will be submitted to a peer-reviewed international journal by November 2025. The initial online database searches, citations of eligible studies, and Microsoft Copilot identified 38,200 studies focusing on GBV, VAWG, and SRHR interventions. To date, 60 studies have been found eligible for inclusion in the review. The majority of these studies were conducted in eastern Africa (n=34), South Africa (n=14), and Asia (n=13). Evidence generated from this review will be made available through journal publications, seminars and workshops with key stakeholders, ministries of health, and local and international conferences.

Conclusions: The study will generate evidence to inform recommendations on addressing and mitigating the effects of GBV and VAWG on SRHR outcomes and coordinated services in the health sectors of Commonwealth and selected African countries.

Trial Registration: PROSPERO CRD42024520594; https://www.crd.york.ac.uk/PROSPERO/view/CRD42024520594

International Registered Report Identifier (IRRID): PRR1-10.2196/67571

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KEYWORDS

gender-based violence; sexual and reproductive health rights; health rights; violence against women and girls; violence against women; Commonwealth; African countries; violence; sexual health; reproductive health; women's health; female health; social factor; social disparity; social inequality; social inequity; systematic review; review; systematic review protocol

Introduction

Gender-based violence (GBV) remains a critical public health issue, particularly affecting women, girls, and individuals with nonbinary gender identities in the Commonwealth and most African nations [1-4]. In a survey conducted by the World Health Organization (WHO), more than a quarter (27%) of women between the ages of 14 and 50 years reported having experienced physical or sexual violence, or both, from an intimate partner [1]. These individuals often face systemic social injustices as well as limited empowerment regarding GBV and sexual and reproductive health rights (SRHR) [4-8] and entrenched patriarchal norms that perpetuate violence and hinder access to essential health services [1,2]. GBV manifests both within and outside the home, with women and girls predominantly experiencing violence in domestic settings, while men often encounter it in public spaces. The forms of violence include physical, emotional, and sexual abuse, all of which adversely affect the survivor's physical, social, and emotional well-being [1,2,9,10]. The consequences of GBV on SRHR are profound. Survivors may experience unintended pregnancies, pregnancy complications, and adverse maternal health outcomes such as low birth weight, miscarriage, and maternal mortality [11-14]. Additionally, GBV can lead to early sexual initiation, unprotected sex, and heightened susceptibility to sexually transmitted infections (STIs), particularly HIV [15-17]. Intimate partner violence also has a higher tendency to increase unwanted pregnancies and abortions. These experiences often occur in health care environments that are gender-insensitive, judgmental, discriminatory, and stigmatizing, lacking privacy and confidentiality, thereby deterring individuals from seeking SRHR services [15].

Furthermore, GBV can result in gynecological issues, such as genital and reproductive tract infections [11]. GBV is also implicated in mental health conditions such as depression, anxiety, and posttraumatic stress disorder [18-20]. These conditions impair individuals' ability to make informed decisions about their SRHR. Factors like insufficient sexual empowerment, lack of emotional and social support, and inadequate mental health services compound the impact of GBV on SRHR outcomes. Studies have demonstrated that GBV is linked to induced and repeat abortions [21-23]. Notably, the cumulative effect of GBV victimization on the likelihood of abortion surpasses that of nonsexual childhood trauma and demographic factors [24]. Across various African countries, including Angola, Chad, Democratic Republic of the Congo, Gabon, Benin, Burkina Faso, Côte d'Ivoire, Gambia, Mali, Comoros, Rwanda, Uganda, Malawi, and Zambia [25], GBV has a stronger correlation with pregnancy termination among adolescent girls and young women. This underscores the need to view GBV-related induced abortion as a pressing public health issue. The impact of GBV extends to the use of reproductive health care services. Survivors may delay seeking care due to unwelcoming health care environments that lack privacy and confidentiality [13,14,24,26]. For instance, survivors of GBV may not have access to contraception; STI treatment or prevention services; HIV testing, prevention, and treatment services; or obstetric and gynecological care [13,27,28]. They may also be unable to access mental health services from professionals trained to work with GBV survivors, who are equipped to offer a safe, supportive, and nonjudgmental environment to discuss their experiences and address any associated psychological and emotional effects of GBV [19,20,29].

Addressing the intersection of GBV, violence against women and girls (VAWG), SRHR, and the health sector necessitates a coordinated and comprehensive response. The health sector must offer survivor-centered care that addresses the physical, mental, and social consequences of GBV. Collaboration with other sectors is essential to tackle the root causes of violence and prevent its recurrence. Providing these services enables survivors to regain control over their reproductive health and make informed decisions about abortion, their bodies, and their futures [13,14,30].

Target 3.7 of the United Nations Sustainable Development Goals (SDGs) and the Minimum Initial Service Package emphasize the critical importance of SRHR in health and development. However, various barriers and SRHR risks persist for women and girls, including individuals of all gender

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identities and sexual orientations, in accessing SRHR services. These barriers range from poor sanitation, inadequate resources and equipment, and substandard health facility conditions to the stigma surrounding GBV and SRHR services, such as judgmental attitudes, discrimination, and labeling, which prevent survivors from accessing and using SRHR services [31]. Health sector responses to GBV are inadequate in most Commonwealth and African countries [30]. This is mainly because of the inability to implement practical interventional strategies. These challenging matters are further compounded by the demand for more capacity in many health care systems to coordinate a multisector response. The Commonwealth Secretariat, health ministries in African countries, and stakeholders are well equipped to support developing a coordinated health sector response. A multisector, coordinated response may significantly reduce rates of GBV and SRHR-related issues. This systematic review aims to consolidate evidence on the health sector's response to GBV, VAWG, and SRHR, focusing on the burden and diversity of health facility–based coordinated responses in the Commonwealth and selected African countries.

Methods

Study Design

A mixed methods systematic review will be carried out following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) guidelines [32] (Multimedia Appendix 1) and the Enhancing Transparency in Reporting the Synthesis of Qualitative Research recommendations [33]. The mixed methods approach will incorporate both qualitative and quantitative analyses of the studies selected for the review.

Ethical Considerations

This systematic review will use data that are available in the public domain, so it is exempt from ethics approval. We will disseminate the findings of this systematic review on multiple platforms, including, among others, international peer-reviewed journals, webinars, stakeholder engagement sessions, digital platforms, and conferences. This systematic review protocol was registered with the International Prospective Register for Systematic Reviews (PROSPERO) with the registration number CRD 42024520594.

Inclusion and Exclusion Criteria

The population, intervention, comparison, and outcome (PICO) framework will inform the criteria for including and excluding papers during the screening and for selecting relevant resources [34]. The review will include published literature from the last 15 years. Studies of any design focused on health sector responses to GBV, VAWG, and SRHR in the Commonwealth and selected African countries will be included. Documents beyond 15 years, commentaries, and documents not available as full texts after a request from the corresponding authors, as well as those not conducted in the 24 Commonwealth and the 4 selected African countries outside the Commonwealth nations, will be excluded from the review (Textbox 1).

Textbox 1. Inclusion and exclusion criteria using the population, intervention, comparison, outcome framework.

Inclusion criteria

- Population: studies focusing on health sector responses to gender-based violence (GBV), violence perpetrated against women and girls (VAWG), and sexual and reproductive health rights (SRHR) in the Commonwealth and selected African countries among women, men, girls, and boys published in the last 15 years (2011-2025) and reported in English
- Intervention: studies that implemented interventions or strategies to prevent and control GBV and VAWG as well as mitigate negative SRHR outcomes
- Comparison: studies that compare different types of GBV, VAWG, and SRHR interventions
- Outcomes: studies that report as main outcomes VAWG, GBV, and SRHR knowledge, attitudes, confidence, and readiness; health-related behavior and practices (eg, identification and disclosure of VAWG and GBV; and provision and uptake of referrals and VAWG, GBV, and SRHR services

Exclusion criteria

- Studies not reporting on at least one aspect of the health sector response to GBV, VAWG, and SRHR in the Commonwealth and selected African countries
- Studies published prior to 15 years
- Studies not written in English

Other Key Factors for Inclusion

We include studies reporting on GBV, VAWG, and SRHR interventions in the 31 Commonwealth and selected African countries. These countries include Malta, Fiji, the United Kingdom, New Zealand, Grenada, Canada, Guyana, Barbados, Antigua and Barbuda, Bangladesh, India, Malaysia, Pakistan, Sri Lanka, Burkina Faso, Central African Republic, Ghana, Guinea Bissau, Kenya, Sierra Leone, South Africa, Ethiopia, Congo, Tanzania, Rwanda, Benin, Senegal, Namibia, and Malawi. Depending on the country's context, GBV, VAWG, and SRHR services can be rendered at any level of the health care system. Relevant peer-reviewed studies published in reputable journals available as full texts will be considered for inclusion.

Search Strategy and Databases

A comprehensive search strategy will be developed to identify relevant studies. The search strategy for the systematic review will be guided by the PICO framework and Medical Subject

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Heading terminology (Multimedia Appendix 2) [35]. The process of developing the search strategy will involve searching multiple databases. Data sources to be used will include PubMed, Google, Google Scholar, Science Direct, EBSCOhost, Web of Science, Medline, Embase, PsycINFO, Cochrane, CINAHL, Index Medicus for the Eastern Mediterranean Region, POPLine, Lilacs, the WHO Reproductive Health Library, and ClinicalTrials.gov. Abstracts and full-text articles will be reviewed using an online systematic review tool (Covidence) and a referencing tool (EndNote). Additionally, reference lists of prior systematic reviews on GBV, VAWG, and SRHR domains in the Commonwealth and selected African countries will be reviewed for potentially relevant studies. These multiple complementary search strategies will be used to ensure that the search is as exhaustive as possible. The purpose is to have a wide net to harness the diversity of GBV, VAWG, and SRHR literature.

Quality Appraisal and Screening

Published literature will be retrieved from the online database search engines and imported into Covidence before the screening process. The quality appraisal of the studies will be done following the Critical Appraisal Skills Programme systematic review checklist, which examines the validity, precision, and generalizability of the research [23]. All duplicates will be excluded from the software during the importation phase. Two authors will screen the imported articles by title and abstract. The articles that meet the criteria based on their titles and abstracts will further be screened as full texts by the 2 reviewers. The screening processes will involve dividing the articles and reports into 3 groups: yes, no, and maybe. A third member will weigh in and make the final decision if there are different opinions.

Data Extraction and Evidence Synthesis

A data extraction database will be in place to extract and populate the information. Information from the eligible articles will be extracted with a Microsoft Excel data extraction tool using relevant headings, such as the study and author names, year of publication, country, study design, study population, interventions, and key findings.

Statistical Analysis

We will analyze data abstracted from included studies to assess the effect of the intervention applied in preventing and controlling GBV and VAWG. Statistical analysis will use Stata (version 18; StataCorp) and R (version 4.4; R Foundation for Statistical Computing). We will analyze dichotomous outcome data as odds ratios (ORs) and/or risk ratios (RRs). All continuous data will be analyzed as mean differences (MDs) with corresponding SDs. We will report all estimates with 95% CIs. We will conduct a meta-analysis if at least 2 similar studies are available so that we can determine the pooled OR, RR, or MD of each of the individual studies. We will present the results graphically as forest plots. We will quantitatively assess, using the I^2 statistic, any heterogeneity that is identified in the different study designs or participants' characteristics that could lead to differences in outcomes between these studies. Where no significant heterogeneity (I^2<50%) exists, fixed effects models will be used to pool the results of the studies. Random effects models will be used if there is either observable or significant heterogeneity (I^2≥50%). Where appropriate, we will use a fixed effects model to obtain pooled estimates of GBV and related propagating factors.

We will perform subgroup analysis to investigate the differences between GBV, VAWG, and SRHR interventions and outcomes among different countries within southern, central, western, and eastern sub-Saharan Africa. This will be done should there be sufficient data to draw upon for such a comparative analysis. Should the meta-analysis include more than 10 papers, a funnel plot will be generated so that publication bias can be evaluated. Statistical tests, if appropriate, will be done for funnel plot asymmetry (Egger test, Begg test, or Harbord test). We will use a meta-regression to assess factors associated with GBV and related outcomes. Lastly, we will conduct a leave-one-out sensitivity analysis for studies that are found to be outliers to evaluate the robustness of the pooled estimates. For qualitative data amenable to meta-synthesis, textual data will be aggregated using the JBI's Qualitative Assessment and Review Instrument and narrative tools. The data will be analyzed using framework methodologies, using both case-based and theme-based approaches.

Integration of the Qualitative and Quantitative Data

Triangulation, as well as complementary and joint display, will be used to integrate the quantitative and qualitative data during the analysis phase. The triangulation method is used to harness data from different sources to explain a particular phenomenon, with the purpose of finding convergence or divergence in the results [36]. Additionally, the complementary method will be used, wherein qualitative data will be used to explain observations seen in the quantitative data or vice versa [37]. For example, the qualitative responses can be used to explain why certain GBV or VAWG interventions were adequate or not in preventing and controlling GBV and VAWG. Additionally, this method can be used to assess how an intervention mitigates the effects of GBV and VAWG on SRHR outcomes. Joint displays such as side-by-side comparisons will be used to integrate GBV and VAWG intervention facilitators and barriers with quantitative data (ie, a meta-analysis) to show the effectiveness of a GBV or VAWG intervention [38,39].

Assessing the Certainty of Evidence Using Grading of Recommendations Assessment, Development and Evaluation

We will use the Grading of Recommendations Assessment, Development and Evaluation (GRADE) to assess the certainty of evidence. This approach is important for evaluating the overall quality or certainty of the evidence on the key outcomes provided by the individual studies included in the review. In this review, as stated earlier, 2 reviewers, at a minimum, will assess the certainty of evidence (by assessing the quality of evidence or the confidence limits in the effect estimates). This will cover the following key domains: imprecision, inconsistency, risk of bias, indirectness, and publication bias. The certainty of evidence will be graded as high, moderate, low, or very low. For each of the outcomes, we will present an overall

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rating of the certainty of the evidence in the form of a table summarizing the findings. This will be presented with the number of studies, participants, study types, and each outcome's relative and absolute effects. We will summarize publication bias using funnel plots and the Egger regression test technique.

Search Results and Study Selection

Published studies were screened and selected by 2 independent reviewers. These was afterwards retrieved and uploaded into Endnote (version X9). Duplicates were screened and removed from further processing. The titles and abstracts of the studies were screened to remove all nonqualifying and irrelevant studies. The full-text articles meeting the inclusion criteria were screened and added to the selected list. Any study that did not qualify for inclusion at this stage was excluded based on having a wrong outcome, study design, or population. Any disagreements between the reviewers regarding study selection were resolved by a fourth reviewer, who intervened and resolved the disagreement.

Results

The PRISMA-P flow chart in Figure 1 summarizes the process of selecting the articles included in this review. A total of 38,200 studies were initially identified through online database searches, as follows: Web of Science (n=13,055), Science Direct (n=6823), PubMed (n=6767), Medline (n=5933), Embase (n=1355), Cochrane (n=612), and PsycINFO (n=3710). Additional studies were identified through reference lists from the eligible studies (n=10) and Microsoft Copilot (n=45). Duplicates were removed after the studies were added to RefWorks and Covidence; there remained 14,238 studies. A total of 24,017 studies were screened, and 18,352 were excluded due to reasons such as not focusing on the 31 Commonwealth and selected African countries (n=6674) and not focusing on GBV, VAWG, and SRHR (n=8060). After the title and abstract assessment, 5344 studies were removed due to there being no full text available (n=788), not being in English (n=1005), or being conference abstracts (n=122). The remaining 321 studies were assessed as full texts, and 60 studies were included in the final review. In terms of geographical distribution, most of the studies came from eastern Africa (n=34), South Africa (n=14), and Asia (n=13). The literature search, data screening, and data extraction for the review will be completed by September 2025. A completed manuscript will be ready by the end of November 2025 and will be submitted for peer review to an international journal.

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Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocol (PRISMA-P) flow chart summarizing the screening process for including eligible articles as of July 21, 2025. GBV: gender-based violence; SRHR: sexual reproductive health and rights; VAWG: violence against women and girls.

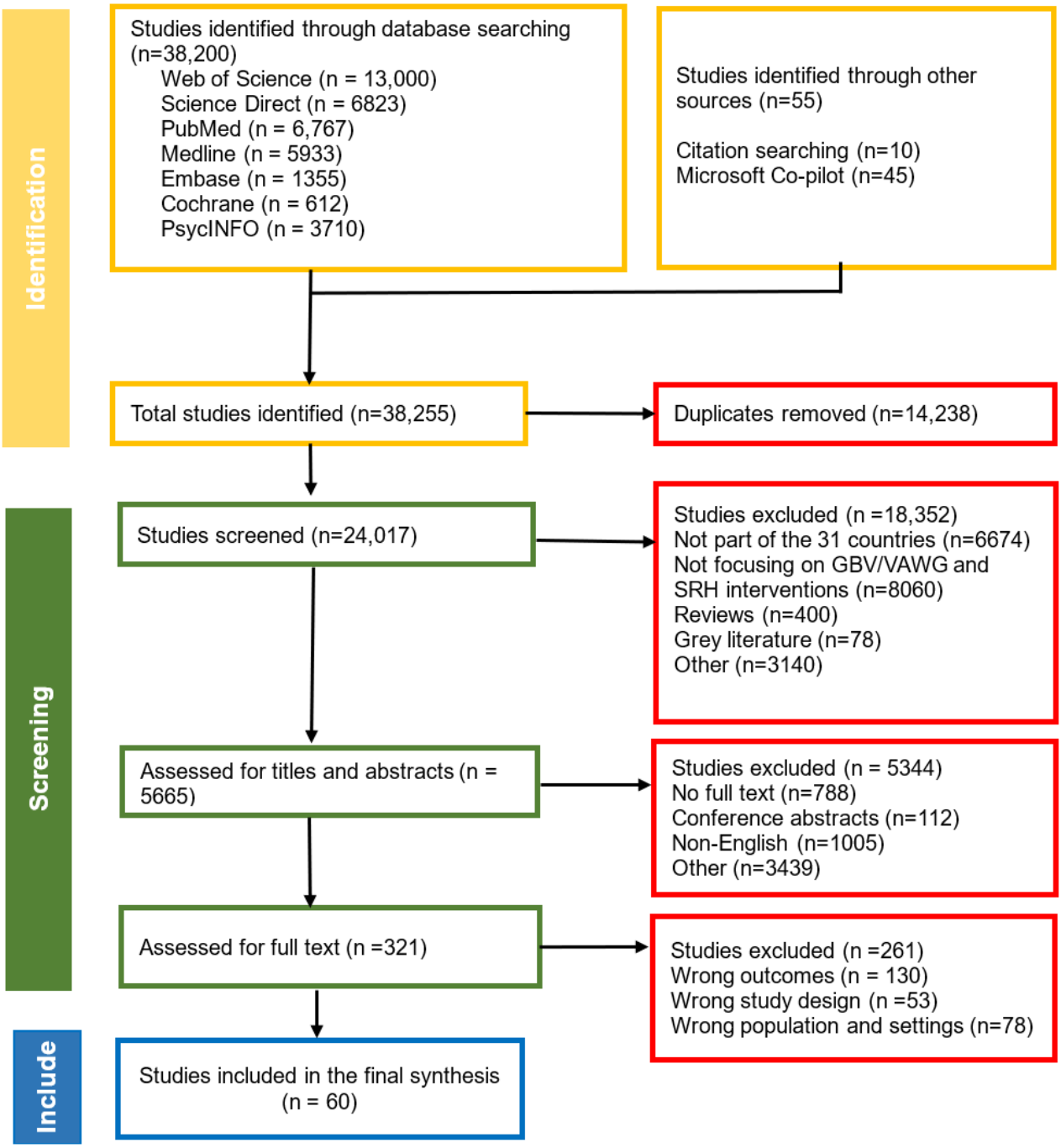

Discussion

Overview

This systematic review will unravel the body of evidence available related to the burden of GBV and health facility–coordinated responses to GBV, VAWG, and SRHR challenges, as well as potential mitigating approaches. It will apply robust methods to address external and internal validity. The external validity assessment will use PICO to streamline and delineate the attributes of the populations, interventions, comparisons, and outcomes. Furthermore, internal validity will address the risk of bias in various domains. The evidence generated from this review will thus provide lessons learned over time, successes observed, and challenges to be mitigated in implementing effective responses to minimize GBV and related SRHR challenges in the Commonwealth and selected African countries. Furthermore, it is anticipated that this systematic review will contribute toward identifying knowledge gaps, strengthening continuity and scale-up of effective interventions, guiding the development of future research agendas, and contributing toward gender equality, inclusivity, and social justice, as well as making the case for future investments. The review will use the PRISMA-P guidelines to ensure the consistency of the methodology and to guide the collection of information and material. Including diverse sources

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(eg, peer-reviewed publications) across different databases will allow the selection of the most relevant studies, enhance cross-validation of data from different sources, and minimize gaps.

Study Limitations

Studies on GBV and SRHR might not be reported adequately due to stigma related to the subject, which might result in publication bias. The review may include research from various settings with different health care systems and cultural norms, which may limit the generalizability of the findings. This might be due to geographic and socioeconomic disparities in how GBV is viewed and managed when reported. Comprehensive analysis may also be limited by incomplete reporting of relevant outcomes of GBV events.

Implications of the Expected Review Findings

The strength of this review will be to pool data from other studies by searching comprehensive databases and describing SRHR interventions that have been implemented to prevent and control GBV. The findings should help develop or modify policies on GBV and related challenges, clinical practice, and research in the Commonwealth and selected African countries. This review will draw attention to the need for more pertinent, focused programs to protect women and girls as well as for effective health care services to support women and girls who have experienced GBV. The results from this review could also help highlight differences in health outcomes according to risk profiles such as low socioeconomic status and geographical characteristics, reinforcing the need for equitable resource allocation and focused public health interventions for GBV among affected individuals in resource-limited settings. These findings may also shape health policies that support better access to care and treatment among GBV survivors, as well as reinforce SRHR and active GBV surveillance and education and discourage practices that may increase GBV against women and girls. This review may also point out gaps in the current body of knowledge about GBV and SRHR and associated impediments to effective reporting, care, and psychosocial counselling services. We believe that the evidence generated from this review will contribute to achieving SDG 3.3 and lead to improved interventions to eliminate GBV and enhance SRHR to improve women's health.

Acknowledgments

The authors would like to acknowledge the Commonwealth Secretariat for commissioning the study titled "The Health Sector Response to Gender-Based Violence and Sexual Reproductive Health Programmes in the Commonwealth and Selected African Countries." Microsoft Copilot was used to conduct additional literature searching and identified 45 studies.

Data Availability

All data generated or analyzed during this study will be included in the published article and its supplementary information files.

Authors' Contributions

OS, RNP-M, EP, and NZ conceived the study. RNP-M, EP, AM, and PN contributed to drafting the protocol and aligning the systematic review and meta-analysis methods. All authors read and approved the final version of this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P checklist.
[DOCX File , 35 KB - resprot_v14i1e67571_app1.docx]

Multimedia Appendix 2
Sample search strategy in PubMed.
[DOCX File , 14 KB - resprot_v14i1e67571_app2.docx]

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Abbreviations

GBV: gender-based violence
GRADE: Grading of Recommendations Assessment, Development and Evaluation
MD: mean difference
OR: odds ratio
PICO: population, intervention, comparison, outcome
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses-Protocol
PROSPERO: International Prospective Register of Systematic Reviews
RR: risk ratio
SDG: Sustainable Development Goals
SRHR: sexual and reproductive health rights
STI: sexually transmitted infection
VAWG: violence against women and girls
WHO: World Health Organization

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Protocol

Neural Activity Disparities in Deficiency and Excess Patterns of Depression: Protocol for a Systematic Review and Meta-Analysis

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Abstract

Background: Major depressive disorder (MDD) is a complex and heterogeneous condition. Current diagnosis relies on symptom-based assessments, leading to varied treatment responses. Data-driven approaches have attempted to identify MDD subtypes, but their clinical applicability remains limited. Traditional Chinese Medicine (TCM) provides a theory-driven classification system that categorizes MDD into syndrome subtypes of deficiency pattern and excess pattern, offering insights into the biological mechanisms and personalized treatment strategies.

Objective: This systematic review and meta-analysis aims to identify potential neurobiological distinctions of TCM-based deficiency and excess patterns in MDD by examining differences in the brain activity by using various functional magnetic resonance imaging (fMRI) modalities, including resting-state and task-based fMRI, diffusion tensor imaging, and magnetic resonance spectroscopy.

Methods: In accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P), we will conduct a comprehensive search of 7 electronic databases (PubMed, Embase, Web of Science, Chinese Biological Medical Literature database, China National Knowledge Infrastructure, Chinese Wanfang database, and Chongqing VIP database) for studies published up to December 2024. Eligible studies will be screened by 2 independent reviewers based on predefined inclusion criteria, followed by data extraction and quality assessment. For the meta-analysis, resting-state fMRI studies will be analyzed in Montreal Neurological Institute space using Seed-based d Mapping-Permutation of Subject Images software (version 6.21), enabling a focused evaluation of brain activity differences in deficiency and excess MDD patterns.

Results: The search and screening for the systematic literature review were completed in December 2024. This study relies on published, publicly accessible data. We found approximately 30 eligible studies in our preliminary search, suggesting that a quantitative meta-analysis is feasible. Data extraction, quality appraisal, and subsequent data synthesis will begin in September 2025. The review should be completed by December 2025, and the study results will be published in 2026.

Conclusions: The results of this study may help to explain the neural mechanisms of depression's neurobiological subtypes from the perspective of TCM.

Trial Registration: PROSPERO CRD42023475178; https://www.crd.york.ac.uk/PROSPERO/view/CRD42023475178

International Registered Report Identifier (IRRID): DERR1-10.2196/68996

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(JMIR Res Protoc 2025;14:e68996) doi:10.2196/68996

KEYWORDS

depression; Chinese Medicine; functional magnetic resonance imaging; fALFF; fractional amplitude of low-frequency fluctuations; subtype

Introduction

Major depressive disorder (MDD) is a complicated disease that imposes a significant worldwide burden of disease [1]. Currently, the diagnosis of MDD depends mainly on structured interviews and scale scores that measure symptoms, functions, and personality [1,2]. This approach leads to significant confusion in the classification of MDD. The treatment response of MDD differs among different patient populations due to factors such as the lack of specificity in symptoms, along with individual variations in the intensity and duration of the disease [3-5]. Therefore, researchers are devoted to investigating the specific etiology and pathology of MDD and identifying more homogeneous subgroups [6]. The existing classification paradigm for MDD subgroups consists of 3 main categories: neurobiological mechanisms [7], genetic variants [8-10] and symptom patterns, as well as clinical characteristics [11,12]. Researchers apply data-driven methods to identify patterns of different subtypes [13,14], with the goal of understanding their clinical significance in treatment responses and predicting individual variations in cognitive and emotional profiles [15-17]. However, the accuracy of these classification outcomes is seldom duplicated in separate test samples, thereby restricting their utility in actual clinical environments [15,18].

Interestingly, in contrast to the data-driven approaches, the syndrome-based classification model of Traditional Chinese Medicine (TCM) is a dependable system for classifying medical conditions, and it has practical use in clinical settings. The TCM syndrome comprises different symptoms and signs that represent the fundamental characteristics of a specific stage of a disease. Syndrome differentiation in TCM is a concise summary of the pathological changes underlying the clinical manifestations. It is determined by the patient's metabolic features and susceptibility to disease and serves as the foundation for clinical practice in TCM [19]. In particular, the clinical value of this classification model has been widely proven in thousands of years of practice. However, this framework for classifying subtypes, which is rooted in the TCM theory, requires a deeper investigation into the biological mechanisms underlying their occurrence. It is crucial to identify objective indicators based on the biological substrates associated with different syndrome types [20]. This will enhance the efficiency of TCM diagnosis and promote the development of standardized diagnostic indicators for MDD.

The TCM syndrome subtypes are assessed using 4 diagnostic methods: inspection, listening/smelling, inquiry, and palpation. Following the classification and codes of diseases and patterns of TCM (GB/*t* 15657-2021), the 2 most commonly applied classifications for MDD in TCM are deficiency pattern (DP) and excess pattern (EP). DP is characterized by clinical manifestations such as fatigue, low energy, pale tongue, and weak pulse, indicating a lack of qi, blood, or organ function. EP is manifested by symptoms such as irritability, chest tightness, constipation, a red tongue with yellow coating, and a wiry pulse, suggesting internal heat, stagnation, or phlegm accumulation.

Currently, functional magnetic resonance imaging (fMRI) offers a nonintrusive method for examining the structure and function of the brain [21]. Despite being more costly and difficult to obtain, various fMRI sequences can detect differences in brain activations and microstructural changes in groups, including those previously thought to be "normal" like depression by using quantitative analyses instead of visual assessments [22]. The general fMRI sequences include blood-oxygen-level–dependent imaging, diffusion MRI, and magnetic resonance spectroscopy. Various studies have employed these techniques and reported that individuals with MDD exhibit regional neural activity disorders, abnormalities in functional connectivity within and between brain areas, and changes in brain structures such as white matter [23-25]. Moreover, multiple fMRI studies on TCM syndrome subtypes have demonstrated distinct fMRI activation patterns in different TCM syndrome subtypes of MDD, highlighting distinct brain responses among these subtypes [26-30]. Further, the high spatial resolution of whole-brain fMRI is in line with TCM's holistic diagnostic approach, enabling a comprehensive mapping of brain responses corresponding to different TCM syndromes in depression.

Hence, we aim to conduct a comprehensive literature review to elucidate the neural mechanisms underlying the neurobiological subtypes of depression through the lens of Chinese Medicine syndromes. This will involve a combined use of quantitative and qualitative methodologies. We will focus particularly on studies that classify patients into DP or EP subtypes by using standardized syndrome differentiations based on TCM guidelines.

Methods

Study Registration

We performed our protocol in accordance with PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) guidelines [31] (Multimedia Appendix 1). This study was registered with PROSPERO (CRD42023475178).

Eligibility Criteria

Studies using fMRI to investigate the brain mechanism of depression based on TCM syndromes are included. All TCM syndrome subtypes must follow the classification and codes of diseases and patterns of TCM (GB/*t* 15657-2021) and be classified into DP and EP. Depression is diagnosed based on the standard diagnostic criteria, including the Diagnostic and Statistical Manual of Mental Disorders, the International

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Classification of Diseases, and the Chinese Classification of Mental Disorders. TCM syndrome differentiation follows the criteria for the diagnosis and the therapeutic effects of diseases and syndromes in TCM. Studies that meet the following criteria are included in the meta-analysis: (1) used an fMRI voxel-wise whole-brain approach of resting-state activation data; (2) reported altered spontaneous functional activities in local brain regions; and (3) reported brain regions with abnormal activations as x/y/z coordinates in standard space: Montreal Neurological Institute template or Talairach atlas.

The following types of studies are excluded: (1) reviews/meta-analyses/single-case studies/dissertations/conference papers/abstracts; (2) letter/comments/viewpoints/summaries for patients/editorials and opinion papers; (3) no assessment of TCM syndromes as exposure; (4) exposure to any active TCM interventions and non-TCM ones such as acupuncture, herbal medicine, moxibustion, massage, psychotherapy, pharmacological treatments, or brain stimulation techniques; (5) animal studies; and (6) duplicate publications of the same data.

Search Strategy

Data Sources

Two independent reviewers (LC and XJ) systematically searched for literature up to December 2024 by using PubMed, Embase, Web of Science, Chinese Biological Medical Literature database, Chinese National Knowledge Infrastructure database, and the Chinese Wanfang and Chongqing VIP databases. The search was conducted using a combination of Medical Subject Headings (MeSH) and unrestricted terms related to (1) depression, (2) Chinese medicine, and (3) MRI.

Search Terms

No limitations will be placed on the publication's time or location. To make sure the search includes the latest data, it is intended to be updated before the final review is submitted. The terms that were used in the search strategy are shown in Multimedia Appendix 2.

Data Management

Every study obtained from the search will be loaded into EndNote, and any duplicates will be eliminated. Two authors (LC and XJ) will independently review the titles, abstracts, and keywords of these studies based on the predefined criteria for inclusion and exclusion. Following that, the studies selected will undergo a second screening process by thorough reading of the complete text. Studies that do not match the specified review criteria will be excluded. If there is a disagreement, a third author (HL) will be responsible for making the ultimate decision.

Data Extraction

Data extraction will also be performed by 2 independent reviewers (LC and XJ). We will design a structured data extraction form based on the fMRI study reporting criteria in order to ensure standardization in the process of extracting data. Any ambiguity or disagreement will be resolved by consulting a third investigator (HL). The following data will be extracted: first author, publication year, study type, sample size per group, age, gender, drug history, diagnosis criteria, ratings of depression and anxiety, modality and metrics of fMRI, type of task performed during functional imaging, fMRI device type, sequence parameters, software for fMRI data analysis, quality score, and reported results. Moreover, the significance level and the peak coordinates with its 2-sided t value or z score or P value will be extracted for the meta-analysis.

Assessment of Study Quality

We will use the Agency for Healthcare Research and Quality scale to evaluate the quality of the clinical research based on the specific types of studies included [32]. Additionally, an fMRI checklist will be used to access the imaging methodology quality. This checklist involves the inclusion and exclusion criteria, population characteristics, diagnosis criteria, sample size, methods for image acquisition and analysis, and the quality of reporting of statistical results and research conclusions [33]. Similarly, the evaluation of quality will be conducted independently by 2 reviewers (LC and XJ). A third researcher (HL) will resolve any disagreement that arises during the evaluation procedure. We will categorize the literature into high, medium, and low quality according to their scores.

Strategy for Data Synthesis

The synthesis of data from the selected studies will involve a combination of quantitative and qualitative methods. We will systematically summarize the clinical and methodological characteristics of the studies through tables and narratives, detailing imaging techniques, statistical approaches, TCM syndromes, and fMRI biological substrates associated with each syndrome. To improve data clarity, we concentrate on the primary DP and EP within the framework of syndrome subtypes methodology as applied in TCM clinical practice. The qualitative synthesis will follow a thematic content analysis approach, using a structured data extraction matrix to categorize imaging findings by brain region, activation direction (increased/decreased), and syndrome type (DP vs EP). Findings will be coded and grouped into emergent neurofunctional patterns that characterize each TCM subtype. The quantitative investigation will assess and contrast the neuroimaging characteristics among the 3 subgroups. We will also perform a direct comparison between the DP and EP groups to identify specific neural activation differences associated with TCM-defined subtype distinctions. Three sets of comparisons will be conducted in the meta-analysis: (1) DP versus healthy control (HC), (2) EP versus HC, and (3) DP versus EP.

The meta-analysis of resting-state fMRI studies will be conducted in Montreal Neurological Institute space using Seed-based d Mapping-Permutation of subject images software (version 6.21). For each comparison (DP vs HC, EP vs HC, and DP vs EP), we will generate effect size maps based on reported peak coordinates and statistical values. Quantitative outcomes of interest will include fractional amplitude of low-frequency fluctuations, amplitude of low-frequency fluctuations, regional homogeneity, and blood-oxygen-level–dependent signal changes in specific brain regions. Where available, other neuroimaging parameters such as functional connectivity measures may also be extracted and synthesized. We will conduct a comparison of brain activities between the DP group and the HC group, as

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well as between the EP group and the HC group. First, we will prepare the text files containing peak coordinates and effect dimensions. For data preprocessing, we will use those files to determine the resulting values of the minimum and maximum potential effect sizes for each voxel. Second, the mean images will be created by averaging the random effects datasets, considering the sample size, study variance, and variations between groups. The effect size maps from various studies will undergo multiple imputations. Third, a family-wise error correction will be used to account for multiple comparisons. If the number of eligible studies permits, we will also conduct subgroup analyses or meta-regression to examine potential moderators (eg, age, sex, imaging parameters).

Results

The search strategy and screening for the systematic literature review were completed in December 2024 (Multimedia Appendix 2). We identified approximately 30 potentially eligible studies that meet the inclusion criteria during a preliminary scoping search of both English and Chinese databases, suggesting that a quantitative meta-analysis is feasible. In alignment with the objectives of this review, the extracted data will focus on fMRI outcomes associated with TCM syndrome subtypes of MDD. A standardized data extraction form has been developed and is provided in Multimedia Appendices 3 and 4. This form incorporates key elements from fMRI study-reporting criteria, including imaging modality, scanning parameters, analysis pipelines, coordinate systems, and statistical thresholds. These elements aim to ensure consistency and comparability across studies during synthesis. The evidence will be summarized both narratively and quantitatively. Data extraction, quality appraisal, and subsequent data synthesis will begin in September 2025. The review should be completed by December 2025, and the final results will be disseminated through publication in a peer-reviewed journal in 2026.

Discussion

Principal Findings

This study protocol proposes a systematic review and meta-analysis to explore the neural mechanisms of TCM-based subtypes of MDD, specifically focusing on DPs and EPs. By applying both qualitative synthesis and quantitative meta-analytic techniques to resting-state fMRI studies, this protocol is designed to assess whether distinct brain activity patterns exist between TCM-defined subtypes. The significant heterogeneity of MDD has historically influenced its diagnosis and therapy [34]. Despite the various classification approaches for MDD, the neurobiological basis of MDD remains poorly understood, and there is still a dearth of compelling evidence for the clinical application value of MDD subtypes in real clinical settings [12]. Although the syndrome-based classification model of TCM (corresponding to the TCM syndrome differentiation and treatment system) is a clinically efficient categorization tool, the connection between this syndrome-based classification model of TCM and the neurological substrate requires further investigation. Our study is the first investigation to comprehensively clarify the neural mechanisms of depression's neurobiological subtypes from the perspective of TCM, employing both quantitative and qualitative approaches.

Comparison to Prior Work

Previous studies have focused extensively on Western medicine–based subtyping approaches to MDD, including symptom clusters, genetic polymorphisms, and machine learning–defined neurobiological patterns [35,36]. However, the clinical applicability of these subtypes has remained limited due to replication challenges and inconsistent outcomes [7]. The TCM syndrome classification offers a complementary, theory-driven alternative, with some preliminary studies suggesting that fMRI markers may differ between TCM-defined subtypes [37,38]. This protocol builds upon such observations and aims to systematically synthesize the evidence, which has not yet been undertaken comprehensively.

Strengths and Limitations

The primary strength of this protocol is its novelty in applying neuroimaging meta-analytic methods to examine brain-based correlations of TCM-defined subtypes of MDD—a field that remains underexplored. In addition, this study follows rigorous methodological frameworks (eg, PRISMA-P, PROSPERO registration) and integrates multiple databases and analytic strategies. Nonetheless, some limitations must be acknowledged. The heterogeneity among the included studies in terms of fMRI parameters, diagnostic criteria, and syndrome classification methods may affect the consistency of the results. The inclusion of non–peer-reviewed literature such as dissertations may also introduce variability in the study quality. Moreover, the current lack of standardized diagnostic criteria for TCM patterns in MDD may challenge cross-study comparability.

Future Directions

Upon completion, this review is expected to offer a neurobiological perspective on the TCM framework and may help identify reliable imaging biomarkers for MDD subtype differentiation. Future research should aim to develop standardized criteria for TCM syndrome diagnosis that are compatible with neuroimaging methodologies and increase sample sizes through multicenter collaboration. Additionally, further prospective clinical studies could validate whether neuroimaging-defined TCM subtypes predict differential treatment responses.

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Authors' Contributions

Protocol design: LC, JW, L Li, JC, XQ, L Liu, HL
Data curation and formal analysis: SL, HZ, XL
Authors HL (13510269808@139.com), L Liu (liulanying@smhc.org.cn), and XQ (qinxiude@foxmail.com) are co-corresponding authors for this article.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P checklist.
[DOC File , 77 KB - resprot_v14i1e68996_app1.doc]

Multimedia Appendix 2
Search strategy for PubMed.
[DOC File , 23 KB - resprot_v14i1e68996_app2.doc]

Multimedia Appendix 3
Methodological challenges in Traditional Chinese Medicine research and functional magnetic resonance imaging data collection and processing.
[DOC File , 30 KB - resprot_v14i1e68996_app3.doc]

Multimedia Appendix 4
Study quality rated by using the Agency for Healthcare Research and Quality scale.
[DOC File , 46 KB - resprot_v14i1e68996_app4.doc]

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Abbreviations

DP: deficiency pattern
EP: excess pattern
fMRI: functional magnetic resonance imaging
HC: healthy control
MDD: major depressive disorder
MeSH: Medical Subject Headings
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
TCM: Traditional Chinese Medicine

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Protocol

Effectiveness and Related Factors of Narrative Messages in Correcting Health-Related Misinformation: Protocol for a Systematic Review

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Abstract

Background: The internet and social media have become essential sources of health information for patients and citizens; however, they often disseminate misinformation that lacks scientific evidence. Health-related misinformation can undermine evidence-based treatment, weaken patient-provider relationships, and contribute to adverse health outcomes. Although narratives have been proposed as a promising approach to countering misinformation, their effectiveness remains inconsistent and influenced by various factors.

Objective: The aim of this study is to assess the effectiveness of narrative messages in correcting health-related misinformation compared to nonnarrative messages. It also seeks to identify message-, sender-, and recipient-related factors that influence the effectiveness of narrative-based corrections.

Methods: This systematic review will follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. Comprehensive searches will be conducted across databases, including PubMed, MEDLINE, CINAHL, PsycINFO, and Web of Science, using keywords related to narratives and correction of health-related misinformation. This review will include quantitative studies evaluating narrative-based corrections for health-related misinformation in experimental and quasi-experimental studies. Studies unrelated to health misinformation or where the full text is unavailable will be excluded. No restrictions on publication year will apply. Only papers written in English will be included. Two independent reviewers will screen the papers using Rayyan QCRI software, with disagreements resolved by a third reviewer. Data extraction will cover health topics (eg, vaccination, tobacco), study characteristics (eg, author, publication year), narrative characteristics (eg, definition of narrative, theoretical foundation), participant characteristics (eg, sociodemographic), methodology (eg, study design, content of interventions and comparators, outcomes and measures, moderating and mediating factors), main results, and discussion. The quality of the eligible studies will be assessed using the Cochrane Risk of Bias 2 tool and the Risk of Bias In Non-randomized Studies - of Interventions tool.

Results: The results will be summarized in tables and presented as a descriptive review addressing the effectiveness of narrative corrections in health-related misinformation and the factors influencing their success. The implications of these results for future studies and practices will be elucidated. The findings of this review will be presented at a relevant conference and submitted to a peer-reviewed journal for publication. The aim is to complete the submission process by the northern summer of 2025.

Conclusions: Narrative messages represent a theoretically promising strategy for countering health-related misinformation; however, their effectiveness is context-dependent. This review will offer critical insights into the factors that influence the success of narrative corrections for health-related misinformation, contributing to the development of improved correction strategies and a theoretical understanding of narrative corrections.

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KEYWORDS

internet; social media; social networks; misinformation; false information; infodemics; infodemiology; debunking; prebunking; correction; refutation; narrative; story; health information; health communication

Introduction

The internet and social media are the major sources for individuals seeking health information, regardless of their age [1,2]. However, these platforms are often rife with health-related misinformation that lacks scientific evidence [3]. Compared to accurate health information, misinformation is more likely to reach a wider audience and maintain its influence over time [4]. This misinformation disrupts appropriate health behaviors and adherence to evidence-based treatments [5], undermines the relationship between patients and caregivers and health care providers [6], and contributes to an increased risk of adverse health outcomes, including mortality [7,8]. To address these challenges, previous studies have focused on developing and evaluating effective strategies to correct health-related misinformation and mitigate its negative effects [9,10].

Many studies have evaluated the effectiveness of corrective strategies by providing factual and didactic explanations highlighting the inaccuracies and logical fallacies of misinformation [9]. However, the findings of these studies are mixed, with outcomes ranging from the successful resolution of misperceptions to the persistence or exacerbation of false beliefs [11]. Researchers have identified several factors that complicate the correction of health-related misinformation. A key factor is the mental models that individuals construct to understand causal relationships among events [12]. These mental models serve as frameworks for interpreting information but are often resistant to change. Individuals are reluctant to discard the presumed causal explanations embedded in their established mental models [13]. Consequently, fact-based corrections alone can be insufficient to provide alternative explanations that override preexisting beliefs, ultimately failing to shift mental models grounded in misinformation [14].

In this review, we define correction as an intentional communication effort to modify beliefs, attitudes, or behavioral intentions that have been shaped by exposure to misinformation. This concept differs from disclosure, which often involves the provision of clarifying or supplementary information—such as price comparisons or risk statements—without directly addressing or aiming to undo prior misperceptions. Prior studies, particularly in the context of prescription drug advertising, have shown that while disclosures may enhance transparency, they do not always lead to correction of misperceptions [15,16]. Our review focuses specifically on corrections that aim to alter misinformation-driven mental models or beliefs.

Researchers have used narratives as a corrective tool. Narratives are defined as messages that depict "connected events and characters that have an identifiable structure, are bounded in space and time, and contain implicit or explicit messages about the topic being addressed" [17]. Previous studies [18-23] have identified several persuasive mechanisms within narratives that make them particularly effective in addressing misinformation. Narratives serve as the fundamental means for individuals to interpret and understand the world. By linking the actions and outcomes experienced by characters in a cause-and-effect framework, narratives can provide a compelling mental model for explaining interconnected events and their underlying causal relationships [18]. The concept of narrative transportation [19], which refers to the immersion of an individual into a story and the ability to envision themselves within events, allows for the mental simulation of the alternative model introduced in the narrative [20]. Consequently, narrative-based corrections have the potential to supplant the existing mental models shaped by exposure to misinformation [21,22]. In addition, narratives are often more persuasive because of their inherent simplicity and accessibility, making them easier to process than argument-based messages [23]. Moreover, narratives are often perceived as having less overt persuasive intent, which reduces audience resistance and minimizes counterarguments [24,25].

Although narrative-based corrections are theoretically promising, empirical evidence regarding their effectiveness has been inconsistent [26]. For instance, one study demonstrated that a narrative-based correction message significantly reduced counterarguments and increased positive beliefs regarding nicotine replacement therapy compared to a nonnarrative correction message [27]. In contrast, another study [28] found no significant difference in the effects of narrative versus nonnarrative corrections on the intentions of participants to vaccinate their children with the measles, mumps, and rubella vaccine.

These conflicting findings suggest that the effectiveness of narrative corrections in combating misinformation may be influenced by a variety of factors, including those related to the message, sender, and recipient. For example, one study explored how emotional language and an emotionally impactful ending could moderate the effectiveness of narrative correction messages [29]. Another study examined the effects of a refutational ending, which explicitly highlights the correction of narrative messages [30]. Regarding sender-related factors, one study investigated the mediating role of the perceived credibility of the information source [28]. Another study focused on the moderating effect of the perceived relational closeness between the sender and recipient of a message [27]. Regarding recipient-related factors, one study explored how the need for cognition of the message recipients moderates the effectiveness of narrative corrections [31]. Another study examined the moderating effect of the motivation of recipients to use social media [32].

Thus, the inconsistencies in the effectiveness of narrative corrections for health-related misinformation observed in previous studies suggest that multiple factors contribute to success. This systematic review aims to synthesize existing studies on the effectiveness of narrative messages in correcting

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health-related misinformation and to identify the various factors that affect their effectiveness. The findings from this review will inform future research and practical applications in the field of health communication. The research questions addressed in this review are as follows.

1. Are narrative messages more effective than nonnarrative messages in correcting health-related misinformation?

2. What message-related factors enhance the effectiveness of narrative messages in correcting health-related misinformation?

3. What sender- and recipient-related factors moderate or mediate the effectiveness of narrative messages in correcting health-related misinformation?

Methods

Overview

This systematic review will be conducted in accordance with the guidelines provided in the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement [33] (Multimedia Appendix 1). This protocol will be registered with PROSPERO after peer review. The literature search had already commenced at the time of acceptance, and the analysis is planned to be completed by March 30, 2025.

Literature Search

Searches will be conducted across several databases, including PubMed, MEDLINE, CINAHL, PsycINFO, and Web of Science. A combination of keywords, informed by previous studies [34,35], will be used to search the abstracts within these databases: (narrative OR story OR storytelling OR testimonial OR anecdote OR exemplar OR episode OR vignette OR experience) AND (debunk* OR prebunk* OR correct* OR refut* OR rebuttal* OR counter* OR combat* OR retract* OR belief correction OR misinformation rejection) AND (misinformation OR disinformation OR misperception OR mislead* OR misbelief* OR fake OR conspiracy* OR myth* OR rumo* OR fals* OR fraud* OR scam* OR wrong OR inaccurate OR incorrect OR gossip OR hoax* OR fallac* OR infodemic OR misperception OR misconception OR suspicion* OR skeptic* OR unverified OR unscientific OR lie OR anti-vaccin* OR anti-vax* OR anti-scien*). No restrictions will be applied to the publication year during the searches. Additionally, the reference lists of the relevant studies will be reviewed to identify other potentially eligible publications.

Eligibility Criteria

Intervention studies that quantitatively evaluated the impact of narrative-based corrections for health-related misinformation will be included. For this systematic review, misinformation will be defined as “information that asserts or implies claims that are inconsistent with the weight of accepted scientific evidence at the time” [36], following the definition proposed in the 2025 Consensus Study by the US National Academies of Sciences, Engineering, and Medicine. This definition emphasizes the scientific status of misinformation, irrespective of the intent behind its dissemination, and provides a consistent foundation for evaluating studies included in this review. Adopting the World Health Organization’s definition of health as “a state of complete physical, mental, and social well-being and not merely the absence of disease or infirmity” [37], a comprehensive interpretation of health-related misinformation will be applied. Therefore, this review will cover topics related to health, such as physical well-being (eg, infectious diseases, obesity, reproductive health) as well as mental and social well-being (eg, nutrition, developmental health); relevant literature in these areas will be included. The eligibility criteria are summarized in Table S1 of Multimedia Appendix 2.

Study Selection

The Rayyan QCRI software [38] will be used for the screening process. Duplicate entries will be automatically identified and removed by this tool. Initially, the titles and abstracts of the studies will be reviewed to determine eligibility based on the selection criteria. The first author (TO) and the second author (HO) will independently assess the titles and abstracts. Any disagreements between the reviewers will be resolved through discussion until a consensus is reached. In cases where consensus cannot be reached, the third author (RY) will be consulted to assist in resolving the issue. Subsequently, the full texts of papers that meet the initial inclusion criteria will be reviewed independently by the first (TO) and second (HO) reviewers. If there are disagreements, the third reviewer (RY) will facilitate resolution through discussion. The screening procedure will be presented using a PRISMA flow diagram.

Data Extraction and Synthesis

The first reviewer (TO) will extract descriptive information from the eligible studies into Microsoft Excel, and the second reviewer (RY) will review the extracted data to identify errors. The data to be extracted are outlined in Table S1 of Multimedia Appendix 3. The outcomes to be extracted will include distinct constructs reflecting the effects of corrections, including (1) belief change (eg, shifts in factual accuracy judgments), (2) attitude change (eg, evaluations of health behaviors or interventions), (3) behavioral intention (eg, willingness to vaccinate), and (4) misinformation rejection (eg, explicit rejection or skepticism toward misinformation), following previous studies that differentiate these constructs as separate outcome categories [39-41].

The results will be summarized in a compact table and synthesized through a descriptive and narrative review. Given the anticipated heterogeneity in study designs, narrative intervention formats (eg, testimonial, anecdote, story, vignette), outcome measures (eg, belief change, attitude, behavioral intention), and types of comparators (eg, non-narrative text, factual correction, or control), this review will not conduct a meta-analysis. The methodological and conceptual diversity across studies is expected to preclude meaningful effect size pooling. Instead, a narrative and descriptive synthesis will be conducted to explore patterns in the effectiveness of narrative corrections and to address the predefined research questions, focusing on message-, sender-, and recipient-related factors. The findings will be discussed along with their implications for future research and practice as each of the research questions is addressed.

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Quality Assessment

To evaluate the methodological quality of the eligible studies, the first reviewer (TO) will apply the Cochrane Risk of Bias 2 (RoB-2) tool for assessing the risk of bias in randomized controlled trials [42]. This tool allows for the assessment of the overall risk of bias in each study by examining areas such as randomization processes, allocation concealment, handling of missing data, outcome measurement, and outcome reporting. Each of these domains will be categorized as low risk, some concerns, or high risk based on the responses to several signaling questions. For nonrandomized studies, the Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) tool will be applied to ensure appropriate assessment of methodological quality [43]. The second reviewer (HO) will verify the quality assessment results by using the RoB-2 tool and ROBINS-I tool, and a third reviewer (RY) will be consulted if required. The results of the quality assessment will not be used as a basis for excluding studies from the review.

Results

The findings will be summarized in tables and presented as a descriptive review. The implications of the results for future research and practices will be explored while addressing the research questions. The results of this review will be shared at an appropriate conference and submitted for publication in a peer-reviewed journal. It is anticipated that the review will be submitted for publication by the northern summer of 2025.

Discussion

Principal Findings

This systematic review aims to be the first comprehensive examination of previous studies comparing the effectiveness of narrative and nonnarrative approaches in correcting health-related misinformation. However, a simple comparison between these 2 approaches is insufficient. Although the use of narratives to correct health-related misinformation holds theoretical promise, the results of previous studies have been inconsistent [26]. This inconsistency is likely to be due to various factors that influence the effectiveness of narratives. Previous studies have explored message-related factors that may affect narrative effectiveness, such as the inclusion of a refutational ending [30] and conversion narratives [32], in which the narrator undergoes a change in belief. This review will examine the types and effects of these message-related factors. Additionally, studies have identified factors that moderate or mediate the effectiveness of narratives in correcting health-related misinformation. These include sender-related factors such as source credibility [28] and the type of endorser [27] and recipient-related factors, including motivations for using social media [32] and issue involvement [30]. This systematic review will provide insights into the types and effects of moderating and mediating factors on the effectiveness of narrative corrections. In summary, this review will be a comprehensive overview of the effectiveness of narrative interventions and the various factors influencing their success in correcting health-related misinformation, thereby contributing to the development of narrative persuasion theories and more effective future correction strategies.

Limitations

This systematic review will have limitations. Despite employing a comprehensive search strategy and using search terms based on previous systematic reviews, the possibility of incomplete retrieval of relevant literature cannot be entirely excluded. In addition, this review may overlook relevant studies published in languages other than English. Although a quality assessment of the studies included will be conducted, the findings of this review may still be influenced by the risk of biases present in the studies. Moreover, the limitations inherent in the qualitative synthesis of evidence as opposed to employing meta-analytical techniques should also be recognized.

Conclusion

Over the past few decades, the infrastructure for communication technologies has become increasingly complex, with social media platforms facilitating the easy dissemination of accurate and inaccurate information. Addressing health-related misinformation has become a critical concern in medicine and public health. This systematic review will examine the potential of narratives as a theoretically promising approach to correcting health-related misinformation. It will provide a comprehensive overview of the effectiveness of narrative-based interventions and explore the various message-, sender-, and recipient-related factors that may influence their success. The synthesis of these findings will contribute to theoretical advances in future research on the use of narratives to combat health-related misinformation and inform more effective corrective practices.

Acknowledgments

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Authors' Contributions

Conceptualization: TO
Methodology: TO
Formal analysis: TO, HO, RY
Writing – original draft: TO
Writing – review & editing: TO, HO, RY
Funding acquisition: TO

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Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA checklist.
[PDF File (Adobe PDF File), 38 KB - resprot_v14i1e69414_app1.pdf]

Multimedia Appendix 2
Eligibility criteria.
[DOC File , 33 KB - resprot_v14i1e69414_app2.doc]

Multimedia Appendix 3
Data extraction.
[DOC File , 31 KB - resprot_v14i1e69414_app3.doc]

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Abbreviations

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RoB-2: Cochrane Risk of Bias 2
ROBINS-I: Risk Of Bias In Non-randomized Studies - of Interventions

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Protocol

Vascular and Cardiovascular Outcomes of Smoking Cessation and Switching to Electronic Cigarette Use: Protocol for a Systematic Review of Prospective Studies

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Abstract

Background: Despite the well-documented adverse health effects of tobacco smoking, it remains prevalent worldwide. Chronic tobacco smoking is associated with significant cardiovascular effects, including an increased risk of cardiovascular disease and vascular dysfunction. In recent years, the use of electronic cigarettes (ECs) has increased, with many former tobacco cigarette smokers switching to ECs to aid in smoking cessation. To date, no systematic review has synthesized prospective evidence on key vascular and cardiovascular outcomes among adult smokers who quit or switch to ECs, with the specific aim of identifying early and clinically meaningful indicators of vascular recovery.

Objective: This systematic review aims to summarize the current prospective studies on the vascular effects of switching to exclusive EC use and the overall effects of smoking cessation on regular tobacco cigarette smokers. The review will focus, in particular, on early indicators of vascular improvement, such as measures of vascular function, including arterial stiffness and endothelial function, as well as on heart rate, blood pressure, nonfatal myocardial infarction, nonfatal stroke, sudden cardiovascular death, and acute heart failure.

Methods: The review will be reported following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A comprehensive search was performed in PubMed and Scopus on January 12, 2025, without restrictions on the publication date. Studies will be included if they focus on cardiovascular outcomes, with study designs, including clinical trials (randomized controlled trials, observational studies), prospective cohort studies, and case-control studies. Studies involving regular smokers, aged 18 years and older, and those reporting on smoking cessation or switching to ECs will be considered. Data will be extracted using a standardized form and synthesized qualitatively. Risk of bias will be assessed using Joanna Briggs Institute's critical appraisal tools, with results informing sensitivity analyses and interpretation.

Results: As of January 2025, the preliminary search retrieved 1479 records across PubMed and Scopus. At the time of this protocol's publication, the first manuscript on vascular function outcomes was completed in July 2025 and is currently under peer review. Each subsequent review will include an updated search before completion.

Conclusions: This review will provide a comprehensive landscape of current literature on the long-term vascular effects of smoking cessation and switching to exclusive EC use. The findings will help identify early indicators of vascular damage reversal, gaps in the current evidence base, and inform future research directions. By disseminating the results through peer-reviewed

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journals, conferences, and digital platforms, the review aims to enhance the understanding of smoking cessation's impact on vascular health and support public health efforts in reducing tobacco-related harm.

Trial Registration: PROSPERO CRD420251016878; https://www.crd.york.ac.uk/PROSPERO/view/CRD420251016878

International Registered Report Identifier (IRRID): PRR1-10.2196/74949

(JMIR Res Protoc 2025;14:e74949) doi:10.2196/74949

KEYWORDS

cardiovascular disease; e-cigarettes; smoking cessation; stroke; vascular function

Introduction

Background

Tobacco smoking prevalence remains high worldwide and causes over 7 million deaths annually from smoking-related diseases [1,2]. Chronic tobacco smoking has significant cardiovascular effects impacting vascular function, leading to increased risk of cardiovascular disease and sudden cardiac death [3-5]. Conversely, stopping smoking has been shown to significantly reduce the risks of cardiovascular events [6,7], and guidelines strongly recommend smoking cessation for primary and secondary prevention of cardiovascular disease [8-10]. Efforts to promote smoking cessation have intensified, with research showing that success rates can double or triple when counseling is combined with pharmacotherapy such as varenicline [11], cytisine [12], bupropion [13], and nicotine replacement therapy [14]. Additionally, Cochrane systematic reviews, meta-analyses, and umbrella reviews suggest that electronic cigarettes (ECs) may also be effective for smoking cessation [15,16]. The US Food and Drug Administration and UK's National Institute for Health and Care Excellence (NICE) recognize ECs as less harmful than conventional smoking and a useful adjunct for smoking cessation [17,18].

Gaps in the Existing Literature

Most evidence linking smoking cessation to improved cardiovascular outcomes and vascular function comes from cross-sectional studies, which cannot establish causality. In addition, prior reviews often aggregate studies with highly heterogeneous designs, populations, and outcome measures, and many focus only on short-term or acute effects following limited EC or nicotine exposure. These limitations hinder our understanding of the long-term vascular consequences of smoking cessation or switching to exclusive EC use. Furthermore, a key limitation in evaluating smoking cessation and harm reduction strategies is the lack of early, sensitive, and clinically meaningful end points. This gap has slowed progress in understanding the full health impact of cessation therapies and reduced-risk nicotine or tobacco products. Advancing regulatory science and clinical research in this area requires identifying early indicators of biological and physiological recovery. Yet, this search remains challenging. Our understanding of early smoking–induced pathophysiological changes is incomplete, and sensitive, clinically relevant end points for early health impact assessment are still poorly defined. Although functional vascular end points are widely used, they often lack the sensitivity to capture subtle, early-stage changes in recent quitters. Specifically, no systematic review to date has synthesized prospective evidence focused on key vascular and cardiovascular end points and incident cardiovascular events among adult smokers who either quit or switch to ECs in order to detect early and clinically significant end points of vascular damage reversal.

Study Objectives

To address these limitations, this systematic review aims to synthesize prospective evidence on the vascular and cardiovascular outcomes associated with smoking cessation and switching to exclusive EC use in order to identify early and clinically relevant indicators of vascular recovery. The review will examine changes in vascular function—including pulse wave velocity (PWV), intima-media thickness (IMT), and flow-mediated dilatation (FMD)—as well as cardiovascular indicators such as blood pressure and heart rate, and the incidence of major events, including nonfatal myocardial infarction, nonfatal stroke, sudden cardiovascular death, and acute heart failure. In addition, it will explore methodological patterns, assess the quality of available studies, and highlight areas for future research.

Methods

The systematic review will be reported following the principles outlined in PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [19] and has been registered in PROSPERO (registration CRD420251016878).

Search Strategy

A thorough literature review was performed in January 12, 2025, by using PubMed and Scopus databases. Search queries have been designed to identify relevant studies in each database. Details of the search strings for each database are provided in Table 1. To identify additional literature, 2 reviewers will examine the reference lists of the included studies. Medical experts will also be consulted to ensure that no recent relevant studies have been overlooked. The search will be conducted without any restrictions on publication date. Only studies published in English will be considered.

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Table 1. Search strategy for each database.

Database	Search query	Date
PubMed	(((“smoking”[MeSH Terms] OR “smoking”[Title/Abstract] OR “smok*”[Title/Abstract] OR “cigarette”[Title/Abstract]) AND (“cessation”[Title/Abstract] OR “quit*”[Title/Abstract] OR “abstinence”[Title/Abstract] OR “stop*”[Title/Abstract])) OR (“ex-smokers”[Title/Abstract] OR “former smokers”[Title/Abstract])) AND (“myocardial infarction”[MeSH Terms] OR “myocardial infarction”[Title/Abstract] OR “ischemic stroke”[MeSH Terms] OR “ischemic stroke”[Title/Abstract] OR “stroke”[MeSH Terms] OR “stroke”[Title/Abstract] OR hemorrhagic stroke[MeSH Terms] OR hemorrhagic stroke[Title/Abstract] OR “Major Adverse Cardiac Events (MACE)”[Title/Abstract] OR “Blood Pressure”[MeSH Terms] OR “Blood Pressure”[Title/Abstract] OR “Arterial Pressure” [MeSH Terms] OR “Arterial Pressure”[Title/Abstract] OR “Heart Rate” [MeSH Terms] OR “Heart Rate”[Title/Abstract] OR “Vascular Stiffness” [MeSH Terms] OR “Vascular Stiffness”[Title/Abstract] OR “Pulse Wave Velocity”[Title/Abstract] OR “Pulse Wave Analysis”[MeSH Terms] OR “Pulse Wave Analysis”[Title/Abstract] OR “Augmentation index”[Title/Abstract] OR AI@75[Title/Abstract] OR AI75[Title/Abstract] OR “Endothelial function”[Title/Abstract] OR “flow mediated dilatation”[Title/Abstract] OR “forearm venous occlusion”[Title/Abstract] OR “plethysmography”[MeSH Terms] OR plethysmography[Title/Abstract] OR “EndoPAT”[Title/Abstract] OR “peripheral arterial tonometry”[Title/Abstract] OR “microscopic angioscopy”[MeSH Terms] OR “microscopic angioscopy” [Title/Abstract] OR capillaroscopy[Title/Abstract]) AND (“follow-up studies”[MeSH Terms] OR follow up studies[Text Word] OR “Cohort Studies”[MeSH Terms] OR “Cohort Studies”[Text Word] OR “prospective studies”[MeSH Terms] OR “prospective studies”[Text Word])	January 12, 2025
Scopus	(“smoking” OR “smok*” OR “cigarette”) AND (“cessation” OR “quit*” OR “abstinence” OR “stop*” OR “ex-smokers” OR “former smokers”) AND (“myocardial infarction” OR “ischemic stroke” OR “stroke” OR hemorrhagic AND stroke OR “Major Adverse Cardiac Events (MACE)” OR “Blood Pressure” OR “Arterial Pressure” OR “Heart Rate” OR “Vascular Stiffness” OR “Pulse Wave Velocity” OR “Pulse Wave Analysis” OR “Augmentation index” OR “flow mediated dilatation” OR “plethysmography” OR “peripheral arterial tonometry” OR “microscopic angioscopy” OR capillaroscopy) AND (“follow-up studies” OR “Cohort Studies” OR “prospective studies” OR “longitudinal studies” OR “longitudinal”)	January 12, 2025

Study Selection

The studies will be selected based on the following inclusion and exclusion criteria.

Inclusion Criteria

The following studies are included.

1. Studies with the following end points: vascular function (eg, PWV, augmentation index, cardio-ankle vascular index, IMT, photoplethysmography, stiffness index, FMD), nonfatal myocardial infarction, nonfatal stroke, cardiovascular death, acute heart failure, heart rate/heart rate variability, blood pressure.
2. Study design: clinical trials (randomized controlled trials), parallel observational or interventional, prospective cohort studies, and case-control studies.
3. Participants: patients aged 18 years and older who are classified as regular smokers according to each study’s own definition. We chose not to apply a strict quantitative threshold at the inclusion stage, as many primary studies do not provide standardized or detailed metrics of smoking exposure (eg, cigarettes per day, duration, pack-years). Instead, we will extract and tabulate all available quantitative indicators of smoking behavior and describe the variability across studies. Where feasible, subgroup or sensitivity analyses will be conducted based on different levels or definitions of exposure to assess their impact on the overall findings.
4. Study populations with conditions defined as risk factors for cardiovascular disease will be included: rheumatoid arthritis, diabetes mellitus, dyslipidemia, and hypertension.
5. Studies on smoking cessation or switching studies (they may include dual EC and tobacco cigarette users).
6. Data (quantitative or narrative) on the effect of smoking cessation on the outcome.

Exclusion Criteria

The following studies are excluded.

1. Preclinical studies, retrospective cohort, cross-sectional, case series/reports.
2. Review studies, conference papers/studies not peer-reviewed.
3. Studies with fewer than 30 participants and without a sample size calculation or justification.
4. Length of study less than 1 week.
5. Switching studies using other smokeless tobacco aside from ECs (ie, snus/shisha).

To ensure alignment with the review’s objective, we will exclude studies where persistent dual use (ie, simultaneous EC and tobacco cigarette use) is not clearly separated from exclusive EC use. If a study includes participants who transitioned from dual use to exclusive EC use, data will be included only if the outcomes are reported after the point of exclusive use and the time frame is explicitly defined. Additionally, when outcomes are stratified by biochemical verification (eg, CO levels), we will consider those subgroups separately. This approach is intended to minimize the risk of confounding and improve interpretability of cardiovascular effects attributed to exclusive EC use.

Two independent reviewers will screen each title and abstract to identify studies for full-text review. Studies that appear suitable for inclusion or cannot be clearly excluded based on the title and abstract will be carried forward for further assessment. The records and duplicates will be managed using EndNote (version 21; Thomson Reuters). Each remaining full-text study will then be independently evaluated by the 2 reviewers to determine its eligibility. Any disagreements will be resolved through discussion and consensus. Studies meeting

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the predefined inclusion criteria will be selected for the qualitative/quantitative synthesis.

Data Extraction and Synthesis of Findings

Data extraction will be performed using a standardized form specifically designed for this purpose. The relevant data, including the lead author's name (surname, first name), publication year, country, study design, mean age of the cohort(s), percentage of male and female participants, sample size, study population, comorbidities (if applicable), prior smoking history (minimum cigarettes per day), prior smoking history (pack years), whether dual use of e-cigarettes and smoking is allowed (yes/no), whether other concomitant nicotine products are allowed (yes/no), follow-up duration (in weeks), vascular and cardiovascular end point, and main findings (focused solely on the effects of abstinence from cigarette smoking on vascular outcomes, with quantitative data provided where available or summarized narratively), will be systematically recorded and organized in a table. Potential limitations and conclusions of the studies will also be noted. In the qualitative synthesis, emphasis will be placed on the clinical impact of smoking abstinence on vascular outcomes.

If sufficient and comparable data are available, a meta-analysis will be performed. The primary measures of effect will be the odds ratio with a corresponding 95% CI for dichotomous outcomes and the mean difference with a 95% CI for continuous outcomes. Due to potential variations in study populations, interventions, and outcome definitions across trials, a random-effects model will be employed to account for potential heterogeneity among studies. The meta-analysis will be conducted using the *STATA/BE* (version 17; StataCorp LT) statistical package. Heterogeneity among the included studies will be assessed using the I^2 statistic, with an I^2 value >50% considered indicative of substantial heterogeneity. Potential publication bias will be assessed visually using funnel plots. If a meta-analysis is not feasible due to substantial heterogeneity among studies, a narrative synthesis will be conducted.

Risk of Bias Assessment

Two authors will independently assess the methodological quality of the included studies, using the Joanna Briggs Institute's critical appraisal tools tailored to each specific study design [20]. Each checklist includes a set of items covering core domains such as participant selection, exposure and outcome measurement, control of confounding, and the appropriateness of statistical analysis. Any disagreements will be resolved through discussion to reach a consensus or by consulting a third author if necessary. Risk of bias assessments will be presented in a tabular or graphical format, with responses recorded for each item per study. A narrative synthesis will accompany the tables, summarizing methodological quality across studies grouped by study design. The risk of bias assessments will inform the synthesis and interpretation of results. In particular, sensitivity analyses will be conducted—quantitative or narrative—by excluding studies presenting multiple methodological limitations as identified through the Joanna Briggs Institute's checklists. Additionally, we will transparently report how the quality of the included studies influences the level of confidence in the findings, especially in the narrative synthesis. This approach will help highlight areas of greater methodological robustness versus vulnerability.

Findings Reporting

To ensure a focused and comprehensive analysis, each major end point category (ie, vascular function, heart rate/blood pressure, and major cardiovascular outcomes) will be addressed in separate publications. These domains are methodologically and clinically distinct, often involving different measures, statistical models, and implications for harm reduction. Rather than merging all the findings into a single, overly complex manuscript, this approach is intended to enhance clarity, support in-depth interpretation, and serve both clinical and research audiences more effectively. To prevent fragmentation, each paper will include a concise overview of the full systematic review protocol and clearly explain the rationale behind the separate reporting. Publications will be cross-referenced to allow readers to easily access related findings. A final synthesis manuscript will integrate all the results and discuss their broader clinical and public health implications.

Results

As of January 12, 2025, the preliminary literature search has been completed for the database searches, with the following results: PubMed (n=1126), Scopus (n=696), duplicates (n=343), and a total of 1479 records. At the time of publication of this protocol, the first manuscript, focusing on vascular function outcomes, was completed in July 2025 and is currently under peer review. The full series of reviews, covering all outcome domains, is scheduled for completion by December 2026. To ensure the inclusion of the most up-to-date evidence, the search strategy will be rerun and updated prior to the finalization of each individual review.

Discussion

This protocol outlines the methodology for a systematic review aimed at synthesizing prospective evidence on the vascular and cardiovascular outcomes associated with smoking cessation and switching to exclusive EC use. By focusing on early indicators of vascular recovery, this review aims to support progress in both regulatory science and clinical research, enabling a more accurate and timely assessment of the long-term cardiovascular effects of smoking cessation and switching to alternative nicotine products.

A clearer understanding of the direct effects of stopping smoking on vascular health and cardiovascular risk factors in people who smoke has been sought in a number of reviews [21,22]. However, their conclusions have been limited by the heterogeneity of the included studies, which predominantly consist of cross-sectional designs. Cross-sectional studies provide only a snapshot of cardiovascular health at a single time point and are inherently limited in their ability to establish causality. Given the dynamic nature of vascular changes following smoking cessation, longitudinal studies are essential for capturing sustained improvements in endothelial function, arterial stiffness, and overall cardiovascular health.

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Additionally, the studies included in these review studies often vary in sample characteristics, smoking history, follow-up duration, and outcome measures, contributing to inconsistent findings. Furthermore, a major limitation of these reviews is their reliance on studies that primarily assess the vascular effects of smoking cessation and switching to ECs in hyperacute settings, rather than focusing on long-term outcomes. Acute studies, which typically measure vascular parameters within hours or days following single-dose or limited-dose exposure, provide valuable insights into immediate physiological responses to nicotine and other aerosol components. However, these short-term changes do not necessarily reflect long-term cardiovascular risks or benefits [23]. Moreover, acute studies may either overestimate or underestimate the actual impact of EC use and smoking cessation, as they fail to account for adaptation mechanisms, compensatory physiological responses, or cumulative exposure effects over time. A more comprehensive understanding requires longitudinal studies that evaluate sustained vascular changes and their clinical relevance over extended periods. Switching studies, which examine the cardiovascular effects of transitioning from combustible cigarettes to ECs, are particularly susceptible to these biases [24-30]. Many of these studies are limited by small sample sizes, short follow-up periods, or lack of adequate control groups [24-27]. We designed this systematic review with these limitations in mind, focusing exclusively on prospective studies with adequate follow-up periods to obtain more realistic and reliable data on the cardiovascular effects of smoking cessation and switching to ECs.

Vascular end points such as PWV, IMT, and FMD were selected due to their well-established roles as surrogate markers of cardiovascular risk. More specifically, PWV reflects arterial stiffness and is strongly associated with future cardiovascular events, including myocardial infarction, stroke, and cardiovascular mortality [31,32]. IMT is a structural indicator of early atherosclerosis and correlates with coronary and cerebrovascular outcomes, particularly in individuals younger than 65 years [33]. FMD assesses endothelial function and has demonstrated predictive value for cardiovascular events; a meta-analysis showed that each 1% improvement in FMD is associated with a 13% reduction in major adverse cardiac events [34]. These markers capture distinct yet complementary aspects of vascular health—mechanical (PWV), structural (IMT), and functional (FMD)—and are sensitive to early changes that may occur following smoking cessation or switching to ECs. Including these end points enhances the capacity of this review to detect early vascular improvements and evaluate their clinical relevance, particularly in the short-to-medium term, where traditional hard end points may not yet be observable.

A key strength of this protocol is the rigorous focus on prospective study designs, which enhances the potential to draw temporally relevant and clinically meaningful inferences. The review's scope is broad enough to capture diverse vascular end points, yet specific in its inclusion criteria to minimize heterogeneity. A potential limitation is the exclusion of retrospective and cross-sectional studies, which may contain useful but less robust observational data. However, this decision was made to prioritize internal validity and reduce the risk of bias.

Upon completion, the findings from this systematic review will be submitted for publication in peer-reviewed journals, presented at international conferences, and disseminated through academic networks focused on tobacco harm reduction and cardiovascular prevention. The results may help inform clinical guidelines, policy discussions, and the design of future longitudinal studies evaluating the health impact of alternative nicotine products.

In conclusion, this systematic review protocol outlines a structured and rigorous approach to evaluating the prospective evidence on the vascular and cardiovascular effects of smoking cessation and switching to exclusive EC use. By focusing on high-quality study designs and clinically relevant early end points, the review aims to produce a meaningful synthesis of the available literature, identify gaps for future research, and contribute to the ongoing discussion around harm reduction and cardiovascular risk mitigation in smokers. The findings will support researchers, clinicians, and policymakers in understanding the long-term impact of these behavioral transitions on vascular health.

Acknowledgments

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Data Availability

Data sharing is not applicable to this study, as no data sets were generated or analyzed during this study.

Authors' Contributions

Conceptualization: RP (lead), JG (equal)
Data curation: GRMLR (lead), JY (equal)
Formal analysis: JG (lead), JY (supporting)
Funding acquisition: RP (lead)
Investigation: JY (lead), GG, DC, and TO (supporting)
Methodology: GRMLR (lead)
Project administration: RP (lead), JG (equal)

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Resources: RP (lead)
Supervision: RP (lead), JG (equal)
Validation: DC (lead), GG, and TO (supporting)
Visualization: JY (lead), GG, and DC (supporting)
Writing – original draft: GRMLR (lead), JY (supporting)
Writing – review & editing: RP and JG (lead), GG, DC, and TO (supporting)

Conflicts of Interest

GRMLR serves as Associate Editor for JMIR Research Protocols. However, she was not involved in any aspect of the editorial process for this manuscript, including its review, decision-making, or handling, which were managed independently according to the journal's policies. RP is professor of Medicine and Director of the Institute for Internal Medicine and Clinical Immunology at Catania University. He has received the grants: U-BIOPRED, AIR-PROM, IRIS, Ministero dell'Università e della Ricerca (MUR) PNRR 3277/2021, PNRR 341/2022, and PNRR 411/2021 funded by NextGenerationEU of the European Commission. He has received investigator-initiated grants from Foundation for a Global Action to End Smoking (formerly known as Foundation for Smoke-Free World), Pfizer, GlaxoSmithKline, CV Therapeutics, NeuroSearch A/S, Sandoz, Merk Sharp & Dohme, Boehringer Ingelheim, Novartis, Arbi Group Srl., Duska Therapeutics, and Forest Laboratories. He is the founder of the Center for Tobacco Prevention and Treatment and of the Center of Excellence for the Acceleration of Harm Reduction at Catania University. He has been consulting for Pfizer, Boehringer Ingelheim, Duska Therapeutics, Forest Laboratories, CV Therapeutics, Sermo Inc., GRG Health, Clarivate Analytics, Guidepoint Expert Network, and GLG Group. He receives textbooks royalties from Elsevier and EDRA. He is Chair of the European Technical Committee for Standardization on Requirements and test methods for emissions of electronic cigarettes (CEN/TC 437; WG4) and scientific advisor at RIDE2Med.

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Abbreviations

EC: electronic cigarette
FMD: flow-mediated dilatation
IMT: intima-media thickness
NICE: National Institute for Health and Care Excellence
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PWV: pulse wave velocity

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Protocol

The Use of Repetitive Transcranial Magnetic Stimulation to Improve Cognitive Impairment in Patients With Stroke Based on rs-fMRI Findings: Protocol for a Meta-Analysis

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Abstract

Background: Poststroke cognitive impairment (PSCI) is a chronic form of poststroke cognitive dysfunction that affects approximately one-third of the survivors of stroke. PSCI significantly increases the rates of mortality and functional disabilities, such as limitations in motor function, speech, and activities of daily living. Therefore, effective treatments are needed for patients with PSCI. Repetitive transcranial magnetic stimulation (rTMS) has been shown to exert beneficial behavioral effects in patients with PSCI. More importantly, a limited number of neuroimaging studies with small sample sizes have reported the beneficial effects of rTMS on brain plasticity and its reciprocal influence on cognitive and behavioral performance. Resting-state functional magnetic resonance imaging (rs-fMRI) has been widely used to study changes in brain activity, but there is no consensus regarding which brain regions play pivotal roles in rTMS for patients with PSCI.

Objective: This study aims to explore the therapeutic effects of rTMS on changes in the brain activity of patients with PSCI, thereby providing robust evidence to elucidate its neuroimaging mechanisms.

Methods: In this meta-analysis, we will systematically search the PubMed, Embase, Cochrane Library, Web of Science, China Biology Medicine, and China National Knowledge Infrastructure databases, VIP Chinese Science and Technology Periodical Database, and the China WanFang Database up to December 2024 to identify randomized controlled trials comparing active rTMS with sham stimulation conditions or conventional control conditions in patients with PSCI. The primary outcomes will include the amplitude of low-frequency fluctuation, fractional amplitude of low-frequency fluctuation, regional homogeneity, and functional connectivity across the whole brain. The secondary outcomes will include the Montreal Cognitive Assessment and Mini-Mental State Examination scores. Statistical analyses will be conducted via Review Manager (version 5.4), Seed-based d Mapping with Permutation of Subject Images (version 6.23), and Stata (version 18.0) software to assess study quality, evaluate the risk of bias, and analyze the outcome measures.

Results: The study will offer a comprehensive analysis of the available evidence on the use of rTMS to improve cognitive impairment in patients with stroke based on rs-fMRI findings. The meta-analysis will be conducted from July 2024 to April 2026, following this predefined protocol. The process encompasses database searching and study screening (to be concluded by October 2025), data extraction and synthesis (to be completed by December 2025), and subsequent manuscript preparation and submission (anticipated by April 2026).

Conclusions: This meta-analysis will provide insights into the therapeutic potential of rTMS to improve cognitive impairment in patients with stroke. It will also highlight the strengths and limitations of the existing literature and suggest directions for future

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research. Ultimately, our study may aid future clinical decision-making concerning PSCI rehabilitation programs and provide evidence-based medical insights into the neuroimaging mechanisms of rTMS treatment for PSCI.

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KEYWORDS

repetitive transcranial magnetic stimulation; stroke; cognitive impairment; resting-state functional magnetic resonance imaging; meta-analysis; protocol

Introduction

Background

Stroke is a serious neurological disease. According to the 2022 release of the *China Stroke Report*, the incidence rate of stroke in China is 2022.0 per 100,000, with an annual incidence of 276.7 per 100,000 and a mortality rate of 153.9 per 100,000 [1]. Poststroke cognitive impairment (PSCI) is defined as a sustained cognitive deficit for at least 6 months after a stroke [2], which affects about one-third of patients with stroke [3]. PSCI significantly elevates mortality risk [4], impedes the recovery of motor and speech functions and activities of daily living [5], and substantially increases the caregiver burden and socioeconomic costs [6]. Therefore, focusing on the rehabilitation of patients with PSCI is of crucial clinical importance.

Repetitive transcranial magnetic stimulation (rTMS) is a safe, efficient, and well-tolerated noninvasive neuromodulation technique [7]. It induces cortical excitability changes through electromagnetic induction [8]. For PSCI, 2 primary therapeutic models exist: the interhemispheric inhibition model and the compensation model. The interhemispheric inhibition model posits that stroke disrupts callosal balance, suppressing the affected hemisphere while hyperactivating the unaffected hemisphere [9]. rTMS counteracts this by upregulating the affected hemisphere excitability (via high-frequency stimulation) or downregulating the unaffected hemisphere activity (via low-frequency stimulation) [10]. The compensation model proposes neuroplastic reorganization around lesions or in contralesional regions to compensate for deficits [11]. These models are integrated in the bimodal balance-recovery model, which recommends selecting rTMS strategies based on the structural preservation in the affected hemisphere [12].

Studies indicate that rTMS can modulate neural activity in specific brain regions [13,14] and improve PSCI behavioral indicators [15-23]. Numerous meta-analyses have consistently supported the effectiveness of rTMS intervention for improving cognitive function in patients with stroke [15-23]. Multiple meta-analyses consistently demonstrate rTMS-induced cognitive improvement in patients after stroke across diverse assessment tools (the Montreal Cognitive Assessment [MoCA], the Mini-Mental State Examination [MMSE], the Loewenstein Occupational Therapy Cognitive Assessment, and the Repeatable Battery for the Assessment of Neuropsychological Status) [16,17]. Significant global cognitive benefits have been observed with both high-frequency rTMS (HF-rTMS) and low-frequency rTMS (LF-rTMS) protocols targeting the dorsolateral prefrontal cortex (DLPFC) [16,17]. Enhanced executive function and working memory (although not memory or attention) have also been observed when rTMS is combined with cognitive training, with optimal effects from HF-rTMS over the left DLPFC or LF-rTMS over the right DLPFC [18]. The superior efficacy of HF-rTMS compared with LF-rTMS for DLPFC stimulation in improving cognition and functional independence (as measured by the Modified Barthel Index) has also been reported [19]. Although these studies have confirmed the behavioral efficacy of rTMS in improving PSCI, the potential neuroimaging mechanisms underlying this behavioral effect remain unclear.

Resting-state functional magnetic resonance imaging (rs-fMRI) provides a noninvasive tool for mapping rTMS-induced neural changes in PSCI [24,25]. Evidence indicates that rTMS can modulate the excitability and functional connectivity (FC) in cognition-related networks (eg, enhanced DLPFC-frontotemporal coupling [26], and increased amplitude of low-frequency fluctuation [ALFF] in the medial prefrontal cortex [27]). Concurrently, cognitive scores (MoCA, MMSE, and Modified Barthel Index) and neural activity have also improved [26-31]. However, systematic evidence quantifying the consistent neuroimaging effects of rTMS remains limited, which hinders the clarification of its mechanistic pathways and clinical optimization. Existing findings are predominantly derived from small-sample, single-center randomized controlled trials (RCTs), resulting in insufficient statistical power and generalizability [27,28]. Although narrative reviews acknowledge the potential of functional magnetic resonance imaging (fMRI) for elucidating rTMS mechanisms, they rely on the qualitative synthesis of methodologically heterogeneous studies and cannot integrate spatial patterns of neural change [32]. Crucially, no quantitative meta-analysis has yet synthesized coordinate-based neuroimaging data to identify robust, spatially convergent neural targets of rTMS in PSCI.

Objectives

This coordinate-based meta-analysis (CBMA) aims to (1) quantitatively synthesize evidence regarding the effects of rTMS on cognitive function in patients with PSCI, (2) identify consistent patterns of rTMS-induced neural changes using voxel-wise meta-analysis of fMRI data, (3) explore the effects of intervention parameters—including stimulation frequency, target location, and intensity—as potential moderators of efficacy, and (4) explore whether rTMS sham stimulation intervention has a placebo effect. This study will pioneer the application of CBMA in rTMS neuromodulation research for PSCI, with the goal of advancing mechanistic understanding

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and supporting evidence-based optimization of stimulation protocols.

Methods

The protocol of this meta-analysis will be conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols (PRISMA-P) statement guidelines [33]. The PRISMA-P checklist is shown in Multimedia Appendix 1. This meta-analysis protocol was registered in PROSPERO (CRD42024562477).

Study Inclusion and Exclusion Criteria

Types of Studies

This meta-analysis will include RCTs reporting rTMS interventions based on rs-fMRI for improving PSCI. Studies comparing rTMS with conventional treatments or sham stimulation will be eligible. All eligible rs-fMRI studies that meet these criteria will be included, regardless of language or publication type. Non-RCTs, such as case reports, conference papers, animal experiments, systematic reviews, and meta-analyses, will be excluded.

Types of Participants

The participants in the study will consist of patients with PSCI, with inclusion criteria independent of sex, nationality, ethnicity, or treatment setting.

Types of Interventions

Interventions

We will consider trials where rTMS is administered for at least 1 session. Interventions include HF-rTMS, LF-rTMS, intermittent theta burst stimulation, continuous theta burst stimulation, and single-pulse stimulation, or comparisons among these 5 rTMS modalities.

Comparators

The control group will receive conventional treatments or sham stimulation.

Combination Interventions

We plan to include combination interventions where rTMS treatment is combined with pharmacological treatment or other clinical intervention methods. We will only include trials where both the intervention and control groups receive identical pharmacological treatments or other clinical intervention methods.

Outcome Measures

Primary Outcomes

Studies reporting any fMRI analysis method capable of effectively assessing changes in brain activity and functional states, such as the ALFF, fractional ALFF (fALFF), regional homogeneity (ReHo), and FC across the whole brain, will be considered eligible for inclusion. The ALFF and fALFF are validated rs-fMRI analysis methods that evaluate neuronal activity by measuring low-frequency oscillations (0.01-0.08 Hz) in the blood oxygen level–dependent (BOLD) signal [34]. The ALFF and fALFF accurately reflect spontaneous neuronal activity in the resting state from an energy perspective; increased ALFF and fALFF indicate heightened spontaneous activity within a brain region, whereas decreased ALFF and fALFF suggest reduced spontaneous activity [35]. ReHo assesses regional synchronization of BOLD signal fluctuations based on local correlations [36]. This analysis method provides stable insights into the temporal coherence of local neuronal activity. FC is defined as the temporal correlation between neurophysiological (functional) measurements obtained from distinct brain regions [37]. FC can reveal the key roles and regulatory influences on the activity of the target brain area of the whole network.

These methods can be used to explore the characteristics and patterns of changes in brain activity in patients with PSCI after rTMS treatment, revealing their neuroimaging mechanisms. All evaluations are conducted via fMRI and reported in the standard stereotaxic space of Talairach or the Montreal Neurological Institute with 3D coordinates (x, y, and z).

Secondary Outcomes

Any study reporting an assessment scale that can effectively reflect cognitive function in patients with PSCI, such as the MoCA and MMSE, will be considered eligible. Both the MoCA score and the MMSE score have been shown to correlate with age and years of education. The MoCA is a simple, stand-alone cognitive screening tool known for its high sensitivity. It assesses important cognitive domains and is a 30-point test. It also has excellent test-retest reliability [38,39]. The MMSE is a concise, standardized assessment tool used to evaluate patients' cognitive status. The maximum score is 30 points. It measures orientation, attention, immediate and short-term memory, language, and the ability to follow basic verbal and written instructions. The test yields a cumulative score that indicates an individual's level of cognitive functioning on a standardized scale [39,40].

Search Methods for the Identification of Studies

Electronic Searches

Our search will include databases such as the PubMed, Embase, Cochrane Library, Web of Science, China Biology Medicine, and China National Knowledge Infrastructure databases, the VIP Chinese Science and Technology Periodical Database, and the China WanFang Database from their inception up to December 31, 2024. Our search strategy will incorporate key terms such as "stroke," "transcranial magnetic stimulation," "cognition," and "magnetic resonance imaging." To ensure comprehensiveness, we will conduct an exhaustive search within each database across all relevant fields (eg, titles, abstracts, and keywords) using both Medical Subject Headings (MeSH) and free-text terms. Taking the PubMed database as an example, the retrieval strategy is shown in Table 1. The search strategies for all the databases are described in detail in Multimedia Appendix 2.

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Table 1. Search strategy for PubMed.

Number	Terms
1	Stroke [MeSH[a] Terms]
2	Strokes OR Cerebrovascular Accident OR Cerebrovascular Apoplexy OR Cerebrovascular Stroke OR Cerebral Infarction OR Cerebral Hemorrhage
3	(Stroke [MeSH Terms]) OR (Strokes OR Cerebrovascular Accident OR Cerebrovascular Apoplexy OR Cerebrovascular Stroke OR Cerebral Infarction OR Cerebral Hemorrhage)
4	Transcranial Magnetic Stimulation [MeSH Terms]
5	Transcranial Magnetic Stimulations OR Repetitive Transcranial Magnetic Stimulation OR rTMS[b] OR Intermittent Theta Burst Stimulation OR Continuous Theta Burst Stimulation
6	(Transcranial Magnetic Stimulation [MeSH Terms]) OR (Transcranial Magnetic Stimulations OR Repetitive Transcranial Magnetic Stimulation OR rTMS OR Intermittent Theta Burst Stimulation OR Continuous Theta Burst Stimulation)
7	Cognition [MeSH Terms]
8	Cognitive Dysfunction [MeSH Terms]
9	Cognition OR Cognitive Dysfunction OR Cognitive Impairment
10	((Cognition [MeSH Terms]) OR (Cognitive Dysfunction [MeSH Terms])) OR (Cognition OR Cognitive Dysfunction OR Cognitive Impairment)
11	Magnetic Resonance Imaging [MeSH Terms]
12	Magnetic Resonance Imaging OR Functional Magnetic Resonance Imaging OR fMRI[c] OR Resting-state Functional Magnetic Resonance Imaging OR rs-fMRI[d]
13	(Magnetic Resonance Imaging [MeSH Terms]) OR (Magnetic Resonance Imaging OR Functional Magnetic Resonance Imaging OR fMRI OR Resting-state Functional Magnetic Resonance Imaging OR rs-fMRI)
14	(((((Stroke [MeSH Terms]) OR (Strokes OR Cerebrovascular Accident OR Cerebrovascular Apoplexy OR Cerebrovascular Stroke OR Cerebral Infarction OR Cerebral Hemorrhage)) AND ((Transcranial Magnetic Stimulation [MeSH Terms]) OR (Transcranial Magnetic Stimulations OR Repetitive Transcranial Magnetic Stimulation OR rTMS OR Intermittent Theta Burst Stimulation OR Continuous Theta Burst Stimulation))) AND (((Cognition [MeSH Terms]) OR (Cognitive Dysfunction [MeSH Terms])) OR (Cognition OR Cognitive Dysfunction OR Cognitive Impairment))) AND ((Magnetic Resonance Imaging [MeSH Terms]) OR (Magnetic Resonance Imaging OR Functional Magnetic Resonance Imaging OR fMRI OR Resting-state Functional Magnetic Resonance Imaging OR rs-fMRI))) AND ((1879/01/01 [Date - Publication] : 2024/12/31 [Date - Publication]))

[a]MeSH: Medical Subject Headings.

[b]rTMS: repetitive transcranial magnetic stimulation.

[c]fMRI: functional magnetic resonance imaging.

[d]rs-fMRI: resting-state functional magnetic resonance imaging.

Reference Lists

We will examine the reference lists of all included trials.

Data Collection and Management

Selection of Studies

The RCTs included will be reviewed by 2 independent researchers (XX and LX). NoteExpress software (version 4.0.0; Beijing Aegean Music Technology) will be used for independent management of the search results from the aforementioned databases. Initially, duplicate publications will be removed. After reviewing titles and abstracts, studies that do not meet the criteria will be excluded. Finally, the full texts of the remaining studies will be downloaded and reviewed to exclude those that do not meet the criteria. Any discrepancies related to study selection outcomes will be discussed and resolved by a third researcher (NZ) following cross-checking. The flowchart detailing all the study screening procedures is shown in Figure 1.

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Figure 1. Literature screening process.

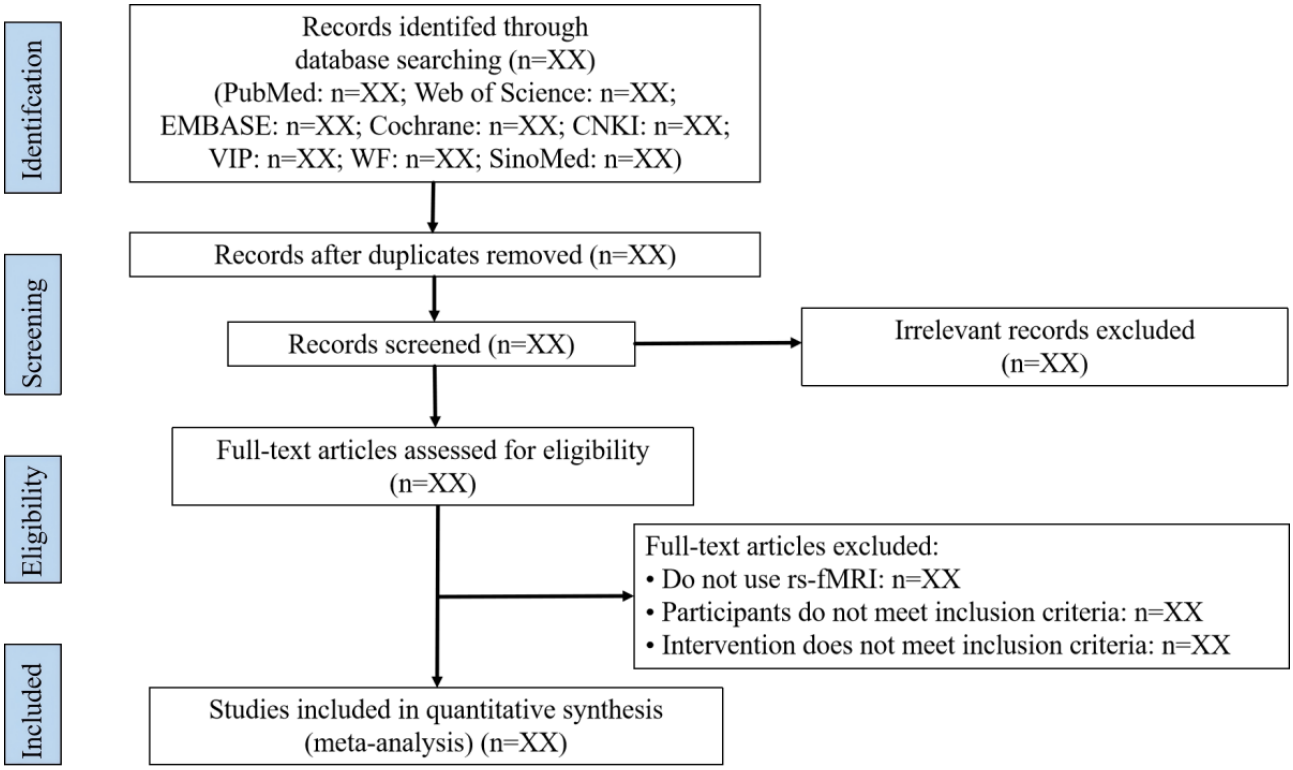

Data Extraction

Two researchers (XX and FL) will independently extract data according to the designed data extraction table. To ensure the consistency of the data extraction process, 2 researchers will be specially trained in advance. Disagreements will be resolved by consulting a third researcher (NZ). The basic information to be extracted will include the following: the essential characteristics of the included literature (first author, publication year, sample size, duration of illness, age, sex, intervention measures, fMRI analysis methods, and secondary outcome measures); specific parameters and treatment protocols of rTMS (stimulation frequency, stimulation intensity, stimulation site, total pulse number, coil type, and duration); and fMRI-related information (peak coordinates, effect sizes [*t* test values, or equivalent *z* scores or *P* values], analysis software, and standard space).

Quality Assessment

On the basis of the assessment approaches adopted in prior neuroimaging meta-analyses [41,42], the methodological quality of the included fMRI studies will be evaluated using a modified checklist. This tool comprises 2 categories and 13 items that assess key aspects such as sample size, methodological rigor, and reporting completeness, with a total possible score of 20 points. Higher scores indicate superior methodological quality. The checklist is shown in Multimedia Appendix 3. In addition, 2 researchers (XX and YR) will independently use the refined risk of bias in randomized trials tool to systematically evaluate the risk of bias across specific domains: bias arising from the randomization process, bias due to deviations from intended interventions, bias due to missing outcome data, bias in the measurement of the outcome, and bias in the selection of the reported result. The assessment of each domain will be rated as "low risk," "some concerns," or "high risk" [43]. Assessments will be conducted independently and then cross-checked. Disagreements will be resolved by consulting a third researcher (NZ).

Data Synthesis and Meta-Analysis

The outcome measures will be statistically analyzed using the following software: Seed-based d Mapping with Permutation of Subject Images (SDM-PSI; version 6.23) and Stata (version 18.0; StataCorp).

Imaging Data

The SDM-PSI will be used to analyze differences in brain activity between groups and within groups. Initially, peak coordinates and effect sizes (*t* test values, equivalent *z* scores or *P* values) from each study report will be extracted to prepare text files of peak values. During preprocessing, the software will use these files to recreate the effect size CIs within studies. A meta-analysis will then be conducted to determine the mean effects of ALFF, fALFF, ReHo, and FC coordinates, weighted by sample size and variance, for each study. Finally, a meta-regression analysis will be conducted to identify relationships between ALFF, fALFF, ReHo, and FC changes and MoCA, MMSE, age, and course of disease.

Behavioral Data

Stata software will be used to analyze behavioral data.

Continuous Outcomes

For outcomes assessed using the same scale, we will summarize the data with mean differences and 95% CIs. For outcomes assessed using different but conceptually similar scales, we will use standardized mean differences and 95% CIs to summarize

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the data. Forest plots will be generated to display the hypothesis test results.

Dichotomous Outcomes

We will summarize dichotomous outcomes using odds ratios, risk ratios, or risk differences, along with their corresponding 95% CIs.

Dealing With Missing Data

We will contact the study authors to obtain the missing data. If we cannot obtain these data, we will directly report the outcomes of these studies rather than include them in the meta-analysis.

Assessment of Heterogeneity

The methodological heterogeneity inherent in fMRI studies presents a challenge for meta-analytic synthesis. To evaluate between-study heterogeneity, we will extract peak coordinates reported in the Montreal Neurological Institute space and quantify statistical inconsistency using the I^2 statistic [44]. An I^2 value <50% will be interpreted as indicating low heterogeneity. For behavioral data, depending on trial homogeneity (P>.10, I^2<50%), fixed-effects or random-effects models will be used for data synthesis. If high levels of heterogeneity are indicated by visual inspection of the forest plots or an I^2 statistic of ≥50%, we will explore the sources of heterogeneity via predefined subgroup analyses or sensitivity analyses.

Assessment of Reporting Bias

Funnel plots will be used to assess publication bias for outcomes that are reported in more than 10 studies. Symmetrical funnels will indicate no publication bias, whereas asymmetry will suggest its presence. For outcomes that are reported in fewer than 10 studies, the Egger test will be used to assess publication bias, and the P value will be reported accordingly.

Analysis of Subgroups

We will perform subgroup analysis according to the following hierarchy: tier 1 (effect modifiers)—intervention strategies (pure rTMS interventions or combination interventions) and type of control intervention (sham rTMS or non-rTMS); tier 2 (stimulation parameters)—stimulation site (DLPFC or non-DLPFC), frequency (low frequency or high frequency), intensity (%Motor Threshold) and pattern (HF-rTMS, LF-rTMS, intermittent theta burst stimulation, continuous theta burst stimulation, or single-pulse stimulation); and tier 3 (clinical characteristics)—age (<60 y or ≥60 y), sex (male or female), disease course (acute: <3 mo, subacute: 3-6 mo or chronic: >6 mo), hemiplegic side (left, right or bilateral), type of stroke (ischemic or hemorrhagic), and lesion location (cortical, subcortical or mixed).

This study will also evaluate the difference in efficacy between pure rTMS interventions and combination interventions using a subgroup interaction test (P<.05 indicates significant interaction), and calculate the E value to quantify how strong residual confounding would need to be to overturn the conclusion (E value >2.0 indicates robustness).

These analyses aim to (1) identify potential effect modifiers contributing to heterogeneity, (2) quantify the magnitude of effect size variations across clinically relevant subgroups, (3) delineate optimal stimulation parameters for specific patient phenotypes, and (4) assess the robustness of primary outcomes by controlling for confounding variables.

Sensitivity Analysis

We will investigate the robustness of our findings using sensitivity analysis. Specifically, we will apply the leave-one-out method. This process involves systematically excluding specific studies to assess their individual impact on the results. We will evaluate the influence of bias risk (excluding studies with high bias risk), data synthesis methodology, and significant heterogeneity (excluding trials identified as major sources of heterogeneity).

Grading of Recommendations Assessment, Development, and Evaluation Assessment

The certainty of the evidence will be evaluated using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) framework [45]. This systematic approach assigns 1 of 4 grades, “high,” “moderate,” “low,” or “very low,” to each outcome, considering limitations in design and implementation, indirectness of evidence, unexplained heterogeneity, imprecision of results, and high probability of reporting bias [46]. Two independent researchers (XX and YR) will use the “GRADEprofiler” software to assess the evidence and then import the findings into the Review Manager software (version 5.4; The Nordic Cochrane Centre, The Cochrane Collaboration). In case of discrepancies between the researchers’ assessments, a third researcher (NZ) will arbitrate.

The GRADE framework was originally designed to assess the quality of evidence for clinical outcomes (eg, mortality, symptom severity, and functional status) and is not directly applicable to neuroimaging-derived biomarkers such as ALFF, ReHo, and FC, which serve as mechanistic or surrogate end points. Therefore, in this study, the GRADE tool will be applied exclusively to behavioral measures (eg, MoCA and MMSE) for evaluating the certainty of evidence.

Results

The results of this meta-analysis will offer a comprehensive analysis of the available evidence on the use of rTMS to improve cognitive impairment in patients with stroke based on rs-fMRI findings. The meta-analysis process began with protocol development and registration in July 2024. A structured literature search and database screening will follow. Title and abstract screening, along with full-text review and eligibility assessment, will be completed by October 2025. Data extraction, synthesis, and analysis of findings will be completed by December 2025. Manuscript drafting will begin in January 2026, and the final review and submission of the completed meta-analysis are anticipated by April 2026.

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Discussion

Anticipated Findings

The study aims to investigate how rTMS improves cognitive function in patients with PSCI at the neuroimaging level. We plan to integrate relevant studies and introduce CBMA to quantitatively synthesize findings from individual neuroimaging studies [47]. In this study, we will apply SDM-PSI, which is a new algorithm for CBMA used for analyzing rs-fMRI imaging data [48,49]. First, we will use CBMA to explore patterns of neuroimaging biomarker changes in patients with PSCI following rTMS intervention. Second, we will use CBMA maps to compare differences in brain region changes before and after interventions and between groups. Third, we will use meta-regression analysis methods to investigate correlations between changes in neuroimaging indicators in different brain regions and behavioral and demographic variables. The importance of this study is that it will provide intuitive and visual imaging evidence for the efficacy of rTMS and may aid in clinical decision-making regarding PSCI rehabilitation programs through CBMA.

Limitations of This Study Design

A potential limitation of this study is that studies using rTMS for the treatment of animals were excluded from our meta-analysis. In addition, our study only reports imaging metrics such as ALFF, fALFF, ReHo, and FC. Other imaging metrics from rs-fMRI, such as effective connectivity and small-world properties, were not considered. Imaging metrics that reflect white matter and gray matter structure, such as diffusion tensor imaging and voxel-based morphometry, were also excluded. Moreover, the field of rs-fMRI still faces challenges. First, temporal variability includes susceptibility to physiological noise (eg, respiratory and cardiac artifacts) and state-dependent fluctuations [50]. Second, interpretive ambiguity arises from difficulty in distinguishing neural from vascular contributions to the BOLD signal [51]. Third, analytical heterogeneity results from issues with cross-study comparability arising from inconsistent preprocessing pipelines and connectivity metrics [52]. These limitations need to be addressed in future related studies.

Conclusions

Our protocol, based on rs-fMRI findings, will summarize the beneficial role of neuroimaging metric changes after rTMS intervention in cognitive-related brain regions compared with the baseline level and the control conditions. Moreover, this meta-analysis will investigate the relationship between neuroimaging changes and behavioral outcomes. In summary, our study may aid future clinical decision-making concerning PSCI rehabilitation programs and provide evidence-based medical insights into the neuroimaging mechanisms of rTMS treatment for PSCI.

Acknowledgments

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

Authors HZ and NZ are co–corresponding authors with equal status in the paper. They made important contributions to the conceptual design, implementation, revision, and improvement of this study and had shared corresponding responsibilities throughout the process. XX, HZ, and NZ designed the research. XX, LX, FL, and YR completed the data selection and extraction. XX participated in writing the original draft. XX, HZ, NZ, HL, LL, YC, and CL were responsible for revising the manuscript. All authors contributed to editorial changes in the manuscript; read and approved the final manuscript; and participated sufficiently in the work and agreed to be accountable for all aspects of the work.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol.
[DOCX File , 20 KB - resprot_v14i1e77931_app1.docx]

Multimedia Appendix 2

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Search strategy.
[DOCX File , 29 KB - resprot_v14i1e77931_app2.docx]

Multimedia Appendix 3
Criteria for objective assessment of the methodological quality of individual studies.
[DOCX File , 13 KB - resprot_v14i1e77931_app3.docx]

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Abbreviations

ALFF: amplitude of low-frequency fluctuation
BOLD: blood oxygen level–dependent
CBMA: coordinate-based meta-analysis
DLPFC: dorsolateral prefrontal cortex
fALFF: fractional ALFF
FC: functional connectivity
GRADE: Grading of Recommendations Assessment, Development, and Evaluation
HF-rTMS: high-frequency repetitive transcranial magnetic stimulation
LF-rTMS: low-frequency repetitive transcranial magnetic stimulation
MeSH: Medical Subject Headings
MMSE: Mini-Mental State Examination
MoCA: Montreal Cognitive Assessment
PSCI: poststroke cognitive impairment
RCT: randomized controlled trial

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ReHo: regional homogeneity
rs-fMRI: resting-state functional magnetic resonance imaging
rTMS: repetitive transcranial magnetic stimulation
SDM-PSI: Seed-based d Mapping with Permutation of Subject Images

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Protocol

Sustainability Evaluation of mHealth Apps and Wearables: Protocol for a Systematic Review

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Abstract

Background: Mobile health (mHealth) technology is widely used in health care systems globally to improve patients' quality of life and reduce the burden on caregivers. Mobile apps allow users to manage different health-related situations from their homes, such as self-monitoring their symptoms, keeping track of progress, and maintaining a profile for a particular condition. However, the benefits of mHealth apps are compromised due to a lack of sustainability evaluation. Currently, there is a lack of all-inclusive research that presents sustainability evaluation from economic, social, and environmental perspectives of mHealth and wearables. Thus, it is important to evaluate the sustainability of newly proposed or already in-use mHealth solutions.

Objective: The objective of this systematic literature review is to deeply understand and analyze different dimensions of sustainability in the health care domain and identify existing evaluation criteria and frameworks for mHealth solutions.

Methods: This protocol was developed following the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines. A planned and systematic approach will be used to identify, evaluate, and synthesize relevant studies reported in English. We have conducted a systematic search focusing on search terms related to sustainable health care, mHealth solutions, and evaluation or assessment criteria in digital databases of Scopus, Web of Science, ACM, PubMed, PubMed Central, and CINAHL.

Results: As of September 19, 2024, preliminary searches have been conducted, identifying 1368 relevant papers that meet the inclusion and exclusion criteria and are eligible for further screening.

Conclusions: This protocol will guide the review of existing literature on essential aspects of the sustainability of mHealth solutions and evaluation frameworks. To the best of our knowledge, the proposed systematic review will be the first review to extensively study essential concepts related to defining sustainable mHealth solutions, identifying key dimensions founding the basis for evaluation frameworks, and discussing the existing sustainability evaluation frameworks for mHealth solutions.

Trial Registration: PROSPERO CRD42024599333; https://www.crd.york.ac.uk/PROSPERO/view/CRD42024599333

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KEYWORDS

sustainability; sustainable health care solutions; mHealth solutions; mobile health apps; wearables

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Introduction

Background

The World Health Organization (WHO) defines mobile health (mHealth) as "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants (PDAs), and other wireless devices" [1]. mHealth innovations can provide quality health care services to the public and health care professionals [2]. These applications serve multiple purposes, such as monitoring, management, and communicating health-related information between a patient and health care provider [3]. Additionally, mHealth technology promises to reduce the burden of meeting in-person health care needs of a growing population, especially older people, by providing facilities like remote consultation and online appointments in accordance with the needs of patients [4]. Theoretically, mHealth solutions are considered a key to strengthening the health care system.

The Concept of Sustainability in the Health Care Domain

Sustainability is defined in terms of creating viable ecological conditions for humans and nature on this earth so that our existence can be ensured for an indefinite time [5,6]. The Brundtland Report, World Commission on Environment and Development (1987), defines sustainability as "meeting the needs of the present without compromising the ability of future generations to meet their own needs" [7]. In terms of mHealth in the health care sector, sustainability is further assessed through economic, social, and environmental dimensions [8,9]. Therefore, the sustainability of mHealth is defined in the literature as follows:

"*Sustainability rests on three components: social, economic, and environmental. In the mHealth sector, this translates into assessing the social, economic, and environmental effects of mHealth innovations*" [9].

Social aspects ensure that mHealth solutions are accessible, equitable, and culturally appropriate for diverse populations. Economic sustainability mainly focuses on the cost-effectiveness, affordability, and long-term financial viability of mHealth interventions. The environmental aspect of sustainability considers the ecological impact of mobile technologies, including energy use, electronic waste, and sustainable device lifecycles.

Lack of Sustainability Evaluation for mHealth Solutions

In 2019, around 2.5 billion people used smartphones worldwide, and 50% had a mHealth app installed [10]. Unfortunately, many users skip using mHealth apps after a short period [9]. One of the reasons behind this behavior is a lack of sustainability evaluation of mHealth solutions during the development and deployment phase, and the absence of a plan for sustainable follow-up action [2]. Moreover, the short lifespan of mHealth solutions may be due to financial structures with misaligned incentives and rapid technological advancements.

The concept of sustainable health care is gaining widespread attention from scholars and health care professionals. In the past, sustainability was associated with environmental aspects such as reducing carbon footprints and waste from product development and processes for health care facilities [11]. However, the latest research findings suggest that sustainability in health care needs to be explored from economic, social, and environmental aspects [9].

Literature [9,12-16] also highlights the importance of evaluating the sustainability of mHealth solutions and a lack of sustainability evaluation frameworks. Moreover, a number of mHealth solutions fail in the implementation and follow-up stage due to ineffective guidelines and regulations for sustainable design [2]. Another study points out that the need for sustainability from the economic and financial perspective limits the long-term and regular use of mHealth solutions by patients [17].

To date, no literature review has provided a comprehensive study on sustainability evaluation frameworks for mHealth apps and wearables together, with a focus on economic, social, and environmental aspects in health care settings.

Toward the goal of successfully studying, identifying, and analyzing these existing studies, we aim to systematically review the concept of sustainability in the health care domain and sustainable mHealth apps and wearables and discuss the success factors in developing an evaluation framework for sustainability. The theoretical assumption of this study is that a sustainability evaluation framework involving 3 pillars of sustainability (economic, social, and health environmental) will assist all stakeholders in achieving the goals of sustainable mHealth solutions.

Research Questions

In this paper, we study the concept of sustainability in health care for mHealth apps and wearables. This review aims to assess the sustainability and benefits of mHealth in terms of economic, social, and environmental sustainability. We investigate key determinants of sustainability from economic, social, and environmental factors for mHealth solutions.

To address these aims, we have set the following research questions:

1. How is sustainability defined for mHealth solutions in the context of digital health care?
2. What are the dimensions and elements of evaluating mHealth solutions' sustainability from economic, social, and environmental perspectives?
3. What metrics, tools, frameworks, and models have been proposed to evaluate the sustainability of mHealth solutions, and what methods have the studies used to propose them?

Objectives

To answer our research questions, we have identified the following objectives for the study. First, we will perform a thorough study of existing literature that defines sustainability in the health care domain, particularly for mHealth solutions, which include mHealth apps and wearables. Second, we will identify different dimensions and aspects related to evaluating

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sustainability, which form the basis for designing sustainability evaluation frameworks. Lastly, our objective is to investigate and identify the sustainability evaluation frameworks and models for mHealth solutions reported in the literature.

Methods

Ethical Considerations

In this protocol paper, we are not required to acquire ethics board approval as defined in the guidelines from the Ethics Committee of Human Sciences [18]. We have followed the University of Oulu ethics process for writing and submitting the protocol paper.

Study Design

This protocol is reported according to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015 guidelines [19]. The protocol is registered on the International Prospective Register of Systematic Reviews (PROSPERO CRD42024599333). PRISMA-P serves as a guideline for researchers to fulfill a checklist for preparing and documenting protocols for systematic literature reviews. The study structure is provided in Figure 1 and explained in detail in the next sections.

Figure 1. Illustration of the study structure.

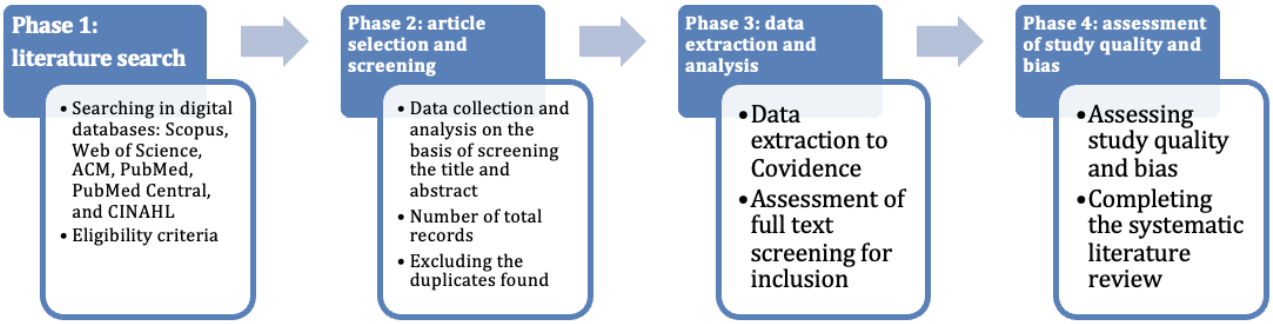

Study Participants

In this systematic review, we will include all studies that describe mHealth solutions in the form of mHealth apps and wearables for individuals or groups to improve health care quality and access to health care services. Study participants will represent all ages, genders, ethnicities, employment statuses, occupations, and roles in the reviewed study (ie, patients, health care professionals, informal caregivers, researchers, designers, and policymakers in health care).

Literature Search

A systematic search for papers published between 2012 and September 19, 2024, was performed in the digital databases of Scopus, Web of Science, ACM, PubMed, PubMed Central, CINAHL, and Google Scholar. During our initial search in these databases, it was observed that most of the research papers relevant to the scope of this study were published from 2012 onward up until 2024. Thus, we selected the time filter to be from 2012 and 2024. The keywords and terms used for searching in these databases are presented in Table 1.

Table 1. Search terms used for data collection.

Field of interest	Search string
Sustainable health (keywords related to sustainability)	(“sustainability” OR “sustainable” OR “sustainable health” OR “social sustainability” OR “economic sustainability” OR “environmental sustainability” OR “ecological sustainability”)
mHealth apps and wearables	(“mHealth“ OR ”m-Health“ OR ”mobile health“ OR ”mobile healthcare“ OR ”wearable device“ OR ”wearable technology“ OR ”wearable sensor“ OR ”smart wearable“ OR ”medical wearable“ OR ”healthcare wearable“ OR ”remote monitoring device“ OR ”biosensor“ OR ”fitness tracker“ OR ”wearable telehealth“
Evaluation methods	(“design” OR “development” OR “Framework” OR “model” OR “assessment” OR “evaluation”)

The search strings focus on three main areas suitable for the systematic literature review discussed in this protocol paper: (1) keywords related to sustainable health, including the 3 sustainability pillars; (2) keywords related to mHealth solutions, which include mHealth apps and wearable devices; and (3) keywords related to evaluation frameworks existing in the literature. An initial search in the digital databases resulted in 1368 papers in total.

Eligibility Criteria

Eligibility will be described by defining the criteria to include and exclude research papers in the literature review. Studies will be selected according to the criteria described in Textbox 1.

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Textbox 1. Eligibility criteria.

Inclusion criteria

- Peer-reviewed articles, conference proceedings, and book chapters.
- Papers available in full text.
- Papers that describe only quantitative, qualitative, or mixed research methods actually evaluating the sustainability of mHealth apps.
- Papers that define [9] and discuss the concept of sustainable health care for mHealth apps and wearables. Examples of mHealth studies without wearable devices include [11,20], which assess mHealth app sustainability, and [21], which evaluates an mHealth app with a wearable.
- Papers focused on economic, social, and environmental sustainability perspectives in the health care domain for mHealth apps and wearables.
- Papers that present or propose an evaluation framework or assessment method for evaluating the sustainability aspects of mHealth and wearables.

Exclusion criteria

- Papers that are purely study protocols, systematic literature reviews, or scoping reviews; abstracts; posters; and short papers.
- Papers that are not in English.
- Papers that are not research articles or publications or are otherwise irrelevant to the topic.
- Papers that are not related to mHealth solutions.
- Papers that only focus on the theoretical definition of sustainable health care rather than providing or doing a sustainability assessment for mHealth solutions.
- Studies on nonsustainability-related evaluation of mHealth apps.
- Studies on the usability or exploration of mHealth apps and wearables that do not address the topic of sustainability evaluation.

Article Selection and Screening

The initial search results from different databases were imported into Covidence, a web-based tool for analyzing systematic reviews [22]. Covidence allows importing the results from various databases and removes the duplicates. Later, the papers included will be first screened by looking at the title and abstracts, keeping the eligibility criteria in mind. The abstracts of all the included papers will be screened by 4 authors (SK, PK, KK, and SGM). Then, a second round of full-text screening will be performed keeping the eligibility criteria in perspective by the same authors. Any disagreements regarding the inclusion or exclusion of studies will be resolved through discussion. The disagreements will be discussed and resolved with mutual consent.

Data Extraction and Analysis

Key information from the articles included will be extracted using the data extraction form provided in Covidence. Prior to data extraction, SK will perform a pilot on a sample of 5 included papers to adjust any changes. Data extraction will be performed independently by 2 reviewers (SK and KK or SK and SGM). Any disagreements will be resolved by discussion.

Assessment of Study Quality and Bias

Quality assessment will be produced in parallel to the data extraction process using a quality assessment form included in Covidence. The study bias assessment will be performed using the checklist proposed by Dybå and Dingsøyr [23] and Yang et al [24]. For each included study, we will report our assessment of the risk of bias (ie, low, high, or unclear risk for each domain) and provide a concise description explaining the reason behind our judgment. Any discrepancies regarding the judgment of the bias of a study will be resolved through mutual discussion among authors.

Data Analysis and Synthesis

This systematic review will study different dimensions of sustainability evaluation and discuss existing frameworks for sustainability evaluation of mHealth solutions. In the included studies, the frameworks for sustainability evaluation will be addressed, and the methods used in the studies to extract the framework will also be discussed. The included publications can be based on quantitative, qualitative, or experimental data. Thus, data synthesis will be performed using quantitative and qualitative data from the full texts of the papers included. To perform data synthesis, a thematic approach will be used to identify and create categories from the results based on similarities and patterns found in different themes. These themes will help extract information about definitions and evaluate criteria or existing frameworks for sustainability in mHealth solutions. Overall, the entire search strategy from search and article selection to data extraction and data synthesis will be piloted using 5 sample papers chosen randomly from the included papers.

Results

As of September 19, 2024, a total of 1368 papers have been found to meet the inclusion criteria defined in Textbox 1. These papers have been imported into Covidence for further screening and analysis.

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Discussion

Anticipated Findings

This systematic review focuses on addressing important concepts related to the sustainability of mHealth solutions. In the health care setting, mHealth solutions claim to strengthen the health care system and its capacity without compromising on the quality of care given to patients. Currently, the growing population presents many challenges to health care systems globally in terms of reducing costs and allocating resources optimally while ensuring high quality of provided services. In such a scenario, caregivers feel a heavy burden of giving quality treatment to patients. mHealth solutions can help in many ways, such as through facilities like remote consultation, online video appointments, maintaining profiles of patients in portfolios, and engaging patients in their personalized treatment journey. However, in the absence of sustainability evaluation of mHealth solutions, these benefits will be undermined.

Hence, this literature review aims to report different concepts related to sustainable health care related to mHealth solutions, such as definitions, aspects, and sustainability evaluation criteria or frameworks. Also, we aim to study the significance of economic, social, and environmental perspectives of sustainability evaluation. Currently, there is a broad scope for exploring the concept of sustainable health care from economic, social, and environmental perspectives. Thus, the systematic analysis of existing evaluation frameworks will help in the future to create evaluation frameworks specifically for the sustainability evaluation of mHealth solutions. This protocol's primary contribution lies in defining the research gap and the research questions, as well as in its structured approach proposed for the literature review to address the gap. This gap focuses explicitly on assessing the sustainability of wearables and mHealth apps and providing guidelines for reviewing existing literature on the subject.

Limitations of This Study

First, this protocol is limited to studies published in English and subject to full text availability. Second, following standardized procedures to include and exclude studies and extract and analyze data, some degree of individual judgment is unavoidable, as is the case in other systematic literature reviews. Third, while there are some definitions of sustainability in the context of mHealth apps, the lack of a universally accepted definition can result in differences in the design of the included studies and the way they have measured the outcomes and reported the results. Lastly, this study is limited to the papers published from 2012 to 2024.

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Authors' Contributions

SK designed the study and wrote the original draft; PK, KK, and SGM contributed to the improvement of the final draft. MI enhanced and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

mHealth: mobile health
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PDA: personal digital assistant
WHO: World Health Organization

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Protocol

Efficacy of Canaloplasty for the Management of Primary Open-Angle Glaucoma: Protocol for a Systematic Review

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Abstract

Background: Glaucoma forms the leading cause of irreversible blindness worldwide, with a disproportionately rising prevalence in Asian and African countries. Primary open-angle glaucoma (POAG) accounts for the majority of cases. Medical therapies for POAG are not without side effects, and surgical treatments carry high complication rates. Ab interno canaloplasty promises a safer, minimally invasive, yet effective treatment option for mild-to-moderate POAG, as well as a cost-effective technique for low-resource countries. However, no systematic review currently exists to verify this procedure's efficacy.

Objective: The aim of this study was to develop a protocol for a systematic review aimed at evaluating the efficacy of canaloplasty against all other forms of POAG treatment.

Methods: This systematic review and meta-analysis will include randomized controlled trials evaluating the short-term, medium-term, and long-term efficacy and safety of ab interno canaloplasty in treating POAG in comparison to all other treatments. Mean changes in intraocular pressure will form the primary outcome measure. Secondary outcome measures include proportion of participants who are medication-free after treatment and mean changes in the health-related quality of life. MEDLINE, Embase, Cochrane Library, and ClinicalTrials.gov databases will be searched for relevant randomized controlled trials. All studies will be subject to prespecified inclusion and exclusion criteria. The quality of the eligible randomized controlled trials will be assessed using the Cochrane risk of bias tool. Data will be extracted with a focus on raw data where possible, and analysis will be performed using RevMan 5.4 software to compare the mean changes in intraocular pressure (mm Hg) between ab interno canaloplasty and other comparator therapies. A funnel plot will be used to assess the risk of publication bias if 10 or more trials are included in the review. I^2 statistics will be used to assess heterogeneity. Sensitivity analysis will be conducted to exclude studies with a high risk of bias and, where possible, on the primary outcome. The GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach will be used to summarize the main findings.

Results: The results of this systematic review are not yet available as it is still at the protocol stage. This protocol was registered on the PROSPERO database for systematic reviews (CRD42024558671) on June 27, 2024. Data collection for this review began on July 14, 2024, with the anticipated completion date being early 2026.

Conclusions: The findings will be important to patients, clinicians, and policymakers worldwide in addressing the growing burden and health inequality of glaucoma.

Trial Registration: PROSPERO CRD42024558671; https://www.crd.york.ac.uk/PROSPERO/view/CRD42024558671

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KEYWORDS

systematic review; ab interno canaloplasty; glaucoma; minimally invasive surgery; meta-analysis; protocol

Introduction

Glaucoma is an umbrella term used to describe a group of chronic progressive optic neuropathies associated with raised intraocular pressure (IOP) [1]. It forms the leading cause of irreversible blindness worldwide, contributing to 11% of all blindness in adults aged 50 years and older in 2020 [2]. Glaucoma currently affects 76 million adults around the globe, and this is predicted to rise to 111.8 million by 2040, with primary open-angle glaucoma (POAG) being the common subtype [3]. Furthermore, this rising prevalence is disproportionately affecting Asian and African populations, with, for instance, a higher incidence and severity of the disease being found in younger adults in Nigeria [4], which can be attributed to poor access to treatment [4]. It is therefore of interest to adopt new, cost-effective yet efficient methods of treatment that may be readily delivered in low-resource countries to ease the rising epidemic of glaucoma. This is not only vital to providing care in low-resource countries most affected by glaucoma and tackling the health inequality but would be of use at a time of increasing health care costs in the United Kingdom [5].

The treatment and prevention of glaucoma progression and thereby preservation of vision is centered around reducing IOP with the regular use of topical eyedrops, laser therapy, and/or surgery [6]. Unfortunately, intolerance of side effects such as dry eye and irritation has resulted in low adherence among patients using eyedrops in comparison to adherence to medications for other chronic conditions [7,8]. Surgical techniques such as the gold-standard trabeculectomy are not without significant risks, with a 78% increase in cataract formation and up to 21.3% of patients requiring complication-related surgery [9,10]. Surgery is therefore reserved for cases refractory to other therapies [11].

Minimally invasive surgical procedures show the potential to effectively reduce IOP in the long term, removing the need for indefinite daily self-administration of eye drops. This may not only be preferable for patients but also prevents vision loss related to nonadherence to topical treatment.

Ab interno canaloplasty is a new, minimally invasive surgical procedure regarded as highly effective in reducing IOP, with fewer complications and a simpler postoperative care regimen than other surgical interventions [12,13]. It acts to permanently dilate Schlemm's canal, which facilitates up to 96% of aqueous humour drainage and is found to be of reduced dimensions in glaucomatous eyes [14,15]. It is currently approved by NICE (National Institute for Health and Care Excellence) for cases of mild-to-moderate POAG [16]. Ab interno canaloplasty promises a safer and more cost-effective alternative to other treatment options in the long term. However, although NICE acknowledges the procedure as safe, there is little evidence on its efficacy [16]. Considering the potential benefits for patients worldwide and the recent uptake of the procedure in the United Kingdom, it is important to critically evaluate the evidence for whether canaloplasty is both efficacious and cost-effective. No systematic review currently exists to consolidate and verify this procedure's efficacy.

This systematic review aims to compare the following.

1. The short-term and long-term efficacy of canaloplasty against all other forms of open-angle glaucoma treatment.
2. The mean IOP changes in canaloplasty to determine the therapeutic effects.
3. The safety of canaloplasty as a treatment against other treatment options for open-angle glaucoma.

Methods

Study Design

We will conduct a systematic review and meta-analysis of randomized controlled trials performing canaloplasty. This protocol will be conducted in accordance with the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocol) statement (Multimedia Appendix 1) and has been prospectively registered on PROSPERO (registration: CRD42024558671). All randomized controlled trials will be included, irrespective of their publication status or language. If studies are not in English, we will use translation assistance (other reviewers who are native to the language or Google PDF translator software).

Types of Participants

Participants included will be those with POAG. We will also include all participants with ocular hypertension, normal-tension glaucoma, or possible glaucoma (suspects for glaucoma). There will be no restrictions regarding region, nation, sex, duration, setting, or demographic factors.

Types of Interventions

We will consider ab interno canaloplasty performed with the OMNI Surgical System or the iTRACK microcatheter. However, we will not apply any particular inclusion or exclusion criteria to these or other treatment delivery parameters. Ab interno canaloplasty will be compared against any comparator, including the following: (1) conventional glaucoma surgery (trabeculectomy), (2) laser treatment (trabeculoplasty) (3) other minimally invasive glaucoma techniques, and (4) medical treatment.

Types of Outcome Measures

Our primary outcome will be the mean change in IOP measured using the Goldmann applanation tonometry. However, the

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reporting of a particular outcome as a criterion is not necessary for eligibility for review nor will we exclude studies solely on an outcome of interest not being included.

Secondary Outcomes

The secondary outcomes will be as follows: (1) proportion of participants who were medication-free (not using eyedrops) after canaloplasty; (2) mean change in the number of IOP - lowering topical eyedrops taken per day; (3) proportion of participants who required further glaucoma surgery, as recorded by the investigators of the included trial; (4) rate of visual field progression (decibels/time) or proportion of participants whose field loss progressed in the follow - up period; (5) mean change in the health-related quality of life; and (6) cost effectiveness reporting for each intervention. The Health-Related Quality of Life Scale [17] will be used in our study.

Adverse Effects

The adverse effects reported are as follows: (1) loss of visual acuity (more than 2 Snellen lines or more than 0.3 logMAR, according to the method of recording visual acuity) or loss of light perception; (2) bleeding, as recorded by the investigators; (3) endophthalmitis, as recorded by the investigators; and (4) IOP spikes (postoperative rise in IOP, measured using Goldmann applanation tonometry, of more than 10 mm Hg compared to the previous assessment, including measurements taken during the first postoperative month).

Search Methods for the Identification of Studies

Electronic Searches

We will search the following electronic databases for randomized controlled trials, placing no restrictions to language or year of publication: (1) Cochrane Central Register of Controlled Trials (which contains the Cochrane Eyes and Vision Trials Register) in the Cochrane Library (February 2024), (2) MEDLINE Ovid (1946 to present), (3) Embase Ovid (1980 to present), (4) International Standard Randomized Controlled Trial Number registry, (5) US National Institutes of Health Ongoing Trials Register ClinicalTrials.gov, and (6) World Health Organization (WHO) International Clinical Trials Registry Platform.

Preliminary searches of the databases yielded 4000 papers that met the search criteria and will be reviewed, although this number may increase by the time we conduct this study. As we are placing no language restrictions on the systematic reviews, we aim to translate and extract data by using the Google PDF translator as well as our diverse authors who possess professional proficiency in English, Urdu, Hindi, Spanish, and Arabic.

Searching Other Resources

To identify further studies that may meet the inclusion criteria, we will search the reference lists of all the included studies. We will also search conference proceedings from the following meetings from 1980 onwards: (1) American Academy of Ophthalmology, (2) Association of Research in Visual Science and Ophthalmology, (3) World Ophthalmology Congress, and (4) World Glaucoma Congress.

Data Collection and Analysis

Selection of Studies

We will remove duplicate references and import the search results into the web-based review management software Covidence. Two review authors (MMA and SI) will independently screen the titles and abstracts for all the studies identified by the search. If abstracts are not available, a full-text screen of the study will be performed. We will then retrieve full - text reports of any potential studies for inclusion to assess eligibility. In the event of any disagreement regarding eligibility, a third review author (AT) will be the arbitrator. If we reject any full text reports, we plan to record the reasons for this. If we have doubts about either the study population or the intervention, we will contact the study authors (via email) for clarification so that the decision to include or exclude can be properly informed. We will give them a month to reply.

Data Extraction and Management

In situations where information from the included studies is missing or unclear, our protocol will involve reaching out to the respective individuals or organizations for clarification. We aim to acquire the most comprehensive numerical data accessible to enhance the analysis of the included studies. Rather than opting for less accurate approaches such as extracting numeric values from graphs, our plan will be to gather the data directly from individuals or organizations. In the event that extraction from graphs becomes necessary, 2 review authors will independently perform the task, with a third review author serving as an arbitrator in case of any discrepancies.

Risk of Bias Assessment in the Included Studies

Two authors (MMA and SI) will independently assess the studies for risk of bias by using the Cochrane risk of bias tool [18]. We will evaluate the 7 domains, reporting bias as low, high, or unclear.

Measures of Treatment Effect

Continuous data will be summarized as the mean difference or standardized mean difference, with a 95% CI comparing canaloplasty with the comparator group. We will express dichotomous data as risk ratios with 95% CIs.

Dealing With Missing Data

For studies with missing data, we will contact study investigators by email and give them 1 month to respond. Ideally, the studies we review will have used intention-to-treat analyses. We will document the proportion of missing data within each trial. We will attempt to assess the reasons for missing data to determine whether they are missing at random. If we consider that they are missing at random, we will use the available data.

Reporting Bias Assessment

A funnel plot will be used to assess the risk of publication bias if 10 or more trials are included in the review. Where appropriate, we will perform statistical tests for funnel plot asymmetry to assess publication bias, as recommended in chapter 13 of the Cochrane Handbook for Systematic Reviews of Interventions [19].

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Synthesis Methods

Data analysis will be performed using RevMan software (version 5.4; Cochrane). We will report funnel plots for bias and risk ratios and synthesize primary outcomes with descriptive statistics as well as funnel plots where appropriate.

Investigation of Heterogeneity and Subgroup Analysis

We plan to assess the heterogeneity between trials by assessing forest plots and examining the I^2 value and 95% CIs. We will examine the I^2 value and use the guidance provided by the Cochrane Handbook for Systematic Reviews of Interventions for interpretation of this value [18].

Sensitivity Analysis

We will conduct a sensitivity analysis, which will exclude studies that are classified as having overall high risk of bias in one or more key domains. Where possible, we will also perform the following sensitivity analyses for our primary outcome: (1) inclusion of only trials with a low risk of attrition bias, (2) inclusion of trials with a total sample size of 50 or more randomized participants to detect potential small - study effects, and (3) inclusion of mixed types of glaucoma in the study population.

Certainty of the Evidence Assessment

We will summarize the main findings, including strengths and limitations of evidence for both primary and secondary outcomes, using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) approach [20]. We plan to provide a summary of the effectiveness of the intervention and general interpretation of the evidence in the context of other evidences and implications for practice and future research. We will also present a "Summary of findings" table for each comparison listed in the "Types of Interventions" for each outcome.

Results

This review aims to evaluate the short-term, medium-term, and long-term efficacy of ab interno canaloplasty in treating patients with suspected or confirmed POAG in comparison to other glaucoma treatments. The results of this review are not yet available, as it is still at the protocol stage. This protocol was registered on the PROSPERO database for systematic reviews (CRD42024558671) on June 27, 2024. Data collection for this review began on July 14, 2024. The anticipated completion date of this review is early 2026. The findings of this review will help verify this procedure's efficacy, which will aid in its adoption worldwide, thereby reducing the level of health inequality and the global burden imposed by this condition.

Discussion

Canaloplasty Versus Current Glaucoma Treatments

Ab interno canaloplasty is an exciting new treatment that, despite its minimally invasive nature, offers promising results with fewer complications and a simpler postoperative care regimen than other surgical interventions [12,13]. It acts to permanently dilate the Schlemm's canal, which is found to be of reduced dimensions in glaucomatous eyes [14,15]. Ab interno canaloplasty is currently approved by NICE for cases of mild-to-moderate POAG [16]; however, there is little evidence on its efficacy [16]. Considering the potential benefits for patients worldwide, it is important to critically evaluate the evidence for whether canaloplasty is both efficacious and cost-effective. To date, no systematic review has been conducted on the efficacy of canaloplasty. Trabeculotomy remains the gold standard in the treatment of glaucoma.

Comparison With Prior Work

Previous reviews of glaucoma treatment document large heterogeneities with a variety of descriptions for IOP and safety outcomes [21]. This can lead to research resource wastage and reduce the quality of strength of glaucoma studies. IOP is the most clinically relevant and consistent end point in glaucoma management and the most frequently used among studies evaluating surgical success. This will improve the validity of the analysis. Furthermore, to ensure that the reporting is standardized with previous evidence of glaucoma care [1], we will report outcomes in the short term (6-18 months), medium term (18-36 months), and long term (36 months or longer). This will also mitigate any variation in the follow-up durations across studies, which are likely to be similar due to the novel nature of the procedure. In the circumstance that the variation is high, we will address this further through subanalysis. Lastly, including health-related quality of life and the proportion of patients remaining medication-free after surgery as secondary outcomes will also complement the IOP measurements to assess surgical success. Due to differences in the technique, notably between OMNI and iTrack, with the former involving both canaloplasty and goniotomy in one procedure and the latter comprising of injecting more viscoelastic fluid inside of Schlemm's canal with potential added efficacy, a subanalysis will also be conducted in the treatment outcomes of the primary and secondary aims to highlight any clinical differences or benefits.

Another systematic review on the primary outcomes of glaucoma care suggested visual field acuity, safety, and optic nerve head morphology as the most important outcomes to glaucoma experts and treatment [22]. In an effort to standardize the reporting of outcomes and strengthen the research, we hope to report mean changes of IOP as our primary outcome, as this is the most reported result in primary studies and most used and important primary outcome [23].

Conclusions

Randomized controlled trials involving eyes can be difficult to conduct. To conduct the most comprehensive review, we plan to exclude within-person studies because of the potential for medical treatment such as 1-eye treatment affecting the other eye results. For the same reason, we will exclude paired - eye studies, which randomize 1 eye to 1 intervention and the other to the alternative intervention. We will however review studies, which include 1 eye per participant. If a study randomized eyes, regardless of whether they were in the same participant, we will contact the study authors for more information. If possible, we will only include eyes that had the first intervention.

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Authors' Contributions

MMA and SI are both joint first authors of this paper having equal contributions to the following domains: writing the original draft, investigation and methodology, and statistical analysis, software, visualization.
Conceptualization: MMA (lead), SI (equal)
Formal analysis: MMA (lead), SI (supporting)
Investigation: AT
Methodology: SI (lead), MMA (equal)
Project administration: CA (lead), AT (equal)
Supervision: AT
Validation: CA
Visualization: AT
Writing – original draft: all authors (equal)
Writing – review & editing: all authors (equal)

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P checklist.
[PDF File (Adobe PDF File), 205 KB - resprot_v14i1e69527_app1.pdf]

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Abbreviations

GRADE: Grading of Recommendations, Assessment, Development, and Evaluation
IOP: intraocular pressure
NICE: National Institute for Health and Care Excellence
POAG: primary open-angle glaucoma
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-analyses Protocols
WHO: World Health Organization

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Protocol

Impact of Connected Mental Health on the Work Environment of Mental Health Clinicians: Protocol for a Systematic Literature Review

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Abstract

Background: Many mental health professionals face work-related stress due to high job demands, limited control, and inadequate institutional support. Connected mental health (CMH) technologies such as mobile apps and teletherapy platforms are increasingly being proposed as tools to alleviate these job demands. However, their actual influence on clinicians' work environments—here understood as the organizational, social, and psychological conditions that shape their workload, job demands, autonomy, and overall well-being—remains underexplored. Existing reviews have primarily focused on traditional organizational interventions, leaving a critical gap in understanding how CMH technologies specifically influence the work environment of mental health clinicians.

Objective: This systematic literature review aims to identify and summarize knowledge about the impact of CMH on the work environment of mental health clinicians.

Methods: A systematic literature review will be performed. The review follows PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines and has been registered in PROSPERO on April 23, 2025. A comprehensive search strategy was developed using the population, intervention, comparison, and outcome (PICO) framework in collaboration with an academic librarian. Studies will be sourced from the PubMed, Scopus, IEEE Xplore, and ACM Digital Library databases. Inclusion criteria are limited to empirical studies involving mental health clinicians using CMH tools, where outcomes explicitly relate to the work environment (eg, job demands, workload, autonomy, stress, or well-being). Eligible studies must be published in English. Data extraction will include publication trends, study methods, and types of CMH technologies. Additionally, the extraction will capture the study results, including qualitative and quantitative findings, along with the measurement instruments used. Two reviewers will independently select articles for review and extract data. Conflicts will be discussed, and a third reviewer will be consulted if a consensus cannot be reached. Descriptive statistics and thematic analysis (via NVivo) will be used to synthesize the findings.

Results: This systematic literature review seeks to explore and synthesize existing research on how CMH technologies affect clinicians' work environments and is expected to be completed by December 2025.

Conclusions: This review will offer a comprehensive overview of how CMH technologies affect the professional work environment of clinicians.

Trial Registration: PROSPERO CRD420251018685; https://www.crd.york.ac.uk/PROSPERO/view/CRD420251018685

International Registered Report Identifier (IRRID): PRR1-10.2196/76668

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(JMIR Res Protoc 2025;14:e76668) doi:10.2196/76668

KEYWORDS

connected mental health; work environment; mental health clinicians; digital mental health applications; burnout; systematic literature review; artificial intelligence

Introduction

Overview

The global rise in mental health conditions has placed significant pressure on health care systems, with an increasing number of individuals seeking support [1]. Although not all individuals with the highest needs seek help due to factors such as stigma, cultural background, or socioeconomic status, those who do contribute to the growing demand for mental health care services [2,3]. This growing demand contributes to a heavier workload and greater responsibility for mental health professionals [4]. Research across various countries has highlighted that professionals working in mental health care often face some of the most challenging working conditions [5-7]. These include high workloads, elevated stress levels, administrative burdens, staffing shortages, limited resources, exposure to violence, interpersonal conflicts, and role ambiguity. It is also important to acknowledge that many mental health care professionals themselves experience burnout and mental health conditions. However, concerns about stigma and professional repercussions often make them reluctant to seek support [8]. Connected mental health (CMH) applications have been proposed as potential solutions to increase access to mental health care services and alleviate some of the pressures faced by mental health professionals [9,10].

CMH refers to the use of information and communication technologies in mental health care to overcome barriers such as stigma, education, and cost [11]. It encompasses various technology-based solutions, including online platforms, mobile apps, and wearable devices, which can aid in diagnosing, managing, and treating common mental health issues [12]. CMH has shown promise in assisting health care workers during the COVID-19 pandemic [11] and in supporting the transition from primary to secondary school [13]. Research indicates an increasing interest in CMH, with journals being the main publication channels and exploratory research dominating the field [11]. Although attitudes toward CMH are generally positive, concerns exist regarding technical issues, the digital divide, and institutional barriers [14].

The work environment is a multidimensional concept encompassing physical, social, and organizational factors that influence employee satisfaction, performance, and well-being [15,16]. It includes job demands, health management, work design, leadership, work-life balance, and recognition [16,17]. A positive work environment can improve organizational outcomes, reduce turnover, and increase engagement [18]. The workplace environment significantly impacts employee morale, productivity, and quality of life [19]. Organizations can enhance employee loyalty and well-being by improving working conditions and the overall environment [20]. Managers must create an atmosphere that attracts, retains, and motivates employees in today's diverse and changing work landscape [18]. Digitalization has introduced both opportunities and challenges for the work environment, potentially enhancing efficiency and flexibility and increasing cognitive load, work intensification, and stress levels [21,22]. Although the specific impact of CMH technologies on work environments remains underexplored, it is important to recognize that mental health care already operates under highly stressful and pressured conditions [23]. Therefore, it is imperative to ensure that CMH implementations are designed to support and alleviate work-related stress rather than inadvertently contributing to additional strain on health care workers.

Several systematic reviews have examined the impact of mental health systems and workplace environments on the well-being of clinicians [24-26]. One major theme emerging from these reviews is the effectiveness of organizational-level interventions in reducing burnout and improving mental health among health care workers. A recent review emphasized that changes in job structure, work tasks, and physical environments are among the most effective strategies for supporting clinicians' mental health [24]. In contrast, reviews of workplace mental health screening programs have shown mixed results. For example, a systematic review and meta-analysis found that screening followed only by advice or referral did not significantly improve outcomes, whereas screening combined with access to treatment produced small improvements [25]. Another review focusing on nurses in critical care settings found that the work environment was a significant contributor to high levels of depression and anxiety, pointing to the need for structural changes [26].

Although existing reviews provide valuable insights into the broader relationship between mental health systems and clinician well-being, they often focus on traditional organizational interventions, general workplace screening programs, or environmental stressors. However, there is a noticeable gap in synthesized knowledge specifically addressing how CMH technologies impact the work environment of mental health clinicians. The shift toward digital care has accelerated in recent years, particularly during and after the COVID-19 pandemic; however, the consequences for clinicians' job demands, autonomy, workload, emotional labor, and professional identity remain fragmented across disciplines and underexplored in reviews. Moreover, although patient outcomes and accessibility are common focal points in CMH research, the clinician perspective, particularly in terms of occupational stress, job satisfaction, technology-induced strain, and ethical concerns, has not been systematically synthesized. This gap is especially critical given that mental health clinicians often manage emotionally intensive caseloads, and the integration of digital tools can both alleviate and exacerbate existing stressors.

In addition to traditional organizational interventions, a growing body of research has explored the use of digital technologies to address employee mental health in workplace settings. Web-based stress management programs and computer-assisted

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interventions have demonstrated benefits in reducing stress and enhancing coping skills among employees [27]. Workplace-delivered digital programs, including mobile apps for mindfulness, resilience, and psychological support, have been associated with improvements in well-being and reductions in anxiety and depression symptoms [28,29]. These studies suggest that technology-enabled interventions can be feasible and effective, but their adoption and sustained use often depend on usability, organizational readiness, and perceptions of confidentiality [29]. Although these advances illustrate the potential of digital tools to improve workplace mental health, evidence remains fragmented, and no systematic review has specifically examined how CMH technologies influence the work environment of mental health clinicians.

Therefore, this review aims to fill this critical gap by synthesizing the available evidence on the impact of CMH technologies on the work environment of mental health clinicians. It will offer insights into both the benefits and challenges of digital integration from a clinician-centered perspective, guiding technology design, policy, and workforce support in mental health services.

Study Objectives

The objective of the proposed systematic review is to synthesize and critically analyze the reported outcomes and impacts of CMH technologies on mental health clinicians' work environments across diverse global contexts.

Research Questions

In the medical domain, the population, intervention, comparison, and outcome (PICO) framework is commonly used and recommended to develop research questions (RQs), especially for systematic literature reviews (Textbox 1) [30,31]. This ensures that only the studies most likely to be relevant will be retrieved and analyzed [32]. Although the PICO framework primarily aims to structure search strategies, past studies have occasionally excluded certain PICO elements based on research requirements such as the comparison component [33,34]. For this study, we also omit this component, as it is not suitable for the study. This is because we do not aim to rank the studies found or to compare them with some other existing approach.

Textbox 1. Population, intervention, comparison, and outcome structure.

- Population: studies that include mental health care professionals such as psychiatrists and psychologists
- Intervention: connected mental health applications
- Comparison: not applicable
- Outcome: the work environment of mental health care professionals such as psychiatrists and psychologists

The population to be included will be mental health care professionals such as psychiatrists and psychologists. The intervention will be CMH applications. The outcomes of interest will be work-related stress or other work environment factors.

The following RQs guided this systematic literature review:

1. What are the positive and negative impacts of using CMH applications on mental health clinicians' work environments?
2. What technical challenges are associated with the impact of CMH applications on mental health clinicians' work environments?
3. Which design features of CMH applications enable their effectiveness in workplace settings for mental health clinicians?

In addition, we will report on the characteristics of the identified publications, including temporal distribution, publication avenues, country of origin, types of studies conducted, and types of CMH applications studied.

Methods

Study Design

This systematic review was submitted for registration with PROSPERO on April 23, 2025 (CRD420251018685) to avoid bias in conducting and reporting findings. According to the progress of the study, amendments will be made if necessary. The PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) checklist [35] is provided as Multimedia Appendix 1.

We selected a systematic literature review approach because our goal is to summarize the research related to the influence of CMH on the work environment and the barriers to adopting CMH, as well as to identify the types of mental health applications currently in use. Therefore, we followed widely recognized guidelines [30,31] to plan and conduct a systematic literature review. Database searches and screening were conducted between April and July 2025. Data extraction and analysis of the included studies are being performed between August and November 2025. The review manuscript is scheduled for submission in December 2025.

Search Strategy

This review will analyze studies that discuss mental health care professionals' use of CMH applications and their impact on the work environment. The search strategy for this systematic literature review was developed in collaboration with Görel Sundström, a librarian at Uppsala University, and the research team (SP, SO, MH, CB, ÅC, and MRS). The PICO statement was used to construct the search strategy, as shown in Table 1.

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Table 1. Search strategy.

Search	Keyword group	Search string
1	Connected mental health	TITLE-ABS-KEY (“e mental health” OR “m mental health” OR ((“psychological health” OR “mental health” OR psychotherapy OR “behavi* therapy”) W/2 (connected OR digital OR mobile OR online OR smart OR tele OR video OR web)))
2	Work environment	TITLE-ABS-KEY (((job OR work*) W/2 (abuse* OR bullying OR condition* OR control* OR demand OR engagement OR environment* OR satisfaction OR stress* OR setting OR situation* OR strain OR violence OR well-being OR wellbeing)) OR “burn* out” OR burnout* OR “effort-reward imbalance” OR “employee* health” OR ergonomic* OR ERI OR “occupational health” OR “occupational safety” OR “occupational stress” OR “work life balance” OR “workplace health”)
3	Mental health professionals	TITLE-ABS-KEY (clinician* OR counsellor or counselor OR doctor* OR “health personnel” OR “health professional*” OR “healthcare professional*” OR “healthcare provider*” OR “healthcare worker*” OR “health care professional*” OR “health care provider*” OR “health care worker*” OR “general practitioner” OR “medical staff” OR nurse* OR “nursing staff” OR physician* OR psychiatrist* OR psychoanalyst* OR psychologist* OR psychotherapist* OR therapist*)
4	Combined search	1 AND 2 AND 3

The refinement of keywords involved multiple strategies: the librarian performed testing, and the team examined the cited articles to identify their keyword choices. The goal was to ensure that the search captured studies that addressed the same RQs using different terminologies.

The search will be conducted across a range of electronic databases: PubMed, IEEE Xplore, Scopus, and ACM Digital Library. The selected databases are chosen for their relevance to the research topic and their broad use in academic and research settings. This systematic review will not involve the collection of sensitive personal data. The search for publications is completed.

Study Selection Criteria

The PICO statement was used to define the eligibility criteria for study inclusion and exclusion as shown in Table 2.

Table 2. Inclusion and exclusion criteria based on population, intervention, comparison, and outcome (PICO) framework.

PICO	Inclusion criteria	Exclusion criteria
Population	Mental health care professionals, physicians, and nurses, with no exclusion based on age or gender	Study participants who are not mental health care professionals, physicians, or nurses
Intervention	Mental health applications (eg, self-guided CBT[a] apps, mood tracking, or AI[b]-driven chat support) and video consultations, which enable remote interaction between patients and mental health professionals.	General health care applications
Comparison	Not applicable	Not applicable
Outcome	Influence on the work environment	Not applicable
Study methods	Qualitative methods, quantitative methods, mixed methods, solution proposal, evaluation research, and experience articles	Reviews (systematic, scoping, meta-analysis, etc)
Publication types	Formally published peer-reviewed journal articles and conference articles	Gray literature, opinion pieces, protocols, and reviews

[a]CBT: cognitive behavioral therapy.

[b]AI: artificial intelligence.

Types of Studies

Qualitative Studies

Qualitative studies include interviews, focus group discussions, usability studies, participatory research, participatory design, case studies, grounded theory research, thematic and content analysis of textual data, phenomenological studies, narrative research, and ethnographic observations.

Quantitative Studies

Quantitative studies include randomized controlled trials, cohort studies, longitudinal studies, experimental studies, case-control studies, cross-sectional studies, and observational studies.

Mixed Methods Studies

Mixed methods studies include those integrating qualitative and quantitative data collection and analysis methods within a single research design, encompassing, but not restricted to, convergent design, sequential explanatory design, and sequential exploratory design.

Language

Because of limited resources, this study will only consider articles published in English. The research team recognizes that this decision restricts the inclusion of studies conducted in various regions and published in other languages.

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Study Screening

An independent librarian will first run a search using predefined keywords aligned with the inclusion and exclusion criteria to find potentially relevant studies. The search results will then be deduplicated by identifying and removing duplicates in EndNote (version 21; Clarivate), following the guidelines by Bramer et al [36]. The remaining studies will then be imported to Rayyan [37]. Data will first be screened on the title and abstract, and finally, on full-text screening. At least 2 reviewers will independently review the titles and abstracts during the first step. They will be blinded to each other's review decision [38]. Thereafter, the potential articles will be screened based on their full text. In case of disagreements between the reviewers, another reviewer will be consulted to reach a consensus.

Data Extraction

Data will be extracted using a standardized form developed by the research team. This form is structured to collect key study details, including (1) identification—study ID, authors, year, country, publication type, and study type (qualitative, quantitative, or mixed methods); (2) study characteristics—clinician demographics, age, sample size, and CMH application (digital platform or software used and delivery medium); and (3) results—findings in both qualitative and quantitative formats and the tools used for measurement.

Additional details may be incorporated if the research team deems them relevant to the analysis. One reviewer will carry out the data extraction independently, and a second reviewer will review the extracted data to ensure accuracy and completeness. All extracted information will be compiled into a predesigned table in Microsoft Excel. In addition, qualitative data related to the results and findings will be collected. These qualitative data will subsequently be analyzed to identify important themes using NVivo (version 14; Lumivero).

Quality Assessment and Appraisal in the Screening Process

The quality of the included studies will be assessed using the Mixed Methods Appraisal Tool (MMAT) [39], which is specifically designed for systematic reviews that include qualitative, quantitative, and mixed methods studies. As shown in previous systematic reviews, the MMAT is reliable and efficient [40]. The assessment will be based on method-specific criteria, including the appropriateness and rigor of the methodology, control of confounding factors, minimization of selection bias, and consideration of study limitations. Two researchers will independently carry out the MMAT assessments and will reach a consensus on their evaluations. In cases of disagreement, a third researcher will be consulted.

Data Analysis and Synthesis

The study selection procedure will be illustrated using the PRISMA 2020 flow diagram, as demonstrated in Figure 1 [41]. Data synthesis will combine quantitative descriptive summaries with qualitative thematic analysis to ensure alignment with the RQs. These will be visualized through tables and charts in Microsoft Excel. Descriptive statistics will be used to address questions related to publication trends, study designs, contexts, and the types of CMH technologies investigated. This will involve frequency counts and distributions presented in tables and figures.

To address RQ1, we will conduct thematic analysis following the 6-phase framework proposed by Braun and Clarke [42]. Extracted data relating to work environment outcomes (eg, job demands, workload, autonomy, stress, and well-being) will be inductively coded. Codes will be collated into themes that represent how CMH technologies influence specific aspects of clinicians' work environments. Themes will be reviewed and refined iteratively by multiple reviewers to ensure consistency, with NVivo software (version 14; Lumivero) used to support coding and transparency.

For RQ2, we will extract data relating to technical barriers (eg, interoperability, usability, system reliability, and data security). These will be coded inductively and synthesized thematically, highlighting how technical challenges shape or constrain work environment outcomes.

To answer RQ3, we will identify and code reported design features (eg, interface design, workflow integration, decision support, communication tools) and analyze them thematically. This synthesis will enable us to link specific design features to the reported positive or negative impacts in clinical work environments.

In addition to thematic analysis, descriptive statistics will summarize bibliometric and study characteristics (eg, year of publication, country, study design, type of CMH technology). These will contextualize the thematic findings and help identify patterns and gaps across the literature. Together, the descriptive and thematic analyses will provide a systematic answer to all 3 RQs.

One reviewer will conduct the coding, and a second reviewer will verify the sample for consistency. The findings will be synthesized narratively and supported by visual representations. The PRISMA 2020 flow diagram will illustrate the study selection process.

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Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

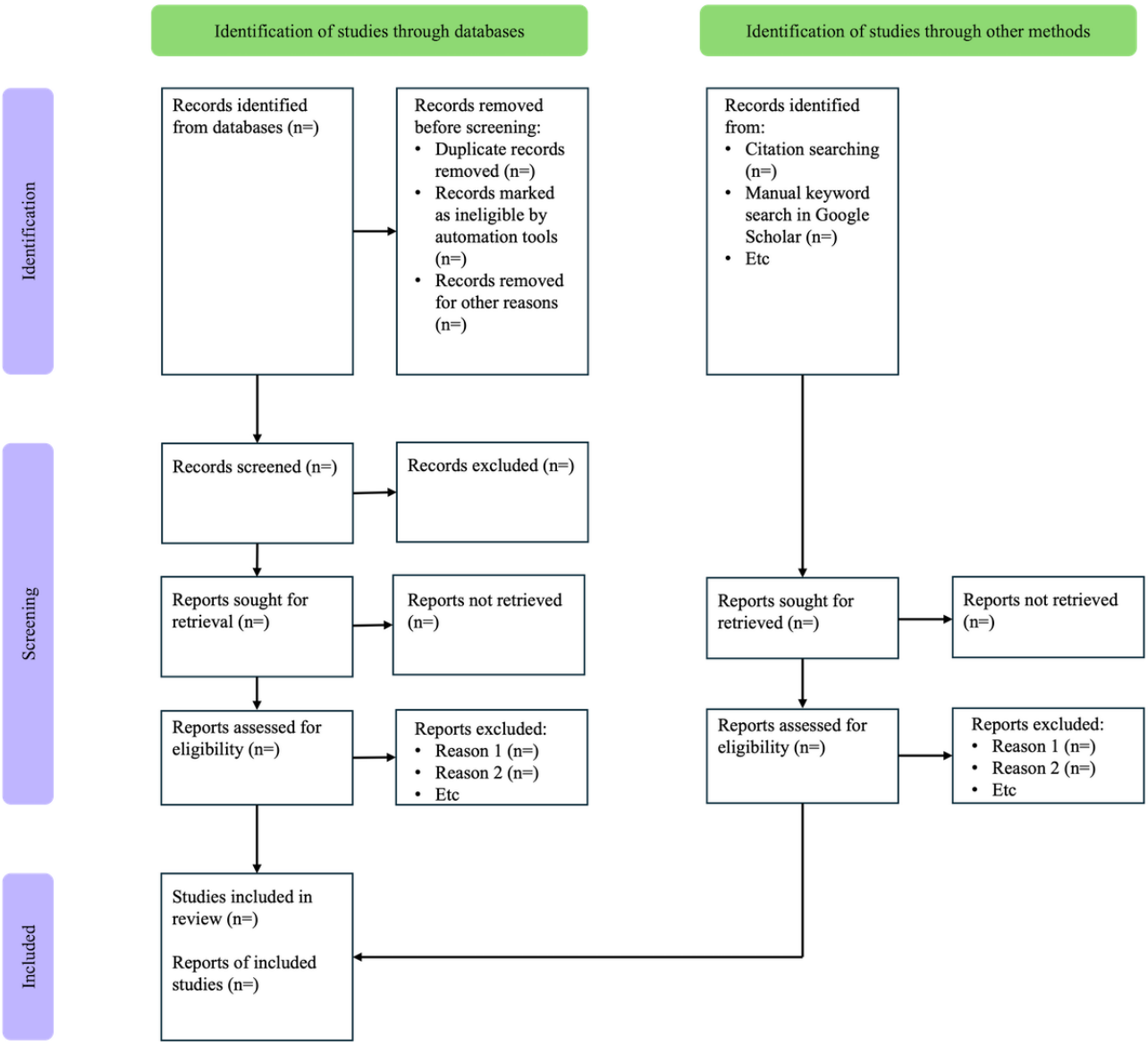

Dissemination Strategy

The results of this study will be disseminated as a scientific publication in a peer-reviewed journal and presented at conferences. Results will also be shared on the blogs of various research groups that the authors are a part of.

Ethical Considerations

According to the Ethical Review Act (2003:460) issued by the Swedish Ethical Review Authority, this research does not require ethics approval.

Results

The authors have conducted 2 pilot searches to test and refine keywords and verify the initial quality of results with the help of the librarian. We have identified 386 studies for screening. Database searches and screening were completed by July 2025. The review team is currently engaged in data extraction and thematic analysis of the included studies, a process scheduled to be concluded by November 2025. The completed systematic review will be submitted for publication in December 2025.

Discussion

Anticipated Findings

This systematic review investigates how CMH applications influence the work environment of mental health clinicians. Although the results are pending, this review is expected to highlight the key trends, tools, outcomes, and challenges in this emerging field. We anticipate identifying a steady rise in publications, signaling a growing interest in CMH among researchers. Commonly studied technologies will likely include mobile apps and teletherapy platforms. Expected outcomes include positive effects such as reduced stress, improved mental well-being, and enhanced support for clinicians. However, the review also aims to uncover challenges such as poor usability, concerns over data privacy, digital fatigue, and limited institutional support, factors that may hinder adoption or long-term use. By focusing on clinicians, this review shifts attention from patient-centered outcomes to the well-being and work conditions of those delivering care. The findings will provide practical insights for developers, health care

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organizations, and policymakers seeking to implement CMH tools that genuinely support clinicians and, in turn, their patients, rather than compounding their burdens.

Comparison to Previous Work

Previous reviews on digital workplace mental health programs have shown benefits for employee well-being, although adoption is shaped by usability and organizational readiness [27-29]. In contrast, our review focuses on clinicians as workers, examining how CMH tools used in patient care affect their own job demands and resources. Research on telemental health highlights implementation barriers, confidentiality, and increased electronic health record workload [43,44], while technostress studies describe how system complexity and poor support reduce well-being [22,45]. Our synthesis will connect these strands to clinicians' work environments using the job demands–resources framework [46].

Expected Contributions

This review is expected to make several contributions. First, it will provide a clinician-centered synthesis of how CMH applications influence work environment factors such as workload, autonomy, collaboration, and well-being—areas that are often overshadowed by patient-focused outcomes in the literature. Second, it will identify the design features and technical challenges most consistently associated with positive or negative impacts, offering insights into how these technologies can be optimized for clinical settings. Finally, by linking these findings to the job demands–resources framework, this review will generate practical guidance for both technology design and organizational implementation, thereby informing future development, policy, and research.

Strengths, Limitations, and Future Directions

A significant strength of this review is that the protocol has been prospectively registered, which enhances transparency and reduces the risk of selective reporting. The review also follows PRISMA guidelines, ensuring methodological rigor in searching, screening, and reporting. Another strength is the use of 3 reviewers in screening and data extraction, which minimizes bias and increases reliability in study selection and coding. In addition, the combination of descriptive synthesis with thematic analysis provides both breadth—through mapping publication trends and study characteristics—and depth—through an interpretive account of how CMH technologies shape clinicians' work environments. At the same time, several limitations of this study must be acknowledged. The included studies are likely to be heterogeneous in design, outcomes, and contexts, which may complicate the synthesis and limit comparability. Some studies may not include formal comparators, making it difficult to directly attribute changes to CMH technologies. Restricting the review to English-language studies also introduces the possibility of language bias, potentially excluding relevant work from non-English or gray literature sources. To mitigate these limitations, we will use transparent coding procedures, map outcomes consistently to the job demands–resources framework to enhance comparability and explicitly acknowledge contextual and methodological gaps in the evidence base.

Conclusions

This protocol outlines a systematic literature review that will evaluate and synthesize evidence on the impacts of CMH technologies on the work environments of mental health clinicians. By systematically analyzing both positive and negative outcomes, technical challenges, and enabling design features, this review will provide an understanding of how CMH applications shape clinicians' job demands, resources, and well-being. The use of a PRISMA-guided methodology, combined with descriptive and thematic synthesis, and alignment with the job demands–resources framework, supports the development of findings that will be robust and practically relevant. The anticipated contribution of this review is twofold: advancing the academic literature by clarifying the state of evidence in this area and informing technology developers, health care organizations, and policymakers seeking to design and implement CMH solutions that are sustainable and supportive of clinicians' work environments. Ultimately, the results are expected to generate insights that can guide future research, design, and policy, while also identifying critical gaps, particularly in underrepresented regions, that warrant further investigation.

Acknowledgments

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Data Availability

Data sharing is not applicable to this study as no datasets were generated or analyzed during this study.

Authors' Contributions

SP, SO, and MH contributed to the conception. SP wrote the initial manuscript draft. The manuscript has been revised by SP, SO, MH, CB, ÅC, and MRS. Visualization was performed by SP. All authors reviewed and edited the manuscript and approved the final version of the manuscript.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P checklist.
[DOCX File , 18 KB - resprot_v14i1e76668_app1.docx]

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Abbreviations

CMH: connected mental health
MMAT: Mixed Methods Appraisal Tool
PICO: population, intervention, comparison, and outcome
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
RQ: research question

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Protocol

Effect of TikTok on Self-Harm and Suicidal Behavior in the Adolescent Population: Protocol for a Systematic Review

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Abstract

Background: Social media use among adolescents and young adults has increased exponentially over the last decade, with TikTok being one of the most popular platforms. In Spain, 61% of adolescents use TikTok, spending an average of 1.5 hours daily on the app. This phenomenon coincides with an alarming increase in the prevalence of self-harm and suicidal behavior among adolescents and young adults. Moreover, suicidal behavior is one of the leading causes of morbidity and mortality in this age group.

Objective: The primary aim of this study is to evaluate the existing evidence on the association of TikTok use with self-harm and suicidal behavior in the adolescent population.

Methods: This systematic review will follow the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) 2020 guidelines to ensure transparency, rigor, and reproducibility. Original studies that evaluate the impact of TikTok use on self-harm and suicidal behavior will be selected. The primary outcome will be the occurrence and prevalence of self-harm and suicidal behavior related to TikTok use among adolescents and young adults. Health science literature databases, including PubMed/MEDLINE, Cochrane, Web of Science, PsycINFO, and Scopus, will be searched. Two researchers will independently select studies that meet the predefined eligibility criteria, and they will extract data from each included study. The risk of bias and methodological quality of the included studies will be assessed using the Risk of Bias in Non-Randomized Studies of Interventions and Joanna Briggs Institute tools, respectively. The methodological characteristics, association measures, and qualitative conclusions of the reviewed studies will be analyzed, and a descriptive synthesis will be presented through tables and graphs.

Results: This systematic review formally began in July 2025, although it has been planned since September 2024. The final systematic review will be performed and reported according to this protocol and the PRISMA guidelines. Initially, the search returned 6126 records, and 3664 records are currently being screened for eligibility. Data from the final included studies will be extracted, collated, and analyzed. The risk of bias and quality of evidence will be determined. A narrative synthesis will be used to summarize the results of the systematic review. When possible, statistical analyses will be presented using graphs and figures. The final systematic review is expected to be published in December 2025.

Conclusions: This systematic review will help to better understand the relationship between TikTok use and self-harm and suicidal behavior among adolescents and young adults. Our findings may support future research, recommendations, and policies in this field, emphasizing the need to incorporate the digital environment as a key factor in adolescent mental health.

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Trial Registration: Open Science Framework MX5CJ; https://osf.io/MX5CJ
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KEYWORDS
adolescents and young adults; self-harm; social media; suicide; TikTok

Introduction

TikTok has established itself as one of the most widely used platforms among teenagers and young adults, characterized by its short video format, a highly personalized recommendation algorithm, and rapid viral dissemination of content [1-4]. These features have been linked to potential mental health risks, including the normalization of self-harming behaviors and the formation of communities around such practices, although specific scientific evidence on TikTok remains limited [5,6].

An increasing number of studies suggest a link between social media use and the deterioration of mental health in adolescents [7,8]. Due to its design and functionality, TikTok may exert a particular influence on the perception and expression of self-harm and suicidal ideation [9]. Documented mechanisms include social contagion, normalization of self-harm, and the creation of online communities that may reinforce vulnerability among adolescents and young adults [10]. Nonetheless, compared with platforms such as Instagram or Facebook, the scientific evidence specifically addressing TikTok remains limited.

Given its highly visual content format and its capacity for rapid viral dissemination, TikTok's influence on adolescent mental health may differ from that of other platforms. For example, one study found that the use of short-form video platforms was more directly associated with eating disorders among boys and more indirectly associated with these disorders among girls, through body image comparison [11]. Another study highlighted how features such as infinite scrolling and personalized recommendations introduce new forms of reward variability, which may promote compulsive use [12]. Despite these insights, most research to date on social media and mental health in adolescents and young adults, including systematic reviews, has focused on the general impact of social media, such as contagion of behaviors or normalization of behaviors, without analyzing the distinctive characteristics of TikTok. This platform has particular characteristics, such as a highly personalized recommendation algorithm, centering on short audiovisual content, and rapid viral dissemination, that may influence adolescent mental health differently compared to other social media platforms. Consequently, a systematic analysis focused exclusively on TikTok is required. Thus, this study seeks to synthesize the available evidence on the relationship between TikTok and adolescent mental health, thereby providing an updated and specific overview lacking in previous reviews, clearly differentiating what is known about social media in general from what has been documented specifically on TikTok to date.

This context highlights the need to investigate the role of TikTok as a potential risk factor or moderating element in adolescent mental health [13]. This review aims to systematically evaluate the existing literature; the findings could have relevant implications for health care professionals, educators, and policymakers, enabling the design of more effective self-harm prevention and risk-mitigation strategies.

Unlike other platforms, TikTok combines elements of intermittent reinforcement through infinite scrolling and algorithms that prioritize highly personalized content. These mechanisms can intensify repeated exposure to material related to self-harm, increasing the risk of behavioral contagion and hindering users' emotional regulation. Therefore, it is not just another social network, but an environment with its own dynamics that require a differentiated analysis.

Although adolescence is generally considered to end between the ages of 19 and 21, the psychosocial vulnerabilities linked to social media use and suicidal behavior remain highly relevant during early adulthood, up to the ages of 24 or 25. For example, longitudinal analyses indicate that social media use continues to influence life satisfaction during late adolescence and early adulthood [14]. Furthermore, studies suggest that TikTok plays a significant role in the lives of both adolescents and young adults, affecting areas such as emotional regulation, self-esteem, identity, and mood [6,7,14]. Therefore, in this review, we use the term "adolescents and young adults" to more accurately describe the target population.

In terms of the PECO (population, exposure, comparator, outcome) framework, the objective of this review is to evaluate the current evidence on whether, among adolescents and young adults (population), the use of TikTok (exposure), compared to nonuse or lesser use (comparator), is associated with self-harm and suicidal behaviors (outcome). To achieve this, a review of the available scientific literature will be conducted to better understand the magnitude of this phenomenon, identify patterns of content exposure, and evaluate the possible implications for prevention and intervention strategies.

Methods

Study Design

A systematic review of association measures will be conducted. The study protocol was developed following, and the methods and results will be reported in accordance with, the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) guidelines [15-17] (Multimedia Appendix 1). Prior to initiating the project, this protocol was registered on the Open Science Framework platform (MX5CJ).

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Any amendments or modifications made to the protocol will be described and communicated in the final document.

Eligibility Criteria

Studies will be selected based on aspects related to study design, population, assessments performed, outcomes, publication type, and language (Textbox 1).

Textbox 1. Eligibility criteria.

Inclusion criteria

- Original studies (randomized controlled trials and quasi-experimental or observational studies)
- Studies that evaluate TikTok use and its association with self-harm and/or suicidal behavior
- Studies that include adolescents and young adults aged 14 to 25 years
- Studies that quantify TikTok use, suicide, and related behaviors using validated assessment instruments

Exclusion criteria

- Studies that analyze social media in general (without focusing on TikTok)
- Studies that do not explore the association between TikTok use and self-harm or suicidal behaviors
- Systematic reviews and gray literature

Study Type

Any study quantifying the frequency of TikTok use and self-harm and/or suicidal behaviors (ie, randomized controlled trials, quasi-experimental studies, or observational studies) will be included. Studies that do not evaluate the association between TikTok use and self-harm and/or suicidal behavior as a primary objective will be excluded. Studies focusing on social media in general, without specifically evaluating TikTok, will also be excluded. Systematic reviews and gray literature (eg, doctoral theses and book chapters) will not be considered.

Population

We will include studies with participants aged up to 25 years, which enables us to cover both adolescents (aged up to 17-19 years) and young adults (aged 18-25 years). This decision was made because both groups are characterized by intensive use of social media and potential exposure to suicide-related risk factors. It is important to note that the protocol specifies that, whenever possible, we will analyze whether the effects of TikTok on suicidal behavior differ between adolescents and young adults. Studies will be included regardless of the sex or ethnicity of the population.

Outcome of Interest

Original studies evaluating the association between TikTok use and the onset, maintenance, or exacerbation of self-harm and/or suicidal behavior will be included. Frequency of TikTok use and self-harm/suicidal behavior will be included if they use valid evaluation instruments (ie, self-reported questionnaires or validated scales).

The primary outcomes of this systematic review will be the prevalence of self-harming behavior and suicidal behavior. For the purposes of this review, self-harm refers to intentional self-inflicted injury without suicidal intent, while suicidal behavior refers to self-inflicted injury with the intent to die, regardless of the outcome. Secondary outcomes will include behavioral patterns in searching for and consuming self-harm or suicide-related content on TikTok [13].

Publication Status

Only original studies indexed in the consulted databases will be considered, regardless of publication status (eg, preprints, scientific articles, or retracted articles).

Language

Only studies published in English will be included, as it is the predominant language in relevant scientific literature.

Sources of Information

For the information search, various electronic databases of health sciences literature will be considered (from the launch year of TikTok, ie, 2016, to November 2024). Specifically, searches will be conducted on MEDLINE (via PubMed), Cochrane, Web of Science, PsycINFO, and Scopus. Additional data sources will be used, such as the reference lists of studies that meet the inclusion criteria, which will be manually checked to verify whether additional original studies can be included in this systematic review. A search will be conducted using Google Scholar to identify related articles, and the authors of the original studies included will be contacted if necessary.

Search Strategy

The search strategy will include keywords related to “TikTok,” “self-harm,” “suicide,” and “adolescents,” combined using Boolean operators, such as “(adolescent) AND (TikTok) AND (self-harm).” The review team will develop the first draft of the search and subsequently peer-review it. This strategy will also be adapted for other databases. The draft strategy is provided in Multimedia Appendix 2.

The authors will attempt to replicate the search strategy on TikTok itself and will convert the terms into TikTok hashtags for that purpose. These terms will be combined with hashtags specifically related to self-harm or suicidal behavior. According to the metrics provided by the app, the videos with the most “likes” will be selected for inclusion (eg, trending challenges, content analysis, influencer impact, and hashtag trends). This

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will be conducted using a TikTok account exclusively dedicated to research in the current year.

A closed list of hashtags related to self-harm and suicidal behavior will be developed based on controlled terminology (Medical Subjects Headings [MeSH] and Emtree), previous literature on digital health, and an exploratory survey on TikTok to identify common synonyms and variations. Searches will be conducted using a TikTok account created exclusively for the research, with no prior history, to minimize algorithmic bias. Each hashtag will be entered individually into the platform's search bar, recording the date, time, total number of results, and the sorting criteria applied ("most popular" or "most recent").

Although content with higher interaction (more likes) will initially be prioritized, less frequent hashtags linked in the literature to risky behaviors will also be included to mitigate popularity bias. This broadens the spectrum of exposure, balancing viral content with emerging but clinically relevant content.

The list of hashtags will be created in three stages: (1) reviewing literature and thesauri (MeSH and Emtree); (2) conducting initial exploration on TikTok to find synonyms and variations; and (3) validation by two independent reviewers. All chosen hashtags, along with exclusion criteria, will be recorded in a supplementary file to ensure reproducibility.

For each hashtag, the first 50 videos will be systematically selected according to the established criteria, prioritizing quantitative metrics provided by the platform (views, likes, and comments). Two reviewers will conduct the searches independently and will compare the results, recording screenshots and metadata to ensure the traceability of the process. This procedure will not constitute a systematic literature review, but rather a systematized analysis of social media content, incorporating principles of rigor typical of systematic reviews (predefined criteria, transparent documentation, and bias control) adapted to the dynamic environment of TikTok.

Study Selection

Once searches have been conducted in all electronic databases, the results will be incorporated into a systematic review management tool. For this purpose, the RefWorks software will be used, and duplicate articles will be removed. Subsequently, two researchers (JVS-O and LMR-B) will independently read the titles and abstracts of all the articles, which will aid traceability, reproducibility, and resolution of discrepancies. In case of discrepancies, conflicting instances will be discussed between the two researchers and submitted to a third researcher (RT-S), who will act as an arbitrator. Articles that do not meet the inclusion criteria, as assessed by both researchers, will be excluded. Both researchers (JVS-O and LMR-B) will read the full articles that were eligible in the previous phase; articles that do not meet the inclusion criteria will be removed and recorded in a list specifying the reasons for their exclusion. Additionally, the references of the selected articles will be reviewed to analyze the possibility of including relevant original articles that were not previously identified.

A flow diagram will be created following the PRISMA guidelines to describe the procedure carried out and number of articles excluded at each step [16].

Data Collection

After reading the articles, two researchers (JVS-O and LMR-B) will independently collect the data; an experienced researcher (RT-S) will supervise the data collection process. Tables will be designed using Microsoft Word or Microsoft Excel to indicate the main characteristics of the studies. The data extracted from the original studies will include the authors, year, origin, study type, participants, methods, and results.

Methodological Quality Assessment

The Risk of Bias in Non-Randomized Studies of Interventions (ROBINS-I) tool from Cochrane will be used to assess the risk of bias in nonrandomized studies [18]. The tool asks reviewers to rate the risk of bias in the following domains: confounding, selection of study participants, classification of interventions, deviations from intended interventions, missing data, measurement of outcomes, and selection of reported results. Additionally, the ROBINS-I tool includes an optional judgment on the direction of bias for each domain.

To ensure information validity, methodological quality will be assessed using the Joanna Briggs Institute (JBI) critical appraisal tools [3,19,20], which were selected owing to their detailed and specific approach. Each study will be evaluated using the corresponding scale according to the study type, rating each criterion as "yes" (meets the criterion) or "no" (does not meet the criterion).

Synthesis of Results

The recommendations of the PRISMA 2020 statement [13] will be followed to present the most relevant results of the search and study selection processes. A narrative synthesis of the main characteristics of the selected original studies will be provided, and all extracted data will be presented in summary tables. Each study will include general, methodological, and transparency elements. A descriptive analysis will be conducted using the frequency and percentage counts of the obtained results, and the results of the methodological quality assessment using the ROBINS-I and JBI tools will be represented in tables or charts (eg, bar diagrams). Finally, the results, strengths, and weaknesses of the original analyzed studies will be discussed.

Given the heterogeneity of the studies included in terms of design, population, variables evaluated, and forms of reporting results, it was not possible to perform a quantitative meta-analysis. Consequently, a narrative/descriptive synthesis was chosen, which allows for rigorous integration of findings and highlights patterns, similarities, and differences between the studies reviewed. This approach is considered the most appropriate for providing a comprehensive overview of the available evidence when quantitative comparison is not feasible.

This review includes studies with participants aged 14 to 25 years, covering adolescents and young adults. This range enables analysis of the life stages of adolescence and the transition to early adulthood. Whenever the data permit, subgroup analyses will be conducted considering age (adolescents aged <18 years

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versus young adults aged 18-25 years) and gender, aiming to explore differences in exposure patterns and associations with self-harm and suicidal behavior.

Ethical Considerations

Due to the nature of this systematic review, which is primarily based on the analysis of previous studies, approval from a research ethics committee is not required.

The authors carefully considered the ethical implications of analyzing potentially sensitive content on TikTok in this study. The material examined corresponds exclusively to publicly accessible posts, and no private information was collected, nor was there any interaction with users, so individual informed consent was not necessary. Nevertheless, measures were taken to minimize ethical risks: (1) the inclusion of identifiers that could enable tracing creators was avoided, and (2) self-care guidelines were implemented for the research team in case of exposure to potentially disturbing content. These precautions aim to safeguard both the integrity of indirectly involved users and the well-being of the research team, in accordance with good practices in digital studies.

Results

This systematic review formally began in July 2025, although it has been planned since September 2024. The final systematic review will be conducted and reported in accordance with this protocol and the PRISMA guidelines [16]. Initially, the search returned 6126 records, and 3664 records are currently being screened for eligibility. Data from the included final studies will be extracted, collated, and analyzed. The risk of bias and the quality of evidence will be ascertained. A narrative synthesis will be used to summarize the findings of the systematic review. Statistical analyses will be presented using graphs and figures to enhance clarity where possible. The final systematic review is expected to be published in December 2025.

Discussion

Anticipated Main Findings

This systematic review aims to investigate the proposed link between TikTok use and self-harm or suicidal behavior in adolescents and young adults. Specifically, it endeavors to determine whether exposure to TikTok might affect the onset, persistence, or worsening of these behaviors, while also highlighting gaps and limitations in the current literature [5,10-14].

Comparison With Previous Work

Previous research has widely linked social media use to impaired adolescent mental health, but evidence focused specifically on TikTok remains limited. Our synthesis aims to clarify whether the structural and functional features of TikTok (eg, short videos, viral trends, and algorithmic recommendations) pose a unique risk compared to other platforms, such as Instagram or Facebook. By situating our findings within this emerging body of evidence, the review will contextualize TikTok's role in influencing self-harm and suicidal behavior among young people.

Strengths and Limitations

A key strength of this review is its systematic and transparent approach, guided by PRISMA 2020 and PRISMA-P, which ensure methodological rigor and reproducibility. Furthermore, the use of the ROBINS-I and JBI tools will strengthen the assessment of bias risk and study quality. However, we also anticipate limitations, such as the potential scarcity of high-quality primary studies specifically addressing TikTok, heterogeneity in study designs and outcome measures, the linguistic restriction to English-language publications, and the exclusion of gray literature. These limitations are likely to influence the comprehensiveness of the findings and may also impact both internal validity (risk of publication bias) and external validity (transferability to different sociocultural contexts), which limits the ability to generalize the findings to the entire global adolescent population. Nevertheless, we believe this systematic review will be a valuable synthesis of the available evidence, offering meaningful insights and a solid foundation for future research in the field.

Future Directions

This review's findings will lay the groundwork for future research by pinpointing specific knowledge gaps, such as the absence of longitudinal studies, limited focus on protective factors, and superficial examination of TikTok's content moderation strategies. We also aim to emphasize the importance of interdisciplinary collaboration between clinicians, educators, policymakers, and technology experts to create targeted interventions and preventive measures suited to the digital landscape.

Specifically, we recommend (1) conducting longitudinal studies that explore causality; (2) researching protective factors such as digital resilience and media literacy; and (3) evaluating the effectiveness of content moderation and regulation strategies on TikTok using quasi-experimental designs.

The clinical and public policy implications should be approached with caution, as the available evidence is preliminary and heterogeneous. This review's results will offer initial hypotheses and guidance but will not establish definitive causal relationships.

Dissemination Plan

The results of this systematic review will be shared through peer-reviewed scientific publications, presentations at academic conferences, and outreach activities aimed at stakeholders such as health care professionals, schools, and youth organizations. In line with the recommendations of *JMIR Research Protocols*, the communication plan will also include summaries designed for nonspecialist audiences, such as parents and educators, to maximize the potential impact of the findings.

Conclusion

This systematic review protocol outlines a thorough approach to synthesizing evidence on the link between TikTok use and self-harm or suicidal behavior in adolescents and young adults. The findings are likely to clarify potential risks and support the development of more effective prevention and intervention strategies. Although conclusions will be constrained by the

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quality and scope of available studies, the outcomes of this review will establish a foundation for future research and policy advice, emphasizing the significance of recognizing the digital environment as a crucial element in adolescent mental health.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P checklist.
[DOCX File , 37 KB - resprot_v14i1e78600_app1.docx]

Multimedia Appendix 2
Key search terms for various databases.
[DOCX File , 33 KB - resprot_v14i1e78600_app2.docx]

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Abbreviations

JBI: Joanna Briggs Institute
MeSH: Medical Subjects Headings
PECO: population, exposure, comparator, outcome
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
ROBINS-I: Risk of Bias in Non-Randomized Studies of Interventions

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Protocol

Effect of Obesity on Perioperative Outcomes Following Lung Cancer Surgery: Protocol for a Meta-Analysis and Systematic Review

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Abstract

Background: Surgical resection is the primary curative treatment for early-stage lung cancer—the leading global cause of cancer mortality, responsible for nearly 1 in 5 cancer deaths in 2022. Obesity is a global health concern that may influence surgical outcomes; yet, its impact on perioperative outcomes following lung cancer surgery remains controversial.

Objective: This protocol outlines a meta-analysis and systematic review to evaluate the association between obesity and perioperative outcomes in patients who underwent a lung cancer resection.

Methods: Observational studies related to patients with lung cancer who underwent surgical resection were searched in 5 English and 3 Chinese literature databases: PubMed, Embase, Cochrane Library, Web of Science, MEDLINE, Chinese National Knowledge Infrastructure, Wanfang, and the Chinese Biomedical Database. The search period for these 8 electronic databases was from inception to 2025. The PROSPERO database and the International Platform of Registered Systematic Review and Meta-Analysis Protocols (INPLASY) database were also searched. Qualified studies were screened and selected by 2 authors independently. The literature obtained were imported into NoteExpress to screen the titles and abstracts. After reading the full text of the remaining studies, the final number of studies were determined. Two reviewers independently extracted data from the included studies by using a predesigned data extraction tool. The Newcastle-Ottawa Scale was used to evaluate the quality of the research. The primary outcome of this study was to evaluate the postoperative mortality in people living with obesity undergoing lung cancer surgical procedures. The secondary outcomes were the postoperative complications, average length of stay, blood loss during the operation, and operation time in people living with obesity undergoing lung cancer surgical procedures. For dichotomous data, we plan to present results as risk ratios with 95% CIs. For continuous data, we will use mean difference with 95% CIs. The Review Manager software (version 5.4) will be used for the meta-analysis and statistical analysis. Sensitivity analysis and Egger test will be performed with Stata software (version 16.0).

Results: The results are not yet accessible because this is a protocol for a systematic review and meta-analysis. The protocol is registered in PROSPERO under the registration number CRD42025648330. By August 26, 2025, we completed the literature search of the 8 databases and completed the selection and extraction of data.

Conclusions: This study will synthesize existing evidence to clarify whether obesity is a risk factor for adverse outcomes or if it confers a protective effect, as suggested by the obesity paradox. These findings will guide clinical decision-making and improve perioperative care for obese people with lung cancer.

Trial Registration: PROSPERO CRD42025648330; https://www.crd.york.ac.uk/PROSPERO/view/CRD42025648330

International Registered Report Identifier (IRRID): PRR1-10.2196/76315

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(JMIR Res Protoc 2025;14:e76315) doi:10.2196/76315

KEYWORDS

obesity; lung cancer; perioperative outcomes; surgery; meta-analysis; protocol

Introduction

Lung cancer remains the leading cause of cancer-related mortality worldwide, with surgical resection serving as the primary curative treatment for early-stage non–small cell lung cancer [1,2]. Despite advancements in surgical techniques, pulmonary resection is still associated with significant perioperative risks, including respiratory complications, cardiovascular events, and mortality [3]. Consequently, identifying modifiable patient factors that influence the surgical risk is a critical focus of preoperative optimization. Although obesity is a well-established risk factor for numerous health conditions, its impact on lung cancer surgery outcomes presents a complex and often contradictory picture. The conventional obesity paradox, where a higher BMI is sometimes associated with improved survival in chronic diseases, conflicts with the known physiological challenges obesity imposes on respiratory and cardiac function [4,5]. This creates a significant dilemma for surgeons assessing preoperative risk. Therefore, elucidating the true relationship between obesity and postoperative complications is essential for refining risk stratification models and for improving surgical outcomes for patients with non–small cell lung cancer. Additionally, the presence of obesity complicates patient outcomes, often leading to poorer prognoses, increased treatment-related complications, and a higher likelihood of comorbid conditions [6]. Despite its association with comorbidities, the impact of obesity on perioperative outcomes in lung cancer surgery remains controversial. Some studies suggest that obesity may increase the risk of postoperative complications such as respiratory complications due to physiological stress and technical challenges during the surgery [7]. Conversely, other studies propose an obesity paradox, where obese people with BMI ≥30 exhibit better survival and fewer complications compared with normal weight and underweight patients following surgical resection of lung cancer [8]. This discrepancy highlights the need for a comprehensive synthesis of existing evidence.

The World Health Organization (WHO) defines overweight individuals as having BMI >25 kg/m^2 and obese individuals as having BMI >30 kg/m^2 [9]. Contemporary diagnostic frameworks such as those proposed by the European Association for the Study of Obesity [10] and The Lancet [11] advance the clinical conceptualization of obesity by emphasizing health impairments (eg, clinical obesity), and the Edmonton Obesity Staging System offers a powerful tool for mortality risk prediction [12]. The WHO BMI classification was selected as the principal typology for this study. This decision is grounded in the research's scope and objectives. The WHO criteria, with its clear BMI thresholds of >25 kg/m² and >30 kg/m², provides an unambiguous and universally applicable metric for categorizing participants. This is essential for ensuring consistency in a large-scale analysis and for enabling direct comparisons with the majority of existing oncological and public health studies that also rely on this standard. Therefore, the WHO definition serves as the most appropriate and practical foundation for this epidemiological investigation.

Obesity is recognized as one of the most important global public health problems, with an increase in its prevalence in almost all countries, rising as high as 2-fold in 70 countries since 1980 [13]. The global obesity epidemic, attributed to sedentary lifestyles, unhealthy diets, genetics, and environmental factors, has led to over 1.9 billion adults being classified as overweight and 650 million living with obesity [14]. Over a third of the global population is currently classed as overweight or obese, with projections suggesting that by 2030, 38% of the adults will be overweight and 20% will develop obesity [6]. This will pose specific challenges for surgeons who must address the physical, technical, and physiological problems associated with thoracic operations in patients living with obesity.

A meta-analysis found a significant positive association between excess body weight and the risk of lung cancer, particularly among nonsmokers and women [6]. One research found that obesity does not increase the perioperative complications in older patients undergoing thoracoscopic anatomic lung cancer surgery [15]. Ferguson et al [16] showed that being overweight or obese did not increase the risk of postoperative complications in any category after a major lung resection. Guerrera et al [17] evaluated the impact of morbid obesity on perioperative clinical outcomes after thoracoscopic lobectomy and found that people living with obesity did not show increased conversion rates, blood loss, and surgical time. Obesity is associated with improved overall survival in patients with non–small cell lung cancer after curative resection when skeletal muscle mass and radiodensity are preserved [18].

This protocol describes a planned meta-analysis to systematically evaluate the effect of obesity on the perioperative outcomes following lung cancer surgery. The primary outcome is postoperative 30-day mortality; the secondary outcomes are postoperative complications, average length of stay, blood loss during operation, and operation time. This study aims to provide evidence-based insights to guide preoperative risk assessment and optimize patient care. The study “Causes for Retraction in the Biomedical Literature: A Systematic Review of Studies of Retraction Notices” [19] is helpful for us to understand the common methodological defects in medical research, which could affect the quality of our meta-analysis research. This knowledge will strengthen our evaluation of the Newcastle-Ottawa Scale (NOS) [19].

Methods

Study Registration

This study is conducted in accordance with the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) statement guidelines [20] and has been registered with PROSPERO under the registration number

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CRD42025648330. Any amendments to this protocol will be documented with a date and a brief rationale. All amendments will be updated in the PROSPERO registry to maintain transparency. The final review manuscript will explicitly report and justify any deviations from the original registered protocol.

Criteria for the Studies

Types of Studies

Observational studies, including cross-sectional, case-control, or cohort studies, are the focus of this meta-analysis. Case reports, case series, review articles, letters, editorials, and commentaries are excluded. The language of the studies has a restriction of English or Chinese.

Types of Participants

People aged 18 years or older living with obesity diagnosed with lung cancer who underwent surgical resection are included in this study. Obesity is classified by WHO BMI of >30 kg/m^2 in Western populations and >25 kg/m^2 in Asian populations. We also use the Edmonton Obesity Staging System to assess obesity severity based on comorbidities and functional status and not just BMI. We present results for obese and overweight groups individually to allow for comparison and identify potential differential effects.

Types of Interventions

The intervention measures are video-assisted thoracoscopic surgery or open lobectomy of obese patients diagnosed with lung cancer.

Types of Comparisons

Nonobese patients diagnosed with lung cancer who underwent video-assisted thoracoscopic surgery or open lobectomy were considered as the control group.

Types of Outcome Measures

Primary Outcomes

The primary outcome considered is the postoperative 30-day mortality in patients living with obesity undergoing lung cancer surgical procedures.

Secondary Outcomes

The second outcomes are postoperative complications, pulmonary complications, cardiovascular complications, average length of stay, the blood loss during the operation, and the operation time in people living with obesity undergoing lung cancer surgical procedures.

Exclusion Criteria

Studies that report the following are excluded.

1. Those that did not include a nonobese reference group.
2. Inconsistencies between the data reported in the manuscript and data represented in tables such as numerical mismatches between text and tables and conflicting results within the manuscript.
3. Studies with overlapping cohorts.

Information Sources

A systematic search was performed in the following 5 English and 3 Chinese literature databases with a restriction of time from inception to 2025 to filter the eligible studies: PubMed, Embase, Cochrane Library, Web of Science, MEDLINE, Chinese National Knowledge Infrastructure, Wanfang, and the Chinese Biomedical Database.

Search Strategy

The following search algorithm and Medical Subject Headings (MeSH) terms were used: [(lung cancer OR lung neoplasm) AND (video-assisted thoracoscopic surgery OR pulmonary surgical procedures) AND (body mass index OR obesity OR obese)]. We considered the specific search strategy in PubMed as a typical example, and the specific steps of the retrieval are shown in Textbox 1.

Textbox 1. Search strategy in PubMed database.

Search items

#1: ((((((((Lung Neoplasms[MeSH Terms]) OR (Neoplasms, Pulmonary[Title/Abstract])) OR (Neoplasm, Pulmonary[Title/Abstract])) OR (Pulmonary Neoplasm[Title/Abstract])) OR (Lung Neoplasm[Title/Abstract])) OR (Lung Cancers[Title/Abstract])) OR (Pulmonary Cancer[Title/Abstract]))

#2: ((((Thoracic Surgery, Video-Assisted[MeSH Terms]) OR (Video-Assisted Thoracic Surgeries[Title/Abstract])) OR (VATSs[Title/Abstract])) OR (Video Assisted Thoracic Surgery[Title/Abstract]))

#3: (pulmonary surgical procedures[MeSH Terms]) OR (Pulmonary Surgical Procedure[Title/Abstract])

#4: #2 or #3

#5: ((Body Mass Index[MeSH Terms]) OR (Quetelet Index[MeSH Terms])) OR (Quetelet Index[MeSH Terms])

#6: Obesity[MeSH Terms]

#7: #5 or #6

#8: #1 and #4 and #7

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Data Collection and Analysis

Study Selection

Qualified studies were screened and selected by 2 independent authors. The literature was imported into NoteExpress to screen the titles and abstracts. After that, we obtained full-text articles of the relevant studies. After reading the full text of the remaining studies, the final included studies were determined. Any disagreements were arbitrated by a third reviewer.

Data Extraction

Data were extracted independently by 2 reviewers into a prepiloted, standardized electronic data collection form created in Microsoft Excel. Any disagreements were resolved by negotiation and discussion. Further controversy was arbitrated by a third reviewer. The following information was extracted. The detailed characteristics of the included studies, the first author's name, published year, country, sample size, age, surgical approach, and tumor staging were extracted. We included studies with the primary outcome of postoperative 30-day mortality and secondary outcomes of postoperative complications, pulmonary complications, cardiovascular complications, total hospital stay, and operation time. Potential confounders (smoking status, comorbidities, cancer staging, surgical duration) were also collected. The GRADE (Grading of Recommendations Assessment, Development and Evaluation) method was used to evaluate the evidence quality of each main outcome index, and its certainty level was clearly reported to ensure the clinical credibility and interpretability of the systematic evaluation conclusion. Results were disseminated via open-access publications, conference presentations, PROSPERO updates, and public summaries for nonacademic stakeholders, with data upon request.

Quality Assessment

NOS was used to evaluate the quality of the research [21]. The NOS provides a checklist of items for evaluating the quality of reporting and the risk of bias of the included studies based on 3 broad evaluation categories: selection, comparability, and exposure/outcomes [22]. The scale has 3 parameters and 8 items with a total score of 9; scores ≤3 are usually considered low quality, scores of 4 or 5 are considered medium quality, and scores ≥6 are usually considered high quality [23]. Two reviewers will independently evaluate the quality of the included studies, and the third team member will verify them. Any differences will be settled through negotiation. To strengthen rigor, we integrated NOS scores into the analysis. Studies scoring ≤3 were excluded. Higher-quality studies (≥6) received greater weighting in the meta-analysis. The GRADE approach was adopted to systematically assess the certainty of evidence for each key outcome. Risk of bias, inconsistency, indirectness, imprecision, and publication bias were evaluated, after which the overall certainty was classified as high, moderate, low, or very low.

Measures of Treatment Effect

For dichotomous data, we plan to present results as risk ratios with 95% CIs. For continuous data, we will use mean difference with 95% CIs. P values less than .05 were considered as statistically significant.

Data Analysis and Heterogeneity Processing

The Review Manager software (version 5.4) will be used for meta-analysis and statistical analysis. Sensitivity analysis and Egger test will be performed with Stata software (version 16.0). Because patients who were operated at different centers may have varying risk profiles and varying selection criteria for each surgical technique, the random effects model will be chosen to take this heterogeneity into account thus has a more conservative value [24,25]. $P<.05$ will be considered statistically significant. Significant heterogeneity will be characterized by $I^2>50\%$ and/or $P<.01$. Besides, the levels of heterogeneity will be assessed by I^2 as follows: 0%-25% indicates homogeneity, 25%-50% indicates low heterogeneity, 50%-75% indicates moderate heterogeneity, and >75% indicates high heterogeneity [26]. To address heterogeneity from differential BMI classifications, we will stratify the meta-analysis by geographic region (Asian vs Western populations) by using their respective standard BMI thresholds. Pooled estimates will be calculated separately for each subgroup.

Subgroup Analysis

Subgroup analyses will be conducted based on the degree of obesity, type of surgical procedure, and geographic region. To mitigate the risks of post hoc subgrouping and interpretive bias, we will prespecify all the subgroups in the analysis plan. We will clearly define obesity severity by standard BMI thresholds, region by geographic or administrative boundaries, and surgical method by specific procedural codes.

Sensitivity Analysis

The stability of the meta-analysis results will be tested through a one-by-one elimination method in the sensitivity analysis. Studies were stratified according to both WHO and region-specific BMI criteria. Sensitivity analyses will be conducted to assess the impact of different BMI thresholds by region on the pooled estimates, thereby ensuring comparability and minimizing potential bias.

Assessment of Reporting Bias

When we select >10 studies consistent with conditions, a funnel plot will be used to detect the publication bias, while the Egger test of bias will be used as a supplement.

Dealing With Missing Data

Should clarification or additional data be necessary from the included studies, the corresponding authors of these studies will be contacted via telephone or email. Duplicate reporting across studies (registry-based publications) will not be screened.

Ethical Considerations

This systematic review and meta-analysis will be based on published data. As researchers did not access any information that could lead to the identification of an individual patient, no concerning ethical issue was raised in this research. Therefore, obtaining ethical approval and consent of participants was waived. Research results may be published in a peer-reviewed journal or disseminated in relevant conferences.

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Results

Results are not yet available because this is a protocol for a systematic review and meta-analysis. This protocol was registered on PROSPERO on February 5, 2025. By August 26, 2025, we completed the literature search of 8 databases, study selection, and data extraction from the selected studies. The specific analysis has not been completed yet. The search and selection process is illustrated in the flow diagram in Figure 1. The results are expected to be published in March 2026.

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. CNKI: Chinese National Knowledge Infrastructure.

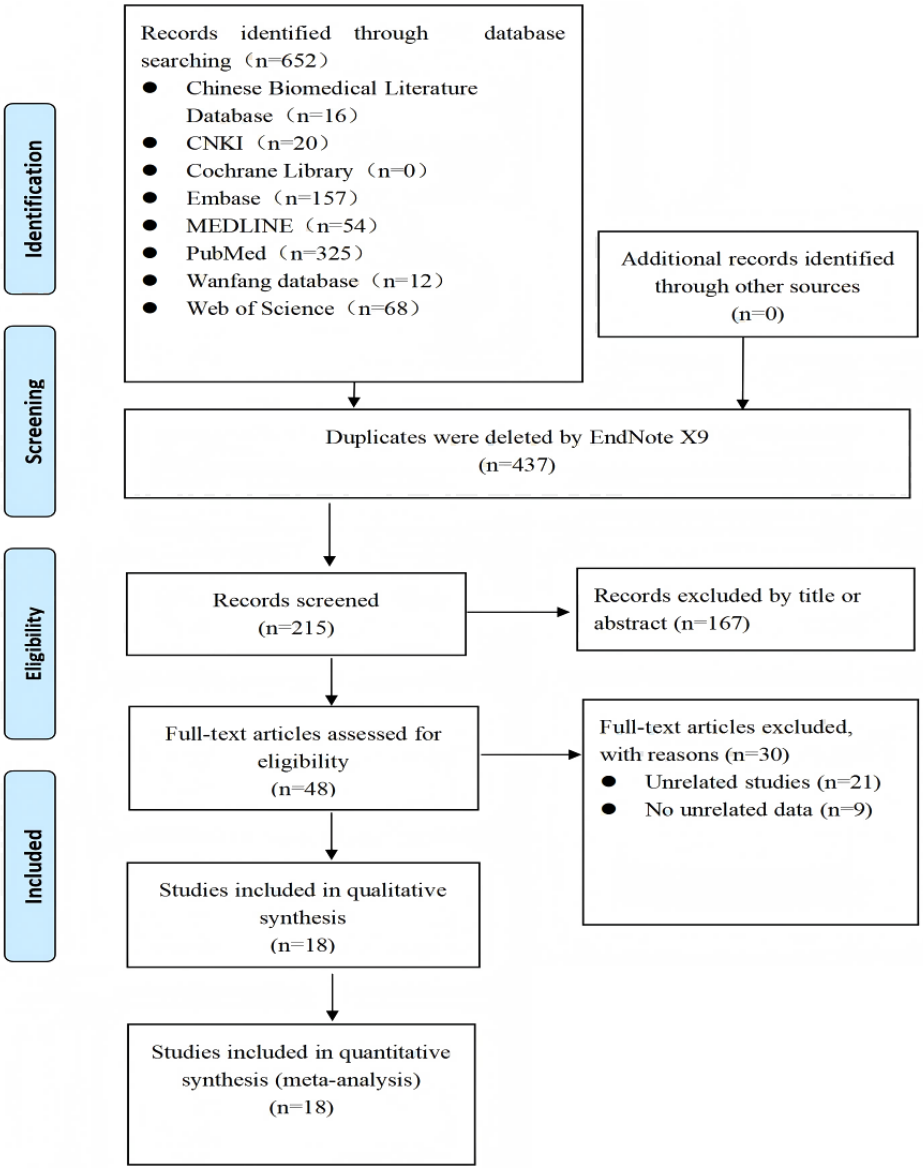

Discussion

This meta-analysis aims to synthesize existing evidence to elucidate the relationship between obesity and perioperative outcomes following lung cancer surgery, providing a comprehensive understanding of the risks and implications for clinical practice. These findings will contribute to a better understanding of the obesity paradox in surgical oncology and may inform preoperative risk stratification and patient counseling. A more insightful analysis would critically examine the methodological heterogeneity across these studies, such as differences in patient cohorts (eg, types of surgery, cancer stages) and, most importantly, the variable adjustments for potent confounders such as smoking, cachexia, or cardiorespiratory fitness. Discrepancies in these elements are likely a primary source of the apparent paradox and warrant explicit elaboration.

The methodological rigor of this meta-analysis, including a comprehensive search strategy, strict inclusion criteria, and robust statistical analysis, will enhance the reliability of the findings. By stratifying results based on BMI categories and adjusting for confounding variables such as age, smoking status, and comorbidities, this study will offer nuanced insights into the impact of obesity on perioperative outcomes. Furthermore, subgroup analyses based on the surgical approach (eg, open vs minimally invasive) and cancer stage will help identify specific populations at higher risk.

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The findings of this meta-analysis have important implications for preoperative risk assessment and patient counseling. If the obesity paradox is confirmed, it may prompt a reevaluation of current risk stratification models and highlight the need for further research into the underlying mechanisms. Osteoarthritis research frequently encounters the obesity paradox, where patients with higher BMI sometimes show unexpected outcomes [27]. This could provide insights into how other researchers have approached similar contradictory findings in their analyses.

In conclusion, this meta-analysis will provide valuable evidence on the effect of obesity on the perioperative outcomes following a lung cancer surgery. By addressing the inconsistencies in the existing literature and exploring potential moderating factors, this study will contribute to the optimization of surgical care for obese people with lung cancer.

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Data Availability

All data generated or analyzed during this study are included in this published article and are available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization: QW, ZL, XW, CW, BL
Data curation: QW, ZL, XW
Formal analysis: XW, CW, BL
Resources: YX
Software: ZL, BL
Writing (original draft): QW
Writing (review and editing): QW, ZL

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P checklist.
[DOC File , 58 KB - resprot_v14i1e76315_app1.doc]

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Abbreviations

GRADE: Grading of Recommendations Assessment, Development and Evaluation
MeSH: Medical Subject Headings
NOS: Newcastle-Ottawa Scale
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
WHO: World Health Organization

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Protocol

Nutritional Supplementation for Obsessive-Compulsive Disorder: Protocol for a Systematic Review of Randomized Controlled Trials

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Abstract

Background: Obsessive-compulsive disorder (OCD) is a chronic mental health condition, and standard treatment often results in incomplete symptom relief. Growing evidence suggests that nutritional supplements, including vitamins, minerals, and amino acids, may serve as potential adjunctive treatments for OCD by influencing neurotransmitter regulation and inflammation.

Objective: Our systematic review aims to assess the comparative efficacy of nutritional supplements on relevant clinical outcomes in individuals with OCD.

Methods: A protocol was developed and registered for this systematic review. Randomized controlled trials assessing the efficacy of nutritional supplementation compared with standard treatments (pharmacological and psychological interventions) will be included. Primary outcomes are changes in cognitive performance, quality of life, and psychiatric symptoms. Secondary outcomes include the presence of comorbidities or multimorbidities (eg, metabolic syndrome). Systematic searches will be conducted in MEDLINE, Embase, CENTRAL, and ClinicalTrials.gov from their inception onward. Two independent researchers will screen the citations and full-text studies. The risk of bias and study quality will be evaluated using validated tools, and association measures with 95% CIs will be calculated. Potential sources of heterogeneity will also be analyzed.

Results: The search commenced in January 2025. Between June and August 2025, studies were identified and the full texts reviewed. Data extraction is anticipated to be completed in September 2025. The final synthesis is scheduled for December 2025.

Conclusions: We aim to address the gaps in the current treatment paradigm for OCD by evaluating the efficacy of nutritional supplementation as an adjunctive therapy. These findings may provide insights into the potential of these supplements to improve cognitive and psychiatric outcomes. This protocol establishes a foundation for the rigorous synthesis of available evidence, which may inform future clinical practices and support the integration of nutritional strategies in OCD management.

Trial Registration: OSF Registries 10.17605/OSF.IO/NZ5MU; https://osf.io/NZ5MU

International Registered Report Identifier (IRRID): DERR1-10.2196/80240

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(JMIR Res Protoc 2025;14:e80240) doi:10.2196/80240

KEYWORDS

obsessive-compulsive disorder; nutritional supplementation; systematic review; cognitive function; quality of life

Introduction

Obsessive-compulsive disorder (OCD) is a chronic and debilitating mental health condition characterized by intrusive thoughts (obsessions) and repetitive behaviors (compulsions). The lifetime prevalence of OCD is estimated to be approximately 2%-3% globally, making it a significant public health concern [1]. Despite the availability of various pharmacological and psychological treatments, a significant proportion of individuals with OCD experience persistent symptoms and impaired quality of life [2]. This underscores the urgent need for innovative therapeutic approaches to improve outcomes in this population.

Recently, interest has emerged in the potential role of nutritional supplements as adjunctive treatments for OCD. Nutritional supplements, including vitamins, minerals, and amino acids, have been hypothesized to influence brain function and mental health by modulating neurotransmitter systems and reducing oxidative stress [3,4]. For example, vitamin D regulates serotonin, a neurotransmitter implicated in OCD pathophysiology [5]. Similarly, vitamin B and glycine have been investigated for their potential to support cognitive function and reduce anxiety symptoms [6].

Existing research has examined various nutritional supplements, including vitamins D and B12 and glycine, with some studies reporting promising results in reducing obsessive-compulsive symptoms [7,8]. Marazziti et al [7] found that vitamin D supplementation significantly improved OCD symptoms in a small cohort of patients. Cleveland et al [8] demonstrated that glycine, an inhibitory neurotransmitter, reduces anxiety and improves cognitive function in individuals with OCD. However, these studies have limitations, including small sample sizes, short follow-up periods, and methodological heterogeneity. Thus, a rigorous synthesis of the available evidence is essential to draw definitive conclusions and guide clinical practice. Moreover, the existing pharmacological treatments for OCD—primarily selective serotonin reuptake inhibitors—are associated with a range of side effects and are ineffective in all patients [9]. Psychological interventions such as cognitive-behavioral therapy are effective but require substantial time and resources, which may not be accessible to all individuals. Consequently, there is growing interest in complementary and alternative therapies, including nutritional supplementation, as additional treatment options [10].

This study aims to assess the comparative efficacy of nutritional supplements on relevant clinical outcomes in individuals with OCD. Our approach involves a systematic review of randomized controlled trials (RCTs) comparing nutritional supplements alone or in combination with standard treatments, with placebo or other active treatments. Adults with OCD will be included according to the diagnostic criteria of the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) [10,11], and standard treatments are defined according to the National Institute for Health and Care Excellence clinical guideline CG31 for OCD and body dysmorphic disorders [12].

Although previous reviews have addressed nutritional supplementation for depression [3] and schizophrenia [4], no systematic review has comprehensively synthesized the evidence specific to OCD. Furthermore, findings in small clinical trials [3] are inconsistent: some report improvements in OCD symptoms, while others show no effect. This discrepancy highlights the need to clarify the role of nutritional supplements in managing OCD and to resolve uncertainties about the type of supplement, dosage, and duration of treatment.

The specific research problem addressed in this study is the need to determine the efficacy of nutritional supplements in improving primary outcomes such as cognition, quality of life, and psychiatric symptoms, as well as secondary outcomes such as comorbidity rates [13,14]. We hypothesized that nutritional supplementation when combined with validated pharmacological and psychological interventions would offer additional benefits in managing OCD symptoms compared with standard treatment alone.

Although this protocol aims to maximize internal validity, particular attention has also been given to ensuring its relevance to real-world populations with OCD by addressing comorbidities, sample heterogeneity, and implementation challenges.

Methods

Study Design and Ethical Considerations

This protocol has been registered in the Open Science Framework (OSF; registration: osf.io/NZ5MU). This study will be conducted according to the guidelines of the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) statement [15,16] (see Multimedia Appendix 1). Ethics approval is not required for the conduct of this study.

Criteria for Considering Studies for This Systematic Review

Types of Studies

We will include RCTs that have compared a nutritional supplement alone or in combination with a standard treatment with a placebo or another alternative active treatment. Standard treatment is defined as treatment validated by the National Institute for Health and Care Excellence clinical guidelines, whether pharmacological and/or psychological.

We will exclude crossover trials because obsessive ideation and compulsions may evolve over time, and washout periods themselves may induce detrimental effects in the second period of the trial. We will also exclude cluster RCTs because of the

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potential for identification/recruitment bias and overestimation of the precision of the results.

Types of Participants

We will include adults aged ≥18 years with OCD. Participants will be defined as having OCD by using the DSM-5 criteria. We will exclude studies in which participants have organic causes of OCD. Additionally, we will exclude participants with comorbid psychiatric disorders such as schizophrenia, bipolar disorder, depressive disorder, eating disorders, and suicidal behavior. Participants presenting with subthreshold symptoms of depression or anxiety will not be excluded, provided that the diagnostic thresholds for another psychiatric disorder are not met.

Participants with organic causes of OCD, including temporal lobe epilepsy, will be excluded to prevent confusion with neurobiological mechanisms. Individuals with subthreshold depressive or anxiety symptoms will be eligible, provided they do not meet all the diagnostic criteria for another psychiatric disorder. This approach ensures that we retain internal validity while keeping our findings relevant to the diverse OCD population encountered in clinical practice.

Types of Interventions

We will include nutritional supplementation (eg, vitamin D, vitamin B12, glycine) combined with pharmacological and psychological interventions that have been clinically validated to reduce obsessive-compulsive symptoms.

Comparator

The comparator will include other nutritional supplements, placebos, or an alternative active drug. Co-interventions will be acceptable in both the intervention and comparison groups provided that they are administered equally across all groups in the trial. If a trial included multiple arms, any arm that met the inclusion criteria will be included.

We will consider intervention durations of 12 weeks or longer because nutritional supplementation is more likely to affect the relevant primary outcomes during this timeframe. We do not impose a limit on the maximum duration of intervention. Studies reporting one or more of our outcomes at least 6 months after the start of the intervention will be included. Therefore, the minimum follow-up duration of the studies will be set at 6 months.

Trials should include a minimum intervention duration of 12 weeks and at least 6 months of follow-up to assess the sustained effects. A sensitivity analysis will also incorporate trials with shorter follow-up periods to assess the robustness of the findings.

Types of Outcome Measures

The primary and secondary outcomes are defined as outlined below. Trials will not be excluded solely because one or several of our primary or secondary outcome measures are not reported in the publication. However, if none of our primary or secondary outcomes are reported, we will include the trial only for information purposes.

Primary Outcomes

We consider the following primary outcomes.

1. Cognition: measured using validated instruments (eg, Stroop Color and Word Test, Complutense Verbal Learning Test, Trail-Making Test).
2. Quality of life: measured using validated instruments (eg, Functional Assessment Short Test and Short Form-36 item Health Survey questionnaire).
3. Psychiatric symptoms: measured using validated instruments that include one or more of the following domains (eg, depression, anxiety, stress, obsessions, compulsions, psychotic symptoms).

Secondary Outcomes

We consider the following secondary outcome: morbidity or comorbidity, which is the occurrence of physical illnesses (eg, diabetes, metabolic syndrome, cardiovascular events) at any time before or after the initiation of the intervention with nutritional supplementation (eg, Kaplan-Feinstein Scale, Charlson Comorbidity Index).

Search Methods for the Identification of Studies

We will attempt to identify all the relevant trials, regardless of their language, publication status (published, in press, or in progress), or publication date. To minimize bias in the search results, we will develop a search strategy following the instructions in the Cochrane Handbook for Systematic Reviews of Interventions [17].

Electronic Searches

We will search the following electronic databases: MEDLINE through PubMed (National Library of Medicine), Embase through the Elsevier platform, CENTRAL via the Cochrane Library, and ClinicalTrials.gov. We will search these databases since their inception. The research team will design and execute a detailed search strategy by using the same strategy with appropriate adjustments for each database. Search terms will include keywords related to names/clusters of nutritional supplements, cognition, quality of life, psychiatric symptoms, comorbidity, and randomized studies. No restrictions will be imposed on the dates. The initial literature searches of MEDLINE, Embase, and the Cochrane Database of Systematic Reviews began in January 2025. The draft strategies for MEDLINE and Embase are provided in Multimedia Appendix 2.

Searching Other Resources

We will search the reference lists of all identified trials, relevant review studies, and current treatment guidelines to identify additional potentially eligible studies. We will contact the authors of the identified studies and research groups known to be active in pharmacological interventions for OCD to request unpublished material or further information on ongoing studies. The search will be conducted and updated as necessary before publication. We will provide the actual dates of the electronic search during the review stage.

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Data Collection and Analysis

Selection of Studies

First, 2 researchers will independently screen the titles and abstracts of the studies obtained from the initial searches, masked to each other's decisions and based on the eligibility criteria. We will obtain the full texts of all potentially relevant reports. Second, these full texts will be examined in detail and screened for eligibility, with the reasons for exclusion recorded. Third, the references of all the considered studies will be manually searched to identify any relevant reports missed by the search strategy. We will examine the full studies and supplementary materials containing data and analyze their general and methodological characteristics and study results. The final versions of the studies available online will also be reviewed.

The authors will be contacted in the case of ambiguity or missing data. Duplicate records will be identified and excluded, and multiple reports from the same study will be collated such that the analysis, rather than individual reports, will serve as the unit of interest in the review. Disagreements will be resolved by consensus or consultation with a third reviewer. If disagreements cannot be resolved, we will categorize the study as "awaiting classification" and contact the authors for clarification. Studies for which relevant data cannot be obtained will also be classified as "awaiting classification."

Data Collection and Management

Once the searches have been performed, items identified in the databases will be imported into Rayyan software (Rayyan Systems) [18]. Following the recommendations of the PRISMA 2020 declaration [19], a flowchart showing details of the studies included and excluded at each stage of the selection process will be provided.

Data from each report will be used to build evidence tables describing the included studies. A standardized data extraction form will include the following information of interest: first author's name, year of publication, type of nutritional supplementation (eg, vitamin B12), outcomes (eg, memory, depression), comparison, participant details (eg, diagnostic criteria, age, sex, years of education, comorbidity, risk factors), and maximally adjusted effect sizes, including corresponding 95% CIs, hazard ratios, odds ratios, and relative risks.

When sufficient data are available, random-effects meta-analyses will be performed. Continuous outcomes will be synthesized as standardized mean differences (Hedges *g*) and dichotomous outcomes as risk ratios with 95% CIs. Heterogeneity will be assessed using the I^2 statistic, and subgroup analyses will be conducted based on supplement class, dose, and duration. Sensitivity analyses will examine the influence of study quality and follow-up duration. If quantitative synthesis proves unfeasible, results will be summarized narratively by supplement type and clinical outcome.

Subgroup analyses will be performed by supplement class (eg, amino acids, vitamins, fatty acids), dose, and duration of treatment. Implementation in practice may be influenced by variability in supplement quality, dosing guidelines, patient adherence, and placebo effect. These factors will be considered when interpreting the results.

If meta-analysis is not feasible, a structured narrative synthesis will be performed, organized by supplement type, outcome measure (symptom severity, cognition, quality of life), and study quality. Findings will be contextualized in relation to methodological rigor and clinical applicability.

Risk of Bias and Quality Assessment in the Included Reviews

At least 2 researchers will independently assess the risk of bias and the quality of each study, and any disagreements will be resolved by discussion. For the RCTs, we will evaluate the risk of bias in each included study by using the Cochrane Risk of Bias 2.0 tool [20]. This tool considers random sequence generation, allocation concealment, blinding of the participants and outcome assessors, incomplete outcome data, selective outcome reporting, and other potential sources of bias. We will judge the risk of bias for each study based on these criteria and classify the studies as having a low, high, or unclear risk of bias. The quality of the RCTs will also be assessed using the Cochrane Collaboration tool to assess the risk of bias [21]. This scale evaluates 7 items as follows: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting, and other biases [22]. Each item will be scored as high risk, low risk, or unclear risk based on the available evidence. Published trial results will be systematically checked against trial registry entries (eg, ClinicalTrials.gov) to assess for selective reporting of results and potential publication bias.

Results

The search commenced in January 2025. Between June and August 2025, studies were identified and the full texts reviewed. Data extraction is anticipated to be completed in September 2025. The final synthesis is scheduled for December 2025.

Discussion

We anticipate that our systematic review will synthesize current evidence from RCTs, offering insights into the efficacy of vitamins, minerals, and amino acids in improving cognitive performance, psychiatric symptoms, and overall quality of life in individuals with OCD.

This protocol describes a systematic review of RCTs that evaluates the efficacy of nutritional supplements as adjunctive treatments for OCD. The systematic review will establish the extent of clinical evidence supporting the association between nutritional supplementation and improvements in cognition and psychiatric symptomatology in a rigorous and reproducible manner.

Emerging evidence suggests potential benefits of nutritional supplementation as an adjunctive treatment to enhance cognitive performance, quality of life, and psychiatric symptoms in individuals diagnosed with OCD. Understanding the complex relationship between nutritional supplementation and clinical

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outcomes in OCD could serve as a foundation for integrating these interventions into clinical practice as complementary approaches to standard treatments. This perspective may be particularly valuable for individuals who are resistant to treatment, experience adverse effects of current pharmacotherapies, or have comorbidities. Although reviews on depression [3] and schizophrenia [4] have highlighted the beneficial effects of nutritional supplements, evidence of their effects in patients with OCD remains scarce and heterogeneous. Our systematic review will address this deficiency by applying standardized risk of bias tools and synthesizing the different classes of supplements.

The proposed systematic review will adhere to the reporting standards outlined in the PRISMA 2020 statement [15,16]. Any amendments made to this protocol will be documented and outlined in the final manuscript. The results will be disseminated through presentations at scientific conferences and through publications in peer-reviewed journals. All data underlying the findings reported in the final manuscript will be deposited in OSF [23], a cross-disciplinary public repository.

The strengths of this protocol include prospective registration, comprehensive search strategies, and adherence to PRISMA-P. Limitations include anticipated heterogeneity among interventions and trial quality, as well as potential publication bias. These challenges will be mitigated by sensitivity analyses and comparison with trial registries.

Finally, we aim to identify the knowledge gaps that future research can address. The implications for future studies will be discussed in the final manuscript. The findings of this review will determine whether specific supplements warrant further large-scale trials for OCD and will guide the refinement of treatment protocols.

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Authors' Contributions

VB-M is the co-corresponding author and can be reached via email: vicente.balanza@uv.es; phone: +34963864744; address: Teaching Unit of Psychiatry and Psychological Medicine, Department of Medicine, University of Valencia, Blasco Ibáñez 15, 46010, Valencia, Spain.

The study protocol was conceived by PSM and JVSO, with critical inputs from PCG, VBM, DMSG, IFD, and RTS. JVSO registered the protocol in the Open Science Framework. All the authors provided input for the study design, edited the draft protocol, and commented on the manuscript for important intellectual content. RTS accepts full responsibility for the finished paper and organizes the decision to publish it. RTS and VBM also contributed equally to this study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P checklist.
[DOCX File , 34 KB - resprot_v14i1e80240_app1.docx]

Multimedia Appendix 2
Detailed search strategies.
[DOCX File , 29 KB - resprot_v14i1e80240_app2.docx]

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Abbreviations

DSM-5: Diagnostic and Statistical Manual of Mental Disorders, fifth edition
OCD: obsessive-compulsive disorder
OSF: Open Science Framework
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
RCT: randomized controlled trial

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Protocol

Effectiveness of Herbal Interventions in the Management of Hypercholesterolemia: Protocol for a Systematic Review

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Abstract

Background: Hypercholesterolemia is a significant risk factor for cardiovascular diseases, necessitating effective management strategies. Herbal interventions have gained attention as potential alternative or complementary therapies to conventional lipid-lowering medications.

Objective: This systematic review aims to evaluate the effectiveness of various herbal interventions in managing hypercholesterolemia.

Methods: A comprehensive literature search will be conducted across multiple databases, including PubMed, MEDLINE, EMBASE, EBSCO, Cochrane Library, DHARA, AYUSH research portal, WHO portal, Shodhganga, and Google scholar as well as dissertations and thesis work available in the public domain and unpublished works from university websites for studies published from January 2020 onward. Randomized controlled trials investigating the impact of herbal interventions on cholesterol levels will be included. The primary outcome is the change in low-density lipoprotein cholesterol and high-density lipoprotein cholesterol levels. Data extraction and quality assessment will be performed independently by 3 reviewers, and discrepancies will be resolved by a fourth reviewer. All statistical analyses will be conducted using the Cochrane Collaboration software program, RevMan Web.

Results: Following an initial screening, 96 studies were identified. After removing duplicates, 7 studies were excluded, leaving 89 studies ready for data extraction. The results of these studies will be synthesized and analyzed upon completion.

Conclusions: This review aims to synthesize evidence on the potential benefits of herbal interventions in managing hypercholesterolemia. Preliminary findings suggest that specific herbal interventions may contribute to lower cholesterol levels, potentially complementing standard hypercholesterolemia management strategies. The findings will be systematically analyzed and presented upon completion of the review, providing insights into the effectiveness of integrating these interventions into current treatment protocols.

Trial Registration: PROSPERO CRD42024548858; https://www.crd.york.ac.uk/PROSPERO/view/CRD42024548858

International Registered Report Identifier (IRRID): DERR1-10.2196/68016

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KEYWORDS

herbal interventions; hypercholesterolemia; systematic review; elevated cholesterol levels; herbal medicines

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Introduction

Lipoproteins are complexes of lipids and proteins essential for transporting cholesterol, triglycerides, and fat-soluble vitamins in the blood. Plasma lipoproteins are classified into 5 major classes based on their relative density: chylomicrons, very low-density lipoproteins, intermediate density lipoproteins, low-density lipoproteins (LDL), and high-density lipoproteins (HDL). Key roles of lipoproteins are to transport dietary lipids from the intestines to tissues requiring fatty acids for energy storage and metabolism and to transport intestinal cholesterol to the liver.

Disorders of lipoprotein metabolism, known as dyslipidemias, are clinically characterized by increased plasma levels of cholesterol, triglycerides, or both [1]. The etiological classification of dyslipidemia is categorized as primary (genetic) or secondary (lifestyle and other). Hypercholesterolemia falls under the primary type of dyslipidemia. Hypercholesterolemia is a polygenic disorder characterized by an increase in cholesterol, whereas in hypertriglyceridemia there is an increase in triglycerides [2]. Plasma lipoprotein levels are significant modifiable risk factors for cardiovascular diseases, with increased levels of LDL contributing to the development of atherosclerosis [3].

According to the Global Health Observatory, raised cholesterol is estimated to cause 2.6 million deaths globally and 29.7 million (2%) disability-adjusted life years [4]. Elevated total cholesterol is a significant cause of disease burden in both high- and low-income countries, serving as a risk factor for ischemic heart disease and stroke [4]. Very low-density lipoproteins and triglycerides contribute to the building up of arterial plaque.

Factors such as genetics, high intake of saturated fats, sedentary lifestyle, and certain medical conditions, including diabetes and hypothyroidism, can lead to hypercholesterolemia. Modification of lifestyle, including changes in food habits, cessation of smoking, reduction of alcohol intake, and regular exercise, is not only necessary to attain normal lipid levels but also represents the very first step in the management of hypercholesterolemia [3]. Standard treatments include statins, ezetimibe, bile acid sequestering resins, proprotein convertase subtilisin/kexin type 9 inhibitors, and nicotinic acid [4].

Studies have shown that garlic [5-7], *Triphala* [8], Nigella sativa seeds [9], and Terminalia arjuna [10] have significant lipid-lowering effects and are effective in managing dyslipidemia. Garlic reduces serum lipid levels, while *Triphala* and Nigella sativa improve lipid profiles safely. Terminalia arjuna also lowers total and LDL cholesterol with antioxidant benefits comparable to vitamin E, making these natural agents promising for cholesterol management. Additionally, there is growing interest in herbal medications as alternative or complementary treatments, as these natural remedies may offer potential benefits in managing cholesterol levels. This systematic review will aim to assess the effectiveness of herbal interventions in hypercholesterolemia.

Methods

Overview

This review protocol was prepared and reported in accordance with the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines and the Cochrane Handbook for Systematic Reviews of Interventions. The trial has been registered in PROSPERO (CRD 42024548858).

Types of Interventions

Overview

The review will include studies on single or polyherbal drugs in any form and dosage, including those combined with dietary regimens, physical activity, or both. Studies evaluating single or polyherbal drugs alongside the standard of care for hypercholesterolemia will be included. If herbal interventions are combined with other treatments such as diet or physical activity, these studies will be categorized as combination therapy and analyzed separately to assess the specific contribution of herbal interventions. In cases where herbal interventions are part of a combination therapy, a hierarchical approach will be used. Priority will be given to the analysis of outcomes directly attributed to the herbal component, if reported separately. Otherwise, the overall effect of the combined intervention will be considered.

Inclusion Criteria

The following studies will be included: (1) randomized controlled trials; (2) systematic reviews and meta-analyses providing relevant data (these will be considered for background information); (3) studies involving adult participants (aged ≥18 years, regardless of sex) diagnosed with hypercholesterolemia or dyslipidemia as per established clinical criteria; (4) studies involving populations with secondary causes of dyslipidemia (eg, diabetes or hypothyroidism) if data specific to hypercholesterolemia are provided; (5) studies evaluating the effects of single or polyherbal formulations, whether in raw, processed, or extract forms; and (6) full-text articles published in any language.

Exclusion Criteria

The following studies will be excluded: (1) studies with insufficient methodological details or unclear reporting of outcomes; (2) nonrandomized controlled trials, animal trials, case series, commentaries, letters to the editor, case reports, narrative reviews, editorials, abstracts, meetings, and studies with insufficient information on herbal interventions and hypercholesterolemia; and (3) research papers with study durations less than 4 weeks.

Comparison or Control Groups

Control groups involving placebo, no intervention, diet, exercise, standard of care, or any combination of these will be considered. If a trial includes multiple arms, any arm that meets the inclusion criteria will be included in the review.

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Outcome Measures

Primary outcomes include LDL cholesterol levels (>130 mg/dl) and HDL cholesterol levels (<40 mg/dl). Additional outcomes include cardiovascular events (high blood pressure, stroke, or coronary artery disease), triglycerides (>150 mg/dl), total cholesterol (>200 mg/dl), and changes in BMI and body weight.

Search Methods for Study Identification

The literature search will be conducted across multiple databases, including the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, EMBASE, EBSCO, AYUSH research portal, DHARA, Google Scholar, and Shodhganga. We will search clinical trial registries for ongoing and recently completed trials (eg, ClinicalTrials.gov, World Health Organization International Trials Registry and Platform, and ISRCTN Registry). The search strategy will combine Medical Subject Headings terms and free text words using the Boolean operators "AND" and "OR." For example, "hypercholesterolemia," "increased cholesterol levels," "dyslipidemias," "hyperlipidemias," "increased lipid levels" AND "herbal interventions," "herbal medicines," "plant extracts," "medicinal plants," "herbs," "Chinese herbal drugs," "Mongolian traditional medicine," "Ayurveda," "Ayurved," "East Asian traditional medicine," "medicine," "biological products". Different search strategies will be used for different databases.

Dissertation and thesis work available in the public domain as well as unpublished postgraduate and doctoral dissertations from university and institutional websites and other potential sources from inception to present will be included. We will use backward and forward citation searching to identify additional relevant papers. Searches will be rerun prior to initiating the final analysis. If published data for a registered trial cannot be found, we will contact the principal investigator via email to obtain the trial data.

Data Collection and Analysis

Selection of Studies

Four review authors (AAT, RVP, AMS and ATP) will independently screen the titles and abstracts of articles identified through the searches to determine suitability. Studies will be classified as included, unclear, or excluded. For studies without an abstract or with a limited abstract, full articles will be retrieved and assessed for inclusion. Three review authors will independently evaluate the full articles using a standardized form with explicit inclusion and exclusion criteria. Any discrepancies will be resolved through consultation with a fifth review author (MKB). The selection of studies will follow the PRISMA guidelines [11].

Data Extraction

The data extraction form will include the following in accordance with the standards prescribed in the PRISMA guidelines: author and year of publication, study setting, study population, participant demographics, study methodology, details of the intervention and comparator, outcome measures, and study results.

Missing Data

If there is incomplete information or a lack of data, we will contact the author by telephone or email. If the missing data cannot be obtained, we will use replacement values to fill in the gaps, if necessary, or consult with experts.

Data Synthesis and Assessing Heterogeneity

All statistical analyses will be conducted using RevMan Web version 5.3 software (Cochrane Collaboration). A P value of <.05 will be considered statistically significant between studies. Heterogeneity will be assessed using the I^2 statistic. RevMan Web is widely recognized as a comprehensible tool specifically designed for conducting systematic reviews and meta-analyses. Its ability to handle heterogeneous data through random-effects models, subgroup analysis, and forest plots makes it particularly suitable for this study.

Subgroup Analysis

If the clinical trials cause heterogeneity, we will perform a subgroup analysis based on interventions, controls, durations of interventions, and outcome measurements. Adverse reactions will be tabulated and then evaluated. Subgroup analyses will be performed to evaluate the effectiveness of single herbal interventions in comparison to polyherbal interventions as well as the impact of herbal therapies used alone compared to those combined with other lifestyle modifications (eg, diet or exercise).

Risk of Bias in Individual Studies

Four review authors (RB, DD, KRG, and AK) will independently assess the risk of bias of each included trial. We will resolve any disagreements by consensus or by consultation with a fifth review author (MKB). If adequate information is not available from trial authors, trial protocols, or both, we will contact trial authors for missing data on risk of bias items. Randomized controlled trials will be assessed by using the Cochrane Risk of Bias tool–2, which classifies studies as having some concern, low risk of bias, or high risk of bias by evaluating domains like randomization process, deviation from the intended interventions, missing outcome data, measurement of the outcome, and selection of the reported results [12]. The risk of bias findings will be presented as a summary and graph.

Assessment of Publication Bias

Potential publication bias will be addressed by including studies published in all languages and considering both published and unpublished data.

Assessment of Strength of Evidence

The strength of evidence will be assessed using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach. GRADE evaluates the quality of evidence based on certain factors. Risk of bias will be assessed for methodological quality and different types of biases of studies. Inconsistency will be assessed by considering the variability of results across studies. Indirectness will be evaluated by analyzing the applicability of the evidence to the research question. Imprecision will be estimated by assessing

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the precision of effect estimates based on confidence intervals and sample sizes.

Data analysis

Descriptive Analysis

The review will summarize the characteristics of the included studies, such as author, year of publication, study design, sample size, population characteristics, and duration of the intervention. Tables and narrative summaries will be used to present the types of herbal interventions used, including dosages and comparison groups. Additionally, the baseline characteristics of participants, such as age, gender, baseline lipid levels, and comorbidities, will be summarized in tables or using descriptive statistics like means, medians, ranges, and standard deviations.

Statistical Analysis

To analyze primary outcomes such as HDL and LDL levels, we will calculate the mean difference or standardized mean difference for these continuous variables between intervention and control groups. We will choose between random-effects or fixed-effects models based on the level of heterogeneity, which can be assessed using the I^2 statistic. For dichotomous outcomes such as the incidence of cardiovascular events, we will use relative risk or odds ratios for the analysis. Similar to HDL and LDL levels, we will calculate the mean difference or standardized mean difference for continuous outcomes like triglyceride and total cholesterol levels. To analyze changes in BMI and body weight, we will calculate the mean difference or standardized mean difference. Additionally, we will consider performing subgroup analyses to explore differences based on the type of herbal intervention.

Ethical Considerations

Ethical approval was not required as systematic reviews are a form of secondary research and the review did not include any confidential information about participants.

Results

Following an initial screening process, a total of 96 studies were identified as relevant. A duplicate-checking procedure was then conducted, resulting in the removal of 7 duplicate studies, with 89 unique studies remaining eligible for further review and data extraction. These studies will undergo a detailed synthesis and analysis to assess key findings, trends, and implications. Data collection began on November 1, 2024.

Discussion

Hypercholesterolemia, a condition characterized by elevated levels of cholesterol in the blood, is a significant risk factor for cardiovascular diseases such as ischemic heart disease and stroke. Recently, there has been growing interest in herbal interventions as alternative or complementary treatments for managing cholesterol levels. Herbal interventions typically exert their cholesterol-lowering effects through various mechanisms. A meta-analysis on garlic concluded that garlic, in powder or nonpowder form, can significantly lower serum lipid levels over a 1- to 3-month period [5], and a clinical trial conducted to evaluate efficacy concluded that the essential oil of garlic exerts a distinct hypolipidemic action in both healthy individuals and patients of coronary heart disease [6]. Additionally, a study examining the effects of garlic on obesity and blood lipid profiles in high-fat diet–induced obese mouse models revealed that administration of garlic significantly reduced high-fat diet–induced weight gain, epididymal fat accumulation, and hypercholesterolemia [7]. However, evidence from a meta-analysis on the effect of garlic on serum cholesterol suggests that the intake of garlic preparations did not produce any significant beneficial effects on serum cholesterol levels [13]. An animal study on the *Curcuma longa* revealed that while lipid accumulation significantly increased in the free fatty acids–treated group compared to the control group, supplementation with the water extract of *Curcuma longa* effectively reduced lipid accumulation in a dose-dependent manner, demonstrating its potential for regulating lipid metabolism [14]. A meta-analysis on *Curcuma longa* suggested that curcumin (ie, turmeric) supplementation may be effective in improving blood levels of total cholesterol, triglycerides, LDL cholesterol, and HDL cholesterol, but may not be capable of improving their pertinent apolipoproteins [15]. A randomized clinical study was conducted to evaluate the efficacy and safety of *Triphala*, an Ayurvedic powder formulation consisting of Terminalia chebula, Terminalia bellerica, and Emblica officinalis. The study found that *Triphala* is both effective and safe for the management of dyslipidemia [8]. A randomized clinical study was also conducted to evaluate the efficacy of Nigella sativa seeds and concluded that they have beneficial therapeutic effects in the treatment of hyperlipidemia [9]. A randomized controlled trial evaluated the antioxidant and hypocholesterolemic effects of *Terminalia arjuna* tree bark powder in patients with coronary heart disease and found that *Terminalia arjuna* significantly reduced total and LDL cholesterol levels, with its antioxidant effects comparable to those of vitamin E, demonstrating potential therapeutic benefits in managing cholesterol levels [10].

Collating all the above results into a common pool of evidence through a systematic review and meta-analysis will hopefully benefit clinicians focusing on hypercholesterolemia. Comparative findings on alternative therapies targeting this spectrum of disease will undoubtedly contribute to building a robust treatment protocol, ultimately promoting an integrative approach. This systematic review aims to provide comprehensive evidence on the effectiveness and safety of herbal interventions in managing hypercholesterolemia. The findings could guide health care professionals in recommending herbal supplements as part of a holistic treatment approach and inform future research directions.

The main limitation of the study is that most clinical trials conducted in alternative medicine, such as Ayurveda, are not yet available in leading journals indexed in major databases. Additionally, clinical trials with positive results, conducted as part of academic work, have not been published or made accessible to the public. This limits the availability of high-quality evidence, potentially affecting the comprehensiveness of the review.

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The systematic review will be published in a peer-reviewed journal and disseminated both electronically and in print. It will be periodically updated, and a GRADE 2.0 evaluation will be conducted to assess the quality of evidence, providing summaries on the future state of the research.

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Data Availability

This is a study protocol. The data will be publicly available after the systematic review is published.

Authors' Contributions

AAT performed the acquisition, analysis, and interpretation of the data. ATP provided critical revisions. RVP and AT reviewed and edited the manuscript AMS and KRG contributed to conceptualization of the study. RB and DD developed the methodology. MKB provided important intellectual content and reviewed and edited the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CENTRAL: Cochrane Central Register of Controlled Trials
GRADE: Grading of Recommendations, Assessment, Development, and Evaluations
HDL: high-density lipoprotein
LDL: low-density lipoprotein
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

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Protocol

Antidepressant and Antipsychotic Drug Use and Cancer Risk: Protocol for an Overview of Systematic Reviews and Meta-Analyses

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Abstract

Background: The relationship between cancer and central nervous system disorders has received increasing attention recently. Consequently, antipsychotics and antidepressants, commonly prescribed for conditions such as depression, bipolar disorder, and schizophrenia, have emerged as potential modulators of subsequent cancer risk. Previous studies have suggested that the use of these medications is associated with a decreased risk of cancer incidence and mortality, making them suitable candidates for drug repurposing. However, the potential therapeutic benefits do not extend to all cancer types, as some data suggest an increased risk for specific tumors.

Objective: This study aims to conduct a comprehensive review of systematic reviews and meta-analyses (review of reviews) that assess whether exposure to antidepressants or antipsychotics influences cancer incidence and mortality.

Methods: To provide a clear overview of this review, we have designed and registered the study protocol. Specifically, we will include systematic reviews and meta-analyses that examine the relationship between previous antipsychotic or antidepressant treatments and the subsequent cancer risk. The primary outcome will be the risk of cancer incidence and mortality (all malignant neoplasms) associated with exposure to psychopharmacological medications. Furthermore, secondary outcomes will include site-specific cancer incidence and mortality (eg, lung cancer). Literature searches will be conducted in multiple electronic databases (from their inception onwards), including PubMed/MEDLINE, Embase, and the Cochrane Database of Systematic Reviews.

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Three researchers will independently screen all citations, abstracts, and full-text articles. We will perform parallel search, selection, and extraction tasks using a large language model (GPT-4o; OpenAI). Data selection and extraction will involve both human reviewers and GPT-4o, whose performance will be validated through human evaluations. Thus, we will verify whether this type of tool can accelerate or even perform the tasks involved in a systematic review. The risk of bias and the quality of individual studies will be evaluated using appropriate tools. Subsequently, we will extract the summary association measures (eg, pooled relative risk, odds ratio, and hazard ratio) as reported in each included systematic review. Where available, we will summarize subgroup and sensitivity analyses as described by the authors.

Results: Planned searches will be conducted in various electronic databases from their creation until September 2025. No results are available or included in this protocol. The expected results will be published in 2026.

Conclusions: This overview of systematic reviews and meta-analyses will provide an updated synthesis of the cancer risk associated with antipsychotic and antidepressant drugs. Furthermore, this study will examine factors that may explain potential study variations. Ultimately, these findings will be published in a peer-reviewed journal.

Trial Registration: OSF Registries 10.17605/OSF.IO/5ACWH; https://osf.io/5acwh/overview

International Registered Report Identifier (IRRID): DERR1-10.2196/78596

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KEYWORDS

antidepressants; antipsychotics; cancer; drug repurposing; large language models; meta-analysis; systematic review

Introduction

Recently, the relationship between cancer and the nervous system has attracted considerable attention for several reasons. Cancer and neurological and mental disorders are among the leading causes of death and are usually chronic, debilitating disorders with profound human and economic consequences [1-3].

Second, many recent preclinical and clinical studies have investigated the crosstalk between the nervous system and cancer. Notably, the nervous system and psychopharmacological interventions can regulate any aspect of cancer biology, from tumor initiation to progression and metastasis. Conversely, cancer and cancer therapies can influence and remodel the nervous system [4,5]. The importance of this evidence has culminated in the emergence of a new discipline termed “cancer neuroscience” (a review is provided elsewhere [6-8]). However, the absence of references to the reciprocal interactions between cancer and neurological and mental disorders in these reviews is surprising.

Third, several systematic reviews and meta-analyses have suggested that neurological and mental disorders such as schizophrenia, mood disorders, autism spectrum disorders, anorexia nervosa, Alzheimer disease, Parkinson disease, and multiple sclerosis are associated with a significantly increased or decreased risk of various cancers, including melanoma and brain, breast, pancreatic, and lung cancers [9-12]. Although knowledge gaps exist regarding these direct and inverse comorbidities, a cross-diagnostic perspective is required to better understand the nervous system–cancer interactions [13].

Fourth, given the established comorbidities between cancer and neurological and mental disorders, the remaining questions are as follows: What are the underlying causes, and how can they be identified? Many factors are thought to generate dependencies among these diseases. They are linked to the environment, lifestyle, drug treatments, genetic factors, and, more probably, a combination thereof. Antidepressants and antipsychotic drugs have emerged as repurposed treatments in oncology [7]. Drug repurposing involves the development of new indications for the use of existing neuroactive compounds to treat drug-resistant forms of cancer. However, these advantages do not extend to all cancer types, as some antidepressants and antipsychotic drugs contribute to tumor proliferation [14].

Fifth, antidepressants and antipsychotics are among the most commonly prescribed pharmacological treatments worldwide. They are also used off-label and for nonpsychiatric indications [15-17]. The neurochemical targets of these medications have been postulated to modulate both cancer risk and oncological outcomes [18-23]. Consequently, based on these observations, antidepressants and antipsychotics can affect cancer risk and mortality [24,25].

Psychiatric and neurological disorders themselves have been associated with an altered cancer risk, possibly due to shared genetic, behavioral, or lifestyle factors. On the other hand, pharmacological treatments with antidepressants and antipsychotics can independently modulate cancer biology through mechanisms such as apoptosis, immune regulation, and angiogenesis. While individual systematic reviews have examined specific classes of drugs (eg, selective serotonin reuptake inhibitors [SSRIs]) or individual cancer sites (eg, breast or lung cancer), no comprehensive review has synthesized the findings across all classes of antidepressants and antipsychotics and a broad spectrum of oncological outcomes. Addressing this gap provides the novelty and necessity of this study. This study focuses specifically on drug exposure, recognizing that underlying comorbidities act as potential confounding factors.

We hypothesize that exposure to antidepressant and antipsychotic drugs may alter cancer incidence and mortality by modulating oncogenic pathways, such as cell proliferation, apoptosis, and tumor angiogenesis. This theoretical framework underpins the study design and guides data synthesis.

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Therefore, this study is an overview of systematic reviews and meta-analyses evaluating the association between antidepressant and antipsychotic drug use and cancer risk and mortality. Further studies are needed to determine whether antidepressant and antipsychotic use has an antineoplastic effect leading to improved oncological outcomes.

Methods

Ethical Considerations

Ethical approval is not required for this study, as it is a general review of systematic reviews based solely on previously published aggregate data and therefore does not involve human participants or identifiable personal data. According to guidelines such as the Cochrane Handbook for Systematic Reviews, ethical approval is not typically needed for systematic reviews of published literature.

Overview of Systematic Reviews (With or Without Meta-Analyses)

An overview of the review protocol has been registered in the Open Science Framework (OSF). It will be conducted following the reporting guidance from the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) statement [26,27] (PRISMA-P checklist is provided in Multimedia Appendix 1 [27]).

This protocol has been assigned the International Registered Report Identifier (IRRID): RR1-10.17605/OSF.IO/5ACWH.

The PICO (Population, Intervention, Comparator, Outcome) question includes people currently receiving psychopharmacological treatment, specifically with antipsychotic or antidepressant medications, including children, adolescents, and adults. The intervention is exposure to antidepressants or antipsychotics, the comparator is unexposed populations, and the outcomes are incidence and mortality of all cancers and localized cancers.

Criteria for Considering Studies for This Overview of the Review

Types of Studies

We will include all systematic reviews (with or without meta-analyses) of observational studies (that is, cohort and case-control studies) and experimental studies (such as randomized controlled clinical trials) focusing on the association between antipsychotic and antidepressant drugs used among children, adolescents, and adults with any central nervous system disorder and cancer risk. We will exclude studies that (1) do not examine the use of antipsychotics and antidepressant drugs, (2) do not assess the outcomes of interest (including, but not limited to, incidence, progression-free survival, disease-free survival, overall survival, and mortality of any cancer type), and (3) include meta-analyses with fewer than 3 original studies. Meta-analyses that include fewer than 3 primary studies will be excluded from the quantitative synthesis to prevent unstable estimates. However, such reviews will be described narratively in the sensitivity analyses, especially when addressing rare cancers. Only peer-reviewed journal articles written in any language will be included. Animal or genetic studies will be excluded. Furthermore, if the same association was examined in 2 or more meta-analyses, associations from different meta-analyses will be considered duplicates. Therefore, the meta-analysis with the largest sample size will be selected to avoid overlap.

We will search registries, preprint servers, and gray literature to ensure comprehensiveness and transparency. Inclusion will be limited to systematic reviews or meta-analyses that report on methods consistent with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) and provide sufficient data for evaluation. Preprint or gray literature reviews will only be included if they meet these minimum information criteria and will be examined in sensitivity analyses (primary analyses will prioritize peer-reviewed publications).

Types of Participants

We will include participants who are being treated with antipsychotic and antidepressant medications, regardless of their diagnosis. The inclusion criterion is the current use of these pharmacological agents rather than the diagnostic category defined by the *DSM* (*Diagnostic and Statistical Manual of Mental Disorders*) or *ICD* (*International Classification of Diseases*) criteria [28,29]. We will extract and, where possible, stratify results by indication (psychiatric diagnosis versus nonpsychiatric or off-label use).

Types of Interventions

The following antipsychotic groups will be considered for the exposure of interest: (1) first-generation (typical) antipsychotics; (2) second-generation (atypical) antipsychotics; and (3) newer agents, including partial dopamine agonists (D2) such as aripiprazole, brexpiprazole, and cariprazine.

The following antidepressant clusters will be considered for the exposure of interest: SSRIs, serotonin/norepinephrine reuptake inhibitors (SNRIs), monoamine oxidase inhibitors (MAOIs), tricyclic antidepressants (TCAs), serotonin modulators, and atypical antidepressants.

A complete list of antidepressants and antipsychotics is provided in Multimedia Appendix 2.

We will include systematic reviews and meta-analyses regarding antipsychotics and antidepressants approved by the European Medicines Agency (EMA) and the Food and Drug Administration (FDA). We will accept any intervention planned identically in the intervention and control groups except for the drug of interest.

To minimize analytical heterogeneity, results will be categorized by major drug classes: SSRIs, SNRIs, TCA, MAOIs, serotonin modulators, atypical antidepressants, and typical versus atypical antipsychotics. When available, analyses will be stratified by cumulative dose, duration of treatment, and latency between drug exposure and cancer outcomes.

We will extract information on the adjustment of the main confounding factors (psychiatric diagnosis, smoking, alcohol, obesity, and socioeconomic status) and consider them in the interpretation of the evidence.

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We will differentiate between studies that evaluate psychiatric indications and those that investigate off-label oncological use, reporting them separately to avoid confusion.

Types of Outcome Measures

Primary Outcomes

The primary outcomes of interest will be cancer incidence and mortality (all malignant neoplasms; *ICD-11* [*International Classification of Diseases, 11th Revision*]: 2A00–2F9Z) associated with exposure to antipsychotic and antidepressant drugs.

Cancers of specific locations will be grouped according to the *ICD* categories (eg, digestive, respiratory, and hematological) to improve reproducibility and transparency.

Secondary Outcomes

Secondary outcomes will include site-specific cancers (such as glioblastoma and melanoma).

Studies should explicitly report the number of cancer events in all the treatment groups of interest. Studies that do not present quantitative data on the association between the evaluated interventions and cancer events or provide sufficient data for computing such measures of association will be excluded [30].

Search Strategy for Identification of Studies

Electronic Searches

The following electronic databases will be searched: MEDLINE [31] is available through PubMed (National Library of Medicine), Embase [32] through the Elsevier platform (Elsevier BV), and the Cochrane Database of Systematic Reviews through the Cochrane Library [33].

Sources of gray literature (conference abstracts and theses), preprint servers, and trial registries (ClinicalTrials.gov, WHO ICTRP) will also be searched to minimize publication bias.

A health sciences librarian (DMS-G) will review and refine the electronic search strategies for each database. The final strategies will be peer-reviewed using the Peer Review of Electronic Search Strategies (PRESS) checklist. All drug names have been verified against EMA and FDA lists and corrected for spelling.

We will use validated search filters to exclude animal studies where appropriate. No restrictions will be placed on age or language. A final search filter for “systematic review” or “meta-analysis” will be applied during the selection stage to improve specificity.

We will search these databases from their inception. The research team will design and perform a detailed search strategy. We will use the same search strategy with appropriate adjustments for each database. Search terms will include keywords related to (1) the exposures of interest: “names/cluster of antidepressant drugs,” and “names/cluster of antipsychotics”; (2) the types of studies: “systematic review” and “meta-analysis,” within which will be specified whether the studies are “observational studies” or “randomized and non-randomized studies”; and (iii) the outcome of interest: “cancer.” No restrictions on data will be imposed. Initial literature searches of MEDLINE, Embase, and the Cochrane Database of systematic reviews will begin in October 2024. The last planned search date was September 2025, reflecting the prospective nature of this protocol. This ensures transparency regarding the planned timeline prior to its completion. Multimedia Appendix 3 provides details of the draft search strategies for MEDLINE and Embase. The GPT-4o (OpenAI) model or similar will be used to obtain article titles relevant to this review, following the previously mentioned search criteria. If this artificial intelligence (AI)–driven title identification is not feasible, we will proceed with the items obtained through the conventional search.

AI-assisted screening with GPT-4o–like will be validated by 2 independent human reviewers. Agreement will be measured using sensitivity, specificity, and Cohen κ index. Discrepancies will be resolved by consensus or by the decision of a third reviewer. Ethical considerations and transparency in rapid reproducibility will be documented. The large language model (LLM) will serve as a complement to, not a substitute for, human reviewers.

When conflicting results arise, priority will be given to higher-quality reviews, larger samples, and more recent publications. Contradictions will be explicitly discussed in sensitivity analyses.

Searching Other Resources

We will also use the following methods: (1) check reference lists of all systematic reviews and meta-analyses for additional references, (2) conduct complementary searches for the Cochrane Global Mental Health Group’s specialized register [34], and (3) contact the authors of the studies if clarification is needed or if the reported data must be completed.

Data Collection and Analysis

Software Considerations

All analyses will be performed using Stata (version 18; StataCorp LP) [35,36], R (version 4.2.0; R Core Team), and Python (version 3.12.5; Python Software Foundation).

Selection of Systematic Reviews

First, a total of 3 researchers, independently and masked, will screen the titles and abstracts of the articles obtained from the initial searches according to the eligibility criteria. Second, the full texts will be examined in detail and screened for eligibility. Third, the references of all considered articles will be manually searched to identify any relevant reports missed during the search strategy. Disagreements will be resolved through discussions, with a fourth researcher consulted if necessary.

The selection phase will be conducted using the articles selected by the LLMs. During this phase, the model will retain articles that meet the proposed criteria and discard those that do not. Once the documents have been selected, we will test the understanding of the subject matter by asking the model to answer a series of questions about the content or evaluate its conclusions or questions about the articles [37,38].

The authors will be contacted in case of ambiguity or missing data. We will identify and exclude duplicates and collate

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multiple reports from the same study such that each analysis, rather than each report, is the unit of interest in the review.

In the event of overlapping primary studies, we will calculate the corrected covered area (CCA) and prioritize the most comprehensive, recent, and highest-quality review. When contradictory results are presented, we will adopt a hierarchy considering methodological quality, sample size, and publication date. Sensitivity analyses will assess the robustness of the conclusions. After calculating the CCA, duplicate effect sizes will be removed to avoid double counting of primary studies in different reviews.

First, all primary studies cited in each included review will be assigned to a citation matrix (primary study × review), after which we will calculate the CCA to quantify overlap and classify it as low, moderate, high, or very high. For duplicate associations involving the same exposure and cancer outcome across reviews, we will retain the review that best represents the evidence, prioritizing (1) the highest overall confidence according to *A Measurement Tool to Assess Systematic Reviews, Version 2* (AMSTAR-2), followed by (2) the most recent publication date, (3) the largest number of primary studies, and (4) the broadest population and outcome coverage. The combined estimate from the selected review will be used in the main synthesis, with alternative estimates described narratively. Sensitivity analyses will then be conducted by excluding lower-priority reviews to assess the robustness of the conclusions.

Data Collection and Management

After the searches have been performed, the items identified in the databases will be imported to a systematic review manager. This will be performed using Rayyan software (Rayyan Systems) [39]. Following the recommendations of the PRISMA 2020 declaration [40], a flowchart showing the details of the included and excluded studies at each stage of the selection process will be provided.

A total of 3 researchers will independently extract data from each included study, and potential conflicts will be resolved through discussion. We will examine the full articles and supplementary materials containing data and analyze the general and methodological characteristics, as well as the study results. In addition, we will review the final versions of articles that are available online. Simultaneously, the same procedure will be conducted independently using an AI system, like OpenAI's GPT-4o model.

We will use OpenAI's GPT-4o–like models as an assistance tool under strict governance. The model version, application programming interface (API) parameters, and all prompts will be recorded and stored in OSF. The LLM will be applied to classifying titles or abstracts and prefilling structured extraction forms; however, the gold standard for decisions remains human reviewers. All title or abstract records will be independently reviewed by 2 human reviewers; the LLM will run in parallel for classification, and its results will be compared to human consensus along all records obtained through the searching phase. The model acceptance thresholds for selection are a sensitivity of at least 80% (to identify potentially eligible records) and a Cohen κ of at least 0.6 against human consensus. The exact metrics that will be considered for evaluating AI's performance are accuracy, sensibility, recall, and F_1-score. To obtain these metrics, the human reviews will be used as ground truth to determine whether AI could have substituted reviewers in this process. For extraction, the accuracy of exact match of key fields must reach at least 90% before machine results are used to prepopulate forms; even then, 2 human reviewers will verify all extracted data. If the thresholds are not met, the LLM will not be used for decision-making. All discrepancies between the LLM and humans will be documented, resolved by consensus or by the decision of a third reviewer, and communicated. The team will not upload identifiable patient data or datasets containing personal information into the model; only bibliographic metadata and anonymized text snippets strictly necessary for selection and extraction will be provided. Use of the model will comply with institutional data protection policies and OpenAI's data processing terms.

GPT-4o model or a similar model will be used for titles and abstracts (metadata) solely for classification purposes. During full-text selection and data extraction processes, the LLM will only receive anonymized text fragments (such as PICO elements or brief results tables), and only when permitted by data processing agreements and publisher terms. No personally identifiable information, raw patient-level data, or proprietary full PDF files will be fed into the model. Use of the model will comply with institutional data protection guidelines, and will be recorded and archived.

Data extracted with GPT-4o or similar will be compared with independent human extractions for at least 20% of the included reviews. Agreement on key variables (effect sizes, CIs) will be reported, and discrepancies will be resolved by consensus.

Data from each report will be used to construct evidence tables describing the included studies. The standardized data extraction form will contain the following information: first author's name, year of publication, drug type or cluster (such as fluoxetine or SSRIs), outcome (including melanoma or its subtypes), comparison, the total number of participants, number of cancer events, and number of included studies extracted from each eligible meta-analysis. The study design (randomized controlled trial or cohort studies), number of participants (control and cases), participant characteristics (such as diagnostic criteria, age, sex, years of education, comorbidity, or risk factors), and maximally adjusted effect size will also be extracted.

The data extraction form will undergo 3 pilot tests to refine its consistency before full implementation. It will undergo 3 testing rounds on about 10% of qualifying reviews (minimum of 5). In the pilot test, 2 independent reviewers will extract data; interrater reliability (Cohen κ) will be measured for key fields, and the form will be refined until a κ of 0.75 or higher is reached. Subsequently, all included reviews will be independently extracted by 2 reviewers, with discrepancies resolved via consensus or with a third party's intervention.

We will extract information on the adjustment for confounding factors described in each review and in the studies included, specifically whether the analyses were adjusted for smoking,

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alcohol consumption, obesity or BMI, psychiatric diagnosis, socioeconomic status, and other risk factors. We will summarize the degree of adjustment for confounding factors and consider this when interpreting the strength and direction of the observed associations.

This study is an overview of systematic reviews. We will not re-extract primary study data nor perform second-order meta-analyses pooling primary study data. Instead, for each included systematic review or meta-analysis, we will extract the effect measures and statistics as reported (eg, pooled relative risk [RR], odds ratio [OR], hazard ratio [HR], 95% CI, I^2, model type). Results will be synthesized narratively with structured summary tables. When multiple reviews report the same association, we will apply the overlap and priority algorithm to prevent double-counting.

Risk of Bias and Quality Assessment in Included Reviews

At least 2 researchers will independently assess the risk of bias and the quality of each study using the AMSTAR-2 [41], and any disagreements will be resolved through discussion. The risk of bias in each study will be judged based on each criterion and classified as critically low (more than one critical defect with or without noncritical weaknesses), low (one critical defect with or without noncritical weaknesses), moderate (more than one noncritical weakness), or high (no or one noncritical weakness). The interrater reliability of AMSTAR-2 assessments will be quantified using Cohen κ index to ensure transparency and reproducibility.

We will quantify the overlap of primary studies in eligible systematic reviews by calculating the CCA using the number of eligible systematic reviews, and all included primary studies [42]. We will classify the degree of overlap according to the percentage as slight (0%-5%), moderate (6%-10%), high (11%-15%), or very high (>15%).

We will also evaluate the strength of the evidence for each outcome presented in the overview using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) classification system. The evidence classifications are divided into “high,” “moderate,” “low,” and “very low” quality to make recommendations [43].

GRADE certainty ratings will incorporate AMSTAR-2 quality, and will be downgraded when systematic reviews have methodological shortcomings. This approach ensures that the synthesis of evidence reflects both quantitative results and methodological rigor. Reviews rated as “critically low” will not contribute to the pooled synthesis but will be described narratively. AMSTAR-2 ratings will be used directly for GRADE assessments, and downgrading will be applied when reviews show methodological deficiencies.

Methods for Evidence Synthesis

Measures of Treatment Effect

The effect size included in each meta-analysis will be extracted, and 95% CIs will be used. Where available, we will extract relative risk and HRs with 95% CIs, ORs, and standardized incidence/mortality (30). Statistical significance will be set at $P<.05$. Effect sizes derived from the models adjusted for the maximum number of potentially confounding variables will be selected.

Contradictory results will be examined, prioritizing higher-quality and more comprehensive reviews. We will also perform sensitivity analyses to assess the robustness of conclusions when conflicting results are presented.

We will not recalculate the pooled estimates from the primary studies. Effect sizes will be extracted as reported in the included systematic reviews and meta-analyses. Narrative synthesis will be used when quantitative pooling is not appropriate. When multiple effect sizes are reported for overlapping results, we will extract only the most comprehensive or adjusted estimate to avoid double counting.

We will not perform second-order meta-analyses of pooled estimates. Instead, we will summarize the results narratively and emphasize methodological differences between reviews.

Assessment of Heterogeneity

The clinical and methodological diversity of participants, interventions, outcomes, and characteristics of the included studies will be assessed to determine the appropriateness of the meta-analysis.

Statistical heterogeneity between studies will be assessed by visually inspecting forest plots and using I^2 statistics. The interpretation of an I^2 value of 0%-40% may not be necessary, 30%-60% may represent “moderate” heterogeneity, 50%-90% may represent “substantial” heterogeneity, and 75%-100% may represent “considerable” heterogeneity [44,45].

All substantial heterogeneity identified will be reported and investigated following the recommendations of the Cochrane Handbook for Systematic Reviews of Interventions [46].

We will extract reported effect estimates and their CIs as presented in each included systematic review or meta-analysis. Harmonization or recalculation of effect measures will not be conducted. When reviews provide subgroup or sensitivity analyses, we will summarize their findings narratively. No second-order meta-analysis or meta-regression will be performed. Reported sources of heterogeneity (as described in each review) will be summarized qualitatively [47].

To limit the risk of post-hoc bias, analyses will be hypothesis-driven and adjusted for multiple testing.

Assessment of Reporting Biases

We will not recalculate the pooled estimates from primary studies or perform second-order meta-analyses or meta-regressions on their data. Instead, we will extract the pooled effect estimates and heterogeneity statistics (I^2) [48,49] as reported in each included review and compile them into structured tables. All meta-regressions or subgroup analyses mentioned in the included reviews will be extracted and explained.

Additional Analysis

If sufficient studies are identified and data points are available, the potential sources of heterogeneity will be further investigated

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using subgroup analyses according to clinical and methodological covariates. We will explore the sources of heterogeneity using the following a priori subgroup hypotheses: (1) study design (observational vs experimental), (2) different drug clusters (antipsychotics vs antidepressants), and (3) type of cancer measure (incidence vs mortality).

To mitigate heterogeneity, subgroup analyses and narrative synthesis (Synthesis Without Meta-Analysis guidelines) will be applied when grouping is not appropriate. Analyses will be stratified by age (children and adolescents vs adults) to account for differences in cancer risk profiles.

The final manuscript will outline and report any amendments made to the study protocol. The results will be disseminated through conference presentations and publications in peer-reviewed journals. All data underlying the findings reported in the final manuscript will be deposited in a cross-disciplinary public repository such as the OSF [50].

Results

Searches will be carried out as outlined in Methods, and findings will be reported in a later manuscript. The final planned search date is September 2025. Results will be shared in peer-reviewed journals. The expected results will be published in 2026. We will present a PRISMA 2020 flow diagram summarizing the selection process (Figure 1; [40]).

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 flow diagram. *Consider, if feasible to do so, reporting the number of records identified from each database or register searched (rather than the total number across all databases/registers). **If automation tools were used, indicate how many records were excluded by a human and how many were excluded by automation tools.

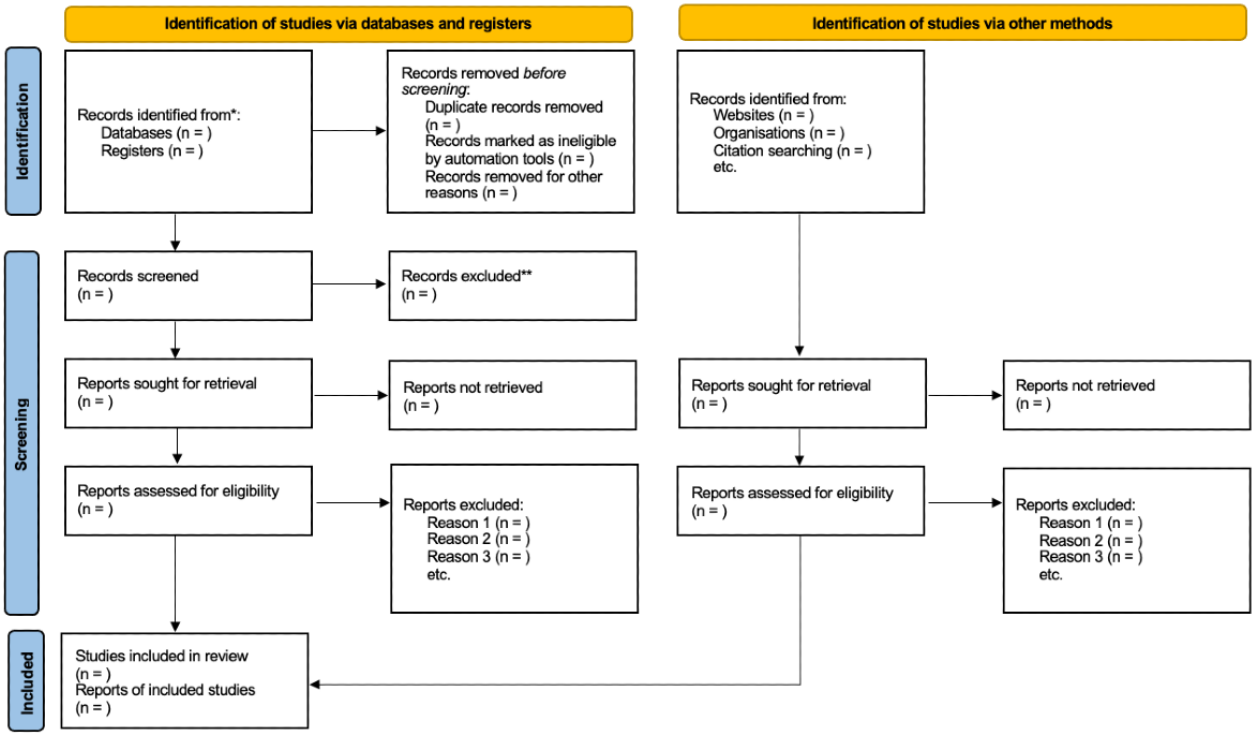

Discussion

Anticipated Main Findings

This systematic review and meta-analysis aims to provide the most comprehensive synthesis to date on the relationship between antidepressant and antipsychotic use and cancer incidence and mortality. Based on previous evidence, we expect that the results will show a complex and varied picture [1,12-14]. Some classes of psychotropic drugs, such as SSRIs and certain antipsychotics, may exhibit potential protective effects against specific types of cancer, possibly through mechanisms such as inducing apoptosis, modulating the immune system, and inhibiting angiogenesis. Conversely, other agents might be associated with an increased risk of tumor development or progression, reflecting the pharmacodynamic diversity among different drugs. The overview is also likely to emphasize the challenge of establishing causal inference, given that psychiatric disorders themselves, lifestyle factors, and socioeconomic variables act as significant confounders. By integrating data from a wide range of systematic reviews, this study aims to identify where strong evidence exists, where contradictions remain, and where methodological variability limits confidence in the conclusions.

Comparison With Previous Work

Previous individual systematic reviews have explored the links between the use of antidepressants or antipsychotics and specific types of cancer, such as breast, lung, or liver cancer [51-55]. Some suggest there are inverse relationships, while others report no significant effect or even an increased risk [56]. However, no previous work has systematically combined this evidence across both drug classes and a wide range of cancers. Compared to earlier reviews, this study will expand the scope by including more systematic reviews, using standard assessment tools like AMSTAR-2 and GRADE, and measuring the overlap between

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the meta-analyses. In this way, the review will clarify whether the associations are consistent, whether they are observed across different study designs and populations, and how much credibility should be given to results that may be biased by methodological flaws or industry ties. By integrating our synthesis into emerging fields such as "cancer neuroscience," this review will also place the potential for repurposing psychopharmacological drugs within a broader biomedical framework.

Strengths and Limitations

One of the key strengths of this review is its methodological rigor, which includes a protocol registered in OSF, systematic searches across multiple databases, the inclusion of publications in both English and other languages, and double screening assisted by humans and AI to ensure reproducibility and efficiency. The use of validated instruments, such as AMSTAR-2 for quality assessment and GRADE for certainty of evidence, further improves reliability. Another strength is the explicit consideration of heterogeneity by drug class, cancer type, treatment duration, and cumulative exposure, enabling more nuanced conclusions.

Nevertheless, it must be recognized that there are notable limitations. Overall systematic reviews are constrained by the quality and scope of the included evidence, and the risk of double counting primary studies in meta-analyses remains a concern, despite plans to compute the corrected area under the curve. Many of the included reviews are based on observational studies, which are inherently susceptible to residual confounding from clinical and lifestyle factors such as smoking, obesity, and psychiatric diagnoses. Publication bias, along with selective reporting, may further distort the observed associations. These limitations could impact both the internal validity and wider applicability of the results, particularly when applied to diverse populations or to oncological uses not indicated in the summary of product characteristics of psychopharmacological agents.

Future Directions

The findings of this review will not offer conclusive causal answers but will serve as a guide for future research. Specifically, well-designed longitudinal studies and randomized controlled trials are necessary to distinguish the effects of drugs from the underlying cancer risk linked to psychiatric disorders. Future research should also include precision medicine approaches, investigating whether genetic or molecular markers influence the impact of exposure to antidepressants and antipsychotics on cancer outcomes. Particular focus should be given to potential protective mechanisms, such as immune regulation, and to identifying high-risk interactions between drugs and cancer. Collaboration across disciplines—such as oncologists, psychiatrists, neuroscientists, and pharmacologists—will be crucial to translating these findings into clinical practice.

Dissemination Plan

Dissemination will go beyond traditional academic channels. Results will be published in peer-reviewed journals and presented at international scientific conferences. To ensure transparency and reproducibility, all underlying data and analytical code will be uploaded to the OSF. In addition to the academic audience, summaries tailored for clinicians, patient associations, and policymakers will be developed to enhance the practical impact of the findings. Where appropriate, communication materials designed for nonspecialist audiences, including patients and the general public, will be made available to raise awareness of the potential oncological implications of widely prescribed psychopharmacological agents.

Conclusion

This study protocol outlines a comprehensive and methodologically rigorous approach to synthesizing evidence on the link between antidepressant and antipsychotic use and cancer risk and mortality. Although the expected results will be limited by the heterogeneity and shortcomings of the current literature, the overview will offer vital insights into the potential for drug repurposing in oncology, identify gaps in existing knowledge, and establish a foundation for future research and policy development in the emerging field of cancer neuroscience.

Acknowledgments

Generative AI (eg, ChatGPT, GPT-4/4o) has not been used to write or edit the text of this manuscript. The researchers intend to use GPT-4o (OpenAI) solely as an aid for data selection and extraction, following the governance outlined in Methods. All model prompts, versions, and results used for validation will be archived in Open Science Framework (OSF) and reported transparently in the final manuscript.

All amendments to the protocol will be documented in the OSF registry and reported transparently in the final manuscript.

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Data Availability

All data generated or analyzed during this study (including extracted data tables, analysis scripts, and LLM prompts and outputs used for validation) will be deposited in the Open Science Framework (OSF) under the project record associated with this protocol. Any results that cannot be shared publicly for legal or copyright reasons will be made available upon reasonable request to the corresponding author, subject to approval by the publisher or licensor.

Authors' Contributions

JVS-O, JF-M, DMS-G, and RT-S conceived the study protocol with critical inputs from V-D, PV-M, MF-R, JS-V, PC-G, VB-M, PS-M, JV-F, ES-O, and AV. JVS-O registered the protocol in OSF. All authors provided input for the study design, edited the draft protocol, and commented on the manuscript for important intellectual content. RT-S accepts full responsibility for the finished paper and organizes the decision to publish it.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P Checklist.
[DOCX File , 20 KB - resprot_v14i1e78596_app1.docx]

Multimedia Appendix 2
Table S1. Complete list of antidepressants and antipsychotics.
[DOCX File , 19 KB - resprot_v14i1e78596_app2.docx]

Multimedia Appendix 3
Key terms for MEDLINE and Embase.
[DOCX File , 18 KB - resprot_v14i1e78596_app3.docx]

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Abbreviations

AI: artificial intelligence
AMSTAR-2: A Measurement Tool to Assess Systematic Reviews, Version 2
API: application programming interface
CCA: corrected covered area

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DSM: Diagnostic and Statistical Manual of Mental Disorders
EMA: European Medicines Agency
FDA: Food and Drug Administration
GRADE: Grading of Recommendations, Assessment, Development, and Evaluation
HR: hazard ratio
ICD: International Classification of Diseases
ICD-11: International Classification of Diseases, 11th Revision
IRRID: International Registered Report Identifier
LLM: large language model
MAOI: monoamine oxidase inhibitor
OR: odds ratio
OSF: Open Science Framework
PICO: Population, Intervention, Comparator, Outcome
PRESS: Peer Review of Electronic Search Strategies
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
RR: relative risk
SNRI: serotonin/norepinephrine reuptake inhibitor
SSRI: selective serotonin reuptake inhibitor
TCA: tricyclic antidepressant

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Protocol

Combining Ecological Momentary Assessment and Social Network Analysis to Study Youth Physical Activity and Environmental Influences: Protocol for a Mixed Methods Feasibility Study

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Abstract

Background: Physical activity (PA) is crucial for youth health, but up to 74% of adolescents fail to meet recommended levels, especially during summer when structured supports associated with school are not available. The social and built environments significantly influence youth PA; yet, their complex interactions remain poorly understood. This study aims to evaluate the feasibility of combining ecological momentary assessment (EMA) and social network analysis to examine bidirectional influences among youth PA, built environments, and social networks during summer.

Objective: The objectives are to (1) evaluate the feasibility and acceptability of the combined EMA and Social Network Analysis protocol, and (2) identify phenotypes using person-level, microtemporal, and dynamic overlap between social and built environments.

Methods: This mixed methods feasibility study with an exploratory observational component will recruit 120 youth aged 12 years to 15 years from an urban school district in Central Texas, US. Participants will first complete a baseline survey to report their general social network patterns and environmental perceptions. Then participants will wear an ActiGraph LEAP accelerometer and respond to EMA prompts via smartphone for 7 days. EMA will assess real-time perceptions of social networks and surrounding built environments, which will be time-matched with accelerometer-assessed PA data. GPS coordinates will be collected with each EMA prompt to assess features of the built environment. Follow-up semistructured interviews will assess protocol acceptability.

Results: This study has been funded by the National Heart, Lung, and Blood Institute. Data collection is expected in the summers of 2025, 2026, and 2027.

Conclusions: This innovative approach combines EMA, SNA, accelerometry, and GPS data to provide unprecedented insights into the dynamic interplay between social networks, built environments, and youth PA during summer. Findings will inform the development of more targeted, effective interventions to promote PA among youth. While limitations include potential participant burden and generalizability, the study's strengths in capturing real-time, contextualized data make it a valuable contribution to understanding youth PA determinants.

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KEYWORDS

physical activity; youth; social environment; built environment; ecological momentary assessment; social network analysis; phenotypes; accelerometry; GPS

Introduction

Background

Physical activity (PA) is crucial for youth health and development, offering a wide range of physical, psychological, and social benefits [1]. However, roughly 74% of young people fail to meet recommended PA levels [2], putting them at risk for various health issues both in the short and long term [1]. Summer presents a unique challenge for youth PA, as it represents a significant departure from the social and built environment supports typically offered by schools [3,4]. During the academic year, schools provide structured physical education classes, organized sports, and supervised recess periods, all of which contribute to youth PA levels [3,4]. The absence of these supports during summer leads to substantial changes and variability in how youth experience and are influenced by their social and built environments [5,6].

The social and built environments have been identified as key modifiable factors influencing youth PA, with research suggesting complex and nuanced relationships between these environmental factors and PA behaviors [7]. The social environment encompasses interpersonal relationships, social networks, and community norms, while the built environment includes physical structures, facilities, and design elements that can either facilitate or hinder PA. Despite growing research in this area, our understanding of how different layers of the social ecological model impact youth PA remains unclear, particularly during the summer months when the structured supports provided by schools are absent [8,9]. This knowledge gap hinders the development of effective interventions to promote PA among youth, especially during critical periods like summer. Moreover, there is considerable variability between youth in terms of the social and built environment factors they are exposed to during the summer months, as well as the impact these factors have on their PA levels [3,4,8]. For instance, some youth may be more affected by built environment barriers (eg, lack of safe parks or playgrounds) despite having a supportive social environment (eg, friends who enjoy physical activities), while others may face disparities in both domains [1,10,11]. This heterogeneity in experiences and influences underscores the need for more sophisticated research approaches that can capture and analyze these complex relationships.

Recent reviews of existing evidence highlight a significant need for more nuanced measurement approaches, including the use of intensive longitudinal data (ILD) to understand the complex variability (both within and between-subject) as well as the independent and mutual effects of social and built environments on youth PA [7,12,13]. Traditional cross-sectional or even longitudinal studies with infrequent measurement points may fail to capture the dynamic nature of these relationships and the day-to-day variations in youth PA behaviors [12,13]. ILD, on the other hand, allows for the collection of frequent, real-time data that can reveal patterns and associations that might otherwise be missed [12,13]. One promising approach to capturing this variability is through the identification of "phenotypes," individual-specific webs of links between social and built environmental determinants [14,15]. These phenotypes have the potential to identify overlaps in ILD and salient intervention targets for health behavior [14-16]. By understanding these phenotypes, researchers and practitioners may be able to develop more personalized and effective interventions to promote PA among youth, considering the unique combination of social and built environment factors that influence an individual's behavior.

Ecological momentary assessment (EMA) has emerged as a valuable method for collecting ILD by gathering real-time self-reports of behaviors, contexts, and perceptions in naturalistic settings [12,13]. EMA typically involves prompting participants multiple times throughout the day to report on their current activities, feelings, and surroundings, providing a rich, contextual dataset that captures the ebb and flow of daily life. This approach offers several advantages over traditional retrospective self-report measures, including reduced recall bias and the ability to capture within-person variability over time [12,13]. However, previous EMA measures of the social environment have been limited to the presence of others or coparticipation in PA, which may not fully capture the complexity of social influences on youth PA [7,13,17]. Social network analysis (SNA) offers the potential to provide more nuanced information, such as dyadic and personal network measures of social bridging, bonding, norms, and influence [17,18]. SNA allows researchers to map and analyze the structure and composition of an individual's social network, providing insights into how social connections and interactions may influence PA behaviors. By combining EMA and SNA approaches, researchers may be able to gain a more comprehensive understanding of the dynamic interplay between social factors and PA in youth's daily lives.

To examine these influences on a more granular level, this project aims to evaluate the feasibility of combining EMA and SNA techniques to collect ILD describing social and built environment associations with youth PA during the summer. This innovative combination of EMA and SNA techniques represents a data-intensive approach, necessitating an evaluation of its feasibility and acceptability in terms of validity, reliability, and respondent burden. The integration of these methods has the potential to provide unprecedented insights into the complex relationships between social networks, built environments, and PA behaviors among youth. For example, EMA data may show a youth's PA spikes when they are with a specific friend, but only if they are within a half-mile radius of a park, as indicated by GPS data. SNA reveals this friend is not particularly active themselves, but rather may be influential in triggering PA in groups, potentially exposing the youth to varied activity opportunities. This complex interplay suggests that interventions targeting both social network dynamics and built environment access could be more effective than addressing either in

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isolation, highlighting the value of integrating EMA and SNA approaches to understand youth PA patterns.

This complex framework also presents challenges in terms of data collection, participant compliance, and analytical complexity. The intensive nature of the EMA protocol, combined with the detailed social network data collection, may lead to significant participant burden, potentially resulting in missing data, reduced compliance over time, or even selective attrition of certain participant subgroups. Moreover, the frequent prompts and awareness of being monitored could introduce reactivity, where participants alter their behavior or reporting patterns, while the complexity of the data collected across multiple platforms (EMA, GPS, and accelerometry) presents substantial challenges in data integration, cleaning, and analysis, requiring sophisticated statistical approaches to handle the multilevel, time-varying nature of the data. By conducting a feasibility study, researchers can identify potential barriers and refine the methodology before implementing it on a larger scale. This study seeks to address the critical need for more comprehensive and nuanced understanding of the complex interplay between social and built environments and their impact on youth PA during the summer months. The findings from this research could inform the development of more effective, targeted just in time adaptive interventions to promote PA among youth, ultimately contributing to improved health outcomes and reduced health disparities in this population.

Study Aims

The study has 2 primary aims. Aim 1 is to evaluate the feasibility and acceptability of an EMA protocol that combines the collection of social network characteristics using SNA and built environment characteristics corresponding to PA among youth during the summer. This aim will assess metrics such as EMA response rates, accelerometer wear time, and qualitative feedback from participants to determine the viability of the combined EMA-SNA approach. Aim 2, which is exploratory, seeks to identify and classify phenotypes by using microtemporal dynamic overlaps between social and built environments. Aim 2 will examine these phenotypes and their association with PA among youth in summer. These aims will use cluster analysis to identify subgroups of social and built environment patterns within the sample followed by dynamic structural equation modeling (DSEM) to analyze the bidirectional dynamics of social and built environment factors and PA [19,20]. These aims will provide a comprehensive assessment of the proposed methodology's feasibility and potential for uncovering nuanced relationships between environmental factors and youth PA during summer.

Methods

Study Design

This study will use a mixed methods approach to evaluate the feasibility and acceptability of combining EMA and SNA techniques for assessing social and built environment influences on youth PA during summer. The research design involves recruiting 120 youth aged 12 years to 15 years (entering the seventh to the ninth grades) from a local school district. An initial cohort of 20 youths will be recruited in year 1 of the project to assess initial feasibility and pilot the measures. Participants will be divided into 2 cohorts (n=50 each) across years 2 and 3, with each cohort further split into 5 groups (n=10) to facilitate data collection throughout the summer.

Conceptual Framework

The conceptual model guiding this study is grounded in a social ecological model, recognizing that youth PA is influenced by multiple, interacting layers of environmental factors [21,22]. At its core, the model posits that youth PA is shaped by a dynamic interplay between social and built environment elements, with each exerting both independent and synergistic effects on PA behaviors [7,23]. The social environment component encompasses the structure and quality of social networks, including aspects such as social bridging, bonding, norms, and influence [17,18,24]. These social factors are theorized to provide support, motivation, and opportunities for PA, but may also act as barriers in some contexts [25,26]. The built environment element includes physical structures, facilities, and urban design features that can either facilitate or hinder PA [27,28]. This includes factors such as neighborhood walkability, access to recreational spaces, and perceived safety [29-31].

Critically, the model emphasizes the reciprocal nature of these relationships, acknowledging that youth's PA behaviors can, in turn, influence their perceptions and interactions with both social and built environments [32,33]. This bidirectional conceptualization allows for a more nuanced understanding of how environmental factors and PA behaviors coevolve [7]. The model also incorporates the concept of phenotypes, representing individual-specific patterns of associations between social and built environment factors and PA [14,34]. These phenotypes are theorized to capture the heterogeneity in how youth respond to and interact with their environments, reflecting the complex, person-specific nature of PA determinants [35,36]. By integrating these various components, the conceptual model provides a comprehensive framework for understanding the multifaceted influences on youth PA, particularly during the unique context of summer months when typical school-based structures are absent [8,9].

Participants and Procedures

The study will recruit 120 youth participants aged 12 years to 15 years (entering the seventh to ninth grades) from a local school district. This age range was selected based on previous research indicating significant declines in PA and increases in peer influences during this developmental period [37,38]. Recruitment will be stratified to ensure equal numbers across sex and grade levels. Participant recruitment will occur through a partnership with a school district in central Texas, United States, which serves a diverse student population. The district-wide demographics include 72% of students classified as being at risk of dropping out of school and 77% eligible for free or reduced-price lunch. The student population is approximately 60% Hispanic or Latinx, 18% Black or African American, and 19% White. Recruitment will occur in 2 phases. First, a feasibility and pilot cohort (n=20) will be recruited in year 1. Next, 2 additional cohorts (n=50 each) will be recruited over years 2 and 3 to manage researcher burden and resource allocation. Each cohort will be further divided into 5 groups

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(n=10) to facilitate data collection throughout the summer with 1 group participating in data collection each week. Participants will be asked to provide a list of weeks that they would be able to participate in the program to avoid scheduled family vacations and other activities that would alter their normal activity level. Participants will then be assigned a week at random from their available weeks. An informational sheet will be sent to eligible youth and their guardians in cooperation with the school district.

The study protocol consists of three main components: (1) an initial survey, (2) a 7-day EMA period, and (3) a follow-up interview. During the initial study visit, participants will complete researcher-administered surveys assessing their personal social networks and perceptions of the built environment around their home. They will also receive training on the use of the EMA application and the ActiGraph LEAP accelerometer. For the 7-day EMA period, participants will wear the ActiGraph LEAP accelerometer on their nondominant wrist 24 hours per day. They will respond to EMA prompts via a smartphone application 6 times daily over 12 hours [39]. The application (LifeData) will be downloaded onto their personal phones (Android or Apple). If the adolescent does not have a phone, a research device will be provided with all other functionality disabled. Prompts will be delivered at random during six 2-hour windows across the day with no prompt being sent within 30 minutes of the previous prompt. The prompting schedule will be adjusted to accommodate each participant's sleep and wake schedule, with 3 options available (8 AM to 8 PM; 9 AM to 9 PM; and 10 AM to 10 PM). Each prompt will include short questionnaires (2-3 mins) assessing momentary perceptions of social and built environments. Following the 7-day EMA period, participants will return for a follow-up visit to return the equipment and participate in a qualitative interview. This interview will assess the acceptability of the EMA and accelerometry protocols and gather additional contextual information about their experiences during the study period.

Survey Variables

The survey component of this study will assess various aspects of the social and built environments and demographic information. These measures are collected during the initial study visit and provide baseline data for each participant.

Demographic Information

Participants will provide demographic information, including age, sex, race, ethnicity, household income (reported by parents or guardians), parental education level, and home address (for Geographic Information System analysis). These data will be used to characterize the study sample and explore potential moderating effects on the relationships between social networks, built environments, and PA.

Social Network Characteristics

To assess social network characteristics, participants will be asked to list up to 10 people (also termed alter) they interacted with most in person over the last 7 days, a method previously used in personal network research [17,18,24]. For each person listed, participants will provide information on relationship type, frequency of contact, perceived frequency of the alter's PA, frequency of coparticipation in PA, perceived closeness, and likelihood of joining the alter in new activities or PA. Participants will also report if each pair of alters knows each other, allowing for the analysis of network structure [17,18]. These data will be used to calculate various social network measures, including social bridging (network size, effective size, and diversity), social bonding (density, proportion of frequent contact, and mean closeness of connection), social norms (frequency of coparticipation in PA and mean perception of alter PA), and social influence (proportion of likely influencers and mean suggestibility) [17,18,40]. In addition, individuals listed in this survey will also be included in EMA prompts as potential responses to items regarding the social environment. In this manner, SNA alters perceptions can be combined with EMA prompt answers to offer opportunities to connect the data set and better explain the social environment as collected by the EMA prompts.

Built Environment Perceptions

To assess built environment perceptions, the Neighborhood Environment Walkability Scale–Youth (NEWS-Y) will be used [31]. This scale, adapted from the adult version and validated for use with youth aged 12 years to 18 years, assesses several domains of neighborhood walkability including PA resource access, land-use mix, walkability, neighborhood aesthetics, safety (crime and traffic), walking and bicycling facilities, street connectivity, and residential density [29]. These measures provide a comprehensive assessment of youth perceptions of their neighborhood-built environment.

EMA Items

The EMA protocol is designed to capture real-time data on participants' social context, built environment perceptions, and PA. EMA prompts will be delivered 6 times per day over a 12-hour period for 7 consecutive days, using a smartphone application [41,42]. Prompts will be delivered at random during six 2-hour windows across the day with no prompt being sent within 30 minutes of the previous prompt. Each EMA prompt is designed to be completed in 2-3 minutes to minimize participant burden while still capturing key variables of interest. The combination of these EMA items with the continuous accelerometer data and GPS coordinates will provide a rich, contextualized dataset for examining the dynamic relationships between social and built environments and youth PA during summer [36,42]. The specific items included in the EMA prompts are in Table 1.

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Table 1. Domains, ecological momentary assessment prompts, and response options.

Domain	Ecological momentary assessment prompt	Response option
Current activity	• "What were you doing right before the beep went off [Choose your main activity]?"	Reading/computer/phone, watching TV/movies, eating/drinking, physical activity/exercising, socializing/hanging out, and others.
Social context	• "WHO were you with just before the beep went off?"	Free response for person(s) listed in the network, other friends, siblings, parents, other family members, others, or people they did not know. (Select all that apply)
Social bridging	• N/A[a]	Measured by the diversity of social context and frequency of persons not known.
Social bonding	• "How close (emotionally) do you feel to those around you at this moment?"	Visual analog scale anchored from "not at all" to "extremely close"
Social norms	• "How physically active do you think the people around you are normally?"	Visual analog scale anchored from "not at all" to "extremely active"
Social influence	• "If someone you are with suggested doing something physically active, how likely would you be to join?"	Visual analog scale anchored from "not at all" to "extremely likely"
Built context	• "Where were you just before the beep went off?"	Home (indoors), home (outdoors), care program (indoors), outdoors (not at home), car/van/truck, and other
Safety	• "How safe do you feel in the current setting?"	Visual analog scale anchored from "not at all" to "extremely"
Pleasantness	• "How pleasant is the physical setting?"	Visual analog scale anchored from "not at all" to "extremely"
Space to be active	• "How much space is there to be physically active where you are right now?"	Visual analog scale anchored from "none" to "a lot"
Affective and feeling states	• "Right now, how SAD do you feel?" • "Right now, how HAPPY do you feel?" • "Right now, how FATIGUED do you feel?" • "Right now, how ENERGETIC do you feel?" • "Right now, how RELAXED do you feel?" • "Right now, how TENSE do you feel?" • "Right now, how STRESSED do you feel?" • "Right now, how FRUSTRATED do you feel?" • "Right now, how NERVOUS do you feel?"	Visual analog scale anchored from "not at all" to "extremely"
Interesting or engaging	• "What is the most interesting/engaging part of the surrounding environment to you right now?"	Free response

[a]N/A: Not available.

Activity Level

Participants will report their current activity at the time of each prompt. Options will include sedentary activities (eg, sitting and lying down), light activities (eg, standing and walking slowly), moderate activities (eg, brisk walking), and vigorous activities (eg, running and sports). This item has been validated against accelerometer measures in previous youth studies [43].

Social Context

To assess momentary social context, participants will respond to questions about who they are with now, the number of people present, how close (emotionally) they feel, their perception of how active those around them are being, and their perception of susceptibility to PA suggestions. Previously mentioned individuals from the initial SNA survey will be provided as response options in these prompts to further understand social influence and norms. These items are designed to capture both the presence of others, social norms related to PA, and susceptibility to influence in the immediate environment.

Built Environment Perceptions

Participants will be asked about their current physical location and their perceptions of the immediate built environment. Questions will address the type of location, perceived safety of the current environment, pleasantness of the surroundings, and availability of space to be physically active. These items are adapted from previous EMA studies on built environment perceptions and PA [36,41].

Mood and Motivation

To capture psychological factors that may influence PA, participants will be asked about their current mood (using a brief affect scale). These items allow for the examination of how momentary psychological states may interact with social and built environment factors to influence PA [41].

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Qualitative Inquiry

To complement the quantitative data collected through surveys, EMA, and accelerometry, this study incorporates a qualitative component to gain deeper insights into participants' experiences and perceptions. Following the 7-day EMA period, semistructured interviews (Multimedia Appendix 1) will be conducted with all feasibility participants (n=20). These interviews will serve multiple purposes: (1) to assess the feasibility and acceptability of the EMA and accelerometry protocols; (2) to gather contextual information about participants' experiences during the study period, such as whether they encountered difficulties answering prompts while engaged in physical activities, if the device interfered with their sleep, or if they felt compelled to alter their behavior due to being monitored; and (3) to explore any anomalies or patterns observed in the quantitative data. The interviews will probe participants' thoughts on answering EMA questions in real time, any privacy concerns they may have had, and their overall experience with the study protocol. In addition, an adapted version of the System Usability Scale will be integrated into the interview to further assess the acceptability and usability of the protocol [44]. These interviews will be audio-recorded, transcribed verbatim, and analyzed using thematic analysis to identify key themes related to the study's feasibility.

Analysis Plan for Feasibility Assessment (Aim 1)

The feasibility assessment will examine multiple quantitative metrics including EMA response rates, with a target of at least 70% completion, accelerometer wear time aiming for 5 or more valid days with more than 10 hours per day, and participant retention rates targeting 80% or higher. We will calculate descriptive statistics including means, SD, and 95% CIs for these metrics. In addition, we will assess patterns of missing data and examine whether compliance varies systematically by participant characteristics using logistic regression models.

Qualitative Analysis Approach

The qualitative analysis will follow the Braun and Clarke [45,46] reflexive thematic analysis framework, which emphasizes the active role of researchers in identifying patterns of meaning across the dataset. The analysis process will begin with data familiarization, during which 2 trained researchers will independently immerse themselves in the data through repeated reading of interview transcripts. This will be followed by systematic initial coding using NVivo (Lumivero) software, with researchers generating codes across the entire dataset and paying particular attention to data related to protocol feasibility and acceptability. The researchers will then develop themes by sorting codes into meaningful patterns and creating a preliminary thematic framework that captures key aspects of participants' experiences. These themes will undergo refinement through review in relation to both coded extracts and the full dataset to ensure they form coherent patterns and accurately represent the data. Clear definitions will be developed for each theme to identify the essence of what each captures about participants' experiences with the protocol. The final analysis will be synthesized into a coherent narrative, supported by illustrative quotes.

Ensuring Qualitative Rigor

To enhance the trustworthiness of our findings, we will implement several complementary strategies [45,47]. For credibility, we will use of investigator triangulation, with multiple researchers independently coding data and comparing interpretations, along with member checking conducted with a subset of participants to verify our interpretations reflect their experiences. To establish dependability, we will maintain a detailed audit trail documenting analytical decisions and theoretical development throughout the analysis process. Confirmability will be addressed through researchers' engagement in reflexive journaling to document their positionality and potential biases, with regular team meetings including discussions of how researchers' backgrounds and perspectives might influence interpretation. For transferability, we will provide rich, detailed descriptions of the study context and participant characteristics to allow readers to assess the applicability of findings to other settings.

Integration of Quantitative and Qualitative Findings

The mixed methods analysis will use a convergent parallel design where quantitative and qualitative data are analyzed separately and then merged to provide a comprehensive understanding of protocol feasibility [48]. Areas of convergence and divergence between quantitative metrics and qualitative experiences will be explicitly examined and discussed. This integrated analysis will inform decisions about protocol modifications and provide crucial insights for implementing these methods in larger-scale studies. The combination of rigorous quantitative metrics with rich qualitative insights will allow us to not only assess the technical feasibility of our protocol but also understand the lived experiences of participants engaging with these novel data collection methods [48].

Analysis Plan (Aim 2)

To address the challenge of integrating data collected at different frequencies and levels of analysis, a multistep data processing approach will be used. Initially, accelerometer and GPS data will be aligned using timestamp information, creating a continuous stream of location-tagged PA data. For each EMA prompt, a time window of more than 30 minutes will be established, extracting the corresponding accelerometer and GPS data. This window allows for the capture of PA and location information immediately before and after each self-report, providing context for the EMA responses. Social network data from the initial survey will be treated as a stable characteristic for each participant throughout the study period, with key network metrics (eg, network size and density) linked to each EMA prompt. To account for potential temporal dynamics in social networks, EMA items assessing momentary social context will be used to create time-varying indicators of social influence. The resulting dataset will be structured hierarchically, with EMA prompts nested within days, and nested within participants. This approach allows for the examination of associations between social network characteristics, built environment features, and PA at various temporal scales, from momentary fluctuations to day-level patterns, while accounting for the different data collection frequencies and levels of analysis.

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The analysis plan for this study incorporates a range of statistical techniques to address the research aims and account for the complex, multilevel nature of the data. For aim 2, which seeks to identify within-day phenotypes, a multistep analytical approach will be used. Associations will be explored at the hour, day, and person levels to determine which temporal associations are strongest. First, intraclass correlation coefficients (ICCs) will be calculated to estimate the impact of clustering (occasions within days, days within individuals) [49]. DSEM will then be used to analyze the within-person time-series data, accounting for the intensive longitudinal nature of the data and examining the bi-directional effects of social and built environments and PA [19]. DSEM allows for the decomposition of variance in PA into within-person and between-person components, estimating autoregressive parameters and cross-lagged parameters. To identify phenotypes, within-person standardized model estimates from the DSEM model will be used in an individual-level cluster analysis, using Ward's Method with Euclidean distance for hierarchical agglomerative clustering [20]. Validity of the clusters will be assessed using ANOVAs and chi-squared tests to examine univariate differences between clusters in terms of PA. Sensitivity analyses will be conducted with varying clustering methods, item rescaling, and time points included to assess the robustness of the cluster profiling [50]. Throughout the analysis, considerations will be made for potential sex and age differences, with exploratory moderation tests conducted. Missing data will be handled using maximum likelihood estimation in the multilevel models. All analyses will be conducted using appropriate statistical software packages, with a significance level set at $P<.05$, adjusted for multiple comparisons where necessary using the Bonferroni correction.

Sample Size Justification and Power Analysis

Our sample size determination was guided by multiple considerations. For aim 1 (feasibility and acceptability), the planned sample size of 20 participants aligns with recommendations for feasibility studies [51]. We will recruit 20 participants in year 1 for initial protocol testing, followed by 2 cohorts of 50 participants each in years 2 and 3. This sample size will allow us to estimate compliance rates with a margin of error of ±9% (assuming 95% CIs), which is adequate for assessing protocol feasibility. For aim 2 (identifying phenotypes), we conducted power analyses using Monte Carlo simulations for DSEM. Based on these simulations, assuming moderate effect sizes ($\beta=0.3$) and ICCs of 0.2, a sample of 100 participants providing 42 observations each (6 prompts per day for 7 days) will provide 80% power to detect significant cross-lagged effects at $\alpha=.05$.

While the study is primarily powered for overall effects, we acknowledge limitations in detecting sex differences. Given our balanced recruitment by sex (50 participants per group), post-hoc power analyses indicate we would only be able to detect large effect size differences ($d>0.7$) between males and females with 80% power. However, previous research in youth PA suggests that while absolute activity levels may differ by sex, the underlying mechanisms of social and built environment influences are generally consistent across sexes [52]. Therefore, while we will explore potential sex differences as secondary analyses, our primary focus is on identifying overall patterns and phenotypes that can inform future intervention development.

Ethical Considerations

This study was approved by the institutional review board at Texas A&M University (STUDY2024-0473). The study will be performed in accordance with the ethical standards as laid down in the 1964 Declaration of Helsinki and its later amendments. All participants will be asked to provide assent to participate. In addition, guardian permission will also be required for all participants. Data will be deidentified using unique study IDs to protect participants privacy. Participants will receive compensation for their involvement, with a tiered incentive structure to encourage compliance. They will receive US $25 gift cards for the initial survey, return devices after the EMA protocol, and participate in qualitative interviews. An additional US $25 will be provided for meeting compliance benchmarks of at least 5 days of valid accelerometer data (more than 10 hours/day) and at least a 70% response rate for EMA prompts, for a potential total of US $100 throughout the study.

Results

The study received funding from the National Heart Lung and Blood Institute in May 2024. Data collection is expected to occur during the summers of 2025, 2026, and 2027. Findings are expected to be published in the fall of 2027.

Discussion

Principal Findings

This study will yield several important findings. First, regarding aim 1, we expect to demonstrate the feasibility and acceptability of combining EMA and SNA techniques to assess social and built environment influences on youth PA during summer. We also expect to identify potential challenges and areas for improvement in the protocol, which will be valuable for future studies using these methods. For aim 2, we anticipate identifying distinct phenotypes that represent different patterns of associations between social and built environment factors and PA. These phenotypes may reveal subgroups of youth who are more or less influenced by specific social or built environment characteristics. For example, we may find a subgroup for whom social network factors are particularly influential on PA, and another for whom built environment features play a more prominent role [7]. We expect these phenotypes to provide insights into the heterogeneity of environmental influences on youth PA, potentially informing more targeted and personalized intervention strategies.

Strengths

This study has several notable strengths. The combination of EMA and SNA techniques represents an innovative approach to capturing the dynamic interplay between social and built environments and youth PA. This method allows for the collection of rich, contextual data in real-time, reducing recall bias and capturing within-person variability [12]. The use of objective PA measures through accelerometry, coupled with GPS data, provides a comprehensive picture of youth PA

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patterns and their environmental contexts [53]. In addition, the mixed-methods approach, incorporating both quantitative and qualitative data, allows for a more nuanced understanding of youth experiences and perceptions. The focus on the summer period addresses an important gap in the literature, as this is a time when youth PA patterns may differ significantly from the school year [8]. Finally, the application of advanced analytical techniques such as DSEM and phenotyping represents a cutting-edge approach to understanding the complex, individual-specific nature of environmental influences on PA [14,19].

Limitations

Despite its strengths, this study has limitations that should be acknowledged. The sample size, while appropriate for a feasibility study, may limit the generalizability of findings, particularly in the identification of phenotypes. The focus on a single geographic area may also limit generalizability to youth in other regions with different social and built environment characteristics. While our sample size is appropriate for our primary aims, we acknowledge limited power to detect sex differences in environmental influence patterns. However, existing literature suggests that fundamental mechanisms of social and built environment influences on physical activity are largely consistent across sexes during early adolescence, even though absolute activity levels may differ. Future larger-scale studies may be needed to fully explore potential sex-specific patterns in these relationships. The intensive nature of the EMA protocol, while providing rich data, may introduce participant burden and potentially affect compliance rates or typical behavior patterns. There is also a possibility of reactivity, where participants may alter their behavior due to awareness of being monitored. In addition, while the study captures a week of data for each participant, this may not represent typical summer PA patterns, which could vary over the course of the entire summer. Finally, while the combination of EMA and SNA provides detailed information on social networks and momentary social contexts, it may not capture all relevant aspects of social influence on PA. Similarly, the built environment measures, while comprehensive, may not account for all relevant features that influence youth PA.

Conclusions

This study represents an important step forward in understanding the complex interplay between social and built environments and youth PA during summer. By employing innovative methodologies and advanced analytical techniques, we expect to gain unprecedented insights into the dynamic, individual-specific nature of these relationships. The findings from this study have the potential to inform more targeted and effective interventions to promote PA among youth, particularly during the critical summer months. While limitations exist, they are outweighed by the strengths of this study's design and its focus on an understudied time period makes it a valuable contribution to the field. Future research can build upon these methods and findings to further elucidate the multifaceted influences on youth PA and develop strategies to promote active, healthy lifestyles among diverse youth populations.

Acknowledgments

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Authors' Contributions

TP conceptualized the study, developed the methodology, and wrote the original draft of the manuscript. GD provided technical expertise on Ecological Momentary Assessment (EMA) methods and contributed to the study design and EMA protocol development. KdH offered expert guidance on Social Network Analysis (SNA) techniques, assisting with the social network measures and analysis plan. CL contributed expertise on spatial analysis, advising on the integration of GPS data and geospatial analysis of the built environment. KPP assisted with the overall study design and methodology. All authors reviewed and edited the manuscript, providing critical feedback and approving the final version for submission.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Qualitative questions.
[PDF File (Adobe PDF File), 120 KB - resprot_v14i1e68667_app1.pdf]

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Abbreviations

DSEM: dynamic structural equation modeling
EMA: ecological momentary assessment
ICC: intraclass correlation coefficient
ILD: intensive longitudinal data
NEWS-Y: Neighborhood Environment Walkability Scale–Youth
PA: physical activity
SNA: social network analysis

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Protocol

Contactless Breathing Monitoring at Home and in the Hospital: Protocol for a Low-Cost Frequency-Modulated Continuous-Wave Radar-Based Device

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Abstract

Background: Contactless monitoring of vital signs, especially the breathing of children, in the hospital is performed on a priority basis because their organs and immune system are immature. Therefore, continuous monitoring of their vital signs with a sensor that is directly attached to their body is not possible, as it irritates the sensitive newborn skin and causes discomfort. A contactless frequency-modulated continuous-wave (FMCW) radar-based device can wirelessly monitor the breathing rate and pattern of a child in the hospital or at home. Signal-processing capability can be added to this device to process breathing data and analyze the apnea condition arising due to irregular breathing patterns.

Objective: This study will develop a contactless FMCW radar-based system to accurately monitor the breathing rate and pattern of neonates and infants in hospitals and at home in order to provide a noninvasive, nonintrusive and contactless alternative to conventional sensor-based methods and address a critical need in neonatal care, potentially improving health outcomes for vulnerable infants.

Methods: The radar transmits a signal toward the body, and the time taken by the signal received to travel from the body to the receiving antenna is analyzed. This time is proportional to the distance between the radar and the body, and the breathing pattern is recognized as a slight, periodic variation in this distance. We will use this concept with multiple antenna systems to monitor the breathing of neonates with improved sensitivity. The radar-based device will be installed, in addition to conventional breathing monitors, in the neonatal intensive care unit. The signals received at the radar and the respiration signals from conventional monitors will be recorded in a database. Signal-processing techniques will be applied to extract breathing signals from the signals received at the radar.

Results: This study was funded in January 2023 by the Science and Engineering Research Board (SERB) of India. The device was designed by May 2024, and a working proof-of concept was verified in the Indian Institute of Technology (IIT) Ropar laboratory. Implementation of the proposed method for initial study began in December 2024. Results are expected to be published in the first quarter of 2025.

Conclusions: The contactless FMCW radar-based system will provide reliable estimation of the breathing rate and pattern, which is close to the conventional reference device values most of the time. Our device will also provide a seamless breathing-monitoring system to be used both in hospitals and at home for newborns and premature babies until they are fully healthy and fit.

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KEYWORDS

radar; contactless vital monitoring; breathing rate monitoring; vital signs; health monitoring

Introduction

In recent times, we have seen advancements in the medical sector, especially in health monitoring, by replacing conventional medical equipment with wireless equipment, which is convenient and accurate for usage. Such advancements have made some vital sign monitoring possible at the home of the patient/subject. As an advanced health-monitoring system, smart homes monitor not only temperature and the environment but also some critical vital signs [1]. Continuously monitoring the breathing rate benefits patient management by early detection of health deterioration and breathing irregularities, if any. For monitoring children and newborns, it is convenient if performed at home. Nearly 15 million infants born prematurely in the world every year need to be monitored until they are healthy and fit [2]. In these children, basic vital parameters, such as breathing, the heart rate, and oxygen saturation, are especially monitored. Initially, these parameters are monitored by a sensor that is directly attached to their body [3], which, however, causes skin irritation and may also lead to pressure necrosis. Regularly observing a patient's vital signs aids medical professionals in identifying early abnormalities and assessing the progression of an illness, as well as evaluating the effectiveness of a treatment method. Contactless monitoring of a patient's vital signs, minimizes inhibition, reduces the risk of infection, and eliminates any discomfort to their skin [4]. Radar is already a promising technology for wireless health parameter monitoring due to its low power, low cost, and security purposes. In this paper, an FMCW radar-based device [5] is proposed to investigate breathing patterns in infants in different scenarios. The device is intended to be used in the hospital or at home for monitoring purposes. Using the proposed design, we will eliminate the requirement of a cannula, which is usually attached to the patient's nose for flow-based breathing-monitoring purposes. Another method that is used as an alternative to interpolate normal breathing is a pulse oximeter, which is attached to the patient's finger for oxygen saturation measurement that correlates with normal/abnormal breathing. Such methods come with the requirement of one or the other kind of attachment to the patient's body, which might create irritation or discomfort for the patient. Thus, we will use a contactless monitoring device for breathing pattern/rate measurement. In this paper, the feasibility of radar technology as a possible means of continuously monitoring vital signs without physical contact will be studied. Radar means detecting an object and estimating its parameters based on its distance from the radar. Continuous-wave radar is used in the microwave range of the spectrum, which means transmit frequencies are within tens of gigahertz [6]. The contactless FMCW radar-based model is based on wireless technology, which includes radio frequency for the transmission of signals and reception after reflection so that direct contact with the patient is not needed, providing an advantage over conventional methods by monitoring health parameters remotely, which is suitable in emergencies and allows health care providers to assess the patient's condition without being physically present at that place.

In this study, we propose a device for contactless breathing rate monitoring. In particular, this device is targeted to be used for the contactless breathing monitoring of newborns to reduce discomfort and potential infection risks due to wired sensor devices by implementing a radar system that will be kept at some distance from the babies so that they do not face any problem during the monitoring of vital signs, especially the respiration rate. For this purpose, we will use the radar for measuring inhalation and exhalation through the outward or inward movement of the abdominal area. This will be monitored in the form of changes in the distance from the radar and the patient being monitored.

Methods

Study Setting

The proposed study will be jointly performed at the Indian Institute of Technology (IIT) Ropar and Government Medical College and Hospital (GMCH) Chandigarh. IIT Ropar is a technology education institute having ~2500 students [7]. The campus also accommodates the staff and faculty members in the on-campus residential facility. The device will be developed at IIT Ropar. The initial study will be conducted on healthy students of the institute who volunteer to be part of the study. The accuracy of the breathing pattern of a healthy human being will be verified. Next, healthy children of the staff and faculty members residing on campus will be enrolled after obtaining informed consent from their parents. Furthermore, a study will be conducted at GMCH Hospital's pediatrics department, which has an inpatient facility for all age groups, including newborn and premature neonates.

Study Design

The proposed study is intended to prove the applicability of contactless methods for breathing rate monitoring in neonates. Further, this study will be useful in the detection and management of apnea conditions due to irregularity in breathing patterns. The primary objectives of the study are as follows:

- Designing a device for noncontact breathing rate monitoring using the FMCW radar principle, which transmits a signal with the frequency varying linearly with time. When this signal reflects off an infant's chest, the received signal has a frequency difference (beat frequency) from the transmitted signal. This frequency difference is proportional to the minute movements caused by breathing. Thus, the beat frequency carries information of the breathing pattern. In addition to the breathing pattern, some unwanted reflected components from multiple objects around the patient being monitored are contained in the radar signal, as illustrated in Figure 1. The primary objective is to design algorithms to suppress the effect of reflections from stationary objects.
- Identifying specific signal fluctuations related to the breathing of the patient being monitored and distinguishing these variations from other persons in the room or other body movements, such as those of limbs. Breathing is

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periodic, so the beat frequency variation is also periodic. Variation due to limb movements and other people is large and aperiodic. Therefore, signal processing techniques, including filtering, can be used to minimize the effects of unwanted reflections and movements.

- Further extending this setup to analyze breathing signals of multiple persons and separating them.

Figure 1. Separating different objects based on reflection. SDR: software-defined radio.

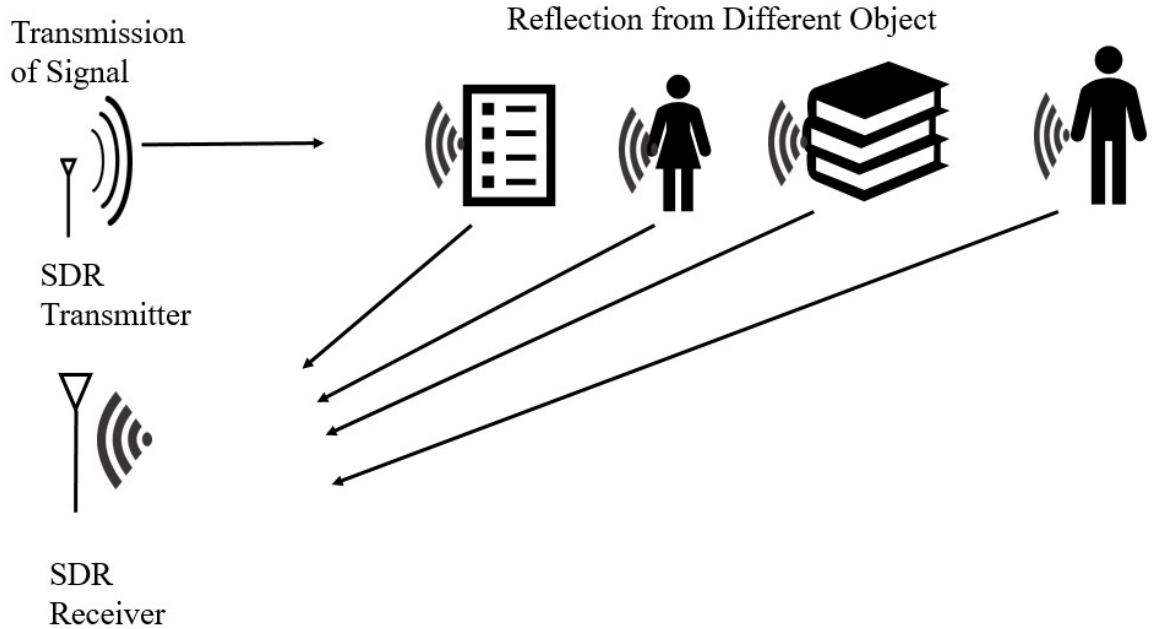

Prototype and Implementation

The main objective of the model is to monitor the breathing of premature and newborn babies without any contact with their bodies. The proposed monitoring device is contactless. Therefore, it will not cause skin injury, irritation, allergy, or infection. Device accuracy is targeted to be more than 90% in all scenarios and more than 98% in a controlled setup [1]. The controlled setup is defined as a laboratory environment or the target patient being instructed to restrict any movement of body parts. This model combines the development of hardware and software, in addition to the testing protocol for the breathing rate. The software contains signal-processing algorithms to clean the received signal after reflection from the target and the other objects or persons in the vicinity, as shown in Figure 2. The waveform is designed and generated to be sent toward the patient being monitored using a software-defined radio (SDR) transmitter [8,9]. The same SDR is used to receive the reflected signal. The broadcast signal is reflected and received with a time delay due to the distance propagated between the device and the target patient. The difference in frequency between the transmitted and received signals, which determines the beat frequency, provides distance information. The distance varies with the state of breathing, such as inhalation results in reduced distance and exhalation results in increased distance due to expansion and contraction of the chest and abdominal region of the patient. The reflected signal's components are reflected from the patient and nearby objects. The reflected signal received at the SDR receiver is converted back to the baseband after dechirping. The dechirped signal is processed further in a general-purpose computer to extract the required breathing signal by mitigating the effects of the reflections from objects other than the patient being monitored. This requires passing the signal through a low-pass filter to obtain the frequency of interest (ie, to retain frequency components that are within the range of the breathing rate). We will also implement the algorithms to separate the reflection from different objects based on their reflection time so that the objects at different distances are separated. Wireless signals travel at the speed of light. Separating these reflections eliminates them from static objects, as their reflections do not change over time [8].

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Figure 2. System model design. RX: receiving; TX: transmission.

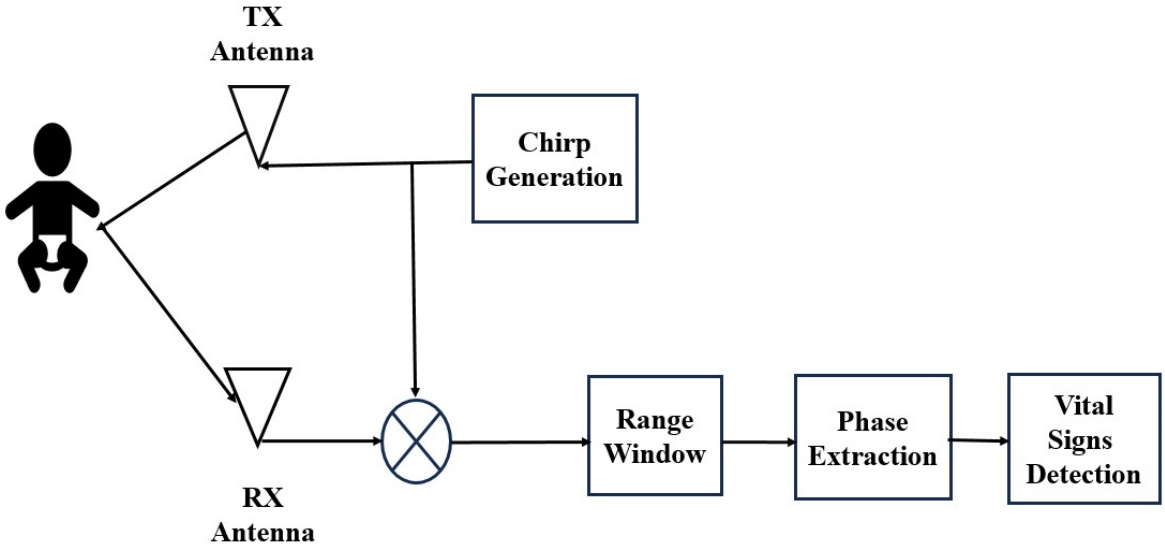

FMCW Radar and Study Measurement

Effective contactless monitoring of each baby in the hospital was initiated after stability criteria were met, such as respiratory status without serious illness. FMCW radar monitoring is performed continuously during the monitoring period [10]. The benefit of this device is that it can be used in hospitals and homes both. Many times, it is only necessary to monitor the breathing, which can be performed at home with the proposed device without admitting the child to the hospital. For the proposed study and initial trial, the infants will be observed with their chest facing the radar at a distance of roughly 1-1.5 m from the low-vibration tripod to which the radar is attached. A research assistant will track each infant's vital signs for 10 minutes, 3 times a day. The effectiveness of the radar-based breathing rate–monitoring device will be evaluated by comparing the device's measurements with clinical recordings.

Sample Size and Data Analysis

A sample of 20-30 premature newborn babies will be included in the study. Data collection will be performed with the help of the neonatology department at GMCH Chandigarh. The radar-based device will be installed, in addition to conventional breathing monitors, in the neonatal intensive care unit. The signals received at the radar and the respiration signals from the conventional monitors will be recorded in a database. An in-depth analysis of radar signals received from each infant will be carried out. All the factors critical for understanding the complexities of the premature newborn condition and care will be observed, providing the diversity and depth of experience necessary for such research [11]. The main idea is to investigate different effects of collecting radar data from the chest and abdominal region, removing the effect of any interference or movements and reflections from the surroundings. Further analysis and algorithm development will be carried out to extract breathing signals when each infant is with the mother. If monitoring of twins is possible, a minimum safe distance will be required to mitigate the radar interface between them. The basic principle that will guide the data collection protocol will ensure seamless operation at GMCH Chandigarh.

Ethical Considerations

The study was approved by GMCH Chandigarh and the Government of India. Informed consent will be obtained from parents. They will be informed about the purpose of the experiment, the procedure, and benefits. We will ensure that they do not face any type of harm and that they voluntarily agree to participate. Data confidentiality will be ensured, and participants' identities will be protected. Ethical approval (approval number GMCH/IEC/2022/730) was obtained from the GMCH Chandigarh Institutional Review Board (IRB) or Ethics Committee to ensure that the study meets ethical standards and that participants are protected from potential harm.

Results

Data collection and implementation of the proposed device was performed with the help of IIT Ropar and GMCH Chandigarh. The study was funded in January 2023 by the Science and Engineering Research Board (SERB) of India. The device was designed by May 2024, and a working proof-of concept was verified in the IIT Ropar laboratory. Implementation started in December 2024. Initially, we will apply this method to monitor a single child, and then, this study will be extended to monitor multiple infants by modifying the device design and signal-processing algorithms. The main outcome of the proposed method is to obtain breathing patterns of infants at home and in hospitals to predict their health condition based on the breathing patterns. We expect to obtain the results of monitoring a single child by the end of the first quarter of 2025.

Discussion

Summary

The proposed study will develop a device for accurate noncontact monitoring of the breathing rate and patterns of neonates and infants in the hospital and at home using an FMCW radar-based system. The working principle of the device is based on capturing, using radar, the pattern of movements in the chest and abdominal region due to inhalation and exhalation. This

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will address the critical need for noninvasive and noncontact continuous respiration monitoring in clinical settings. With the system being noncontact and portable, it can also be used at home to monitor the patient's condition. Unlike wearable devices that may be affected by environmental factors and require direct contact, the proposed system offers a significant advantage over conventional chest-mounted devices that may cause discomfort and privacy concerns. The typical range for an infant's respiratory rate is between 40 and 60 breaths per minute [12]. A breathing rate outside this range indicates that the patient is not healthy. Through the usage of the proposed technology, we plan to demonstrate high accuracy in identifying respiratory irregularities, such as apnea, aligning with the study's objective to enhance neonatal care. Contactless radar systems [13-17] have been proven to be a more convenient option for users compared to wearable devices due to immunity to environmental constraints, wider coverage, the absence of privacy concerns, and importance for heavy-burned and newborn babies, enhancing usability. The ability to detect vital signs, particularly the breathing rate, is typically required to identify human presence in short-range environments. However, the system's accuracy may be affected by movement artifacts, physical abstraction, clothing, cobedding, and positioning. Other constraints related to the proposed method are a trade-off between range and resolution due to bandwidth constraints, and further validation in diverse clinical settings is required. Despite these limitations, the signal-processing techniques will be used to improve the performance and bring about significant advancements in neonatal respiratory care, with broader implications for improving patient care and monitoring in various clinical and home settings. Once the designed device is developed, it will be tested in the neonatology department of GMCH Chandigarh, where breathing rate monitoring will be compared with conventional methods. We will have a database of signals received at the proposed device and those from conventional devices. This database can be used to test various algorithms. Future research will focus on refining the device's accuracy and expanding its applicability to a wider range of patients and conditions. The device design can be modulated to monitor multiple individuals through use of multiple antennas and advanced signal-processing techniques.

Conclusion

An FMCW device can measure submillimeter-range shifts because of its improved precision in measuring displacements. Breathing using an FMCW radar-based device [18-20] is useful for pathologies that are difficult to detect solely with the use of an electrocardiogram (ECG). FMCW devices are cheap and easy to operate. Our model will also have the advantage of better resolution compared to other radar-based model designs and will be based on radio frequency signals from a radar to detect the patient's position and extract respiration data [21-23]. With the help of this system, we can detect the breathing of patients within the range of up to 45 cm and possibly improve spatial resolution and range with additional radar and antenna units.

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Data Availability

The data from this trial will be accessible to the public and research community. The research team will decide on the dissemination method once the trial ends and our results are published. Although the data will not be made immediately public, they can be requested from the corresponding author.

Authors' Contributions

All authors have read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

FMCW: frequency-modulated continuous-wave
GMCH: Government Medical College and Hospital.

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IIT: Indian Institute of Technology
SDR: software-defined radio.

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Protocol

Codevelopment of an mHealth App With Health Care Providers, Digital Health Experts, Community Partners, and Families for Childhood Obesity Management: Protocol for a Co-Design Process

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Abstract

Background: Childhood obesity is increasing in Singapore, with most cases persisting into adulthood and leading to poor health outcomes. The current evidence for childhood obesity interventions shows a clear dose-response effect, where effectiveness improves with an increasing number of treatment hours. A minimum threshold of ≥26 hours over a 2- to 12-month period is required to achieve significant outcomes. The Kick Start Move Smart program is the first online community-based multidisciplinary program to treat pediatric obesity in Singapore. It has demonstrated feasibility and acceptability, with 70% of participants completing the recommended ≥26 hours of intervention. Preliminary data show significantly lower BMI and improved quality of life in participants compared to controls. Successful families are positive outliers who developed strategies for health in the context of an obesogenic environment. This positive outlier approach indicates that solutions to challenges that a community faces exist within certain individual members, and these strategies can be generalized and promoted to improve the health of others in the same community. A mobile health (mHealth) app targeting parents is a critical missing link in the currently available interventions to support parental self-management of childhood obesity. Using a combination of behavioral theory and user-centered design approaches is important for designing mHealth apps. One recommended framework is Integrate, Design, Assess, and Share (IDEAS), which aims to facilitate the development of more effective interventions by engaging perspectives from different stakeholders.

Objective: This study aims to (1) describe the co-design protocol of an mHealth app using the IDEAS framework as a low-intensity intervention or as an adjunct to more intensive existing pediatric obesity interventions and (2) assess the usability, acceptability, and engagement of the app by parents.

Methods: A clinician-led co-design approach will be undertaken with a multidisciplinary team using the IDEAS framework. Phase 1 involves stakeholder engagement and the formation of a core committee and a parent advisory board. Phase 2 involves developing the app content through focus group and expert panel discussions. Phase 3 involves developing a prototype app and gathering feedback. Phase 4 involves piloting the minimum viable product by parent users and evaluating its effectiveness through interviews and questionnaires.

Results: In April 2023, a parent advisory board was formed, and stakeholders were engaged as part of phase 1. Phases 2 and 3 were completed in June 2024. Focus group discussions were held with the parent advisory board and stakeholders to identify family strategies and patient-centric outcomes and provide feedback on the app. As of January 2025, the app is complete, and

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we are now in the middle of data collection from participants. Participants will provide feedback to the research team, and the app will be updated accordingly.

Conclusions: An evidence-based, theory-driven mHealth app developed using a structured design framework can bridge the gap in delivering multidisciplinary care in community settings for families with overweight children.

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KEYWORDS

childhood obesity; mHealth; mobile health; co-design; IDEAS framework

Introduction

Childhood obesity rates are rising in Singapore, with most cases persisting into adulthood and leading to adverse long-term psychosocial and health effects. A recent systematic review and meta-analysis highlighted the importance of access to multidisciplinary interventions for children with obesity. The current evidence for childhood obesity interventions shows a clear dose-response relationship, where effectiveness improves with an increasing number of treatment hours. A minimum threshold of ≥26 hours over a 2- to 12-month period is required to achieve significant outcomes [1]. The Kick Start Move Smart (KSMS) program is the first online community-based program to treat pediatric obesity in Singapore. The pilot evaluation has demonstrated feasibility and acceptability, with 70% of the participants completing the recommended ≥26 hours of intervention. Preliminary data on the effectiveness of the program show significantly lower BMI scores and improved quality of life in program participants compared to the control group. Families who achieved the recommended treatment hours in the program also demonstrated improvements in their child's quality of life, health behaviors (such as increased intake of fruits and vegetables), and BMI. Successful families are positive outliers who developed strategies for health in the context of an obesogenic environment. The theoretical underpinning of the positive outlier approach is that solutions to problems a community faces often exist among certain individuals and that these successful strategies can be generalized and promoted to improve the outcomes of others in the same community [2]. Typically, there is a high degree of heterogeneity in response to lifestyle interventions in pediatric obesity treatment; thus, adopting the positive outlier approach can facilitate the best solutions to support families.

An evidence-based, theory-driven mobile health (mHealth) app that targets parents is a critical missing link in currently available interventions to support parental self-management of childhood obesity [3]. While there has been a rapid growth of mHealth apps to support chronic disease management, achieving meaningful health improvements through the use of mHealth apps remains elusive. Combining approaches from behavioral theory and user-centered design to guide intervention development, coupled with rigorous approaches for evaluation and dissemination, is important to achieve the full potential of mHealth apps. Integrate, Design, Assess, and Share (IDEAS) is one recommended framework, which aims to facilitate the development and dissemination of more effective interventions by engaging the perspectives of different stakeholders [4]. This framework builds on design thinking and integrates user insights throughout the stages of development and the inclusion of theory-driven behavioral strategies.

We hypothesize that codevelopment with health care providers, digital health experts, and successful families to create a high-quality mHealth app for childhood obesity can increase its acceptability and engagement from families. First, we aim to co-design an mHealth app with health care providers, digital health experts, community partners, and successful families using the IDEAS framework. The app will be evidence-based and theory-driven and consist of three core components: (1) consolidation of positive outlier strategies and development of patient-centric outcomes for self-monitoring, (2) synthesis of evidence-based guidelines and integration of theory for behavioral strategies, and (3) incorporation of community resources and integration with community programs. The mobile app is designed to be used independently as a low-intensity intervention or as an adjunct to more intensive existing pediatric obesity interventions to increase overall engagement and effectiveness. Second, we aim to assess the usability, acceptability, and engagement of the mHealth app by parents in the pilot testing phase. Specifically, the usability and acceptability of the mHealth app will be assessed using the validated Mobile App Rating Scale (uMARS) [5] and by self-monitoring of patient-centric outcome measures as determined in the primary aim.

Methods

Overview

A clinician-led co-design approach will be undertaken with a multidisciplinary team of researchers, parents of children with obesity, community stakeholders, and digital health experts using the IDEAS framework [4]. The experience-based co-design principle will be followed to design the mHealth app, including gathering stakeholders to participate in the design process and developing a set of feasible care paths by sharing their experiences [6]. Based on the IDEAS framework and co-design principles, 4 iterative phases for the prototype mHealth app have been developed, which are summarized in Table 1.

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Table 1. Phases of the project and their estimated timelines.

Phase	Activities	Duration	Stakeholders (n=21)
1	• Stakeholder engagement • Forming the parent advisory board	• 4 months	• Multidisciplinary health care providers (10/21, 48%) • Parent advisory board (5/21, 24%) • Community stakeholders from Sport Singapore and Health Promotion Board (4/21, 19%) • Digital health experts and app developers (2/21, 10%)

2	• Developing content
	  • Patient-centric outcomes that are clinically relevant
	  • Successful positive outlier strategies
	  • Integration with community resources
	  • Implementation of the app in daily lives
		• 6 months	• Multidiscpilinary health care providers
			• Parent advisory board
			• Community stakeholders

3	• Sharing proposed contents and features based on results from phase 2 and revisions • Sharing prototype app	• 6 months	• Multidiscpilinary health care providers • Parent advisory board • Community stakeholders • Digital health experts and app developers
4	• Evaluating and refining the MVP[a] to assess usability and acceptability and improvement of the app functions	• 9 months	• Parents of children with obesity • Digital health experts and app developers

[a]MVP: minimum viable product.

Ethical Considerations

Ethical approval has been sought from the SingHealth Centralized Institutional Review Board (2022/2035).

Phase 1: Stakeholder Engagement and Formation of the Core Committee and Parent Advisory Board

Stakeholder Engagement

The multidisciplinary team of health care providers will consist of pediatricians, dietitians, nurses, physiotherapists, exercise physiologists, psychologists, and social and medical workers with expertise in childhood obesity, who provide their clinical input in the co-design process. Digital health experts and app developers will also advise on the feasibility of the mHealth app's requirements and involve the vendor at appropriate time points to effectively transform the information into system requirements and design considerations to achieve an optimal design solution. The app's privacy and security features and compliance with the Personal Data Protection Act will also be considered. These features have emerged as fundamental from both clinical and patient perspectives in an evaluation of an mHealth app [7].

Parent Advisory Board to Learn From Positive Outliers

Patient advisory committees have been used in numerous co-design approaches to obtain patient input on a variety of health care processes. This ensures that the posed research questions and selected outcome measures are relevant and important to patients [8]. In this project, we will convene a parent advisory board to inform the mHealth app development. The parent board will consist of at least 5 parents who previously participated in the KSMS pilot study and successfully attended at least 26 hours of the program. The parent advisory board will be part of 2 focus group discussions in phase 2 and 1 focus group discussion in phase 3 of this project.

Formation of the Core Committee

Given the networked nature of the project, which includes the multidisciplinary team, community stakeholders, digital health experts, app developers, and a university partner, the core committee is critical for the project's success. It builds off our 2 years of experience working with multiple stakeholders across institutions for the KSMS program. The core committee will be chaired by the principal investigator with 2 members from the multidisciplinary team, 2 members from community stakeholders, 1 member from the digital health expert team, 1 member from the parent advisory board, 1 member from the partner university, and 1 clinical research coordinator. At defined intervals (intended to be one per quarter and as required), the core committee will meet by teleconference to review the strategic course and resource allocations. The clinical research coordinator, who is also the project coordinator for KSMS, serves as the lead administrator. The core committee is responsible for initiating and reviewing overall project progress and undertaking operational decisions to ensure that the project goals are aligned. This committee plays a vital role in the mHealth app's successful implementation into clinical practice and in ensuring the project's sustainability.

Phase 2: Development of the mHealth App's Contents

Overview

In phase 2, we plan to conduct 2 focus groups with the parent advisory board (5/21, 24%), 1 focus group discussion with community stakeholders (4/21, 19%), and 2 expert panel discussions with the multidisciplinary health care team (10/21,

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48%) to develop the 3 main components of the mHealth app, as detailed in the subsequent sections.

Consolidating Contextually Tailored Positive Outlier Strategies and Developing Patient-Centric Outcomes for Self-Monitoring

The 2 focus group discussions with the parent advisory board will identify practices that facilitated their engagement in the intervention and change in health behaviors as well as highlight outcomes that matter most to their families in relation to weight management. These successful positive outlier strategies will be generalized and incorporated into the app with the aim of improving other families' outcomes. Patient-centric outcomes will be incorporated as part of the self-monitored outcome measures for parents. Parents will also provide input on integrating the app into their daily lives. Parents' detailed input on activity and nutrition suggestions will be used to make these recommendations actionable and tailored contextually (eg, based on time and day of the week), increasing the effectiveness of "push" notifications and suggestions.

Synthesizing Evidence-Based Guidelines and Integrating Theory for Behavioral Strategies

The multidisciplinary team of health care providers will consist of pediatricians, dietitians, nurses, physiotherapists, exercise physiologists, psychologists, and social workers trained in pediatric obesity management. Focus groups with the multidisciplinary team will consolidate practices and incorporate evidence-based strategies, guided by expert committee recommendations for pediatric obesity prevention and Singapore's Integrated 24-Hour Activity Guidelines for Early Childhood (0-6 years) [9]. The multidisciplinary team will also review strategies from parent advisory board focus groups and evidence-based guidelines to select optimal theory-driven behavioral strategies for guiding the mHealth app design [10]. Incorporating motivational interviewing (MI) in health care settings has been shown to improve intervention engagement and commitment to the behavioral change process [11]. MI is a person-centered counseling method that supports individual autonomy and uses collaborative and nonauthoritarian interaction to work toward an individual's goal.

Incorporation of Community Resources and Integration With Community Programs

The focus group with community stakeholders aims to integrate currently available community resources (web-based and physical) that are relevant to the target population, such as community-based sports programs designed for families.

Phase 3: Development of the Prototype App

The results of phase 2 will be shared with digital health experts and app developers to outline the required app features and guide the development of multiple prototypes. Studies have shown that developing multiple prototypes in parallel (versus sequentially) leads to a superior final prototype [12]. The prototype will be developed in regulated phases before being shared with the parent advisory board, multidisciplinary team, and community stakeholders to gather their feedback through 3 separate focus groups (one for each stakeholder). The feedback obtained will include user experience, visual design, content, and logic (such as a graphical representation of families' data). Feedback will be gathered from the clinical team on the integration of the app into clinical workflows, its prescription to families, and the visualization of intervention-related data. The digital health experts and app developers will then review the feedback for integration into the prototype app before a final minimum viable product (MVP) is published.

Phase 4: Piloting the MVP and Evaluation

A fully functional MVP will be developed to focus on details beyond the prototype phase. The MVP will be pilot-tested by 10 parents for 4 weeks to detect usability issues before the final prototype is developed. Parents of children aged 4 to 7 years old with obesity will be recruited from outpatient clinics. A sample size of 10 participants in think-aloud studies has been shown to detect 80% of usability issues [13]. At the start of the pilot testing, think-aloud walkthrough interviews will be conducted. Participants will be instructed to use the app as they would any newly downloaded app, verbalizing their thoughts throughout the process. They will be encouraged to freely explore the app and ask questions to provide insights into their user experiences. Following the walkthrough interviews, participants will be asked to use the app for 4 weeks.

At the end of the 4-week period, semistructured interviews and the uMARS questionnaire will be administered. The interviews will consist of open-ended questions on participants' previous experience with mobile apps, general perceptions of the app, its most/least useful features, suggestions for improvement and usage, possible features that could exclude potential users, and factors related to engagement. Inputs on the push notifications will be obtained from parents to optimize their timing and delivery to target behavior change.

Analytics will be integrated into the app to collect a rich dataset, capturing patterns of use, particularly in relation to accessing information and completing patient-centric outcomes as defined in our secondary aims. The usability and acceptability of the mHealth app's "pull" features (educational materials and graphical representations of monitored outcomes) will be evaluated using uMARS, a 20-item measure that includes 4 objective quality subscales (engagement, functionality, aesthetics, and information quality), 1 subjective quality subscale, and 1 perceived impact scale, all measured on a 5-point Likert scale. A score of 4 and above indicates good quality [5].

High usability and acceptability will be defined as a median score of 4 out of 5 in all domains (information, engagement, functionality, aesthetics, impact, and acceptability) for parents. The user engagement aims will be defined as (1) recruited parents accessing ≥70% of the information and (2) completing patient-reported outcome measures over the 4-week period.

Results

This study received funding in February 2023. As part of phase 1, a parent advisory board was formed in March 2023 with parents who had previously participated in the KSMS pilot study and completed at least 26 hours of the program. Stakeholders were engaged in April 2023 to co-develop the mHealth app.

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Stakeholders included the multidisciplinary health care team from KK Women's and Children's Hospital, the Health Promotion Board (HPB), and Sport Singapore. Digital health experts and app developers from the National University of Singapore School of Computing were also involved in developing the mHealth app.

Phase 2 was completed between April 2023 and December 2023. The first focus group discussion with the parent advisory board was held in April 2023 to identify positive outlier strategies. A preliminary mock-up app was developed and shared in focus group discussions for feedback with community stakeholders (HPB and Sport Singapore) in May 2023, followed by the multidisciplinary team in July 2023. Discussions were held with community stakeholders between June 2023 and December 2023 to integrate existing community resources and programs into the mHealth app. A second round of individual interviews with the parent advisory board was conducted in October 2023 to identify patient-centric outcomes and review the mock-up app.

Revisions were made to the mHealth app following feedback from the stakeholders and parent advisory board. Focus group discussions and individual interviews were conducted in phase 3 to obtain feedback on the revised mock-up app with stakeholders and the parent advisory board, completed between April and June 2024.

The final stage of the mHealth app development was completed in December 2024 with an MVP app. Participants were recruited to pilot-test the mHealth app and provide feedback from January 2025. Recruitment will resume in April 2025, and feedback will be collected from the participants to enhance the mHealth app.

Discussion

Expected Findings

This study outlines the co-design process of an mHealth app with health care providers, digital health experts, community partners, and families, using the IDEAS framework. We hypothesize that the app, developed through the IDEAS framework, will be usable, acceptable, and engaging for parents in managing childhood obesity.

Patient advisory committees have become increasingly important in health care, offering valuable insights into various health conditions [14]. Engaging parents as active participants in the design of this app is important to ensure that the strategies recommended for other parents will be relevant and meaningful. For patient-centric outcomes, we anticipate focusing on themes related to psychosocial wellness, as seen in other studies [15], especially considering the lower quality of life among Singaporean children with obesity [16].

Some successful positive outlier strategies identified in a United States–based study [15] include (1) making family-centric changes in health behaviors rather than child-centric changes, (2) establishing rules around health behaviors, (3) shared decision-making with health care providers on child weight management, and (4) using community resources for behavioral change. We anticipate some common themes among our local population, especially around family-centric changes, rule implementation on behavior change, and the use of immediate outcomes, which align with findings from our previous study [17]. However, strategies like shared decision-making with health care providers and the use of community resources are less likely to emerge as important themes. This is because obesity is commonly perceived as a lifestyle factor, rather than a chronic disease, with treatment not claimable under private or public health care insurance [18]. These factors may hinder help-seeking for obesity treatment and pose challenges in developing community programs for childhood obesity management. Thus, the development of this mHealth app aims to bridge the gap in available resources for managing childhood obesity.

Despite research showing that parents are an integral part of pediatric obesity prevention and treatment, the currently available apps do not target parents or families but focus solely on the child. A review of mHealth apps for pediatric obesity prevention and treatment also found that most apps lacked any expert recommendations. mHealth apps have also been found to lack a theoretical basis for their development, thereby limiting their efficacy [19]. There is currently no mHealth app that integrates the strategies learned from positive outlier families with locally available community resources. Thus, this project will be the first theory- and evidence-informed mHealth app for pediatric obesity management targeted toward parents. The successful development of this mHealth app, through the use of the IDEAS framework, will also provide important information for the future development of mHealth apps for other chronic diseases, such as diabetes mellitus, to facilitate behavioral change and improve patient outcomes.

Currently, primary care providers and patients can only access pediatricians, dietitians, physiotherapists, and exercise physiologists trained in pediatric obesity management when they are referred to tertiary pediatric centers. This reliance on specialized centers can result in these services becoming overwhelmed. An mHealth app that is evidence-based, theory-driven, and developed within a design framework, can bridge this gap in providing multidisciplinary care in the community setting. Health care providers in both tertiary and primary care often face significant time constraints during consultations. Engaging these health care providers in the app's development and evaluation process can enhance its usability and acceptability, enabling its incorporation into clinical care processes.

The proposed mHealth app will thus provide the foundation for accessible multidisciplinary care in the community, scaling up the KSMS program to provide evidence-based treatment to every family with overweight children. This approach aims to help reduce complications associated with obesity.

By evaluating the potential effectiveness of these multimodal complex interventions (Figure 1) in reducing childhood obesity, improving quality of life, and reducing health care visits, this study could provide cost-effectiveness data to support informed decisions for nationwide implementation.

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Figure 1. Proposed mechanism of the mobile health (mHealth) app and its future integration into health care settings, health care provider training, and community programs.

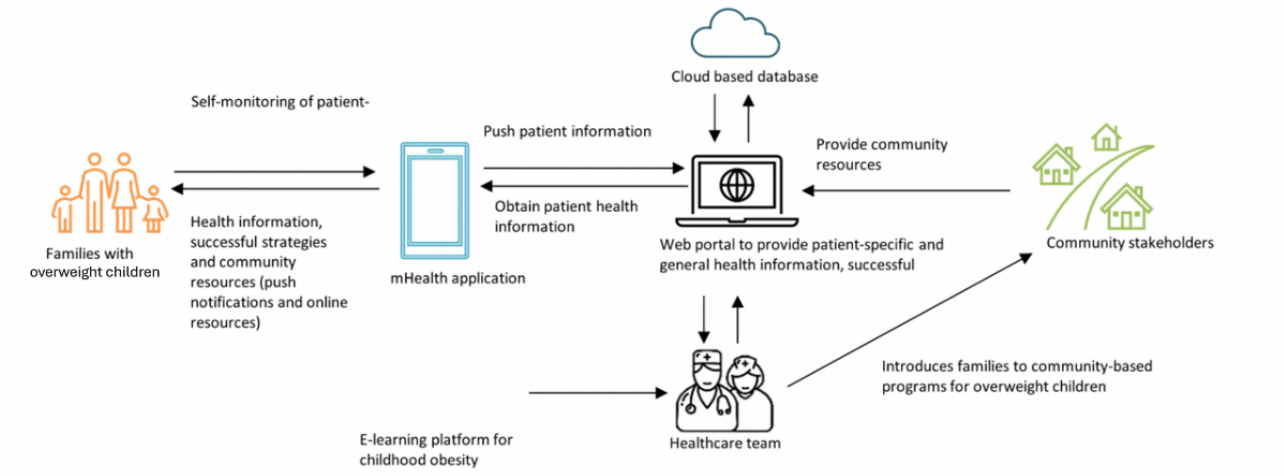

Strengths and Limitations

The key strengths of this study include the co-design approach with a multidisciplinary team and parents, as well as the development of an evidence-based, theory-driven mHealth app. These elements are critical for ensuring effective digital interventions that promote behavior change in childhood obesity management.

However, this study has limitations. Nonresponder bias may arise, as responses from participants not identified as positive outliers are not captured. Additionally, the effectiveness of the mHealth app compared to standard care is being assessed in this study.

Conclusions

An evidence-based, theory-driven mHealth app developed within a structured design framework can bridge the gap in providing multidisciplinary care for families with overweight children in the community setting. This app will also empower families to improve self-management of childhood obesity. Future studies are required to examine the effectiveness of this mHealth app in managing childhood obesity and promoting better self-management compared to standard care.

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Data Availability

Data sharing is not applicable to this article as no datasets have been generated or analyzed during this study.

Authors' Contributions

SHT drafted, critically reviewed, and revised the manuscript. KBK, CD, ZQO, and EJKL critically reviewed and revised the manuscript. CSEC conceptualized and designed the study and critically reviewed and revised the manuscript. All authors have approved the final manuscript as submitted and agree to be accountable for all aspects of the work.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the Human Potential Prenatal / Early Childhood Grant Office Agency for Science, Technology, and Research (Singapore).
[PDF File (Adobe PDF File), 179 KB - resprot_v14i1e59238_app1.pdf]

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Abbreviations

HPB: Health Promotion Board
IDEAS: Integrate, Design, Assess, and Share
KSMS: Kick Start Move Smart
mHealth: mobile health
MI: motivational interviewing
MVP: minimum viable product
uMARS: Mobile App Rating Scale

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Proposal

A Gamified mHealth App to Promote Physical Activity and Reduce Sedentary Behavior in Autistic Adults: Protocol for a Remotely Delivered Pilot Intervention Study

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Abstract

Background: Research indicates that many autistic adults are insufficiently active and overly sedentary. There is limited evidence on effective strategies to increase physical activity (PA) and reduce sedentary behavior (SB) in this population. Gamified mobile health (mHealth) interventions show promise for addressing these challenges by leveraging autistic individuals' strengths in visuospatial learning and their affinity for digital gaming. Despite this potential, it remains unclear how well these interventions translate to real-world settings. This gap is compounded by the lack of community-based participatory approaches in the development of mHealth intervention for autistic adults.

Objective: This study aims to (1) formulate gamification and behavior change strategies for the PuzzleWalk v2 app using a community-based participatory approach and (2) evaluate its feasibility and acceptability for increasing PA and reducing SB among autistic adults, including those with mild intellectual disability, in real-world settings.

Methods: This study, consisting of 2 sequential phases, will be conducted entirely remotely: (1) online community-based design workshops to refine the PuzzleWalk gamified mHealth system with input from key autism stakeholders, including autistic adults and caregivers, and (2) an 8-week field deployment to assess real-world usability and engagement. In Phase I (completed), weekly workshops and usability testing focused on understanding autistic adults' technology preferences, evaluating PuzzleWalk v1 and v2 prototypes, and incorporating stakeholder feedback into iterative app development (n=9). Phase II (in progress) will involve a single-arm clinical trial where approximately 70 participants will use the app alongside research-grade activity-tracking accelerometers to measure PA and SB. Outcome measures, including sedentary time, step counts, PA intensities, and app engagement (eg, time spent using the app), will be collected across 4 specific time points (ie, baseline and weeks 3, 5, and 8). Repeated measures ANCOVA will be performed to examine changes in participants' objective levels of PA and sedentary time before, during, and after the intervention.

Results: Phase I of the study, involving community-based participatory design workshops and usability testing, was completed in November 2024. Key autism stakeholders recognized the gamified PuzzleWalk app as a viable tool for enhancing motivation toward PA and SB changes among autistic adults. Data collection for Phase II, the field deployment, is currently underway and is expected to end in August 2025. As of July 2025, we had enrolled 69 participants in the study. The findings of these studies will be shared in a subsequent peer-reviewed publication.

Conclusions: Results of the ongoing field deployment study (Phase II) will further clarify the app's effectiveness and real-world applicability.

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International Registered Report Identifier (IRRID): DERR1-10.2196/71631

(JMIR Res Protoc 2025;14:e71631) doi:10.2196/71631

KEYWORDS
gamification; autism; physical activity; mobile health; participatory research

Introduction

Background

Increased awareness and advancements in diagnostic methods have made autism spectrum disorder (ASD) one of the most rapidly growing developmental disabilities in the United States [1,2]. However, poor health outcomes among autistic adults have emerged as a significant public health concern. Approximately 5.4 million American adults were diagnosed with this lifelong neurodevelopmental condition, with or without co-occurring intellectual disability [3]. Autistic adults are at higher odds of lifestyle-related chronic health conditions, including obesity (1.4-fold), dyslipidemia (2.1-fold), and diabetes (2.2-fold) [4,5].

The *Healthy People 2030* initiative highlights the importance of regular physical activity (PA) participation for maintaining overall health among individuals with and without disabilities. However, more than one-quarter of American adults, including autistic adults, participate in no leisure-time PA [6]. Research findings indicate that individuals with ASD often exhibit lower PA levels and increased sedentary behavior (SB) with age, potentially due to diminished intrinsic motivation to move and heightened sensory sensitivities in public environments [7,8]. Moreover, evidence [9] categorizes SB as a distinct health risk factor, as prolonged sitting contributes to adverse health outcomes even among those meeting PA guidelines (ie, accumulating ≥150 minutes a week of moderate-to-vigorous PA [MVPA] or ≥75 minutes a week of vigorous aerobic PA) [10]. Physical inactivity and excessive sitting may contribute to the high prevalence of chronic health conditions in autistic adults [4]. Despite these concerns, strategies to enhance preventive health behaviors in autistic adults remain under-researched. Studies investigating PA and SB in autistic adults frequently show methodological limitations, such as small sample sizes and the underrepresentation of individuals with co-occurring intellectual disability [11].

Gamified mobile apps hold promise for effectively promoting positive changes in PA and SB in autistic adults by leveraging their unique strengths in visuospatial learning and digital gaming [12-15]. It is well documented that technology particularly appeals to autistic adults because it provides a structured, consistent experience with lower social demands than face-to-face communication [13,16]. Gamified behavioral interventions delivered via smartphone apps have rapidly expanded the potential for improving health behaviors in a way that is engaging and cost-effective. The gamification approach can enhance a user's perception of autonomy, fostering intrinsic motivation and contributing to enjoyable experiences, which collectively sustain their engagement [17]. However, most evidence on the efficacy of gamification approaches in promoting free-living PA comes from studies involving typically developing young people, with a lack of rigorously designed empirical studies involving autistic populations [18]. Financial incentive–based apps have also emerged as a viable strategy for increasing PA and reducing sedentary time, particularly for individuals with low motivation for voluntary behavior change [19]. Although preliminary evidence suggests that such apps can improve PA and reduce SB in both autistic and nonautistic groups, questions remain about the long-term sustainability of these interventions. Early versions of gamified mobile health (mHealth) apps, such as PuzzleWalk v1, laid a significant foundation as innovative, strength-based interventions for autistic adults, but they did not yield long-term improvements in PA and SB changes in a small sample of autistic adults [20]. Existing mHealth interventions aimed at promoting PA often encounter pragmatic barriers, including difficulty of use, limited system integration, poor scalability, and lack of personalization, which can lead to reduced user engagement and adherence [21-23]. These challenges may be more pronounced for autistic adults who often face additional barriers related to sensory sensitivities and the need for structured routines and consistent feedback [4,7,8]. Furthermore, few efforts have been made to integrate community input during the design and development of mHealth apps [18]. This gap directly informed this study, which centers on the co-design of PuzzleWalk v2 to enhance both real-world usability and sustained engagement for autistic adults.

While most studies on PA have disproportionally focused on young adults (eg, 18-30 years old) without co-occurring intellectual disability, a substantial proportion of young autistic adults remains insufficiently active [11,24]. Current evidence on interventions designed to promote PA and reduce SB in autistic adults remains limited and is frequently characterized by poor methodological rigor in the development and evaluation of intervention strategies [11]. Gamified mHealth interventions represent a promising approach for facilitating positive PA and SB changes by leveraging the distinct strengths and preferences of autistic individuals. Addressing adoption challenges and evaluating the real-world applicability of gamified mHealth interventions are essential for improving preventive health behaviors within this community.

Study Aims

This paper presents a study protocol for the remote co-design and field-testing of a novel mHealth system, guided by gamification and behavior change theories. The overarching objective of this study is to develop an effective and sustainable mHealth intervention that promotes regular PA participation and reduces SB in autistic adults using a community-based participatory research approach. The study's specific aims are

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to (1) develop practical gamification strategies that promote PA and SB changes in autistic adults and (2) evaluate the feasibility and acceptability of the PuzzleWalk v2 mobile app in increasing free-living PA and reducing SB among autistic adults. Developed by the corresponding author's research team, PuzzleWalk v1 demonstrated the potential to induce short-term behavioral changes in a previous feasibility deployment study [20]. Building on these preliminary findings, this study will refine evidence-based design principles to promote sustained improvements in PA and SB in autistic adults, including those with and without mild intellectual disability.

Methods

Study Design

This study comprises 2 sequential phases: (1) online community-based participatory design workshops with autism community stakeholders (Phase I; completed) and (2) an 8-week field deployment of the PuzzleWalk v2 mHealth system in real-world settings (Phase II; in progress).

Phase I: Community-Based Participatory Design Workshop

The first phase involved weekly online design workshops with key community stakeholders, including 7 autistic adults, 1 parent or caregiver, and 1 speech therapist with over 15 years of experience working with individuals with ASD. These remote workshop sessions utilized individual interviews and online surveys to evaluate preferences and technology usage patterns, identify applicable gamification and behavior change strategies to enhance engagement and adherence, and review the app's previous (v1) and current (v2) functional prototypes. Specifically, the workshop sessions focused on (1) exploring technology-related factors that influence PA participation and prevalent SBs in autistic adults, (2) discussing the current features of PuzzleWalk v1 (eg, strengths, weaknesses, and opportunities for improvement), and (3) identifying best-practice intervention strategies to address challenges associated with autism symptoms and enhance user adherence during field deployment (Table 1). Meeting formats were adapted to accommodate the diverse needs and preferences of stakeholders based on the Academic Autistic Spectrum Partnership in Research and Education (AASPIRE) guidelines [25]. Data from interviews and surveys were analyzed using frequency and narrative data analysis methods. The core findings were shared with the software development team and iteratively incorporated into the PuzzleWalk v2 system. The multiformat co-design workshop guide provides the core questions and discussion prompts used throughout the participatory design phase (see Multimedia Appendix 1). Finally, pilot usability testing was executed with various iPhone models to ensure the app's technical compatibility and functionality before field deployment.

Table 1. Focused activities in community-based participatory design workshops.

Timeline	Activities	Format
Week 1	Screening interviews and general inquiry on demographics, patterns of PA[a] and SB[b], and overall health among key stakeholders with ASD[c]	Phone call or virtual meeting
Week 2	Exploration of preferences and patterns of general technology use and its influence on PA and SB among autistic adults	Survey or email
Weeks 3-4	Identification of factors influencing PA participation and perceived health benefits of PA	Survey or email
Weeks 5-6	Evaluation of the core features (eg, step-to-game conversion) and identification of areas for improvement in PuzzleWalk v1	Virtual meeting
3-month period	Integration of key findings into PuzzleWalk v2	Not applicable
Weeks 7-8	Autism-friendly intervention design and pilot compatibility and functionality testing of PuzzleWalk v2 in real-world settings[d]	Survey or email

[a]PA: physical activity.

[b]SB: sedentary behavior.

[c]ASD: autism spectrum disorder.

[d]5 stakeholders who own an iPhone participated in this activity.

Phase II: Field Deployment of PuzzleWalk v2 mHealth System

Autistic adults who consent to participate in this single-arm clinical trial (NCT06566131) will receive study materials via the United States Postal Service, including a research-grade accelerometer/monitor (ie, ActiGraph CentrePoint Insight wristwatch), a cable charger, and study instruction sheets. Participants will also receive visual guidelines for wearing the monitor and returning study materials. The monitor wear guide will instruct the participants to wear the monitor comfortably on their nondominant wrist during waking hours, removing it only for water-related activities such as showering or swimming. Each night before bed, participants will record their monitor wear time in their tracking log and remove the watch during sleep. Reminders will be sent to participants every 3 weeks to 4 weeks to ensure uninterrupted use per the manufacturer's recommendation for the monitor's charging. The return guide will instruct participants to return the study materials by placing the monitor, charger, and tracking logs in a provided Ziplock bag, sealing them in a prepaid Priority Mailbox, and mailing them back to the research team via United States Postal Service

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(see Multimedia Appendix 2). Upon receipt, the research team will confirm the return by text message or email.

Before baseline data collection, we will provide a ramp-up familiarization period to help participants understand the study protocol and requirements, and to ensure they are comfortable wearing the activity-tracking accelerometer on their nondominant wrist. Throughout the deployment period, the research team will use SimpleTexting to communicate regularly with study participants and to promptly respond to any questions they have. SimpleTexting is an SMS text messaging service provider that allows the research team to send mass text messages and engage in real-time conversations with participants. Field data collection will begin once the participant completes a demographic survey and confirms receipt of the study package. This includes gathering data on PA and sedentary time using ActiGraph CentrePoint Insight watches and app engagement (eg, time spent using the app and number of session logins) using Voyager, an open-source Laravel administration package (The Control Group). The Voyager database management system will enable the research team to monitor user engagement and manage user profiles in near real time. Specifically, this administration system will be used to identify participants' mobile devices and update their unique usernames on the leaderboard of PuzzleWalk v2. Starting week 3, participants will begin using PuzzleWalk v2, following a visual, step-by-step user guide, and continue using the app until the end of week 8 (total 6-week intervention). Outcome measures will be collected during 4 time periods: week 1 (baseline), week 3 (intervention start), week 5 (midintervention), and week 8 (intervention end). Periodic reminders and reinforcement messages, incorporating evidence-based behavior change techniques, will support their continued engagement with the app and PA participation (Figure 1).

Figure 1. Data collection flowchart in Phase II. PA: physical activity; SB: sedentary behavior.

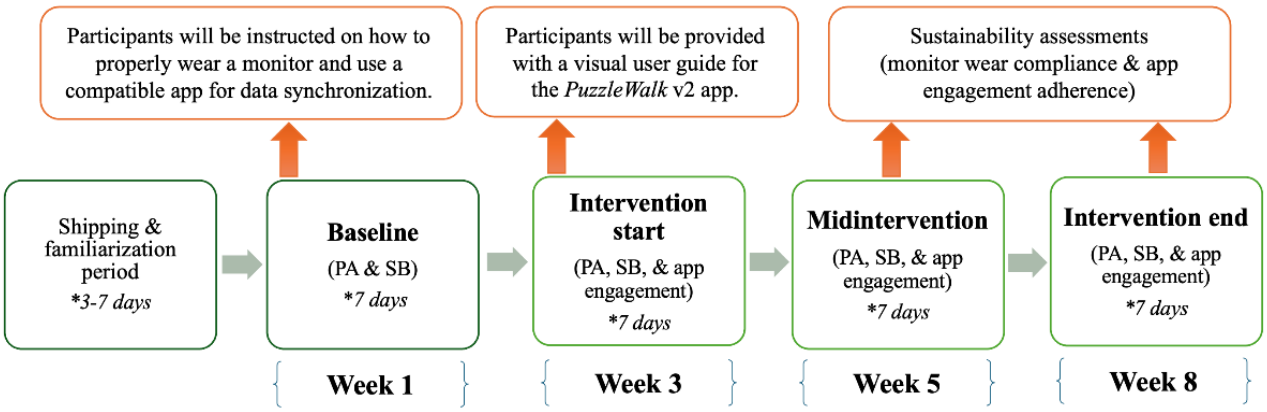

Sample and Recruitment Strategies

This pilot study acknowledges the potential for selection bias because individuals who volunteer for this PA-related study may already have a relatively high level of motivation to change their behavior. According to a priori power analysis using G*Power 3.1 [26], considering an α level of .05, an estimated effect size (f) of 0.2, an anticipated correlation of 0.4 among repeated measures, and 4 measurement levels of within-subjects factors, we project a total sample of 55 autistic adults to achieve a power of 0.9. To be eligible, prospective participants must (1) be adults aged 18 years to 55 years, (2) have received a formal diagnosis of ASD from a qualified medical professional, and (3) own and regularly use a compatible iPhone (iOS 14+ operating system). Android version development is underway, and its users will be invited to participate in future clinical trials. Individuals with moderate-to-profound intellectual disability or orthopedic conditions that significantly interfere with independent information processing or ambulation (eg, using a wheelchair or crutches) will be excluded from the study. These individuals may encounter challenges in engaging with the cognitive and physical aspects of the intervention, such as understanding verbal or written instructions, independently using the app, or meeting study requirements (eg, returning study materials to the research team). Therefore, only individuals who live semi-independently or independently, have autonomy for daily living, and are capable of making their own research-related decisions will be given an informed consent form to sign and subsequently invited to participate in the study. Future research shall explore adaptation strategies to make the mHealth interventions more accessible to a broader autistic population, including those with co-occurring moderate-to-profound intellectual disability.

All participants will provide written or digital consent before participating in study activities. The research team established a multisource recruitment model that leverages national and regional autism advocacy organizations (eg, Autism Speaks, Autism Delaware), Simons Foundation Powering Autism Research for Knowledge (SPARK) research match services, ResearchMatch.org, and online autism support groups on social media (eg, Reddit and Facebook). The study flyer will be posted on the Autism Speaks research search portal (*approval pending*), ResearchMatch.org (*approved*), and relevant group pages on social media channels (eg, Autism Delaware Facebook page; *approved*). Individuals interested in participating in the study can contact the research team directly and undergo a screening interview to verify their eligibility. SPARK's research match service (*approved*) will identify potential participants based on study criteria and send them study invitations. Our research team will be provided with the diagnostic and contact information of those who consent. Individuals recruited through other channels will undergo a screening interview to confirm

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their eligibility. The interview will explore details about when and how the ASD diagnosis was made, as well as common autism symptoms. Based on the results from preliminary studies [20,27,28], we expect to recruit all eligible participants within the first 3 months of the study using this multisource recruitment model.

Ethical Considerations

The study was reviewed and approved by the University of Delaware Institutional Review Board (IRB #2098388), with all procedures adhering to institutional and national ethical standards for research involving human participants. In Phase I, which has been completed, all participants provided written or digital informed consent before engaging in remote community-based design workshops and usability testing. Only individuals with sufficient cognitive and communicative capacity to provide autonomous consent were enrolled. Data collected during this phase were de-identified prior to analysis, and any identifiable information, such as email addresses, was promptly destroyed following data collection. Participant privacy was protected using encrypted communication protocols and secure data storage systems accessible only to authorized personnel, such as the principal investigator and their research assistants.

Phase II, the ongoing field deployment, involves similar ethical safeguards. Participants provided informed consent prior to receiving study materials, including accelerometers and study instructions. They were fully briefed on the study protocol and expectations. Participants are being compensated with a US $100 Amazon e-gift card upon verified completion of study requirements, including consistent accelerometer wear and tracking log submissions over the 8-week data collection period. Additional incentives in the form of e-gift cards are offered to top performers on the app's gamified leaderboard to encourage engagement. All data collected during this phase continue to be anonymized and securely managed through access-controlled systems. No identifiable participant images or information will be included in future manuscripts or supplementary materials.

PuzzleWalk mHealth System

PuzzleWalk is a gamified, behavior change theory–guided mobile app designed to promote regular PA participation among autistic adults by leveraging practical behavior change techniques and principles of self-determination theory [12,20,28]. Key innovative features include a step-to-game conversion algorithm, which translates users' daily step counts into time for solving image-based puzzle games, highlighting iconic cityscapes from around the world. This user-centered design builds on the strengths of autistic individuals in visual learning and fosters intrinsic motivation through autonomy, relatedness, and competence. To achieve these core elements of self-determination theory, PuzzleWalk incorporates self-monitoring of step counts to support autonomous app engagement, visual puzzle games, contingent rewards to enhance competence, and a competition-based leaderboard and shared goals to foster relatedness among autistic users. PuzzleWalk v2 builds on the original version through iterative design enhancements guided by feedback from key stakeholders during the participatory workshop phase. A major advancement in PuzzleWalk v2 is the inclusion of improved accessibility features, such as step-by-step visual guides, simplified interface navigation, and animated icons and buttons to enhance user-friendliness. Another key improvement from v1 to v2 is the introduction of a gamified goal-tracking feature that uses a quest-based design, allowing users to unlock puzzle rewards by reaching step count milestones (Figure 2). The leaderboard scores are determined by combining accumulated step counts and puzzle points. Top scorers on the leaderboard are eligible to receive tangible incentives (eg, Amazon e-gift cards) at the end of each month. Importantly, the PuzzleWalk system automatically resets leaderboard scores at the end of each month to encourage consistent PA engagement among users. Detailed descriptions of the PuzzleWalk v1 system can be found in previous studies [20,28].

Figure 2. Functional interfaces of PuzzleWalk v2.

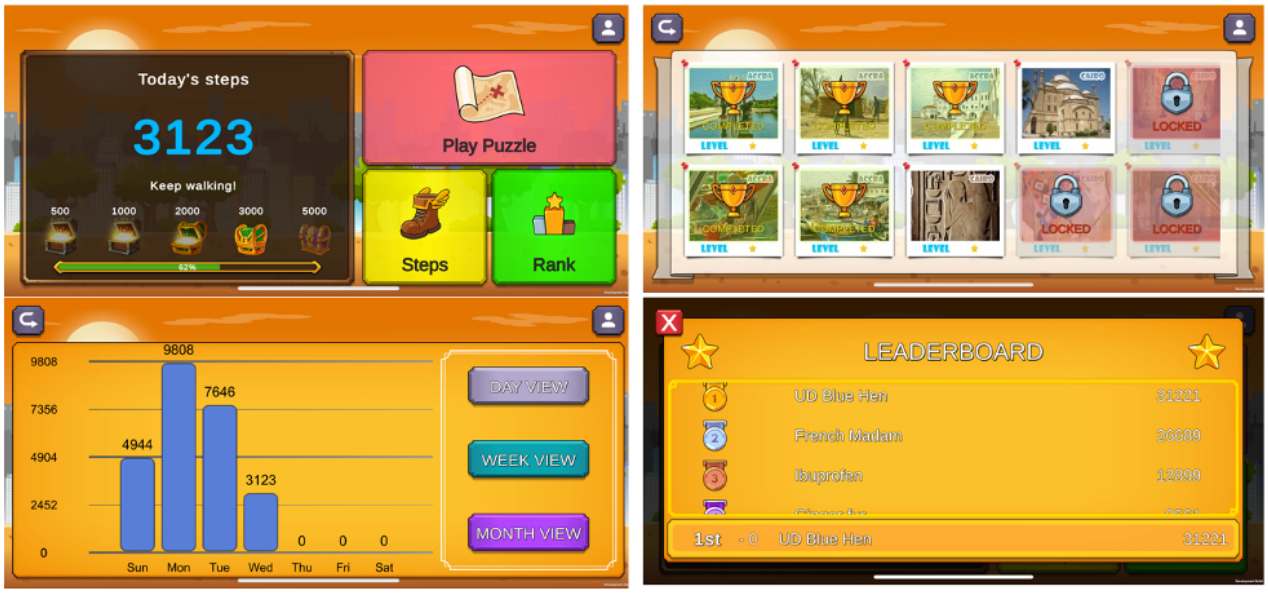

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PA and SB Assessment

PA, including daily step counts, light PA, and MVPA, as well as sedentary time, will be measured using research-grade CentrePoint Insight Watches (ActiGraph). Triaxial accelerometers by ActiGraph have been widely used to provide objective assessments of PA and sedentary time, demonstrating moderate-to-high reliability across diverse clinical populations [29]. All participants will wear an accelerometer on their nondominant wrist during waking hours, except during water activities. They will be instructed to continuously wear an accelerometer for 7 consecutive days, capturing behavioral data from at least 3 weekdays and 1 weekend day across the 4 data collection intervals (ie, weeks 1, 3, 5, and 8). Compliance will be supported through regular check-ins and reminders.

Accelerometers will be programmed to collect data in 60-second epochs. Levels of activity intensity and sedentary time will be classified using activity counts per minute (CPM) cut point values: sedentary (<2860 CPM), light PA (2860-3940 CPM), and MVPA (≥3941 CPM) [30]. These cut point thresholds, established by Montoye et al [30], underwent cross-validation in both structured laboratory and free-living conditions with adults. A valid day will be defined as a minimum of 10 hours of accelerometer wear time a day. To be included in the data analysis, participants must have at least 3 valid days of accelerometer wear during each data collection period [31]. Despite the absence of a definitive consensus on the required number of valid days, previous research commonly accepts 3 days to 4 days as adequate for reliable estimation of one's general patterns of PA engagement [32,33]. Nonwear time will be defined as 90 minutes of consecutive zero activity counts, with a 2-minute spike tolerance [34]. The accelerometers will be programmed to record PA and sedentary time at a default sampling frequency of 32 Hz. The CentrePoint cloud portal will streamline management and initial analysis of accelerometry data through a manufacturer-provided mobile app (ie, CentrePoint Connect app). Given the project's timeline, participants will be required to install the app on their devices to remotely synchronize accelerometry data and prevent data loss before the device storage capacity (ie, 30 days or 512 MB) is reached. Processed raw accelerometry data will be securely managed and stored in the customizable CentrePoint cloud, and the research team will have a real-time overview of participant compliance (eg, at least 10 hours of accelerometer wear per day), data outcomes, and overall study progress.

App Engagement Assessment

The level of user engagement in the PuzzleWalk intervention will be measured through a Laravel-based backend system, which uses the Voyager administration system for data visualization and management (eg, frequency and duration of app use, step counts, and puzzle points). Time spent on the app in a minutes-per-day format will be calculated to represent each participant's level of user engagement. These app engagement metrics will be aligned with accelerometer-derived PA and sedentary time to explore how engagement levels relate to daily behavior patterns. Although the study does not include a control group, a 7-day baseline measure will enable within-subject comparison over time. Additional sensitivity analyses will examine how variations in app engagement influence behavioral outcomes during the intervention period. Only activities related to the PuzzleWalk app will be accessed by the software developer and corresponding author as a principal investigator. Any identifiable information, such as email address, will be destroyed immediately upon completion of data collection to ensure participant confidentiality. Follow-up interviews will be conducted after the intervention ends to explore participants' perceived acceptability, individual experiences (eg, satisfaction challenges), and factors that may have contributed to (dis-)continuation of the app use during and beyond the study. To secure and facilitate dataflow in the PuzzleWalk system, the user authentication process using Apple ID (ie, account credentials) will involve several key steps. First, the user initiates authentication through their Apple ID on the PuzzleWalk app. The app then obtains an authentication token from Apple, and forwards it to the backend server for verification with Apple's authentication system. Once the token is verified, the backend server generates a session token, enabling the app to access the server application programming interface (API). This session token will facilitate secure API communication, allowing the backend server to interact with the database in real time and manage user requests efficiently (see Figure 3).

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Figure 3. PuzzleWalk system dataflow. JSON: JavaScript Object Notation; JWK: JSON Web Key.

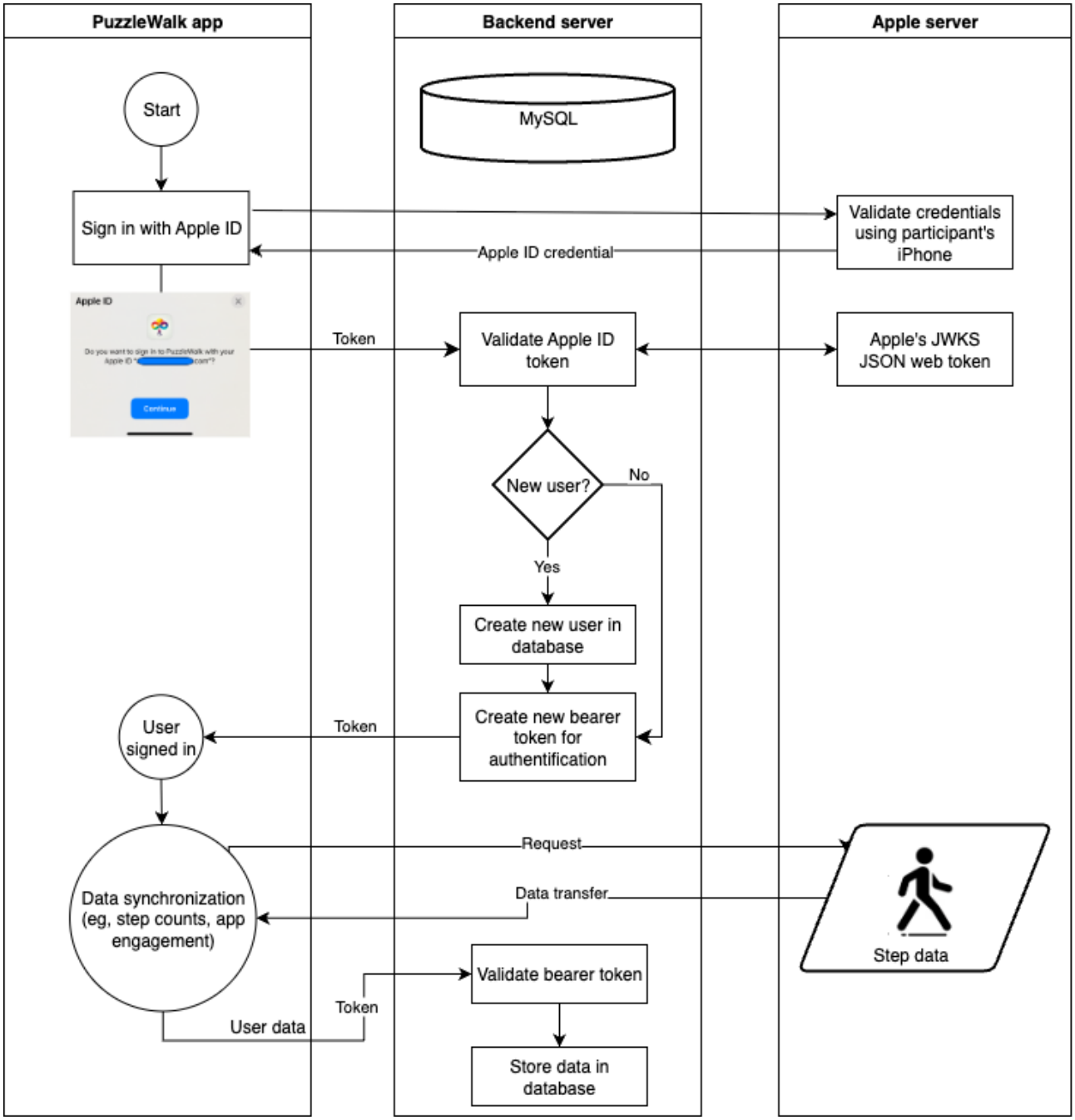

Data Analysis

Accelerometry data will be systematically analyzed by inspecting ranges and addressing missing values in accordance with the previously outlined validation protocol. The raw accelerometry output will be transformed into CPM values and processed using ActiLife software (ActiGraph). To account for the typical lifespan of mHealth interventions (eg, ≤3 months) [35], an intention-to-treat approach will be applied to ensure external validity. Baseline comparisons between autistic adults with and without mild intellectual disability, as well as between male and female autistic adults, will be conducted using independent *t* tests and chi-square tests. We will perform repeated measures ANCOVA to examine the changes in participants' objective levels of PA and sedentary time before, during, and after the 6-week intervention, adjusting for baseline characteristics, including age, sex, mild intellectual disability, and BMI. Bonferroni post hoc tests will be performed if a significant difference is found between time points. Dependent variables will include light PA, MVPA, sedentary time (minutes per day), MVPA in bouts of >10 minutes per day, steps per day, and user engagement (eg, number of app login sessions and time spent on app use per day). Independent variables will be each time point and intervention. Pearson correlation analyses will be used to examine the relationship between the levels of PA, sedentary time, and user engagement during the intervention period. We will perform data analyses using SPSS v29 (IBM Corp), and the significance level will be set at $P<.05$ (2-tailed).

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Results

Phase I of the project, community-based participatory design workshops (n=9; 4/9, 44% women) was recently concluded. The findings revealed that key autism stakeholders highly valued the app's self-monitoring and step tracking feature, leaderboard, and visual design. These features were perceived to enhance their perceived motivation for PA engagement and fostered a sense of friendly competition among users. Most stakeholders indicated that the app helped increase PA, reduce SB, and provide a sense of achievement. Autistic traits such as perfectionism and competitiveness reportedly influenced the level of engagement, sometimes enhancing motivation but occasionally causing discouragement due to the difficulty of the puzzle games. Overall, the app was viewed as a potentially beneficial tool for promoting PA and reducing SB in autistic adults (see Table 2). Data collection for Phase II of the project, which involves field deployment (approximate n=70), is currently underway and is expected to be completed in August 2025. As of July 2025, we enrolled 69 participants in the study. The results of this study will be shared in a subsequent publication.

Table 2. Key findings of community-based participatory design workshops.

Activities	Key findings
Screening interviews and general inquiry on demographics, patterns of PA[a] and SB[b], and overall health among community stakeholders with autism	1. Most autistic collaborators were diagnosed with ASD[c] during their early childhood by a medical professional and preferred communication via text messaging or email. 2. Walking was the most preferred form of PA participation among collaborators with autism, but its frequency varied from "rarely" to "four times a week."
Exploration of preferences and patterns of general technology use and its influence on PA and SB among autistic adults	1. Health-related mobile apps were generally seen as frustrating or unengaging due to complex interfaces or a lack of engaging features. Feedback highlighted the need for more intuitive functionality and fewer notifications. 2. When it comes to gaming mobile apps, collaborators with autism tended to prefer simple or classic games rather than complex or time-intensive ones. 3. Most collaborators with autism used their smartphones at home or work and typically kept them in a pocket when walking.
Identification of factors influencing PA participation and perceived health benefits of PA	1. Motivation factors for PA among collaborators with autism varied, ranging from social support provided by family members or therapists to using PA as a means to reduce stress and anxiety. 2. Perceived barriers included low stamina, preference for sedentary activities (eg, watching TV or using social media), and mental health challenges or overthinking. 3. Most collaborators acknowledged the health benefits of PA, particularly its positive effects on physical and mental well-being, as most indicated that they felt happier, healthier, and more fulfilled after engaging in PA.
Evaluation of the core features and identification of areas for improvement in PuzzleWalk v1	1. Several collaborators suggested adding more puzzle levels and variety to keep the app more engaging. 2. Overall concept (eg, taking steps to play puzzle games) and competitive aspects of the app (eg, leaderboard) were viewed as strengths. 3. Few collaborators recommended incorporating quest-based milestones for unlocking puzzles and intuitive reward systems to motivate continued PA engagement.
Autism-friendly intervention design and pilot compatibility and functionality testing of PuzzleWalk v2 in real-world settings	1. All 5 collaborators who owned an iPhone during the study successfully installed and tested the app on their devices without any functional issues. 2. Although collaborators appreciated the reward-based system, leaderboard, and step tracking features, 2 of them found the puzzles too challenging, which reduced their perceived enjoyment and continuation desire. 3. According to user feedback, collaborators felt the app effectively promoted self-monitoring of PA and provided a sense of community (eg, competing with other autistic users on the leaderboard) and motivation to be more active during the testing period.

[a]PA: physical activity.

[b]SB: sedentary behavior.

[c]ASD: autism spectrum disorder.

Discussion

This paper outlines the research protocol for developing and field-testing PuzzleWalk v2, a novel mHealth system designed to promote regular PA and reduce SB in autistic adults with and without mild intellectual disability. The system uses gamification and evidence-based behavior change strategies developed with key autism stakeholders. The protocol establishes a structured methodology for the co-design process and remote deployment of a gamified mHealth intervention that can be scalable in real-world settings. By incorporating community input into the app's refinement and using replicable, remote data collection methods, this study is positioned to yield critical insights into behavior change strategies and underlying mechanisms among autistic adults. The detailed procedures and supporting resources provided in this paper lay a strong foundation for future evaluation and broader dissemination of tailored digital health interventions for individuals with ASD.

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It is anticipated that high user engagement with PuzzleWalk v2 will be associated with increased MVPA, higher step counts, and reduced sedentary time among participants with ASD in Phase II.

It is important to note that the vast majority of autism research has focused on understanding the pathology, etiology, and symptoms of this condition with little attention to helping autistic adults live healthy lifestyles [36]. There are limited data on the preventive health behaviors of autistic adults measured by objective and reliable wearable devices in a real-world context [11]. Previous findings on objectively measured PA and SB in individuals with autism have been interpreted with caution because of the small sample sizes with moderate-to-low statistical power [11]. Due to the lack of dedicated surveillance systems, autistic adults who live semi-independently, with and without mild intellectual disability, have not been precisely monitored, as they are mostly not affiliated with community organizations or public school systems [3]. Identifying effective recruitment strategies to upscale the sample size and verifying the feasibility of remote intervention delivery methods are major strengths of this protocol.

Given the prevalent social and sensory challenges, traditional face-to-face PA interventions in community-based public settings may not be a sustainable behavior change model nor an effective strategy for autistic adults [37,38]. Due to the complexities of the intervention delivery and assessment protocols, the existing evidence is insufficient to confirm that traditional exercise interventions lead to long-term improvements in PA levels in this population [11]. Although the benefits of regular, face-to-face PA participation are well-documented, it is critical for researchers, educators, and service providers to diversify the PA options for autistic adults by creating environments that are inclusive, relevant, and sensitive to their needs and preferences [15,39]. While mobile technology research has made significant progress in improving the life skills of autistic individuals (eg, social and communication skills) [40], only a few technological attempts have been made to address PA engagement issues in this population. Gamification strategies have emerged as a viable approach for enhancing PA levels and reducing sitting time, especially in those with low intrinsic motivation for voluntary behavior changes [19,41]. However, research on the practicality of this gamification approach in mHealth interventions remains in its early stages and is not yet fully understood for autistic adults, who may have unique preferences, motivational factors, and barriers to behavior change [15]. In addition, mHealth-guided behavior change interventions generally result in only short-term participant engagement [42]. Rigorous empirical research is essential to develop replicable and comprehensive interventions grounded in evidence-based frameworks and to promote sustainable PA behavior changes for autistic adults [15].

Historically, autism research has often misrepresented the autism community by excluding individuals with ASD from the research process, using outdated or stigmatizing language, and prioritizing research agendas that may not align with autism community values [25,43]. In response to the increasing demand for collaborative autism health research, this study used community-based workshops to identify achievable strategies for mHealth-guided PA and SB changes. Subsequently, these workshops also informed the gamification design aesthetics for tailoring the intervention to the needs of autistic adults. To establish alignment between the research team and key autism stakeholders, we leveraged the practical guidelines for collaborative autism research, informed by AASPIRE [25]. The results of the field deployment study (Phase II) will be shared with the workshop participants, and their additional input will be sought to refine the intervention protocol for future clinical trials with a control group (eg, longitudinal randomized controlled trials).

A limitation of this study is the restriction of eligibility to iPhone users, which may introduce sampling bias. Although an Android version of the app is currently in development, this criterion may exclude individuals who cannot afford iPhones or prefer Android devices. Consequently, a significant portion of autistic adults, particularly those with financial constraints or differing technology preferences, may be underrepresented. Therefore, future work should focus on expanding and evaluating PuzzleWalk v2 across a wide range of smartphone brands and models to enhance accessibility and scalability. Given that individuals who choose to participate in this game-oriented mHealth study may have a greater interest in or familiarity with mobile gaming, the use of a robust recruitment strategy and inclusion of a diverse and adequately powered sample are expected to reduce sampling bias and to enhance the generalizability of the findings. Study results will be disseminated through various channels, including scholarly conference presentations and peer-reviewed publications. Furthermore, findings from this study will guide the continued refinement of the PuzzleWalk system, with the long-term goal of facilitating its future public release and broader implementation. Future research should also explore the influence of community-level factors on the successful implementation of PA intervention strategies. Given the importance of ecological validity in PA research [44], community-level factors, including associability and affordability of community resources, social support networks, and environmental conditions that facilitate PA participation, should be considered in designing and evaluating PA interventions for autistic adults.

Conclusions

The PuzzleWalk app demonstrates its usability as an innovative tool for enhancing both PA motivation and intervention engagement through tailored gamification and behavior change strategies. The results of our ongoing field deployment study will clarify the app's effectiveness and real-world applicability in promoting PA and reducing SB in autistic adults.

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Authors' Contributions

DL, LM, and AB contributed to conceptualization. DL, LM, and SK performed data curation and formal analysis. DL and LM wrote the first draft. DL, LM, SW, MLM, VV, IO, and RS contributed to writing, reviewing, and editing. DL and AB performed supervision. DL handled project administration. DL, AB, IO, and RS handled funding acquisition. All authors read and agreed to the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Multi-format Co-Design Workshop Guide.
[DOCX File , 29 KB - resprot_v14i1e71631_app1.docx]

Multimedia Appendix 2
Monitor wear and return guidelines.
[PDF File (Adobe PDF File), 1433 KB - resprot_v14i1e71631_app2.pdf]

Multimedia Appendix 3
Peer review report by the Autism Intervention Research Network on Physical Health and the University of Delaware's Maggie E. Neumann Health Sciences Research Fund.
[PDF File (Adobe PDF File), 1588 KB - resprot_v14i1e71631_app3.pdf]

Multimedia Appendix 4
SPIRIT Checklist.
[DOCX File , 44 KB - resprot_v14i1e71631_app4.docx]

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Abbreviations

AASPIRE: Academic Autistic Spectrum Partnership in Research and Education
API: application programming interface
ASD: autism spectrum disorder
CPM: counts per minute
mHealth: mobile health
MVPA: moderate-to-vigorous physical activity
PA: physical activity
SB: sedentary behavior
SPARK: Simons Foundation Powering Autism Research for Knowledge

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Protocol

An AI-Based Telerehabilitation Solution to Improve Mobility in People With Multiple Sclerosis (the PLATINUMS Project): Protocol for an Implementation and Evaluation Study

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Abstract

Background: Multiple sclerosis (MS) is a chronic, progressive, and neurodegenerative disease affecting more than 2.8 million people globally. Mobility impairments are among the most significant challenges faced by people with MS, leading to physical inactivity, deconditioning, and disability progression (for some, even irreversible disability). This negatively impacts mental health, social participation, and quality of life while placing a considerable economic burden on society. Exercise can improve mobility and mitigate disability progression, but facility-based options are often inaccessible, especially for those in remote areas. Telerehabilitation offers a promising alternative, but current systems are limited by complexity and hardware requirements.

Objective: The PLATINUMS (Implementation of an Advanced Telerehabilitation Solution for People With Multiple Sclerosis) project proposes an AI-driven telerehabilitation system to deliver accessible, cost-effective, and home-based exercise therapy for people with MS.

Methods: The PLATINUMS project begins with working package (WP) 1, focusing on obtaining ethical approval and recruiting staff. Following this, WP2 involves a 4-week system feasibility and usability study (n=40) to assess and refine the digital platform. WP3 comprises a validity study (n=60) to evaluate remote mobility tests via the system, such as the Short Physical Performance Battery (SPPB), functional reach, and sit-to-stand tests, to ensure their reliability for use in WP4, the feasibility multicenter randomized controlled trial (RCT). The 10-week multicenter feasibility RCT will be conducted in MS centers across Denmark, Ireland, Israel, and Italy, with 96 participants varying in disability levels. The primary objective is to evaluate the efficacy of the AI-powered telerehabilitation system on mobility outcomes compared to usual care. Finally, WP5 will assess the cost-effectiveness of the telerehabilitation system by analyzing implementation costs, adherence, and use of health care. The PLATINUMS project aims to revolutionize exercise therapy for people with MS by demonstrating the feasibility, validity, and preliminary efficacy of the AI-driven telerehabilitation system. This approach addresses barriers such as accessibility, privacy, and standardization while promoting patient and therapist acceptance.

Results: Funding for the PLATINUMS project was obtained in February 2024. WP2 data collection began in April 2025 across 4 European sites. WP3 is scheduled to launch in July 2025, with WP4 (the feasibility RCT) planned for January 2026. Initial WP2 results are expected by October 2025, with first publications anticipated in mid-2026.

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Conclusions: The PLATINUMS project is expected to generate critical insights into the feasibility, usability, and preliminary efficacy of an AI-based telerehabilitation system for people with MS. By leveraging widely available technology and real-time feedback, the system addresses key barriers to traditional rehabilitation. Findings from this protocol may inform future large-scale trials and support the broader implementation of digital health solutions in neurological rehabilitation.

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KEYWORDS

multiple sclerosis; telerehabilitation; mobility; feasibility study; randomized controlled trial; remote exercise; validation; cost-effectiveness

Introduction

Multiple sclerosis (MS) is a chronic and progressive disease of the central nervous system that affects more than 2.8 million people worldwide (35.9 per 100,000 people) [1]. One of the most common problems reported by people with MS is impaired mobility, specifically the inability to walk safely and independently [2,3]. Approximately 85% to 90% of people with MS report difficulties with mobility during the disease course [4], and these difficulties can commence very early after onset [5,6]. Due to progression of the disease, most people with MS will eventually require a walking aid (ie, a cane or walker) [7], and in some more severe cases, mobility is possible only by using a wheelchair or scooter [8]. Decreased mobility is, in part, also caused by reductions in physical activity [9], likely mediated through deconditioning of different physiological systems (eg, the cardiorespiratory system) [10]. At some critical points, mobility is limited to such an extent that there is an irreversible disability, resulting in secondary health conditions that are difficult, if not impossible, to treat [11]. This progression of disability also impacts mental health, which further contributes to decreased social, recreational, and vocational participation in society and ultimately results in a poor quality of life [12]. The decrease in participation and work productivity, in combination with an increase in secondary health conditions and medical needs, significantly impacts the global economy worldwide [13,14]. Since MS is the leading cause of disability in young and middle-aged adults, maintaining mobility is essential. Therefore, measures to combat or reverse this downward spiral and progression of disability must be developed and implemented to reduce the burden of this disease.

Exercise can improve mobility and perhaps decrease the rate and extent of disability (ie, impaired physical function) in people with MS [15,16]. Exercise programs based in hospitals and clinical facilities, particularly among other people with MS or under the supervision of MS experts, may help people with MS participate in exercise or exercise at a higher, more intense level [17]. However, a lack of access to these programs, especially for those who live in remote areas where there are few options or where there are health care and medical facilities but no MS experts, may make it difficult to engage in facility-based exercise training programs [18-20]. The COVID-19 pandemic highlighted the need to find alternative solutions to increase exercise and physical activity in the population with MS. In a series of studies involving members of the present consortium, we reported that physical activity and exercise activities, especially at moderate and high intensities, decreased during the pandemic in people with MS [21,22]. Moreover, the research consortium has strongly concluded that to ensure the continuity of exercise training for people with MS during future pandemics, health care stakeholders should be highly encouraged to provide training via advanced remote technologies concurrently with professional guidance and support [23].

Telerehabilitation has excellent potential for providing accessible and cost-effective options for exercise in the home environment for people with MS, particularly if there is ongoing communication with knowledgeable exercise personnel who ensure that exercise is carried out safely and optimally (ie, required movements are performed correctly). However, only a few studies have tested the capability of telerehabilitation to increase exercise and physical activity participation in people with MS, with some encouraging results [24-26]. Nevertheless, despite the advantages associated with the use of telerehabilitation, several limitations still exist that prevent the use of this technology on a large scale. In particular, most commercially available solutions do not provide feedback when the patient does not perform the exercise correctly or require special hardware (eg, movement sensors) that can be hard to set up for nonexpert users [27].

In this project, we intend to implement cutting-edge artificial intelligence (AI) technology designed by WizeCare [28] for a home-based exercise therapy program for people with MS. One of the advantages of this system is its technical simplicity. The system requires only a mobile phone, tablet, or personal computer and has no need for additional third-party hardware. This feature is essential for people with MS with low digital literacy [29]. Moreover, the technology incorporates an AI algorithm that calculates the range of motion and movement speed based on acquired videos of the user performing a specific exercise, enabling real-time feedback and positive encouragement during practice. Lastly, the system includes over 800 exercise drills classified according to targeted body regions and aspects of treatment (ie, flexibility, strength, or coordination) that the therapist can customize to create a personalized exercise program according to each patient's goals and needs. Notably, the telerehabilitation system has been implemented in numerous health care services with thousands of users (mainly in orthopedic rehabilitation) and has yielded encouraging results in conjunction with positive feedback from patients, physical therapists, and stakeholders. Nonetheless, it has never been systematically tested in the population with MS.

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Therefore, our overall goal is to implement an innovative telerehabilitation exercise training system for people with MS by assessing its efficacy in improving mobility. For this primary aim, we propose a pilot multicenter randomized controlled trial (RCT) in established MS centers across the European Union community in Italy, Ireland, and Denmark, as well as in Israel, to establish trial feasibility and to compare exercise delivery via telehealth with usual care. Further innovative aims of the project include (1) assessing the impact of a telerehabilitation exercise training program on mood and quality of life; (2) validating a set of remote mobility clinical tests delivered via the telerehabilitation system to evaluate balance and functional mobility in people with MS; and (3) examining the cost-effectiveness and value of the telerehabilitation exercise intervention program for people with MS. This information is scarce in the treatment of people with MS.

Ultimately, the knowledge obtained from this research will be relevant not only for people with MS; it is expected to also be of great value in understanding the most helpful way to deliver the benefits of home-based exercise therapy to other vulnerable populations, including many older adults who may appear healthy but are not, and others with neurological impairments (eg, stroke or Parkinson disease).

Methods

Overview

Our main objective is to collect evidence to facilitate the implementation of an innovative AI telerehabilitation exercise training system in MS clinical practice. After the completion of working package (WP) 1, which focuses on obtaining ethical approval and recruiting staff, our first objective (WP2) will be to investigate the usability and feasibility of the WizeCare system in MS centers in 4 European countries, encompassing a range of people with MS with varying disabilities and demographics. The second objective (WP3) will be to develop and psychometrically test a range of mobility measures collected by the telehealth system. The third objective (WP4) will be to compare exercise delivered via telehealth with usual care. The primary outcome will be trial feasibility, with preliminary efficacy for mobility, mental health, social participation, and quality of life outcomes. The fourth objective (WP5) will be to conduct an economic evaluation of exercise program delivery via telehealth compared with in-person care. The final objective will be to work collaboratively with clinicians, policymakers, and people with MS and to widely disseminate the knowledge generated by this program to optimize implementation. Figure 1 presents the WPs of the PLATINUMS (Implementation of an Advanced Telerehabilitation Solution for People With Multiple Sclerosis) project, while Table 1 illustrates its expected timeframe.

Figure 1. PLATINUMS (Implementation of an Advanced Telerehabilitation Solution for People With Multiple Sclerosis) project overview based on working packages (WPs). DMSH: Danish Multiple Sclerosis Hospitals; FAIR: findable, accessible, interoperable, and reusable; RCT: randomized controlled trial; TAU: Tel Aviv University; UC: University of Cagliari; UL: University of Limerick.

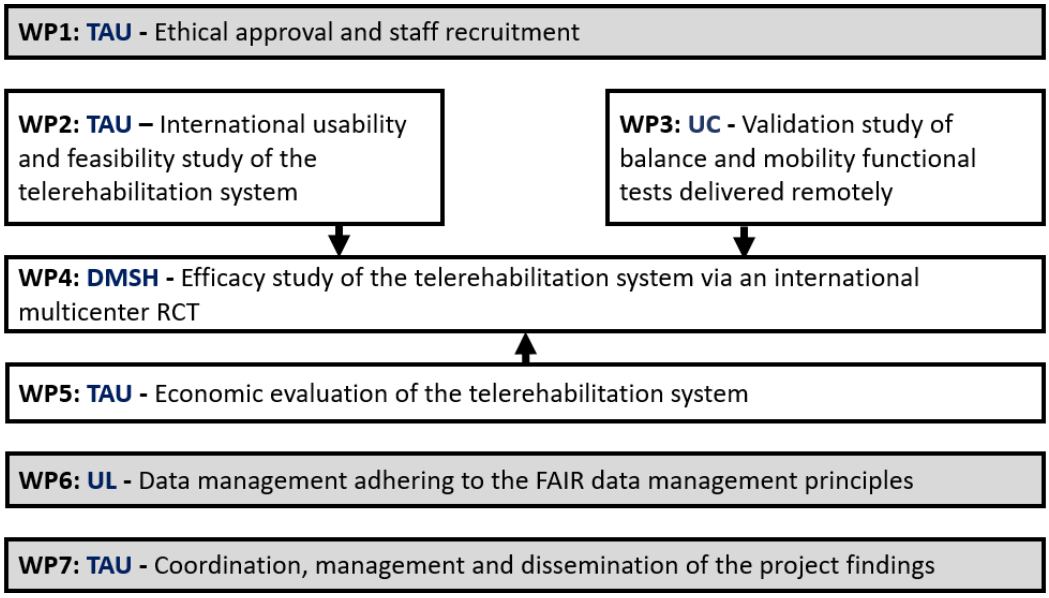

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Table 1. PLATINUMS (Implementation of an Advanced Telerehabilitation Solution for People With Multiple Sclerosis) Gantt chart describing each working package (WP) and task (T).

	Year 1				Year 2				Year 3			
	Q1	Q2	Q3	Q4	Q5	Q6	Q7	Q8	Q9	Q10	Q11	Q12
WP1: Ethical approval, staff recruitment	✓											
WP2: International usability and feasibility study of the telerehabilitation system		✓	✓	✓	✓							
T2.1. Installation of the telerehabilitation system, including private data security and cloud data management		✓										
T2.2. Harmonization between staff members operating the telerehabilitation system and intervention program		✓										
T2.3. Testing the system on a small group of participants for feasibility (patient/therapist), integrity, security, and proper transfer of data			✓	✓	✓							
WP3: Development and validation study of balance and mobility functional tests delivered remotely		✓	✓	✓	✓	✓						
T3.1. Development of mobility assessment tests to be delivered remotely via the telerehabilitation system		✓	✓									
T3.2. Establishing reliability and validity of the remote mobility tests			✓	✓	✓	✓						
T3.3. Developing standardized instructions and training materials						✓						
WP4: Efficacy study of the telerehabilitation study via a pilot multicenter RCT[a]						✓	✓	✓	✓	✓	✓	
T4.1. Coordination between staff members operating the intervention programs and blind assessors on all procedures related with the outcome measures						✓						
T4.2. Implementation of intervention programs						✓	✓	✓	✓	✓		
T4.4. Data analysis of remote and clinical outcome measures										✓	✓	
T4.5. Assessing adherence to and satisfaction with (among participants/therapists) the telerehabilitation intervention program										✓	✓	
WP5: Economic evaluation of the telerehabilitation system						✓	✓	✓	✓	✓	✓	
T5.1. Identifying the perspective of the economic evaluation and finalizing the specific study questions in terms of economics						✓						
T5.2. Identifying all the costs associated with the implementation of the telerehabilitation system and intervention program						✓						
T5.3. Following costs of the RCT and identifying all the benefits of the telerehabilitation system and intervention program						✓	✓	✓	✓	✓		
T5.4. Cost-effectiveness (cost-utility) analyses											✓	
TS.5. Interpretation and reporting of results												✓
WP6: Data management adhering to the FAIR[b] data management principles	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
WP7: Coordination, management, and dissemination	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
17.1. Dissemination of project findings							✓	✓	✓	✓	✓	✓
Meetings	F[c]	O[d]	O	O	O	F	O	O	O	O	O	F

[a]RCT: randomized controlled trial.

[b]FAIR: findable, accessible, interoperable, and reusable.

[c]F: face-to-face.

[d]O: online.

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Research and Innovation Questions

This innovative project will include 5 key research questions (RQs), which we propose will fill in the gaps in our current knowledge.

RQ1 (WP2) is as follows: In people with MS, what is the usability and feasibility of an advanced telerehabilitation system in facilitating remote exercise training? Qualitative and quantitative measures will be used to evaluate the usability and feasibility of the telerehabilitation system in 4 countries. Following necessary system upgrades and adaptations, findings will be incorporated into the feasibility multicenter RCT (WP4). Based on data from other patient populations, we hypothesize that the innovative telerehabilitation system will score highly for usability and feasibility among the participants with MS.

RQ2 (WP3) is as follows: In people with MS, are scores provided by clinical mobility tests obtained via tele-rehabilitation valid and reliable? Evidence for remote mobility evaluation does not currently exist for people with MS. We will evaluate 5 tests developed from commonly used clinical measures. We hypothesize that innovative remote mobility tests will demonstrate good-to-excellent validity and reliability.

RQ3 (WP4) is as follows: In people with MS, is a large multicenter RCT possible, and can it show preliminary efficacy of an individualized exercise program delivered via telerehabilitation to improve mobility compared with in-person physical therapy? An international pragmatic multicenter feasibility RCT will be conducted to compare the effectiveness of delivering the individual exercise program via telerehabilitation versus in person by a physiotherapist. We hypothesize that both exercise intervention programs will improve mobility in people with MS; however, nonsignificant differences in mobility outcome measures between groups (telerehabilitation vs usual care) will be demonstrated.

RQ4 (WP4) is as follows: In people with MS, does an individualized exercise program delivered via telerehabilitation have a comparable effect on mood and quality of life (QoL) compared with standard physical therapy (facility based)? This RQ will be answered in the planned international multicenter feasibility RCT, preceded by a feasibility and usability study. Consequently, our hypothesis is that mood and QoL will be improved in participants whose symptoms are significant at baseline.

RQ5 (WP5) is as follows: In people with MS, does a personalized exercise program delivered via telerehabilitation yield comparable cost-effectiveness value compared with standard physical therapy (facility based)? We hypothesize that the telerehabilitation system will be more cost-effective than personal exercise provided by a physiotherapist. We will account for several potential confounders, such as (1) disability, (2) geographic location, and (3) comorbidities.

Methodology, Approach, and Study Population

The different WPs of the research project and timeline are presented in Figure 1 and Table 1. The first phase of this project will examine the system usability and feasibility of an innovative advanced telerehabilitation system in people with MS (WP2). The system usability and feasibility study will be conducted in each participating country (Israel, Italy, Ireland, and Denmark) with a small group of people with MS (n=10 per center) with varying disability. Participants will be recruited according to the following criteria: aged 18 years or older; confirmed diagnosis of MS based on the McDonald criteria [30] (both relapsing-remitting and progressive MS); an Expanded Disability Status Scale (EDSS) score of 2.5-6.5; willing to travel to the local study site for the evaluation sessions; and internet service, and having a device (eg, smartphone, tablet, or PC) equipped with a camera that meets the technical specifications recommended by the telerehabilitation system manufacturer. Individuals who have had a documented relapse during the past 3 months will be excluded, as will those who are unable to follow simple instructions.

Following assessment and exercise prescription, participants will complete an exercise program delivered by the telerehabilitation system. The short-term program will include 8 exercise training sessions (45- to 60-minute sessions twice weekly for 4 weeks). The amount of training throughout the short-term program will be sufficient for collecting data and taking note of the safety, usability, and feasibility of the advanced rehabilitation technologies [31]. The primary outcome measure of WP2 will be collected at the end of the short-term telerehabilitation exercise program with the Telehealth Usability Questionnaire (TUQ) [32], a solid, robust, and versatile tool used to measure the quality of the telehealth system's interaction and services. In addition, qualitative data will be collected through semistructured interviews with key stakeholders (people with MS and therapists) and analyzed thematically.

In parallel with the system feasibility and usability study, we plan to develop and psychometrically test a set of remote balance and functional mobility tests delivered via the telerehabilitation system (WP3). We will adapt and manualize 5 remote mobility tests that are collected through the telerehabilitation system: the 30-second sit-to-stand (30STS) test, timed-up-and-go (TUG) test, functional reach test (FRT), 20-second single-leg stance (20SLS) test, and the Short Physical Performance Battery (SPPB). The SPPB includes the following tests: side-by-side stand (10 seconds), semitandem stand (10 seconds), tandem stand (10 seconds), a gait speed test over 3 meters, and a 5-time repeated chair stand test. Upon completion of the developmental phase, we will conduct a test-retest reliability study for in-person and telehealth data capture and a criterion validity study comparing telehealth and in-person data with 15 people with MS (EDSS 2.5-6.5) at each site (n=60).

To examine the efficacy of the advanced telerehabilitation solution for people with MS, we propose an international feasibility multicenter RCT (WP4). We will include a target sample of 24 participants per country (in 4 countries; 96 participants in total) based on the stepped rule of thumb proposed by Whitehead et al [33], who estimated the optimal sample size for an early-stage/pilot RCT to be 24. Importantly, as the results may differ across countries, we consider each country an individual site for the feasibility RCT. Statistical analysis will be performed for the total group and each country separately. The participants will be randomly allocated (individual randomization) into one of two groups: (1)

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home-based telerehabilitation exercise training via the WizeCare platform [28] or (2) usual care. The sample criteria for the feasibility multicenter RCT will be the same as those for WP2.

Intervention and Comparators

As previously mentioned, the telerehabilitation intervention program will be delivered through the AI telerehabilitation platform designed and marketed by WizeCare [28]. WizeCare is a medium-sized digital health company that has developed an innovative solution for remote physical therapy and exercise training at home. The system includes over 800 exercises that encompass strength, coordination, and flexibility, targeting the lower and upper body and core muscle groups and joints, enabling the therapist to create a tailored exercise program. Moreover, the system includes a technology called MoveAI (patent no. US 11,636,777 B2), which identifies, tracks, and analyzes the user's movement without requiring customized sensors but instead using the camera available on a smartphone, tablet, or PC. This will provide the user (ie, patient) with immediate feedback and guidance. Figure 2 illustrates key features of the telerehabilitation digital platform. The system is safe and has been confirmed by several security certificates of the highest standard (ISO/IEC 27001:2013; ISO27799:2016; AMAR [Israeli standard]: 29460001). Additional data on adherence and compliance will be collected via the WizeCare telerehabilitation platform.

Figure 2. Key elements of the telerehabilitation digital platform.

The telerehabilitation exercise intervention program will comprise a 10-week, physiotherapist-prescribed, evidence-based, individualized exercise program based on the exercise guidelines for people with MS and the physiotherapist's clinical reasoning [34]. Eligible participants will receive tailored exercise instructions, which will include performing 8 to 10 exercises in accordance with their abilities and functional needs. Following the first week of training, the participant will be contacted by a physical therapist (via video or audio chat through the system) to monitor participation, progress, and adverse events. Participants in the telerehabilitation group will be compared to those in usual care. Since the term "usual care" is broad, particularly across countries, and physical activity participation varies, participants in both groups will provide weekly information about their physical activity based on the FITT-VP (frequency, intensity, time, type, volume, and progression) principles [35]. To measure adherence, all participants will receive a diary and be requested to log their exercises and submit reports weekly. The report submission will be monitored weekly with a phone call by a physical therapist.

Outcome Measures for the Feasibility Multicenter RCT

The outcome measures for WP4 will include the 30STS [36] (primary outcome), SPPB [37], 6-minute walk test (6MWT)

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[38], timed 25-foot walk test (T25FWT) [39], mini-BESTest (balance) [40], FRT [41], and a self-report questionnaire, the 12-item MS Walking Scale (MSWS-12) [42]. In accordance with the project's secondary aims, we will examine the impact of the intervention programs on mood (ie, depression and anxiety with the State-Trait Anxiety Inventory [STAI] [43] and Quick Inventory of Depression Symptomology [QIDS] [44]), quality of life (EQ-5D-5L [45]) and the impact of MS (29-question Multiple Sclerosis Impact Scale; MSIS-29 [46]).

All outcome measures will be collected at baseline (at the initiation of the intervention program), and after the intervention period's completion. Assessors (physical therapists) will be blinded to group allocation, and patient report outcomes will be collected using an online form. Other significant disease-related factors collected solely at baseline (together with demographic and relevant clinical information) will include perceived fatigue (Modified Fatigue Impact Scale; MFIS [47]) and cognition (Symbol Digit Modality Test; SDMT [48]). Additionally, we will collect baseline information on digital literacy, which may confound the intervention's effectiveness. All outcome measures used for the study have been validated in people with MS and are recommended for rehabilitation and clinical trials.

Data Analysis and Statistical Plan

Each research question is addressed through specific outcome measures. For RQ1, usability and feasibility will be assessed via the TUQ, adherence rates, dropout rates, and stakeholder interviews, with qualitative data analyzed thematically. RQ2 involves psychometric evaluation of remote assessments (e.g., SPPB, STS, and TUG) using intraclass correlation coefficients for test-retest reliability and Pearson correlations to compare remote and in-person scores. RQ3 and RQ4 outcomes (eg, 30STS, MSWS-12, EQ-5D-5L, STAI, and QIDS) will be analyzed using linear mixed models to assess within- and between-group effects over time. The primary analysis will follow an intention-to-treat principle, including all randomized participants in the groups to which they were originally assigned, regardless of adherence to the intervention protocol. A per-protocol analysis may be conducted as a secondary exploratory analysis. Missing data will be addressed using multiple imputation, assuming data are missing at random, and sensitivity analyses will be performed to assess the robustness of results.

As part of RQ5, the study also incorporates a comprehensive economic evaluation of the telerehabilitation system, which complements the clinical analyses and addresses a critical gap in MS rehabilitation research. A cost-utility analysis will be conducted to compare the telerehabilitation intervention and usual care, using incremental cost-effectiveness ratios derived from health care service use data and EQ-5D-5L–based quality-adjusted life years. Cost data will include implementation, infrastructure, maintenance, training, support services, and any differences in health service use or patient-reported outcomes. These data will be collected alongside the RCT to ensure alignment between clinical effectiveness and economic impact.

Ethical Considerations

Ethical approval has been obtained for WP2 from the Sheba Institutional Review Board (IRB; SMC-1154-24; May 1, 2024); the University of Limerick Education and Health Sciences Research Ethics Committee (2025_01_17_EHS; May 11, 2025); and the Central Denmark Region Committees on Health Research Ethics (1-10-72-140-24). Approval of the ethics application for WP3 is expected by September 2025. Ethics applications for the remaining WPs, including the multicenter feasibility RCT (WP4) and the economic evaluation (WP5), will be submitted to the appropriate IRB in each participating country prior to their initiation.

For WP2, all participants provide written informed consent prior to enrollment. The consent process includes comprehensive information on the study procedures, risks, benefits, and data confidentiality. All collected data are deidentified prior to analysis and securely stored in accordance with institutional data protection policies. Participants in WP2 do not receive financial compensation but may be reimbursed for travel expenses when applicable. Compensation for WP3 and future phases will be determined and approved through local IRB processes. No identifiable images or personal information will be included in the manuscript or any supplementary materials. If such materials are necessary for dissemination, explicit written consent will be obtained and submitted as required.

Results

The PLATINUMS project received official funding in February 2024. Data collection for WP2 (the system usability and feasibility study) began in April 2025 across participating sites in Israel, Italy, Ireland, and Denmark. WP3 (validation of remote mobility measures) is scheduled to launch in September 2025, and the multicenter RCT (WP4) is planned to begin in January 2026. Project coordination and dissemination activities (WP7) have been ongoing since March 2025. Initial findings from WP2 are expected to be available by October 2025, with preliminary publications planned for mid-2026.

Discussion

The PLATINUMS project aims to evaluate an innovative AI-based telerehabilitation system for people with MS, and if successful, it is expected to significantly advance the way rehabilitation is delivered to this population. The system is designed to provide accessible, individualized exercise programs with real-time feedback and therapist supervision, thereby overcoming some of the longstanding barriers to facility-based care. Through its structured, multiphase approach, the project will generate essential data on usability, feasibility, clinical validity of remote assessments, and preliminary efficacy of telerehabilitation interventions.

This protocol builds on a growing body of research demonstrating the potential of telerehabilitation to support physical function in people with MS while addressing several limitations observed in earlier studies. A recent scoping review identified two main categories of telerehabilitation interventions, exergaming and web-based physical therapy, both of which

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have shown promising results in improving gait and balance in people with MS [49]. For example, exergaming systems such as Microsoft Kinect–based virtual reality and home-based balance training tools led to significant improvements in ambulation speed, dynamic balance, and postural control [50,51]. Similarly, web-based physical therapy programs, including both those with real-time supervised and asynchronous formats, have demonstrated improvements in gait function and balance scores [52,53].

While previous interventions often lacked scalability or relied on specialized hardware, the PLATINUMS system leverages AI and widely available consumer devices, making it more practical for widespread use. The planned international feasibility trial further enhances the study's relevance by including participants across diverse health care contexts, thereby increasing the potential for future implementation.

A particular strength of this study is its integration of technological innovation with a rigorous clinical and economic evaluation. By examining feasibility alongside psychometric testing and cost-effectiveness, the project will provide comprehensive insights into the practicality of scaling up such solutions in real-world settings. The inclusion of both patient-centered outcomes and system-level data will allow for a nuanced understanding of how AI-driven telerehabilitation can influence care delivery for people with MS. Still, as this is a protocol, all conclusions must remain provisional until data collection is complete. It will be important to interpret future findings with an understanding of the feasibility trial's exploratory nature.

Several limitations and potential challenges should be acknowledged. First, as a feasibility study, the sample size may not be sufficient to detect small but clinically meaningful effects, and findings may not be generalizable beyond the populations and settings involved. Second, adherence to home-based interventions can be variable and difficult to monitor objectively outside controlled settings. To address this, we will incorporate remote use tracking, patient engagement strategies, and therapist follow-up. Third, technical issues such as hardware compatibility, internet connectivity, and user literacy may affect intervention delivery. These will be documented throughout the study and considered in the interpretation of results. Importantly, as with any AI-enabled solution, algorithm transparency, how well it can adapt to individual needs, and potential biases must be critically evaluated before broader deployment. Given that this is a feasibility protocol, any conclusions will remain provisional until the trial is completed and the data are evaluated.

Looking forward, the outcomes of this study are expected to inform the design of a fully powered RCT, as well as broader efforts to integrate digital health technologies into routine clinical practice. The knowledge generated may also prove relevant to other neurological conditions where mobility impairments are prevalent. A dedicated dissemination strategy has been developed to ensure that findings reach key stakeholders, including clinicians, patients, and health policy decision-makers. Ultimately, the PLATINUMS project seeks not only to assess a novel intervention but to lay the groundwork for a more accessible, personalized, and sustainable model of rehabilitation for people with MS.

Acknowledgments

This research was supported by the European Partnership on Transforming Health and Care Systems, Funding Program: Horizon Europe–the Framework Program for Research and Innovation (2021-2027), and the Joint Translational Call 2023 (grant 1538).

Data Availability

Data sharing is not applicable at this stage as the PLATINUMS project is currently in progress. Data collection for WP2 is ongoing, and WP3 is set to commence in September 2025. Once data collection and analysis are complete, deidentified datasets may be made available upon reasonable request and subject to ethical approval and data protection regulations. Future datasets will be considered for deposition in a publicly accessible repository in accordance with Horizon Europe open science guidelines and JMIR's data sharing policy.

Authors' Contributions

LH: conceptualization, methodology, writing (review and editing), and project administration; SC: conceptualization, methodology, writing (review and editing), and project administration; MP: conceptualization, methodology, writing (review and editing), and project administration; AK: conceptualization, methodology, writing (original draft), project administration, supervision, and funding acquisition.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOC File , 122 KB - resprot_v14i1e75983_app1.doc]

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Multimedia Appendix 2
Peer-review report from the funding agency (THCS Call Steering Committee; European Partnership on Transforming Health and Care Systems (THCS), Horizon Europe, European Union.
[PDF File (Adobe PDF File), 288 KB - resprot_v14i1e75983_app2.pdf]

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Abbreviations

20SLS: 20-second single-leg stance
30STS: 30sec-sit-to-stand test
6MWT: 6-minute walk test
AI: artificial intelligence
EDSS: Expanded Disability Status Scale
FITT-VP: frequency, intensity, time, type, volume, and progression
FRT: functional reach test
IRB: institutional review board
MFIS: Modified Fatigue Impact Scale
MS: multiple sclerosis
MSIS-29: 29-item Multiple Sclerosis Impact Scale
MSWS-12: 12-item Multiple Sclerosis Walking Scale
PLATINUMS: Implementation of an Advanced Telerehabilitation Solution for People With Multiple Sclerosis
QIDS: Quick Inventory of Depression Symptomology
RCT: randomized controlled trial

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RQ: research question
SDMT: Symbol Digit Modality Test
SPPB: Short Physical Performance Battery
STAI: State-Trait Anxiety Inventory
T25FWT: timed 25-foot walk test
TUG: timed up and go test
TUQ: Telehealth Usability Questionnaire
WP: working package

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Protocol

Promoting Comprehensive Care for People With Rare Diseases in a Tertiary Care Setting in Brazil: Protocol for a Mixed Methods Implementation Study

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Abstract

Background: Rare diseases (RDs) have gained attention in public policy due to their complexity and low prevalence and the challenges they present in health care settings. Comprehensive care for people with RDs requires strengthening of services, programs, and care levels. It is imperative to make digital health tools available to support epidemiological surveillance, facilitate patient follow-up, and enhance the education and awareness of health care professionals (HCPs) regarding these conditions.

Objective: This study aims to implement enhanced actions aligned with the Brazilian National Policy for Comprehensive Care for People with Rare Diseases to improve the attention and care provided to individuals. This will be achieved by developing a computational tool and establishing guidelines to optimize the regulation of the reference services for RDs, providing updated information to expedite diagnosis and promote collaboration.

Methods: The methodology includes mapping the regulation processes in the Clinics Hospital of Ribeirão Preto Health Complex. Participants will include HCPs from the hospital complex and associated primary care centers and patients with a confirmed or suspected RD selected through medical records and patient associations. Data collection methods include questionnaires, semistructured interviews, and patient tracking using health information systems. The project will apply the 5W2H (what, who, where, when, why, how, and how much) framework to align tasks, responsibilities, and resources. Integrating digital tools adhering to the findability, accessibility, interoperability, and reusability principles will promote real-time monitoring, improved resource allocation, and enhanced workflow efficiency. Training initiatives will boost awareness and capacity among HCPs, while the computational tool seeks to streamline patient follow-up and tracking. Digital integration and interoperability will reduce referral process inefficiencies and support evidence-based decision-making. Education and awareness campaigns will fill knowledge gaps among HCPs and patients.

Results: Ethics approval was granted on December 9, 2024. We conducted technical meetings with the IT team to align procedures for obtaining secondary data. Concurrently, we identified key guidelines and applied a knowledge management maturity questionnaire based on which we began mapping RD-related management processes. A computational ontology is currently under

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development to ensure semantic interoperability. This framework supported initiatives promoting education and awareness regarding RDs, targeting HCPs and patients.

Conclusions: The study emphasizes the potential of digital health solutions to transform RD care by improving coordination, resource allocation, and stakeholder education. When effectively adopted, these solutions can enhance access to specialized care, reduce inefficiencies, and inform public health policies. Future efforts will focus on expanding the tool's implementation, refining its functionalities, and evaluating its long-term impact on patient outcomes and system efficiency. This initiative highlights the crucial role of integrating digital technologies in managing RDs and underscores the need for ongoing collaboration among health care stakeholders to achieve sustainable improvements in patient care and policy development.

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KEYWORDS

rare disease; digital health; comprehensive care; public health policy; implementation science

Introduction

Background: Evolution of Public Policies for Rare Diseases

Attention to rare diseases (RDs) has increasingly gained relevance in public policy discussions. The National Policy for Comprehensive Care for People with Rare Diseases (NPCCPRD), established by Ordinance 199/2014 of the Brazilian Ministry of Health (MoH), aims to reduce mortality, morbidity, and secondary manifestations while improving the quality of life and equitable access to health services [1].

The policy's main objectives include strengthening the RD care network, enhancing the qualifications of health care professionals (HCPs), promoting scientific research, and encouraging knowledge production. Furthermore, the ordinance emphasizes coordination between institutions and governmental bodies, improving information flow through more robust registration and surveillance systems and increasing education and awareness about RDs [1]. However, implementing these policies faces significant challenges and difficulties [2].

Although RDs collectively affect a large portion of the global population, individual conditions remain rare. These diseases are characterized by their complexity, diversity, and severity, often presenting debilitating and chronic symptoms. It is estimated that there are >7000 identified RDs [3], making it challenging to establish standardized approaches and universal guidelines applicable to all RDs. The need for comprehensive, updated information on incidence and prevalence also hampers the planning of health services and the adequate allocation of resources [4].

A significant obstacle to progress is low awareness and knowledge among HCPs and society. The lack of familiarity and specialized training can delay early diagnosis and appropriate referral of patients with RDs [5]. Therefore, coordination and integration between various sectors, including health care, research, the pharmaceutical industry, and patient organizations, are crucial for the effective development and implementation of RD initiatives [4]. Collaboration between these actors is often complex, given divergent interests, resource limitations, and coordination challenges. However, promoting partnerships between government institutions, patient organizations, HCPs, and the academic sector can significantly improve patients' quality of life [5].

Over time, the evolution of public policy for RDs has been a gradual but continuous process. Initially, these conditions were ignored by government authorities and the pharmaceutical industry. However, social movements and patient organizations worldwide have voiced the needs of individuals with RDs, contributing to the recognition of RDs as a global public health issue [6]. Advances in genetics and medicine have facilitated a greater understanding of RDs and more accurate diagnoses. This progress has led to identifying patient groups, creating research networks, and establishing reference centers for RDs (RCRDs) for high-quality care [2]. Since the publication of the NPCCPRD, 27 RCRDs have been accredited by the MoH, reflecting progress in policy implementation and improving care for people with RDs in Brazil. However, challenges remain, such as expanding coverage and ensuring adequate resources for comprehensive care for these patients. Continuous monitoring and improvement of the NPCCPRD are essential to address these challenges and promote more effective and inclusive care [7].

Discussions on public policies to support the population with RD have intensified recently. In addition to the NPCCPRD, São Paulo State Law 14.806 emphasizes raising awareness about these diseases [8]. Furthermore, São Paulo State Law 15.669 of January 12, 2015, addresses the RD treatment policy in São Paulo and outlines the objectives of the RCRD, which include diagnosing and mapping RDs and promoting effective RD treatment, monitoring patients, serving as research and teaching centers, and providing early diagnosis to minimize additional disabilities [9]. Globally, the inclusion of RDs in the World Health Assembly agenda in 2019 was a landmark, establishing RDs as a priority in international health policy [10].

The Council of Rare Diseases International highlighted the potential of digital health technology in accelerating access to diagnosis and specialized care for patients with RDs. The need for standardized definitions, classifications, codifications, and validations by the World Health Organization, including tools such as the Human Phenotype Ontology and the *International Classification of Diseases*, was emphasized as the key to success [11]. The European Reference Networks demonstrate how digital technologies can improve care coordination, facilitate

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expert collaboration, and accelerate research, promoting a patient-centered digital transformation [12,13].

As we advance into the digital era, new obstacles and opportunities arise in the evolution of public policies. Comprehensive care for people with RDs requires not only the implementation of basic actions for diagnosis and care but also the strengthening of existing services, programs, and levels of care. These efforts depend on the health care network's financial, technical, human, and infrastructural resources [14,15]. Therefore, it is crucial to continuously evaluate and improve the policy landscape for RDs, adapting to new realities and ensuring that patients receive the necessary support to face the challenges posed by their conditions.

Objectives

In this scenario, developing digital health tools becomes imperative to contribute to epidemiological surveillance, patient follow-up, and awareness among HCPs. These tools should facilitate patient registration, monitoring, and follow-up as well as store information related to treatments, tests, and hospitalizations. Digital tools can significantly improve data collection, reduce losses, and allow better analysis and management of knowledge, ultimately leading to better care and disease management.

Thus, the primary objective of this paper is to implement and enhance actions aligned with the NPCCPRD to improve the attention and care provided to individuals with RDs. This will be achieved by developing a computational tool and establishing guidelines to optimize the regulation (referral and counterreferral) for the reference services for RDs (RSRDs). This includes mapping the regulation scenarios for patients within the Clinics Hospital of Ribeirão Preto (HCRP [Hospital das Clínicas de Ribeirão Preto]) care network. In addition, continuous evaluation and refinement of the digital health strategies applied within the HCRP complex are needed to expand the reach, effectiveness, adoption, implementation, and maintenance of actions as per the NPCCPRD. Finally, awareness programs and specialized second opinion tools should be implemented to support continuous education, informed decision-making, and the discussion on confirmed or suspected RD cases within the care network.

Given the importance of records for conducting scientific research that can promote the evaluation and monitoring of patients and reduce diagnosis time through a national database, the project aims to provide information on symptoms, diagnostic tests, and available RSRDs to those interested in the subject, similar to the approaches described by Gong et al [16] and Vandeborne et al [17]. The absence of public policies directed at RDs [7] intensifies the urgency of addressing this issue.

Methods

Study Design

This applied research with a mixed methods approach will follow procedures based on action research, literature review, surveys, and field research. Action research will foster change through continuous collaboration with HCPs and other stakeholders to address specific issues related to RD care. The literature review will provide a comprehensive understanding of existing knowledge and gaps in the field, guiding the development of new insights and approaches. Surveys will be conducted to collect quantitative data from a broad range of participants, ensuring a representative understanding of the current state and challenges of RD care. Field research will involve in-depth qualitative studies, including interviews and observations, to gather detailed contextual information and firsthand accounts of experiences within the health care network. The interview guide is provided in Multimedia Appendix 1. This combined methodology aims to integrate diverse perspectives and data sources, enhancing the robustness and applicability of the research findings [18].

To structure the knowledge consolidated during the initial phases of the study, a computational ontology will be developed, focused on the domain of RDs within the context of the Unified Health System (SUS; Sistema Único de Saúde). This development will follow the guidelines established by the World Wide Web Consortium for the standardization of informational elements on the web. The ontology will serve as the foundation for designing an interoperable informational repository structure, an essential aspect for optimizing communication within a networked health care system [19,20].

Subsequently, to gain a deeper understanding of the management processes intrinsic to the care of patients with RDs at the study site, these processes will be mapped using the Business Process Model and Notation. This is a well-established approach aimed at accurately and transparently modeling organizational processes, enabling the clear identification of opportunities for improvement and strategic points for generating service performance indicators. In addition to supporting decision-making and achieving better management outcomes, this methodology contributes to enhancing the quality of services provided and holds potential for reducing operational costs within the organization [21,22].

The 5W2H (what, who, where, when, why, how, and how much) methodology, a widely used tool in project management, was used to structure and organize the proposed actions. This approach is based on addressing 7 fundamental questions: "what" (what will be done?), "why" (why will it be done?), "who" (who will be responsible?), "when" (when will it be done?), 'where' (where will it be executed?), "how" (how will it be done?), and "how much" (how much will it cost?). This methodology provides a clear, actionable framework for defining tasks, responsibilities, and resources, ensuring stakeholder efficiency and alignment [23]. Adopting structured frameworks in health information management is essential to optimize decision-making and improve service quality, particularly in resource-constrained environments such as the RD scenarios. This ensures a comprehensive understanding of the project's scope and facilitates the elimination of inefficiencies, as recommended in lean management principles applied to health care systems [24].

Study Participants

Certified as an RSRD in 2019, the HCRP has had a medical genetics service since 1974 and is a reference center in RD care [25]. The hospital offers high-complexity clinical and laboratory

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investigations, including genetic counseling and genomic testing [26]. The use of this system in health services to integrate follow-up actions and the resolution of these actions will be evaluated. In addition, a sociotechnical approach will be applied for training, necessary system modifications and awareness and education actions that will be implemented for primary care centers and HCRP units.

Primary care centers were created to support didactic activities in primary and secondary care, promoting interinstitutional integration and the technical-scientific improvement of faculty. Furthermore, they aim to train HCPs, develop human resources, and produce relevant scientific knowledge. Therefore, the impact of implementing integration and interoperability methods on data quality improvement and organizational management will also be assessed.

The research will use diverse criteria to select participants, including geographic diversity and representation of different RD groups. A comprehensive mapping of patients, HCPs, and health managers in specific health services units will be conducted using medical records, patient associations, information systems, and care networks. To collect data, questionnaires and semistructured interviews will be adapted to address aspects of access to the care network concerning RDs. The type of registry to be implemented will be a notification system, allowing for the systematic collection of information on RD cases. The development process of the registry will include the definition of indicators and the evaluation of data quality obtained according to current legislation and the region's specific needs [27,28].

The study participants comprise 2 main groups: HCPs working within the network of the HCRP and the broader health care network of Ribeirão Preto and patients with medical records in associated databases. Eligibility criteria for HCPs include the type of institution where they work, such as basic health units and family health centers, excluding those who do not directly manage patients with RDs. For patients, inclusion criteria include a confirmed or suspected RD, relevant signs and symptoms, and being under follow-up at the HCRP. Patients with incomplete or low-quality records will be excluded. Patient data will be accessed through the HCRP health information systems and municipal health records, with some participants potentially excluded if they do not meet the established criteria or if their records lack sufficient information.

However, the HCRP Academic Health Complex and its various units and services, as presented in Figure 1, face challenges in regulation, the implementation of procedures, and the financial and epidemiological aspects of RDs. Financial difficulties include underfunding and a need for more resources for tests and procedures, which, in turn, impact the hospital's ability to provide quality services. Implementing methods is also challenging due to unclear regulations and difficulties in internal agreements. The lack of knowledge about the epidemiology of RDs is another barrier, making it difficult to plan and implement appropriate health policies for these conditions.

Figure 1. Clinics Hospital of Ribeirão Preto (Hospital das Clínicas de Ribeirão Preto) unit composition. AME: specialty medical outpatient clinic; CCMS: Community Health and Social Services Center; CER: rehabilitation center; CIR: integrated rehabilitation center; CSE: teaching health center; HE: state hospital; NSF: family health units; UE: emergency hospital.

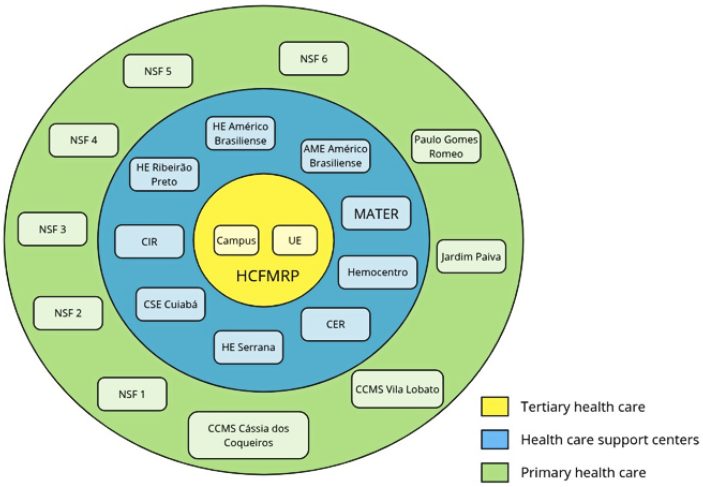

Phases

Although the project's 3 phases are articulated, as shown in Figure 2, the flowchart provides a degree of independence between its stages. In phase 1, there is a scenario of detailed diagnosis and planning of the needs and challenges faced by HCRP in managing people with RDs within its care network. A survey of current practices in registration, monitoring, and referral will be conducted, identifying points for improvement to support the definition of protocols and a referral and counterreferral model to be implemented. Phase 2 corresponds to implementing and evaluating the planned strategies and interventions that will be developed to improve these patients' registration, monitoring, and referral.

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Figure 2. Alignment between the scientific and public management components. CIA: Information and Informatics Center; DAS: department of health care; HCRP: Clinics Hospital of Ribeirão Preto (Hospital das Clínicas de Ribeirão Preto); GGA: general outpatient management; PCC: primary care center; RD: rare disease; RG: research group; WG: working group.

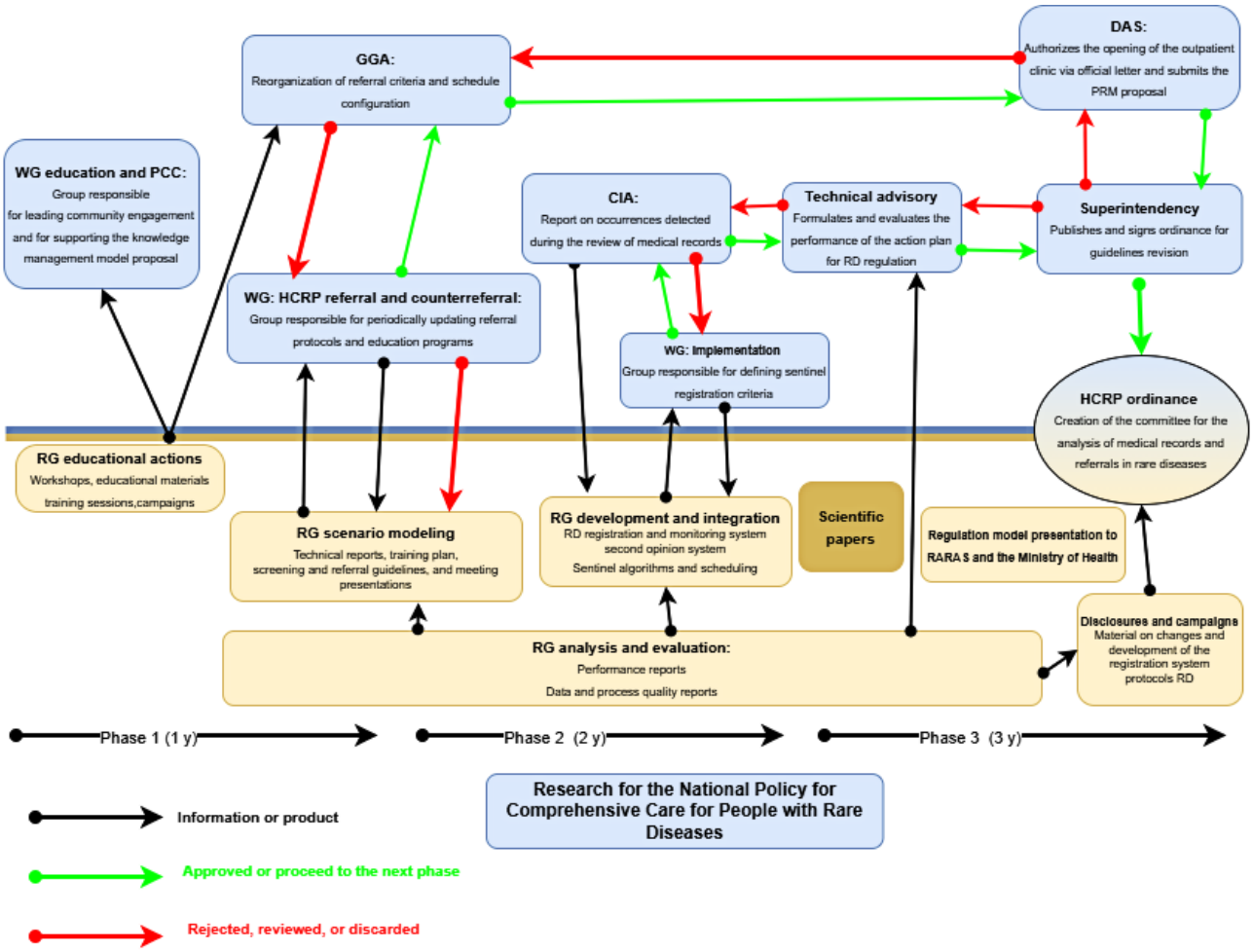

Finally, in phase 3, the impact of the results obtained throughout the study will be analyzed from 2 main aspects: the availability of the achieved results about public management needs and the impacts generated by the research on the public management process during the project's term. It is important to emphasize that the 3 action lines specified earlier are transversal to the project, which is synergistically presented in the 3 phases mentioned earlier.

Computational Infrastructure

The data collection instruments will use consolidated and validated international standards, such as the *International Classification of Diseases, 10th Revision*, Human Phenotype Ontology, ORPHAcode, and OMIM, enabling comparison with data from other platforms, such as Orphanet [14,29,30]. These instruments were established according to the NPCCPRD guidelines and World Health Organization recommendations and validated by the National Rare Diseases Network (RARAS; Rede Nacional de Doenças Raras) experts. The selection of registry variables will be based on a systematic review conducted by the RARAS group, which verified the RD minimum dataset used in health networks in different countries [12].

REDCap (Research Electronic Data Capture; Vanderbilt University [31]) will be used for data collection and management, and auxiliary curation tools, such as REDbox [32], will ensure the quality and integrity of the collected information. In this project, we will use the REDCap instance managed by the Brazilian Society of Medical Genetics and Genomics and used by RARAS [31,33]. In addition to REDCap, the project will take advantage of the technological infrastructure of the RARAS network to implement the registry, with strict security and privacy procedures following the General Data Protection Law (GDPL) [34].

Ethical Considerations

Human Participant Ethics Review Approvals

The ethics committee of the HCRP (Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto), University of São Paulo approved this project (82571424.4.0000.5440). This study will follow the guidelines of the *Good Clinical Practice Manual* of the International Conference on Harmonization [35]. Furthermore, the project will be submitted to the MoH to be included as research of strategic interest for the SUS, following Resolution 580/2018.

Informed Consent

The research team will obtain informed consent through the signing of an informed consent form before any patient's involvement in the project activities. Participants will be

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informed of their rights, including the right to withdraw their consent at any time without any cost and request full removal from the study.

Privacy and Confidentiality

All research activities will be conducted accordingly to the Brazilian General Personal Data Protection Law (number 13.709/2018) and the MoH Ordinance 2073/2011. Anonymized data will only be considered personal if the anonymization and deidentification process is reversed, as defined in Article 12 of the Brazilian General Personal Data Protection Law. In addition, only nonidentifiable information may be exported or transferred, similar to analyses, reports, consolidated datasets production, or research repositories' availability. They must not contain or use personally identifiable data, as such information is unnecessary for these activities and may violate participants' privacy. Personal and sensitive data will be premapped, and computational techniques will be used for anonymization and pseudonymization, along with manual validation by the responsible researcher before any data are made available or transferred.

Compensation

No financial compensation will be provided to any participant for their involvement in this research. Nonetheless, participation is voluntary, and withdrawal will not result in any form of disadvantage or loss of health care services.

Data Storage, Preservation, and Sharing Policies

The data will be stored on servers hosted on the cloud computing infrastructure of the University of São Paulo (USP), with a contingency physical server. Daily backups will be performed and stored on cloud storage media, separated from the sources, with a retention period of 7 days.

The data will be preserved for at least 10 years and maintained under conditions that ensure their integrity and accessibility following best data management practices. The data can be exported and made available in formats, preferably open and nonproprietary (eg, CSV).

The preservation and sharing policies aim to maximize benefits for all stakeholders while respecting ethical and privacy guidelines and encouraging reproducibility and subsequent developments. The data will be available under the Creative Commons Attribution 3.0 Unported license, which permits the data's use, sharing, and modification, provided the source is appropriately cited. In addition, depending on the data repository, other licenses may apply. The results will also be made available through the following:

- Scientific articles to ensure research transparency and replicability
- The São Paulo State Network of Scientific Data Repositories [36,37]
- FAIRsharing [38]
- Presentations at national and international scientific events

RD Awareness Efforts

Collaboration agreements, population screening surveys, information sharing, access to existing databases, and cooperation will be established to facilitate awareness efforts. Strategic partnerships with health care institutes, laboratories, and patient associations will also contribute to data collection, and these will collaborate with HCRP service units' screening registry. The aim is to engage critical stakeholders in the research, creating a robust care and knowledge-sharing network. This collaboration will enhance the project's educational aspect, yielding high-quality educational materials that contribute to RD awareness and knowledge. In addition, the specialized second opinion platform will contribute to creating a complex database based on scientific and clinical evidence derived from real problems and synchronous and asynchronous discussion groups. The knowledge produced will be public and educational, supporting HCPs' decision-making in similar situations initially discussed through the second opinion platform.

To gather, organize, share, and disseminate structured, evidence-based knowledge, a knowledge management model will be implemented according to the context in which the HCRP operates and the demand of its audience. This model will be based on the knowledge management model for the Brazilian public administration by the Institute for Applied Economic Research (Instituto de Pesquisa Econômica Aplicada) and will focus on citizen-oriented results. This process consolidates a knowledge management plan into 4 well-defined phases: diagnosis, planning, development, and implementation [39,40]. These phases will be executed following the principles outlined in the National Health Information and Informatics Policy [41] and the information standards and technologies recommended by the World Wide Web Consortium [20].

Educational materials, including informational guides, explanatory videos, and infographics, will be available on the RARAS web portal [42]. Digital strategies, including newsletters, thematic campaigns, search engine optimization, and social media promotion, will be used to reach a broad audience. The educational intervention will target HCPs, health care students, and the general community through in-person and virtual workshops as well as partnerships with schools and patient associations, aiming to raise awareness, reduce stigma, and include people with RDs [43].

The effectiveness of interventions in network access, patient registration, and educational actions will be measured using digital strategies, pre- and postintervention questionnaires, validated assessment scales, and health outcomes evaluations. These assessments will provide a comprehensive view of changes in perception and understanding of RDs and measure the impact on network access, early diagnosis, and appropriate treatments. On the basis of the results, continuous adjustments and improvements will be made.

Evaluation Framework

Implementation research (IR) will be conducted to explore the impact of digital technologies in real-world settings [44]. Even where there is evidence, challenges related to implementing new technology and strategy play a significant role in how proven approaches in research conditions will work in real-world situations [44].

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IR represents an essential interface between the availability of tools, strategies, and interventions and their use within a health care system. The reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) framework will measure the success of implementing an intervention, considering 5 essential dimensions: reach, effectiveness, adoption, implementation, and maintenance. Reach refers to the number or proportion of individuals affected by the intervention. Effectiveness refers to the intervention's outcomes (including adverse effects, quality of life, and others) and includes reasons for the intervention's success or the lack of positive results. Adoption refers to the proportion and representativeness of settings and providers and agents of the intervention. Implementation refers to the elements of the intervention, such as delivery on time and as intended, adaptations made, and their acceptance by end users. Maintenance measures the level at which an intervention is sustained over time, including the system, provider, and individual levels [45,46].

In addition, the Standards for Reporting Implementation Studies (StaRI) [47] will provide a comprehensive framework to enhance the transparency and consistency of reporting in IR. By distinguishing between the implementation strategy and the intervention, StaRI ensures that studies clearly describe what is being implemented and how it is delivered, facilitating replication and critical appraisal across diverse contexts.

This approach will ensure that the intervention is efficiently evaluated and optimized within the health care system. These domains are essential for the final impact of the recommendations, and each stage requires a different evaluation approach. Thus, each evaluation phase will provide valuable information and tools to support evidence-based decisions in public management [44,45]. The data analysis strategy will be developed considering different stages and types of data. For data collection at the HCRP, an initial descriptive analysis will be conducted to define disease prevalence indicators and geographic, demographic, and socioeconomic information according to the axes described in the NPCCPRD [1]. These analyses can be conducted globally, covering all HCRP units, or individually to understand the system better.

The research will not be limited to understanding patients with RDs at HCRP but will also analyze the health care system. The analysis of the collected data on services will identify relevant indicators, such as the average diagnosis time and the availability of procedures related to RDs. Experts will evaluate each indicator to define objectives and network needs. In addition, satisfaction surveys will be conducted in 2 stages: analyzing participants' demographic information [48] and evaluating their responses using satisfaction questionnaires, aiming to identify key points to consider in notification systems and care networks [49].

The global and individual approach to measuring RDs as a public health issue helps visibility, goal identification, appropriate resource allocation, and effective interventions [13]. Therefore, analyses encompassing all proposed lines will be organized and synthesized in periodic reports, providing essential insights to support the decision-making of HCRP managers. The results will be shared with involved stakeholders, allowing continuous monitoring and adaptation of actions as needed.

Data Analysis Methods

Following data collection, a comprehensive descriptive analysis will be performed to summarize, systematize, and present the data in an interpretable framework. This phase serves to (1) provide a rigorous overview of the processes under investigation; (2) establish foundational insights into the dataset's structure; and (3) identify intrinsic patterns, directional trends, and statistical anomalies. Beyond understanding the data, this stage transforms raw information into actionable knowledge while ensuring transparent reporting of preliminary findings [50].

This initial analytical phase establishes the essential foundation for subsequent and more sophisticated data exploration. The descriptive insights will enable the application of advanced analytical frameworks, such as machine learning methodologies, specifically designed to extract deeper layers of knowledge from the collected data. These techniques will systematically transform raw observations into extracted knowledge by (1) revealing latent structures and nonobvious relationships within the data ecosystem, (2) quantifying complex interactions between data, and (3) generating data-driven applications. Furthermore, we aim to predict future bad outcomes based on previously observed records, thus providing relevant insights to support the project's objectives and facilitating data-driven decision-making [51].

Performance Evaluation Plan and Risks

Risks encompass various scientific aspects and implications for the study participants. This detailed examination is crucial for ensuring the safety and ethical integrity of the study and maintaining transparency in our research methodology. Table 1 presents the identified risks, their causes and consequences, and mitigation strategies.

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Table 1. Risks associated with the scientific aspects related to the study and its participants.

Risks	Causes	Consequences	Mitigation measures
For the study			
Inadequate sample	Incorrect or unrepresentative selection of participants	Results not generalizable or not applicable on a large scale	Dissemination of the study to other services and competitive inclusion strategy between participating locations
Delay in ethics approvals	Indication of pending issues by regulatory bodies	Delay in the planned date	Meetings with representatives of ethics bodies and activities review
Difficulty in acquiring or accessing databases	Delay in the analysis process, authorization by the administrative body, and malfunction of the collection equipment or environment	Delay in the planned date for starting the analysis	Allocation of human resources
For the participant			
Entry of study participants without an adequate consent process	Inadequate team training	Deviations and violations of good practices and study protocol	Training of the team and retraining, if necessary
Errors in study procedures	Systematic errors in the details of the execution of procedures	Deviations and protocol violations, data quality issues, and bias	Team training, objective communication to those responsible, and data quality management

The performance assessment plan details the indicators used to evaluate the program's objectives and monitor project performance. For each stage of the public management process linked to a scientific result, we present, on a scale of 0 to 4 (0=knowledge not available at the stage; 4=knowledge fully available in an appropriate time and format), the availability of scientific results, taking into account the operational aspects of the project. The relationship between the need for scientific knowledge at each stage of the public management process and its availability is presented in Table 2.

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Table 2. Representation of the operational aspect.

Stage in public management	Scientific result	Score	Justification	Indicator
Coordination with the community and health care professionals with WG[a] education and PCC[b]	Technical report outlining the criteria and necessary support for program formulation and scenario modeling	3	As this is an iterative and continuous evaluation strategy, some scenarios will be analyzed after the completion of the underlying steps, and a new report will be provided.	The number of people reached by educational programs and participation rate in training programs
Scenario modeling with the reference and counterreference WG	Detailed technical report with modeling results and support in defining education plans and referral criteria	4	__[c]	Number of viable scenarios and consensus between groups
Registration, monitoring, second opinion platform, and algorithms for WG implementation	Software, registration, sentinel criteria, and algorithmic association rules	2	The acquisition process and data quality may require structural adaptations and impact the scientific result.	The number of registered patients and the system use rate
Performance analysis, data quality, and processes	Performance report, data quality, and processes	4	—	Adequate referral rate and reach, adoption, effectiveness, implementation, and maintenance of actions
Regulation model	Preparation of a presentation for experts from the RARAS[d] network and representatives of the MoH[e]	0	This is the pending stage of implementation and performance analysis of the proposed model.	Average time to access diagnostic resources
Disclosure and campaigns	Educational materials and content for campaigns, professional training, and management protocols	2	The stage is conditioned by the subsidies defined by the reference and counterreference WG and the achievement of registration implementation.	Second opinion platform use rate, the number of people reached by educational actions, and approval rate in training programs

[a]WG: working group.

[b]PCC: primary care center.

[c]Not applicable.

[d]RARAS: National Rare Diseases Network (Rede Nacional de Doenças Raras).

[e]MoH: Ministry of Health.

The scenario modeling and performance analysis, data quality, and process stages will be responsible for identifying possible needs for changes in management processes. On a scale from 0 to 4 (0=no use of scientific knowledge; 4=full use of scientific knowledge), we present the expected effects or changes in the strategic aspect of the project (Table 3).

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Table 3. Representation of the strategic aspect.

Expected change in public management	Scientific result	Score	Justification	Indicator
Implementation of a reference and counterreferral model for RDs[a] with screening and referral guidelines and protocols	A monitoring system with efficiency and effectiveness indicators for each implementation phase (training and registration structuring) that enables independent updating of reference scenarios by the HCRP[b]	1	The lack of financial and human resources, resistance to change on the part of HCPs[c], and the complexity of the implementation process may not make maintaining the model sustainable.	The number of tools and guidelines available as well as the average time for diagnosis of RDs
Adoption of an effective and sustainable RD recording and monitoring system	MDS[d], mapping between terminologies and encodings, and validated digital deployment and evaluation strategies	3	—[e]	Adhesion rate, the level of satisfaction, and HCP coverage; effectiveness and financial sustainability; and data quality and integration
Incorporation of a knowledge management model to support education and awareness processes about RDs for employees and patients	Joint action of the WG[f] and HMs[g] responsible for educational actions in training and disseminating digital health guidelines and strategies	2	The lack of financial resources, employee resistance, and other institutional priorities may not make maintaining the model sustainable.	Organizational knowledge management maturity level

[a]RD: rare disease.

[b]HCRP: Clinics Hospital of Ribeirão Preto (Hospital das Clínicas de Ribeirão Preto).

[c]HCP: health care professional.

[d]MDS: minimum dataset.

[e]Not applicable.

[f]WG: working group.

[g]HM: health manager.

Expected Outcomes

RD Public and Scientific Management

Figures 3-5, respectively, illustrate the practical application of the 5W2H methodology for each of the project's action lines, providing a clear overview of the planned activities, responsibilities, and required resources.

Furthermore, the project encompasses technical-scientific and innovative results through the development of patient registration and monitoring software for RDs as well as another for second opinion formation. Accordingly, it is planned to apply the intellectual property law and protect the software through registration at the National Institute of Industrial Property, allowing for technology transfer to the HCRP and, consequently, reproducibility for the SUS. This process will ensure that research conducted with public resources can be translated into societal benefits, contributing to the resolution of public health issues. In addition, detailed technical reports will facilitate the sharing of results, support the study's replicability, and inform managers' decision-making.

Establishing a regulatory model that emphasizes patients with RDs will include guidelines and protocols for screening and referral, which are also expected outcomes. Moreover, through the RARAS network, all results will be presented to representatives of the MoH responsible for conducting actions related to RDs in the country.

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Figure 3. Facilitated access to the care network (line 1). HCRP: Clinics Hospital of Ribeirão Preto (Hospital das Clínicas de Ribeirão Preto); HCP: health care professional; HM: health manager; NPCCPRD: National Policy for Comprehensive Care for People with Rare Diseases; RCRD: reference center for rare diseases; RD: rare diseases; RSRD: reference service for rare diseases.

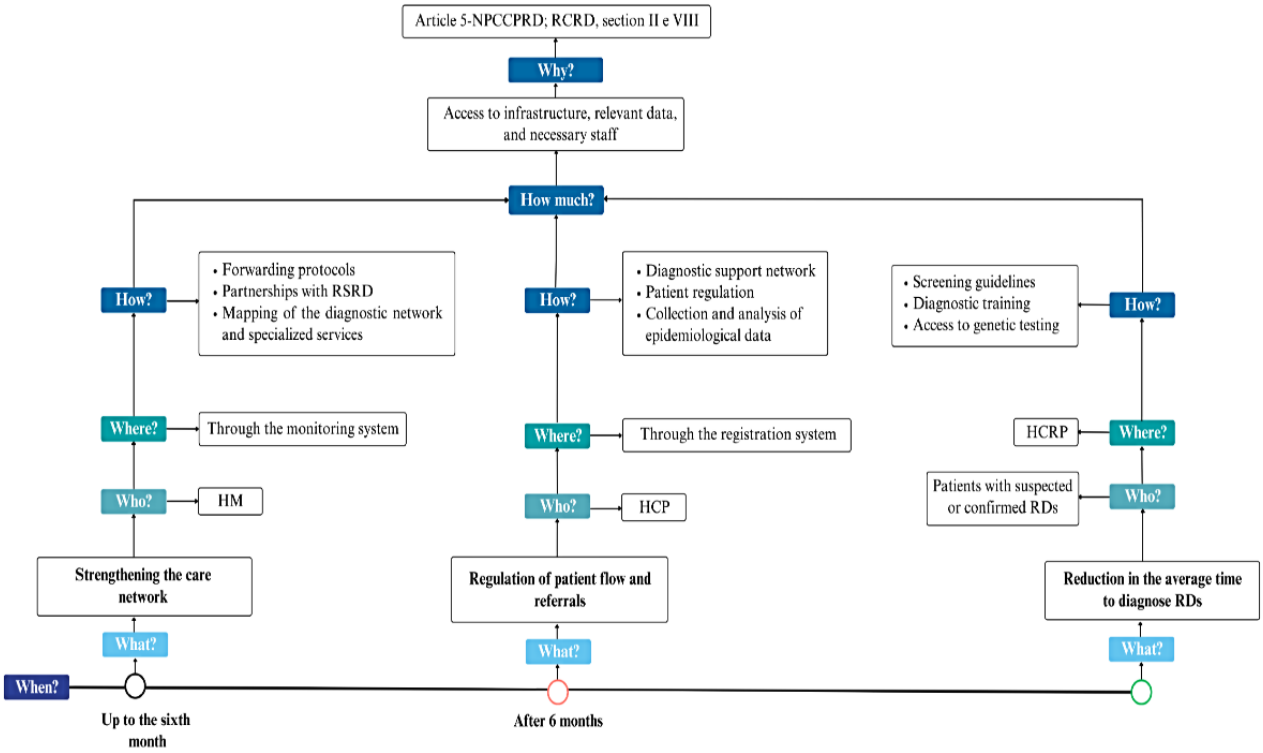

Figure 4. Registration and monitoring (line 2). HCRP: Clinics Hospital of Ribeirão Preto (Hospital das Clínicas de Ribeirão Preto); HCP: health care professional; HM: health manager; NPCCPRD: National Policy for Comprehensive Care for People with Rare Diseases; RCRD: reference center for rare diseases; RD: rare disease.

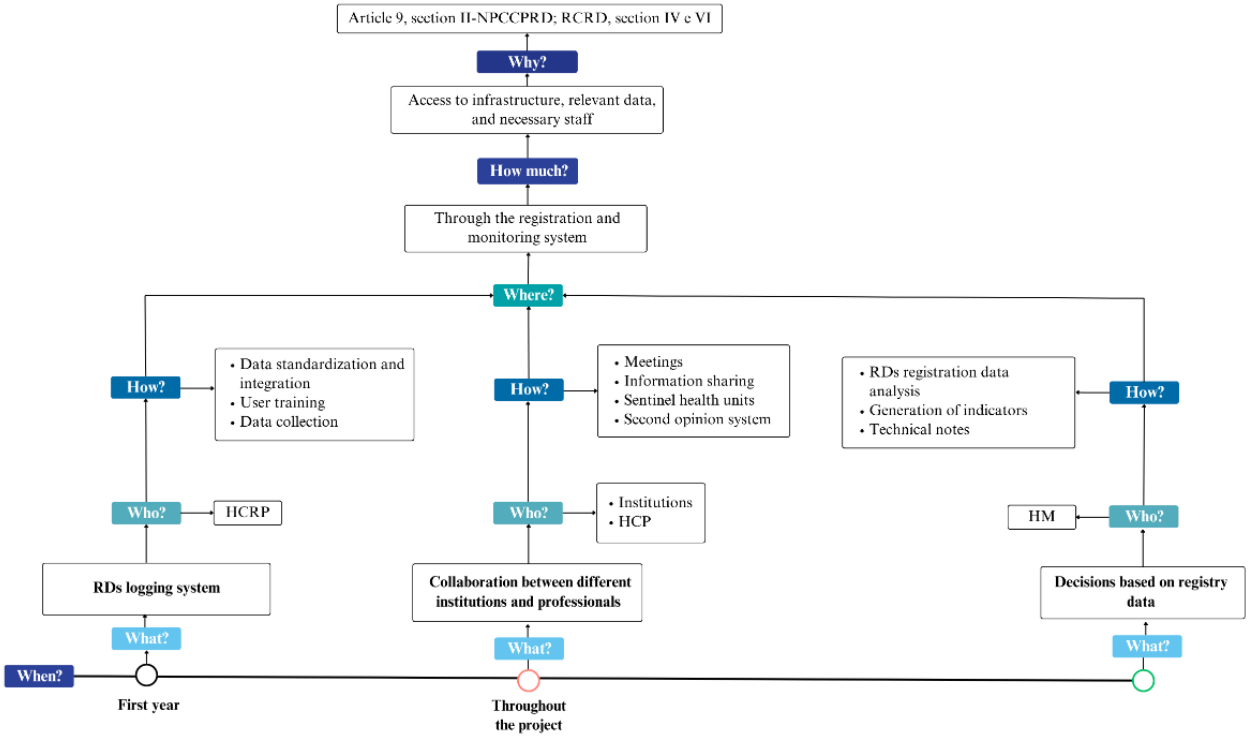

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Figure 5. Education and awareness (line 3). HCP: health care professional; HI: health care institute; NPCCPRD: National Policy for Comprehensive Care for People with Rare Diseases; RARAS: National Rare Diseases Network (Rede Nacional de Doenças Raras); RD: rare disease.

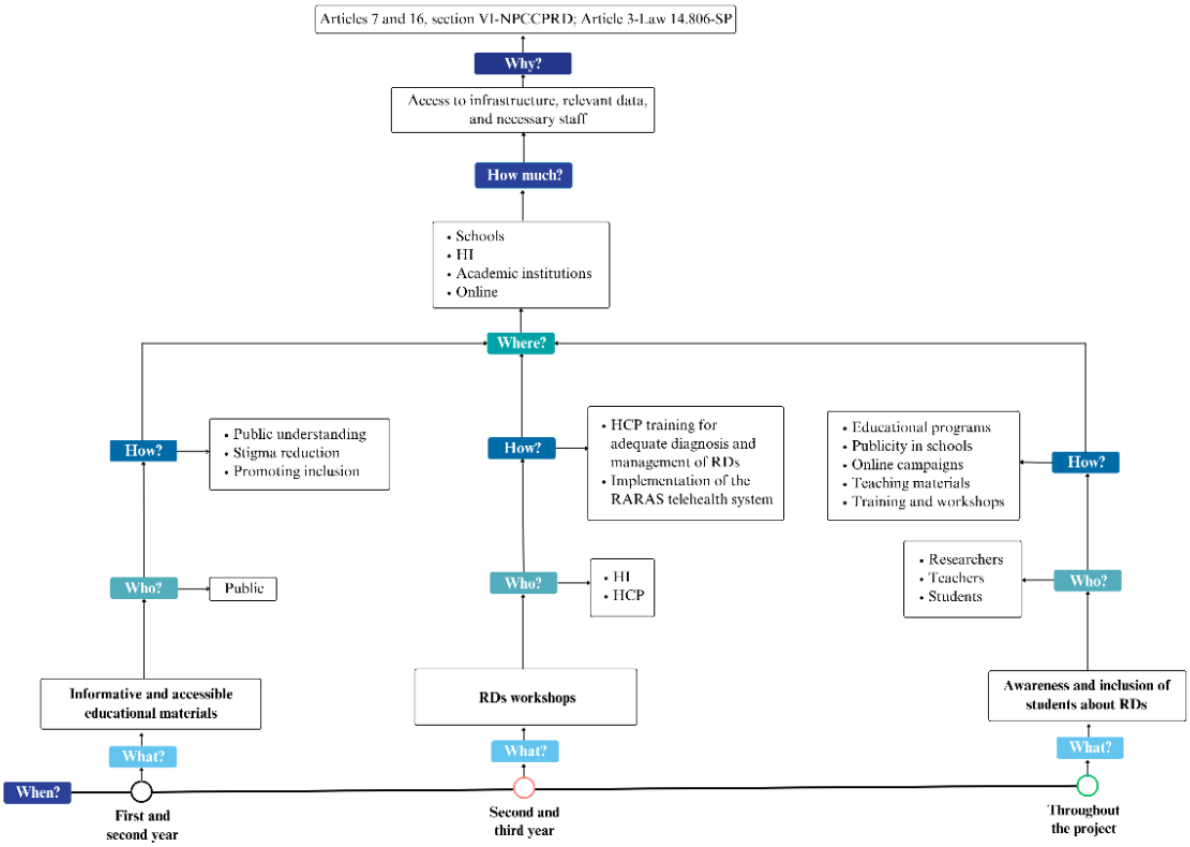

Produced Data and Metadata

The data and metadata produced may be structured or unstructured. Detailed clinical patient information will be collected, including diagnoses, treatments, and clinical evolution examinations. In addition, epidemiological data, such as the incidence and prevalence of RDs within the HCRP, will be recorded. For this purpose, the demographic profiles and associated risk factors of these patients will be used. When possible, registry and monitoring data will also be obtained, encompassing screenings, referrals, and outcome results from the patient's diagnostic journey. The information generated from educational and awareness actions, including produced content, description, characterization of the target audience, and the impact of interventions, will be stored.

The metadata will complement the study set by providing (1) descriptive information related to interpreting the study results and (2) statistical information concerning the reach, effectiveness, adoption, implementation, or use of the strategies and products generated by the study's 3 lines of action.

Furthermore, the project will use existing data from various information systems that may contain essential information about RDs. Due to the different data sources, there may be variations in formats, sizes, and structures from the initial entry of patient information to its conclusion.

The REDCap platform will ensure the secure collection and management of data. It offers a user-friendly interface for data entry, validation, and export. Each user will have password-protected access, with specific rights according to their role in the project (eg, data collector and health manager).

Results

This project received 3 years of funding starting in February 2024. We initiated technical meetings with the IT team at the HCRP-USP and the reference management team of the State Health Department to collect data on RDs from patient medical records covering the period from January 2020 to December 2024. On August 8, 2024, we submitted the research project to the HCRP-USP Research Ethics Committee. Some missing documentation was initially identified, and we were requested to make the necessary adjustments.

After addressing these issues, the project was resubmitted to the research ethics committee on August 23, 2024, and the adjustments were approved. Once the documentation was complete, the project was forwarded for evaluation by a committee rapporteur. On November 11, 2024, the rapporteur identified additional issues, including the need for a more detailed description of the research protocols concerning the locations and health units involved, the recruitment approach and dissemination methods, the invitation to participate, explanations regarding the questionnaires, improvements to the informed consent form, and adjustments to specific fields.

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The project was adjusted and revised per the suggested improvements and resubmitted to the research ethics committee. On December 9, 2024, it was approved and authorized for data collection at the study site. Following the selection and adaptation of a knowledge management maturity assessment instrument, with input from health specialists in the relevant context, on January 23, 2025, we distributed the questionnaire to health care managers involved with RDs at the study site. This step aimed to map the institution's level of maturity in knowledge management and will guide our subsequent developments.

In parallel, we mapped the management and informational processes inherent to the domain of RDs at the study site using the business process model and notation method. On the basis of these findings, we started to structure this knowledge in a semantic and interoperable way through a computational ontology. These processes are currently under development. A scoping review is also being conducted to identify the main guidelines for education and awareness on RDs. On the basis of the preliminary results of this investigation, we developed awareness-raising materials on the topic.

These materials were used in both digital and in-person awareness actions. Among the in-person initiatives, the most notable were the activity held at the HCRP-USP during World Rare Disease Day (February 28, 2025) and the public-facing event in downtown Ribeirão Preto on March 22, 2025.

Discussion

Anticipated Findings

This implementation study is expected to result in 3 main contributions: improved access to comprehensive care for people with RDs through a digitalized and interoperable network; enhanced patient registration and tracking supported by standardized data structures based on findability, accessibility, interoperability, and reusability principles [52]; and strengthened awareness and knowledge dissemination through training, educational materials, and second opinion support tools. These anticipated outcomes reflect an integrated approach involving technological innovation, governance, and collaborative networks that align with national and international public health strategies for RDs.

People living with RDs often endure an arduous diagnostic journey, averaging 7 years of inconclusive consultations and potential misdiagnoses. This leads to delays in effective treatments and inefficient use of health care resources. Incorporating up-to-date scientific knowledge provides a solid foundation for informed decision-making and implementing more effective strategies. Overall, using best practices, innovative approaches, and proven solutions is essential to address patients' challenges [53]. The engagement and use of the infrastructure and collaboration of the RARAS network, aligned with the governance and excellence of the HCRP as an RSRD, are crucial in achieving the objectives of this project. RARAS, composed of information systems [14], researchers, and specialized professionals, provides a solid foundation of collaboration and expertise needed to address the complex challenges we propose to solve. In turn, the efficient governance of the HCRP offers the necessary framework for coordinating activities, setting clear goals, and making strategic decisions.

Governance encompasses not only the internal management of the service but also network collaboration with other health care institutes, governmental bodies, and relevant stakeholders, aiming to maximize resources and optimize outcomes. At a global level, there is a consensus on the urgent need to develop a unified computerized system that allows for patient registration, monitoring, and evaluation, storing information ranging from the most basic data to screening, diagnosis, treatment, and hospitalization records. In other words, this involves digitizing the entire service to facilitate data collection and improve its analysis, visualization, and management. These tools can provide health intelligence to support evidence-based decision-making and actions, guide resource allocation and management, and assist in operationalizing the different levels of a health care network [15,54]. Despite the strong advocacy for enhanced digital technologies at national and local levels, implementing critical priorities in this research area has been slow, and actual funding remains a fraction of what is needed to make progress [55].

According to the Pan American Health Organization and the Brazilian MoH, digitalization and interoperability of health systems are fundamental to ensure more efficient and equitable care. However, implementing digital priorities at both national and local levels has been slow, delayed by inadequate funding and challenges in enhancing infrastructure [56,57]. In this context, the rapid and efficient transmission of information must be prioritized. When a manager, HCP, or patient needs to check what resources are available, they often lack the means to obtain this information. In addition, resource availability can change in real time due to the lack of interoperability between information systems, and the time spent searching for, allocating, and delivering services becomes excessive [58].

To address the prevalent problems of delayed diagnoses, inefficient resource allocation, and suboptimal patient outcomes, it is crucial to increase the availability of information and guidance for RD stakeholders in identifying appropriate institutions for specific care [14]. The interoperability of information systems is essential to ensure that there is a seamless and secure data flow among health care institutions, mitigating lengthy and inefficient processes in resource allocation. In addition, a systematic review showed that electronic health records could improve patient care by enhancing safety and lowering the risk of data errors, mainly in high-income countries, emphasizing the need for integrated systems to improve patient outcomes [59]. Studies, including one focused on COVID-19, demonstrate how frameworks, such as Hyperledger Fabric, can improve data security and interoperability, creating a patient-centric system for health data management [60].

Integrating digital technologies with international frameworks represents a pivotal innovation in RD management. It promotes interoperability and minimizes data redundancy. As Zanello et al [61] highlighted, global interoperability among clinical research networks is essential for advancing the diagnosis and treatment of RD. This project enhances data collection and

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analysis by adopting FAIR principles, facilitating evidence-based and timely decision-making. Implementing systems that standardize health data and enable secure sharing among stakeholders will significantly improve the quality and efficiency of care [61].

However, several limitations must be acknowledged. In regions with limited infrastructure, implementing digital tools faces significant challenges, including connectivity issues and cultural resistance to change [55]. Furthermore, the standardization of health data remains a challenge due to the diversity of systems and terminologies, underscoring the need for continued efforts toward harmonization [55]. The diversity of approaches found in the literature highlights the importance of this study in digital health as a means to advance the generation of knowledge that encompasses the complexity of using data information systems to assist in the care and follow-up of patients with RDs [14,15,62]. Through monitoring and coordination among different levels of care, information sharing through formal and informal mechanisms among various health services should acknowledge the need to use this information to guide epidemiological, clinical, and health management decision-making systems. To mitigate these limitations, the project includes codeveloped training programs, partnerships with local institutions, expert validation of ontologies and variables, and triangulation of multiple data sources to ensure data integrity.

The anticipated impact on health care systems is substantial, particularly in RD management. When integrated into digital health networks, structured data enhance operational efficiency and reduce the cognitive load on HCPs by centralizing critical information on inaccessible platforms [61].

These inefficiencies cause significant delays and low-quality service delivery despite the efforts of all stakeholders. Therefore, more access to specialized care and essential resources is needed. To address the prevalent problems of delayed diagnoses, inefficient resource allocation, and suboptimal patient outcomes, it is crucial to increase the availability of information and guidance for RD stakeholders in identifying appropriate institutions for specific care [14]. In addition, international benchmarks, such as the european reference networks, demonstrate that collaboration and interoperability can accelerate research and improve treatment access, aligning with this project's objectives [61].

Despite establishing the NPCCPRD, practical education and awareness efforts remain challenging due to persistent stigmas and limited information about specific conditions. These problems hinder referral, diagnosis, and treatment processes, imposing a significant burden on society. To address this bottleneck, knowledge management approaches provide effective techniques, standards, and technologies to identify critical points in these processes where targeted interventions can be implemented, aligning with the objectives of the national policy [63,64].

Interventions include providing educational materials in accessible language to the public, such as posters, guides, videos, social media posts, and mobile apps, as well as conducting training sessions and workshops to enhance the curricula of HCPs. Furthermore, comprehensive awareness campaigns targeting diverse audiences and specific events, such as International Rare Disease Day, play a critical and fundamental role. Promoting and supporting networks, patient groups, and associations for individuals and families affected by these conditions is equally important [65,66].

This study will follow the StaRI to guide reporting health interventions in real-world settings to ensure methodological transparency and reporting quality. Furthermore, the RE-AIM framework remains central to the project's evaluation strategy. These frameworks help ensure that the intervention is adaptable, sustainable, and adequately evaluated, offering insights for future scaling and policy-making.

Therefore, our proposal will benefit synergistically from the appropriation and application of scientific knowledge, resulting from the participation of a collaborative network with access to human and technological resources capable of supporting the effectiveness and efficiency of the expected interventions. The immersion and leadership of HCRP, in turn, transcend the activities carried out within the research network, as it is not only widely recognized for its excellence in research but also considered one of the 27 RSRDs in Brazil [25].

Conclusions

This research protocol outlines a strategic, evidence-informed approach to enhancing the care of individuals with RDs in Brazil. By integrating digital health solutions, institutional collaboration, and a comprehensive evaluation framework, the project aims to address persistent challenges, such as delayed diagnosis, inefficient resource allocation, and fragmented data systems.

By leveraging HCRP's leadership and the RARAS network's collaborative strength, this initiative has the potential to promote interoperable data systems, improve patient tracking and follow-up, and foster educational and awareness efforts. Implementing a unified digital infrastructure guided by FAIR principles and reinforced by structured training and knowledge management is expected to contribute to scalable and sustainable improvements in care coordination.

Beyond technical advancements, the project seeks to strengthen governance practices and inform public health decision-making, ultimately contributing to more inclusive, timely, and adequate health care for people with RDs. The systematic application of the RE-AIM framework and adherence to StaRI guidelines support the study's implementation and evaluation rigor.

These efforts are aligned with national and global priorities for RDs and illustrate how digital innovation, combined with strategic policy alignment and stakeholder engagement, can inform improvements in RD management within the SUS and beyond.

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Data Availability

The datasets generated or analyzed during this study will not be made publicly available for privacy reasons but will be available from the corresponding author on reasonable request.

Authors' Contributions

All authors contributed to the revisions of the intellectual content. All authors have approved the final manuscript. Contributions included conceptualization; methodology; investigation; and writing, reviewing, and editing the manuscript. FAB served as the team coordinator, overseeing project administration and ensuring collaborative progress throughout all stages of the research.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guide.
[DOCX File , 11 KB - resprot_v14i1e68949_app1.docx]

Multimedia Appendix 2
Peer-Review Report (English Version) by the Technological Innovation Programs/PPPP - Public Policy Research Program, São Paulo Research Foundation (FAPESP, Brazil).
[PDF File (Adobe PDF File), 268 KB - resprot_v14i1e68949_app2.pdf]

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Abbreviations

5W2H: what, who, where, when, why, how, and how much
HCP: health care professional
HCRP: Clinics Hospital of Ribeirão Preto (Hospital das Clínicas de Ribeirão Preto)
IR: implementation research
MoH: Ministry of Health
NPCCPRD: National Policy for Comprehensive Care for People with Rare Diseases
RARAS: National Rare Diseases Network (Rede Nacional de Doenças Raras)
RCRD: reference center for rare diseases
RD: rare disease
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
REDCap: Research Electronic Data Capture
RSRD: reference service for rare diseases
StaRI: Standards for Reporting Implementation Studies
SUS: Unified Health System (Sistema Único de Saúde)
USP: University of São Paulo

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Protocol

Cultural Adaptation of Together+, a Status-Neutral mHealth Intervention to Improve HIV Prevention and Care for Adolescent and Young Men Who Have Sex With Men in Vietnam: Protocol for a Co-Design Study

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Abstract

Background: Adolescent and young men who have sex with men (AYMSM) are experiencing an ongoing epidemic in Vietnam. HIV testing and preexposure prophylaxis uptake among AYMSM remain low in Vietnam, especially compared to older men. AYMSM living with HIV are also less likely to initiate HIV care. M-Cubed is a status-neutral mobile intervention developed in the United States focusing on HIV prevention and care among men who have sex with men. The app has the potential to significantly contribute to improving the HIV prevention and care continuum for AYMSM.

Objective: We propose to adapt the M-Cubed app for AYMSM in Vietnam to create Together+, a status-neutral app that promotes HIV testing, preexposure prophylaxis use, and HIV care.

Methods: Adaptation will focus on ensuring that the content, features, and design of the app are culturally relevant to AYMSM in Vietnam. The adaptation process will comprise five phases: (1) adaptation and creation of videos and messages in Vietnamese, (2) in-depth interviews to further inform app adaptation, (3) app prototype development, (4) app theater testing, and (5) beta testing of the adapted app. AYMSM aged between 15 and 19 years and health care staff in Hanoi, Vietnam, will be recruited for in-depth interviews in phase 1 and focus group discussions in phase 4. Qualitative data will be analyzed thematically, and results will be generated after reviewing memos, code reports, and the matrix. To evaluate the feasibility and usability of the Together+ app, we will provide access to 30 AYMSM and encourage them to use the app for 30 days. We will assess observed use and collect quantitative and qualitative data from test users. After 30 days, we will evaluate the usability and feasibility of the Together+ app through in-app analytics as well as online quantitative surveys and individual exit interviews with participants.

Results: As of September 2025, we are in the process of adapting the set of 15 videos for Vietnamese AYMSM (phase 1) and analyzing qualitative data from in-depth interviews (phase 2). Data collection for the pilot phase will be completed by August 2026.

Conclusions: Adaptations of proven effective interventions are a promising and efficient way to develop interventions for new service populations but require formal adaptation and evaluation in the new service population. Once culturally adapted for AYMSM in Vietnam, the Together+ app has the potential to significantly contribute to improving the HIV prevention and care continuum for this population. The findings of the adaptation process will document the level of usability and feasibility of the Together+ app and shed light on the perceptions of AYMSM and other stakeholders in Vietnam regarding status-neutral mobile health interventions.

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KEYWORDS

mobile health; mHealth; adolescents and young men who have sex with men; Vietnam; HIV; status neutral

Introduction

Background

The Asia-Pacific region ranks second highest among all regions in new diagnoses of HIV infection. The region accounts for almost a quarter of all new cases globally [1]. More than 90% of the people with HIV live in 6 countries in this region, including Vietnam [2]. In Vietnam, new HIV cases are primarily among men who have sex with men (MSM), among whom the HIV prevalence has more than doubled in the last 5 years [3]. Many of the newly identified cases in Vietnam are among adolescent and young MSM (AYMSM), and the prevalence of HIV among them is 12% [4]. In response to this epidemic among AYMSM, the Vietnamese government has recently allowed adolescents aged between 15 and 17 years to get tested for HIV without parental consent [5]. However, HIV testing and preexposure prophylaxis (PrEP) uptake among AYMSM in Vietnam have remained low; 58% of the AYMSM had never been tested for HIV, and 63% had never used PrEP before [6]. When compared with older MSM, AYMSM were also less likely to initiate HIV care promptly after HIV diagnosis [7]. Therefore, specific interventions are needed to reach the unique subgroup of AYMSM with HIV prevention and care services.

To end the HIV epidemic, people with and without HIV must be aware of and have access to treatment and prevention options (Figure 1 [8]). The status-neutral approach bridges the divide between HIV treatment and prevention [8]. This approach is advantageous for several reasons [8,9]: (1) HIV status-neutral interventions encompass testing, prevention, and treatment; therefore, common barriers to HIV testing; PrEP use; and HIV care, including difficulties navigating the health system, structural stigma, and health inequity, can be overcome [8,9]; (2) combining HIV prevention and treatment tools can create a unified setting that makes it more convenient for a person to access a comprehensive range of essential services for HIV testing, prevention, and treatment [8]; and (3) health equity may be improved by normalizing and destigmatizing HIV testing, PrEP use, and treatment [9].

Figure 1. HIV status-neutral approach (adapted from US Centers for Disease Control and Prevention Issue Brief [8]). This figure illustrates a status-neutral HIV care framework. Individuals who test negative for HIV are linked to prevention strategies such as preexposure prophylaxis (PrEP), condom use, and sexually transmitted infection (STI) testing. Those who test positive for HIV are connected to antiretroviral (ART) treatment, viral suppression, and retention in care.

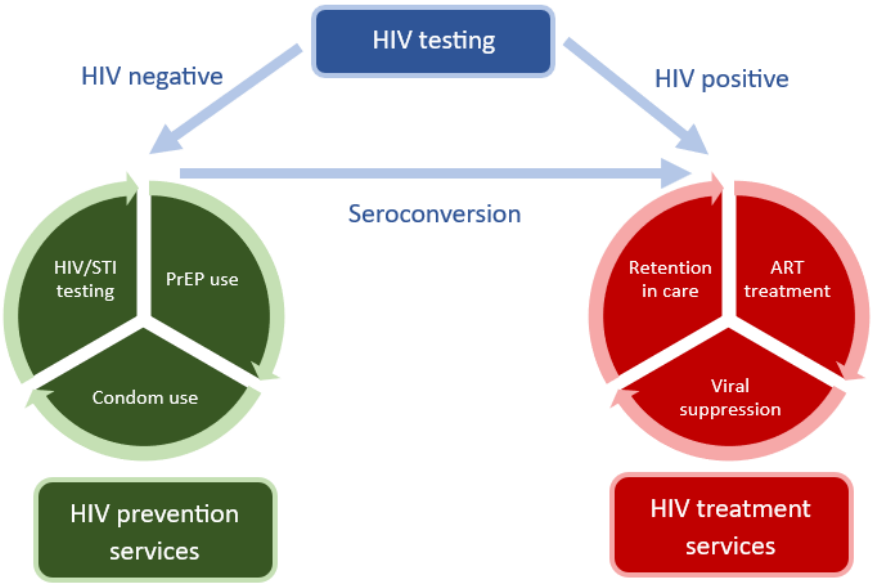

The use of mobile health (mHealth) is a promising approach for youth in low- and middle-income countries (LMIC), who are usually more technology savvy than older generations [10]. Many AYMSM are avid users of smartphones and might prefer receiving HIV-related information in a familiar and discreet environment [11,12]. The advantages of mHealth interventions include easy access, privacy, low cost, and the ability to reach hidden populations [10]. In Vietnam, 89% of youth considered themselves as having intermediate or advanced levels of mobile phone proficiency, and 81% had used a health care app before [13]. In a survey of MSM in Vietnam, 92% reported owning a smartphone, and 75% reported using their smartphones to find information related to HIV or sexually transmitted infections (STIs) online [14]. Nevertheless, mHealth interventions have rarely been developed specifically for AYMSM in LMIC [15,16]. For example, in a systematic review, we found that

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fewer than 20% of technology-focused intervention studies for MSM were conducted in LMIC, and fewer than 10% of the studies focused on young MSM (all of which were conducted in the United States) [16].

To end the HIV epidemic, people with and without HIV must be aware of and have access to treatment and prevention options. People of either serostatus are not distinct populations but rather 1 group with similar medical and social service needs [8]. The status-neutral approach in HIV care is a public health strategy that provides a unified pathway to care regardless of whether a person is living with HIV or at risk of acquiring HIV. This approach is designed to bridge the divide between HIV treatment and prevention [8]. Status-neutral mHealth interventions might offer unique opportunities to reach AYMSM in these settings. To the best of our knowledge, no apps that support both HIV prevention and care for AYMSM have been specifically designed and tested in Vietnam. In this study, we will adapt M-Cubed, an evidence-based intervention (EBI) developed in the United States, to create the Together+ app. We selected M-Cubed to adapt for AYMSM in Vietnam because the platform app on which M-Cubed was developed has high acceptability and feasibility [17]. In a randomized trial conducted by Sullivan et al [18], it was concluded that MSM who used the M-Cubed app were approximately twice as likely to use PrEP and undergo HIV testing compared to those who did not. The M-Cubed app is listed in the Compendium of EBIs and Best Practices for HIV prevention by the US Centers for Disease Control and Prevention (CDC) [19].

Aims

We conduct this study with the following aims: (1) to understand barriers to and facilitators of HIV testing, PrEP use, and HIV care among AYMSM in Vietnam; (2) to explore perspectives and preferences of AYMSM and other key stakeholders for status-neutral mHealth interventions to promote HIV testing, PrEP use, and HIV care among AYMSM in Vietnam; and (3) to adapt the M-Cubed app to develop a status-neutral mHealth intervention to promote HIV testing, PrEP use, and HIV care among AYMSM in Vietnam. We hypothesize that AYMSM and key stakeholders will express interest in a status-neutral mHealth intervention. We also hypothesize that the M-Cubed app can be successfully adapted to the Vietnamese context and will be perceived by AYMSM as acceptable, culturally appropriate, and feasible to use for promoting HIV testing, PrEP uptake, and linkage to HIV care, regardless of HIV status.

Methods

Study Design and Setting

We will conduct this study in Hanoi, the capital of Vietnam. Hanoi has the largest estimated MSM population in the country, with more than 30,000 MSM [20]. We will collaborate with a local app developer to tailor the M-Cubed app to address the specific needs of AYMSM related to HIV testing, PrEP use, and HIV care. Adaptation will focus on ensuring that the concepts, language, and context of the app are culturally relevant for AYMSM in Vietnam. The adaptation process will comprise five main phases: (1) adaptation and creation of videos and messages in Vietnamese, (2) in-depth interviews (IDIs), (3) prototype development, (4) theater testing, and (5) beta testing (Figure 2).

Figure 2. Study phases. This figure outlines the phased process of adapting and testing the Together+ app.

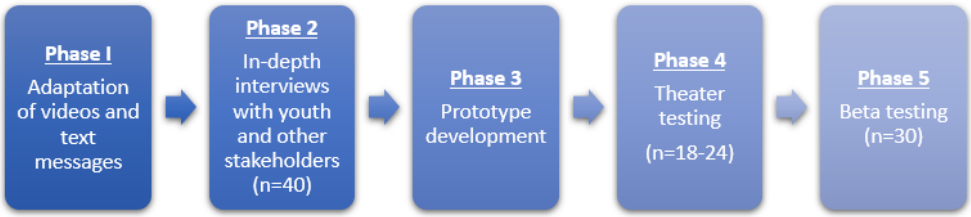

This study uses a co-design approach by actively involving AYMSM throughout the adaptation process. To understand the preferences and needs of AYMSM for status-neutral mHealth interventions and enhance the cultural relevance of the app, AYMSM and health care workers in Vietnam will be engaged throughout the adaptation process using IDIs, focus group discussions (FGDs), and community advisory board (CAB) meetings.

The Original App

The M-Cubed app is a status-neutral mobile intervention for HIV prevention and care needs of MSM [18]. It was developed and tested in the United States and is based on the social cognitive theory [21]. The intervention offers a range of HIV testing, prevention, and care services. Key features of the app include self-screening for HIV and STI risk, a scheduling and reminder system for HIV and STI testing, a PrEP and postexposure prophylaxis eligibility screener, an ordering platform for delivery of at-home test kits and condoms, and locators for HIV services [18] (Table 1). The M-Cubed app also provides written and video messages customized to the participant's risk, HIV status, and corresponding needs [18].

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Table 1. Key features of the M-Cubed app.

	Key features
Initial and monthly risk assessments	Tailored, HIV-related prevention suggestions based on quiz responses
PrEP[a] screener	Assess PrEP eligibility using a questionnaire
nPEP[b] screener	Assess nPEP eligibility using a questionnaire
Find my frequency	Suggest HIV testing frequency based on risks
Compare HIV tests	Comparison and recommendation on HIV tests
My test plan	Users can plan an HIV test by date, time, and location
Reminders	Reminders to take PrEP or get tested for HIV
Ordering	Free at-home HIV test kits, condoms, and lubricants
Location details and map	Provide a map and details about testing locations
Written and video messages	Focus on condom use, HIV and STI[c] testing, PrEP use, condom use, ART[d] use, and engagement in care
FAQs[e]	Frequently asked questions related to HIV

[a]PrEP: preexposure prophylaxis.
[b]nPEP: nonoccupational postexposure prophylaxis.
[c]STI: sexually transmitted infection.
[d]ART: antiretroviral therapy.
[e]FAQ: frequently asked question.

Community Advisory Board

The study team has established a CAB consisting of 8 members (n=4, 50% AYMSM with both HIV statuses; n=4, 50% HIV health care workers, ie, physicians, nurses, and counselors). The app's name (Together+) was suggested by the CAB to reflect the app's inclusive approach to supporting all AYMSM regardless of their HIV status. Both the word "Together" and the "+" sign emphasize unity, community, and shared experiences of users of both HIV statuses. We will meet with CAB members regularly to ensure that the contents of Together+ follow current Vietnamese guidelines for HIV testing, PrEP initiation, and HIV care and include information about HIV and PrEP clinics in Hanoi. We will also consult with them about the social, cultural, and legal contexts of HIV service delivery in Vietnam.

Study Phases

Phase 1: Adaptation and Creation of Videos and Messages in Vietnamese

The original M-Cubed app has 15 videos with a total duration of 23 minutes. These are CDC-made, public service announcements developed in the United States. The videos have 5 domains: condoms, PrEP, HIV testing, STI testing, and antiretroviral therapy use or engagement in care. The study team will collaborate with the CAB to review the content of these videos and make necessary changes to ensure that they are culturally relevant to the current HIV landscape in Vietnam. The CAB will provide feedback on the appropriate video formats for each type of content, including live-action videos and animated and motion-graphic videos, and content not included in the original set of videos, such as event-driven PrEP, long-acting injectable PrEP, and Undetectable=Untransmittable (U=U) message, will be added. A new set of 15 videos in Vietnamese, featuring Vietnamese actors, will be created. Text messages will be translated into Vietnamese and refined by the study team and the CAB to fit the local context.

Phase 2: IDIs With AYMSM and Other Stakeholders

We will recruit up to 40 participants from 3 groups for IDIs: AYMSM with HIV (n≈15); AYMSM with unknown HIV status or without HIV (n≈15); and key stakeholders (n≈10), including health officials and staff from HIV and PrEP clinics. A trained Vietnamese interviewer will ask participants about their perspectives on the acceptability, feasibility, and potential impacts of the Together+ app to improve HIV testing, PrEP use, and HIV care for AYMSM in Vietnam. The IDI guide is included in Multimedia Appendix 1. Key features of the original app will be summarized, and participants will share their opinions on desired contents, features, and design of the Together+ app. Feedback and suggestions for the set of videos and messages will also be collected during the IDIs.

Phase 3: Prototype Development

On the basis of input from the CAB members and the results of the IDIs, we will summarize data on the preferred content, features, and design of the app and use those summaries for discussion with a local app developer to create the prototype of the app. Prototype development is an iterative procedure where the study team will oversee the process and conduct weekly meetings with the app developer. During these meetings, we will provide an update on the progress, share materials, discuss any issues, and refine the prototype before using it for theater testing.

Phase 4: Theater Testing

When the prototype is available, theater testing will be conducted through 3 FGDs (6-8 participants each), 2 for AYMSM and 1 for health care workers who care for AYMSM.

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During theater testing, participants will interact with the Together+ prototype and provide feedback on the functionality, appearance, and usability of the platform. During the FGD with AYMSM, the interviewer will ask participants to identify the components of the app that they like or dislike and features that could facilitate app engagement among youth. The FGD with other stakeholders will aim to understand their perspectives on the HIV and PrEP contents to be included and aspects of the app that could be improved to encourage HIV testing and PrEP uptake among AYMSM. The FGD guide is included in Multimedia Appendix 2. Data will be used to refine the app and create the beta version.

Phase 5: Beta Testing

Even though the platform on which the M-Cubed app was developed has been proven to be highly acceptable and feasible [17], beta testing will be conducted to ensure that the Together+ app is usable and its features are used as intended by the target population. A total of 15 AYMSM living with HIV and 15 not living with HIV or having unknown HIV status will be invited to participate in beta testing. Study staff members will be trained on the contents and features of the app beforehand. During the study visit, staff members will help participants download the app and provide instructions on how to use it. Participants who provide consent to download the app on their own will be encouraged to use the app for 30 days and take advantage of all features that are of interest to them. After 30 days, we will evaluate the usability and feasibility of the Together+ app through an online quantitative survey and individual exit interviews with each participant.

Participants and Recruitment Strategy

We will recruit AYMSM and other stakeholders into the study. Recruitment methods for AYMSM will include posting advertisements on popular social networking websites (eg, Facebook and Instagram), distributing flyers about the study, and direct outreach at community-based organizations and clinics serving MSM and people with HIV in Hanoi. Other stakeholders are health care workers who will be recruited through referral and direct outreach to Hanoi CDC and HIV and PrEP clinics in Hanoi. Interested participants will be referred to the study staff for eligibility screening over the phone. During phase 2 (IDIs) and phase 4 (theater testing), eligibility criteria for AYMSM include the following: (1) aged between 15 and 19 years, (2) biologically male at birth, (3) identifying as male, and (4) having previously engaged in anal sex with another man. We will purposively sample an equal number of AYMSM from 2 groups: AYMSM with HIV-negative or unknown status and AYMSM with HIV-positive status. In addition, AYMSM participating in theater and beta testing are required to own a smartphone. For beta testing, AYMSM will be ineligible if they are unwilling to provide contact information or plan to leave Hanoi in the next 3 months.

Eligibility criteria for other stakeholders include the following: (1) health officials working in HIV prevention or HIV care at Hanoi CDC for at least 6 months or (2) counselors or health care providers working in HIV and PrEP clinics in Hanoi for at least 6 months.

Data Collection

Before IDIs and FGDs, basic demographic characteristics will be collected from each consenting respondent. IDIs and FGDs will be conducted in a private room by trained interviewers and will be audio recorded. During beta testing, we will assess the usability of the adapted app using the System Usability Scale (SUS) through an online survey sent to participants. The SUS is a validated 10-item measure that has been extensively used in mHealth research to measure the acceptability of mobile apps [22]. Feasibility will be evaluated based on data on app engagement collected through app analytics, such as the number of times participants accessed the app over 30 days, features used, and duration of use. Beta testers will be interviewed online at the end of this phase to provide feedback on app functionality, technical performance, errors, and overall experiences using the app. This in-depth exit interview will be completed on Zoom (Zoom Communications, Inc) by a trained interviewer. All interviews will be audio recorded and transcribed.

Data Analysis

For qualitative data in phases 2 and 4, memos of emergent themes and patterns will be written for each interview. A codebook will be developed based on the main topics, and the coding process will include 2 investigators to ensure intercoder reliability. A qualitative matrix will be created to document similarities and differences in the perspectives of participants. Study results will be generated after reviewing memos, the codebook, and the matrix.

After beta testing, we will summarize the mean SUS score as well as app use data to evaluate usability and feasibility, respectively. Data from the SUS will be scored from 0 to 100, and a score of 50 or greater indicates that the app is acceptable [23]. We will apply a rapid qualitative approach to summarize and analyze data from exit interviews at the end of the beta testing phase. For each question in the interview guide, the notetaker will take real-time summary descriptions of participant responses in Vietnamese, using a template of the interview, consistent with previously described approaches for generating interview summaries in real time [24,25]. Two investigators will use matrix or table-based analysis methods to summarize major discussion points across the templated summaries [24,25]. Rigor and validity will be established by independently coding and assigning these data in the matrix, along with discussions with the larger team. These data will be used to refine the beta testing for further and larger-scale evaluation of the adapted app.

Sample Size

Following recommendations for qualitative studies, a sample size of 30 to 40 participants for the qualitative study would likely be sufficient for saturation [26]. In addition, our sample size for the adaptation phases is similar to other pilot studies involving the development of mHealth interventions for young MSM [27,28]. The inclusion of different groups of participants in our study allows for the exploration of various perspectives from different types of stakeholders.

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Ethical Considerations

This study has been reviewed and approved by the institutional review board at Hanoi Medical University (1555/GCN-HMUIRB). All research activities involving human participants complied with institutional and national ethical guidelines.

Participants will provide written informed consent before participation. For participants aged between 15 and 17 years, assent will be obtained, and parental consent will be waived. All participants will be informed of their right to withdraw from the study at any time without any consequences.

Data collected during the study were deidentified at the point of entry and stored securely on password-protected, encrypted servers accessible only to authorized research personnel. No identifiable images or information are presented in this paper or the multimedia appendices.

Participants will receive compensation of VND 300,000 (US $11.4) to VND 500,000 (US $19) to cover transportation and time spent during study participation. This amount was determined to be aligned with local standards for ethical participant compensation.

Results

As of September 2025, we are implementing phase 1 and 2of the study. The study team has conducted 3 meetings with the CAB, and we plan to conduct meetings with them every 3 months. We are in the process of adapting the set of 15 videos for Vietnamese AYMSM (phase 1). We have finished recruiting AYMSM and other stakeholders for IDIs and we are transcribing and analyzing these data (phase 2). Data collection for the last phase will be completed by August 2026, and study results are expected to be available by the end of 2026.

Discussion

Anticipated Findings

AYMSM in Vietnam and similar low-resource countries bear disproportionate burdens of HIV. This population urgently requires attention and intervention. AYMSM have unique needs for HIV prevention and care due to the major physical and emotional changes that they undergo during adolescence [29]. We hypothesize that AYMSM in Vietnam will identify both structural (eg, stigma and limited access) and individual-level (eg, low-risk perception and mental health challenges) barriers to HIV testing, PrEP use, and HIV care while also recognizing facilitators of HIV care, such as peer support, digital health tools, and youth-friendly services. We also hypothesize that AYMSM will prefer features that offer privacy, tailored health information, motivational messaging, and easy linkage to youth-friendly HIV services in the status-neutral app.

This study addresses the urgent need for culturally tailored, accessible, and effective HIV prevention and treatment solutions for AYMSM in Vietnam—a population with high HIV prevalence that is underserved in traditional health care settings. To improve the HIV prevention and care continuum for AYMSM, we are creating the culturally adapted Together+ app. The findings of this study will assess the usability and feasibility of the Together+ app and shed light on perceptions of AYMSM and other stakeholders in Vietnam on status-neutral mHealth interventions.

Our approach builds on evidence from the global literature that mHealth interventions can significantly enhance HIV prevention behaviors among key populations [10]. Previous work with MSM in high-income settings has demonstrated that tailored, mobile-based interventions improve engagement with HIV testing and PrEP uptake [18,30]. In addition, our use of a status-neutral framework, which emphasizes services for individuals regardless of HIV status, aligns with emerging global public health strategies that aim to reduce stigma and fragmentation in care delivery [31,32]. The status-neutral approach facilitates the simultaneous management of health care and social service needs of all people affected by HIV. This approach is relatively novel in Vietnam and contributes to a growing body of work promoting more inclusive, person-centered care models.

Given the ubiquity of smartphones among AYMSM and the effectiveness of mHealth interventions on HIV-related outcomes, our status-neutral app will have the potential to reach and benefit this vulnerable population. We opted to adapt an existing effective app rather than design a new app from scratch because adapting EBIs for low-resource settings is more efficient than de novo development. Lessons learned and other data from the adaptation process can be disseminated and applied to the adaptation of other technology-based interventions in LMIC.

Strengths and Limitations

This study exemplifies a co-design approach by actively engaging AYMSM and health care workers in shaping the creation of the Together+ app. Rather than making top-down modifications based solely on theory and expert opinion, the process integrates user insights at multiple stages, from content creation to theater and beta testing, ensuring that the app is culturally relevant and meets the specific needs of AYMSM in Vietnam. Collaboration with a local app developer further supports this participatory approach, allowing for iterative refinements based on user feedback. By incorporating diverse perspectives through IDIs, FGDs, and CAB meetings, we will foster a sense of ownership among stakeholders, ultimately enhancing the app's usability and effectiveness.

Due to the limited timeline and funding received by this research, we could only conduct field testing of the Together+ app in a sample of AYMSM in 1 city in Vietnam. We may experience challenges recruiting AYMSM with HIV, but we expect to be able to enroll our small sample size, especially given our experience of recruiting AYMSM. If enrollment challenges arise, we will partner with community-based organizations, HIV clinics, and peer networks while leveraging social media outreach to improve recruitment rates among AYMSM with HIV. In addition, we will ensure confidentiality of participants and consult with the CAB to build trust with and encourage participation from AYMSM.

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Future Directions and Dissemination Plans

Building on the results of this formative study, we plan to conduct a larger, multisite randomized controlled trial to assess the effectiveness of the Together+ app in improving HIV prevention and care outcomes among AYMSM. Future studies should also investigate the app's impact on mental health, sexual well-being, and social connectedness, which are often interconnected with HIV-related behaviors in this population.

In parallel, we will disseminate lessons learned from the adaptation process to support other researchers and practitioners aiming to adapt technology-based HIV interventions in LMIC contexts. By advancing the science of culturally informed, status-neutral, and youth-centered mHealth design, this study contributes to global efforts to reduce HIV incidence and improve care engagement among vulnerable populations.

Conclusions

This protocol details the adaptation process of the M-Cubed app to create the Together+ app, a version for use among AYMSM in Vietnam. By adapting an evidence-based status-neutral mHealth intervention from the United States, this research ensures that the contents, features, and design of the app align with the unique social, cultural, and structural factors influencing HIV risk and care in Vietnam. Findings will inform the planning for a future hybrid effectiveness-implementation randomized controlled trial to rigorously test the effectiveness of the Together+ app and explore factors affecting its scaling up in Vietnam.

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Data Availability

Data sharing is not applicable to this paper as no datasets were generated or analyzed during this phase of the study.

Authors' Contributions

MXN, WCM, and PSS designed the research study. MXN, WCM, LMG, and PSS conceptualized the research question. MXN drafted the paper. MXN, WCM, LMG, and PSS revised it critically for important intellectual content. All authors read and gave final approval for the publication of the manuscript.

Conflicts of Interest

Author PSS is an Associate Editor for *JMIR Public Health and Surveillance*.

Multimedia Appendix 1
In-depth interview guide.
[DOCX File , 19 KB - resprot_v14i1e73895_app1.docx]

Multimedia Appendix 2
Focus group discussion guide.
[DOCX File , 19 KB - resprot_v14i1e73895_app2.docx]

Multimedia Appendix 3
Peer review report by Collaborative Initiative for Paediatric HIV Education and Research (CIPHER) Grant Review Committee, International AIDS Society (IAS).
[PDF File (Adobe PDF File), 545 KB - resprot_v14i1e73895_app3.pdf]

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Abbreviations

AYMSM: adolescent and young men who have sex with men
CAB: community advisory board
CDC: Centers for Disease Control and Prevention
EBI: evidence-based intervention
FGD: focus group discussion
IDI: in-depth interview
LMIC: low- and middle-income country
mHealth: mobile health
MSM: men who have sex with men
PrEP: preexposure prophylaxis
STI: sexually transmitted infection
SUS: System Usability Scale

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Protocol

Digitally Mediated Occupational Therapy to Increase Physical Activity in Urban and Rural Breast Cancer Survivors: Protocol for a Single-Arm Feasibility Trial

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Abstract

Background: The 5-year survival rate for breast cancer (BC) has increased in recent years. However, functional limitations associated with BC treatment (eg, loss of strength, fatigue, and lymphedema) often have far-reaching effects on survivors' physical and mental health. Aerobic physical activity (PA) and muscle-strengthening exercise (MSE) can reduce functional limitations, and occupational therapy (OT) can support these health-promoting behaviors after treatment. Yet, barriers to access among BC survivors (eg, time burden and distance to the OT clinic) limit participation in OT programing. This is particularly true in Oklahoma, where 33% of residents live in rural counties. Digital technologies (eg, telehealth) can help urban and rural BC survivors circumvent these barriers.

Objective: We are investigating the feasibility of a novel OT program among urban and rural BC survivors that features (1) 8 once-weekly telehealth OT sessions targeting constructs grounded in Self-Determination Theory (SDT), and (2) self-regulatory strategies known to support aerobic PA and MSE in BC survivors including self-monitoring via a wearable PA tracker, goal setting, and the provision of timely feedback.

Methods: This is a single-arm feasibility trial. We are recruiting 38 BC survivors using community-based recruitment approaches and via referral from collaborating oncologists. Participants include individuals who have undergone primary treatment and/or breast-conserving surgery or mastectomy for BC in the last 24 months and who do not meet recommended PA levels at the time of enrollment. We will assess self-reported program acceptability and feasibility via recruitment rates, study retention, and protocol adherence. We will also evaluate program safety by tracking BC-related lymphedema events, musculoskeletal injuries, and other adverse events. Finally, we will assess changes in aerobic PA, MSE, and health-related quality of life during the program period using accelerometry and self-report measurement tools.

Results: We received funding in March 2024 and institutional review board approval in September 2024. We began recruiting in November 2024. We anticipate completing data collection in early 2026. We hypothesize that the SDT-grounded OT program will be acceptable, feasible, and safe. We also expect pre- to post-program improvements in (1) SDT-informed determinants of PA, (2) levels of aerobic PA and MSE engagement, and (3) health-related quality of life.

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Conclusions: The novel OT program under investigation is designed to decrease barriers to engaging in aerobic PA and MSE among people who have undergone various BC treatments. It is centered on facilitating a successful transition from active treatment to the posttreatment period and combines OT with the benefits of telehealth delivery and health behavior change theory. This program is amenable to wide-scale dissemination and, if shown to be acceptable and feasible, will represent a promising approach to supportive cancer care.

Trial Registration: ClinicalTrials.gov NCT06671730; https://clinicaltrials.gov/study/NCT06671730

International Registered Report Identifier (IRRID): DERR1-10.2196/73554

(JMIR Res Protoc 2025;14:e73554) doi:10.2196/73554

KEYWORDS

Self-Determination Theory; muscle-strengthening exercise; telehealth; supportive care; mobile phone

Introduction

Background

The 5-year breast cancer survival rate across all races is 90% [1]. However, given that most breast cancer diagnoses lead to either breast-conserving surgery or mastectomy, survivors tend to experience considerable functional limitations caused by both cancer and its treatment. These functional limitations include lymphedema, reduced range of motion, fatigue, and pain, and often impact survivors' physical and mental health-related quality of life (HRQoL) [2]. Unfortunately, these functional limitations can restrict participation in health-promoting activities, such as aerobic physical activity (PA) and muscle-strengthening exercise (MSE) [3], placing survivors at an increased risk of morbidity and premature mortality [3,4]. Therefore, developing programs that reduce functional limitations and engage breast cancer survivors in aerobic PA and MSE is critical to improving health and well-being while decreasing risk factors.

PA is safe and beneficial for most cancer survivors [2,5] and can improve HRQoL via increased self-efficacy and physical, emotional, social, and functional well-being [6]. Yet, less than 20% of breast cancer survivors meet recommended aerobic PA and MSE guidelines [7-9]. Qualitative research highlights that breast cancer survivors are uncertain about how to integrate aerobic PA and MSE into their lives after transitioning out of formal care settings. Support is needed to help this population with lingering functional limitations to transition into sustained, self-directed PA and MSE in community- and home-based settings [10].

Occupational therapy (OT) is uniquely capable of addressing the functional limitations that restrict PA and MSE in breast cancer survivors through a combination of rehabilitation for physical function, adaptation of activity for functional limitations, environmental modification, and through developing supportive habits and routines. The goal of OT for cancer survivors is to safely and independently return to activities of daily living following cancer treatment. As such, OT is a critical posttreatment component for breast cancer survivors, who are likely experiencing multiple functional limitations. Self-Determination Theory (SDT) posits that the satisfaction of people's core psychological needs (ie, autonomy, competence, and relatedness) facilitates the formation of autonomous motivations for health-related behaviors (ie, enjoyment, interest, identity, and values) [11,12]. Importantly, SDT has been proposed as an ideal theoretical framework for guiding OT (Figure 1) [13,14]. Grounding OT treatment in SDT can support sustained, self-directed PA, and MSE through orienting survivors toward growth and development.

Figure 1. Conceptual model for a Self-Determination Theory–informed occupational therapy program for sustained physical activity. OT: occupational therapy; PA: physical activity.

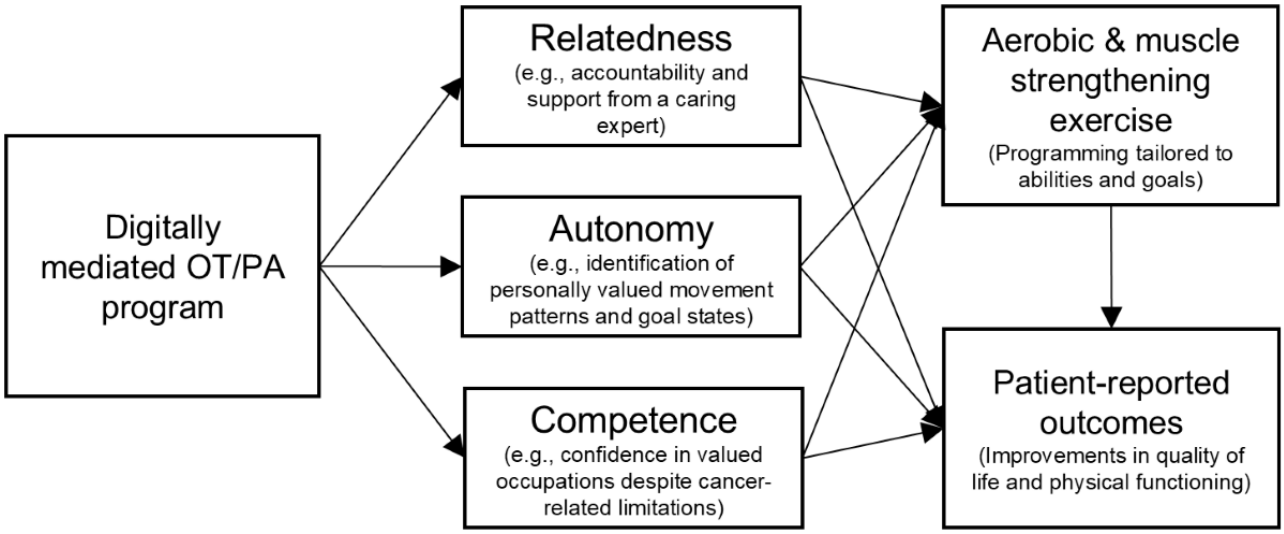

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Digitally mediated OT is uniquely suited to helping breast cancer survivors (in particular, rural survivors) transition to sustained community- and home-based PA after undergoing primary breast cancer treatments (eg, lumpectomy and partial or full mastectomy), dramatically increasing the accessibility of expert-provided PA and MSE programing. The use of digital technologies, such as telehealth, can help urban and rural breast cancer survivors circumvent challenges (eg, time burden and distance to OT clinic) to receiving OT programing [15-17]. In Oklahoma, breast cancer continues to pose a significant health challenge, with incidence rates around 124.5 per 100,000 women [18]. Survivors in rural areas often face barriers to care, including long travel distances, limited access to specialists, and socioeconomic constraints. To address these challenges, telerehabilitation has emerged as a promising solution. Emerging evidence suggests that technology-mediated OT is feasible for urban and rural breast cancer survivors [19,20]; however, a review of the literature highlights a lack of accessible and individualized programs to improve PA engagement in this population [21].

To that end, we are conducting an Obesity-Related Behavioral Intervention Trials Phase II trial [22] to investigate the acceptability and feasibility of a novel 8-week OT program among 38 urban and rural breast cancer survivors that features (1) 8 once-weekly telehealth OT sessions, and (2) self-regulatory strategies known to support aerobic PA and MSE adoption and maintenance [23,24], emphasizing components of the SDT, and the provision of a wearable device (eg, a fitness tracker) programed to supplement individually tailored goals. Our specific aims, hypotheses, and milestones are detailed in the following sections.

Aim 1

Assess participants' perceptions of the acceptability and usefulness of the SDT-grounded, OT-based aerobic PA and MSE program (hereafter "program"). Hypothesis 1: participants will report the program's components to be acceptable, useable, and useful. Milestone 1a: thematic analyses of qualitative data will suggest that the program was enjoyable and improved physical and mental well-being. Milestone 1b: quantitative assessments of items reflecting program acceptability will have a median of 5 or higher on a 7-point Likert-type scale.

Aim 2

Evaluate program feasibility and safety. Hypothesis 2: the program will be feasible and safe as demonstrated by satisfactory participant retention and adherence to program components and no serious adverse events related to the program. Milestone 2a: at least 70% of participants who complete baseline measures will subsequently complete post-program measures. Milestone 2b: participants will average ≥80% attendance at OT sessions. Milestone 2c: the frequency of breast cancer–related lymphedema, musculoskeletal injuries, and any adverse events will be at or below normative values—indicative of a safe program [25-27].

Exploratory Aims

Evaluate pre- to post-program changes in (1) SDT-related constructs (autonomy, competence, and relatedness) as key mechanisms of action, (2) aerobic PA and MSE, and (3) patient-reported outcomes (PROs, eg, physical function, anxiety, and pain intensity and interference) and goal attainment. Exploratory hypotheses: pre- to post-program changes in SDT-related components, aerobic PA and MSE behaviors, and PROs and goal attainment will be favorable. Milestone 3a: measures of perceived autonomy, competence, and relatedness—key SDT components in the context of aerobic PA and MSE—will improve from pre- to post-program [28]. Milestone 3b: participants will demonstrate a median aerobic PA increase of ≥10 minutes per day and will engage in at least 2 MSE bouts per week by post-program. Milestone 3c: an average pre- to post-program change of 2-6 t-score points, dependent on the PRO being assessed, as measured by the Patient-Reported Outcomes Measurement Information System (PROMIS), with most participants (≥75%) achieving their pre-program goals by post-program.

Methods

Participants and Recruitment

Participants (N=38) in this feasibility trial are urban and rural breast cancer survivors within Oklahoma City and the greater state of Oklahoma. We define rurality using the US Department of Agriculture Economic Research Service's 2020 Rural-Urban Commuting Area codes [ie, metropolitan (1-3) vs micropolitan, small town, and rural (4-10)]. We are conducting rolling recruitment, with a target accrual rate of approximately 5 participants per month. We are recruiting English-speaking participants from local survivorship organizations and events, by approaching patients and posting flyers at the Stephenson Cancer Center, through The University of Oklahoma Health Sciences (OUHS) social media advertising, and via direct referral from a collaborating oncologist. We are evaluating the eligibility of prospective breast cancer survivor participants using a screening questionnaire administered via REDCap (Research Electronic Data Capture). Qualifying breast cancer survivors are then contacted by a study team member to set up their baseline consenting and orientation appointment. Eligible participants must be aged 18 years and older, able to speak and read English and provide informed consent, must have received a histologically confirmed diagnosis of invasive breast carcinoma, have undergone primary treatment and/or surgery for breast cancer in the last 24 months, own a smartphone or computer with internet access, and be willing to participate in once-weekly telehealth-delivered OT sessions for 8 weeks. Individuals are ineligible if they are currently undergoing chemotherapy or radiation as primary cancer treatment, planning or preparing for surgery as primary treatment or as a reconstruction procedure in the next 3 months, have a distant metastasis, or report a Physical Activity Readiness Questionnaire score that indicates that PA may potentially be unsafe, unless the participant produces a signed doctor's note. Additionally, individuals are eligible if they are already engaging in ≥75 minutes per week of vigorous-intensity PA; ≥150 minutes per week of moderate-intensity PA, or an equivalent combination of both over the last 3 months; if they are currently seeking OT or physical therapy treatment; or if they are a prisoner, pregnant, or planning to become pregnant. Although a power analysis

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was not appropriate due to our study's pilot classification, a sample size of 38 participants was chosen, given that, anticipating attrition, this sample size (1) facilitates the detection of feasibility issues and provides sufficient data for useful parameter estimates, and (2) strikes a practical balance between our scientific objectives and available resources [29]. This trial is registered on ClinicalTrials.gov (NCT06671730).

Program Description

The telehealth-based OT program is grounded in SDT (Figure 1), with the participant timeline throughout the study presented in Figure 2. The program is designed to help breast cancer survivors transition from recovery after surgery to achieving levels of aerobic PA and MSE that are recommended according to each participant's specific treatment course and desired outcomes [2,10,30]. Participants are engaging in 8 once-weekly OT sessions with a licensed occupational therapist using videoconference software (Zoom; Zoom Communications). Each session lasts up to about an hour and is centered on psychoeducational and skill-building techniques to (1) reduce functional limitations associated with cancer and its treatment and (2) develop behavioral skills for maintenance of aerobic PA and MSE. We chose an 8-week program duration with once-weekly sessions because this duration and cadence aligns with typical OT treatment plans and was deemed to provide sufficient time to support meaningful changes in physical and psychological health outcomes while maintaining participant engagement, minimizing attrition, and ultimately supporting program scalability.

Figure 2. Participant timeline. BC: breast cancer; HRQoL: health-related quality of life; MSE: muscle-strengthening exercise; OT: occupational therapy; PA: physical activity; SDT: Self-Determination Theory.

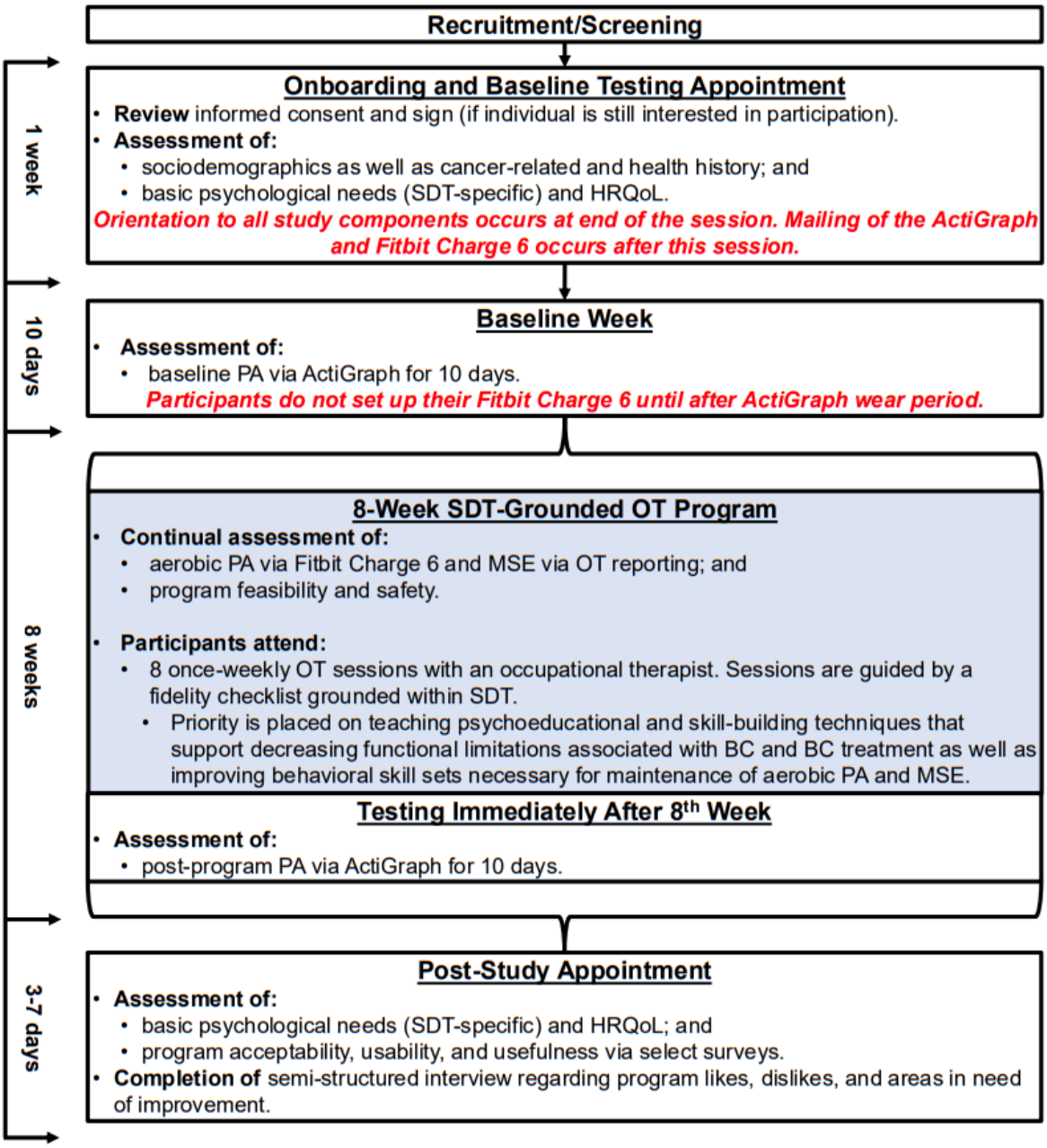

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During the first session, participants work with the occupational therapist to choose exercise equipment from a list of options (Multimedia Appendix 1) that supports their preferences and valued occupations (value of up to US $100). The selected equipment is then mailed to the participant by the research team. During the second OT session, the occupational therapist works with participants to identify and set goals related to aerobic PA and MSE choices that align with their values, interests, and strengths. Participants then use their selected exercise equipment to engage in tailored aerobic PA and MSE throughout the remainder of the sessions, with the occupational therapist also tracking participant attendance at each week's OT session for each participant as one of several adherence measurements.

Participants are also provided with a Fitbit Charge 6 fitness tracker. The occupational therapist has access to these trackers' data via a cloud-based platform, Fitabase (Fitabase; Small Steps Lab LLC), that queries the Fitbit application programing interface. During the weekly OT sessions, the occupational therapist promotes self-regulatory techniques known to be useful for PA initiation and maintenance [12]. These include the provision of timely feedback on PA levels; encouraging specific, attainable goal setting (eg, planning gradual increases in step counts); use of strengths-based problem-solving; and action planning (eg, when and how participants plan to meet aerobic PA or MSE goals). Table 1 outlines the general tasks and emphases of each week's OT session. Fidelity of each OT session is being evaluated using an established fidelity checklist method with occupational therapist and supervisor assessment [31]. Briefly, Zoom sessions are being videorecorded, and 20% of the sessions will be randomly selected for review and rating by a PhD-level occupational therapist (TCK) [31]. Furthermore, participants' goal attainment throughout the program is being evaluated with the Goal Attainment Scale [32] embedded within the fidelity checklist. Finally, participants wear the ActiGraph GT3X accelerometer for 10 days before and after receiving the 8-week OT program. Wear instructions and a tracking log to document accelerometer wear patterns are being provided.

Following the 8-week program and completion of all other study tasks (eg, ActiGraph wear and poststudy survey), the research coordinator is conducting an end-of-study semistructured interview with each participant to better understand their program experience. The goal of this interview is to gauge the usability, usefulness, and enjoyability of the program, by asking questions such as "How useful was experiencing this OT and physical activity program for you?" and, "How could we improve upon the program?"

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Table 1. Occupational therapy elements targeting self-determination theory constructs for sustained physical activity.

SDT[a] construct	OT[b] objectives and techniques
Session 1	
Relatedness	• A discussion regarding the participants' overarching "why" for participating in the program is designed to facilitate mutual understanding between the therapist and the participant and support therapeutic rapport.
Autonomy	• The participant is noted as the expert in their needs and desires and encouraged to take a lead role in their values-based goal setting while receiving support from the occupational therapist. • Participants are encouraged to take a lead role in the selection of their study-provided exercise equipment.
Competence	• Participants rate their confidence in their ability to achieve their values-based goals and discuss what they feel performing much better, somewhat better, somewhat worse, and much worse would look like with the occupational therapist. • The occupational therapist suggests specific action planning processes to put in place to support values-based goal attainment.
Sessions 2-7	
Relatedness	• The occupational therapist engages in a semistructured "grounding" process before each session that includes a focus on adopting the client's perspective, using neutral language, building therapeutic rapport, and understanding the participant. • The occupational therapist presents an evolving, thoughtfully curated OT program designed to help the participants meet their goals and support their values.
Autonomy	• All sessions explicitly include evocation and discussion of participants' overarching "why" for participating in the program. • All sessions include a weekly goal-setting discussion centered on encouraging the participant to identify short-term goals that align with their valued occupations.
Competence	• The evolving, personally tailored program is explicitly designed to "meet participants where they are" and support incremental improvement in valued movement patterns. Qualitative and quantitative information (eg, goal attainment scaling) helps the occupational therapist to modify programing to best meet participant's changing needs, abilities, and interests. • In each session, the occupational therapist refers back to the participant's explanation of what they felt performing much better, somewhat better, somewhat worse, and much worse than last week's goal would look like. This helps participants to recognize progress and select appropriate weekly goals. Participants then rate their confidence in their ability to achieve the current week's values-based goals and discuss what performing much better, somewhat better, somewhat worse, and much worse would look like. • The occupational therapist suggests specific action planning processes to put in place to support values-based goal attainment.
Session 8	
Relatedness	• Session 8 features a semistructured maintenance and continuity plan discussion. • In addition to many of the objectives and techniques used in sessions 2-7, the maintenance and continuity plan includes a discussion of positive changes observed by the occupational therapist and experienced by the participant over the course of the program.
Autonomy	• In addition to many of the objectives and techniques used in sessions 2-7, the maintenance and continuity plan includes an evocation and discussion of participants' overarching "why" for participating in the program and a discussion of "meaningful takeaways" experienced by the participants over the course of the program.
Competence	• In addition to many of the objective and techniques used in sessions 2-7, the maintenance and continuity plan includes a discussion of how participants can maintain their momentum upon conclusion of the program.

[a]SDT: Self-Determination Theory.

[b]OT: occupational therapy.

Protocol Changes

We now have institutional review board (IRB) approval to recruit breast cancer survivors having completed any type of primary treatment for breast cancer within the last 24 months. Our previous criterion considered eligible only those who had undergone some type of breast-conserving surgery or a partial or full mastectomy within the last 12 months. Our discussions with participating breast cancer survivors as well as breast cancer survivors at local survivorship events informed this decision, with many noting marked limitations even in the absence of more aggressive treatment (eg, a full mastectomy).

Outcomes, Measurements, and Analyses by Study Aim

We are collecting sociodemographic and medical information at baseline to describe our sample, including age, sex, race and ethnicity, education, height and weight, marital status, annual household income, date of breast cancer diagnosis and stage at diagnosis, type of treatments received, comorbidities (eg, type 2 diabetes), readiness to change, and overall health status.

Aim 1: OT Program Acceptability and Usefulness

To assess participants' perceptions of the OT program's acceptability, we are using qualitative and quantitative methodologies. For qualitative aim 1, a research team member

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is conducting semistructured interviews with each participant following study completion. Interviews are guided by a predetermined list of questions about the program meant to discern what program components participants liked (ie, found acceptable and useful) and disliked, as well as which aspects of the program they believe could be improved (ie, to enhance the program in future iterations). The research team member probes participants for further context regarding their answers as needed. Qualitative interviews are recorded and will be transcribed verbatim by a Health Insurance Portability and Accountability Act–compliant third party. Transcripts will be analyzed via thematic content analysis using qualitative analysis software [33]. The investigators will perform coding together for 2 transcripts to establish a consensus for coding procedures and then code the remaining transcripts independently. The thematic content analysis will include both deductive codes (ie, codes determined a priori that reflect program acceptability) and inductive codes (ie, codes reflecting emergent phenomenon noted by data analysts). Identified themes will then be discussed among the investigators, with discrepancies noted and resolved and final themes reported. Our quantitative aim 1 assessment of program acceptability and usefulness will be measured post-program. Participants will complete a questionnaire designed to provide insight into various facets of program acceptability (eg, perceived usability, usefulness, enjoyability, etc).

Aim 2: OT Program Feasibility and Safety

We are assessing program feasibility via measurements of recruitment rates, study retention, and protocol adherence. Recruitment rates are being reported as the proportion of breast cancer survivors enrolled in the study divided by the number of breast cancer survivors who complete the screening survey. Enrollment will be considered feasible if ≥70% of breast cancer survivors expressing interest, and who are eligible, ultimately enroll in the study. Study retention is being evaluated similarly, with the number of breast cancer survivors completing the program divided by the number that started. Retention will be considered feasible if ≥70% of breast cancer survivors who complete the baseline measures also complete measures post-program. The number of weekly telehealth-delivered OT sessions (out of 8 total sessions) that each participant attends is being used as the program adherence metric. Adherence will be considered feasible if at least 80% of participants average ≥80% attendance at their OT sessions. Assessments of program safety are being assessed by tracking any breast cancer–related lymphedema events, musculoskeletal injuries, and adverse events. The occupational therapist is tracking this information each week during each participant's telehealth-delivered OT session. The program will be considered safe if these events occur at or below published normative values [25-27]. Results for program feasibility and safety will be reported descriptively as frequencies and percentages.

Exploratory Aims: SDT-Related Constructs, Aerobic PA and MSE, and PRO Changes

The proposed project is a pilot trial focused on testing a new interventional model and using observations to refine various program components. The project is not powered to detect statistically significant changes in outcomes. As such, while we propose measuring the outcomes below to properly inform future larger studies, we will calculate only descriptive statistics (ie, means and 95% CIs) for study outcomes [34,35]. Notably, we will use the Clopper-Pearson exact method to calculate all 95% CIs.

We are assessing participants' pre- to post-program changes in SDT constructs through examinations of basic psychological needs satisfaction in exercise. We are operationalizing these constructs using the Basic Psychological Needs in Exercise Scale (BPNES) [36-39] The BPNES is an 11-item Likert-type scale that features 3 subscales that measure perceptions of autonomy, competence, and relatedness (1: "I don't agree at all"; 5: "I completely agree"). Psychometric analyses have provided support for this scale's reliability, discriminant validity, and measurement invariance across gender and various cultures, and we will score subscales individually using the recommended protocol [36-39]. We are also evaluating theory intervention fidelity at post-program using the Theory-Intervention Fidelity Test. This measure will allow us to assess participants' perceptions of having experienced the SDT's underlying mechanisms of behavior change (autonomy, competence, and relatedness) as well as meaning associated with the program's aim (ie, to increase engagement in personally meaningful PAs). Responses are on a 5-point Likert-type scale (1: "Strongly disagree"; 5: "Strongly agree"). For the BPNES, we will calculate participant's pre- to post-program change in perceived autonomy, competence, and relatedness (each construct will be calculated separately). Using these data, we will calculate participants' mean change scores and corresponding 95% CIs. For the Theory-Intervention Fidelity Test, we will present data descriptively overall and for each construct (ie, autonomy, competence, relatedness, and meaning).

Measurements of pre- to post-program changes in aerobic PA are being measured using ActiGraph GT3X accelerometers. Daily durations of moderate-vigorous physical activity, light physical activity, and sedentary behavior (SB) will be reported. ActiGraph GT3X accelerometers have demonstrated evidence of validity for the measurement of free-living PA and SB [40]. To ensure the collection of reliable data, participants are wearing the accelerometers at baseline before the first OT session and donning of the Fitbit as well as during the 9th week following the OT program. Established protocols for placement and duration are being followed [41]. Wear instructions and an accelerometer wear log are also provided to all participants. We will exclude days not meeting established thresholds (≥10 hours per day of wear time, at least 3 weekdays, and 1 weekend day). We will then use established cut points to analyze PA durations per day for all valid days at each time point for each participant [42]. Daily durations of SB, light physical activity, and moderate-vigorous physical activity will be reported for baseline and the 9th week, with mean pre- to post-program changes and associated 95% CIs calculated. Notably, we may also use data from participant's Fitbit Charge 6 to calculate more granular data on the above PA metrics as well as daily steps. Critically, Fitbits, and the Fitbit Charge Series, have good accuracy versus criterion for PA tracking in laboratory settings, with only slight underestimations in free-living settings (approximately 1 step

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per minute with outliers removed) [43,44]. Pre- to post-program changes in weekly MSE bouts are being tracked as the occupational therapist discusses PA goals with each participant during their once-weekly OT session. The occupational therapist's notes will be used to determine the percentage of program weeks that breast cancer survivors meet the recommended 2 bouts of MSE per week [45].

Finally, we are evaluating pre- to post-program changes in HRQoL using PROs. We are assessing the following 8 components of physical and psychological health at baseline and post-program using the PROMIS: physical functioning, fatigue, anxiety, depression, pain interference, pain intensity, sleep impairment, and sleep disturbance [46]. Measurements on the PROMIS are on a 5-point Likert-type scale, with 5 reflecting worse outcomes on all components aside from physical function wherein a higher score reflects better physical function. These PROMIS measures have been observed as reliable tools for the assessment of these outcomes [47]. Baseline and post-program scores for each of the 8 PROMIS components will be calculated using established procedures and then converted to t-scores. A pre- to post-program change of 2-6 t-score points is considered a minimal important change relative to published normative values [47,48]. These PROMIS measures have been observed as reliable tools for the assessment of these outcomes [47]. We are measuring goal attainment via goal attainment scaling. Goal attainment scaling allows for reporting the extent to which a participant meets weekly goals using a 5-point scale (–2: performance was much worse than expected; +2: performance was much better than expected). Measurement of pre-post changes will be obtained through transforming responses into a single aggregate score using established protocols [32].

Missing Data

We are working to enhance participant retention and, therefore, data completeness through follow-up phone calls, incentives, and focusing on meaningful participant goals. Our research coordinator is also frequently checking for missing data, which will be flagged in our study database, located in REDCap. We are identifying and coding any missing data (ie, nonresponse to questions and missed study visits), looking for patterns, and identifying the appropriate assumptions of missing data (ie, missing completely at random, missing at random, or missing not at random). Due to the nature of the study, we will not need to perform sensitivity analyses; however, if we have multiple participants with incomplete data, we will decide between a complete case analysis and a last observation carried forward analysis at the recommendation of our biostatistician.

Ethical Considerations

This study was approved by the OUHS IRB (number 16601). Participants are consented to the study prior to engaging in any study activity. Furthermore, participants can opt out of participation at any point during the study period. All participant data are deidentified, with data accessible to only those on the study team. Participants will be compensated with a US $50 gift card upon completion of all study tasks, US $100 worth of exercise equipment selected by the participant, and a Fitbit Charge 6.

Privacy and Confidentiality

All data are being securely stored in REDCap. As this is a multiple principal investigator (MPI) study, the MPIs are jointly responsible for monitoring the safety environment of participants and ensuring that appropriate medical care and coverage are provided to all participants if necessary. The primary mentor (DEK) has also pledged to take responsibility to help lead and oversee all aspects of the research with human participants. The safety monitor (study oncologist; CH) has also pledged to oversee participant safety.

The MPIs are also responsible for monitoring procedures during conduct of the study for each participant, including eligibility, enrollment, data collection, evaluation of study outcomes, problems with informed consent, and participant safety and well-being. This is being undertaken under the guidance of the primary mentor. The plan includes (1) weekly review of screening results by the MPIs; (2) immediate reporting of adverse events by team members to the MPIs and then to the IRB, if needed; (3) quarterly review of collected data by the MPIs; (4) annual review by the MPIs, primary mentor, and OUHS IRB; and (5) to ensure safety, the study oncologist is providing an ad hoc review of adverse events. They will be sent this information within 2 weeks, or immediately for potentially serious or severe events.

Screening data are being reviewed weekly during recruitment periods by the MPIs. The MPIs are ensuring that any values indicating ineligibility or unsafe practices are flagged. Flagged participants may be excused from the study or instructed on safer practices, as needed. These decisions are being made in consultation with the study oncologist. We will not convene an external data safety and monitoring board. Should the study sponsor or the collaborating cancer center request that we do so, we will take advantage of protocols used in the past by investigators associated with our university.

Anticipated nonserious adverse events include nonserious injuries (eg, joint pain) and illnesses, minor discomfort, and possible loss of confidentiality. If an anticipated adverse event occurs, the MPIs and primary mentor will determine whether the event requires reporting to the IRB and to the study sponsor. The attribution and impact of each event on the overall project's risk:benefit ratio will then be determined in consultation with the study mentor and oncologist.

All unanticipated, serious, fatal, and life-threatening adverse events will be immediately reported to the IRB within 24 hours of occurrence. The IRB, MPIs, and primary mentor are responsible for determining whether modifications are needed to the consent form or protocol based on the event. All protocol modifications will be reported to the IRB. If a determination is made that participants are exposed to unacceptably high risk in comparison with benefit, the study will be suspended until proper modifications are made for participant safety. Should cessation of study activities be required (temporarily or permanently), the program officer will be notified immediately.

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Results

This research study was funded in March 2024. We received approval from the OUHS IRB in September 2024, and we began recruiting in November 2024. We anticipate having all data collected by Spring 2026 and that the primary results manuscript submitted for publication in Summer 2026.

Discussion

Anticipated Findings

We anticipate that study participants will view the program favorably, and that the program will be safe and feasible to implement. We also anticipate that pre- to poststudy changes will demonstrate plausibility of the program's effectiveness. Moreover, we expect that the program will compare favorably with previous and contemporary research concerning enjoyability, usefulness, and effects on determinants of sustained PA (eg, SDT constructs). This is because OT is oriented toward building capacity in participant-defined valued occupations; by integrating the promotion of active living in this autonomy-supportive context, we expect that this program will resonate with participants in ways that may support lasting behavior change.

Pitfalls

In similar interventions, the most common pitfalls are adherence to the intervention and study processes, technology use, and safety of the participants. We will use the following strategies to improve adherence: (1) follow-up phone calls, (2) compensation via stipends and personalized exercise equipment, (3) virtual delivery of the program, and (4) the use of a participant goals–focused program that establishes therapeutic rapport. To address technological issues, we provide written guides for using the Fitbit and its app and technological assistance for Zoom. We also have a research coordinator available to troubleshoot any technological issues as they arise. We will ensure participant safety through standardized processes for (1) evaluating readiness for exercise, (2) reporting of adverse events, and (3) close monitoring by a licensed occupational therapist, a professional trained in safely supporting PA.

Future Directions

We will use the observations from this feasibility trial to further refine this intervention protocol and scale the program for an effectiveness-implementation type 1 hybrid trial. This research aligns with the National Cancer Institute's and American Cancer Society's priority funding areas: using technology to improve access to survivorship care and testing evidence-based interventions that lead to reaching adequate levels of PA.

Dissemination Plan

We will present our preliminary and final results, as well as exploratory observations, at major scientific meetings held by relevant scientific organizations. Furthermore, we will share information regarding our study through peer-reviewed publications that outline the study design and methods as well as overall study results. We will target top-tier journals for publishing and disseminating these observations. Importantly, we intend to work with the personnel at the Stephenson Cancer Center as well as the communication teams within the TSET Health Promotion Research Center and the OUHS to package our observations in research briefs for broad dissemination through all media avenues locally and globally, including social media.

Strengths and Limitations

This study has a few notable strengths. First, our program addresses a critical transitional period for breast cancer survivors (acute posttreatment recovery) when support for reengaging in PA is most needed. Second, the program's grounding in the SDT, a well-established behavioral framework, and incorporation of evidence-based strategies such as goal setting and self-monitoring with wearable activity trackers should assist participants with PA initiation and maintenance. Finally, the program's delivery via telehealth addresses a significant access barrier for rural populations, which are often underrepresented in behavioral intervention research, while also facilitating the scalability and accessibility of OT.

Limitations include the use of a single-arm design, which constrains our ability to draw causal inferences about program effectiveness. The relatively small sample size (N=38) may also limit generalizability and statistical power to detect meaningful changes in PA and other outcomes. The reliance on self-report data for some measures introduces potential recall and social desirability biases. Finally, recruitment through local organizations and referrals may lead to a sample with higher baseline motivation (ie, selection bias), which could limit applicability to broader survivor populations.

Conclusions

This study addresses a common and serious problem for individuals who have undergone breast conserving surgery or mastectomy: insufficient engagement in aerobic PA and MSE during the transition period from active treatment to everyday life. This health behavior theory–grounded program uses the expertise of occupational therapists to adapt, modify, and integrate these exercises into daily routines while delivering the program via telehealth (decreasing salient barriers to accessing supportive care) in a manner that is personally meaningful, thus increasing the likelihood of continued PA engagement post-program.

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Data Availability

Due to the pilot nature of this study and potential for participant identification, data from this study will not be shared with outside entities.

Authors' Contributions

The multiple principal investigators (MPIs; ZCP, MCR, and TCK), CH, and DEK are credited with the conceptualization of this research. The MPIs are credited with the development of the methodology, acquisition of resources, development of software, supervision, validation, and visualization of the study. Planned data curation and formal analysis will include the MPIs, NS, and AW. The processes involved with investigation are carried out by the MPIs, NS, and AW. Project administration is overseen by the MPIs and NS. The writing of the original draft was completed by the MPIs, and review and editing were completed by all authors. Finally, funding was acquired through the efforts of the MPIs and DEK.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Exercise equipment catalog.
[PDF File (Adobe PDF File), 7599 KB - resprot_v14i1e73554_app1.pdf]

Multimedia Appendix 2
Peer review report from the American Cancer Society.
[PDF File (Adobe PDF File), 185 KB - resprot_v14i1e73554_app2.pdf]

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Abbreviations

BC: breast cancer
BPNES: Basic Psychological Needs in Exercise Scale
HRQoL: health-related quality of life
IRB: institutional review board
MPI: multiple principal investigator
MSE: muscle-strengthening exercise
OT: occupational therapy
OUHS: The University of Oklahoma Health Sciences
PA: physical activity
PRO: patient-reported outcome
PROMIS: Patient-Reported Outcomes Measurement Information System
REDCap: Research Electronic Data Capture
SB: sedentary behavior
SDT: Self-Determination Theory

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Protocol

AI Virtual Human–Augmented Game-Based Teaching to Enhance Emotional Intelligence in Nursing Students: Protocol for a Single-Group Pretest-Posttest Action Research Study

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Abstract

Background: The rapid advancement of IT and the complexity of health care demand innovative nursing education that moves beyond lectures and workshops. Nursing students must acquire clinical knowledge alongside emotional intelligence (EI), empathic communication, and crisis management to respond to patients at risk for suicide. In Taiwan, suicide is the second leading cause of death among university students, underscoring the urgency of suicide prevention training. Generative artificial intelligence (AI) platforms such as AI virtual humans provide immersive, scenario-based simulations that can integrate game-based learning into psychiatric nursing curricula.

Objective: This study evaluates the effectiveness of combining game-based pedagogy with AI virtual human simulations in enhancing nursing students' EI, empathic communication, and psychological crisis management. Specifically, it aims to (1) foster self-awareness and emotion regulation, (2) strengthen crisis assessment and coping strategies, (3) increase motivation and engagement, and (4) establish an evidence-based framework for nursing education innovation.

Methods: An action research design will be conducted over 2 instructional cycles (36 weeks) within a psychiatric nursing course at a Taiwanese university. Participants are third-year postbaccalaureate nursing students recruited through convenience sampling. In phase 1, five simulation scenarios involving suicide risk presentations—major depressive disorder, bipolar disorder, schizophrenia, substance use disorder, and borderline personality disorder—were developed and validated by experts. Phase 2 applies 2 action research cycles (week 1 to 18 and week 19 to 36) with a single-group pretest-posttest design. Quantitative data include the Adult Emotional Intelligence Scale, administered at baseline and after the intervention. Qualitative data consist of reflection journals and classroom observations. Analysis employs descriptive statistics, paired sample 2-tailed *t* tests or Wilcoxon signed-rank tests, effect sizes, linear mixed-effects models, and thematic analysis.

Results: Scenario development and expert review were completed in phase 1. Cycle 1 (weeks 1-18) has begun from September 2025, with 37 students enrolled, exceeding the sample size target of 32. Postintervention Adult Emotional Intelligence Scale results will be collected by week 16, followed by cycle 2 with a new cohort. Final integration and analysis will occur after week 36 to evaluate intervention effectiveness.

Conclusions: Integrating game-based learning with AI virtual human simulations introduces an innovative, technology-enhanced model for psychiatric nursing education. Anticipated outcomes include improved EI, enhanced empathic communication, and stronger crisis management abilities. Through iterative refinement across 2 cycles, this study will provide empirical evidence on the role of generative AI in nursing education, informing curriculum innovation and supporting AI-driven simulation as a sustainable strategy for competency-based training.

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KEYWORDS

emotional intelligence; artificial intelligence; AI virtual patient; game-based learning; nursing education innovation; protocol

Introduction

Background

From the perspective of nursing education, the rapid advancement of IT and the continuous evolution of medical knowledge have significantly impacted health care delivery models and the demand for clinical competencies. Modern nurses are expected not only to possess fundamental clinical skills but also to demonstrate professional knowledge, problem-solving ability, critical thinking, and effective collaboration within interdisciplinary teams. Traditional teaching approaches such as lectures, demonstrations, seminars, and workshops are increasingly insufficient to meet the needs of student-centered learning models. A recent meta-analysis found that virtual simulation significantly enhanced clinical reasoning skills among nursing students, especially when scenarios were longer than 30 minutes as well as nonimmersive and followed by debriefing [1]. In response, nursing education has gradually shifted toward innovative and diversified teaching strategies, including problem-based learning, clinical reasoning, and scenario-based simulation. These approaches aim to foster self-directed learning, integrate theory into clinical practice, enhance motivation, promote peer discussion, and cultivate lifelong learning skills.

Generative artificial intelligence (AI), including tools such as ChatGPT and virtual assistants, has been introduced into educational contexts to support personalized learning, prepare students for complex clinical situations, and improve engagement. A scoping review [2] categorized AI-based teaching strategies in nursing into simulation-based learning, AI-augmented instruction, and AI-generated content and tools and reported improvements in clinical understanding and student participation. In Taiwan, research on AI literacy among nursing students, such as the integration of ChatGPT and Copilot into academic writing courses, has shown significant gains in AI competence and writing performance [3].

From a public health perspective, suicide remains a critical global issue. According to the World Health Organization [4], more than 700,000 people died by suicide in 2019—more than from HIV, malaria, breast cancer, or war—making it one of the leading causes of death worldwide. World Health Organization data indicate that 1 in every 100 deaths is due to suicide, prompting new global policies to strengthen suicide prevention efforts and improve training for health care professionals.

In Taiwan, suicide rates have risen steadily in recent years, particularly among individuals aged 15 to 24 years. According to the Ministry of Health and Welfare [5], suicide is the second leading cause of death among young people, with university students facing heightened risks related to academic pressure, interpersonal stress, and mental health challenges. A series of student suicides in 2020 drew national attention to the complexity of suicide-related factors such as academic stress, emotional distress, and interpersonal difficulties. These incidents have highlighted the need for improved mental health awareness and support within educational settings, enabling both students and faculty to better recognize psychological distress, regulate emotions, and manage stress effectively.

International studies suggest that short-term suicide prevention education can enhance nursing students' confidence, skills, and attitudes toward suicide prevention. However, suicide prevention programs in most Taiwanese universities remain limited to optional "gatekeeper" lectures or brief workshops, making it difficult to evaluate their effectiveness or ensure knowledge transfer to clinical practice. Given that frontline nurses frequently encounter patients at risk for suicide—including those outside of psychiatric departments—there is a pressing need to integrate effective suicide assessment training into nursing curricula. This forms the foundation of this teaching research project, which aims to use generative AI to create AI virtual human simulations. These simulations will allow students to apply knowledge learned in the classroom by engaging in virtual assessment conversations with AI virtual patients, thereby enhancing the students' suicide risk assessment and recognition skills.

Nursing students not only face academic demands but also the psychological pressures of clinical internships, such as managing emotional responses during patient and family interactions or witnessing medical emergencies. These stressors can lead to emotional distress, anxiety, or burnout. Despite growing awareness of these challenges, few interventions have systematically addressed the dual need for emotional intelligence (EI) development and suicide prevention training in Taiwanese nursing education. Therefore, this study proposes an innovative AI-based teaching approach that integrates EI enhancement, empathic communication, and crisis management skills through game-based learning (GBL) and AI virtual human simulations. The specific aim of this study is to evaluate the effectiveness of this integrated model in improving nursing students' EI, suicide risk assessment, and psychological crisis management skills, thereby addressing a critical gap in current literature.

EI Among University Students and Its Relevance in Nursing Education

EI has become a significant focus in mental health research among university students in Taiwan, particularly due to its association with reduced psychological distress and enhanced coping abilities. Multiple studies have shown that higher EI is positively correlated with better mental health outcomes, including lower levels of stress and anxiety; for instance, a study of university students in southern Taiwan revealed a positive relationship between EI and interpersonal relationships, with female students scoring higher in EI than their male counterparts [6]. Another study identified EI as a protective factor that helps buffer the negative psychological effects of stress and adverse life events [7]. In addition, EI can be enhanced through

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education. A study evaluating an emotion regulation course for Taiwanese university students reported significant improvements in EI scores and reductions in psychological distress after the intervention, highlighting the effectiveness of education-based approaches to fostering EI [8].

In the context of nursing education, EI is not only important but also foundational. The development of self-awareness is a key starting point, as it enhances communication, clinical decision-making, and interpersonal competence. Research has demonstrated a positive correlation between self-awareness and communication ability among nursing students, and courses that emphasize self-awareness have been shown to significantly improve these skills [9]. Furthermore, the integration of mindfulness with self-awareness has proven effective in helping nursing students manage emotional challenges such as countertransference, thereby improving emotion regulation and professional behavior [10].

Emotion awareness and EI are particularly critical in psychiatric nursing, where students must respond to patients with emotionally complex needs. A study by Por et al [11] found that higher levels of EI were significantly associated with better stress management, clinical decision-making, and subjective well-being among nursing students. However, more recent research has revealed that while nursing students may perform relatively well in managing social emotions, they often score lower in emotion awareness—indicating a gap that may hinder emotion regulation in clinical settings. As such, it has been recommended that EI training be formally integrated into nursing curricula to strengthen critical thinking and decision-making skills, leading to improved educational and clinical outcomes [12].

Integration of GBL Into Nursing Education

GBL has emerged as an innovative educational strategy that incorporates game design elements to enhance engagement, enjoyment, and learning outcomes. While nursing education traditionally emphasizes the development of professional skills and critical thinking, conventional instructional methods often fall short in motivating students or sustaining their interest. As a result, a growing body of research has examined the effectiveness of applying GBL within nursing curricula.

Studies have demonstrated that GBL contributes to improved student motivation and academic performance; for instance, a systematic review by Xu et al [13] found that GBL significantly enhanced nursing students' learning experiences, particularly by increasing motivation and emotional engagement. Similarly, Reed reported that game-based teaching approaches not only improved knowledge retention [14] and test performance but also elicited more positive student feedback and engagement during class.

A randomized controlled trial by Blanié et al [15] compared game-based simulation with traditional teaching for developing clinical reasoning skills among second-year nursing students in France. Participants were randomly assigned to either a group that used interactive game-based case simulations or a group that studied the same material through text-based methods. Both groups were evaluated using the script concordance test immediately after instruction and again 1 month later. While no significant differences were found between the 2 groups in immediate or delayed clinical reasoning performance, the study highlighted higher levels of student satisfaction and learning motivation in the simulation by gaming game-based simulation group. Students reported that the game simulations provided a more engaging, interactive, and contextually meaningful learning experience.

These findings suggest that GBL holds substantial educational potential in nursing education, particularly in enhancing student motivation, satisfaction, and selected clinical competencies. However, successful implementation requires careful consideration of design, technological integration, and contextual factors. Further research is needed to explore the long-term effects of GBL across diverse educational settings and nursing specialties.

Integration of AI Technology Into Nursing Education

With the rapid advancement of IT, nursing education has increasingly incorporated various forms of digital and mobile learning interventions. These include mobile apps, electronic learning platforms, and immersive technologies such as augmented reality and virtual reality (VR). In recent years, the global rise of AI has further expanded educational possibilities, although AI has been more extensively developed and applied in clinical health care practice than in nursing education. The emergence of generative AI technologies—particularly after the release of ChatGPT in November 2022—has signaled a transformative shift in education. In light of these developments, nursing education must adapt accordingly.

A meta-analysis by Chen et al [16] on mobile learning interventions in nursing education revealed that, compared to traditional lecture-based instruction, mobile learning strategies significantly improved students' clinical knowledge, nursing skills, and confidence, while also receiving higher satisfaction ratings from students. In a recent quasi-experimental randomized controlled trial involving 166 third-year nursing students, the effectiveness of simulated learning using AI virtual patients was compared to that of standardized patient simulations. Both methods were found to enhance clinical safety awareness, reduce errors, and improve clinical competence and decision-making. However, students in the AI virtual patient group demonstrated significantly better outcomes in anxiety reduction, confidence building, and decision-making performance, with results reaching statistical significance ($P<.001$). These findings suggest that AI-based simulation in nursing education not only supports the acquisition of evidence-based clinical knowledge but also enhances communication, critical thinking, and patient safety skills [17].

Although nursing has long intersected with technology, the development and application of AI have typically been seen as the domain of computer science, software engineering, and robotics. However, educators should no longer rely solely on traditional classroom methods. Instead, they must actively enhance their technological competencies by integrating tools such as ChatGPT to support content creation and instructional design. When combined with clinical expertise, generative AI technologies can lead to the rapid development of innovative,

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high-quality teaching materials that increase student engagement and learning outcomes.

In this project, faculty members have been granted exclusive authorization to use the Virti AI virtual human scenario design platform, developed by HTC. After receiving training on AI-generated dialogues using ChatGPT, educators can create customized virtual patient simulations in as little as 30 minutes—enhancing efficiency by a factor of 10 to 100. Virti's integration of natural language processing further enables dynamic, student-led interactions with AI-simulated patients, promoting clinical reasoning, communication, and knowledge retention. This AI-powered educational approach has the potential to transform nurse training by significantly improving humanistic communication skills in patient care settings.

Aim

This study has 4 main objectives. First, it aims to enhance nursing students' EI by helping them better recognize and understand their own emotional responses and those of others, using reflective and interactive simulations. Second, it seeks to strengthen students' crisis management abilities through virtual patient scenarios that simulate high-stress situations, allowing them to practice appropriate coping and decision-making strategies. Third, the project aims to improve student engagement and motivation by integrating game-based and AI-enhanced learning, assessing their impact on participation, interest, and satisfaction. Finally, the study intends to provide empirical support for innovative nursing education by establishing a framework that combines game-based pedagogy with AI simulation to meet the evolving demands of clinical practice. This approach integrates practice and research through iterative cycles of planning, action, observation, and reflection to address real-world instructional challenges and support continuous improvement.

Methods

Overview

The innovative teaching strategy in this project integrates traditional classroom lectures, clinical case discussions, and instructional video analyses with additional components such as GBL, hands-on technical practice, and interactive software using AI virtual humans. These combined approaches aim to support nursing students in developing EI—particularly self-awareness and emotion recognition regulation—along with empathic communication skills. Furthermore, students will engage in suicide risk assessment training with virtual patients representing various psychiatric conditions.

This teaching research project aims to explore how the integration of game-based pedagogy and AI virtual human interaction can enhance nursing students' EI and psychological crisis management abilities. To achieve this, the study will use an action research methodology involving 2 iterative cycles. After implementing the first cycle and collecting both quantitative and qualitative data, revisions will be made to the intervention based on the findings before initiating the second cycle. Each cycle will incorporate a single-group pretest-posttest design to evaluate the effectiveness of the intervention using quantitative measures. Through this iterative process, the study seeks to optimize the impact of innovative teaching methods on students' learning outcomes. The research design flowchart is shown in Figure 1.

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Figure 1. Research flowchart. AEIS: Adult Emotional Intelligence Scale; PI: principal investigator.

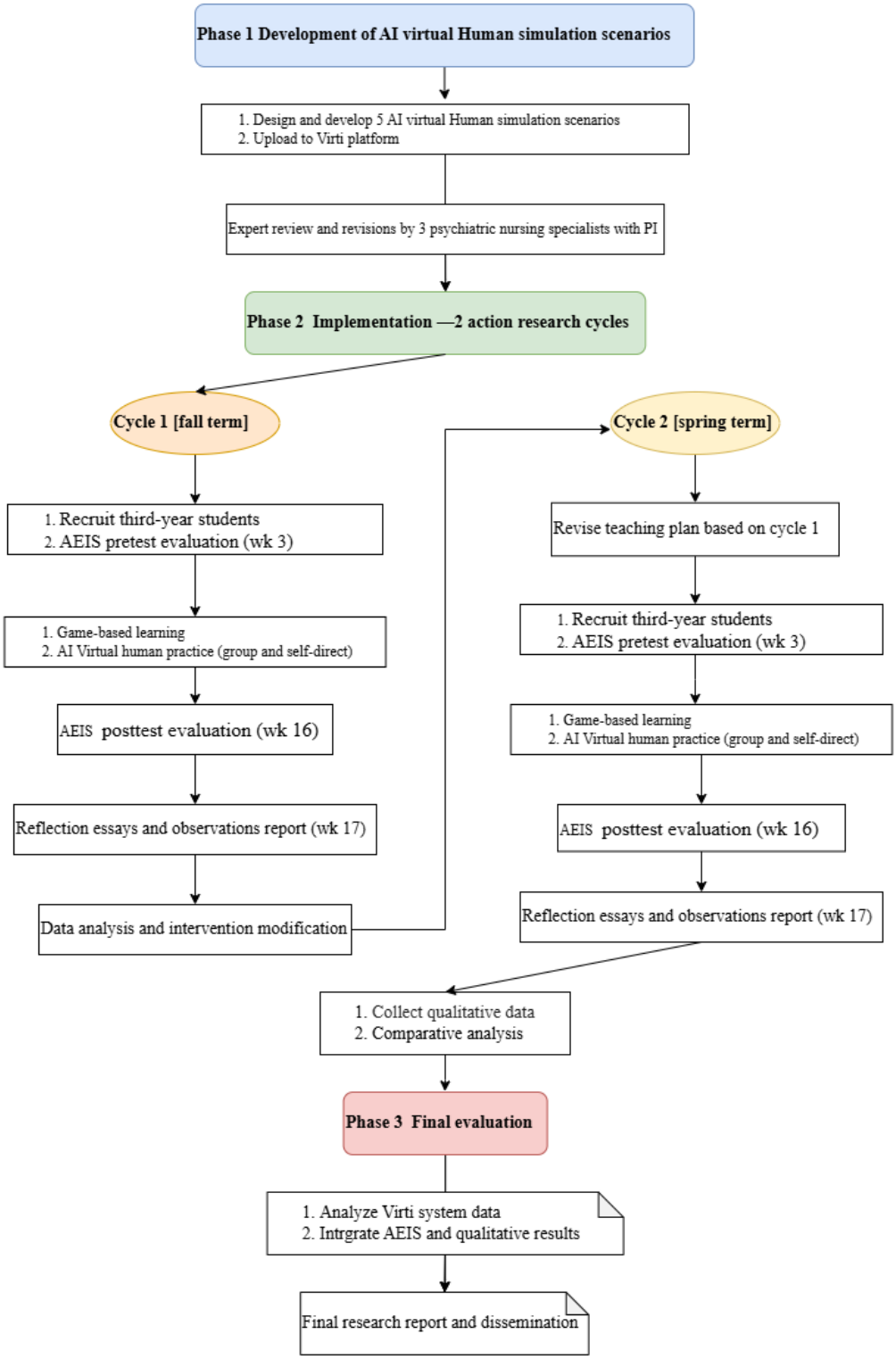

Phase 1: Development of an Innovative Teaching Plan Incorporating Generative AI Virtual Humans

During this phase, generative AI technologies will be applied to develop 5 AI virtual human simulation scenarios, which will be hosted on the platform provided by HTC. These include 1 scenario focused on empathic communication skills and comprehensive assessment of 5 core psychiatric domains, those scenarios representing different psychiatric diagnoses or clinical conditions: major depressive disorder, bipolar disorder (depressive episode), schizophrenia, substance use disorder, and borderline personality disorder. Each scenario will feature AI-simulated patients exhibiting suicide ideation and behaviors associated with suicide risk.

The principal investigator has obtained certification as a seed instructor for immersive VR teaching scenario development through the HTC medical VR program (Virti VR platform). Accordingly, the project will use the Virti AI virtual human

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platform to design intelligent, interactive case scenarios using generative AI. The content of the 5 scenarios will undergo expert panel review by 3 psychiatric mental health nursing professionals and the principal investigator. These expert consultations will guide revisions to ensure that the simulation scenarios accurately reflect realistic communication patterns and clinical presentations found in psychiatric settings.

Once the AI virtual human scenarios are finalized, students will be able to access them anytime and anywhere during phase 2 via the web-based platform. They will engage in interactive simulations with virtual psychiatric patients, practicing empathic communication, emotion recognition, and skills in psychological crisis and suicide risk assessment. All student-AI interactions will be automatically recorded on the backend of the system to facilitate evaluation and scoring by instructors.

Phase 2: Implementation Phase—Integrating GBL and Generative AI Virtual Human Instruction (2 Action Research Cycles With Pretest-Posttest Evaluation in Each Cycle)

Design

This teaching research project adopts an action research methodology, which is a practice-oriented and participatory approach that emphasizes solving real-world problems through iterative cycles of planning, action, observation, and reflection. Action research is widely applied in diverse fields, including education, health care, management, and the social sciences. At its core, it involves close collaboration between researchers and participants to implement systematic actions and evaluations that lead to both practical improvements and theoretical development [18]. In recent years, action research has been increasingly recognized as a “multimethodology” approach due to its flexibility in integrating both qualitative and quantitative methods to address complex problems [19]. The typical process of action research consists of five key steps: (1) identifying the problem and defining the research objectives; (2) planning the action, including designing the intervention and anticipating possible outcomes; (3) implementing the action and collecting relevant data; (4) evaluating the outcomes to determine whether the objectives have been achieved; and (5) reflecting on and refining the action plan for subsequent cycles. The strengths of action research lie in its practical orientation and its participatory nature, which fosters the growth of knowledge and skills among participants [20].

EI refers to the ability to perceive, understand, and manage one’s own emotions as well as those of others. Its core components include self-awareness, self-regulation, social awareness, and relationship management [21]. In recent years, EI has gained widespread attention in both educational and clinical psychology domains. In Taiwan, researchers have developed a culturally adapted Adult Emotional Intelligence Scale (AEIS) [22], which has demonstrated strong reliability and validity in both nursing professionals and university student populations. Higher total scores on the AEIS indicate greater EI [22]. Accordingly, this teaching research project will be conducted through 2 iterative action research cycles. A single-group pretest-posttest design will be used for the quantitative component, while qualitative data will be collected through student reflective writings and classroom observations to analyze their emotion awareness, communication behaviors, and responses to the teaching intervention.

Sampling and Recruitment

Participants will be recruited from third-year nursing students enrolled in the Mental Health and Psychiatric Nursing course at a university in Taiwan. Convenience sampling will be used. The inclusion criteria are as follows: (1) students must be aged at least 20 years; and (2) they must be currently enrolled in the course, voluntarily agree to participate in the study, and be willing to complete both the pretest and posttest AEIS questionnaires as well as submit a written reflection. Students who have suspended their studies or are on academic leave at the time of recruitment will be excluded. Recruitment will be conducted through in-class announcements and information sheets provided by the course instructor. All participants will receive detailed explanations about the study procedures and their rights, and written informed consent will be obtained before participation.

Data Collection and Analysis Plan

This study adopts a single-group pretest-posttest design implemented across 2 instructional cycles (first and second semesters). Quantitative data will be gathered with the AEIS—a validated 26-item instrument covering 4 subscales: emotion awareness (items 1-7), emotional expression (items 8-12), emotion regulation (items 13-17), and emotional use (items 18-26). Each item is scored on a 4-point Likert scale (ranging from 0=strongly disagree to 3=strongly agree); higher scores denote greater EI [22]. Permission to use the AEIS has been obtained from the original author. The scale will be administered in week 3 (pretest evaluation) and week 16 (posttest evaluation) of each semester. Qualitative data will consist of students’ reflective reports—collected throughout both cycles—and classroom observations conducted in week 17 to document behavioral engagement during gameplay and AI-patient interactions.

At the item level, AEIS subscale scores will be prorated when no more than 1 item per subscale is missing; otherwise, the subscale will be set to missing. At the record level, patterns of missingness will be inspected with the Little MCAR test [23]. As linear mixed effects models (LMMs) provide unbiased estimates under a missing-at-random assumption, incomplete cases will be retained in the primary analyses. For ancillary paired sample 2-tailed *t* tests or Wilcoxon signed-rank tests, missing posttest values will be multiply imputed (20 imputations using predictive mean matching); the imputed results will be pooled following the rules formulated by Rubin [23] and compared with complete-case outputs as a sensitivity check.

Descriptive statistics (means and SDs or medians and IQRs) will be reported for all variables. The normality of pretest-posttest difference scores will be checked with the Shapiro-Wilk test. If the distribution is normal, within-participant changes in AEIS total and subscale scores will be analyzed with paired sample 2-tailed *t* tests; otherwise, the Wilcoxon signed rank test will be used. Effect sizes will be

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expressed as Cohen *d* with 95% CIs. To compare change trajectories between cycles, an LMM with random intercepts for participants will be fitted, including fixed effects for time (before the intervention vs after the intervention), cycle (1 vs 2), and their interaction (time × cycle). Holm-Bonferroni adjustment will control the family-wise error rate across AEIS subscales. All analyses will follow an intention-to-treat principle (participants with ≥1 posttest record retained); sensitivity checks with complete-case data will evaluate robustness. Statistical significance is set at α=.05 (2-tailed). Analyses will be conducted in SPSS software (version 29.0; IBM Corp) and R (version 4.4.0; R Foundation for Statistical Computing; *lme4* package for LMMs).

To capture students' experiences and perspectives, we collected qualitative data through structured reflective reports and oral and written feedback after the implementation of the innovative teaching practices. Each student was required to complete a reflective report structured around 5 open-ended questions aligned with the core learning domains of self-awareness, emotional self-awareness, social awareness, empathic communication, and crisis management competence; for example, students described personal insights gained from participating in the card-based educational game, emotional reactions experienced during gameplay, and strategies for recognizing and responding to peers' emotional cues. They also reflected on their ability to demonstrate empathy in simulated dialogues with AI virtual patients and articulated how these experiences contributed to their confidence in managing psychological crises. Each reflective entry was expected to exceed 100 Chinese characters, thereby encouraging deeper engagement and detailed narrative accounts of their learning processes.

In addition to written reflections, student oral and written feedback were gathered during debriefing sessions immediately after the teaching interventions. These interactive discussions invited participants to share their impressions of the AI virtual patient encounters and the gamified learning with card play, highlighting both challenges and perceived benefits. Students frequently commented on the authenticity of the AI-driven dialogues, which prompted them to practice empathic responses, and on the playfulness of the card game, which fostered self-discovery and peer interaction. Oral and written feedback not only provided spontaneous, unstructured accounts but also allowed for triangulation with the reflective reports, offering complementary insights into how the innovative teaching strategies shaped EI and learning engagement. Together, these qualitative materials provided a rich and multifaceted dataset for thematic analysis, illuminating both individual developmental trajectories and collective learning dynamics within the cohort.

During the practical sessions with AI virtual patients, investigators used structured observation rubrics to evaluate student performance across five domains: (1) the ability to recognize the patient, introduce themselves, and demonstrate proactive caring; (2) the use of appropriate communication skills during interviews or technical procedures; (3) the demonstration of empathy in patient interactions; (4) the accuracy of relevant assessments such as symptom evaluation or suicide risk assessment; and (5) the quality of group reflective sharing after practice. Each domain was equally weighted at 20 points, for a total of 100 points in the rubric.

Student reflection reports and student oral and written feedback from the implementation of the innovative teaching practices and observation notes will be thematically analyzed in NVivo 14 (Lumivero) using the 6-step framework proposed by Braun and Clarke [24]. The analysis will proceed systematically through 6 phases: (1) familiarization with the data through repeated reading and note taking, (2) generating initial codes across the dataset, (3) searching for candidate themes by collating codes, (4) reviewing themes in relation to both coded extracts and the entire dataset, (5) defining and naming themes to refine their scope and focus, and (6) producing a coherent report with representative extracts. To ensure rigor and transparency, coding decisions will be documented in an analytic memo trail, and at least two researchers will independently code a subset of data before discussing discrepancies to enhance reflexivity and credibility. The analytic approach will follow recent guidance that emphasizes active, reflexive engagement by the researcher rather than striving for consensus coding or reliability metrics, thereby acknowledging the researcher's interpretative role in meaning making [24]. In addition, Braun and Clarke [25] highlighted common pitfalls and provided 10 recommendations for producing methodologically coherent thematic analysis, underscoring the importance of distinguishing between topic summaries and interpretative meaning-based themes. Their commentary further emphasizes that researchers must "own" their perspectives, ensuring that analytic practices remain theoretically consistent with the chosen thematic analysis approach [25]. Qualitative findings will be triangulated with quantitative results to elucidate mechanisms underlying observed changes in EI and learning engagement.

Cycle 1: Sampling and Recruitment

This cycle will be implemented during the first semester (fall term) of the third year in the nursing program. An innovative course will be introduced, incorporating GBL strategies and hands-on practice with an AI virtual human platform. Each student will be provided with a personal log-in account to access the system. During the practical sessions, students will work in small groups to engage in guided online simulations. In addition, they will be encouraged to access the platform outside of class time to enhance their empathic communication, emotion recognition, suicide risk assessment, and clinical decision-making skills. Both quantitative and qualitative data will be collected during this phase to inform revisions and improvements for the second cycle of the action research.

Cycle 2: Sampling and Recruitment

This cycle will be conducted during the second semester (spring term) of the third year for a new cohort of nursing students. On the basis of the results, feedback, and reflective evaluations gathered from faculty and students during the first cycle, the instructional content and design of the GBL activities and AI virtual human interactions will be refined. The revised intervention will then be implemented as part of a second action research cycle, with the aim of enhancing the overall

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effectiveness of the innovative teaching approach and achieving the study's educational objectives.

Phase 3: Final Evaluation of the Innovative Teaching Intervention

At the conclusion of the 2-semester implementation period, the principal investigator will conduct a comprehensive evaluation of student learning outcomes. This will include analysis of system-generated learning data from the Virti platform, along with the pretest and posttest results from the AEIS administered during both cycles. A comparative analysis of students' learning outcomes across the 2 implementations will be conducted, integrating both quantitative and qualitative data. The final phase will conclude with the preparation of a comprehensive research report summarizing the findings and implications of the teaching innovation.

Figure 2 presents the combined SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 schedule of enrollment, interventions, and assessments for the full 36-week study. Consistent with the SPIRIT 2013 recommendations, the figure maps all key events across 2 action research cycles: cycle 1 (weeks 1-18) and cycle 2 (weeks 19-36). Shaded cells pinpoint the specific weeks in which each activity occurs: enrollment (week 1 and week 19), baseline administration of the AEIS (week 3 and 21), weekly game-based workshops, AI virtual human practice sessions, biweekly reflection logs (even-numbered weeks), and postintervention AEIS assessments (week 18 and week 36). A vertical dashed line at weeks 18-19 delineates the transition between cycles, providing a clear visual alignment of recruitment, intervention delivery, and outcome measurement throughout the study.

Figure 2. Combined SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) schedule of enrollment, interventions, and assessments for cycle 1 (weeks 1-18) and cycle 2 (weeks 19-36).

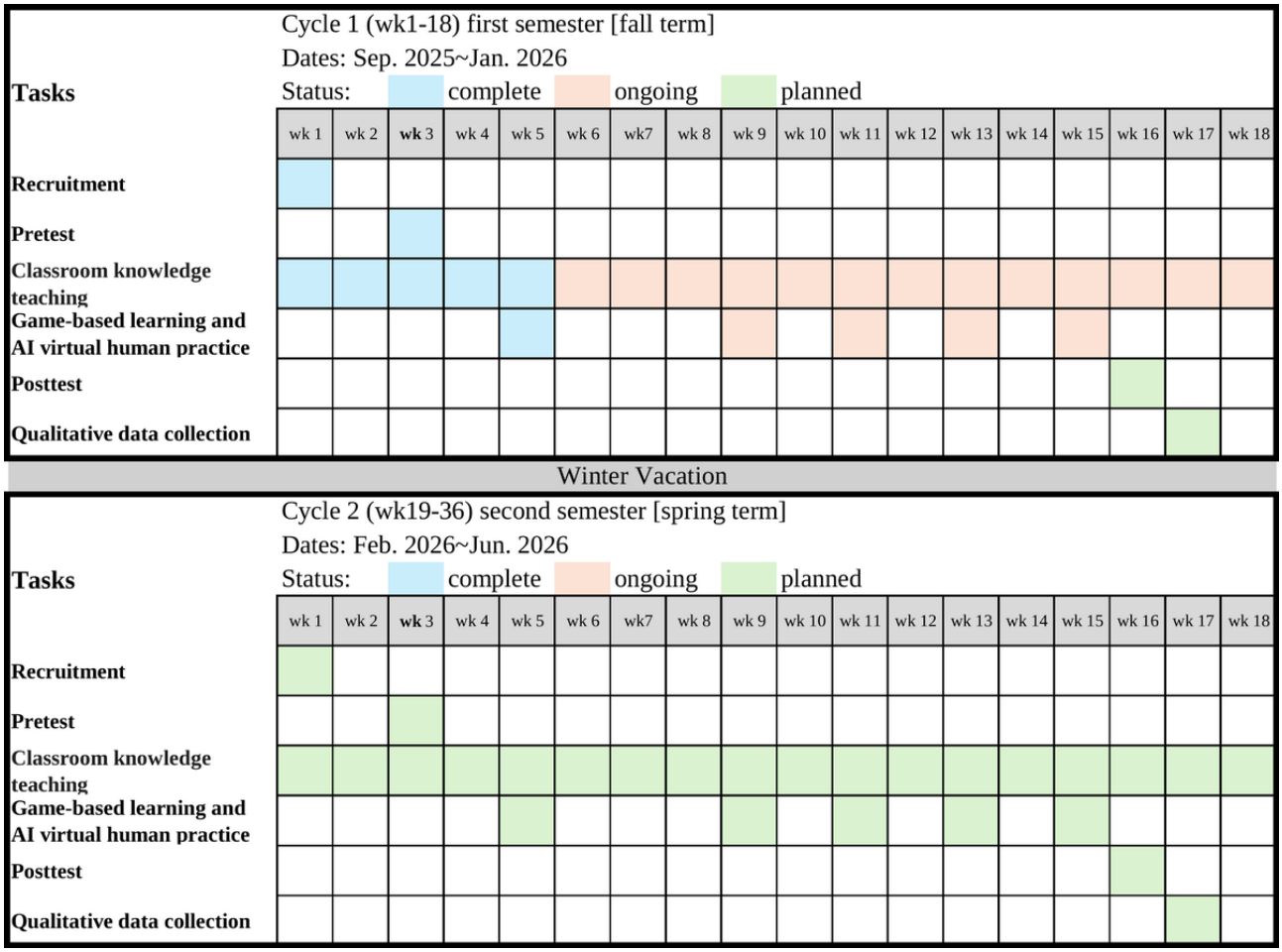

Sample Size and Power Analysis

Using G*Power 3.1 (Heinrich Heine University) for a paired sample 2-tailed *t* test ("Means: difference between two dependent means, matched pairs"), we set α=.05, desired power=.80, and a medium anticipated effect size of Cohen *d*=0.50—consistent with meta-analytic estimates for short educational interventions targeting EI. The calculation yielded a required completer sample of 32 students to detect the pretest-posttest difference with 80% power. Allowing for typical nursing-course attrition of 15% to 20%, we plan to recruit 40 participants per cycle, ensuring that at least 32 remain for posttest analysis.

Reporting-Guideline Compliance

This protocol has been prepared in accordance with the SPIRIT 2013 checklist, and the intervention is described in detail using the TIDieR (Template for Intervention Description and Replication) 12-item checklist. The completed SPIRIT and TIDieR checklists are provided as Multimedia Appendix 1 and

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Multimedia Appendix 2, respectively. As the study uses a single-group pretest-posttest design, we also plan to report outcomes following the TREND (Transparent Reporting of Evaluations with Nonrandomized Designs) 22-item statement; a draft TREND checklist will be submitted alongside the future results manuscript.

Rigor in Qualitative Data

The qualitative component of this study, which includes students' reflective reports, oral feedback, and structured observation notes, will be conducted with attention to methodological rigor. Following the criteria outlined by Lincoln et al [26], the study emphasizes transparency, reflexivity, and systematic documentation to ensure the trustworthiness of the findings.

Confirmability will be ensured through a coding record, allowing others to trace how findings were reached. The principal investigator, with years of psychiatric nursing and teaching experience, will keep reflexive journals to record assumptions and reflections. Triangulation across reflective reports, oral feedback, and observation notes will enhance confirmability, while peer debriefing with nursing experts will provide external checks for the AI virtual human scenario for patients with suicidal thoughts and mental illness. These strategies ensure that interpretations are grounded in data rather than influenced by researcher bias [26].

Dependability will be addressed by documenting each step of the research process, including scenario design, recruitment, data collection, and analysis. Iterative action research cycles provide opportunities to refine procedures while maintaining stability. Expert meetings will review progress and adapt interventions consistently. A methodological log and external expert audit will support transparency and replicability. Following the framework proposed by Lincoln et al [26], these practices demonstrate that the process is logical, traceable, and dependable.

Credibility will be supported through triangulation of multiple data sources and member reflections during debriefings. The principal investigator's expertise in psychiatric nursing ensures prolonged engagement and contextual understanding. The methodological process will document how interpretations are shaped, while peer debriefing with a faculty member offers external validation. These approaches confirm that the findings authentically represent participants' experiences, aligning with the standard for credibility in qualitative research established by Lincoln et al [26].

Transferability will be enhanced by providing thick descriptions of participants, course context, and intervention details, including AI virtual human simulations and game-based activities. Rich excerpts from student reflections and oral feedback will allow readers to judge the relevance of the findings for their own contexts. By situating the study within Taiwanese nursing education while highlighting the universal themes of EI and crisis training, the research facilitates applicability beyond its immediate setting [26].

Ethical Considerations

This teaching project has been approved for funding (see Multimedia Appendix 3) and is under review by the central regional research ethics committee of China Medical University, Taichung, Taiwan review board (T-AU-36938) to ensure adherence to ethical standards in research involving human participants. All data collected in this study will be handled in accordance with institutional review board ethical guidelines to ensure participant privacy and data security. Participants will be assigned unique ID codes, and no personally identifiable information will be linked to the analysis. Digital data, including survey responses, reflection journals, and system use logs, will be stored on encrypted and password-protected institutional servers accessible only to the principal investigator and authorized research team members. All documents will be kept in locked cabinets in secure university offices. All data will be retained for a maximum of 5 years and then permanently destroyed in accordance with institutional policies. Results will be reported in aggregate form to prevent individual identification. Participation in this study is voluntary, and informed consent will be obtained from all participants before data collection. Participants may withdraw at any time without penalty or impact on their academic standing.

Results

This project aims to develop 5 AI virtual human simulation scenarios. One scenario will focus on practicing empathic communication skills and conducting comprehensive psychiatric assessments across 5 core domains. The scenarios will present AI-simulated patients demonstrating suicide ideation and suicide risk related to different psychiatric diagnoses, including major depressive disorder, bipolar disorder (depressive episode), schizophrenia, and borderline personality disorder. The anticipated outcomes of this study include enhanced EI and improved psychological crisis management skills among nursing students. Furthermore, the findings are expected to contribute to an evidence-based foundation for innovative instructional strategies in nursing education that incorporate AI-driven simulation technology.

In terms of the research timeline, data collection will be conducted during cycle 1, including both qualitative and quantitative data. A preliminary analysis will be performed by the end of cycle 1, followed by a second expert panel meeting during the winter vacation. Based on the results of cycle 1 and expert feedback, the AI simulation lesson plans will be refined before the implementation of cycle 2. During cycle 2, both qualitative and quantitative data will again be collected. Upon completion of the 2 action research cycles, an overall data analysis will be conducted, and the final results and manuscript are expected to be completed and submitted within 3 months the research project is completed.

Discussion

Anticipated Findings

This project aims to comprehensively enhance the professional competencies and psychological resilience of third-year

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postbaccalaureate nursing students, preparing them for the challenges of future clinical practice. By integrating GBL with an AI virtual human platform, the intervention is designed to strengthen students' EI, including their ability to recognize, understand, and manage emotions effectively. The program also seeks to improve students' psychological crisis management skills, fostering adaptive coping and decision-making under stress. In addition, it aims to promote empathic communication and emotional connection with patients, while enhancing clinical judgment and problem-solving abilities through immersive, scenario-based learning. The innovative teaching strategies are expected to increase student motivation and engagement, making the learning process more interactive and appealing. Furthermore, the intervention will familiarize students with the application of AI technologies in nursing education, thereby improving their technological adaptability. Finally, the program encourages self-reflection and self-assessment to support ongoing professional development and lifelong learning.

Strengths and Limitations

This study is expected to introduce an innovative educational approach by integrating GBL with AI virtual human interactions to enhance nursing students' EI and psychological crisis management skills. A key anticipated strength lies in the use of experiential and technology-enhanced learning strategies within an action research framework, which may facilitate iterative refinement of teaching practices and encourage reflective learning. The planned use of both quantitative and qualitative methods is also likely to provide a comprehensive assessment of learning outcomes, capturing changes in knowledge, emotional competence, and communication behaviors.

Nevertheless, several potential limitations should be considered. As the study will adopt a single-group pretest-posttest design, the lack of a control group may limit the ability to draw causal inferences. However, implementing a control group in an educational setting may raise ethical concerns regarding unequal access to innovative teaching strategies, potentially leading to student dissatisfaction or perceptions of unfair treatment. In addition, the sample will be limited to third-year postbaccalaureate nursing students from a single institution, which may affect the generalizability of the findings. The AI virtual human platform, while offering interactive and standardized scenarios, may not fully capture the complexity and unpredictability of real-world clinical encounters. Furthermore, the relatively short duration of the intervention may limit the ability to evaluate sustained or long-term impacts on clinical competence and professional development.

Conclusions

This study presents an innovative, technology-enhanced teaching model that integrates GBL and AI virtual human simulations into psychiatric nursing education. By combining traditional instruction with immersive and interactive elements, the project aims to enhance nursing students' EI, empathic communication, and psychological crisis management skills. Through the implementation of 2 iterative action research cycles, the study is designed to evaluate and refine the intervention based on both quantitative outcomes from the AEIS and qualitative insights from student reflections and classroom observations. The use of generative AI technology and the Virti platform represents a novel approach to experiential learning in mental health nursing. The anticipated findings may offer valuable evidence to support the integration of AI-driven simulations into nursing curricula and provide a foundation for future innovations in competency-based education.

Acknowledgments

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Data Availability

The datasets generated and analyzed during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

Study design: YCC (lead), YCH (equal)

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT 2013 checklist.
[DOCX File , 15 KB - resprot_v14i1e80290_app1.docx]

Multimedia Appendix 2
TIDieR checklist.

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[DOCX File , 27 KB - resprot_v14i1e80290_app2.docx]

Multimedia Appendix 3
The peer-review report from the Teaching Practice Research Project of the Ministry of Education, Republic of China (Taiwan).
[PDF File (Adobe PDF File), 173 KB - resprot_v14i1e80290_app3.pdf]

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Abbreviations

AEIS: Adult Emotional Intelligence Scale
AI: artificial intelligence
EI: emotional intelligence
GBL: game-based learning
LMM: linear mixed effects model
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TIDieR: Template for Intervention Description and Replication
TREND: Transparent Reporting of Evaluations with Nonrandomized Designs
VR: virtual reality

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Protocol

Cocreation of a Mobile App (AYABytes) by Physicians and Adolescents and Young Adults With Cancer to Improve Access to Cancer-Related Resources and Reduce Distress: Protocol for a Single-Arm Feasibility Study

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Abstract

Background: Adolescents and young adults with cancer require dedicated and tailored management that bridges adult and pediatric oncology services. At the National Cancer Centre Singapore, 40% of newly diagnosed adolescents and young adults report significant distress due to uncertainty about prognosis, treatment, and disruption of life milestones. A major unmet need is access to reliable, age-appropriate information. Prior studies demonstrate that digital technology can effectively deliver such support.

Objective: This study describes the protocol for evaluating AYABytes (Adolescent and Young Adult Building Youths, a Technology for Education and Sharing), a mobile app cocreated by patients and health care professionals to improve health-related quality of life for adolescent and young adult oncology patients. An iterative information-gathering process was conducted, including semistructured interviews with 2 clinicians, 3 cancer survivors, and 3 care partners to cocreate this mobile app. AYABytes is an interactive, phone-based intervention designed to engage adolescent and young adult oncology patients with personalized education, mood, and symptom self-management resources with an inbuilt algorithm that responds to patient-reported questionnaires.

Methods: The app will be evaluated in 2 phases—a pilot test and an implementation test. In the pilot test, the app will be launched to a test group of 20 adolescent and young adult oncology patients aged between 16 and 45 years, selected for representation among the age group and their malignancies. Patients will be allowed to use the app for 1 month. Feasibility and acceptability were assessed via a semistructured survey. In the implementation stage, 200 patients will be allowed to use the app over 6 months and will complete an EQ-5D-5L questionnaire at baseline and at the 1- and 6-month marks. Evaluation of the mobile app was performed via the mHealth App Usability Questionnaire at similar intervals.

Results: Funding for the development and trial of AYABytes was awarded in October 2020 through a National Cancer Centre Singapore research grant. Pilot testing was completed in May 2024. The implementation phase began in June 2024 and is currently ongoing.

Conclusions: We believe that AYABytes, a novel eHealth mobile app, will be both beneficial and easily used by adolescent and young adult oncology patients. Evaluating the app and its quantifiable impact on improving the quality of life of adolescent

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and young adult oncology patients will help enrich the evidence for mobile health interventions. It will also validate new digital approaches to help adolescent and young adult oncology patients reduce their distress and address unmet needs and concerns.

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(JMIR Res Protoc 2025;14:e69453) doi:10.2196/69453

KEYWORDS

adolescents and young adult oncology patients; mobile app; innovation; oncology; cancer

Introduction

Background

Adolescent and young adult oncology patients are a unique group of individuals who are starkly different from their pediatric and adult counterparts. Defined as patients with cancer diagnosed between the ages of 16 and 45 years, they face significant medical and psychosocial challenges during and after treatment [1].

A recently published pilot study in our institution found that up to 40% of our adolescents and young adults with cancer have a significant distress level in the first 6 months of diagnosis [2]. Much of these distresses are related to a lack of age-appropriate information, a perceived lack of knowledge with regard to treatment details, possible side effects, financial concerns, and generalized anxiety. Studies and reports have shown that a large proportion of adolescent and young adult oncology patients are dissatisfied with the amount and quality of information and education that they receive during and after their cancer journey [3-5]. This lack of information also results in a negative impact on cancer control [6]. In addition, it has been found that up to 50% of adolescent and young adult oncology survivors report having their information and service needs unmet. This percentage of unmet information needs was similar regardless of cancer type [3] and despite the fact that many adolescent and young adult oncology patients report that receiving such information is important to them [7].

The methods by which people obtain information have been largely revolutionized with the advent of the internet and mobile gadgets. Digital health interventions (DHIs) offer a much-needed solution to plug this information gap in an accessible manner. Digital health platforms can be used in multiple ways, including for information delivery, 2-way communication, or longitudinal assessment [8]. The widespread use of the internet for health purposes has enhanced the ease of accessibility of DHIs [9]. This is particularly relevant for adolescents and young adults, who are pervasive users of technology.

Over the years, there has been a surge in the number of studies investigating the potential benefits of DHIs. However, adolescent and young adult oncology patients remain excluded from many of these important trials. A scoping review conducted by Lee et al [10] showed that the most common population involved were adults and older adults, with cancer survivors being the primary recipients of DHIs across studies. In addition, most DHIs target patients with early-stage cancer or patients with cancer in general. The benefit of DHIs should not be limited to cancer survivors; it should also be extended to adolescent and young adult oncology patients while they navigate their cancer journey. Adolescent and young adult oncology patients receiving treatment must make difficult decisions that can affect their long-term health and well-being [11]. Due to the often intense treatments that they have to undergo, many experience severe side effects during treatment. They also have to deal with long-term treatment-related toxicities and face a higher risk of secondary cancers during survivorship. DHIs that offer self-managing services and patient education regarding red flag symptoms will certainly improve outcomes of adolescent and young adult oncology patients [9,12,13]. AYABytes (Adolescent and Young Adult Building Youths, a Technology for Education and Sharing) hopes to be able to address this need by being a 1-stop platform where adolescent and young adult oncology patients, regardless of which stage of the cancer journey they are at, can obtain the necessary information that they need.

This Protocol

This paper aims to describe the protocol for the development and evaluation of a digital app, AYABytes, that provides rapid access to information relevant to the cancer journey of Asian adolescent and young adult oncology patients. This will allow our own and regional adolescent and young adult oncology patients to have an accurate resource that they can turn to. By reducing barriers to information access, AYABytes will bring information sharing to a new level and pave the way for digital analytics in the future.

Methods

Overview

This is a single-center interventional study with the primary aim of developing a digital app to provide rapid access to information relevant to the cancer journey of adolescent and young adult oncology patients and to evaluate the capacity to implement this as an intervention arm.

We hypothesize that adolescent and young adult oncology patients prefer a digital informative platform in the form of an app to assess oncology-related educational materials. Our primary aim is to develop a digital app designed to provide rapid access to information relevant to their cancer journey and to evaluate the feasibility and acceptability of this digital app. We hypothesize that this app will be used actively by 60% or more of adolescent and young adult oncology patients. Feasibility will be determined by the percentage of participants who log into the app at least 2 times within the 6 months. We will assess the acceptability of the app with the mHealth App Usability Questionnaire (MAUQ) as our objective measure of satisfaction at the 1- and 6-month mark of use. We will be administering

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questionnaires to evaluate their preferences and their adoption as well. Frequent users are determined as 2 log-ins into the mobile app within 6 months, while nonfrequent users are determined as less than 2 log-ins into the app within the 6-month study period.

Our secondary aim is to measure the improvement in distress levels (National Comprehensive Cancer Network [NCCN] distress thermometer [DT]) for the frequent users of the app for further efficacy studies and the 5-level EQ-5D to study changes in health-related quality of life among young adults with cancer after using the app. We will measure distress levels and the EQ-5D before using the app, and at the 1- and 6-month marks after using the app.

Participation and Recruitment

This study aims to recruit 200 newly diagnosed adolescent and young adult oncology patients over 18 months from the National Cancer Centre Singapore (NCCS) clinics in the Outram Campus. Eligible patients will be identified by their attending physicians and consented to during their in-person clinic consultation.

For this study, we will include patients who (1) are Singaporean citizens or permanent residents, (2) are aged between 16 and 45 years (parental consent will be obtained for patients aged <21 years), (3) speak English, (4) are newly diagnosed with any malignancies, (5) have the ability to provide informed consent and adequate mental capacity for the completion of the questionnaire, and (6) have brain metastases or primary brain cancers as long as they can provide informed consent and have adequate mental capacity for completion of the questionnaire. We will exclude patients who (1) are unable to comply with the follow-up and study protocol and (2) have medical conditions deemed inappropriate by the primary oncologist.

Development and Data Sharing

The primary intervention is a smartphone app, AYABytes, which is a mobile health app designed for adolescent and young adults with cancer and cancer survivors. After the initial literature review, a team for idea generation was set up, consisting of 3 adolescent and young adult oncology patients, 1 medical oncologist, 1 palliative care physician, 1 medical social worker, 1 nurse, and 2 research associates. A cocreation project was subsequently embarked on to develop and design a smartphone app for adolescent and young adult oncology patients.

To inform the development and design of the AYABytes app, a targeted literature search was conducted between October 2020 and March 2021 using PubMed, Scopus, and Google Scholar. Search terms included combinations of “adolescent and young adult oncology,” “digital health interventions,” “mobile application,” “patient education,” “co-design,” “health literacy,” and “psychosocial support.” Studies were included if they were published in English within the past 10 years and focused on digital interventions for adolescents and young adults with cancer or other chronic illnesses. Gray literature, institutional reports (eg, the World Health Organization and National Cancer Institute), and app store reviews were also examined to benchmark app features, usability design principles, and engagement strategies. This process informed the selection of core functions, such as symptom tracking, personalized educational content, and storytelling, and guided the choice of validated evaluation instruments such as the MAUQ.

In parallel, we conducted a review of digital health implementation frameworks and outcome measures, focusing on feasibility and usability assessment tools. We also performed a legal and regulatory review of local and international data protection standards, including the Singapore Personal Data Protection Act and the General Data Protection Regulation, to guide data governance and risk management planning. Security clearance for the app was obtained from Synapxe, Singapore’s national HealthTech [14] agency, to ensure infrastructure compatibility, cybersecurity compliance, and adherence to institutional standards for mobile health app deployment.

The study mobile app will be an added tool for the participants’ cancer care delivery process. The app will be developed by an independent mobile app developer, and licensing will be provided to SingHealth Synapxe. Participants will be logged into the app via an anonymous and deidentified username. No patient details will be obtained through the mobile app. We intend to design and build this app by working with a specialized app developer, Stone&Archer. The technology selected for implementing the intervention is a smartphone app (for both the Android and Apple iOS systems). Curated and appropriate information will be uploaded into this app. There will be inbuilt algorithms that the patient can select to further individualize the information received to personalize their experience with the interface.

Primary Intervention and AYABytes App Features

Information sharing is an important mediator of patient outcomes [14]. From our pilot study, we have identified the key concerns that an adolescent and young adult oncology patient may have in the local Singapore context. These concerns fall into the following domains: (1) information about cancer diagnosis, (2) investigation process and implications, (3) treatment process and possible complications, (4) fertility preservation, (5) financial costs, (6) cancer screening and prevention, and (7) diet and complementary medicine. Consequently, AYABytes will contain substantial informative articles, endorsed by NCCS oncologists, covering the abovementioned topics. AYABytes seeks to reduce the distress experienced by adolescent and young adult oncology patients by resolving the uncertainty that comes with insufficient understanding surrounding their diagnosis, and current and long-term plans.

The AYABytes framework is anchored on 3 core design tenets—information sharing, individualized care, and community support—each linked to specific in-app features (Table 1). AYABytes hopes to achieve this by giving adolescent and young adult oncology patients a platform to chart the physical manifestations of their cancer, the side effects of their treatment, and their emotional response toward it in real time (Figure 1). With this visual overview of how the cancer treatment affects the adolescent and young adult oncology patients’ life, the team can optimize the treatment regimen such that their well-being is not significantly compromised in favor of inconsequential gains in treatment efficacy. Nonetheless, this monitoring of

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patient-reported outcomes also helps adolescent and young adult oncology patients better manage their symptoms, increase satisfaction with their treatment, and improve communication with their physicians regarding their concerns and expectations [15].

Table 1. Overview of the design tenets underpinning the construct of AYABytes (Adolescent and Young Adult Building Youths a Technology for Education and Sharing).

Design tenets	Associated key AYABytes features
Information sharing	Informative articles endorsed by National Cancer Centre Singapore oncologists on topics relevant to local adolescent and young adult oncology patients
Individualized care	In-app mood and symptom tracking
Community support	Testimonials by fellow local adolescent and young adult oncology patients

Figure 1. Mood and symptom tracking interface.

AYABytes' last tenet focuses on the creation of a supportive community for adolescent and young adult oncology patients to find peace and solace when it comes to coping with their disease. Receiving a cancer diagnosis is destabilizing, and many adolescent and young adult oncology patients experience an increase in distress in trying to maintain a normal lifestyle while coping with cancer. Furthermore, it is not uncommon for adolescent and young adult oncology patients to feel alone throughout the course of their cancer journey [16]. AYABytes will contain authentic patient-submitted stories of their journey through their cancer diagnosis (Figure 2). Reading these first-hand patient narratives allows other adolescent and young adult oncology patients to have a better idea of what they are about to go through. More importantly, it shows them that their experience is not unique, that many before them have had a similar experience, and that they will be able to find the strength to make it through this difficult period as well [17].

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Figure 2. Cancer-specific articles and testimonies of cancer survivors.

Phase 1: Pilot Testing

The app will be launched to a test group of 20 adolescent and young adult oncology patients. Recruitment will be targeted for an appropriate representation of gender and age groups across the adolescent and young adult oncology patient spectrum. During the pilot test, patients will use the app over the course of 4 weeks. During both phases 1 and 2, patients will not be given any specific instructions on the frequency with which they should use the app. They will be instructed to use the app as they see fit. Patients will provide their evaluation on the feasibility and acceptability of the app through a semistructured survey.

Phase 2: Implementation Testing and Quality of Life Evaluation

There are various outcome assessments that are part of this study. The primary aim would be to evaluate AYABytes' feasibility as well as usability among adolescent and young adult oncology patients. Secondary end points would include the estimates for the extent of improvement in distress levels (NCCN DT) as well as health-related quality of life (EQ-5D-5L) for the frequent users of the app. Table 2 shows the surveys that will be administered to the participants during the study.

Table 2. Survey assessment timeline for recruited adolescent and young adult oncology patients.

Time	Surveys
Baseline	• NCCN[a] distress thermometer • EQ-5D-5L
First month	• MAUQ[b] • NCCN distress thermometer • EQ-5D-5L
Sixth month	• MAUQ • NCCN distress thermometer • EQ-5D-5L • Exit interview survey

[a]NCCN: National Comprehensive Cancer Network.

[b]MAUQ: mHealth App Usability Questionnaire.

Feasibility is determined based on how frequently adolescent and young adult oncology patients use AYABytes. Frequent users are determined as having at least 2 log-ins into AYABytes within the 6 months, while nonfrequent users are determined as having less than 2 log-ins into AYABytes over 6 months.

Usability is assessed via a few metrics. We use the MAUQ as our objective measure of satisfaction. The MAUQ was designed by Zhou et al [18] based on several existing questionnaires used in previous mobile app usability studies. Psychometric analysis indicated that the internal consistency of MAUQ is high and correlates strongly with many well-validated questionnaires (System Usability Study and Poststudy System Usability Questionnaire). The MAUQ will be administered at the 1- and 6-month mark.

Usability will also be assessed via the following objective outcome measures: (1) the proportion of eligible participants

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enrolled and reasons for nonparticipation, (2) proportion of participants retained in the study, and (3) intervention fidelity (ie, occurrence of technical problem). The number of individuals assessed for study eligibility, reasons for exclusion or noncompletion, and numbers included in the analysis will all be recorded to examine the acceptance of the intervention and identify issues with the intervention or technology affecting participation.

All participants will undergo a final exit survey within 1 month after completion of the study. The exit survey will involve feedback regarding the impact of the intervention, its utility, relevance of the algorithms, value or burden of item repetition in the algorithm, symptoms or problems that were not addressed by the mobile app, and general comments. Participants will also be asked to share what actions have been taken in response to the information obtained from AYABytes.

We intend to use the NCCN DT as the objective measure of distress level. This was chosen due to its ease of use and specificity. It has also been validated for use in patients with cancer in Singapore and has been used in studies concerning local adolescent and young adult oncology patients [19]. The DT involves the following five domains: (1) practical, (2) family, (3) emotional, (4) spiritual and religious, and (5) physical problems. The DT functions on an ordinal scale from 0 to 10, with 0 being the lowest and 10 being the highest score. A score of more than 4 would correspond to clinically significant distress in patients with cancer according to current guidelines.

In this study, we will also pilot the use of the 5-level EQ-ED (EQ-5D-5L) questionnaire for future efficacy studies [20]. This questionnaire produces a 5-digit health state profile representing the level of reported problems on each of the 5 dimensions of health. They include mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Therefore, we have chosen to pilot the EQ-5D-5L because of its widespread use and validated multiattribute utility for measuring health-related quality of life. An outline of the study protocol is depicted in Figure 3.

Figure 3. Overview of the AYABytes (Adolescent and Young Adult Building Youths, a Technology for Education and Sharing) protocol.

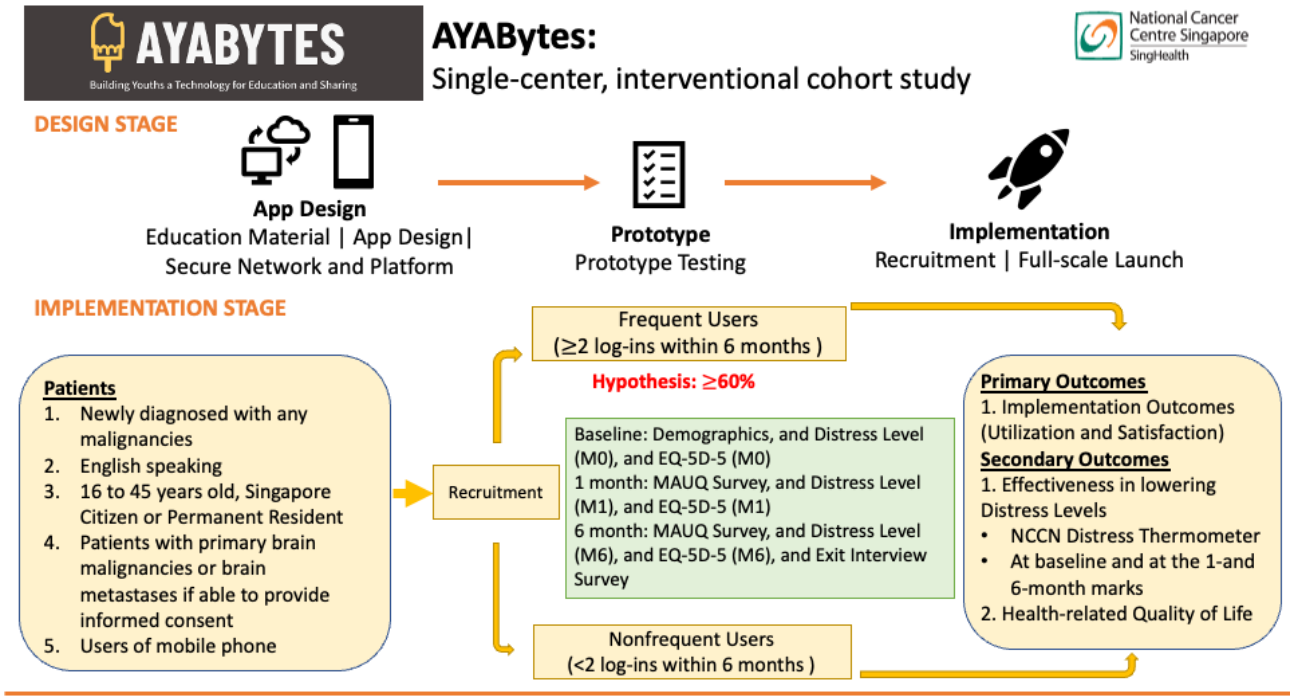

Statistical Analysis

The primary end point of this study is the proportion of frequent users of the digital app. Assuming the proportion of frequent users to be 50%, a sample size of 97 patients is required to estimate this proportion with a 2-sided 95% CI and a 10% margin of error. We have assumed 50% of the users to be frequent users because this will require the largest sample size to achieve the specified precision of the 95% CI for the parameter of interest. In the pilot study, 60% of the patients completed all the DT questionnaires at baseline, 1 month, and 6 months. Adjusting for a 40% dropout rate, 160 patients will be recruited in this study.

All data collected in this study will be summarized using descriptive statistics. Frequency and percentages will be reported for categorical variables. Median with interquartile ranges or mean with SD will be reported for continuous variables. The proportion of frequent users will be reported with a 95% CI estimated using the exact method. Distress levels will be reported as a proportion of adolescent and young adult oncology patients with a score of greater than 4 for each of the 39 items in the DT at baseline, 1 month, and 6 months. Mean and SD of the total distress score will also be reported across the 3 time points, together with any changes in total distress score at 1 and 6 months from baseline. Satisfaction ratings will be reported for 1 and 6 months. Results on distress levels, satisfaction ratings, and exit surveys will be broken down by frequent and infrequent users of the app.

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Ethical Considerations

All research involving human participants is reviewed and approved by the SingHealth Institutional Review Board (2022/2559). Participants will provide informed consent after receiving detailed explanations of the study's objectives and procedures. Participant privacy and confidentiality were rigorously maintained. Identifying information will be anonymized or omitted in reporting, and the data will be stored securely in compliance with institutional and legal standards. No compensation will be provided.

Results

Funding for the development and trial of AYABytes was awarded in October 2020 through a NCCS research grant. The design team conducted 3 cocreation meetings with adolescents and young adults, clinicians, and care partners between October 2020 and June 2021 to inform the app's initial features and content. The design and programming of the AYABytes mobile app for both Android and iOS platforms were completed in June 2023. The app is optimized for compatibility across both operating systems.

Pilot testing of AYABytes was completed in May 2024 and involved 20 adolescent and young adult participants. The implementation phase began in June 2024 and is currently ongoing. Recruitment for the implementation phase is expected to conclude by December 2025. An overview of the study design, key phases, participant activities, and timeline is presented in Table 3.

Table 3. Overview of study design, phases, participant activities, and timeline for the AYABytes (Adolescent and Young Adult Building Youths a Technology for Education and Sharing) protocol.

Phase	Activity	Sample size	Duration	Outcomes assessed
Predevelopment (October 2020-June 2021)	Literature review, stakeholder interviews, legal and cybersecurity review, and app prototype development	__[a]	9 months	App design requirements and privacy compliance
Development phase (July 2021-June 2023)	App design, programming, and internal testing with developers	—	24 months	Functionality verification and internal quality assurance
Phase 1: pilot study (March-May 2024)	Pilot-testing of the app among 20 adolescent and young adult oncology patients	20	4 weeks per participant	Feasibility, acceptability, and MAUQ[b] usability
Phase 2: implementation study (June 2024-December 2025)	Full rollout to 200 participants	200	6 months per participant	EQ-5D-5L, NCCN[c] distress thermometer, and MAUQ

[a]Not applicable.

[b]MAUQ: mHealth App Usability Questionnaire.

[c]NCCN: National Comprehensive Cancer Network.

Discussion

Anticipated Findings

The landscape of cancer management in the current age is very different from that just 10 years ago. Patients, especially adolescent and young adult oncology patients, are taking more control over their health. It has become commonplace for patients to search for their symptoms from multiple online sources before their first consultation with a physician. This dependence on online services as the first-line management for the occasional benign ailment certainly does not cause much harm [21]. However, this may not be as reliable when it comes to seeking out cancer information as cancer care is often more complex. With uncurated information on the internet, any unverified information may potentially be nebulous at best [22]. This uncertainty can lead to more significant distress regarding their symptoms and disease. Moreover, sifting through tons of conflicting data often leads to delays in accessing health care services and its associated medical complications [23,24].

This shift is paralleled by a corresponding change in patient expectations within the health care system, moving from the traditional paternalistic approach to a more collaborative model [25]. Patients want to participate actively in their care and desire transparency and shared decision-making [26]. In this fast-paced health care environment, patients increasingly expect swift access to health information and solutions to their concerns [21]. With abundant health information online, they are driven to conduct their research and arrive at appointments with established ideas and concerns [22]. This underscores the importance of creating reliable health resources for patients to access as needed, as their primary team cannot realistically address their concerns with the same efficiency as the various online platforms. DHIs allow for patients' concerns to be addressed proactively, promptly, and accurately while concurrently optimizing the efficiency and effectiveness of their next face-to-face consultation. DHIs have demonstrated their effectiveness in improving health care outcomes, but it is crucial to recognize that they cannot function in silos. DHIs improve patients' quality of life and functional capacity while reducing the frequency of unplanned admissions and the total duration of hospitalization [27,28]. However, they do not replace regular care or contact time with physicians. Thus, while DHIs hold immense promise, their true potential lies in their integration and synergy within broader health care systems.

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With the current diversity of DHIs available on the market, it is vital to take a step back to identify critical features of existing DHIs that allow them to have a long-standing impact on adolescent and young adult oncology patients. DHIs need to be intuitive, engaging, and user-friendly. It also needs to be comprehensive and safe [10]. With this understanding, AYABytes will be prototyped and undergo consumer testing before final implementation. All information available on the app will also be evaluated for clarity and accuracy. Perhaps more prominently, the next frontier for DHIs, such as AYABytes, that seek to offer care throughout the cancer continuum would be connectivity and systems integration. We aim for AYABytes to be linked with local health care systems so that adolescent and young adult oncology patients outside the NCCS and the broader SingHealth infrastructure will benefit from it. Consequently, this will also allow for more convenient follow-up and management of adolescent and young adult oncology patients throughout Singapore. With all these strategies laid out, we have optimistic expectations for AYABytes to catalyze the transformation of cancer care delivery for local adolescent and young adult oncology patients and improve their cancer outcomes, ushering in a new era of cancer care.

Limitations

This project could be limited by the population size of adolescent and young adult oncology patients in Singapore. We estimate the dropout rate to be 40%, requiring us to enroll at least 160 patients so that enough completed questionnaires will be available for analysis. With approximately 400 to 500 adolescent and young adult oncology patients diagnosed yearly, recruiting and retaining approximately 200 patients might pose a challenge. To mitigate and minimize this limitation, our study coordinator will follow up by calling patients who did not complete the online questionnaires to assist with collecting responses. We will aim to publish our final results once we have at least 97 patients completing all 6 months of survey assessments. In addition, given that AYABytes is a mobile app, we can only recruit patients who own a digital device running the Android or iOS system. Given the age range of our sample population, there will likely be minimal selection bias.

Conclusions

AYABytes represents a contemporary approach to digital health. Its function as an encyclopedia of adolescent and young adult oncology patient–specific cancer information will improve health literacy, patient engagement, and health outcomes among adolescent and young adult oncology patients. With additional features, such as symptom monitoring and sharing of patient stories, AYABytes seeks to capture the essence of what it means to be diagnosed with cancer in Singapore in this decade. Adolescent and young adult oncology patients are not alone in their recovery, and AYABytes represents this collaboration between the physician and the patient, with the wider adolescent and young adult oncology patient community playing a crucial role. This protocol paper describes the process of creating and executing the AYABytes app. With the positive feedback and interest gathered from our pilot study, we are optimistic that AYABytes will live up to the expectations of our adolescent and young adult oncology patients as a reliable cancer resource for years to come, with the entire adolescent and young adult oncology patient community serving as active participants.

Acknowledgments

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Authors' Contributions

EYTW, WLG, VHMW, DSCQ, YPT, YYT, STLC, MFBHR, and EYLP contributed to conception and design. WLG, SNQBAL, and NBMS contributed to administrative support. EYTW, WLG, SNQBAL, NBMS, and EYLP contributed to the provision of study materials or patients. EYTW, BSTW, WLG, SNQBAL, and NBMS contributed to the collection and assembly of data. All authors contributed to data analysis and interpretation, manuscript writing, and final approval of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review comments from the Institutional Fund Committee, National Cancer Centre Singapore.
[PDF File (Adobe PDF File), 1329 KB - resprot_v14i1e69453_app1.pdf]

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Abbreviations

AYABytes: Adolescent and Young Adult Building Youths, a Technology for Education and Sharing
DHI: digital health intervention
DT: distress thermometer
MAUQ: mHealth App Usability Questionnaire
NCCN: National Comprehensive Cancer Network
NCCS: National Cancer Centre Singapore

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Proposal

Acceptance and Commitment Training for Family Caregivers of People with Neurodevelopmental Disabilities: Protocol for a Collaborative Implementation Study

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Abstract

Background: Family caregivers of individuals with neurodevelopmental disabilities (NDDs) often experience stress, anxiety, and depression; however, few evidence-based interventions are designed to improve their mental well-being. To address this gap, we developed an acceptance and commitment training (ACT) group–based workshop cofacilitated by trained caregivers and clinicians (Caring for the Caregiver Acceptance and Commitment Training [CC-ACT]).

Objective: This study evaluates the real-world implementation of this innovative, evidence-based ACT workshop aimed at enhancing caregiver mental health and resilience.

Methods: Guided by the reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) implementation science framework, this study examines the workshop across these 5 domains. We delivered the CC-ACT workshops virtually or in-person across 11 intervention sites in Canada, including hospital and community agencies that provide services to children with NDDs and their families. Family caregivers (ie, a parent, grandparent, or adult sibling) of someone with an NDD were eligible to participate in the workshops, with site-specific criteria set by each host agency. Caregivers participated in preintervention, postintervention, and 3-month follow-up assessments measuring stress, resilience, and self-compassion using validated instruments (21-item Depression, Anxiety and Stress Scale; Parenting Stress Index, 4th Edition; Brief Family Distress Scale; Multi-System Model of Resilience Inventory; and Self-Compassion Scale–Short Form), alongside ACT process measures (Cognitive Fusion Questionnaire, Valued Living Questionnaire, and Acceptance and Action Questionnaire-II). Implementation fidelity was assessed through checklists and surveys. Focus groups with caregiver facilitators, clinician facilitators, workshop participants, and organizational leaders were held to qualitatively evaluate the implementation process and the caregiver-clinician cofacilitation model. Qualitative data will be analyzed using descriptive content analysis, a flexible approach that can be used to systematically

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summarize different types of qualitative data. Quantitative data will be analyzed through repeated measures ANOVA and mixed-effects modeling, with subgroup analyses and multiple imputation for missing data.

Results: The CC-ACT workshops successfully reached 195 caregivers of individuals with NDDs. Two focus groups that included 5 caregiver workshop participants, 13 facilitators, and 5 organizational leaders were conducted. We anticipate that the workshops will demonstrate positive impacts on caregiver well-being, with variability in effectiveness based on participant characteristics and real-world implementation contexts. The findings are expected to identify key predictors of outcomes, equity and access barriers, and best practices for scaling and sustaining high-fidelity, adaptable caregiver interventions across diverse Canadian settings. Funding began in January 2022, data collection was completed in 2024, and data analyses will be completed by the end of 2025.

Conclusions: The CC-ACT workshop is a promising approach to enhancing the mental well-being of caregivers of individuals with NDDs. The RE-AIM framework helps capture process data systematically, documenting the balance between fidelity and adaptation. The study findings should support the refinement of implementation strategies and support the broader scalability of the intervention to diverse community settings.

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KEYWORDS

Acceptance and Commitment Training; caregivers; neurodevelopmental disabilities; peer facilitation; implementation science; adaptation; equity

Introduction

Background

Family caregivers (hereafter referred to as caregivers) of individuals with neurodevelopmental disabilities (NDDs) report high levels of stress, anxiety, and depression [1-3]. Their vulnerability was highlighted during the COVID-19 pandemic, when they had to navigate the sudden loss of structure, support, and routine for their loved ones [4]. Unfortunately, few evidence-based interventions are available to support the well-being and resilience of caregivers. Furthermore, these programs are limited in scope (eg, restrictions around age or disability of the individual being cared for), or in availability (eg, only in regions with extensive resources) [5,6].

Caregiver interventions help support the caregiver and, by extension, the entire family, including the child with a disability or neurodevelopmental condition [7]. While caregivers may benefit from individual support, group-based and peer-led interventions may confer additional benefits, address feelings of isolation and provide opportunities for personal growth, connection, and mutual learning [8,9]. Typically, these interventions are delivered by trained clinicians [10]; however, there is emerging evidence that caregivers can also play an important role as peer cofacilitators, ultimately empowering caregivers' voices while enhancing the success and feasibility of interventions [11].

To support caregivers of children with autism, early evidence demonstrated the benefits of acceptance and commitment training (ACT), a mindfulness-based workshop [12], as well as a study demonstrating the engagement of mothers as peer mentors in delivering a mindfulness-based intervention [13]. On the basis of our previous work using ACT in nonclinical populations to promote well-being and address issues related to stigmatizing attitudes, we adapted a 2-day in-person group-based ACT workshop for caregivers of children with autism to increase their resilience in the face of stressors, co-delivered by caregivers and clinicians together [14,15].

Early efficacy research demonstrated that our in-person ACT workshop was effective in reducing stress, depression, physical health concerns, and social isolation in mothers of children with autism and youth [16]. Additionally, the workshop helped these caregivers detach themselves from their distressing thoughts and act in ways that were more consistent with their values [14]. In a follow-up randomized controlled trial (RCT), caregivers of individuals with autism who participated in the workshop showed significant improvements in symptoms of depression and family distress relative to a waitlist control group, as well as significant treatment group improvements in stress, psychological acceptance, and cognitive fusion, which were not found in the waitlist group [17]. Workshop respondents also reported that a key element to the success of the workshops was the caregiver-clinician partnership. We have started to explore the use of our workshop for caregivers of other NDDs, such as individuals with fetal alcohol spectrum disorder (FASD) [18]. With the onset of the pandemic, we adapted our in-person group workshop into a virtual group workshop. Virtual delivery also addressed access barriers, such as a lack of childcare, distance from services, and transportation costs.

Research Objectives

The aim of this study is to evaluate the community implementation of the Caring for the Caregiver ACT (CC-ACT) model, designed to enhance the mental health and resilience of caregivers of individuals with NDDs, co-delivered by caregiver-clinician facilitation teams. Our research objectives and questions are presented in Textbox 1.

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Textbox 1. Research objectives and questions.

1. Evaluate the implementation of a caregiver and clinician-partnered Caring for the Caregiver Acceptance and Commitment Training (CC-ACT) workshop delivered in communities across Canada to support the mental health and resilience of caregivers of individuals with neurodevelopmental disabilities.
   - Is it feasible to recruit caregiver participants across study sites, and what proportion of participants complete the workshop?
   - Does the workshop lead to enhanced mental health and resilience in participants, and is this change maintained at follow-up?
   - What demographic, clinical, and organizational variables predict or moderate change, for example, whether the workshop is delivered to a mixed or homogeneous disability caregiver group, delivered in-person or virtually, or to caregivers of children or young adults?
   - How is the workshop perceived by various community groups, including participants, clinician facilitators, caregiver facilitators, and organizational leaders?
   - What adaptations become necessary as the workshop is implemented in various real-world settings?
   - What is the long-term sustainability of the workshop program in terms of its resource use, time, and potential for wide-scale adoption?
2. Evaluate the unique collaboration between caregivers and clinicians codelivering the workshop.
   - What are the facilitators and barriers to successful caregiver-clinician collaborations with regard to facilitator training and workshop delivery?
   - What is the value of this collaboration from various community group perspectives, including participants, clinician facilitators, caregiver facilitators, organizational leaders, and the research team?

Methods

Implementation Science Framework: Reach, Effectiveness, Adoption, Implementation, and Maintenance

The study is guided by the reach, effectiveness or efficacy, adoption, implementation, and maintenance (RE-AIM) implementation science framework [19], providing an overarching structure to examine the processes and outcomes of the real-world implementation of evidence-based health workshops in 5 areas: reach, effectiveness, adoption, implementation, and maintenance. *Reach* is a measure of participation at the individual level, such as the number or characteristics of program participants. *Effectiveness* includes an assessment of the positive and negative outcomes of the program. *Adoption* examines the uptake at the individual or organizational level. *Implementation* examines the degree to which the program is conducted as intended in various real-world settings. *Maintenance* evaluates the extent to which the program impact is enduring at the individual and organizational levels.

CC-ACT Workshop Description

Our workshop is a group intervention based on ACT, which aims to increase psychological flexibility through training in 6 core processes: defusion (relating to thoughts as merely thoughts), acceptance (willingness to experience thoughts and feelings rather than avoiding them), contact with the present moment (being in touch with the here and now rather than being stuck in the past or worrying about the future), self-as-context (being in contact with a transcendent sense of self rather than being stuck with self-labels), values (clarifying what gives life value and meaning), and committed action (persisting in value-guided actions). The intervention consists of experiential exercises, mindfulness practices, and small and large group reflective sharing [20].

Groups are guided by trained cofacilitators, including at least one clinician with experience in the NDD community and at least one family caregiver of an individual with an NDD. Each group can accommodate 10 to 15 participants. For in-person delivery, the workshop is delivered over 2 consecutive sessions, an evening session (3 h) and a full-day session (8 h), followed by a final evening session (3 h) 1 month later (Table 1; refer to Fung et al [20] for more details on intervention content). For virtual delivery, the workshop is conducted over 4 to 5 consecutive weekly 2-hour sessions, with an additional 2-hour session occurring 1 month later.

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Table 1. Overview of Caring for the Caregiver Acceptance and Commitment Training (CC-ACT) content across delivery modalities.

Virtual intervention (5 to 6 sessions; 2 h per session)	In-person intervention (3 sessions: S1 half-day [3 h], S2 full day [8 h], and S3 half-day [3 h])
S1: • Overview of ACT (eg, hexaflex and hand gestures) • Contact with the present moment exercise (eg, meditation with self-object, leaves on a stream)	S1: • Overview of ACT (eg, hexaflex and hand gestures) • Contact with the present moment exercise (eg, meditation with self-object and leaves on a stream)
S2: • Acceptance exercise (eg, keeping the count)	S2: • Acceptance exercise (eg, chair sculpture) • Defusion exercise (eg, paired sharing) • Values exercise (eg, values wordlist and 100th birthday) • Committed action exercises (eg, bull's eye and bus driver)
S3: • Defusion exercise (eg, adventures of the pink elephant and our song)	__[a]
S4 (or S4 and S5): • Values exercise (eg, values wordlist and 100th birthday) • Committed action exercises (eg, bull's eye and fireside chat)	__[a]
After a 4-week break, S5 (or S6): • Review of ACT model (eg, hand gestures and matrix) • Self-as-context exercise (eg, who I am)	After a 4-week break, S3: • Review of ACT model (eg, hand gestures and matrix) • Self-as context exercise (eg, LE'GO)

[a]Not applicable.

Project Description

The proposed project was conducted in 3 overlapping phases.

Phase 1: Preparation and Contextualization

In this initial phase, research ethics and institutional approvals were obtained. Community partner organizations and family advisers were engaged to refine the implementation process. Site-specific discussions helped identify local needs and preferences, including in-person versus virtual delivery and whether to offer mixed or homogeneous caregiver groups (eg, caregivers of individuals with autism, FASD, Down syndrome, or spina bifida). A core implementation protocol and a fidelity checklist were developed to evaluate adherence and document adaptations. Each site completed the Health Equity Impact Assessment (HEIA) tool [21], a structured implementation support tool, to identify potential barriers to accessing or participating in the workshop for vulnerable populations and mitigation strategies. Facilitator teams—composed of experienced caregivers and clinicians—were trained and supported based on the specific needs of each site.

Phase 2: Implementation

From 2022 to 2024, we partnered with 11 sites to deliver up to 2 ACT workshops per site, with each workshop targeting 10 to 15 caregiver participants. Sites across Canada included hospitals and community agencies providing services for children or families with NDDs (Table 2). Facilitators at each of the sites completed 20 hours of basic training from our team. Caregivers were eligible to participate in the workshops if they identified as a family caregiver (ie, parent, grandparent, or adult sibling) of someone with an NDD. Depending on the mandate of the host agency, workshops were held for caregivers of people of specific ages (ie, children, youth, or adults) or specific NDD diagnostic groups (ie, autism or FASD). Workshops were conducted in 2 waves (6-9 mo apart) to allow learnings from the first wave to inform the second and ensure adequate recruitment time.

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Table 2. Implementation sites.

Organization	Organization type	Province	Target population	Workshop format
1	Mental health hospital	Ontario	Two populations: caregivers of people aged >16 y with NDDs[a] and fathers of people aged >16y with NDDs	5-wk virtual
2	Community health center	Ontario	Caregivers of children, youth, and adults with NDDs	5-wk virtual
3	Nonprofit organization: IDD[b]	Ontario	Caregivers of children, youth, and adults with NDDs	6-wk virtual
4	Nonprofit organization: sibling disabilities	Canada	Adult sibling caregivers of people with NDDs	6-wk virtual
5	Rehabilitation hospital	Ontario	Caregivers of children and youth with disabilities and complex health conditions	6-wk virtual
6	Nonprofit organization: disabilities	British Columbia	Caregivers of children and youth with NDDs and complex health conditions in early intervention and school-age programs	6-wk virtual
7	Nonprofit organization: disabilities	Ontario	Caregivers of children and youth with NDDs	6-wk virtual
8	Nonprofit organization: IDD	Quebec	Caregivers of children, youth, and adults with NDDs	6-wk virtual
9	Nonprofit organization: disabilities	Ontario	Caregivers of children, youth, and adults with NDDs	6-wk virtual
10	Nonprofit organization: developmental services	Ontario	Caregivers of individuals with fetal alcohol spectrum disorder	6-wk virtual
11	Community health center and nonprofit autism organization	Nova Scotia	Caregivers of people with autism	In-person

[a]NDD: neurodevelopmental disability.

[b]IDD: intellectual or developmental disability.

Experienced CC-ACT peer coaches provided virtual coaching to local facilitation teams as needed. After each ACT session, facilitators completed fidelity checklists noting the exercises they completed or did not complete and why, as well as describing how well the exercises worked and any ad hoc adaptations. After the workshop, facilitators completed a survey detailing their experiences delivering the intervention, the support they received (virtual coaching), and reflections on caregiver-clinician collaboration. CC-ACT peer coaches also completed a survey about their experience in coaching each of the local facilitation teams.

To evaluate effectiveness, caregiver participants completed electronic surveys at 3 time points: before intervention (T1), after intervention (T2), and 3-month follow-up (T3). The survey included demographic, outcome, and ACT process measures, as presented in Textbox 2.

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Textbox 2. Demographic, outcome, and acceptance and commitment training (ACT) measures.

Demographic measures

- Parent age, ethnicity, education, and family composition
- Child's neurodevelopmental disability diagnosis, time since diagnosis, age, and living situation

Outcome measures

- Depression, Anxiety and Stress Scale: 21-item measure of depression, anxiety, and stress [22]
- Parenting Stress Index, 4th Edition: 11 items from Health and Isolation subscales to assess stress specific to parenting [23]
- Brief Family Distress Scale: Single-item 10-point scale for family distress [24]
- Multi-System Model of Resilience Inventory: 27-item scale assessing internal, external, and mediating resilience factors [25]
- The Short Warwick–Edinburgh Mental Well-being Scale: 7-item scale measured on a 5-point scale to assess mental well-being [26]
- Patient Health Questionnaire-4 (Kroenke et al [27]): 4-item scale for capturing anxiety and depressive symptoms [27]

ACT process measures

- Cognitive Fusion Questionnaire: 7-item scale assessing cognitive fusion, the degree to which individuals become entangled with their thoughts [28]
- Valued Living Questionnaire: 10-item 2-part tool evaluating value importance and alignment [29]
- Acceptance and Action Questionnaire-II: 7-item scale measuring psychological flexibility, the main target of acceptance and commitment training [30]
- Self-Compassion Scale–Short Form: 12-item measure of self-compassion [31]

Following the completion of the intervention, workshop participants were asked survey questions that measured their satisfaction with the CC-ACT program. Questions addressed the workshop content (how easy it was to understand, how relevant it was to their family, how interesting it was, and whether it contained new information), how much the workshop addressed the goals important to them, whether it provided skills that could be used in everyday life, the perceived value of having caregivers and clinicians colead the workshop, and how much the participants felt supported and valued throughout the workshop. Responses were provided on a 5-point Likert-type scale, ranging from strongly disagree (1) to strongly agree (5).

In addition, we conducted 3 focus groups, one each with caregiver workshop participants, facilitators, and organizational leaders, to explore perceptions of the intervention and caregiver-clinician collaboration (Multimedia Appendix 1).

Phase 3: Data Analysis and Knowledge Translation

Overview

In this final phase, we are analyzing quantitative and qualitative data. Lessons learned, particularly technical ACT-related facilitation tips, have been compiled into an implementation toolkit based on shared insights from facilitators and CC-ACT peer coaches. When we complete the analysis of the study outcomes and implementation data, we will publish and disseminate the findings to inform future intervention development and policy recommendations.

Project Evaluation Plan

The project is being evaluated using a mixed methods design to address the two primary research questions: (1) evaluation of CC-ACT intervention implementation using RE-AIM (Table 3) and (2) evaluation of caregiver-clinician collaboration (Textbox 3).

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Table 3. Implementation process evaluation.

RE-AIM[a] dimensions	Evaluation indicators and data sources
Reach	• Number of people who expressed interest, number of people who were recruited, number of people who completed, and % of completers • Sociodemographic and other participant characteristics (eg, type of NDD[b]) comparisons: • Cross-site comparisons
Effectiveness	• Before versus after comparisons: outcome measures; process measures • Analysis of moderators on outcome measures • Mediational analysis of process measures on outcomes • Estimated cost ranges for staff, materials, and other items necessary to run the workshops • Perceived benefits from cross-site focus groups
Adoption	• Perceived feasibility, acceptability, and fit from focus groups
Implementation	• Fidelity checklists • Health Equity Impact Assessment • Postworkshop surveys completed by facilitators and CC-ACT[c] peer coaches
Maintenance	• Before versus after versus follow-up survey data and focus groups • Tracking of agencies implementing regular programming based on our model

[a]RE-AIM: reach, effectiveness, adoption, implementation, and maintenance.

[b]NDD: neurodevelopmental disability.

[c]CC-ACT: Caring for the Caregiver Acceptance and Commitment Training.

Textbox 3. Caregiver-clinician collaboration evaluation.

Evaluation Focus Areas

- Barriers and facilitators to successful collaborations in terms of training and intervention delivery
- Stakeholder perspectives on the value of the collaboration

Evaluation indicators and data sources

- Postworkshop surveys completed by facilitators and Caring for the Caregiver Acceptance and Commitment Training peer coaches
- Perceived benefits of collaboration from cross-site homogeneous and mixed focus groups (eg, caregiver facilitators, clinician facilitators, workshop participants, and organizational leaders)
- Perceptions of the partnered model on the postintervention survey

Ethical Considerations

Overview

The study was approved by the institutional research ethics board of our team's mental health teaching hospital, the Centre for Addiction and Mental Health (REB#037-2017), and all participants provided informed consent online through REDCap (Research Electronic Data Capture; Vanderbilt University), an online survey platform, before commencing the study.

Surveys

Participation in the research evaluation was voluntary, and individuals could attend the workshops without taking part in the evaluation. Study data were collected and managed using REDCap electronic data capture tools hosted at the Centre for Addiction and Mental Health [32,33]. REDCap is a secure web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for data integration and interoperability with external sources.

Eligible family caregivers and facilitators completed consent online through REDCap, directing them to preintervention (T1) surveys, including demographic information (eg, gender, race, and age). Postintervention (T2) and follow-up (T3) surveys were completed similarly and included repeated measures and qualitative reflection questions. Each survey took approximately 20 to 30 minutes for family caregivers and 10 to 20 minutes for facilitators to complete. Survey participants received honoraria in the form of a CAD $50 (US $35.74) e-gift card at the end of the data collection period.

Focus Groups

Workshop facilitators, organizational leadership, and workshop participants were invited to participate in separate virtual focus groups via email. Focus group participants participated in the group virtually using WebEx (Cisco Systems, Inc), a secure, web-based videoconference platform. The focus groups were

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recorded, transcribed verbatim, and anonymized. Focus group participants received honoraria in the form of a CAD $50 (US $35.74) e-gift card following their participation.

Statistical Analysis

Quantitative Analysis

To evaluate reach, we will examine the number, attendance, and demographic profiles of participants at each site. To evaluate effectiveness and maintenance of the intervention, we will assess changes in outcome measures (21-item Depression, Anxiety and Stress Scale; Parenting Stress Index, 4th Edition; Brief Family Distress Scale; Multi-System Model of Resilience Inventory; Short Warwick–Edinburgh Mental Well-being Scale; and Patient Health Questionnaire-4) and ACT process measures (Cognitive Fusion Questionnaire, Valued Living Questionnaire, and Acceptance and Action Questionnaire-II) across 3 time points (before workshop, after workshop, and follow-up). We will first conduct a within-subjects repeated measures ANOVA, checking assumptions of normality (via skewness and kurtosis *z* values) and the absence of outliers (via boxplots). Where significant main effects are found, we will perform Bonferroni-adjusted pairwise comparisons (pretest-posttest, before follow-up, and after follow-up). In addition, we will use mixed-effects modeling to account for repeated measures within individuals and variability across study sites, and to examine potential predictors and moderators (eg, delivery modality, group composition, and demographic variables). Subgroup analyses will be stratified by gender identity, age, racial or ethnic identity, and living situation, exploring both the main effects and interactions. Missing data will be addressed according to the intention-to-treat principle, using multiple imputation in SPSS (IBM Corp) with all demographic and baseline outcome variables included as predictors.

Qualitative Analysis

The evaluation of all components of RE-AIM will also be undertaken using a qualitative approach. All qualitative data (focus groups, survey open-ended responses, and meeting notes) will be analyzed using descriptive content analysis [34]. This is a flexible approach that can be used to systematically summarize different types of qualitative data and is often used in applied research settings. Two team members will review the data and generate a codebook informed by the RE-AIM framework. Data will be independently coded, and reviewers will use a consensus. Several strategies will be used to establish trustworthiness for the qualitative components of this study, including credibility, dependability, transferability, and confirmability [35,36]. Data collection instruments (ie, focus group guide and open-ended survey questions) will be codeveloped by members of our multidisciplinary team, including caregivers and clinicians, to ensure they are clear, relevant, and easy to understand. We will create an environment in which participants feel comfortable expressing their opinions, including ensuring that focus groups are facilitated by an external individual who is not directly involved in delivering the intervention, and we will hold separate groups for caregivers, facilitators, and organizational leadership. An iterative coding process will be used based on multiple readings of the data and the perspectives of multiple team members. An audit trail will be used to clearly document each step of the analysis process. Thick description will be used in reporting to contextualize findings.

Data Management

Quantitative data were deidentified, and qualitative data were anonymized to safeguard participant confidentiality. Data are stored in a password-protected database on a secure computer network, accessible only to authorized research staff who will abide by the confidentiality regulations set by the Research Ethics Board. Each survey participant was assigned a unique ID number, which was used to link their data across all research activities and time points. The master list linking participant IDs to identifying information is stored in a separate, secure folder on the computer network.

Survey and focus group data are securely managed using a REDCap database designed and maintained for this study. Data are monitored and reviewed frequently by study investigators to ensure adherence to confidentiality protocols, Research Ethics Board guidelines, and protocol design. At the end of the study, all data will continue to be securely stored in compliance with institutional and regulatory requirements.

Results

As of August 2025, data collection was complete, and we are analyzing data based on the protocol outlined earlier. Our CC-ACT workshops reached a total of 195 caregivers of individuals with NDDs, of whom 113 (57.9%) consented to participate in the research evaluation. Among these 113 participants, there were 4 (3.5%) dropouts or withdrawals from the study. In total, 3 focus groups were conducted, including 5 caregiver workshop participants, 13 facilitators, and 5 organizational leaders.

The team is in the middle of systematically analyzing these findings, with contributions from both researchers and individuals with lived experience. Qualitative survey and focus group data have undergone initial coding and are now being reviewed by the full team. Multiple data sources are being analyzed in parallel, each with dedicated leads: (1) RE-AIM framework implementation data; (2) participant outcome data, including self-reports and attendance records; (3) facilitator surveys and fidelity checklists; and (4) qualitative interview transcripts from caregivers, facilitators, and organizational leaders.

Our goal is to finalize all data analyses by the end of 2025, which will inform the preparation of best-practice guidelines (Table 4). Our analyses will help identify sociodemographic and process variables that moderate or mediate outcomes, helping to clarify the mechanisms contributing to improvements in psychological flexibility and resilience. Evaluation of the implementation processes using the RE-AIM framework will further illuminate the factors related to feasibility, acceptability, fidelity, adaptations, and resource use. These insights will help guide the broader adoption of the ACT intervention model across community settings.

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Table 4. Project timeline.

Project activities	2022	2023	2024	2025
Engage, train, coach, prepare, and support implementation teams	✓			
Ethics approval	✓			
Implement first set of workshops	✓			
Implement second set of workshops	✓	✓		
Implementation evaluation	✓	✓	✓	
Conduct focus groups		✓		
Data analysis and knowledge translation		✓	✓	✓
Knowledge Translation and Exchange (forums, conferences, website, publications, and toolkit)		✓	✓	✓

Discussion

Anticipated Findings

Previous studies, including our own work, support the efficacy of CC-ACT to support the mental well-being of caregivers. This study will be important as there is a lack of effective evidence-informed interventions for caregivers of people with NDDs in Canada, and even fewer that have been studied in real-world settings. A meta-analysis found that ACT has significant effects on depressive and anxiety symptoms, stress, and quality of life in caregivers of various chronic conditions such as dementia, chronic pain, asthma, multiple sclerosis, and neurodevelopmental conditions [37]. Findings from this study will help to elucidate the practical implementation of this evidence-informed intervention across diverse settings in Canada, which may also pave the way for scale-up for caregivers of other chronic conditions as well.

All participating sites have successfully recruited and completed their planned workshops. As we formally analyze the data, we anticipate that we will gather nuanced implementation experiences under the RE-AIM framework.

In terms of reach, we will examine the sites' challenges and successes in recruiting caregivers. Analysis of parameters, such as the preferred time of the year for the workshops, will inform how best to organize and plan caregiver interventions in the future. Furthermore, analysis of the HEIA data, conducted in phase 1, will be valuable in identifying regional and contextualized equity and access barriers, such as ethnicity, gender, SES, and language.

Our earlier work demonstrated the overall efficacy of our workshops among caregivers of people with autism, as implemented in the context of a hospital-based research study [14,16,17]. We anticipate similar positive results with the current protocol. However, we anticipate that the degree of effectiveness may vary with implementation in real-world contexts, for example, due to population differences as well as implementation fidelity. Given the diversity of workshop participants across sites, we expect to be able to identify some predictors of effectiveness (eg, education, ethnicity, and gender) and to examine whether different ACT processes mediate outcomes across participant subgroups. Follow-up data may also shed light on the factors associated with the individual maintenance of ACT skills.

Our evaluation of the implementation across the 11 sites will help us explore and understand the balance between fidelity and adaptation. We anticipate that the workshop fidelity will generally be high, as our intervention exercises have built in flexibility, and we have offered customized coaching to the facilitation teams. Consistent with Lake et al [38], we anticipate that the complementary perspectives of caregiver and clinician facilitators can enhance the experience of facilitator teams as well as the workshop.

With the structure and support provided by the study, all sites successfully adopted the workshop model. We anticipate that the analysis of feedback from site facilitation teams and organizational leadership will reveal factors that facilitate or hinder adoption, as well as identify what is needed for long-term maintenance beyond the study period. Throughout the study, we systematically documented the implementation processes and contextual factors at the participating sites. They will be analyzed to identify common facilitators, barriers, and effective delivery strategies. Insights will be synthesized into a set of evidence-informed best-practice guidelines to support future community-based workshop implementation. These guidelines will include recommendations on facilitator training, participant engagement, cultural and contextual adaptations, and resource planning, with the aim of enhancing scalability, fidelity, and sustainability across diverse community settings.

Strengths and Limitations

One of the key strengths of our intervention workshop is its cofacilitation model, as workshops are delivered jointly by caregivers and clinicians. This approach grounds the intervention in lived experience, enhances participant engagement, and promotes relevance to caregivers. Our ACT exercises are uniquely experiential, allowing flexible in-session adaptation to participants' needs while maintaining fidelity to core principles. Delivery across diverse geographical regions and organizations with varied cultures and challenges enables the examination of contextual factors that influence implementation.

During the study, we developed and refined a detailed protocol, fidelity checklist, and implementation supports (eg, handouts and email templates), as well as a flexible, peer-led coaching system. These supports facilitated the consistent delivery of the workshops in the study, as well as for future use, while providing an opportunity to evaluate the need and effectiveness of coaching in facilitating high-quality implementation. The use

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of a mixed methods design, guided by the RE-AIM framework, allows a comprehensive assessment of both intervention effectiveness and implementation processes.

This study also has several limitations. It was not conducted as an RCT, which limits causal inference, although RCTs are not always necessary in implementation research. We did not assess child outcomes, despite the potential indirect benefits for the children of participating caregivers—an important avenue for future research. Our outcomes relied on self-report measures, which may be subject to recall and social desirability bias. The study may also be limited by selection bias, as some caregivers might not have been reached by our study due to various systemic factors, and not all workshop participants consented to complete the research study. Although the HEIA tool was used to help identify potential gaps in accessibility, this study was not designed to address all identified issues. Limitations in site mandates, resources, and policies constrained our ability to adapt to certain groups; for example, targeting only English-speaking populations in Quebec due to the resource constraints for linguistic and cultural adaptations in this study.

Next Steps and Future Directions

We have been collecting observations from coaches, facilitators, and workshop participants and have begun updating the program website accordingly. Once the final results are analyzed and published, the website will serve as a central platform for disseminating evidence-informed practices. Since 2015, our community of practice has grown to include over 250 individuals trained in the ACT Caring for the Caregiver programs. This network will be engaged in sharing information through the website, quarterly newsletters, and social media channels. Partner agencies, already actively involved in the project, will also contribute to dissemination efforts through presentations in their community. In addition, the findings will be presented at academic conferences and submitted for publication in peer-reviewed journals.

Our findings will not only inform future iterations of the ACT workshops but also guide best practices in scaling caregiver mental health programs, especially in virtual and hybrid formats. Understanding factors that facilitate or hinder implementation—such as populations not reached and systemic barriers to adopting the clinician-caregiver cofacilitation model—will be critical to ensuring the long-term sustainability and equitable reach of such interventions.

Conclusions

This study aims to offer valuable insights into the real-world implementation of a caregiver-clinician cofacilitated ACT workshop across diverse communities in Canada. Embedding the intervention within the existing community agency infrastructures and tailoring delivery to local contexts will help ensure a practical and scalable approach to address caregiver mental health. As implementation continues across various sites, we anticipate that promising practices will emerge through local adaptations, coaching, and facilitator reflections.

Given the diversity in caregiver demographics and community needs, intervention supports and delivery methods must also be adapted to meet their unique needs. We expect that equity-related gaps will surface, particularly in relation to language, accessibility, and cultural relevance. These findings will be critical in informing future iterations of the intervention to ensure that it is not only effective but also inclusive and responsive to the diverse needs of caregiver communities. Through ongoing learning and refinement, we aim to contribute to more equitable, sustainable, and community-driven models of mental health support for families of individuals with NDDs.

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Data Availability

The datasets generated or analyzed during this study are not publicly available because the research participants did not consent to data sharing at the time of data collection, but are available from the corresponding author on reasonable request.

Authors' Contributions

KF, YL, JL, LS, JW, MP, NB, CM, BR, JS, and KT conceived the study and developed the overall research objectives. KF, AS, and SM contributed to the methodological design and drafting of the study procedures. KF and AS developed the data analysis plan. SM and JL prepared the ethics application and managed the correspondence with the research ethics board. UN, DC, and SP led the study at their respective organizations. YL and JL provided resources and institutional support for the project. SM led the project administration and coordinated team communication. KF, JL, and SM drafted the initial manuscript. All authors critically reviewed, revised, and approved the final version of the manuscript.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Semistructured interview guide for focus groups.
[DOCX File , 23 KB - resprot_v14i1e75049_app1.docx]

Multimedia Appendix 2
Peer review report by Kids Brain Health Network, Brain Canada Foundation, Health Canada.
[PDF File (Adobe PDF File), 1360 KB - resprot_v14i1e75049_app2.pdf]

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Abbreviations

ACT: acceptance and commitment training
CC-ACT: Caring for the Caregiver Acceptance and Commitment Training
FASD: fetal alcohol spectrum disorder

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HEIA: Health Equity Impact Assessment
NDD: neurodevelopmental disability
RCT: randomized controlled trial
RE-AIM: reach, effectiveness, adoption, implementation, and maintenance
REDCap: Research Electronic Data Capture

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Protocol

Development of an Ecological Momentary Assessment Study to Identify Real-Time Predictors of Physical Activity Among Older People With HIV: Protocol for a 2-Phase Mixed Methods Study

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Abstract

Background: People with HIV are aging rapidly and face accelerated aging-related comorbidities, including cardiovascular diseases and cognitive impairment, due to prolonged HIV-associated inflammation. Physical activity (PA) is a well-established intervention to mitigate these risks; yet, most older people with HIV remain sedentary. Despite considerable efforts to understand PA determinants and design interventions for people with HIV, outcomes have been suboptimal.

Objective: The overarching goal of this project is to use an ecological momentary assessment (EMA) approach to capture ecologically valid relationships between the personal experiences of older people with HIV and PA, as they engage in their normal daily activities.

Methods: This study will adopt a 2-phase mixed methods research design. The first phase focuses on developing the EMA questionnaire through in-depth interviews with older people with HIV to explore the relevance of candidate real-time predictors of PA, identified using the capacity, opportunity, motivation—behavioral framework and literature review, to their daily experiences. These interviews will validate and refine the constructs for the EMA survey. In phase 2, a 2-week EMA study will collect data from 70 sedentary older people with HIV through smartphone surveys (3 times per day) and Fitbit-measured step counts and moderate to vigorous intensity PA minutes. Multilevel modeling will be used to examine how these factors predict daily PA levels.

Results: This research project was funded in June 2024. To date, 13 eligible participants have completed the qualitative interviews. All participants agreed that the constructs of EMA survey are relevant to their PA experiences and acknowledged their time-varying nature. On the basis of the participants' input, the EMA survey has been finalized.

Conclusions: By advancing the understanding of real-time determinants of PA, this study addresses a critical gap in the literature and offers a foundation for designing just-in-time adaptive interventions that provide tailored, context-specific support to enhance PA engagement and promote healthy aging among older people with HIV.

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KEYWORDS

HIV; physical activity; predictors; ecological momentary assessment; protocol

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Introduction

Background

This paper describes the rationale and design of an ecological momentary assessment (EMA) study to improve understanding of physical activity (PA) among older people with HIV. By capturing within-person, time-varying factors that influence the daily PA levels of older people with HIV, it is anticipated that the study will offer novel insights into predicting PA behavior among older people with HIV. The study findings are expected to lay the foundation for designing precision-based PA behavioral interventions tailored to participants' individualized needs in real time, which will increase PA levels effectively and lead to improved health outcomes and reduced health care burdens for both older people with HIV and their caregivers. In doing so, it addresses health disparities in the context of healthy aging among older people with HIV.

According to the World Health Organization, approximately 39 million people worldwide were estimated to be living with HIV by the end of 2023; in the United States, the number was approximately 1.2 million [1]. Owing to the introduction of effective antiretroviral therapy, life expectancy in people with HIV has significantly improved, leading to HIV being increasingly considered a chronic disease [2]. In the United States, approximately 52% of people with HIV are aged >50 years [3], and this is projected to increase to 70% by 2030 [4]. The advancing age in people with HIV carries an increased risk for a wide range of comorbid conditions, such as cardiovascular diseases and cognitive impairment, due to prolonged HIV-associated inflammation, distress, and side effects of antiretroviral therapy [5,6]. Indeed, older people with HIV are 50% more likely to develop cardiovascular diseases [7] and 58% more likely to develop dementia [8], which often interferes with medication adherence [9] and is associated with a higher mortality rate [10]. PA, as an established lifestyle intervention, plays a crucial role in promoting overall well-being [11]. To achieve substantial health benefits, PA needs to be performed regularly and maintained across the life span [12]. However, less than 20% of older people with HIV engage in at least 150 minutes of moderate to vigorous intensity PA (MVPA) per week [13], as recommended by public health guidelines [14]. Given the growing number and health burden of older people with HIV, there is a pressing need for a deeper understanding of the predictors of PA levels among this group.

Historically, methods for measuring PA have been limited by the lack of technologies capable of capturing behavior in real time. Most research has relied on cross-sectional study designs to identify correlates of PA participation in people with HIV. For example, a recent quantitative systematic review of 45 cross-sectional and cohort studies highlighted key barriers to PA among people with HIV [15], including older age, lower educational attainment, decreased $CD4^+$ T-cell count, exposure to antiviral therapy, body pain, and depression. While these studies have provided valuable insights, they primarily focus on between-person factors (interindividual differences) rather than within-person factors, such as daily experiences or situations, that may influence PA levels. Consequently, little is known about how time-varying, context-specific factors impact daily PA levels among older people with HIV.

Advances in mobile and sensor technologies offer promising solutions to these methodological limitations. These technologies enable real-time data collection strategies, such as EMA, which is particularly well suited for examining time- and context-dependent fluctuations in PA determinants [16]. EMA involves the use of smartphones to collect real-time self-reports of behaviors, contexts, emotional states, beliefs, attitudes, and perceptions in naturalistic settings [17]. By capturing data proximal to the time and place of behavior, EMA reduces recall errors and biases, enhancing ecological validity [18]. Unlike traditional cross-sectional or retrospective methods, EMA is uniquely equipped to study phenomena that vary over time, offering a dynamic perspective on PA behavior and its correlates [19]. This approach provides opportunities to test and refine explanatory models, enabling researchers to gain deeper insights into the mechanisms underlying PA behaviors.

The application of EMA in PA research is expanding rapidly. This time-intensive approach has demonstrated the ability to generate novel insights into the real-time determinants of PA behavior. However, to our knowledge, no studies have used EMA to investigate real-time predictors of PA among older people with HIV. This represents a critical gap in the literature, as understanding these predictors is essential for developing tailored, real-time behavioral interventions to promote PA in this population. Older people with HIV face unique challenges in maintaining sustained PA engagement and experience significant health disparities in healthy aging outcomes.

This study aims to address this gap using EMA to explore real-time predictors of PA among older people with HIV. These insights are essential for the development of just-in-time adaptive interventions (JITAIs), which can deliver tailored, context-specific support to promote sustained PA engagement and improve health outcomes in this vulnerable population.

Theoretical Framework

Among various syntheses of different theories, the capability, opportunity, motivation, and behavior (COM-B) model, rooted in evidence and derived from 19 frameworks of behavior change theories, serves as a comprehensive framework for understanding behavior change [20]. The COM-B framework consists of 3 constructs: capability, opportunity, and motivation.

Capability within the COM-B model encompasses a person's knowledge, cognitive abilities, and physical strengths necessary to perform a health behavior [20]. Among these factors, physical strengths, such as fatigue and pain, are inherently time varying. Fatigue and pain are among the most prevalent symptoms experienced by older people with HIV. Research indicates that approximately 55% to 65% of older people with HIV report fatigue [21], whereas chronic pain affects an estimated 30% to 80% of this population [22,23]. Both quantitative and qualitative studies consistently identify fatigue and pain as significant barriers to PA engagement among older people with HIV [15,24]. However, the relationships between these physical experiences and PA are seldom examined using within-person methods. Differentiating within-person versus between-person

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associations between the physical experiences of older people with HIV and their PA levels would provide valuable insights into whether and how these experiences influence PA daily. Such insights could inform tailored interventions aimed at mitigating these barriers to promote sustained PA engagement in this population.

Opportunity refers to external factors that either facilitate or hinder PA participation [20]. These include environmental factors (eg, access to safe and convenient exercise facilities), social factors (eg, support from family or friends), and economic factors (eg, availability of affordable sports equipment). While environmental and economic factors are relatively stable and will not be explored in this study, the dynamic nature of social interaction suggests it can fluctuate throughout the day, influenced by factors such as availability of social support. Previous studies have highlighted that social support is one of the strongest facilitators of PA engagement [24]. Understanding these fluctuations allows a more nuanced view of how social interactions affect PA engagement in real time among older people with HIV.

Motivation, within the COM-B framework, is categorized into 2 primary types: reflective and automated [20]. Reflective motivation encompasses conscious and deliberate processes that shape behavior, whereas automated motivation is primarily driven by emotions. In this study, we examine intention and mood as proxies for reflective and automated motivation, respectively. Both factors are dynamic and subject to contextual fluctuations over time. While substantial research has demonstrated that PA engagement is negatively associated with concurrent negative affect [25], there has been limited empirical investigation into whether negative or positive affect prospectively predicts PA. Gaining a deeper understanding of the relationship between mood states and subsequent PA among older people with HIV could provide valuable insights into the emotional predictors of PA in this vulnerable population.

In summary, the COM-B framework is used to identify candidate real-time determinants of PA levels among older people with HIV. Informed by the COM-B framework and a literature review, 5 candidate real-time factors are proposed: pain, fatigue, mood, intention, and social support. The relevance of these determinants to the daily PA experiences of older people with HIV will be examined through qualitative interviews. Subsequently, a final list of real-time determinants of PA will be developed and tested in an EMA study.

Aims

The overall aim of this study is to determine the real-time predictors of PA levels among older people with HIV. The following 2 specific aims are proposed:

1. To develop the EMA survey based on the theory, literature review, and inputs of older people with HIV. To achieve this aim, initially, the team will use the COM-B framework to draft a list of potential real-time predictors of PA based on existing literature. Following this, in-depth qualitative interviews will be conducted with older people with HIV to validate, expand upon, and identify additional predictors of daily variations in PA level within this population.
2. To implement the EMA study to determine the role of the candidate real-time predictors of PA level (identified in aim1) in predicting variations in PA levels (step counts and MVPA minutes assessed by Fitbit [Fitbit Corporation]) among older people with HIV. This aim will use a 2-week longitudinal design that uses bursts of mobile-based surveys (3 times per day) with older people with HIV (n=70). Multilevel models that address the nested structure of EMA data will be used to evaluate the study aims.

Methods

Overview of Research Approach

Figure 1 depicts the overview of the research approach for the entire study. This study will adopt a mixed methods research design. The first phase focuses on developing the EMA questionnaire through in-depth interviews with older people with HIV to explore the relevance of candidate real-time predictors of PA, identified using the COM-B model and literature review, to their daily experiences. These interviews will validate and refine the constructs for the EMA survey. In the second phase, the finalized survey will be implemented in a 2-week EMA study to examine the role of these predictors in influencing variations in PA levels, measured through Fitbit step counts and MVPA minutes, among older sedentary people with HIV. Findings from this study will lay the foundation for designing JITAIs to address time-varying factors that impact daily PA levels in this population.

Figure 1. Overview of the research approach for the whole study. EMA: ecological momentary assessment; PA: physical activity.

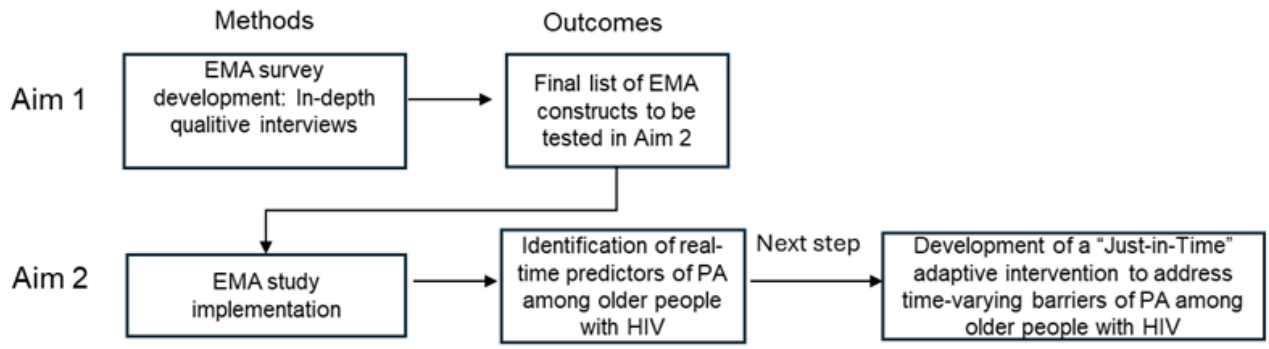

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Methods for Aim 1: Development of the EMA Survey

Research Design

This phase of the study involves conducting in-depth structured interviews to explore the perspectives of older people with HIV on the relevance of items derived from the literature review and COM-B theory to their own PA behavior. We plan to engage approximately 10 to 15 participants. Additionally, the interviews will solicit input on constructs or items that may have been overlooked during the initial review. These interviews will validate the relevance of identified predictors and offer critical insights to refine and expand the constructs for the EMA study outlined in aim 2. This iterative approach [26] will ensure that the EMA survey comprehensively captures the dynamic and multifaceted factors influencing PA behaviors among older people with HIV.

Participants and Setting

The target population is sedentary older people with HIV. Inclusion criteria are as follows: (1) age 50 to 80 years, (2) sedentary lifestyle defined as practicing less than 150 minutes of PA per week for the last 6 months [14], (3) known HIV infection, receiving a stable antiretroviral therapy regimen for at least 12 months before enrollment, and (4) owning a smartphone. Participants will be excluded if they have contraindication to PA according to the American College of Sports Medicine [27], including severe arterial hypertension and uncontrolled arrhythmia. Participants will not be excluded based on sex assigned at birth or gender identity. We will recruit ethnically diverse participants from a local community partner that provides HIV or AIDS services to thousands of people in Florida. The sample size in the qualitative interview will be based on thematic saturation. If we do not reach thematic saturation with 15 participants, we will continue the recruitment until we do.

Procedure

In-depth interviews will be conducted in person, guided by a predeveloped semistructured interview framework to ensure systematic and comprehensive exploration of participant responses while maintaining focus on the research objectives. Participants will be asked to share their thoughts on the relevance of items derived from the literature review and COM-B framework to their daily PA experiences. They will also be invited to suggest additional factors that may have been overlooked. The semistructured interview guide (detailed in Multimedia Appendix 1) will support this process. Each interview, lasting 30 to 60 minutes, will be audio recorded, transcribed verbatim, and supplemented with the notes of principal investigator. Informed consent will be obtained before participation, and participants will receive a US $20 Amazon gift card as compensation.

Data Analysis

For the qualitative data, 2 researchers (SD and XTZ) will independently analyze the transcripts using directed content analysis [28]. The goal is to validate the relevance of the constructs derived from the literature review to the daily PA experiences of older people with HIV and potentially expand the list of constructs. Any coding disagreements will be reviewed, and discrepancies will be resolved through discussion until consensus is reached. A third researcher (YJY) will be involved as needed throughout the process. Through an iterative approach, the final list of construct codes relevant to increased or decreased daily PA will be determined.

Methods for Aim 2: Implementation of the EMA Study

Research Design

This phase of the study involves conducting an EMA study to examine how real-time predictors of PA, identified in aim 1, influence variations in PA levels among sedentary older people with HIV. Participants will be visited twice. During the first visit, they will sign informed consent, provide sociodemographic data (eg, sex, age, educational level, ethnicity, race, and years living with HIV) via an electronic survey and receive instructions for the data collection through EMA surveys. Following this visit, participants will enter a 14-day monitoring period, during which they will complete 3 EMA surveys daily via text message and wear an accelerometer to monitor their PA level. After the 14 days, a second appointment will take place to conduct a brief exit interview to assess any challenges encountered during the EMA study and gather feedback on preferences for future PA interventions. Figure 2 shows a timeline of enrollment and data collection procedures.

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Figure 2. Enrollment and data collection procedures.

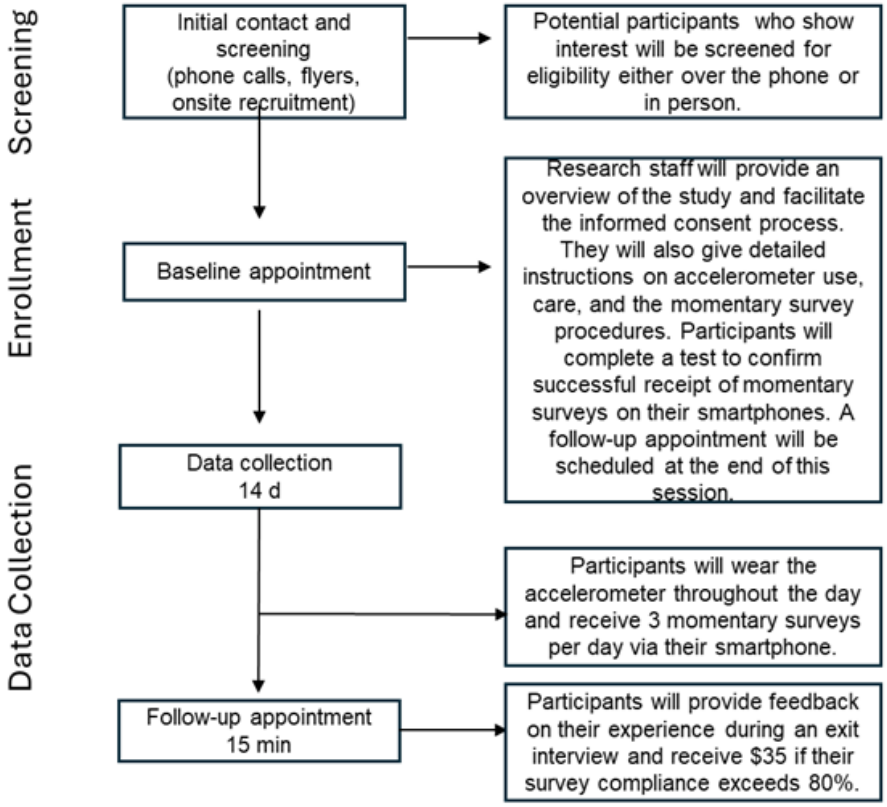

Participants and Setting

The sample size for the EMA study will be determined through power analysis. All models will use fixed effects, a standard diagonal matrix, and group mean centering of predictors to address clustering of observations within participants. Under these conditions, a sample size of 55 will provide a power of 0.80 to detect moderate effect sizes (β>.40) in multilevel analyses. This calculation assumes up to 5 predictors with moderate multicollinearity (variance inflation factor 2.0), a moderate intraclass correlation coefficient of 0.50, and a significance level (α) of .05. Additionally, to account for potential attrition, a sample size of 70 participants is determined, factoring in a 20% attrition rate.

EMA Survey

The COM-B framework serves as a guiding framework for compiling the initial version of the questionnaire, incorporating items previously used in research. These items encompass aspects, such as fatigue, pain, mood, intention, and social support. Subsequently, as part of aim 1, semistructured interviews will be conducted with older sedentary people with HIV. Insights gathered from these interviews will inform further adjustments to the questionnaire, ensuring its relevance and comprehensiveness. Each survey construct will be assessed using a 4-point Likert scale, ensuring the assessment is brief and minimizes participant burden [29].

PA Level

To measure participants' PA levels, all participants will wear a Fitbit wristband on their nondominant wrist for 14 consecutive days during the time-based EMA period. Fitbit wristbands are widely recognized for their reliability and validity in assessing PA, as demonstrated in numerous studies [30]. Participants will be instructed to wear the device throughout the day and night, removing it only for water-based activities. PA measurements will include step count and minutes of MVPA. Fitbit's proprietary algorithm calculates MVPA minutes (referred to as "active minutes") by comparing the participant's current energy expenditure to their resting energy expenditure. When the ratio is ≥3, the algorithm classifies the activity as MVPA [31]. Fitbit data will be retrieved using the manufacturer's consumer-facing data portal and application programming interface, allowing researchers to download participants' minute-by-minute data.

EMA Survey Schedule, Distribution, and Monitoring

EMA surveys will be delivered via text messages containing embedded web links using the digital health platform of the Florida State University College of Nursing [32]. This platform has been proven effective in supporting digital behavioral interventions by distributing real-time content [33]. EMA survey schedule will begin the day after the baseline visit and follow a fixed-interval schedule with 3 assessments daily (10 AM, 1 PM, and 4 PM) over 14 consecutive days. These times are strategically chosen to capture PA patterns throughout the day (ie, morning, afternoon, and evening) while minimizing recall errors. Building on a previous National Institutes of Health–funded EMA study that explored PA predictors among middle-aged women using a 10-day protocol [34], we extended the time frame to 14 days for this study. Participants will receive a text message at each designated time, with a second reminder sent 30 minutes later if the first goes unanswered. Participants may complete the survey immediately or postpone it for up to 30 minutes, after which the survey will close until the next

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scheduled time. Participants who complete more than 80% of the surveys during the 14-day EMA study will receive a US $35 Amazon gift card as a token of appreciation.

Data Analysis

We will first examine within-person (day-by-day) and between-person (stable over time) variation on each of the PA measures (steps and MVPA minutes) using graphical displays and intraclass correlation coefficients. Then, we will test the effects of within-person survey variables on PA measures via within-person multilevel models using SPSS (version 27; IBM Corp). Our models will use restricted maximum likelihood estimation to generate β coefficients, which compensates for missing data by imputing a distribution within each participant's scores based on all available data points.

Analyses examined the lagged effects of candidate predictors occurring during a specified time interval (T−1) on PA level (step counts and MVPA minutes) during the subsequent (lagged) time interval (T) within each day of monitoring. For example, it is determined whether fatigue reported at 10 AM predicts subsequent PA reported at 1 PM on that same day. Each predictor's effect on each of the 2 outcome variables will be tested separately. For each outcome variable, each possible predictor will be tested individually using a minimally restrictive α=.05 level. All variables that pass this screening step will then be combined into a single multivariable model to identify the most parsimonious set of predictors that together account for daily variations in PA among older people with HIV. In the multivariable models, predictors will be entered in block order, and backward elimination will be used to remove redundant predictors within each block and in the final model. Age and gender will be considered as covariates and will be examined as person-level moderators of within-person relations.

Ethical Considerations

Ethical approval for this study was obtained from Florida State University Institutional Review Board on July 19, 2024 (STUDY00005096). This study's protocol adheres to all relevant ethical guidelines for research involving human participants, including medical records and patient information.

Informed consent will be obtained from all participants before data collection. During the consent process, participants will receive detailed instructions about this study, including its objectives, procedures, potential benefits, and any associated risks or discomforts. They are also informed of their rights, including the ability to withdraw from this study at any time, to ensure that their participation is completely voluntary. This comprehensive approach is designed to ensure that all participants fully understand this study before providing their consent.

To protect participants' privacy, all data collected will be anonymized by assigning each participant with a study number to ensure that no personally identifiable information is directly linked to the data. Demographic, personal, and exercise test data will be securely stored in REDCap (Research Electronic Data Capture; Florida State University) databases, which are secure, password-protected databases. Access to these data will be limited to authorized research personnel, and all information obtained during this study will be used for research purposes only. Participants will receive US $35 for their completion of the EMA survey. In addition, participants will receive US $20 for the interview sessions to ensure fairness and transparency in recognition of their time and effort.

Results

To date, 13 eligible participants have completed the qualitative interviews for aim 1. The median age of the participants is 63 (range 57-74) years. Of the 13 participants, 7 identified as African American, 6 identified as White, and the majority identified as male, with 3 identifying as female. Additionally, 6 participants reported not completing a bachelor's degree, whereas others had attained an associate's or technical degree. All participants agreed that the listed factors such as pain, fatigue, intention, mood, and social support, are relevant to their PA experience and acknowledged their time-varying nature. For instance, 1 participant remarked, "Pain is always there; some days it's worse, some days it's better." These fluctuations were noted to significantly influence their engagement in PA. Additionally, when asked about other factors they felt were missing from the list, 4 participants identified weather as a contextual factor that plays an important role in their PA experience. A total of 3 participants mentioned that bad sleep was associated with fatigue, suggesting that sleep quality should also be included as a relevant factor. Regarding the EMA survey schedule and distribution, all participants found the proposed schedule (10 AM, 1 PM, and 4 PM) to be acceptable. When shown a prototype of the EMA survey link, participants agreed that it was easy to complete. On the basis of the participants' input, the EMA survey has been finalized, as shown in Figure 3. To incorporate the weather data identified as relevant, we will document local weather conditions during data collection.

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Figure 3. Display of the ecological momentary assessment survey.

At this moment, please select the option that best describes your current state:				
Questions	Levels			
How would you describe your sleep last night? (first survey of the day only)	Poor	Average	Good	Excellent
Are you experiencing fatigue?	Not at all	Somewhat	Moderate	A lot
Are you experiencing any physical pain?	Not at all	Somewhat	Moderate	A lot
How much are you experiencing low mood?	Not at all	Somewhat	Moderate	A lot
How motivated are you to be physically active in the next few hours?	Not at all	Somewhat	Moderate	A lot
How are the people you're with influencing your physical activity right now?	Encouraging	Neutral	Discouraging	Not applicable (I'm alone)

Discussion

Anticipated Findings

The aim of this project is to use an EMA approach to capture ecologically valid relations between the personal experiences of older people with HIV and PA as they engage in their normal daily activities. This paper describes our approach in developing this EMA study and highlights existing challenges and future directions.

Methodological Advantages

First, we adopted a human-centered approach by actively incorporating participants' feedback into the study design, including the confirmation of relevant factors, such as pain and fatigue, the identification of new factors, such as weather and sleep, and the evaluation of the acceptability of the EMA schedule. This iterative process ensured that the study design is both participant-informed and closely aligned with the needs, preferences, and lived experiences of the target population.

Additionally, the use of EMA surveys represents a significant methodological strength, as it enables the collection of real-time data on factors influencing PA, thereby minimizing recall bias and enhancing data accuracy. This approach also facilitates a deeper understanding of the dynamic and context-dependent influences on PA engagement. By capturing both group-level trends and individual-level variations, EMA surveys offer a comprehensive view of the interpersonal and intrapersonal interplay between personal experiences and contextual factors that shape PA engagement. This dual-level insight is critical for tailoring interventions to address both shared and unique barriers to PA within the target population.

Methodological Challenges and Decisions

While EMA study design is widely recognized as a robust research method for capturing behaviors and experiences in real-time and naturalistic settings, it does present several limitations, particularly in relation to participant burden and compliance [35]. The repeated prompts required in EMA can be demanding, potentially leading to lower response rates or incomplete data. To mitigate these challenges, we have designed the EMA prompts to be brief, requiring only 2 to 3 minutes to complete, thereby reducing the time burden for participants. Furthermore, participants will have the flexibility to postpone prompts when necessary, allowing them to balance study participation with their daily routines.

To further address compliance concerns, the principal investigator will provide clear, detailed instructions and regular reminders to participants, emphasizing the importance of timely responses. Additionally, an incentive structure has been incorporated to enhance motivation and maintain engagement throughout the study.

Another limitation of this EMA study is its reliance on convenience sampling, which may introduce sampling bias and restrict the generalizability of the findings to broader populations. However, the representativeness of the participants in the aim 1 qualitative studies aligns closely with the demographic characteristics of the national population of older people with HIV, providing a reasonable degree of confidence in the relevance of the findings to this target group. These strategies collectively aim to address the inherent limitations of this EMA study while maximizing the validity and applicability of the study outcomes.

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Significance and Future Directions

Most older people with HIV are sedentary, and increasing PA within this population has remained an elusive goal. Behavioral interventions that rely on "one-size-fits-all" approaches have consistently failed to achieve meaningful increases in PA levels among sedentary older people with HIV [36-38]. To optimize personalization and sustain PA engagement, it is crucial to leverage real-time data to dynamically tailor behavioral support to individuals' unique, moment-to-moment challenges.

JITAIs offer a promising framework for addressing these challenges. Designed to deliver the right support at the right time, JITAIs adapt to an individual's changing context and needs [39]. A foundational step in developing a JITAI to promote PA in older people with HIV is understanding the determinants of daily variations in PA levels. While cross-sectional studies have identified between-person correlates of PA, they offer limited insight into how day-to-day experiences and situational factors (within-person determinants) influence PA levels. This study aims to directly address this knowledge gap by using an EMA design that captures both between-person differences and within-person variations in PA. This approach allows a more comprehensive understanding of the dynamic factors influencing PA engagement among this underserved clinical population.

The findings will inform the development of tailored intervention strategies for a JITAI, providing real-time, personalized support to promote PA engagement. This work not only advances the field of precision lifestyle interventions but also addresses critical gaps in promoting healthy aging and improving quality of life for older people with HIV.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization: DS
Data curation: DS, YY
Funding acquisition: DS, YY
Supervision: LH-W, JW
Writing—original draft: DS
Writing—review and editing: YY, TX, LH-W, JW

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guide for exploring physical activity experiences among older people with HIV.
[DOCX File , 24 KB - resprot_v14i1e81238_app1.docx]

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Abbreviations

COM-B: capability, opportunity, motivation, and behavior
EMA: ecological momentary assessment
JITAI: just-in-time adaptive intervention
MVPA: moderate to vigorous physical activity
PA: physical activity
REDCap: Research Electronic Data Capture

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Protocol

Piloting a Novel eHealth Technology for the Control and Management of Elevated Blood Pressure in Rwanda (HeartCare@Home Project): Protocol for a 2-Phase Crossover Study

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Abstract

Background: Effective blood pressure (BP) monitoring is vital for the management of hypertension, allowing timely adjustments in treatment. This study focuses on the development and implementation of an innovative, locally designed eHealth technology, the HeartCare@Home system, to enhance the control and management of hypertension in outpatient noncommunicable disease (NCD) clinics in Rwanda. The HeartCare@Home system comprises a mobile health app that incorporates rapid SMS technology, an integrated dashboard for signal reception at the clinic office level, and a clinical decision support algorithm.

Objective: This study aims to assess the clinical efficacy, feasibility, and acceptability of a novel eHealth technology, the HeartCare@Home system, that uses home and clinic-based automated BP monitoring with real-time management of elevated BP in an outpatient NCD clinic in Rwanda.

Methods: This pilot study will use an interventional design with a crossover approach to test the clinical efficacy of the HeartCare@Home system at the NCD clinic of Kibagabaga District Hospital. A total of 140 patients with hypertension will take part in the study. All enrolled patients will be allocated to either the interventional group or the standard of care group. The follow-up for each group will be 6 months (3 months in each group follow-up). The data for the intervention group will be generated by our mobile health app, while data for the control group (standard care) will be retrieved from usual patient files at the NCD clinic. Data extraction sheets will be used for standard care data retrieval. The Feasibility of Intervention Measure and Acceptability of Intervention Measure tools will be used to cross-sectionally evaluate the feasibility and acceptability of the HeartCare@Home system. Data will be summarized with descriptive statistics. A paired sample 2-tailed *t* test will be used to test for differences between the pre- and postintervention records for hypertension control.

Results: This study will yield a technical infrastructure, the HeartCare@Home system, to support the control and management of hypertension in outpatient NCD clinics. It will introduce a new model of health care delivery through innovative technology that enables home-based BP monitoring. This will offer a unique technology to enable elevated BP control and timely hypertension management and will also ensure a real-time communication linkage between patients and the appropriate level of care. Furthermore,

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the findings from the assessment of the clinical efficacy, feasibility, and acceptability of the HeartCare@Home system will inform possible scalability of the system to more NCD clinics. The study is currently in the implementation stage.

Conclusions: The HeartCare@Home project will address the important gap of low BP control rates in patients with hypertension, which has contributed to delayed consultations and increased cardiovascular mortality. Such eHealth technology infrastructure may also be scalable to other settings.

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KEYWORDS

eHealth technology; eHealth innovation; heart care at home; hypertension; Rwanda

Introduction

Background

Cardiovascular disease (CVD) is the leading cause of mortality globally, accounting for 17.9 million deaths each year, and hypertension is the leading risk factor associated with CVD [1,2]. In low- and middle-income countries of sub-Saharan Africa with rapid epidemiological, demographic, sociocultural, and economic transitions, the risk of hypertension results in more than 80% of deaths annually [3]. In Rwanda, the prevalence of hypertension is approximately 15.3%, with rates as high as 40% in individuals aged 55 to 64 years [4]. According to the 2019 National Institute of Statistics in Rwanda projections, an estimated 1.1 million Rwandan people aged between 15 and 69 years have hypertension [4]. However, data from the national health management information system show that only 70,200 individuals, approximately 6.3% of patients with hypertension, receive care at noncommunicable disease (NCD) clinics. Therefore, more effective and rapid hypertension control interventions are essential to reduce CVD-related morbidity and mortality.

Effective hypertension control intervention measures, such as blood pressure (BP) monitoring for early clinical decisions to seek care and access to evidence-based interventions for early management of hypertension, are still limited in Rwanda [4]. Geographical barriers such as long distances to health services, prolonged waiting times, and inadequate patient follow-up may lead to late diagnosis of hypertension, poorly managed hypertension, and increased risk for CVD. In clinical practice, physicians often check hypertension status and make medication decisions based on 1 or 2 instant measurements despite the known variability of BP [5]. There is a need for more focused and personalized decision-making supported by richer data, such as daily BP measurements.

Increasing evidence supports the use of eHealth solutions to control hypertension by collecting high-volume data from rural and urban community-based patients for quick clinical decision-making [6,7]. eHealth tools support improved BP monitoring and contribute to increased adherence to antihypertensive treatments, thus improving early effective BP control [8,9]. However, the role of team-based care for BP control involving task-shifting benefits and resources that constitute the complex procedure carried out in a BP telemonitoring are not well documented [10-13]. There is evidence for improved health by hypertension control through BP telemonitoring [14]. Furthermore, the role of an eHealth intervention model in achieving adequate hypertension control requires further exploration within the Rwandan context, given the country's diverse social and cultural beliefs. Research on the implementation outcomes of eHealth technology for BP telemonitoring could inform interventions for improved policy and practice in Rwanda. Therefore, this study aims to pilot test and investigate the clinical efficacy and feasibility of a novel eHealth technology, the HeartCare@Home system, with real-time BP telemonitoring for control of hypertension in Rwanda. What distinguishes this solution from existing market offerings is its fully homegrown design, making it both affordable and accessible for Rwandans. Its local origin also ensures easier local maintenance and local support, promoting readiness for integration into the Rwandan health system. Furthermore, the system's dashboard and the clinical decision support (CDS) algorithm are tailored specifically to the Rwandan context, enabling real-time data reception and patient monitoring. Figure 1 describe the proposed theory of change of this project.

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Figure 1. Theory of change.

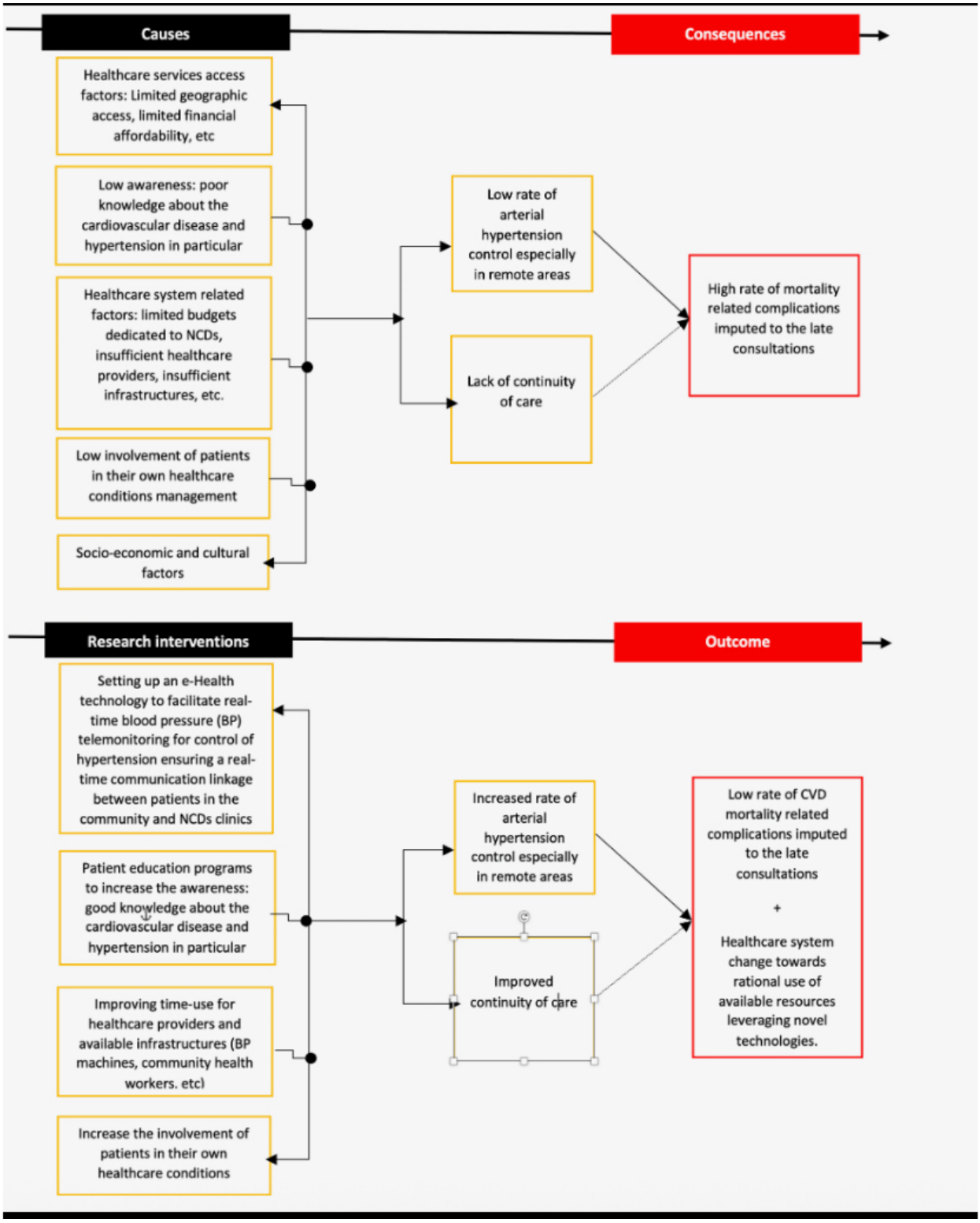

Aims

The specific aims of the project are as follows:

1. To assess the clinical efficacy of an innovative eHealth technology (home and medical automated evaluation of the BP with live management of elevated BP) in an outpatient NCD clinic in Rwanda. For this aim, we will be hypothesizing that patients using HeartCare@Home system will have a lower systolic and diastolic BP and higher control rates than individuals in standard of care.
2. To determine the feasibility and acceptability of the eHealth technology in an outpatient NCD clinic in Rwanda.

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Description of the HeartCare@Home System, a Home-Based BP Telemonitoring Novel Technology in Rwanda

The HeartCare@Home system is an eHealth technology that enables remote data transmission of BP measures and additional information on patients' health status from their homes to the physician's office or the hospital. This project will use 4 main novel technologies to facilitate real-time BP telemonitoring for control of hypertension, ensuring a real-time communication linkage between patients in the community and the appropriate level of care (NCD clinics). These main technologies include a rapid SMS gateway technology embedded in a mobile health (mHealth) app, a central database, and an integrated dashboard with the existing medical record system (OpenMRS), a CDS algorithm that will send BP measurements with signal outputs (color codes) with red flags on abnormal BPs measurements, and internet of things technology to support communication between the central database and the mHealth app.

The HeartCare@Home system will involve individual patients and community health workers (CHWs) taking BP measurements at the community level and sending the measurements to an allocated physician using an mHealth app. The patients and CHWs will use the mHealth app to record BP measurements twice weekly and send them to the central server located at the hospital. The mHealth app will also be complemented by the provision of BP machines for daily BP measurements. The mHealth app will also be used as a reference tool to upgrade patients' health literacy regarding hypertension self-management.

In addition, the central server will display the recorded BPs on an integrated dashboard (integrated within OpenMRS and linked to patient health records) using a CDS algorithm that displays alerts (red flags) for the abnormal BPs in the OpenMRS used by NCD clinics to enable prompt clinician notification and timely action based on real-time BP measurements. The clinicians will be able to initiate physical appointments for patients with uncontrolled BPs based on real-time BP measurements. The caring physicians will also be able to initiate and adjust hypertension drug treatment based on real-time BP measurements. Figure 2 shows the HeartCare@Home prototype.

Figure 2. HeartCare@Home system prototype. BP: blood pressure; CDDS: clinical decision support system; CHW: community health worker; mHealth: mobile health.

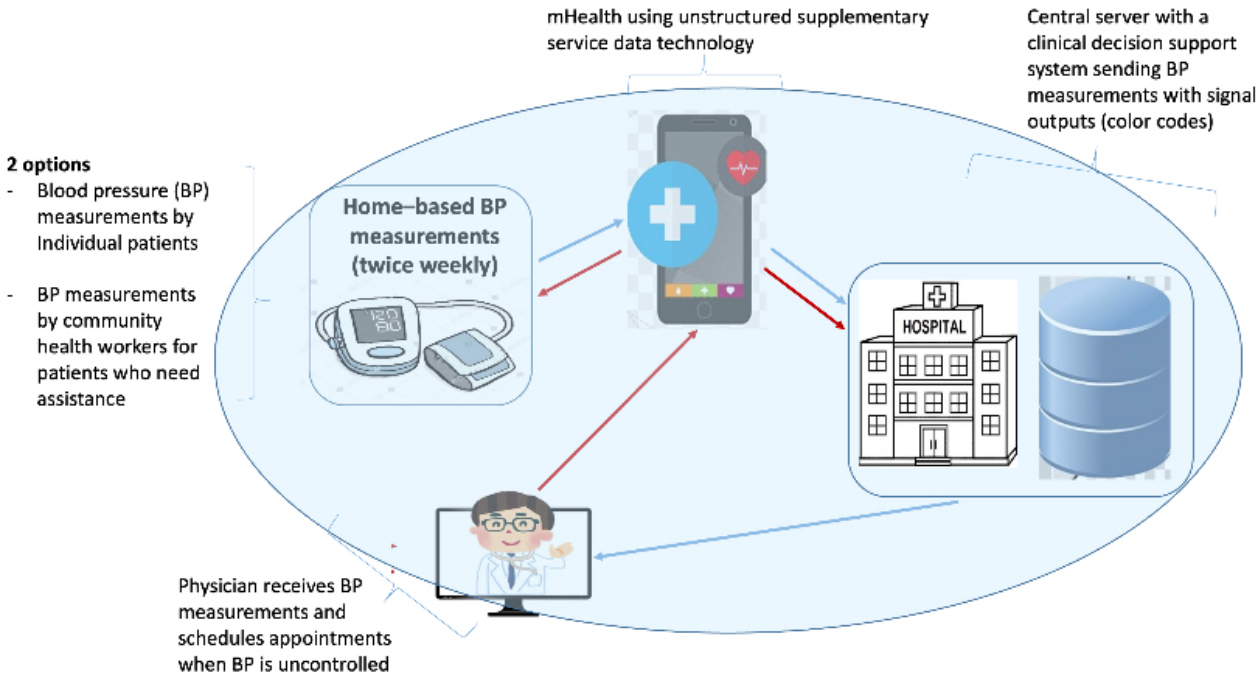

Methods

Study Setting

The study will be conducted in the NCD clinic of Kibagabaga District Hospital located in Gasabo District, Kigali, Rwanda. This study site was selected as a potential piloting setting because of the high number of patients with hypertension enrolled in the NCD clinic.

Study Population

This research will enroll individual patients with known diagnosis of hypertension, aged 45 to 65 years, from the Gasabo District community enrolled in the Kibagabaga Hospital's NCD clinic. All study participants who will be willing to participate in the study will be continuously linked to the NCD clinic for further processing of BP measurement data. Two internist physicians working in the NCD clinic will also be involved in the study. The NCD clinic was selected for logistical feasibility, as it has been one of the first clinics in Rwanda to provide hypertension care services for more than 3 years.

Sample Size Calculation

The study will enroll 140 participants diagnosed with hypertension, aged between 45 and ≥65 years, from the community of Gasabo District in Kigali, Rwanda. The sample size was estimated based on testing hypothesis 1, using the approach for sample size calculation for comparison between

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2 groups when the end point is quantitative data [15]. The expected difference in BP (both systolic and diastolic) will be fixed at 3 mm Hg (effect size of 0.20). The level of significance was fixed at 5%, and the power of study was fixed at 80%.

Study Design

This study will use an interventional design with a crossover approach to test the clinical efficacy hypothesis. All identified patients will be allocated to either the intervention group or the standard of care group. The follow-up for each group will be 6 months (3 months in each group follow-up). A comparison of the standard care and the home-based BP telemonitoring program will be conducted using a record review approach. The data for the intervention group will be generated by our mHealth app, while data for the control group (standard care) will be retrieved from usual patient files at the NCD clinic. Data extraction sheets will be used for standard care data retrieval. Figure 3 illustrates the study design for testing the clinical efficacy of the HeartCare@Home system, while Figure 4 shows the flowchart for the comparison of standard care and the home-based BP telemonitoring program. The specific outcomes will be evaluated using variables such as BP values before and after the intervention, which will guide clinical recommendations, including lifestyle modifications, cardiovascular risk assessment, and treatment.

Figure 3. Study design (hypothesis 1). SoC: standard of care.

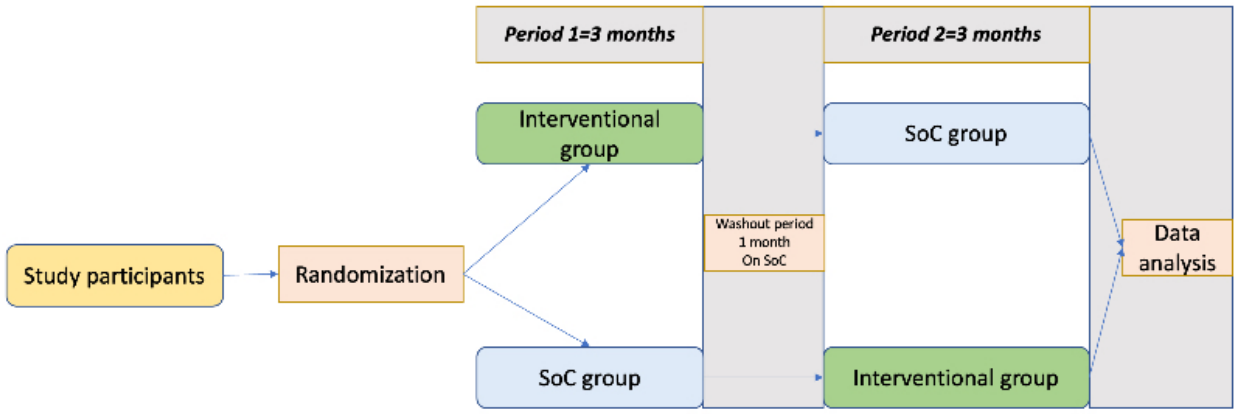

Figure 4. Flowchart for the comparison of the standard care and the home-based blood pressure (BP) telemonitoring program. CHW: community health worker; CVD: cardiovascular disease.

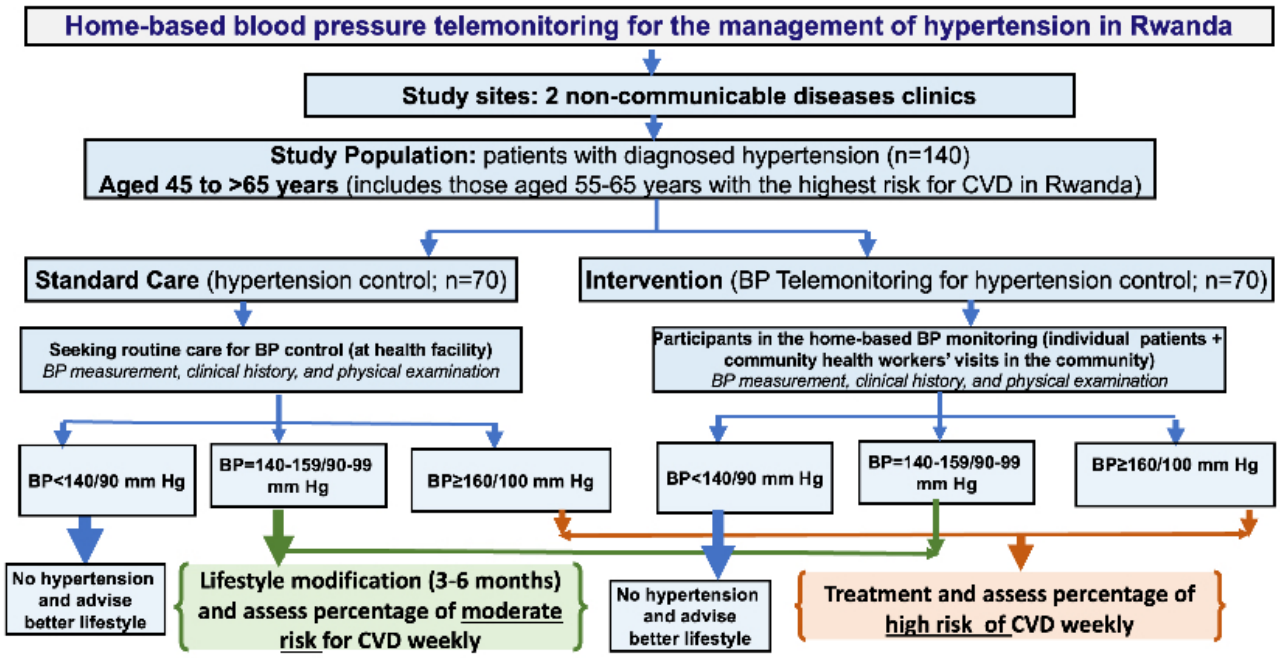

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To assess the feasibility and acceptability of the HeartCare@Home system, a cross-sectional study methodology using Likert-scale questionnaires, the Feasibility of Intervention Measure and Acceptability of Intervention Measure [16], will be adopted. The outcome measures will include measures of acceptability and feasibility, such as perceived approval, likability, and willingness to adopt the system.

Recruitment of Study Participants

Study participants will be identified by the researcher in collaboration with district and village administrators and CHWs in consideration of their hypertension diagnosis and age. Both genders will be included. Participants will be invited through verbal communication and written letters.

Data Collection

We will conduct a preintervention record review of hypertension control data. The intervention entails the implementation of a home-based BP telemonitoring program for a period of 6 months in the Gasabo District communities. A total of 6 months after the intervention, the clinical efficacy of the home-based BP telemonitoring program will be evaluated by comparing the rate of hypertension control during the BP telemonitoring program implementation with the previous rate of hypertension control within usual care using a record review approach. The standard BP measurement at home procedures will be followed. These include having the patient sit in a comfortable chair with their back supported for at least 5 minutes before the reading, placing both feet flat on the ground with legs uncrossed, resting the arm with the cuff on a table at chest height, and then measuring the BP [5]. On the basis of the implementation research framework by Proctor et al [17], we will evaluate the feasibility and acceptability of the home-based BP telemonitoring program. The Acceptability of Intervention Measure and the Feasibility of Intervention Measure [16] tools will be used for data collection. The original tools will be translated into Kinyarwanda. Both the original and the translated versions of the tools will be used to collect data. Informed consent will be obtained from each study participant before the start of data collection. CHWs will participate as data collectors and remunerated for their time and effort as per the Ministry of Health guidelines.

Data Management and Analysis

Data analysis will be conducted using Stata (StataCorp LLC) software. Double data entry will be used to maximize the accuracy of data entry. Data cleaning will be carried out using the study questionnaire to check whether data from participant's answers match with the answers that will be in the questionnaire. Data will be summarized with descriptive statistics. Cleaned data would be cross-tabulated to determine relationships between different variables. A paired sample 2-tailed *t* test will be used to test for differences between the preintervention and postintervention records review data for hypertension control.

Ethical Considerations

Ethics approval has been obtained from the Rwanda National Research Ethics Committee (06/RNEC/2024). Approval has also been sought from the hospital authorities to access electronic medical records. Informed consent will be sought from all the study participants before participation in this study. Anonymity will be ensured by not collecting participants' names and instead using pseudonyms. This study will be carried out in accordance with relevant guidelines and regulations outlined in the ethical declarations.

Results

Expected Study Results

This pilot project aims to induce a long-term change in the health care delivery system in Rwanda and in other similar settings with a new way of monitoring and managing patients with NCD. In addition, the results from evaluating the clinical efficacy, feasibility, and acceptability of the HeartCare@Home system will guide its potential expansion to additional NCD clinics. The overall ambition is to complete a successful 2-year pilot phase and subsequently expand the system nationwide in Rwanda, with the potential to include other NCDs.

Innovation and Impact

This project supports scientific and technological advancement as Rwanda endeavors to become a middle-income country by 2050. The project will use 4 main novel technologies to facilitate real-time BP telemonitoring for control of hypertension, ensuring a real-time communication linkage between patients in the community and the appropriate level of care (NCD clinics), as demonstrated in Figure 2.

Community Outreach Plan

This research will facilitate a real-time communication linkage between patients at the community level and the appropriate level of care. Community outreach is essential for this study to effectively engage the Rwandan community and raise awareness about the project. A detailed outreach plan will be prepared in the work package 5 to create awareness of the project's rationale within the Rwandan society and later disseminate study findings. Information about this study will be communicated to citizens through Rwanda's health system communication channels and CHWs.

Dissemination of Study Results

The dissemination and exploitation activities plan will mainly focus on the elevated BP handling gap in Rwanda and the need for Rwandan homegrown solutions. This has already been initiated with a project kickoff meeting, CHWs meetings, and series of workshops and technical development hackathons. The aim of the dissemination will be to ensure the optimal use of the project's findings after its completion and therefore speed up the potential for their uptake by health care providers, researchers, regulators, and policymakers. This research project consortium includes the Rwanda Biomedical Centre, a technical body of Ministry of Health in Rwanda, which will ensure that the project outcomes contribute to the Government of Rwanda priorities and needs in terms of NCD prevention and management. In addition, this project through the work package 5 will use a multilevel approach, including tailor-made dissemination tools and activities depending on the respective target audiences and their needs. The dissemination plan also includes the organization and coordination of all means for

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project dissemination and outreach, such as scientific articles, oral or posters presentations, meetings, seminars, and scientific conferences. We anticipate publishing findings of this study in peer-reviewed journals. A copy of the published paper or abstract outlining the study findings will be shared at local and international academic forums and meetings. The study findings will also be presented to hospital administrators and community members.

Discussion

Anticipated Findings

The study will primarily develop a novel Rwandan, homegrown eHealth technology as a ready-to-use, software-as-a-service, marketable product comprising different packages (an mHealth app with rapid SMS gateway, a central server and an integrated dashboard, and a CDS algorithm) that will facilitate health care services for the control of hypertension among individuals diagnosed with hypertension in communities of Rwanda. The main outcome from the HeartCare@Home system innovation will be to enable a change in health care delivery for patients with hypertension in Rwanda, improving monitoring, early detection of BP worsening, reducing hypertension complications and cardiovascular risk, and allowing health care providers to handle more patients in less time.

After pilot testing and establishing the eHealth technology system as operational in 1 NCD clinic, further large-scale research will be needed to evaluate its scalability across Rwanda and potentially in other similar settings in sub-Saharan Africa. This is a crucial contribution to health care systems and science, particularly in the African region, which is currently facing emerging NCDs, including hypertension. Additionally, the lessons learned from the HeartCare@Home project may inform the establishment of a scalable system that can be applied in other disease areas. The HeartCare@Home system may also be adaptable to other cardiovascular conditions, such as arrhythmias, or NCDs, integrating additional home or portable electrocardiograms devices, and for NCDs (integrating other wearable devices).

Anticipated Research Limitations

This study will not generalize findings, and it will recruit a relatively small sample (n=140 participants). However, the findings from this study will inform a larger study aimed at evaluating the implementation outcomes of the home-based BP telemonitoring program on a large scale.

Acknowledgments

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Authors' Contributions

All authors were involved in the conception and design of the study. AN, JG, and RM prepared the initial draft of the manuscript. All authors contributed to and reviewed the manuscript until the final version. All authors read and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the Vlaamse Interuniversitaire Raad, Universitaire Ontwikkelingssamenwerking (VLIR-UOS) / Flemish Interuniversities Council, University Development Co-operation (Belgium).
[PDF File (Adobe PDF File), 91 KB - resprot_v14i1e66211_app1.pdf]

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Abbreviations

BP: blood pressure
CHW: community health worker
CVD: cardiovascular disease
mHealth: mobile health
NCD: noncommunicable disease

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Protocol

Development and Validation of a Cross-Device Platform for Anhedonia Trend Visualization by Using Ecological Momentary Assessment and Moving Averages (Part I): Protocol for a Methodological Pilot Study

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Abstract

Background: Anhedonia is a core symptom of depressive disorders. Although group-level cutoff points for the Snaith–Hamilton Pleasure Scale (SHAPS) are established, real-time, individual-level monitoring remains limited. Ecological momentary assessment (EMA) enables high-frequency sampling, and simple moving averages (SMA; 7/14/30 days) offer an interpretable way to smooth daily signals and surface early-warning trends.

Objective: The aim of this study was to develop and validate a cross-device platform that collects EMA-based SHAPS responses and visualizes SMA trends for individual anhedonia monitoring. This part I protocol focuses on platform design, feasibility, usability, data quality, and initial analytical validity to inform subsequent evaluation.

Methods: We will conduct a single-arm methodological pilot in approximately 24 adults, recruited from an outpatient psychiatry clinic (clinical cohort) and a university setting (nonclinical cohort). After baseline assessment, participants will complete 30 days of daily EMA-SHAPS. Primary outcomes are feasibility (adherence, missingness patterns, timing fidelity) and usability/face validity (eg, System Usability Scale, qualitative feedback). We will also describe expert content validity ratings for key visual elements and exploratory analytic checks of within-person variability and the descriptive behavior of 7/14/30-day moving averages; these analyses are not powered for confirmatory hypothesis testing.

Results: This protocol specifies the design–validate sequence, recruitment procedures, and predefined adherence and missing-data rules for computing moving averages. Recruitment for the year-1 feasibility pilot is scheduled to begin in March 2026 following institutional review board approval (approval 114006; approval date: June 10, 2025), with feasibility metrics, usability indices, and parameter estimates used to refine alert logic and power calculations for a planned part II evaluation.

Conclusions: Combining EMA-SHAPS with SMA-based trend visualizations may provide an interpretable way to summarize daily anhedonia signals and generate candidate early-warning indicators. This methodological pilot will deliver feasibility,

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usability, and preliminary analytic parameters needed to support a subsequent controlled evaluation of the platform's clinical utility.

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KEYWORDS

anhedonia; Snaith–Hamilton pleasure scale; ecological momentary assessment; moving average; early warning systems; digital health; mHealth; data visualization

Introduction

Background

Major depressive disorder is a leading cause of disability worldwide, with enduring effects on social functioning, quality of life, and health care utilization [1]. Among its heterogeneous features, anhedonia—the diminished capacity to experience pleasure—is both a core diagnostic criterion and a prognostically salient dimension linked to poorer outcomes [2,3].

The Snaith–Hamilton Pleasure Scale (SHAPS) is one of the most widely used self-report instruments for assessing hedonic tone, with robust psychometric support across clinical and nonclinical samples [4,5]. Cross-cultural work has further demonstrated utility in Chinese-speaking contexts, facilitating screening and risk stratification [6]. Building on this literature, our prior work established group-level SHAPS cutoff points to differentiate clinical from nonclinical cases, enabling population-level identification of high-risk groups [7].

However, thresholds optimized for between-person discrimination are not designed for dynamic, within-person monitoring. Traditional assessments also rely on retrospective recall, which is vulnerable to memory biases and insensitive to short-timescale fluctuations [8-10]. Ecological momentary assessment (EMA) addresses these limitations by repeatedly sampling experiences in naturalistic settings, enabling high-frequency, context-sensitive tracking of affect and behavior [9-11]. Converging evidence suggests that changes in momentary affect and variance can precede transitions in depressive states, motivating early-warning approaches that leverage intensive longitudinal data [12-14].

The analytic challenge is to convert dense EMA streams into signals that are both statistically principled and clinically interpretable. Simple moving averages (SMAs) provide an intuitive smoothing approach long established in time-series analysis [15-17] and are closely related to exponentially weighted moving averages used for sensitive change detection [18]. Short-window averages emphasize responsiveness to recent changes, whereas longer windows emphasize stability; jointly visualized, they can reveal trend direction, volatility, and potential regime shifts in a manner that is easily communicated to clinicians. In parallel domains, rule-based use of multiple moving averages has been shown to detect regime changes in complex noisy systems, underscoring the translational potential of this interpretable family of filters [19,20]. In public health surveillance, related smoothing and alignment procedures such as delay correction and multi-indicator integration are routinely applied to stabilize noisy signals and improve interpretability [21,22].

At the delivery layer, smartphone-enabled platforms now make it feasible to deploy EMA at scale and integrate active reports with passive sensing, a paradigm often described as digital phenotyping [23,24]. For anhedonia monitoring, combining EMA-based SHAPS with SMA-based trend visualization may offer a pragmatic balance between statistical rigor and bedside interpretability: short/medium/long SMA windows (7/14/30 d) support multi-timescale inspection, while alert candidates (eg, fast–slow crossovers; deviations from individualized baselines) can be parameterized and evaluated within a transparent framework grounded in prior early-warning theory [12-14,18].

To our knowledge, this protocol is the first to systematically integrate EMA-SHAPS with SMA-based trend/alert visualization in a cross-device platform and to prospectively evaluate feasibility, usability, and initial analytical validity. Part I (this study) emphasizes platform design, human-factors evaluation, and parameter estimation to finalize alert logic (see Table 1 for feasibility of borrowing moving-average theory for emotional monitoring).

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Table 1. Feasibility of borrowing moving-average theory for emotional monitoring.

Indicator/rule	How it works (moving average domain)	Mapping to psychiatry (EMA[a]-SHAPS[b])	Clinical interpretation and part I feasibility
Short-window SMA[c] (7 d)	Emphasizes most recent observations, fast response to changes, higher sensitivity to noise	Smooths day-to-day SHAPS to expose short-horizon fluctuations in hedonic tone	Early movement detector; may flag brief dips/spikes. Feasible with 30-d diary; risk of false positives mitigated by corroboration with 14/30-d windows
Medium-window SMA (14 d)	Balances responsiveness and stability, dampens idiosyncratic daily noise	Tracks fortnight trends in anhedonia burden, complements 7-d and 30-d perspectives	Context anchor for "meaningful change." Feasible and robust in 30-d series; supports cross-window triangulation
Long-window SMA (30 d)	Maximal smoothing within part I; highlights macrotrend and regime shifts	Approximates a monthly hedonic baseline for each participant	Stability reference; fewer false alarms but slower to turn. Feasible by design (30-d pilot).
Fast–slow crossover (7 over 30)	When short SMA crosses long SMA, indicates potential regime change in level or trend.	Up-cross: deterioration momentum in anhedonia; down-cross: improvement momentum	Operational early-warning candidate; parameterized and logged without triggering actions in part I

[a]EMA: ecological momentary assessment.

[b]SHAPS: Snaith–Hamilton Pleasure Scale.

[c]SMA: simple moving average.

Objectives (Part I)

This part I study specifies development and preliminary validation objectives for a cross-device SHAPS platform with 7/14/30-day SMA trend and alert visualizations. The focus is on feasibility, usability, content validity, and exploratory analytic behavior of moving-average–based indicators, with the aim of informing a subsequent, adequately powered part II evaluation.

Primary Objective

The primary objective is to develop a cross-device platform that (1) collects daily EMA-based SHAPS responses for 30 days, (2) computes and visualizes SMA (7/14/30 d) trends, and (3) implements candidate alert logic, including fast–slow moving-average crossovers and deviations from individualized baselines.

Secondary Objectives

The secondary objectives are as follows:

1. Feasibility and adherence: quantify completion/adherence rates, missingness patterns, and timing fidelity of entries.
2. Usability and face validity: evaluate user experience (eg, System Usability Scale) and perceived interpretability/acceptability of trend and alert panels.
3. Expert content validity: obtain expert ratings of content relevance/clarity for key interface elements and alert explanations (eg, content validity index).
4. Analytical checks: provide descriptive summaries of internal consistency of EMA-SHAPS, within-person variability, and the behavior of 7/14/30-day SMA windows (eg, correlations between daily SHAPS and windowed averages, simple indicators of trend stability), recognizing that this pilot is not powered for robust inferential tests.
5. Exploratory objectives: Estimate plausible parameter ranges for alert logic (eg, crossover lengths, thresholds, and persistence rules) and describe how these candidate rules behave in this small pilot sample, with the sole purpose of refining design assumptions and power calculations for a planned part II evaluation against an individual-level SHAPS benchmark.

Methods

Study Design

This part I development and validation study follows a design-validate sequence—needs assessment, system design and implementation, and a 30-day pilot in clinical and nonclinical cohorts—to evaluate feasibility and validity. A month-by-month timeline of the design–validate sequence and key milestones is provided in Table 2.

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Table 2. Part I study timeline and milestones (August 2025 to July 2026).

Activities	August 2025	September	October	November	December	January 2026	February	March	April	May	June	July 2026
Requirements analysis and system architecture design	✓	✓	✓	✓	✓	✓						
Frontend/backend development and core feature implementation	✓	✓	✓	✓	✓	✓						
System testing and performance optimization				✓	✓	✓						
Platform validation: face validity and user experience testing							✓					
Platform validation: content validity							✓					
Pilot: participant recruitment and screening								✓	✓	✓		
Pilot: 30-d EMA[a]-SHAPS[b] data collection								✓	✓	✓		
Pilot: user feedback synthesis								✓	✓	✓		
Results integration and report writing											✓	✓
Synthesis of development outputs/preparation for year 2											✓	✓

[a]EMA: ecological momentary assessment.

[b]SHAPS: Snaith–Hamilton Pleasure Scale.

Measurements

The following measurements were performed.

Demographic Characteristics

The cross-device SHAPS platform will collect demographic data on gender, age, educational attainment, employment, marriage, region of residence, and socioeconomic status in both groups.

SHAPS

The cross-device SHAPS platform will measure anhedonia by using SHAPS, a 14-item self-report measure that captures recent hedonic experience across 4 domains: interests/pastimes, social interaction, sensory experience, and food/drink [4]. Multiple language versions are available, including simplified and traditional Chinese. The simplified Chinese version uses a 4-point Likert response format from “definitely agree” to “definitely disagree,” yielding total scores from 14 to 56, with reported test-retest reliability of 0.64 and Cronbach α of 0.85 [6]. The traditional Chinese version has demonstrated good readability and ease of response in pilot testing (n=13), indicating favorable face validity, and has shown test–retest reliability of 0.87 with Cronbach α of 0.91. Convergent and discriminant validity are supported by positive correlations with Patient Health Questionnaire-9 items (r=0.52) and the Positive and Negative Suicide Ideation–Negative Suicidal Ideation subscale (r=0.28), and negative correlations with self-esteem (r=−0.51) and the Positive and Negative Suicide Ideation–Positive Ideation subscale (r=−0.54). Collectively, these findings indicate that the Chinese versions of the SHAPS are reliable and valid [25].

Study Population and Setting

Participants will be recruited from two settings: (1) an outpatient psychiatry clinic at the collaborating medical center (clinical cohort) and (2) a university campus (nonclinical cohort). The clinical cohort will consist of adults aged 18-65 years with a treating psychiatrist–assigned ICD-10 (International Classification of Diseases, 10th Revision) mood disorder diagnosis in the F32-F39 range documented in the medical record (eg, depressive episode [F32.-], recurrent depressive disorder [F33.-], other persistent mood disorders [F34.-, F34.9], and unspecified mood disorder [F39.-]). The nonclinical cohort will consist of university students aged 18-23 years recruited from campus settings as an age-restricted comparison group. After baseline assessment, all participants will be invited to complete 30 consecutive days of daily EMA-SHAPS entries by using the cross-device platform.

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Eligibility Criteria

Inclusion Criteria

Inclusion criteria (both cohorts) are as follows: adults aged ≥18 years with sufficient capacity to provide informed consent, ability to communicate in Chinese, regular access to a smartphone or web-enabled device, and willingness to spend approximately 15-20 minutes completing the baseline questionnaire battery. For the clinical cohort, participants must be outpatients aged 18-65 years at the collaborating psychiatry clinic with a treating psychiatrist–assigned ICD-10 mood disorder diagnosis in the F32-F39 range documented in the medical record. For the nonclinical cohort, participants must be university students aged 18-23 years recruited from campus settings.

Exclusion Criteria

The exclusion criteria are as follows: other severe mental disorders such as schizophrenia-spectrum disorders or bipolar disorder or neurological/medical conditions that substantially impair cognitive function; acute high suicide risk at screening, as judged by the treating clinician; and other medical or functional reasons that would prevent the participant from using the digital platform or from sustaining repeated questionnaire completion. These exclusion criteria apply to both cohorts and are intended to ensure participant safety and the feasibility of the 30-day EMA protocol.

Measures and Data Collection

The following measures were used:

1. SHAPS with EMA prompts (14 items, 4-point responses) at baseline and scheduled intervals via the app.
2. Usability/face-validity questionnaires; expert content validity indexing for platform features and visualizations.

For the clinical cohort, primary psychiatric diagnosis, comorbid conditions, and concurrent treatments (eg, psychotropic medications, psychotherapy) will be extracted from the medical record at baseline. For the nonclinical cohort, participants will complete a brief self-report form on past and current mental health treatment. These variables will be summarized descriptively to characterize the sample and to explore whether anhedonia trajectories differ by diagnostic profile or treatment exposure; no stratified hypothesis tests are planned in this pilot.

Feasibility outcomes will focus on adherence, timing fidelity, and patterns of missing data. For each participant, adherence will be defined as the proportion of completed daily EMA-SHAPS entries out of the 30 scheduled days. A priori, we consider adherence of ≥70% (≥21 of 30 d completed) and the absence of any run of ≥5 consecutive missing days as an acceptable benchmark for individual-level feasibility. Timing fidelity will be defined as the proportion of completed entries submitted on the same calendar day as the scheduled prompt, with ≥80% same-day completion regarded as an acceptable benchmark. We will summarize the distribution of these metrics and report the proportion of participants who meet the adherence and timing thresholds in the clinical and nonclinical cohorts separately.

Digital Platform and Moving Average Indicators

The digital platform will have the following features.

1. Cross-device capture, secure backend, dashboards for participants and clinicians
2. Visualization of SMA (7/14/30 d); candidate alert logic (fast–slow moving average crossover; deviation from individualized baselines)
3. Data quality monitoring for missingness and compliance; encryption for data in transit and at rest

An example of the end-to-end user flow is shown in Figure 1, and the trend/alert panel is shown in Figure 2.

Figure 1. End-to-end user flow: app entry and baseline SHAPS → EMA capture → backend moving average computation (SMA) → change detection → alert logging → dashboards. EMA: ecological momentary assessment; SHAPS: Snaith–Hamilton Pleasure Scale; SMA: simple moving average.

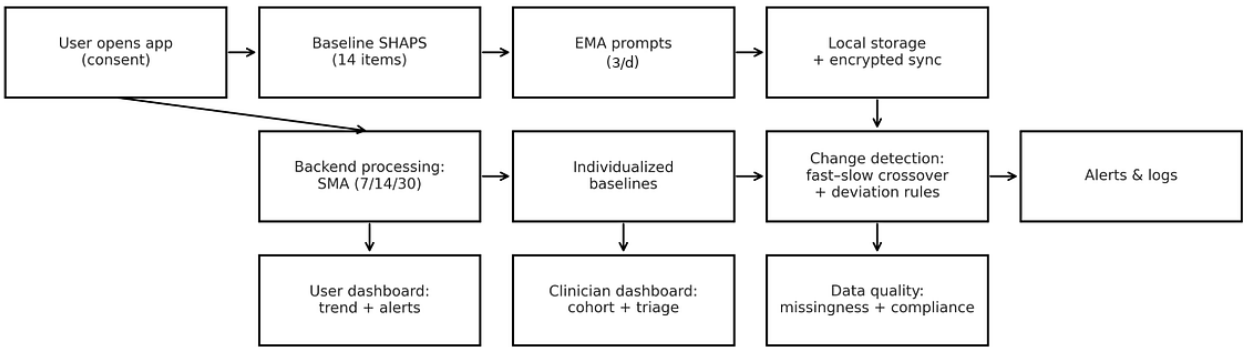

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Figure 2. Example of a trend/alert panel for EMA-SHAPS showing daily values and simple moving averages (7/14/30 d). The 30-day SMA serves as a participant-specific monthly baseline; alert badges are generated by prespecified candidates (eg, fast–slow moving average crossovers; deviations from individualized baselines). Display is for research use in part I and does not drive clinical action. EMA: ecological momentary assessment; SHAPS: Snaith–Hamilton Pleasure Scale; SMA: simple moving average.

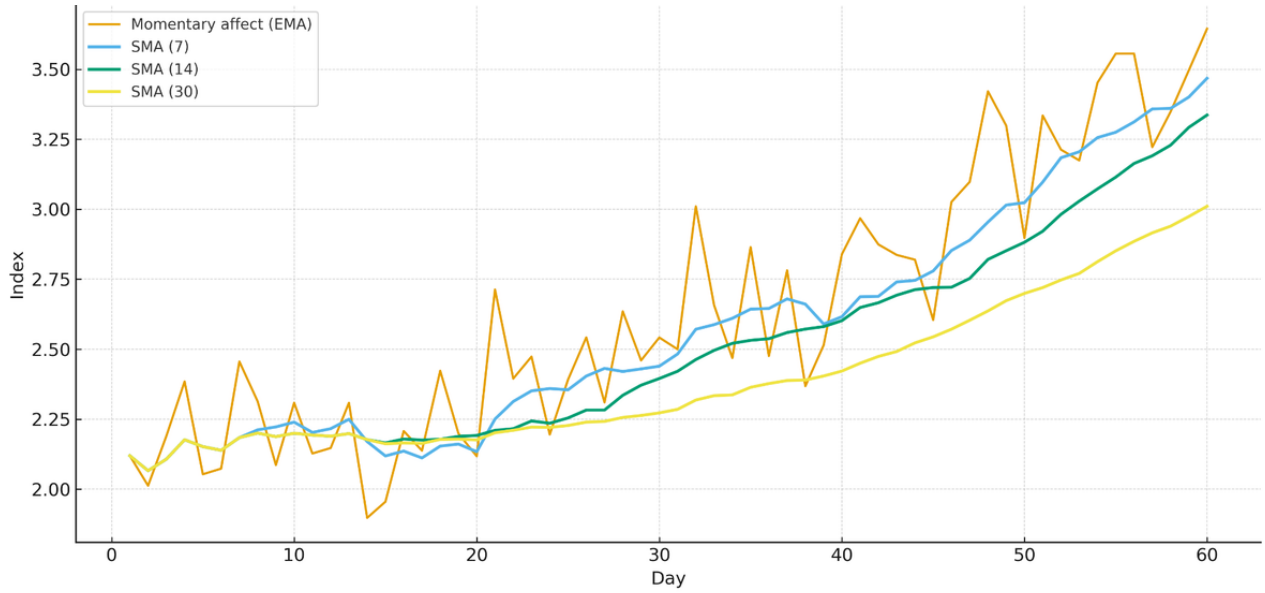

Sample Size and Statistical Analysis

As a development and validation pilot, part I is designed primarily to provide feasibility, usability, and descriptive analytic information rather than to support formal hypothesis testing. We will recruit approximately 24 participants (≈12 per cohort), consistent with a widely cited "12-per-group" rule of thumb for pilot and feasibility studies that aim to estimate variability rather than detect small effects [26]. All primary analyses will be descriptive, reporting means, standard deviations, medians, interquartile ranges, and 95% CIs, where informative.

For each participant and each time window, 7-, 14-, and 30-day SMAs of EMA-SHAPS scores will be computed only when at least 50% of days in the window contain valid entries (ie, ≥4 of 7, ≥7 of 14, and ≥15 of 30 d, respectively). Windows that do not meet this criterion will be flagged as data sparse and excluded from primary SMA summaries. We will distinguish intermittent missingness (isolated missing days or gaps of <5 consecutive days) from systematic missingness (gaps of ≥5 consecutive missing days or early dropout). Primary analyses will not impute missing values; instead, we will conduct sensitivity analyses that (1) compare SMA summaries with and without windows spanning systematic missingness and (2) examine how adherence levels relate to the stability and interpretability of SMA-based indicators. Internal consistency of EMA-SHAPS will be summarized using Cronbach α, and exploratory correlations between daily scores and SMA windows will be reported with appropriate caution, given the limited sample size.

Ethical Considerations

This study protocol was approved by the Institutional Review Board of Tsaotun Psychiatric Center, Ministry of Health and Welfare, Taiwan (approval 114006). All participants will provide written informed consent before any study procedures. During consent, participants are informed that participation is voluntary, that they may decline to answer any question, and that they may withdraw from the study at any time without any consequences for their clinical care or academic standing. The collected data will be pseudonymized so that no personally identifiable information is included, and only the research team will have access to the analytic data set. All data will be stored securely on password-protected servers for at least 7 years after study completion. As a token of appreciation, participants in each cohort will receive a gift voucher valued at NT $100 (approximately US $3) upon completion of the 30-day EMA-SHAPS assessments and end-of-pilot questionnaires.

Results

Recruitment for the year-1 feasibility pilot will begin following institutional review board approval (approval date: June 10, 2025) and completion of platform qualification, with data collection scheduled from March 2026 through May 2026. No data have yet been collected or analyzed. Enrollment will proceed in parallel at the clinical and nonclinical sites until the predefined target sample is reached. Because each participant contributes a 30-day EMA-SHAPS series, the last participant is expected to complete end-of-pilot assessments approximately 30 days after enrollment closure. Data analyses will then be performed and reported. A month-by-month timeline of the planned milestones is provided in Table 2.

In this year-1 feasibility pilot, we also expect to produce a working cross-device prototype that delivers daily EMA-SHAPS assessments and visualizes 7-, 14-, and 30-day SMA trends at the individual level. We will obtain expert-rated content validity indices for key interface elements and alert explanations, together with participant-reported usability and interpretability metrics (eg, System Usability Scale scores). In addition, we will generate feasibility metrics for EMA completion, patterns of missingness, and timing fidelity, as well as a descriptive

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characterization of moving average–based indicators (eg, crossovers, deviations from individualized baselines, and gaps in data coverage) and preliminary parameter ranges that can be carried forward to refine the design and powering of part II.

Discussion

Principal Anticipated Findings

Year 1 is expected to deliver a functioning cross-device platform that supports daily EMA-SHAPS data collection and visualizes 7/14/30-day SMA trends at the individual level. If recruitment and adherence targets are met, the pilot will provide (1) feasibility metrics for daily anhedonia monitoring across clinical and nonclinical cohorts, (2) usability and perceived interpretability indices for the user interface and trend/alert panels, (3) expert content-validity ratings for key visual elements and explanations, and (4) preliminary descriptive information on the behavior of SMA-based indicators under real-world missingness patterns. These outputs are intended to inform refinement of platform features and alert parameters and to guide the design and powering of a subsequent controlled evaluation rather than to establish clinical efficacy on their own.

Comparison With Prior Work

Existing digital mental health platforms increasingly use smartphones and wearables to capture intensive longitudinal symptom data and ecological context [8-11,23,24]. However, most current anhedonia assessments still rely on cross-sectional questionnaires or infrequent follow-ups and do not systematically integrate early-warning indicators derived from time-series analysis or moving average theory [12-18]. By focusing on EMA-SHAPS and SMAs, this protocol adapts tools that have been widely used in engineering and epidemiologic surveillance [15-18,20-22] to a clinically meaningful affective dimension. Rather than proposing complex forecasting models, we prioritize transparent, user-friendly visualizations (eg, short/long SMA crossovers, deviations from individualized baselines) that can be explained to patients and clinicians and empirically calibrated in later phases.

For anhedonia specifically, prior work has validated SHAPS cutoff scores for between-person discrimination [4-7], but there is little guidance on how within-person fluctuations should be summarized or visualized for ongoing self-management. This pilot responds to that gap by testing whether an SMA-based dashboard is acceptable and interpretable to both end users and experts while keeping analytic choices simple enough to be incorporated into routine care if later evaluations support benefit.

Strengths and Limitations

The proposed study has several strengths. It uses a cross-device platform that mirrors real-world technology use, includes both clinical and nonclinical cohorts to sample a range of anhedonia severity and treatment contexts, and prespecifies adherence thresholds and missing-data rules for computing SMA indicators. The protocol also combines quantitative feasibility metrics with expert content-validity ratings, providing converging information about whether the platform is usable and conceptually sound.

At the same time, key limitations reflect the pilot nature of part I. The planned sample size (~24 participants) is sufficient for feasibility and usability assessment but underpowered for robust inferential tests of trend stability, variance components, or alert performance. All analytic checks of SMA behavior must therefore be interpreted as preliminary and descriptive. In addition, recruitment from a single outpatient clinic and 1 university limits generalizability, and we will not examine clinical outcome changes or treatment decisions in this phase. Anticipated practical challenges include sustaining EMA engagement over 30 days, handling missing and noisy data, managing cross-device heterogeneity (eg, operating systems, screen sizes), and calibrating individualized alert thresholds without overtriggering. To partially mitigate these challenges, we prespecify adherence and timing benchmarks, implement in-app reminders and data-quality monitoring, standardize onboarding and support procedures, and treat all alert parameters as modifiable candidates for later evaluation rather than fixed clinical rules.

Future Directions

If the pilot demonstrates acceptable feasibility, usability, and content validity, subsequent work (part II) will focus on evaluating the analytic and clinical performance of moving average–based indicators in larger and more diverse samples. This may include testing whether specific SMA-derived features (eg, crossing events, sustained deviations from baseline) predict movement toward or away from validated SHAPS cutoff points or broader depressive symptom outcomes, and whether providing dashboard feedback to patients and clinicians improves shared understanding of anhedonia trajectories. Over time, the platform could be extended to incorporate additional EMA items, passive sensor data, or adaptive sampling schedules, provided that the resulting complexity remains interpretable for end users.

Dissemination Plan

In line with the emphasis on transparent and reusable digital health research, we plan to disseminate findings from this methodological pilot through peer-reviewed publications and conference presentations in psychiatry, nursing, and digital mental health. Subject to institutional and funder policies, we will also consider sharing nonidentifiable platform specifications, example pseudonymized dashboards, and analytic codes for SMA-based indicators via institutional repositories or open-source platforms. These dissemination activities aim to support replication, integration into related research programs, and eventual translation into routine mental health care if later evaluations demonstrate clinical utility.

Conclusion

Combining EMA-SHAPS with SMA-based trend visualizations may provide an interpretable way to summarize daily anhedonia signals and to generate candidate early-warning indicators for clinical and self-management use. This year-1 methodological pilot is not intended to establish clinical efficacy; rather, it will deliver feasibility, usability, content-validity evidence, and preliminary analytic parameters for 7/14/30-day SMA-based indicators. These outputs will be used to refine platform features

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and alert logic and to support the design and powering of a subsequent controlled evaluation of the platform's clinical utility.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report from the National Science and Technology Council (NSTC), Taiwan.
[PDF File (Adobe PDF File), 253 KB - resprot_v14i1e84024_app1.pdf]

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Abbreviations

EMA: ecological momentary assessment
ICD-10: International Classification of Diseases, 10th Revision
SHAPS: Snaith–Hamilton Pleasure Scale
SMA: simple moving average

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Protocol

Community-Based 4-Level Intervention Targeting Depression and Suicidal Behavior in Europe: Protocol for an Implementation Project

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Abstract

Background: The community-based, 4-level intervention of the European Alliance Against Depression (EAAD) is simultaneously addressing depression and suicidal behavior. Intervention activities target primary care health professionals (level 1), the general public (level 2), community facilitators (level 3), and patients and their relatives (level 4). Activities comprise the digital iFightDepression tool, a guided self-management tool based on cognitive behavioral therapy.

Objective: This study aimed to present the European Union–cofunded EAAD-Best study protocol, aiming at the implementation, dissemination, and evaluation of the 4-level intervention and the iFightDepression tool in several countries across Europe.

Methods: The 4-level intervention has been implemented for the first time in Bulgaria, Estonia, Greece, and Poland. In 3 countries that have already implemented the 4-level intervention (Hungary, Ireland, and Spain), activities have been extended to new regions. In addition, the nationwide uptake of the iFightDepression tool by patients with depression has been promoted in all mentioned countries and Italy.

Results: To evaluate the implementation of the 4-level intervention and the iFightDepression tool, data related to the process, output, and outcome were collected between 2022 and 2024. Data processing and analyses started in 2023. Analyses are expected to be completed in 2024. Results are expected to be published in 2025.

Conclusions: This paper informs researchers, practitioners, and stakeholders on how to implement best practices in mental health promotion and evaluate their effectiveness.

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KEYWORDS

depression; suicide; mental health; European Alliance Against Depression; EAAD; 4-level community-based intervention; iFightDepression; cognitive behavioral therapy; mHealth

Introduction

Depression is one of the most prevalent, severe, and undertreated mental disorders [1]. Having a diagnosis of depression is associated with a reduction in life expectancy of around 10 years or more [2]. Contributing to this is the fact that depression increases the risk of another important mental health issue—suicidal behavior [3]. Approximately 703,000 people die by suicide every year [4] and the number of attempted suicides is considerably higher and rising [5]. The vast majority of completed suicides occur in the context of depressive disorders and other mental illnesses [2].

Due to the numerous factors contributing to suicidal acts, the best approach to address suicidal behavior is multifaceted interventions [6] that have been shown to be most effective [7]. Such multilevel intervention programs have been developed in different countries and either focus exclusively on suicidal behavior or simultaneously aim to improve care for people with depression [6]. A recent systematic review concluded that the most promising multifaceted intervention to prevent suicide is the 4-level intervention approach by the European Alliance Against Depression (EAAD) [8]. The authors reviewed 56 publications (describing 47 unique studies) in Linskens et al [8] on community-based or population-level suicide prevention strategies. EAAD's 4-level intervention offered the most evidence for its effectiveness, while evidence for other single- or multistrategy interventions was either unclear, inconsistent, or lacking. The authors, therefore, suggest that further randomized or observational studies are needed. The EAAD-Best project introduced in this paper will contribute to this identified research need.

The 4-level intervention has been implemented in local communities and simultaneously runs activities at 4 intervention levels (Figure 1).

- Level 1: Interventions aim to improve the capacity of general practitioners (GPs) and mental health care professionals (MHCPs) regarding the management of depression and suicidality. This is achieved by training sessions focusing on early detection, diagnosis, and treatment.
- Level 2: Interventions target the broader public and aim to raise awareness, increase knowledge on depression and suicide, reduce stigma, and improve help-seeking behavior. This is achieved through a public awareness campaign. It emphasizes the need for treatment, the availability of effective treatment options, and support services. Key messages are (1) depression is a real disease; (2) depression can affect anyone; (3) depression has many faces; and (4) depression can be treated.
- Level 3: Interventions aim to improve the capacity of community facilitators and gatekeepers concerning the recognition and handling of depression and suicide risk. Community facilitators and gatekeepers are nonmedical professionals who have a public and social function in society (geriatric caregivers, priests, pharmacists, police, journalists, counselors, midwives, teachers, social workers, managers, and company physicians). They frequently interact with people who are experiencing depression or suicidal ideation and are therefore well positioned to provide general preventive and supportive services. Journalists are informed about the risk of triggering the so-called Werther effect (copycat suicides) and are offered a media guide with recommendations on how to report and not to report about suicidal acts in order to reduce the risk of unwanted effects of media coverage. Capacity building is achieved through train-the-trainer sessions adapted to the specific needs of (subgroups of) community facilitators.
- Level 4: Interventions aim to support patients who are depressed and/or suicidal and their relatives by supporting self-help (eg, implementation of self-help groups and promoting the iFightDepression tool) and providing information about depression, suicidal behavior, and treatments. Identifying locations where people frequently take or attempt to take their lives in a certain region and starting activities to secure these places is also an element within the 4-level intervention.

Implementation of the 4-level intervention is supported by the EAAD coordination center that developed an implementation guide, a catalog of step-by-step recommendations (eg, how to organize a press conference and how to recruit GPs), and has accumulated a broad range of intervention and evaluation materials over the last years. Many materials have already been translated into various languages including the iFightDepression awareness website [9]. This website provides information about depression, its causes, symptoms, and treatments and is publicly accessible. The effectiveness of the 4-level intervention to reduce suicidal behavior was demonstrated by several studies in different countries, although not all evaluated community-based interventions showed the expected positive effects [10-13].

Within the 4-level intervention, the web-based iFightDepression tool is an important intervention component that can help reduce the treatment gap concerning psychotherapeutic interventions [14]. It is based on the principles of cognitive behavioral therapy and supports the self-management of people with mild-to-moderate forms of depression. Access and guidance to the tool are provided by health care professionals. The safety [15] of the tool and its efficacy [14,16] have been assessed for mild-to-moderate symptoms of depression in a randomized controlled trial with an active control group [14] and a study with a treatment-as-usual control group [16]. It is possible that patients with severe depression can benefit from digital interventions [17], but the risk of failing to use the intervention due to motivational problems that are often part of major depression also seems more likely and could cause further frustration and self-criticism. The recommended use of the iFightDepression tool is therefore currently limited to the patient

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groups for which solid evidence is available, but as research progresses, this might be extended.

Figure 1. European Alliance Against Depression's community-based, 4-level intervention.

The 4-level intervention has been successfully adapted to different cultures and health care systems in more than 120 regions within and outside of Europe [18]. Important lessons that have been learned with growing experience are summarized as follows:

1. Targeting optimized care of depression and suicide prevention simultaneously is highly cost-effective and sensible for several reasons. Both are highly important mental health issues and depression is one of the key causal factors of suicidal behavior. Suicide-preventive measures unrelated to depression, such as access to lethal means, can easily be integrated in the 4-level intervention program. Given the high prevalence of depression, a public campaign on depression is likely to have a greater resonance than an exclusive suicide prevention campaign. The latter may further bear the risk of reducing the threshold for suicide due to the normalization of suicidal behavior or unfavorable secondary reporting, for example, in social media.
2. Being simultaneously active at all 4 intervention levels creates synergistic and catalytic effects [19]. An example of a synergistic effect is that the public health campaigns (level 2) not only increase awareness and knowledge in the general population but also increase the motivation of GPs and gatekeepers to participate in the training offered (levels 1 and 3). An example of a catalytic effect is the observed improvement of intersectoral cooperation between health professionals in communities participating in the 4-level intervention, an effect that has not directly been targeted by the activities [19].
3. Depending on the culture and health care system, intervention activities must find the right balance between bottom-up and top-down approaches. A bottom-up approach creates an ownership feeling in the community and is helpful to achieve sustainability. However, in countries with a less developed civil society and a more hierarchical political culture, more top-down support is required.
4. The pharmaceutical industry should not be involved in funding and implementation activities as this may reduce credibility and create conflicts of interest.
5. The implementation of the 4-level intervention in an initial model region raises interest in other regions, causing them to follow suit. The creation of a learning network of all implementing regions, which meet 2 or 3 times per year to exchange experiences and support each other, has proven useful.

Taking these and other lessons learned into account, the EAAD-Best project (full title: "Adapting and implementing EAAD's best practice model to improve depression care and prevent suicidal behavior in Europe") was set up and received funding from the Third Health Program (HP-PJ-2020) of the European Union (EU). As the title describes, the overall objective was the improvement of depression care and suicide

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prevention in Europe given the strongly identified need for correct diagnoses of depression and suicidality as well as effective, evidence-based interventions. The project ran from April 2021 to March 2024 and allowed us to further adapt the 4-level intervention to new contexts and evaluate its effectiveness to add to the sparse database available for multifaceted suicide prevention interventions [8]. This paper aims to introduce the EAAD-Best project as a best practice model for the implementation of mental health interventions and their evaluation.

Methods

Goals of EAAD-Best

The central goals of EAAD-Best were the dissemination of the 4-level intervention to further regions in Europe and the nationwide uptake of the digital iFightDepression-guided self-management tool. These goals were achieved by:

1. The implementation of the 4-level intervention in model regions of EU countries in which the intervention had not yet been established (ie, implementation countries).
2. The dissemination of the 4-level intervention to new regions in EU countries in which this approach had already been implemented in a model region (ie, transfer countries).
3. The nationwide promotion the iFightDepression tool in participating countries and recruiting health professionals as guides who offer the tool to their patients.

Overview of EAAD-Best Activities

Overview

The basic structure of EAAD-Best activities is illustrated in Figure 2.

The participating countries were chosen to represent the different regions of the EU. They differ not only in population and gross national income per inhabitant but also in their health care systems and national approaches to mental health, including the regional health care system facilities for patients with depression.

Figure 2. Basic structure of activities within EAAD-Best. *Due to the dropout of the Italian consortium member, Italy is no longer a full-fledged implementation country but focuses on the implementation of the iFightDepression tool and awareness website. BG: Bulgaria; EAAD: European Alliance Against Depression; EE: Estonia; ES: Spain; GR: Greece; HU: Hungary; IE: Ireland; IT: Italy; PL: Poland.

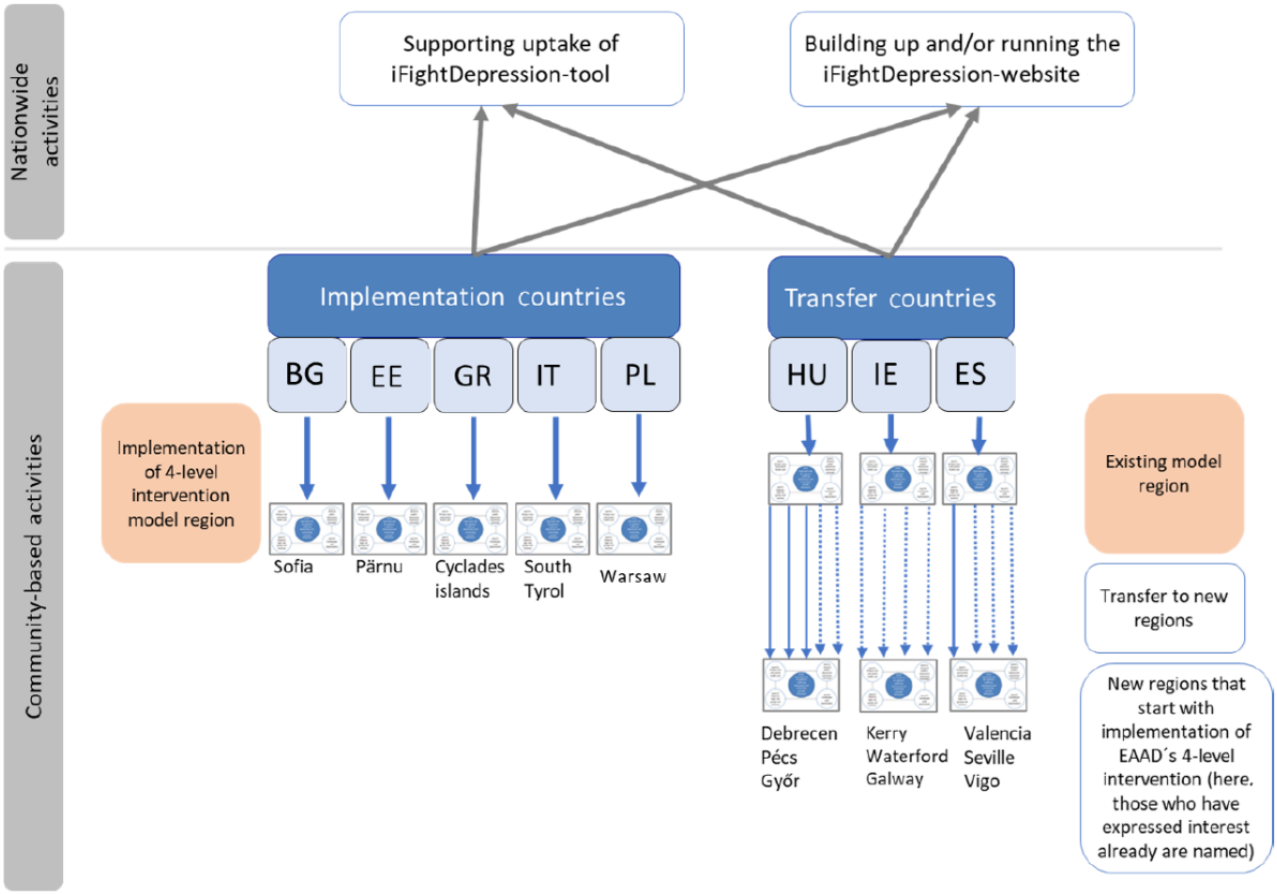

Implementation Countries

In 4 countries, the 4-level intervention was implemented for the first time: Bulgaria, Poland, Estonia, and Greece. Italy was named as another implementation country in the initial EAAD-Best proposal, but the Italian partner changed during the project duration and therefore could only participate in the implementation of the nationwide uptake of the iFightDepression tool.

Model regions were Sofia (Bulgaria), Warsaw central district (Poland), Pärnu (Estonia), and 2 regions in Greece (ie, North

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Attica and Cyclades Islands). They were chosen based on accessibility for project partners and identified needs.

Transfer Countries

A total of 3 countries (Ireland, Spain, and Hungary) with previous experiences with the 4-level intervention and existing model regions offered the intervention to new regions. Ireland extended activities to Kerry and Cork. Spain targeted Valencia, Seville, Alcala la Real, and Vic, and Hungary focused on Szeged, Békéscsaba, Szentendre, and Baja. The regions were chosen based on accessibility for project partners, identified needs, and expressed interest.

The iFightDepression tool was promoted nationwide in all participating countries. It targets persons with mild-to-moderate forms of depression. Specific inclusion criteria are (1) age ≥15 years; (2) access to a computer, an internet connection, and an email account; and (3) mild-to-moderate forms of depression. Exclusion criteria are (1) age <15 years, (2) severe depression, (3) acute suicidality, and (4) current substance abuse.

Implementation Processes in EAAD-Best

Initial Implementation of the 4-Level Concept in Implementation Countries

The process of implementing the 4-level intervention in implementation countries can be broken down into 3 steps:

- Step 1: Planning, design, and strategy
- Step 2: Preparation
- Step 3: Implementation

Within each step, there is a range of tasks and actions to consider (Figure 3).

Figure 3. Foreseen activities for planning, preparing, and implementing the European Alliance Against Depression's 4-level concept in the implementation countries. EAAD: European Alliance Against Depression; GP: general practitioner.

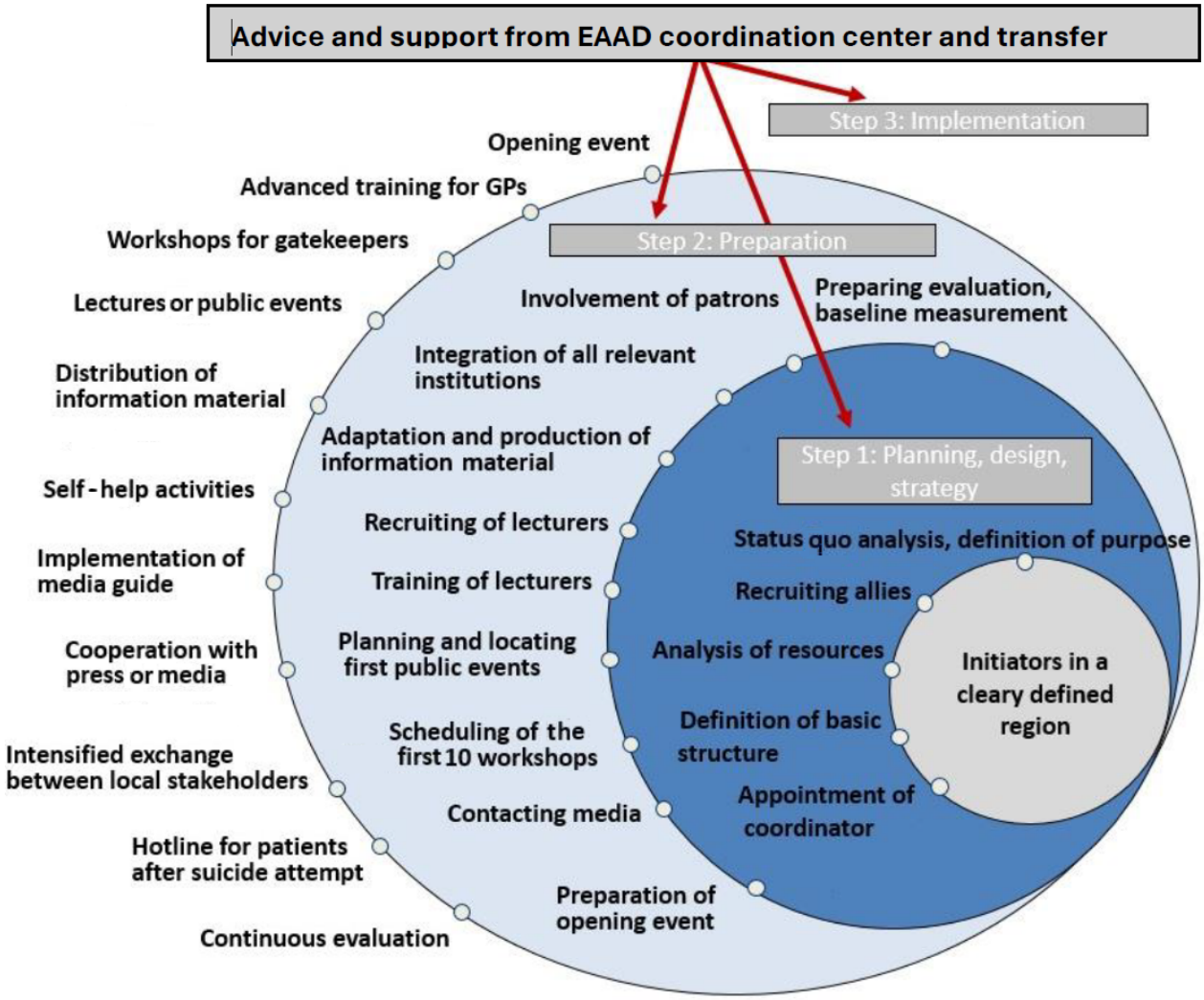

Step 1: Planning, Design, and Strategy

Status quo analyses in the model regions identify relevant stakeholders and institutions as well as potential gaps and limitations of the local care system (ie, "As Is" state). Next, the "To Be" state is defined (ie, what the local alliance seeks to achieve). Specific objectives can be derived by comparing the "As Is" state with the "To Be" state.

The identified network of stakeholders should be broad and include existing local health care initiatives and personal links

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and partnerships. Stakeholders or potential sponsors should be involved in the preparation phase to increase their identification with the alliance.

Next, the alliance initiator is identified. It can be a person (eg, a psychiatrist), a small organization (eg, a self-help group), or an institution (eg, a psychiatric hospital). They should decide about the basic structure of the local alliance (eg, will it be part of an existing organization or will a nongovernmental organization be founded?). A small steering group (about 2-5 people) for leadership of the alliance should be formed and a local coordinator should be appointed.

Step 2: Preparation

In the preparation phase, the alliance is being formed and the interested institutions and stakeholders become integrated. Regular meetings are crucial, as most questions and fundamental decisions occur in this stage.

Materials required for activities on all 4 intervention levels must be translated and culturally adapted to regional needs (eg, public relation campaign materials, level-1 and -3 training materials, and iFightDepression awareness website). Templates are provided by the EAAD coordination center.

The professional groups that will receive training as part of intervention activities on levels 1 and 3 are defined and recruited as lecturers to run training sessions for other GPs, MHCPs, and community facilitators or gatekeepers. The first of these train-the-trainer training sessions take place and further ones are scheduled, so that respective dates can be announced at the opening ceremony and activities can start immediately afterward. A train-the-trainer information package including the referral of patients to the iFightDepression tool is provided by the EAAD.

A large public opening ceremony and further public events are prepared. Many types of public events are possible, such as public talks, podium discussions, theme nights, information booths, school projects, art exhibitions, or religious services. A range of events that are best suited to maximize contact with the target group is advisable.

A prominent and broadly respected person in the region should be involved as a patron. They do not need to have any connection with depression or suicide but should be willing to publicly support the alliance and its aims. A prominent patron will help gain support and cooperation from many partners, including the media.

The media are contacted actively, for example, by offering press releases on events or interviews on depression-related topics to journalists. The use of social media is also advised. It is recommended to appoint a person within the alliance responsible for all social media activities and “marketing” of the campaign.

Step 3: Implementation

During the implementation phase, different activities will be run simultaneously at the 4 levels. EAAD-Best partners focus on maintaining effective and frequent channels of communication with all alliance partners in this phase. Regular project meetings are essential to evaluate the status of all work, determine the next steps, and monitor the financial resources and compliance with an agreed timeline. Alliance partners receive feedback on their work to ensure high motivation and quality of work. If necessary, they are reminded of their responsibilities.

One key activity is the opening ceremony with all the stakeholders and patrons. Holding a press conference at the opening ceremony is advisable and is a good opportunity to provide local media with a press kit and media guidelines on reporting on suicides. A leaflet about the regional alliance against depression with basic information about depression and a map of contacts where to get help locally and ways to support the alliance (by donating, as a volunteer) should be distributed at the event. Setting up a public newsletter is a good way to promote the alliance and attendees at the opening ceremony can be invited to sign up for it. A range of material templates for the opening ceremony are provided by EAAD.

The main activities during the implementation phase are the recruitment and training of health professionals (level 1) and community facilitators or gatekeepers (level 3). The training can be delivered in person or through videoconferences.

Other activities concern an ongoing involvement with the media and the distribution of informative materials (especially flyers and posters) as a crucial aspect of the public awareness campaign (level 2). Talks and public events should take place continuously during the intervention period, as this not only benefits the dissemination of alliance activities but also indirectly raises awareness about depression as a health problem. Patients and relatives should be included as speakers at the events, as this will help fight stigma.

Dissemination of the 4-Level Concept to New Regions in Transfer Countries

In the 3 transfer countries, the goal was to expand the 4-level intervention activities from an existing model project to new regions. To achieve this goal, the following intervention steps were taken:

- Through press releases and other media activities, national and regional health politicians and stakeholders as well as nongovernmental organizations and self-help organizations were informed about the 4-level intervention concept. These activities should raise interest and motivation to start their own local alliances against depression and suicidal behavior in different communities.
- Those who were interested in starting a new regional alliance were supported in several ways: (1) financial support (ie, with a start-up budget of €3.800 [US $4.02]), (2) train-the-trainer sessions, (3) access to EAAD implementation materials and help with their local adaptation, and (4) continuous advice by the EAAD coordination center.
- The existing National Coordination Centre established a national learning and dissemination network of regional alliances by inviting all interested stakeholders (those implementing or interested in implementing regional 4-level interventions) to regular meetings. These allowed us to exchange experiences and best practices but also involved

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workshops on topics such as fundraising, involving volunteers, or organizing press conferences.

Nationwide Uptake of the iFightDepression Tool in All Participating Countries

In order to make the iFightDepression tool available nationwide in all participating countries (ie, implementation and transfer countries), the following intervention steps have been implemented: (1) translation and cultural adaptation of the tool for all countries as needed; (2) in Greece, Italy, Hungary, and Spain, the iFightDepression tool was already implemented, and in all other intervention countries (Estonia, Bulgaria, Poland, and Ireland), a coordination site was appointed to manage the use of the iFightDepression tool; (3) advertised the tool to the general public and health professionals (GPs, MHCPs) through press releases, other media activities, and approaching professional organizations for GPs and MHCPs; and (4) trained health professionals to become guides and give patients access to the tool. The trainings were delivered in person or through videoconferences. e-Learning materials for GPs have been developed that allow them to complete the training at their convenience. It is followed by a test assessing correct understanding.

Evaluation of the Implementation of the 4-Level Concept in Implementation and Transfer Countries

Overview

Our evaluation approach considered monitoring and outcome measures. The monitoring evaluation involved process indicators addressing the extent to which planned activities took place in implementation and transfer countries. It also considered output indicators assessing the quantity and quality of the implemented activities. The outcome evaluation will test to what extent the 4-level intervention generated the expected positive effects in health professionals, community facilitators, and iFightDepression tool users.

Evaluation activities in implementation and transfer countries use the same materials and procedures described below.

Monitoring Evaluation

Process and output indicators were collected through a monitoring instrument twice per year. It presented a selection of core indicators of the 4-level intervention activities (eg, occurrence of the opening event and the number of attendees) to track whether planned activities took place and to assess their quantity and quality.

Outcome Evaluation

Given the limited time frame of this project, it was not feasible to evaluate whether the intended long-term outcomes of the 4-level concept (ie, reduction of suicidal behavior and improvements in the care of patients with depression) were achieved. Therefore, intermediate outcome indicators that are more directly linked to the operational goals of the 4-level intervention were selected. These are changes in self-judgment of the performance, importance, and competence of treating persons with depression and suicidal ideation. They were measured in health professionals and community facilitators participating in the level-1 and level-3 training sessions using self-developed questionnaires.

Data were collected at 2 measurement time points: before and immediately after the level-1 and -3 trainings. Informed consent was obtained before the first training session.

Evaluation of the iFightDepression Tool in All Participating Countries

To evaluate the iFightDepression tool and its effects, users were asked to complete 2 outcome measures. Their informed consent was obtained when registering for the iFightDepression tool, and all data were directly collected within the application. First, after their registration, users were asked to complete a self-developed survey measuring initial expectations regarding the tool. Then, over the following 8 weeks, mental well-being was assessed on a weekly basis with the Patient Health Questionnaire (PHQ-9) [20].

Ethical Considerations

Participating in any evaluation activity will require informed consent. Ethical approval has been obtained in all implementation and transfer countries before the start of data collection. The names of the ethics committees that approved the study are as follows: (1) Bulgaria: Central Ethics Committee of the Ministry of Health Republic of Bulgaria; (2) Estonia: Tervise Arengu Instituudi inimuuringute eetikakomitee, Research Ethics Committee of the National Institute for Health Development; (3) Greece: Department of Education, Research and Documentation Association of Regional Development and Mental Health; (4) Poland: ethics committee of the Maria Grzegorzewska University; (5) Hungary: Egészségügyi Tudományos Tanács, Tudományos és Kutatásetikai Bizottság; (6) Ireland: Clinical Research Ethics Committee of the Cork Teaching Hospitals; and (7) Spain: Comité Ético de Investigación Clínica de Galicia; Comité Ético de Investigación del Hospital Clínico de Valencia; and Comité de Ética de Investigación de los Hospitales Universitarios Virgen Macarena.

Results

Data collection was completed in March 2024. Data processing and analyses commenced in the autumn of 2023 and are expected to be completed by the end of 2024. Results are expected to be published in 2025.

Discussion

Principal Outcomes

EAAD-Best had three main objectives: (1) implementation of the 4-level intervention in model regions of EU countries in which the intervention had not yet been established, (2) dissemination of the 4-level intervention to new regions in EU countries in which it had already been implemented, and (3) nationwide promotion of the iFightDepression tool in participating countries. In general, all these objectives have been successfully achieved, as alliances against depression were established in all participating countries, iFightDepression guides were trained, and increasing numbers of people started using the tool. Analyses of the collected monitoring data

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(currently ongoing, results expected to be published in 2025) will allow a more fine-grained conclusion regarding the quantity and quality of intervention activities. In line with previous studies (eg, [8,14]), we anticipate that the outcome evaluation (results expected to be published in 2025) will show that training of GPs, MHCPs, and gatekeepers will increase their subjective competence and their willingness to treat persons with depression and suicidal ideation in the future. Furthermore, iFightDepression tool users are expected to report a decrease in depressive symptoms. The anticipated results will add to the scarce literature on suicide prevention interventions [8] and, most importantly, will extend existing evidence on the effectiveness of the 4-level intervention and the iFightDepression tool to new regions and countries across Europe.

The following sections will discuss some practical issues involved in implementing and evaluating the 4-level concept and the iFightDepression tool and will highlight not only some of the challenges but also the strengths of the approach.

Participation of Professionals in EAAD Training

Participation in EAAD training sessions is completely voluntary. Professionals will not be remunerated for their participation. Recruiting GPs can be especially challenging due to time constraints and high workloads. Accordingly, trainings focus on practical materials for GPs and their patients, and are delivered in a convenient fashion (eg, in the evenings and online). The introduction of e-learning materials to allow GPs to complete the iFightDepression guide training has been very well received. It has also proven helpful to be able to award Continuing Medical Education points for training completion.

Training professionals will strengthen both their expertise in recognizing mental health issues and their ability to offer support. It is important to stress those benefits in communications. In particular, becoming a guide for the iFightDepression tool enables GPs to provide self-management support based on cognitive behavioral therapy to their patients.

Potential Risks and Benefits of Using the iFightDepression Tool

Previous studies have shown that the iFightDepression tool has beneficial effects on mental health without causing any adverse effects [14,15]. Therefore, the benefits of participation are expected to outweigh any potential risks (eg, suicidal crises can be overlooked) and unwanted effects (eg, an increase in rumination and somatization due to self-monitoring). In addition, all participants will remain within the usual care of their GPs or MHCPs while using the iFightDepression tool.

The expected benefits of the iFightDepression tool include increased uptake of treatment as online self-help tools are more accessible than traditional forms of psychological support. Hence, the iFightDepression tool has the potential to close the gap between people with depression seeking help and the limited immediate access to psychotherapy [1]. Furthermore, there will be a lower threshold to engage certain people who may be reluctant toward traditional mental health services. Given that the iFightDepression tool is used online and anonymously, users face no risk of stigmatization. The early detection of suicidal ideation and severe symptoms of depression through the inclusion of the PHQ-9 within the tool will help prevent attempted and completed suicides. In particular, the PHQ-9 contains 1 item that directly addresses suicidal ideation. If participants choose a response option indicating that they are experiencing suicidal thoughts or obtain a total score of 15 or above (indicating moderate-to-vigorous symptoms of depression), they will receive an automatic message suggesting contacting their health care professional, GP, or a quality-assured support service. Finally, the tool will strengthen the coping skills of participants, enabling them to manage current and future experiences of depression better.

Sustainability

The ultimate goal of EAAD-Best is that activities will continue to run and expand from model projects to national networks of alliances against depression upon project completion. In general, sustainability is a key aspect of the 4-level intervention. It has been considered in its development, for example, by making it as cost-effective as possible, flexible, and adaptive to various contexts and encouraging activities leading to an ownership feeling in the communities. Sustainability is further considered within implementation activities by asking partners after a defined intervention phase (2-3 years) to reflect on previous and ongoing activities, their main partners and stakeholders, experienced challenges, and facilitators so on. EAAD further recommends partners to create a national coordinator position that, on the basis of the experiences from the model project, can support and coordinate the dissemination of the approach in further cities and regions to make it efficient, cost-effective, and impactful.

Evaluation Challenges

Performing applied research like the presented implementation science project can pose challenges such as variability in implementation fidelity. This project tried to minimize such risks by implementing certain measures or processes. In general, questionnaires were always kept to a minimum to avoid overburdening project partners, professionals involved in trainings, and patients using the iFightDepression tool. The dedicated work package running evaluation activities in EAAD-Best provided templates for all assessments and reported completion rates at consortium meetings so that potential difficulties in certain countries could be identified and addressed right away. The training evaluations could be completed online or through paper and pencil to suit the local preferences and increase data completion. To match repeated assessments of training participants, a subject-generated identification code was used to allow correct matching while ensuring anonymity. Future publications on the results of the EAAD-Best project will discuss identified challenges and the chosen solutions in more depth.

Conclusion

The EAAD-Best project will contribute to improved depression care and prevention of suicidal behavior in Europe by extending the application of the 4-level intervention and the uptake of the iFightDepression tool. Besides supporting the implementation of best practices in mental health promotion and treatment,

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EAAD-Best will also add to the implementation research evidence base in the area of mental health interventions. Implementing and evaluating a multilevel intervention, such as the 4-level intervention, bears certain risks and challenges, for example, convincing health professionals to join level-1 trainings, establishing wide and consistent networks of stakeholders, and finding funding opportunities to maintain and extend activities upon project completion, and so on. Lessons learned and identified pitfalls will be shared once the monitoring and outcome analyses have been completed (expected by the end of 2024 with resulting publications in 2025), to avoid costly mistakes and ensure an efficient implementation process with a wide and enduring impact beyond the EAAD-Best project in the future.

Acknowledgments

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Data Availability

The datasets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

KMS and KA wrote the original draft. UH provided supervision, especially with editing and conceptualization. All authors reviewed the original draft and the final manuscript.

Conflicts of Interest

VPS reports the following: grants from CIBERSAM, ISCiii, UE H2020, EAAD, Compass, Novartis, Lundbeck, and Janssen; honoraria or consulting fees from Janssen, Otsuka, and Esteve; and participation in the speakers bureau for Janssen, Otsuka, GSK, Exeltis, ABBVIE, Abbot, Lundbeck, Esteve, Novartis, and Angelini.

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Abbreviations

EAAD: European Alliance Against Depression
EU: European Union
GP: general practitioner
MHCP: mental health care professional
PHQ-9: Patient Health Questionnaire

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Protocol

Examining Weight Suppression, Leptin Levels, Glucagon-Like Peptide 1 Response, and Reward-Related Constructs in Severity and Maintenance of Bulimic Syndromes: Protocol and Sample Characteristics for a Cross-Sectional and Longitudinal Study

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Abstract

Background: Bulimia nervosa and related syndromes (BN-S) characterized by binge eating vary considerably in illness severity and course. Using the Research Domain Criteria framework of the National Institute of Mental Health, we developed a model positing that the same set of physiological consequences of weight suppression (WS; defined as the difference between the highest and current adult body weight) contribute to binge-eating severity and maintenance by (1) increasing the drive or motivation to consume food (reward valuation effort [RVE]) and (2) decreasing the ability for food consumption to lead to a state of satiation or satisfaction (reward satiation).

Objective: Our funded project aimed to test concurrent associations among WS, physiological factors (leptin concentrations and postprandial glucagon-like peptide 1 [GLP-1] response), behavioral indicators of RVE (breakpoint on progressive ratio tasks) and reward satiation (ad-lib test meal intake), self-report of these core constructs, and binge-eating severity in BN-S (aim 1); test prospective associations to determine whether WS predicts BN-S maintenance in longitudinal models and whether posited mediators also predict BN-S maintenance (aim 2); and determine whether associations between WS and BN-S severity and maintenance are mediated by alterations in leptin levels, GLP-1 response, RVE, and reward satiation (aim 3).

Methods: We aimed to recruit a sample of 320 women with BN-S or noneating disorder controls, with BMI from 16 kg/m^2 to 35 kg/m^2, for our study. The study included diagnostic interviews; questionnaires; height, weight, and percentage of body fat measurements; weight history; fasting leptin level; postprandial GLP-1 and insulin responses to a fixed meal; and ad-lib meal and progressive ratio tasks to behaviorally measure reward satiation and RVE, respectively, at baseline, with at least 78.1% (250/320) of the participants providing data at 6- and 12-month follow-up visits. Data will be analyzed using structural equation models to test posited pathways.

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Results: Data collection began in November 2016 and ended in April 2023, pausing in-person data collection from March 2020 to February 2021 due to the COVID-19 pandemic. Of 399 eligible women enrolled, 290 (72.7%) provided clinical, behavioral, and biological data at baseline, and 249 (62.4%) provided follow-up data. Measures demonstrated strong psychometric properties.

Conclusions: We seek to identify biobehavioral predictors to inform treatments that target key factors influencing the severity and course of binge eating. These data, supported solely through federal funding, can inform questions emerging from recent interest and controversy surrounding the use of GLP-1 agonists for binge eating.

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KEYWORDS

binge eating; weight suppression; leptin; glucagon-like peptide 1; insulin; reward; satiation; longitudinal; behavior; Research Domain Criteria

Introduction

Background

On March 6, 2013, the National Institute of Mental Health (NIMH) released a request for applications titled "Advancing Eating Disorders Research through Dimensional Studies of Biology and Behavior (R01)" to stimulate research using the Research Domain Criteria (RDoC) framework to identify mechanisms underlying eating disorders. In response, our team submitted an application that addressed key requirements. Specifically, we proposed a model that (1) was transdiagnostic, bridging categories in the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (*DSM-5*) that involve recurrent binge eating; (2) was based on 2 RDoC positive valence domain constructs to explain the 2 defining features of binge eating in the *DSM-5*, including overconsumption of food and loss of control (LOC) over eating; (3) measured constructs and clinical features dimensionally, from a state of health to disease; and (4) used 3 units of analysis, including self-report via interview and questionnaire and biological and behavioral measurement. Our model translated work emerging from basic neuroscience studies of ingestive behavior in rodents to understand the severity and maintenance of bulimia nervosa (BN) and related syndromes (BN-S). This report provides an overview of our explanatory model, supporting literature informing our aims and hypotheses; our protocol for testing hypotheses and adjustments required by the onset of the COVID-19 pandemic; our data analytic plan; our timeline, including recruitment and retention over follow-up; a description of our sample; and psychometric properties of our measures. With data collection completed, this report addresses the feasibility of our approach to testing our model, and our discussion focuses on the implications of potential findings for the assessment, diagnosis, and treatment of eating disorders characterized by binge eating.

Explanatory Model

A comprehensive review of our explanatory model, including background literature and preliminary data, is available in an open-access article [1]. We proposed that weight suppression (WS), originally defined as the difference between the lifetime highest adult weight and current weight [2], represented a dimensional, transdiagnostic risk and maintenance factor for binge eating in eating disorders. Furthermore, we proposed that WS, independent of current adiposity, contributed to reduced circulating leptin levels, which contributed to a blunted glucagon-like peptide 1 (GLP-1) response to food intake, and that these reductions contributed to alternations in 2 RDoC constructs, reward valuation and reward satiation. Reward valuation represents "benefits of a prospective outcome [...] by reference to external information, social context (eg, group input), and prior experience" [3], and reward valuation effort (RVE) can be measured as the amount of work a reward is worth [4]. In contrast, reward satiation represents "the change in incentive value of a reinforcer over time as that reinforcer is consumed or experienced" [3], and reward satiation can be measured as the termination of reward consumption when it is freely available [4]. Disrupted RVE explains excessive appetitive drive to consume a reward, despite its costs, leading to LOC while eating. Perturbed reward satiation explains the diminished ability to reach a state of completion or satisfaction during consumption, leading to excessive food intake. LOC and excessive food intake represent the defining features of binge-eating episodes, and our model sought to explain both the severity and maintenance of BN-S defined by binge-eating episodes across *DSM-5* eating disorder diagnoses.

Supporting Literature

Women with BN often have a BMI within the range considered healthy [5], belying an average WS of 7.8 kg [6-14]. Cross-sectional and prospective studies support significant associations between greater WS and BN-S severity [9,14,15] and maintenance [6,8,9], controlling for age, BMI, body image disturbance, and dietary restraint [9,14]. In addition, robust evidence supports that greater WS predicts future weight gain [7,10,16-19]. This last point underscores how WS represents a state resulting from weight loss, which is difficult to maintain due to biological consequences known to influence ingestive behaviors. Our literature review focused on findings translated from basic neuroscience into clinical research that contribute to weight gain and may also impact the risk for binge-eating episodes.

Biological Consequences of Weight Loss

Weight loss includes loss of white adipose tissue, the primary source of the hormone leptin [20]. Leptin crosses the blood-brain barrier, providing a signal of stored energy to neural regions influencing ingestive behavior [20]. In addition to significant and large (r>0.90) positive associations between fat mass and circulating leptin levels [21], weight loss impacts leptin levels

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independently of BMI [21,22]. Our previous work supported a significant association between greater WS and lower leptin levels, controlling for BMI [23,24] and body fat percentage [23].

Importantly, although WS and leptin levels represent states rather than traits, both demonstrate relative stability throughout the day and are unlikely to directly influence eating onset and termination. Instead, leptin modulates peripherally released meal-related signals that dynamically respond to changes in nutritional intake and impact ingestive behavior [25]. These signals include ghrelin, cholecystokinin, insulin, glucose-dependent insulinotropic polypeptide, secretin, peptide tyrosine tyrosine, insulin-like peptide 5, neurotensin, substance P, and GLP-1. The hormones relay information to the brain about acute changes in energy needs via stimulation of the vagus nerve, with some signals crossing the blood-brain barrier to bind to receptors in neural circuits that impact feeding [25]. Among these, our model focused on GLP-1 based on emerging research on its role in both reward valuation and reward satiation led by one of our investigators [26-30].

GLP-1 is released by L cells in the intestine, and research in rats suggested that leptin potently stimulated postprandial GLP-1 release via leptin receptors on intestinal L cells [31,32]. Thus, our model posits that lower leptin level is associated with blunted postprandial GLP-1 response. Supporting this prediction, individuals with higher leptin levels have demonstrated more robust GLP-1 responses to food intake [33]. These cross-sectional associations appear to reflect the influence of leptin on GLP-1 levels, rather than the reverse, as neither meal-induced increases in GLP-1 nor exogenous GLP-1 administration influence leptin levels in healthy volunteers [34,35]. Thus, our model predicts associations among greater WS, lower leptin levels, and blunted GLP-1 response to food intake, which then influence food intake via alternations in RVE and reward satiation.

Impact of Peripheral Leptin Levels and GLP-1 Response on Reward Valuation and Reward Satiation

Circulating leptin crosses the blood-brain barrier and binds to leptin receptors in many brain regions, including those involved in reward valuation (ventral tegmental area [VTA] and nucleus accumbens [NAc] [36] and reward satiation (several regions of the hypothalamus and the hindbrain) [37]. Peripherally administered leptin inhibits dopamine projections from the VTA to the NAc [36]. In the arcuate nucleus (Arc) of the hypothalamus, leptin inhibits neurons containing neuropeptide Y and agouti-related protein (NPY/AgRP) and activates neurons containing pro-opiomelanocortin and cocaine- and amphetamine-regulated transcript (CART) [37]. Mesolimbic dopamine signaling impacts many aspects of reward responsiveness [4,38], including RVE, measured as greater effort (breakpoint) in a progressive ratio (PR) task for reinforcers (eg, food, drugs of abuse, and intracranial self-stimulation) [39-42]. Manipulation of leptin receptor function in the VTA supports leptin's role in reward valuation. In a PR task for food reward, breakpoint was increased by knockdown of leptin receptor expression in the midbrain, including the VTA, but not the hypothalamus [43] and directly in the VTA, but not the substantia nigra [44].

Leptin activation of pro-opiomelanocortin/CART neurons decreases food intake in ad-lib meals across species, including humans [45]. In contrast, NPY/AgRP potently stimulate increased food intake [37]. Thus, when an organism loses adipose tissue (a state marked by WS), leptin levels decrease, activation of pro-opiomelanocortin/CART neurons decreases, and NPY/AgRP neurons remain active and increase ad-lib intake to return the organism to a state of energy balance [37]. Leptin infusions in the Arc [46] decrease ad-lib food intake in rats, and selective deletion of leptin receptors in pro-opiomelanocortin and AgRP neurons increased meal size in mice [47]. Thus, lower leptin levels contribute to diminished responsiveness to satiating signals during food intake. However, the clear causal effects of acute leptin administration in animal models may not reflect the physiological role of leptin in humans, given the noted within-day stability of both WS and circulating leptin levels. That is, an organism cannot lose and gain sufficient white adipose tissue from one meal to the next or within one meal to account for meal initiation or termination via physiological changes in leptin levels. Moreover, our previous work supported significant associations between greater WS and both lower leptin levels and a higher breakpoint on a PR task, and it also found a small negative association between leptin levels and breakpoint [23], further supporting a potential intermediary role for GLP-1.

Peripheral GLP-1 stimulates the vagus nerve, causing activation of the nucleus of the solitary tract (NTS), where central GLP-1 preproglucagon neurons are located [48]. Similar to the effect of leptin levels on GLP-1 release in the periphery, central leptin administration enhances GLP-1 release from preproglucagon neurons of the NTS [49,50]. GLP-1 neurons of the NTS project to multiple brain regions, including the VTA and NAc, where GLP-1 influences RVE [26,31,50-52], as well as to the Arc, paraventricular nucleus of the hypothalamus, and hindbrain, where it contributes to reward satiation [31,52]. In rats, 50% of VTA dopamine neurons express GLP-1 receptors [51], 30% of GLP-1 neurons in the NTS project to the VTA [53], and 40% project to the NAc [26,53]. This positions GLP-1 as a prime candidate for examining how *acute* changes in food intake influence reward pathways in the brain. Infusion of the potent GLP-1 agonist Exendin 4 in the VTA and NAc reduced breakpoint on a food PR task [54], and peripheral administration of a GLP-1 receptor antagonist blunted gastrointestinal nutrient-induced suppression of breakpoint on a food PR task [28]. Exendin 4 diminished conditioned place preference for cocaine [55], implicating GLP-1 signaling in reward responsiveness to a nonfood, noncaloric reinforcer. In healthy humans, meal-induced increases in GLP-1 levels reduced willingness to work for food rewards [56]. Thus, similar to leptin, GLP-1 appears to reduce RVE; however, work in humans has not clearly dissociated the effect of GLP-1 on reward valuation from its clear impact on reward satiation.

Similar to leptin, GLP-1 agonist treatment activates pro-opiomelanocortin and CART neurons [57], and peripheral or central GLP-1 administration suppresses ad-lib food intake and meal size in rodents [58-60]. In humans, peripheral GLP-1

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infusion increased satiation and decreased food intake [61], and a meal pattern that increased GLP-1 response was associated with a 10% reduction in food intake during a subsequent ad-lib meal [56]. Moreover, since we initiated data collection to test our model, a plethora of research has emerged demonstrating the effects of GLP-1 agonists on weight via changes in food intake [25,62], and peripherally administered GLP-1 agonists cross the blood-brain barrier where they exert central effects on ingestive behaviors [63].

To summarize, animal-based studies show that leptin and GLP-1 reduce RVE through inhibitory effects in the mesolimbic dopamine pathway and increase reward satiation through a combination of inhibitory and excitatory actions in the Arc. We predicted that lower leptin levels would contribute to blunted postprandial GLP-1 release, which in turn would contribute to both increased RVE and decreased reward satiation. These behavioral consequences increase weight gain and increase the risk of experiencing large, out-of-control binge-eating episodes. We predicted that increased reward valuation would be associated with, and predict, increased frequency of LOC over eating, while decreased reward satiation would be associated with, and predict, consuming unusually large amounts of food.

Although no previous study has examined posited associations dimensionally and prospectively in humans, eating disorders characterized by binge-eating episodes are associated with lower leptin levels [23,64]; reduced GLP-1 response [65,66]; increased RVE, as measured by breakpoint on PR tasks [23,67-70]; and decreased satiation via greater food intake in ad-lib meals [71-77] compared to controls. Our laboratory was able to demonstrate hypothesized differences between women with BN and noneating disorder controls on each of these factors [23,66,78] and extended evidence of blunted GLP-1 response [66] and decreased satiation [78] in women with BN compared to those with purging disorder, which is a condition characterized by purging in the absence of binge-eating episodes [5]. This last finding addresses model specificity to eating disorders characterized by binge eating defined by LOC while eating an unusually large amount of food [5]. Finally, our cross-sectional analyses found that leptin levels statistically mediated the association between WS and reported duration of illness in BN-S [24].

Aims

Our funded project included the following aims. Aim 1 was to test concurrent associations among WS, physiological factors (leptin concentrations and postprandial GLP-1 response), behavioral indicators of RV-E (breakpoint on PR tasks) and reward satiation (ad-lib test meal intake), self-report of these core constructs, and binge-eating severity in BN-S. Aim 2 was to test prospective associations to determine whether WS predicts BN-S maintenance in longitudinal models and whether posited mediators also predict BN-S maintenance. Aim 3 was to determine whether associations between WS and BN-S severity and maintenance are mediated by alterations in leptin levels, GLP-1 response, RVE, and reward satiation.

Hypotheses

For examining BN-S severity using cross-sectional data, we hypothesized that greater WS would be associated with lower leptin levels, and lower leptin levels would be associated with lower postprandial GLP-1 response. We hypothesized that lower postprandial GLP-1 response would be associated with greater reward valuation and lower reward satiation. We predicted that greater reward valuation would be associated with a higher frequency of LOC over eating. We predicted that lower reward satiation would be associated with larger eating episode sizes, extending from eating episodes that were not large in control participants to objectively large binge-eating episodes in participants with BN-S across the full severity range (“eating/binge-eating episode size”). We also predicted a significant indirect pathway from WS to LOC frequency via leptin levels, GLP-1 response, and reward valuation. We predicted a significant indirect pathway from WS to eating/binge-eating episode size via leptin levels, GLP-1 response, and reward satiation. If supported, findings would demonstrate that biological concomitants of WS explain differences in the severity of binge eating via alterations in reward valuation and reward satiation.

For examining BN-S maintenance using longitudinal data, we hypothesized prospective associations in which greater WS would prospectively predict lower leptin levels, which would be associated with lower postprandial GLP-1 response. We hypothesized that lower postprandial GLP-1 response would be associated with greater reward valuation and lower reward satiation. We predicted that greater reward valuation would prospectively predict a higher frequency of LOC over eating. We also predicted that lower reward satiation would prospectively predict larger eating episode sizes.

To examine the mediation of the association between WS and BN-S severity and maintenance via biobehavioral alterations, we predicted that reward valuation and reward satiation would mediate associations between WS and changes in LOC frequency and eating/binge-eating episode size. If supported, findings would translate findings from animal models in neuroscience to clinical outcomes in humans and identify GLP-1 as a potential target in future treatment studies of eating disorders characterized by binge eating, including BN-S.

Methods

Protocol

All data and sample collections, as well as assays, were conducted in a clinical research laboratory at Florida State University (FSU). Figure 1 presents an overview of study visits for participants enrolled before and after the onset of the COVID-19 pandemic.

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Figure 1. Study protocol for participants enrolled before (left) and after (right) the onset of the COVID-19 pandemic. GLP-1: glucagon-like peptide 1; PR: progressive ratio.

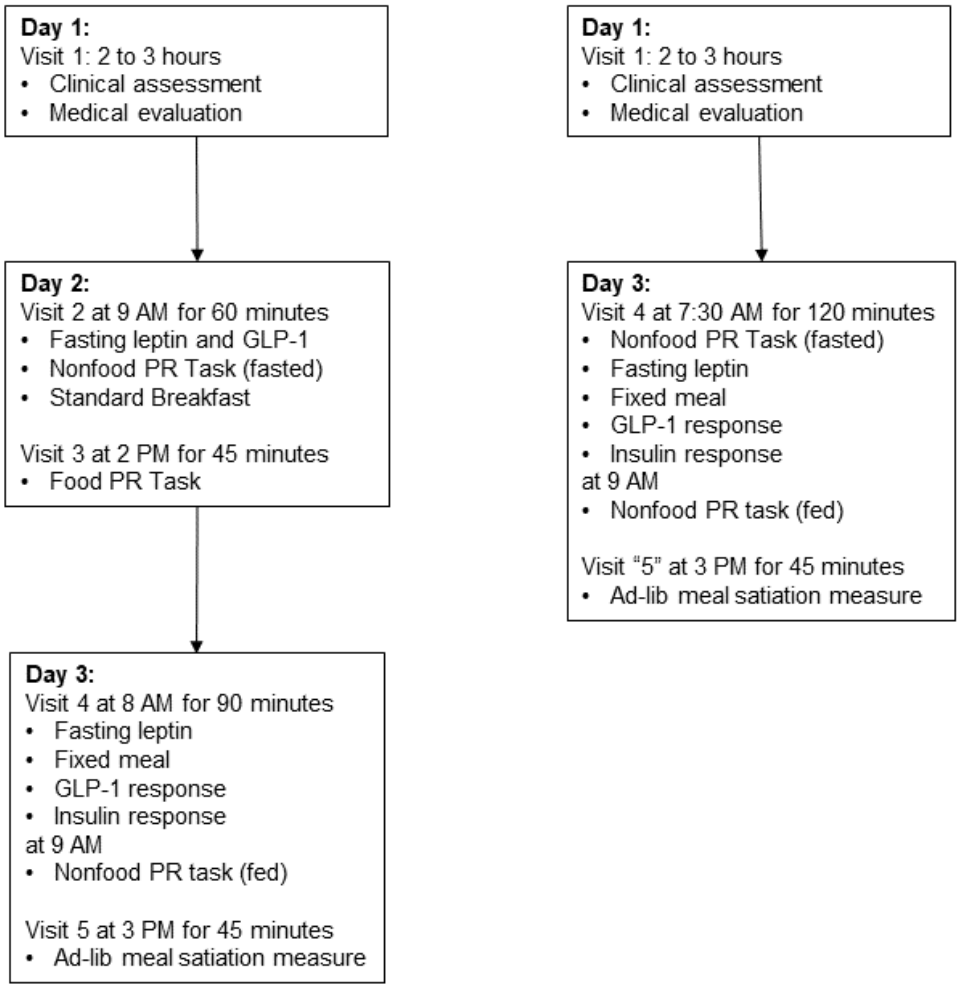

Day 1 or Visit 1: Psychological and Medical Evaluation

At baseline, all participants completed in-person structured clinical interviews with clinical doctoral students and questionnaires on a laboratory computer (Measures section); a pregnancy test; an objective assessment of height, weight, percentage of body fat, and vital signs; and a medical screening. At baseline, participants also played Angry Birds (Rovio Entertainment) for 2 minutes, tasted M&M's (Mars, Inc) and frozen yogurt, and consumed the fixed meal used in visit 4 to ensure the ability to follow instructions in subsequent visits. After the onset of the COVID-19 pandemic, remote follow-up clinical assessments were offered via a Zoom (Zoom Communications) link, which complies with the Health Insurance Portability and Accountability Act (HIPAA), for interviews and a secure web-based link for questionnaires.

Days 2 and 3 Visits

The original protocol included 2 visits on day 2 at 9 AM (visit 2) and 2 PM (visit 3) and day 3 at 8 AM (visit 4) and 3 PM (visit 5). Start times were adjusted by up to 1 hour before or after indicated times, and any adjustment was held constant across a participant's visit. Participants were asked to abstain from eating or drinking anything except water and from purging or exercising after 11 PM before and between visits on both days. Participants were required to leave personal belongings, including mobile phones, books, and other items, in a bin outside the testing rooms. At the beginning of the morning visits, height, weight, body fat percentage, and vital signs were objectively measured, and a screening confirmed compliance with instructions and captured the past week's eating patterns and eating disorder symptoms. Task instructions were presented in print and via audio recording. We used digital video monitoring to detect technical problems and participant noncompliance during behavioral tasks. The revised protocol eliminated the day 2 visit but retained visit 2 tasks (Visit 2: Leptin, GLP-1, RVE for a Nonfood Reinforcer in Fasted State state).

Visit 2: Leptin, GLP-1, and RVE for a Nonfood Reinforcer in Fasted State

Participants had 5 ml of blood drawn by a registered nurse and completed momentary assessments before and after a PR task to play Angry Birds [79]. Briefly, participants were instructed that they could earn 1 minute of playtime in Angry Birds by pressing the space bar; the task consisted of up to 10 trials for up to 10 minutes of playtime, with the number of required presses increasing across trials (50 presses for trial 1, 250 presses for trial 2, 450 presses for trial 3, and so on up to 1850 presses

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for trial 10). Participants were instructed that they should continue for as long as they wanted to play the game; they could stop at any time, and there were no right or wrong answers. When participants reached the criterion for a trial, a window opened, and they could play the game for 1 minute. After 1 minute, the screen automatically closed, and the participants were returned to the PR task, where they could work to gain access to continue the game. RVE was operationalized as a breakpoint, defined as the number of key presses in the last completed trial [80]. At 10 AM, participants consumed a standardized breakfast (300 kcal of yogurt parfait and juice) [23].

Visit 3: RVE for a Food Reinforcer

Participants completed momentary ratings before and after a PR task for M&M's [23], using the same design, instructions, and PR schedule as the nonfood task, to earn 10 M&M's per trial, with the potential to earn up to 100 M&M's over 10 trials. When participants reached the criterion for a trial, 10 M&M's dropped into a cup, and they were instructed to consume all M&M's before continuing to work for additional M&M's. The revised protocol eliminated the food PR task and associated momentary ratings.

Visit 4: GLP-1 Response to a Fixed Meal and RVE for a Nonfood Reinforcer in Fed State

A registered nurse placed an indwelling catheter into the participant's arm and allowed the participant to rest for 5 minutes. Participants completed momentary ratings before the nurse drew a fasting blood sample (5 ml) at –5 minutes for leptin, GLP-1, and insulin. Then, participants consumed a fixed liquid meal (Ensure Plus, Abbott Nutrition; 900 kcal in 660 g of fluid: 30% fat, 15% protein, and 55% carbohydrate) from –5 to 0 minutes. To capture GLP-1 and insulin responses to the fixed meal, 2 ml blood samples were drawn at +5, +15, and +30 minutes. Momentary ratings were completed immediately before each blood draw. After the last blood draw, participants had their intravenous catheter removed, rested for 5 minutes, and completed momentary ratings before and after the nonfood PR task (fed state). In the revised protocol, the fasted nonfood PR task and associated momentary ratings were completed before the first fasting blood draw, such that blood samples were drawn shortly after, rather than before, the fasted nonfood PR task.

Breakpoint on the nonfood PR task demonstrated excellent test-retest reliability (intraclass correlation [ICC]=0.91; 95% CI 0.80-0.96) over 2 weeks and convergent validity with the food PR task (r=0.51; P<.001) [79]. Consistent with animal models, breakpoint was lower in fed compared to fasted states across tasks (B=321.01, SE 552.40; P<.001). Finally, the nonfood task demonstrated discriminant validity from the measurement of satiation [79].

Visit 5: Ad-Lib Meal Assessment of Reward Satiation

Participants completed momentary ratings immediately before and after an ad-lib meal comprising 1.5 quarts (1420 g) of vanilla frozen yogurt (1.5 kcal/g) served at an individual place setting. Participants were presented with instructions in print and audio recorded to eat until they felt full or satisfied. Yogurt was weighed twice both before and after the meal using a top-loading, self-calibrated electronic balance, and the total intake was calculated in grams and kilocalories [81].

Training and Interrater Reliability

PKK provided all training and supervision for structured clinical interviewers and held biweekly assessment meetings. Interrater reliability (IRR) was examined via independent coding of audio recordings from 127 (16.5%) out of 769 interviews, randomly selected from each interviewer's assessments annually.

Participants

Textbox 1 presents the inclusion and exclusion criteria. Local recruitment was conducted via advertisements on social media platforms (eg, Instagram; Meta Platforms, Inc), billboards, pamphlets distributed to clinics, posters, outreach to college-based student organizations for ethnic or racial minority groups and churches, and emails to students at local universities with a link to a web-based eligibility screening. We received permission to send the mass email to female students aged 18 to 35 years once per academic term for all terms in which we recruited new participants at FSU and for one of the terms at a local Historically Black College and University. The mass email was the most effective recruitment tool, yielding the largest response. All prospective participants underwent telephone screenings to assess potential eligibility. Full eligibility was determined during the in-person assessment at baseline. The NIMH Data Archive (NDA) collection includes data from all eligible participants (N=399) and a small number of participants (n=6, 1.5%) who were later determined not to meet full eligibility criteria (details present in the Data Availability section).

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Textbox 1. Eligibility criteria for participants.

Inclusion criteria

- Sex: female
- Age: 18 to 35 years
- BMI: 16 to 35 kg/m^2
- Free of psychotropic medications or stable dose of selective serotonin reuptake inhibitors for 8 weeks
- Free of alcohol, illicit drugs, and medications for 72 hours before reward valuation effort, reward satiation, and fixed meal tasks

Additional inclusion criteria for bulimia nervosa and related syndromes

- Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (*DSM-5*), binge episodes
  - ≥1,000 kcal within a 2-hour period and larger than what most people would eat in a similar context
  - Loss of control over eating during the episode
- More than 12 episodes of behavioral eating disorder symptoms (including binge, purging, and nonpurging behaviors) over the past 12 weeks
- Undue influence of weight or shape on self-evaluation, intense fear of gaining weight or becoming fat, or marked distress regarding binge eating
- *DSM-5* criteria for anorexia nervosa binge-purging, bulimia nervosa, binge eating disorder, or other specified feeding or eating disorder using the past 12 weeks as a measure of the past 3 months
- For current other specified feeding or eating disorder, score >16 on the Clinical Impairment Assessment; marked distress regarding binge eating; or impairment in one or more areas of life on the Structured Clinical Interview for DSM-5
- For atypical anorexia nervosa, BMI ≥18.5 to <19 kg/^{2} or >5% BMI reduction over a 1-month period

Exclusion criteria

- Medical condition or other treatment that could influence appetite, weight, or ability to participate
- Currently pregnant, nursing, or planning to become pregnant within the next year
- Planning to move >2 hours away from the laboratory within the next year
- Current blood, injection, or injury phobia

Additional exclusion criteria for noneating disorder controls

- Current eating disorder symptoms on the Eating Disorder Examination
- Current dietary restriction to lose weight on the Eating Disorder Examination (dietary restriction to prevent weight gain was permitted)
- History of any eating disorder symptoms on the Structured Clinical Interview for *DSM-5*
- Three-Factor Eating Questionnaire cognitive restraint subscale score ≥10
- Clinical Impairment Assessment score ≥16

To measure the severity of BN-S dimensionally from a state of health to disease, we included noneating disorder controls and participants with BN-S ranging from mild to severe. We deliberately recruited more participants with BN-S than controls to collect data appropriate for parametric analyses by minimizing variables with a modal value of 0. This strategy also prioritized the recruitment of participants with BN-S at baseline, as predictors of illness maintenance and the examination of GLP-1 dysfunction as a potential treatment target were most relevant for this group. Finally, this strategy reflected our previous research experience and the expectation that controls would demonstrate limited variance at baseline, when they were required to be free of eating pathology, and over the course of follow-up when the incidence of eating disorders would be rare. With reduced variability, a smaller number was expected to provide sufficiently narrow CIs on any secondary group-based analyses comparing controls to participants with BN-S.

Participants provided multiple and preferred methods of contact (phone calls, SMS text messages, and email). Participants also provided the name and contact information for at least 1 individual who would know how to reach them if the participant could not be contacted by their mobile number and gave permission for us to contact that individual if we lost contact. We used several strategies to enhance retention. First, we offered financial incentives to participants prorated by visit and a bonus for completing all visits as scheduled (details present in the Ethical Considerations section). Second, we provided written and verbal reminders and instructions for subsequent visits via calls, SMS text messages, and emails for 3 days and 1 day before visits and wake-up calls for morning visits. Third, we established clear participation policies: participants who missed 2 scheduled visits without prior notification were discontinued, and we limited rescheduled visits to 3 per sequence. Fourth, if ≥12 weeks passed between the day 1 interview and the final visit,

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we required confirmation of continued eligibility via reassessment. Finally, a 6-month follow-up could begin 4 to 8 months after baseline, a 12-month follow-up could begin ≥10 months after baseline, and 6-month participation was not required to complete a 12-month follow-up. Assessment dates are included in the NDA collection.

Measures

BMI, WS, and Body Fat Percentage

Current weight and height were measured each day using a digital scale and stadiometer to calculate BMI (kg/m^2). We observed stability in BMI across days (r>0.95; P<.001), with no significant changes between days 1 and 2 (Cohen d=0.09), 2 and 3 (Cohen d=–0.07), and 1 and 3 (Cohen d=–0.007). WS was calculated as a percentage of BMI loss from the highest previous BMI, using self-reported highest adult weight at current height to calculate the highest BMI. At 6- and 12-month follow-up visits, we again asked about the highest adult weight to capture possible changes over time. Body fat percentage was measured using bioelectrical impedance analysis (Tanita Corporation of America), which demonstrates high correlations (r=0.88 to 0.94) with dual x-ray absorptiometry scans [82], supporting its feasibility (lower cost) and safety (no radiation exposure) in longitudinal studies with larger samples. We measured duration at current weight, time since highest weight, and duration of highest weight via self-report. WS represents our exposure variable, and BMI and body fat percentage represent covariates.

Interviews

The *Eating Disorder Examination* (EDE) *17.0D* [83] was selected due to previous evidence of good discriminant validity [84-87], IRR (0.83 to 0.99) [88,89], and good internal consistency of the restraint and body image subscales (Cronbach α>0.70) [90]. The EDE provided 3D outcome variables of eating disorder severity and maintenance, each with high IRR in the current project determined through ICC: LOC frequency (ICC>0.99), size of largest eating/binge-eating episode (in kcal; ICC=0.82), and the Global Scale score (ICC>0.99). LOC frequency represented the total number of eating episodes during the previous 12 weeks during which participants did not feel in control of their eating, regardless of the amount of food consumed. The size of the largest eating/binge-eating episode was captured by asking participants to report the largest amount of food they had eaten during the previous 12 weeks and recording the types and amounts of food consumed within 2 hours and converting these to kilocalories as described previously [78,91]. The EDE also provided scores with high IRR for restraint (ICC>0.99); eating concern (ICC=0.98); weight (ICC=0.99) and shape concerns (ICC>0.99); and symptoms for algorithms to diagnose current *DSM-5* anorexia nervosa (AN), BN, and binge-eating disorder (BED) in combination with objectively measured BMI. EDE symptom frequencies and durations permitted differential diagnoses of other specified feeding or eating disorder (OSFED) proposed by Keel [92]. IRR for symptom frequency or severity (ICC) and associated diagnostic thresholds over 3 months (κ) were good: objective binge episode size (κ=0.71), objective binge episode and inappropriate compensatory behavior frequency (ICC=0.97 and κ=0.93; ICC=0.96 and κ=0.91, respectively), fear of gaining weight or becoming fat (ICC=0.99 and κ=0.91), behavior to prevent weight gain (ICC=0.96 and κ=0.96), weight misperception (ICC=0.98 and κ=0.95), self-evaluation unduly influenced by weight (ICC=0.87) or shape (ICC=0.89 and κ=0.90), characteristics associated with binge episodes (ICC=0.78 and κ=0.73), and marked distress regarding binge eating (ICC=0.91 and κ=0.91). Marked distress regarding binge eating on the EDE was 1 of the 3 indicators of clinical significance for OSFED. The EDE was administered at baseline and 6- and 12-month follow-up assessments.

The Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (SCID-5) [93] captured eating (lifetime) and related disorder diagnoses (lifetime and current). Previous work supported good IRR for SCID diagnoses, with κ=0.92 for major depressive disorder, κ=0.75 for dysthymic disorder, κ=0.81 for any substance use disorder, κ=0.85 for panic disorder, κ=0.91 for social phobia, κ=0.73 for specific phobia, κ=1.00 for obsessive-compulsive disorder, and κ=0.90 for posttraumatic stress disorder [94]. We confirmed the absence of lifetime eating disorder symptoms in noneating disorder controls by ignoring skip rules [95]. The OSFED addendum provided a second indicator of clinical significance. The overview covered current and past treatment, including medication use, to confirm eligibility. At follow-up, we evaluated but did not exclude based on the use, type, dose, and duration of medication, and information may be included as covariates. Follow-up assessments focused on the period since the previous interview (eg, the past 6 months) to reduce participant burden. Current depressive and substance use disorders are covariates.

Self-Reported Questionnaires

C*linical Impairment Assessment* [96] established impairment and distress specifically linked to eating disorder symptoms in the domains of personal, social, and cognitive function. Previous work supported high internal consistency (>0.90), test-retest reliability (0.86), and concurrent and discriminant validity [96,97]. A score ≥16 was a third indicator of clinical significance for OSFED [96].

The *Three-Factor Eating Questionnaire* [98] comprises scales for cognitive restraint, which has successfully differentiated dieters from nondieters for our study's threshold for determining eligibility of controls, and disinhibition and hunger, which distinguish between purging women based on binge episode size [89,91]. Previous work supported good 1-month test-retest reliabilities for cognitive restraint, disinhibition, and hunger subscales of >0.90, 0.80, and 0.83, and internal reliabilities of >0.90, 0.91, and 0.85, respectively [98].

The *Visual Analog Scales* (VAS) assessed momentary states by presenting a single item on each page of a booklet with a 100-mm horizontal line anchored from "none or not at all" to "extreme or extremely." These provided self-reported levels of reward valuation and reward satiation during behavioral tasks. Participants marked the line to record how they felt "Right Now," regarding hunger, fullness, satiation, how much they wanted M&M's and to play the game, how much they liked M&M's and the game, and how rewarding they found M&M's

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and gameplay, urge to binge, urge to vomit, nausea, stomach discomfort, sadness, anxiety, tension, and preoccupation with weight and shape. VAS dimensional scores are sensitive to momentary changes associated with postprandial gut peptide responses to a fixed meal, and responses to an ad-lib and fixed meal differ significantly between controls and participants with eating disorders [78,99].

The following measures were included to supplement the clinical description of participants based on the measures described earlier for determining eligibility, exposure, and outcome variables; in response to comments provided during the grant review (Multimedia Appendix 1); and in anticipation of potential questions that may emerge during the review of manuscripts presenting tests of our model.

The *Body Shape Questionnaire* [84] measured feelings and attitudes about body shape and weight as a possible covariate, based on previous evidence of its high test-retest (0.88) [100], high internal reliability (>0.98) [100,101], and good discriminant and concurrent validity.

The *Positive and Negative Affect Scale* [102] assessed trait levels during visit 1 and state levels of positive and negative affect before and after biobehavioral assessments in visits 2 to 5 to examine these as possible covariates of RVE and reward satiation. The Positive and Negative Affect Scale is a widely used measure due to its high internal consistency, test-retest reliability, and construct validity [102,103].

The *Behavioral Inhibition and Behavioral Activation Scales* [104] and the *Sensitivity to Punishment and Sensitivity to Reward Questionnaire* [105] measure reward-related traits. The former measure has demonstrated high internal consistency (0.82) in previous work [104] and concurrent and discriminant validity with the latter measure in eating disorder samples [105].

Leptin, GLP-1, and Insulin Assessments

Enzyme-linked immunosorbent assays (MilliporeSigma) of plasma samples were used to measure leptin (EZHL-80SK) [106], active GLP-1 (EZGLPHS-35K [107], total GLP-1 [EZGLP1T-36K] [108]), and insulin (EZHI-14K) [109] levels. Insulin was added to the protocol in response to grant reviewers' (Multimedia Appendix 1) concerns about the narrow focus on GLP-1 and the evidence that insulin, similar to GLP-1, might influence reward valuation, in addition to its already defined role in satiation [63]. Blood samples were collected into prechilled K2 EDTA vacutainers, following protocol instructions, including the preparation of vacutainers with DPP-IV inhibitor (10 µl/ml of blood) for active GLP-1, before centrifuging at 2000 revolutions per minute for 15 minutes at 4 °C. Plasma was then pipetted into prechilled, aliquot tubes labeled by participant number, analyte, visit, date, and sample number, and immediately placed on ice and transferred to a –80 °C freezer. We extracted up to 4 aliquots, providing up to 3 backup samples for each analyte.

DLW supervised all assays and approved results without knowledge of the participant's clinical status. All participant samples were run in duplicate in 1 assay (eg, baseline leptin from visits 2 and 4) and batched to ensure a balanced representation of control and BN-S participants across assays. When results were outside the detection limits or the intra-assay coefficient of variation (CV) exceeded 10%, backup aliquots were run in subsequent assays to ensure reliable estimates. Preliminary analyses indicated low stability of fasting active GLP-1 levels from visit 2 to 4 (r_{191}=0.18, P=.01) at baseline, raising concerns about fasting active GLP-1 as a sole measure of individual differences in GLP-1 function across visits. We added assays of total GLP-1 in backup samples to the protocol, which had been proposed in our grant application in the section on potential pitfalls and solutions in response to grant reviewers' (Multimedia Appendix 1) concerns about measuring active GLP-1. Total GLP-1 demonstrated adequate stability for fasting concentrations from visit 2 to 4 (r_{193}=0.70; P<.001). The NDA collection includes both active and total GLP-1 values. For participants enrolled after the onset of the COVID-19 pandemic, all GLP-1 values represented total GLP-1 and came from visit 4. Importantly, multilevel model analyses demonstrate that visit 4 VAS fullness ratings were significantly predicted by changes in active GLP-1 (B=0.83, 95% CI 0.65-1.01; t_{734}=9.06; P<.001) and total GLP-1 (B=0.40, 95% CI 0.27-0.54; 2-tailed t_{708}=5.91; P<.001) values, with greater effect size for active GLP-1 level. Thus, both provide valid indicators of GLP-1 function, with total GLP-1 providing more stable, "trait"-like information and active GLP-1 value providing more sensitive, "state"-like information.

The kit user guides and information published on the MilliporeSigma (Merck Group) website and included in assay kits reported the following upper limits of interassay and intra-assay CVs, respectively: 6.2% and 4.6% for leptin [106], <15% and <10% for active GLP-1 [107], <12% and <5% for total GLP-1 [108], and 11.4% to 6.95% for insulin [109]. In our project, mean intraassay and interassay CVs, respectively, were 4.3% and 9% for leptin, 7.4% and 9.5% for active GLP-1, 2.9% and 10.3% for total GLP-1, and 3.9% and 8.9% for insulin. We observed comparable or better CVs compared to published estimates, except for the higher interassay CV for leptin. Date and assay (numbered consecutively) are included in the NDA collection so that future users can control for interassay variability.

Data Structure and Missing Data

NDA data are organized by measure and stored in long form. Variable names indicate visits via the "_#" naming convention. Regardless of when participants were enrolled, variable names retained their original designations. The "_2" suffix reflects variables collected before, during, and after the fasted nonfood RVE task. Similarly, data collected from the fixed meal assessment of GLP-1 and insulin responses are identified by the "_4" suffix, and data collected from the ad-lib meal assessment are identified by the "_5" suffix. Each visit has a "Notes" column to indicate protocol deviations that may impact data quality. In addition to attrition, participants skipping questions, experimenter error, and equipment failures contributed to missing values. Technical problems included M&M's jamming the dispenser and not dispensing the reward after participants reached the criterion (the apparatus was redesigned part way through the project to minimize this problem) and the computer program freezing. When a

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participant's effort for reward exceeds the planned ratio, data from the session are included in the data collection but will not be included in planned analyses. Refer to the study by Keel et al [79] for an example of main analyses, which excluded values from sessions with noted problems and sensitivity analyses, including all available data. The NDA collection includes all available data; several variables must be calculated (eg, breakpoint).

Data Analytic Plan

For concurrent tests of severity, we plan to use structural equation models (SEM) in MPlus (version 8; Muthén & Muthén) to obtain estimates of overall model fit; account for shared variance; and provide path estimates within the model, including tests of indirect effects using bias-corrected bootstrapped CIs with 10,000 samples to include all available data in the model from the 399 eligible participants enrolled in the study. This strategy includes running correlations between all variables in the model as a first step, followed by SEM with WS as the sole exogenous variable and the remaining variables as endogenous variables. Both RVE and reward satiation will be modeled as latent variables, with pathways from both behavioral tasks and self-reported states from VAS ratings. For prospective associations and temporal mediation predicting illness maintenance, we proposed cross-lagged SEM with bootstrapping methods for testing indirect effects [110]. Model fit will be evaluated with common fit indices, with the following thresholds for interpreting good fit: root mean square error of approximation, comparative fit index, and Tucker-Lewis Index ≥0.90; root mean square error of approximation value ≤0.05, 95% CI >0.00 to ≤0.08; and standardized root mean square residual ≤0.08 [111-116]. Coefficients and their 95% CIs will be used to evaluate the significance of hypothesized direct and indirect pathways, and only direct pathways that are in the predicted direction, with 95% CIs that do not include 0, will be interpreted as supporting the a priori hypotheses generated by our model.

Sensitivity analyses will evaluate the impact of adding covariates with pathways to each endogenous variable in the model on overall model fit and parameter estimates. Covariates include age, BMI, body fat percentage, enrollment before and after the onset of the COVID-19 pandemic, hormonal contraceptive use, selective serotonin reuptake inhibitors use, current depressive disorder diagnosis, and current substance use disorder diagnosis. Because sensitivity analyses involve nonnested models, we will evaluate whether there is a qualitative change in the adequacy of model fit, from inadequate to adequate or from adequate to good. When there is no qualitative change in model fit, lower values on the Akaike information criterion and Bayesian information criterion will be interpreted as evidence of improved fit.

Power Analyses

We conducted power analyses in R (R Foundation for Statistical Computing) with PowMedR for mediation as our least-powered analyses. Across the posited indirect effects (eg, GLP-1 mediates the association between WS and reward satiation), a sample size of n=195 provides 80% power with path coefficients ≥0.22 from the initial variable to the mediator and from the mediator to the outcome variable, while controlling for the initial variable. Analyses on multiple imputed datasets indicated 80% power with path coefficients ≥0.20 to test indirect effects. We aimed for longitudinal data from 250 participants to permit exploratory moderation analyses for potentially weaker effects at higher BMIs, where leptin levels might be high despite high WS and high food consumption [1].

Ethical Considerations

The FSU Institutional Review Board Human Subjects Committee reviewed and approved the study protocol and materials (HSC 2016.15338/STUDY00000353). Written informed consent was obtained from all study participants before their participation. All data have been deidentified and only a study-generated ID number and a globally unique identifier number in the NDA have been retained. For the original protocol, participants were paid US $75 for day 1, US $50 for day 2, US $100 for day 3, and a US $35 bonus for a total potential compensation of US $780 for baseline and 6- and 12-month follow-up visits. For the revised protocol, participants were paid US $75 for day 1, US $110 for day 3, and a US $15 bonus for a total of US $400 for baseline and 6-month follow-up.

Results

Overview

The project was funded as an investigator-initiated R01 in August 2016, and data collection began in November 2016. Data collection from participants was completed in April 2023, and assays of analytes were completed in June 2023. Information presented on recruitment and retention addresses the feasibility of our design and provides context on information reported on the reliability of measures in the current sample.

Timeline and Recruitment

We aimed to recruit 320 women over a 5-year period to provide clinical, biological, and behavioral data. We estimated that 250 (78.1%) out of 320 women would complete 6- and 12-month follow-up visits, including approximately 78% (200/256) with BN-S and 78% (50/64) control participants. By March 2020, we had recruited 301 eligible participants. Due to the COVID-19 pandemic, the laboratory closed that month for in-person assessments. To retain participants with baseline data who had not completed 12-month follow-up, institutional review board (IRB)–approved, NIMH-approved, and HIPAA-compliant remote clinical assessments were added to our protocol.

On February 19, 2021, we reopened the laboratory for in-person follow-up visits for those who had completed all baseline visits before laboratory closure, implementing IRB-approved safety precautions. The precautions included (1) a screening checklist for symptoms, potential COVID-19 exposure, and a temperature check completed with the participant outside the laboratory before admitting them into the laboratory; (2) allowing only 1 participant into the laboratory at a time; (3) reducing study staff to the minimum required to complete a visit; (4) following masking and social distancing guidelines; (5) sanitizing all surfaces before and after running each participant; and (6) continuing to allow participants to complete follow-up clinical assessments via remote means. The final precaution reflected

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evidence of minimal differences between in-person versus remote follow-up assessments conducted among those enrolled before the onset of the COVID-19 pandemic [117]. We adjusted pandemic-related precautions as needed, including periodically pausing in-person assessments in response to spikes in new variants and relaxing precautions with growing community immunity.

On October 8, 2021, we enrolled our first new participant since laboratory closure, supported by 2 no-cost extensions of our NIMH-funded grant and a US Department of Education Higher Education Emergency Relief Fund awarded to FSU. Before enrolling new participants, and with prior approval from the FSU IRB and the NIMH, we revised the protocol to reduce the number of in-person visits to conserve remaining funds and further minimize the risk of COVID-19 exposures. Changes were also informed by evidence of the reliability and the convergent and discriminant validity of our task for measuring RVE for a nonfood reward [79]. We completed data collection in April 2023. We experienced no known incidents of COVID-19 exposure in our laboratory during the project.

Retention

Figures 2 and 3 show retention across study visits and follow-up for participants enrolled before and after the onset of the COVID-19 pandemic, respectively. Among those 399 eligible, 321 (80.5%) had a current BN-S, 78 (19.5%) were noneating disorder controls. A total of 290 (72.7%) out of 399 women completed all baseline assessments, including 226 (70.4%) out of 321 with BN-S and 64 (82.1%) out of 78 controls (χ^2_1=4.3; *P*=.04; ϕ=0.10). Given the uncertainty surrounding the duration of the COVID-19 pandemic–related closures and concerns for participant safety, participants (91/399, 22.8%) without complete baseline assessments were considered ineligible to continue (n=83, 91% with BN-S and n=8, 9% controls). We estimate that the COVID-19 pandemic impacted 3.3% (13/399) participants' ability to complete baseline assessments, all of whom had BN-S. The mean time between days 1 and 2 was 17.7 (SD 15.1) days, between days 2 and 3 was 16.5 (SD 17.3) days, and between days 1 and 3 was 28.1 (SD 19.3) days. There was no significant difference between groups in days between study visits (*P* values ranged from .72 to .07, and effect sizes were small; Cohen *d*=–0.09 to 0.29).

Among the 290 women eligible for follow-up, 249 (85.9%) provided follow-up data, including 96 (33.1%) with 6-month, 123 (42.4%) with 6- and 12-month, and 30 (10.3%) with 12-month data. Groups did not differ in participation at 6-month (χ^2_1=3.5; *P*=.06; ϕ=0.11) or 12-month follow-up (χ^2_1=0.0; *P*=.95; ϕ==0.004). The mean time between baseline to 6-month follow-up was 6.0 (SD 2.2) months, 6- to 12-month follow-up was 8.5 (SD 7.8) months, and baseline to 12-month follow-up was 14.6 (SD 5.6) months and did not differ significantly between groups (*P* values ranged from .82 to .30, and effect sizes were small; Cohen *d*=–0.09 to 0.29).

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Figure 2. Participant flow through the study for participants recruited before the onset of the COVID-19 pandemic. At the 6-month follow-up, 2 additional participants with BN-S completed questionnaire assessments but did not complete interviews for study visit 1. Participants who completed all visits at baseline were recruited to participate at the 12-month follow-up, whether or not they had completed 6-month follow-up. BN-S: bulimia nervosa and related syndromes.

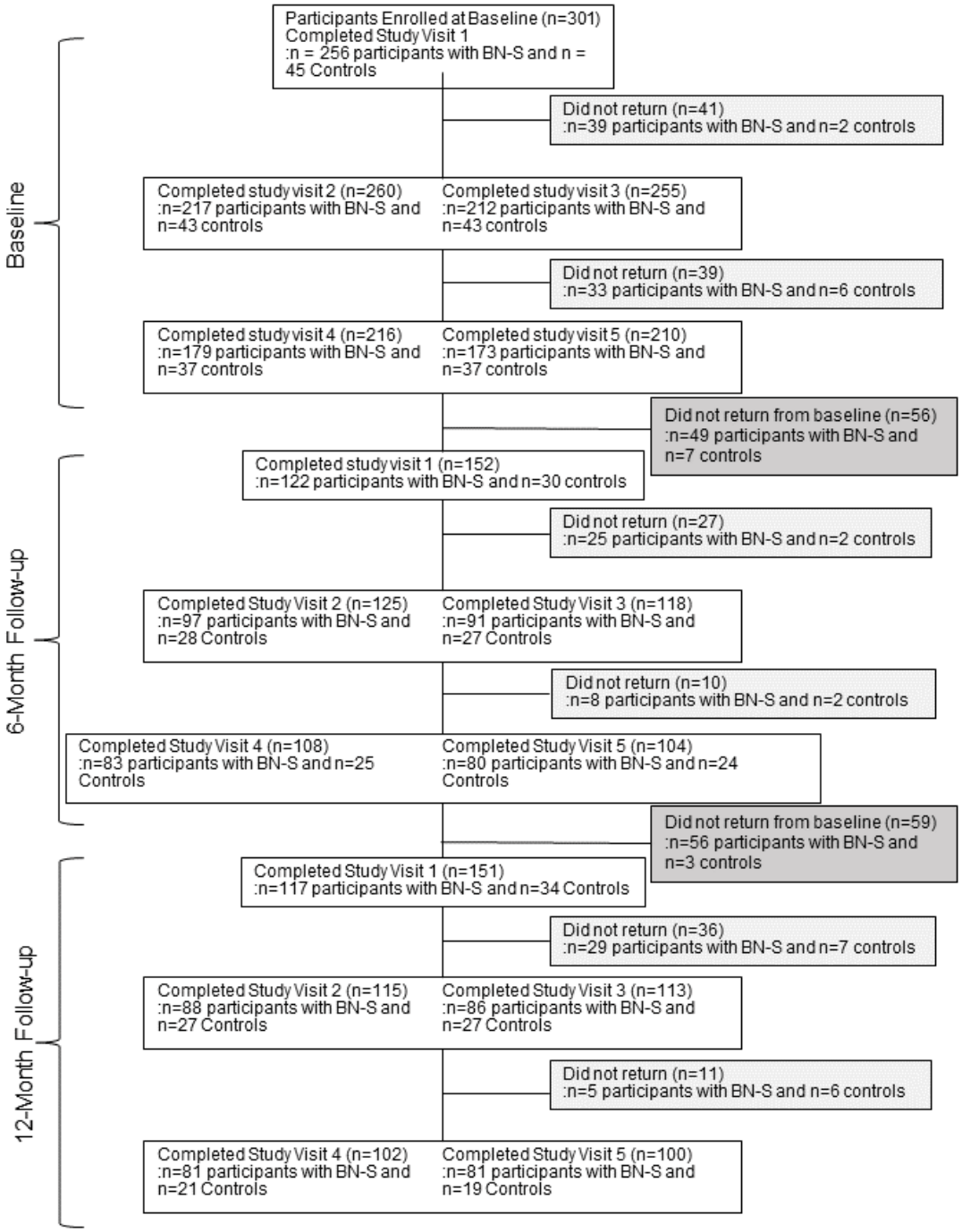

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Figure 3. Participant flow through the study for participants recruited after the onset of the COVID-19 pandemic. BN-S: bulimia nervosa and related syndromes.

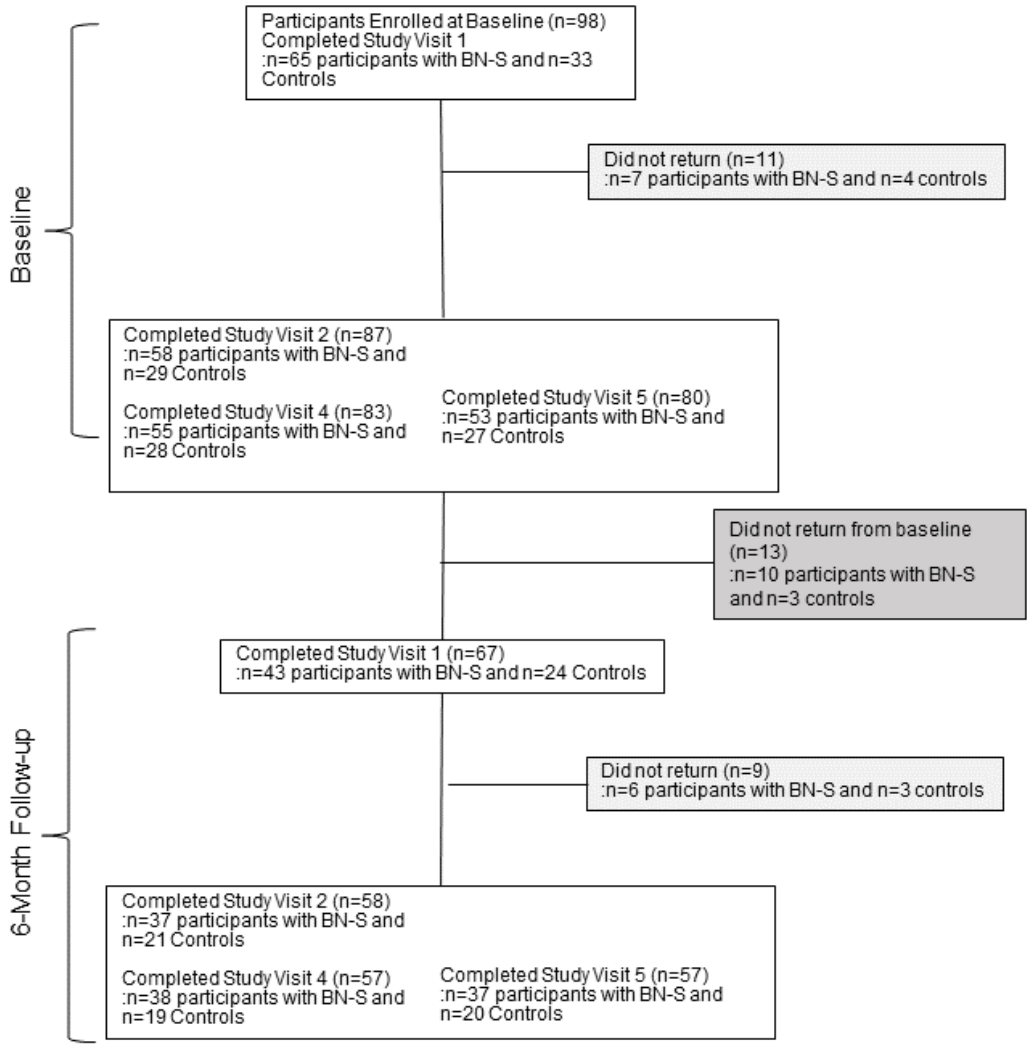

Sample Descriptors

Table 1 describes sample characteristics. Biological sex as female at birth was required for all participants (Textbox 1), and almost all endorsed being cisgender individuals. We did not assess sexual orientation. According to 2020 US Census data [118], the racial or ethnic composition of Leon County, Florida, was 0.4% American Indian or Alaska Native, 3.8% Asian, 32.1% Black or African American, 8.3% Hispanic or Latino, 0.1% Native Hawaiian or other Pacific Islander, 61% White (54.1% non-Hispanic and non-Latino), and 2.6% multiracial. Racial or ethnic composition of the sample differed from the county population (χ^2_5=91.9; P<.001; Cramer V=0.008), with lower participation among individuals identifying as Black or African American (χ^2_1=72.2; P<.001; ϕ=0.02) and greater participation among those identifying as Native Hawaiian or other Pacific Islander (χ^2_1=4.3; P=.04; ϕ=0.004) or multiracial (χ^2_1=6.7; P=.01; ϕ=0.005) relative to those identifying as White individuals. Furthermore, we observed greater participation among individuals identifying as Hispanic or Latinx compared to non-Hispanic or Latinx (χ^2_1=193.8; P<.001; ϕ=0.03).

There was no significant association between racial or ethnic identity and whether or not participants completed baseline visits (χ^2_5=2.1; P=.84 and χ^2_1=0.0; P=.99) and 6-month (χ^2_5=0.6; P=.99 and χ^2_1=1.3; P=.72) or 12-month (χ^2_5=1.6; P=.90 and χ^2_1=0.1; P=.79) follow-up (all effect sizes for all associations; η^2<0.01). Table 2 presents 6-month sample characteristics, and Table 3 presents 12-month sample characteristics.

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Table 1. Characteristics of the sample at baseline for all eligible participants (N=399).

Characteristic	Total, n (%)	Bulimic syndrome group (n=321), n (%)	Control group (n=78), n (%)
Female	399 (100)	321 (100)	78 (100)
Gender			
Woman	397 (99.5)	320 (99.7)	77 (98.7)
Nonbinary	1 (0.2)	0 (0)	1 (1.3)
Not reported	1 (0.2)	1 (0.3)	0 (0)
Ethnicity			
Hispanic or Latino	110 (27.6)	91 (28.3)	19 (24.4)
Not Hispanic or Latino	289 (72.4)	230 (71.7)	59 (75.6)
Race			
American Indian or Alaska Native	2 (0.5)	2 (0.6)	0 (0)
Asian	14 (3.5)	8 (2.5)	6 (7.7)
Black	47 (11.8)	36 (11.2)	11 (14.1)
Hawaiian or other Pacific Islander	2 (0.5)	2 (0.6)	0 (0)
Multiracial	23 (5.8)	20 (6.2)	3 (3.8)
White	311 (77.9)	253 (78.8)	58 (74.4)
Educational level			
Part college	346 (86.7)	284 (88.5)	62 (79.5)
Associate degree	10 (2.5)	6 (1.9)	4 (5.1)
Bachelor degree	10 (2.5)	6 (1.9)	4 (5.1)
Part graduate school	30 (7.5)	24 (7.5)	6 (7.7)
Graduate degree	3 (0.8)	1 (0.3)	2 (2.6)
Relationship status			
Married or having a partner	33 (8.3)	25 (7.8)	8 (10.2)
Divorced or annulled	1 (0.3)	0 (0)	1 (1.3)
Single	241 (60.4)	198 (61.7)	43 (55.1)
In relationship	122 (30.6)	96 (29.9)	26 (33.3)
Other	2 (0.5)	2 (0.6)	0 (0)
Age (y), mean (SD; range)	20.3 (2.6; 18-35)	20.2 (2.5; 18-35)	20.4 (2.5; 18-34)
BMI (kg/m^2), mean (SD; range)	24.6 (4.2; 16.6-35.6)	25.2 (4.2; 16.9-35.6)	22.2 (3.2; 16.6-33.2)
Percentage of body fat, mean (SD; range)	30 (8.2; 6.1-48.7)	31.1 (8; 11.4-48.7)	25.5 (7.4; 6.1-45.8)
Highest BMI (kg/m^2), mean (SD; range)	26.2 (4.8; 17-45.0)	27.0 (4.8; 17.5-45.0)	23.1 (3.6; 17-37.9)
Highest BMI duration (d), mean (SD; range)	202 (276; 0-1825)	189 (256; 0-1460)	253 (340; 2-1825)
Days since highest BMI, mean (SD; range)	461 (642; 0-5110)	467 (649; 0-5110)	434 (614; 0-3650)
Current BMI duration (d), mean (SD; range)	237 (421; 1-5475)	191 (392; 1-5475)	429 (485; 1-2555)

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Table 2. Characteristics of the sample at 6-month follow-up (n=221).

Characteristic	Total, n (%)	Bulimic syndrome group (n=167), n (%)	Control group (n=54), n (%)
Female	221 (100)	167 (100)	54 (100)
Gender			
Woman	221 (100)	167 (100)	54 (100)
Ethnicity			
Hispanic or Latino	64 (29)	50 (29.9)	14 (25.9)
Not Hispanic or Latino	157 (71)	117 (70.1)	40 (74.1)
Race			
American Indian or Alaska Native	1 (0.4)	1 (0.6)	0 (0)
Asian	9 (4.1)	5 (3)	4 (7.4)
Black	27 (12.2)	19 (11.4)	8 (14.8)
Hawaiian or other Pacific Islander	1 (0.4)	1 (0.6)	0 (0)
Multiracial	12 (5.4)	10 (6)	2 (3.7)
White	171 (77.4)	131 (78.4)	40 (74.1)
Educational level			
Part college	170 (76.9)	131 (78.4)	39 (72.2)
Associate degree	8 (3.6)	4 (2.4)	4 (7.4)
Bachelor degree	10 (4.5)	6 (3.6)	4 (7.4)
Part graduate school	19 (8.6)	16 (9.6)	3 (5.6)
Graduate degree	2 (0.9)	0 (0)	2 (3.7)
Relationship status			
Married or having a partner	15 (6.8)	11 (6.6)	4 (7.4)
Divorced or annulled	0 (0)	0 (0)	0 (0)
Single	136 (61.5)	103 (61.7)	33 (61.1)
In relationship	63 (28.5)	48 (28.7)	15 (27.8)
Other	2 (0.9)	2 (1.2)	0 (0)
Age (y), mean (SD; range)	20.9 (2.8; 18-35)	20.9 (2.8; 18-33)	20.9 (2.9; 18-35)
BMI (kg/m^2), mean (SD; range)	24.7 (4.4; 17.4-37.7)	25.4 (4.5; 17.4-37.7)	22.5 (3.3; 17.5-35.0)
Percentage of body fat, mean (SD; range)	30.1 (8.0; 11.3-48.6)	31.1 (8.2; 11.3-48.6)	27.2 (6.7; 17.7-45.9)
Highest BMI (kg/m^2), mean (SD; range)	26.4 (5.1; 18-45.2)	27.4 (5.2; 18-45.2)	23.1 (2.9; 18.2-31.3)
Highest BMI duration (d), mean (SD; range)	196 (294; 1-1825)	162 (212; 1-1095)	302 (452; 1-1825)
Days since highest BMI, mean (SD; range)	460 (683; 0-4380)	513 (739; 0-4380)	294 (431; 0-1460)
Current BMI duration (d), mean (SD; range)	192 (298; 1-1825)	142 (190; 1-730)	351 (472; 7-1825)

Participants' mean age did not differ between groups, and BMI was significantly higher in BN-S than control participants ($t_{141.92}$=6.73; P<.001; Cohen d=0.85). Neither age nor BMI was associated with completing baseline or 6-month follow-up (P values ranged from .76 to .19, and Cohen d ranged from –0.13 to 0.03). However, older age (mean 20.6, SD 3.1 vs mean 20.0, SD 2.2 years; $t_{250.04}$=2.12; P=.04; Cohen d=0.24) and lower BMI (mean 23.9, SD 3.9 vs mean 25.0, SD 4.4; $t_{350.24}$=–2.53; P=.01; Cohen d=–0.25) at baseline predicted 12-month follow-up participation. WS was significantly greater in the BN-S group compared to control participants ($t_{157.57}$=4.08; P<.001; Cohen d=0.52) and was not significantly associated with completing baseline or 6- or 12-month follow-up (P values ranged from .31 to .93, and Cohen d ranged from –0.11 to 0.01).

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Table 3. Characteristics of the sample at 12-month follow-up (n=153).

Characteristic	Total, n (%)	Bulimic syndrome group (n=119), n (%)	Control group (n=34), n (%)
Female	153 (100)	119 (100)	34 (100)
Gender			
Woman	153 (100)	119 (100)	34 (100)
Ethnicity			
Hispanic or Latino	41 (26.8)	35 (29.4)	6 (17.6)
Not Hispanic or Latino	112 (73.2)	84 (70.6)	28 (82.4)
Race			
American Indian or Alaska Native	1 (0.7)	1 (0.8)	0 (0)
Asian	6 (3.9)	3 (2.5)	3 (8.8)
Black	16 (10.5)	11 (9.2)	5 (14.7)
Hawaiian or other Pacific Islander	1 (0.6)	1 (0.8)	0 (0)
Multiracial	11 (7.2)	8 (6.7)	3 (8.8)
White	118 (77.1)	95 (79.8)	23 (67.6)
Educational level			
Part college	110 (71.9)	88 (73.9)	22 (64.7)
Associate degree	5 (3.3)	4 (3.4)	1 (2.9)
Bachelor degree	12 (7.8)	8 (6.7)	4 (11.8)
Part graduate school	15 (9.8)	13 (10.9)	2 (5.9)
Graduate degree	5 (3.3)	2 (1.7)	3 (8.8)
Relationship status			
Married or having a partner	14 (9.2)	13 (10.9)	1 (2.9)
Divorced or annulled	0 (0)	0 (0)	0 (0)
Single	76 (49.7)	60 (50.4)	16 (47)
In relationship	57 (37.2)	42 (35.3)	15 (44.1)
Other	0 (0)	0 (0)	0 (0)
Age (y), mean (SD; range)	21.9 (3.0; 19-35)	21.8 (2.9; 19-34)	22.5 (3.4; 20-35)
BMI (kg/m^2), mean (SD; range)	24.4 (4.4; 16.7-39.8)	25.0 (4.6; 16.7-39.8)	22.5 (3.1; 17.6-33.4)
Percentage of body fat, mean (SD; range)	28.3 (7.9; 11-50.9)	29.3 (8.1; 11.0-50.9)	24.9 (6.1; 15.2-42.5)
Highest BMI (kg/m^2), mean (SD; range)	25.9 (4.7; 17.7-45.0)	26.7 (4.8; 18.9-45)	23.0 (2.8; 17.7-32.6)
Highest BMI duration (d), mean (SD; range)	216 (363; 1-3650)	177 (196; 1-1095)	375 (702; 14-3650)
Days since highest BMI, mean (SD; range)	490 (648; 0-2555)	511 (649; 0-2555)	413 (651; 0-2190)
Current BMI duration (d), mean (SD; range)	230 (412; 0-3650)	171 (222; 0-1095)	467 (772; 7-3650)

Eating Disorder and Psychiatric Diagnoses and Treatment

Table 4 presents *DSM-5* eating disorder and other psychiatric diagnoses and features at baseline. BN was the most common diagnosis, followed by OSFED-BN of low frequency or duration, with few participants meeting the criteria for current AN, BED, or their related OSFED. Diagnosis was significantly associated with completing baseline visits (χ^2_3=8.9; P=.03; ϕ=0.10), occurring in 7 (88%) out of 8 participants with AN binge-purging, 118 (77.1%) out of 153 participants with BN, 2 (50%) out of 4 participants with BED, and 99 (63.5%) out of 156 participants with OSFED diagnoses.

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Table 4. Lifetime and current eating disorder and other psychiatric diagnoses and treatment at baseline (N=399).

	Total, n (%)	Bulimic syndrome group (n=321), n (%)	Control group (n=78), n (%)
EDE[a] current diagnosis			
AN[b] binge-purging	—[c]	8 (2.5)	—
BN[d]	—	153 (47.7)	—
BED[e]	—	4 (1.2)	—
OSFED[f]	—	156 (48.6)	—
OSFED subtypes[g]			
Atypical AN[h]			
Broad	—	11 (3.4)	—
Narrow	—	9 (2.8)	—
BN low frequency or duration			
Broad	—	136 (42.3)	—
Narrow	—	118 (36.8)	—
BED low frequency or duration			
Broad	—	4 (1.2)	—
Narrow	—	3 (0.9)	—
Other or unspecified			
Broad	—	5 (1.6)	—
Narrow	—	26 (8.1)	—
SCID-5[i] lifetime ED[j] diagnosis			
AN (κ=0.93)	—	42 (13.1)	—
BN (κ=0.92)	—	230 (71.7)	—
BED (κ=0.88)	—	62 (19.3)	—
OSFED[k] (κ=0.92)	—	159 (49.5)	—
Atypical AN	—	14 (4.4)	—
BN low frequency or duration	—	124 (38.6)	—
BED low frequency or duration	—	11 (3.4)	—
PD[l]	—	2 (0.6)	—
NES[m]	—	0 (0)	—
Other or unspecified	—	8 (2.5)	—
SCID-5 diagnoses (κ)			
Major depressive disorder			
Lifetime (κ=0.85)	183 (45.9)	175 (54.5)	8 (10)
Current (κ=0.74)	46 (11.5)	46 (14.3)	0 (0)
Persistent depressive disorder			
Lifetime (κ=0.87)	118 (29.6)	113 (35.2)	5 (6)
Current (κ=0.94)	73 (18.3)	71 (22.1)	2 (3)
Any mood disorder			
Lifetime (κ=0.98)	270 (67.7)	256 (79.8)	14 (18)
Current (κ=0.95)	121 (30.3)	118 (36.8)	3 (4)

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	Total, n (%)	Bulimic syndrome group (n=321), n (%)	Control group (n=78), n (%)
Alcohol use disorder			
Lifetime (κ=0.92)	149 (37.3)	139 (43.3)	10 (13)
Current (κ=0.81)	96 (24.1)	90 (28)	6 (8)
Cannabis use disorder			
Lifetime (κ=0.90)	113 (28.3)	107 (33.3)	6 (8)
Current (κ=1.00)	74 (18.5)	71 (22.1)	3 (4)
Any substance use disorder			
Lifetime (κ=0.90)	197 (49.4)	183 (57)	14 (18)
Current (κ=0.83)	136 (34.1)	128 (39.9)	8 (10)
Any anxiety disorder			
Lifetime (κ=0.94)	213 (53.4)	203 (63.2)	10 (13)
Current (κ=0.97)	183 (45.9)	178 (55.5)	5 (6)
Obsessive-compulsive disorder			
Lifetime (κ=0.82)	55 (13.8)	53 (16.5)	2 (3)
Current (κ=0.85)	46 (11.5)	45 (14)	1 (1)
Posttraumatic stress disorder			
Lifetime (κ=0.91)	106 (26.6)	104 (32.4)	2 (3)
Current (κ=0.68)	49 (12.3)	49 (15.3)	0 (0)
Any trauma-related disorder			
Lifetime (κ=0.98)	115 (28.8)	111 (34.6)	4 (5)
Current (κ=0.73)	63 (15.8)	62 (19.3)	1 (1)
Suicide-related variables			
Lifetime ideation	177 (44.4)	167 (52)	10 (13)
Past week ideation	19 (4.8)	19 (5.9)	0 (0)
Lifetime suicide attempt	43 (10.8)	42 (13.1)	1 (1)
Psychological treatment			
Inpatient: lifetime	23 (5.8)	21 (6.5)	2 (3)
Any treatment: lifetime	226 (56.6)	200 (62.3)	26 (33)
Current outpatient	64 (16)	57 (17.8)	7 (9)
Current medications			
Stable SSRI[n] over 8 wk	38 (9.5)	34 (10.6)	4 (5)

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	Total, n (%)	Bulimic syndrome group (n=321), n (%)	Control group (n=78), n (%)
Hormonal contraceptive	183 (45.9)	146 (45.5)	37 (47)

[a]EDE: Eating Disorder Examination.

[b]AN: anorexia nervosa.

[c]Not applicable.

[d]BN: bulimia nervosa.

[e]BED: binge-eating disorder.

[f]OSFED: other specified feeding or eating disorder.

[g]Guidelines presented by Keel [92] were followed for differential diagnosis of OSFED. There were no cases of current purging disorder due to the requirement of recurrent objectively large binge episodes as an inclusion criterion for participants with BN and related syndromes. In addition, 2 sets of criteria were used. Broad criteria were based on the key features that distinguish among the OSFEDs, such as significant weight loss of atypical AN, the presence of binge eating and inappropriate compensatory behaviors for BN of subthreshold duration or frequency, and the presence of binge eating and absence of recurrent inappropriate compensatory behavior for BED of subthreshold duration or frequency. Narrow criteria required the associated cognitive and affective features for each OSFED diagnosis so that narrow criteria for atypical AN indicated that all criteria for AN were met except for low weight, all criteria for BN were met except for duration or frequency of behavioral symptoms, and all criteria for BED were met except for duration or frequency of binge-eating episodes.

[h]Significant weight loss was defined as >5% reduction in BMI within 30 days or BMI <19 kg/m^2.

[i]SCID-5: Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

[j]ED: eating disorder.

[k]Lifetime OSFED diagnoses were based on clinical interviewer assessments in the SCID-5. Given the possibility of meeting a lifetime diagnosis for >1 OSFED, no diagnostic hierarchy was used; however, parsimony was applied in making lifetime OSFED diagnoses to avoid diagnosing a prodromal phase or period of partial remission as a separate diagnosis.

[l]PD: purging disorder.

[m]NES: night eating syndrome.

[n]SSRI: selective serotonin reuptake inhibitor.

Most BN-S participants had a lifetime mood (256/321, 79.8%), substance use (183/321, 57%), or anxiety disorder (203/321, 63.2%), whereas most noneating disorder controls did not (14/78, 18%; 14/78, 18%; 10/78, 13%). All suicide indicators were more common in BN-S participants compared to controls (lifetime suicidal ideation: χ^2_1=39.1; P<.001; ϕ=0.32; past week suicidal ideation: χ^2_1=4.4; P=.04; ϕ=0.11; and lifetime suicide attempt: χ^2_1=9.1; P=.003; ϕ=0.15). No suicide attempts were reported in the week before the interview. Reflecting group differences, lifetime treatment for mental health was twice as likely in BN-S compared to control participants (χ^2_1=21.5; P<.001; ϕ=0.23).

Eating disorder diagnosis was not associated with participation at 6- or 12-month follow-up (Table 5 outlines 6-month follow-up data and Table 6 outlines 12-month follow-up data). Participants with current or lifetime obsessive-compulsive disorder at baseline were significantly less likely to participate at 12-month follow-up (χ^2_1=4.6; P=.03; ϕ=0.11 and χ^2_1=5.7; P=.01; ϕ=0.12, respectively). There were no other significant associations between completing baseline or follow-up visits and current or lifetime psychiatric diagnoses, suicide-related variables, or treatment.

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Table 5. Current eating disorder and other psychiatric diagnoses and treatment at 6-month follow-up (n=221).

	Total, n (%)	Bulimic syndrome group (n=167), n (%)	Control group (n=54), n (%)
EDE[a] current diagnosis			
No eating disorder	72 (32.6)	19 (11.4)	53 (98)
AN-bp[b]	5 (2.3)	5 (3)	0 (0)
BN[c]	38 (17.2)	38 (22.8)	0 (0)
BED[d]	2 (0.9)	2 (1.2)	0 (0)
OSFED[e]	102 (46.2)	101 (60.5)	1 (2)
OSFED subtypes			
Atypical AN[f]			
Broad	9 (4.1)	9 (5.4)	0 (0)
Narrow	5 (2.3)	5 (3)	0 (0)
BN low frequency or duration			
Broad	62 (28.1)	62 (37.1)	0 (0)
Narrow	49 (22.2)	49 (29.3)	0 (0)
BED low frequency or duration			
Broad	5 (2.3)	5 (3)	0 (0)
Narrow	2 (0.9)	2 (1.2)	0 (0)
Other or unspecified			
Broad	26 (11.8)	25 (15)	1 (2)
Narrow	46 (20.8)	45 (26.9)	1 (2)
SCID-5[g] current diagnoses			
Major depressive disorder	15 (6.8)	15 (9)	0 (0)
Persistent depressive disorder	29 (13.1)	27 (16.2)	2 (4)
Any mood disorder	47 (21.3)	45 (26.9)	2 (4)
Alcohol use disorder	38 (17.2)	34 (20.4)	4 (7)
Cannabis use disorder	27 (12.2)	24 (14.4)	3 (6)
Any substance use disorder	58 (26.2)	52 (31.1)	6 (11)
Any anxiety disorder	73 (33)	66 (39.5)	7 (13)
Obsessive-compulsive disorder	23 (10.4)	22 (13.2)	1 (2)
Posttraumatic stress disorder	20 (9)	18 (10.8)	2 (4)
Any trauma-related disorder	23 (10.4)	21 (12.6)	2 (4)
Suicidal ideation in the past week	9 (4.1)	9 (5.4)	0 (0)
Current treatment and medications			
Outpatient	31 (14)	28 (16.8)	3 (6)
SSRI[h]	16 (7.2)	15 (9)	1 (2)
Hormonal contraceptives	75 (33.9)	57 (34.1)	18 (33)

[a]EDE: Eating Disorder Examination.
[b]AN-bp: anorexia nervosa binge-purging.
[c]BN: bulimia nervosa.
[d]BED: binge-eating disorder.
[e]OSFED: other specified feeding or eating disorder.
[f]AN: anorexia nervosa.

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[g]SCID-5: Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.
[h]SSRI: selective serotonin reuptake inhibitor.

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Table 6. Current eating disorder and other psychiatric diagnoses and treatment at 12-month follow-up (n=153).

	Total, n (%)	Bulimic syndrome group (n=119), n (%)	Control group (n=34), n (%)
EDE[a] current diagnosis			
No eating disorder	63 (41.1)	30 (25.2)	33 (97)
AN-bp[b]	3 (2)	3 (2.5)	0 (0)
BN[c]	16 (10.5)	16 (13.4)	0 (0)
BED[d]	0 (0)	0 (0)	0 (0)
OSFED[e]	69 (45.1)	68 (57.1)	1 (3)
OSFED subtypes			
Atypical AN[f]			
Broad	3 (2)	3 (2.5)	0 (0)
Narrow	3 (2)	3 (2.5)	0 (0)
BN low frequency or duration			
Broad	41 (26.8)	41 (34.5)	0 (0)
Narrow	31 (20.3)	31 (26.1)	0 (0)
BED low frequency or duration			
Broad	3 (2)	3 (2.5)	0 (0)
Narrow	3 (2)	3 (2.5)	0 (0)
Other or unspecified			
Broad	22 (14.4)	21 (17.6)	1 (3)
Narrow	32 (20.9)	31 (26.1)	1 (3)
SCID-5[g] current diagnoses			
Major depressive disorder	10 (6.5)	10 (8.4)	0 (0)
Persistent depressive disorder	24 (15.7)	23 (19.3)	1 (3)
Any mood disorder	33 (21.6)	32 (26.9)	1 (3)
Alcohol use disorder	25 (16.3)	24 (20.2)	1 (3)
Cannabis use disorder	17 (11.1)	16 (13.4)	1 (3)
Any substance use disorder	39 (25.5)	38 (31.9)	1 (3)
Any anxiety disorder	44 (28.8)	43 (36.1)	1 (3)
Obsessive-compulsive disorder	15 (9.8)	14 (11.8)	1 (3)
Posttraumatic stress disorder	11 (7.2)	11 (9.2)	0 (0)
Any trauma-related disorder	15 (9.8)	15 (12.6)	0 (0)
Suicidal ideation in the past week	2 (1.3)	2 (1.7)	0 (0)
Current treatment and medications			
Outpatient	27 (17.6)	26 (21.8)	1 (3)
SSRI[h]	4 (2.6)	4 (3.4)	0 (0)
Hormonal contraceptives	57 (37.3)	43 (36.1)	14 (41)

[a]EDE: Eating Disorder Examination.
[b]AN-bp: anorexia nervosa binge-purging.
[c]BN: bulimia nervosa.
[d]BED: binge-eating disorder.
[e]OSFED: other specified feeding or eating disorder.
[f]AN: anorexia nervosa.

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[g]SCID-5: Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

[h]SSRI: selective serotonin reuptake inhibitor.

Psychometric Properties of Measures

IRR was excellent for all lifetime and substantial for current SCID-5 diagnoses [119,120]. Table 4 includes κ statistics for lifetime and current SCID-5 diagnoses based on IRR assessment from an independent review of 127 interviews across the full project, including baseline and follow-up assessments. Estimates include in-person and remote interviews.

Table 7 presents internal consistency and Table 8 provides test-retest reliability for EDE interview and questionnaire scales. Cronbach α exceeded thresholds for acceptability across all assessments and compared favorably to published estimates for all measures. Test-retest reliability was good and generally higher over shorter intervals, likely reflecting true change in constructs over time.

Table 7. Internal consistency reliability of measures at baseline and follow-up.

Measures	Cronbach α at baseline	Cronbach α at 6 mo	Cronbach α at 12 mo
Eating pathology			
Eating Disorder Examination interview			
Global	0.90	0.91	0.90
Restraint	0.83	0.81	0.81
Eating concern	0.76	0.77	0.81
Shape concern	0.92	0.91	0.91
Weight concern	0.86	0.87	0.82
Self-report			
Clinical impairment assessment	0.96	0.97	0.96
Body shape questionnaire	0.98	0.99	0.98
Three-Factor Eating Questionnaire			
Cognitive restraint	0.92	0.93	0.91
Disinhibition	0.90	0.89	0.90
Hunger	0.78	0.79	0.74
Reward or inhibition			
Behavioral inhibition scale	0.81	0.77	0.79
Behavioral Activation Scale	0.85	0.89	0.88
Drive	0.78	0.84	0.86
Fun seeking	0.73	0.74	0.79
Reward responsiveness	0.73	0.77	0.77
Sensitivity to Reward and Sensitivity to Punishment Questionnaire			
Sensitivity to reward	0.77	0.78	0.81
Sensitivity to punishment	0.89	0.88	0.89
Affect			
Positive and Negative Affect Schedule			
Positive affect	0.89	0.90	0.94
Negative affect	0.89	0.92	0.93

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Table 8. Test-retest reliability of measures across assessment waves.

Measures	Baseline to 6 mo, *r*	6 to 12 mo, *r*	Baseline to 12 mo, *r*
Eating pathology			
Eating Disorder Examination interview			
Global	0.85	0.79	0.76
Restraint	0.74	0.64	0.67
Eating concern	0.65	0.60	0.53
Shape concern	0.84	0.79	0.76
Weight concern	0.79	0.78	0.70
Self-report			
Clinical impairment assessment	0.79	0.82	0.71
Body shape questionnaire	0.85	0.85	0.82
Three-Factor Eating Questionnaire			
Cognitive restraint	0.85	0.82	0.82
Disinhibition	0.84	0.78	0.78
Hunger	0.70	0.59	0.60
Reward or inhibition			
Behavioral Inhibition Scale	0.68	0.78	0.70
Behavioral Activation Scale	0.68	0.68	0.57
Drive	0.65	0.57	0.54
Fun seeking	0.65	0.68	0.58
Reward responsiveness	0.59	0.65	0.50
Sensitivity to Reward and Sensitivity to Punishment Questionnaire			
Sensitivity to reward	0.68	0.75	0.66
Sensitivity to punishment	0.83	0.90	0.82
Affect			
Positive and Negative Affect Schedule			
Positive affect	0.59	0.79	0.67
Negative affect	0.64	0.65	0.49

Discussion

Principal Findings

The study protocol is designed to test an explanatory biobehavioral model for the association between WS and severity and maintenance of BN and related eating disorders characterized by binge eating. For BN-S severity, we expect significant cross-sectional associations between greater WS, lower leptin levels, lower GLP-1 response, greater reward valuation, and lower reward satiation. We also anticipate that greater reward valuation will be significantly associated with higher LOC frequency and a significant indirect pathway from greater WS to higher LOC frequency via lower leptin levels, lower GLP-1 response, and greater reward valuation. Furthermore, we expect that lower reward satiation will be significantly associated with larger eating/binge-eating episode size and a significant indirect pathway from greater WS to larger eating/binge-eating episode size via lower leptin levels, lower GLP-1 response, and lower reward satiation. If supported, findings would demonstrate that biological concomitants of WS explain variance in binge-eating severity via alterations in reward valuation and reward satiation. For BN-S maintenance (vs remission), we hypothesized significant prospective associations between these variables, with reward valuation and reward satiation temporally mediating associations between WS as the exposure and changes in LOC frequency and eating/binge-eating episode size, respectively, as the outcomes. If supported, findings would have implications for the assessment, diagnosis, and future clinical trials of eating disorders characterized by binge eating.

Current standardized eating disorder assessments, including the SCID-5 [93] and the EDE 17.0D [83], secure information about current body weight and lowest body weight in relation to height. However, neither includes a question about the highest lifetime adult weight. If findings support hypotheses, then future assessments would benefit from including this question to calculate WS as a prognostic indicator.

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Results may inform diagnostic criteria for eating disorders. The *DSM-5* currently uses BMI as a severity indicator for AN, frequency of inappropriate compensatory behaviors for BN, and frequency of binge-eating episodes for BED [5]. If our model supports WS as a marker of severity transdiagnostically, then WS could provide a common metric across eating disorders and potentially explain differences in outcomes among them. Beyond broad, transdiagnostic implications, findings may also refine the discrepancies between the *DSM-5* and *International Classification of Diseases, 11th Revision* (*ICD-11*) in the definition of a binge-eating episode for diagnosis of BN and BED. Our model focuses on the *DSM-5* definition, which requires the consumption of an objectively large amount of food in addition to LOC. The *ICD-11* requires a subjective LOC combined with eating either "notably more or differently than usual" [121]. If findings support posited pathways from WS to episode size and LOC, this would support the validity of the *DSM-5* definition over the *ICD-11* definition.

Finally, given recent interest and controversy surrounding the use of GLP-1 agonists for binge eating (eg, semaglutide in Wegovy and Ozempic) [122,123], these longitudinal data, funded solely by the NIMH and the US Department of Education, can elucidate mixed findings from early clinical trials [124-126] and inform the design of future investigations. Specifically, our model contextualizes the impact of GLP-1 function for those who have lost weight, predicting greater disruptions associated with greater WS. Previous studies supporting the potential efficacy of GLP-1 agonists have relied on secondary analyses of data collected in open trials [125-127] or a randomized controlled treatment trial for obesity without placebo control [128]. In the sole double-blind, randomized controlled trial testing a GLP-1 agonist against a placebo for the treatment of BED [124], no significant differences emerged in remission of binge eating or BED. Similar to other studies of GLP-1 agonists, weight loss was significantly greater in the active compared to the control condition. However, participants on placebo lost only 0.9 (SD 0.7) kg over 17 weeks. Comparing improvements in binge eating on a placebo without weight loss may not provide a valid comparison against those treated with liraglutide, who lost 4.7 (0.8) kg of weight and experienced decreases in binge eating [124]. If our hypotheses are supported, future evaluations of GLP-1 efficacy will examine WS at intake and relative changes in weight over treatment as covariates in predicting changes in binge-eating severity.

Strengths of the project include the large, diverse sample; inclusion of multiple units of analysis; and longitudinal design, with high retention across multiple visits at baseline and high retention over follow-up. We retained 290 (72.7%) out of 399 women for all clinical, behavioral, and biological assessments at baseline, and 249 (85.8%) of these 290 women provided longitudinal data. This supports the feasibility of our approach even in the face of unanticipated challenges encountered with the onset of the COVID-19 pandemic. Studies using laboratory-based feeding paradigms [81] have included anywhere from 7 to 103 participants in PR tasks and fixed or ad-lib meals. Our combination of all methods in 290 participants far exceeds these benchmarks. Furthermore, most biobehavioral studies were constrained by their cross-sectional design, limiting conclusions regarding the role of observed disruptions as correlates, consequences, or contributors to pathology. Our measures had strong psychometric properties that minimized random error, and initial analyses indicate that effect sizes will exceed original estimates. Thus, we will have sufficient power for prospective analyses.

Project weaknesses include the absence of sexual orientation information and the exclusion of male participants. Eating disorders, including AN binge-purging, BN, BED, and their OSFED variants, predominantly affect female individuals [129,130]. Although restricting recruitment to women limits generalizability to men due to potential biologically based differences in the influence of ovarian hormones on GLP-1 function [65], it was not feasible to recruit enough men to directly examine sex as a biological variable. This limitation was due to the large sample size required for adequately powered analyses and the low prevalence of eating disorders in men. Despite this limitation, findings may impact the assessment, diagnosis, and treatment of a majority of those with eating disorders characterized by binge eating, given the preponderance of these disorders in women [129,130]. Furthermore, the sample demonstrated limited diversity in socioeconomic status. Participation requirements were likely too high for most individuals with limited resources or full-time commitments at work or home. These factors will impact the generalizability of findings. Attrition was related to age, BMI, and the presence of a BN-S at baseline. Greater attrition in BN-S may reflect a higher participant burden in this group, including longer interview duration due to greater pathology and behavioral task duration due to higher RVE and lower reward satiation. BN-S participants endorsed greater impairment, which may extend to impaired ability to follow through with study participation. Among participants who provided full baseline data and were eligible for longitudinal follow-up, we did not observe significant differences between BN-S and control groups. We advise using all available data with imputation for missing values to minimize the influence of biased attrition.

Finally, in using the RDoC approach to participant recruitment, we did not set a priori goals for the recruitment of participants who would fall into specific *DSM-5* diagnostic groups, and this may have limited the extent to which our sample has a transdiagnostic representation of all eating disorders characterized by binge eating. The requirement that participants be medically healthy and free of medications that could influence weight or appetite was necessitated by our interest in biological factors underlying RVE and satiation, consistent with the RDoC approach. This may have restricted the number of participants who presented with AN or BED, given the associations between extreme BMI and medical conditions. This, combined with our age range, may explain the large number of participants with *DSM-5* BN and OSFED characterized as BN with low duration or frequency. The latter group could lead to misinterpretation of the sample as including participants with "subthreshold" eating disorders. However, all participants had a full-threshold *DSM-5* eating disorder. Further, the minimum behavioral symptom frequency ensured that all participants met the minimum symptom frequency required for a *DSM-5* diagnosis of BED. Many of our OSFED participants

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were engaging in binge eating frequently enough for a diagnosis of BN or BED, but the frequency of inappropriate compensatory behaviors was too high for a diagnosis of BED and too low for a diagnosis of BN.

Conclusions

Preliminary data from subsets of participants in this project have been included in other reports [1,79,131-133]; however, this is the first report presenting data from all participants and all waves. Future papers will focus on testing our model to predict the severity and maintenance of BN-S. Beyond testing our RDoC-informed model, biological and behavioral variables will be examined in novel combinations as predictors of changes in eating disorder expression and comorbidity. A careful review of this paper will help researchers accessing data through the NDA identify which data are most relevant (eg, active vs total GLP-1), their context (eg, pre– vs post–COVID-19 pandemic), and other factors that may influence interpretations. Grounding analyses with a full understanding of methods will facilitate rigorous and reproducible research.

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Data Availability

The datasets generated or analyzed during this study are available in the National Institute of Mental Health Data Archive repository [134].

Conflicts of Interest

JA serves on the Advisory Board of EMD Serono on HIV-related research. All other authors declare no other conflicts of interest.

Multimedia Appendix 1
Peer-review report from the Center for Scientific Review Special Emphasis Panel Member Conflict: Sleep, Memory, Anxiety, and Reward (ZRG1 BBBP-Z [02]; National Institutes of Health).
[PDF File (Adobe PDF File), 137 KB - resprot_v14i1e66554_app1.pdf]

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Abbreviations

AN: anorexia nervosa
Arc: arcuate nucleus
BED: binge-eating disorder
BN: bulimia nervosa
BN-S: bulimia nervosa and related syndromes
CART: cocaine- and amphetamine-regulated transcript
CV: coefficient of variation
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EDE: Eating Disorder Examination
FSU: Florida State University
GLP-1: glucagon-like peptide 1
HIPAA: Health Insurance Portability and Accountability Act
ICC: intraclass correlation
ICD-11: International Classification of Diseases, 11th Revision
IRB: institutional review board
IRR: interrater reliability
LOC: loss of control
NAc: nucleus accumbens
NDA: National Institute of Mental Health Data Archive
NIMH: National Institute of Mental Health
NPY/AgRP: neuropeptide Y and agouti-related protein
NTS: nucleus of the solitary tract
OSFED: other specified feeding or eating disorder
PR: progressive ratio
RDoC: Research Domain Criteria
RVE: reward valuation effort
SCID-5: Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
SEM: structural equation model
VAS: Visual Analog Scale
VTA: ventral tegmental area
WS: weight suppression

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Protocol

Evaluation of Noninvasive Adjuncts for Early Detection of Oral Cancer in Oral Potentially Malignant Disorders and Development of Risk-Based Management Strategies: Protocol for a Prospective Longitudinal Study

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Abstract

Background: Oral potentially malignant disorders (OPMDs) constitute the most important precursors of oral cancer. Histopathological examination of a biopsy from a clinically suspicious lesion is still the gold standard for the diagnosis of oral cancer. Adjunctive techniques such as autofluorescence, toluidine blue (TB), and others have been evaluated among high-risk individuals such as chronic tobacco chewers or in patients with suspicious lesions. However, evaluation of these noninvasive adjunctive techniques has not been performed in primary health care settings. Since the first point-of-contact of individuals living in rural and semiurban areas are the primary health care workers, evaluation of these noninvasive adjuncts is likely to assist and strengthen the population-wide oral cancer screening in high-burden countries such as India.

Objective: This prospective longitudinal study aims to evaluate the noninvasive adjuncts in oral cancer screening in the field settings, specifically in detecting foci of oral cancers in various OPMDs.

Methods: After staff recruitment and training, we shall conduct oral cancer screening camps in the community for the recruitment of individuals with OPMDs after obtaining informed consent. All patients with OPMD shall undergo further screening via autofluorescence and TB staining for detection of lesions suspicious of oral cancer. Sensitivity, specificity, and negative and positive predictive values of these adjunctive techniques (autofluorescence and TB) in the detection of oral cancer shall be calculated using biopsy as the gold standard. In addition, this study will also focus on the validation of the 2022 consensus guidelines on risk-based stratification and appropriate management protocols for the OPMDs at the primary and referral health care centers. Our primary outcome is the diagnostic use of autofluorescence and TB in oral cancer detection among OPMDs as well as the robustness of the risk-based management protocols for these patients.

Results: Participant recruitment has been initiated at all sites. Staff recruitment and training in the oral visual examination have been conducted. Procurement of the autofluorescence device is in progress. All the study sites have begun conducting oral screening camps.

Conclusions: The results of this study shall provide robust evidence for the diagnostic use of autofluorescence and TB staining in early oral cancer detection among patients with OPMD. The use of these noninvasive adjuncts by primary health care providers

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can significantly improve oral cancer screening in our country. The validation of risk-based stratification and management of patients with OPMD shall assist in the refinement of the national guidelines for these interventions. This study has been approved by the respective ethics committee of ICMR-National Institute of Cancer Prevention and Research and the collaborating institutes. The findings of this study shall be disseminated through scientific publications in peer-reviewed journals as well as meetings with the concerned stakeholders at the district and state health departments.

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KEYWORDS

oral potentially malignant disorder; noninvasive adjunct; toluidine blue; autofluorescence; risk stratification; management

Introduction

Oral cancer constitutes the second most common cancer in India contributing 10.3% of incident cancer cases [1]. A large majority (80%) of oral cancers develop from oral potentially malignant disorders (OPMDs) [2]. Risk factors such as tobacco chewing, alcohol use, areca nut chewing, and infection by human papillomavirus are common among OPMDs and oral cancer [3]. Other common factors include chronic oral trauma from ill-fitting dentures or broken teeth, chronic inflammation, microbiome alterations, systemic sclerosis, genetic dysregulation of DNA metabolism, and nutritional deficiencies [4].

OPMDs are a heterogeneous group of diseases with distinctive histopathological entities including oral leukoplakia (OL), erythroplakia, erythroleukoplakia, oral lichen planus (OLP), and oral submucous fibrosis (OSMF) [4]. The risk of malignant transformation differs among the different entities, ranging from low in homogenous leukoplakia to high for erythroleukoplakia, proliferative verrucous leukoplakia, OSMF, and very high in EP [5].

Oral cancer control and prevention efforts have been hindered by the lack of awareness and the attendant late diagnosis in the majority of cases, especially among high-risk populations including tobacco, alcohol, or areca nut users [6]. The gold standard for OPMD and oral cancer diagnosis is oral visual examination (OVE) with histopathological examination of the suspicious oral lesions [4]. However, in high-burden and resource-constrained countries such as India, the availability of health care providers trained in OVE and performing tissue biopsies as well as pathologists who would examine these biopsies at the primary health care facilities are far from ideal. As per the NHFS-5 (National Family Health Survey 5; 2019-21), only 0.9% of females and 1.2% of males have ever undergone an oral examination for oral cancer. OVE is not able to detect foci of malignant transformation within the OPMD lesions [7]. This low sensitivity of OVE in detecting dysplastic lesions exerts an undue burden on health care facilities for oral biopsy [4]. Hence, adjunctive tests are required to help detect lesions that are likely to have a malignant focus within them, thereby indicating when and where to take a biopsy. Two such noninvasive adjunctive tests are autofluorescence and toluidine blue (TB) staining. Autofluorescence makes use of the change in tissue fluorescence in dysplastic foci. Normally, tissue autofluorescence is produced due to natural fluorophores such as collagen, tryptophan, elastin, keratin, etc, which can be excited by short wavelengths and emit light of longer wavelengths [8]. In OPMDs and oral cancers, a change in the fluorophore concentration leads to alterations in light scattering and absorption by tissues [8]. TB or tolonium chloride is a metachromatic dye staining nucleic acids (DNA and RNA). This property of TB is used in the rapid on-site evaluation of fine needle aspiration cytology, especially in visceral organ nodules [9]. Studies have shown the sensitivity and specificity of TB as 92.6 and 67.9%, respectively with an accuracy of 80% for the detection of oral cancer [10]. A recently published systematic review and bivariate meta-analysis showed the diagnostic odds ratio as 7.017 with sensitivity and specificity of 73% and 69% [11]. However, the majority of the studies on these noninvasive adjuncts have been conducted in selected populations or patients attending hospitals for various oral lesions.

The therapeutic strategies currently being practiced for OPMD are empirical. A set of consensus guidelines have been published in 2022 for the management of OPMDs [12]. These guidelines have not been evaluated yet in the field settings. Since the first point of contact for the majority of the Indian population is the primary health center, the optimal evaluation and management strategies for various OPMDs need to be delineated for future implementation.

Hence, the main aim of the study is to evaluate the effectiveness of noninvasive adjuncts in the early detection of oral cancer among cases of oral potentially malignant disorders by primary health care providers. In addition, a secondary objective is to validate the risk-based management protocols for patients with OPMDs. The research questions of this study are as follows:

1. Can autofluorescence or TB improve early diagnosis of oral cancer among OPMDs as compared with OVE alone?
2. Can standardized treatment protocols based on risk-based stratification of patients with OPMD improve treatment outcomes?

Methods

Overview

This is an observational prospective longitudinal study.

Recruitment

The study is ongoing at 2 sites, Gautam Budh Nagar district in Uttar Pradesh in collaboration with the Centre for Dental Education and Research, New Delhi, and Gandhinagar in Gujarat, India. For participant recruitment, community-based

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outreach camps for oral cancer screening shall be organized in collaboration with the concerned district authorities and local community health workers. The staff shall be trained in OVE and the use of noninvasive screening adjuncts. Individuals with oral lesions suggestive of one of the OPMDs shall be recruited in the study after obtaining informed consent.

Inclusion Criteria

Individuals diagnosed with OPMDs on OVE as per the World Health Organization clinical diagnostic criteria [13] and categorized clinically as OL, EP, OLP, OSMF, tobacco pouch keratosis, smoker's palate, and proliferative verrucous leukoplakia. For the assessment of diagnostic accuracy of the noninvasive adjuncts, 2 types of controls shall be included, a group of healthy adults with a history of tobacco or areca nut use and normal oral mucosa on OVE and a group of healthy adults with no tobacco or areca nut or alcohol habits and normal oral mucosa.

Exclusion Criteria

Individuals shall be excluded from this study if they have complete trismus preventing adequate mouth opening to allow OVE or the noninvasive adjuncts, history of cancer in the oral cavity, and are unwilling to participate in the study.

Study Procedures

Following inclusion into the study, the sociodemographic profile of the individuals along with health behavior and clinic-pathological characteristics shall be recorded in a predesigned proforma (Multimedia Appendix 1). OVE shall be performed in all patients and intraoral photographs of the oral mucosa shall be captured in a standardized format. Screening adjuncts shall be used on all OPMDs in the following order: autofluorescence followed by TB staining, as depicted in Figure 1. Images of each method shall be captured before advancing to the next technique. The procedures of these 2 adjuncts are described in the subsequent sections. All participants shall also be trained in mouth self-examination techniques. Individuals with tobacco, areca nut, or alcohol habits shall be offered behavioral counseling for cessation of the respective substance use. Patients with OPMD shall be asked to follow up after 15 days for routine investigations before the oral biopsy. Using oral biopsy as the gold standard, the sensitivity and specificity of autofluorescence and TB for oral cancer detection shall be computed.

Figure 1. Flowchart depicting the study methodology. AF: autofluorescence; ICMR: Indian Council for Medical Research; OPMD: oral potentially malignant disorder; TB: toluidine blue.

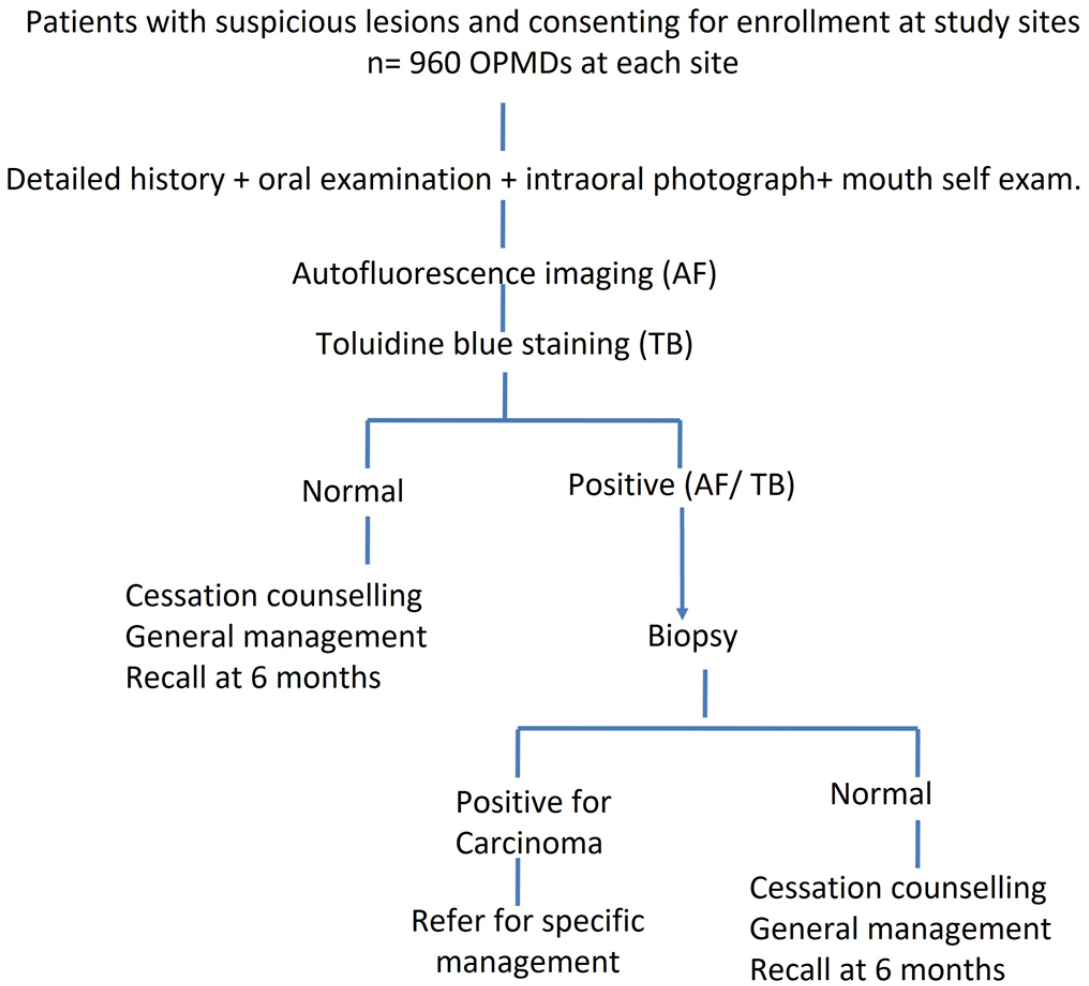

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Patients with histopathological evidence of moderate to vigorous dysplasia or malignancy shall be referred to the collaborating hospitals for further management as per the risk-stratified protocols discussed later. Patients not reporting for follow-up shall be contacted via home visits or telephonically. In total, 5 such attempts shall be made before considering the participant as lost to follow-up.

Procedure for the Use of Autofluorescence

Following the conventional OVE and intraoral photograph of the abnormal lesion, autofluorescence light from the selected device shall be used for an oral examination, focusing on the abnormal area seen on OVE. The operator and the patient shall wear safety glasses during the procedure. An intraoral photograph shall be taken with the autofluorescence light.

For visual autofluorescence, a VELscope (Visually Enhanced Lesion scope) or similar equipment that uses a fluorescent light with a wavelength of 400-460 nm shall be used. Using this wavelength of light, normal mucosa appears pale green while abnormal tissue looks dark, since the quantity and quality of fluorophores are reduced [14].

Use of Vital Staining With TB

In this technique, any abnormal area shall be first swabbed with 1% acetic acid for 20 seconds to remove the food debris and mucus followed by the application of 1% TB for 20 seconds on the abnormal area seen by OVE or autofluorescence. This shall be followed by swabbing with 1% acetic acid for 20 seconds to remove the extra retained TB and an intraoral photograph of the stained area shall be captured.

Risk-Based Management of OPMDs

OPMDs shall be classified into low-risk and high-risk as follows (Textbox 1).

Textbox 1. Risk-based classification of oral potentially malignant disorders.

- Low-risk oral potentially malignant disorder (OPMD)
  - Mild to moderate oral submucous fibrosis.
  - Nonerosive oral lichen planus.
  - Homogenous oral leukoplakia.
  - Tobacco pouch keratosis.
  - Smoker’s palate.
  - Mild dysplasia.
- High-risk OPMD
  - Severe oral submucous fibrosis.
  - Erosive oral lichen planus.
  - Nonhomogeneous oral leukoplakia.
  - Proliferative verrucous leukoplakia.
  - Erythroplakia.
  - Oral lichenoid lesions.
  - Moderate to vigorous dysplasia.
- All patients with OPMDs and those with any one or more of tobacco, areca nut, or alcohol habits with normal-appearing mucosa shall be offered cessation counseling.
- Other general measures for all patients with OPMD shall include removal of chronic irritation and infections, diet advice with antioxidant-rich foods, adequate control of systemic diseases, and training on self-examination of the mouth.
- Specific medical or surgical management based on the type and severity of OPMD shall be undertaken.

Statistical Analysis

Demographic and clinical data including risk factors for OPMD, clinical examination features, findings of OVE, autofluorescence, TB, and histopathological features shall be recorded in a predesigned proforma.

The association between risk factors and the presence of OPMD or oral cancer will be studied. Descriptive statistics will be applied to qualitative and quantitative data, as applicable. Performance characteristics (sensitivity, specificity, positive, and negative predictive value) shall be calculated for autofluorescence and TB using histopathology of oral biopsy as the gold standard. This shall be compared with an OVE.

Sample Size

Considering the sensitivity and specificity of autofluorescence and TB as 0.89 and 0.8 and 0.88 and 0.67, respectively, and CI as 0.07 (width of the confidence interval), the required number of individuals with and without the disease is:

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This gives the required sample size of 80 individuals with disease and 131 without disease.

Considering the positivity rate of oral biopsy in clinically suspected individuals as 25%, a total of 320 participants shall be required to undergo oral biopsy to achieve the required number. We intend to increase this number by 50% accounting for the denial or opt-out from oral biopsy, taking this number to 480 patients with OPMD requiring biopsy.

Ethical Considerations

The study involves human participants and adheres to all applicable ethical standards and procedures. The study has been approved by the Institutional Ethics Committee, ICMR-NICPR, Noida, and the respective ethics committees of the collaborating institutes (NICPR/Ethics/2023, IEC-167/11.04.2023; SIMS/SIMS-EC/RP02/80/2024). An informed consent form shall be used in the study. For data management, the study shall implement a secure system to protect patient confidentiality. Only authorized individuals involved in the study with legitimate access to the data shall be permitted to do so. All procedures in the study shall follow the Declaration of Helsinki.

Results

The study is being supported by a grant from the Indian Council of Medical Research under its Intramural Research Projects (No. 79/3/IIRP-NICPR/Onco/2023-NCD-III). Funds for the study were received in February 2024. The timeline of the study is shown in Figure 2. Participant recruitment has been initiated at all sites. Staff recruitment and training in OVE has been conducted. Procurement of the autofluorescence device is in progress. All the study sites have begun conducting oral screening camps. As of date, a total of 38 patients with OPMD have been recruited in the study. However, patient recruitment shall be enhanced once the autofluorescence device is available at the study sites. The study results shall be published in a peer-reviewed indexed scientific journal and presented at national and international conferences.

Figure 2. Timelines with achievable targets. AF: autofluorescence; MSE: mouth self-examination; OVE: oral visual examination; TB: toluidine blue; TCC: tobacco cessation counseling.

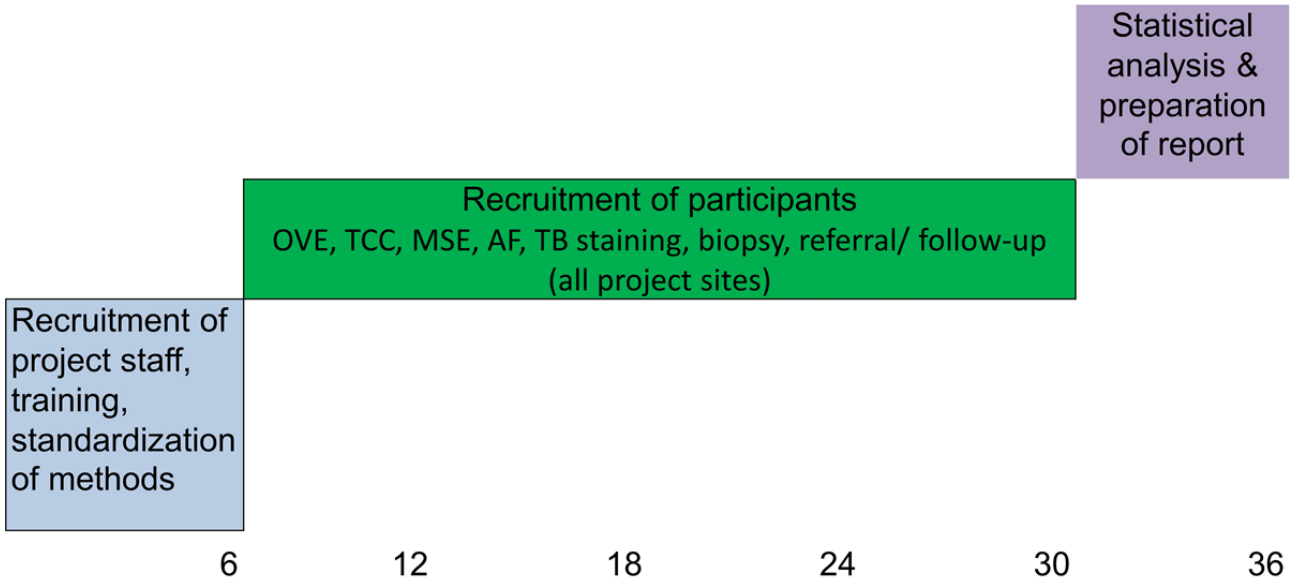

Discussion

Principal Findings

This study will provide robust scientific evidence on the sensitivity, specificity, and positive predictive value of diagnostic adjuncts for early diagnosis of oral cancer among patients with OPMD. A recently published review of systematic reviews reported a variable sensitivity and specificity of autofluorescence techniques for the detection of OPMD and oral cancer. Hence, the authors recommended that autofluorescence or TB staining could not replace conventional oral examination or oral biopsy [15]. However, the usefulness of these noninvasive techniques as “adjuncts” to be used by primary health care workers for early detection of oral cancer in patients with OPMD has not been evaluated fully yet. Mitbander et al [16], in their recent study, have demonstrated the potential use of multimodal imaging in assisting health care workers in the identification of the need for further evaluation in patients with oral lesions. The provision of such diagnostic adjuncts in the hands of frontline health care workers, dentists, and other primary health care providers can significantly improve the early diagnosis of oral cancer at the community level. Furthermore, the feasibility assessment of these diagnostic adjuncts at the community level will help in designing training protocols, monitoring, and mentoring or supportive supervision plans for the large-scale rollout of oral cancer screening. The noninvasive adjuncts are not meant to replace oral biopsy but rather to guide the clinician in selecting the patients with OPMD to undergo biopsy and also to guide the best possible lesional area to biopsy. This intervention can help in making an impact on the oral cancer control efforts in India. An ancillary outcome

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of this study may be the estimation of the quit rate of tobacco andareca nut habits among patients with OPMD.

We are likely to face challenges in ensuring cessation of the tobacco, areca nut, and alcohol habits by the individuals enrolled in this study due to the deep-rooted social acceptance of these habits. The lack of oral cancer awareness among the general population may also pose a hindrance to the successful conduct of the screening camps in the community. However, the involvement of the community stakeholders in the study might assist in overcoming this barrier.

Recently, the consensus guidelines on the management of noncancerous OPMDs have been released. Some of these patients with OPMD have a high chance of progressing to oral cancer in the future. Hence, risk-based classification of these OPMDs becomes imperative to treat patients with a high risk of developing oral cancer at an appropriate early stage to either halt or slow their progression to malignancy. This study will also evaluate risk-based OPMD management protocols for implementation at various levels of health care system. These protocols will help refine the national-level guidelines for OPMD management in noncancerous patients with OPMD.

Dissemination Plans

The results of this study shall be disseminated through paper presentations in professional conferences and peer-reviewed publications in high-impact scientific journals. In addition, the results shall be shared with the relevant stakeholders and policy makers for potential implementation in a population-wide manner.

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Authors' Contributions

RG conceived the study and participated in the design involved in drafting and finalizing the manuscript. AR, SRG, and HH participated in the design of the study, drafting the manuscript, and revising it critically for important intellectual content. LS contributed to the design of the study, with particular input on the analysis and interpretation of data. RG and PKS has been involved in the preliminary discussion around the acquisition of data, contributing to the design of the study, and will be involved in the analysis and interpretation of data. SS contributed to the design of the study and was involved in drafting the manuscript and revising it critically for important intellectual content.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Study proforma.
[PDF File (Adobe PDF File), 194 KB - resprot_v14i1e66285_app1.pdf]

Multimedia Appendix 2
Peer-review comments from the Indian Council of Medical Research - Intramural Project (New Delhi, India).
[PDF File (Adobe PDF File), 227 KB - resprot_v14i1e66285_app2.pdf]

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Abbreviations

NFHS-5: National Family Health Survey 5
OL: oral leukoplakia
OLP: oral lichen planus
OPMD: oral potentially malignant disorder
OSMF: oral submucous fibrosis
OVE: oral visual examination
TB: toluidine blue
VELscope: Visually Enhanced Lesion scope

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Protocol

Understanding the Gendered Impact of COVID-19 on Young Self-Employed Nigerian Women and Coproducing Interventions That Foster Better Systems and Well-Being: Protocol for a Multimethods Study

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Abstract

Background: The COVID-19 pandemic has had disproportionate economic and health impacts on self-employed workers in Nigeria, particularly self-employed women and youth. Though uniquely different, the COVID-19 pandemic shares similarities with events such as childbirth, family, and health emergencies. Self-employed young women lack adequate support structures to cope with disruptive life events, which have negative consequences for their well-being. This is concerning, as 86% of women in the Nigerian labor force are self-employed.

Objective: The project's first objective is to conduct a gendered situational analysis to address the question of how the COVID-19 pandemic and other life events affect the paid and unpaid work and the physical, mental, and social well-being of self-employed young women in Nigeria; their strategies for coping with such events; and how their experiences compare with those of self-employed young men. Informed by this analysis, the second objective is to coproduce and pilot-test a gender-transformative intervention that integrates social protection and promotes well-being.

Methods: This multimethod project has 3 components. The first is a situational analysis of the impact of the pandemic and other significant life events on the work and well-being of self-employed young women vis-à-vis self-employed young men. This involves qualitative interviews with approximately 60 self-employed young women and men and a digital storytelling initiative to represent some of these stories in video format. Secondary data analysis of the Nigerian General Household Survey and the COVID-19 Longitudinal Phone Survey will be conducted. Furthermore, a scoping review of the impact of significant life events, including the COVID-19 pandemic, on self-employed workers in low- and middle-income countries will be conducted. The

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second component is the coproduction of interventions involving qualitative interviews with self-employed young women, members of their support network, and policy makers to find out their views on how to support self-employed women. It also entails an analysis of policies relevant to self-employed women in Nigeria and theory of change workshops to create a map for achieving the long-term goal of improving their resilience. Furthermore, a systematic review of interventions to improve the job quality and well-being of self-employed workers will be conducted. The third component is a pilot of the coproduced interventions in a quasi-experimental study involving 300 participants to assess feasibility, acceptability, cost, and potential effectiveness.

Results: This project was funded in October 2022. Data collection for the project commenced in May 2023 and will end in November 2025. Data collection for the situational analysis and coproduction of intervention phases have been completed while the pilot of intervention packages is underway.

Conclusions: This project will advance knowledge of the impact of the COVID-19 pandemic and other significant disruptive life events on the work and well-being of self-employed young Nigerian women and provide coproduced solutions to mitigate their effects.

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KEYWORDS

COVID-19 pandemic; low- and middle-income countries; self-employed women; resilience; well-being; coproduction; Nigeria

Introduction

Background

The COVID-19 pandemic has had disproportionate economic and health impacts on self-employed workers. In high-income countries, self-employed workers lost more earnings and jobs than employees [1,2]. In low- and middle-income countries (LMIC), the economic consequences of the pandemic were even greater. With little to no social protection, paid sick leave, savings, or access to credit, many self-employed workers in LMIC continued to go out to work at the height of the pandemic, exposing them to an increased risk of infection [3]. They also faced adverse mental health consequences, including fear of infection and income-related anxieties [4,5].

According to the International Labour Organization, self-employed persons are workers whose remuneration directly depends on the profit from the goods and services they produce. They include employers, own-account workers, members of producers' cooperatives, and contributing family workers [6]. Self-employment accounts for 70% of employment globally [7]. LMIC generally have a higher proportion of self-employed workers in their labor force [8]. In Nigeria, 80% of workers and 86% of women in the labor force are self-employed, making it an apt setting to examine the impacts of the COVID-19 pandemic on self-employed workers [9,10]. Self-employed workers in Nigeria usually work in agriculture, wholesale and retail trade, catering and food services, fashion design, machinery repair, the digital economy, etc. Many self-employed workers operate in the informal economy, where economic activities are unregulated by the government and other formal institutions of society [11].

Self-employed women face certain disadvantages in the labor market. They have fewer employees and lower earnings and profits [12-15]. A report from the Organisation for Economic Co-operation and Development [16] suggested that compared to self-employed men, self-employed women earn less and have smaller businesses because they have less access to capital, enter into less competitive sectors, and are more likely to operate in the informal economy. The COVID-19 pandemic heightened these disadvantages. United Nations Women [17] reported that 25% of self-employed women lost their jobs during the pandemic compared to 21% of self-employed men. Furthermore, the US Global Leadership Coalition revealed that in every region of the world, female-owned businesses experienced higher closure rates during the first year of the pandemic compared to male-owned businesses [18]. In Nigeria, about 44% of women-led businesses closed during the pandemic compared to 33% of men-led businesses [19].

Data from Ibadan in the southwestern part of Nigeria collected in 2021 revealed the pandemic's heightened impacts on self-employed women [20]. The data came from 29 semistructured interviews and 504 questionnaires administered to self-employed young men and women from diverse sociodemographic backgrounds working in various sectors. Many self-employed workers experienced financial hardship, resulting in distress. The lockdown prevented 38.8% of self-employed young women from doing business-related tasks and forced 23.6% of women (vs 17.8% of men) to run their businesses from home. Fewer women than men (32.5% vs 40.6%) continued going out to work during lockdowns. During the pandemic, 65.8% of women reported facing "much" or "a lot" of financial hardships. Among self-employed youth who had started their businesses before the COVID-19 pandemic, 3.5% of 255 women (vs 7.6% of 197 men) were able to start a new revenue stream to cope with the effects of the pandemic, and only 1 woman received government monetary assistance.

Though uniquely unexpected and disruptive, the COVID-19 pandemic has similarities with other disrupters of paid work, such as childbirth, family, and health emergencies. Such events especially affect women, who are seen as traditional caregivers and perceived to have more time flexibility. This leads to greater economic losses compared to men, leaving women more vulnerable, further perpetuating gender inequities. Many women lack adequate support to deal with such events. Thus, building supportive structures for self-employed young women is an urgent imperative.

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In Nigeria, there are ongoing programs sponsored by the government and other financial institutions targeted at women in business. An example is the *Women in Self-employment Program* domiciled in the Small and Medium Enterprises Development Agency of Nigeria (SMEDAN), which provides self-employed women with financial assistance, business training, mentorship, and access to markets [21]. Another example is the *Womenpreneur Pitch-a-ton* organized by Access Bank, which offers mini Master of Business Administration scholarships to beneficiaries alongside grants [22]. There have been testimonials on the positive effects of these programs, but the evidence for these remains anecdotal. The impact of these programs is not evaluated in the systematic way that trials are done, thus limiting the examination of their effectiveness and generalizability. In addition, the development and implementation of most of these programs lack the vital element of coproduction, thus limiting impact. Coproduction [23] is a collaborative, participatory approach where those who will ultimately benefit or be impacted by research or an intervention initiative are a part of its development process; research or the intervention development and implementation is conducted with them rather than on them. Participatory approaches are more likely to result in research or interventions that are shaped by the needs, values, and goals of the stakeholders, thereby increasing the uptake of the output. Beyond these instrumental gains, coproduction with those with lived experience is also an ethical and rights-based imperative. In sum, our Advancing Resiliency in Self-Employed Young Women in Nigeria (ARISE&WIN) study seeks to bridge these gaps in the lack of in-depth knowledge about the lives, stressors, and coping strategies of young self-employed women and the lack of coproduced and well-evaluated interventions to support their resilience and well-being.

Research Aims

The project's first aim is to conduct a gendered situational analysis of how the COVID-19 pandemic and other significant life events (childbirth, family, and health emergencies, etc) affect the paid and unpaid work and mental, physical, and social well-being of self-employed young women in Nigeria; their strategies for coping with such events; and how their experiences compare with those of self-employed young men. To achieve this aim, the project has the following objectives:

1. Explore through qualitative interviews, digital storytelling, and a scoping review self-employed young women's and men's experiences of the COVID-19 pandemic and life events that impact work and well-being
2. Quantitatively examine the gender-differentiated impact of the pandemic on the work and well-being of self-employed young people in Nigeria using longitudinal secondary data

The project's second aim is to coproduce nationally scalable intervention packages in order to support self-employed young women in Nigeria to cope better with disruptions to their work and promote their well-being. The specific objectives under this aim are as follows:

1. Synthesize existing evidence on interventions for social protection, job quality, and well-being promotion for self-employed youth using a systematic review, policy analysis, as well as qualitative interviews with self-employed young women, members of their support network, and policy makers
2. Coproduce, using theory of change and co-design workshops, intervention packages to improve the resilience of self-employed young women in Nigeria against significant life events

The third aim of the project is to pilot and assess the feasibility, acceptability, cost, and potential effectiveness of the coproduced intervention packages on the resilience, job quality, and mental and physical well-being of self-employed young women, using a quasi-experimental study. The study focuses on young women aged between 15 and 35 years [24].

Methods

Study Setting

The project is being conducted in Oyo State in southwest Nigeria. Oyo State is a suitable site to capture a wide range of self-employed young workers' experiences, given its large and diverse population, with migrants from across Nigeria, and the baseline data that the research team has from here. The study is being conducted in urban, periurban, and rural local government areas (LGAs) of Ibadan, the capital of Oyo State, because of the proximity to certain facilities of the Oyo State Government that will be used in the pilot of the coproduced intervention packages. Ibadan is the third most populous city in Nigeria and has about 4 million inhabitants [25]. The main economic activities carried out by the inhabitants are agriculture, trade, public service employment, handicrafts, and factory work [26]. Ibadan is a highly commercial city, with the presence of markets and businesses all over the metropolitan area. Many young people in the state are engaged in self-employment across sectors, such as garment making, shoemaking, hairdressing, building construction, catering, and food vending. They also work as graphic designers, printers, electricians, auto mechanics, etc.

Study Design

This is a multistage, multimethod research project. This project incorporates integrated knowledge mobilization strategies right from the development of the research aims through its implementation, evaluation, and dissemination to ensure that it is relevant to the target population of self-employed young women as well as feasible for and scalable by policy actors [27]. Self-employed young women were involved in the development of the research proposal and have been playing an integral part throughout the project, bringing their perspectives and experiences. Policy makers and decision makers were also involved in proposal development and have been playing an important role in the execution of this project to enable the integration of its findings into Oyo state policy as well as policies for other states in Nigeria.

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Data Collection Strategies

Aim 1: Situational Analysis

Overview

The aim of the situational analysis component of the project is to examine the impact of the COVID-19 pandemic and other significant life events on the work and well-being of self-employed young women compared to men as well as their coping strategies for dealing with such events. Furthermore, we are examining cultural, social, psychological, and physical factors that might put self-employed young women at a disadvantage compared to self-employed young men. To develop a comprehensive understanding, semistructured interviews, quantitative secondary data analysis, a scoping review, and digital storytelling will be conducted. The findings from this situational analysis will inform the coproduction of intervention packages to improve the resilience of self-employed young women in Nigeria in the face of significant disruptive life events.

Semistructured Interviews

Overview

Semistructured interviews will explore and help compare and contrast self-employed young women's and men's experiences during the pandemic and other events that disrupted their businesses. These interviews also explore respondents' strategies for coping with disruptive events, including leveraging social networks. The interview guide is provided in Multimedia Appendix 1.

Sampling

Self-employed young women and men will be sampled from urban, periurban, and rural areas in the Ibadan metropolitan area using both purposive and snowball sampling techniques until theoretical saturation is reached. Self-employed young women and men will be sampled from various types of businesses, including services, commerce, craftsmanship, primary production, and manufacturing, and self-employed youth with various levels of educational attainment will also be included. They will be recruited through various trade and business-related associations and other economic or social networks. Self-employed youth who are particularly vulnerable, including those with mental and physical disabilities, and adolescents will be purposively sampled. The total number of planned participants for the semistructured interviews is 60, roughly evenly divided between women and men based on an estimate of the number of participants we think we need to reach theoretical saturation (informed by previous qualitative studies of similar topics) [20]. Interviews will be audio recorded and transcribed verbatim. Transcripts will be analyzed as the study is ongoing, and the team will meet and decide whether the sample size needs to be reduced if theoretical saturation is achieved earlier (ie, the same themes repeat across interviews) or increased if it is not achieved (ie, new themes are still emerging).

Analysis

The audio-recorded interviews will be transcribed. Interviews conducted in Yoruba will be transcribed in Yoruba and translated into English, with caution taken to ensure that any nuances in communication are not lost. A practical thematic analysis will be conducted using ATLAS.ti software (version 24; Lumivero). Practical thematic analysis reframes the reflexive thematic analysis by Braun and Clarke [28] into 3 steps: reading, coding, and theming [29]. All members of the qualitative coding team will read through all the transcripts and code a few of the transcripts to develop a codebook. Then, each transcript will be coded independently by 2 members of the team, and the codebook will continue to be updated. There will be regular meetings to discuss emerging codes, and team members will be encouraged to regularly write reflective memos on their positionality as well as emerging findings. After the transcripts are coded, themes will be drawn out, and a thematic analysis session will be held, bringing all members of the qualitative analysis team together to decide on the final themes. To ensure the trustworthiness (credibility, dependability, transferability, and confirmability) of this qualitative research undertaking, researchers involved in collecting and analyzing the data will be encouraged to be reflexive by regularly writing field notes during data collection and memos during analysis. Insights from the field notes and memos will be incorporated while writing up to contextualize our findings. Reflecting our coproduction approach, self-employed young women are involved in data collection and analysis. To ensure the confirmability of our findings, the coding team will hold regular meetings to review and discuss emerging codes and themes. We will also do a member check-in with some of our participants so they can review the accuracy of our findings.

Quantitative Secondary Data Analysis

The Nigerian General Household Survey (GHS), Panel 2018-2019, and the COVID-19 National Longitudinal Phone Survey (COVID-19 NLPS), which covered all 36 states of Nigeria and the Federal Capital Territory, are being analyzed to assess the impact of the pandemic on the work and well-being of self-employed youth [30,31]. The COVID-19 NLPS sampling frame was derived from the GHS, so data from both surveys can be merged. The GHS panel collected individual and household-level data from 4976 households and the COVID-19 NLPS from 1950 households. The GHS panel data, collected before the COVID-19 pandemic, are serving as baseline data. From 2020 to 2021, 12 NLPS rounds were conducted, which can be compared with the GHS to understand the impacts of COVID-19. Both surveys have questions on health, employment, income status or changes, and coping with shocks. We are analyzing how factors such as sociodemographic characteristics, well-being, unpaid work, and access to banking and technology facilities affect the exit from self-employment to unemployment. The analysis will involve descriptive statistics and mixed models for longitudinal data. The work and health outcomes of self-employed young men and women are being compared, and self-employed youth are being compared with other age groups. Findings from these analyses will yield a comprehensive picture of the impact of the pandemic on self-employed young people.

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Scoping Review

Overview

We are conducting a scoping review on the gendered impact of the COVID-19 pandemic and other significant life events and experiences on the job quality and well-being of self-employed workers in LMIC. The scoping review protocol has been registered with the Open Science Framework [32].

Thus far, no scoping review has been conducted to examine the impact of the COVID-19 pandemic and other significant life events on self-employed workers. Our scoping review will answer the following research questions:

1. What are the common significant life events and experiences that self-employed workers in LMIC face?
2. How do these significant life events and experiences, including the COVID-19 pandemic, affect the job quality and well-being of self-employed workers in LMIC, and how do they cope?
3. Are there differences between self-employed women versus men in terms of the occurrence and impact of significant life events and experiences and COVID-19 on their well-being and job quality and how they cope?

Eligibility Criteria

Studies where self-employed workers are the population of interest will be included. We will include studies that examine the impact of the COVID-19 pandemic and significant life events on the job quality and well-being of self-employed workers. Studies conducted in LMIC, based on the World Bank's classification, will be included. The review will examine both peer-reviewed and gray literature published between 2003 and 2023. No study designs will be excluded from this review. We will not place a language restriction on the studies included in the scoping review. Non-English studies, which can be translated using Google Translate or through the services of native speakers, will be included.

Information Sources

The following databases will be searched: Global Health, Education Resources Information Center, PsycINFO, Business Source Ultimate, EconLit, Scopus, Sociological Abstracts, (ASSIA), Social Services Abstracts, ABI/INFORM Collection, Sociology Database, Social Science Database, SciELO, MEDLINE, and Cochrane CENTRAL. We will also search the websites of the World Bank and the International Labour Organization for relevant reports and working papers.

Search Strategy

The search strategy will include key terms derived from the scoping review research questions, including "self-employed worker," "entrepreneur," "business owner," "significant life event," "COVID-19 Pandemic," "job quality," "quality of work," "physical wellbeing," "mental wellbeing," "social wellbeing," and "coping." The Cochrane Effective Practice and Organisation of Care filter for LMIC will also be used [33]. A sample search strategy for the MEDLINE (Ovid) database is included in Multimedia Appendix 2.

Selection of Sources of Evidence

Studies identified through the search will be imported to Covidence (Veritas Health Innovation Ltd). Covidence is a web-based collaboration software platform that streamlines the production of systematic and other literature reviews [34]. Two independent reviewers will screen the title and abstract to select eligible studies. After titles and abstracts are screened, we will conduct a full-text screening of the studies. Any screening-related conflicts will be resolved by a third reviewer.

Data Charting Process

Data charting will be done independently by 2 reviewers. Any disagreements between 2 reviewers will be resolved by referring to a third reviewer for adjudication. We will hold a calibration exercise where the data charting form will be piloted by members of the team to ensure that it captures all relevant data.

Data Items

We will extract data on the dimensions specified in Table 1.

Table 1. Data items.

Dimensions	Details
General information	Author, year, country of study, and study setting (urban or rural)
Study characteristics	Objectives of the study and study methodology
Study population	Sampling strategy, sample size, and sociodemographic characteristics of participants
Significant life events and experiences	Various kinds of significant life events and experiences that self-employed workers face
Impact of significant life events	Impact of significant life events on job quality and well-being
Impact of the COVID-19 pandemic	Impact of the COVID-19 pandemic on job quality and well-being
Coping	Coping strategies of self-employed workers to deal with job quality and well-being
Gender differences	Gender differences in the impact of significant life events and the COVID-19 pandemic on job quality and well-being as well as coping strategies of self-employed workers

Synthesis of Results

We will present a narrative synthesis of the extracted data on the impact of significant life events and experiences, including the COVID-19 pandemic, on job quality and well-being of self-employed workers in LMICs. The findings will be thematically analyzed and organized as advised by Levac et al [35]. A summary table will be presented showing the extracted

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data items (article characteristics, study characteristics, and key findings). Any relevant descriptive statistics obtained during data extraction will be used to supplement the narrative synthesis. The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist is in Multimedia Appendix 3.

Digital Storytelling

This arts-based participatory method combines storytelling and technology to produce a film telling a personal or community story [36]. Digital stories are 3- to 5-minute videos that showcase a person's story. Digital storytelling will capture the experiences of self-employed young women and how they coped with the pandemic and other significant disruptive life events. In total, 10 women will be recruited to participate in the digital storytelling. The digital storytelling workshop manuals will be coproduced, and self-employed young women will be guided through the process of crafting narratives and producing their digital storytelling videos in a series of workshops. During these workshops, self-employed young women will have the opportunity to brainstorm ideas and choose their own individual stories they want to share via this medium. The focus of the stories will be on reflecting on their significant life experiences and how they overcame them. They will be supported to develop their story idea into a storyboard detailing how they will incorporate music, pictures, and other elements in the video. They will also be provided with technical support to convert these storyboards into videos capturing their experiences. After the digital storytelling videos have been completed, we will host a film screening of the digital stories, which will include discussion sessions involving the self-employed women whose stories are being told as well as other relevant stakeholders, such as other self-employed young women and men, policy makers, researchers, and the public. These discussion sessions will provide a forum for self-employed women to talk about their experiences developing digital stories and for other stakeholders to reflect on the thoughts and feelings after listening to or watching these videos. To get more information about the film screening attendees' perceptions of the stories shared for those who might not have been able to talk in the discussion sessions, a short web-based and phone survey will be administered to attendees after the film screening. A narrative analysis of the digital stories will be conducted to identify motifs emerging from the digital stories. The discussion sessions and survey will also be thematically analyzed to provide more insights into the impact of significant life events on self-employed young women and the community. The digital stories will be disseminated through web-based forums. The data from the digital storytelling process will shed light on the experiences of self-employed young women and the role stories can play in promoting resilience.

Aim 2: Coproduction of the Intervention Packages

Overview

The study's second component is the coproduction of intervention packages to improve the resilience of self-employed young women. The intervention packages are being informed by synthesizing available evidence from the situational analysis phase of the project and stakeholders' inputs. A theory of change approach will guide the coproduction of the intervention packages. This will facilitate the theory-driven design and evaluation of our proposed interventions and ensure their effectiveness and scalability [37]. The following methods will be used to coproduce the interventions: a systematic review, focus group discussions (FGDs) with self-employed young women and members of their support network and semistructured interviews with policy makers, policy analysis, and theory of change and coproduction workshops. Findings from the semistructured interviews with self-employed young men and women, quantitative secondary data analysis, digital storytelling, scoping review, systematic review, and qualitative interviews with members of the support network of self-employed young women and policy makers will be presented at the theory of change workshops. This will help inform the codevelopment of the theoretical map that will guide the choice and delivery of interventions on the project. In addition, the findings from the situational analysis and coproduction phases will inform the components of the intervention that will be developed and fleshed out in coproduction workshops.

Systematic Review

Overview

The systematic review will examine which interventions are effective in improving the job quality, well-being, and coping strategies of self-employed youth. The systematic review protocol titled "Protocol of a Systematic Review of Policies, Programs, and Interventions Designed to Improve the Job Quality and Well-being of Self-Employed Workers" has been registered on PROSPERO [38]. To improve the resilience of self-employed workers to withstand significant life events, it is important to identify which interventions will be most effective in improving their job quality and well-being. Furthermore, it is important to know to what extent self-employed workers were involved in the development of these interventions because coproduction is crucial in ensuring an intervention is relevant to its target population. The systematic review answers the following questions:

1. Which interventions are effective for improving the job quality, well-being, and coping strategies of self-employed workers? Are there gendered differences in the impact of these interventions?
2. To what extent have interventions that have been tested to improve the job quality, well-being, or coping strategies of self-employed workers included them as co-designers or taken gender into consideration?

The review will be reported in line with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [39]. The PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) checklist is included in Multimedia Appendix 5.

Eligibility Criteria

The participants of interest in this study are self-employed workers. Studies that report on interventions, programs, training packages, policies, and projects that aim to improve the job quality and resilience or well-being of self-employed workers

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will be included. Studies that have comparisons (control groups of individuals that did not have any intervention or those that had a less intensive or a different type of intervention) will be selected. Studies will be eligible if they include the primary outcomes of interest (well-being, job quality, and coping strategies) or secondary outcomes of interest (business performance, productivity, level of formality of their enterprises, and resilience). The review will consider the following study designs: randomized controlled trials (RCTs; including individual RCTs, cluster RCTs, and stepped-wedge designs), cohort studies, case-control studies, controlled before-and-after studies, interrupted time series studies, and controlled trials. The review will also include studies that use difference-in-difference estimation, synthetic control group methods, studies based on covariate matching, propensity-score–based methods, doubly robust methods, regression adjustment, regression discontinuity designs, and instrumental variable estimation. Systematic reviews, meta-analyses, and qualitative studies will be excluded. The review will include both peer-reviewed and gray literature published after January 1, 2023, until the date of the search. We will consider studies published anywhere across the globe. There is no language restriction on the studies that will be included in the systematic review.

Information Sources

The following databases will be searched: Global Health, Education Resources Information Center, PsycINFO, Business Source Ultimate, EconLit, Scopus, Sociological Abstracts, ASSIA, Social Services Abstracts, ABI/INFORM Collection, Sociology Database, Social Science Database, SciELO, MEDLINE, and Cochrane CENTRAL. The World Bank and International Labour Organization websites will also be searched.

Search Strategy

The search strategy is derived from the key terms in the research questions, including “self-employed worker,” “entrepreneur,” “intervention,” “program,” “policy,” “co-produced program,” “co-designed program,” “job quality,” “quality of work,” “wellbeing,” and “coping” alongside their synonyms. The search strategy will be tailored to the unique command language of each of the included databases. A sample search strategy for the MEDLINE (Ovid) database is included in Multimedia Appendix 4.

Selection Process

We will use Covidence, a web-based systematic review software, to manage the article selection and extraction process. Two reviewers will conduct title and abstract screening as well as full-text screening independently. Any conflicts arising during the abstract and full-text screening process will be resolved by a third reviewer who is an expert in the field.

Data Collection Process

Two reviewers will extract data from each eligible study. The information will be extracted from the eligible studies with the aid of Covidence and ATLAS.ti.

Data Items

The information presented in Textbox 1 will be extracted from each study.

Textbox 1. Data items.

- Participants: sample size, size of intervention arms, and demographic information (age, gender, and employment)
- Interventions: type of intervention, length of intervention, content of intervention, implementation context, and consideration of gender in the design and development of intervention
- Outcomes: primary outcomes of job quality, physical well-being, mental well-being, and social well-being as well as secondary outcomes of business performance, level of formality of the enterprises, productivity, resilience, coping, and their follow-up time points
- Methods: study design, follow-up time points, study location, study time frame, and the use of coproduction involving self-employed workers
- Results: effect sizes (mean differences and risk ratios), CIs, and *P* values

Study Risk of Bias Assessment

The risk of bias will be assessed using the revised Cochrane Risk of Bias tool for randomized trials [40] and Risk of Bias in Nonrandomized Studies of Interventions [41] at the outcome level. If there are sufficient studies for a meta-analysis, sensitivity tests will be conducted to examine the risk of bias judgments and exclude studies of poor quality.

Synthesis Methods

We will present a narrative synthesis of the findings to describe study participants, study context, study design, intervention components, and outcomes of the included studies. This information will also be presented in tabular form for each study. If there are sufficient studies with consistent designs and outcomes, a meta-analysis will also be conducted using R software (R Foundation for Statistical Computing). Sensitivity analyses will be used to exclude poor-quality studies from the meta-analysis. Subgroup analyses will also be conducted based on the following characteristics: (1) age of the self-employed workers undergoing the intervention and (2) gender.

Reporting Bias Assessment

A thorough assessment of selective nonreporting or underreporting of results in the studies included in the meta-analysis (if carried out) will be used to assess the risk of bias due to missing results.

Certainty Assessment

The Grading of Recommendations Assessment, Development and Evaluation approach will be used to assess the certainty in the body of evidence that will be generated through this systematic review. This review will yield insights that will be helpful in developing the intervention packages for this project.

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FGDs and Semistructured Interviews

Interventions from the literature cannot be applied to self-employed young women in Oyo State without ensuring their feasibility and cultural relevance. Focus groups will be conducted with self-employed young women and members from their support network (eg, husbands and parents) to determine appropriate elements in a coproduced intervention. Interviews will be conducted with policy makers involved in the development or implementation of policies and programs that are of relevance to self-employed young women, such as policy makers in the Federal Ministry of Women Affairs; the Federal Ministry of Youth Development; the Federal Ministry of Industry, Trade and Investment; and the Development Agenda for Western Nigeria Commission to gain their perspectives on appropriateness, fundability, and alignment with policy priorities for potential interventions, as it was considered more acceptable and feasible to conduct interviews (and not focus groups) with policy makers. Sample sizes will be based on theoretical saturation considerations, but we anticipate the participation of 28 self-employed young women and 21 members of their support network in the FGDs. We also anticipate the participation of 8 policy makers in the semistructured interviews. The sample size estimations are informed by previous qualitative studies on similar topics [42]. The audio recordings of the FGDs and semistructured interviews will be transcribed. The Yoruba transcripts will be translated into English. We will analyze the transcripts using reflexive thematic analysis with the aid of ATLAS.ti to identify what self-employed young women, members of their support networks, and policy makers consider to be contextually appropriate interventions. There are Yoruba-speaking members on the team to ensure that the analysis is contextual. Similar procedures will be followed as detailed in the analysis of semistructured interviews under the Aim 1: Situational Analysis section to ensure the trustworthiness (credibility, transferability, confirmability, and dependability) of the analysis process.

Policy Analysis

The policy analysis focuses on analyzing policies of relevance to self-employed youth in Nigeria to inform the development of contextually appropriate interventions. As part of the policy analysis, we will identify policies relevant to self-employed youth in Nigeria. We will also evaluate the effectiveness of policy strategies and policy implementation in supporting self-employed women in Nigeria and enhancing their resilience against disruptive life events. To accomplish this objective, we will thematically analyze policy documents and secondary literature that evaluate the effectiveness of identified policies. The analysis of these policies has been informing the identification of policy goals for the project as well as the mapping of relevant stakeholders to achieve the policy goals.

Theory of Change and Coproduction Workshops

While developing the protocol for this study, theory of change workshops were held in June 2022 involving the entire team, comprising self-employed young women, policy makers, and researchers, to develop a theoretical framework to guide the choice of interventions for this study. The theory of change map developed through these workshops can be found in Figure 1. Following this, a few more theory of change workshops have been held, which have led to the refinement of this map. The overall impact detailed in the theory of change map in Figure 1 is “improved resilience of self-employed young women to withstand disruptive life events.” This theory of change map details 4 broad categories of potential interventions. The intervention categories are capacity building, social protection and network building, health and wellness, and social protection interventions. The theory of change map also includes short- and long-term outcomes.

Coproduction workshops will also be held, bringing together self-employed young women, policy makers, and researchers to develop the content of the intervention packages. At the coproduction workshops, participants will brainstorm the contents of the intervention packages as well as develop, review, and refine intervention materials.

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Figure 1. First Version of Theory of Change Map.

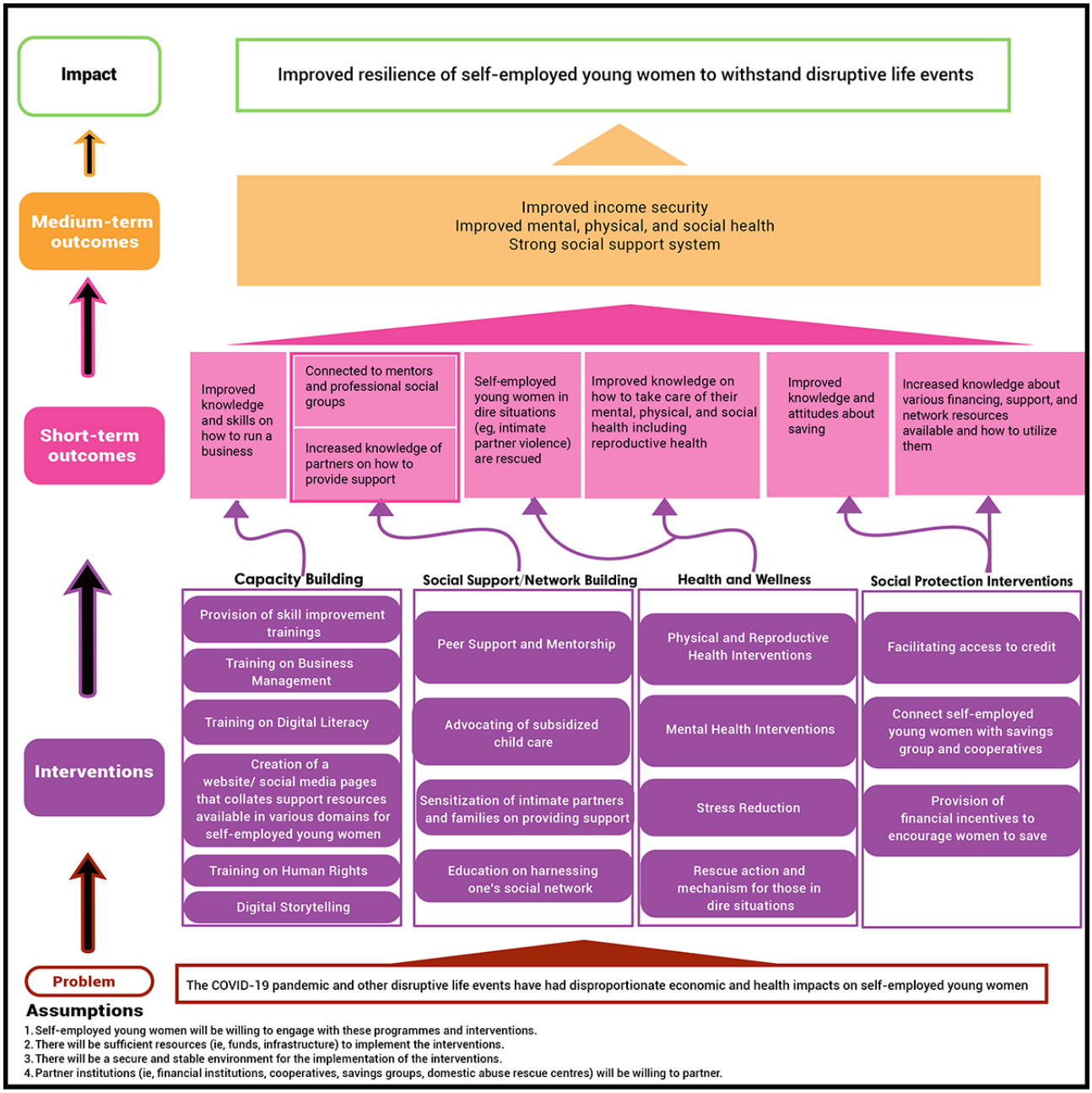

Aim 3: Pilot Trial of the Intervention Packages

Overview

The aim of this phase of the project is to pilot the coproduced intervention packages developed in phase 2 of the project to assess their feasibility, acceptability, cost, and potential effectiveness. This phase will also assess the factors that facilitated and hindered the implementation of the piloted intervention packages and what needs to be learned before scaling up.

The pilot of the ARISE&WIN interventions has been planned as a quasi-experimental study with a prepost design. The design was chosen because there was unanimity around it being feasible while allowing us to draw conclusions about the potential effectiveness of various interventions. The study will consist of 3 arms. One of the intervention groups will receive the capacity building intervention package. The second intervention group will receive the social protection intervention package in addition to the capacity building intervention package. The capacity building and the social protection interventions will be finalized during the coproduction process. The third group will be a control group serving as a comparison group, and participants will not receive any intervention. The pilot will be conducted in the LGAs of Greater Ibadan, where situational analysis has been conducted. The LGAs will be stratified into urban, periurban, and rural LGAs and randomly assigned to 1 of the 2 intervention groups or the control group. On the basis of recommendations from literature [43,44] on pilot trials, a sample size of 120 participants would be large enough to assess feasibility and other outcomes of interest in the pilot study. To account for possible attrition, the sample size would be rounded up to 150 in total, with 50 participants per arm of the trial. Frequency matching will be conducted to ensure that across the

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intervention and control LGAs, the participants will have similar characteristics based on age and their sector of occupation. Participants will be recruited through advertisements on social media platforms where self-employed young women are active. Announcements will also be made at business association meetings to identify eligible participants. Participants will also be recruited through partner organizations (SMEDAN and the Centre for Support of Women in Unpaid and Informal Employment in Nigeria) that work with self-employed young women.

All groups will participate in a preintervention survey. Then, the interventions will be delivered over a period of 4 months. Follow-up surveys will be conducted at 6 weeks at the end of the capacity building intervention and months 4, 6, and 12. As part of a process evaluation, in-depth exit interviews will be conducted with approximately 20 participants to gain deeper insights into their perceptions about the interventions they receive. In addition, a survey will be administered to intervention facilitators while a subset of them will participate in in-depth interviews.

Feasibility

The feasibility of recruitment will be measured by the percentage of the sample size that is recruited. To measure the retention rate of participants, the attendance of the participants in the intervention training sessions and their level of compliance with intervention guidelines will be recorded. Furthermore, facilitators and participants in the intervention will be asked questions about the feasibility of scaling the intervention and conducting a similar but larger-scale trial in both the survey questionnaires and in-depth interviews that will be administered at the end of intervention delivery.

Acceptability

To assess the acceptability of the interventions to the participants, they will be asked about how helpful they found the intervention, whether they liked the way the intervention was delivered, and their thoughts about the data collection instruments and the frequency of administration. The acceptability of the RCT design will also be assessed.

Cost

Comprehensive records of all costs incurred in implementing the intervention will be kept, including the costs of recruiting the participants and other intervention implementation costs, such as facilitator and participant compensation, training materials, equipment and venue renting, catering costs, transportation, and childcare costs of the participants. This will be used to calculate total costs as well as per-unit costs for participants.

Outcomes

The primary outcome of this study is well-being (financial, mental, and physical). Financial well-being will be measured using the Consumer Financial Bureau Financial Well-Being Scale [45]. Mental and physical well-being will be measured using the 9-item Patient Health Questionnaire [46], the 12-item General Health Questionnaire [47], as well as the 12-item Short-Form Health Survey [48].

The secondary outcomes that will be measured are earnings, savings, perceived social support, as well as access to health care. Earnings will be measured by asking questions about participants' revenues, costs, and profits from their sales. Savings will be measured by asking about the various persons, institutions, or organizations with which they save; how frequently they save; and how much they save each time they do. Social support will be measured using the Multidimensional Scale of Perceived Social Support [49] and the Self-Employment Social Support Scale [20].

In order to understand the pathways through which the interventions could affect the outcomes, questions will also be asked, which evaluate the knowledge, attitude, and practices of the self-employed young women who participate in the intervention in the various domains of the intervention, including business management; the use of digital technologies; the management of their personal and business finances; the use of resources available to self-employed young women in Oyo State; and caring for their mental, physical, and social health. Questions will also be asked to find out the number of business associations and other social groups that self-employed young women belong to, whether they have been rescued from any dire situations (eg, domestic violence), and how many of them are enrolled in health insurance. Questions will also be asked to members of the support network of self-employed young women who participate in the intervention to assess changes in their knowledge, attitudes, and practices toward providing support to the self-employed young women in their lives. Furthermore, the pre- and postintervention survey will include 3 rated items and an open-ended question about the impact of the last experienced significant life event on participants' ability to meet their needs and on their well-being and work.

Analysis

Participants' background characteristics will be summarized using frequencies and percentages for categorical variables, such as education, religion, marital status, etc. Means and SDs will be computed for numerical variables, such as age and income. The comparison of study outcomes across the 3 groups will be done using chi-square tests and 1-way ANOVA, as appropriate, at $P<.05$. Pairwise comparisons will also be done to compare the 2 intervention groups with the control group. Bonferroni adjustment will be made to correct for error rates that may be introduced by multiple comparisons. If necessary, generalized linear models will be fitted to adjust for confounders and pertinent variables that exhibit baseline differences between the study groups (eg, education status). Descriptive statistics and multivariate regressions will be adopted to analyze the Likert-scale questions in the survey on the feasibility and acceptability of the interventions to the participants and facilitators. All qualitative data in the study will be analyzed using the reflexive thematic analysis method.

Ethical Considerations

The project will follow international research standards and be guided by the Principles for Global Health Research by the Canadian Coalition for Global Health Research. Ethics approval has been obtained from the Oyo State Ministry of Health Research Ethics Committee (reference number:

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NHREC/OYOSHRIEC/10/11/22), University of Ibadan and University College Hospital Ethics Committee (reference numbers: UI/EC/23/0256 and UI/EC/24/0809), and McGill University Ethics Committee (reference number: A11-B42-23A). Written informed consent or assent will be obtained from all participants before their enrollment into the study. Participants aged <18 years will be required to provide assent, while informed consent will be obtained from their parents. No names or any other forms of identification will be used in publications or reports resulting from the study without the permission of the participants. In keeping with recommendations for digital storytelling, participants will have the choice of identifying themselves and sharing their testimony. The consent and assent forms, interview guides, and questionnaires have been translated to Yoruba, the local language of the study location, using World Health Organization–recommended translation and back-translation procedures. This has been done to ensure that participants understand the study procedure fully and make an informed decision about whether to participate or not. Participants will be compensated monetarily for their time participating in this study as well as their transportation costs. This compensation will range from 2000 Nigerian naira to 10,000 Nigerian naira depending on the number of hours of participation. The conversion rate is 1 naira=US $0.00062).

Data Management

All data will be digitally stored on the secure servers of the University of Ibadan and McGill University. Data will be stored in nonproprietary file formats wherever possible. All data will be anonymized and delinked from identifying information to ensure privacy and confidentiality. Knowledge translation materials will be openly available and uploaded to the International Development Research Centre repository. Scientific publications will be available open access.

Integrated Knowledge Translation

Table 2 lists target groups for the research project and the knowledge mobilization strategies that will be used to engage them.

Knowledge mobilization strategies have been continuously further refined based on the input of other stakeholders. The principles of coproduction and equity have been guiding knowledge mobilization activities (eg, plain language summaries will be created for self-employed young women and tailored summaries for policy makers and associations). Our project steering committee has also been advising us on knowledge translation for scale and impact. In summary, our knowledge translation will guide Oyo State, Nigerian, and global efforts to enhance the resilience, health, and well-being of self-employed young women against significant disruptive life events.

Table 2. Integrated knowledge mobilization strategies.

Knowledge users	Strategies
Self-employed young women	• Involvement of self-employed young women in the development, implementation, and dissemination of the findings of the project • Presentation of findings by “experts by experience” to associations and groups that the self-employed young women belong to • Dissemination of videos created through digital storytelling
State, regional, and national policy and decision makers	• Involvement of state and regional policy makers in the design and implementation of the project • Targeted dissemination of policy briefs, intervention guidelines, digital storytelling videos, and peer-reviewed articles to policy makers • Meetings and seminars with policy makers to inform them of the findings of the project and advocate for the scale-up of coproduced interventions
Scientific community and researchers	• Peer-reviewed publications • Conference presentations
General public	1. Dissemination of the findings of the project through press releases, social media platforms, and web content, as well as open-access publications

Results

The recruitment of participants for the situational analysis phase of the project began in May 2023 and ended in January 2024. The recruitment of participants for the pilot study began in November 2024 and will be completed in January 2025. Data collection will be completed in November 2025. Table 3 gives details on the status of the various components of the study.

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Table 3. Status of various components of the Advancing Resiliency in Self-Employed Young Women in Nigeria (ARISE&WIN) study.

Activity	Status
Semistructured interviews with self-employed young women and men	Interviews have been conducted and are being analyzed.
Quantitative secondary data analysis	Analysis of secondary data is ongoing.
Scoping review	We are currently conducting full-text screening.
Digital storytelling	Digital stories have been created and disseminated. We are writing our analysis of these stories and their reception.
Systematic review	We are extracting data and conducting risk of bias assessments for selected studies.
Focus group discussions with self-employed young women and members of their support network and key informant interviews with policy makers	Interviews have been conducted and are being analyzed.
Policy analysis	Policies have been analyzed. We are writing the results.
Theory of Change and coproduction workshops	Theory of change and coproduction workshops have been conducted.
Pilot trial of the intervention packages	The intervention packages are currently being delivered. Data collection will be completed in November 2025.

Discussion

This is a gender-transformative project that will provide a greater understanding of the impact of the COVID-19 pandemic and other significant disruptive life events on the working lives and well-being of self-employed young women in Nigeria and the norms, attitudes, and structures that perpetuate gender inequity. Through a collaboration between the researchers, self-employed young women, policy makers, and other relevant stakeholders, the project will result in suitable and contextually appropriate gender-transformative interventions to enable young women to better cope with events that disrupt their work and well-being and improve their income security; their mental, physical, and social health; and their social support system. The interventions that will be developed will consider the perspectives and needs of women who are particularly marginalized, including those with mental and physical disabilities and those with little or no formal education. These interventions will differ from previous interventions for self-employed young women in this context because they will be coproduced, and intentional attention will be paid to gender dynamics in their design. The results of the pilot study will be used to ascertain the feasibility, acceptability, cost, and potential effectiveness of the coproduced intervention packages. The results of the pilot study will be used to refine the intervention packages in preparation for a large-scale efficacy trial.

Research and policy-related findings will be disseminated through peer-reviewed articles, policy briefs, intervention guidelines and manuals, press releases, social media, and web content. Multistakeholder meetings involving self-employed young women, government officials, impact investors, researchers, and other relevant individuals will be organized to disseminate and discuss the findings from the various stages of research over the course of the project. The partnership with Oyo State Ministry of Women Affairs and Social Inclusion, SMEDAN, and the Centre for Support of Women in Unpaid and Informal Employment in Nigeria in the development and rollout of this project will enhance the uptake and scale-up of the intervention. Our partnership with the Development Agenda for Western Nigeria Commission, an organization responsible for facilitating policy design and implementation for the 6 states in the southwest of Nigeria, will enable the scale-up of the policy findings from this project to other Nigerian states.

This project will build capacity among self-employed young women to coproduce and contribute to research and policy development. The project will also develop their capacity by improving their knowledge and skills on how to run a business, improve their knowledge on how to take care of their health, and enable them to harness existing networks to better support their businesses through disruptive events. The project will enhance the capacity of the research team and policy makers in coproduction so that research and policy have greater relevance to the lived realities of young, self-employed Nigerian women.

Ultimately, this project will help advance Sustainable Development Goal (SDG) 3 “to ensure healthy lives and promote well-being for all at all ages”; SDG 5 to “achieve gender equality and empower all women and girls”; and SDG 8 “to promote sustained, inclusive, and sustainable economic growth, full and productive employment, and decent work for all.” It will also advance SDG 1 “nobody will live in extreme poverty,” SDG 2 “end hunger and achieve food security,” and SDG 16 “promote peaceful and inclusive societies for sustainable development.”

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

O Omigbodun, SNI, IKM, AT, O Owoade, JA, FMO, AFA, OE, and OT contributed to conceptualization. O Omigbodun and SNI contributed to funding acquisition. O Omigbodun, SNI, JA, FMO, AT, and IKM contributed to the methodology. IKM and O Omigbodun contributed to project administration. O Omigbodun and SNI contributed to supervision. CO contributed to visualization. IKM contributed to writing the original draft. AT, JA, O Owoade, FMO, AFA, OE, OT, OA, RT, AA, CO, SNI, and O Omigbodun contributed to reviewing and editing the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guides for semistructured interviews and focus group discussions.
[DOCX File , 50 KB - resprot_v14i1e69577_app1.docx]

Multimedia Appendix 2
Scoping review sample search strategy.
[DOCX File , 20 KB - resprot_v14i1e69577_app2.docx]

Multimedia Appendix 3
PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist.
[PDF File (Adobe PDF File), 668 KB - resprot_v14i1e69577_app3.pdf]

Multimedia Appendix 4
Systematic review sample search strategy.
[DOCX File , 17 KB - resprot_v14i1e69577_app4.docx]

Multimedia Appendix 5
PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) checklist.
[DOCX File , 25 KB - resprot_v14i1e69577_app5.docx]

Multimedia Appendix 6
Peer review report by the International Development Research Center (Canada).
[PDF File (Adobe PDF File), 156 KB - resprot_v14i1e69577_app6.pdf]

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Abbreviations

ARISE&WIN: Advancing Resiliency in Self-Employed Young Women in Nigeria
COVID-19 NLPS: COVID-19 National Longitudinal Phone Survey
FGD: focus group discussion
GHS: Nigerian General Household Survey
LGA: local government area
LMIC: low- and middle-income countries
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT: randomized controlled trial
SDG: Sustainable Development Goal
SMEDAN: Small and Medium Enterprises Development Agency of Nigeria

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Protocol

Establishing a System for Medical Certification of Cause of Death for Noninstitutional Deaths in a Selected Area of Kolar District, Karnataka, India: Protocol for a Population-Based Feasibility and Validation Study

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Abstract

Background: Medical Certification of Cause of Death (MCCD) coverage in India is only 22.5%, largely due to a significant proportion of deaths occurring outside hospitals (noninstitutional deaths). The cause of death (CoD) in such cases is unlikely to be certified by any doctor. This study attempts to address this gap by developing an MCCD system for noninstitutional deaths in India.

Objective: This study will assess the feasibility of a physician-derived cause of death (PhyCoD) approach for deducing CoD in noninstitutional deaths in a selected area of Kolar Taluk, Karnataka, and validate this approach.

Methods: This population-based feasibility and validation study will be conducted in 4 selected hospitals and 2 Primary Health Centre (PHC) areas in Kolar taluk, Kolar district, Karnataka, India. We developed 4 PhyCoD questionnaires: maternal, neonatal, child, and adult. Institutional deaths that occurred over the previous 10 months in these selected hospitals with detailed case records available were selected as “gold standard” cases. Trained investigators abstracted the history from these case records into the questionnaires and deduced the CoD sequence of events. The investigators then elicited the history from the deceased’s relatives using the PhyCoD questionnaire and deduced the CoD sequence of events. This will be compared with the gold standard CoD sequence of events deduced from medical records. The extent of agreement will be measured. The tool will be revised based on the pilot phase experiences. For all brought dead cases to the 4 hospitals and home deaths in the 2 PHC areas over a 3-month period, doctors in these hospitals and PHC medical officers, respectively, will elicit the history from the deceased’s kin using the PhyCoD questionnaires and arrive at a CoD sequence of events. This CoD sequence of events will be validated against the gold standard autopsy whenever possible (in brought dead cases). The PhyCoD approach will also be tested for inter-rater reliability by independent investigators on a random sample of noninstitutional deaths.

Results: Institutional ethics committee clearance (January 2024), recruitment and training of project staff (January 2024-January 2025), preparation of questionnaires and application (August 2024-February 2025), pilot phase data collection (48 cases; August 2024-December 2024), and training of the doctors in the participating hospitals and PHC medical officers (December 2024) are complete. A total of 48 cases (32 adult, 7 child, 3 maternal, and 6 neonatal) were included in the pilot phase. Data review and analysis of the pilot phase data are underway.

Conclusions: The study is expected to provide information about the validity and feasibility of the PhyCoD approach. Depending on the study’s outcomes, the tool may be adopted by more states, leading to increased coverage of noninstitutional deaths under MCCD, improved accuracy, and reduced delay of CoD reporting for noninstitutional deaths.

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KEYWORDS

Medical Certification of Cause of Death; noninstitutional deaths; physician-derived cause of death; PhyCoD

Introduction

Reliable age and gender-wise cause of death statistics are required on a regular basis by administrators, policy planners, and others for evidence-based decision-making regarding identifying the priority areas for resource allocation, monitoring of various indicators, and other related activities in the area of public health. Keeping this in mind, the Medical Certification of Cause of Death (MCCD) scheme was introduced in India under the provisions of the Registration of Births and Deaths (RBD) Act, 1969. The cause of death information is recorded in the prescribed formats (form 4 for institutional deaths and 4A for noninstitutional deaths) by doctors attending to the decedent during their last illness and submitted to the local registrars (Figure 1). However, the coverage of MCCD for the total number of registered deaths in India is dismal, at 22.5%, and this low coverage has hardly improved over the last decade [1]. This is largely attributed to a significant proportion of deaths (60%-70%) occurring outside the hospital (deaths at home, such as deaths during sleep and sudden deaths, and those occurring during travel to the hospital), which are classified as noninstitutional deaths. The cause of death in such cases is unlikely to be certified by any doctor.

Figure 1. Medical Certification of Cause of Death (MCCD) data flow in India. CoD: cause of death; CRS: civil registration system; ICD: International Classification of Diseases.

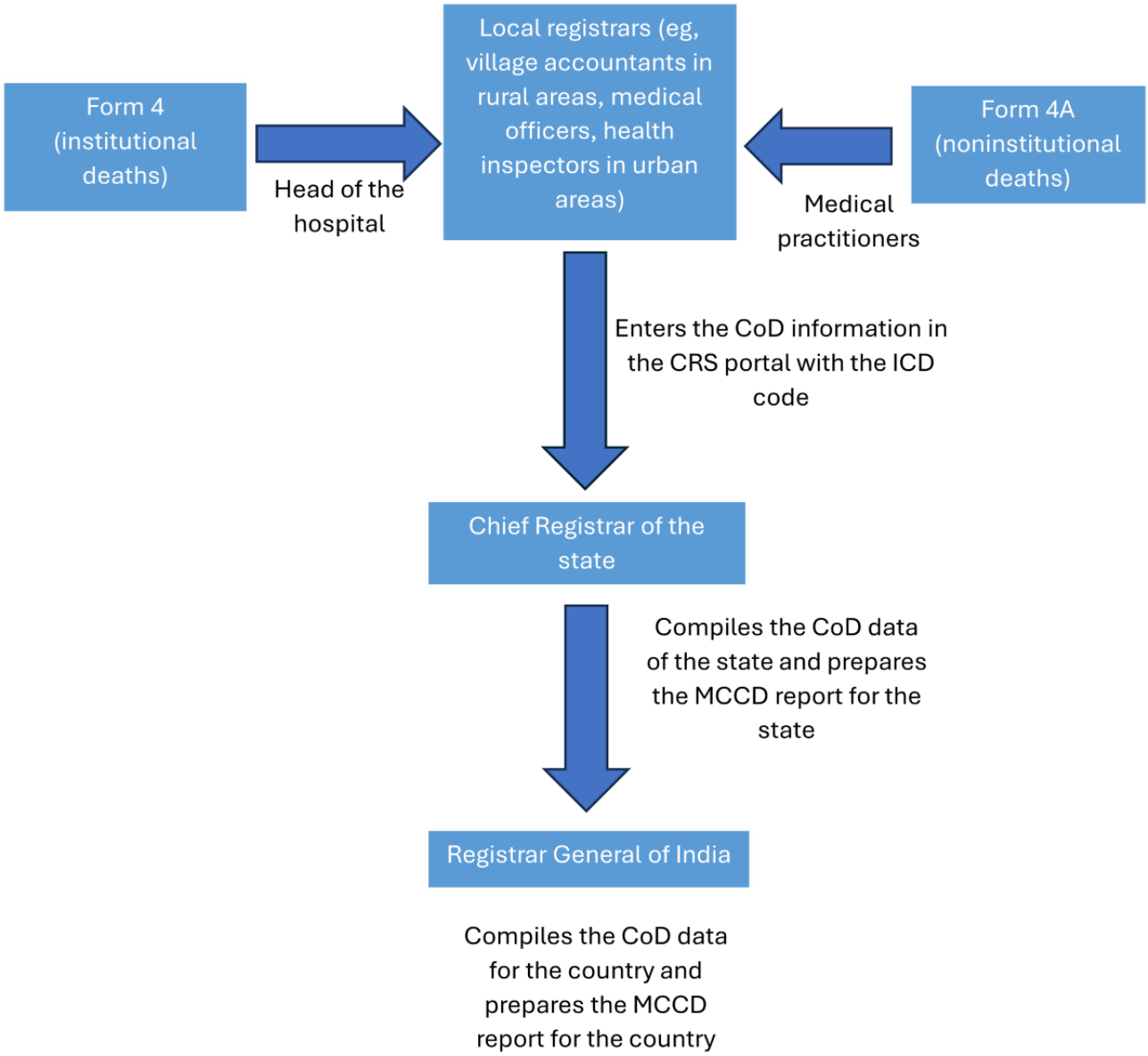

In instances of persons declared as "brought dead" to the hospital where an unnatural cause is suspected, an autopsy is performed as per legal procedures. Even in instances where an unnatural cause is not suspected, autopsy is advised to determine

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the cause of death. However, the relatives of the deceased refuse an autopsy in most such cases. There are very few hospitals in India where a clinical autopsy is performed. The physician in the hospital does or can not certify the cause of death in such cases, as he/she has not treated the case. Hence, such deaths end up without a documented cause of death. A large proportion of deaths occurring in homes (eg, old age) may not even reach the hospital or a doctor at all.

The RBD Act, 1969, and its recent amendment in 2023 clearly state that, for all deaths, the cause of death has to be certified by the doctor who attended to the decedent in his/her recent illness. However, it does not clarify how the cause of death can be certified for an individual who has not received any medical care in the immediate period before death [1,2].

In recent times, most of the states in India have mandated that hospitals submit form 4 (MCCD form) for all deaths occurring in institutions in order to complete the death registration. However, for "noninstitutional deaths" (deaths occurring in any place other than medical institution), the MCCD form (form 4A) is neither insisted upon nor is any suitable guidance provided. As a result, noninstitutional deaths, which account for 60%-70% of all deaths in India, end up without a medically certified cause of death. This was one of the important observations in an implementation research study conducted in 6 states by the Indian Council of Medical Research - National Centre for Disease Informatics and Research (ICMR-NCDIR), Bengaluru. The scenario is similar across most low-income countries [3,4].

This study attempts to develop a system to address the gap in MCCD coverage for noninstitutional deaths. The recent MCCD report of India states that there is some type of contact with a medical facility just before death in 54.6% of registered deaths [1]. Hence, it may be worthwhile to establish a system for deriving the cause of death for noninstitutional deaths by involving medical doctors.

This would add to the already existent methods of arriving at an underlying cause of death: (1) MCCD for institutional deaths (under the civil registration system [CRS]) and (2) verbal autopsy (VA) under the sample registration system (SRS). VA is conducted by lay workers called SRS supervisors who collect the history from the family members of the deceased using a validated tool, and the information is subsequently reviewed by physicians to derive the cause of death (physician-coded VA). This 2-step process is time-consuming and delays assignment of the cause of death. Moreover, SRS is limited by the population coverage for deriving cause of mortality statistics at the state or national level and by the availability of doctors proficient in reviewing the narratives in many regional languages [5,6].

In this study, doctors will use a validated questionnaire to collect the history of the deceased using multiple available sources of information like relatives, medical records, and investigations to arrive at the cause of death events. As doctors are well versed in taking the history and abstracting the cause of death information to the MCCD form, this approach using a physician-derived cause of death (PhyCoD) is likely to significantly reduce time and resources in arriving at the cause of death and increase the reliability as compared with SRS VA. In this context, this study will be conducted to assess the feasibility of a PhyCoD approach for deducing the cause of death in noninstitutional deaths in a selected area of a Taluk of Kolar district, Karnataka, and to validate this approach.

Methods

Data Collection

This population-based feasibility and validation study will be conducted for a duration of 24 months (February 2024-January 2026) in Kolar Taluk (Taluk is an administrative subdivision of a district), Karnataka. Kolar is a district in the south Indian state of Karnataka, with a population of 15,36,401 (2011 census) and an MCCD coverage of 9.9% (much below the state level of 26.7%) [7-9]. The district is a pioneer for several health-related projects like Digital Nerve Centre of Tata Community Services and Kolar Comprehensive Primary Health Care Initiative of the Society for Community Health Awareness, Research and Action (SOCHARA) [10,11]. Four hospitals (1 government district hospital and 3 private hospitals, of which 1 is a medical college) and 2 PHC areas (1 urban and 1 rural) in Kolar Taluk have been identified to be part of the study. The identified hospitals and PHC areas are those with the highest case load and highest population, respectively, in the Taluk. ICMR-NCDIR had recently (2022-2024) conducted an implementation research study in 6 states of India. Kolar district of Karnataka was also a part of the study, and 3 of the 4 hospitals selected in this study were part of the earlier implementation research study. Hence, Kolar district was selected for the study.

The study is being implemented by the principal investigator (PI), co-PIs, and project staff from ICMR-NCDIR, Bengaluru, as per the timelines in Figure 2. Permissions have been obtained from the Department of Health and Family Welfare, Government of Karnataka, and Chief Registrar of Births and Deaths, Karnataka, and nodal officers in the district have been designated by their respective departments for further coordination. Participating hospitals and PHCs were identified based on the inputs of these nodal officers, and necessary directions were issued to these hospitals and PHCs for their cooperation.

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Figure 2. Timeline of the project. IEC: institutional ethics committee; PHC: Primary Health Centre.

Sl No	Activity	1-3 months	4 -6 months	7-9 months	10-12 months	13-15 months	16-18 months	19-21 months	22-24 months
1.	IEC clearance								
2.	Recruitment and training of project staff								
3.	Communication with the Dept of Health, Office of Chief Registrar, Hospitals								
4.	Codal formalities with hospitals and PHC								
5.	Preparation of the tools, training of doctors								
6.	Pilot Phase								
7.	Implementation Phase (I and II)								
8.	Data analysis								
9.	Dissemination of findings								

The PhyCoD tool has been developed and comprises of 4 questionnaires, as follows: (1) questionnaire for neonatal deaths (deaths postbirth to 28 days), (2) questionnaire for child deaths (deaths 29 days onward to 14 years), (3) questionnaire for maternal deaths (for deaths of women aged 15 years to 49 years during pregnancy, delivery, or within 42 days of delivery including deaths during and within 42 days of abortion), and (4) questionnaire for adult deaths (all other deaths).

The age criteria for these questionnaires align with the SRS VA questionnaires [12]. The PhyCoD questionnaires are similar to history-taking questionnaires routinely used by doctors and comprise fields such as chief complaints, history of presenting illness, past history, examination findings, and investigations with a checklist within the questions based on the World Health Organization (WHO) and SRS VA questionnaires so as not to miss any information. Both WHO and SRS VA questionnaires contain a checklist to capture the history of the deceased, which will help the reviewing doctor arrive at the cause of death. Although the WHO VA tool has a wider focus and scope to capture a wide variety of presentations and causes of death, the ability of the SRS VA questionnaires to capture these is limited [12,13].

The chief complaints are listed in each of the PhyCoD questionnaires considering the causes of death for each of these groups as per the recent MCCD report [1]. In addition, provision has been made to capture other presentations, if any. The questionnaires also have a provision to record the narrative as given by the kin of the deceased so as to understand the sequence of events leading to death.

The study will be conducted in 2 phases: (1) pilot phase and (2) implementation phase (Figure 3).

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Figure 3. Methodology of the pilot and project phases. CoD: cause of death; MO: Medical Officer; PHC: Primary Health Centre; PhyCoD: physician-derived cause of death.

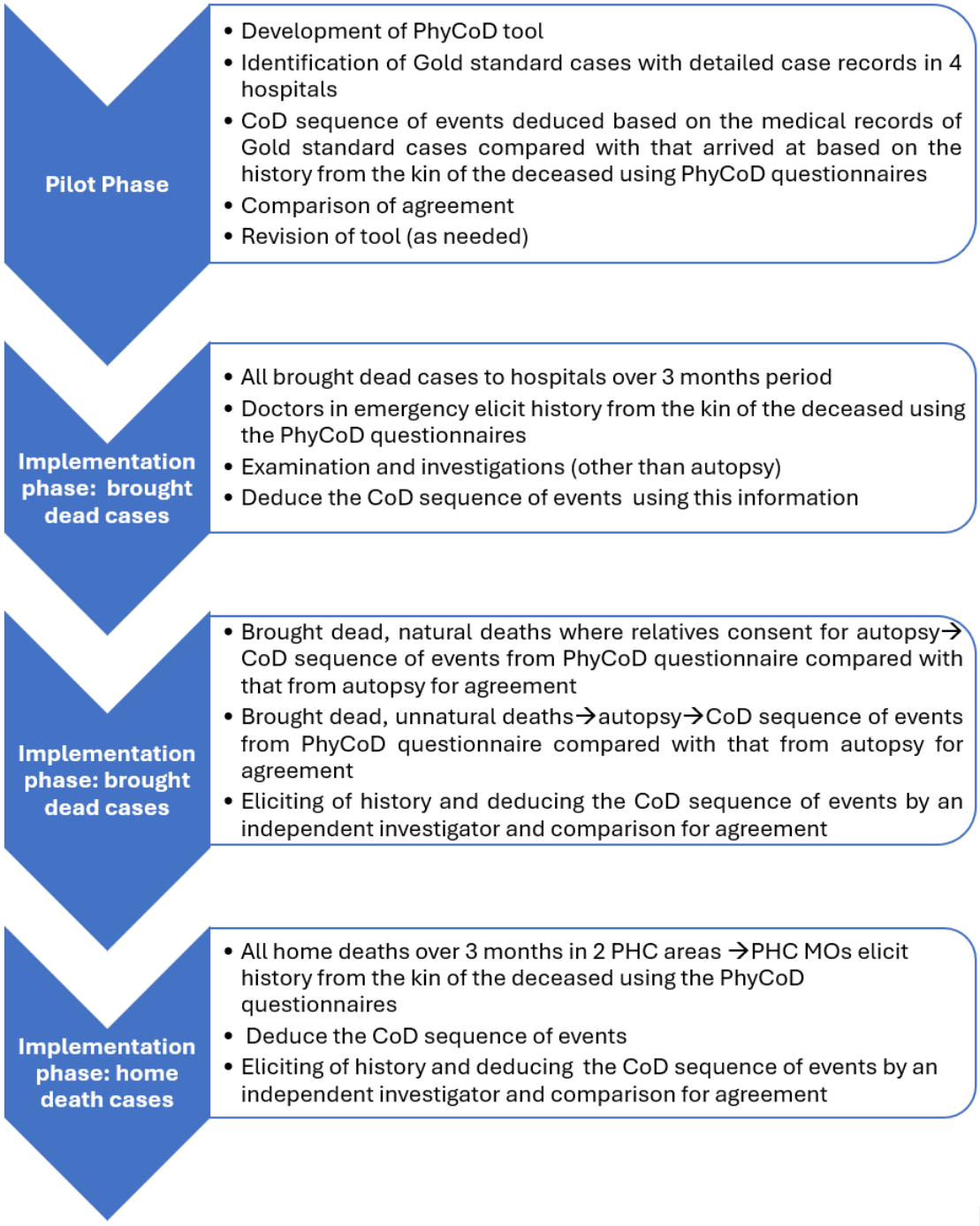

During the pilot phase, institutional deaths with detailed case records that had occurred in the previous 10 months in the District Hospital and Medical College were selected. Trained investigators (who included faculty from the Community Medicine Department of the medical college and postgraduates in dental sciences and public health) and the PI abstracted the case history into the PhyCoD questionnaires and arrived at the cause of death sequence of events (ie, immediate, antecedent, and underlying) using the information. The houses of the deceased were located with the help of the district health officials and local PHC staff. These trained investigators subsequently conducted a home visit and administered the tool among relatives of the deceased to elicit the history of the deceased including a review of any available medical records and derived the cause of death sequence of events. Abstraction of the case history (at the hospital) and eliciting the history from the kin of the deceased (during the home visit) were conducted by all the investigators. However, arriving at the cause of death sequence of events was performed by medical doctors (ie, the PI and faculty from the Community Medicine Department). Blinding was ensured in such a manner that the investigator conducting the home visit for a particular case was different from the one who abstracted the case history in the hospital.

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The cause of death sequence of events determined based on the history elicited from the kin of the deceased during the home visit will be compared with the "gold standard" cause of death sequence of events derived from the medical records. The agreement between the PhyCoD and the gold standard with respect to the underlying cause of death and major cause group will be measured. Based on the experiences in the initial pilot phase, the questionnaires were revised to make them more specific and user-friendly and to prevent any information from being missed. For example, new questions like treatment received for current illness were added, and specific subquestions were added within open questions like past history and antenatal, natal, and postnatal history.

The final versions of the questionnaires are available in Multimedia Appendices 1-4.

A minimum of 30 cases was selected as the sample size for the pilot phase based on the proportions of maternal, neonatal, child, and adult deaths in the CRS and SRS, as shown in Table 1 [14,15].

Table 1. Proportions of maternal, neonatal, child, and adult deaths in the civil registration system (CRS) and sample registration system (SRS).

Death	Proportion in CRS, %	Proportion in SRS, %	Proportion out of 30 (CRS), %	Proportion out of 30 (SRS), %
Maternal	7	6.1	2.1	1.8
Neonatal	0.2	0.5	0.1	0.1
Child	3.3	14.5	1	4.3
Adult	89.5	78.9	26.8	23.7

Accordingly, it was decided to have at least 3 maternal, 2 neonatal, 5 child, and 27 adult cases. In addition, for each type of death, an attempt was made to include the different types of cause of death within the category (eg, communicable diseases, noncommunicable diseases, external cause for adult) subject to availability.

The pilot phase has been completed, and data review and analysis are underway.

In the implementation phase, the tool will be administered in 2 settings: (1) brought dead cases to the 4 hospitals and (2) home deaths in the 2 selected PHC areas.

The process of handling the brought dead cases in the hospital and the roles and responsibilities of various stakeholders will be mapped. Similarly, the process of reporting, death registration, and MCCD in home death cases will be mapped. At least 1 doctor from the major departments (where deaths occur) in each of the 4 hospitals and the Community Medicine Department (in case of the medical college) and medical officers from the 2 PHC areas have been trained in MCCD, collecting history using the PhyCoD tool, and arriving at cause of death sequence of events using this information in noninstitutional deaths. All noninstitutional deaths (deaths at home and during travel to the hospital or clinic, including unnatural deaths) that occur over a 3-month period will be considered. Post hoc power analysis will be done at the end of the study to determine the power.

Brought dead cases to the 4 hospitals over a period of 3 months starting from January 1, 2025, will be considered. Doctors in casualty or assigned for the research study will elicit the history from the kin of the deceased using the PhyCoD questionnaire including a review of available medical records. They will also perform the examinations (other than autopsy) and investigations that are relevant for arriving at the cause of death and will record all these findings in the PhyCoD questionnaire [16]. Based on all this information, the doctors will arrive at the cause of death sequence of events.

All brought dead cases that are suspected to be unnatural will undergo an autopsy as per the rules. In cases of brought dead cases that are likely to be natural deaths, the attending doctors will counsel the relatives about the need for a clinical autopsy to determine the cause of death for public health purposes. In the instances where the relatives agree, a clinical autopsy will be performed. The PhyCoD sequence of events will be compared with that from the autopsy report to determine the extent of agreement.

History will be collected from one or more attendants accompanying the deceased. They may include relatives, friends, or acquaintances of the deceased who lived with the deceased or know the medical history of the deceased as well as eyewitnesses like co-passengers, passersby, and police at the time of death.

Deaths occurring over a period of 3 months (starting from December 24, 2024) at home in the 2 PHC areas will be considered. Information on deaths will be obtained from health workers of the PHC and District Statistical Office.

The PHC medical officers of the 2 PHC areas will visit the houses of the deceased after the grieving period but within 1 month of death and elicit the history using the PhyCoD tool from the relatives, review the medical records if any, and deduce the cause of death sequence of events. Community Health Officers (nursing graduates) in the PHC area have also been trained to elicit a history using the PhyCoD questionnaires to complement the doctors in the event of the PHC Medical Officer being unable to cover all home deaths. However, deducing the cause of death sequence of events will be done by the PHC Medical Officer only, based on the review of history collected using the PhyCoD questionnaire.

History will be collected from one or more informants, who may include relatives, friends, or acquaintances of the deceased who stay with the deceased or know the medical history of the deceased as well as eyewitnesses at the time of death.

Data collection for the project phase started on January 1, 2025, and is expected to be completed by May 31, 2025.

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Validation

In brought dead cases for which an autopsy is performed, the PhyCoD sequence of events will be compared with that from the autopsy report (gold standard) for accuracy.

In a 20% sample of home deaths in the 2 PHC areas and a 10% sample of brought dead cases (other than those for which autopsy is done) in 4 hospitals selected by simple random sampling, an independent trained physician will elicit the history from the kin of the deceased using the PhyCoD tool and deduce the cause of death sequence of events. The extent of agreement between the cause of death sequence of events deduced by the 2 physicians will be measured (inter-rater reliability).

Data Collection, Software Development, and Database Management

A web-based application has been developed to capture information pertaining to neonatal, child, adult, and maternal deaths using the latest Microsoft technologies and MS SQL Server. The questionnaires have skip patterns, validations, and built-in quality checks (eg, for all female deaths, the pregnancy and delivery-related field in the MCCD form is mandatory; for all deaths for which autopsy field is completed in the questionnaire, a mandatory second MCCD form is enabled to be completed by the doctor conducting the autopsy) to capture accurate information. The application has access-based privileges for data entry, searching records, and downloading records. The web-based application allows access from any location with an internet connection, and the data will be synced directly with the online database server hosted by ICMR-NCDIR.

Data will be collected using tabs by the doctors of the 4 participating hospitals and 2 PHC Medical Officers. All data collected will be stored on a secure server at ICMR-NCDIR for subsequent retrieval and analysis.

Statistical Analysis

The kappa statistic will be used to measure extent of agreement between the cause of death sequence of events (1) deduced from the case records and that arrived at using the PhyCoD questionnaire from the kin of the deceased during the home visit (pilot phase), (2) deduced by the physician and that deduced by autopsy (implementation phase), and (3) deduced by doctors at the participating hospitals and PHC Medical Officers and that by independent assessors (implementation phase)

The extent of coverage of brought dead cases in the 4 hospitals and home deaths in the 2 PHC areas for eliciting the history using the PhyCoD questionnaire will be measured. The challenges encountered by various stakeholders during implementation will also be recorded.

Ethical Considerations

Ethical clearance has been obtained from the ICMR-NCDIR Institutional Ethics Committee (number NCDIR/IEC/3073/2023, 21/02/2024). Written informed consent will be obtained from the kin of the deceased in the presence of impartial witness(es). Identity of the deceased and contact details of the kin of the deceased will be collected for the purpose of clarification, if any, pertaining to the history at a later stage. However, these will be kept strictly confidential and will not be shared with any unauthorized third party or revealed in any publications. Data will be stored in password-protected systems, and only the PI and co-PIs will have access.

Results

The following activities have been completed (Figure 2): institutional ethics committee clearance (January 2024), recruitment and training of project staff (January 2024-January 2025), preparation of questionnaires and the web application (August 2024-February 2025), pilot phase data collection (48 cases; August 2024-December 2024), and training of center PIs, doctors at the 4 participating hospitals, and 2 PHC Medical Officers (December 2024).

Although a total of 60 cases were selected for the pilot phase, 12 were not reachable for home visits. Hence, a total of 48 cases (32 adult, 7 child, 3 maternal, and 6 neonatal) were included in the pilot phase. Data review and analysis of the pilot phase data are underway.

Discussion

This study intends to address the gap in coverage as well as accuracy of MCCD for noninstitutional deaths in India, which account for more than 60% of the registered deaths. The study intends to develop a tool for physicians to deduce the cause of death for noninstitutional deaths. The study will also describe the feasibility of completing the MCCD for noninstitutional deaths using existing manpower and infrastructure as well as the likely challenges in achieving this. It will also validate the approach.

The findings of the study shall be shared with the Office of the Registrar General of India, Chief Registrar of Births and Deaths of Karnataka, and the Department of Health, Karnataka. Based on the outcomes of the project, the approach may be subsequently implemented in other districts and states of the country to increase the coverage of MCCD for noninstitutional deaths.

The likely challenges that may be encountered during the implementation of the project are described in the following paragraphs. There may be very limited history available in a significant proportion of cases such as sudden death in healthy middle-aged persons with no other previous illnesses and frail older adults (>80 years) presenting with only generalized weakness and no other morbidities.

In such cases, the doctors would have to rely on investigations and clinical autopsy, which may be helpful in arriving at the cause of death. These may be refused by the kin of the deceased in a significant proportion of cases.

In a certain proportion of cases, there will be limited information available in the medical records or from the kin of the deceased. This would pose an important challenge in validating the questionnaires during the pilot phase. In addition, in a significant proportion of cases, especially individuals with multiple morbidities, it could be difficult to delineate the cause of death

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sequence of events. This could be an important challenge during the implementation phase.

The strength of the study is that it attempts to leverage the experience and skills of medical doctors from within the health system for increasing the coverage of MCCD for noninstitutional deaths. Studies in the past have only attempted to strengthen the quality of VA under SRS. The limitation of VA is that history is collected by a lay person (SRS supervisor) from the kin of the deceased and subsequently reviewed by a medical doctor (who is located far away is not aware of the context) to arrive at cause of death. Because of this, there are chances of information being lost or misinterpreted. Also, the history collected in VA under SRS is in the local language. Hence, a considerable number of medical doctors proficient in various regional languages need to be available. This is a challenge in the case of some regional languages. In addition, because of the complicated process, there is a considerable delay in arriving at cause of death (approximately 9 months) [5,17]. These limitations are likely to be addressed by this approach. The medical knowledge of the doctors may significantly augment the quality of history elicited. In addition, the doctor has an opportunity to perform a physical examination of the body in brought dead cases, which is also likely to add to the accuracy of the derived cause of death.

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GenAI was not used in any portion of manuscript generation.

Data Availability

The data will be deposited into the institutional data repository of the Indian Council of Medical Research-National Centre for Disease Informatics and Research (ICMR-NCDIR), and access to other researchers will be provided subject to approval of the competent authority.

Authors' Contributions

Conceptualization: MM, SR, PM
Funding acquisition: MM
Methodology: MM, SR, VK
Software: PD, MBV
Writing – original draft: MM, SR
Writing – review & editing: MM, SR, VK, PM

Conflicts of Interest

None declared.

Multimedia Appendix 1
Maternal death questionnaire.
[PDF File (Adobe PDF File), 289 KB - resprot_v14i1e72330_app1.pdf]

Multimedia Appendix 2
Adult death questionnaire.
[PDF File (Adobe PDF File), 296 KB - resprot_v14i1e72330_app2.pdf]

Multimedia Appendix 3
Neonatal death questionnaire.
[PDF File (Adobe PDF File), 302 KB - resprot_v14i1e72330_app3.pdf]

Multimedia Appendix 4
Child death questionnaire.
[PDF File (Adobe PDF File), 301 KB - resprot_v14i1e72330_app4.pdf]

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Abbreviations

CRS: civil registration system
ICMR: Indian Council of Medical Research
ICMR-NCDIR: ICMR-National Centre for Disease Informatics and Research
MCCD: Medical Certification of Cause of Death
PHC: Primary Health Centre
PhyCoD: physician-derived cause of death
PI: principal investigator
RBD: Registration of Births and Deaths
SOCHARA: Society for Community Health Awareness, Research and Action
SRS: sample registration system
VA: verbal autopsy
WHO: World Health Organization

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Protocol

Optimizing Availability and Appropriate Use of Assisted Vaginal Birth: Protocol for Generic Formative Research of an Implementation Preparation

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Abstract

Background: Assisted vaginal birth is a lifesaving procedure where health workers use special devices to expedite birth vaginally when some complications emerge, such as due to prolonged labor. When the use of assisted vaginal birth is possible and appropriate, it provides benefits over cesarean section. These benefits include shorter recovery, reduced hospital stays, lower risks of complications, cost savings, and greater likelihood of vaginal birth in future pregnancies. Despite these benefits, the use of assisted vaginal births has declined in recent years. Challenges remain on how to implement assisted vaginal birth effectively, equitably, and at scale in different health systems. Formative research is useful to understand local health system preparedness, acceptability, feasibility, and resource availability for designing and implementing health interventions.

Objective: We developed a generic formative research protocol that can be used to design and implement interventions to optimize use of assisted vaginal birth in any setting and context.

Methods: This formative research protocol is to be conducted in the setting where interventions to optimize assisted vaginal birth will be implemented. The formative research has three components: (1) document review, (2) readiness assessment, and (3) primary qualitative research. Document review will examine existing policy and guidelines, while readiness assessment will assess the service delivery context. The 2 components aim to identify potential barriers and facilitators to use of assisted vaginal birth. Primary qualitative research will involve women, families, community members, health workers, facility administrators, and policy makers. Interview questions are structured around potential interventions to optimize use of assisted vaginal birth. This protocol includes all the essential study instruments.

Results: This is a generic research protocol that can be used by any stakeholder aiming to optimize assisted vaginal birth in any setting. Serving as a preparatory guide, it provides a structured approach for planning and implementing evidence-based and context-specific strategies aligned with best practices in maternal health care. No data collection or analysis has been conducted to date.

Conclusions: This generic protocol can serve as a guide in conducting formative research as intervention preparation to optimize use of assisted vaginal birth. The results can inform the design and implementation of appropriate interventions from the perspectives of important stakeholders. Therefore, we recommend that trialists, clinicians, researchers, administrators, and policy makers use this protocol before implementation to understand local context and incorporate perspectives of key stakeholders to promote equitable, high-quality, and women-centered care.

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KEYWORDS

assisted vaginal birth; ventouse; vacuum; forceps; implementation science; childbirth; labor; cesarean section; formative research; qualitative research; behavior change

Introduction

Background

Assisted vaginal birth is a lifesaving procedure where health workers use special medical devices to help women give birth vaginally. Assisted vaginal birth instruments include forceps and vacuum extractors. Since 2009, the World Health Organization (WHO) has included assisted vaginal birth as one of the "essential signal functions" of basic and comprehensive emergency obstetric care [1]. Women may benefit from an assisted vaginal birth during the second stage of labor when challenges around prolonged labor exist [2]. These challenges may be due to the baby's head position, fetal distress, maternal exhaustion, or medical indications that limit women's ability to push or require speeding up the birth [2]. When the use of assisted vaginal birth is possible and appropriate, it provides advantages compared with cesarean birth [3-5]. Compared with cesarean birth, assisted vaginal birth is linked to faster recovery, shorter hospital stays, lower risk of hemorrhage and infection, cost-effectiveness, and increased likelihood of spontaneous vaginal birth in subsequent pregnancies [3-5].

However, assisted vaginal birth also has some risks, including increased likelihood of perineal tears, long-term pelvic floor dysfunction, and maternal sepsis [6-8]. Neonatal trauma, including superficial scalp or facial lacerations and cephalohematoma, can occur with assisted vaginal births [6,9]. In rare cases, more severe injuries such as brain hemorrhage, skull fractures, and nerve-related problems may also occur [2]. However, the likelihood of experiencing these adverse complications from assisted vaginal birth is exceedingly low [2,6], especially compared with the risks associated with a cesarean section at full cervical dilatation [2]. Furthermore, it is difficult to determine whether these risks are associated with assisted vaginal birth, or with the conditions that lead to the need of the intervention [2]. Mitigating these risks necessitates the careful selection of women for whom assisted vaginal birth may be appropriate, and trained and skilled professional to perform the procedure [6]. Furthermore, effective communication with women regarding the potential benefits and risks of assisted vaginal birth is crucial for informed decision-making.

Despite the potential benefits, assisted vaginal birth has decreased in recent years [10-13]. Globally, there are wide variations in assisted vaginal birth rates, ranging from 1.1% in Latin America, 1.7% in Africa, 2.5% in Asia, 3.1% in the United States, and 6.8% in Europe [10-13]. Variations are also observed within regions: in Europe, assisted vaginal birth rates exceed 12% in France, United Kingdom, Spain, and Ireland, but remain below 2.5% in Romania, Croatia, Lithuania, Slovakia, and Latvia [12,13]. Assisted vaginal birth is more common in high-income countries than in low- and middle-income countries (LMICs) [10,14]. The reasons for the low use of assisted vaginal birth are multifactorial. Women and health workers may prefer cesarean birth to assisted vaginal birth due to its perceived safety, quick action, convenience in scheduling, and when analgesia for assisted vaginal births is not available [15-17]. Limited training, equipment, supervision, and support, and fear of litigation also contributed to the low use of assisted vaginal births by health workers [18,19].

Improving Appropriate Use of Assisted Vaginal Birth

Improving availability and quality of assisted vaginal birth may reduce maternal and neonatal morbidity and mortality without resorting to cesarean birth [2]. This is particularly beneficial in LMIC settings where many births occur in primary care facilities with limited access to timely emergency care [3,20]. In these settings, cesarean safety may not be guaranteed, and cesarean birth may require referral to a higher-level facility [3,20,21]. However, challenges remain on use of assisted vaginal birth, particularly on how it can be implemented effectively, safely, equitably, and at scale in LMICs [3]. A 2023 technical brief from WHO identified the critical gaps in optimizing assisted vaginal birth [13,22]. This included gaps in how to best educate and train health workers to acquire and maintain knowledge and skills to perform assisted vaginal birth [13]. Gaps also remain in evidence-based guidelines and protocols, equipment availability, pain relief for women, clinical and supervisory support, and the sustainability of these resources [13]. Additionally, evidence gaps exist on how to effectively inform and engage women in assisted vaginal birth decision-making [23] and to prevent misconceptions and foster informed decision-making. Given these complexities, stand-alone training interventions are likely to be insufficient to optimize use of assisted vaginal birth [13]. Instead, integration of training into multifaceted interventions to improve physiological labor management may be needed [13]. Designing such interventions should consider various factors influencing their success, which include women's and families' preferences and values, health worker behaviors, and health system and legal contexts. WHO recommends that programs aiming to optimize assisted vaginal birth should conduct formative research before implementation to identify and explore context-specific factors that may influence the availability and appropriate use of assisted vaginal birth [13].

We developed a generic formative research protocol to understand context-specific barriers and facilitators in the use of assisted vaginal birth. This formative research should be considered as the first stage of a multistage research project. The next stage would be to design implementation strategies to address the identified barriers and reinforce facilitators, followed by implementation and evaluation. This protocol serves as a

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guide and includes research instruments to assist research teams in conducting formative research in any context and setting. Throughout this protocol, we used the term "optimizing" when referring to improving the availability and appropriate use of high-quality and timely assisted vaginal birth. This term is to consider 2 different settings. First, in settings where cesarean has replaced assisted vaginal birth and is no longer practiced; therefore, reintroduction of assisted vaginal birth is needed. Second, in settings where use of assisted vaginal birth is limited and increased use may play an important role in improving outcomes.

Objectives

The specific objectives of the formative research are to (1) explore national and health facility policies that may impact the availability and feasibility of interventions aimed at optimizing assisted vaginal birth; (2) assess the readiness of health facilities to implement any interventions aimed at optimizing use of assisted vaginal birth; (3) explore preferences, expectations, acceptability, and feasibility of the interventions aimed at optimizing use of assisted vaginal birth from the perspectives of key stakeholders: women, communities, health workers, and policy makers; and (4) explore potential factors (barriers and facilitators) that may influence intervention implementation.

Methods

Conceptual Framework

Factors Influencing the Use of Assisted Vaginal Birth

Decision-making on whether to use assisted vaginal birth is complex, occurring in emergency settings influenced by preferences, knowledge, and experiences of health workers, women, and the health care environment. Health workers may not have the knowledge and skills to decide to or to conduct assisted vaginal birth [3]. Where health workers have been trained, they may hesitate to perform assisted vaginal birth, due to the perceived complexity of assisted vaginal birth, fears of failed attempts, litigation following poor outcomes, or HIV transmission [3]. Addressing these challenges requires improving health workers' knowledge and skills, task clarity, mentoring, task sharing, and ensuring resources and equipment availability [3]. Moreover, unsupportive work environments can hinder use, especially when clinical protocols for transitioning from assisted vaginal birth to cesarean birth are unclear [3]. Thus, clear protocols, supportive supervision, and local ownership over assisted vaginal births initiatives are critical [3].

Women's perceptions and experiences are also essential to consider [23]. Women may have fears about assisted vaginal birth due to pain relief absence, exclusion from decision-making, and lack of partner or family support [3]. Negative interactions with health workers can also hinder use, often stemming from power imbalances, poor communication, and mistrust of health systems [3]. Therefore, ensuring pain relief availability and fostering positive communication between health workers, women, and partners or families are critical. Figure 1 demonstrates the complexity of assisted vaginal birth uptake, emphasizing the importance of examining various influencers from different stakeholders before implementing any intervention.

Figure 1. Ecological model on assisted vaginal birth decision-making. Adapted from Bohren et al [24] on factors influencing cesarean birth.

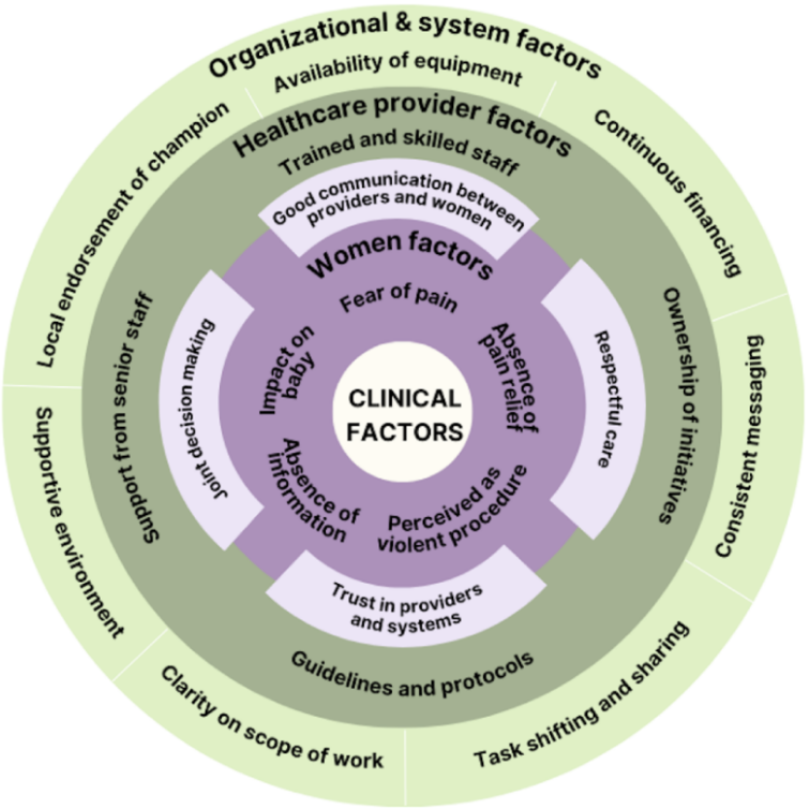

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Set of Interventions to Optimize Assisted Vaginal Birth

Interventions proposed to optimize use of assisted vaginal birth are often part of broader interventions to improve labor management [3], an approach also encouraged by the WHO [13]. These may include education and training, appointing opinion leaders, providing equipment, implementing guidelines, task shifting and sharing, and audit and feedback [3]. The education and training should cover both assisted vaginal birth and broader physiological labor and birth management [3]. To date, most interventions have focused on addressing health facility and health worker factors, with little consideration of women, partners, or community views. WHO has emphasized the need to understand women's knowledge, belief, and fears about assisted vaginal birth. Information sharing with women and joint decision-making are paramount to women's involvement, and exploring how best to achieve this is crucial [13,23]. Figure 2 depicts the potential interventions that may be helpful to optimize use of assisted vaginal birth [3,13] In this study protocol, we provide options to explore which interventions may be suitable to address the identified facilitators and barriers in any given setting. We propose using behavior change frameworks to map barriers and facilitators identified in the formative research, which will help identify potential strategies.

Figure 2. Schematic representation of potential interventions to optimize use of assisted vaginal birth.

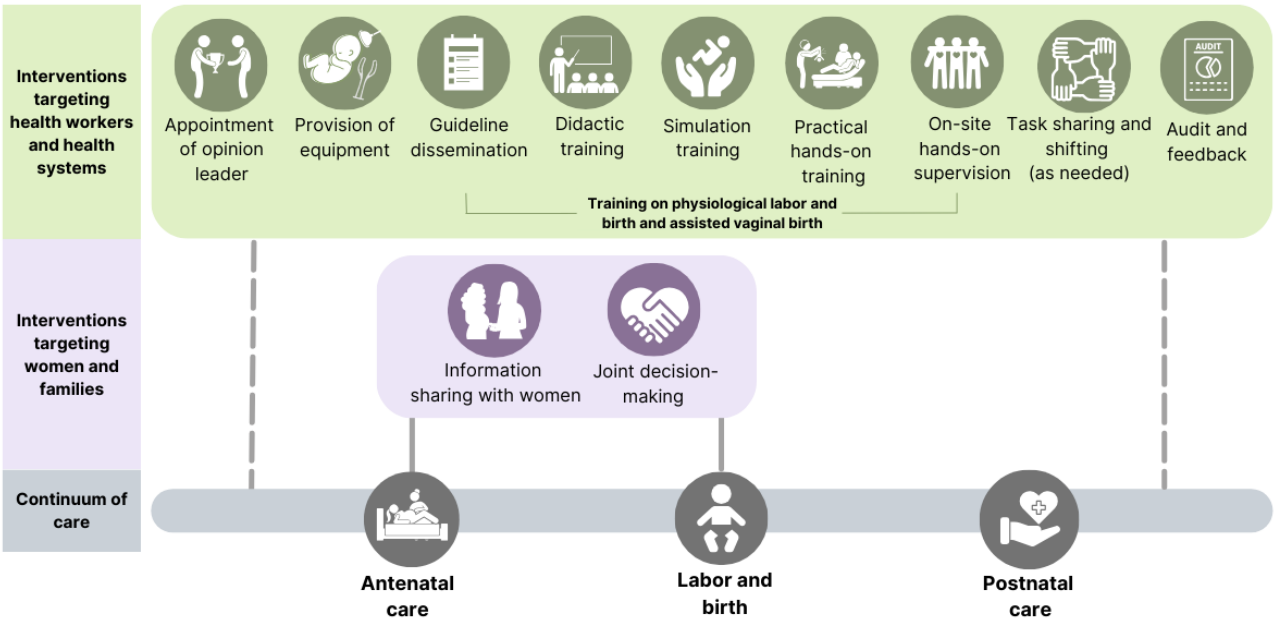

Linking Intervention Design to Behavior Change and Implementation Science Frameworks

Growing evidence indicates that understanding and addressing individual and organizational behaviors are critical to improve implementation of evidence-based practices [25,26]. One model that captures the complexity of different behaviors is the COM-B (Capability, Opportunity, and Motivation) model of behavior change [26]. COM-B posits that individuals require capability, opportunity, and motivation to perform a desired behavior [26]. Capability points to individual capacity, including knowledge and skills, which influences the desired behavior [26]. Motivation includes drivers of the desired behavior, such as goals, emotions, beliefs, and impulses [26]. Opportunity refers to external factors outside of the individual that may influence the desired behavior [26]. Opportunity includes existing policies, communities' perceptions, and environmental structures [26]. Both an individual's capability and opportunity influence their motivation, which in turn affects their intended behavior [26]. Similarly, the intended behavior then impacts their overall capability, motivation, and opportunity [26]. The Theoretical Domains Framework (TDF) expands the COM-B model to categorize the barriers and facilitators to change [27]. The barriers and facilitators under the COM-B and TDF domains can be mapped to the Behavior Change Wheel to identify potential interventions that address barriers and reinforce facilitators [26]. The Behavior Change Wheel comprises 9 types of interventions and 7 policies that can be implemented to promote behavior change [26].

In this protocol, we propose the use of the COM-B and TDF frameworks to guide the study design and instruments to identify barriers and facilitators influencing the optimization of assisted vaginal birth. The "desired behavior" is defined as appropriate use of assisted vaginal birth. In addition to these frameworks, this protocol development was guided by the potential interventions identified by Torloni et al [3], the ecological framework in Figure 1, and the WHO technical brief on optimizing use of assisted vaginal birth [13].

Study Designs and Settings

This formative research consists of three research components: (1) document review, (2) health facility readiness assessment, and (3) primary qualitative research. This formative research will be conducted in communities, health offices, and health facilities where interventions to optimize assisted vaginal birth will be implemented. The study sites will be health facilities that provide childbirth care services. These could be public and private health facilities and of different levels (tertiary, secondary, and primary), as appropriate in the study setting.

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Site-specific adaptations of this protocol may be necessary, which should be discussed within the research team.

Document Review

Document review can inform methods to evaluate intervention impact, identify resources and procurement change needs, and help understand factors affecting an intervention's sustainability postintervention [28]. The type of documents to review should be discussed with the research team and relevant stakeholders, such as health workers, government officers, and policy makers. The documents may include, but are not limited to, national guidelines, policies, professional responsibilities including reference to legal status on who and where assisted vaginal birth can be conducted, training materials, health system capacity, human resources availability, functional equipment, clinical protocols, algorithms, or decision-making charts [28]. Although some documents may be publicly available, the research team might need to contact relevant authorities to obtain them. If public or aggregate data are unavailable, the team may need to request facility-specific data. In this formative research, the document review focuses on maternity care context and information about assisted vaginal birth. The research team will review the relevant documents and enter the extracted information into a designated instrument. This document review instrument (Multimedia Appendix 1) is designed based on SUPPORT tools using evidence from local conditions [28].

Health Facility Readiness Assessment

Following the document review, the research team will be better informed to conduct readiness assessment. Readiness assessment aims to describe and assess the service delivery context ahead of implementation. Logistically, readiness assessment can be conducted simultaneously with qualitative research and should be conducted at all study sites. The readiness assessments ensure that intervention design and implementation considerations are informed by the actual context. The readiness assessment will describe physical space, health workforce, models of care, clinical protocols, data availability, training needs, and audit and feedback practices in study health facilities. These service environment descriptions can be synthesized with primary qualitative research results to identify important barriers and facilitators to address. The readiness assessment instrument can be found in Multimedia Appendix 2.

The readiness assessment will be conducted at each health facility involved in the study. Approval will be sought from the management of the health facilities before conducting the readiness assessment. The research team will arrange meetings with facility managers to explain the readiness assessment's purpose, scope, and methods, and request approval to proceed. Once approval is received, all relevant staff will be informed of the purpose and procedures of the readiness assessment. Since there will be no direct interaction or consultation with women, their consent will not be sought for the readiness assessment observations.

At least 1 team member with clinical knowledge will visit the health facility to observe the labor ward and relevant documents (eg, associated guidelines and clinical protocols). The readiness assessment may take several hours, depending on how busy the facility is. The readiness assessment will be scheduled with the facility managers to ensure minimal disruption to routine clinical duties. It may be helpful to conduct assessments during non–peak hours to reduce interference with clinical work. The research team will wear an identification badge and maintain a respectful distance to ensure that privacy is not compromised and to avoid encountering sensitive or clinical interactions.

Primary Qualitative Research

This study proposes using in-depth interviews (IDIs) and focus group discussions (FGDs) to understand barriers and facilitators to the use of assisted vaginal birth use from the perspectives of women, family and community members, health workers, facility administrators, and policy makers. These perspectives encompass perceptions, preferences, experiences, acceptability, expectations, and feasibility concerning assisted vaginal birth, interventions to optimize its use, and how to best implement them. A suitable mix of stakeholder groups should be identified through consultation with the local research team, health workers, and community members.

Given the limited use of assisted vaginal birth globally, many participants may not be familiar with this procedure, making it challenging to engage meaningfully in IDI and FGD. To address this, we have developed educational materials, consisting of a comic and a frequently asked questions document (Multimedia Appendices 3 and 4), to facilitate participants' understanding. When a participant is unfamiliar with assisted vaginal births, data collectors will first explain the frequently asked questions document and participants will be given time to review it, followed by presenting the comic to further illustrate the procedure. These materials will be delivered in the participant's preferred language, using culturally appropriate terminology. To ensure consistency across IDI and FGD, all data collectors will be trained on how to introduce assisted vaginal birth with the comic and frequently asked questions document. This will standardize how the educational materials are introduced and explained.

The use of comics for disseminating health information to lay people has been previously used in clinical and public health settings [29-31]. Comics can be easily read and transcend barriers of literacy, language, knowledge, age, and culture [30], making them a potential tool for conveying information easily about assisted vaginal birth. To avoid triggering anxiety among participants, the comic focuses on the continuum of care, depicting the entire birth process rather than assisted vaginal birth as a stand-alone procedure. To ensure cultural acceptance of the comic and the frequently asked questions document, the research team may need to discuss and adapt to their setting.

Participants

The following participants are proposed for the primary qualitative research to better understand the care context:

1. Maternity service users, including
   - women who gave birth in the past 6 months and experienced assisted vaginal birth;
   - women who gave birth in the past 6 months and have not experienced assisted vaginal birth;

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- women's representatives who work in women's organizations and agencies;
- women's partners;
- mothers-in-law; and
- community members (traditional birth attendant, queen mother, village champion, older adult women, or others depending on the settings).

2. Health workers involved in antenatal care and childbirth, including
   - obstetricians and other doctors who work in the maternity ward, including trainees and medical officers;
   - midwives and nurses; and
   - other skilled birth attendants, as appropriate.
3. Facility administrators, including
   - matron-in-charge of the labor ward;
   - head of obstetrics;
   - medical director; and
   - finance, legal, and other administrators.
4. Policy makers, including
   - ministry of health staff, and
   - local health office staff.

We propose to talk to women who gave birth in the past 6 months—both who *have* and *have not* experienced assisted vaginal birth in the past 6 months—and women's representatives from women's organizations and agencies. A 6-month postpartum time frame is set to ensure that women have sufficient recovery time while still recalling their birth experience. There will be no exclusion criteria imposed, such as clinical complications, mode of birth, intrapartum stillbirth, and so on. In settings where some degree of assisted vaginal birth is practiced, we suggest conducting IDIs with women who have assisted vaginal birth in the past 6 months, FGDs with women who have given birth in the past 6 months, and IDIs with women's representatives. However, we acknowledge that it may be challenging to find women who underwent assisted vaginal birth in settings with limited or no use of the procedure. In this type of setting, we propose to conduct only FGDs with women who have given birth in the past 6 months and IDIs with representatives from women's organizations and agencies.

Other than women, FGDs will also be conducted with women's partners, family members, and community members. The selection of community member types will depend on local contexts. Partners, family members, and community members will participate in combined FGDs; however, to account for gender dynamics, we propose to conduct separate sessions for men and women. The study will also involve IDIs with health workers and facility administrators at health facilities. It may also be useful to conduct IDIs with health professional associations where appropriate, and decision should be made within the research team. Finally, IDIs will be conducted with policy makers at the ministry of health or local health offices. Relevant policy makers will be those overseeing maternal and newborn health and have experience in health policy formulation around labor management, guideline development, or resource supply and distribution. We will invite participants aged 18-49 years to participate. However, depending on the context, it may be appropriate to invite women younger than 18 years, such as in settings where adolescent pregnancy is high or young pregnant women are considered emancipated [24].

Sampling

Maximum variation sampling will be used [32]. Maximum variation sample encourages recruitment and sampling based on diversity and uses specified parameters to stratify the sample [24,32]. Including individuals from diverse backgrounds is critical to ensure that research findings accurately reflect the perspectives of local stakeholders. Adapting a previously developed generic formative research protocol for cesarean birth that has demonstrated feasibility and usefulness [24], we have developed a sampling grid for this study (Table 1). The sampling grid will guide the recruitment, sampling approaches, and number of participants to be recruited. However, data collection should continue until data saturation is reached [33,34]. Data saturation will be determined when no new codes or themes emerge in at least 2 consecutive interviews or focus groups. The determination of saturation will be made through regular debriefings by the qualitative lead and the research team, ensuring consistency in interpretation.

The research team should ensure diverse participant representation, such as women from urban and rural areas, with different parity, modes of birth, various ethnicities, religions, and ages. Depending on the scope of planned implementation, it may not be necessary to conduct IDIs and FGDs with women in all study facilities. If the number of facilities involved in the planned implementation is small (eg, less than 5), conducting IDIs and FGDs with women in all facilities may be appropriate. However, if the number of health facilities is large (eg, more than 5), selecting some facilities may be more feasible and appropriate. Suppose a subsample of health facilities is chosen. In that case, the selected health facilities should reflect diversity based on geographical region, urban or rural settings, level of care (eg, tertiary, secondary, and primary), and number of annual births.

IDIs with health workers should be conducted at all health facilities involved in the study, as the health facility–specific barriers and enablers may vary. Facility administrators will be sampled based on their roles and, at a minimum, should include the head of obstetrics and the matron-in-charge of maternity. A diverse group of health workers will be recruited based on gender, age, and working years. In particular, the research team will ensure a balanced representation of gender among the health workers who participate in the study. Depending on the scope of planned implementation, policy makers should be sampled from both the ministry of health and the regional or district health offices.

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Table 1. Proposed sampling grid for primary qualitative research.

Participant groups	n (per study facility)	Types of diversity to consider
Maternity care users	5-9 IDIs[a], 1-2 FGDs[b]	Depending on the settings, where assisted vaginal birth is high or low.
Postpartum women who experienced assisted vaginal birth in the past 6 months	3-6 IDIs	Interviewing this women's group may be feasible only in settings where assisted vaginal birth is practiced. In these contexts, consider recruiting women from both higher and lower-level health facilities to understand potential referral pathways. Additionally, diversity in race or ethnicity, parity, urban and rural locations, and age should be ensured to reflect diverse views.
Postpartum women who gave birth in the past 6 months, regardless of mode of birth	1-2 FGDs (5-10 people per group)	Consider including various birth modes—cesarean section and vaginal birth—along with diversity in race or ethnicity, parity, urban and rural locations, and age to ensure a comprehensive representation of views among participants.
Women representatives from women's associations or organizations	2-3 IDIs	Women's associations should focus on women's health and rights or those that advocate for maternal health.
Maternity care users' family and community members	2-4 FGDs	Depending on the context, consider gender dynamics and diversity in community member groups.
FGDs with women only	1-2 FGDs (5-10 people per group)	This group will include mothers-in-law of women participating in interviews or focus groups, and community members. The selection of community members (traditional birth attendants, queen mothers, village champions, older adult women, or others) will depend on the context.
FGDs with men only	1-2 FGDs (5-10 people per group)	This group will include partners of women participating in interviews or focus groups, and community members. The selection of community members (traditional birth attendants, queen mothers, village champions, older adult women, or others) will depend on the context.
Health workers	6-9 IDIs	Depending on the context, diversity in terms of the level of health facilities should be considered, including both lower-level and higher-level facilities.
Doctors	2-3 IDIs	Different types of doctors, such as obstetricians, medical officers, and doctors in training, should be included. Gender, racial or ethnic, working years, and age diversity of health workers should be considered to reflect diverse views.
Midwives and nurses	2-3 IDIs	Different working years, genders, races or ethnicities, and ages should be considered to reflect diverse views.
Administrators (eg, matron in charge)	2-3 IDIs	Different types of administrators should be considered, including clinical directors, matron-in-charge, head of obstetrics, finance, and legal officers.
Policy makers	2-3 IDIs	Different levels of policy makers, such as the ministry of health to the regional or district health office, gender, and working years, should be considered.

[a]IDIs: in-depth interviews.

[b]FGDs: focus groups discussions.

Recruitment

Recruitment posters in local languages will be displayed at the health facility's waiting area, consultation rooms, community halls, public health centers, and health offices to recruit potential women, community members, health workers, facility administrators, and policy makers. The posters will contain information about the study, eligibility criteria, and how to join the study. Depending on the settings, the study team may use the phrase "women and other pregnant people" in recruitment posters to ensure inclusivity.

Additionally, the study team will approach women who gave birth in the past 6 months during their postpartum or vaccination visits, with 1 non–health facility staff member present on-site to engage potential participants. This helps prevent power imbalances between health workers and women, which could lead to feelings of coercion in participation. Using facility records, women who indicated receiving assisted vaginal birth in the past 6 months will also be contacted to invite them to participate in the study. Conversely, the research team will approach women's representatives, partners, family members, community members, and policy makers using snowball

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sampling through recommendations from gatekeepers, networks, and participating women. Health workers and administrators will be recruited at the health facility, with the research team reaching out during department meetings or via telephone or email using staff records. However, the recruitment strategy for health workers should be discussed with the maternity ward heads to decide on the best approach.

Potential participants interested in participating will be given a plain language statement (Multimedia Appendix 5), informed consent form (Multimedia Appendix 6), and time to read and decide to participate. After a few days, research team members will contact the potential participants to confirm their interest in participating and arrange an IDI or FGD at a convenient time and location. The location and time will be scheduled based on participants' convenience and, ideally, IDIs and FGDs with women will be conducted after 4-6 weeks postpartum. The potential participants will be asked to bring the signed informed consent form to the location of the interviews. IDI and FGD guides can be found in Multimedia Appendices 7-9.

Qualitative Study Procedures

Before the IDIs and FGDs commence, participants will be informed again about the study in more detail through a plain language statement (Multimedia Appendix 5). If they agree, they will be asked to provide consent (written or verbal, depending on the context; Multimedia Appendix 6). Trained research team members with social science or qualitative research backgrounds, and who are not affiliated with participants' care or workplace, will facilitate the IDIs and FGDs. The gender and age of facilitators will be considered to help participants feel comfortable; for example, FGDs with women will be facilitated by a female researcher whenever possible. FGDs will be stratified by participant type (eg, women-only groups and health workers–only groups) to reduce hierarchical dynamics. Facilitators will use strategies such as turn-taking, inviting quieter participants to speak, and cofacilitation to support inclusive discussion and reduce dominance by more vocal individuals. We propose to conduct IDIs and FGDs in person; however, if not possible, the research team may opt to conduct them on the web. IDIs and FGDs will be approximately 45-90 minutes long and audio recorded. We suggest including 5-10 women per FGD. Field notes will be recorded during data collection and used during analysis to complement transcripts.

In cases where participants are unaware of assisted vaginal birth, facilitators will use comics and frequently asked questions documents to introduce women to the procedure (Multimedia Appendices 3 and 4). Participants will be reimbursed for their time and contribution, if possible, with the amount and form determined by local customs to avoid incentivizing participation. Once IDIs and FGDs are completed, participants will not be followed up unless member checking is conducted. Member checking involves returning to participants to confirm whether their perspectives have been accurately captured during transcription and analysis [35].

Data Management and Quality Assurance

All research team members should undergo training with practice sessions before data collection. This includes principal investigators, social scientists, research coordinators, research assistants, transcribers, translators, admin, and other team members. The training workshop will cover project background, research designs, study tools, ethical considerations, project implementation plan, and manuals. Research monitoring will also be conducted throughout the study to ensure that issues can be addressed promptly. Research leads should communicate regularly with the research team members to address any issues promptly during data collection.

Verbatim transcription of audio recordings should occur alongside the data collection, ideally by the interviewer or facilitator, to enhance the trustworthiness of the data. Each transcription will be reviewed for data quality, themes that need further exploration, feedback for future data collection, and data saturation. During transcription, audio recordings will be deidentified by assigning pseudonyms to participants. After transcription, original audio recordings will be deleted to prevent identification. All data will be permanently deleted or destroyed after a specified retention period. Local data protection laws and requirements of study sites and stakeholders (ie, ethics committee) will determine this period. Raw and deidentified data will not be shared externally, although deidentified data may be reused in future research.

Translation may be needed if research teams comprise people with diverse language abilities. The research team will determine the appropriate timing for translation, whether during transcription or after, based on the language used during the interview. The suitability of these approaches will depend on the research team's language skills, cultural considerations, and consideration that linguistic nuances could be lost during translation.

Data Analysis

We suggest using a thematic analysis approach for the qualitative research, as described by Braun and Clarke [36]. We recommend starting with an analysis by participant groups to identify variations in perspectives based on their backgrounds and experiences. In the next stage, perspectives from the different groups can be compared to explore similarities and differences based on participants' backgrounds. We suggest coding data line-by-line and assigning relevant text to specific codes. These emerging codes can be organized into hierarchical groups by grouping related codes into overarching themes and patterns. The emerging themes can then be reported narratively to report the study findings. The team will explore overarching themes across different study sites to site-specific differences that must be considered during implementation. Data analysis will be conducted separately for each participant group, with triangulation used to support in-depth understanding and to assess both convergence and divergence in perspectives. We recommend conducting data analysis simultaneously with data collection to facilitate adaptations and cross-checking, and collaboratively among research team members, incorporating expertise in qualitative research, midwifery, and obstetrics to

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ensure high-quality analysis. Qualitative analysis software can help manage the analysis process but is optional.

The results from thematic analysis can then be mapped to the behavioral change frameworks, COM-B and TDF. Each barrier and facilitator will be mapped to the 3 COM-B domains and 14 TDF domains to diagnose the core domain driving the behaviors. Based on the domain mapping diagnoses, the Behavioral Change Wheel linked with COM-B will be used to identify the most appropriate intervention to address this. For example, if the barriers were related to reflective motivation, training and enablement can be implemented as interventions to promote the behavior [26]. For an example of how to conduct this type of analysis, see the results from a qualitative formative study to inform intervention development for postpartum hemorrhage [37,38].

Data analysis workshops may be held to facilitate analysis, interpret findings within the local context, refine effective interventions, and discuss practical implementation strategies. The workshop findings will help inform the intervention's development and implementation considerations. The research team will facilitate the workshop, involving all relevant stakeholders, such as health facility staff, community members, and women. The research findings can then be disseminated to community leaders and members through meetings, presentations, posters, and social media.

Study Instruments

All study instruments are available in Multimedia Appendices 1-9. These instruments include document review and readiness assessment forms, IDIs and FGDs guides, education materials (comic and frequently asked question document), plain language statements, and consent forms. The questions in the study instruments are aligned with behavioral change framework domains to help identify barriers and facilitators related to the desired behavior.

Researcher Reflexivity

Reflexivity refers to the research team's awareness of their role in the project and how their assumptions, experiences, and beliefs may influence the research process [39]. This research team's positionality can be reflected throughout the research process. Reflexivity can be practiced through team discussions, debriefing, challenging assumptions and beliefs, individual note-taking, and being transparent. We anticipate the research team to comprise people from multidisciplinary disciplines, such as clinicians, social scientists, implementation science, and maternal health researchers. Reflexive discussions can, therefore, help multidisciplinary teams to find common ground, challenge assumptions, and improve the quality of data collection and analysis.

Research Team Composition

We recommend that the research team include individuals with diverse expertise in qualitative research, community engagement, obstetrics, midwifery, and intervention and implementation research. At a minimum, we suggest that the research team comprise (1) principal investigator: coordinate and provide leadership on day-to-day implementation, (2) social scientist lead: coordinate qualitative components and help interpret the findings' social implications, (3) facility-level research coordinators: gatekeepers at the facility site for data collection, and (4) data collectors: conduct qualitative data collection, preferably some with clinical backgrounds.

Ethical Considerations

Ethics approval has been received from the WHO Ethics Review Committee (A66054) and the WHO Human Reproduction Programme Review Panel on Research Projects (Multimedia Appendices 10 and 11). In addition, ethics approval will be obtained in each specific setting before implementing this formative research. All participants will provide written informed consent prior to data collection. Participation is voluntary, and participants may withdraw at any time without any negative consequences. No deception will be used. Confidentiality will be strictly maintained: all data will be deidentified before analysis, stored securely, and accessible only to authorized members of the research team. Any quotations included in publications will be anonymized. No financial compensation will be provided to participants; however, reimbursement for transport or other minimal expenses may be offered where appropriate in line with local ethics approval. The contact of the local research team will be available for participants in case they need more information or require any assistance from the team.

Results

This is a generic research protocol that can be used by any stakeholder aiming to optimize assisted vaginal birth in any setting. Its generic nature allows for application across various health care contexts, irrespective of resource availability or system complexity. It is important to note that this protocol serves as a preparatory guide, and no data collection or analysis had been initiated at the time this protocol was published. Its purpose is to provide a structured approach for clinicians, researchers, or health policy makers to planning and implementing strategies to increase, reintroduce, or enhance assisted vaginal birth practices, ensuring that interventions are evidence-based, context-specific, and aligned with best practices in maternal health care.

Aligned with the ecological framework guiding this study, the expected outputs include a comprehensive understanding of factors at the women, health workers, organizational, and system levels that influence the use of assisted vaginal birth. These findings will be mapped into the COM-B and the TDF frameworks to inform the development of context-specific, acceptable, and feasible interventions to optimize appropriate use of assisted vaginal birth. For example, if a key barrier identified is a lack of health workers' skills in performing assisted vaginal birth, this would point to the need for targeted educational interventions, such as hands-on training, to address the gap. On the other hand, if the research identifies a lack of functioning equipment as a significant barrier, the strategy will need to focus on improving supply chains, ensuring equipment availability and maintenance, and addressing system-level logistics. This approach draws on implementation science principles to ensure that interventions are evidence-based,

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theory-informed, and responsive to local contexts. This protocol development was funded on November 1, 2021, by UNDP/UNFPA/UNICEF/WHO/World Bank Special Programme of Research, Development and Research Training in Human Reproduction (Human Reproduction Programme), Department of Reproductive Health and Research, World Health Organization.

Discussion

Assisted vaginal birth is not an innovation. Having been around for over a century, various instruments have been evaluated for their success in achieving vaginal births and their impact on women and babies [40]. Implementing assisted vaginal birth requires not only physical instruments availability but also skills, competence, and expertise to conduct the procedure safely [13,41]. In addition, views and decisions around assisted vaginal birth are strongly shaped by sociocultural factors, including family, community, health workers, and the broader health care system [18,19]. Understanding influences on use of assisted vaginal birth through formative research is essential to ensure that interventions can be implemented effectively. This protocol aims to provide guidance in conducting formative research to design and implement the most appropriate interventions to optimize use of assisted vaginal birth. Conducting formative research ensures that women's and stakeholders' voices are considered in intervention development, prioritizing equality and rights during implementation.

The formative research described in this protocol is expected to generate in-depth understanding and actionable insights into the behavioral, cultural, and systemic barriers and facilitators of assisted vaginal birth use in the settings of interest. By exploring perspectives across all the key stakeholders, the study will identify key points where change is possible within labor management practices to optimize appropriate use of assisted vaginal birth. These findings will inform the design of tailored interventions, whether educational, organizational, or policy-based, that aim not only to optimize appropriate assisted vaginal birth use but also to promote respectful and women-centered care. For example, improving health workers' skills and confidence in assisted vaginal birth may shift clinical norms away from default reliance on cesarean section. At the same time, addressing women's concerns and preferences through culturally sensitive materials and counseling on assisted vaginal birth can strengthen shared decision-making during labor. Ultimately, the study will contribute to the broader challenge of implementing complex interventions in dynamic health systems, where both technical skill and women-centered care matter deeply. The insights generated will support the development of interventions that are both acceptable and feasible, grounded in the realities of the settings in which they are implemented.

All women have rights to high-quality and respectful care during childbirth, yet the underuse of lifesaving procedures, such as assisted vaginal birth, takes these rights from women. Optimizing the use of assisted vaginal birth can not only save women's and babies' lives but also ensure the protection of women's rights during childbirth. Furthermore, as the "essential signal function" presents the least coverage among the 9 basic and comprehensive emergency obstetric care functions [1], prioritizing improvements in quality care on assisted vaginal birth is essential. In an era where assisted vaginal birth is almost nonexistent, it is equally important to ensure that "high-quality" assisted vaginal birth can be delivered.

Ensuring assisted vaginal birth is accessible to all women who need it, regardless of gender, ethnicity, race, socioeconomic status, or geographical location, is paramount to achieving the equitable core of high-quality care and fulfillment of human rights [41]. Despite this, appropriate use of assisted vaginal birth varies globally, with high-income countries having higher prevalence than LMICs [10,12,13]. In LMICs, health workers may resort to cesarean birth without considering an assisted vaginal birth, even for women in whom it may be appropriate. This may be due to a lack of skills, difficulty, or delay in referrals, which may jeopardize the lives of women and babies. Therefore, it is essential to understand and address the challenges related to appropriate use of assisted vaginal birth in LMICs to ensure that it is available to women who need it.

Providing assisted vaginal birth while considering women's views and needs is crucial to achieving high-quality care. However, gender inequality and power imbalances between women and health workers often strip women of their rights to actively participate in their care. During emergency situations, women often reported feeling uninformed and unprepared about the interventions they received [19,42]. This may increase women receiving procedures they do not desire or not receiving the procedure they need. This also resulted in women's perceived negativity toward their birth experience more holistically [19,43]. Power dynamics between women, their partners, or families can also affect a woman's autonomy regarding assisted vaginal birth. If a woman's partner or family is unsupportive or hesitant about the procedure, it can prevent the woman from receiving the necessary procedure when required. Ensuring women are informed about assisted vaginal birth—understanding what it is, when it is needed, and its availability—is pivotal for optimizing care and outcomes. Therefore, this protocol emphasizes that providing assisted vaginal birth while considering women's views and needs is crucial for achieving high-quality care.

Finally, given that most people giving birth identify as women, the term "women" is used throughout this protocol. However, the protocol aims to be inclusive of all gender-diverse individuals who give birth, regardless of their gender identities. We recognize that the term "women" may exclude nonbinary or gender-diverse people. Nevertheless, we emphasize that all women and gender-diverse people giving birth may experience marginalization, and all deserve respectful maternity care and consideration.

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Acknowledgments

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Data Availability

This published article and its supplementary information files include all data generated or analyzed during this study.

Authors' Contributions

MAB and APB conceptualized the study. MAB and APB conceptualized the study. SLB contributed to the design and development of the comics used in the formative research. She is a student at Haute école d'art et de design – Genève (HEAD – Genève). All authors drafted the protocol and educational materials and read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Document review instrument.
[DOCX File , 30 KB - resprot_v14i1e69808_app1.docx]

Multimedia Appendix 2
Readiness assessment instrument.
[DOCX File , 28 KB - resprot_v14i1e69808_app2.docx]

Multimedia Appendix 3
Assisted vaginal birth comics.
[PDF File (Adobe PDF File), 14381 KB - resprot_v14i1e69808_app3.pdf]

Multimedia Appendix 4
Frequently asked questions about assisted vaginal birth.
[DOCX File , 29 KB - resprot_v14i1e69808_app4.docx]

Multimedia Appendix 5
Plain language statement.
[DOCX File , 53 KB - resprot_v14i1e69808_app5.docx]

Multimedia Appendix 6
Informed consent form.
[DOCX File , 21 KB - resprot_v14i1e69808_app6.docx]

Multimedia Appendix 7
Instruments for interview or focus group discussion with maternity care users, their family, and community members.
[DOCX File , 40 KB - resprot_v14i1e69808_app7.docx]

Multimedia Appendix 8
Instruments for interview with health workers.
[DOCX File , 33 KB - resprot_v14i1e69808_app8.docx]

Multimedia Appendix 9
Instruments for interview with policy makers.
[DOCX File , 30 KB - resprot_v14i1e69808_app9.docx]

Multimedia Appendix 10
World Health Organization ERC approval.
[PDF File (Adobe PDF File), 462 KB - resprot_v14i1e69808_app10.pdf]

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Multimedia Appendix 11
World Health Organization RP2 approval.
[PDF File (Adobe PDF File), 69 KB - resprot_v14i1e69808_app11.pdf]

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Abbreviations

COM-B: Capability, Opportunity, and Motivation
FGD: focus group discussion
IDI: in-depth interview
LMICs: low- and middle-income countries
TDF: Theoretical Domains Framework
WHO: World Health Organization

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Protocol

Developing an Interprofessional Pediatric Rehabilitation Model of Care in Northern Cree First Nation Communities: Protocol for a Needs Assessment and Codeveloped Intervention With a Qualitative and Participatory Action Approach

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Abstract

Background: In Canada, the Indigenous population is the youngest and fastest growing, yet ongoing health disparities for Indigenous peoples are widely recognized. There is a concerning lack of research on childhood disabilities and health conditions in Indigenous populations in Canada. For children with disabilities and chronic health conditions, ongoing access to rehabilitation services, such as occupational therapy, physical therapy, speech-language pathology, and audiology, is critical in promoting positive health and developmental outcomes. Elders and the Peter Ballantyne Cree Nation health services board have guided a critical priority for addressing access challenges to pediatric rehabilitation in 3 specific northern Indigenous communities.

Objective: The purpose of this manuscript is to outline the protocol for a community-directed needs assessment and subsequent development of a multidisciplinary pediatric rehabilitation service in 3 specific northern Indigenous communities.

Methods: The study involves 3 phases. In phase 1, the needs assessment process was led by 2 physiotherapy clinician researchers and 2 graduate students working with health care professionals in pediatric speech-language pathology, audiology, physiotherapy, and occupational therapy with experience in both private and public health entities. The process consisted of multiple parts, which included a community-led request, a preliminary literature review, survey development, interview guide development,

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communication and feedback with health care professionals, a test phase with pediatric family members, and finalization of the survey and interview guides for deployment. In phase 2, the findings from phase 1 will inform the codevelopment of a pilot hybrid-care, interprofessional pediatric rehabilitation clinic for each of the communities. In phase 3, a stakeholder meeting will take place to facilitate knowledge sharing and open discussion regarding the implementation of phase 2 as well as considerations for the sustainability of this model of care.

Results: The final survey was multidisciplinary, with 6 content areas covered in 15 items. Guides for 1-on-1 interviews and sharing circles included 10 questions for community members and 12 questions for health care providers. Participant recruitment began in April 2024. Final results are anticipated in early 2026.

Conclusions: This manuscript details the process of a community-directed needs assessment, which will inform the development and implementation of a model of care for pediatric rehabilitation services. Our process was driven by a request from the community for a needs assessment and emphasized the involvement of key stakeholders early and often during assessment development. A clear purpose of the project was identified with community direction. We used multidisciplinary inputs from both public and private sectors and maintained clear goals during our survey question design process. This study aims to inform the codevelopment and implementation of an interdisciplinary, hybrid model of pediatric rehabilitation care for remote First Nation communities, ultimately leading to improved access to patient- and family-centered care for pediatric rehabilitation.

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KEYWORDS

telerehabilitation; Indigenous peoples; pediatrics; remote care; rehabiltation

Introduction

In Canada, the Indigenous population is the youngest and fastest growing [1], yet there is evidence for ongoing health disparities [2-4]. Within the scope of this paper, Indigenous refers to all of First Nations, Métis, and Inuit peoples. There is a concerning lack of research to provide accurate data on childhood disabilities and health conditions in Indigenous populations in Canada [2,4]; however, based on a community-driven request and community knowledge, there is a growing need for rehabilitation services for pediatric families in specific northern Indigenous communities in Saskatchewan. Previous research conducted in Saskatchewan has identified barriers to rehabilitation care, impacts on family and quality of life, and recommendations for improving services for rehabilitation in an Indigenous community [5].

In 2007, Jordan's Principle was created to ensure that Indigenous children had appropriate access to health care [4]; despite this, they are still not able to appropriately access the care they need [2,6]. In 2016, the Canadian Human Rights Tribunal highlighted important shortcomings regarding early intervention and family programs offered to Indigenous peoples and concluded that the Canadian government was systematically discriminating against Indigenous peoples [7]. Beyond the specific challenges associated with Jordan's Principle, children in rural and remote areas, including Indigenous children, face significant additional barriers to access services. These include incredibly long wait times and the necessity for families to travel, which brings associated challenges, such as appropriate transportation, adverse weather conditions, financial costs, time constraints, and the need for childcare for other children in the family [5,8,9]. Indigenous children often encounter additional health disparities rooted in historical, social, and economic factors that necessitate a holistic and culturally sensitive approach to rehabilitation [6].

For children with disabilities and chronic health conditions, ongoing access to rehabilitation services, such as occupational therapy (OT), physical therapy (PT), speech-language pathology (SLP), and audiology (AUD), is critical for promoting positive health and developmental outcomes [10]. Interprofessional collaboration among these disciplines is considered to promote best practice in rehabilitation as it can enhance efficiency, patient outcomes, and clinician and patient satisfaction [11]. In Indigenous communities, the implementation of interdisciplinary rehabilitation for pediatrics is imperative due to the unique challenges faced by children and their families in these populations. Interdisciplinary rehabilitation, involving collaboration among health care professionals in PT, OT, SLP, and other disciplines with guidance and teaching by community experts is essential to address the multifaceted needs of Indigenous pediatric patients and their families. By integrating diverse expertise, practitioners can tailor interventions to consider cultural contexts, traditional healing practices, and community dynamics. This approach not only enhances the effectiveness of rehabilitation but also fosters a comprehensive understanding of the child's well-being within the broader cultural and familial context, ultimately contributing to more meaningful, culturally responsive, and sustainable health outcomes for Indigenous pediatric populations and their families.

The purpose of this manuscript is to outline the protocol for a community-directed needs assessment and subsequent development of a multidisciplinary pediatric rehabilitation service in 3 specific northern Indigenous communities. The research uses a single group, with a participatory action approach, following an ethical space and two-eyed seeing framework [12-14]. The protocol follows an identified critical priority area guided by Elders and the Peter Ballantyne Cree Nation (PBCN) health services board in order to address access challenges to pediatric rehabilitation in 3 specific northern Indigenous communities. The protocol includes a final critical

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phase for a multistakeholder meeting to facilitate knowledge sharing and open discussion.

Methods

Ethical Considerations

This research has been approved by the University of Saskatchewan Behavioural Research Ethics Board (REB, #3486). Protocol amendments will be approved by the REB. Each participant will be provided with a consent form approved by the REB (Multimedia Appendix 1) with an opportunity to review the research project details with a research team member or community research assistant (CRA) verbally to ensure complete understanding and informed consent. Translators will be provided as needed to ensure understanding. All data will be deidentified. Complete anonymity will not be possible due to the nature of the sharing circles. Patient participants will receive honorarium for their participation following the University of Saskatchewan protocol for research honorarium. All data will be held by the principal investigator in a secure, password-protected, web-based data platform approved by the University and REB. We will request input from patients and sharing groups as to how they would like to find out about the results of the study and ensure that the preparation of desired methods occurs at the direction of the community.

This needs assessment and plan to develop a pilot hybrid, interprofessional care model for remote and in-person pediatric rehabilitation was based on a community-identified need and request. The request came from an Elder's Advisory Council and was based on successful research projects involving remote models of care for adult populations [15,16]. The council and the PBCN health services board identified the specific communities in need. Eligible participants were recruited from these communities with self-reported pediatric rehabilitation needs across any one or combination of disciplines (PT, OT, SLP, or AUD). Eligible health care participants were any health care provider, service coordinator, or administrator serving at least one of the identified communities. A patient-oriented research approach was used following ownership, control, access, and possession principles and adhering to chapter 9 of Tri-Council policy statement 2 on research involving First Nations, Inuit, and Métis peoples of Canada [17-19]. Our diverse multidisciplinary research team includes patient partners, respected Elders, and Knowledge Keepers, with support from local community health directors and Jordan's Principle experts. Our research team has experience in Indigenous health, health services research, collaborative models of care, musculoskeletal health, mixed methods, rural and remote health service delivery, community-based participatory action health research approaches, virtual health, and Jordan's Principle. Team members VM and SL have over 15 years and 10 years, respectively, of collaborative relationships with the Pelican Narrows Elders and PBCN.

This research was grounded in community-based participatory action research, a two-eyed seeing and ethical space framework [12-14]. Community-based participatory action research emphasizes collaboration between researchers and all stakeholders throughout the entirety of the research process—beginning from developing the research questions through to data collection, analysis, and dissemination of the findings [13]. This process ensures that the research is based on the needs and concerns of the community involved and supports or enhances strategic action in resolving community issues while maintaining an emphasis on invaluable community knowledge and equal inclusion and collaboration [13].

Phase 1: Needs Assessment and Relationship Building

Overview

Phase 1 included relationship building, planning, developing sharing circle guides, and trips to participating communities for needs assessment data gathering (sharing circles and semistructured interviews when requested, sharing of meals, and gifting to community members) to identify community and family strengths; cultural needs, preferences and considerations; as well as barriers to the provision of interprofessional telerehabilitation services.

The needs assessment process was led by 2 physiotherapy clinician researchers and 2 graduate students who worked with health care professionals in pediatric SLP, PT, OT, and AUD with experience in both private and public health entities and collaboration with Indigenous communities. The process consisted of multiple phases, which included a community-led request, preliminary literature review and scoping review [20], survey development, interview guide development, communication and feedback with health care professionals, a test phase with pediatric family members, and finalization of the survey and interview guides for deployment for data collection. The interview guide and survey were developed with community Elders and persons with lived experience. Schematics of the protocol and needs assessment process are outlined in Figures 1 and 2, respectively. CRAs will identify and liaise with potential community members and Elders to participate in the recruitment of family participants, data collection, and organization of semistructured interviews and sharing circles. The needs assessment will include 8-10 families with children with neurodevelopmental or orthopedic rehabilitation needs in each community as well as 2-3 Elders and 2-3 health care providers identified through consultation with the PBCN health services board and patient team members and supporters. Translation will be provided to ensure inclusion of those who are interested. All participants will reside within the 3 identified remote communities and have identified pediatric rehabilitation needs.

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Figure 1. Schematic of the protocol.

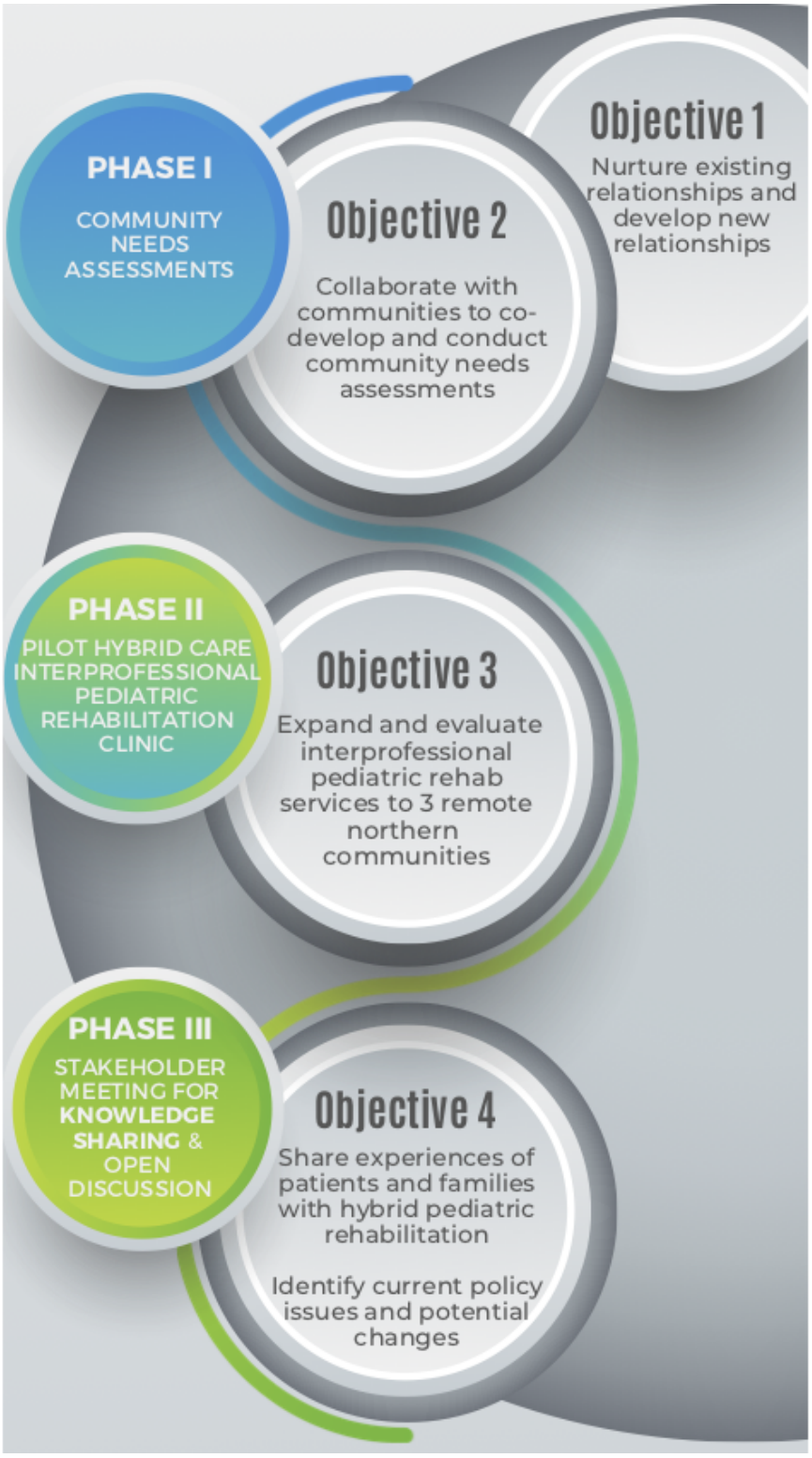

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Figure 2. Outline of the needs assessment process.

Web-Based Survey

A demographic and general health questionnaire (Multimedia Appendix 2) will be completed before interviews or sharing circles take place. The web-based questionnaire will be filled out using the research electronic data capture (REDCap) web application [21,22] with an option for a paper questionnaire based on preference. Assistance will be provided by our research assistants or student researchers. A completion check will be performed prior to the interview.

Interviews and Sharing Circles

The use of sharing circles as an Indigenous methodology in research allows participants to safely share stories [23,24]. Participants will be provided the option for an individual interview or participation in a sharing circle. Up to 20 individual interviews and 1-3 sharing circles will take place. The final sample size will be determined by the emerging analysis; however, we anticipate this estimated sample size is reasonable to reach data saturation based on our team's previous work in similar qualitative analyses. Interviews or sharing circles will be held in person or remotely using a videoconference platform (Zoom) or the remote presence robot in the community health

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center, based on participant preference. An approved interview guide will be used (Appendices 3 and 4). Interviews will be recorded, transcribed using Otter.ai, and analyzed thematically using qualitative coding software (NVivo, QSR International). Participants will have the opportunity to review transcripts prior to data analysis and synthesis. Interview and sharing circle findings will be examined together with the research team, including patient advisor team members, during the analysis phase to guide the next stage of the project. Analysis will involve a qualitative, interpretive research approach with inductive thematic analysis [25,26]. To support reflexivity, an intersectional approach, and a patient-oriented research approach, the team will meet and collaborate multiple times. This process will ensure that Indigenous worldviews, language, culture, community practices, and protocols continue to guide the research.

Phase 2: Pilot Hybrid-Care, Interprofessional Pediatric Rehabilitation Clinic

Phase 2 will be informed by the findings from phase 1 and will feature codevelopment and implementation of a pilot hybrid-care, interprofessional pediatric rehabilitation clinic in each community using a combination of remote presence technology (RPR) and in-person care. For example, the types of care provision and combinations of services needed and the complexity of care will be revealed through the survey responses, further defining the community's needs. Patient experiences and needs will be further understood through qualitative analyses, followed by deliberation with patient partners, health care providers, community partners, and Knowledge Keepers to codevelop and implement a pilot hybrid-care pediatric rehabilitation clinic.

Planning will occur in collaboration with community families and Elders. CRAs will bring Indigenous community protocols, practices, and knowledge to our team approach, which is essential to guiding academic team members in respectful community engagement. It is anticipated that the team will comprise urban-based PT, OT, SLP, and AUD providers in addition to the CRAs who will be physically present. CRAs will receive formal training by team partners in research protocols and team functioning and will be supported through RPR technology as well as Zoom and email.

The urban-based rehabilitation providers will join remote families and their local primary care providers for assessment using RPR and provide follow-up care through remote and in-person sessions, as determined by the practitioner. It is anticipated that in-person sessions will be required for some components of assessment and care provision. A total of 15 participants from each of the 3 communities will participate in the assessment and 2 additional follow-up treatments (at least one of which will be in person).

Demographic, functional, and cost outcomes will comprise the quantitative data. Outcome measures will be developed in partnership with Elders, patient team members, and persons with lived experience to ensure community direction in the evaluation and may include quality of life and pediatric functional and cognitive measures. Family, community, and provider stories and experiences will provide qualitative information. Following participation in the hybrid interprofessional care clinic, pre- and posttest data collection by researchers and in partnership with the CRA will be quantitatively analyzed. Follow-up, semistructured interviews with participants will be audio recorded and transcribed using Otter.ai. Qualitative analysis will proceed as described earlier in phase 1. All participants will receive honorarium for their participation.

Phase 3: Stakeholder Meeting for Knowledge Sharing and Open Discussion

This phase will include a stakeholder meeting where food and reciprocal knowledge will be shared and open discussion will occur to review experiences and findings from the needs assessments and interprofessional pediatric rehabilitation clinics. This process will be developed specifically with the PBCN health services board and Jordan's Principle experts so the context is correct, as recommended by Smylie et al [27]. Families will be invited to share their stories. System and jurisdictional issues will be discussed, and idea generation from unique stakeholder perspectives will be used to develop considerations and recommendations to ensure sustainability and encourage uptake of the model locally and across other Indigenous communities. Participants will include families and community members, PBCN health services board and community Chief and Councils, education sectors, provincial and federal health governance administrators, researchers, and health care providers.

Results

The final survey was multidisciplinary, with 6 content areas covered in 15 items. Content covered in the web-based survey included the following categories: about your child, about your child's birth and development, about your child's health history, use of equipment, more about your child (eg, strengths and favorite activities and toys), and about your family (Multimedia Appendix 2). Interview guides for community members included 10 questions, with a focus on allowing space for participants to share about their child and the conditions requiring rehabilitation services, how this has affected the child's and family's life, experiences in accessing rehabilitation services, and opinions on using remote technology with the support of local health care providers (Multimedia Appendix 3). Interview guides for health care providers included 12 questions, with a focus on allowing space for participants to share broadly about their observations regarding children and families needing pediatric rehabilitation services in the community. These included barriers and facilitators for children and their families to access appropriate services and supports, opinions on using remote technology with the support of local health care providers, as well as culturally safe practices and pediatric outcome measures (Multimedia Appendix 4).

The results of the needs assessment survey, interviews, and sharing circles will inform the development and implementation of the multidisciplinary hybrid model of care, using both in-person and RPR sessions. The results of the pilot model of care will provide information on multidisciplinary needs of families and children and a collaborative approach to

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rehabilitation care. We anticipate learning of further gaps in care and improvements to the model, including efficiencies across disciplines, information and resource sharing implications, and other logistics that may impact policy and decision-making for funding considerations. Finally, the results of the community engagement stakeholder meeting will provide critical information on future research directions to inform rehabilitation models of care and policy implications for sustainability of the model locally and across other Indigenous communities.

This protocol paper was first submitted in November of 2024. Since that time, we have completed the initial data collection from 22 pediatric patients from 20 different families, as some families had more than 1 child with rehabilitation needs. We have completed interviews with 4 health care providers for the phase 1 needs assessment. Our team travelled to 1 community in 2023, 1 in May 2024, and 1 in April 2025, with another trip planned to the first community in September 2025. We have had ongoing communication with all 3 communities throughout the needs assessment phase as well as regular research team meetings. It is anticipated that the 3 codeveloped hybrid clinics will be fully operational between June and September of 2025. The phase 2 evaluation is anticipated to take place early 2026, with the phase 3 stakeholder gathering anticipated for the spring of 2026.

Discussion

Anticipated Findings

Based on advisement from Elders and the community, it is anticipated that study's findings will reveal unmet needs for pediatric rehabilitation services. We anticipate complex care needs in many cases, where the services needed will include PT, OT, SLP, AUD or a variety of combinations of multiple services. We anticipate pediatric and family desires for a hybrid in-person and remote care model. The codevelopment of services will likely be complex and varied across the communities based on variations in current strengths and gaps in care, with recommendations for further improvements after implementation. The study is also expected to reveal process considerations to ensure effective integration into the existing, strong local health care system. It is anticipated that a hybrid model of care will improve access to needed services in these communities.

This research project is positioned to contribute significantly to our understanding of remote Cree community pediatric rehabilitation needs, gaps in care, and community preferences for the provision of services. The anticipated development of a community-led rehabilitation model of care that is culturally responsive and community-specific aligns with the principles of community-based participatory action research and the two-eyed seeing framework. Two-eyed seeing is a research framework that combines knowledge of both Western and Indigenous worldviews. Although it is not a local teaching, this framework was chosen by our team to serve as a reminder to equally consider and integrate the viewpoints of both Indigenous and Western ways of knowing in this research while prioritizing Indigenous knowledge and experiences. By engaging patients and stakeholders, the project aims to build capacity for future patient-oriented research endeavors, reflecting a commitment to inclusive and respectful practices.

Evidence for the use of telerehabilitation or remote care models to provide care to Indigenous children and their families is scarce. Through a scoping review of the literature, only 3 articles investigating remote care model interventions were identified [20]. Only 1 study was conducted in the Canadian context and explored the feasibility of conducting speech and language assessments of Indigenous children through videoconferencing [28]. Seven children aged 4 to 13 years were evaluated using various tools both onsite and offsite by different SLPs. Results from that study were promising, as the agreement was high for some tests (eg, receptive language and vocabulary abilities) and children responded well to the offsite evaluator. The authors highlighted the importance of in-person visits to ensure cultural responsiveness in the provision of services and develop and nurture relationships and specified that an assistant located in the community is essential to reduce potential evaluation bias and errors in scoring, entertain the child, and handle technological difficulties [28].

A recent systematic review suggests that telehealth is a promising solution for families with children with multiple diagnoses and chronic conditions or developmental disabilities. There is strong evidence for the use of telehealth as an efficient method to improve access to services, decrease waiting times, and improve child-related outcomes in a way that is acceptable for parents [29-32]. Family-oriented services, like coaching aimed at parental support, knowledge transfer, and interventions targeting parental capacity building, seem to be more efficient when delivered remotely [30]. However, for family-centered interventions to have meaningful impacts on Indigenous families' lives, they must be anchored in Indigenous knowledge, principles, and visions of child development. Such interventions have the potential to provide tools and support to parents and families.

Cultural worldviews, lived experiences, and the influence of language impact the experiences of Indigenous peoples with health systems and health care. Unique community strengths can contribute to the well-being of individuals and children, providing them with a safe environment to learn and grow, and promotes health sovereignty in communities. Methods and systems of health care that work in urban areas are not necessarily appropriate for remote areas, and Western systems and models are not necessarily culturally responsive or appropriate for remote Indigenous communities.

Community needs and cultural safety in practice will vary between urban and rural or northern services and across Indigenous communities whose histories, resources, and resiliencies are different [33]. This has been demonstrated with Indigenous children with presumed or diagnosed neurodevelopmental challenges and their families in rural, isolated, or northern communities; however, there is very little practical guidance for Western-trained practitioners to engage in culturally safe pediatric rehabilitation practices within Indigenous communities in Canada [33]. This project is community-led, with engagement from multiple groups and

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knowledge users, including patient team members and interdisciplinary rehabilitation experts with extensive experience in pediatric rehabilitation across public and private health entities.

Strengths and Limitations

Given the dearth of evidence on rehabilitation models of care for Indigenous pediatric patients and their families, this collaborative research will inform future models of care that address community needs, improved accessibility to rehabilitation services, and communities' perspectives on RPR technology. The project is designed to be community-led, gathering both patient and health care provider perspectives, in order to address barriers to accessing care while realizing current strengths within each community. The research will be conducted using an ethical space framework emphasizing the creation of space for dialogue and collaboration where diverse worldviews and knowledge systems are acknowledged and respected with the Cree philosophy *wahkohtowin*, based on kinship and the importance of relationship-building throughout the process [12]. The final phase allows for further community input during and after the intervention is designed and implemented.

The limitations of this research include the focus on 3 specific communities in Saskatchewan, which may not allow for direct generalizability across other communities. The participating communities use the Cree TH dialect, which may not be generalizable to the languages and worldviews of other Indigenous communities. We anticipate challenges in predicting weather or environmental occurrences (eg, wildfires) for clinical travel requirements to the communities, which may affect the ability to provide in-person services at different times seasonally. These limitations will affect the provision of services and potentially increase reliance on remote services during these periods.

Future Directions

This research project aims to uncover and understand pediatric rehabilitation needs in northern remote First Nation communities while positioning itself as a catalyst for positive change in rehabilitation practices. By combining community-led approaches, engagement with diverse stakeholders, and a commitment to cultural responsiveness, the project has the potential to make meaningful contributions to the field of pediatric rehabilitation, especially within Indigenous communities in Canada. Future directions will include continual improvement of the model with the addition of future team members identified as needs during the intervention and expansion to other First Nation and Métis communities in Saskatchewan. Dissemination components will be determined through collaboration with community experts and patient partners. This may include culturally specific and relevant language for the development of appropriate pediatric rehabilitation education materials.

Acknowledgments

This research is funded by the Saskatchewan Health Research Foundation.

Data Availability

Datasets generated and analyzed for this research can be requested by contacting the principal investigator at stacey.lovo@usask.ca and will be provided upon reasonable request. Discussion with the First Nation community would need to occur in keeping with the principles of ownership, control, access, and possession of data for First Nations community-led research.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Consent form.
[DOCX File , 67 KB - resprot_v14i1e69438_app1.docx]

Multimedia Appendix 2
Survey.
[DOCX File , 28 KB - resprot_v14i1e69438_app2.docx]

Multimedia Appendix 3
Interview guide for patients and families.
[DOCX File , 24 KB - resprot_v14i1e69438_app3.docx]

Multimedia Appendix 4
Interview guide for health care providers.
[DOCX File , 23 KB - resprot_v14i1e69438_app4.docx]

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Abbreviations

AUD: audiology
CRA: community research assistant
OT: occupational therapy
PBCN: Peter Ballantyne Cree Nation
PT: physical therapy
REB: Research Ethics Board
REDCap: research electronic data capture
SLP: speech-language pathology
RPR: remote presence technology

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Protocol

Cancer Care Experiences Among Adolescents, Caregivers, and Health Care Providers in a Regional Canadian Context: Protocol for a Qualitative Study

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Abstract

Background: Adolescents diagnosed with cancer face significant disruptions to their development, education, and social lives. These challenges are pronounced in regional settings, where access to specialized, developmentally appropriate oncology care is limited. In Ontario, Canada, youth aged 12 to 18 years often fall between pediatric and adult care systems, leading to fragmented services, unmet psychosocial needs, and long-term disparities in survivorship. While international literature has examined the cancer experiences of adolescents and young adults, most research originates from the United States, limiting its relevance in the Canadian context. In Ontario's regional hospitals, youth and families face disparities in care quality, specialist access, and logistical challenges. More research is needed to inform equitable, youth-centered cancer care models.

Objective: This study aims to explore the lived experiences of youth cancer survivors, their caregivers, and health care providers (HCPs) in a regional Canadian context. The study investigates four research questions: (1) What are the daily experiences and psychosocial needs of youth during and after treatment? (2) How do caregivers navigate cancer care for youth? (3) What are HCPs' perspectives on delivering cancer care for youth? (4) What recommendations can youth, caregivers, and HCPs offer to improve cancer care systems for youth?

Methods: We applied a qualitative descriptive design using semistructured web-based interviews and reflexive thematic analysis. Participants were recruited through a multimethod strategy, including clinician referral, posters, digital outreach, and professional networks. The anticipated sample includes 24 participants: 8 (33%) youth cancer survivors (aged 12 to 18 years at diagnosis), 8 (33%) caregivers, and 8 (33%) HCPs. Eligibility criteria were defined to ensure safety, diversity, and relevance. Interviews were conducted via Microsoft Teams, transcribed verbatim, and analyzed using the 6-phase reflexive thematic analysis approach described by Braun and Clarke. NVivo software supported coding and theme development. Demographic data were analyzed descriptively to contextualize the findings.

Results: As of September 2025, 14 participants had completed interviews: 6 (43%) caregivers, 6 (43%) HCPs, and 2 (14%) youths. Youth recruitment has been challenging due to the developmental stage and competing commitments. Data collection concluded in December 2024. Preliminary transcript coding was completed in early 2025, with final analysis and synthesis of themes completed in June 2025. This study was funded in August 2023, and results are expected to be published in Fall 2025 and Winter 2026.

Conclusions: This study will provide critical insight into cancer care delivery for youth in a regional Canadian setting. Integrating youth, caregiver, and HCP perspectives will illuminate systemic gaps, relational dynamics, and context-specific barriers. The

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findings will inform policy, education, and service innovations aimed at improving equity, continuity, and developmental responsiveness in oncology care for adolescents and young adults in Canada.

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KEYWORDS

adolescents and young adults; cancer; caregivers; health providers; protocol; qualitative research

Introduction

Impact of Cancer on Youth

The onset of cancer at any age can have a devastating impact on a person's physical and mental health. This experience may be especially distressing for youth, who are establishing their identity, values, and autonomy while also learning to navigate relationships and life transitions during adolescence [1]. Studies have shown that youth often perceive cancer treatment as emotionally and psychologically challenging, as they confront uncertainty and the possibility of death [1-3]. Many report feelings of isolation and hopelessness, which contribute to difficulties adhering to treatment plans and delays in accessing appropriate supportive care [4]. During treatment, some youth may continue attending school. However, cancer and its treatments can impair cognitive function, memory, abstract reasoning, and arithmetic skills, making reintegration into the classroom environment challenging [5]. Socially, these youth may experience differential treatment from peers, which can further exacerbate their sense of isolation [1,2].

The transition to young adulthood is often an exciting and pivotal time [6]. However, for youth diagnosed with cancer, this period may be disrupted by health adversities. A cancer diagnosis can delay their ability to complete education, secure employment, and form new relationships, setting them back in their developmental trajectory [1,7]. Research also indicated that adult survivors of childhood cancer face long-term physical and mental health complications [1,8,9]. These issues may be compounded by complex socioenvironmental factors, such as low socioeconomic status, geographic isolation, and limited social and community support [10]; for instance, inadequate communication between health care providers (HCPs) and schools regarding accommodations for youth undergoing treatment for cancer reflects a systemic gap that may hinder educational continuity and psychosocial development [5,11]. Adult survivors also report long-term difficulties in employment, intimate relationships, and social participation, issues that often begin during treatment and persist throughout survivorship [12]. Providing age-appropriate, integrated clinical and psychosocial care is crucial for mitigating these challenges. However, in the Canadian province of Ontario, oncology care is distinctly divided into pediatric and adult systems, failing to address the unique needs of adolescents and young adults adequately [13]. These youth may be overlooked without early intervention and tailored support.

Existing Research on Cancer Care for Adolescents and Young Adults

The majority of research examining the cancer experiences of adolescents and young adults (AYAs) has been conducted in the United States, where studies have identified unique challenges faced by this population that differ from those of both pediatric and adult patients with cancer [11,14-16]. While both American and Canadian families face challenges related to geographic access and wait times, these issues are shaped by distinct health care structures. In the United States, barriers often vary by insurance status, while in Canada, they stem from regional resource distribution within a publicly funded system [13,17,18]. Furthermore, US research frequently focuses on resourcing urban tertiary care centers with specialized AYA programs [17,19,20]. By contrast, the Canadian health care landscape is characterized by a more distributed model of regional care delivery, and structural differences in educational support frameworks may influence how findings translate across contexts [21-23].

Disparities in the Regional Health System That Impact Youth With Cancer

Regional hospitals in Ontario are designed to deliver centralized care to their local populations [13,23]. However, studies highlight significant disparities in the availability and quality of cancer care between tertiary and regional treatment centers [24]. Youth receiving care in regional centers may have access to some outpatient and routine oncology services. However, these facilities often cannot manage youth with acute or complex medical conditions. As a result, families must travel outside their communities to access essential care, disrupting social support systems and imposing emotional, logistical, and financial burdens that can negatively affect overall quality of life [25]. These disparities underscore the need for more equitable and developmentally appropriate care across regions. Adolescents have needs that are distinct from those of children and adults; yet, these needs often remain unaddressed due to a lack of awareness, guidelines, and available resources [7,9].

Regional pediatric oncology clinics in Ontario, supported by the Pediatric Oncology Group of Ontario, primarily offer supportive and clinical care to patients up to 18 years of age [26]. However, for initial diagnoses or the management of complications, youth and their families must travel to tertiary centers [11,24,27]. The need to travel outside their communities to seek care can be particularly stressful due to unexpected costs, lost work hours for parents, and separation from family and community supports [10,17,28]. These challenges are often amplified for youth from single-parent households, immigrant families, or low-income backgrounds, where access to social

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supports is limited, contributing to long-term mental health consequences [1,24].

A literature review on the impact of travel on cancer treatment decisions highlighted that travel is perceived as a barrier to treatment adherence [25]. Transportation mode, parking access, reliance on hospital transport, and travel comfort all influence the overall cancer care experience [25]. However, most studies to date have focused on adult populations; little is known about how these travel-related barriers affect youth with cancer living far from tertiary centers, who may rely on others for transportation. These systemic challenges also place a burden on HCPs in regional settings, who are often the first point of contact for these patients [10,27]. Studies reveal that HCPs experience challenges in identifying and addressing the emotional and practical needs of youth with cancer and their families [18,29,30]. Youth may present with symptoms and psychosocial challenges that differ from those of younger children or adults, making specialized training essential. A lack of training can lead to delays in care and unmet needs [7,31,32]. While referral to tertiary centers may provide access to specialist care, enhancing training and resources in regional and community hospitals is critical [13]. Building local capacity through targeted education and support for HCPs is necessary to ensure timely, effective, and youth-appropriate cancer care closer to home [1,30].

Context Specific to Southwestern Ontario

Ontario's pediatric oncology care operates under a hub-and-spoke model where specialized pediatric oncology services are centralized in major urban centers (Toronto, Ottawa, Hamilton, and London), with regional satellite clinics such as Windsor Regional Hospital (WRH) providing supportive care closer to home [23]. This structure can complicate transitions between pediatric and adult services, especially for adolescents with complex needs [33,34]. The Windsor-Essex region, serving approximately 422,000 residents with significant immigrant populations and diverse socioeconomic backgrounds, faces additional complexities as a border community with unique demographic characteristics and economic patterns tied to the automotive manufacturing industry [35]. In Windsor-Essex, youth experience longer wait times for mental health care and limited access to specialized AYA supports, adding to the aforementioned challenges [21,33].

Research Gap in the Canadian Context

No published Canadian studies have specifically examined the lived experiences of adolescent patients with cancer and their families within regional health care settings. While Canadian cancer surveillance data provide epidemiological insights [26], there is a lack of qualitative research exploring how the unique features of Canada's regional care delivery shape the cancer experience for young people and their families. This gap is especially significant, given that approximately 40% of Canadian youth live in nonmetropolitan areas, where regional hospitals serve as their primary points of care [15,26]. This study was developed in response to these gaps and informed by guidance from the funding agency (Multimedia Appendix 1).

Study Objectives

Given the research gap in Canadian context–specific AYA cancer research and the unique health care delivery challenges faced by youth in regional settings such as Windsor-Essex, this study addresses important knowledge needs that cannot be met through extrapolation from US-based literature. This study examines the impact of Ontario's regional cancer care system and health care structure on the experiences of adolescents, caregivers, and HCPs. The research questions guiding this study are as follows:

1. What are the everyday experiences and psychosocial and support needs of youth during and after routine cancer treatment?
2. How do parents and caregivers navigate the process of receiving routine cancer treatment with their youth?
3. What are the perspectives of HCPs about youth receiving routine cancer treatment?
4. What recommendations do the youth, parents and caregivers, and HCPs have for relevant decision-makers and partners (eg, community organizations, government and policymakers, and hospital administration) to improve cancer care for youth?

Methods

Study Design

This study used a qualitative descriptive approach, guided by the reflexive thematic analysis approach described by Braun and Clarke [36], to explore the lived experiences, care processes, and recommendations related to cancer treatment among youth, caregivers, and HCPs in Windsor-Essex Region. This protocol and subsequent reporting adhere to the COREQ (Consolidated Criteria for Reporting Qualitative Research) guidelines, ensuring comprehensive and transparent reporting of the qualitative research methodology and findings [37]. While much of the existing research on the cancer experiences of youth originates in the United States, contextual differences in health, education, and social systems necessitate Canada-specific inquiry [1,38]. Guided by the four research questions outlined in the Study Objectives subsection, this study focused on (1) the day-to-day experiences and psychosocial needs of youth during and after cancer treatment, (2) the caregiving and care navigation experiences of parents and caregivers, (3) the perspectives of HCPs, and (4) key member–informed recommendations for improving care. Data were collected through web-based semistructured interviews and analyzed using inductive thematic analysis.

Participant Demographics

This study was conducted in Southwestern Ontario and focused on youth receiving regional oncology care. The sample size of 8 participants per group was determined based on qualitative research guidelines, which suggest that thematic saturation typically occurs within 6 to 12 interviews per homogeneous group [39]. Given the perspectives of 3 distinct key members (youth, caregivers, and HCPs) representing different experiential domains, we anticipated that 8 participants per group would provide sufficient data richness within each stakeholder

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category. A purposive sampling strategy was planned to ensure diversity in participant experiences and demographics. Recruitment actively sought participants from different racial and ethnic backgrounds, including the region's Arab, South Asian, and other immigrant communities, with varying socioeconomic statuses, cancer diagnoses (including both hematologic and solid tumor malignancies), and treatment experiences. Recruitment materials were distributed through culturally diverse community organizations, recognizing that the English fluency requirement may limit participation from some non–English-speaking families.

Eligible youth participants included those diagnosed with cancer between January 2014 and December 2023 and who were aged between 12 and 18 years at the time of diagnosis. Youth must have received part or all of their oncology care at a regional hospital and demonstrate sufficient cognitive and communicative ability to consent and participate in an interview independently. Primary caregivers of eligible youth will also be invited to take part in the study.

HCPs, such as oncologists, nurses, therapists, or social workers, were eligible if they were currently employed at regional hospitals and provided care to youth with cancer and their families. As noted earlier, participation was limited to English-speaking individuals due to resource constraints, which may affect the diversity of the sample. Youth were excluded if they were diagnosed with cancer within the 3 months before study enrollment or if the referring pediatric oncologist determined that participation may be psychologically harmful. This may include cases in which the youth's cancer experience was traumatic, and participation could trigger significant mental health concerns. This sampling approach ensures that participants are prepared to reflect meaningfully on their experiences in a supportive research environment.

Recruitment

A multimethod sampling strategy was used to recruit youth cancer survivors, their parents or caregivers, and HCPs involved in their care. Recruitment occurred through 4 different means to support broad accessibility, minimize selection bias, and enhance participant diversity. The main recruitment involved clinician-facilitated referral at the regional hospital satellite oncology clinic. During routine outpatient visits, eligible youth and caregivers were introduced to the study by their oncology clinician using a standardized study information letter. This letter provided an overview of the study's objectives, procedures, and ethical safeguards, and included a QR code linking to a secure REDCap (Research Electronic Data Capture; Vanderbilt University) screening form. Interested individuals completed the form independently at their convenience using a personal device. To protect voluntariness and reduce the potential for perceived coercion, clinicians were not informed of who proceeded with enrollment.

To complement this approach, recruitment posters were displayed throughout clinical settings, including waiting rooms, outpatient areas, and staff bulletin boards. Posters were tailored to each participant group, such as youth, caregivers, and HCPs, and included a QR code linking to the REDCap screening form. This passive recruitment strategy allowed potential participants to self-identify and engage with the study without direct clinician involvement. Digital recruitment was conducted through the website of the Pediatric Oncology Group of Ontario and the research team's social media channels, including Twitter (subsequently rebranded as X) and Instagram, to further broaden outreach beyond the clinical environment. Electronic flyers were designed specifically for youth and caregivers and contained a study email address and a QR code directing those interested to the REDCap screening form. This digital strategy was intended to reach individuals who may no longer be in regular contact with oncology care services, thereby improving accessibility.

In parallel, HCPs were recruited through email invitations distributed by clinical managers and department heads at a regional hospital. These emails contained a study summary, assurances regarding voluntariness and confidentiality, and a link to the REDCap screening form. Posters were also displayed in staff common areas to reinforce recruitment messages. While clinical leaders promoted the study broadly, they will not be involved in identifying or enrolling individual participants. This ensures a clear separation between research and professional roles.

Once a screening form was submitted, the research assistant reviewed responses to determine eligibility based on predefined inclusion and exclusion criteria. Eligible participants were then contacted, provided with the study letter of information, given the opportunity to ask questions, and invited to schedule a web-based consent appointment. A follow-up email was sent if no response was received within 2 business days. Individuals deemed ineligible received a standardized email indicating that they did not meet the study criteria. The research team independently conducted all consent and enrollment procedures to uphold ethical standards and maintain participant confidentiality.

Data Collection

Data were collected through interviews using Microsoft Teams, a secure videoconferencing platform licensed and supported by the University of Windsor. Before the interview, we completed a brief demographic questionnaire with all participants via REDCap to gather descriptive information, including age, gender identity, location, relationship to the youth (for caregivers), and clinical role (for HCPs). These data will help characterize the sample and provide important context for interpreting the qualitative findings [40].

The research team developed the interview guides (Textbox 1) for each participant group (youth, parents, and HCPs), drawing from existing literature and the study's research questions. Draft guides were reviewed by the research team (JT and JCK) and assessed to ensure that questions were clear and sensitively worded. Revisions were made based on this feedback before finalizing the guide. The research team piloted the guide to ensure clarity, relevance, and sensitivity to participant experiences [41]. Questions were open-ended and conversational, encouraging participants to reflect on their experiences in their own words. Youth interviews focused on daily life, emotional well-being, and transitional challenges experienced during and after treatment. Caregiver interviews

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focused on the emotional impact of caregiving, experiences with accessing and navigating services, and care coordination responsibilities. HCP interviews examined routine cancer care delivery, interdisciplinary collaboration, systemic barriers, and recommendations for improving care for youth [1,42].

Textbox 1. Interview guides for youth, parents or caregivers, and health care providers.

Interview guide for parents or caregivers and youth diagnosed with cancer

1. Can you tell me a little bit about yourself and your family?
2. What has it been like for you and your child to live with cancer?
3. Can you tell me about the resources that you used or were referred to during your cancer treatment journey? In what ways did you find them helpful or not helpful?
4. What kinds of things do you and your parent (or you and your child) talk about when it comes to the cancer experience?
5. Can you tell me about how your health care providers prepared you (or your child) for treatment and what to expect afterward?
6. Can you tell me a bit about what is most important to you in life right now?
7. What do you hope to see improved in terms of cancer care for youth living in Southwestern Ontario?
8. Is there anything else you feel that we did not cover today or that you feel is important for me to know about this topic?

Interview guide for health care providers

1. Can you tell me a little bit about yourself and your role as a (health care provider, eg, oncologist, dietitian, registered nurse, or occupational therapist) in the oncology satellite unit?
2. What experience do you have providing oncology care specifically to the adolescent and young adult population?
3. Could you describe the kinds of community and hospital or clinic resources that are available in Southwestern Ontario for youth diagnosed with cancer and their families?
4. What do you think are some of the important considerations that youth have in mind when undergoing their cancer treatment?
5. How do you think cancer care in the oncology satellite unit at the regional hospital can be improved for youth with cancer?
6. Is there anything else you feel that we did not cover today or that you feel is important for me to know about this topic?

Each interview was scheduled at a time convenient for the participant and lasted approximately 1 hour. Participants had the option to pause or take breaks at any time. The research assistant was available to coordinate a follow-up session for those choosing to complete their interview in 2 parts. Verbal reconfirmation of consent was obtained before resuming a second session. The principal investigator, coinvestigator, or a trained research assistant conducted interviews. To support participant comfort and ensure confidentiality, interviewers were not individuals currently or formerly involved in the participants' clinical care.

All interviews were audio recorded with participant consent, transcribed verbatim, and deidentified during transcription. The research team reviewed transcripts for accuracy. Once transcription was complete, audio files were permanently deleted. All interview procedures and communications were designed with flexibility and sensitivity to accommodate varying levels of comfort and emotional readiness, particularly given the potentially distressing nature of reflecting on cancer-related experiences [1,42]. A list of mental health and community resources was provided at the time of consent and again after the interview to ensure that participants were supported throughout the process.

Data Analysis Plan

Interview data are being analyzed using reflexive thematic analysis, following the 6-phase methodology outlined by Braun and Clarke [36]. This approach is consistent with the study's qualitative descriptive design and pragmatic orientation, allowing for a systematic exploration of how youth, caregivers, and HCPs experience and make meaning of routine cancer care [40]. The study is situated within a relativist ontology and constructionist epistemology, recognizing that participants' realities are subjectively constructed through their lived experiences [43]. This philosophical positioning aligns with the study's goal of capturing diverse perspectives and meaning-making processes across participant groups. The research team transcribed all interview recordings verbatim, deidentified them, and verified their accuracy before coding. The transcripts were then imported into NVivo 14 (Lumivero), which is being used to support data management, code organization, and theme development.

The analytic process is iterative and reflexive, guided by the study's 4 core research questions. Analysis begins with open coding, allowing for the inductive identification of meaningful data across transcripts. Codes are grouped into categories and abstracted into themes across participant groups [40,41]. Multiple research team members are involved in coding, theme generation, and theme refinement to enhance analytic rigor. Regular team meetings are held to compare interpretations, resolve discrepancies, and ensure consistency in analytic decision-making.

Thematic saturation is assessed using an iterative approach during concurrent data collection and analysis. Saturation is considered achieved when (1) no new codes emerge from

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consecutive interviews within each participant group, (2) existing themes are well developed with sufficient depth and variation, and (3) additional interviews yield redundant information that does not enhance thematic understanding. The research team meets after every 6 interviews within each group to assess progress toward saturation. If the eighth participant in any group does not achieve saturation, recruitment will continue with up to 2 additional participants per group until saturation is reached. Given the recognized challenges in recruiting youth participants due to their developmental stage and competing life priorities, the assessment of saturation for the youth group is evaluated with particular attention to the depth and richness of available data rather than strictly adhering to numerical targets. If youth data do not meet saturation criteria, this limitation will be acknowledged and the available data analyzed for depth and contextualized with caregiver and HCP perspectives. The final sample size will be determined by data adequacy rather than predetermined numbers.

To establish credibility, debriefing occurs within the research team throughout the analytic process. Transferability is addressed by providing a rich description of participant contexts and characteristics, enabling readers to assess the applicability of the findings to other settings [44]. Trustworthiness is established through the use of participant quotes for each theme, demonstrating how the original data support the interpretations. Dependability is ensured by documenting all analytic decisions, including coding frameworks and iterative changes to themes. An audit trail is maintained to establish confirmability, linking thematic interpretations to original data excerpts and providing transparency in the analytic process, as positioned by each research team member [45].

To further contextualize the findings, thematic comparisons are made between youth, caregiver, and HCP interviews to identify convergence, divergence, and potential gaps in perspectives across these groups. This synthesis supports the generation of nuanced insights and informs evidence-based recommendations for improving cancer care for youth in the Canadian context [1,42]. Quantitative demographic data are analyzed using descriptive statistics (eg, means, SDs, and frequency distributions) to characterize the sample. These findings will be presented alongside the qualitative results to provide context for the participant narratives in the manuscripts.

Ethical Considerations

This study has received approval from the University of Windsor Research Ethics Board (24-027). Informed consent was obtained electronically using REDCap after a clear explanation of the study was provided. Participants were assigned a study ID to maintain confidentiality, and all data were deidentified and stored securely in password-protected OneDrive (Microsoft Corporation) folders at the University of Windsor. The research team adhered to the Personal Health Information Protection Act and institutional policies to ensure participant confidentiality. Audio recordings were securely deleted after transcription and analysis, and all deidentified study data will be destroyed after 7 years. The anticipated risk of participation was assessed as low to moderate. Some youth and caregivers may have experienced emotional discomfort during interviews due to reflections on illness experiences. The principal investigator, a registered pediatric nurse, trained research assistants to identify signs of distress. If distress occurred, interviews were to be paused, and participants were to be offered support or referred to psychosocial services. The coprincipal investigator, a licensed clinical and health psychologist, was available for urgent consultation and triaging, if necessary. All participants were provided with a mental health resource sheet. Participation was voluntary and did not influence the clinical care that participants received. Each participant received a CAD $30 (approximately US $21.70) electronic gift card via email after their interview, regardless of whether it occurred in one or multiple sessions. Participants were able to withdraw at any time during the interview. Withdrawal after interview completion is not possible due to subsequent deidentification of the data and analyses of the data in aggregate. Participants who withdrew during an interview were still eligible to receive the full compensation for their participation.

Results

Participant recruitment commenced in November 2023 after ethics approval was obtained. As of September 2025, a total of 14 participants had completed semistructured interviews, including 6 (43%) caregivers, 6 (43%) HCPs, and 2 (14%) youths. Youth recruitment has been limited, likely due to their current life stage, as many are in remission and balancing employment or postsecondary education. Follow-up outreach efforts yielded minimal responses. The final achieved sample represents 58% (14/24) of the planned recruitment target, with caregiver and HCP recruitment reaching 75% (6/8) of their respective targets, while youth recruitment achieved only 25% (2/8) of the intended sample. Interview transcription was conducted between January and March 2025, with all interviews ranging from 45 to 75 minutes. Currently, preliminary analysis is in progress, with 2 research team members having independently coded initial transcripts and met to compare and refine coding. Initial coding has revealed themes related to care coordination challenges, psychosocial support gaps, and systemic barriers within regional cancer care delivery, although comprehensive thematic development awaits completion of the full analytic process. Coding and theme generation were finalized in June 2025.

Discussion

Expected Contributions

This study seeks to generate contextually rich insights into the lived experiences of youth cancer survivors, their caregivers, and HCPs in a regional Canadian setting. While most US research has focused on challenges such as insurance issues, treatment costs, and access to specialized AYA programs in large urban tertiary centers, this study examines how Canada's public health care system and regional care delivery models shape the cancer experience for adolescents and their families. Using reflective thematic analysis, we explore how youth navigate the psychosocial, emotional, and practical challenges of cancer care; how caregivers manage care coordination; and how HCPs address the unique needs of this population. This

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multiperspective approach brings together different experiences to better understand how the overall care journey is shaped by relationships; systemic barriers; and local factors such as health care infrastructure, geographic access, and social support. The findings may highlight service gaps and suggest ways to improve continuity, developmental responsiveness, and equity in cancer care. They will also contribute evidence to support capacity building in regional settings and guide local and provincial planning. This work fills a gap in Canadian research and supports ongoing improvements in care delivery and health system design, building on insights from participants' lived experiences.

Dissemination Plans

The findings from this study will be disseminated to engage knowledge users. Study results will be shared with youth, caregivers, clinicians, administrators, and policymakers through multiple formats tailored to their preferences. Dissemination activities include academic publications and presentations at provincial and national oncology conferences.

Future Directions

This protocol lays the groundwork for several future research initiatives. First, insights from this study will inform the design of a larger, multisite study examining cancer care for youth across different provinces and health system models in Canada. Second, the findings may be used to codevelop and pilot an intervention targeting identified gaps, such as youth-centered survivorship planning or caregiver navigation support. Given the anticipated identification of system-level barriers and training needs among HCPs, future work may also focus on cocreating and evaluating continuing education modules to enhance provider competence in youth-centered oncology care, especially in regional settings. In addition, longitudinal follow-up with youth participants could explore how their experiences evolve during the transition to adulthood, including re-engagement with the health care system, vocational development, and long-term psychosocial adjustment.

Strengths and Limitations

A key strength of this study is its focus on a population often underrepresented in oncology research: youth in regional settings who must navigate complex care pathways with limited support. The use of a qualitative descriptive design and reflexive thematic analysis, grounded in a pragmatic orientation, allows for rich, context-sensitive insights to emerge directly from participants' narratives. The inclusion of multiple perspectives (youth, caregivers, and HCPs) enables the triangulation of findings and highlights systemic patterns and relational dynamics that would otherwise remain invisible. Web-based interviews increase accessibility and flexibility for participants, which is particularly important for those balancing work, school, and health-related appointments.

However, there are also limitations. Recruitment challenges among youth in remission may limit the impact of youth perspectives beyond the current subgroup that is represented in this study. The reliance on a single regional setting may reduce transferability to other geographic contexts with different health system configurations. In addition, while efforts were made to ensure diversity in participants' sociodemographic backgrounds, those with limited internet access or English fluency may have been unintentionally excluded. Finally, despite efforts to take the research team's positioning into account through reflexive analysis and team-based coding, interpretation remained subject to the perspectives and lens of the research team [45].

Conclusions

Adolescents with cancer face unique and often overlooked challenges as they navigate treatment, schooling, social transitions, and their emerging identities. These challenges are often compounded for youth living in regional settings, where access to developmentally appropriate and specialized oncology care is often limited. Despite growing international interest in AYA oncology, there remains a critical gap in Canadian, context-specific research that captures the lived experiences of youth, their caregivers, and the HCPs who support them. This study offers in-depth insights into how youth and families experience cancer care in a regional Canadian setting, identifying key factors that influence equity and continuity. By examining multiple perspectives and centering the perspectives of youth, this work will potentially inform future research, practice, and policy development aimed at improving equity and responsiveness in cancer care for adolescents. Through its focus on local context, collaborative dissemination, and implications for broader system change, the study lays the foundation for scalable improvements that better reflect the realities of youth navigating cancer within the Canadian health care system.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

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Authors' Contributions

JT contributed to conceptualization, methodology, software, investigation, project administration, formal analysis, writing (original draft), and writing (review and editing). JCK contributed to conceptualization, methodology, software, investigation, project administration, formal analysis, and writing (review and editing). MJ contributed to conceptualization and methodology. TY contributed to conceptualization and methodology.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by Multidisciplinary Research Assessment Committee, WE-SPARK Igniting Discovery Grant Program.
[PDF File (Adobe PDF File), 422 KB - resprot_v14i1e76877_app1.pdf]

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Abbreviations

AYA: Adolescent and young adult
COREQ: Consolidated Criteria for Reporting Qualitative Research
HCP: health care provider
REDCap: Research Electronic Data Capture

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Protocol

High-Throughput Computing to Detect Harmful Drug-Drug Interactions in Older Adults: Protocol for a Population-Based Cohort Study

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Abstract

Background: Drug-drug interactions (DDIs) are a major concern, especially for older adults taking multiple medications. Although Health Canada and the US Food and Drug Administration (FDA) use population-based studies to identify adverse drug events, detecting harmful DDIs is challenging due to the millions of potential drug combinations. Traditional pharmacoepidemiologic studies are slow and inefficient, often missing important harmful DDIs.

Objective: This protocol outlines a novel approach to efficiently identify harmful DDIs using administrative health care data.

Methods: Using high-throughput computing, we will conduct multiple population-based, new-user cohort studies using Ontario's linked administrative health care data. The cohorts will be selected from the population of Ontario residents aged 66 years and older who filled at least one oral outpatient drug prescription from 2002 to 2023. In each cohort, the exposed group will comprise individuals who are regular users of one drug (drug A) who start a new prescription for a second drug (drug B); the referent group will comprise regular users of drug A not taking drug B. We will evaluate 74 acute outcomes within 30 days of cohort entry, including hospitalizations, emergency department visits, and mortality. Propensity score methods will balance exposed and referent groups on more than 400 baseline health characteristics. Modified Poisson and binomial regression models will estimate risk ratios (RRs) and risk differences (RDs). To ensure findings are both statistically and clinically meaningful, we will apply prespecified thresholds for effect sizes (eg, lower bounds of 95% CIs≥1.33 for RRs and ≥0.1% for RDs) and control the false discovery rate at 5% using the Benjamini-Hochberg procedure to address multiplicity. Subgroup and sensitivity analyses, including negative control outcomes and E-values, will assess robustness.

Results: In a preliminary analysis, we identified approximately 3.8 million older adults who filled prescriptions for over 500 unique medications during the study period (2002-2023), and therefore, approximately 200,000 potential drug combinations will be available for study. The initial drug pair cohorts had a median of 583 new users per cohort (IQR 237-2130); the median overlap in drug pair prescriptions was 57 days (IQR 30-90). The protocol was finalized on August 30, 2025, and outlines the analysis of data from 2002 to 2023. The analysis is scheduled to be completed by fall 2026, with results interpreted in 2027. The final manuscript submission is planned for December 2028.

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Conclusions: This study aims to identify credible signals of harmful DDIs in older adults in routine care. This study will use an innovative approach that leverages data from provincial administrative health care databases and integrates high-throughput computing and rigorous pharmacoepidemiologic methods to generate robust real-world evidence that can inform safer prescribing practices and regulatory decision-making.

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KEYWORDS

older adults; high-throughput computing; drug-drug interactions; machine learning; drug safety

Introduction

Drug-drug interactions (DDIs) occur when two or more medications interact in ways that alter their effectiveness or safety [1,2]. The drug being affected is termed the *object drug*, while the drug causing the interaction is known as the *precipitant drug* [3,4]. The precipitant drug can influence the object drug through pharmacokinetic (PK) mechanisms (affecting absorption, distribution, metabolism, or excretion) or pharmacodynamic (PD) mechanisms (altering the drug's effects at its target site) [3]. An interaction may increase the effect of an object drug, leading to toxicity. Alternatively, an interaction may lessen the effect of an object drug, leading to reduced efficacy or treatment failure [5].

DDIs pose a significant risk for older adults due to polypharmacy and age-related changes in drug metabolism and elimination [6-8]. Approximately one in six hospitalizations among older adults is attributed to adverse drug events [9]. Additionally, older adults are often excluded from clinical trials, limiting our understanding of how DDIs affect this population. Drugs with a narrow therapeutic index are particularly concerning, as even minor interactions can have serious clinical consequences [10,11].

Although premarket clinical trials evaluate PK DDIs in healthy volunteers, many clinically significant DDIs are only identified after drug approval through case reports, small observational studies, and large-scale pharmacoepidemiologic research [12,13]. Traditional DDI detection methods often analyze one drug pair at a time, which can be slow and inefficient. These limitations are a concern worldwide: international efforts using electronic health records, claims data, or national prescription registries have made progress, but such approaches may not scale fast enough to keep pace with the thousands of new drug combinations entering the market each year, highlighting the need for rapid, large-scale, and systematic surveillance methods.

High-throughput computing and automated analytical pipelines have been applied in other contexts to rapidly screen for potential DDIs. For example, researchers in the United States and Europe have used these approaches with large electronic health care databases to identify clinically relevant DDI signals [14,15]. Bykov et al [14] validated a case-crossover–based method by successfully flagging known interactions in large US claims databases. Similarly, Leonard et al [15] demonstrated the ability of high-throughput pharmacoepidemiologic screening using a self-controlled case series design to confirm known DDI risks and identify novel potential interactions in real-world data. Although Bykov et al [14] and Leonard et al [15] have demonstrated the potential of high-throughput screening for DDIs in US health care databases using self-controlled designs, our study complements and extends these approaches by applying high-throughput computing to Ontario's population-based, linked administrative health care data within a universal health care system using a population-based, new-user cohort design [16]. This will allow us to systematically evaluate over 200,000 medication combinations in older adults, integrating PK, PD, and epidemiologic evidence for robust, real-world signal detection at a scale and scope not previously achieved. By applying these methods in a Canadian context, we aim to identify potentially harmful DDIs that may warrant further validation, address key knowledge gaps, and generate findings relevant to both national and international health care systems. To the best of our knowledge, this represents the first application of such an approach in Canada, leveraging the strengths of a universal health care setting to further enhance the generalizability and clinical relevance of detected DDI signals. The results of this work have the potential to support safer prescribing practices, generate signals that could inform clinical decision-making once validated, and guide health care policy aimed at reducing adverse drug events in older adults.

This protocol outlines our plan to detect harmful DDIs more efficiently in routine care using high-throughput computing and automation. To do this, we will simultaneously conduct more than 200,000 population-based, new-user drug safety studies using 21 years of data from Ontario's administrative health care databases (2002-2023). These databases contain encrypted data on all health care visits and hospitalizations of Ontario residents—all of whom have universal access to hospital care and physician services through a government-funded single-payer system, with Ontarians aged 65 years and older also receiving universal outpatient prescription drug coverage.

Following the application of inclusion and exclusion criteria, we will analyze a refined set of medication cohorts, each containing an exposed group (individuals prescribed a certain pair of medications) and a referent group (individuals prescribed a single medication). The exposed and referent groups will be statistically balanced on more than 400 baseline health characteristics. We will assess 74 clinically relevant outcomes and conduct extensive sensitivity and bias analyses to minimize false discoveries. Harmful DDIs that meet prespecified criteria will be further examined in additional and exploratory analyses. This study's objective is to identify credible signals of harmful DDIs in older adults in routine care.

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Methods

Study Design and Data Sources

Using high-throughput computing and automation, we will conduct over 200,000 population-based, new-user drug safety cohort studies using linked administrative health care databases in Ontario, Canada. The study period will span from July 1, 2002, to March 1, 2023. All study data will be obtained from Ontario's linked administrative health care databases housed at the Institute for Clinical Evaluative Sciences (ICES) [17]. These databases contain encrypted, person-level data for Ontario residents, who have universal access to hospital care and physician services through a government-funded, single-payer system. A description of the databases is provided in Table 1.

Table 1. Description of study databases.

Database	Description
National databases/registries	
Canadian Institute for Health Information's Discharge Abstract Database (CIHI-DAD)	Contains diagnostic and procedural information for all hospitalizations, collected by each province
Canadian Organ Replacement Register (CORR)	National registry that includes information on vital organ transplantation and dialysis activities
National Ambulatory Care Reporting System (NACRS)	Contains information on hospital and community-based ambulatory care visits
Ontario databases	
Ontario Mental Health Reporting System (OMHRS)	Contains adult inpatient mental health information
Registered Persons Database (RPDB)	Contains information on patient demographics, including sex, birth dates, and death dates
ICES[a] Physician Database (IPDB)	Contains physician-related information, such as birth dates, sex, education, and specializations
Ontario Drug Database	Contains claims for prescription drugs received under the ODB[b] program
Ontario Health Insurance Plan (OHIP)	Contains diagnostic information and health claims for inpatient and outpatient services
Ontario Laboratories Information System (OLIS)	Contains laboratory test orders and results from hospitals, community labs, and public health labs

[a]ICES: Institute for Clinical Evaluative Sciences.

[b]ODB: Ontario Drug Benefit.

Residents aged 65 years and older receive universal outpatient prescription drug coverage through the Ontario Drug Benefit (ODB) program (while residents of all ages only receive universal prescription drug coverage for medications dispensed in emergency departments or during hospital admissions). Consequently, our study will leverage comprehensive outpatient prescription data for residents aged 65 years and older. We have previously used these databases to examine adverse drug events and health outcomes [16,18-21].

These databases are expected to be complete for all study variables, except for prescriber specialty (10%-20% missing), rural residence, and neighborhood income quintile (less than 2% missing). The only source of loss to follow-up is emigration from Ontario, which occurs at an estimated rate of 0.5% per year [22].

The study conduct and reporting will adhere to recommended guidelines for observational pharmacoepidemiology studies that use routinely collected health data (Multimedia Appendix 1) [23,24]. More details on the databases, study variables, and the codes used to define baseline comorbidities are provided in Multimedia Appendix 2. The integration of data from different sources is summarized in Multimedia Appendix 3. The process of building the cohorts is summarized in Figure 1, and the analytic steps are summarized in Multimedia Appendix 4.

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Figure 1. Study flow diagram. DAD: Discharge Abstract Database; NACRS: National Ambulatory Care Reporting System; ODB: Ontario Drug Benefit; OHIP: Ontario Health Insurance Plan; RPDB: Registered Persons Database.

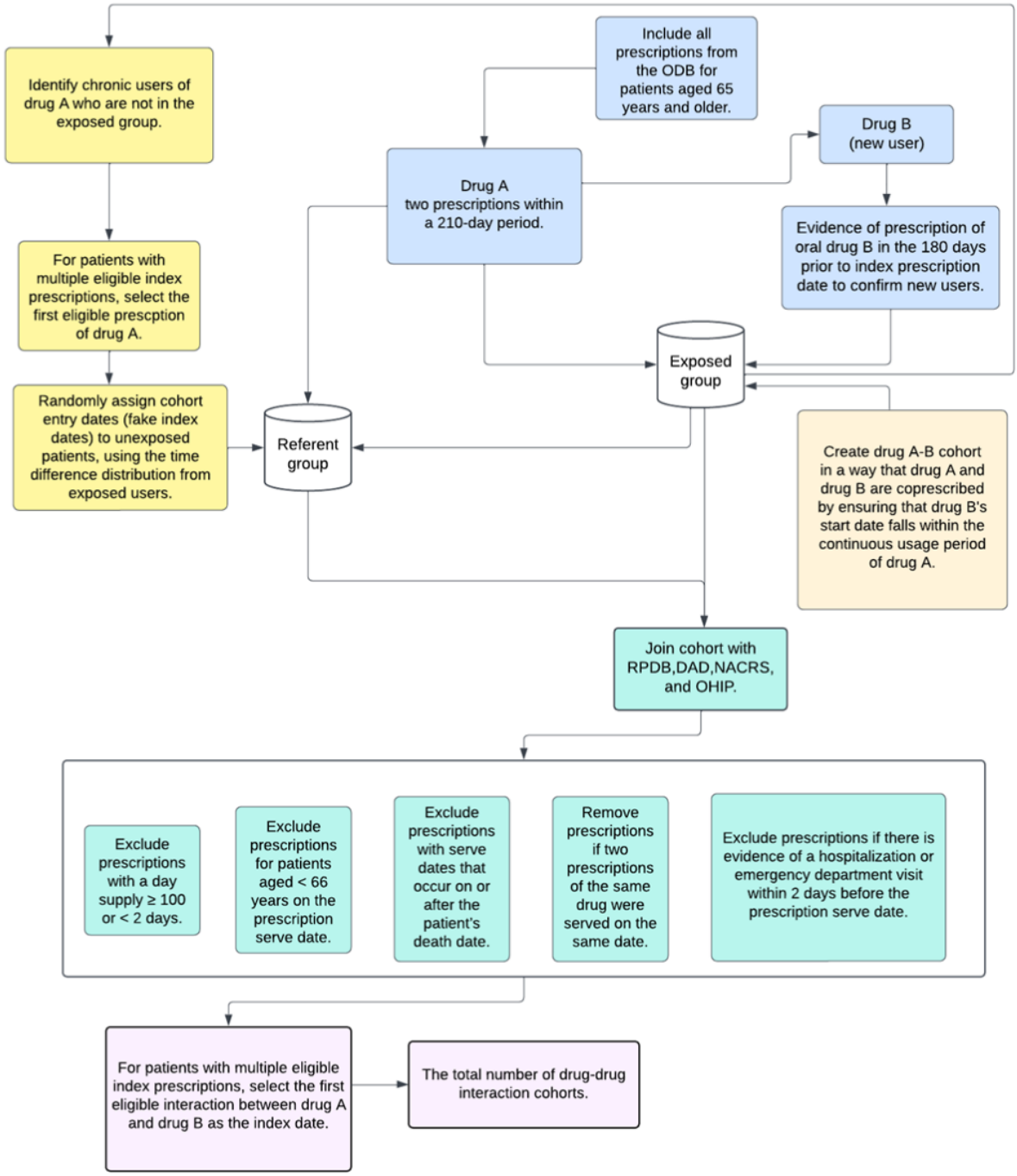

Source Population

The source population will comprise adults aged 66 years and older who filled at least one oral outpatient drug prescription with a supply duration of at least 3 days, dispensed between July 1, 2002, and March 1, 2023 (codes for nonoral versions are provided in Multimedia Appendix 5). The age criterion will ensure that individuals in this population have at least 1 year of prior ODB prescription drug coverage.

Cohort Builds

The study cohorts will be constructed using the process described later. Each cohort will be selected from the source population and contain an exposed group (individuals prescribed a pair of medications: drugs A and B) and a referent group (individuals prescribed drug A), as defined next.

Regular Users of Drug A

We will first select individuals with at least two prescriptions for the same medication (drug A) within a 210-day period, with

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a maximum allowable gap equivalent to 150% of the days' supply of the previous prescription.

New Users of Drug B

From the sample of regular users of drug A, we will select individuals who start a prescription for a new medication (drug B) that is taken concurrently with drug A, meaning drug B's start date is on the same date as the most recent drug A fill date or falls within drug A's supply duration.

Cohort Entry Dates for Exposed and Referent Groups

The exposed group will comprise regular users of drug A and new users of drug B, as described earlier. The cohort entry date for individuals in the exposed group will be the start date of drug B. The referent group will comprise regular users of drug A who are not coprescribed drug B. The cohort entry date for individuals in the referent group will be assigned based on the distribution of the time differences between the most recent prescription for drug A and the initiation of drug B for individuals in the exposed group, ensuring similar observation periods between groups [25].

Individual-Level Exclusion Criteria Applied to the Exposed and Referent Groups

We will exclude individuals who meet any of the following criteria:

- Individuals prescribed drug B within 180 days before the cohort entry date (to ensure those in the exposed group are new users of drug B and that those in the referent group were not previously exposed).
- Individuals prescribed another medication in the same class as drugs A and B on the cohort entry date. For example, if drug A or B is sertraline, which is a serotonin reuptake inhibitor (SSRI), individuals prescribed a nonsertraline SSRI on the cohort entry date will be excluded.
- Individuals discharged from the hospital or emergency department within 2 days before the cohort entry date (to ensure that prescriptions are new outpatient prescriptions).
- Individuals whose day supplies for drug A or B are ≥100 days or <2 days.
- Individuals who are nonpermanent Ontario residents, are aged <66 or >105 years on the cohort entry date, or have a date of death on or before the cohort entry date (data cleaning exclusions).

An individual can only enter a cohort once; if an individual meets the eligibility criteria multiple times, the first eligibility date will serve as the cohort entry date.

Cohort-Level Exclusion Criteria

To ensure meaningful results, only cohorts with a minimum sample size of 1000 patients, with at least 200 individuals in the exposed group and 200 individuals in the referent group, will be considered for further analysis.

Outcomes

We will examine 74 outcomes within 30 days of cohort entry (Textbox 1). The outcomes were chosen using a prespecified analytic approach and considering the clinical significance of the outcomes and the observed rates in the study region [16]. Many of the algorithms used to identify these outcomes have been validated in previous studies and demonstrate high sensitivity and specificity [26-30]. Shorter and longer follow-up times for outcomes will be examined in additional analysis (see the *Additional Analysis to Characterize the Signals* section).

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Textbox 1. Final set of 74 clinically relevant outcomes (ordered alphabetically).

Clinically relevant individual outcomes (n=56):

- Abdominal aortic aneurysm repair/aortic bypass
- Achilles tendon rupture
- All-cause mortality (prespecified)
- Arthroscopy
- Asthma
- Atrial fibrillation/flutter or other arrhythmia (pacemaker insertion, palpitations, tachycardia unspecified, atrioventricular block, supraventricular tachycardia, or other conduction disorders)
- Bowel obstruction
- Bradycardia
- Bronchoscopy
- Carotid endarterectomy
- Carotid ultrasound
- Cataract, unspecified
- Chest X-ray
- Cholecystitis, unspecified
- Clostridium difficile colitis
- Colposcopy
- Computed tomography: abdomen
- Computed tomography: head
- Computed tomography: thorax
- Cutaneous drug reaction
- Cystoscopy
- Depression
- Disorders of calcium metabolism
- Emergency department visit for any reason (prespecified)
- Gout
- Guillain-Barré syndrome
- Head trauma
- Hearing loss
- Hospital admission for any reason (prespecified)
- Hyperkalemia
- Hypoglycemia
- Hypokalemia
- Hyponatremia
- Intensive care unit admission
- Kidney stones
- Laparoscopy
- Liver disease toxicity
- Lower limb amputation
- Major abdominal surgery
- Major cardiovascular surgery
- Osteoarthritis

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- Pancreatitis
- Parkinson's disease
- Physician visit for any reason (prespecified)
- Pneumonia
- Renal biopsy
- Retinal detachment
- Rhabdomyolysis
- Rheumatoid arthritis
- Self-harm
- Sepsis
- Surgery (for any reason other than major abdominal surgery, major cardiovascular surgery, lower limb amputation and fracture, and major ortho procedure)
- Severe respiratory depression
- Urinary incontinence
- Urinary retention
- Venous thromboembolism

Clinically relevant composite outcomes (n=18):

- Acute dialysis or acute kidney injury
- Aplastic anemia (unspecified), neutropenia, or other agranulocytosis, or thrombocytopenia (unspecified)
- Cardiac arrest or ventricular arrhythmia
- Cardiac catheterization or coronary revascularization
- Colonoscopy or esophagogastroduodenoscopy
- Diabetic ketoacidosis, hyperglycemia, or hyperosmolar nonketotic coma
- Delirium or other encephalopathy
- Delirium, fall, or other encephalopathy
- Echocardiography or Holter monitoring
- Electroencephalography or seizures
- Emergency department visit or hospital admission for any reason (prespecified)
- Fall, fracture or major orthopedic procedure, or fracture
- Fall or hypotension
- Fall or syncope
- Heart failure or myocardial infarction (most-responsible diagnosis), or ischemic stroke (most-responsible diagnosis)
- Hemarthrosis or hemorrhage (not elsewhere classified), intracerebral hemorrhage (unspecified), lower gastrointestinal bleed, other nontraumatic intracranial hemorrhage, subarachnoid hemorrhage (unspecified), or upper gastrointestinal bleeding
- Hypotension or syncope
- Urinary tract infection or urine culture

Statistical Analysis Plan

All analyses will be programmed and automated using Python, SAS, the JavaScript library D3, and R (R Foundation for Statistical Computing) and will be conducted on the Health Artificial Intelligence Data Analytic Platform, a high-performance computing environment for analyzing ICES data. The open source JavaScript library D3 will be used to develop interactive visualizations.

Analysis to Balance the Exposed and Referent Groups in Each Cohort

Propensity scores will be calculated using multivariable logistic regression, incorporating more than 400 baseline characteristics (the complete list and coding definitions are provided in Multimedia Appendix 2). Characteristics include calendar year, prior use of drug A, demographics (eg, age, sex, neighborhood income quintile, urban vs rural residence, geographic region [31], and long-term care home residency), comorbidities (eg,

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asthma, diabetes, coronary artery disease) assessed over the 5 years before cohort entry, health care use in the year prior (eg, hospitalizations, emergency room visits, specialist consultations), and prescription drug dispensing within 120 days before cohort entry. The 120-day lookback period accounts for potential delays in prescription refills, ensuring comprehensive capture of medication dispensing.

The propensity scores will estimate the probability of a patient being in the exposed group versus the referent group, given their baseline characteristics. To enhance the comparability of the exposed and referent groups, we will exclude (1) individuals in the referent group with propensity scores lower than the lowest 1% of scores in the exposed group and (2) individuals in the exposed group with propensity scores higher than the highest 99% of scores in the referent group. This will also ensure that we do not violate the positivity assumption in causal inference, which requires that there should be a nonnull probability across each stratum of baseline characteristics within both the exposed and referent groups [32].

Inverse probability of treatment weighting (IPTW) using average treatment-effect-in-the-treated (ATT) weights will then be used to balance the exposed and referent groups on baseline characteristics as follows: Individuals in the referent group will be weighted using ATT weights, defined as their odds of being in the exposed group (propensity score/[1 − propensity score]). Individuals in the exposed group (the medication pair group) will receive weights of 1. This method will produce a weighted pseudosample of individuals in the referent group with a distribution of measured characteristics similar to that of the exposed group [33,34]. Between-group differences in baseline characteristics in the weighted samples will be examined using standardized differences (SDs) [35].

Cohorts will be excluded from further analysis if fewer than 95% of the baseline characteristics are balanced between the exposed and referent groups (ie, the SDs must be <10% for ≥95% of the characteristics).

Regression Analyses

A visual summary of the regression and additional exploratory analyses is provided in Multimedia Appendix 4. In each cohort, outcomes will be eligible for analysis if there are at least six outcome events in both the exposed and referent groups. Reporting fewer than six events could lead to potential patient reidentification and substantial estimation errors.

For each eligible cohort, we will use a modified Poisson regression model [36] to estimate the weighted risk ratio (RR) and its 95% CI for each outcome in the exposed group compared to the referent group. Additionally, a binomial regression model with an identity link function will be used to estimate the weighted risk difference (RD) and its 95% CI. If all 74 outcomes for a particular cohort are eligible, up to 74 regression models will be run.

Criteria for Identifying Potential Signals of Harmful DDIs

Associations between a drug pair and an adverse outcome that meet the following criteria will be considered potential signals of harm and analyzed further:

- Thresholds for RRs and RDs. The lower bound of the 95% CI for the RR must be ≥1.33, and for the RD, it must be ≥0.1%. These thresholds were chosen to ensure that only clinically significant increases in risk (of sufficient magnitude to be of concern) are considered. This analysis will focus solely on potential harms from drug combinations rather than protective benefits.
- Statistical significance. The *P* values from the modified Poisson regression model (for RRs) and the binomial regression model (for RDs) must be statistically significant after applying the Benjamini-Hochberg correction. This correction accounts for multiple comparisons across all outcomes and drug pair cohorts. The false discovery rate will be set at 5%, and the highest *P* value below the Benjamini-Hochberg critical value will be considered statistically significant, along with all *P* values below it. This correction will minimize the risk of false-positive discoveries (type I errors).

Drug pair cohorts that do not generate significant signals will not undergo further analysis.

Sensitivity and Bias Analyses to Guard Against Spurious Discoveries

Signals of potentially harmful DDIs will undergo the following sensitivity and bias analyses to ensure that identified signals are not artifacts of statistical or methodological bias but are credible associations worthy of further investigation:

- Survival analysis. To assess whether the initial signal persists when analyzed using a time-to-event approach, we will conduct a Cox proportional hazards regression with a 30-day follow-up period, censoring on death when all-cause mortality is not the outcome of interest. We will test the proportional hazards assumption by including an interaction term between the new-user status and follow-up time. This analysis will help determine whether the signal is robust across different modeling techniques.
- Negative-control exposure analyses. To detect potential biases from unobserved confounders, we will perform negative-control exposure analyses. A negative-control exposure is a variable that shares the same sources of bias as the drug of interest but cannot plausibly cause the outcome. We will rerun the regression analyses for the initial signals using a control exposure period starting 90 days before cohort entry [37]. This analysis will help identify any confounding factors that may have influenced the initial signal. Notably, the outcome of all-cause mortality cannot be examined with this method, as all patients lived to their cohort entry date. A positive association (ie, RRs and RDs significantly different from null, with $P<.05$) in this analysis would suggest potential confounding, whereas the absence of an association would bolster the credibility of the original signal.

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- E-value analysis. We will conduct E-value analyses to quantify the minimum strength of association an unmeasured confounder would need to have with both the drug combination and the outcome to negate the observed signal [38]. Larger E-values indicate that substantial unmeasured confounding would be required to explain away the signal, whereas smaller E-values suggest that minimal unmeasured confounding could do so. For an initial signal to be considered robust, the E-value must exceed 2.
- Propensity score matching. To further validate the robustness of the signal, we will use 1:1 propensity score matching to balance the exposed and referent groups on baseline characteristics [39]. This method estimates the average treatment effect in the treated and mitigates the influence of extreme weights, which can occur with IPTW. Consistency between the results of this analysis and the initial findings will strengthen the validity of the signal.
- Bootstrap analysis. We will use a multiplier bootstrap procedure to compute RRs and RDs across 200 random samples, each of the same size as the original cohort. This method helps correct SEs and CIs, ensuring they have the correct coverage rates [36,40]. For the signal to be considered robust, at least 90% of the bootstrap samples must yield results consistent with the original findings, with $P<.05$ and CIs for RRs and RDs in the same direction as initially observed.

Additional Analysis to Characterize the Signals

Signals of potentially harmful DDIs that are supported by the aforementioned sensitivity and bias analyses will be further explored and characterized as follows:

- Longer and shorter follow-up periods. To better understand the effects of prolonged medication exposure, we will extend the follow-up period beyond 30 days. We will rerun the regression analyses to examine the RRs and RDs for outcomes occurring within 60 and 90 days after cohort entry. We will also assess shorter follow-up periods by examining outcomes that occur within 7 and 14 days of cohort entry.
- Number needed to harm (NNH). To further quantify the absolute risk, we will calculate the NNH, which is derived from the RD (NNH=1/RD). This metric indicates how many patients would need to take the medication combination to result in harm to one additional patient who otherwise would not have been harmed. A lower NNH indicates a greater potential for harm [41].
- Population attributable fraction (PAF). We will calculate the PAF using the formula Pe(relative risk − 1)/[1 + Pe(relative risk − 1)], where Pe represents the proportion of the population exposed to the drug combination [42]. A PAF close to 1 suggests that eliminating the drug pair exposure could significantly reduce the number of adverse outcomes in the population, while a PAF close to 0 implies that reducing exposure would have minimal impact at the population level. Separate PAFs will be calculated for each outcome, and the results will be combined as a composite outcome before calculating the PAF for each cohort.

Bidirectional Exposure Analysis to Assess Signal Robustness

We will specifically highlight instances where the addition of drug B to drug A, and, conversely, drug A to drug B, yield concordant results for the outcome of interest. Observing consistent effects in both directions, particularly for chronic medications, will strengthen confidence in the validity of the signal and suggest that findings are less likely to be explained by residual confounding or treatment selection bias.

Exploring the Data Using Interactive Visualization

To facilitate data exploration, we will develop an interactive visualization tool. The tool will enable users to visually explore the outputs from our analyses, providing an overview of the data with the ability to access, filter, and modify the displayed information [43,44]. Users will be able to apply filters based on RRs or other metrics to identify associations that meet specific criteria. The tool will support manual exploration, enabling users to interactively query and sort the data.

Overall Framework to Identify, Characterize, and Validate Signals of Harmful DDIs

Signals identified in the high-throughput computing analysis will be rigorously evaluated for clinical relevance by examining evidence from PK, PD, and epidemiological studies, as well as by using clinical validation tools to prioritize and confirm the most clinically significant interactions as follows (Figure 2):

- Step 1: signal identification. Signals of potentially harmful DDIs identified in the high-throughput analysis must (1) meet predefined thresholds for RRs and RDs, (2) remain statistically significant after the Benjamini-Hochberg correction for multiple comparisons, and (3) be supported in sensitivity and bias analyses.
- Step 2: PK and PD assessment. PK and PD evidence will be evaluated to assess the biological plausibility of the interaction. For PK assessment, published studies on enzyme inhibition, drug metabolism, and clearance will be reviewed. For example, sulfamethoxazole inhibits CYP2C9, which metabolizes warfarin, leading to increased warfarin levels and a higher risk of bleeding [11,45]. For PD assessment, synergistic and antagonistic interactions will be examined. For example, the concurrent use of two antiplatelet agents can increase the risk of bleeding.
- Step 3: cross-validation with drug interaction checkers and product monographs. Signals will be cross-validated using DDI checkers, such as Lexicomp, Micromedex, and Drug Interaction Facts, along with regulatory product monographs (eg, from Health Canada and the US Food and Drug Administration [FDA]). Interaction severity will be classified as major, moderate, or minor based on standardized clinical guidelines. Recommended interventions for major interactions include (1) avoiding coadministration, (2) adjusting doses, and (3) monitoring relevant biomarkers (eg, the International Normalized Ratio [INR] for warfarin interactions).
- Step 4: prioritization of high-quality epidemiological evidence. Evidence from epidemiological studies will be examined and prioritized as randomized controlled trials

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(RCTs), high-quality cohort studies, and case-control studies. We will also prioritize evidence from studies of vulnerable populations (eg, older adults, patients with chronic kidney disease, and polypharmacy cohorts).

- Step 5: alternative evidence when high-quality epidemiological studies are unavailable. Complementary signal detection methods (eg, disproportionality analyses of pharmacovigilance databases, such as FAERS and VigiBase), case reports, and case series will be reviewed to assess the interaction's potential clinical significance when high-quality epidemiological evidence is unavailable. For disproportionality analyses, pharmacovigilance databases (eg, FAERS, VigiBase) will be analyzed to determine whether drug coadministration is disproportionately associated with adverse events compared to the administration of a single medication. When large-scale epidemiological data are lacking, case reports and case series may provide supporting evidence.
- Step 6: final signal validation and decision-making. Evidence from PK, PD, and epidemiological studies, pharmacovigilance data, and clinical decision-support tools will be synthesized to assess the credibility of the signal.

Figure 2. Framework to identify, characterize, and validate signals of harmful DDIs. DDI: drug-drug interaction; PD: pharmacodynamic; PK: pharmacokinetic; RD: risk difference; RR: risk ratio.

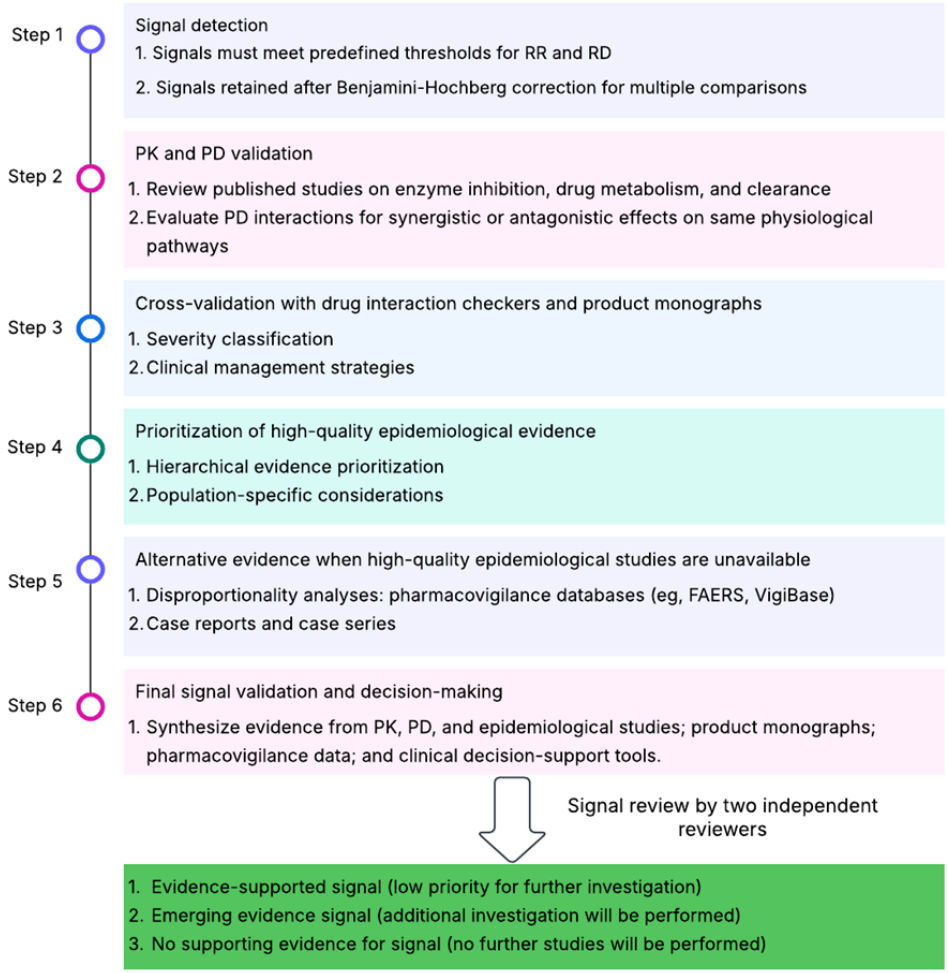

Each signal will be independently reviewed by two reviewers using the aforementioned criteria. The reviewers will classify each signal based on the strength and consistency of supporting data as an evidence-supported signal, an emerging evidence signal, or a signal with no supporting evidence. To minimize subjectivity, we will calculate an interrater agreement measure (eg, Cohen κ) to assess the level of concordance between the reviewers and determine whether they reach the same conclusion [46,47]. Any discrepancies will be resolved through discussion and, if needed, adjudicated by a third reviewer.

The criteria for classifying a signal as an evidence-supported signal (regulatory and clinical action may be warranted), an emerging evidence signal (additional investigation will be performed), or a signal having no supporting evidence (no further studies will be performed) are summarized in Table 2. Briefly, a signal will be considered evidence supported if multiple lines of evidence support a causal effect, it will require further study if the existing evidence is conflicting, and it will be dismissed in the absence of supportive evidence.

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Table 2. Summary table for criteria for signal confirmation, further study, or dismissal.

Category and criteria	Key indicators	Next steps
Evidence-supported signal[a] (low priority for further investigation)		
Multiple independent sources align	• PK[b]/PD[c] evidence supports a plausible interaction. • High-quality epidemiological data (RCTs[d], cohort studies) confirm increased risk. • Product monographs or clinical decision-support tools (eg, Lexicomp) classify it as a major interaction.	Regulatory and clinical action may be warranted, such as labeling changes or guideline updates.
Emerging evidence signal[a] (additional investigation to be performed)		
Conflicting evidence	• PK/PD data suggest a risk, but epidemiological studies do not confirm it. • Epidemiological findings are inconsistent or based on low-quality studies (eg, small sample size, case reports only). • Product monographs or clinical decision support tools give mixed or uncertain classifications.	A pharmacoepidemiological study should be conducted.
Limited population-specific data	• High-risk populations (patients with chronic kidney disease, older adults, polypharmacy patients) are underrepresented in studies. • Current evidence is based on general population data but lacks subgroup analyses.	A pharmacoepidemiological study should be conducted.
Emerging signal in pharmacovigilance databases	• Disproportionality analysis (eg, FAERS, VigiBase) suggests a safety concern but lacks validation in clinical studies. • Case reports describe severe but rare adverse events needing further confirmation.	A pharmacoepidemiological study should be conducted.
No supporting evidence for signal[a] (no further studies to be performed)		
No clear biological or clinical risk	• There is a lack of PK/PD plausibility (eg, drugs do not share metabolic pathways or receptor targets). • There is no statistically significant association in large epidemiological studies. • There are no case reports/case series. • Product monographs or clinical decision-support tools classify it as a low-risk (minor) interaction or report no interaction.	No further action is needed.

[a]Signals retained after Benjamini-Hochberg correction for multiple comparisons.

[b]PK: pharmacokinetic.

[c]PD: pharmacodynamic.

[d]RCT: randomized controlled trial.

Exploring Harmful DDIs Using Machine Learning

We will explore an alternative strategy for further investigating harmful DDIs using a machine learning algorithm. This complementary approach will integrate key components from our six-step validation framework, including empirical evidence from PK and PD data; findings from epidemiological studies; and clinical validation tools, such as drug interaction checkers (Lexicomp, Micromedex) and product monographs (eg, from Health Canada and the US FDA). We will combine these diverse sources of evidence to train the model, aiming to identify patterns that can help prioritize high-risk DDIs for further investigation. We will also use natural language processing (NLP) algorithms to extract important insights from clinical monographs, published research papers, and other medical literature. This step will help us better understand the context around each signal and provide a richer foundation for analysis. Although still exploratory, this method seeks to refine our ability

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to distinguish clinically significant interactions from spurious associations, ultimately improving how we prioritize potential risks in clinical practice.

We will first use known, previously validated DDIs identified through our six-step validation process to train the model. All sources of evidence collected—including high-throughput computing, PK and PD data, clinical validation tools (eg, drug interaction checkers and product monographs), epidemiological studies, and pharmacovigilance databases—along with insights from the six-step validation framework, will form a comprehensive training dataset for our machine learning model, enabling it to generate risk scores and rank potential interactions based on predicted clinical significance. To ensure robustness, the model will undergo k-fold cross-validation and bootstrap sampling. We will apply interpretability techniques, such as Shapley additive explanations (SHAP), to identify the most influential factors driving each prediction. By automating signal ranking and prioritization, this machine learning approach will explore new opportunities to enhance the identification of clinically meaningful DDIs, supporting safer prescribing and improved postmarket drug surveillance.

Ethical Considerations

This research is exempt from Research Ethics Board (REB) review because the data to be used are authorized under Section 45 of Ontario's Personal Health Information Protection Act (PHIPA), which allows for the use of personal health information for health system evaluation and planning without requiring REB review [48]. The data will be analyzed at ICES [17], an independent, not-for-profit research institute authorized under PHIPA to collect and use personal health information without consent for these authorized purposes. Individual consent from Ontario residents will not be required for this study, as ICES's legal status under PHIPA authorizes the secondary use of provincial health care records.

All analyses will be performed at ICES using linked, coded (deidentified) data. Researchers will not have access to any identifiable personal information, and strict privacy and security safeguards will be in place to protect confidentiality. No compensation will be provided, as this study will use existing health administrative data and will not involve direct participant recruitment or interaction. This study will not include images, videos, or any identifiable information from individual participants. On completion, the results of this population-based study will be submitted to a peer-reviewed biomedical journal for publication and presented at relevant conferences.

Results

In a preliminary analysis, we identified approximately 3.8 million older adults who filled prescriptions for over 500 unique medications during the study period. Each drug can serve as drug A or drug B in various combinations, resulting in approximately 200,000 potential drug pairs for analysis. The initial drug pair cohorts had a median of 583 new users per cohort (IQR 237-2130), with a median overlap duration of 57 days (IQR 30-90). For example, in a chronic-chronic drug pair cohort where levothyroxine was drug A and rosuvastatin was drug B, the median overlap duration was 135 days among 128,762 patients, with 73.1% (n=94,036) females and a median age of 66 years. In a chronic-acute drug pair cohort (eg, levothyroxine as drug A and amoxicillin trihydrate as drug B), the median overlap was 10 days among 197,057 patients, with 74.8% (n=147,399) females and a median age of 67 years. In an acute-chronic drug pair cohort (eg, amoxicillin trihydrate as drug A and rosuvastatin as drug B), the median overlap was 10 days among 2702 patients, with 51.6% (n=1394) females and a median age of 66 years. Lastly, in an acute-acute drug pair cohort (eg, amoxicillin trihydrate as drug A and ciprofloxacin as drug B), the median overlap was 10 days among 4220 patients, with 59.4% (n=2507) females and a median age of 70 years. The protocol, finalized on August 30, 2025, outlines the analysis of data from 2002 to 2023. The high-throughput computing analysis is planned for completion by fall 2026, and findings from the analysis will be assessed in 2027 for clinical relevance by integrating PK, PD, and epidemiological evidence, supported by clinical validation tools. The final results will be prepared for dissemination, with manuscript submission planned for December 2028.

Discussion

Summary

This study aims to identify harmful DDIs by analyzing Ontario health care databases using high-throughput computing. We will process data from over 3.8 million residents aged 66 years and older, evaluating more than 200,000 medication pairs and examining associations with 74 acute outcomes, including hospitalizations, emergency department visits, and mortality. High-throughput computing will enable us to identify and test thousands of medication combinations. We will compare individuals prescribed medication pairs with those on single medications, using propensity score methods to balance comparison groups on over 400 baseline health characteristics. We will conduct extensive sensitivity and bias analyses to ensure that potential signals are not artifacts of statistical or methodological bias. Additionally, machine learning algorithms will be used to complement the high-throughput computing approach.

High-throughput computing and automated analytical pipelines have proven effective for detecting potential DDIs in large health care datasets in other countries, such as the United States. Previous studies by Bykov et al [14] and Leonard et al [15] have demonstrated that these methods can efficiently confirm known interactions and identify novel signals. However, these approaches have largely been limited to single-object drugs, specific outcomes, or nonrepresentative datasets (derived from a specific subset of the population, such as those with a certain type of insurance, rather than the entire population), which may restrict generalizability. Building on these advances, our study will use high-throughput computing to analyze Ontario's population-based, linked administrative databases, which capture comprehensive prescription and outcome data across the province's universal health care system. Using a population-based, new-user cohort design, we will systematically evaluate nearly 200,000 medication pairs among

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3.8 million older adults—an effort that would be impractical with traditional methods. This approach will not only fill a critical gap by providing large-scale, real-world evidence in a Canadian context but also enhance generalizability, generate signals that could inform clinical decision-making once validated, and strengthen postmarketing pharmacovigilance efforts for older adults. To the best of our knowledge, this represents the first application of such an approach in Canada, leveraging the strengths of a universal health care setting to further enhance the generalizability and clinical relevance of detected DDI signals.

The cohort study is designed to mimic typical clinical scenarios, for example, an individual who has been taking digoxin for 7 months and is then newly prescribed sulfamethoxazole-trimethoprim to treat a urinary tract infection. In DDI studies, such scenarios are categorized as follows:

- Precipitant triggered: Individuals initiate the object drug first, followed by the precipitant, with follow-up starting on the day the precipitant is initiated.
- Object triggered: Individuals initiate the precipitant first, followed by the object drug, with follow-up starting on the day the object is initiated.

Our approach will be hypothesis free since it does not assume beforehand whether drug A or drug B will function as the object or the precipitant. Analyzing initiation orders separately is highly recommended in traditional DDI studies—if feasible—as it addresses different clinical questions, better controls confounding, and increases the validity of the results [2].

Strengths of the Study

A key strength of this study is the use of Ontario's administrative health care databases. These databases include comprehensive, encrypted data on health care visits, hospitalizations, lab results, and prescription records for residents aged 65 years and older [17]. This extensive data coverage enables the capture of a wide range of adverse outcomes, providing a detailed picture of the potential risks associated with specific drug interactions [16].

The application of high-throughput computing and automation will significantly enhance the efficiency and scalability of our analyses [49]. This approach will allow us to simultaneously evaluate numerous drug interactions, which would be impractical using traditional methods. By automating the creation of cohorts and statistical analysis, we can quickly and accurately identify potential DDIs, facilitating more rapid updates to clinical guidelines and regulatory policies [4,50].

Challenges and Limitations

Despite using advanced statistical techniques to control for confounding, residual confounding may still be present [51]. Factors that are not captured in the administrative data or that are measured with error could bias our results [52]. To address this, we will conduct multiple sensitivity analyses and use negative control outcomes to assess the robustness of our findings [37].

Our study focuses on acute (30-day) outcomes, which will not capture the effect of long-term exposure [53]; however, we will conduct additional analyses to assess longer follow-up times.

The study is designed to identify harmful DDIs with a moderate-to-high risk in magnitude in cohorts of at least 1000 individuals, and therefore, it will have limited statistical power to detect small risk increases.

Our study does not include data on nonprescription (over-the-counter) drugs, drugs prescribed in hospitals, or comprehensive outpatient prescription drug use in children or adults aged under 65 years. These exclusions may limit the generalizability of our findings to a broader population. However, the focus on older adults is justified, given their higher risk of polypharmacy and adverse drug interactions.

Given the large number of comparisons being made, there is a risk of spurious findings due to multiple testing [16]. To mitigate this, we will apply the Benjamini-Hochberg procedure to control the false discovery rate and use E-values to assess the robustness of our findings against unmeasured confounding [31].

Implications for Clinical Practice and Policy

This study has the potential to significantly improve drug safety, particularly in older adults, by identifying harmful DDIs more efficiently. If replicated in other jurisdictions, the findings could provide clinicians with new insights into the risks associated with specific drug combinations, leading to more informed prescribing practices and enhanced patient monitoring. The evidence generated could also inform regulatory agencies, such as Health Canada and the US FDA, helping refine product label warnings and support regulatory decisions. Ultimately, the findings could contribute to safer medication use on a population level, improving medication safety practices worldwide. Moving forward, we will prioritize and verify high-throughput signals across Ontario and beyond, ensuring the continued refinement and application of this approach to achieve more precise and informed medication safety practices.

Conclusion

This protocol outlines an innovative approach to detecting harmful DDIs in older adults using high-throughput computing and automation. By leveraging Ontario health care data and using advanced analytical techniques, we aim to enhance the efficiency and comprehensiveness of postmarket drug surveillance. The results of this study, if replicated in other jurisdictions, have the potential to significantly improve medication safety, inform clinical practice, and guide regulatory policies. Ultimately, this research aims to reduce the burden of adverse drug events in older adults and lay the foundation for more precise, data-driven medication safety practices worldwide.

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Authors' Contributions

FTM, SSA, NR, AXG, JS, EM, KS, and MW obtained the funding and developed the study idea. FTM, SSA, AXG, EM, and RS designed the study. FTM, SSA, AXG, EM, NC, and RS contributed to the study design, methodology, and analysis plan. NR and RS drafted the initial manuscript, and all authors critiqued the protocol manuscript. All authors have approved the attached manuscript for publication and are accountable for all aspects of the work.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Checklist of recommendations for reporting of observational studies using the RECORD (Reporting of Studies Conducted Using Observational Routinely Collected Health Data) statement.
[DOCX File , 21 KB - resprot_v14i1e77224_app1.docx]

Multimedia Appendix 2
Study variables and the codes used to ascertain baseline comorbidities (sorted alphabetically).
[DOCX File , 35 KB - resprot_v14i1e77224_app2.docx]

Multimedia Appendix 3
Process of integrating data from different sources.
[PNG File , 708 KB - resprot_v14i1e77224_app3.png]

Multimedia Appendix 4
Overview of the plan to perform the primary analysis and additional exploratory analysis.
[PNG File , 179 KB - resprot_v14i1e77224_app4.png]

Multimedia Appendix 5
Codes for nonoral drugs.
[DOCX File , 14 KB - resprot_v14i1e77224_app5.docx]

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Abbreviations

ATT: average treatment-effect-in-the-treated
DDI: drug-drug interaction
FDA: Food and Drug Administration
ICES: Institute for Clinical Evaluative Sciences
IPTW: inverse probability of treatment weighting
NNH: number needed to harm
ODB: Ontario Drug Benefit
PAF: population attributable fraction
PD: pharmacodynamic
PHIPA: Personal Health Information Protection Act
PK: pharmacokinetic
RCT: randomized controlled trial
RD: risk difference
REB: Research Ethics Board
RR: risk ratio
SD: standardized difference
SSRI: serotonin reuptake inhibitor

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Engagement With and Impact of an mHealth App for Childhood Obesity Prevention and Management: Protocol for a Mixed Methods Study

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Abstract

Background: Childhood obesity is a serious global health concern that affects approximately 20% of children worldwide. Digital health behavior change interventions have the potential to improve behaviors that can contribute to childhood obesity, such as diet and physical activity, but often lack sufficient user engagement to achieve significant impact.

Objective: The aim of this project is to develop evidence to better understand how users engage with digital interventions and how behavior change techniques can be leveraged to support engagement. Specifically, the study will examine the impact of a family-focused app for childhood obesity prevention on health behaviors, health outcomes, and communication between families and health care professionals (HCPs).

Methods: A pretest-posttest, mixed methods evaluation will examine the impact of the NoObesity app on families' physical activity and dietary behaviors and on HCPs' self-efficacy at communicating with families about childhood obesity. Secondary outcomes will include well-being, usability, and users' engagement with and perceptions of the intervention. An initial sample of 1000 families (children and young people of any weight and age under 18 years and their parents) and 180 HCPs will be recruited to participate in the study; a subset of these participants will be invited to take part in qualitative semistructured interviews. The study implementation and follow-up period will last for 6 months, with the outcomes measured at baseline and 3 and 6 months after baseline. Quantitative outcomes will be compared over time using repeated measures ANOVA, and qualitative data will be analyzed thematically and triangulated with app use data.

Results: Ethics approval was granted by the Newcastle University Faculty of Medical Science Ethics Committee (2688/41816) on March 22, 2024. Recruitment has not yet started but will involve capturing informed consent (and assent from participants younger than 16 years).

Conclusions: The project's key contributions will be to generate evidence of the potential for a family-based digital intervention to support families' health behavior change and HCPs' confidence in their ability to support them and to improve our understanding of how particular behavior change techniques can be used to support engagement with the intervention and its target behavior. Findings will be disseminated through peer-reviewed journals and shared with the general public, with support from patient and public involvement representatives.

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KEYWORDS

telemedicine; mobile apps; mobile health; mHealth; pediatric obesity; healthy lifestyle; exercise; diet; behavior change; engagement

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Introduction

Background

Childhood obesity is a growing, global public health concern [1,2]. Certain behaviors that contribute to obesity (eg, diet and exercise) are well-established factors in noncommunicable diseases such as cancer, heart disease, stroke, and type 2 diabetes [3], and obesity is strongly associated with increased likelihood of various mental and physical health conditions [3-5]. The ubiquity of cell phones and internet access in the general population has made digital technology a powerful, cost-effective means of supporting key health behavior interventions [6]. Mobile health apps have demonstrated the potential to support dietary and physical activity behavior change [7-10], but many do not have robust evidence of long-term positive impact [9,11-14]. A key limiting factor for impact is low engagement and adherence [15,16]. To achieve positive outcomes, there is a need to understand how digital tools for pediatric weight management can best support users' engagement with interventions and their target health behaviors to achieve positive outcomes. This study will aim to assess the impact of such an intervention on health behavior change and explore how engagement can be best supported.

The worldwide prevalence of overweight and obesity is growing rapidly in children [17], particularly in countries such as the United States and the United Kingdom, where approximately 2 in 5 children are overweight or obese by the age of 11 years [18,19]. In the United Kingdom in 2015, approximately £6 billion (approximately US $9 billion) was being spent annually on obesity-related health care; by 2050, this is expected to increase to almost £10 billion (approximately US $15 billion) [20,21]. There are various determinants of childhood obesity—including factors that are difficult to modulate on an individual level, such as deprivation and genetics [22-24]—but behavioral factors such as diet and activity can influence weight and health outcomes [25-29]. Health care professional (HCP) involvement can help support family engagement with healthier behaviors, but weight can be a difficult and sensitive topic for them to discuss [30,31]. Barriers to effective communication include fear of upsetting or offending families and losing their trust, concerns about influencing eating disorders in children, stigma and negative attitudes about obesity, and time constraints [30-33]. A key factor affecting all of these barriers is a lack of sufficient education and training in the clinical skill of raising and supporting concerns about children's weight [30-32].

As health care becomes increasingly digitized, digital tools such as mobile apps have the potential to provide widely accessible behavioral support; however, long-term benefit relies on sufficient engagement to achieve outcomes [13,34]. As studies have linked high levels of engagement with more positive health outcomes [35,36], improving engagement with digital behavior change interventions (DBCIs) could increase their potential impact [37,38]. Behavior change techniques (BCTs) [39] incorporated in DBCIs can help support engagement and impact [16,40], but evidence for associations between specific BCTs and engagement with DBCIs is limited [41], and there is a lack of clarity in the literature about which BCTs are most effective, in what contexts, and in what combinations [42].

This study will build on a recent examination of barriers and facilitators to parents' engagement with a family-focused app for childhood obesity prevention and management (NoObesity) [43,44]. In line with previous digital health research, potential impact was limited by a lack of sufficient engagement to achieve the intervention aims ("effective engagement" [15]). Our previous evaluation identified factors influencing engagement and impact related to capability, motivation, and opportunity and provided theoretically and empirically grounded recommendations for addressing these barriers [43].

Objectives

This study aims to develop evidence to better understand how users engage with DBCIs and how BCTs can be leveraged to support engagement, specifically in the context of obesity prevention and management, and to examine the impact of a family-focused app for childhood obesity prevention on health behaviors, health outcomes, and communication between families and HCPs.

Methods

Study Design

The study will use an implementation science-centered approach to evaluate the impact of a family-focused app for childhood obesity prevention (NoObesity) on users' engagement and behaviors and to gather feedback to enable further refinement of the intervention. A single-arm, pretest-posttest interventional study design will examine the impact of the app on families' physical activity and dietary behaviors and HCPs' self-efficacy at communicating with families about childhood obesity, how participants engage with the app, and how specific BCTs may be associated with engagement and impact. A single-arm study will allow the collection of a large dataset to explore engagement processes while also providing early evidence of potential health behavior change. The primary outcomes—family health behaviors and HCP self-efficacy—will be assessed with validated questionnaires (detailed in the *Outcomes* section). Mixed methods will be used to triangulate qualitative feedback from interviews with quantitative data to gather a more in-depth understanding of users' engagement with the NoObesity app and their experiences using the app (Figure 1). The Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) checklist (Checklist 1) [45] was used to ensure the comprehensiveness of this protocol.

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Figure 1. Study logic diagram. BCT: behavior change technique; HCP: health care professional; mHealth: mobile health.

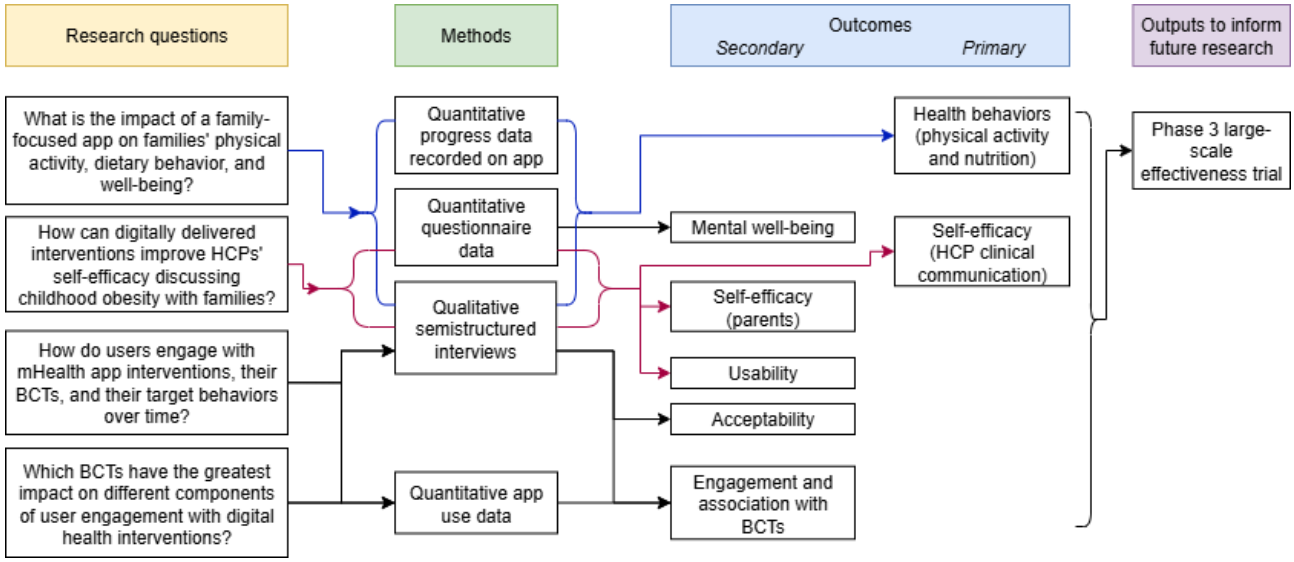

Intervention

The NoObesity app was originally developed by Health Education England (now known as the South East School of Public Health, Workforce Training and Education Directorate, NHS England) in collaboration with the Universities of Bournemouth and Southampton to support childhood obesity management and prevention [46]. The aim of the intervention was to provide health behavioral support for families via goal setting, self-monitoring, and educational games and resources and to deliver training for HCPs on communicating with families about childhood obesity. Descriptions of the app's features have been previously published [43]. The NoObesity app is being redesigned based on our initial evaluation [43] and the Behaviour Change Wheel [47]. The final version of the app that will be evaluated will have the same intended purpose as the original; its design and features will be detailed in the results paper.

Patient and Public Involvement

Patient and public involvement groups, including parents and guardians, children, and HCPs, will be established to collaborate on the redesign of the app via recruitment on Voice UK and email invitations via clinical networks. Sessions will be held so that the patient and public involvement group members can guide the finalization of the app design and features, which will be incorporated in the version of the app evaluated in this study.

Participants, Setting, and Eligibility

The target population of the study will include families—children and young people (≤18 years old) and their parents, regardless of their weight or BMI—and HCPs (Textbox 1). All eligible participants will be included. As the intervention is delivered digitally, participants can engage with it in various settings in their daily lives.

Textbox 1. Eligibility criteria.

Inclusion criteria

- All participants: willing and able to provide informed consent (aged >16 y) or assent to participate (aged <16 y), able to speak English, and own a mobile device capable of supporting the NoObesity app (iPhone; Apple Inc).
- Parents and guardians: parent or guardian of at least 1 child aged ≤18 years, of any weight or BMI.
- Children and young people: any age (up to and including children aged 18 y) and weight or BMI; no lower age limit will be set to enable parents to determine with their child whether they want to and feel capable of participating (eg, completing questionnaires and interviews).
- Health care professionals: working with families around weight, including but not limited to general practitioners, health visitors, school nurses, practice nurses, pediatricians, and pediatric nurses.

Exclusion criteria

- All participants: previous involvement in the development or testing of the NoObesity system, inability to provide self-consent (aged >16 y) or unwillingness to provide assent (aged <16 y), and a preexisting relationship with any member of the research team (eg, friends, family members, and colleagues).
- Children and young people: currently receiving specialist treatment for childhood obesity (tiers 3 or 4 obesity services).

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Outcomes

Primary Outcomes

To gather preliminary evidence of efficacy, the primary analysis for families will be health behavior change, specifically related to physical activity and dietary behavior (Table 1). These outcomes will be assessed using a combination of measures to enable triangulation and mitigate potential bias. This will include behavioral data captured via the app (self-report or sensor), repeated questionnaires, and qualitative feedback from semistructured interviews (SSIs). The Family Nutrition and Physical Activity Scale was selected because it examines the 2 main target behaviors (physical activity and healthy eating), has been validated for use with children aged ≤18 years, is easy to use, and is not too long [48,49].

Table . Primary and secondary outcomes and measures.

Outcomes		Participant	Outcome measure
Primary outcomes			
	Health behavior (physical activity and healthy eating)	Parents and CYP[a]	• Self-reported goal progress in the app's self-monitoring feature • Linked phone or wearable sensors where captured (eg, step counts as measured by Apple Health or Fitbit) • Qualitative feedback from SSIs[b] • Family Nutrition and Physical Activity [49]
	Self-efficacy	HCPs[c]	• Self-Efficacy Questionnaire [50] • Qualitative feedback from SSIs
Secondary outcomes			
	Engagement	All	• App use data • Uptake and dropout rates • TWente Engagement with Ehealth Technologies Scale [51] • Digital Behavior Change Intervention Engagement Scale [52] • Qualitative feedback from SSIs
	Well-being	Parents and CYP	• Warwick-Edinburgh Mental Wellbeing Scale [53]
	Self-efficacy	Parents	• Qualitative feedback from SSIs
	Acceptability	All	• Qualitative feedback from SSIs (structured using the Theoretical Framework of Acceptability) [54]
	Usability	All	• mHealth[d] App Usability Questionnaire [55] • Qualitative feedback from SSIs

[a]CYP: children and young people.

[b]SSI: semistructured interview.

[c]HCP: health care professional.

[d]mHealth: mobile health.

For HCPs, the primary outcome will be the impact of the app on their perceived knowledge, skills, and confidence discussing obesity and weight-related topics with families. This will be examined using a self-efficacy questionnaire and explored in more depth in the qualitative SSIs. The Self-Efficacy Questionnaire was designed and validated to assess HCPs' self-efficacy in the context of clinical communication skills training [50].

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Secondary Outcomes

User engagement with NoObesity will be assessed using a combination of complementary measures [56], including system use data, questionnaires, and qualitative SSIs. Mixed methods approaches help capture the cognitive, behavioral, and affective components of engagement, providing a better understanding of users' experience engaging with the intervention and the behavior change process [16,56-60]. Two recently developed measures of engagement with DBCIs are based on this multifaceted conceptualization and have similar psychometric properties: the Digital Behavior Change Intervention Engagement Scale [52] and the TWente Engagement with Ehealth Technologies Scale [51]. The scales are short (10 and 9 items, respectively), so both will be included as outcome measures to enable additional insights into user engagement [59]. We will also explore how engagement is associated with recruitment methods—whether participants found out about the study via their HCP or via social media advertisement—as previous research has found a positive relationship between clinical referral and engagement [61].

Other secondary outcomes will include usability (measured using the mHealth App Usability Questionnaire), self-efficacy and acceptability (explored in the qualitative SSIs), and well-being. Well-being will be included as a health outcome because of its positive correlation with improvements in physical activity and healthy eating [62]. The Warwick-Edinburgh Mental Wellbeing Scale [53] has been validated in many populations, including children and teenagers aged >11 years, so it is a good measure to capture parents' perspectives and children's and young people's perspectives [63,64]. No weight-related measures will be captured; this is discussed further in the *Limitations* section.

Sample Size

The target sample size was developed using a power calculation and expected dropout rates. On the basis of the literature, for the primary outcomes (Family Nutrition and Physical Activity Scale and Self-Efficacy Questionnaire), a sample of 199 families and 90 HCPs would achieve 80% power for an effect size of 0.2 and 0.3 (α=.05), respectively. High dropout is common across digital health research [65,66]; recent meta-analyses of mobile apps found pooled estimates of dropout rates between 40% and 50%. As our previous study had a high rate of attrition [43], we are aiming to enroll at least 1000 families, which would enable us to achieve the target sample size with 80% attrition. We will aim to recruit at least 180 HCPs to account for 50% attrition.

A subset of 20 to 30 participants will be selected to participate in SSIs using a stratified random sampling technique. This is within common estimates for qualitative sample sizes and in accordance with our capacity to conduct the study. Participants will be grouped based on demographic characteristics (eg, gender, ethnicity, and level of deprivation, which will be assessed by postcode [67]) and randomly selected from within these groups using a computer random number generator to achieve a diverse sample.

Recruitment and Consenting Procedure

The study will be advertised using social media (Google Adwords and Meta Ads). After downloading the app from the Apple App Store, users will see an onboarding screen that includes a link to the study website. This will enable recruitment of people who came across the app in an app store without previously seeing recruitment materials.

Recruitment posters will be distributed to local general practitioner centers, children's centers, schools, and other community organizations or networks. We will target centers and organizations in more disadvantaged areas, identified using the English Indices of Deprivation (2019) [68], to enhance sample diversity. This is a key target cohort to recruit, as there are strong links between obesity and deprivation [69]. The recruitment materials encourage potential HCPs to discuss the study with the families they work with and families to discuss the study with their HCPs to increase recruitment by word of mouth.

Recruitment materials will provide a brief overview of the study and link to the study website. Participant information sheets designed for various participant types—parents and guardians, children aged between 16 and 18 years, children aged between 10 and 15 years, children aged <10 years, and HCPs—will be accessible on the website to provide details about the study, including the potential benefits and risks; how data will be used, anonymized, and stored; and what participation will involve. No incentives will be provided for participation in the study, as we want to evaluate users' engagement with the app without external incentives that would not be present in a real-world context.

Informed consent will be collected using the Qualtrics (Qualtrics International Inc) web-based software; if completed, the survey will continue to collect demographic data (eg, age, gender, ethnicity, and postcode as a proxy for the level of deprivation). Participants will also be asked how they found out about the study, as previous research has indicated that clinical referral is associated with engagement. For parents, the consent and demographics survey will include a question about the age or ages of their child or children. Depending on their response, a triggered email will be sent with the appropriate age-targeted participant information sheets and consent (for children aged between 16 and 18 y) or assent forms (for children aged <10 y and children aged between 10 and 15 y) so that they can discuss them as a family and email the research team with any questions they might have. Parents will complete informed consent on behalf of children <16 years, but 2 different simplified versions of an assent form will be provided for children aged <10 years and children aged between 10 and 15 years. All informed consent and assent forms will be delivered and completed through the Qualtrics platform.

Data Collection

Quantitative demographic data and outcome measures will be collected using a web-based survey platform (Qualtrics). All outcome measures will be captured at baseline, 3 months, and 6 months, except for the mHealth App Usability Questionnaire (captured only at 3 mo). App use data will be automatically

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stored through the app. SSIs will be conducted with a subset of users at approximately 3 months by the research team, who have no involvement in families' care (Figure 2). A topic guide will provide a framework for the interviews (Multimedia Appendix 1 [16,54,57,60]). Interviews will be conducted using video or telephone conferencing software and recorded for transcription. If participants do not want the interview recorded, notes will be taken by hand and verified with the participant after the interview.

Figure 2. Participant flow diagram. CYP: children and young people; DBCI-ES: Digital Behavior Change Intervention Engagement Scale; FNPA: Family Nutrition and Physical Activity Scale; HCP: health care professional; MAUQ: mHealth App Usability Questionnaire; SE-12: Self-Efficacy Questionnaire; TWEETS: TWente Engagement with Ehealth Technologies Scale; WEMWBS: Warwick-Edinburgh Mental Wellbeing Scale.

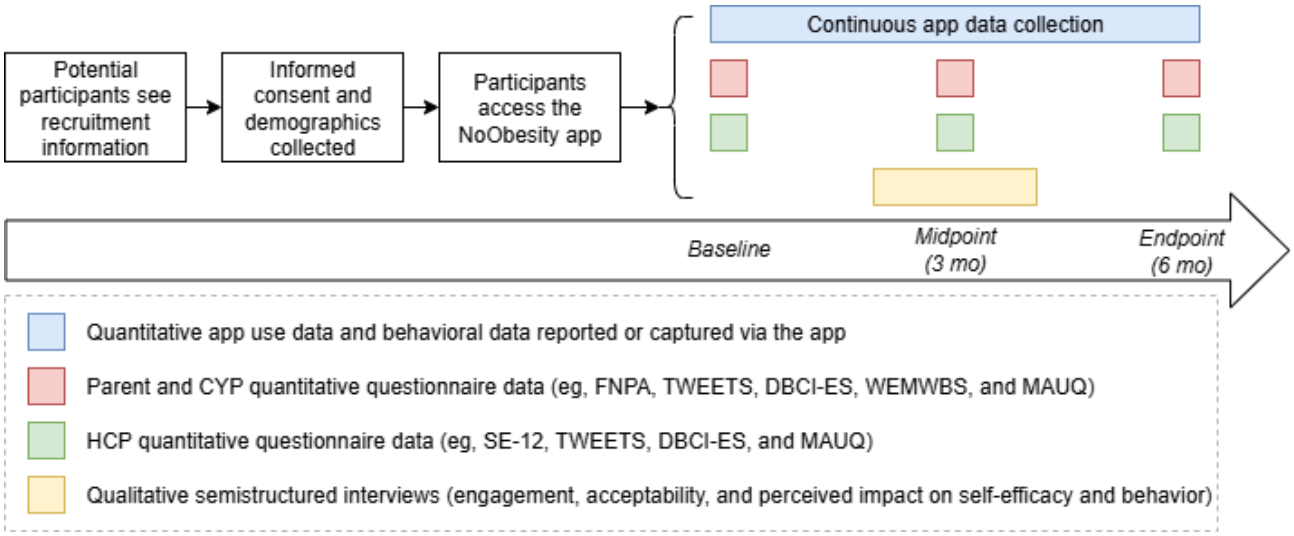

Ethical Considerations

The ethics approval was received from the Newcastle University Faculty of Medical Science Ethics Committee (2688/41816) on March 22, 2024.

Written informed consent will be collected from participants via Qualtrics. The inclusion of children and young people as participants presents ethical considerations. As the app is designed for families, children and young people will be invited to participate alongside their parents or guardians to ensure that their perspectives are captured. Children aged <16 years will only be included if a parent or guardian provides informed consent and the child also provides assent; young people aged between 16 and 18 years will provide their own informed consent. Another consideration is the potential risk that topics arising in the interview may cause harm or distress (eg, triggering feelings of embarrassment or low self-esteem). To mitigate this risk, interview questions will primarily focus on participants' experience with the app, which is not expected to be a sensitive subject, and questions related to behavior will specifically explore the app's influence and not the types or extent of behaviors engaged in. Data privacy and confidentiality will be maintained as described in the following section.

Data Management

Each participant will be given a unique identifier. Data will be analyzed using the unique IDs so that the overall dataset is pseudonymized. The transcription service receiving SSI recordings will only receive reference to the unique identifiers. The original audio recording will be destroyed after transcription. Records of consent will be kept for 10 years after the publication of final study results. All files containing participant data will be stored in the university's secure Microsoft OneDrive.

The NoObesity system will store identifiable data in compliance with the UK Data Protection Act 2018. Organizations involved in this study will undertake a data protection impact assessment to ensure compliance with relevant data protection regulation, where needed. Participants will have the option to link external sensors (eg, Apple Health and Google Fitbit) to their app; only data included in the app will be anonymized and analyzed in line with other app use data.

Data Analysis

Repeated measures ANOVA (or a nonparametric alternative, if initial checks identify that key assumptions are not met) will be used to compare differences between the means across the 3 time points (baseline, 3 mo, and 6 mo) for primary and secondary quantitative outcomes (health behavior, self-efficacy, and well-being). ANOVA is an appropriate method in this case, as it focuses on group-level trends over time, rather than subject-specific patterns. Missing data will be addressed through transparent justification of exclusions, and the context for missing data will be explored via qualitative analysis. This primary analysis will be conducted on the sample of participants who complete the outcome measures at each time point. Descriptive statistics will be used to evaluate the other quantitative outcomes (eg, usability scores and app use data). SSIs will be coded by 2 investigators using thematic analysis [70]. Triangulation of the quantitative questionnaire and system use data and qualitative SSI data will be conducted to validate the findings.

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Results

The study will be registered on ClinicalTrials.gov before recruitment begins. A series of co-design workshops were conducted with families and HCPs with lived experience to shape the redesign of the app from October to December 2024; these findings will be published separately. Development of this new version of the app is ongoing. An evaluation of the original version of the app is also published separately [43,44]. Recruitment and data collection dates will be finalized following completion of the app development process. As of September 9, 2025, no recruitment or data collection for the study has taken place.

Discussion

Limitations

Although the aim of the intervention is to support the prevention and management of childhood obesity, the study will focus on evaluating behavior change rather than weight-related outcomes. This is a limitation, as we will not capture evidence of clinical impact or determine if the app is associated with weight change. There were 2 main reasons for this decision. First, our aim is to evaluate the impact on engagement, HCP self-efficacy, and family behavior, in line with the app's intended purpose. Although the overall aim of this behavior change is to mitigate childhood obesity, several participants in our previous evaluation reported feeling uncomfortable with weight measurements, especially for their children [43]. On the basis of this finding, we also expect that participants may be less likely to provide those data or participate if this measurement is required. Second, there is a logistical challenge in collecting high-quality data, as participants would have to self-report measurements, which introduces potential bias or inaccuracy if there are differences in scale calibration or performance of measurements. Likewise, the lack of a control group limits our ability to make causal inferences and introduces potential bias around external influences on the health behavior outcomes; however, a single-arm design will enable us to capture more data to understand engagement, which is a necessary prerequisite for behavioral and clinical impact. These limitations should be addressed in future, large-scale studies if the evaluation provides good evidence of the impact of the app on health behaviors.

Technical limitations of the app will affect generalizability. At present, patients without access to an iPhone will not be able to use the system and are therefore not eligible for inclusion in the study. If the study shows evidence of potential impact on health behaviors, we would aim to also create an Android (Google LLC) version of the app. In addition, as the app is currently only available in English, non–English-speaking patients will be excluded from the study, also limiting the representativeness of the sample.

There is also potential bias in the qualitative analysis from 2 sources: the influence of the interviewer on how participants respond (eg, social desirability bias) and the interpretation of participant responses. The first potential bias will be assessed by examining the balance of positive and negative feedback and by comparing the qualitative and quantitative data about NoObesity's usability, acceptability, and impact. The second will be addressed by having multiple researchers conduct the thematic analysis to challenge individual perspectives and preconceived ideas.

Conclusions

There is an urgent need to address the issue of childhood obesity. Family-based interventions have previously demonstrated positive impact on behavioral and health outcomes, particularly when involving HCP support [71], but this can be difficult to deliver on a large scale. This study will build on a previous evaluation of the NoObesity app by incorporating feedback and theory to improve the intervention and will assess its ability to positively impact families' health behaviors and HCPs' confidence in supporting them. We predict that engagement with the app will lead to improved physical activity, dietary behavior, and well-being for families and improved self-efficacy for HCPs. More broadly, we anticipate that this evaluation will provide useful insights into how users engage with DBCIs and how particular BCTs can support affective, cognitive, and behavioral engagement with the intervention and health behaviors, which will help inform future development of various DBCIs.

Acknowledgments

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Authors' Contributions

MMI and EM conceived the study topic and designed and drafted the protocol. SRH and JA contributed to drafting and revising the protocol, and the final revision was completed by MMI, AA, and EM.

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Conflicts of Interest

EM is the editor-in-chief of *JMIRx Med*. All other authors declare no other conflicts of interest.

Multimedia Appendix 1
Sample topic interview guide.
[DOCX File, 22 KB - resprot_v14i1e71551_app1.docx]

Checklist 1
SPIRIT checklist.
[DOCX File, 30 KB - resprot_v14i1e71551_app2.docx]

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Abbreviations

BCT: behavior change technique
DBCI: digital behavior change intervention
HCP: health care professional
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SSI: semistructured interview

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Protocol

The Application of Machine Learning Algorithms to Predict HIV Testing in Repeated Adult Population–Based Surveys in South Africa: Protocol for a Multiwave Cross-Sectional Analysis

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Abstract

Background: HIV testing is the cornerstone of HIV prevention and a pivotal step in realizing the Joint United Nations Program on HIV/AIDS (UNAIDS) goal of ending AIDS by 2030. Despite the availability of relevant survey data, there exists a research gap in using machine learning (ML) to analyze and predict HIV testing among adults in South Africa. Further investigation is needed to bridge this knowledge gap and inform evidence-based interventions to improve HIV testing.

Objective: This study aims to determine consistent predictors of HIV testing by applying supervised ML algorithms in repeated adult population-based surveys in South Africa.

Methods: A retrospective analysis of multiwave cross-sectional survey data will be conducted to determine the predictors of HIV testing among South African adults aged 18 years and older. A supervised ML technique will be applied across the five cycles of the South African National HIV Prevalence, Incidence, Behavior, and Communication Survey (SABSSM) surveys. The Human Science Research Council (HSRC) conducted the SABSSM surveys in 2002, 2005, 2008, 2012, and 2017. The available SABSSM datasets will be imported to RStudio (version 4.3.2; Posit Software, PBC) to clean and remove outliers. A chi-square test will be conducted to select important predictors of HIV testing. Each dataset will be split into 80% training and 20% test samples. Logistic regression, support vector machines, random forests, and decision trees will be used. A cross-validation technique will be used to divide the training sample into k-folds, including a validation set, and models will be trained on each fold. The models' performance will be evaluated on the validation set using evaluation metrics such as accuracy, precision, recall, F_1-score, area under curve-receiver operating characteristics, and confusion matrix.

Results: The SABSSM datasets are open access datasets available on the HSRC database. Ethics approval for this study was obtained from the University of Johannesburg Research and Ethics Committee on April 23, 2024 (REC-2725-2024). The authors were given access to all five SABSSM datasets by the HSRC on August 20, 2024. The datasets were explored to identify the independent variables likely influencing HIV testing uptake. The findings of this study will determine consistent variables predicting HIV testing uptake among the South African adult population over the course of 20 years. Furthermore, this study will evaluate and compare the performance metrics of the 4 different ML algorithms, and the best model will be used to develop an HIV testing predictive model.

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Conclusions: This study will contribute to existing knowledge and deepen understanding of factors linked to HIV testing beyond traditional methods. Consequently, the findings would inform evidence-based policy recommendations that can guide policy makers to formulate more effective and targeted public health approaches toward strengthening HIV testing.

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KEYWORDS

predictive modelling; testing; support vector machines; random forest; supervised machine learning; decision trees; adult; population-based; South Africa; protocol; HIV/AIDS; HIV testing; retrospective analysis; cross-sectional survey; chi-square test; logistic regression; public health; epidemiology; infectious disease

Introduction

HIV/AIDS remains a public health threat, affecting 39 million people globally, of whom 25.6 million are within the Sub-Saharan African region [1]. More than half of the global HIV prevalence is concentrated in East and Southern Africa, according to the World Health Organization and the Joint United Nations Program on HIV/AIDS (UNAIDS) [1,2]. HIV testing is a crucial component of the HIV prevention and care continuum [3] and a pivotal step in realizing the UNAIDS's goal of ending AIDS by 2030 [4]. It aims to diagnose and minimize HIV transmission rates while enabling early and effective treatment. Rolling out HIV testing coverage and accessibility to populations with low HIV testing prevalence could assist in improving HIV epidemic control and elimination efforts [3-7].

South Africa has made significant progress toward the UNAIDS 2030 target, ensuring 90% of people living with HIV are aware of their status by the end of 2022 [8,9]. However, the country remains behind schedule as the 90% attainment was set for 2020. Furthermore, there still exist numerous barriers to the uptake of HIV testing [10]. According to Simbayi et al [10], lack of HIV testing is one of the key drivers of HIV infections among the South African adult population.

Previous studies have identified sociodemographic factors, sociobehavioral factors, socioeconomic factors, sexual behaviors, knowledge, attitudes, and perceptions about HIV that could influence an individual's decision to undergo HIV testing [6,7,11,12]. The uptake of HIV testing was found to be very low (34.9%) among Ethiopian youth due to regional variations [11]. The study revealed that being a male, following a protestant religion or orthodox religion negatively influenced the uptake of HIV testing [11]. The same study [11] noted that Ethiopian youth might undergo HIV testing if they have a good knowledge of HIV, engage in risky sexual behavior, are married, are rich, and have access to media. A retrospective analysis of the 2017 South African National HIV Prevalence, Incidence, Behavior, and Communication Survey (SABSSM) survey by Jooste et al [12] highlighted geographic variations by districts and sex in HIV testing among individuals aged 15 years and older. The districts with the lowest HIV testing were uMkhanyakude (54.7%) and Ugu (61.4%) in KwaZulu-Natal and Vhembe (61%) in Limpopo [12]. On the other hand, the uptake of HIV testing was higher among women than men in most of the districts [12]. Probably stemming from the common perception that women are at the highest risk of HIV, numerous studies substantiated a greater hesitancy in HIV testing uptake among men compared to women [11,12]. Socioeconomic factors such as rural residence, low education, household income, and high alcohol consumption have also been associated with low HIV testing uptake [13].

Traditional statistical and testing approaches have been widely used to scale up HIV testing interventions worldwide; while they are effective, they can be subject to certain limitations, such as accuracy, precision, and privacy issues [14]. In contrast, machine learning (ML) models are designed to address these limitations, as they can analyze complex datasets to uncover latent variables associated with HIV testing beyond the reach of conventional methodologies [15,16]. ML refers to the use and development of computer systems that learn and adapt without following explicit instructions, and algorithms are used to analyze and draw conclusions from data patterns [17,18]. The algorithms rely on domain knowledge of the data to develop features that make them work [18]. Various disciplines, including health care, use 3 major types of ML, namely, supervised machine learning (SML), unsupervised machine learning, and reinforcement learning [17-19].

A growing number of studies are developing predictive models to classify HIV high-risk populations for improved HIV testing in a resource-efficient manner [20-24]. Ovalle et al [25] applied support vector machines (SVM), random forest, and logistic regression within a Gay Social Networking Analysis Program, an intelligent web-based health-promotion intervention framework. This study explored the link between social media messages and participants' offline sexual health and substance use outcomes, deriving HIV risk scores for targeted HIV testing [25]. Various SML algorithms such as logistic regression, SVM, random forest, and XGBoost were used to accurately predict HIV risk in South Africa, in which age, being a female, and condom use were significantly associated with HIV positivity [26].

Evidently, ML techniques facilitate the development of economically viable HIV testing methods that offer optimal value for resources invested [16]. Importantly [16], asserts that HIV risk prediction with ML techniques could increase the HIV-diagnosed fraction to 96.5% by 2030, compared to the current traditional method projection of a diagnosed fraction of 93.8% by the same year in South Africa.

Although a significant amount of survey data is available on the factors associated with HIV testing in South Africa, there has been limited research on using ML approaches to analyze

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and forecast these factors. Thus, it is against this backdrop that this study is pioneering in using four SML algorithms (logistic regression, random forest, SVM, and decision trees) across all five cycles of the SABSSM surveys to provide new insights into the determinants of HIV-testing behavior in South Africa. The primary aim of this study is to determine consistent predictors of HIV testing and to compare the performance of the four SML models using repeated adult population-based surveys in South Africa to develop an evidence-based predictive model to enhance HIV testing.

Methods

Study Design

A retrospective analysis of data from multiple cross-sectional surveys will be used to predict factors associated with HIV testing across the five cycles of the SABSSM survey using SML algorithms. The analysis will involve four SML algorithms in developing an HIV testing predictive model for the South African adult population. This protocol followed several guidelines and checklists, such as the STROBE (Strengthening the Reporting of Observational Study in Epidemiology) checklist [27] (this can be found in Multimedia Appendix 1), the updated guidance for reporting clinical prediction models that use regression or ML [28] (this can be found in Multimedia Appendix 2), and the development and validation of observational and qualitative study protocol reporting checklists for novice researchers (ObsQual checklist) [29].

Data Source and Population

This secondary data analysis will make use of the 5 cycles of the SABSSM surveys conducted by the South African Human Science Research Council (HSRC). The SABSSM surveys are a series of nationally representative surveys conducted periodically in South Africa to assess the prevalence, incidence, behaviors, and communication related to HIV/AIDS [10]. The first SABSSM survey was conducted in 2002 with 9963 individuals interviewed, followed by SABSSM 2005 (n=23,275), SABSSM 2008 (n=20,826), SABSSM 2012 (n=38,431), and SABSSM 2017 (n=36,609) being the fifth survey [10,30-33]. All five cycles of the SABSSM datasets were made available to the research team on August 20, 2024, after filling and submitting the digital request form via the HSRC website [34]. This study's analysis will focus on adults aged 18 years and older, using data from the five cycles of the SABSSM survey—2002, 2005, 2008, 2012, and 2017. The final sample size for this study will be determined after cleaning and removing outliers from the datasets.

Inclusion and Exclusion Criteria

The SABSSM dataset is a combination of children's, adolescents', and adults' data. This analysis will only include male and female individuals aged 18 years and older from the SABSSM survey. Data outside the defined age bracket from the SABSSM survey data will be excluded from this analysis.

Study Variables

The outcome variable for this study will be HIV testing. The exposure variables are sociodemographic (age, sex, ethnicity or race, education level, marital status, employment, and rural and urban residence), socioeconomic (household income, financial status, and access and usage of health care facilities), sexual behaviors (history of sexually transmitted infections, knowledge of HIV transmission, number of sexual partners, and condom use), HIV knowledge and awareness (knowledge toward HIV prevention, testing and treatment services, and knowledge of HIV status), and perceptions and attitudes (attitudes toward HIV testing, perceived risk of infection, stigma, and discrimination related to HIV). Table 1 describes a few selected variables that are consistent across all the five SABSSM survey datasets. The complete list of the dependent and independent variables extracted from 2002, 2005, 2008, 2012, and 2017 SABSSM survey datasets can be found in Multimedia Appendix 3 (SABSSM 2002 variables), Multimedia Appendix 4 (SABSSM 2005 variables), Multimedia Appendix 5 (SABSSM 2008 variables), Multimedia Appendix 6 (SABSSM 2012 variables), and Multimedia Appendix 7 (SABSSM 2017 variables).

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Table 1. Summary of variable and variable definitions from the SABSSM[a] dataset[b].

Variable name and variables	Variable descriptions	Variable recode
Outcome variable (HIV testing)		
HIV testing		
Ever had an HIV test	• Yes • No • No response	• Yes • No
Exposure variables		
Sociodemographic		
Age		
Respondent's age in years	Integer	• <20 • 20-24 • 25-29 • 30-34 • 35-39 • 40-44 • 45-49 • ≥50
Sex		
Sex of the respondent	• Male • Female	• Male • Female
Geotype		
Geographical location	• Urban formal • Urban informal • Rural formal • Rural informal	• Urban • Rural
Race		
Race	• African • White • Colored • Indian or Asian • Other	• African • Colored • Indian • White
Highest level of education		
Respondent's highest level of education obtained	• No schooling • Up to Std[c] 1/Gr[d] 3/ABET[e] 1 • Std 2-Std 3/Gr 4-Gr 5/ABET 2 • Std 4-Std 5/ Gr 6-Gr 7/ABET 3 • Std 6-Std 7/Gr 8-Gr 9/ABET 4 • Std 8/Gr 10/NTC[f] 1 • Std 9/Gr 11/NTC 2 • Std 10/Gr 12/Matric/NTC 3 • Certificate or diploma with Gr 12 • Bachelors degree • Postgraduate degree (HDE/Hons/Masters/PhD)	• No schooling • Primary • Secondary • Tertiary
Sociocultural		
Age at first marriage		
How old was the respondent when married for the first time	Integer	• <18 • 18-23 • 24-29 • 30-35 • >35
Male circumcision status		

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Variable name and variables	Variable descriptions	Variable recode
Whether the male respondent is circumcised	• Yes • No	• Yes • No
Independent variable (socioeconomic)		
Employment status		
Employment status	• Unemployed • Sick or disabled and unable to work • Student or pupil or learner • Employed or self-employed • Other	• Unemployed • Sick or disabled and unable to work • Student or pupil or learner • Employed or self-employed • Other
Independent variable (sexual history, sexual behavior, and lifestyle)		
Ever had sexual intercourse		
Whether the respondent ever had sexual intercourse	• Yes • No • No Response	• Yes • No
Number of sexual partners in a lifetime		
Number of people the respondent had sexual intercourse within a lifetime	Integers	• 1 person • 2-5 • >5
Condom use decision		
Who suggested using a condom? The second most recent person	• Yourself • Your partner • Mutual agreement	• Yourself • Your partner • Mutual agreement
Independent variable (health status or pre-existing medical conditions or disabilities or stigma or violence)		
General well-being		
In general, would you say that your health is excellent, good, fair, or poor?	• Excellent • Good • Fair • Poor	• Excellent • Good • Fair • Poor
Independent variable (knowledge, awareness, and perception of HIV/AIDS)		
Knowledge of HIV/AIDS		
Can AIDS be cured?	• Yes • No • I don't know	• Yes • No • I don't know

[a]SABSSM: South African National HIV Prevalence, Incidence, Behavior, and Communication Survey.

[b]Only a few selected variables that are common across the five SABSSM surveys were included in Table 1. Please see Multimedia Appendices 1-5 for the complete list of dependent and independent variables.

[c]Std: standard.

[d]Gr: grade.

[e]ABET: adult basic education training.

[f]NTC: National Technical Certificate.

Data Extraction

A data extraction tool (Table 2) with headings such as study year, sample size, study population, age group study settings, and main variables was used to describe the characteristics of the available datasets of the SABSSM surveys. Each dataset was examined, and key variables that could influence HIV testing were identified using additional tools (Table 1, Multimedia Appendix 3 [SABSSM 2002 variables], Multimedia Appendix 4 [SABSSM 2005 variables], Multimedia Appendix 5 [SABSSM 2008 variables], Multimedia Appendix 6 [SABSSM 2012 variables], and Multimedia Appendix 7 [SABSSM 2017 variables]).

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Table 2. Characteristics of the five SABSSM[a] survey datasets[b,c].

Study name and year	Sample size, n		Prevalence of HIV testing (reported), %
	Calculated	Individual Interview Response	
SABSSM 2002 [30]	14,450	9963	21.4
SABSSM 2005 [31]	24,236	23,275	30.5
SABSSM 2008 [32]	23,369	20,826	50.8
SABSSM 2012 [33]	42,950	38,431	65.5
SABSSM 2017 [10]	39,132	36,609	75.2

[a]SABSSM: South African National HIV Prevalence, Incidence, Behavior, and Communication Survey.

[b]The study is focused on the general population of South African adults aged 18 years and older.

[c]Study variables were extracted and redefined to guide the data cleaning and preprocessing, as detailed in the data preprocessing section.

Data Preprocessing and Feature Selection

The SABSSM survey datasets are open access data available upon request through the HSRC website [34]. All five cycles of the SABSSM datasets were accessed on August 20, 2024. We have explored them to understand the patterns and the nature of all the variables needed to develop an HIV testing predictive model. For this analysis, RStudio (version 4.3.2; Posit Software, PBC) will be used. The research team will first clean and process the available data to handle outliers and missing values and identify relevant dependent and independent variables in the five cycles of the SABSSM survey to be included in the predictive modeling. This will be followed by feature selection to eliminate redundant and irrelevant variables. Numerical features will be standardized to ensure consistency scaling, and the features will be analyzed to categorize those that will most likely influence HIV testing. We will conduct a chi-square test between the dependent variable (reported HIV testing status) and the independent variables (Table 1). Variables (features) with $P<.05$ will be considered important predictors and will be retained in the final model for predicting HIV testing status. Potential confounders and redundant variables will also be addressed during the feature selection, as detailed in the risk for bias assessment section. One-hot encoding will be used to encode the important HIV testing predictors based on the information available on the SABSSM surveys. One-hot encoding is the process of transforming categorical variables into binary variables, represented by values of 0 and 1, enabling their usage by ML algorithms [35]. This procedure will be accomplished by an R package known as “dplyr” [36].

Algorithms

This study will use four SML algorithms that are widely used in the field of health care, namely, logistic regression, decision trees, random forests, and SVM [37]. Logistic regression is a statistical method commonly used in ML for classification and predictive analytics tasks [38]. It solves classification problems by assigning multiple observations to a discrete set of categories or cases [38]. Another classifier that will be used in this analysis is SVM, a group of SML algorithms that can be applied to classification or regression [39]. The SVM can act as nonprobabilistic binary linear classifiers, depending on their configuration. For instance, a linear kernel function would make an SVM perform as a binary linear classifier. Moreover, SVM can also handle nonlinear classification tasks [39]. Similarly, a decision tree is also an SML classifier that categorizes or predicts depending on prior sets of questions [40]. According to Jo [19], a decision tree resembles a tree that classifies based on the branches of its root nodes. Random forest is also a very popular SML algorithm [22]. It is a robust SML algorithm well-suited for classification tasks involving complicated relationships between different features.

Training and Model Validation

After the preprocessing and feature selection, each cleaned dataset will be split into 80% training and 20% testing samples. The 80/20 rule is the most used splitting ratio, and anecdotal evidence has supported it as being an effectively valid rule [41]. Training and validation will be done to set a probability threshold to predict those factors associated with HIV testing. Four standard SML algorithms will be applied to the training sample, such as logistic regression, decision trees, random forests, and SVM [37]. A cross-validation technique will be used, in which the training sample will be divided into k-folds, including a validation set, and models will be trained on each fold. Usually, k is taken to be 5 or 10, but may differ depending on the dataset size [42]. This study will use either a 5-fold or 10-fold cross-validation technique, depending on the compatibility with the available datasets. The models’ performance will be evaluated on the validation set using the following evaluation metrics: accuracy, precision, recall, F_1-score, area under curve-receiver operating characteristics, and confusion matrix.

Evaluation and Algorithms Selection for Predicting HIV Testing

Model evaluation involves selecting the best-performing model by providing an unbiased estimate of how well the models generalize on new or unseen data [18]. Upon completing the model development, the performance of the four SML models will be assessed on the testing sample using standardized performance evaluation metrics, including accuracy, precision, recall, F_1-score, area under curve-receiver operating characteristics, and confusion matrix [43]. This procedure will assess the performance of logistic regression, SMV, random forest, and decision trees in order to select the best-performing models in predicting HIV testing status using the five cycles of the SABSSM datasets. Figure 1 [21,43] depicts the data

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processing stages, HIV testing predictive models to be used, and performance evaluation criteria.

Figure 1. Data preprocessing and HIV testing prediction modeling (created using PowerPoint [version 16.0.1; Microsoft Corp] diagram flow and concept guided by Mutai et al [21], Chingombe et al [38] and Chingombe et al [43]. AUC-ROC: area under curve-receiver operating characteristics; SABSSM: South African National HIV Prevalence, Incidence, Behavior, and Communication Survey.

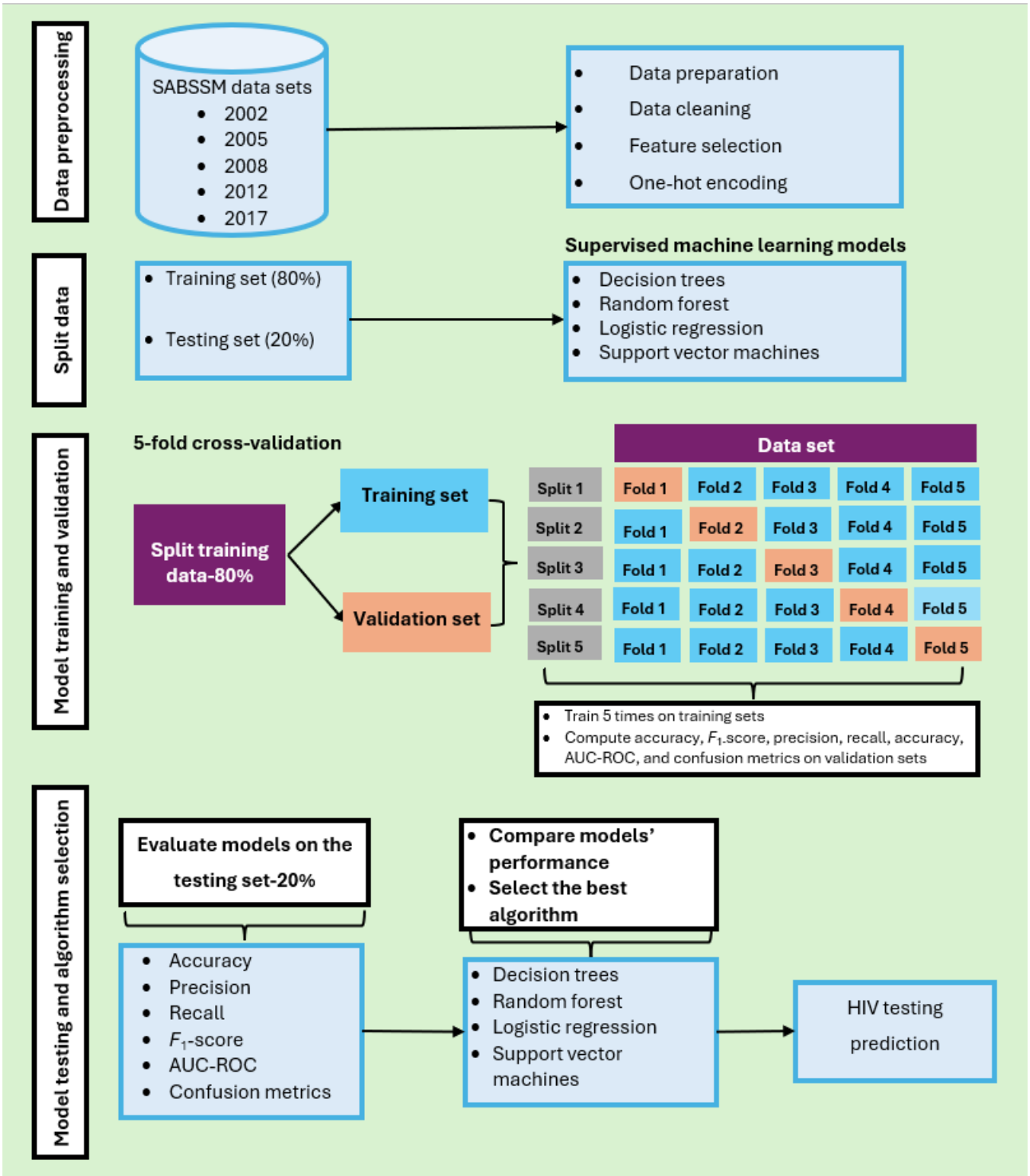

Risk for Bias Assessment

Since the proposed study will analyze secondary data from multiple cross-sectional data, it is pertinent to assess and mitigate potential bias to ensure the validity and reliability of the results. The Joanna Briggs Institute Critical Appraisal Checklist for Analytical Cross-Sectional Studies (this can be found in the Multimedia Appendix 8) will be used to mitigate the risk of bias in this study. At first, the researchers reviewed published reports of the five SABSSM surveys to understand the study designs, study population, sample biases, study variables, and the data collection methods used in each survey by the HSRC. This process guided the development of the study design, eligibility criteria, and variable selection for this study. As of August 20, 2024, the authors have started exploring the SABSSM datasets to clean the data and treat missing values.

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Imbalanced data occurs when one class has significantly more observations than the other, leading algorithms to be biased toward the majority class. In such cases, the researchers will use various techniques to address this and ensure fair model performance. Potential confounders of HIV testing will be identified based on consultations with the literature, as well as the use of statistical measures. Additionally, a variance inflation factor will be used to detect multicollinearity and remove redundant variables associated with HIV testing. This process will also inform the selection of features to be used for the HIV testing predictive modeling.

Data Management

This predictive modeling will use the SABSSM datasets sourced from the HSRC, with no personal information collected from the study participants. Following the data preprocessing and analysis, the preliminary results will be maintained securely using a memory stick that requires an access code. Only the researcher and the research team will be able to review these findings. The results to be published will not contain any identifying information. The electronic data will be stored in the Boloka data repository, password-protected with username access. The Boloka project aims to harness big heterogeneous data to evaluate the impact of HIV responses among key populations in generalized epidemic settings in Sub-Saharan Africa. All the data used in this study will be managed in compliance with the Protection of Public Information Act. The data generated from this study will be securely stored in the Boloka data repository for five years following the study's completion. It is important to note that the SABSSM datasets are governed by an End User License. As per the data-sharing conditions stipulated by the HSRC, the study's data cannot be duplicated, reshared, or sold without prior approval from the rights holder [34].

Ethical Considerations

This study protocol forms part of a doctoral study at the University of Johannesburg (UJ) by the first author (MJ), titled, "Integration of machine learning algorithms to predict HIV testing associations using repeated cross-sectional survey data in an adult South African population: an HIV testing predictive model." The study protocol was approved by the UJ Research and Ethics Committee on April 23, 2024; ethics approval REC-2725-2024 (this can be found in Multimedia Appendix 9). Further, the doctoral study falls under an umbrella project funded by the South African Medical Research Council under the South African Medical Research Council/UJ Pan African Centre for Epidemics Research Extramural Unit, titled: "Harnessing big heterogeneous data to evaluate the potential impact on HIV responses among the key populations in generalized epidemic settings in Sub-Saharan Africa" (ethics approval: REC-1504-2022). Since this study will analyze secondary data, a waiver of informed consent for secondary data use was obtained from the UJ Research and Ethics Committee (this can be found in Multimedia Appendix 9). According to Shisana and Simbayi [30], Shisana et al [31-33], and Simbayi et al [10], all the SABSSM surveys have been approved by the HSRC REC, and studies were conducted in accordance with international ethical standards, as well as the South African Children ACT 2007. Additionally, the SABSSM research team ensured that participants obtained voluntary informed consent. The authors of this study received the SABSSM datasets without any identifying information, and no further efforts will be made to reidentify the study participants during the analysis. The SABSSM datasets are open access data governed by an End User License that cannot be duplicated, reshared, or sold without prior approval from the rights holder (HSRC) [34]. This study will adhere to these data-sharing conditions and all the ethical standards governing the use of secondary data of human participants.

Results

The authors were given access to the SABSSM datasets for this retrospective analysis by the HSRC on August 20, 2024. All 5 datasets were downloaded from the HSCRC database and explored to identify the independent variables likely to influence HIV testing uptake as of September 30, 2024. The selected dependent (HIV testing status) and dependent variables (age, sex, province, marital status, knowing a place to test for HIV, male circumcision, condom use, sex debut, knowledge and perception of HIV, STI symptoms, visit a doctor, and contraceptive use) were recorded for each SABSSM dataset as similar to Table 1 (complete list of variables can be found in Multimedia Appendix 3 [SABSSM 2002 variables], Multimedia Appendix 4 [SABSSM 2005 variables], Multimedia Appendix 5 [SABSSM 2008 variables], Multimedia Appendix 6 [SABSSM 2012 variables], and Multimedia Appendix 7 [SABSSM 2017 variables]). The preprocessing and feature selection phase described in the methods section will determine which variables are to be used for the HIV testing predictive modeling. This process is expected to be completed by November 30, 2024.

The results of this study will be available by January 31, 2025, and each step of the analysis will be visualized and presented in tables and graphs. The anticipated date of publication for the proposed study is June 2025.

Discussion

Principal Findings

The proposed study seeks to identify intricate patterns and relationships among various sociodemographic, behavioral, and contextual variables that contribute to individuals' decisions to undergo HIV testing in South Africa. Since the first SABSSM survey in 2002, varying rates of HIV testing among South Africans have been reported by the HSRC, showing increased trends in each cycle until 2017 (Table 2). By applying SML learning techniques across the five cycles of the SABSSM survey datasets, the findings of this study will ascertain consistent variables predicting HIV testing uptake among the South African adult population over the 20-year period. Furthermore, the study will evaluate and compare the performance metrics of the four different SML algorithms, and the best model will be used to develop an evidence-based predictive model to enhance HIV testing among the South African adult population.

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The emergence of ML applications in health care has demonstrated significant progress. However, predictive modeling in the context of HIV testing is relatively low in developing countries due to challenges such as usability issues, lack of expertise, and insufficient health care data [44]. Steadily, research institutions within specific African countries are increasingly expressing interest in this field.

A study conducted in Tanzania applied SML algorithms, including XGBost and random forest, to develop a model aimed at enhancing HIV index testing, with the recommendation that other health facilities use their model to simplify their work [18]. The study found that knowledge of HIV, age, sex, and marital were significantly associated with HIV index testing [18]. Likewise, a South African study by Majam et al [26] confirms that SML models can be built using digital surveys from low- and middle-income countries to predict high HIV groups for enhanced HIV testing. The models predicted, with over 80% accuracy, that female individuals hesitant to report condom use, and those who had not undergone HIV tests within the past year were at the highest risk of HIV [26]. In addition, an SML technique was used to assess the sociobehavioral predictors of HIV from Demographic and Health Survey data in 10 East and Southern African countries. According to the study, seven male and five female individuals would need to be tested to find one HIV-positive individual [37]. It is also important to consider HIV testing preferences for individuals undergoing HIV testing. Confidentiality, distance from the testing center, and method of data collection were identified as factors determining individual HIV testing preferences in South Africa [45].

The proposed study will expand on the existing knowledge of HIV testing predictors through the application of SML algorithms. Our choice of using SML is based on their heightened predictive accuracy, interpretability, efficiency, and adaptability. The proposed study aims to develop a predictive model to forecast HIV testing associations using repeated cross-sectional survey data in an adult South African population. The developed evidence-based model would assist relevant stakeholders in devising targeting HIV testing interventions in striving toward the UNAIDS 2030 goal of eradicating AIDS in South Africa.

Strengths and Limitations

To the best of our knowledge, this will be the first study to conduct HIV testing predictive modeling using all 5 cycles of the SABSSM surveys by applying SML algorithms. The large volume of data will be crucial for the generalizability of the developed models, as well as the major findings. It is also important to mention that the research involves a multidisciplinary team of experts across public health, epidemiology, biostatistics, and data science. The well-equipped team will devise a comprehensive methodological approach to developing an adaptable HIV testing predictive model.

However, this study is expected to face some limitations as the SABSSM surveys may contain missing values; proper imputation techniques will be used to address this issue. Since some ML models are not well developed, causing spatial and temporal variations, this could also be a limitation in our proposed study. Furthermore, because the analysis focuses on secondary datasets gathered using cross-sectional designs, the researchers are aware of potential limitations such as biases and lack of control over the variables included. The Joanna Briggs Institute Critical Appraisal Checklist will be used to mitigate the risk of bias in this study.

Conclusions

This study will contribute to knowledge and deepen understanding of factors linked to HIV testing beyond traditional methods. Consequently, the findings would inform evidence-based policy recommendations that can guide policy makers to formulate more effective and targeted public health approaches toward strengthening HIV testing in South Africa.

Acknowledgments

The study presented in this publication is within the scope of the Boloka Project and forms an essential part of a doctoral study by MJ conducted within the South African Medical Research Council/University of Johannesburg (SAMRC/UJ) Pan African Centre for Epidemics Research (PACER) Extramural Unit. The research outlined here was made possible through funding from SAMRC under its Division of Research Capacity Development, supported by the South African National Treasury (Project Code: 57035, SAMRC File ref: HDID8528/KR/202). The content of this paper remains the sole responsibility of the authors and does not necessarily represent the official views of SAMRC or UJ. Additionally, this paper forms an integral part of MJ's PhD study and is generously funded by the Global Excellence Stature (GES) 4.0 Scholarship at UJ. The authors express their gratitude to the SAMRC/UJ PACER and the UJ GES 4.0 for providing financial support for this study. We also extend our sincere appreciation to the Human Science Research Council and all the participants of the SABSSM surveys for providing the data used in this study.

Data Availability

The datasets to be analyzed in the proposed study are not publicly available due to the data-sharing conditions of the Human Science Research Council (HSRC; prohibition of the duplication, resharing, or selling of data without prior approval from the rights holder) but are available from the HSRC on reasonable request [32].

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Authors' Contributions

MJ, RNP-M, EP, and YAS conceived and designed the study. MJ, RNP-M, and EP reviewed the literature. MJ wrote the first draft of the paper. MJ and YAS developed the methodology and identified machine learning models that will be used for predictive modeling of HIV testing. RNP-M, EP, and YAS reviewed and supervised the work. MJ, RNP-M, EP, and YAS edited the manuscript. All the authors contributed to this paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
STROBE (Strengthening the Reporting of Observational Study in Epidemiology) checklist.
[DOCX File , 41 KB - resprot_v14i1e59916_app1.docx]

Multimedia Appendix 2
TRIPOD+AI (Transparent Reporting of a multivariable prediction model of Individual Prognosis Or Diagnosis–Artificial Intelligence) checklist.
[PDF File (Adobe PDF File), 927 KB - resprot_v14i1e59916_app2.pdf]

Multimedia Appendix 3
SABSSM (South African National HIV Prevalence, Incidence, Behavior, and Communication Survey) 2002 variables.
[DOCX File , 42 KB - resprot_v14i1e59916_app3.docx]

Multimedia Appendix 4
SABSSM (South African National HIV Prevalence, Incidence, Behavior, and Communication Survey) 2005 variables.
[DOCX File , 42 KB - resprot_v14i1e59916_app4.docx]

Multimedia Appendix 5
SABSSM (South African National HIV Prevalence, Incidence, Behavior, and Communication Survey) 2008 variables.
[DOCX File , 42 KB - resprot_v14i1e59916_app5.docx]

Multimedia Appendix 6
SABSSM (South African National HIV Prevalence, Incidence, Behavior, and Communication Survey) 2012 variables.
[DOCX File , 43 KB - resprot_v14i1e59916_app6.docx]

Multimedia Appendix 7
SABSSM (South African National HIV Prevalence, Incidence, Behavior, and Communication Survey) 2017 variables.
[DOCX File , 45 KB - resprot_v14i1e59916_app7.docx]

Multimedia Appendix 8
JBI (Joanna Briggs Institute) checklist.
[PDF File (Adobe PDF File), 554 KB - resprot_v14i1e59916_app8.pdf]

Multimedia Appendix 9
Ethics Approval Letter.
[PDF File (Adobe PDF File), 88 KB - resprot_v14i1e59916_app9.pdf]

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Abbreviations

HSRC: Human Science Resource Council
ML: machine learning
SABSSM: South African National HIV Prevalence, Incidence, Behavior, and Communication Survey
SML: supervised machine learning
STROBE: Strengthening the Reporting of Observational Study in Epidemiology
SVM: support vector machine
UJ: University of Johannesburg
UNAIDS: Joint United Nations Program on HIV/AIDS

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Protocol

Feasibility of a Mobile App–Based Cognitive-Behavioral Perinatal Skills Program: Protocol for Nonrandomized Pilot Trial

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Abstract

Background: Mental illness is one of the top causes of preventable pregnancy-related deaths in the United States. There are many barriers that interfere with the ability of perinatal individuals to access traditional mental health care. Digital health interventions, including app-based programs, have the potential to increase access to useful tools for these individuals. Although numerous mental health apps exist, there is little research on developing programs to address the unique needs of perinatal individuals. In an effort to fill this gap, a multidisciplinary team of experts in psychology, psychiatry, obstetrics, and pediatric primary care collaborated to develop the novel Perinatal Skills Program within Maya, a flexible and customizable cognitive-behavioral skills app. Maya-Perinatal Skills Program (M-PSP) uses evidence-based strategies to help individuals manage their mood and anxiety symptoms during pregnancy and post partum.

Objective: This pilot study aims to assess the feasibility, acceptability, and usability of M-PSP and explore links between program use and symptoms of anxiety and low mood.

Methods: This single-arm trial will recruit 50 pregnant or postpartum individuals with mild-to-moderate anxiety or mood symptoms. Participants will be recruited from a variety of public and private insurance-based psychiatry, obstetrics, and primary care clinics at a large academic medical center located in New York City. Participants will complete all sessions of M-PSP and provide feedback. Outcome measures will include qualitative and quantitative assessments of feasibility, acceptability, and usability, passively collected program usage data, and symptom measures assessing mood, anxiety, and trauma. Planned data analysis includes the use of the grounded theory approach to identify common themes in qualitative feedback, as well as an exploration of possible associations between quantitative data regarding program use and symptoms.

Results: The recruitment began on August 2023. As of October 2024, a total of 32 participants have been enrolled. The recruitment will continue until 50 participants have been enrolled.

Conclusions: Digital health interventions, like M-PSP, have the potential to create new pathways to reach individuals struggling with their mental health. The results of this study will be the groundwork for future iterations of M-PSP in the hopes of providing an accessible and helpful tool for pregnant and postpartum individuals.

Trial Registration: ClinicalTrials.gov NCT05897619; https://classic.clinicaltrials.gov/ct2/show/NCT05897619

International Registered Report Identifier (IRRID): PRR1-10.2196/59461

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(JMIR Res Protoc 2025;14:e59461) doi:10.2196/59461

KEYWORDS

perinatal mood and anxiety disorders; apps; smartphones; digital intervention; cognitive behavioral therapy; feasibility; pilot trial; mobile phones

Introduction

Maternal mental health plays a pivotal role in influencing the health and well-being of both mothers and their children. In the United States, there is a growing maternal health crisis, in which mental health conditions rank among the top causes of preventable pregnancy-related deaths for mothers [1,2]. During pregnancy and the postpartum period, perinatal mood and anxiety disorders (PMADs) significantly influence a mother's ability to function, care for, and bond with their newborn, which can have an impact on the child's subsequent socioemotional developmental trajectory [3-5].

Though PMADs remain prevalent, with global perinatal depression rates at 26.3%, there is a serious lack of effective, accessible, and affordable mental health care for individuals in the perinatal period [6]. This is particularly true in low- and middle-income communities and countries. In these areas, a general scarcity of maternal mental health services is further exacerbated by stigma, fewer financial resources, and logistical barriers that interfere with connecting to care [7]. As such, many struggling individuals suffer in silence, without appropriate recognition or intervention for their pressing maternal mental health needs [8].

Fortunately, the digital age offers a beacon of hope in bridging the divide between growing community needs and barriers to care, and digital health interventions have the potential to improve maternal mental health outcomes [9]. Specifically, smartphone apps may be able to offer accessible and user-friendly platforms that teach useful coping strategies, which may be especially beneficial for mothers who have difficulty accessing traditional mental health services [10]. However, the landscape of mobile health apps using evidence-based information or psychological interventions is relatively sparse, and efforts to tailor these tools to meet the unique needs of the perinatal population are in the early stages of the field [11,12]. There are numerous mobile health apps targeting this population, with a range of tools for prevention, screening, and treatment, and varying content that includes psychoeducation, symptom monitoring, cognitive behavioral therapy (CBT), mindfulness, and attention bias modification training. Thus far, evidence regarding the effectiveness of existing mobile health interventions is mixed. Recent meta-analyses and systematic reviews demonstrate that app-based interventions are effective for individuals with mild-to-moderate symptoms of perinatal depression and anxiety and may be effective at preventing and treating postpartum depression compared to control groups [12,13]. Few of the existing apps use both evidence-based strategies and provide psychoeducation, as well as target both pregnant and postpartum individuals and both depression and anxiety. More research is needed to aid in the development of technology that is feasible, acceptable, and effective for pregnant and postpartum individuals who need tools to support their mental health.

To help address the critical gap in care needs, this study will present a protocol to assess the feasibility and acceptability of the novel Perinatal Skills Program within Maya, a cognitive-behavioral skills app. Maya-Perinatal Skills Program (M-PSP) is a 12-session mobile app–based program teaching evidence-based strategies to manage mood and anxiety symptoms for perinatal individuals. Following a community-based participatory research model, the study team is seeking feedback from users throughout the early stages of program development. User input will help inform future iterations of the app-based program in hopes of creating a tool that can effectively meet the needs of this population. This protocol represents the first step in the development of a tool designed to increase access to evidence-based skills for individuals with PMADs.

Methods

Aims

The primary aim of this study is to assess the feasibility and acceptability of M-PSP. Specifically, the team will evaluate the mobile app–based program in terms of user satisfaction, perceived use of the program, and engagement with the program. A secondary aim of the study is to look for any associations between program completion and engagement with mental health symptoms.

Design

This study is a mixed methods open pilot trial assessing the feasibility, usability, and acceptability of M-PSP in a perinatal population. There are no comparison arms in the trial. Outcomes will include a combination of quantitative and qualitative data gathered via self-report questionnaires, interviews, and data passively collected through the app. This methodology will allow for the collection of symptom data, participant perceptions and feedback on their experience using the app, and information on app use and engagement. Results will provide information on the potential use of this program in helping pregnant and postpartum individuals manage mood and anxiety symptoms, as well as future directions for program development.

Setting

The study is being conducted through a large academic medical center in New York City. Participants will be recruited through various departments within the medical center, including a psychiatry specialty center, primary care and pediatric settings, and obstetrics and gynecology clinics. These sites range in providing services through private pay, private insurance, or public insurance.

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Participants

The study is currently open to recruitment, with the aim to recruit 50 pregnant or postpartum individuals across all sites. In prior studies, feasibility studies often include a sample size of approximately 50 participants, which is deemed appropriate to ensure robust findings and comprehensive insights into app usability and effectiveness, balancing the need for inclusivity and accurate representation while accounting for potential participant attrition in digital mediums [14,15]. The inclusion criteria for study participation include (1) aged 18 years or older; (2) pregnant or up to 12 months post partum; (3) scoring 8-16 on the Edinburgh Postnatal Depression Scale (EPDS) [16] or 5-14 on the Generalized Anxiety Disorder-7 Scale (GAD-7) [17]; (4) able to read and speak English; (5) have access to a smartphone or mobile device capable of receiving SMS pushes and supporting Qualtrics Surveys and App (Weill Cornell Medicine); and (6) available to speak by phone or secure videoconference. The exclusion criteria include (2) safety concerns at the time of enrollment; (2) current substance use disorder; (3) current symptoms of psychosis or mania; and (4) history of bipolar or psychotic disorder.

M-PSP is designed to address mild-to-moderate anxiety and depression symptoms and may not be appropriate for more severely impaired individuals. In order to secure feedback from participants matching the app's target population, the inclusion criteria include those scoring in the mild-to-moderate range on anxiety and depression ratings. Participants with safety concerns at the time of intake, including recent suicidal ideation or self-harm, are excluded as they are at higher risk for heightened symptoms and risk in the perinatal period. Eligibility is not impacted by receipt of clinical care outside of the study, and participants are not excluded if they are receiving concurrent treatment for depression or anxiety.

Study participants may be disenrolled from the study if they are nonresponsive to 16 outreach attempts across 4 consecutive weeks or if their pregnancy ends.

Outcome Measures

Primary Outcome Measures

Feedback Interviews

Feedback interviews, led by staff via phone or video calls, include open-ended questions aimed to elicit qualitative feedback on program content, structure, and functionality, as well as user engagement and satisfaction. Questions such as "What ways could the app have been better tailored to help expectant or postpartum individuals?" will be asked to have a better gauge of acceptability, while questions like "What suggestions or comments do you have about the total number of sessions?" help address the feasibility of an intervention during and after pregnancy.

In-App Surveys

Weekly in-app feedback surveys are self-report measures that include Likert-scale questions regarding participant experience with specific session-by-session app-based content and structure (eg, "How helpful was Cognitive Practice [TINTED or Thinking Like a Lawyer]?"; "How likely are you to review any part of Session 3 again [eg, video, exercises, or quiz]?"). In particular, questions such as "How helpful was the content for you as an individual who is pregnant or postpartum?" and "How easy was it to fit using the app into your day-to-day life?" inform us of the acceptability and feasibility of the app, respectively, throughout the study.

User Version of the Mobile Application Rating Scale

Whereas the in-app surveys elicit session-by-session feedback, the user version of the Mobile Application Rating Scale (uMARS) elicits more global feedback on the overall app experience. The uMARS [18] is a validated 27-item self-report questionnaire evaluating engagement, functionality, aesthetics, information, subjective quality, and perceived impact of the app-based program. In particular, engagement, aesthetics, and information subscores will be used to measure acceptability and the functionality subscale will reflect the app's usability.

Mean scores are derived for each of these subsections, which can then be averaged to determine an overall App Quality Score. Responses are rated between 1 and 5, with 5 indicating higher levels of satisfaction. Stoyanov et al [18] found that uMARS exhibited satisfactory internal consistency (α=.90).

Passive Data Collection

M-PSP passively collects data, encompassing information captured without active user input, such as when sessions were completed, frequency of program usage, and program completion. These data points will serve as measures of program feasibility and user engagement.

Secondary Outcome Measures

Intake Survey

Participants will complete an intake questionnaire comprising questions related to demographics, health, mental health, and pregnancy history.

Edinburgh Postnatal Depression Scale

The EPDS [16,19] is a 10-item self-report measure of mood symptoms in perinatal individuals. Responses are coded on a scale of 0=lowest severity to 3=highest severity, with 30 being the highest score possible. Cutoffs are as follows: scores 7 and below indicate depression is unlikely, scores 8-13 indicate mild depression, 14-18 indicate moderate depression, and 19 and higher indicate severe depression [20]. Cox et al [21] found that the EPDS is a valid screening scale for depression and has satisfactory sensitivity (79%) and specificity (85%).

The Edinburgh Anxiety Subscale

The Edinburgh Anxiety Subscale [22] uses items 3, 4, and 5 from the EPDS to assess levels of anxiety among perinatal individuals. A score of 5 and above indicates the presence of anxiety [23].

Pregnancy Symptom Tracker

The daily Pregnancy Symptom Tracker (PST) is an ecological momentary assessment tool that aims to merge and consolidate gold-standard symptom measures into a format that is friendly and efficient for users, while also tracking information related to sleep, exercise, and daily behaviors. Developed by a group

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of psychiatrists and reproductive psychiatrists, the measure takes 30-60 seconds to complete. Users use a sliding scale to indicate the degree of each symptom or behavior present within the last 24 hours.

GAD-7

The GAD-7 [17] is a 7-item self-report measure assessing symptoms of anxiety. Responders indicate the frequency of symptoms on a scale of 0=not at all to 3=nearly every day, with total scores running from 0 to 21. A score of 0-4 indicates minimal anxiety, 5-9 indicates mild anxiety, 10-14 indicates moderate anxiety, and 15-21 indicates severe anxiety. Spitzer et al [17] found that the GAD-7 exhibited reliable sensitivity (89%) and specificity (82%), validating its effectiveness as a screening tool for generalized anxiety disorder.

Patient Health Questionnaire-9

The Patient Health Questionnaire-9 (PHQ-9) [24] is a validated 9-item self-report measure assessing symptoms of depression. Responders indicate the frequency of symptoms on a scale of 0=not at all to 3=nearly every day. Scores can range from 0 to 27, with an additional qualitative question regarding the level of difficulty caused by symptoms ranging from no difficulty at all to extreme difficulty. Scoring interpretation is as follows: 1-4 (minimal depression), 5-9 (mild depression), 10-14 (moderate depression), 15-19 (moderately severe depression), and 20 and greater (severe depression). Kroenke et al [24] found that a PHQ-9 score ≥10 exhibited a satisfactory sensitivity of 88% and a specificity of 88% for major depressive disorder.

Perinatal-Post Traumatic Stress Disorder Questionnaire-II

The Perinatal-Post Traumatic Stress Disorder Questionnaire-II (PPQ-II) [25] is a validated 14-item self-report measure assessing symptoms of trauma among postpartum individuals. Frequency and duration of symptoms are rated on a 5-point Likert scale from 0=not at all to 4=often for more than a month, with total scores ranging from 0 to 56. Scores of 19 above indicate a clinical range of symptoms that would benefit from additional support. Komurcu Akik and Durak Batigun [25] found that the PPQ-II demonstrates validity and reliability as a scale for assessing the perinatal post-traumatic stress symptoms experienced by mothers.

The M-PSP Intervention

The Perinatal Skills Program was developed within Maya, a CBT skills app that is customizable and allows for the creation of individualized programs for multiple populations. M-PSP was adapted from one such program, Maya-Cognitive Behavioral Skills Program (M-CBT), which was a 12-session program that provided gold-standard, evidence-based strategies to help young adult users learn tools to manage anxiety and low mood. Preliminary data from a feasibility and acceptability trial of M-CBT suggest that the app is feasible and acceptable, and results showed a substantial decrease in both depression and anxiety from pre- to post-intervention [26]. In response to rising maternal mental health needs, an expert team of clinical psychologists specializing in CBT and reproductive psychiatrists with expertise in perinatal mental health adapted M-CBT into M-PSP. The team also consulted with physicians within pediatric primary care and obstetrics departments to better understand the needs of expectant and new parents. Changes to the original program included tailoring language and examples to address concerns that are common during and after pregnancy, as well as modifying skills as appropriate for the perinatal population. Several new skills were added, such as tools for managing communication and relationships as an expectant or new parent (Multimedia Appendix 1).

Users can work through each M-PSP session on their own schedule and are able to unlock up to 2 sessions per week. This pacing mirrors typical CBT session structure, allowing time for homework and practice between sessions, which is crucial for skill development and mastery [27,28], and acknowledges research showing that most people engage with apps for a limited duration, necessitating a structured yet flexible format to maximize engagement and effectiveness [29,30]. Each session in the program includes 3 main sections: learn (where new information and skills are shared), practice (where users can try out the skills they learned), and review (wrap-up of key lessons and takeaways). Users are introduced to a range of evidence-based tools throughout the 12 sessions (Table 1). There are also homework assignments for each session allowing users to practice what they have learned throughout the week. Users can individualize their experience by entering and tracking mood and anxiety ratings, planning for real-world skills use, personalizing examples, choosing preferred exercises to try, and reflecting on skill practice. The app has been programmed to help users see their progress through the app and track change toward self-identified goals. Users are also able to make use of tabs within the app for quick access to specific information, such as videos, skill practice, and favorite tools. Study staff have weekly meetings to ensure protocol is adhered to.

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Table 1. M-PSP[a] session content.

Session	Session objectives and content
Session 1: Understanding symptoms and treatment	• Psychoeducation on perinatal anxiety and mood symptoms • Sleep tips for pregnancy and post partum. • Identifying common perinatal patterns of thoughts, feelings, and behaviors
Session 2: Facing challenges	• Identifying how emotions impact behavior during the perinatal period • Learning to gradually approach and overcome challenging tasks • “Face It!” exercise to craft an individualized goal ladder for daily practice
Session 3: Shifting thoughts	• Cognitive restructuring techniques to reframe unhelpful thinking • Guidance on effective communication and managing evolving relationships • Introduction of “TINTED Thoughts” exercises to recognize and correct cognitive distortions
Session 4: Relaxing your body and mind	• Introduction to relaxation exercises and audio-guided muscle relaxation meditation session. • Distress tolerance tips to manage stressful moments • “Face It!” exercise to craft an individualized goal ladder for daily practice
Sessions 5-10: Practice and use skills	• Revisiting the list of challenging situations and tracking progress • Continued practice of helpful thoughts and “Face It!” exercises • Introduction to problem-solving skills and additional distress tolerance exercises
Sessions 11-12: Maintenance and relapse prevention	• Guided selection of an exercise for ongoing skill practice • Skill review and reflection exercise • Guidance on next steps to support sustained mental health

[a]M-PSP: Maya-Perinatal Skills Program.

Procedure

As of October 2024, the study is open to recruitment. Recruitment strategies involve advertisements through listservs, clinician information sessions, and flyers within inpatient and outpatient departments. Interested individuals can complete a digital contact information form via a Health Insurance Portability and Accountability Act–compliant survey platform or have their providers complete the contact forms on their behalf.

Study staff reach out to individuals who have completed the form to screen for eligibility. Eligible participants are given further details about study involvement and complete informed consent. Study staff help participants download the app and provide an orientation, with recommendations to use the program for 10 minutes a day, 4 days a week. While it is recommended to complete the program within 6 weeks, sessions can be completed at the participant’s convenience. All participants will be allowed up to 18 weeks for completion in order to account for delays or interruptions that may have occurred during pregnancy or after labor and delivery. Within 1 week of the study orientation, the research assistant will conduct a brief 5-minute phone check-in using a scripted protocol to ensure participants have been able to access and start the app, check on potential technical issues, and answer any questions related to app navigation.

Throughout participation, participants will be able to complete up to 2 sessions per week and will complete the in-app feedback surveys after each session. They will also be sent a text to their phone with a link to complete the daily PST. Additional assessments occur at midpoint (following completion of session 6), post (completion of session 12), and follow-up (6 weeks after post). These assessments include the staff-led feedback interviews via phone or videoconference, as well as the uMARS and all symptom measures. When risk items are endorsed on the daily PST, symptom measures, or during the assessments, study staff are notified and the participant is contacted by a licensed provider to conduct a formal risk assessment and safety plan as necessary.

To aid in retention and study completion, study staff monitor app completion progress and maintain contact with participants to schedule feedback interviews (Table 2). Through these methods, staff are able to problem-solve technical difficulties and other barriers to session completion as needed. Participants are encouraged to reach out via email or phone with any questions or concerns. Study staff follow institutional review board (IRB) guidelines to report any adverse events within the required timeline.

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Table 2. SPIRIT[a] checklist.

	Prestudy	Intake	Weeks 1-6	Midpoint	Weeks 7-12	Post	6-week follow-up
Contact form	✓						
Eligibility screen		✓					
Informed consent		✓					
Download of Maya		✓					
Background questionnaire		✓					
App sessions			✓		✓		
In-app feedback			✓		✓		
Symptom measures		✓		✓		✓	✓
Daily symptom tracker			✓	✓	✓	✓	✓
Feedback interview and uMARS[b]				✓		✓	✓
Adverse event monitoring	✓	✓	✓	✓	✓	✓	✓

[a]SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials.

[b]uMARS: user version of the Mobile Application Rating Scale.

Data Analysis Plan

To analyze qualitative data from the feedback interviews, the grounded theory approach [31] will be used to review all responses and develop a consensus on existing themes. The data will then be systematically coded using these themes in order to identify core concepts and response patterns to derive meaningful interpretations of the feedback.

Data passively collected from the app will be transformed into practical means and ranges that will be used to understand user engagement and program feasibility. Means and SDs will be computed for demographic information and relevant symptom and acceptability questionnaires. Continuous scores from symptom scales and acceptability questionnaires will be analyzed in relation to app use and engagement. Correlations between these variables with be assessed using either Pearson or Spearman correlation depending on data distribution. For example, we will examine the correlation between EPDS symptom scores and app completion rates to explore whether postpartum depression symptoms are related to program feasibility. Hypothesis testing will be conducted with a P value=.05 as the threshold for statistical significance, and clinical significance will be considered for correlations that meet a meaningful cutoff (eg, 0.6 or 0.8). This analysis will help identify any demographic characteristics or symptoms that may require greater attention in future iterations of the program to ensure its effectiveness for a broad range of perinatal individuals. For participants who dropped out before study completion, all available data will be included, and any missing data will be handled using simple imputation. A correlation matrix will be generated to explore the relationships between symptom scales (eg, EPDS and GAD-7) and app engagement variables (eg, frequency of use, duration of use), allowing us to investigate possible associations without the need to correct for multiple testing in this exploratory pilot study.

Ethical Considerations

The study was granted approval through the Biomedical Research Alliance of New York IRB (BRANY #23-02-134-380) and the internal IRB within the academic medical center at which the trial is being conducted. The study has been registered at ClinicalTrials.gov (protocol number NCT05897619). This protocol was written in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (Multimedia Appendix 2) [32]. All participants provided informed consent and were made aware that they could withdraw from the study at any time without penalty. Participants are not compensated for their participation. All participants may continue to use the MAYA app following study completion if they so choose and will be given a list of resources, including referrals for clinical care.

While no individual data will be reported, the study team will report results via publication following trial completion. Health care providers within the Weill Cornell Medicine or NewYork-Presbyterian network may be given access to a summary of qualitative and quantitative outcomes. Every participant is given a unique study identifier. All data collected were confidential and safely stored per protocol approved by the IRB. As a small, unblinded study that does not involve invasive procedures or greater than minimal risk, there is no data monitoring committee. The study is internally sponsored, with no external funding organization involved in study design, management, monitoring, or analysis. The study is fully monitored by internal co-investigators, with IRB oversight through BRANY.

Results

The pilot trial received internal funding in August 2023 and data collection started in September 2023. As of October 2024, 32 participants have been enrolled in the study. It is anticipated that enrollment will continue throughout 2024, with projected

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recruitment completion in December 2024. Data analysis will be completed upon study completion of the last participant.

Discussion

This study aims to assess the feasibility, usability, and acceptability of the M-PSP, a 12-session program teaching skills derived from CBT and adapted to suit the unique needs of a perinatal population. Regarding feasibility, it is anticipated that outcomes will indicate the program is able to be worked through by users, but that pacing and session length may need more flexibility in future versions of the app to account for the particular demands of this population. It is hypothesized that users will find the skills to be acceptable, but that some of the sample videos need revision to more directly reflect mood and anxiety concerns during and after pregnancy. Further, the study team anticipates that users will have input on specific content that could be added to improve their satisfaction with the app. Regarding usability, it is anticipated that the app will be user-friendly and easy to work through. As the secondary aims are exploratory, there are no specific hypotheses related to symptom measures as they are related to engagement. These outcomes will inform future iterations of the program in hopes of developing a widely accessible and useful tool for pregnant and postpartum individuals.

While the findings from this pilot study will provide valuable insights, several limitations must be acknowledged. This study relies on self-report data, which may introduce biases such as social desirability or recall errors. In future studies, clinician assessment of symptoms could help to mitigate these concerns. In this and future studies, the use of passively collected app usage data should provide some objective metrics regarding engagement and feasibility. A further limitation is the small sample size. As a pilot trial, this study is not powered to detect statistical significance, as the primary aim is to assess feasibility and acceptability rather than efficacy. Therefore, these findings should be interpreted as preliminary, and further research with larger samples will be necessary to assess the program's effectiveness in improving mental health outcomes.

Despite these limitations, this study is an important step in helping to fill the gap between an increasing maternal mental health crisis and barriers to appropriate support. By using a community-based-participatory research model, the development team has been able to consider input from researchers and clinicians across different specialties and will be able to incorporate feedback from end users through each stage of program development. Once feedback has been considered and incorporated into the program, the team will look to conduct future studies to assess the effectiveness of the tool in helping perinatal individuals manage anxiety and mood symptoms. Per guidelines on progressing from a pilot trial to a fully powered randomized controlled trial (RCT) [33], the research team has outlined a number of criteria that will influence the next steps. To ensure adequate participant numbers for an RCT, the pilot trial will need to demonstrate a 50% retention rate between screening and enrollment. The team will also move forward if 75% of participants complete primary outcome measures, which consist of feasibility, acceptability, and usability feedback interviews and surveys. While the study team will track adherence to the intervention (ie, completing M-PSP sessions), this will not be used as a criterion for progressing to a full RCT as nonadherence may be attributable to feasibility or acceptability concerns that the pilot study intends to illuminate so that future versions of the app can be modified prior to an RCT.

Acknowledgments

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Data Availability

The datasets generated during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

ATY led study conception and design, development of the intervention, and manuscript drafting. AH, SG, and SB made substantial contributions to study conception and design. LB, LO, and CG have contributed significantly to the study design. AA and EB have led data acquisition and drafted portions of this manuscript. AD, AO, ML, MS, and IS have drafted portions of this manuscript. MS and SZ contributed to the development of the intervention and design for data acquisition. AF led the development of the original intervention and conception of the overall app-based programming.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Sample screenshots of the MAYA Perinatal Skills Program.
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Multimedia Appendix 2
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 1505 KB - resprot_v14i1e59461_app2.pdf]

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Abbreviations

CBT: cognitive behavioral therapy
EPDS: Edinburgh Postnatal Depression Scale
GAD-7: Generalized Anxiety Disorder-7 Scale
IRB: institutional review board
M-CBT: Maya-Cognitive Behavioral Skills Program
M-PSP: Maya-Perinatal Skills Program
PHQ-9: Patient Health Questionnaire-9
PMAD: perinatal mood and anxiety disorder
PPQ-II: Perinatal-Post Traumatic Stress Disorder Questionnaire-II
PST: pregnancy symptom tracker
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
uMARS: user version of the Mobile Application Rating Scale

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Protocol

Novel Procedures for Evaluating Autism Online in a Culturally Diverse Population of Children: Protocol for a Mixed Methods Pathway Development Study

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Abstract

Background: Current autism assessment procedures are costly and resource-intensive. The COVID-19 pandemic accelerated the adoption of telemedicine, highlighting the benefits of innovative diagnostic tools. Telemedicine-based pathways could enhance accessibility and equity in autism diagnostics.

Objective: The Children with Autism Technology Enabled Assessment (CHATA) project aims to develop and pilot an open-source autism diagnostic pathway for children up to 5 years old, delivered through telemedicine. The pathway is designed to be culturally and linguistically adaptable, increasing its applicability to diverse populations and integrating with existing National Health Service digital systems.

Methods: Initial pathway development was informed by systematic evidence reviews, coproduction, and mixed methods usability. CHATA comprises 2 key elements: online self-completed standardized autism questionnaires and a structured online interview and observation by a trained clinician. Out of 60 families near the top of the local waiting list will be invited to participate in the pilot evaluation, assessed using both the CHATA and usual assessment pathways. Sensitivity and specificity will be calculated by comparing the diagnosis of autism through CHATA with usual care. Quantitative usability assessment will be gathered from all families using the System Usability Scale (where a mean above 68 indicates above-average usability). A subset of CHATA assessments will be reviewed for interrater reliability (measured by the Cohen κ for categorical data [diagnosis present or absent], with values indicating the level of agreement; eg, <0 indicating no agreement, 0.61-0.80 indicating substantial agreement). Qualitative data on acceptability, feasibility, and usability will be gathered from semistructured interviews with a subset of families and health care providers. We will recruit 60 families for the main pilot study (including the usability testing) and 10-15 participants for the qualitative substudy. Data will estimate CHATA's diagnostic accuracy, validity, reliability, usability, and acceptability. Patient and public involvement will be integral throughout. The study will take place in a socio-economically deprived, ethnically diverse inner-London Borough within a community-based child health National health service responsible for the Autism assessment of children and young people up to the age of 13 years.

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Results: Ethics approval was received in June 2023 (Research Ethics Committee reference 22/LO/0751; IRAS project ID 320499). Data collection commenced in April 2023 and completed in October 2024. Project end date is March 2025. As of November 2024, we had enrolled 57 participants to the pilot study and 12 to the qualitative substudy.

Conclusions: The CHATA project aims to establish a novel, culturally sensitive, equitable, and accurate online autism assessment pathway. By addressing geographical and linguistic barriers, this pathway seeks to reduce service costs, shorten waiting times, and promote equity in autism diagnosis. The procedures developed are expected to be generalized to other populations nationwide.

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KEYWORDS

autism; child; telehealth; co-development; feasibility; acceptability; assessment; diagnosis; online; evaluation; diagnostic; intervention; pilot implementation evaluation study

Introduction

Autism spectrum disorder (ASD) is a complex neurodevelopmental condition marked by difficulties in social communication, restricted and repetitive behaviors, and sensory sensitivities [1]. Despite a significant increase in autism prevalence in the United Kingdom among children aged 10-14 years, only about 1 in 190 children are diagnosed during the preschool years [2]. Consequently, many children are not identified or assessed until they have been in school for several years, leading to educational disadvantages. As of December 2023, over 170,000 people in England were awaiting an autism assessment, with 85% waiting beyond the recommended 13 weeks [3]. While data on waiting lists for older children in child and adolescent mental health services are available, equivalent data for preschool assessments is less reliable [4]. However, anecdotal evidence suggests lengthy waiting times of 36-42 months for preschool appointments, with some regions having no availability at all. Autism can be reliably identified by 24 months [5], but the average diagnosis age is >5 years in Europe and North America [6,7].

Structural inequity exists in autism assessment. Girls, and people from ethnic minorities or lower socioeconomic groups, receive support later than their peers, if at all. The 2024 Child of the North (UK) report found that ethnicity and associated language barriers play an important role in determining who gets assessed; overall, children of white heritage are substantially more likely to receive an autism diagnosis than children of Asian heritage [8,9].

Traditional autism evaluations involve developmental history, current behavior descriptions, and direct observation of social interaction skills. The COVID-19 pandemic has increased interest in using telehealth for preschool autism assessments. Various tools and methods are used in telehealth, including video-based observations, digital questionnaires, and online behavioral checklists. These tools can be used for both live (synchronous) and recorded (asynchronous) assessments, providing flexibility in how evaluations are conducted. Telehealth offers benefits like flexible scheduling, increased accessibility, fewer no-shows, optional audio and video recording, reduced travel and costs, fewer room bookings, and lower environmental impact [10]. Families in rural or underserved areas can now access diagnostic services more easily through remote assessments [11]. In addition, telehealth can significantly reduce wait times by enabling quicker initial screenings and follow-ups, which is especially beneficial given the high demand for autism assessments and the limited number of specialists available [11]. Our recent systematic review found that Telehealth assessments are as accurate as in-person assessments, with over 80% diagnostic agreement [12]. Online asynchronous parental reports and behavioral observation tools also show high validity and reliability, with agreement rates of 82%-88% compared with in-person assessments.

However, telehealth also faces several limitations. Technological barriers are a significant issue, as not all families have access to the necessary technology or reliable internet connections [13]. This can create disparities in who can benefit from telehealth services. In addition, there is a need for more training for clinicians to effectively use telehealth tools and ensure consistent and accurate assessments [14]. The standardization of telehealth procedures is still evolving, which can affect the reliability of these assessments. Equity issues are another concern. Telehealth may not be equally effective for all populations, as cultural and language differences can impact the accuracy of assessments. Moreover, telehealth tools may not be validated for diverse populations, potentially leading to biased outcomes.

We have developed a telemedicine assessment pathway - Children with Autism Technology Enabled Assessment (CHATA) that combines both asynchronous (parent online questionnaires) and synchronous (online clinical assessment) elements. Designed currently for children up to 5 years old, it has been developed to optimize linguistic and cultural accessibility. Given the potential limitations of the telemedicine approach, refining approaches such as CHATA and conducting pilot trials are crucial. These efforts can help improve the efficiency of autism screening and diagnosis by developing more reliable and user-friendly telehealth tools. They can also address disparities in telehealth access and effectiveness, ensuring that all children, regardless of their background, receive accurate, and timely diagnoses. Furthermore, refining CHATA can contribute to the standardization of telehealth procedures, making them more consistent and reliable across different settings. Ultimately, this study aims to enhance the efficiency and equity of autism assessments for children. Our objectives are to refine the pilot version of the CHATA diagnostic assessment for preschool children with suspected autism,

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evaluate its usability, acceptability, feasibility, and interrater reliability, and estimate its sensitivity and specificity.

Methods

Study Design

This mixed methods study integrates pathway refinement, pilot evaluation, and implementation, using both qualitative and quantitative approaches. It focuses on usability, acceptability, feasibility, clinical validity, and reliability. The research framework is grounded in Behavioral Science and Participatory Action Research [15]. This approach captures diverse challenges and resilience factors among families, addressing the limitations of solely using survey questionnaires. Qualitative data will enrich quantitative findings, providing a comprehensive understanding of individual experiences. The study timeline is provided in Figure 1.

Figure 1. Study timeline. CHATA: Children with Autism Technology Enabled Assessment.

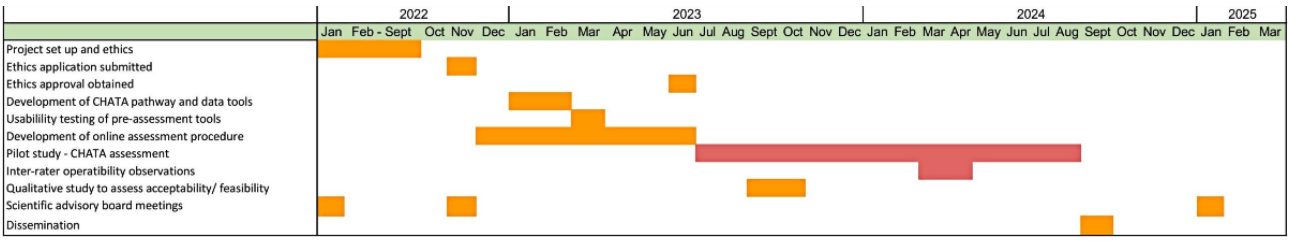

Study Setting

The study will take place in the London Borough of Newham (LBN), UK, known for its high ethnic and linguistic diversity, with approximately 78% of the population from ethnic minority groups and over 140 spoken languages. LBN is also among the most deprived areas in England, with over 50% child poverty. The East London National Health Service (NHS) Foundation Trust provides community child health services, including the Children with Autism in Newham–Diagnosis Service (CHAND) for children up to 13 years old. Due to underfunding and increased demand during the COVID-19 pandemic, over 1200 children are currently awaiting assessment by CHAND (personal communication as of June 14, 2024).

Patient and Public Involvement

To inform the initial development of CHATA and this pilot study protocol, 2 patient and public involvement (PPI) workshops were held with 8 parents of children who had online autism assessments during the COVID-19 pandemic. The group included 5 Asian or Asian British parents and 3 Black or Black British parents, 1 requiring an interpreter. While most preferred face-to-face appointments, they accepted online assessments for reduced waiting times. A “Parent Voice” representative, an Asian parent of children with autism is a named co-investigator, who will participate in regular meetings, assist with study design, and analysis, and provide ongoing feedback.

Stakeholder Engagement

A Scientific Advisory Board will guide the development of the online autism assessment pathway, meeting biannually with regular email updates. Additional engagement with the National Institute for Health and Care Excellence guideline stakeholders will explore novel provisions. Study outcomes will be disseminated through an event with local clinical service stakeholders, and key findings will be shared through the NHS Trust website. In addition to scientific manuscripts and presentations, a pamphlet will publicize the study’s outcomes and policy implications.

Usual Autism Pathway Procedures in Study Setting

The usual care pathway in LBN, referred to as the “CHAND reference pathway,” currently includes the following steps:

1. Referral: made to CHAND.
2. Triage: conducted by a multidisciplinary team (MDT) based on referral information, resulting in 1 of 3 outcomes: acceptance, request for additional information (eg, school report), or rejection.
3. Assessment decision: if accepted, the triage team determines whether the case is straightforward or complex based on demographics (eg, age) and clinical factors.
4. Assessment: straightforward cases are booked to see a pediatrician or senior speech and language therapist alone. Complex cases are booked for a multidisciplinary assessment involving at least 2 clinicians (eg, pediatricians, speech, and language therapists, psychologists, and occupational therapists). One clinician conducts an Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) assessment [16], and the other takes a case history. If a diagnostic outcome is not reached, the case is discussed at a wider MDT meeting, including representatives from pediatrics, speech and language therapy, occupational therapy, and psychology. Additional assessments may include a school visit, a Diagnostic Interview for Social and Communication Disorders with parents [17], or an informal observational assessment to evaluate mental health difficulties or masking in girls.
5. Feedback and follow-up: diagnostic feedback and psychoeducation about autism and autism-specific supports are provided. Local signposting and invitations to postdiagnosis group workshops or one-to-one sessions with a parent connector are offered.

The service is diagnostic only and does not provide postdiagnosis support or interventions. Onward referrals for occupational or speech and language therapy are made with the family’s consent. All children under 5 undergo a face-to-face physical examination with a pediatrician, where blood and genetic testing may be considered.

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CHATA Index Assessment Procedures

The CHATA index pathway, designed to be compatible with National Institute for Health and Care Excellence guidelines for autism assessment [18] and to replace, where appropriate, usual care CHAND assessment step 4 above, involves 2 steps:

1. Digital questionnaires: participants complete a series of self-administered questionnaires within 45 minutes on an NHS-compatible digital platform.
2. Online clinical observation: this is followed by a real-time, semistructured parent-child interaction through video conferencing, taking between 30 and 60 minutes depending on the need for interpreting.

Both the questionnaire and observational data are hosted on Drupal, a secure, open-source web application, locally hosted on an NHS server.

Digital Questionnaires

The questionnaire was developed by integrating items that effectively identified autistic behaviors in preschool children from the following sources:

1. 3di interview, a computerized diagnostic tool used by UK Autism assessment teams [19]. The full 3di comprises nearly 200 questions, applicable across the full range of children and adolescent ages. We developed a preschool version using data from 1,437 children referred to the Great Ormond Street Hospital Social Communication Disorder Clinic (2005-2023). Using a discriminant function analysis, we identified 41 questions that best discriminated preschool children (n=356) assigned an autism diagnosis by the multidisciplinary clinic. From nearly 200 questions, 41 were selected for their effectiveness in distinguishing autism in preschool children. These interview questions were reconfigured into questionnaire format for CHATA.
2. The Modified Checklist for Autism in Toddlers, a screening tool for children under 30 months, consisting of 20 questions for parents [20].
3. The Developmental Check-In, a brief ASD screening tool validated for Hispanic children aged 24-60 months, includes 26 questions with accompanying photographs to aid parents with limited literacy [21,22].

An audit of the CHAND waiting list identified Urdu and Bengali (Sylheti and Dakar dialects) as the most frequently spoken languages after English. Questionnaires were professionally translated and back-translated, with parent focus groups assessing their accuracy and acceptability. Audio descriptions were created for participants with low literacy and uploaded alongside the written questionnaires.

Five parents/carers of children under 5 years of age who had undergone autism assessment participated in usability testing using the “think aloud approach” and the quantitative System Usability Scale (SUS; Multimedia Appendix 1), standard usability assessments [23,24]. Usability feedback was broadly positive, with critical feedback focused on the need to ensure clear instructions for accessing the questionnaires.

Online Observations

The online observations will be conducted by an experienced clinician in preschool autism assessment, trained in the ADOS-2 autism assessment. Parents will use a broadband phone camera for the session, guided by the clinician through semistructured interactions with their child. This online observation was developed informed by the TELE-ASD-PEDS model, where the clinician remotely observes and instructs the caregiver in real-time tasks [25]. Scoring will align with the ADOS-2 methodology [16]. For the purposes of this pilot study sessions will be recorded for independent analysis to assess inter-rater reliability.

The assessment includes a 10- to 20-minute clinical interview, followed by a structured real-time observation. The clinician will review preassessment results to tailor the interview, focusing on specific concerns. During the observation, the child will perform activities with common household items and toys, guided by detailed instructions provided in advance. This will assess social communication, interaction, and restricted or repetitive behaviors. Interpreters will assist families who do not speak English as their first language, translating instructions and responses.

Recruitment to Pilot Study

Families receiving health services at an inner London clinic, specifically those on the autism assessment waiting list, will be recruited. Potential participants will be contacted through telephone or email and provided with detailed study information. Participants can discuss any questions with the research assistant through various communication methods. Cultural advocates will ensure cultural sensitivity during recruitment (see inclusion and exclusion criteria in Textbox 1).

Cultural advocates and trained research team members will ensure a supportive environment.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Parents and caregivers of children aged 5 or younger on the autism assessment waiting list in Newham, East London.
- Residents of Newham.
- Parents and caregivers aged 18 or older.

Exclusion criteria

- Inability to give consent.
- Known safeguarding concerns.
- Nonspeakers of English, Urdu, or Bengali.

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Sample Size and Sample Size Justification

We will recruit 60 families for the main pilot study (including the usability testing) and 10-15 participants for the qualitative sub-study.

For clinical validation with approximately 80% power and an estimated 90% prevalence, a minimum sample size of 34 is needed to detect high sensitivity [26]. To detect high specificity with similar power, a minimum of 310 is required. A prestudy audit of the CHAND service showed a 90% autism diagnosis rate, like the 86% conversion rate in Bradford Autism Services [9]. Given the pilot nature of this study, we chose a pragmatic sample size of 50-60, prioritizing sensitivity assessment over specificity.

The sample size for quantitative usability testing is driven by the overall pilot sample size.

Approximately 15 participants are anticipated for the qualitative study, sufficient to reach thematic saturation and thoroughly explore core themes and patterns.

Estimated Diagnostic Accuracy

Families will complete both parts of the CHATA assessment, the online questionnaire and a structured videoconferencing clinical assessment, before their usual face-to-face CHAND clinical assessment. Following the CHATA assessment, children will proceed with the standard clinical assessment, including an in-person physical examination by a pediatrician and review at the MDT meeting for complex cases. This process (from the first CHATA assessment to the initial CHAND assessment) is expected to be finished within 6 weeks and will not affect their position on the clinical service waiting list.

Families will receive general autism information but no diagnosis from the CHATA assessment. The CHATA assessment results will be classified as autistic, nonautistic, or unsure by the research clinician but will not be shared with families or the clinical team to maintain blinding. The CHAND clinical team will record their own assessment outcomes and disclose them to the family as per usual processes. An independent researcher will compare the CHATA diagnostic outcome with the CHAND diagnostic outcomes from electronic health records to determine sensitivity and specificity.

Quantitative Usability

All families enrolled in the pilot will complete the SUS after completing the online questionnaires [24]. The SUS is a validated, widely used tool for measuring the usability of systems, with scores ranging from 0 to 100. The SUS consists of 10 items, with responses recorded on a 5-point Likert scale ranging from “Strongly Disagree” to “Strongly Agree.” Participants’ responses will be anonymized and collected into a database for analysis.

Qualitative Acceptability, Feasibility, and Usability Substudy

A qualitative study will include 10-15 families from the main study, chosen to represent diverse languages and experiences. This subset will help assess the acceptability and feasibility of the CHATA process, focusing on both positive aspects and areas for improvement. Recruitment will end when thematic saturation is reached, meaning no new themes emerge from the data. Data analysis will continue until no new codes appear, only recurring themes. In addition, 2-5 health care providers involved in autism assessments will be interviewed to gather their perspectives on the CHATA assessment, including its strengths and challenges. All interviews will be recorded with the participants’ consent.

Time Taken for Assessment

Informed by a recent study estimating the cost taken to undertake autism assessments in UK NHS services [27], we will estimate the time taken for each child to be seen under the usual care pathway, recording the grade of health care providers undertaking the assessments and compare that to the time taken to be seen under CHATA. We will then estimate costs associated with these using standard NHS outpatient costings.

Quantitative Data Analysis

Usability Data

The SUS score for each participant will be calculated using the standard method: for each of the 10 items, scores range from 0 to 4. Positive items (1,3,5,7,9) will have 1 subtracted from the response, while negative items (2,4,6,8,10) will have the response subtracted from 5. The total score will be multiplied by 2.5, resulting in a final SUS score ranging from 0 to 100.

To summarize the CHATA online questionnaire usability, we will compute the mean, median, and SD of SUS scores. Scores will be interpreted as follows: above 68 is considered above average, 50 to 68 is marginally acceptable, and below 50 may indicate usability issues. We will perform subgroup analyses to compare SUS scores across different demographics (eg, age, language, and education) using *t* tests or ANOVA, as appropriate. The mean SUS score, with a 95% CI, will provide a precise estimate of usability, and significant differences between groups will be reported. If the mean SUS score falls below the acceptable threshold of 68, we will conduct qualitative follow-up interviews to explore specific usability issues. The findings will inform any necessary revisions to improve the CHATA pathway’s usability.

Diagnostic Accuracy

To evaluate the diagnostic accuracy of the CHATA pathway, we will calculate sensitivity, specificity, and positive predictive value (PPV; Multimedia Appendix 2). Sensitivity measures the pathway’s ability to correctly identify autism, calculated as the number of true positives divided by the sum of true positives and false negatives. Specificity, reflecting the pathway’s ability to correctly identify nonautistic cases, is calculated as the number of true negatives divided by the sum of true negatives and false positives; however, we may not have sufficient power to calculate this. PPV, which indicates the likelihood that a positive result truly indicates autism, is determined by dividing the number of true positives by the total number of positive results. These metrics will be assessed using data from the pilot cohort to evaluate the CHATA pathway’s accuracy in diagnosing autism in young children from diverse backgrounds.

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Interrater Reliability

A second clinician will review about 10% of the online pilot assessment recordings and compare their diagnostic decisions with those of the original clinician. For inter-rater reliability, we will analyze the consistency of ratings across independent reviewers who are blinded to the initial results. Out of 13 observations, randomly selected from 60, will be reviewed independently by a second clinician and supervised by a third senior clinician. All reviewers will be trained to ensure consistent understanding of the assessment criteria. The primary measure of inter-rater reliability will be Cohen κ for categorical data (diagnosis present or absent), with values indicating the level of agreement (eg, <0 as no agreement, 0.61-0.80 as substantial agreement). The analysis will determine the consistency of the CHATA pathway across different clinicians, with high reliability indicating reliable use of the pathway and lower reliability suggesting areas for improvement. Results will be reported with CIs, and significant discrepancies will prompt a follow-up review to address potential issues in training, criteria, or guidance.

Qualitative Analysis

We will transcribe and, if necessary, translate the interview data for analysis using reflexive thematic analysis with an inductive approach. This analysis will evaluate the acceptability, feasibility, usability, and barriers or enablers of the assessment tools. A feasibility study will gather insights from parents, caregivers, and clinicians on both online and in-person assessments to identify effective aspects and challenges.

Interviews will be conducted within 2 weeks of the online assessment, either in-person at Child Development Clinics or online based on participants' preferences. The interviews will be broad to capture diverse experiences, with topic guides (Multimedia Appendix 3) adjusted as new themes emerge. Qualitative data will be analyzed using NVivo [Lumivero] software, guided by the Theoretical Framework of Acceptability and the Theoretical Domains Framework [28,29]. The Theoretical Framework of Acceptability examines acceptability across 7 domains, including affective attitude and perceived effectiveness. The Theoretical Domains Framework integrates 33 behavior change theories and 14 domains to explore factors influencing behavior change, helping to identify barriers and enablers to implementation. We will use thematic analysis as outlined by Braun and Clarke [30], a widely used method for identifying, analyzing, and interpreting patterns of meaning within data. This approach is flexible and provides a detailed, nuanced understanding of the data, making it well-suited for the exploratory nature of this study. Since the study is qualitative and does not start with a pre-existing hypothesis, thematic analysis is particularly appropriate for uncovering insights.

The analysis will be reflexive, meaning it will involve continuous reflection and iteration by the research team. Out of 2 team members will independently familiarize themselves with the data, then regularly meet to discuss themes, resolve discrepancies, and finalize the themes and subthemes. The findings from this analysis will inform further iterations and refinements of the assessment tools to ensure they are as acceptable and effective as possible for both providers and recipients of the assessments.

Ethical Considerations

This study has been approved by the London Bloomsbury Research Ethics Committee (reference 22/LO/0751).

Measures to support participants include clear communication, confidentiality assurance, flexible scheduling, addressing recruitment barriers, providing interpreters, offering supporting letters for nursery absences, and incentives like vouchers.

Children flagged for concerns related to Adverse Childhood Experiences or safeguarding will be assessed using the standard pathway, following all ELFT safeguarding protocols.

Before participation, each participant will review the information sheet (Multimedia Appendix 4) and consent form with a research team member, who will address any questions. Consent can be provided in various formats: face-to-face, by post, email, video call, or telephone. Participants will indicate their preferred communication method and availability. Materials and consent forms will be translated into participants' preferred languages if needed. Non-English speakers will have the option to discuss the study with an interpreter through phone. Before the observation assessment, participants will receive detailed instructions and consent to record the session if desired. Researchers will be trained in consent processes, including assessing mental capacity. Parents will assess their child's willingness to participate; if a child shows discomfort or resistance, they will not be enrolled in the study.

Data will be anonymized once data collection is completed and before any analysis. Digital recordings from qualitative interviews will be securely transferred to a dedicated NHS server drive and permanently deleted from recording devices and video conferencing platforms once verified. Pseudonymized transcripts will be stored on this secure drive, separate from the original recordings, which will be kept in a password-protected folder. Participants' contact details will be stored in a separate, password-protected database on NHS servers. Hard copies of pseudonymized transcripts and research notes may be printed and kept in locked filing cabinets. Anonymized data will be retained on secure servers for 10 years before permanent deletion. All data handling will comply with the Data Protection Act 2018, with the participating NHS Trust as the Data Controller and Chief Investigators as data custodians.

Results

Chata project funding commenced in April 2021, ethics approval obtained in June 2022 pilot study data collection commenced in April 2023, and completed in Oct 2024. Pilot study end date is March 2025. As of Nov 2024, we had enrolled 57 participants in the pilot study and 12 in the qualitative substudy.

Discussion

Overview

This paper outlines our protocol for refining and evaluating a novel online autism assessment system tailored for children

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under 5 within East London's culturally and linguistically diverse population. The primary goal is to address the limitations of traditional autism assessments, which include high costs, lengthy procedures, and extensive waiting lists that often exceed 2 years, as well as reduced applicability to non-White and non–English-speaking groups. By the end of this study, we anticipate being able to describe the sensitivity, specificity, quantitative and qualitative usability, interrater reliability, acceptability, and feasibility of the CHATA pathway.

Feasibility and Strategies

Conducting this trial presents inherent challenges due to the complexity of autism assessments in young children and the diverse needs of our target population. We are focusing on developing tools that are effective across diverse cultural and linguistic backgrounds. By integrating feedback from PPI and using non–English languagebased methods, we aim to ensure that the tools are culturally and linguistically appropriate. This approach is supported by previous research emphasizing the importance of cultural sensitivity in diagnostic tools [31,32]. To maximize the use of available clinical time, we are collecting parental information online before the assessment and ensuring that direct observations are concise. Literature supports this approach, noting that preassessment data collection and streamlined observations can significantly improve diagnostic efficiency [33].

We recognize the potential risks associated with implementing a novel assessment tool, including issues with engagement and the accuracy of online assessments. To mitigate these risks, we have designed a comprehensive evaluation process that includes both quantitative and qualitative assessments. This involves calculating sensitivity, specificity, and PPV to ensure diagnostic accuracy and conducting interrater reliability checks to maintain consistency [16,25].

We are taking several steps to minimize risks. All clinicians involved in the assessment process will undergo thorough training to ensure consistent application of the assessment criteria. This is critical for maintaining the reliability and validity of the assessments, as highlighted in previous research [33]. We have established robust protocols for data handling to ensure confidentiality and compliance with the Data Protection Act 2018. This includes secure storage of digital recordings and pseudonymized transcripts, as well as safeguarding participants' contact details. Adherence to these protocols is essential for protecting participant privacy and maintaining trust [34]. The study will incorporate iterative feedback from participants and clinicians to continuously refine the assessment tools. This iterative approach, supported by research on diagnostic tool development, emphasizes the importance of ongoing evaluation, and adjustment to effectively meet user needs [35].

Conclusion

Our study aims to develop a novel online autism assessment tool that addresses the limitations of traditional methods while being adaptable to diverse populations. By incorporating a range of assessment methods, ensuring rigorous training, and adhering to data protection standards, we strive to overcome the inherent challenges of this trial. Although the study is not designed to assess the cost-effectiveness of the assessment, it will focus on refining the tools and evaluation methods. Next steps include optimizing the efficiency of the questionnaire by reducing the redundancy of items and including visual content that has been created with ethnically diverse populations. Future research will need to assess sensitivity and specificity in a larger sample, address the long-term impact and cost-effectiveness of the online assessment system, and evaluate its applicability to a broader population, including those with lower digital literacy. The findings from this study will contribute valuable insights into autism diagnostics and provide a foundation for future trials aimed at improving assessment practices and reducing waiting times for autism services nationwide.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
System Usability Scale.
[DOCX File , 287 KB - resprot_v14i1e55741_app1.docx]

Multimedia Appendix 2
Calculator for sensitivity, specificity, and positive predictive value (PPV).
[DOCX File , 235 KB - resprot_v14i1e55741_app2.docx]

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Multimedia Appendix 3
Topic guides for parents and clinicians.
[PDF File (Adobe PDF File), 1454 KB - resprot_v14i1e55741_app3.pdf]

Multimedia Appendix 4
Information sheets.
[PDF File (Adobe PDF File), 1748 KB - resprot_v14i1e55741_app4.pdf]

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Abbreviations

ADOS-2: Autism Diagnostic Observation Schedule, Second Edition
ASD: autism spectrum disorder
CHAND: Children with Autism in Newham – Diagnosis Service
CHATA: Children with Autism Technology Enabled Assessment
LBN: London Borough of Newham
MDT: multidisciplinary team
NHS: National Health Service
PPI: patient and public involvement
PPV: positive predictive value
SUS: System Usability Scale

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Protocol

Screening and Management of Obstructive Sleep Apnea and Daytime Sleepiness Among Professional Drivers in Tunisia: Protocol for a Machine Learning Study

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Abstract

Background: Obstructive sleep apnea (OSA) is highly prevalent among professional drivers; however, its true burden in this population remains underexplored and likely underdiagnosed.

Objective: This study aims to determine the prevalence of OSA and excessive daytime sleepiness (EDS) and identify their risk factors among a large representative sample of professional drivers in Tunisia. We will also evaluate the risk of accidents associated with OSA and EDS before and after the treatment.

Methods: This will be a population-based and prospective study of about 3000 professional drivers. Participants will receive a structured questionnaire to evaluate five main outcomes: the likelihood of OSA, EDS, drowsy driving, related sleepiness near misses and accidents, as well as work productivity. Validated self-report measures will be used to evaluate these outcomes. Participants suspected of having OSA or EDS will undergo sleep laboratory investigations, including a sleep study. Participants who have moderate-to-severe OSA will be recommended continuous positive airway pressure (CPAP) treatment. After one year of follow-up, all participants will be re-evaluated with self-report questionnaires. For those treated with CPAP, they will undergo the Maintenance of Wakefulness Test (MWT). We will evaluate several widely used machine learning models in medical diagnosis that are known for their high accuracy, including random forests, extreme gradient boosting, and deep neural networks, to predict the probability of OSA and its association with road traffic accidents.

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Results: A total of 127 male drivers participated in the study, with a mean age of 39.22 (SD 8.62) years. Most participants (76/127, 60.3%) had completed secondary education, 54.3% (69/127) were smokers, and the median BMI was 25.6 kg/m^2. A medical history was reported by 20.5% (26/127) of patients. The median driver experience was 8 (IQR 4.0-15.0) years. Among the drivers, 49 (39.5%) were working night shifts, and 30 (23.6%) were in hazardous materials transportation. Machinery (41.3%) was the most common mode of transportation, followed by trucks (34.9%), and light vehicles (22.2%). Notably, 11 drowsiness accidents were avoided. The overall score of presenteeism was 12.25 out of 100, whereas absenteeism was 1.74 out of 100. The overall daily activity impairment and productivity loss were 11.46 out of 100 and 12.76 out of 100, respectively. Overall, 30 (23.62%) cases were identified with either a pathological Epworth Sleepiness Scale or a positive Berlin score.

Conclusions: Our preliminary findings revealed that a significant proportion of drivers were at a high risk of OSA. Our results will pave the way for the creation of a clinical screening instrument that can identify sleep-wake disturbances in professional drivers. This is likely to have a significant impact on the legal regulations concerning driving fitness and road safety.

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KEYWORDS

professional drivers; Tunisia; obstructive sleep apnea; daytime sleepiness; drowsy driving; work productivity; epidemiology; machine learning; deep learning; neural network

Introduction

Obstructive sleep apnea (OSA) is a chronic breathing sleep disease characterized by recurrent episodes of complete (apnea) or partial (hypopnea) upper airway collapse during sleep, which results in repetitive pauses in breathing, brain arousals, sleep fragmentation, intermittent hypoxemia, and increased sympathetic nervous system activity. OSA is highly prevalent worldwide, with almost 1 billion adults (30-69 y) affected, with prevalence rates ranging from 9.3% to 77.2%, depending on the country [1]. Untreated OSA is associated with adverse health outcomes, including increased cardiovascular disease, metabolic diseases, impaired quality of life, mood disorders, and excessive daytime sleepiness (EDS) [2].

Professional drivers, including bus, taxi, and long-haul truck drivers, are an understudied and medically underserved population, despite their high rates of health issues. Compared to the general population and other occupations, professional drivers often have irregular sleep patterns and tend to smoke and drink more but exercise less, which predisposes them to several comorbidities such as obesity, cardiovascular diseases, cerebrovascular diseases, diabetes, musculoskeletal disorders, mental health disorders, uncorrected visual defects as well as sleep and vigilance disturbances. This increased morbidity seems to be associated with an increased likelihood of accidents and fatalities on the road [3].

In previous studies, professional drivers had been found to have high prevalence rates of OSA, ranging from 28% to 78% [4,5], likely because they tend to be obese, male, and middle-aged adults, the 3 most common risk factors for OSA. People with untreated OSA often experience daytime sleepiness, impaired psychometric vigilance, and do worse in driving simulator studies. Therefore, they are 2-3 times more likely to be involved in traffic accidents in comparison with those without OSA. Despite its heavy disease burden, medical awareness as well as appropriate screening and sleep study referrals of OSA in professional drivers are still lacking, leading to underdiagnosis and undertreatment.

There are about 67503 professional drivers currently employed in Tunisia. Most are men (93.8%), with an average age range of 40-49 years old [6]. According to the National Road Safety Observatory (Observatoire National de la Sécurité Routière), Tunisian roads registered 5796 accidents over 2023 with 1216 deaths [7], most caused by road transport professionals: heavy goods vehicle drivers, bus drivers, collective taxis, and cab drivers. Besides speeding, drunk driving, cell phone use and nonuse of seatbelts, distraction, and drowsiness behind the wheel were identified among the main causes of road accidents. Despite all these alarming statistics, to our knowledge, there are no studies available that have performed large-scale analyses on sleep and vigilance disturbance among Tunisian professional drivers.

The primary objective of this study is to determine the prevalence of OSA and EDS and their risk factors among a large representative sample of Tunisian professional drivers. The secondary objective is to evaluate the accidental risk associated with OSA and EDS before and after treatment. In addition, we aim to develop a reliable screening tool for detecting sleep-wake patterns among professional drivers.

Methods

Study Design and Settings

This is a population-based prospective cohort study that will be conducted by the Department of Respiratory and Sleep Medicine at Hedi Chaker University Hospital of Sfax, Tunisia, in collaboration with the Tunisian Occupational Health and Safety Institute. Data collection will be performed from May 1, 2024, to July 31, 2025.

Population

Participants' Eligibility Criteria

All professional drivers in the private sector, including light vehicle drivers, bus drivers, truck drivers, and bulldozer drivers, who have been working regularly for at least 1 year in any of the 24 provinces of Tunisia, are eligible to participate in the study. Public sector drivers are excluded from the study due to challenges in accessing this demographic in Tunisia, such as

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bureaucratic obstacles and lengthy approval processes required for research.

Noninclusion Criteria

Drivers of the public sector and those who refuse to participate in the study will not be included.

Sample Size

To ensure accurate and representative data, we estimated the required sample size using the following equation [8] as . "$Z_{\alpha/2}$" (=2.33) was the normal deviate for a 1-tailed hypothesis at a 1% level of significance; ("P=.28") was the prevalence of OSA reported in a previous study involving 406 professional drivers [4], "Δ" represents the precision which is arbitrarily fixed at 6%. Using the above formula, the estimated sample size was 3000 professional drivers.

Data Collection

Data collection will be performed using a 10-minute face-to-face questionnaire designed in literary Arabic. The questionnaire is introduced by a brief description including information about the study's purpose and authors, a statement on confidentiality, and specific instructions for each question if needed. It's composed of a series of forced-choice questions that cover 6 main topics: sociodemographic data, habits, health status and morbidities, and a series of validated self-report measures related to OSA, ESD, and work productivity. At the end of the questionnaire, 2 open-ended questions were added to collect any comments or further information that participants would share with researchers. To assess the reliability and validity of the questionnaire, a pilot test was performed with 40 volunteers before the implementation of the full survey.

Measures

Sociodemographic Data

Demographic data will be collected, including age, gender, weight (kg), height (cm), residence type (rural or urban areas), educational level, and marital status. We will also gather information about the occupational characteristics of the participants, such as seniority at work, engagement in night work, categories of vehicles, average hours per "day" or "week," and average miles driven per "day" or "week."

Habits and Morbidities

We will collect data on tobacco smoking, alcohol use, hypnotic consumption, and prevalent morbidities such as otolaryngologic, respiratory, cardiovascular, metabolic, autoimmune, and psychiatric diseases, as well as SARS-CoV-2 infection. Participants will also be asked if they were previously investigated or treated for any breathing sleep disorder (snoring, OSA, etc).

OSA Evaluation

Participants who do not have a pre-existing diagnosis of OSA will be evaluated using the validated Arabic version of the Berlin questionnaire (Cronbach α=0.92; Multimedia Appendix 1) [9]. This is a self-administered questionnaire designed to identify participants at increased risk for OSA. It consists of 10 questions that assess three categories of OSA symptoms and signs: (1) snoring and its intensity, frequency and inconvenience to others, as well as witnessed apneas during sleep; (2) EDS and its severity; and (3) history of arterial hypertension or obesity, as defined by a BMI 30 kg/m^2. In category 1, a positive score is defined as persistent symptoms (3-4 times/wk) in at least 2 questions about snoring. In category 2, a positive score is defined as persistent (3-4 times/wk) EDS, drowsiness behind the wheel, or both. In category 3, a positive score is defined as a history of arterial hypertension or a BMI 30 kg/m^2. Participants exhibiting more than one positive category are identified at an increased risk for OSA [10] (Figure 1).

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Figure 1. Flow diagram of the study population. AHI: Apnea-Hypopnea Index; CPAP: continuous positive airway pressure, MWT: Maintenance of Wakefulness Test, OSA: obstructive sleep apnea.

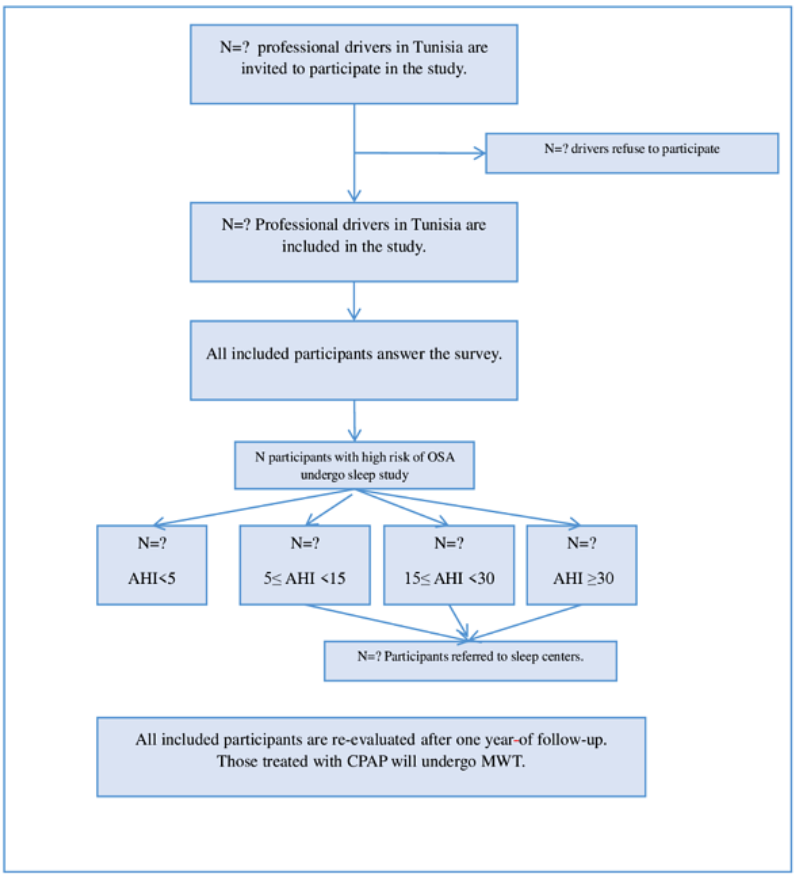

Daytime Sleepiness

All the participants will be asked to answer a validated Arabic version of the Epworth sleepiness scale (ESS; Cronbach α=0.86; Multimedia Appendix 2) [11]. This is a self-reported questionnaire, which is shown to provide a subjective assessment of the severity of daytime sleepiness over the last 3 months. The ESS is based on a list of questions referring to 8 daily life situations in which the participants rated their tendency to doze off or fall asleep on a scale of 0 (no chance of dozing) to 3 (high chance of dozing). The total ESS is the sum of responses to all individual 8 items and ranges from 0 to 24, with a higher score indicating a higher level of daytime sleepiness. In this study, an ESS score ≥11 is considered suggestive of EDS, while an ESS score ≥16 indicates severe EDS [12].

Drowsy driving is investigated by the following questions [13]: “Have you ever dozed off or fallen asleep while driving.” Each response is rated based on the frequency of drowsy driving episodes: “almost every day,” “1 to 2 times per week,” “1 to 2 times per month,” less than “1 time per month,” or “never or almost never.” For statistical analysis, participants are categorized into 2 groups based on how frequently they experience drowsy driving: those who drive drowsy at least once a month and those who do so less than once a month.

The occurrence of sleep-induced vehicular accidents and near-misses in the last year is recorded by the following question: “Have you ever had or avoided an accident due to drowsiness while driving?” A near-miss accident is defined as an event with a limited impact that could cause an accident (eg, drifting from the lane or crossing a white line) but did not result in any damage. An accident is defined as an event that results in physical injury or property damage.

Work Productivity

We will use an Arabic-validated edition of the Work Productivity and Activity Impairment Questionnaire: General Health version 2.2 (WPAI: GH 2.0; Multimedia Appendix 3) to measure how much the general health and symptoms severity affected work productivity and regular activities during the past week.

The WPAI-GH 2.2 is a set of six questions as follows: (1) Currently employed? (2) Number of hours missed from work due to health problems in the past week? (3) Number of hours missed from work due to other reasons in the past week? (4) Number of hours worked in the past week? (5) Degree to which health affected productivity while working (using a 0-10 Visual Analogue Scale)? (6) Degree to which health affected productivity in regular unpaid activities (using a 0-10 Visual Analogue Scale)?

Four main outcomes are generated from the WPAI: GH 2.0 and presented as percentages by multiplying the following scores by 100:

1. Percent of work time missed due to health=Q2/(Q2+Q4) for those who were currently employed.

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2. Percent impairment while working due to health=Q5/10 for those who were currently employed and worked in the past week.
3. Percent overall work impairment due to health=Q2/(Q2+Q4) + ((1–Q2/(Q2+Q4)) × (Q5/10)) for those who were currently employed.
4. Percent activity impairment due to health=Q6/10 for all respondents.

For questions 2 to 6, the recall period is one week. For participants who missed work and did not work in the past week, the percentage of overall work impairment due to health will be the same as the percentage of work time missed due to health [14].

Sleep Study

We will evaluate the OSA by an overnight type III polysomnography (Nox A1, ResMed). This will involve the monitoring of several physiological signals including airflow using nasal canulae, snoring by a contact microphone placed on the anterior neck, movement of the chest and abdomen wall using respiratory inductance respiratory belts, transcutaneous arterial oxygen saturation and pulse rate by pulse oximetry as well as body position and sleep-wake pattern using actimetry. Recordings will be manually scored according to the 2012 American Association of Sleep Medicine (AASM) manual for the scoring of sleep and associated events [15]. The analysis will include the Apnea Hypopnea Index (AHI), the 3% oxygen desaturation, as well as the percentage of recording time with transcutaneous arterial oxygen saturation of <90% (T90%).

The severity of OSA will be classified as follows: non-OSA for AHI of less than 5 events per hour, mild OSA for AHI ranging from 5 to 14.9 events per hour, moderate OSA for AHI ranging from 15 to 29.9 events per hour, and severe OSA for AHI of 30 or more events per hour [16].

Maintenance of Wakefulness Test

The maintenance wakefulness test (MWT) is conducted throughout the day, right after the overnight full polysomnography. Its purpose is to objectively assess the ability to stay awake in drowsy conditions. The procedure will consist of 4 trials, each lasting 40 minutes with a 2-hour interval between them. It will be conducted at 8 AM, 10 AM, noon, and 2 PM using the international 10-20 system electroencephalogram electrodes F3, F4, C3, C4, O1, and O2 referred to M1 and M2, with bilateral electrooculogram and submental electromyogram, according to AASM recommendations [17].

All the trials will take place in the same bedroom, which will be soundproof and insulated from external light. The bedroom will be equipped with dim lighting, and the ambient temperature will be recorded at the beginning of each trial and maintained as close to 22 °C (72 °F) as possible. Breakfast will be provided at least an hour before the first MWT trial and lunch immediately after the noon trial. During each trial, participants will be instructed to sit up in bed with their backs and heads supported by a bedrest cushion to ensure that the neck would not uncomfortably flex or extend during any sleep episode that might occur. Their backs will be positioned at an angle of 45°-90° relative to the bed, and their legs will be straight out with some flexing at the knees to maximize comfort. Before each trial, the participants will receive the following instructions: “Please sit calmly and try to remain awake for as long as possible. Keep your gaze straight ahead and avoid looking directly at the light.” The participants will not be permitted to use any extreme measures, such as slapping their faces or singing, to stay awake. The recordings will be monitored by a trained technologist who will observe the patient via digital video and mark eye-opening and closing on the recording Each trial will end when the participant falls asleep for the first time (known as sleep onset) or after being in bed for a maximum of 40 minutes if sleep onset does not occur. Sleep onset will be defined as 3 consecutive 30-second epochs of stage 1 or any single 30-second epoch of another sleep stage (II, III, IV, or rapid eye movement). If a participant sleeps for more than 10 minutes during the first 3 trials, they will be excluded from the test. A person’s participation in the test will end after the fourth trial. MWT sleep latency will be defined as the time from trial onset to the first epoch of any sleep stage. If the participants remained awake during the whole recording session, 40 minutes were used in the calculation of the mean sleep latency (MWT, 4 trials of 40 minutes each). A mean MWT sleep latency of 19 minutes or less will indicate EDS, as suggested by the French group [18].

Study Procedure

Our research teams will consist of 30 voluntary occupational physicians, with at least 1 representative from each of Tunisia’s 24 provinces. Members of the research team will recruit participants at their periodic medical visits.

When eligible individuals are approached for participation, they will receive a Participant Information Sheet (PIF), and the researcher will provide an oral explanation of the project. Participants will have the opportunity to ask any questions they may have. To ensure that drivers provide accurate information regarding their work productivity and traffic accident history, participants will be assured that their responses will be kept confidential, addressing any concerns they might have about their employment. If they consent to take part, they will be asked to sign an informed consent form. Following this, they will be invited to complete the survey. The initial meeting will last approximately 30 minutes.

Individuals who display a high likelihood of OSA or EDS will be personally informed and referred to sleep centers for appropriate investigations and management. This will mainly include a sleep study and specific treatment if required.

Continuous positive airway pressure (CPAP) will be indicated for participants with severe OSA regardless of symptomatology or moderate OSA combined with ESS of 11 or greater, drowsy driving, or a history of sleep-related near misses or vehicular accidents [19].

After 1 year, all participants will be re-evaluated for their BMI, daytime sleepiness, drowsy driving, sleep-induced near misses and vehicular accidents, and work productivity. Those treated with CPAP will undergo MWT, according to the French National Authority for Health (Haute Autorité de Santé [HAS]) [20]. Adherence, tolerance, and consistency of CPAP usage will

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be recorded. Good compliance will be considered for those who use CPAP for at least 4 hours per night, for more than 5 days a week, and on at least 70% of nights over 30 consecutive days. We estimate the final results will be available by September 2026.

Prediction of OSA Probability and Associated Road Traffic Accidents

Machine Learning Models

We will test several widely used machine learning models in medical diagnosis, known for their high accuracy. Predicting road traffic accidents using machine learning is an active area of research, with many studies leveraging various algorithms and datasets to improve accuracy and provide actionable insights. Previous studies on road traffic accident prediction have explored various machine learning algorithms. Prior studies [21-24] have shown that the best results were achieved using random forests, extreme gradient boosting, and deep neural networks. These methods have consistently demonstrated superior performance in terms of accuracy, robustness, and ability to handle complex, nonlinear relationships in traffic accident data. Random forests and extreme gradient boosting are particularly effective for structured or tabular data, offering interpretability and high predictive power, while deep neural networks excel in capturing intricate patterns in large-scale and high-dimensional datasets, especially when dealing with spatiotemporal or sequential data. Together, these methods represent the state-of-the-art in traffic accident prediction [21-24].

Preprocessing Data

The data will be split into 2 sets: a training set and a test set. The training set will be used to train machine learning models. The test set will be used to evaluate the models' performance. A crucial step is planned before training the classification models, which is preprocessing. The main steps we will apply can be summarized as follows:

1. Data cleaning: handle missing values and duplicates.
2. Feature encoding: convert categorical and text data.
3. Handle outliers: detect and treat outliers.
4. Feature scaling: normalize or standardize numerical features.
5. Data splitting: divide into training, validation, and test sets.
6. Feature selection: remove irrelevant or redundant features.

Model Evaluation

We will proceed with predicting OSA and associated road traffic accidents as a classification problem. In classification tasks, metrics, such as accuracy, precision, receiver operating characteristic area under the curve recall, and F_1-score are the most relevant because they provide different perspectives on a model's performance. Each metric highlights specific aspects of how well the model is classifying data, and their importance depends on the problem context and the cost of errors.

Statistical Analysis

The data analysis will be conducted using SPSS Statistics for Windows, version 23.0 (IBM Corp). To determine the normal distribution of data, we will use the Kolmogorov-Smirnov test. We will report continuous variables with normal distribution as the mean and SD, while nonnormally distributed variables will be reported as the median and IQR. We will compare the means of 2 and 3 or more groups of continuous variables that are normally distributed by using the independent samples *t* test and ANOVA, respectively. The median of nonnormal continuous variables will be compared using nonparametric tests such as the Mann-Whitney *U* test and Kruskal-Wallis. Categorical variables will be presented as counts and frequencies. We will compare the frequencies of categorical variables using Pearson chi-square or Fisher exact test, when appropriate. To determine independent risk factors of OSA, EDS, drowsy driving, near misses or vehicular accidents, and impaired work productivity, we will use univariate logistic analyses. We then fit significant variables as well as those previously reported in the literature into a multivariate regression model to delineate independent factors [25]. A P value of <.05 will be considered significant.

Ethical Considerations

Human Participants' Ethics Review Approvals

The study received approval from the Ethics Committee of the Hedi Chaker University Hospital in Sfax, Tunisia (Reference comité éthique 04/2024, April 17, 2024). All research procedures adhered to institutional guidelines, the Declaration of Helsinki, and good clinical practice standards.

Informed Consent Process

Participants were given sufficient time to consider their participation in the research. To ensure voluntary participation, efforts were made to minimize the possibility of coercion or undue influence. The informed consent document was written in clear language to help participants understand the purpose, procedures, risks, benefits, and alternatives associated with the study. Consent was documented through signed forms, which were securely stored to maintain confidentiality. Participants were informed of their right to withdraw from the study at any time without facing penalties or loss of benefits. This right was clearly stated in the consent document and communicated during the consent process. No waiver of consent was requested or granted for this study. All participants provided written informed consent before their involvement. Elsewhere, this study did not include a secondary analysis of existing data.

Privacy and Confidentiality

While the data collected in this study were not anonymized, rigorous measures were implemented to ensure the confidentiality of participants' information. All data were stored in a secure, password-protected environment, accessible only to authorized personnel involved in the study. Access to the data was strictly restricted to researchers directly involved in the analysis, and all personnel received training on confidentiality protocols. Electronic data were encrypted during both storage and transfer to prevent unauthorized access. Physical data storage areas were locked and monitored to deter

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unauthorized physical access. Participants were fully informed about the confidentiality measures during the consent process to ensure they understood how their data would be protected.

Compensation Details

Participants did not receive financial or material compensation for their involvement in this study. No identifiable images or data were included in the manuscript or supplementary materials.

Results

Sociodemographic and Health Characteristics

The study group included 127 professional drivers recruited between May and June 2024. The mean age of participants was 39.22 (SD 8.62) years, with 66.2% (83/127) of them being married. Most lived in urban areas and had completed either secondary (76/127, 60.3%) or university-level education (35/127, 27.8%). Rates of smoking and alcohol consumption were 54.3% (69/127) and 7.1% (9/127), respectively. The mean BMI was 25.6 (SD 4.22) kg/m², ranging from 15.15 to 38.87 kg/m² and 20.5% (26/127) of participants had chronic morbidity. One participant reported chronic use of hypnotics (Table 1).

Table 1. Sociodemographic and health characteristics of the study sample.

Variables	Study sample (N=127)
Age (years), mean (SD)	39.22 (8.62)
Male, n (%)	127 (100)
BMI, kg/m², mean (SD)	25.6 (4.22)
Education level, n (%)	
Primary school	15 (11.9)
Secondary school	76 (60.3)
University-level education	35 (27.8)
Marital status, n (%)	
Single	39 (30.7)
Married	83 (66.2)
Divorced	4 (3.1)
Residential environment, n (%)	
Urban	109 (87.2)
Rural	16 (12.8)
Smoking status, n (%)	
Current smoker	69 (54.3)
Former smoker	14 (11)
Nonsmoker	44 (34.6)
Pack-years, mean (SD)	12 (10.47)
Chronic alcoholism, n (%)	
Yes	9 (7.1)
No	118 (92.9)
Chronic hypnotic use, n (%)	
Yes	1 (0.8)
No	126 (99.2)
Chronic comorbidities, n (%)	
Yes	26 (20.5)
No	101 (9.5)

Occupational Characteristics

Regarding occupational characteristics, the average professional seniority was 8 (SD 8.07) years, ranging from 1 to 35 years. Their average workday was 8.8 (SD 1.91) hours, and they drove a mean distance of 148.2 (SD 209.58) km daily. Machinery operators formed the largest subgroup (52/127, 41.3%), followed by truck drivers (44/127, 34.9%). Night shifts were worked by

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49/127 drivers (39.5%). Among the drivers, 49/127 (39.5%) worked night shifts, and 30/127 (23.6%) were involved in transporting hazardous materials (Table 2).

Table 2. Occupational characteristics, sleep parameters, and work productivity of the study sample.

Variables	Study sample (N=127)
Occupational characteristics	
Light vehicle, n (%)	28 (22.2)
Truck, n (%)	44 (34.9)
Semitrailer truck, n (%)	2 (1.6)
Machinery, n (%)	52 (41.3)
Seniority (years), mean (SD)	8 (8.07)
Hours worked per day, mean (SD)	8.84 (1.91)
Hours worked per week, mean (SD)	49 (9.03)
Distance driven per day, km, mean (SD)	148.2 (209.58)
Night work, n (%)	49 (39.5)
Transport of hazardous materials, n (%)	30 (23.6)
Sleep disturbances, n (%)	
Snoring	26 (20.6)
ESS[a] score ≥ 11	24 (19.4)
Berlin Questionnaire positive (high Risk of OSA[b])	13 (11.1)
Sleepiness while driving	33 (26.8)
Sleep-induced near-miss vehicle accidents	10 (7.9)
Sleep-induced vehicular accidents	2 (1.6)
WPAI: GH 2.0[c] scores, mean (SD), %	
Absenteeism	1.74 (10.89)
Presenteeism	12.25 (24.85)
Productivity loss	12.76 (26.11)
Daily activity impairment	12.76 (23.45)

[a]ESS: Epworth Sleepiness Scale.

[b]OSA: obstructive sleep apnea.

[c]WPAI: GH 2.0: Work Productivity and Activity Impairment Questionnaire: General Health V2.2.

Sleep Disturbances, Work Productivity, and Activity Impairment

Almost one-fifth of the participants reported habitual snoring, and more than 1 quarter reported experiencing sleepiness while driving. Based on the ESS, 19.4% (24/127) of the drivers scored 11 or higher, indicating EDS. The Berlin Questionnaire classified 11.1% (n/N) as having a high risk for OSA. Regarding driving safety outcomes, 7.9% (10/127) reported at least one near-miss vehicle accident, while 1.6% (2/127) reported involvement in a vehicle crash. A total of 30 cases (30/127, 23.62%) were identified with either a pathological ESS (ESS ≥11) or a positive Berlin score, all these individuals were referred to specialized sleep centers for further evaluation and therapeutic management.

Professional drivers exhibited considerable variation in work productivity and activity impairment (Table 2). The mean score for absenteeism was 1.74% (SD 10.89%), while presenteeism had a higher mean score of 12.25% (SD 24.85%). The mean score for total productivity loss was 12.76% (SD 26.11%), indicating that both personal and work-related issues significantly affect overall productivity. Daily activity impairment, with a mean score of 12.76% (SD 23.45%), reflected the overall productivity loss.

Discussion

Strength of the Study

This cohort study has the goal of providing accurate information regarding the prevalence of sleep-wake disturbance among professional drivers, and how it affects work productivity and road safety. The study also aims to develop a simple and reliable screening tool for OSA among professional drivers and to improve treatment practices. It will be the first large-scale study of its kind in Tunisia, a country with a high rate of road accidents. Professional drivers are at high risk of OSA, which

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is often going undiagnosed or untreated, and it may contribute significantly to these accidents. Currently, there are no clear regulations in Tunisia regarding fitness-to-drive for individuals with sleep-wake disturbances, and physicians may not be sufficiently aware of these issues.

The study will use a range of validated self-reported measures in the local language to investigate sleep-wake status and work impairment, which will improve response rates and data accuracy. Participants who are deemed to be at high risk of OSA or have EDS will be referred to sleep centers for investigations which may help obtain a more accurate estimation of the OSA prevalence among professional drivers. Those diagnosed with moderate to severe OSA with EDS will be treated with CPAP and re-evaluated after 1 year of follow-up with self-report questionnaires and MWT. This will allow us to assess the impact of CPAP on daytime wakefulness and work productivity.

The study results will be shared with internal and external stakeholders to raise awareness about this issue and improve screening and treatment practices. It would also have a significant impact on legal regulations regarding fitness-to-drive in sleep-wake disturbances, which would improve road safety in the country. The study team believes that road safety should be a priority, and they hope that the results will help achieve this objective. The demonstrated cost savings and crash reduction reinforce the importance of standardized screening protocols, a point we emphasize in discussing policy recommendations for Tunisian transport sectors [26].

Limitations of the Study

This study has several limitations that should be considered. First, similar to the findings of Burks et al [26], we recognize that fear of job loss or related stigma may prevent drivers from disclosing their symptoms of obstructive sleep apnea. This underscores the importance of using anonymized data collection methods, collaborating with third-party health organizations, and implementing legal protections to encourage individuals to disclose their health issues without fear of negative consequences. In addition, using police reports to cross-reference accident data with objective crash records can help mitigate biases associated with self-reporting.

Second, the small number of women in our sample makes it difficult to ensure that our findings accurately reflect the prevalence of OSA and EDS among female professional drivers. To address this, we will analyze the data separately by gender to gain a clearer understanding of the situation. In addition, our method for screening snoring relies solely on self-reports from participants, which may underestimate its prevalence since some individuals may be unaware of their snoring, especially if they sleep alone. Finally, while type 1 polysomnography is considered the gold standard for diagnosing OSA, our financial constraints limit us to conducting only type 3 overnight polysomnography in this study, which may also lead to an underestimation of OSA prevalence.

Conclusion

This study is the first of its kind in Tunisia, aiming to investigate the prevalence of OSA, EDS, and work productivity impairment among professional drivers. The main objective of this research is to raise awareness among physicians about sleep and wake disturbances among drivers and to improve OSA screening and treatment practices. Furthermore, we plan to develop a simple algorithm for screening OSA during prerecruitment examinations or periodic visits. We also hope that the study's findings will help establish legal guidelines in Tunisia regarding the fitness-to-drive of individuals with sleep-wake disturbances. We firmly believe that ensuring road safety should become a political priority in cities, and we hope that our research will be beneficial in achieving this objective in our country.

Acknowledgments

The authors would like to thank all the participants for their time and willingness to be involved in this study. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

Authors' Contributions

SM contributed to conceptualization, methodology, investigation, data curation, formal analysis, and writing-original draft preparation. NK was responsible for conceptualization, visualization, writing, reviewing, and editing. RG handled methodology, visualization, and investigation. R Khemekhem was involved in writing-review and editing. AT performed data collection, visualization, and investigation. NA participated in investigations. SF was responsible for writing-review and editing. KK managed conceptualization, validation, and project administration. R Kammoun assisted with investigations. HB performed machine learning engineering. SK handled supervision, conceptualization, validation, and project administration. LDELG contributed to the methodology and investigation. SMB, AA, CA, and MT contributed to investigation.

Conflicts of Interest

None declared.

Multimedia Appendix 1
English version of the Berlin questionnaire.
[DOCX File , 276 KB - resprot_v14i1e70441_app1.docx]

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Multimedia Appendix 2
English version of the Epworth Sleepiness Scale (ESS).
[DOCX File , 418 KB - resprot_v14i1e70441_app2.docx]

Multimedia Appendix 3
English version of the Work Productivity and Activity Impairment Questionnaire: General Health V2.2 (WPAI: GH 2.0).
[DOCX File , 317 KB - resprot_v14i1e70441_app3.docx]

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Abbreviations

AASM: American Association of Sleep Medicine
AHI: apnea hypopnea index
CPAP: continuous positive airway pressure
EDS: excessive daytime sleepiness
ESS: Epworth Sleepiness Scale
HAS: Haute Autorité de Santé
MWT: Maintenance of Wakefulness Test
OSA: obstructive sleep apnea
PIF: participant information sheet
WPAI: GH 2.0: Work Productivity and Activity Impairment Questionnaire: General Health V2.2

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Protocol

Collecting and Sharing Person-Centered AI Clinical Summaries Across Frailty Services Provided by the National Health Service and Voluntary, Community, and Social Enterprise: Protocol for a Co-Design and Feasibility Study

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Abstract

Background: Due to its association with multimorbidity, frailty gives rise to multidimensional needs for different services. Too often, patient preferences and service encounter information are not adequately shared.

Objective: This developmental study aims to co-design, collect, and analyze encounter data from multiple community and primary-based multidisciplinary teams (MDTs) providing services for people with frailty to develop prototype large language models that can generate clinical and person-centered care summaries.

Methods: Engaging stakeholders in 2 primary care networks, we will co-design the large language model to ensure it meets local needs and preferences as well as infrastructure, information governance, and regulation requirements. General practitioners will identify 50 patients with frailty requiring MDT engagement. Three consecutive encounters between the patients and different members of MDTs will then be audio-recorded. Recordings will be transcribed into text for concept design and model pretraining. These data combine stakeholder engagement insights to develop sensitive artificial intelligence (AI) models responding to stakeholders' needs, workflows, and preferences. To generate the person-centered summaries, we will test 2 approaches to modeling the encounter data: graph-based modeling and hierarchical transformers. The AI-generated summaries will be compared to human-written summaries of the same encounter data and assessed for accuracy, quality, fluency, and person-centeredness. They will also be shared with the original MDT members for validation. We will capture inputs, processes, and outcomes across all key phases of the implementation journey to identify capability requirements, determinants of implementation (including key challenges and best practices to overcome them), and the value added by the technology.

Results: This protocol aims to review implementation evidence and engage stakeholders in co-design. This work package will aid the development of contextually sensitive, longitudinal, and AI-generated person-centered summarization tools. Model development will aim to achieve longitudinal person-centered summaries tested against MDT standards. If deemed suitable for deployment, optimum ways of integrating these summaries into shared care records will be explored with local key system leaders. Model evaluations will provide conclusive insights into such technologies' benefits and risks. As of August 2025, this study has not yet been funded, nor has ethical approval for the project been obtained. Consequently, dates of data collection and numbers of recruited participants are not applicable at this time.

Conclusions: Our protocol provides a robust method of co-designing, evaluating, and implementing a longitudinal AI medical summary tool. Including key stakeholders at multiple stages facilitates an iterative development strategy that is designed to solve implementation challenges as they emerge. This project fits within our long-term vision to deliver a multimodal AI tool that saves

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clinicians time and deepens the health care professional–patient relationship. Future studies should include a larger patient sample, video-recorded health care professional–patient encounters, and a more extensive longitudinal evaluation.

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KEYWORDS

artificial intelligence; AI; health care; future; medical documentation; data interoperability, person-centered care, multidisciplinary team; care coordination

Introduction

Background

Due to its association with multimorbidity, frailty gives rise to multidimensional needs for different services [1-4]. To reduce fragmentation and duplication of services and enhance person-centered care (PCC), information about patients' clinical needs, service encounters, and preferences should be shared across multidisciplinary teams (MDTs). Too often, this information is neither adequately recorded nor shared [5,6].

Evaluation of a "what matters to you" (WMTY) initiative for patients with frailty in one of our local trusts found that WMTY conversations were often happening too late and in the wrong setting (hospital as opposed to primary or community setting), did not always involve the right people (eg, general practitioners [GPs] and voluntary sector and care workers), were subject to key trade-offs concerning staff time (eg, peripatetic community staff working in geographically dispersed settings entering encounters notes at the end of the day), and were not shared with other members of the MDT. Indeed, due to organizational pressures prioritizing patient flow, many WMTY conversations are overly focused on facilitating hospital discharge.

However, important conversations are happening every day with members of MDTs (GPs, community nurses, social workers, domiciliary carers, volunteers, and pharmacists) from the community to hospital settings. Too often, this information is neither adequately recorded nor shared, leaving an untapped source of valuable information about patients' needs, beliefs, and personalized goals. Artificial intelligence (AI) tools such as large language models (LLMs) have been used to have a good effect on the summarization of synthetic patient-physician conversations [7]. However, these models tend to focus on clinical needs, drawing from notes written after a conversation, and offer little more than physicians' usual clinical summaries. Summarization models are needed to generate automatic summaries that include clinical needs and WMTY information from multiple MDT consultations without recall bias from health care professionals (HCPs).

Previous research and funding efforts have laid the groundwork for this proposal. We received support from the National Institute for Health and Care Research Invention for Innovation Funding At the Speed of Translation program to validate LLMs for generating automatic person-centered (PC) summaries of GP consultations [8]. Extensive engagement with patients and staff in 3 Plymouth practices and 1 Somerset GP practice informed our understanding that true PCC for this complex group of patients requires a better exchange of clinical and WMTY information into clinical records.

Our project proposes a feasibility study to co-design, collect, and analyze data to develop summarization models using an LLM to generate PC summaries of multiple primary and community service encounters among patients with frailty. Despite the good performance of current large language summarization models [7], implementation is challenging due to a lack of user engagement; ethical, legal, and data governance issues; and poor integration with existing data and workflows [9-11]. Importantly, intelligent data-driven care must also rely on unbalanced, missing, and incomplete clinical data drawn from imperfect real-world settings. Thus, careful preprocessing (eg, cleaning and substituting values) is essential to ensure good predictive modeling and prevent biases and unreliable outputs [12]. Our models, built on patients' and key stakeholders' preferences, values, and concerns, will be uniquely designed to generate interoperable PC summaries.

To this end, we will (1) engage stakeholders to understand technical, human factor, ethical, and regulatory barriers and enablers; (2) work with 2 primary care networks (PCNs) to audio record and transcribe primary and community encounters with 50 patients with frailty resulting in at least 150 audio-recorded conversations (eg, 3 encounters per patient); (3) develop and evaluate our LLMs ability to generate gold standard PC summaries that work for patients, carers, and MDT staff; (4) co-design implementation strategies and deploy pilot PC summary data into 2 PCNs; and (5) evaluate the summaries capacity to save HCPs' time, improve PCC, and patient well-being.

What Problem Are We Trying to Address?

The geography of older age in the United Kingdom is highly skewed toward coastal and rural areas, such as the Southwest Peninsula [13]. As people age, they experience more ill health and disability, resulting in higher rates of frailty and multimorbidity in these regions compared to urban areas. The British Geriatric Society, Age UK, and the Royal College of General Practitioners advocate for a proactive, PC, coordinated, and community-based response to frailty care [3]. However, individuals with frailty often navigate multiple care pathways, take numerous medications, and interact with various HCPs who do not communicate well with each other [5,6,14-17].

Key advocacy groups emphasize that improving communication between HCPs and emphasizing PCC is crucial to reducing service fragmentation. It is argued that PCC addresses patients' emotional needs; aligns care with their spiritual and personal beliefs, social activity desires, and self-care goals [18-22]; and

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creates personalized goals that help reconcile conflicting health objectives across an MDT [23]. At a minimum, then, HCPs should ask, “What matters to you?” instead of “What is the matter with you?” However, in practice, there are concerns that WMTY conversations in acute hospital settings have become overly standardized due to organizational pressures prioritizing patient flow, reducing patient engagement time, and increasing compassion fatigue [14,24,25].

Moreover, these conversations often occur outside the hospital, between patients and their GPs, community nurses, social workers, domiciliary carers, pharmacists, volunteers, and informal carers. They are not adequately recorded or shared. This reduces care continuity across MDTs and overlooks valuable patient information that could enhance shared decision-making [26,27]. Realistically, the health system’s capacity for PCC is reduced because, in acute settings, the pressured context reduces implementation effectiveness, and in community or primary settings, HCPs lack the time to write summary notes covering WMTY and clinical needs.

Finally, many technical requirements remain, and there are potential challenges in building and implementing LLMs in health systems. Particularly, the ethical, practice, cultural, and information governance barriers to recording encounters require close engagement with patients, practitioners, and managers to ensure the feasibility and acceptability of data collection and that summarizations work for all end users [28-30]. Consequently, this project aims to understand and address these AI-related health care implementation gaps.

Proposed Technological Solution

There is growing interest in generating medical summaries using LLMs to condense complex patient information from text or voice-recorded datasets [7]. For example, LLMs have also shown great potential in summarizing clinical reports [31]. However, only some have reached the quality required for clinical decision-making. In the United States, most summarization tools inform insurance and legal workflows and provide summary information for electronic patient records [32]. We similarly propose developing LLMs to summarize information rather than triggering clinical decisions. Even though multiple LLMs can generate high-quality clinical summaries [7], it is important to note that these models, such as the one used in this study [8], mimic what physicians do (ie, focus on clinical needs) as opposed to PC summaries. Our proposed solution addresses this gap in focus (Figure 1).

Figure 1. A diagram highlighting how the person-centered care (PCC) summarization tool would function. GP: general practitioner; PC: person-centered.

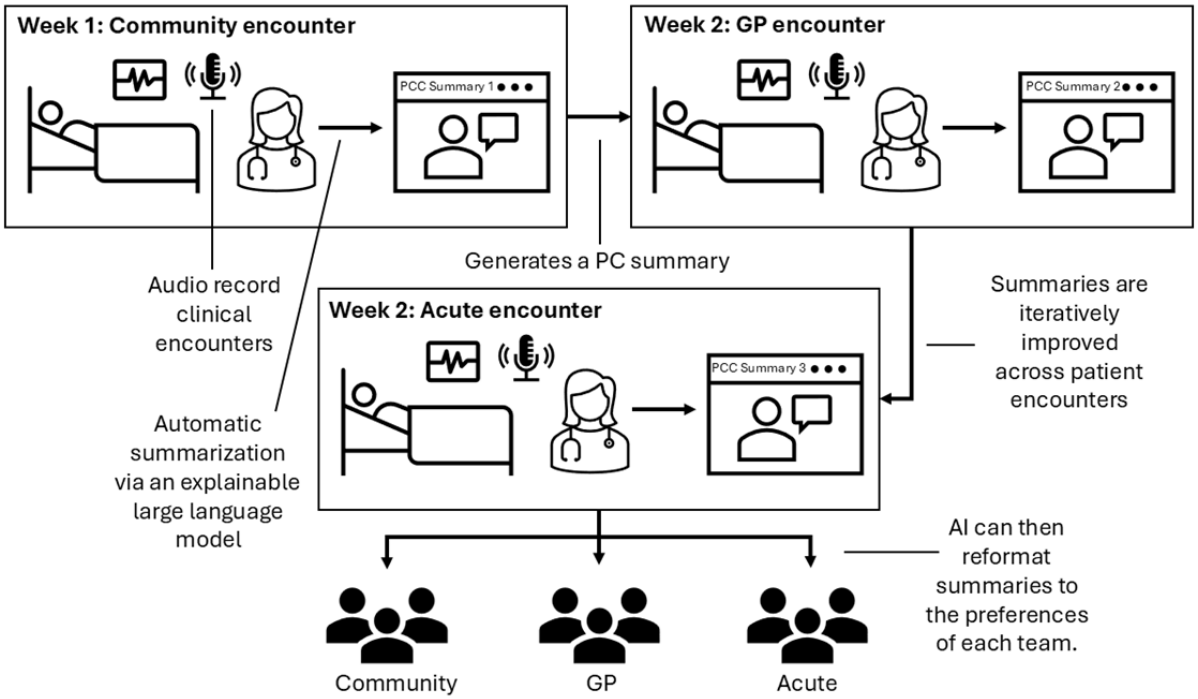

We evaluate whether LLMs can generate PC summaries from audio-recorded patient-physician conversations, fine-tuning the models to develop these summaries and then validating such models [8]. This modeling solves the problem of inadequate capture of PC information. However, achieving PCC requires developing or adapting LLMs for longitudinal summarization from multiple community or primary patient-physician MDT encounters. As part of an integrated, preventive, and community-focused care model, this ensures the meaningful transfer and acceptability of information across MDTs and hospital settings, and mitigates ethical, legal, and governance challenges

If successful, this technology will enhance PC community frailty care. Our PC and clinical data summaries will reduce administrative load, allowing more patient-clinician time in community or primary settings, which is crucial for PCC [5,33]. The synthesis and needs-based distribution of PC encounter data will also improve interoperability, enabling MDT practitioners to access relevant clinical and PC information instantly, reducing service fragmentation, and improving health outcomes [5].

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Proactive, anticipatory care for older people with escalating levels of frailty identified in primary care, supported by sufficient capacity for holistic MDT assessment, personalized care planning, and tailored interventions, can also significantly reduce hospital admissions and facilitate earlier discharge [26,27,34-38]. In the National Health Service (NHS) Devon alone, the number of bed days occupied by patients over 75 years old for more than 21 days accounted for 238,340 bed days in 2022, equivalent to 244 beds. Our summarization models could play a significant role in supporting community-focused preventive care.

Methods

Overview

We will develop model designs that respond to end users' requirements regarding usability, interpretability, explainability, risk aversion, and privacy concerns. By integrating end-user feedback and understanding the sociotechnical context, we aim to ensure that our model supports clinical efficiency and wins the hearts and minds of patients and staff. This comprehensive approach will address the unique needs of local populations and foster the adoption of advanced health technologies in diverse health care settings (see Figure 2).

Figure 2. A flowchart summarizing the 5 research stages and their objectives. LLM: large language model.

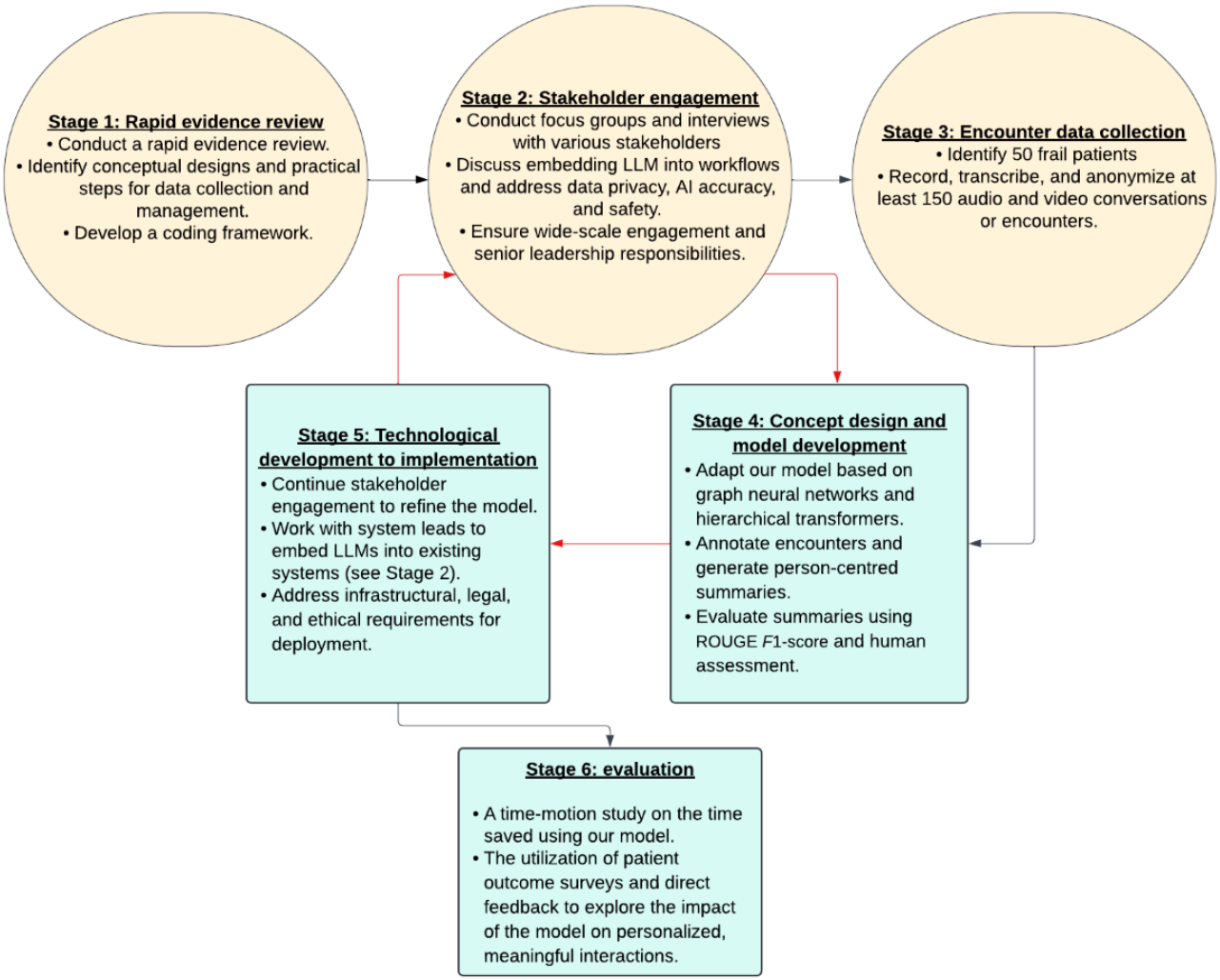

Stage 1: Rapid Evidence Reviews

Embedding AI-generated PC summaries into care records is more than a technical exercise. There are feasibility concerns around the initial collection of data (eg, audio recording, staff and patient concerns around privacy, and possible impacts on the nature of encounters), its storage and related information governance requirements (eg, who owns the recording equipment and data), and how summary data should best be presented and integrated into the clinical records. We will undertake a rapid evidence review of AI models focused on patient-clinician research to summarize the current qualitative evidence of common ethical, practice, cultural, and information governance issues. These issues will center upon collecting encounter data (ie, patient-clinician conversation) and integrating summarization AI models into health care systems.

The review aims to understand the best practices and potential barriers to integrating automatic clinician-patient summaries from this rapid review of evidence. This understanding should help establish our models' data collection, storage, and governance guidelines. It should also provide insights into potential low-fidelity model prototypes, preferences regarding the user-interface functionality, and the types of summaries that

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fit within existing end users' workflows and implementation strategies. Finally, this review of evidence will provide a strong coding framework for analyzing the stakeholder engagement section in stage 2.

Stage 2: Stakeholder Engagement

Two different focus groups will be held with a wide range of stakeholders to co-design and explore the ethical, practical, cultural, and information governance themes around the collection of patient-clinician conversations. Collected data from stage 2 helps form a key part of our participatory, co-design approach to model development and helps with later strategy development for integrating the functional prototype into a health care system. Findings from stage 1 inform the themes explored in the focus groups described subsequently.

Our first focus group's key stakeholders (n=15) will include patients and carers, voluntary, community, and social enterprise (VCSE) representatives, GPs, community nurses, social workers, domiciliary carers, pharmacists, and acute health of older people teams. The discussions are likely to include the following topics: (1) how to embed the AI summarization model into health systems; (2) ethical issues around compliance with UK data privacy laws, AI accuracy and safety standards, measures to safeguard patient-clinician relationships, and clinical autonomy, and minimize biases and medicolegal liabilities; (3) cultural issues, including stakeholders past interactions with AI technologies and ensuring the technology is culturally sensitive and adapts to diverse needs; (4) practical discussions that aim to forecast and address barriers related to relevance, acceptability, and usability of AI summarization models; and (5) how they can be integrated into existing workflows, considering ease of use and integration into daily practices.

Insights from these discussions will guide the refinement of the AI summarization model and inform the development of implementation strategies. We aim to develop a strong understanding of ethical, practical, cultural, and information to code usable, functional LLM models that fit the participating health systems' existing workflows, cultures, and concerns. From this discussion, we may realize it is important to code specific added measures to safeguard against harm to patient-clinician relationships, clinical autonomy, recall biases, and other medicolegal liabilities.

The second focus group (n=15) will consist of local information governance specialists, IT services, data specialists, managers (hospital, primary care network, and care homes), local authorities, integrated care boards, and regional NHS regulatory boards. This group aims to produce agreements, understandings, and adaptations to improve our models' viability and likelihood of implementation. The questions will likely explore ensuring wide-scale engagement, senior leadership responsibilities, adapting the basic concept model (Figure 2) to meet localized infrastructural needs, who owns the data collected, where it should be stored, and the potential of these data to be shared and accumulated across multiple nodal points in the MDT. These group discussions then shape model development to meet local data governance standards and agreements on who across the MDT will own the data produced by our LLM, where the data will be stored, and how best to ensure its interoperability. It should also identify senior leadership oversight and responsibilities, and required inputs from MDT managers through development and later implementation.

We know that technologies can fail because of poor design, which stems from a lack of understanding of the actual requirements of the end users. Thus, this phase involves embedding co-design into the project and winning hearts and minds. The stakeholder engagement stage aims to enhance our co-design efforts, creating a truly PC model that addresses the needs of patients, staff, managers, and infrastructure specialists. By improving our co-design process, we can foster support and understanding, ultimately aiding in the successful development and implementation of our model.

Stage 3: Encounter Data Collection

Audio recordings of encounters between different members of an MDT team and patients with frailty will occur in 2 different PCNs, one between months 6 and 12 and another between months 9 and 15. The first PCN is more experienced in cross-team data sharing and deploying AI solutions and is more prepared to test the feasibility of audio recording encounters than the second PCN, which is more digitally immature. If necessary, access to these patient participants may also be supported by the Clinical Research Network Southwest Peninsula, which can assist the team in contacting other GPs who can help identify suitable and eligible research participants.

Working with GPs, we will identify 50 patients with frailty who require MDT engagement and ensure that MDT members know the project, its aims, methods, and data management protocols. To mitigate the limitations posed by our relatively small sample size, we will apply purposive stratification, ensuring a balanced representative sample across key frailty-associated factors, such as differing clinical frailty scores, typical comorbidity clusters, and social determinants.

To capture a patient's data from multiple encounters between them and their community-based HCP, the research team will liaise closely with each patient participant and their community carers, encouraging them to provide updates on each future engagement over 2 months to record 3 to 5 consecutive encounters. Each patient will need to agree to participate in at least 3 encounters.

When the researcher is informed of an upcoming encounter, a consenting HCP or patient will notify the researcher of the time, date, and location. The researcher will then attend and record the conversation using high-quality audio-recording devices (Shure SM7B microphones). Patients will need an individual identifier to link encounter data from different MDT members and validate summarizations. Along with these identifiers, each encounter will be identified sequentially, from the first recording to the last. Each patient will participate in at least 3 encounters with HCPs (MDT members), resulting in approximately 150 conversations or encounters. All recordings (with anonymized identifiers) will be transcribed into text for concept design and model pretraining.

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Stage 4: Concept Design, Model Design, and Validation

Data from stages 1 to 3 will be collated, synthesized, and shared with the model developers to adapt an AI summarization model that responds to different stakeholders' needs, workflows, and preferences.

PC AI summarization has been previously defined by Ponce Ponte [8] as a model capable of summarizing clinical issues as well as patients' preferences and values. The exact themes of patients' preferences and values will be derived from further public and patient involvement and engagement (PPIE) with patients and staff in 3 GP practices involved in prestudy PPIE, across 2 counties in southwest England.

Annotators will be trained to generate PC summaries based on audio-recorded conversations between patients and HCPs. This will be carried out following the sequence of a patient's encounters with their HCP's (start visit 1, continue to visit 2, etc).

Two approaches have successfully generated automatic summaries from multiple documents: (1) graph-based modeling and (2) hierarchical transformers. On the basis of these approaches, we will adapt our patient-centered AI summarization model [8]. Multiple document summarization approaches are necessary because conversations between patients with frailty and MDT members will accumulate over time. The first model will be developed using graph neural networks, which follow an extractive summarization approach. We will develop a graph structure by encoding words and sentences and generating words and sentence nodes related to an edge. The edge represents how strong their relationship is and will be calculated with the term frequency and inverse document frequency method [39]. This learning will be done per encounter via an iterative process. Once a second encounter is completed, the process will be conducted again. This time, a third level of node will be created, the document node, and this will be included in the learning process to generate a new graph structure. This will continue until the last encounter. After every encounter, we will use the graph structure to extract sentence nodes, follow a trigram blocking for decoding, and generate an extractive PC summary. The training will be done to predict the sequence of sentences from the gold-standard PC summary.

The second model to be tested is based on a hierarchical model. We will develop this by comparing and integrating multiple pretrained LLMs, for example, LLaMA (version 3.1), Falcon, Mistral, and bidirectional encoder representations from transformers and its variants (BioBERT, etc) [40]. Our method to compare these models will require evaluating each using a Recall-Oriented Understudy for Gisting Evaluation ROUGE F_1-score, assessing their capacity to compare PC themes. We will then add a hierarchical adapter on the encoder layer to contextualize sentence semantics or meaning. The overall objective of the model is to predict the next word. Then, to generate the PC summary, we will use retrieval-based selection to choose the most salient content using sentence similarity.

We will automatically evaluate the quality of these summaries using ROUGE F_1-score. This metric compares the AI-generated summaries against our gold-standard summaries. Trained, blinded evaluators will perform human-based evaluations. They will assess their informativeness, fluency, quality, and person-centeredness (number of PC themes captured by the summaries).

Stage 5: From Technological Development to Pilot Implementation

After stage 4, we continue to engage with key stakeholders until we reach a saturation level whereby the model's development either deeply reflects the complexity of localized needs and preferences in the concept design, making the technology more suitable for deployment and integration, or is deemed unfeasible.

Doing this will require repeated prototype engagement and daily discussion sessions with HCPs using the system. This session will be conducted specifically with our first focus group, including patients and carers, VCSE representatives, GPs, community nurses, social workers, domiciliary carers, pharmacists, and acute health of older people teams. Each session will include an introduction explaining the purpose of improving the tool and meeting clinical needs, a brief demonstration, an opportunity to test and use the prototype in small groups, and then report on their experiences. The group of 15 participants will then be subdivided into 5 groups of 3 (20%) participants each and asked to complete the following tasks: use the device to generate a summary based on a prerecorded pseudoanonymized patient-clinician interaction, review its associated AI-generated summary, edit it, and integrate it into an electronic patient record. After completing these tasks, prototype engagement participants will return to the larger focus group to share their experiences, challenges, and suggestions. Topics will likely include ease of use and intuitiveness, clarity and relevance of the summaries, to what extent they could imagine the technology fitting within existing workflows, responsiveness of the tool to correction and feedback, consistency and acceptability of the terminology, and recommendations for enhancements. This process will be repeated at least twice but primarily until saturation is reached, which is defined as broad HCP satisfaction with the usability of the devices.

After saturation, if stakeholder support for these model implementations exists, the research team will then work closely with the second focus group from stage 2, which includes local information governance specialists, IT services, data specialists, managers (hospital, primary care network, and care homes), local authorities, integrated care boards, and regional NHS regulatory boards (n=15). Across 3 sessions, this group will aim to create bespoke implementation strategies to reflect the 2 PCN systems' infrastructure limitations, support teams' specific needs embedding the models into daily practice, and deliberate methods of providing an ongoing support system for later pilot-testing and wider-scale deployment. In session 1, the group outlines a strategy to implement our system into their existing workflows and IT systems and identifies necessary adjustments to enable the model's integration. Session 2 will ensure that the previous strategy meets regulatory and ethical guidelines, and finally, session 3 outlines a package of technical support and seeks to achieve agreement on responsibilities and channels for accessing this support channel and who provides the training.

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After ensuring that both adopters and key stakeholder implementers are happy with the technology and that it could be implemented into their health systems, we will reach out to each clinical team engaged in its implementation, alongside local PCN technology deployment and support specialists, to finalize an agreed upon implementation and evaluation timeline and ensure they are happy with our proposed evaluation objectives and metrics (see stage 6 described subsequently). Once approved, we will engage each team and deliver essential training on using the system. This training will include preparing the microphone, recording, creating the PCC summary, sharing the summary in the electronic patient record, and building on past summaries with new clinical encounters for the same patient. Once all teams are happy with setting up, creating, sharing summaries, and accessing support, final verification of resources, allocation training, and support will be conducted, and then the AI system will go live.

Stage 6: Evaluation of Implementation

Overview

The final part of this study will evaluate the implementation of the AI summarization model within a health care setting. This evaluation will explore whether the summarizations positively impact HCPs and patients. To do this, we will analyze the impact on clinical workflows, patient outcomes, and perceptions of the impact on perceived workload; assess the usability and acceptability; and determine whether any biases or medicolegal risks emerge and if the system positively impacts personalized and meaningful patient-clinician interactions and relationships.

Time-Motion

This evaluation will first address the impact on clinician workflows. The process will include a time-motion study with 9 HCPs based across primary care clinic (n=3, 33%), intermediate care (n=3, 33%), and domiciliary care (n=3, 33%). We will observe HCPs in their respective work settings under 2 conditions for each participant. First, we observe HCP-patient interaction and their documentation process with standard non-AI methods. Second, we observe HCP using the AI PCC summarization system.

To do this, the research team breaks down the process into stages, one measuring normal practice workflow. In normal practice, stages include (1) reviewing previous records before engagement; (2) engaging in HCP-patient interaction; (3) documenting the consultation in the electronic patient record postencounter; and (4) HCP submitting, sending, or embedding the summary into the electronic patient record. Our AI system includes the following stages: (1) reviewing AI PCC summary before a patient engagement; (2) setting up the recording device; (3) engaging in the HCP-patient interaction; (4) packing away the device; (5) HCPs checking the summary for acceptability; and (6) HCP submitting, sending, or embedding the summary into the electronic patient record. We will then analyze the data to identify (1) whether the implementation of our system reduces the time taken and (2) if there are further opportunities to streamline and better embed the technology into a care pathway [41,42].

Acceptability and Usability

To evaluate the model's usability and acceptability, we also apply a longitudinal mixed method approach involving semistructured interviews (n=15) and the System Usability Scale (SUS; n=20). Participants include HCPs (eg, general practitioners, community nurses, social workers, and domiciliary carers). Longitudinal interview and questionnaire assessments will occur at 3 time points: baseline, 1 month after intervention, and 6 months after intervention.

Semistructured interviews will be conducted face-to-face or via videoconferencing platforms (n=15) to receive feedback from HCPs to help understand their perceptions of whether the model has streamlined the documentation, perceived workload, and ease of use; how effectively the model adheres to ethical, privacy, and information governance standards; and any challenges encountered and suggestions for improvement. Importantly, as interpretability and explainability are now a mandatory regulatory requirement in various regulatory contexts, such as the European Union, participants will discuss their comprehension of the rationale behind AI-generated recommendations, clarity and interpretability of outputs, and ability to identify potential inaccuracies or biases. This identification of challenges will be documented, and the model adapted accordingly [43].

Immediately after the interview, participants will complete the SUS, a validated 10-item questionnaire that measures perceived usability. Responses are scored between 0 to 100. Higher scores indicate better usability [44-46]. Finally, this process will be repeated in our longitudinal assessments at 3 time points: baseline, 1 month after intervention, and 6 months after intervention. Together, these provide a helpful insight into the model's usefulness as it becomes more deeply embedded into day-to-day practices.

Impact on PCC

To evaluate the impact of AI summarization on PCC, interviews with HCPs (n=10) will assess their perceptions of how the system influences their ability to provide PCC. These interviews will explore, when compared to a standard practice, if HCPs perceive an improvement in their capacity to understand patient priorities through the summaries, whether the summaries enhance their engagements and enable what they regard as more PCC outcomes, helped patients become active participants, and whether they felt they had the necessary skills to use the WMTY summaries [47].

Patient Benefit Measures

To evaluate the impact of the summarization tools on the quality and delivery of PCC, we will use multiple self-reported and validated measures, each capturing different aspects of potential patient benefit. Numerous tools are available for these purposes; however, the EQ-5D, collaBORATE tool, and Meaning in Life Questionnaire have been chosen as they are fast, reliable, and sensitive to changes over time. Two groups are needed to evaluate the impact: a control group (standard care without AI summaries) and an intervention group (care incorporating the AI-generated PCC summaries). Patients in both groups will be matched based on demographic and clinical characteristics to

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minimize confounding variables. Longitudinal assessments will occur at 3 time points: baseline, 1 month after intervention, and 6 months after intervention.

The EQ-5D is a standardized health-related quality-of-life measure that evaluates mobility, self-care, usual activities, pain or discomfort, and anxiety and depression [48]. The collaBORATE measure of patient-reported shared decision-making will help us evaluate how the AI-generated PC summaries facilitate the development of care plans aligned with patient values and preferences [49]. Finally, recognizing PCC involves developing personalized goals that produce health outcomes and improving a patient's perception of meaning in life [21]. The Meaning in Life Questionnaire assesses the extent to which the AI system influences patients' sense of meaning [50,51]. Patients in both groups will complete this questionnaire at baseline, 1 month, and 6 months postintervention.

A total of 100 participants will be recruited—50 (50%) participants in the control and 50 (50%) participants in the intervention group. Participants will be sourced from the 2 PCNs as in other stages of the study.

Risks

Participants' well-being will be prioritized with minimal risks through careful study design and continuous monitoring. Participants can contact the principal investigator or data protection team with any data collection concerns. Interviews are scheduled to last 40 to 60 minutes, with focus groups lasting between 60 and 120 minutes. Recognizing that these time lengths may be demanding for older people and busy frontline clinicians, we implement the following mitigation strategies: provide flexible scheduling to minimize disruption; clear objectives and structured questions to make discussion efficient; offer frequent breaks to reduce fatigue, allowing people to step away if necessary; and provide options for remote participation. The facilitator will also continuously monitor participants during the session and be prepared to pause or end the session if fatigue is noticed. All interviews and focus groups will be conducted in private rooms to ensure privacy.

This research focuses on co-designing our AI models for end users, ensuring functionality and acceptability of audio recording clinical encounters to patients, clinicians, and health systems, and ensuring that these devices ethically and safely share data across an MDT. Consequently, the interviews avoid areas of cultural and psychological sensitivity and are low risk. We also expect that MDT members and hospital managers will have full ability to understand and consent, given their professional involvement in the program, its implementation, and associated improvements.

However, the participant pool will involve an older adult population, often with multimorbidity conditions, including dementia, learning disability, or mental health issues. Therefore, additional protection will ensure their safety and comfort, such as providing breaks and a supportive environment. In distress, participants will be directed to appropriate support services such as the Samaritans. The researcher will also follow a careful protocol to assess capacity to make decisions in line with the Mental Capacity Act 2005, which states that "a person must be assumed to have capacity unless it is established that he or she lacks capacity."

Patients and staff may also disclose risks to themselves or others, such as professional malpractice and complaint issues. Thus, the research team will be updated with their mandatory safeguarding training. They will also have completed a Disclosure and Barring Service check before working with study participants. Using honorary NHS contracts, the research will also use NHS email accounts to ensure confidentiality and security when conveying sensitive material or collected data. They will also have a policy in place should the researchers become aware of any risks, safety issues, or concerns (ie, self-injury or suicidality) during interviews or focus groups. This escalation policy is taken from Devon's Safeguarding Adults Partnership.

Study Governance

A research ethics committee will review the study, and the team will obtain approval from the Health Research Authority through the Integrated Research Application System to protect participants' rights, safety, dignity, and well-being.

A research management group will oversee the research. The research management group will be a learning partnership between 2 NHS integrated care boards, their subsidiary PCNs, and the university. This partnership group will oversee the delivery and direction of the research and meet regularly (bimonthly, every 2 weeks). Its membership will include a GP from each PCN, a deputy director of innovation and transformation, a chief clinical information officer, and senior researchers at the university's center for health technology. Distributing the leadership ensures commitment and buy-in from the 2 organizations and a true partnership initiative.

Ethical Considerations

This project has not yet been submitted to an institutional review board or the NHS Research Ethics Committee.

Informed Consent

HCPs and other associated stakeholders (n=30), excluding patients and carers, will be approached initially via an appropriate email introduction for an interview or focus group. These stakeholders will be identified within the 2 PCNs previously discussed. Initial contact will likely be bridged via a collaborating GP or one of their administrative team members. The introductory email will clarify the study's aims and objectives, the organization's consent to participate, the voluntary nature of participation, and the date by which they can withdraw their contributions without providing reasons or facing any consequences.

A participating HCP will first approach older patients (n=50) from the 2 PCNs. Using the participant information leaflet, they will provide an overview of the research. If interest is shown, a team researcher will provide further details, including the purpose of the research, a participant information sheet, and a consent form. These sheets will be adapted to ensure readability for older people, breaking down the stages of co-design, recording encounters, and evaluation. The researcher will explain the participant information sheet, the importance of the

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participant's input, data use, sources for further information or queries, and withdrawal options. After 24 hours, participants can ask additional questions and provide consent.

Data Management

The research team will comply with the Data Protection Act 2018 requirements regarding collecting, storing, processing, and disclosing personal information. Electronic personal data (eg, consent forms) will only be stored on the university's mainframe computer network, which is secure and password-protected. Paper copies of personal data will be destroyed using the university's confidential waste management service. Each participant will be given a unique ID number that will be kept separate at the first stage of data storage. The key to IDs will be held in a safe and password-protected file on the university's secure main computer drive. This password will not be shared with anyone except the principal investigator and their research assistant. The local custodian of the data will be the principal investigator at the university. In line with current recommendations around NHS-based research, all personal data are destroyed 3 months after the study's completion.

Audio-recorded interviews and clinical encounters will be stored securely on PCN services and computers. The research team will transcribe all audio recordings, and all data will be pseudonymized. All audio-recorded conversations will be anonymized using Adobe Audition audio-editing software to silence location names and alter the voice's pitch. Once anonymized encounters are transferred securely to the university's OneDrive database on password-protected, encrypted university laptops. Subsequently, anonymized clinical encounters will be shared with the research team (n=4) and inputted into the AI model (n=150). No confidential or patient-identifiable data will leave an NHS setting at any stage.

Similarly, data related to developing and training LLMs will be stored securely on the university's secure encrypted servers, including model configurations, training data, and evaluation metrics. Safeguards will be in place to ensure the integrity and confidentiality of the modeling data following institutional data security policies. In line with current recommendations around NHS-based research, this research data will be retained for 5 years after the study. After this, it will be archived in the university's electronic archive and research repository and another suitable national or international data repository for long-term curation.

Results

Stages 1 and 2: Review and Stakeholder Engagement

The rapid evidence review will provide detailed qualitative insights regarding feasibility, privacy, interpretability, explainability, and information governance concerns. This understanding establishes foundational guidelines for data collection, storage, model development, and governance strategies.

Our stakeholder engagement groups then aim to produce contextually sensitive insights that enable the development of our model and implementation strategy that reflects the needs, capacities, and constraints. Our first discussion aims to develop a strong understanding of ethical, practical, cultural, and information to code usable, functional LLM models that fit the participating health systems' existing workflows, cultures, and concerns. For example, from our first stage 2 discussions, we may realize it is important to code specific added measures to safeguard against harm to patient-clinician relationships, clinical autonomy, recall biases, and other medicolegal liabilities. Our second discussion, with managerial and technical stakeholders, aims to shape model development to meet local data governance standards across the MDT, establishing clear agreements regarding data ownership, storage, and interoperability.

Stages 3 and 4: Model Development and Validation

This stage collects audio recordings from approximately 150 MDT encounters with 50 purposively sampled patients with frailty. By collecting 3 consecutive encounters with each patient, we will yield a robust dataset for beginning to test, train, and validate our summarization model. This validation process explores the models capacity to improve the HCPs' understanding of their patients' PCC needs over time. Our dataset will also represent a range of frailty levels, comorbidity clusters, and demographic characteristics, ensuring comprehensive model training. This representativeness should suffice for early-stage model training.

Graph-based and hierarchical transfer models will be developed and compared after encounter collection. Specifically, we will produce a comparative performance metric, using ROUGE 1, for each model against a human-generated gold-standard summary. The results will indicate the strengths and weaknesses of each approach, guiding further model refinement. Human evaluators will also qualitatively assess the AI-generated summaries, providing insights on their accuracy, quality, fluency, and person-centeredness. Overall, this process will identify which model most effectively summarizes PC information from longitudinal MDT encounters and carefully reflects the unique needs of PCNs and their related community assets.

Through repeated engagement sessions, prototyping evaluations by MDT members will refine the usability and capacity of implementing the AI summarization tool. This iterative prototyping, codeveloped with local stakeholders, should enable sufficient alignment with workflow integration, IT system compatibility, regulatory compliance, and necessary training and support infrastructure for implementation. This process will also help identify necessary training needs. Stage 5 should produce an implementation strategy and training program that reflects consultation with HCPs and management teams. If a feasible prototype and implementation strategy are not achieved, a comprehensive report will be produced outlining key problems and potential solutions for implementation attempts.

Finally, if stage 5 is successful, our stage 6 evaluation will clarify the time saved, usability, acceptability, and the patient and clinical benefits of the model. Time-motions will evidence the potential time saved compared to HCP's usual documentation processes. The SUS scores and thematically analyzed qualitative data identify the model's degree of usability and acceptability. In addition, analyzed interview data indicates whether HCPs perceive an improvement in their PCC practices.

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Finally, we will understand the benefit of the tool for patients, such as its impact on quality of life, meaning in life, and the patient's perception of PCC, via multidimensional surveys.

Discussion

Anticipated Findings

Using audio equipment to record clinical encounters and automatically summarize them to elicit key PC information can reduce the administrative burden on staff across the MDT [7,52,53]. Technology development in this area should allow staff to spend more time on face-to-face engagements and less on administrative tasks. It may afford practitioners more time for PCC-related training schemes. Furthermore, with less need to record the notes and thus more time to allow conversations to flow naturally, it may act against tendencies for PCC to become overprotocolized regarding questions asked and notes taken [14,33,54]. In essence, emerging summary models can increase the time HCPs engage in meaningful patient interactions, thus improving patient reports of PCC [14].

However, this project aims to make an exciting development in LLM modeling to support PC, community-focused health care for older adults. At present, summary notes are being developed to combine diagnostic decision support systems to highlight the most relevant clinical information [55], developing intelligent methods to structure, organize, and improve the accuracy of summaries [56] and reduce critical fact omissions and hallucinations [57]. We have begun exploring how to enhance the relevance and usability of summaries for different clinical teams [58,59]. However, these models mimic current summarization practices and do not generate PC summaries. Alternatively, our model integrates longitudinal encounter summaries to iteratively improve the PC summary and adapt the summaries for varied MDT needs.

We aim to produce effective models to support integrated PC frailty care pathways. These summaries would provide HCPs with an iteratively improved understanding of "what matters" to a patient, developed through successive encounters. HCPs, no longer reliant on poorly transmitted or incomplete WMTY data from across an MDT, will receive an instant, up-to-date, meaningful PC summary in a format that reflects HCP and patient preferences. This should make it easier to organize and prioritize the MDT's objectives based on the superordinate preferences and values of the patients [5,23]. This enhancement in care coordination is expected to improve clinical outcomes, enhance patient experiences, reduce service fragmentation, and increase the meaningfulness of the work for health care staff [22,60,61].

In addition, this project helps improve data-sharing capacities across the MDTs (voluntary sector and primary, acute, and social care) and the implementation of novel AI and audio-recording technologies [62]. This integration is invaluable with a growing array of data points from wearables, smart devices, and environmental sensors that could help identify and support preventive health care (eg, intervening at the early signs of deterioration and spotting anomalies in usual behaviors, such as diet) [63].

Limitations

Potential limitations to this study can be identified. Most important is the limited sample size of 100 patients (control group: n=50, 50%; intervention group: n=50, 50%). Such a sample size may limit the generalizability of our findings, especially given the heterogeneous and complex nature of a person with frailty's health presentations when they encounter the health system. In a bid to mitigate this potential generalizability, such as UK studies on population with frailty, we use purposive stratification for its small sample, ensuring our research reflects various key characteristics, such as severity, age, comorbidity clusters, and living circumstances [64-66].

In addition, conducting our stakeholder engagement and co-design with only 2 PCNs while making the project more feasible and inexpensive may limit the generalizability of our results for similar development and implementation projects in different health systems or elsewhere in the United Kingdom. Nonetheless, the study design includes a diverse patient population, various clinical settings, and a range of key stakeholders, from macropolicy to meso-organizational and microclinical levels.

Moreover, the success of this project depends on overcoming significant technical challenges. For example, aiming to generate increased PCC summary complexity across iterative engagements will require continuous feedback and human assessment to ensure accuracy and reliability. In addition, the United Kingdom's NHS has fragmented electronic patient record systems, which often differ from primary care, social care, voluntary sector, and systems records. This variation in functionality and compatibility will present a challenge for effectively transmitting these data across different platforms, particularly at the implementation stage. Our co-design and stakeholder engagement section seeks to overcome these challenges using interim solutions, such as a stand-alone application or partial integration.

Our study lacks any interim results, except for some nonresearch stakeholder engagement that indicated the system functionality preferences of GPs and patients. Consequently, the methods presented in this protocol paper may require adaptation to ensure they apply to real-world settings. To mitigate these concerns, the study prioritizes building strong relationships with selected PCNs, encouraging active participation in study design and model co-design.

Future Directions

Recognizing some of the key limitations of this study leads us to fruitful pathways for developing this research. First, future studies should include a larger and more diverse patient cohort. Recruiting multiple PCNs in varied urban, rural, and socioeconomic settings and doubling the participant pool should aid generalizability in future phases. Second, a future longitudinal study spanning 6 months to a year could also explore the longer-term impact of these summaries. Additional qualitative interviews could also explore how these summaries adapt MDT workflows and clinical management across time. Finally, during a future validation of the PC summaries, integrating a wide range of stakeholders, including patients and

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caregivers, could strengthen the person-centeredness of the models' outputs.

We envision a future AI-enabled secure platform whereby each clinical interaction is seamlessly video and audio recorded and uploaded. On this platform, generated from previous encounter data and existing data in patient records, up-to-date PC summaries will be easily accessed by HCPs before each consultation in prefigured and personalizable formats. Patients will be notified of the summary provided to the HCP, so they know the information they need to share and what they do not. This should prevent patients from having to repeat their stories.

The AI-enabled platform, accessible by patients and authorized staff, family, and friends, will also have a ChatGPT or other online LLM-styled chatbot so they can ask questions about the patient record and request the AI to create multimodal summaries based on their moment-to-moment needs. For example, one may request to receive longer and more detailed PCC summaries, TikTok-style video summaries of past clinical encounters, a medication plan, or soundbites that can be played through a person's phone or smart speaker. On the basis of our previous PPIE, this platform could also automatically generate meaningful graphs highlighting the interlinkages between psychosocial concerns and medical ailments. However, achieving this will require several future projects.

The AI tool could help ensure that care plans aim for medical goals, meaning in life, and connectedness to others when illness drastically affects their mental capacity. For example, with a long-term dataset spanning a lifetime, an AI could prompt HCPs based on previous interactions and suggest personalized care methods. The model would work to understand *the spirit* of a person—an essence of who they are and what they care about, across time. Of course, these needs and preferences would need to be evaluated with the understanding and support of the caregivers and careful and close attention to the patient's response to the types of support they receive. However, this approach may again prove fruitful.

Developing the AI capacity and digital readiness to implement these technologies successfully will also necessitate radical and positive changes to how information is owned, distributed, and integrated across the NHS and other health care service providers. For example, we envision our model embedded within a broader and regional orchestration layer for the input and sharing of multiple remote monitoring devices and the capacity to receive and effectively share information between the voluntary sector service to create opportunities for a greater depth of AI summarization. This means that our summarization tools will also be able to consider and summarize information from other AI systems and databases that monitor such things as vital signs, gait, and activities of daily living. Importantly, these data would be owned by the patient.

Conclusions

Incorporating AI-generated PCC summaries from audio-recorded encounters could reduce the time clinicians spend on notetaking, improve the quality of notes, and allow these notes to meet the various needs of different members across the MDT. We are developing a unique approach to LLM development by facilitating highly interoperable and time-efficient PC notes. The study can also elicit key understandings of implementing AI technologies in digitally immature, demographically aging coastal regions. Finally, there is great scope for the development of these technologies to become increasingly personalized to the needs of different staff in a variety of formats, and with the AI model expanding to receive inputs from various sources, such as nursing homes, personal writings, telephone calls, and existing PC information documents.

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Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
GP: general practitioner
HCP: health care professional

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LLM: large language model
MDT: multidisciplinary team
NHS: National Health Service
PC: person-centered
PCC: person-centered care
PCN: primary care network
PPIE: patient involvement and engagement
ROUGE: Recall-Oriented Understudy for Gisting Evaluation
SUS: System Usability Scale
VCSE: voluntary, community, and social enterprise
WMTY: what matters to you

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Taabo Multigenerational Birth Cohort in Côte d'Ivoire: Protocol for Establishing a Longitudinal Multigenerational Birth Cohort to Guide Health Policy

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Abstract

Background: A large number of sociodemographic, economic, environmental, and psychosocial changes have contributed to the epidemiological transition of African countries and fundamentally shifted the primary drivers of health. Cohort studies are essential for understanding and improving population health but remain scarce in sub-Saharan Africa.

Objective: The main objective of the Taabo Multigenerational Cohort (MGC) project is to establish a large, regionally representative multigenerational cohort. The cohort will be established within the Taabo Health and Demographic Surveillance System (HDSS) and used for studying the life course and intergenerational dynamics of disease in the south-central part of Côte d'Ivoire.

Methods: The Taabo MGC project focuses on children born between January 1, 2024, and December 31, 2025, in the Taabo HDSS, as well as their parents, grandparents, and great-grandparents. Eligible women and their children are enrolled during pregnancy, and women who do not report during pregnancy are enrolled after the birth. After enrollment of pregnant women, biological ancestors of the index child who are still alive and living in the study area are recruited into the cohort. The cohort is expected to enroll at least 3000 pregnant women and their children, as well as the infants' fathers, grandparents, and great-grandparents, with an expected sample size of approximately 15,000 individuals. To ensure the entire local population is covered in this study, we will also include 100 adults without children. The baseline assessments cover data on demographics, household wealth, tobacco and alcohol consumption, diet, physical activity, health history, quality of life, environmental exposures, depression, anxiety, stress, resilience, obstetric history, birth outcomes, cognitive function, and, for older adults, physical performance. We will also collect anthropometric measurements, blood pressure, and hemoglobin levels and check for *Plasmodium* infection (the causative agent of malaria) among all participants.

Results: As of December 2024, the Taabo MGC project has enrolled 3239 women and 6501 family members. The enrollment of pregnant women and their children's biological ancestors will continue until the end of 2025, aiming to reach at least 15,000 adults.

Conclusions: The Taabo MGC project is designed to become one of the largest cohort studies in the region. Once established, the Taabo MGC project should become a platform for future observational and interventional studies at the local level and contribute to the much-needed evidence base on lifetime disease risk in this part of Côte d'Ivoire. We hope that our work will stimulate research and guide health policy elsewhere in sub-Saharan Africa.

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KEYWORDS

birth; cohort study; Côte d'Ivoire; multigenerational cohort; Taabo HDSS; Taabo Health and Demographic Surveillance System

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Introduction

Background

Côte d'Ivoire, like most countries in sub-Saharan Africa (SSA), faces several major health challenges. Despite being one of the fastest-growing economies on the subcontinent [1], life expectancy in Côte d'Ivoire remains one of the lowest globally, with an average life expectancy of 59 years at birth in 2022 [2]. Low literacy, lack of quality health care for both newborns and mothers, and lack of accessible water and sanitation have been identified as the main drivers of low life expectancy [3,4]. While the burden of communicable diseases (CDs) continues to be high, rapidly rising noncommunicable diseases (NCDs) further challenge the health system [5]. The CDs causing the highest disease burden are malaria, tuberculosis, and HIV/AIDS. The NCDs causing the highest burden of disease are cardiovascular disease, chronic respiratory disease, cancer, and diabetes [6].

The Taabo Health and Demographic Surveillance System (HDSS) has been monitoring vital statistics in the south-central part of Côte d'Ivoire since 2009 [7]. Most recent estimates from the Taabo HDSS suggest that CDs caused 59% of all deaths reported, while NCDs were the primary cause in 19% of reported deaths. These NCD deaths were mostly due to cardiovascular diseases [8]. Capacity for NCD screening and management remains limited despite the high prevalence of prediabetes (47%), diabetes (8%), prehypertension (34%), and hypertension (31%) among adults aged 35 years and older [9-11]. In order to meet the ambitious health-related targets of the Sustainable Development Goals by 2030, high-impact and tailored interventions will be needed at the individual, household, community, and health system levels.

A growing body of evidence suggests that a substantial part of adult morbidity may be attributable to adversity in early life. The fetal origin hypothesis by Barker [12,13] postulates that inflammatory prenatal environments may induce molecular changes that predispose the fetus for (early) development of diseases in later life. To study such long-term relationships in low-income settings, detailed data on internal (genetic and biological) and external (eg, physicochemical, psychosocial dietary environment) exposomes are needed. Birth cohorts are ideal for such studies, as they allow an in-depth study of inter- and transgenerational traits that predetermine health outcomes over the life course [14-19]. While SSA has the highest burden of maternal, perinatal, and child deaths globally, birth cohorts that would allow life-course epidemiology and the use of biomarker research technologies remain scarce [20-22], limiting urgently needed research of the time- and context-specific risk factors underlying the high morbidity and mortality levels currently observed [23].

While the HDSS has been collecting data on all vital events (pregnancies, births, deaths, and migrations) as well as data on causes of death since 2009, data on biological, behavioral, environmental, genetic, and other risk factors have for the first time been collected systematically in the area in the context of the novel and innovative Côte d'Ivoire Dual Disease Burden (CoDuBu) cohort. The CoDuBu cohort has established the first population-based biobank in Côte d'Ivoire embedded into a broad exposome concept and study protocol [9-11,24].

The Taabo Multigenerational Cohort (Taabo MGC) project is completely independent of CoDuBu and focuses on differences in health behaviors and outcomes across generations. CoDuBu studies a population of approximately 1000 adults from both a behavioral and biomedical perspective, with rich biomarker and genetic data. The Taabo MGC project does not contain much biomedical information but instead collects basic behavioral and health outcomes for a much larger and diverse population of children and adults of all ages. The data and evidence emerging from this cohort will help identify high-impact and cost-effective interventions across specific time points in the life course and guide health policies at the country and regional level. The data will also be useful to further strengthen local research infrastructure and offer new opportunities for global comparative epidemiology.

Objectives

The Taabo MGC aims to study the life course and intergenerational dynamics of disease in the south-central part of Côte d'Ivoire. Specifically, the Taabo MGC project aims to generate health data and evidence needed to guide health policy at the country and regional level. This will be accomplished by establishing a large, representative multigenerational cohort within the Taabo HDSS; investigating the prevalence of common health risks and diseases—including patterns of over- and undernutrition, anemia, *Plasmodium* infections, high blood pressure, adiposity, subjective well-being among adults, and mental health conditions; mapping and analyzing health care access across different age groups, sexes, and socioeconomic strata; and analyzing the intergenerational transmission of health risk factors and outcomes.

The goal of this protocol paper is to describe the scope and content of Taabo MGC as a reference for future studies using data from this cohort. We also hope that this study will generate additional interest in this cohort.

Methods

Study Setting

With a surface area of 322,462 km^2, Côte d'Ivoire is a West African country bordered in the North by Mali and Burkina Faso, in the West by Liberia and Guinea, in the East by Ghana, and facing the Atlantic Ocean in the South. With a current estimated population of 29 million, Côte d'Ivoire's population has more than doubled since 1990 [25]. In 2021, 52% of the population was urban, and 21.5% of the country's total population lived in Abidjan as the largest urban area of the country [26]. Côte d'Ivoire is thought of as a subregional economic powerhouse, making a major contribution (40%) to the West African Economic and Monetary zone's GDP and exports. Côte d'Ivoire's economy is based on the primary sector, mainly agriculture (20% of GDP in 2021); the secondary sector (29% of GDP), mainly mining, energy, agri-food, and building and public works; and the tertiary sector (51% of GDP), mainly telecommunications, transport, trade, and financial activities [27].

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Taabo MGC will be established in the Taabo HDSS, located around 160 km northwest of Abidjan. In 2018, the site had a total population of 46,847 spread across 14 villages (the small town of Taabo-Cité, 13 main villages, and more than 100 small hamlets). Since 2022, the surveillance zone has been extended to 21 localities illustrated in Figure 1 with a population of over 60,000. The study area is mainly rural, but the epidemiological transition is progressing rapidly. More detailed information on the Taabo HDSS can be found elsewhere [7].

Figure 1. Health and demographic surveillance area in the south-central part of Côte d'Ivoire

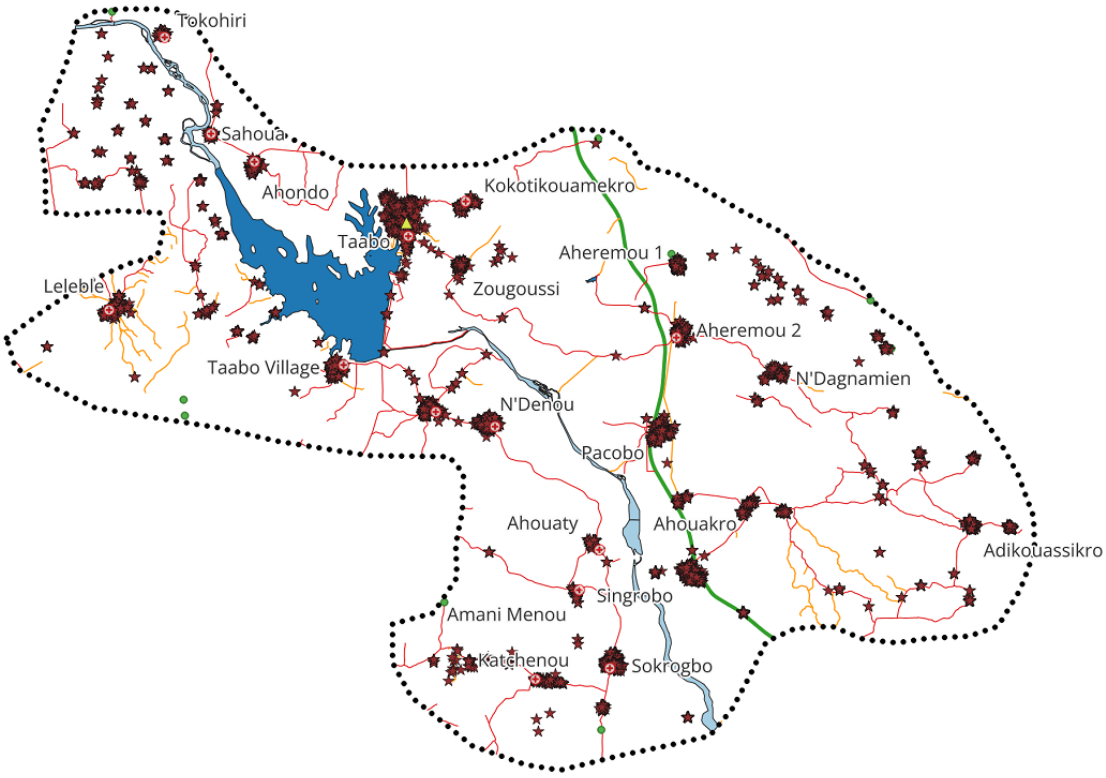

Study Design

The Taabo MGC is a prospective longitudinal health-focused cohort centered around pregnant mothers. The study was launched with the ambition to follow individuals over longer time periods and to study participant survival as well as a wide range of health outcomes. We will enroll all pregnant women over a 2-year enrollment period (November 2023 to September 2025) and then recruit their future children as well as all parents, grandparents, and great-grandparents who are still alive and living in the study area into the study.

Inclusion Criteria

Pregnant women with expected delivery dates in 2024 or 2025 living in the Taabo HDSS area who provide written informed consent for enrollment and for contacting ancestral family members will be eligible for this study. Ancestral family members to be included in the study must also live in the Taabo HDSS area, provide informed consent to participate, and be biological ancestors of the index child. All pregnant women or ancestral family members who fail to meet any of these criteria will be excluded from the study.

Study Procedures

Figure 2 illustrates the main study procedures. All people who are not cognitively impaired who agree to take part in the study will undergo a lengthy interview questionnaire and a health examination. On the other hand, the caregivers of people experiencing cognitive impairment will be asked to complete a short questionnaire. With the phone number of the pregnant woman, each month, they are contacted to monitor the progress or term of the pregnancy. A postpartum questionnaire will be completed by each pregnant woman at the end of her pregnancy.

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Figure 2. Study conceptual framework of the Taabo Multigenerational Cohort project in the south-central part of Côte d'Ivoire.

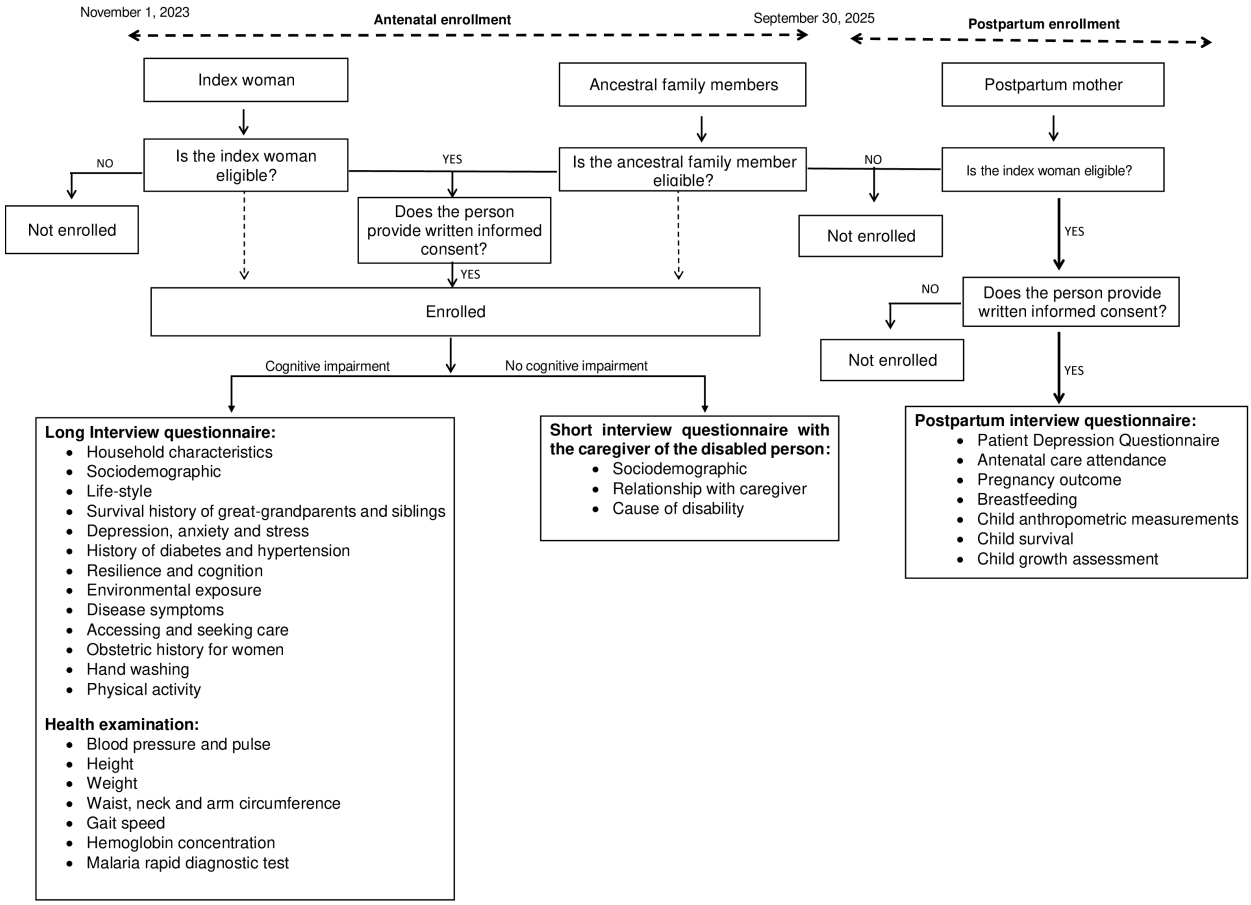

Ancestral biological family members who are related to more than one child will be enrolled only once. Similarly, the characteristics of a household with more than one participant will be collected only once.

Participants

The eligible members of each family will be recruited through its family tree, which will be built from the link between each member and the index child (Figure 3). The estimated sample size for the Taabo MGC is 3000 index families with an estimated 15,000 family members residing in the Taabo HDSS area. We anticipate enrolling 3000 pregnant women over a period of 2 years with an expected due date between January 1, 2024, and December 31, 2025. For each child born in the study period, we will also enroll the biological father as well as biological grandparents and great-grandparents if they are still alive and reside within the Taabo HDSS area. We plan on enrolling approximately 6000 parents, 6000 grandparents, and 3000 great-grandparents. In order to also cover childless adults living in this area, we will include an additional sample of approximately 50 adults aged between 40 years and 59 years and 50 adults aged 60 years or more in the study.

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Figure 3. Enrollment pathway of the Taabo Multigenerational Cohort. HDSS: Health and Demographic Surveillance System.

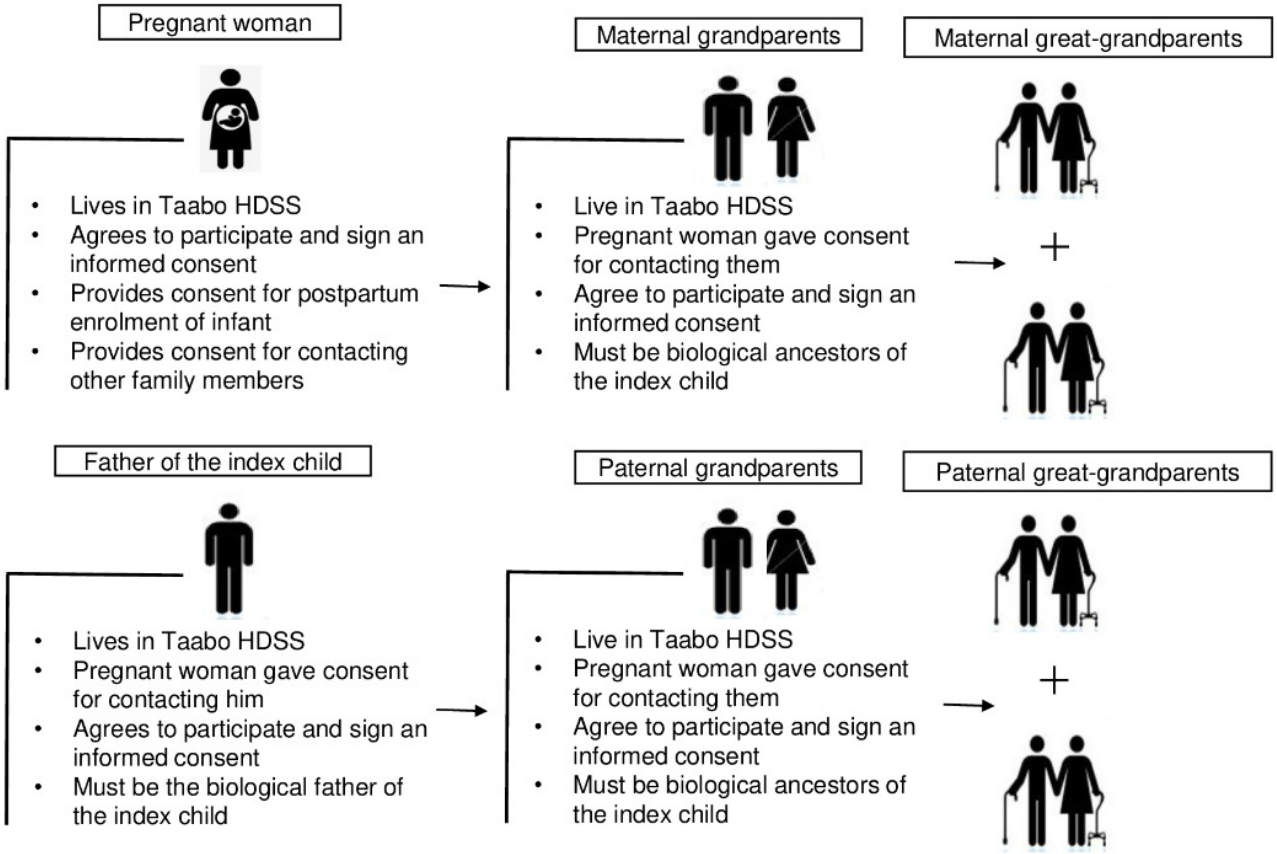

Ethical Considerations

Overview

Ethics approval was obtained from the Ethics Committee Northwest and Central Switzerland (2023‐00049) and the National Ethics Committee for Life Sciences and Health in Côte d'Ivoire (139‐23/MSHPCMU/CNESVS-km). This research project will be carried out in compliance with the protocol, the Declaration of Helsinki [28], the Swiss Human Research Act, and the Swiss Human Research Ordinance [29], as well as other locally relevant regulations.

Compensation

No remuneration of participants is planned in this study. All subjects receive a summary report capturing the results of their physical examination, including blood pressure, height, and weight, as well as hemoglobin levels and *Plasmodium* infection for subjects consenting to these tests. Results will be explained in person and written on the summary report (Multimedia Appendix 1). If the test results suggest hypertension, anemia, or malaria infection, participants will be advised to go to their nearest health center for management.

Consent to Participate

Through an initial visit, the study team will explain the purpose and procedures of the study to each eligible participant. Written informed consent to participate will be obtained from all participants. Newborn consent will be sought from the pregnant woman. For participants aged less than 18 years, written informed consent to participate in the study will be sought from a parent or guardian in the household. Illiterate participants will be assisted by an additional witness. Participation is voluntary, and participants may withdraw from the study at any time or may refuse to answer any questions without having repercussions on their participation. If the participant decides to withdraw from the study, they may request that their information already obtained be destroyed and electronic data be deleted and not be used for evaluation. Confidentiality of information will be assured to the participants.

Recruitment

As part of routine population surveillance, the field enumerators of the Taabo HDSS visit all the households within the Taabo HDSS 2 to 3 times per year to record vital events such as pregnancies, births and deaths, and migration. All pregnant women identified during routine surveillance will be invited by field enumerators to join the study. In addition, key informants will be recruited by the study team to allow for an early reporting of pregnancies.

Once a pregnant woman is identified, she is visited in person by study staff and invited to participate in the study. Once written informed consent has been obtained, information about all the biological ancestors (father, mother, grandparents, and great-grandparents) of the indexed pregnancy or child (if recruited postpartum) is obtained and documented in a family tree form. This family tree form provides basic demographic information about the child's relatives and gives details on which of them are still alive in the study area and therefore eligible for the study (Figure 4). The family tree document is reviewed and completed as interviewers receive additional

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information during the recruitment and interviewing of other family members. The family tree document is then used to recruit additional family members. These family members (fathers, grandparents, or great-grandparents of the index child) will then be visited in person and enrolled into the study conditional on their written informed consent.

Figure 4. Family tree of the index women of the Taabo Multigenerational Cohort project. HDSS: Health and Demographic Surveillance System.

	Is the mother alive? yes ☐ no ☐	**Is the grandmother alive?** yes ☐ no ☐	**Is the grandfather alive?** yes ☐ no ☐
	Name:	Name:	Name:
	Country:	Country:	Country:
	Village:	Village:	Village:
	ID HDSS:	ID HDSS:	ID HDSS:
	Phone:	Phone:	Phone:
	Date of brith	Date of brith	Date of brith
	Age at death (if deceased)	Age at death (if deceased)	Age at death (if deceased)
Pregnant woman	Year of death (if deceased)	Year of death (if deceased)	Year of death (if deceased)
Name:	To be surveyed: yes ☐ no ☐	To be surveyed: yes ☐ no ☐	To be surveyed: yes ☐ no ☐
	Date of survey:	Date of survey:	Date of survey:
	Consent obtained? yes ☐ no ☐	Consent obtained? yes ☐ no ☐	Consent obtained? yes ☐ no ☐
Country:	Status (participant surveyed?) yes ☐ no ☐	Status (participant surveyed?) yes ☐ no ☐	Status (participant surveyed?) yes ☐ no ☐
Village:	**Is the father alive?** yes ☐ no ☐	**Is the grandmother alive?** yes ☐ no ☐	**Is the grandfather alive?** yes ☐ no ☐
ID HDSS:	Name:	Name:	Name:
Phone number:			
Date of birth	Country:	Country:	Country:
Age at death (if deceased)	Village:	Village:	Village:
Year of death (if deceased)	ID HDSS:	ID HDSS:	ID HDSS:
Consent obtained? yes ☐ no ☐	Phone:	Phone:	Phone:
Status (participant surveyed?) yes ☐ no ☐	Date of brith	Date of brith	Date of brith
	Age at death (if deceased)	Age at death (if deceased)	Age at death (if deceased)
	Year of death (if deceased)	Year of death (if deceased)	Year of death (if deceased)
	To be surveyed: yes ☐ no ☐	To be surveyed: yes ☐ no ☐	To be surveyed: yes ☐ no ☐
	Date of survey:	Date of survey:	Date of survey:
	Consent obtained? yes ☐ no ☐	Consent obtained? yes ☐ no ☐	Consent obtained? yes ☐ no ☐
	Status (participant surveyed?) yes ☐ no ☐	Status (participant surveyed?) yes ☐ no ☐	Status (participant surveyed?) yes ☐ no ☐

Study Staff

The field enumerators were recruited and trained for this study and work full-time to establish the cohort baseline. Their role is to establish and maintain contacts with village leaders, health centers, and study participants. In each study village, an information meeting was held with key informants at the beginning of the study. These meetings were organized in collaboration with the village authorities and representatives of the health services (hospital and health centers). After the initial meeting, study field enumerators kept in contact with health services in order to obtain information on newly registered pregnant women. Births were recorded from household visits and local health centers and hospitals to identify recent births and enroll new mothers and their babies.

Furthermore, in the course of their duties, study field staff may sometimes be confronted with complaints or refusals due to the length of the interview. In order to respect the participant's wishes and reduce the risk of unfinished interviews, we negotiate an additional appointment with the participant whenever necessary. It can also happen that participants overlap because they belong to the family trees of different families at the same time. Similarly, interviewers may forget to carry out a household survey for a given participant. All these errors are detected and corrected thanks to weekly internal consistency checks in each data file and external consistency checks between the different data tables.

Data Collection Instruments

Overview

The Taabo MGC uses 3 main questionnaires: an adult questionnaire, a late enrollment questionnaire, and a household questionnaire. The adult form contains 3 main blocks of questions: a core block of questions that concerns all participants without exception, a second block of aging-related questions that are asked only to persons aged 50 years or older, and a third block of maternal and child health–related questions that are only asked to women with current or recent pregnancies.

Table 1 gives an overview of data collection tools used for the Taabo MGC.

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Table . Overview of data collection tools for the Taabo multigenerational birth cohort.

Questionnaire sections	Adults' age (<50 y)	Pregnant women	Women	Adults' age (≥50 y)	Adults' age (≥60 y)	Adults who are disabled
Demographic characteristics	✓	✓	✓	✓	✓	✓
Mental health (depression, anxiety, stress, posttraumatic stress disorder): PHQ-9[a], GAD-7[b], and stress scale	✓	✓	✓	✓	✓	
Resilience	✓	✓	✓	✓	✓	
Personality assessment	✓	✓	✓	✓	✓	
Behavioral measurements (tobacco and alcohol; STEPS[c])	✓	✓	✓	✓	✓	
General diet	✓	✓	✓	✓	✓	
Dietary salt	✓	✓	✓	✓	✓	
Raw food consumption	✓	✓	✓	✓	✓	
Handwashing practices	✓	✓	✓	✓	✓	
Physical activity	✓	✓	✓	✓	✓	
Cognition and memory test	✓	✓	✓	✓	✓	
Pattern recognition	✓	✓	✓	✓	✓	
Environmental exposure	✓	✓	✓	✓	✓	
Sibling and parent mortality	✓	✓	✓	✓	✓	
Health history (diabetes, hypertension, cholesterol, disability, and cardiovascular disease)	✓	✓	✓	✓	✓	
Quality of life	✓	✓	✓	✓	✓	
Physical examination	✓	✓	✓	✓	✓	
Instrumental activities of daily living scale				✓	✓	
Hasegawa dementia scale					✓	
Physical performance (balance, gait speed, and strength tests)				✓	✓	
Cervical cancer screening		✓	✓			
Obstetric history		✓	✓			
Breastfeeding initiation, exclusivity, and duration		✓	✓			

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Questionnaire sections	Adults' age (<50 y)	Pregnant women	Women	Adults' age (≥50 y)	Adults' age (≥60 y)	Adults who are disabled
Antenatal care		✓	✓			
Short form						✓
Physical measurements (height, weight, waist and hip circumference, leg and trunk length, blood pressure, and heart rate)	✓	✓	✓	✓	✓	
Malaria rapid diagnostic test	✓	✓	✓	✓	✓	
Hemoglobin	✓	✓	✓	✓	✓	

[a]PHQ-9: Patient Health Questionnaire-9.

[b]GAD-7: General Anxiety Disorder-7.

[c]STEPS: World Health Organization's STEPwise Approach to Surveillance.

All Women, Including Pregnant Women

The sections of the questionnaire completed by all women included questions on their prepregnancy obstetric history (cesarean section, miscarriage, stillbirth, live birth, and abortion experience; breastfeeding; place of delivery, child's weight at birth; child's civil registration; and current school attendance). Only the index woman was asked about their current pregnancy experience (their weight in kilograms, antenatal care attendance, use of supplements and antenatal services, and plans for delivery). If enrollment occurred after birth, a late enrollment questionnaire similar to the adult form was completed.

Adult Family Members

The core modules collected from all adults build heavily on the validated CoDuBu cohort questionnaire and health examination [11]: (1) study information and consent for participation (including pregnant women and covering their unborn children) and (2) sections on sociodemographic characteristics; behavioral measurements of tobacco use, alcohol consumption, diet, and physical activity; health history; anthropometric measurements such as blood pressure, height and weight, and waist circumference; questions from the World Health Organization's STEPwise Approach to Surveillance to chronic disease risk factor surveillance [30]; health examination findings (blood pressure and pulse, gait speed, hemoglobin, and malaria infection assessment); self-rated general quality of life [31]; parents' survival history and siblings of the adult; depression, anxiety, stress, and resilience score, based on the Patient Health Questionnaire-9 [32], the Resilience scale [33], Generalized Anxiety Disorder Screener [34], and the Depression Anxiety Stress Scale [35]; and cognition measured through the digit span [36] and progressive matrices tasks [37]. When the adult is not cognitively capable of completing the interview, a few basic questions (gender, date of birth, and cause of disability) are addressed to the person caring for the disabled participant. The question on cervical cancer screening was only asked to women.

Special Module for Older Adults (Aged 50 Years and over)

Individuals aged 60 years and above are asked to complete three additional aging-related modules: (1) Brody Instrumental Activities of Daily Living Scale [38], (2) the Revised Hasegawa's Dementia Scale for cognitive function assessment [39], and (3) the Short Physical Performance Battery to assess physical fitness. The Short Physical Performance Battery covers 3 main areas: balance (standing in 3 positions), gait speed (walking speed at a normal pace), and strength (standing up and sitting in a chair) [40].

Household Questionnaire

The household survey questionnaire captures additional household background information, including household size; source of drinking water; lighting mode; toilet facilities; mosquito net use; main material of household roof, walls, and dwelling floor; wealth and assets; cooking mode; and agricultural and livestock property. We will only collect one household form for households hosting multiple study participants.

Planned Fieldwork

During the first phase of this study (that we focus on in this protocol), the main goal is to enroll all index women and their families into the study. As part of this first phase—scheduled to end in June 2026—we will also conduct a short follow-up with women approximately 6 months after delivery to confirm pregnancy outcomes and verify basic childbirth characteristics (location, weight, and survival).

We aim to track cohort survival through the Taabo HDSS, which will collect basic sociodemographic information (survival, marriage, schooling, and employment) for all local residents at least annually in the foreseeable future. Additional future follow-up rounds could be used to collect additional behavioral or medical data; we also see this cohort as a platform to test specific interventions.

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Retention of Participants

To minimize the risk of participant attrition, we established a retention framework based not only on the collection of contact information but also on compensation to encourage continued engagement. Each participant is asked to provide their full name, phone number, the name of the household head, and the full name and phone number of the pregnant woman to whom the participant is linked, as well as the household ID and geographic coordinates. Furthermore, participants receive a summary report capturing the results of their physical examination, including blood pressure, height, and weight, as well as hemoglobin levels and *Plasmodium* infection for participants consenting to these tests. Results are explained in person and written on the summary report. If the test results suggest hypertension, anemia, or *Plasmodium* infections, participants are advised to go to their nearest health center for management. Moreover, at the end of the interview, each participant receives a gift of 2 pieces of soap worth around US$ 2.

Participation is voluntary, and participants may withdraw from the study at any time or may refuse to answer any questions without having repercussions on their participation. If the participant decides to withdraw from the study, they may request that their information already obtained be destroyed and electronic data be deleted and not be used for evaluation.

Data Management

The interview data are collected by field enumerators using portable electronic devices (tablets) with incorporated data entry forms. Data collection is done using the Open Data Kit (ODK) package. Data storage is on a secure server at the Swiss Tropical and Public Health Institute (Swiss TPH) using the ODK Aggregate server and secured via SSL. This server hosts questionnaires and collected data. Once the data are uploaded on the server, they become accessible through the web interface of ODK Aggregate after the user logs in to the system.

Statistical Analyses

The study will provide descriptive epidemiologic statistics on children and their families' current health and health issues, including incidence and prevalence estimates, disease geospatial distributions, the intergenerational distribution, and determinants of common health risks and diseases of public health relevance to the Taabo department. Cox proportional hazards models will be used to analyze survival as the primary outcome of the study. Associations between outcomes and explanatory variables will be tested using multivariable statistical analysis, with statistical significance set at $P<.05$. Logistic regression models will be used to analyze binary outcomes, and ordinary least squares linear regression models will be used to analyze quantitative variables of interest. All statistical analyses will be performed using Stata software (version 19; StataCorp College Station). Missing data will be handled using multiple imputation to replace missing values.

In order to provide a sense of how comparable this cohort is to the general population of Côte d'Ivoire, we compare average characteristics of pregnant women as well as enrolled households to those reported in the latest nationally representative household survey, which is the Demographic and Health Survey collected in 2021.

Results

As of December 2024, a total of 3239 women and 6501 family members were enrolled in the Taabo MGC. The enrollment of families will continue until December 2025, with the aim of covering a sample of at least 15,000 participants.

Table 2 compares the data collected to date to the 2021 Côte d'Ivoire DHS. The pregnant women are overall quite similar to the national average, with a higher share of pregnant women aged less than 20 years and a slightly lower share in the age range between 25 and 29 years. In terms of educational attainment, women in the cohort are more likely to have attained primary education and less likely to not have attended school or attended college. All of the biomarkers collected—height, weight, and hemoglobin levels—are remarkably similar to the national averages.

At the household level, average asset ownership is also fairly similar, with almost identical rates of water access, TV ownership, and radio ownership. Compared to the national average, there is substantially lower access to improved sanitation (as well as much higher rates of open defecation) and increased ownership of bicycles and motorbikes.

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Table . Comparison of the Taabo Multigenerational Cohort participants and national averages.

Pregnant women	Taabo MGC[a,b]	Côte d'Ivoire 2021[c]
Age (y), n (%)		
15 - 19	768 (21.3)	92 (13.5)
20 - 24	971 (26.9)	191 (28.0)
25 - 29	707 (19.6)	171 (25.0)
30 - 34	574 (15.9)	124 (18.1)
35 - 39	426 (11.8)	75 (11.0)
40 - 44	146 (4.0)	22 (3.3)
>45	16 (0.4)	8 (1.2)
Education, n (%)		
No education	1659 (46.0)	380 (55.6)
Primary education	1059 (29.4)	147 (21.5)
Secondary education	857 (23.8)	131 (19.2)
Higher education	33 (0.9)	24 (3.6)
Marriage status, n (%)		
Never married	1133 (31.4)	103 (15.1)
Married	1340 (37.1)	575 (84.2)
Divorced	28 (0.8)	5 (0.7)
Patient characteristics		
Height (cm), mean (SD)	159.4 (6.1)	159.6 (5.8)
Weight (kg), mean (SD)	62.1 (11.4)	61.9 (11.9)
BMI (kg/m^2), mean (SD)	24.4 (4.1)	24.3 (4.2)
Hemoglobin, mean (SD)	100.7 (14.0)	103.2 (14.8)
Anemic, n (%)	2615 (72.5)	417 (65.9)
Household characteristics, n (%)		
Has piped water	1763 (36.6)	5363 (36.3)
Has a flush toilet	872 (18.1)	5311 (36.0)
Has no toilet at all	2469 (51.3)	2689 (18.2)
Has a radio	2157 (44.8)	6900 (46.7)
Has a television	2443 (50.8)	8204 (55.6)
Has a fridge	756 (15.7)	2953 (20.0)
Has a bicycle	2717 (56.5)	3619 (24.5)
Has a motorbike	2051 (42.6)	4538 (30.7)
Has a car	104 (2.2)	722 (4.9)

[a]On the basis of data collected up to June 18, 2025.

[b]MGC: Multigenerational Cohort.

[c]On the basis of Côte d'Ivoire Demographic and Health Survey 2021.

Discussion

Anticipated Findings

This paper describes the design of a large, regionally representative multigenerational cohort within the Taabo HDSS that will help identify appropriate interventions and guide health policies at the country and regional levels. To our knowledge, this is the first birth cohort study that is being carried out within an active HDSS area to assess the links between exposure factors and the occurrence of health events starting in early childhood. The data from this study can further strengthen local research infrastructure and open new opportunities for global comparative epidemiology. Ultimately, we hope to enroll at least 3000 pregnant women, including their children, the children's fathers,

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and their grandparents and great-grandparents, to reach a sample of at least 15,000 participants. Births of interest to the Taabo MGC are those of children born during the 24 months following January 1, 2024. To date, 6655 eligible participants have been registered from the enrollment of 2502 women (n=2146, 85.8% during pregnancy and n=356, 14.2% post partum), equivalent to an average of around 3 participants per family. This is well short of the theoretically possible 14 family members illustrated in Figure 3 (2 parents, 4 grandparents, and 8 great-grandparents). There are several reasons contributing to the unexpectedly small family sizes recruited so far. First, in some cases, pregnancies are not recognized by fathers, making it impossible to recruit the paternal side of the family. Second, the proportion of adults living beyond the age of 60 years has been low historically, limiting the number of grandparents and great-grandparents alive today [2]. Third, and maybe most importantly, the Taabo area is home to a large population not originating from this region, including large Burkinabe and Malian communities that settled there in the late 1970s when the Taabo hydroelectric dam was built [41]. The fishing opportunities in the lake created by the dam, as well as the suitability of the local soil and climate for cocoa farming, have also resulted in substantial in-migration from other regions of Côte d'Ivoire as well as neighboring countries, frequently separating families with young children from their parents and grandparents.

The relatively small size of local families is a first finding of this cohort and a societal aspect to be investigated in future studies.

Given that the entire population of the study area is under surveillance, we are confident that we can trace the cohort well over time and minimize the risk of loss to follow-up. We are confident that the cohort will provide key data on local population health, such as the prevalence of risk factors and morbidity in the short run. In the longer run, we hope that the Taabo MGC can provide a broad platform for future local observational and interventional studies, promote international collaborations and consortia, and contribute to the much-needed evidence base on lifetime disease risk in SSA. We also hope to use this cohort as a resource to create policy-relevant findings and hope to be in regular exchange with local policy makers to share insights from this cohort. While the cohort is only representative of a very specific region of the country, the data presented here suggest that the population under surveillance is rather similar to the national average in many respects.

Conclusions

We trust that the new Taabo MGC cohort will provide ample opportunities to study health behaviors and outcomes across generations in a rural African setting. Recruitment into the cohort should be completed by the end of 2025—we hope to follow participating families for many years through the established and productive HDSS system.

Acknowledgments

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Data Availability

Data sharing does not apply to this paper as no datasets were generated or analyzed during this study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Medical information sheet.
[PNG File, 277 KB - resprot_v14i1e70771_app1.png]

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Abbreviations

CD: communicable disease
CoDuBu: Côte d'Ivoire Dual Disease Burden Cohort
HDSS: Health and Demographic Surveillance System
MGC: multigenerational cohort
NCD: noncommunicable disease
ODK: Open Data Kit
SSA: sub-Saharan Africa

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Protocol

Scaling Up Kangaroo Mother Care Through a Facility Delivery Model in Rural Districts of Pakistan: Protocol for a Mixed Methods Study

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Abstract

Background: The neonatal mortality rate in Pakistan is the third highest in Asia, with 8.6 million preterm babies. These newborns require warmth, nutrition, and infection protection, typically provided by incubators. However, the high maintenance and repair costs of incubators pose a barrier to accessibility for many premature and low birth weight neonates in low- and middle-income countries. This study aims to implement a context-specific kangaroo mother care (KMC) model in Sanghar within secondary health care facilities and catchment communities.

Objective: This study aims to achieve at least 80% KMC coverage for premature and low birth weight neonates.

Methods: This research uses a mixed methods design grounded in implementation science principles, with the goal of developing adaptive strategies tailored to district and facility managers, as well as health care workers, leveraging previous evidence on the benefits of KMC. The research is conducted in the district of Sanghar, Sindh with an emphasis on promoting KMC for infants weighing between 1200 and 2500 g in three facilities. It includes preimplementation data collection, training of health care providers and lady health workers, and intervention involving mother-baby skin-to-skin contact, breastfeeding initiation, and postdischarge follow-ups. Ethical considerations and data management are prioritized, to improve KMC coverage and neonatal health outcomes.

Results: This research will be implemented over a period of 18 months. The primary objective of this research is to achieve an 80% improvement in KMC coverage, with the secondary objective to promote optimal breastfeeding practices among postpartum mothers. Key indicators include the proportion of eligible infants enrolled in KMC, the percentage of mother-baby pairs receiving skin-to-skin care postdischarge, and the duration of KMC during the neonatal period. Additionally, the study will assess exclusive breastfeeding rates, neonatal weight gain, and neonatal deaths within the cohort. The data management team will evaluate the effectiveness of the model in achieving the targeted KMC coverage.

Conclusions: The integration of KMC into the health care system will provide valuable insights for policy makers regarding effective implementation and scaling strategies. The study's findings will highlight facilitators and barriers to KMC adoption, benefiting regions across Pakistan and globally. Additionally, these findings will offer valuable insights for the development of future newborn care programs.

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KEYWORDS

kangaroo mother care; scale up intervention; health facility; community; preterm infants

Introduction

Neonatal mortality continues to be a significant challenge for public health systems in low- and middle-income countries (LMICs), despite the global reduction in newborn deaths from 5 million in 1990 to 2.4 million in 2019. The majority of neonatal deaths occurred in India, Nigeria, and Pakistan [1]. Of these, 75% occurred during the first week of life, due to factors like preterm birth, intrapartum-related complications, low birth weight (LBW), birth asphyxia or lack of breathing at birth, infections, and congenital disabilities [2]. The leading cause of neonatal death is the preterm complication, defined as the live birth of a newborn before 37 weeks of gestation. An estimated 15 million babies are born prematurely every year, and approximately 1 million children die each year due to preterm birth complications. Additionally, many survivors face lifelong disabilities, including learning disabilities and visual and hearing impairments [3].

In Asia, Pakistan ranks third in neonatal mortality, with 8.6 million preterm babies. Premature and LBW neonates require warmth, adequate nutrition, and protection from infection [4]. Typically, these newborns are cared for using incubators, which are ventilated, sterile, moist, and oxygenated devices that provide life support by maintaining body temperature and ensuring a safe environment [5]. However, the maintenance and repair of incubators have significant financial implications, making this care modality challenging and inaccessible for most premature and LBW neonates in low- and middle-income countries, including Pakistan.

In Pakistan, 32% of neonates are born with LBW, representing one-third of all births in the country. In November 2015, the World Health Organization (WHO) identified kangaroo mother care (KMC) as the primary method of managing LBW and premature births [6]. The WHO has defined KMC as a practice of early, continuous, and prolonged skin-to-skin contact between mother and babies, in addition to exclusive breastfeeding or breastfeeding, early discharge after the onset of KMC in the hospital with continuation at home, and adequate support and follow-up for mothers at home [7].

The KMC strategy comprises three main components: thermal care by continuous skin-to-skin contact, support for exclusive breastfeeding or provision of other appropriate nutrition, and early detection and response to any complications that may arise. A systematic review has indicated that KMC is an effective and safe alternative to conventional neonatal care for LBW infants, especially in resource-limited settings [8]. For clinically stable LBW infants <2500 g, implementation of KMC has shown potential to reduce mortality, and if widely applied, could reduce premature deaths [9,10]. Globally, KMC has been recognized as an integral component of the newborn health initiative following the Every Newborn Action Plan [11]. WHO and the United Nations Children's Fund have advocated for facility-based KMC as a routine method of care for clinically stable LBW newborns [12]. However, recent data from the Pakistan Demographic and Health Survey 2017-2018 revealed that only 6.3% and 6.5% of skilled birth attendants (SBAs) in rural Sindh and Balochistan, respectively, conducted newborn care practices that involved placing the newborn in skin-to-skin contact with the mother during childbirth [13].

In a recent study conducted by the Saving Newborn Lives program and Maternal and Child Health Integration Program, a situational analysis of 5 Asian countries, including Pakistan, was carried out to evaluate facility-based KMC [14]. Findings from the Maternal and Child Health Integration Program project implementation in Pakistan suggested that ensuring facility readiness, improved capacity of service providers at facility and community, and focused community mobilization effectively help program planners implement KMC at both levels of care [9,10]. India, on the one hand, has demonstrated substantial improvement in newborn and infant survival using a community-based KMC implementation and interpreted that community-initiated KMC substantially improves newborn baby and infant survival [7]. In Pakistan, researchers in newborn health have recently highlighted KMC as a top preterm intervention as part of the Every Newborn Action Plan [9,11]. Despite KMC being recognized as a cost-effective intervention, its adoption in Pakistan, both at the community and facility level, has been minimal.

The primary objective of this scaleup project is to introduce a context-specific KMC model in Sanghar focusing on secondary health care facilities and catchment communities, with the aim of attaining a minimum of 80% KMC coverage for premature and LBW neonates. Following the implementation of the KMC model in the targeted facilities and communities, the study also aims to assess the impact of this low-cost intervention on reducing neonatal morbidity and mortality among premature and LBW newborns within the rural health system of Sindh, Pakistan. This project will involve and encourage the adoption of the low-cost KMC model by public health facility leadership and community. Additionally, an implementation model tailored to the local context will be developed and assessed to achieve enhanced coverage. The findings of this study will hold significant implications for the government and other stakeholders in implementing and scaling up KMC at the district, provincial, or national level.

Methods

Study Design

A mixed methods design will be used with the principles of implementation science to develop an adaptive strategy to help district managers, facility managers, and health workers both at the facility and the community to identify ways to improve implementation. Considering the evidence from prior studies in Sindh and Pakistan proven to reduce the risk of hypothermia,

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improve the rate and duration of breastfeeding, improve early initiation of breastfeeding practices, improve mother-infant attachment and bonding, and reduce parental distress related to their infant's well-being due to constant attachment [15-18], we aim to scale up the current practices for reaching over 80% coverage of KMC from the baseline. In the preimplementation phase of formative research, we will gather data on components of the health system and the organization of services, knowledge and skills of health care providers, and the community perceptions, acceptance, and challenges. Findings will be used to inform the development of an initial implementation model, addressing facility and community challenges, improving provider's skills, and community acceptance, and improving service delivery to strengthen the health system services. This will be followed by regular assessments at different levels of KMC coverage.

We will implement the research in three facilities in District Sanghar. Our intervention promotes KMC for babies born weighing >1200 and <2500 g, both within the facility and its catchment area.

Setting

The study will be conducted in Sanghar, which is in central Sindh; the total population of the district is 47.9 million, with 71% of the population residing in rural areas and 29% residing in urban areas. The district has a strong primary care setup with 60 basic health units and 6 rural health centers. Sanghar has 6 Mother and Child Health Centers and 2 maternity homes. The district is comprised of 38.3% public health facilities and 32.4% private health facilities, which translates into 70.7% institutional deliveries. Regarding assistance during delivery, District Sanghar has 72.2% of deliveries with SBAs compared to 82.7% of deliveries with SBAs in Sindh. The district reports poor maternal and child health indicators and a high neonatal mortality rate at 33 per 1000 live births, followed by infant and under-5 mortality rates at 47 and 56 per 1000 live births, respectively.

The intervention period for the study will be 18 months (from January 2022 to June 2023). Three public health facilities will be selected to adopt the KMC model. The selection of these facilities will be based on the availability of Maternal, Newborn, and Child Health services, as well as logistical considerations, such as availability of Basic Emergency Obstetric and Neonatal Care services, immediate referral capabilities, availability of human resources, and the monthly turnover of women seeking outpatient care for maternal health services, including the average number of deliveries (approximately 80-120) during the finalization of study sites.

Study Population

Inclusion Exclusion Criteria

All stable newborns provided relevant consent of birth weight >1200 and <2500 g delivered at a targeted health facility or home in the catchment area of the correspondent health facility within District Sanghar will be considered for study. Newborns who are sick according to predefined criteria (ie, do not tolerate oral feeds, severe respiratory distress including respiratory rate of <20 breaths per minute, grunting, central cyanosis, very severe chest in-drawing, convulsions, unconsciousness, and severe hypothermia of <32 °C) will not be included. They will first be stabilized and referred to advanced care facilities. Newborns delivered outside the catchment area and those whose families did not provide consent will not be included.

Sample Size

We will include all newborns delivered in the selected facilities according to the inclusion and exclusion criteria over the 18-month implementation period.

Intervention and Study Implementation Strategy

The study will implement the KMC model in District Sanghar which involves skin-to-skin contact between the mother and the infant for a minimum of 6-8 hours within a 24-hour period, along with exclusive breastfeeding. Implementing the KMC delivery model (Figure 1) will take place in 3 stages: prefacility, facility, and postfacility. At each of these stages, various activities will be conducted, which include, enhancing the capacity of both the facility and community health care providers, establishing effective referrals from the community to health care facilities for institutional deliveries and KMC interventions, providing education on KMC to mothers, families, and the community to improve newborn health outcomes, and reinforcing follow-up procedures for both the community and health care facility.

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Figure 1. KMC implementation model. IEC: information, education, and communication; KMC: kangaroo mother care; LBW: low birth weight; LHV: lady health visitor.

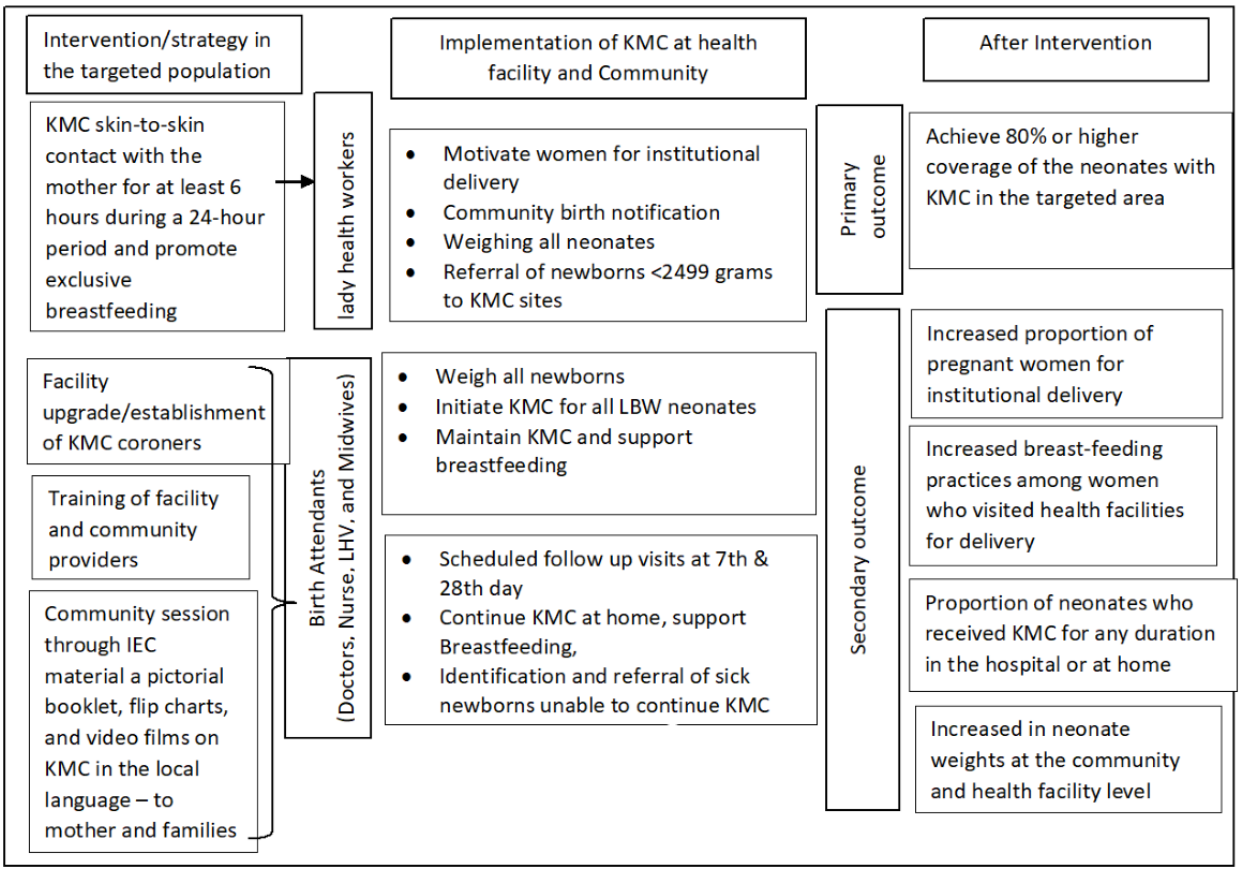

All stable enrolled newborns (with relevant consent obtained) will be placed with skin-to-skin contact and breastfeeding will be initiated within the first hour of life. Mothers will be given tutorials on administering KMC by a trained physician or nurse or lady health visitor at the facility within 6 hours after delivery. At discharge, mothers and family members will be provided with counseling and encouraged to continue KMC practice at home.

Formative Research Phase

We will use our (Umeed-e-Nau project) [10] project baseline data to assess KMC in the community, to review the current health care system, infrastructure, and resources available in the district. The available information will also help assess the existing newborn care practices, health care staff capacity, and community awareness about KMC. For successful KMC implementation, the study will identify key stakeholders involved in newborn care, including health care providers, administrators, policy makers, community leaders, and parents, and engage them in the planning process, ensuring their perspectives are considered and addressing any potential barriers to successful implementation. As part of our research planning, we will conduct interviews (focused group discussion and in-depth interviews with them to gain insights into the local context and factors influencing newborn care practices). In addition, we will also conduct observations to understand health system barriers, bottlenecks, community beliefs, knowledge, and attitudes toward KMC and further identify any cultural or social barriers that may need to be addressed. For this assessment, we will use the COM-B (Capability, Opportunity, Motivation, and Behavior) [18] to understand better the factors influencing behavior change within the community.

We will adopt a multipronged approach that involves active participation from both mothers and health care staff. This approach will address the various components required for behavior change: capability (knowledge or skill needed to perform a behavior), opportunity (a social environment that enables a behavior), and motivation (effective counseling and follow-ups to encourage and activate behavior change). Based on the findings from the formative phase, we will develop a plan for scaling up KMC across the targeted health facilities within District Sanghar.

Intervention Phase

Prefacility Level

The prefacility-level activities will include training of health care providers, and promoting facility birth by involving lady health workers (LHWs) to refer pregnant women for institutional delivery. This has already been implemented by LHWs, who provide immediate referrals for LBW babies delivered at home or in other facilities through KMC counseling.

Counseling during antenatal care visits by LHWs will help increase institutional deliveries and facilitate intrafacility referrals of LBWs to KMC sites. Each month, LHWs will prepare a list of pregnant women as part of their routine activities, submitting this list with their monthly reports to their

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respective lady health supervisors. Data collectors will validate this information during their monthly visits to the LHWs.

Pregnant women in the community will be encouraged to visit health facilities for antenatal care and institutional delivery through the LHWs, as this is part of their mandate. This antenatal visit and counseling will also include information about KMC. This activity aims to identify the total number of pregnant women who can be referred to the facility for delivery and KMC if their neonates meet the inclusion criteria of weighing >1200 and <2500 g.

All neonates will be screened at birth, and those with a birth weight of >1200 and <2500 g will be referred to the KMC functional site in their respective tehsils or districts. The KMC intervention will be initiated with all LBW babies meeting the inclusion criteria who are delivered within the study catchment area, either at the KMC site or by referral to the KMC sites.

Training of Health Care Staff

KMC experts from Aga Khan University (AKU) will serve as master trainers for the training, based on educational material on KMC in the local language for mothers, families, health facility providers (physicians, nursing staff, and lady health visitor staff), LHWs, and study staff at the district level. The training routine will consist of a 1-day classroom and 2-day real-life field scenario for facility providers. Similarly, the LHWs of the selected facility catchment area will also be trained for institutional delivery referral, KMC case notification, and follow-ups. They will be trained to deliver information, education, and support for the KMC practices at the household level in a 2-day training workshop by respective health facility providers. At discharge, mothers and family members will be counseled so that KMC can be continued at home. Facility staff will notify the data collector of discharges and schedule follow-up visits on the 7th and 28th day (Figure 2).

Figure 2. Flow diagram for study implementation. LHW: lady health worker.

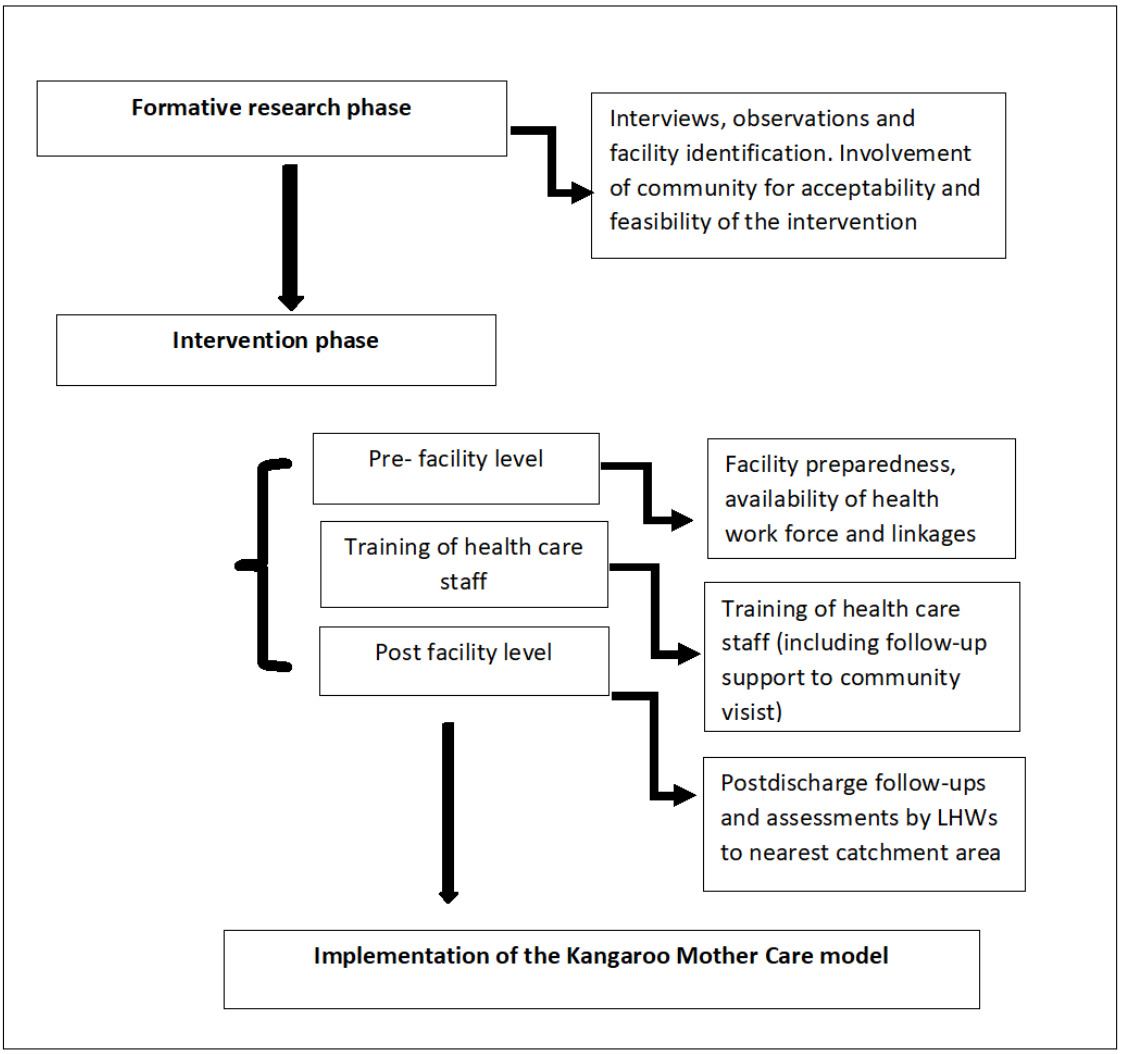

Postfacility Level

Community-based KMC will be administered at home by LHWs exclusively to enrolled neonates discharged from facilities and those born at home within the catchment population of a designated KMC facility. Postdischarge, follow-up will be conducted by respective LHWs. They will visit the home on the 7th and 28th days to assess the implementation of the postfacility KMC protocol. The follow-up team will continue to monitor the newborn at each visit, using a checklist to assess KMC practices, including skin-to-skin contact duration (hours per day) and breastfeeding status, and recording the newborn's

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weight. Additionally, the team will identify and refer sick newborns to the facility and assist with the referral process. This approach, aligned with the health systems strengthening component (continuum of care), aims to create a linkage between facility and community, encouraging the continuation of KMC at home.

Implementation of KMC (The Delivery Model)

The most effective KMC delivery strategy will be determined based on program findings. Data will be gathered from all established KMC sites to assess coverage and adherence to KMC guidelines, including the utilization of communication and training materials and the effectiveness of implementation tools. The results on progress and compliance with process indicators will be shared at the District Health Program Management Team meeting. This meeting will convene key stakeholders, such as health facility managers, LHW program focal persons responsible for managing outreach components, and other individuals involved in the design, implementation, and rollout of the KMC delivery model. Continuous collaboration with these provincial-level stakeholders will enable the integration of best practices and adjustments at the facility level to promote effective KMC and its sustained benefits for vulnerable populations (Figure 3).

Figure 3. Continuous scale-up model of KMC, Umeed-e-Nau, at the facility level. ANC: antenatal care; KMC: kangaroo mother care; LBW: low birth weight; LHW: lady health worker.

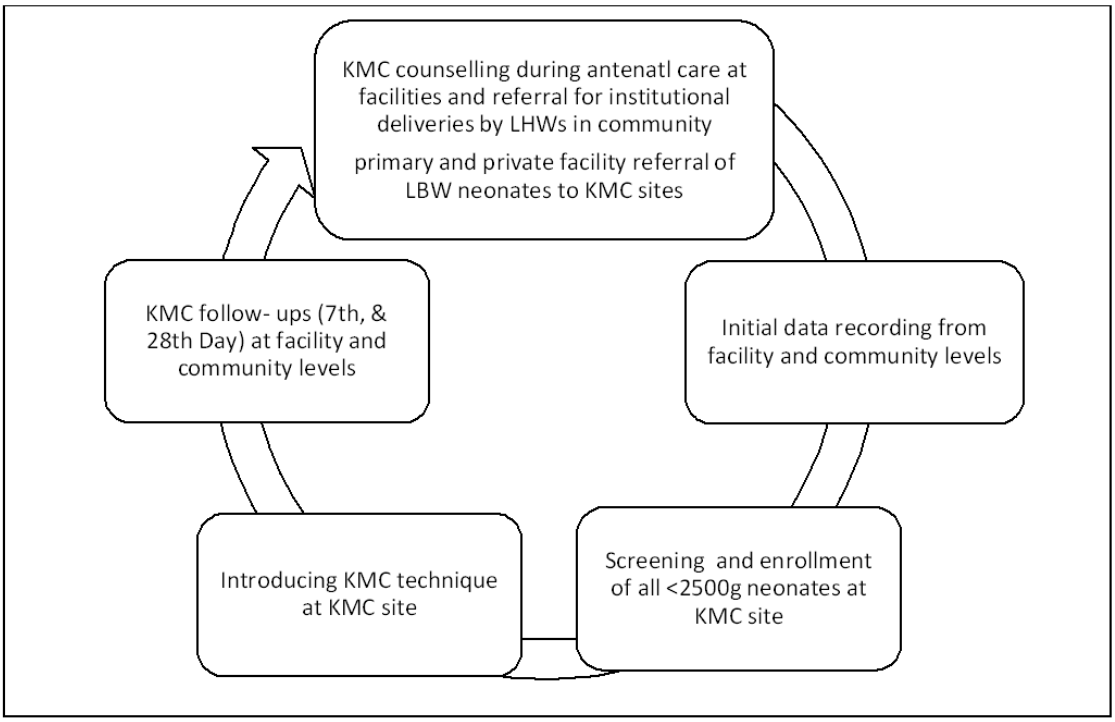

Data Collection Teams

The KMC intervention will be carried out by health workers, including facility staff and LHWs, employed by the district or provincial government at both health facility and community levels. The role of the AKU research team in implementation will primarily be supportive, initially focusing on the formulation of the study design and ongoing process assessment for monitoring and evaluating the intervention's outcomes in the target population. The AKU team will also facilitate data collection by conducting interviews with various stakeholders, such as health care providers, administrators, policy makers, community leaders, and parents, to evaluate the feasibility and acceptability of the intervention. Additionally, the team will provide quality assurance and guidance to health facility staff and community-based health care providers to ensure the effective execution of the KMC intervention within a supportive environment.

Data Management

The collected dataset will be linked to participant identification numbers, separate for mothers and newborns. The cleaned dataset will be presented in monthly review meetings with the principal investigator for review and feedback. Data quality assurance methods would include digital real-time checks for missing values and inconsistency, random spot checks, and data validation coupled with independent monthly audits. The collected data will be stored in a password-protected file and only the data manager from the data management unit will be allowed to access the data and will share the analysis elsewhere needed.

Ethical Considerations

The study was approved by the ethical review committee of the AKU, Karachi-Pakistan (2021-6444-19970). Before enrollment into the study, a verbal explanation of the research will be provided, and written consent will be obtained from the mother or an adult family member. In cases where the participant cannot read the informed consent form, a research team member will read it out to them before recruitment. The participants will be

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fully informed that they have the right to withdraw from the study at any time, without any negative consequences or compensation, and their decision to withdraw will not impact their access to any services provided by the facility. The study will be scaled up within the existing health system so monetary compensation will be provided. However, all the LBW neonates enrolled in the study will be provided with standardized KMC kit which includes, a shirt for mother and baby suites 3 zero size, diapers, woolen cap, socks, soap bar for neonates.

We will also maintain the participant's confidentiality during our research, all identified information of the study participants will be kept confidential and can only be accessed by the principal investigators or supervisors. The findings will be conveyed to the communities through the health system's channels, as well as district, provincial, and national health authorities will be informed through project dissemination and publication in peer-reviewed journals.

Results

Expected Results

Through the implementation of this research, our results include achieving an 80% improvement in KMC coverage and promoting optimal breastfeeding practices among postpartum mothers. The data collection of our research is completed and so far, 12499 live births have been reported and we enrolled 3046 LBWs for KMC and we successfully followed up all registered neonates. We are currently cleaning and refining our data sets for analysis and the actual results of our research will be available in the original research article. The key indicators to be measured include the proportion of eligible infants enrolled in KMC, the percentage receiving skin-to-skin care within specified timeframes post discharge, and the duration of KMC during the neonatal period. Additionally, the study will assess the proportion of eligible infants exclusively breastfed at various intervals, along with monitoring neonatal weight gain and tracking neonatal deaths within the enrolled cohort. The data management team will evaluate the model's effectiveness in achieving the targeted KMC coverage among the entire study population, as outlined in the outcome measurement section.

Evaluation

Effective KMC coverage is defined as the number of newborns receiving KMC divided by the total number of newborns eligible for KMC (>1200 and <2500 g) at the facility and communities during the evaluation period. To measure the denominator for effective KMC coverage, it is preferred that all facility births be identified during facility visits by reviewing birth registers from all facilities. In addition, the data collector will liaise with LHWs to obtain the number of home births and their birth weights. To calculate the numerator for effective KMC coverage, the data management team will quantify the number of newborns weighing >1200 and <2500 g who received KMC in the study population. All enrolled newborns will be followed by the data collector in the facility or at home to collect data at two points: the 7th and 28th day of initiation of KMC. At each time point, the team will record the data through the KMC checklist. We will disseminate the scaling-up findings of KMC across facilities in Sanghar districts with further dissemination of this scale-up at the provincial and national levels to encourage its implementation within other provinces.

Discussion

Increasing Coverage for Premature and LBW Neonates

This will be the first implementation research project to develop and evaluate scale-up models for achieving high population coverage with KMC in Pakistan. Implementation of a context-specific KMC model in Sanghar within secondary health care facilities and surrounding communities will help to achieve at least 80% KMC coverage for premature and LBW neonates. The model in the targeted facilities and communities will also assess the impact of this low-cost intervention on reducing neonatal morbidity and mortality among premature and LBW newborns within the rural health system of Sindh, Pakistan.

This project is a collaborative initiative between AKU and the provincial government, aiming to evaluate the effectiveness of scaling up KMC coverage. Preliminary data indicates that KMC is currently practiced for <5% of LBW infants in these settings, with no competing interventions promoting KMC at the study sites [6]. There is existing literature on the barriers and facilitators of KMC within health facilities [19-21]. This project presents a timely opportunity to integrate KMC into the existing health care system in partnership with the government. The goal is to identify effective scale-up models for implementation in large, countrywide settings. While the study focuses on KMC coverage as a key outcome, we aim to develop a model that integrates KMC as an essential component of newborn care, rather than projecting it as a standalone vertical program.

The study will exclude community-based follow-ups to evaluate improvements in newborn weight for families that do not provide consent for such follow-ups. Further, the accuracy and reliability of outcome measurements, such as growth parameters and developmental milestones, were not used.

Conclusions

The outcomes of this implementation research will extend beyond the study area to benefit other regions within Pakistan and globally. The findings will inform strategies to enhance essential newborn care provision at health care facilities, seamlessly integrating KMC without the need for a separate vertical program. Insights gained from this research will not only illuminate the challenges associated with scaling up KMC but also offer effective solutions to address them. Furthermore, these experiences hold promise for shaping the design and implementation of future infant and childcare programs, facilitating their swift adoption by both health systems and communities. The findings of this study will provide robust evidence to inform the development of policies and programs aimed at preventing neonatal mortality and improving maternal and child health and growth outcomes in resource-limited settings.

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Acknowledgments

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Authors' Contributions

ZAB led the funding acquisition of the main kangaroo mother care scaleup intervention project. SM conceptualized the study design with guidance from ZAB. SA, SS, and ZM provided inputs on public sector service delivery platforms. HN, AAS, and SK drafted theoretical framework. SM drafted the first version of the manuscript and HN incorporated feedback from all the coauthors. All authors reviewed subsequent manuscript drafts. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AKU: Aga Khan University
COM-B: Capability, Opportunity, Motivation, and Behavior
KMC: kangaroo mother care
LBW: low birth weight
LHW: lady health worker
SBA: skilled birth attendant
WHO: World Health Organization

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Protocol

Characterization and Evaluation of Department of Veterans Affairs Commission on Accreditation of Rehabilitation Facilities–Accredited Interdisciplinary Pain Rehabilitation Programs: Protocol for a Mixed Methods Program Evaluation

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Abstract

Background: Veterans are more likely to experience chronic pain than civilians, with significant negative impacts on long-term health outcomes. Evidence for the effectiveness of prescription opioids for chronic pain management is limited, and chronic use of opioids is associated with an increased risk of sleep-disordered breathing, cardiovascular complications, and bowel dysfunction, as well as opioid misuse and overdose. Veterans Affairs (VA) and Department of Defense guidelines are prioritizing low-risk, evidence-based interdisciplinary pain management strategies while optimizing pain-related outcomes (PRO) for veterans. Commission on Accreditation of Rehabilitation Facilities (CARF)–Accredited VA Interdisciplinary Pain Rehabilitation Programs (IPRPs) have shared characteristics, while maintaining their unique characteristics as individual pain management programs. Though little is known about the characteristics of VA's IPRPs (eg, staffing, services, and patients served), implementation, and sustainability of these mandated programs.

Objective: The goals of our operational partner-driven evaluation are to (1) characterize IPRPs across multiple program factors, including but not limited to, service delivery methods, team composition, program characteristics, services and modalities offered, and patients served; (2) triangulate data to inform data visualization that characterizes and illustrates the IPRPs individually and collectively as a system of care; and (3) identify patient-reported outcomes (PROs) and metrics to measure program effectiveness and determine overlap across IPRPs.

Methods: This partnered-driven program evaluation will use a sequential mixed methods prospective design, including interviews and surveys. The Consolidated Framework for Implementation Research (CFIR), Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework, and Expert Recommendations for Implementing Change (ERIC) strategies will be used

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to contextualize qualitative data. Rapid content analysis will be used to iteratively analyze qualitative data, while descriptive statistics will be used to analyze quantitative data. Datasets will be triangulated to support data visualization for partners to inform clinical and operational decision support.

Results: As of April 2025, All IPRP sites are engaged, and survey and interview data have been collected and prepared for analysis. The results and deliverables will inform VA CARF-accredited IPRP characterization, evaluation, and implementation as a learning health system.

Conclusions: The results of this evaluation will characterize CARF-accredited IPRPs and identify determinants affecting the implementation of this complex intervention, made up of multiple evidence-based practices. Partner-driven data will inform the state of implementation at each site, and quantitative measures will provide options for collecting standardized outcome measures for continued program evaluation. This operational partner-driven evaluation will inform future efforts for quality improvement to improve veterans' pain management outcomes. This protocol informs the use of a mixed methods approach to evaluate a multimodal intervention (ie, IPRP), made up of multiple evidence-based practices to treat a complex comorbid condition. Future work may include data management infrastructure development and cost evaluations to inform clinical and operational decision-making.

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KEYWORDS

chronic pain; veterans; interdisciplinary; pain program; pain rehabilitation; pain management; multidisciplinary

Introduction

Background

More than 50 million American adults (20.4%) are estimated to have chronic pain [1]. Chronic pain is defined as persistent pain lasting more than 3-6 months after initial onset [2]. High-impact chronic pain is indicated by the presence of pain that significantly reduces social, occupational, and self-care activities on at least half of the days over this time period [3,4]. Compared with civilians, veterans are more likely to experience chronic pain (29.1% vs 19.5%) [1] and high-impact chronic pain (9.1% vs 6.4%), with significant negative impacts on long-term quality of life [5] and affecting overall functioning [6,7]. In an effort to manage chronic pain, some veterans become reliant on prescription opioids [8,9], which have numerous unintended health consequences such as increased risk of sleep-disordered breathing, cardiovascular complication, and bowel dysfunction, as well as opioid misuse and overdose [10-13]. In recent years, there has been increased attention on low-risk interdisciplinary treatment options for chronic pain management in the Department of Veterans Affairs (VA) system [14].

Currently, VA promotes an interdisciplinary integrative approach to pain management [15,16]. Subtitle A of the 2016 Comprehensive Addiction and Recovery Act (CARA) mandates that each VA medical center have a designated pain management team to treat and coordinate pain care for veterans [15]. This approach to pain management favors a biopsychosocial approach, which conceptualizes chronic pain conditions as complex and multidimensional, emphasizing interdisciplinary integrated models of care, as outlined in the VA's Stepped Care Model for Pain Management (SCM-PM) [16-18]. Current VA and Department of Defense guidelines suggest that the potential benefits of interdisciplinary pain treatment for complex comorbid conditions including substance use disorders, outweigh potential harms [16]. The VA's Interdisciplinary Pain Rehabilitation Programs (IPRPs) are empirically supported for improving pain-related outcomes (PRO) in the veteran population [14]. Policy [17,18] and evidence-based practice [14,19] have fueled the expansion of the VA's IPRPs. Despite implementation throughout the system, little is known about the characteristics of the IPRPs (eg, staffing, services, and patients served), including implementation and sustainability factors (Office of Pain Management, Opioid Safety, and Prescription Drug Monitoring Program [PMOP], personal communication, March 2023).

This protocol describes a national evaluation designed to characterize the VA Step 3 Commission on Accreditation for Rehabilitation Facilities (CARF)–accredited IPRPs. The aims of this project were to conduct an evaluation of IPRPs to (1) characterize IPRPs across multiple program factors, including but not limited to, service delivery methods, team composition, program characteristics, services and modalities offered, and patients served; (2) triangulate data to inform data visualization to characterize and illustrate the IPRPs individually and collectively as a system of care; and (3) identify patient-reported outcomes (PROs) and metrics to measure program effectiveness and determine overlap across IPRPs. Deliverables from this project will support IPRP implementation and sustainability. Protocol components are reported in accordance with the SQUIRE 2.0 (Standards for QUality Improvement Reporting Excellence) guidelines [20].

IPRP Overview

Published in 2009, Veterans Health Administration (VHA) Directive 2009-053 [18] established the SCM-PM as a practical framework to contextualize the national standards of care for treating veterans with chronic pain based on needs and risk. The SCM-PM begins with low-intensity interventions delivered in primary care settings where more common pain conditions are seen (step 1) and progresses to specialty pain care services provided by interdisciplinary pain management teams (step 2), and step 3 tertiary pain care based on pain complexity, risk

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factors, and veteran needs (eg, comorbidities), which includes services such as IPRPs [17]. In addition, VHA Directive 2009-053 mandated the implementation of at least one CARF-accredited IPRP in each region of the VHA (ie, Veterans Integrated Service Networks [VISNs]) [18]. In the 10 years following the publication of VHA Directive 2009-053, the number of CARF-accredited IPRPs in VHA increased 10-fold, from 2 to 20. Conversely, CARF-accredited IPRPs in the US (outside the VA) decreased from 210 in 1998 to 87 in 2019 (58.57%) [14,19]. Since 2019, additional VA IPRPs have continued to pursue and receive CARF-accreditation. VA also has a robust community of practice (CoP) for IPRPs to share information and support. Important congressional mandates including CARA [15], and the emergence of the national VA whole health-oriented, integrative health care priorities [21] reinforce the importance of IPRP development and implementation.

Interdisciplinary pain rehabilitation programs consist of multimodal, interdisciplinary provider teams with a shared "mission, philosophy, and set of objectives" to improve patient care using a biopsychosocial approach [7]. By design, IPRPs support interdependence among team members, which allows for consistent, open communication and collaboration with decision-making, as well as setting, reviewing, and revising treatment goals [7,19,22,23]. This integrated team-based approach is conducive to providing evidence-based, person-centered care that addresses the multifactorial elements of chronic pain.

Interdisciplinary pain rehabilitation programs may be heterogenous with respect to numerous characteristics (eg, team composition, modalities offered, program length, etc) [7,14,19,23-25]. The most common team members include medical (ie, physicians, nurse practitioners, and physicians' assistants), behavioral health (ie, psychologists and social workers), and rehabilitation (ie, physical therapists and occupational therapists), with the expected associated modalities provided, respectively (ie, medical management, behavioral therapies, and exercise programs). Less represented but highly valuable additional team members may include pharmacists, nutritionists and dietitians, recreation therapists, vocational rehabilitation specialists, support staff, health and wellness coaches, nurses, nurse program coordinators, and administrative support [7,14,23]. Team integration, regular communication, and care coordination are shared philosophies of IPRPs [7,14,19,22]. More comprehensive overviews of IPRP are published elsewhere [7,19,22,26,27].

Empirical Support for IPRPs

Systematic reviews and meta-analyses support the effectiveness of IPRPs with most evidence coming from the public sector. Evidence from a focused review and meta-analysis of interdisciplinary pain rehabilitation pre-post and follow-up effects [25] found pre-post improvement across a variety of pain-related (intensity and interference), psychological (anger, anxiety, depression, and self-efficacy), and functional (physical and social) PROs, with improvements typically maintained at follow-up. A review of 4 model IPRPs largely supported these findings across similar outcomes [23]. Compared with usual care, IPRPs have demonstrated small size improvements for pain intensity and disability, with moderate evidence quality [28]. Meta-analyses comparing IPRPs to active interventions (eg, physical treatments and surgery) found medium effect sizes for improvements in pain and disability but with significant heterogeneity in findings and low evidence quality [28,29].

The VA is a national leader in IPRP delivery and growth with various veteran outcomes studies. Murphy et al [30,31] examined large national samples of veterans that completed the CARF-accredited Tampa VA inpatient IPRP. Veterans typically experienced pre-post improvements in pain-related (intensity, interference, fear of movement, and catastrophizing), psychological (negative affect and relaxation), and functional (vitality and sleep) PROs with effect sizes ranging from small to large. Outcomes were similar between veterans who tapered off of their prescription opioids during the program compared with those not taking opioids [30]. More recent small-scale studies at the CARF-accredited San Francisco VA IPRP found that veterans experienced pre-post improvements in pain catastrophizing, depression, as well as disability, with mixed results for pain intensity [32,33]. A recent study by this group found mostly similar results between their in-person (prepandemic) and online (postpandemic) program iterations with lower dropout in the online program [34]. Finally, a large multisite VA IPRP evaluation examined pre-post improvements on common PRO measures administered across all sites. They also characterized each IPRP (Albuquerque, New Mexico; Cleveland, Ohio; Puget Sound, Washington; San Francisco, California; Tampa, Florida [inpatient], Tampa, Florida [outpatient]) including factors such as program time commitment, team composition, and modalities offered. This study found that VA IPRPs were heterogenous in their program structures. Significant improvements in pain-related outcomes including intensity, catastrophizing, interference (mobility and activities of daily living), fear of movement, negative affect, vitality, and insomnia severity were observed. Aggregate effect sizes across IPRPs were in the small-to-medium range.

Interdisciplinary pain rehabilitation programs are an essential part of complex pain care and are empirically supported for improving PROs in the veteran population [14]. There has been important policy support [17,18] and substantial clinician-led grassroots efforts to expand IPRPs in the VA system [14,19]. This national evaluation to characterize the VA step 3 CARF-accredited IPRPs will support current and future implementation, sustainability, and policy for these valued programs. This protocol leverages established methods for evaluating multimodal interventions made up of multiple evidence-based practices for complex comorbid health conditions [35]. This approach can be applied to evaluating pain rehabilitation in VA and non-VA learning health systems in high-reliability organizations.

Methods

Concept and Design

This partnered evaluation will be conducted through a sequential mixed methods process [36,37] and in close collaboration with the study sponsors. Our team has established methods for

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evaluating complex interventions made up of multiple evidence-based practices for complex comorbid health conditions such as chronic pain [35]. In this partnered mixed methods sequential design, we will use multiple steps. In step 1, our operational partners will provide us with the list of VA step 3 CARF-accredited IPRPs to be evaluated including points of contact (POCs) to be recruited for key informant interviews. In step 2, POCs that will be targeted for recruitment will be able to refer additional key informants for recruitment. In step 3, we will leverage the previous characterization of a subset of VA step 3 CARF-accredited IPRPs [14] as the starting point for the development of this protocol. In step 4, we will iteratively develop the qualitative interview guides and program characteristics survey through multiple rounds of partnered feedback. In step 5, following data collection and analysis, we will deliver findings to our partners who validate our data and iteratively advise us on whether additional information needs to be collected. Finally, in step 6, we will leverage relationships with partners at the operations and IPRP levels to determine dissemination opportunities and product development (Figure 1).

Figure 1. Interdisciplinary Pain Rehabilitation Programs (IPRPs) partnered evaluation collaborative roles. PMOP: Department of Veterans Affairs Office of Pain Management, Opioid Safety, and Prescription Drug Monitoring Program. VA: Veterans Affairs. IPRP: Interdisciplinary Pain Rehabilitation Program.

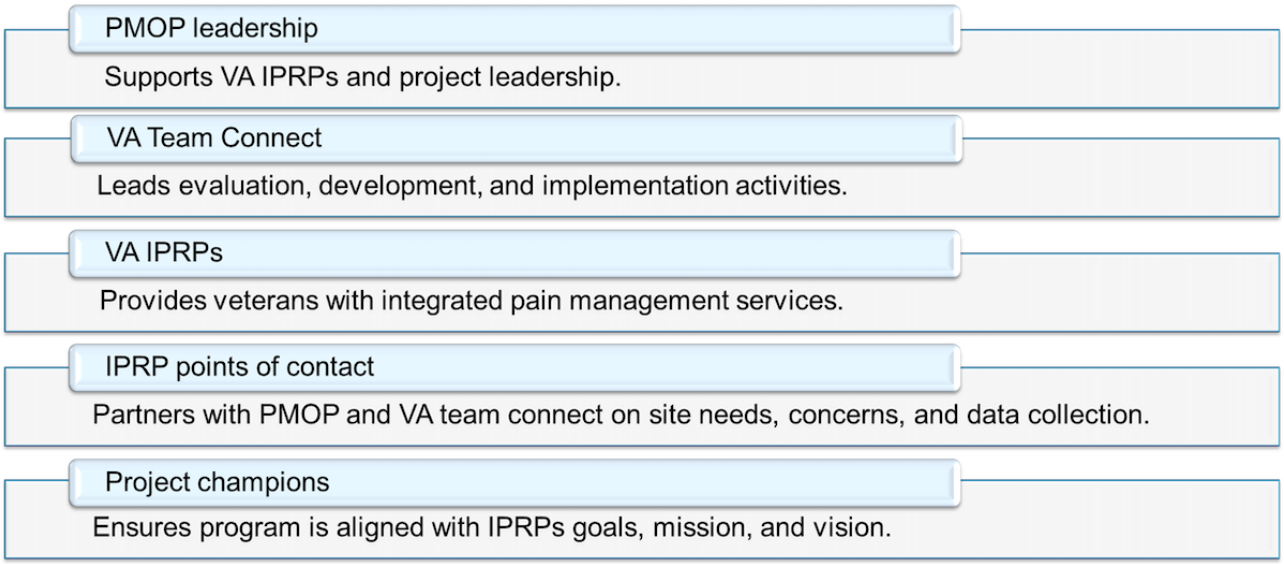

Sampling and Sample Size

This program evaluation will use purposive and referral-based sampling methodologies to recruit participants for key informant interviews at the population level for all CARF-accredited and accreditation-seeking VA IPRPs. Specifically, a planning meeting between the research team and the study sponsors was held in July 2023 to clarify and discuss the goals of the evaluation. The sponsors provided the evaluation team with names and contact information for POCs at all CARF-accredited and accreditation-seeking VA IPRPs. These POCs will be targeted as key informants to provide information about their IPRPs. Furthermore, POCs from each IPRP, typically the program director, will also be able to identify and refer additional IPRP personnel (eg, former IPRP director, data manager, program coordinator, etc) to be recruited for key informant interviews.

In total, 23 VA IPRPS (21 CARF accredited and 2 in the accreditation process) will be evaluated (Figure 2). Furthermore, one of the CARF-accredited VA IPRPs is mirrored across two independent VA medical centers (Brooklyn and Manhattan). We will conduct separate interviews with a POC at each of these VA sites which have their own independent staffing and within-facility factors (eg, collaboration, team dynamics, community resources, etc). In total, 24 POCs will be targeted to complete key informant interviews and an IPRP characteristics survey.

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Figure 2. Pain Management, Opioid Safety, and Prescription Drug Monitoring Program (PMOP) in Interdisciplinary Pain Rehabilitation Programs (IPRPs) site map. IPRP: Interdisciplinary Pain Rehabilitation Program.

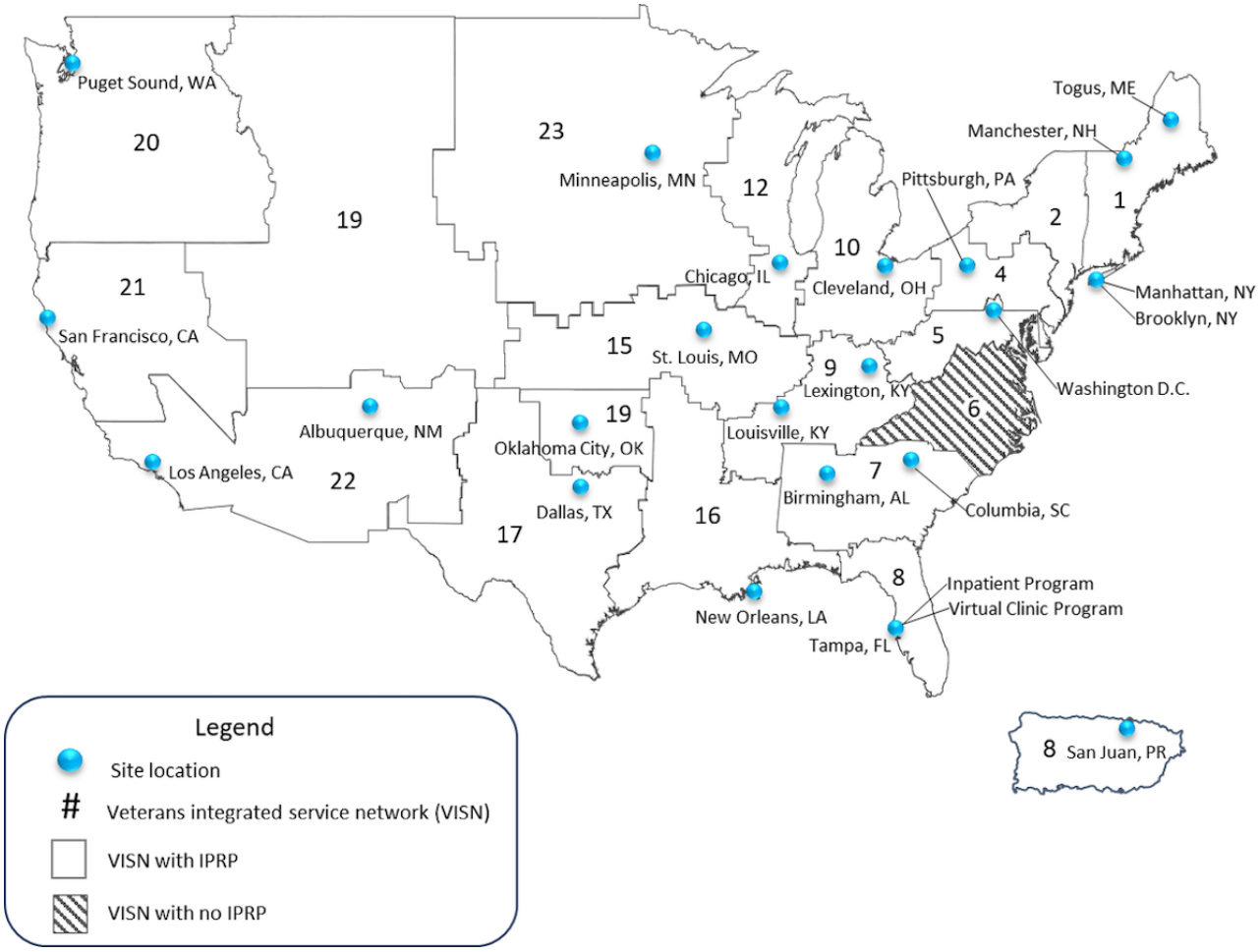

Qualitative Interview Guides

Two semistructured key informant interview guides will be iteratively developed with operational partners. The first interview guide will contain broad questions about the strengths and weaknesses of the IPRPs, how the IPRP coordinates with other pain services within and outside the facility, changes to the program over time, and the use of telehealth. The second interview guide will emphasize data collection, analysis, and use of PRO measures, as well as collaboration with other IPRPs. Interview guides will be structured by the domains of implementation, as outlined by the Consolidated Framework for Implementation Research (CFIR) [38]. Interview guides were piloted internally by the qualitative team to ensure flow and proper timing.

Program Characteristics Survey

The IPRP program characteristics survey will target specific information about the size and scope of VA IPRPs. This survey was designed based on characteristics from a previous IPRP multisite evaluation [14] and input from our operational partners. These will include the number of veterans served, treatment modalities, staffing, and service delivery among other characteristics (refer to Table 1).

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Table 1. Interdisciplinary Pain Rehabilitation Program (IPRP) characteristics.

Characteristic and scale	Description
IPRP[a] time commitment	
Program length (weeks)	Total program time commitment for veterans participating in IPRP.
Days per week	—[b]
Hours per day	—
Total hours	—
Mode of delivery	
In-person (Y or N[c])	IPRP offers in-person or online health delivery of their services.
Online (Y or N)	—
Team composition	
Specialty (Y or N)	Team members' specialties and time commitment dedicated to delivering IPRP services.
FTE[d] (%)	—
Services offered	
Services (Y or N)	Treatment modalities offered by IPRPs (eg, physical therapy, behavioral therapies, medication management, etc).
Collaboration	
Collaboration (Y or N)	Services that IPRPs collaborate with (eg, services, referrals, resource-sharing, etc).
IPRP referrals, enrollment, and capacity	
Referrals	Total number of veterans referred to IPRP in FY[e]23.
Acceptance rate	Total number of veterans accepted to IPRP in FY23.
Enrollment	Total number of veterans enrolled in IPRP in FY23.
Program completers	Total number of veterans that completed IPRP in FY23.
Program outcomes	
Metrics	PROs[f] and metrics used to assess IPRP effectiveness.

[a]IPRP: Interdisciplinary Pain Rehabilitation Program.
[b]Not applicable.
[c]Y or N: yes or no.
[d]FTE: full-time employment.
[e]FY: fiscal year.
[f]PROs: patient-reported outcomes.

Procedure

This evaluation will be promoted to IPRPs using multiple approaches. In October 2023, the study author (CAF) informally presented the project and recruitment process at the monthly VA IPRP CoP call. In January 2024, author CAF provided a 45-minute "site activation" presentation to describe the evaluation and expectations on the VA IPRP CoP call. The study sponsor (PMOP) distributed a national memo to describe the evaluation and anticipated activities with input from study authors (CAF, JNH, and LMB). From March to May 2024, authors (CAF and JNH) attended and presented the evaluation at 3 monthly VA regional pain conferences.

IPRP POCs will be contacted by a study team member (SAK) via email to schedule their interview. Key informant interviews will be led by one of three experienced qualitative researchers (MCM, and JNH) and a second research team member will take notes during the interview (JNH, BH, CAF, and LMB).

Following the completion of their first interview, POCs will be sent the program characteristics survey via Qualtrics (Qualtrics International Inc), a Federal Risk and Authorization Management Program that is an approved, secure, cloud-based data collection platform [39] that has demonstrated feasibility for electronic data collection within the VA system [40]. If POCs do not complete the survey before the second interview, the interviewer will complete it with the respondent during the interview. A team member (CAF) will serve as the IPRP liaison and follow up with IPRP POCs for clarifying information as needed. The follow-up key informant interview will be scheduled and completed using the same procedures as the first interview. The final interview protocols and survey instrument can be found in Multimedia Appendix 1.

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Qualitative Analysis

Interview data will be analyzed using rapid iterative qualitative analysis [41]. The process will begin with the generation of field notes by the note taker, which will then be reviewed and verified by the interviewer. The field notes will then be exported into a Microsoft Excel (Microsoft Corp) workbook for rapid coding and analysis. The three interviewers will develop a coding scheme consisting of deductive, relevant codes applicable to questions about program facilitators, barriers, challenges, and strengths. In addition, they will develop an inductive coding scheme for questions involving specific program issues (eg, Who enters the PRO data and where is the data entered?). The inductive coding scheme is designed to group participant responses. The 3 team members will code one interview together, and then 2 interviews individually to compare responses. This process will lead to some refining of the coding schemes. Next, the 3 team members will independently code an additional interview, and intercoder reliability will be established. All remaining interviews will be coded by a single team member and then verified by a second team member.

Once coding is completed, the codes for individual questions will be totaled, and team members will develop brief descriptions of the trends and findings from the coded data. These descriptions will then be thematically sorted using CFIR [42], Reach, Effectiveness, Adoption, Implementation, Maintenance (RE-AIM) [43], Levesque's model of access [44], and Powell's implementation strategies [45]. These themes will be used to organize the findings, which will then be organized into descriptive and comparison matrices to summarize the findings and highlight key differences between sites. When applicable, specific examples and salient quotes will be pulled from the field notes to help illustrate key findings. During this process of data collection and analysis, the research team will meet regularly to discuss emerging findings. Data will be extracted and analyzed to characterize VA CARF-accredited IPRPs and to develop an implementation research logic model [46,47]. In addition to the team's process of validating the reliability of the analysis, the team will iteratively engage IPRP representatives and operational partners to address the validity, dependability, and representation of data findings and summaries. This partnered approach ensures data validation and representation from the partners' perspective and data outcomes [48,49].

Quantitative Analysis

Survey data will be analyzed using basic descriptive statistics (eg, counts and means) to display data in tables and figures. For participant demographics and IPRP characteristics, frequencies and percentages will be used to describe categorical variables. Normally distributed continuous variables will be described using their range, mean, and SD. Skewed continuous variables will be described using range, median, and IQR.

Triangulation of Data

Qualitative and quantitative datasets will be triangulated to contextualize the characterization of the IPRPs, as well as understand the determinants, strategies, and outcomes associated with their implementation, per our conceptual model. When appropriate, programmatic quantitative descriptive data may be used to create cohorts of IPRPs that share characteristics to explore and understand qualitative findings. Likewise, qualitative findings on determinants and strategies may be triangulated with quantitative data to examine relationships reflecting the sites' unique characteristics.

Ethical Considerations

The project protocol was reviewed by the Research and Development Committee of the James A. Haley Veterans' Hospital (IRBNet 1777324). This project was determined to be nonresearch, and Institutional Review Board approval was not required because the data collection activities were for quality improvement and not for research. Participants only provided consent to be recorded during interviews for data confidentiality purposes. All methods were carried out in accordance with relevant guidelines and regulations. All staff interview tools, including interview guides and the program characteristics survey, were approved by the National VA Union. No compensation was provided to the participants in this quality improvement project. Participants' identities were confidential and deidentified, and data were stored behind the VA firewall. Data will be presented anonymously in an aggregate form in accordance with the VHA policies and regulations. Nevertheless, all participants will be informed of the purpose and intended use of the data collected, assured confidentiality, and informed that they can decline to answer any question or cease participation at any point without penalty. All interviews will be completed via videoconference using Microsoft Teams (Microsoft Corp). All respondents will be provided oral consent to participate in the interviews.

Results

Project activities and funding began in October 2023. As of April 2025, key informant interviews have been completed at all 23 IPRPs. The first key informant interviews (n=31) were completed between February and May 2024. Follow-up key informant interviews (n=30) were completed between May and July 2024. Program characteristics surveys have been completed by 21 of 23 IPRPs and will be finalized for the remaining two sites. Findings will be disseminated in mid-2025 and thereafter to inform characterization and support program-level and system-level efforts.

Discussion

Principal Findings

The primary goal of this evaluation protocol is to complete the first system-wide characterization of VA step 3 IPRPs to better understand these unique programs. Findings from this mixed methods evaluation will identify targets for supporting VA IPRPs through multiple mechanisms. First, findings will inform the development of a measure-outcomes infrastructure to provide IPRPs with better access to system-wide IPRP data based on an adopted PMOP Pain Measures Set. This process will also establish a capacity to conduct standardized evaluations of the effectiveness of VA IPRPs from the individual program level to the system-level [50]. Second, the findings will provide a

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framework for further characterization, implementation, and evaluation efforts across the VA IPRP system. Third, this evaluation will inform system-wide PMOP funding and staffing initiatives directed toward facilitating and sustaining the adoption of state-of-the-art pain management practices within the VA. These steps are essential to support PMOP and step 3 IPRPs as a learning health system.

Future Directions

This protocol is the first phase of a 5-year VA IPRP evaluation and implementation project. In fiscal year (FY) 2025, our team will begin phase 2 with the primary focus on the iterative development of a dynamic data dashboard with the capacity to collect and descriptively analyze pain outcomes from a recently implemented PMOP Pain Measures Set [50], as well as other key metrics (eg, Veterans served). The PMOP Pain Measures Set is a brief multidimensional PRO battery designed to introduce a standardized measurement plan to assess VA pain management services nationwide including pain intensity, pain interference, pain catastrophizing, pain self-efficacy, anxiety, depression, sleep quality, subjective health status, overall well-being, and perceived impact of treatment. The first iteration of this dashboard will be informed by barriers and facilitators to data collection and analysis reported by key informants during qualitative interviews. Primary goals for dashboard development are to (1) streamline data collection, analysis, and reporting to reduce the burden for the individual IPRPs, (2) encourage communication and collaboration among IPRPs to learn from each other on how to improve their outcomes, and (3) to build capacity to conduct regular evaluations of the IPRPs across the VA system. Human-centered design and partner feedback will be used throughout the iterative development of the IPRP dashboard. The latter goal fulfills the VHA Directive 2009-053 mandate for IPRPs to conduct consistent and timely assessments of veterans' pain outcomes to examine the effectiveness of pain management interventions [18].

Phase 3 (FY26) of this evaluation will conduct mixed methods efforts including piloting our dynamic data dashboard to collect PMOP Pain Measures Set [50] outcomes data in a small subsample of champion VA IPRPs. Our data dashboard will be used to provide dynamic reporting of descriptive PROs and additional program statistics collected by our dashboard to our IPRP partners. This quantitative data collection effort will be used to determine the feasibility and initial efficacy of our data dashboard. Key informant interviews conducted at pilot sites will inform a second iteration of our data dashboard to meet current and future PMOP and VA IPRP needs.

In the final phase (FY27-28), we will expand on our pilot study by implementing our dynamic data dashboard to all CARF-accredited VA IPRPs and conduct a mixed methods 12-month national evaluation. An expanded version of the PMOP Pain Measures Set will be implemented in the future, which will allow for more consistent evaluation of PROs across programs. The collection of additional data will allow us to estimate the number of veterans served by all VA IPRPs in real time. Key informant interviews will be conducted to gain insights into the usability of our centralized data collection dashboard system-wide. Qualitative data will also be leveraged to continue iteratively tailoring our data dashboard to meet the future needs of our IPRP partners.

Limitations

There are multiple limitations to consider when reviewing this protocol. First, at the current time, we do not have a methodology for capturing real-time changes in IPRP staffing or implementation of new modalities, which can address the needs of these programs in a timely manner. While this is out of the scope of the current project, a staffing tool is being piloted to address pain program staffing needs across the VA [51]. A second potential limitation is aiming for 0% attrition across 23 IPRPs for 3 study activities (eg, initial interview, program characteristics survey, and follow-up interview). Several steps are taken to help facilitate participation including (1) multiple presentations to the target audience to present the evaluation aims and potential benefits to IPRP, and (2) drafting a memo with PMOP to outline anticipated program participation. Third, POCs may have misconceptions regarding the purpose of the interview and provide socially desirable or expected responses (eg, demand characteristics) [52]. The evaluation team will aim to reduce these effects by providing transparency throughout the process, including informing participants that their interview responses will be examined in the aggregate, their names will not be linked to any of their responses, and that this evaluation is designed to develop mechanisms to improve the IPRP process. Finally, the current evaluation does not address the cost-effectiveness of VA IPRPs, which is beyond the scope of this project. However, this remains an important area of future study because IPRPs are very resource-intensive but have demonstrated cost-effectiveness in the private sector via reduced service utilization postrehabilitation [22,26].

Management Plan and Timeline

Operational partners were engaged to develop a comprehensive timeline for anticipated deliverables (Multimedia Appendix 2). Their input also informed the development of the proposed work and approval of evaluation methods and processes. In addition to project deliverables, the evaluation team will develop quarterly and annual reports to keep partners abreast of study progress (eg, current and completed tasks, recruitment, data collection, preliminary findings, and lessons learned). Our partners will also provide feedback on deliverables (eg, presentations and papers) and tools developed for the current evaluation (eg, interview guides and program characteristics survey).

Conclusions

In summary, the characterization of the VA's CARF-accredited pain programs is critical to the national-level program evaluation of outcomes. This effort is also informing the development of a national effort to implement PRO measurement infrastructure for quality improvement to optimally serve veterans in managing their chronic pain. These data will support efforts to establish CARF-accredited pain programs as part of the VA learning health system. The successful implementation and dissemination of this program evaluation will contribute to (1) optimizing pain management services for veterans, (2) developing an infrastructure to monitor patient outcomes regarding health and

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function, (3) advancing the science of evaluating complex interventions (ie, multiple evidence-based practices) for complex comorbid conditions associated with pain management, and (4) demonstration of VA CARF-accredited pain programs as a learning health system.

Acknowledgments

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Data Availability

Data for this project are available from the authors upon reasonable request. The corresponding author, as a US government employee, has the right to grant on behalf of all authors and hereby does grant on behalf of all authors, a nonexclusive worldwide license to the publishers and its licensees in perpetuity, in all forms, formats, and media (whether known now or created in the future), to (1) publish, reproduce, distribute, display, and store the contribution; (2) translate the contribution into other languages, create adaptations, reprints, include it within collections, and create summaries, extracts, and/or abstracts of the contribution; (3) create any other derivative work(s) based on the contribution; (4) exploit all subsidiary rights in the contribution; (5) include electronic links from the contribution to third-party material, wherever it may be located; and (6) licensee any third party to do any or all of the above.

Conflicts of Interest

None declared

Multimedia Appendix 1
Interview protocols and survey instrument.
[DOCX File , 49 KB - resprot_v14i1e72091_app1.docx]

Multimedia Appendix 2
Timeline of study activities by year.
[DOCX File , 27 KB - resprot_v14i1e72091_app2.docx]

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Abbreviations

CARA: Comprehensive Addiction and Recovery Act
CARF: Commission on Accreditation of Rehabilitation Facilities
CFIR: Consolidated Framework for Implementation Research
CoP: community of practice
FY: fiscal year
IPRP: Interdisciplinary Pain Rehabilitation Program
PMOP: Pain Management, Opioid Safety, and Prescription Drug Monitoring Program
POC: point of contact
PRO: patient-reported outcome
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
SCM-PM: Stepped Care Model for Pain Management
SQUIRE 2.0: Standards for QUality Improvement Reporting Excellence
VA: Department of Veterans Affairs
VHA: Veterans Health Administration

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Protocol

Associations Among Diet, Health, Lifestyle, and Gut Microbiota Composition in the General French Population: Protocol for the Le French Gut – Le Microbiote Français Study

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Related Article:

This is a corrected version. See correction statement: https://www.researchprotocols.org/2025/1/e80127

Abstract

Background: Over the past 2 decades, the gut microbiota has emerged as a key player in human health, being involved in many different clinical contexts. Yet, many aspects of the relationship with its host are poorly documented. One obstacle is the substantial variability in wet-laboratory procedures and data processing implemented during gut microbiota studies, which poses a challenge of comparability and potential meta-analysis.

Objective: The study protocol described here aimed to better understand the relationship between health, dietary habits, and the observed heterogeneity of gut microbiota composition in the general population. “Le French Gut – Le microbiote français” aimed to collect, sequence, and analyze 100,000 fecal samples from French residents using a high-quality shotgun metagenomic pipeline, complemented with comprehensive health, lifestyle, and dietary metadata.

Methods: “Le French Gut – Le microbiote français” is a prospective, noninterventional French national study involving individuals, the creation of a biological collection (feces), and the exploitation of data from questionnaires and the National Health Data System (Système National des Données de Santé). This national study is open to all metropolitan French adult residents, excluding those who have undergone a colectomy or digestive stoma, or who have had a colonoscopy or taken antibiotics in the last 3 months. This is a home-based trial in which volunteers complete a questionnaire with insights about their health and habits, and in which stool samples are self-collected. Data analysis is structured into 6 work packages, each focusing on a specific aspect of the gut microbiome, including its composition and associations with lifestyle, quality of life, and health.

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Results: This paper outlines the study protocol, with recruitment having started in September 2022 and expected to continue until the end of December 2025. As of January 2025, a total of 20,000 participants have been enrolled. The first scientific publications based on the data analysis are expected by mid-2025.

Conclusions: "Le French Gut" aims to provide a reference database and new ecosystem tools for understanding the relationship between the gut microbiota, its host, and diet. We expect to be able to find new signatures or targets and promote the design of innovative preventive strategies, personalized nutrition, and precision medicine.

Trial Registration: ClinicalTrials.gov NCT05758961; https://clinicaltrials.gov/study/NCT05758961

International Registered Report Identifier (IRRID): DERR1-10.2196/64894

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KEYWORDS

gut microbiome; health; chronic diseases; symbiosis; gut; French citizen; French; fecal; fecal samples; nutritional; clinical data; Gut microbiota; gut flora; microorganisms; microbiome; relationship; dietary habit; ecosystem; ecosystem tools; innovation

Introduction

Background

The gut microbiota is composed of all the micro-organisms (archaea, bacteria, microeukaryotes, viruses, etc) that inhabit the intestine. It can be considered as an organ in its own that has coevolved with its host in a symbiotic relationship, contributing to the physiological homeostasis known as "symbiosis" [1]. The gut microbiota is a highly complex ecosystem that can be studied at different levels of resolution. This includes examining diversity parameters, characterizing enterotypes [2,3], exploring various taxonomic ranks ranging from the superkingdom to the species level, and even delving into bacterial strain–specific differences. In addition, the functional potential of the microbiota can be assessed, focusing on the metabolic and biochemical capabilities of the gut microbiome and how these are exchanged with the host.

The establishment and evolution of the intestinal microbiota throughout life is multifactorial, with the environment and dietary habits playing a major role [4-10]. Advances in research demonstrate how crucial this symbiosis is for an individual's health and well-being [11]. Conversely, an imbalance or "dysbiosis" of the gut microbiota is associated with the risk of onset of various chronic diseases, such as those observed in intestinal and liver diseases (inflammatory bowel disease, irritable bowel syndrome, colorectal cancer, nonalcoholic fatty liver disease, and cirrhosis) [6,12,13], obesity [3,14,15], diabetes [16], autoimmune diseases [17-19] and more recently, in neurological diseases via the gut-brain axis [20-26]. Microbial alterations associated with the emergence of pathological conditions affect all microbial strata. Observed alterations include a reduction in microbial diversity [6,13,14,18,19,27], an increase in the proportion of Enterotype B2 [3], as well as disruptions across the different taxonomic ranks [6,13,16,18,19,21,23,25-27]. These alterations extend to their associated metabolic outputs, notably including a reduction in the production of short-chain fatty acids or butyrate [13,15,19,25-27].

Currently, most available microbial studies, including clinical and nutritional data in France and worldwide, are based on relatively small sample sizes, usually ranging from a few dozen to a few hundred individuals, and use different sampling and analysis methods, which makes meta-analysis complex.

To gain a better understanding of the interactions between gut microbiota, diet, and health, it is essential to significantly increase the number of samples of gut microbiota processed in a homogenous manner and cover the widest possible spectrum of phenotypes. For this reason, several large-scale initiatives have emerged, such as "The American Gut project," launched in 2012, which involves more than 10,000 participants, and more recently the Million Microbiomes from Humans Project (MMHP), launched in 2019, which involves several countries around the world and aims to sequence 1 million metagenomes. Building on this momentum, "Le French Gut" was launched in September 2022 with the aim of describing the gut microbiota and associated nutritional and clinical data of 100,000 major individuals living in France, and the ambition to accelerate microbiota science, a source of innovation for tomorrow's medicine and nutrition.

Aims of the Study

By collecting 100,000 gut microbiota profiles combined with metadata on diet, health, and lifestyle, "Le French Gut – Le Microbiote Français" aims at (1) better understanding the heterogeneity of healthy gut microbiota and its link with nutrition, lifestyle, and anthropometric characteristics and (2) predicting changes in gut microbiota associated with diseases such as chronic diseases, neurodevelopmental disorders, and neurodegenerative conditions.

Methods

Study Design

"Le French Gut – Le Microbiote Français" is a prospective, noninterventional national study collecting human fecal samples and connecting them with data from self-filling questionnaires and from the Système National des Données de Santé (SNDS). The trial was conducted according to the recommendations of Standard Protocol Items for Clinical Trials 2013 [28]. The project aims at collecting and analyzing 100,000 stool samples from adult volunteers living in France. The duration of this inclusion phase is estimated at 5 years, and the study is planned to run for 20 years, with active (additional questionnaires) and passive follow-up thanks to its link with the SNDS. Ancillary

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studies could be linked to this main project during this period, including extending it to French overseas departments and territories and to minors.

The study is being carried out in the general population targeting adult volunteers. Participation in the project is free of charge and takes place exclusively via the Le French Gut website [29]. Volunteers are informed about the study through various communication campaigns (national and local media, as well as social networks; Multimedia Appendix 1) and are invited to register on the dedicated website. Questionnaires and forms can be filled in using a user-friendly web interface where all data and personal information security measures are guaranteed, in particular by hosting data in a secure sovereign Health Data Hosting (HDS) certified cloud and General Data Protection Regulation compliant. After reading the information note, volunteers are asked to sign an electronic informed consent form. This procedure generates a permanent inclusion identifier. To become a participant, volunteers must follow the participant's journey (Figure 1). After verifying eligibility for the study, the participant is asked to complete a 53-item questionnaire about their health, lifestyle, and dietary habits (generally completed in 15 minutes as mentioned in the information note). Once the questionnaire has been completed, a stool sampling kit is automatically sent to the volunteer's address. The volunteer collects the stool sample at home using the kit and then sends the stool sample tube to the L'Assistance Publique - Hôpitaux de Paris laboratory via regular mail using a prestamped envelope approved for biological material shipment. Once the integrity and quality of the sample have been checked, the samples are pseudonymized and sent to an INRAE (French National Research Institute for Agriculture, Food, and the Environment) laboratory for biobanking and metagenomic analysis, under a secured ISO (International Organization for Standardization) 9001 and ISO 27001 certified pipeline.

It will also be possible to supplement the basic protocol with various questionnaires within ancillary protocols, targeting either the whole population or selected subsamples according to a particular phenotype (age, gender, area of residence, health status, etc).

Participants will have access to the project's collective scientific feedback, on the website or their personal web page, and will be kept informed of project progress via regular newsletters.

Figure 1. Le French Gut's volunteer timeline. The timeline starts with the profile registration. After filing the noninclusion form, the nonopposition form, the personal identifying form, the registered becomes a volunteer. The volunteer becomes a participant once the questionnaire has been completed and the stool sample returned to the investigation team.

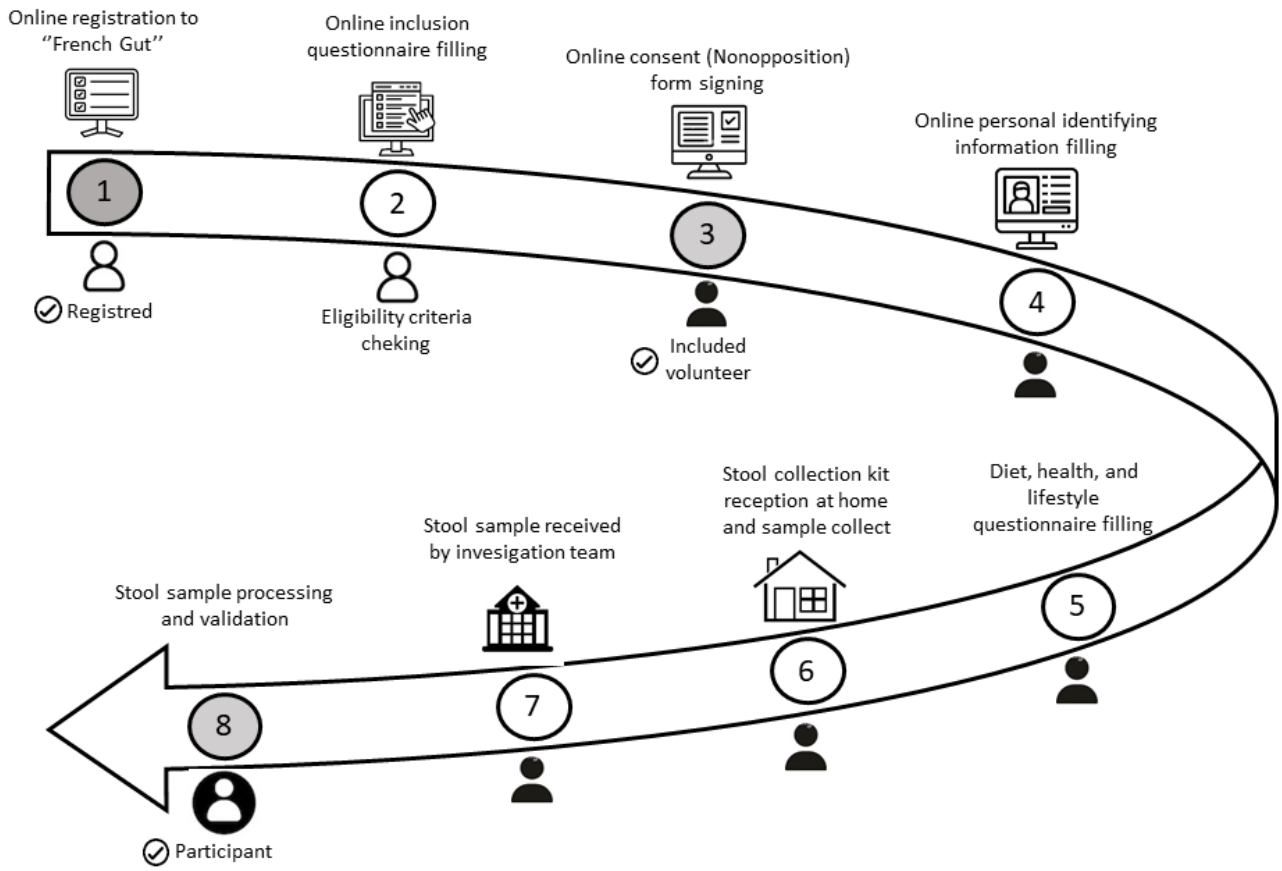

Primary Outcome

The primary outcome is to characterize the heterogeneity and diversity of the gut microbiota of individuals living in France.

The gut microbiota of participants in the "French Gut" project will be characterized by describing the presence and abundance in the samples of each gut microbial genes listed in our up-to-date gene catalog [30]. From these data, the presence and abundance of the different taxonomic ranks will be inferred,

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ranging from a fine granularity at species and strain level to a more "zoomed out" phylum level. The richness and diversity of the microbiome (genes and species) will be described. The functional modules, corresponding to the metabolic pathways encoded by the species detected in each sample, will be determined.

Secondary Outcomes

The secondary outcomes are to study the variations in the gut microbiota of participants as a function of microbial profile, age, sociodemographic and anthropometric characteristics, lifestyle and eating habits, presence of known pathologies at inclusion, occurrence during follow-up of certain pathologies identified by analysis of data from health questionnaires and SNDS data.

Recruitment

The recruitment of participants is mainly based on a direct approach with "public" communication around the project. Participants learn about the project "Le French Gut" through various communication campaigns, including social media, television, radio, national and regional newspapers, magazines, and events. Volunteers can find all the information they need to take part in the project on the website [29]. Communication also aims to raise awareness on the intestinal microbiota, its link with health, and how to care for it through diet. To this end, several communication tools and podcasts are broadcast to the general public and widely distributed on social media.

Partnerships with existing cohorts will also enable their members to take part in this project. Specific populations, such as members of associations or networks, may be included once the scientific committee has validated the interest of these targeted recruitments. Registration procedures for individuals recruited in this way will be similar to those for the general public.

Eligibility Criteria

Le French Gut is a national contribution open to anyone meeting the eligibility criteria. Eligible individuals are adult men and women living in mainland France, with an electronically signed participation agreement. Detailed inclusion and noninclusion criteria are presented in Textbox 1. These eligibility criteria may be different in ancillary projects.

Textbox 1. Le French Gut eligibility criteria.

Inclusion criteria

- Adult men and women residing in mainland France
- Electronically signed consent form

Noninclusion criteria

- Nonadult person
- Person not living in France
- Persons subject to a protective measure, in particular, under guardianship or curatorship or unable to express their consent
- Person underwent a colectomy
- Person with a digestive stoma
- Person who has not signed the consent
- Person who did not answer to the inclusion questionnaire
- Person who did not send a compliant stool sample
- Person having taken antibiotic in the 3 months before inclusion
- Person who underwent a colonoscopy in the 3 months before inclusion

Sample Size

The sample size was calculated taking into account the main objective, which is to specify the presence and the abundance of over 2500 microbial species of the digestive tract and, in particular, the number of subjects required to characterize the enterotype B2 [3]. The enterotype B2 is a fairly rare ecological configuration of the microbiota that is most frequently associated with low-grade inflammation, higher prevalence of cardiometabolic conditions, and predictive of nonresponse to a diet designed to promote weight loss. According to a power test performed on French fecal samples from the MetaCardis cohort, with a population of 100,000 individuals and an expected prevalence of enterotype B2 of 5%, we will have the statistical power needed to characterize 74% of the microbiome that makes up the enterotype B2 with an α risk of 0.05 and β risk 0.80. A total of 100,000 participants will provide sufficient statistical power to assess the link between the composition of the gut microbiota and diseases of interest, but also to assess the composition of the intestinal microbiota of asymptomatic individuals at high risk of developing a disease. Indeed, diseases of interest include type 2 diabetes (prevalence of 6.4% in 2022), heart disease (8.3%), long-term psychiatric disease (4.1%) but cancer (2.3%) [31].

Ethical Considerations

Human Subject Ethics Review Approvals or Exemptions

This study has been approved by the the "Comité de Protection des Personnes" Sud-Est IV (CPP, 21.00225.000006) and the

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"Commission Nationale Informatique et Liberté" (CNIL, DR-2022-141).The study registered in France under reference 2021-A01439-32 was authorised on October 15,2021. Detailed trial registration dataset is presented in Multimedia Appendix 2.

Informed Consent

All participants were asked for their consent to participate in this study before enrollment and agree to its privacy policy and terms of service required for the remote collection of their information. The participation is entirely voluntary. Electronic informed consent form to participate is obtained from all study participants. Participants can opt out of the study anytime by going on its account. The participant may withdraw from the study at any time without justification (under the "management of my participation" section in his personal space). The participant is aware that the withdrawal will not affect any activities conducted or the use of data obtained based on the informed consent given before the withdrawal, in accordance with the Public Health Code. Furthermore, the participant consents to the reuse of his data under pseudonymized in the case of a study extension, or for ancillary studies within the same research field (microbiota), and only after approval of relevant authorities.

Participants have access to all studies in which their data have been used, and can withdraw their participation at any time from any study.

Privacy and Confidentiality

After logging into the French Gut registration site, participants will be assigned a pseudonym that will be created using the anonymization or pseudonymization techniques recommended by the National Agency for the Security of Information Systems and the French Data Protection Authority (CNIL). This pseudonym is guaranteed to be nonidentifiable. The reference is unique and will be retained for the entire duration of the study. Furthermore, the results will be reported only in aggregate form and not on an individual basis.

Compensation Details

Participants will be kept informed about the progress of the study and its overall results through regular newsletters, shared on participants' accounts, as well as through webinars exclusively dedicated for them. Participation in this research is voluntary and does not offer any possibility of personal benefit, nor does it entitle participants to any compensation, except the one mentioned above.

Participant Journey

To take part, volunteers need to answer a 53-item online questionnaire about their health, lifestyle, and dietary habits, and collect a compliant stool sample. The participant's journey is detailed in Figure 1.

Registration and Questionnaire

To take part in the study, volunteers need to create a personal account on the project's website [29]. Registration and data collection take place directly on the project website, using an end-to-end encrypted connection. The questionnaire and data are stored in an HDS-certified environment (SKEZIA), provided by a company specializing in eHealth solutions and e-cohorts. The entire platform was initially developed and tested in a development environment before being deployed in production and made accessible to participants. After checking that the volunteer is eligible and has signed the informed consent form, the volunteer completes the questionnaire, which consists of 53 items divided into 3 different parts (Multimedia Appendix 3). The first part of the questionnaire provides sociodemographic data (duration of residence in mainland France, mode of delivery, etc) as well as lifestyle data (smoking habits, sedentary lifestyle, and physical activity). The second part of the questionnaire provides information on anthropometric characteristics (weight and height) used to calculate the BMI. This section also collects health data, including chronic diseases. In order to characterize the digestive health of the volunteers, the questionnaire also includes questions relating to gastrointestinal symptoms and factors influencing digestive health. This questionnaire also includes the Bristol Stool Consistency Scale [32]. It also contains questions to define an assessment of a participant's mental well-being called the "Perceived Stress Scale 4" or PSS-4 [33]. The third part of the questionnaire is devoted to the dietary habits. First, food exclusions and specific types of diet are addressed. The volunteers then indicate, for each of the food families present in the questionnaire, the frequency of their usual daily or weekly consumption. In addition, the questionnaire focuses on the specific dietary factors that have an impact on the gut microbiota. Overall, the 53 questions are distributed across 4 web pages. These questionnaires are adaptive, and each page contains an average of 16 questions (ie, the request for clarification on certain items only appears if the participant answered "yes" to the first question, for example, to provide a specific digestive disease). Full completion of the questionnaire is mandatory to move on to the next stage, that is, receiving the kit at home. Volunteers can modify their answers as long as they have not submitted the questionnaire. Once submitted, the participant can contact the investigation team at any time to indicate whether any of the eligibility criteria have changed (ie, antibiotics taken between completion of the questionnaire and sample collection), or to modify their responses after the submission of the questionnaire. The questionnaire is a one-shot and can only be completed once.

As the project progresses, additional questionnaires will be offered to participants who have agreed to be recontacted for further contribution to scientific explorations. These questionnaires will be more detailed on health, lifestyle, and dietary habits. They will not be mandatory, but they will help us to answer specific scientific questions that emerge as the project progresses.

The validity of the data is verified by input and consistency checks. The questionnaire database is stored in an HDS environment and the metagenomic data on the MGP's information technology infrastructure, as close as possible to the sequencing instruments and the heavy bioinformatics processing.

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Stool Sampling

After completing the initial questionnaire, a stool sampling kit is sent to the volunteer. The stool sample is collected at home by the volunteer in a tube containing a stabilizing liquid buffer (DNA and RNA shield). The date and time on which the sample was taken is handwritten by the volunteer on the pouch containing the tube. After sampling, the tube is mailed directly to the investigation team via a prepaid envelope. The investigation team checks the conformity of the sample (eg, presence of identification data on tube, missing sample, and broken tube). Samples that do not pass the initial quality control are flagged up and a new sampling is scheduled. Quality control–validated samples are stored at –80 °C at the MGP-SAMBO BRC (Biological Resources Center), which is ISO 9001–certified and labelled GIS-IBiSA (CRB N°242), until further processing.

Stool Sample Processing

DNA Extraction and Shotgun Sequencing

Total fecal DNA will be extracted using an in-house automated protocol that has been developed and improved on the International Human Microbiome Standards (IHMS) standard procedures (SOP 07 [34]). Extracted DNA is evaluated by fluorometric quantification, purity assessment, and fragment size analysis, then if suitable, sequenced using a high-throughput short-read DNA sequencer. A minimum of 2×20 million paired-end reads of 150 nucleotides is produced for each sample.

Microbial Gene Abundance Table and Taxonomical Profiling

Sequencing data are cleaned to (1) remove remaining sequencing adapters, (2) trim low-quality reads, and (3) discard reads too short (<60 bp) using Alien Trimmer (v0.4.0) or equivalent quality trimming software [35]. Reads mapping to the human genome are removed using Bowtie2 (v2.5.4) [36]. Microbial gene abundance and taxonomical profiling are then performed using Meteor2 [37] with our up-to-date gene microbial genes [30] and species (clustered with MSPminer [38]) catalogs of the human microbiota. Gene abundance profiling table is generated by mapping the reads onto the genes catalog. Species abundances are estimated as the mean abundance of the species marker genes. Richness and diversity parameters are computed using the species abundance table with Vegan R package [39]. Our catalogs will be continuously updated throughout the project based on newly identified clustered species, newly available taxonomy, gene annotations, and genomes.

Contribution of the SNDS

The French national health data system also referred to as SNDS contains individual data for all reimbursements of health expenses for more than 99% of residents of French territory, that is, more than 65 million people. This system enables powerful analyses both in terms of the number of subjects involved and the hindsight now available (data collected since 2007). Available data are both administrative and medical. Administrative data are mainly sociodemographic data (age, sex, complementary universal health cover [named CMU-c], etc). Medical data include, among others, the list of chronic diseases of the volunteers that are 100% reimbursed by the French medical system or, for example, the exhaustive list of reimbursed drugs that have been prescribed over the years. Collecting the social security number during inclusion allows direct matching between the SNDS data and gut microbiota data from Le French Gut study.

This matching will allow us to gain a deep insight on the connection between the present participant's health and its gut microbiota. It will also bring light on how the participant's medical history is connected to its present gut microbiota profile.

Statistical Methods

The statistical plan is designed to address both primary and secondary outcomes. It is structured into 6 distinct work packages, each targeting key aspects of the gut microbiome and its interactions.

First, microbial ecology and variability: this work package aims to characterize microbial ecology, variability, and composition across the French population. The main objective is to consolidate validated ecological tools and develop new ones leveraging the statistical power of this study. These tools will capture microbial variations at multiple levels, including alpha and beta diversity metrics, enterotypes [2], local partitioning [40], microbial guilds, and taxonomic ranks down to the strain level. These ecological tools will be analyzed across the entire French population. In addition, this work package will investigate how regional environmental exposures (air, water, soil, etc) correlate with microbiome variations.

Second, gut microbiome in healthy individuals: this work package focuses on establishing baseline profiles of the gut microbiome in healthy individuals. The first objective is to define and characterize a healthy population based on lifestyle habits, dietary patterns, and quality of life. Clustering techniques will be applied to classify individuals based on lifestyle factors (eg, smoking, alcohol consumption, and physical activity), dietary habits, and quality-of-life indicators (eg, sleep quality, digestive symptoms, and perceived stress). These clusters will allow us to explore whether the microbiome can reflect and influence the accumulation of risk factors in the healthy French population. The second objective is to assess the predictive potential of the microbiome for future health outcomes. Using the SNDS database, we will evaluate whether participants develop pathologies over a 10-year follow-up and identify microbiome signatures associated with disease onset.

Third, this work package investigates the relationship between the gut microbiome and the presence of pathological conditions. The pathological population will be characterized in terms of lifestyle habits, dietary patterns, and existing conditions. The project's extensive statistical power will enable the stratification of pathologies, facilitating validation of known microbial signatures and identification of novel microbial markers linked to disease progression.

Fourth, this work package explores interactions between dietary patterns and microbiome composition. The first step involves characterizing dietary habits within the French population, both globally and with a focus on specific food components such as proteins, fibers, and polyphenols. We will then analyze how

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these dietary patterns influence and are influenced by the gut microbiome.

Fifth, this work package focuses on characterizing nonbacterial components and subdominant members of the microbiome. The large sample size will enable the exploration of less-studied gut ecological niches and microbes, including archaea, viruses, fungi, and protozoa. Their distribution, abundance, and associations with lifestyle, quality of life, and health conditions will be examined. In addition, we will investigate subdominant microbial species and strains that remain unexplored due to limited sample sizes in previous studies.

Sixth, this work package examines the influence of environmental exposures, including antibiotic and other medication use, on the microbiome. The first step involves stratifying the population based on medication and antibiotic usage. We will then assess microbiome responses to these exposures, with a specific focus on antibiotics. Thanks to the SNDS database, we will analyze antibiotic exposure data spanning the 20 years before participants' enrollment (ie, up to 2006), allowing an in-depth investigation of the relationship between multiple antibiotic exposures and antibiotic resistance in the gut microbiome.

Given the explanatory nature of Le French Gut, each work package statistical plan will be further refined as data exploration progresses.

Each work package will use comparable statistical tools, methods, and analytical approaches. Except for work packages 1 and 5, the initial statistical step in each work package consists of characterizing the data collected from all included volunteers. Descriptive statistics (eg, mean and SD for continuous variables and contingency tables for categorical variables) will be used to summarize the data. Graphical visualizations, univariate analyses (eg, *t* tests and ANOVA), and multivariate analyses (eg, principal component analysis, factorial analysis for mixed data, and network analysis) will be performed to explore data structure, detect outliers, and identify potential stratifications.

For univariate analyses, conventional statistical tests (eg, Mann-Whitney-Wilcoxon, *t* test, Kruskal-Wallis, and chi-square tests) will be used to compare microbial, dietary, sociodemographic, and clinical variables across predefined volunteer groups. *P* values will be adjusted using the Benjamini-Hochberg procedure to control the false discovery rate. Correlation analyses will be conducted to examine associations between microbial species of interest and sociodemographic, lifestyle, environmental, nutritional, and clinical parameters.

Multivariate analyses will serve both descriptive and predictive purposes. Descriptive multivariate methods such as principal component analysis, factorial correspondence analysis, clustering, multidimensional scaling, and bacterial co-occurrence network analyses will be used to structure and synthesize the data. Specific complexity-reduction approaches include enterotype classification, which discretizes microbial heterogeneity into a limited number of states [2], and microbial guilds, which identify clusters of species with coabundance patterns across conditions. In addition, unsupervised clustering methods will be used to define microbiome-based subpopulations independently of phenotypic characteristics, allowing unbiased subgroup discovery.

For predictive modeling, supervised learning techniques such as discriminant analysis, random forests, and regression models will be applied to assess the microbiome's ability to predict phenotypes of interest, including disease presence, nutritional profiles, environmental exposures, and health trajectories. These models will be trained and validated using independent test subsets to evaluate their predictive performance.

Integration of the "Le French Gut" Project Into the MMHP

Metagenomic data from the "Le French Gut" will be shared anonymously as part of the collaborative science project (MMHP) which involves many countries worldwide including France, Sweden, Denmark, Latvia, and China as founding members. This project aims at sequencing one million human microbial metagenomes coming from the gut, mouth, skin, and other human organs. It will make available to researchers the metagenomic data associated with the sampling date, the sampling site, and protocols as well as a limited amount of metadata, such as age, sex, BMI, geographical location (France for this study) and "healthy" or "ill" status (with *ICD-10* [*International Statistical Classification of Diseases, Tenth Revision*] disease code if available).

Results

Recruitment started in September 2022. As of January 2025, we enrolled 20,000 participants. The first scientific publications based on the data analysis are expected by mid-2025.

Discussion

Anticipated Findings

Le French Gut is a national participatory science project designed to explore the heterogeneity of gut profiles within the French resident population with an ambitious statistical power, 100,000 subjects. By leveraging robust statistical methods and state-of-the-art bioinformatics tools, Le French Gut seeks to offer novel insights into the definition and organization of the gut microbiome. While the project intends to shed light on its variations within the national population, it also aims to provide a better understanding of the shifts potentially associated with the onset of pathological conditions. However, the full implications of these shifts and their direct link to specific health outcomes will require further investigation.

One of the main advantages of this protocol is the simplicity of the participant route. Everything can be done at home. This ease of use, coupled with large public communication and awareness campaigns, is an asset toward reaching 100,000 participants. Like the MMHP, The American Gut, The British Gut, The LifeLines Deep, The 10K, or also The Flemish Gut projects, Le French Gut is part of this worldwide willingness to drastically increase the available number of gut microbiota profiles. Le French Gut will constitute a significant database with 100,000 shotgun-sequenced gut microbiota profiled up to the strain

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levels. In addition to the microbiome data, information on participants' lifestyles, medical history, and a detailed characterization of their dietary habits will also be included. While this comprehensive dataset has the potential to provide valuable insights, the complexity of interpreting such data means that drawing definitive conclusions about the relationships between microbiota, lifestyle, and health outcomes will require careful analysis and further research. Another main strength of Le French Gut is the high-quality standards used to biobank and process all microbial samples. One of the main biases when comparing metagenomics projects is the absence of sample processing information and quality measures between the projects being compared, whether in terms of sampling, storage, extraction, or sequencing. Within the Le French Gut project, the 100,000 microbiome profiles will be processed with protocols that will follow the IHMS [41] or higher standards that will arise during the course of the project. In addition, Le French Gut's flexible recruitment process allows an interesting opportunity for synergistic collaborations with other cohorts aimed at deeply characterizing patients or healthy subjects. This strategic approach will facilitate the gathering of valuable data and promote cross-cohort research initiatives. In addition to the core project, we plan to extend the recruitments to children and teenagers (Le French Gut Kids) and to overseas territories.

Le French Gut will contribute to a better understanding of the organization of the intestinal microbiota and the factors related to its variations. Thanks to its statistical power, Le French Gut will have to potential to help validate well-known ecosystemic tools (diversity measures, enterotypes, etc) and confirm well-known discoveries. It will also provide an opportunity to deploy novel tools, such as microbial guilds, gut microbiota global, and local partitioning [40] at a larger scale, and new microbial metabolic reconstruction pathways. In conjunction with nutritional data, these ecosystemic tools offer an opportunity to explore the connection between diet and the diverse range of ecological states of the human gut microbiota. With this project, we anticipate to lay the foundation for precision nutrition approaches aimed at defining diets or supplements tailored to specific gut microbiota states. In addition, Le French Gut will provide the scientific community with valuable insights into the heterogeneity of microbial profiles within a healthy population, offering a clearer understanding of how the gut microbiota may potentially serve as a predictor for future health issues. Thanks to the SNDS, gut microbiota profiles will be integrated into each participant's overall past, present, and future health landscape. We expect to discover new biomarkers that could lead to possible new preventive strategies through personalized nutrition, diagnostics, or therapeutics. Finally, Le French Gut is expected to provide recommendations for more systematic use of the microbiota as a tool to support clinical management.

Conclusions

"Le French Gut" aims at providing a reference French gut microbiome database and new ecosystem tools for understanding the relationship between the gut microbiota, its host, and diet. We expect to be able to find new signatures or targets and promote the design of innovative preventive strategies, personalized nutrition, and precision medicine.

Acknowledgments

The authors thank all those who have participated in the design, elaboration, and supervision of the project. Special thanks to the steering committee and the executive committee (Multimedia Appendix 4) for their substantial involvement and commitment.

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ChatGPT-4-turbo was used to correct spelling, vocabulary, or syntax mistakes. Any suggestion of correction provided by ChatGPT was reviewed and validated by the authors.

Data Availability

The datasets analyzed during this study and statistical code are available from the corresponding author on reasonable request, as is the whole protocol.

Authors' Contributions

CC contributed to the design and the regulatory aspects of the research and to the writing of the manuscript. She is involved in the supervision of the study. SF contributed to the design, the implementation and the promotion of the research, and to the planning and the writing of the manuscript. He is involved in the supervision of the study. MB contributed to the reviewing and correction of the manuscript. He is involved in the supervision of the study. A-SA contributed to the promotion of the research and the recruitment of volunteers by developing and implementing the communication strategy and to the writing of the manuscript. NP contributed to the design and implementation of the research. He is involved in the supervision of the study. BQ, CM, and SDE contributed to the design of the research. EB-D contributed to the regulatory aspects of the research. J-AN contributed to

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the design of the questionnaire. FH contributed to the design, the implementation, and the regulatory aspects of the research. KV contributed to the design, the promotion, and the funding of the research. She is involved in the supervision of the study. AC contributed to the design and to the promotion of the research. He is involved in the supervision of the study. HB contributed to the design and implementation of the research. He is involved in the supervision of the study. PV contributed to the design, the implementation and the promotion of the research and to the writing of the manuscript. He is involved in the supervision of the study. MA contributed to the design, the implementation, and the promotion of the research and to the writing of the manuscript. He is involved in the supervision of the study. JD contributed to the design, the implementation, the promotion of the research, and to the writing of the manuscript. He is involved in the supervision of the study. RB is the principal clinical investigator of the study, contributed to the elaboration of the project, implementation of the research, and to the writing of the manuscript. He is involved in the supervision of the study.

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All authors have contributed to writing and reading the manuscript and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Flyer Le French Gut.
[PDF File (Adobe PDF File), 3165 KB - resprot_v14i1e64894_app1.pdf]

Multimedia Appendix 2
Trial status.
[DOCX File , 15 KB - resprot_v14i1e64894_app2.docx]

Multimedia Appendix 3
Le French Gut main questionnaire.
[DOCX File , 39 KB - resprot_v14i1e64894_app3.docx]

Multimedia Appendix 4
Executive and steering committee.
[DOCX File , 13 KB - resprot_v14i1e64894_app4.docx]

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Abbreviations

CNIL: Comité National Informatique et Liberté
HDS: Health Data Hosting
ICD-10: International Statistical Classification of Diseases, Tenth Revision
IHMS: International Human Microbiome Standards
INRAE: French National Research Institute for Agriculture, Food, and the Environment
ISO: International Organization for Standardization
MMHP: Million Microbiomes from Humans Project
SNDS: Système National des Données de Santé

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Proposal

The Digital Library of Health Care Consultations and Simulated Health Care Student Teaching: Protocol for a Repository of Recordings to Support Communication Research

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Abstract

Background: Miscommunication in health care is a major source of poor health outcomes, complaints about health care professionals, and poor patient satisfaction. Recordings from real-life consultations provide valuable data for communication research and education. Additionally, recordings from simulation-based education of health care students can provide valuable data for health care education research.

Objective: The Digital Library is a data repository supporting high-quality health care communication research. This is the single-source citation for all projects that use the Digital Library in Australia.

Methods: This protocol outlines the logistics and consent process for recording and safely storing the recordings of health care consultations and simulation-based education. The processes are outlined for primary health care settings and health care educational settings as well as for health care narratives from consumers. The repository will be used to answer research questions about health care communication and provide a valuable resource for health care education.

Results: Data collection for the Digital Library commenced in 2023 and is ongoing at the time of submission of this protocol. The Digital Library has been approved by Monash University's Human Research Ethics Committee.

Conclusions: The Digital Library will provide a national resource for the study of health care communication in community settings, general practice, and other environments. The health care narratives may be a valuable resource for sharing the patient perspective when living with different conditions. The research that uses this repository will be shared through regular academic channels as well as the community-based dissemination strategies of the National Centre for Healthy Ageing.

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KEYWORDS

health care communication; patient-physician relationship; community health care; medical education; health care education

Introduction

It is estimated that more than 18,000 deaths occur each year in Australia due to medical errors [1,2]. The Organisation for Economic Co-operation and Development estimates that 15% of hospital expenditure can be attributed to treating the consequences of patient safety failures [3]. Miscommunication in health care is known to impact and cause some medical errors [4], and is the second highest reason consumers raise complaints with health care regulators in Australia [5]. There are many and varied clinical situations where communication failures can occur, including poor handover between clinicians about a patient's condition, inadequate consent processes, and poor rapport or bedside manner, particularly in the context of sensitive health discussions. A taxonomy of communication failures in the United Kingdom highlighted more than 50 categories of communication errors [6].

The harms of communication failures have been investigated in multiple areas of clinical practice and population groups, for example, communicating medication prescriptions with older adults following discharge from the hospital [7] and communicating with people with disability [8]. Poor communication between older adults who are culturally and linguistically diverse and health care workers has also been shown to lead to health disparities and discrimination, miscommunication, unmet needs, difficulties providing care [9], underreporting of symptoms [10], lower satisfaction with care [11], and increased use of potentially unnecessary diagnostic tests [12]. There are also communication issues that have been investigated that cut across population groups and clinical specialties, such as the investigation of unconscious biases influencing communication and that result in health inequities [13]. Recordings of health care consultations allow researchers a real-world view of communication as it happens, negating the effects of recall bias that occur with other research designs.

Several benefits have been identified by strengthening the communication skills of health professionals. Strong health care professional communication skills have been shown to improve health outcomes, particularly for pain [14], and positive communication can have placebo-like effects with improvements in patients' anxiety, mood, and satisfaction [15]. Satisfaction with physician communication skills has been linked with better adherence to medications for hypertension [16] and improved patient-centered outcomes for older patients [17]. This points to communication skills training as a modifiable area for improving health care safety and quality and consumer satisfaction and engagement in their health care journey. Recordings of educational sessions that focus on communication skills are an opportunity to investigate best practices for learning.

The rise of virtual health care, including telehealth, has added another dimension to the investigation of how communication impacts health outcomes. Virtual care consultations have become a commonly used modality of health care delivery, particularly since the COVID-19 pandemic. Understanding the interaction between different communication techniques and this medium is important to promote safe and effective care [18]. While technology enables these consultations, research is only beginning to explore the unique communication dynamics between clinicians and patients in virtual settings. Understanding and refining these skills is essential, particularly given that virtual care consultations, often referred to as "black boxes" [19], occur behind closed doors, leaving much unknown about effective engagement strategies. With the emergence of virtual care, we need health care communication research that focuses on the complexity of communicating when cues such as body language, tone, and movement are missing.

Despite the impact of miscommunication in health care, there are few dedicated research infrastructures in the world to support research and education on real-life health care communication. In the Netherlands, there is a large repository held at Nivel, the Netherlands Institute for Health Services Research, that contains health care consultations from multiple disciplines [20]; in New Zealand, there is the Applied Research on Communication in Health Corpus at the University of Otago [21]; and in the United Kingdom, there is a repository of hundreds of general practice consultations called "One in a Million" at the University of Bristol [22].

The Digital Library, as a part of the National Centre for Healthy Ageing, will provide a window into real-life consultations in the Australian clinical environment and simulated health care consultations in education settings to support health care communication research and education. This research infrastructure aims to provide resources to improve consumer satisfaction and health care quality for health care consumers in Australia. This protocol outlines the process for data collection and storage, is the single-source citation for research that uses data from the Digital Library, and can also provide a framework for other groups internationally looking to establish a similar resource.

Methods

Overview

This protocol describes the recruitment, types of data, and logistics and storage for recordings being collected. This repository is a research infrastructure that will support research on health care communication practices to enhance patient health care safety and quality. The recordings can also be transcribed and used as scripts for recorded health care consultations with simulated actor patients and health care professionals. An overview of the types of video recording that will be housed in the Digital Library is provided in Figure 1.

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Figure 1. Types of video recordings to be housed in the Digital Library.

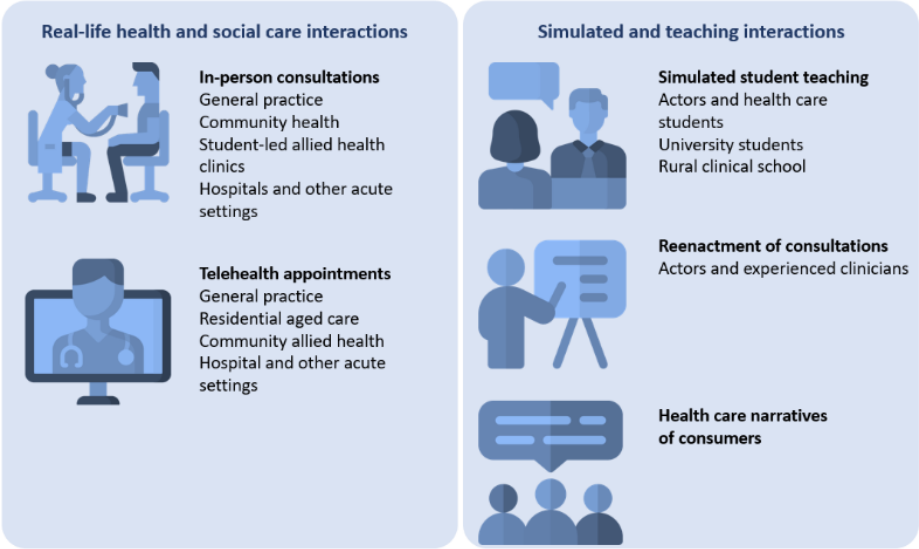

Setting

Health care settings include primary health clinics (eg, general practices, allied health clinics), health care educational settings (simulated teaching sessions between students, instructors, and trained actors), and student-led health care clinics that occur in-person and via virtual care.

Patient and Public Involvement

Patients or the public were not involved in the design of this protocol but will be involved in future advisory groups that will shape the direction of the Digital Library and the research that is undertaken on the collected data.

Types of Data in the Library

The Digital Library will include in-person interactions and consultations, virtual consultations, health care narratives, and simulated interactions used in the teaching of health care professionals. Reenactments of these real-life scenarios will also be undertaken with simulated actor patients to enable wider dissemination across Australia while safeguarding privacy. The reenactments will be recorded on-site in Melbourne using anonymized scripts from the real-life consultations, with details changed to ensure confidentiality. An overview of the types of data and collection, storage, and retrospective access can be found in Figure 2.

Figure 2. The logistics of data recording, storage, and access of the Digital Library.

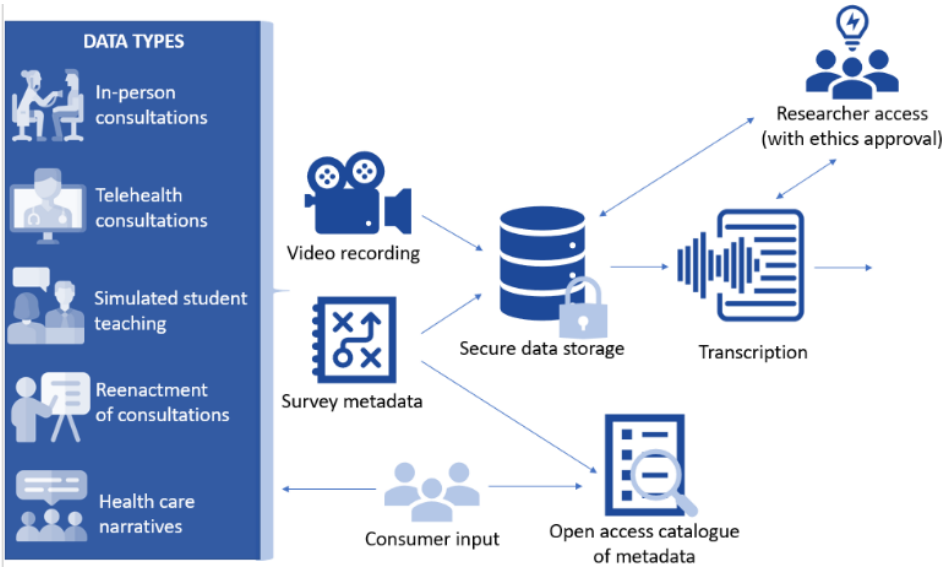

As funding allows, investigators will add the following data to the Digital Library:

- Tailored metadata is ingested into a publicly available catalogue.
- Natural language processing is used to allow for increased discoverability of the data.

Recruitment

Health Care Settings

Recruitment will occur in two stages: first, clinicians will be recruited, and then patients will be invited to participate on a recording day.

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Recruiting Clinicians in Primary Health Settings

All types of clinicians working in primary health are eligible to be part of the Digital Library, including, but not limited to, general practitioners, practice nurses, nurse practitioners, and allied health clinicians. Investigators will use their professional networks and publicly available contact information. Health care professionals will be invited by email by the investigators through the following process:

- An initial letter or email of invitation will be sent to the clinician explaining the project and asking them to be involved. The email will include the information sheet for the project. The email will ask the participant to reply via email to arrange a time to discuss the project if interested.
- A phone call or email from the research team to the clinician will be undertaken 1-2 weeks after the letter/email. Clinicians who participate will be asked if they know of other clinicians who may be interested (snowball sampling).

Investigators will also post recruitment advertising on social media (Facebook, LinkedIn).

Research staff will first obtain written informed consent from health care professional participants. At this point, health care professional participants will be asked to complete a survey with demographic and professional experience details. Depending on the funding structure of the project, health care professionals may be provided an honorarium for their participation.

Recruiting Patients in Primary Health Settings

Patients who attend a participating clinic will be invited to be part of the Digital Library, with the intent to record their clinical interaction on that day. Any person who is acutely unwell, distressed, or unable to give written consent in English will not be approached to participate. All patients will be invited to participate when they attend the clinic, and when the patient is younger than 18 years, the parent/guardian will be invited. Reception staff will make potential patient participants aware that a study is occurring and provide them with an information sheet. Next, the research staff will approach the potential participant or parent to answer any questions they may have about the study and obtain written consent. When the patient is a child, they will be invited, provided a video about the project, and required to assent before participation. In the setting of virtual care, the health care professional will first explain that they are part of a research project. They will ask permission from the patient to record the telehealth consultation. They will also seek the patient's permission to give their name and phone number to the research team. Using the patients' contact details shared with their consent by their clinicians, the investigators will then contact the patient and explain the project in detail and obtain written consent from the patient by email. The patient can decline at this stage, and the recording will be deleted if written consent is not obtained or if the investigators cannot contact the patient.

Patients will be asked for consent to:

- Complete pre- and postconsultation surveys: The preconsultation survey will only be administered after the consultation in the telehealth setting. The patient will be emailed the surveys by the research team once they have received informed consent from the patient.
- Video recording of their consultation
- Permission to keep their video recording on a secure server as part of a library of consultations: These consultations will only be used for research, and any further study outside of this remit will require ethics approval. Research requests to use the Digital Library data require approval from the Digital Library governance team as well as appropriate ethics approval.

Simulated Teaching Sessions

Overview

Education sessions that involve simulation or role-plays will be eligible for recording. Our team of investigators has connections with the health professional training programs at our university. All health care disciplines are eligible for recording, including, but not limited to, medicine, podiatry, physiotherapy, paramedicine, occupational therapy, social work, and radiation therapy. Consent will occur in two steps.

Recruitment of Educators in University Health Care Programs

Educators will be invited by email from their public staff profile. An initial email of invitation will be sent explaining the project, and it will include the explanatory statement. Educators will be asked to reply by email to permit us to contact them to arrange a meeting to discuss the project in detail. Educators who participate will be asked if they know of other educators who may be interested in participating. The Digital Library will also advertise in professional newsletters, on social media, and using flyers on campus.

Recruitment of Health Care Students

Students will be approached in person outside the classroom before their simulated teaching session. Research assistants will hand out an explanatory statement, verbally explain the project, and obtain written consent. For online teaching and student-led telehealth clinics, the course coordinator or lecturer associated with the teaching unit or clinic will send the students the project information and ask them to contact the research team if they are interested. This will preserve students' privacy as students will give their details to the research team directly.

Health Care Narratives

Investigators will collect health narratives from a diverse range of health care consumers with their informed written consent. Health care consumers will be invited to narrate their own story and experience of health care for inclusion in the Digital Library. Participants are invited via an online consumer platform at the National Centre for Healthy Ageing as well as public announcements at National Centre for Healthy Ageing events. There are no exclusion criteria for health care narrative participants. All underrepresented or marginalized population groups (including but not limited to Indigenous and First Nations peoples, people living with disability, people who speak English as a second language, and those who are gender diverse) are encouraged to participate. Purposeful recruitment strategies will be undertaken to reduce any equity-related communication

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barriers to participation. This includes, for example, partnering with community organizations to support safe and inclusive engagement and participation.

Researchers will use an unobtrusive interviewing style and ask broad questions only (Multimedia Appendix 1). Investigators will recruit participants via professional networks, contacts via the health care teaching programs, and community advertisements. Consumers may be offered an honorarium depending on the funding available in appreciation of their time and effort. Recordings will be made in a setting that is convenient for the participant. Consumers will be able to choose how they would like their narrative to be accessed: for research purposes, for educational purposes (eg, to be shown in teaching sessions), or for community viewing (eg, on a public website).

Data Collection

In health settings, investigators will collect data from:

- Clinician survey: The clinician will be asked to fill in a survey that includes demographic and professional experience details before the day or early on the day of recording (Multimedia Appendix 1).
- Health care consumer surveys (pre- and postconsultation): Health care consumers will be asked to complete a survey before their consultation detailing their demographics, reason for visit, and how long they have known the clinician. Post consultation, they will be asked to complete a survey detailing their consultation experience, including whether they felt respected, felt listened to, and had enough time (Multimedia Appendix 1).
- Video recording of the consultation: A camera will be placed in the consultation room aimed at the full face of the clinician without the patient in view, but with both voices being recorded. No physical examination that takes place away from the camera will be video recorded. The audio recording will remain on for the full consultation.

In educational settings, data will be collected from:

- Educator survey including demographic and professional experience details (education and clinical; Multimedia Appendix 1).
- Video recording of the educational setting

At this stage, students will not complete a survey. This may be added later should it prove to be useful for research purposes.

In health care narrative settings, investigators will collect data from:

- Participant demographic survey (Multimedia Appendix 1).
- Video recording of the participant sharing their narrative in their home, a private space at a Monash University campus, or via a Zoom (Zoom Communications) call

Data Storage and Security

Storage

This protocol mediates between the opposing forces of the need for reliable, accessible data for research and training, and the need to protect the privacy of participants. Table 1 illustrates our approach to the accessibility, privacy, and rediscoverability of the video recordings.

The Digital Library will be accessible while respecting the privacy and confidentiality of participants. It will also be built to embody the findable, accessible, interoperable, and reusable (FAIR) principles, and our activities will consider the collective benefit, authority to control, responsibility, and ethics (CARE) principles of data storage [23]. All participants provide informed consent that their data will be stored indefinitely and potentially accessed in the future. This is justified and ethically approved, as the purpose of the Digital Library is to grow a data resource that can provide real-world insights into the changes to health consultation interactions across time, similar to Nivel in the Netherlands. Participants are made aware through the consent process and encouraged to contact the Digital Library if they wish their data to be removed moving forward. There is no re-consent process as this is the responsibility of the participant. Participant data will be removed immediately following any such request. If participants do not consent in the first place, their data is not stored in the Digital Library.

The data will be stored indefinitely and discoverable in three tiers:

1. Raw data of the recorded real-world consultations: accessible through in-person, private screening pods on-site at Monash University within the National Centre for Healthy Ageing, or after relevant ethics approvals
2. Transcripts and reenactments: accessible off-site after ethics approvals
3. Curated metadata: open access, searchable catalog that allows researchers worldwide to know what is available in the Digital Library and plan their research accordingly

This approach enables us to work within the FAIR and CARE principles of research data access, allowing the research platform to be used by as many people as possible while preserving the privacy of participants (Table 1).

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Table 1. The types of data in the Digital Library and accessibility across Australia.

Recording types	Level of sensitivity	Data access		
		Video recordings	Deidentified transcriptions	Catalog of metadata
In-person consultations	High	On-site with ethics approval	Off-site with ethics approval	Open access
Telehealth appointments	High	On-site with ethics approval	Off-site with ethics approval	Open access
Simulated student teaching	Medium	On-site with ethics approval	Off-site with ethics approval	Open access
Reenactment of consultations	Low	Open access	—[a]	Open access
Health care narratives	Low	Open access	—	Open access

[a]Not applicable.

Video Recordings

The recordings will be stored on a separate on-site computer that can only be accessed by a primary investigator and research staff who specifically require access. Monash University's Information Technology Department will secure the computer so that it is the only device able to access the recordings. The computer access will be housed in the National Centre for Healthy Ageing at the Peninsula Campus of Monash University. The real-life recordings will only be accessed for research purposes.

Paper-Based Surveys

All paper surveys will be scanned and stored on a secure, password-protected network drive. Once stored, the paper copies will be destroyed. The survey answers will be transferred to an electronic file that is maintained on a secure, password-protected network drive.

Confidentiality

The participants' names will be linked to a unique identifier. This will be kept in an electronic file, separate from the recordings and paper-based surveys, and maintained on a secure, password-protected network drive. This information will be kept so that the patient can request deletion of their video at any time in the future via email or phone call to the research team. If the video has been used for research that is in progress or completed, the video cannot be removed from the research. However, the video will be destroyed so that it cannot be used in future research.

Access to the Digital Library for Researchers

Access to the data aligns with the policies of the National Centre for Healthy Ageing and Monash University, and ethical and legal requirements. Researchers can contact the Digital Library team using an expression of interest form on the Digital Library website, which includes details of the project methodology, research aims, specific data they are requesting access to, and proof of ethics approval from their governing body. This application is then assessed by our wider governance team for approval. The governance team consists of experts in primary and allied health care, partner organizations, and marginalized community group representatives who are trained in bias influence, power, and equity issues in research. The approval process first consists of an application assessment from the governance team review committee to determine the sensitivity level of the data requested. Low sensitivity data can be approved at this stage, and mid-to-high sensitivity data is then assessed by the governance team. The governance team will assess the application against a set of standard requirements. This includes ethical considerations, appropriateness of the research, and whether the application is aligned with community needs. The governance team will assess applications independently and then discuss results as a team to approve or decline data release.

If approved, the researchers sign a confidentiality agreement and are given access to the required set of data that they need on-site at the Peninsula Campus on a secure-patched computer.

Results

The Digital Library has ethics approval from Monash University's Human Research Ethics Committee. It has received initial funding from the National Centre for Healthy Ageing and began collecting data in 2023. At the time of protocol submission, data collection from health care settings, education settings, and health care narratives was ongoing.

Discussion

Over time, the Digital Library will house the largest collection of health care interactions in Australia, providing research infrastructure to accelerate new knowledge in the areas of miscommunication in health care, communication techniques and aids, and clinical handover, including from clinician to patient.

The Digital Library will support methods such as conversation analysis, linguistics, multimodal video analysis of speech and nonverbal aspects of communication, and direct consumer insights. Examples of research that have used the pilot dataset include:

- A conversation analysis of general practitioner (GP) consultations to investigate GP and patient laughter when discussing lifestyle [24]
- An interview study while watching their recorded consultation with patients from low socioeconomic groups on what makes a good GP consultation [25]
- A secondary analysis of video recordings to examine how GPs discuss weight in consultations [26]
- An interview study where allied health professionals (physiotherapists and podiatrists) discuss lower limb conditions that result in chronic pain (in progress)

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- A student training resource where a podiatrist is performing a nail surgical procedure and talking to the patient during and after the procedure (in progress)
- A simulation of initial domestic violence assessment and safety planning for social work trainees (planned)

It is also possible to conduct experimental studies using innovative communication techniques and real-life observational data [15,27]. The data from the Digital Library will support evidence-based health care communication research to ultimately improve health care quality and patient satisfaction. The new knowledge generated via the library will be relevant for clinician training and professional development, health care models of access, and consumer-driven health care improvements.

Acknowledgments

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Authors' Contributions

EAS wrote the first draft of the paper, and KN, TH, and CW completed the first overview. All authors contributed to the final manuscript. All authors agreed on the final submitted manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Study surveys.
[PDF File (Adobe PDF File), 460 KB - resprot_v14i1e67910_app1.pdf]

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Abbreviations

CARE: collective benefit, authority to control, responsibility, and ethics
FAIR: findable, accessible, interoperable, and reusable
GP: general practitioner

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Protocol

Exploring the Current Situation and Developing Strategies for Behavior Change to Improve Antibiotic Use in West Africa: Protocol for a Multidisciplinary Interventional Research Project

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Abstract

Background: Antimicrobial resistance (AMR) is recognized as a global concern, with particularly severe consequences in low- and middle-income countries. Although it may occur naturally, it is also an anthropogenic problem linked to the irrational use of antibiotics in humans and animal husbandry and the use of pesticides in plant agriculture. Generally, data on AMR and evidence of effective and feasible multifaceted interventions are limited in many African countries.

Objective: This study aims at (1) assessing baseline data on AMR pathogens in Burkina Faso and Ghana; (2) understanding perceptions and quantifying use of antibiotics among health care workers, communities, and livestock farmers; and (3) defining and refining an AMR intervention using a design thinking approach.

Methods: This multidisciplinary study will be conducted in two rural districts and will consist of two phases. First, baseline data will be collected on AMR pathogens along dominant food production chains. extended-spectrum beta-lactamase (ESBL)–producing Escherichia coli and Klebsiella pneumoniae will be selected as indicator mechanisms for AMR because of their high occurrence among animals and humans. The perception and understanding of AMR and antibiotic use among different stakeholders and community members will be assessed using epidemiologic and socio-anthropological methods. Qualitative methods will include participant observations, in-depth and key informant interviews, and focus group discussions. The quantitative part will consist of the development of an inventory of circulating antibiotics and a household survey. Second, key informant and in-depth interviews will be conducted with One Health stakeholders in preparation for the intervention development. Subsequently, multidisciplinary “design teams” will develop ideas for an intervention on AMR using a design thinking approach.

Results: Data collection started in April 2022. The analysis of microbiological, anthropological, and socio-epidemiological data is ongoing in both countries. The intervention development has been initiated in Ghana but has not started yet in Burkina Faso.

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All results are planned to be submitted to peer-reviewed journals by December 2025. First, manuscripts will be published for each discipline. Afterward, the results of the 3 disciplines will be combined in multidisciplinary papers, and a publication of the evaluation of the intervention will follow.

Conclusions: Owing to the multifactorial nature of AMR, different perspectives need to be considered to develop a holistic context-based intervention that is tailored to local needs. This study stands out in its combination of different disciplinary and epistemological perspectives following the One Health paradigm and taking a design thinking approach to develop an intervention. Thereby, collaboration across disciplines and social levels and a participatory bottom-up approach will be promoted to achieve a common understanding of problems and needs and to develop an accepted and efficacious intervention. The national AMR networks and policymakers will be continuously involved in the project.

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KEYWORDS

antimicrobial resistance; One Health; design thinking; multidisciplinary; intervention; sub-Sahara Africa; mixed methods

Introduction

Overview

Antimicrobial resistance (AMR) is rising to dangerously high levels in all parts of the world and presents a threat to public health, food security, and (economic) development [1]. Currently, AMR is presented as being responsible for 700,000 deaths per year and could result in 10 million annual deaths per year by 2050 if no action is taken [1]. As new resistance mechanisms are emerging and spreading globally, the ability to treat common infectious diseases and enable chemotherapies, operations, and many other activities is threatened [2,3]. It is acknowledged as an urgent global problem that concerns every country irrespective of its level of income and development, but effects are hypothesized to be even more significant in low- and middle-income countries (LMIC) [1,4]. In social sciences, however, experts highlight how AMR can be exploited for political ends [5], the invisibility of several causes of AMR [6], and significant scientific knowledge gaps on this subject [7]. Legido-Quigley et al [8] described AMR as a “wicked problem,” as it encompasses complex networks of different stakeholders with incompatible interests.

AMR is spread via diverse agents including humans, animals, alimentation, soil, and water. Although resistance can emerge naturally through evolutionary processes [9,10], it can also occur through anthropogenic pressure resulting from an overreliance on antibiotics. Infections in humans and animals caused by extended-spectrum beta-lactamase (ESBL)–producing *Escherichia coli* and *Klebsiella pneumoniae* are increasingly resistant to most antibiotics globally due to their high diversity and rapid mutation [11,12]. The evaluation of these two gram-negative bacteria could serve as an important indicator for the prevalence of AMR in local settings.

It is critical to recognize how human practices interact with natural microbial ecology in compounding AMR risks. Within the human health sector, the reliance on broad-spectrum antibiotics, especially in the absence of diagnostics, has been identified as a major contributor to the emergence of AMR [13]. The widespread use of antibiotics in livestock exceeds direct human consumption and is driven by economic imperatives to maximize production, prevent disease, and enhance growth [7,14,15]. As most of these antibiotics are not fully metabolized but released into the environment as waste products, misguided antibiotic use has a concurrent ecological impact by affecting wild bacteria populations and promoting further antibiotic resistance development [16]. This highlights the ecological consequences of antibiotic misuse and the entangled nature of environmental, agricultural, and health systems. Additionally, the soil contains microorganisms with naturally occurring genes that can facilitate the development of AMR in the natural environment [3,7].

The relevance of this research project is multifaceted: First, the availability of information on AMR in Africa is limited. This stems from weak laboratory and surveillance systems and processes, where only a small fraction of facilities conducts bacteriological testing and the microbiological data that do exist are often of poor quality [4,17,18]. Similarly, more data on antibiotic consumption and access to health care in animal and human health are needed [19]. In addition, a One Health approach should be implemented in future studies to develop efficient interventions on AMR and improve AMR surveillance and control in Africa [19,20]. Second, the rates of AMR are higher in certain LMIC, while individual antibiotic consumption is lower in comparison with high-income countries, indicating that other factors are influencing the prevalence of AMR [9]. Third, the effects of AMR on various societal sectors, including health and economic consequences, risk being more significant in African countries due to predominant livelihoods and living conditions [21,22]. In recent years, the use of antibiotics in LMIC has increased substantially both for humans and animals because of economic growth and changes in diet [23]. At the same time, antibiotic policies concerning manufacture, dispensation, and prescription in many LMIC are often missing or lacking regulatory enforcement due to socioeconomic challenges, large population size, and challenged health care systems [24]. Fourth, the current body of literature “has created little clarity about what interventions are best suited to achieve AMR goals across contexts, cultures and health systems” [25]. The need to act on AMR at a global level is well-known and agreed upon; however, an implementation gap of action and interventions can be observed [26]. Evidence of effective and feasible multifaceted interventions in sub-Saharan African countries is limited, and studies show that challenges for

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implementation of interventions are numerous. Nevertheless, several initiatives at international and local levels have demonstrated that effective interventions are feasible in LMIC and that contextualization is essential [27].

Study Objectives

This paper presents the study protocol for a multidisciplinary research project on AMR in 2 districts of Burkina Faso and Ghana using a One Health perspective and design thinking approach. The study has the following aims: (1) assessing baseline data on AMR pathogens along the food chain in the Kossi Province, Burkina Faso, and the Asante Akim North District, Ghana; (2) understanding and quantifying perceptions and use of antibiotics among health care workers, communities, and livestock farmers as well as defining patterns of access and utilization of antibiotics; and (3) defining and refining an intervention aimed at reducing the impact of AMR and improving the way this issue is addressed using a stakeholder-driven approach.

Methods

Study Setting

The research project will be conducted in Burkina Faso and Ghana, both located in the West African subregion. The research site in Burkina Faso is the rural Kossi Province, located in the northwest of the country and corresponding to the Nouna Health District. The population is mostly living in the semi-urban town Nouna, representing the administrative center of the province [28]. Nouna Health District has a population size of about 320,232 inhabitants and a surface area of 7464 km^2 [28]. The main economic activities are farming and animal breeding [29]. A Health and Demographic Surveillance System has been established in the province and is managed by the Centre de Recherche en santé de Nouna (CRSN; Nouna Health Research Center). Burkina Faso has a national human and animal surveillance system for AMR consisting of 15 designated laboratories since 2018 and is enrolled in the Global Antimicrobial Resistance and Use Surveillance System (GLASS) of the World Health Organization (WHO) but is not yet reporting data to the system [30]. Burkina Faso's National Action Plan (NAP) was published in 2018 but has not been implemented by the government yet [30].

The research site in Ghana is in the semi-urban and rural Asante Akim North District, which is in the eastern part of the Ashanti Region. The district has a size of 1218 km^2 and approximately 85,788 inhabitants [31]. Approximately 72% of the district's work force is employed in the agrarian sector [32]. Multiple health institutions are serving in the district and are constituted by private sector actors, religious missions, and public sector actors [32]. Ghana is enrolled in the WHO GLASS. However, there is no precise nationwide surveillance system on antimicrobial use and AMR prevalence, and no data were contributed in 2020 and 2021 [33-36]. The establishment of a nationwide AMR surveillance system is outlined in the NAP but has yet to be implemented [36,37]. Ghana is considered a leading country on the African continent for handling AMR due to its work and approach including the establishment, in 2011, of the Ghana National Policy Platform on AMR, which consists of various stakeholders from diverse institutions and sectors, thereby integrating the One Health approach [36]. Moreover, the NAP on AMR (2017-2021) and a policy document on antimicrobial use and resistance were officially launched in April 2018 in the country [36,38]. However, policy and project implementation is lagging due to poor coordination of the different stakeholders, insufficient financial resources and infrastructure, and enforcement of regulations [36].

Ghana and Burkina Faso are neighboring countries but different in many respects, such as the socioeconomic level, the structure of the health system, the presence of industries, and national security. Therefore, it would be of interest to contrast the information collected between the two study sites and to see the influence of these factors on AMR and what this could mean for possible interventions. In addition, through the development of a south-south collaboration between the two countries, knowledge can be shared, and synergy effects can be used for a holistic approach to AMR.

Study Design

Overview

This research project consists of 2 phases (Figure 1). Phase 1 consists of multidisciplinary research on AMR, looking at it from different perspectives, namely, microbiology, anthropology, and socioepidemiology. This will consist of baseline data collection on AMR pathogens (ie, microbiology [1.1.]) We will explore perceptions and use of antibiotics among health care workers, communities, subsistence and semi-intensive livestock farmers, and institutional actors (ie, anthropology [1.2.] and socioepidemiology [1.3.]). Thereby, we are following an exploratory sequential mixed methods design by initially using qualitative methods to then develop quantitative tools in the next step. In the second phase, we will use a design thinking approach to develop a targeted intervention in collaboration with different stakeholders to improve the way of addressing the issue of AMR (ie, interventional research component [2.]). The identified stakeholders will be involved from the beginning of the project, with their opinions and perceptions of the problem and suggested solutions prioritized in the design thinking process.

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Figure 1. Research design: triangulation between 3 disciplines to develop an intervention using a design thinking approach. AMR: antimicrobial resistance.

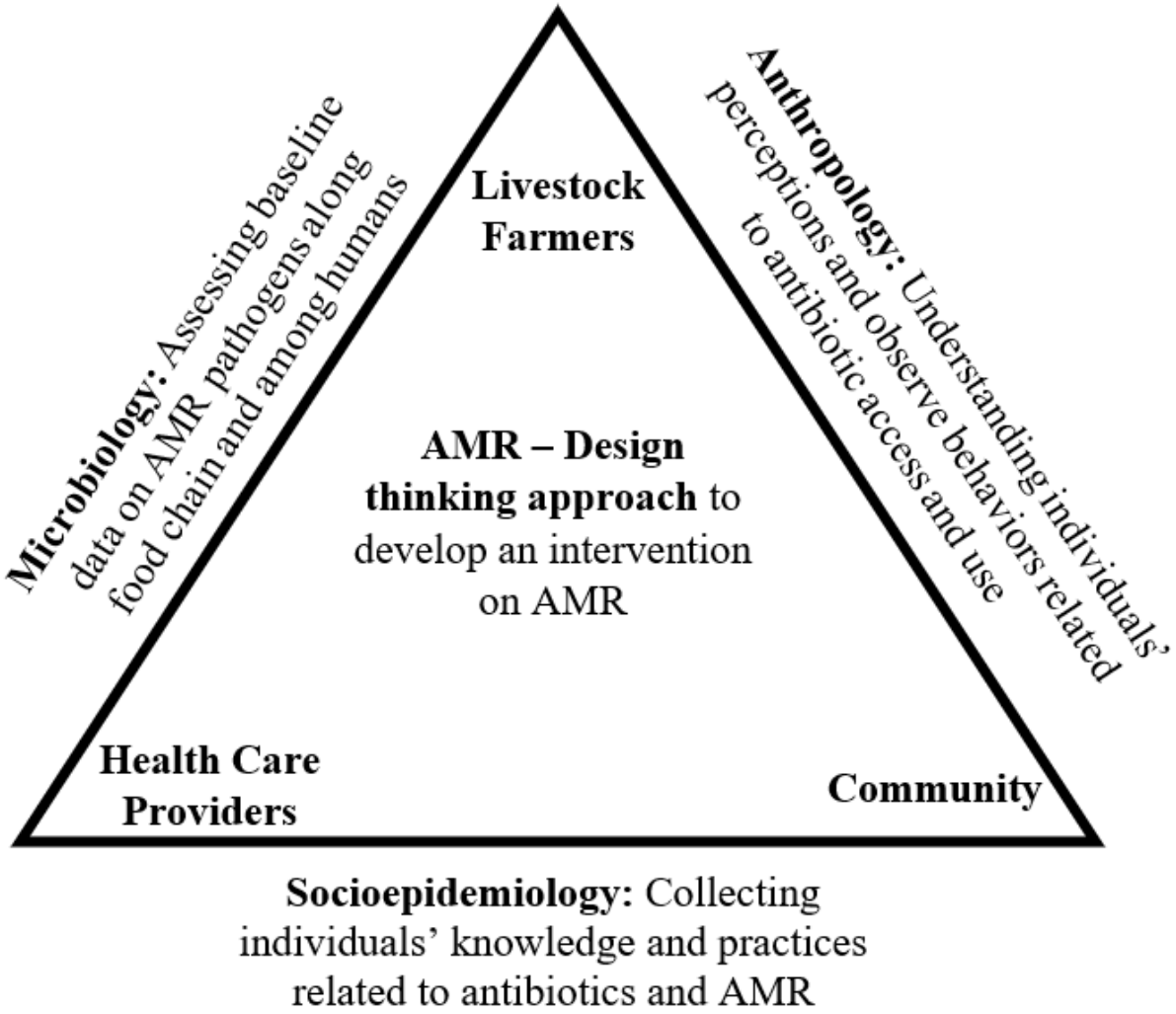

Phase 1.1: Microbiology

First, we will assess baseline data on AMR pathogens along the dominant food chains: poultry in Ghana and poultry and beef in Burkina Faso. ESBL-producing *E. coli* and *K. pneumoniae* will be selected as the indicator mechanisms due to their high prevalence among animals and humans. Farms will be included in the sample if their poultry or cattle are sent to the local abattoir and sold in sampled local markets and retail shops. Due to local practices, the AMR prevalence will also be tested among free-range, so-called backyard, chickens in the villages.

A total of 1500 fecal samples will be collected from poultry, along with 500 meat samples from markets, 200 from retail shops, and 100 from abattoirs. During each sampling visit, individual fecal droppings from broilers (on poultry farms) or cattle (on farms) will be collected in sterile containers. These samples will then be placed in a transport box maintained at 2 °C to 4 °C to ensure proper preservation. In markets, retail shops, and the abattoir, meat samples of approximately 1 gram each will be collected into a sterile plastic bag and transported on ice to the Kumasi Centre for Collaborative Research in Tropical Medicine laboratory in Kumasi. In a biosafety cabinet, the samples will be transferred into sterile disposable petri dishes, and the meat will be diced into smaller pieces with a sterile surgical blade and transferred into Brain Heart Infusion (Oxoid) broth. After incubation at 37 °C for 18 hours to 24 hours in normal atmosphere, the broth will be plated on Chromagar supplemented with ESBL-selective antibiotics (CHROMagar) and incubated at 37 °C for 18 hours to 24 hours. Presumptive *E.coli* colonies and *K. pneumoniae* colonies will be subcultured onto Columbia blood agar and further tested using biochemical methods. Antibiotic sensitivity testing will be performed using the Kirby-Bauer method, and ESBL confirmation will be conducted using the double-disk diffusion method. ESBL-producing bacteria under investigation will be subjected to whole genome sequencing to describe phylogenies as well as virulence and AMR. Data will be entered into a REDCap database, and bacteriological data will be analyzed using STATA (StataCorp). The number and percentage of samples along with descriptive statistics (ie, median, IQR, minimum, and maximum) will be reported for continuous non-normally distributed data. Categorical variables will have the number and percentage of patients reported. Proportions of positive test results will be calculated as percentages of positive results among all valid tests, with exact binomial 95% CIs.

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Phase 1.2: Anthropology

Ethnographical studies, including daily immersions, participant observations, free discussions, and semistructured interviews, will be used. For the qualitative investigations in human health, a research assistant will be living in a community area of the rural town where the research will take place (Nouna in Burkina Faso, Agogo in Ghana) for a total of 12 months. He or she will become part of the community and, during an exploratory phase, will observe and talk to as many people as he or she meets during their daily life (neighbors; the people he or she meets when shopping, eating, and investigating places where medicines are distributed and care is provided). During the 12 months, he or she will travel to a rural locality around where he or she will live for 2 months and become integrated and that he or she will explore in the same way as previously in the town. Subsequently, he or she will conduct semistructured interviews in 15 households in the urban community and in 15 households in the rural locality (if possible, with the mother and the father). These households will have at least 1 child younger than 10 years and will be chosen to represent different socioeconomic statuses ("affluent" households, "intermediate" households, "deprived" households).

For the qualitative investigations in poultry farms, ethnography will be performed in approximately one-half of the active farms in the rural town in each country. We will choose the farms according to their operating time (from before 2000 until now) and the number of animals raised (500 to 8000 chickens).

Antibiotic use by individuals and farmers and waste management practices at the household, farm, and health care system levels will be investigated. In addition to antibiotic use, the overall living and working conditions, constraints experienced, and factors influencing health-seeking behaviors for both humans and animals will be studied. We will also explore practices of professional actors in biomedicine and veterinary medicine in addition to developing an exhaustive inventory of antibiotics in circulation. Semistructured interview guides used within the anthropology work package for the ethnographies conducted on farms and villages can be found in Multimedia Appendix 1 and Multimedia Appendix 2, respectively, and the observation guide for households in the villages for human health and animal health is shown in Multimedia Appendix 3. All other observation guides can be accessed from the corresponding author upon request. All the data will be analyzed using thematic sorting in NVivo 14, identifying redundant themes and subthemes that are relevant to understanding the social realities being studied.

Phase 1.3: Socioepidemiology Quantitative

A household survey about the perception of AMR and the use of antibiotics will be implemented at the community level. In Ghana, a double-stage random sampling method will be used, while in Burkina Faso, simple randomization will be used due to the availability of a Health and Demographic Surveillance System. The sample will include approximately 1000 households per country. The questionnaire will be designed using the Multi-Country Public Awareness Survey from the WHO and previous literature. It will consist of 2 sections: one for the head of the household, covering socioeconomic status, demographics, and antibiotic use in livestock and another focusing on knowledge, attitudes, and practices (KAP) related to antibiotics and AMR awareness. Participants belonging to a household will be selected randomly by the interviewer. Data collection will be conducted using tablets by two separate teams in Ghana and Burkina Faso, both of whom will undergo a 5-day training before the start of fieldwork activities.

Data will be analyzed using STATA 17. Descriptive analysis will be conducted to summarize sample characteristics using frequencies and percentages for categorical data and means with standard deviations for linear data. Socioeconomic status will be calculated using principal component analysis and classified into quintiles. KAP will be assessed by assigning points to correct responses; respondents will then be categorized into groups based on their scores. Regression analysis will be conducted for both countries to explore associations. Collinearity will be assessed to ensure the reliability of the regression models.

We will look at the circulation of antibiotics in the formal sector in the two districts analyzing the register of the district pharmacy for a period of 2 years. Subsequently, we will investigate the overall quantity of antibiotics according to antibiotic classes and the AWaRe classification. Results will be reported to the general population of the district.

Phase 1.3: Socioepidemiology Qualitative

A qualitative survey focusing on prescription patterns and perceptions of AMR will be conducted among health care providers of primary and secondary health care facilities, including Community-based Health Planning and Service compounds, health centers, policlinics, and a district hospital, using in-depth interviews and focus group discussions. Sampling will be done using a stratified purposeful sampling strategy aiming for maximum variation within the 3 strata, namely nurses, physician assistants, and medical doctors. The semistructured interview guide that will be used for this can be found in Multimedia Appendix 4. The semistructured guide developed for the focus group discussions can be accessed from the corresponding author on request. Content analysis will be applied to data coding and analysis with the COM-B (capacity, opportunity, motivation, behavior) model as the underlying framework [39].

Phase 2: Interventional Research Component

Using the design thinking approach (Figure 2), a targeted intervention to improve the way of addressing the issue of AMR will be developed in collaboration with different stakeholders in the second phase [40]. Within a system of overlapping nonsequential and iterative spaces of understanding, exploring, and materializing, the following steps will be repeated over time: empathize, define, ideate, prototype, test, and implement [41].

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Figure 2. Description of the design thinking approach.

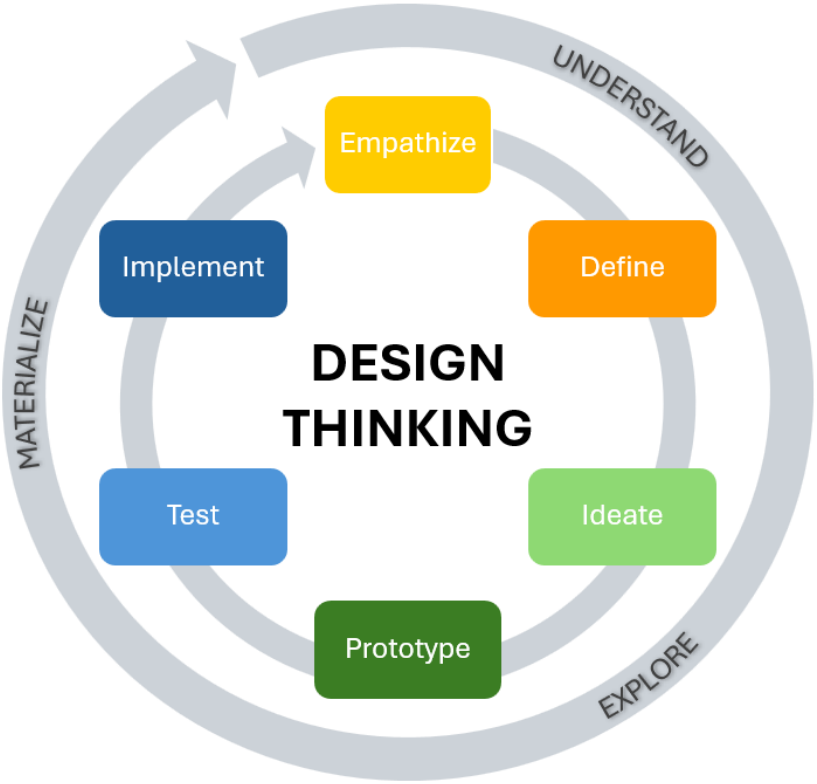

Building on the results of the previous study phase and in preparation for the workshops, key informant interviews will be conducted with institutional actors, and in-depth interviews will be conducted with community members and farmers to understand the perception and understanding of AMR among different One Health stakeholders. Institutional actors will be selected via purposeful sampling and will be eligible if involved in a One Health sector, namely animal, environmental, and human health. Community members and farmers will be sampled using a customer-exit strategy at points of sales of antibiotics. The semistructured interview guides used for interviews with farmers and community members can be found in Multimedia Appendix 5 and Multimedia Appendix 6, respectively. Interview guides for institutional actors have been jointly developed by the anthropology and socioepidemiology team and will slightly differ according to the sector of the interview partners. An example of the interview guide for the human health sector can be found in Multimedia Appendix 7. The two remaining interview guides for institutional stakeholders in the environmental and human health sector can be accessed from the corresponding author upon request. All interviews will be transcribed verbatim in French or English. Subsequently, we will code transcripts through a mixed approach of inductive and deductive coding using thematic analysis.

The design thinking approach follows a human-centered and emerging design and is a collaborative and iterative process aiming to produce relevant results according to the needs and local situation [42,43]. Therefore, initial ideation workshops in both study sites will combine the research results collected in the first phase of the project. Research results will be discussed by workshop participants before collecting ideas on possible interventions on AMR through participatory methods. Therefore, multidisciplinary and collaborative “design teams” will be developed and include the research team, policymakers from the involved countries, and members of nongovernmental organizations working on AMR as well as health care workers, veterinary professionals, livestock farmers, and community members. Discussions will be recorded and transcribed, followed by qualitative data analysis to summarize the ideas generated for an intervention on AMR. Based on these results, the design teams will meet again in each study site to develop the prototype of an intervention. Although the outcome of the design teams’ work will depend on this participatory process, we assume that the intervention could possibly be targeting the community level due to the variety of stakeholders involved in the intervention development. Generally, interventions at the community level, such as education interventions, have been shown to result in positive changes in knowledge and attitudes; however, there is a lack of evidence on the effect of improved knowledge on behavior change [44].

The intervention will be implemented in Kossi Province and Asante Akim North District and evaluated using a mixed methods triangulation approach combining questionnaires and interviews with stakeholders at different levels to evaluate the process and outcome of the intervention. This will allow refinement and modification of the intervention according to the local needs. Eventually, dissemination meetings will be organized, and policy briefs will be written to ensure wide access to the results by policymakers and scientists in the countries of interest and abroad. In addition, continuous contact with policymakers and the national AMR networks in Burkina Faso and Ghana from the beginning of the research process has the potential to increase the acceptability and scaling of the developed intervention.

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Ethical Considerations

Ethical approval was obtained from the ethical committee of Heidelberg University Hospital (S-826/2021), National Ethical Committee in Burkina Faso (number 2021-12-270), Nouna Health Research Centre ethical committee (number 2021-018-MS/SG/INSP/CRSN/CIE), Kwame Nkrumah University of Science and Technology Committee on Human Research Publication and Ethics (CHRPE/AP/580/21), and Ghana Health Service Ethics Review Committee (GHS-ERC 004/11/21).

Informed consent and the ability of participants to opt out of the study at any point will be provided together with an information sheet on the project. Additionally, all data will be de-identified to ensure privacy and confidentiality. All recordings will be deleted once transcription is completed and checked. Participants of the workshops in phase 2 will receive beverages and a meal during the workshops and compensation for their attendance once the workshop has ended, as this presents a day-long commitment. Otherwise, no compensation will be provided for study participants.

Results

The study received funding in May 2021. Ethical approvals were granted from the various committees between November 2021 and April 2022. Renewal of the ethical approval is requested and received annually from the Kwame Nkrumah University of Science and Technology Committee on Human Research Publication and Ethics.

Data collection started in April 2022 and was completed in November 2023. For the quantitative socioepidemiology part, we conducted a cross-sectional survey among 1114 participants in Ghana and 1011 participants in Burkina Faso. These numbers were based on prior sample size calculation and reflect completed data collection as of November 2023. Qualitative components in the anthropology work package included daily immersions, participant observations, free discussions, and semistructured interviews, and semistructured interviews and focus group discussions in the socioepidemiology work package. Given the exploratory nature of these methods, participants were recruited progressively across multiple target groups, with data collection continuing until saturation was reached.

The analysis of the microbiological, anthropological, and socioepidemiological data is ongoing in both countries. The intervention development has been initiated, and the first prototype meeting took place in Ghana in July 2024. The pretesting of the intervention in Ghana is expected to be completed by August 2025. The process of intervention development has not started yet in Burkina Faso, as we are experiencing a delay due to the political situation. All results are planned to be published in peer-reviewed journals before December 2025. Initially, the 3 disciplines involved in the research will analyze their data separately while exchanging information on a regular basis. This will also allow us to put the different results into perspective. For example, to combine microbiological and anthropological results, parasite resistance rates on a specific farm will be considered alongside observations of antibiotic use on the same farm. This could include an assessment of whether resistances described by microbiologists in the geographical contexts studied can be understood based on the descriptions of perceptions and uses of medicines produced by anthropologists in the same context. The congruence or noncongruence of the overall analysis between the disciplines will then be discussed and problematized. Eventually, without strictly comparing our results on each of the questions addressed, we will propose scientific articles providing an overall interpretation of AMR, cross-referenced between microbiology and anthropology and between microbiology, socioepidemiology, and anthropology. Results will not be strictly compared for each question addressed but will be embedded in a holistic analysis of AMR in the specific study contexts.

First, manuscripts will be published for each discipline. Afterward, the results of the 3 disciplines will be combined in multidisciplinary papers, and a publication of the evaluation of the intervention will follow.

Discussion

Overview

Research has shown that “magic bullet” approaches to AMR focusing on highly technological and biomedical approaches such as surveillance and the development of new antibiotics will not be sufficient to combat the global and multifactorial problem of AMR [13,45]. Even though we currently do not have much data on the prevailing situation in the regions we will be studying, we know that the irrational use of antibiotics in humans and animals significantly contributes to AMR [3,10,26]. Policies and underlying infrastructure of antibiotics, perceptions, understanding, and knowledge of stakeholders and community members need to be understood to develop sustainable and effective solutions while considering their social and economic capital as well as behavioral, ethical, political, and cultural factors [4,15,26,45]. Therefore, the multifactorial nature of AMR, the diverse reasons and drivers underlying the use of antibiotics, and the local contexts and constraints need to be considered and integrated into all efforts.

Phase 1

The first phase of the research project will add to the field of One Health by examining the issue of AMR from microbiology, anthropology, and socioepidemiology perspectives. Therefore, this study will address the challenge of disciplinary silos through close multidisciplinary collaboration. It stands out in the combination of different disciplinary and epistemological perspectives through multilateral collaboration between the Burkinabe, Ghanaian, German, and French research institutions. Microbiological data will contribute to a clear picture of prevalent resistance in animals and improve the biomedical understanding of AMR in the study sites. Generally, both AMR surveillance and data on AMR are limited in western sub-Saharan Africa [46]. Furthermore, available studies are mostly done at the health care level, investigating resistance levels in ESBL-producing *E. coli* and *Klebsiella* spp. isolates [46] or in febrile children younger than 5 years [47]. Few studies exist on ESBL-producing *E. coli* and *Klebsiella* spp. in livestock;

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however, these have been conducted in urban settings such as Ouagadougou in Burkina Faso [48]. Data on AMR bacteria and their genotype distribution in meat are still scarce especially in rural areas of Ghana and Burkina Faso, for example. In our study, strains will be genotyped to describe phylogenies, mechanisms of resistance, and virulence. Data collected from livestock can also be compared with a human strain collection of an ongoing AMR surveillance system in the 2 districts where the study is implemented in order to describe transmission reservoirs in these parts of Africa.

Anthropological studies will add to the understanding of antibiotic access and utilization patterns, perceptions, and uses of antibiotics among human and animal health care workers, communities, livestock farmers, medicines suppliers, and institutional actors. It will also identify and outline the constraints and enablers of these actors and how these factors influence their behavior. The socioepidemiology data collected among health care workers will generate knowledge on their perception of AMR and the logic of their prescription patterns, while the household survey will quantify community members' knowledge of antibiotics, AMR, and antibiotic consumption practices. The anthropology and socioepidemiology perspectives will enable a description of the underlying infrastructure and the social, cultural, economic, and political structures that impact the development and spread of AMR. Thereby, this study will add to available literature on health care–seeking behaviors outside of health care facilities, antibiotic use across different levels of health care providers, and access among community members in Burkina Faso [49-51]. Furthermore, by combining the microbiological data on AMR with the perception of institutional actors at different levels, community members, and farmers, we will be able to develop a holistic description of the situation in the 2 study sites. This will represent a necessary step to develop an intervention reflecting the local context and needs.

Phase 2

The second phase of the project will result in the development of an intervention using the design thinking approach, which is increasingly used in global health to apply social innovation for diverse health issues representing "both a social need and a social problem" [52]. A scoping review indicated that design thinking is used within various initiatives of different organizations and institutions to improve human health [52]. Design thinking is iterative, measurable, and result-driven and places the people being served in the center of the design, innovation, and implementation process [42,43]. Therefore, stakeholders' actual needs and expectations are met, and acceptable, equitable, effective, and sustainable health solutions can be developed through this active engagement [53-55]. Design thinking consists of stakeholder and cross-disciplinary collaboration and a multistep approach to gain an understanding of the situation and context, brainstorm, test, and revise the best solution in a collaborative process [53]. Therefore, the following steps are repeated over time: define, ideate, prototype, test, and implement [41].

The mixed methods approach and subsequent triangulation of research results will contribute to increasing knowledge and developing a holistic understanding of AMR, which is essential for the development of appropriate interventions at the study sites. Using the One Health perspective, both human and animal health will be examined in this study. The One Health approach will allow us to gain insights into the interconnection of the 2 sectors and to develop a holistic intervention that takes different perspectives and needs into account. Therefore, to follow the One Health paradigm, collaboration across disciplines will be promoted, and actors from different professions and social levels, particularly community members, will be encouraged to bring forward their ideas for solutions. By challenging disciplinary boundaries and through the collaboration of different disciplines within the research team itself and the design teams during the intervention phase, synergy effects and strengths can be brought together to capitalize on innovative potentials. This will be facilitated by a design thinking approach to support innovative potential through the close collaboration of stakeholders and community members, both directly and indirectly affected by AMR. The stakeholder-driven and participatory bottom-up approach to the multifactorial problem of AMR has the potential to result in a common understanding of needs and problems and the subsequent development of a common solution that is tailored to the local situation, context, and needs. Furthermore, it has been shown that moving away from a traditional top-down to a value-driven and participatory bottom-up approach could lead to increased efficacy and acceptability of interventions and improved antibiotic use [26].

In addition, continuous contact with policymakers and the national AMR networks in Burkina Faso and Ghana from the beginning of the research process has the potential to increase the acceptability and scale-up of the resulting intervention that will be developed. By engaging these stakeholders, existing networks, policies, and projects will be incorporated from the first to the last phase of the design thinking approach, which will be built on existing structures and approaches to ensure acceptability, efficacy, and sustainability of the resulting intervention. Moreover, a south-south collaboration will be facilitated within the research project through sharing of competencies and technical know-how within and between the researchers and AMR networks via regular exchanges and through research and dissemination meetings.

Limitations and Further Considerations

The main limitation of this study is the limited involvement of the environmental sector. The influence of environmental factors on AMR has not been highlighted within the scope of this study. Currently no data have been collected from environmental sources to add to the human and animal data sources. However, we intend to complement this research with such data (collaborations are currently being developed to add this component). In addition, environmental stakeholders from the local and national levels will be included in the qualitative interviews and the development of interventions in the 2 countries.

A diversity of approaches to AMR exists, ranging from research and development of new antibiotics; antibiotic stewardship; improved hygiene; and infection, prevention, and control to behavior change and education of patients and health care

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professionals. However, social scientists have identified a problematic focus on the causes of AMR linked to the behavior of individuals, both consumers and prescribers, that depoliticizes AMR and isolates it from our modes of life and economies, thereby not acknowledging that AMR is not only a natural phenomenon but also a social fact [56]. Therefore, social scientists urge us to question our way of living in the world, caring for it, and taking care of it [56]. We acknowledge that AMR is a complex and multifaceted issue that needs to be addressed at different levels, taking social and systemic factors into account. For this study, we decided to focus on the behavioral aspects, as these are proven to be an important factor contributing to AMR and lie within the scope of our community-based and participatory approach to develop an intervention. Nonetheless, systemic challenges might become clear within the course of our project and provide important insights for future research projects and policy and decision makers.

Although this study's multidisciplinary approach offers innovative potential through the close collaboration of different disciplines during continuous (online) meetings and design thinking workshops, it will also present a challenge due to different perspectives, epistemologies, and methodologies. Furthermore, considering current realities and power relations within science, between disciplines and institutions in the so called "Global North" and the "Global South," we acknowledge that the approach we are promoting through this work, although bottom-up and participatory through actively including community members and other stakeholders, can be challenged from many points of view. Therefore, this study will provide useful insights on how to mitigate such challenges and ensure equitable collaboration.

The generated results will be primarily relevant to the districts of the research project. However, due to direct contact with local, regional, and national stakeholders, the developed intervention can serve as a pilot project for a subsequent scale-up within Burkina Faso and Ghana, as well as other countries. It is expected that these interventions will contribute to improving the way the issue of AMR is addressed among communities, health care providers, livestock farmers, and institutional actors in LMIC. If the interventions in Kossi Province and Asante Akim North District provide positive results, the potential scale-up will be supported by the research team. To facilitate this process, national stakeholders will be informed and engaged right from the project's inception. The results of this study will provide rigorous scientific evidence on the prevalence of AMR along the dominant food production chains and the perspectives and understanding of AMR among community members and stakeholders from the animal, environmental, and human health sectors in the 2 districts in Burkina Faso and Ghana. Furthermore, insights will be provided regarding the development of an AMR intervention through a participatory bottom-up approach using the design thinking process and the multidisciplinary One Health perspective.

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Data Availability

The data sets used and analyzed during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

AS, DD, CB, ASi, and JHA conceived the study, developed the concept, and drafted the study protocol. DD, CWA, and BC developed the sampling procedure, laboratory processes (collection and analyses of the samples), and data processing for the microbiology part. CB, DA, and BB developed the methodology, selected the research units, collected the data, and analyzed the data for the anthropology component. AS developed the socio-epidemiology component part, with JA, ASi, and LMA, for the health care worker qualitative survey and the community survey. LMA, JHA, BC, and ASi were responsible for the ethical aspects and ethical committee procedures. The co-authors contributed to this manuscript in the aforementioned sections according to their contribution to the aforementioned development of the different work packages. Finally, all co-authors have read and approved this manuscript, which was written by MN.

Conflicts of Interest

None declared.

Multimedia Appendix 1

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Interview guide in intensive or semi-intensive livestock farms.
[DOCX File , 20 KB - resprot_v14i1e66424_app1.docx]

Multimedia Appendix 2
Interview guide in villages for human and animal health.
[DOCX File , 21 KB - resprot_v14i1e66424_app2.docx]

Multimedia Appendix 3
Observation guide and open discussion with households in the villages for human health and animal health.
[DOCX File , 20 KB - resprot_v14i1e66424_app3.docx]

Multimedia Appendix 4
In-depth interview questionnaire for health care workers in the Ashanti region, Ghana.
[DOCX File , 25 KB - resprot_v14i1e66424_app4.docx]

Multimedia Appendix 5
IDI Interview Guide for Farmers in Asante Akim North Municipality.
[DOCX File , 20 KB - resprot_v14i1e66424_app5.docx]

Multimedia Appendix 6
IDI Interview Guide for Community Members in Asante Akim North Municipality.
[DOCX File , 20 KB - resprot_v14i1e66424_app6.docx]

Multimedia Appendix 7
Interview Guide (Institutional) Actors AMR – Human Health.
[DOCX File , 19 KB - resprot_v14i1e66424_app7.docx]

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Abbreviations

AMR: antimicrobial resistance
COM-B: capacity, opportunity, motivation, behavior
CSRN: Centre de Recherche en santé de Nouna
ESBL: extended-spectrum beta-lactamase
GLASS: Global Antimicrobial Resistance and Use Surveillance System
KAP: knowledge, attitudes, and practices
LMIC: low- and middle-income countries
WHO: World Health Organization

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Proposal

Use of Naltrexone for Patients With Stimulant Use Disorder in Malaysia: Protocol for a Retrospective Cohort Study

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Abstract

Background: Naltrexone is an opioid receptor antagonist. Naltrexone is used to block the euphoric and sedative effects of drugs such as heroin, codeine, and morphine. The medication helps to bind and block opioid receptors to decrease opioid cravings. In Malaysia, naltrexone has been used for maintenance treatments for heroin and alcohol since 1996. However, since 2011, naltrexone has been used as an off-label stimulant use disorder (StUD) treatment to achieve abstinence.

Objective: This study aims to determine the abstinence among StUD and non-StUD patients treated and without naltrexone.

Methods: We will conduct a retrospective cohort study on the effect of naltrexone or treatment as usual (TAU) by examining the data for both StUD and non-StUD patients. We will use patients' clinical records from the hospital registry. All adult patients (aged 18-65 years) diagnosed with StUD or other substance use disorders who were treated with naltrexone and standard care from January 1, 2011, to December 31, 2023, will be screened. All StUD and non-StUD patients who were offered the naltrexone treatment or TAU at the beginning of treatment will be recruited. All data will be extracted using a standardized data extraction form. Descriptive analysis will be performed to describe the distribution of patient characteristics, sociodemographic profiles, and percentages of abstinence and treatment retention. We will conduct univariable analysis to determine the association of stimulant abstinence and treatment retention between naltrexone and TAU among both StUD and non-StUD patients. All significant independent variables will be further analyzed using a cross-sectional time series method for categorical variables.

Results: Recruitment began in July 2025. Data analysis will begin after completing data collection, planned for January 2026.

Conclusions: The expected main outcome of this study is to observe the significant associations of stimulant use abstinence and treatment retention between TAU and naltrexone among StUD and non-StUD patients. The findings from this study may provide preliminary evidence regarding the use of naltrexone in treating StUD. Currently, there is no specific medication to treat amphetamine or methamphetamine use disorder. The effect of naltrexone with psychosocial interventions for StUD is unclear. Public health approaches recognize the multifaceted nature of substance misuse and focus on addressing the myriad individual, environmental, and social factors that contribute to StUD.

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KEYWORDS

naltrexone; stimulant use disorder; abstinence; Malaysia; protocol

Introduction

Stimulant use disorder (StUD) is a global epidemic characterized by continued use of stimulants that leads to clinically significant impairment or distress, resulting in tens of thousands of deaths annually [1]. Cocaine, amphetamine-type substances, and other prescribed drugs [2,3] are categorized as stimulant drugs. Amphetamine-type stimulants (ATSs) such as 3,4-methylenedioxymethamphetamine (MDMA or ecstasy) and methamphetamine are currently reported as the second most commonly used drug type, surpassing cocaine and heroin users. Over one-third of amphetamine users are from East and Southeast Asia [3,4]. A report from Malaysia's National Anti-Drug Agency's 2020 data stated that ATSs were the most used drug in Malaysia [5]. This observed trend was accompanied by the concerning fact that StUD results in several detrimental effects associated with not only medical conditions, such as strokes, aneurysm rupture, and seizures, but also violent crime cases in Malaysia [6-11].

Thus far, treatment for amphetamine users in emergency departments and psychiatric clinics has focused on behavioral interventions and management of acute and short-term consequences of amphetamine dependence, such as withdrawal symptoms, amphetamine-induced psychosis, and associated depression [12]. Other treatments for amphetamine use disorder include acupuncture and pharmaceutical interventions such as antidepressants, antipsychotics, and anticonvulsants [12]. Besides, nonpharmacological treatments such as cognitive behavioral therapy, contingency management, community reinforcement (incentivize patients to remain engaged in treatment in community-based substance use or mental health clinics), and relapse prevention have also been introduced [13].

Naltrexone is an opioid receptor antagonist. Naltrexone inhibits the euphoric and sedative effects of substances like heroin, codeine, and morphine by binding and blocking opioid receptors. This decreases patients' craving and tolerance to opioids [14-17]. Few studies have proposed naltrexone as a treatment for StUD and demonstrated a significant effect in reducing the consumption and craving for amphetamine [18-20]. Besides, an acute dose of naltrexone blunted the subjective effects of amphetamine under experimental laboratory conditions, for example, decreasing the percentage of amphetamine-positive urine samples in patients with chronic amphetamine dependence. This indicates the possibility of naltrexone pharmacotherapeutic treatment for amphetamine dependence [18-21]. In contrast, research by Schottenfeld et al [22] stated that the effect of naltrexone in patients with heroin use disorder was not statistically different from a placebo when compared to buprenorphine. The aforementioned studies [18,20] have been included in a systematic review in addition to other studies demonstrating inconsistent findings [23]. Despite extensive research elucidating the neurobiological effects of amphetamines, effective pharmacotherapies remain elusive [24]. However, this review does not include empirical investigations into associations between nonstimulant substance use disorders and neurological traits.

In Malaysia, naltrexone has been used for maintenance treatment of heroin dependence since the late 1990s, with studies supporting both its clinical effectiveness and cost-efficiency in the local context [22,25]. Although its use for alcohol and stimulant dependence has been explored internationally [26,27], evidence specific to Malaysia remains limited. Since 2011, naltrexone has been used off-label as a treatment option for StUD [23]. However, no study to date has examined the association between naltrexone and abstinence outcomes or treatment retention among patients with StUD in the Malaysian setting. Therefore, this study will be conducted to test the hypothesis that naltrexone can be effective in achieving abstinence among patients with StUD and that naltrexone is effective as part of a treatment strategy for stimulant use. Furthermore, this study will also support clinicians by providing the best practice for patients with StUD. These efforts will require precision and accuracy in our translation of the literature. Thus, this study will also describe the rationale and targets for pharmacotherapies for ATS dependence, identify other emerging pharmacogenetic data, and propose directions for future work.

Methods

Study Design

We will conduct a retrospective cohort study by viewing the patients' files to measure the effect of naltrexone compared to treatment as usual (TAU). The researchers, clinicians, nurses, and medical assistants who will be involved in this study will be trained for 3-4 sessions before data collection. Patients will be identified by the trained hospital staff (clinicians, nurses, and medical assistants). Adult patients aged 18-65 years diagnosed with StUD and non-StUD (ie, those with other substance use disorders, such as alcohol and smoking) treated with or without naltrexone from January 1, 2011, to December 31, 2023, will be recruited. We will collect the data using a standardized data extraction form or clinical report form (Multimedia Appendix 1), which will be piloted with 30 patients in this study. We will extract the data from the patients' clinical records. The data will be anonymized prior to data extraction. Data will be collected through web-based Google Forms by the trained researcher and hospital staff. We will include all patients with StUD and non-StUD who were offered the option of naltrexone treatment or TAU. We will exclude the patients who were younger than 18 years.

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Study Locations

The study locations will be randomly selected using stratified random sampling based on the zones in Malaysia. Hence, we will identify a total of 15 government hospitals across Malaysia with addiction specialists.

Sample Size Calculation

We have calculated the sample size using a two-proportion formula using Power and Sample Size Calculation (version 3.1.2; WD Dupont and WD Plummer) for both StUD and non-StUD patients. A previous study indicated that the probability of stimulant abstinence among patients with StUD was 0.5 when treated with a placebo and 0.65 when treated with naltrexone [7]. A minimum of 113 patients with StUD receiving TAU with naltrexone and 339 patients with StUD receiving TAU without naltrexone are needed to be able to reject the null hypothesis, where abstinence for StUD with and without naltrexone is equal, with the power set at 80%. The type 1 error probability associated with the test of this null hypothesis is 0.05. We will use an uncorrected χ^2 statistic to evaluate this null hypothesis. Considering 20% of data being incomplete or missing, a total of 136 patients with StUD treated with naltrexone and 136 patients with StUD treated without naltrexone are needed for this study.

The sample size calculation for the non-StUD group referred to a previous study that indicated a 0.23 probability for stimulant abstinence among non-StUD patients treated with a placebo and 0.17 for non-StUD patients treated without naltrexone [11]. A similar formula, accounting for type 1 error probability and 20% incomplete or missing data, was used for the calculation. Therefore, both non-StUD groups need a minimum total of 490 non-StUD patients, with 245 treated with naltrexone and 245 treated without naltrexone.

Study Variables

The following definitions of the cohorts and related terms will be used during data collection:

- Cohort 1: patients diagnosed with StUD and treated with naltrexone and TAU
- Cohort 2: patients diagnosed with StUD and treated with TAU
- Cohort 3: patients diagnosed without StUD and treated with naltrexone and TAU
- Cohort 4: patients diagnosed without StUD and treated with TAU
- Abstinence: the state of being abstinent from a substance (drug free), specifically stimulants (ATSs)
- Treatment retention: Patients with StUD continue naltrexone and TAU

Research Tool

The data extraction form will be divided into five sections: (1) sociodemographic profile, (2) medical and clinical background, (3) stimulant use (dosage, duration, and routes of administration), (4) StUD or non-StUD treatment, and (5) urine screening.

Section 1: Sociodemographic Profile

This section will collect information about the sociodemographic profile of the patients, such as gender, age, ethnicity, marital status, education, occupation, and current housing area.

Section 2: Medical and Clinical Background

This section will collect information on the patients' medical and clinical history, including the hospital where treatments are received; history of psychiatric illness; history of hypertension, diabetes, cardiovascular disease, renal disease, or other disease; and history of any behavioral addiction such as gambling disorder or internet addiction.

Section 3: Stimulant Use

This section will collect information on the use of stimulants by the patients. This includes the name of the stimulants, stimulant dosage, routes of administration, frequency of use, age (in years) when stimulant use started, reason for taking stimulant, and duration of use.

Section 4: StUD or Non-StUD Treatment

This section will collect information on the treatment received by patients with StUD and whether the patient received naltrexone. Other information includes the start date of treatment, doses of treatment received, duration of treatment received, and reason for stopping treatment, if applicable.

Section 5: Urine Screening

This section collects the results of urine drug tests for amphetamine and methamphetamine to study the abstinence from stimulants among patients with StUD treated as usual with and without naltrexone. A similar method will be applied to the non-StUD group. Records of positive and negative results from urine tests for stimulant metabolites will be obtained every 3 months for 1 year (admission, month 3, month 6, month 9, and month 12).

Statistical Analyses

We will analyze the data separately in a few categories regarding abstinence from substances (drug free) for 1 month, 3 months, 6 months, 9 months, and 12 months. A similar timeline will be applied when investigating treatment retention for both StUD and non-StUD patients while receiving treatment with naltrexone and TAU. The patients will be separated into 4 groups for analysis: (1) patients with StUD treated with naltrexone, (2) patients with StUD treated without naltrexone, (3) non-StUD patients treated with naltrexone, and (4) non-StUD patients treated without naltrexone. If there is any missing data, we will try to search for the patients' old notes or files, or ask clinicians to contact the patients to obtain the data.

We will analyze the data using Stata software (version 17; StataCorp), along with data cleaning and data verification. Before conducting analyses, data will be verified for errors, statistical assumptions, and potential confounding variables to examine as covariates. Descriptive analysis will be performed to describe the characteristics of the patients, sociodemographic profiles, and percentages of abstinence and treatment retention. Continuous variables will be summarized using means (SDs). Categorical variables will be presented as counts (n) and

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percentages (%). Univariable analysis will be performed using the χ^2 test to determine the association of abstinence from stimulants and treatment retention between the naltrexone and TAU groups among StUD and non-StUD patients. We will perform cross-sectional time series analysis for any significant associations ($P<.05$) in the univariable analysis based on the time points of 1 month, 3 months, 6 months, and 12 months.

Ethical Considerations

This study will be funded by the National Centre of Excellence for Mental Health, Ministry of Health, as a mental health study. We have registered this study with the National Medical Research Register, Ministry of Health Malaysia, with the registration number NMMR ID-24-00626-TBA. We have received ethics approval from the Medical Research & Ethics Committee, Ministry of Health, Malaysia with the reference number NMRR ID-24-00626-TBA (IIR). The Medical Research & Ethics Committee allows the use of secondary data if the data is anonymized; therefore, no informed consent was needed. Patients' IDs will be anonymized or deidentified, and new IDs will be given by the researcher that will be used in place of their name or other identifying information. All data will be kept in secure, password-protected files. Although we plan to make the data publicly available for reanalysis, we will carefully deidentify the data first. For publications or presentations of the results, any information that could identify the participant will not be provided.

Results

Recruitment began in July 2025. Data analysis will begin after data collection, planned for January 2026. For a full study schedule, see Multimedia Appendix 2. We plan to disseminate the results from this study at an international conference or publish in an international journal.

Discussion

Expected Findings

Significant associations in StUD abstinence and treatment retention between TAU and naltrexone among StUD and non-StUD patients are expected to be observed. The findings from this study may provide preliminary evidence to update the clinical practice guideline on the use of naltrexone in treating stimulant misuse.

Currently, no medication is approved for the treatment of amphetamine or methamphetamine use disorder [13], and the effects of naltrexone combined with psychosocial interventions for StUD remain unclear [21]. Clinically, naltrexone's role in improving abstinence has been observed in patients with alcohol use disorder [26], smoking dependence [27], and amphetamine dependence [19], although contrasting findings have also been reported [23]. However, no local studies in Malaysia have examined the role of naltrexone in treating StUD, despite the significant social impact substance misuse has on communities. Naltrexone is currently used off-label for both StUD and non-StUD populations. Therefore, this study aims to provide evidence on the effectiveness of naltrexone in supporting abstinence among Malaysian patients with StUD and non-StUD, ultimately contributing to best clinical practices and bridging the local research gap on this treatment approach.

This study will also highlight the need for public health approaches to recognize the multifaceted nature of substance misuse and focus on addressing the myriad individual, environmental, and social factors that contribute to StUD. Since prevention programs address risk and protective factors that are common in a range of behavioral problems, a naltrexone program for the treatment of StUD will produce positive outcomes not only in preventing drug misuse but also in reducing aggression, early behavioral change, and impaired driving, and improving mental health and educational outcomes.

Limitations

There are a few limitations that should be considered for this study. As this study will collect the data from the patients' files, the patients' information regarding abstinence and treatment retention may be different, and therefore, we will separate the analysis into a few categories: 1 month, 3 months, 6 months, 9 months, and 12 months to overcome this problem. Some of the data may not be complete, such as history of other psychiatric diseases or health issues.

Dissemination

This study is intended for publication in a psychiatric journal such as *JAMA Psychiatry*, *World Psychiatry*, or *BMC Psychiatry*. We may also publish in high-impact journals that are suitable for our topic, such as *BMJ*, *PLoS*, or a JMIR Publications' journal. A few findings will be presented at both local and international conferences. The preliminary findings will be presented to the Psychiatry Clinical Practice, Ministry of Health, Malaysia. This study will also help clinicians decide the best treatment for the patients and might be used as a reference when developing clinical practice guidelines. We will also produce plain language summaries that will be shared with the public through social media and health care websites.

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Norsuhana Sainal (Sultanah Fatimah Specialist Hospital Muar, Johor, Malaysia), Rennu Marimuthu (Hospital Tengku Ampuan Rahimah Klang, Selangor, Malaysia), Assvin Alaga (Hospital Kuala Lumpur, Kuala Lumpur, Malaysia), Nik Lili Ariantie Ahmad (Hospital Raja Perempuan Zainab II, Kelantan, Malaysia), Sasitharan Moorthi (Hospital Tuanku Jaafar, Seremban, Malaysia), Muhammad Zul Azmi Muhammad Yusoff (Hospital Tuanku Fauziah, Perlis, Malaysia), Lim Kuok Quan (Hospital Melaka, Melaka, Malaysia), Omar Ali (Hospital Sultanah Bahiyah Alor Setar, Kedah, Malaysia), Haslina Mohd Yusof (Hospital Permai, Johor, Malaysia), and Lim Hui Ying (Hospital Sultanah Bahiyah Alor Setar, Kedah, Malaysia).

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Data Availability

The data will be provided with the final manuscript in an Excel sheet format.

Authors' Contributions

Conceptualization: NAM, MAMR, NC, NA
Data analysis and interpretation: NAM, IAR
Writing – original draft: NHM
Data collection: NHM, NHJ, TPNTBS, NSM, FNL
Approval of final manuscript: NAM

Conflicts of Interest

None declared.

Multimedia Appendix 1
Data extraction form.
[DOCX File , 180 KB - resprot_v14i1e64101_app1.docx]

Multimedia Appendix 2
Timeline.
[DOCX File , 17 KB - resprot_v14i1e64101_app2.docx]

Multimedia Appendix 3
STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklist.
[PDF File (Adobe PDF File), 91 KB - resprot_v14i1e64101_app3.pdf]

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Abbreviations

ATS: amphetamine-type stimulant
MDMA: 3,4-methylenedioxymethamphetamine
StUD: stimulant use disorder
TAU: treatment as usual

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Protocol

Best Practice Guidance for Male Individuals Using Anabolic Androgenic Steroids in Recreational Sports Within Primary Care: Protocol for a Modified Delphi Consensus Study

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Abstract

Background: The nonmedical use of anabolic androgenic steroids (AASs) has become a considerable substance use concern worldwide, and it is a growing public health risk, particularly among male individuals in recreational sports. Individuals who use these substances for recreational purposes may experience various medical problems. However, there is a lack of high-quality guidance and consensus among medical experts regarding the adequate provision of medical care for this population.

Objective: This study aims to develop best practice guidance for health care professionals providing medical care to individuals engaging in the nonmedical use of AASs by achieving consensus on relevant and feasible measures for the Swiss primary care context.

Methods: The Delphi consensus method will be applied in this study to develop best practice guidance, following the criteria for conducting and reporting Delphi studies (DELPHISTAR). The development of evidence-based, relevant, and feasible measures for primary care practice follows a mixed methods approach to identify the problem area by conducting 4 substudies: a scoping literature review, incorporation of medical experience, peer involvement, and the selection of a heterogeneous research steering group of medical experts based on individual and group discussions. This Delphi consensus study consists of 3 rounds of anonymous web-based surveys with medical experts in primary care (N=25 Delphi panelists). Recruitment will occur through a network of primary care experts at the University of Zurich. Participants will rate each measure for relevance and feasibility using a 5-point Likert scale and provide comments and recommendations for additional measures. Each measure will require more than 75% agreement in both relevance and feasibility to achieve consensus. Descriptive statistics will be used. Aggregated ratings will be statistically analyzed for response rates, level of agreement, medians, and IQRs. Qualitative responses will be analyzed thematically and evaluated by the steering group for inclusion in subsequent rounds. The final draft of the resulting best practice guidance will be reviewed by an external board of medical associations, and approval will be sought before publication and dissemination.

Results: The resulting best current clinical guidance is expected to be published in the summer of 2026. Ethics approval was received from the local ethics committee for this study.

Conclusions: With the development of high-quality best practice guidance for health care professionals in primary care, this Delphi study will help close the existing treatment gap among people using AASs. As a strength, primary care offers low-threshold access to health care, chronic care management, and coordination within the health care sector for patients experiencing multiple AAS-related health complications. The Delphi technique is an appropriate study design to develop consensus among a group of medical experts, with the strength of maintaining anonymity throughout the survey process.

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KEYWORDS

anabolic androgenic steroids; doping; image- and performance-enhancing drugs; primary care; study protocol; protocol; male; user; steroids; recreational sports; Delphi consensus; androgenic steroid; questionnaire technique

Introduction

Background

The nonmedical use of anabolic androgenic steroids (AASs) and other image- and performance-enhancing drugs (IPEDs) for optimizing personal esthetic goals and improving sports performance represents one of the newest major global substance use concerns [1-4]. IPEDs comprise different groups of substances, with AASs being the most commonly used [2,3,5-9]. According to a systematic review and meta-analysis, the global lifetime prevalence of AAS use is estimated to be 3.3% in the general population, 6.4% among male individuals, and 18.4% among recreational sportspeople [10]. Considering that the popularity and prevalence of IPED use may have increased in recent years, the problematic use of these substances should be considered a serious and growing risk for public health [4,5]. In Switzerland, the use of anabolic agents appears to be widespread, with an estimated 200,000 to 300,000 users [11,12]. IPEDs can easily be acquired from unregulated drug markets [8,13].

Acute and long-term complications of AAS use can be complex, potentially severe, and life-threatening, affecting all levels of health (ie, physical, mental, and social health) [3,5,14-16]. Importantly, the mortality from natural and unnatural causes among people who use AASs appears to be higher than that in the general population [17-20]. The great extent of harms associated with AAS consumption emphasizes the urgent need for comprehensive and integrated treatment and harm-reduction strategies.

An extensive treatment gap may exist for AAS users. Most people using AASs report experiencing side effects and complications from the use of these substances, but only a minority group of people appear to attend medical care, even though these services are commonly desired by AAS users [3,21-24]. Patients who access medical care often do not disclose the use of these substances due to fear of stigma and lack of trust in health care professionals, leading to inadequate care and decision-making by health care professionals [2,3,22]. Most often, people who use AASs report self-medicating for medical problems, seeking information and support from nonmedical sources (ie, experienced users and peers or online forums) [3,22,25,26].

Further barriers include existing legal restrictions for the provision of medical care for users of AASs worldwide [27,28]. IPEDs, in the context of sports or “doping,” are banned by the World Anti-Doping Agency and prohibited by regulatory agencies [8,13]. Doping policies in Switzerland can criminalize physicians who provide medical care to these patients under certain circumstances [11,29]. Health care providers face legal uncertainty when providing care for patients using AASs, and legal aspects can hinder open discussion and engagement with health care providers from a patient perspective [30,31]. Knowledge of antidoping regulations is crucial to help physicians avoid legal problems and address their concerns.

Objectives

In recent years, a few clinics in Europe have established novel care models that aim to provide medical care and harm-reduction services for this population, and important clinical and health research data have emerged [7,32-37]. Despite these advances, many knowledge gaps remain regarding the optimal provision of care, particularly within a primary care context. Although some expert opinions are available in the published literature, current practice guidance is often not comprehensive, focuses on one disease area, demonstrates a lack of consensus among health care experts, and challenges clinical practice [2,7,32-42]. This study aims to develop best practice guidance for health care professionals providing medical care to individuals engaging in the nonmedical use of AASs by achieving consensus on relevant and feasible measures for a Swiss primary care context.

Methods

Justification for Study Design

For the development of best practice guidance, the Delphi method will be used. The Delphi method is a questionnaire technique that uses multiple iterations designed to build a justified consensus concerning a specific topic among an expert panel [43,44]. It has played a pivotal role over the past few decades in addressing research gaps within health science. The development of best practice guidance is achieved using collective intelligence in areas where research and high-quality data are limited. The strengths and suitability of the Delphi technique for this study include participant anonymity and flexible design compared to other consensus models (eg, focus groups) [44].

This Delphi study will focus solely on AAS use based on the epidemiology of use and the development of androgen dependence syndrome [3,45,46]. Notably, the use of AASs compared to other anabolic agents and IPEDs is most prevalent [3,6]. Substances other than AASs are beyond the scope of this research.

Methodology and Reporting Guidelines

The critical appraisal of a Delphi study in health care follows the methodological process suggested by Nasa et al [47]. The conduct of this study follows the DELPHISTAR (Delphi studies in social and health sciences–recommendations for an interdisciplinary standardized reporting) criteria for conducting and reporting Delphi studies [48].

Scope and Context for Use

The development of best practice guidance is aimed at general practitioners in primary care settings in Switzerland who provide medical care for male users of AASs in recreational sport (ie, noncompeting recreational sportspeople, weightlifters, or

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bodybuilders). The provision of medical care for competitive athletes (ie, those who belong to a control pool within the framework of the World Anti-Doping Code) is outside the legal scope of this project.

Study Setting

This study will be conducted collaboratively by the Arud Centre for Addiction Medicine in Zurich, the Institute of Primary Care at the University of Zurich, and the University Hospital of Zurich. The Arud Centre established integrated primary care and treatment services for users of AASs in Zurich in June 2023 [29]. In Switzerland, the Arud Centre provides integrated medical care services for users of AASs, including general internal medicine, psychiatry, and addiction medicine. The Institute for Primary Care in Zurich provides expert opinion on health service research, focusing on integrated care in the primary care setting.

Project Governance

A project governance group has been established with the responsibility of overseeing the conduct of the project. The group consists of representatives from the Arud Centre (RM and PB) and the Institute of Primary Care (OS and SN-J).

Study Design

The Delphi consensus study is conducted sequentially in a four-step methodological process, including (1) identification of the problem area (mixed methods approach), (2) selection of the panel (medical experts), (3) iterative Delphi rounds, and (4) closing criteria (consensus and primary outcome). The complete workflow for this study is presented in Figure 1.

Figure 1. Delphi study workflow.

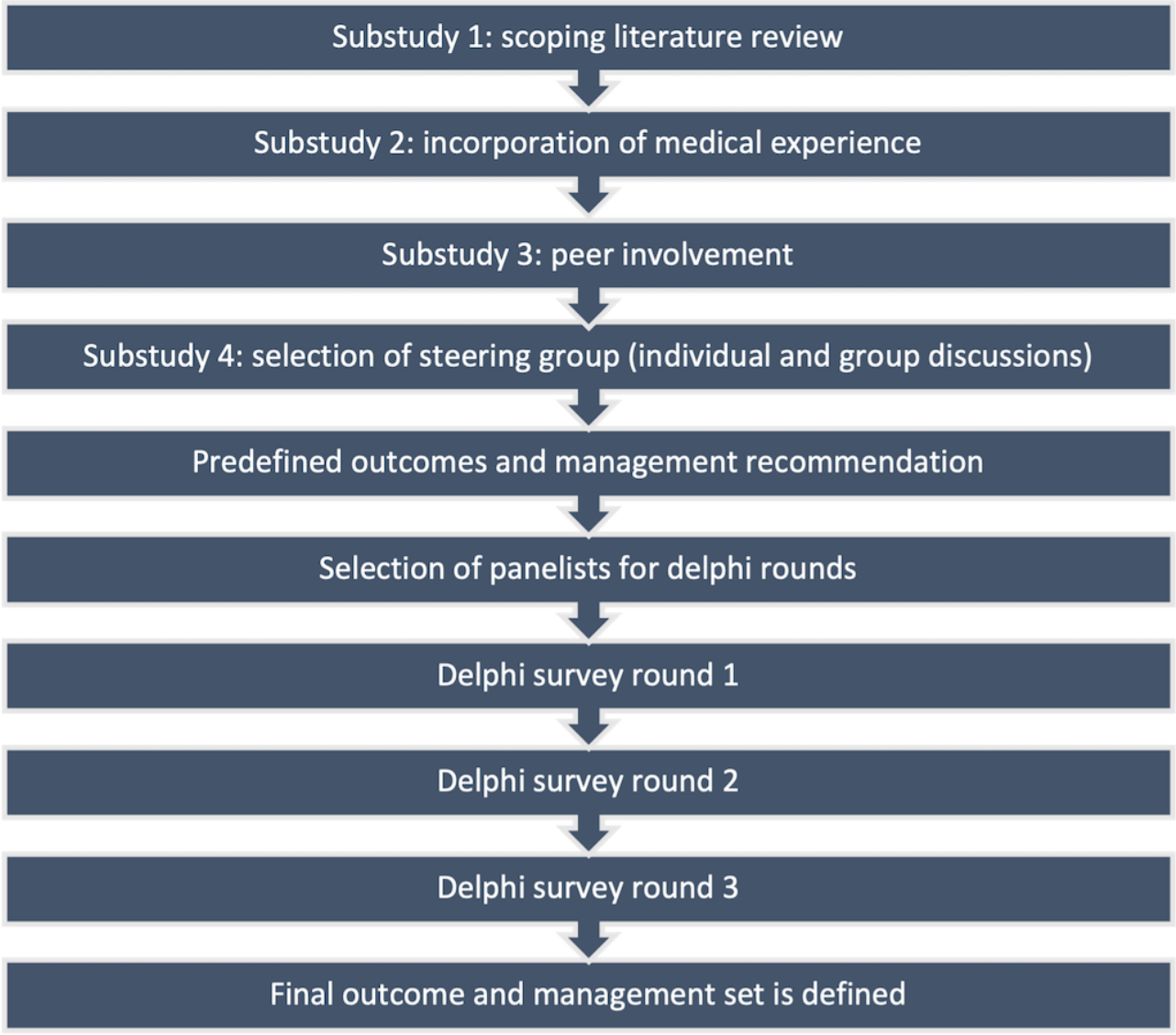

Systematic Identification of Problem Area

The identification of problem area will be achieved by conducting four substudies, including (1) a scoping literature review, (2) incorporation of medical experience, (3) peer involvement, and (4) selection of a research steering group with individual and group discussions.

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Substudy 1: Scoping Literature Review of Peer-Reviewed Medical Literature

A scoping literature review will be conducted to systematically identify, evaluate, and synthesize existing research related to the following:

1. How to screen for and diagnose AAS use
2. Mapping side effects and complications from AAS use
3. Mapping management recommendations for side effects of and complications from AAS use

This scoping review will follow the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines (Multimedia Appendix 1 [49]). The eligibility criteria are established to ensure relevance and quality. The inclusion criteria comprise peer-reviewed articles published between 2005 and 2025 in English and that were related to the aforementioned topics. The exclusion criteria comprise non–peer-reviewed articles, non-English publications, and articles unrelated to the study topics.

A comprehensive search strategy will be undertaken in electronic databases (ie, PubMed, MEDLINE, and Embase). Additional sources, such as reference lists of identified articles, will also be searched to supplement the database results. Furthermore, existing guidelines from medical societies will be assessed for management recommendations (ie, testosterone replacement therapy). The search strategy will involve structured keywords and Boolean operators and can be found in Multimedia Appendix 2.

Two independent and experienced reviewers will screen titles and abstracts for relevance based on the eligibility criteria. Full-text articles of potentially relevant articles will be obtained and reviewed independently by the same reviewers. The proposed explicit consensus criteria in the final paper will reference the available evidence where possible. This will be achieved by the research steering group undertaking a detailed literature review following the recommendations and processes set out by the Grading of Recommendations Assessment, Development, and Evaluation guidelines [50].

A standardized data extraction form will be used to chart relevant data from the included studies. The form will capture study characteristics (ie, author, year, and country), study design and methodology, and principal findings related to the research question. The extracted data will be analyzed using a thematic synthesis approach. The findings will be organized into themes and subthemes to provide an overview of the current state of research on the topics. Quality assurance of individual studies will not be assessed as per the typical scoping review methodology. However, the review process will be documented in detail to ensure transparency. The results will be presented descriptively, using tables and figures to illustrate key findings and thematic categorizations.

Substudy 2: Medical Experience

In Switzerland, a primary health care practice for users of AASs was established in 2023 at the Arud Centre for Addiction Medicine in Zurich, in collaboration with the Institute for Primary Care at the University of Zurich [29]. Experiences and data derived from this health care service will be used to support the literature review and fill existing knowledge gaps.

Substudy 3: Peer Involvement

Peer support services within addiction medicine, which incorporate peers with lived experiences, have been used in various clinical settings to assist individuals with substance use disorders [51]. Peers among people using AASs currently play a crucial role in providing information about use and offering harm-reduction advice for this population [2,3,22]. There is a need to incorporate lived experiences from users and engage peers in developing comprehensive harm-reduction strategies. Outcomes and management recommendations established through previous steps will be reviewed by a selected group of peers (n=5) before being finalized for use in the Delphi rounds. The selection of peers will occur from the established patient cohort at the Arud Centre [29].

Substudy 4: Selection of the Research Steering Group With Individual and Group Discussions

A research steering group will be selected by the study team to conduct this research. They will be responsible for preparing and circulating the content of the Delphi rounds. The research steering group will comprise heterogeneous medical experts and health care professionals with various backgrounds. The selection of experts is based on outcomes and disease areas established during the previous steps (eg, cardiology, psychiatry, and endocrinology). Selection criteria for steering group members include expertise in managing side effects and complications from the use of anabolic steroids, as well as holding a Foederatio Medicorum Helveticorum (Swiss Medical Association) specialization or title in their respective field or certification or license in their respective fields, where applicable (eg, addiction medicine, sports medicine, and andrology). The research steering group will not participate in the surveys; they will supervise and monitor the process and provide expert guidance. Outcomes and management recommendations established through previous steps will be reviewed by the expert steering group before being finalized for use in the Delphi rounds. Disagreements will be resolved by consensus among the steering group members through individual and group discussions for the final draft to be used in the Delphi rounds.

Selection and Identification of the Expert Panel

The members who participate in the voting process of the Delphi survey are called panelists. The panel will consist of clinical or research-based experts with relevant backgrounds in primary care. A homogeneous panel of medical experts in primary care will be selected according to predefined criteria to achieve generalization of consensus and assessment of the relevance and feasibility of management recommendations.

Recruitment

Participants will be identified through self-nomination and identification by the project team based on their track record. Individuals identified will be sent a personalized invitation letter. Self-nomination as Delphi panelists will occur through networks for primary care physicians. The institute has established a network of primary care physicians who are

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engaged in teaching and research activities. A unique identifier will be assigned to each participant to enable monitoring of completion and ensure anonymity.

Eligibility Screen

All identified experts will be invited to participate. The potential participants will receive materials to inform them about the study. They will be sent an invitation letter, a participant information sheet, and a participant consent form. Panelists will be provided specific information about the project and asked for their consent to participate. Experts will be screened at this stage for eligibility to participate, which includes holding a Foederatio Medicorum Helveticorum specialization or title in primary care medicine and having an intrinsic interest in this user population and in anabolic agents. Potential participants will be asked to declare any possible conflicts of interest. Participants will be asked to commit to completing all required rounds of the Delphi process; incentives will be provided only upon completion of all Delphi rounds. Participants will be able to withdraw from the project at any time. Potential participants will be provided with a clear explanation of the anticipated process, including the requirement that participation will be over a period of months with multiple rounds of questioning and feedback. They will be asked to sign a written consent form to be involved in the Delphi process.

Panel Size

There is no standard sample size for the panel members. However, due to data management challenges and logistic issues, a panel size of approximately 30 to 50 members is recommended as optimal for conducting homogeneous Delphi rounds according to the literature, with a minimum number of 12 members [47,52]. According to a systematic review that analyzed quality indicators in Delphi studies, most panels consisted of 11 to 31 members, with a median of 17 members [53]. This study will aim to recruit a minimum of 25 participants.

Design and Content of the Survey

The study will be conducted entirely on the web. The Delphi survey rounds will be designed and administered electronically using an established and validated Delphi Manager software. The previously determined questionnaire items will be incorporated into the initial questionnaire. Quantitative Delphi rounds will then be conducted among the expert panelists. These rounds will ask experts to rate items in terms of relevance (appropriateness in primary care) and feasibility (implementability in primary care) based on predetermined concepts. Quantitative rounds will also provide space for additional (qualitative) comments, allowing experts to suggest amendments or additions to the items. Qualitative feedback will be mapped by disease area and discussed among the research steering group based on relevance and feasibility for inclusion in subsequent Delphi rounds.

Each round is estimated to take up to 60 minutes to complete and will be accessible for 3 weeks. To enhance the response rate, Delphi panelists will receive weekly reminders if the survey is not completed. Results will be analyzed for at least 2 weeks between rounds. Subsequent rounds will provide detailed feedback about responses to previous rounds, including individual and group responses or consensus and median (IQR) for each item. Participants will receive up to 3 email reminders to complete each round.

Rating Process

Participants will be asked to rate each item for relevance and feasibility in 3 rounds of the Delphi survey using a 5-point Likert scale (ie, relevance: 1=irrelevant and 5=relevant; feasibility: 1=not feasible and 5=feasible). Textboxes will be available for participants to provide comments, including recommendations for additional items, for each subgroup of indicators. In round 1, participants will be asked to provide demographic information once (ie, name, age, gender, professional details or area of practice, number of years of primary care practice, and level of experience with AAS users). Then, they will be asked to rate the questionnaire items. Items that reach consensus will be removed. In round 2, participants will be presented with items that did not reach consensus, as well as new items or item changes based on qualitative feedback. Furthermore, they will receive a summary feedback of previous responses from round 1 and be given the opportunity to re-evaluate or change their previous responses. In the final round, that is, round 3, the rating process from round 2 will be repeated.

Data Analysis

Descriptive statistics will be used to summarize and analyze the data. Demographics of the Delphi panelists will be analyzed using Microsoft Excel. Aggregate results of the panelists' responses will be analyzed for response rates, levels of relevance and feasibility for each item, and medians and IQRs [54]. The final score for relevance and feasibility will be calculated as the percentage of Delphi panelists who assigned a combined rating of 4 or 5, divided by the total number of responses, and multiplied by 100. Regarding qualitative feedback, the research team will analyze the data and discuss possible changes in items and the inclusion of new items. To maintain rigor, the response rate of each Delphi round should not fall below 70% [55]. No subsequent rounds will be launched if the response rate of the previous round is below that threshold. In case of missing data, those responses will be removed, and datasets for each item will be analyzed with a reduced sample size if the response rate is 70% or more.

Closing Criteria

The levels of consensus in the Delphi methodology can vary depending on the size of the expert panel and the aim of the research. Each item will require 75% or greater agreement in both relevance and feasibility to achieve consensus [56]. The final consensus will present issues upon which the experts agree (consensus), along with the items that remain controversial (nonconsensus).

Data Management

Demographic data collected from Delphi panelists and consent forms will be stored in a Microsoft Word or PDF document. An Excel spreadsheet will be created in which participant names will be assigned an ID number. Survey files will be assigned using the participant's number to ensure anonymity. Hard copies of documents will be stored in a locked filing cabinet at the

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University of Zurich. Statistical analyses will be performed using R statistical software (version 4.2.2; R Foundation for Statistical Computing) [57]. Digital data will be stored on a secure cloud-based system at the University of Zurich.

External Validation

The final draft of the resulting best practice guidance will be reviewed by an external board before publication and dissemination. Approval will be sought from the quality commission of the Swiss Society of General Internal Medicine, the Swiss Society of Addiction Medicine, and the Sport and Exercise Medicine Switzerland (SEMS).

Ethical Considerations

This Delphi study was reviewed by the Cantonal Ethics Committee Zurich, Switzerland (Business Administration System for Ethics Committees, BASEC-Nr Req-2024-00643) and was determined not to fall within the scope of the Human Research Act.

Before the Delphi rounds, panelists will receive an email providing detailed information regarding the investigators, the purpose of the study, a description of the research, participant involvement, risks and potential benefits, confidentiality, authorization and withdrawal procedures, compensation, the voluntary nature of participation, assurance of anonymity, a request for consent, and an approximate estimation of the survey's duration.

During the Delphi rounds, panelists will remain anonymous to each other but not to the researchers. Data will be anonymized and will be accessible only to authorized study personnel. Anonymity of the panelists will be guaranteed throughout the Delphi rounds. Upon conclusion, panelists who complete all Delphi rounds will be offered the choice to remain anonymous or receive acknowledgment in the publication for their participation (ie, name and organization). All medical information obtained within this study will be considered confidential.

Small incentives will be provided for expert panelists for their contributions in the Delphi rounds. A total financial incentive of CHF 500 (US $628.78) will be given to each panel expert upon the completion of all Delphi rounds at the end of the study.

Legal aspects and professional ethics principles in medicine need to be considered when providing medical care to individuals engaged in recreational sports. Regarding the implementation of clinical practice in Switzerland, we have previously discussed the legal aspects of providing medical care elsewhere and demonstrated its feasibility within the legal scope at the Arud Centre [11,29]. Importantly, the medical support and care provided are not intended to support doping but rather to combat addiction and problematic consumption based on a clear medical indication. Taking legal and professional principles into account, it is essential for health care professionals to be aware of the legal limitations of providing care to protect themselves from possible legal repercussions.

Results

As of February 2025, the research has commenced with the scoping literature review (ie, systematic identification of the problem area), and no Delphi participants have been recruited. The tentative timeline is outlined in Textbox 1. Results are expected to be published in the summer of 2026. The SEMS granted funding for the conduct of this research in September 2024. Ethics approval for the conduct of this study was received in May 2024.

Textbox 1. Delphi study timeline.

Study protocol development (before 2025)

- Identification of problem area: January 2025 to July 2025
- Survey development and selection of expert panel: August 2025 to December 2025
- Iterative quantitative Delphi rounds: January 2026 to April 2026
- Manuscript development: May 2026 to July 2026

Discussion

Anticipated Findings

This study protocol describes the design for a Delphi study aimed at reaching consensus among health care experts in primary care on a set of relevant and feasible measures to optimize the provision of current medical care for AAS users in a recreational sports setting. Findings from this Delphi consensus study will address knowledge gaps in the medical literature and provide high-quality recommendations for future use by health care providers in primary care. Measures to be evaluated in this Delphi study will be derived from a mixed methods approach, incorporating a review of existing medical literature. This study will further build on these initial results and close existing knowledge gaps with opinions from medical experts in specialized medical fields, peers, and anabolic steroid management specialists with clinical experience in this population. This mixed methods approach is critical for addressing the many medical challenges arising from this substance use.

Principal findings from reviewing the medical literature demonstrate that the consumption of AASs is associated with many harms, including cardiovascular complications and the development of cardiomyopathy [17,33,42,58-60]; liver and kidney injury [16,61-64]; endocrine, reproductive, and metabolic disorders [15,40,46,65-67]; infectious diseases [68,69]; negative mental health outcomes [70-72]; and even cancer development [14,16,73]. Furthermore, health risks may arise and culminate in this population due to consumption practices (ie, supraphysiologic doses of AASs in complex user patterns, length

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of consumption over weeks or months, use of extensive polypharmacy, and concomitant illicit substance use [74-79]); high-risk behavioral practices (eg, injection-related, sexual, exercise, and nutritional practices [62,80]); addiction-related medical factors (eg, anabolic steroid dependence, muscle dysmorphia, and concomitant substance use disorders [65,76,81]); or individual factors (eg, genetic, sociodemographic, and economic factors [19]). The great extent of harm to multiple organ systems and further risks associated with AAS consumption emphasize the need for a multidisciplinary approach in developing comprehensive medical guidance, which represents a strength of this study design. The primary care setting appears to be most suitable for providing comprehensive medical care to people using these substances, as it offers low-threshold access to health care, provides long-term and chronic care, and coordinates within the health care sector when dealing with multiple complications from this substance use [29].

This study design offers additional strengths for the development of clinical guidance. The Delphi technique is an appropriate tool to develop consensus among diverse experts because it offers anonymity to participants and minimizes bias from possibly dominant experts compared to other consensus development methods (ie, focus groups). The use of scoring criteria for approval of each consensus item is expected to ensure its relevance and feasibility in clinical practice. Furthermore, participants can review individual and group results from previous rounds and reassess their responses. In addition to seeking consensus from health care experts, the study team will seek broad institutional approval from different medical associations (ie, Swiss Society of General Internal Medicine, Swiss Society of Addiction Medicine, as well as SEMS). This is a unique attribute of this Delphi study design regarding future implementation and rollout of the final guidance. Results will be disseminated in peer-reviewed scientific journals; presented at national and international conferences; and circulated through professional organizations relevant to primary care medicine, sports medicine, and addiction medicine. The final manuscript will also be circulated to all participants. Another important feature of this project is to create awareness of the legal aspects that need to be considered when providing medical care to AAS users and the urgent need for policy changes. The development of adequate best practice medical guidance can further strengthen the alliance between different stakeholders and medical experts for future guidance on policy changes by demonstrating the extent of the problems that arise through this substance use and its possible negative public health outcomes.

Limitations of the Delphi technique need to be mentioned. The study methodology does not involve direct interactions with the panelists, which may limit their ability to generate ideas during the consensus process. Furthermore, this study is designed specifically for the Swiss primary care context and may not represent the primary care setting in other countries, thus challenging the generalization of results.

Conclusions

The use of AASs among younger male individuals in recreational sports has become a major global health concern. The nonmedical use of these substances may be associated with a sequela of harms on many organ systems, as well as substance dependence and many more risks that can arise from a wide range of high-risk behaviors. The optimal provision of medical care for this population is challenged by limited data in the medical literature and a lack of consensus among health care experts. The Delphi consensus study, comprising a mixed methods study design, is an appropriate tool to gain consensus from different stakeholders and health care experts. Results from this study will create a consensus-based best current clinical guidance for primary care providers in Switzerland. The primary care setting may be the best place to provide integrated and comprehensive medical care and harm-reducing measures to patients with AAS-related health complications.

Acknowledgments

The Sport and Exercise Medicine Switzerland (SEMS) has granted CHF 10,000 (US $12,575.5) for this study. The ideas and opinions expressed herein are those of the authors and do not necessarily reflect the opinions of the SEMS.

Data Availability

No underlying data are available for this paper because no datasets were generated or analyzed during this study.

Authors' Contributions

RM, OS, and PB conceived the idea. RM drafted the manuscript. SN-J provided methodological expertise. RM and OS acquired funding. All authors reviewed, edited, and approved the final version of the manuscript.

Conflicts of Interest

RM works part-time at ViiV Healthcare, Switzerland. The company did not participate in the design, data analysis, interpretation, or drafting of this paper. All other authors declare no other conflicts of interest.

Multimedia Appendix 1
PRISMA-ScR checklist.
[DOCX File , 84 KB - resprot_v14i1e65233_app1.docx]

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Multimedia Appendix 2
Scoping literature review search strategy.
[DOCX File , 14 KB - resprot_v14i1e65233_app2.docx]

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Abbreviations

AAS: anabolic androgenic steroid
IPED: image- and performance-enhancing drug
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
SEMS: Sport and Exercise Medicine Switzerland

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Protocol

Understanding the Link Between Physical Activity and Work Ability in University Staff: Protocol for a Gender-Sensitive Cross-Sectional Study

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Abstract

Background: Physical inactivity represents a significant public health issue with substantial socioeconomic costs. In the autonomous Community of Madrid, 39.17% of the population does not meet the World Health Organization recommendations for physical activity (PA). Gender, sex, and occupational factors are well-established determinants of leisure-time physical activity (LTPA); yet, few studies have examined these factors among university staff.

Objective: This study aims to analyze the relationship between LTPA and work ability among university staff in the autonomous Community of Madrid, considering the potential modifying effect of occupational PA. Secondary objectives include examining associations between LTPA, musculoskeletal disorders, health-related quality of life, physical and mental workload, and working conditions, with a focus on sex and gender differences.

Methods: A cross-sectional study was designed involving 885 university staff members from the University of Alcalá, Madrid, Spain. Participants will complete an online survey, including sociodemographic questions and validated instruments: the Global Physical Activity Questionnaire, Work Ability Index, Nordic Musculoskeletal Questionnaire, Short Form-12 Health Survey, and the National Aeronautics and Space Administration Task Load Index. Descriptive and inferential statistics will be performed to assess the associations between LTPA, occupational PA, and work ability, adjusted for relevant covariates.

Results: This study was approved by the ethics committee of the University of Alcalá in November 2024. Recruitment began in December 2024 and will continue until June 2027. Data analysis will be conducted progressively. Results will be disseminated in peer-reviewed journals and presented at scientific conferences following gender-sensitive and transparent reporting standards.

Conclusions: Understanding the determinants of PA and their interaction with work ability and gender may inform the development of targeted, culturally sensitive interventions to reduce sedentary behavior and its associated health and economic burdens in university staff.

Trial Registration: ClinicalTrials.gov NCT06723808; https://clinicaltrials.gov/study/NCT06723808

International Registered Report Identifier (IRRID): DERR1-10.2196/80298

(JMIR Res Protoc 2025;14:e80298) doi:10.2196/80298

KEYWORDS

physical activity; sedentary behavior; working conditions; occupational health; gender perspective; leisure activities

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Introduction

Background

Physical activity (PA) is widely recognized as a cornerstone of public health due to its proven effectiveness in preventing and managing noncommunicable diseases [1]. However, PA has emerged as an escalating global health and socioeconomic challenge [2], significantly impacting the Spanish population, particularly in the autonomous Community of Madrid (CAM), where more than 39% of the adults fail to meet World Health Organization (WHO) guidelines [3]. In occupational contexts, this is especially concerning due to the negative association between inactivity and work ability, a key predictor of productivity, employment sustainability, and healthy aging in the workforce [4,5].

PA can be classified into different domains, with leisure-time physical activity (LTPA) and occupational physical activity (OPA) being particularly relevant in work-related health research [6,7]. OPA refers to the physical effort involved in work-related tasks [8], whereas LTPA encompasses voluntary activities, such as exercise, sports, and recreation [6]. Although both contribute to total PA, their effects on health are not equivalent [4,6-9].

Substantial evidence links high levels of LTPA with enhanced overall health, lower risk of noncommunicable diseases, and improved mental and musculoskeletal health [1,9]. Conversely, high OPA levels have been associated with increased risks of musculoskeletal disorders (MSDs) [10], cardiovascular diseases [10,11], and higher mortality rates. This apparent contradiction, referred to as the "PA paradox," highlights that OPA often lacks sufficient intensity, involves prolonged durations without recovery, and typically occurs under low-autonomy conditions [11]. This paradox provides a relevant conceptual framework for this study, reinforcing the importance of examining LTPA and OPA as distinct domains with potentially divergent effects on work ability.

Moreover, while LTPA has been shown to positively influence occupational outcomes, including work ability [12], reduced absenteeism [13,14], greater job satisfaction [15], improved performance, and higher productivity [16,17], an imbalance between OPA and LTPA may lead to diminished functional capacity, increased absenteeism, and an elevated risk of burnout [11-13,17-21].

Although international guidelines, such as those issued by the WHO, define minimum PA thresholds for various age groups and conditions [20], social determinants of health, including gender, sex, socioeconomic status, and workplace environment, play a significant role in shaping individuals' ability to meet these recommendations [22-29]. In this context, unequal access to LTPA opportunities contributes to the persistence of health disparities [20,21].

Gender and sex play a particularly important role in shaping PA behavior and work-related outcomes. Women tend to engage in less LTPA than men, a pattern observed in Spain and the CAM region, where 46.89% of the women report being sedentary compared to 30.61% of the men [3]. This disparity is likely driven by a combination of gender- and sex-related factors. Gender-based determinants may include unequal caregiving responsibilities, reduced time for leisure due to social roles, and cultural expectations regarding self-care and productivity, which can limit women's participation in LTPA [22,23,30]. In contrast, sex-related factors, such as menopause, endometriosis, and urinary incontinence (biological or physiological processes specific to female reproductive health), may directly impact physical capacity and perceived work ability [24]. These distinct but intersecting influences are often overlooked in occupational health research, highlighting the need for a gender-sensitive and sex-aware approach.

MSDs further complicate this picture, as they are among the most prevalent occupational health issues in Europe and have been consistently linked to reduced work ability and quality of life [25-28]. Given their potential association with both PA levels and occupational demands, they represent a relevant outcome for understanding the interplay between LTPA, OPA, and workforce health. University staff represent a highly relevant study population given their exposure to elevated cognitive and sedentary workloads as well as their strategic role within knowledge-based economies. The university setting also provides a distinct methodological advantage, encompassing diverse occupational profiles with markedly different levels of OPA. PDI (Personal Docente e Investigador): Teaching and Research Staff, PI (Personal Investigador): Research Staff (not Principal Investigator), PTGAS (Personal Técnico, de Gestión, de Administración y de Servicios): Technical, Management, Administrative, and Services Staff often perform duties involving higher levels of physical effort. This internal heterogeneity allows for the examination of different domains of PA and work ability within a single institutional context, making it particularly well-suited for exploring the PA paradox.

Although physical fitness and higher LTPA levels have been associated with greater work ability and fewer musculoskeletal concerns [14,29,31], much of the existing literature does not adequately distinguish between OPA and LTPA or focuses predominantly on male or younger populations [13,32]. Furthermore, limited attention has been given to the role of sex and gender in moderating these relationships as well as the broader influence of social determinants of health, such as sex, gender, and occupational context, on PA behaviors and work-related outcomes [33-40]. Therefore, further research is needed to examine the interplay between LTPA, OPA, and work ability, incorporating a gender perspective and accounting for the influence of the social determinants of health. Such knowledge is critical to informing the development of healthy, equitable, and sustainable work environments.

Objectives

On the basis of the aforementioned background, the primary objective of this study is to analyze the relationship between LTPA and work ability among university staff in the CAM, considering the potential modifying effect of OPA, and exploring differences by sex and gender. The secondary objectives are to (1) determine the prevalence of MSDs in this population and analyze their association with LTPA and OPA levels using validated questionnaires; (2) evaluate the relationship between both domains of PA and perceived physical

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and mental workload, adjusting for occupational role and sociodemographic factors; (3) examine the association between LTPA and OPA and self-perceived health-related quality of life (HRQoL); and (4) explore whether these associations vary according to sex, gender, and occupational category.

Methods

Study Design

This is a descriptive, cross-sectional, population-based study with a gender perspective. The study was registered on ClinicalTrials.gov before data collection (NCT06723808).

Study Population and Setting

The study population consists of university staff working in the CAM. A representative sample of 885 workers from the University of Alcalá (UAH), Alcalá de Henares, Madrid, Spain, was selected. Participants include members of the PTGAS, PDI, and PI.

Inclusion criteria are (1) aged ≥18 years and (2) having sufficient proficiency in Spanish to complete study procedures. The questionnaire will be administered exclusively in Spanish, as it is the official and working language in the study setting. Consequently, only participants with adequate Spanish comprehension will be eligible. While this approach ensures the reliability of self-reported data, it may limit the generalizability of the findings to non–Spanish-speaking university staff.

Exclusion criteria include (1) cognitive impairment preventing comprehension of study information or completion of the survey, (2) severe neurological deterioration, and (3) diagnosed severe mental illness preventing the provision of informed consent.

Recruitment and Sampling

Due to the institutional data protection constraints, it is not possible to distribute the survey invitation directly to all university employees. Consequently, a multichannel recruitment strategy is being implemented. The study information sheet and participation link are being disseminated via email to deans, faculties, departments, and the human resources department of the UAH, who may forward it to relevant bodies at their discretion. In addition, posters containing QR codes and brief study details are placed on bulletin boards across UAH buildings to increase visibility. Participants are also encouraged to share the study with colleagues to broaden its reach and improve participation rates, thereby introducing a secondary snowball component.

While this strategy incorporates elements of exponential snowball sampling, it is designed to promote broad participation across different occupational roles while complying with data protection policies. This approach facilitates access to diverse occupational profiles and enhances heterogeneity in the study sample.

Sample Size

The sample size was calculated for a finite population using Microsoft Excel based on the total UAH workforce (N=3117). A minimum of 796 (25.53%) participants were required to achieve a 95% CI, 3% margin of error, and population proportion of 0.5. This last value was chosen due to the absence of previous prevalence data on the variables of interest, as it maximizes sample size under conditions of uncertainty and ensures sufficient statistical power across all outcomes. Accounting for a potential 10% dropout rate, the final estimated sample size was determined to be 885 (28.39%) participants.

Study Measures

Data collection includes sociodemographic variables and validated questionnaires in Spanish to assess the primary and secondary study outcomes.

Primary Variables

The primary variables include LTPA, OPA, and work ability. LTPA and OPA are assessed using the Spanish version of the Global Physical Activity Questionnaire [41]. This tool assesses PA in 3 domains: occupational, active transport, and leisure, yielding weekly metabolic equivalent of task (MET) minutes for each. MET minutes are calculated by multiplying activity duration by the standard MET values.

The official Spanish version of the questionnaire, endorsed by the WHO, has shown good test-retest reliability (intraclass correlation coefficient=0.70-0.90) and moderate concurrent validity (Spearman ρ≈0.42) compared with the accelerometry in European and Latin American Spanish-speaking populations. Although it has not been formally validated in Spain, its widespread international use and standardization support its inclusion in this study [42].

Work ability is being assessed with the Spanish version of the Work Ability Index (WAI) [43]. The WAI measures 7 dimensions: current work ability compared to lifetime best, work ability in relation to job demands, physician-diagnosed illnesses, estimated work impairment due to illness, sick leave over the past year, prognosis of work ability over the next 2 years, and mental resources. Total scores classify work ability into 4 categories: poor (7-27), moderate (28-36), good (37-43), and excellent (43,45-49). The WAI has been adapted and endorsed by the Spanish National Institute for Safety and Health at Work (NTP 1147) for the Spanish occupational context [43]. It was validated in a sample of 1184 Spanish health center workers, demonstrating satisfactory reliability (intraclass correlation coefficient>0.75), a stable 2-factor structure, and convergent validity with measures of health and productivity, reflecting strong psychometric properties in occupational settings [44].

Secondary Variables

Secondary variables include the prevalence of MSDs, HRQoL, and physical and mental workload. MSDs are being evaluated using the Spanish version of the Standardized Nordic Questionnaire [45], which identifies symptoms across various anatomical regions and their functional impact. It includes symptom checklists and related consequences, such as reduced activity or health care visits. This questionnaire has been validated across multiple Spanish occupational samples. In a study of 526 nursing assistants in Asturias, the questionnaire demonstrated good test-retest reliability (Cohen κ=0.60-0.81)

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and internal consistency (Kuder-Richardson 20=0.74-0.87) [46]. In addition, in a separate validation among 312 professional musicians in Madrid, similar values were observed (Cohen κ=0.60-0.81; Kuder-Richardson 20=0.737-0.873), and construct validity was supported by significantly higher disability and pain scores in anatomical regions with reported symptoms [45]. The tool also demonstrated high feasibility, with an average completion time of 6 (SD 2) minutes [45].

HRQoL is being assessed using the Short Form-12 Health Survey [47], which covers 8 health dimensions across physical and mental domains. Scores are standardized to a population mean of 50 (SD 10); scores greater than 50 indicate better-than-average perceived health. The Short Form-12 Health Survey, validated in a representative Spanish adult population (n≈11,000), reported high internal consistency (Cronbach α=0.87 for the physical component summary and Cronbach α=0.86 for the mental component summary). It accounted for more than 90% of the variance observed in the Short Form-36 Health Survey, further supporting its reliability and construct validity for assessing HRQoL [48].

Workload is being evaluated using the National Aeronautics and Space Administration Task Load Index [49], which includes 6 subscales: mental, physical, and temporal demand, performance, effort, and frustration. After weighting each subscale, participants rate them on a scale of 0 to 100. Weighted scores are averaged to compute a total workload score. This index has been validated in Spain in a sample of 398 workers across 7 occupational sectors. The instrument demonstrated strong internal consistency (Cronbach α>0.80) and confirmed its intended factorial structure, supporting its suitability for assessing perceived workload in diverse occupational groups [50]. The Instituto Nacional de Seguridad y Salud en el Trabajo recommends its use to estimate perceived mental workload in real work environments due to its sensitivity to variation in cognitive and physical demands and its nonintrusive nature (NTP 544) [49].

Sociodemographic data collected include age, sex, gender, menopause status and related symptoms (if applicable), anthropometric variables, education level, work role (PTGAS, PDI, and PI), work schedule (split, continuous, or mixed), workday type (full time or part time), gross annual income, and number of cohabitants.

Data Collection

Data collection began after receiving ethics approval in November 2024 (clinical research ethics committee: CEID/2024/3/061). At the time of manuscript submission, no statistical analyses had been conducted; this protocol describes the planned methodology in detail in accordance with the journal's protocol submission requirements. Participants are completing an ad hoc online form created in Microsoft Forms, accessible on any internet-enabled device. The form includes all questionnaires and measures described earlier. Completion time is approximately 25 minutes. To optimize response rates and minimize perceived burden, this estimated completion time is clearly communicated in the invitation message. This duration was deemed acceptable for participants to balance respondent convenience with the need for comprehensive data collection. To further support participation, reminder messages will be sent at regular intervals to prompt responses and ensure questionnaire completion.

Data are stored automatically in a secure Microsoft Excel database, accessible only to the principal investigator, who ensures data completeness and accuracy, oversees coding, and securely maintains the dataset for subsequent statistical analysis.

Planned Data Analysis

Descriptive analyses will summarize all variables, reporting means, medians, SDs, and quartiles for continuous variables and frequency distributions for categorical variables. Normality will be assessed using the Kolmogorov-Smirnov test.

To examine associations between PA levels (both OPA and LTPA) and the primary outcomes (work ability, musculoskeletal health, and quality of life), multiple linear and logistic regression model analyses will be performed, depending on the nature of the outcome variable. These models will adjust for relevant covariates, including age, sex, occupational group, and key social determinants of health. Moderation by gender will be assessed through the inclusion of interaction terms, and stratified analyses by sex and gender will be conducted to explore potential differential effects.

To account for the expected heterogeneity across occupational roles, key analyses will be stratified by job category (PDI or PI vs PTGAS). Occupational role will also be included as a covariate in multivariable regression models to adjust for its potential confounding effect. In addition, subgroup analyses will be conducted to explore interaction effects between occupational role and levels of OPA and LTPA on primary and secondary outcomes, including work ability, MSDs, perceived workload, and HRQoL. PA levels will be categorized using WHO-recommended cutoffs, with high PA defined as 600 MET-minutes per week or more, allowing for group comparisons (eg, high vs low OPA or LTPA) in relation to health and occupational outcomes.

Furthermore, mediation analyses will be conducted to evaluate whether MSDs mediate the relationship between PA and work ability. These analyses will follow sequential multiple regression models, applying the approach described by Preacher [51] and Hayes [52] and adapted for cross-sectional data. Model fit will be assessed using the R^2 coefficient and F test. Statistical significance will be set at $P<.05$, and 95% CIs will be reported for all regression coefficients.

This analytical approach aligns with a gender-sensitive framework, enabling the detection of differential effects and the potential moderating roles of gender in the relationships between PA, occupational factors, and health outcomes.

The online questionnaire is programmed so that all questions must be completed before submission, thereby minimizing the likelihood of missing data. Consequently, the proportion of missing values is expected to be negligible. In the unlikely event that incomplete data are detected (eg, due to technical errors or partial dropouts), a descriptive analysis of missingness will be performed. In such cases, listwise deletion will be applied.

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All analyses will be conducted using SPSS Statistics (version 27.0; IBM Corp) by a blinded statistician working with coded data.

Ethical Considerations

This study is being conducted in full accordance with the ethical principles of the Declaration of Helsinki. Participant confidentiality is ensured in compliance with Organic Law 3/2018 of December 5 on the Protection of Personal Data and Guarantee of Digital Rights, as well as Regulation (European Union) 2016/679 of the European Parliament and Council of April 27, 2016 (General Data Protection Regulation). All participants received an information sheet and provided voluntary, written informed consent prior to any data collection. No compensation was provided to participants for their participation in this study. The results will be reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [53].

Results

This study was approved by the clinical research ethics committee of the UAH in November 2024 (CEID/2024/3/061), in compliance with the European data protection regulations. Recruitment began in December 2024 and is currently ongoing. As of July 2025, data collection was actively underway and is expected to continue until June 2027, the planned study completion date. Participants are completing the online questionnaire using Microsoft Forms, as detailed in the Methods section.

All responses are automatically collected and securely stored in a cloud-based spreadsheet accessible only to the principal investigator. Preliminary checks are being performed to ensure data completeness and consistency. No statistical analyses have been conducted to date, as data collection is still ongoing.

Upon completion of data collection, the final dataset will be analyzed following the predefined statistical plan. Study results, irrespective of their significance, will be disseminated in peer-reviewed national and international journals and presented at academic conferences. The dissemination strategy will adhere to the principles of a gender-sensitive and transparent reporting approach, aligned with current research integrity and open science standards.

Discussion

Anticipated Findings

The primary aim of this study is to investigate the relationship between LTPA and work ability, considering variations in OPA among university staff in the CAM, as well as to assess sex and gender differences within this population. In addition, this study explores potential sex and gender differences in these associations as well as the role of MSDs, physical and mental workload, and HRQoL.

Previous studies have identified positive associations between LTPA and work ability [31,32]. However, the so-called PA paradox suggests that high levels of OPA may attenuate or even negate the benefits of LTPA on work ability [54]. Holtermann et al [11] proposed several mechanisms to explain this paradox: OPA often lacks sufficient intensity or involves prolonged duration to improve cardiorespiratory fitness; it elevates heart rate and blood pressure during and after activity (over 24 hours); it is typically performed without adequate recovery; and it often occurs under conditions of low worker autonomy and high inflammatory load. Therefore, OPA may not only fail to confer the health benefits of LTPA but could, in some cases, be harmful.

In this context, research examining the influence of occupational demands on LTPA's impact on work ability remains limited. Many existing studies have focused on male-dominated samples [32] or occupations characterized by high OPA [55]. In a recent study of the Korean workforce, Ko et al [54] observed that, while LTPA generally correlated positively with work ability among older adults in physically demanding jobs (high OPA), LTPA was paradoxically associated with lower productivity and work ability. Given the scarcity of similar studies in Spain, this study, which involves a heterogeneous sample of university staff with varied occupational demands, may help elucidate these associations in the local context.

Sex and gender are addressed in this study as central determinants of health, given their potential to shape PA behaviors, work ability, and health outcomes in complex and interrelated ways. Globally, women engage in less PA than men [2], a pattern also observed in Spain where inactivity rates range from 22.9% to 40.3% in men and 30.5% to 32.3% in women [2,56,57] and in the CAM region where 46.89% of the women report being sedentary compared to 30.61% of the men [3]. This disparity may reflect traditional caregiving roles, which often limit women's opportunities for recreation (including LTPA) and self-care [22,23,30] as well as unique physiological and pathophysiological processes related to women's health [24]. These factors suggest that women may derive fewer benefits from LTPA for work ability under equivalent occupational demands. Furthermore, life stages, such as menopause, are associated with decreased work ability [58,59], highlighting the relevance of exploring these associations in this subgroup.

MSDs, included in this study, are the most common and disabling occupational illnesses [27,60]. They are linked to reduced HRQoL [26], diminished functional capacity [61], and lower work ability [25-27,62]. While high OPA levels may contribute to MSD development [10], appropriate levels of LTPA could serve a protective role [1,63]. However, MSDs may also limit participation in LTPA, potentially creating a feedback loop that further compromises work ability. Similarly, high physical and mental workload is associated with lower LTPA participation [19], higher occupational demands, reduced work ability [64], and increased MSD prevalence, as reported by Saremi et al [65].

Finally, despite numerous workplace PA interventions aimed at improving work ability, many have failed to achieve outcomes beyond physical fitness [4]. This may be partly due to insufficient consideration of occupational demands and individual factors when designing LTPA programs [4]. The findings of this study will provide critical insights into the balance between LTPA and OPA, supporting the design of

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future interventions with a gender-sensitive approach. Ultimately, this could serve as a valuable tool to prevent noncommunicable diseases and promote optimal work ability among the working population in CAM.

Strengths and Limitations

This protocol presents several strengths. First, it uses validated and widely used instruments to assess LTPA, OPA, work ability, and relevant covariates, alongside comprehensive sociodemographic data. The online, self-administered format of the questionnaire reduces potential bias associated with interviewer-led responses and facilitates participation across diverse occupational groups. By collecting key covariates, this study is designed to account for potential confounding factors, ensuring that observed associations are more likely attributable to the primary research objectives. In addition, the estimated sample size provides adequate statistical power to detect significant associations, and the inclusion of participants with varied occupations and occupational demands enhances the generalizability of findings to the broader CAM working population.

The primary limitation of this study is its cross-sectional design, which precludes causal inference between the variables of interest. Longitudinal and interventional studies will be necessary to establish causal relationships and evaluate the effectiveness of tailored PA interventions. In addition, the use of a nonprobability sampling strategy, necessitated by institutional data protection constraints, may introduce selection bias and limit representativeness. However, the multichannel recruitment approach has been carefully designed to promote broad dissemination across occupational groups, and the anticipated heterogeneity of the sample is considered sufficient for the study's exploratory objectives. Moreover, the use of self-reported measures introduces the possibility of reporting bias, which could affect the accuracy of certain variables. Nevertheless, the use of validated instruments mitigates this concern to some extent. Finally, the absence of objective PA measurements (eg, accelerometers or step counters) may limit the precision of exposure assessment; however, this was a deliberate decision made during the study design phase to prioritize anonymity and feasibility, and it will be addressed in future phases involving subsamples with identifiable data.

As all questionnaire items are mandatory, missing data are not expected. Nonetheless, any unexpected data loss (eg, due to technical issues) will be managed using listwise deletion.

Conclusions

This study aims to analyze the relationship between occupational and LTPA and work ability among university staff with diverse occupational demands in the CAM. By incorporating a gender-sensitive perspective, the findings are expected to provide insights into how different domains of PA, particularly leisure time versus occupational, interact with musculoskeletal health, mental and physical workload, and HRQoL.

The methodological design, grounded in validated measurement tools and a representative university population sample, is intended to generate robust and transferable evidence. By including both male and female participants, this study also seeks to address critical gaps in the literature regarding sex- and gender-based differences in the effects of PA and occupational demands.

The results of this research may inform the development of workplace health strategies that promote balanced PA, support sustainable work ability, and prevent noncommunicable diseases in knowledge-based work environments. Moreover, this study has the potential to guide future interventions and public policies aimed at reducing gender-based disparities in occupational health and equitable access to PA, in alignment with global health priorities and the Sustainable Development Goals.

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Authors' Contributions

LL-G conceptualized and designed the study and is currently leading its implementation and data collection. SM-P and MRM-C contributed to the dissemination strategy and participant recruitment. The remaining authors (BN-B and MT-L) contributed to scientific oversight, supervision of the research process, and critical revisions to the study protocol and manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CAM: Community of Madrid
HRQoL: health-related quality of life
LTPA: leisure-time physical activity
MET: metabolic equivalent of task
MSD: musculoskeletal disorder
OPA: occupational physical activity
PA: physical activity
PDI: teaching and research staff
PI: research staff
PTGAS: technical, management, administrative, and services staff
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
UAH: University of Alcalá
WAI: Work Ability Index
WHO: World Health Organization

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Protocol

Developing and Validating an Inclusive and Cost-Effective Prediction Algorithm for Survival and Death Among People Living With HIV in Sub-Saharan Africa: Protocol for a Meta-Analysis and Case-Control and Cost-Effectiveness Study

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Abstract

Background: Premature death in people with HIV in sub-Saharan Africa (SSA) is highly preventable. However, the lack of inclusive, cost-effective prognostic tools remains challenging. Most prognostic tools have been developed in high-income economies. The distinct cultural dynamics in HIV-related death epidemiology makes them unsuitable for the region. Additionally, the models lack systematic stratification of death determinants based on clinical relevance, and some included factors are too expensive for people with HIV in SSA.

Objective: We aimed to create a tailored predictive model that considers the unique context of SSA, including cultural dynamics, cost-effectiveness, and clinical relevance.

Methods: This is a 2-phase study. In the development phase, we will use a combination of evidence synthesis, namely meta-analysis, application epidemiology, biostatistical, and economic paradigms, to develop a prognostic model for people living with HIV in SSA. The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) protocol will be followed in the structuring of the meta-analysis. From their creation to the present, we will search African journals (Sabinet) and the PubMed, Scopus, MEDLINE, Academic Search Complete, Directory of Open Access Repository, Cochrane Library, Web of Science, EMBASE, and Cumulative Index for Nursing and Allied Health Literature databases. Only cohort studies with moderate to high quality will be included. The primary outcome variables include the predictors of HIV-related death and their corresponding effect sizes (adjusted relative risk). A random-effect meta-analysis model will be used to synthesize the unbiased estimate of risk (relative risk) per predictor. Epidemiological metrics such as risk responsiveness, geotemporal trend, risk weight (Rw), clinical minimum important difference (CMID), predictors interaction density (PID), critical risk points, and potential cost implication will be computed. A combination of Rw and CMID will be used for risk stratification. The model's constituent items will be selected based on the combination of Rw, CMID, PID and cost implication. In the validation phase, we will apply the emergent model to classify participants using a secondary data obtained from a cohort of people living with HIV in East and West Africa, with outcomes including sensitivity, specificity, calibration, and area under the receiver operating characteristic curve (AUC).

Results: The study is projected to commence in October 2025 and end in September 2026. The expected result will be published in November 2026. The result will be presented using narrative and quantitative synthesis. Indices of causality namely as strength of association, temporality, consistency, biological gradient, and specificity of the predictor-outcome association will be presented in a tabular format. TheAUC will be used to decide the optimal critical risk point for the emergent predictive algorithm.

Conclusions: Effective prognostication coupled with intense monitoring and evaluation, and prioritizing of therapeutic targets could positively turn around the fate of millions of people living with HIV at risk of premature death in SSA.

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Trial Registration: PROSPERO CRD42023430437; https://www.crd.york.ac.uk/PROSPERO/view/CRD42023430437
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KEYWORDS
HIV; survival; death; mortality; sub-Saharan Africa; prognosis; prediction

Introduction

Background

The prevalence of HIV-related death in sub-Saharan Africa (SSA) constitutes a critical public health concern, reflecting the region's disproportionate burden within the global HIV epidemic landscape [1]. With approximately 25.6 million people living with HIV in this region, the toll of AIDS-related illnesses is starkly evident, as evidenced by the staggering figure of about 380,000 deaths in 2022 [1]. Beyond mere mortality statistics, the impact of HIV reverberates throughout families, communities, and economies, engendering multifaceted challenges and implications [2,3]. Of particular concern are adolescent girls and young women, who bear a disproportionate share of new HIV infections in the 15-to-24-year age group, accounting for over 77% of new cases in SSA [4,5]. The death of young lives because of HIV in SSA portends a negative demographic dividend for the region in the coming days [6]. Addressing this vulnerability in this demographic cohort assumes paramount importance in curbing the further spread of the virus and mitigating its deleterious consequences including premature death [7]. The high prevalence of HIV-related death not only strains health care systems but also exacerbates existing challenges within social support networks and impedes economic development efforts in the region [6]. The limited emphasis on improving survival and preventing premature death through an effective surveillance and monitoring system might be responsible for the huge burden of HIV-related death in SSA. The poor prognosis of people living with HIV in the region [7] underscores the need for a tool to rapidly and accurately predict the risk of HIV-related death in the region.

The development of an accurate and cost-effective prediction algorithm tailored specifically to the nuances of the SSA context emerges as an imperative. Such models hold the potential to not only improve survival rates but also optimize the allocation of scarce resources, thereby maximizing the impact of interventions and bolstering overall health outcomes [8]. There exist some prognostic tools for the assessment of survival or risk of death in people living with HIV. They include the prognostic nomogram by Jiang et al [9], prognostic model by Wang et al [10], shared random-effect model [11], joint latent class model [11], and the model by Auld et al [12]. However, the existing prognostic models designed to predict survival and death outcomes among individuals living with HIV are fraught with limitations vis-à-vis the SSA context, thereby necessitating the development of a new model tailored specifically for the region. Principally, these limitations encompass 4 areas including a lack of African data, ethnotemporal dynamics, statistical versus clinical significance, and heterogeneity of the African population. A lack of representation of African data within the existing models is noted as available models predominantly originate from economically affluent regions [9-11], with the exception of one model [12]. Consequently, the generalizability and applicability of these models to SSA without formal validation studies within the SSA context is questionable. Moreover, ethnotemporal dynamics, characterized by variations in the epidemiology of HIV and HIV-related mortality across different regions, pose a significant challenge to the use of existing models in the SSA. For example, respiratory disease, non-AIDS nonhepatitis malignancy, and central nervous system–related deaths were reportedly the 3 most frequent causes of death among people living with HIV in Europe, while substance abuse, respiratory disease, and non-AIDS nonhepatitis malignancy were the 3 most common causes of HIV-related deaths in North America [13]. In low- and middle-income economies, particularly the SSA, AIDS and tuberculosis were the leading causes of death in people living with HIV before 2008 and between 2008 and 2018, respectively [1,14]. These dynamics manifest through variations in cultural norms, risk factors, social determinants of health, and disease progression patterns, underscoring the need for models that are sensitive to the unique contextual factors prevalent in SSA.

Furthermore, the cost-ineffectiveness of existing models presents a formidable barrier to their use within resource-constrained settings such as SSA [15]. Incorporating factors with high investigative costs renders these models unaffordable and impractical for health care practitioners and people living with HIV in SSA. In addition, the discrepancy between statistical and clinical significance in selection of model items, otherwise known as predictors, within existing models further exacerbates their limitations [9-12]. Models prioritize predictors solely based on statistical significance risk overlooking factors that hold clinical relevance, thereby compromising the accuracy and use of the predictive model. For example, in the prognostic model by Wang et al [10], a weight of 0.5 was assigned to tuberculosis and a score of 0.6 was assigned to hepatitis C virus (HCV). From a clinical and contextual perspective, we argue that tuberculosis and HCV could not share similar risk weight (Rw) in the SSA context, where tuberculosis is the leading cause of death. The inherent heterogeneity within the African population further underscores the inadequacy of existing models, necessitating the development of models that can effectively account for and accommodate this diversity within SSA. The African race constitutes the world's largest population of the Black race and is heterogeneous in nature [16,17]. In 2009, a genetic clustering study that genotyped 1327 polymorphism markers in various African populations identified 14 ancestral groups that share cultural or linguistic orientations and correlate with self-described ethnicity [16,18]. An Afrocentric prognostic model should be derived from the data representative of most

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parts of the region, while taking into consideration any possible regional and periodical variations in the determinants of HIV-related death [19].

The imperative for developing a new predictive model specific to SSA is underscored by several compelling reasons. First, such a model would be instrumental in addressing the unique cultural, epidemiological, and economic nuances prevalent in SSA, thereby enhancing its contextual relevance and applicability. Second, a tailored predictive model holds the promise of improving the accuracy of predicting HIV-related mortality within the region, thereby facilitating more informed clinical decision-making and resource allocation. Finally, the development of a cost-effective and clinically relevant predictive model holds immense potential in equipping health care practitioners in SSA with the necessary tools to effectively manage and mitigate the impact of HIV within their respective communities [20,21].

Research Question

Can an inclusive and cost-effective predictive model be developed and validated for predicting survival and death in people living with HIV in SSA?

Aim

We aimed to create a tailored predictive model that considers the unique context of SSA, including cultural dynamics, cost-effectiveness, and clinical relevance. By validating this model using real-world data, researchers seek to enhance accuracy in predicting HIV-related outcomes and improve health care strategies for people living with HIV in the region.

Methods

In this study, we will use a 2-phase approach. The methodology for each phase is presented in subsequent sections.

Phase 1

The aim is to develop an inclusive and cost-effective predictive model for survival and death in SSA. We will use a novel technique involving meta-analysis, epidemiological, biostatistical, and economic paradigms to assemble the emergent model. This will address the shortcomings of the current predictive or prognostic models, which include the glaring omission of African data, the inability to resolve the enormous disparity between statistical and clinical significance and ethnotemporal dynamics in the epidemiology of HIV-related death, and cost-ineffectiveness.

Population, Exposure, Comparison, Outcome, and Time Criteria

The population of the review includes a cohort of people living with HIV with known exposure status who were followed up until the incidence of deaths, as in a prospective cohort; individuals who were reported dead as a result of HIV and who were retrospectively followed up to identify the cause and determinant of death, as in a retrospective cohort [22]. The primary outcomes are determinants of survival in people living with HIV such as age, route of HIV acquisition, CD4 count, coinfection with tuberculosis, coinfection with HCV, obesity (BMI), hemoglobin, CD4 cell count, platelet count, aspartate transaminase, income, aloneness, and plasma glucose, among others. The corresponding risk estimate (adjusted relative risk) for each predictor. In addition, outcomes such as risk estimates namely risk responsiveness (Ri), predictors interaction density (PID), geotemporal trend, clinical minimum important difference (CMID), and risk weight (Rw) Rw will be derived [19,23,24]. The review will cover the time between the inception of the oldest database (1961) and May 2025.

Protocol and Registration

This protocol is registered with the International Prospective Register of Systematic Reviews (PROSPERO; CRD42023430437). A systematic review using a meta-analysis technique, risk stratification, and ethnotemporal analysis of homogeneity of the predictors of HIV-related death in SSA will be used to generate the model items. The systematic review component will be structured using the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) checklist [25] and adhered to the recommendations of Meta-analysis of Observational Studies in Epidemiology [26].

Eligibility Criteria

The inclusion and exclusion criteria for the studies are presented in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria for studies.

Inclusion criteria

- Studies must be peer-reviewed sub-Saharan African (SSA) studies.
- Studies must use reported predictors or determinants of HIV-related death in SSA and their corresponding risk estimates (relative risk [RR] or hazard ratio) or provide sufficient information for the risk estimate to be calculated and transformed into RRs.
- Studies that used a cohort study design.
- Studies with low or moderate risk of bias.
- A predictor has to be reported by at least 3 studies to be included in the meta-analysis. There will be no restriction regarding study setting, period of study, age, and gender. However, only studies conducted among adults will be included.

Exclusion criteria

- Cross-sectional studies.
- Studies that have a high risk of bias.
- Studies that have been published in languages other than English or French.
- Studies that have no reported risk estimate (ie, RR or its equivalent), despite reporting predictors of HIV-related death.

Sources of Information

We will search the MEDLINE**,** PubMed, Academic Search Complete, EMBASE, Cochrane Library, CINAHL, Web of Science, and Scopus databases and African journals (Sabinet) from inception (1966) to January 2025. In addition, we will search the Directory of Open Access Repository. A piloted and refined PubMed search strategy is provided in Multimedia Appendix 1. The long list of the databases is to ensure that no eligible articles are left out.

Search Strategy

An information specialist, together with MN developed, tested, and refined the search strategy. Search terms were identified from the key concepts in the review title. A variety of terms from medical subject categories were used in each search. To obtain comprehensive results, a combination of index terms, keywords, and Boolean operators (AND and OR) was used. To determine whether the search strings were appropriate, a pilot PubMed search was conducted (Multimedia Appendix 1). Keywords were searched in the title, abstract, and keyword fields, in addition to MeSH terms. We will also use truncation and wildcards for the keywords. The search terms will be modified to match the subject headings and syntax of the remaining databases: MEDLINE, PubMed, EMBASE, Academic Search Complete, Cochrane Library, CINAHL, Web of Science, Scopus, and Directory of Open Access Repository and African journals (Sabinet).

Data Management

Duplicate entries will be removed from the literature search results after they are exported to EndNote 20 (Clarivate). Following the removal of duplicates, the articles will undergo a preliminary title and abstract screening using EndNote 20. The full texts of all eligible articles will be reviewed for potential exclusion. EndNote 20 will also be used to organize and export included and excluded articles for generating the PRISMA flowchart and in-text citations.

Study Selection and Data Extraction

The initial screening of titles and abstracts will be conducted by 2 trained research assistants: Kenechukwu Maryjane Ukwuoma and Praise Peter-Oyirinnaya. The principal investigator, MN, will undertake the training of the research assistants. In the event of conflicting results, discussion between Kenechukwu Maryjane Ukwuoma and Praise Peter-Oyirinnaya, followed by consultation with MN as an impartial reviewer, will be used to resolve discrepancies. Data extraction will be executed independently by Kenechukwu Maryjane Ukwuoma and Praise Peter-Oyirinnaya. Similarly, any conflicting results will be resolved through discussion and in consultation with MN, SCI, and AM. We will contact the relevant authors of the full-text articles in the event of missing relevant data items. The flow of the studies during the selection process and the justification for exclusion will be shown in detail in the PRISMA diagram.

Outcomes and Data Items

Outcome measures may include both laboratory and nonlaboratory measures. These may include, but are not limited to, age, route of HIV acquisition, CD4 count, coinfection with tuberculosis, coinfection HCV, obesity, hemoglobin, CD4 cell count, platelet count, aspartate transaminase, and plasma glucose. The methods or techniques used to determine and quantify the predictors will be reported to examine their comparability in the SSA setting. Secondary data will include study characteristics such as type of HIV, stage of HIV, setting, study design, sample size, and period of study, among others

Risk of Bias Assessment

We will assess the risk of bias in the studies using the Joanna Briggs Institute risk of bias assessment tools for cohort studies [27,28]. The risk-of-bias assessment will be carried out by the research assistants. Before assessment, MN will train the research assistants. Several training sessions will be undertaken until an interrater agreement of at least 80% is achieved between MN and Kenechukwu Maryjane Ukwuoma and Praise Peter-Oyirinnaya each. To obtain the interrater agreement, we

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will calculate the ratio of the total number of articles accurately rated by MN, Kenechukwu Maryjane Ukwuoma, and Praise Peter-Oyirinnaya each to the total number of the eligible full-text articles.

Effect Measures

Primary basic data will include the predictors or determinants and their corresponding estimates (relative risk [RR]) or proportion of events used for the computation of RR and the risk of bias score. The derived primary data items will include the responsiveness (Ri), CMID, Rw, and critical risk point (CRP).

Grading of Evidence

The strength of the evidence on the predictive potential of the determinants of death among people living with HIV in SSA will be evaluated using the Grades of Recommendation, Assessment, Development, and Evaluation (GRADE) [29] as presented in subsequent sections:

Bias Risk

The Joanna Briggs Institute risk-of-bias assessment tool for cohort studies [27] will be used to evaluate the quality of the eligible articles. Risk of bias will be categorized into low, moderate, and high risk of bias. The grade of evidence otherwise known as the level or certainty of the evidence may be lowered by 1 level for high risk of bias or by 2 levels for moderate risk of bias, respectively, if there are significant concerns about the possibility of bias [29].

Inconsistency

This refers to significantly different effect estimates that are obtained from the variation or heterogeneity in research findings. It is indicative of the true differences in effect estimate (less bias) [30]. Inconsistency will be assessed using the I^2. I^2 values indicate greater inconsistency (<40% is considered low, 30%-60% is considered moderate, 50%-90% is considered substantial, and 75%-100% is considered significant) [30]. Evidence will be downgraded by one level in the event of significant heterogeneity [30].

Indirectness

Variations in patients, exposures, comparisons, or results may render the evidence for a research question implicit. According to Guyatt et al [31], the certainty of the evidence will be reduced by one level when there are notable variations between the population, comparisons, or outcomes of interest and those measured in the available evidence.

Imprecision

Research involving a small number of patients, a small number of events observed, or a large degree of variability in patient effects typically yields results with broader CIs and less precision [32]. If a study's CI is larger than the predetermined threshold or its dataset is not sufficiently large, diminishing the evidence's certainty, it is deemed imprecise. Succinctly, a finding may be termed imprecise if the CIs, in relation to the clinically important difference, are overlapping. As a general guideline, RRs of 0.75 and 1.25 will be used to evaluate the precision of the findings [32].

Publication Bias

When studies are not fully reported in the published literature, biases in reporting may arise. According to Guyatt et al [33], publication bias increases studies' eligibility for inclusion in a systematic review or guideline. Hence, the existence of publications may reduce the grade of evidence by 1 or 2 points, depending on the severity of bias [33].

Risk Estimate

RR will be used in this study to evaluate a given predictor's predictive potential, which will be obtained through meta-analysis. When there is a minimum 2-fold decrease or increase in risk of death, the quality of the evidence will be rated one level higher; when there is a minimum 5-fold reduction or increase in risk, the rating will be 2 levels higher [34].

Data Synthesis and Analysis

All eligible studies were included in the data synthesis. Mean and SD will be used to describe the quantitative characteristics of the participants such as age, duration of HIV, duration on antiretroviral therapy, age at death, length of follow-up, medication adherence rate, and other quantitative study characteristics such as ample size. The participants' educational achievements, gender, type of cohort design, setting, country, period of study, and sampling technique will be summarized in percentages.

Meta-Analysis

First, using a prespecified evidence table, we will undertake a narrative synthesis to examine the distribution of the predictors of HIV-related death in SSA based on study setting, country, subregion, and period of study. All risk estimates (effect sizes) will be converted to RR when appropriate and for the sake of comparison [35-37]. To group all effects into a single frame, we will convert RR to 1/RR when RR <1 [38]. Similarly, we will use a multiplier effect ($1/RR^2$) to frame the CI when RR <1. The pooled RR as well as measures of heterogeneity (I^2) and publication bias will be calculated for each predictor using the random-effect meta-analysis model. The comprehensive meta-analysis software, which uses the inverse variance method, will be used to synthesize the aggregate RR for each predictor. The CRP will then, correspondingly, be found in the fourth quartile. Statistical analysis will be supplemented with the SPSS (IBM Corporation). The level of significance was set at Cronbach α=0.05.

Meta-Bias

To assess publication bias, we will generate and inspect a funnel plot, with its symmetry tested using the Egger test. Publication bias will be considered present when a statistical significance demonstrating the asymmetry of the funnel plot is found [39].

Confidence in Cumulative Evidence

To assess the confidence in the quality of evidence used to construct the model, we will use the GRADE as previously described [40]. The GRADE assigns 4 levels of confidence, certainty, or grades—namely high, moderate, low, or very low—depending on study quality, precision, consistency,

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directness, and absence of publication bias and size of effect estimate, which in our context is the RR [41].

Determining the Clinical Responsiveness and Risk Weight of the Identified Predictors

The proportion of the studies reporting clinical significance for a particular predictor is referred to as risk responsiveness or risk stability (Ri), provided there is no publication bias. The Ri is given by $f_s/\sum f$. It is a measure of how consistently a given factor is said to be a predictor, provided there is no publication bias otherwise known as selective reporting. Rw is a multiplicative function of Ri and risk estimate (RR). Hence, Rw=RR×Ri [19].

Examining the Homogeneity or Inclusiveness of Predictors of HIV-Related Death in SSA

A predictor will be said to be homogeneous (Afrocentric) if it is reported and found to be clinically relevant in at least 3 of the 4 traditional SSA regions, with a geotemporal trend of at least 0.6. However, we provide a narrow window of exceptions for emerging risk factors for HIV-related mortality that are associated with high investigative cost. In total, we will guarantee that 3 out of 4 criteria are met by 75% of the predictors that will be incorporated into the predictive model [19].

Stratification of the Predictors of HIV-Related Death Using Emerging Indexes of Clinical Relevance

Stratification of the predictors of HIV-related deaths in SSA will be carried out using Rw, which is a product function of the risk estimate (RR) and Ri. As long as there is no publication bias or selective reporting, the Ri is a measure of how consistently a given factor predicts the death. It will be computed as follows: $Ri=fs/\sum f$, where fs is the number of publications or articles classifying a given predictor of HIV-related death as a clinically relevant factor and $\sum f$ is the total number of studies that reported a given predictor of HIV-related death in SSA [19].

Determining the CRP

The CRP is the point on a risk curve at which risk of the outcome under consideration is incident and where, in a high-risk preventive strategy, a pre-emptive intervention should be commenced [19]. The CRP falls in the upper risk quartile (between the 76th and 100th percentile) of the Rw distribution for high-risk strategies or targeted screening. These points should also be precisely high enough to include most clinically significant markers. Using quartile division, the generated risk point will be divided into 4 classes. The Rw values in the lower, middle, and upper classes correspond to first (25th percentile) and second quartile (≥50%) and third quartile (51%-≥75th percentile) [19].

Selection of Model Components or Items

The CMID, which is defined as a change in RR by at least 50% [32], will be combined with the Rw to determine which model components (predictors) to include [19]. The CRP will be considered during the selection process. While there are multiple ways to determine risk based on the CRP, factors that are cost-effective, clinically relevant, and inclusive will be given priority [19].

Determining Cost-Effectiveness

A transaction is considered cost-effective when maximum benefit is obtained at a relatively small cost [42]. Any prudent combination of responsive and clinically relevant predictors or biomarkers can be used to build the model by computing the CRP, as long as the combination satisfies the critical point [19]. In this study, prudence will be defined as high model performance and cost-effectiveness. The average investigative cost associated with these responsive and clinically relevant model factors or biomarkers, as obtained from the representative SSA nations, will serve as the basis for defining cost-effectiveness.

Laboratories in the representative nations will provide information on the investigative cost associated with identifying and measuring the clinically relevant predictors. According to Nweke et al [23], a representative country in a given region (Central, East, Southern, or West Africa) is one that has contributed the most data toward the development of the HIV-related death predictor in that region. We will use the dollar-to-currency midrate histories [43] to make the necessary adjustments in inflation rate gaps where price data were obtained from a year before 2025. The formula for calculating the inflation rate is (B−A)/A×100, where A represents the midrate from the year before and B represents the rate from the current year. Therefore, when going from the year before to the current year, the new adjusted price is equal to (Old price+[inflate rate×B]); when going the other way, it is equal to (New price−[inflate rate×B]) [19]. Prices will be gathered and converted into US dollars for comparison's convenience. If the associated investigative cost falls within the average cost, the predictor—also referred to as a model component—will be considered cost-effective. According to Nweke et al [19], a model is considered cost-effective if the expenses associated with the investigation are comparable to the average cost.

To determine the cost-effectiveness of the emerging model, the components of the emergent model and those of comparator models—prognostic model by Wang et al [9], model by Jiang et al [10], and model by Auld et al [12]—will be listed in the order of increasing cost. Next, we will choose a specific risk level or category, such as low, moderate, or high risk as defined in the comparators, and investigate every avenue that could lead to the risk category in the emergent model. We will then calculate the average costs for the various paths taken to reach the specific risk level in both emergent and comparator models. Finally, the computed average cost implication of using the emergent model will be compared with those of the comparator prognostic models to determine the cost benefit of using the emergent model.

Using the summative Rw, we will analyze each model's overall ability to predict HIV-related death to evaluate the efficacy (performance) of the emerging model. If the summative or cumulative Rw of a model is at least equal to the CRP, the model will be deemed effective. Therefore, a model will be termed cost-effective if is "less costly and at least as effective or more effective and costlier, with the added benefit worth the added

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cost, or less effective and less costly, with the added benefit of the alternative not worth the added cost or cost saving with an equal or better outcome" [44]. Interestingly, any logical combination of responsive and clinically relevant predictor or biomarkers may be used to create the model as long as the CRP is reached [23].

To test the hypothesis that the emerging model will be more cost-effective than the comparators, we will define cost-effectiveness in terms of the incremental or marginal cost-effectiveness ratio [45]. In this context, it refers to the cost of using the emerging model instead of the prognostic model by Wang et al [10]. Incremental cost-effectiveness is defined as the ratio of the difference in cost to the difference in effectiveness, that is, the cost difference between the emergent model and each comparator divided by the corresponding difference in performance as measured by the Rw [45].

Phase 2

Phase 2 is the validation of the inclusive and cost-effective predictive model for survival or death in SSA, using a secondary data analysis of a prospective Arican cohort.

Design

This is the secondary analysis of data from a prospective African cohort of people living with HIV. The study aims to validate an emergent predictive model for survival or death among people living with HIV in SSA. Hence, the study will be conducted as per the guidelines by Cuschieri [46] and supplemented by the Standardized Reporting of Secondary Data Analyses–2 checklist [47]. In this study, we will apply the emergent model to a secondary dataset to test its performance.

The Emergent Model

The emergent predictive model for survival or death among people living with HIV tailored for SSA will mark a significant advancement in addressing the unique challenges surrounding HIV-related survival and mortality in the region. Unlike existing models, this innovative approach accounts for SSA's contextual intricacies, including cultural, epidemiological, and economic factors. It will incorporate predictors relevant to the diverse African population, ensuring inclusivity and accuracy. Moreover, it will prioritize cost-effective predictors, facilitating wider adoption within resource-constrained SSA. Emphasizing clinical relevance over mere statistical significance, the model enhances predictive accuracy by considering factors directly associated with HIV-related death in SSA. Dynamic in nature, the model adapts to evolving trends, ensuring continued relevance and effectiveness in predicting outcomes. Comprehensive in scope, it will cover a wide range of predictors, capturing the multifaceted nature of HIV-related outcomes in SSA. Therefore, this emergent predictive model will offer a culturally sensitive, cost-effective, and clinically relevant approach to improving survival predictions for people living with HIV in SSA.

Unit of Analysis

The unit of analysis will comprise the dataset from Kibuuka et al [48], which examined the incidence, causes, and the predictors of death among people living with HIV. The ongoing study was established in 2013 and longitudinally assesses the impact of clinical practices, biological factors, and sociobehavioral issues on HIV infection and disease progression in an African context as previously described [49]. The study was carried out at 12 sites in selected SSA settings, namely Kenya, Uganda, Tanzania, and Nigeria. Incidence of death and predictors of death among people living with HIV constitute the primary outcomes.

Participants, Sampling, and Sample Size

Choosing the dataset for validation by Kibuuka et al [48] offers several compelling reasons: first, it provides real-world data on HIV-related death among people living with HIV, encompassing known properties such as variance, collinearity, and multivariate dependence. This ensures that the validation process accurately reflects the conditions encountered by health care practitioners. Second, the dataset was derived from a study conducted across 12 sites in SSA (Kenya, Uganda, Tanzania, and Nigeria), aligning closely with the context for which the emergent model is being developed. This geographic representation captures the diverse epidemiological dynamics specific to the region. Moreover, the dataset includes varying sample sizes (n=50, 500, and 5000), enabling the assessment of model performance across different data availability scenarios. Furthermore, the dataset contains predictor profiles relevant to HIV-related death, such as CD4 count, viral load, and clinical factors. These predictors resonate with the emergent model's emphasis on clinical relevance and cost-effectiveness. Hence, the dataset by Kibuuka et al [48] presents a valuable opportunity to validate the emergent predictive model within a representative SSA context, considering both statistical properties and real-world applicability.

Eligibility Criteria

The inclusion and exclusion criteria for datasets are presented in Textbox 2.

Textbox 2. Inclusion and exclusion criteria for datasets.

Inclusion criteria

- Datasets of people with HIV whether surviving or dead
- Datasets of participants aged ≥18 years
- Datasets of participants in which death was confirmed through autopsy or from a relative
- Datasets of people living with HIV whose predictor profiles were completely reported

Exclusion criteria

- Datasets of people living with HIV whose risk predictor profiles were incompletely reported (with missing relevant variables) will be excluded

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Data Collection and Organization

Variables

In this study, our primary variables will include predictors of death in the cohort. The predictors of HIV-related death include CD4 ≤350, viral load, recent fever, BMI <18.5 kg/m^2, clinical depression, World Health Organization stage III, hemoglobin, and age. Our secondary outcome variables include sensitivity, specificity, calibration, discrimination, the optimal risk score, and concurrent validity of the emergent predictive model.

Instruments

Data on the predictor profile of the participants are available in the datasets [48]. Hence, no further instrumentation will be required. Risk of deaths among people living with HIV will be calculated using the emergent Afrocentric predictive model and 4 major existing risk models, namely the model by Auld et al [12], by Wang et al [10], and by Jiang et al [9]. The diagnostic or predictive properties including sensitivity, specificity, calibration, discrimination, the optimal risk score, and concurrent validity of the emergent predictive model will be established through statistical analysis.

Validation Procedure

To evaluate the performance, namely sensitivity, specificity, calibration, discrimination, area under the curve (AUC) or optimal score, and concurrent validity of the emerging model, we will apply the emergent predictive model and the 4 previous models to the 2724 datasets of people living with HIV with or without death and score them individually. The diagnostic properties will be calculated for the emergent model and each of the 4 previous models. The performance of the emergent model will be compared with the 4 preexisting models.

Data Analysis

For the validation of the emergent predictive model, we will use specific statistical methods and analyses. These statistical methods will rigorously evaluate the emergent predictive model's accuracy, discrimination, and calibration using the dataset by Kibuuka et al [48]. Receiver operating characteristic (ROC) analysis assesses the model's discriminatory power by plotting the true positive rate (sensitivity) against the false positive rate (1-specificity) across different threshold values. The area under the ROC curve quantifies overall performance, with a higher AUC indicating better discrimination. Calibration and discrimination analysis evaluates how well-predicted probabilities align with observed outcomes using calibration plots or Hosmer-Lemeshow goodness-of-fit tests. Ideally, predicted probabilities should match actual outcomes across different risk groups. We will calculate the Harrel C-statistic and Somer D-statistic to measure discrimination and the H-L test to measure calibration.Sensitivity and specificity measure the proportion of correctly predicted positive outcomes (deaths) and negative outcomes (survival), respectively. These metrics will be calculated at various threshold levels to assess model performance. Optimal risk score determination involves identifying the threshold that maximizes both sensitivity and specificity, thereby balancing predictive accuracy for high-risk individuals. Concurrent validity assesses how well the emergent model aligns with existing models (eg, those by Auld et al [12], Wang et al [10], and Jiang et al [9]) by comparing performance metrics (AUC, sensitivity, and specificity) between the emergent model and comparator models.

All data analyses will be performed using R (version 3.6.2) and SPSS (version 30).

Results

The study commenced in May 2025 and is projected to end in October 2025. The expected results will be published in November 2025. The selection process for included and excluded studies will be described and presented using the PRISMA flow diagram. The results of the individual studies will be presented using narrative and quantitative synthesis. The results of risk assessments for each eligible study will be presented in a tabular format. Indices of causality, such as strength of association, temporality, consistency, biological gradient, and specificity of the exposure outcome association, will be synthesized and presented in tables. Heterogeneity, publication bias, and sensitivity will be reported alongside the meta-analysis results in a tabular format. The emergent and cost-effective model will be represented using Rothman causal pie (set) model. The ROC will be used to decide the optimal CRP for the emergent predictive algorithm. On the basis of the CRP, a high-risk model will be fitted, taking into consideration the CMID, PID and potential cost.

Discussion

Anticipated Findings

We anticipate developing a highly accurate and cost-effective algorithm for predicting survival and death among people living with HIV, with the potential of being transformed into a mobile app. Of the 14 prognostic models, 13 were developed in high-income countries [49-61], 1 in China [10], and none in Africa. Hence, our proposed model will be the first prognostic algorithm among people living with HIV to be derived from African data. The conversion of the model into an app will improve accessibility and use across the region [62]. Effective prognostication coupled with intense monitoring and evaluation, and prioritizing of therapeutic targets, possesses the potential to positively transform the fate of millions of people living with HIV at risk of death in SSA [63]. Intense monitoring and evaluation of people living with HIV at risk of death in SSA could be achieved by translating the emergent model into an app that is capable of data capturing and communication. In discussing the findings of the study, diagnostic properties including sensitivity, specificity, and total accuracy will be compared across models. Existing models [49-61] exhibit varying sensitivity and specificity levels based on their predictor selection and generalizability. Existing models may prioritize specificity differently, potentially at the expense of sensitivity or vice versa. Trade-offs between sensitivity and specificity are common but should be determined on whether the predictive algorithm is a part of a population-wide strategy or a more targeted nonmass strategy [64]. Existing models may strike different balances, resulting in varied diagnostic properties. High specificity may be preferred in a high-risk (targeted)

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preventive strategy, while a high sensitivity and low and scalable screening may be preferred in a mass preventive strategy [64], especially for a serious and modifiable outcome [65] such as death in people living with HIV. The AUC, summarizing a model's discriminatory power, reflects its ability to distinguish between deaths and survivals [66]. Comparing AUC values across models elucidates their relative performance in this regard. Clinically, high sensitivity aids in early detection and intervention, while high specificity ensures accurate predictions, minimizing false alarms [66]. The emergent model's balance between these properties will impact its practical use. Therefore, comparing diagnostic properties across models provides insights into their relative strengths and weaknesses.

Should the emergent model surpass existing models in performance, clinicians stand to benefit from enhanced accuracy in risk predictions. This improvement translates directly into more effective patient care strategies, enabling targeted interventions tailored to individual patient needs. Particularly noteworthy is the potential for early identification of high-risk people living with HIV, facilitated by the model's high sensitivity. This early detection allows for proactive monitoring and intervention, with the aim of averting adverse outcomes and improving patient prognosis. Moreover, the model's cost-effectiveness offers health care systems in SSA an opportunity to optimize resource allocation, ensuring that interventions are prioritized based on the model's recommendations, thus maximizing the impact of limited resources. However, to maximize the potential benefits of the proposed algorithm, the model will be applied to inform the construction of evidence-based mobile apps for the prediction of survival or death among people living with HIV. The validated app will be introduced to patients early to determine prognosis and informed treatment intensification strategies, in view of available resources. The app may be used by individuals, with the data reviewed periodically to monitor the risk of death and inform actional steps in the care for people living with HIV.

Limitations

Although the CRP may fall within the upper quartile (76th-100th percentiles) for a targeted nonmass strategy, and 51-75th percentiles for mass strategy, the subjectivity in deciding the CRP at the development stage constitutes a limitation. However, this is simply a reflection of the imbalance between sensitivity and specificity. High CRP will definitely be more specific and less sensitive, whereas a lower CRP will be more sensitive but less specific. This dichotomy will be resolved during the validation with the ROC analysis sued to refine and identify the optimal CRP. Although, the dataset by Kibuuka et al [48] provides a list of predictor variables relevant to people living with HIV, it is possible that it does not include all putative predictors of death or survival in people living with HIV of the SSA extraction. This constitutes a limitation and might limit the number of relevant and interactive paths through which predictors may induce and facilitate survival or death in people living with HIV.

Future Research Directions

Looking ahead, several avenues for future research emerge. Independent validation of the emergent model across diverse SSA regions is imperative to ascertain its robustness and generalizability. Longitudinal studies exploring the model's performance over extended follow-up periods offer insights into its stability and adaptability to evolving health care contexts. Furthermore, successful validation may pave the way for the integration of the model into electronic health records or decision support systems, thereby enhancing its practical utility in clinical settings. Research efforts should also extend to investigating the impact of model predictions on patient-centered outcomes such as quality of life and survival rates, thereby elucidating the broader implications of model implementation.

Conclusions

Effective prognostication coupled with intense monitoring and evaluation and prioritizing of therapeutic targets could positively turn around the fate of millions of people living with HIV at risk of death in SSA.

Acknowledgments

The authors wish to acknowledge the authors of all the primary studies included in the systematic review as a part of the meta-analysis. The authors gratefully acknowledge the foundational contributions of those who came before them, whose work has enabled the pursuit of this innovation. Special thanks to Kibuuka et al [48], who will provide the authors with the secondary data to test the model. The study protocol was prepared in pursuit of the Gilead Sciences (Public Health) program.

Data Availability

The study data are available from the corresponding author upon reasonable request.

Authors' Contributions

MN conceived the study and conducted preliminary searches. MN will undertake the training of the research assistants who will carry out the initial and full-text screening and data extraction. SCI, AM, and JDP, who are mentors to MN, will supervise the study activities. The manuscript was drafted by MN. All authors read through and approved the final draft of the manuscript.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
PubMed Search strategy.
[DOCX File , 13 KB - resprot_v14i1e63783_app1.docx]

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Abbreviations

AUC: area under the curve
CMID: clinical minimum important difference
CRP: critical risk point
GRADE: Grades of Recommendation, Assessment, Development, and Evaluation
HCV: hepatitis C virus
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-analyses
PROSPERO: International Prospective Register of Systematic Reviews
RR: relative risk
Rw: risk weight
SSA: sub-Saharan Africa

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Protocol

Pain, Agitation, Delirium, and Iatrogenic Withdrawal Syndrome Management in Children Who Are Critically Ill: Protocol for a European Clinical Practice Guideline Using the Grading of Recommendations Assessment, Development, and Evaluation Approach

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Abstract

Background: In pediatric intensive care units, pain, sedation, delirium, and iatrogenic withdrawal syndrome (IWS) must be managed as interrelated conditions. Although clinical practice guidelines (CPGs) exist, new evidence needs to be incorporated, gaps in recommendations addressed, and recommendations adapted to the European context.

Objective: This protocol describes the development of the first patient- and family-informed European guideline for managing pain, sedation, delirium, and IWS by the European Society of Paediatric and Neonatal Intensive Care.

Methods: This guideline will follow the Grading of Recommendations Assessment, Development, and Evaluation ADOLOPMENT approach across seven phases: (1) setup—establish 3 groups, namely a steering committee, development panel (experts and patient and family partners), and patient and family partner advisory panel, to define guideline scope through voting and consensus; (2) preparation—vote on 30 summary recommendations compiled from existing CPGs of medium quality or above; prioritize new research questions; update the search for CPGs to match new research questions with recommendations using population, intervention, comparator, and outcome elements; prioritize outcomes for effectiveness questions using a 9-point Likert scale; with validation from patient and family partners; (3) evidence identification, analysis, and data extraction—develop individualized search strategies for each research question (2 independent appraisers will select and appraise studies and conduct data extraction); (4) evidence synthesis—expert pairs will summarize findings in evidence profiles and evidence-to-decision (EtD) frameworks (in the absence of evidence, the expert panel will be surveyed to assess current practices); (5) guideline development—expert pairs will draft recommendations, then topic-specific subgroups will reach consensus before full development panel voting (>80% approval needed; subgroups will determine the need for additional supporting content); (6) review—conduct internal, society-level, and external international expert reviews using surveys with Likert scales and open-ended comments; and (7) issue and update—publish the guideline and monitor literature to assess the need for updates before 5 years.

Results: In phase 1, a total of 21 clinical experts and 17 patient and family partners were recruited, and the guideline scope was finalized with 80% to 100% agreement. In phase 2, a total of 23 summary recommendations and 17 new research questions (total=40) were selected. The updated CPG search identified 2 low-quality CPGs, which were excluded from recommendation matching. Of the 17 new research questions, 4 matched existing recommendations. Of the 3 effectiveness questions, one had 7 prioritized outcomes, whereas two had 9 outcomes for inclusion in EtD frameworks. The final CPG is expected by spring 2026, with search strategies, EtD frameworks, and recommendations included.

Conclusions: This protocol ensures a transparent Grading of Recommendations Assessment, Development, and Evaluation–based development process, leading to a trustworthy and credible guideline tailored to the European context for managing pain, sedation, delirium, and IWS in children who are critically ill.

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KEYWORDS

assessment; comfort; critical care; pediatric intensive care; treatment

Introduction

Background

Analgesia and sedation in children who are critically ill remain challenging for health care professionals in pediatric intensive care units (PICUs) due to the heterogeneous responses of patients to the same medications and the potential for drug side effects [1]. Suboptimal sedation can cause discomfort, agitation, and increased medication use [2]. Undersedation can increase anxiety, stress, and the risk of accidental medical equipment

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removal, including unplanned extubation [2,3], whereas oversedation may cause complications such as respiratory depression, hemodynamic instability, altered bowel function, increased morbidity risk, and prolonged PICU stay [2,4]. Prolonged use of analgesics and sedatives is associated with iatrogenic withdrawal syndrome (IWS) and delirium [5,6], both leading to long-term cognitive, emotional, and social impairments in children and causing significant distress for families [7,8]. Therefore, achieving optimal analgosedation levels in children who are critically ill is fundamental for their comfort and safety and requires close monitoring.

Accurate assessment is a prerequisite for appropriate management. The 2016 European Society of Paediatric and Neonatal Intensive Care (ESPNIC) recommendations emphasized the importance of using validated measurement instruments to monitor pain, depth of sedation, delirium, and IWS [9]. However, recent surveys have highlighted wide variations in assessment practices and choice of drugs for managing pain, sedation, delirium, and IWS (hereafter referred to as the 4 conditions) [10-12]. In addition, compliance with these recommendations has been inconsistent, with up to 69% of clinicians not selecting the correct measurement instruments, 30% misapplying them, and 3% to 58% not using them at all [13], leading to potential under- or overuse of medications and adverse events.

To improve assessment and management practices of pain, sedation, delirium, and IWS, clinical practice guidelines (CPGs) have been developed to synthesize evidence into evidence-based recommendations [14]. Since 2022, CPGs addressing these 4 conditions have been published [15,16]; however, newer pharmacological approaches and new evidence have emerged since then, necessitating a reassessment to determine the need for updated or newer recommendations. In addition, a recent narrative review identified 15 gaps in current CPG recommendations [17], further emphasizing the need for an updated CPG.

To ensure the highest quality and transparency of CPG development, it is essential that development panels follow a standardized methodology. The Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach is an internationally recognized standard for creating high-quality and transparent CPGs. In addition, guideline panels wishing to adopt or adapt recommendations from existing CPGs using the GRADE-ADOLOPMENT approach require the inclusion of clearly defined clinical questions and access to evidence-to-decision (EtD) tables [18,19]. These elements allow development panels to assess the credibility and relevance of existing recommendations before integration into a new CPG [18,19].

Objectives

Given the emergence of new evidence, the necessity for European contextualization, and the importance of adhering to rigorous and transparent methodology, there is a need to develop an updated CPG. With the endorsement of ESPNIC and strict adherence to GRADE-ADOLOPMENT methodologies and reporting [18,19], we aim to develop a comprehensive and trustworthy European CPG for managing pain, sedation, delirium, and IWS in children who are critically ill.

Methods

Overview

The protocol for developing our CPG was registered in the Practice Guideline Registration for Transparency under registration number PREPARE-2024CN859 [20,21].

The GRADE-ADOLOPMENT approach will be followed for guideline development, using a consensus-based process for each step and action, with prioritized research questions and outcomes [18,19]. The development process involving 7 phases, 13 steps, and 24 actions, along with the proposed timeline for completion, is summarized in Figure 1 and described in the following sections. As no reporting checklist exists for guidelines, one was developed based on the work by Xun et al [22] (Multimedia Appendix 1).

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Figure 1. Phases, steps, and actions of the guideline development process, progress, and proposed timeline. ESPNIC: European Society of Paediatric and Neonatal Intensive Care.

1—setup	Progress (timeline)
1) Establish 3 groups (steering committee and development and advisory panels) i. Formalize steering committee ii. Call for clinical experts for development panel iii. Invitation for patient and family partners to collaborate (guideline development or advisory panels)	(1) Completed
2) Scoping the guideline iv. Determination of scope (population, condition, purpose, and users) by expert panel members v. Patient and family partner consultation on scope	(2) Completed
2—preparation	
3) Vote on summary recommendations and prioritize new research questions vi. Vote on summary recommendations (consolidated from existing guidelines) vii. Prioritize new research questions viii. Patient and family partner input and validation	(3) Completed
4) Identify source guidelines and match new research questions with recommendations ix. Identify potential source guidelines by updating systematic review of guidelines x. Matching new research questions with recommendations from selected guidelines	(4) Completed
5) Health outcome prioritization xi. For new *effectiveness* questions, prioritize health outcomes	(5) Completed
3—evidence identification, analysis, and data extraction	
6) Systematic search for evidence xii. Develop search strategies xiii. Conduct search and study selection for each research question	(6) May 2025–September 2025
7) Appraisal and data extraction xiv. Study appraisal xv. Data extraction and synthesis	(7) May 2025-September 2025
4—evidence synthesis	
8) Evidence synthesis xvi. Summarize evidence xvii. Survey of current practice in the absence of evidence	(8) July 2025–December 2025
5—guideline development	
9) Recommendation development xviii. Draft recommendations xix. Vote and approval of recommendations	(9) July 2025–January 2026
10) Draft guideline xx. Draft guideline xxi. Identify or develop supporting content	(10) August 2025–February 2026
6—review	
11) Review of guideline xxii. 3 levels of review (internal, ESPNIC level, and external experts)	(11) February 2026-March 2026
7—issue and update	
12) Publish xxiii. Format to journal requirements and submit guideline	(12) April 2026
13) Update xxiv. Monitor searches for new evidence to determine need to update before the 5-year mark	(13) April 2031

While this work is supported and endorsed by ESPNIC, none of the expert panel members receive payment for their contributions. The funding provided by ESPNIC will cover an annual subscription to the GRADEpro software (McMaster University and Evidence Prime Inc) and remuneration for patient and family partners for their time and may also support the librarian's work on literature searches, with a total budget of €7160 (US $8174). ESPNIC will have no influence on the content of the CPG or forming recommendations, and no executive committee members will participate in voting activities.

Phase 1: Setup

The setup phase comprises 2 steps and 5 actions.

Step 1: Establishing 3 Groups

In total, 3 groups will be formed: the steering committee, the development panel, and the patient and family partner advisory panel.

Action 1: Formalizing the Steering Committee

The steering committee includes a pediatric intensivist (AA), a PICU nurse and researcher (ASR), and a nurse methodologist (IMD). The steering committee will oversee, organize, and coordinate the development process. Committee members ASR and AA are institution supported and receive no funding for their work, whereas the chair (IMD) is supported by a postdoctoral fellowship for her role and will also take on all administrative support tasks. Invited guests to the steering committee will be the lead health sciences information

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specialists (AC-T and CJ), who will assist with planning and conducting the literature reviews.

Action 2: Call for Clinical Experts for the Development Panel

The development panel will include clinical experts and patient and family partners (the recruitment of all patient and family partners is explained in action 3).

In April 2023, a call for expressions of interest to join the development panel was sent to the Analgosedation CONSORTIUM from the Pharmacology Section and the Nurse Science Section of ESPNIC, and an open invitation was extended to participants at the June 2023 ESPNIC conference. Interested members completed a declaration of interest and conflict of interest (COI) form (Multimedia Appendix 2). The expert panel will include nurses, intensivists, and pharmacists from as many European countries as possible who will volunteer their time.

Action 3: Invitation for Patient and Family Partners to Collaborate

Clinical expert panel members will identify families or patients from their existing networks who have experience with one or more conditions covered in the CPG. Identified individuals will be provided with a patient and family partner information sheet outlining the purpose and description of involvement across the 2 groups, as well as an expression of interest form that includes a COI declaration (Multimedia Appendix 3) [23-27]. Interested patients and family members will be able to choose to join either the development panel or the patient and family partner advisory panel depending on their level of comfort with the English language and ability to engage regularly. They will indicate their group preference on the expression of interest form.

Children will be included in the patient and family partner advisory panel to represent the pediatric perspective in a consultative capacity. With parental support, children can provide their insights based on their experiences. Parental consent will be provided for all children, and the steering committee lead will only contact them through their parents. Children aged 12 years will be invited to participate in patient and family partner advisory panel activities such as surveys or interviews as they have the capacity for health-related decision-making at this age [28]. Before engaging, assent will be obtained from each child to ensure that they understand the activity and their role with parental presence. For any activity, their role and participation are entirely voluntary. All data and experiences will be anonymized to maintain confidentiality. Infants will be represented through their parents or carers, who will provide input based on their experiences with the child in the PICU.

For all patient and family partner activities, if translation of forms or surveys is required, an established translation method will be used [29]. This involves an initial translation using online software followed by verification by a bilingual clinical expert who is a native speaker to ensure accuracy. Given the multiple languages involved, all meetings will be held on the web, allowing participants to enable captioned or real-time translation as needed. All meetings will be recorded and stored on a web-based project management platform where all members will have access to all materials.

The roles, responsibilities, and level of engagement and involvement across the 3 groups are outlined in Table 1.

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Table 1. Roles and responsibilities of the 3 groups.

	Steering committee	Development panel	Patient and family partner advisory panel
Role	Oversees and coordinates the guideline's development and ensures that all preparatory tasks are completed	Extensive discussions to draft, revise, and formalize the guideline	Provides patient and family perspectives, confirms decisions, and reviews the guideline
Responsibilities			
Scope	Draft	Establish	Advise and validate
Vote on summary recommendations	No	Yes	Advise and validate
Prioritizing new research questions	No	Yes	Advise and validate
Prioritizing outcomes for effectiveness questions	No	Yes	Yes
Updating systematic review of guidelines	Yes	No	No
Matching research questions to recommendations	Yes	No	No
Updating searches	Yes	Yes	No
Screening titles and abstracts	Yes	Yes	No
Full-text review	Yes	Yes	No
Appraisal of studies	Yes	Yes	No
Data extraction	Yes	Yes	No
Creating evidence tables	Draft	Pairs—draft, review, and revise	Review and provide input from a patient and family perspective
Formulating recommendations	Draft	Pairs—draft; subgroups—revise	Provide input and confirm
Vote on drafted recommendations	No	Yes	Yes
Writing the guideline	Draft	Pairs—draft; subgroups revise	No
Creating accompanying materials	Draft	Draft	Possibly draft
Reviewing the guideline	Yes	Yes	Yes if able

All members of the development panel will complete a COI form covering financial, academic, clinical, and community aspects [30]. At the beginning of each development panel meeting, the steering committee chair will ask whether any members have changes to their COIs to declare. If yes, a new COI form will be completed. The steering committee will monitor COIs; members with a declared COI will not participate in the development or voting on recommendations related to their COI.

Withdrawing from participation in any group is acceptable at any stage of the development process and for any reason without the need for disclosure. Patient and family partners should inform the chair if they choose to withdraw but may also simply stop responding to requests (eg, surveys). Expert panel members must notify the chair if they decide to leave the development panel. While there is no formal process for expelling members due to inappropriate behavior, this will be left to the discretion of the steering committee.

Training will be provided either during panel meetings or through available online resources [31-33].

Clinical expert panel members will have their information presented in a table, including all relevant information (ie, organization, geographic location, role on the development panel, and COI) as specified in item 3 of the Appraisal of Guidelines for Research and Evaluation (AGREE) II instrument [34]. The basic characteristics of patient and family partners and PICU experiences of children will be presented in 2 separate tables.

Step 2: Scoping the Guideline

Action 4: Determining the Scope

The population, conditions, purpose, and users of the CPG will be determined during the first development panel meeting with clinical experts through consensus-based discussions.

Action 5: Patient and Family Partner Consultation on Scope

The results of action 4 will be sent to all patient and family partners for review, input, and validation using SurveyMonkey (SurveyMonkey Inc) [35]. Patient and family partners will indicate whether they "reject," "accept," or "accept with modifications" in each area, indicating any desired changes. A percentage for acceptance or rejection will be calculated for

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each area, with consensus defined as ≥80% for confirmation. The steering committee will review and revise as needed and will present any modifications at the next scheduled development panel meeting, where a final consensus of 80% agreement of participating clinical experts will be needed.

The results of scoping will be presented in a table outlining the progression from clinical expert drafting to patient and family partner consultation to final consensus.

Phase 2: Preparation

The preparation phase includes 3 steps and 6 actions. To help illustrate the development process, Figure 2 provides the development flowchart.

Figure 2. Guideline development flowchart. AGREE: Appraisal of Guidelines for Research and Evaluation; ESPNIC: European Society of Paediatric and Neonatal Intensive Care; PFP: patient and family partner.

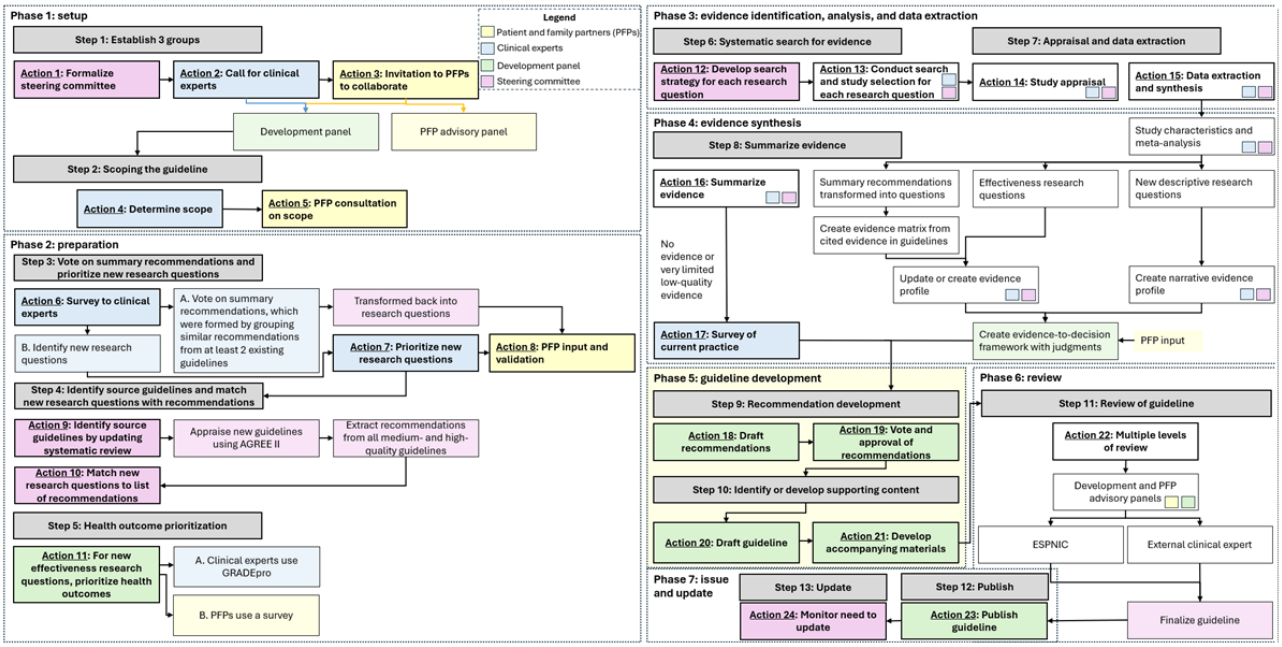

Step 3: Voting on Summary Recommendations and Prioritizing New Research Questions

Action 6: Vote on Existing Summary Recommendations

The 30 summary recommendations as synthesized from common recommendations found across multiple existing CPGs of medium and higher quality, as identified in a systematic review [36]. These serve as a preliminary set of recommendations reflecting current practices and evidence to establish a baseline set of "included recommendations."

The voting process will use the GRADE-ADOLOPMENT step [18], whereby the summary recommendations will be added to SurveyMonkey [35] and each clinical expert will vote to "accept (adopt)," "reject," or "accept with modifications (adapt)" each summary recommendation, specifying modifications if needed. Responses will be tallied, with "accept" and "accept with modifications" grouped together. A consensus of ≥80% will be needed for inclusion. Summary recommendations that fail to meet this threshold will be discussed during a consensus meeting with the development panel, where a final decision will be made. The survey will also include an open-ended question asking about clinical areas in which new research questions are needed (action 7). Initially, clinical experts will vote, whereas all patient and family partners will provide input later (action 8).

Action 7: Prioritizing New Research Questions

A list of research questions will be created based on the gaps identified by Mondardini et al [17] and areas without recommendations from the earlier survey (action 6). These questions will be entered into the GRADEpro Guideline Development Tool (GDT), a web-based tool that helps development panels brainstorm, prioritize questions and outcomes, and create evidence profiles and summary of findings tables [37].

The prioritization process in the GRADEpro GDT involves the following steps:

1. Consolidation and reformulation—the steering committee will consolidate the questions by removing duplicates and, where possible, reformatting them into population, intervention, comparator, and outcome effectiveness questions [38]. Nonactionable or descriptive questions will also be included.
2. Brainstorming—clinical experts will independently review and comment on the questions and suggest new questions if needed.
3. Second consolidation—the steering committee will refine and reformat questions from the brainstorming round to prepare for voting.
4. Voting—clinical experts will independently rate the importance of each question on a 9-point Likert scale (1-3=nonimportant, 4-6=important, and 7-9=critically

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important). The GRADEpro GDT will calculate mean scores and rank the questions from highest to lowest [39].

5. Decision-making—the steering committee will review the voting results and decide the outcome of each question—reject (mean rating of 1-3), answer (mean rating of 7-9), or list for potential inclusion in future CPGs (mean rating of 4-6).
6. Approval—clinical experts will review the refined list of questions and comment if not approved. GRADEpro GDT will generate a matrix showing the percentage of approval for each question [39]. These results will be shown at the next development panel meeting, where clinical experts will discuss and approve all final questions for inclusion in the guideline. Questions with >80% agreement will be retained.
7. Final decisions—a member of the steering committee will enter the approval questions into GRADEpro GDT. For any effectiveness questions, evidence profiles will be developed directly in the GRADEpro GDT.

Action 8: Patient and Family Partner Input and Validation

The final list of summary recommendations (action 6) and retained new research questions (action 7) will be sent to patient and family partners using SurveyMonkey [35]. They will confirm their agreement by selecting “yes,” “no,” or “yes with modification.” Patient and family partners can also propose new questions if they believe any are missing. A consensus of ≥80% is needed to retain questions and recommendations. The steering committee will review and revise based on suggested modifications, and the results will be discussed during the next development panel meeting with clinical experts.

The results of step 3 will be presented as a pair of tables that outline the clinical expert, patient and family partner, and consensus meeting results for both summary recommendations and new research questions.

Step 4: Identifying Source Guidelines and Matching New Research Questions With Recommendations

The cornerstone of the GRADE-ADOLOPMENT approach is adopting and adapting recommendations from existing CPGs by matching them to questions [18]. This process involves evaluating the relevance, applicability, and strength of the original recommendations [18].

Action 9: Identifying Potential Source CPGs by Updating the Systematic Review of CPGs

To ensure an up-to-date list of recommendations for matching the prioritized new questions from action 7, the systematic review of CPGs for managing the 4 conditions will be updated following the same methods used previously [36] with two changes. First, 2 appraisers instead of 3 will be used. Second, they will review their results for consensus to ensure that no important criteria elements are missed during the appraisal, thereby minimizing the risk of skewed scoring when reducing to 2 appraisers, which is the minimum number recommended when using the AGREE II tool [34]. If domain 3 (rigor of development) is >60% (calculated as a percentage of the maximum possible score for each domain, based on consensus between reviewers), the CPG will be retained, and its recommendations will be used for matching. The search results will be presented using a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram [40] and a table of the AGREE II consensus scores.

Action 10: Matching New Research Questions With Recommendations From Selected Guidelines

The steering committee members will assess whether any new research question matches recommendations from the 6 medium- and higher-quality CPGs [9,15,16,41-43] from our systematic review [18] or from any CPGs identified during the update of this systematic review (action 9). All recommendations have been extracted from the preselected CPGs; if additional CPGs are identified, 1 steering committee member will extract these and add them to the list. The same steering committee member will then assess each new research question against this list of recommendations to determine whether there is a match. A match is based on the population, intervention, and comparator and at least one shared outcome matching. After initial matching, the other 2 steering committee members will verify all matches, and consensus must be reached through discussion among all 3 members. The results of this action will be presented in a table outlining the progression from matching to consensus.

Step 5: Health Outcome Prioritization (Action 11: Health Outcome Prioritization)

This step focuses on prioritizing health outcomes for unmatched new research questions that are related to effectiveness. This excludes any new research questions that are nonactionable or descriptive.

In total, 2 simultaneously administered methods will be used to prioritize health outcomes, one for clinical experts using the GRADEpro GDT (the process will mirror that of action 7) and one for patient and family partners using SurveyMonkey [35]. For clinical experts, the process will be as follows: (1) brainstorming—the steering committee will generate a list of important health outcomes for the PICU from the literature [36,44-46], health outcomes will be assigned to each effectiveness question, and clinical experts will independently review these and suggest others; (2) condense—the steering committee will review and consolidate health outcomes as needed; and (3) voting—clinical experts will independently rate the importance of each health outcome for each question using a 9-point Likert scale (1-3=nonimportant, 4-6=important, and 7-9=critically important).

For patient and family partners, a survey will be created using SurveyMonkey [35] that includes each effectiveness question along with the outcomes identified from the PICU literature [36,44-46]. These will be sent to patient and family partners, and they will independently rate the importance of each health outcome for each question using a 9-point Likert scale (1-3=nonimportant, 4-6=important, and 7-9=critically important), along with adding and rating any missing health outcomes.

The fourth step in this process is decision-making (from this step onward, the results of both groups are used). The steering committee will review the voting results from both groups together to decide which health outcomes to reject (mean rating

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of 1-3), include in EtD tables (mean rating of 7-9), or list in the body or text (mean rating of 4-6) for each effectiveness question. A maximum of 7 health outcomes is recommended for inclusion in EtD tables per question [47,48]. The steering committee will include the top 5 health outcomes from both prioritizing activities (assuming some overlap). If more than 7 health outcomes are identified as critically important (mean rating of 7-9), all of them will be included. The fifth step is approval. The results will be presented to the clinical experts at the next development panel meeting for final approval (≥80% agreement is needed for consensus).

The results of this step will be presented in a table outlining the progression from prioritization to consensus across both groups.

Phase 3: Evidence Identification, Analysis, and Data Extraction

Step 6: Systematic Search for Evidence

This phase involves systematic searching for evidence using 2 distinct search approaches, one for summary recommendations (search approach 1) and one for new research questions (search approach 2), as illustrated in Figure 3. Summary recommendations will be transformed back into research questions to aid in developing a search strategy for each.

Figure 3. The 2 search approaches.

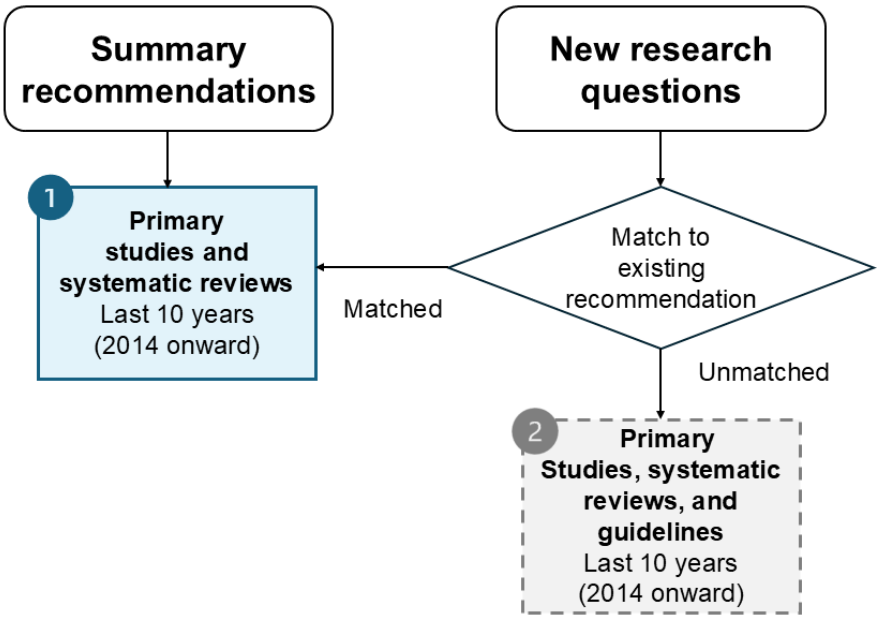

Action 12: Development of Search Strategies

For summary recommendations a search for primary studies and systematic reviews will be conducted (search approach 1). CPGs are omitted as summary recommendations originate from CPGs.

For new research questions a combined search for primary studies, systematic reviews, and CPGs will be conducted [49].

Both search approaches will limit the results to the last 10 years to ensure up-to-date evidence.

Searches will be conducted in 4 electronic databases for both search approaches: MEDLINE ALL (Ovid), Embase, CINAHL with Full Text (EBSCO), and Epistemonikos.

For approach 2, the same guideline repositories and society websites used in our systematic review [36] will be searched to identify relevant CPGs.

To update the evidence for each summary recommendation and answer each new research question, a customized search strategy will be developed by the steering committee (IMD) in consultation with a health sciences librarian (ACT or CJ) using index and free terms describing the conditions of interest and the population of interest (children aged 0 to 18 years), and the comparison, outcome, and intervention will be adapted for each. Another health services librarian will peer review each search strategy using the Peer Review of Electronic Search Strategies checklist [50]. All search strategies will be included in the supplementary material of the published CPG.

No language restrictions will be applied; non–English-language studies will be translated using a standardized method [29]—DeepL Translator (DeepL SE) [51] to translate and then verified by a native speaker on the development panel or found via panel members' networks. If one cannot be found, the study will not be included.

Action 13: Conducting the Search and Study Selection for Each Research Question

For each search (summary recommendations and new research questions), retrieved records will be imported into EndNote (version 20; Clarivate Analytics), and duplicates will be removed using the Deduklick automated algorithm (Risklick) [52]. Screening and full-text review will be independently conducted by 2 reviewers using Rayyan (Qatar Computing Research Institute) [53]. Disagreements will be resolved through consensus or by a third reviewer. For each research question, the selection process will be documented using a PRISMA

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flowchart [40] and a table of excluded studies, which will be included in the supplementary materials of the published CPG.

Step 7: Appraisal and Data Extraction

Action 14: Study Appraisal

Appraisal will be conducted based on study type—systematic reviews, primary studies, or CPGs—by 2 independent appraisers.

For summary recommendations, all the referenced studies from the source guidelines will be extracted. One member of the steering committee will evaluate each reference for relevance to and support for the recommendation using a 4-point Likert scale (1=*extremely*; 4=*not at all*) to determine whether the study should continue to be included for the development of the evidence profile (action 16; Multimedia Appendix 4, Table 1).

For all identified studies (including those from summary recommendations and new studies identified from searches in action 13), the following appraisal tools will be used.

For systematic reviews, quality will be assessed using A Measurement Tool to Assess Systematic Reviews 2, a 16-item tool that evaluates overall quality, ranging from critically low to high based on the presence of critical flaws [54].

The JBI checklists will be used to assess the quality of primary studies—randomized controlled trials [55], quasi-experimental studies [56], qualitative research [57], prevalence studies [58], cohort studies [59], economic evaluations [60], diagnostic test accuracy studies [61], case reports [62], case-control studies [62], and analytical cross-sectional studies [62]. Each appraiser determines the level of bias for each item, including a decision to “include,” “exclude,” or “requires more information.”

All systematic reviews and primary studies will be retained regardless of quality, and results will be analyzed accordingly, with higher-quality studies given more weight and systematic reviews prioritized over primary studies.

The AGREE II, a 23-item validated appraisal instrument, will be used to evaluate the quality of CPGs using a 7-point Likert scale across 6 domains [34]. Based on consensus between reviewers, each domain will be scored as a percentage of the maximum possible score, if domain 3 (rigor of development) scores >60%, the CPG will be retained.

The results of all appraised studies will be presented in tables describing the characteristics of the included studies for each research question.

The literature will continue to be monitored via monthly saved searches and added up until the development panel completes its final voting on recommendations (action 19).

Action 15: Data Extraction and Synthesis

One person will extract data from each study, and this will be verified by another person using a predefined Microsoft Word document that includes descriptive information on the study characteristics, health outcome results, and any patient and family perspectives (qualitative or quantitative; Multimedia Appendix 4, Table 2). This will be pilot-tested by 2 members, and any changes will be reported in the published CPG.

For effectiveness questions, health outcomes will be extracted as means for potential meta-analysis if at least 3 studies exist with the same health outcome data. If medians and IQRs are reported, the method by Wan et al [63] and the Microsoft Excel tool will be used to transform them.

Meta-analyses will be conducted using the Stata software (version 17; StataCorp) [64]. Random-effects models applying the Sidik-Jonkman method will be used with the standardized mean difference for continuous variables or odds ratios for dichotomous variables. The I^2 test will be used to assess statistical heterogeneity, with values of 40% considered low, values of 30% to 60% considered moderate, values of 50% to 90% considered substantial, and values of 75% to 100% deemed considerable [65]. If heterogeneity is ≥40%, a sensitivity analysis will be conducted by removing one study at a time to assess its influence on the overall effect size [65]. In addition, sensitivity analysis will be conducted on population, intervention, comparator, and outcome elements; study design; or risk of bias if sufficient studies (>2) are available to explore other sources of heterogeneity. The results will be presented as forest plots and funnel plots, with the Egger test used to assess publication bias, especially type I error [66]. If a meta-analysis is not possible, the results will be described narratively.

Phase 4: Evidence Synthesis

Step 8: Evidence Synthesis

Action 16: Summary of Evidence

The GRADE approach focuses on using the best available high-quality evidence, typically from systematic reviews [65]. To do this, 2 types of GRADE evidence tables [67] will be created.

The first type is evidence profiles, which provide information about the body of evidence and the judgments made about the quality of the evidence, included as statistical results for each outcome, per question [67]. These are completed at the end of phase 3 by 2 reviewers using the GRADEpro GDT for new effectiveness questions. The categories addressed by these tables include outcomes, number of studies, study design, quality of evidence factors, risk, effect, and overall quality of evidence (high, moderate, low, or very low). Evidence quality is determined by reviewing 5 factors that can lead to downgrading (risk of bias [37], inconsistency [68], indirectness [69], imprecision [70], and publication bias [71]) and 3 factors that can lead to upgrading (a large magnitude of effect, a dose-response gradient, and when all plausible confounders would increase the confidence in the effect [65,72,73]; Multimedia Appendix 5, Table 1).

These are used to create the EtD framework, which is the second type of evidence table. These simplified tables summarize the evidence profile without judgment details and will include information on other factors such as health benefits and harms, equity, feasibility, acceptability, and cost [18,67] (Multimedia Appendix 5, Table 2 [74]).

For nonactionable or descriptive questions, narrative evidence profiles will be created using the Etd framework table but

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merging the column containing the summary of findings and describing the results of the studies.

The steering committee will assign 2 clinical experts from the development panel to each summary recommendation and new research question (hereafter collectively referred to as "research question") based on their domain of expertise to complete both tables. Once completed, the EtD framework will be sent to patient and family partners for feedback on any missing elements related to their experiences. Following reception of this feedback, the pair of clinical experts will complete the summary judgment table based on the GRADEpro GDT [39] (Multimedia Appendix 5, Table 3).

Action 17: Survey of Current Practice in Absence of Evidence

If search results for a specific research question reveal little to no supporting evidence, the steering committee will develop a survey with open-ended questions to gather information on current practices from clinical experts on the development panel, emphasizing cases and outcomes [75,76]. The results will be included in an EtD framework.

Phase 5: Guideline Development

Step 9: Recommendation Development

The recommendation development process will include several steps within each action.

Action 18: Drafting of Recommendations

The first step is drafting the recommendations. Paired clinical experts will draft recommendations based on the evidence profile, EtD framework, and summary judgment tables using the recommendation table based on the GRADEpro GDT [39] (Multimedia Appendix 6). Recommendations will be categorized as *strong* (desirable effects outweigh undesirable effects, and the recommendations are applicable to almost all patients), *conditional* (desirable effects probably outweigh undesirable effects, and the recommendations are applicable to most patients but sensitive to preferences), or *good practice statements* (highly relevant, with benefits far outweighing harms even with indirect supporting evidence [all surveys of current practice with clinical experts will automatically be considered as a good practice statement; action 17]) [72]. The recommendation table includes the recommendation, its direction (for or against), its strength (recommend or suggest), balance of consequences, justification, considerations for subgroups (different populations or conditions), implementation considerations, monitoring and evaluation criteria, and identified research gaps.

Recommendations for any accompanying documents or materials will be sent to the steering committee (ie, resources for implementation, patient information sheet, and monitoring criteria).

The second step is subgroup review. The steering committee will form subgroups focused on pain, sedation, delirium, IWS, and "other" topics, with each subgroup including pairs assigned to specific research questions within the topic area. Subgroups will meet to review, revise, and update the recommendation table for all their assigned research questions. A steering committee member will be present to address methodology questions. The goal is to reach consensus of at least 80% on the wording, direction, and strength of each recommendation. If consensus is not reached, the recommendation will be discussed at the next development panel meeting.

In the published CPG, all accompanying recommendation tables, along with results from the consensus steps, will be provided by research question in the supplementary materials.

Action 19: Vote and Approval of Recommendations

The first step is recommendation approval voting. For each recommendation, the related tables (evidence profiles, EtD framework, summary of judgment, and recommendation) will be sent in one document to all development panel members for review at least 2 weeks before the next planned panel meeting. During the meeting, members will vote to "accept," "reject," or "accept with modifications." At least 80% of panel members must be present to commence voting, with 80% consensus required for approval on each recommendation. Recommendations not reaching 80% approval will require further subgroup revision and voting until 80% approval is achieved.

The second step is recommendation review by the patient and family partner advisory panel. The final list of approved recommendations will be sent to the patient and family partner advisory panel using SurveyMonkey [35] for review and comment. They will be asked to "accept," "reject," or "accept with modifications" each recommendation.

The third step is recommendation finalization. The steering committee will make changes based on any suggested modifications. An update and discussion will take place at the next scheduled meeting, followed by consensus to approve any recommendation modifications.

All consensus results of voting will be documented and provided in the final publication of the CPG.

Step 10: Drafting the Guideline and Accompanying Content

Action 20: Drafting the Guideline

Once recommendations are finalized, each recommendation pair will draft their section for the CPG. This will then be reviewed by the entire subgroup before sending to the steering committee. The steering committee will compile, standardize, and expand (if needed) each recommendation.

Action 21: Identifying or Developing Supporting Content

The steering committee will convene to review all suggestions for supporting materials from panel pairs (the first step of action 18) and make decisions on what is needed and feasible. Necessary materials will be brought to a development panel meeting for discussion, and work will be distributed to subgroups or patient and family partners. Subgroups will first identify any readily available resources online and verify their copyright status. If freely available to use, they will be included in a compiled list of resources supporting that recommendation. Once finalized, the subgroup will then distribute this list, and each subgroup member will assess the suitability of each resource based on the target audience, level of language, number

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of languages available, and relevance to the recommendation using a 5-point Likert scale. The results will be tabulated, and the subgroup will meet to reach a consensus on which resources to recommend as supporting material. If no suitable resources are identified, the subgroup will determine whether new materials should be developed.

Supporting content will be included either under a subheading in the main text related to each recommendation or under the implementation and monitoring section of the published CPG, or as supplementary materials, depending on the type of content.

Phase 6: Review (Step 11: Review of the CPG and Action 22: 3 Levels of Review)

The draft CPG will undergo three separate and sequential reviews: (1) internal review by the development panel and the patient and family partner advisory panel, (2) consultation open to all ESPNIC members, and (3) external review by invited international experts identified by the steering committee and development panel.

These reviews will be conducted through a web-based survey using SurveyMonkey [35], with a link sent via email from the steering committee chair using the ESPNIC internal distribution list and personal contacts. Reviewers will evaluate the CPG for overall agreement and clarity by section using a 9-point Likert scale. Each section will have a comment area for missing information, suggestions for modifications, setting-specific issues, and implementation implications.

The steering committee members will compile information on those who reviewed and their feedback from each review stage and revise the draft accordingly. Any major change that substantially alters the CPG will be discussed at a development panel meeting, with changes requiring 80% approval. The changes and review will be documented and appended to the final CPG.

Phase 7: Issue

Step 10: Publishing (Action 23: Format to Journal Requirements and Submission of Guideline)

The CPG development process will culminate in its publication in a peer-reviewed journal. The steering committee will format the final CPG using the instructions for authors from the target journal. The RIGHT-Ad@pt checklist [77] will be used to ensure the transparent reporting of the adoption process, and the AGREE II instrument will be used to ensure the quality and reporting of the CPG [34] The target date for completing this CPG is by the end of spring 2026.

Step 11: Updating (Action 24: Monitoring Searches for New Evidence to Determine the Need to Update Before the 5-Year Mark)

As each recommendation will have an established search strategy, an annual review of new publications will be conducted by the guideline lead. If new evidence emerges that could change a recommendation from conditional to strong, the steering committee will be convened to assess whether an update is warranted. Otherwise, new evidence will be continuously monitored and accumulated, and at the 5-year mark, an update will commence.

Ethical Considerations

The CPG development process is focused on transparency, integrity, and respect for all contributors. As neither clinical experts nor patient and family partners will undergo medical procedures or be required to follow specific rules of behavior as defined by the Medical Research Involving Human Subjects Act [78], formal institutional ethical review board approval was deemed unnecessary. While formal ethics submission is not required, all clinical experts and patient and family partners will complete COI forms to ensure impartiality during the development process. In addition, patient and family partners will provide informed consent for their participation in any patient and family partner advisory panel activities, such as surveys collecting patient and family partners' experiences and perspectives, to ensure their participation is voluntary and that their role in shaping the CPG is acknowledged. All surveys are anonymized to protect privacy and confidentiality.

Regarding compensation, clinical experts volunteer their time and are not compensated. Patient and family partners on the development panel will be compensated at an hourly rate (€60 [US $70]) for their participation in panel meetings. For tasks outside of meetings, such as voting and reviewing, all patient and family partners will receive a flat-rate compensation of €90 (US $103). These compensation rates were determined by averaging rates used by represented countries and by referring to recommendations from the National Institute for Health and Care Research [79].

Results

The setup and preparatory phases of the guideline development process have been completed, with the results described in the following sections.

Phase 1: Setup

Step 1: Establishing Groups (Steering Committee and Development and Advisory Panels)

Action 1: Formalizing the Steering Committee

The 3-member steering committee was formalized before the writing of this protocol and was approved during the first online meeting of clinical expert members in February 2024.

Action 2: Call for Clinical Expert Members

Following calls for participation from members of the Analgosedation CONSORTIUM from the Pharmacology Section and the Nurse Science Section of ESPNIC and at the ESPNIC 2023 congress, 21 clinical experts from 14 countries submitted expressions of interest to join the development panel and completed their COI forms. A table listing all clinical experts, including their names, institution, location (city and country), professional designation, areas of expertise, and any identified COIs, is included in Multimedia Appendix 7 (patient and family partners not included).

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Action 3: Invitation for Patient and Family Partners to Collaborate

Clinical experts began reaching out to potential patient and family partners in May 2024. By March 2025, 17 patient and family partners completed expression of interest forms, including COI disclosure. This group consisted of 76% (13/17) parents (with 2 families involving both parents choosing to participate, totaling 4 individuals) and 24% (4/17) children aged 6 to 16 years. These patient and family partners represent 6 countries. The characteristics of the patient and family partners are detailed in Table 2, whereas the characteristics of the children who have experienced the PICU are detailed in Table 3. No COI were reported by any patient and family partners.

Table 2. Characteristics of patient and family partners who submitted expressions of interest.

Characteristic	Patient and family partners	
	Parents (n=13), n (%)	Children (n=4), n (%)
Sex		
Female	9 (69)	0 (0)
Country		
Switzerland	4 (31)	2 (50)
United Kingdom	4 (31)	0 (0)
Italy	2 (15)	1 (25)
Hungary	1 (8)	1 (25)
Spain	1 (8)	0 (0)
Turkey	1 (8)	0 (0)

Table 3. Characteristics of the children who experienced the pediatric intensive care unit (PICU; N=12).

Characteristics and categories	Children
Sex, n (%)	
Female	8 (67)
Medical reason for admission, n (%)	
Respiratory	4 (33)
Surgery	3 (25)
Cardiac	2 (17)
Sepsis	1 (8)
Inflammatory syndrome	1 (8)
Cancer	1 (8)
Supported on mechanical ventilation, n (%)	11 (92)
Experience with conditions, n (%)	
Delirium	7 (58)
Iatrogenic withdrawal syndrome	8 (67)
Age (y), mean (SD)	7.5 (6)
Time in PICU (d), mean (SD)	262 (515)
Time on mechanical ventilation (h), mean (SD)	11,716 (2740)

Step 2: Scoping the Guideline

Action 4: Determining the Scope

During the first meeting with clinical experts, an initial scope was drafted (second column of Table 4).

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Table 4. Evolution of scope based on consensus rounds.

Scope elements	Initial draft	Patient and family partner suggestions for modification	Development panel discussion and decision	Final decision
Purpose	To develop a high-quality, evidence-based clinical practice guideline tailored to the European context. This guideline will incorporate the perspectives of patients, families, and health care professionals, aiming to improve the management of the interrelated conditions of pain, sedation, delirium, and IWS[a] for children who are critically ill in PICUs[b] by providing actionable, trustworthy, and credible recommendations.	• Including children in intermediate care and children hospitalized for oncological diseases	• As the focus was on children who are critically ill in the PICU, it was determined that these suggestions were already encompassed within the purpose. • It was slightly rearranged for ease of comprehension.	To develop a high-quality, evidence-based guideline informed by the perspectives of patients, families, and health care professionals to improve the management of the interrelated conditions of pain, sedation, delirium, and IWS in children who are critically ill. This guideline aims to provide actionable, trustworthy, and contextually relevant recommendations for health care professionals caring for children who are critically ill in PICUs (primary setting), but the guideline could also be applicable to health care professionals managing children who are critically ill in settings such as the emergency department (awaiting transfer) and intermediate care unit to support continuity and consistency of care.
Population	Children who are critically ill aged 0 to 18 y in PICUs as the primary setting, but including those awaiting admission (eg, emergency department or during transport)	• It could also include children being on a temporary home leave directly from (curated by) the PICU (eg, with a provided oxygen ventilator machine or oxygen cylinder) • Including children in intermediate care and children hospitalized for oncological diseases	• While other settings or conditions may be important, the focus is on children who are critically ill in the PICU. These additional populations and settings were not included. In addition, to ensure clarity regarding included population, excluded populations were added.	Children who are critically ill aged 0 to 18 y admitted for any medical reason to the PICU as the primary setting, but it can also include children who are critically ill in the emergency department (awaiting transfer) and the intermediate care unit. Patients receiving palliative or end-of-life care, neonates in neonatal intensive care units, and adults are excluded.
Users	This guideline is intended for health care professionals working in PICUs, including physicians, nurses, pharmacists, and other relevant allied health practitioners. It will also serve as a resource for patients, families, and caregivers.	• Including health care professionals in intermediate care and pediatric oncology (children undergoing oncology treatment can also face these issues, for example, in the event of medication administration errors)	• Not aligned with the focus on staff working in the PICU • More precision needed to define the “other health care professionals”	This guideline is intended for health care professionals involved in the care of children who are critically ill in PICUs, including physicians, nurses, pharmacists, and other health care professionals. Depending on the patients’ needs and clinical status, other relevant health care professionals include physiotherapists, occupational therapists, respiratory therapists, physician assistants, psychologists, or child life specialists. The guideline will also serve as a resource for patients, families, and caregivers.
Conditions covered	Pain, sedation or agitation, delirium, and IWS	• None	• None	No change

[a]IWS: iatrogenic withdrawal syndrome.

[b]PICU: pediatric intensive care unit.

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Action 5: Patient and Family Partner Consultation

A survey was conducted among all patient and family partners in February 2025 to review and comment on the 4 drafted scope elements. In total, 10 of the eligible 16 patient and family partners completed the survey (63%), with agreement on the 4 elements ranging from 80% to 100% acceptance (Multimedia Appendix 8 details the agreement with scope elements).

Some modifications were suggested by patient and family partners, among them the inclusion of patients with cancer and the intermediate care unit, which was repeated across multiple scope elements. These suggestions were discussed with the clinical experts at the next meeting. It was agreed that the primary focus is on critically ill children in the PICU. Additional populations such as patients with cancer would not be included as they fall outside the primary focus. However, the intermediary care unit was added, with the emphasis being that the CPG applies only to children who are critically ill within this setting. Table 4 outlines the suggestions provided by patient and family partners (third column), the decisions made by the clinical experts (fourth column), and resulting in the final scope elements following modifications (last column).

Phase 2: Preparation

Step 3: Voting on Summary Recommendations and Prioritizing New Research Questions

Action 6: Vote on Existing Summary Recommendations

In July 2024, the clinical experts voted on 30 summary recommendations. All but 5 (26/30, 87%) achieved an agreement of >80%, with a 90% (19/21) response rate. The results of voting, consensus discussion, and patient and family partner validation are presented in Multimedia Appendix 9.

Following the consensus discussion, 23 transformed research questions were formulated from the 26 voted-upon summary recommendations as, during the consensus meeting, some summary recommendations were rejected, whereas others were merged or split into 2 distinct research questions.

Action 7: Prioritizing New Research Questions

The clinical experts began the prioritization process of the new research questions in November 2024. A total of 52 new research questions were generated; the steering committee then consolidated these questions by removing duplicates or too specific questions into 40 (77%), which were put forth to the experts for prioritization using the 9-point Likert scale in the GRADEpro GDT. In total, 90% (19/21) of the clinical experts completed prioritization; of the 40 questions, 24 (60%) were rated as critically important (mean rating of 7-9), 16 (40%) were rated as important (mean rating of 4-6), and none were rated as not important (mean rating of 1-3). During a consensus meeting with 71% (15/21) of the panel members, the research questions were further reduced to 17 to be answered by the CPG (Multimedia Appendix 10 includes the new research question prioritization process with both clinical experts and patient and family partners and the consensus results). Figure 4 illustrates clinical experts' prioritization and consensus across summary recommendations (action 6) and new research questions (action 7).

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Figure 4. Clinical experts' prioritization and consensus on summary recommendations and new research questions.

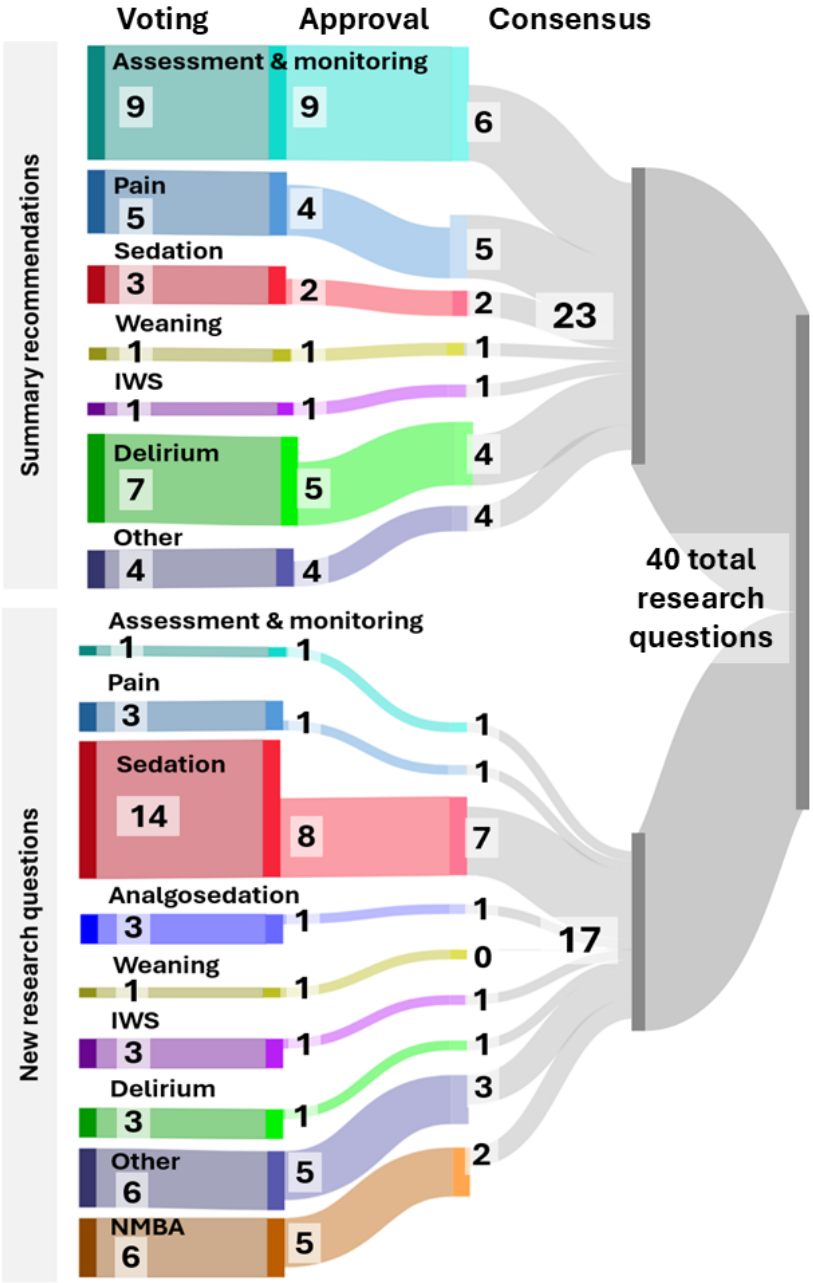

Action 8: Patient and Family Partner Input and Validation

In February 2025, the patient and family partners received their welcome email that included 3 SurveyMonkey links (one in English, one in French, and one in Italian based on the language preferences indicated in their expression of interest forms). Ten patient and family partners completed the survey: 7 (70%) in English, 3 (30%) in French, and none in Italian.

All patient and family partners agreed with the 23 transformed research questions resulting from the summary recommendations (ranging from 80% to 100%). These results can be found in Multimedia Appendix 9.

Of the 17 new research questions, using the median for determining the importance rating, 14 (82%) were rated as critically important, and 4 (24%) were rated as important (Multimedia Appendix 10). At the end of this section of the survey, patient and family partners were asked whether, from their perspective, there were any missing questions, and 6 were included from 40% (4/10) of the patient and family partners. However, these were not questions or were considered as included under the existing research questions (Multimedia Appendix 11 includes the suggested new research questions and the reasons for not including them).

The final list of all 40 research questions classified as either summary recommendations or new research questions is included in Multimedia Appendix 12 to clarify discrepancies as 3 summary recommendations were converted into new research questions but their classification varied between the two categories during the prioritization and voting processes.

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Step 4: Identifying Source Guidelines and Matching New Research Questions With Recommendations

Action 9: Identifying Potential Source CPGs by Updating the Systematic Review of CPGs

The searches were finalized in November 2024. A total of 1901 records were identified from the electronic databases after removing duplicates. Of these 1901 records, 22 (1.16%) studies underwent full-text review, from which 2 (9%) new CPGs were identified [80,81]. No additional CPGs were found through searches of guideline repositories, society websites, or Google Scholar. Figure 5 presents the search process as a PRISMA flow diagram [40]. Additional information on the excluded studies and the reasons for their exclusion can be found in Multimedia Appendix 13.

Figure 5. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram—updated search for the systematic review of clinical practice guidelines for managing pain, sedation, delirium, and iatrogenic withdrawal syndrome in pediatric intensive care units.

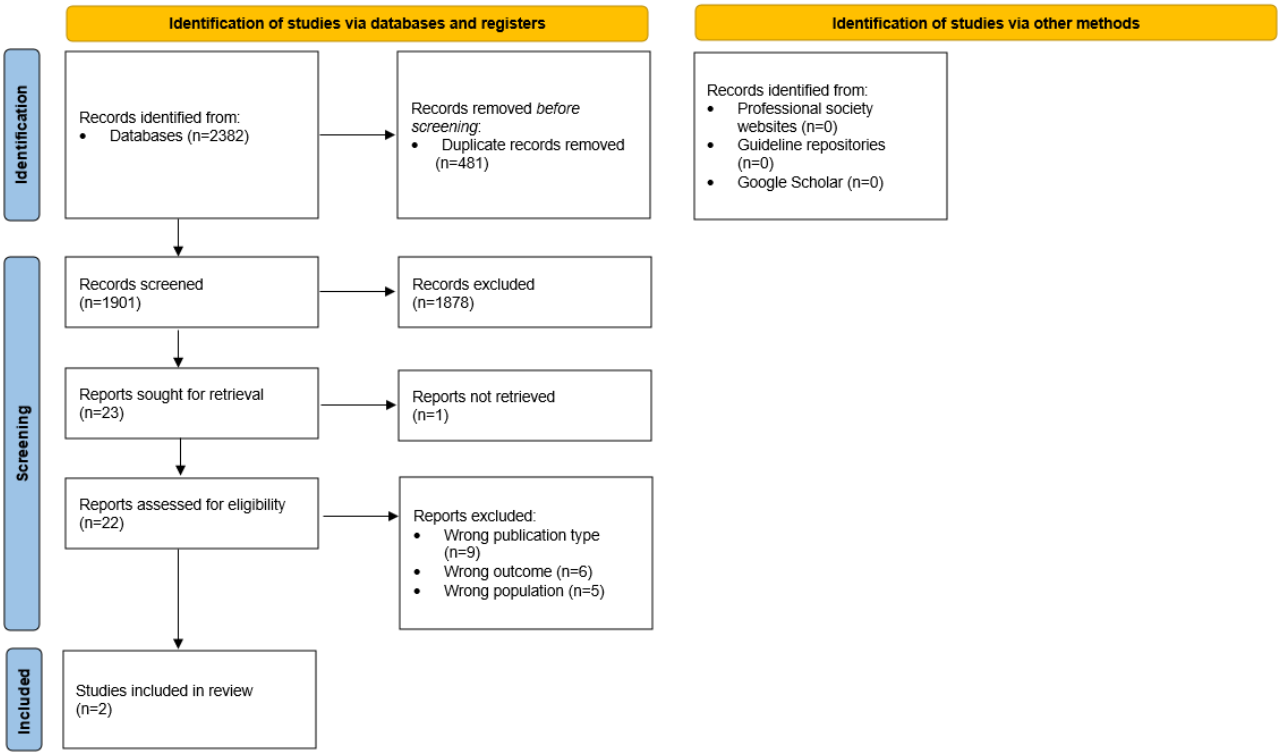

Both CPGs found were rated as low quality using the AGREE II instrument [34], therefore, will not be included in the next step of recommendation matching. The characteristics of the 2 included CPGs can be found in Multimedia Appendix 14, and the AGREE II consensus-based scores can be found in Multimedia Appendix 15.

Action 10: Matching New Research Questions With Existing Recommendations From Selected CPGs

Of the 17 new research questions, the steering committee agreed that 4 (24%) matched (see Multimedia Appendix 16 for details). Of these 4 questions, 3 (75%) were considered effectiveness questions and moved on to action 11.

Step 5: Health Outcome Prioritization (Action 11: Health Outcome Prioritization)

This process started in February 2025 with the clinical experts brainstorming health outcomes for each of the 3 effectiveness questions.

For the first question—"Should inhaled sedatives vs intravenous sedatives be used in difficult to sedate critically ill pediatric patients?"—the clinical experts prioritized 50% (16/32) of the health outcomes as critically important, whereas the remaining outcomes were rated as important. In contrast, the patient and family partners prioritized 92% (11/12) of the health outcomes as critically important, with the remaining outcome rated as important. Patient and family partners received a reduced list of health outcomes limited to those identified in the literature as the survey was sent at the same time as the clinical experts' brainstorming process. However, they were given the opportunity to include any additional outcomes they considered important, effectively having a modified brainstorming process (Multimedia Appendix 17 presents the results of the health outcome prioritization for the 3 effectiveness research questions for both groups). By selecting the top 5 outcomes from each group, 7 health outcomes will be included in the evidence profile and EtD framework for this question.

For the second question—"Should sufentanil vs morphine be used for optimizing patient outcomes in mechanically ventilated critically ill children?"—the clinical experts prioritized 50% (18/36) of the health outcomes as critically important, whereas the remaining outcomes were rated as important.

For the third question—"Should fentanyl vs morphine be used for optimizing patient outcomes in mechanically ventilated critically ill children?"—the clinical experts prioritized 42% (14/33) of the health outcomes as critically important, whereas the remaining outcomes were rated as important.

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For both the second and third questions, the patient and family partners prioritized 93% (13/14) of the health outcomes as critically important, with the remaining outcome rated as important. One patient and family partner added the health outcome of long-term consequences on cognitive development. By selecting the top 5 outcomes from each group, 9 health outcomes will be included in the evidence profile and EtD framework for these questions.

Discussion

Principal Findings

This protocol outlines a comprehensive methodology using the GRADE-ADOLOPMENT approach for adapting, developing, and contextualizing a CPG for managing pain, sedation, delirium, and IWS in children who are critically ill. By addressing existing gaps in clinical knowledge and practice, it will provide updated, evidence-based recommendations incorporating emerging research and clinical advancements. The rigorous methods included question and outcome prioritization. In phase 1 (setup), the steering committee established 3 groups: the steering committee, development panel, and patient and family partner advisory panel. A total of 21 clinical experts and 17 patient and family partners were recruited, representing diverse expertise, European countries, and lived experiences. Through structured voting and consensus processes, the scope of the CPG was finalized with 80% to 100% agreement among clinical experts and patient and family partners. In phase 2 (preparation), clinical experts voted on 30 summary recommendations compiled from existing medium- to high-quality CPGs, selecting 23 summary recommendations for inclusion. In addition, 17 new research questions were prioritized, bringing the total number of research questions to be addressed to 40. In total, 24% (4/17) of the new research questions matched existing recommendations. Using summary recommendations and matching to existing recommendations helps streamline the evidence review process. Of the 3 effectiveness questions, 1 (33%) had 7 prioritized health outcomes, whereas 2 (67%) had 9, all of which will be included in evidence profiles and EtD frameworks. The updated CPG search identified 2 low-quality CPGs, which were excluded from recommendation matching.

It is hypothesized that adhering to the GRADE and GRADE-ADOLOPMENT approaches for evaluating evidence quality and the strength of recommendations, along with the creation of evidence profiles and EtD frameworks (that will be readily available), will assist future CPG developers and updates. The methods used will ensure a high-quality, transparent, and accessible CPG that promotes consistent, standardized care and improved outcomes in PICUs. This protocol describes the GRADE-ADOLOPMENT approach when EtD tables are unavailable, offering a step-by-step process for those considering using this approach for CPG development or adaptation.

Strengths and Limitations

A key strength of this CPG is the inclusion of patient and family partners early and throughout all phases of the CPG development process, addressing a limitation in previous CPGs [36]. This patient- and family-centered approach considers a broad range of patient and family partner experiences, enhancing the CPG's relevance and applicability. In addition, involving a wide range of experts and patient and family partners from across Europe ensures representativeness and contextual sensitivity. The collaborative approach with continuous consensus meetings aims for alignment and buy-in from all development panel members. The summary recommendation voting, research question prioritization exercises, and identification of gaps in the literature as part of the recommendation table (action 18) will identify research gaps for prioritization and future research.

There are several limitations. First, achieving consensus may be challenging due to diverse perspectives across many stakeholders and languages. To establish consensus, a combination of surveys and meetings will be used to gather input. To address the language barriers, we will offer translated materials and captioning during web-based meetings. In addition, a bilingual speaker will always be present for direct translation when necessary. Another limitation inherent to the current state of knowledge is the availability and quality of evidence for certain conditions or interventions, which may be limited. However, by consolidating this information in a transparent and accessible manner and using surveys with the members of the large development panel will assist in forming credible recommendations. In addition, a standardized translation method for published studies might introduce new evidence previously not included.

Comparison With Prior Work

Most societies have their own manuals outlining their processes for developing CPGs [82], but few have incorporated the GRADE-ADOLOPMENT approach. Until recently, there were limited published protocols specifically detailing CPG development [83-85] and none explicitly using the GRADE-ADOLOPMENT approach. Given the number of existing CPGs, the need for systematic adaptation instead of de novo development has led to a growing interest in the GRADE-ADOLOPMENT approach. However, the literature on its use primarily consists of broad methods included within published CPGs, leaving little room for detailed reporting, or postdevelopment publications presented as exemplars and discussions of experiences with the approach [86-88] rather than step-by-step protocols that can aid teams interested in this approach with writing their own protocol. To guide teams considering the GRADE-ADOLOPMENT approach, a recently published guidance document should be used to provide structure to their protocol and development process [19].

Despite advancement in methodological guidance, many society-level manuals fail to provide explicit direction on how to incorporate patient and family partners into the CPG development process [89]. Patient and family partner involvement has gained increasing interest as a means of ensuring that the recommendations meet patients' needs. However, our review of existing CPGs for managing the 4 conditions found that almost none meaningfully included patient and family partners [36]. The methods for effectively integrating patient and family partners remain unclear, along with the definitions of how to describe their involvement and engagement [90]. Reporting is also limited to the postdevelopment phase

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[24,91]. When patient and family partners are involved, they most commonly participate in identifying key questions and reviewing the draft CPG [92], but their contributions often do not extend to formulating recommendations. This approach does not align with GRADE, which emphasizes the importance of considering benefits and harms to patients when formulating recommendations [18]. In this respect, patient and family partners have an important role in ensuring recommendations have the most impact on outcomes for future patients. Given the critical role that patient and family partners can play in shaping care strategies and improving health outcomes, their involvement should go beyond tokenistic participation to ensure that their perspectives are incorporated throughout the CPG development process in a transparently reported manner. Many groups are currently working to develop guidance on patient and family partner involvement, but these resources are not yet available [93,94] except for the newly published Guidelines International Network–McMaster Guideline Development Checklist extension for engagement [95].

Conclusions

This protocol outlines a comprehensive approach to developing a CPG for managing pain, sedation, delirium, and IWS in pediatric patients who are critically ill that will integrate the most up-to-date evidence and diverse perspectives. By involving clinical experts and patient and family partners, the resulting CPG aims to be scientifically robust, patient centered, and contextually relevant.

Voting on summary recommendations and question prioritization, along with a thorough literature review to develop evidence profiles and EtD frameworks, ensures that the CPG addresses important clinical issues. This CPG is designed to promote optimal patient outcomes, making it valuable for clinicians, policy makers, patients, and families.

Acknowledgments

The authors would like to sincerely acknowledge the patient and family partners who contributed their experiences and insights during the initial development of this CPG in phases 1 and 2. The authors appreciate their time and dedication in shaping this CPG and recognize their contributions to improving the care of children who are critically ill in the PICU.

Data Availability

All data generated or analyzed during this study are included in this published article and its supplementary information files.

Authors' Contributions

Conceptualization: IMD, AC-T, CJ, GDC-F, PADC, SNdW, DD, JE, PCF, SG, IG, AH, JH, KH, EI, SM, TM, MCM, MO, MHP, KP, FS, BW, NY, AA, ASR
Data curation: IMD
Formal analysis: IMD, GDC-F
Funding acquisition: IMD, AA, ASR
Investigation: IMD
Methodology: IMD, AC-T, CJ, GDC-F, PADC, SNdW, DD, JE, PCF, SG, IG, AH, JH, KH, EI, SM, TM, MCM, MO, MHP, KP, FS, BW, NY, AA, ASR
Project administration: IMD, AA, ASR
Resources: ASR
Supervision: ASR
Validation: AC-T, CJ, GDC-F, PADC, SNdW, DD, JE, PCF, SG, IG, AH, JH, KH, EI, SM, TM, MCM, MO, MHP, KP, FS, BW, NY, AA, ASR
Visualization: IMD
Writing—Original draft: IMD
Writing—review and editing: AC-T, CJ, GDC-F, PADC, SNdW, DD, JE, PCF, SG, IG, AH, JH, KH, EI, SM, TM, MCM, MO, MHP, KP, FS, BW, NY, AA, ASR

Conflicts of Interest

None declared.

Multimedia Appendix 1
Checklist for guideline protocol reporting.
[PDF File (Adobe PDF File), 124 KB - resprot_v14i1e67930_app1.pdf]

Multimedia Appendix 2
Declaration of interest form and conflict of interest—clinical experts.
[PDF File (Adobe PDF File), 143 KB - resprot_v14i1e67930_app2.pdf]

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Multimedia Appendix 3
Information sheet, expression of interest form including conflict of interest—patient and family partners.
[PDF File (Adobe PDF File), 318 KB - resprot_v14i1e67930_app3.pdf]

Multimedia Appendix 4
Foundational data extraction—tracing and appraisal of guideline evidence, and study characteristics.
[PDF File (Adobe PDF File), 43 KB - resprot_v14i1e67930_app4.pdf]

Multimedia Appendix 5
Evidence synthesis tables.
[PDF File (Adobe PDF File), 94 KB - resprot_v14i1e67930_app5.pdf]

Multimedia Appendix 6
Recommendation drafting table.
[PDF File (Adobe PDF File), 56 KB - resprot_v14i1e67930_app6.pdf]

Multimedia Appendix 7
Panel member role information and conflicts of interest.
[PDF File (Adobe PDF File), 86 KB - resprot_v14i1e67930_app7.pdf]

Multimedia Appendix 8
Patient and family partner agreement with scope elements.
[PDF File (Adobe PDF File), 46 KB - resprot_v14i1e67930_app8.pdf]

Multimedia Appendix 9
Evolution of voting on summary recommendations, consensus decision, and patient and family partner validation.
[PDF File (Adobe PDF File), 197 KB - resprot_v14i1e67930_app9.pdf]

Multimedia Appendix 10
Evolution of voting on new research questions and consensus decision by clinical experts and patient and family partners.
[PDF File (Adobe PDF File), 93 KB - resprot_v14i1e67930_app10.pdf]

Multimedia Appendix 11
Suggested new research questions by patient and family partners with reasons for exclusion.
[PDF File (Adobe PDF File), 49 KB - resprot_v14i1e67930_app11.pdf]

Multimedia Appendix 12
List of 40 research questions to be answered by the guideline.
[PDF File (Adobe PDF File), 86 KB - resprot_v14i1e67930_app12.pdf]

Multimedia Appendix 13
Excluded clinical practice guidelines with reasons.
[PDF File (Adobe PDF File), 141 KB - resprot_v14i1e67930_app13.pdf]

Multimedia Appendix 14
Characteristics of 2 included clinical practice guidelines.
[PDF File (Adobe PDF File), 139 KB - resprot_v14i1e67930_app14.pdf]

Multimedia Appendix 15
Appraisal of Guidelines for Research and Evaluation II consensus scores.
[PDF File (Adobe PDF File), 112 KB - resprot_v14i1e67930_app15.pdf]

Multimedia Appendix 16
Decisions for recommendation matching of new research questions.
[PDF File (Adobe PDF File), 208 KB - resprot_v14i1e67930_app16.pdf]

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Multimedia Appendix 17
Top 5 health outcomes prioritized by each group.
[PDF File (Adobe PDF File), 99 KB - resprot_v14i1e67930_app17.pdf]

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Abbreviations

AGREE: Appraisal of Guidelines for Research and Evaluation
COI: conflict of interest
CPG: clinical practice guideline
ESPNIC: European Society of Paediatric and Neonatal Intensive Care
EtD: evidence-to-decision
GDT: Guideline Development Tool
GRADE: Grading of Recommendations Assessment, Development, and Evaluation
IWS: iatrogenic withdrawal syndrome
PICU: pediatric intensive care unit
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

Validation of an Infarction Code Care Checklist and Determination of its Relationship With Other Patient Safety Indicators: Protocol for a Prospective Study

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Abstract

Background: In the care of time-dependent illnesses, facilitating care and systematizing actions with a checklist provides security to health professionals and reduces errors, thereby increasing patient safety. However, despite the widespread use of checklists in other clinical contexts, no studies have yet validated a checklist specifically for infarction code care.

Objective: The objective of this study is to validate the checklist and determine its relationship with the rest of the patient safety indicators in the primary care teams of the Catalan Health Institute of Central Catalonia.

Methods: This is a prospective study for the validation of a checklist for infarction code care. In this study, 2 clinical scenarios of varying difficulty are defined, and the correct answers are established in each case according to the gold standard guidelines. During the first 3 months of the ongoing year, we held an annual training meeting where infarction code referents from various primary care teams gathered to review the new guidelines and outline the training strategy for the next year. These referents conducted annual training sessions for their respective teams before Easter, during which they explained the new guidelines. On the same day as the training, the 2 clinical scenarios were completed using the online version of the checklist for the first time for all participants. The checklist was sent in digital format to all health professionals who responded the first time, and then a reminder was sent to respond a second time at 30, 45, and 90 days to obtain the maximum number of second responses, as the checklist should be completed twice to assess internal reliability and temporal robustness. The number of hits was compared with respect to the gold standard for both the first and the second response. The results obtained from the responses and accuracies, when compared with the gold standards, were evaluated against other available patient safety indicators in the region.

Results: Between January 2023 and May 2023, we obtained 615 responses to the online version of the checklist. We conducted analyses to assess both internal consistency and temporal robustness of the responses and have also structured the framework for comparing these results with other patient safety indicators available in the region. Data analysis is currently underway, and we expect to publish the results in early 2026.

Conclusions: If the checklist demonstrates strong internal consistency and temporal robustness and shows a meaningful relationship with patient safety indicators, it could be implemented across primary care centers using the infarction code. This would support safer, more standardized care in time-sensitive clinical situations.

Trial Registration: IDIAP Jordi Gol 4R22/343; https://idiapjgol.org/grup-recerca/prosaaru/projectes/

International Registered Report Identifier (IRRID): DERR1-10.2196/66584

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(JMIR Res Protoc 2025;14:e66584) doi:10.2196/66584

KEYWORDS

myocardial infarction; checklist; patient safety; primary health care; quality indicators; health care

Introduction

Background

Cardiovascular diseases are the leading causes of death worldwide. According to the data from the World Health Organization (WHO), an estimated 17.9 million people died from cardiovascular diseases in 2019, representing 32% of all deaths, of which 85% deaths were from ischemic heart disease and cerebrovascular disease [1].

A cardiovascular risk factor (CVRF) is a biological characteristic of individuals that increases the probability of developing or dying from cardiovascular disease. However, as this is a probability, having no risk factors does not preclude individuals from developing cardiovascular disease nor does the presence of one or more CVRFs necessarily imply a future cardiovascular disease [2]. CVRFs, such as unhealthy diet, physical inactivity, or harmful consumption of alcohol and tobacco, are highly prevalent in Spain. Thus, the optimal setting for a comprehensive approach to the prevention and follow-up of cardiovascular pathologies is primary care.

In the context of primary care, health education through a comprehensive approach to CVRFs is essential in the prevention of cardiovascular diseases. In this regard, the preventive measures to be carried out once cardiovascular risk has been assessed should include interventions aimed at the adoption of healthy lifestyles and relevant pharmacological measures [2]. In addition, the clinical guidelines of the Spanish Society of Cardiology on myocardial infarction state that strategies should focus on minimizing the delay in initiating reperfusion treatment (both by pharmacological and mechanical means) because this pathology is characterized by being time dependent [3].

The latest management guidelines for this pathology establish as a priority an electrocardiogram– percutaneous coronary intervention (PCI) time of no more than 120 minutes [4]. The delay in these times is mainly determined by 3 factors: the delay in the patient's consultation, the delay in the interpretation of the semiology by the health care professionals, and the delay in transport. Delay in any of these 3 factors leads to an increase in the electrocardiogram-PCI time [5]. Although response times in rural areas are longer than in urban areas, studies suggest that all guidelines should be complied with equally well [4]. Delayed care in rural areas is mainly due to delayed transport, which increases the number of deaths from acute coronary syndrome with ST-segment elevation [5]. Therefore, the potential impact on mortality and morbidity of the measures carried out in the period immediately after acute myocardial infarction (AMI) justifies the development of strategies with the aim of arranging, prioritizing, and systematizing actions. If we implement these strategic measures in scattered population centers that are located farther from the centers where PCI can be performed, the need for such measures becomes even more important.

One possible strategy that could be useful would be to try to minimize the time to initiate treatment. Despite the use of information and communications technologies, experience with training videos for health care personnel is not very evident. However, several sources claim to have evidence of good results for training videos that teach necessary techniques; therefore, greater expertise could reduce the time taken by the practitioner to act [6-8]. The study by Lane et al [9], in which 75 health professionals participated, concluded that training videos improved their knowledge regarding the application of assessment scales. Most studies also show that the comfort level of health professionals with a given technique or procedure increases after viewing a training video [10]. By contrast, designing a checklist and providing training in this tool, so that health professionals are familiar with it, gives security to health professionals and reduces errors in assistance [11,12]. The checklists are applied and validated in surgical care in particular [13,14], and they allow individuals to systematize actions and address them in order of priority, ensuring that if the checklist is followed, adverse incidents in care will be minimized, and no step that compromises the safety of care or patient safety will be forgotten.

Checklists have been studied and implemented in emergency departments not only for the management of specific syndromes but also to systematize actions and guide diagnoses. Their use has been shown to increase adherence to established protocol, reduce differential diagnostic errors, improve patient examination findings in specific syndromes, and decrease errors in test interpretation [15-17]. It has been shown that in situations of cognitive overload, such as emergency departments where long shifts, high-stress, and urgent situations are common, checklists can make diagnosis or interpretation easier as they help manage the overload [18].

Most checklist validations are conducted based on expert consensus, such as the WHO Surgical Safety Checklist [19]; other studies have used Delphi methodology [20,21], and there are no checklist validations published in the literature using the proprietary methodology of questionnaire validation.

In 2017, a checklist for action in the AMI code in Central Catalonia was drawn up with the aim of facilitating data collection and guiding the action to be taken by the primary care health care team. The checklist was formulated by a working group created specifically for this task, along with the participation of primary care physicians from the Catalan Health Institute (ICS) of Central Catalonia, the Territorial Directorate of the Medical Emergency System of Central Catalonia, and the person responsible for the AMI code of the Medical Emergency System of Central Catalonia at the time. A checklist was agreed upon by following the guidelines in force at the time and the care protocols of the 2 institutions.

Central Catalonia is made up of 6 counties: Bages, Berguedà, Lluçanès, Moianès, Osona, and Anoia, corresponding to a

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population of 525,000 inhabitants and 32 primary care teams (one of which is a prison team). It is mostly rural territory with a high dispersion index. AMI code training is mandatory for all ICS medical and nursing professionals once a year and is done via an online course or through regulated clinical sessions. The sessions are led by the AMI code referents of each team, who are medical or nursing professionals who receive updated training each year and are responsible for disseminating the information from the training to their colleagues. In those training sessions, the use of the checklist is explained to the participants.

The checklist is available in paper format in all emergency departments of primary care centers, local clinics, continuous care points, and primary care emergency centers and also with the prison primary care team. Copies are also available in urgent and emergent care backpacks, as part of our procedures for urgent and emergent situations. However, the use of the checklist is not mandatory, and practitioners can choose whether to use it.

Given this situation of nonuniformity in the use and lack of validation of the tool, it was decided to take advantage of the checklist developed in 2017 and validate it for infarction code (AMI) care in primary care, demonstrating that it can increase patient safety as shown by numerous studies [22-24] or the WHO's own Surgical Safety Checklist [19].

Objectives

Therefore, the aim of this study is to validate the infarction code care checklist in terms of internal consistency and temporal robustness and explore its relationship with existing patient safety indicators in primary care settings in Central Catalonia (Table 1).

Table 1. Available patient safety indicators.

Indicator	Explanation
GLPI[a] (incident logging in the territory's own incident collection application)	Indicator of continuous care notifications; section on urgent care includes incidents involving the care of pathologies that must be treated between primary care and hospital care
EQPF[b] (pharmaceutical prescription quality standard [25])	Cardiovascular disease indicator and safety self-audit; allows us to know how well or poorly one is prescribing treatment to users with cardiovascular disease
EQA[c] (standard of care quality [26])	An indicator of cardiovascular disease; reports on the degree of compliance with the agreed-upon care guidelines for cardiovascular diseases and the good or bad monitoring of patients according to the indicators of these guidelines
Number of safety incidents reported to the Safety Incident Notification System of Catalonia [27]	Encompasses the collection of patient safety incidents reported by practitioners related to unscheduled, urgent, and emergent care
Degree of use of the checklists of the Proactive Patient Safety Application of Catalonia [28].	Indicators of the emergency department checklist; indicators of the use and supplementation of the checklist for the equipment and spaces where urgencies and emergencies are treated in primary care centers, which should be used by health professionals

[a]GLPI: incident logging in the territory's own incident collection application.

[b]EQPF: pharmaceutical prescription quality standard.

[c]EQA: standard of care quality.

Methods

Design and Setting of This Study

This is a prospective study for the validation of a checklist for infarction code care. The author of the initial checklist, who is also the leader of the first working group, along with the principal investigator of this study, has updated the 2017 checklist in accordance with the current guidelines (Multimedia Appendix 1). To facilitate data collection during the study, the updated checklist has been converted into a Microsoft 365 Forms questionnaire, an ICS corporate tool, to be completed online.

Two clinical scenarios of different clinical difficulty have been defined. The gold standard was determined by the authors for these 2 scenarios, complementing a checklist for each scenario following the guidelines in force at that time.

To validate the checklist as an effective intervention tool, we compared the information collected in the checklist from 2 proposed clinical scenarios with the gold standard guidelines, asking the health professionals to complement it. This allowed us to determine the internal consistency. In addition, the health professionals were asked to complete the checklist again after a few days. We assessed the temporal robustness by comparing the data collected in the first and second responses.

To ascertain the relationship with patient safety, the available safety indicators (Table 1) allowed us to compare the success of both scenarios with the safety culture of the teams.

Participants

All physicians and nurses of the 32 primary care teams, the 3 territorial continuous care emergency care teams, and the prison primary care team of Central Catalonia of the ICS who were working from January 2023 to April 2023 were invited to respond, totaling 921 health professionals. A total of 921 health professionals were invited to respond.

Procedure

Starting from the checklist agreed upon in 2017 by a group of experts, the author of the first checklist (from the 2017 proposal) and one of the collaborators and principal investigator of this study updated the paper format with the new European guidelines for action [4].

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Once the checklist was updated, it was transformed into an online format via Microsoft 365 Forms to validate it through 2 simulated clinical scenarios (Multimedia Appendix 2) of different difficulty levels and presentations.

The functionality was tested with the authors involved in this study. Once the best option was agreed upon, the checklist was tested with the AMI code referents (n=39) to check its functionality, and they were asked for their opinion and whether they thought improvements were needed to facilitate its implementation. Their inputs were considered, and some changes were made to improve the online version of the checklist.

The correct answers or the correct complementation for both scenarios were defined as the "gold standard." They were determined for each of the 2 scenarios, complementing a checklist for each scenario following the guidelines in force at that time (Multimedia Appendix 3).

At the same time as the actualization of the checklist, the AMI code referents from the different primary care teams were called to a training meeting to review the criteria for action according to the new guidelines, define how to provide training for the following year, agree on the dates with them to ensure that it has been completed in the first quarter of the current year, and explain them the operation of the checklist.

This procedure is already common in the region; AMI code training is organized through the AMI code referents in each team. They are the ones who receive the updates and pass them on to their teams.

The plan was that the AMI code referents would provide the annual training to the teams, and during that time, they would explain the checklist to the nurses and physicians of their teams and ask them to complete 1 checklist for each clinical scenario. On the same day as the training, the 2 checklists were completed for the first time (day 0). Therefore, the 2 checklists were completed for the first time (day 0) during annual AMI code training by all medical and nursing professionals during the period from January 2023 to May 2023.

All those health professionals who complete the checklist on day 0 will be asked to complete it again for a second time randomly after 30, 37, or 45 days to see the evolution of the answers over time. Half of them will be sent an email after 30 days, and if they do not answer, an email will be sent again after 37 days. The other half will be emailed after 37 days and, if they do not respond, they will be emailed again after 45 days. There will be a final roundup between 45 and 60 days with a reminder being sent to all those who have not responded (Figure 1).

Figure 1. Sampling procedure. AMI: acute myocardial infarction; CL: checklist.

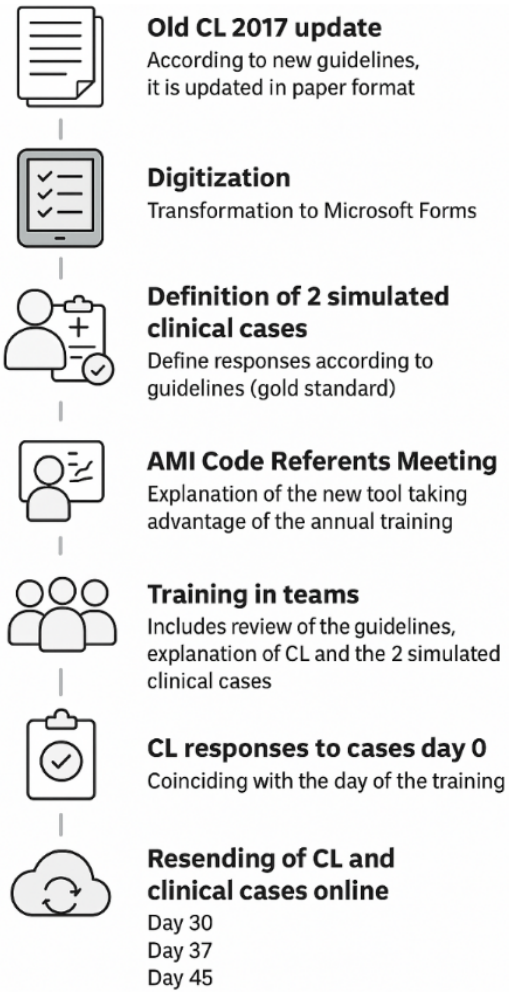

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Potential biases in participant selection could be as follows: health professionals do not attend the annual AMI code training, health professionals do not complete the online version of the checklist during the annual AMI code training, and health professionals do not complete the checklist a second time when it is sent to them online.

The strategies that can possibly avoid these biases are mentioned subsequently. AMI code training is mandatory for all health professionals and is linked to the payment of variable remuneration based on objectives. During the training, AMI code referents supervise and encourage health professionals to participate, and during the second time of completing the checklist, several reminders are sent by email asking participants to complete the checklist.

The questionnaire will have different sections. In the first part of the online questionnaire, health Professionals must read and sign the informed consent and agree to the data protection terms. In this first part, the health professionals will be informed that they need to complete the questionnaire a second time 30, 37, or 45 days after the completion of the first questionnaire, and they will be asked for their corporate email ID (which they can provide voluntarily) so that we can resend the questionnaires.

In the second part of the questionnaire affiliation data will be collected, including health professional category, year of graduation, how many years they have been practicing their profession, how long they have been trained in the AMI code, in which team they work, and the time they need to fill in the checklist. To compare the answers of the same health professional between the first response and the second response to the questionnaire, a code that is the same both times (4 letters of the health card and the last 4 digits of the personal telephone number) must be entered into the questionnaire.

In the third part, the health professionals will then move on to the questionnaire part, where they will find the clinical scenarios and then the questions or actions of the checklist that they will have to check or complete. Only completed checklists will be analyzed. To proceed with the online version, selecting an option is mandatory; questionnaires that are not completed till the end will not be counted, as incomplete responses are not saved in Microsoft Forms 365.

Sampling Method

This study followed a convenience sampling method. A total of 921 medical and nursing professionals were invited to participate, and the questionnaire was sent out at 30, 45, and 90 days to respond again.

To obtain estimates with 95% CIs and a replacement rate of 5% and assuming percentages of 50% to ensure all estimates, 405 health professionals will need to respond to the questionnaire.

Statistical Analysis

The sociodemographic variables of the sample of health professionals who responded to the checklist will be described by means of absolute frequencies and percentages. To evaluate the use of the checklist of clinical scenarios, a total score will be obtained for each case by adding the total number of items answered correctly. The total score for clinical scenario 1 is 40 points, and the total score for clinical scenario 2 is 42 points. There are 2 questions in the 2 scenarios where the maximum score is 2: name and onset of pain. In these 2 questions, if answered correctly, a score of 2 points is obtained; conversely, if answered with minor variations in the correct answer, a score of 1 point is obtained. The scoring system is accurately explained in Multimedia Appendix 3.

The results were converted to a 10-point scale for easier interpretation. The total scores of each case were described for the total sample and according to each category of the variables analyzed with means and SDs. ANOVA contrast will be used to compare scores between categories. In addition, the percentage of items answered correctly or incorrectly will be evaluated.

To validate the checklist, the “Fleiss κ” value will be estimated to analyze internal consistency and the intraclass correlation coefficient value to evaluate temporal consistency. In addition, the scores obtained in each clinical scenario will be compared between the response times (test retest).

The analyses will be performed using the statistical software R (version 4.2.1; R Foundation for Statistical Computing); the 95% CIs and the significance level will be set at 5%. On the one hand, we will have the responses collected from the checklist questionnaire sent using Microsoft 365 Forms, and on the other hand, we will have the data from the dashboards of the different patient safety applications (Table 1).

Ethical Considerations

All data extracted for the study will be anonymous, and confidentially will be maintained following the ethical principles of the 1964 Declaration of Helsinki, the European Data Protection Regulation 2016/679, and the Spanish legislation via Law 3/2018 of April 27 on Data Protection. The Organic Law 3/2018 of December 5 on the Protection of Personal Data and the Guarantee of Digital Rights will also be complied with.

We ask for consent in the first part of the online questionnaire as stated in the Procedure section. All information will be treated confidentially; there is a personal commitment to confidentiality that prevents the dissemination of the data consulted for the preparation of the work.

The research team will have no access to identifying data of the participants, directly or indirectly, under any circumstances. The participants will be informed in the same online questionnaire about the objectives of the study and will also be asked to accept the conditions by signing the informed consent in the same questionnaire. The participants did not receive any financial or material compensation for their participation in the study.

To validate the checklist, the data from the checklist questionnaire database will be coded because the participants who complete the checklist will generate a code, which the researchers can then cross-check to compare results, and at no time will they be able to reidentify the person.

This study received ethics approval from the research ethics committee of the Foundation University Institute for Primary Health Care Research Jordi Gol i Gurina (22/211-P).

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Results

We collected 615 responses to the online version of the checklist between January 2023 and May 2023. Throughout 2024, we analyzed the internal consistency and temporal robustness of the responses. The framework for integrating these results with patient safety indicators from various applications has been developed, although the comparative analysis is not yet included in this version of the manuscript. Data analysis is currently underway, and we expect to publish the results in early 2026.

Discussion

Overview

This study aims to validate a checklist designed for infarction code care in primary care settings by assessing its internal consistency and temporal robustness. We anticipate that the checklist will demonstrate strong reliability across repeated applications and that higher checklist scores will be associated with better performance on established patient safety indicators. These findings would support the checklist's potential as a useful tool for standardizing care and enhancing patient safety in a time-dependent clinical situation as AMI.

Anticipated Findings

The primary objective of developing and validating a checklist is to enhance patient safety. The use of simulated clinical cases or scenarios has been used by various authors as a method for testing checklists [11,24]. Therefore, the proposed study represents a valuable approach to validation, particularly given the limited number of existing studies that go beyond expert consensus or the Delphi methodology [20,21].

Comparison to Prior Work

According to Kohn et al [29], checklists play a crucial role in the patient safety improvement process. First, they help avoid reliance on the health professional's memory. By standardizing processes and reducing dependence on the memory of health professionals who may be unfamiliar with the procedures or equipment, checklists contribute to safer care. Both protocols and checklists in this context can enhance patient safety. Second, checklists help reduce the need for health professionals to remain vigilant for extended periods. By providing a checklist and mandating its use, some actions can be automated, further improving safety.

However, checklists can also increase patient safety indirectly by improving other aspects of care. They increase risk identification and decrease errors [24]; improve emergency management and guide the actions of health professionals [11]; provide a record of tasks or actions to be performed, increasing the likelihood that they will be performed [30]; increase cooperation among health professionals; and prevent some adverse effects [22].

It has also been shown that the identification of communication errors is the common root cause of many adverse events and patient safety incidents. This fact has motivated the development of actions to improve communication, including the development of checklists that reduce the variability of clinical practice, standardize the transmission of information, and help avoid forgetting some details [31].

Strengths and Limitations

In AMI code care, especially in primary care and in rural areas where extensive travel is required, the availability of a checklist may be essential to guide the actions of nonexpert professionals [11] in a pathology that is time dependent [4]. Working with checklists provides a record of the work to be done, but it is difficult to know if it has actually been done as stipulated. However, the mere reminder of the things to do from the checklist increases the safety of the patient, no matter how little the increment is [30].

That being said, it should be kept in mind that checklists only work if there is a knowledge base to organize clinical practice, and they are not a "one size fits all" solution. The systematization of compliance of "done" tasks is not a guarantee that they are really done or that other details not contemplated in the checklist are not missing [31], and training for their use is needed [24].

Although checklists are not a definitive solution, they can standardize care by decreasing variability and complications and allowing for continuous quality improvement of care teams [11]. In this sense, the availability of a validated, contrasted tool that is adjusted to the knowledge of the health professionals of the territory can guide the actions and improve the care of patients with this pathology.

The main limitations of the study are that the response time of the checklist is long and that it has to be answered twice, which can lead to participant losses, considering that the maximum number of people who can respond is approximately 900. Furthermore, the degree of training in the AMI code is different among health professionals. Although training is mandatory for health professionals once a year, it cannot be assured that they have completed it or that they have completed other complementary training. In addition, care guidelines are frequently updated, and we may encounter changes in the gold standard. Another limitation is the problem of external validation due to a small convenience sample without geographic stratification or stratification according to health professionals' experiences as well as the ecological validity of the study due to using only simulated instances and not real cases.

As for the last limitation, we might find that health professionals do not agree to being contacted via corporate email after 30, 37, or 45 days.

Future Directions

The analysis of checklist responses and their persistence over time (at 30, 37, and 45 days) will provide insight into whether health professionals retain the necessary knowledge and are able to act appropriately following training. Furthermore, it will help identify potential deficiencies in training or management, as reflected by unsatisfactory responses. Teams that perform well in quality and prescription standards typically demonstrate a strong patient safety culture and, consequently, are expected to achieve higher scores in the completion of other checklists (Proactive Patient Safety Application of Catalonia) [28] and in

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patient safety applications, such as the Safety Incident Notification System of Catalonia [27].

In parallel, the checklist could be further validated with more health professionals to have a more representative sample and ensure external validity as well as incorporate real-world cases in addition to the simulated ones.

Dissemination Plan

If the checklist is validated, we plan to disseminate it across all primary care teams of the ICS in Central Catalonia and the rest of the ICS teams. The dissemination strategy will include the development of training materials, integration into annual AMI code training sessions, and publication of implementation guidelines through institutional channels. Results will be shared in professional meetings and presentations. In addition, we aim to publish the final findings in peer-reviewed journals and present them at national and international conferences to support broader adoption and encourage replication in other health care settings.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are not publicly available but are available from the corresponding author on reasonable request.

Authors' Contributions

All authors contributed to the design and content of the study protocol. ESF was responsible for study design and coordination and writing the initial draft of the manuscript. AF-C and JVA were responsible for data collection. ESF, QMC, and JLG-D were responsible for data processing and exploitation. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Checklist description.
[DOCX File , 17 KB - resprot_v14i1e66584_app1.docx]

Multimedia Appendix 2
Clinical scenario description.
[DOCX File , 14 KB - resprot_v14i1e66584_app2.docx]

Multimedia Appendix 3
Gold standard responses.
[DOCX File , 20 KB - resprot_v14i1e66584_app3.docx]

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Abbreviations

AMI: acute myocardial infarction
CVRF: cardiovascular risk factor
ICS: Catalan Health Institute
PCI: percutaneous coronary intervention
WHO: World Health Organization

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Protocol

Urban Chinese Community-Dwelling Older Adults' Expectations Regarding the Delivery of Integrated Care Through Case Managers: Protocol for a Mixed Methods Study

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Abstract

Background: The rising burden of chronic diseases among older adults in China underscores the urgent need for an integrated and efficient health care system. Existing services are often fragmented, lacking coordination and accessibility, particularly for urban community-dwelling older adults with multiple comorbidities. There is a critical demand for person-centered integrated care that enables resource sharing, expert guidance, and the safe, continuous management of chronic conditions.

Objective: This study aims to extend the theoretical understanding of case-managed integrated care informed by the Program of Research to Integrate the Services for the Maintenance of Autonomy (PRISMA) model within urban Chinese communities. It will examine older adults' expectations for case-managed integrated care, develop and validate a measurement instrument to quantify these expectations, and build an evidence-based framework to adapt the PRISMA model to the Chinese context.

Methods: An exploratory sequential mixed methods design will be used across 3 phases. Phase I involves qualitative interviews with community-dwelling older adults and other stakeholders to explore unmet health care needs and perceptions of case-managed integrated care. Phase II entails the development and psychometric validation of a questionnaire informed by the findings from phase I. Phase III involves a large-scale cross-sectional survey in Wenzhou, Taiyuan, and Hainan to quantify expectations for case-managed integrated care and identify associated sociodemographic factors. A data integration approach will be used to synthesize both qualitative and quantitative findings, providing a comprehensive understanding of expectations regarding the proposed integrated care.

Results: Data collection is scheduled to begin in December 2025, with the study expected to last 24 months. Ethics approval has been obtained from the Institutional Ethics Committee.

Conclusions: This study seeks to evaluate the feasibility of culturally adapting the PRISMA model for case-managed integrated care to address critical gaps in existing health care service delivery. The findings are expected to inform policy formulation, guide the implementation of integrated community care strategies, and ultimately improve health outcomes and quality of life for older adults in urban China.

Trial Registration: OSF Registries 825ah; https://osf.io/825ah

International Registered Report Identifier (IRRID): PRR1-10.2196/71394

(JMIR Res Protoc 2025;14:e71394) doi:10.2196/71394

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KEYWORDS

aging; chronic diseases; case management; person-centered care; qualitative research; quantitative research

Introduction

Background

The National Bureau of Statistics reported that by the end of 2023, China's aging population (60 years or older) surpassed 290 million, representing approximately 21.1% of the total population [1]. More than half of this demographic faces high morbidity rates, with highly prevalent conditions such as type 2 diabetes, chronic obstructive pulmonary disease, and hypertension [2,3]. Furthermore, approximately 96 million older adults experience varying degrees of disabilities [4], creating significant demands for medical services and nursing care, including home visits for medication, health monitoring, health care education, and psychological counseling [5-7]. The growing burden of chronic disease highlights the urgent need for more coordinated and effective older adult care systems [8].

The majority of older adults prefer "aging in place", a choice deeply rooted in the traditional Chinese value of "filial piety" [9,10]. The "9073" care model serves as the primary framework for older adult care in China, wherein 90% of older adults rely on home-based care with community support, 7% reside in community-based institutions or daycare centers, and 3% live in long-term care facilities [11]. However, this model becomes increasingly critical when older adults encounter difficulties performing basic activities of daily living (ADL) due to frailty [12]. Notably, less than 10% of home-based older adults with varying levels of care dependency have received adequate community services, reflecting a significant gap between care provision and demands [13].

To address these challenges, China launched the Integrated Care for Older People program (ICOPE-CHINA) in 2020, following the World Health Organization's ICOPE framework. While this program integrates health care services, daily living assistance, and social services, many older adults remain unaware of available resources due to limited information and low health literacy [14-16]. Developing accessible and navigable community-based care is therefore a pressing priority [17].

Literature Review

Globally, several models of integrated care have emerged in response to aging populations and the growing burden of chronic disease. These include the chronic care model (CCM), the Kaiser Permanente model, and the Program of Research to Integrate the Services for the Maintenance of Autonomy (PRISMA). The CCM focuses on clinical settings, self-management support, and proactive care, but it requires extensive system-level transformation, making large-scale implementation difficult in China due to uneven development and constrained resources [18,19]. The Kaiser Permanente model, which integrates funding, information technologies, and payment mechanisms, has proven effective within vertically integrated private systems [20]. However, in the Chinese health care system, it may be more feasible to strengthen collaboration across medical specialties, partner with community organizations and enterprises, and pursue reforms at the county or community levels [21,22]. The PRISMA model was explicitly designed for publicly funded universal health care systems and emphasizes collaboration among otherwise independent service providers [23]. Rather than requiring structural mergers, it establishes mechanisms for linkage and collaboration across health care providers, social service agencies, and community organizations.

The current older adult care system in China comprises community medical centers, community elderly care facilities (CECFs), and voluntary agencies, all of which have evolved in response to government policies, financing mechanisms, consumer demands, and market dynamics [24]. Particularly, CECFs operate under government supervision, offering daycare and temporary services designed to alleviate the burdens of family caregivers. These services include basic nursing care, health case management, household support, rehabilitation, and counseling [25]. In several pilot cities, community-based initiatives have been launched, beginning with the deployment of social workers and the establishment of CECFs to support older adults across multiple ecological levels [26-29]. From a theoretical perspective grounded in the Social Ecological Model [30], existing models differ in their suitability for China's multilevel, publicly dominated care structure [31]. To assess the models' contextual fit, the IMPACT Framework is adapted to guide and compare their matching across 6 dimensions (Multimedia Appendix 1 [18-34]) [35]. At the implementation and policy levels, the CCM's emphasis on individual self-management and clinical integration is not aligned with China's fragmented, community-based care system [18,19]. The Kaiser Permanente model, though effective in private integrated systems, is less adaptable to China's fragmented, public-sector-dominated context [21,22,31].

In contrast, the key components of the PRISMA model, including needs assessment, case management, and coordinated referrals, address the major weaknesses observed in China's current community-based care system. These components directly respond to the challenges faced by Chinese urban community-dwelling older adults, such as limited awareness of available services, fragmented resource use, and insufficient continuity of care [32,33,36]. In particular, the central role of case managers in PRISMA provides a feasible mechanism to guide older adults and their families through complex service pathways, thereby ensuring equity in access and promoting better integration of community resources [37-47]. The detailed functions of case managers are summarized in Table 1.

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Table 1. The roles and functions of case managers [48].

Main function	Working scope
Advocacy	Advocates for patients' rights and interests, addressing systemic barriers to care.
Care coordination	Facilitates communication and coordination among patients, caregivers, and health care providers, ensuring seamless care transitions.
Case monitoring and patient needs assessment	Assesses patient needs, sets care goals, and monitors care plans for effectiveness.
Community engagement	Collaborates with community groups to disseminate knowledge and raise funds.
Education	Educates patients, caregivers, and health care professionals on treatments, complications, and financial support options.
Administration and research activities	Mobilizes resources, ensures cost-effectiveness, and supports health care research.
Psychosocial support	Provides emotional support, grief counseling, and crisis intervention.
Navigation of services	Connects patients and caregivers to relevant health care services and resources.
Reduction of barriers	Minimizes obstacles to accessing timely services and treatments.

Case manager certification has been included in China's National Occupational Classification since 2005, reflecting formal recognition of this role, and the number of graduates trained in care management continues to grow [49]. Although a few studies have piloted case management interventions in China, showing potential in reducing emergency attendance, hospital readmission, health care costs, and enhancing patient satisfaction [50,51], these studies primarily focus on hospital-based applications, with limited attention given to community older adult care, where most older adults reside [52,53]. Beyond this limited focus, fragmented communication among stakeholders further undermines continuity of care in community settings [7]. A previous study found that community residents aged 18 years or older with chronic diseases placed high demands on service continuity, convenience, coordination, responsiveness, and upward information sharing, where case managers could play a critical role [54]. However, limited research has focused on the multifaceted needs of older adults and their centrality to person-centered care. Critically, there is no validated measurement tool to assess older adults' expectations of case-managed integrated care in the Chinese context. These gaps hinder both policy adaptation and practical implementation of integrated care at the community level.

Study Objectives

This study aims to extend the theoretical understanding of case-managed integrated care informed by the PRISMA framework within urban communities under a non-Western, publicly funded health care system. It will also contribute to the literature by elucidating how culturally embedded expectations shape the acceptability and potential adaptation of case-managed integrated care in China.

We hypothesize that the urban Chinese community-dwelling older adults with complex health needs and limited access to coordinated services will demonstrate high acceptability of the PRISMA model and express strong expectations for case-managed integrated care. To address this hypothesis, the study primarily pursues the following objectives: (1) investigate the expectations of urban Chinese community-dwelling older adults for case-managed integrated care; (2) develop and validate a measurement instrument to quantify their expectations; and (3) formulate an evidence-based framework for adapting the PRISMA model to the Chinese context. In the study process, we will also explore unmet health care needs, assess the acceptability of a PRISMA-informed case management model, and analyze expectation levels together with associated sociodemographic factors.

Methods

Overview

An exploratory sequential mixed methods approach will be used to address the study objectives, ensuring both depth of exploration and measurement validity. The Checklist of Guidelines for Conducting and Reporting Mixed Research for Counselor Researchers will be used to guide the study process and reporting results (Multimedia Appendix 2) [55]. Guided by the PRISMA model (Figure 1), the design consists of 3 interconnected phases [23]. In phase I, a qualitative inquiry will involve in-depth interviews and focus groups to explore urban community-dwelling older adults' expectations for case-managed integrated care to address objective 1. Thematic analysis will identify key domains of expectations and unmet health care needs among urban community-dwelling older adults and their family members. The acceptability of the PRISMA-informed case management model will be assessed. Phase II will focus on developing and validating a questionnaire to address objective 2. Phase III will use a quantitative survey conducted in 3 selected cities representing the eastern, north-central, and southern regions of China, which are culturally and geographically diverse [56]. The validated instrument will be used to examine expectation levels and associated sociodemographic factors. These empirical data will inform the formulation of an evidence-based framework tailored to the Chinese context and aimed at facilitating the real-world implementation of case-managed integrated care for urban older adults, thereby addressing objective 3. A data integration approach will be used, where themes and codes identified in the qualitative inquiry will inform the development of questionnaire items. Quantitative results will then be analyzed in relation to the initial qualitative findings to confirm, refine,

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or expand the emerging patterns, ensuring methodological rigor and enhancing integration validity [57].

Figure 1. The Program of Research to Integrate the Services for the Maintenance of Autonomy (PRISMA) model of integrated care.

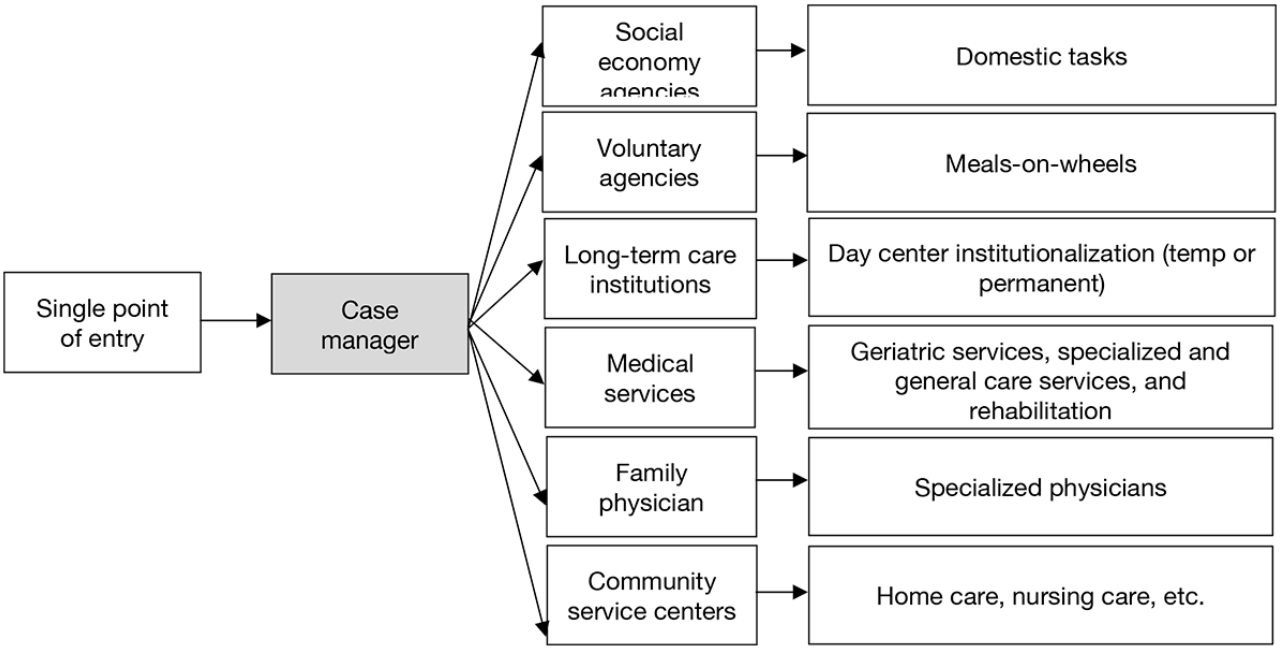

Ethical Considerations

Ethics approval for this study was obtained from Zhejiang Dongfang Polytechnic, China (approval number GZSQ202408120010). All participants will receive an information sheet explaining the study purpose, procedures, potential risks, and their right to withdraw at any time without penalty. Written informed consent will be obtained from all participants before interviews or surveys. No identifiable personal information will be included in the future publication.

Phase I: A Qualitative Study

Overview

During phase I, a qualitative case study will be conducted using purposive sampling to recruit participants [58]. The study aims to investigate unmet health care needs of the older adults in the existing urban health care services or systems, assess the acceptability of the PRISMA model, and explore practical requirements for integrated care facilitated by case managers among urban Chinese community-dwelling older adults. Participants will be introduced to the PRISMA model and provided with a semistructured interview guide in simplified Chinese, which includes probing questions. Discussions of health care needs will consider the current health care landscape in China [59]. Three trained investigators will conduct interviews on-site.

Settings

The study will be carried out in community medical centers or CECFs located in Wenzhou, Zhejiang Province, China, which play a pivotal role in older adult care by providing essential medical treatment, disease prevention, rehabilitation, and care services to older adults [60,61]. Wenzhou is characterized by a substantial aging population, with older adults accounting for 19.3% of its total population, positioning the city on the trajectory toward a super-aging society [62]. Moreover, Wenzhou has planned a program where community social workers coordinate social services and health care assistance for older adults living in the community, assigning one social worker for every 500 older adults [63]. Participants will be selected from these settings based on their engagement with health care services [64].

Participants

Adults aged 60 years or older living in urban communities will be included in the study. The purposive sampling approach will guide participant selection, aiming to capture diverse sociodemographic factors. Inclusion criteria include (1) having 2 or more physician-diagnosed chronic conditions such as ischemic heart disease, stroke, chronic obstructive pulmonary disease, or type 2 diabetes, as documented in their medical records [65]; and (2) self-report visits to community medical centers or hospitals more than 12 times per year for chronic disease management, verified through medical records [66]. To enhance data richness, perspectives from the adult children of eligible older adults, care administrators, and health care professionals within communities will also be invited to the study. They will comprise approximately 50% of the interviews and will be proportionally distributed across the 3 study cities to ensure regional balance and facilitate integration into the analysis and subsequent questionnaire development. Exclusion criteria include unwillingness to participate or having communication difficulties caused by language barriers, cognitive impairments such as dementia, or swallowing disorders like dysphagia.

Sampling Process

To achieve demographic diversity and minimize selection bias, recruitment will take place across multiple urban communities

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with diverse socioeconomic profiles. Investigators will engage both high- and low-income districts to ensure a diverse background of participants. Multiple strategies will be used to approach participants, including direct contact, staff referrals, and distribution of flyers. Demographic factors will be monitored during recruitment to guide further purposive selection. Detailed study information, including the PRISMA model and interview procedures, will be explained to participants.

Data Collection

Data will be collected through in-depth interviews and focus groups conducted either face-to-face or online by WeChat (the most popular Chinese app). Each focus group will include up to 4 participants. Informed consent will be obtained, and the PRISMA model, along with the role of case managers, will be explained in clear and accessible language. Semistructured interview guides with probing questions will be used to elicit detailed responses. Interviews will be recorded in video or audio format. Prior to the main investigation, a pilot interview with 2-3 participants will be conducted to refine interview questions. Sociodemographic factors including age, education level, income, presence of chronic diseases, and living arrangements, will be collected. Additionally, the Chinese version of the Barthel Index (BI) will assess participants' ADL. A total of 30 participants are planned for recruitment, with the final sample size determined by data saturation. A sample of open-ended questions and probes is included in Multimedia Appendix 3.

Qualitative Data Analysis

Raw data will be managed using NVIVO (version 11; QSR International Pty Ltd) or ATLAS.ti (version 8; ATLAS.ti Scientific Software Development GmbH). Interviews will be transcribed verbatim by trained investigators, with a second investigator conducting an audit for accuracy. Thematic analysis will combine both inductive and deductive approaches, guided by the PRISMA model and the framework method. The latter consists of 6 steps: transcript review, coding, team discussions, theme comparison, theme definition, and report writing [67].

Phase II: Questionnaire Development and Validation

Overview

The objective of phase II is to develop and validate a questionnaire based on the PRISMA model and the findings from phase I, guided by an item adoption quality control method [68]. This measurement instrument aims to assess older adults' expectations for case-managed integrated care, capturing both general and specific expectations.

Questionnaire Design and Measurement

The questionnaire will consist of 2 main sections. Section 1 will include the sociodemographic factors such as age, income, presence of chronic diseases, assessment of ADL, and one item related to the acceptability of case-managed integrated care. Section 2 will be informed by the qualitative outcomes of phase I related to expectations, with variables derived from coded data and scales aligned with identified themes. Questionnaire items will be constructed using quotations from the qualitative study, guided by the PRISMA model and emerging codes from phase I. A 5-point Likert scale will be used to quantify the level of expectations. Responses will be categorized into 3 levels: low, medium, and high. This categorization can be applied at both the item and construct levels, depending on the properties of the scale. The final questionnaire is expected to include fewer than 50 items related to expectations, with an estimated completion time of approximately 30 minutes. To minimize potential respondent fatigue, the questionnaire will undergo pretesting with older adults to assess burden and ensure acceptability.

Questionnaire Validity and Reliability

The face and content validity of the questionnaire items will be evaluated by a panel of at least 6 experts, such as nurses, geriatricians, statisticians, health care case managers, and social workers, as well as older adults. Feedback from the panel will be used to calculate the Content Validity Index for each item [69]. The relevance, comprehensibility, and comprehensiveness of the items will be assessed using the consensus-based standards for the selection of health status measurement instruments checklist [70]. Exploratory factor analysis will be used to examine the underlying factor structure, retaining factors with an eigenvalue greater than 1. Items with factor loadings below 0.40 or with significant cross-loadings with another item will be excluded [71]. Structural Equation Modeling will then be used to assess model fit, ensuring alignment with the hypothesized factor structure. Internal consistency will be measured using Cronbach α, with a threshold of 0.70 or higher indicating acceptable reliability [72]. Additionally, intraclass correlation coefficients will be used to assess test-retest reliability among participants from distinct geographic regions. A random sample of at least 50 participants (16-17 participants at each site) will complete the questionnaire twice, with a one-month interval between administrations [70]. An intraclass correlation coefficient value between 0.50 and 0.75 indicates moderate reliability, while a value of 0.75 or higher signifies good reliability [73]. Beaton's cross-cultural adaptation framework will be applied to ensure the PRISMA model is culturally appropriate for the Chinese context. This process will include a forward-backward translation procedure conducted by 2 independent bilingual translators, followed by a review from an expert panel consisting of 3-6 professionals, and cognitive interviews with 10 Chinese older adults [74]. In addition, pretesting with 30-40 participants will be conducted to assess clarity, cultural relevance, and comprehension, or as part of the reliability and validity testing in Phase III [75]. Items judged as unclear or culturally inappropriate for ≥20% of participants will be revised or excluded [76].

Phase III: A Quantitative Study Through a Survey

Overview

In Phase III, a survey will be conducted to examine the expectations of case-managed integrated care among urban Chinese community-dwelling older adults, along with their associated sociodemographic factors, using the validated questionnaire developed in Phase II. The questionnaire will be administered in Chinese via a web-based platform wjx.cn or distributed as printed hard copies along with consent forms. A triangulation matrix will align key research questions with both

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qualitative and quantitative data sources, supporting convergence and complementarity across datasets. In the final phase, the merged data will be analyzed to provide a more comprehensive understanding of complex phenomena, test hypotheses, and deepen insights [77]. Based on the results, an evidence-based framework will be developed to bridge the gap between the global model and local implementation.

Settings

China's population distribution and economic development vary significantly across regions, with a general decline in economic indicators from east to west and north to south, reflecting substantial sociodemographic diversity [78]. To capture this diversity, the survey will be conducted in 3 major cities: Wenzhou, Taiyuan, and Hainan Island, each representing distinct geographic, economic, and demographic profiles. Wenzhou, located along China's eastern coast, is an economically developed area characterized by a thriving private economy and a significant aging population who predominantly prefer to age in place within their communities [79,80]. Taiyuan, the capital of Shanxi province in northern-central China, has an older adult population exceeding 21.9%, indicating a super-aged society. However, average income levels are slightly below the national level, reflecting a less economically developed context [81,82]. Hainan, China's southernmost island province, is experiencing rapid aging, with older adults comprising 15.5% of its population. The province is notable for its diverse aging demographic, which includes seasonal migrants from 27 provinces, providing a unique representation of mobility patterns and demographic heterogeneity among older adults [83,84]. The inclusion of these 3 locations ensures the study's findings will be generalizable across varied socioeconomic, cultural, and geographic contexts, thereby enhancing the representativeness of the aging population in China.

Participants and Sample Size Estimation

Participant selection will focus on older adults aligned with the inclusion criteria in phase I, including (1) age of 60 years and older, (2) living independently in the community, (3) having 2 or more chronic conditions, and (4) visiting community medical centers or hospitals more than 12 times per year for chronic disease management. Exclusion criteria are unwillingness to participate, language barriers, or cognitive impairments. This study primarily aims to estimate the proportion of older adults expecting integrated care services and to examine sociodemographic factors associated with different expectation levels. Sample size estimation was conducted using multiple scenarios. Assuming a 95% CI level (Z=1.96) and a margin of error (e=0.05), the required sample size varies according to the expected proportion (P) of older adults expressing high expectations for integrated care. If P is 0.5 (indicating maximum variability), the required sample size is 385. Additionally, to allow for subgroup analysis (eg, by income, education, or ADLs) and to detect a medium effect size (Cohen w=0.3) [85] with 80% power using chi-square tests across 3 groups (low, medium, and high expectation levels), the minimum required sample size is approximately 108 per group, totaling 324 participants. To ensure representativeness and account for a 20% nonresponse rate, the target sample size will be at least 480 participants (160 in each city).

Sampling Process

A stratified random sampling method will ensure representation across the diverse aging population. Enumerators (2 in each city) will identify 4 communities in each city where older adults comprise over 21% of the population. Two of the communities will then be randomly selected using an online random number generator, such as Random.org, or the RAND function in Excel. Recruitment will occur through posters, flyers, announcements, and outreach via digital platforms within the community, such as medical centers or CECFs. Participants will provide demographic information, which will be used to stratify the sample by age and chronic disease status before random selection within each stratum.

Data Collection Process

At each site, one investigator and one research assistant will oversee data collection. On-site investigators will screen older adults against the inclusion criteria and provide eligible participants with detailed study information. Informed consent will be obtained from participants. To facilitate follow-up and support test-retest reliability, participants may optionally provide telephone numbers. All collected data will be entered into a database and subjected to a double-checking process by investigators and research assistants to ensure completeness.

Measurement

At the beginning of the questionnaire, a concise explanatory note in Chinese will be provided to describe the modified PRISMA model. This note outlines the concept of integrated care, managed through a single-entry point by a case manager, to ensure participants understand the key concept before proceeding. Verbal explanations will be provided upon request. To ensure ethical rigor, additional safeguards will be applied for participants with potential cognitive impairments, including the use of simplified consent materials, a brief assessment of decisional capacity prior to enrollment, and involvement of family members to support understanding. Investigators will be trained to identify signs of distress or reduced comprehension, ensuring the voluntary and informed participation of all respondents.

Sociodemographic Factors

Age and the frequency of hospitalization in the past year will be collected as numerical variables. Other variables, including gender (male or female), health status (healthy, living with one chronic disease, and living with 2 or more chronic diseases), monthly income (<US $375, US $375-749, >US $749), education level (no formal education, elementary school, middle school, high school, bachelor degree or higher), occupation (employed, unemployed, and retired), insurance (no insurance, Urban Employee Basic Medical Insurance, Urban Resident Basic Medical Insurance, and New Rural Cooperative Medical Insurance), number of children (no child, 1 child, 2 children, and 3 or more children), and living arrangements (alone, with a partner, with children, with a partner and children, and with others such as a housemaid) will be categorical variables.

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BI

The BI scale will assess participants' self-care abilities across 10 domains, including bowel and bladder control, feeding, bathing, dressing, and walking. Each domain will be scored on a scale of 0-15 points, reflecting the levels of assistance required [86]. The validated Chinese version of the BI scale will be used [87,88], with scoring categories as follows: 100-91 (complete independence), 90-61 (slight dependence), 60-21 (moderate dependence), and ≤20 (severe dependence) [89].

Expectation Section

The final questionnaire will categorize variables into individual items and grouped constructs to measure participants' overall and specific expectations of case-managed integrated care. A 5-point Likert scale (1=low expectation, 5=high expectation) will be used.

Data Analysis for the Quantitative Study

Quantitative data will be analyzed using SPSS Statistics (version 26; IBM Corp). Data from digital questionnaires will be exported to SPSS, while hard-copy data will be manually entered into the dataset. Mean expectation scores will be analyzed either as a continuous variable or divided into tertiles (lowest, middle, and highest). Chi-square tests will examine associations between sociodemographic factors and expectation levels. Statistical significance will be set at $P<.05$, with 95% CIs. Multiple logistic regression models will be used to evaluate the association between independent variables and expectation levels, with the lowest subgroup serving as the reference category. Variables with a P value <.20 in univariable regression will be included in the multivariable model. Multicollinearity will be assessed using a tolerance threshold of <0.4 or a variance inflation factor of ≥2.5. Model adequacy will be evaluated through Q-Q plots for normality, residual plots for linearity, and tests of homogeneity. For missing data, descriptive analyses will be conducted to assess the extent and patterns of missingness. When the proportion of missing data is low, complete-case analysis will be applied. In cases of substantial missingness, multiple imputation will be used if feasible; otherwise, simple imputation methods such as mean substitution for continuous variables and mode substitution for categorical variables will be considered [90]. Multilevel logistic regression will also be considered to assess and account for the possible geographic clustering and contextual variation across regions. Results from both statistical strategies above will be compared and interpreted accordingly. These modeling strategies aim to ensure robust and reliable findings that inform evidence-based health care frameworks for older adults in Chinese communities.

Results

This study was funded in February 2025 and received ethical approval from the Institutional Ethics Committee (approval number GZSQ202408120010). Data collection is scheduled to begin in December 2025 and is expected to be completed by December 2027. As of manuscript submission, participant recruitment has not yet commenced, and data analysis has therefore not begun. The primary results are expected to be available in late 2027.

Discussion

This study aims to explore the expectations of case-managed integrated care among older adults in Chinese communities. The PRISMA model, emphasizing a single-entry point, case management, and multidisciplinary collaboration, provides a robust theoretical foundation to guide the study design and interpret outcomes across 3 phases. By contextualizing this model within a non-Western, community-based care system, the study seeks to bridge the gap between evidence and practice and to examine how culturally embedded expectations influence the acceptability and adaptation of case-managed integrated care in China. Additionally, the study aims to identify effective pathways to support the implementation of integrated care initiatives, such as the ICOPE-CHINA program.

The acceptability and implementation of case management in China must be understood within the framework of traditional cultural values, such as filial piety and family-centered care. Older adults have traditionally relied on their adult children for care and support [91]. However, demographic and social changes, particularly the one-child policy, have reshaped family structures, resulting in an increasing number of older adults living alone or without immediate family support [92]. Today, the living arrangements of older adults are increasingly influenced by social support and health conditions, making co-residence with children less common or feasible [93,94]. As a result, the role of the family is shifting from direct caregiving to supervisory and coordinating functions, creating opportunities for community-based integrated care and more effective resource navigation [95].

The PRISMA model's core tenets, such as individual autonomy, personalized care planning, and self-directed decision-making, often reflect individualistic care paradigms that may not align with collectivist norms in China, where health care decisions are often made within family units [96,97]. This cultural incongruity may affect the model's acceptability and implementation in Chinese communities. To address this, the expectations of other key stakeholders will be investigated in phase I, particularly the adult children who often play a central role in care-related decisions, to assess whether and how the PRISMA model's individualistic foundations can be adapted to align with collectivist norms, including shared decision-making, filial responsibility, and the involvement of extended family and community networks.

Unlike existing instruments used in China, the questionnaire developed in phase II is theoretically grounded, empirically testable, and specifically tailored to assess the expectations of urban community-dwelling older adults regarding case-managed integrated care. For example, the Patient-Reported Experience Measures mainly capture hospital-based experiences and may overlook patients' perspectives on continuity and coordination across community and social care settings [98,99]. The Chinese version of the Rainbow Model of Integrated Care Measurement Tool evaluates the effectiveness of integrated care from system-level or provider perspectives [100]. These instruments also lack alignment with the micro-level expectations of older adults. Similarly, the Chinese Patient-Centered Integrated Care

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scale addresses patient-centeredness but does not emphasize aging populations or the role of case management [54]. In line with the IMPACT framework, particularly the matching dimension, this study ensures theoretical coherence by aligning the PRISMA model's macro-level foundation with meso- and micro-level constructs derived from qualitative findings [35]. This alignment enhances both conceptual clarity and practical relevance. The construct development process also reflects parsimony by focusing on core expectation dimensions, with empirical testability supported through pilot testing and expert validation. Furthermore, the questionnaire is culturally adapted to China's evolving community-based older adult care system, thereby enhancing its contextual fit. Collectively, these features position the instrument as a novel and relevant contribution to the evaluation and model design of integrated care for older adults in similar settings.

A key strength of this study lies in its adoption of a mixed methods design, integrating qualitative and quantitative approaches to comprehensively address complex research questions and ensure triangulation of findings, guided by a validated checklist [55,57]. This integrated, multiphase approach ensures that qualitative insights inform the development of a context-specific measurement instrument, validated through rigorous quantitative analysis.

Phase I will gather qualitative data through in-depth interviews with Chinese older adults to explore unmet health care needs, perspectives on the PRISMA model, and expectations for a case manager system. A purposive sampling approach will ensure demographic diversity among participants. Reflexive practices, including audio recordings, detailed transcriptions, involvement of multiple investigators, and peer debriefing, will mitigate potential interpretive bias, enhance credibility, and ensure methodological transparency and rigor. Collectively, these strategies uphold the trustworthiness of the qualitative findings, forming a robust foundation for the subsequent quantitative phase.

Phase II will focus on developing and validating a measurement instrument grounded in findings from phase I, aligned with the principles of the PRISMA model. Validation will involve both qualitative methods (expert review) and quantitative techniques (statistical analysis) to ensure reliability, construct validity, and cultural relevance.

In phase III, a cross-sectional survey will be conducted in multiple urban regions using stratified sampling to capture demographic and geographic diversity. The newly developed instrument will be deployed to reduce measurement bias and enhance consistency. Data collection strategies will include trained on-site investigators, real-time supervision, periodic field audits, and quality checks of completed surveys to promote reliability and minimize research bias. Follow-up reminders and incentives will be used to maintain high response rates. Advanced statistical techniques will analyze relationships between key variables while controlling for potential confounders, generating findings that are both reliable and generalizable, with practical implications for implementing integrated care models.

Moreover, integrating findings across all phases will ensure that the qualitative insights meaningfully inform quantitative measurement. The study is expected to yield actionable recommendations for implementing structured, integrated care that addresses health care disparities and supports sustainable, evidence-based older adult care solutions tailored to the Chinese context.

However, reliance on self-reported data may introduce recall bias, and the cross-sectional design may limit the ability to infer causality or track changes in older adults' expectations over time. While this design is appropriate for assessing the psychometric properties of the newly developed tool, it constrains the study's capacity to capture temporal dynamics. Moreover, potential sampling bias may arise from recruitment primarily through community medical centers or CECFs, which may not fully capture the diversity of the broader older adult population, potentially those experiencing greater isolation, different health beliefs, or worse mobility. To mitigate this limitation, recruitment will be expanded to include a wide range of community organizations and senior activity groups. Furthermore, stratified sampling based on key demographic factors will be used to ensure representativeness. This will be checked against official census data if available from the government, or against contemporaneous population studies conducted around the same time period as this study.

The study targets urban-dwelling older adults, which may limit the generalizability of findings to rural or remote populations. However, this choice is intentional, as urban-rural disparities in China remain significant in terms of care infrastructure, service availability, professional workforce, and financial support, such as pension and insurance coverage [101-103]. In addition, findings should be interpreted with caution when applied to rural populations, where resource constraints and limited service networks may pose distinct challenges [104]. For example, urban communities have increasingly developed the structural capacity to support integrated care, exemplified by the government's initiative to build "15-minute older adult care service circles" that provide accessible services such as meal assistance, rehabilitation, and health monitoring within walking distance [105,106]. Given these conditions, urban settings offer an operationally feasible context for the initial implementation of case-managed integrated care. Insights gained from urban experience can serve as a foundation for future adaptation, helping to identify which components of integrated care are transferable and what modifications are needed to ensure feasibility and equity in less-resourced rural contexts.

While this study highlights the potential of adapting the PRISMA model in urban China, several barriers may constrain its translation into practice. Workforce shortages remain a critical challenge, as the supply of trained case managers and health care professionals is insufficient to meet the growing demand. Fragmented care delivery driven by financial constraints at both the community and system levels may also limit the scalability of new care models. Moreover, policy inertia and the complexity of governance may delay the operationalization of initiatives. Nevertheless, the evidence-based framework from this study could serve as an invaluable guide to policymakers, health care stakeholders,

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researchers, and entrepreneurs to facilitate the implementation of case-managed integrated care for older adults in China.

In conclusion, this study aims to generate empirical evidence to support the adaptation of the PRISMA model in Chinese communities. While findings may provide actionable insights for policy and practice, their impact will depend on addressing structural barriers such as workforce shortages, financial limitations, and policy inertia. By situating recommendations within these constraints, this study provides both evidence and a realistic roadmap for advancing integrated care in non-Western contexts. To ensure the effective translation of research findings into policy, the reporting of results will consider established guidelines for Patient and Public Involvement in Research, such as the Guidance for Reporting Involvement of Patients and the Public checklist [107]. Additionally, the authors plan to engage key stakeholders and patient research partners to facilitate the future adaptation and implementation of the study findings.

Acknowledgments

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Authors' Contributions

YYZ contributed to the writing of the original draft and will be responsible for all stages of manuscript preparation, creation, and presentation of the published work. BHC and FZ provided critical review and supervision, and will also contribute to writing through review and editing. YHT and HZ will assist with the investigation process, which includes conducting research activities, as well as collecting and analyzing data.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplement File 1: Theoretical Model Selection based on the IMPACT Framework.
[DOCX File , 28 KB - resprot_v14i1e71394_app1.docx]

Multimedia Appendix 2
Supplement File 2: The Checklist of Guidelines for Conducting and Reporting Mixed Research for Counselor Researchers.
[DOCX File , 20 KB - resprot_v14i1e71394_app2.docx]

Multimedia Appendix 3
Supplement File 3. Open-end Questions and Probes.
[DOCX File , 13 KB - resprot_v14i1e71394_app3.docx]

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Abbreviations

ADL: activities of daily living
BI: Barthel Index
CCM: chronic care model
CECF: community elderly care facility
ICOPE: Integrated Care for Older People program
PRISMA: Program of Research to Integrate the Services for the Maintenance of Autonomy

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Protocol

The Malaysian Burden of Disease Study: Protocol for Mortality, Morbidity, and Risk Factor Evaluation

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Abstract

Background: Knowledge of the burden of disease at the national level is crucial for understanding regional health patterns and epidemiological trends. Regular updates and methodological enhancements are essential to produce accurate estimates that effectively represent the current health landscape, thereby assisting policymakers in resource allocation and strategic planning.

Objective: The objective of this study protocol is to revise the list of diseases and injuries; estimate years of life lost (YLLs), years lived with disability (YLDs), and disability-adjusted life years (DALYs) in phase 1; and identify the list of risk factors and determine risk-attributable burdens in phase 2.

Methods: The Malaysian Burden of Disease (MBOD) Study adopts the Global Burden of Disease Study approach, using various metrics to quantify health loss related to specific diseases, injuries, and risk factors. These metrics include deaths, YLLs, YLDs, and DALYs, which are calculated in terms of counts, age-specific rates, and all-age rates. In addition, this MBOD Study calculates risk-attributable deaths, YLLs, YLDs, and DALYs for all relevant risk factors. This study also conducts focus group discussions to develop the lists of diseases and injuries as well as risk factors.

Results: By December 2024, we had successfully completed the focus group discussions, which led to the development of an updated and comprehensive list of diseases and injuries. Furthermore, mortality data collection is complete, and the calculation of YLLs is currently in progress. The YLD calculation is expected to conclude by the end of 2025. While phase 1 is underway, phase 2, which addresses risk factor estimation, is scheduled for completion in mid-2026.

Conclusions: This MBOD Study offers a comprehensive and current framework for assessing the burden of disease in Malaysia, with continuous improvement initiatives to enhance the list of diseases and injuries and refine the methodology for more accurate estimation and risk factor analysis.

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KEYWORDS

Malaysia; disease burden; disability-adjusted life years; risk factors; population health

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Introduction

Background

The Global Burden of Disease (GBD) Study uses published and publicly accessible data to provide an extensive evaluation of incidence, prevalence, and mortality for a wide range of diseases [1,2]. Disability-adjusted life years (DALYs) quantify healthy life lost due to diseases and injuries, combining mortality, measured as years of life lost (YLLs), and morbidity, measured as years lived with disability (YLDs) [3]. The GBD Study applies a standardized framework that enables national-level quantification and assessment of the burden of disease across more than 200 countries [3]. However, the GBD Study relies primarily on global modeling methods, with limited use of localized data, which may impact the granularity and accuracy of its findings for individual countries.

The Malaysian Burden of Disease (MBOD) project was initiated by the Institute for Public Health, Ministry of Health Malaysia, to close this gap. The first estimates were produced for the year 2000, and the most recent completed MBOD Study covers the year 2019. The project's goal is to evaluate the burden of disease at the national level while providing a regional perspective on health trends and epidemiological shifts [4-6].

Among the most common causes of disease burden among Malaysians, noncommunicable diseases (NCDs) continue to be a major public health concern [7]. Since 2021, COVID-19 has also emerged as a major contributor to the national burden of disease [3], which highlights the need for up-to-date data. However, no recent study has been conducted to assess the impacts of COVID-19 and NCDs burden trends.

Knowledge of the burden of disease is important for developing relevant and effective public health policies, particularly in a pandemic-impacted health system. Current and detailed information on disease burden is critical for identifying emerging health concerns and highlighting diseases that cause the most fatalities and preventable deaths. The MBOD project has made significant progress in its methodologies and scope over the past 2 decades [8-10]. The availability and granularity of data have substantially increased, and the list of diseases and injuries assessed has expanded, providing more detailed insights [5]. Long-standing gaps in the accuracy of mortality statistics have been successfully addressed by methodological improvements such as the use of verbal autopsy data and the redistribution of ill-defined causes of death [5,11]. Moreover, the MBOD Study continues to generate findings that are highly relevant for shaping public health policies and decision-making by integrating localized data and highlighting risk-attributable burden. Importantly, this protocol represents a significant advancement in Malaysia, as it is the first framework to include calculations of risk-attributable burden in MBOD studies.

The comparative risk assessment tool, developed by the GBD project, is a useful way of quantifying the burden of disease attributable to various risk factors [1,12]. By using standardized and internationally comparable measurements, the MBOD project's inclusion of components on risk factors, mortality, and morbidity fills important knowledge gaps. This comprehensive approach not only strengthens the MBOD research protocol but also allows for more accurate estimations of Malaysia's burden of disease. The MBOD Study's findings on risk factors provide insights into the modifiable risk factors contributing to health loss, helping to identify the determinants of mortality and morbidity and providing a road map for targeted public health interventions and resource allocation.

Objectives

This study aims to provide a comprehensive and up-to-date assessment of the burden of disease in Malaysia for the year 2023. The primary objective will be addressed in 2 phases: phase 1 focuses on revising the list of diseases and injuries and estimating YLLs, YLDs, and DALYs, while phase 2 aims to identify risk factors and determine their attributable burdens.

Methods

Overview

The study methodology involves selecting diseases, injuries, and risk factors, followed by estimating deaths, YLLs, YLDs, and DALYs from diseases and injuries as well as risk-attributable deaths, YLLs, YLDs, and DALYs. All metrics are calculated by age and sex across 18 age groups (from birth to 80 years or older) and are disaggregated by male individuals, female individuals, and both sexes combined. These metrics are calculated in counts, age-specific rates, and all-age rates focusing on data for the year 2023. An overview of the study workflow is presented in Figure 1. Phase 1 focuses on estimating mortality and morbidity. This involves identifying the relevant list of diseases and injuries as well as gathering and analyzing data. Phase 2 will focus on risk factor analysis. This includes identifying the list of risk factors, collecting exposure data, and performing data analysis to determine risk-attributable burden.

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Figure 1. Flowchart of the study.

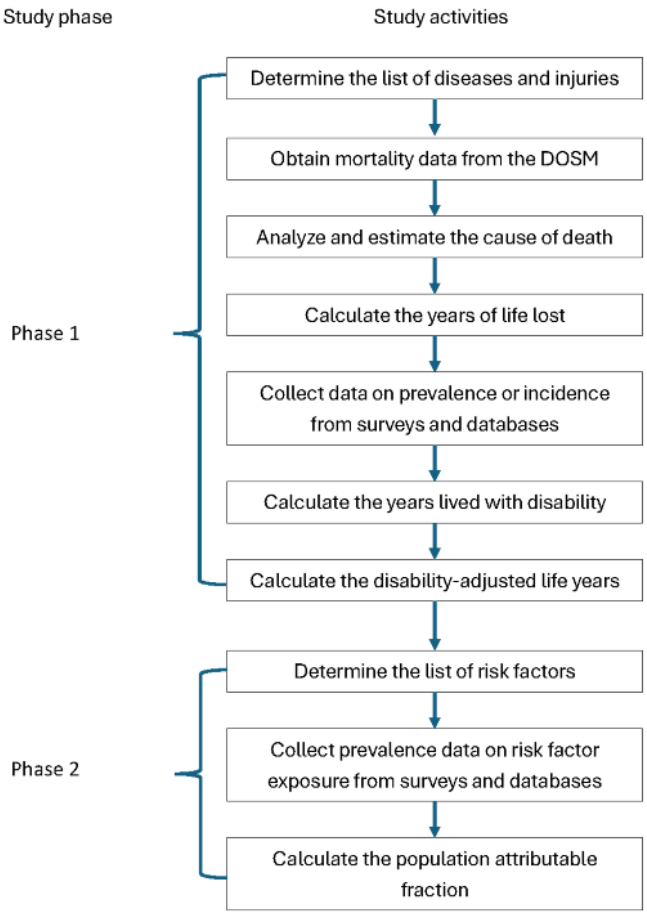

Determination of Reference Year (2023)

The year 2023 was chosen because updated prevalence data from the National Health and Morbidity Survey conducted that year [13] are available and essential for our calculations. In addition, following the stabilization of data after several years of the COVID-19 pandemic, 2023 serves as a reliable baseline for forecasting future trends. Furthermore, this study integrates newly available data sources and applies refined methodological approaches for mortality estimation.

Determination of the Lists of Diseases, Injuries, and Risk Factors to be Included in the Study

Overview

The lists of diseases, injuries, and risk factors for the MBOD Study are guided by the GBD Study framework. The GBD disease and injury list is organized into 4 hierarchical levels: level 1 includes 3 broad categories (communicable, maternal, neonatal, and nutritional diseases; NCDs; and injuries); level 2 further categorizes these into 22 categories; and level 3 and level 4 comprise 174 and 301 specific causes, respectively. Across all levels, there are a total of 369 diseases and injuries [2]. The GBD risk factor list is also structured into 4 levels: level 1 includes behavioral, environmental and occupational, and metabolic categories, followed by level 2 with 20 individual risks or clusters, level 3 with 52 risk factors or clusters, and level 4 with 69 specific risk factors. Across all levels, there are a total of 87 risk factors [12].

Focus Group Discussions

To adapt the GBD lists to the Malaysian context, focus group discussions are conducted to evaluate the relevance of diseases, injuries, and risk factors, along with the availability of associated data. Focus group discussions have been chosen as the data collection method because they allow for interactivity between participants in focused discussions guided by researchers [14]. This approach can generate critical insights for clinicians, experts, and policymakers regarding the importance of diseases, injuries, and risk factors relevant to the local context.

Purposeful sampling is used to select individuals based on their capacity to provide relevant information in response to the research questions. Participants are selected based on their expertise and experience in related disciplines. One expert is selected from each disease group or risk factor category to ensure representation and comprehensive input across all relevant areas. These experts, including specialists, consultants, and subject matter experts, are invited to contribute their perspectives. They are contacted by letter and follow-up telephone calls, with a clear explanation of the study's objectives provided to potential participants. No further inclusion or exclusion criteria are applied.

To develop a comprehensive and contextually relevant list of diseases and injuries for the MBOD Study, 10 focus group discussions were carried out to discuss the relevance of diseases and the availability of data for each condition. Each group consisted of 7 to 12 experts [14], including disease burden

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experts, disease experts, and researchers. These sessions were moderated by an experienced researcher who facilitated discussions aimed at gathering opinions and recommendations and ultimately achieving consensus on the inclusion and prioritization of diseases and injuries for the MBOD Study. During these focus group discussions, participants were asked to evaluate each disease or injury based on several criteria, including the probable magnitude of the disease or injury (≥0.01%) as a cause of death, the level of health services associated with the disease or injury, the public health importance of the disease or injury in the local context, the availability of morbidity data, and the relevance of that specific disease or injury to policy in Malaysia. In addition, the availability of local data sources was reviewed to ensure that the disease or injury could be reliably quantified and used in the calculations.

For the selection of the risk factor list, 3 additional focus group discussions will be organized to discuss the relevance of, and data availability for, each risk factor. Participants will be grouped by their field of expertise and according to level 1 risk factor categories. Each focus group comprises 7 to 12 participants. The sessions are moderated by experienced researchers who guide the discussions. The discussions aim to gather opinions and recommendations and ultimately reach an agreement on developing the risk factor list for the MBOD Study. The inclusion of risk factors is prioritized based on nationwide relevance, clarity of identification without excessive specificity, availability of evidence linking them to disease causation, accessibility of information on their distribution across the population, and their modifiability. This structured methodology ensures that the final lists of diseases, injuries, and risk factors are both scientifically rigorous and contextually relevant for the MBOD Study.

Calculation of YLLs

Mortality data from January to December 2023 will be included in this study. Data on deaths, including sex, age, and cause of death, will be obtained from the Department of Statistics Malaysia (DOSM). All data provided by the DOSM will have personal identifiers removed to comply with Malaysia's Personal Data Protection Act.

Improvements to Cause-of-Death Data Estimation in the MBOD Study 2023

Improvements in Redistribution of Nonmedically Certified Deaths

In the MBOD Study 2023, we will make improvements to the redistribution process for nonmedically certified deaths to enhance the accuracy of mortality data. It is important to note that nonmedically certified deaths do not capture all diseases and injuries; only certain causes are included. To address this limitation, we will apply proportions derived from medically certified deaths to redistribute causes of nonmedically certified death cases that lack specificity. In addition, we will apply cause-specific mortality fraction obtained from verbal autopsy to ensure more accurate representation of the causes of death. Subsequently, age group distribution and the envelope adjustment technique will be applied to the nonmedically certified death data. The purpose of these procedures is to ensure that the total number of deaths is consistent across specific sex and age groups.

Expansion of Disease and Injury List and Inclusion of COVID-19 Estimates

In the MBOD Study 2023, the list of diseases and injuries included in the estimating framework will be expanded and revised. Adding conditions and diseases not previously included allows for a more complete evaluation of mortality and morbidity. The selection of diseases and injuries is based on international guidelines and local health goals. In addition, COVID-19 will be included in the estimating procedure because of its significant impact on population health, highlighting the pandemic's effect on recent death trends and ensuring that this study is current and relevant. Adding COVID-19–specific estimates and expanding the disease and injury list enhances the accuracy and comprehensiveness of Malaysia's burden of disease estimates.

Steps for Determining Causes of Death

Mortality data will be classified into 2 categories: medically certified deaths and nonmedically certified deaths. Medically certified deaths occur in medical facilities, and the cause of death is certified by the attending physician. Nonmedically certified deaths occur outside of medical facilities and are reported by the family of the deceased to the local police, who provide nonexpert opinions on the cause of death.

To enhance the quality of mortality data, we will use cause-specific mortality fraction for nonmedically certified deaths, derived from verbal autopsy, to reduce the number of ill-defined and nonspecific causes of death [9]. When there is insufficient information to determine the exact cause of death, we will categorize the causes of death under "garbage codes." It should be noted, however, that garbage codes compromise the usefulness of cause-of-death information from a policy perspective. To address this, MBOD experts will analyze the garbage codes listed by the World Health Organization and GBD studies [5]. Subsequently, ill-defined causes of death will undergo reclassification, and redistribution methods will be used to refine the data. The analysis will calculate the number of deaths attributed to each disease, disaggregated by age and sex groups.

Sensitivity and Uncertainty Analyses

Overview

To verify the stability and robustness of the results, a sensitivity analysis will be conducted by comparing the distribution of mortality data with and without nonmedically certified deaths. This analysis aims to ensure that the redistribution process produces cause-of-death patterns consistent with those observed in medically certified deaths across the major disease categories.

The same technique used in the GBD Study will be applied in this study to quantify uncertainty. Monte Carlo simulation will be performed using R software (R Foundation for Statistical Computing). Final estimates will be generated as the average estimate of 1000 samples. The 95% uncertainty interval will be

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derived based on the 2.5th and 97.5th percentiles of the bit-sorted distribution of 1000 samples.

Steps for Calculating YLLs

Relevant R packages will be used to calculate deaths and YLLs. The R packages that will be used in the MBOD Study 2023 include *dplyr* and *tidyr* for data manipulation, *readxl* and *openxlsx* to read the data obtained from the DOSM, and *ggplot2* for generating data visualizations. The calculation of premature mortality in Malaysia for 2023 will follow the methodologies developed by Murray and Lopez [15] for the GBD Study to compute YLLs [2]. YLLs will be determined by multiplying the number of deaths attributed to a specific disease by the remaining life expectancy for the corresponding age and sex group. Life expectancy data will be obtained from DOSM life tables.

Calculation of YLDs

Sources of Morbidity Data

Prevalence estimates for each disease and injury will be identified from all potential data sources (eg, national surveys, surveillance reports, census records, monitoring programs, disease registries, and hospitalization records) and assessed for comparability, relevance, representativeness, currency, accuracy, creditability, and accessibility or timeliness. A data quality assessment matrix will be used to evaluate all morbidity data sources. This matrix is modeled on the Australian Burden of Disease Study, which prioritizes the use of the highest-quality data available [16]. In instances where local data are lacking, data from meta-analyses, systematic reviews, or the Global Health Data Exchange (created and hosted by the Institute for Health Metrics and Evaluation) using statistical modeling will be used, with DisMod II (version 1.04) applied to re-estimate local relevance.

Steps for Calculating YLDs

YLDs represent the impact of nonfatal diseases and injuries. Prevalence estimates for each disease and injury, which include a breakdown of the severity proportion and percentage contributing to the sequelae, will be calculated. The YLD calculation will be based on this prevalence and a set of disability weights for each condition obtained from the GBD 2019 Supplement [2]. Data sources for YLD calculations will include locally available surveys and hospital discharge records. When relevant data sources are not available, the Global Health Data Exchange and more specifically the GBD Study results will be used to obtain the incidence or prevalence statistics. These data will then be processed using DisMod II to generate prevalence estimates by taking into account factors such as incidence, prevalence, remission, case fatality, duration, mortality, and relative risk (RR) mortality, based on a limited amount of local data [17].

Microsoft Excel and relevant R packages will be used to calculate YLDs. In addition to the previously mentioned R packages, *lubridate* will be used to handle time calculations for YLD data. The YLD will be determined by multiplying the prevalence of each disease sequela by its disability weight [15], stratified by age and sex. The total YLD for each disease and injury will be derived by summing the YLDs from all sequelae associated with that disease or injury.

Calculation of DALYs

DALYs provide a comprehensive measure of the burden of disease and injury by combining YLLs and YLDs. For each disease and injury, the DALY will be calculated as the sum of YLL and YLD. The overall burden of disease will then be determined by aggregating DALYs across all diseases. Calculations will be performed using relevant R packages.

Calculation of Risk-Attributable Burden

Sources of Risk Factor Prevalence Data

Prevalence estimates for each risk factor exposure will be identified from all potential data sources (eg, national surveys, surveillance reports, census records, and monitoring programs) and assessed for comparability, relevance, representativeness, currency, accuracy, creditability, and accessibility or timeliness. A data quality assessment matrix will be used to evaluate all sources. This matrix is modeled on the Australian Burden of Disease Study, which prioritizes the use of the highest-quality data available [16].

Steps for Calculating Risk-Attributable Burden

In this study, linked diseases are conditions from the disease list that are associated with known risk factors. We will adopt the relevant linked diseases from the GBD Study 2019 framework [12] and review the linked diseases corresponding to selected risk factors to ensure local relevance. Malaysia-specific exposure distributions and contextually relevant RR estimates from local cohort studies, surveys, or administrative datasets will be prioritized. In the absence of local RR data, we will rely on global estimates while recognizing the limitations and potential variability in risk-outcome relationships.

GBD-linked risk-outcome pairs from the GBD Study will be adapted as the foundational framework. The list of risk factors will be refined to reflect Malaysia-specific exposures and epidemiological patterns; for example, dietary risk will be adapted to include high palm oil consumption [18]. To ensure local relevance and modification, the selection of risk-attributable burdens will be discussed in focus group discussions with expert consultants and stakeholders to link disease risk and outcome.

To estimate the attributable burden for each risk-outcome pair, the GBD methodology requires four key inputs: (1) the burden estimate for the outcome (eg, number of deaths, YLL, and DALY), (2) spatially and temporally resolved exposure estimates for the risk factor, (3) the counterfactual or theoretical minimum risk exposure level (TMREL), and (4) the RR or exposure-response relationship for the outcome relative to the TMREL [12]. We will calculate the population attributable fraction (PAF), which represents the proportion of the outcome that, for a given population and year, would be eliminated if the risk factor were reduced to the TMREL. The risk-attributable burden will then be estimated for each risk-outcome pair by age group and sex. Relevant R packages will be used to calculate the PAF.

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Uncertainty will be addressed using interval estimates. Specifically, 95% uncertainty intervals for prevalence data and RR values will be generated through Monte Carlo simulation.

Ethical Considerations

This study was approved by the Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR ID-24-01855-INU). It involves secondary data analysis, with raw mortality and morbidity data obtained with written permission from the director of the DOSM, the Ministry of Health Malaysia, and through various surveys. All researchers adhere to the principles of the Declaration of Helsinki and the Malaysian Good Clinical Practice Guidelines, where applicable. This study complies with Malaysia's Personal Data Protection Act, with all data obtained in deidentified form.

Results

The MBOD Study 2023 consists of 2 phases: phase 1 focuses on mortality and morbidity estimation, and phase 2 focuses on risk factor estimation. As of December 2024, phase 1 is underway, with phase 2 scheduled for completion in mid-2026. Focus group discussions with clinicians (19/37, 51%) and policymakers (18/37, 49%) have been completed, leading to the development of an updated list of diseases and injuries. Mortality data collection has also been completed, and the calculation of YLLs is currently in progress. Phase 1, including YLD calculation, is expected to be completed by the end of 2025, while phase 2 (risk factor estimation) is scheduled to begin thereafter and conclude by mid-2026.

Discussion

Summary

This is the sixth MBOD Study since the first one for the year 2000 and marks a significant milestone as the first to provide a comprehensive analysis of both disease burden and risk factors. It addresses a major knowledge gap by using standardized and internationally comparable metrics to analyze the burden of disease, encompassing premature death, morbidity and disability, and risk factors, that contributes to poor health in the Malaysian population.

The MBOD Study has provided regular updates on population health in Malaysia since its first publication. With each subsequent cycle, both the methodology and data sources used to estimate the burden of disease have been substantially updated. For the year 2000, mortality and morbidity estimates were reported for 103 diseases and injuries. By the most recent cycle (2015-2017), these estimates had expanded to include 113 diseases and injuries [6]. Another MBOD project is currently in progress, using new disease and injury list for the year 2019, reflecting a more comprehensive and locally relevant representation of health conditions in Malaysia.

Preliminary findings from our study seem consistent with trends observed in prior MBOD cycles, where NCDs have been the dominant contributors to DALYs since the early 2000s. Early estimates suggest that the increasing burden of cardiovascular diseases, diabetes, and cancers is likely to remain the primary driver of the overall disease burden. These patterns align with global trends reported by the GBD Study [3], in which NCDs dominate the health burden in middle-income countries, including Indonesia [19]. A similar trend is seen across other Association of Southeast Asian Nations (ASEAN) countries, where cardiovascular disease is the fastest growing NCD [20]. Among ASEAN countries, Malaysia has the highest age-standardized prevalence rate of cardiovascular diseases, followed by Indonesia, while Singapore has the lowest rate. However, Malaysia's disease burden pattern also reflects its unique epidemiological transition: although both communicable diseases and injuries are declining, they remain significant contributors to the overall burden [6]. Ischemic heart disease, stroke, and diabetes remain the leading cause of DALYs, while lower respiratory infection has risen in rank compared to the 2015-2017 MBOD estimates, indicating a worsening local trend compared to the global situation [21]. Data from the National Health and Morbidity Survey further reinforce these findings, showing increasing prevalence of obesity, hypertension, and diabetes in Malaysia [13]. These patterns strongly correlate with our preliminary findings on the rising burden of NCDs and highlight the urgency of national action.

Although other countries have reported on the disease burden attributable to various risk factors [22], no study has assessed an extensive list of risk factors applicable to Malaysia or explored the full extent of disease burden attributable to these factors. Only a few studies in Malaysia have quantified the national disease burden attributable to specific risk factors within an integrated framework; for instance, tobacco smoking and excess weight are established risk factors for cancer [23], while overweight and obesity contribute substantially to the overall disease burden [24]. Our study addresses this gap by incorporating a comprehensive set of risk factors and quantifying their associated health burden, thereby providing a more complete picture of the burden of disease in Malaysia.

In addition, the inclusion of COVID-19 and its attributable burden represents a novel contribution, distinguishing this study from previous MBOD reports. Although mortality estimates for COVID-19 have been reported by several sources [25], no previous publications have specifically quantified its morbidity estimates for Malaysia. While the GBD Study 2021 provides global estimates of the COVID-19 burden [3], local DALY estimates due to COVID-19 have not been previously published in Malaysia. This study, for the first time, expands the list of diseases and injuries, incorporates COVID-19, and provides national-level estimates of disease burden attributable to risk factors. By integrating COVID-19 into the analysis, this study offers a more comprehensive understanding of Malaysia's health priorities in the postpandemic context and underscores the need for resilient, data-driven public health strategies moving forward.

This study demonstrates several strengths that substantially enhance its quality and relevance. The expanded disease list provides a more complete assessment of health conditions, accurately reflecting Malaysia-specific health challenges such as tropical diseases [26]. The study also enhances mortality estimation, particularly in refining data distribution for nonmedically certified deaths. In addition, the study optimizes local data quality through expert consultations and the use of

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national surveys, administrative data, and disease registry data, ensuring the use of the highest-quality, most representative Malaysian data for estimating the burden of disease and risk factors.

Limitations

This study has several limitations that should be considered for balanced interpretation of the findings. First, regarding mortality data, only two-thirds of the deaths were medically certified, necessitating redistribution methods for nonmedically certified deaths and deaths coded under garbage codes. Although these methods are standardized within the burden of disease framework, they introduce a degree of uncertainty in cause-of-death estimation. Continued efforts to reduce the proportion of garbage codes and increase the use of verbal autopsy are essential to improve data quality and the accuracy of cause-of-death estimation.

Second, the estimation of YLDs relies heavily on data from national surveys, hospital records, and disease registries, which are often incomplete or outdated in the Malaysian context. As a result, some disease prevalence estimates depend on data extrapolated from the literature or small-scale studies rather than directly observed data. This may limit the accuracy and representativeness of the YLD estimates, particularly for conditions with limited reporting systems.

Third, when locally available data are unavailable, such as for the prevalence of certain diseases or the proportions of disease severity used in YLD estimations, this study relies on information from the GBD Study or regional estimates. Similarly, in contexts where local evidence is limited, we will adopt TMREL and RR estimates from the GBD Study for calculating PAFs. We acknowledge that incorporating more local data would enhance the accuracy of the results. To address data gaps and enhance internal consistency, DisMod II will be used to synthesize available local and international data to produce disease prevalence and incidence rates. Although this method improves comparability and coherence, the estimates remain sensitive to the assumptions and quality of the input data.

In addition, this study excluded post–COVID-19 condition from the current COVID-19 morbidity (YLD) estimates. While the analysis captures the acute disease burden, it does not account for post–COVID-19 condition health impacts experienced by individuals after recovery. Future studies should incorporate this component using updated disability weights from the GBD Study 2021 and, where available, Malaysia-specific clinical data to more comprehensively estimate the COVID-19 burden.

Finally, due to the limited variables available in this study, DALYs will only be stratified by sex and age groups. Future research could explore DALYs disaggregated by socioeconomic status and ethnicity, which would align with the United Nations' Sustainable Development Goal (SDG) 10 of reducing inequalities.

Implications of This Study

The findings of this study are expected to have far-reaching implications for health policy, public health planning, and research in Malaysia. The results will guide policymakers and program managers in prioritizing and strategizing health initiatives to strengthen the nation's health care system, ultimately enhancing the health and productivity of the population [27]. By providing critical insights into the burden of disease, particularly for NCDs, the MBOD Study 2023 will inform the development of targeted interventions aimed at reducing preventable disease burdens, thereby contributing to the improvement of population health outcomes. Moreover, the data-driven approach supports the Malaysia National Strategic Plan by providing actionable data to strengthen health system resilience and guide resource allocation [28]. At the global level, this study aligns with the SDGs, particularly SDG 3, by contributing to efforts to reduce premature mortality and combat NCDs [29].

The analysis of risk-attributable burden is particularly significant, as it sheds light on the social and economic implications of disease in Malaysia. Understanding these risk factors enables more informed decision-making, prioritization of public health initiatives, and optimization of budget planning to ensure cost-effectiveness. Furthermore, this study provides evidence for targeted interventions in areas such as nutrition, physical activity, and mental health by measuring the impact of diseases and associated risk factors. It also contributes to addressing the economic burden of health care costs and reducing productivity losses. In addition, evaluating and comparing common health risk factors enables more focused, targeted public interventions aimed at the primordial and primary prevention of disease, fostering a more proactive and long-lasting approach to population health improvement [30,31].

From a methodological perspective, this study provides more accurate local estimates tailored to Malaysia's unique context. It incorporates region-specific health priorities and underrepresented tropical diseases, ensuring that the health data are culturally relevant and applicable. Enhanced methodologies and harmonized datasets generate accurate mortality and morbidity estimates, which are essential for evaluating current health initiatives and determining priority areas for intervention. The expanded disease list, which takes into consideration Malaysia's unique health challenges, ensures that the study remains relevant while aligning with international best practices. Finally, the study establishes a strong foundation for future research, fostering collaborations to address emerging health challenges and improve Malaysia's overall health landscape.

Conclusions

The MBOD Study 2023 marks a pivotal step forward in understanding Malaysia's health challenges. By expanding the disease list and incorporating comprehensive risk factor analysis for the first time, this study delivers a nuanced perspective on mortality, morbidity, and modifiable health determinants. These advancements not only address the limitations of previous iterations but also enhance the accuracy of health data, ensuring that the data reflect Malaysia's unique health profile, including underrepresented tropical diseases. The refined methodologies and integration of diverse datasets provide a holistic view of population health, enabling stronger evidence-based monitoring of trends, evaluation of interventions, and guidance for future

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research. This study establishes a vital benchmark for continuous health assessments and supports Malaysia's commitment to improving population health outcomes and achieving sustainable health system resilience. Moving forward, it is essential to be provide annual updates on mortality data. However, the current plan is to produce the MBOD report every 4 years, in alignment with the publication of the National Health and Morbidity Survey on NCDs, to ensure the use of up-to-date prevalence data for YLD calculations.

Acknowledgments

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Data Availability

The datasets generated and analyzed during this study are not publicly available due to data protection regulations but are available from the Department of Statistics Malaysia on reasonable request and with the necessary permissions.

Authors' Contributions

WFK contributed to the conception of the study, formulated the research aims, acquired financial support for the project, and wrote the original draft. NA, SWT, KSW, NHN, and NDR assisted with data interpretation and preparation of the original draft. SSG and MAO contributed to validating the study methods. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ASEAN: Association of Southeast Asian Nations

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DALY: disability-adjusted life year
DOSM: Department of Statistics Malaysia
GBD: Global Burden of Disease
MBOD: Malaysian Burden of Disease
NCD: noncommunicable disease
PAF: population attributable fraction
RR: relative risk
SDG: Sustainable Development Goal
TMREL: theoretical minimum risk exposure level
YLD: year lived with disability
YLL: year of life lost

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Improving Work-Related Challenges in Psychiatric-Psychosomatic Clinics: Study Protocol for an Internet-Based Needs Assessment and Co-Design of a Training

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Abstract

Background: Medical, psychiatric-psychosomatic facilities are confronted with a variety of daily challenges that affect working conditions, the mental health of employees, and the quality of patient care. This project focuses on the work-related challenges faced by health care professionals in psychiatric-psychosomatic clinics in Germany.

Objective: The aim of the current research is to investigate the interactions between individuals and their social environment, identify psychological and organizational challenges and job demands, and use these findings to inform the development of a participatory, evidence-based intervention.

Methods: This 2-phase research is grounded in the job demands-resources model (JD-R). Study phase (needs assessment) uses a cross-sectional online survey with health care professionals in German psychiatric-psychosomatic clinics to assess job demands, resources, and outcomes in a target sample of *N*=600 participants (power analysis). Study phase 2 (co-design of a training) involves co-creatively designing an intervention based on survey findings through participatory workshops with at least *N*=20 participants. Analyses include regression and moderation tests (SPSS; IBM Corporation) and qualitative data analysis to co-design training.

Results: The recruitment of participants is planned to be finished by December 2025. The co-designing of workshops (phase 2) will be started in February 2026. As this is a study protocol, results are not available yet.

Conclusion: This current research examines the work-related challenges faced by health care professionals in psychiatric-psychosomatic clinics. It is expected that burnout, engagement, and psychological safety will likely emerge as central mediating and moderating variables. As the findings of phase 1 serve as a basis for the development of an intervention, this research seeks to improve the well-being of health care professionals in psychiatric-psychosomatic institutions sustainably.

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KEYWORDS

health care providers; patient safety; occupational well-being; prevention & control; psychology

Introduction

Background

Medical, psychiatric-psychosomatic clinics face a multitude of daily challenges, including digital and technological changes [1-4]. With patient safety as the top priority [3-5], health care professionals are under significant pressure, leading to numerous reports of burnout, general job dissatisfaction, and intentions to quit [3]. This exacerbates the existing shortage of specialists in the German health care system [6]. Despite ongoing organizational discussions about systemic changes, the situation for health care professionals is improving only slowly or even stagnating [1,7]. Thus, attention must focus on the individual and team levels to enact meaningful changes.

Due to the unique emotional and psychological demands of treating patients with complex mental health needs, combined with the lack of focus in previous studies, it is essential to understand and support health care professionals better. This is also necessary to ensure high-quality care for patients with mental health disorders and create a work environment where health care professionals feel recognized and cared for [8]. To support all people involved to become and remain empowered by medical internet research to make effective, informed decisions, take control of their health and well-being, and live happier and healthier lives, this research takes up the research

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gaps and will perform a needs assessment and co-design of a training. The current paper describes the protocol and study design, including its practical and theoretical backgrounds.

Context and Relevance of the Research

The German health care system, as an example for many others in different countries around the world, is under enormous pressure: health is considered to be one of the highest human goods, but economic constraints, skills shortage, and demographic change are challenging [9]. Accordingly, the health care system is subject to a high level of attention and therefore also high pressure [9]. In Germany, the health care system operates within a tightly regulated economic framework [3], which is incorporated into decisions about changes. In its complexity and its embedding in diverse social contexts (including scientific and technological progress), the health care system is subject to increasingly rapid change [3]. Furthermore, the complexity of the health care system necessarily creates many contradictions in the system, which are: on the team level, between the individual employees and their professional (interests) groups and between the political and corporatist system levels (the level of self-administration and associations [3]).

Authors from various disciplines, like politics, business, public health, and medicine, have already pointed out individual issues and problems in the health care system. It has been shown that changes within and between the levels are possible and necessary [3,10]. These problems, requirements, and perspectives relate to both inpatient and outpatient care within the German health care system.

Hospitals are a central pillar of the health care system. The complexity of the health care system is represented in a concentrated (perhaps even potentiated) form in them: staff from a wide variety of disciplines with different levels of seniority and training have to provide round-the-clock (and often emergency) care for a wide variety of patients and work together to this end [11]. The complexity and resulting problems of the health care system turn hospitals into a so-called “high-risk organizations” [3]. Dorn [12] views the hospital as a complex organization in which the different functional, organizational, and professional logics collide. The resulting interrelationships produce organizational conflicts and uncertainties.

Psychiatric-psychosomatic clinics are an integral part of this health care system. The collective term covers clinics that treat patients with psychiatric diagnoses. Some clinics specialize in certain clinical conditions, others in a certain clientele or catchment area (due to care mandates from the federal states). They vary in size (number of patients, employees, beds, and wards) [8]. Clinics are usually structured similarly to hospitals that primarily treat physical illnesses and are also grouped together with them in scientific studies [10]. The problems appear somewhat similar: the care index is too low due to staff shortages and financial reasons or reasons at the organizational level and employee satisfaction is reduced [1].

There are some crucial and aggravating factors in psychiatric-psychosomatic clinics that distinguish them from other inpatient facilities that specialize more in physical health problems: first, the relative recency of the branch. This is due to a prolonged stigmatization that has persisted over time and continues to exist in a weaker form. The product is the stigmatization of mental illness and the underplaying of mental illness. Second, the type of diagnoses that are treated there: the treatment of mental disorders is different from that of physical disorders. In particular, it is more difficult to determine whether a previous treatment had negative side effects or whether it has been applied successfully and correctly [10]. It is only possible to determine relatively roughly whether a specific procedure was wrong or inappropriate in a specific situation with a specific patient. The treatment guidelines for certain clinical pictures or a certain therapy school-specific procedure leave a relatively large amount of degree of freedom [8].

The work in psychiatric-psychosomatic clinics is organized in a team of different professions in which different functions, organizational, and professional logics collide [12]. These interdisciplinary conditions of multiprofessional teams [12] create challenges like communication problems between the different professional groups, role ambiguity, as well as hierarchical differences [12].

Health care professionals in psychiatric-psychosomatic institutions are exposed to numerous risks and challenges [13,14], which lead to health problems and illnesses, such as burnout [15-17]. As a consequence, there is frequent staff turnover and high fluctuation between wards [10]. Job satisfaction may also be reduced [1]. Psychiatric-psychosomatic facilities face a variety of daily challenges that impact working conditions, employee mental health, and the quality of patient care. With patient safety as a top priority, health care professionals are under considerable pressure, often leading to burnout, job dissatisfaction, and the intention to change careers. This is exacerbating the already existing workforce shortage in the German health care system. Despite ongoing discussions about social systems, ranging in complexity and dynamically changing over time, and systemic changes, the situation for health care professionals is only slowly improving. There are unique problems in psychiatric care: distinct structures and processes in psychiatric settings complicate the direct application of solutions from other health care domains.

Collaborative, Co-Creative Approaches in Times of Internet-Based Medical Services

Research into the collaborative aspects of digital health interventions could potentially address various challenges within the health care system and related services in an increasingly digitalized world. Specifically, investigating effective strategies for including researchers, health care professionals, developers, and target groups (such as individuals with disabilities, patients, or clients considered as co-creators) may help reduce costs, enhance user responsibility and engagement, and improve the likelihood of successful implementation and sustainability in practice. This is particularly relevant when developing, marketing, and implementing new technologies [4]. Collaborative approaches in research and practice have been used over the past century [18].

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The dissolution of barriers between researchers and target groups can be traced back to Lewin's use of Action Research in 1946 [3,6,10,19,20]. In Action Research, the researcher is also a member of the target group and takes part in evaluating an intervention (or an action, as termed by Lewin). Both researchers and target groups, such as health care professionals, engage in a process of reflection to test new actions; planning how to test the new action, acting, and finding results about the action.

Another example of the partnership of researchers and target groups is Kristen Nygaard's work in 1972 in Norway [21]. Nygard was a computer scientist tasked with developing training material on workplace information technology (IT) systems. To develop the material, Nygaard recruited 4 local union shops geographically spread over southern Norway. With his team, Nygaard developed a textbook on "Data processing, planning and control," which allowed employees to leverage IT systems; Nygaard's work is regarded as the precursor to participatory approaches [18].

Different terminologies and definitions for collaborative (research) practices also arose, relating to technology and digitalization, such as the above-described co-creation, co-design, and participatory approaches. A reliable management of collaboration is needed, aiming for improving social equality and participation by using technology [4]. The involvement of health care professionals in psychiatric-psychosomatic institutions requires recognizing them as valuable individuals with unique needs, in addition to generic requirements. Their involvement and responsibilities require potential bridges, such as supporting individuals to "translate" for them or technology to aid communication and interaction. As digital demands are faced in the workplace, their efficient use could help this population in times of staff shortage, increased diversity, and workplace requirements [18].

Internet-based, technological, and digital solutions range from electronic patient-reported outcome measures to eHealth interventions, including online interventions and apps empowering individuals with topics like healthy lifestyles or safe communication and shared decision making [22,23], facilitating group psychotherapy from home [24,25], or monitoring biomedical markers and getting biofeedback [26-28]. Digital solutions also involve technological support systems, like digital psychotherapy for mental health disorders, robot systems for individuals with dementia, and exoskeletons to help people who lost their legs walk again. While there are many advantages, adoption might be burdensome, or their use might be hampered. Thus, health care professionals in psychiatric-psychosomatic institutions need to know about how to use these options and prevent related problems; otherwise, they do not understand their potential, do not start with it, or may drop out quickly. Thus, co-creation and co-design can make a significant difference with its actual impact, including effectiveness [18].

Previous Evidence

Due to the unique emotional and psychological stresses associated with treating patients with complex mental illnesses, it is crucial to examine the working conditions of health care professionals in this field in more detail. Previous studies [29,30] have addressed specific challenges in psychiatric-psychosomatic clinics, but these have often been limited in scope or focus. While the workloads of nursing staff are generally considered to be relatively well documented [29,30], little is known about nursing staff in inpatient psychiatric health and nursing care [31].

Another challenge for research is that social complexity within the health care system, including the use of technology adoptions, leads to contradictions, organizational tensions, and uncertainty [12]. Despite this, there is currently a lack of research that examines the team level—the space between individual employees, their professional groups (nurses, psychologists, and physicians), and the broader political and organizational systems [3]. Yet, clinical work is typically structured around teams, which brings specific challenges for interprofessional collaboration and coordination among staff. Due to the great pressure and risk to job satisfaction and psychological safety, concepts such as "just culture" have been introduced to foster a supportive work environment [3].

A systematic overview of the current literature shows that various strategies and approaches to psychological safety exist [3]. Above all, the responsibility of leadership is discussed [3]. At this stage, for example, the case is being made for a safety culture for the entire system, including all individuals, professional groups, teams, organizations, associations, and the health care system [10]. Previous research has identified the challenges with technology and opportunities for quality improvement, research, and policy development [4]. Despite these opportunities to support health care professionals in understanding their performance, engaging in reflective practice, and enhancing professional and workplace learning, there is only limited systematic research [4]. At this stage, approaches are being pursued that no longer focus solely on patient safety but concentrate more on a patient- and employee-oriented risk and safety culture. Psychological safety is fundamental to all these aspects [3,32].

Although promising approaches exist, few have been implemented concretely in the specific context of psychiatric-psychosomatic clinics, highlighting the need for more systematic and theory-based research [33,34]. Above all, the team composition with the special role of psychologists and the change in social dynamics, as well as their role itself, has to be further researched [35]. In order to find out how health care professionals deal with these conditions, difficult situations, or new challenges in clinical practice, Bandura [36] formulated in his social-cognitive theory that self-efficacy beliefs have a greater influence on motivation, emotions, and actions than objective factors such as ability level [36-39]. Self-efficacy is a key factor in human behavior that influences performance, motivation, and resilience [40,41]. Heinrich et al [42] showed in their studies on the health care sector that high self-efficacy is a protective factor against burnout [42,43]. In the context of health psychology, self-efficacy plays a prominent role: higher self-efficacy is associated with better health (outcomes) [8,44]. Self-efficacy has been successfully integrated into interventions [45], though applications in psychiatric-psychosomatic contexts remain rare or underexplored. Most interventions primarily

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target individuals rather than teams, despite the central importance of team dynamics in this context [46].

The job demands-resources (JD-R) model [47,48] provides a suitable framework for analyzing the working conditions of health care professionals in psychiatric-psychosomatic clinics. Key indicators, such as high sickness rates [15,16], frequent staff turnover and interward fluctuations [49], technologization [4], and reduced job satisfaction [1], highlight the relevance of this model in capturing occupational stressors and resource deficits.

Theoretical Framework: the JD-R Model

The JD-R model [47] (Figure 1) emphasizes the importance of job demands (high workload and emotional stress) and job resources (social support and self-efficacy) for the job satisfaction, engagement, and burnout risk of employees.

Figure 1. The job demands-resources model.

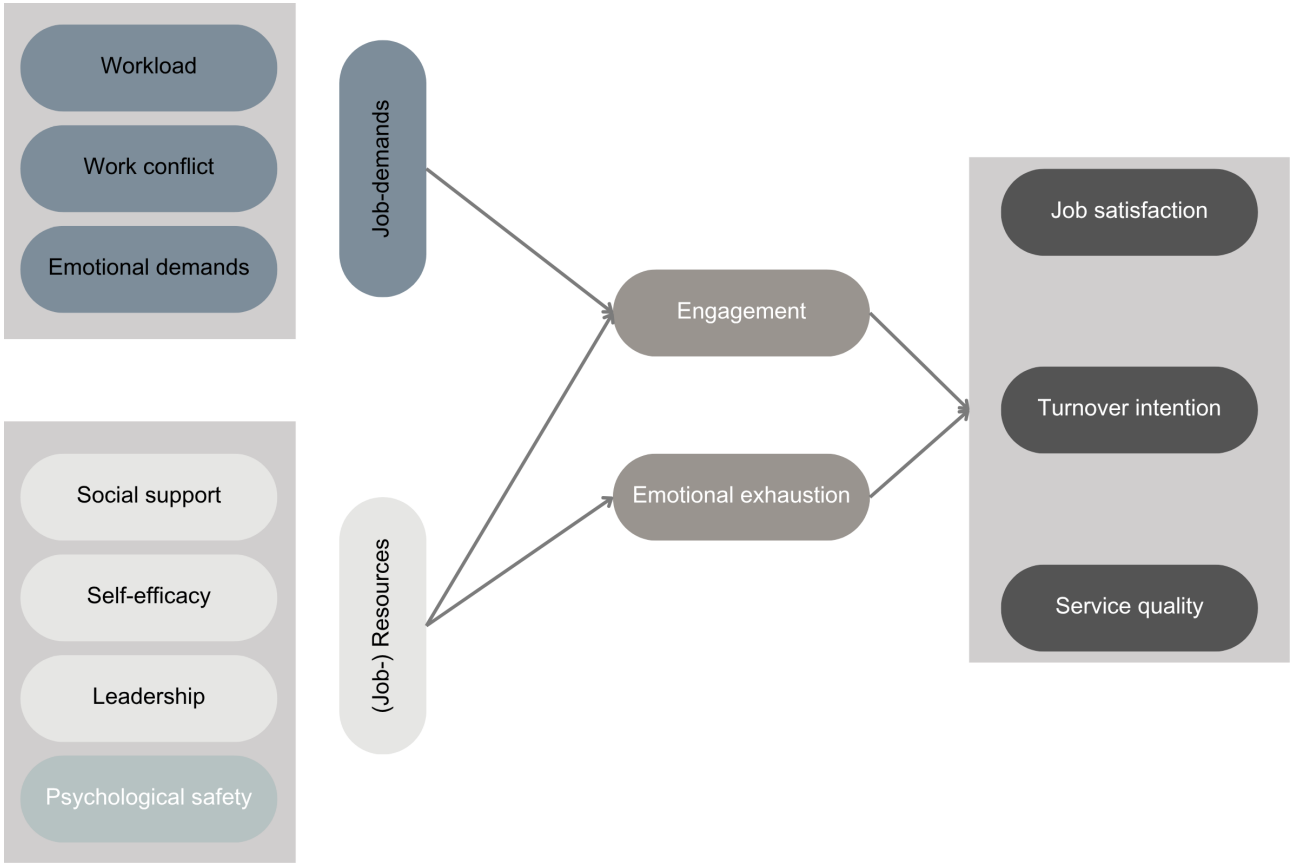

The JD-R theory explains how job demands and job resources influence job performance through employee well-being (including burnout and emotional exhaustion and work engagement) and how employees use proactive as well as reactive work behaviors to impact job demands and resources [50,51]. However, the following should be noted for the psychiatric-psychosomatic health care sector: the different structures and processes in psychiatric settings described above make it difficult to directly apply solutions from other health care sectors.

Against the background of the working conditions in psychiatric-psychosomatic clinics described above, it is precisely the 2 fundamental concepts of the model—the concept of burnout and the concept of job demands—that make the JD-R model attractive for research into this area of health [52]. The model integrates various job stress and motivational perspectives [50,51].

Bakker et al [47] underpin the theoretical and empirical conceptualization of the constructs of burnout and work engagement with numerous (meta) studies on situational factors and individual factors of burnout and work engagement. The JD-R model is a widely used instrument and has been applied in numerous studies [53]. However, the distinct structures and processes in psychiatric settings described above complicate the direct application of solutions from other health care domains.

The findings of Halbesleben [54] are relevant to the present research, as he proved that job resources and self-efficacy go hand in hand with work engagement. Mäkikangas et al [55] also add self-efficacy, optimism, and self-esteem. With regard to health-related outcomes, Bakker et al [47] explained that there is wide empirical evidence showing that the experience of burnout leads to several health-related issues. Yang and Hayes [49] conducted a systematic review of 44 studies carried out between 2009 and 2020. They concluded that psychotherapists enduring burnout are at risk of developing a wide range of health-related problems, including anxiety and depressive disorders, secondary traumatic stress, back and neck pain, sleep deprivation, and insomnia [47]. In a systematic review, Patel et al [56] showed that physicians' burnout leads to serious

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outcomes, such as increased risk of malpractice or increased number of medical errors.

Accordingly, this research examines how these factors influence job satisfaction, the intention to change jobs, and subjective service quality. A particular focus is placed on the mediators of burnout and commitment, as well as on the role of psychological safety as a moderator between job demands and the outcomes mentioned [57]. Figure 1 shows the structure of the relationships in the model. A special focus is placed on the mediator's burnout and emotional exhaustion and engagement, as well as on the role of psychological safety as a moderator between job demands and the outcomes mentioned (job satisfaction, the intention to change jobs, and subjective service quality). By investigating these relationships, a deeper understanding of the psychological factors that influence health care professionals in psychiatric-psychosomatic clinics can be gained.

For the current research, job demands include the following: workload, work conflict, and emotional demands. Further, the job resources include the following factors: social support, self-efficacy, leadership, and psychological safety. The selection is justified as follows: 9 central propositions are developed in the JD-R theory, which will guide the outlined research [47].

The first proposition on the basis of the JD-R theory is that all job characteristics can be modeled using 2 distinctive categories, namely job demands and job resources [58]. Job demands are defined as the physical, psychological, social, or organizational aspects of the job that require sustained physical, cognitive, or emotional effort and are therefore associated with certain physiological or psychological costs [58]. In contrast, job resources are defined as the physical, psychological, social, or organizational aspects of the job that have motivating potential, that are functional in achieving work goals, that regulate the impact of job demands, and that stimulate learning and personal growth [51].

The second proposition of JD-R theory is that job demands and resources instigate 2 different processes: in the first process, the health impairment process, the frequency and severity of job demands leads to increased effort and may lead to job strain, exhaustion, and health problems [58]. A study on health care professionals, Molero et al [59] shows that job demands (eg, time pressure and emotional stress) lead to burnout, which in turn acts as a mediator between demands and negative outcomes (eg, job satisfaction and intention to leave). In the second process, the motivational process, job resources (eg, skill variety, social support, and feedback) satisfy basic psychological needs and produce work engagement. The experience of work engagement consequently leads to creative performance [60]. In a multinational study in 4 organizations, Schaufeli and Bakker [61] were able to show that work resources promote commitment, which in turn refers to the mediating role of commitment.

The third proposition is that job demands and resources have a multiplicative impact on employee well-being (including burnout and work engagement). Several studies have shown that job resources such as skill variety, performance feedback, and opportunities for recovery can mitigate the impact of various job demands (eg, workload, cognitive demands, and emotional demands) on strain, including psychological distress, burnout, and psychosomatic complaints [47,62-64]. Personal resources are positive self-evaluations that refer to individuals' sense of their ability to control and impact their environment successfully [65]. Thus, the fourth proposition on the basis of the JD-R theory is that personal resources, such as optimism, self-efficacy, and resilience, have a reciprocal relationship with job resources. This means that employees with more personal resources are expected to also have access to more job resources, and vice versa. Indeed, using a longitudinal design, Xanthopoulou et al [66] found that employees who were more self-efficacious and optimistic also reported higher levels of autonomy, performance feedback, and opportunities for growth over time. In addition, job resources have had a lagged positive effect on personal resources. Schaufeli and Bakker [61] and Bakker et al [62] show that high job resources not only increase engagement, but also job satisfaction. A meta-analysis by Podsakoff et al [67] confirms that work resources such as social support and feedback reduce the intention to change, while high demands increase it.

A further proposition (proposition 9 according to Bakker et al [47]) of the model that is fundamental to this research is that of the loss cycle, which states that job strain is both an outcome and a predictor of dysfunctional and job demands. Thus, over the course of time, employees may enter a loss cycle. Specifically, when employees experience job strain in the form of exhaustion, anxiety, or depressive complaints, they deplete their energy resources and engage in dysfunctional coping.

In this research, the factor of psychological safety is added to the job resources. It plays a central role in the context of psychiatric-psychosomatic care. Psychological safety has been studied less frequently in this context to date and is also not explicitly listed as a job resource by Bakker et al [47,50]. However, others also include psychological safety as a job resource and thus justify psychological safety climate as a precursor to conducive work environments [57]. Psychological safety in the health care workplace—as mentioned before—is fundamental. It can also be seen as a mediator for job satisfaction [3].

Psychological safety is therefore a central element of this research. With regard to psychological safety, Hecker [3] emphasizes that the current discussion is moving away from the following "one-sided" definition of patient safety [68]. The current debate is about a so-called "patient- and employee-oriented risk and safety culture" [3]. A working environment in which patients and employees feel accepted and respected is characteristic of and fundamental to psychological safety [3,32,69]. In order to support employees, it is necessary to create a psychologically safe environment [3].

Woodward speaks of a "restorative just culture," where nobody is afraid to speak up and where employees are supported and encouraged without blame, especially when mistakes happen [3]. Although the just culture is well founded [3], everyday life in hospitals is mostly quite different: mistakes are tried to be concealed and employees avoid speaking up out of fear of negative consequences. There are hardly any publications on

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how to implement the just culture and thus also the psychological safety of employees [3].

By examining these relationships between job demands and job resources in relation to job satisfaction, turnover intention, and service quality (see Figure 1), a systematic understanding of the psychological factors that influence health care professionals in psychiatric-psychosomatic clinics can be used for designing innovative interventions.

Research Objectives and Questions

The aim of this paper is to investigate the interactions between individuals and their social environment in health care professionals working in psychiatric-psychosomatic clinical settings in Germany. The ultimate goal is to co-design a tailored intervention to improve their well-being.

Grounded in the JD-R model [47], the research adopts a 2-phase design with the overarching research goal of identifying psychological and organizational challenges and using these findings to inform the development of a participatory, evidence-based intervention. Thereby, we build on previous evidence and developments (for instance [4]).

Phase 1 serves as a comprehensive needs assessment. It aims to investigate how the assessed resources and demands of health care professionals impact job satisfaction, turnover intention, and subjective service quality. In this context, the research particularly considers how emotional exhaustion and engagement function as mediators, and how psychological safety may act as a moderator in these associations. The results of phase 1 will form the empirical foundation for a context-sensitive intervention tailored to the specific needs of clinical staff to be developed in phase 2.

The central research question for phase 1 is: How do the assessed resources and demands interrelate with job satisfaction, the intention to leave the job, and the subjective service quality of health care professionals in psychiatric-psychosomatic clinics? To address this question in greater depth, phase 1 focuses on the following specific subquestions: how do the surveyed resources and demands of health care professionals impact job satisfaction, turnover intention, and subjective service quality? What roles do burnout, engagement, and psychological safety play as mediators and moderators in these relationships? What are the key challenges and resources identified by health care professionals in their daily work within psychiatric-psychosomatic settings?

Drawing on the theoretical assumptions of the JD-R model, the research tests the following hypotheses: (Hypothesis 1) higher job demands are negatively associated with job satisfaction and service quality and positively associated with turnover intention. (Hypothesis 2) Higher job resources are positively associated with job satisfaction and service quality. (Hypothesis 3) Burnout acts as a mediator between demands and outcomes. (Hypothesis 4) Engagement mediates the positive effect of resources on the outcomes. (Hypothesis 5) Psychological safety moderates the relationship between demands and negative outcomes.

Building on the findings of the first phase, phase 2 pursues the primary objective of co-creatively developing an intervention aimed at enhancing the well-being of health care professionals in psychiatric-psychosomatic settings in times of digitalization and increased impact of technology. This participatory development process involves key stakeholders and practitioners to ensure practical relevance, acceptability, and contextual sensitivity. In addition to the intervention design, phase 2 also aims to evaluate the feasibility and acceptability of the intervention and to explore its preliminary potential to improve job satisfaction, reduce turnover intention, and enhance perceived service quality.

Taken together, this 2-phase research project seeks first to systematically examine the demands and resources present in psychiatric-psychosomatic practice and their impact on central psychological and occupational outcomes, and second, to design an evidence-based intervention that incorporates the perspectives of those directly affected by these challenges, especially in times of increased technological demands.

Methods

Overview

This research uses a 2-phase approach to investigate the interactions between individuals and their social environment to study the self's embeddedness in diverse social systems. Concretely, the work evaluates work-related challenges among health care professionals in German psychiatric-psychosomatic clinics and develops a tailored intervention. Phase 1 consists of a cross-sectional online survey to identify key stressors and resources, while phase 2 involves a participatory co-creation process to design an evidence-based intervention [70].

Phase 1: Internet-Based Needs Assessment

Study Design

A cross-sectional online survey will be conducted to examine associations between job demands, job resources, and work-related outcomes (job satisfaction, turnover intention, and perceived service quality) using the JD-R model [47,48]. Data will be collected at a single time point via the SoSci Survey [71] platform (SoSci Survey GmbH), ensuring efficient and scalable data collection.

Target Group and Recruitment

We conducted a priori power analysis using G*Power 3.1 [72] to determine the required sample size for our primary analysis incorporating 7 predictors (3 job demands and 4 job resources). The analysis indicated that n=178 participants would be needed to detect small-to-medium effects (f^2=0.15) with 80% power at α=.05. This effect size estimate is empirically supported by: (1) meta-analytic findings in JD-R research reporting comparable effects (f^2≈0.12 - 0.18 [73]), (2) health care studies of psychological safety (β=.32 - .41 [32,52]), and (3) recent JD-R meta-analyses in mental health settings (f^2=0.10 - 0.20 [52,74,75]).

For subgroup analyses across 3 professional groups (nurses, psychologists, and physicians), we calculated that 159 participants per group (n=477 total) would be required to detect medium-sized effects (η^2=0.06) with 80% power [76,77]. Accounting for 20% anticipated attrition, we established a final

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target of n=600 (200 per group). This sample size follows recommendations from occupational health research [51,53] and provides 70% power for exploratory analyses of experience levels (d=0.65 [74]), while maintaining practical feasibility in clinical research settings.

Eligibility criteria include: (1) age ≥18 years, (2) current employment in a psychiatric-psychosomatic clinic, and (3) sufficient German language proficiency. Exclusion criteria apply to nontarget professions (eg, administrative staff) and professionals outside specified clinical settings. Primary recruitment will occur through clinic administrators who will distribute survey invitations via email. Emails will be sent out via a list of clinics that primarily treat patients with psychological/psychosomatic disorders, or that have specific wards that focus on these patients. Recruitment will be limited to Germany. Supplementary methods include targeted social media advertisements and informational posters in participating institutions. Participation is voluntary, with guaranteed anonymity and the right to withdraw without consequences.

Data Collection

Data collection for this study will be conducted through an online survey to be administered via SoSci Survey [71], with an estimated completion time of 8 minutes. The survey will use standardized measures adapted from established instruments to assess key constructs within the JD-R [51], with primary reliance on the Copenhagen Psychosocial Questionnaire (COPSOQ [78]).

Job demands will be assessed through three key dimensions. Workload will be measured using five items evaluating work pace and time pressure (eg, “How often do you have to work very fast?”), to be rated on a 5-point frequency scale (1=always to 5=never), adapted from the COPSOQ [78]. Work conflict will be assessed through 4 items examining interpersonal tensions and workflow disruptions (eg, “Do you often have arguments with some colleagues?”) using the COPSOQ’s conflict scale (4-point agreement scale; 1=not at all to 4=completely true). Emotional demands will be evaluated through items assessing emotional strain (eg, “Is your work emotionally demanding?”) to be rated on 5-point intensity and frequency scales from the COPSOQ [78].

Job resources will be measured through several dimensions. Social support will be assessed using 4 items evaluating collegial and supervisory support (eg, “How often do you receive help from colleagues when needed?”), to be rated on a 5-point frequency scale (1=always to 5=never) from the COPSOQ [78]. Self-efficacy will be measured through nine items assessing problem-solving confidence and adaptability (eg, “I can always find solutions to difficult problems”), using a 4-point agreement scale (1=not at all to 4=completely true), based on established self-efficacy scales [79]. Burnout refers to a work-related state of exhaustion and a sense of cynicism. In contrast, work engagement is a positive motivational state of vigor, dedication, and absorption [79].

Leadership quality will be evaluated through 4 items examining motivational and fair leadership behaviors, to be rated on a 4-point agreement scale adapted from the COPSOQ. Psychological safety will be assessed using seven items (eg, “In this team, difficult topics can be discussed openly”) adapted from Edmondson’s [69] team psychological safety measure, to be rated on a 7-point Likert scale (1=strongly disagree to 7=strongly agree).

Psychological states will include work engagement and emotional exhaustion. Work engagement will be measured using three items from the Utrecht Work Engagement Scale (UWES [80]) assessing energy, enthusiasm, and absorption (5-point frequency scale). Emotional exhaustion will be evaluated through 3 items (eg, “How often are you emotionally exhausted?”) to be rated on a 5-point frequency scale from the COPSOQ [78].

Outcome variables will comprise job satisfaction, turnover intention, and service quality, all adapted from the COPSOQ [78]. Job satisfaction will be assessed through seven dimensions (eg, satisfaction with colleagues, management, and salary) using 5-point Likert scales. Turnover intention will be measured with two items assessing frequency of thoughts about leaving the profession or job (5-point frequency scale). Service quality will be evaluated through 3 items (eg, “The care provided on my unit is reliable”) using a 7-point Likert scale.

Demographic and occupational characteristics will include comprehensive background information to enable subgroup analyses: Age (continuous variable in years), gender (male, female, diverse, and prefer not to say), professional role (nurse, psychologist, and physicians), years of professional experience (continuous), weekly working hours (continuous), shift work status (yes, no), team size (number of colleagues typically worked with), and participation in continuing education (hours per year).

All measures have been selected based on their established reliability and validity in prior research. The survey will maintain participant anonymity and comply with GDPR requirements. Electronic consent will be obtained before participation, and participants will be able to withdraw at any time without penalty. The standardized administration through SoSci Survey will ensure consistent data collection across participants.

Statistical Analysis

The statistical analysis will be conducted using SPSS Version 29 (IBM Corp). Initial data screening will include comprehensive checks of distributional properties, focusing on skewness (absolute values <2) and kurtosis (absolute values <7), along with identification of multivariate outliers using Mahalanobis distance (P<.001). Assumptions for parametric tests will be verified through examination of multicollinearity (variance inflation factors <3) and homoscedasticity using the Breusch-Pagan test.

Descriptive statistics including means, SDs, and frequencies will be computed with 95% CIs to characterize the sample. Bivariate relationships will be assessed using Pearson correlations, with false discovery rate correction applied to control for multiple comparisons. Hierarchical regression analysis will be used to examine predictors of primary outcomes, with change in R^2 reported at each step to evaluate the

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contribution of different predictor blocks. For group comparisons between professions, one-way ANOVAs will be conducted with Games-Howell post hoc tests to account for potential unequal variances, accompanied by effect size estimates (η^2) with 90% CIs.

Missing data will be handled through a systematic approach beginning with an examination of missing patterns using Little's MCAR test. Where data are missing at random, multiple imputations with 50 iterations will be performed using predictive mean matching. Sensitivity analyses comparing results from complete cases versus imputed datasets will be conducted to evaluate the robustness of findings. All analyses will use 2-tailed tests with an alpha level of .05, and effect sizes will be reported in accordance with APA Style Journal Article Reporting Standards [81].

Phase 2: Co-Design of Training for Medical Staff

Development of an Intervention

Building on findings from phase 1, we will use an adaptive participatory action research framework to co-create tailored interventions [4,70]. Co-design means designing an intervention together with the target group to make interventions ideally fitting and engaging, which lead to optimal outcomes. The intervention can be improved in terms of service quality and more satisfactory services for all individuals, including ones with disabilities [82].

Collaboration between different groups of stakeholders to achieve mutually beneficial outcomes is perceived as more effective, trustworthy, and sustainable [83]. The terms co-design and co-creation encompass collaborative approaches characterized by collective creativity, involving diverse views of relevant stakeholders in developmental and problem-solving processes aimed at achieving a shared goal [84]. Participatory health research considers the challenges and advantages of collaborative approaches between individuals with lived experience and organizations.

Participants are seen as active partners, equally important and with equal expertise as health care providers or researchers [18]. This can be ensured by considering all individuals as co-facilitators or stakeholders and active participants in the design of service and care, including accreditation processes. While participation remains more with consultation (like asking about needs, options, or preferences), co-approaches relate more to

- partnership
- shared decision making,
- shared power
- accountability and responsibility
- active control given to all stakeholders.

Benefits of such actions can improve health outcomes and satisfaction [82]. Thus, co-creation, co-design, and co-production harbor great potential for use in different research disciplines due to the active involvement of relevant stakeholders providing their perspectives in the context of intervention design, implementation, and evaluation. Participatory and co-approaches can improve research processes as well as scientific outcomes, including dissemination potential [82,83].

The concrete procedure will be determined through ongoing collaboration with stakeholders, allowing the methodology to evolve based on initial results and practical constraints identified in phase 1. Rather than predetermining group compositions or session numbers, we will adopt a responsive approach where workshop structures emerge organically from the needs assessment data with at least 20 participants. The same holds true regarding the analysis of transcribed verbal data: qualitative content analysis will use software like MaxQDA (VERBI Software GmbH), QCAmap (Association for Supporting Qualitative Research), or QualCoder (Dr. Colin Curtain).

The development process will follow established principles of co-creation in health care settings [70]. Dynamic facilitation techniques will be used to identify intervention priorities while respecting profession-specific perspectives [70,82]. Subsequent refinement cycles may involve either homogeneous or heterogeneous groupings, depending on the emerging themes [70]. For instance, separate sessions might be convened to address profession-specific challenges identified in phase 1, while interdisciplinary workshops would focus on systemic solutions. The development of this participative training for medical staff offers all team members the opportunity to contribute regardless of hierarchy, experience, or personality. This is in line with Edmondson's call for an inclusive team culture, which contributes to psychological safety and ultimately leads to an innovative corporate culture as proposed by Edmondson [85].

Expected Components and Feasibility

The intervention design will be grounded on outcomes of phase 1 and the JD-R framework (Figure 1), directly addressing the specific demands and resources identified as most salient in phase 1 [86]. Drawing on the quantitative and qualitative findings from the initial study phase, the intervention will target modifiable factors that emerged as critical predictors of well-being, while remaining acutely sensitive to the substantial time constraints and emotional burdens characteristic of psychiatric-psychosomatic care settings [87].

Core components will likely focus on three interrelated domains informed by the JD-R analysis. First, stress management elements will address the most prevalent job demands identified, potentially including modules on emotion regulation techniques tailored to high-intensity clinical encounters and strategies for managing workload pressures [88]. These will be designed as brief, skill-based trainings that can be readily integrated into daily practice [89]. Second, team communication enhancements will aim to bolster psychological safety and social support, resources that may emerge from phase 1 as particularly impactful buffers against strain [90]. This could involve structured protocols for interdisciplinary case discussions or conflict resolution processes adapted to mental health care contexts. Third, resource-building components will target both organizational and personal protective factors, such as increasing job control through workflow adjustments or strengthening recovery experiences during nonwork time [91].

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The format and delivery methods will be carefully developed through participatory design to minimize additional burden on this already overextended workforce [92]. Early stakeholder input suggests hybrid approaches combining digital and in-person elements may offer an optimal balance between effectiveness and feasibility [93].

Potentially, brief digital micro-interventions delivered through mobile platforms could provide just-in-time support during workdays, while selective in-person sessions would focus on team-based skill building. Particular attention will be given to ensuring all components can be feasibly implemented within existing workflows, potentially through strategies like manager-protected time for participation or integration into regular team meetings [94].

Implementation planning will incorporate systematic assessment of time requirements and workflow impacts, with iterative refinements to reduce participation barriers [95]. The intervention will be designed not as an added obligation, but as a supportive framework that actively reduces current strains while building sustainable resources, aligning with the JD-R perspective's dual focus on demand reduction and resource enhancement [96]. This approach recognizes that for overburdened health care professionals, even well-intentioned interventions can become counterproductive if not thoughtfully adapted to real-world constraints [97].

Ethical Considerations

The study 1 was conducted in full compliance with the European Union's General Data Protection Regulation (GDPR; European Parliament, 2016, Art. 6(1)(a)) and received ethical approval from the Ethics Committee of Bremen International Graduate School of Social Sciences (BIGSSS), Germany (No. BIGSSS20241127; approved on November 27, 2024). A comprehensive data protection plan was approved on the 11.03.2025 by the responsible data security officer during the study design process. Participants receive detailed written information about the study's purpose, procedures, and data handling practices before providing electronic informed consent through the SoSci Survey platform. Participation is voluntary, and participants can withdraw with no consequences at any time. They did not receive any material or financial incentive for their participation.

Data collection followed strict anonymization protocols, with no collection of personally identifiable information (eg, names, IP addresses, or workplace identifiers). The approved data protection plan specified a 10-year retention period for research data, after which secure deletion would occur following institutional protocols. The plan included comprehensive access logging and procedures for potential data breaches compliant with GDPR requirements. Participants were informed of their rights under GDPR, including access, correction, withdrawal, and complaint procedures. The authors can be contacted by the participants for any complaints or concerns via a provided email address in the survey.

Phase 2 will follow established ethical protocols in line with institutional and GDPR requirements. Before beginning, we obtained the necessary ethical approval for all activities, including specific authorization for the qualitative components. Participants are fully informed about the study and provide consent before taking part.

Confidentiality will be prioritized throughout the qualitative data collection. Workshop and interview recordings will be transcribed with all identifying details removed. The research team will store and handle all data securely using encrypted systems with controlled access.

The approach is designed to protect participants while allowing for necessary adjustments during the intervention development process. Regular reviews will help ensure ongoing compliance with data protection standards.

Results

The data collection for phase 1 began in March 2025 and is scheduled to be closed by December 2025. Data analysis will follow, and phase 1 is scheduled to be finished by January 2026. Ethics approval has been obtained.

Phase 2 will be built on that. The co-creative workshops are planned for March and April 2026. Phase 2 is scheduled to be finished by May 2026.

No results are available at this stage. This paper reports only the study protocol.

Discussion

Anticipated Outcomes and Significance

This study aims to research work-related challenges faced by health care professionals in psychiatric-psychosomatic clinics. It identifies job demands (eg, workload, work conflicts, and emotional demands) and work resources (eg, social support, self-efficacy, leadership qualities, and psychological safety). Based on these findings, this study aims to fill the gaps in research on the working conditions of health care professionals and to develop evidence-based interventions that improve staff well-being and the quality of patient care [32,51-53].

The first phase of the study described above is intended to identify the most important professional requirements and resources that are relevant for mental health professionals in psychiatric-psychosomatic clinics. Hypotheses we anticipated on burnout, engagement, and psychological safety will be tested. In doing so, key hypotheses derived from the theoretical framework are tested, specifically, (Hypothesis 1) the negative association between job demands and job satisfaction and service quality, (Hypothesis 2) the positive association of job resources with these outcomes, (Hypothesis 3) the mediating role of burnout, (Hypothesis 4) the mediating role of engagement, and (Hypothesis 5) the moderating role of psychological safety.

To our knowledge, there are currently few published, comparable studies on daily practice in psychiatric-psychosomatic clinics [14,29,31]. The findings will provide a detailed picture of professional challenges and support structures (in line with the primary research question and hypotheses [Hypothesis 1–Hypothesis 5]). The second phase

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of the research will result in a co-designed intervention tailored to the unique needs of the target group [70]. This 2-phase approach bridges assessment and action, generating both empirical insight and practical solutions.

The strengths of this 2-phase approach lie on the one hand in the use of the well-established theoretical JD-R model [47]. It offers a broad sample including multiple health care professions. On the other hand, there is an advantage in the combination of quantitative (survey) and qualitative (intervention design) methodologies. The survey records individual perceptions and assessments of job requirements, resources, job satisfaction, intention to change jobs, and service quality. By describing these relationships, a deeper understanding of the psychological factors that influence health care professionals in psychiatric-psychosomatic clinics will be gained [4]. These participatory methods ensure high contextual relevance and potential acceptance. Another strength of this research is the high ethical and data protection standards observed throughout.

There are some potential limitations and suggestions for follow-up of this research that should be noted: The cross-sectional design of phase 1 does not allow for causal conclusions. This would be valuable in order to represent social dynamics within a team of health care professionals. While a longitudinal approach would be ideal, in these 2 phases, it was not feasible due to practical constraints, including the need to reduce participant burden, anticipated staff turnover, and limited comparability across time points. There is also a risk of self-report bias due to the use of only subjective survey responses. To mitigate this, we used neutral question phrasing and ensured anonymity. There is furthermore a risk of potential sample bias due to the self-selection of participants. To address this, recruitment materials emphasized confidentiality, and targeted outreach was conducted to encourage participation across diverse facilities.

Future research should aim to validate these findings with nonreactive data, in international contexts, and across other health care disciplines. Longitudinal studies are needed to explore changes over time in job satisfaction, turnover intentions, and health care quality. Furthermore, RCTs are recommended to evaluate the effectiveness of the co-designed intervention. Follow-up studies should also assess long-term outcomes, including staff turnover rates and patient-related service quality metrics. This research provides a foundation for such future investigations and is planned to be published as two papers (phase 1 and 2) in scientific journals.

This study significantly contributes to answering the central research question of how the resources and requirements influence job satisfaction, the intention to change jobs, and the subjective service quality of health care professionals in psychiatric-psychosomatic clinics. It empirically tests the theoretically grounded hypotheses (Hypothesis 1–Hypothesis 5), thereby linking theoretical assumptions with practical findings. It contributes to the under-researched field of occupational well-being in psychiatric-psychosomatic health care settings. Also, the research provides valuable significance for the practice in designing an evidence-based intervention that incorporates the perspectives of those directly affected by these challenges.

The project is characterized by innovative aspects: the first innovative aspect lies in the provision of empirical evidence for designing organizational and individual-level interventions, taking interactions between individuals and their social environment into account. Second, it offers actionable insights for clinic administrators and policymakers. Another important outcome is that it supports sustainable workforce strategies in mental health care. Thus, the project can encourage interprofessional cooperation and mental health promotion among staff in times of increasing complexity and dynamic changes over time and in interaction with medical internet research.

The research, with its 2 phases, provides a deeper understanding of the psychological factors affecting health care professionals in the mental health sector. Beyond that, it addresses the need to improve support for psychiatric-psychosomatic care in times of digitalization and increased medical internet use.

Conclusions

This research examines the work-related challenges faced by health care professionals in psychiatric-psychosomatic clinics. It is expected that burnout, engagement, and psychological safety will likely emerge as central mediating and moderating variables. As the findings of phase 1 serve as a basis for the development of an intervention, this research seeks to improve the well-being of health care professionals in psychiatric-psychosomatic institutions sustainably. With that, this research acts as a role model for other approaches, especially in times of increased internet-supported activities in medical workforces.

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Data Availability

The datasets generated or analyzed during this study are not publicly available due to them containing information that could compromise the privacy and consent of the participating health care professionals, but are available from the corresponding author on reasonable request.

Authors' Contributions

KS and SL developed the initial methodology. KS wrote the first draft for publication. SL reviewed drafts and managed submission.

Conflicts of Interest

None declared.

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Abbreviations

APA: American Psychological Association
BIGSSS: Bremen International School of Social Sciences
BMBF: Bundesministerium für Bildung und Forschung
BWFGB: Behörde für Wissenschaft, Forschung, Gleichstellung und Bezirke
COPSOQ: Copenhagen Psychosocial Questionnaire
DFG: Deutsche Forschungsgemeinschaft/ German Research Foundation
GDPR: General Data Protection Regulation
HAW: Hamburg University of Applied Sciences
IT: information technology
model: job demands-resources model
RCT: randomized controlled trial
SCT: social-cognitive theory
UWES: Utrecht Work Engagement Scale

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Developing and Evaluating a Bundled Digital Tool to Improve Complex Care and Self-Management of Patients With Inflammatory Bowel Disease: Protocol for a Hybrid Effectiveness-Implementation Study

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Abstract

Background: Individuals with inflammatory bowel disease (IBD) require comprehensive care to address the physical and psychosocial burden of their disease. The demand for IBD care often exceeds availability, resulting in delayed access and suboptimal management. As a result, patients with IBD are required to self-manage significant aspects of their disease between appointments with their medical team. Digital self-management tools may help address this gap by empowering patients to be more engaged in managing their disease, potentially improving outcomes and reducing the strain on the health care system.

Objective: This study aimed to design, implement, and evaluate a bundled digital health tool, MyIBDToolkit, with the overarching goal of improving the quality of care and self-management for patients with IBD in Alberta, Canada.

Methods: A bundled digital health tool, MyIBDToolkit, will be integrated into our provincial electronic health record system to ensure broad accessibility and continuity of care. We will use a type 2 hybrid effectiveness-implementation design to evaluate both the clinical impact and real-world integration of the toolkit. We will assess effectiveness through changes in key outcomes such as health care utilization (eg, emergency visits, hospitalizations), disease burden on patients (eg, quality of life, symptom control), and burden on the health care system. These outcomes will be measured using comprehensive health care administrative data. A dual-comparison approach will be used: a within-subject comparison of health care utilization and disease burden before and after implementation of the MyIBDToolkit, and a between-group comparison of outcomes among toolkit users versus nonusers. To evaluate implementation success, we will examine reach (ie, number of patients and providers using the tool), fidelity to the planned timeline, sustained use over time, and factors influencing adoption and maintenance. Our goal is to reach 10,000 patients across Alberta, Canada, within three years.

Results: We received funding for this project in January 2023. In preparation for the pilot launch, we have identified key stakeholders, including patients, health care providers and, administrators, and developed strategies to assess their readiness for MyIBDToolkit. We are also collecting mixed-methods data from patients to explore potential barriers and facilitators to using MyIBDToolkit. The first phase of MyIBDToolkit was launched in October 2024.

Conclusions: MyIBDToolkit represents a scalable and patient-centered approach to the self-management of IBD care. By empowering patients to self-manage their disease between health care visits, we aim to reduce the burden of IBD on patients, providers, and the health care system. By evaluating the effectiveness and the implementation of the MyIBDToolkit, we aim to generate actionable and sustainable improvements to IBD care in Alberta.

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KEYWORDS

digital health; self-management; electronic medical records; quality of life; diet; mental health; inflammatory bowel disease; social determinants of health; implementation

Introduction

Inflammatory bowel diseases (IBDs) are chronic illnesses of the gastrointestinal tract that include ulcerative colitis and Crohn's disease. IBD is characterized by inflammation of the digestive tract, causing affected individuals to experience remitting and recurring symptoms such as diarrhea, pain, fatigue, and weight loss [1]. The occurrence of these physical symptoms can be challenging to predict, even with optimal medication management [2]. The unpredictability of the disease, combined with the effects of the physical symptoms, can cause IBD to negatively impact additional aspects of a person's life, including their ability to work, socialize, and engage in leisure [3]. Consequently, this can contribute to poor mental health and quality of life [1,4], highlighting that the effects of IBD extend beyond a patient's physical well-being.

The interplay between mental health, nutrition, and gastrointestinal health [5,6] highlights the importance of adopting a multipronged approach to the treatment of IBD, that considers the physical and mental effects of the disease [7,8]. While a multifaceted approach to the treatment of IBD is encouraged by most international treatment guidelines [9,10], adherence to multifaceted treatment by health care providers (HCPs) remains low [11], for a variety of reasons, including a perceived lack of time during appointments to discuss factors outside of physical symptoms and medications [12]. This low adherence to a widely accepted approach for treatment emphasizes the need for solutions to help close this gap [13].

Currently, the management of many aspects of IBD, including mental health and diet, falls on the patients, requiring them to self-manage parts of their care [14]. This self-management of the several elements of IBD can be overwhelming and difficult for individuals, and can sometimes result in poor symptom control [15]. A possible solution to improve the self-management of IBD is to leverage the data collection potential of electronic medical records (EMRs), which can allow patients to log and monitor their symptoms between appointments with their HCP [16]. An advantage of EMR use stems from the fact that their HCP can view this patient-entered information, facilitating timely access before the appointment [16,17]. Previously, several studies demonstrated that leveraging EMRs for the care of patients with IBD can improve disease management and contribute to more personalized models of treatment [17,18]. EMRs can be implemented on a large scale and help standardize the quality of IBD treatment while still offering individualized medical aid for those suffering from chronic illness [19].

Starting in 2019, the provincial health care governing body, Alberta Health Services (AHS), began rolling out a provincial EMR system, ConnectCare (Epic Systems). ConnectCare (CC) is a provincially mandated EMR system that allows physicians to access and update patient information across the province. Currently, most major care centers in Alberta have access to CC, with the remaining health care sites being granted access in November 2024. Our study aims to develop and implement a series of health tools into the existing CC infrastructure, thereby standardizing and improving the quality of IBD care in the province.

Methods

Ethical Considerations

This study was approved by the University of Alberta Research Ethics Board (Pro00139915). A waiver of consent was approved for the extraction of secondary health data and no compensation will be provided. Participants will provide written informed consent before participating in any of the evaluation surveys. Survey data will be deidentified.

Objectives and Setting

MyIBDToolkit is a bundled digital tool consisting of patient- and HCP-targeted tools built into CC.

A team of gastroenterologists from sites across Alberta, Canada, were originally assembled to outline what elements would ideally be included in a self-management tool for patients with IBD. Together, they highlighted components of care that may be important for patients to track and the type of additional resources that could help them manage these aspects of their care. Following this, a patient advisory council was assembled to help guide the development of MyIBDToolkit and ensure that it addressed the needs of the patient population. The patient advisory council and the gastroenterology health care provider advisory team co-designed the patient-targeted tools to facilitate patient access to symptom-tracking support, diet education, and mental health resources. Table 1 details all the patient-facing tools that will be integrated into the MyIBDToolkit.

The HCP-targeted tools are designed to standardize evidence-based care and to allow for co-management with other HCPs, such as family physicians and internists, throughout the province. These HCP tools contain embedded decision-support based on the most recent IBD treatment and management guidelines. These tools will also standardize how information about a patient's disease is entered and collected into CC. Standardizing data entry into a patient's chart will allow for improved visualization of disease history and facilitate data extraction for future research studies. Table 2 details all the provider-facing tools that will be integrated into MyIBDToolkit.

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Table . Summary of patient-facing tools included as a part of MyIBDToolkit.

Purpose of tools	Details of the tools
Patient-Entered questionnaires and flowsheets	
Symptom tracking and self-management	• Stool diary • Side effects • Missed school/work days • Activity indices – Harvey Bradshaw Index [20], partial Mayo Score [21] • Flare questionnaire • Patient history questionnaire
Quality of life	• Health-related quality of life questionnaire
Social determinants of health	• Depression screening and inventory using the Patient Health Questionnaire-2 [22] and 9 [23] • Anxiety screening and inventory using the Generalized Anxiety Questionnaire-2 and 7 [24]
Mini self-management pathways	
Mental health pathway	• Screening tools for depression and anxiety • Identify those at risk and referral path to mental health professionals • Recommended self-management tools (existing apps/programs, including some local ones vetted for some evidence to support use in IBD[a] and free to patients)
Diet / nutrition pathway	• Screening tools using the Canadian Nutrition Screening Tool [25] and symptoms assessment • Locally developed nutrition recommendations and associated resources (developed in collaboration with local IBD outpatients)
AHS[b] IBD webpage	
“One-stop shop” for patients	• Links to IBD information resource • Links to credible education resources such as Crohn’s and Colitis Canada, BadGut, and Canadian Digestive Health Foundation • Links to self-management pathways • Links to ConnectCare patient portal onboarding videos
Implementation outcomes	
Evaluate implementation	• Patient satisfaction, usability questionnaires

[a]IBD: inflammatory bowel disease.

[b]AHS: Alberta Health Services.

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Table . Summary of provider-facing tools included as a part of MyIBDToolkit.

Purpose of tool	Details of tool
Standardization of care and shared care	
Documentation	• IBD[a] Overview, Pre-testing, Follow Up Smartforms • IBD Navigator – "one-stop shop" for all resources/management related to IBD care
Management (as per Clinical Care pathways)	• Smartsets, preference lists • Decision support • Synopsis
Quality of care	• IBD Reporting Dashboard • Tableau IBD page
Implementation outcomes	
Satisfaction and usability	• Provider satisfaction, usability questionnaires

[a]IBD: inflammatory bowel disease.

Study Design

The Reach, Effectiveness, Adoption, Implementation, Maintenance (RE-AIM) Planning and Evaluation Framework guided the design of this study [26,27]. The five dimensions assessed by this framework are reach, effectiveness, adoption, implementation, and maintenance.

To evaluate MyIBDToolkit in these five domains, this study uses a type 2 hybrid effectiveness-implementation design, with the effectiveness aim being to determine the clinical effectiveness of the MyIBDToolkit and the implementation aim being to assess the feasibility of the implementation strategy. We will evaluate the effectiveness and feasibility at two-time points: preimplementation and postimplementation, with postimplementation evaluations occurring at one and three years. A visual representation of the trial design is available in Figure 1.

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Figure 1. An overview of the type 2 hybrid effectiveness-implementation design to be used. ER: emergency room; HCP: health care provider; IBD: inflammatory board disease; RE-AIM: Reach, Effectiveness, Adoption, Implementation, Maintenance

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Participants

MyIBDToolkit will be available to HCPs and patients with IBD with access to CC across Alberta through acute, inpatient, or outpatient care. Providers who do not use CC for outpatient clinical work will be guided to the AHS Webpage for alternative access to the digital tools. Patients will be able to access MyIBDToolkit through their IBD HCP, indicating access to the tool is limited to individuals with a confirmed IBD diagnosis.

We will evaluate the effectiveness and implementation of MyIBDToolkit in six major cities across Alberta: Edmonton, Grande Prairie, Red Deer, Calgary, Medicine Hat, and Lethbridge. We have engaged IBD providers from academic and community sites within each city and will provide resources to them, explaining how to use all the tools within the MyIBDToolkit.

The patients of these IBD providers will be eligible for inclusion in the trial. Strategies to reach patients include providing their HCP with materials, posters, promotional material, and patient handouts to direct them to the AHS Webpage, which explains how to use MyIBDToolkit.

A maintenance of certification program will be created to incentivize HCP engagement and allow them to receive credits toward continuing professional development.

All included HCPs and their patients will be given contact information for a MyIBDToolkit support email. The research team will manage this email, which will help HCPs and their patients work through questions or issues they may have while accessing any of the tools.

Effectiveness

Effectiveness will be evaluated using a controlled before-and-after study design. Our primary effectiveness outcome is to assess the reduction in patient health care utilization, including hospitalizations, emergency room visits, and outpatient visits.

Our secondary effectiveness outcomes will be to evaluate changes to the burden of IBD on patients and the health care system using quality of life scores, disease activity, maintenance of remission, direct health care costs, and indirect health care costs. A detailed summary of all effectiveness variables that will be extracted for analysis is available in Table 3.

Table . Effectiveness outcomes to be extracted for analysis.

Outcome	Definition
Number of patient visits to gastroenterology clinics	Follow-up appointments with gastroenterology providers, with the primary appointment reason being IBD[a]
Number of emergency department visits for IBD or IBD-related complications	Emergency department visits with the primary admission or discharge diagnosis noted as IBD or a complication of IBD
Number and length of hospitalizations for IBD or IBD-related complications	Acute hospitalizations and their length with the primary admission or discharge diagnosis noted as IBD or an acute complication of IBD
Number of IBD surgeries for IBD or IBD-related complications.	Surgical procedures with the primary admission or discharge diagnosis noted as IBD or a complication of IBD
Number of patients with IBD prescribed advanced therapy	Biologic therapies and small molecule therapies dispensed for patients with an IBD diagnosis
Cost of advanced therapy for Alberta Health Services	Cost of biologic and small molecule therapies prescribed and dispensed while IBD patient is admitted to hospital
Cost of advanced therapy for patients	Cost of biologic and small molecule therapies dispensed at community pharmacies
Loss of productivity associated with IBD	1. Cost of lost productivity associated with the days patients with IBD spend in emergency departments, in hospital, or in surgery. 2. Work productivity questionnaire
Wait time for first IBD appointment	Number of days between referral for a suspected case of IBD and first appointment with a gastroenterologist
Quality of life scores	The proportion of patients with high, moderate, and low quality of life scores
Disease activity scores	The proportion of patients with active and inactive disease based on Harvey Bradshaw Index and Partial Mayo Score scores
Mental health scores	The proportion of patients with high, moderate, and low mental health scores
Malnutrition scores	The proportion of patients at risk of malnutrition

[a]IBD: inflammatory bowel disease.

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Statistical Analysis

Relevant IBD records will be extracted from provincial health administrative databases. Historic data on healthcare utilization, from the year before the introduction of MyIBDToolkit, will be used to compare to the rate of utilization in the second year after implementation.

We will evaluate the effectiveness outcomes using two different models:

1. Before-and-after analysis: This will be done by using MyIBDToolkit users as their own controls. We will compare the outcomes of MyIBDToolkit users before the launch of MyIBDToolkit to the outcomes of MyIBDToolkit users after the launch.
2. Users and nonusers: This will be done by comparing the outcomes of patients using MyIBDToolkit to patients not using the tool following the launch of MyIBDToolkit.

To assess the clinical effectiveness of MyIBDToolkit, the interrupted time-series analysis will follow a linear regression model in tandem with standard time-series methods to assess autocorrelation; these tests will include the Durban Watson test.

We based our sample size calculations on the effectiveness outcomes and results from a similar study by De Jong et al [19]. For our sample size calculations, we performed mathematical simulations that accounted for varying panel sizes, rates of visits and admissions for each physician, and rates of uptake by patients within physician panels. The statistical power of the tests was very robust despite variations. In the simulations with our most extreme conditions, (including an average 50% uptake by patients), a sample size of 15 physicians and 4400 patients provided over 90% power to detect the effect on hospital admissions.

Implementation

Implementation outcomes will be assessed using the RE-AIM framework, and the focus will be on the reach, adoption, and maintenance of MyIBDToolkit as well as the implementation of it.

The outcomes we will be extracting to evaluate implementation include the proportion of patients and providers using MyIBDToolkit, number of MyIBDToolkit tools being used by patients and providers, and the proportion of providers documenting and adhering to IBD quality indicators. These outcomes will be assessed at different time points (ie, yearly) to gain an understanding of the long-term effects of the intervention.

The implementation of MyIBDToolkit will be assessed using both qualitative and quantitative methods, including structured surveys and interviews as well as administrative data. This hybrid approach will allow us to measure reach, adoption, patterns of use, barriers and facilitators, characteristics of users and nonusers, adaptation, and sustainability of use across Alberta. To analyze the data collected, we will use individual-level data in mixed-effects negative binomial regression models that include random patient intercepts and effects nested within physicians, adjusted for age, sex, disease classification, and region.

The duration of the study is 3 years; however, follow-up evaluation will extend to 5 years. Our study will be developed and subsequently launched in a series of phases.

Phase 1: Key Stakeholder Engagement

In this stage, we will engage key stakeholders (eg, operations, patient partners, clinicians, nurses, and Digestive Health Strategic Clinical Network (DHSCN)) in the co-development of MyIBDToolkit, which will be crucial, as it will greatly impact uptake and successful implementation. A mixed-method research study will be designed to evaluate the barriers, facilitators, and contextual influences related to using digital resources. This sub-study will be co-designed and co-led by the patient advisory board and will consist of 5 - 6 patients or caretakers of varying backgrounds and demographics.

During this phase, research staff will work together to compile and design resources that will be included in MyIBDToolkit.

Phase 2: Preparing for Implementation

Clinicians will be approached to participate in a phased roll-out plan in line with CC waves (as HCPs must be CC-trained). At least one clinician from each of the six communities with a large IBD practice has agreed to participate. Additional clinicians with interests in IBD will be approached later by the study leads. MyIBDToolkit will be demonstrated to HCPs (clinicians, nurses, and medical office assistants) through in-person, virtual sessions or videos. Similarly, the study team will demonstrate the patient portal through videos to educate patient participants.

Phase 3: Pilot Implementation

MyIBDToolkit will be piloted for 6 months at one site in the first launch city (Edmonton) before expanding to the remainder of the sites in the city. The pilot phase will allow us to identify and resolve any technical or recruitment challenges.

Phase 4: Feedback and Rolling Implementation

MyIBDToolkit will be rolled out to the remaining cities after the pilot phase. The phased roll-out will be continued with 1 - 2 new cities added every six months. A phased roll-out is necessary to enable the collection and analysis of implementation measurements to help inform and refine the next iteration. The research team will set up mechanisms for timely technology support and feedback. Education videos will be housed on the AHS collection page during and beyond the funding period for HCPs to share with new patients (facilitated by DHSCN).

Phase 5: Continuing Improvement and Maintenance

MyIBDToolkit content and the implementation plan will be adapted based on implementation measurement tools and feedback. Technology support and ongoing updates will be used to ensure the accuracy of the content. The postevaluation survey is available in Multimedia Appendix 1.

Results

We received funding for MyIBDToolkit in January 2023 from Alberta Innovates. The tools that make up MyIBDToolkit are currently in development. The HCP-facing tools have been built

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into CC and are awaiting final approval from the provincial health care administration. The patient-facing tools have been synthesized, and some original tools to address diet and nutrition are in development.

We have identified all the relevant stakeholders that may be affected by the implementation of MyIBDToolkit. We have divided stakeholders into three groups: core, secondary, and tertiary. The core group represents all the impacted groups that require a practice change or awareness of the MyIBDToolkit intervention. The secondary group outlines all the impacted groups involved in the intervention design and supporting the implementation efforts. The tertiary group represents impacted groups that are involved in the evaluation of the intervention. Figure 2 includes a breakdown of the stakeholders belonging to each group.

Figure 2. Stakeholders involved in the development and implementation of MyIBDToolkit. AHS: Alberta Health Services; IBD: inflammatory bowel disease.

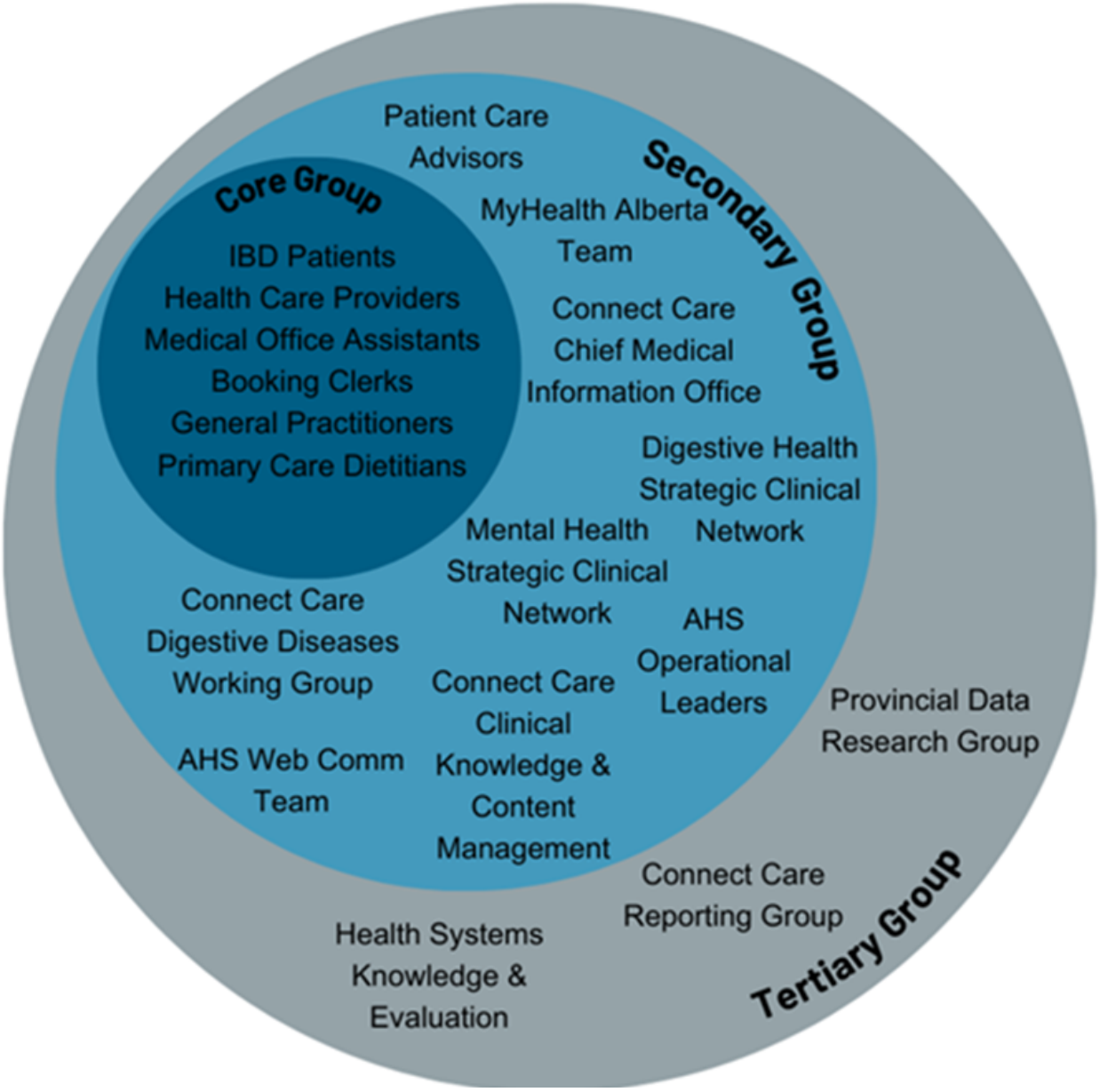

As a part of our preimplementation plan, we have engaged patients with IBD from across the province in a mixed methods study. This mixed methods study includes a survey and semistructured interviews and aims to identify the barriers and facilitators to using digital health tools such as MyIBDToolkit. This study took place from May-August 2024 and the findings have been published [28].

As of July 2025, we have begun enrolling patients to evaluate the toolkit.

As a part of our preimplementation plan, we have engaged patients with IBD from across the province in a mixed methods study. This mixed methods study includes a survey and semistructured interviews and aims to identify the barriers and facilitators to using digital health tools such as MyIBDToolkit. This study took place from May-August 2024 and the findings have been published [28].

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Discussion

Potential Impact

According to a recent study, administrative data suggest that the prevalence of IBD in Alberta in 2014 was 709 per 100,000 persons. Prediction models suggest that the prevalence of IBD in Alberta will continue to rise, with the rate expected to reach 1036 per 100,000 persons by 2035 [29] .

Based on the number of patients with IBD seen by HCPs at the sites participating in our study, we aim to reach 2000 patients with IBD in year 1, 6000 in year 2, and 10,000 in year 3 and engage them in using MyIBDToolkit. Using 10,000 patients as our anticipated study population, we estimate the potential effect of MyIBDToolkit by assuming similar effects to those of a similar bundled digital tool explored in a study by De Jong et al [19] Implementing their tool resulted in an adjusted estimated intervention effect of −0.05 hospital admission per patient and −0.79 outpatient visits per patient over the 12-month study period.

According to provincial administrative health data, the average costs for IBD care in Alberta in 2019 were CAD $9191.14 per inpatient admission and CAD $295.74 per outpatient or ER visit. If the intervention effects are similar to those in the study by De Jong et al [19] study, the reduction in hospital admissions and outpatient visits in our sample population could result in approximately CAD $1.3 million in savings for the health care system in the first year, approximately CAD $4.2 million in the second year, and approximately $6.9 million in the third year.

If MyIBDToolkit is scaled up to the entire province, the reductions in health care utilization may translate into savings of approximately CAD $35 million annually for our provincial health care system, and significant increases in inpatient and outpatient capacity. Although this estimate assumes 100% provider and patient uptake, it does not account for the expected increase in prevalence of IBD over time. these two sources of error are expected to compensate for each other.

Limitations

Our proposed study is not without limitations. One of the major limitations of our study is the use of administrative databases as primary data source. Health care administrative records can be time-saving and cost-effective for collecting large amounts of data; however, they are limited by the search parameters used to filter the records and the accuracy of the records themselves. This study is also limited as our pilot launch is limited to a single site. Piloting MyIBDToolkit at a single site is advantageous from a logistical point of view; however, it does not allow us to receive feedback from HCPs working at rural sites or HCPs with little experience using CC.

The ability of HCPs and their patients to use MyIBDToolkit is limited by their access to and willingness to use the existing EMR system. By November 2024, CC will be available to all HCPs across Alberta; however, its use is not mandated outside tertiary and acute care centers. This limitation means that some primary care providers or external allied health professionals who support the health maintenance of patients with IBD may not have access to MyIBDToolkit. We have tried to limit this drawback by offering as many of the components of MyIBDToolkit on an external webpage; however, converting all of the resources to print was not possible. AHS continues to advertise CC, and with time, we hope that with more awareness will encourage more primary care providers to join CC and gain access to MyIBDToolkit.

Acknowledgments

We would like to acknowledge the support of the many organizations and groups who have supported the project to date. This includes the DHSCN, Alberta Strategy for Patient Oriented Research Support Unit, Alberta Innovates, and Nutrition Services. We would also like to extend our appreciation to Louise Morrin for her support throughout the project's development. Our proposed study is funded by an Alberta Innovates Grant (Grant #222300176).

Conflicts of Interest

None declared.

Multimedia Appendix 1
Post-implementation patient satisfaction questionnaire to be administered following the launch of MyIBDToolkit.
[DOCX File, 34 KB - researchprotocols_v14i1e65659_app1.docx]

Peer-review report 1
Peer-Review Report from Alberta Innovates Grant Committee (Alberta Health Services, Canada).
[PDF File, 215 KB - researchprotocols_v14i1e65659_app2.pdf]

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Abbreviations

AHS: Alberta Health Services
CC: ConnectCare
DHSCN: Digestive Health Strategic Clinical Network
EMR: electronic medical record
HCP: health care provider
IBD: inflammatory bowel disease
RE-AIM: Reach, Effectiveness, Adoption, Implementation, Maintenance

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Protocol

Telehomecare Monitoring for Patients Receiving Anticancer Oral Therapy: Protocol for a Mixed Methods Evaluability Study

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Abstract

Background: Telehomecare monitoring (TM) in patients with cancer is a complex intervention. Research shows variations in the benefits and challenges TM brings to equitable access to care, the therapeutic relationship, self-management, and practice transformation. Further investigation into these variations factors will improve implementation processes and produce effective outcomes.

Objective: This study aims to concurrently analyze implementation and evaluate the effectiveness of TM for patients receiving anticancer oral therapy. The objectives are to (1) contextualize how and why TM is implemented according to (a) site characteristics, (b) team characteristics, and (c) characteristics of patients receiving anticancer oral therapy; (2) assess TM effectiveness for recording electronic patient-reported outcome measures (ePROMs) and patient-reported experience measures (ePREMs) according to the site, implementation process, and patient characteristics; (3) describe the acceptability and feasibility of TM from the perspectives of the people directly or indirectly involved and provide evidence-based actionable guidance in anticipation of provincewide implementation.

Methods: This type II hybrid effectiveness-implementation study uses a concurrent mixed methods design. Evaluability assessment is integrated into an emerging practice in 3 participating sites to enable the evaluation of implementation strategies on TM clinical outcomes. Quantitative data for ePROMs and ePREMs will be collected using validated oncology questionnaire. Descriptive statistics and repeated measures using multiple linear mixed models and generalized estimating equations analyses

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will be undertaken alongside interpretive descriptive coding of qualitative data. Qualitative data will be gathered from key informants guided by the RE-AIM (reach, efficacy, adoption, implementation, maintenance) framework and its extension, PRISM (practical robust implementation and sustainability model). The concurrent approach allows results at multiple stages of this study to be integrated iteratively. The methodological choice aims to provide real-world data that are rigorous, rapidly usable in practice, and transferable to other settings.

Results: Questionnaires were pretested and the technological platform was codeveloped with members of the cancer care team and patients. Preparatory work was carried out to configure the TM platform and activate coordinating mechanisms between members of the cancer care team, patients, information technology experts, and the research team. A steering committee with 3 working groups was established to oversee the technological, clinical, and evaluation aspects of this study. Recruitment of patients for ePROMs started in February 2024, and data collection is expected to continue until March 2025. Interviews with members of the cancer care team began in November 2024. Full analysis should be completed by September 2025.

Conclusions: This study will clarify how, why, for whom, and under what conditions TM can complement current care models. Our evaluability assessment will help to address implementation complexities and better understand intervention-to-practice operationalization so that implementation might be adapted to contextual factors without potentially harmful or inequitable impacts on patients.

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(JMIR Res Protoc 2025;14:e63099) doi:10.2196/63099

KEYWORDS

telehealth; virtual care; telehomecare monitoring; anticancer oral therapy; oncology; electronic patient-reported outcomes; electronic patient-reported experience; evaluability study; mixed methods; implementation.

Introduction

Background

Use of anticancer oral therapy, administered alone or in combination, is increasing rapidly in patients with cancer [1,2]. Anticancer oral therapy offers patients the convenience of taking medication at home, which has considerable benefits (eg, reduced hospital visits, time spent in waiting rooms and transport, transportation costs, as well as increased autonomy) [3,4]. However, there are important concerns around nonadherence to treatment [5] and the transfer of responsibility for drug administration, management of side effects, and monitoring of warning signs from the members of the cancer care team to the patients and primary care professionals, who are not always comfortable with these roles. Interdisciplinary cancer care teams (oncologists, nurses, pharmacists, psychologists, social workers, and others) are part of multiteam systems [6] that include primary care professionals (family physicians, nurses, social workers, and community pharmacists), patients, lay caregivers, nonprofit community organization workers, managers, and policy makers. Not everyone is necessarily prepared for the role and practice changes required by telehomecare monitoring (TM) [4,7,8]. Several conditions must be met to assure the safety of patients receiving anticancer oral therapy. For example, patients require capacities for self-management and adherence to treatment, the support of a family member or lay caregiver, and timely access to members of the cancer care team when needed. These team members need to establish regular and proactive monitoring, as well as effective communication and coordination, to ensure prompt response in case of need [3,7,9]. The proposed study aligns with priorities for research on TM [10] by looking specifically at its use among patients receiving anticancer oral therapy. This study focuses on the importance of structuring the increasing use of TM in such a way as to maintain the therapeutic relationship and optimal communication between patients and members of the cancer care team. The proposed structure involves a digital platform that is easy for patients to use and is regularly monitored by members of the cancer care team and alerts them when follow-up is required. This study addresses the integration into clinical processes and the effectiveness of TM on patient-reported outcomes and experience of receiving anticancer oral therapy treatments [11] based on differences in setting, team, and patient characteristics.

There are multiple terms (eg, telecare, virtual care, and eHealth) and definitions of telehealth that frequently overlap [12]. In this study, the term TM is used to describe interactions between patients in their own homes and members of the cancer care team. Telehealth generally refers to a health or social service provided at a distance using synchronous or asynchronous videoconferencing, digital applications, or telephone to improve health [11,13]. Telehealth is not new, but before the COVID-19 pandemic, its use was uncommon in cancer care and limited in most health systems [14]. For example, a 2019 study reported that only 0.6% (3/464) of family physicians in Québec, a province in Canada, had ever used telehealth, compared to 4.2% (108/2569) of the respondents in the rest of Canada [15]. Little data are available on the postpandemic use of telehealth in Canada. A national survey of 1038 participants in the United States found that the proportion of professionals in cancer care teams (oncologists, nurses, and residents) using telehealth increased from 19% to 84% during the COVID-19 pandemic [16].

In the oncology context, a systematic review (2017-2020; where, it should be noted, only 3 of 37 studies were conducted in Canada) concluded that telehealth is appropriate for symptom evaluation in adult patients during active treatment and survivorship [17]. Studies report several telehealth benefits for patients [17-20], namely improved accessibility, satisfaction,

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effectiveness, and comfort (especially in people with moderate symptoms or physical limitations); better adherence and treatment persistence; reductions in transportation costs and absences from work for medical follow-up; less decline in quality of life; and fewer emergency department visits. Benefits for members of cancer care teams include the potential to work remotely and thus contribute to maintaining service accessibility [21], real-time monitoring of patients-reported outcomes, and maintenance of communication among the teams involved along the care trajectory [19]. At the health system level, one study finds that telehealth can reduce missed appointments and has the potential to positively impact the efficiency of human resources [22].

However, the limitations of telehealth must also be recognized. Recent studies find that some patients prefer in-person consultations and do not wish to continue with TM after the pandemic [17], while others prefer a hybrid approach that considers their needs and preferences [21]. Some studies [20,23] warn against a model that replaces in-person visits with telehealth to reduce health care costs or deal with shortages of human resources. Other limitations include poor internet access, the cost of computers and tablets, and difficulties with remote communication, especially for people with low technological or health literacy [24]. It is crucial that recourse to telehealth does not create disparities in access to care, notably for people who may have problems using technology [17,25] and people in situations of vulnerability who require in-person psychosocial support [26]; the risk of disparities is heightened when telehealth is hastily planned, as was the case during the pandemic [24]. For members of the cancer care team, the use of TM depends on new practices, supported by legitimate leaders and dedicated resources, and a context that includes a history of successful transformation [27]. Structures must be in place to identify implementation barriers and find means of overcoming them to prevent undesirable organizational effects (eg, interpersonal conflict, lack of organizational support, burnout, intention to quit, and absenteeism) [28,29] or jeopardize the quality of care (eg, depersonalization of care, diminished partnership in care, and threats to the therapeutic relationship and relational continuity) [30]. The compatibility between TM and established practices, and perception of its usefulness, have a strong impact on TM use and on team members' satisfaction [31]. At an institutional level, major changes require attention to organizational, legal, and ethical challenges (patient records, protection of personal information, professional responsibility, and technological evolution) [32]. To summarize, the scientific literature identifies the benefits and limitations of telehealth in cancer care. However, the diversity of participants and clinical conditions in available studies, the various research methods used, and the plurality of contexts make it difficult to grasp the nature and extent of challenges around TM implementation and effectiveness in a given context [20]. Our study aims to improve understanding of these challenges by producing evidence specific to the local context on predictors of real-world adherence to TM and its potential effects.

TM can be conceptualized as a multifaceted telehealth intervention that involves a network of heterogeneous groups (eg, patients, managers, members of the cancer care team, primary care professionals, decision makers, nonprofit community organization workers, information technology experts, and professional orders or associations), with different and even competing goals and interests and acting at different system levels. The novelty of TM differs between users. Our previous work shows that multifaceted interventions produce anticipated results when the network of people involved rally around a common objective [27], with shared leadership [33], and in partnership with patients [30].

Theoretical and Operational Model

From the perspective of actor-network theory (ANT) [34,35], translating TM into practice occurs through nonlinear processes: common definition of the problem and rationale for TM (problematization), expectations and strategies to engage team and patients (interest generation), role attribution and engagement of the people involved (enrollment), coordination of network action (mobilization), and sustainability (irreversibility). These building blocks, also considered as management tools [36], are consistent with an evaluability assessment [37]. They guide our participatory approach to providing evidence-based and actionable guidance on the use of TM that will benefit patients, their caregivers, and members of the cancer care team. At the operational level, this study is based on the RE-AIM (reach, efficacy, adoption, implementation, and maintenance) framework [38], and its PRISM (practical robust implementation and sustainability model) extension [39]. The RE-AIM/PRISM framework encourages consideration of the characteristics of patients, members of the cancer care team, and their practice setting (Figure 1).

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Figure 1. TM study framework adapted from RE-AIM/PRISM. QCN: Québec Cancer Network; PRISM: practical robust implementation and sustainability model; RE-AIM: reach, efficacy, adoption, implementation, maintenance; TM: telehomecare monitoring.

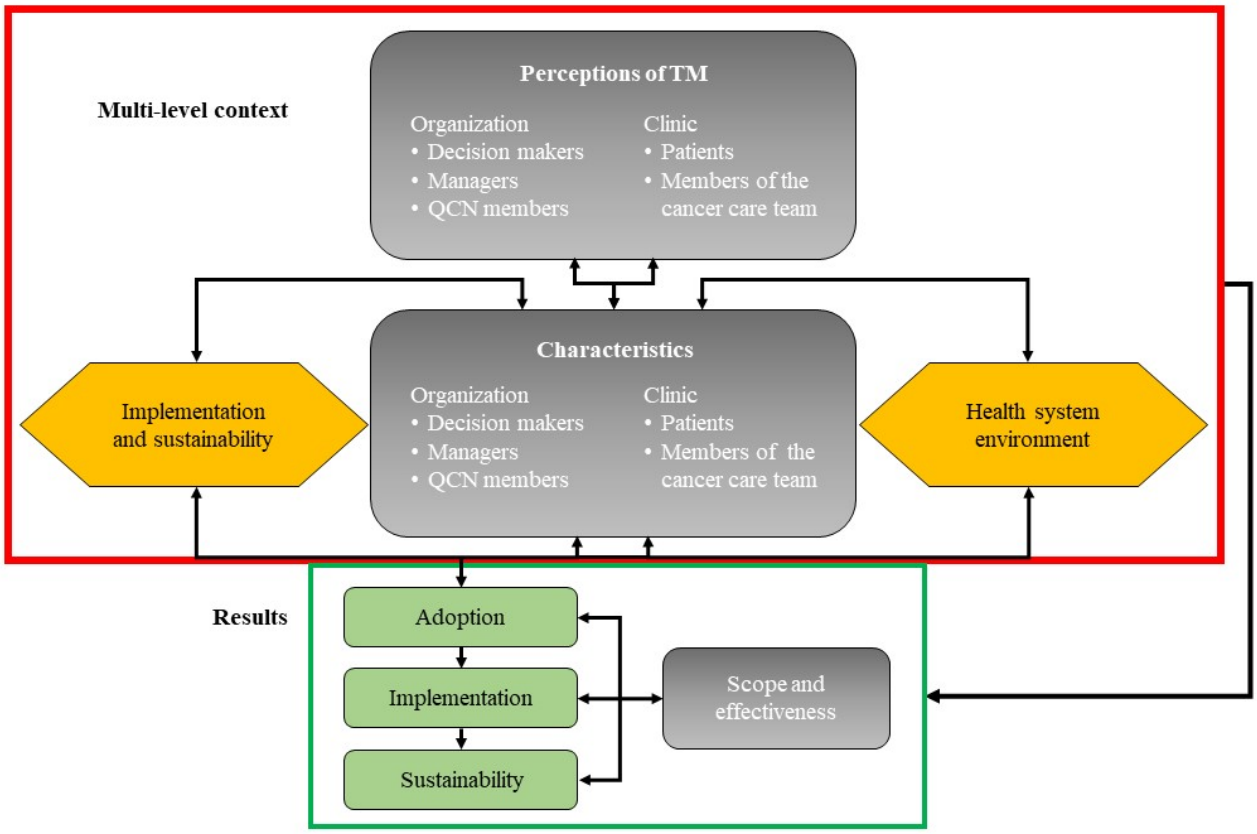

Preparatory Work

The national telehomecare platform is supported by the Québec Ministry of Health and Social Services. The telehealth coordination office, housed in one integrated health and social services center [13], has a mandate to manage the platform's deployment in several hospital centers. TM is based on evidence and adaptation achieved through experimentation in clinical settings. The platform was co-developed with the formal participation of stakeholders (eg, patients, managers, information technology expert collaborators, clinical leaders, and researchers). Preliminary work allowed the TM platform to be configured for use with patients [40]. Locally, its configuration was conceived and undertaken collectively by pharmacists, pivot nurses in oncology, and patients. Various strategies were implemented to support TM use to report symptoms and support self-management (eg, demonstration video, support resources, educational modules, symptom management messages, warning signs or "red flags" with decision supports, and accompaniment by survivors of cancer). Preimplementation indicators were the frequency of evaluations by patients, warning sign thresholds for clinical tools, specific alert management algorithms to guide cancer care team members' interventions, range of monitoring (percentage of potential patients, percentage who accepted, percentage who refused, and percentage of red flags addressed), and teaching and training needs. This preliminary work was financially supported (salaries, equipment, and expertise) and closely accompanied by members of the cancer program of the Québec Ministry of Health and Social Services. The preparatory work revealed challenges in implementation (eg, identifying members of the cancer care team to assign to TM, redistributing work, leadership style, and pace of patient recruitment). Facilitating and impeding factors need to be systematically assessed to achieve expected effectiveness and guide scale-up across the province.

Aim and Objectives

This study aims to concurrently examine the implementation process and evaluate the effectiveness of TM for patients receiving anticancer oral therapy. In line with the conceptual framework, the specific objectives are as follows:

1. To contextualize how and why TM is implemented according to (a) site characteristics (location, mandate, resources, and supports), (b) team characteristics (members of the cancer care team, managers, and coordination with primary care and nonprofit community organizations), and (c) characteristics of the patients receiving anticancer oral therapy.
2. To assess TM effectiveness for digitally recording electronic patient-reported outcome measures (ePROMs) and electronic patient-reported experience measures (ePREMs) according to the site, implementation differences, and patient characteristics.
3. To explore the acceptability and feasibility of TM from the perspective of the people directly or indirectly involved and provide evidence-based actionable guidance in anticipation of provincewide implementation.

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Methods

Study Design

This mixed methods evaluability study uses a type II hybrid effectiveness-implementation design. An evaluability assessment is appropriate for all stages of a novel intervention [37,41,42]. It enables (1) formative assessment of clinical, organizational, and technological components through reflection "on and in practice" and rapid feedback on findings; (2) better planning; (3) accelerated integration of research findings through constant interaction between researchers and stakeholders; and (4) identification of new ways of doing things to achieve scale-up objectives [37,41,42]. A type II hybrid effectiveness-implementation design enables in-depth analysis of TM integration in a natural setting (objective 1) and effectiveness for patients receiving anticancer oral therapy (objective 2) [43,44]. Type II refers to the concurrent study of implementation and effectiveness, an approach that is recognized in cancer care interventions [45] and is consistent with the RE-AIM/PRISM framework [43] (objective 3). A mixed concurrent approach, suited to participatory evaluability assessment [37], integrates quantitative and qualitative data [46]. The voluntary participation methodology allows for the inclusion of multiple perspectives, and equity, diversity, and inclusion considerations [47]. Our study adheres to ethical research standards [48] and responsible research conduct [49]. Researchers will endeavor to maintain relationships based on trust and mutual respect by being attentive to issues around the social acceptability of health research, by protecting the identity of participants, and by involving patient partners from the very start of our study [50].

Our study comprises the following interdependent phases:

1. Preparing the ground (objective 1; duration 4 months) includes presentation of the TM study to the actors involved, development of reciprocal engagement between the research team and TM leaders including patient partners and community actors, and an environmental scan [51] to understand local dynamics (potential participants; rate of inclusion in TM; technical, professional, and personal challenges; and workforce or resource challenges). This process of collecting, interpreting, and using information from the internal and external TM environment informs strategic decision-making, guides accompaniment efforts, and ensures the progress of this study by resolving difficulties that may arise.
2. Analysis of implementation and clinical effectiveness based on RE-AIM/PRISM (objectives 1 and 2; duration 12 months) assesses achievement of TM goals and evaluates expected benefits and absence of unexpected negative effects related to its use, ePROMs and ePREMs, and resource use. Markers of TM use will be defined according to patients' perspectives, cancer care team reorganization of work and collaboration with primary care and nonprofit community organization partners, use of human and financial resources in local arrangements, and levers and means used to overcome obstacles to safe implementation while upholding equitable access to care for patients.
3. Integrated planning for sustainability and spread (objective 3; duration 4 months) extracts lessons for eventual changes to be brought to TM to improve sustainability and future scale-up to other groups of patients (eg, intravenous therapy, immunotherapy, postsurgical cancer follow-up, palliative non–end-of-life care, and survivorship follow-up) [4]. This stage will identify the clinical, organizational, and equity challenges of TM as a complex highly context-dependent intervention. The transferability of this real-world study must also be optimized [43], especially where geographic and local dynamics differ.
4. Dissemination of results (duration 4 months) relates to the plan described in the later section of the protocol on integrated knowledge translation, for presenting findings to various groups of end users.

Study Sites

This study will be conducted in 3 cancer centers in the province of Québec, Canada, that have introduced TM over various periods (1 year or 1 month) and dedicated varying levels of human and financial resources. These cancer centers are located in hospitals that are part of the Québec Cancer Network. These centers have distinguishing characteristics (Table 1): geographic location (mega-urban, semiurban, or urban) [52], population served, mandate (academic or community), size of the cancer care team, team caseload (number of visits or number of treatments), primary care centers (number of community service centers or number of family medicine groups), TM work redistribution between members of the cancer care team (designated leadership or shared leadership), and formal partnership with survivors of cancer trained for TM support and research.

Differences between study sites will help understand perceptions of TM in real-world contexts and the influence of various factors on adoption, implementation, effectiveness, and potential sustainability, as illustrated in Figure 1.

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Table 1. Characteristics of participating cancer centers[a].

	Site 1	Site 2	Site 3
Organizational			
Geographic location	Mega-urban	Urban	Semiurban
Population, n	229,359	172,713	199,376
Mandate	Community	Academic	Community
Size of the cancer care team	Large	Large	Small
Clinical			
Radiotherapy	Yes	Yes	Yes
Hemato-oncology	Yes	Yes	Yes
Visits to hemato-oncology services, n	63,405	44,245	13,180
Treatments, n	14,758	23,534	5403
Primary care centers			
Community service centers, n	2	5	3
Family medicine groups, n	8	10	8
Implementation			
Patient partners, n	0	1	0
Telehomecare monitoring coordination model[b]	Shared leadership	Designated leadership	Shared leadership

[a]Publicly accessible data (2021-2022).

[b]Coordination model apparent in early implementation.

Participants and Sampling

This study involves key informants knowledgeable of TM. The sampling strategy for patients is nonprobabilistic, based on eligibility criteria preestablished by the cancer care team. Inclusion criteria are receiving anticancer oral therapy, being interested in TM for a minimum duration of 6 months, having internet access and experience using it, being able to report symptoms with existing tools, being open to educational material, and being able to recognize warning signs. For key informants (patients, members of the cancer care team, managers, institutional decision makers, and nonprofit community organization workers), purposive sampling [53] aims to obtain a cross-section of views from people at different decision-making levels around TM (clinical, organizational, or system). These strategies are appropriate given the exploratory nature of an evaluability study.

We estimate from hospital administrative records that between 100 and 200 patients receive anticancer oral therapy each year (N=400 in 3 participating centers). Preparatory work since March 2022 shows that about 160 of these patients would meet our inclusion criteria and about half would continue completion of the ePROMs questionnaires over 6 months (80 patients × 26 weeks × 3 times a week=6240 results) and the ePREMs experience of care questionnaire at 3 months (ePREMs: n=80). A sample of 40 participants is considered sufficient for an exploratory study of a health services intervention [54]. We estimate that about 12 individual interviews per site with patients, members of the cancer care team, and managers (n=36) would allow for theoretical saturation of qualitative data [55]. This will be supplemented by interviews with decision makers (eg, policy level, professional orders, and national organizations; n=9), for a total of 45 interviews of about 60 minutes. Participants will be offered CAD $60 (US $41.90) compensation.

Quantitative Data Collection

Clinical data collection tools for ePROMs are based on those used in the Patient Reported Outcomes to Enhance Cancer Treatment study [56]. Ten questions, with French versions available for Canada [57], are taken from the PRO-CTCAE (Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events) library of the National Cancer Institute (eg, nausea or vomiting, diarrhea, constipation, dyspnea, stomatitis, skin problems, acne, hand-foot syndrome, edema, pyrexia, and more). The items are reported on a 5-point scale. Six questions on symptoms from the Edmonton Symptom Assessment System-revised are included (pain, depression, anxiety, insomnia, and fatigue) [58]. Subquestions on self-management support were created by the interdisciplinary team at the integrated health and social services center overseeing implementation to direct patients to educational modules on the TM platform. The ePROMs responses are collected 1 to 3 times per week according to patients preference. In preparatory work, 90% (144/160) preferred 3 times a week. The ePREMs questionnaire includes dimensions on health system responsiveness adapted for patients [27], satisfaction [56], and health-related quality of life [59], all measured with validated tools. Along with these dependent variables, self-reported clinical data (tumor site, time since diagnosis, treatment type, and comorbidities) and sociodemographic data (sex, gender, age, education, perceived health status, and

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economic situation) are collected (control variables) to enable comparison with other studies [56]. The ePREMs questionnaire will be administered 3 months after the start of TM [56]. The time for completing the questionnaire is estimated at 20 minutes, and compensation of CAD $20 (US $13.97) is anticipated. We will monitor the indicators to associate contextual factors with clinical and implementation data and promptly identify unanticipated undesirable effects of TM. These are the dependent variables of this study.

Qualitative Data Collection

Semidirected individual interviews conducted at the mid-point in this study aim to describe enabling and impeding factors for each of the dimensions of the RE-AIM/PRISM framework, which include multilevel aspects (eg, perceptions of TM and characteristics of organizational and clinical stakeholders, the context of implementation and sustainability, and the impact of the wider health system environment) and mechanisms that support adoption, implementation, and sustainability to achieve the scope and effectiveness of TM (Figure 1). For example, questions inspired by other studies [17,56] and adapted to respondent type address the following: ease of understanding and using TM, usefulness and relevance of self-reported items, quality of communication and accessibility, clinical utility, and sense of self-efficacy for patients. Specific questions for members of the cancer care team to focus on the following: effects on their work, time management, ability to adapt their practice, adjustment of follow-up algorithms, and ways that data influence (or not) their discussions with patients. All participants will be questioned about their satisfaction and proposed improvements for scale-up and their perception of added value to the quality and safety of care.

Data Analysis Procedure

Standard descriptive statistics will enable data to be summarized (ePROMs, ePREMs, sociodemographic, symptom severity, and percentage of indicators of the scope of TM). For ePROMs, the number of questionnaires completed will be calculated for each patient, and the number of completed weekly ePROMs questionnaires will be divided by the number of expected questionnaires. Intrasite comparisons between measures will detect differences in exposure to TM and establish key periods on the patients trajectory. Relationships between the ePROMs items and patient characteristics will be described using Spearman correlations and chi-square tests. Multiple linear mixed models and generalized estimating equations for repeated measurements on the ePROMs [60] will be used to assess relationships between patient characteristics, ePROMs items, and ePREMs dimensions. Statistical significance will be $P<.05$. These analyses will identify the most important determinants of health status, relevant indicators, and appropriate moments for measurement.

Recorded and transcribed interviews will be analyzed using a descriptive interpretive approach [61] with 2 coders independently coding meaning units. A first coding cycle will focus on themes of the RE-AIM/PRISM framework, and a second interpretive cycle will identify links between context, implementation, and effects [61]. Finally, a synthesis of this qualitative process integrating quantitative results [62] will be codeveloped with volunteers from patients, people involved in care, and the research team.

The integration (qualitative data+quantitative data) will occur at several stages: (1) methodology, with linking sampling strategies, where participants for interviews are selected from among patients receiving anticancer oral therapy; (2) data collection, by adopting a simultaneous interactive approach [63] in which emerging results will iteratively lead to adjustments to future interview questions; and (3) interpretation, in partnership with spokespersons from the various groups involved (eg, professionals, patients, lay caregivers, nonprofit community organization workers, managers, and policy makers). Attention will be paid to quality criteria for qualitative [61] and mixed methods [62] studies to mitigate study limitations.

Ethical Considerations

This project was approved by the Research Ethics Board of the Research Centre of the Montérégie-Centre Integrated Health and Social Services Centre, which serves as the review board for all sites in this multicenter project (MP-04-2024-825, initial approval: August 29, 2023; renewed approval: June 7, 2024). This study will be conducted according to the Helsinki Declaration, and informed consent will be obtained from all individual participants [48]. Study results will be presented at the group level and will ensure that no individual, whether patients or staff, will be identifiable. Participation is voluntary and participants can withdraw from this study at any time.

Integrated Knowledge Translation

The integrated knowledge translation plan (Textbox 1) includes approaches suited to use during and at the end of the project [64]. The research team considers it important to establish bidirectional exchanges between knowledge producers and users and involves knowledge users at all stages of this study. This approach is chosen strategically for its positive impact on the adoption of new evidence-based practices, as well as for its potential contribution to managing problems that may arise during this study. ANT provides the basis for considering the heterogeneity of people involved in TM. ANT has been widely used in applied research to study the production and use of research evidence [64]. It contributes to a better understanding of why research results do not translate easily and are not integrated rapidly into settings for which the research was produced. This is consistent with the idea that people (professionals, patients, lay caregivers, nonprofit community organization workers, managers, and policy makers) as well as context (technology platform, computers, equipment used, and funding) act on the implementation and effectiveness of TM. The plan is inscribed in a project where sustainability and scale-up are anticipated right from preliminary work. It also aims to amplify the impacts of the research at provincial, national, and international levels. As a result, the activities, format, timing of, and vehicle for dissemination will be adapted to each target audience.

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Textbox 1. Integrated knowledge translation plan of audience and activities.

Actors in the field

- Early detection of barriers, facilitators, controversies, and potential solutions
- Accessibility of the research team to actors in the field
- Discussion of interim findings in each setting
- Debriefing meetings to triage adjustments during implementation
- Newsletter published every 4 months on our website, distributed to partner networks of coresearchers and collaborators
- Support for team members for cancer and local managers
- End-of-project presentation of results in each site

Academic and research communities and trainees

- Generation of interest among the next generation of researchers in the renewal of cancer care: graduate students, oncologists, physicians, and health care professionals
- Dissemination of this study and its results in courses offered by research team members in their universities
- Mobilization of the coauthors' networks
- Sharing of tools developed and found useful for consolidating patients-reported outcomes and for team resilience in facing the challenges of telehealth
- Development of evaluative, interventional, and theoretical application of actor-network theory studies and conceptual studies based on the RE-AIM (reach, efficacy, adoption, implementation, maintenance) framework and its extension, PRISM (practical robust implementation and sustainability model)

Institutional stakeholders and knowledge brokers

- Mobilization of partner networks at multiple decision-making levels
- Presentations at collaborator and stakeholder events
- International peer-reviewed scientific conferences
- Websites to reach a wider audience
- Publication in open-access peer-reviewed journals

General public

- Tailored appropriate messages to share knowledge with different interest groups and the general public as part of an open science approach to broad dissemination

Results

An interdisciplinary steering committee including various stakeholders such as researchers, managers, members of the cancer care team, decision makers, and community actors, has been implemented to oversee the TM implementation. Its members are involved in 3 working groups that report to the steering committee; these groups will support the technological, clinical, and evaluation aspects of this study and address and assist in the resolution of controversies. At the onset of the project, our discussions with patients raised awareness that "imposing substitution on everyone could jeopardize the trust that is essential to our relationship with the cancer care team and increase the stress on us and our families; we don't want that."

An expert committee comprising the TM leader, a pharmacist, a pivot nurse, an information technology expert, and the principal investigator supports organizational readiness, ensuring that local needs for implementation are met and that the TM platform is operational at all sites. This committee developed a PowerPoint (Microsoft Corp) presentation aiming to (1) inform members of the cancer care team and managers of the state of science about TM content, structure, and patient-professional communication mechanisms; (2) describe the potential benefits and limitations of TM for patients, members of the cancer care team, and organizations; (3) present the objectives of the evaluability assessment and effectiveness-implementation study design; and (4) describe the ePROMs monitoring platform and ePREMs questionnaire. Between November 2023 and February 2024, a total of 72 members of cancer care teams from the participating settings took part in the 90-minute session and received continuing education credits. Meanwhile, the codebook for ePROMs was developed and questionnaires for ePREMs were pretested in two cycles by a team of patient partners, researchers, and knowledge users.

Access to the TM platform by the research coordinator and principal investigator required institutional authorization and engagement to ensure adherence to strict measures to protect personal data and confidentiality. This authorization process

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was initiated in December 2023, with permission granted in March 2024.

Between February and July 2024, a total of 35 patients were enrolled and had completed ePROMs on the TM platform 1 to 3 times a week; 6 interviews of patients had been conducted. As of November 2024, a total of 1831 ePROMs and 41 interviews had been completed. Further, data collection with team members and other people concerned with the implementation had been initiated. The collection of quantitative and qualitative data is expected to be completed by March 2025, and the full analysis is expected to be completed by September 2025.

Preliminary interpretive coding of interviews suggested that the TM platform was easy to use and that members of the cancer care team provided prompt feedback when symptoms persisted despite self-management and educational material. Patients expressed they would like access to the TM platform on small devices that was not yet available and questioned how their oncologist was informed about the ePROMs. Clarification around the roles of nurses and pharmacists was desired to avoid confusion. The most important positive impact was the implication of a patient partner who explained the platform, how to fill in information, and could be reached for further support in using the platform.

Discussion

Expected Findings

This study will produce new data on the deployment of TM to support ambitions to modernize services available to patients [65]. The results will help inform decisions by integrating clinical, organizational, and health system considerations. This multilevel study will contribute to efforts to satisfy the growing appetite for telehealth, as well as its acceptability and feasibility [66]. Expected impacts are (1) a clinical contribution by informing the use of patient-reported outcomes, achievement of self-management objectives, and prompt team response to needs; (2) an organizational contribution by producing information on contextualized best practices, centered on the needs and preferences of patients, that improve access to care and appropriate use of resources and serve as a complement to and not substitution for clinical contact; and (3) a social win-win type contribution by reducing inequalities of access related to geographic or social distance, while providing essential data on opportunities and risks perceived by some groups of patients.

A recent review on telehealth reports that TM is promoted as a promising future direction for the management of anxiety and depression in patients with cancer [67]. Our study will contribute to efforts to identify types of symptoms that can be managed with TM and asynchronous interventions along with others that require in-person encounters. As patients cautioned us during the preimplementation phase, TM should not be a substitute for face-to-face interventions or be used for workforce rationalization. Additionally, our integrated knowledge translation strategy will activate the dissemination of best practices that recommend establishing the patient-professional relationship before integrating telehealth into care [68]. In the context of health human resources, TM promoters should be aware of the temptation to limit the face-to-face component of care, which may be harmful to the quality of care. Although proximity can be established through in-person or online encounters [69], patients participation [30] and collaborative governance [70] appear essential to prevent the expedient use of TM.

This study may also contribute to reducing disparities arising from the uneven use of telehealth technologies. However, other organizational priorities can increase the risk of TM program failure and increase disparities in access according to the capacities of individual patients and the availability of family caregivers to accompany them in using TM.

Strengths and Limitations

The inclusion of 3 settings chosen for their different characteristics increases the originality of this study's contribution. Multisite studies offer a wider perspective and will add to findings from single-institution studies on teleconsultation [17]. Our evaluability assessment will provide new empirical data on models of care that integrate TM services in advancing the quintuple aim of better health, improved care experience, well-being of members of the cancer care team, and health equity throughout the cancer journey. Our focus on how complementarity is achieved between TM and traditional face-to-face encounters aligns with calls for practical evidence in most recent reviews [17,67].

Some limitations are also anticipated in this study. The methodologies have potential biases. These include selection bias arising from convenience sampling and the fairly small sample size of participants, and observation bias due to real-world data collection that may compromise the application of results to wide-scale implementation [71]. These limitations could be compounded by the use of mixed methods [46] and by linking the implementation process to effectiveness in the specific participating sites. However, the production of such evidence provides detailed information that supports knowledge users in their decision-making and helps save time and avoid TM implementation failure.

Conclusions

TM is a complex intervention at the interface of clinical and organizational domains. Telehealth services for patients with cancer emerged as a key theme during the COVID-19 pandemic and will only become more important in the future. Our evaluability assessment will provide new empirical data on how to design TM services that prioritize a patients-centered approach aligned with patient needs, preferences, and realistic expectations. The focus on how complementarity between TM and traditional face-to-face encounters takes shape will answer the call for practical evidence to inform implementation. Our knowledge translation plan will create opportunities to share the successes that emerge and inspire other settings. Findings may also help to improve follow-up care for patients receiving other types of anticancer treatment that require close monitoring and management. In the event of implementation failure in this study, information on contributors to failure will help prevent

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TM promotors from falling into some of the potential traps of implementing complex interventions.

Acknowledgments

We are grateful to all members of the cancer care teams and patients who were involved in the preparatory work and will be participating in this study for their time and contributions. We thank the Fonds de recherche du Québec–Santé for their financial support. The funding source has had no role in this study's design and will have no role in the collection, analysis, or interpretation of data, in writing this paper, or in the decision to submit for publication. This study has received funding from the provincial research funder Fonds de recherche du Québec–Santé (Oncopole ACCES-Onco, grant 326483-2023).

Data Availability

The datasets generated or analyzed during this study will not be publicly available due to ethical considerations (ie, conditions of consent received from participants) but will be available from the corresponding author on reasonable request.

Authors' Contributions

DT, TJ-M, AD, MCB, DB, JC, MD, CF, BG, M Larivière, FL, M Lemonde, ÉM, NM, MP, SS, and CW handled the conceptualization, funding acquisition, methodology, and review and editing of the writing of this study. DT, TJ-M, and AD administered the project. DT did the supervision, visualization, and writing of the original draft. DT and DB worked on the validation of this study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the Accélération de la recherche et des soins pour le cancer au Québec (ACCES-Onco) (Québec, Canada). [PDF File (Adobe PDF File), 139 KB - resprot_v14i1e63099_app1.pdf]

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Abbreviations

ANT: actor-network theory
ePREM: electronic patient-reported experience measure
ePROM: electronic patient-reported outcome measure
PRISM: practical robust implementation and sustainability model
PRO-CTCAE: Patient-Reported Outcomes Version of the Common Terminology Criteria for Adverse Events
RE-AIM: reach, efficacy, adoption, implementation, maintenance
TM: telehomecare monitoring

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Protocol

Preventing Premature Family Maladjustment: Protocol for a Multidisciplinary eHealth Study on Preterm Parents' Well-Being

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Abstract

Background: The consequences of preterm birth extend beyond the clinical conditions of the newborn, profoundly impacting the functioning and well-being of families. Parents of preterm infants often describe the experience of preterm birth and subsequent admission to the neonatal intensive care unit (NICU) as a disruptive event in their lives, triggering feelings of guilt, helplessness, and fear. Although various research examines changes in parents' well-being and perception of self-efficacy during the stay in the NICU, there is a lack of research analyzing what happens in the transition phase at home after the baby's discharge. Recently, scholars have advocated for the use of web-based support programs to monitor and prevent preterm family maladjustment and assist parents.

Objective: This interdisciplinary research will develop a sociopsychological model focused on assessing the well-being of parents of premature infants during and after their stay in a NICU. Specifically, the study aims to (1) monitor the mental health of parents of premature infants both at the time of the child's discharge from the NICU and in the first 6 months after discharge to prevent family maladjustment, (2) deepen our understanding of the role of digital tools in monitoring and supporting preterm parents' well-being, and (3) study the potential impact of the relationship with health care professionals on the overall well-being of parents.

Methods: This project combines mixed methods of social research and psychological support with an eHealth approach. The well-being of parents of premature infants will be assessed using validated scales administered through a questionnaire to parents of preterm infants within 6 NICUs at the time of the child's discharge. Subsequently, a follow-up assessment of parental well-being will be implemented through the administration of the validated scales in a web application. In addition, an ethnographic phase will be conducted in the NICUs involving observation of the interaction between health care professionals and parents as well as narrative interviews with health care staff. Finally, interactions within the digital environment of the web application will be analyzed using a netnographic approach. We expect to shed light on the determinants of well-being among parents of premature infants in relation to varying levels of prematurity severity; sociodemographic characteristics such as gender, age, and socioeconomic status; and parental involvement in NICU care practices. With the follow-up phase via web application, this project also aims to prevent family maladjustment by providing psychological support and using an eHealth tool.

Results: The results are expected by October 2025, the expiration date of the Project of Relevant National Interest.

Conclusions: The eHealth Study on Preterm Parents' Well-Being aims to improve preterm parents' well-being and, indirectly, children's health by reducing social costs. Furthermore, it promotes standardized neonatal care protocols, reducing regional disparities and strengthening collaboration between parents and health care staff.

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KEYWORDS

preterm birth; parental well-being; sociology of health; digital-based monitoring; mixed methods research; eHealth

Introduction

Background

The World Health Organization defines as preterm a birth that occurs before 37 weeks of gestation [1]—in Italy, approximately 6% of newborns are born before term [2]. Preterm birth is a multiproblematic event with 3 main consequences. First, it poses a medical risk to the newborns as many of these infants are in critical condition and can experience a range of substantially and potentially life-threatening medical complications. The second consequence concerns the economic and medical cost of caring for these babies given the advances in perinatal and neonatal care that have contributed to a substantial increase in the survival rate of these infants, particularly for extremely premature ones who, until a few decades ago, had no chance of surviving [3]. The third consequence is that the premature birth of a child and the subsequent admission to the neonatal intensive care unit (NICU) are distressing experiences for parents. Parental stress and parenting difficulties in the first years of the child's life are well-known consequences [4]. Moreover, many longitudinal studies have described how prematurity negatively affects infants' development [5,6], and evidence has been gathered supporting that parent well-being and infants' long-term developmental outcomes are closely related [7]. Parents often describe premature birth and the subsequent hospitalization in a NICU as an emotional roller coaster and a disruptive life event [8]. An unexpected birth can trigger feelings such as guilt for not completing the pregnancy, helplessness, and fear of not being able to protect one's child [6]. Moreover, parent-infant separation once admitted to the NICU represents a major source of stress for both parents and their infants [9]. Prematurity affects not just the child and parents as individuals (eg, by delaying the exploration of the parental role) but also the family triad (and potential siblings) as it hinders the initiation of mutual understanding and the consolidation of affectionate and meaningful relationships. Indeed, the hospital environment limits the parent-child relationship, which primarily develops through the incubator's windows [10]. These restrictions, while serving to protect infants from pathogens, complicate the interaction between parents and newborn, making it even more challenging to activate caregiving modes necessary for the infant's psychological development, a task primarily undertaken by medical staff for clinical reasons [11]. Another important factor to consider, highlighted by Russo et al [12], is that the sociodemographic characteristics of parents act as independent stress predictors, with gender, occupational status, and age particularly playing a role in the levels of stress and depression among parents of hospitalized children. Furthermore, few studies have investigated fathers' experiences in these particular circumstances [6]. In Italy, especially during the COVID-19 pandemic, many NICUs applied restrictions regarding the frequency and time of parents' access, and fathers are usually less involved than mothers in practices such as skin-to-skin contact and kangaroo care, managing to start building a relationship with their babies only after discharge. As researchers have pointed out [13], it is important to consider the characteristics and points of view of both mothers and fathers as both parents are at risk after preterm births. Research suggests how parents' negative feelings can be reduced by giving them value as actors who can make decisions for the newborn [14]. The Family Integrated Care (FICare) model represents an example of a way to address the need for humanization and parent participation in health care for high-risk newborns admitted to the NICUs. Through this approach, parents have the opportunity to become increasingly engaged in their responsibilities, and their active involvement in care is a prerequisite for the consolidation of parenting skills, which are essential to cope with the separation through the NICU [15]. However, a recent study has pointed out that, although most units in different European countries report a neonatal care policy that encourages parents to take part in the care of their infants, parental involvement is still generally limited in Italy [6].

In addition, there is some evidence suggesting that the feasibility of implementing FICare with families of infants who are severely premature or critically ill remains a concern [16]. These cases often involve significant medical complexity, requiring intensive care, which may limit opportunities for parental involvement. Furthermore, the emotional and psychological toll of caring for an infant who is critically ill can hinder parents' ability to participate actively in caregiving activities, highlighting the need for tailored support to address these challenges. Although various research examines changes in parents' well-being and perception of self-efficacy during the stay in the NICU, there is a lack of research analyzing what happens in the delicate transition phase at home after the baby's discharge [17]. Moreover, to the best of our knowledge, no studies have specifically examined how socioeconomic factors such as parental income or geographic distance from the NICU influence participation in FICare. This represents a gap in the literature as these factors may pose challenges for certain families. To fill this gap, the intervention and participatory project aim to give voice to preterm parents and their experiences. An interdisciplinary study to set neonatal practices and enhance families' well-being (the Study on Preterm Parents' Well-Being [ParWelB]) was designed by the Department of Sociology and Social Research of the University of Milano-Bicocca (principal investigator: AD) and funded by the Cariplo Foundation. Starting in May 2021, ParWelB has been promoting constructive communication and collaboration among and between caregivers and parents in the NICU.

Recent studies highlight the importance of fostering the parent-newborn bond, showing that strengthening this interaction benefits both parents—through reduced anxiety and depression—and children, who experience improved neurological outcomes [6]. Longitudinal research further suggests that parental stress and anxiety can impair bonding and family adjustment, with potential consequences for the development of preterm infants [5]. Parental self-efficacy and social support play a crucial role in adapting after an adverse

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situation such as preterm birth [18]. Scannel [19] recently suggested how interventions that target the development of parental self-efficacy and social support can strongly impact the sense of competence, satisfaction in the parenting role, and resilience of all members of the family. Furthermore, Ionio et al [20] highlight in their work that having more information on how parents perceive neonatal care and an understanding of their needs also after the discharge of their newborn may allow health care staff to identify parents at risk, plan early interventions to meet their needs, and promote family functioning. Given the importance of building parents' self-efficacy, new neonatal practices (for upcoming preterm infants and parents) should be shaped based not only on the biomedical knowledge perspective but also on preterm parents' values, lived experiences, and perspectives.

The transition from the NICU to the home is a pivotal and challenging period for parents of preterm infants. It involves adjusting from the highly structured and professionally supported NICU environment to taking on full caregiving responsibilities at home. This shift can heighten feelings of uncertainty and stress, particularly as parents face reduced access to health care professionals and must navigate complex medical or developmental needs independently.

Our study is an interdisciplinary research project that, building on the premises of the ParWelB project, strives to assess preterm parents' well-being during and after the hospitalization in the NICU by combining mixed methods (using research strategies such as standardized questionnaires with internationally validated scales and ethnography) and psychological support through an innovative and technology-driven approach. Recently, scholars have championed the use of web- and app-based support programs to both monitor and prevent preterm family maladjustment and assist parents who struggle with transitioning to the home [21,22]. Furthermore, the work of Garfield et al [23] with infants with very low birth weight showed that parents who received an app-based support program improved parental self-efficacy and discharge preparedness compared with the control group. Therefore, the Bicocca research unit decided to team up with the Department of Psychology of the Catholic University of the Sacred Heart of Milan to design an eHealth (information and communications technology use to the advantage of human health) research project that assesses parents' well-being, particularly at the crucial time of discharge and the first 6 months at home, offering support to parents who are more fragile. Parenting self-efficacy has been understood as the way in which parents perceive their ability to care for their child [24] and has been associated with positive parental outcomes [25]. The well-being of parents refers to the fact that, given that preterm birth is a highly stressful event for parents [26], considering the difficulties and uncertainties they experience during this acute phase is of significant importance to prevent family maladjustment [27]. Families' involvement in the care of their high-risk neonates at NICUs represents the main axis of parent-partnered care initiatives. Each preterm parent develops a personal way to evaluate the situation based on the NICU lived experience. Specific characteristics may also influence the response to the hospitalization of one's child. Significant effects have been identified in relation to gender (mothers and fathers seem to differ in responses and relation to certain measures) and to the degree of social support that parents have access to. The latter has been found to impact positively the resiliency factor associated with coping strategies of families who have a child with a chronic illness [28], and there is a great need for studies investigating its impact on preterm parents.

Thus, the main focus of this research project is to develop a sociopsychological model focusing on the assessment of preterm parents' well-being during and after admission to a NICU with the use of eHealth.

Objectives

Stemming from these premises, our research's main aims could be synthesized as follows: (1) to monitor the mental health of parents of premature infants, with a plan for early intervention and a 6-month follow-up to prevent family maladjustment; (2) to stimulate eHealth growth by advancing knowledge on the role of digital-based tools in monitoring and supporting the well-being of parents whose infants have been hospitalized in the NICU for critical health situations (prematurity but also a wide spectrum of disabling or fatal diseases); and (3) to study the potential impact of the relationship with health care staff on the overall well-being of parents. In addition, our research aims to investigate potential differences in psychological well-being between parturients and nonparturients by also studying the impact of certain social characteristics (eg, nationality, educational level, employment status, and cultural enjoyment).

Methods

Ethical Considerations

Participation in the study will be on a strictly voluntary basis. According to the Declaration of Helsinki, respondents will receive written and oral information about the study and provide signed consent. They could withdraw consent at any time with no consequences for the future treatment of themselves or their infants. The eHealth ParWelB (e-ParWelB) project is financed by the Italian Ministry of University and Research with Next Generation EU and was approved in 2022 as a Project of Relevant National Interest (protocol 20225R7XB3). The project was submitted for approval to the ethics committees of the involved universities (University of Milano-Bicocca and Catholic University of the Sacred Heart of Milan) and, subsequently, to the 6 different territorial ethics committees to which the hospitals involved in the study are affiliated. The data are pseudoanonymized, meaning that each questionnaire is linked to a unique alphanumeric code that can be traced back to the user's web application code. Protective measures include compliance with legal and ethical standards; restricted access; and security protocols to prevent unauthorized access, disclosure, modification, or destruction. Finally, the project will not provide specific compensation to participants.

Recruitment

This study will be conducted simultaneously in 6 different Italian NICUs. Focusing on several units simultaneously has several advantages. First, it enables us to build a sample of satisfactory size within a reasonable time frame. Italy has a low birth rate,

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and therefore, concentrating on only 1 unit would pose a significant risk of obtaining an inadequate sample for any complex statistical analysis. In addition, the presence of various NICUs introduces a comparative dimension to the study. Previous research on neonatal intensive care [29] has shown that each unit has its own unique identity with different routines, idiosyncrasies, and decision-making processes. This identity is strongly influenced not only by the cultural context in which the unit is embedded but also by the administrative structure of the hospital and the legislative framework foreseen for neonatal care practice. This is particularly relevant in the Italian case, where the management of the public health system happens mainly at the regional level, with relevant differences between regions. Moreover, this study includes 5 NICUs from the public sector and 1 belonging to a private hospital, adding another possible layer of differences in the work culture of the units.

This research focuses mainly on the population of preterm parents—more specifically, parents of children born before 36+6 weeks of gestational age (GA) and hospitalized in intensive or subintensive care units for at least 10 days (critical threshold of hospitalization length). Considering the research objectives, it is crucial to distinguish infants according to the severity of prematurity because of the strong impact that the latter has on the health of the child and the duration of the hospitalization period. Therefore, there will be 3 groups: children born before 28 weeks of GA, infants born between 28+1 and 32 weeks of GA, and children born between 32+1 and 36+6 weeks of GA.

To be included, parents of preterm infants must meet the following criteria: (1) they must speak fluent Italian or English, (2) they must be aged ≥18 years, and (3) their children must not have other genetic pathologies or other pathologies not linked to the preterm birth.

These 3 limitations help us in creating a more consistent sample and, therefore, in obtaining more focused results. Situations such as teenage pregnancies or genetic pathologies further complicate a family's life and, therefore, the task of assessing its well-being. While we acknowledge that they are both worthwhile topics of research, they are beyond the scope of what could reasonably be studied within the framework of our research.

To determine a satisfactory sample size for this research, we calculated using G*Power (Heinrich-Heine-Universität Düsseldorf) that the minimum sample size required, considering a probability of α error of .05, power ($1 - \beta$ error probability) of 0.95, and an effect size of 0.345, will be 175 preterm infants (350 parents).

We want to stress the fact that, due to the very peculiar nature of the studied population, this will not be a probabilistic sample but rather a *convenience* sample. As explained previously, the decline in Italy's birth rate does not allow us to use the yearly average estimation of preterm babies born in each of the partner hospitals as a reliable predictor for constructing our sample.

Research Design

To achieve the research objectives, this study will use a mixed methods approach that combines ethnographic observations with standardized questionnaires. The goal of this approach is to enhance the results by complementing the strengths of different methodologies [30]. The quantitative aspect of this research aims to investigate the potential impact of preterm birth on the psychological well-being of parents during the early months of their child's life. Recent literature emphasizes that preterm birth can have a significant impact on parental well-being, exposing them to a high likelihood of developing anxious, depressive, and sometimes even posttraumatic stress symptoms [31]. The questionnaires with validated scales used in this research will be used to create composite statistical indexes that measure, for each responding parent, levels of stress, depression, anxiety, perception of parental self-efficacy, quality of the bond established with their child, and the perception of the social support received. The reasons that prompted us to consider such tools stem from the literature highlighting the necessity of using specific instruments in investigating parental distress in the postpartum period, to adequately capture the specific reasons leading to the experience of such unique feelings [32]. Moreover, questionnaires with validated scales are a valuable tool in psychological research. They allow data to be collected from a large number of participants in an inexpensive and standardized manner. The ease of administration and access to personal information encourage the disclosure of candid data, reducing the social reaction effect as well as allowing people to respond more freely. The qualitative aspect of this research involves the use of the range of methods provided by ethnography, considered particularly suitable for studying the dynamics of critical health practice in action [29,33] as the ethnographic approach allows for an understanding of how medical discourse (eg, protocols, standards, and knowledge) forms within everyday medical practices (eg, informal actions, skills, behaviors, and the physician-patient relationship) that are involved in care trajectories [34]. The e-ParWelB project will use a focused ethnographic research approach with different methods. During the NICU stay, we will combine research strategies, including focused ethnography, which entails observing the relational dynamics between different staff members and between staff and parents; discussing with neonatologists their notes and accounts regarding the neonate's care pathway; observing the habits and procedures of health care staff to reveal how prognostic knowledge is shaped; and, finally, conducting narrative interviews with the staff to capture narratives about family needs and perceptions of care practices.

Parents will be approached and recruited by a psychologist within the NICU or sub-NICU when the medical staff announce their child's discharge. At this stage, the project will be thoroughly explained to them, and they will be requested to provide written informed consent. Parents of premature infants will be invited to participate in this study a few days before the discharge. The timing of recruitment will be individually determined based on the assessment conducted by the neonatologist considering the infant's prognosis. When the health care staff informs the parents that their baby will be discharged, allowing them to envision their return home, an interview will be conducted within the NICU wards (T0). During this session, a structured interview will be administered along with specially designed questionnaires combining internationally validated scales with standardized questions related to

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socioeconomic status (Figure 1). The administration of the self-report questionnaires will be carried out via the Qualtrics XM platform (Qualtrics International Inc; managed by the scientific coordinators of the e-ParWelB) accessible through the Qualtrics offline app using tablets.

Figure 1. Study model. BiTS: Birth Trauma Scale; EPDS: Edinburgh Postnatal Depression Scale; NICU: neonatal intensive care unit; NPST: Nurse-Parent Support Tool; PBQ: Postpartum Bonding Questionnaire; PSAS: Postpartum Specific Anxiety Scale; PSI-SF: Parenting Stress Index–Short Form; PSS:NICU: Parental Stressor Scale: Neonatal Intensive Care Unit.

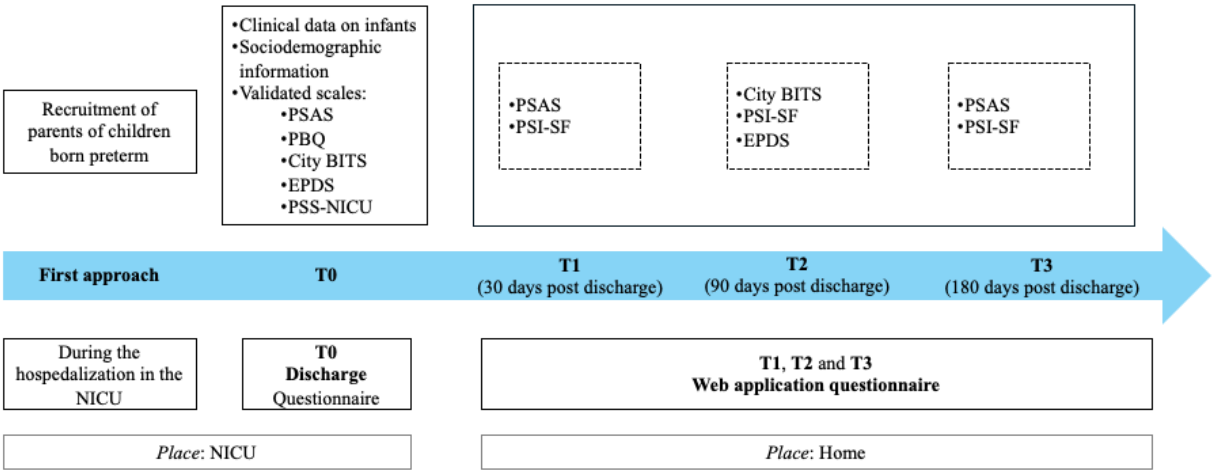

Subsequently, the study includes a follow-up phase to monitor the psychological well-being of parents of premature infants after discharge. The follow-up will be conducted through the use of a specially designed web application accessible only to participants that will allow for the monitoring of parents' adaptation and psychological well-being for up to 6 months after the newborn's discharge from the NICU. Parents will be asked to complete validated scales at 3 specific time points: 30 days (T1), 90 days (T2), and 180 days (T3) after discharge from the NICU (Figure 1). The presentation order of the validated scales will vary during the 3 follow-up time points. This choice will ensure that no mechanisms of response automation based on memory are created. The responses provided by parents to the validated scales used within the web application will trigger automated alerts signaling difficult or potentially risky situations. Parents whose responses have triggered an alert will be contacted by a psychologist to offer them psychological support and possible referral to dedicated services. In addition, during this monitoring period, a series of support forums will be implemented within the e-ParWelB web application—in fact, the web application will incorporate a space for peer discussion where issues related to, for example, daily care practices or family well-being can be discussed; a private messaging channel for psychological support where each user will be able to turn to an experienced psychologist for support in case of need; and, finally, a technical forum where each user can report malfunctions or request technical support regarding the web application's functionality.

A brief overview of the validated scales used in the surveys (in the discharge questionnaire and the follow-up questionnaires) and the topics covered by the standardized questions, which are more sociologically oriented, present in the discharge questionnaire is outlined in the following sections. Finally, a brief description of the netnography and of the focused ethnography that will take place in the NICUs and the related data collection techniques is presented.

Measures and Instruments

Measures at T0 (Discharge Questionnaire)

At the time of the child's discharge from the NICU, the investigation will focus on assessing anxiety, depressive, and posttraumatic symptomatology while also investigating parents' perceptions of their self-efficacy in bonding with their child within the chaotic and stressful environment of the NICU.

For this purpose, several validated scales will be used. Most of the literature on postpartum anxiety [35-37] refers to measures of generalized anxiety, which can often prove problematic from a psychometric perspective [38]. To date, the only available questionnaire specifically measuring postpartum anxiety is the Postpartum Specific Anxiety Scale (PSAS) [39,40]. Furthermore, the instrument has demonstrated excellent psychometric properties (ω ranging from 0.72 to 0.90 across the 4 scales and $\lambda 4$ ranging from 0.71 to 0.92 across the 4 scales). For these reasons, the research team deemed it the most sensitive and appropriate tool for capturing the construct under investigation in the target population.

Postnatal depression is the most widely measured disorder in the postpartum population, which today, in Italy, is mostly subject to routine screenings for this condition. Following a careful analysis of the most recent literature [41,42], the Edinburgh Postnatal Depression Scale (EPDS) [43,44] emerged as the most widely used self-report questionnaire for measuring postpartum depression due to its ease of administration, cultural adaptability, and excellent psychometric properties. The validated Italian version has demonstrated good validity and reliability (Cronbach α=0.7894), confirming the validity of the EPDS in identifying postnatal depression. For these reasons, the research team deemed it the most sensitive and appropriate tool for capturing the construct under investigation in the target population.

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Research on posttraumatic stress disorder (PTSD) during the postpartum period has typically adapted questionnaires developed for other populations, such as war veterans, which often prove poorly suited for capturing the specificities of childbirth trauma. Perinatal research comparing general PTSD measures with specific postpartum PTSD measures has found that, although highly correlated, the agreement between these scales in identifying PTSD diagnoses is low [45]. Therefore, the choice of measurement type is crucial for identifying cases of postpartum PTSD. In addition, the criteria of the American Psychiatric Association for PTSD measurement have significantly changed in the transition from the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition. Therefore, it is essential to adhere to these new measurement criteria. The City Birth Trauma Scale [46] is a tool specifically developed to measure childbirth-related PTSD according to the recent Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, criteria and is, to the authors' knowledge, the only instrument with these specificities. This instrument has previously demonstrated excellent reliability (Cronbach α=0.92). For these reasons, the research team deemed it the most sensitive and appropriate tool for capturing the construct under investigation in the target population.

The Parental Stressor Scale: Neonatal Intensive Care Unit [47,48] aims to capture parents' perception of distress experienced during their children's stay in the NICU. To reconstruct parental distress, the underlying model of the scale considers the interaction between various psychological and physical stress factors, such as stress related to sounds, lights, noises, and other sensory experiences typical of a highly technologized health care setting [47]. The Parental Stressor Scale: Neonatal Intensive Care Unit provides the opportunity to obtain various types of information: levels of stress related to specific situations experienced by parents with preterm infants, overall stress levels, individual stressful elements, and overall tension levels. The translation and validation study in Italian has found good psychometric properties of this tool [48].

Scientific research on the complex experience of preterm birth increasingly emphasizes that such an experience can pose significant challenges for parents, particularly in the development of bonding, which is the early relationship that develops post partum between mother and child [49]. A careful analysis of the literature [50,51] allowed us to select a questionnaire widely used in investigating bonding in the postpartum period: the Postpartum Bonding Questionnaire (PBQ) [52,53], a tool designed to measure the quality of the bond between parents and children and identify whether there are disturbances in the relationship. The Italian adaptation of the PBQ was developed using the back translation procedure [54]. Studies demonstrate that the Italian version of the PBQ has good psychometric properties and can be implemented in the Italian cultural context to assess early mother-child relational difficulties [53].

Moreover, the assessment at discharge will also take into account further aspects in light of the fact that several studies have shown that some minor stress factors such as the distance from one's home to where the child is hospitalized may contribute to a higher level of maternal discomfort [55]. The socioeconomic characteristics of family units, such as educational level, social class, job insecurity, employment status, and migration background, have also been examined as risk factors for preterm birth [56,57]. In addition, the study by Miles et al [58] revealed that the marital status of the mother is also a significant factor in predisposing to or preventing the development of a mood disorder. Specifically, married women who perceived a high level of support from their partners reported lower levels of postpartum depression than unmarried women. Conversely, among women with preterm infants, maternal age or level of education do not appear to be correlated with the onset of mood disorders [59]. Another factor that seems to mitigate the onset of mood disorders in parents of preterm infants is a high level of social support [60]. For these reasons, the discharge questionnaire will gather basic sociodemographic information from parents, such as gender, age, nationality, geographic origin, family composition, and educational level. A series of self-assessment questions will be used to evaluate the perceived social support of parents of premature infants. In particular, we have designed 6 items that inquire about perceived social support from partners, family members, friends, and health care personnel. Furthermore, respondents will be presented with a series of questions regarding the frequency of cultural activities, which will serve as indicators of their level of cultural capital, along with a series of questions aimed at capturing their occupational situation.

Finally, a validated scale will be used to gather information regarding parents' perception of nursing support during the infant's hospitalization, the Nurse-Parent Support Tool (NPST) [61]. Scientific research has highlighted the crucial role of parents' perceptions of the actual support provided by nursing staff in mitigating the stressful effects of the NICU stay [62]. In light of this evidence, Miles et al [61] devised the NPST, a scale specifically addressing the educational and informational aspects of staff support as perceived by parents that is widely used in NICUs today [63]. The NPST is a 5-point Likert-scale questionnaire consisting of 21 items divided into 4 groups: informational support, emotional support, appraisal and parental esteem support, and caregiving support. Each item is rated on a scale from 1 (*Almost never*) to 5 (*Almost always*), with higher scores indicating a higher perceived level of support provided by the nursing staff. The validity and reliability of the Italian version of the NPST were assessed by Montirosso et al [48].

Follow-Up Measures at T1, T2, and T3 (Web Application Questionnaire)

At the time of discharge, the involved parents will be invited to register on the web application specially designed for this research. Through the web application, participants will independently complete 3 short questionnaires at the 3 different times designed for follow-up (T1 at 30 days after discharge of the newborn, T2 at 90 days after discharge of the newborn, and T3 at 180 days after discharge of the newborn) to monitor their mental health status. In the web application, some validated scales already proposed at the time of discharge will be implemented. The scales are presented to participants in different moments to minimize potential bias due to response based on learning or recollection. Specifically, (1) *during T1*, participants

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will be invited to independently complete the PSAS and the Parenting Stress Index–Short Form (PSI-SF); (2) *during T2*, participants will be invited to independently complete the City Birth Trauma Scale, the EPDS, and the PSI-SF; and (3) *during T3*, participants will be invited to independently complete the PSAS and the PSI-SF.

The only validated scale for which completion will be required at every follow-up time point is the PSI-SF [64,65]. The existing literature has highlighted the possibility of early identification of stressful parent-child systems to develop interventions aimed at reducing stress that could decrease the frequency and intensity of emotional and behavioral disorders in children in our society [65,66]. The characteristics of the child, those of the parent, the family context, and particularly stressful life events are some of the elements of the parent-child system that have been identified as important [64,67]. The Parenting Stress Index was developed in response to the need for an assessment measure of these characteristics. For the purposes of this scientific research, the PSI-SF was adopted, which is an abbreviated version of the Parenting Stress Index that investigates parental distress, dysfunctional parent-child interactions, and difficult child behaviors. The brevity of the PSI-SF allows primary health care providers to identify families most in need of follow-up services [68]. Furthermore, the PSI-SF represents an extremely interesting, agile, easy-to-administer, and interpretable tool. The Italian version of the PSI-SF has been translated and validated by Guarino et al [69] and investigates stressful systems through 3 subscales: parental distress, dysfunctional parent-child interaction, and difficult child behaviors.

Our intention is to use the PSI-SF as a potential *risk screening tool*, namely, a technique that can identify parent-child systems under excessive stress and, thus, serve as an important component within prevention programs aimed at reducing the frequency and intensity of emotional and behavioral disorders [69]. The responses provided by parents to all validated scales used within the web application, in cases in which they exceed the threshold values established for each scale, will indeed allow for the automated activation of alert signals for situations of difficulty or potential risk. Finally, as mentioned previously, all psychological scales used in this study are internationally validated, ensuring their reliability across diverse populations, including those with preterm infants. The sociodemographic section of the questionnaire was tested in a pilot study involving 104 parents [12], which preceded this project and allowed for refinement of the questions to better suit the target population. While these tools provide a strong foundation for data collection, future research could explore additional validations to further tailor the measures to this specific group.

Netnography

As mentioned previously, the web application will feature three specific communication channels through which users can interact: (1) a public forum for peer discussion only where users will be able to post messages, share opinions and ideas, or ask questions on issues related to the daily childcare at home; (2) a private communication channel through which users can contact the psychologist to ask for support in case of discomfort, uneasiness, or other states of distress; and (3) a forum dedicated to the technological tools available to participants in which it is possible to both report technical malfunctions to IT staff and discuss among parents and researchers the impacts of the eHealth tool on its users and their well-being.

The textual corpora produced by users will be downloaded and will form the empirical basis for data analysis through an approach of digital ethnography.

For many years now, computer-mediated communication has been fully integrated into people's daily lives, blurring the distinction between offline and web-based social worlds as they both coexist and fully overlap [70]. Therefore, it has become increasingly important and relevant for social researchers to study society in and through the internet. Although methodological reflections around digital research have been manifold and have also given rise to different terminologies and definitions, in this contribution, we use the term *netnography*, coined by Kozinets [71], to illustrate our digital ethnography approach that adapts the typical techniques and tools of ethnography to the study of web-based communities, which interact through a computer-mediated communication. The presence of the researchers, as well as the fact that messages written in the forums will be subject to analysis, is clear to the participants from the outset, so our netnography will use an overt observation technique.

In our project, the web-based community is closed, meaning that the web application and its tools can only be accessed through a username and password if one participates in the study and has agreed to take part in the follow-up phase. Some methodological perspectives on web-based research place great importance on the medium [72] and, by consequence, on the specific digital environment and its characteristics that shape the spaces, times, opportunities, and constraints under which web-based interactions take place. In our case, one of the main constraints is that messages in the public forums (*n. 1*, a public forum for peer discussion, and *n. 3*, a forum dedicated to the technological tools) will be published subject to approval by the members of the research team to avoid the use of inappropriate language or extremely off-topic communications. If some messages are rejected, they will also end up in the analysis, but they will obviously not affect the overall interaction as they will not be visible to other users. Time is another important feature that will have consequences for the flow and volume of communications as the web application will see the asynchronous access of participants, who are gradually recruited over time. Although the messages in the public forums will remain fixed and always visible, participants who complete the 180-day follow-up period may have less incentive to access the web application, resulting in no further discussion with other newly recruited participants. On the other hand, the accumulation of messages over time could stimulate other interactions, also providing an incentive for participants to use the web application not only as a tool for filling out periodic questionnaires. From a research point of view, we are particularly interested in the volume, modalities, and content of the digital interactions between participants, aware of the constraints to which such communications are subjected. It will be useful to understand the representations, perceptions, and perspectives of premature parents and the impact of prematurity

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and of the care practices in daily life. Moreover, we will pay attention to the adaptation processes carried out to cope with the transition period after discharge from the NICU and how parents deal with their new domestic life. In the analysis, even though the participants are pseudoanonymized through a unique alphanumeric code, we can trace and use as a segmentation variable the one that discriminates between the partner who gave birth and the one who did not, for example, to account for differences in the prevalence and occurrence of the messages and topics reported. Furthermore, the *n. 3* forum has the goal to explore how digital-driven changes affect families. It is dedicated to specifically discussing the tools in the web application through a process of facilitation by a member of the research team stimulating dialogue on dedicated questions. As previously stated, this section of discussion about the web application is intended not only as technical support but also as a space for group reflection on the impact of the digital tools introduced by e-ParWelB to support families' well-being. The material created by users in this section will then be analyzed with the aim to explore whether web-assisted alerts and expert and peer support on the web were beneficial to families' well-being and, eventually, how these tools might be improved in the future. This phase of research will also allow us to reflect upon the implications of introducing a digital medium in the relationship between the health care staff and families [73], as in the tradition of sociology and science and technology studies working together on health care issues [74].

Ethnography

The qualitative part of this research aims to study the NICU environment through the use of focused ethnography [75,76]. This term indicates a research method based on brief and intensive observations with the aim of analyzing well-defined phenomena within a specific context. While the classic form of ethnography is centered on the study of broad topics, such as the holistic observation of social groups or institutions, focused ethnographies narrow down their perspective to the analysis of specific actions, interactions, and social situations. This implies a few changes in the position of the observer compared to the situation of traditional ethnography. First, the researcher cannot face the fieldwork unprepared but must be at least theoretically confident with the context of the actions that are to be studied. Second, traditional ethnography provides a range of observer positions, from participant as observer to observer as participant [77], whereas focused ethnography does not involve the same opportunity for observing as a participant because of the nature of the object of study. It would be both highly inappropriate and technically impossible for the focused ethnographer to participate actively in, for example, a medical examination or an operation. Instead, a more distant observer position is possible. In this way, the focused ethnography researcher may be excluded from contextual factors of importance. While traditional ethnography affords the chance to actually participate in the life of the studied social milieu, focused ethnography does not offer the same opportunities of active participation. This usually happens due to the inherent characteristics of the participants under investigation. Active participation in skill-intensive activities would be both highly unrespectful and unfeasible for the focused ethnographer. Consequently, it is said that, in focused ethnography, researchers are not doing observant participation but that they are participating as observers.

A brief recap of the main traits of focused ethnography and its difference from traditional ethnography is shown in Table 1.

Table 1. Comparison between focused ethnography and traditional ethnography derived from the study by Andreassen et al [78].

Characteristic	Focused ethnography	Traditional ethnography
Subject matter	• Episodes in social fields • Clear research focus • Familiar cultures • Background knowledge before data collection • Applied research	• Entire social fields • Broad research purpose • Foreign cultures • Gaining knowledge from engagement in the field • Basic research
Data collection	• Relatively long planning phase • Intermittent visits with particular time frames • Focused exploration • Video or audio recordings or detailed, focused field notes • Often multi-sited • Time intensity	• Relatively short planning phase • Full-time participant observation over a longer period • Open exploration • Extensive and in-depth written field notes • Often single sited • Time extensity
Researcher role	• Alterity • Observer as participant • Selected informants who hold a specific knowledge serve as key participants	• Strangeness • Participant as observer • Participants are often those with whom the researcher develops close relationships
Data analysis	• Analysis intensity • Collective data analysis sessions	• Experiential intensity • Solitary data analysis

Focused ethnography is a particularly appropriate technique for our research due to the traits of medical practice, which comprise bounded and clearly delineated social occurrences or scripted exchanges. This statement has been proved true by an increasing number of studies using this technique within the hospital setting in recent years [79-82]. This technique affords the means to

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investigate particular episodes or interactions within social milieux such as NICUs, facilitating nuanced and comprehensive insights into the influence of sociocultural factors on the interaction between the NICU staff and preterm parents. This specific effort of focused ethnography will be divided into 2 steps, each involving the staff members of NICUs in hospitals collaborating with the project. First, the researcher will observe the routine practices that constitute what is defined as *ward life*, trying to create as little interference as possible with the staff's activities. At this stage, the researcher's focus will not be on individuals but rather on the overall context of neonatal intensive care and the social interactions occurring within it. Second, the researcher will use narrative interviews to gather additional information from the NICU staff. The use of interviews is quite common in focused ethnography, as explained by the relevant literature on the topic: "The focused ethnography researcher may be precluded from contextual factors of importance. Applying method triangulation as a cornerstone in ethnography is a way of overcoming this dilemma. For example, combining short observations with interviews will give opportunities to ask about the context in which the observations take place, as well as to explore how the participants experience being observed" [78]. In these narrative interviews, the researcher will aim to involve staff members with profiles as diverse as possible regarding their roles, length of service, gender, and age. The objective is to achieve what the literature calls a "maximum variation sample" [78], maximizing sample diversity (while acknowledging that this is a nonprobabilistic convenience sample) across certain characteristics to capture the complexity of the studied reality.

Throughout both of the aforementioned steps, this research will try to analyze the meaning and effects of the NICU staff decisions and practices on the parents' well-being. This focus on the analysis of existing procedures in skill-intensive contexts, especially medical-related ones, has been referred to in previous research as *exnovation*. *Exnovation* refers to the attempt to foreground what is already present—though hidden—in specific practices to render explicit what is implicit in them [83]. A focus on exnovation allows us to bring to light implicit matters of actual practice and develop a fresh perspective on the ingenuity of the professionals and the specific structure of their practices. It offers insights into their specific modes of ordering day-to-day practices [84]. Exnovation, in other words, elucidates competencies of coordination and alignment of these modes of ordering of which those involved are not always aware [29]. In other words, this research aims to reflect on existing practices of care aimed at preterm parents and their children and deepen our understanding regarding their effects with the aim of preventing family maladjustment after a traumatic event such as preterm childbirth.

Regarding the organization of the qualitative tools for the research, the access to the field will be negotiated separately in each NICU to take measures to avoid disrupting staff work and minimize impact on organizational routines. To conduct an ethical and respectful data-gathering process, NICU staff will be informed about the research in advance by the department heads, with whom a partnership has been established for the project, thus ensuring that they are aware of the research procedures. Once access is granted, the researcher present in the department will autonomously organize interviews with the staff.

Expected Outcomes

The e-ParWelB central impact will be developing and piloting a model of sociopsychological assessment tailored for parents whose infants have been hospitalized in the NICU for critical health situations connected to prematurity. The model, by increasing preterm parents' perception of self-efficacy and well-being, will allow for the prevention of family maladjustment [5,6] and, therefore, the indirect improvement of preterm child health outcomes [7]. The mixed methods social research that we designed is expected to achieve the following results: (1) to reduce the discomfort and maladjustment caused by prematurity on preterm parents and assess their perceptions of social support (from family, friends, potential employers, and colleagues), perceptions of preparedness, and parental self-efficacy from the time of discharge and for the following 6 months; (2) to analyze the difference between mothers' and partners' responses to preterm birth in terms of stress, negative feelings, and perceptions of parental self-efficacy and social support; (3) to determine which neonatal care practices, forms of communication, and environmental settings of the NICU are more likely to reduce negative feelings and foster the well-being of preterm parents; and (4) to advance the knowledge on the role of a digital-based tool in monitoring and supporting families' well-being during the follow-up.

On the latter point, e-ParWelB intends to engage in the relationships among science, technology, and society by addressing how the hospitalization experience of preterm families may inform technology and science development. At the same time, we aim to identify the effect of the introduction of a digital technology–driven assessment and support model on families' well-being and on care practices in the neonatal intensive care wards. In particular, the e-ParWelB project directly connects with the objectives of (1) developing a public health system enhancing investments in terms of human, digital, structural, instrumental, and technological resources; and (2) improving scientific research in the biomedical and health field.

Indeed, the interdisciplinary approach to promote eHealth in premature families enhances the dialogue between science (health care and medical knowledge) and society (families' perspectives) on the topic of preterm birth through the aid of digital technology. This will be possible with the implementation of the e-ParWelB web application, which will follow processes of responsiveness and adaptation as well as considering criteria of accessibility following responsible research and innovation principles. As the web application constitutes both a tool to periodically monitor parents' well-being and a digital space for sharing and discussion, both with a psychologist and among peers, the project has a multi-side technological and scientific impact.

At the same time, we aim to identify the effect of the introduction of digital technology on families' well-being and on care practices. For instance, through the netnographic exploration of the web-based space of discussion within the e-ParWelB web application, we aim to address the eventual

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health care web-based community of practice forming in the forum [85]. Drawing on the idea by Timmermans and Berg [86], an orientation of *technology in practice* allows for a critique by scholars in the social sciences regarding the complicated modalities in which the *social* and the *material* intertwine in technologies for health care, as well as possibly influencing their creation and implementation. Thus, referring to what in science and technology studies literature is known as the *sociotechnical approach*, we are interested in how the social and health care aspects influence the development of the digital technology and, at the same time, in modalities through which the digital medium affects families and the care process, especially after discharge [87,88]. Therefore, we also aim to understand the impact of the web application on families' well-being.

Results

We expect to observe these results by the end of October 2025, the date set as the conclusion of the Project of Relevant National Interest funded by the Ministry of University and Research.

Discussion

Impact

This research project aims to identify the social determinants of preterm parents' well-being. It will monitor their feelings and perceptions of well-being during the baby's hospitalization and after discharge, with the goal of reducing their distress and discomfort. Unlike previous studies, this project places a significant emphasis on both mothers and fathers, analyzing how gender differences and parental roles influence their experiences and affect outcomes related to perceived well-being and social support. Furthermore, using ethnographic methods, this study delves into the everyday life of NICU wards. It examines these environments both as sites of high-skill professional practice and as arenas of social interaction between staff and parents. The aim is to understand the social arrangements and practices that facilitate staff work and parental participation and involvement during the sensitive period of their baby's hospitalization. Finally, the use of technology in this study serves a dual purpose. Instrumentally, it enables the monitoring of parental well-being after discharge, but it also prompts deeper sociological inquiries into its role at the intersection of medical science and society. In addition, technology acts as a medium for mutual aid, fostering specific web-based peer discussions and shaping new forms of social support and community among parents of preterm infants.

The e-ParWelB project not only contributes to scientific and technological development, but its impact on the social and economic dimensions also stems from the premise that, by increasing the well-being of preterm parents it is possible to indirectly improve their infants' health outcomes. As scholars have argued, the abrupt disruption of the establishment and development of parental mental representations, combined with the possibility that both the baby and the mother are in critical condition, can make preterm birth a traumatic event for parents [89]. Therefore, reducing the family's maladjustment enhances future health—including mental health—in premature children [7]. Moreover, parents' mental health is supported, as well as their self-efficiency, preventing a large set of repercussions. For society at large, this also means introducing factors of prevention in terms of social and economic costs that unhealthy individuals and families might incur. Furthermore, the situation of premature birth care in Italy sees scattered NICUs applying different protocols for what concerns the role played by the parents of hospitalized newborns. As the latest report of the Italian Society of Neonatology shows, for instance, just 63% of the NICUs allow free-time access for parents [90]. When looking at the regional location, we observe an unequal distribution of the free-time access wards. Indeed, in the northern regions, 88% of NICUs do grant free-time access, whereas in the south, just 34% percent do [90]. Thus, by developing a piloted model for preterm parents' sociopsychological assessment, e-ParWelB will produce knowledge about the best practices to be implemented in NICUs, enhancing the opportunity for stakeholders and policy makers to make neonatal care protocols less regionally uneven and more efficient when concerning the collaboration between parents and health care staff.

Strengths and Limitations

The e-ParWelB project was preceded by the ParWelB project (principal investigator: AD), and although with a different institutional setup and collaborations with different NICUs, the 2 projects stand in a relationship of continuity, building on the same theoretical and methodological premises. Therefore, practical experiences and careful analyses regarding actual strengths and limitations have already been carried out for the previous project [10].

In general, the greatest strength of the entire research project lies in listening to and empowering the parents of premature children who participate in the study, making them more aware of and helping them deal with the challenging situation of prematurity, advancing deep reflections that do not stop at purely medical practices but also promote a person-centered approach to stimulate new neonatal practices and foster the well-being of families.

In this context, it is essential to reconnect the social dimension with the medical experience, also owing to the support of technology, and this is one of the main objectives of the project.

Indeed, we aim to study a model for monitoring and assessing parental well-being and look at the relationship between the medical-nursing staff and the parents of premature babies from a sociological and psychological perspective with the aim of promoting public awareness and participation, also by involving the medical-nursing staff with respect to the values, personal experiences, and point of view of the parents.

These strengths are accompanied by deep reflection in mapping out the potential limitations of the project and strategies to mitigate them.

Among these, access to the study is worthy of consideration. An actual constraint on access for preterm parents is language—the lack of cultural mediators and translators in the project allows only for participation of people fluent in Italian and English. As Italian and English were also the only languages in the previous ParWelB project, we have already ascertained

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that a nonnegligible proportion of parents, often with migration backgrounds, were unable to participate in the study, and we expect this situation to be repeated. This is uncomfortable for mainly 2 reasons. First, it does not allow a specific population of parents, who often are more likely to be in situations of marginality or social isolation, to access the direct and indirect benefits of the project, such as stimulating self-reflections on their parental role and gaining access to psychological support after discharge. Furthermore, from a purely scientific point of view, there is less opportunity to investigate how certain cultural differences and social support (which is often lacking or expressed in different ways among people with a migratory background) impact the well-being of preterm parents and their experiences in the NICU.

One of the main aspects to consider when reflecting upon the pros and cons of this project is the possible bias introduced by the implementation of the web application, which is a digital technology not necessarily available to all social groups. Digital literacy, availability of connection to the internet, and access to digital devices are all necessary conditions to participate in the study, and the lack of one of these aspects may act as an additional exclusion factor, possibly affecting marginalized social groups or groups with specific needs [91,92]. Nonetheless, parents excluded from the digital space are necessarily excluded from tools of expert and peer support.

In addition to access barriers to the study, this project faces other possible limitations regarding engagement and participation during the research activity that can be reversed. In the previous ParWelB project, due to the COVID-19 pandemic, researcher access to the NICU was restricted, so parent recruitment, discharge survey administration, and web application registration were performed entirely by NICU staff, usually by psychologists or neonatologists. Overall, in this way, NICU staff were more involved, but some methodological forms of control by the researchers were lacking regarding modalities of both study presentation and survey administration to parents [93]. In the new e-ParWelB project, while we no longer have the limitations of the pandemic, a blended approach was chosen as we will maintain a deep involvement by NICU staff, especially psychologists, in recruitment, survey administration, and web application enrollment at discharge. Above all, previous experience has shown that the relationship of trust built between the NICU staff and parents is central to engaging the latter in the project. Therefore, it is in the project's interest to maintain these relationships both to provide parents with referents whom they consider reliable and with whom they have already become familiar during their stay in the NICU and to engage the medical-nursing staff further, stimulating an even closer relationship between these 2 social actors beyond purely medical practice. On the other hand, in the previous project, the participation rate dropped by 10% for parents recruited in the second half of the project timeline, an indicator that the motivation and consequent convincing power of the NICU staff toward parents slightly declined over time [93]. Therefore, the presence of a researcher can also be decisive in rekindling motivation and emphasizing the importance of parental participation throughout the recruitment phase. In the e-ParWelB project, in some NICUs, there will be a constant presence of a project researcher, who will take part in recruitment together with the staff and will personally take care of survey administration at discharge and invite participants to register on the web application. In NICUs where the constant presence of the researcher is not expected, it will be arranged if no one in the NICU can recruit parents or the research team notices a decline in the participation rate. Therefore, this flexible choice allows us to maintain and strengthen the bond between the parents and the NICU staff and, at the same time, provide help and support to the participants or NICU staff and ensure the correct conduct of the research from a methodological and ethical point of view.

In conclusion, one of the critical aspects of the ParWelB project was the high dropout rate during the follow-up surveys using the web application. To address this issue, the new project, e-ParWelB, proposes a lighter monitoring approach, with a shorter total period and lower frequency (6 months of monitoring instead of 1 year and 3 surveys instead of 12), thus impacting participants to a lesser extent. A less intrusive follow-up, both in terms of frequency and volume of questionnaire completion, will not affect the capacity of researchers to monitor the well-being of the participants, whereas it will lower the commitment required from users, allowing them to allocate their time and energy to other activities related to the web application, such as forums.

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Data Availability

The datasets generated or analyzed during this study are not publicly available due to the inclusion of sensitive information, such as respondents' psychological distress, diagnosis of psychopathology, and clinical data on infants admitted to the neonatal intensive care unit. However, deidentified data may be made available from the corresponding author on reasonable request in accordance with ethical and legal considerations.

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Authors' Contributions

AD, FP, GL, MFF, CR, MN, BF, GC, and CI were responsible for conceptualization and investigation. AD, FP, GL, MFF, and CI conducted the methodology and formal analysis. AD and CI managed resources and project administration. The original draft was written by FP, GL, and MFF. AD, FP, GL, MFF, CR, MN, and CI contributed to the review and editing process. Supervision was provided by AD and CI. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the Italian Ministry of University and Scientific Research - Project of National Relevance - Bando 2022 / Ministero dell'Università e della Ricerca - Direzione Generale della Ricerca del MUR (Italy).
[PDF File (Adobe PDF File), 65 KB - resprot_v14i1e63483_app1.pdf]

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Abbreviations

e-ParWelB: eHealth Study on Preterm Parents' Well-Being
EPDS: Edinburgh Postnatal Depression Scale
FICare: Family Integrated Care
GA: gestational age
NICU: neonatal intensive care unit
NPST: Nurse-Parent Support Tool
ParWelB: Study on Preterm Parents' Well-Being
PBQ: Postpartum Bonding Questionnaire
PSAS: Postpartum Specific Anxiety Scale
PSI-SF: Parenting Stress Index–Short Form
PTSD: posttraumatic stress disorder

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Protocol

Exploring the Link Between Visual Attention to Familiar or Novel Food Stimuli and Food Choice Using Integrated Electroencephalography and Eye Tracking: Protocol for Nonrandomized Pilot Study

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Abstract

Background: Understanding the factors influencing food choice is critical for developing effective strategies to promote healthier eating habits and creating policies that support public health. Attentional bias, the inclination to focus attention on specific stimuli, plays a significant role in shaping food preferences by affecting how individuals perceive and react to various food-related elements. Various methodologies exist to examine attentional bias, including the dot-probe task, which measures reaction times to probes appearing after paired stimuli (eg, novel vs familiar food images); eye-tracking, which tracks gaze patterns and fixations to determine visual attention; and electroencephalography, which records brain activity, capturing early and late neural responses (eg, N100, P300) linked to attention processing; however, integrated approaches combining these methods to assess bias toward familiar versus novel foods remain underexplored.

Objective: This study aims to examine differences in attention toward familiar versus novel food stimuli using integrated eye-tracking, dot-probe, and electroencephalography methods, and to explore associations with self-reported food choice.

Methods: A total of 40 healthy adult participants will be recruited. Participants will be presented with pairs of familiar or novel food images, while their visual attention and brain activity are recorded concurrently. Eye-tracking metrics, including time to first fixation and total fixation duration, will be used to assess visual attention. Electroencephalography data will be collected to measure the amplitude of event-related potential components, such as P300 and N100, associated with attentional processing. Reaction times will also be recorded as a behavioral measure of attentional engagement with familiar versus novel food items. Data analysis will involve repeated measures ANOVA to examine the effects of food familiarity and novelty on attentional bias metrics. Correlation analyses will also be conducted to explore the relationships between eye-tracking, electroencephalography, and dot-probe measures.

Results: This study was approved by the Ethics Committee of the Iran University of Medical Sciences in February 2021 and funded in January 2022. Data collection began in November 2022 and is expected to be completed in July 2025. As of the submission of this study, 36 individuals have been recruited. Data analysis has not yet commenced, but it is planned to begin upon the completion of data collection. The results are anticipated to be published by December 2025. The protocol was registered with the Open Science Framework in September 2024.

Conclusions: The main outcome of this study is identifying differences in attentional bias metrics toward familiar versus novel food stimuli at different presentation times. These findings will provide preliminary data on the application of an integrated approach for capturing attentional bias to food-based stimuli based on their familiarity or novelty, and how these biases may be linked to food choice behaviors.

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KEYWORDS

attentional bias; eye tracking; stimuli familiarity; dot-probe; electroencephalography

Introduction

Food decision, including choices around types, timing, and portions, is a response shaped by various stimuli and directly influences both energy and nutrient intake [1,2]. Food choices are influenced by individual preferences and postconsumption reactions to food intake. The attention individuals give to food depends on the stimuli that automatically act on them (bottom-up factors) and is also determined by their interests and goals (top-down factors) [3,4]. Bottom-up and top-down processing occur simultaneously and interact with each other [5]. Bottom-up factors act automatically on the consumer and include certain characteristics for processing basic stimuli such as size, color, or shape [6]. Top-down factors are related to the person themselves [7]. They include the consumer's voluntary search for and attention to specific food product information [8], as well as the processing of individual experiences, motivations, and expectations. In research on the impact of information provision on food choices, it is often assumed that individuals attend to all provided information. However, individuals may not notice or perceive all the information presented [9]. If information is unattended to, it cannot inform choice [10]. Thus, it is important to evaluate if and how people pay attention to information, and the factors influencing such attention or inattention.

Visual attention is an important factor in the food decision-making process, providing a key contribution to subsequent decision-making [7]. Understanding attentional bias, where individuals preferentially process specific types of information, has been critical in understanding food-related behaviors in the context of consumer behavior or etiology of diseases, namely obesity [11]. Attentional bias has been measured using novel psychophysiological methods, including eye-tracking [12]. Eye-tracking technology provides an objective way to measure eye fixation duration and movement, capturing visual attention toward prominent stimuli [13,14]. In eye-tracking, participants are presented with pictures, either concurrently with reaction- and time-based paradigms or with instructions to simply gaze at pictures presented. One well-documented reaction time paradigm is the dot-probe task. In this task, participants are presented with cues of varying duration, which impacts the interpretation of attentional bias [15]. Previous research suggested stimulus presentation lengths of ≤200 milliseconds being associated with automatic orientation of attention, whereas presentation lengths ≥500 milliseconds are associated with maintained attention [16]. Currently, there are several studies in the literature applying either eye tracking or dot-probe to investigate the attentional bias to different food or nonfood stimuli among the healthy population or across disorders, such as anxiety, obesity, and eating disorders [17-20]. While visual probe tasks are the most commonly implemented task assessing food-related attentional bias, some current evidence has called their test-retest reliability into question and suggests combining different methods of attentional bias assessment for obtaining more reliable results [21].

While some previous studies have suggested a role for visual attentional bias toward familiarity and novelty of stimuli [22], there is a paucity of studies using electroencephalography to examine this, particularly in the context of food choice behavior. Electroencephalography is a noninvasive technique used to measure brain activity in response to stimuli by recording event-related potentials (ERPs). So far, only a few studies have explored integrating electroencephalography, eye-tracking, and dot-probe methods to study attentional bias to food-related stimuli [23]. Of note, no previous study has taken stimulus novelty and familiarity into consideration, nor how the results of this integrated approach associate with the self-report food choices. Familiar stimuli evoke trust and perceived quality from previous positive experiences are suggested to influence an individual's choices [24]. However, novel products require more cognitive effort to evaluate, leading to longer information processing times [25]. Thus, the main objective of this pilot study is to examine differences in attention to novel compared with familiar food stimuli, using 3 different attention indexes, including electroencephalography, eye tracking, and dot-probe. Indeed, it is hypothesized that participants will exhibit shorter reaction times (RTs) and longer total fixation durations (TFDs) for familiar compared to novel food items, indicating a stronger attentional bias toward familiar foods. In addition, familiar food items will elicit greater P300 amplitudes compared with novel food items, suggesting enhanced attentional engagement and processing.

Methods

Objectives

The secondary objectives of this study are to obtain preliminary data on the quality of the data, along with the potential correlations between visual attention metrics as assessed by eye tracking, RTs in response to the dot-probe task, and amplitude of ERP components. In addition, an exploratory objective of this study is to investigate the association between the data of attentional bias tools with the self-reported food choice to further our understanding of the potential of ERP and eye-tracking data in predicting the individual's ultimate food choice, particularly taking stimulus familiarity into consideration.

Study Design

This nonrandomized pilot study aims to use different measures of attention, via an integrated eye tracking and electroencephalography methodology, to study different aspects of the food-related attentional bias. Synchronization will ensure that eye movements and neural responses are recorded concurrently in response to the same stimuli during the dot-probe task, allowing precise alignment of data for accurate analysis.

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Study Setting

Data collection will be completed at the Iran University of Medical Sciences in Tehran, Iran, by trained research assistants and technicians.

Eligibility Criteria

The inclusion criteria include participants (1) aged between 18 and 50 years; (2) with a BMI within the healthy range (18.5-24.9 kg/m^2), to avoid confounding effects of weight status on food preferences and attentional biases; (3) with normal or corrected-to-normal vision (required for accurate eye-tracking data and visual task completion; (4) who are right-handed, to control for hemispheric dominance effects in electroencephalography recordings, as handedness can influence attentional processing and ERP components (eg, P300, N100), reducing variability in neural responses; (5) with no history of neurological or psychiatric disorders, to minimize potential confounding factors that could influence the study outcomes; (6) with no use of medications affecting cognitive function or appetite including psychiatric medications, stimulants, or appetite suppressants; and (7) who are willing to complete the study tasks, including questionnaires, electroencephalography recordings, eye-tracking, and the dot-probe task.

The exclusion criteria include individuals with (1) a history of eating disorders or current disordered eating patterns; (2) a history of visual or motor impairments; (3) high sensitivity to visual stimuli, including photosensitivity, severe migraines, and epilepsy; or (4) an unwillingness to adhere to study protocol or incomplete or insufficient data collection during the study.

Visual Stimuli Selection

We aim to identify the perceived familiarity of a range of food items among a test sample to categorize them into “highly familiar,” “familiar,” “somewhat familiar,” or “novel” for the main study. This will ensure that the familiar or novel food stimuli in the main experiment reflect participants’ everyday experiences. In this regard, we will create a list of food items, including a diverse range of food items from the categories we plan to use in the main study (eg, milk, oil, sauces, and beverages). Food products of “everyday” life, which have moderate visual complexity (no complex dishes), will be chosen as possible stimuli. To achieve a balanced set, we will include items commonly found in the target population’s diet (eg, whole milk, olive oil) and novel items they are less likely to encounter (eg, hemp milk, truffle oil). We will organize the food items into the categories we will be using in the main study to facilitate easy comparison (eg, “Beverages” might include orange juice, kombucha, and matcha latte). Accordingly, we will create a structured survey using Google Forms where each item will be rated based on familiarity using a Likert scale: 1=highly unfamiliar (I have never seen or heard of this product); 2=somewhat unfamiliar (I have rarely seen or heard of this product); 3=somewhat familiar (I know of this product but don’t use it often); 4=familiar (I use this product occasionally); and 5=highly familiar (I use this product regularly). We aim to recruit 100 participants to ensure diverse responses, taking demographic diversity (eg, age, gender, dietary preferences) into account to get a representative sample. Before launching the main survey, we will conduct a small pilot test with a handful of individuals (5-10 people) to identify any issues with wording, scale clarity, or question order.

Finally, we will calculate the mean familiarity score for each food item and classify items based on their mean familiarity score, based on the following scores:

- Highly familiar: average score of 4-5
- Familiar: average score of 3-4
- Somewhat familiar: average score of 2-3
- Unfamiliar: average score of 1-2

Items falling into the “Highly Familiar” or “Familiar” categories will be used as familiar stimuli, while those in the “Unfamiliar” category can serve as novel stimuli for the main study. Based on the survey results, we will select the top 2 items from each category (eg, milk, oil, sauces, biscuits, and beverages) to be used as stimuli in the main study. Special care will be taken to select pictures of good quality, comparable lighting, and size. The pictures of each pair will be shown side by side and matched as closely as possible with regard to the shape, color, and position of the photographed object as well as background color. One choice out of the 5 choice sets (milk, oil, sauces, biscuits, and beverages) will be used as a warm-up to familiarize the participants with the procedure and will not be included in the data analysis.

Intervention

Participants who meet the inclusion criteria will be recruited to complete a dot-probe task while integrated electroencephalography and eye-tracking data are recorded. Each participant will conduct a series of attention-related tasks (an eye-tracking task, a visual probe task, and an ERP task), and, hereafter, a Food Choice Questionnaire (FCQ) to assess food choice. The intervention involves presenting participants with both familiar or novel food items from 4 categories (milk, oil, sauce, and beverages) simultaneously during the dot-probe task to assess attentional biases. In this task, pairs of images (one familiar and one novel food item) will be displayed on a computer screen, followed by a dot-probe appearing in the location of either the familiar or novel item. Participants will be instructed to respond as quickly and accurately as possible by pressing a key corresponding to the location of the dot-probe. Reaction times to the dot-probe will be recorded. Neural responses will be captured using electroencephalography to identify specific brain activity patterns associated with processing the food stimuli, offering insight into the cognitive and neural mechanisms underlying attention. Eye-tracking technology will also be used concurrently to monitor gaze patterns and fixation duration (FD) on each food item, enabling us to quantify the amount of visual attention allocated to familiar versus novel items. No intervention modifications are planned in this study, as they do not apply to the type of intervention used.

Procedure

On the day of the main study, participants will first complete a demographic questionnaire. After this, they will have a brief period to relax and prepare for the tasks ahead. The study will use 3 attention indexes, all featuring the same food item images:

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an eye-tracking paradigm (measuring gaze direction and duration), a visual dot-probe task (assessing reaction times), and the recording of electrophysiological brain activity (evaluating the amplitude of the P300 and N100 ERPs). Before starting the tasks, electrodes will be positioned and adjusted, using the Cz electrode as the reference point (located at the center of the electroencephalography cap). A potassium chloride solution will be applied to the electrodes' sponges to lower impedance to below 5 kΩ. Participants will then be seated 60 cm away from the eye-tracking system, with the camera calibrated to optimally capture their eye movements, followed by a 9-point calibration procedure to ensure accurate eye-tracking data. After successful calibration, participants will be instructed to keep their heads still and focus on the images displayed on the screen. They will read the instructions and complete 5 practice trials to familiarize themselves with the task.

Briefly, participants will be instructed to respond as quickly and accurately as possible by pressing a key corresponding to the dot's location during a dot-probe task, with ERPs being recorded via electroencephalography. Participants' gaze position will also be tracked every 16 milliseconds (60 Hz) throughout the experiment. The entire experiment will take place in a controlled environment, minimizing electromagnetic interference and maintaining consistent lighting. Once the integrated methods are completed and all recordings have been captured, participants will be asked to fill out the food choice questionnaire.

Outcomes

Primary Outcome

The primary outcome includes identifying the difference in 3 attentional bias metrics toward familiar or novel food stimuli at different presentation times. Detailed descriptions of these outcome measures are provided in the "Outcome Measures" section below.

Secondary Outcomes

The secondary outcomes focus on evaluating the correlations between ERP data obtained from electroencephalography recordings and the metrics captured through eye tracking and RTs from the dot-probe task.

Exploratory Outcomes

Exploratory outcomes investigate the effects of food familiarity or novelty on food choices and assess the potential of visual attentional bias data, derived from 2 well-established tools, to predict final food choices among healthy adults.

Outcome Measures

In this study, several key metrics will be used to assess visual and neural responses to food stimuli, which are listed in Textbox 1.

Textbox 1. Outcome measures.

Time to first fixation (TTFF)

The interval from the onset of the stimulus to the first fixation on the target. TFF indicates the initial orienting response towards a stimulus. A shorter TTFF suggests quicker attentional capture by the target, reflecting the efficiency of visual attention and its alignment with task-relevant stimuli [26]. This measure is crucial for understanding how quickly participants direct their gaze to familiar versus novel stimuli.

Total fixation duration (TFD)

The cumulative time spent fixating on a target during a given trial. TFD reflects the allocation and engagement of attention over time. A longer TFD on a target implies greater sustained attention and interest, indicating how engaging or relevant the stimulus is perceived to be. This measure elucidates how familiarity affects sustained visual attention toward different products [27].

Reaction times (RTs)

The time taken by participants to respond to the dot-probe after it appears, measured from the onset of the probe. RTs provide insights into attentional biases and decision-making speeds. Shorter reaction times suggest faster processing and quicker attentional shifts towards the location of the dot-probe, helping determine how stimulus familiarity influences the speed of attention allocation and the efficiency of task-related responses [15].

Event-related potential (ERP) components

ERP components capture the neural responses associated with processing visual stimuli. A total of 2 key components will be analyzed:

- P300: A positive deflection occurs approximately 300-600 milliseconds post stimulus. The P300 component is linked to attention and memory processes, reflecting the allocation of attentional resources and the processing of significant or novel stimuli. Higher P300 amplitudes suggest greater attentional engagement and relevance of the stimulus, providing insights into how product familiarity influences cognitive processing [28].
- N100: A negative deflection occurs approximately 100 milliseconds post stimulus. The N100 component is associated with early sensory processing and selective attention, indicating the initial detection of and orienting toward a stimulus. Variations in N100 amplitude can reveal differences in early attentional processing between familiar and unfamiliar products [29].

Participant Timeline

The protocol was prepared according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (the SPIRIT checklist can be found in Multimedia Appendix 1) [30]. In addition, Table 1 provides an overview of the study timeline.

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Table 1. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) report of enrollment, interventions, and assessments.

Study period	Enrolment ($-t_1$)	Allocation (0)	Postallocation (t_1)	Close-out (t_2)
Enrolment				
Eligibility screen				
Informed consent	✓			
Demographic data	✓			
Interventions				
Allocation		✓		
Dot-probe task			✓	
Assessments				
Reaction times			✓	
Eye-tracking metrics			✓	
Event-related protentional components (P300, N100)			✓	
Food choice questionnaire				✓

Sample Size

An a priori power analysis was conducted using G Power version 3.1.9.7 (Department of Psychology, Heinrich Heine University Düsseldorf) to determine the appropriate sample size needed to achieve sufficient statistical power for our study. The analysis was designed for an *F* test, with an assumed medium effect size of F=0.35, a significance level of α=.05, and a desired statistical power of 0.80. Based on these parameters, the calculated sample size required was 40 participants. Specifically, the number of groups (between-subject factor) was set at 2 (500 ms vs 2000 ms), and the number of measurements (within-subject factor) included 8 (2 stimulus types [familiar or novel] across 4 food categories). In addition, the correlation among repeated measures was conservatively set at 0.5. The medium effect size was chosen based on the existing literature on attentional bias studies, which commonly report medium to large effect sizes [23]. Under these specifications, G Power estimated an achieved power of 0.820, exceeding the commonly accepted threshold of 0.80 for adequate power. This indicates that a sample size of 40 participants is sufficient to detect a medium effect size in our primary outcome using repeated measures ANOVA, ensuring the study is powered to identify meaningful changes while balancing feasibility within the constraints of a pilot study.

Recruitment

Participant recruitment will be conducted using a multifaceted approach, combining both physical and internet-based strategies. This will include distributing flyers in community centers, libraries, and university campuses, as well as posting digital flyers on social media platforms (eg, Instagram). We will also use email invitations, university newsletters, and internet-based research recruitment platforms. Potentially eligible individuals will be identified, and members of the study team will reach out to them via phone or email to provide detailed information about the study and extend an invitation to participate. Interested individuals will be directed to complete an electronic screening survey to assess eligibility. Those who qualify and express interest will be contacted by the study team to verify screening information. During this meeting, the study team will review the study procedures, answer any questions, and go over the consent process.

Data Collection Plan

Dot-Probe Task

The dot-probe task will be implemented using E-Prime 3.0 software (Psychology Software Tools, Inc) for both eye-tracking and ERP components. Each trial will commence with a 500-millisecond presentation of a fixation cross at the center of the screen. This serves to focus participants' attention on the central point before the food stimuli are displayed. Following the fixation cross, a pair of images (one familiar and one novel) will be shown side-by-side for either 500 or 2000 milliseconds. The side on which each type of image appears is randomized to control for location bias. After the image pair is presented, a dot-probe will appear in the location previously occupied by one of the images. The dot will remain visible for 500 milliseconds. Participants will indicate the location of the dot by pressing the "L" key if the dot appears on the left side of the screen, or the "R" key if it appears on the right side. The response time and accuracy will be recorded for each trial (Figure 1).

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Figure 1. Schematic view of the dot-probe task design.

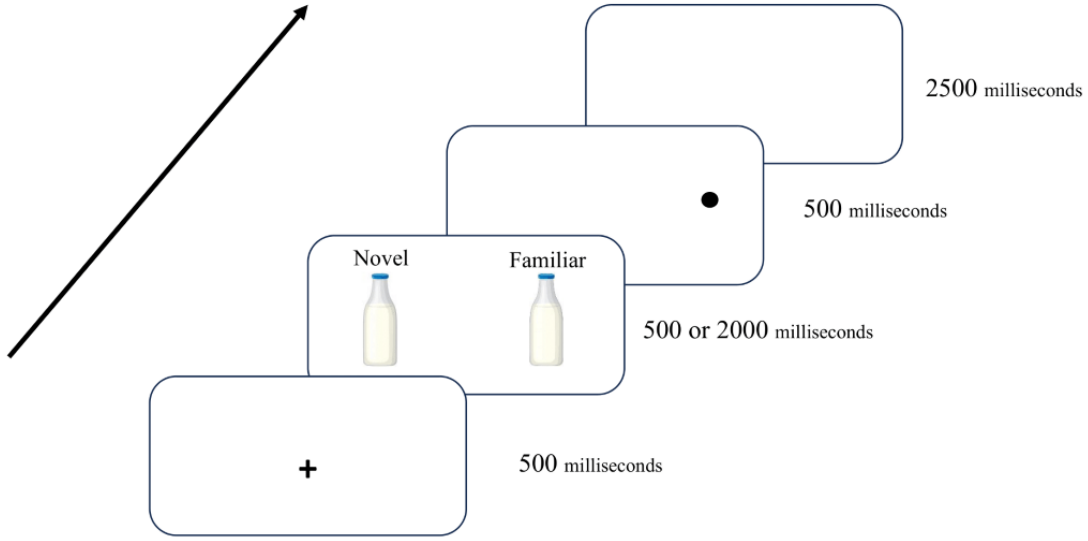

Each image pair will be displayed 8 times throughout the experiment, ensuring all possible dot-probe locations are tested. This results in a total of 128 trials, with varying combinations of familiar or novel images appearing in each trial. Reaction times in all trials will be recorded. RTs refer to the time it takes for participants to respond to the target stimulus by pushing the right or left key after the presentation of the stimulus. RTs are extracted as a measure of the speed at which individuals can shift their attention from the cue to the target. The inter-trial interval will be 2500 milliseconds. Reaction times of incorrect responses as well as reaction time outliers (reaction times less than 200 ms, greater than 1500 ms) will be excluded from the analyses. Temporal dynamics refer to variations in the duration of stimulus presentation. Shorter durations (eg, 500 ms) are often used to capture initial orienting responses. A quick reaction during a brief presentation may indicate a rapid attentional capture by the cue. Longer durations (eg, 2000 ms) are used to explore sustained attention and processing.

Eye Tracking

The eye-tracking component of this study will be conducted using the Tobii Nano Pro (Tobii Tech), a screen-based eye tracker known for its high precision in capturing gaze data. The Tobii Nano Pro offers a sampling rate of 60 hertz, which translates to data collection at intervals of 16.67 milliseconds. This high frequency allows for detailed tracking of eye movements and gaze patterns. To ensure accurate gaze data, a standard 9-point calibration procedure will be performed at the beginning of each session. This process involves directing the participant's gaze to 9 specific points on the screen to map their eye movements accurately. The calibration will be verified for precision before starting the main trials to ensure reliable spatial and temporal tracking. Participants will be seated approximately 60 cm from the Tobii monitor, which has a resolution of 1600 × 1200 pixels. Participants will be instructed to maintain a still head position and focus attentively on the images displayed on the screen. Participants will view pairs of pictures displayed side by side for 500 or 2000 milliseconds each. Each image pair is matched for shape, color, and background to control for these variables. The following eye-tracking parameters will be measured:

1. TTFF: time elapsed between the appearance of a picture and the user's initial gaze fixation within an area of interest. In this case, each product will be defined as a separate area of interest.
2. First fixation duration: time participants gaze at their first fixation point.
3. TFD: length of all fixations within a specific area of interest (in seconds). Average TFD will be used for statistical analyses.
4. Fixation count: number of fixations on stimuli.
5. Eye movement data will be analyzed using Tobi software.

Fixations are defined as periods where the gaze remains stable within a 30-pixel radius for at least 100 milliseconds, and these fixations must be initiated at least 100 milliseconds after picture onset to exclude anticipatory eye movements.

Electroencephalography Acquisition

As an electrophysiological measure of attention, electroencephalography will be recorded during the exposure to food stimulus pictures to determine the P300 and N100 ERPs. Electroencephalography signals will be recorded using the 9-channel B-Alert EEG system, which captures neural signals at a sampling rate of 256 hertz, providing data acquisition approximately every 3.91 milliseconds. This setup ensures the high temporal resolution necessary for detailed analysis of ERPs. Electrodes will be positioned following the international 10-20 system to ensure consistent and reliable data collection. The 9-channel configuration will cover standard locations to accurately capture neural signals. To maintain a clear signal acquisition, the impedance for each electrode will be kept below 5 kΩ, and impedance levels will be checked before data collection begins. An additional 2 electrodes will serve as reference and ground electrodes to improve the accuracy of the recordings. To address ocular artifacts, additional electrodes will be placed at the left and right mastoids, as well as at the supraorbital and suborbital positions of the left eye (for vertical electrooculography, VEOG), and the outer canthi of both eyes

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(for horizontal electrooculography, HEOG). Then, preprocessing will be performed using the B-Alert software (Advanced Brain Monitoring, Inc) to remove noisy segments of the signal. Subsequently, the signals will be epoch-referenced, with epochs spanning from the onset of the dot presentation to 1000 milliseconds after the presentation of the stimuli. The signal will be filtered at 50 hertz by the device, so there will be no need for additional filtering for power line noise and harmonics. Under appropriate conditions, the amplitude of the P300 indexes response categorization and the depth of encoding of the stimuli; larger amplitude P300s are thought to represent the amount of processing necessary to update neural networks about the changing environment. While there are a number of complementary and competing models of P300 [28], and several identified factors that affect the amplitude and latency of the P300 [31], all agree that stimuli garnering more attentional resources produce larger amplitude P300s. The collected electroencephalography data will be preprocessed using the EEGLAB environment, a tool library for processing electroencephalography data in MATLAB. The adjust plugin in EEGLAB will be used to discard artifacts due to eye movement and muscle activity.

Software Coordination

The E-Prime software will be integral for stimulus presentation and task control. It will manage the timing of stimulus presentation and coordinate trigger signals to synchronize the eye-tracking and electroencephalography systems. E-Prime will insert data markers into both the eye-tracking and ERP data streams at the beginning and end of each stimulus presentation, ensuring precise alignment of the data during analysis. For temporal accuracy, eye-tracking data will be aligned with ERP data using timestamps from the synchronization triggers, ensuring that each data point from the eye-tracker corresponds to the same point in time as the neural data. Any potential latency differences between the systems will be identified and corrected during the data analysis phase using these synchronized timestamps. A custom script in MATLAB will integrate the eye-tracking and ERP data based on synchronization markers provided by E-Prime.

Questionnaires

Demographic

The demographic questionnaire will be used to collect baseline information on participants to ensure that the study population is adequately characterized. The demographic questionnaire will collect information on age, gender, education level, socioeconomic status, smoking status, etc. The data gathered will be used for descriptive statistics, to stratify analyses, and to ensure that participants meet eligibility criteria.

Food Choice Questionnaire

Participants will be asked to self-report their final selection from the food items presented during the study. They will also be asked to complete a 36-item FCQ [32] for each familiar or novel item in each food group. FCQ consists of 9 subscales designed to assess the significance of various factors influencing food choices. These subscales measure the importance of health considerations, convenience in terms of preparation and purchase, price and value for money, sensory appeal (including taste, smell, and texture), natural content and the absence of additives, mood regulation, and the use of food to manage stress, familiarity with the food, ethical concerns related to origin and packaging, and weight control (the questionnaire can be found in Multimedia Appendix 2).

Data Management

All data collected during the study will be securely stored and managed to ensure participant confidentiality and data integrity. Each participant's data will be assigned a unique identifier to maintain anonymity. Data from the dot-probe task, eye-tracking, and electroencephalography recordings will be directly entered into secure, password-protected databases. Data entry will be verified by cross-checking with the original source files to ensure accuracy. All electronic data will be stored on encrypted servers with regular backups. Physical data, such as consent forms, will be stored in locked cabinets accessible only to authorized personnel. Access to the data will be restricted to the research team members directly involved in the study. Any data sharing with external collaborators will be conducted under strict data-sharing agreements ensuring confidentiality and compliance with ethical standards.

Statistical Analysis

ERP data will be preprocessed with EEGLAB v14.1.2 toolbox for MATLAB [33], involving noise removal, epoching from stimulus onset to 1000 milliseconds post stimulus, and averaging across epochs to extract ERP components. Potentials reflecting ocular or muscle-related artifacts were removed using logistic infomax independent component analysis [34]. Further artifacts will be removed using the clean_rawdata plugin for EEGLAB.

Regarding dot-probe and electroencephalography attention-related measures (RTs, and N100 and P300 amplitudes, respectively), repeated measures ANOVA will be conducted, including the stimulus type (familiar vs novel across 4 food categories) as a within-subject factor, and group (500 ms vs 2000 ms) as a between-subject factor. Similarly, ANOVA will also be conducted to examine eye-tracking measures (TTFF, FD) between groups (500 ms vs 2000 ms). Post-hoc analyses will be conducted with Bonferroni adjustments for multiple comparisons. In addition, relationships between eye-tracking measures (TTFF, FD) and ERP components (P300 and N100 amplitudes) will be calculated by the Spearman correlation analysis. IBM SPSS Statistics 20 (IBM Corp) software will be used to analyze the data. No interim analyses are scheduled for this study.

Ethical Considerations

The study protocol has been approved by the Research Ethics Committee of Iran University of Medical Sciences (ethics approval code: IR.IUMS.REC.1399.1340), in accordance with institutional and national ethical standards and the principles outlined in the Declaration of Helsinki.

Before consent, prospective participants will be sent a copy of the consent form to review and discuss further with family and friends if needed. Potential participants will then attend a pre-enrollment consent review call (phone or internet-based).

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Participants will be informed that participation is voluntary and that they may leave the study at any time without prejudice. When the study participant arrives at the Brain and Cognition Clinic, Iran University of Medical Sciences, any additional questions will be answered, and additional explanations will be provided as needed before they will be asked to sign and date their agreement to participate in the study. A paper or scanned copy of the signed consent form will be provided to the study participant for their records.

All participant data will be anonymized to ensure no individual is identifiable in any published report or supplementary materials. No images or information that could identify individual participants will be included. Each member of the research team has been trained in maintaining confidentiality to ensure the protection of participant information throughout the study.

Participants will receive monetary compensation upon completion of the experiment to acknowledge their time and effort. The compensation (US $15) will be provided in the form of a gift card and does not require any financial contribution from participants.

Results

This study was approved by the Ethics Committee of the Iran University of Medical Sciences in February 2021 and funded in January 2022. Data collection officially commenced in November 2022 and is projected to conclude by July 2025. As of the time of this study's submission, 34 participants have been successfully enrolled in the study, aligning with recruitment goals. Data analysis is planned to start immediately following the completion of data collection to ensure a timely and thorough evaluation of the findings. The study results are expected to be finalized and submitted for publication by December 2025. In addition, this protocol was registered with the Open Science Framework in September 2024 (osf.io/ctfyb), emphasizing the study's commitment to transparency and open science practices.

Discussion

Principal Findings

This study aims to investigate the attentional biases associated with food stimuli, comparing familiar or novel food items, using different attention indexes. We hypothesize that participants will exhibit shorter RTs and longer TFD for familiar food items compared with novel food items, suggesting a stronger attentional bias toward familiar foods. In addition, we expect familiar food items to elicit greater P300 amplitudes in electroencephalography recordings, indicating enhanced attentional engagement and processing. Furthermore, we anticipate that eye-tracking measures will correlate with electroencephalography-derived ERP components, highlighting the joint contribution of neural and ocular markers to attentional bias toward food stimuli. Finally, we anticipate that various attentional bias measures, including RTs, ERP amplitudes, and eye-tracking metrics, would predict self-reported food choices, demonstrating the relevance of attentional mechanisms in consumer behavior.

While previous research has explored the effects of familiarity on consumer preferences and decision-making [35,36], the combined use of eye-tracking and electroencephalography metrics remains underexplored, particularly when taking the participant's food choice into consideration. The integration of these technologies allows for a comprehensive analysis of both spatial and temporal aspects of attention, capturing where and how long participants focus on food stimuli and the neural dynamics underlying these attentional processes [37]. Previous research has highlighted the relevance of visual attention in the food decision-making process. For instance, in the study by Gere et al [38], the authors proposed using alternative models to analyze visual attention patterns during food choices. Their approach emphasized the use of multimodal data, such as eye-tracking and neurophysiological measures, to predict food preferences and decision outcomes more accurately, which supports the use of combined methodologies in our pilot study to capture these intricate cognitive processes. In addition, Wang et al [39] used eye-tracking and electroencephalography to investigate how emotional states influence attention to food-related stimuli. The findings revealed distinct neural patterns associated with processing positive versus negative stimuli and suggested that emotional context significantly modulates visual attention towards food. This insight aligns with our aim to explore potential neural mechanisms (eg, P300 and N100 ERP components) that may underlie attentional biases in response to food stimuli, indicating that factors such as familiarity and novelty could similarly impact cognitive responses. Furthermore, research comparing attentional differences in overweight or obese versus normal-weight females under hunger and satiety conditions demonstrated that hunger states amplify attention to high-calorie foods, while satiety reduces such biases [23]. These findings suggest that attentional biases are dynamic and can be influenced by both physiological states and personal food-related experiences.

Integrating these perspectives, our study seeks to build upon these observations by investigating how familiarity and novelty interact with attentional biases, potentially offering a new understanding of how these factors shape food choices. A recent study investigating electroencephalography measures of attention toward food-related stimuli in neophobic individuals proposed that food neophobia might be associated with attentional biases toward novel foods. However, the results indicated that implicit behavioral and attentional processing were affected across all food types, regardless of familiarity [40]. This finding, alongside several other studies [23,41] examining attentional differences toward food stimuli based on factors such as calorie content and familiarity across diverse populations, underscores the importance of using multiple methods to capture different dimensions of attention. This study serves as an initial step in piloting an integrated approach, combining electroencephalography, eye tracking, and a dot-probe task, to gather preliminary data on the feasibility of using this multimodal framework to assess attentional responses to familiar versus unfamiliar food stimuli in healthy adults. A recent systematic review and meta-analysis on attentional bias toward food in individuals with overweight and obesity [42] highlighted the poor reliability of eye tracking and the dot-probe task, 2 commonly used methods for measuring attentional bias.

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The review emphasized that the poor psychometric properties of these measures represent a significant limitation in attentional bias research. In light of this, the present study's integration of 3 different attentional bias tools is a key strength, offering a more comprehensive approach to capturing multiple dimensions of attentional processes. In addition, this study has several other strengths. First, the integration of eye-tracking, electroencephalography, and the dot-probe task is a novel approach that allows for a comprehensive analysis of attentional biases towards food stimuli. Second, by examining attentional biases toward familiar or novel food stimuli, the study addresses an important aspect of consumer behavior with implications for both health behaviors and marketing strategies. Third, the use of multiple measures (eg, TTFF, TFD, RTs, P300, N100) enhances the reliability of the findings and provides a solid foundation for validating results in future studies.

However, the study protocol is also subject to several limitations. The relatively small sample size of 40 participants, while typical for pilot studies, may limit the generalizability of the findings and reduce statistical power to detect smaller effects. In addition, the lack of a more diverse sample, including individuals who are overweight or obese, a wider age range, and not including the satiety status, may limit the generalizability of the findings to broader populations. The simultaneous use of electroencephalography and eye-tracking introduces potential technical challenges and artifacts in the data, which could affect measurement accuracy. Finally, the study's focus on a limited number of food categories (milk, oil, sauces, and beverages) may not fully capture the range of food stimuli that influence attentional biases and food choices.

Following the pilot study, conducting larger-scale studies with more diverse samples would enhance the generalizability and robustness of the findings. This could involve multiple sites and a broader range of food categories.

Dissemination Plans

The results will be submitted to peer-reviewed journals in fields such as neuroscience, psychology, nutrition, and consumer behavior. This ensures that the findings are scrutinized by experts and accessible to the academic community. Presenting the findings at national and international conferences will facilitate knowledge exchange with other researchers and practitioners. Organizing workshops at universities and research institutions to share the methodology and findings with students and faculty. This can also include training sessions on the integrated use of eye-tracking and electroencephalography. Collaborating with policy makers, health organizations, and the food industry to translate the research findings into practical strategies for promoting healthier eating habits and informing marketing practices.

In summary, the integration of eye-tracking and electroencephalography data in our study will allow for a detailed examination of attentional processes, building on previous research that underscores the importance of capturing both visual and neural indicators when exploring food-related decision-making. Such insights will not only enhance our understanding of attentional mechanisms in food choice but also contribute to developing strategies to promote healthier food decisions.

Conclusion

Future directions could include developing and testing interventions based on the findings, such as strategies to modify attentional biases toward healthier food choices, which could have practical applications in public health and consumer behavior. Notably, expanding the research to include different populations, such as individuals with obesity, eating disorders, or diverse cultural backgrounds, would provide a more comprehensive understanding of attentional biases in various contexts and further inform intervention strategies.

Acknowledgments

The authors extend their gratitude to the study participants, as well as the research interns, for their contributions to the study's execution. This study would not have been possible without the support of the Iran University of Medical Sciences. Funding for this study will be provided by the Iran University of Medical Sciences.

Data Availability

Given the nature of this study protocol, no data or materials are currently available. Upon study completion, all data generated or analyzed will be included in the published article and its supplementary information files.

Authors' Contributions

MAN and AS contributed to the methodology. MAN and FA performed the conceptualization, formal analysis, and investigation. FA wrote the original draft. MAN, FA, and AS contributed to the review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
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Multimedia Appendix 2
Food Choice Questionnaire.
[PDF File (Adobe PDF File), 58 KB - resprot_v14i1e69541_app2.pdf]

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Abbreviations

ERP: event-related potential
FCQ: Food Choice Questionnaire
FD: fixation duration
RT: reaction time
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trial
TFD: total fixation duration
TTFF: time to first fixation

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Protocol

Impact of Pharmacist-Led Continuous Glucose Monitoring on Clinical Outcomes in People With Type 2 Diabetes in Primary Care: Protocol for a Prospective Cohort Study

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Abstract

Background: Continuous glucose monitoring (CGM) is increasingly being recognized as the new standard of care for glycemic monitoring in people with type 2 diabetes (T2D). However, despite advances in therapeutics and technology, glycemic control remains suboptimal. Team-based approaches involving pharmacists, particularly in primary care, have shown to be effective in addressing these shortcomings yet have not been rigorously evaluated in the literature.

Objective: Herein we present the protocol for a study that seeks to evaluate the change in hemoglobin A_{1c} (HbA_{1c}) in people with T2D using CGM under a pharmacist-led approach as compared with a pharmacist-led approach using no CGM (only self-monitoring blood glucose with a glucometer). We will also assess changes in CGM-derived glycemic outcomes, health behavior, and safety outcomes among the pharmacist-led CGM cohort.

Methods: This is a 12-week prospective cohort study in an academic family medicine department. We will enroll adults with T2D and a HbA_{1c} level of ≥8%. Participants in the intervention cohort will wear a CGM sensor (FreeStyle Libre 2) for 12 weeks and receive structured diabetes self-management education and support from a pharmacist. Each participant in the intervention group will have 5 visits with a pharmacist. The primary objective is the between-group difference in change in HbA_{1c} levels from baseline to 12 weeks between the intervention and historical cohort. Secondary objectives include a change in CGM-derived metrics among the intervention group from baseline to 12 weeks, and a change in health behavior via the Summary of Diabetes Self-Care Activities measure from baseline to 12 weeks in the intervention cohort. A CGM survey will also be administered to participants in the intervention cohort to evaluate changes in diet, physical activity, general lifestyle, and medication adherence. Safety endpoints will also be evaluated. The primary and secondary outcomes will be analyzed within and between groups using descriptive statistics, with a multivariable regression analysis conducted as appropriate to adjust for potential known confounding effects.

Results: This study was funded in July 2023. We began enrolling participants in December 2024. At the time of writing, 3 participants have been enrolled. It is anticipated that we will conclude this study in December 2025 and expect to disseminate results in March 2026.

Conclusions: Results of this study will further elucidate the role of pharmacist-led CGM in primary care.

Trial Registration: ClinicalTrials.gov NCT06572306; https://clinicaltrials.gov/study/NCT06572306

International Registered Report Identifier (IRRID): PRR1-10.2196/67014

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(JMIR Res Protoc 2025;14:e67014) doi:10.2196/67014

KEYWORDS

type 2 diabetes; continuous glucose monitoring; pharmacist; primary care; family medicine; prospective study

Introduction

More than 38 million adults in the United States have diabetes, with the prevalence estimated to triple by 2060 [1]. The majority of those with diabetes have type 2 diabetes (T2D) [1]. Frequent patient self-monitoring of blood glucose (SMBG) in conjunction with hemoglobin A_{1c} (HbA_{1c}) testing is often required in people living with T2D [2]. HbA_{1c} and SMBG have long been recognized as the standard of care for assessment of glycemic control [3]. However, limitations to these metrics exist. HbA_{1c} is an average of glycemia over 2-3 months, with variability in the average glucose range at any HbA_{1c} level [4]. People with similar HbA_{1c} levels can have vastly divergent glycemic patterns [4]. Limitations also extend to SMBG, as it only provides glucose data at one point in time, thereby missing time spent in the normal glycemic range, and potential identification of hyperglycemia or hypoglycemia [4].

Continuous glucose monitoring (CGM) provides glycemic metrics beyond HbA_{1c} and SMBG [5]. CGM is increasingly being recognized as the new standard of care for glycemic monitoring in people with T2D [6-8]. CGM-derived glycemic metrics provide more actionable data for patients and clinicians versus HbA_{1c} and SMBG. Importantly, CGM has also been shown to improve patient engagement and positive health behavior change, improve glycemic control, and reduce hypoglycemia in people with T2D [9-11].

Despite advances in therapeutics and technology, glycemic control remains suboptimal with 50% of patients unable to reach glycemic goals [12]. Failure to reach these goals increases the risk of microvascular and macrovascular diabetes complications [13]. While the reasons for failure to reach glycemic control are multifactorial, clinical inertia has been shown to be associated with an inability to achieve glycemic control [14]. In addition, patient inertia may result from lower self-efficacy and a lack of effective tools to make behavior change, further driving this issue [14,15].

Our recent work suggests that pharmacist-led interventions in close collaboration with medical providers in primary care settings may overcome diabetes-related inertia [16-18]. The trend in team-based care involving a pharmacist is widely recognized at the national and international level and is now the standard of care in a number of medical centers [19]. Several small retrospective studies have found improvements in glycemic control with a pharmacist-led CGM clinical service [20]. However, in our recent scoping review, we identified only 1 published prospective study evaluating a pharmacist-led CGM service [20]. The aim of this work is to further elucidate the impact of pharmacist-led CGM on glycemic control and change in health behavior in people with T2D.

Methods

Study Objectives

The primary objective of this study is to determine the impact of pharmacist-led CGM on glycemic control in people with T2D. The secondary objectives are to assess change in CGM-derived glycemic outcomes, change in health behavior, and safety outcomes.

Practice Setting

This study will take place in the University of South Florida (USF) Health Department of Family Medicine, where people with T2D are routinely managed by pharmacists for chronic disease state management in collaboration with their primary care physician. Routine care consists of appointments that involve reviewing a patient's blood glucose log or CGM sensor readings, ordering laboratory tests, and adjusting or initiating medication therapy under supervision and in collaboration with medical providers. The study procedures will be incorporated into the patient's routine appointments. No change in the patient's routine medical care will occur with their primary care provider or other medical specialists as a result of participating in this study.

Study Design

This is a 12-week prospective cohort study. Inclusion and exclusion criteria are shown in Textbox 1. Enrolled participants in the intervention group will wear a CGM sensor (Abbott FreeStyle Libre 2; n=20) and receive structured diabetes self-management education and support (DSMES) from a pharmacist in a family medicine clinic. Each participant in the intervention group will have 5 visits with a pharmacist. DSMES will be provided in line with the 2022 National Standards for DSMES [21].

A historical cohort will be used to compare outcomes against the intervention group for the primary outcome. The historical cohort will include participants with T2D and a HbA_{1c} level of ≥8% seen by a pharmacist practicing under a similar scope of practice in a different outpatient clinic within the same health system between January 1, 2020, and January 7, 2024. Participants in this cohort (n=20) will have only used SMBG, and not used CGM within 6 months of the index date (defined as the first visit with a pharmacist during the study time frame). Reporting of research for this cohort study will follow the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) checklist (Multimedia Appendix 1).

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Type 2 diabetes.
- Hemoglobin A_{1c} level of ≥8%.
- Compatible smartphone with FreeStyle Libre 2 continuous glucose monitoring system.
- Current use and access to a glucometer for self-monitoring of blood glucose.

Exclusion criteria

- Any continuous glucose monitor use within 6 months before study enrollment.
- Pregnant and planning to become pregnant during the study time frame.
- History of hypoglycemia requiring third-party assistance.
- History of diabetic ketoacidosis or hyperosmolar hyperglycemic state within 6 months before study enrollment.
- Known allergy to medical-grade adhesives.
- Current use of systemic steroids for any medical condition.
- Current use of dialysis.

Recruitment

Recruitment began in December 2024, with an expected study completion date of December 2025. Participants included in the intervention group will be recruited from the USF Health Department of Family Medicine. Screening and enrollment will be performed by the pharmacist on the basis of routine care. Participants already scheduled for a visit with a pharmacist for diabetes care and education will be screened for eligibility by review of the medical record. Informed consent will be completed at the first visit.

Sample Size

The sample size (n=40) was determined on the basis of available research funding, balancing statistical power with financial constraints. While a larger sample could enhance the external validity of findings, budgetary limitations necessitated an approach that maximized efficiency while maintaining sufficient power to detect meaningful effects. This sample size aligns with previous studies of similar scope and ensures the study remains methodologically rigorous within resource constraints [16-18,20].

Study Visits

An overview of activities that will take place at each study visit for participants enrolled in the intervention cohort is shown in Table 1.

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Table 1. Study activities.

Study activity	Visit 1 (baseline)	Visit 2 (week 2)	Visit 3 (week 4)	Visit 4 (week 6)	Visit 5 (week 12)
Review eligibility	✓				
Obtain informed consent	✓				
Collect patient baseline characteristics	✓				
Collect vital signs (blood pressure, weight, pulse, and oxygen saturation)	✓	✓	✓	✓	✓
Review and collect medications	✓	✓	✓	✓	✓
Assess diet and fitness activity at baseline	✓				
HbA_{1c}[a] blood sample	✓				✓
FSL2[b] CGM[c] sensor placement and education	✓				
Provide 5 FSL2 CGM sensors to participants		✓			
Review ambulatory glucose profile and upload into electronic health record		✓	✓	✓	✓
Administer structured diabetes self-management education and support	✓	✓	✓	✓	✓
Provide food and fitness logs	✓				
Assess and collect food and fitness logs		✓	✓	✓	✓
Administer CGM survey		✓	✓	✓	✓
Administer summary of diabetes self-care activities measure	✓				✓
Assess CGM-related adverse events		✓	✓	✓	✓
Provide after-visit summary to participants	✓	✓	✓	✓	✓

[a]HbA_{1c}: hemoglobin A_{1c}.

[b]FSL2: FreeStyle Libre 2.

[c]CGM: continuous glucose monitoring.

Outcomes and Covariates

Glycemic Control

To evaluate the primary objective the between-group difference in change in HbA_{1c} levels from baseline to 12 weeks will be compared between the intervention and historical cohort.

CGM-Derived Metrics

For the secondary objective, the CGM-derived metrics shown in Textbox 2 will be compared within the intervention group from baseline to 12 weeks.

Textbox 2. Continuous glucose monitoring–derived glycemic metrics.

- Change in time in range (TIR) at 12 weeks (%).
- Change in mean sensor glucose concentration at 12 weeks (mg/dL).
- Change in time below range at 12 weeks (%).
- Change in time above range at 12 weeks (%).
- Change in glycemic variability (SD and coefficient of variance) at 12 weeks.
- Change in the number of participants increasing by 5% or more in TIR at 12 weeks.
- Change in the number of participants increasing by 10% or more in TIR at 12 weeks.
- Change in the number of participants achieving >70% TIR at 12 weeks.
- Change in the number of participants achieving hemoglobin A_{1c} <7% at 12 weeks.
- Change in the number of participants achieving hemoglobin A_{1c} <8% at 12 weeks.

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Summary of Diabetes Self-Care Activities

To evaluate change in health behavior we will administer the Summary of Diabetes Self-Care Activities Measure (SDSCA) at baseline and week 12 in the intervention cohort. The within-group difference from baseline to week 12 will be assessed. The SDSCA is a valid and reliable measure of diabetes self-management, which assesses diet, exercise, blood-glucose testing, foot care, and smoking [22]. The strength of the SDSCA includes its brevity and ease of scoring. The SDSCA is a survey scored on an 8-point Likert scale (0-7). Higher scores indicate better compliance with diabetes self-care, whereas a lower score indicates poor self-care performance [22].

CGM Survey

We will administer a CGM survey (Table 2) at each visit following the first visit in the intervention cohort. The within-group difference in responses from baseline (second visit) to the end of the study among the intervention group will be evaluated.

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Table 2. Continuous glucose monitoring survey.

Domain and questions	Response
Dietary habits	
Have you noticed how different foods affect your glucose levels since using CGM[a]?	• Yes • No • Not sure
Have you changed your consumption of sugared beverages since using CGM?	• Yes, I have reduced or avoided them • No, my consumption is the same • I did not consume them before CGM use
Have you changed your consumption of high-carbohydrate foods (eg, rice and cereals) since using CGM?	• Yes, I have reduced them • Yes, I have avoided them • No, my consumption is the same • I did not consume them before CGM use
Do you read nutrition labels more frequently since using CGM?	• Yes • No • I already did this before CGM use
Physical activity	
Have you increased your physical activity levels since using CGM?	• Yes • No • I was already active before CGM use
Are you more likely to engage in physical activity (eg, go for a walk) if you see a rise in your glucose levels?	• Yes • No • Not sure
General lifestyle change	
Do you feel that using CGM has contributed to a healthier lifestyle overall?	• Yes • No
Since using CGM, how often do you scan to check your glucose levels?	• Less than once a day • 1-3 times a day • 4-6 times a day • More than 6 times a day
How motivated are you to manage your diabetes since using CGM?	• Not motivated • Slightly motivated • Moderately motivated • Highly motivated
Medications	
Since wearing a CGM, I take my diabetes pills, insulin or both at the right time and as prescribed.	• Always • Usually • Sometimes • Rarely • Never • I already took my medicine at the right time and as prescribed before CGM use
Open-ended questions	
What specific changes have you made to your diet since using CGM?	__[b]
What specific changes have you to your physical activity routine since using CGM?	—
How has CGM affected your overall approach to managing your diabetes?	—

[a]CGM: continuous glucose monitoring.

[b]Not applicable.

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Safety

Safety endpoints will include an assessment of cutaneous reactions at the site where the CGM sensor is placed. Specific sensor site reactions that will be assessed include erythema, itching, rash, pain, bleeding, bruising, edema, and induration. If any participant experiences a serious cutaneous reaction from the sensor defined as pain, or serious bleeding, they will be withdrawn from the study. If 3 people are withdrawn for that reason, the study will be stopped.

Participants will be screened at the initial visit for any contraindications to using the Abbott Freestyle Libre 2 sensor (including planned magnetic resonance imaging, computed tomography scan, or high-frequency electrical heat (diathermy) treatment during the study time frame.

Statistical Analyses

Groups will be compared at baseline to determine if any significant differences exist in patient characteristics. The change in the primary and secondary outcomes will be analyzed within and between groups using descriptive statistics (eg, means and SDs for continuous variables such as age, and percentages for categorical variables such as gender). Nonparametric analyses will be used in situations where the variables are not normally distributed. A multivariable regression analysis will be conducted as appropriate to adjust for potential known confounding effects.

The analysis will use an intention-to-treat approach for data analysis. Any participants with missing data or those lost to follow-up will still be included in the analysis. Attempts will be made to match patients on the basis of diabetes medication type and baseline HbA_{1c} in the intervention versus the historical cohorts.

Ethics Approval

The study protocol was approved by the USF institutional review board (STUDY007451). Informed consent to participate in the study will be obtained from each participant in the intervention cohort. A waiver of informed consent was obtained for participants in the control group as it is not feasible to obtain since participants may no longer establish care at USF. In addition, the electronic health record may have unreliable or inaccurate contact information for the participants, or the participant may be deceased.

All data will be stored in REDCap (Research Electronic Data Capture, Vanderbilt University), a web-based HIPAA (Health Insurance Portability and Accountability Act)-compliant platform hosted at USF that is password protected. All data will be deleted 5 years from when the study has concluded. Confidential data will not be disclosed outside of the study team except as required by law or as allowed by the consent (eg, with the USF institutional review board or those who monitor the study). All data will be deidentified for the analysis. Participants will not receive any compensation for their participation.

Results

This study was funded in July 2023. We began enrolling participants in December 2024. At the time of writing, 3 participants have been enrolled. It is anticipated that we will conclude this study in December 2025 and expect to disseminate results in March 2026.

Discussion

Principal Findings

To our knowledge, this will be the first study to prospectively analyze the impact of a pharmacist-led CGM intervention on glycemia and health behavior in people with T2D in a primary care setting. Our study is unique in that it is not only designed to assess the glycemic benefits of CGM in people with T2D in primary care but also aims to elucidate behavior change resulting from CGM use under a pharmacist-led approach.

We hypothesize that the mean change in HbA_{1c} will be greater for participants enrolled in the intervention cohort as compared to the historical control cohort at 12 weeks. We also hypothesize that participants enrolled in the intervention cohort will experience an improvement in CGM-derived metrics (time in range, mean glucose, time below range, time above range, and glycemic variability) at 12 weeks. For health behavior, we hypothesize that the mean SDSCA score will be higher at 12 weeks compared with baseline. Finally, we hypothesize that an improvement in diet, physical activity, general lifestyle, and medication adherence will be observed on the CGM survey from baseline (second visit) to the end of the study among the intervention group.

Comparison to Previous Work

Although CGM was first approved for use over 20 years ago, recent technological advancements have made this technology more user-friendly and attainable for a greater number of people living with diabetes, particularly those with T2D. In people with T2D, prospectively driven CGM studies involving pharmacists are currently lacking. In our recent scoping review, we identified only 1 published prospective study evaluating a pharmacist-led CGM service, among a total of 11 published studies in the literature [20,23]. Our methods differ from Fantasia et al [23] in that we are using unblinded CGM devices, which are more commonly used in clinical practice, and are comparing our intervention to a historical cohort managed by a pharmacist in a similar practice setting, rather than to endocrinologists.

In addition, results from our scoping review demonstrated that pharmacist-led CGM was associated with an improvement in glycemic control, with an absolute mean reduction in HbA_{1c} in the literature ranging from –0.4% to –1.8%, which is clinically significant [23-27]. We also found that pharmacist-led CGM was associated with improvements in diabetes self-efficacy [25], improvements in self-care, and improvements in health behavior [28].

Strengths and Limitations

Several limitations to this study must be mentioned. First, as an observational study design, the lack of randomization may lead to selection bias. For example, it is possible that participants seeking care and who agree to participate in the intervention group might differ in their overall health status and adherence to medical care versus those who do not seek routine medical

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care. Furthermore, without randomization, differences in baseline characteristics such as medication adherence, lifestyle factors, and socioeconomic status could impact outcomes. Without randomization, it remains difficult to isolate the true effect of the intervention.

In addition, this study may have low external validity, since pharmacist scope of practice varies widely geographically and among health care systems. Further, concerns such as data from a single site and small sample size must also be considered.

On the other hand, several strengths to this study exist, making it a valuable addition to the literature, such as the measurement of clinically significant outcomes (HbA_{1c}) as well as the measurement of CGM-derived metrics, which is lacking in many studies. In addition, our study is also using validated measurement tools (ie, SDSCA) to measure health-behavior change. Finally, although observational, the prospective nature of our study establishes a temporal relationship between exposure (to the intervention) and the outcomes, as well as reflecting real-world clinical practice in a primary care setting.

Future Directions

Our overarching aim is to use the data from this study to support funding to conduct a larger randomized controlled trial that can more rigorously test our hypothesis that pharmacist-led CGM is an intervention that can overcome clinical inertia and improve diabetes-related outcomes in primary care settings.

Dissemination Plan

The results of this prospective cohort study will be disseminated through presentation in national or international peer-reviewed scientific journals, and at annual meetings of professional conferences.

Conclusions

There is a need for additional evidence supporting novel approaches to implementing CGM in primary care settings. A prospective cohort study can provide valuable insights into the association of a pharmacist-led approach to implementing CGM.

Acknowledgments

This study was funded by the University of South Florida New Researcher Grant (principal investigator: KC). A peer review of the grant proposal can be found in Multimedia Appendices 2 and 3.

Data Availability

Data are not included in this protocol. The datasets generated and/or analyzed during the current study are not publicly available because this study's institutional review board does not allow for this study data to be in a public repository. Requests to access the datasets should be addressed to the corresponding author (KC).

Conflicts of Interest

KC received research contract support from Sanofi Pharmaceuticals and grant support from Abbott Diabetes Care and University of South Florida. RTW received grant support from American College of Clinical Pharmacy and Abbott Diabetes Care. NWC received research contract support from Sanofi Winthrop Industrie.

Multimedia Appendix 1
STROBE (Strengthening the Reporting of Observational studies in Epidemiology) statement and checklist.
[PDF File (Adobe PDF File), 116 KB - resprot_v14i1e67014_app1.pdf]

Multimedia Appendix 2
Proposal review score sheet for reviewer 1.
[PDF File (Adobe PDF File), 71 KB - resprot_v14i1e67014_app2.pdf]

Multimedia Appendix 3
Proposal review score sheet for reviewer 2.
[PDF File (Adobe PDF File), 71 KB - resprot_v14i1e67014_app3.pdf]

Multimedia Appendix 4
Peer-reviewer report from the University of South Florida New Researcher Grant Program.
[PDF File (Adobe PDF File), 269 KB - resprot_v14i1e67014_app4.pdf]

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Abbreviations

CGM: continuous glucose monitoring
DSMES: diabetes-self management education and support
HbA_{1c}: hemoglobin A_{1c}
HIPAA: Health Insurance Portability and Accountability Act
REDcap: Research Electronic Data Capture
SDSCA: Summary of Diabetes Self-Care Activities Measure
SMBG: self-monitoring of blood glucose
STROBE: Strengthening the Reporting of Observational studies in Epidemiology
T2D: type 2 diabetes
USF: University of South Florida

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Protocol

Improving the Predictive Accuracy of the National Early Warning Score 2: Protocol for Algorithm Refinement

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Abstract

Background: The National Early Warning Score 2 (NEWS2) has been widely adopted for predicting patient deterioration in health care settings using routinely collected physiological observations. The use of NEWS2 has been shown to reduce in-hospital mortality, but it has limited accuracy in the prediction of clinically important outcomes, especially over longer time periods.

Objective: This project aims to improve the predictive accuracy of the NEWS2 scoring system, particularly its accuracy over more than 24 hours and its predictive value in older patients and children. It will investigate whether using the currently collected data differently and the inclusion of additional data would result in an improved algorithm.

Methods: The study will use historical patient data from the Newcastle upon Tyne Hospitals NHS Foundation Trust, including observational data (eg, vital signs), BMI- related data, and other outcome-related variables (eg, mortality rates) to train and test an algorithm to predict the risk of key clinical outcomes, including mortality, intensive therapy unit admission, sepsis, and cardiac arrest, to demonstrate a proof of concept for a modified scoring system. The algorithm's performance will be assessed based on its accuracy, precision, F_1-score, area under the curve, and receiver operating characteristic curve.

Results: The study is expected to start in April 2025. The findings are expected to be produced by the end of 2026 and will be disseminated at symposia, conferences, and in journal publications.

Conclusions: The refined NEWS2 algorithm will address limited accuracy in predicting clinical deterioration beyond 24 hours in the original system by incorporating additional variables. Improved accuracy in the early detection of deterioration can lead to timely interventions, potentially reducing mortality and adverse clinical events. The enhanced algorithm also has the potential to be integrated into existing clinical decision support systems to facilitate health care professionals' decision-making.

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KEYWORDS

clinical deterioration; National Early Warning Score; performance; proof-of-concept

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Introduction

The National Early Warning Score 2 (NEWS2) system is a widely used tool for the systematic documentation and identification of clinical deterioration. It has been demonstrated to be effective at reducing in-hospital mortality [1-4], it facilitates effective communication between clinicians and enables timely interventions to improve patient outcomes, but NEWS2 has limited positive and negative predictive accuracy [5-7], particularly in predicting adverse events beyond 24 hours [8-10].

The use of digital technologies in health care presents an opportunity to evaluate whether the inclusion of additional routinely collected variables would improve the predictive accuracy of an early warning score and thus reduce patient risk. The same technologies could then be used to provide clinical decision support using artificial intelligence–derived algorithms that would not be practical using paper observation charts and health care records [1,11].

This further personalization of risk prediction is increasingly important in our aging population. Older adults are particularly vulnerable to sudden changes in physiological status [12], but this group was not included in the development of NEWS2 [13]. Improved predictive accuracy in this growing frail and vulnerable group could significantly improve patient outcomes [13-15].

In an evaluation of the performance of the original National Early Warning Score (NEWS), it demonstrated consistent predictive accuracy across multiple patient groups [5]. However, the performance of NEWS2 varies between care settings and between patients with different characteristics [11,16,17]. NEWS2 has been found to have significantly lower specificity, sensitivity, and positive predictive value for those who were at risk of type II respiratory failure, but higher specificity and positive predictive value for those with documented type II respiratory failure status, than the original NEWS [16]. The accuracy of NEWS has also been found to vary between care settings [17]. These observations suggest that the inclusion of individualized patient and care setting characteristics may improve the predictive accuracy, sensitivity, and specificity of the system and thus improve outcomes in a range of health care settings and in diverse patient groups.

To determine which variables may improve the risk prediction of NEWS2, we have reviewed 6 databases (CINAHL, PubMed, Embase, ScienceDirect, Cochrane Library, and Web of Science) [18]. Our preliminary findings show that demographic variables including age and ethnicity [6,19], trend data [20-22], and adjustments to component weighting [23,24] may improve the performance of NEWS2 in predicting clinical deterioration.

The principal aim of this work is to develop an algorithm that can improve the predictive accuracy and thus clinical value of the NEWS2 system. The objectives of this study are as follows:

1. To determine which additional variables have been previously used to enhance the accuracy of clinical early warning scores, including NEWS2.
2. To collect a large set of patient data that links observations, demographic, and admissions data with key deterioration-related outcomes.
3. To use these data to train an artificial intelligence model to determine which variables, and what weightings, provide optimal predictive accuracy.
4. To test the accuracy, sensitivity, and specificity of the algorithm.
5. To consider how the new model could be applied across a wide range of health care settings, including different physiological observation equipment, different electronic patient record systems, or paper-based clinical record systems.

Methods

Overview

The study is a retrospective cohort study using historical, anonymized patient data to explore ways in which a new alerting system could improve NEWS2. The Newcastle Hospitals National Health Service (NHS) Foundation Trust has an established information governance system for the use of anonymized patient data for research. This study will use historical, anonymized hospital inpatient and emergency care data from the Newcastle upon Tyne Hospitals NHS Foundation Trust, collected routinely over 6 years (December 2018 to June 2024).

Patient and public involvement (PPI) refers to research being carried out “with” or “by” members of the public rather than “to,” “about” or “for” them [25]. To support PPI in research, we will recruit PPI members through the Newcastle BRC Informatics and Precision Care for an Ageing Population theme and Newcastle University’s Clinical Trials Unit. They will be included in all project management group meetings and will provide their lived experience with hospital monitoring to highlight any concerns or barriers they foresee in the adoption and implementation of a modified NEWS system. At least 1 older adult will be included to ensure that we are including a perspective that has been missing in the development of previous NEWS systems. A logic diagram of the study design is presented in Multimedia Appendix 1.

The model will be developed following the recommended process of building a predictive model with machine learning [26,27]. The research question and a clear goal of building a model will be first defined. The following types of data (Table 1) will then be obtained from the Trust.

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Table 1. Input variables.

Type	Input variables
General	• Patient ID
Demographic data	• Age • Biological sex • Ethnicity
Observational data (vital signs and other measures)	• Observation date, time, and location • Encounter: ID and type • Heart rate • Temperature • Respiratory rate • Need of oxygen therapy • Level of consciousness or new confusion (Alert, Verbal, Pain, or Unresponsive score) • Blood pressure (systolic and diastolic) • Paired value One (lying blood pressure) • Paired value Two (standing blood pressure) • Oxygen therapy percentage—inspired oxygen fraction (FiO2) • Oxygen saturation (SpO2) • Nursing concern • Urine output • Pain score • Mask code (oxygen therapy device used) • Partial Obs set (NEWS2[a] variables) • Partial Obs set (additional variables)
BMI data (in separate data file)	• Height (numeric, units, date, and time) • Weight (numeric, units, date, and time) • BMI (score date and time)
Outcome-related data	• Mortality • Cardiac arrest • Resuscitation • Unplanned admission to critical care: include either intensive therapy unit or high-dependency unit • Sepsis • NEWS2 score • Northumbria Healthcare NHS[b] Foundation Trust risk rating (NuTH)- overwrite thresholds (NuTH specific)

[a]NEWS2: National Early Warning Score.

[b]NHS: National Health Service.

The data will then be deidentified before the research team can access it within a secure project environment in the Trust's IT network for training and testing the algorithm. Data will also be prepared by handling missing values and any inconsistencies or imbalances. Deidentified data from the Trust's clinical data marts, including patient observations, admissions information, demographic data, and outcomes data, will be divided into training and testing subsets. A decision will then be made on whether to test the performance of multiple existing models with additional data or improve the performance of 1 model (eg, eXtreme Gradient Boosting). Using these datasets, we will train and test an algorithm that optimizes the variables and their weightings to predict the risk of key clinical outcomes, including mortality, intensive therapy unit admission, sepsis, and cardiac arrest, to demonstrate a proof of concept for a modified scoring system.

The following metrics will be used to evaluate the model's performance. Definitions and equations are obtained from the literature [28,29].

1. Accuracy: the number of correct predictions divided by the total number of predictions.
2. Precision: the ratio of true positives and total positives predicted.
3. F1-score: the harmonic mean of precision and recall.
4. Area under the curve (AUC): the probability that the model, if given a randomly chosen positive and negative example, will rank the positive higher than the negative. The closer the AUC is to 1.0, the better the model's ability to separate classes from each other.
5. Receiver-operating characteristic curve: this curve is typically plotted in terms of true positive rate and false positive rate. It is drawn by calculating the true positive rate and the false positive rate at every possible threshold (in practice, at selected intervals), then graphing the true positive rate over the false positive rate.

The performance of the model will be optimized through hyperparameter tuning and configuration refining. The final model will be tested with the test set against predetermined

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metrics. Depending on funding availability, the model may be validated using external collaborator's datasets.

Ethical Considerations

This study (Integrated Research Application System Project ID 344472) has received ethical approval from the UK Health Research Authority Research Ethical Committee (Rec reference 25/WA/0060). Informed consent and compensation do not apply to the study, as no human participants will be involved. A data scientist at the Trust will exclude all data from patients who have opted out of their data being used for research purposes through local or national processes. All patient data used in this project are fully deidentified by the NHS before being accessed by the research team, ensuring no personal information about participants is collected. Data sharing is restricted to authorized team members with NHS-approved credentials and access is managed through secure NHS systems with strict monitoring. During the project, data analysis will be conducted within password-protected environments. After the project, data will be securely archived or deleted following NHS policies. Patients will not be identified in any way in the findings to ensure participant confidentiality.

Results

Algorithm development has not yet commenced as of February 26, 2025. Work is expected to start in April 2025 and findings are expected to be produced by December 2026. By the end of this study, we will have trained and tested an algorithm based on historical patient data from the Newcastle upon Tyne Hospitals NHS Foundation Trust. This will provide a proof-of-concept of whether and which additional data can improve the predictive accuracy of the NEWS2 system.

After refinement, the algorithm is expected to be able to predict clinical disease deterioration accurately. This will be assessed by comparing the algorithm's predictions against observed outcomes, including mortality, cardiac arrest, unplanned admissions to critical care units (intensive therapy units or high-dependency units), resuscitation events, and the occurrence or progression of sepsis. A summary of outcome items and measures is listed in Table 2.

Table 2. Outcome items and measures.

Item	Definition	Measure	Expected result
Mortality	Whether the patient survives within a specified time frame	Quantitative: mortality rate	High accuracy and precision against patient records
Cardiac arrest	Sudden loss of all heart activity	Quantitative: number of correctly predicted cardiac arrest cases	High accuracy and precision against documented cardiac arrest cases
Unplanned critical care admissions	Whether the patient requires admission to intensive care	Quantitative: number of correctly predicted admissions	High accuracy and precision against observed admissions to critical care units
Resuscitation events	Process of reviving acutely ill patient	Quantitative: number of correctly predicted resuscitation events	High accuracy and precision against the actual number of events
Sepsis	Life-threatening reaction to an infection	Quantitative: number of correctly predicted sepsis events	High accuracy and precision against documented sepsis cases

Discussion

Principal Findings

The anticipated results of the study include the algorithm's increased predictive accuracy. There are 2 main ways in which this could improve patient outcomes (1) improving the system's ability to accurately predict patients who will deteriorate within and beyond 24 hours would allow health care professionals to optimize their care and prevent deterioration and (2) reducing false positive alerts would allow care to be concentrated where it will achieve the greatest benefit.

Comparison to Prior Work

Several studies have developed machine learning algorithms (eg, logistic regression, support vector machine, gradient boosting decision tree, and XGBoost) to predict clinical deterioration in emergency departments, such as in-hospital cardiac arrest, clinical deterioration, and mortality, using historical prehospital data or emergency department data in China and Korea [30-32]. While these algorithms achieved high accuracy (AUC over 0.8) in predicting clinical deterioration in emergency department patients, their relevance and potential generalizability to different population demographics and health care contexts remain unknown. This study uses historical patient data from a UK-based NHS Trust, making the algorithm more relevant to the UK health care system. In addition, it includes more demographic variables (ie, age and ethnicity) and BMI-related data to inform a more comprehensive risk assessment. However, this study still requires validation with external datasets to increase its generalizability.

Future Directions

Patient and Public Involvement and Engagement members will help guide the dissemination of the results of the study to the population through publicly accessible forums. Following this work, we will test the new system on data in other NHS Trusts across the United Kingdom to assess its generalizability. In 2026, we will conduct implementation studies in Newcastle and then in other NHS Trusts to assess the adoption of the system and gather initial data on patient outcomes to construct a learning health care system to evaluate the real-world performance of the algorithm and facilitate continual improvement. By 2029, we aim to implement the system in

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NHS Trusts across the United Kingdom and conduct large-scale trials to evaluate its effectiveness in improving patient outcomes.

Strengths and Limitations

This work highlights the importance of investigating the use of additional clinical variables to those used in NEWS2 in the development of a National Early Warning Score. The study design was informed by an evidence synthesis of the literature. Despite these strengths, this project also has limitations. Some retrospective datasets may be of low quality or incomplete. Furthermore, external validation will be needed to test algorithm generalizability.

Conclusion

This work has identified potential areas of improvement to the NEWS2 system and outlined a project for improving its ability to predict adverse outcomes through the use of additional patient data or changes to the scoring process. The project's outputs will be shared widely to facilitate collaboration between health care professionals, researchers, and policymakers to support the implementation of improved clinical early warning systems in diverse populations.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

CP contributed to conceptualization, funding acquisition, writing—review and editing. CC contributed to writing—original draft, writing—review and editing. MM contributed to methodology, writing—original draft. LT contributed to writing—review and editing. PLR contributed to writing—review and editing. EM contributed to conceptualization, supervision, writing—review and editing.

Conflicts of Interest

EM is the Editor-in-Chief of *JMIRx Med*.

Multimedia Appendix 1
Study logic diagram.
[PNG File , 76 KB - resprot_v14i1e70303_app1.png]

Multimedia Appendix 2
Peer review report from the NIHR Newcastle Biomedical Research Centre (National Institute for Health and Care Research, UK).
[PDF File (Adobe PDF File), 144 KB - resprot_v14i1e70303_app2.pdf]

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Abbreviations

AUC: area under the curve
NEWS: National Early Warning Score
NEWS2: National Early Warning Score 2
NHS: National Health Service
PPI: patient and public involvement
XGBoost: extreme gradient boosting

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Protocol

Developing an Equitable Machine Learning–Based Music Intervention for Older Adults At Risk for Alzheimer Disease: Protocol for Algorithm Development and Validation

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Abstract

Background: Given the high prevalence and cost of Alzheimer disease (AD), it is crucial to develop equitable interventions to address lifestyle factors associated with AD incidence (eg, depression). While lifestyle interventions show promise for reducing cognitive decline, culturally sensitive interventions are needed to ensure acceptability and engagement. Given the increased risk for AD and health care barriers among rural-residing older adults, tailoring interventions to align with rural culture and distinct needs is important to improve accessibility and adherence.

Objective: This protocol aims to develop an intelligent recommendation system capable of identifying the optimal therapeutic music components to elicit engagement and resonate with diverse rural-residing older adults at risk for AD. Aim 1 is to develop culturally inclusive user personas for rural-residing older adults to understand their goals and challenges for music-based digital health intervention. Aim 2 is to develop knowledge embedding–based machine learning (ML) models that use music metadata and survey response data to identify optimal therapeutic music components for enhancing engagement and emotional resonance for depression among rural-residing older adults at risk for AD. Aim 3 is to assess acceptability for personalized therapeutic music sessions and ML-based music recommendations with a separate sample.

Methods: Participants (N=1200) will be aged 55 years or older and residing in the United States. In phase 1, participants (n=1000) will receive 5 randomized songs and complete a survey to understand the sentiment, cultural relevance, and perceived benefit for each song. Brief, researcher-created Likert surveys will be used. In phase 2, survey data will be used to develop ML algorithms in collaboration with the University of Massachusetts Amherst Center for Data Science and Artificial Intelligence. These ML models will be integrated into the digital music intervention and tested with a separate sample of 200 participants. Similar to phase 1, participants will be provided with sets of songs generated by the recommendation system based on the target goal (ie, to reduce depression). The recommendation accuracy of the ML algorithm will be assessed using multiple performance metrics, including root-mean-square error and normalized discounted cumulative gain as well as the mean acceptability score with a goal of 85% user acceptability.

Results: Participant recruitment is complete for phases 1 and 2 as of June 2025. Data analysis for the results of aims 1, 2, and 3 are underway and results are expected to be published in the fall of 2025.

Conclusions: This protocol seeks to use ML to improve the equitability and accessibility of a digital lifestyle intervention for AD.

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(JMIR Res Protoc 2025;14:e73711) doi:10.2196/73711

KEYWORDS

Alzheimer disease; digital health; lifestyle; machine learning; music

Introduction

The prevalence of Alzheimer disease (AD) is expected to increase from 55 million cases worldwide in 2021 to an estimated 78 million cases by 2030 [1]. In 2024, the estimated health care cost of AD in the United States was $360 billion [2]. By 2050, it is estimated that the total annual health care cost will be $140,012 per US individual with AD, adding up to a total annual cost of $1.5 trillion [3]. Given the rising societal impact of AD, there is an urgent need for more preventative interventions.

One such preventative intervention is a lifestyle-based approach focusing on addressing modifiable risk factors of AD, such as smoking, diet, and depression [4]. Research investigating lifestyle interventions has yielded promising results [5,6]. The Finnish Geriatric Intervention Study to Prevent Cognitive Impairment and Disability randomized controlled trial examined a 2-year multidomain intervention for adults aged 60 years or older aimed at nutrition, physical activity, cognitive training, social support, and vascular risk factors [5]. The trial intervention showed beneficial changes in cognition and risk of cognitive decline and demonstrates the promise of lifestyle interventions for reducing the risk of overall cognitive decline (control group odds ratio=1.31; intervention group odds ratio=1) [5]. Research has also shown that treating depression can significantly reduce the risk of dementia [7]. Lifestyle-based approaches hold promise for preventing AD when designed to be accessible, especially for those at high risk of developing AD.

Older adults in rural communities face unique health challenges that place them at an even greater risk for AD. Social determinants of health, such as health care access and social engagement, coupled with psychosocial barriers (eg, stigma and medical mistrust) often exacerbate their risk [8,9]. These individuals face greater barriers to accessing lifestyle interventions, including limited health care resources, unreliable transportation, and reduced access to psychosocial support [10]. However, the majority of rural residents have access to broadband internet services [11], meaning digital lifestyle interventions may offer a more feasible, accessible, and cost-effective way to mitigate AD risk compared to traditional methods [12].

Although emerging research highlights the promising utility of lifestyle interventions, there remains a critical need for culturally sensitive approaches. Rural communities are often underrepresented in the development of digital cognitive and mental health tools, despite being disproportionately affected by cognitive and mental risk factors [13]. Research shows that interventions designed to be culturally sensitive can result in higher adherence and engagement with the intervention [14,15]. Additionally, intentional and meaningful inclusion of rural perspectives during the development of digital health interventions ensures individuals from rural, underrepresented communities actively participate in shaping their cognitive health landscape. Given the potential benefits of lifestyle interventions, culturally engaging and accessible interventions are needed to ensure utility and adherence.

One digital music intervention, SingFit, was developed to improve well-being and mood symptoms for both those at risk for and those living with AD (Figure 1). The use of singing to manage symptoms of depression is based on research showing that music interventions and music learning are associated with improvements in cognitive reserve, well-being, and mood symptoms related to depression [16-19]. A network meta-analysis found evidence supporting the use of music therapy or music listening ≥60 minutes a week for improving depression in persons aged 60 years and older [20]. Furthermore, research has shown that music-based interventions reduce anxiety, agitation, and other neuropsychiatric symptoms associated with AD [21-23]. SingFit encourages active engagement in music-making by providing an auditory lyric prompter before each sung phrase. It uses music associated with each user's reminiscence bump, which is the tendency for older adults to recall more personal memories associated with adolescence and young adulthood [24,25]. The app follows music therapy guidelines and clinical practice, where familiar, preferred music is often used to promote relaxation and positive affect [26]. This music is specifically chosen to elicit engagement, long term memory, and narrative speech. This intervention is further described in Brown and Myers [27].

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Figure 1. The SingFit mobile health app.

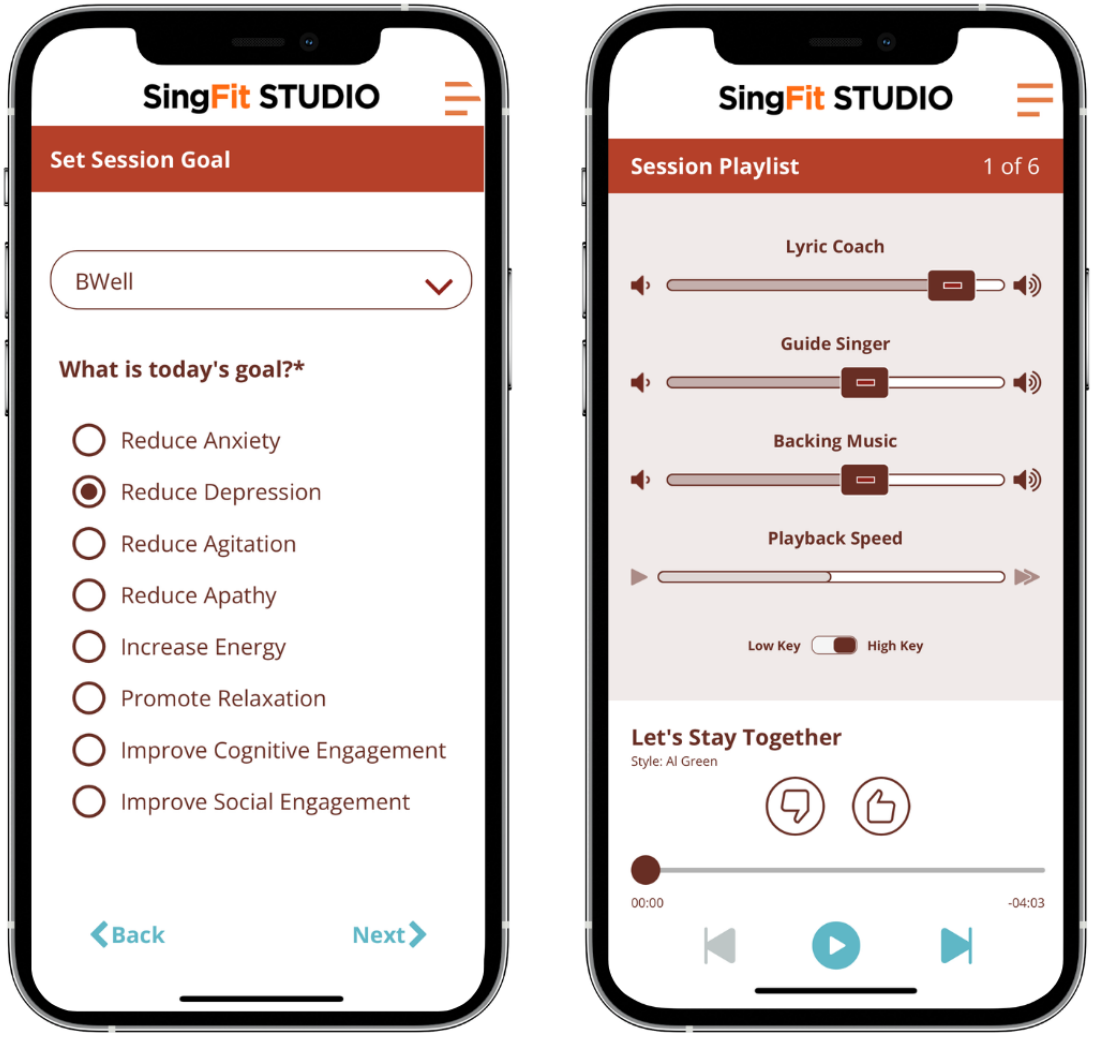

Due to the need for accessible and culturally relevant lifestyle interventions aimed at reducing AD risk, this protocol seeks to improve the cultural responsiveness of an existing digital music-based intervention, SingFit, aimed at improving depressed mood for individuals at risk for or experiencing AD. Much like digital health tools, cultural considerations are important for music-based interventions. Older adults from rural communities tend to prefer traditional genres of music such as country, folk, and gospel; are less likely to embrace newer music trends; and are often influenced by their family's and community's musical preferences [28,29]. The purpose of this study is to develop a machine learning (ML) recommendation system driven by the attitudes and cultural preferences of rural-residing adults. Since acceptability and engagement are important to the success of any health intervention, cultural considerations are at the forefront of this intervention design [30]. This is reflected by the study's aims, which are as follows:

1. Develop culturally inclusive user personas for rural-residing older adults to understand their goals and challenges for music-based digital health intervention.
2. Develop a knowledge embedding (KE)–based ML model that uses user data to identify optimal therapeutic music components for enhancing engagement and emotional resonance among rural-residing older adults at risk for AD.
3. Assess the acceptability of personalized therapeutic music sessions and ML-based music recommendations in a digital music intervention.

Methods

Participants

This survey study will lay the foundation for developing ML algorithms for an accessible music intervention for rural-residing older adults who are at risk for AD. Twelve hundred participants will be enrolled in the study. Eligibility for this study includes participants aged 55 years or older who have possession of a smartphone and the ability to read and understand English. Participants with self-reported presence of a diagnosed psychiatric or neurological condition, including AD, will be excluded. Recruitment was facilitated using a crowdsourcing research platform, Prolific.

Ethical Considerations

The Salus Institutional Review Board determined that the present study was exempt in accord with 45 CFR 46.104(d)(2i, 2ii, 3A & 3B) on June 17, 2024. The exemptions fall under

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benign behavioral interventions or educational surveys where disclosure of responses would not result in risk of harm or civil liability, and where the information being recorded is anonymous or cannot be readily ascertained or linked to participants. Broad informed consent was obtained via an introductory paragraph on the survey, where participants were directed to continue with the survey to indicate acceptance. Participants were provided information on opting out of the study by emailing the principal investigator. Obtaining a signed informed consent would identify participants' names, thus increasing the risk of linking information back to individuals. All participant data collected through Prolific was anonymized by the platform's design. Prolific assigns participants a unique alphanumeric ID that is not linked to any personally identifying information. Researchers do not have access to names, email addresses, IP addresses, or any direct identifiers. Participants are paid $8 total for their participation in this study to complete the 45-minute survey. The CHERRIES (Checklist for Reporting Results of Internet E-Surveys) guidelines were used to guide the reporting of this protocol [31].

Phase 1: Data Collection and Preprocessing

In phase 1, web-based survey data will be collected from up to 1000 older adults. Participants will be instructed to sing along to a playlist designed to reduce mood symptoms associated with depression. This goal was selected because depression is known to significantly increase the likelihood of AD and accelerate cognitive decline [32]. Participants will receive 5 songs randomly chosen from a set of songs based on age and musical arousal—2 factors known to be associated with mood and relevance to older adults. Songs will be selected based on participants' "reminiscence bump" [24] and will use the iso principle to modulate from low arousal to moderate arousal [33,34]. In past studies of the musical "reminiscence bump," the strongest associations and familiarity with music was found to be between the ages of 15-24 years [25,35]. SingFit's music selections are chosen from participants' adolescence and young adulthood to ensure familiarity and narrative memory associations with the music. The iso principle gradually shifts the music from matching the participant's emotional state (eg, sad) to their desired state (eg, calm). In phase 1, songs with high arousal were not included in order to modulate arousal and affect gradually for a depression playlist in keeping with the iso principle. Surveys will use 5-point Likert scales to measure song familiarity, perceived benefit, sentiment, relevance, and preference for each song, which will be analyzed in conjunction with music metadata (described below) to better understand musical factors associated with mood symptoms of depression. Participants will receive an open survey link to the Qualtrics survey and either listen or sing along to each song while completing survey questions for each song (ie, song preference or sentiment).

For the development of user personas and the ML model (aims 1 and 2), the planned sample size of 1000 participants was determined following deliberation with the study's data consultants to balance feasibility and analytical utility within the scope of this pilot project. This sample was identified as the minimum viable cohort necessary to support adequate model training, validation, and initial testing of the recommender system.

Measures

Measures for this study are brief researcher-created surveys to measure song preference, expectation, and helpfulness for each song (see Multimedia Appendix 1). These measures were chosen to understand user preference in order to build a KE ML model and user personas for aims 1 and 2. These same measures will again be collected in a smaller sample for aim 3 to assess the acceptability of the ML-based music recommendations. Web-based surveys were developed by JRM and tested for usability and technical functionality by JRM and CSB prior to participant recruitment. Participants will be asked to answer each question for each song. Questions are 5-point Likert scales to measure song preference (strongly dislike to strongly like), sentiment (very sad to very happy), expectation for hearing that particular song for the goal of reducing depression (strongly disagree to strongly agree), and helpfulness (eg, "Would this song be helpful in making you feel better if you were very sad?"; strongly disagree to strongly agree). Participants will also be asked to assess their mood (eg, "How depressed are you?") and engagement in daily activities prior to and directly following their survey on an 11-point Likert scale (0-10). Participant demographics will also be collected excluding directly identifying information that would link survey responses to participants.

Zip codes will be collected to verify geographical residence (rural, urban, or suburban) in order to build specific user personas tailored to each group (aim 1). After verification, only the first 3 digits of the zip code will be stored for each participant, and the digits will be changed to 000 in instances for which the zip codes contain less than 20,000 people.

Bot detection for survey entries based on reCAPTCHA was used, and any duplicate survey entries based on Prolific IDs were removed. Prolific uses participants' email address and phone number to verify participants and IP address detection to ensure participants do not participate in studies more than once. There were an average number of 6.5 items per page with 8 total pages. All questions required an answer in order to submit the survey. Demographic questions included a "none of the above" or "prefer not to say" option, while music preference questions required a response on a 5-point Likert scale.

Music Metadata

Each song in the SingFit catalog has been tagged with metadata for dozens of different parameters. Musical metadata include linguistic syntax and semantics (assessed with text analysis software), tempo and key (assessed using song analyzer software), genre, popularity, arousal, and others. The full list of metadata is proprietary to Musical Health Technologies but encompasses a wide range of cognitive and affective factors associated with known therapeutic benefits. These metadata will be used to understand the musical factors associated with user preference and clinical factors related to improvement in depressed mood. Music metadata is used in SingFit's current song recommendation algorithms and will be used in knowledge

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graphs for comparing various KE model architectures during phase 1.

Phase 2: Machine Learning Model Implementation and Evaluation

Music recommendation is an active area of research within the information retrieval community, with researchers facing unique challenges, such as data sparsity, complexity in evaluation, and personalization for cultural and situational awareness. The cold start problem, a lack of historical information for making decisions about new users or items, is a common issue across many recommendation systems that persists in the music domain [36,37]. Recent work has found promising results by using neural network models and incorporating metadata features such as song artist or genre with user interaction data to form a collaborative knowledge graph [37,38]. In particular, users, songs, and metadata categories are treated as nodes in a graph. Connecting edges represent semantic meaning, like a song belonging to a genre or a user favoriting a song. Neural network–based approaches like DeepWalk can be used for learning latent representations of the graph's nodes in vector space [37,39]. At recommendation time, a song is compared to others in vector space, returning the most similar songs to the end user. This approach will allow the system to make recommendations based on the preferences of similar users in conjunction with shared music metadata and clinical features to maximize the relevance of recommendations.

The modeling architecture will largely follow Bertram et al [37] for creating knowledge graph embeddings of songs and relevant metadata features of both users and songs. Authors LD and VP will conduct explorations to vary the metadata features included in the knowledge graph and tune hyperparameters of the DeepWalk model. This will allow for thorough exploration of feature selection and model architecture choices, with the best performing modeling pipeline deployed for user testing. Models and data processing will be implemented in Python (Python Software Foundation) with widely used ML libraries, *scikit-learn* and *pytorch*, and support for graph structures with *pytorch-geometric* and *networkx*. The algorithms will be developed in collaboration with the data core at the University of Massachusetts Center for Data Science and the Massachusetts AI and Technology Center.

The data will be split into training, validation, and testing sets by user using 5-fold cross-validation. This will balance training and evaluation variances and allow for more efficient use of the relatively sparse data compared to using a single data split for training, validation, and testing sets. Splitting data at the user-level will simulate the cold start problem in our experiments. The model with the best average performance across the 3 test sets will be retrained on the entire dataset, a standard practice in ML. Baseline performance will be measured using a purely random recommendation system and a content-based learning-to-rank approach that relies solely on metadata features. These baseline benchmarks will help gauge the added benefit of more complex neural network recommendation algorithms.

Because clinical features may be in tension with musical preferences or musical features, multiple metrics are needed in order to understand the trade-off being made by the recommendation algorithm. The metrics that will be used to evaluate performance are root mean square error, normalized discounted cumulative gain, and a user-reported satisfaction score [36]. Root mean square error will be used to evaluate the error between the recommendation system's estimated satisfaction score and the user's true satisfaction score to ensure that it can accurately predict the user's label of the song. Normalized discounted cumulative gain, a ranking quality metric, will be used on the songs recommended by the system to ensure that the test data songs are being recommended in an order equivalent to their user-preferred ranking. As part of further testing, a sample of users will be given a set of playlists recommended by the system and asked to answer the survey questions from phase 1. By comparing the satisfaction scores across phases, a comparison can be made as to the direct effects on the listener of the songs recommended.

For Aim 3, the goal is to develop a ML model with ≥80% accuracy in creating individualized therapeutic music playlists and achieve a user acceptability score of 85% or higher among rural-residing older adult users. Using the same survey questions from phase 1 (see Multimedia Appendix 1), the user acceptability score will be based on the average ratings for questions regarding the overall preference, relevance, and perceived benefit of the playlists. An a priori power analysis was conducted using G*Power version 3.1 [40] to determine the required sample size for a 1-sample *t* test for aim 3. The goal of the analysis was to detect a mean acceptability score significantly greater than 4.25 (indicating 85% acceptability), with a margin of error of 0.2 and an estimated SD of 1.2. Assuming a medium effect size (d=0.30), an α level of .05, and a desired power of 0.80, the analysis revealed that a minimum of 139 participants would be needed to ensure adequate statistical power.

Results

Participant recruitment for the final protocol was initiated on December 31, 2024. In June of 2025, participants had completed the phase 1 and 2 web-based survey studies (Figure 2). Data preprocessing and analysis is underway to prepare publication of the results.

Due to challenges with participant recruitment and high attrition related to the initial study protocol, the study team made 2 changes to the initial study design. All modifications were administratively reviewed by the external institutional review board and subsequently implemented in compliance with ethical guidelines. First, the initial eligibility criteria for participants included 2 or more risk factors for AD based on the Australian National University-Alzheimer's Disease Risk Index (eg, education level). An amendment to the original study protocol was made to the "at least 2 risk factors" eligibility requirement. Additionally, due to the high attrition noted, the survey removed the need to download the SingFit app and moved all songs (.mp3 files) to Qualtrics. Multiple recruitment methods were planned, including word-of-mouth, crowdsourcing platforms (eg, Prolific), social media, and web-based caregiving organizations. However, once the above changes were made,

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recruitment was accomplished rapidly on a crowdsourcing platform (Prolific).

Figure 2. Study timeline. IRB: institutional review board; ML: machine learning.

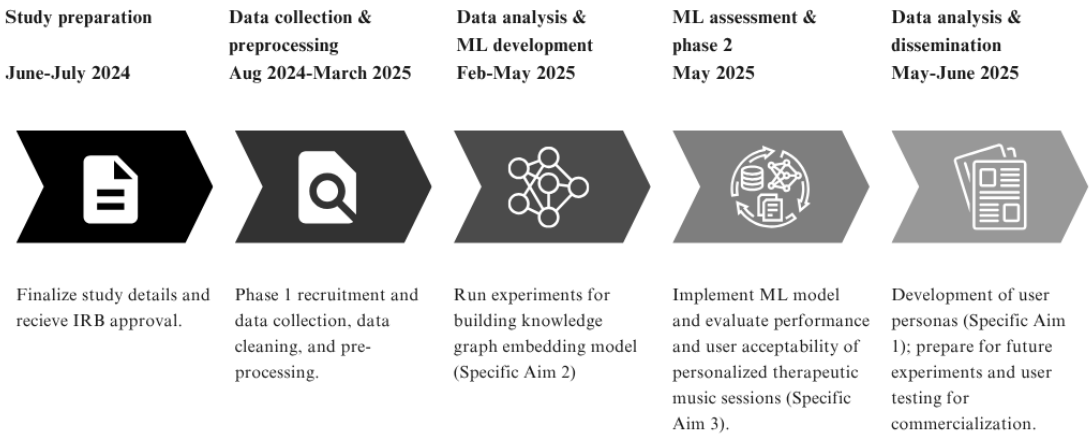

Discussion

Principal Results

To our knowledge, this is the first digital singing intervention aimed at lifestyle factors associated with AD, such as depression, for those aged 55 years or older. It is important to improve intervention fit and cultural acceptability to ensure accessibility and usability for rural-residing older adults who may benefit the most from this type of intervention. While other music interventions are available, none are specifically aimed at managing symptoms of depression and cognitive reserve in cognitively healthy adults. Using ML to improve the existing intervention algorithms should improve music recommendations and engagement in end users. ML models should also allow the research team to better understand musical factors associated with sadness and depression symptoms, furthering knowledge on the most appropriate music interventions for mood symptoms in rural-residing older adults.

Limitations

A significant limitation of this work is that the music files were moved from the app and hosted in Qualtrics due to issues with recruitment and retention in phase 1. Participants were not exposed to the app user interface during the music preference surveys in phases 1 and 2, which may have altered the experience of the music intervention. However, only elements present in the app (ie, length of song play, liking songs, and music metadata) were used for building the ML models. Second, participants with cognitive impairment or AD were excluded. This may limit the generalization of the recommendation system and findings to cognitively health older adults. Lastly, the sample size of this pilot project was constrained by the 1-year funding period. Although 1000 participants represents a meaningful sample for a pilot study, it is relatively small for training KE models and may impact the model's predictive performance for music recommendations. Future phases of this project will include additional training and refinement of the model using larger datasets to enhance the model's performance and overall generalizability.

Comparison With Prior Work

While music interventions are not the first line of treatment for depression, they may provide an engaging, less invasive, ancillary treatment option for disengaged populations, such as rural-residing older adults or those with cognitive decline. When looking at comparative efficacy of depression treatments among individuals with dementia, cognitive stimulation (ie, reminiscence or art therapy) combined with exercise and social interaction or a cholinesterase inhibitor showed higher efficacy than some pharmacotherapies [41]. This demonstrates that psychosocial interventions such as music therapy or singing interventions that target multiple domains through cognitive stimulation, movement, and social interaction may provide valuable support for depression in those with AD. Music interventions provide a treatment approach for those with concerns of polypharmacy or those who may be unable to engage in psychotherapy (ie, those with AD).

A network meta-analysis showed moderate to high certainty evidence for active music interventions (ie, singing or playing instruments) at a dosage of ≥60 minutes per week in improving depression in adults aged 60 years or older [20]. An ongoing longitudinal study aimed at depression symptoms will improve our understanding of music interventions on both depression and neuroplasticity once the results are published [42]. This 3-group randomized controlled trial protocol compares 12 months of singing lessons versus physical activity or control (no intervention) in those with mild dementia or mild cognitive impairment [42]. Their primary hypothesis is that weekly singing can improve brain plasticity (brain age gap estimation measured by functional magnetic resonance imaging) and depression (assessed using the geriatric depression scale) and secondarily improve cognition and activities of daily living. This study is still in progress, but should improve our understanding of the associations between music and physical activity interventions on decelerating or preventing AD.

Digital interventions can be valuable for improving accessibility to rural populations. A pilot project of a web-based music therapy program provided 3 sessions for tailored recommendations and music activities for persons with AD and their caregivers [43]. The intervention component focused on

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mood symptoms was to recommend singing between caregiver and the person with AD. Due to the small sample (n=13 caregiver and person with AD dyads), this study was not powered to show statistical significance, but it did demonstrate trends for ameliorating agitation—the mean neuropsychiatric inventory score for the agitation item preintervention was 1.0, while the postintervention score was 0.69—and improved the caregiving relationship, with 84.7% of participants reporting that music therapy improved communication between themselves and the person with AD. While web-based sessions improve the reach of these types of services for rural populations, this intervention lacks widespread scalability. To our knowledge, no other existing digital singing interventions have been aimed at AD risk factors.

Conclusions

There is an urgent need to offer culturally sensitive digital lifestyle interventions for underrepresented populations at risk for AD to optimize long-term efficacy. Results from the protocol will contribute to the advancement of such interventions for older adults in rural communities by addressing the critical culture gap observed in digital health. Through the development of a KE-based ML recommendation system, this protocol seeks to improve the equitability and accessibility of a digital lifestyle intervention focused on reducing depression as a means of AD prevention.

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Data Availability

The data from this study are available upon reasonable request. Certain parts of the data, including music metadata, are proprietary to SingFit and cannot be hosted on a publicly available repository.

Conflicts of Interest

CSB and JRM were involved in the development of the SingFit app and algorithms used in this study as employees of Musical Health Technologies where they also received compensation. The authors have no further conflicts of interest such as patents or royalties to report.

Multimedia Appendix 1
Music preference survey.
[DOCX File , 14 KB - resprot_v14i1e73711_app1.docx]

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Abbreviations

AD: Alzheimer disease
CHERRIES: Checklist for Reporting Results of Internet E-Surveys
KE: knowledge embedding
ML: machine learning

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Protocol

The Use of Mobile Health Technology and Behavioral Economics to Encourage Adherence to Statins and Blood Pressure–Lowering Medication in Adolescents with Familial Hypercholesterolemia or Hypertension: Protocol for a Pre-Post Cohort Study

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Abstract

Background: Cardiovascular disease (CVD) is a leading cause of mortality and morbidity in the United States, with risk factors such as hypertension and elevated low-density lipoprotein (LDL) cholesterol originating in childhood. While statins and blood pressure–lowering medications can mitigate these risks, adherence is often poor, particularly among youth. Innovative solutions, such as monetary incentives via smartphone apps, may enhance adherence, but evidence in youth is lacking.

Objective: This study aims to evaluate the efficacy of a smartphone app (Wellth) offering financial incentives to improve adherence to statins and blood pressure–lowering medications among youth aged 12 to 19 years at risk for cardiovascular disease.

Methods: We initially designed a randomized controlled trial to compare the efficacy of 2 different incentive structures in youth treated with a statin for familial hypercholesterolemia with inadequate adherence. After facing recruitment challenges, the study protocol was changed to evaluating a single incentive in a pre-post design. The primary outcome was the change in adherence rate over the 60-day incentive period compared to the adherence rate during the 14-day run-in period. The secondary outcome was a change in LDL cholesterol level. Adjustments to the protocol were made in response to recruitment challenges during the COVID-19 pandemic, simplifying the incentive structure and expanding eligibility criteria.

Results: The study is currently undergoing recruitment and collection of data from the first participants. The study has faced recruitment challenges exacerbated by the COVID-19 pandemic, necessitating protocol modifications. Detailed analysis of adherence rates and LDL cholesterol changes is ongoing.

Conclusions: This study explores the efficacy of monetary incentives delivered through a smartphone app to improve medication adherence in youth at risk for CVD. The findings will be used to build upon the existing literature in an effort to improve medication adherence throughout the life course and ultimately reduce CVD.

Trial Registration: ClinicalTrials.gov NCT04458766; https://clinicaltrials.gov/study/NCT04458766

International Registered Report Identifier (IRRID): DERR1-10.2196/65105

(JMIR Res Protoc 2025;14:e65105) doi:10.2196/65105

KEYWORDS

dyslipidemia; hypertension; adherence; mobile health; incentives; behavioral health; youth

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Introduction

Cardiovascular disease (CVD) is the leading cause of death and disability in the United States. It leads to US $216 billion in direct costs and an additional US $147 billion in indirect costs each year [1]. While the presentation of CVD events primarily occurs in adulthood, the significant risk factors for CVD, including hypertension and elevated low-density lipoprotein (LDL) cholesterol, have their antecedents in childhood [2,3]. With the use of statins [4-17] and blood pressure–lowering medications [18], substantial reductions in this risk are possible.

However, adherence to statins and blood pressure–lowering medications is needed to accrue these potential benefits. Unfortunately, medication adherence is frequently poor, with up to 50% of adults not taking all their prescribed medications [19-23]. In adults, nonadherence is associated with an increased risk for CVD events and all-cause mortality [20,24], as well as almost US $44 billion annually in additional health care costs [25,26]. Although studies are limited, adherence to statins and blood pressure–lowering medications also has been shown to be inadequate in youth [27-30]. Youth seem to be particularly vulnerable to nonadherence [31], even in conditions in which the consequences of nonadherence can lead to rapid disease progression or severe, acute symptoms, such as bipolar disorder [32], HIV infection [33], or asthma [34].

Multiple factors impact adherence (Figure 1), including patient-related factors (eg, beliefs and expectations), socioeconomic factors, medication-related factors (eg, complexity of the regimen and adverse effects), the disease being treated, and the health care system [35]. Unfortunately, successful interventions to improve medication adherence overall are rare in both adults [36] and youth [36,37]. Further, there are no formally tested interventions to improve adherence to statins or blood pressure–lowering medications in youth. One potential solution to improve adherence is to provide monetary incentives. Traditional economic theory suggests that providing individuals with incentives to complete an action will lead to increased frequency of the occurrence of the desired action. Studies in adults have shown monetary incentives to be modestly successful in certain diseases [38-40], but not all studies have shown positive results [41]. Further, it is unclear if these findings translate to youth.

Figure 1. Five components of medication adherence as proposed by the World Health Organization [35]. The green curved arrows indicate components expected to respond to incentives, while the dashed black arrows are components that are less likely to respond.

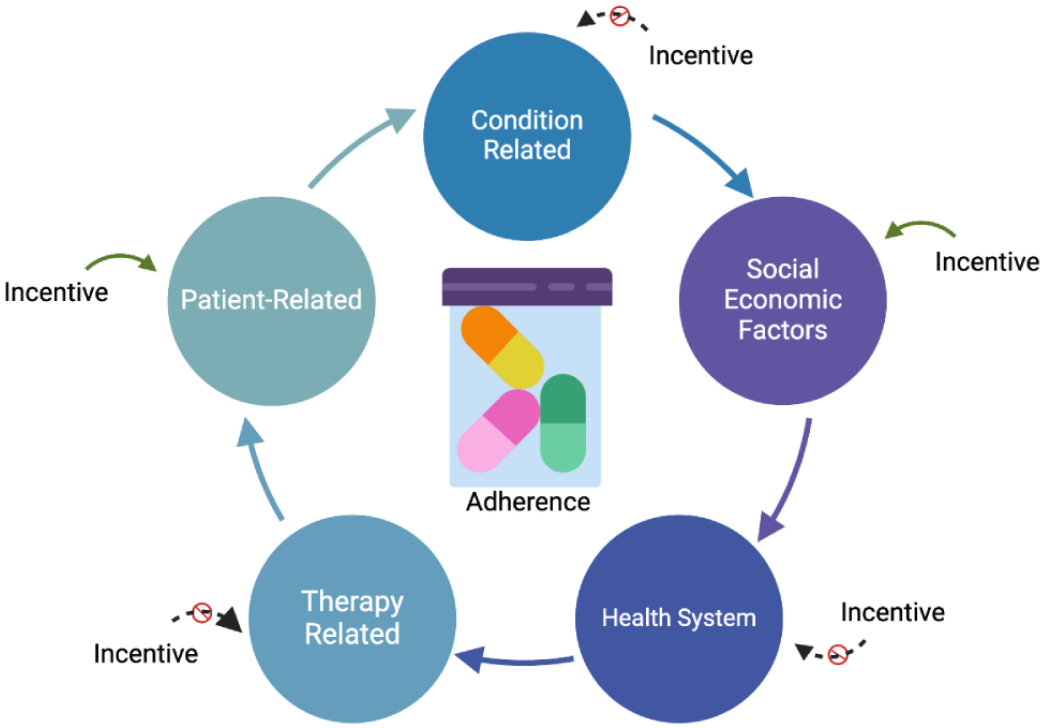

To address this gap, we planned a study using a smartphone app (Wellth) to provide financial incentives to improve medication adherence in youth at risk of CVD. Smartphone apps are promising interventional tools as they are familiar to most youth [42,43]. Data suggests using smartphone apps in a health care setting is of interest to youth [44] across a diverse set of socioeconomic and cultural backgrounds [42]. The Wellth app is designed to improve medication adherence through reminders and by providing monetary rewards for taking a medication as prescribed.

The objective of this paper is to describe the original study design, recruitment methods, outcomes, analysis plan, strengths, and limitations. In addition, we highlight modifications to the design and recruitment strategies because of social distancing requirements related to the COVID-19 pandemic and the need to improve recruitment. The principal aim of our study is to determine if financial incentives are effective at improving adherence to medications in youth who are at an increased risk of CVD.

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Methods

Study Design

The study, originally titled "Use of Mobile Health Technology and Behavioral Economics to Encourage Adherence to Blood Pressure–Lowering Medications and Statins in Youth at Risk for Cardiovascular Disease," was designed as a randomized control trial to compare the efficacy of 2 interventions on improving medication adherence to statins in youth aged 12 to 19 years using a smartphone app (Figure 2). The 104-day study consisted of a 14-day run-in period, 2 periods of 30 days in which participants received incentives, and a 30-day follow-up period in which participants were asked to record adherence but did not receive any incentives. During the run-in and follow-up periods, all features of the Wellth app were available, but the participants did not receive any monetary incentives. This approach was used to isolate the effect of the monetary incentive from the other features of the app and to provide an objective baseline measure of adherence. After the 14-day run-in, the participants were eligible to receive incentives during two 30-day incentive periods. Incentives were disbursed at the end of period 1 (day 44) and period 2 (day 74). In addition, we also measured the patients' adherence in the 30-day period after the incentive periods to determine if the effect of the intervention was sustained. The study was approved by the research ethics board at the Boston Children's Hospital with a waiver of individual participant consent as this research used data that had previously been obtained through a departmental quality improvement project. Patients who were older than 18 years at any time while participating in the study signed an informed consent form. For patients who were younger than 18 years, informed consent was obtained from their legal guardian, and assent was obtained from the participant.

Figure 2. Final study timeline. The fasting lipid profile included total cholesterol, triglyceride level, high-density lipoprotein cholesterol, and low-density lipoprotein cholesterol.

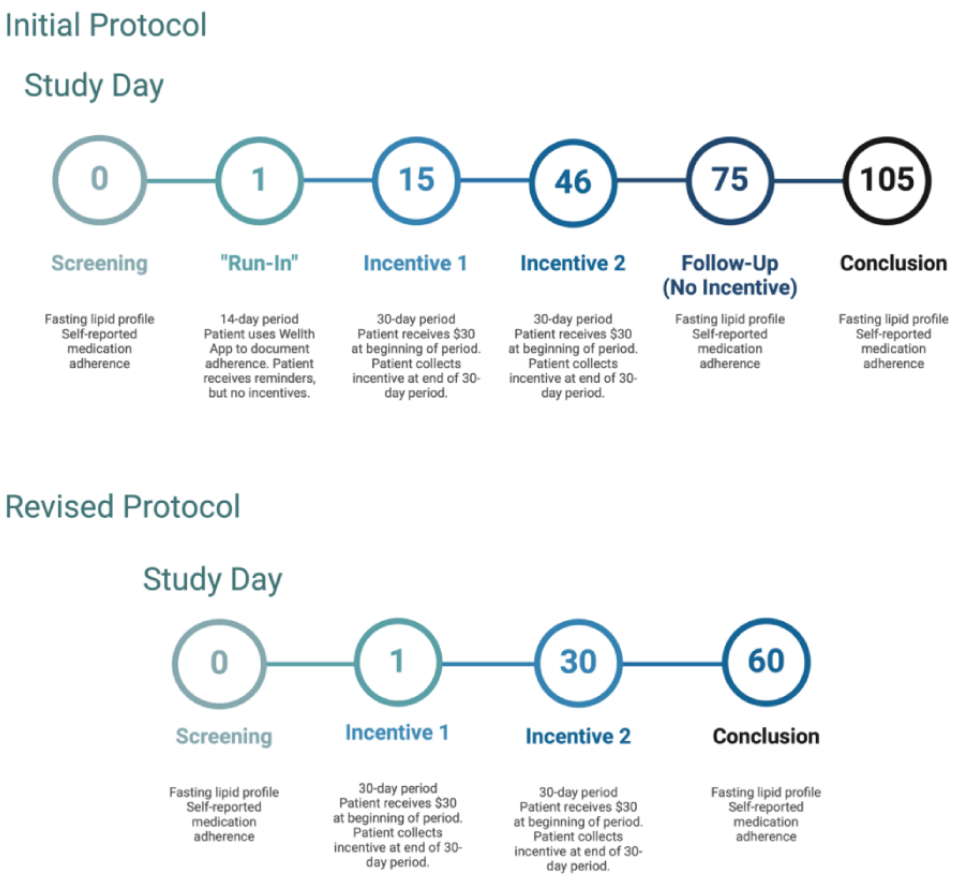

Eligibility Criteria

The original eligibility criteria are described in Textbox 1. Patients were eligible to participate if they were aged 12 to 19 years, had a diagnosis of familial hypercholesterolemia (FH), were prescribed a statin, and reported less-than-ideal statin adherence. The diagnosis of FH was based on genetic testing or if the patient met the National Lipid Association recommendations, which are an LDL cholesterol level greater than or equal to 160 mg/dL or a non–high density lipoprotein cholesterol level greater than or equal to 190 mg/dL in patients younger than 20 years [11,19,20,45].

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Textbox 1. Eligibility and exclusion criteria.

Eligibility criteria

- Less-than-ideal adherence by self-report
- Age 12 to 19 years
- Diagnosis of familial hypercholesterolemia (FH) based on National Lipid Association criteria and/or genetic testing or a diagnosis of hypertension
- Prescribed a statin or blood pressure–lowering medication
- Ability to provide written informed consent or have a parent or guardian provide written informed consent

Exclusion criteria

- Homozygous FH
- Residence in a long-term care facility where medications are administered
- Being pregnant/possibility of becoming pregnant
- History of adverse effects or allergies to a statin or blood–pressuring lowering medication or any ingredient in one of these medications

Recruitment

We recruited patients from a tertiary care hospital and its satellite outpatient clinics. Recruitment took place at outpatient clinic visits in a preventive cardiology clinic. The study clinicians approached eligible patients and provided a brief overview of the study. If the participant was interested, the clinician determined the patient's eligibility based on self-reported adherence [46,47]. If the patient was eligible and agreed to participate, the clinician conducted the informed consent and enrollment procedures.

We supplemented clinic recruitment by recruiting patients with FH treated with a statin by phone using a database maintained by the preventive cardiology program, which includes approximately 400 patients. We estimated that 20 patients per month who met the eligibility criteria would be seen. If 50 percent of those patients agreed, we expected to complete the recruitment of 30 patients in 6 months (power calculation shown below). Patients could be removed from the study if there was concern for their safety or there was a change in the medication that they were prescribed. Patients could voluntarily stop participating in the study at any time.

Outcomes

The primary outcome was medication adherence as measured by the Wellth app and defined as the proportion of doses taken per doses prescribed. The adherence rate used in the analysis was measured over one 14-day period and three 30-day periods (days 1-14, days 15-44, days 45-74, and days 75-104). Secondary outcomes included change in the LDL cholesterol level from baseline until the end of the intervention period (day 74). LDL cholesterol was considered a baseline measurement if it was obtained within 60 days from the day of consenting to the study. The covariates we included in the analysis were gender, age, and race/ethnicity.

Description of Wellth App

The Wellth app was the primary tool used in the study to promote medication adherence. Patients used the app to receive reminders, make check-ins (ie, document adherence), check their reward balance, and view their adherence history. Participants downloaded the app to their smartphone without any additional software or encryption needed. In order to prevent patients from being excluded based on the costs of the necessary hardware, we provided a smartphone and data plan free of charge to patients. Wellth monitored app use and uploaded photos through a secure, customized analytics dashboard for data monitoring and customer support.

Structure of Incentives

Initially, participants were to be randomized to 1 of 2 incentive structures. The first structure of the incentive was based on the principles of present bias and loss aversion. Present bias refers to the tendency of individuals to prefer more immediate rewards and outcomes and to discount future risks [48]. For instance, studies suggest that even small rewards, if provided frequently and immediately after a participant completes a desired task, can improve adherence in adults and may be more effective at promoting behavior change than larger rewards provided in the distant future [36,49,50]. The principle of loss aversion was included to help strengthen the incentive and is based on findings from studies that suggest individuals place more value on money or objects that they have than on new objects of the same value [51].

Participants received US $30 at the beginning of each of the two 30-day periods but were only able to access the money at the end of the 30-day periods. However, participants could view their balance within the app at any time. For each missed check-in, the participant lost US $2 from the amount to be paid out at the end of the 30-day period. Participants who missed more than 15 check-ins did not receive any money at the end of the 30-day period.

In the second incentive approach, we planned for participants to not receive rewards for each check-in but instead receive the *chance* to receive a reward of varying amounts. This incentive structure is similar to that of a slot machine. As in the first incentive structure, the total amount a participant could receive over the two 30-day periods was US $60. However, participants would not lose money if a check-in was missed; rather, they would lose an opportunity to receive a reward. The random distribution of the reward was structured to ensure that a fully

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adherent participant would receive a full US $60 over the study period. However, in this arm of the study, it was also possible that a participant could receive US $60 even if they were not fully adherent.

Power

Power calculations were planned to be performed for the primary outcome variable of adherence rate at the end of the 60-day period. The mean difference in adherence rates at 60 days after the start of the intervention (day 74) would be compared to 0%, which was the value that would be expected if there was no difference between the two interventions using a 2-sided paired *t* test conducted at the .05 level of significance. The mean adherence rate was hypothesized to be 80% when patients received small frequent awards and 74% when receiving a large, randomly delivered reward, suggesting a mean within-patient difference of 6%. The SD of the adherence rate was assumed to be 10% at each time point [27], and the correlation between the two measures of adherence was assumed to be 0.50, resulting in an SD of differences in adherence rate of 10%. If the correlation between measurements of adherence was conservatively assumed to be 0.30, the SD of differences in adherence rate was estimated to be 11.8%. We expected to enroll 30 patients.

Statistical Analysis

Data were planned to be analyzed on an intention-to-treat basis. Baseline patient characteristics measured prior to randomization would be compared between the two intervention groups to look for imbalances. Primary and secondary outcomes would be compared between groups on day 44, day 74, and day 104. Continuous variables would be compared using the 2-sample *t* test or Wilcoxon rank sum test. Differences in categorical variables would be assessed using the Fisher exact test. Analyses of the primary outcome variables (ie, percentage change in LDL cholesterol and proportion of days adherent) would use a significance level of .025 at each follow-up time point; all other comparisons would be performed at the .05 level of significance. If differences in baseline characteristics were detected between the two groups, linear regression would be used to perform additional comparisons of the primary and secondary outcomes, controlling for these potential confounders. Transformations would be applied to continuous outcomes that were not normally distributed.

Ethical Considerations

This study was approved by the Boston Children's Hospital Institutional Review Board (IRB-A00032841-2).

A majority of participants in the proposal are younger than 21 years and thus meet the National Institutes of Health's definition of children. The study will not exclude participants based on race/ethnicity, gender, or sexual preference. The final study sample will be representative of the patient population of the Boston Children's Hospital Preventive Cardiology Program. Our sampling plan was developed in consultation with a statistician to ensure appropriate representation of all groups.

Privacy is a fundamental concern any time that personal information is transmitted electronically, especially if a third party is involved. Wellth does not share patient data with any third party. Wellth uses deidentified datasets wherever possible, including internal reports and communications. Wellth will share data with members of the Boston Children's Hospital study team needed for data analysis and patient safety monitoring. Wellth uses HITRUST (Health Information Trust Alliance)-certified, HIPAA (Health Insurance Portability and Accountability Act)-compliant application hosting services provided by HealthcareBlocks. All computers used by Wellth are encrypted, including hosting computers. Every member of the company performs annual HIPAA compliance training. All software development and company activities are performed inside the United States. We specifically instructed participants not to upload photos that include any personally identifying information.

Results

The intervention was developed to encourage patients to take their medication every day, and the pre-post study was used to determine the efficacy of this intervention. The findings of the study will help determine if monetary incentives can lead to increased adherence and help determine if this is a viable strategy that can be expanded. Recruitment started in August 2019 and concluded in August 2024 (n=9 participants were recruited). Data collection was ongoing throughout the trial and will be analyzed after study completion. The study's findings are to be published after study completion, which is expected in December 2025 or January 2026.

Discussion

Anticipated Findings

We expect to find that providing small, frequent financial incentives will improve medication adherence among youth taking medications to reduce their risk for cardiovascular disease. We expect that this improved adherence will be demonstrated by an increase in adherence as measured by the Wellth app.

Unfortunately, only a few studies with adolescents have used incentives to promote behavioral change. In a study with youth with type 1 diabetes, incentives had a positive impact on glucose monitoring frequency and adherence to the prescribed insulin regimen [50]. However, patients with diabetes mellitus fundamentally differ from those with hypertension or dyslipidemia, as the latter conditions are typically asymptomatic [7]. While studies in adults have had mixed results [52], adolescents differ substantially regarding attitudes toward health, and they have less mature cognitive function and capacities than adults [49].

COVID-19 Pandemic

Our initial protocol and recruitment strategy had to be modified in response to the challenges that arose during the COVID-19 pandemic. In the original proposal, we planned to recruit patients seen during routine outpatient visits. However, in the early months of the pandemic, outpatient clinic appointments were limited to those with urgent concerns, which rarely included patients with dyslipidemia. Enrolling participants remotely,

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though, posed several challenges. The first was connecting the patient to our research assistant. Unlike an in-person clinic visit in which the research assistant is readily available, connecting the research assistant with the patient during a remote encounter required arranging additional contact with the patient. We found that if there were any delays in connecting to the research assistant, eligible participants seemed to quickly lose interest.

A second problem arose in obtaining written consent from participants seen via telehealth visits. Unfortunately, the infrastructure for obtaining an electronic signature was initially unavailable and written consent was required by our institution. The written consent was rarely completed during the course of a virtual visit. Instead, families typically planned to send the signed consent forms that evening or the next day, which often did not occur despite repeated attempts to contact eligible patients. In addition, errors in the consent, such as missing signatures or illegible handwriting, often led to patients not participating, as obtaining corrected consent forms was challenging.

The third barrier that arose was related to technical issues signing patients up for the Wellth app. While configuring the app for the patient was not cumbersome, and there were no complaints by participants enrolling in the study, adding study-related information (eg, participant identification number and study codes) was sometimes technically challenging. We could not have the participant download the smartphone app until the consent was finalized, which often meant arranging a separate time to ensure the app was operational, and some participants dropped out after signing the consent form because of the additional time commitment.

Low Recruitment

Recruitment for the trial was more difficult than expected, in part related to the COVID-19 pandemic. We were concerned that the complexity and duration of the trial were deterrents. Over the first year, we made a series of changes to simplify the intervention.

First, we decided to use only the first intervention, which involved small, frequent rewards, while removing the second intervention, which entailed random, variable rewards. This was based on our perception that the first intervention was conceptually easier for pediatric participants to understand. Since we would no longer be comparing two types of incentive structures, we also removed randomization and created a pre-post study design (Figure 2). Adherence measures collected via the app during the 14-day run-in period would be used as the baseline adherence measure to be compared to adherence recorded on day 44, day 74, and day 104.

The second modification was to shorten the trial duration by removing the 30-day follow-up period. We received feedback from potential participants during recruitment that the length of the trial prevented them from participating. As this portion of the trial was included mainly to assess the sustainability of the incentive, it made more sense to remove it rather than shorten the incentive period.

Third, we expanded the protocol to include patients with hypertension who had been prescribed a blood pressure–lowering medication (eg, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, or calcium-channel blockers) to increase the pool of eligible participants. We did not change the incentive structure, even for those patients who were prescribed regimens with twice-daily dosing. In these patients, we required both doses to be taken to earn the reward. The diagnosis of hypertension was based on chart review (ie, hypertension-associated diagnosis codes in the *International Classification of Diseases*, ninth or tenth revisions) and was not based on blood pressure–specific thresholds.

Limitations

As has been acknowledged, recruiting for pediatric studies can be difficult. To overcome this obstacle, we changed the protocol and recruitment strategies. In the future, we plan to increase the pool of recruits by expanding to other clinics outside of Boston Children's Hospital. Another potential limitation is the inability to ensure that the increase in adherence is specifically from the incentives and not another component of the Wellth app. We have tried to mitigate this potential problem by not offering the incentive for the first two weeks. We will compare the adherence during the first two weeks with adherence during the periods when incentives are provided to isolate the effect of the incentive.

Future Directions

This research protocol will test whether providing incentives that leverage the principles of behavioral economics can improve medication adherence in youth with FH and hypertension. Understanding the effectiveness of different types of incentives is crucial to improve medication adherence. The incentive structure in regard to the type of reward, frequency of receiving the award, and timing of delivery of the reward can lead to different responses. In fact, there is evidence that inappropriate reward structures can serve as a negative enforcer.

In addition, this proposal will harness the power of digital health technology, taking advantage of the fully developed Wellth app to reduce costs and simplify the intervention. Digital health apps allow for automating patient–health care provider interactions, improving monitoring using cameras with embedded metadata (eg, date and time), and reducing the complexity of interventions, allowing for more widespread distribution of interventions.

Patients with FH and hypertension provide an ideal cohort to explore the role of different incentive packages. FH is rarely symptomatic in youth, and treatment is typically well tolerated. One critical factor is that missed doses do not generally lead to acute complications in either disease. Therefore, health care providers and caretakers can safely distance themselves from interfering, which prevents adding biases introduced by frequent health care provider engagement.

It should be acknowledged that there are important differences between those prescribed lipid-lowering therapy for an inherited condition and those treated for hypertension, which is typically an acquired condition. Further, blood pressure–lowering medications have a different side effect profile than statins and

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may be prescribed more than once daily, which may impact adherence.

Conclusion

This proposal will elicit information critical for creating developmentally appropriate incentive structures to improve medication adherence in youth with risk factors for CVD. However, the efficacy of monetary incentives is extrapolated from adult studies, and it remains to be seen if they are ideal for youth.

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Data Availability

The datasets used and analyzed in this study are available from the corresponding author on reasonable request.

Authors' Contributions

All authors contributed to the study conception and design. JH, SdF, and TP-W were responsible for the primary design of the study. Material preparation and data was collected by JH and SdF. The first draft of the manuscript was written by JH, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report form the HLBI Mentored Patient-Oriented Research Review Committee - Heart, Lung, and Blood Initial Review Group MPOR (MA) - National Heart, Lung, and Blood Institute (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 143 KB - resprot_v14i1e65105_app1.pdf]

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Abbreviations

CVD: cardiovascular disease
FH: familial hypercholesterolemia
HIPAA: Health Insurance Portability and Accountability Act
HITRUST: Health Information Trust Alliance
LDL: low density lipoprotein

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Protocol

“PrevenganT2,” a Culturally Responsive Family-Based Diabetes Prevention Intervention for Hispanic or Latino Adults at High Risk for Type 2 Diabetes: Protocol for a Proof-of-Concept Evaluation

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Abstract

Background: Despite the efficacy of lifestyle interventions for preventing or delaying diabetes, community translations to date have failed to engage Hispanic or Latino participants effectively. Previously identified barriers to engagement include lack of family support and the burden of time-intensive year-long programs. Integrating family members and reducing program length may have the potential to increase engagement in lifestyle interventions to prevent type 2 diabetes in Hispanic or Latino individuals.

Objective: Given the potential impact of cultural adaptation on such interventions, our community-academic research team used the Obesity-Related Behavioral Intervention Trials (ORBIT) model to guide an adaptation of the core 16 modules of the National Diabetes Prevention Program’s PrevengaT2 curriculum to meet the needs of Hispanic or Latino communities in Utah. We describe our evaluation of this adaptation in an ongoing proof-of-concept trial. We will evaluate whether Hispanic or Latino participants at high risk for type 2 diabetes increase their weekly moderate-to-vigorous physical activity (MVPA) in the context of an ongoing proof-of-concept trial of the adaptation.

Methods: Target participants at risk for type 2 diabetes and a family member were invited to participate in PrevenganT2. In earlier phases of a larger project, our academic-community research team created the 14-week lifestyle intervention by adapting the Centers for Disease Control and Prevention’s PrevengaT2 curriculum. Objective MVPA was measured for 7 days at preintervention and postintervention using ActiGraph GT3X-BT accelerometers. Participants additionally completed questionnaires at preintervention and postintervention, and weight and self-reported MVPA were recorded at lifestyle intervention classes. Physical activity data will be analyzed to determine the percentage of target participants with clinically significant pre-post increases in MVPA.

Results: Data collection concluded in October 2024. Data cleaning and preparation for analysis are ongoing. We expect that results will be submitted for publication by June 2025.

Conclusions: This study serves as a first step in evaluating a novel, culturally adapted lifestyle intervention to prevent type 2 diabetes in Hispanic or Latino adults. Although this small study is not without limitations, findings will inform our team’s next steps for this early-phase intervention work.

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KEYWORDS

community-based participatory research; cultural adaptation; family-based diabetes prevention; family support; health behavior change; Hispanic or Latino; lifestyle intervention; type 2 diabetes

Introduction

Type 2 diabetes impacts an estimated 34-36 million Americans [1]. The rate of type 2 diabetes is expected to increase substantially in the coming decades and is increasingly common in younger adults [2]. Hispanic or Latino populations in the United States are disproportionately impacted, having significantly higher rates of type 2 diabetes adjusted for age and sex (22.1%) relative to non-Hispanic racial and ethnic groups (ie, 12.1%, 19.1%, 20.4%, 18.5% for White, Asian, Black, and other race, respectively) [3]. Hispanic or Latino individuals also tend to have worse type 2 diabetes outcomes, including poorer glycemic control and higher rates of diabetes-related complications [4-6]. Notably, the Hispanic or Latino population is one of the largest and most rapidly growing racial and ethnic minority groups in the United States [7] and in Utah [8] where the current project is based, highlighting the need to improve health outcomes in this population.

Lifestyle interventions, which focus on changing health behaviors (eg, increasing moderate-to-vigorous physical activity [MVPA] and improving nutrition), have shown efficacy in successfully preventing or delaying type 2 diabetes across racial and ethnic groups, including Hispanic or Latino individuals [9]. Despite this, when lifestyle interventions are translated to community and health care settings (most notably, the National Diabetes Prevention Program [National DPP]), Hispanic or Latino participant outcomes are poorer than those of other racial and ethnic groups [10]. This disparity is largely explained by low attendance rates, as each additional intervention session attended is associated with an additional 0.31% weight loss [10]. Hispanic or Latino participants in the National DPP had lower attendance and retention rates, with only 52.6% of Hispanic or Latino participants being retained through the 18th week of the year-long intervention, compared to 70.5% for non-Hispanic or Latino White individuals [11]. Hispanic or Latino participants were also underrepresented among National DPP participants (only 10% of enrolled participants were Hispanic or Latino) [10], a result that is particularly concerning given the high prevalence of type 2 diabetes in this group [3]. Thus, despite the disproportionate impact of type 2 diabetes on Hispanic or Latino individuals, large-scale real-world translations of efficacious lifestyle interventions for diabetes prevention have not effectively enrolled and retained Hispanic or Latino individuals.

Further research to explain this pattern is sparse. Disparities in engagement might be related to cultural incongruence between aspects of the lifestyle intervention program curriculum in addition to previously reported structural barriers. Critically, qualitative evidence suggests the typical length of lifestyle interventions for diabetes prevention (eg, 22 classes over the course of 1 year in the National DPP) is a barrier to participation and completion of the program for Hispanic participants [12,13]. Another key barrier cited by Hispanic participants in the National DPP is the lack of family support [14].

There is substantial evidence that the health and lifestyles of family members tend to be concordant [15]. While research has increasingly recognized and emphasized the importance of the social context of an individual in influencing lifestyle change, diabetes prevention interventions have not systematically integrated family members into programs. A family-based approach may be beneficial for Hispanic or Latino participants given the core Hispanic or Latino cultural value of familism, which emphasizes the family unit [16]. A family-based approach may facilitate increased family support, which is needed given that lack of family support was a top barrier identified among Hispanic or Latino National DPP participants [14]. There is preliminary work to support this idea. For example, in a secondary analysis of participant engagement in a predominantly Hispanic or Latino-serving National DPP, participants had higher rates of retention when participating with someone in their household, and Hispanic or Latino participants were more likely to participate with a household member relative to non-Hispanic or Latino participants [17]. Further, in a culturally adapted lifestyle intervention for individuals with type 2 diabetes or at high risk for the disease, Hispanic or Latino participants who participated with at least one family member or friend had, on average, statistically significant weight loss by the end of the program, whereas Hispanic or Latino participants who participated alone did not [14]. Qualitative results illustrated that participants found support and attendance from family members crucial to their success in the program. This work provides preliminary support for incorporating family members into the National DPP, as participating with a family member might improve engagement and outcomes in Hispanic or Latino individuals.

Culturally adapting lifestyle interventions for diabetes prevention is an increasingly supported avenue for improving engagement in minoritized communities [18]. In the National DPP specifically, Hispanic or Latino participants had higher rates and longer lengths of attendance when they enrolled in programs that used cultural adaptations to tailor the program to specific community needs [19]. Thus, while lifestyle interventions hold promise for preventing or delaying type 2 diabetes in Hispanic or Latino individuals, specific adaptions may facilitate more effective engagement and retention in these individuals. In the current project, we focused on decreasing the length of the program and systematically incorporating family members into the intervention.

In the context of a larger community-based participatory research project, we developed PrevenganT2, a family-based lifestyle intervention designed to meet the needs of Hispanic or Latino adults in Utah. The larger project, Adapting Diabetes Interventions to Improve Outcomes and Stop Type 2 Diabetes in Hispanic or Latino Communities (ADIOS T2D!) [20], is

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guided by the Obesity-Related Behavioral Intervention Trials (ORBIT) framework for early-phase intervention development [21,22]. Described in more detail below, the adaptation (ie, ORBIT phase 1b, "refine" phase) was based on data collected from Hispanic or Latino family dyads in a formative evaluation trial of the core curriculum (ie, first 16 classes) of the 2021 version of the Centers for Disease Control and Prevention (CDC) Spanish-language PrevengaT2 curriculum. Specific changes were recommended by members of a Community Advisory Board (CAB) who are coauthors of this manuscript.

Here, we describe the protocol for a proof-of-concept study. In the ORBIT model, a proof-of-concept trial is one of 3 approaches to preliminary testing of a behavioral intervention. The primary goal of a proof-of-concept (ORBIT phase 2a) study is to evaluate whether the intervention alters a treatment target in a clinically significant way (ie, whether there is a "clinically significant signal" of PrevenganT2 on MVPA, the primary outcome and treatment target of focus) in Hispanic or Latino adults at high risk for type 2 diabetes in a community setting in Utah. Consistent with ORBIT recommendations for this subphase of "preliminary testing," the design was nonrandomized and included a small sample of participants in each of 2 counties [23]. If warranted, additional preliminary testing trials will evaluate feasibility and acceptability, including recruitment and retention (ie, phase 2b; feasibility pilot trial) as well as efficacy (ie, phase 2c; phase II efficacy trial) [23]. The results of this trial will determine our next steps in this intervention development work to better meet the needs of Hispanic or Latino communities. If the intervention meets prespecified criteria for a "clinically significant signal" on MVPA (Data Analysis), additional preliminary testing will follow. In contrast, if the intervention does not meet the prespecified criteria, additional ORBIT phase 1 work (ie, refinement) will be carried out instead.

Methods

PrevenganT2 Development

For a visual overview of the larger ADIOS T2D project, refer to Figure 1. We used an iterative approach to intervention development guided by the ORBIT framework and members of the Hispanic or Latino community. A 7-member CAB formed in January 2023 included individuals with personal or professional experience with diabetes prevention in the Hispanic or Latino community. Members included health care providers, community health workers (CHWs) with prediabetes experience, people with prediabetes, family members of someone with prediabetes, and community members.

Figure 1. Overall project timelines. ADIOS T2D!: Adapting Diabetes Interventions to Improve Outcomes and Stop Type 2 Diabetes in Hispanic or Latino Communities.

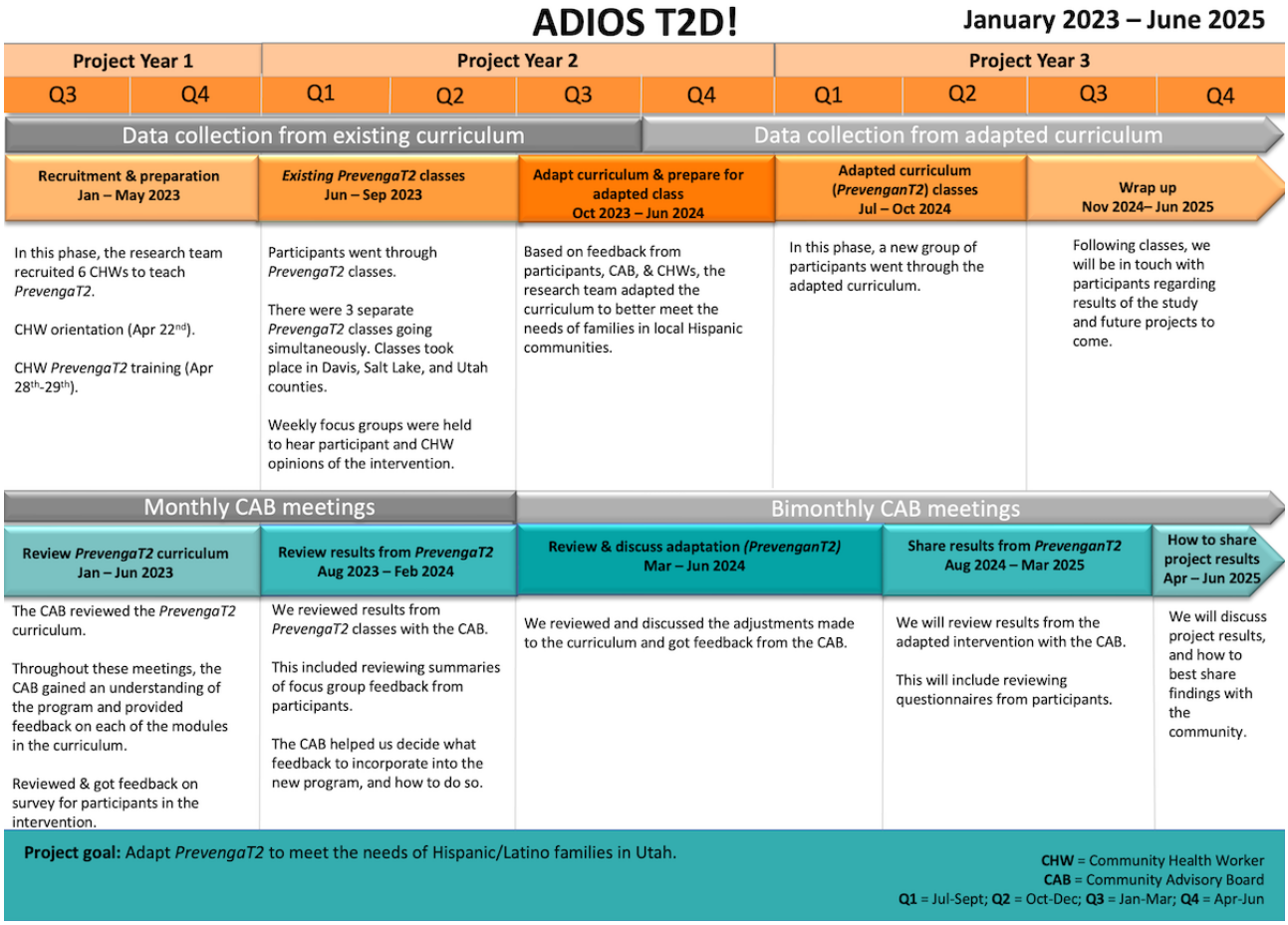

First, the CAB reviewed the existing PrevengaT2 core curriculum and provided initial feedback. This feedback informed focus group questions for participants in a formative evaluation trial. Additional details about the formative

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evaluation trial methods and results are available from the study authors. Immediately following each of the 16 modules delivered weekly by CHWs in the formative evaluation, separate focus groups were held for target participants (ie, individuals at high risk for type 2 diabetes) and family members (ie, adult family members living in the same household as the target participant). The team also conducted brief CHW debrief meetings following each module. Following qualitative coding of focus groups and CHW debrief meetings, the research team presented deidentified results to the CAB. The CAB provided guidance to the research team on how feedback from participants and CHWs could be implemented in the adaptations of the PrevengaT2 core curriculum.

The CAB members recommended 14 weekly classes, lasting 1 hour each, and changing the language of the curriculum to include a warmer and more inviting tone as well as inclusive discussion of family members. Visuals were enhanced to incorporate more vibrant colors and culturally relevant imagery that resonates with Hispanic or Latino participants, such as food and family-oriented images. The curriculum incorporated links to Spanish-language resources on exercises, recipes, and mental health to address requests for more comprehensive information. Finally, the focus on weight was deemphasized to more effectively promote health behaviors such as balanced nutrition and physical activity. Weight-centric messaging in PrevengaT2 was not viewed as motivating by participants and was upsetting for some.

PrevenganT2 Location/Setting

This intervention took place in Utah. The project is a collaboration between researchers at the University of Utah and a local Hispanic or Latino-serving community-based organization, Alliance Community Services. A total of 2 cohorts of dyads (one in each of 2 local counties) participated in the intervention.

Recruitment, Eligibility, and Participants

Recruitment occurred in June and July of 2024. CHWs recruited participants through in-person contact, phone calls, and outreach to community members who previously agreed to future contact from Alliance Community Services during a project focused on diabetes screening. CHWs aimed to recruit 10-12 target participants along with an adult family member (n=20-24) across 2 counties (ie. 5-6 family dyads per county). Given the emphasis in an ORBIT proof-of-concept trial on examining whether there is a clinically significant change in behavior under ideal conditions [23,24], our sample size was based on what we thought would be the ideal number of participants in each of the 2 groups based on the previous experience of our team. Specifically, we delivered the CDC National DPP curriculum to dyads in the intervention refinement phase of the larger study, members of the team have been involved with intervention delivery to romantic partner dyads in couple-based work [25], and Alliance Community Services team members have delivered interventions in the Hispanic or Latino community for decades. Based on these experiences, we determined 5-6 dyads to be large enough to encourage discussion among members while small enough to maintain a focus on the specific needs of the individuals in the room.

To be eligible for participation in the study, target participants were required to be at least 18 years old, identify as Hispanic or Latino, be fluent in English or Spanish, and be at high risk for type 2 diabetes based on the American Diabetes Association/CDC diabetes risk test [26,27]. Target participants were also required to have a family member living in their home willing to participate in the study with them. Inclusion criteria for family members were being at least 18 years old and fluent in Spanish or English. Exclusion criteria for targets and family members included having type 1 or type 2 diabetes, current medication for diabetes, current enrollment in a lifestyle intervention for prediabetes or obesity, and being a CAB member in this study. Trained and experienced CHWs (n=2) delivered PrevenganT2 in each of the 2 counties (Salt Lake County, Davis County).

Intervention Procedures

Participants (ie, both targets and family members) attended up to 14 weekly PrevenganT2 intervention classes, each lasting 60 minutes. Each class focuses on a different module from the adapted curriculum, including physical activity, nutrition, tracking physical activity and nutrition, and stress management. The intervention was delivered in Spanish. In addition to compensating participants for their time completing study assessments, participants received incentives at each class. CHWs chose incentives related to the topic of a given class. If needed, participants were given vouchers for childcare and transportation to and from the classes.

Assessment Procedures, Outcomes, Measures, and Materials

Assessment Procedures

Before beginning the intervention (pre), participants completed consent forms and filled out a series of questionnaires in Spanish. In addition, target participants engaged in a 7-day assessment during which they wore ActiGraph GT3X-BT accelerometers on their waists to measure MVPA. Participants were instructed to wear accelerometers 24 hours/day around their waist and were sent a link to an internet-based questionnaire each morning to validate the accelerometer data. These procedures were repeated after the final intervention class (post).

Measures and Materials

We selected target partner MVPA as the primary outcome of this study. Although other health behaviors are targeted in the National DPP and measured as secondary outcomes (eg, sleep), the emphasis in the CDC intervention is primarily on increasing MVPA and improving nutrition. As increases in MVPA affect cardiovascular risk [28], and MVPA was the primary behavioral outcome in both the initial efficacy trial [9] and the National DPP evaluation [10], this was selected as the primary behavioral outcome in this proof-of-concept trial. We use accelerometry to assess MVPA. Objective approaches are recommended for precise measurement of physical activity in the context of lifestyle interventions [29,30]. Accelerometry is the most common objective approach for physical activity measurement in daily life [31] and the preferred tool for assessing the effects of interventions on physical activity [32]. As described above,

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target participants were fitted with waist-worn Actigraph GT3X-BT devices that they were instructed to wear for 7 consecutive days before (pre) and after (post) the intervention. To be considered a valid week of objective MVPA data, participants must have had at least 4 valid days of data (including at least one weekend day). A valid day of data is defined as at least 10 hours of wear time while awake [32,33]. The Freedson Adult VM3 2011 algorithm, along with sedentary cut points based on previous recommendations [34] will be used to calculate MVPA, operationalized as the total minutes at 2690 counts per minute and higher on valid days [34,35]. For participants with a valid week of data, MVPA minutes over the course of the week will be determined by multiplying the average MVPA minutes across all valid days by 7 days.

To contextualize the sample, self-report measures in the prequestionnaire included demographic information, the American Diabetes Association/US Centers for Disease Control and Prevention Prediabetes Screening Test [26,27], and cultural factors (ie, acculturation, measured by the Short Acculturation Scale for Hispanics [SASH)] [36] and familism, measured by the Short Attitudinal Familism Scale [SAFS]) [37]. Although the emphasis in a proof-of-concept trial is on whether there is a change in a specific behavioral target [23], we also collected secondary outcome data from participants, including measures of health behaviors (ie, nutrition, measured by the Latino Dietary Behaviors Questionnaire [LDBQ] [38] and physical activity, measured by the International Physical Activity Questionnaire [IPAQ]) [39], mental health (ie, symptoms of anxiety, measured by the Generalized Anxiety Disorder-7 Scale [GAD-7] [40], and depression, measured by the Patient Health Questionnaire [PHQ-8]) [41], and social support from participating family members (ie, for diet, measured with the Social Support for Diet scale [SSDS], and exercise, measured with the Social Support for Exercise scale [SSES]) [42]. In addition, CHWs recorded program engagement (ie, attendance) at each class; participant weight was measured with a medical-grade scale at classes 0, 4, 8, and 13; and participant-reported MVPA minutes from the previous week were reported at each of classes 7-13.

When possible, we used measures developed in Spanish or Spanish translations of measures subject to psychometric evaluation among Latino participants. These measures include the SAFS [37], International Physical Activity Questionnaire [43], SASH [36], PHQ-8 [44], GAD-7 [45], SSDS [46], and SSES [46]. For measures that lacked culturally appropriate translations (ie, for measures not originally developed for use in Spanish or had not been validated in Latino samples), English measures were translated by a team of certified translators and subsequently reviewed by the CAB prior to use. In addition, minor edits were made to the wording of questions and responses for clarity, simplicity, and grammar on the SSES, GAD-7, PHQ-8, SASH, and LDBQ. For example, we made edits to the SASH [36], for proper punctuation (ie, “que” to “qué”). Edits were also made to the language of secondary measures to incorporate the family-based approach. The language was changed from a singular participant to the family members participating in the program with them as they are going through the program as a unit (ie, “usted” to “ustedes”). This approach of translation was not validated but was changed to fit the needs that the participants suggested. Changes were also made to the tone of the language to be more inviting and engaging. Information regarding all specific edits made to questionnaires is available from the corresponding author upon request.

Planned Data Analysis

A clinically significant increase in MVPA among target participants will be calculated using pre and post-accelerometer data and will be defined as either (1) meeting the recommendation of MVPA ≥ 150 minutes per week at post (among those not meeting it at pre), or (b) a pre-to-post increase ≥ 35 MVPA minutes per week. These criteria are based on current adult physical activity guidelines in the United States [47] as well as the finding that the equivalent of 5-6 minutes per day of brisk walking is the “minimum clinically important difference” in physical activity to reduce cardiovascular risk among inactive adults [28]. Although we took steps to collect a valid week of accelerometer data, some target participants may not have a valid week of accelerometer data in pre or post. Target participants with invalid data at one or both time points may meet the criteria for clinically significant increase in MVPA based on subjective measures (ie, IPAQ or self-reported MVPA recorded at classes). Although subjective assessment of physical activity is not considered the gold standard method of assessment, the efficacy trial and National DPP evaluation used MVPA self-reports [9,10], and our team determined the costs of the potential loss of data to outweigh the costs of using subjective methods in a small number of cases.

We will report the percentage of target participants demonstrating a clinically significant increase in MVPA, descriptive statistics of sociodemographic characteristics at pre, and descriptive statistics of all outcomes at pre and post. While we do not have the power to evaluate pre-post changes with inferential statistics, we will observe patterns in secondary outcomes to contextualize findings and inform our next steps.

Ethical Considerations

All participants provided informed consent. This study protocol was approved by the University of Utah institutional review board (#0017800) on June 18, 2024. Each participant provided written informed consent in Spanish prior to beginning the study. As part of the consent process, participants were given the option to consent to or opt out of data sharing. All data will be deidentified following data collection. Participants were compensated up to US $200 in gift cards for completing study assessments.

Results

This trial was in progress at the time of the initial submission of this paper. Data collection concluded in October 2024 and data cleaning and preparation for analysis are ongoing.

Discussion

Overview

The results of this proof-of-concept trial of PrevenganT2, a culturally adapted lifestyle intervention, will inform our team’s

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next steps. We expect the majority of target participants will illustrate clinically significant increases in MVPA from preintervention to postintervention. If this is the case, our team will proceed with additional preliminary testing to determine the feasibility and acceptability of PrevenganT2 and a randomized study protocol (ORBIT phase 2b), as well as the initial efficacy of PrevenganT2 (ORBIT phase 2c), before carrying out a larger randomized trial. If the majority of target participants do not demonstrate clinically significant pre-post increases in MVPA, we will carry out additional intervention refinement (ie, ORBIT phase 1b). As noted above, we do not have the power to evaluate pre-post changes with inferential statistics, but will contextualize our findings by observing patterns of change that inform our next steps. The results of this study will be disseminated through publication in a peer-reviewed journal and presentation at local and national conferences. In addition, results will be disseminated directly into the community in meetings with the CAB and with our community partners at Alliance Community Services.

Comparison to Prior Work

As a whole, individually focused lifestyle interventions to prevent type 2 diabetes have failed to effectively engage Hispanic or Latino individuals and have not systematically integrated family members into interventions. In recent years, there has been increased recognition of the need to develop culturally responsive lifestyle interventions to address the disproportionate burden of type 2 diabetes in Hispanic or Latino communities. In turn, a number of such interventions have been developed and some illustrated the potential efficacy of culturally tailored lifestyle interventions in reducing the risk of type 2 diabetes through relevant outcomes like a clinically significant reduction in hemoglobin A_{1c} [48] and weight [48,49] in Hispanic or Latino communities. However, these studies have varied substantially in factors such as the level of cultural adaptation (eg, many have simply translated the program from English to Spanish), the extent of community engagement, and outcomes assessed (eg, looking exclusively at weight or hemoglobin A_{1c}). Further, evidence for the impact of these prior interventions on physical activity and other behavioral outcomes is weak, and to our knowledge, no studies have specifically examined changes in MVPA [50]. Moreover, none of these studies have systematically included family members in the lifestyle intervention and most have methodological limitations. The results of this study will be interpreted in the context of these limitations to prior work.

Strengths and Limitations

This project has a number of strengths. Most notably, it was designed and carried out in close collaboration with members of local Hispanic or Latino communities. Our strong community partnerships and formation of a CAB to guide the larger project allowed us to adapt the intervention to the specific needs of local community members. Further, hiring CHWs from the Hispanic-serving organization, we partnered with facilitates capacity building within the organization and in turn, the potential sustainability of the intervention. Another strength of this project is the use of the ORBIT model to guide this early intervention development work. This model will guide us in refining and strengthening aspects of the intervention and study protocol if needed before scaling up to a larger trial that requires substantially more resources. Another strength is our objective measurement of physical activity. The use of accelerometers minimizes much of the bias introduced by self-report measures of physical activity.

Despite these strengths, this project also has limitations. Although we consider our community-based approach and use of the ORBIT model a strength, the primary focus in proof-of-concept trials is on whether there is a “clinical signal” on a primary behavioral outcome under ideal conditions [23,24]. Despite the strong scientific rationale for our focus on MVPA as the primary outcome, our experience with the broader ADIOS T2D! project suggests that MVPA may not be the most culturally relevant outcome for Hispanic or Latino communities. As noted above, MVPA was not a behavioral outcome in previous evaluations of diabetes prevention work in Hispanic or Latino communities. Inadequate representation of Hispanic or Latino participants in much of the science on which our primary outcome rationale was based is a clear limitation that in hindsight should have been more carefully considered together with the CAB. Whereas community engagement is in no way inconsistent with the ORBIT model, the field would benefit from recommendations for how to optimally engage communities in intervention development guided by the ORBIT model. Based on our experience, we recommend researchers explicitly discuss with community members the most relevant behavioral outcomes in their community when selecting primary and secondary outcomes. Further, we recommend researchers working with minoritized communities critically evaluate the extent to which the community has been represented in the relevant research literature. In the meantime, the narrow focus of this trial, along with the small sample size and nonrandomized design, limit the potential conclusions we can draw. Feasibility outcomes including attendance of target and family member participants will be formally evaluated in future preliminary testing (ie, in an OBBIT phase 2b feasibility trial). In addition, the program is limited to individuals with a family member who is willing and able to participate in the intervention. Although we carefully considered how to increase access to the program by limiting known barriers to lifestyle intervention engagement (eg, offering participants childcare and transportation vouchers and use of incentives), the requirement of family member participation may restrict intervention access to those with more social resources.

Conclusions

Type 2 diabetes preventive interventions that meet the needs of Hispanic or Latino communities are critical and have the potential to substantially improve health outcomes in the Hispanic or Latino population. This study addresses this through close partnerships with community members and by leveraging family relationships. Although the conclusions we can draw from this small trial are limited, they will inform the next steps of our team and others. This project represents the next step in our understanding of the potential for family-based lifestyle interventions to increase engagement, improve outcomes, and increase health equity in the Hispanic or Latino community.

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Data Availability

The datasets generated during this study are not publicly available to protect the identities and information of participants from vulnerable populations. Data from participants who consented to data sharing are available from the corresponding author pending agreement to conditions of data access.

Authors' Contributions

KJWB, SCS, AA, and ASB were responsible for conceptualization of the study. SCS, JV, and KJWB were responsible for project administration. KJWB was responsible for supervision. BEF, BLM, EZB, YC, JC, and KJWB wrote the first draft.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review reports by the American Diabetes Association Research Grant Review Committee.
[PDF File (Adobe PDF File), 207 KB - resprot_v14i1e66317_app1.pdf]

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Abbreviations

ADIOS T2D!: Adapting Diabetes Interventions to Improve Outcomes and Stop Type 2 Diabetes in Hispanic or Latino Communities
CAB: Community Advisory Board
CDC: Centers for Disease Control and Prevention
CHW: community health worker
DPP: Diabetes Prevention Program
GAD-7: Generalized Anxiety Disorder-7 Scale
IPAQ: International Physical Activity Questionnaire
LDBQ: Latino Dietary Behaviors Questionnaire
MVPA: moderate-to-vigorous physical activity
ORBIT: Obesity-Related Behavioral Intervention Trials
PHQ-8: Patient Health Questionnaire
SAFS: Short Attitudinal Familism Scale

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SASH: Short Acculturation Scale for Hispanics
SSDS: Social Support for Diet scale
SSES: Social Support for Exercise scale

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Protocol

Development of a Novel Web-Based Intervention Targeting Pain-Related Outcomes in Individuals With Chronic Orofacial Pain: Protocol for a Mixed Methods Study

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Abstract

Background: Chronic orofacial pain (COP) is common, costly, and associated with substantial pain interference and emotional distress. Psychosocial treatments for COP are scarce and limited (eg, rely on talking, which is often painful for this population; require intensive resources, limiting scalability). Here, we describe the study protocol for developing *Face-Forward-Web*, a "talk-free" web-based mind-body intervention for patients with COP.

Objective: We aim to (1) develop *Face-Forward-Web* with the aid of live-video focus groups with adults with COP and (2) optimize *Face-Forward-Web* and our study protocol through beta testing followed by an open feasibility trial.

Methods: We will accomplish these aims in 2 phases, incorporating user-centered design principles. For phase 1, we conducted semistructured focus groups (n=4 groups, 22 participants) with individuals with COP. We are using rapid data analysis followed by thematic analysis to gauge treatment needs, preferences, and perceptions of the proposed platform and skills. This information will inform session structure and content as well as development of a wireframe followed by a prototype. For phase 2, we will conduct beta testing (up to n=10) followed by a feasibility trial (up to n=20) with exit interviews to gather feedback. The primary outcomes are feasibility benchmarks such as recruitment (≥70% of the eligible participants will participate), acceptability (≥70% of the participants complete ≥4 or 5 sessions), credibility, expectancy (≥70% above the Credibility and Expectancy scale's midpoint), and satisfaction (≥70% above the User Experience Questionnaire's midpoint).

Results: Recruitment for phase 1 began in October 2024 and concluded in January 2025. Data analysis for phase 1 will conclude in fall 2025 and for phase 2 in 2026. Results will iteratively guide the development of the intervention.

Conclusions: *Face-Forward-Web* will be the first talk-free web-based intervention tailored to the needs of adults with COP. Results will inform a future efficacy trial.

Trial Registration: ClinicalTrials.gov NCT06754917; https://clinicaltrials.gov/study/NCT06754917

International Registered Report Identifier (IRRID): DERR1-10.2196/71839

(JMIR Res Protoc 2025;14:e71839) doi:10.2196/71839

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KEYWORDS

chronic orofacial pain; mind-body; psychosocial; web-based platform; asynchronous

Introduction

Chronic orofacial pain (COP) is common [1], costly [2], and associated with substantial pain interference (ie, pain-related activity limitations) and emotional distress [3-5]. COP includes a group of conditions that involve pain in the hard and soft tissues of the head, face, and neck that last for more than 3 months [6]. Although the etiological aspects of COP are heterogeneous, COP conditions are unified by a psychosocial profile of substantial maladaptive coping (eg, pain-related fear, pain catastrophizing) [7-9], pain interference, and emotional distress (eg, depression, anxiety) [3,4,10-14], which worsen each other over time [15,16]. Treatments are typically biomedical [4], mostly ineffective [17], and often involve adverse side effects [18], misdiagnoses or incomplete diagnoses [17], and unnecessary/painful procedures (eg, tooth extractions, occlusal adjustment) that may lead to irreversible damage [4,19]. Such treatments do not typically address and often exacerbate activity limitations, maladaptive coping, and emotional distress [4,19]. These psychosocial factors are critical causative elements of COP but are mostly overlooked in COP treatment [20].

Psychosocial interventions such as cognitive behavioral therapy [21-28] and other behavioral programs [29-32] show promise in improving outcomes in individuals with COP [21-32]. However, the existing interventions are limited in several ways: these interventions (1) almost exclusively rely on talking, which is often painful for patients with COP and limits treatment engagement [20,33]; (2) are resource-intensive and require availability of trained providers, limiting accessibility, particularly for underserved communities [34]; (3) often involve costs, travel, and limited insurance coverage [35]; (4) carry a mental health stigma, which limits treatment-seeking and participation [36]; (5) tend to focus on an incomplete diagnosis and mostly temporomandibular disorder, limiting generalizability, and (6) are typically unimodal (eg, cognitive behavioral therapy alone), despite evidence that multimodal interventions work better for complex conditions like COP, which have high psychiatric comorbidity [24,37]. Talk-free asynchronous multimodal web-based platforms can bypass these limitations while maintaining effectiveness [38]. However, to our knowledge, no such interventions exist. Delivering COP interventions through a web-based platform holds potential to expand accessibility, increase scalability, and address this population's largely unmet needs [20,39].

To this end, we will develop *Face-Forward-Web*, the first web-based platform adapted and refined via mixed methods for COP by using user-centered design principles [40-43]. *Face-Forward-Web* will be adapted from *GetActive*, a mind-body and activity intervention for individuals with chronic musculoskeletal pain [44]. *Face-Forward-Web* will be delivered via a talk-free asynchronous web platform and will address some of the unique and often unaddressed challenges faced by individuals with COP, including difficulty with talking due to pain [20,33], emotional distress [3,5,20], orofacial pain interference and pain intensity [8], and coping with unpredictable pain [20].

Our conceptual model (Figure 1) is informed by the fear-avoidance framework [45,46] and poses that improvement in pain interference, pain, and emotional distress after participation in *Face-Forward-Web* will be explained by improvement in the mechanistic targets of pain catastrophizing, fear of pain, and mindfulness. Our guiding hypothesis (to be tested in future work) is that the *Face-Forward-Web* intervention will be an effective, efficient, and scalable strategy to address the unmet needs and challenges of pain interference and distress among patients with COP.

Figure 1. The Face-Forward-Web conceptual model.

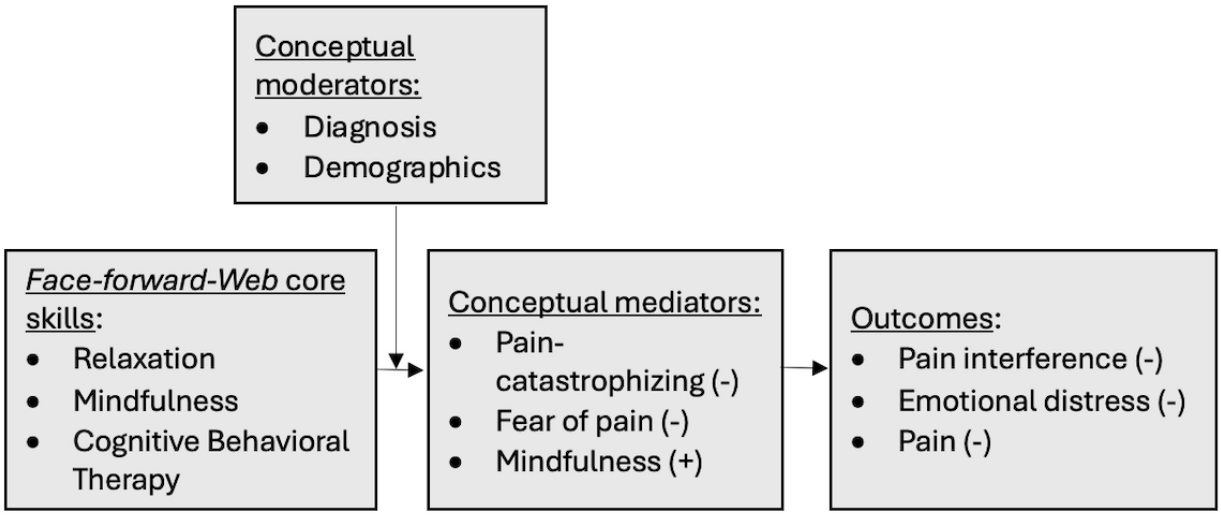

This study aims to (1) develop *Face-Forward-Web* with the aid of live video focus groups with adults with COP and (2) optimize *Face-Forward-Web* and our study protocol through beta testing (n=up to 10) to refine the intervention followed by

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a feasibility trial (n=up to 20). The results will inform future efficacy research, evaluating *Face-Forward-Web* versus an active control web platform in improving pain interference, depression, and anxiety.

Methods

Study Design and Setting

This study protocol adheres to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 statement (Multimedia Appendix 1). Our approach is consistent with the National Institutes of Health (NIH) stage model for behavioral intervention development [47,48]. The proposed phases address stages 1A (intervention development and refinement) and 1B (feasibility testing). For phase 2, the primary outcomes are feasibility benchmarks (ie, feasibility of recruitment, credibility and expectancy, acceptability of treatment, adherence to homework, satisfaction [user experience], feasibility of assessments, adverse events).

This study will be completed in 2 main phases conducted at a large academic hospital. In phase 1, we conducted 4 virtual focus groups (22 patients with COP) at which point we reached saturation [49]. We aimed to understand their treatment needs and preferences, perceptions, and recommendations for a web platform delivery, and the best ways to engage and retain participants. We also gathered participants' feedback on program content via sample videos similar to those intended to be used in the *Face-Forward-Web* program. We are using this information to inform adaptations from the *GetActive* intervention for chronic musculoskeletal pain intervention to the *Face-Forward-Web* intervention for chronic orofacial pain as well as for the development of a wireframe for *Face-Forward-Web*, followed by a prototype [42].

In phase 2, we will conduct beta testing (up to n=10) and revise *Face-Forward-Web* and the study procedures according to the feedback and information gathered. We will then conduct a feasibility trial (up to n=20) with rapid iterative development of the prototype intervention [50].

Inclusion and Exclusion Criteria

We plan to include participants aged ≥18 years, with English fluency and literacy, chronic nonmalignant COP (>3 months), who express ability and willingness to participate in a live-video focus group/web platform intervention, are free of concurrent psychotropic medications for at least 2 weeks prior to treatment, or stable on current psychotropic medication for ≥6 weeks, and have pain intensity ≥4/10. We will exclude individuals who practiced mindfulness >45 min/wk in the past 3 months and those who have participated in mind-body or cognitive behavioral therapy in the past 3 months; have severe untreated mental health (eg, psychosis) or active suicidal ideation; or are pregnant (per our institutional review board).

Recruitment

For both phases of the study, we will recruit from sources such as the Facial Pain Association—a large organization providing support, education, and advocacy for individuals with COP—the Facial Pain Clinic at Massachusetts General Hospital, social media, and other sources. We will prioritize recruitment of racial and ethnic minorities and aim to reflect the US population (38% of the minorities). Individuals who participate in phase 1 focus groups may participate in phase 2 feasibility testing.

Procedures

Ethical Considerations

Methodology, including interview script and recruitment strategies and materials, were approved by the institutional review board of the Massachusetts General Hospital. The institutional review board determined that phase 1 activities were exempt from written informed consent. Instead, all participants viewed an online study fact sheet during enrollment and provided consent to participate (protocol 2024P001309). Participants in phase 2 will provide written informed consent and may opt out at any time during the study (protocol 2024P003501). All focus group and exit interview transcripts are deidentified prior to analysis, and any quantitative data exported for analysis will also be deidentified. Participants can receive payment up to US $50 via check for completing all phase 1 activities and up to US $170 for completing all phase 2 activities.

Phase 1: Developmental Phase With Focus Group Feedback

We have developed a semistructured qualitative interview script with items assessing treatment needs, preferences, and perceptions of the intervention skills and structure (Multimedia Appendix 2). We completed recruitment and data collection for phase 1 in January 2025. We recruited individuals with COP. Study staff screened potential participants and obtained verbal consent. Then, eligible patients were invited to participate in one of the 4 focus groups. Upon enrollment, participants completed an electronic demographic questionnaire and were aided with downloading and installing the video software (Zoom) as needed. All qualitative interviews were audio-recorded, transcribed, organized, and analyzed using the NVivo 12 qualitative statistical package (QSR International). We will use the qualitative results of phase 1 to develop *Face-Forward-Web* and the treatment manual to be piloted in phase 2.

Phase 2: Beta Testing and Feasibility Trial With Exit Interviews

Beta Testing

After screening, consent, and enrollment, up to 10 individuals with COP will beta test *the Face-Forward-Web* intervention. The research coordinator will schedule an orientation session, in which she will outline how to navigate the *Face-Forward-Web* platform. Participants will then independently complete the intervention. After each module, participants will be asked to indicate their level of satisfaction from the module on a 1-4 Likert scale and provide feedback on their impressions from the module in a textbox. At the conclusion of the intervention, participants will participate in exit interviews over Zoom. Exit interviews will last ~30 minutes and will be audio-recorded and transcribed. Similar to phase 1, the exit interviews will involve a semistructured script, followed

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by rapid data analysis and qualitative thematic analysis using NVivo 12. We will utilize results to further refine the intervention's content manual and procedures as well as refine *Face-Forward-Web* prior to the feasibility trial.

Feasibility Testing

Participants will be recruited, screened, and enrolled using the methods described above. After consenting, participants (n=up to 20) will complete a set of valid and reliable online questionnaires over the secure Research Electronic Data Capture (REDCap) system. The estimated time for completion is 20 minutes. If participants miss an item, they will be prompted to complete it, thereby minimizing missing data. Participants will complete the questionaries at 2 additional timepoints—after completing the intervention and again 3 months later. After baseline assessments, participants will participate in an orientation session. Then they will complete the intervention and subsequent exit interviews following similar procedures as in the beta testing.

The Face-Forward-Web Intervention

Face-Forward-Web consists of 5 sessions (Table 1), which teach relaxation (eg, body scan, deep breathing), mindfulness, and cognitive-behavioral skills (eg, adaptive thinking, reducing negative affective reactivity). The content is consistent with *GetActive* [44] and adapted to the unique needs of people with COP and for delivery via the web platform. Due to the individual/asynchronous format of *Face-Forward-Web*, we were able to condense the *GetActive* content into 5 sessions, which may maximize feasibility and engagement (to be tested in the proposed studies). Each session consists of a combination of short (~5-10 minutes) videos conveying educational content and skill delivery. Each session ends with an interactive quiz covering the session's content to gauge comprehension and facilitate material absorption, which can be an effective intervention element for people with chronic pain [51]. Audio and video clips will be available to guide participants through their daily home practice. Once invited by a research assistant, participants will log in and access the first session's materials. Contingent on completion of the interactive quiz at the end of each session, access to the subsequent session will be granted in the following week. Participants will be free to review and practice all the skills and materials from the completed sessions until the 3-month follow-up assessment and will be encouraged to use the platform for daily practice. The platform will be easily accessible across multiple interfaces such as a website and mobile app through any internet-enabled device (eg, smartphone, tablet, computer). We will track participants' homework completion and platform activity. To encourage retention, we will text reminders about the sessions and home practice through the Health Insurance Portability and Accountability Act–compliant texting service, as previously successfully implemented by our group and deemed useful by participants [52].

Table 1. Face-Forward-Web session topics and examples of content.

Session	*Face-Forward-Web* topic	Skills and examples of content/videos
1	Taking charge of orofacial pain	• Orofacial "Pain alarm" (reactions to COP[a]) • Debunking myths about COP • Downward and upward spirals (COP is associated with thoughts, feelings, and behaviors that can be maladaptive or adaptive) • Deep breathing
2	Managing emotional challenges in orofacial pain	• Mindfulness • Body scan
3	Working with negative thoughts	• Identifying NATs[b] • Checking NATs • Challenging NATs
4	Not letting orofacial pain get the best of us	• Acceptance • Using Face-Forward-Web skills to reengage in activities (eg, daily, recreational, social, family, work-related)
5	Facing forward: "Rolling" with orofacial pain and staying resilient	• Mindfulness of discomfort and pain • Review all skills • Create personalized plan

[a]COP: chronic orofacial pain.

[b]NAT: negative automatic thought.

Treatment Delivery and Protocol Adherence

Participants will continue their usual care as determined by their medical providers (eg, medication, occlusal splits and adjustments, physical therapy). We will determine fidelity to *Face-Forward-Web* via a user experience software such as Google Analytics [53]. This will enable us to track participants' frequency and time spent on each of the web platform's pages and clicks on exercises and quizzes and evaluate participation, even on partially completed sessions, thereby increasing the accuracy of attendance evaluation.

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Assessments

Pain Severity and Pain Interference

The Graded Chronic Pain Scale [54] is a 7-item scale measuring pain severity and pain interference. The time frame of reference will be the past week, consistent with prior work [55,56]. The Numerical Rating Scale [57] is a single item measure assessing pain severity.

Anxiety

The Generalized Anxiety Disorder Scale [58] is a 7-item scale that assesses the severity of the anxiety symptoms over the past 2 weeks.

Depression

The Patient Health Questionnaire [59] is a 9-item measure that assesses depression symptoms over the past 2 weeks.

Catastrophic Thinking About Pain

The Pain Catastrophizing Scale [60] is a 13-item measure assessing hopelessness, helplessness, and rumination about pain.

Fear of Pain Due To Movement

The Tampa Scale for Kinesiophobia for Temporomandibular Disorders [61] is a 12-item scale assessing fear of pain due to facial movement and adapted to heterogeneous orofacial pain [62] (ie, expanding references from “jaw” to “jaw or face”)

Mindfulness

The Cognitive and Affective Mindfulness Scale-Revised [63] is a 12-item questionnaire that measures an individual's level of mindfulness, including present-focused attention, awareness of thoughts and feelings, and nonjudgmental acceptance of internal experiences. The Applied Mindfulness Process Scale [64] is a 15-item questionnaire that measures respondents’ application of mindfulness practices in daily life.

Treatment Satisfaction

The User Experience Questionnaire assesses users’ satisfaction and experience with digital products, software, and platforms [65]. This assessment is administered at 1 timepoint, immediately after the intervention.

Treatment Credibility

The Credibility and Expectancy Questionnaire assesses how believable and logical patients perceive the treatment to be [66]. This assessment is administered at 1 timepoint, immediately after the intervention.

Data Analysis

Phase 1: Focus Groups

We used rapid data analysis during focus groups to enable timely application of key findings to iterative refinement of our prototype and procedures. Next, we will use thematic analysis following a hybrid deductive-inductive approach [67,68] for a deeper analysis to gauge treatment needs, preferences, and perceptions of the intervention. We will analyze qualitative data from the interviews by using NVivo 12, which enables reliability assessment (κ) of theme-coding between independent coders. Coders will discuss and resolve potential discrepancies until they reach agreement and sufficient reliability, indicated by κ>.80. We will use the results to make specific adaptations to the program content and procedures based on focus group data to best meet participants’ needs and challenges.

Phase 2: Beta and Feasibility Testing With Exit Interviews

We will use frequency and proportions to assess the feasibility of the recruitment and retention procedures. We will determine treatment satisfaction and credibility by the proportion of participants who score above the scale midpoint in the User Experience Questionnaire [65] and Credibility and Expectancy Questionnaire [66], respectively. See Table 2 for further details on the feasibility, credibility, and acceptability benchmarks, consistent with other established feasibility work [67-69]. We will analyze qualitative data from the exit interviews by using the same procedures described in phase 1.

Table 2. Feasibility benchmarks.

Outcome	Acceptable	Excellent
Credibility and expectancy	>70% of the participants with score over scale mid-point.	>75% of the participants with score over scale midpoint.
User experience	>70% of the participants with score over scale mid-point.	>75% of the participants with score over scale midpoint.
Feasibility of recruitment	>70% of eligible participants agree to participate.	At least 80% of eligible participants agree to participate.
Acceptability of treatment	>70% of the participants attend 3 out of 5 sessions.	>80% of the participants attend 3 out of 5 sessions.
Adherence to homework	>70% of the participants practice >1 skill on 3 d/wk.	>80% of participants practice >1 skill on 3 d/wk.
Feasibility of assessments	>70% of the participants have no measures fully missing.	>90% of the participants have no measures fully missing.
Adverse events	Minimal	None

Results

This study is funded by the National Institute of Dental and Craniofacial Research grant 1R21DE033502-01A1 to JG and AMV. Recruitment began in October 2024 for phase 1. Data collection for phase 1 was completed in March 2025. Primary data analysis for phase 1 is expected to conclude by fall 2025 and in 2026 for phase 2. As of August 2025, we have completed

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4 planned focus groups with a total of 22 participants representing a variety of COP diagnoses, including temporomandibular joint dysfunction, trigeminal neuralgia, and burning mouth syndrome. The rapid data analysis is complete, and we are beginning thematic analysis. We are starting to create intervention content, informed by results from our focus groups. Once available, we will share the data and results in the Vivli global clinical research data sharing platform.

Discussion

Pain interference and emotional distress are prevalent among people with COP [62] but are commonly neglected in current treatments [20,39]. Available psychosocial interventions such as cognitive behavioral therapy [21-28] and other behavioral programs [29-32] show promise in improving outcomes in individuals with COP [21-32] but are often not suitable for people with COP due to several limitations. Most notably, these interventions typically rely on verbal communication, which is often painful for this population due to facial pain symptoms, which can be exacerbated by talking. Additionally, such interventions can be associated with stigma and require extensive resources (eg, availability of a trained live clinician). Here, we describe a protocol to develop, test, and refine *Face-Forward-Web*, the first talk-free web-based intervention for adults with heterogeneous COP, tailored specifically to meet their needs and challenges. By teaching mind-body (eg, mindfulness, relaxation) and cognitive behavioral skills within a talk-free modality, this intervention holds potential to bypass barriers and address these commonly neglected needs [38].

We anticipate that the results of phase 1 will align with our preliminary work underscoring the need for a COP intervention that addresses psychosocial factors [20] and uses a web-based platform. We also anticipate findings to highlight specific elements of the intervention's content, structure, and study procedures that can be tailored to maximize fit for this population's needs. Assuming the successful integration of these findings, we hypothesize that phase 2 will demonstrate high levels of feasibility across domains (eg, user experience, acceptability, adherence) and no adverse events related to study participation.

We follow the NIH stage model [48] and prioritize establishing feasibility and iterative refinement of the intervention prior to efficacy testing. By integrating qualitative methods, our approach centers on participant needs and preferences, ensuring that the intervention is best positioned to support those impacted by COP. Once both phases are complete, these results will inform a future efficacy trial of *Face-Forward-Web* versus an active control platform.

Potential limitations should be considered. First, the study relies on participants' self-reported diagnoses and symptoms. This limitation is partially mitigated by our recruitment methods, which include referrals from COP medical specialists and established advocacy groups. Second, our broad diagnostic inclusion criteria may reduce the specificity of the findings. However, our preliminary research suggests that individuals across diagnostic categories share more common needs than differences. This inclusive approach enhances the potential for generalizability to a broader population and may be considered a potential strength. Other strengths include the use of established feasibility benchmarks, validated measures, and following the NIH model for behavioral intervention development.

Our work has yielded a few lessons learned thus far. First, given our small budget, we have had to carefully prioritize spending and have chosen to focus on the remuneration of participants [70]. Additionally, for recruitment, we have found both professional networks (providers who treat COP) and community resources (Facial Pain Association) to be effective. However, meeting our goal of including the perspectives of diverse populations, including a variety of COP diagnoses, as well as racial, ethnic, and medically underserved areas [71] has required additional strategies such as direct engagement of referral providers.

In summary, this protocol describes the development, refinement, and feasibility testing of *Face-Forward-Web*, the first talk-free web platform for adults with heterogeneous COP, tailored specifically to their needs and challenges by using mixed methods. We will utilize the NIH stage model for behavioral intervention development [47,48], the Science of Behavioral Change framework [72], and a user-centered design process to maximize the intervention's fit for this population's needs [40,41]. Our results will establish feasibility and directly inform a subsequent efficacy trial.

Acknowledgments

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Authors' Contributions

AMV and JG are the shared senior authors for this study.
Conceptualization: JG and AMV (co-lead)
Funding acquisition: JG, AMV (co-lead)
Investigation: JG, AMV (co-lead), BCL (supporting)
Methodology: JG, AMV (co-lead)
Project administration: JG
Resources: RK, JRS

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Supervision: JG (lead), AMV (supporting)
Writing – original draft: BCL
Writing – review & editing: JG (lead), JB (supporting), RK (supporting), HTC (supporting), SH (supporting), AMV (supporting)

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOCX File , 31 KB - resprot_v14i1e71839_app1.docx]

Multimedia Appendix 2
Focus group interview script.
[DOCX File , 28 KB - resprot_v14i1e71839_app2.docx]

Multimedia Appendix 3
Peer review report by BMHO - Biobehavioral Medicine and Health Outcomes Study Section Risk, Prevention and Health Behavior Integrated Review Group (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 167 KB - resprot_v14i1e71839_app3.pdf]

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Abbreviations

COP: chronic orofacial pain
NIH: National Institutes of Health
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Deep Learning–Based Pattern Recognition for Detecting Penile Abnormalities: Protocol for Developing a Mobile App for Circumcision Eligibility

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Abstract

Background: Circumcision is a widely practiced procedure with cultural and medical significance. However, certain penile abnormalities—such as hypospadias or webbed penis—may contraindicate the procedure and require specialized care. In low-resource settings, limited access to pediatric urologists often leads to missed or delayed diagnoses. Artificial intelligence (AI)–based image recognition presents a scalable solution to facilitate early detection and informed decision-making.

Objective: This study aims to develop and validate an AI-powered image classification system integrated into a mobile app to detect penile abnormalities and assess circumcision eligibility. The system is designed to support preliminary screening by general practitioners and caregivers in underserved areas.

Methods: A prospective cohort study was conducted involving pediatric patients at Cipto Mangunkusumo Hospital, Jakarta, Indonesia. Digital images will be collected prospectively from pediatric patients at Cipto Mangunkusumo Hospital captured by health care professionals or caregivers. High-resolution penile images were systematically captured from ventral, dorsal, and lateral angles and subsequently classified as either having normal or abnormal anatomy by urologists. Leveraging pretrained deep learning architectures, the AI models were developed to accurately classify these images and assess circumcision eligibility based on anatomical criteria. Image preprocessing included resizing, normalization, and augmentation. Transfer learning techniques were used to enhance accuracy. The model was developed using TensorFlow and Keras. Performance evaluation used accuracy, sensitivity, specificity, and F_1-score. Following development, the model will be embedded into a mobile app to enable real-time analysis, with feedback on whether further clinical evaluation or referral is needed.

Results: Model development began in January 2024 and is currently ongoing. Integration into the mobile app and deployment testing are scheduled across 3 sequential phases—refinement, integration, and user testing—through January 2026. Preliminary models have been trained, and refinement is underway to improve diagnostic accuracy and usability.

Conclusions: The proposed AI-based system offers a promising tool to support early diagnosis of penile abnormalities and safe circumcision decision-making in resource-limited settings. Its integration into a mobile app enables preliminary screening outside specialized centers, facilitating telemedicine and optimizing referral pathways.

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KEYWORDS

circumcision; artificial intelligence; penile abnormalities; mobile app; prospective cohort study

Introduction

The surgical procedure of circumcision, involving the removal of the foreskin that covers the glans of the penis, is widely practiced around the world. This ancient practice holds substantial importance both medically and culturally [1]. Medically, circumcision is linked to several health benefits, including a lower risk of urinary tract infections, sexually transmitted infections, and penile cancer, as well as improved genital hygiene [2,3]. Culturally and religiously, circumcision is considered an essential ritual in various societies, making it a common procedure in many communities [4].

However, not every individual is a suitable candidate for circumcision. Contrary to popular belief, circumcision carries potential risks, particularly in the presence of certain penile abnormalities [1,5]. Conditions such as hypospadias, epispadias, buried penis, webbed penis, and ambiguous genitalia can contraindicate the procedure, necessitating more complex surgical interventions by specialized health care providers. The accurate identification of these anomalies is crucial to avoid complications and ensure optimal patient outcomes [6].

In many low-resource settings, the challenge of accurately diagnosing penile abnormalities is exacerbated by limited access to specialized health care providers. This can lead to delayed or missed diagnoses, resulting in suboptimal care and increased anxiety for families [7-11]. Advances in telemedicine and digital health technologies present promising solutions to these challenges by enhancing the accessibility and accuracy of medical assessments [12,13].

This research aims to develop a digital pattern recognition system using deep learning techniques to identify penile abnormalities and assess eligibility for circumcision. By integrating this system into a mobile app, we hope to provide a reliable and accessible tool for health care providers and families, ultimately improving the circumcision decision-making process and patient care.

Methods

Overview

This research uses a prospective cohort design to develop a sophisticated digital image recognition system designed to identify penile abnormalities. The study will enroll participants from Cipto Mangunkusumo Hospital in Jakarta, Indonesia, who meet specific inclusion criteria. Digital photographs of the penile region will be taken by health care professionals such as general practitioners or by the patients' guardians, if necessary.

This protocol adheres to the guidelines outlined in the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 checklist for reporting protocol studies [14]. During execution of the protocol, any modifications made by the lead researcher will be reported in the subsequent publications.

Participants will be selected using a consecutive sampling method until a sufficient number of images are obtained to ensure robust training and validation of the artificial intelligence (AI) model. The inclusion criteria for this study require participants to be male patients younger than 18 years who have not undergone prior circumcision or penile surgery. Exclusion criteria include cases where adequate image quality cannot be obtained due to medical or technical constraints, as well as situations in which the patient's guardians do not provide consent for data collection or participation. These criteria ensure that the study includes a relevant patient population while maintaining ethical and methodological integrity.

Digital images will be captured from 3 angles—ventral, dorsal, and lateral—to provide a comprehensive view of the penile anatomy. Data collection will be performed upon agreement to participate by the patients' guardian by the attending physician.

Prior to capturing penile images, both general practitioners and the patient's guardians will be provided with a standardized reference illustration. This visual guide aims to minimize variations in camera angles across different perspectives, ensuring consistency in image acquisition. The standardization process is informed by established methodologies from previous research [15]. Examples of photographs of the penis structure are shown in Figure 1.

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Figure 1. Example of photographs taken for the (A) ventral aspect, (B) lateral aspect, and (C) dorsal aspect of the penis.

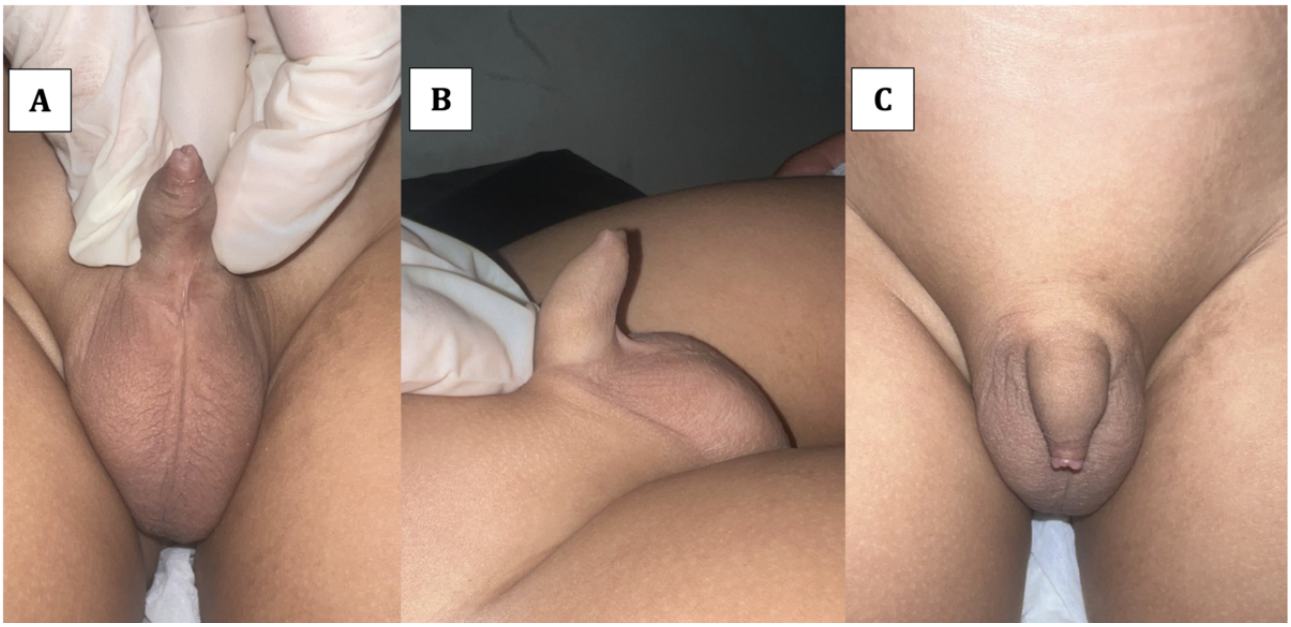

The collected images will undergo preprocessing to standardize dimensions and ensure uniformity. These images will be categorized according to the angle of the image taken. Duplicate images will be removed to avoid bias, and images will be resized to a standard dimension suitable for deep learning models. The annotated images will be categorized into 2 groups: those showing normal penile anatomy and those depicting abnormalities.

The AI model will be developed using advanced deep learning architectures including VGG16 [16], MobileNet [17], and DenseNet121 [18], selected for their effectiveness in medical image classification. The initial dataset will be split into training, validation, and testing subsets to facilitate model development and optimization. Data augmentation techniques will be used to enhance the training dataset by artificially increasing its size and diversity [19].

The AI models will be trained using the TensorFlow framework [20] and the Keras library [21], which offer streamlined processes for constructing, training, and validating deep learning models. Transfer learning will be used to overcome the challenges posed by a limited dataset, leveraging pretrained models to improve accuracy. Digital images from the collected dataset will be randomly categorized into training, validation, and testing data by a team of authors dedicated to developing the AI model. An external dataset will not be used in order to conform uniformity in the format of image taken.

Performance evaluation will be conducted using standard classification metrics, including accuracy, sensitivity, specificity, and F_1-score. AI-generated results will be compared against the clinical diagnoses documented in patients' medical records based on their physical examinations. Additionally, the functionality and usability of the mobile app will be assessed through user feedback, which will be collected and analyzed to identify areas for improvement. A web-based questionnaire developed by the authors will be distributed to urologists recruited to use the app. The questionnaire will consist of both open-ended questions and Likert scale items designed to assess user experience with the AI model and the mobile app. Participants will be recruited through web-based invitations sent to local urologists.

Upon completion of model development, the AI system will be integrated into a novel mobile app. This app will allow health care providers and guardians to capture and upload penile images, which will then be analyzed in real-time by the AI model. The system will provide immediate feedback on the presence of penile abnormalities, aiding in the decision-making process for circumcision eligibility.

Ethical Considerations

Ethical guidelines, as per the Declaration of Helsinki, will be strictly followed. The study protocol has received ethical approval from the Medical Research Ethics Committee at Universitas Indonesia (22-03-0310). Informed consent will be obtained from the guardians of all participants by the research team. Collected images will be anonymized and securely stored, ensuring privacy and confidentiality. Research databases will only be made accessible to authors. The identities of patients will not be revealed to AI model developers. Patients' identities are only kept by the physician performing the corresponding physical examination and capturing the photograph.

Results

The enrolment of study participants commenced in January 2023, while the development of the digital recognition system and mobile app began in January 2024. With adherence to this protocol, the study's findings are anticipated to be finalized by January 2026 and will be shared via publications.

Currently, the study has successfully pooled a total of 633 penis images, comprising 338 normal and 295 abnormal penis images. These images have been successfully integrated into 3 pretrained AI models. Although the current results are promising, we aim to further improve the model's accuracy before clinical

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implementation to ensure greater reliability and robustness. Thus, the next stage of the project involves both AI model refinement and AI model development testing. In this phase, we aim to further enhance the model's accuracy by expanding the dataset and experimenting with integrating various pretrained AI models. This phase is expected to take approximately 6 months, depending on the complexity of dataset expansion and model integration.

Simultaneously, we will initiate the model integration phase, embedding the AI model into our mobile app to evaluate its performance within the product environment. This phase is projected to last 3 months, allowing time for troubleshooting, bug fixes, and initial user testing within the app.

Upon successful integration, the project will progress to the model deployment testing phase, which will include comprehensive user testing to gather valuable feedback. This phase is expected to take 3 months to allow adequate time for user feedback, analysis, and necessary adjustments based on the findings. This feedback will guide our team in fine-tuning model integration and optimizing user experience, ensuring the product meets practical and clinical needs. In light of this, the project is expected to be completed by January 2026.

Discussion

Principal Findings

This study introduces an AI-driven digital pattern recognition system designed to detect penile abnormalities and assess circumcision eligibility. By leveraging deep learning methodologies and mobile technology, this research aims to enhance diagnostic accuracy and accessibility, particularly in resource-constrained settings [13,22]. The proposed system enables real-time analysis, providing immediate clinical decision support for health care professionals and guardians [23]. By addressing the limitations of traditional diagnostic approaches, this study has the potential to reduce missed or delayed diagnoses, thereby improving patient outcomes and health care efficiency [7,9]. In practice, these findings suggest that AI-assisted real-time examination could help screen patients before circumcision. If no penile abnormalities are detected, the patient would be deemed eligible and could safely proceed with the procedure.

Comparison With Prior Work

Existing literature has demonstrated the efficacy of AI in medical imaging across multiple disciplines, including dermatology, radiology, and ophthalmology [19]. However, research on AI applications within urology, particularly in evaluating circumcision eligibility, remains scarce [15,24]. Prior studies on digital health solutions for genital abnormalities have predominantly focused on telemedicine-based consultations rather than automated diagnostic tools [22,25]. This study builds upon previous advancements by introducing a novel, AI-based approach tailored specifically for penile abnormality detection [8,9]. Unlike conventional clinical evaluations that necessitate specialized expertise, the proposed system offers a scalable, cost-effective alternative that enhances diagnostic capabilities in low-resource settings [11,26].

Strengths and Limitations

A key strength of this study lies in its innovative application of AI for detecting penile abnormalities and assessing circumcision eligibility [13]. By integrating a digital image recognition system into a mobile platform, the proposed solution facilitates real-time decision-making and broadens access to specialized care [22,23]. Additionally, the study uses a structured methodological framework, incorporating robust data collection, preprocessing, and validation techniques to ensure model reliability and accuracy [19,27].

Despite these strengths, the study has certain limitations. The reliance on digital images captured by nonspecialists (ie, guardians) may introduce inconsistencies in image quality, potentially affecting the AI model's performance [7,9,26]. Furthermore, while data augmentation techniques are used, the dataset size remains a limitation, as deep learning models typically require large, diverse datasets to achieve optimal generalizability [19,28,29]. Ethical considerations related to image collection, data security, and patient confidentiality also pose challenges that must be meticulously addressed through stringent privacy measures and adherence to ethical research standards [14,23,27]. Future research should prioritize dataset expansion, enhanced image standardization techniques, and continuous validation to mitigate these limitations and improve model robustness [25,28,30].

Future Directions

To further refine the AI system, future research should explore advanced deep learning architectures and optimization strategies that enhance model accuracy and efficiency [13,19,29]. Expanding the dataset to encompass a wider demographic range will improve the system's generalizability and reliability [9-11]. Additionally, implementing an interactive feedback loop within the mobile app by enabling health care providers to verify and refine AI-generated diagnoses could strengthen its clinical applicability [7,10,11]. Investigating the integration of AI with complementary diagnostic modalities, such as ultrasound imaging, may further enhance the system's diagnostic precision [13,25,27]. Longitudinal studies evaluating real-world implementation and user experience will be crucial in ensuring the system's efficacy and scalability [22,23,30].

Dissemination Plan

The findings of this study will be disseminated through high-indexed Scopus, peer-reviewed journal publications and international conference presentations to engage the academic and medical communities. Collaboration with health care institutions, policymakers, and professional organizations will facilitate the implementation of the AI-based system in clinical practice [4,24]. Additionally, integrating AI-assisted decision-making tools into existing clinical workflows will be explored to enhance accessibility and user adoption among health care providers. By leveraging multidisciplinary partnerships and outreach strategies, this research aims to contribute to the broader advancement of AI-driven telemedicine and digital health interventions, ultimately improving patient care and clinical decision-making processes.

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Acknowledgments

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Data Availability

The datasets generated and analyzed during the current study are not publicly available due to ethical and privacy restrictions, as they contain identifiable clinical images of pediatric patients. Access to anonymized data may be made available from the corresponding author upon reasonable request and with approval from the Medical Research Ethics Committee of Universitas Indonesia, in accordance with institutional and national data protection regulations.

Conflicts of Interest

None declared.

Multimedia Appendix 1
User acceptance test questionnaire for the mobile app.
[DOCX File , 23 KB - resprot_v14i1e65811_app1.docx]

Multimedia Appendix 2
Peer-Review Report by Kementrian Riset Dan Teknologi/Badan Riset Dan Inovasi Nasional Deputi Bidang Penguatan Riset Dan Pengembangan (RISTEK-BRIN; Ministry of Research and Technology/National Research and Innovation Agency - Deputy for Strengthening Research and Development) (Jakarta, Indonesia).
[PDF File (Adobe PDF File), 431 KB - resprot_v14i1e65811_app2.pdf]

Multimedia Appendix 3
SPIRIT checklist.
[PDF File (Adobe PDF File), 90 KB - resprot_v14i1e65811_app3.pdf]

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Abbreviations

AI: artificial intelligence
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Clinical Utility of Early Intervention Including the 5-Step Precision Medicine Method in First-Episode Psychosis: Protocol for a Cohort Study With Nested Economic and Process Evaluations

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Abstract

Background: Psychotic disorders such as schizophrenia present a significant challenge to health care systems due to their high disability rates and treatment costs. With discontinuation rates for antipsychotics reaching over 40% in the first year and 80% after 3 years, it is crucial to tailor antipsychotic selection and dosing early in treatment. Personalized precision psychiatry, underpinned by pharmacogenetics, holds considerable potential in individualizing antipsychotic treatment for patients with first-episode psychosis. An internationally pioneering method called 5-step precision medicine (5SPM) focuses on the application of pharmacogenetics to clinical practice. The recently launched Prevention and Early Intervention in Mental Health (PRINT) program in Salamanca, Spain, integrates this method to enhance early intervention for adolescents and young people with first-episode psychosis.

Objective: The Clinical Utility of Early Intervention Including the 5SPM Method in First-Episode Psychosis (CLUMP) project aims to explore whether an early intervention model of personalized precision psychiatry including pharmacogenetics improves adherence to antipsychotic medicines and, therefore, clinical and functional outcomes in young people experiencing the first episode of a psychotic illness.

Methods: To achieve our objectives, we shall compare adherence to the first prescribed antipsychotic medication and clinical and functional outcomes between patients with first-episode psychosis. We shall compare 2 cohorts: cohort 1 will receive the recently introduced PRINT program including the 5SPM method, and cohort 2 will have received standard care provided by mental health services before the PRINT program implementation. The primary outcome to measure treatment adherence will be all-cause discontinuation proportions during the 1-year follow-up. Secondary outcome measures will include pragmatic efficacy, tolerability, and functional outcome measures. For additional comparative purposes, we shall analyze the environmental, clinical, and pharmacogenetic information of patients with psychotic disorders of more than 5 years of evolution and with other mental disorders whose data are currently stored and have been ethically approved for research use. A total of 300 patients will be included in the study. Analyses will include descriptive statistics, comparison tests, Kaplan-Meier survival curves, multivariate log rank tests, qualitative analysis, and cost-benefit evaluation.

Results: Ethics approval was obtained in June 2023. Recruitment for the CLUMP project began in January 2025, and enrollment for cohort 1 will continue until May 2026. All data collection is expected to be completed by June 2027. Data analyses are estimated to take approximately 6 months. The project is scheduled to conclude in December 2027.

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Conclusions: The CLUMP project is set to provide the first clear blueprint for implementing and evaluating the impact of personalized precision psychiatry based on pharmacogenetics in the context of early intervention programs for the benefit of young people experiencing the first episode of a severe mental illness such as schizophrenia.

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(JMIR Res Protoc 2025;14:e74408) doi:10.2196/74408

KEYWORDS

first-episode psychosis; early intervention; precision medicine; personalized precision psychiatry; antipsychotics; schizophrenia

Introduction

Background

Psychotic illnesses such as schizophrenia and related conditions are a major issue for public health care systems; they cause severe disability and are expensive to treat. As the illness becomes manifest during adolescence or young adulthood, nonspecific signs such as anxiety, depression, and emerging psychotic features form a prelude to the full psychotic syndrome that may last for months or even years before patients seek help or receive treatment. This duration of untreated psychosis is inversely related to outcome. Therefore, providing effective treatments as soon as possible, shortening the duration of untreated psychosis, may prevent the development of a more severe illness, improve quality of life, and lead to recovery in many cases [1,2]. Many people at an early stage of their psychotic illness, in addition to delusions or hallucinations, may develop cognitive problems that underpin disability. These impairments contribute to problems in functional outcomes that are considered by patients and their relatives to be as important as the phenomena that professionals focus on. Furthermore, the evolution of psychotic disorders varies hugely and raises the question of why certain people improve and others stay unwell despite having gone through similar interventions [1].

The development of specific psychological and pharmacological treatments to tackle first presentations of psychotic illnesses has been relatively slow. However, services to deliver existing evidence-based interventions to people at that early clinical stage have changed dramatically over the last 2 decades. Traditional multidisciplinary community mental health teams now work as specialized early intervention in psychosis teams. Seminal work, especially from Australia and the United Kingdom, has led to widespread adoption of these assertive treatment programs for young people in the initial phases of psychotic illnesses. In this context, rapid access and adherence to effective pharmacological treatments, specifically antipsychotics, play a fundamental role in “the shorter the DUP, the better the outcome” motto that early intervention in psychosis is predicated upon [1,2]. In fact, there is a plethora of evidence demonstrating that adherence to antipsychotic treatment has a positive impact on psychotic illness progression and longer-term outcomes such as hospital admissions, functioning, and suicide rates [3-5].

The introduction of early intervention programs has led clinicians toward a more accurate identification of the psychological and social interventions that each patient can benefit from; however, clinicians still face difficulties in selecting the antipsychotic medicine that better suits their patients [6-8]. Thus far, pragmatic randomized controlled trials have been the main source of scientific information to decide on the most effective and tolerable antipsychotics for patients with first-episode psychosis. These studies have found all-cause discontinuation rates for individual antipsychotics of approximately 40% or above during the first year of follow-up, which increases to 80% after 3 years of treatment even in the context of traditional early intervention in psychosis services [7,8]. These results fall short in terms of shifting clinicians’ trial-and-error approach to prescribing antipsychotics in clinical practice, which often ends in changes from those that do not yield sufficient therapeutic response or cause adverse effects [4]. This is further complicated by the fact that patients’ early experiences of antipsychotics nurture long-term perceptions of them; therefore, experiencing side effects or a lack of efficacy can make young individuals develop negative attitudes toward these drugs [9]. In fact, the high prevalence of adverse reactions in young, drug-naïve patients and lack of therapeutic response from antipsychotics are significant contributors to treatment discontinuation [9,10]. This stresses the need to tailor antipsychotic (and dose) selection to each patient from the very early stages of their psychotic illness.

While the use of pharmacogenetics (the effect of genetic factors on reactions to medicines) in people treated with antipsychotics has already found strong associations between treatment responses, side effects, and genetic variations, studies describing the clinical utility of pharmacogenetics are still very scarce and mainly limited to patients with severe and enduring psychotic disorders and poor response to treatment [11-13]. Notably, the systematic implementation of pharmacogenetics and its clinical effect on those experiencing the first episode of a psychotic illness has still not been tested. Personalized precision psychiatry using pharmacogenetics could help individualize antipsychotic treatment for patients with first-episode psychosis. It could reduce the time needed to find a tolerable and effective antipsychotic drug for people that were never exposed to such medications. Pharmacogenetics would simply be another tool that early intervention services could adopt and implement within their treatment pathways to improve medication adherence [13].

At the Salamanca University Healthcare Complex (CAUSA) in Spain, specifically in the Salamanca University Hospital (HUS), our unit of pharmacogenetics and precision medicine has been working on the application of pharmacogenetics to clinical practice for more than a decade [14]. We have developed an internationally pioneering method called 5-step precision medicine (5SPM) that addresses most of the implementation

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challenges outlined previously. The award-winning 5SPM model is based on updated scientific knowledge, integrating new technologies from up-to-date, highly efficient genotyping to state-of-the-art bioinformatics and artificial intelligence [13-17]. In fact, the 5SPM model is paving the way for the implementation of pharmacogenetics across different clinical specialties. In contrast to other existing methodologies, which are mostly guided by laboratory genetic results, the 5SPM method also addresses the specific needs and characteristics of the patient whom it is applied to, taking into consideration clinical and epidemiological variables as well as any other factor, such as polypharmacy, that could affect treatment response. Operationally, it is structured in the following five steps: (1) collection of clinical, epidemiological, and treatment data, including current prescriptions, diagnosis, and treatment response; (2) study of pharmacological interactions based on drug-specific pharmacokinetic pathways by processing databases such as the Pharmacogenomics Knowledge Base, PubMed–National Center for Biotechnology Information, Charite's SuperCYP-Transformer, and the Pharmacogene Variation Consortium; (3) pharmacogenetic analysis of the genes that code enzymes involved in drug-specific metabolism; (4) modification or introduction of pharmacotherapy according to the data obtained in the previous 3 steps; and (5) analysis of the treatment outputs and, depending on clinical evolution, reassessment if needed.

The 5SPM model relies on a multidisciplinary approach, implying that technical and clinical staff must work closely together, and strictly adheres to ethical requirements such as comprehensive informed consent. This method has already shown quantifiable positive impact on the quality of life of patients in different clinical fields, including psychiatry. Since its inception, more than 1000 patients have benefited from it, and it has also generated additional phamacogenetics knowledge [13,16,18]. This is corroborated by a significant scientific body of evidence supporting the effectiveness and cost-efficiency of this method in real-world settings when compared to treatment as usual. The 5SPM approach has been successfully implemented in diverse psychiatric populations, including individuals with chronic psychotic disorders, bipolar disorder, and complex multimorbid presentations involving polypharmacy [13-19]. Clinical protocols guided by the 5SPM approach integrate pharmacogenetic data—particularly cytochrome P450 (CYP450) genotyping—with a patient's clinical, pharmacological, and biological history to optimize treatment selection. In patients with poor response to antipsychotics, this approach has identified high rates of gene-drug and drug-drug interactions, allowing for targeted therapeutic adjustments that significantly reduced polytherapy and daily dosages, thereby lowering the risk of adverse effects and enhancing adherence [13]. Moreover, in broader psychiatric cohorts, pre-emptive pharmacogenetic testing has shown utility in preventing affective switching in bipolar disorder and mitigating side effects associated with selective serotonin reuptake inhibitor treatment based on cytochrome P2D6 and P2C19 metabolizer status [18]. These interventions have not only improved clinical outcomes but also demonstrated economic value, with cost-benefit ratios exceeding 3:1 in some studies and consistent reductions in hospitalization and treatment costs across patient groups [19]. Collectively, these findings support the clinical scalability of the 5SPM approach and its potential to enhance safety, efficacy, and cost-efficiency in precision psychiatry.

Objectives

We have fully integrated the 5SPM method into our recently launched Prevention and Early Intervention in Mental Health (PRINT) program and shall evaluate its impact. The PRINT program is a novel clinical service that aims to provide early, comprehensive care to adolescents and young adults experiencing first-episode psychosis in Salamanca. This is one of only a few services of this kind in Spain, where early intervention is still not widespread. Considering that there is still a marked heterogeneity in treatment engagement and response among patients with first-episode psychosis in early intervention services worldwide [20], the PRINT program is refreshing the early intervention model by optimizing pharmacological choices for such a clinical group following the 5SPM methodology. Thus, the Clinical Utility of Early Intervention Including the 5SPM Method in First-Episode Psychosis (CLUMP) project aims to explore whether an early intervention model of personalized precision psychiatry including pharmacogenetics improves adherence to antipsychotic medicines and, therefore, clinical and functional outcomes in young people experiencing the first episode of a psychotic illness.

We hypothesize that integrating the 5SPM method into PRINT will significantly improve adherence to antipsychotic treatment and, consequently, enhance both clinical and functional outcomes.

The CLUMP project's objectives will be to (1) introduce an innovative early intervention model of personalized precision psychiatry including the 5SPM method for patients with first-episode psychosis; (2) ascertain whether such a model can reduce the elevated discontinuation rates of antipsychotic medications among this group within the first year of follow-up by clinical services; (3) assess the impact of the new model on pragmatic efficacy measures such as hospital admissions and functional outcomes such as return to work or education; (4) determine whether this innovation can bring cost benefits to the public health care system and the wider economy; and (5) establish a blueprint for implementing this precision medicine model, specifically pharmacogenetics, across early intervention in psychosis programs nationally and internationally.

Methods

Study Design

To test our hypothesis and achieve our objectives, we shall compare adherence to the first prescribed antipsychotic medication and pragmatic clinical and functional outcomes between 2 cohorts of patients with first-episode psychosis. One cohort will comprise patients treated before the implementation of an early intervention in psychosis model of personalized precision psychiatry, including pharmacogenetics, and the other will comprise patients treated under this new model. In addition, we shall compare the pharmacogenetic profiles and possible phenocopies (variations of phenotypes produced

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environmentally, eg, due to polypharmacy, rather than genetically) between these patients with first-episode psychosis and a national sample of patients with longer-term psychotic disorders or other mental health conditions to evaluate potential implications for clinical management at different stages of a psychotic illness and across mental disorders.

Participants

A total of 300 patients will be included in this project. We shall include 2 different cohorts. Cohort 1 will be a prospective sample of patients with first-episode psychosis referred over 18 months to the new early intervention in psychosis program of personalized precision psychiatry (PRINT) at CAUSA. Cohort 2 will be a retrospective, consecutive (in reverse chronological order as registered in the CAUSA electronic health records) sample of patients who experienced a first episode of psychosis before the implementation of PRINT.

Inclusion and exclusion criteria for both cohorts will be aligned with the PRINT program referral acceptance criteria, which are predominantly inclusive.

Inclusion criteria are as follows: patients (1) with a diagnosis of first-episode psychosis, either nonaffective or affective; (2) aged 12 to 35 years; and (3) followed by clinical services for at least 1 year or earlier if there was evidence of antipsychotic treatment discontinuation (see the Outcome Measures section). In addition, patients in cohort 1 or their family or legal representatives will have to provide written consent to take part in the CLUMP project, including pharmacogenetics analysis (see the Ethical Considerations section). For patients in retrospective cohort 2, this will not be an inclusion criterion, but all of them will be approached by our research team seeking their consent to obtain their pharmacogenetic profile for research purposes.

Exclusion criteria are as follows: patients (1) with first-episode psychosis due to organic causes, for example, brain diseases such as Huntington or Parkinson disease, HIV, syphilis, dementia, brain tumors or cysts, or brain injury; (2) with moderate to severe intellectual disability; and (3) who spent (cohort 2) or plan to reside during (cohort 1) most of the 1-year follow-up period in a locality out of the PRINT program's catchment area.

For additional comparative purposes, we shall analyze the environmental, clinical, and pharmacogenetic information of patients with psychotic disorders of more than 5 years of evolution or with other mental disorders whose data are currently stored and have been ethically approved for research use in our unit of pharmacogenetics and precision medicine at the HUS.

Clinical Management and Pharmacogenetics Analysis

Patients in cohort 1 will receive the recently introduced PRINT program, an early intervention in psychosis model, including the 5SPM method based on pharmacogenetics developed by our unit of pharmacogenetics and precision medicine at the HUS. As mentioned previously, the 5SPM method includes five steps: (1) collection of clinical, epidemiological, and treatment data; (2) study of pharmacological interactions based on drug-specific pharmacokinetic pathways; (3) pharmacogenetic analysis of the genes that code enzymes involved in drug-specific metabolism; (4) introduction of or change in pharmacotherapy according to the data obtained in the previous 3 steps; and (5) analysis of the treatment outputs and reassessment if needed. These steps will be preceded by an informed consent process. This preliminary procedure plus steps 1 to 4 will be conducted as soon as possible, ideally when a patient with a first episode of psychosis is identified by clinical services, aiming to minimize the time between the initial presentation and pharmacogenetics-informed decisions on pharmacotherapy. Step 5 (treatment review) will be carried out 6 months after antipsychotic treatment initiation. All steps will require a multidisciplinary approach and a shared decision-making process including patients or their family or legal representatives, especially if the patient lacks the mental capacity to make such decisions.

For the pharmacogenetics analysis (step 3), we shall use mass spectrometry and real-time polymerase chain reaction to study the genes encoding enzymes 1A2, 2B6, 2C9, 2C19, 2D6, 3A4, and 3A5 of the CYP450 family, in addition to transporter ABCB1. The CYP450 superfamily contains highly polymorphic genes. The usual approach to the relationship between genotypic variability and the metabolism of CYP450 substrates is based on the definition of metabolic phenotypes with their characteristic pharmacokinetic implications according to different genetic mechanisms. Metabolic profiles will be considered to make decisions on antipsychotic treatment choices. We already have enough technical support and pharmacogenetics evidence for most antipsychotics used in the early stages of a psychotic illness (ie, olanzapine, risperidone, paliperidone, quetiapine, aripiprazole, amisulpride, lurasidone, cariprazine, haloperidol, and zuclopenthixol).

Cohort 2 will have received standard care provided by mental health services before the PRINT program implementation, specifically by mental health professionals working in generic community mental health teams that offer assessment and treatment to people who reside in their geographical catchment areas and experience a wide range of mental disorders, not only psychotic disorders.

Patient and Public Involvement

Patients have been involved in the design and will participate in the delivery of this trial. For instance, patients with first-episode psychosis were consulted on the feasibility of running this project, and some of them were involved in its design, specifically on what information to include in the informed consent form to carry out the pharmacogenetics analyses. In addition, we shall constitute a CLUMP patient and carer advisory group, which will also contribute to the identification of themes for the qualitative evaluation (see the Qualitative Evaluation section).

Outcome Measures

Primary Outcome Measure

The primary outcome to measure treatment adherence will be all-cause discontinuation of the initially prescribed antipsychotic medication following the patient's or treating clinician's decision. All-cause discontinuation rates in the CLUMP project

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will be defined by all-cause discontinuation proportions during the 1-year follow-up and the mean time to such discontinuation.

For cohort 1, the 1-year follow-up period will start when an antipsychotic medication is prescribed taking into consideration the pharmacogenetics advice emerging from the 5SPM method. For cohort 2, follow-up would begin on the date when the first antipsychotic medication was prescribed. For both cohorts, the first prescribed antipsychotic will be the initially prescribed antipsychotic drug for maintenance treatment, not only for short-term use to control psychomotor agitation. In addition, in accordance with existing scientific consensus, the discontinuation date will be defined as the first day of a 2-week or longer interruption of the first prescribed antipsychotic. In cohort 2, treatment discontinuation dates will be determined by examining clinical records. Where only approximate dates are available, the first, middle, or final day of the month will be used as best estimates. In cases in which cross-titration of medication took place, the date of discontinuation will be the first day of the cross-tapering process.

All-cause discontinuation will also be stratified by 4 reasons: insufficient efficacy, adverse events, lack of adherence, and other. Insufficient efficacy will be established at the treating clinician's judgment only after at least 3 weeks of treatment. If more than one reason for discontinuation was present, we shall select one by applying the ranking order as stated previously.

Secondary Outcome Measures

We shall also collect pragmatic efficacy, tolerability, and functional outcome measures in both cohorts. These will include evaluations during the follow-up period regarding hospital admissions; visits to accident and emergency departments and outpatient clinics; changes in and number of medications; changes in antipsychotic dose over time; use of chlorpromazine dose equivalents as reference; type and number of side effects, including impact on BMI; and initiation or return to work or academic activities.

As part of routine practice, patients in cohort 1 will also be assessed using the quality-of-life self-completion questionnaire EQ-5D-5L to determine overall improvement over time. Scores from this questionnaire will also feed into the 5SPM step 5 to make treatment decisions at month 6. This cohort will also be evaluated using a battery of questionnaires, including the Positive and Negative Syndrome Scale [21], Calgary Depression Scale for Schizophrenia [22], Brief Negative Symptom Scale [23], and Udvalg for Kliniske Undersøgelser Side Effect Rating Scale [24].

Effect and Sample Size

We conducted a power calculation for the main outcome: the proportion of patients with first-episode psychosis who, by their treating clinician's or their own decision, discontinue, for any reason, the first prescribed antipsychotic medication within 1 year. As stated previously, recent research studies, mostly carried out in early intervention settings, concur that 40% of patients with first-episode psychosis experience first prescribed antipsychotic drug discontinuation during the first year following treatment initiation [7,8]. This proportion may be even higher in patients receiving mainstream psychiatric care, such as our cohort 2. Considering the expectations behind the use of personalized precision medicine, PRINT should aim to reduce discontinuation rates to 10%. Therefore, for a power of 80% with (1) a significance level of .05 (2-sided), (2) all-cause discontinuation rate in cohort 1 (intervention) of 0.4, (3) all-cause discontinuation rate in cohort 2 (treatment as usual) of 0.1, and (4) an expected dropout or loss to follow-up rate of 0.2, our calculations would require a sample size of at least 38 patients in each cohort. We used the R statistical software *pwr* package for this calculation (version 4.4.2 for Windows; R Foundation for Statistical Computing).

In CAUSA, we have found an administrative incidence of 50 new patients aged 12 to 35 years every year. Thus, we would expect at least 75 patients eligible to be recruited for cohort 1 over 18 months. Using a conservative approach, if 25 patients (approximately 35%) do not agree to take part, we would still enroll 50 patients. This would be in addition to another 50 patients in our retrospective cohort 2 and pharmacogenetic data currently available at CAUSA from 100 patients with psychotic disorders of more than 5 years of evolution and another 100 patients with other mental disorders that we shall use for further comparative purposes, as outlined previously. This all accounts for a total of 300 participants contributing to this project.

Statistical Analysis

Comparisons of the main outcome (ie, discontinuation rates) will be carried out using the chi-square test. Kaplan-Meier survival curves and multivariate log rank tests will be used to assess time to all-cause antipsychotic discontinuation. For these analyses, patients will be followed up on for a year, from antipsychotic treatment initiation until discontinuation. Thus, we shall censor survival time by the end of the 1-year observation period or before such date if there is enough evidence of antipsychotic discontinuation. We shall describe and compare sociodemographic information and clinical and functional outcomes within and between groups. Means and SDs will be used to describe quantitative variables. We shall use the chi-square test or Fisher exact test for categorical variables and Mann-Whitney *U* test for continuous variables, among others. Data analyses will be conducted using the R statistical software (version 4.4.2 for Windows).

Qualitative Evaluation

We shall aim to interview 15 patients from cohort 1 to obtain their views on the PRINT program, specifically on the implementation of the 5SPM method. We shall recruit participants who complete the 1-year follow-up but also some who might withdraw from treatment before then. In principle, the interviews will explore the following thematic questions: (1) To what extent the goals of personalized precision psychiatry based on pharmacogenetics were aligned with the patients' own goals? (2) Did the PRINT program help in achieving their goals, what did not, and why? (3) Is there anything that could have been performed differently during the informed consent and 5SPM processes? (4) What might have contributed to nonengagement and treatment discontinuation? (5) What would help them meet their goals and priorities better and why?

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As stated in the Patient and Public Involvement section, the CLUMP patient and carer advisory group will also contribute to the identification of additional themes for the qualitative evaluation.

Sampling will be purposive, with quota stratification by gender and clinical background, to enhance transferability through thick description of participant characteristics and context. The CLUMP project team will also be interviewed to characterize their perspectives on implementing the new model and triangulate experiences of model implementation. An independent researcher trained in qualitative methods will conduct all the interviews, which will be audio recorded and transcribed verbatim. Data analysis will be based on the constant comparative method [25]. This will involve intensive engagement with the data using comparison across datasets to generate higher-order themes with explanatory value. An audit trail—including coding logs, analytical memos, and interview minutes—will be maintained to support dependability and confirmability of findings. To strengthen credibility, this study will use data triangulation (patients and professionals), peer debriefing within the research team, and member checking with the patient and carer advisory group [26,27]. The NVivo software (QSR International) will be used to assist in coding the data.

Economic Evaluation

We shall explore cost-benefit using the primary outcome measure: all-cause discontinuation. The time horizon will be 1 year after antipsychotic initiation for both cohorts. Costs and outcomes will be compared at the final follow-up point and presented as mean values with SDs by cohort. The costs will be estimated using service use data. We shall collect these data using an adapted Spanish-language version of the Early Intervention Adult Service Use Schedule [28], which contains costs that are easy to track and calculate in the Spanish health system. The Early Intervention Adult Service Use Schedule will be completed for both cohorts. This measure covers the use of all health and social care services over 12 months (with an interim collection at 6 months), as well as sociodemographic information and employment status. In cohort 1, we shall also conduct a cost-utility analysis using quality-adjusted life years derived from the EQ-5D-5L.

Data Management

Data collected for the CLUMP project will be narrative and numeric and will be obtained from interviews, review of clinical records, and blood tests. They will include sociodemographic information; pragmatic outcome measures; questionnaires to measure efficacy, functioning, and tolerability; and pharmacogenetic information.

As with all clinical data, the findings of this study will be kept confidential to protect personally identifiable information. To ensure that all information collected about participants remains confidential, we will only use anonymized participant information. Codes linking the identity of the participants to clinical data will be stored on a secure password-protected database. Personal data needed to contact the participants will be securely stored on a separate database. Only the project team and professionals working at the clinical services that the individuals are recruited from or at the unit of precision medicine and pharmacogenetics at the HUS will have access to the participants' personal data. Only nonidentifiable participant data will be transferred to a central database for the project, and only nonidentifiable information will be made available to any other researchers or collaborators involved in the study. All data will be encrypted and stored in secure databases on a secure network using established procedures. All study personnel will have to be certified to conduct research involving human participants and will be aware of the importance of maintaining strict confidentiality. Clinical notes will not be accessed by those outside the direct health care team, which includes members of the research team, until consent from participants is in place. Any hard copies of all data and records, including consent forms, will be stored in locked filing cabinets in locked rooms in security-protected buildings. Electronic and hard copies containing data from the project will be stored at CAUSA buildings and electronic facilities for a minimum of 10 years in accordance with good research practice. The storage of blood sample leftovers will be addressed in accordance with the informed consent form signed by the patients and current legislation.

The final responsibility over the use of personal data will rest with the Specialized Clinical Assistance Managerial Office at CAUSA, and the data protection officer at the Regional Ministry of Health will be contactable by all personnel involved and research participants. All data processing will be subject to the Spanish Organic Law 3/2018 for personal data and digital rights protection and the European Union General Data Protection Regulation 2016/679. General Data Protection Regulation articles 6 (on lawfulness of data processing) and 9 (on processing of special categories of personal data, such as genetic information) will be particularly relevant for this project. In addition, participants will have the right to have access to and rectify their data or, eventually, limit or oppose their use under the terms included in articles 15 to 23. They can execute these rights before the principal investigator for this project and the data protection officer. Participants will be informed that they can also present complaints with regard to the use of their data to the Spanish Agency of Data Protection.

Ethical Considerations

Approval for this project was obtained from the Ethics Committee for Research With Medicines of the Salamanca Health Area (reference PI 2023 06 1308) on June 24th 2023. Written informed consent will be obtained from all participants and their legal representatives to ensure that they understand the study requirements, risks, and benefits. If potential participants accept an invitation to participate in the study, they will be provided with a participant information sheet and consent form for consideration and sign off. There will not be economic compensation for participating in the study.

Results

Recruitment for the CLUMP project began in January 2025, and enrollment for cohort 1 will continue until May 2026. All data collection is expected to be completed by June 2027. Data

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analyses are estimated to take approximately 6 months. The project is scheduled to conclude in December 2027. Figure 1 provides a schematic Gantt chart for the project, including timelines for each task.

Figure 1. The Clinical Utility of Early Intervention Including the 5-Step Precision Medicine (5SPM) Method in First-Episode Psychosis (CLUMP) project Gantt chart.

Discussion

Expected Findings

The CLUMP project aims to improve the adherence and outcomes of patients with first-episode psychosis through the implementation and evaluation of an innovative early intervention program of personalized precision psychiatry based on pharmacogenetics.

To date, the uptake of pharmacogenetics testing in psychiatry has been limited to very few contributions and mainly focused on affective disorders such as depression [6,11]. This is at odds with strategies worldwide planning to implement precision medicine as part of policies to enhance the uptake of genomic-driven medicine, including in psychiatry. For instance, the UK National Health Service has set up the Genomic Medicine Service with the aim of making pharmacogenetics part of routine clinical practice. Recently, the Royal Dutch Association for the Advancement of Pharmacy, Dutch Pharmacogenetics Working Group, and Clinical Pharmacogenetics Implementation Consortium have developed evidence-based pharmacogenetics prescribing guidelines, which are compiled in the Pharmacogenomics Knowledge Base and rated by gene-drug pairing level of evidence, ie, how confident we are that a person's genetic variation affects their response to a specific drug [6,11,29,30]. These guidelines include antipsychotics and recommend that clinicians consider genotyping of patients who experience inefficacy or side effects from any of the drugs that have enough pharmacogenetic evidence. This information could then be used to personalize prescribing decisions. Pharmacogenetics in psychiatry has mainly focused so far on pharmacokinetics, and there is consensus that genetic information related to enzymes of the CYP450 family, such as cytochromes P2D6 and P2C19, can be used to provide treatment advice. In fact, it is estimated that between 36% and 62% of the population have variants of these 2 isoenzymes that may modify the metabolism of psychiatric medications [6,31]. However, although current pharmacogenetics guidelines are used by an increasing number of mental health professionals, they do not take polypharmacy into consideration, and their full integration into mental health care is still a worldwide challenge [6].

Even though patients and clinicians perceive the value of pharmacogenetics in mental health and the potential positive impact on patients' engagement with and trust in both the prescribed medication and the prescriber, certain barriers preclude its successful implementation. For instance, mental health professionals feel that they lack pharmacogenetics theoretical and practical knowledge (ie, how to make use of it as part of their practice) and have concerns about how to integrate it within their workloads without increasing consultation times or delaying treatment decisions for too long. They worry about this genetic information replacing clinical judgment or the risk of misinterpretations by mixing up the strength of drug-gene interactions with overall drug effectiveness and not paying enough attention to other important environmental and biological factors that play a role in treatment response. In addition, this innovation is not free of ethical considerations, such as the potential psychological consequences of disclosing pharmacogenetics results to patients or matters related to genetic privacy. Furthermore, research studies have rarely measured the clinical effects or cost-benefit associated with pharmacogenetics application, and existing guidelines mostly advise on the pharmacogenetics of individual drugs without considering the common use of polypharmacy in clinical practice [6,11]. This all reflects, to a large extent, the lack of clear methodologies to embed and measure the impact of pharmacogenetics in day-to-day psychiatric practice.

Therefore, the problem that we strive to solve is cultural, linked to prevailing trial-and-error prescribing of antipsychotics in clinical practice, as well as structural, concerning the evidence-policy-practice gap for tailoring drug treatments to patients with psychotic disorders at the earliest opportunity. Nonetheless, our new joint venture of early intervention in psychosis and applied precision medicine, combined with our previous experience using the 5SPM method for patients with mental disorders, should give us scientific and logistic traction

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to achieve our aims. Indeed, a guided implementation of pharmacogenetics for real-world clinical settings following the 5SPM methodology could help overcome patients' and clinicians' uncertainties and facilitate the use of this evidence-based innovation not only to address poor response to or adverse events from psychiatric medications in patients with established psychotic disorders but also to promote personalized and pre-emptive drug prescription [11]. The CLUMP project should be able to provide the first clear blueprint for implementing and evaluating the impact of personalized precision psychiatry based on pharmacogenetics in the context of early intervention programs for the benefit of young people experiencing the first episode of a severe mental illness such as schizophrenia.

Limitations

As we will carry out the CLUMP project in 1 center, this might affect the generalizability of our results. Nevertheless, Salamanca has a university that attracts more than 40,000 students within our participants' age range every year and is a province with a diverse young population, some of them living in socially deprived areas. These characteristics will temper this limitation. On the other hand, given our project's originality, we considered it important to test our hypothesis in a relatively circumscribed location and, later, move toward its implementation at scale. In addition, our prospective cohort 1 may be affected by a status quo bias (ie, attempts to maintain pharmacogenetically guided prescription despite lack of efficacy or presence of adverse events). This will be controlled through other pragmatic outcome measures and the 5SPM step 5 at month 6, which will include questionnaires such as the EQ-5D-5L to inform treatment maintenance or change.

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Authors' Contributions

JP, MIG, CTG, DHJ, BGB, CLR, and CMG were involved in conceptualization and funding acquisition for this project. MIG, JP, OG, CGC, PSA, and AdlSP participated in the development of materials for data collection. MIG, DHJ, BGB, SLH, and EMV designed and decided on laboratory methodologies and technical support. JP, CGC, PSA, RGG, VBM, AMC, BRM, BBB, LGU, CLR, and CMG developed the strategy for clinical evaluations and will support all clinical aspects of this study. JP and MIG wrote the first draft of the manuscript. OG reviewed and completed this draft. All authors reviewed and contributed to the final version of the manuscript. JP and MIG will supervise this project.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from Carlos III Health Institute (Instituto de Salud Carlos III), General Subdirectorate of Evaluation and Research Promotion, Ministry of Science and Education, Spain.
[PDF File (Adobe PDF File), 4173 KB - resprot_v14i1e74408_app1.pdf]

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Abbreviations

5SPM: 5-step precision medicine
CAUSA: Salamanca University Healthcare Complex
CLUMP: Clinical Utility of Early Intervention Including the 5-Step Precision Medicine Method in First-Episode Psychosis
CYP450: cytochrome P450
HUS: Salamanca University Hospital
PRINT: Prevention and Early Intervention in Mental Health

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Protocol

Clinical Performance Evaluation of an Artificial Intelligence–Based Tool for Predicting the Presence of Obstructive Coronary Artery Disease: Protocol for a Cohort Observational Study

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Abstract

Background: A significant number of individuals undergoing coronary computed tomography angiography (CCTA) for suspected (CAD) have nonobstructive or no CAD. There is a need for clinically proven models that can predict the pretest probability of stable CAD and help to identify low-risk individuals. Optimizing patient stratification is of paramount importance to improve diagnostic yield and cost-effectiveness.

Objective: We aimed to determine whether each patient needs to undergo CCTA because of suspected CAD. The main objective of this study is to evaluate the clinical performance of an artificial intelligence (AI)-based tool in predicting significant coronary artery stenosis (>50%), as well as its utility by medical professionals.

Methods: Data for this study have been acquired from 750 participants as part of routine clinical practice in AHEPA (American Hellenic Educational Progressive Association) General Hospital of Thessaloniki. The dataset has several features, including demographics (eg, age, gender), medical history (eg, diabetes mellitus, arterial hypertension), and clinical variables (eg, creatinine, epicardial fat volume). At least 2 expert cardiologists and 2 expert radiologists are involved in this study, who provide the ground truth. A trained AI-based model embedded in an easy-to-use and user-friendly web application is implemented in practice. Several AI algorithms are being examined, and the model found to perform best so far is the Optimized Voting model, which is a combination of the best performing iterations of random forest and extreme gradient boosting. The performance metrics that are being used are accuracy, precision, recall, F_1-score, area under the receiver operating characteristic curve, and area under the precision-recall curve.

Results: Recruitment for this study began in July 2023. Data collection, development, training, and deployment of the AI web tool were completed by May 2024. In total, data from 500 individuals were collected for training and internal validation, while the best performing model was validated externally in another 250 individuals. For training and internal validation, the dataset was split into 70% for training and 20% for validation and 10% for testing. Currently, the best performing model achieves an accuracy of approximately 82% in successfully predicting stenosis greater than 50%. Additionally, an explainable AI algorithm is used to provide explanations in relation to the decisions made aiming to increase the trust of the clinicians in the tool.

Conclusions: The proposed study represents a novel approach of a web-based AI-driven solution with explainability features for optimizing patient stratification with the goal of improving diagnostic yield and cost-effectiveness of CCTA utilization within the context of cardiology clinical practice.

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KEYWORDS

coronary computed tomography angiography; CCTA; CAD; coronary artery disease; cardiology; stenosis prediction; AI; protocol; ML; machine learning; artificial intelligence

Introduction

Background

A conventional routine in clinical practice over the years has been to employ validated diagnostic models of the pretest probability (PTP) of stable, albeit obstructive, coronary artery disease (CAD) [1] in order to direct downstream testing. After the first screening, adults with suspected CAD with existing symptoms and low-to-intermediate PTP undergo coronary computed tomography angiography (CCTA) [2], including calcium scoring.

Most existing models have modest performance (with remarkable overestimation of risk in certain subgroups such as women), while very few studies have data regarding the effect of PTP-based models on clinical decision-making regarding further testing or patient outcomes [3]. The European Society of Cardiology clinical practice guidelines for the management of stable chest pain congruently suggest CCTA as a first-line diagnostic option in symptomatic cases, which are thought to have a low-to-intermediate pretest odds of being diagnosed with obstructive CAD [4]. Specifically, suspected cases during their checkup routine or individuals with suspected CAD undergo a computed tomography (CT) scan with coronary artery calcium scoring, along with other examinations and finally CCTA to obtain the final diagnosis. Results evaluation (laboratory results, CCTA analysis, coronary artery geometric features, coronary artery calcium score, etc) is based exclusively on the treating cardiologist's experience. In case of suspected coronary heart disease, patients might receive further, more extensive, but possibly unnecessary examinations such as invasive coronary angiography or single-photon emission CT, which last up longer tying up hospital resources, increase patients' radiation exposure, and may have adverse effects.

However, in day-to-day clinical practice, a significant number of individuals undergoing CCTA have minimal or no CAD. As a direct consequence of the expanding use of CCTA, there is a growing interest within the medical community regarding ways to optimize patient stratification with the goal of improving diagnostic yield and the cost-effectiveness of CCTA utilization within the context of clinical practice. Hence, there is a need for clinically validated models that can predict the PTP of stable CAD and as a result function as gatekeepers to identify low-risk individuals who are unlikely to have obstructive CAD and unlikely to need further diagnostic testing, including CCTA. Such models can be based on powerful machine learning (ML) algorithms that have already proven effective in several health care–related problems [5].

Objectives

In the context of this study, an artificial intelligence (AI)-based predictive model integrated into a web application was developed. Patients' clinical results and variables extracted from the screening procedure in combination with demographics, medical history, social history, and other medical data were entered into the application, which indicated, with an accuracy of at least 70%, whether each individual has over 50% stenosis, which leads to the need to undergo CCTA, including calcium scoring, because of suspected CAD. The specific objectives of the study are listed below.

Primary Objective

The primary objective of this study was to evaluate the clinical performance of the AI-based tool developed, which was measured as the percentage of successful predictions, confirmed by experienced medical staff.

Secondary Objective

The secondary objective was to evaluate the professionals' satisfaction regarding the AI-based tool based on the feedback after its use.

Methods

Study Environment

The data for this study were collected from individuals visiting the cardiology outpatient clinic of AHEPA (American Hellenic Educational Progressive Association) General Hospital of Thessaloniki, Greece.

Framework

The main portion of this study was conducted during the pilot phase of the "Hospital Smart development based on AI - HosmartAI" project [6], which falls under the Horizon 2020 initiative and has received funding from the European Commission (grant 101016834). The HosmartAI project ran from January 2021 to May 2024 and aimed to transform health care by integrating AI and robotics. It brought together 24 partners from 12 countries to develop the HosmartAI Hub, an open platform supporting AI-driven solutions through tools like a marketplace and benchmarking functionalities. Through 8 pilots across various medical domains, the project improved diagnosis, treatment, and care delivery, fostering a more efficient and sustainable health care ecosystem in Europe.

Participants

Data were acquired from 750 individuals (500 for algorithm training and testing and 250 during the external validation) as part of routine clinical practice in AHEPA General Hospital of Thessaloniki. At least 2 expert cardiologists and 2 expert

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radiologists were involved in this study, who provided the ground truth.

Inclusion Criteria

Individuals eligible for data collection met the following criteria: (1) age ≥18 years and (2) individuals experiencing chest pain who underwent CCTA to exclude obstructive CAD.

Exclusion Criteria

Individuals were excluded if they refused to give written consent to participate in the study.

Data Collection Plan

Study participants visiting the AHEPA General Hospital of Thessaloniki for examination and deemed eligible for data collection by the collaborating medical team were invited to participate in this study. Enrollment in this study and data acquisition were performed on the same day. Study participants first reviewed the study information sheet and then gave informed consent. Once consented, they were assigned a coded ID number. Afterwards, basic demographics, medical history, social history, prior laboratory results, and other medical variables formerly indicated by the medical staff were recorded linked with the participant's ID. CCTA outcome (actual scan file and analysis variables) acquisition followed based on standard clinical practice. At the end of the study, data on the satisfaction of the participating health care professionals were also collected.

Ethical Considerations

During the consent process, study participants are duly informed about their rights concerning the collected data as per the guidelines laid out in the General Data Protection Regulation and Greek law (4624/2019). Each participant provided written consent after gaining a comprehensive understanding of the procedures involved. The investigator or a member of the study staff thoroughly explained the consent forms and procedures, including the study's objectives, methodologies, potential benefits, and risks. Before enrolling into the study, the individuals signed these consent forms, indicating their voluntary participation. They were explicitly informed that they retain the option to withdraw from the study at any time without affecting their treatment care. Ample time was provided for participants to review the study information and consent form and seek clarifications, if needed. Additionally, upon signing the informed consent document, each participant received a copy for their records. Data were anonymized before being used. No compensation was given to the participants. This study was submitted and approved by the Research Ethics and Conduct Committee of the Aristotle University of Thessaloniki (94517/2022).

Data Management

All CCTAs were performed at the AHEPA General Hospital of Thessaloniki by experienced cardiologists using the hospital's equipment. Study personnel of the AHEPA General Hospital of Thessaloniki were responsible for the proper management of data stored at the hospital. All data, including the professionals' satisfaction results, were stored in a dedicated, password-protected computer of the AHEPA General Hospital of Thessaloniki, with limited access. Study hard copy documents, including signed informed consent documents, were kept in locked cabinets with limited access.

Access to Data

Investigators from the First Department of Cardiology, the Laboratory of Radiology and Radiodiagnostics, and the Laboratory of Medical Physics and Digital Innovation of AUTH who are authorized by the principal investigator were given access to the acquired, deidentified data sets, to ensure participant confidentiality. In case of data transfer over a computer network, this took place through safe processes, and data were stored in secure digital structures with limited access.

In the context of research reproducibility, completely deidentified datasets could be published to one or more data repositories for sharing purposes, accompanied by an appropriate license that were agreed among the First Department of Cardiology, the Laboratory of Radiology and Radiodiagnostics, and the Laboratory of Medical Physics and Digital Innovation of AUTH, in accordance with FAIR (Findable, Accessible, Interoperable, and Reusable) principles.

Study participants have access to the data they contributed to the study, in compliance with the respective mandate of the General Data Protection Regulation. Participants are also able to request for their data to be deleted. Instructions for requesting, receiving, or deleting data are included in the study information sheet. The professionals' satisfaction results were collected anonymously at first hand.

Data Analysis

In the process of data analysis, ML algorithms were studied, reviewed, and tested for highest accuracy. Specifically, the random forest [7], extreme gradient boosting (XGBoost) [8], Bagging [9], and Optimized Voting algorithms were considered and tested. Random forest is an ensemble method that constructs numerous decision trees during training and merges their outcomes to enhance accuracy and reduce overfitting. XGBoost is an advanced gradient boosting algorithm known for its efficiency and performance on structured data, capable of handling missing values and reducing overfitting. Bagging is an ensemble technique that improves the stability and accuracy of ML algorithms by training multiple models on different subsets of the data and combining their predictions. Optimized Voting is a method that aggregates the predictions of several models to make a final decision, aiming to achieve superior performance compared to any single model. Hyperparameters for each model were fine-tuned using Bayesian optimization [10]. Moreover, given that interpretability is crucial in clinical applications to allow health care professionals to understand the reasoning behind model predictions, SHAP (Shapley Additive Explanations) [11] was employed for this purpose.

Training, validation, and testing of these methods were achieved using the dataset collected in the study. Stenosis >50%, that is, if there is more than 50% stenosis and hence confirming that there is the need for the more invasive CCTA procedure, was used as the predictor variable. Stenosis >50% is the point where further actions are necessary [12]. Regarding the whole process, standard practices were followed, that is, a 3-part partition of

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the data was performed: 500 individuals (100%) were classified into a training (70%), validation (20%), and testing (10%) set. An additional set of 250 individuals was exclusively used for external validation. Once each algorithm was trained and optimized through the training and validation set, they were applied to the testing set to determine the final accuracy of each method. Six standard evaluation metrics were used to assess the predictions of all the classifiers. These include area under the receiver operating characteristic curve, area under the precision-recall curve, accuracy, precision, recall, and F_1-score. The area under the receiver operating characteristic curve reflects the best balance between sensitivity and specificity, whereas the area under the precision-recall curve shows the balance between precision and recall. Ten-fold cross-validation was used to avoid overfitting. Finally, the algorithm with the highest prediction accuracy was selected for use in the system.

Additionally, to collect the opinions of health care professionals, a set of cardiologists with different experience levels was selected. They were provided with the web application and specific instructions on how to use it, and they completed 2 questionnaires. Specifically, the usefulness, satisfaction, and ease of use (USE) questionnaire [13] was employed to assess perceived usefulness, while the System Usability Scale (SUS) questionnaire [14] was used to evaluate perceived usability. The replies of all the participants were collected, and descriptive statistics were calculated based on them.

Implementation of the ML Algorithms and the Web Tool

In parallel with the development of the predictive model, a comprehensive web application was also developed. This application integrates multiple technology platforms, including Keycloak, Angular, HAPI FHIR, Python, and Nginx, each contributing essential features to create a cohesive system that meets the set requirements. The architecture is divided into several modules, each addressing specific functionalities within the system. These modules include User Authentication and Authorization, the front-end application for data input and management, the Health Care Data Management Backend for secure data storage and retrieval, the Predictive Analytics Application for generating outcome predictions, and Networking and Load Balancing to ensure optimal performance and resource allocation. The integration of these components results in a user-friendly, secure, and performance-optimized application. This application provides valuable insights to health care providers, supporting data-driven decisions that can lead to more effective treatments and improved patient outcomes.

Results

The study began with the submission of the study protocol to Aristotle University of Thessaloniki ethics committee in March 2022, followed by approval in April 2022. Data collection started in May 2022 and concluded in June 2023, with a total of 500 patients enrolled. These data were used for the development and testing of ML models designed to predict stenosis greater than 50%. The development of the AI algorithms was finalized in March 2024. Additionally, an explainable AI component was developed to clarify the decisions made by the algorithms and enhance their acceptability among health care professionals. Both the ML models and the explainable AI component were integrated into a web-based tool. This tool was subsequently evaluated externally by using data from additional 250 cases. The data from this external validation are currently being analyzed. The best performing model so far achieves an accuracy of approximately 82% in successfully predicting stenosis greater than 50%. Moreover, the web tool was assessed by several health care professionals. Specifically, a total of 12 cardiologists participated by responding to the USE and SUS questionnaires, with the sample comprising 10 male (83%) and 2 female (17%) physicians. Concerning usefulness, over 60% (8/12) of the participants responded positively to each question in this category, confirming the application's utility in daily medical practice. Regarding usability, 25% (3/12) of the participants rated the application as D (poor), another 25% (3/12) rated it as B (good), and 33% (4/12) rated it as A (excellent). The average score on the SUS questionnaire was 72.08, corresponding to a grade of B (good).

Discussion

Comparison to Prior Work

Several attempts have been made to create systems that accurately detect and classify coronary artery plaque and stenosis. For example, Zreik et al [15] suggest a noninvasive, automatic approach for identifying patients in need of invasive coronary angiography. To do so, they employed ML techniques, including a support vector machine classifier, to analyze coronary arteries in cardiac CCTA images with promising results. In a similar vein, a study by Han et al [16] investigated the feasibility of using deep learning algorithms to analyze CCTA images in patients with coronary artery stenosis. To create autoreconstructed CCTA images based on a sequence of 2D CT scans, they designed a CCTA reconstruction pipeline by using deep learning and transfer learning methodologies;150 patients who had CCTA and digital subtraction angiography were studied retrospectively. Their results show that when compared to conventional approaches, AI significantly lowers the time required for postprocessing and diagnosis.

Furthermore, for diagnosing functionally obstructive CAD, Coenen et al [17] compared the diagnostic performance of ML-based CT-fractional flow reserve (CT-FFR) to CTA and computational fluid dynamics–based CT-FFR; 351 individuals were studied at 5 facilities throughout Europe, Asia, and the United States, with 525 vessels undergoing invasive FFR comparison. On the CTA data, ML-based and computational fluid dynamics–based CT-FFR were conducted, and diagnostic performance was assessed using invasive FFR as a reference. Diagnostic accuracy increased from 58% with CTA to 78% by using ML-based CT-FFR on a per-vessel basis.

Cho et al [18] used a sample of 1501 patients with stable and unstable angina aiming to categorize lesions as having an FFR of 0.80 by using an angiography-based supervised ML system that was developed. Specifically, XGBoost employed 24 computed angiographic characteristics based on the diameter plot, as well as 4 clinical features (age, sex, body surface area, and involve segment). We used 2000 bootstrap iterations to

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train and evaluate the model separately. A total of 79 patients were used for external validation. Using all 28 characteristics, the ML model predicted an FFR of 0.80 in the 1204 training samples, with an overall diagnostic accuracy of 78% (SD 4%). At the same time, Han et al [19] aimed to determine the incremental value of resting myocardial CT perfusion over coronary stenosis in predicting ischemia by using an ML-based computational system. They used CCTA and invasive FFR that were performed on 252 individuals. Resting CT perfusion analysis was conducted utilizing supervised ML with a gradient boosting classifier. Their results show that resting CT perfusion data obtained by ML approaches may increase the prediction usefulness of severe ischemia over coronary stenosis.

Yang et al [20] focused on aortic stenosis classification, and they used cardio-mechanical signals that were collected with wearable inertial sensors. Data were collected from 21 patients with aortic stenosis and from 13 participants with no stenosis. Features were generated using a continuous wavelet transform and reduced based on an Elastic Net framework. The performance of different ML techniques was compared. Additionally, a 2D convolutional neural network was constructed using a custom-built architecture and a convolutional neural network trained using transfer learning on MobileNet. Their findings demonstrate the framework's usefulness in terms of feature selection and categorization. Additionally, they provide a strong potential for using deep learning technologies in the categorization of aortic stenosis.

Lin et al [21] conducted a multinational, multicenter study that included 9 cohorts of patients who had CCTA at 11 locations and were randomly allocated to training and test sets. A unique convolutional neural network trained using deep learning was used to segregate coronary plaque in 921 individuals (5045 lesions). The deep learning network was subsequently applied to an independent test set consisting of 175 patients (1081 lesions) with external validation and 50 patients (84 lesions) with intravascular ultrasonography within 1 month after CCTA. They assessed the prognostic value of deep learning–based plaque measurements for fatal or nonfatal myocardial infarction (the primary outcome) in 1611 patients enrolled in the prospective SCOT-HEART trial by using multivariable Cox regression analysis with adjustment for the ASSIGN clinical risk score. Expert readers and intravascular ultrasonography agree well with the deep learning system's estimations of plaque volume and stenosis severity from CCTA, which may be predictive for future myocardial infarction.

Finally, the purpose of a retrospective multicenter research conducted by Xu et al [22] was to determine the diagnostic accuracy and generalizability of a well-established fully automated deep learning method for identifying coronary stenosis based on CCTA. A total of 527 patients with suspected CAD who underwent CCTA and invasive coronary angiography were recruited. The diagnostic accuracy of the deep learning algorithm in detecting 50% stenosis was compared to that of professional readers by using invasive coronary angiography as a standard reference. According to the authors, the deep learning algorithm had good generalizability and time efficiency and performed similarly to expert readers on CCTA in terms of CAD diagnosis.

Compared to previous works, our study leverages ML for the prediction of significant coronary artery stenosis. The developed ML model was trained and tested using a real dataset, and it was further validated in a real-world clinical setting. Notably, our model does not rely on contrast-enhanced CCTA, thereby reducing patient exposure to contrast agents and associated risks, lowering costs, and making the screening process safer and more accessible for a broader range of patients. Although the results are still being analyzed, they appear promising. Furthermore, the ML model was integrated in a web-based application designed for routine clinical use, enhancing both usability and transparency. Finally, our approach incorporates explainable AI techniques, enabling clear and interpretable predictions, which is an essential factor for clinical acceptance and trust.

Limitations

When interpreting the findings of our study, a number of restrictions should be considered. First, all the information used in this study came from the AHEPA General Hospital in Thessaloniki, Greece. Thus, the results might not apply to other populations or clinical settings, particularly those with various demographic traits or health care systems. Second, the small sample size of this study might make it difficult for the AI tool to reliably predict CAD in a wide range of patient populations. The model's performance across various subgroups will be evaluated in future studies with larger and more diverse samples. Third, because the study depends on the accuracy of the data entered into the AI tool, any errors in data entry could have an impact on the outcomes. Fourth, as the AI tool is used in the real world, its predictive accuracy will need to be continually assessed and adjusted based on ongoing performance metrics. Finally, it is crucial to continuously monitor and address the ethical issues relating to data privacy, security, and patients' capacity to comprehend and consent to the use of AI in their care.

Conclusions

The goal of this pilot study was to determine whether an AI-based predictive model can help individuals with suspected CAD avoid unnecessary diagnostic tests. The proposed model was intended to predict whether a patient has more than 50% stenosis, which would call for additional testing, using data from patient screenings along with other pertinent information (demographics, medical history, etc). This strategy fits with a growing trend in health care that uses ML algorithms to enhance clinical practice and patient outcomes. Our research expands on earlier studies that classified and identified coronary artery plaque and stenosis by using ML techniques. Although encouraging, these studies have brought attention to the need for larger and more varied datasets to increase the predictive precision of the ML models. Our study also considers the insightful comments provided by the clinical professionals who use the AI tool, which helps to make it practical for use in real-world scenarios. The developed AI tool has the potential to speed up diagnosis, increase clinical satisfaction, and improve clinical performance in the diagnosis of CAD. For the validation of the efficacy of this AI tool in a real-world clinical setting, the findings of this pilot study are essential.

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Data Availability

The datasets generated during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

Authors GR and EL shared the first authorship for this paper, while PB and AB shared the senior authorship for this paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report by Horizon 2020 - Research and Innovation Framework Programme, European Commission.
[PDF File (Adobe PDF File), 237 KB - resprot_v14i1e67697_app1.pdf]

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Abbreviations

AHEPA: American Hellenic Educational Progressive Association
AI: artificial intelligence
CAD: coronary artery disease
CCTA: coronary computed tomography angiography
CT: computed tomography
CT-FFR: computed tomography-fractional flow reserve
FAIR: Findable, Accessible, Interoperable, and Reusable
FFR: fractional flow reserve
ML: machine learning
PTP: pretest probability
SHAP: Shapley Additive Explanations
SUS: System Usability Scale
USE: usefulness, satisfaction, and ease of use
XGBoost: extreme gradient boosting

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Protocol

Implementation and Effectiveness of the Power Over Pain Portal for Patients Awaiting a Tertiary Care Consultation for Chronic Pain: Protocol for a Pilot, Prospective, Cohort, Mixed Methods Study

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Abstract

Background: Chronic pain (CP) affects approximately 8 million people in Canada. Access to CP care is challenging, and there is no robust monitoring system to support patient care and decision-making. The Power Over Pain (POP) Portal was developed by people living with CP, health care providers, researchers, health system decision-makers, policymakers, and community partners to address these concerns. The POP Portal is a comprehensive web-based platform that provides rapid access to a continuum of free, evidence-informed resources for the self-management of CP, mental health, and substance use health. The POP Portal also offers self-assessment tools that enable users to track their progress and receive personalized recommendations.

Objective: This hybrid implementation-effectiveness type III pilot study aimed to determine the feasibility (ie, recruitment, integration, facilitators and barriers, patient engagement, usability, and acceptability) of the POP Portal's implementation for people waiting for care at a tertiary pain clinic.

Methods: A cohort of 80 adults living with pain was recruited from the waitlist of a tertiary care pain clinic over a 3-month period. Following an orientation on the POP Portal, participants were encouraged to use it according to their needs and preferences. They were also asked to complete questionnaires at baseline (0 months) and the 3-month follow-up. Primary feasibility measures included recruitment and retention rates and portal acceptability using the Acceptability E-scale. We also measured usability using the System Usability Scale, evaluated engagement through portal analytics, and identified facilitators and barriers via semistructured interviews with 12 to 15 study participants. These interviews further assessed the acceptability and usability of the portal for participants. Exploratory measures included pain severity, pain-related interference, self-efficacy, coping strategies, and symptoms of anxiety and depression.

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Results: We will present descriptive data on the cohort's sex and gender, age, rural or urban status, and ethnic background, as well as the acceptability, usability, and feasibility of the portal. Measures of central tendency will be reported for continuous variables, and frequencies and proportions will be reported for categorical variables. We will also present change in clinical outcomes across time and a synthesis of qualitative and thematic data.

Conclusions: We anticipate that most patients awaiting care at a tertiary pain clinic recruited will use the POP Portal and find it to be acceptable for addressing some of their pain and associated health concerns. If the feasibility of recruiting and retaining patients is demonstrated as anticipated, we will be able to move forward with a multisite study to evaluate the implementation and effectiveness of the POP Portal among patients waiting for a tertiary care consultation.

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KEYWORDS

chronic pain; self-management; patient portal; virtual care; mental health; substance use; implementation science; feasibility study; protocol; online

Introduction

Background

Chronic pain (CP) affects approximately 1 in 5 Canadians, including youth and adults, and costs the Canadian economy an estimated CAD $40 billion (US $28.9 billion) per year [1]. Approximately 60% of people with CP have co-occurring mental health disorders [2,3], and approximately 29% do not use opioids as prescribed [4]. Improving access to care for CP and co-occurring mental health and substance use concerns are among the field's top research priorities [5]. People living with pain often wait for extended periods before receiving specialized pain care. While wait times in excess of 6 months have been deemed medically unacceptable [6], wait times for Canadian CP clinics have not changed over the last 10 years [7]. More than 50% of patients are not seen at these clinics within the recommended wait time, often waiting for several years [7], and as a result, they experience concomitant deterioration in function and quality of life [6].

Considering management options for CP, psychosocial interventions delivered virtually have been shown to be effective in improving pain interference, pain severity, psychological distress, and health-related quality of life when comparing to control groups [8]. Currently, no cohesive set of virtually delivered interventions for pain management exists within an integrated framework that augments the current continuum of care. Rather, there has been a reliance on stand-alone mobile apps, which present several issues that can impact their effectiveness and user adoption.

One concern is variability in the quality and reliability of the content provided, as not all apps are developed based on evidence-based practices [9]. In addition, there are privacy and data security concerns regarding storing information on multiple stand-alone apps as sensitive health information could be at risk if not properly protected [10]. The lack of personalized feedback and continuous outcome monitoring and the inability to adapt to individual patient needs can also limit the effectiveness of these apps [11]. Usability and accessibility are also significant concerns as older adults or those with limited technological proficiency may find these apps difficult to navigate [12]. Furthermore, while some are free, many apps require a purchase or subscription, which can create a financial barrier for some users, limiting equitable access to these potentially beneficial resources [13]. Finally, the engagement with and adherence to app-based interventions can be low as users might lose interest over time without proper motivation and support [12]. Addressing these issues is crucial for the successful integration of mobile apps into pain management strategies.

Our team (ie, a collaborative group of people living with pain, health care providers, researchers, health systems decision-makers, policymakers, intervention providers, and community partners) developed the Power Over Pain (POP) portal to remedy this gap. The POP Portal offers rapid access to free, evidence-informed virtual resources and interventions for the self-management of CP, mental health, and substance use aligned along a continuum of care. The portal also facilitates continuous outcome monitoring to provide feedback to people living with pain about their progress, promote behavior change, improve health decision-making, and enhance communication between health care providers and people living with pain. Importantly, the POP Portal was developed in accordance with the Stepped Care 2.0 model, a framework to integrate resources and interventions along a continuum of care that can support patients and their health care providers in achieving therapeutic goals. This model is resiliency based, grounded in recovery-oriented principles (eg, person driven and strength based), and self-corrective [14]. Stepped care approaches have been demonstrated to be acceptable and cost-effective for delivering mental health [15] and substance use [16] care. These approaches have also been studied in managing certain CP conditions such as low back pain [17], musculoskeletal pain [18], and osteoarthritis [19]. However, a 2019 review concluded that stepped care models for CP were inconsistently applied and that studies conducted on them were of low quality [20]. Our team adapted and implemented Stepped Care 2.0 for adult CP care at our tertiary care institution [21], which led to a substantial reduction in clinical appointment wait times [22]. The POP portal [23] was launched in November 2022 and reached 250,000 unique visitors in November 2024 through a promotional campaign targeting different relevant organizations in Canada. Many tertiary pain clinics in particular were enthusiastic to learn about the portal and its potential in improving pain care access. However, in addition to meeting

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discussions on how best to implement the portal in this context, strong evidence-based implementation strategies were lacking, limiting the success of portal use and benefits within tertiary pain clinics.

Objectives

In preparation for an adequately powered multisite trial to evaluate the implementation and effectiveness of the POP Portal, this pilot study aimed to determine the feasibility of implementing the POP Portal for people living with pain who had been referred to a tertiary pain clinic in Canada and were awaiting their first appointment. The objectives of the pilot study were to determine the (1) feasibility of recruiting people living with pain who were waiting for their first appointment, (2) proportion of patients who agreed to have their health care number used for a future study (eg, impact of the POP Portal on health care use), (3) participant engagement with and usability and acceptability of the POP Portal, (4) facilitators of and barriers to the POP Portal's implementation, (5) statistical parameters of effectiveness outcomes (outlined in the following sections), and (6) preliminary evidence of intervention effectiveness (ie, estimates of effect and variance for the secondary outcome).

Methods

Ethical Considerations

This protocol was reviewed and approved by the Ottawa Health Science Network Research Ethics Board, REB #20220443-01H. Participants were informed that their privacy would be respected and their personal information kept strictly confidential, unless release was required by law. Participants provided verbal informed consent before taking part in the study and were informed that they could withdraw their participation at any time and would not lose access to the portal if they chose to do so. The Ottawa Health Science Network Research Ethics Board may review relevant study records under the supervision of PP and their research staff for audit purposes. Adverse events that could reasonably be attributed to the use of the POP Portal were self-reported by the participants and tracked using an adverse event form. Study participants were not compensated for accessing the virtual POP Portal or its resources. Participation was incentivized in the following ways: participants who completed the 3-month follow-up questionnaire and interview were provided with a CAD $20 (US $14.46) and CAD $30 (US $21.69) Amazon gift card, respectively. Participants were not asked to pay fees for any part of this study.

Study Design

This project was a hybrid implementation-effectiveness type III pilot study using a prospective cohort mixed methods design. We used the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 [24,25] checklist to guide our reporting for this protocol with adaptation for feasibility studies [25]. The enacted study will be reported in accordance with the CONSORT (Consolidated Standards of Reporting Trials) guidelines extension to randomized pilot and feasibility trials [26]. A workflow of the study can be found in Figure 1.

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Figure 1. Workflow of the study. POP: Power Over Pain.

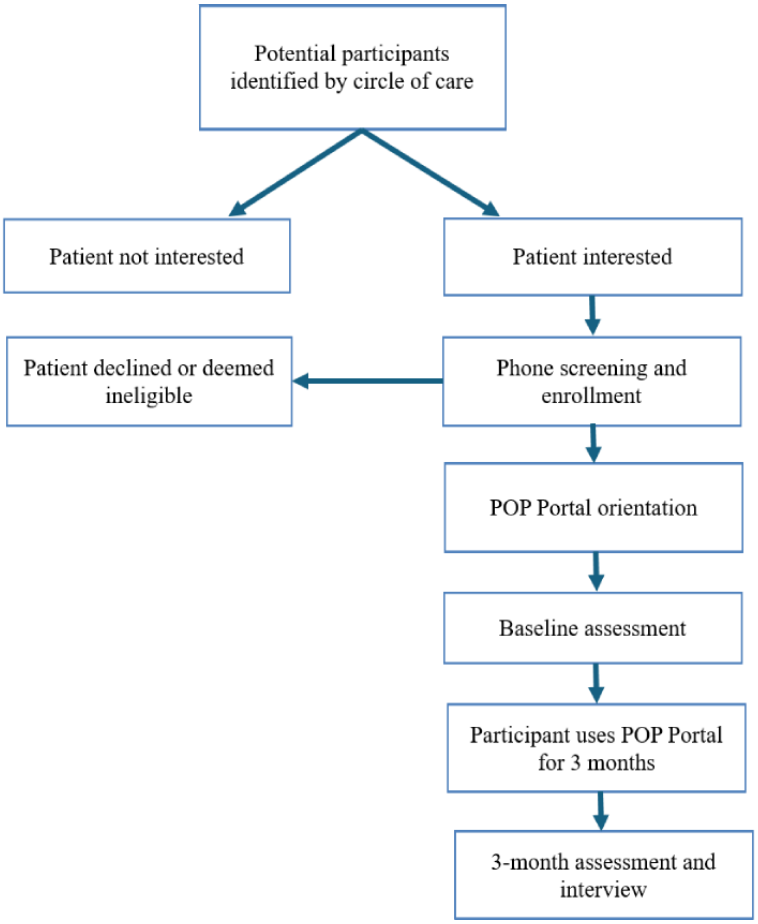

Eligibility Criteria

Inclusion criteria were (1) adults (aged >18 years) referred to a tertiary care pain clinic (ie, awaiting triage or first appointment), (2) experience of CP (ie, ongoing, persistent, or recurrent pain for more than 3 months), (3) sufficient fluency in English or French to engage with the POP Portal's programs and resources, (4) capacity to provide informed consent in English or French, (5) access to an electronic device with connection to the internet, and (6) agreement to be contacted for research.

Exclusion criteria were (1) self-reported barriers to the use of technology during the initial screening appointment, (2) experience of cancer-related pain, (3) inability to complete the study questionnaires and assessments, and (4) self-disclosure of an unmanaged mental health condition or suicidal ideations during the first study visit.

Study Procedures

Overview

We identified prospective participants for this study in 2 ways. First, the pain clinic clerk called patients accepted for care at the pain clinic and informed them about the study; those who expressed an interest were referred to the study coordinator for screening and to discuss participation. Second, the study coordinator screened electronic health records to identify those whose consultation request had yet to be triaged and who had provided institutional permission to be contacted for research.

The study coordinator contacted eligible patients via phone. During this call, the coordinator described the study background, expectations of participation, voluntariness, rights to withdrawal, and risks and benefits and obtained verbal consent. The study coordinator ensured that verbal consent was recorded during this initial phone call. Consenting participants were sent a study information sheet along with a web link to complete a baseline questionnaire. In addition, the coordinator scheduled a videoconference session with participants to orient them to the POP Portal (see details in the following sections).

The study coordinator sent participants a web link to complete a follow-up assessment 3 months after the orientation session (Figure 1), and selected participants were invited to undergo follow-up interviews at this time (see the Data Collection and Outcomes section for more details).

Study Intervention Delivery

Following the initial call, participants took part in a 15-minute orientation session that introduced the POP Portal and its resources, including detailed information about (1) navigating the portal and its resources, (2) creating an account, (3) registering for courses, and (4) completing self-assessments. Following this session, participants were asked to use the POP Portal for a 3-month period. Participants could ask for guidance on any aspect of the portal covered in the orientation session at any time over this period (eg, usability difficulties). However, the participants were not provided with further instructions on what resources or services they should use on the POP Portal

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(ie, resource recommendations), nor were there restrictions on concomitant care or interventions.

Sample Size

We aimed to recruit 80 participants from a tertiary care pain clinic over a 3-month recruitment period. We anticipated recruiting 20 to 30 adults per month. For the qualitative interviews, we purposively (eg, sex, gender, pain type, duration with pain, and comfort with technology) invited 12 to 15 adults, which we anticipated would be sufficient to achieve saturation [27].

Study Intervention

Overview

The POP Portal is a comprehensive virtual platform co-designed by a diverse group of health care providers, researchers, decision-makers, and Canadians who live with CP. The POP Portal (1) provides rapid access to free, evidence-informed virtual resources for CP, mental health, and substance use health arranged along a stepped care continuum of offerings; and (2) facilitates continuous outcome monitoring through optional self-assessments to allow for rapid adjustment to resource recommendations and program evaluation.

Recognizing the difference in the needs and preferences of youth and adult populations, 2 distinct portals were created to better serve each population. This study focused on an adult population, and thus, the adult POP Portal is described in the following sections.

Stepped Care Resources

In line with the Stepped Care 2.0 framework, the resources available on the POP Portal are designed to vary in intensity, corresponding to different levels of user commitment. These resources enhance a continuum of care and are accessible at any time, thereby enabling users to engage with them according to their individual preferences and needs.

Step 1: Educational Resources

Participants who wanted to learn basic facts about CP, including the relationship among CP, mental health, and substance use, had access to a range of evidence-informed educational resources (eg, articles, videos, and podcasts), including (1) Pain U Online, developed by the Toronto Academic Pain Medicine Institute, which covers topics on CP mechanisms; factors that influence pain; pharmacological, physical, and psychological strategies for pain management; insomnia; and a healthy lifestyle; and (2) LivePlanBe+, developed by Pain BC, which currently hosts 23 modules on pain science, nutrition, self-management techniques, sleep, symptom management, and communication, among others.

Step 2: Virtual Self-Guided CP Self-Management Courses

Participants were encouraged to create a free account to gain access to free virtual self-guided CP self-management courses, including (1) The Pain Course, developed at the eCentreClinic, Macquarie University; and 2) Empowered Management, developed by the Toronto Academic Pain Medicine Institute.

The Pain Course is an online 8-week cognitive behavioral therapy–based self-management program that includes six modules: (1) CP education, (2) understanding CP and the relationship between pain and emotions, (3) managing unhelpful thoughts, (4) managing uncertainty and problem-solving, (5) managing physical symptoms and maintaining physical activity while minimizing fatigue and pain exacerbation, and (6) maintenance strategies and relapse prevention. It has been evaluated among individuals with diverse CP conditions and shown to be acceptable and associated with improved pain, pain interference, depression, and anxiety [28-30].

Empowered Management is an online program specifically designed for patients living with CP who are waiting for tertiary pain care. It aims to improve their readiness for change and provide them with self-management skills that will enhance their interaction with health care providers in CP clinics. The modules include (1) setting expectations; (2) what is CP; (3) biopsychosocial factors and approaches to CP; (4) empowered management; (5) self-awareness, compassion, and acceptance; (6) values; (7) goal setting; and (8) communication. The program includes a reflection journal that accompanies the psychoeducational modules and weekly assignments [31]. It was recently tested in 2 Ontario Chronic Pain Network clinics and found to be acceptable and usable (personal communication, Rosemary Wilson, August 25, 2024).

Step 3: Peer Support

Participants had access to different peer support services to help them connect with peers, including peer support groups and health coaching.

Participants were able to connect with different communities of support (ie, peer support groups) and find a safe space to talk with people who may know better where they were coming from, including the People in Pain Network. The People in Pain Network is a national community of people with persistent pain helping other people with persistent pain improve the quality of their lives by offering education and support through monthly virtual and in-person meetings.

Participants had access to health coaching via Ontario Self-Management, a free one-on-one web-based support program to help people living with pain manage their condition. The health coaches are people with lived experience trained in self-management support and communication skills.

Step 4: Live Interactive Workshops

Participants had access to a suite of live interactive workshops covering various topics related to CP, mental health, and substance use health, some of which included pain neuroscience, sleep, nutrition, gentle movement, communication, pacing and planning, and engaging in meaningful activities.

Step 5: Individual Counseling

Participants who wished to access individual counseling were directed to free services available in their jurisdiction.

Self-Assessments

Regarding other POP Portal uses, participants had the option to complete self-assessments once every few weeks and were

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presented with a visual depiction of their results to help them track their symptoms over time. These self-assessments consisted of the following valid and reliable patient-reported scales: the Patient-Reported Outcomes Measurement Information System Pain Intensity instrument; Pain Disability Index; 2-item short form of the Pain Self-Efficacy Questionnaire; Patient Health Questionnaire–4; Patient-Reported Outcomes Measurement Information System Sleep Disturbance Short Form instrument; 1 item modified from the World Health Organization Alcohol, Smoking, and Substance Involvement Screening Test; and the Global Appraisal of Individual Needs substance use subscale. These scales are described in Table 1.

Once the participant completed a self-assessment, their results were displayed, and feedback was provided based on where they scored within predefined categorical groupings (eg, low, moderate, or high). Resource recommendations were preselected by our team for each domain measured (eg, pain-related disability and sleep disturbance) per scoring categorical groupings. The self-assessments were fully integrated within the POP Portal through an automated electronic data capture system maintained by our technology partner. The goal of the self-assessments was to provide personalized feedback generated by the platform about potential intervention targets for CP, mental health, or substance use health. We asked participants for consent to use their self-assessment data for this study.

Table 1. Description of the Power Over Pain Portal self-assessment measures.

Scale	Description
PROMIS[a] Pain Intensity instrument	The PROMIS Pain Intensity instrument is a 1-item numerical rating scale from 0 to 10 for measuring pain intensity [32].
PDI[b]	The PDI is a 7-item form (including responsibility of home and family, self-care, occupation, sexual behavior, social activity, recreation, and life support activities) that assesses the magnitude of self-reported pain-related disability of the participant regardless of the pain area or pain-related diagnosis. The pain-related disability questions are scored on an 11-point numerical rating scale (0-10) [33].
PSEQ-2[c]	The PSEQ-2 is a 2-item survey with a 7-point numerical rating scale (0-6) to assess patients' pain self-efficacy or belief in one's capability to perform activities despite having pain. The PSEQ-2 has high validity and internal consistency, with evidence for its test-retest reliability, sensitivity to change, and convergent validity [34-36].
PHQ-4[d]	The PHQ-4 is a brief 4-item survey of core symptoms and signs of depression (PHQ-2) and anxiety (GAD-2). The total PHQ-4 score provides an overall measure of symptom burden as well as functional impairment and disability. Its total score (sum of 4 items) measures psychological distress rated as normal (0-2), mild (3-5), moderate (6-8), and severe (9-12); a GAD-2[e] score of ≥3 suggests potential anxiety symptoms, and a PHQ-2[f] score of ≥3 suggests potential depression symptoms [37].
PROMIS Sleep Disturbance Short Form	The PROMIS Sleep Disturbance Short Form is a 4-item form exploring the participants' sleep characteristics and difficulties over the previous 7 days. The participant is asked to select, for the first question, from 1 of 5 options ("very poor," "poor," "fair," "good," or "very good") and, for the last 3 questions, from 1 of the following 5 options for each question: "not at all," "a little bit," "somewhat," "quite a bit," and "very much" [38].
WHO-ASSIST[g]	A single item modified from the WHO-ASSIST will be used to evaluate the risk associated with the client's substance use and whether this use is hazardous and likely to cause harm (now or in the future) if it continues. We ask patients to indicate whether they have concerns regarding any of the substances from a list provided to them [39].
GAIN[h] Short Screener	The GAIN Short Screener will be used to identify individuals who are experiencing challenges or are at risk of developing challenges as it pertains to mental and substance use issues. We administer 5 items to the participants, each scored on a 4-point numerical rating scale (0-3) [40,41].

[a]PROMIS: Patient-Reported Outcomes Measurement Information System.

[b]PDI: Pain Disability Index.

[c]PSEQ-2: 2-item short form of the Pain Self-Efficacy Questionnaire.

[d]PHQ-4: Patient Health Questionnaire–4.

[e]GAD-2: 2-item Generalized Anxiety Disorder scale.

[f]PHQ-2: Patient Health Questionnaire–2.

[g]WHO-ASSIST: World Health Organization Alcohol, Smoking, and Substance Involvement Screening Test.

[h]GAIN: Global Appraisal of Individual Needs.

Data Collection and Outcomes

Overview

Outcomes for this pilot study were derived through advisory committee meetings with patient partners who are people living with pain, previous research in the field, and clinical experience of the multidisciplinary team at the tertiary care pain clinic (eg, clinicians, nurses, psychologists, and social workers). Participants were asked to complete a baseline assessment and a 3-month assessment (after portal use) through a web-based survey (LimeSurvey GmbH). Scales included as primary and secondary feasibility outcomes were collected only at the 3-month assessment, whereas all exploratory clinical effectiveness outcomes were collected at both baseline and the 3-month assessment.

Primary Feasibility Outcomes and Interpretation

Our primary feasibility outcomes were recruitment rate (ie, number of patients consenting), 3-month retention rate (ie,

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3-month assessment completion), and participant acceptability assessed using the Acceptability E-scale 3 months after participant recruitment [42] and through interviews. The Acceptability E-scale is a 6-item questionnaire that uses a 5-point Likert scale to evaluate participants' experiences with the program. The form has been shown to have strong psychometric properties to assess participants' acceptance and perception of digital health interventions [42,43].

Secondary Feasibility Outcomes

Secondary feasibility outcomes comprised (1) rates of participant accrual, dropout, screening, eligibility, and 3-month assessment completion; (2) participants' satisfaction, assessed using the Acceptability E-scale 3 months after participant recruitment [42]; (3) participants' perceived barriers and facilitators regarding the portal, which will be tracked throughout the study and through participant interviews (see the following section); and (4) portal usability, assessed by the participants using the System Usability Scale 3 months after recruitment [44]. The System Usability Scale is a 10-item questionnaire asking participants about the usability of the POP Portal. Each question has a 5-point numerical rating scale (1-5), with 1 indicating strong disagreement and 5 indicating strong agreement. It has been shown to be both valid and reliable in providing a global view of subjective assessments of usability [44-46].

We also explored participant engagement with the portal and its resources throughout the 3 months of portal use through system analytics. We collected metrics that were maintained by our technology partner and guided by those that were collected for Wellness Together Canada [47], including sign-ups; sign-ins; first-time user activation (ie, rate at which new users engage in a meaningful way with the portal, including assessment completion, or view of progress over time); type, nature, and frequency of resources accessed; number of self-assessments completed; participant retention (eg, 1 week vs 3 months after study enrollment); and impact (eg, correlation between participants' improvement in pain, mood, or substance use and resource use).

Interviews

We conducted semistructured interviews with a random sample of 12 to 15 participants who used the POP Portal's resources or courses to further assess the acceptability, usability, and impact of the POP Portal. Interviews spanned 30 to 45 minutes in duration and were conducted via Microsoft Teams. We developed an interview guide using components of the theoretical domains framework [48], theoretical framework of acceptability [49], the System Usability Scale [44], and theoretical domains framework questionnaire in implementation research [50]. The interview guide was refined through discussion with pain experts across Canada and with people living with pain. The guide was intended to provide structure and context for the participants' responses. Through these interviews, we aimed to better understand the experience of participants with the resources offered to them in the POP Portal, what they liked or disliked about it, benefits and harms experienced from the portal, level of confidence in and comfort with the portal, barriers to the portal's implementation or delivery, and potential improvements or additions. Interviews were conducted by trained study research staff, recorded, and transcribed verbatim.

Exploratory Clinical Effectiveness Outcomes

Informed by a consensus-driven minimum dataset [51] for adults with CP from the Centre hospitalier de l'Université de Montréal (University of Montreal Health Centre), participants' pain type, location, onset, duration, frequency, and diagnosis were collected if known. We also examined whether there were changes in the following clinical outcomes from before enrollment to 3 months after enrollment: (1) pain intensity and interference (Brief Pain Inventory), (2) pain self-efficacy (2-item short form of the Pain Self-Efficacy Questionnaire), (3) pain coping skills (Chronic Pain Coping Inventory), (4) attitudes toward and beliefs about CP (Survey of Pain Attitudes), (5) health-related quality of life (12-Item Short Form Health Survey version 2), (6) symptoms of anxiety (7-item Generalized Anxiety Disorder scale), and (7) symptoms of depression (Patient Health Questionnaire–8). We also assessed participants' perceived overall effectiveness using the Patient Global Impression of Change at the follow-up visit. These scales are described in Table 2.

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Table 2. Description of study exploratory clinical effectiveness outcomes.

Scale	Description
BPI[a]	The BPI will be used to measure pain severity (4 items on an 11-point numerical rating scale) and pain interference with daily functioning (7 items on an 11-point numerical rating scale). Participants' "worst pain" or the arithmetic mean of the 4 severity items can be used as a measure of pain severity; the arithmetic mean of the 7 interference items (general activity, walking, work, mood, enjoyment of life, relations with others, and sleep) can be used as a measure of pain interference. The BPI has sufficient reliability (Cronbach α coefficients are frequently higher than 0.80), construct validity, and responsiveness in several pain and other populations [52-57]. Worse pain and average pain scores of 1-4 are viewed as indicative of mild pain, scores of 5-6 are viewed as indicative of moderate pain, and scores of 7-10 are viewed as indicative of severe pain [58].
PSEQ-2[b]	The PSEQ-2 will be used similarly to its use for the portal's self-assessments described in Table 1.
CPCI[c]	The CPCI is an 8-item questionnaire covering the use of pain coping skills, including the scales on guarding, resting, asking for assistance, relaxation, task persistence, exercise and stretch, seeking, and coping self-statements. It asks the patient to indicate the number of days during the previous week in which they used each of the strategies to deal with pain. The questionnaire has been shown to have strong internal consistency reliability, test-retest stability, and validity in CP[d] populations [59,60].
SOPA[e]	The SOPA is a 7-item form to assess patients' attitudes toward and beliefs about their CP. It includes scales on pain control, disability, harm, emotion, medication, solicitude, and medical cure. Patients are asked to indicate how much they agree or disagree with each statement on a 5-point numerical rating scale (0-4). The survey has good internal consistency, test-retest reliability, and convergent and discriminant validity [61].
SF-12[f] version 2	The SF-12 version 2 is a 12-item survey that measures health-related quality of life, functional health, and well-being across physical and mental health domains. We will evaluate limitations to participants' physical activities due to their current health using the physical functioning subscale. The SF-12 version 2 has shown good psychometric validity and reliability for evaluating health-related quality of life in both general [62-65] and specific populations, including those with CP [66], cancer [67], hemophilia [68], mental illnesses, and behavioral health diagnoses [69], among others.
GAD-7[g]	The GAD-7 is a 7-item scale used to screen for potential signs and symptoms of anxiety and assess the severity of generalized anxiety disorder. Scores range from 0 to 21, and a clinically meaningful change is 5 points or more. The GAD-7 has high internal consistency and convergent validity (Cronbach α values are frequently above 0.82) across heterogeneous psychiatric populations [70,71], as well as sound diagnostic validity, with sensitivity of 0.66 to 0.89 and specificity of 0.80 to 0.82 for generalized anxiety disorder and anxiety disorders including social anxiety, posttraumatic stress disorder, and panic disorder [72,73].
PHQ-8[h]	The PHQ-8 is an 8-item scale to assess the frequency of depressive symptoms, with scores ranging from 0 to 24. A total score of 0-4 represents no significant depressive symptoms, a score of 5-9 represents mild depressive symptoms, a score of 10-14 represents moderate depressive symptoms, a score of 15-19 represents moderately severe depressive symptoms, and a score of 20-24 represents severe depressive symptoms. The PHQ-8 has been shown to be reliable and have good construct and criterion validity to screen for depression in patients with heart failure and in the general population [74-76].
PGI-C[i]	The PGI-C scale [77] is a 1-item scale to evaluate the perceived effect of disease management, asking the participants about their overall status at follow-up; it includes 7 options, ranging from "very much worse" to "very much improved." The scale has demonstrated to have high test-retest reliability and is a potentially clinically meaningful measure for a variety of pain populations, with evidence of good validity [77-80].

[a]BPI: Brief Pain Inventory.

[b]PSEQ-2: 2-item short form of the Pain Self-Efficacy Questionnaire.

[c]CPCI: Chronic Pain Coping Inventory.

[d]CP: chronic pain.

[e]SOPA: Survey of Pain Attitudes.

[f]SF-12: 12-Item Short Form Health Survey.

[g]GAD-7: 7-item Generalized Anxiety Disorder scale.

[h]PHQ-8: Patient Health Questionnaire–8.

[i]PGI-C: Patient Global Impression of Change.

Demographic Characteristics

We collected age, sex and gender, ethnic background, and the first 3 digits of participants' postal codes from medical records to provide basic demographic characteristics.

Data Management

Personal information was kept confidential unless release was required by law. Participants were identified in study data through a unique study identification number. Project data were encrypted, password protected, and locally stored on The Ottawa Hospital's Microsoft 365 SharePoint or OneDrive subject to the institution's policies and procedures regarding security and backup. Questionnaire data were collected using LimeSurvey and then downloaded by the study coordinator at least biweekly into a spreadsheet securely stored on the institution's Microsoft 365 SharePoint or OneDrive. Data were deleted from LimeSurvey after all study data were securely transferred and stored locally on the research institution's network. Only the research team members directly involved in conducting the research had access to the data. Passwords were stored in a master list, with only the principal investigator, research program manager, and study coordinator having access.

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The data safety and monitoring committee was guided by a charter of roles and responsibilities and consisted of a statistical expert, a person with lived experience of CP, a pain medicine specialist, and a health psychologist who are independent of the research team. This group met with the study steering committee on a monthly basis during study recruitment and intervention to review recruitment, accumulating study data, and adverse events and provided guidance regarding any needed action.

Data Analysis

Quantitative Analyses

The primary feasibility outcomes and secondary outcomes previously mentioned were described using descriptive statistics (frequencies and proportions), point estimates, and 95% CIs. For this pilot study, we did not stratify or analyze the acceptability or usability outcomes by type or amount of resources used. Even though we were underpowered for efficacy, we explored ranges of effect sizes using point estimates of change across time and associated 95% CIs for each resource [81]. Graphs and tables of descriptive data were prepared. Study data were imported into SPSS (IBM Corp) for statistical analysis. Open-text responses were reviewed by the study team for converging themes. Missing data were handled using multiple imputation; single-point estimates were determined using parameter estimates and SEs of 10 imputed datasets.

Qualitative Analyses

Interviews were transcribed, and analyses and coding were completed by 2 research staff members using the NVivo software (QSR International) and following the method described by Saldaña [82]. The study staff acquainted themselves with the data through reading the transcripts independently and started developing the codebook. They then met to compare coding, with any disagreements resolved through consensus or discussion with the senior author. We then used a deductive thematic analysis approach [48] to map emerging categories and themes to constructs within the theoretical framework of acceptability and theoretical domains framework. We triangulated our data by comparing themes identified during the analyses of participant interviews with quantitative data collected to validate our findings and expand our understanding of the effectiveness, acceptability, and usability of the portal wherever possible

Feasibility Interpretation

Following recommendations for feasibility studies, we developed a priori criteria on our primary feasibility outcomes to indicate whether progression to an adequately powered trial was feasible. The a priori criteria were organized through a traffic light system (Textbox 1).

Textbox 1. A priori feasibility criteria.

- Green: continue without modifications; this will be indicated if (1) we recruit a minimum of 80 adults at the tertiary care pain clinic over 3 months, (2) we achieve a minimum of 80% retention rate (ie, participants completing the Pain Course resource delivered through the Power Over Pain [POP] Portal and pretest-posttest outcome measures), and (3) most (≥70%) of the participants deem the POP Portal to be acceptable for addressing some of their pain and associated health concerns, as measured using study questionnaires, portal self-assessments, or interviews.
- Yellow: continue but modify protocol with close monitoring; this will be indicated if we recruit 40-79 adult participants over 3 months, achieve a 50%-79% retention rate, or 50%-69% of the participants find the POP Portal acceptable.
- Red: definitive trial not feasible; this will be indicated if we recruit <40 adult participants over 3 months, achieve a <50% retention rate, or <50% of the participants find the POP Portal acceptable.

Results

The Ottawa Health Science Network Research Ethics Board cleared all study procedures and materials for ethical compliance on October 24, 2022, in their initial version. The protocol in the current and final version (version 2) was cleared on May 16, 2023. Participants were able to enroll in the study between March 25, 2023, and August 7, 2023. Data collection was extended to November 18, 2023. Following the International Committee of Medical Journal Editors guidelines for authorship, the results were published in an open access journal—*Digital Health*; a qualitative manuscript was published in October 2024, and a quantitative manuscript was published in March 2025. Findings were also disseminated to different knowledge users of the portal through presentations and webinars offered by POP partners. No protocol deviations were noted.

Discussion

Expected Findings

Most patients referred to tertiary care for pain management have not had access to pain education, self-management, and peer support before referral. The POP Portal fills that gap by providing rapid access to a stepped care continuum of virtual self-management resources for CP. This study tested the feasibility and explored the effects of implementing the POP Portal in tertiary care with the hope of conducting a fully powered multisite implementation-effectiveness trial. As patients await their first visit to a tertiary care pain program (which could take months), we anticipate that (1) 80% of approached patients will be interested in being informed about the portal, (2) 70% of patients oriented to the portal will access some of its resources, and (3) most (≥70%) of the participants who use the portal will report it to be acceptable for addressing some of their pain and associated health concerns. In terms of feasibility of the study protocol, we anticipate the ability to recruit a minimum of 80 participants over 3 months and achieve a minimum of 80% retention rate. If our anticipated findings are true, we will

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be able to progress to an adequately powered multisite trial without modifications to the protocol.

Studies looking at the implementation of a comprehensive portal providing evidence-informed online resources on education, self-management, and peer support to empower patients with a health condition are limited. During the COVID-19 pandemic, Wellness Together Canada was quickly developed and successfully implemented, providing much needed access to online mental health resources [83]. While the platform is no longer active, Wellness Together Canada was one of the first examples of the benefits of providing a range of resources and services on a stepped care continuum at a population level and was the inspiration for the development of the POP Portal. As previously mentioned, our team developed 2 distinct portals, one for adults and one for youth living with CP. A hybrid implementation-effectiveness trial is currently underway, testing the Youth Portal (popyouth.ca) across Canada [84].

There are a multitude of interventions for self-management of pain that have been developed [85]. For example, The Pain Course was developed and well tested, showing efficacy across different populations [28-30]. However, most interventions being developed rarely become available or accessible to the public [1]. A platform such as the POP Portal provides a space to host these resources and make them accessible to the public (outside the research sphere). It also provides the opportunity to continue the evaluation of those resources at a larger scale using a real-world pragmatic approach.

Limitations

The POP Portal is an online platform that provides virtual resources. We acknowledge that people with no internet access or low digital literacy will not derive equal benefit from this type of innovation. Although no explicit strategies were in place at the time of study start to reach these groups, we planned to document reasons to decline participation in the feasibility study to inform strategies in future studies. This study also used a simple pretest-posttest design for outcome measures, which could limit the capture of user experience evolution. Multiple time points during the intervention should be considered for future similar protocols. As a first step in the implementation of the POP Portal, this study relied primarily on self-reported engagement with the portal (eg, interviews and scales) rather than system analytics, which could be seen as a limitation in terms of fidelity of portal use. However, we have observed that the quality and usefulness of engagement, even if they are minimal (eg, use of a single resource), can translate into meaningful improvement. This type of information is better captured through interviews.

Future Directions

Our ultimate goal with the POP Portal is to improve care access for people living with pain across Canada so that they can receive the appropriate care at the appropriate time according to their needs and preferences. To reach this goal, our future directions are 3-fold. First, regarding portal improvement, implementation, and evaluation, we will continue the development of the POP Portal based on studies evaluating the experiences of users and gathering feedback on portal improvement (eg, interviews, focus groups, and mass surveying). Using implementation science frameworks, we will conduct studies examining barriers to and facilitators of the implementation of the POP Portal in different contexts, such as tertiary care and primary care [86] as well as remote rural and Indigenous communities [87]. Finally, we will also conduct studies to evaluate the effectiveness of the portal in its entirety but also of specific components of it (eg, the effects of taking a self-directed course on the portal). We will also assess how users navigate the portal using system analytics of the POP Portal platform.

Conclusions

The POP Portal aims to empower people living with CP and associated mental health or substance use health needs with rapid access to flexible, responsive, and individualized resources to improve their overall quality of life and functioning. We anticipated that most recruited patients awaiting care at a tertiary pain clinic will use the POP Portal and find it to be acceptable for addressing some of their pain and associated health concerns. If the feasibility of recruiting and retaining patients is demonstrated as anticipated, we will move forward with a definitive multisite study evaluating the implementation and effectiveness of the POP Portal among patients waiting for a tertiary care consultation.

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Authors' Contributions

All authors contributed to the conceptualization and methodology of this protocol. AZ, EJB, YS, and PP contributed to writing the original draft and project administration. DR, NZN, LC, DJ, JAR, RB, and TR contributed to reviewing and editing the manuscript. PP and DJ contributed to funding acquisition and supervision.

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Conflicts of Interest

AZ, EJB, YS, NZN, LC, JAR, RB, and PP were involved in the development of the POP Portal, the web-based platform being evaluated in this study.

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
CP: chronic pain
POP: Power Over Pain
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Facial Feminization Surgery and Quality of Life in Transgender Women: Protocol for a Cohort Study

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Abstract

Background: Transgender women face significant health inequities. Facial feminization surgery is an intervention that aligns craniofacial structures with female anatomical norms and gender identity. Although international studies suggest that facial feminization surgery improves psychosocial outcomes, most studies have focused on aesthetic results or relied on generic quality-of-life instruments that have not been validated for this population. In Chile, no study has evaluated the multidimensional impact of facial feminization surgery using patient-centered measures combined with objective cephalometric and photometric analyses. Moreover, no validated Spanish-language quality-of-life instrument exists for transgender women undergoing this surgery.

Objective: This study aims to (1) develop and validate a culturally appropriate quality-of-life questionnaire for transgender women undergoing facial feminization surgery in Chile, and (2) evaluate postoperative changes in quality of life, perception of facial femininity, and cephalometric and photometric parameters.

Methods: The study will include 2 methodological phases: a cross-sectional validation study and a longitudinal cohort study. Phase 1 involves questionnaire development and validation, following the COSMIN (Consensus-Based Standards for the Selection of Health Measurement Instruments) guidelines, with a systematic literature review conducted according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, expert panel content validation, pilot testing, and psychometric evaluation in a cohort of ≥200 transgender women. Phase 2 is a longitudinal cohort study conducted at San Juan de Dios Hospital in Santiago, Chile, following the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines. Thirty transgender women scheduled for facial feminization surgery will be assessed at baseline and 12 months postoperatively. Outcomes include quality of life, self-perceived and third-party–rated femininity, and cephalometric and photometric changes (using cone beam computed tomography). Data analyses include exploratory and confirmatory factor analyses, Cronbach α, paired 1-tailed *t* tests or Wilcoxon signed-rank tests, chi-square or Fisher tests, and linear regression models.

Results: This study was funded in October 2023. Phase 1 (January 2024 to January 2025) included 216 participants, exceeding the minimum sample size requirement. Data analysis is ongoing, and results will be reported separately. Phase 2 is in progress, with preoperative cone beam computed tomography scans and photographs being collected. The validated preoperative questionnaire will be administered in late 2025, with surgeries scheduled throughout 2026. Data collection is expected to conclude in 2027.

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Conclusions: This protocol addresses a critical evidence gap in Latin America by integrating psychometric validation and longitudinal evaluation of facial feminization surgery outcomes among transgender women in Chile. The project is expected to develop the first validated Spanish-language quality-of-life instrument specific to facial feminization surgery, alongside multidimensional evidence of surgical outcomes. The findings will inform clinical decision-making, contribute to inclusive patient-centered care, and support the development of evidence-based policies for transgender health in the region.

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KEYWORDS

facial feminization surgery; transgender health; quality of life; cephalometry; gender-affirming care; Latin America; psychometric validation

Introduction

Background

Some countries face persistent challenges related to health inequities, influenced by factors such as socioeconomic status and geographical distribution. These disparities affect access to health care services across multiple population groups, including transgender individuals.

Transgender women are defined as individuals who identify with the female gender, independent of any medical or surgical interventions they may have undergone [1]. Facial appearance is a key determinant in gender recognition and social perception [2]. Facial characteristics typically associated with masculinity have been linked to increased exposure to social stigma and discrimination, which may contribute to mental health disparities within this population [2-4]. In Chile, available data indicate that the prevalence of depression among transgender individuals is approximately 10 times higher than in the general population, with suicidal ideation rates reaching 68%, compared with 2.2% in the general population [5,6].

Facial feminization surgery is a gender-affirming surgical intervention aimed at modifying facial structures to align with female anatomical norms [7-9]. Although this surgery has been associated with improved psychological and social outcomes, there is limited research evaluating its impact on quality of life using standardized, validated, and population-specific instruments. To date, no studies in Chile have systematically assessed the outcomes of facial feminization surgery, incorporating objective morphological measurements and validated patient-reported outcome measures.

Instruments commonly used to assess quality of life among transgender individuals were originally designed for the general population and later adapted for use in transgender contexts. However, these tools may not comprehensively capture the specific needs and expectations of transgender women undergoing facial feminization surgery [2,3,7,9-12]. Furthermore, most available instruments have been translated from English without undergoing formal validation for use in Spanish-speaking populations, potentially limiting their applicability in Latin American health care settings. Currently, no validated questionnaire exists in Spanish specifically addressing the quality of life of transgender women undergoing facial feminization surgery in Chile [13,14].

The surgery involves modifications to both hard and soft tissues, which can be assessed using cone beam computed tomography (CBCT) and standardized clinical photography. The international literature identifies the frontal-naso-orbital complex (including the forehead, supraorbital crest, frontomalar prominence, temporal ridges, and frontonasal transition) and the mandibular region (chin, mandibular body, angle of the mandible, ascending ramus, and basilar ridge) as the primary anatomical determinants of facial gender. Secondary regions of importance include the nose, zygomatic region, and thyroid cartilage [1,8,15,16]. However, there is a lack of local data in Chile describing the frequency and extent of surgical modifications to these anatomical regions.

Cephalometric differences between male and female facial structures are influenced by biological sex, ethnic background, and genetic inheritance. Typically, male faces have larger craniofacial dimensions, more acute nasolabial angles, and more obtuse mandibular angles, while female face exhibit more convex profiles, smaller nasal dimensions, and less prominent chins [8,15-19].

Objectives of the Study

This study aims to develop and validate a culturally and linguistically appropriate quality-of-life questionnaire specifically tailored to the transgender population in Chile. It also seeks to evaluate the impact of facial feminization surgery through the analysis of changes in cephalometric and photometric parameters and their association with perceived femininity, as assessed both by third-party evaluators and the participants themselves.

This study hypothesizes that transgender women undergoing facial feminization surgery will experience measurable improvements in quality of life, particularly when facial parameters align more closely with female anatomical standards. In addition, variables such as social participation, employment status, self-perception, and psychosocial stress will be examined to provide a comprehensive understanding of the effects of facial feminization surgery. By integrating multidimensional assessments of psychological well-being, facial morphology, and gender perception, the study aims to generate evidence to inform clinical decision-making and support the development of inclusive, evidence-based health care policies for transgender individuals.

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Methods

Study Design

This study consists of 2 complementary methodological components: questionnaire development and validation and a longitudinal cohort study.

Questionnaire Development and Validation

A cross-sectional study will be conducted to develop and psychometrically validate a novel quality-of-life instrument tailored for transgender women undergoing facial feminization surgery in a public hospital in Santiago, Chile. The study will follow the COSMIN (Consensus-Based Standards for the Selection of Health Measurement Instruments) guidelines for the development and evaluation of patient-reported outcome measures (Multimedia Appendix 1). The validation process will include assessments of content validity, structural validity, internal consistency, and reliability in accordance with the COSMIN methodology.

Longitudinal Cohort Study

A prospective longitudinal cohort analytical study following the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [20] will be conducted to evaluate the effects of facial feminization surgery across three primary domains: (1) quality of life, (2) perception and self-perception of facial femininity, and (3) cephalometric and photometric changes in hard and soft facial tissues (Multimedia Appendix 2).

Quality of life will be assessed using the validated questionnaire, administered preoperatively and at least 12 months postoperatively. Femininity perception will be evaluated through standardized facial photographs assessed by independent raters. Cephalometric and photometric changes will be measured using CBCT and analyzed with Dolphin Imaging software (version 12; Dolphin Imaging and Management Solutions).

Study Phases

Phase 1: Questionnaire Development and Validation

Overview

The instrument, titled Quality of Life and Perception of Femininity in Facial Feminization Surgery, will be developed and validated for use in both pre- and postoperative contexts. The development and validation process will follow 5 sequential stages [21,22]. First, a comprehensive review of the scientific literature will be conducted following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [23] to analyze instruments and tools used to assess quality of life in adult transgender women undergoing facial feminization surgery. The search will be performed in PubMed, Google Scholar, and SciELO databases for studies published between 2010 and 2024 in English or Spanish, using the terms “Quality of life,” “Quality of life instruments,” “Facial feminization surgery,” “Gender affirming surgery,” and “Facial gender affirming surgery” (Multimedia Appendices 3 and 4). Second, the initial construction of the questionnaire will integrate the specific needs and expectations of transgender women undergoing facial feminization surgery, the clinical and technical priorities of the surgical team experienced in facial feminization surgery, and evidence from validated quality-of-life instruments and clinical cases reported by other surgical teams. Third, content validation will be carried out by an expert panel composed of maxillofacial surgeons with experience in facial feminization surgery, sociologists specialized in gender studies, psychologists, public health professionals with expertise in instrument development, and transgender women from civil organizations. Panel members will independently assess the relevance, clarity, language, and cultural appropriateness of each item. A series of meetings will be held between the panel members and the research protocol authors. On the basis of this collaborative process, items will be revised, removed, or added to optimize content validity. Fourth, pilot testing of the preliminary version of the questionnaire will be conducted among transgender women enrolled in the gender identity program at San Juan de Dios Hospital. The objective of this phase will be to evaluate the clarity, acceptability, and comprehensibility of the items, as well as the overall structure and administration time of the instrument. Between 5 and 10 participants will complete the questionnaire in a supervised setting, followed by interviews aimed at identifying any difficulties in item interpretation, relevance of the content, and potential sources of confusion or discomfort. Finally, statistical validation of the questionnaire will involve a larger and more diverse sample of transgender women. Participants will be recruited from multiple sources to ensure variability in sociodemographic backgrounds and health care access. The final version of the questionnaire will be self-administered online.

Participants

Participants eligible for the questionnaire validation study must meet the following inclusion criteria: self-identifying as a transgender woman, being aged 18 years or older, living in Chile at the time of questionnaire completion, and being proficient in Spanish (speaking, reading, and comprehension).

Recruitment and Questionnaire Distribution

Participants for the validation phase will be recruited through multiple channels to ensure a diverse and representative sample of transgender women in Chile. Recruitment strategies will include telephone outreach to individuals currently enrolled in the gender program at San Juan de Dios Hospital; invitations extended to patients receiving private care from professionals affiliated with the gender program; snowball referrals, whereby participants may suggest other eligible transgender women within their social networks; and open call dissemination through social media platforms and digital networks of civil society organizations.

The questionnaire will be distributed digitally through a hyperlink and hosted on the Google Forms platform. This format will allow participants to complete the instrument remotely at their convenience while ensuring data security and accessibility, and may also help reduce response bias.

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Sample Size for Questionnaire Validation

Sample size determination for questionnaire validation was based on established methodological recommendations for psychometric studies. While some authors suggest including 5 to 10 participants per item of the instrument, others propose a minimum of 200 participants to ensure sufficient statistical power and stability of factor structures, regardless of the number of items. Following these recommendations, the validation phase of this study will include a minimum of 200 Spanish-speaking transgender women [24,25].

This sample size is deemed sufficient to perform exploratory factor analyses and, when applicable, confirmatory analyses, while also enabling the evaluation of internal consistency and strengthening the generalizability and reliability of the final instrument.

Data Analysis

Exploratory and confirmatory factor analyses will be conducted using polychoric correlation matrices and maximum likelihood estimation. Internal consistency will be assessed using Cronbach α, with a threshold of ≥0.70 considered acceptable. All analyses will be independently conducted by 2 researchers to ensure methodological rigor and reproducibility [26].

Phase 2: Longitudinal Cohort Study

Participants

This cohort will consist of transgender women undergoing facial feminization surgery at the San Juan de Dios Hospital in Santiago, Chile. Participants eligible for the longitudinal cohort study phase must meet the predefined inclusion criteria, as presented in Textbox 1.

Textbox 1. Inclusion criteria.

- Self-identified transgender women aged ≥18 years
- Currently enrolled in the gender program at San Juan de Dios Hospital
- Clinical indication for facial feminization surgery, including but not limited to genioplasty, mandibular reshaping (angle and basilar crest modification), frontal-nasal-orbital complex remodeling, rhinoplasty, and zygomatic-malar complex remodeling
- Absence of craniomaxillofacial syndromes or contraindications to surgery
- Completion of a multidisciplinary evaluation by a psychologist and a social worker, confirming psychological and emotional readiness for surgery
- Willingness to undergo pre- and postoperative cone beam computed tomography scans and standardized facial photography
- Proficiency in Spanish (speaking, reading, and comprehension)
- Capacity and willingness to provide written informed consent.

Sample Size Calculation for Cohort Study

The gender program at San Juan de Dios Hospital currently includes 70 transgender women undergoing hormone therapy and attending regular medical follow-up appointments. On the basis of this population size, a sample of 30 participants was calculated using a 95% confidence level and an estimated margin of error of 12%. This adjustment reflects logistical and ethical considerations related to long-term follow-up while maintaining sufficient statistical validity for exploratory analyses of surgical outcomes.

Data Collection

Quality of Life Assessment

Participants in the cohort study will complete the validated quality-of-life questionnaire before surgery and again at 12 months postoperatively.

Femininity Perception Assessment

Femininity will be assessed through both self-perception and third-party evaluation. Self-perceived femininity will be measured using the questionnaire responses regarding this matter.

To assess changes in third-party perception of femininity, a blind evaluation will be conducted using standardized frontal and lateral clinical photographs taken preoperatively and at least 12 months postoperatively. All images will be coded using an alphanumeric identifier (eg, FFS01, for “facial feminization surgery participant 01”), which will not be visible to evaluators. A control group of cisgender women will be included, using anonymized clinical photographs from the Maxillofacial Surgery Service at San Juan de Dios Hospital, authorized for academic and research purposes.

Forty undergraduate students from nonhealth-related fields (eg, arts, philosophy, architecture, and social sciences) at the University of Chile will serve as evaluators. Participants will be recruited through institutional emails and social media platforms.

Inclusion criteria require students to be aged more than 18 years, without training or experience in health, facial anatomy, or aesthetics. Exclusion applies to students with previous engagement with transgender individuals from the hospital’s gender program. Each student will provide informed consent. Evaluators will rate randomized images (including preoperative, postoperative, and control cases) using a 5-point Likert scale ranging from “feminine appearance” (1) to “non-feminine appearance” (5).

Four groups of 10 evaluators each will be formed, ensuring diversity in gender and age. Each group will be randomly assigned a set of photographs, including preoperative, postoperative, and control images, all displayed in a randomized sequence. As a critical methodological safeguard, pre- and postoperative images of the same patient will not be included within the same group to minimize direct comparative bias.

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Cephalometric and Photometric Analysis

Facial morphological changes will be measured pre- and postoperatively using CBCT, an imaging software, and extraoral pictures taken in a frontal and lateral view. The following parameters will be assessed: forehead inclination, true vertical distance, nasofrontal angle, mandibular angle, mandibular plane angle, facial profile, nasolabial angle, mentolabial angle, and mentocervical angle.

Data Analysis for the Cohort Study

Descriptive statistics will be used to summarize sociodemographic variables (absolute and relative frequencies). The Shapiro-Wilk test will assess the distribution of continuous variables. Normally distributed variables will be reported as mean and SD; nonnormally distributed variables will be reported as median and IQR. Pre- and postoperative comparisons of continuous variables will be made using paired *t* tests or Wilcoxon signed-rank tests, as appropriate. Categorical variables will be compared using Pearson chi-square or Fisher exact test. Linear regression models will evaluate the associations between cephalometric and photometric changes and perceived femininity scores. Statistical significance will be set at $P \leq .05$. All analyses will be conducted using Stata (version 11; StataCorp).

Ethical Considerations

This study will comply with international ethical standards for human participant research, including the principles outlined in the Declaration of Helsinki. To protect participant confidentiality, each participant will be assigned a unique identification code consisting of the acronym FFS (facial feminization surgery) followed by a sequential number based on the order of enrollment (eg, FFS01), which will be used consistently across all phases of the study.

Informed consent will not be required for the questionnaire validation, as this component involves no direct intervention or risk to participants. However, written informed consent will be obtained from all participants enrolled in the longitudinal surgical cohort. Both the research protocol and the informed consent form were approved by the Scientific Ethics Committee of San Juan de Dios Hospital on January 13, 2025. Data will be securely stored in password-protected files and locked in physical storage, accessible only to the authorized research team members. All data will be retained for 5 years following study completion, after which its continued storage will be reassessed; if no longer necessary, it will be permanently destroyed to preserve anonymity.

Results

This study was funded in October 2023. Phase 1, corresponding to the development and initial psychometric validation of the Quality of Life and Perception of Femininity in Facial Feminization Surgery questionnaire, was conducted between January 2024 and January 2025. A total of 216 transgender women participated in the study, which exceeded the estimated sample size.

The initial questionnaire design was based on a structured literature review conducted according to PRISMA guidelines, which identified existing tools and dimensions used to assess the quality of life of transgender women undergoing facial feminization surgery (Multimedia Appendices 3 and 4). Data analysis is currently in progress, and the corresponding manuscript is expected to be submitted for publication before the end of 2025.

Concurrently, phase 2 of the study—the longitudinal cohort assessing surgical outcomes—is ongoing. Standardized facial photographs and CBCT scans are being collected for presurgical cephalometric and photometric analysis.

The validated presurgical quality-of-life questionnaire will be administered starting in the fourth quarter of 2025 to more than 30 transgender women currently on the waiting list for facial feminization surgery. The surgeries are planned to take place throughout 2026, with the administration of the postsurgical quality-of-life questionnaire starting 12 months after surgery. Data collection is expected to conclude in 2027.

All relevant data underlying the preliminary findings of this study will be made available through the openICPSR repository. Data will be deidentified to protect participant confidentiality in accordance with ethical guidelines. Access to sensitive data that cannot be fully anonymized will be restricted because of ethical considerations. Requests for access to restricted data can be directed to the Scientific Ethics Committee of San Juan de Dios Hospital, Santiago, Chile, and will be considered on a case-by-case basis.

In case of early study termination, an ethically responsible discontinuation plan will be implemented, including notification to the ethics committee and participants, documentation of reasons, appropriate data analysis, and submission of a final report to ensure transparency and scientific value.

Discussion

Anticipated Findings

One of the main challenges of this study lies in the complexity of its design. The development and validation of a quality-of-life questionnaire specifically tailored to transgender women in Chile presents a substantial methodological undertaking. The absence of preexisting instruments written and validated in Spanish for this population necessitated the creation of a new tool that is both culturally sensitive and contextually relevant.

The validation process involved multiple stages, including expert review, pilot testing, and large-scale field validation. A total of 216 participants were successfully recruited and completed the questionnaire, exceeding the initial target of 200. This larger sample size enhances the robustness of the psychometric analysis and increases the reliability of the findings. The use of a nonprobabilistic sampling strategy—based on community outreach, institutional networks, and social media—facilitated access to a geographically and socially diverse population but may introduce selection bias, potentially limiting the generalizability of the results to the broader transgender population in Chile.

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The longitudinal cohort evaluating surgical outcomes includes 30 participants, a number determined by the eligible population currently enrolled in the gender program at San Juan de Dios Hospital. Although appropriate for exploratory analysis and reflective of real-world clinical constraints, this sample size may reduce the statistical power to detect subtle associations between cephalometric changes and psychosocial variables.

This study has several limitations that should be considered when interpreting the results. First, participant retention during the 12-month follow-up period may be affected by emotional fatigue, life transitions, or reduced interest, potentially leading to attrition and incomplete datasets. Second, the reliance on self-reported measures for quality of life and femininity perception may introduce response bias, particularly in contexts shaped by stigma or social desirability. To minimize this potential bias, the questionnaire was designed to be completed online in a self-administered format, thereby minimizing interviewer influence and reducing the likelihood of socially desirable responding. Third, while third-party assessments are included to complement self-perceptions, evaluations of gender expression and facial aesthetics remain inherently subjective and culturally variable. Finally, although a control group of cisgender women is incorporated, normative comparisons may still influence the interpretation of femininity scores.

Despite these challenges, this study is supported by several strengths that enhance its feasibility and scientific relevance. The project is developed in a health network that serves a significant proportion of Santiago's population, ensuring access to clinical infrastructure, a well-defined study population, and robust ethical oversight. Collaboration with civil society organizations in Santiago strengthens recruitment and fosters meaningful community engagement. To mitigate attrition risks, this study will implement participant-centered retention strategies, including regular follow-up through mobile messaging and social media to address potential geographic and logistical barriers.

Ultimately, this study is expected to make a valuable contribution to transgender health research in Latin America by addressing the critical evidence gap and introducing a validated, culturally appropriate instrument for clinical and academic use.

Conclusions

This study protocol outlines a 2-phase research project designed to address critical gaps in the evaluation of facial feminization surgery among transgender women in Chile. By developing and validating a culturally appropriate quality-of-life questionnaire and by assessing postoperative changes in femininity perception and facial morphology, this study aims to provide multidimensional evidence to inform both clinical practice and public health strategies. Despite logistical and methodological challenges, the integration of quantitative, anatomical, and psychosocial data is expected to generate meaningful insights that will contribute to more inclusive, patient-centered gender-affirming care in Latin America.

Acknowledgments

The authors acknowledge the Gender Program of San Juan de Dios Hospital and the transgender women participating in this study. The authors also thank the Scientific Ethics Committee of San Juan de Dios Hospital and the Research Office of the Faculty of Dentistry, University of Chile, for funding the publication of this manuscript. The sponsors had no role in the design, conduct, or reporting of this study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
COSMIN-based checklist for reporting the development and validation of a patient-reported outcome measure.
[DOCX File , 34 KB - resprot_v14i1e75065_app1.docx]

Multimedia Appendix 2
STROBE statement—checklist of items that should be included in reports of observational studies.
[DOCX File , 37 KB - resprot_v14i1e75065_app2.docx]

Multimedia Appendix 3
Study characteristics and quality of life assessment.
[DOCX File , 31 KB - resprot_v14i1e75065_app3.docx]

Multimedia Appendix 4
PRISMA flow diagram for inclusion and exclusion of studies.
[DOCX File , 64 KB - resprot_v14i1e75065_app4.docx]

Multimedia Appendix 5

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Peer review report from the Research Directorate (DIFO) of the Faculty of Dentistry, University of Chile.
[PDF File (Adobe PDF File), 195 KB - resprot_v14i1e75065_app5.pdf]

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Abbreviations

CBCT: cone beam computed tomography
COSMIN: Consensus-Based Standards for the Selection of Health Measurement Instruments
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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Protocol

Implementation, Experiences, Impact, and Costs of Artificial Intelligence in Chest Diagnostics: Protocol for a Mixed Methods Evaluation

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Abstract

Background: The ability to perform complex tasks has seen artificial intelligence (AI) used to support radiology in clinical settings, including lung cancer detection and diagnosis. Evidence suggests that AI can contribute to accurate diagnosis, reduce errors, and improve efficiency. The National Health Service England (NHSE)–funded Artificial Intelligence Diagnostic Fund (AIDF) is currently supporting 12 National Health Service (NHS) networks to implement AI for chest diagnostic imaging. There is, however, limited evidence on real-world AI implementation and use, including staff, patient, and caregiver experience, and costs and cost-effectiveness. A National Institute for Health and Care Research Rapid Service Evaluation Team Phase 1 evaluation provided insights into the early implementation of these tools and developed a framework for monitoring and evaluation of AI tools for chest diagnostic imaging in practice.

Objective: This mixed methods evaluation of AI tools for chest diagnostic imaging aims to address previous research gaps by exploring the implementation of AI tools for chest diagnostic imaging, the impact and costs of implementing these service models, and the experiences of patients, caregivers, and staff.

Methods: This study will be a mixed method evaluation of implementation, experiences, impact, and costs of AI for chest diagnostic imaging in NHS services in England, with the evaluation informed by the Major System Change Framework. Trust-level case studies (3 in-depth and up to 9 light-touch) will be performed, including staff member, patient, and caregiver; NHSE AIDF team interviews; meeting observations; and analysis of key relevant documentation. Qualitative data will be analyzed using Rapid Assessment Procedures and inductive thematic analysis, supplemented by in-depth deductive thematic analysis. Data from case study sites and other relevant sources will be used to assess outcomes at the other sites and for comparators. A pragmatic economic model of the chest diagnostic imaging pathway will be developed to estimate key costs and resource use associated with AI tool deployment. Together with input from national stakeholders and staff workshops, the study findings will then be finalized for reporting.

Results: As of September 2025, trust-level research and development approvals with participating sites are complete, and data collection has commenced. Results are expected to be reported by the end of February 2026.

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Conclusions: The study will provide new insights into the facilitators and barriers to the adoption of AI technology in health care and the perceptions of both the general public and health care staff on its use. It will also inform best practices in approaches for service performance evaluation, for the implementation of AI into existing care pathways, and for the development of models to best support evidence-based decision-making. It will thus establish a framework upon which the greatest benefits of the use of AI in health care can be realized.

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KEYWORDS

artificial intelligence; diagnostic imaging; lung cancer; mixed methods evaluation; patient outcomes; cost-effectiveness; patient experience

Introduction

Background and Rationale

In recent years, UK health care policy and guidance [1-10] and international research have highlighted the potential for artificial intelligence (AI)—advanced technology that can perform complex tasks associated with human intelligence [11-14]—to support and transform health care in areas such as radiology. Research has indicated potential benefits regarding a range of outcomes (eg, detection accuracy, error reduction or prevention, efficiency, decision-making, and reducing workforce burden) [13,15,16]. However, there is mixed evidence for some outcomes (eg, diagnostic accuracy) [17].

UK health policy increasingly recognizes the potential value of AI in supporting the efficiency and effectiveness of services provided by the National Health Service (NHS, the publicly funded health care system). In June 2023, NHS England (NHSE, a public body that runs and oversees the running of the NHS in England) announced the Artificial Intelligence Diagnostic Fund (AIDF), which has invested £21 million (US $27.93 million) to accelerate the deployment and implementation of AI diagnostic tools [18]. The fund focuses on chest x-ray (CXR) and chest computed tomography (CT) scans to improve the diagnosis of lung cancer and other conditions [18] and potentially help to address the current unmet need for faster CXR reporting [18]. In the longer term, the NHS proposes that using AI to assist with the early detection of lung cancer may improve patient care and outcomes [18]. However, guidance from the National Institute for Health and Care Excellence (a public body that assesses cost-effectiveness of health care interventions and provides guidance and recommendations on use of these interventions) has identified numerous evidence gaps that must be addressed in relation to AI for chest diagnostic imaging, including gaps on time saving and resource use, adverse effects, performance in different patient groups, ease of use, and impact [1].

In October 2023, the National Institute for Health and Care Research (NIHR) Rapid Service Evaluation Team (RSET) was commissioned to conduct a rapid evaluation of the implementation and outcomes of AIDF. Phase 1 aimed to establish existing evidence for implementing AI in radiology diagnostics, analyze early implementation of AIDF, and identify approaches for future evaluations of changes of this kind [19]. It comprised a systematic scoping review and an empirical study of network-led procurement of AI tools for chest diagnostic imaging, early deployment of AI tools within NHS hospital organizations; empirical work drew on qualitative, quantitative, and health economic perspectives [19]. The systematic scoping review identified potential benefits of AI in chest diagnostic imaging and radiology more broadly [20-22]. It also identified important gaps in knowledge, especially around real-world implementation, including how AI tools are procured, processes to support preparation for deployment, how staff, patients, and caregivers experience and perceive AI for diagnostics, and impact on service effectiveness and resources; this was partly because there are very few studies of real-world implementation of AI tools for radiology diagnostics [20-22]. The empirical study focused on procurement and early deployment of AI tools for chest diagnostics through AIDF [20,22,23]. It established that these processes took longer than anticipated by national leadership. Findings suggested that procurement and preparation for deployment were complex sociotechnical processes, placing significant demands on already busy staff. Key obstacles included variations in local imaging technology, extensive governance processes, and variable local data infrastructure, while important facilitators included advice and support from program leadership, networks sharing expertise and capacity, commitment from hospital staff and AI suppliers, and dedicated project management [20,22,23]. Phase 1 also delivered insights on implications for future evaluations, identifying several data sources that may support measurement of effectiveness and cost-effectiveness within the English NHS, but also noted that limitations to data availability need to be addressed [20,22].

Importantly, phase 1 was unable to evaluate the impact of AI on clinical practice, patient care and outcomes, and cost-effectiveness, and the perspectives of patients, caregivers, and those in the wider care pathway [20,22,24].

The implementation of AI for chest diagnostic imaging is currently operating across 12 imaging networks of NHS trusts (organizations that provide a range of health care to local populations). Deploying AI tools in this way has the potential to change organization and delivery of care both within and across these organizations, with the aim of improving service delivery and outcomes at regional levels. Therefore, these programs may be conceptualized as examples of "major system change," defined as "a coordinated, systemwide change affecting multiple organizations and care providers, with the goal of significant improvements in the efficiency of health care delivery, the quality of patient care, and population-level patient

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outcomes" ([25], p422). The framework of Major System Change of Fulop et al [26] outlines that it is necessary to evaluate all stages of implementation, including the decision to change, the decision on which model to implement, the implementation approach used, the implementation outcomes, and the intervention outcomes. This framework has been used to evaluate several national system changes within the English health care system (eg, reconfiguration of stroke services [26,27], specialist cancer services [28], COVID-19 remote home monitoring [29,30], and prenatal exome sequencing [31]).

While research has shown that AI diagnostic tools have the potential to support and improve the detection of lung cancer, little is known about how effective and cost-effective these tools are, or how staff, patients, and caregivers experience them. For recommendations to be made regarding the implementation of AI diagnostic tools, these knowledge gaps need to be addressed [4].

Aims and Objectives

This mixed methods evaluation of AI tools for chest diagnostic imaging aims to address previous research gaps by exploring the implementation of AI tools for chest diagnostic imaging, the impact and costs of implementing these models, and the experiences of patients, caregivers, and staff.

Research Questions

Table 1 provides details of our research questions (RQs) and which workstreams will address them.

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Table 1. Workstreams and research questions.

WS[a] and research question	Subquestions
1	
RQ1[b]. How has AI[c] for chest diagnostic imaging been implemented and used in practice in England?	• How AI is being used—what are the key functions, where it is being used in the diagnostic care pathway? • How are staff (clinicians, managers, and administrators) involved in using AI? • How did early implementation work, for example, in terms of planning and facilitation? • How are patients informed about the use of AI, for example, in terms of communication or consent? • How is AI for chest diagnostic imaging being governed, for example, in terms of information and safety? • How have relationships with or between services, networks, and suppliers influenced the organization and delivery of AI? • Have there been any adaptations in the service model, associated services along the care pathway, or governance over time? • To what extent was AI for chest diagnostic imaging implemented, for example, in terms of uptake, spread, and fidelity? • How did implementation approaches (eg, leadership, planning, and facilitation) and service models influence implementation outcomes (eg, uptake, spread, and fidelity) • What are the implications for equity, diversity, and inclusion? • Have there been any unintended consequences of implementing AI? • What are the implications for sustainability? • Which factors have been influential for implementation, for example, functions of AI, patient groups, organizational context, network leadership, national program or policy?
RQ2. What are the experiences of staff involved in delivering care supported by AI tools in chest diagnostic imaging?	• What are staff experiences of using AI for chest diagnostic imaging? • What are the factors (barriers or facilitators) that influence the delivery of AI tools for chest diagnostic imaging?
RQ3. What are the experiences of patients and caregivers who had chest x-rays or computed tomography (CT) investigations that were analyzed by staff (supported by AI tools)?	• How have patients found the care received as part of the diagnostic pathway (including the use of AI to support diagnostics)? • Are patients and caregivers informed or made aware of the use of AI? If so, how? • How are results communicated to patients? • What are the experiences of patients and caregivers with different demographic and clinical characteristics? • Which factors influence patient and caregiver experience of receiving care supported by AI tools in chest diagnostic imaging? (eg, trust and perceptions of AI) • What could be done to improve patient and caregiver experiences?
2	
RQ4. What is the impact of using AI for chest diagnostic imaging on service delivery and the wider system?	• What is the impact on patients, service delivery, and the wider system? (includes (1) process outcomes such as patient waiting times, processing times, knock-on effects on the overall pathway, ease of use, and resourcing and (2) clinical outcomes such as patient outcomes, safety, and diagnostic accuracy). What levels of AI performance will have a notable impact on these outcomes? • What are the implications for patients with different demographic and clinical characteristics, for example, age, sex, and ethnicity? • How do data quality and data completeness affect the evaluation of impact? • Which factors are likely to be most influential on impact, for example, the function of AI, IT infrastructure, and patient profile? • How are implementation approaches and service models likely to influence impact (eg, service delivery and patient outcomes)?
3	
RQ5. What are the cost and resource implications of setting up and delivering AI for chest diagnostic imaging?	• What are the implications for staff time, skill mix, and support in implementation and use (including tool maintenance)? • How does the implementation of AI for chest diagnostic imaging impact workforce requirements and workload distribution, including changes in staff roles, training needs, and potential shifts in resource allocation across diagnostic and operational workflows? • What are the wider resource implications of changes, for example, support at trust and network levels? • What are the costs associated with the fee structure—product cost, deployment services, training, and length of license? • What are the implications for equity, diversity, and inclusion? • Are there any unintended consequences, for example, for the workload?

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WS[a] and research question	Subquestions
4	
RQ6. What are the lessons for future implementation and evaluation of AI in diagnostics?	• Is AI for chest diagnostic imaging sustainable? Which factors might influence this? • How transferable are the lessons to other health care diagnostics settings? • How did services and networks use learning from their local evaluation processes? • How might local and national evaluation support learning more effectively in the future?

[a]WS: workstream.

[b]RQ: research question.

[c]AI: artificial intelligence.

Methods

Design and Theoretical Framework

This is a multisite rapid study that combines qualitative, quantitative, and health economic methods. This evaluation (phase 2) was informed by the findings from the phase 1 evaluation of AI tools for chest diagnostic imaging) [20-22], scoping conversations (eg, with academics, clinicians, policy representatives, professional bodies, and third-sector organizations and regulators) and previous research, and was developed in collaboration with the study Patient and Public Involvement and Engagement (PPIE) group. The evaluation will take place over 12 months (January 2025 to December 2025).

The implementation of AI tools for chest diagnostic imaging may be seen as an example of Major System Change. This study will thus be informed by the Major System Change Framework [26], which was designed to understand the processes, outcomes, and sustainability of such changes, in addition to the relationships between different stages of major system change (Figure 1) [26].

We will employ a 2-level case study design, including 3 in-depth case study trusts and up to 9 light-touch case study trusts, with the aim to ensure our evaluation can contribute both depth and breadth in its lessons across the workstreams (Table 2).

Figure 1. How workstreams will contribute to addressing components of the major system change framework [1]. AIDF: Artificial Intelligence Diagnostic Fund; WS: workstream.

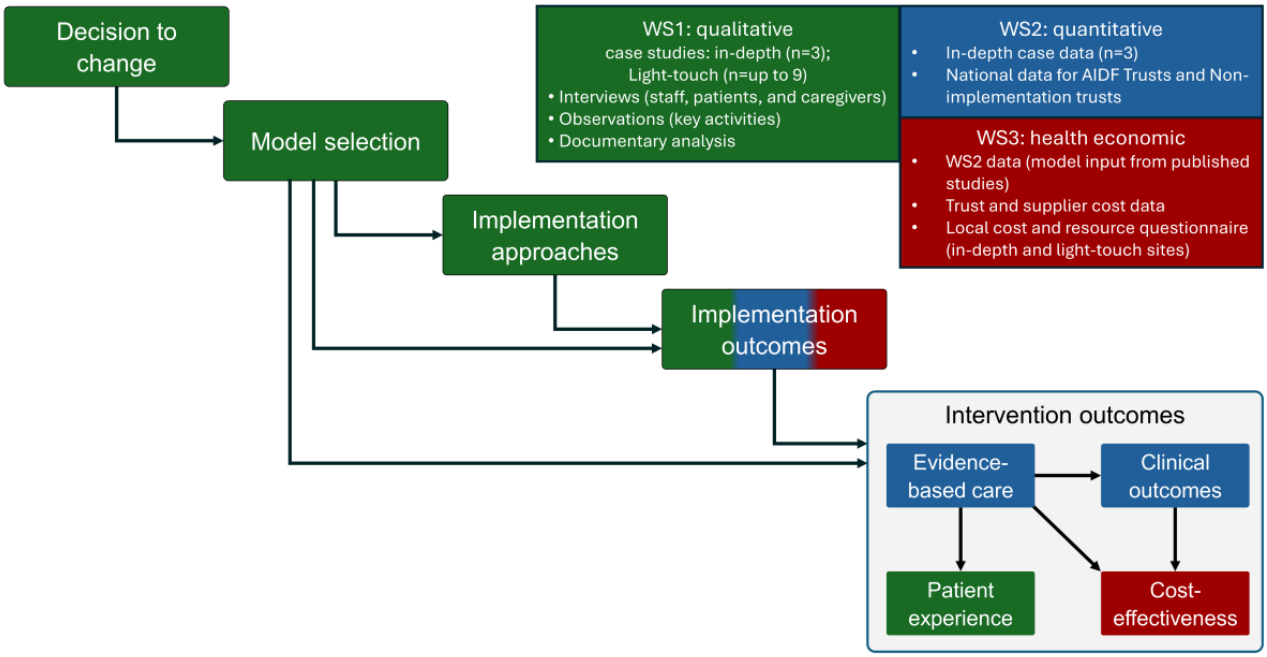

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Table 2. Summary of activity in in-depth and light-touch case study services.

	In-depth case studies	Light-touch case studies
Number of trusts	3	Up to 9
Workstream 1 activity	• Staff interviews (up to 11 per service), with potential follow-up interview of service lead • Patient and caregiver interviews (up to 6 per trust) • Nonparticipant observations (up to 10 per trust) • Documentary analysis	• Staff interviews (up to 2 per service), with potential follow-up interview of service lead • Documentary analysis
Workstream 2 activity	• Local datasets (eg, RIS[a])	—[b]
Workstream 3 activity	• Local datasets (workstream 2) • Comprehensive data • Cost or resource questionnaire • Relevant material raised in workstream 1 interviews	• Cost and resource questionnaire

[a]RIS: radiology information system.

[b]Not applicable.

The study has been developed and will be performed in compliance with NIHR RSET equality, diversity, and inclusion requirements, with interpretation of findings and final project write reviewed in consultation with the study PPIE group, advisory group, and wider team (Multimedia Appendix 1).

Workstreams

Workstream 1: Implementation, Staff, Patient, and Caregiver Experience of AI Tools for Chest Diagnostic Imaging (RQs 1-3)

This workstream will focus on the implementation of AI tools for chest diagnostic imaging in NHS services, staff experience with using AI tools for chest diagnostic imaging, patient and caregiver experiences of receiving care supported by AI tools for chest diagnostic imaging, and factors influencing implementation and experiences. The study will be of qualitative design, comprising semistructured interviews, meeting observations, and documentary analysis (Table 3).

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Table 3. Summary of primary data collection methods within workstreams 1 and 4.

Activity	Study participants	Approx. time
Workstream 1		
• In-depth • Interviews with staff • Interviews with other relevant staff	• Up to 32 staff members (10-11 per trust). This will include • Staff with direct involvement in AI[a] for chest diagnostic imaging (eg, radiologists—specialist and general, diagnostic and reporting radiographers, AI suppliers, PACS[b] and RIS[c] managers and suppliers, and teams who have been outsourced to provide reporting capacity) • Members of the chest or lung MDT[d] (eg, doctors, nurses, oncologists, and pathologists) • Staff with wider oversight or experience of development (eg, information governance teams, clinical safety teams, data managers, project managers, digital and AI leads, and radiology physicists) • Imaging network lead • Wider system staff (eg, GPs[e] or ED[f] staff)	30-60 minutes, with a potential follow-up interview with the service lead toward the end of data collection
• Light-touch • Interviews with staff	• Up to 18 staff (up to 2 per trust) • Service lead • Imaging network lead	30-60 minutes, with a potential follow-up interview with the service lead toward the end of data collection
• In-depth • Interviews with patients and caregivers	• Up to 18 patients and caregivers (6 per trust) who have received a CXR[g] or chest CT[h] that was supported by the AI tools for chest diagnostic imaging	30-60 minutes
• Documentary analysis of trust-level documents	• Relevant trust level documents pertaining to the implementation of AI for chest diagnostic imaging (eg, project plans, risk documents, meeting minutes, examples of anonymized AI reports, training materials, standard operating procedures, patient pathways, and AI specifications)	N/A[i]
• Observations of meetings	• Up to 30 meetings relevant to implementation of AI tools for chest diagnostic imaging. Meetings include • Project meetings • Training sessions • Trust governance meetings • ICB[j] oversight meetings	Duration of observed meeting
• Interviews with AIDF[k] program staff	• Up to 3 interviews with the national AIDF program team	30-60 minutes
Workstream 4		
• Online workshops	• Two online workshops (n=up to 20 participants) • Staff working in services that have implemented AI tools for chest diagnostic imaging (n=1 workshop, 8-10 participants per workshop) • Policymakers and other system leaders (n=1 workshop, 8-10 participants per workshop)	60-90 minutes

[a]AI: artificial intelligence.
[b]PACS: picture archiving and communication systems.
[c]RIS: radiology information system.
[d]MDT: multidisciplinary team.
[e]GPs: general practices.
[f]ED: emergency department.
[g]CXR: chest x-ray.
[h]CT: computed tomography.
[i]NA: not applicable.
[j]ICB: integrated care board.
[k]AIDF: Artificial Intelligence Diagnostic Fund.

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Sample

Site Selection

The study sample will comprise 3 of the 66 trusts as in-depth case studies, with up to 9 trusts as light-touch case studies. Site selection will be informed by our learning from the phase 1 evaluation [20-22] and an expression of interest process, whereby all trusts implementing AI for chest diagnostic imaging (through the national meetings) will be contacted for expressions of interest for study participation. Eligibility criteria for site selection are presented in Textbox 1 and for wider data collection in Textboxes 2 and 3. Sites meeting implementation and data quality criteria have been identified through local network engagement and implementation progress tracking, with study inclusion guided in collaboration with imaging network and service leads.

Textbox 1. Eligibility criteria for site selection.

- All sites will have implemented artificial intelligence (AI) in their chest diagnostic imaging service
- In-depth trusts will have sufficient prospects of good data quality (eg, local picture archiving and communication system [PACS] or radiology information system [RIS] data reports) to facilitate evaluation across workstreams 2 and 3
- Light-touch trusts will not be located in the same networks as the in-depth case studies.
- The study will seek to ensure representation across a range of service characteristics and contexts, including
  - The purpose of the AI tool (prioritization, identification of lung cancer vs identification of other chest conditions)
  - Scan type (chest x-ray vs chest computed tomography)
  - AI tool supplier
  - Geographical location (eg, urban, rural, and coastal)
  - Other relevant characteristics that will support decision-making (eg, referral pathways, leadership approach [imaging network vs trust], and local PACS and RIS set-up [local arrangement vs regional platform])

Textbox 2. Eligibility criteria for data collection.

Staff interview participants

- The National Health Service staff who work in or with the participating trusts, and who are involved in organization or delivery of care to patients receiving chest diagnostic imaging which have been supported by the artificial intelligence (AI) tools for chest diagnostic imaging; also, Artificial Intelligence Diagnostic Fund (AIDF) program staff
- Over the age of 18 years
- English-speaking or able to participate in an interview with an interpreter
- Able to provide informed consent

Patients and caregivers

- Patients and their caregivers (including family members) who have had a chest x-ray or computed tomography (CT) scan that has been supported using AI for chest diagnostic imaging, at one of the 3 trusts included in this study
- Over the age of 18 years
- English-speaking or able to participate in an interview with an interpreter
- Able to provide informed consent

Workshop participants

- National stakeholders with relevant job roles (eg, policymakers, commissioners, system leaders, and third-sector organizations) relating to the implementation of AI, or local staff involved in implementing AI from the eleven networks and 60 trusts implementing AI for chest diagnostic imaging as part of the AIDF
- Over the age of 18 years
- English-speaking or able to participate in an interview with an interpreter
- Able to provide informed consent

Documentary analysis

- Any documents pertaining to the implementation of AI for chest diagnostic imaging at the participating 3 trusts

Meeting observations

- Any meetings relevant to the implementation of AI chest diagnostic imaging at the participating 3 trusts

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Textbox 3. Exclusion criteria.

- Anyone under the age of 18 years
- Anyone who cannot provide informed consent
- Patients and caregivers for which the artificial intelligence tool was not involved in supporting their care
- Patients and caregivers at sites not included in this study

Recruitment and Consent: Initial Identification

Case Study Trusts

To recruit participating trusts, we will present the study plans at existing AIDF network meetings and invite trusts to express interest in taking part. Sampling will be informed by findings from our phase 1 evaluation [20]. In addition, and to ensure a diverse sample, sites will be asked to provide some basic information to enable sites to be purposively sampled (eg, data availability, the purpose of the AI tool, type of scan, supplier, geographical location, referral pathway, leadership approach, and local picture archiving and communication system [PACS] or radiology information system [RIS] setup).

Staff Interviews

The researchers will work with leads at each site to identify potential staff groups at their trust that may be appropriate for an interview. Researchers will contact potential participants via email to invite them to participate. Staff may also cascade details of the study (and an invite for anyone to contact the researchers if interested) to their staff networks to support recruitment.

Patient and Caregiver Interviews

The researchers will work with staff leads or R&D contacts at each trust. The staff leads (or research nurses, if available) will contact potential patients and caregivers who meet the eligibility criteria (by telephone, email, or post) to share a study advert and see if they would be interested in participating in the study. Potential participants will be asked to contact the research team directly if they are interested in participating; alternatively, potential interviewees may ask the staff lead or R&D contact to securely pass on their details to the researcher (using the secure UCL Data Safe Haven) if preferred. The researcher will then contact the patient or caregiver to provide further information.

In the first phase of our evaluation, the team learned that services are taking varied approaches to informing patients about the use of AI in the diagnostic process, with some sites choosing not to inform people explicitly. Therefore, the invitation to be interviewed may be the first time patients are made aware that AI supported their diagnostic process: this may cause patients concern or a desire for more information. To accommodate this eventuality, patients will be made aware of the purpose of this study and signposted to national and local sources of information at each stage of the identification and recruitment process, for example, in invitation and recruitment documentation.

The team recognizes that hospital services are extremely busy. Therefore, when recruiting in-depth sites, we will ensure that the proposed approach to identification, invitation, and recruitment is feasible in these sites; further, we will work with local research nurses in sites where they are available to support our work.

Note: For the purposes of patient and caregiver interviews, sites will be classified as Patient Identification Centres.

Meeting Observations

The researchers will liaise with staff leads at each trust to identify appropriate meetings to observe. For each meeting type, we will liaise with the lead of the event (eg, meeting chair or lead trainer) regarding whether observation will be possible and appropriate.

Workshops

To recruit workshop participants, we will circulate study adverts via existing AIDF channels and networks, professional groups, social media, local third-sector organizations, and direct invitations.

AIDF Staff

The researchers will work with the AIDF program leads to identify staff that may be appropriate for an interview. Researchers will contact potential participants via email to invite them to participate.

Details of informed consent processes are presented under the Ethical Considerations section.

Data Collection

Interviews

Interviews will last 30-60 minutes, and will be semistructured and audio-recorded (subject to consent). Interview topic guides have been developed iteratively, informed by phase 1 findings [20-22], scoping conversations, the Major System Change Framework [26], and previous research [32-35].

For in-depth case studies, the aim is to interview up to 32 staff members covering key clinical and organizational roles (Table 3) and sampling patients and caregivers across a range of characteristics, including health outcome following review of scan (and therefore care pathway) and sociodemographic characteristics (eg, gender, age, ethnicity, and disability). We anticipate that patient characteristics may influence how interviewees experience diagnostic imaging services supported by AI (eg, many sociodemographic characteristics may influence AI performance, with underserved groups being disadvantaged). Sampling patients in this way, therefore, ensures a range of perspectives are captured.

The semistructured interviews will be guided by topic guides tailored to stakeholder groups (Multimedia Appendix 2). Interviews will be transcribed verbatim by a professional transcription service and stored securely for analysis by the

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research team. In light-touch trusts, we will aim to interview up to 18 staff, with members of the NHSE AIDF program team also interviewed for their independent perspective (Table 3).

For all interviewees, sociodemographic information will be sought (on a voluntary basis), including job role and length of time in post (staff) or health outcome, comorbidities, age, gender, ethnicity, disability, sexuality, and employment status (patients and caregivers). All participants will also be informed that they are free to withdraw up to 2 weeks after the date of their interview.

Staff Interviews

Staff interviews will explore the interviewees' role and professional background, their views on the reasons and drivers for implementing AI tools for chest diagnostic imaging, the aims, purpose, and function of AI tools, how AI tools are intended to be used and being used in trusts, how care is supported by AI in their trust, their experience of using AI for chest diagnostic imaging (including training, support, etc), perceived impacts and examples of perceived impacts, governance, data monitoring and evaluation, resource use, impacts on (in)equality, unintended consequences of using AI, barriers and facilitators to implementation and delivery, key learnings, and future use. Interviews will be scheduled to take place during regular working hours, as staff are not being compensated for their study participation.

Patient and Caregiver Interviews

Patient and caregiver interviews will explore the care they experienced, investigations and outcomes received to date (eg, scan received and process of receiving their report), information provision (eg, whether and in which ways they were informed about use of AI), the experience of the care they have received (things they liked and things they disliked), timeliness of care, and barriers and facilitators to their care experience. If previously unaware of the use of AI in their care, they will be provided with a short vignette that explains the use of AI in their local trust followed by questions on their knowledge and views on AI, how it can be used in health care, whether and how the use of AI had been communicated to them, whether they would like to find out more from their care providers (and if so, how), views on the benefits and challenges of AI, perceptions of the impact of AI, possible unintended consequences of its use, and how AI should be used in the future. At the end of the interview, all patients and caregivers will be provided with a secure link to add any further information they would like to share in written format. Participant information sheets and consent forms to be translated, with translation services available for the interview itself, if needed.

Meeting Observations

Activities to be observed will include up to 30 meetings (up to 10 per in-depth trust) relevant to the use and governance of AI for chest diagnostic imaging, and health care affected by the implementation of AI in chest diagnostic imaging, AI implementation project meetings, AI training sessions, multidisciplinary team meetings, safety and quality committees (directorate- and trust-level), and regional oversight meetings.

Documentary Analysis

Local documents pertaining to the implementation of AI for chest diagnostic imaging (eg, project plans, risk documents, meeting minutes, examples of anonymized AI reports, training materials, standard operating procedures, patient pathways, AI specifications, local audits, and evaluation plans) will be analyzed across all participating trusts.

Data Analysis

A medium Q thematic analysis approach [36], combining inductive thematic analysis and the use of a coding framework [37], will be used to analyze findings. Real-time notes will be used for postinterview completion of Rapid Assessment Procedure (RAP) sheets [38], guided by RQs and the Major System Change Framework [26]. The categories used in the RAP sheet will be based on the interview topic guides. There will be flexibility to add categories during the research process.

Initial themes and subthemes will be developed using inductive thematic analysis [37], the interim findings of which will be shared with key stakeholders throughout the study. The themes developed during the rapid analysis will be applied to interview transcripts and observation field notes to develop an in-depth coding framework for final themes and subthemes with cross-case comparisons made across the case study sites and staff characteristics (eg, to explore barriers or inequities relating to implementation, delivery, and patient experience), where possible.

Workstream 2: The Impact of AI Tools for Chest Diagnostic Imaging (RQ 4)

This workstream focuses on evaluating the impact of AI tools for chest diagnostic imaging, performing mathematical modeling analysis on data from sample sites and relevant patient record datasets.

Design

Quantitative analysis of data derived from Hospital Episode Statistics (HES), Diagnostic Imaging Database (DID), and NHSE Benefit Register (where available) from all trusts that have implemented AI for chest diagnostic imaging through AIDF (n=63), including all networks involved in the AIDF program. More detailed analysis of imaging data from the 3 in-depth trusts. Given data availability limitations and the immaturity of postimplementation data, mathematical modeling of the chest diagnostic pathway will be informed by the sample data, supplemented with relevant evidence from published studies or the gray literature (these studies need not have investigated the use of AI).

Relevant data collected in workstream 1 will be analyzed to identify factors and implementation approaches likely to influence the impact of AI deployment.

Sample

Local data sampled from in-depth sites as described in workstream 1 unless where necessary (eg, due to data extraction or poor data quality issues). All 63 AIDF sites will be included for analyses of data sourced from HES, DID, and NHSE Benefit

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Metrics where it is available. Trusts that have not implemented AI for chest diagnostic imaging will be included as comparators.

Measures

The measures we will investigate will focus on (1) caseloads and workflow (eg, referral volumes, results of tests by category), (2) false positive and false negative results, (3) patient flow and waiting times (eg, time from CXR to CT scan, time to confirmed cancer diagnosis), (4) image processing and reporting (eg, turnaround times), (5) AI use and performance (eg, agreement with clinician, AI failure rates), (6) impact by patient characteristic, (7) influence on early detection (ie, the stage at which cancer is diagnosed), and (8) noncancer pathways outcomes.

False positives will include follow-up CT examinations with negative results (for CXR applications only) and subsequent cancer diagnoses that are negative. False negatives will include cancer cases that are missed by the diagnostic imaging supported by the AI. In all cases, the accuracy of the human reader with the AI tool in a decision support role is being measured.

Data Collection

We will seek empirical data from the in-depth sites (aggregated or summary, RIS or PACS system data), together with data from currently accessible resources, for sample and comparator sites: DID, HES, and NHSE Benefits Registers.

A short feasibility study supported by expert advice will also be undertaken to assess the value of HES in its ability to support the analysis of how AI deployment may impact inequalities.

Further data on the performance of AI may be sought from the AI suppliers or trusts, depending on local arrangements, and the availability of linkage to cancer diagnostic data for sites will be explored. The proposed use of each source of data is summarized in Table 4.

The extent to which we can investigate these metrics will depend on what we are able to glean from these data sources, and their quality and completeness. Since many sites are in the early stages of deployment, this is not yet clear, and the influence of data quality and completeness is included within the workstream.

For example, clinical outcome measures can only be obtained from sites where data are linked between radiology systems and cancer registries, allowing us to chart patients' diagnostic journeys to a definitive clinical outcome.

Understanding how outcomes differ for different types of patients, that is, understanding implications of deployment on inequalities, will require access to record-level data available from HES. The value of HES in supporting this analysis will need to be explored first to understand its capabilities and limitations, so, to this end, we will undertake a short feasibility study supported by expert advice.

Where we plan to use DID or HES for comparators, we will use longitudinal data both before and after deployments and apply statistical methods that will account for deployment at different times. When using patient-level data, trust factors can be included as random effects, and we could simultaneously explore any influence of patient characteristics. We cannot, however, account for simultaneous interventions that may be happening in comparator sites that aim to improve backlogs.

We will work alongside workstream 3 to develop a model of the lung cancer patient pathway supported by site data alongside available evidence from published sources on diagnostic accuracy, including resource constraints and efficiency. These will map the progress of patients from initial tests through to any confirmed cancer diagnosis with progressions dependent on the underlying cancer stage. The purpose of these models will be to link different levels of AI performance to outcomes such as volumes of follow-up tests, missed cancer diagnoses, and stage of cancer at first diagnosis. This would lead to more generalizable findings.

Once we scope data in HES and DID, we will know the degree to which we can investigate process outcomes (imaging processing, patient flow, etc). After speaking with individual sites regarding their data linkage, we will know whether we can look at clinical outcomes and match radiology data with the cancer registry. We will use existing evidence as well, but acquiring local data is important in centering this analysis around AIDF sites.

The nature of any potential bias that might affect our quantitative results have been, or will be, discussed with advisors, other stakeholders, and sites. We have attempted to request data from local sites and national datasets that include factors related to potential bias, where available. These will then be adjusted for in our analyses. Mindful that each trust organizes its local data differently, we are being thorough in our understanding of each field of data (in the form of continued correspondence with local data managers) to ensure that bias resulting from incorrect interpretation does not occur.

We will ensure that we define metrics that are less likely to be affected by missing data, that is, where a sample of cases will provide sufficient information. If there is missing data from local sites and it is important to our analysis, we will liaise with those sites to see if the issue can be rectified. In some cases, we can use proxy measures, for example, numbers of suspected cancers after x-ray as a proxy for numbers of follow-up CT scans.

Together with the work performed in workstream 3, these data and analyses will be used to develop a model of the lung cancer patient pathway from initial referral through to any confirmed cancer diagnosis. Evaluation of AI deployment will thus be enabled via generalizable study findings from the linkage of the impacts of AI deployment to diagnostic imaging and care pathway outcomes (eg, follow-up test volumes, missed cancer diagnoses, and stage of cancer at first diagnosis).

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Table 4. Proposed data sources for workstreams 2 and 3.

Data source	Proposed use	Advantages	Disadvantages
NHSE[a] Benefits Registers	• Measures relating to case volumes, the change in processing times, times to follow-up tests, resourcing, and cancer diagnoses • Measured at baseline and postdeployment (6 months, 12 months) • Used for metrics not covered by other sources • Mainly descriptive analysis	• Available for all sites • Data submission requirements of each site in order to obtain AIDF[b] funding • Ranges across most of the relevant outcomes	• Historic baseline available only • Processing times measured as averages • Not all data can be provided by all sites • Incomplete recording of new data fields (eg, image prioritization categorization) • Lacks the granularity required for study aims
Data from local sites	• Data underpinning the Benefits Register metrics available in greater detail • Within site exploration of variation by patient characteristics • Within site comparisons, for example, patients with normal and abnormal imaging results • Exploration of issues arising from workstream 1 interviews • Findings from local studies	• Can request greater data granularity • Can obtain greater detail on processing times • Can analyze data by patient characteristics • Potential to analyze specific noncancerous conditions (eg, infections, pulmonary embolism)	• Since these data inform the Benefits Registers, the issues of data completeness are the same • Agreements need to be put in place with each site we select • Aggregated data may restrict levels of granularity due to suppression of low numbers
DID[c]	• Analysis of outcomes relating to processing times. Comparison with non-AIDF sites	• Can be obtained for all sites and non-AIDF sites for comparison • Data completeness and quality assessments are also issued alongside publication • Longitudinal data • Can obtain greater detail on processing times • Can analyze data by patient characteristics	• Only available for a limited number of outcome measures • Approximate 5-month time lag • Aggregated data may restrict levels of granularity due to suppression of low numbers • Cannot identify patient cohorts with abnormal chest x-ray results
HES[d]	• This depends on the outcome of the feasibility study. Potential outcomes include times between diagnostic tests and treatments. Analysis of differences due to patient characteristics	• Easily available • Patient-level longitudinal data • Can analyze data by patient characteristics • Can analyze data for non-AIDF sites for comparison • Can isolate GP[e] referrals	• Feasibility is uncertain. It may lack some required detail • Diagnostic information in outpatient records may be limited, particularly because the type of procedure performed is not always specified in the data • Unable to distinguish suspected lung cancers from other reasons for CT[f] referral • Approximate 3-month time lag
Postmarket surveillance data	• Assessing the performance of the AI[g] tools such as clinician-tool agreement and AI failure rates	• Probably the only source of these data	• Agreements may need to be put in place with the suppliers
AI supplier cost data	• Key cost component for evaluation of AI deployment in workstream 3	• Cost data collated for all suppliers involved with the procurement process across all trusts in the AI deployment	• Aggregate estimates will not be fully representative of the specific costs applicable to individual trusts
Published AI platform performance metrics (sensitivity, specificity)	• False positive and false negative result rate estimates (where non-AI diagnostic imaging or AI supplier data are unavailable)	• Published large sample study data	• Published data may not reflect real-world service performance, given the variation in care pathways and AI platform application

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Data source	Proposed use	Advantages	Disadvantages
Participant trust questionnaires	• Collection of resource use and cost data relevant to the AI deployment and patient diagnostic pathway (eg, staff type, numbers, and time, equipment, and IT infrastructure)	• Able to pose questions specific to the requirements of workstream 3	• Knowledge required for completing the questionnaire may not reside with one individual or group • Risk of inaccuracy, bias, and generalizability for retrospective anecdotal evidence
Published lung cancer patient pathway cost and outcome data[h]	• Will be used to populate the care pathway are beyond the scope or resource capacity of the RSETi project	• Peer-reviewed estimates of costs and health outcomes for lung cancer patients in the UK population	• The need to assume that the published data are generalizable to the patient sample in the participating trusts

[a]NHSE: National Health Service England.
[b]AIDF: Artificial Intelligence Diagnostic Fund.
[c]DID: Diagnostic Imaging Database.
[d]HES: Hospital Episode Statistics.
[e]GP: general practice.
[f]CT: computed tomography.
[g]AI: artificial intelligence.
[h]By stage of diagnosis or associated with false negative or false positive diagnosis.
[i]RSET: Rapid Service Evaluation Team.

Workstream 3: The Cost and Cost-Effectiveness of AI Tools for Chest Diagnostic Imaging (RQ 5)

This workstream focuses on evaluating aggregate costs and cost-effectiveness of AI tool deployment in the diagnostic chest imaging stage of the lung cancer care pathway, across a small sample of participating sites for chest diagnostic imaging.

Design

Given the limitations of the resource capacity and timeframe of this project, a pragmatically designed economic model of the lung cancer care pathway will be developed, mapped to a simplified version of the National Optimal Lung Cancer Pathway (Figure 2) [39].

Figure 2. Overview of the lung cancer diagnostic pathway. Adapted from National Optimal Lung Cancer Pathway, NHS England, 2020 [40]. A&E: accident and emergency; CT: computed tomography; CXR: chest x-ray; GP: general practice; LC: lung cancer; NICE: National Institute for Health and Care Excellence. *Includes follow-up CT or CXR for patients with indeterminate results. **Rapid diagnosis pathway, where detailed staging and fitness investigations are not needed to guide management (eg, patients with advanced disease not suitable for curative intent treatment). ***False negatives are presumed to re-present at A&E.

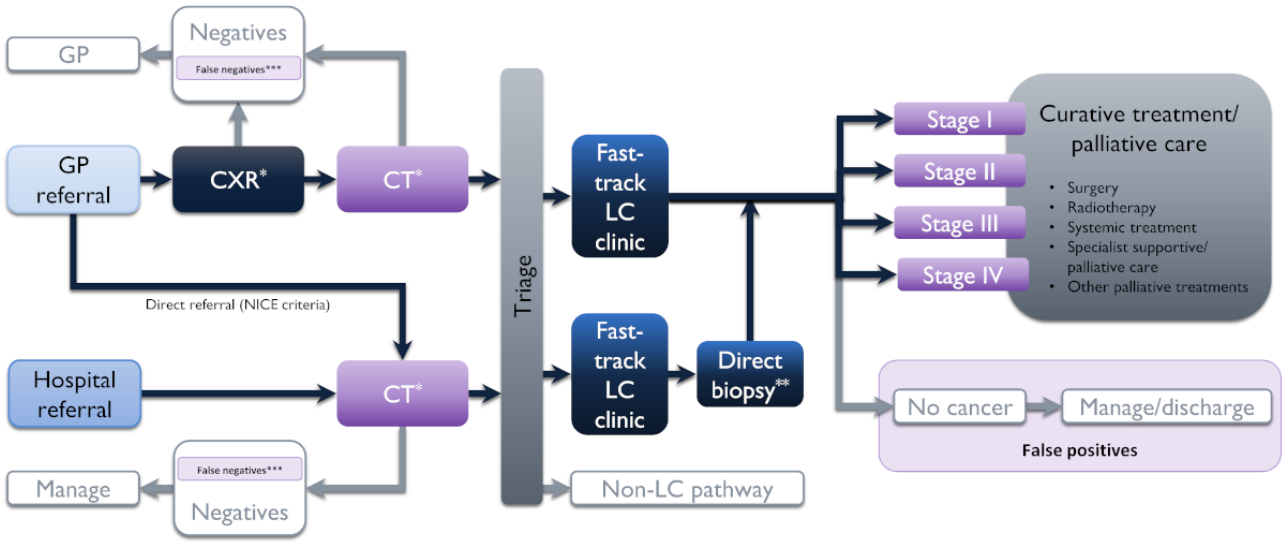

The model will adopt a decision tree approach with an NHS and Personal Social Services perspective, and a lifetime time horizon. Patient flow and short-term costs and outcomes from the chest diagnostic imaging stage of the care pathway will be informed by data collected in this study. Long-term costs and outcomes for lung cancer patients (by stage at diagnosis) will be derived from published estimates from relevant studies in a UK setting and from appropriate health service datasets.

The comparator for AI deployment will be the usual care pathways for chest diagnostic imaging predeployment (without AI assistance). Data for these pathways will be drawn from the same sites pre-AIDF implementation, plus data from sites where

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AI tools for chest diagnostic imaging have not been implemented.

Sample

The model will be populated by relevant data collated and synthesized from workstream 2 (local datasets from the in-depth participant trusts), responses to a participant questionnaire (completed by both in-depth and light-touch participant trusts), relevant AIDF material (eg, procurement documentation), and any relevant information raised during participant interviews in workstream 1. Data required for populating the model, which is otherwise unavailable from these sources (eg, beyond the time or resource scope of this project), will be obtained from relevant health care datasets or published studies.

Where comparative (AI vs non-AI) estimates are used to inform model input parameters, these will be evaluated relative to baseline data from the respective sites, or from sites which do not use AI in the care pathway (where available). Pre- and postdeployment data obtained during the collection period of the evaluation will be converted to annualized estimates for costs and outcomes, weighted by the respective chest diagnostic imaging activity of the participating trusts.

Measures

Relevant measures for informing the economic model are outlined in Table 5. Those to be obtained (where possible) from this study will include the measures listed in Textbox 4.

Measures for the economic modeling obtained from published studies or appropriate published datasets will include the items listed in Textbox 5.

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Table 5. Key inputs for the economic model[a].

Description	Category			Source[b]
	Care pathway	Cost	Outcome	
GP[c] referrals				
Total referrals, CXR[d] and CT[e] (n)	✓	✓		A
Referrals to CXR (n or % of total)	✓	✓		A
Referrals to CT scan (n or % of total)	✓	✓		A
Positive predictive value, CXR (%)	✓			A, B
Positive predictive value, CT (%)	✓			A, B
Hospital referrals				
Total referrals, CT (n)	✓	✓		A
Positive predictive value, CXR (%)	✓			A, B
Positive predictive value, CT (%)	✓			A, B
Chest imaging				
CXR costs (AI[f], non-AI)	✓	✓		A, C
CT costs (AI, non-AI)	✓	✓		A, C
CXR sensitivity and specificity (AI, non-AI)	✓	✓		A, C
CT sensitivity and specificity (AI, non-AI)	✓	✓		A, C
AI imaging failure rate (CXR, CT)		✓		A
Post imaging				
Confirmatory diagnostic testing, true positive	✓	✓	Disutility	A, B
Confirmatory diagnostic testing, false positive	✓	✓	Disutility	A, B
Fast-track LC[g] clinic				
Clinic MDT[h], no biopsy (n or % of total)	✓	✓		B
Clinic MDT, biopsy (n or % of total)	✓	✓	Disutility	B
Curative treatment or palliative care				
Treatment or care, by stage of diagnosis, true positive (n or % distribution)		✓	LY[i], QALY[j]	B
False negatives				
Patient re-presentation (GP, A&E[k])	✓	✓	Disutility	B
Chest imaging, confirmatory diagnostic testing, fast-track clinic (±biopsy)	✓	✓	Disutility	A, B
Treatment or care, by stage of diagnosis (n or % distribution)	✓	✓	LY, QALY	B
Other metrics: clinical safety				
AI incidents (Datix reports)	—[l]	—	—	A

[a]Inputs applicable for care pathways with the use of AI in either CXR or CT scans.
[b]A: RSET study data; B: health care datasets or published studies; C: supplier data.
[c]GP: general practice.
[d]CXR: chest x-ray.
[e]CT: computed tomography.
[f]AI: artificial intelligence.
[g]LC: lung cancer.
[h]MDT: multidisciplinary team.
[i]LY: life years.
[j]QALY: quality-adjusted life years.
[k]A&E: accident and emergency.

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[l]Not applicable.

Textbox 4. Measures collected for economic modeling.

- Patient caseloads and workflow (eg, referral volumes and results of tests by category)
- False positive results (based upon sites' data or published specificity data for non–artificial intelligence (AI) diagnostic imaging and from AI suppliers, where the former are unavailable)
  - Costs and outcomes subsequent to false positive results will be modeled on the assumption that patients progress for diagnostic testing and multidisciplinary team confirmation of no lung cancer, prior to discharge
- False negative results (based upon sites' data or published sensitivity data for non-AI diagnostic imaging and from AI suppliers, where the former are unavailable)
  - Costs and outcomes subsequent to false negative results will be modeled on the basis that patients present to either their general practice or accident and emergency (A&E) and are referred for diagnostic imaging following a delay after receipt of the false negative result, with a corresponding progression in stage of lung cancer at diagnosis
- Any costs and outcomes associated with patient flow and waiting times (eg, training for rapid delivery of results to patients, time from chest x-ray to computed tomography (CT) scan, time to confirmed cancer diagnosis)

Textbox 5. Measures from published studies or datasets.

- Distributions of cancer diagnosis, by stage (after true positive or false negative results)
- Post—chest imaging costs for confirmation of diagnosis (eg, multidisciplinary team case review, follow-up diagnostic and staging tests, and biopsy)
- Costs and health outcomes associated with lung cancer by stage of diagnosis, or with a false positive or false negative result

Costs and outcomes associated with other (noncancer) conditions which may diagnosed via chest imaging (incidentally or by specific request) will be out of scope for this evaluation.

Data Collection

Further to data relevant to the economic evaluation, which will be collected in workstream 2, data will be sought from the following sources.

Site-specific data on deployment, and AI use and performance (eg, staff type or mix, image assessment and reporting time, AI failure rates), will be sought via a data collection questionnaire which will be distributed by the project team to trusts during the project data collection stage.

AI supplier cost data are available in a protected area of the FutureNHS web portal. Owing to its commercial sensitivity, these data will be aggregated prior to use or publication.

Data Analysis

The proposed use of each source of data is shown in Table 4. To address concerns about the comparability of sites, we will use statistical adjustment for trust-specific and patient-specific characteristics (eg, age, comorbidities, and socioeconomic status) to control for differences between sites and populations. This approach will ensure that any observed differences in outcomes between AI and non-AI sites are not confounded by these variables.

Alternative models of AI implementation (eg, case prioritization, decision support, and autonomous AI reporting of high-confidence normal cases) will be explored for their relative potential impact on organizational and clinical outcomes.

Workstream 4: Developing Lessons to Inform Future Implementation and Evaluation of AI for Chest Diagnostic Imaging

This workstream will integrate findings from workstreams 1 to 3 and develop lessons to inform future implementation programs and evaluations (RQ 6, Table 1; see Table 4 for primary data collection methods).

Design

Integration of the workstreams will take place throughout the evaluation to enable complementarity of the workstreams (eg, workstream 1 has ensured interview topic guides cover issues relevant to workstreams 2 and 3; workstreams 2 and 3 will seek to analyze quantitative and resource data that are relevant to themes emerging from workstream 1; and workstreams 2 and 3 will collaborate on modeling work). Findings from workstreams 1 to 3 will be synthesized and then triangulated across workstreams (eg, aligning relevant workstream 1 findings on perceptions of impact, resource use, and explanatory factors to workstreams 2 and 3). Further, weekly meetings will enable qualitative, quantitative, and health economic researchers to share findings and interpretations across workstreams. Findings and developing recommendations will be integrated around our RQs and the Major System Change framework and will be presented at 2 stakeholder workshops.

Stakeholder Workshops

We will hold 2 online workshops with up to 20 participants (8-10 per workshop). The details of participants and workshop format are presented in Table 6. Further to the workshops, stakeholders will also be invited to provide further feedback

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during the development of drafts relating to specific findings (eg, quantitative evaluation guide).

Table 6. Stakeholder workshops.

Workshop	Participants	Workshop format
1: Staff	8-10 participants, including • Networks and trusts that are implementing AI[a] • AIDF[b] and non-AIDF sites	RSET[c] present • Findings and lessons learned (workstreams 1-3) • Recommendations on • Implementation of AI for chest diagnostics • Future research and evaluations
2: National stakeholders	8-10 participants, including • Payers • Policymakers • System leaders • Third-sector organizations	Participants discuss and make recommendations on • Study findings and lessons • Future and sustainability of AI tools • Chest diagnostics • Radiology diagnostics more generally

[a]AI: artificial intelligence.

[b]AIDF: Artificial Intelligence Diagnostic Fund.

[c]RSET: Rapid Service Evaluation Team.

Data Collection

Information sheets will be sent to interested participants, and consent for data collection will be sought in advance of the online workshops. Each workshop will last between 90 and 120 minutes, with discussions audio-recorded on an encrypted Dictaphone (subject to consent) and detailed notes taken to capture key findings. Recordings will be transcribed verbatim by a professional transcription service, anonymized and kept in compliance with General Data Protection Regulation (GDPR) 2018 and Data Protection Act (2018). Participants will be informed that while they can withdraw from the discussion, any data provided up until that point will be kept as it would not be possible to remove individual data from group discussions.

Data Analysis

Researchers will analyze workshop findings using inductive thematic analysis [37], organized around key themes and findings from workstreams 1 to 3. Workshop findings will support the validation and further development of recommendations for AI implementation and evaluation that result from this work.

Ethical Considerations

Human Subject Ethics Review Approvals

Based on the Health Research Authority (HRA) decision tool and consultation with the UCL and UCLH Joint Research Office, most components of this evaluation (staff-focused qualitative work, quantitative work, and health economic work) can be classified as a service evaluation; these evaluation components have received ethical approval from the UCL Life and Medical Sciences Research Ethics Committee (Project ID 0603). The patient and caregiver-focused qualitative work has received HRA ethical approval from the North West – Greater Manchester West Research Ethics Committee (Project ID 25/NW/0137).

Although this is a relatively low-risk evaluation, we are aware of the sensitive nature of this work for organizations and individuals, especially patients and caregivers. The research team has experience in conducting health and care research on similarly sensitive topics. We will maintain the independence of the research, follow an informed consent process, and maintain the anonymity of participants and organizations.

Informed Consent

Interviews and Workshops

All potential interviewees upon expressing interest in participating will be sent a participant information sheet and consent form (either by email or post, depending on preference). They will be given at least 48 hours to review the information and consider whether to participate. Participation is fully voluntary, and this is communicated clearly on recruitment documentation. If potential interviewees are happy to take part, they will be asked to provide consent prior to the interview or workshop. An informed consent process using participant information sheets and written consent (scanned forms or typewritten or electronic signature), or audio-recorded verbal consent will be used for recruitment to ensure and demonstrate informed and voluntary participation. If participants would prefer to post consent forms back, they will be sent a prepaid envelope to support this. If patients are not able or willing to take part in the interview but would still like their views to be included, we will ask patients if we can approach their caregiver (if they have one) to capture their perceptions of the patient's journey and overall experience with the service.

For interviews, the researcher will then arrange a time to conduct the interview over the phone or an online platform (Zoom or Microsoft Teams). If preferred or an individual interview is not possible, staff can choose to take part in a joint or group interview (where feasible). Similarly, patients and caregivers can choose whether they would like to take part in an interview separately or jointly.

For the workshop, participants will be sent the link to join once consent has been provided. Participation is fully voluntary, and this is communicated clearly on recruitment documentation.

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Meeting Observations

We will send the chair or event lead the information sheet and consent form. Participation is fully voluntary, and this is communicated clearly on recruitment documentation. If the event lead is happy in principle for the meeting to be observed, they will be asked to provide written consent, and information and consent forms will be shared with event attendees for information. Researchers will offer to present to the meeting an overview of the evaluation and what observations will involve. At the start of each meeting, we will also gain verbal consent from meeting or event attendees for the study team to observe and take anonymized notes.

Privacy and Confidentiality

Qualitative Data (Workstreams 1 and 4)

Participant interviews and workshops (qualitative data) will be recorded on an encrypted, password-protected digital recorder (only the researcher will know the password). Data will be collected by a team of qualitative researchers from RSET. Staff, patient, and caregiver interview, observation, and workshop consent forms, audio recordings, anonymized notes, and any documents received will be securely transferred using the Data Transfer portal onto the UCL Data Safe Haven (DSH, a secure electronic environment, certified to ISO27001 information security standard and conforms to the NHS Information Governance Toolkit). Once transferred onto the UCL DSH, the data will be cleared from the Dictaphone.

Any participant consent forms received via post will be sent to our RSET team members at University College London (UCL) and securely transferred onto the UCL DSH. Paper copies will be securely destroyed once scanned and uploaded to the UCL DSH. Electronic copies of consent forms received via email will be transferred onto the UCL DSH. If patients and caregivers would prefer to provide written consent or submit responses to sociodemographic questions using a secure survey link instead of verbally during the interview, the research team will develop online survey versions using the platform REDCap (Research Electronic Data Capture; Vanderbilt University). Patients and caregivers would be sent a link, and responses would be returned directly into the UCL Data Safe Haven via REDcap and would only be accessible by the qualitative research team.

Digital audio recordings of participant interviews and workshops will be sent to a UCL-approved contractor for transcription (TP Transcription Limited). Transcripts will be fully anonymized (names and places) and organized by participant codes. Anonymized transcripts and other relevant data will be stored in a secure folder to which only the named researchers (RSET qualitative team) have access. Only the research team will have access to participants' personal data (ie, name and contact details). Participant identifier codes will be stored in the UCL DSH and kept separate from study data.

Impact and Cost Data (Workstreams 2 and 3)

Trust and network-level benefits registers will be accessed via NHSE and transferred to the UCL DSH, where it can only be accessed by members of the research team. These data are aggregated across the deployment sites and will, therefore, not contain any person-identifiable information.

Lung cancer diagnostics and outcome data from individual sites will not contain any person-identifiable information and will be processed within the UCL DSH (where it can only be accessed by members of the research team), after transfer from the network sites via the FutureNHS website**.** These data will either be aggregated with low numbers suppressed or in the form of summary statistics reflecting data distributions (eg, medians and standard errors of turnaround times). Data sharing agreements will be drawn up for each site from which we request data.

Data from the DID will come from NHSE and in an aggregated form. This will be kept within the AI folder on the Nuffield OneDrive for analysis. An appropriate data acquisition form will be completed.

HES outpatient, inpatient, and emergency care datasets are held by the Nuffield Trust and stored on its secure server. An agreement is already in place with NHSE to allow Nuffield Trust staff to use these data for NIHR RSET projects. Staff undertaking patient interviews will have no access to these data and, similarly, all details on patient interviews will be stored on the UCL DSH in an area that will be inaccessible to staff using the HES datasets. This mitigates against interviewed patients being identified in HES.

AI supplier cost data will be held on DSH and will be accessed from a protected area of the FutureNHS. Data will be anonymized and aggregated to mean overall estimates for the respective diagnostic imaging method, prior to use. Returned participant questionnaires will be securely transferred onto the UCL DSH (electronic copies), and if applicable, paper copies will be securely destroyed once scanned and uploaded to the UCL DSH.

Our use of HES is covered by an agreement with NHSE for its use in RSET projects, which will cover secondary analysis without consent (ref: DARS-NIC-194629-S4F9X). Other national data (DID) is aggregated, so no such approval is necessary. Data received from trusts is either nonpersonal aggregated data or, if patient-level, received under terms agreed by the trust that covers the use of the data for secondary analyses without primary consent.

Data Handling and Management (All Workstreams)

A Data Sharing and Processing Agreement is in place between the research team and NHSE for the purposes and duration of this evaluation. This covers documents held and developed by the AIDF program.

The study is compliant with the requirements of GDPR (2016/679) and the Data Protection Act (2018). All researchers and study site staff will comply with the requirements of the GDPR (2016/679) with regard to the collection, storage, processing, and disclosure of personal information, and will uphold the Act's core principles.

UCL will act as data controller for this study, with principal researcher (AIGR) leading on associated processes. He will process, store, and dispose of all data in accordance with all applicable legal and regulatory requirements, including GDPR and the Data Protection Act (2018) and any amendments thereto.

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Only relevant and necessary data will be collected in line with the aims of this study. Data will not be transferred to any party not identified in this protocol and are not to be processed and transferred other than in accordance with the participants' consent.

In line with GDPR guidelines on data minimization, we are only collecting personal data that is relevant and necessary for this study.

Compensation Details

Participants will receive no compensation or incentive to take part in this evaluation.

PPIE

Members of the PPIE group have and will continue to contribute extensively throughout the life of the project. These contributions will include participation in dedicated PPIE workshops, attendance of study team meetings, and supporting the development of study methodology, the consideration of key findings, and the drafting of public-facing outputs for dissemination (Multimedia Appendix 1).

Results

As of October 2025, trust-level research and development approvals with participating sites are complete, and data collection has commenced. Results are expected to be reported by the end of February 2026.

Discussion

Expected Findings

This protocol describes the methodology for a mixed methods study aimed at providing a greater understanding of the use of AI tools in chest diagnostic imaging.

The study comprises four concurrent workstreams: (1) qualitative exploration of the facilitators and barriers to the implementation of AI in chest diagnostic services, and views on AI implementation from patient, caregiver and health service member perspectives; (2) quantitative evaluation of the impact of AI tools on chest diagnostic imaging, based upon mathematical modeling analysis of key service metrics data from sample sites and from relevant patient record datasets; (3) evaluation of aggregate costs and cost-effectiveness of AI tool deployment in the diagnostic chest imaging stage of the lung cancer care pathway; and (4) integration of findings from workstreams 1 to 3 for the development of recommendations to inform future implementation programs and implementation evaluations.

This study builds on the work in the phase 1 study [24], which reinforced the appreciation of a sparse landscape for publications on the real-world use of AI, including the perspectives of patients, caregivers, or general public, or the effects of AI on inequalities and service costs. Despite the potential for AI to help with diagnosis and an initial overall positive outlook from health care staff on the future use of AI, implementation for chest diagnostic services took longer than anticipated. The process of implementation was resource-intensive, covering multiple tasks including AI tool procurement, ensuring it worked safely within hospital systems, meeting clinical and organizational governance requirements, and establishing service audit and performance monitoring frameworks. Initial indications of facilitators (eg, support/input from specialists or experienced colleagues) and barriers (eg, dedicated time and resources) to the implementation process were also identified.

These findings provide a framework from which the phase 2 study can explore these and other areas of interest in greater breadth and depth. This will result in the production of a complementary series of findings which will inform best practice for communicating the role and benefits of AI in health care, the advancement of AI adoption in health care service delivery, and in the provision of robust evidence for future health service planning.

Limitations

We acknowledge several limitations in this study, some inherent to rapid evaluations, and others specific to the context of AI deployment.

It is noted that participating sites are "early adopters" of AI technology in the context of chest diagnostic imaging: this may represent a risk in the generalizability of lessons identified. To help address this, we will seek to include later adopting services within our light-touch sample. We will also explore the extent to which our sampling represents a limitation to the learning generated in any resulting reports from this evaluation.

Our qualitative workstream will collect data from most of the imaging networks participating in AIDF and capture evidence from services that use AI tools differently in diverse organizational contexts. However, it is likely that we will be unable to analyze the full range of experiences of implementing AI tools. Our light-touch sites will capture less data and from fewer stakeholders and will not include patient and caregiver perspectives. Our patient and caregiver sample will cover a diverse range of backgrounds and experiences but will be unable to capture the full range of different patient groups experiencing AI-supported diagnostics. Finally, we will be unable to observe clinicians reading AI-supported diagnostic outputs.

Although national datasets will be used for analysis where applicable, participating sites for the study will be limited to a small sample with sufficiently mature postimplementation data for analysis and that are able to ensure timely access to their data. While we seek to be able to evaluate whether observed changes in these sites are significant, generalizable findings from their data alone may be difficult or potentially not possible. Moreover, the expected accessibility of data, timescales for project and site implementation, and the linkage of data across the care pathway will affect the extent to which we can explore and draw inferences from key service metrics, may preclude the observation of longer-term impacts (eg, stage of cancer at diagnosis) and the ability to chart patient journeys through the care pathway.

The AIDF program was implemented at a time when many networks and trusts were simultaneously experiencing interventions aimed at addressing service backlogs as a consequence of the COVID-19 pandemic. In our analysis, it

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will not be possible to account for the impact of these simultaneous interventions in the comparator sites.

For the economic modeling, we will endeavor to ensure that population of model parameters for the comparator (usual care) pathway is as robust as possible. We acknowledge, however, that this will depend on the availability and quality of data from the relevant sources, and where these are insufficient, appropriate data from existing studies will be sought to inform the model.

Conclusions

AI has the potential to transform the delivery of health care across multiple clinical specialisms, in terms of improvements to diagnostic accuracy, error reduction or prevention, productivity, clinical decision-making, and reducing workforce burden. To date, however, there is mixed evidence for the realization of this potential, which is a risk given the notable financial and resource investment that would likely be required for a national implementation program.

Obtaining greater insights into facilitators and barriers to the adoption of AI technology, perceptions of both the general public and health care staff on the roles AI may play in health care delivery, best practice for the implementation of AI into existing care pathways and service infrastructure, accurate service performance evaluation, and the development of models to best support evidence-based decision-making, are important in establishing a framework upon which the greatest benefits of the use of AI in health care can be realized.

Acknowledgments

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The study funding has been reviewed by the UCL (University College London) Research Office and is sufficient to cover the requirements of the study.

The NIHR Rapid Service Evaluation Team (RSET) team and Public Contributors are grateful to all participants in the study, including national stakeholders, local teams (including implementation leads and clinicians), the independent project advisory group of researchers, policymakers, the voluntary sector, and patient or caregiver representation, for their work in oversight of the study and protocol development.

Data Availability

The availability of original data for the study will be restricted subject to data sharing agreements for the participating trusts and for electronic patient record dataset access, in accordance with their terms of use (eg, Hospital Episode Statistics).

Authors' Contributions

AIGR led the development of the project and protocol overall. Development of individual workstreams was led by AIGR, NH, RL, CL, HW, and NJF (workstream 1); CS-J, SB, and MB (workstream 2); KH and SM (workstream 3); and AIGR (workstream 4). KH led drafting of the initially submitted protocol. All authors discussed and made substantial contributions to the design of the protocol, approved the final version of the protocol, and agree to be accountable for all aspects of the work.

Conflicts of Interest

AIGR is a trustee of the Health Services Research UK and was an associate member of the NIHR HS&DR Commissioned Board (2014-15) and associate member of the NIHR HS&DR Board (2015-18). RM is a trustee of the Middlesex Association for the Blind (April 2015 – present; chair since December 2020), trustee of the Research Institute for Disabled Consumers (October 2018 – present; vice-chair since August 2020), a nonexecutive director of Evenbreak (February 2016 – present), and trustee of the Thomas Pocklington Trust (November 2019 – present). SM is currently (2022–) a member of the SBRI Healthcare panel. His post is funded in part by RAND Europe, a nonprofit research organization. He is also deputy director of Applied Research Collaboration East of England (NIHR ARC EoE) at Cambridgeshire and Peterborough NHS Foundation Trust. He was formerly a member of the NIHR HS&DR Programme Funding Committee (2014-2016), the NIHR HS&DR Evidence Synthesis Sub Board (2016), the NIHR Unmet Need Sub Board (2019), the NIHR HTA Clinical Evaluation and Trials Board (2007-2009), the NIHR HTA Commissioning Board (2009-2013), the NIHR PHR Research Funding Board (2011-2017), and the NIHR PGfAR expert subpanel (2015-2019). He was also an associate member of the NIHR HS&DR Commissioned Board (2014-15) and an associate member of the NIHR HS&DR Board (2015-18). JS is a nonexecutive director at Care City (June 2019 – present), advisor to the Harley Street Health District (September 2024 – present), senior associate at ZPB Associates (February 2024 – present), and an RSA fellow (December 2019 – present). NJF is currently a nonexecutive director at Covid-19 Bereaved Families for Justice UK (August 2022 – present) and a member of the National Emergencies Trust Advisory Board (September 2025 – present). She has also been a nonexecutive director at Whittington Health NHS Trust (October 2018 to October 2024), trustee with Health Service

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Research UK (to November 2022), and formerly a member of the following: the UKRI and NIHR College of Experts for Covid-19 Research Funding (2020), the NIHR Health and Social Care Delivery Research (HS&DR) Programme Funding Committee (2013-2018), and the HS&DR Evidence Synthesis Sub Board (2016). All other authors have no conflicts of interest to declare.

Multimedia Appendix 1
Additional information on governance and oversight.
[DOCX File , 110 KB - resprot_v14i1e81421_app1.docx]

Multimedia Appendix 2
Topic guides for semistructured interviews.
[DOCX File , 100 KB - resprot_v14i1e81421_app2.docx]

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Abbreviations

AI: artificial intelligence
AIDF: Artificial Intelligence Diagnostic Fund
CT: computed tomography
CXR: chest x-ray
DID: Diagnostic Imaging Database
GDPR: General Data Protection Regulation
HES: Hospital Episode Statistics
HRA: Health Research Authority
NHS: National Health Service
NHSE: NHS England
NIHR: National Institute for Health and Care Research
PACS: picture archiving and communication system
PPIE: Patient and Public Involvement and Engagement
RAP: Rapid Assessment Procedure
REDCap: Research Electronic Data Capture
RIS: radiology information system
RQ: research question
RSET: Rapid Service Evaluation Team
UCL: University College London
UCL DSH: UCL Data Safe Haven

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Protocol

Automated Personalized Goal Setting for Individual Exercise Behavior: Protocol for a Web-Based Adaptive Intervention Trial

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Abstract

Background: The incidence of chronic diseases associated with physical inactivity is on the rise, being one of the leading risk-increasing factors for early death rates throughout the world. Often, physical activity interventions fail to deliver sustained adherence over time due to limiting tailoring to individual baseline characteristics, leaving out contextual changes over time. One solution for this issue may be the use of adaptive interventions relying on contextual multiarmed bandits, a type of reinforcement learning algorithm, that can use baseline and contextual individual data to personalize aspects of the intervention, such as developing personalized workout plans.

Objective: The main objectives of this study are (1) to determine the effectiveness of contextual bandits for automated goal setting in the context of a web-based physical activity intervention, (2) to understand the role of user characteristics impacting ideal workout schedules based on adherence to predetermined goals, and (3) to explore the influence of user autonomy on recommendation effectiveness.

Methods: We developed a protocol for a web-based adaptive intervention trial to investigate the effectiveness of goal recommendation (task difficulty) based on reinforcement learning. The web application (named Apptivate) creates workout routines with 3 different difficulty levels, changing the total workout duration as well as rest times between exercises. Physical activity professionals validated the routine design, ensuring that workouts match recommended guidelines for healthy adults. An initial pilot was conducted, aiming for 800 university students to test the web application for 1 week, to provide initial data to calibrate the algorithm as well as overall feedback for the web application. For the main study, a total of 500 university students will be recruited to participate for 40 days during early 2026. Participants will be divided into 3 groups: user choice (no recommendation), user choice with automated recommendations (contextual bandits), and automated plans without choice.

Results: The pilot was conducted in September 2025. Data analysis for the pilot is undergoing, and the main study is planned for early 2026. Our main statistical analysis includes a direct comparison (paired tests) between success rates across intervention arms, as well as by difficulty level and individual characteristics.

Conclusions: Physical activity maintenance is key to achieving long term health goals. Tailored digital interventions are promising strategies for physical activity adherence, but personalization often fails to consider dynamic contextual changes. The proposed protocol for a physical activity intervention using adaptive experimentation can provide robust causal inference on the role of choice versus autonomy when goal difficulty is tailored under an adaptive data-driven approach.

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KEYWORDS

contextual bandits; behavior change; adaptive experiments; personalized exercise; machine learning; user autonomy

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Introduction

Regular physical activity (PA) is essential for maintaining overall health and well-being [1]. Extensive research has demonstrated that consistent exercise is associated with numerous health benefits, including improved sleep quality, enhanced mood, and a reduced risk of noncommunicable chronic diseases such as diabetes, stroke, depression, and dementia. In contrast, physical inactivity has been identified as one of the leading risk factors for premature mortality and a significant contributor to the rising health care costs [2-4]. Despite the well-documented benefits of PA and risks associated with a sedentary lifestyle, 31% of the global adult population—equivalent to 1.8 billion adults—fail to meet the recommended levels of PA [5]. Even with unwavering global efforts from national and international policy, mass media campaigns, and social support and educational programs [6], the number of adults who are physically inactive has been steadily increasing in high-income countries [7].

To address this public health issue, researchers have designed and implemented various interventions aimed at promoting regular exercise adherence, many of which are based on prominent social and psychological theories [8,9], such as theory of planned behavior [10] or self-determination theory [11]. Although these interventions have shown promise in increasing individuals' intentions to engage in PA, a key challenge lies in translating these intentions into sustained behavior [12,13]. This discrepancy is known as the "intention-behavior gap," emphasizing that goal intentions only partially materialize on corresponding actions [14]. Studies indicate that individual factors such as lack of motivation and low self-efficacy, as well as environmental barriers, such as time constraints, can hinder individuals from acting on their intentions, even when they recognize the benefits of PA [13,15]. Moreover, these factors are highly heterogeneous across individuals and time. Thus, addressing these challenges requires individualized, flexible, and engaging interventions that consider individual needs, preferences, and contexts, and that promote self-efficacy and focus on closing the intention-behavior gap.

Mobile apps have emerged as promising platforms for delivering effective health interventions owing to widespread technological access and potential for personalization or tailoring [16]. While the overall evidence on the effectiveness of app-based mobile health (mHealth) interventions on PA engagement is mixed [17-19], interventions that allow for tailoring (ie, fitting interventions to users), especially considering changes in context over time, show promising results [16]. For example, a study in 2006 demonstrated that computer-tailored interventions, which provide personalized feedback and actionable recommendations, significantly increased PA levels among participants compared to generic advice [20]. Similarly, researchers in 2011 found that interventions incorporating goal-setting, self-monitoring, and personalized planning were more effective in promoting sustained behavior change [21]. These approaches recognize that a "one-size-fits-all" strategy is often insufficient, as individuals face unique challenges such as time constraints, lack of social support, or low self-efficacy. By addressing these barriers through tailored solutions, such as adaptive goal-setting, context-specific reminders, or individualized support systems, interventions can better align with participants' lifestyles and may potentially enhance their ability to act on their intentions [22,23].

The taxonomy of personalization features is extensive, as apps allow for data-driven mechanisms that can respond to user behavior and real-time context, delivering messages, adapting to user experience, tailoring interactions with other participants, and providing user targeting, among other features [23]. However, in most apps, personalization is designed to increase user engagement with the app rather than focusing on sustained behavior adoption [24], which may be a consequence of lacking integration between app-based health research and existing theoretical frameworks explaining behavior adoption [25]. Evidence from such behavioral models, such as the integrated behavior change (IBC) model [26,27], propose that behavior adoption requires sustained effort, that is, a sustained focus on realizing behavior change goals (ie, plans) over time (Figure 1). Therefore, one way to potentially enhance the effectiveness of tailoring in app-based interventions is to focus on such goals, with personalized goals that are selected to fit individuals' unique profile (eg, adapting difficulty to individuals' preferences or characteristics) in order to maximize the likelihood of goal completion over time. Such personalization should acknowledge time-variant factors (or contexts) that can affect individuals on a daily basis, as well as time-invariant aspects that could vary dramatically across users. Earlier work on message tailoring has suggested that including elements of multiple dominant psychological theories into tailoring approaches increases overall effectiveness [28], suggesting the IBC model, which integrates across the major dominant psychological theories [26,27], is well-suited for developing tailoring approaches.

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Figure 1. Integrated behavioral change model (source: Hagger and Chatzisarantis [26]).

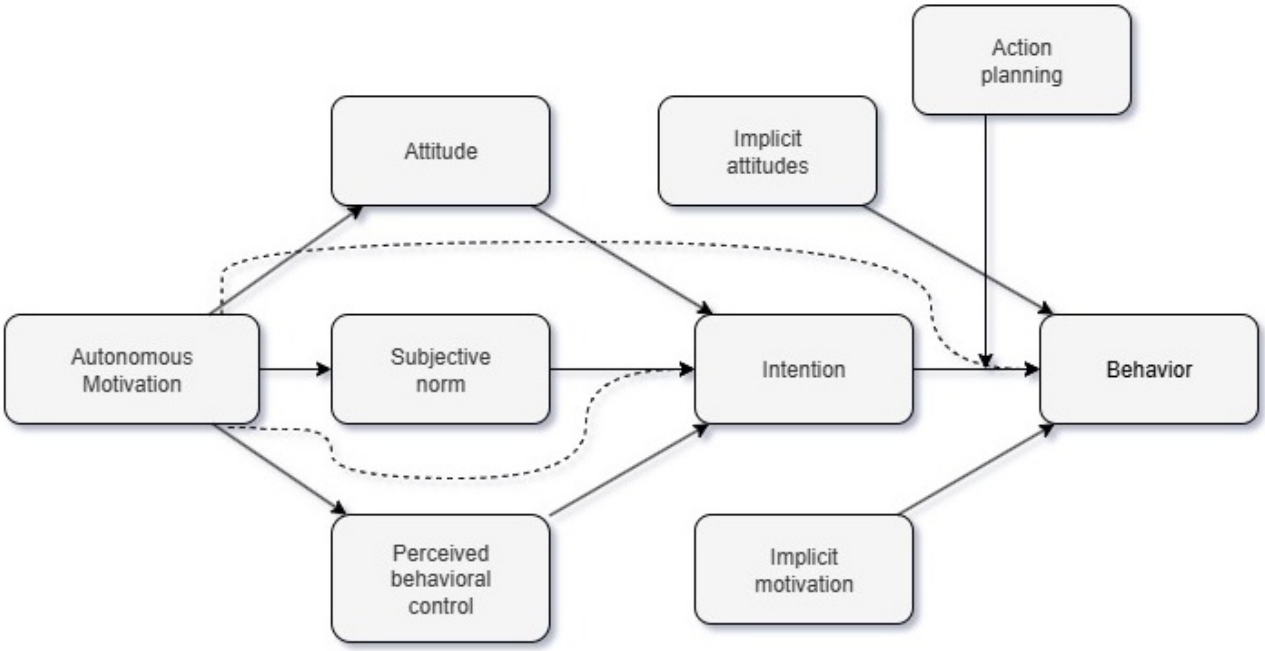

With technological advances in artificial intelligence, personalization has become easier to implement in dynamic settings, where users are interacting repeatedly with tailored components. In particular, contextual multiarmed bandits, or simply contextual bandits (CBs), have become an effective reinforcement (machine) learning personalization tool in the health behavior domain, where treatment (option) recommendations are optimally determined to maximize user performance using individual characteristics and behavior [29]. In short, CB algorithms use all available data to predict the action that would provide the best outcome to a given user, while learning from the relative performance of all possible actions. In experimental literature, there is a novel approach using CBs named adaptive interventions, emphasizing the idea that we can pose a sequential field experiment with an adaptive sampling procedure that aims to determine which types of individuals benefit from certain intervention arms over time, while also learning about the average effectiveness of each arm [30,31]. Adaptive interventions allow us to estimate the relative effectiveness of each arm while providing the optimal path for each user, based on their expected behavioral response. Overall, CBs have important advantages as an automated personalization tool, requiring less data to determine which interventions are more effective overall and allowing an understanding of which characteristics are most likely to influence individuals' performance.

Adaptive interventions using CB algorithms have become popular in the public health domain, with promising results [16,23,32]. Systematic reviews for adaptive interventions targeting PA and sedentary behavior reveal that most studies focus on tailored feedback as the main personalization component, with few interventions focusing on goal tailoring. Moreover, studies designed with goal setting features mostly focus on difficulty progression over time (eg, increasing duration or reducing resting time) or alternating types of exercises (eg, cardio, strength, and flexibility) based on the user's health profile [23]. In particular, while difficulty progression seems reasonable as mastery increases, evidence on motivation shows that dynamic environmental factors can strongly influence goal completion as difficulty increases [33]. Altogether, to date, it is still unclear to what extent automated personalized goal difficulty recommendations over time and individual preferences influence health behavior adoption.

While machine learning approaches such as CBs offer promise by matching individuals based on their characteristics or context, this optimal recommendation could be seen as a directed action (data-driven), or a recommendation, mediated through individual choice. This is particularly relevant in the context of exercise, where preferences for workout intensity and capabilities to do more demanding exercises can differ widely between individuals [34]. Enabling respondents to choose their workouts, rather than be assigned one through machine learning, respects these diverse preferences and could enhance intervention effectiveness. That is, according to self-determination theory, an influential psychological theory of motivation, being able to choose enhances autonomy, a key driver of intrinsic motivation [35]. Furthermore, evidence suggests that individuals may benefit from a process of self-experimentation to find what works best for them [36]. A meta-analysis shows the potential of choice-based interventions in the context of health behaviours (including exercise), showing improved adherence and reduced dropout across various health behaviors [37]. Past research has found that providing individuals with choice in PA positively influences their perception of exercise [38,39], general well-being [40], as well as adherence to the intervention regime [41]. However, enabling choice is not without risks; individuals may opt for interventions that are ineffective for them due to, for instance, misjudging their own self-control [42] or selecting appealing but ultimately ineffective strategies [43]. Thus, in the context of machine learning–based tailoring, incorporating a "choice" arm allows for the investigation of how algorithmically assigned interventions compare with those selected by

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individuals themselves, enabling a direct comparison between data-driven assignment of exercise goals versus self-chosen goals.

This study explores three research questions to evaluate the effectiveness of adaptive interventions that focus on goal difficulty and user choice:

1. Can CBs outperform performance success rate (goal completion) relative to user-chosen workouts?
2. Which user characteristics are most relevant for determining choice probabilities among intervention arms?
3. To what extent does user autonomy in choosing a workout plan influence the effectiveness of recommendations based on CBs?

By addressing these questions, this experiment aims to contribute to the growing body of research on adaptive behavior change interventions. Understanding the interplay between user choice and data-driven recommendations can inform the development of more effective mHealth apps [44].

Methods

Apptivate

For this project, the experiment will be conducted using the web application "Apptivate" [45], extending its initial functionally to incorporate CB algorithms connected to a routine difficulty assignment. Apptivate creates workout routines with 3 different difficulty levels, changing the total workout duration as well as rest times between exercises. PA professionals validated the routine design, ensuring that workouts match recommended guidelines for healthy adults. The overall design allows users to conduct exercises without equipment following the in-app instructions, covering different muscle groups as well as providing both warm-up and stretching exercises.

Apptivate adopts the IBC model for PA [26] as a framework for tailoring workout difficulty recommendations (ie, goals). By leveraging the IBC model, the app ensures that its recommendations address not only dynamic changes in behavior over time but also the psychological factors that influence behavior change. In particular, we capture data on the psychological constructs defined in the IBC model, which are later used as contexts for the algorithm learning process. Participants that take part in the main study will be assigned to 1 of 3 conditions:

- Choice-driven: Users select their desired workout difficulty level from a predefined menu. This approach provides users with a sense of autonomy and control over their exercise routine. Choice-driven tailoring leaves the selection of the intervention to the user, allowing individuals to reveal their preferences in a participatory process [33].
- Data-recommended: The CB algorithm determines optimal workout difficulty (based on user data and the IBC model) and provides a recommendation to the user, but the user retains the option to choose an alternative. This design allows us to investigate the interplay between user autonomy and the effectiveness of data-driven recommendations [27].
- Data-driven: The CB algorithm automatically recommends workouts based on user data, including contextual features based on the IBC model, without any opportunity to opt into a different difficulty level. This method leverages a machine learning approach to personalize workout plans and potentially optimize user performance (measured as goal completion).

Apptivate also includes several personalization features to enhance user engagement [15,23]. Users can change their username and avatar, as well as opt for timed notifications. The system includes motivational messages, a progress tracker, and routine feedback (Figure 2).

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Figure 2. Apptivate main menu and workout view.

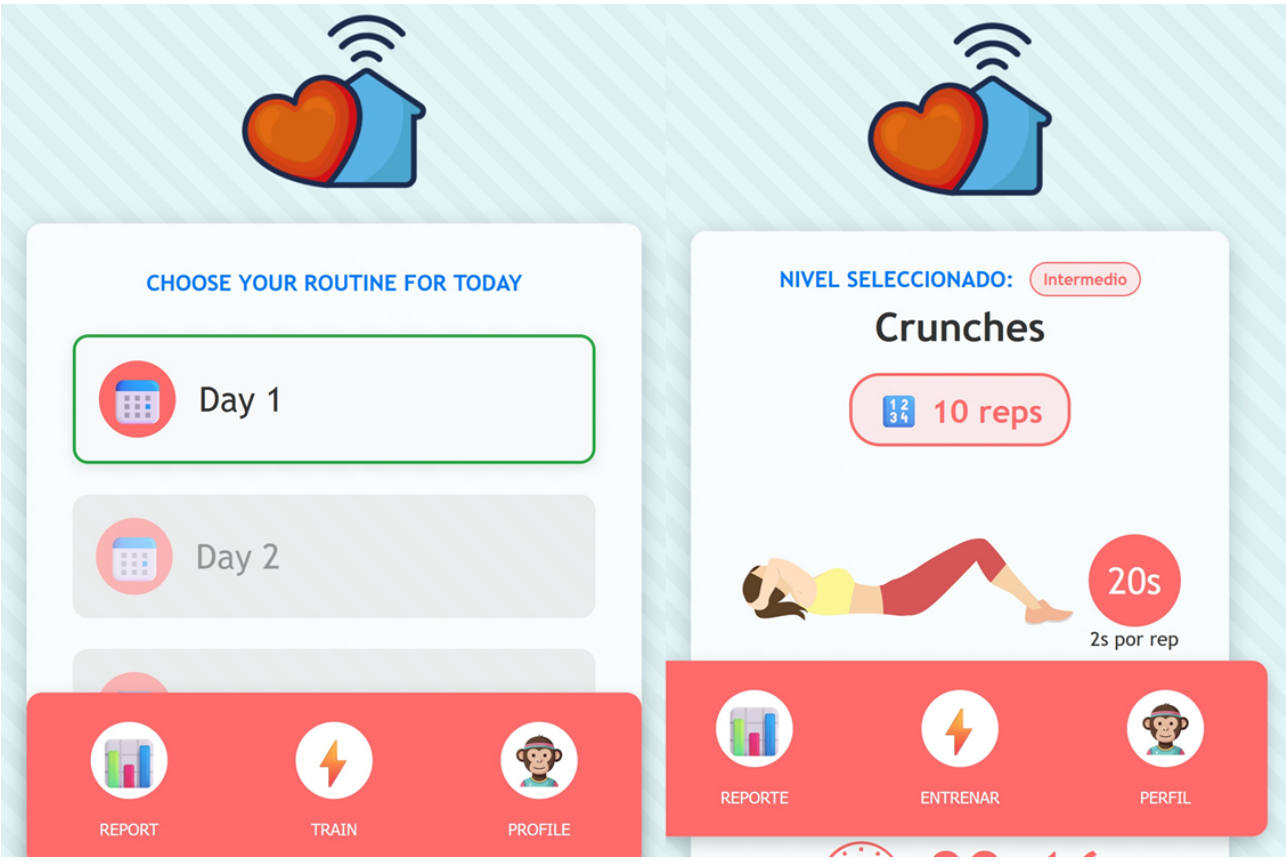

Contextual Bandits Algorithm

The contextual multiarmed bandit model used in this study is a type of reinforcement machine learning approach, which uses experimentation to learn about users' performance and recommend the best potential option. As shown in Figure 3, the algorithm incorporates users' past outcomes (target) and context (features) to assign probabilities to each treatment option and recommend the best possible treatment in the future (higher likelihood of success, noted in green). Once given a recommendation, users respond (either positively or negatively in this case), and this information is used for further training the algorithm for the next interaction. There are several algorithms developed to solve CB models, differing in how probabilities for each option are updated (learning) and the degree of exploration (randomness) involved in providing users with different options.

Figure 3. Contextual bandit algorithm design.

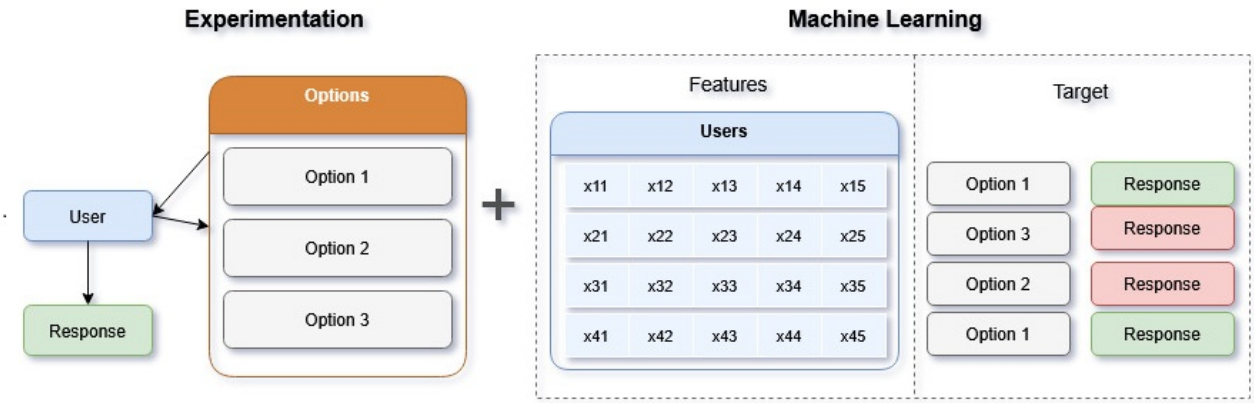

Formally, at each round t=1,...,T, we observe the individual's context ($x_t \in$ X), from which the algorithm recommends an action ($a_t \in$ A), and the environment reveals a reward ($r_t \in$ [0,1]). Intuitively, the algorithm needs to choose the policy $\pi \in \Pi$ that maximizes the cumulative reward , where Π is a mapping of all policies relating context to actions ($\Pi \subseteq \{X \rightarrow A\}$). We can define the average reward of a policy π as:

Based on this idea of expected cumulative reward, we can then determine the cumulative regret from a given policy as the

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difference between the observed reward for the recommended action and the expected reward of the recommended action:

In this setup, the different types of CB algorithms differ in their proposed approaches to achieve regret minimization. In practice, some algorithms will be better suited for different empirical applications, depending on the number of rounds, the possible set of actions, and the heterogeneity in the context from which the algorithm learns to allocate the best recommendation [31]. As such, the pilot phase is critical to determining the best approach for this experiment.

Study Design

This study poses two main hypotheses: (1) goal personalization with CBs decreases the intention-behavior gap for some users, and (2) the effectiveness of such goal personalization on behavior is mediated through individual choice. To explore these hypotheses, participants will be randomly assigned to 1 of 3 groups: choice-driven, data-recommended, or data-driven.

The target population are university students (both undergraduate and graduate) from different institutions, allowing for differences in region, language, and time zone of the participants. Randomization will be stratified by baseline demographic factors, including household composition, income, age, and gender, to ensure a representative sample within each institution. The inclusion criteria require participants to be physically healthy adults (aged older than 18 years), with access to a smartphone compatible with the mobile web application. Exclusion criteria include significant physical disabilities or medical conditions limiting exercise, based on the Physical Activity Readiness Questionnaire [46], as well as individuals actively participating in competitive sports. The participant assignment procedure will use block randomization to reduce bias and ensure even group distribution, with allocations concealed and blinded from both participants and researchers through a secure system managed by the data specialist team. Data will be stored at a secure server at the University of Concepcion, with backups of the database each hour. A deidentified version of the data and dictionary can be made available upon request.

Since there is no prior evidence regarding effect size for this study, sample size was determined using 1000 simulations, following existing guidelines [47]. Sample sizes were estimated considering the particularities of adaptive experiment design. Simulations based on the relevant populations were conducted using the epsilon-greedy algorithm. Based on simulated data, a sample size of 500 participants during 10 rounds is sufficient to evaluate differences between intervention arms and conduct statistical inference, particularly regarding demographic and behavioral characteristics between participants. The authors are currently working on a publication describing the simulations and associated power analysis, which will become available in late 2025.

To train the reinforcement learning algorithm for the study, initial data are required for which a pilot stage was designed. In this stage, 800 participants will be recruited at one university in order to provide 1 week of activity using the app (two 3-day rounds with a rest day in between). In order to determine the sample size for the pilot, standard power calculation was assumed with a uniform distribution over 3 arms (standard randomized controlled trial). With 665 observations, the pilot is sufficient to detect differences between users. The data from round 1 will be used to estimate the optimal arm for round 2, which will be used for calibration. Participants complete a comprehensive baseline survey eliciting the IBC model as well as several other relevant characteristics (eg, time and risk preferences; see Multimedia Appendix 1) and then are assigned randomly between the 3 difficulty levels for the first round. After completion, participants are compensated for their time. Individuals can opt out from the study at any time.

During the main part of the study, 500 participants will be recruited from multiple sites expecting to participate in a medium-term challenge, completing 10 rounds, equivalent to 39 consecutive days using the app (including rest days). As noted earlier, this provides 5000 unique examples for the algorithm to determine optimal policy over time. Users will be allocated to each arm based on their baseline survey and the trained algorithm during the pilot stage. Regardless of their initial difficulty assignment, each participant will be randomly allocated with equal probability between (1) choice-driven, (2) data-recommended, and (3) data-driven arms. Participants will be compensated for their time, and there will be additional prizes using a lottery mechanism that favors (in probability) those users completing more consecutive workout routines over the course of the study. In both the pilot and main experiment, participants will stay engaged via direct email, push notifications, and social media campaigns.

Data Collection

Data collection in this study spans multiple dimensions, capturing individual characteristics, app usage patterns, and most importantly, user performance. This multifaceted approach allows us to provide insights on the potential heterogeneous impact of tailored goal-setting interventions.

- Baseline survey: Participants will complete an online survey to gather demographic information (eg, age, gender, and socioeconomic status), fitness history (eg, frequency and type of PA), and constructs from the IBC model, such as perceived behavioral control, motivation types (autonomous and controlled), and self-regulatory capacities.
- Fitness app data: The app will track participant engagement and outcomes, including goal completion rates, total time spent on physical activities, and engagement metrics (eg, frequency of app interactions).
- Algorithm data: The CB algorithm embedded in the app will collect data on contextual features (eg, user preferences, past performance, and fitness level) and reward functions to predict optimal goals and adapt recommendations over time.

Statistical Analysis

Statistical analysis will focus on comparing goal completion rates, engagement metrics, and user satisfaction across the 3 intervention groups. To address missing data, a multiple

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imputation approach will be applied to ensure robustness in outcome estimates. The primary analysis will estimate the conditional average treatment effect for each intervention arm, with subgroup analyses to identify variations by demographics, baseline fitness, and psychological factors. Mixed-effects models will account for repeated measures and clustering within participants, while sensitivity analyses will assess the robustness of the findings under varying assumptions.

During the pilot phase, multiple CB algorithms will be evaluated based on metrics such as regret minimization (difference between actual and optimal rewards) and balance between exploration and exploitation. The main experiment will focus on estimating the conditional average treatment effect and analyzing differences in goal completion rates and engagement metrics. Subgroup analyses will explore how demographic characteristics (eg, age and gender), motivational factors, and baseline fitness levels influence responsiveness. Metrics such as cumulative reward, prediction accuracy, and contextual feature importance will be analyzed to evaluate the algorithm's ability to personalize recommendations effectively.

Ethical Considerations

Our study is considered an adaptive experiment or adaptive intervention trial [30,31]. Unlike a randomized controlled trial, sampling is not fixed, but instead each round is controlled by a recommendation algorithm, as noted in the previous section. As such, based on institutional guidelines, this study does not meet the criteria for a clinical trial. The Ethics, Bioethics, and Biosafety Committee of the Vice Presidency of Research and Development at the University of Concepción has reviewed our study under Project Fondecyt (11240325), titled "Tailored goals versus individual choice: a field experiment on commitment devices for health behavior," submitted in the Fondecyt Initiation 2024 Call by Dr Juan Carlos Caro Seguel, as the lead researcher and faculty member at the School of Engineering at the University of Concepción. The Committee has confirmed that it meets the ethical and bioethical standards and procedures established nationally and internationally for research involving human participation. Although this protocol does not correspond to a clinical trial, we included a SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist to facilitate study implementation (Multimedia Appendix 2).

Results

This research is supported by the Fondecyt Initiation Grant 2024 (grant ANID 11240325; funding period 2024-2026). The pilot was conducted in September 2025. Data analysis for the pilot is undergoing, and the main study is planned for early 2026. Preliminary results from the pilot data will be available in November 2025. Our main statistical analysis includes a direct comparison (paired tests) between success rates across intervention arms, as well as by difficulty level and individual characteristics. We anticipate publishing the findings in late 2026. Dissemination will be conducted simultaneously via a web-based seminar for all participant institutions during 2026.

Discussion

Anticipated Findings

This study introduces a novel approach to promoting sustained PA through a mobile app, leveraging CB learning for personalized goal difficulty recommendations, under an IBC framework. By combining this theory-informed machine learning approach with different levels of user autonomy, the intervention addresses critical gaps in existing mHealth literature, particularly the role of autonomy and motivation on personalized goal setting. We expect to find heterogeneity in both (1) individual behavioral responses to personalized goals, and (2) autonomy preferences for choice versus automation. Such heterogeneity should align with the IBC model and reflect the particular hurdles of motivation versus goal difficulty.

Findings from this field experiment will contribute to the growing field of adaptive digital health technologies, offering practical insights for scaling effective interventions for sustained health behavior. Ultimately, this research has the potential to inform public health strategies by providing evidence on the interplay between user autonomy and data-driven recommendations, fostering more engaging and effective health behavior change digital tools.

There are limitations to this study. First, participant dropout may introduce bias if attrition is nonrandom, reducing overall statistical power. Our sample size considers a maximum 20% dropout rate, to maintain statistical validity. Second, findings may not generalize to populations of different ages or health statuses or to those without smartphone access and from other cultural contexts beyond those included in the study. In an effort to provide better external validity, we aim to implement this study in countries with different languages and cultural backgrounds.

Conclusions

PA maintenance is key to achieving long term health goals. Tailored digital interventions are promising strategies for PA adherence, but personalization often fails to consider dynamic contextual changes. The proposed protocol for a PA intervention using adaptive experimentation can provide robust causal inference on the role of choice versus autonomy when tailoring goal difficulty is done under an adaptive data-driven approach. Dissemination plans will focus both on participants and the scientific community, and all participatory events are designed to be conducted simultaneously via a web-based seminar for all participant institutions during 2026.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Baseline questionnaire.
[DOCX File , 19 KB - resprot_v14i1e73766_app1.docx]

Multimedia Appendix 2
SPIRIT 2025 checklist of items to address in a randomized trial protocol.
[DOCX File , 26 KB - resprot_v14i1e73766_app2.docx]

Multimedia Appendix 3
Peer review report by INTERTRANSDISCIPLINARY Evaluation Group, FONDECYT, Agencia Nacional de Investigación y Desarrollo, (ANID; National Agency for Research and Development, Chile).
[PDF File (Adobe PDF File), 284 KB - resprot_v14i1e73766_app3.pdf]

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Abbreviations

CB: contextual bandit
IBC: Integrated Behavior Change
mHealth: mobile health
PA: physical activity
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

A Novel Digital Platform to Support Child and Family Mental Health in Australia (Child and Family eHub): Protocol for a Mixed Methods Evaluation

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Abstract

Background: Child mental health disorders are a significant Australian public health issue with high prevalence rates compounded by inequitably higher rates for those living in families with lower income, lower levels of parental education, and higher levels of unemployment. Prevention and early intervention approaches are critical to address problems early. When caregivers seek information and services to support their child’s mental health needs, they commonly use many untested online search strategies. To address this, we developed a digital Child and Family eHub (eHub) prototype through a user-centered design process involving families experiencing adversity and local service providers. The eHub provides online navigation and evidence-based information

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for families and aims to increase equitable access to and use of (1) information and (2) the existing primary health, mental health, and social services system to improve mental health outcomes for caregivers with children aged 0-12 years. This protocol outlines how we will evaluate the eHub.

Objective: This study aims to evaluate the feasibility, acceptability, appropriateness, and preliminary impact of the eHub digital platform for caregivers of children aged 0-12 years, particularly those experiencing adversity. The evaluation will assess implementation outcomes, caregiver and child mental health outcomes, and help-seeking behaviors over a 6-month period.

Methods: A prospective cohort of 270 caregivers of children aged 0-12 years will be recruited from 3 socioeconomically diverse Australian sites (Wyndham Vale in Victoria and Marrickville and Fairfield in New South Wales). Participants will be recruited through local community hubs, health and social service providers, and social media, and will enroll via the REDCap (Research Electronic Data Capture; Vanderbilt University) survey platform. A mixed methods type 3 implementation impact evaluation will be undertaken, which tests an implementation strategy while observing and gathering information on the intervention's impact on relevant outcomes. In this protocol, implementation will be assessed as a primary outcome using Proctor's outcomes for the implementation framework, and secondary outcomes will include caregiver access and use of the eHub and associated child and parent mental health outcomes. Data will be collected at baseline and 6 months. Quantitative data will be analyzed using descriptive statistics and regression models; repeated measures will be analyzed using generalized estimating equations. Qualitative data will be analyzed using framework analysis.

Results: The study was funded in December 2021. Participant enrollment for the study began in February 2024, with participants involved in the eHub evaluation for 6 months.

Conclusions: The results of this study will be instrumental in refining the intervention for future scaling to other Australian sites. This study has the potential to offer an accessible, cost-effective, and scalable digital solution to improve service navigation and mental health outcomes for children and families experiencing adversity.

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KEYWORDS

child mental health; consumer health information; child health services; digital health technology; family supports

Introduction

Current Mental Health Concerns

Consistent with other international research [1,2], 1 in 7 Australian children aged 4-11 years reports mental health disorders in a year, with attention-deficit/hyperactivity disorder and anxiety being the most reported disorders [3]. Additionally, regulatory problems, such as excessive crying, sleeping, or feeding problems in infancy, are known predictors of later behavioral and mental health problems [4], with the Australian prevalence rates for 1 or more of these regulatory problems in infants between 7.3% and 25.2% [5]. The distribution of mental health disorders, however, is inequitable, with much higher rates in children and adolescents associated with lower socioeconomic status of families, lower levels of parental education, and higher levels of unemployment. Recent Australian national data identify additional mental health burden on children and their parents as a result of COVID-19 [6], with 50% of parents reporting their children as anxious [7], and even higher rates among children from families experiencing financial distress [8]. These data reinforce the urgent need to implement effective and equitable prevention and early intervention strategies to mitigate the continuing and unequal rise in child mental health issues.

Early Intervention

Investing in innovative prevention and early intervention approaches is time critical for the following reasons: (1) despite increasing Australian government investment in mental health services (eg, over US $1.7 billion nationally in 2018-2019 to enhance community mental health services) [9], existing services are unable to meet the growing demand for children's mental health, and there has not been a detectable reduction in the prevalence of psychological distress for youths [10]; (2) only 9%-27% of young children experiencing emotional and externalizing problems access Medicare-rebated services, with the lowest rates among families of low socioeconomic status or single parents and those with English as a second language [11]; (3) failing to intervene early costs the government (US $10.7 billion) annually [9]; and (4) there is currently strong policy commitment for mental health including the National Child Mental Health and Wellbeing Strategy [12].

To increase the efficiency of the support systems, we need to make better use of the existing (and already funded) health and social care system. In a National Child Health poll of 2000 Australian parents prior to COVID-19, only 44% reported feeling confident that they would know where to go for professional help if their child was experiencing social, emotional, or behavioral difficulties [13]. Indeed, caregivers often feel overwhelmed by the amount and complexity of information and need accessible, reliable, and relevant support to guide them through the process of accessing services relating to their child's social, emotional, and behavioral problems [14]. Rather than looking for mental health services per se, caregivers seek practical tips, connections to a range of services, and reassurance of the best approach to take with their family and

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child's mental health. These findings were recently corroborated (Honisett, PhD, unpublished data, January 2024). Low levels of access and use of community and mental health services are thought to be due to a combination of barriers including financial, cultural, transport, and health literacy barriers [15]. The process of navigating a complex community and mental health service system leads to inequities in access, missed (and costly) opportunities for early intervention, and subsequent inequities in outcomes for children.

Caregivers' Current Help-Seeking Behavior and Use of Information and Services

Caregivers already use a range of digital search strategies and social media to seek information and services to support their child's health needs. These findings were recently corroborated (Honisett, PhD, unpublished data, January 2024). Common challenges for caregivers seeking online information or services are too much or not enough relevant or trusted information, lack of time to source information or services, a sense of burden felt by caregivers to find an appropriate solution, and getting "stuck" and unsure how to progress seeking appropriate support. Caregivers report that they want to find practical actions to resolve their concerns or issues, connect with existing technologies and services, and not feel judged. These findings were recently corroborated (Honisett, PhD, unpublished data, January 2024).

Digital Solutions

Digital solutions offer great potential to provide high reach, low stigma strategies to deliver information, programs, and services [16], which can be tailored to a family's needs. While there are many digital apps and platforms available, very few have been developed for children aged 0-12 years and their families or specifically offer service navigation support for childhood adversities or their associated mental health problems [17]. Adversities include childhood maltreatment (eg, physical, verbal, or sexual abuse) and household dysfunction (eg, parental mental illness and family substance abuse) [18] as well as broader social determinants of health—nonmedical factors that influence health outcomes, including the conditions in which people are born, grow, work, and live [19].

To address this need, our team has developed a prototype or minimum viable product (MVP) for a digital Child and Family eHub (eHub) using a user-centered design process. The process involved local service providers and caregivers experiencing adversity. The eHub aims to optimize caregiver information and local service-seeking experience and satisfaction. The user-centered design process for the eHub is outlined in previous research. The eHub connects caregivers to evidence-based information and a range of health, education, justice, and social services to support broader adversities families experience. The eHub (1) is tailored to the specific needs of caregivers with young children aged 0-12 years; (2) is designed to deliver varying levels of supported navigation based on individual need or capacity; and (3) addresses specific issues related to the social determinants of health, diversity, and reach. Improving access to information, services, and supports we hypothesize will lead to improved and more equitable mental health outcomes for children.

Objectives

This protocol details the methods to evaluate the primary and secondary outcomes of the eHub for caregivers with children aged 0-12 years, with a specific focus on populations with low education, diverse languages, and socioeconomic deprivation. We will undertake a type 3 implementation impact evaluation as defined by Curran et al [1]. Type 3 implementation impact evaluation tests an implementation strategy while observing and gathering information on the intervention's impact on relevant outcomes. In this protocol, implementation will be assessed as a primary outcome using Proctor's outcomes for the implementation framework [20]. Secondary outcomes will include family information and service access and use, as well as child and caregiver mental health.

Methods

Study Design

A multisite type 3 mixed methods hybrid implementation or impact evaluation will be conducted [1]. The approach will assist in understanding access and use of the eHub by caregivers via the collection of users' data analytics on the eHub platform and via a prospective cohort sample, which will provide a "deep dive" into factors affecting caregiver access and use of the eHub and associated child and caregiver mental health outcomes. Quantitative (survey) and qualitative (semistructured interview) data will be collected in parallel and integrated during data analysis and interpretation. This protocol was informed by the Standards for Reporting Implementation Studies framework [21], and where relevant, it incorporates principles from the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 checklist.

Site Selection

eHub sites were chosen based on populations experiencing several adversities—as defined via low socioeconomic status, cultural diversity, child vulnerability, unemployment, and low education levels. Sites in Australia include Marrickville and Fairfield in Sydney and Wyndham Vale in Melbourne (Table 1). To note, the Marrickville suburb experiences significant pockets of disadvantage among areas of advantage. These 3 sites also had an existing physical Child and Family Hub within the local service system, which integrated health and social care for children and their families.

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Table 1. Sites involved in evaluation.

State	Site	Population details[a]				
		Socio-Economic Index for Area[b]	Australian Early Development Census—Children vulnerable in 1 domain (national comparison: 22%) (%)	Population 15+ years unemployed (national comparison: 5.1%) (%)	Population completed year 12 or equivalent (national comparison: 51.9%) (%)	Population born overseas (national comparison: 27.7%) (%)
Victoria	Wyndham Vale	972 (second quintile)	24.2	7.3	48.8	40.1
New South Wales	Marrickville	1050 (fourth quintile)	15.5	4.7	64.9	35.1
New South Wales	Fairfield	838 (first quintile)	28.6	8.7	48.2	56

[a]Percentage proportions reported for comparison as the population size varies across sites.

[b]Socio-Economic Index for Area is a group of 5 indexes that provides a relative measure of socioeconomic advantage and disadvantage for small geographic areas; 1000 is the average, lower scores indicate more disadvantage, first quintile=most disadvantaged.

Child and Family eHub MVP

The eHub MVP was developed using user-centered design with caregivers and local service providers and aims to support and guide caregivers through a local, proportionate approach including increasing tiers of support. These tiers, outlined in Figure 1, include self-navigation for all families (tier 1) through to guided chatbot technology and finally, human navigator assistance, which has been shown to be effective [22] for those most in need (tier 4). Figure 1 also includes a brief overview of each tier of the eHub. Caregivers determine the level of support they need based on their ability to find and access information and services that suit their family needs. Each caregiver enters the eHub at tier 1 and progress to additional tiers based on their needs, for example, filtering topics or geographic areas to find appropriate information or local services (tier 2), using a chatbot to assist with defining the mental health topic most suitable to their needs (tier 3), or speaking to a personal navigator to understand the child's or families' specific information or service needs and assist with navigation to services (tier 4). It is anticipated that 90%-95% of eHub users will interface with tiers 1-3 based on theories of proportionate universalism [23,24], with only 5%-10% of users requiring the more intensive element of the eHub personal navigator.

Figure 1. Tiers of support provided through the eHub. eHub: Child and Family eHub.

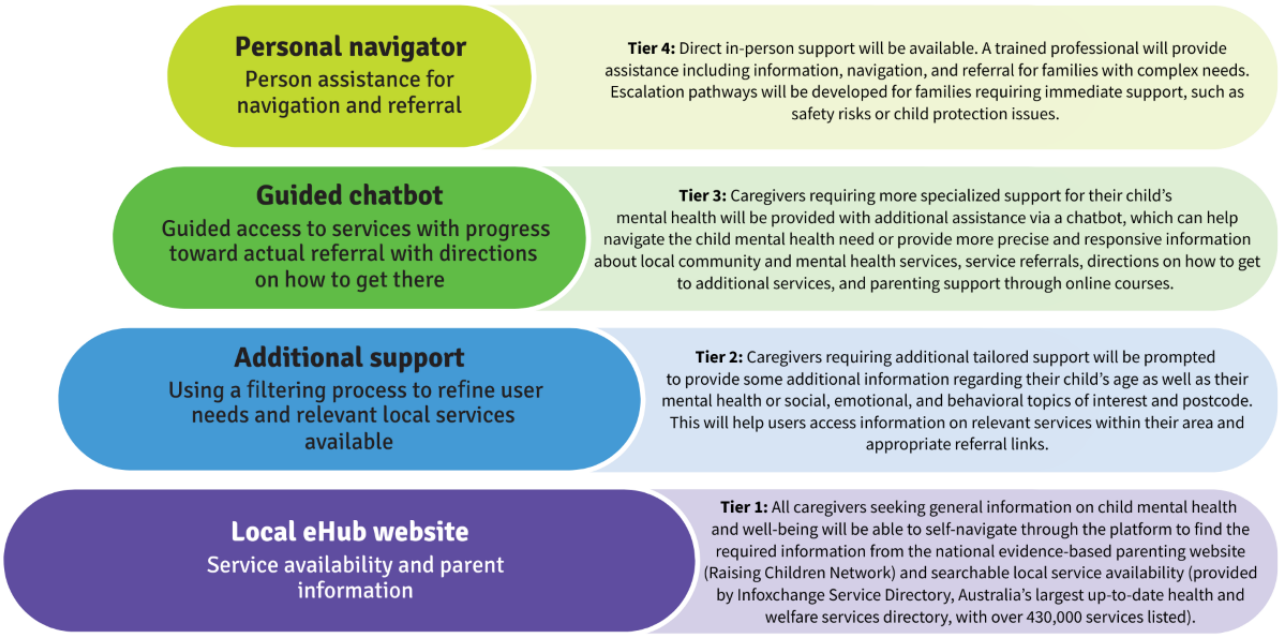

Recruitment

Prospective Cohort of Caregivers

The study will recruit 270 caregivers of children aged 0-12 years from the 3 identified sites (Table 1). To ensure representation of caregivers experiencing a range of adversities, the eHub will be advertised widely in the community in each site through posters and flyers with QR codes at physical primary care, community health and nongovernment organization hub sites, local community groups, schools, parent groups, playgroups, and social media to recruit caregivers with children aged 0-12 years. Interested caregivers will follow the QR code link to REDCap (Research Electronic Data Capture; Vanderbilt University)—a secure, web-based data capture platform hosted

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by the research team, where they can watch an informational video about the study and provide informed consent to be involved. Caregivers will then complete a baseline survey for the evaluation, including whether they meet the inclusion criteria (listed below); this will be our prospective cohort sample of caregivers. If caregivers respond "no" and would prefer not to participate in the evaluation, they can continue to use the eHub. eHub data analytics will be collected on all users of the eHub, including those involved in the evaluation and those who are not. Those not involved in the evaluation will not require consent to participate, as all eHub data analytics collected will be unidentifiable. Demographic details of participants will be collected through pop-up surveys on the eHub site. Figure 2 outlines the caregiver journey through the evaluation. Recruitment for the evaluation commenced in February 2024 and continued for each caregiver involved for 6 months.

The caregiver inclusion criteria are as follows: parents or primary caregivers with at least 1 child aged 0-12 years, noting that only 1 primary caregiver per family unit can enroll in the evaluation study; live in eligible intervention sites (Marrickville and Fairfield in New South Wales or Wyndham Vale in Victoria); can speak sufficient English to participate in the study and complete the survey, noting that although each of the study sites are culturally diverse, many residents speak English; and provide informed consent.

Figure 2. Caregiver journey for the evaluation trial. eHub: Child and Family eHub; REDCap: Research Electronic Data Capture.

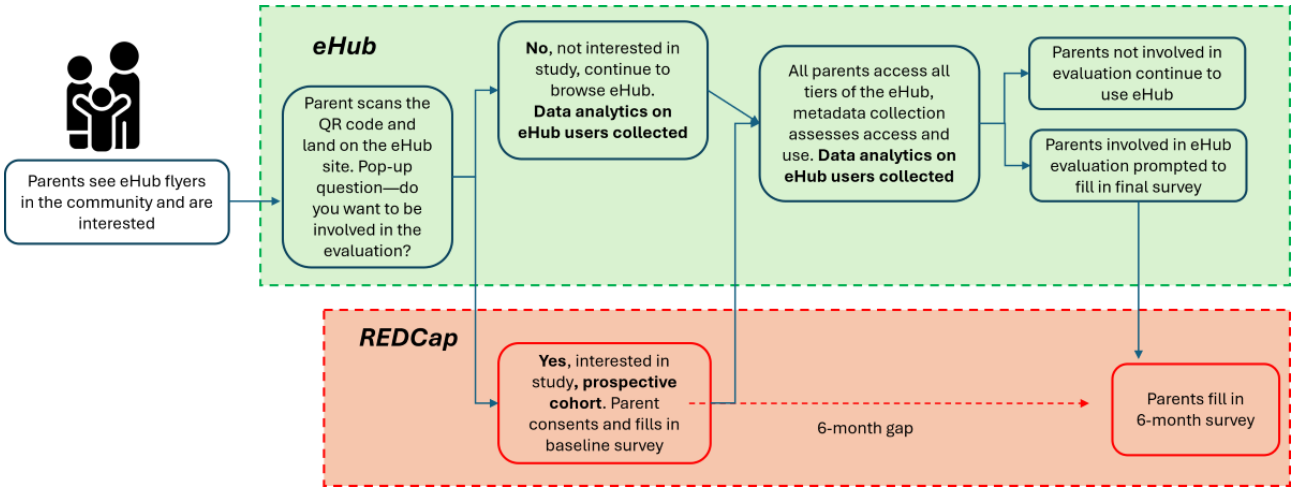

Escalation Pathways for Child or Family Concerns

To ensure appropriate clinical governance, escalation pathways were developed with each study site with support from the steering committee (1) to support caregivers if they are distressed or unsafe when calling the personal navigator related to tier 4 of the eHub and (2) to support eHub personal navigation phoneline staff.

Cross-Sectoral Service Providers

We will purposively recruit service provider participants who meet the inclusion criteria (listed below) within each study site to participate in semistructured interviews at 6 months from the eHub first going live. Site leads at the 3 trial sites will provide access to individual service provider contact details who may wish to take part. We will then directly approach these primary care, mental health, health, welfare, and community providers to take part, ensuring that they meet the inclusion criteria and consent to be involved in the evaluation. Many of these service providers are represented through networks that we have existing relationships within Wyndham Vale, Fairfield, and Marrickville, such as Wyndham Child and Family Alliance (Victoria) and the Local Council Vulnerable Children's Group (New South Wales). Potential participants will be sent a personalized email of invitation to participate in qualitative interviews at the 6-month time point with information about the details of the study objectives and providing the service provider participant information sheet.

The cross-sectoral service provider inclusion criteria are as follows: adults aged 18 years or older; work within the study intervention areas—Marrickville, Fairfield, or Wyndham Vale in health, or social service located at the Marrickville Community Health Service, Karitane in Fairfield or IPC Community Health Service in Victoria; and provide verbal informed consent.

Baseline Data Collection: Prospective Cohort Caregiver Baseline Survey

For those who consent to be involved in the eHub evaluation, when accessing the eHub for the first time, caregivers' baseline data will be collected via an online survey, which includes the research measures outlined in Table 2. This online survey will be built into a secure online portal (REDCap) [25,26] through the eHub as outlined in Figure 3. If consented families do not complete the baseline questionnaire, they will be contacted by a research assistant by phone, email, or text to complete.

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Table 2. Study activities and timeline.

Activity	Timeline
Funding and concept development	December 2021
User-centered design and minimum viable product development	June 2022 to December 2023
Ethics approval	June 2023
Participant recruitment commenced	February 2024
6-Month evaluation period per participant	February 2024 to November 2024
Quantitative and qualitative data collection	February 2024 to February 2025
Data analysis	February 2025 to May 2025
Dissemination of findings	2026

Figure 3. Evaluation overview. PDSA: Plan-Do-Study-Act.

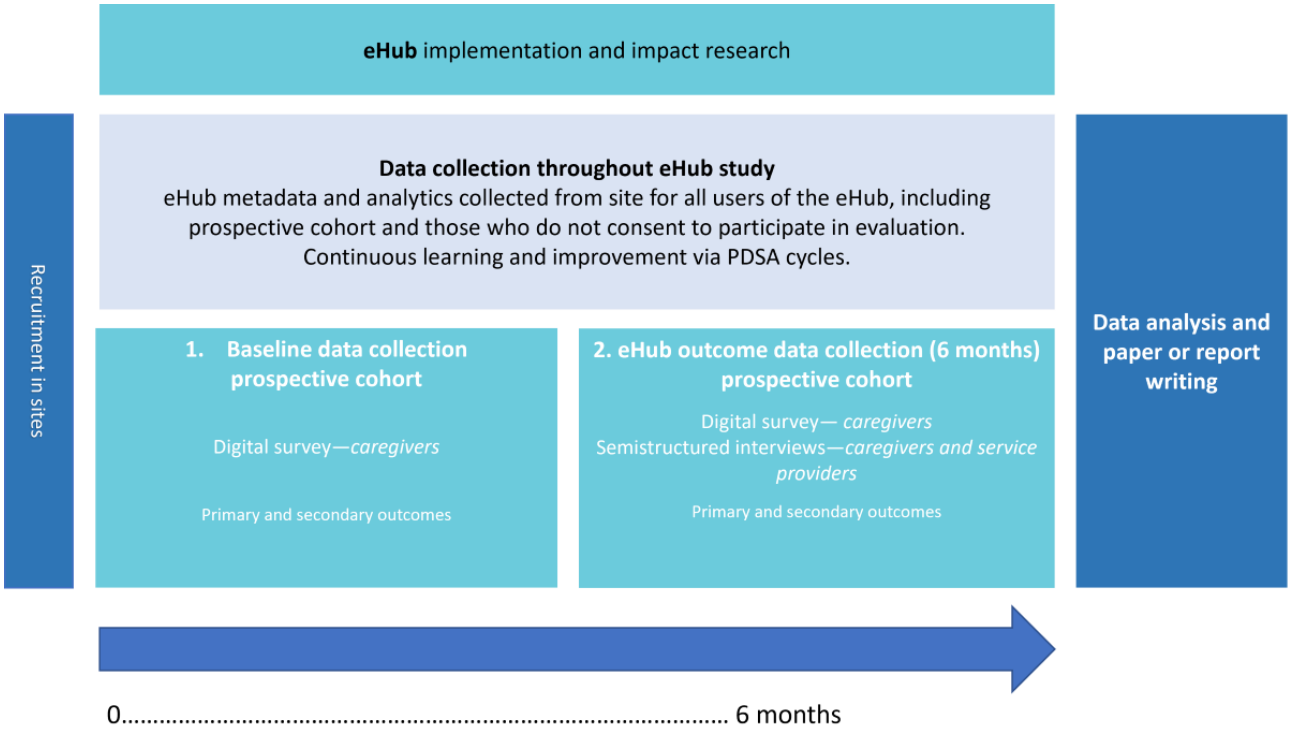

Data Collection Throughout the eHub Study

Data Analytics on eHub Users

eHub metadata and digital analytical data on participants' average session length and frequency, page use, and tiers of service use when using the eHub, as well as satisfaction scores and responses to short online surveys and questionnaires, will be collected for any users of the eHub using Google Analytics and Hotjar (Contentsquare; a web-based feedback poll that pops up on the eHub screen during an episode of use). Additionally, brief demographic data, including postcode and country of birth of user, will be collected. Tables 3 and 4 show the primary and secondary evaluation objectives and quantitative and qualitative data collected in parallel and integrated during data analysis and interpretation.

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Table 3. Primary evaluation outcomes and associated measures.

Primary outcomes: eHub[a] implementation outcomes	Measure
eHub access	
Reach: What is the proportion of caregivers within each site who access the eHub?	• Data analytics on eHub users: Proportion of people who have accessed the eHub (numerator) among families that have children younger than 15 years of age based on Australian Bureau of Statistics reports for each site (denominator).
Coverage: Is the eHub reaching the intended audience of priority families (defined by residential socioeconomic disadvantage [SEIFA[b] IRSD[c] score in the lowest quintile or quartile?] and parental country of birth [parents born overseas?])	• Data analytics on eHub users: User visits to each tier mapped against their demographic data including suburb to determine socioeconomic disadvantage, based on SEIFA scores and nomination of whether user was born overseas. This indicator measures the proportion of vulnerable families with children younger than 15 years who have accessed the eHub. Vulnerability is based on caregiver demographics—such as postcode (linked to SEIFA) and country of birth—compared to ABS caregiver data. The numerator is the number of vulnerable families who accessed the eHub, and the denominator is the total number of vulnerable 1- and 2-parent families with children younger than 15 years.
eHub use	
Engagement: Are families engaging with the eHub?	• Data analytics on eHub users: Do caregivers passively use the eHub? Page hits, links opened to information, services within each tier of the eHub, and actively use the eHub, that is, searches undertaken through tiers 2 and 3 and clicking through to tier 4 support. eHub user data will include: • Length of time on site or session length • Visits or time per critical feature • Interactions with filters • Number of engaged sessions and engagement rate • Engaged sessions per user or IP address • Average engagement time • Views per session or user
Acceptability: Do caregivers view the eHub as satisfactory?	• Data analytics on eHub users: Pop-up surveys on satisfaction, Did you find what you were looking for? Or Was this useful? (Thumbs up or down or smiley or sad face) • Survey (6 months): Satisfaction with content, delivery, level of support provided, credibility.
Adoption: To what extent can caregivers find and use information, services, and supports on the eHub?	• Prospective cohort survey and interview (6 months): • Did caregivers find the information provided useful for their needs? • Were caregivers able to find an appropriate service or information to support their or their child's needs? • Did caregivers use or intend to use the strategies provided in the information? • Changes to caregivers' behavior (eg, help-seeking and implementing new strategies)
Appropriateness: Do caregivers perceive the eHub as useful and relevant? Did the caregiver feel reassured or supported by the information or services provided?	• Prospective cohort survey (6 months): Perceived fit, relevance, compatibility, suitability, usefulness, practicability.
Barriers and enablers: Accessing and using information, services, and supports on eHub?	• Prospective cohort caregiver and service provider qualitative interviews (6 months).
Cost	
Cost of providing the eHub, intersectoral service use, and effectiveness of eHub	• Prospective cohort survey (6 months): Costs of implementation and national scaling of the model will be estimated (using study protocols, budgets, and population of children). The costs associated with caregiver-reported intersectoral service use will be estimated. Cost-effectiveness estimated based on the number of families engaged and those with unmet needs being met.
Demographics	
Postcode, single or couple parent, country of birth, language spoken at home, education status, number of adversities	• Prospective cohort survey (baseline): The population cohort—eHub metadata will provide demographic characteristics of caregivers who access the eHub, including postcode to link SEIFA and parents' place of birth compared with caregiver data from ABS.

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[a]eHub: Child and Family eHub.
[b]SEIFA: Socio-Economic Index for Area.
[c]IRSD: Index of Relative Socio-Economic Disadvantage.
[d]ABS: Australian Bureau of Statistics.

Table 4. Secondary evaluation outcomes and associated measures.

Secondary outcomes: impact	Measure
Information and service access and use	
Service access and use: Did the eHub assist caregivers with finding and connecting with relevant services including those relevant to social determinants of health and adversity? If not, why?	• Prospective cohort survey (baseline and 6 months): Using the general [27] and actual [28] help-seeking questionnaires: • Intention to seek help • Actual help-seeking
Information access and use: Did caregivers find the information needed? If not, why? Did accessing information change the caregiver's behavior?	• Prospective cohort survey (6 months): Did you find the information you needed? If not, why?
Caregiver mental health	
Caregiver distress: Is eHub exposure associated with improvements in caregiver levels of distress?	• Prospective cohort survey (baseline and 6 months): Kessler Psychological Distress Scale (K10) [29]
Caregiver stress: Is eHub exposure associated with reduced caregiver stress related to (1) access to services and (2) their child's mental health?	• Prospective cohort survey (baseline and 6 months): Study designed Likert scale of stress
Child mental health	
Child mental health needs met: Did the caregivers' child have unmet mental health care needs? If yes, were they met by the eHub resources?	• Prospective cohort survey (baseline and 6 months): Unmet child mental health need [30]
Child mental health symptoms: Is eHub exposure associated with improvements in parent-reported child mental health symptoms?	• Prospective cohort survey • Child aged 2 months to 2 years—Survey (baseline and 6 months) of Well-Being of Young Children [31] • Child aged 2-12 years—Strengths and Difficulties Questionnaire [32]

Continuous Learning and Improvement of the eHub Throughout Evaluation

Members from each evaluation site will form a project team alongside researchers to identify and respond to barriers for caregivers in accessing and engaging with the eHub. Using implementation science activities, the team will conduct 2-3 short Plan-Do-Study-Act quality improvement cycles [33] over the 6 months of implementation, including review of caregiver satisfaction with the navigation processes and content and whether caregivers are progressing to higher tiers of support. These short learning cycles will allow agile minor improvements of the eHub.

eHub Outcome Data Collection (6 Months)

Prospective Cohort Caregiver Outcome Surveys (6 Months)

Caregivers involved in the evaluation will be sent an email or SMS text message invitation to complete an online survey at 6 months after baseline to measure outcomes on access and use of health services, accessibility, and overall experience of using the eHub. Secondary outcomes will also be measured via the caregiver outcome survey. All measures and associated data are outlined in Table 3. Surveys will be collected in REDCap, a secure online portal. Research assistants will follow-up those caregivers who do not complete the caregiver outcome survey via phone, text, or email.

Prospective Cohort Caregiver and Cross-Sectoral Service Provider Semistructured Interviews

Caregivers (n=15-20 in total) and intersectoral service providers (n=15-20 in total) from the evaluation sites will be invited to participate in individual semistructured interviews at 6 months after eHub implementation. Interviews will be conducted by web-conferencing platform (Zoom; Zoom Video Communications). Participants will be invited to provide their perspectives on barriers and enablers of using the eHub, such as were caregivers' needs satisfied by using the eHub? Was the eHub able to support their unmet social needs? Did caregivers use or intend to use strategies provided in information sourced on the eHub? And were there changes to caregivers' behavior (eg, help-seeking and implementing new strategies)? (see Multimedia Appendix 1 for interview guide). Participants will be invited to expand on any points they feel are important, and the interviewer may ask follow-up questions to elicit further details. The research assistant will be trained and experienced in qualitative methods; the interviews are expected to last between 20 and 30 minutes.

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Statistical Analysis

Sample Size Estimation for Impact Evaluation

We will recruit a total of 270 caregivers to give the study 90% power to detect an 11% increase in the proportion of caregivers accessing services via the eHub, that is, from 9% to 20% based on previous research [34], with a hypothetical 5% increase without the intervention. This allows for a 10% loss to follow-up.

Statistical Methods for All Quantitative Outcomes

We will describe the characteristics of the caregivers and children using the mean (SD) and median (IQR) for continuous data (based on data distribution) and proportions for categorical data, at each time of measurement. To evaluate changes in key outcomes over time (baseline and 6 months), we will analyze the prospective cohort survey data using logistic and linear regression models for binary and continuous outcomes, respectively, specified in Table 3. Binary outcomes will be reported as odds ratios (as change in proportions) with 95% CIs; continuous outcomes will be reported as mean differences (as change in means) with 95% CIs. We will conduct a generalized estimating equation approach to account for repeated measures (ie, baseline and 6 months) for each participant. We will undertake stratified analyses by service site to explore whether outcomes vary by site. In consideration of the change in participants' characteristics between baseline and 6-month surveys due to loss to follow-up, we will control for family socioeconomic characteristics. Missing data will be handled using appropriate statistical techniques (such as multiple imputation for missing at random). We will describe the proportions of measures derived from data analytics from eHub users (specified in Table 3). We will conduct all analyses using STATA (version 16) or SAS (SAS Institute) statistical software packages.

Qualitative Data Analysis: Caregiver and Intersectoral Service Provider Interviews

Experienced research assistants at each site will use deductive and inductive analysis of stakeholder interviews using framework analysis. Framework analysis is suitable for this applied study because the technique is not aligned with any specific epistemological stance and places the research questions at the forefront of the analysis [35]. Interviews will be transcribed, and NVivo (version 14; Lumivero) will be used to code data from interviews. The first 10% of interviews at each site will be double-coded by research assistants, and any issues will be resolved prior to finalizing coding for all interview participants.

Health Economic Analysis

Using study protocols and budgets, the cost of implementing the eHub model will be estimated. This will include fixed or upfront costs of building the eHub as well as variable ongoing costs of maintaining and staffing. The cost of caregiver-reported intersectoral service use will be estimated. Cost effectiveness will be calculated as a cost per additional child or caregiver engaged with the program and a cost per additional child with unmet needs who accesses the eHub model. The cost of a national roll-out of the eHub model will be estimated based on the number of children serviced by the study versus the whole Australian population of children. An estimation will be made on the number of eHub local modifications needed nationally.

Ethical Considerations

This study received ethics approval from the Royal Children's Hospital Human Research Ethics Committee (HREC #84970). All participants will provide informed consent prior to enrollment. Caregivers will access study information and consent materials via a secure online platform (REDCap) and will have the opportunity to ask questions before providing electronic consent. Participation is voluntary, and individuals may withdraw at any time without consequence. All data collected during the study will be deidentified prior to analysis. Participant information will be stored on secure servers in accordance with institutional data security protocols to protect privacy and confidentiality. Only approved members of the research team will have access to identifiable information, which will be stored separately from deidentified datasets. Participants will be reimbursed with a US $20 gift voucher for their time and contribution to the study.

Results

This study received funding in December 2021, followed by user-centered design of the eHub MVP with families and local service providers. The study was registered with the ISRCTN Registry in June 2023. Following ethics approval in June 2023, participant enrollment and data collection for the study began in February 2024, with participants involved in the eHub evaluation for 6 months. Analysis of data was conducted from February 2025 to May 2025. Table 2 outlines the study timelines across major phases.

Discussion

This study anticipates that the eHub will be a feasible, acceptable, and appropriate digital solution for caregivers of children aged 0-12 years, particularly those experiencing adversity. We hypothesize that implementation of the eHub will result in increased access to and engagement with relevant health and social services, improved caregiver satisfaction with the information-seeking process, and reductions in caregiver distress and child mental health concerns.

Despite significant increases in mental health needs, families with young children (aged 0-12 years), especially from priority groups, are still not accessing services and supports early, and they often present after complexities and comorbidities have set in and experience a significant emotional burden of seeking help [14]. Lack of timely access to supports and services is further compounded by the poorly coordinated and fragmented Australian child and family health and social care service systems that families find difficult to navigate. While there are some digital applications available for practitioners to help families support their children's developmental needs in the preschool period, including coordinating wraparound social care [36,37], none of the available tools focus on families of children aged 0 to 12 years with mental health concerns, while

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also incorporating support for broader social determinants of health and mental health, such as housing, finances, food insecurity, employment, and legal issues.

The eHub provides online navigation and evidence-based information for families and aims to increase equitable access to and use of (1) information and (2) the existing primary health, mental health, and social services system to improve mental health outcomes for caregivers with children aged 0-12 years. Whether these digital applications can be feasibly implemented and adopted, especially within diverse and limited-income populations within Australia, remains largely unknown.

This protocol outlines a mixed methods implementation-impact evaluation that uses Proctor's outcomes framework [20] to assess the reach, engagement, adoption, appropriateness, and acceptability of the eHub. Quantitative and qualitative data will be collected in parallel to examine user access patterns, satisfaction, and changes in help-seeking behaviors and caregiver or child outcomes. The majority of caregivers are expected to engage with the lower tiers of the eHub (tiers 1-3), consistent with a proportionate universalism approach, with a smaller proportion using tier 4 (human navigation support).

In this protocol, we outline the methodology to assess the uptake, usability, acceptability, appropriateness, and cost of the eHub, noting a complementary quality improvement approach to improve as implemented [1]. This study builds on the MVP that has already been developed, and it will validate the design by testing the eHub, optimizing its existing functions, and informing future features.

While several digital tools exist, few have been specifically developed for children aged 0-12 years or explicitly address the intersection of mental health and social adversity [38,39]. Internationally, digital platforms to support child and family mental health have emerged in various forms; however, most are targeted toward adolescents or focus solely on mental health content without integration of social care navigation. For example, programs like the United Kingdom's "Kooth" platform [40] or the US-based "MyStrength" [38] target older populations and are not co-designed with caregivers of young children. In contrast, the eHub is uniquely tailored for caregivers of children aged 0-12 years, combining access to both health and social service information with a user-centered design approach involving families experiencing adversity. This locally grounded, system-oriented model may offer transferable insights for international contexts facing similar challenges related to service fragmentation. The eHub directly addresses the literature gap by integrating co-designed content with tiered navigation supports, helping caregivers overcome common barriers to service access such as health literacy limitations, time constraints, and stigma.

Given the current gap in the existing "market" for this type of digital service, it will be essential to consider how best to learn from the evaluation to enhance its replicability to other sites. Furthermore, this study will provide insights into potential mechanisms underlying the intervention's impact; shed light on the effectiveness, or ineffectiveness, of its various components; and offer possible explanations that will, again, be essential for replication.

Strengths of the study include its multisite design across 3 diverse communities, the use of real-world user data and embedded quality improvement processes, and the integration of caregiver and provider perspectives through semistructured interviews. One potential limitation of this study is the relatively short 6-month evaluation period, which may not capture long-term impacts on mental health outcomes or sustained service use. However, this time frame may be appropriate, given that digital applications are often designed for targeted, time-limited use, with peak engagement typically occurring during periods of greatest need or relevance to users. Another limitation is the inclusion criterion requiring sufficient English proficiency to participate in the study and complete the survey. Although each study site is culturally diverse and many residents speak English, this focus may limit the generalizability of findings to caregivers from non-English–speaking backgrounds.

Despite these limitations, this study will provide critical evidence on whether the eHub is effective in meeting the needs of priority populations and addresses inequitable access and uptake of support and services for families who are experiencing a range of adversities. Future directions may include testing longer-term outcomes of eHub use, examining cost-effectiveness over time, and adapting the platform for broader populations, including those speaking languages other than English. Results from this study may also inform the development of an implementation guide to support scale-up to other Australian sites.

Dissemination of the study findings will include publication in a peer-reviewed journal paper. On completion of the trial, and after publication of the paper, results will be presented to relevant state and federal government contacts and presented at relevant domestic and international conferences. Feedback will also be shared with participating community partners and made accessible through the eHub platform to ensure that knowledge is translated back to service users and providers.

In summary, the results of this study will provide much-needed data and insight into the wider sustainable implementation of the eHub to facilitate equitable access to relevant evidence-based information and services to support child and family mental health. In addition, this project has the potential to increase our understanding of how digital solutions can improve navigation to information and services for a variety of health and social issues in a cost-efficient manner at a national level.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Caregiver interview guide.
[DOCX File , 286 KB - resprot_v14i1e72548_app1.docx]

Multimedia Appendix 2
Peer review report from the National Health and Medical Research Council, Australia, and The Royal Children's Hospital Melbourne.
[PDF File (Adobe PDF File), 196 KB - resprot_v14i1e72548_app2.pdf]

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Abbreviations

eHub: Child and Family eHub
MVP: minimum viable product
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Development of a Cocreated Perioperative Joint Replacement Digital Care Pathway to Improve Surgical Outcomes Following Joint Replacement: Protocol for a Mixed Methods Study

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Abstract

Background: Recently, perioperative care has gained attention for its ability to improve outcomes, reduce costs, and enhance patient satisfaction, especially when multidisciplinary support is involved. Despite these benefits, patient compliance remains low due to limited engagement in program design and practical barriers such as transportation, particularly for older adults. Co-designed digital health solutions offer a promising, scalable approach to delivering personalized, accessible perioperative care, with emerging evidence supporting their feasibility and effectiveness in patients who undergo joint replacement.

Objective: The objectives of this study protocol are to outline the methods to address three study aims: (1) understand gaps and unmet needs, including knowledge, perceptions, barriers, and acceptability, during the perioperative patient journey of hip and knee arthroplasty; (2) co-create a novel patient-centric digital care pathway (DCP) that provides education and systematically captures patient-reported outcomes; and (3) evaluate the feasibility of implementation, appropriateness, and acceptability of the pathway when tested in patients undergoing nontraumatic hip and knee joint arthroplasty.

Methods: This mixed methods co-design and implementation study will be conducted across 3 phases informed by the generative co-design framework for health care interventions. In phase 1 (predesign), patient interviews and journey mapping will be used to identify perioperative care gaps to be addressed in the DCP. In phase 2 (co-design), care gaps will be collaboratively framed, and iterative prototyping of the DCP will be conducted with consumer feedback and pilot testing. In phase 3 (evaluation), the feasibility of the DCP will be assessed using a previously reported framework. Inclusion criteria will vary across phases, focusing on people with lived experience or undergoing hip or knee joint replacement and relevant clinical or administrative staff.

Results: The study was funded in September 2024, with phase 1 commencing in July 2025 and phase 2 in October 2025. Phase 3 is projected to commence before the end of 2025 and conclude 6 months later. As of October 2025, 13 people had been recruited, interviews were completed for phase 1, and recruitment for phase 2 had commenced.

Conclusions: This protocol enhances methodological transparency by detailing the co-design approach, strengthening the evidence base, and supporting the development of a credible, transferable DCP. It addresses the lack of patient-centric perioperative programs in joint replacement care by incorporating individual needs and preferences. The digital format helps overcome access barriers, such as transport limitations, enabling patients to engage with the pathway anywhere. Additionally, patient-reported outcome measures collected through the DCP will improve understanding of recovery trajectories following hip and knee replacements.

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KEYWORDS

arthroplasty; rehabilitation; co-design; digital health; patient education

Introduction

Surgery plays a major role in health care systems worldwide, with an estimated 310 million surgeries performed globally each year [1,2]. However, surgery is associated with significant risks and the burden of complications [1,2]. Despite advances in surgical technology, anesthesia, and perioperative care, postoperative complications remain common. For orthopedic surgery, 20% to 40% of people experience postoperative complications manifesting in reduced functional and psychological capacity, such as fatigue, sleep disturbance, and decreased quality of life [2-4]. These complications lead to poor health outcomes, prolonged hospital stays, and high readmission rates [5-7].

Over the past decade, perioperative care strategies have received greater attention as a mechanism to improve postoperative outcomes [8]. High-quality perioperative care reduces health care costs, length of stay, and postoperative complications, while simultaneously improving patient satisfaction [4,8-10]. Patients generally report high satisfaction with these interventions, particularly when multidisciplinary support is provided [11,12]. However, despite these reported benefits, patient compliance remains low (<50%) [11]. This is often attributed to the absence of engagement with end users in their design and development, leading to a lack of patient-centric programs that consider patients' individual needs and preferences [11,13]. This is further inhibited by practical barriers, such as travel and transport difficulties, particularly among older adults [14]. Patients want early, comprehensive information and support for preoperative preparation [2,15], often resorting to self-directed efforts or information from their general practitioner [2], highlighting a gap in readily accessible, patient-centered pathways for these patients.

Co-designed digital health solutions have been proposed as practical and scalable methods to address barriers to accessing and completing perioperative care. Digital health, using information and communication technologies, has the potential to deliver personalized, accessible, and patient-centered perioperative care that patients can engage with at their own pace, regardless of location [16,17]. Emerging evidence highlights that digital prehabilitation interventions are acceptable and feasible for people preparing for hip and knee arthroplasty [2,17-19], with telehealth rehabilitation demonstrating comparable clinical and patient-reported outcomes to in-person physical therapy [20,21]. However, there remains limited research examining the codevelopment of digital health resources and their successful implementation within public health services [13,19]. A codeveloped digital care pathway (DCP) may augment patient monitoring and provide effective perioperative clinical care for people undergoing hip and knee arthroplasty. A DCP is an application-based digital adjunct used to facilitate patient care [22]. This enables the delivery of accurate and relevant education and self-management resources while also facilitating the routine collection of patient-reported outcomes, thereby facilitating the early identification of patients at risk of poor long-term outcomes [22,23]. Therefore, the aims of this study are as follows:

1. Understand gaps and unmet needs, including knowledge, perceptions, barriers, and acceptability, during the perioperative patient journey of hip and knee arthroplasty.
2. Co-create a novel patient-centric DCP that provides education and systematically captures patient-reported outcomes.
3. Evaluate the feasibility of implementation, appropriateness, and acceptability of the pathway when tested among patients undergoing nontraumatic hip and knee arthroplasty.

Methods

Study Design

This mixed methods co-design and implementation study will be reported in accordance with the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement [24]. To address the 3 distinct aims, the study will be conducted across 3 phases informed by the generative co-design framework for health care interventions [25], as outlined in Textbox 1 [26-29]. A learning community will be established, comprising patients, health care staff, administrators, and researchers, to inform and guide each stage of the co-design process.

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Textbox 1. Phases of co-design used to develop the digital care pathway.

Phase 1: Predesign (understand)

- Contextual inquiry: patient journey mapping [26-28] to describe the perioperative pathway and identify service gaps, and interviews with consumers. Reporting informed by prompts from Davies et al [26].
- Preparation: establishment of a learning community involving patients, staff, administrators, and researchers.

Phase 2: Co-design

- Framing issue: identification of care gaps and collaborative development of potential solutions.
- Generative design: iterative prototyping of digital care pathway features with feedback from the learning community.
- Sharing ideas: pilot-testing of the refined prototype with a sample of patients.

Phase 3: Postdesign (evaluate)

- Data analysis: assessment of feasibility using the framework for feasibility studies by Bowen et al [29].
- Requirements translation: conversion of co-design outputs into workflows and technical specifications, aligned with perioperative processes.

Ethical Considerations

This study has been approved by the St Vincent Hospital Human Research Ethics Committee (2024/PID00354 LRR 288/24) under the National Health and Medical Research Council of Australia National Mutual Acceptance Scheme. The study has also received research governance approval from La Trobe University (LRR 288/24), with Northern Health research governance to be sought before any direct recruitment of Northern Health staff or patients. Participants will provide consent as follows: (1) written informed consent for patient and staff interviews, and (2) implied consent for the use of data generated through the completion of the DCP. Participants' privacy and confidentiality will be maintained in accordance with ethical approval conditions and local laws. People with lived experience of joint arthroplasty that participate in the interviews in phase 1 or phase 3 will receive an Aus $20 (US $13.07) gift card following the interview. Individuals who participate in the DCP, as well as organizational and clinical staff, will not receive compensation for their participation.

Setting

The study will be conducted at Northern Health, Victoria, Australia [30]. Northern Health is the major provider of acute, subacute, and specialist services in Melbourne's rapidly growing outer north corridor. The health service caters to a diverse population of patients who speak more than 100 languages. The catchment has lower levels of income, educational attainment, and health literacy and higher rates of unemployment than the Victorian state averages [31]. Northern Health has pioneered digital health integration through initiatives such as the Victorian Virtual Emergency Department [32] and DCPs [22].

Current Joint Arthroplasty Touchpoints With Opportunities for a DCP

The key touchpoints associated with elective arthroplasty in the public health service are illustrated in Figure 1. Each touchpoint provides an opportunity to reinforce education provided by clinicians through electronic or digital resources, codeveloped with patients. For example, when patients are deemed suitable for surgery, there can be long wait periods from the preadmission clinic to the surgery date. This provides an opportunity to deliver evidence-based education and structured prehabilitation, aimed at optimizing physical function, managing comorbidities, supporting psychological readiness, and promoting healthy lifestyle behaviors. At the preadmission clinic, patients could receive additional resources to support their preparation for surgery. These resources might include information on pain management strategies, expectations regarding acute recovery, guidance on postoperative mobilization, and discharge destination. Other potential resources, highlighted in a recent systematic review, that have been used in prehabilitation include, but are not limited to, general hospital and surgical information, daily living and home preparation, and psychosocial and supportive aspects (eg, to reduce fear and anxiety around surgery) [10]. The integration of patient-reported outcomes and remote patient monitoring could enable patients and clinicians to follow the trajectory of recovery with benchmarked standards [33].

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Figure 1. High-level overview of key touchpoints with elective joint replacements in the public health service and a potential perioperative digital care pathway.

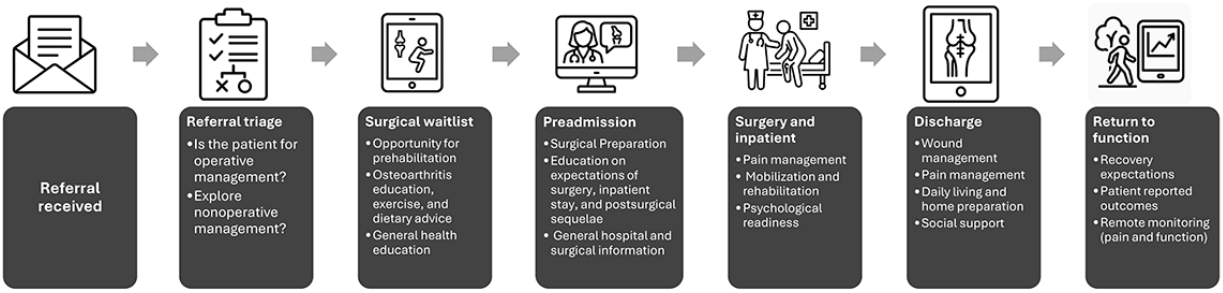

Participants

Formal participant inclusion and exclusion criteria for phases 1 and 2 of the study are outlined in Textbox 2. For phase 2, people with lived experience of arthroplasty from phase one, as well as Northern Health staff working in perioperative hip or knee arthroplasty surgical care, will be invited to participate in co-design workshops and provide feedback on the development of the DCP consistent with the co-design steps of the generative co-design framework for health care innovation [25].

Textbox 2. Overview of phase 1 (understand) and phase 3 (evaluate) inclusion and exclusion criteria.

Phase 1

- People with lived experience
  - Inclusion criteria: individuals aged 18 y or older who have undergone hip or knee arthroplasty surgery in the last 12 mo
  - Exclusion criteria: unable to understand spoken or written English
- Organizational and clinical staff
  - Inclusion criteria: not applicable
  - Exclusion criteria: not applicable

Phase 3

- People with lived experience
  - Inclusion criteria: any patient undergoing hip or knee arthroplasty surgery at Northern Health in the first 6 mo of implementing the digital care program into standard care
  - Exclusion criteria: unable to understand spoken or written English
- Organizational and clinical staff
  - Inclusion criteria: any primary or secondary contact clinician working in perioperative hip or knee arthroplasty surgical care at Northern Health, or any administrator working in perioperative hip or knee arthroplasty surgical pathway at Northern Health
  - Exclusion criteria: unable to understand spoken or written English

Procedures

Phase 1: Understand

Step 1: Contextual Inquiry

People with lived experience of a total hip or knee arthroplasty will be recruited via widespread print and social media advertising. Semistructured interviews (Multimedia Appendix 1) will be conducted to encapsulate their perioperative journey, with a focus on barriers, enablers, gaps, and unmet needs across common care touchpoints. The interviews are expected to capture the physical (functional) and emotional (experiential) dimensions of care, providing insights into common patient experiences along their care pathway. The interviews aim to elicit the behaviors, feelings, motivations, and attitudes of people with lived experience across their entire episode of care [26].

This interview guide has been developed using the capability, opportunity, motivation-behavior (COM-B) model of behavior change [34]. COM-B is a theoretical framework that proposes that any behavior (B) results from the interaction of 3 components: capability (physical and psychological), opportunity (social and environmental factors), and motivation (reflective and automatic processes) [34]. Drawing on this framework ensures that the interview questions address a broad

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range of influences on patient behavior, including functional abilities, social context, and motivational drivers. In this study, COM-B will be used solely to inform the design of interview questions, ensuring comprehensive coverage of factors that may shape patient experiences across their perioperative journey.

Following data collection, qualitative data from the interviews will be imported into NVivo (QSR International) and analyzed using the framework method (transcription, familiarization, coding, developing an analytic framework, indexing, data charting, mapping, and interpreting) [35]. We will use a combined inductive and deductive coding approach, guided by the 6-step method developed by Terry et al [36]. In the first round, 2 researchers will familiarize themselves with the data by reading through all transcripts (step 1). They will then independently inductively code all transcripts (step 2). Following this, the researchers will meet to compare and collapse all similar codes (step 3) and will refine them until there is a final, agreed-upon set of codes (step 4). In the second round of coding, the agreed-upon codes will be applied to the entire dataset independently by the 2 researchers (step 5). In the final round, themes will be visually concept-mapped across critical touchpoints, barriers, and enablers to develop an initial journey map of the patient experience (Figure 2).

Figure 2. Overview of the proposed journey mapping touchpoints.

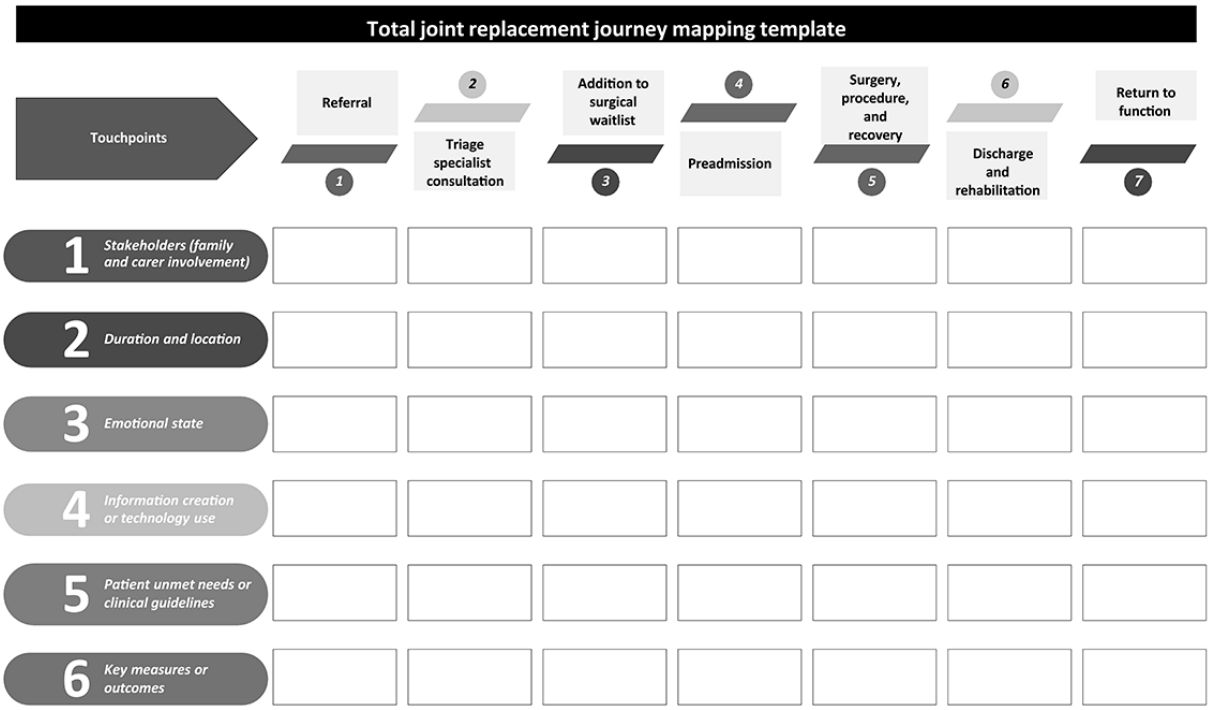

Step 2: Preparation

A learning community will be established, comprising key stakeholders, including people with lived experience of arthroplasty, system-level representatives (eg, health service managers), clinicians (eg, physiotherapists, surgeons, and nurses), and administrators and researchers. Accessibility requirements will be established during this step, and we will purposively include consumers with diverse literacy levels, cognitive needs, physical limitations, and cultural backgrounds. As part of the co-design process, we will identify barriers to digital engagement, preferred modes of interaction, and required functional supports. Members will be oriented to the project, provided with relevant resources, and prepared for participation in subsequent phases of the co-design process. Recruitment will draw on participants from step 1, as well as word-of-mouth, professional networks, and organizational invitations. These stakeholders will be embedded in each decision-making stage and contribute to the co-creation process, as appropriate.

Phase 2: Co-create

Step 3: Framing the Issue

Insights from step 1 will be synthesized to identify gaps in perioperative care and potential areas for service improvement. Preliminary models, pathways, and resources will be developed based on these findings and used to frame key issues for discussion with the learning community. This process will ensure that the problems and priorities reflect both the lived experience and system perspectives.

Step 4: Generative Co-Design

Draft pathways and resources will be presented to the learning community during a series of workshops or interviews, conducted either face-to-face or by videoconference. Participants will collaboratively critique and refine these prototypes, providing feedback on feasibility, usability, and acceptability. Iterative adjustments will be made following each session, resulting in progressively refined pathway models and supporting resources. During the DCP development, we will ensure alignment of content and design with web accessibility

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standards and health literacy design principles. This will include ensuring that the digital interfaces use plain language (tested using the Flesch Kincaid readability test and will aim for a grade level of 5), closed captions for multimedia (available in multiple languages), and easy-to-see and hear text content using preferred fonts for readability, accessible colors, and sufficient contrast.

Step 5: Sharing Ideas

The draft DCP prototype will be implemented on a small scale in patients undergoing total knee or hip arthroplasty at Northern Health. This stage will provide an opportunity to share the model with patients and staff, observe how it operates in practice, and capture early feedback on its use within standard care. All patients triaged for arthroplasty during the first 6 months of implementation will be invited to participate in the pathway. Insights from this process will inform the refinement of the pathway and identify practical considerations to be explored in the evaluation stage.

Phase 3: Postdesign (Evaluate)

Step 6: Data Analysis

Overview

Data generated during the pilot implementation (step 5) will be analyzed to assess the feasibility of introducing the DCP into routine perioperative care. A mixed method data analysis will be used to explore the acceptability, appropriateness, barriers, and enablers to implementation.

Feasibility will be assessed using a mixed methods approach informed by the framework developed by Bowen et al [29]. This will include the domains of demand, acceptability, implementation and practicality, and pilot effectiveness of the DCP. Notably, the assessment of these domains during the initial 6-month period is to understand the DCP's initial implementation. The intention is developmental, supporting iterative refinement, and identifying additional resource needs and allocations, rather than determining the DCP's overall success.

Demand

Demand will be based on uptake of the DCP from those invited to participate (all individuals undergoing a hip or knee arthroplasty in the first 6 months of implementation). Demand outcomes will include application downloads, completion of the patient-reported outcomes, and resource views.

Acceptability

We will assess dimensions related to the Theoretical Framework of Acceptability by Sekhon et al [37], including confidence in recommending to family and friends, the level of burden associated with the DCP, and whether the desired outcome was achieved. These will be assessed using a survey administered by Research Electronic Data Capture at the preadmission clinic and 12 weeks after discharge.

Implementation and Practicality

We will assess implementation and practicality via semistructured interviews (Multimedia Appendix 2) with staff and individuals with lived experience to explore their perspectives to identify factors influencing implementation, resource requirements, and timeliness of delivery.

Pilot Effectiveness

Patient-reported outcomes will assess pain, function, and quality of life over time using the short form hip or knee osteoarthritis outcome score [38], with additional measures to be informed by patients as part of phase 2. This will be assessed at the following time points (before surgery, discharge, 2 weeks after surgery, 6 weeks after surgery, 12 weeks after surgery, and 6 months after surgery).

Demographic Analysis

Participant demographics and baseline characteristics will be reported using descriptive statistics, as appropriate, based on normality.

Demand and Acceptability Analysis

Outcomes will be reported as counts, frequencies, and proportions or by parametric or nonparametric descriptive statistics as appropriate based on the individual outcome and normality.

Implementation and Practicality Analysis

Semistructured interview recordings will be transcribed and provided to the participant within 14 days for the participant to confirm that the data reflects their perspective. The transcript will be deemed accurate if no feedback is received within 14 days. Data will be analyzed using reflexive thematic analysis [39] to identify themes, with coding conducted by 2 independent researchers and compared to identify present themes [39].

Limited Efficacy and Effectiveness Analysis

Patient-reported outcome measure data will be analyzed in accordance with previous DCP evaluations [22]. Recovery trajectories of patient-reported outcomes will be summarized using linear mixed-effects models to account for missing data. Data will be presented as linear or nonlinear trajectories based on the best model fit (as assessed by the Akaike information criterion) [40]. Full information maximum likelihood will be used to account for missing data. All statistical analyses will be conducted using R statistical software (R Foundation for Statistical Computing) with an alpha value of .05.

Sample Size: Patient and Staff Interviews

Interviews will continue until data saturation is reached. Saturation will be predefined as 3 consecutive interviews where no new theoretical categories are identified past an initial minimum sample of 12 [41,42].

Sample Size: DCP Pilot Implementation

No priori sample size was defined for DCP completion, consistent with feasibility study objectives.

Step 7: Requirements Translation

Findings from the pilot evaluation will be synthesized into a finalized model of the DCP. This model will integrate the requirements articulated by co-design participants with the practical considerations identified during the evaluation (eg, feasibility, acceptability, workflow fit, and resourcing). In line with guidance on feasibility and implementation outcomes

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[29,43], the evaluation will determine which components are core and must be preserved, and which can be adapted for local contexts. Processes, workflows, and supporting materials will be refined to ensure that the DCP is ready for translation into routine practice.

Results

The study was funded in September 2024, with phase 1 commencing in July 2025 and phase 2 in October 2025. Phase 3 is projected to commence before the end of 2025 and conclude after 6 months of recruitment. As of October 2025, 13 participants were recruited. Interviews were completed in phase 1 and recruitment for phase 2 commenced.

Discussion

Anticipated Findings

Developing a protocol that explicitly outlines the co-design methods proposed for the DCP is important, given the inconsistent reporting evident in the existing literature. The umbrella review by Kilfoy et al [13] highlighted that while co-design is widely promoted as a strategy to enhance the effectiveness and sustainability of digital health interventions, its application is inconsistently reported, with details of participant involvement and methodological rigor often lacking. The absence of clear reporting impedes the evaluation, reproducibility, and progression of existing work, restricting the incorporation of equity and stakeholder perspectives in digital innovation. By specifying our co-design approach, this protocol contributes to methodological transparency, strengthens the evidence base, and ensures that the resulting pathway is both credible and transferable to other contexts and settings. Therefore, we present our study protocol for this mixed methods co-design and implementation study that aims to understand the lived experience of people with knee and hip arthroplasty, co-create a DCP and evaluate its feasibility and appropriateness of implementation.

This study will inform the development and ongoing iterative improvements of a DCP for people undergoing arthroplasty, underpinned by the engagement with end users. This engagement aims to address the lack of patient-centric programs in perioperative joint replacement care and allow the health services to better consider patients' individual needs and preferences [11,13]. The digital nature of the care pathway aims to address access barriers associated with a lack of transportation [14] and allows patients to engage with their ongoing care at any time, regardless of their location [16,17].

The patient-reported outcome measures collected through this DCP will provide a greater understanding of symptom recovery trajectories of people undergoing hip and knee arthroplasty. Our current understanding is limited to isolated studies [33], which may not reflect the current patient outcomes. We hope to supplement this work by capturing rich, real-time data, allowing patient recovery to be mapped and compared with benchmarked trajectories over time. The data obtained will also inform patient education regarding realistic recovery expectations and timelines, and underpin the development of further resources to support this. Although this study aims to evaluate the DCP over the first 6 months of its implementation, the objective is to integrate the pathway into ongoing standard-of-care practices. As a result, the DCP will undergo continual refinement on an iterative basis to adapt to the changing landscape of the health care system [22].

Conclusions

This mixed methods co-design implementation study is consumer-driven, with patients and carers actively involved from problem identification to solution design and evaluation. This approach ensures that the development of a DCP for joint replacement is grounded in lived experience, addressing real gaps in care and unmet needs. By embedding co-design principles and drawing on established frameworks, this study privileges consumer voices, promotes collaboration between patients and clinicians, and increases the likelihood that the resulting pathway will be acceptable, relevant, and sustainable in practice.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

AIS contributed to conceptualization, methodology, resources, writing the original draft, visualization, project administration, and funding acquisition. RJ contributed to conceptualization, methodology, resources, writing the original draft, project administration, and funding acquisition. RD contributed to conceptualization, methodology, writing, reviewing, editing, and funding acquisition. SG contributed to writing, reviewing, editing, visualization, and project administration. HG contributed to resources, writing, reviewing, editing, and project administration. ECB contributed to conceptualization, methodology, writing

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the original draft, project administration, and funding acquisition. SMQ contributed to methodology, writing the original draft, and project administration. JG contributed to conceptualization, resources, writing, reviewing, editing, and funding acquisition. UP contributed to resources, writing, reviewing, and editing. KS contributed to resources, writing, reviewing, editing, and funding acquisition. RG-O contributed to resources, writing, reviewing, and editing. JB contributed to resources, writing, reviewing, and editing. HH contributed to conceptualization, writing, reviewing, editing, and funding acquisition. TW contributed to resources, writing, reviewing, editing, and funding acquisition. MGK contributed to conceptualization, methodology, writing the original draft, visualization, project administration, and funding acquisition.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Patient interview guide for phase 1.
[DOCX File , 33 KB - resprot_v14i1e85701_app1.docx]

Multimedia Appendix 2
Patient interview guide for phase 3.
[DOCX File , 17 KB - resprot_v14i1e85701_app2.docx]

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Abbreviations

COM-B: capability, opportunity, motivation-behavior
DCP: digital care pathway
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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Protocol

Smartphone-Based Physical Activity Program to Reduce "Chemo-Brain" Symptoms and Improve Health in Cancer Survivors With and Without Type 2 Diabetes: Protocol for a Single-Arm Pre-Post Pilot Trial

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Abstract

Background: The US cancer survivor population is projected to hit 26M by 2040. Chemotherapy is an effective cancer treatment, but can diminish cancer survivors' quality of life—particularly cognitive function—through select pathophysiological processes, including immune system and antioxidant dysregulation. The resulting cytokine release can impair cerebrovascular function—likely contributing to chemotherapy-induced cognitive impairment (CICI; "chemo-brain"). Type 2 diabetes mellitus (T2DM)—a common cancer survivor comorbidity—shares underlying pathophysiology with CICI. Cancer survivors with T2DM might thus have a higher CICI risk than those without T2DM. Physical activity (PA) counteracts CICI's and T2DM's pathophysiology, but little to no research has been conducted assessing the impact of PA on this joint pathophysiology.

Objective: To compare cerebrovascular and cognitive function as well as proinflammatory, cardiometabolic, epigenetic, and psychosocial outcomes between ancer survivors with and without T2DM pre- to postengagement in a 12-week technology-based PA program grounded in the Social Cognitive Theory. We hypothesize that cancer survivors with and without T2DM will demonstrate similar pre to poststudy improvements in psychosocial outcomes, but that changes in cerebrovascular and cardiometabolic outcomes, as well as PA engagement, will be greater for cancer survivors with T2DM. We also believe that each group will have distinct epigenetic profiles that will change pre to poststudy.

Methods: We are conducting a 30-participant pilot study in cancer survivors with (n=15) and without (n=15) T2DM—all of whom report currently experiencing "chemo-brain." To account for attrition, we are recruiting 38 cancer survivors from Oklahoma City, OK, and the surrounding area. Among the most important eligibility criteria are the self-report of cognitive difficulties following primary cancer treatment, being ≥18 years old, being within 3 years of primary cancer treatment, and not meeting nationally recommended PA guidelines. Participants receive 2 smartphone apps. One smartphone app provides health education

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and the ability to set goals and journal about their wellness journey. The other provides a workout program continually tailored to each participant via their communication with the study exercise physiologist, with resistance bands and a wearable device provided to support the program. At Baseline and Poststudy, we assess cerebrovascular function (transcranial doppler [TCD]), cognition (National Institutes of Health Toolbox), cardiometabolic outcomes (venipuncture), and epigenetics (saliva collection). Participants also wear accelerometers at Baseline and Poststudy to objectively assess PA, with Baseline, Midpoint, and Poststudy surveys assessing psychosocial outcomes. We will use *t* tests and chi-square tests to assess baseline differences and repeated-measures ANCOVA to assess changes over time.

Results: Participant recruitment started in March 2025, and we expect to recruit until late 2026. We will begin analyzing baseline data in 2026.

Conclusions: Successful study completion will provide valuable insights into the remote delivery of PA-oriented supportive care for cancer survivors experiencing chemo-brain, as well as how T2DM and PA contribute to the mechanistic underpinnings of chemo-brain.

Trial Registration: ClinicalTrials.gov NCT06725953; https://clinicaltrials.gov/study/NCT06725953

International Registered Report Identifier (IRRID): DERR1-10.2196/79739

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KEYWORDS

resistance training; aerobic physical activity; wearable technology; smartphone applications; social cognitive theory

Introduction

Background

While incident cancer cases of any site remain stable, 5-year cancer survival rates have increased [1]. In January 2022, >18M individuals in the US were cancer survivors—defined here as those diagnosed with cancer onward [2]—with a projected increase to 26M by 2040 [3]. Although modern cancer treatments are effective, these treatments can worsen cancer survivors' health-related quality of life (HRQoL) [4-6]. Several cancer treatments—most notably, chemotherapy—are associated with cognitive difficulties [7-9]. While chemotherapy effectively treats many malignancies, it also negatively impacts vascular endothelial cells [10-12]—leading to pathophysiological processes contributing to cancer survivors' often-reported chemotherapy-induced cognitive impairment (CICI; aka "chemo-brain") during/after treatment [7,8]. As the number of cancer survivors increases, CICI mitigation research is crucial to improve HRQoL.

CICI likely occurs for several reasons. Chemotherapy can induce immune and antioxidant dysregulation [13-16]. This dysregulation can lead to peripheral proinflammatory cytokines being released, which damage and cross the blood-brain barrier [13,14,17]—contributing to central proinflammatory cytokine release [18-21] and causing neuroinflammation-related impairments in the myelination process [22]. Endothelial dysfunction and cerebral autoregulation failure can also result from this damage [12,23-25]. Reviews [10,11] suggest these mechanisms alter cerebrovascular function more broadly by impairing cerebral perfusion, glucose metabolism, and angiogenesis; thus contributing to CICI.

Type 2 diabetes mellitus (T2DM) is both a risk factor for developing several common cancers and, given its prevalence, a common cancer survivor comorbidity [26,27], heightening cancer recurrence risk [28,29]. Several pathophysiological mechanisms underlying CICI are observed with T2DM [30]. Insulin resistance can result in repeated hyperglycemic episodes and subsequent proinflammatory cytokine elevation [31-35]—possibly explaining why insulin resistance is correlated with diminished cerebrovascular and cognitive function in individuals with T2DM but without cancer [36-38]. This might also explain why, in newly diagnosed cancer survivors with proinflammatory comorbidities (eg, T2DM), higher proinflammatory cytokines and poorer cognitive function have been observed relative to cancer survivors without comorbidities—even prior to chemotherapy [39]. CICI mitigation research that compares those with and those without T2DM may help clarify the magnitude to which T2DM contributes to the mechanisms underlying CICI. Notably, CICI mitigation research may also benefit from the inclusion of assessments of the epigenome, given that upregulated proinflammatory cytokines, a hallmark of chemotherapy and T2DM, may lead to changes in DNA methylation via histone modification [21,40,41].

Aerobic physical activity (PA) and resistance training (RT) have robust health benefits counteracting much of the pathophysiology underlying CICI and T2DM [42,43]. Reviews [44,45] suggest better cerebrovascular function in those who are more active or fitter relative to those who are less active or fit, with greater fitness positively associated with cognitive function in other at-risk populations [46,47]. In those with T2DM, research has shown that PA is impactful at lowering proinflammatory cytokines [42,48-50] and improving insulin sensitivity [51,52]. Yet, research is needed on how increasing PA in cancer survivors with T2DM reporting CICI improves cerebrovascular and cognitive health through improved fitness. Notably, cancer survivors prefer supportive, individualized, home-based PA programming that includes RT and aerobic activities such as walking [53]. Home-based programs are recommended by the American Cancer Society [54] given their ability to circumvent some of the barriers to PA program participation (eg, distance to clinic, lack of time) among those living with and beyond cancer. Smartphone app technology can assist in providing this home-based PA program access. Relative to routine care, smartphone app–based supportive care among

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cancer survivors has been observed to improve HRQoL, self-efficacy, and symptoms of distress and depression [55]. Further, multicomponent interventions that include personalized PA programming delivered via smartphone apps, with wearable devices to supplement behavior change, have shown promise for increasing PA among cancer survivors [56,57].

We are conducting a 30-participant pilot study in cancer survivors with T2DM (n=15) and without T2DM (n=15)—all self-reporting "chemo-brain"—that includes personalized PA programming and education delivered via 2 smartphone apps, with a wearable device provided for further behavior change support. We have detailed our Specific Aims and Hypotheses below.

Specific Aim 1

Characterize cerebrovascular function, cognitive function, proinflammatory cytokines, and cardiometabolic outcome differences between cancer survivors with and without T2DM. We hypothesize that cancer survivors with T2DM will have (1) poorer measures of middle cerebral artery velocity and cerebrovascular conductance, reactivity, and resistance; (2) lower executive function scores; (3) higher C-reactive protein, interleukin-6, and monocyte chemoattractant protein 1 concentrations; and (4) higher blood pressure and insulin resistance.

Specific Aim 2

Examine pre- to post-PA program differences for changes in Specific Aim 1's outcomes between cancer survivors with and without T2DM. We hypothesize that greater pre- to post-PA program improvements in these outcomes will be observed for cancer survivors with T2DM.

Specific Aim 3

Assess pre- to post-PA program differences for changes in Social Cognitive Theory–based (SCT-based) [58,59] constructs, select psychosocial outcomes, HRQoL, and PA between cancer survivors with and without T2DM. We hypothesize that cancer survivors with and without T2DM will demonstrate pre- to post-PA program improvements in (1) SCT-based, PA-related self-efficacy, outcome expectations, enjoyment, social support, and barriers; (2) stress, anxiety, mood, and depressive symptoms, and that cancer survivors with T2DM will have greater improvements than cancer survivors without T2DM; (3) in HRQoL due to greater improvements in physical functioning as well as pain intensity/interference, and (4) overall PA participation due to greater increases in light and moderate PA.

Exploratory Aim

Characterize epigenetic profiles of biologically relevant pathways related to neurocognition, energy metabolism, and proinflammatory processes in cancer survivors with and without T2DM, and whether changes are observed in these profiles pre- to post-PA program. We hypothesize that distinct epigenetic profiles will be evident between groups but that both groups will show pre- to post-PA program changes in these profiles.

Methods

Study Design and Recruitment

We are conducting a National Institutes of Health Stage 1 trial [60], and we have registered this trial on ClinicalTrials.gov (NCT06725953). Moreover, we used the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials)-Outcomes Guidelines to guide the construction of this manuscript [61]. We are recruiting individuals within Oklahoma City and the greater state of Oklahoma. Our accrual target is 38 participants to allow our desired number of 30 participants to be achieved when accounting for an anticipated 20% attrition rate [62]. We are conducting rolling recruitment and are recruiting via (1) emailed and posted flyers; (2) digital advertising to local survivorship groups; (3) oncologist referral; and (4) chart reviews/assistance from the Stephenson Cancer Center Clinical Trials Office. Potentially eligible individuals are sent a REDCap-based (Research Electronic Data Capture–based) screening survey, and, whenever possible, we are verifying cancer diagnosis, chemotherapy regimen, and T2DM status via medical records. We are evaluating individuals against stringent eligibility criteria. Specifically, our inclusion criteria are as follows: (1) 18 years or older; (2) ability to speak/read English; (3) ability to provide informed consent; (4) underwent treatment within the last 3 years for a non–brain-related cancer with said treatment having included chemotherapy and not currently undergoing any active cancer treatments (ongoing endocrine/hormonal therapy or immunotherapy, when either are used for maintenance purposes, are acceptable); (5) self-reported cognitive difficulties following cancer treatment; (6) (for cancer survivors with T2DM) current T2DM diagnosis as classified by a fasting blood glucose of ≥126 mg/dL, 2-hour oral glucose tolerance test of ≥200 mg/dL, HbA_{1c} level of ≥6.5%, or use of medications (eg, Metformin) or insulin to treat hyperglycemia or (for cancer survivors) no current T2DM diagnosis as classified by a fasting blood glucose <100 mg/dL, 2-hour oral glucose tolerance test <140 mg/dL, or HbA_{1c} level of <5.7%. Presence/absence of T2DM to be confirmed preferentially via physician's documentation or via our measurement of participants' fasting blood glucose during the blood draws within Part 2 of Baseline Testing (Figure 1); (7) own smartphone or computer with internet access; and (8) willing to participate in the 12-week remotely-delivered PA program. Our exclusion criteria are as follows: (1) reporting a Physical Activity Readiness Questionnaire score indicating PA may be unsafe unless a doctor's note clearing a prospective participant for study participation can be provided; (2) engaging in ≥75 min/week of vigorous-intensity PA, ≥150 min/week of moderate-intensity PA, or an equivalent combination of both over the last 3 months; (3) currently undergoing active cancer treatment or planning more treatment within the next 3 months; (4) classified within the prediabetes range for their fasting blood glucose measurement (100-125 mg/dL) during Part 2 of Baseline Testing. Notably, those with T2DM verified via a physician's documentation and who report the use of medications or insulin to treat hyperglycemia, who are found to be in the prediabetes range, will still be enrolled within the T2DM group and study. These results would indicate a participant with well-controlled

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T2DM, not prediabetes; and (5) currently a prisoner, pregnant, or planning to become pregnant during the study.

We will terminate a participant's participation if (1) the participant desires to voluntarily withdraw from the study or (2) the investigators feel a participant is unable to complete the study protocol due to changes in health status. All adverse events are being tracked within a REDCap tool that meets Common Terminology Criteria for Adverse Events 5.0 requirements. Adverse events are reviewed by the study's lead investigators (ZCP, MK, and PM) and the study's oncologist (CH) and reported to the institutional review board (IRB) as necessary (full protocol available upon reasonable request). We do not currently have a Data and Safety Monitoring Board for this study.

Figure 1. Experimental design. HRQoL: health-related quality of life; NIH: National Institutes of Health; SCT: Social Cognitive Theory.

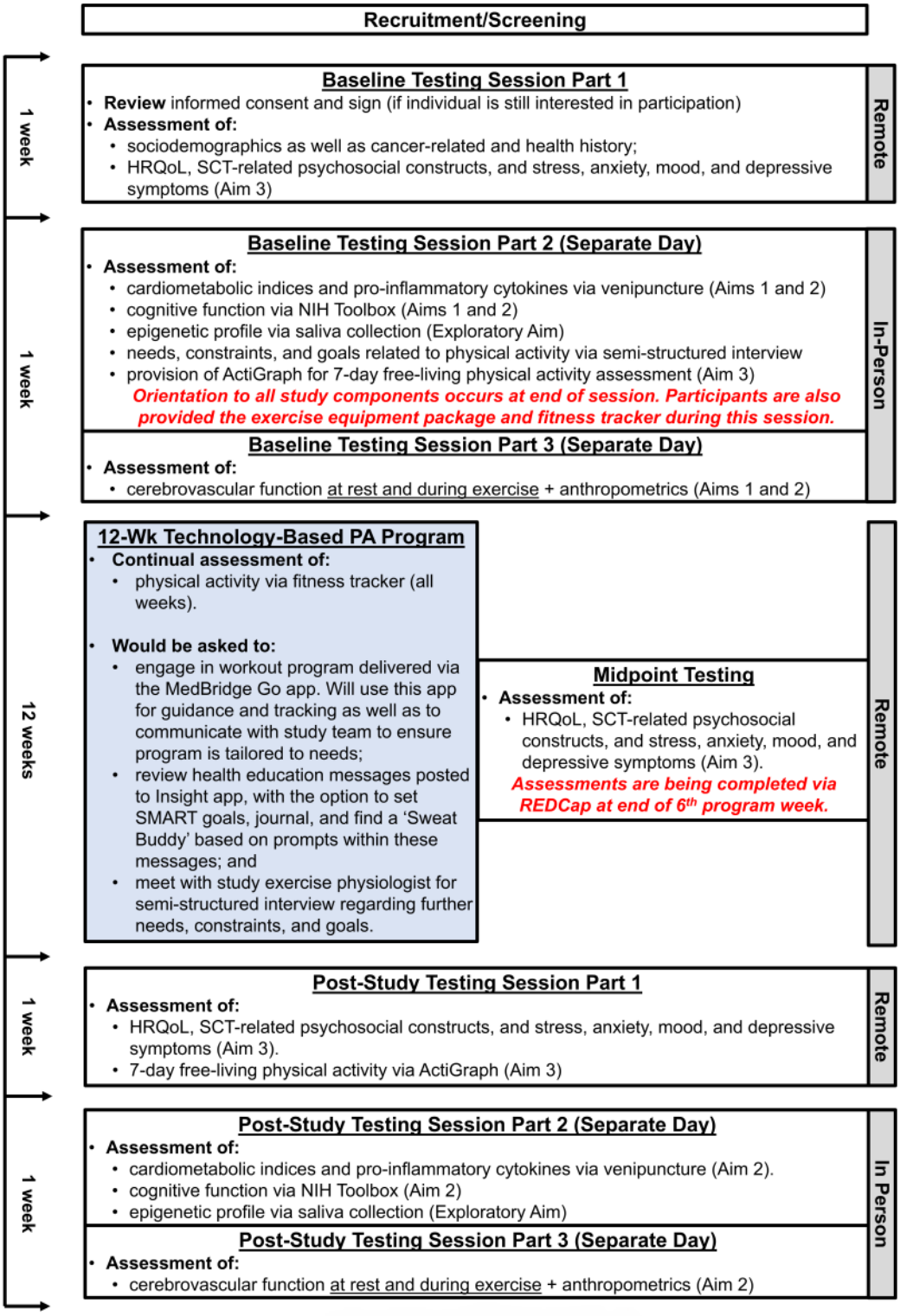

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Study Design

Overview

Figure 1 overviews our study design. While participants come to 2 separate laboratories during Baseline and Poststudy Testing Sessions Parts 2 and 3, given the nature of the assessments to be performed, the study is otherwise entirely remote, as shown on the right side of Figure 1. The left side of Figure 1 shows the approximate duration of each study component. We detail each aspect of the Baseline and Poststudy Testing Sessions noted within Figure 1 in the "Brief Aim-Specific Outcome Assessments" subsection. We detail the "12-Week Technology-based PA Program" noted within Figure 1 immediately below.

12-Week Technology-Based PA Program

We are using a 12-week intervention strategy grounded in the SCT. Figure 2 outlines how this intervention aligns with the SCT's reciprocally determinant constructs [58,59]: (1) personal cognitive factors; (2) environmental factors; and (3) supporting behavioral factors.

Figure 2. Social Cognitive Theory-informed study components. HRQoL: health-related quality of life; PA: physical activity; RT: resistance training; SCT: Social Cognitive Theory.

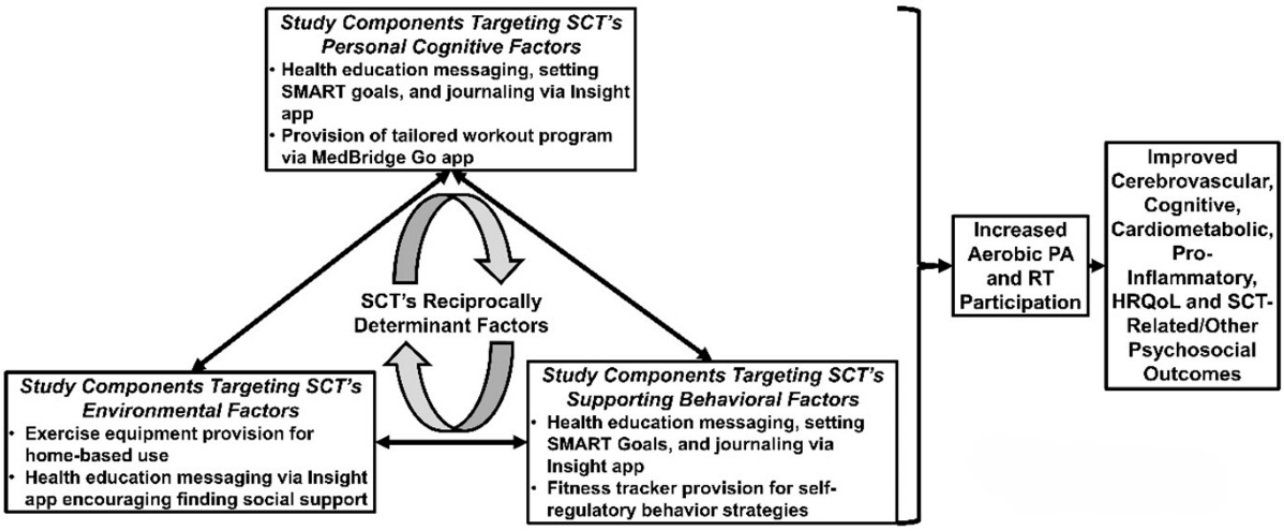

We are using smartphone app (hereafter, "app") technology to deliver our SCT-informed program. Via an Insight app developed specifically for this study (Figures 3A-3F), participants are receiving health-related educational messaging twice weekly in addition to continued access to information on the benefits of aerobic PA and RT for cancer survivors [63-65]. The health education messages are modeled after our prior studies [66-69]. These health education messages periodically request certain actions, such as setting "SMART Goals" and journaling, with the Insight app having locations where participants can continuously set and review their goals (Figure 3C) and journal entries (Figure 3D). These Insight app-delivered study components are targeting the SCT's personal cognitive, environmental, and supporting behavioral factors. We developed this study-specific app as a research team and in collaboration with the Stephenson Cancer Center mHealth Shared Resource, which manages the Insight mHealth Platform [70]. While commercially available PA-oriented smartphone apps exist with some of these features, the content we are delivering to participants (enumerated above), as well as the delivery schedule for this content, is unique to our PA program—necessitating a customized app.

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Figure 3. Insight smartphone app. CICI: chemotherapy-induced cognitive impairment; PA: physical activity.

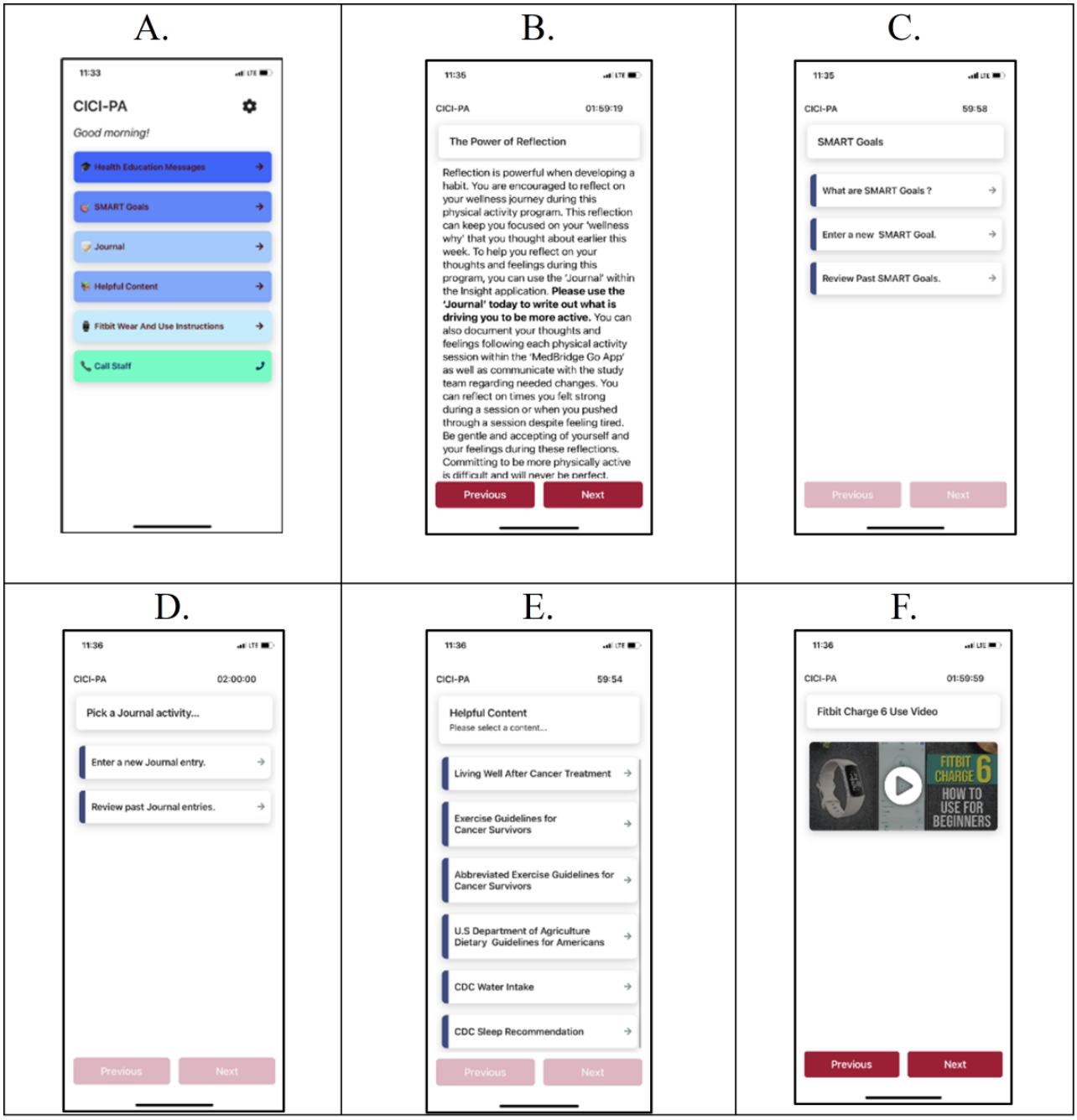

The MedBridge GO app (MedBridge Inc) (Figure 4A-E) is being used to deliver workout programs comprised of aerobic PA and RT to participants. We are implementing these workout programs via MedBridge GO, given the MedBridge GO app's strong security measures and large exercise library (8000+ exercises) in addition to the platform's ability to measure other items critical to the safe delivery of a PA program (eg, pain and difficulty scales for each prescribed exercise). Participants use MedBridge GO to select days each week on which they desire to complete workouts and set associated reminders (we recommend at least 2 workout sessions/week to all participants). Throughout Baseline Testing, we are collecting information about participants' access to workout equipment, as well as their needs, constraints, and goals related to PA, via the study's screening survey and a semistructured interview completed with the study's exercise physiologist (ZCP). All workouts delivered via MedBridge GO have instructions and associated videos to ensure proper form/safety, and participants use MedBridge GO to note if an exercise was too difficult or if they did not like the exercise. They can also communicate any further needs with the study's exercise physiologist using MedBridge GO's messaging feature. Thus, workouts are continuously tailored to each participant throughout study participation based on these different routes of communication. This communication engenders an element of supportive accountability [71] into this SCT-based, technology-delivered PA program. Briefly, the semistructured interviews regarding values and PA-related needs/constraints at Baseline and Midpoint (below), as well as regular communication with the study team via the MedBridge GO app, allow participants to develop a trusting, positive relationship with experts who prioritize their well-being [71]. To further increase the robustness of the PA program delivered

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via MedBridge GO, we are (1) providing resistance bands to each participant for incorporation into their workouts and (2) conducting another semi-structured interview at study midpoint—adjusting their PA programming for the second 6 weeks of the study in a manner that best meets each participant's needs. The MedBridge GO workouts/training tutorials and exercise equipment package are targeting the SCT's personal cognitive and environmental factors. Finally, participants are tracking their PA with the Fitbit Charge 6 during the study, provided during Baseline Testing Session Part 2, and complementing all other intervention components while facilitating self-regulatory behavioral skills. Improving skills, such as goal setting, related to the practice of a behavior, are notable SCT behavioral factors. We connect the Fitbit Charge 6 with Fitabase, a cloud-based platform for obtaining Fitbit/Garmin data [72].

Figure 4. MedBridge GO smartphone app.

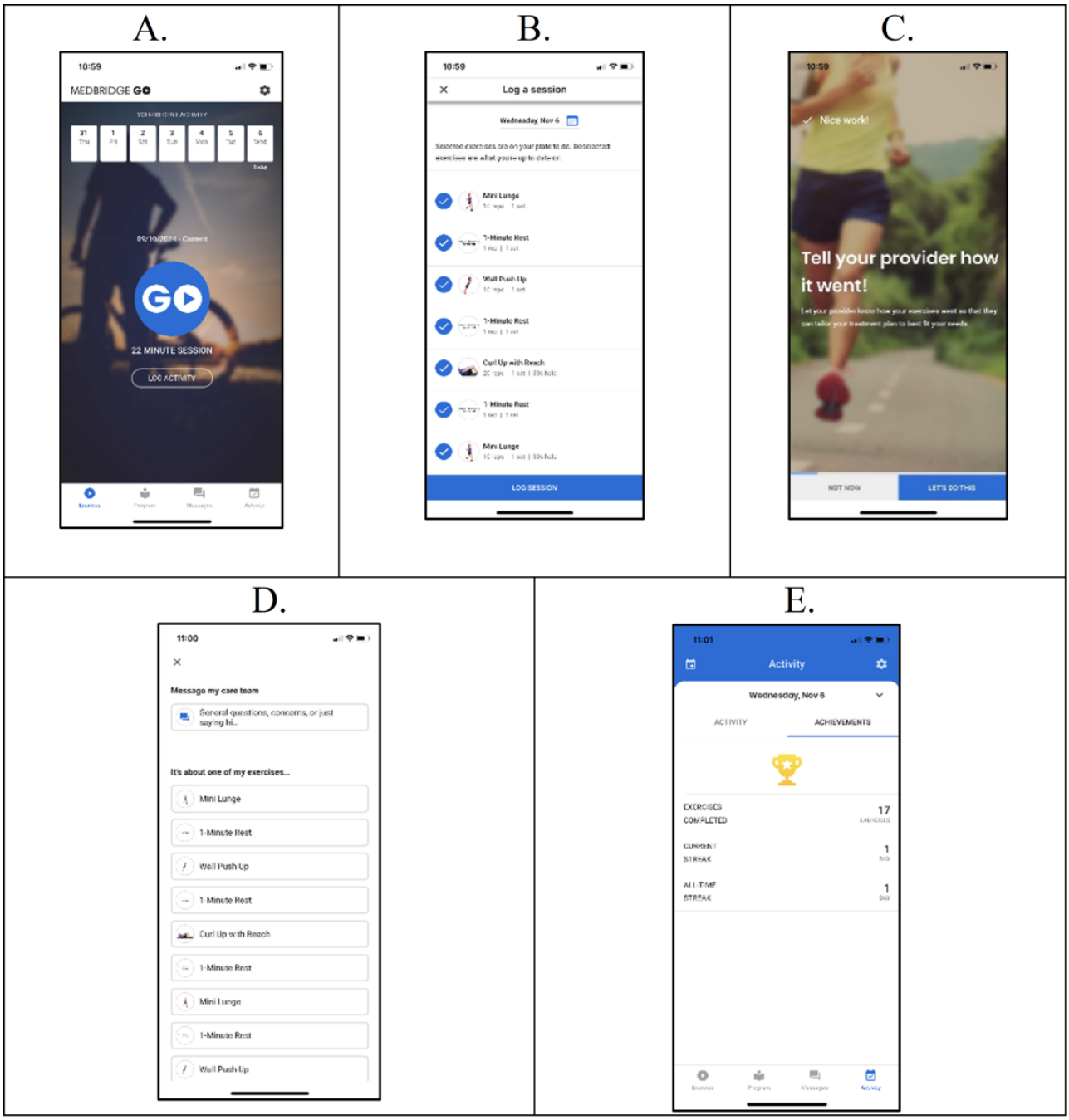

Brief Aim-Specific Outcomes and Measurement

Sociodemographic and Health Characteristics

We are assessing sociodemographics (age, sex, race/ethnicity, etc) and cancer-related and general health history using our Screening and Baseline Surveys as well as chart reviews before/during Baseline Testing Session Part 1.

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Cerebrovascular and Cognitive Function as Well as Cardiometabolic, Proinflammatory, and Epigenetic Outcomes

Part 2 of Baseline and Poststudy Testing involves participants coming to one of the study laboratories (Oklahoma City, Oklahoma) following an 8-hour fast, 12 hours of caffeine abstinence, and 24 hours of no alcohol, vitamins, other health supplements, or nonsteroidal anti-inflammatory drug use. They may continue taking medications aligned with health conditions. Participants are also required not to have exercised intensely in the last 24 hours. During this session, participants first complete blood pressure measurements and then blood and saliva sample collections. Blood samples are being collected through traditional venipuncture of the antecubital vein by trained study personnel. Samples are immediately processed and stored at –80 °C. From these blood samples, we assess high- and low-density lipoprotein and total cholesterol, and fasting blood glucose, among other outcomes, using the Lipid Panel+ kit of Piccolo Xpress (Abbott, Chicago, Illinois). Further, we will use enzyme-linked immunosorbent assays to assess high-sensitivity C-reactive protein as well as interleukin-6 and monocyte chemoattractant protein 1—analyses to be run nearer the end of the study to ensure minimal batch effects. These data will allow us to measure cardiometabolic and proinflammatory cytokines aligned with CICI and T2DM pathophysiology [10,11,21]. Finally, we collect saliva with a DNA Genotek OMNIgene Saliva DNA and RNA collection kit (OMR-610; Ottawa, Ontario). Participants spit 1 mL of saliva into the collection tube to a marked fill line, snap the tube closed, and provide it to research staff, after which it is stored at –80 °C. For the purposes of this study, genomic DNA isolations will be performed from whole blood and saliva for epigenetic analyses, namely, DNA methylation. Similar to the enzyme-linked immunosorbent assays, epigenetic analyses will also take place nearer to the end of the study in order to randomize samples to minimize batch effects.

We use the National Institutes of Health Toolbox [73,74] to deploy a standardized cognitive battery following blood and saliva collection and after participants have had the opportunity to have a snack of their choice. This testing includes the following five tests: (1) Dimensional Change Card Sort (executive function); (2) Pattern Comparison Processing Speed; (3) List Sorting Working Memory; (4) Flanker Inhibitory Control and Attention; and (5) Picture Sequencing Memory. These tests will be analyzed per established standards [75,76] to yield a Fluid Composite Score—standards used validly in similar studies examining how exercise impacts the cognitive function of middle-aged and older adults with mild cognitive impairment [77].

We are completing cerebrovascular function and select cardiometabolic outcome measurements during Part 3 of Baseline and Poststudy Testing within a second study laboratory (Norman, Oklahoma). Participants come to this Testing Session following the same fasting and “no exercise” requirements as Part 2 of Baseline and Poststudy Testing (above). We first measure height, weight, and waist and hip circumference, and complete a pregnancy test, if needed. Participants then complete transcranial doppler (TCD) measurements using 2MHz pulse-wave probes and a headpiece (Nuerovision Transcranial Doppler Ultrasound, Multigon Industries, Elmsford, New York). We then have participants complete a test of cerebrovascular reactivity to CO_2. This test involves participants breathing through a facemask connected to a 3-way sliding valve connected to a meteorological balloon filled with a safe medical-grade gas mixture (CO_2= 3%, O_2= 40%, N_2= 57%) until their partial pressure of end tidal CO_2 reaches 10 mmHg above baseline levels (takes ≈2 minutes). We complete 2 trials separated by 5 minutes of rest, averaging data across trials per established standards [78,79]. Then, participants’ dynamic cerebral autoregulation is assessed via the Thigh Cuff Release Challenge technique [80]. Large bilateral blood pressure thigh cuffs are rapidly inflated (rapid cuff inflation/deflation system; D.E. Hokanson, Inc., Bellevue, Washington) to occlude the lower limbs. Blood flow is monitored in the dorsalis pedis artery, and the initial thigh cuff pressure starts at 20 mmHg above systolic blood pressure. If blood flow is still detected, thigh cuff pressure increases gradually until occlusion is confirmed. The occlusion is held for 2 minutes. After 2 minutes of occlusion, the cuff pressure is rapidly deflated [80]. Both of these tests are completed while the participant is in a supine position. A second set of TCD measurements is then made while participants engage in a graded exercise protocol on a recumbent bike (Lode Corival Recumbent CPET; Groningen, The Netherlands) to assess fitness. This graded exercise protocol starts with 3 minutes of baseline rest. Following this rest period, the protocol then begins at 20W and increases by 20W increments every 3 minutes until volitional exhaustion or the inability to maintain at least 50 revolutions per minute on the bike. Participants report their rating of perceived exertion at the end of every 3-minute stage (0=no exertion; 10=maximal exertion).

The above measurements provide the following metrics: middle cerebral artery velocity and cerebrovascular resistance, conductance, and pulsatility indexes. As cerebral blood pressure autoregulation difficulties can result from mechanisms underlying CICI [25], we will also use transfer function analysis of TCD measurements, as well as the autoregulation index, to measure dynamic cerebrovascular autoregulation. Analyses will be performed using the most recent Cerebrovascular Research Network recommendations [81]. Other relevant measurements generated during this testing include (1) heart rate calculated by R-R intervals using a Bluetooth II-lead ECG (EQ Life Monitor, Equivital Limited, Cambridge, United Kingdom); (2) mean arterial blood pressure, cardiac output, stroke volume, and total peripheral resistance measured via finger photoplethysmography (Finapres NOVA, Finapres Medical Systems B.V, Enschede, The Netherlands); (3) prefrontal cortex oxygen saturation assessed using wireless near-infrared spectroscopy using a small probe placed unilaterally on the right-side of the forehead (Portalite, Artinis Medical Systems, Elst, The Netherlands); (4) arterial blood oxygenation evaluated using finger-tip oximetry on the right index finger (Oximeter pod, ADInstruments, Sydney, New South Wales, Australia); and (5) end-tidal CO_2, partial pressure end-tidal CO_2, and maximum oxygen consumption collected and analyzed via a gas analyzer and pneumotachometer on a breath-by-breath basis

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(Gemini End-Tidal O_2 and CO_2 Analyzer, CWE Incorporated, Ardmore, Pennsylvania).

SCT-related Construct, Psychosocial, HRQoL, and PA Outcomes

We are measuring all Aim 3 outcomes during Part 1 of participants' Baseline and Poststudy Testing Sessions, as well as during Midpoint Testing. The exception is PA, which is only measured at Baseline and after the 12th study week. We are assessing SCT-related psychosocial outcomes using validated surveys delivered via REDCap. Self-efficacy is being assessed using a 9-item measure from Rodgers et al [82]. Participants are noting their confidence during different PA-related situations ("0%: Not confident at all" to "100%: Extremely confident"; 10% increments). Social support is being evaluated using the Social Support and Exercise Survey, with participants reporting frequency of PA support over the last 3 months from family and, separately, friends ("1: None" to "5: Very often") [83]. PA-related enjoyment is being measured via the 18-item Physical Activity Enjoyment Scale [84], with feelings related to PA-related statements/situations reported on a 7-point scale (varied response options). We are using a 14-item scale [85] to assess agreement between hypothetical PA barriers and participants' perceived barriers ("1: Strongly disagree" to "4: Strongly agree"). Last, we are using the 13-item Outcome Expectations for Exercise Scale-2 [86] to assess agreement with listed positive and negative benefits of PA ("1: strongly agree" to "5: strongly disagree").

We are assessing stress, anxiety, mood, and depressive symptoms and HRQoL using validated instruments. We are measuring chronic stress with the 10-item Cohen Perceived Stress Scale [87]. Participants report stress frequency over the last month ("0: Never" to "4: Very often"). We measure chronic anxiety with the State-Trait Anxiety Inventory [88,89], which includes 20 items, each on state and trait anxiety ("1: Almost never" to "4: Almost always"). Chronic mood is being assessed by the Positive and Negative Affect Scale [90]. This scale has 10 items, each for positive and negative affect ("1: Very slightly or not at all" to "5: Extremely"). Chronic depressive symptoms are being assessed by the 9-item Patient Health Questionnaire-9 [91] ("0: Not at all" to "3: Nearly every day"). For HRQoL, the following components of physical and psychological health are being assessed using the Patient-Reported Outcomes Measurement Information System: physical functioning, fatigue, anxiety, depression, pain interference, pain intensity, sleep impairment, and sleep disturbance [92,93]. Measurements are on a 5-point scale, with 5 being the worst on all components aside from physical function, where higher scores are better.

We are assessing PA between Baseline Testing Session Parts 2 and 3 and just after the 12th study week with ActiGraph wGT3X-BT accelerometers—valid for free-living PA assessments [94]. Established protocols for placement and wear duration are being followed by participants [95], and accepted thresholds (≥10 hours/day of wear time; at least 4 days, including one weekend day) are used to clean these data. Established cut points will be used to analyze PA durations per day [96]. Daily average minutes of moderate-to-vigorous PA, light PA, and sedentary behavior will be reported.

Statistical Analyses

We will first inspect all data for outliers/errors and normality, with analyses done in SPSS (version 29; IBM Corp) and R (R Foundation), depending on the metrics being analyzed. Baseline differences between cancer survivors with and without T2DM for (1) sociodemographics, (2) health characteristics, and (3) Aim 1/Exploratory outcomes (ie, cerebrovascular and cognitive function, cardiometabolic outcomes, proinflammatory cytokines, epigenome) will be compared using *t* tests or chi-square tests, as appropriate. Repeated measures ANOVA will analyze between-group differences for changes in Aim 1/Exploratory outcomes during the PA program (Aim 2) and Aim 3 outcomes (ie, SCT-related constructs, psychosocial outcomes, HRQoL, PA). If any sociodemographic or health characteristics differ at baseline between cancer survivors with and without T2DM, we will use repeated measures ANCOVA. Consistent with recommendations for pilot research [97,98], no a priori power analyses have been performed. Indeed, this study is designed to generate the data necessary to develop larger, properly powered, and federally funded studies on this critical topic.

Ethical Considerations

This study was approved by the University of Oklahoma Health Campus Institutional Review Board (IRB #17332). Participants consent to the study prior to engaging in any study activity. Further, participants can opt out of participation at any point during the study period. All participant data is deidentified, with data accessible to only those on the study team. Participants are compensated with a US $132 gift card upon completion of all study tasks, covering their time participating and travel, while also being able to keep resistance bands and a Fitbit Charge 6.

Privacy, Confidentiality, and Safety

All data are being securely stored in REDCap and on encrypted University servers. As this is a Multiple Principal Investigator (MPI) study, the MPIs are jointly responsible for monitoring the safety environment of participants and ensuring that appropriate medical care and coverage are provided to all participants, if necessary. The safety monitor (study oncologist; CH) has also pledged to oversee participant safety (eg, reported adverse events). The MPIs are specifically responsible for monitoring all procedures during the conduct of the study for each participant, including eligibility, enrollment, data collection, evaluation of study outcomes, problems with informed consent, and participant safety and well-being.

Results

We received funding for this study in July 2024 from the Harold Hamm Foundation via a Harold Hamm Diabetes Center-Stephenson Cancer Center Team Science Grant (Award Number: HR23-061-2). Initial IRB approval was received in July 2024 from the University of Oklahoma Health Sciences, with the most recent IRB modification approval received on 09/21/2025 (IRB #: 17332). We started recruiting cancer survivors in March 2025, and we expect to recruit participants until late 2026. We will begin analyzing baseline data in early 2026.

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Discussion

Principal Observations

We are investigating (1) whether cancer survivors with T2DM have differential cerebrovascular, cognitive, proinflammatory, cardiometabolic, and epigenetic profiles versus cancer survivors without T2DM and (2) if a 12-week SCT-based [58,59], technology-delivered PA program results in differential between-group changes in these outcomes as well as SCT-related constructs, select psychosocial metrics (stress, anxiety, mood, etc), HRQoL, and PA. Compared to cancer survivors without T2DM, we expect cancer survivors with T2DM to have poorer measures of cerebrovascular, cognitive, proinflammatory, and cardiometabolic outcomes, as well as distinct epigenetic profiles, during Baseline Testing. However, we expect cancer survivors with T2DM to demonstrate greater improvements in these outcomes during the 12-week PA program relative to cancer survivors without T2DM. Finally, we expect that both groups will demonstrate similar improvements in SCT-related constructs and select psychosocial metrics pre- to post-PA program, but that, compared to cancer survivors without T2DM, cancer survivors with T2DM will have greater improvements in HRQoL and PA.

Strengths and Limitations

This study has several strengths. First, we are using an expansive methodology (eg, TCD, venipuncture, saliva collection) and a team science-informed approach to address an important mechanistic question applicable to a high proportion of cancer survivors who have T2DM, or may be at risk for T2DM [26,99], and are currently experiencing cognitive difficulties following cancer treatment. Second, our use of behavior change theory to inform the components and implementation of a PA program personalized to each participant has merit and should help increase the likelihood of the program's success. Third, and relatedly, the use of technology (2 smartphone apps, a wearable device) to deliver the PA program is notable, as study observations would have implications for how to best provide supportive care to cancer survivors who do not have readily available access to supportive care posttreatment (eg, cancer survivors living in nonurban areas).

Despite the study's strengths, a few limitations must be considered. First, TCD cannot image the middle cerebral artery diameter; thus, we are holding the middle cerebral artery diameter constant in this study's analyses. This reduces the ability to measure absolute middle cerebral artery blood flow velocity. However, our test of cerebrovascular reactivity to CO_2 has a strong relationship (r=0.85) with changes in cerebral blood flow [100] and, therefore, helps to partially overcome this limitation. Second, we are recruiting a relatively small sample with limited power to detect significant differences between groups, and, relatedly, there is an absence of a true control group, which may limit the ability to discern true intervention effectiveness. However, the a priori purpose of this study was to gather the data necessary for a future, larger, and fully-powered randomized trial—a trial that would be able to concurrently address both of these limitations. Finally, we are currently recruiting individuals diagnosed with a broad range of cancer types who were treated with chemotherapy. This strategy aligns with the stated study aims and enhances the feasibility of completing this study in a timely manner. Yet, we acknowledge the need to consider specific cancer types that may most benefit from this type of program and, further, how other treatments (eg, radiation) may also be contributing to cognitive difficulties among cancer survivors.

Future Implications and Plans

We expect the observations made in our study, particularly during the PA program underpinning Aims 2 and 3, to elucidate unique insights regarding the cognitive benefits of PA at the mechanistic level among cancer survivors, particularly those with T2DM. We want to expand this program to include not only a multisite investigation of how a well-defined PA program in cancer survivors with T2DM improves the outcomes discussed, but also how integration of intervention components regarding other health behaviors (eg, proper sleep, nutrition) might provide additional benefits. For example, integrating a low-touch sleep component into this multisite investigation would be prudent given that up to 75% of cancer survivors experience sleep difficulties [101], which has deleterious impacts on cognitive function and HRQoL while also increasing daytime fatigue—the latter lessening the likelihood of PA participation.

Acknowledgments

We did not use generative artificial intelligence to assist with drafting this manuscript.

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Data Availability

The datasets generated or analyzed during this study are not publicly available due to the pilot nature of this study, but are available from the corresponding author on reasonable request.

Authors' Contributions

ZCP, MK, AY, MCA, JAO, and CH are credited with the conceptualization of this research as well as the funding acquisition, resource/software provision, and study design visualization. ZCP, MK, AY, PM, and MMR are responsible for project administration and supervision. ZCP, MK, AY, PM, MCR, JAO, CH, SJB, and MMR are credited with the initial and further development of the study's methodology. ZCP is credited with writing the original draft, with all other listed authors credited with review and editing. Planned data curation and formal analysis will include all listed authors in various capacities.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review comments from the Harold Hamm Diabetes Center-Stephenson Cancer Center Team Science Grant Committee, Harold Hamm Foundation.
[PDF File (Adobe PDF File), 349 KB - resprot_v14i1e79739_app1.pdf]

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Abbreviations

CICI: chemotherapy-induced cognitive impairment
HRQoL: health-related quality of life
IRB: institutional review board
MPI: Multiple Principal Investigator
PA: physical activity
REDCap: Research Electronic Data Capture
RT: resistance training
SCT: Social Cognitive Theory
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
T2DM: type 2 diabetes mellitus
TCD: transcranial doppler

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The BREATH-TRACHER 2 Trial: Protocol for a Retrospective Mixed Methods Study to Establish the Utility of a Wearable Device in the Detection of Chronic Obstructive Pulmonary Disease Exacerbations

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Abstract

Background: Acute exacerbations of chronic obstructive pulmonary disease (eCOPD) are a major clinical challenge, often leading to frequent emergency room visits and significantly reducing patients' quality of life. Early detection through wearable devices could facilitate timely interventions at the community level, reducing hospital admissions and disease-related morbidity and mortality.

Objective: This study seeks to retrospectively assess the feasibility and reliability of the Frontier X2 wearable device for continuous monitoring of clinically relevant physiological signals in volunteers with chronic obstructive pulmonary disease (COPD) who experience acute exacerbations. In particular, the study aims to characterize early physiological alterations that may occur prior to the exacerbation of COPD, assessing the ability of the device to capture these changes in the real-world settings.

Methods: This single-center feasibility study involves prospective physiological data collection with retrospective analytical evaluation of physiological changes occurring around clinically confirmed COPD exacerbations. A total of 30 participants with COPD (Modified Medical Research Council Grades 1‐4) who have experienced at least one exacerbation within the past 12 months will be included. Each participant will wear a continuous physiological monitoring device in their free-living environment for up to 18 months or until an eCOPD event occurs. The device will continuously collect physiological signals, including heart rate, respiratory rate, and heart rate variability. Data will be analyzed using statistical quality control methods, specifically the Cumulative Sum approach, to identify physiological deviations occurring within 7 days (168 h) prior to an exacerbation event. These findings will be correlated with clinical records and qualitative data. Qualitative information will be obtained through biweekly self-administered questionnaires assessing symptom changes and through additional adherence and usability questionnaires completed during home visits conducted every 2 weeks by the researcher.

Results: Recruitment for this study started in June 2024 and was completed in July 2025. It is anticipated that data collection will be completed within 18 months of study initiation, with data analysis finalized by December 2025. Final results will be published in January 2026.

Conclusions: The BREATH-TRACHER 2 study will evaluate the use of the Frontier X2 device in participants with COPD in home settings. The Frontier X2 device, if successful, has the potential to transform COPD management and support proactive care, leading to enhanced clinical outcomes and reduced disease mortality and morbidity.

Trial Registration: ClinicalTrials.gov NCT06419062; https://clinicaltrials.gov/study/NCT06419062

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KEYWORDS

chronic obstructive pulmonary disease; respiratory; home monitoring; wearable device; respiration; vital signs; digital health; acute; feasibility study; protocol; COPD; exacerbation

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Introduction

Background

Chronic obstructive pulmonary disease (COPD) represents a significant public health challenge, with individuals often enduring the disease for many years [1]. It ranks among the top three leading causes of death globally, responsible for 3.23 million deaths in 2019 [2], and the United Kingdom has the third highest COPD mortality rate in Europe [3]. Projections suggest that by 2060, annual global deaths attributable to COPD will exceed 7 million [4].

In the United Kingdom, the burden is equally concerning. In 2019, approximately 21,000 COPD-related deaths were reported [5], while more recent estimates indicate that COPD claims around 30,000 lives annually in the United Kingdom [6]. Currently, 1.4 million people in the United Kingdom are diagnosed with COPD, a figure that has risen steadily over the past decade [7] and is projected to be 1.62 million by 2040 [8]. Each year in the United Kingdom, around 115,000 people are newly diagnosed with COPD, equating to a diagnosis occurring every 5 minutes [3].

Globally, the World Health Organization estimates that 64 million people are living with COPD [9]. In the United Kingdom, the economic burden of the disease is of major concern. Annual management costs to the National Health Service (NHS) are estimated at £1.9 billion (US $3.13 billion) [10], and COPD accounts for 29% of all respiratory disease–related health care expenses, as shown in Table 1. Given that the total cost of respiratory diseases has been estimated at £165 billion (US $271.6 billion), COPD alone contributes approximately £48 billion (US $79 billion) to this burden [10].

Table . Economic burden of COPD and total lung conditions in the United Kingdom, based on 2014 estimated data[a].

	Annual expenditure (£m)	
Category	COPD expenses	Total lung conditions
Direct costs	1847	9895
Indirect costs	61	1222
Intangible costs	46,636	154,241
Total economic burden in the United Kingdom	48,545	165,357

[a]Adapted from [10].

Emergency hospital admissions constitute the largest share of COPD-related costs, representing 72.8% of the total, while prescription medications account for 12.2% [11]. Exacerbations further intensify the economic impact, with moderate episodes costing approximately £118 and severe episodes ranging between £3,329 and £3,726 across UK territories [12,13].

The overall yearly direct health care expenses for individuals with COPD in England, which encompass the costs of moderate and severe exacerbations as well as maintenance, were projected to rise from £1.50 billion in 2011 to £2.32 billion by 2030 [12]. This data highlights the urgency for innovative health care models focused on early intervention and the prevention of exacerbations.

The clinical course of COPD is marked by chronic respiratory symptoms, airflow limitation resulting from airway or alveolar abnormalities, and exacerbations, which are pivotal events in disease progression [14]. These exacerbations, defined by the Global Initiative for Chronic Obstructive Lung Disease, involve an acute worsening of respiratory symptoms beyond typical day-to-day variation. They are often triggered by bacterial or viral infections, environmental factors like air pollution or weather changes, and occasionally by unknown factors [1]. Exacerbations significantly impact patient outcomes, including increased hospitalization rates, a decline in quality of life, and heightened mortality risks [15,16]. Moreover, exacerbations serve as indicators of disease progression and predictors of future health outcomes [17].

Unreported exacerbations remain a persistent challenge in COPD management, often influenced by factors such as age, gender, and socioeconomic status [18]. The failure to report these events leads to undertreatment, prolonged recovery, and diminished quality of life while also underestimating the patient's risk of subsequent exacerbations. Treatment delays further exacerbate outcomes, with research indicating a median delay of 4.8 days from onset of an exacerbation to recognition, 9.3 days from recognition to action, and 8.3 days from recognition to general practitioner (GP) visit [19]. Early treatment is associated with faster recovery, reduced hospital admissions, and improved health-related quality of life, highlighting the importance of prompt medical intervention and patient education regarding exacerbation symptoms [20]. The management of acute exacerbations of COPD emphasizes the significance of effective disease management, which includes implementing a self-management plan that features a self-administered rescue pack containing antibiotics and steroids [21]. However, there is currently a limited understanding of patient self-management and appropriate use of the rescue pack. This often results in improper medication usage, delays in treatment, and instances of both overuse and underuse of medications [21,22].

Preventing hospital readmissions is a key strategy in alleviating the overall burden of COPD. Understanding the physiological changes that occur during exacerbations is essential for improving disease management. Studies show that some physiological signals begin to change before an overt clinical exacerbation, providing an opportunity for earlier detection and intervention [23,24]. Continuous monitoring of vital signs also has the potential to reduce the frequency and severity of exacerbations. However, earlier studies have encountered limitations such as small participant samples, potential conflicts

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of interest, and the complexity of monitoring devices that require frequent and precise usage [25]. Although advancements in wearable technologies have improved accessibility for continuous vital sign monitoring, their accuracy and reliability remain a cause for concern [26].

The BREATH-TRACHER 2 study aims to utilize the Frontier X2 wearable device to detect early indications of exacerbations of COPD (eCOPD). The aim is to identify physiological changes sooner than otherwise feasible, which could help reduce hospitalizations and alleviate the overall burden of the disease. By monitoring heart rate (HR), breathing rate (BR), and other physiological parameters in individuals with COPD, this study aims to assess whether early signal changes can be detected prior to a clinical exacerbation. Earlier identification may support timelier treatment and could potentially reduce the impact of exacerbations in future applications.

In the literature, several studies have investigated the use of wearable technologies to detect eCOPD using physiological parameters such as HR, BR, and HR variability (HRV). These parameters have shown promising potential as early indicators of eCOPD. However, most previous studies have relied on photoplethysmography or accelerometer-based technologies, which are more susceptible to motion artifacts, environmental noise, and signal interruptions—particularly in free-living conditions. While the goal of these studies was to enable remote, real-world monitoring, the accuracy of photoplethysmography and motion-based sensors can be significantly affected by such external factors.

Remote monitoring technologies are increasingly used for the diagnosis, treatment, and tracking of disease progression across a wide range of conditions. They can be evaluated and compared according to factors such as predictive accuracy, cost, usability, patient comfort, and physical design [26]. Some earlier studies have employed bulky or portable systems that are unsuitable for continuous monitoring in daily life, whereas lightweight, user-friendly devices are better suited for long-term free-living applications and can improve adherence and data quality. Device cost is also a key consideration for large-scale clinical deployment.

The Frontier X2 device used in this study operates using continuous single-lead electrocardiography (ECG) technology, which measures the heart's electrical activity through electrodes embedded in a chest strap. The device records the depolarization and repolarization of cardiac muscle during each heartbeat, producing high-fidelity HR and BR signals derived directly from the ECG waveform. The system automatically filters noise from muscle movement and other artifacts, ensuring stable data capture. Frontier's proprietary software detects R-peaks and provides raw respiratory rate (RR) intervals, from which HRV parameters such as the SD of normal-to-normal intervals can be calculated. Owing to its lightweight design (approximately 20 g), continuous data collection capability, and relatively low cost, the Frontier X2 represents a practical and reliable option for long-term physiological monitoring in COPD populations.

Rationale for Study and Potential Impact

The rationale of the study is to address the need for earlier identification of an acute exacerbation in people with COPD and to explore the potential of remote monitoring using a Frontier X2 wearable device to monitor changes in RR and cardiac signals (HR and HRV).

Detecting exacerbations at an early stage is crucial as timely intervention and appropriate management can prevent severe exacerbations and their associated complications. By utilizing a wearable device for remote monitoring, the study aims to continuously collect physiological signals from patients with COPD during their daily activities. This approach offers the opportunity to monitor patients in their natural environment and capture subtle changes that may indicate disease progression or exacerbations before they are clinically conspicuous.

Aims and Objectives

Aims

The study aims to establish whether the Frontier X2 wearable device is suitable to monitor the clinical health of a person with COPD and immediately identify when it begins to deteriorate. Earlier notification of disease worsening could improve rate of patients seeking therapy at a community level and reduce likelihood of hospital admission. Additionally, a wearable device could provide real-world insights into the effectiveness of regular prescribed medications and measure the impact of any rescue interventions.

Primary Objective

The primary purpose of the study is to retrospectively establish if the Frontier X2 medical device can accurately identify when a person with COPD is starting to experience a clinical exacerbation.

Secondary Objectives

The secondary objectives of this study are to (1) explore if the device can monitor volunteer compliance of their inhaler usage; (2) explore instances of signal-clinical discordance (ie, situations where physiological patterns captured by the device do not fully align with the clinically documented eCOPD event); (3) explore if the device can stratify disease severity in individual volunteers; (4) explore if the device can identify responsiveness to intervention treatment following a COPD exacerbation; (5) assess device adherence, usability, and comfort;, and (6) explore how soon the device can identify when a person with COPD is starting to experience a clinical exacerbation.

Methods

Overview

An eCOPD refers to an acute worsening of dyspnea, cough, and sputum production occurring within a 14- day period. It may also present with tachypnea and tachycardia and is commonly associated with local or systemic inflammatory responses triggered by respiratory infections, environmental pollutants, or other irritants affecting the airways [1]. eCOPD is considered a sign of disease progression, a predictor of future health and outcomes, and a leading cause of morbidity and mortality, and

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it increases disease costs [17]. Early identification and timely reporting of symptom deterioration are therefore essential to minimize hospitalization and reduce disease burden, underscoring the importance of reliable exacerbation detection in patients with COPD.

Building on this rationale, this study adopts a mixed methods, observational, open-label, uncontrolled cohort design with prospective physiological data collection and retrospective analytical evaluation to explore the feasibility and potential of continuous physiological monitoring for detecting early changes of eCOPD. Participants will be continuously monitored throughout their participation in the study, including before, during, and after their COPD exacerbation using a wearable device that records physiological signals. The 168-hour pre-exacerbation period and the subsequent return-to-baseline period after the event will be retrospectively examined using the physiological data captured by the device. COPD exacerbation will be identified and cross-validated from information provided by participants via individual COPD symptom questionnaires and cross-validated through clinical records in the participants' GP electronic medical system. The study aims to recruit 30 volunteers who have previously experienced COPD exacerbation-induced hospitalization within a 1-year period prior to recruitment.

There is no specific medical intervention planned as part of the study; participants will continue to receive their usual standard of care throughout the study period. However, wearing a medical monitoring device may lead to behavioral changes (Hawthorne effect) among participants, such as increased disease awareness or improved adherence to medication (eg, inhaler) use. These potential behavioral effects are acknowledged as possible outcomes of the monitoring process.

Primary and Secondary End Points

Primary End Point

The primary end point is the retrospective analysis of physiological signals following a clinically validated COPD exacerbation. Exacerbations will be confirmed via the electronic GP system, either upon hospital admission or when managed at home using a prescribed rescue pack.

We will retrospectively analyze physiological data to identify the earliest point at which alterations in signals become detectable prior to a clinically confirmed exacerbation. The analysis will continue until the participant's signals return to baseline. This window is expected to span approximately 7 days (168 h); both the timing and duration of physiological deviations may vary depending on device sensitivity and the nature or severity of the exacerbation, and these variations will be examined descriptively. This study aims to investigate these pre-exacerbation physiological alterations and evaluate the potential of the wearable device to detect these early changes, potentially supporting future clinical monitoring and management in individuals with COPD.

Secondary End Points

The secondary end points are to (1) evaluate the everyday usability of the wearable device in a primary care setting; (2) appraise the ability of the wearable device to monitor daily disease burden and impact of regular medication use on the long-term health management of a person with COPD; (3) determine the potential of the wearable device to assess the effectiveness of any clinical intervention provided during an exacerbation.

Study Design

Recruitment

The SPIRIT guidelines were used in the construction of this manuscript (Checklist 1). The participant process flow diagram (Figure 1) outlines the study process. Eligible volunteers will be recruited through NHS Scotland's Primary Care clinical database. Those who qualify will receive a recruitment pack that contains a recruitment letter, participant information sheet, and consent form and will have 2 weeks to review the materials, discuss the study with an independent researcher, and decide whether they wish to participate. Following this period, a follow-up telephone call will be made to confirm the receipt of the recruitment pack and to determine if the individual is interested in joining the study.

Individuals expressing interest will be asked to provide signed consent and will be invited to a screening visit, which can take place either at the surgery or in their home. During this visit, the study will be explained in detail, and any additional questions will be addressed. Participants will have the opportunity to view and test the wearable device, as well as learn how to use the accompanying app, with support from the research team to set up the device and initiate their participation in the study.

Participants will have the freedom to withdraw from the study at any time and for any reason without any impact on their care and without the obligation to provide a reason for their withdrawal.

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Figure 1. Participant process flow diagram.

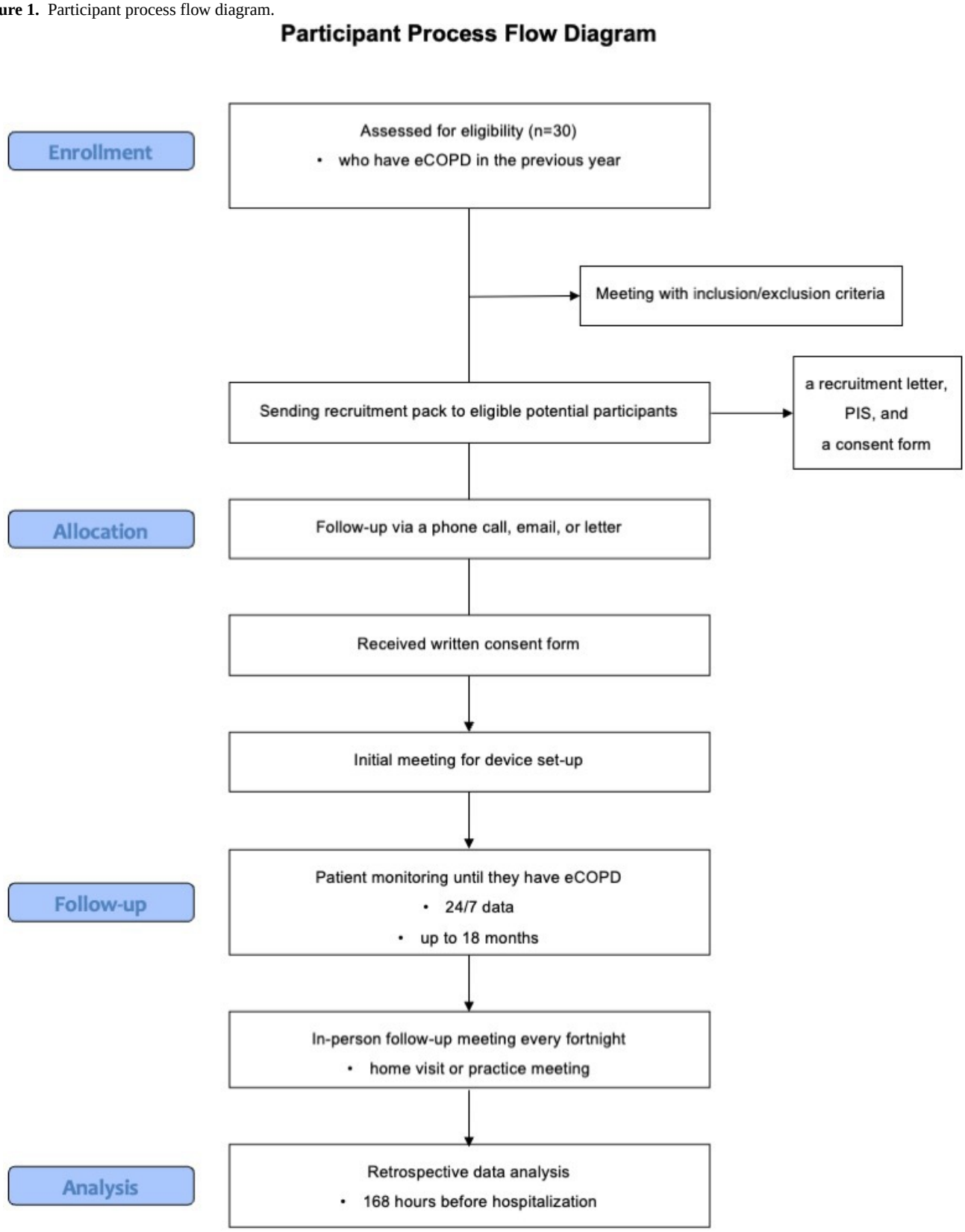

Participant Training

Each participant will be provided with the necessary equipment, including the Frontier X2 device, battery charging materials, cleaning products, and a detailed instruction manual. Participants will also be required to download the Frontier X2 app onto a suitable smartphone, and they will be creating an account using their designated study code and email. For participants who do not own a smartphone, one will be supplied by the research team. Similarly, those without a stable Wi-Fi connection will receive a SIM card to enable cellular data access.

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Throughout the participation period, participants will receive guidance on how to properly use and maintain the device, which includes instructions on the following:

- Device usage: How to wear and operate the Frontier X2.
- Data collection: Procedures for syncing data with the app.
- Charging protocols: Ensuring the device remains functional throughout the study.
- Light signals: Understanding the various light patterns emitted by the device, which indicate its status.

Patient Population Size

The study will recruit a total of 30 volunteers, all of whom have been diagnosed with COPD and have experienced at least one exacerbation, resulting in hospitalization within the 12 months prior to enrollment. This inclusion criterion increases the likelihood that participants will experience an additional exacerbation during the 18-month follow-up period.

According to a previous study [27], it has been found that COPD exacerbation rates range from 0.5 to 3 events per person per year. Over an 18-month period, this corresponds to an expected 0.75 to 4.5 exacerbations per individual. While only the first exacerbation is relevant to the primary end point of this study, this range suggests that a large proportion of participants—potentially 70% or more—are likely to experience at least one exacerbation within the study timeframe. Therefore, a sample size of 30 participants is expected to yield a sufficient number of exacerbation events for retrospective physiological signal analysis, while accounting for variability in exacerbation frequency and potential loss to follow-up.

Study Assessments

A researcher will separately meet each participant every 2 weeks to monitor progress and enquire whether they have experienced any exacerbations that have required medical attention. Two questionnaires will be completed by the participant. A COPD symptom questionnaire is used to assess any changes in the participant's symptoms as independent variables, including appetite, breathing, cough, energy levels, general wellness, and medication usage. In addition, a Device Usage and Adherence Questionnaire will evaluate the participant's experience with the Frontier X2 device, focusing on ease of use, adherence to the study protocols, and any challenges they may have faced while using the device. Following the completion of the questionnaires, the researcher will address any technical issues related to the device or app, offer troubleshooting assistance, and answer any questions the participant may have about the study. These visits will ensure regular communication and allow the researcher to provide support, ensuring that participants are comfortable with the device and that any concerns are promptly resolved.

Study Setting

The primary setting for this study will be remote, real-time home-based monitoring, allowing participants to use the device in their everyday environment. Data will be collected continuously in this real-life setting, ensuring that the study reflects the participants' typical routines and lifestyle conditions, thereby enhancing the validity of the results.

Study Participants

Inclusion Criteria

The participant must meet all the following criteria to be considered eligible for the study: (1) any person aged 18 years or over, (2) current diagnosis of patients with COPD who have experienced exacerbation-induced hospitalization in the previous year, (3) be willing and able to comply with study procedures and be available for study visits, (4) be able to use a "smartphone, tablet, or computer," (5) be able to give written consent, and (6) able to understand written and spoken English.

Exclusion Criteria

The participant may not enter the study if any of the following applies: (1) the inability to give written informed consent; (2) known respiratory disorders other than COPD which, in the opinion of the investigator, is the main contributor to the patient's symptoms (eg, asthma, lung cancer, sarcoidosis, other interstitial lung diseases, tuberculosis, lung fibrosis, cystic fibrosis, and non-COPD-related bronchiectasis); (3) a known history of significant systemic and other organ-related diseases, other than COPD, which, in the opinion of the investigator, is likely to interfere with the study or impact on participant safety (eg, severe rheumatoid arthritis and lupus, kidney, liver, endocrine, psychological disorders); (4) known to be severely alpha-1-antitrypsin deficient (PiSZ or PiZZ); (5) any known history of violence/chaotic substance misuse based on their medical records; (6) having undergone lung surgery (eg, lung volume reduction, lobectomy) within the last 6 months; (7) have cancer or other terminal condition which, in the opinion of the investigator, has a mortality of 12 months or less; (8) taking high-dose oral corticosteroid medication (equivalent to a daily dose of ≥10 mg of prednisolone) for more than 3 consecutive months; (9) being pregnant; (10) patients already involved in an ongoing research study; (11) participation in an interventional clinical study within 3 months of Visit 1 or participation in a study using an investigational medicinal product either in the previous 3 months or in the interval from last using the investigational medicinal product to 5 times its half-life; (12) patients with other significant lung disease, unable to consent, unable to use the technology (eg, inability to use the data device or complete the questionnaires), or at the clinician's discretion for other more significant medical/social reasons; (13) known allergy to any chest strap; (14) on long-term oxygen therapy; and (15) acute exacerbation of COPD within 6 weeks prior to inclusion.

Study Device

The Frontier X2 is a chest-worn wearable device designed to monitor physiological parameters in real time. This compact device captures key metrics including HR, BR, HRV, continuous ECG, and physical activity, making it well-suited for continuous health monitoring. The device employs Bluetooth Low Energy technology for data synchronization and is IP67-rated, providing water resistance up to 1.5 m. It also meets international industry standards including International Electrotechnical Commission; International Organization for Standardization; Registration, Evaluation, Authorization and Restriction of Chemicals;

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Conformité Européenne; and Restriction of Hazardous Substances, ensuring regulatory compliance and durability.

Although initially developed for sports performance monitoring, the Frontier X2 incorporates features with strong relevance for clinical research, such as extended ECG recording and onboard vibration alerts. In this study, the device will be used in passive data collection mode, without real-time alerts being activated. Data are stored locally for up to 24 hours. Given the protocol requirements, participants will be asked to sync data daily via Bluetooth.

Previous studies have demonstrated that the Frontier device has the potential for disease management for people with different chronic diseases [28,29]. Ongoing and future research, including the present study, aims to contribute to the growing body of evidence regarding its accuracy, reliability, and potential applications in chronic disease management. Full specifications and an image of the Frontier X2 can be found at the manufacturer's website [30].

Monitoring

The study will monitor both subjective symptom scores and objective physiological metrics to evaluate participants' health status. Symptom scores will include measures related to appetite, breathing, cough, energy levels, overall wellness, and medication usage, providing insights into fluctuations in COPD symptoms (see Multimedia Appendix 1). Objective physiological parameters, such as HR, BR, ECG, HRV, strain, and daily step count, will be continuously recorded to identify significant changes potentially associated with COPD exacerbations.

Physiological data are collected prospectively, but no real-time clinical monitoring or automated alerts will be used. Data will be reviewed only during scheduled biweekly visits, and participants initiated contact if they reported worsening symptoms, device issues, or unexpected physiological readings. This ensures that the study remains observational and noninterventional. No real-time clinical monitoring or medical decision-making will be performed.

This combined approach, integrating subjective symptom scores with objective physiological data, aims to provide a comprehensive analysis of factors contributing to COPD exacerbations, enabling timely interventions and improved disease management.

Data Collection

Biometric data will be continuously uploaded to a secure cloud platform, ensuring that the integrity and fidelity of the data are always maintained. The biometric data will be automatically synchronized with the cloud system via the Frontier X2 device and its associated application. In the event of an automatic synchronization failure, participants will be instructed to manually sync the data within the app, thereby ensuring that all relevant information is captured. Wear-time expectations are not enforced; instead, actual wear-time (days/hours worn) will be recorded and reported as an adherence outcome.

The analysis of the biometric data will be conducted using proprietary software developed by the device manufacturer, which is designed to prevent any manipulation that could introduce bias into the analytical process. This rigorous approach to data collection safeguards the validity of the findings and upholds the principles of good clinical practice.

Qualitative data will be collected through a self-administered questionnaire (see Multimedia Appendix 2). This qualitative information will be transcribed into an electronic file, and data integrity will be verified by an independent third-party researcher.

Statistical analyses performed on the collected data will undergo scrutiny by an independent University statistician. No observational data will be collected during this study.

At the conclusion of the project, patients will be provided with a lay summary of the research findings, and it will be additionally distributed through a variety of channels, such as the University website, media outlets, and charities, such as the British Lung Foundation and Chest Heart & Stroke Scotland.

Data Analysis

The data analysis will incorporate both qualitative and quantitative methodologies to ensure a thorough evaluation of the collected data.

Qualitative Analysis

Thematic analysis will be undertaken to identify and interpret key themes, categories, and patterns emerging from the qualitative data. Using NVivo software, coding and categorization will facilitate a structured and systematic approach to data interpretation, enabling researchers to gain deeper insights into participants' experiences and perceptions. This process will provide a foundation for generating hypotheses and addressing the study's research objectives.

Quantitative Analysis

Time-series analysis will be conducted on physiological data to identify patterns and trends over time. Statistical software including SPSS, Minitab, and Python will be used for data processing and analysis. Control chart techniques, particularly the Cumulative Sum (CUSUM) chart, will be applied to evaluate physiological changes before, during, and after COPD exacerbations. The adequacy of the selected time-series models will be assessed through autocorrelation analysis and examination of residual distributions to ensure accurate representation of the underlying data structure.

Physiological parameters, including HR, HRV, and its derived metrics—the root mean square of successive differences, the SD of normal-to-normal intervals, low-frequency power, high-frequency power, and the low-frequency to high-frequency ratio—as well as RR, will be used for quantitative analysis. As this feasibility study is conducted in free-living conditions, it is not possible to fully control contextual factors that may influence HR, RR, or HRV, such as medication changes, intercurrent infections, sleep variability, or changes in daily activity. These factors will therefore be documented during biweekly follow-up visits and reviewed descriptively when interpreting physiological deviations. Analyses will focus on within-participant deviations from each individual's baseline rather than between-participant comparisons.

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The CUSUM chart approach will follow methodologies previously described by Montgomery [31], which enables detection of small, sustained deviations from baseline values in time-series data. For each participant, baseline data will correspond to a stable period with no reported symptom worsening—specifically, the first 7 days of participation. The reference value (k) and decision threshold (h) will be individually calculated based on this baseline period. In accordance with the inclusion criteria, all participants must have been free from any eCOPD events for at least 6 weeks prior to recruitment, supporting the selection of the initial stable days as an appropriate baseline.

CUSUM chart performance will be evaluated in terms of sensitivity and specificity. Sensitivity will be defined as the correct detection of a true eCOPD event when the cumulative deviation exceeds the decision threshold (h) within the defined pre-event window. Specificity will be defined as the absence of false alarms (ie, no threshold exceedance) during stable periods. Validation will be performed at both individual and group levels to estimate participant-specific and overall sensitivity and specificity.

The pre-event window will be defined as 7 days (168 h) prior to the clinically confirmed onset of exacerbation; however, this duration may vary among individuals depending on their clinical course. Some participants may require hospital admission on the first day of symptom worsening, whereas others may experience a delay of several days. While all available data will be analyzed, the primary focus will remain on the 7-day pre-exacerbation period.

Missing data handling will involve evaluating several imputation techniques, including interpolation, Kalman filtering, Last Observation Carried Forward, and Predictive Mean Matching. The most appropriate method will be selected for each dataset based on data structure and continuity.

If a participant experiences more than one eCOPD event during the study period, each episode will be treated as a separate exacerbation. To minimize participant burden, data collection will be terminated immediately after confirmation of an eCOPD event through the participant's GP record. CUSUM-detected signals will be cross-validated against contemporaneous meeting notes obtained during regular follow-up sessions to ensure consistency with the first self-reported symptoms of worsening.

The onset time of each COPD exacerbation will be confirmed using clinical information from GP and hospital records. The onset will be defined as either the date on which the participant begins using their prescribed rescue pack or the date of hospital admission.

In this study, the aim was to observe and analyze each participant's adherence and device usage in their natural living environment without imposing any burden or obligation to use the device. Adherence, device usage, and the duration of recorded data will be reported as study outcomes to evaluate the practicality and real-world applicability of using a wearable device in individuals with COPD. Since one of the main challenges of wearable or medical devices in free-living conditions is maintaining consistent adherence, no fixed adherence target was predefined. Instead, the number of days and hours the device was worn will be reported as adherence outcomes. This approach enables assessment of device acceptability, user compliance, and usage patterns, particularly during eCOPD periods, during unsupervised, real-world conditions without external reminders or enforced wearing schedules.

Ethical Considerations

This study complies with the Declaration of Helsinki [32] and adheres to Good Clinical Practice guidelines [33]. Participation in the study is completely voluntary, and participants may withdraw at any time without providing a reason, with no impact on their future medical care. Ethical approval for the study was granted by the NHS London - Stanmore Research Ethics Committee (Protocol number UEC23/71; IRAS project ID 32,823), and the study has been registered on ClinicalTrials.gov (NCT06419062). If there are any significant deviations from the study protocol, the investigator will submit an amendment for further approval by the ethics committee. No participants were compensated during their involvement in the study.

Data Management

All data collected in this project will comply with the General Data Protection Regulation, the Caldicott Guardian principles, and the NHS Code of Confidentiality. Personal health data will be anonymized or pseudonymized wherever feasible and stored securely using encrypted electronic platforms. Short questionnaires completed by volunteers will be anonymized with unique numerical codes, and data will be transcribed into encrypted files. Researchers will adhere to the confidentiality policies of the University of Strathclyde and the UK General Pharmaceutical Council.

Anonymized physiological data will be securely stored within the Fourth Frontier Technologies Ltd cloud system, in full compliance with UK data protection and general data protection regulations. Data analyzed or generated at the University of Strathclyde will be securely stored within the university's encrypted cloud infrastructure.

Each participant will be assigned a unique project identity code to ensure anonymity. The mapping file linking participant identity codes to personal information will be stored electronically in an encrypted cloud folder, with a physical backup kept in a locked filing cabinet at a secure university location. Access to these files will be strictly limited to the PhD researcher and their academic supervisor.

Hard-copy questionnaires completed by participants will be stored in a lockable briefcase until transferred to a secure university facility. Within 10 working days, responses will be transcribed into an encrypted digital file on the university cloud system, after which the physical copies will be shredded and disposed of through a university-approved confidential document disposal service.

To maintain confidentiality, all personal information will be pseudonymized, ensuring that no individual can be directly identified in the unlikely event of data loss. A unique email address and study ID will be generated for each participant to

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further protect identity. Within the Frontier dashboard, all uploaded physiological data are anonymized and accessible only via these identifiers.

For data processing and analysis, physiological recordings will be downloaded as CSV files from the Frontier dashboard for each activity session. All analyses will be performed independently of the manufacturer's proprietary platform using open-source analytical tools such as Excel, Minitab, and Python. The Frontier device automatically uploads raw physiological data directly to the secure cloud without alteration. Although raw data are initially stored on the Frontier cloud, copies of all exported files will be securely downloaded and stored in the University of Strathclyde's OneDrive system for independent analysis.

The University of Strathclyde will act as the data controller, and Fourth Frontier Technologies Ltd will act solely as the data processor, providing secure data transmission and temporary cloud storage during participant involvement.

Results

Following ethical approval of the study protocol, the first patient was enrolled in June 2024, and recruitment was completed in July 2025. Data collection is ongoing and is expected to be completed by December 2025, within the planned 18-month study period. Statistical analysis is being conducted simultaneously with data collection. Final results are expected to be submitted for publication in January 2026. The findings, regardless of whether they are positive or negative, will be disseminated through peer-reviewed journals.

Discussion

Strengths and Limitations

There are no direct potential benefits to the patients while they participate since it is only an observational study. However, the research team will periodically review participants' physiological data as part of the ongoing analysis. If the biometric data indicate a potentially concerning clinical pattern, the participant's health care provider will be informed, which may prompt an unscheduled but potentially beneficial clinical intervention. There is also the possibility that agreeing to participate in the study may result in a "Hawthorne effect," where there is a change in behavior as a response to observation and assessment either by the volunteer themselves (eg, better medication adherence, cessation of cigarette smoking) or by their health care provider (eg, more frequent monitoring or review of their medication).

The size of the cohorts and the duration of the study might not be enough to get accurate and expected results, but this is typical for most pilot studies, as we intend to determine the correct size and duration of the study required for expected results, which can be further used to plan future longitudinal studies. This can be partly mitigated by attempting to recruit people who are at high risk of exacerbation.

Previous studies have demonstrated that physiological changes, particularly increases in HR and RR, can occur up to 72 hours before an eCOPD event, supporting the feasibility of detecting early physiological alterations. However, these studies did not characterize these changes as continuous signal trends or apply them for the prediction of exacerbation onset. The present study aims to address this gap by identifying early physiological deviations that may serve as negative predictive signals and by exploring how these could inform the timely initiation of therapeutic interventions. Furthermore, by monitoring when physiological parameters return to baseline, this study has the potential to evaluate the effectiveness of treatment and the dynamics of recovery following an eCOPD event.

Potential Challenges and Alternatives

The potential risks to participants are considered to be low or mild. Volunteers will have to continuously wear the device (Frontier X2). This may be associated with minor discomfort of the device being situated on their chest that may cause mild positional discomfort while undertaking certain activities, such as having to adopt an alternative sleeping position. The device is secured to the chest by an elastic chest strap, composed of a hypoallergenic material, although there is still a small possibility that it may cause a skin irritation if it is worn for prolonged periods in the same position.

The device has a battery life of 24 hours and can be fully recharged in 45 minutes. Users will be provided with the necessary equipment for charging the device and are expected to charge their device every 24 hours. This can be a burden for participants. Volunteers will be expected to complete a 10-minute symptom questionnaire every 2 weeks to see if this correlates with device biometric data capture. This questionnaire will be collected when the PhD researcher undertakes a site visit to the volunteer's house to check the battery for the device and to provide any additional technical support. These would discontinue if there were any discomfort.

The non-invasive physiological measurements involve minimal burden.

Conclusions

This study aims to build upon the limited existing validation of the Frontier X2 device for monitoring patients with COPD in real-life settings. The continuous monitoring capabilities of the device may support earlier clinical interventions, reducing the need for hospital admissions and improving patient outcomes. By shifting the focus from reactive to proactive care, such technologies have the potential to enhance clinical management and reduce morbidity and mortality rates associated with COPD.

Acknowledgments

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Disclaimer

The views expressed in this paper are solely those of the authors and do not necessarily reflect the positions or opinions of the University of Strathclyde, the National Health Service, or any affiliated institutions.

Data Availability

The datasets generated or analyzed during this study are not publicly available to protect volunteer confidentiality but are available from the corresponding author on reasonable request.

Authors' Contributions

BT led the conceptualization of the study, curated the data, conducted the formal analysis, developed the methodology, administered the project, and prepared the original draft of the manuscript. ABM provided supervision throughout the project, contributed to the conceptualization, methodology, validation, and formal analysis, and reviewed and edited the manuscript. LH contributed to the investigation. BKB supported the review and editing of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Symptom and self-management checklist used during in-person follow-up visits. The checklist includes yes/no items on breathlessness, sputum production, cough, fatigue, appetite, medication adherence, hospital admissions, and self-management practices, as well as questions on recent symptom worsening or improvement.
[DOCX File, 287 KB - resprot_v14i1e79503_app1.docx]

Multimedia Appendix 2
Device-related questionnaire used to assess long-term usability and comfort of the wearable device.
[DOCX File, 610 KB - resprot_v14i1e79503_app2.docx]

Checklist 1 SPIRIT checklist. [DOCX File, 35 KB - resprot_v14i1e79503_app3.docx]

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Abbreviations

BR: breathing rate
COPD: chronic obstructive pulmonary disease
CUSUM: Cumulative Sum
ECG: electrocardiography
eCOPD: exacerbation of chronic obstructive pulmonary disease
GP: general practitioner
HR: heart rate
HRV: heart rate variability
NHS: National Health Service
RR: respiratory rate

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Aligning a Household-Level Service Array Through a Jurisdiction-Wide Child Maltreatment Prevention Effort: Protocol for a Geospatial and Counterfactual Modeling Study

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Abstract

Background: Child maltreatment is associated with multiple negative outcomes at the individual and societal levels. Children experiencing maltreatment are at greater risk of a host of negative outcomes (eg, psychological disorders, substance use, violent delinquency, suicidality, and adverse educational outcomes).

Objective: This study aims to prevent and ameliorate child maltreatment by using a combination of geospatial smoothing via a risk terrain modeling (RTM) framework and counterfactual modeling to identify risky areas and determine the optimal (re)allocation of services to maximally improve maltreatment outcomes.

Methods: A 3-stage process is proposed that can iteratively be applied within a collaborating jurisdiction to enable responsive and sustained achievement of identified child welfare outcomes. This process makes use of 2 analytic approaches: geospatial smoothing via an RTM framework and counterfactual modeling. RTM is a spatial analytic approach that uses spatial machine learning methods to estimate the risk of maltreatment based on previous cases of maltreatment and risk factors of the built environment provided by the participating jurisdiction. Using previously validated cases of maltreatment as our target variable (eg, substantiated claims of abuse and neglect) and violent crime data and built environment data as our primary predictor variables, we estimate a series of machine learning models to geospatially smooth the historically identified places at increased risk of child maltreatment. Areas identified as higher risk receive extensive services associated with preventing or limiting child maltreatment, such as prenatal or postnatal care, subsidized daycare, and parental counseling. We make use of counterfactual explanation modeling to optimally align service allocation to maximally improve maltreatment outcomes for future service allocations within a collaborating jurisdiction. The technique leverages a statistical model associating household-level information with maltreatment outcomes to explore combinations of services that would be predicted to achieve optimal and practical recommendations for future service allocation efforts. Constraints can be introduced to this logic, such as service availability and cost. Algorithmic fairness is also a potential consideration during aggregation, with possibilities for both measuring and balancing metrics such as "recourse fairness."

Results: As of September 2025, a participating jurisdiction is being recruited.

Conclusions: This protocol sets forth a novel approach for the allocation of supportive services for families at risk of child maltreatment through geospatial smoothing via an RTM framework and the maximization of service impact through a counterfactual explanation model. Child maltreatment is an unfortunate and ubiquitous issue in the United States. This proposal builds on jurisdiction-wide public health strategies to allocate services in a data-informed fashion and further align future iterations of the allocation strategy using outcomes-based counterfactual modeling at the household level. The flexibility of the proposed methodology enables its application regardless of the collaborating jurisdiction's preferences and constraints.

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KEYWORDS

counterfactual modeling; geospatial modeling; child maltreatment; public service provision; human services

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Introduction

Background

In 2022, the United States Children's Bureau reported 558,899 cases of child maltreatment and 1990 fatalities [1]. Although the rates of child sexual and physical abuse have declined in the United States since 1990 [2], the incidence of child maltreatment fatalities has risen since 2008. Child maltreatment is underreported [3], and actual fatalities are estimated to be 2 to 3 times higher than reported due to inconsistencies in definitions and reporting standards across states [4]. Child maltreatment is linked to the development of medical illness and psychiatric disorders, as well as poor education, employment, economic, interpersonal, and community outcomes [5-13].

The estimated cost per survivor of nonfatal child maltreatment is US $830,928 (2015), and the average lifetime cost associated with each child maltreatment fatality is estimated at US $16.6 million (2015). In 2015, the economic burden of child maltreatment in the United States was estimated at US $428 billion for substantiated cases and US $2 trillion for annually investigated incidents [14]. This significant economic burden becomes even more substantial when considered in the broader context of its impact on children, families, and communities.

Given the immense personal and societal costs of child maltreatment, it is important to design programs and policies to not only alleviate but also prevent maltreatment. Young children (ages 0 - 3 years) are particularly exposed to the risks of maltreatment [15], and many children who die due to maltreatment are not known to child protection agencies [16,17]. Given these sobering facts, identifying places and families at increased risk of maltreatment may allow authorities to proactively intervene. Policies such as pre- and postnatal counseling, subsidized childcare, and parental counseling may all have protective effects with respect to potential maltreatment if agencies can successfully identify families at risk [18].

Beyond the general system-wide challenges in child welfare, maltreatment outcomes and preventive service availability demonstrate severe geographical inequities [19]. These service inequities span supportive and preventative services, including child welfare involvement itself [20]. Spatial modeling approaches can identify underserved areas and areas with disproportionately poor outcomes [21].

Therefore, this protocol aims to address three enduring issues: (1) targeting of primary prevention resources, (2) expansion of prevention programs to span risk factors, and (3) identification of the bundle of programs that effectively prevent child maltreatment for a given region or household. To accomplish this, the proposed study protocol seeks to identify areas with children at increased risk of experiencing maltreatment and to target these areas with extensive support programs to reduce and prevent maltreatment.

The study is composed of 3 stages, which can be iteratively applied within a collaborating jurisdiction to enable responsive and sustained achievement of the aforementioned goal. Stage 1 is the development of a smoothed risk surface of child maltreatment using spatial machine learning approaches within a "risk terrain modeling" (RTM) framework [22]. This stage also includes working with the collaborating jurisdiction to define child maltreatment, which can vary greatly depending on policy requirements, societal norms, and data availability [23-25]. Stage 2 comprises the resulting service allocation process for areas of increased estimated risk identified in Stage 1. Stage 3 uses a counterfactual explanation model (CEM) to optimally align service allocation to maximally improve maltreatment outcomes.

We propose the use of spatial risk modeling to improve targeting of primary prevention resources, coordination of the delivery of voluntary prevention programs that span individual and contextual risks using targeted universalism, and identification of the most cost-effective bundle of primary prevention programs using counterfactual modeling. It is important to note that this work is not concerned with simply validating whether individual support programs or their various combinations are effective in a general sense across a collaborating jurisdiction. This work seeks to expand the utility of classic program evaluation models by identifying household-specific combinations of available support programs that optimally improve household-specific outcomes.

General Study Design

The study protocol is divided into three stages: (1) Stage 1: geospatial service recommendations, (2) Stage 2: execution of the service array in the collaborating jurisdiction, and Stage 3: counterfactual modeling of service array impact (refer to Figure 1). The results from Stage 3 can then be used iteratively to inform the geospatial service recommendations moving forward. In Stage 1, geospatial information about historical child maltreatment events is leveraged in an RTM framework to produce a smoothed outcome surface of child maltreatment. The top areas of risk identified by the RTM (eg, the top quartile of "neighborhoods") provide a recommended set of locations to receive expanded child welfare–related services. In Stage 2, the services are offered and allocated within the collaborating jurisdiction guided by the geospatial service recommendation map from Stage 1. After a period of service delivery of sufficient duration to allow for a long-arc child maltreatment outcome window (eg, 5 years total, with 3 years of service delivery and a 2-year outcome window), Stage 3 involves the development of a CEM to develop actionable jurisdiction-wide recommendations based on the impact of the service array on child maltreatment in the jurisdiction. Rather than provide a simplified pre-post evaluation of service effectiveness, CEM offers a tailored approach to identify optimal service arrays at the household level, thus further aligning the geospatial service recommendations offered in Stage 1. Several details of the protocol, including the specific services offered, duration of Stage 2, and the final format of the actionable recommendations, will be determined during the design phase, which will involve feedback and specifications provided by the collaborating jurisdiction. This study protocol seeks to propose a methodological framework that is robust to the various configurations and challenges that may arise during the final determination of the study details, which will be highly

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dependent on the governing body in the collaborating jurisdiction.

Figure 1. The 3 stages of the proposed study design.

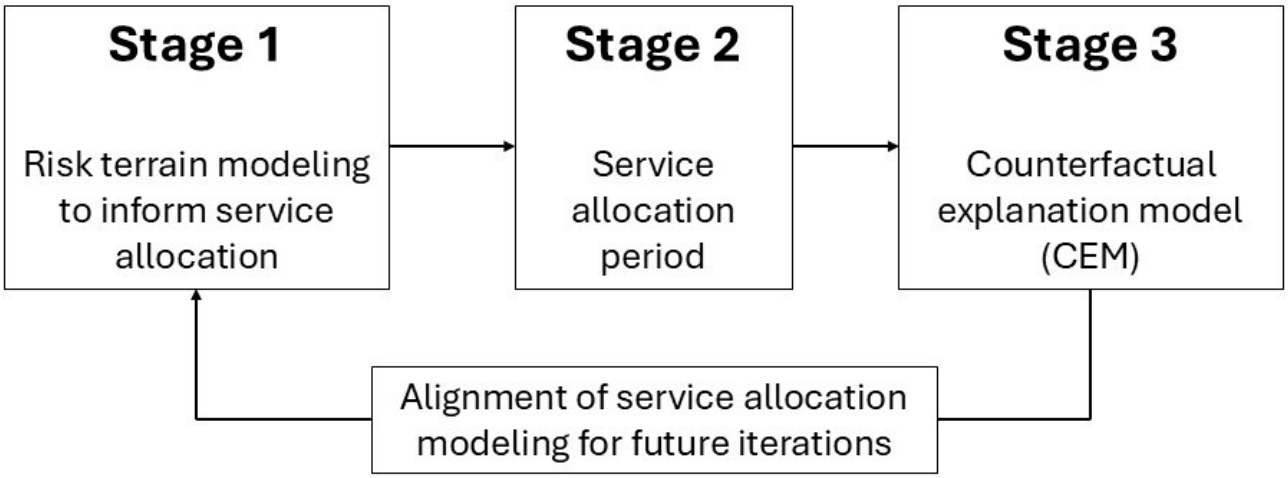

RTM: Theoretical Background and Use Cases

RTM is a spatial analytic approach developed by Caplan [26] for the purpose of estimating spatial risk with respect to environmental determinants of crime. While RTM has roots in criminology literature, the basic approach is an application of existing spatial analytic approaches. The ultimate goal is the identification of risky places as opposed to individuals. The environmental criminology literature has long argued that certain environmental features can increase or decrease the risk of certain crimes occurring. Brantingham and Brantingham [27] theorized that there are 2 major types of features in the built environment that influence crime: crime attractors and crime generators. Crime generators are areas that attract numerous people and thus offer increased opportunities for crime. Stadiums or entertainment districts are 2 examples of crime-generating spaces. Crime attractors, conversely, are places that offer opportunities for crime and are attractive to potential offenders because of the opportunity to engage in certain types of crime. Open-air drug markets are an example of such a place. RTM, then, is an application of the basic logic set forth by Brantingham and Brantingham [27] through the use of spatial predictive modeling.

The classic use cases for RTM include estimating neighborhood risk profiles with respect to a variety of crime types. Violent crimes, such as shootings or robberies, are often studied [28]. Recently, RTM has also been used to identify places at higher risk of child maltreatment [22,29].

Service Allocation Period

The service allocation period will rely on the geospatial analysis from Stage 1 and involves the actual service delivery of various prevention programs to households in the jurisdiction. The jurisdiction-wide service delivery expansion effort is influenced by previous work in public health strategies for the deployment of large-scale service delivery efforts. Refer to the “Stage 2-Service Allocation” section for further details.

CEMs: Theoretical Background and Use Case Examples

CEMs are statistical models of real-world phenomena that can produce actionable recommendations to maximize or minimize the probability that some alternative outcome would have occurred. CEMs have generated considerable recent interest due to (1) their ability to resolve interpretations from “black box” models [30,31], (2) their structural alignment with both scientific and everyday reasoning about the world [32], and (3) their ability to offer deployable and testable courses of action for policymakers and practitioners. CEM methodologies can produce counterfactual courses of action for a single observational input (eg, how a loan applicant can improve their standing, how a medical course of action can improve the survival of an intensive care unit (ICU) patient, or how a given service combination can improve the child welfare outlook of a single household).

The classic use case example for CEMs is the financial loan scenario: consider a statistical model that predicts whether a lendee will repay a loan within a given timeframe. By perturbing the input factors in the statistical model, the lending institution can discover a set of “solutions” that would be predicted to convert an unsuccessful loan applicant into a successful loan applicant, thus offering recommendations to rejected applicants. Another recent example from the field of health care is the proposal for CEM in an intensive care unit [33]. In the proposal, a CEM built on historical data offers treatment recommendations to maximize patient survivability. If a patient is predicted to have low chances of survival upon ICU intake, the CEM offers a treatment array sequence to maximally improve the chance of survival. Thus, researchers leveraged a statistical model linking treatment combinations to health outcomes to provide actionable individual-level treatment array recommendations.

Counterfactual Analysis in Child Welfare

Statistical approaches to investigate the decision-making in the area of child welfare often deploy methodology that uses the term “counterfactual.” One such approach is counterfactual causal modeling, which aims to determine hypothetical outcomes under different child welfare decision policies [34,35].

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Another approach uses an economic formulation of "counterfactual" analysis to investigate alternative hypothetical mechanisms for assigning child welfare cases to government workers [36]. "Counterfactual" modeling has also been used for evaluating the effectiveness of a substance use intervention program by generating simulated treatment and control groups [37]. While these approaches are counterfactual in the general sense, they differ from the approach specified in this work. Specifically, this work seeks to model service delivery information and outcomes to optimize service array combinations at the family level. It is possible that jurisdictions have internally planned or developed similar methodology, but the authors are unaware of any publicly acknowledged efforts to develop or deploy such a technique.

Characteristics of CEMs

A variety of theoretical work has considered the evaluation of a CEM's quality [38]. This previous work generally considers 4 domains for the evaluation of a given CEM: validity, proximity, diversity, and actionability [39].

Validity can refer both to the performance (eg, area under the curve, accuracy, and smoothness of the data manifold) of a CEM's underlying statistical model, as well as the CEM's ability to provide truly counterfactual predictions [39]. Individual predictions are truly counterfactual when the resulting outcome is in a different class than the original outcome (ie, perturbing the features of a given input vector results in a different predicted binary outcome). Thus, statistical models whose predicted outcomes are invariant to alterations in the input vector values are not valid for use as a CEM.

Proximity refers to the minimally required alteration of an input vector CEM to generate effective counterfactuals (ie, altered input vectors which result in a different prediction class). CEM models with superior proximity generate counterfactual input vectors using minimal perturbations to the original input vector [40-42].

Diversity refers to the size or cardinality of the set of counterfactual options resolved by a CEM [42]. For example, for a given individual input vector (ie, the quantitative description of a household's features and services), a CEM might recommend a large and varied set of counterfactual feature configurations that all successfully convert the prediction to the more ideal class. While not necessarily a detriment, large sets of "other possible worlds" offer a conundrum to CEM deployment, as many differing and often competing courses of action must be further compared and evaluated. This challenge, known as the Rashomon Effect [43], requires practitioners to select a single available counterfactual option from a large and varied set of options. The development of a framework to compare these options is available in the "Compute Counterfactual Service Arrays" section.

Actionability refers to the level of controllability of the input vector features perturbed by the CEM [44]. For example, an ICU treatment model that counterfactually recommends that a patient become taller is not actionable. This proposal seeks to maximize actionability by only perturbing input vector features that relate to the application of specific family services.

Methods

Overview

The study consists of 3 stages, which can be iteratively applied within a collaborating jurisdiction. Stage 1 is the development of a smoothed risk surface of child maltreatment. Stage 2 is the resulting service allocation process for areas of heightened risk identified in Stage 1. Finally, Stage 3 uses a CEM to determine optimally aligned service allocation for future iterations of the service array.

Stage 1-RTM

Overview

The objective of Stage 1 is neither to predict when or where the outcome will occur nor to identify regions of latent risk, but rather to apply RTM to initially identify the regions that might reasonably be expected to benefit from service allocation. To this end, we propose smoothing the historical outcome surface across the jurisdiction via the development of a geospatial machine learning algorithm, where regions corresponding to higher values from the trained smoother will inform the initial service allocation encompassed by Stage 2.

Within the jurisdiction of interest, the observational units of this geospatial smoother are regular polygons, the size of which will depend upon the collaborating jurisdiction. Henceforth, these observational units are referred to as "fishnet" grid cells. This fishnet is a regular grid of polygons (in this case, squares) with an area sufficient for block-to-neighborhood-level modeling but smaller than standard census geographies. The outcome being smoothed will pertain to child maltreatment, as defined by the collaborating jurisdiction, with the specific form (eg, rate, count, and so on) likely being determined after initial exploratory data analysis. The feature set will consist of variables based on the built environment, crime, and census data both within the cell and within neighboring cells, as well as the value of the outcome in neighboring cells (ie, auto-features), where a variety of isotropic neighborhood structures will be considered (eg, first-order, second-order, and so on).

RTM requires appropriately robust models that describe the environment. Traditionally, this has involved the use of administrative data sources, such as US census data, arrest or crime data from local law enforcement, as well as "environmental" data. For this study, our primary datasets will include address-level child welfare data on substantiated cases of maltreatment (eg, neglect, physical, sexual abuse, and so on), local law enforcement arrest data for violent crimes (eg, assaults, domestic disturbance calls, homicides, and so on), socioeconomic data from the US Census, and built environment data from the jurisdiction's open data sources as well as state-level administrative data where possible.

Local socioeconomic environmental variables from the US Census will be represented by the Neighborhood Deprivation Index [45]. This index is a validated and supported composite measure of neighborhood deprivation derived from the first principal component of a set of 20 census variables. The final

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index makes use of 8 of those variables found in the first component: share of males in management and professional occupations, share of crowded housing, share of households in poverty, share of female-headed households with dependents, share of households on public assistance, share of households earning less than US $30,000 a year, share of the population with less than a high school diploma, and share unemployed. Built environment data will include recognized risk factors in child maltreatment, including alcohol-serving establishments (both bars/restaurants and liquor stores), cannabis dispensaries (where recreational cannabis is legal), dangerous buildings from local code violations data, transit stops, and supportive/protective land uses such as community centers, daycares, and houses of worship.

Two approaches to creating the smoothed surface will be considered, with goodness-of-fit measures used to identify the better of the 2. The first, kernel density estimation [26], is expected to be inferior and will serve as the baseline approach. The second, a tree-boosted learner (eg, XGBoost [Extreme Gradient Boosting] [46]), is more complicated but is expected to be superior. For the boosted learner, k-fold cross-validation—with the spatial neighborhood structure dictating the partitioning of the folds—will be used. All risk factors will be included in the final model. Tree-based models such as XGBoost are generally robust to issues of multicollinearity and other risks of high-dimensional data. Hyperparameter tuning will be led by a grid search based on a range of hyperparameter values [47]. The combination of the grid search and spatial-based k-fold validation should allow for the estimation of a strong predictive model while guarding against overfitting and excessive residual spatial autocorrelation. For this protocol, the smoother produced through RTM is used to identify areas of heightened risk of child maltreatment to guide the initial round of service allocation decisions. Model predictive accuracy will be assessed using a spatial cross-validation approach.

Algorithmic Fairness of Geospatial Smoother

Within the paradigm of person-level algorithms and related decision-support tools, there exists a robust literature on algorithmic fairness. Among other things, this literature posits numerous definitions of algorithmic fairness [48,49] for an identified, and potentially multidimensional, protected attribute, along with a number of mitigation procedures for "correcting" the output of such person-level algorithms with respect to the protected attribute [50-52]. Unfortunately, within the paradigm of geospatial algorithms and related decision-support tools, there is a relative dearth of literature [53] pertaining to algorithmic fairness.

In light of this reality, one approach sometimes used is an assessment of the geospatial algorithm's generalizability across coarse categorizations of poverty (high- vs low-poverty), race (majority White vs majority non-White), or some combination thereof, based on census data [54]. Such assessments are akin to a type of algorithmic fairness audit, but provide no clear course of action in the face of poor generalizability.

Here, we propose a relatively simple approach encompassing the algorithmic fairness of the geospatial smoother and the corresponding identification of fishnet cells for service allocation. Our goals with this procedure are to enable a simple, coarse auditing of the geospatial smoother's outputs across a census-derived protected attribute and to provide a means for the subsequent and corresponding equitable allocation of services across the levels of the protected attribute.

The approach to algorithmic fairness consists of 2 steps. In Step 1, unsupervised machine learning (eg, clustering) is used to identify "levels" (eg, clusters) of a protected attribute. Such unsupervised learning would use relevant (as identified by the jurisdiction of interest) features from the census data (eg, racial percentages, poverty percentages, and so on). If the proposed unsupervised learning "fails" (ie, is uninformative for identifying groups or levels of a protected attribute), then we will default in Step 1 to a poverty- and/or race-based protected attribute consisting of only a few levels. In Step 2, the limited number of fishnet cells identified for allocation of services within Stage 2 is based on protected attribute-level stratification of the geospatial smoother's output. Such identification of fishnet cells for Stage 2 is consistent with an equitable allocation of services, where the form of equity is ultimately determined by the collaborating jurisdiction. For example, a jurisdiction could elect to allocate each level of the protected attribute an equal number of fishnet cells receiving services, with the specific fishnet cells within each protected attribute level being identified according to higher values of the geospatial smoother.

While this proposed approach to algorithmic fairness related to the geospatial classifier is relatively "simple," it is important to recognize that the norm is to ignore considerations of algorithmic fairness altogether. Furthermore, while there may understandably be concern that this geospatial smoother may inadvertently perpetuate existing biases, either with or without our proposed approach to algorithmic fairness, it is important to recognize that the proposed "intervention" (ie, Stage 2) consists of providing optional supportive services rather than imposing nonoptional punitive measures. Hence, the proposed approach elevates the standard by incorporating algorithmic fairness and inherently mitigates fairness concerns by allocating optional and supportive services.

Stage 2-Service Allocation

The service array provided to the households within the fishnet cells identified in Stage 1 will be finalized with input from the collaborating jurisdiction, although the following list presents a core set of service programs and/or service types, with the target population included for each item. The service array will be selected to impact the various known major risk factors for child maltreatment or adverse childhood experiences. These services include nurse-family partnership for pregnant people and young families [55], cure violence (neighborhood) [56-58], crime prevention through environmental design (neighborhood) [59-61], universal basic income (household) [62,63], early head start (child and young families) [64,65], pregnancy prevention (eg, Upstream USA; adults and families) [66,67], mobile medical clinics (household) [68,69], crisis intervention teams (neighborhood and household) [70], free college tuition (both municipal or state) [71,72], and Stewards of Children: Darkness to Light Training (children) [73].

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Each service has a demonstrated impact on one or more of these major risk factors. This comprehensive, multiservice, jurisdiction-wide approach uses a public health strategy [74,75] to expand preventive services to households that may not already be known to the collaborating jurisdiction's child welfare system. The entire set of services chosen by the collaborating jurisdiction will be available to every qualified household within each fishnet cell identified in Stage 1.

Data records will track household-level service delivery and participation, allowing for the quantification of service array information for use in Stage 3. A centralized service allocation database will be maintained by the jurisdiction. To properly quantify service delivery in a manner that is quantifiable for the CEM, data must include the service delivery period and the type and/or subtype of the service delivered by the provider. In the feature specification phase of the CEM construction, the service delivery features will be identified as Boolean values (ie, did or did not receive the service). Therefore, it may be necessary to define a single service type as multiple mutually exclusive features. For example, if data investigation reveals a distribution of service delivery periods for a specific service type, further discussion with the jurisdiction and service provider may motivate the differentiation of a given service type into 2 or multiple features (eg, service type A [≤1 month], and service type A [>1 month]). Careful analysis of the service delivery tracking database, along with input from the collaborating jurisdiction and service providers, will be required for the appropriate specification of the service type features used in the CEM.

Stage 3-Service Alignment Recommendation via CEM

Maltreatment Classifier Model Construction and Selection

The first step of Stage 3 is to develop a statistical model to associate available and quantifiable features with the selected child welfare outcome of interest. Model specification and selection will consider the 4 characteristics of CEMs identified above. While data availability details will not be finalized until the completion of Stages 1 and 2 in the collaborating jurisdiction, previous work suggests it is reasonable to anticipate that machine learning models can be trained to associate quantifiable household factors with child maltreatment outcomes with high performance, high algorithmic fairness, and high computational efficiency [52,76,77]. One novel contribution of this study protocol will be to extend the use of such models to inform the alignment of jurisdiction-wide service deployment strategies by maximizing the potential for positive outcomes at the household level.

Observational Unit and Data Universe

The granularity of the statistical model will be the household level. All households in the collaborating jurisdiction with at least one child member will comprise the data universe. The data set used to train and validate the statistical model will consist of the union of three mutually inclusive subsets of the data universe: Set 1: Households eligible to receive services as identified in Stage 1 of the protocol, Set 2: households that actually received services in Stage 2 of the protocol (some of which may not have been in Set 1), and Set 3: households found in the Statewide Automated Child Welfare Information System (SACWIS) [78]. Thus, the union of these 3 sets encompasses all households who either were eligible to receive services and/or are known to have the necessary SACWIS records to define an outcome. Households in the jurisdiction universe that fall out of this union set will be available as a counterfactual inference set. That is, despite not having a defined service record, their features will be available to construct an input vector for the statistical model, allowing for a predicted outcome and, in turn, an optimized counterfactual service array.

Sources of Model Features

A feature engineering stage will attach available quantifiable information to each household observation. These features will reflect information drawn from four general sources: Source (1) Household-level data available from consumer and market data, Source (2) local built environment data attached to nearby households, Source (3) Governmental reporting and services data, and Source (4) the household's actual service array experience during Stage 2. During counterfactual optimization, Sources 1 and 2 remain static. At the same time, Source 4 (the service array) is perturbed in order to minimize (or maximize) the predicted probability of the chosen child welfare outcome of interest. In this way, maximum actionability is preserved, since no household-level features beyond the controllable service array are perturbed as part of the counterfactual modeling. Importantly, administrative data from the SACWIS system will not be included as model features. This allows for the counterfactual model to be deployable for households that have not been involved with the collaborating jurisdiction's child welfare system. Governmental reporting and services data (Source 4) can act as important predictors as well as inform a potential post hoc outcomes analysis (refer to "Stage 2-Service Allocation"). The following list presents potential data elements for Source 4: (1) health care/hospital may include indicators such as preterm birth, very low birth weight, failure to thrive, neonatal abstinence syndrome, pediatric physical/developmental disabilities, teen birth, preventable hospital admissions, Prevention Quality Indicators (hospital visits), Pediatric Quality Indicators (area level), psychiatric hospitalizations, injuries from violence, pediatric lead poisoning, maternal morbidity/mortality, substance abuse, substance-related overdoses, accidental deaths, sexual violence/rape, and prenatal care visits; (2) data from the Department of Health/Medical Examiner may encompass infant/child deaths, premature deaths, excess mortality, and marriage/divorce; (3) crime/emergency service records may include arrests, incarcerations, domestic disturbance/violence, assault, gunshot/shooting/stabbings, intoxication, drug abuse/manufacturing, animal abuse/control, sexual assault/rape, arson, DUI, homicide, harassment, juvenile kidnapping, reckless driving, suicide, and welfare checks; and (4) education/employment data may capture graduation rates, truancy rates, higher education/trade school matriculation, kindergarten readiness, third-grade reading level, unemployment, and poverty indices.

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Model Outcome

The outcome will be defined via a joint venture with the collaborating jurisdiction's governing body and will relate to child maltreatment at the household level. Defining child maltreatment is a classic family-resemblance challenge, with no universally agreed-upon definition having emerged from over a century of academic and governmental interest in the phenomenon [25]. Previous work has considered various maltreatment-related outcomes that vary by intensity and prevalence, such as reports or referrals of child maltreatment (ie, community members reporting alleged child abuse or neglect to a child welfare agency), whether a child protective services investigation occurred for an alleged child survivor in the household, whether a child protective service investigation determined substantiated maltreatment in the home, and whether a child in the home was removed and placed into some form of substitute care as a ward of the state [23,24]. Outcome windows can also vary in length, although typical durations include 6 months, 1 year, and 2 years [52,79-81]. Outcome availability will differ between households depending on whether the question at hand is a question of reporting potential maltreatment, whether an investigation should occur, or the question of substantiation of child maltreatment 3, although it will be possible to both predict and define an outcome for each observation. For example, a household that was eligible for services and received services but was not found in the SACWIS system (ie, a member of Sets 1 and 2, but not Set 3) will be defined as "maltreatment absent," that is, there was no detected household maltreatment. However, it will still be possible to calculate a predicted probability of "maltreatment present," thus allowing for defining a counterfactual service array that could have further decreased any potential for maltreatment present in the household.

Model Selection Criteria

Best practice will be followed in order to construct and select between statistical model specifications that best satisfy the requirements for an acceptable associative model for use in the CEM stage [82-84]. This best practice includes (1) exploring a range of diverse machine-learning classifier types (eg, XGboost, support vector machines, neural networks, and so on), (2) comparing classifier performance on a validation set (eg, area under the curve, accuracy, specificity, sensitivity, and so on), (3) comparing the performance-fairness tradeoff for each model, with the aim of achieving large gains in algorithmic fairness at minimal cost to performance, (4) assessing computational demands (as the CEM stage would ideally use an exhaustive search over thousands of perturbed input vectors for each observation), and (5) ensuring the ability of the statistical model to underlie a CEM that produces counterfactual results that are valid, proximal, diverse, and actionable (refer to "Characteristics of Counterfactual Explanation Models" section above).

Potential Algorithmic Fairness Correction

The resulting statistical model will produce predicted probabilities that will be used ordinally within an observation's counterfactual array (refer to the "Compute Counterfactual Service Arrays" section). However, it is possible that the final deployed CEM will require between-observation comparison at the aggregation stage to meet the use-case requirements selected in collaboration with the jurisdiction. In the case that predicted probabilities will be directly compared between observations, and therefore between households at different levels of a protected attribute, algorithmic fairness corrections will be considered. The construction of such correctional procedures will follow the guidance of the well-established literature referenced in the "Algorithmic Fairness of Geospatial Smoother" section above [52]. In particular, the collaborating jurisdiction will determine, ideally with input from corresponding stakeholders, both the protected attribute of interest and the relevant definition of algorithmic fairness. Once these decisions are made, one or more appropriate correction procedures from the peer-reviewed literature can be identified and implemented to improve the fairness of the service-allocation recommender across the levels of the protected attribute.

Compute Counterfactual Service Arrays

The statistical model identified above through the selection criteria will become the underlying classification mechanism of the CEM. This CEM will produce service alignment recommendations by computing counterfactual service arrays for each historical observation at the household level. This will be accomplished by optimizing the service array vector for each household observation with respect to certain criteria or constraints, such as minimizing the predicted probability of the maltreatment outcome while also minimizing the number of additional services required. The following computational methodology outlines how this is accomplished: (1) an input vector is constructed for each household observation, which includes both the household characteristic features and the binary service array features (ie, a 0 signifies the household received Service A, while a 1 signifies the household did not receive Service A); (2) the permutations of the binary service array vector are considered to create a set of (at most) 2^n candidate input vectors (where n is the number of available services), one of which represents the actually received service array; (3) a predicted probability of the maltreatment outcome is computed for each candidate input vector; and (4) each of the 2^n candidate input vectors is quantified in terms of CEM characteristics for use in the aggregation stage. Ideally, a brute-force search will be used in this protocol to exhaustively consider all service array permutations, precluding various challenges with CEM deployment associated with the possibility of missing globally optimal regions of the search space [85]. However, if computational demands outweigh the available resources, nonexhaustive optimization algorithms (eg, mixed-integer programming [86] or genetic algorithm search [87]) are available to identify counterfactual service arrays that significantly lower the inferred probability of maltreatment.

In Step 4 above, each candidate input vector (of the 2^n defined for each household observation) is described by certain characteristics. These characteristics are (1) the change in predicted probability of the maltreatment outcome between original input vector and the candidate input vector (eg, +4% and −10%), (2) the proximity of the candidate service array vector to the original service array vector in Hamming distance

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(ie, the number of services that differ between the original and the candidate counterfactual under consideration [88]), and (3) the proximity of the candidate input vector to a known alternative input vector from the newly predicted class, representing a proxy for generalizability confidence (by Gower's distance [89], with 1 representing equality and 0 representing maximal distance in the set). In this way, the full set of counterfactual service array candidates for a given household observation can be sorted, filtered, and evaluated to serve specific purposes in the Recommendation Aggregation stage.

For example, consider a household observation whose maltreatment outcome was positive (with retroactive predicted probability of 85%) and whose actual service array vector was {0, 0, 1, 0, 1, 0} (ie, in Stage 2, the household received services C and E). For clarity, consider 3 members of its resulting 2^n candidate input vectors. Table 1 describes these candidate input vectors and the resulting CEM characteristics A-D for each candidate. Identifying a single recommendation from the resulting counterfactual candidates requires developing certain standards or rules. These criteria will be developed in conjunction with the collaborating jurisdiction to maximally adhere to their pragmatic considerations, such as resource constraints. For this example, consider how these candidates might be compared to one another. Candidate 1 reduces the predicted probability by 5%, which is less than the other 2 candidates; however, it requires only 1 additional service and is also very similar to a known observation in which maltreatment was actually prevented. Candidate 2 reduces the predicted probability by 35%, requires a net change of 1 service (1 subtracted and 2 additional), and has moderate similarity to a known observation in the alternative class. Candidate 3 reduces the predicted probability by 40%, more than the other candidates, but requires 3 additional services and is minimally similar to a known observation in the alternative class. If the determined considerations called for identifying recommendations that would require minimal additional services and maximize proximity to known observations of the maltreatment-prevention class, then Candidate 1 would be selected. If the determined considerations called for identifying recommendations that would maximize the reduction of predicted maltreatment, regardless of the number of additional services and regardless of the confidence provided by proximity to known observations, then Candidate 3 would be selected. A balanced approach might result in the selection of Candidate 2. In this way, the comprehensive quantification of each candidate result works to anticipate the myriad potential weighting scenarios from which one will be chosen as the guiding principle for selecting household-level counterfactual recommendations.

Table . Example comparison of 3 counterfactual candidates computed from an observation using the counterfactual explanation model (CEM). A walkthrough of this table is available in the "Compute Counterfactual Service Arrays" section.

Input vector description	Service array vector	Predicted probability of maltreatment	Change in predicted probability of maltreatment	Change in services required	Proximity to known member of the No-Maltr. class
Actual	{0,0,1,0,1,0}	85%	—	—	0.31
CEM[a] candidate 1	{0,0,1,1,1,0}	80%	−5%	Net 1 (+1)	0.99
CEM candidate 2	{1,1,0,1,1,0}	50%	−35%	Net 1 (+1, - 2)	0.67
CEM candidate 3	{1,1,1,0,1,1}	45%	−40%	Net 3 (+3)	0.42

[a]CEM: counterfactual explanation model.

Technical Considerations

Technical challenges may arise, such as entity resolution and data quality issues. Because joining the disparate datasets is critical, the challenge of entity resolution may require the deployment of one or more technical solutions. These solutions can range from fuzzy matching to deep learning [90,91]. In addition, data quality issues such as missingness, time period availability, and confounds due to policy change over time will likely be present. Expertise and experience in the data engineering of administrative data will be vital to ensure maximal validity and reliability of the results [92,93].

Change Management Considerations

Access to the family-level recommendation information provided by this protocol will undoubtedly constitute an implementation challenge for the jurisdiction. Thus, it will be critical to engage with the jurisdiction's change management entities, including implementation teams, continuous quality improvement teams, and communication teams, to develop a plan to execute the resulting recommendations. Conversations with these teams will expose the practical, policy, and legal challenges that must be addressed by the business framework surrounding the use of the information [94,95].

Ethical Considerations

The execution of this protocol will require input from the collaborating jurisdiction regarding data governance and ethical considerations. While requirements for ethics review approvals and informed consent differ greatly for governmental agencies relative to public research institutes, the protocol must comply with the jurisdiction's data governance requirements. This includes data security, data use agreements, data privacy, and the masking of personally identifiable information.

A central ethical concern in the area of predictive analytics and child welfare is the stigmatization of individuals, households,

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and neighborhoods via automated labels such as "high risk" [96]. To minimize stigmatization, the use of technical and statistical terminology should be separated from the communication and design concepts that govern any public-facing or user-facing material, dashboards, or deployable implementation that results from this protocol [97,98]. For example, one practical deliverable from this protocol could be a family-specific report that can guide a human services caseworker or supervisor to additional services that might promote more positive outcomes for a family. Framed as a guide for improving the family's outcomes, the material should avoid terminology such as "high risk." In summary, the protocol must adhere to the specific data governance and ethical considerations of the collaborating jurisdiction.

Results

As of September 2025, a participating jurisdiction is under recruitment.

Discussion

Principal Findings

The household-level counterfactual recommendations described in the previous section will be aggregated into actionable recommendations. The primary actionable recommendation will directly inform future iterations of Stage 1 by providing a model-informed approach for determining eligible regions. Other secondary recommendations are also possible if the final project scope calls for other ways to aggregate the results to fit various project goals. The overall conceptual method for generating these recommendations is to aggregate household-level counterfactual service array candidates into an actionable result [99].

There are several methods and strategies for aggregating the resulting household-level counterfactual service arrays. The first step is to select, for each household observation, which of the 2^n service array permutations should be selected. The previous section details how this selection logic can be specified to reflect the jurisdiction's overall project goals and constraints. The second step is to aggregate or "roll up" the household-level counterfactual service arrays into spatial subregions. These subregions could be the fishnet grids specified in Stage 1, or any other chosen subregion definition, such as ZIP code, census tract, or school district. Bespoke logic can determine the most pragmatic approach for grouping service recommendations into subregions. The simplest method is to, for each service type, sum the number of households in the subregion that were determined to benefit from the service. Constraints can be introduced to this logic, such as service availability and cost. Algorithmic fairness is also a potential consideration during aggregation, with possibilities for both measuring and balancing metrics such as "recourse fairness" [100]. Finally, these results are organized into an actionable recommendation strategy that can be provided to the jurisdiction to improve its future service delivery.

Comparison With Previous Work

This protocol sets forth a novel approach for the allocation of supportive services for families at risk of child maltreatment through geospatial smoothing via an RTM framework and the maximization of service impact through CEM. Child maltreatment is an unfortunate and ubiquitous issue in the United States. This proposal builds on jurisdiction-wide public health strategies to allocate services in a data-informed fashion and further align future iterations of the allocation strategy using outcomes-based counterfactual modeling at the household level. The flexibility of the proposed methodology enables its application regardless of the collaborating jurisdiction's preferences and constraints.

Strengths and Limitations

While there are challenges in setting up and implementing the proposed 3-stage process, including, but not limited to, data collection, privacy, and stigmatization, the potential benefits within a collaborating jurisdiction are numerous. Achievable benefits include, among other things, reduced child welfare involvement and reduced adverse childhood experience scores, more focused and efficient allocation of services and programs, as well as increased school attendance and graduation rates within the neighborhoods of the collaborating jurisdiction.

It is worth noting that while the objective of the presented protocol is to reduce child maltreatment within the collaborating jurisdiction, post hoc descriptive analyses related to changes in jurisdiction-wide outcomes known to be associated with child maltreatment (eg, adverse childhood experience scores, violent crime, and so on; refer to "Sources of Model Features" section for an expanded list) are possible and may be of interest to both the collaborating jurisdiction and corresponding service providers. For example, the Cure Violence program will likely be interested in whether aggregate measures of violent crime in the collaborating jurisdiction have declined pre- versus post implementation of a given iteration of the implemented service array. Importantly, however, whether such associated outcomes are causally improved as a result of the implemented service array cannot be nor is intended to be answered by the presented protocol. Such associated outcomes may or may not be causally related to child maltreatment, and therefore, reducing child maltreatment may not result in, for example, a reduction in violent crime across the collaborating jurisdiction. Regardless, such post hoc analyses are possible and can be informative for both the collaborating jurisdiction and corresponding service providers.

Future Directions

This proposal represents a maturation of machine learning and artificial intelligence in the public policy space. By leveraging the historical information in a narrowly focused machine learning approach, jurisdictions can develop data-driven recommendation tools that continuously improve over time. As explained in the "Strengths and Limitations" section, future stages of this approach can involve an enhanced underlying machine learning model based on new incoming data and outcomes from the previous stages. In this way, the general

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approach represents a continually evolving strategy rather than a single piece of analysis.

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Data Availability

Data sharing is not applicable to this article, as no datasets were generated or analyzed during this study.

Authors' Contributions

JG, BG, and JP contributed equally to writing the original draft, methodology, and conceptualization. DD provided lead supervision and project administration and contributed supporting writing through review and editing.

Conflicts of Interest

None declared.

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Abbreviations

CEM: counterfactual explanation model
ICU: intensive care unit
RTM: risk terrain modeling
SACWIS: Statewide Automated Child Welfare Information System
XGBoost: Extreme Gradient Boosting

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Generation of a Free-Living Ground-Truth Validation Dataset for Wearable Measures of Physical Activity, Sedentary Behavior, Sleep, and Heart Rate in Adults (OxWEARS): Protocol for a Cross-Sectional Study

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Abstract

Background: Wearable devices enable continuous measurement of physical activity, sedentary behavior, sleep, and heart rate under free-living conditions. However, most validation studies rely on small, homogeneous samples; are conducted under laboratory conditions; or lack gold standard ground-truth measurements, limiting the generalizability and accuracy of derived metrics. There is a pressing need for open-access, large-scale, free-living validation datasets that include multisensor data from diverse body locations and participant demographics to aid in model development.

Objective: The Oxford Wearable ECG, Activity, Circadian Rhythm, and Sleep Validation Study (OxWEARS) aims to (1) validate accelerometer-based measurement of physical behaviors across 5 body sites against annotated camera data; (2) validate measurements of sleep and sleep staging from 5 different body sites against polysomnography; (3) validate wrist-worn photoplethysmography heart rate measurements against chest-worn electrocardiogram; and (4) generate a comprehensive, annotated, and anonymized dataset for open-access research use.

Methods: This cross-sectional study will recruit approximately 160 adults (aged ≥40 years) stratified by age, sex, and BMI from the Oxford BioBank. Over 3 days and 4 nights, participants will wear sensors on the wrists, chest, hip, thigh, and ankle. Ground-truth measures will be obtained from a chest electrocardiogram patch for heart rate, a first-person camera for activity annotation, an ankle-worn accelerometer for step count, and at-home polysomnography for sleep. An under-mattress sensor will collect measures of sleep, respiration rate, and bedtime, and a subjective sleep diary will also be obtained. Signals from different wear locations will be compared against the ground truth using precision, recall, F_1-score, κ, and agreement metrics.

Results: Recruitment commenced in November 2024, with 15 participants enrolled by May 2025. Overall, 50% of eligible adults contacted were happy to consent to the study, with excellent compliance with the protocol observed to date. Data collection is ongoing and expected to conclude in 2026, with the final annotated dataset made publicly available as soon as possible thereafter.

Conclusions: The OxWEARS study will generate an openly accessible dataset containing more than 10,000 annotated hours from a stratified sample of adults. This will directly support scalable, generalizable human activity recognition efforts, while also enabling robust development and benchmarking of wearable-derived health metrics.

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KEYWORDS

validation; wearables; machine learning; physical activity; sedentary behavior; sleep; heart rate

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Introduction

The use of wearable devices for the assessment of physical activity, sedentary behavior, and sleep allows for the quantification of 24-hour human physical behaviors without the recall and social desirability biases associated with self-reported measures [1-3]. While these behaviors are commonly measured using commercial- and research-grade devices within epidemiological studies, the accuracy of the derived metrics against gold standard ground truth is currently uncertain. To date, most activity and sleep validation studies of wearables have been of poor quality—conducted in small, homogeneous cohorts; under laboratory conditions for a single day; and often without a gold standard reference [4,5]. Additionally, most studies focus on either sleep or physical activity, resulting in a lack of ground-truth reference measures for all behaviors across the 24-hour day.

While some accelerometer models have been trained using free-living validation data, significant room for improvement exists in model generalizability and specifically in improved performance in analyzing physical activity, sedentary behavior, and sleep. For example, some validation studies have collected wrist-based accelerometer data paired with first-person camera images for behavior classification [6,7], and these methods have subsequently been adopted in large epidemiological studies for health research [8,9]. However, these data were collected in a convenience sample over a single day without deference to age, sex, and BMI [10]. Additionally, more multisensor datasets are needed to compare data collected concurrently from different wear locations, as reflected in the existing literature. For example, large datasets exist with accelerometers worn on the wrist [8,11], hip [12], and thigh [13-15]; however, there is limited evidence regarding the harmonization of physical behavior phenotypes generated from different wear locations for subsequent statistical analyses. Furthermore, combining different signals from newer devices, such as photoplethysmography (PPG) and accelerometry, may improve the detection of sleep, physical activity, and sedentary behavior by providing additional data streams for model development. Finally, in most validation studies, raw data are not published, hampering external validation efforts and method development to improve performance [4,16].

Therefore, our overarching aim is to collect a free-living validation dataset, annotating wearable sensor data with gold standard, ground-truth labeled data, for application to large-scale accelerometer datasets with linked health records.

The main aims of this study are as follows:

1. To validate the measurement of physical activity and sedentary behavior from accelerometers worn on the wrist, chest, waist, hip, thigh, and ankle compared with ground-truth annotations from wearable camera data.
2. To validate the measurement of sleep and sleep staging from accelerometers worn on the wrist, chest, waist, hip, and thigh compared with gold standard polysomnography (PSG) sleep metrics.
3. To validate the measurement of heart rate and heart rate variability from wrist-worn PPG sensors against a ground-truth chest-worn electrocardiogram (ECG) patch.
4. To generate an anonymized dataset of annotated physical activity, sedentary behavior, sleep, and cardiac monitoring data for unrestricted use by the wider scientific community.

Methods

Ethical Considerations

Ethics approval was received from the University of Oxford Central University Research Ethics Committee on August 1, 2023 (R74559). Before the initiation of any study procedures, all participants were provided with an information sheet (Multimedia Appendix 1) and gave written informed consent using a digital signature platform compliant with ISO 27001 standards (E-Sign; E-Sign Ltd). Participants' privacy is of the utmost importance to us; therefore, no identifying information will be published, and individual data will be deidentified before any data release. Participants will receive no compensation for their participation but will be provided with a nondiagnostic report on their sleep and physical behaviors during the course of the monitoring period. Conforming to current ethical frameworks [17,18], written consent to be recorded by the video camera is not required from bystanders; however, participants will be instructed to obtain verbal permission from and provide an explanation of the device to family members, cohabitants, workplace managers or supervisors, or other people in settings where a reasonable expectation of privacy exists. This approach was considered reasonable. A script and information card will be provided for use if participants are questioned by members of the public. While we obtain consent, we will also ask participants to sign a privacy agreement for the recording of video for this study in public and private settings (Multimedia Appendix 2). Participants will be instructed on how to cover the camera or pause data collection at any time when they need privacy or feel uncomfortable or unsafe. Examples of this include using the bathroom (in public or private), using public changing rooms, interacting with unrelated children, or working in contexts where intellectual property must be protected. In line with the ethical framework established by Kelly et al [17], participants can request the removal of any unwanted or sensitive footage potentially caught on camera. Privacy concerns related to the wearable camera data are of critical importance. Therefore, raw video footage will never be released, and any examples used (such as for annotator training) will be confined to the University of Oxford research team. All data will remain on University of Oxford servers.

Data Deidentification

In line with previous research, no wearable camera data will be shared outside of the University of Oxford [7]. Each participant will be assigned a unique study identifier, which will be used to label all associated raw data files. Because participants could potentially be deidentified based on combined age, sex, and BMI, we will report only the subgroup to which each participant belongs, as described earlier. Finally, the start dates of the raw data will be randomized, and time stamps will also be shifted by a small random amount so that they do not reflect the true

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dates and times of the data. Similar steps have been used previously to ensure deidentification of participants taking part in studies [7].

Recruitment

OxWEARS is a cross-sectional study and will recruit a target sample of 160 participants from the Oxford BioBank [19]. A sample size of 160 will provide 80% power to detect a difference of 0.05 in Cohen κ score (effect size=0.25, assuming an SD of 0.25 from previous studies [20]) between 3 age groups using a fixed effects one-way ANOVA test (α=.05). The Oxford BioBank is a population-based cohort of approximately 9000 participants aged 25 to 55 years recruited in Oxfordshire, United Kingdom, from 1999 onward. Inclusion and exclusion criteria for this study are presented in Textbox 1. Recruitment will target the creation of a final study cohort evenly balanced by sex, age (40 - 54 years, 55 - 64 years, and ≥65 years), and BMI (18.5 - 25 kg/m^2, 25 - 30 kg/m^2, and >30 kg/m^2). The distribution of invitations will be regularly rebalanced to achieve 13 to 14 participants in each subgroup by the end of the study.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Enrolled participant of the Oxford BioBank
- Healthy adults aged 40 years and older
- Able to ambulate (with or without a walking aid)
- Willing to wear multiple sensors over 3 days and 4 nights of data collection

Exclusion criteria

- Unable to speak or understand English
- Self-reported neurological conditions or diagnosed sleep impairment
- Self-reported clinicians, teachers, caregivers, or anyone working in environments where image capture would be inappropriate and who cannot commit to 3 consecutive days of image capture outside of these sensitive environments
- Unwilling to wear all the monitors according to the study protocol

Study Timeline

A study timeline is presented in Figure 1, outlining the overall data collection period. Data collection will be conducted in the free-living environment for 3 full days and 4 consecutive nights. Following receipt of consent, an in-person study setup visit is arranged, wherein 2 members of the research team will meet the participant at their home to set up and deploy the wearable sensors, camera, and under-mattress sleep analyzer for the data monitoring period, in addition to the PSG sleep assessment for the first night only. One night of PSG was chosen to balance participant and researcher burden with the inclusion of a gold standard sleep assessment. The distribution of ambulatory wearable sensors across the body is presented in Figure 2, with further description in the following methodological subsections.

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Figure 1. Overview flowchart of study activities during the data collection window. Green activities are conducted by the OxWEARS research team, and blue activities are conducted or collected by the study participant. ECG: electrocardiography; PSG: polysomnography.

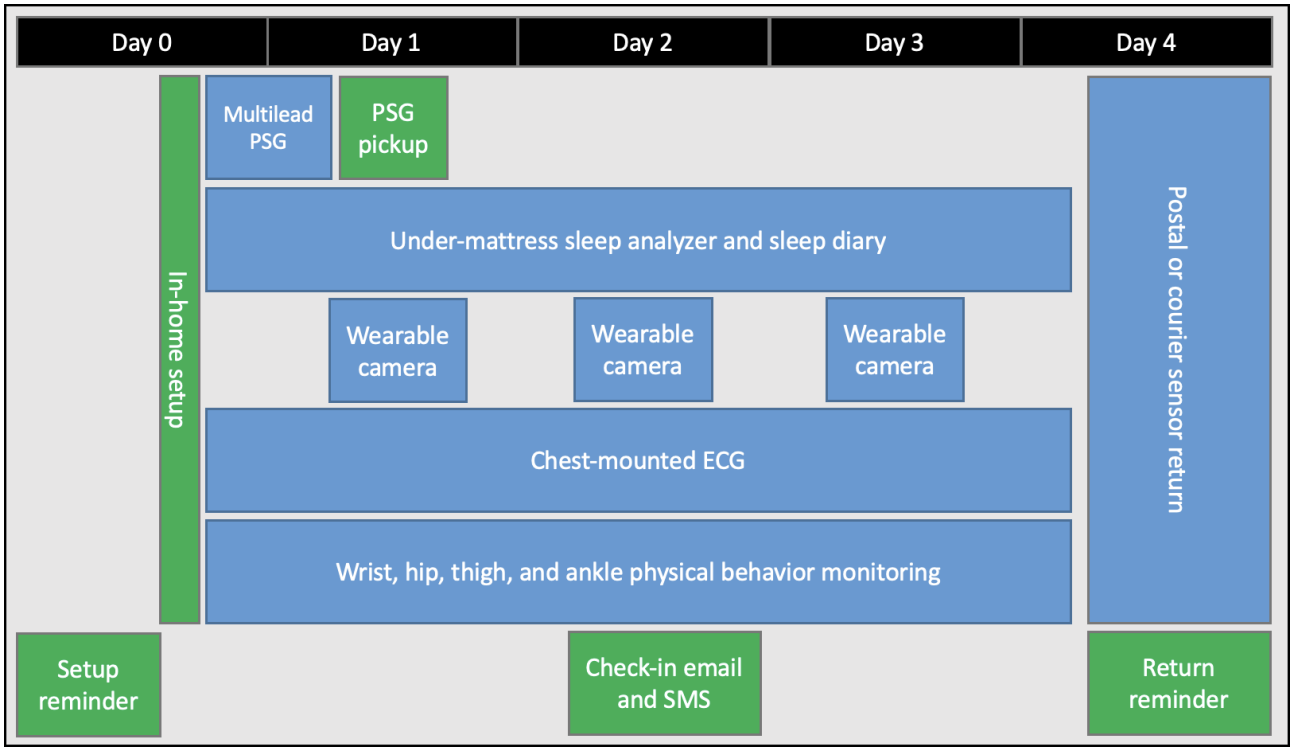

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Figure 2. Distribution of wearable sensors for 3-day and 4-night ambulatory monitoring, including wrist, waist, thigh, and ankle accelerometers; a chest-mounted ECG and accelerometer patch; and an automated camera. *Denotes ground-truth or reference measurements (image designed by Freepik).

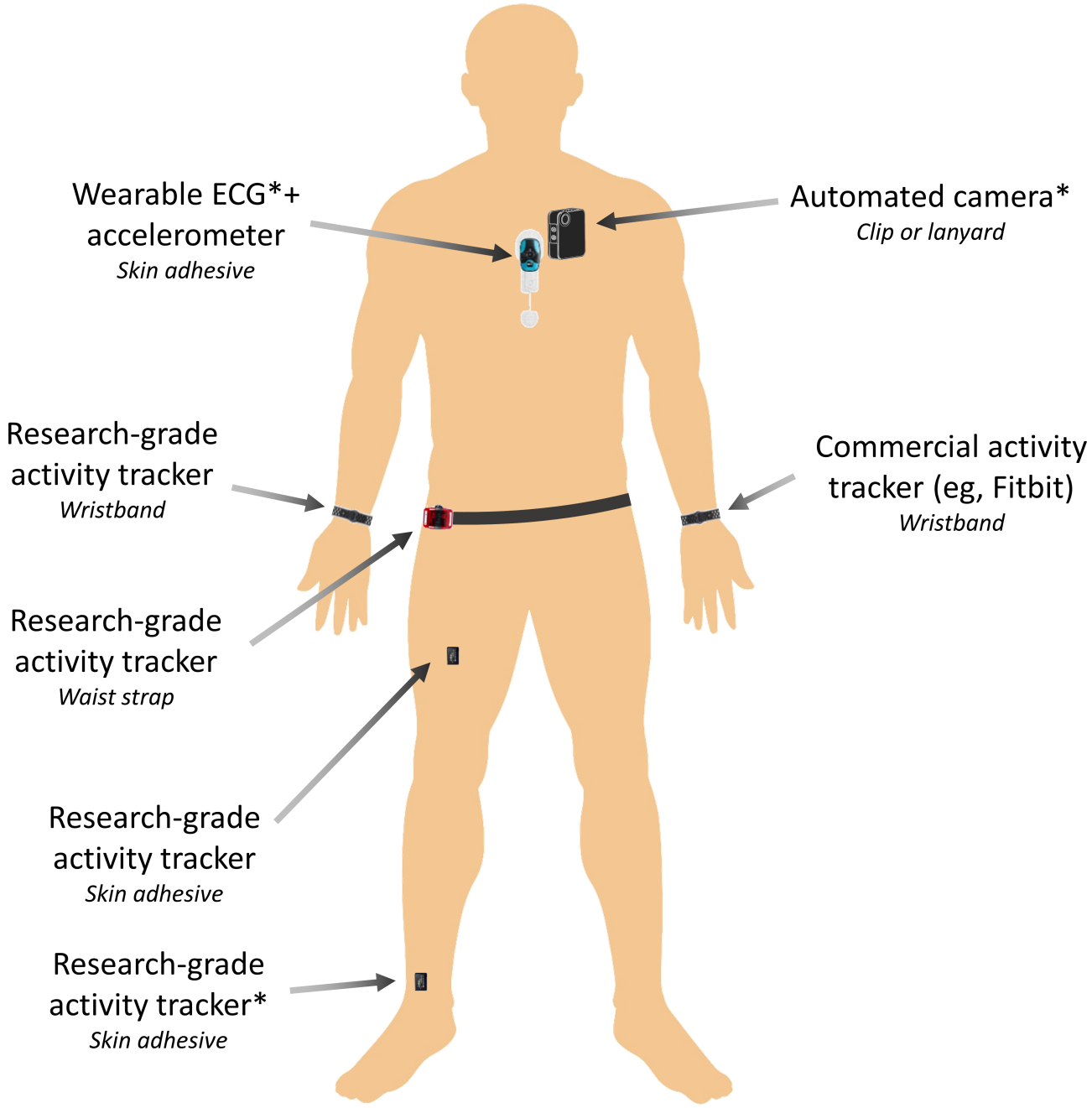

Ground-Truth ECG Data Collection

Ground-truth cardiac monitoring will be conducted using a clinical-grade single-lead wearable ECG patch (Bittium Faros 180; Bittium) affixed in a vertical orientation directly to the skin on the chest immediately inferior to the jugular notch and superficial to the sternum. Before adhesion, participants with chest hair will be instructed to shave the designated area to ensure adequate adhesion as per manufacturer guidelines. Continuous single-lead ECG data will be collected at 250 Hz and logged directly onto the ECG device for the entirety of the monitoring period (24 hours/day). In addition to raw ECG data, the monitor will be set to record continuous raw triaxial accelerometer data at the chest at a sampling rate of 100 Hz and with a dynamic range of ±4*g*.

Ground-Truth Physical Behavior Data Collection

To obtain ground-truth data on everyday activities, participants will wear a first-person perspective video camera (MIUFLY) during waking hours for 3 days, mirroring procedures from prior studies using first-person image capture to annotate physical activity and sedentary behavior [7,21]. In this study, a wearable camera is worn by the participant via a chest harness, neck mount, clip, or lapel and continuously records video during participant waking hours. Previous automated camera studies of this nature have reported wear time compliance of more than 80% [22,23]. No audio is captured by the camera, and all footage is encrypted on the device so that only the research team can download and view the video. Participants will be instructed on how to cover the camera or pause data collection at any time when they desire privacy or feel uncomfortable or unsafe.

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Examples of this include using the bathroom (public or private), public changing rooms, interacting with unrelated children, or working in contexts where intellectual property must be protected.

Ground-Truth Sleep Assessment

On the first study night, ground-truth sleep data will be collected with an ambulatory diagnostic multichannel PSG system (SOMNO HD Eco; S-Med Limited). The electroencephalogram (EEG) array will be attached in accordance with the 10-20 system of electrode placement [24]. The montage and recording settings (30-second epochs, 256 Hz sampling rate for EEG channels) will conform to the American Academy of Sleep Medicine (AASM) recommendations [25]. The following channels will be recorded: scalp EEG (F3, F4, C3, C4, O1, and O2), bilateral references on the mastoid processes (M1 and M2), grounding electrode (placed on FpZ), a common scalp reference electrode (Cz), bilateral electro-oculogram, 2-lead ECG, and 3-lead submental electromyography. Participants will be asked to change into sleeping clothes prior to sensor setup to minimize the risk of electrode disturbance. Prior to recording, researchers will check signal quality via a tablet and replace electrodes with high impedance values (>5 kΩ). The in-home sleep study will be conducted for 1 night only. Participants will be instructed to blink several times to indicate lights off at the time of their choosing. Participants will be instructed on how to remove the electrodes themselves following sleep, and a member of the research team will make a return visit the morning following the at-home visit to collect the PSG equipment and answer any further questions regarding the study.

Wearable-Based Physical Behavior Monitoring

Participants will be asked to wear 5 stand-alone wearable devices continuously (24 hours/day) throughout the course of the study period (Figure 2). The wear locations for the sensors were selected based on their popularity in previous validation studies [4,5]. The recording specifications of each device and sensor are detailed in Table 1. Wrist-measured physical behavior data will be collected using a combination of research-grade and consumer-grade devices. Specifically, a multimodal research-grade device (ActiGraph LEAP: ActiGraph LLC) consisting of triaxial accelerometer, gyroscope, and PPG sensors will be worn on the participant's dominant wrist. Similarly, a consumer-grade device (Fitbit Sense 2; Fitbit by Google) with comparable multimodal sensors to the ActiGraph LEAP will be worn on the participant's nondominant wrist, according to manufacturer's instructions.

Table . Wearable device data capture.

Device	Location	Sensors and recording settings	Heart rate
Bittium Faros 180	Chest	Accelerometer: 100 Hz, ±4*g*	1-channel ECG[a]: 250 Hz
ActiGraph LEAP	Dominant wrist	Accelerometer: 32 Hz, ±8*g*; gyroscope: 128 Hz and ±2000 dps[b]	PPG[c]: green (530 nm), 128 Hz
Fitbit Sense 2	Nondominant wrist	60 s epoch proprietary phenotypes	60 s epoch heart rate average
ActiGraph GT3X-BT	Waist or hip	Accelerometer: 100 Hz, ±8*g*	[d]—
Axivity AX6	Dominant thigh	Accelerometer: 100 Hz, ±8*g*; gyroscope: 100 Hz, ±2000 dps	—
Axivity AX6	Dominant ankle	Accelerometer: 100 Hz, ±8*g*; gyroscope: 100 Hz, ±2000 dps	—

[a]ECG: electrocardiogram.
[b]dps: degree per second.
[c]PPG: photoplethysmography.
[d]Not applicable.

Participants will wear an ActiGraph GT3X-BT monitor (ActiGraph LLC) on their hip continuously throughout the data collection period, removing it only for water-based activities. The device will be worn using an adjustable belt strap, with a buckle for easier removal.

For thigh monitoring, a medical-grade hypoallergenic adhesive dressing will be used to affix an accelerometer (Axivity AX6; Axivity Ltd) on the anterior aspect of the participant's dominant thigh, wrapped in a nitrile sleeve for protection. The Axivity AX6 houses a triaxial accelerometer and triaxial gyroscope, which will both record at a sampling frequency of 100 Hz and dynamic sensor ranges of ±8*g* and ±2000 degrees per second, respectively.

As an additional measurement point for physical activity, a further Axivity AX6 device (with matching recording characteristics) will be mounted on the dominant-side ankle, wrapped in a nitrile sleeve using medical adhesive tape. This is of specific interest for potential step count validation [26], for which a separate study including video-captured daily steps with concurrent ankle- and wrist-worn Axivity AX6 devices will be conducted to assess the validity of the ankle as a suitable ground-truth measure for step count in 50 adults, incorporating machine learning methods to estimate step count compared with proprietary algorithms assessed previously [26]. This model will then be applied to OxWEARS to compare step count from the ankle with each of the other wear locations (chest, both wrists, hip, and thigh).

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Nearable-Based Sleep Assessment (Under-Mattress Sensor)

In addition to the ground-truth PSG sleep assessment, a popular consumer-grade sleep device (Withings Sleep Analyzer; Withings) will be set up by the researcher for the full 4 nights of the study. The Withings Sleep Analyzer will be placed under the participant's mattress in line with where the heart would be while the participant lies in bed. It uses ballistocardiography and a built-in microphone to estimate sleep duration, efficiency, sleep onset latency, sleep staging (awake, light, deep, or rapid eye movement sleep), as well as breathing rate and snoring events, using proprietary algorithms. It has shown some early promise as a potential "nearable" device for individuals to monitor long-term sleeping patterns without the need to physically wear a device [27].

Subjective Sleep Assessment

As a final complementary measure of sleep duration and quality, participants will additionally be asked to complete a standardized self-report sleep diary on each of the 4 study nights [28], which captures times the participant got into bed, went to sleep, woke up, and got out of bed. We have further adapted this to capture information on perceived sleep quality and whether any naps were taken outside of the primary sleep window (Multimedia Appendix 3).

Data Processing and Analysis

Physiological reference metrics derived from the ground-truth clinical-grade cardiac monitor will include participant heart rate and heart rate variability. There is ongoing work to develop and validate an ECG algorithm, which will be made publicly available in the future. During this process, clinical experts with extensive experience will review ECGs for RR intervals to determine algorithm performance. Derived heart rate and variability will be calculated on a per-epoch basis in 10-second windows and will serve as the ground-truth labels of heart rate for the study. Comparisons will then be made between these cardiac monitor–derived metrics and PPG-derived metrics [29] from both wrist-worn devices in terms of epoch-level accuracy and agreement across participant age, sex, and BMI subgroups.

Physical activity behaviors derived from the camera will take the form of video annotation of labeled activities based on posture (eg, lying, sitting, and standing) and whole-body movements (eg, walking, running, and cycling), in line with previous research [30]. Each participant's camera data will be annotated by an annotator who has completed a rigorous training regimen and is certified for annotation after consistently reaching a κ agreement of >0.8 against a series of day-long reference participants. If multiple annotators are required, we will additionally assess for interrater reliability scores. Further annotation and assessment will be conducted against machine learning–based automated image and video annotations [31]. These annotations will serve as the basis for retraining machine learning behavior classification models to better identify periods of sedentary, light, moderate, and vigorous physical activity [9,32].

Ground-truth sleep metrics, including time of sleep onset, waking time, and sleep staging, will be scored according to the AASM 2023 guidelines [25] by a single AASM-accredited sleep scientist with additional European Sleep Research Society accreditation and more than 15 years of experience working with EEG data. Sleep stages (non–rapid eye movement sleep [stages N1, N2, and N3], rapid eye movement, and awake) will be assigned for every epoch (30 seconds). A subsample of recordings (10% - 20%) will be scored by a secondary accredited researcher to assess interrater reliability. As per recommendations in the field, scoring will be adjusted until interrater agreement reaches >80%. Similar to the physical activity behavioral ground-truth annotations, sleep annotations derived from the in-home PSG will serve as the basis for comparison of sleep time, sleep efficiency, and sleep staging derived from other accelerometers and the under-mattress sleep nearable, in addition to current accelerometer-based machine learning sleep models [33,34].

Data quality will be assessed regularly throughout the data collection period to check protocol adherence. This will involve processing the raw accelerometer data from the research-grade wearables through existing analytic software, such as Biobank AccelerometerAnalysis (University of Oxford) [8] and Stepcount (University of Oxford) [35], to assess device recording duration and nonwear detection based on accelerometer thresholds. The Fitbit- and Withings-derived data will be checked at the summary level to flag possible poor compliance. PSG data quality will be assessed within the manufacturers' software using an automated sleep-stage classification system. We will report on the technical validation of the data when we publish the complete dataset, including the number of participants and the volume of camera-labeled data, both separately and when combined with concurrent data from other devices.

The primary aim of this study is to collect a high-quality validation dataset to facilitate new ways of analyzing time-series wearable data. As such, there will be many future imaginative analyses of these data that we do not anticipate at present. At present, we anticipate that mean precision, recall, F_1-score, Cohen κ, and accuracy will be used to evaluate model performance for all comparisons with ground-truth labels. Additionally, summary metrics will be assessed against the ground-truth measure using mean absolute bias, mean amplitude percentage error, Cohen κ [36], and Bland-Altman plots [37].

Metadata Description

Our complete dataset and metadata will be hosted by the Oxford University Research Archive under the Creative Commons "Attribution 4.0 International (CC BY 4.0)" license. Raw accelerometry, ECG, and PPG data will be provided as compressed CSV files in folders for each participant. We will provide separate CSV files containing a dictionary of annotation labels for scored PSG data, a full annotation schema, labels for wearable camera data, and participant characteristics (age category, sex, and BMI category).

Results

To date, 150 participant information sheets have been sent to members of the Oxford BioBank database. Of these, 30 (20%) have expressed interest, and 15 (50% of those expressing

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interest) have provided consent. Common reasons for not progressing to consenting so far include ineligibility due to occupation (teacher or health care worker), requests to be contacted at a later date, and inability to make contact with the participant. The first participant consented and completed data collection in November 2024. As of May 2025, we had enrolled 15 participants, with 12 (80%) completing the monitoring period with excellent adherence to the protocol. Data collection is expected to be completed in 2026.

Discussion

This protocol details the design of a new free-living validation dataset to more accurately characterize physical behaviors and heart rate using wearable-based sensors on the wrist, chest, waist, hip, thigh, and ankle. By establishing ground-truth metrics for physical activity, sedentary behavior, sleep, and heart rate in a cohort of middle-aged and older adults, we attempt to create the largest resource for the validation of current and future methods for deriving physical behaviors and heart rate that is freely accessible to the wider research community. Furthermore, the methods that we implement in this study overlap with past research [7,38]; ongoing studies at the University of Oxford (S van Duijvenboden, unpublished data, December 2025); and future planned studies in low- and middle-income countries, such as India, South Africa, and Malaysia. This will foster efforts to improve the generalizability of machine learning models by training on diverse datasets, in addition to providing suitable datasets for external validation and pooled analyses. Large cohort studies currently hold rich datasets of unlabeled data. The creation of this curated dataset, comprising labeled behaviors for all popular sensor wear sites [39], will support the development of more accurate and novel phenotyping. The application of these phenotypes into epidemiological research will then be used to provide novel insights into human health, with respect to risk prediction, discovery of target mechanisms, and new methods to prioritize and assess the impact of potential treatments on day-to-day physical activity, sedentary behavior, and sleep.

Chest-worn ECGs are increasingly being used in cohort and clinical trials, where long-term monitoring of ECG data during free living can provide a more comprehensive understanding of heart function during daily activities, exercise, and sleep. The validation of ECG data from chest-worn wearables supports ongoing and future long-term cardiac monitoring trials such as the UK BioBank cardiac monitoring substudy [40]. At present, there is promising, but very limited, evidence on the validity of accelerometer-derived physical behavior phenotypes from chest-worn accelerometers based on simulated free living in small samples [41,42]. Incorporating physiological parameters, such as heart rate and other ECG parameters—key markers of cardiovascular health—could provide deeper insights into the intensity and impact of physical activity. For example, several activities performed at moderate-to-vigorous intensity, such as cycling, resistance exercises, or walking on an incline, are assessed with limited certainty with accelerometry [43] and are likely to be better captured by including heart rate monitoring, as it is not affected by the modality biases inherent to single-site accelerometry. Kuo et al [44] demonstrated an increase in reliability of 10% to 15% when including heart rate on top of accelerometry at 5 different wear sites to estimate energy expenditure during treadmill exercise at different speeds and gradients. This study was limited to a small sample of 16 young, healthy men and a treadmill protocol. Free-living behaviors captured in a larger, stratified sample, such as in this study, will further enhance our understanding of the added value of combining accelerometer data with heart rate, as these measures become increasingly available in research and consumer markets.

Identification of sleep stages that involve minimal movement may also benefit from additional physiological metrics to enhance their accuracy and reliability. This has been demonstrated previously in 31 adults who wore an Apple watch during a PSG assessment [45]. The combination of accelerometer with additional PPG sensor did not improve overall wake-sleep classification. However, sleep staging classification accuracy improved by 15% to 25% when heart rate was added as a feature on top of accelerometry signal alone and showed similar performance when applied to a large heterogeneous sample of approximately 6800 US adults from the National Sleep Research Resource [46]. This study will generate the largest accessible free-living dataset with ground-truth annotations for model development to improve human activity recognition at the chest for immediate application to clinical trial and prospective cohort datasets.

Strengths of this study include the large, stratified sample to create a more heterogeneous, multimodal dataset; the inclusion of ground-truth measures of physical activity, sedentary behavior, sleep, and heart rate; and the planned release of the data to the wider research community. One limitation of this study is the lack of dietary or cognitive data, meaning certain behaviors cannot be linked to physiological metrics, for example, postmeal sedentariness and heart rate variability. Future work could explore the capture of these behaviors to provide additional context to physiological responses. Furthermore, despite recruiting a large sample size in comparison to existing device validation studies, subgroup analyses may be challenging when assessing algorithm performance. However, due to our methodology, it would be possible for these data to be combined with other datasets (eg, Capture-24) to increase the statistical power of these comparisons in the future. Finally, although we recruit a sample stratified by age, sex, and BMI, our sample does not include younger adults aged <40 years, those with chronic illnesses, or non-English speakers. Therefore, the results will only be applicable to healthy adults with a demographic profile similar to the recruited participants. Future work should strive to include representativeness of these characteristics in addition to improving representativeness from low- and middle-income countries to assess generalizability of machine learning algorithms trained on this dataset. Despite these limitations, we anticipate that the study's strengths will make the resulting dataset the largest and most comprehensive open-access validation dataset worldwide.

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Authors' Contributions

BDM and SRS drafted the original manuscript with support from LB. AD and SRS conceptualized the study. BDM, TP, SvD, and LB contributed to data curation. All authors contributed to the development of the methodology and analysis plan and provided feedback on manuscript drafts.

Conflicts of Interest

SRS is currently an employee of Novo Nordisk, but work was completed under association with the University of Oxford only. AD's team creates new methods based on wearable device validation dataset that are made available via academic-use software licenses. If used for commercial use, commercial entities pay his institution to purchase a license. In such circumstances, AD receives personal payment via the University of Oxford for sold software licenses.

Multimedia Appendix 1
Participant information sheet.
[DOCX File, 1069 KB - resprot_v14i1e78779_app1.docx]

Multimedia Appendix 2
Equipment and privacy agreement.
[DOCX File, 31 KB - resprot_v14i1e78779_app2.docx]

Multimedia Appendix 3
Sleep diary.
[DOCX File, 31 KB - resprot_v14i1e78779_app3.docx]

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Abbreviations

AASM: American Academy of Sleep Medicine
ECG: electrocardiogram
EEG: electroencephalogram
PSG: polysomnography

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The Influence of Virtual Reality Glasses Use on the Quality of Life of Older Adults: Protocol for a Prospective, Longitudinal Quasi-Experimental Study

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Abstract

Background: Older adults are a rapidly growing demographic and often face social isolation and limited access to outdoor activities due to mobility issues, health conditions, and environmental barriers. These limitations can negatively impact their well-being, leading to reduced physical activity, cognitive decline, and emotional distress. Virtual reality (VR) technology offers a promising solution to bridge this gap by enabling access to immersive virtual environments, which may enhance the quality of life for residents in nursing homes.

Objective: The aim of this study is to assess whether the use of VR glasses in nursing homes improves the quality of life of older adults by reducing the challenges they face in participating in recreational activities outside their care facilities.

Methods: This study will adopt a prospective, longitudinal quasi-experimental design conducted in nursing homes within a basic health area of Catalonia, Spain. The intervention period will span 1 year. Participants will use VR glasses to interact with virtual environments, and their quality of life will be measured using the Rivas-Borda Quality of Life Scale, based on other validated scales.

Results: Outcomes will focus on variations in quality-of-life scores before and after the intervention, as determined by the Rivas-Borda Scale. Statistical analysis will include detailed metrics such as sample size, confidence intervals, and *P* values to evaluate the intervention's effectiveness.

Conclusions: This research seeks to confirm that VR technology can be a valuable tool for enhancing the quality of life in older adults residing in nursing homes, addressing issues like social isolation and limited access to outdoor activities in an innovative and engaging way.

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KEYWORDS

virtual reality; quality of life; aged; primary health care; public health

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Introduction

Background

Quality of life (QoL) in older adults is a multidimensional concept that encompasses various crucial aspects of well-being and fulfillment as individuals age [1]. The global increase in the older adult population, projected to nearly double from 12% in 2015 to 22% in 2050, presents significant challenges for societies worldwide [2]. This demographic shift requires innovative approaches to maintain and enhance the QoL for older adults, particularly as they face unique physical, cognitive, and social challenges associated with aging.

Active aging has emerged as a holistic framework aimed at enhancing physical, cognitive, and emotional health, thereby improving the QoL for older adults. By promoting physical activity, social engagement, and healthy lifestyle choices, active aging effectively addresses the challenges associated with aging [3-6]. Recent research has highlighted the importance of multifaceted interventions that target various domains of well-being, including physical health, cognitive function, and social connectivity [7,8].

In recent years, emerging technologies—including robotics, virtual reality (VR), and smart textiles—have gained prominence for fostering healthy lifestyles among middle-aged and older adult populations. These innovative technologies play a crucial role in addressing issues such as social isolation and supporting active aging [9]. VR, in particular, has demonstrated considerable versatility and moderate cost, with applications spanning health domains including pain management, cognitive health, physical rehabilitation, and social well-being [10-15].

The potential of VR in health care for older adults has been extensively explored in recent literature. Studies have shown promising results in areas such as fall prevention, cognitive stimulation, and physical therapy [16,17]. Moreover, VR interventions have been found to improve mood and reduce anxiety in older adults, contributing to overall psychological well-being [18,19].

Despite these advancements, some studies have primarily focused on enhancing physical and cognitive functional capacities of individuals affected by specific diseases; a holistic perspective on QoL improvement remains underexplored. Current studies predominantly focus on neurodegenerative diseases and fall prevention in neurological patients, often overlooking broader determinants of QoL and their integration into aging interventions [20-22].

This study aims to assess whether 4 practical sessions, conducted using VR glasses, can improve QoL in older adults residing in geriatric facilities—a population frequently experiencing diminished well-being. Furthermore, this research emphasizes the importance of collaboration across various societal domains to address the multifaceted challenges of aging. Specifically, it integrates the social dimension, leveraging the support of the local municipal organization VallsGenera; the educational dimension, through partnerships with local schools; the technological dimension, using VR technology; and the health care dimension, by addressing the well-being and mental health of older adults in geriatric facilities. By fostering these interdisciplinary collaborations, this innovative approach aspires to bridge the digital divide faced by older adults and comprehensively enhance their QoL.

The integration of VR technology in geriatric care represents a promising avenue for enhancing the quality of life of older adults. By providing immersive experiences that stimulate cognitive function, promote physical activity, and facilitate social interaction, VR interventions have the potential to significantly impact various dimensions of well-being [8,19]. This study contributes to the growing body of research on technology-assisted interventions for older adults and aims to provide valuable insights into the efficacy of VR in improving overall quality of life in geriatric populations.

Hypothesis

Participants who engage in the VR experience will report a significant improvement in perceived psychosocial well-being, as measured by the study-specific questionnaire.

Methods

Study Objectives

The general objective of this study is to evaluate whether conducting 4 practical VR sessions using VR glasses improves the quality of life of older adults.

The specific objectives are as follows:

- To analyze whether the emotional and cognitive well-being of participants improves according to the questionnaire created for this study.
- To identify whether there is an improvement in the sociofamiliar and physical dimension areas of the participants according to the questionnaire created for this study.
- To assess user satisfaction with practical VR sessions using VR glasses for older adults.

Study Design, Setting, and Period

This is a prospective longitudinal quasi-experimental study designed to assess the impact of VR sessions on the QoL of older adults. The study will be conducted in all nursing homes within the basic health area of Valls (Catalonia, Spain). Valls is an inland city in the southern part of Catalonia and has a population of 25,047 [23].

The intervention period will span 1 year. The general framework and participant timeline of this study are shown in Figure 1.

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Figure 1. Flowchart of the VRLife study, showing the process of the screening, preintervention, intervention, and postintervention phases. QoL: quality of life.

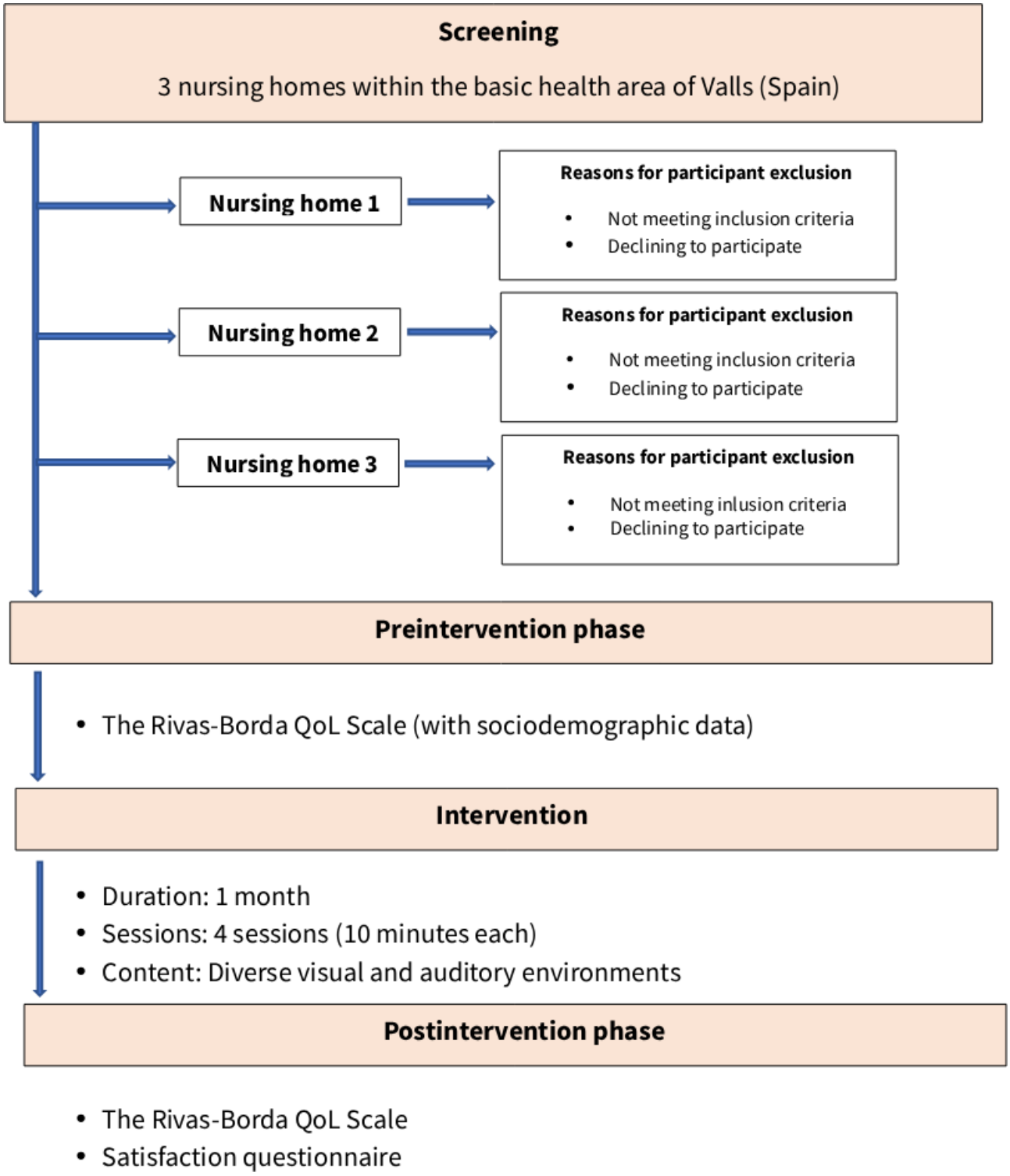

Institutional Involvement

The study involves collaboration with multiple entities: the Narcís Oller Institute, where students volunteered to assist with the intervention; VallsGenera, which will provide the necessary resources for the study; and all geriatric residences of Valls, named Alt Camp, Montserrat Cuadrada, and l'Alba, which will actively participate in the project.

Secondary school students from the Narcís Oller Institute, who were previously invited to participate, will visit the residential facilities to support the VR intervention. Their role has been clearly defined to focus primarily on technical assistance, with limited and standardized social interaction. Students will receive structured training from the nurses leading the study, which specifies the aspects of the intervention they may guide or assist with, ensuring consistency across sessions and minimizing variability in interpersonal interactions. The nurses will oversee all intervention procedures, provide supervision, and coordinate

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scheduling with both the educational institution and residential centers to arrange the sessions.

Participant Selection

Eligible participants will include older adults residing in nursing homes in Valls who experience limitations in participating in recreational activities outside their care facilities. All residents who meet the criteria will be considered as potential participants. Invitations to participate will be extended in accordance with the predefined inclusion and exclusion criteria.

Inclusion criteria are as follows:

- Aged 65 years or older
- Individuals presenting with slight, moderate, significant, or complete impairment in social resources, as assessed by the Older Americans Resources and Services (OARS) methodology developed by Duke University (1978), which was adapted into a Spanish version [24].

Exclusion criteria are as follows:

- History of frequent migraines or motion sickness
- Moderate to severe cognitive impairment (≥5 errors on the Abbreviated Pfeiffer Test) [25]
- Advanced visual and/or hearing impairment
- Inability to communicate in either Spanish or Catalan

Recruitment and Data Collection

The study will be presented to the management teams of the participating nursing homes. Upon approval, all residents will be informed about the study and invited to participate. Eligible individuals will be identified by the research team based on their residence in the basic health area of Valls and their compliance with inclusion and exclusion criteria. Those meeting the inclusion criteria and none of the exclusion criteria will be formally invited to participate.

Interested participants will receive detailed information about the study and will be asked to provide written informed consent prior to enrollment. As part of the screening process, participants will complete both the Abbreviated Pfeiffer Test and the OARS questionnaire, which will be used to assess cognitive status and social resources, respectively, in relation to the eligibility criteria.

Sample Size

The effect size of VR on QoL has been established at 20 points [26]. Accepting an α risk of 0.05 and a power of 0.9 in a 2-tailed test, 59 subjects are needed in the observed group to recognize a difference as statistically significant. A dropout rate of 15% has been anticipated. The sample size was calculated using GRANMO (version 8) [27], a general, independent power analysis program for commonly used statistical tests in research.

Description of the Intervention

Following the screening process, all eligible participants will undergo the intervention (Multimedia Appendix 1). The program consists of 4 VR sessions, each lasting 10 minutes, delivered once per week over a 1-month period. Sessions will take place in a safe, open space that allows for comfortable movement, with participants seated and supervised by trained nursing staff. Participants will use Conformité Européenne–marked NK VR headsets to access immersive 360° videos featuring passive, recreational content. These videos depict outdoor landscapes such as forests, beaches, mountains, and parks. A total of 10 distinct videos are available, and participants may choose freely among them and repeat any session if desired. The VR experience includes both visual and auditory elements to enhance the sense of presence and engagement. The intervention is standardized across all sessions and participants, ensuring consistency in delivery while allowing for individual preferences in video selection.

VR headsets will be disinfected between each use in accordance with institutional hygiene protocols to ensure participant safety and minimize the risk of cross-contamination.

To assess outcomes, participants will complete the World Health Organization Quality of Life of older adults (WHOQOL-OLD) questionnaire at 3 time points: baseline (preintervention), immediately postintervention, and at follow-up (3 - 5 mo after the intervention). This validated instrument serves as the primary measure of QoL in this study.

In addition, participants will complete the Rivas-Borda QoL Scale, an exploratory tool developed ad hoc for this project. This scale assesses 4 dimensions of quality of life—sociofamilial, physical, emotional, and cognitive—using a 4-level frequency rating (never/almost never, sometimes, frequently, always/almost always). Although not yet formally validated, the scale is theoretically grounded in established instruments such as WHOQOL-OLD [28], EQ-5D [29], and the 36-Item Short Form Health Survey [30]. Detailed information about the Rivas-Borda Scale is provided in Multimedia Appendix 2.

Study Variables and Data Sources

The primary outcome will be the difference in QoL scores before and after the intervention, measured using the Rivas-Borda QoL Scale.

The criteria used to establish QoL will be the following:

- Adequate level of QoL: 81 - 104 points
- Risk of QoL deterioration: 54 - 80 points
- Impaired QoL: 23 - 53 points

Independent variables included:

- Sociodemographic data included in the Rivas-Borda QoL Scale: gender (woman, man, or nonbinary), age (years), and marital status (single, widowed, married or with a partner living in the nursing home, married or with a partner not living in the nursing home)
- Satisfaction regarding the intervention, measured through a satisfaction questionnaire composed of a 3-question survey with 4 response options (Multimedia Appendix 3)
- Cognitive impairment, measured with the Pfeiffer Abbreviated Test
- Social resources, measured with the OARS

It is important to note that this information will be provided voluntarily by the older adult participants in the study and will

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be pseudonymized. Different variables are specifically detailed in Table S1 in Multimedia Appendix 4.

Statistical Analysis

Quantitative data following a normal distribution will be presented as means and standard deviations, while nonnormally distributed quantitative data will be expressed as medians and interquartile ranges. The normality of variables will be assessed using the Kolmogorov-Smirnov test. Categorical data will be reported as frequencies and percentages.

First, a descriptive analysis of the study population will be conducted. Then, comparisons will be made to evaluate changes in variables before and after the intervention within the same group (paired analysis). For nonnormally distributed variables or sample sizes smaller than 30, the Wilcoxon signed-rank test will be used. In contrast, the paired Student *t* test will be applied to variables that follow a normal (Gaussian) distribution.

Ethical Considerations

The study will be conducted in agreement with the principles of the Declaration of Helsinki and the guidelines of Good Clinical Practice. The Clinical Research Ethics Committee of the Primary Care Research Institute Jordi Gol (IDIAP Jordi Gol) (23/155P) approved this protocol. Data confidentiality will be protected by the Spanish law governing the protection of personal data (*Ley Orgánica de Protección de Datos de Carácter Personal y garantía de los derechos digitales*; 03/2018, of December 5). All participants will receive an information sheet from which they will be informed that their participation is anonymous, confidential, and voluntary and that they have the right to change their mind (not to participate) at any time up to data verification. Participants will be able to ask questions and receive clarification from the research team before deciding to participate. Verbal and written consent will be obtained from all participants to participate and be audio-recorded in the study. There will be no financial compensation for participation in the study.

All of the information from the study will be recorded consistently using a data collection questionnaire designed for this purpose. Each participant will be assigned a personal identification code upon inclusion. All information obtained will be stored using a digital application accessible only from the corporate intranet of the Catalan Health Institute in Tarragona. Access to this site is restricted and will be controlled by a personal password for each investigator, who will be responsible for data entry for all of the participants recruited. This data will not be publicly available, but the principal investigator may access it upon reasonable request and with the approval of the Research Ethics Committee for Human Subjects at IDIAP Jordi Gol. To disseminate the findings, a summary of the results will be emailed to the participants' residential centers and presented to the research teams. The findings will also be shared with the scientific community through peer-reviewed publications and conference presentations, and dissemination in nonspecialized settings is also planned.

Results

The study anticipates that VR interventions will significantly enhance the QoL of older adults, with expected improvements in cognitive engagement, emotional regulation, physical activity, and social participation [27]. Moreover, by introducing this technology, participants may gain confidence in interacting with digital tools, contributing to reduced technological apprehension and fostering broader digital inclusion.

This research has not received any specific grant funding from public, commercial, or nonprofit funding agencies as of December 2025. The research team will apply for specific funding opportunities. As of December 2025, the research team has conducted a pilot study with 22 participants. Preliminary data analysis has been completed, and the results are expected to be published during the first half of 2026.

Discussion

Rationale and Study Design

The study has been designed to address the often-overlooked aspect of QoL in older adults, emphasizing its importance across cognitive, physical, and emotional domains. By using VR technology, we seek to improve various dimensions of well-being, including cognitive, physical, and emotional domains. This approach aligns with recent research highlighting the potential benefits of VR in health care applications for older adults, such as cognitive stimulation, physical rehabilitation, and emotional well-being [31,32].

Furthermore, the research seeks to bridge the digital divide experienced by older adults by introducing and familiarizing them with new technologies, aiming to reduce the gap in digital literacy and promote a sense of empowerment and inclusion.

Strengths

One of the key strengths of this study is its focus on QoL, a critical factor that is often neglected in older adults despite its profound influence on several dimensions of well-being including cognitive, physical, and emotional. By introducing VR technology in a supportive environment, we aim to increase digital literacy and access to technological benefits among this demographic [32].

The use of VR also provides a safe and controlled setting for older adults to engage in activities that might otherwise be challenging or impossible in their daily lives, such as travel or physical exercise [33].

Another strength of our approach is the potential for VR to positively enhance the mental health of older adults, particularly those with cognitive impairments, by eliciting positive affective states and enhancing emotional regulation [34]. This intervention could significantly improve health-related QoL in this population.

Limitations

It is important to acknowledge the limitations of our study. First, the focus on a specific locality may limit the generalizability of our results to other geographic or cultural contexts.

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Additionally, there is a general lack of knowledge about the integration of VR in clinical contexts, which may pose challenges in the implementation and interpretation of results.

Previous research in this field has often been characterized by small sample sizes and controlled designs, with significant diversity in VR systems and content used across studies. This heterogeneity makes it difficult to draw direct comparisons between studies and underscores the need for more rigorous methodological approaches [35,36].

A significant challenge in implementing VR technology with older adults is the potential complexity of use, especially for those unfamiliar with such devices. Some participants may find it difficult to incorporate VR into their daily lives or to learn how to use it effectively [37]. This difficulty can lead to feelings of frustration or inadequacy, potentially impacting the overall experience and outcomes of the intervention.

A limitation of this study is the relatively short duration and low frequency of the intervention (four 10-minute VR sessions over one month). This intervention may not be sufficient to produce measurable or sustained improvements in multidimensional outcomes such as QoL. The decision to adopt this format was based on feasibility and safety considerations in an institutionalized older adult population, where tolerance and fatigue are relevant concerns. Nevertheless, future research should evaluate more intensive interventions, including multiple sessions per week over extended periods, as well as the inclusion of follow-up assessments (eg, 3 - 5 months postintervention) to better capture potential long-term effects.

Conclusion

This study aims to fill gaps in existing research by demonstrating the potential benefits of VR technology in improving QoL for older adults. The limitations identified highlight the importance of continued exploration and iterative development of VR tools. Efforts should also be directed toward ensuring accessibility and addressing usability challenges, thereby making these technologies truly inclusive and effective for this population.

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Data Availability

The data generated and analyzed during this study will not be deposited in a public repository due to privacy and ethical considerations related to the study population. However, the datasets will be made available upon reasonable request to the corresponding author. Requests will be evaluated to ensure compliance with ethical standards and data protection regulations.

Authors' Contributions

Conceptualization: DBF, SRL
Funding acquisition: CRR, FMML
Investigation: all authors
Methodology: SMT, CRR, FMML
Project administration: DBF, SRL, CRR
Resources: DBF, SRL
Supervision: SMT, CRR
Validation: SMT, CRR
Visualization: DBF, SRL
Writing – original draft: all authors
Writing – review & editing: all authors
All authors declare that generative artificial intelligence was not used at any stage in the preparation of this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
RATE-XR information.

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[DOCX File, 14 KB - resprot_v14i1e74298_app1.docx]

Multimedia Appendix 2
Rivas-Borda Quality of Life Scale.
[DOCX File, 18 KB - resprot_v14i1e74298_app2.docx]

Multimedia Appendix 3
Satisfaction questionnaire.
[DOCX File, 14 KB - resprot_v14i1e74298_app3.docx]

Multimedia Appendix 4
Table S1. Description of the variables and the source of information about the Rivas-Borda Quality of Life Scale.
[DOCX File, 15 KB - resprot_v14i1e74298_app4.docx]

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Abbreviations

OARS: Older Americans Resources and Services
QoL: quality of life
VR: virtual reality
WHOQoL-OLD: World Health Organization Quality of Life of older adults

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An eHealth and Health Literacy Educational Training to Support Older Patients With Type 2 Diabetes: Protocol for the JACARDI Interventional Study

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Abstract

Background: Type 2 diabetes is a prevalent chronic condition, particularly among older adults, and is associated with significant morbidity, mortality, and health care costs. Effective disease self-management is crucial for achieving glycemic control and preventing complications.

Objective: This pilot study aims to evaluate the effectiveness of a structured, 5-week training program in improving eHealth literacy among older adults with type 2 diabetes and to assess its impact on health literacy, self-efficacy, psychological well-being, and clinical outcomes.

Methods: In total, 200 community-dwelling adults aged ≥60 years with type 2 diabetes, a Mini-Mental State Examination score ≥24, a Geriatric Depression Scale score <9, and a low eHealth Literacy Scale score (≤29) will be recruited. Participants will attend five 90-minute weekly training sessions combining didactic and interactive modules focused on health literacy, diabetes self-management, and the use of digital tools. Assessments will be performed at baseline (T0), post intervention (T1), and at 1-month (T2) and 6-month (T3) follow-up. The primary outcome will be the change in eHealth literacy, as measured by the eHealth Literacy Scale, from baseline to post intervention. In addition, a wide range of secondary outcomes will be examined to capture the program's multidimensional impact: improvements in general health literacy, self-efficacy in diabetes management, psychological well-being, and quality of life; reductions in diabetes-related emotional distress, body weight, and BMI; and better metabolic control, as measured by hemoglobin A_{1c} and lipid profiles. Finally, participants' experiences, satisfaction, and perceived benefits will be explored to inform the future scalability and refinement of the program. A prestudy will be conducted, involving stakeholders, older adults, and caregivers, to refine the training content using co-design techniques. Descriptive statistics will be used to summarize sample characteristics. Preintervention and postintervention changes will be evaluated using 2-tailed paired *t* tests or their nonparametric equivalents, with repeated-measures models applied to follow-up data. A *P* value <.05 will indicate statistical significance.

Results: The prestudy phase began in April 2025. Improvements in both health literacy and eHealth literacy are expected to be observed among participants, as assessed through validated instruments administered before and after the intervention.

Conclusions: The Joint Action on Cardiovascular Diseases and Diabetes (JACARDI) study provides a structured and participatory approach to addressing the digital divide in chronic disease management among older adults. By focusing on personalized, evidence-based training, the study offers a promising model for empowering patients and improving health outcomes through enhanced digital and self-management competencies.

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KEYWORDS

eHealth literacy; health literacy; older people; type II diabetes; educational training; protocol; pilot study

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Introduction

Background

Diabetes is a chronic disease that affects people of all ages worldwide. It occurs when the pancreas does not produce enough insulin or when the body is unable to effectively use the insulin it produces. The former is known as type 1 diabetes, while the latter is known as type 2 diabetes. According to the World Health Organization (WHO), diabetes represents a global epidemic [1]. In fact, the number of people with diabetes has quadrupled since 1980 and is expected to continue growing. For example, in 2024, there were over 588 million individuals aged 20 to 79 years with diabetes worldwide, accounting for around 11% of all adults in this age group [2]. In Italy, slightly less than 5% of adults aged 18 to 69 years reported a diagnosis of diabetes in the biennium 2022 - 2023; this percentage rose to almost 9% among individuals aged 50 to 69 years [3].

Given the widespread and growing prevalence of diabetes, it is essential to consider not only its health impact but also its broader complications and economic consequences. Beyond its health implications, the rising prevalence of diabetes imposes a significant economic burden on health care systems, accounting for around 12% of the total global health spending [2]. Due to their complexity and long-term treatment needs, complications resulting from poor diabetes management, including cardiovascular disease, kidney failure, and amputations, significantly increase the financial pressure on health systems [4].

Therefore, investing in effective prevention, education, and management strategies is a public health and economic priority [5].

Furthermore, while premature mortality due to other major noncommunicable diseases is decreasing, early deaths due to diabetes are increasing: there was a 5% increase between 2000 and 2016. Missed diagnosis or inadequate management of diabetes can lead to serious risks of debilitating and irreversible complications, including severe damage to the heart, eyes, kidneys, and nerves, which increases the risk of limb amputation, vision loss, and premature death [1].

One of the most important behavioral and therapeutic goals in the treatment of diabetes is glycemic control, which is a major aspect for reducing morbidity and mortality in people with type 2 diabetes (the most common type) [6].

At the core of diabetes management, glycemic control primarily involves patient self-management [7], which is achievable when a person with diabetes acquires the necessary knowledge (such as healthy nutrition, physical activity, blood glucose monitoring, and adherence to medication) and skills (eg, problem solving and healthy coping mechanisms) for behavior modification to better cope with the disease [8,9]. All these self-management behaviors fundamentally rely on health literacy as a foundational skill, as the ability to access, understand, and apply health information determines how effectively people with diabetes can engage in prevention, treatment adherence, and long-term disease control [10].

Indeed, people with lower health literacy levels tend to experience poorer overall health, higher rates of hospitalization and mortality, a lower ability to manage chronic diseases, and higher health care expenditures. In contrast, those with higher health literacy levels have a higher probability of using available health care services and making well-informed health care decisions [11]. Therefore, while a low level of health literacy may hinder the development of diabetes self-management skills [12], a high level is associated with confidence in diabetes self-management [13].

In this regard, studies have shown that interventions can improve glycemic control, quality of life, diabetic complications [8], and knowledge and skills of diabetes management [14].

However, despite these proven benefits, access to structured and effective self-management education remains uneven and inadequate in many cases, particularly among the most vulnerable populations with low socioeconomic status, limited education, language barriers, or limited access to health infrastructure [15]. These individuals often face additional difficulties in acquiring, understanding, and applying health information and, as a result, may be less likely to engage in sustained self-care behaviors, adhere to treatment regimens, or benefit from early prevention strategies. Therefore, addressing these gaps is essential to ensure that self-management interventions reach their full potential in improving population-level disease control.

However, digital exclusion can contribute to health inequalities and poorer health outcomes, particularly affecting older adults, marginalized groups, and people with disabilities, who have fewer opportunities to access or use digital health platforms. In response, 75% of WHO European Member States with digital health strategies have prioritized improving digital literacy and ensuring equitable access to fast, safe, and reliable internet [16]. Therefore, addressing eHealth literacy and digital inclusion is important in supporting effective diabetes self-management.

Goal of the Study

This paper presents the protocol for the Joint Action on Cardiovascular Diseases and Diabetes (JACARDI) field trial, which aims to reduce the burden of cardiovascular disease and diabetes in European Union (EU) countries, at both the individual and societal levels. JACARDI is designed to integrate validated best practices and cost-effective interventions across countries and regions through transnational pilot initiatives, thereby complementing and reinforcing existing policies and programs. JACARDI will enhance cross-national collaboration, maximizing the exploitation of lessons learned through a clear strategy; engaging groups of interest; and promoting integration and sustainability of approaches to achieve high-level impact, including the implementation of effective interaction, cooperation, and cocreation between science and policy. In particular, this pilot study focuses on improving health literacy and awareness of cardiovascular disease and diabetes risks and risk factors, at both the individual and societal levels. It aims to reach people living with cardiovascular disease and diabetes and their care providers and to improve service pathways, self-management, and labor participation.

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Methods

Field Trial

The JACARDI trial is a multicenter study coordinated by the Istituto di Ricovero e Cura a Carattere Scientifico-Istituto Nazionale di Riposo e Cura per Anziani (IRCCS INRCA) and conducted also at the Clinic of Endocrinology and Metabolic Diseases of the Azienda Ospedaliero-Universitaria delle Marche. Adopting a blended approach combining didactic and interactive training, the study primarily aims to improve eHealth literacy in older adults with type 2 diabetes, thereby promoting independent living and reducing the risk of health deterioration and impaired quality of life. The study consists of five phases: (1) recruitment and screening, (2) baseline assessment (T0), (3) a 10-week educational intervention, (4) postintervention assessment (T1), and (5) follow-up evaluations at 1 month (T2) and 6 months (T3).

Prior to the trial, a prestudy will be conducted to co-design and finalize the training content. A group of volunteers whose characteristics are similar to those of the target population will participate in focus groups to refine the training content and practical aspects prior to recruitment. The protocol was developed in accordance with the SPIRIT guidelines (Checklist 1).

Figure 1 shows the design of the JACARDI study.

Figure 1. Flowchart of the study design, illustrating the screening process, the intervention and follow-up assessments, and the final sample analyzed.

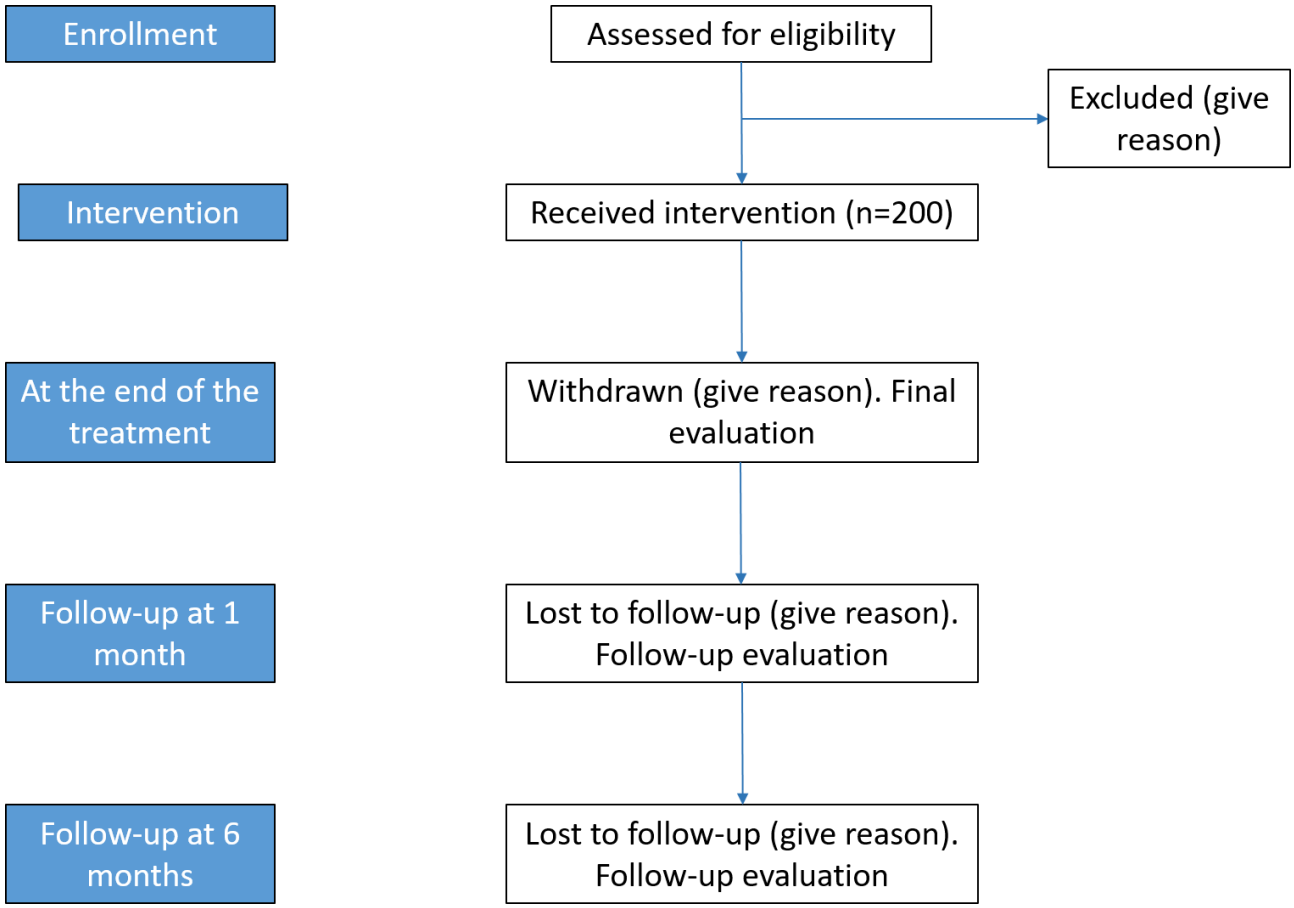

Prestudy Phase for Refinement of the Training Content

To evaluate the core concepts, strategies, and format for the pilot study, a preliminary prestudy will be conducted with a range of stakeholders, as outlined below:

1. Context analysis: A total of 10 semistructured interviews will be conducted with local experts (ie, service providers, regional and local policymakers, facility managers, and nongovernmental organizations) and health professionals (ie, medical doctors, nurses, psychologists, dietitians, and physiotherapists) to identify the enablers of and potential barriers to the pilot implementation, on the basis of the Consolidated Framework for Implementation Research (CFIR).
2. Focus groups: Two focus groups, each comprising 10 older adults, and one focus group consisting of 10 informal caregivers (not necessarily linked to the patients participating in the study) will be conducted to assess the validity of the proposed training concepts. Co-design techniques such as 6-3-5 brainwriting, simplified scoring, and open discussion will be used to refine the training content and practicalities.

The focus groups and interviews will be audio-recorded and subsequently transcribed in full. Then, the transcripts will be coded and analyzed using thematic analysis to identify key patterns and themes. Two researchers who will compare and discuss their findings to ensure consistency and credibility will collaboratively conduct the analysis and interpretation of results. Any discrepancies in interpretation will be resolved through

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discussion with a third senior researcher. The involvement of participants with a range of roles will contribute to the validity of findings. These procedures will enhance the rigor and trustworthiness of the co-design phase.

Indeed, the results of the prestudy phase will facilitate the refinement of the training sessions' core content, which will be assessed through the pilot intervention. Specifically, the content, format, and delivery methods of the intervention will be adapted according to the themes that emerge from the focus groups and interviews. This will ensure that the final program reflects the needs, preferences, and lived experiences of the target population and stakeholders. The inclusion and exclusion criteria set for the JACARDI trial will be adopted in the prestudy phase as well, with the objective of involving older patients who exhibit the same characteristics as those in the final trial. Regarding caregivers and other stakeholders such as policymakers, there are no specific criteria in place other than being a carer of a diabetic person and working in the health policy sector, respectively.

Participant Recruitment

The recruitment will be conducted in the selected centers under the coordination of the IRCCS INRCA. Following a 2-week reflection period, individuals who confirm their wish to participate in the research in writing or verbally, after having read the information letter and the consent form received by email, will be invited by the investigator to consult a doctor in the 3 months preceding the start of the research. The doctor volunteering to carry out the inclusion visits will first provide the participant with the information letter and 2 consent forms. After the participant and the doctor carefully read and sign the consent forms, the doctor will use anamnesis, the Mini-Mental State Examination (MMSE), the Geriatric Depression Scale (GDS, 5-item version), and the eHealth Literacy Scale (eHEALS) to ascertain the participant's eligibility for the research study. This medical examination will take place before the study begins. Participants who sign the consent form but for whom the fulfillment of the inclusion criteria is not confirmed by the doctor will not be included in the research.

To ensure participants' ability to engage actively in the training activities and complete the assessments, certain criteria were applied to assess cognitive health (MMSE score ≥24) and physical health (eg, absence of severe mobility limitations, advanced neurodegenerative diseases, or significant sensory impairments). These requirements are intended to minimize participant burden, ensure safety during in-person group sessions, and reduce attrition due to difficulties in attending sessions or completing questionnaires. While this approach improves the internal validity and feasibility of the pilot implementation, it may limit the representativeness of the sample with respect to the broader population of older adults with type 2 diabetes. The inclusion and exclusion criteria are reported in Textbox 1.

Textbox 1. Inclusion and exclusion criteria for patients.

Inclusion criteria

- Age ≥60 years
- Capacity to consent
- With type 2 diabetes
- eHealth Literacy Scale (eHEALS) score ≤29 (validated cutoff for low eHealth literacy [17])
- No acute or untreated medical problems
- Mini-Mental State Examination (MMSE) score ≥24 (validated cutoff for cognitive function [18])
- Geriatric Depression Scale (GDS) score <2 (validated cutoff for depressive symptoms [19])

Exclusion criteria

- Failure to meet the inclusion criteria
- Simultaneous participation in other studies
- Lack of written informed consent
- History of a myocardial infarction or stroke within the past 6 months
- Painful arthritis, spinal stenosis, amputation, painful foot lesions, or neuropathy, limiting balance and mobility
- Uncontrolled hypertension
- Advanced Parkinson disease or other neuromuscular disorder
- Diagnosis of metastatic cancer or treatment with immunosuppressive therapy
- Significant visual or hearing impairment

Following the medical visit, the investigator will contact the potential participant by email or telephone to discuss the study and confirm their interest in participation. At this stage, detailed information about the study procedures will be provided, and written informed consent will be obtained before any study-related activities are initiated. The schedule for the visits and the procedures for conducting the research at the participant's home will then be agreed upon according to

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participant availability. When recruitment is complete, participants included in the study will undergo all routine clinical investigations, such as collection of blood samples to assess their glycemic and lipid profiles and measurement of BMI. In addition, a researcher will perform the preliminary evaluation (T0). The scales described in Textbox 2 will be administered, and then an interview will be conducted. The participant will undergo training sessions at the study centers with the other study participants. After 10 weeks, the final evaluation will be conducted (T1). Participants will be required to complete a series of questionnaires, the details of which can be found in Table 1. During this phase, blood sample collection and BMI measurement will not be performed.

During the 2 follow-up visits (1 month and 6 months following the conclusion of the intervention), any alterations in the patient's medical history will be recorded. All routine clinical investigations and all planned assessment scales will be administered. Blood sample collection to assess the glycemic and lipid profiles and BMI measurement will be performed exclusively at T3.

Textbox 2. Outcomes of the study.

Primary outcomes

- Improvement in eHealth literacy, assessed using the eHealth Literacy Scale (eHEALS) [17]

Secondary outcomes

- Improvement in self-efficacy, evaluated using the Diabetes Management Self-Efficacy Scale (DMSES) [20]
- Reduction in emotional distress related to diabetes, measured using the Problem Areas in Diabetes Questionnaire (PAID) [21]
- Improvement in psychological well-being, assessed using the Psychological Well-Being Scale (PWB) [22]
- Improvement in quality of life (QoL), assessed using the EQ-5D-5L Visual Analog Scale (VAS) [23] and 12-item Short Form Health Survey (SF-12) [24]
- Reduction in body weight (measure routinely collected at the Diabetology Unit)
- Reduction in BMI (measure routinely collected at the Diabetology Unit)
- Improvement in the glycemic profile (glycated hemoglobin; measure routinely collected at the Diabetology Unit)
- Improvement in the lipid profile (directly related to cardiovascular risk; measure routinely collected at the Diabetology Unit)
- Collection of information about the participants' experience with the training, their level of satisfaction, any benefits they have experienced, and any improvement suggestions, using an ad hoc questionnaire
- Improvement in health literacy, assessed using the 16-item European Health Literacy Survey Questionnaire (HLS-EU-Q16) [25]

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Table . Tools and dimensions of the protocol.

Dimension	Tool	R[a]	T0[b]	T1[c]	T2[d]	T3[e]
Cognitive status	MMSE[f]	X	—[g]	—	—	—
Psychological status	GDS[h] 5-item version	X	—	—	—	—
General information	Sociodemographic questionnaire	X	—	—	—	—
Quality of life	EQ-5D-5L VAS[i], SF-12[j]	—	X	X	X	X
Psychological well-being	PWB[k] (18 items)	—	X	X	X	X
eHealth literacy	eHEALS[l]	X	—	X	X	X
Health literacy	HLS-EU-Q16[m]	—	X	X	X	X
Diabetes-related emotional distress	PAID[n]	—	X	X	X	X
Self-efficacy	DMSES[o]	—	X	X	X	X
Training experience	Ad hoc questionnaire	—	—	—	—	X

[a]R: recruitment.
[b]T0: first evaluation.
[c]T1: final evaluation.
[d]T2: follow-up 1 month after the end of the training.
[e]T3: follow-up 3 months after the end of the training.
[f]MMSE: Mini-Mental State Examination.
[g]not applicable
[h]GDS: Geriatric Depression Scale.
[i]VAS: Visual Analog Scale.
[j]SF-12: 12-item Short Form Health Survey.
[k]PWB: Psychological Well-Being Scale.
[l]eHEALS: eHealth Literacy Scale.
[m]HLS-EU-Q16: 16-item European Health Literacy Survey Questionnaire.
[n]PAID: Problem Areas in Diabetes Questionnaire.
[o]DMSES: Diabetes Management Self-Efficacy Scale.

Intervention Through Training

The training is structured as a blended program combining didactic and interactive educational methods, designed to strengthen health and eHealth literacy and to support diabetes self-management in older adults. The program is organized into 5 modules over a 10-week period (1 session every other week). The average duration of each session will be 90 minutes. Active engagement will be encouraged throughout the sessions, with participants involved in discussions, scenario-based activities, and guided reflection. This approach aims not only to promote meaningful learning but also to foster confidence, autonomy, and sustainable behavioral change in managing type 2 diabetes. The overarching objectives of the training program are grounded in the three key learning competencies outlined by the European Qualifications Framework, which are articulated through the following three dimensions:

1. Knowledge: The program aims to cultivate awareness and critical understanding regarding health and eHealth literacy. The objective is to empower participants with comprehensive knowledge of health-related issues and eHealth literacy challenges. By delving into these subjects, participants will grasp their significance and explore effective strategies for addressing them.
2. Skills: The training is designed to equip older adults with advanced skills that are specifically tailored to their interactions with digital tools in the context of health and eHealth literacy. Through personalized instruction, participants will be equipped with the necessary capabilities to navigate digital platforms effectively, thereby fostering proficiency in the use of these tools to enhance health literacy among older adults.
3. Competencies: The program is committed to ensuring the sustainability of the skills acquired during the training and their practical application in real-world scenarios. Beyond mere knowledge acquisition, the objective is to catalyze meaningful behavior change. The training environment is designed to encourage the adoption, adaptation, and

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maintenance of positive behavioral habits, thereby addressing health and eHealth literacy challenges comprehensively.

The training program is divided into the following modules:

1. Module I: raising awareness of eHealth and health literacy: introduction to the aims and context of JACARDI and diabetes
2. Module II: achieving new knowledge: health literacy and self-management of diabetes
3. Module III: achieving new knowledge: technological and nontechnological strategies to support the self-management of diabetes
4. Module IV: practicing new skills: usability with practice session
5. Module V: self-evaluation and sustainability of the improvement (final questionnaire)

Module I aims to enhance participants' awareness of the importance of eHealth and health literacy, highlighting their crucial role in managing type 2 diabetes among older adults. To this end, the module is divided into two distinct parts: a lecture session and a group discussion. The first part focuses on analyzing the definition and relevance of eHealth and health literacy, highlighting the difficulties older adults may encounter in adopting digital tools for health care. An overview of the Italian initiatives and projects that focus on the digitization of health care services for older adults is also provided. Particular attention is paid to the obstacles to implementation, such as regulatory issues, privacy concerns, economic sustainability, and challenges posed by multimorbidity. The use of practical examples and short demonstrations facilitates the understanding of the theoretical concepts. The second part of the module consists of a group discussion, during which participants will be invited to reflect on and share their opinions on the role of technology in health care. This part of the module employs guided discussion techniques and real-world scenarios to encourage dialogue on the acceptance or rejection of technological tools and to identify the main barriers to access. The barriers include motivational limitations, deficiencies in digital skills, material constraints, and usability challenges. This configuration facilitates the learning process, combining a solid theoretical foundation and practical activities, emphasizing the direct correlation between learning objectives and final outcomes.

Module II aims to address issues related to improving self-management and health literacy among older adults with type 2 diabetes, foster a greater understanding of the disease, and support the adoption of effective strategies for the daily management of type 2 diabetes. The session is structured around interactive lessons that offer participants the opportunity to learn fundamental information about the disease and prevention of its negative consequences. During the first part, definitions and guidelines will be shared on key topics such as treatment management, importance of physical activity, adoption of a personalized nutritional plan, and diabetic foot care. The goal of this phase is to reduce inadequate health literacy, which is often associated with difficulties in understanding medical information, limited knowledge of the disease, poor adherence to treatment, worsening health, and increased costs. Classes will include hands-on demonstrations and the use of concrete examples to facilitate learning and make complex medical concepts more accessible. The second part of the session is structured as a group discussion moderated by a clinical psychologist. In this context, participants will have the opportunity to share and discuss the most common obstacles and fears encountered in the diabetes management journey as well as to discuss concerns about the consequences of the disease and the impact of the diagnosis on their lives. The methodology adopted, which is based on real-world scenarios and direct comparison, helps foster behavioral change, sustain motivation, and promote practical strategies for successfully addressing everyday challenges.

Module III is designed to assist older patients with type 2 diabetes in acquiring and understanding the concepts of health literacy and eHealth literacy. The objective is to support them to make more informed health decisions and use digital tools effectively for their physical and mental well-being. The module combines a theoretical component with a practical experience. Initially, the key concepts, the available resources, and the relevant associations and stakeholders, including peer support groups, will be presented and discussed. The goal is to demonstrate to the participants the range of technological and nontechnological strategies that are effective in enhancing eHealth skills and facilitating diabetes management. The teaching methods adopted include interactive presentations, guided discussions, and hands-on activities. The digital applications selected for the program are chosen on the basis of a preliminary study that evaluated their ease of use and reliability using focus groups and interviews. During the practical session, participants will engage in exercises designed to select safe and intuitive digital apps, with the aim of promoting a more autonomous and informed approach to managing their health. The learning-by-doing methodology will enable participants to directly test practical tools, verify their functionality, and gain greater confidence in using digital technologies, integrating these skills into their daily diabetes management. This approach facilitates the integration of digital solutions into participants' daily routines, optimizing health management practices and fostering the development of skills useful for greater autonomy and decision-making capacity.

Module IV explores the pivotal concept of usability in the context of digital and technological devices and services, with the aim of raising awareness of interaction with technology among older patients with type 2 diabetes. The session is designed as a lecture, with the objective of conveying to participants the idea that technology is not inherently good or bad in itself. Rather, shortcomings in the usability of tools are often the main cause of frustration and, consequently, rejection. The module focuses on the most common difficulties and errors in using technology, assisting participants in distinguishing between issues stemming from insufficient digital skills and limitations related to the usability of a tool or service. The methodology combines theoretical explanations and practical activities. In the final part of the module, participants will engage in a practical usability test, with a focus on frequently used digital platforms, such as those employed for scheduling

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medical appointments, which are particularly relevant to the health care needs of older people. This exercise enables participants to directly experience the main usability issues encountered on these platforms, addressing the difficulties that can arise in everyday life. Through a problem-solving approach, participants will identify the most common obstacles in interacting with technology and acquire strategies to overcome them, thus improving their independence and effectiveness in using digital services. By actively participating in the hands-on exercise, patients will refine their abilities in navigating digital platforms, thereby fostering a more informed and constructive interaction with technology. This contributes not only to more independent management of digital services but also to improved health care and monitoring.

Module V is designed to encourage participants to self-reflect, with the objective of evaluating their level of awareness, knowledge, and skills in technology and digital health literacy. This session represents the final stage of the training program, including a component dedicated to evaluating the effectiveness of the educational activities and methods used during the program. The method adopted involves a trainer guiding participants through the completion of the final questionnaire, explaining its characteristics and providing practical support during the completion. During this phase, participants will complete a series of validated instruments, described in detail in the Results section of the protocol, which will measure changes in quality of life, psychological well-being, health literacy, eHealth literacy, self-efficacy, and diabetes-related distress. The use of standardized scales ensures that the assessment is measurable and comparable across multiple time points, thereby providing clear indicators of the program's effectiveness. This quantitative evaluation is complemented by a final discussion, in which participants' reflections, feedback, and suggestions for maintaining the skills acquired will be collected. Consequently, the evaluation process evolves from a mere descriptive exercise to one that is also actionable, as the collected data will be systematically analyzed and used to identify strengths and areas for improvement, guiding the refinement of future training cycles. The module includes instructions for completing the questionnaire, reflecting on personal progress in relation to the training objectives, and receiving constructive feedback. By actively participating in this self-assessment process, participants will have the opportunity to strengthen their digital and health literacy skills, while trainers will use the information gathered to optimize future training initiatives and ensure continuous improvement of digital health literacy interventions. In this manner, the program combines theory and practical application to foster ongoing change and hold participants accountable for their learning journey.

The training sessions will be facilitated by a multidisciplinary team of health care professionals and educators with expertise in diabetes management, health literacy, and digital health. The trainers will generally include doctors, nurses, dietitians, and clinical psychologists, each with previous experience in patient education and group facilitation. At each center, depending on the staff present and the topic of the session, the facilitators may vary.

To ensure consistency and fidelity across sessions and locations, the coordination center will be responsible for the preparation of all training materials, including manuals, slides, and practical exercises. These materials will be disseminated to all locations before the program begins. In addition, online and in-person familiarization sessions will be conducted for all trainers to review content, clarify any questions, and practice delivering the modules. This will ensure that all trainers are familiar with the course materials. Trainers will also receive guidance on specific strategies for addressing particular issues, such as managing emotional challenges or promoting autonomy, to maintain a supportive approach throughout the program. These sessions are designed to ensure that training is conducted in the same way across all centers, while still allowing trainers to adapt to the needs of participants.

Outcomes

The primary end point of the study is defined as an improvement in eHealth literacy following the implementation of the training program, scheduled to span a period of 10 weeks, as described in Textbox 2. Then, the field trials will focus on improvements in health literacy, self-efficacy, psychological well-being, and quality of life, in addition to glycemic and lipid profiles. Moreover, the study aims to minimize emotional distress and reduce body weight and BMI, as shown in Textbox 2.

For these reasons, the protocol includes study-specific questions on demographics, emotional distress, psychological well-being, and physiological aspects. All scales used in the study have been validated in the languages of the pilot sites and are deemed suitable for administration to the patients enrolled in the study. Data will be collected at baseline (T0), immediately post intervention (T1), and at the 1-month (T2) and 6-month (T3) follow-up visits, as detailed in Table 1.

Statistical Analysis

The eHEALS score was used for sample size calculation. Specifically, the sample size was determined using the combination of a pilot study [26] and a larger study [27].

In the first case, considering a 1-tailed *t* test for paired samples in which the primary outcome eHEALS score varies from a mean of 24.3 (SD 8.9) to 28.4 (SD 8.1) [26], corresponding to an effect size of 0.48, an α error of .05 and a power of 90%, the sample size should be 39 participants. Considering a dropout rate of 15%, the sample size increases to 45 participants. While larger effect sizes reported in the literature [27] would suggest even smaller sample sizes, we decided to include 200 participants for several reasons: (1) to ensure robust and generalizable results across a diverse population of older adults with type 2 diabetes, (2) to account for potential variability in baseline eHealth literacy and other characteristics, (3) to maintain statistical power for secondary outcomes and subgroup analyses, and (4) to address existing gaps in the literature by providing sufficiently powered evidence on the efficacy of the intervention.

The initial phase of the data analysis will entail the description of the sample. Continuous variables will be reported as either the mean and SD or the median and IQR on the basis of their distribution (assessed using Kolmogorov-Smirnov test).

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Categorical variables will be expressed as an absolute number and percentage. In the context of group comparisons, continuous variables will be compared using independent or 2-tailed paired *t* tests for normally distributed data and Mann-Whitney *U* or Wilcoxon signed-rank tests for nonnormally distributed data, whereas categorical variables will be compared using chi-square or Fisher exact tests, as appropriate. A significance level of $P<.05$ will be applied. Corrections for multiple comparisons (eg, the Bonferroni or Holm method) will be applied where necessary. The results will be compared with the data from the other partner countries. Descriptive statistical analyses will be performed on the quantitative data with SPSS software (version 29.0.1.0; IBM Corp) or Rstudio (version 4.4.1; Posit PBC).

Ethical Considerations

The Marche Territorial Ethics Committee (CET MARCHE) approved the study on June 27, 2024 (Prot. INRCA 23332). The study protocol was registered on ClinicalTrials.gov (NCT06904690).

The study adheres to the principles of the Declaration of Helsinki and Good Clinical Practice guidelines [28,29]. All participants in this study will be required to provide written informed consent. Personal data collected during the trial will be handled and stored in accordance with the General Data Protection Regulation (GDPR) 2018 [30]. To this end, data will be anonymized at the end of the study. The use of the study data will be controlled by the principal investigator. All data and documentation related to the trial will be stored in accordance with applicable regulatory requirements, and access to the data will be restricted to authorized study personnel. The consent form includes detailed information on study procedures, risks and benefits, data protection and storage, right to withdraw or request erasure of personal data, and the possibility of data being used in anonymized form for future research, in line with the EU Open Research Data guidelines.

Data Management and Protection

Personal identifiers will be stored separately from the research data and pseudonymized at the time of collection. The pseudonymized datasets will be stored on secure institutional servers with password-protected access restricted to authorized study personnel only. Screening data will be discarded at the conclusion of the project, and research data will be anonymized and made openly available for secondary analyses 3 years after project completion, in accordance with the EU Open Research Data requirements. Participants will be informed of their rights to access, correct, withdraw, or erase their data at any time.

Study oversight will be provided by the principal investigator and the ethics committee. Participants will be monitored throughout the intervention period, and any adverse events or protocol deviations will be documented and reported to the ethics committee according to institutional procedures.

Results

The recruitment process is scheduled to start in September 2025 and will continue until September 2026. The prestudy phase, aimed at evaluating the core concepts, strategies, and format designed for conducting the pilot study and refining the training content, began in April 2025. The rating scales used are shown in Table 1, grouped by study phase. Improvements in both health literacy and eHealth literacy are expected to be observed among participants, as assessed through validated instruments administered before and after the intervention. Enhancements in diabetes self-management behaviors, such as medication adherence, dietary habits, and glucose monitoring, are also anticipated. Moreover, an increased level of literacy is expected to result in greater self-efficacy and confidence in the use of digital health tools. Positive changes in psychosocial outcomes, including quality of life, perceived autonomy, and reduction in diabetes-related distress, are also expected. These outcomes will be systematically evaluated as part of the JACARDI study, providing comprehensive evidence on the effectiveness of the intervention and its impact on the health literacy, self-management, and psychosocial well-being of older adults.

Discussion

The JACARDI pilot study addresses a critical public health concern, namely the management of type 2 diabetes in older adults, through the enhancement of eHealth and health literacy. The study design integrates a robust evidence-based rationale with a comprehensive, blended educational intervention that is innovative both in its methodology and in its participatory, patient-centered approach.

By focusing on older adults with low eHealth literacy, the project targets a particularly vulnerable population often excluded from digital health innovations due to age-related barriers, cognitive limitations, and digital divides. it is an established fact that older adults with low eHealth literacy often encounter significant barriers such as unfamiliarity with technology, limited access to devices or internet, and low confidence in navigating digital platforms. This population is frequently underrepresented in digital health initiatives, despite bearing a significant disease burden and having the greatest potential to benefit from accessible, supportive interventions. Addressing these disparities is crucial for ensuring that technological advances in health care do not widen existing health inequities. The modular approach allows for the gradual development of knowledge, skills, and behavioral competencies required for the autonomous management of chronic conditions.

The inclusion of a prestudy phase involving stakeholders and potential beneficiaries allows for co-design and adjustment of the training materials, thereby increasing the relevance, usability, and acceptability of the intervention. Additionally, the training content includes not only theoretical and technical skills but also emotional and motivational components that are critical for sustaining long-term behavioral change. The modules encompass not only disease-specific knowledge but also stress management strategies and coping techniques to enhance behavioral change. Special attention has been paid to promoting self-efficacy, with activities designed to increase self-confidence and reduce anxiety when using digital tools.

From a methodological point of view, the study adopts a robust evaluation framework using validated tools and multiple follow-up time points, thereby enabling both short-term and midterm outcome monitoring. The use of both subjective (eg,

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questionnaires) and objective (eg, glycemic and lipid profiles) measures allows for a multidimensional evaluation of the intervention's impact.

However, it is important to acknowledge some limitations. This being a pilot study, the generalizability of the results may be constrained by the specific characteristics of the local settings and participants. Moreover, despite efforts made to personalize the intervention, its scalability across different health care systems and sociocultural environments may require further adaptations. Potential barriers include disparities in digital access or digital literacy among older adults, as well as local infrastructure constraints that may affect intervention delivery. To address these issues, the study will employ a blended training format combining digital and in-person components and provides technical support and guidance to participants. Feedback will be collected to inform future adaptations for broader implementation. In addition, the exclusion criteria—particularly the exclusion of individuals with severe mobility limitations, advanced Parkinson disease, and significant visual or hearing impairment—may restrict the external validity of the findings. The establishment of these criteria was deemed necessary to ensure the attendance of all participants to the requisite training sessions and to facilitate their effective engagement with the digital tools that will be introduced. Nevertheless, they also exclude subgroups that may be among the most vulnerable to poor digital health engagement. It is recommended that future studies consider tailored strategies (eg, home-based or caregiver-assisted training, accessible digital interfaces) to reach these populations and evaluate whether adapted interventions can address their specific needs.

Despite these challenges, the JACARDI pilot study represents a valuable contribution to the growing field of digital health literacy and chronic disease self-management.

The JACARDI pilot project is designed to provide valuable insights for future large-scale interventions aimed at reducing health inequalities among older adults with type 2 diabetes. The integration of digital health literacy into chronic disease management has the potential to foster greater patient accountability, improve self-care practices, and contribute to reducing the burden on health care systems. Should this approach prove effective, it could be replicated and adapted to different settings, thereby supporting ongoing efforts to transform health literacy principles into patient-focused interventions. Further research is required to assess the long-term sustainability, clinical effectiveness, and cost-effectiveness of these programs, as well as their potential introduction into routine care.

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Data Availability

The datasets generated during this study are available from the corresponding author on reasonable request.

Authors' Contributions

RB and EM led the writing of the manuscript; CG, TE and FL reviewed and edited the manuscript; RB, ET, and PML designed and developed the methodology; RB was responsible of the study protocol in Italy; ARB registered the protocol on clinicaltrials.gov; RM and AM contributed to the data management in the protocol.

Conflicts of Interest

None declared.

Checklist 1
SPIRIT checklist.
[PDF File, 515 KB - resprot_v14i1e78254_app1.pdf]

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Abbreviations

CFIR: Consolidated Framework for Implementation Research
eHEALS: eHealth Literacy Scale
EU: European Union
GDPR: General Data Protection Regulation
GDS: Geriatric Depression Scale
IRCCS INRCA: Istituto di Ricovero e Cura a Carattere Scientifico - Istituto Nazionale di Riposo e Cura per Anziani
JACARDI: Joint Action on Cardiovascular Diseases and Diabetes
MARCHE: Marche Territorial Ethics Committee
MMSE: Mini-Mental State Examination
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
T0: first evaluation
T1: final evaluation
T2: follow-up 1 month after the end of the training
T3: follow-up 3 months after the end of the training
WHO: World Health Organization

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Impact of a Multicomponent Intervention to Build Capacity of Public Health Workers to Make Algorithmic Diagnosis and Management of High-Risk Pregnancies in Uttar Pradesh, India: Protocol for a Matched-Control, Before-After, Quasi-Experimental Study With a Mixed Methods Design

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Abstract

Background: In India, 20% - 30% of pregnancies are high-risk, contributing to 75% of perinatal mortality and morbidity. An effective approach to reduce this mortality and morbidity is early identification, effective management, and timely referral of high-risk pregnancies (HRPs). The Integrated High-Risk Pregnancy Tracking and Management program aims to enhance the capacity of auxiliary nurse midwives (ANMs), medical officers (MOs), and specialist gynecologists by (1) providing algorithmic, color-coded, detailed yet simple HRP protocols, customized for each role; (2) offering live training; (3) delivering digital training and handholding; and (4) tracking management details for HRPs. Equipping health workers (HWs) with these interventions supports early identification, effective management, and timely referral of HRPs, ultimately improving primary care and enhancing satisfaction of mothers with HRPs. These interventions are implemented in the intervention arm for over 18 months. During this time, HWs of intervention and control arms will continue to receive routine training through state and national programs, and pregnant women of both arms have access to standard maternity services.

Objective: At the system level, the program evaluates the impact on the knowledge and skills of HWs in diagnosing and managing HRPs. At the community level, it assesses translation of this knowledge into practice in terms of early diagnosis and protocol-based management of women with HRPs.

Methods: The program will be implemented in 2 intervention (Sambhal and Shravasti) and 2 matched control districts (Budaun and Gonda) of Uttar Pradesh, on 6 HRPs. The study uses a “quasi-experimental, before-and-after design” with intervention and control arms. However, the impact of the program will be assessed only on 3 HRPs: moderate or severe anemia, pregnancy-induced hypertension, and antepartum hemorrhage. System-level impacts will be assessed through qualitative data from district officials, specialist gynecologists, MOs, and ANMs at baseline and end line. The community-level impacts will be assessed by comparing quantitative data from recently delivered women at baseline and end line. Community-level impact assessed using the difference-in-difference (DiD) technique. The study received ethical approval.

Results: By November 2024, all the ANMs, MOs, specialist gynecologists, staff nurses, and community health officers in 2 intervention districts were trained on 6 HRP protocols, after the protocols were vetted by the Government of Uttar Pradesh. A digital learning tool and WhatsApp-based support system were introduced to facilitate continued learning and handholding of ANMs in managing HRPs and to address queries. Baseline data were collected from 2 arms during June-October 2024.

Conclusions: This trial will provide valuable insights into the feasibility and effectiveness of the program at system and community levels in an emerging state like Uttar Pradesh. These insights can feed into capacitating HWs across all the districts and support expansion of the program to include additional HRPs, with significant potential for improving maternal and neonatal outcomes.

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KEYWORDS

antenatal care; before-after; capacity building of health workers; diagnosis and management; high-risk pregnancies; impact of program; intervention control arm; quasi experimental

Introduction

Overview

Most maternal health complications that lead to maternal or newborn death develop during pregnancy, and with quality antenatal care (ANC), most of these complications can be prevented or treated [1]. Although the goal is to ensure a nonproblematic pregnancy, all pregnancies carry some risk. Pregnancy risks are categorized as low, moderate, and high risk [2]. A high-risk pregnancy (HRP) is defined as one that is complicated by factors that adversely affect the pregnancy outcome (maternal, perinatal, or both). An HRP may result from conditions that exist either before pregnancy (eg, diabetes and hypertension) or complications from a previous pregnancy, or conditions that develop during pregnancy or delivery [3].

Globally, around 20 million pregnancies are classified as high-risk, leading to approximately 800 maternal deaths per day [4], and over 70% of maternal deaths are because of complications of pregnancy and childbirth, such as hemorrhage, hypertensive disorders, sepsis, and abortion [5]. Excluding moderate anemia, 30%‑37% pregnancies globally can be classified as high-risk, accounting for 70%‑80% of perinatal mortality and morbidity [6]. In India, 20%‑30% pregnancies are high-risk and are responsible for 75% of perinatal morbidity and mortality [7]. According to a recent (2019‑2020) analysis in India, prevalence of HRPs was 49.4%, with 33% having single high-risk condition and 16.4% having multiple high-risk conditions [8]. Prevalence of HRPs across different states ranges from 18% to 59% [9-12], perhaps due to differences in estimation methods. According to the National Family Health Survey (NFHS)-5 (2019‑2021) estimate, 59% of Indian women were anemic. Despite high levels of anemia, only 44% of pregnant women consumed the recommended dose of iron-folic acid (IFA) for 100 days [13]. The only effective approach to reducing maternal and neonatal mortality and morbidity resulting from HRPs is early identification, timely referral, and efficient management throughout pregnancy before conditions progress to a critical stage.

In India, particularly in rural areas, routine ANC, including HRP identification, management, and referral, is provided at 3 primary care facilities: (1) health subcenters (HSCs) managed by auxiliary nurse midwives (ANMs), (2) primary health centers (PHCs) by medical officers (MOs), (3) and community health centers (CHCs) by specialist gynecologists, while women with HRPs are mostly referred to advanced centers in cities. Textbox 1 lists the responsibilities of ANC providers. The HSCs primarily provide ANC and birthing services; PHCs provide either basic emergency obstetric and newborn care (BEmONC) or only birthing services; and CHCs, although, are supposed to provide comprehensive emergency obstetric and newborn care (CEmONC), mostly provide BEmONC or even less. These facilities primarily focus on child birthing services and fail to address management of complications in early pregnancy [14]. Also, there are gaps in knowledge of emergency treatment for obstetric complications during pregnancy and prereferral first aid. Staff generally lack confidence and do not have adequate resources to manage obstetric complications [15]. Staff nurses, posted at PHCs and CHCs, have a limited role in decision-making when it comes to managing these complications. However, all the staff desire skill building, mentoring, moral support, and motivation [15]. Studies have identified deficits in maternal and newborn-related skills among ANMs, highlighting the need to strengthen their skills, especially through in-service training [16]. In addition to these gaps, there is often a confusion regarding the individual roles of the ANM, MO, and specialist gynecologist in managing HRP conditions, resulting in many pregnant women falling through the gaps in the system after being diagnosed with an HRP condition. With limited or no resources to manage HRPs, staff in these 3 settings should be highly competent in prevention, risk assessment, stabilization of complicated HRPs, and arranging transfer and care at functional higher referral levels [17].

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Textbox 1. Responsibilities of antenatal care (ANC) providers.

Auxiliary nurse midwives (ANM)

- Placed at health subcenter (1 per 5000 population; 3000 in tribal areas).
- Provides ANC, vaccinations, iron supplements, safe deliveries, postnatal care, newborn immunization, and family planning.
- Identifies high-risk pregnancies, facilitates referrals, and maintains health records.

Medical officers

- Placed at primary health center (1 per 30,000 population).
- Supervises ANMs and nurses, conducts ANC, manages pregnancy complications, performs normal deliveries, and handles obstetric emergencies.
- Initiates referrals, administers life-saving treatments, and supports family planning services.

Specialist gynecologists

- Placed at community health centers (1 per 120,000 population) and district hospitals.
- Manages high-risk pregnancies, performs cesarean sections, and handles obstetric emergencies.
- Provides specialized ANC, supervises labor, trains staff, and ensures quality maternal care.

Accredited social health activist

- Placed at the village level (1 per 1000 population).
- Mobilizes pregnant women for ANC, institutional deliveries, and immunization. Educates on nutrition, danger signs, and family planning.
- Assists in postnatal care, escorts women to facilities, and facilitates Janani Suraksha Yojana benefits.

Anganwadi worker

- Placed at anganwadi center (1 per 1000 population; 700 in tribal areas).
- Supports maternal and child health under the Integrated Child Development Services.
- Provides supplementary nutrition, monitors growth, promotes ANC, immunization, breastfeeding, and family planning.
- Identifies malnutrition, educates mothers, and coordinates with accredited social health activists and ANMs for health care referrals.

The following literature provides quantitative evidence on the extent of gaps in correct management and referrals to HRPs at different levels of the public health care system in low- and middle-income countries, including India. A systematic review in India reported that due to the inability of PHCs to provide basic HRP care, the proportion of unjustified referrals to higher-level facilities ranged between 25% - 52% [18]. A study from Himachal Pradesh and Andhra Pradesh (AP) in India highlighted systemic gaps among health workers (HWs) across 3 tiers of the public health care system, as only 31% (47/147) of HWs from 3 tiers of the public health care system reported screening only for 10 out of 16 most common HRP conditions. Even among the 10 HRPs screened, only 35% (17/49) of HWs at PHCs and 51% (18/35) at CHCs reported managing identified HRPs at their facilities, while the remainder referred such cases. To specifically assess HRP management competencies, scenario-based assessments were conducted; "a second-trimester moderate anemia case scenario was given to HWs at 3 tiers of health care system in 2 states." While nearly all HWs correctly diagnosed the condition and over 75% prescribed oral iron, only 5% - 45% prescribed iron injection, negligible prescribed tablet Mebendazole, and <10% provided nutritional counseling. Around 50% of HWs across tiers referred the case, although PHCs and CHCs are supposed to manage moderate anemia cases. Similarly, when a third-trimester pregnancy-induced hypertension (PIH) case scenario was given, all HWs made correct diagnosis. However, appropriate treatment varied, with 42% of PHCs and 71% of CHCs prescribing antihypertensive drug ($MgSO_4$). Additionally, 94% at HSCs, 85% at PHCs, and 45% at CHCs reported referring such cases, although CHCs are supposed to manage PIH and preeclampsia cases. Thus, this study concluded that most referrals were very early and unnecessary, and few delayed referrals were coupled with poor prereferral management [15]. On preeclampsia and eclampsia diagnosis and management in 6 African countries, knowledge of diagnosis was excellent (>80%) in HWs, while knowledge on correct management varied (33% - 77%) and management in the event of convulsions was ≤51% [19]. A situational assessment study conducted in Telangana, India (2021 - 2022) found that ANMs mainly manage anemia, and 94% of them refer all high-risk cases to specialists, thereby bypassing the established referral chain. The MOs and specialists also felt the need for training support in managing HRPs, as 25% of MOs lack clarity and confidence in handling HRPs, and only 60% - 65% of specialists possessed the requisite knowledge [20]. An important reason for suboptimal knowledge, lack of confidence, and confusion in role clarity in HRP management and referral across the 3 tiers of the health care system is the absence of standardized management and referral protocols for HRPs tailored according to these 3 tiers of health care system in India and other low- and middle-income countries.

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For early identification, management, referral, and follow-up of HRPs, all pregnant mothers need to undergo screening for HRPs, and those identified should be managed and followed up regularly [21]. The World Health Organization's (WHO's) 2015 guidelines on HRPs recommend early assessment, as they serve as a guide for clinical decisions and are primarily intended for primary care at the facility and community level [22]. Although the revised guidelines describe the management of obstetric complications at the district level according to the period of gestation [23], their application at different facilities and levels of referral system in low-resource settings is not well understood [15]. In India, the skilled birth attendant guidelines on HRP management and referral provide guidance only on clinical management of low-risk and common HRPs and complications during pregnancy, childbirth, and postpartum care, and suggest referral, if the facility is incapable of managing a case [24]. Although in India, programs like Pradhan Mantri Surakshit Matritva Abhiyan, Labor Room Quality Improvement Initiative, Surakshit Matritva Aashwasan, Live Saving Anaesthesia Skills, etc, were initiated to address HRPs [25], their focus is primarily on strengthening BEmONC and CEmONC services, with limited or no focus on building the capacity of ANMs at HSCs or MOs at PHCs, who are the first point of contact for mothers with HRP conditions.

Problem Statement and Research Gap

Thus, in India, despite programs like Pradhan Mantri Surakshit Matritva Abhiyan and Surakshit Matritva Aashwasan, the provision of continuum of care for HRPs remains inadequate. This includes gaps in early identification, understanding causes and complications, appropriate treatment and referral, follow-up care, including need-based laboratory investigations and follow-up after discharge or until safe delivery [26]. This may be due to (1) nonavailability of evidence-based, condition-specific, and role-specific guidelines for identification and management of HRPs, (2) confusion regarding specific roles of HWs in managing the HRPs, (3) and poor knowledge, skills, and lack of confidence, particularly among ANMs and MOs. As a result of all these issues, there is an increase in irrational or unnecessary referral of women with HRPs to higher facilities, thereby compromising on the quality of ANC. Thus, we strongly believe that, through effective management of HRPs and by preventing pregnancy complications in non-HRP women, the quality of ANC services can be ensured, leading to a significant impact on reduction in maternal deaths, stillbirths, and early neonatal deaths—a triple return on investment [27].

We also identified the following research gap that, although several programs under the National Health Mission seek to strengthen frontline HWs' knowledge and skills related to maternal and child health outcomes, few studies in India have rigorously examined providers' perspectives on HRP screening and management [28]. Evidence on the effects of capacitating ANMs and MOs in HRPs management and referral is even more limited, particularly with respect to system-level outcomes (eg, improvements in clinical knowledge, diagnostic capacity, and confidence in managing HRPs) [15], as well as community-level outcomes (eg, improvement in quality of ANC services and the appropriate diagnosis and management of HRPs as reported by pregnant women). To the best of our knowledge, we have not come across studies that have assessed the impact of capacitating ANMs, MOs, and specialists on strengthening HRP management skills and ensuring appropriate care for women with HRPs in Uttar Pradesh (UP), India's most populous state. Our study addresses this critical gap in a context characterized by a high maternal mortality ratio of 141 per 100,000 live births in 2020 - 2022 [29].

How Our Interventions Will Address the Problem

The Integrated High-Risk Pregnancy Tracking and Management (IHRPTM) program by ARMMAN (Advancing Reduction in Mortality and Morbidity of Mothers, Children, and Neonates), a nonprofit organization, has been improving health-seeking behavior of pregnant women by building capacities of HWs to ensure efficient antenatal and child care, and timely diagnosis, management, and referral of HRPs. The program is designed to address gaps in HRP management through an integrated, comprehensive, multistep, systemic approach for improved identification, tracking, and end-to-end management of HRPs. Its aim is to reduce delayed, complicated, and irrational referrals to tertiary facilities, allowing these facilities to focus on truly critical cases, leading to satisfaction of women and families with HRP conditions. By capacitating, motivating, and handholding HWs, we anticipate the prevention of pregnancy complications among non-HRP women. Integration of different interventions also leads to improvement in quality of ANC services, thereby lowering overall maternal and neonatal mortality and morbidity in the intervention area.

Key Interventions of the Program

The program includes several key interventions to strengthen the management of HRPs. Color-coded protocols are developed as algorithmic tools that are simple yet comprehensive, designed for the end-to-end management, referral, and follow-up of 35 HRPs. These protocols are tailored for ANMs, MOs, and specialist gynecologists. They remain concise and uncluttered, ensuring absolute clarity at every level while adhering to local practicalities.

Live training sessions are conducted for HWs (ANMs, MOs, and specialists) to enhance their skills in identifying and managing HRPs within the facilities where they work. The training refreshes their knowledge and skills on the early diagnosis of HRPs and provides them with tailored decision-support tools in the form of protocols. These tools guide case management based on the resources available at the facility and offer algorithm-based instructions for referring cases that cannot be managed locally to higher-level facilities.

To encourage continuous, self-paced learning, the program also introduces a digital learning app designed specifically for ANMs. The app contains learning materials, such as videos, Microsoft PowerPoint presentations, practice questions, and quizzes, all organized according to HRP protocols. A new protocol is released every 2-3 weeks. As a self-paced learning tool, the app enables ANMs to upgrade their skills at their own convenience.

In addition, a WhatsApp-based support helpline combines mobile technology with personalized guidance, enabling doubt resolution and handholding for ANMs as they engage with the

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learning content and apply it in real-life field situations. Queries raised by ANMs are answered within 24 hours by state-appointed MOs, trainers-of-trainers, or dedicated ARMMAN staff. Together, the learning app and the WhatsApp helpline create an almost real-time platform for addressing doubts related to the management and referral of HRP cases.

Finally, HRP-specific data are linked with the state's monitoring system to improve tracking and decision-making across different levels of the public health care system. This digital tracking system functions as a real-time data collection and decision-support tool integrated with the state's HRP monitoring platform (Reproductive and Child Health [RCH] portal). It captures the management and referral journey of women with HRP conditions from anywhere in the state. The tracking app also guides HWs in recording relevant signs, symptoms, and diagnostic interventions, thereby ensuring that appropriate care is provided at every stage of management and referral for women with HRP conditions.

Our interventions are human-centric and user-focused, incorporating facility-specific actions tailored to the needs and responsibilities of each cadre within the health care system. The vision of the IHRPTM program is to improve the functioning of the public primary health care system and achieve a sustained reduction in irrational, delayed, and complicated referrals to higher-level facilities. This will ensure HSCs and PHCs manage mild to moderate HRPs, while only serious cases are referred to higher facilities. In turn, this reduces the burden on secondary and tertiary facilities, thereby improving the functioning of the 3 tiers of public health care system.

Thus, our innovative "tech plus touch model" leverages the existing public health care system to strengthen the capacity of HWs to manage HRPs, thereby facilitating scalability across districts or states. This approach includes an inbuilt sustainability model, as the IHRPTM program is integrated within the existing public health care system, without creating a parallel structure that would be resource intensive in terms of human and financial capital. Ultimately, a capacitated health care system and its stakeholders will create demand among mothers with HRPs for timely and appropriate care.

Interventions and Anticipated Theory of Change

The program's theory of change is shown in Figure 1, with inputs and interventions leading to short-term outputs, which in turn lead to medium-term outcomes, and finally long-term impacts. The HRP condition–specific, algorithm-driven, color-coded protocols tailored for 3 cadres of HWs serve as readily accessible reference documents for managing HRP cases. Since these protocols have been vetted and formally endorsed by the UP health department, and since ARMMAN is implementing the program in partnership with health departments of 2 intervention districts, we anticipate cooperation from district health systems throughout the 18 months of the implementation period. This cooperation is expected to include nomination of ANMs, MOs, and specialists for training and other supportive supervision initiatives. Classroom training on HRP protocols is designed to refresh and strengthen HW's knowledge and skills to manage HRPs. It is expected to provide them with around 10% immediate gain in theoretical knowledge and skills to manage or refer HRPs (based on evidence from phase-1 protocols in Telangana, which showed 8% - 17% gain in knowledge among ANMs) [30]. Training supplemented with digital interventions provides HWs, particularly ANMs, with real-time responses to queries they get during management or referral of HRP cases in actual field conditions. These processes translate knowledge into practice, resulting in early diagnosis and appropriate management or referral of the HRP cases according to type of health facility (short-term output).

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Figure 1. Logical framework conceptualizing the theory of change of program to improve knowledge and skills of health workers (HWs) to diagnose and manage high-risk pregnancies (HRPs). ANC: antenatal care.

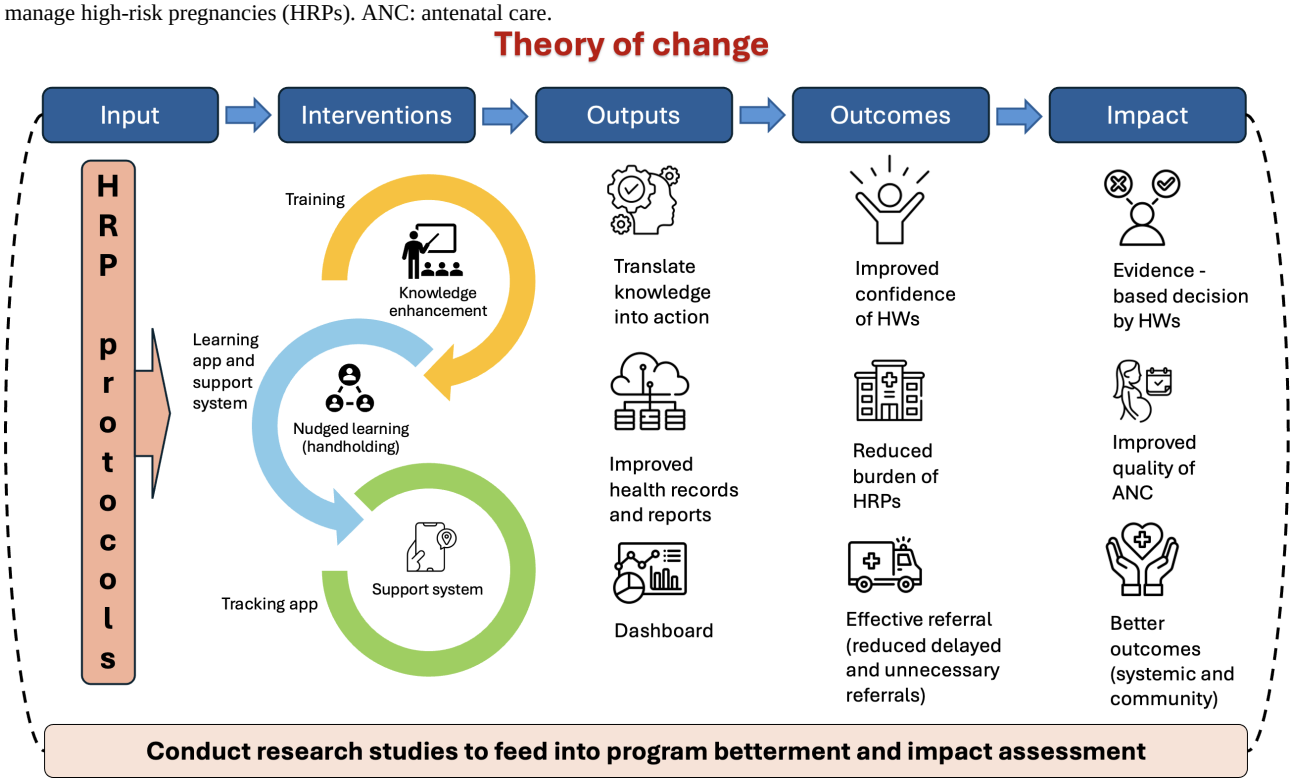

When training and digital interventions are supplemented with the tracking app, comprehensive details on the management and referral pathways adopted for each HRP case are generated. These cumulative data lead to the creation of dashboards on the IHRPTM program at different levels of health care system (short-term output). With continued handholding of interventions over 9 - 12 months, the ANMs and MOs are expected to gain confidence to diagnose and manage HRPs as per the protocols, and there will be a reduction in the number of delayed or unnecessary referrals of HRP cases to higher facilities, and thus ultimately leading to a reduction in the burden of HRPs (medium-term outcomes).

Finally, when all the ANMs and MOs in the intervention districts consistently manage or refer HRPs using standardized protocols over a 12 - 18-month period, we anticipate impact on both system- and community-level outcomes. These include evidence-based management of HRPs by all 3 cadres of HWs, timely relief of women diagnosed with HRPs prior to delivery, and ultimately, improvement in overall quality of ANC (long-term impacts).

Anticipated Challenges to Program Implementation

Our program, implemented in partnership with the district and state health department, is both a source of strength and a potential challenge. In the intervention arm, the program must navigate several systemic issues, including the double burden of noncommunicable and communicable diseases, reproductive health problems, underfunding, weak procurement and logistics systems (eg, supply of essential medicines and vaccines), an uneven distribution of HWs, weak regulatory mechanisms, and issues such as inappropriate prescription and use of medicines [31]. Through our handholding interventions and continuous engagement with stakeholders across the 3 tiers of the public health care system, we aim to mitigate some of these challenges.

Almost all the ANMs in UP have an internet-enabled smartphone or tablet. However, despite this universal access, a feasibility assessment and user feedback study conducted in Telangana with 2790 ANMs identified several digital challenges. These included permission restrictions for installing digital apps, poor internet speed, login difficulties, overheating or slow device performance, delays in receiving new content in digital apps, data inaccuracies, and issues with switching languages in the learning management system app. We expect similar digital challenges in the 2 intervention districts. The program addresses these issues through continuous handholding and support.

As our program does not work with private or unregulated health care sector, there is a lack of data on the capacity of these players in HRP management. However, in UP, around 30% of the ANC services were exclusively provided by private or NGO (nongovernmental organization) sector and an additional 13.5% by a combination of public or private or NGO sector providers [13,30]. This implies that our program interventions will not influence or will only partially influence 30% - 44% of pregnant women in the state. Also, women seeking ANC or HRP services from private or NGO providers are going to influence the quality of ANC indicators at community level.

Rationale for the Study

Overview

The IHRPTM program in UP was developed with a comparative advantage, as it was informed by learnings from the implementation of 6 phase-1 protocols in Telangana and AP. In UP, the program was designed for a shorter duration (18 months vs 5 years in Telangana and AP), on a smaller scale (6

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protocols vs 21 in Telangana and 20 in AP), and in a more limited geography (2 districts in UP vs 33 in Telangana and 26 in AP) as IHRPTM program was initiated as part of UP Government's Ending Preventable Maternal Mortality (EPMM) initiative launched in mid-2024. As the impact evaluation of the IHRPTM program in Telangana and AP is going to take more time (2027 or beyond), the government of UP, before implementing the program at scale across all the 75 districts with around 20 HRP conditions, decided to first implement the program on a pilot basis. This pilot phase is of shorter duration (18 months), limited to 6 HRP conditions, and covers only 2 intervention districts. The 6 HRPs prioritized by the government of UP are quality ANC (QANC), anemia (moderate and severe), PIH, antepartum hemorrhage (APH; including placenta previa and abruptio placenta), heart disease or shortness of breath, and fever. Hence, the UP initiative was conceptualized as a pilot project, with the explicit aim of informing future scale-up across all 75 districts, expanding to additional HRP protocols, and generating early evidence of the program's impact at both system and community levels.

While designing the impact evaluation of the UP pilot, the following contextual variations in the scale of direct beneficiaries were considered. The program engaged ANMs (>400 in UP vs >9000 in Telangana and >15,000 in AP), MOs (>100 in UP vs >1000 in Telangana and >1800 in AP), and specialists (>10 in UP vs >400 in Telangana and >500 in AP). Indirect beneficiaries also varied substantially, with approximately 60,000 pregnancies per year in UP compared with 700,000 in Telangana and 900,000 in AP, translating to roughly 18,000 HRPs per year in UP versus 200,000 in Telangana and 300,000 in AP. Training timelines also differed, while training all ANMs on 6 phase-1 protocols required approximately 1 year in Telangana and 9 months in AP, >400 ANMs in UP were trained in just a few days. Moreover, digital interventions were introduced within 2-3 months of program initiation in UP, compared with more than 3 years in Telangana and 1 year in AP, as these digital interventions were still evolving when implementation began in Telangana.

Thus, considering UP's comparative advantage over Telangana and AP, sufficient number of direct and indirect beneficiaries, the rapid introduction of all interventions in quick succession, and additional scope for keeping a control arm, the UP impact evaluation design is expected to provide generalizable evidence on the program's impact, even with its shorter duration (18 months) and smaller scale (2 intervention districts and 3 HRP protocols). In UP, the impact evaluation will be confined to the following 3 HRP conditions: anemia (moderate and severe), PIH, and APH.

Reasons for Not Conducting Impact Evaluation on the Below HRPs

Quality ANC is excluded from the impact evaluation as it is not an HRP condition but rather a set of well-established, evidence-based processes that health functionaries are expected to follow across the 3 levels of public health care system. ARMMAN has included QANC as one of the protocols as it sensitizes ANMs and MOs to the importance of a comprehensive history taking and conducting trimester-specific ANC examinations and tests, thereby contributing to overall quality of the ANC services. The program's effect on QANC will be assessed using the following proxy indicators: proportion of women who received 3 essential tests and examinations (weight, hemoglobin, and blood pressure) in all the ANC visits, proportion of women who received a complete ANC package (at least 4 ANC visits, at least 1 tetanus toxoid injection, and consumed at least 100 IFA tablets or consumed IFA for a minimum of 100 days), and proportion of women whose third trimester ANC visit took place at CHC or higher-level facility.

Heart disease or shortness of breath is excluded from impact evaluation due to its low prevalence (0.3% - 3.5%) [32]. Evaluating changes for a condition with such a low prevalence over an intervention period of 18 months would require an unfeasibly large sample size of recently delivered women (RDW) with the condition. Also, severe cases with this condition require care at medical college hospitals or specialized facilities with 24×7 availability of cardiologists, surgeons, anesthetists, etc [33], are beyond the scope of this program.

Fever in pregnancy is excluded from impact evaluation, as it is generally a comorbidity associated with non-HRP conditions (eg, dengue, hepatitis E, urinary tract infection, and vector- or water-borne diseases) [34].

Hypothesis and Outcomes

The program's impact evaluation will test the following research hypotheses: (1) Does the program, implemented over 18 months, enhance knowledge, skills, and confidence of the ANMs and the MOs to make early diagnosis and manage the 3 HRPs in the intervention arm, compared to usual care arm? (2) Can the capacitated ANMs and MOs translate their knowledge and skills into practice, particularly for early diagnosis and end-to-end management of the 3 HRP conditions in the intervention arm, compared to the control arm? (3) Does the program improve the quality of ANC services in the intervention arm, compared to the usual care arm?

At the system level, the primary outcomes focus on changes in the knowledge and skills of HWs. The first outcome is the net change in correct knowledge and skills of ANMs to manage (treat, counsel, refer, and follow-up) women with any of the 3 HRP conditions (anemia, PIH, and APH) from baseline to end line, comparing intervention and control arms. The second outcome is the net change in correct knowledge and skills of MOs to manage (treat, counsel, refer, and follow-up) women with any of the 3 HRP conditions (anemia, PIH, and APH) from baseline to end line, comparing intervention and control arms. The percentage of correct knowledge and skills for ANMs and MOs will be calculated based on the number of correct responses provided out of a total of 45 questions on the 3 HRPs, administered at baseline and end line surveys.

The system-level secondary outcomes include the net change in the ability of ANMs to correctly identify HRP-related signs and symptoms from baseline to end line, in intervention versus control arm and net change in the ability of MOs to do the same. Other outcomes include changes in the confidence level of ANMs and MOs to manage HRPs between baseline and end line across 2 arms and to document qualitatively whether any

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systematic barriers reported by district officials at baseline survey were overcome by the end line, by comparing intervention and control arms.

At the community level, the primary outcome includes net change in the proportion of RDW with any of the 3 HRP conditions (anemia, PIH, and APH) whose problem was resolved prior to delivery and who reported satisfaction with the management of the condition, from baseline to end line, in intervention versus control arm. Satisfaction level of RDW is measured using a 5-point Likert scale on the topics of "attitude and behavior of staff," "cleanliness and hygiene," "comfort and care," and "overall satisfaction with management of HRP condition at the facility."

The community-level secondary outcomes include net change in proportion of RDW who received the complete ANC package during their last pregnancy, from baseline to end line, in intervention versus control arm. Also includes the net change in proportion of RDW who were sensitized about HRPs by ANM or MO during their last pregnancy, during baseline and end line, in intervention versus control arm. Other secondary outcomes include net change in the mean gestational month of first diagnosis of 3 HRPs by an ANM, from baseline to end line, in intervention versus control arm, and net change in the proportion of RDW diagnosed with any of the 3 HRPs who received protocol-based management or referral from an ANM, from baseline to end line, in intervention versus control arm. We also measure the net change in proportion of RDW diagnosed with any of the 3 HRPs, received protocol-based management or referral from MO, from baseline to end line in intervention versus control arm.

Methods

Study Design

The study adopts a "matched, before-after quasi-experimental design with a control (usual care) arm," as a randomized control study design is not feasible for this kind of system and community-based implementation study. Both qualitative and quantitative data will be collected at the system and community levels, respectively, during baseline (prior to implementation of interventions) and end line (after 18 months of interventions), in the intervention and control arms. The program's effectiveness at the system level will be evaluated by assessing the capacity of ANMs and MOs to diagnose and manage the 3 HRPs and at the community level by measuring the proportion of RDW with any of the HRP conditions, whose HRP problem got resolved prior to delivery and who were satisfied with the care they have received for the HRP condition. Effectiveness of the program through quantitative indicators will be analyzed using the difference-in-difference (DiD) technique.

However, keeping in view the quasi-experimental design of this study, to control for potential baseline differences between intervention and control arms due to nonrandom allocation, we will lock the analysis plan by prespecifying primary outcomes and covariates of the quantitative data. Prior to advanced analyses, we will implement near-matching of intervention and control data on key covariates, such as age, parity, caste, and literacy. In addition, during the main analysis stage, we will apply DiD models with covariate adjustment to further control for any residual imbalance and to strengthen causal inference.

Duration of Interventions and Justification for Creating a Usual Care Arm

In 2 intervention districts, the IHRPTM program will be implemented district-wide for 18 months, starting June-July 2024 and ending February-March 2026. The 18-month duration is necessary, as the introduction of different interventions in both the intervention districts requires 3 - 6-month time. Also, for converting system level changes into outcomes is a time-consuming process [35]. Given the relatively short implementation period, we are not proposing a midline evaluation. However, the uptake, quality, and coverage of interventions will be continuously monitored through a robust monitoring system. Dipstick studies will be conducted depending upon the need. Any mid-course corrections will be based on findings from the baseline, monitoring data, and dipstick studies.

In the usual care arm, HWs will receive routine capacity-building sessions conducted by the state and the national governments. Pregnant women in both arms will have access to antepartum, intrapartum, and postpartum care programs provided by the state and the national governments. It implies that while general system strengthening interventions are provided in both the arms, the IHRPTM interventions are the only additional interventions confined to the intervention arm. At the community level, the IHRPTM program does not directly work with pregnant women in either arm. The control arm was included to isolate the effect of the IHRPTM interventions from the general system strengthening activities and to assess whether IHRPTM interventions had any incremental effect or value addition beyond what general system strengthening interventions alone can achieve. Thus, this study design ensures ethical equity while also allowing us to isolate the incremental effect of the IHRPTM program interventions by comparing changes in outcomes that go beyond improvements expected from broader system strengthening efforts.

Study Geography

For this study, the government of UP has identified Shravasti and Sambhal as the intervention districts to implement the program. Keeping in view the 2-arm nature of the study, the study team has identified 2 usual care arm districts that closely match with the intervention districts using latest socio-demographic, antenatal, and immediate postpartum care indicators for the district (NFHS-5, 2019 - 2021) [13]. Identified Gonda as the matching usual care arm district for Shravasti. The distance between these 2 districts is less than 50 km. Identified Budaun as matching usual care arm district to Sambhal. The distance between these 2 districts is less than 100 km. Table 1 provides sociodemographic and ANC and delivery practices in 4 study districts, and Figure 2 depicts the 4 study districts. The matched control districts were approved by the government of UP.

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Table . Sociodemographic and health care–seeking profile of 4 study districts.

	Intervention arm districts		Usual care arm districts	
	Shravasti	Sambhal	Gonda	Budaun
Sociodemographic profile[a]				
Population (2011), n	1,117,361	2,199,774	3,433,919	3,681,896
Sex ratio of population, (females per 1000 males)	881	891	921	871
Urban population, %[b]	4	3	7	22
Tahsils, n	3	3	4	6
Villages, n	541	993	1817	2061
Literacy, %[b]	47	55	59	53
Scheduled caste population, %[b]	16.9	16.6	15.5	17.7
ANC[c], delivery, and immediate postpartum care indicators (2019 - 2021)[d], %[e]				
Received at least 4 ANC visits	42.3	32.9	41.7	40.6
Mothers protected against tetanus toxoid	94.4	90.3	90.4	90.1
Mothers who consumed 100 iron-folic acid	16.6	21.3	17.2	15.9
Institutional births	80.4	74.2	81.8	72.3
Mothers who received postnatal care in 2 days	68.3	67.5	68.6	62.4
Mothers received MCP[f] card	95.9	93.5	97.1	94.4

[a]Master data: Census 2011-state and district wise primary census abstract.

[b]These are census percentages.

[c]ANC: antenatal care.

[d]International Institute for Population Sciences (IIPS) and ICF. 2021. National Family Health Survey-5, India, 2019 - 21: Uttar Pradesh. Mumbai: IIPS.

[e]Weighted percentages.

[f]MCP: Mother and Child Protection.

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Figure 2. Intervention and control districts of Uttar Pradesh (adapted from OpenStreetMap data [36] using DataWrapper software [37], and published under Creative Commons Attribution-ShareAlike 2.0 Generic License [38]).

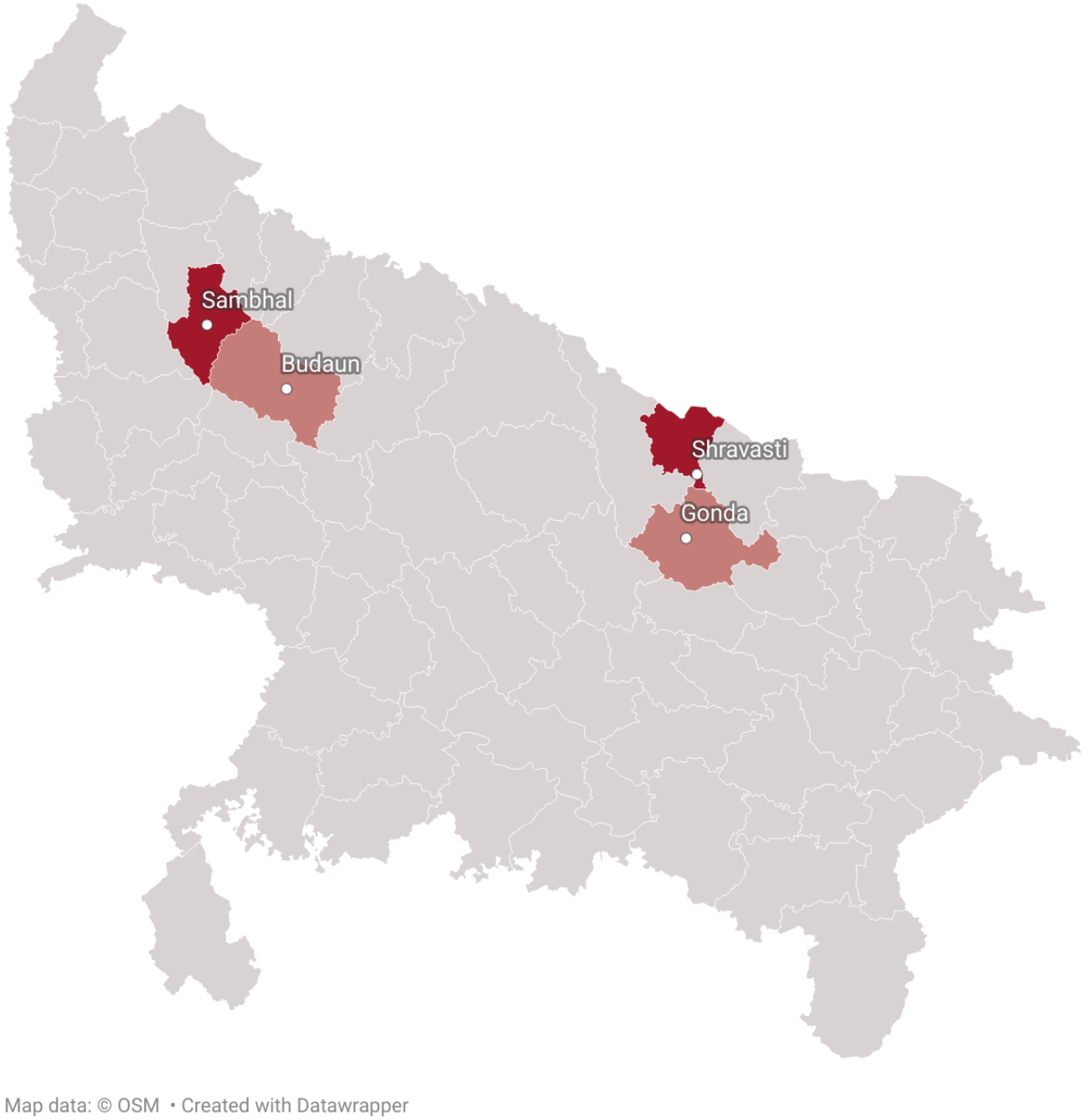

Study Tools

Baseline and end line surveys will use qualitative methods for collecting data from the system stakeholders and quantitative methods for collecting data from the community, specifically the RDW. The data collection tools were pretested in Telangana in 2022-2023 and subsequently adapted to align with the programs and policies of UP. Table 2 provides details of respondents interviewed using qualitative data collection technique.

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Table . Respondents, data collection method, sample size, and information areas of qualitative data collection tools.

Type of respondent and tool	Data collection method	Sample size	Who collects data?	Recruitment strategy	Key information areas of tool
Chief medical officer (Multimedia Appendix 1)	In-depth interview	1 per district	Qualitative researchers	Purposive	• District policies and programs on maternal and newborn health • Facilitators and barriers to implement IHRPTM[a] program in district
Associate chief medical officer (Multimedia Appendix 2)	Semistructured interview	1 per district	Qualitative researchers	Purposive	• Most prevalent HRPs[b] in district • Vulnerable areas or populations • Issues with collection of RCH[c], HMIS[d], or HRP data • Human resources availability
Specialist gynecologists (district hospital; Multimedia Appendix 3)	In-depth interview	1 per district	Qualitative researchers	Purposive	• ANC[e] case load at facility • HRP case load at facility • Volume of high-risk cases referred to facility • Volume of late and unnecessary referrals • Strategies for coping with referrals
Medical officers working in PHC[f] and CHC[g] (Multimedia Appendix 4)	Semistructured interview	4 - 5 per district	Qualitative researchers	From 4 randomly selected PHCs of 2 blocks in a district	• Support systems available for ensuring quality ANC • Case load of ANC and HRPs • Knowledge about 3 specific HRPs • Management skills to care for women with 3 HRPs • Knowledge about referral practices to woman with 3 HRPs

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Type of respondent and tool	Data collection method	Sample size	Who collects data?	Recruitment strategy	Key information areas of tool
ANMs[h] working in HSCs[i] (Multimedia Appendix 5)	Semistructured interview	8 - 10 per district	Qualitative researchers	2 ANMs per PHC, from above 4 randomly selected PHCs of 2 blocks in a district	• Support systems available for ensuring quality ANC • Case load of ANC and HRPs • Knowledge about 3 specific HRPs • Management skills to care woman with 3 HRPs • Knowledge about referral practices to woman with 3 HRPs

[a]IHRPTM: Integrated High-Risk Pregnancy Tracking and Management.
[b]HRP: high-risk pregnancy.
[c]RCH: reproductive and child health.
[d]HMIS: health management information system.
[e]ANC: antenatal care.
[f]PHC: primary health center.
[g]CHC: community health center.
[h]ANM: auxiliary nurse midwives.
[i]HSC: health subcenter.

Community-Level Data Collection

RDW who gave birth within the past year, regardless of HRP status, will be surveyed in all the 4 study districts, at baseline and at end line. Some unique features of the RDW tool are documentation of the previous pregnancy, including details of HRP condition (if applicable), as a story in mother's own words; a picture of the Mother and Child Protection card to supplement with the question-specific data collected from the RDW through interview; ANC details; and HRP-specific detailed questions, where applicable (Table 3; Multimedia Appendix 6).

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Table . Key data collected in the recently delivered women tool.

Data point collected	Details
Pregnancy and delivery details	Age, delivery date, type and place of delivery, outcome of delivery, child's age, birth weight, term and preterm status, MCP[a] card availability, and HRP[b] status
Reproductive history	Children ever born and surviving, and pregnancy terminations
MCP card photo	With details of each ANC[c] visit, in picture format
Story of recent pregnancy in mother's own words	Investigators ask the mother to describe about her most recent pregnancy in her own words, from conception to delivery, including details of any HRP, if applicable. The story told by mother is documented here in a text format
ANC characteristics	Number of ANC visits, details of first ANC visit, experience of risk factors, TT[d] and IFA[e] usage, supplementary nutrition, and high-risk conditions experienced, including duration of problem and referrals made for the HRP
Delivery and newborn characteristics	Breech presentation, prolonged labor, excessive bleeding, facility stay after delivery, congenital anomalies, and reasons for cesarean section
Details about severe or moderate anemia, PIH[f], APH[g], and other HRP conditions experienced by mother in most recent pregnancy (if applicable)	Timing of first diagnosis of HRP and who diagnosed, risk factors associated with the HRP, and management, referral, counseling, and follow-up details related to the HRP condition
Satisfaction	Level of satisfaction with care received if HRP was present
Background characteristics	Literacy, schooling, religion, caste or tribe, occupation, and owning of own mobile phone by the mother

[a]MCP: Mother and Child Protection.
[b]HRP: high-risk pregnancy.
[c]ANC: antenatal care.
[d]TT: tetanus toxoid.
[e]IFA: iron-folic acid.
[f]PIH: pregnancy-induced hypertension.
[g]APH: antepartum hemorrhage.

Sample Size of the Quantitative Surveys

The sample size of RDW to be included in the baseline and end line surveys was determined to generate indicators for each of the 3 HRP conditions (moderate or severe anemia, PIH, and APH) separately for the intervention and usual care arms. To achieve this, the sample size was estimated based on the HRP condition, with the lowest prevalence among the 3 conditions. This approach ensures that the sample size estimated for an HRP condition with the lowest prevalence will suffice for the HRP conditions with higher prevalence as well, using the most recent prevalence data for the HRP conditions among the pregnant women in India or North India.

From recent available literature in India, the prevalence of moderate or severe anemia among pregnant women in the north zone was 25% [39], PIH in India ranged from 5% - 17% [40], and prevalence of only APH is 2% - 5%, and placenta previa is 4% - 5% [41]. It implies, among the 3 HRP conditions, PIH has the lowest prevalence. Assuming the prevalence of PIH among RDW in the intervention arm and in the control arm, at baseline and end line surveys is 5%, the estimated sample size for PIH is not expected to differ by more or less than 1% (ie, 4% - 6% is the margin of error), with a 95% confidence level, the sample size of RDW required in both the intervention and in usual care arms, at baseline and at end line surveys is 1825 (rounded to 2000) [42]. It means we need to interview 2000 RDW in each arm, both at baseline and end line surveys to generate required sample size for each HRP condition. Assuming the above prevalence of HRPs holds true in the 2 study arms, by interviewing 2000 RDW cross-sectionally in each arm, we anticipate at least 400 - 500 RDW with moderate or severe anemia, 120 - 200 RDW with APH, placenta previa, or abruptio placenta, and 100 - 340 women with PIH. Some of these RDW may have more than 1 of the 3 HRP conditions. Approximately 900 - 1000 RDW in each arm will be without any of the 3 HRP conditions.

Given the low prevalence of PIH and APH (around 5%), with 1% margin of error, our study (2000 RDW per arm) is adequately powered at 95% (a conservative estimate). With a higher margin of error (say 1.5%), although the required sample size per arm will reduce to 821, the power of the study will fall below 95%, and the anticipated number of RDW with PIH and APH would be too small to compare (approximately 70 - 130 per arm). This would result in high CIs, making HRP-specific impact evaluation a challenging task.

As different respondents will be surveyed at baseline and end line, there is no risk of data attrition. However, since HRP conditions data in this study is relying on self-reports by RDW

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and expected low prevalence of PIH and APH conditions (around 5%) in India, nonparticipation by RDW with these conditions could compromise the statistical power of the study. To overcome this problem, we have set a narrow margin of error (1%, ie, prevalence could range between 4% - 6%) for baseline and end line estimates in each arm. Our sample size calculation also accounts for a 10% nonresponse rate per arm at both baseline and end line. To increase the effective prevalence of the APH condition, the inclusion criteria for this condition encompass APH, placenta previa, and abruptio placenta. With recent estimates in India showing an increase in prevalence of PIH to 11% [43], while moderate or severe anemia was stagnant at around 26% [39], we are confident of including sufficient RDW with these 2 conditions. Nevertheless, if the prevalence of any of the 3 HRPs falls below 4% at baseline or end line in either arm, the statistical power of the study for that HRP condition will be compromised. We acknowledge this as a limitation of the study.

Survey Design

A multistage sampling approach will be used to select RDW from each arm. As census data at the village and ward level is old (2011), the accredited social health activist (ASHA) jurisdiction will be used to serve as a primary sampling unit (PSU). A total of 50 PSUs per district (100 per arm) will be selected using a 2-stage sampling approach. During baseline, the 2023 list of RDW in an ASHA's jurisdiction served as the basis for the selection of a PSU. Assuming an average PSU will have 20 RDW, we expect to cover 1000 RDW per district (2000 per am) at baseline and end line surveys.

As part of the first stage of sampling, 50 PSUs in each district were allocated according to the proportion of the block population of the district. As part of the second stage of sampling approach, the allocated number of PSUs in a block was selected using the probability proportionate to size sampling technique.

During the baseline, in a selected PSU, the list of women who were delivered in the past 1 year, regardless of delivery outcome, and the delivery data maintained by ASHA and anganwadi workers (AWWs) served as the basis for identifying the eligible respondents for survey. This list by ASHA and AWWs was cross-verified with the list available with the ANM of the respective PSU, and a comprehensive list of RDW to be approached for interview was prepared. By adopting this strategy, we eliminated the need for doing households listing exercise to identify eligible RDW in the selected PSUs.

In a sampled PSU, all the households with eligible respondents (RDW) were approached by female investigator or supervisor for consent or assent for a face-to-face interview (Multimedia Appendix 7). All consented RDW participants were interviewed by female investigators, mostly in RDW's home. To ensure 100% enumeration of eligible respondents in a PSU, a "snowballing" technique was also used with interviewed RDW to check if any peer RDW in her neighborhood was missed by the ASHA, AWW, or ANM list. If any new RDW is found through the snowballing technique, she was interviewed, provided she belongs to the selected PSU. Table 4 provides the inclusion and exclusion criteria used for selecting the respondents for the baseline and end line surveys in the 4 study districts of UP.

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Table . Inclusion exclusion criteria for respondents of baseline and end line surveys.

Respondent	Data collection method	Inclusion criteria	Exclusion criteria
RDW[a]	Personal interview	• Woman aged 15 - 49 years, have had delivery during the past 1 year from the date of survey • Details of such woman are available with ASHA[b], AWW[c], and ANM[d] in the sampled PSU[e] or woman was identified through snowballing technique from an interviewed RDW • RDW who is resident of non-sampled PSU but had delivery in sampled PSU in past 1 year and is willing to participate in survey	• All those who do not give consent to participate in the survey • RDW listed by ASHA, AWW, and ANM, but not available for interview on days of survey • Had delivery just within 3 days of survey • Maternal deaths and RDWs with severe illness and unable to participate in interview
District officials and Specialist gynecologists	IDI	• Currently serving in the stated position in the survey district	• With less than 1 year of experience in the current position, in the survey district • Who do not give consent to participate in the survey
Medical officer and ANM	SSI	• Currently serving in the stated position in the sampled PHC[f] and HSC[g]	• With less than 1 year of experience in the current position in sampled PHC and HSC • Who do not give consent to participate

[a]RDW: recently delivered women.
[b]ASHA: accredited social health activist.
[c]AWW: anganwadi worker.
[d]ANM: auxiliary nurse midwife.
[e]PSU: primary sampling unit.
[f]PHC: primary health center.
[g]HSC: health subcenter.

Using the above-stated survey design, tools, and inclusion and exclusion criteria, data for the baseline survey component of the impact evaluation of the IHRPTM program were collected during June-October 2024. Baseline qualitative data from system stakeholders were collected by ARMMAN researchers from 4 districts during June-August 2024. Baseline quantitative data were collected from >4000 RDW by around 75 female investigators and supervisors, during September-October 2024, from 200 PSUs, spread across 4 districts and 2 arms.

Ethical Considerations

Overview

Qualitative data at baseline and end line surveys will be collected by ARMMAN researchers using computer-assisted personal interview (CAPI) tools, while quantitative data will be outsourced to a professional data collection agency, with prior experience in collecting maternal and child health–related data in UP. At baseline, a 2-day meeting of the qualitative researchers was held to discuss specific nuances of each question of the qualitative tool, how to ensure uniformity while asking questions, distribution of qualitative data collection workload, etc. For the baseline RDW tool, the investigators and supervisors of the shortlisted agency were trained for 5 days by ARMMAN program's research team on the following topics: IHRPTM program and its objectives, ethical practices to be adhered to while collecting data from RDW, how to and when to approach potential gatekeepers, which RDW are eligible for consent or assent, how to obtain consent or assent, how to collect data using CAPI technique; importance of privacy during data collection, confidentiality of data, data quality, and potential risks and mitigation measures. Baseline RDW data were collected by female investigators or supervisors using the CAPI tool. All the tools were translated into Hindi and back translated into English, to ensure accuracy and retain the meaning of questions and most of the questions in the background, ANC, and delivery care sections were tried and tested in other large-scale surveys like NFHS.

All listed RDW in a PSU were approached by a female investigator or supervisor for participation in the survey using the RDW tool (Multimedia Appendix 6). Only those RDWs who expressed interest to participate in the survey were interviewed after obtaining informed consent. Respondents who were literate and comfortable in reading the informed consent form were given the option to read the form themselves or the

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investigator read it aloud to them. Once informed consent is received, the survey began. If the respondent felt the time was not appropriate to participate in the survey, a convenient time was sought, and the investigator returned at the time specified by the respondent to conduct the interview. Prior to approaching RDW, the gatekeepers of RDW (village leaders, teachers, religious heads, household heads, etc) were sensitized about the study and the safety of the RDW participating in the study by supervisors. For minors, informed consent was attained from the adult guardian, with assent from the minor. While interviewing RDW with severe morbidities, the procedure involved the presence of a guardian during the interview. The informed consent was obtained from the participant in the presence of the guardian. If she is unable to answer or give a consent, the Mother and Child Protection card was copied with the consent of the guardian. Including severe HRP cases in the survey would provide us with specific signs and symptoms associated with severity of the HRP condition, including gaps in diagnosis and management of these cases. Excluding severe HRPs from survey preview may result in collecting data only from the mild or moderately severe cases, and such data are not representative of the actual situation on the ground; hence, we have instructed investigators to collect data from severe HRPs by adhering to stated ethical norms.

A few women with severe HRPs may get distressed during the interview. To handle distress, investigators were trained using real field examples in trauma-informed and empathetic interviewing techniques. This included training on how to create a conducive environment (private, quiet, and comfortable place) for interview. During moments of distress, investigators responded empathetically by saying things like, “I can understand the pain,” offering water or tissues or keeping silent for a while. Keeping in view the distress level (tearfulness, prolonged silence, nervousness, or withdrawal), the investigator stopped the interview until the RDW’s distress had fully subsided. The interview was resumed only when she indicated she was ready to continue.

Privacy

While collecting qualitative or quantitative data from the field, there will be situations when interviews cannot be conducted in complete privacy, as participants may be surrounded by other adult members or coworkers. During the training of data collection teams, the issue of privacy was discussed in detail, specifically focusing on two subtopics: (1) ways to minimize situations where the investigator is surrounded by other adults (starting the interview with generic issues like crops, yield, etc, till other adults move and the supervisor tries to move other adults to a separate location, etc) and (2) strategies (such as preinterview briefings about privacy, choosing alternate locations, and scheduling flexible times when fewer people are around) that can be adopted during data collection to move other people away from the interview site.

Confidentiality

During data collection, the respondent’s name will not be recorded whenever possible. In cases where names are collected during qualitative interviews, these will be converted into numeric codes (eg, ANM-1 and ANM-2) while presenting the results. At the time of in-depth interviews (IDIs) with district officials, although we record the name of the respondent on the hard copy of the tool, this is done solely to ensure we are interviewing the correct person. Identification details of these respondents will be anonymized once the transcription and translation of the IDIs are complete. IDIs were not audio recorded and were conducted in the presence of a notetaker. Identification details of IDIs were anonymized once the notes were converted into digital data.

During baseline, after completing the RDW interview, the interviewer saved and closed the file before leaving the interview site. Each interviewer was provided a password for sharing and uploading the completed files through email. A unique ID was assigned to each RDW to protect their identity. The uploaded datasets were downloaded centrally at the ARMMAN Hyderabad office on a password-protected computer. All electronic data were stored securely on a password-protected computer at ARMMAN until the completion of the end line survey. Access to identifiable information is restricted only to the research team. The data files, containing identifiers, will be stored separately from other data files and will be password-protected, with access restricted to the research team. To ensure confidentiality and secure data transfer or sharing, files containing identification details will be password-protected and encrypted. All hard copy records will be destroyed at the end of the project.

Data Storage and Sharing Policy

In accordance with the principles of transparency and reproducibility, all deidentified datasets (both qualitative and quantitative) will be securely stored on password-protected servers at ARMMAN for a minimum of 5 years following project completion. Thereafter, data will either be archived for secondary use or permanently destroyed. Only deidentified, aggregate-level data may be shared upon reasonable request from accredited researchers or institutions, contingent on prior approval from ARMMAN’s scientific review board and Sigma’s institutional review board (IRB), and in compliance with national data protection regulations.

Approvals

The study got approvals from ARMMAN’s scientific review board (017/2024) and Sigma, New Delhi’s IRB (10009/IRB/24 - 25).

Data Analysis

The qualitative data will be analyzed using Braun and Clarke’s [44] inductive thematic analysis framework. Interviews with system stakeholders (eg, chief MOs, associate chief MOs, MOs, and ANMs) conducted in Hindi and transcribed verbatim will be translated into English and back-translated to ensure both linguistic and conceptual accuracy. The 2 researchers will independently code the transcripts using ATLAS.ti (ATLAS.ti Scientific Software Development GmbH) or NVivo (Lumivero) software. The analysis will follow a structured process: (1) initial data familiarization, (2) development and iterative refinement of an inductive coding framework, (3) systematic application of codes, (4) and identification of emergent codes where necessary. Themes will be generated through synthesis

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and organization of the coded data. Anticipated themes include training and handholding of ANMs and MOs on HRPs, motivation and job satisfaction of ANMs and MOs, quality ANC, facilitators and barriers to HRP management, facility and community support to ANMs and MOs, workforce shortages, sociocultural barriers to ANC and HRP care, and demand for services. Interrater reliability will be ensured by having 2 researchers independently code 20% of the transcripts. Any discrepancies will be resolved through consensus. Thematic findings will be validated against existing literature and substantiated with verbatim participant quotations. This rigorous, transparent, and software-supported approach will ensure analytical robustness of the findings.

Using data validation checks, the quality of the quantitative data will be assessed for coverage, consistency, and completeness by ARMMAN researchers. The analysis of these data will be done using SPSS (version 21.0; IBM) or STATA (version 12.0; Stata Corp, LLC) software. Preliminary analysis includes frequency tables and cross-tabulations, while as part of advanced analysis, multivariate analysis techniques will be used. The cleaned data will be analyzed according to background characteristics; coverage and quality of the ANC, delivery, postnatal care; the outcome and output indicators; satisfaction with the care; etc. Advanced analysis will be carried out to quantify associations of the background characteristics with output and outcome indicators. As far as possible, quantitative results will be reported with effect estimates, 95% CIs, and significance levels.

We will use the DiD technique to estimate the causal effect of program interventions on outputs (eg, RDW sensitized and HRPs diagnosed early) and outcomes (eg, protocol-based management and referral of HRPs). This approach compares changes in outputs and outcomes over the intervention period (18 months) between the intervention and the usual care arms. For each quantitative output and outcome indicator summary, descriptive DiD or net change will provide causal effect of intervention on the indicator. The DiD-specific regression models will then be used to test whether interventions were significantly associated with changes in the outcomes and to assess the extent of changes relative to the control group.

To address the issue of missing data in the RDW dataset, before applying DiD, we will assess the extent and patterns of missingness—whether missing data are at baseline, end line, or both—and examine whether missingness is random or systematically related to intervention status or outcomes by comparing covariates and outcomes between complete and missing cases. Given the robust data quality assurance measures implemented during both surveys, we anticipate minimal missingness, and any missing data are expected to be missing at random. If the proportion of missing at random for any outcome or covariate exceeds 10%, we will apply appropriate imputation methods prior to fitting the DiD model. The DiD model will then include intervention and control status, baseline and end line survey indicators, and interaction terms between outcomes and covariates.

During the granular analysis of testing the association between background characteristics and output and outcome indicators, we will draw upon the WHO's Social Determinants of Health framework [45]. Intersectionality between the background and confounding variables will be explored using subgroup analysis. In the multivariate regression model, predictor variables will only be included after testing for multicollinearity using variance inflation factor to ensure stability and reliability of the model.

Triangulation of Mixed Methods Data

As part of the impact evaluation, one of the hypotheses being tested is "'whether capacitated ANMs and MOs are able to translate their knowledge and skills to manage HRPs into practice." This hypothesis will mainly be tested by triangulating both the datasets on the listed themes and indicators, particularly, during the end line (Table 5).

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Table . How qualitative and quantitative datasets will be triangulated and integrated?

Theme or indicator	System level data (qualitative)	Community level data (quantitative)
Training and handholding of ANMs[a] and MOs[b] on HRPs[c]	• Early diagnosis of HRPs reported by ANMs or MOs • Improved knowledge and skills to manage HRPs by ANMs and MOs • Improved confidence to manage HRPs	• Proportion of HRPs diagnosed in the first trimester • Protocol-based management of HRPs • Protocol-based referral of HRPs • Proportion of unnecessary or irrational referrals
Motivation and satisfaction of ANMs and MOs	• Digital tools facilitating improved counseling and follow-up of women with HRPs by ANMs and MOs	• Proportion of mothers with HRPs counseled and followed up by ANMs and MOs • Proportion of mothers with HRPs highly satisfied with management and referral practices of ANMs and MOs
Quality ANC[d]	• Improvement in quality of ANC services reported by ANMs and MOs	• Proportion of mothers whose weight, hemoglobin, and blood pressure were collected at least 4 times in pregnancy • Proportion of mothers who received complete ANC package of services
Facilitators and barriers to HRP management	• Specific nuances of facilitators and barriers to HRP management reported by system stakeholders	• Proportion of mothers with HRPs using public health facilities for management • Proportion of mothers using public health facilities for ANC, delivery, and PNC[e] care

[a]ANM: auxiliary nurse midwife.

[b]MO: medical officer.

[c]HRP: high-risk pregnancy.

[d]ANC: antenatal care.

[e]PNC: postnatal care.

To operationalize triangulation as a methodological practice, the study will use structured integration matrices, defined timelines, and clearly delineated roles. The process will take place during the end line analysis phase (March-June 2026), once both qualitative and quantitative datasets have been collected and validated.

An integration matrix (Table 5) has been developed to align qualitative themes (eg, training, handholding, barriers, and motivation) with corresponding quantitative indicators (eg, timely diagnosis, referral patterns, and satisfaction with care). Systematic side-by-side mapping of these themes will facilitate the comparison of convergence, complementarity, and divergence between system-level perspectives of HWs and community-level experiences of pregnant women.

The qualitative team will conduct thematic analysis, while the quantitative team will undertake statistical analyses, including regression and DiD. A joint synthesis committee comprising senior researchers, program investigators, and biostatisticians will meet regularly during the end line analysis phase to review the matrices, address discrepancies, and ensure methodological rigor.

The integrated findings will be presented as narratives and summary tables, clearly highlighting areas where the 2 data streams converge or diverge. This structured approach enhances transparency, strengthens the validity of results, and ensures that triangulation moves beyond the conceptual intent to systematically document the facilitators and barriers to translating the knowledge gained from the program into practice on the ground by the HWs.

Use of Study Findings

Baseline study and impact evaluation findings will initially be shared with the government of UP, through Microsoft PowerPoint presentations and respective reports. The reports will also be shared with district officials of the 4 program districts for their review and consideration. Using data from baseline and end line surveys, ARMMAN will also develop research briefs on specific themes and look for opportunities to share these findings at various forums. If possible, the findings will also be disseminated through publication in scientific and peer-reviewed journals as well as through presentations at professional meetings and conferences. Once impact evaluation findings are available, ARMMAN plans to host meetings with state government officials and academicians to share relevant research findings, which could have implications for program modification when planning scale-up in other districts or states.

Results

The impact evaluation protocol and the protocols for 6 HRP conditions were vetted by the government of UP in May-June 2024. In the 2 intervention districts of Sambhal and Shravasti, in June-July 2024, implementation of listed interventions started in a phased manner, and these interventions will continue for 18 months (until March 2026), in collaboration with district health officials. By November 2024, in the 2 intervention

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districts, the following interventions had been introduced: (1) protocols on 6 HRP conditions; (2) training of ANMs, MOs, specialist gynecologists, staff nurses, and community health officers on these protocols; and (3) a digital learning tool and a WhatsApp-based support system for ANMs. Baseline data from system stakeholders and community data from recently delivered women were collected during June-October 2024. From November 2024 to October 2025, the listed interventions will continue in the 2 intervention districts, and baseline data from both arms are being analyzed. By November 2024, all the ANMs, MOs, specialist gynecologists, staff nurses, and community health officers of 2 intervention districts were trained on 6 HRP protocols, the learning app for ANMs on the 6 HRPs, and the WhatsApp support system for real-time clarification of doubts by the ANMs (tech plus touch approach) was also introduced. The tracking and data integration system for improved tracking of the HRPs by health facilities at different levels of public health care system is yet to be introduced.

The proposed interventions, designed, developed, implemented, and evaluated using a tech plus touch approach, will capacitate HWs at different levels to make early diagnosis of the HRPs and provide protocol-based management of the diagnosed condition. The findings of the study will identify issues that require need-based planning to ensure quality ANC, delivery, and HRP care services by public health care system, and particularly the ANMs and MOs, who work at the grassroots. At the policy level, findings of the study will provide cues on facilitators and barriers to pregnancy care services at the block and district level, for necessary corrections. The study intends to make an important contribution by evaluating the usefulness and effectiveness of the proposed program and suggesting further improvements or modifications when scaled up across the entire state of UP, a region that is larger than many European countries.

Discussion

Overview

One of the major strengths of this study is that this study is being implemented in partnership with state and district health departments. Through our multicomponent interventions, the capacity of public health care system stakeholders (ANMs, MOs, and specialists) is being built to diagnose and manage HRP conditions at their respective facilities. If ANMs and MOs manage HRPs at their level, there will be a reduction in unnecessary or late referrals to tertiary or higher-level facilities, allowing these facilities to concentrate mainly on the most critical cases. The study will establish a robust system for not only managing HRPs but for ensuring quality ANC services and continuum of care in geographies with poor maternal outcomes (Table 1). If the program is successful in these areas, it will pave the way for future implementation efforts in other states.

The proposed study anticipates a few limitations, such as delays in getting permissions to collect data from ANM, MOs, specialists, and RDW from the 2 control districts. In intervention districts, many MOs have recently joined the service, and their focus is on preparing for higher studies. Therefore, they may not be very keen to participate in this program. Also, if they get admission in higher studies, they will leave the service, and refilling the position may take time. We are also concerned about the support for the program from system stakeholders who are nearing retirement and working on a contractual basis. The end line qualitative results, particularly from the 2 intervention districts, might be influenced by social desirability bias, as by then, the majority of the system stakeholders will be aware of the purpose of the program and its objectives. To minimize the social desirability bias, we will do data collection methods triangulation and information triangulation (collecting same data from multiple question formats). To minimize the bias, we will also triangulate both qualitative and quantitative data, wherever feasible. Frequent transfers of district and state officials may also create hurdles in the timely implementation of interventions and getting approvals for implementing interventions on the ground.

Conclusions

The study will test the hypothesis of whether an integrated, comprehensive, system-driven intervention for improved identification, tracking, and end-to-end management of HRPs is feasible in geographies with poor maternal outcomes or not. At the community level, the study will provide insights on the role of sociodemographic, as well as ANC and delivery factors, that influence HRP management and referral practices. This trial will provide valuable insights into the feasibility and effectiveness of the program, at system and community levels, in low-resource settings like UP. If successful, these insights can feed into capacitating HWs, at scale, in all the districts on diagnosis and management of HRPs, with significant potential for improving maternal and neonatal outcomes of the state. We will also explore the options for scaling the program to include conditions beyond the 6 HRPs in other districts of UP.

For this study, the Transparent Reporting of Evaluations with Nonrandomized Designs (TREND) statement was followed [46] to ensure transparent and comprehensive reporting (Multimedia Appendix 8). Our protocol adheres to around 20 of the 23 items in the TREND checklist.

Acknowledgments

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Data Availability

The data and multimedia appendices that support the findings of this manuscript are available from corresponding author, HRM, upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Chief Medical Officer Questionnaire.
[DOCX File, 134 KB - resprot_v14i1e74993_app1.docx]

Multimedia Appendix 2
Semistructured interview with Associate Chief medical officer
[DOCX File, 146 KB - resprot_v14i1e74993_app2.docx]

Multimedia Appendix 3
In-depth interview with specialist.
[DOCX File, 70 KB - resprot_v14i1e74993_app3.docx]

Multimedia Appendix 4
Medical officer.
[DOCX File, 136 KB - resprot_v14i1e74993_app4.docx]

Multimedia Appendix 5
Auxiliary nurse midwife tool.
[DOCX File, 190 KB - resprot_v14i1e74993_app5.docx]

Multimedia Appendix 6
Recently delivered women tool.
[DOCX File, 294 KB - resprot_v14i1e74993_app6.docx]

Multimedia Appendix 7
For recently delivered women - Consent or Assent form.
[DOCX File, 133 KB - resprot_v14i1e74993_app7.docx]

Multimedia Appendix 8
TREND checklist for evaluating Integrated High-Risk Pregnancy Tracking and Management program's impact on outcomes.
[XLSX File, 10 KB - resprot_v14i1e74993_app8.xlsx]

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Abbreviations

ANC: antenatal care
ANM: auxiliary nurse midwife
AP: Andhra Pradesh
APH: antepartum hemorrhage
ARMMAN: Advancing Reduction in Mortality and Morbidity of Mothers, Children, and Neonates
ASHA: accredited social health activist
AWW: anganwadi worker
BEmONC: basic emergency obstetric and newborn care
CAPI: computer-assisted personal interview
CEmONC: comprehensive emergency obstetric and newborn care
CHC: community health center
DiD: difference-in-difference
EPMM: Ending Preventable Maternal Mortality
HRP: high-risk pregnancy
HSC: health subcenter
HW: health worker
IDI: in-depth interview
IFA: iron-folic acid
IHRPTM: Integrated High-Risk Pregnancy Tracking and Management

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IRB: institutional review board
MO: medical officer
NFHS: National Family Health Survey
NGO: nongovernmental organization
PHC: primary health center
PIH: pregnancy-induced hypertension
PSU: primary sampling unit
QANC: quality antenatal care
RCH: Reproductive and Child Health
RDW: recently delivered women
TREND: Transparent Reporting of Evaluations with Nonrandomized Designs
UP: Uttar Pradesh
WHO: World Health Organization

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Behavioral Intervention to Prevent HIV/AIDS Among Young Adults Using Motivational Culture-Based Communication: Protocol for a Research and Development Study

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Abstract

Background: HIV/AIDS is an epidemic in 190 countries, with Indonesia having more than half a million people living with the virus. Risk factors include risky sexual activity and alternating needle usage. The majority of cases are young adults (aged 18 to 30 years). The Indonesian National HIV/AIDS strategy aims to reduce new cases to less than a thousand per year. Nowadays, effective prevention involves avoiding free sex and adopting healthier lifestyles.

Objective: This research aimed to explore young adults' needs, perceptions, and cultural aspects of HIV/AIDS prevention, develop the intervention model, analyze its effectiveness, and examine its effect on HIV prevention behavior.

Methods: We conducted the study in three phases: qualitative research, model development, and quantitative research. In the first phase, we used descriptive phenomenology and focus group discussion to collect data from young adults and stakeholders in Batang and Pekalongan regencies. The second phase developed a motivation model for HIV/AIDS prevention using motivational culture-based communication (MK-U) through website media. We designed the model in consultation with an information technology team and experts to ensure its suitability. The third phase involved a pre- and posttest with a control group quasi-experiment involving young adults aged 20 - 30 years in Batang and Pekalongan districts. The intervention group received culture-based motivational interviewing, while the control group received standard counseling. We analyzed the data using a generalized linear model and multivariate analysis of variance.

Results: We expected to develop the MK-U model for HIV prevention behavior among young adults. In 2025, we implemented a community-based nursing research program for the MK-U model to prevent HIV/AIDS.

Conclusions: In this research, we compare the results with similar studies, which will benefit program implementers and policymakers in both regions and enhance the effectiveness of HIV prevention programs.

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KEYWORDS

HIV/AIDS prevention; community-based intervention; young adults; intervention development; cultural health messaging; motivational strategies

Introduction

HIV/AIDS has become an epidemic in nearly 190 countries around the world. The prevalence in the last 40 years has reached more than 80 million people worldwide [1]. The estimated number of people living with HIV/AIDS in Indonesia from 2005 to 2021 reached 543,100. The three highest risk factors for HIV/AIDS transmission in Indonesia are risky sex in heterosexuals and homosexuals, as well as the use of alternating needles among injecting drug users. The age range of 25 - 49 years accounts for the majority (68.1%) of HIV/AIDS cases. This is associated with the window period of HIV/AIDS (8 - 10 years), so it is likely that HIV transmission occurs in the age range of 20 - 30 years. The number of HIV/AIDS cases in the young adult group also increased by approximately 1% compared to 2021 [2].

Despite a notable increase in HIV infections among young adults aged 20 - 30 years in Indonesia, existing programs have not

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been adequately adapted to address the evolving needs of this demographic. There remains a significant lack of knowledge about HIV/AIDS and youth-friendly prevention, limiting accessibility and engagement [3-6]. Furthermore, digital and social media platforms—highly relevant for youth outreach—have been underutilized in HIV prevention [7]. Engagement efforts targeting individuals aged 15 - 30 years have been insufficient, despite evidence indicating early age of transmission and risk exposure [8]. In addition, cultural and religious norms continue to impede open discussions about sexual health and the promotion of condom use, further exacerbating the challenges in HIV prevention among youth [6,9]. This trend is likely to persist, and potentially worsen, if comprehensive and targeted efforts are not implemented to curb the transmission of HIV/AIDS in Indonesia, particularly among young adults.

In the absence of an effective vaccine for HIV, prevention efforts primarily rely on behavioral strategies aimed at reducing the risk of transmission. One widely recognized framework is the ABC approach—abstinence, be faithful, and condom use—which promotes risk avoidance through sexual abstinence, monogamous relationships, and consistent condom use [10]. Behavioral change interventions (BCIs) are central to HIV prevention, as they support individuals in adopting safer practices and healthier lifestyles. Among these, community outreach and mentoring have proven to be effective strategies. Such interventions often include motivational health education to discourage casual sexual encounters, the development of problem-solving skills, and access to counseling services, all of which contribute to informed decision-making and risk reduction [11,12].

Primary prevention serves as the frontline strategy in reducing the incidence of disease, employing approaches at the individual, family, and community levels [10]. Its effectiveness is significantly enhanced when supported by strong commitment and collaboration from both the community and government. One key primary prevention strategy aimed at reducing risky sexual behavior among young adults involves delaying sexual initiation and promoting sexual abstinence. Avoiding early and unprotected sexual activity during young adulthood has been shown to significantly lower the risk of HIV/AIDS transmission.

In the provision of nursing care, it is essential for nurses to apply theoretical models that are designed to guide and support individuals, families, and groups in the prevention, management, or recovery from illness [13]. One such nursing theory applicable to group-based care is Johnson's Behavioral System Model (JBSM). This conceptual model is founded on the premise that nursing practice should be guided by an understanding of behavioral systems, analogous to how medical practice is grounded in the biological systems of the human body. Johnson's model emphasizes the importance of assessing and managing human behavior systematically, thereby enabling nurses to develop comprehensive care plans that promote behavioral balance and overall well-being.

To maintain balance within each behavioral subsystem, individuals must engage in three essential activities: protection, maintenance, and stimulation. When these functional requirements are met across all subsystems—namely attachment and affiliation, dependency, ingestion, elimination, sexuality, aggression, and achievement—the individual is considered to be in a state of health that supports adaptive functioning and self-preservation [14,15]. Johnson proposed four key assumptions regarding the structure and function of each behavioral subsystem: drive, set, choice, and observable behavior. These components collectively form the foundation of the JBSM, which provides a structured framework for nursing interventions. JBSM can be effectively applied in community-based nursing care, particularly in group settings, to guide the prevention of diseases such as HIV/AIDS by promoting behavioral balance and adaptive responses among at-risk populations.

The behavioral approach is recognized as an effective method for HIV/AIDS prevention, as it enables individuals to modify risky behaviors and adopt healthier lifestyles [16]. BCIs represent a commonly used strategy aimed at reducing high-risk behaviors and promoting the maintenance of positive behaviors through a series of activities tailored to the specific needs of target groups. These interventions seek to create supportive environments at both individual and collective levels. BCIs can be implemented through the delivery of communication, information, and education strategies or through structured group education programs [17,18].

BCIs can be further developed into comprehensive intervention models designed to influence individual behavior within the context of HIV/AIDS prevention [19]. This development may involve pilot testing within research studies to ensure the model's applicability and effectiveness. The formulation of such a model may require the integration of existing theoretical frameworks, the consideration of influencing factors, and contextual adaptation based on the specific challenges identified in the study setting. One widely applied framework is the information, motivation, and behavioral skills (IMB) model, which has been used extensively to identify modifiable determinants of behavior and to guide the development of effective behavioral interventions [20,21].

However, several limitations have been identified in the IMB model. First, the information construct within the model has been shown to be a relatively weak and sometimes inconsistent predictor of behavior. While information is necessary, it alone is often insufficient to drive behavioral change. For instance, a study by Eggers et al [22] found that behavioral skills predicted actual behavior through motivation, as hypothesized by the IMB model, but not directly through knowledge about sexually transmitted infections. The second limitation concerns the overlap between the constructs of information and motivation, which are often not clearly distinct in practice. This interdependence presents challenges in testing and validating the model, as it complicates the interpretation of their individual effects. Lastly, the IMB model does not incorporate environmental and cultural factors, which are critical in predicting and explaining behavior, particularly in diverse sociocultural contexts. The exclusion of these factors limits the model's predictive power and its applicability across different populations [23].

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Therefore, in response to the limitations identified in the IMB model, a modification will be undertaken by integrating the motivation construct of the IMB model with another theoretical framework, the integrated change model (ICM). This integration aims to examine additional variables that may enhance the explanatory power of the model by accounting for human characteristics, environmental factors, temporal changes, and contemporary cultural influences. The ICM conceptualizes behavior change as a process comprising three phases: awareness, motivation, and action [24,25]. Moreover, the ICM incorporates predisposing factors, including social and cultural determinants, which address a notable gap in the IMB model that does not explicitly consider these influences. This study will utilize a culturally contextualized communication approach as a novel application of the combined model. The integrated and modified framework, termed the motivational culture-based communication (MK-U) model, will be empirically tested to assess its effectiveness in enhancing self-awareness, behavioral intentions, and preventive actions related to HIV/AIDS. This evaluation will be conducted through a series of research phases aimed at validating the model's applicability within the target population.

One of the primary objectives of the Indonesian National HIV/AIDS Strategy is to reduce the annual incidence of new HIV infections to fewer than 1000 cases. Achieving this ambitious target necessitates a phased, multilevel approach, with particular emphasis on reaching vulnerable populations such as young adults aged 20 to 30 years. District- or city-level interventions targeting this demographic are crucial components of this strategy, as localized efforts allow for tailored prevention and treatment initiatives that reflect the unique epidemiological and sociocultural contexts of each area. However, preliminary data from two districts in Central Java—Batang and Pekalongan—indicate that current efforts remain suboptimal in effectively engaging this key age group.

Several factors contribute to this shortfall. First, epidemiological data show that the majority of new HIV/AIDS cases (65.4%) occur within the broader age range of 25 - 49 years, suggesting that prevention efforts may not be sufficiently targeted or timed to intercept risk behaviors early among younger adults before infection occurs. Second, mobile voluntary counseling and testing (VCT) services, which serve as critical entry points for diagnosis and linkage to care, have predominantly focused on key populations such as sex workers and men who have sex with men, inadvertently overlooking the broader young adult population at risk. Additionally, these VCT activities have yet to fully leverage internet-based platforms and eHealth approaches, such as websites and mobile apps, which are increasingly recognized as effective tools for outreach, education, and engagement among digitally connected youth.

Furthermore, the absence of active youth organizations dedicated to HIV/AIDS awareness and advocacy limits peer-to-peer education and support mechanisms that are vital for influencing behavioral change within this age cohort. The role of the AIDS Commission (Komisi Penanggulangan AIDS [KPA]), which is pivotal in coordinating multisectoral HIV/AIDS responses at the district level, has also been constrained by budgetary restrictions exacerbated by the lingering economic impacts of the COVID-19 pandemic. This financial limitation has hindered the commission's capacity to sustain outreach programs, implement innovative interventions, and maintain consistent community engagement.

Addressing these gaps requires a comprehensive, multifaceted approach. Integrating digital health technologies into VCT and prevention programs could enhance accessibility and appeal to young adults who are frequent users of social media and online platforms. Strengthening partnerships with youth-led organizations and incorporating peer-led models may increase trust and relevance in prevention messaging. Moreover, advocating for the restoration and expansion of funding for local AIDS commissions is critical to ensure sustained program delivery. Finally, employing data-driven targeting that accounts for local epidemiology and behavioral risk patterns can improve the precision and impact of interventions aimed at reducing new infections among young adults, ultimately supporting Indonesia's goal of curbing the HIV epidemic.

Based on this background, this study seeks to develop a website-based outreach model targeted at young adults as a strategic intervention for HIV/AIDS prevention, with the ultimate goal of contributing to the reduction of HIV/AIDS incidence in Indonesia. The research is grounded in the urgent need for culturally sensitive, youth-oriented approaches that leverage digital platforms to promote awareness, intention, and behavior change. Accordingly, the question of this research is how effective is the MK-U model in increasing self-awareness, behavioral intention, and preventive behavior related to HIV/AIDS among young adults aged 20 to 30 years in Central Java, Indonesia.

The objectives of this research are as follows: (1) to explore the needs, perceptions, and behavioral determinants of young adults in relation to HIV/AIDS prevention, (2) to examine the programs, strategies, and sociocultural dimensions employed by local stakeholders in HIV/AIDS prevention efforts targeting young adults, (3) to design and develop the MK-U model framework, including an intervention module, workbook, evaluation instruments, and a web-based outreach platform tailored to the needs of young adults, (4) to assess the effectiveness of the MK-U model in enhancing self-awareness and behavioral intention related to HIV/AIDS prevention among young adults, and (5) to evaluate the impact of the MK-U model intervention on the adoption of preventive behaviors among young adults at risk of HIV/AIDS.

Methods

Study Design

This study used the research and development method to develop the MK-U model. This method was used to create specific products or models and to evaluate their effectiveness. Three phases comprised the research process: qualitative research, model development, and quantitative research, in order to produce a specific product or model. The duration of phases is described in the study outline (see Figure 1).

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Figure 1. Study outline.

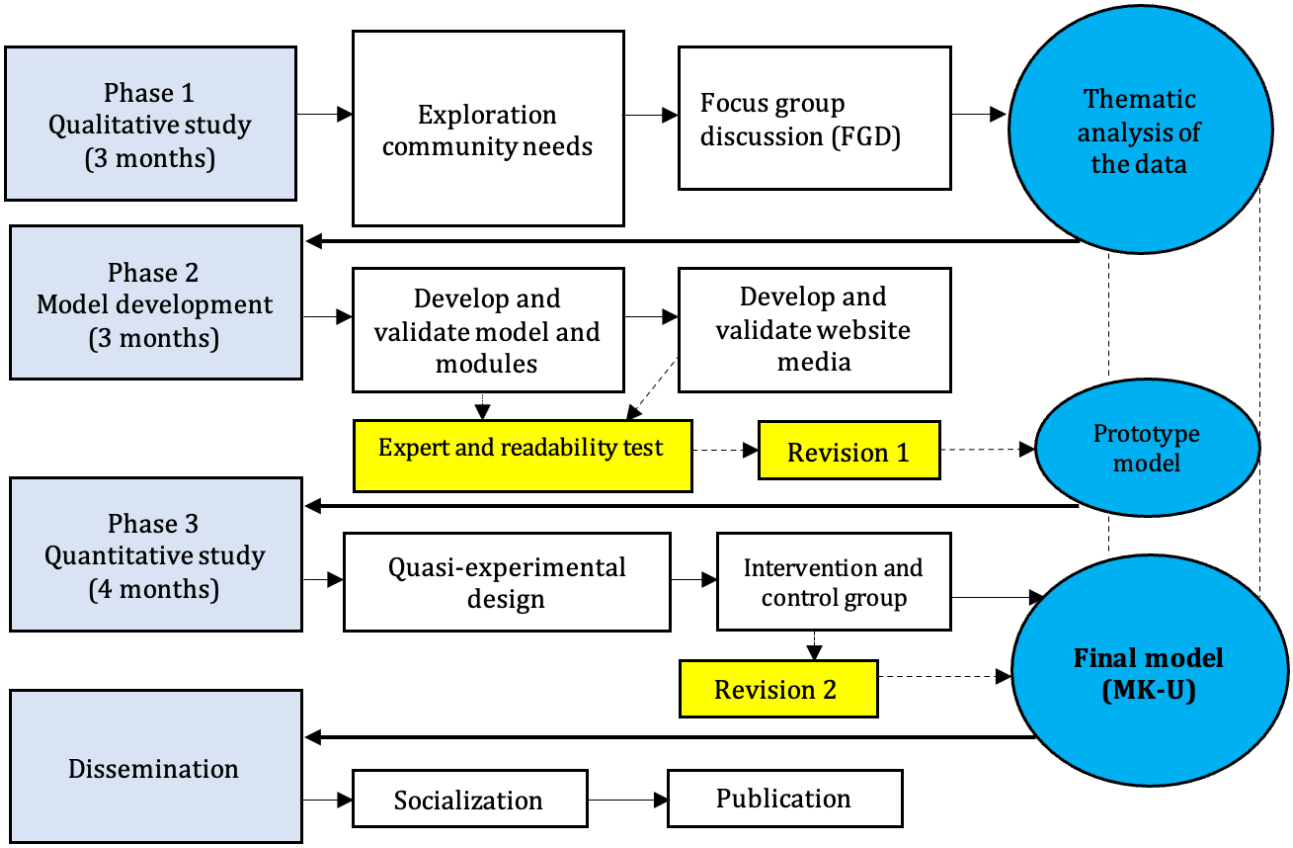

Phase 1: Qualitative Study

Study Setting

The research was conducted in a community setting in Pekalongan and Batang Regencies, Central Java, Indonesia. The primary objective of the first phase of the research explored the perceptions and needs of young adults in order to enhance their HIV/AIDS preventive practices. In addition, exploration needed to be done with stakeholders, namely nurses as program implementers, the Health Office, the District AIDS Commission, and nongovernmental organizations (NGOs), to explore cultural aspects and programs that have been carried out for HIV/AIDS prevention in Pekalongan and Batang Districts.

The research approach carried out in this study was a descriptive phenomenology with focus group discussion (FGD) as a data collection method. This approach was very effective for studying, better understanding, and describing important phenomena from human experience or participants [26,27]. The results of this study were used as material to develop the MK-U model by utilizing website media.

Participants

The study consisted of two distinct groups of participants: young adults and stakeholders from the Batang and Pekalongan regency areas. The young adult group consisted of a total of 20 participants, separated into two subgroups. Specifically, there were 10 male young adults and 10 female young adults from each regency. Engaging both male and female young adults in this research enabled the capture of gender-specific insights concerning knowledge gaps, communication patterns, stigma, and prevention behaviors within the key demographic at heightened risk of HIV infection. This gender-inclusive approach facilitated a more comprehensive understanding of the differential factors influencing HIV-related attitudes and practices, thereby informing the development of targeted interventions that address the unique needs and challenges faced by each gender group in the context of HIV prevention.

The stakeholder's group consisted of a total of 20 participants as well, separated into two subgroups. Specifically, there were 10 participants from health workers and 10 participants from nonhealth workers from each regency. The health workers included the health care provider at the public health office (Dinas Kesehatan) and nurses at public health center (Puskesmas). This group consisted of 2 participants from public health office and 8 participants from public health center (Puskesmas) in each regency. This study uncovered provider-level stigma, training needs, and systemic barriers that hinder effective service delivery and coordination of HIV care. By including health workers from both administrative and frontline roles, the research facilitated a comprehensive exploration of their attitudes, knowledge levels, and existing training gaps. Understanding these dimensions was essential, as they directly influenced the accessibility, quality, and responsiveness of HIV prevention and care services at the local level. This approach also highlighted structural and institutional challenges that must be addressed to strengthen the overall effectiveness of community-based HIV interventions.

In addition, nonhealth stakeholders participating in this study included the District AIDS Commission (KPA) coordinators, NGO coordinators, and community leaders from both Batang

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and Pekalongan districts. This group comprised 3 participants from the KPA, 4 from NGOs, and 3 community leaders in each district. FGDs continued until data saturation was reached within each stakeholder group. The inclusion of nonhealth stakeholders was critical for capturing the broader social dynamics, cultural norms, and collaborative mechanisms that shape HIV prevention efforts and influence stigma at the community level. Their perspectives provided valuable insights into how societal attitudes, community leadership, and local advocacy shape the effectiveness of existing interventions. Furthermore, this approach allowed for a deeper understanding of the strengths and limitations of current partnerships among governmental, nongovernmental, and community actors in addressing HIV-related challenges.

Participants Recruitment

The research used purposive sampling as the sample technique. The participants focused on the specified inclusion requirements, which require them to be young people between the ages of 20 and 30 years, unmarried, and eager to actively participate. The exclusion criteria pertained to young individuals who have mental illnesses. NGOs were engaged to facilitate the recruitment of key informants in both areas. Meanwhile, stakeholder participants were invited through agency leaders to represent them in the research process.

Data Collection

The researcher recruited a research team consisting of four people to assist in the research process. Semistructured interview guidelines were used to perform FGDs. Each FGD group had a session that lasted roughly 90 - 120 minutes. Throughout the FGD process, the research team transcribed and recorded participants' names and comments. The seating arrangement was based on the attendees' preferences. Researchers recorded the whole FGD session, capturing the process from the beginning to the end, using a voice recorder and digital camera. If one of the informants was absent, the researcher confirmed the reason for not being able to attend and then recorded it in the field notes. The FGD process proceeded based on the number of participants present. The research team summarized and analyzed each FGD session, then presented a written or oral report to the participants. All comments and grammatical mistakes were reviewed and fixed as necessary.

Data Analysis Plan

A content and thematic analysis was used for data analysis using four steps, including bracketing, analyzing, intuiting, and describing [26,28]. Then, the credibility technique was used to explain the degree or truth value of the data generated, including the data analysis process from the research conducted. We implemented two strategies to ensure data validity: the first involved the researcher, who also used FGD discussions and participant observation to ensure the data were truly accurate. The second strategy was member check, which involved anyone who participated in the research in checking the findings to ensure that they were consistent with their experience. We also used descriptive validity and interpretative validity techniques to ensure the validity of the data. Descriptive validity refers to the report's factual accuracy, whereas interpretive validity refers to the report's interpretation. The report was based on the participants' language and relied as much as possible on their own words and concepts. When summarizing the results, the researcher was cautious because there were jumps from the participants' words and actions that affected the conclusions. The entire FGD process was in Bahasa Indonesia. All data were performed manually with Microsoft Excel, ensuring a thorough and reflective engagement with the data.

Phase 2: Model Development

Study Procedures

The goal of phase II research was to develop a motivation model for HIV/AIDS prevention among young adults using MK-U through internet media. After obtaining findings from the first phase of the research, researchers proceeded with reviewing literature derived from textbooks and previous articles published in scientific journals. This literature review focused on the examination of HIV/AIDS preventative behavior among young adult populations, using a cultural framework facilitated by online media or telehealth platforms. Thus, the present study ascertained and established the development of this model by analyzing the findings of phase 1 research and three conceptual models, namely the IMB model [21], the ICM [24], and the JBSM [29], which were used in this study.

Subsequently, the researchers collaborated with an information technology (IT) team to design a website that aligns with the objectives. Following this, the researchers and the IT team scrutinized the website's requirements, pinpointing the system's users and defining its functional and nonfunctional needs, in order to offer a preliminary outline of the system's construction during its implementation. Researchers also formed a content creation team to create website materials and media tailored to user needs. Finally, using reference sources that aligned with the topic and needs, researchers formed a team to prepare a draft module that integrates with the MK-U model. We then subjected the draft modules and workbooks to expert and readability tests to ensure their suitability for use.

Expert and Readability Tests

We conducted the first expert consultation to gather input, suggestions, and approval for the draft website, module, and workbook. Then, we compiled it before the trial. The instrument for the expert consultation was a questionnaire. The researcher presented a series of statements and asked the expert to clearly assess their appropriateness for the young adult age group. We used these statements as content on the website, developed modules, and sourced workbooks from several relevant pieces of literature. Regarding the website draft, it was consulted with technology experts who were experienced in making websites. Experts in content creation also provided advice on incorporating content like videos and photos into the website.

Then, specifically for the nursing training module, an expert test was conducted to determine the training materials for counseling with a culturally based motivational interviewing (MI) approach or communication style for health care nurses. In the context of initial content validation for a small-scale training module, the engagement of three to five subject-matter experts is widely regarded as methodologically sound and

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appropriate. This range is supported in the literature as sufficient for obtaining expert judgment on the relevance, clarity, and importance of instructional materials, particularly during early stages of development [30].

Following the initial identification of key materials, a panel of experts was invited to review the preliminary list to evaluate its completeness and relevance. Experts were encouraged to suggest additional materials they deemed important but were not included in the original compilation. Based on their feedback, the list was revised accordingly. Subsequently, a second round of expert review was conducted, during which the experts were asked to rank each material on a scale from 1 to 4, with higher scores indicating greater importance for inclusion in the training module. This ranking process aimed to establish a prioritized understanding of content relevance, ensuring that the most critical materials would be emphasized in the final training design.

As part of the expert validation process for the training module, a 1 - 4 ranking scale will be employed to assess the relative importance of selected content materials. Ranking is particularly effective in expert-based content validation as it requires participants to differentiate and prioritize items, thereby offering clearer insights into which materials are perceived as most essential. Unlike rating scales, ranking forces a comparative judgment across items, minimizing the risk of score inflation or central tendency bias. The use of a 4-point ranking scale is both purposeful and practical. Given the small number of items under consideration, a limited set of ranking options helps maintain cognitive ease for the experts while still producing meaningful distinctions between materials. Additionally, the even-numbered format avoids the inclusion of a neutral midpoint, thereby encouraging more decisive judgments regarding each item's relative importance. This enhances the discriminative power of the expert feedback and supports better prioritization in the final training content. The purposive sampling technique will select experts based on the inclusion criteria, which include panels and experts actively involved in HIV/AIDS prevention efforts at both national and regional levels for a minimum of 5 - 10 years. Additionally, we included technology experts who have accumulated at least 5 - 10 years of experience in IT and eHealth website development.

A pilot study was conducted to evaluate the usability, functionality, and content effectiveness of the developed website or training material prior to full-scale implementation. A purposive sample of 5 to 10 participants representative of the target audience was recruited, as this size was generally sufficient to identify most usability issues. During the pilot, participants were asked to complete specific tasks while navigating the website or materials, allowing the researcher to observe ease of navigation, clarity of content, technical performance, and overall user satisfaction. Data collection included observation checklists, standardized usability questionnaires, and qualitative feedback obtained through interviews. Quantitative data were analyzed descriptively to assess usability ratings, while qualitative data were thematically analyzed to identify common barriers and areas for improvement. Findings from the pilot study informed necessary revisions to optimize the user experience and enhance the effectiveness of the training content before the main implementation phase.

Phase 3: A Quasi-Experimental Study

Study Design

After the draft model was developed in the second stage of research, the next stage of research was to test the effectiveness of the model. In research and development, we used quantitative research methods to test the model's effectiveness. The research design in this study was a pre-post test with a control group quasi-experiment design.

Study Population and Eligibility Criteria

Young adults aged 20 - 30 years, residing in Batang and Pekalongan districts, possessing internet-connected gadgets, and not married met the inclusion criteria. Young adults with a history of mental disorders and HIV/AIDS infection met the exclusion criteria.

Sample Size

The formula's sample calculation indicates that this study included 109 samples for both the intervention and control groups. To anticipate dropout, the sample was increased by 20% [31]. Therefore, the total sample in this study was 130, consisting of 65 for the intervention group and 65 for the control group.

Recruitment

We utilized simple random sampling as a sampling technique, adhering to the following sequences: (1) prospective respondents will register as members on the provided website; (2) after becoming members, they will be asked to indicate their willingness to participate in the study; (3) respondents who meet the inclusion and exclusion criteria will be randomly selected to participate in the research process; and (4) respondents may refuse participation or withdraw at any time without consequence. To ensure allocation concealment, the randomization sequence was generated by an independent researcher using computer software, and assignments were kept confidential until the point of selection to prevent selection bias. Due to the nature of the study, blinding of participants and researchers may not be feasible; however, outcome assessors were blinded to participants' group assignments to minimize detection bias and enhance the study's internal validity.

Data Collection Methods

Researchers obtained research permits from the governments of Pekalongan and Batang Regency to conduct research in these areas. The study spanned 4 months, with the research secretariat based in Pekalongan Regency and the University of Pekalongan managing the website server. Researchers made sure that the website, media content, and MK-U model materials used in the research process are suitable for use in accordance with the procedure, based on the findings from the first and second stages of research. Researchers recruited 20 public health nurses who served as counselors during the research process: 10 nurses became control group counselors, and 10 nurses became intervention group counselors. For 3 days, nurses who served as counselors in the intervention group received standardized

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training on the culture-based communication model and MI techniques, training in one type of MK-U model intervention, specifically counseling with a culture-based MI approach. The training included workshops, role-playing exercises, and practice sessions with feedback. A manualized intervention protocol was also developed to ensure consistent delivery across all sessions and counselors. Researchers prepared research tools such as questionnaires, modules, workbooks, training modules, and counseling process forms. Researchers prioritized respondents from the Batang and Pekalongan Regency areas who access the study's website. Researchers and their team conducted research activities with respondents in 13 weeks for the intervention and control group (see Table 1).

Table . Activities of respondents during the research process.

Weeks	Intervention group activities	Control group activities
Week 1 (Drive)	• Respondents fill out the pretest. • Respondents access a website that contains content and materials about HIV/AIDS. • The nurse provided one counseling session with a culture-based MI approach to increase encouragement.	• Respondents fill out the pretest. • Respondents access a website that contains content and materials about HIV/AIDS. • The nurse provided one counseling session as usual.
Week 2 (Set)	• Respondents access a website that contains content and materials about HIV/AIDS. • The nurse provides one counseling session with a culture-based MI approach to be able to set a change plan.	• Respondents access a website that contains content and materials about HIV/AIDS. • The nurse provided one counseling session as usual.
Week 3 (Choice)	• Respondents access a website that contains content and materials about HIV/AIDS. • The nurse provided one counseling session with a culture-based MI approach to improve the ability to choose.	• Respondents access a website that contains content and materials about HIV/AIDS. • The nurse provided one counseling session as usual.
Week 4 (Behavior)	• Respondents access a website that contains content and materials about HIV/AIDS. • The nurse provided one counseling session with a culture-based MI approach to establish positive behavior.	• Respondents access a website that contains content and materials about HIV/AIDS. • The nurse provided one counseling session as usual.
Week 5	• Respondents access a website that contains content and materials about HIV/AIDS. • The nurse provides one counseling session with a culture-based MI approach to create an action plan for HIV/AIDS prevention behavior. • Respondents fill out the first posttest.	• Respondents access a website that contains content and materials about HIV/AIDS. • The nurse provided one counseling session as usual. • Respondents fill out the first posttest.
Week 6 - 8	• Allocate time if a process remains unfinished.	• Allocate time if a process remains unfinished.
Week 9 - 12	• Respondents perform activities independently.	• Respondents perform activities independently.
Week 13	• Respondents in the intervention group complete the second posttest.	• Respondents in the control group complete the second posttest.

Outcomes

The intervention group conducted a pretest before initiating the MK-U model intervention action, followed by two posttests: one after the intervention was completed and another 3 months later. The intervention group received the MK-U model intervention, which included access to HIV/AIDS information on the website, modules, and a counseling process using a culture-based MI communication approach by nurses. To ensure consistency in the delivery of MI, we incorporated a fidelity monitoring process using structured observation checklists based on the Motivational Interviewing Treatment Integrity coding system. Sessions were recorded (with participant consent), and a random sample was reviewed by an independent expert to assess adherence to MI principles. Conversely, the control group experiences the standard counseling process from nurses. The objective is to ascertain the variation in the average of variables among the participants before and after the implementation of the intervention program.

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Data Analysis Plan

The obtained data were processed using statistical software compatible with the Windows operating system. We used a generalized linear model with multivariate analysis of variance to analyze the effect of the MK-U model intervention. The analysis assumed that the dependent variables are multivariate normally distributed and that variance–covariance matrices are homogeneous across groups. To assess these assumptions, we conducted the Shapiro-Wilk test for normality, Box's M test for equality of covariance matrices, and Levene's test for homogeneity of variances. Independence of observations and linearity between dependent variables and covariates were also evaluated. Multicollinearity among dependent variables was assessed through correlation matrices, and significant outliers were identified using Mahalanobis distance. If any assumptions were violated, appropriate data transformations or alternative nonparametric methods were employed to ensure the validity of the analysis.

Results from the generalized linear model with multivariate analysis of variance were reported with test statistics, degrees of freedom, *P* values, and effect sizes for each dependent variable. Multivariate test results were presented to indicate the overall effect of the MK-U model intervention across outcome measures. When significant multivariate effects were detected, follow-up univariate analyses were conducted to determine which dependent variables contributed to the effect. Confidence intervals were reported alongside point estimates to indicate precision. All assumption checks, data transformations, or alternative analyses performed were transparently documented. The interpretation of results considered both statistical significance and practical relevance by examining the magnitude and direction of observed effects within the context of the study.

Ethical Considerations

This research was conducted by considering the principles of research ethics, including consent, confidentiality, and anonymity, as well as protection from discomfort and harm [27,30]. This study has received ethical approval from the Research Ethics Committee, Faculty of Nursing of Universitas Indonesia (approval number: KET-001/UN2.F12.D1.2.1/PPM.00.02/2024, with an amendment on January 2, 2024).

To obtain consent, the researcher provided information sheets and explained research procedures to respondents. Then the participants filled out and signed the consent form to take part in the research. Participants have the right not to participate in the study. The study does not pose any harmful side effects to participants. Although no compensation is provided in the form of payment, each participant will receive a souvenir as a gesture of appreciation for completing the study procedures. Researchers maintained the confidentiality of all data collected from respondents, including personal information such as name, address, and other personal details. Meanwhile, protection from discomfort and harm referred to the researchers' measures to ensure that participants are not in danger, are free from harmful actions, both oral and written, and are provided with comfort throughout the research process. The study also did not involve any invasive measures, nursing, or medical treatments. If there is any discomfort or disadvantage during the study, respondents can withdraw from the research process.

A password-protected computer stored data in the form of soft files, and the researcher's office housed all research files for a period of 3 years. Upon completion of the research activities, we destroyed all documents, information sheets, and consent forms, including those stored on the computer during that period. The research results were presented in the form of data groups within the research report.

Results

The results of this study provided evidence on the feasibility, usability, and preliminary efficacy of the MK-U web-based outreach model in promoting HIV/AIDS preventive behaviors among young adults in the districts of Pekalongan and Batang.

Quantitative data included pre- and postintervention measures of HIV knowledge, self-awareness, behavioral intention, and HIV prevention behavior. The findings are expected to inform the development of scalable, digitally enabled interventions for use by public health nurses and HIV prevention practitioners across similar contexts. This study is expected to develop an adapted, web-based outreach strategy aimed at enhancing self-awareness, behavioral intention, and HIV prevention behaviors among young adults.

This research is currently in process at Phase 1 data analysis.

Discussion

Principal Findings

Recent evidence underscores that the provision of information alone is insufficient to produce sustained changes in HIV prevention behaviors among young adults. While traditional interventions have often prioritized knowledge dissemination, such approaches frequently neglect the internal cognitive and motivational mechanisms that underpin behavior change. Research increasingly highlights the critical role of factors such as self-awareness, intention, self-efficacy, and behavioral skills in fostering effective and long-term preventive behaviors [32-35]. For instance, digital HIV interventions that integrate MI, behavioral theory, and user-centered design have shown greater success in promoting consistent condom use, HIV testing uptake, and preexposure prophylaxis adherence [36-39]. Moreover, engagement with these interventions has been found to be significantly mediated by digital literacy, further emphasizing the importance of tailoring approaches to users' technological competencies [40,41]. The MK-U model directly addresses these gaps by incorporating cognitive and motivational components into a culturally contextualized, digitally enabled framework, offering a more comprehensive and responsive strategy for influencing HIV-related behaviors among young adults.

This study has several methodological and conceptual strengths. The use of a mixed-methods design enhances both the breadth and depth of the analysis. Furthermore, the study's focus on digital literacy as both an outcome and a mechanism of change is particularly timely and relevant in the current technological

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context. However, certain limitations should be acknowledged. Due to the nature of the intervention, blinding of participants and implementers is not feasible, which may introduce bias in self-reported outcomes. Additionally, the study is context-specific and conducted in Bahasa Indonesia, which may limit the generalizability of findings to other cultural or linguistic populations.

Dissemination Plan

The findings of this study are disseminated through national and international academic journals and conferences, particularly those focused on public health nursing and HIV/AIDS. It is anticipated that public health nurses will be able to utilize the resulting intervention model within their respective practice settings to enhance community-level HIV/AIDS prevention efforts.

Conclusions

We believe that the results of the study will help provide solutions to prevent the spread of HIV/AIDS, especially among young adults in Pekalongan and Batang. We expect this research to enhance the outcomes of previous studies. The study's findings are reported by comparing and discussing them with the results of previous similar studies. As a result, HIV/AIDS prevention program implementers and policymakers in both regions can benefit.

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Authors' Contributions

All authors (MKU, AS, HP, MM) contributed equally to all stages of the study, including making substantial contributions (concept, methodology, and data extraction), drafting and revising the manuscript, giving final approval of the version to be published, and agreeing to be accountable for all aspects of the work.

Conflicts of Interest

None declared.

Checklist 1
SPIRIT checklist.
[PDF File, 119 KB - resprot_v14i1e72996_app1.pdf]

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Abbreviations

BCI: behavioral change intervention
FGD: focus group discussion
ICM: integrated change model
IMB: information, motivation, and behavioral skills
JBSM: Johnson's Behavioral System Model
KPA: Komisi Penanggulangan AIDS
MK-U: motivational culture-based communication
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
VCT: voluntary counseling and testing

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The Physical Activity, Imaging, and Ambulatory Testing (PHIAT) Project: Protocol for a High-Frequency Ambulatory Assessment Study

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Abstract

Background: Multiple independent lines of research on self-regulation point to executive cognitive ability (executive function/cognitive control) as a factor that underlies the capacity to successfully regulate one's thoughts, emotions, and behavior. Critically, while leading theories point to the role of executive control in modifying "in-the-moment" regulatory processes (eg, enacting physical activity, resisting a poor dietary choice, reflecting on a stressful experience), few studies have tested the executive hypothesis at this timescale. Moreover, given the normative changes in executive control across the adult lifespan, it is essential to understand how cognitive aging might impact these processes.

Objective: The Physical Activity, Imaging, and Ambulatory Testing (PHIAT) project was designed to test how variation in executive control at multiple timescales (from moment-to-moment within days to age differences across decades) influences self-regulation across the adult lifespan.

Methods: A 14-day, high-frequency, ambulatory assessment protocol was designed for this study. The study was conducted in a measurement burst design and included a 14-day ecological momentary assessment (EMA) protocol involving 6 assessments per day. Ultra-brief ambulatory cognitive assessments of multiple domains of cognition were included in the EMA protocol. Throughout the measurement burst, participants also wore 3 activity monitors on the hip, thigh, and wrist to measure physical activity/exercise, measure sedentary behavior, and self-monitor physical activity behavior, respectively.

Results: A total of 221 participants ranging from 18 to 89 years of age completed the PHIAT protocol over the course of 2021-2024, and data collection is complete. EMA data were collected from participants reflecting a wide range of psychosocial factors surrounding participation in health-promoting behaviors (motivation, intention, stress, built environment, and social cognitive factors). This EMA data stream is complemented by data from high-frequency, ambulatory cognitive assessments measuring processing speed, working memory capacity, inhibitory control, and divided/sustained attention administered 5 times per day throughout the 14-day burst. In addition, health-promoting behaviors, including sleep, diet, hydration, physical activity, and exercise, were assessed throughout the 14-day burst through a combination of EMA self-report and continuous activity monitoring.

Conclusions: A rich, high-frequency dataset was generated by the PHIAT project that will provide a range of novel insights into the motivational factors, information processing, and environmental factors that surround self-regulation of health-promoting behavior.

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KEYWORDS

self-regulation; executive control; EMA; ambulatory cognitive assessment; physical activity; imaging; ambulatory testing; ambulatory assessment; emotion; exercise; self-monitor; health-promoting behavior

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Introduction

Background

A defining feature of human cognition is the ability to behave in a goal-directed manner in the face of a myriad of competing, and often salient, alternatives (our ability to self-regulate) [1-3]. Behaviors that promote long-term health, such as physical activity (PA), are often described as "effortful" or "difficult" and thus require effective self-regulatory control to align momentary behavior (going for a walk) with long-term goals (to remain healthy) [4-8]. Regular PA is associated with a wide range of long-term health benefits, including reduced risk for preventable chronic disease (eg, cardiovascular disease and type 2 diabetes) and age-related neuropathology (eg, Alzheimer disease and related dementias) [9-14]. In addition, regular PA may support long-term cognitive health throughout the adult lifespan [15,16]. Thus, a virtuous cycle has been speculated to exist between cognition and PA behavior [5,17,18]. Critically, however, substantial individual differences exist in the ability to translate one's motivation and goals to maintain or increase PA into overt daily behavior (known as the PA "intention-behavior gap") [6,8,19,20]. Despite great efforts to understand why such a gap exists and how to successfully intervene, the antecedents and moderators of successful self-regulation remain poorly understood. Moreover, it remains unclear whether these factors play a stable role in PA self-regulation across the adult lifespan.

Recent attention has turned to cognitive ability, specifically executive control, as a possible source of individual differences in self-regulatory capacity [21-24]. Several recent studies evaluating the executive hypothesis, including our own work, support this claim showing that control over information processing moderates and independently contributes to health outcomes and health promotion behavior over and above self-reported intentions or tendency to self-regulate [6,21,22,25,26]. However, executive control abilities are not stationary and may vary as a function of time (eg, time of day) and context (eg, in response to a stressful interaction) [27-29]. Moreover, the underlying neurocognitive resources (the frontoparietal brain structure and function) are particularly subject to age-related decline and alteration [30-38]. These multitimescale alterations may influence *when* an individual is prepared to successfully self-regulate and may modify the process of self-regulation over the course of the adult lifespan. However, few studies have examined these mechanisms across these timescales or in an age-diverse sample.

The Project

The Physical Activity, Imaging, and Ambulatory Testing (PHIAT) project was a high-frequency, ambulatory assessment study conducted over the course of 2019-2024. The project was sponsored by the National Institute on Aging of the National Institutes of Health as part of an R00 Career Development Award (R00AG056670; principal investigator: JGH). The project was designed as an adult lifespan, microlongitudinal observational study of real-time variation in cognitive executive control and self-regulation of health-promoting behavior. The overall aims of the PHIAT project were as follows: (1) to examine variation in executive control and self-regulation of PA in real time and (2) to examine age-variant and invariant contributions of brain structure, function, and executive control in self-regulation of health-promoting behaviors. The overarching hypothesis examined by the PHIAT project was that *executive control is a resource upon which successful self-regulation depends* (an *executive hypothesis* of self-regulation; see also [8,22-24]).

To accomplish the PHIAT project aims, we chose an ecological momentary assessment (EMA) approach. The EMA protocol was conducted over a 14-day measurement burst (6 assessments/d). This approach was complemented by the contemporaneous use of multiple wearable activity monitors (to measure PA, sedentary behavior, and self-monitoring behavior) and the administration of ultra-brief, ambulatory cognitive assessments during EMA surveys to examine short-term variation (within- and between-day) in multiple domains of cognition.

These high-frequency data streams were designed to be integrated at multiple timescales to accomplish the study aims. A central focus of the project was on short-term variation in executive control. In a previous set of studies, we rigorously designed and parameterized ultra-brief adaptations of complex span working memory tasks for EMA administration [27]. Based on our development and testing, we selected the ultra-brief (~1 min) rotation span task as our primary indicator of executive control in PHIAT. We also included other ultra-brief experimental indices of attention and executive control, including a go/no-go task and a multiple object tracking task, as well as a previously validated indicator of processing speed (symbol search task) [39]. Each of these tasks was administered during 5 of the 6 daily EMA surveys (morning survey, plus 4 beeped surveys), providing a detailed time series of variation in multiple domains of cognition both within and between days in the study.

Conceptual Framework

Overview

In many studies, successful self-regulation is inferred from the exhibition of a target behavior (eg, meeting recommended levels of weekly PA, achieving a healthy diet, adaptive affective responses, and successful behavior change). In the PHIAT project, we aimed to test the executive hypothesis at a more granular level by extending two existing frameworks to a higher-frequency sampling approach: a *dynamic action control framework* and a *momentary contextual reactivity framework*. A major assumption underlying this approach is that no one is *always* successful at regulating their thoughts, emotions, and behavior, and that by intensively monitoring behavior, we might be able to generate a more detailed picture of the factors that drive self-regulatory success and failure (ie, moderators).

Dynamic Action Control Framework

The process of translating/realizing one's motivation into real-world behavior has been a major focus of study for decades [1,20,40]. Among research focused on the psychological antecedents of behavior, the formation of an intention has emerged as among the most proximal to action [20,41]. The

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action control framework proposes that there may be several factors that guide the translation of (or failure to translate) intentions into behavior. In the case of PA, modifiers of action control ranging from psychological (eg, social cognitive variables, personality, affect, and identity) to behavioral (eg, habit/previous behavior) have been well-studied [41]. A limitation of previous work has been the focus on explaining the PA intention-behavior gap in cross-section (ie, *who* successfully translates their intentions into behavior). In the PHIAT project, we extended this framework to accommodate day-to-day variation in factors that might help explain the gap at a more process-oriented level (ie, *when* do individuals successfully translate their intentions into behavior; see also [42]; Figure 1A). Several aspects of PA *orientation* (intention, goals, perceived control, and social cognitive factors) were monitored on a daily basis throughout the protocol, with a focus on short-term variation in executive control as the primary hypothesized modifier. In addition, the inclusion of an adult lifespan sample provides the opportunity to evaluate how age-associated changes in factors surrounding action control modify the process.

Figure 1. The Physical Activity, Imaging, and Ambulatory Testing (PHIAT) project conceptual framework. Two frameworks for operationalizing self-regulation as a within-person process are included in the PHIAT project. (A) *Dynamic action control framework*: The ecological momentary assessment (EMA) protocol is designed to examine whether a person's daily orientation toward PA (motivation, intentions, and goals) manifests in that day's PA behavior. (B) *Momentary contextual reactivity framework*: The EMA protocol surveils for PA opportunities and examines whether a person's behavior in those contexts is consistent with their characteristic or daily PA orientation. (C) The EMA protocol lasted for 14 days and included 6 assessments per day. (D) General within-person analytical approach. Multilevel moderation analyses are planned to examine the executive hypothesis, which predicts a stronger association between today's intention to be physically active and today's physical activity behavior on days with higher working memory capacity. PA: physical activity.

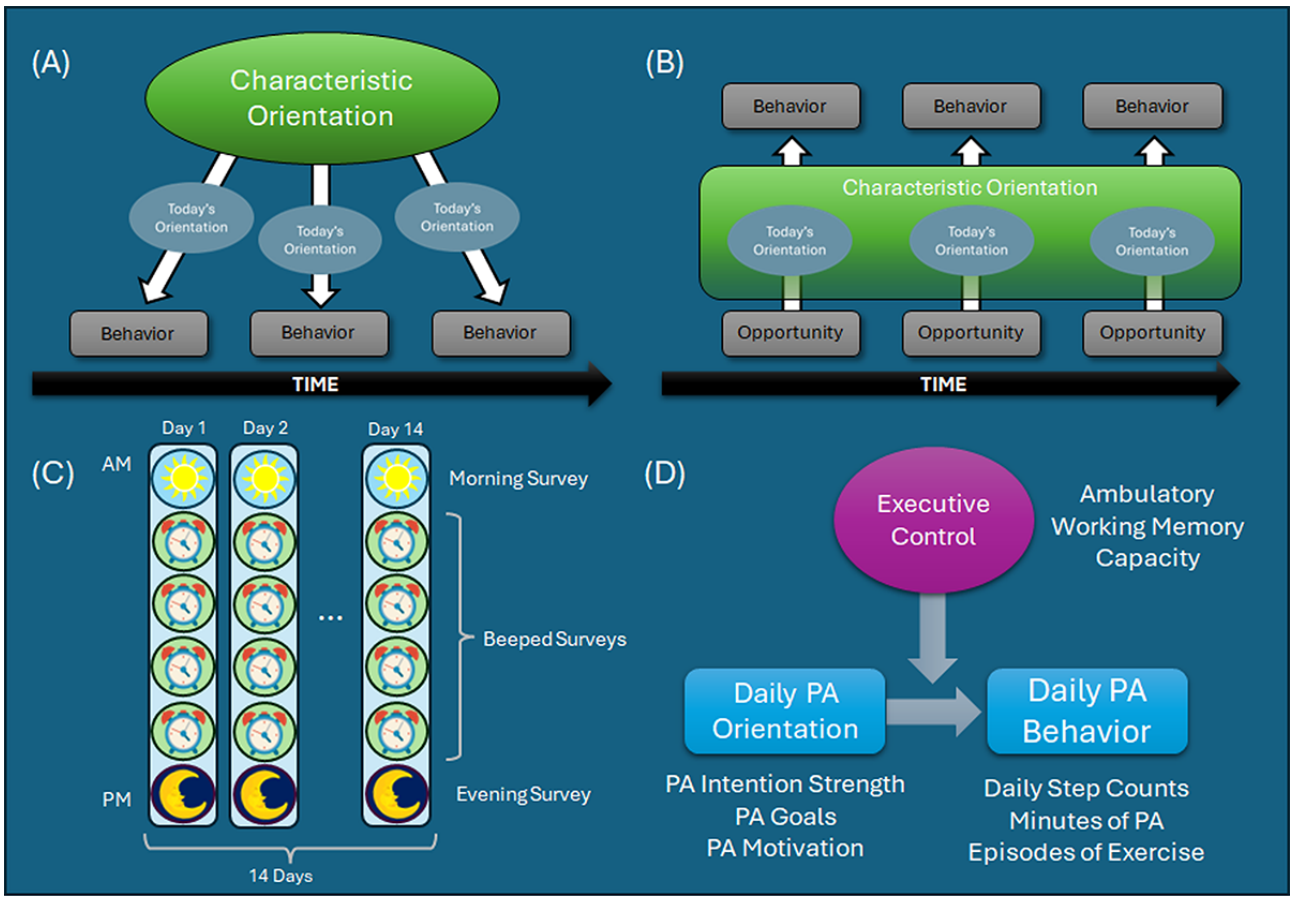

Momentary Contextual Reactivity Framework

The second framework we extended to examine self-regulation in daily life is the contextual reactivity approach. Contextual reactivity refers to an individual's response to an exposure in their everyday environment. In previous research, this approach was used to study other domains of self-regulation (eg, affective reactions to everyday stressors) [43,44], and reactivity under these circumstances is often taken to reflect a stable trait characteristic even if sampled with a higher-frequency approach (eg, daily diary). In our recent work, we found that short-term variation in executive control (momentary working memory capacity) may modify a person's reaction to an everyday stressor exposure, suggesting that the momentary *state* of one's executive control ability may play a role in determining their reaction [28]. In PHIAT, we aimed to, similarly, capture how individuals react when exposed to an environment that is conducive/supportive of enacting PA behavior and examine whether that reaction is consistent with an individual's overall orientation for PA or even their orientation for that day. PA contextual reactivity was indicated by behavior during exposure to environments that were conducive to PA (PA *opportunities*; Figure 1B). PA opportunities were assessed during all beeped and evening EMA surveys.

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In each case, by closely monitoring motivational and contextual dynamics, the PHIAT protocol represents a high-frequency, natural experimental framework and provides a stronger test of the executive hypothesis than can be generated through cross-sectional, observational approaches. Our central analytical approach involves examining whether associations between PA orientation, PA opportunities, and PA behavior are moderated by within- and between-person variation in executive control (eg, rotation span performance either during that moment/day or average performance across all observations; Figure 1D).

Another key feature of the PHIAT project was the integration of a commercially available wrist-worn activity monitor and the software used to administer the EMA protocol. The face of the activity monitor was configured to only display the time of day, while information about accumulated activity (step counts) was transmitted via Bluetooth to the EMA software installed on investigator-provided smartphones. Participants were provided the opportunity to check their step counts throughout the day using a *check my steps* button made available through the EMA software main menu. Self-monitoring behavior, a construct central to many theories of self-regulation [45], was operationalized as the number of times a participant accessed the *check my steps* button, providing an objective measure of real-time self-monitoring behavior.

Methods

Participants

Participants were recruited from a combination of social media postings, internal institutional resources (eg, "StudyFinder"), secondary recruitment from other studies conducted at Penn State, and the community surrounding health care sites of Penn State Health system. Participants were included if they were aged 18 years and older, were ambulatory, were fluent in English, had access to a reliable cellular network or Wi-Fi connectivity for onboarding, and had an email account for communication of remote consent procedures. Participants were excluded if they had a motor or visual impairment that would interfere with the operation of the study-provided smartphone, had a history of neurological injury or disease or significant health problem that could be complicated by PA, were unable to consent, were younger than 18 years, or were a prisoner.

Ethical Considerations

All participants provided written informed consent and received compensation for their participation. The compensation rate for the study was US $5 per day of participation (14 d × US $5 = US $70), with a US $30 incentive payment for completing >75% of expected surveys (maximum compensation: US $100).

All experimental procedures were approved by Pennsylvania State University's Institutional Review Board for the ethical treatment of human participants under protocol number STUDY00013106. All participants provided electronic informed consent via REDCap prior to engaging with any study procedures. All study data were deidentified to ensure participant privacy and confidentiality.

Materials and Procedure

The study protocol involved 3 phases: (1) participants completed a remote study onboarding visit where informed consent was documented, a telephone adaptation of the Montreal Cognitive Assessment [46] was administered, and participants received a study overview, study materials (study-provided smartphone, tablet, activity monitoring wearables, and EMA app), and instructions for completing the EMA surveys and ambulatory cognitive assessments; (2) questionnaires were administered on a study-provided tablet during the week leading up to the EMA measurement burst; and (3) participants completed a 14-day EMA measurement burst while wearing the activity monitors.

EMA Protocol

Participants were asked to carry a study-provided smartphone for a period of 14 days (Xiaomi Mi A2 model phones configured with Android One OS, v8.0; Xiaomi Corporation, Beijing, China). A custom Android EMA mobile app, the "Mobile Monitoring of Cognitive Change" (M2C2) app, was loaded onto the study-provided phones and used to administer the EMA protocol, including self-report survey items and 4 ambulatory cognitive assessments. Phones were configured into a "kiosk" mode where only the study app was available to the participant. EMA surveys were administered to each participant over 14 consecutive days in a measurement burst design. Each day involved 1 self-initiated *morning* survey, followed by 4 pseudorandomly signaled *beeped* surveys, and 1 self-initiated *evening* survey (Figure 1C). Participants were instructed to begin the morning survey as soon as they woke up and the evening survey before going to bed. At the start of the study, participants provided their typical waking time. From this information, the EMA protocol was initialized so that the first beeped survey would be delivered at a pseudorandomly determined time within 2 hours of their reported waking time. The remaining 3 beeped surveys were each separated by 3.75 hours and with a start time that was pseudorandomly jittered each day in the burst by up to 30 minutes. Beeped surveys "timed-out" (were unavailable) if the participant did not respond within 30 minutes of the notification. All ambulatory cognitive assessments were administered at the end of each morning and beeped survey but not during the evening survey to limit participant burden.

EMA Measures

Ambulatory Cognitive Assessments

Four ambulatory cognitive assessments from the M2C2 platform were administered during morning and beeped surveys (Figure 2). A brief description of each task and chosen parameters is provided below, and a complete and detailed description of each task can be found elsewhere [47].

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Figure 2. Ambulatory cognitive assessments. (A) symbol search task, (B) rotation span task, (C) letter go/no-go, and (D) multiple object tracking. Each was administered 5 times per day throughout the 14-day protocol.

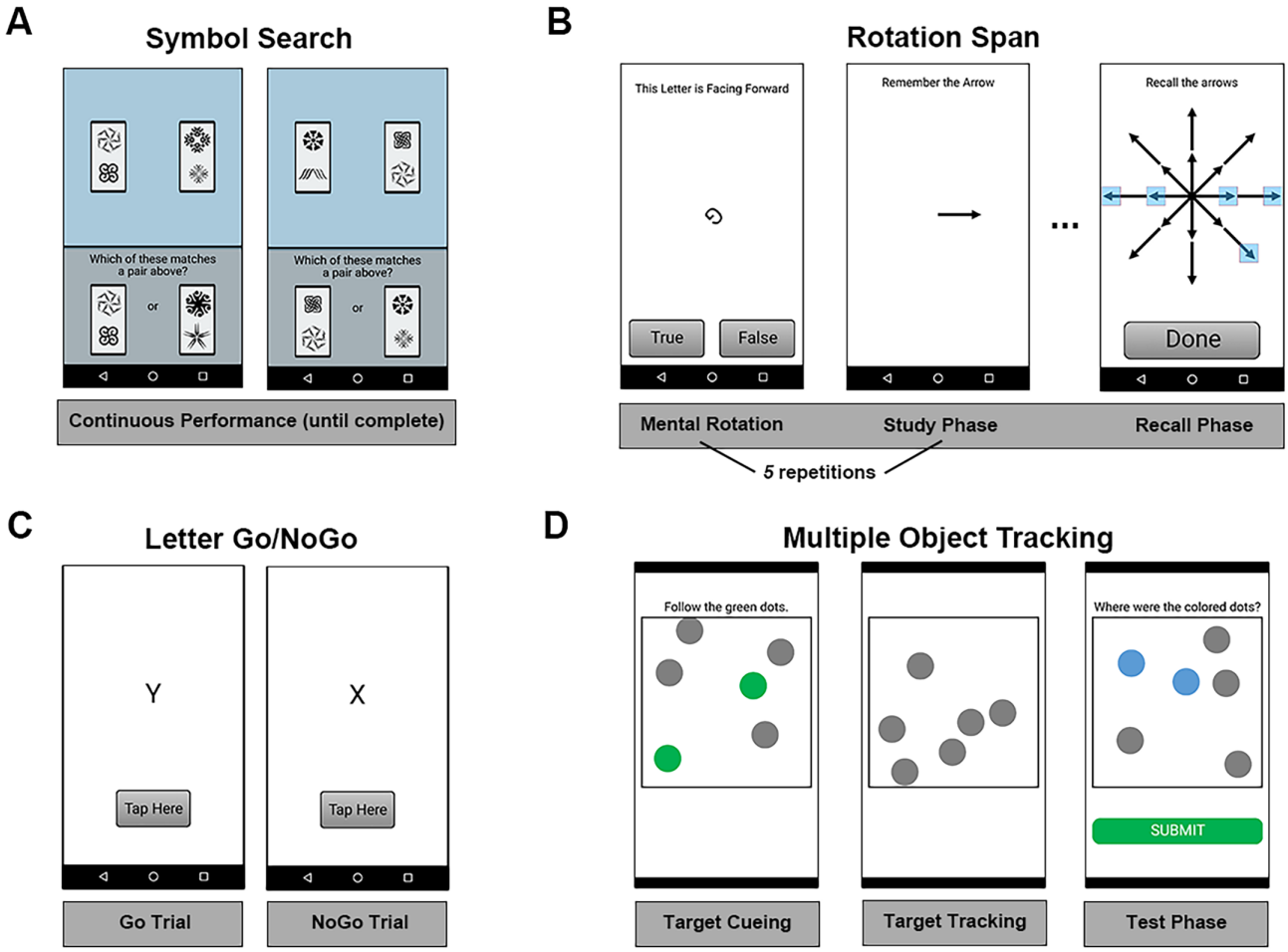

Symbol Search

The symbol search task was selected as a measure of processing speed. Eighteen trials were administered during each session. Three target tiles were presented during each trial, and lure tiles occurred on 50% of trials.

Rotation Span

The rotation span task was selected as a measure of working memory capacity. Three trials were administered during each session. The set size was 5 for each trial.

Letter Go/NoGo

The letter go/no-go task was selected as a measure of response inhibition. A total of 24 trials were administered during each session. “X” was the “NoGo” target, and all other letters of the English alphabet were used as possible “Go” stimuli. The go/no-go ratio was 5:1.

Multiple Object Tracking

The multiple object tracking task was selected as a measure of divided attention. Six trials were administered during each session, including 3 trials where the dots moved at a slower speed and 3 trials where the dots moved at a faster speed. The sequence of trials was fixed so that the 3 slow trials were administered first, followed by the 3 fast trials.

EMA Surveys

Brief ~1-minute self-report surveys with items covering the domains listed below were administered at the beginning of each survey administration (ie, *session*). EMA surveys were designed to provide an in-depth description of participants’ daily experiences, exposures, thoughts, and behaviors (all surveys), as well as their outlook and expectations for each day (during the morning surveys) and review and inventory of each day as a whole (during the evening surveys). A particular emphasis was placed on participation, and factors surrounding participation, in healthful behaviors (PA being of primary interest). For example, each morning survey included items such as “Today, I intend to be *physically active*.” These items were included to model daily within-person self-regulatory processes, including associations between daily variation in PA motivation and behavior (measured via activity monitors, see below). Throughout each day, exposures that might facilitate or act as a barrier to engagement in healthful behaviors (eg, opportunities for PA, exposure to stressful events) were sampled to model short-timescale variation in engagement and other processes (eg, moment-to-moment, within-day variation in PA behavior). Table 1 presents a complete list of all items included in the protocol.

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Table . Physical Activity, Imaging, and Ambulatory Testing (PHIAT) ecological momentary assessment protocol.

Item	Survey	Type	Response options
Context			
Location	AM[a], BEEP[b], PM[c]	Multi	Multiple options
Company	AM, BEEP, PM	Multi	Multiple options
Healthy behaviors			
Physically active	AM, BEEP, PM	Radio	Yes/no
PA[d] intensity[e]	AM, BEEP, PM	Radio	Light, moderate, vigorous
PA duration[e]	AM, BEEP, PM	Select	Minutes (5-min increments)
PA exercise[e]	AM, BEEP, PM	Radio	Yes/no
PA environment	BEEP, PM	Slider	Not at all-extremely
Food	AM, BEEP, PM	Radio	Yes/no
Food healthy rating[f]	AM, BEEP, PM	Slider	Not at all-extremely
Water	AM, BEEP, PM	Radio	Yes/no
Ounces consumed[g]	AM, BEEP, PM	Select	0 - 32 (4-oz increments)
Other consumed items	AM, BEEP, PM	Multi	Multiple options
Sleep			
Refreshing	AM	Slider	Not at all-extremely
Disruptions	AM	Slider	Not at all-extremely
Difficulty onset	AM	Slider	Not at all-extremely
Time in bed	AM	Time	Hour/min
Time waking	AM	Time	Hour/min
Affect			
Arousal	AM, BEEP, PM	Slider	Sleepy/tired-awake/alert
Mood	AM, BEEP, PM	Slider	Bad-good
Content	AM, BEEP, PM	Slider	Not at all-extremely
Worry	AM, BEEP, PM	Slider	Not at all-extremely
Happy	AM, BEEP, PM	Slider	Not at all-extremely
Fatigued	AM, BEEP, PM	Slider	Not at all-extremely
Stressed	AM, BEEP, PM	Slider	Not at all-extremely
Sad	AM, BEEP, PM	Slider	Not at all-extremely
Other			
Pain	AM, BEEP, PM	Slider	Not at all-extremely
Subjective age	AM, PM	Slider	0 - 100
Forecasting			
Expect today stressful	AM	Slider	Not at all-extremely
Expect today busy	AM	Slider	Not at all-extremely
Expect today distractions	AM	Slider	Not at all-extremely
Expect today enjoyable	AM	Slider	Not at all-extremely
Expect today social	AM	Slider	Not at all-extremely
Intentions			
PA intention	AM	Slider	Not at all-extremely
Healthy meals intention	AM	Slider	Not at all-extremely

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Item	Survey	Type	Response options
Hydrated intention	AM	Slider	Not at all-extremely
Sleep intention	AM	Slider	Not at all-extremely
PA goal			
Step count goal	AM	Radio	Yes/no
Step goal amount[h]	AM	Select	0 - 20000 (500-step increments)
Goal perceived control[h]	AM	Slider	Not at all-extremely
Goal efficacy[h]	AM	Slider	Not at all-extremely
Goal cog expectations[h]	AM	Slider	Not at all-extremely
Goal affect expectations[h]	AM	Slider	Not at all-extremely
Goal utility[h]	AM	Slider	Not at all-extremely
Goal set	PM	Radio	Yes/no
Goal achieved[i]	PM	Radio	Yes/no
Goal realistic[i]	PM	Slider	Not at all-extremely
Goal easy[i]	PM	Slider	Not at all-extremely
Goal rewarding	PM	Slider	Not at all-extremely
Goal within control[i]	PM	Slider	Not at all-extremely
Goal facilitators[i]	PM	Multi	Multiple options
Goal attribution[i]	PM	Slider	Not at all-extremely
Goal barriers[i]	PM	Multi	Multiple options
Subjective cognition			
Slow	BEEP, PM	Slider	Not at all-extremely
Foggy	BEEP, PM	Slider	Not at all-extremely
Sharp	BEEP, PM	Slider	Not at all-extremely
Concentration	BEEP, PM	Slider	Not at all-extremely
Everyday memory failures	PM	Multi	Multiple options
Everyday attention failures	PM	Multi	Multiple options
Thoughts and disruptions			
Distractions	BEEP, PM	Slider	Not at all-extremely
Busy	BEEP, PM	Slider	Not at all-extremely
Control train of thought	BEEP, PM	Slider	Not at all-extremely
Mind-wandering	BEEP, PM	Slider	Not at all-extremely
Forgetting	BEEP, PM	Slider	Not at all-extremely
Stress			
Stressful exposure	BEEP, PM	Radio	Yes/no
Impact of stressors[j]	BEEP, PM	Slider	Not at all-extremely
Stress avoidance[j]	BEEP, PM	Slider	Not at all-extremely
Daily wrap-up			
Good day	PM	Slider	Not at all-extremely
Satisfied with activities	PM	Slider	Not at all-extremely
Satisfied with social life	PM	Slider	Not at all-extremely

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Item	Survey	Type	Response options
Sense of belonging	PM	Slider	Not at all-extremely
Responsibility impact	PM	Slider	Not at all-extremely
Memory interference	PM	Slider	Not at all-extremely
Memory appraisal	PM	Slider	Not at all-extremely
Attention interference	PM	Slider	Not at all-extremely
Attention appraisal	PM	Slider	Not at all-extremely
Overall PA today	PM	Slider	Not at all-extremely
Overall PA effort	PM	Slider	Not at all-extremely
Overall PA satisfaction	PM	Slider	Not at all-extremely
Exercise today	PM	Radio	Yes/no
Exercise enjoyment[k]	PM	Slider	Not at all-extremely
Exercise appraisal[k]	PM	Slider	Not at all-extremely
Overall food healthy	PM	Slider	Not at all-extremely
Overall food effort	PM	Slider	Not at all-extremely
Overall food satisfaction	PM	Slider	Not at all-extremely
Overall food enjoyment	PM	Slider	Not at all-extremely
Overall hydration effort	PM	Slider	Not at all-extremely
Overall hydration satisfaction	PM	Slider	Not at all-extremely

[a]AM: morning survey.
[b]BEEP: beeped survey.
[c]PM: evening survey.
[d]PA: physical activity.
[e]Branched items under parent branching item “Physically active.”
[f]Branched items under parent branching item “Food.”
[g]Branched items under parent branching item “Water.”
[h]Branched items under parent branching item “Step count goal.”
[i]Branched items under parent branching item “Goal set.”
[j]Branched items under parent branching item “Stressful exposure.”
[k]Branched items under parent branching item “Exercise today.”

PA Monitoring

ActiGraph

Participants were asked to wear an ActiGraph activity monitor (Model GT3X, ActiGraph LLC, Pensacola, FL) at their hip (on their belt or waistband) from waking until bedtime throughout the 14-day measurement burst. ActiGraph GT3Xs were programmed to sample at 30 Hz, and participants were also provided a belt clip to secure the device.

ActivPAL

Participants were asked to wear an ActivPAL activity monitor (Model 4, PAL Technologies, Ltd, Glasgow, Scotland) affixed to their nondominant thigh via Hypafix (BSN Medical, Hull, United Kingdom) 24 hours per day throughout the 14-day measurement period. The device was programmed to sample at 20 Hz and was provided to participants wrapped in a nitrile sleeve and hypoallergenic athletic tape.

Commercial Activity Monitor

A wrist-worn commercial activity monitor was provided to participants for continuous tracking of step counts. The screen of this device was programmed to only display the time (clock) and battery charge level. Data from this device were transmitted via Bluetooth to the EMA app for self-monitoring of PA. Self-monitoring behavior was operationalized as the number of times participants checked their step counts via the EMA app on the provided smartphone.

Participant Background and Characterization

Demographics

A demographics questionnaire was included that captured information on participants’ backgrounds, including age, race, ethnicity, education level, occupation status, income, living situation (living alone/with other individuals), and caregiver status.

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PA and Social Cognitive Factors

Self-reported PA and motivational factors were assessed via the International Physical Activity Questionnaire [48], Outcome Expectations for Exercise [49], Self-Efficacy for Exercise [50], and the Self-Report Habit Index (adapted to capture habit strength for PA [51]).

Self-Regulation

Indicators of a trait orientation toward self-regulation included the Consideration of Future Consequences Scale [52], the 10-item Personality Inventory [53], the Self-Control Scale [54], and the Emotion Regulation Questionnaire [55].

Social Connectedness and Well-Being

Three indicators of social connectedness (social network, isolation, and loneliness) were collected, including the Oslo Social Support Scale [56], the NSHAP Social Disconnectedness Scale [57], and the UCLA 3-item Loneliness Scale [58]. Well-being was assessed via the Satisfaction With Life Scale [59], Subjective Happiness Survey [60], Mindful Attention Awareness Scale [61], Food Insecurity Module [62], Self-Rated Health [63], Perceived Vulnerability to Illness [64], Recent Colds History [64], and the PROMIS Physical Function Short Form [65].

Aging Attitudes

Two questionnaires assessing attitudes toward aging were collected, including the Awareness of Age-Related Change [66] and Expectations Regarding Aging [67] scales.

Statistical Analysis Approach

The high-frequency sampling methodology inherent to EMA protocols results in complex nested data structures. Each observation ("moment") can be considered as nested within a day of the protocol and, in turn, nested within an individual. Statistical analysis approaches that can adequately account for these complex data structures will be used to achieve the study aims. Mixed-effects modeling and dynamic structural equation modeling are two leading approaches to analyzing EMA data that will be used [68]. In each case, all observations will be "centered" in a manner that provides for unambiguous interpretation of effects at each "level" of the study design (ie, within-person, between-person) [69].

For analyses related to the *dynamic action control* framework, linear mixed-effects models will be estimated where day-to-day variation in behavior (eg, daily step counts) will be regressed on within- and between-person (ie, "characteristic") variation in morning intention ratings. To examine how the characteristic level of, for example, PA intention strength modifies associations between daily variation in PA intention strength and daily PA behavior, cross-level interactions between characteristic PA intentions, and within-person daily variation in PA intention strength will be included in the model. For analysis of *momentary contextual reactivity* effects, linear mixed-effects models will be estimated to examine how momentary variation in the outcome of interest (eg, negative affect, PA behavior between surveys) is affected by exposure to a given context (eg, stressor, opportunity for PA), consistent with our previous work [28,70].

In each case (dynamic action control and momentary contextual reactivity), the central hypothesis being tested in the PHIAT project, the *executive hypothesis* of self-regulation, will be examined at both the between- and within-person levels. To test the hypothesis, within-person variation and characteristic level of executive control (momentary and average performance on the ambulatory cognitive assessments, respectively) will be included as moderators of action control and contextual reactivity effects. For example, we will include within and between interactions between momentary and characteristic working memory capacity (rotation span task performance) and PA intention strength in dynamic action control models to evaluate how within- and between-person executive control ability modifies associations between intentions to engage in PA and PA behavior.

Results

The aims of this study were revised in response to the COVID-19 pandemic, as the opportunity to conduct in-person magnetic resonance imaging (MRI) with higher risk populations (ie, adults ≥60 y of age) was lost for the majority of the project period. The entire study was pivoted to a remote format in response to the pandemic, including all study procedures (eg, electronic consent, video conference–based onboardings, sanitization, and courier-based delivery and return of all study devices), and all study data were collected after the onset of the pandemic. The sample size for the EMA protocol was increased as resources were redirected from MRI scans to additional recruitment.

We proposed to recruit 150 participants for the PHIAT project. After pivoting the study to fully remote procedures and closing the MRI study, we revised the proposed EMA protocol sample size to 250. A total of 302 participants were screened for eligibility, 243 participants signed informed consent, and 22 withdrew from the study. A total final sample of 221 participants, ranging from 18 to 89 years of age, completed the EMA protocol (mean age = 56.7, SD = 17.9 years). Participants in the final sample were 80% female. About 86% of the sample identified as White, 1.4% Black or African American, 4.5% Asian, 0% Native Hawaiian or other Pacific Islander, 0% American Indian or Alaska Native, 3.2% reported more than one race, and 1.4% identified as Hispanic or Latino. Recruitment began in June 2021 and continued through May 2024 when the study was completed.

Discussion

Principal Findings

We expect data generated by the PHIAT project to provide new insights into the intersection of cognitive executive control ability, self-regulation, and health-promoting behaviors. In particular, we anticipate that the ability to link the high-frequency assessment protocol and activity monitoring devices at multiple timescales will help bring the dynamic processes surrounding self-regulatory success and failure into sharper relief. Few previous studies have examined how short-timescale variation in these factors interacts in determining participation in health-promoting behavior, and the current study

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is an initial step in moving from a cross-sectional/individual difference approach to action control, contextual reactivity, and the executive hypothesis toward a within-person, process-level description.

The 3 activity monitoring devices selected for the study, the thigh-worn ActivPAL monitors, hip-worn ActiGraph GT3X devices, and the wrist-worn commercial fitness monitor, were each chosen to capture different aspects of PA and self-regulatory behavior. The long battery-life ActivPAL devices, being affixed to the thigh, allowed for near-continuous measurement of posture and movement throughout the 14-day protocol. From the ActivPAL devices, we expect to obtain high-fidelity estimates of total PA volume (eg, step counts) as well as estimates of time spent in various postures/behaviors (eg, stepping time, sitting time). The ActiGraph GT3X devices are a widely used tool for estimating PA at different intensity thresholds (eg, moderate-to-vigorous intensity PA) [71]. Because the sample includes adults throughout the lifespan, the selection of activity intensity cut points will require careful consideration [72]. Finally, while the activity data generated by the wrist-worn fitness watch is not expected to be an outcome of interest, participants' use and interaction with the "check my steps" feature of the EMA application (which was connected via Bluetooth to this device) will be examined in studies of how self-monitoring of PA behavior is influenced by goal setting and variation in executive control.

The wide age range of the PHIAT study sample will allow for investigation into how age-associated changes in each factor either independently or mutually alter self-regulatory processing throughout the adult lifespan. Previous work has shown that many of the individual factors under study undergo normative age-associated change. For example, it is well-established that older age is associated with reductions in PA, increases in sedentary behavior, and reduced executive cognitive ability [73-79]. In addition, previous work on psychosocial aspects of aging (eg, affective and cognitive well-being) has demonstrated that factors such as perspective, world view, and cognitive capacity may play a role in altering the strategies we select and rely on to manage our thoughts, emotions, and behavior in older adulthood [24,80-82]. The PHIAT project offers an opportunity to connect this line of work from the fields of psychosocial aging and human development to these areas of health promotion theory.

Limitations

While the strengths of the PHIAT project study design reviewed above offer the potential to gain new insights into self-regulation of health promotion, there are several limitations. While every effort was made to recruit a generalizable and representative sample, the final sample was disproportionately female and White. We suspect this was driven, in part, by our advertising and recruiting methods, which included a health system–associated marketing campaign over social media. In addition, despite recruiting community members throughout the region with our sampling methodology, the PHIAT project involves a volunteer convenience sample that may not fully generalize to the broader population. While the inclusion of an adult lifespan sample has significant advantages, as reviewed above, there are systematic changes in the factors under study that are known to occur with age. Careful consideration of how to bring chronological age into analytical models will need to be given (eg, as a continuous factor, through group stratification), as well as attention to how changes in the effective sample size within each strata (younger/older, decade by decade) affect statistical power. Finally, while EMA studies that examine how individuals behave in response to everyday exposures can be viewed in many ways as naturalistic experiments, the project still involves an observational study design, and findings will require further experimental work to tease apart causality and mechanism of action.

Conclusions

The PHIAT project involved a novel study design and an adult lifespan sample. The design included near-continuous sampling of thoughts, emotions, context, cognition, and behavior, and is amenable to a wide array of multilevel, time series, latent variable, and other modeling approaches for developing insights into these rich and nested data streams. The inclusion of community-dwelling adults ranging from 18 to 89 years of age will help provide insights into how self-regulation of health-promoting behaviors changes throughout the lifespan and help identify potential mechanistic targets for health promotion interventions.

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Data Availability

The datasets generated by this study are not publicly available as of the date of protocol publication. A complete public repository of the data will be made available by January 2027. In the meantime, data are available from the corresponding author upon request.

Authors' Contributions

Conceptualization: JGH
Funding acquisition: JGH

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Investigation: JGH
Methodology: JGH, DBE
Resources: JGH
Supervision: JGH
Validation: JGH
Writing – original draft: JGH, TQ
Writing – review & editing: JGH, TQ
Formal analysis: DBE
Software: DBE
Data curation: JNA, JLC, BMK
Project administration: JNA, AMT, JLC, BMK

Conflicts of Interest

None declared.

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Abbreviations

EMA: ecological momentary assessment
M2C2: Mobile Monitoring of Cognitive Change
MRI: magnetic resonance imaging
PA: physical activity
PHIAT: Physical Activity, Imaging, and Ambulatory Testing

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Supporting Individuals With Cognitive Impairment and Family Members in Rural Communities: Protocol for a Mixed Methods Digital Health Study

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Abstract

Background: The health and economic burdens of Alzheimer disease and related dementias (ADRD) are exacerbated for people living in rural social contexts who experience geographic barriers to care. There are currently few resources specifically designed to support socioculturally diverse rural ADRD care dyads, including early detection of potential precursors to ADRD such as mild cognitive impairment (MCI) and subjective cognitive decline (SCD).

Objective: The primary objective of the Northern Arizona Memory Study (NAZMS) is to develop culturally informed and scalable resources to identify and support rural families at risk for ADRD. The purpose of this study is to introduce the NAZMS protocol and discuss its role in addressing dementia risk and promoting cognitive health in rural communities.

Methods: This dyadic study will use a mixed methods, digital health approach. A sample of rural care dyads with MCI or SCD will be screened and recruited through partnerships with community centers across Northern Arizona. Consenting dyads will complete semistructured interviews to answer questions about technology preferences for monitoring symptoms and engaging in remotely delivered interventions. Next, care dyads will complete separate baseline questionnaires assessing dyadic (eg, experiences with caregiving or care receiving) and health factors. Participants with cognitive impairment will then complete a 14-day mobile protocol of brief end-of-day surveys and cognitive assessments delivered via study-provided smartphones.

Results: Data from the qualitative interviews will provide dyad preferences for intervention development. Data from the quantitative protocol will specify for whom (ie, between-person) and on which days (ie, within-person) modifiable factors are related to better cognitive health in everyday life.

Conclusions: This study will take a mixed methods, digital health approach to supporting rural families at risk for ADRD by understanding intervention preferences and identifying the modifiable protective and risk factors that influence cognitive health in everyday life. The findings are expected to directly support rural Arizonans and respond to national priorities in ADRD research for the development of community-based disease education programs and the use of digital assessments of cognitive health and well-being.

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KEYWORDS

mixed methods; digital health; rural health; community-engaged research; community-based participatory research; cognitive impairment; caregiving; dementia; mild cognitive impairment; subjective cognitive decline

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Introduction

Background

The aging of the US population has brought an unprecedented increase in the prevalence of Alzheimer disease and related dementias (ADRD). More than 6 million individuals in the United States live with ADRD, and this number is expected to increase dramatically in the coming years [1-3]. ADRD is costly, with annual direct medical expenditures calculated to be US $14,508 per older adult with ADRD versus US $10,096 per older adult without ADRD [2]. Individuals with ADRD may exhibit disruptive cognitive and behavioral symptoms such as impaired memory and decision-making, confusion, and agitation several years before the disease is recognized and supports are put into place [4]. This is distressing for the individual facing these symptoms, as well as untrained caregivers who often serve as the primary source of daily support. Caregivers are at high risk for health problems such as depression, poor sleep quality, high blood pressure, and heart disease [5-8]. This situation is exacerbated for care dyads (ie, people with cognitive impairment and their care partners) living in rural social contexts who are isolated [9], have few resources [10], experience geographic barriers to care [11], and lack basic access to ADRD-related information and services [12,13]. Compared with urban areas, rural individuals with ADRD experience more days in nursing homes and significantly higher mortality [14,15]. The likelihood that cases of ADRD in the United States are underdiagnosed and undercounted complicates our understanding of this emerging public health problem and leads to additional challenges for families [9,16].

Lack of access to specialty care (ie, neuropsychological evaluations) and geographic or transportation barriers make timely detection and early screening of cognitive impairment an ongoing challenge [17,18]. Local community centers in Northern Arizona offer unique potential to compensate for the lack of formal services in memory care deserts [17] and rural areas [18], but need to be more intentionally integrated into community-based screening efforts to address this gap. Community-based participatory approaches in rural communities can foster relevant service delivery (eg, screening, referrals, and brain health education), strengthen care networks, and support sustainability [19]. Local community centers for older adults are ideally situated to support brain health in socioculturally diverse rural communities because they serve as trusted resource hubs for older adults and caregivers [20]. Further, older adults from historically minoritized communities may be distrustful of formal health care systems or researchers and place more trust in community-based organizations [21,22], reinforcing the value of these networks.

There are currently few resources and interventions specifically designed to identify and support socioculturally diverse rural ADRD care dyads, including protocols for the early detection of potential precursors to ADRD, such as mild cognitive impairment (MCI) or subjective cognitive decline (SCD), and validated strategies for community-based delivery of support [23,24]. Early detection of MCI and SCD is crucial for maximizing the effectiveness of interventions and clinical trials while efficiently allocating resources toward people at greater risk of transitioning to Alzheimer disease (AD) [25]. Without early detection and intervention, diverse families living in rural areas are left to cope in isolation, leading to devastating individual, interpersonal, and community-level consequences. Further, decreasing risk factors and increasing protective factors for ADRD, MCI, and SCD can prevent or delay up to 40% of ADRD cases [26].

The Northern Arizona Memory Study (NAZMS) applies a preventive digital health approach to develop technologies and resources necessary to identify and support rural dyads with MCI or SCD at risk for ADRD. Our work is situated within the cognitive decline and impairment stage of the typical disease progression of AD, beginning with preclinical AD (ie, no observable symptoms but potential for changes in the brain), followed by SCD (ie, self-reported difficulty and decline in memory and thinking domains) and MCI (ie, mild impairment in objective performance across multiple domains), and ending in mild, moderate, and severe stages of Dementia due to AD [1]. Specifically, NAZMS focuses on individuals with MCI or SCD and their caregivers because these individuals are at an elevated risk of transitioning to ADRD. Early detection of SCD and MCI is crucial for maximizing the effectiveness of interventions and clinical trials while efficiently allocating resources toward people at greater risk of transitioning to AD [27]. Addressing SCD is especially relevant for diverse communities in Northern Arizona, as one in six Indigenous adults reports SCD, with nearly two-thirds of these individuals reporting their SCD interferes with day-to-day activities [27]. Among the 22 federally recognized tribes in Arizona, many Tribal Nations have lands and strong cultural connections to Northern Arizona, including the Hopi Tribe, Navajo Nation, Hualapai Tribe, Havasupai Tribe, Kaibab-Paiute Tribe, and San Juan Southern Paiute Tribe [28]. Our community-based participatory approach to identifying and supporting care dyads emphasizes community strengths and self-determination, as well as care dyads' ability to express agency in their health care and in life in general.

By directly collaborating with local community centers for our study's recruitment and outreach, we align our study to the unique needs, cultural norms, and practical realities that will ensure culturally informed supports and resources that are relevant for communities across Northern Arizona [29]. Our digital health study design and focus for future intervention development were further informed by the technology acceptance model for older adults, which recognizes that social context, user intention, perceived and confirmed usefulness, and ease of learning and use impact older adults' acceptance or rejection of technologies [30]. The dyadic nature of NAZMS was informed by the developmental-contextual model of coping [31], which posits that dyadic illness appraisal (eg, illness ownership—yours or mine vs ours) and dyadic coping (eg, problem- and emotion-focused support) are key drivers of adjustment for care dyads. In this way, NAZMS ensures that both care partner and care receiver share their lived experiences, preferences, and insights throughout the study protocol.

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Objective and Aims of NAZMS

The primary objective of NAZMS is to develop culturally informed and scalable resources to identify and support rural families at risk for ADRD. The purpose of this study is to introduce the NAZMS protocol and discuss its role in addressing dementia risk and promoting cognitive health in rural communities. NAZMS uses a dyadic mixed methods, digital health approach to address the following two aims: (1) determine culturally appropriate care dyad preferences for identifying and monitoring cognitive and behavioral symptoms of MCI and SCD, and for engaging in remotely delivered supportive interventions to contend with or reduce symptoms and associated problems from MCI and SCD; and (2) examine the impact of modifiable multilevel (eg, individual, dyadic, family, and environmental) risk and protective factors on daily cognitive health among rural individuals with MCI or SCD.

Methods

Overview

NAZMS uses a convergent mixed methods design [32,33], in which qualitative and quantitative data are collected separately and then merged to develop a comprehensive understanding of rural care dyads at risk of ADRD.

Participants and General Procedure

We are recruiting an initial target of 30 rural care dyads with MCI or SCD, who are interviewed [33,34] and purposively recruited [35] through partnerships with community centers in the 4-county Northern Arizona region. Recruitment efforts include local newspaper and community center advertisements (eg, flyers) and announcements made at community centers by center staff and study team members. The physical addresses of the community centers and participant homes were entered into the Health Resources and Services Administration rural eligibility tool [36] to determine rurality.

Target individuals ("people with memory or thinking challenges") are included if they (1) live in the community, not in a nursing home; (2) score below 19 on the Montreal Cognitive Assessment (MoCA) Blind or report presence of decline in memory or thinking or concern in these domains; and (3) can identify a primary caregiver who is able and willing to participate in the study (spouse, adult child, other family member or friend, or family of choice). Both dyad members must be (1) capable of using technology with coaching and support; and (2) able to communicate in English and provide informed consent. Dyads are excluded if either dyad member is (1) under the age of 18 years; (2) pregnant; (3) has untreated severe mental illness, alcohol or drug abuse, or suicidality; or (4) has another neurological condition that significantly impacts function. Participants were considered capable of using technology with coaching and support if they indicated their willingness and capacity to engage with study-provided technology (eg, tablet for baseline survey and smartphone for 14-day daily diary) alongside trained study team members (eg, coaching and support). Exclusion criteria were applied to reduce the risk of confounding variables and health statuses that may obscure the focus of cognitive functioning in SCD or MCI due to AD [37,38]. If both dyad members experience MCI or SCD, the individual with the lower MoCA Blind score or more SCD is considered the target individual for this study.

Upon completion of the semistructured interview, care partners and individuals with cognitive impairment complete a baseline questionnaire. The participants with cognitive impairment are then invited to participate in the quantitative 14-day daily diary component of the study. Recruitment and data collection began in fall 2024 and will continue throughout 2026. Figure 1 provides a visual timeline of the NAZMS protocol from community referral to in-person or remote participation in the mixed methods protocol.

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Figure 1. Visual timeline of the dyadic Northern Arizona Memory Study (NAZMS) protocol using a mixed methods, digital health approach. Following community referral, individuals are screened for eligibility and complete the consent process. Phase 1 data collection includes qualitative in-person or remote semistructured interviews with the person with mild cognitive impairment or subjective cognitive decline and the care partner. Phase 2 includes quantitative in-person or remote baseline surveys with both dyad members. The person with mild cognitive impairment or subjective cognitive decline is then provided with a study smartphone to complete a 14-day mobile protocol. MCI: mild cognitive impairment; SCD: subjective cognitive decline.

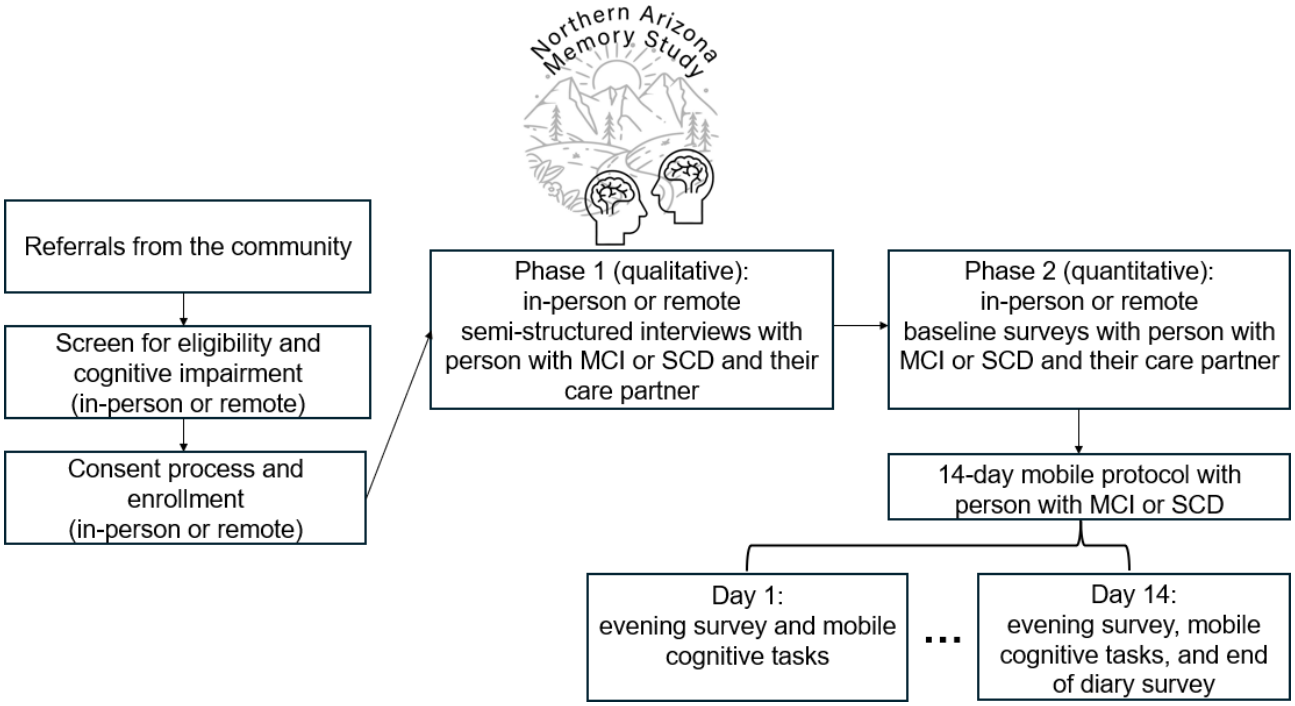

The technology support provided by trained study team members and the mixed methods, multicomponent nature of our protocol support participation in NAZMS across a wide spectrum of technology proficiencies and cognitive statuses. We provide the cognitive screening as a free community service without a requirement to enroll in the NAZMS protocol. This screening does not require tablet or smartphone technology use, as it can be conducted in person with responses provided to a team member. The qualitative arm of the protocol does not require any technology use from the respondents who participate in person, and care partners can assist with technology connections for qualitative interviews conducted on Zoom (Zoom Video Communications, Inc). As long as the participant is open to receiving coaching and support from study team members (eg, hands-on training and troubleshooting phone calls and emails), they can participate in the quantitative arm of the protocol. NAZMS is a first step in developing supports and resources for rural care dyads at risk for dementia. This study can lay the foundation for future work that expands modalities of protocol administration (eg, mailed paper-and-pencil booklets and more frequent road trips to rural communities for in-person administration) and language accessibility (eg, Spanish, Native languages within nearby Tribal Nations) to better represent populations across Northern Arizona.

Materials and Specific Procedures

Screening Protocol

Community-dwelling adults with cognitive impairment are screened using the MoCA Blind [39] to screen for MCI and adapted items from the Einstein Aging Study Health Self-Assessment [40,41] to screen for SCD. Participants are considered potentially eligible with MCI if they score ≤18 out of 22. The MoCA Blind was selected because it can be administered both in-person and via telephone, and it accommodates participants with vision or motor limitations. In contrast to the full MoCA scoring subcategories of mild, moderate, and severe impairment, the MoCA Blind has only been validated to distinguish cognitively unimpaired from potential MCI (scores ≤18/22). Thus, it is not possible to classify severe impairments consistent with dementias using this version of the MoCA. Participants unable to provide informed consent for the qualitative or quantitative arms of data collection will not be permitted to participate (this will likely refer to individuals with dementia who receive our screening). Participants answer items on perceived decline in memory and concern about these changes in memory (4 questions), perceived decline in thinking abilities and concern about these changes in thinking (4 questions), and 1 question on whether they have discussed their memory or thinking challenges with a health care provider. Participants are eligible with SCD if they report a decline in memory or thinking and/or concern in these domains.

Qualitative Protocol–Semistructured Interview

Textbox 1 provides the semistructured interview guide for the NAZMS qualitative protocol. Team members participated in training and practice sessions with the co-principal investigators to ensure familiarity with the semistructured interview process and engagement with people with MCI or SCD and their care partners. The semistructured nature of the interview allows flexibility to accommodate cognitively unimpaired participants and those with impairment (eg, interviewers had the questions as a road map, but did not need to ask every question in the same way to each participant). Questions were divided into a

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section on technology (eg, "What are your thoughts about if and how these kinds of technologies could be used to monitor memory or thinking challenges?") and a section dedicated to memory and thinking challenges (eg, "What things have helped you to access support for memory or thinking challenges?"). Interview questions about dyad preferences for identifying and monitoring symptoms, as well as engaging in remotely delivered interventions, build on previous work with care dyads for neurological conditions (eg, stroke survivor–family caregiver dyads) [42,43] and are informed by the technology acceptance model for older adults [30] and the developmental-contextual model of coping [31].

Textbox 1. Semistructured qualitative interview guide.

Prompts on technology:

1. What kinds of technology do you use in your everyday life? Some examples include: landline phone, cell phone, iPhone or other Android smartphone, tablet computer, email, home computer, internet websites, social media (Instagram, Snapchat, and Facebook), and Zoom or FaceTime video calls.
2. How easy are these technologies for you to use?
3. How confident are you using these technologies?
4. What would make you feel more confident using these technologies?
5. What are some advantages you see to each of these technologies when it comes to communicating with family, friends, health care providers, etc?
6. What are some disadvantages?
7. What are your thoughts about whether and how these kinds of technologies could be used to monitor memory or thinking challenges for yourself or the person participating in the study with you?
8. What advantages and disadvantages of these technologies can you imagine for monitoring memory or thinking challenges?
9. What do you think about technologies for delivering support for memory or thinking challenges remotely (not face-to-face)? That is, to provide support, education, and tools for remembering things?
10. What advantages of these technologies can you imagine for providing support?
11. What about disadvantages?
12. What might help you to use these technologies to get support for memory or thinking challenges?
13. What might hinder you from using these technologies to get support for memory or thinking challenges?

Prompts on memory or thinking challenges:

Now we would like to talk about the memory or thinking challenges that you or your family member faces. Some examples of memory or thinking challenges include forgetting to do things, trouble staying focused or concentrating, misplacing items in your home, finishing everyday tasks such as paying a bill, losing your train of thought, having trouble following a conversation, finding it hard to make decisions, finishing a task or following instructions, or having poor judgment.

1. What are some symptoms of these memory or thinking challenges that you've noticed either in yourself or in the person participating in the study with you?
2. Tell me about what it has been like for you to deal with this.
3. In what ways have memory or thinking challenges impacted your everyday life? Practically speaking, as well as any emotional impacts they may have.
4. How have they impacted the person participating in the study with you, including your relationship with that person?
5. How do you communicate with the person participating in the study with you about memory or thinking challenges?
6. What strategies do you use to deal with memory or thinking challenges?
7. What have your experiences been accessing support to deal with memory or thinking challenges? For example, from health care or social service providers, friends, or other family members, etc.
8. What things have helped you to access support for memory or thinking challenges?
9. What things have hindered you from accessing support for memory or thinking challenges?
10. What advice do you have for other people with memory or thinking challenges and their family members as they deal with symptoms and seek outside support?

Quantitative Protocol–Baseline Survey

Upon completion of the semistructured interview, caregivers and individuals with cognitive impairment complete their own baseline questionnaires assessing sociodemographic and health factors, caregiving, and technology preferences (Table 1). If participants have vision or motor limitations, a trained study team member can read the survey (ie, questions and answer

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options) directly to the participant and score responses. We assess a wide range of sociodemographic and health factors (eg, age, race, distance and transportation used for medical appointments, and mental health) to understand individual differences in preferences for supports, resources, and factors associated with daily cognitive health. Caregiver characteristics (eg, age, gender, and relationship), demands (eg, symptoms, types of care needed, hours spent providing care each day, and strain), cultural justification for providing care, and dyadic coping styles are assessed to evaluate the dyadic composition of caregiver and care receiver. We also obtain ratings of preferred symptom identification and monitoring technologies, intervention technologies, and data use considerations and comfort using an investigator-designed form, similar to what we have done in previous studies [42]. Table 1 provides additional details on the quantitative measures assessed at baseline.

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Table . Baseline survey measures.

Target and construct	Response options	Items and operational detail	Relevant reference
Sociodemographic and health factors			
Sociodemographic factors	Checkbox or radio button	Age, ethnicity, race, gender, sexual orientation, birthplace, education, employment status, marital status, languages spoken at home, adults and children in home, health insurance status, number of medical visits in the last year, distance and transportation used for medical appointments, and household income	13
Health	Multiple options	General health (excellent-poor) and physical and mental health (days with poor health)	44
Anxiety	Not at all–nearly every day	Generalized Anxiety Disorder (GAD-2)	45
Depression	Not at all–nearly every day	Patient Health Questionnaire (PHQ-2)	45
Perceived control	Strongly disagree–strongly agree	1-item on global perceived control	46
Cultural practices	Multiple options	Religiosity, spirituality, prayer frequency, and the importance of cultural heritage	47,48
Caregiving			
Characteristics	Multiple options	Relationship type, diagnosis, length of time providing the care, and distance from care receiver	13
Demands	Multiple options	Symptoms, types of care needed, hours spent providing care each day, and burden	49,50
Informal supports	Checkbox	Types of informal services received from unpaid friends or family	47
Formal supports	Checkbox	Types of formal services received from paid professionals	47
Cultural beliefs	Strongly disagree–strongly agree	10-item Cultural Justification for Caregiving Scale	51
Dyadic coping	Very rarely–very often	10items from the Dyadic Coping Inventory	52
Technology preferences			
Access	Checkbox	Which technologies do you have access to?	43
Usability	Checkbox	Which technologies do you know how to use?	43
Data use considerations	Checkbox	Which types of data would you consider allowing researchers to use to answer research questions about memory and aging? (activity monitoring, heart rate, bed-based sleep sensor, and geolocation [GPS])	53
Data use comfortability	Extremely uncomfortable–extremely comfortable	Comfort with each type of data being used to answer research questions about memory and aging	53

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Quantitative Protocol–14-Day Diary Design With Mobile Cognitive Tests

The participants with cognitive impairment are then invited to participate in the quantitative daily diary component of the study. All participants who agree to participate in the mobile protocol receive instructions and a mobile device preloaded with the quantitative survey and cognitive assessment application. If participants complete the interview and baseline survey in person at a community center, the kit of study supplies is provided to them in person. If the participant completes the protocol remotely on Zoom, the kit of study supplies is mailed to the participant. A 30-minute training is provided with the option of in-person or remote (ie, Zoom) administration to facilitate familiarity with the protocol and provide an opportunity to answer any questions before beginning the protocol. The collection kit includes an instructional sheet on how to complete the mobile protocol and contact information to use if they encounter any problems with the mobile device. A trained study team member is available to answer any technology-based questions from dyads, assist with setup, and provide any troubleshooting that may emerge during the mobile protocol.

The nightly mobile survey asks about the participant's daily experiences, with questions about contextual factors, daily stress, daily events, time use, daily psychosocial experiences, daily physical health indices, and daily cognitive health. The evening survey measures were adapted from the National Study of Daily Experiences (eg, [54]) to facilitate cross-study harmonization between this rural sample of care dyads at risk for ADRD and a national adult lifespan sample with up to 30 years of longitudinal follow-up. Table 2 provides additional details on the surveys assessed in the mobile protocol. After each survey, participants complete 3 brief performance-based cognitive tasks (described below; screenshots provided in Figures 2 and 3, and Figure 4). At the end of the 14 days of daily diary, participants complete an "End of Diary" survey in which they complete an additional brief set of questionnaires and rate their satisfaction and ease of use when participating in the mobile protocol. Upon completion of the protocol, participants return the mobile device and charger to our university using a self-addressed mailer box or in-person delivery at a community center.

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Table . Mobile protocol measures.

Target and construct	Response option	Items and operational detail	Relevant reference
Contextual factors			
Location	Radio button	Where are you right now? (My home, other person's home, community center, etc.)	55
Social company	Multiple options	Who are you with right now? (No one, spouse or partner, friend(s), pet(s), etc)	55
Daily Inventory of Stressful Events (DISE)			
Stressor exposure	Yes or no	Composite across 6 stressor types	54
Stressor type	Yes or no	Arguments, avoided arguments, work, home, discrimination, network, and other	56
Who was involved	Multiple options	Spouse/partner, child, parent, sibling, friend, coworker, etc	57
When did it happen	Yesterday or today; AM or PM	Yesterday versus today; what time of day?	58
Stressor appraisals			
Severity	None at all-very	How stressful was this for you?	59
Control	None at all-a lot	How much control did you have over the situation?	60
Resolution	Yes or no	Is the situation resolved?	61
Resource risk	None at all-a lot	Financial, health and safety, schedule, and socioemotional	62
Stressor reactivity	Calculated slope	Emotional, behavioral, or biological reactions to stressors on the same day	63
Stressor residue	Calculated slope	Prolonged responses extending to the following day	61
Stressor diversity	Calculated index	Dispersion of stressors across multiple domains; can it be calculated using Shannon's entropy index?	64
Anticipatory stress	Not at all-very	How stressful do you expect tomorrow to be?	65
Daily events			
Positive events	Yes or no	Interaction, work, home, network, and other	66
Who was involved	Multiple options	Spouse or partner, child, parent, sibling, friend, coworker, etc	66
When did it happen	AM or PM	What time of day?	66
Anticipatory pleasantness	Not at all-very	How pleasant do you expect tomorrow to be?	66
Support exchanges	Yes or no	Give and/or receive unpaid assistance and emotional support	67
Received care	Multiple options	Did you need help in any of the following areas? (physical, financial, etc)	48
Who was involved	Multiple options	Paid caregiver or unpaid caregiver (family, friend, etc)	48
Time providing care	Hours	How many hours did they spend helping you?	48

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Target and construct	Response option	Items and operational detail	Relevant reference
Provided care	Multiple options	Did you provide help in any of the following areas? (physical, financial, etc)	48
Who was involved	Multiple options	As a paid caregiver or an unpaid caregiver (family, friend, etc)	48
Time providing care	Hours	How many hours did you spend helping them?	48
Everyday discrimination	Yes or no	Nine items with follow-up reasons for discrimination (eg, race, gender, and age)	68
Time use			
Work, volunteer, and unpaid assistance	Hours and minutes	How much time is spent working, volunteering, and providing unpaid assistance?	69
Physical activity, leisure, TV, and sitting	Hours and minutes	How much time is spent on physical activity, leisure, TV, and sitting?	70
Daily psychosocial experiences			
Negative affect	None of the time-all of the time	Fourteen items for "How much of the time today did you feel (affect item)?"	71
Positive affect	None of the time-all of the time	Thirteen items for "How much of the time today did you feel (affect item)?"	71
Quiet ego	Not at all-a great deal	Four items on quiet ego (eg, "Today, I felt aware and less judgment of myself as well as others.")	72
Daily physical health indices			
Health behaviors			
Cigarette smoking	Quantity	How many cigarettes did you smoke?	73
Vape and e-cigarettes	Hours and minutes	How much time is spent vaping or using e-cigarettes?	74
Alcohol drinks	Quantity	How many drinks did you have?	75
Fast food	Yes and no	Did you eat at a fast-food restaurant?	76
Self-rated physical symptoms			
Experience	Yes and no	Headache, fatigue, fever, muscle weakness, chest pain, etc	
Severity	Very mild-very severe	How severe was this symptom?	58
Sleep quantity and quality	Hours and minutes	What time did you wake up today? How many hours of sleep did you get last night?	77
Sleep quality	Very poor-very good	How would you rate the quality of your sleep last night?	78
Daily cognitive health			
Memory lapses			
Frequency	Yes and no	Forget errand, medication, appointment, and someone's name	79
Irritation	Not at all-very much	How much did forgetting this bother you?	79

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Target and construct	Response option	Items and operational detail	Relevant reference
Interference	Not at all-very much	How much did forgetting this interfere with your routine?	79
Unconstructive repetitive thoughts	None of the time-all of the time	Think about personal problems, trouble concentrating, etc	80
Mobile cognitive tasks			
Symbol match	Response time	~60-second task measuring processing speed	65
Grid memory	Error score	~60-second task measuring spatial working memory	65
Color shapes	Hit and error percentage	~60-second task measuring memory binding	55

Figure 2. Screenshots of symbol match mobile cognitive task. Participants complete this cognitive task during the evening assessment for 14 consecutive days.

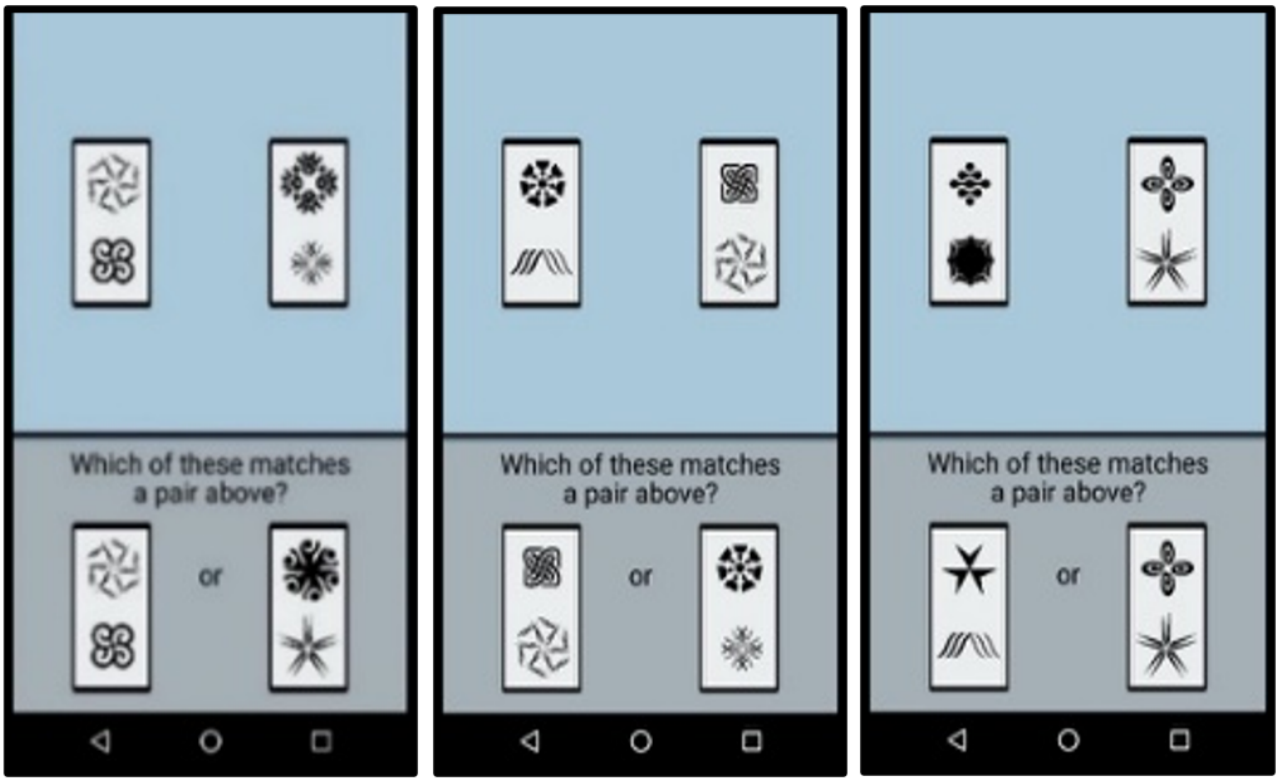

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Figure 3. Screenshots of the grid memory mobile cognitive task. Participants complete this cognitive task during the evening assessment for 14 consecutive days.

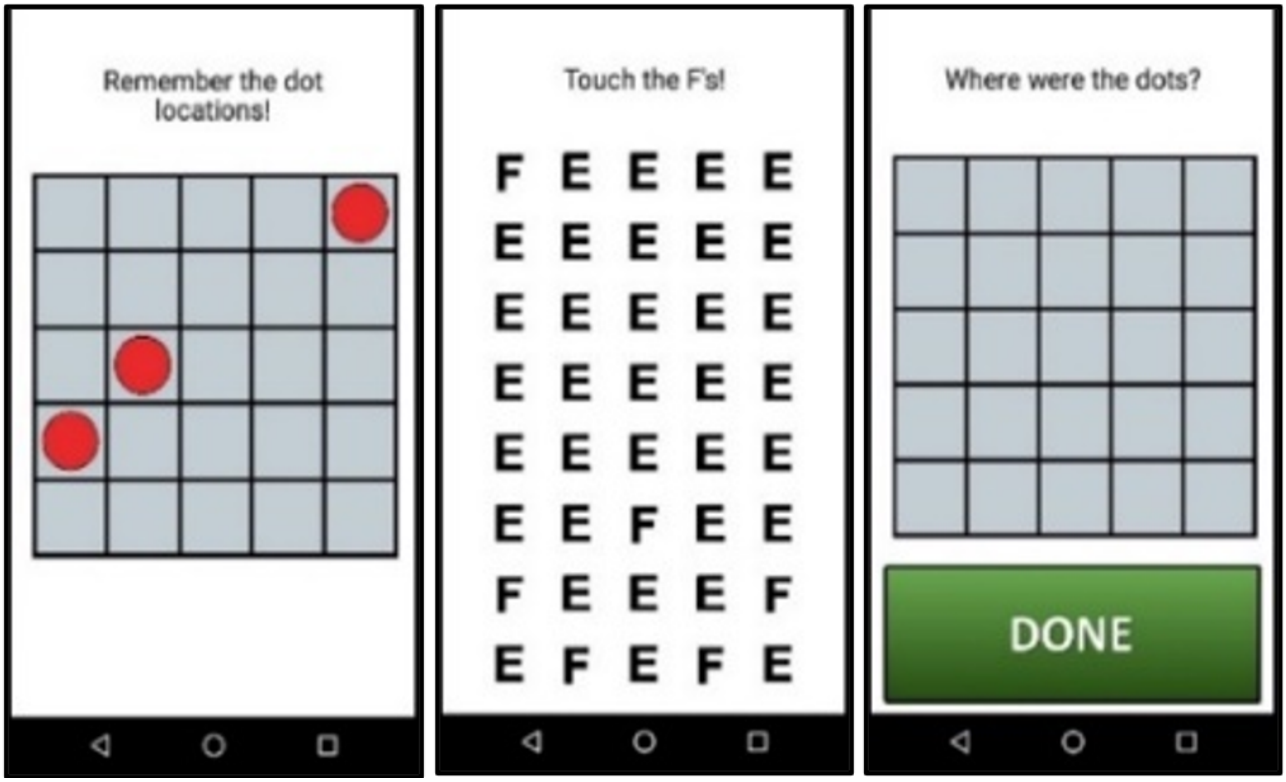

Figure 4. Screenshots of the color shapes mobile cognitive task. Participants complete this cognitive task during the evening assessment for 14 consecutive days.

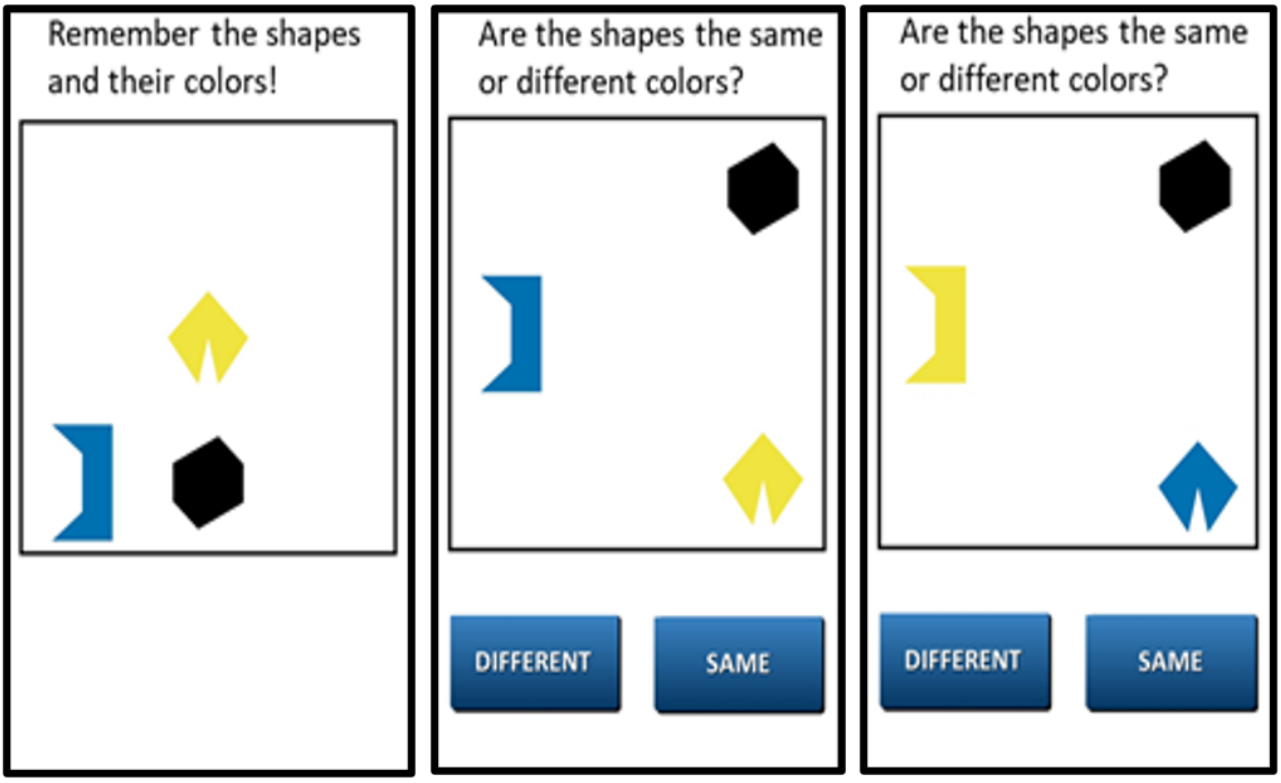

The mobile device includes 3 tasks assessing processing speed, spatial working memory, and memory binding. These tasks were selected based on their reliability when administered repeatedly over a brief time interval [81] and their sensitivity to both daily contextual factors [65] and AD [82]. Completion of these tasks takes 3‑4 minutes following the survey. Adherence in completing these tasks during a previous study

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among diverse older adults with MCI and those who were cognitively unimpaired was over 80% [55].

The processing speed task requires participants to compare 2 symbol pairs at the top of the screen with 2 symbol pairs at the bottom of the screen and decide as quickly as possible which of the bottom-screen pairs matches a top-screen pair. In the spatial working memory task, participants memorize the location of 3 red dots that appear on a 5×5 grid for 3 seconds. After an 8-second visual distractor, participants then recall their locations. The memory binding task requires participants to memorize the shapes and colors of 3 different colored polygons for 3 seconds. Participants then must recognize whether newly presented polygons are identical to the originals. Collectively, performance on these tasks represents the 3 dependent variables of cognitive health examined in Aim 2.

Our naturalistic assessment of performance-based mobile cognitive health situates the NAZMS protocol within the National Institutes of Health (NIH)-funded Mobile Monitoring of Cognitive Change (M2C2) assessment infrastructure. M2C2 is an open-source and flexible assessment infrastructure designed to advance accurate and sensitive measurement of cognitive change via mobile assessments (for more information, refer to [83]). The M2C2 mobile tests are being used in a wide range of NIH-funded studies, including the Einstein Aging Study, which is using these mobile assessments in a longitudinal study of MCI and dementia risk (eg, [55]), as well as the newest wave of data collection currently underway for the National Study of Daily Experiences, which is using these mobile assessments to monitor psychosocial and developmental contributors to cognitive health across a national adult lifespan sample. This assessment infrastructure facilitates cross-study harmonization of cognitive testing and direct comparison of M2C2 cognitive tests across NAZM's rural sample of Northern Arizonans and different NIH-funded aging studies across the United States.

Planned Analyses

Data from qualitative interviews will provide dyad preferences for identifying and monitoring MCI and SCD symptoms and for engaging in remotely delivered supportive interventions to contend with or reduce symptoms and associated problems of cognitive impairment. These interviews will also reveal information on essential components of a culturally appropriate intervention for rural ADRD dyads for intervention development, including the types of technology and comfort level with technologies for the detection of cognitive impairment and receiving support. The interviews may further inform the roles of technology access (eg, internet and broadband availability), comfort level with using technologies, and preferences toward written materials, digital tools, or online supports across different rural communities in Northern Arizona. For example, we may learn preferences that help inform a future pilot intervention for brain health support that could include combinations of written and digital-based screening, interactive features via website or mobile apps, accessible training materials, as well as live support or coaching. This is an important consideration for rural communities in the mountainous region of Northern Arizona, where the signal may be comparatively weaker or less consistent than the signal in more densely populated cities. Data collection will continue until saturation [32,84]. Data analysis will be informed by the principles of interpretative description [85], which include an emphasis on practical application of findings for practice. Interviews are audio recorded, professionally transcribed, quality-checked for accuracy, and analyzed using Dedoose (version 10.0.25; SocioCultural Research Consultants, LLC [86]). Development of analytic codes will be based on the framework method, which is recommended for qualitative health research and can be adapted for both deductive and inductive coding [87]. We plan to use deductive coding based on established models of technology acceptance [30,33] and dyadic processes [31], as well as inductive coding to understand unique and emergent patterns in the data provided by our analytic sample of rural dyads in Northern Arizona. Study interviewers will maintain field notes to provide context for data analysis. We will develop and adhere to a protocol to promote the credibility, transferability, dependability, and confirmability of qualitative findings [88].

Data from the quantitative protocol will specify for whom (ie, between-person) and on which days (ie, within-person) modifiable factors are related to better daily cognitive health. Our 14-day digital health approach repeatedly measures cognitive health in people's natural environments, improving ecological validity, reducing recall bias, and enabling examination of unique signatures of variability in cognitive performance not possible in conventional single-shot assessments completed in clinics [55]. We will use multilevel models (MLMs) with maximum likelihood estimation to accommodate the nested structure of the data (14 days nested within people) and intermittent missing data using SAS (version 9.4; SAS Institute [89]). Day-level within-person deviation scores for psychosocial, sociocultural, and contextual social determinants will be computed by subtracting an individual's average amount of the variable from their daily score [90,91]. Within-person deviation scores facilitate examination of which days modifiable protective and risk factors are related to better (or worse) cognitive health. Models will be adjusted for systematic trends across days, as well as relevant covariates (eg, caregiver strain and MoCA Blind score) and adherence rate to the protocol (to adjust for potential missing data patterns). Separate MLMs will be estimated for each cognitive outcome. To examine relationships between caregiver factors, dyadic factors, and the care receiver's cognitive health, we will regress each cognitive health outcome on the caregiver factors and dyadic factors assessed at baseline. To examine daily influences of modifiable protective and risk factors on cognitive health among individuals with MCI, the day-level cognitive health outcomes will be regressed on the day-level within-person deviation scores for psychosocial, sociocultural, and contextual factors.

Sample Size Considerations

Our initial target sample size is 30 rural care dyads. We determined 30 rural care dyads as a starting point for NAZMS data collection based on its mixed methods design components (qualitative and quantitative), the dyadic nature of interviews (30 caregivers and 30 participants with cognitive impairment), and statistical power analysis for quantitative analyses. For the

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qualitative arm, 30 dyads will be sufficient to adequately address our research questions and reach saturation based on our theoretical grounding and qualitative analytic framework [92,93]. For the quantitative arm, statistical power for quantitative protocol analyses among the target 30 participants with cognitive impairment was determined using techniques recommended by Cohen [94] for determining power to detect effects using repeated-measures ANOVA and NAZMS details. Our proposed MLM approach is more powerful than repeated-measures ANOVA and uses all available data from up to 14 measurements; therefore, this calculation provides a conservative estimate of power to detect effects. Power analysis was conducted using G*Power (Franz Faul, Edgar Erdfelder, Albert-Georg Lang, and Axel Buchner [95]), power=0.80, target (n=30), and α=.05. We have 80% power to detect small-to-medium effects of daily predictors for cognitive health outcomes (Cohen f=0.15).

Our team intends to expand NAZMS data collection capacity in subsequent years as we learn from this initial target sample. Specifically, our goal is to expand the NAZMS sample size beyond these initial 30 dyads to build our capacity to better characterize supports for people with cognitive impairment and their family members in rural communities across the Southwest.

Ethical Considerations

All participants provided written or verbal (if administered remotely via Zoom) informed consent and received compensation for their participation. All procedures were approved by our university's Institutional Review Board (IRB; approval no. 2090130). Participants were eligible to receive up to US $100 in gift cards for their participation (US $50 after completion of the qualitative interviews and surveys and an additional US $50 upon completion of the daily diary protocol).

Results

As of September 2025, 39 adults have participated in cognitive screenings. Of the 39 adults, 17 have screened positive for MCI, and 38 have screened positive for SCD. Eleven dyads have been recruited to complete the NAZMS protocol with plans to continue recruitment this year and expand data collection capacity in subsequent years. Results from this study are expected to be published by summer 2027.

Discussion

Implications for Rural Communities

Through the project activities and subsequent data analysis, there are multiple implications for care dyads at risk for ADRD living in memory care deserts and rural areas. First, we will determine culturally appropriate methods and technologies for identifying rural families facing cognitive impairment in community-based settings (Aim 1). Second, through the convergence of interviews and daily cognitive assessment over 14 days, we will be able to characterize rural caregiver-receiver dyads with information from not only intervention content and engagement preferences, but also the modifiable protective and risk factors that influence cognitive health in everyday life (Aim 2). Third, we will establish the content needed to develop an intervention for this population (Aim 1). Fourth, we will establish collaborative relationships with regional community centers and Tribal Nations that will be needed for future research and resource distribution with rural ADRD care dyads (Aim 1). Finally, we will share what we learn through community forum events and brain health workshops designed to educate rural communities by confronting stigma and anxiety associated with cognitive impairment and to promote cognitive screenings and the importance of early detection (Aims 1 and 2).

Implications for Designing Digital Health Technologies

Digital health tools and interventions can be viable ways to support people with cognitive impairment [96] and caregivers [97]. However, the needs and preferences for different digital health technologies vary depending on cognitive status and caregiving demands [98], with recent systematic reviews and meta-analyses calling for future research to address issues around accessibility, acceptability, and sustainability of digital health interventions in these populations [97] and rural communities [99]. For example, a mixed methods evaluation of a web-based platform designed to improve the quality of life for people with cognitive impairment and reduce burden for caregivers recognized the need for end users to be involved in the development of the digital health tools [98]. Our dyadic data collection, intentionally connecting with both members of the care dyad, will address the gaps outlined by this previous research and situate NAZMS in a broader literature of digital health technologies that can support both people with cognitive impairment and their family members living in rural communities.

Developing Partnerships With Tribal Nations for Future Collaboration

We are in the process of developing partnerships with Tribal Nations to provide the NAZMS protocol to Indigenous communities residing on Tribal lands. In spring 2025, we received conditional approvals from our university's Office of Native American and Indigenous Advancement's Tribal Consultation process and IRB to seek formal Tribal IRB approval that can expand recruitment to Tribal lands in the future. Building on culturally informed frameworks [100] and community-engaged approaches with Tribal Nations [101], we look forward to examining unique protective and risk factors for ADRD in Indigenous communities [102] and supporting Indigenous care dyads in the Southwest.

Conclusions

The NAZMS dyadic mixed methods digital health protocol aims to support rural families at risk for ADRD by understanding intervention preferences and identifying the modifiable protective and risk factors that influence cognitive health in everyday life. The findings will respond to national priorities in ADRD research [27] for the development of community-based education programs and the use of digital assessments of cognitive health and well-being [1].

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Authors' Contributions

ESC, MCM, JM, and MJM contributed to the study's design. ESC, MCM, MM, TJS, RD, TJA, JM, LL, and MJM coordinated the study. ESC, MCM, MJM, and FRS drafted the manuscript. MM, TJS, RD, TJA, GP, RAL, ADB, JM, and LL revised the manuscript. ESC, MCM, MJM, and FRS drafted specific sections. ESC prepared the tables/figures. ESC, MCM, and MJM formulated the statistical analysis plan.

Conflicts of Interest

None declared.

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Abbreviations

AD: Alzheimer disease
ADRD: Alzheimer disease and related dementias
IRB: Institutional Review Board
M2C2: Mobile Monitoring of Cognitive Change
MCI: mild cognitive impairment
MLM: multilevel model
MoCA: Montreal Cognitive Assessment
NAZMS: Northern Arizona Memory Study
NIH: National Institutes of Health
SCD: subjective cognitive decline

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Protocol

Trajectories of Change, Illness Understanding, and Parental Worries in Children and Adolescents Undergoing Internet-Delivered Cognitive-Behavioral Therapy for Functional Abdominal Pain Disorders: Protocol for a Single-Case Design and Explorative Pilot Study

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Abstract

Background: Functional abdominal pain disorders (FAPDs) are common in young people and are characterized by persistent or recurrent abdominal symptoms without apparent structural or biochemical abnormalities. FAPDs are associated with diminished quality of life, school absence, increased health care use, and comorbid anxiety and depression. Exposure-based internet-delivered cognitive behavioral therapy (ICBT) has demonstrated efficacy in alleviating abdominal symptoms and improving quality of life. However, a deeper understanding of effect mechanisms and identification of possible additional treatment targets could refine treatment.

Objective: This protocol paper aims to describe a study focusing on children and adolescents undergoing ICBT for FAPDs, aiming to further investigate the underlying mechanisms of effect.

Methods: Children (8-12 years), adolescents (13-17 years) with FAPDs, and their respective parents will be included for 10 weeks for ICBT. First, detailed trajectories of effect are examined through a randomized single-case design study involving 6 children and 6 adolescents (substudy 1). Following this, an open-ended explorative pilot study with 30 children and 30 adolescents explores potential illness-related cognitive biases and interoceptive accuracy before and after treatment (substudy 2). Finally, spanning across these 2 substudies, including all parents from substudies 1 and 2, we will assess parental distress and illness worries before and after treatment, and how these factors impact the treatment adherence and outcomes of the child or adolescent (substudy 3).

Results: Recruitment of participants began in June 2022 and is finalized for substudy 1 and ongoing for substudies 2 and 3. Recruitment is expected to be completed by January 2025, with final data collection during April 2025.

Conclusions: The findings have the potential to contribute to the ongoing improvement of specialized psychological treatment for FAPDs in young people.

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Trial Registration: ClinicalTrials.gov NCT05237882; https://clinicaltrials.gov/study/NCT05237882; ClinicalTrials.gov NCT05486585; https://clinicaltrials.gov/study/NCT05486585; OSF Registries osf.io/c49k7; https://osf.io/c49k7

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KEYWORDS

functional abdominal pain disorders; abdominal pain; internet-based intervention; cognitive behavioral therapy; interoception; attentional bias; parental distress; single case study; children; adolescents; youth; study protocol; quality of life; treatment; medication; psychological treatment; psychology

Introduction

Functional abdominal pain disorders (FAPDs) affect up to 15% of children and adolescents and are characterized by recurrent or persistent abdominal pain and other debilitating gastrointestinal symptoms such as changes in defecation patterns and nausea [1,2]. The disorders are associated with reduced quality of life, high absence from school, and increased health care use [3]. Psychiatric comorbidities, especially anxiety and depression, are prevalent [4] and up to 40% persist in reporting abdominal symptoms into adulthood [5].

The pathophysiology of FAPDs is not fully understood but recent research suggests a biopsychosocial perspective where the complex interactions of physiological processes such as visceral hypersensitivity, psychological factors like emotional distress and anxiety, and social factors including family dynamics and environmental influences can contribute to the development and maintenance of gastrointestinal symptoms [6]. These factors combined are related to altered processing of sensory stimuli along the brain-gut axis with persistent or recurrent experience of abdominal pain and other gastrointestinal symptoms [7-10]. This altered processing can be understood within the framework of predictive processing, a theory suggesting that the brain consistently evaluates predictions regarding sensory inputs and discrepancies from these predictions [11]. Crucial factors contributing to the development of maladaptive predictive processes encompass cognitive biases marked by symptom-related fear and catastrophizing with an attentional bias toward pain or gastrointestinal stimuli [12-15]. This may be accompanied by the avoidance of situations expected to trigger symptoms [4,16-18] and changes in the interoceptive ability to sense, process, and interpret body signals [19]. Parental behaviors, such as solicitous responses, fearful communication about symptoms, and encouraging avoidance of situations that may provoke symptoms, can further influence the child's perception of bodily stimuli [20-23].

In summary, understanding the pathophysiology of FAPDs involves navigating a complex system of various factors and processes. Consequently, treatment may encompass different targets, including both child-specific and contextual, that is, typically parental-specific factors.

In line with this, cognitive behavioral therapy (CBT) is the treatment supported by the strongest evidence of effect [24-26], with its main focus on restructuring potential child symptom-related maladaptive cognitions, emotions, and behaviors, and often with parental involvement. Swedish studies have documented the efficacy of internet-delivered cognitive behavioral therapy (ICBT) aimed at children and adolescents with FAPDs and their parents [27-29]. The ICBT focuses especially on exposure exercises and parental management of their child or adolescent's symptoms. By enabling the child or adolescent to manage symptoms in previously avoided situations and thereby minimizing the gastrointestinal-specific fear, the treatment reduces the proposed visceral hypersensitivity, which over time leads to fewer abdominal symptoms.

Still, a proportion of the young patients do not improve from ICBT as the number needed to treat has been reported to be around 4, meaning approximately 4 patients must receive the treatment for 1 additional patient to experience adequate symptom relief [27,29]. Therefore, a deeper understanding of the mechanisms of change and the potential influence of additional modifiable factors on the treatment effect is required to improve treatment effects even more.

In the current study, we will evaluate translated versions of the Swedish ICBT for children and adolescents with FAPDs in a Danish context. The treatments target both children (aged 8-12 years) and adolescents (aged 13-17 years) and their parents, which provides a unique possibility to examine both child or adolescent and parental factors before and after treatment. The aims of the study are to (1) investigate the detailed trajectory of the effect of ICBT in children and adolescents with FAPDs, (2) explore potential illness-related cognitive biases and interoceptive accuracy in children and adolescents with FAPDs compared with healthy controls, and if these factors are changed after ICBT, and (3) explore if parental distress, illness worries, and behaviors may impact the child or adolescent's treatment adherence and outcome.

This protocol article is reported following the SPIRIT (Standard Protocol Items Recommendations for Interventional Trials) guidelines [30].

Methods

Study Design

The study includes 2 recruitment phases. The first phase concerns a single case experimental design (SCED) study (substudy 1) with a total of 12 patients (6 children and 6 adolescents, respectively). The second phase concerns an open pilot study on cognitive biases and interoceptive accuracy (substudy 2) with a total of 60 patients (30 children and 30 adolescents, respectively).

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Consequently, a total of 72 children and adolescents, along with a corresponding number of parents, will undergo ICBT for FAPDs throughout the entire study. Parental distress and illness worries will be assessed before, during, and after the treatment in all included parents (substudy 3; Figure 1).

Figure 1. Overall study design. BY-GIS: biases in youth toward gastrointestinal-related stimuli; DSQ: daily short questionnaire; HRD: heart rate discrimination; ICBT: internet-delivered cognitive behavioral therapy; ICD-10: International Statistical Classification of Diseases, Tenth Revision.

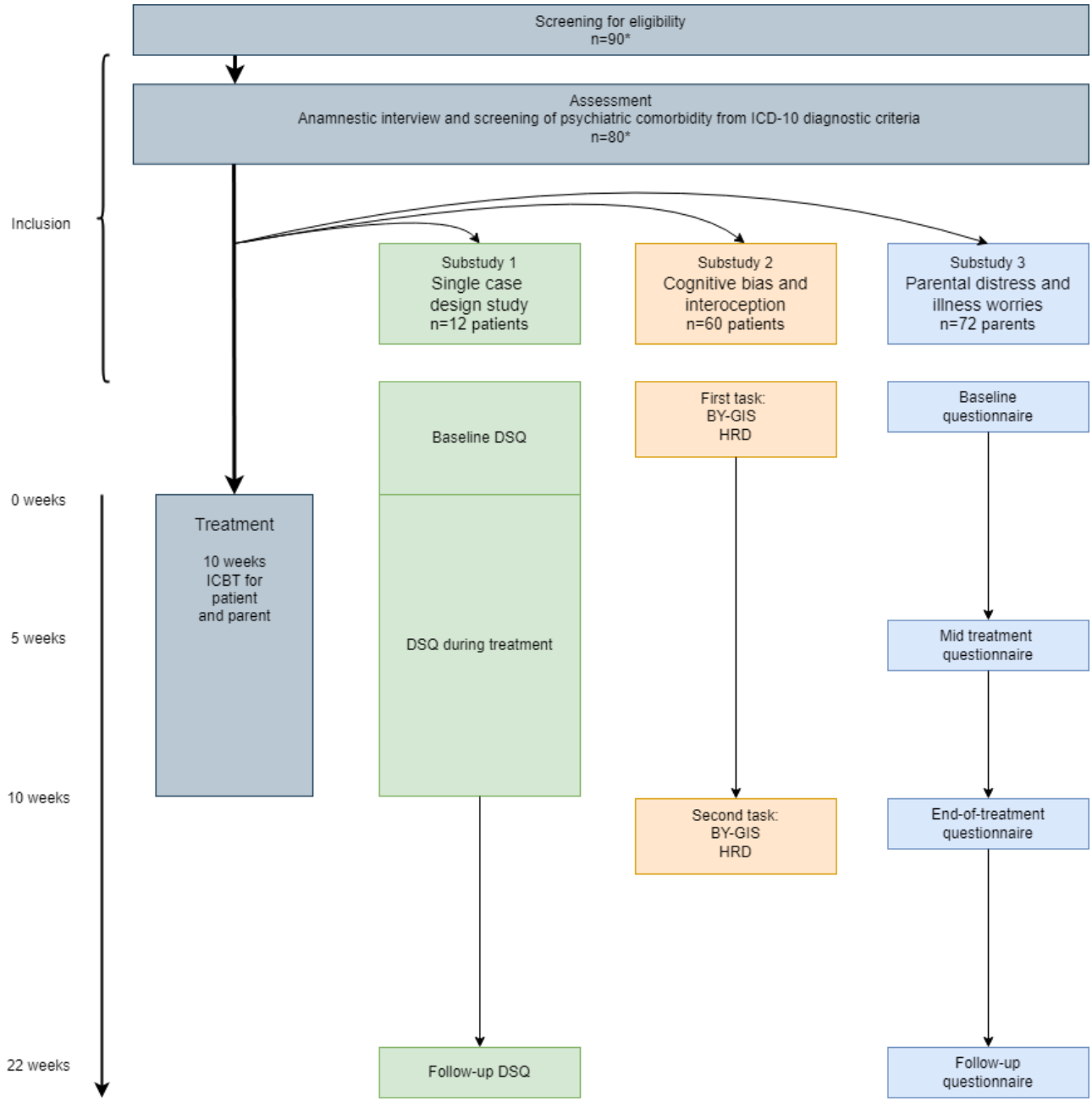

Study Setting and Recruitment

Children and adolescents diagnosed with FAPD will be referred to the project from pediatric departments located at 4 hospitals (1 university hospital and 3 regional hospitals, respectively) as well as from private pediatric practitioners in the Central Denmark Region. Due to a slow referral rate of adolescents, we have been granted permission from The Central Denmark Region Committees on Health Research Ethics to expand the inclusion area to include additional regions (the North Denmark Region and the Region of Southern Denmark). We will maintain continuous communication with referring pediatricians to ensure sufficient participant enrollment. This will include in-person meetings, emails, and newsletters.

Eligibility Criteria

Eligible participants will be invited for an assessment interview at the Department of Child and Adolescent Psychiatry, Aarhus University Hospital Psychiatry. The assessment will include psychiatric comorbidities, such as neurodevelopmental disorders, mood disorders, and suicidal risk, systematically evaluated according to the *ICD-10* (*International Statistical Classification of Diseases, Tenth Revision*) diagnostic criteria. Assessments

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will be performed by medical doctors who are either trainees or specialists in child and adolescent psychiatry.

Inclusion Criteria

First, age 8-17 years. Second, a primary diagnosis according to the ROME-IV criteria of one of the FAPD subtypes—irritable bowel syndrome (IBS) or functional abdominal pain not otherwise specified (FAP-NOS) documented by the child's regular pediatric physician [31]. The somatic evaluation includes recommended routine medical investigations, that is, growth, fecal calprotectin, and blood samples (TSH [thyroid stimulating hormone], total IgA [immunoglobulin A], IgA-tissue transglutaminase, complete blood count, C-reactive protein analysis, and liver enzymes). Third, stable dosage of regular FAPD-related medication such as laxatives, antidiarrheal medicines, or psychopharmacological medication during the past month.

Exclusion Criteria

First, another medical or psychiatric disorder that better explains the symptoms. Second, severe child psychiatric or social problems (eg, high level of suicidal ideation, school absence of more than 40% during the past month, or ongoing substance abuse). Third, ongoing psychological treatment. Fourth, insufficient language or computer skills (patients and parents). Fifth, severe family problems (eg, child maltreatment, parental substance abuse or severe psychiatric illness, and custody fight).

Intervention

Translation Procedure

For this study, the Swedish ICBT programs were translated into Danish. The translation procedure was stepwise; first, a direct translation was performed by native Danish speakers familiar with the Swedish language; second, a mutual discussion of the Danish translation took place within the research group, including a discussion of problematic sentences or wordings; third, remaining issues were discussed with the Swedish authors, and a final consensus on the Danish translation was reached. This translation was reviewed by both a Danish language expert and a clinician with experience with the patient group to make further refinements. Finally, in the last step, the revised translation was reviewed again by the Danish research group for final adjustments.

Design and Content of Treatment

The 4 distinct ICBT programs used in this study are targeted children (8-12 years), adolescents (13-17 years), and the parents of each group, respectively. The treatment lasts for 10 weeks and consists of 10 modules for children, adolescents, and parents of children (with a new module every week) and 5 modules for parents of adolescents (with a new module every other week). An overview of treatment content can be seen in Table 1. The programs include sections with videos, exercises, and quizzes designed to actively engage the child or adolescent in the treatment. Psychoeducation regarding FAPDs, detection of avoidance behavior, a brief mindfulness exercise called "SOL (Stop, observe, let go)" and graded repeated exposure exercises comprise some of the central components covered in the programs for both children and adolescents. The first modules of treatment introduce the above-mentioned concepts whereas later modules focus on repeated exposures. The purpose of "SOL" is Stopping, Observing how the stomach feels, and Letting go of the focus on the stomach and continuing with the activity. The parental programs emphasize supporting their child or adolescent's exposure, decreasing attention to their child or adolescent's abdominal symptoms, and prioritizing shared positive activities. Each module ends with planning of the homework assignments which are evaluated first thing in the next module.

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Table 1. Overview of the content of treatment for each module.

Module	Children (8-12 years)	Parents	Adolescents (13-17 years)	Parents
1	• Introduction to the treatment format • Psychoeducation on FAPDs[a] (video) • Mapping "stomach behaviors" (control, avoidance, safety) • Setting treatment goals • Homework: Self-monitoring	• Introduction to the treatment format • Positive attention • Focus shift • Mapping common parental behaviors • Handling personal frustrations • Homework: Focus shift, breaks, involving peers	• Introduction to the treatment format • Psychoeducation on FAPDs (video) • Setting treatment goals • Homework: self-monitoring	• Introduction to the treatment format • Focus on positive attention and shared moments • Mapping common parental behaviors • Homework: Shared positive moments
2	• Psychoeducation on impact of thoughts and "SOL"[b] (video) • Constructing an exposure hierarchy. • Homework: Utilize "SOL" in everyday situations.	• Golden moments • Board game with rewards for exposure exercises. • Homework: Golden moments, focus shift, planning rewards"	• Mapping "stomach behaviors" (control, avoidance, safety) • Behavior analysis • Homework: Behavioral experiment (avoiding "stomach behaviors")	
3	• Behavior analysis • Psychoeducation on exposure exercises (video) • Homework: Exposure exercises.	• Supporting child's exposure exercises • Managing school absences • Homework: board game rewards, golden moments, focus shift	• Psychoeducation on impact of thoughts and "SOL" (video) • Toilet habits (frequent visits, urgency) • Homework: "SOL" and new toilet habits	• Psychoeducation on FAPDs (video) • Acknowledging and shifting focus to reduce symptom focus • Homework: Shared positive moments, letting go of parental behaviors, focusing on alternative adolescent behaviors
4	• Toilet Habits (frequent visits, urgency) • Behavior analysis • Homework: Exposure exercises, new toilet habits, "SOL"	• Parental stress and recreational activities • Homework: recreation, golden moments, board game rewards, focus shift	• Psychoeducation on exposure exercises (video) • Behavior analyses • Construct exposure hierarchy • Homework: "SOL," toilet habits, finish exposure hierarchy	
5	• Repetition • Behavior Analysis • Homework: Exposure exercises, toilet habits, eliminating safety behaviors, "SOL"	• Repetition • Mapping challenges • Homework: recreation, golden moments, board game rewards, focus shift	• Exposure exercises • Anticipatory anxiety • Emotional versus behavioral goals • Homework: Exposure exercises, "SOL," toilet habits.	• Encourage and support the adolescent's exposure • Psychoeducation on exposure exercises (video) • Homework: Shared positive moments, support and encouragement, support adolescent's exposure
6	• Positive analysis of new behaviors • Advancing exposure difficulty • Homework: Advancing exposure exercises, toilet habits, "SOL"	• Problem-solving with child • Homework: recreation, golden moments, board game rewards, focus shift, problem-solving	• Further details on exposure and rewards • Homework: Exposure exercises, "SOL," and toilet habits	

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Module	Children (8-12 years)	Parents	Adolescents (13-17 years)	Parents
7	• Positive behavior analyses • Evaluation of Treatment Goals (from Module 1) • Homework: Exposure exercises, toilet habits, “SOL”	• Parental behavior analyses in child interaction • Homework: recreational, golden moments, board game rewards, focus shift	• Level up exposure exercises • Homework: Exposures exercises, “SOL,” toilet habits	• Managing personal frustrations • Engaging in recreational activities • Listening effectively • Homework: Shared positive moments, support and encouragement, support adolescent’s exposure, active listening, parental recreation
8	• Positive behavior analyses • Advancing exposures to a “Super Hard Day” • Homework: Exposure exercises, the “Super Hard Day,” toilet habits, “SOL”	• Review of progress • Reward for efforts • Homework: recreation, golden moments, board game rewards, focus shift, parental reward	• Emphasis on more challenging exposures • Homework: Challenging exposure exercises, “SOL,” toilet habits	
9	• Treatment repetition using quizzes • Progress evaluation • Homework: Final exposure exercises, toilet habits, “SOL”	• Progress evaluation • Challenge evaluation • Homework: recreation, golden moments, board game rewards, focus shift.	• Focus on how to further challenge oneself. • Homework: Exposure exercises	• Review of treatment • Parental behavior evaluation (comparison with module 1) • Future training and relapse prevention plan
10	• Treatment goal and exposure hierarchy evaluation • “Stomach behavior” evaluation (comparison with module 1) • Future training and relapse prevention plan	• Parental behavior evaluation (comparison with module 1) • Future training and relapse prevention plan	• Treatment goal and exposure hierarchy evaluation • “Stomach behavior” evaluation (comparison with module 1) • Future training and relapse prevention plan	

[a]FAPDs: Functional abdominal pain disorders.

[b]SOL: Stop, observe, let go.

Modifications and Web Page

The Danish versions of the ICBT programs were pretested in 2 children and 2 adolescents with biweekly feedback from the patients and parents on overall experience and content (telephone interviews performed by a research assistant). Minor modifications were performed, mainly in the adolescent program where the IBS treatment was adjusted to include IBS and FAP-NOS. Furthermore, the mindfulness exercise “SOL” was integrated in the adolescent program to further support the process of labeling thoughts and sensations.

All treatment elements are delivered through a web page specifically designed for this study (Figure 2). Each family will choose 1 primary parent to participate in the treatment at the assessment. All 4 treatment programs are supported by a therapist who provides written feedback after each module. The affiliated therapists will be psychologists and medical doctors with knowledge of CBT. They will receive weekly supervision from Danish specialists in CBT and further supervision from the Swedish research team, who developed and tested the original programs.

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Figure 2. Screenshot of the start page for the Danish treatment programs (all text is translated from Danish to English).

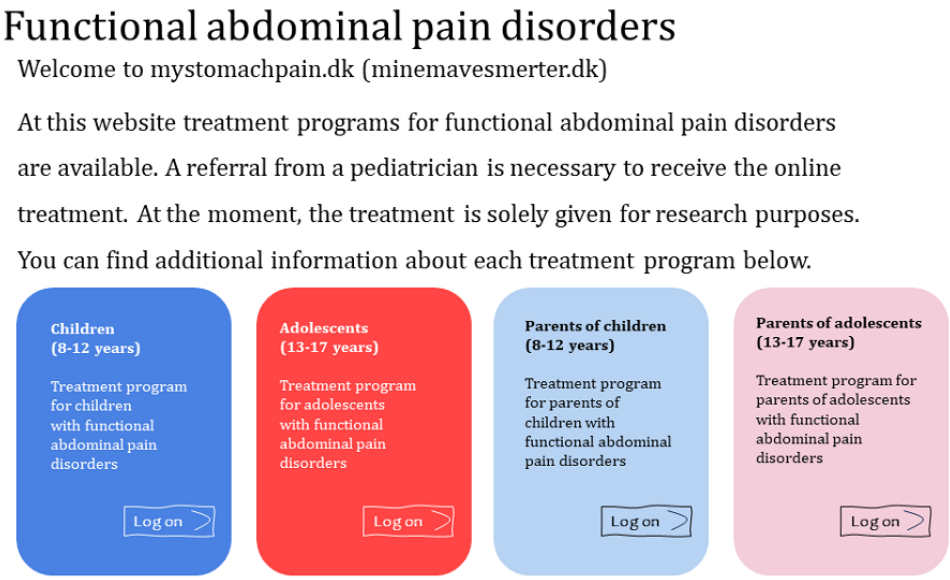

Measures

Measures in the Single Case Design Study (Substudy 1)

Children and adolescents will answer a daily short questionnaire (DSQ) throughout a pretreatment baseline period, randomized to last between 5 and 15 days, throughout the 10 weeks of treatment, and for a final 7-day follow-up period 3 months after treatment. The DSQ is an 8-item questionnaire, designed in line with the SCRIBE (Single-Case Reporting guideline In BEhavioural interventions) guidelines [32], addressing specific targets of the intervention, with items from different validated questionnaires for children and adolescents [32,33]. The full DSQ questionnaire is shown in Textbox 1. The primary outcome in the SCED study is the level of gastrointestinal symptoms assessed using 2 items from the Pediatric Quality of Life Inventory (PedsQL) Gastrointestinal Symptoms Questionnaire [34]. Secondary outcomes include illness worries, avoidance behavior, and level of pain acceptance as measured by the Visceral Sensitivity Index (VSI), irritable bowel syndrome behavioral response questionnaire (IBS-BRQ), and the Chronic Pain Acceptance Questionnaire – Adolescent Short Form (CPAQ-A8), respectively [35-37]. The items have been modified into questions concerning the last 24 hours and are rated on a 0-10 scale (“not at all” 0, “all the time” 10).

Textbox 1. Daily short questionnaire (DSQ).

During the last 24 hours, on a scale from 0 (not at all) to 10 (all the time)

1) Did your stomach hurt?

2) Did you feel discomfort in your stomach?

3) Did you worry about the problems in your belly?

4) Were you frightened when you felt discomfort in your belly?

5) Did you avoid going out in case you had belly problems?

6) Did you spent more time on the toilet than you ideally would like?

7) Did you do things that are important and things that are fun even though you have problems in your belly?

8) Has the most important thing been to keep your symptoms under control whenever you did something?

Measures on Cognitive Bias and Interoception (Substudy 2)

Cognitive biases will be assessed before and after treatment using a newly developed experimental design with a computerized web-based task: biases in youth toward gastrointestinal-related stimuli (BY-GIS) [38]. The BY-GIS task consists of a combination of a word task, which is a modified version of the Health Norms Sorting Task [39-41] and a picture task inspired by Gehrt et al [42]. The BY-GIS task is adapted to be appropriate for children and adolescents, featuring gastrointestinal-related stimuli (ie, words related to abdominal symptoms and pictures of food, leisure, and school situations). The BY-GIS task has 3 phases—encoding, free recall, and recognition. In the encoding phase, participants are asked to rate words and pictures presented to them. In the free recall phase, participants are instructed to recall as many words and pictures from the encoding phase as possible, and in the recognition phase, they are presented with words and pictures from the encoding phase along with new words and mirror images of the original pictures. They are then asked to mark which items have been presented to them before. The

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development, test, and full procedure of the BY-GIS task are described by Bjerre-Nielsen et al [38].

Interoception will be investigated before and after treatment using a psychophysical measure of cardiac interoception, that is, the heart rate discrimination (HRD) task, developed by Legrand et al [43]. During the HRD task, participants have their heart rate monitored using a pulse oximeter while they are presented with auditory and visual stimuli from a computer and answer questions about their sensations of heart rate and subjective confidence in their answers. Thereby, the interoceptive performance (psychometric threshold, slope, and reaction time) and the metacognitive performance (confidence) can be measured. In collaboration with researchers from the Center of Functionally Integrative Neuroscience at Aarhus University, the task was adapted for a younger age group and pretested in 3 children and adolescents. Adaptations consisted of shortening the test by reducing the number of repetitions of trials, as well as replacing written instructions about the conduction of the test with direct oral guidance from a research assistant.

For both studies in substudy 2, we will perform parallel studies on healthy controls. The BY-GIS task was already tested in 96 healthy controls [38], and the interoception test setup will be performed in 60 healthy controls (all aged 8-17 years).

Measures of Parental Factors and Child Treatment Effects (Substudy 3)

To assess how parental distress, illness worry, and behavior impact the child's overall treatment effects in various domains and treatment adherence, all participating parents and children or adolescents in the ICBT programs will answer extensive questionnaires before assessment (T1: baseline), halfway through treatment (T2: mid-treatment), at end of treatment (T3: end of treatment), and 3 months after the end of treatment (T4: follow-up; Figure 1). Furthermore, the number of completed treatment modules will be obtained from the treatment web page after the end of treatment. The specific measures to be used are shown in Table 2 and described subsequently.

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Table 2. Overview of questionnaires in substudy 3.

Outcome	Instrument	Time points and respondents[a]			
		T1	T2	T3	T4
Parental factors					
Parental distress	SCL-8[b] [44,45]	P	P	P	P
Parental illness worries	HAPYS[c] [46,47]	P	P	P	P
Parental illness behavior	ARCS[d,e] [48-50]	P	P	P	P
Child treatment effects					
Main measures					
Gastrointestinal symptoms	PedsQL Gastro[f] [34]	C, A, P	C, A, P	C, A, P	C, A, P
Pain intensity	Faces Pain Rating Scale – revised [51,52]	C, A, P	C, A, P	C, A, P	C, A, P
Additional measures					
Quality of life	PedsQL[g] [53]	C, A, P	C, A, P	C, A, P	C, A, P
Overall symptom load	CSSI[h] [54]	C, A, P		C, A, P	C, A, P
Depressive symptoms	MFQS[i] [55,56]	C, A		C, A	C, A
General anxiety	SCAS-S[j] [57,58]	C, A, P		C, A, P	C, A, P
Gastrointestinal anxiety	VSI[k]-short [35,59]	C, A	C, A	C, A	C, A
Avoidance and control behavior	IBS-BRQ-C[l] [36,60]	C, A	C, A	C, A	C, A
Illness perception	B-IPQ[m] [61,62]	C, A, P	C, A, P	C, A, P	C, A, P
Illness worries	CIAS[n,o] [63]	C, A	C, A	C, A	C, A
Pain acceptance	CPAQ-A8[p,q] [37]	C, A	C, A	C, A	C, A
Other measures					
Adverse events	Yes or no, and open question			A, P	
Treatment satisfaction	ESQ[r] [64]			C, A, P	
School absence	Hours past month	A, P	A, P	A, P	A, P
Work absence	Days past month	P	P	P	P

[a]Time points; T1: baseline, T2: mid-treatment, T3: end-of-treatment, T4: follow-up; Respondents: C: child, A: adolescent, P: parent.
[b]SCL-8: Symptom Check List-8.
[c]HAPYS: The Health Anxiety by Proxy Scale.
[d]ARCS: Adult Responses to Children's Symptoms.
[e]The monitor and protect subscales.
[f]PedsQL Gastro: Pediatric Quality of Life Inventory – Gastrointestinal symptoms.
[g]PedsQL: Pediatric Quality of Life Inventory.
[h]CSSI: Children's Somatic Symptom Inventory.
[i]MFQS: Mood and Feelings Questionnaire Short.
[j]SCAS-S: Spence Children Anxiety Scale – Short.
[k]VSI: Visceral Sensitivity Index.
[l]IBS-BRQ-C: irritable bowel syndrome behavioral response questionnaire – Child-adapted short version.
[m]B-IPQ: Brief Illness Perception Questionnaire.
[n]CIAS: Childhood Illness Attitude Scale.
[o]The fear factor subscale.
[p]CPAQ-A8: Chronic Pain Acceptance Questionnaire – Adolescent Short Form.
[q]One question from the pain willingness factor, one from activity engagement.
[r]ESQ: Modified Experience of Service Questionnaire.

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Parental Factors

Parental distress will be assessed by the Symptom Checklist-8, an 8-item subscale from the Symptom Checklist Revised-90, screening for emotional symptoms. Items are rated on a 5-point scale from 0 “not at all” to 4 “a whole lot,” with a total range from 0 to 32. Higher scores indicate more emotional distress [44,45].

Parental illness worries will be assessed by the Health Anxiety by Proxy Scale (HAPYS), a newly developed questionnaire assessing parents’ worries about their child’s health [46]. The questionnaire covers 26 items about health anxiety by proxy, rated on a 5-point scale (from 0 “not at all” or “never” to 4 “a whole lot” or “most of the time”), with a sum score range from 0 to 104. In addition, there are 6 items about the impact of the worries rated on a 4-point scale (from 0 “no” to 3 “yes, severely”), with a sum score range from 0 to 18. Higher scores indicate a high level of health anxiety by proxy and the impact of the anxiety, respectively. HAPYS is a valid measure of health anxiety by proxy with good psychometric properties, including high internal reliability and known-groups validity [47].

Parental illness behavior will be measured by the Adult Responses to Children’s Symptoms, which is originally a 29-item questionnaire [48]. In this study, 2 subscales (monitor and protect subscales) comprising 15 items will be used. Items are rated on a 5-point scale from 0 “never” to 4 “always” with a score range from 0 to 60. Higher scores indicate a higher degree of monitoring and protective responses [49,50].

Child or Adolescent Treatment Effects—Main Measures

Gastrointestinal symptoms will be assessed by PedsQL gastrointestinal symptoms [34]. This is a 9-item questionnaire assessing gastrointestinal symptoms related to functional or organic gastrointestinal diseases, during the past month, on a 5-point scale from 0 “never” to 4 “almost always.” Scores are reversed and transformed into a 0-100 scale, with high scores indicating greater quality of life. Pain intensity will be assessed by the Faces Pain Rating Scale – revised (FPS-R) [51]. The FPS-R score includes 6 pictures of faces, each showing an increasing amount of pain and scored on a 2-step scale between “no pain” (0) and “worst pain” (10). The scale is validated in children and adolescents and found to be sensitive to change [52].

Child or Adolescent Treatment Effects—Additional Measures

Quality of life will be measured by the 23-item PedsQL [53], which is a widely used questionnaire to assess quality of life during the past month in children and adolescents. Items are scored on a 5-point scale from 0 “never” to 4 “almost always.” Scores are reversed and transformed into sum scores between 0 and 100, with high scores indicating higher quality of life.

Overall symptom load will be assessed by the Children’s Somatic Symptom Inventory. It measures somatic symptoms during the last 2 weeks using 24 items, rated on a 5-point scale from 0 “not at all” to 4 “a whole lot,” with a range in scores from 0 to 96. High scores indicate a high symptom load. The questionnaire is found to be reliable and psychometrically sound for children and adolescents with abdominal pain disorders [54].

Depressive symptoms will be measured using the Mood and Feelings Questionnaire Short. It comprises 13 items rated on a 3-point scale from 0 “not true” to 2 “true,” with a range from 0 to 26, where higher scores indicate more depressive symptoms. The questionnaire is found reliable for evaluating depressive symptoms in both clinical and community populations of children and adolescents [55,56].

Anxiety levels will be assessed with 2 different questionnaires—the Spence Children Anxiety Scale Short (SCAS-S) [57,58] for general anxiety, and the Visceral Sensitivity Index-Children (VSI-C) [35,59] for gastrointestinal-specific anxiety. SCAS-S contains 19 items which are answered on a 4-point scale from 0 “never” to 3 “always,” with a total range from 0 to 57, where higher scores indicate higher anxiety levels. The questionnaire is designed for use in children and adolescents, and the short version is validated for screening of anxiety levels in children and adolescents [58]. The VSI-C is a shortened child-adapted version of the VSI for adults [35], with 7 items answered on a 6-point scale from 0 “strongly disagree” to 5 “strongly agree,” with a range from 0 to 42, where higher scores indicate more GI-anxiety. It has been found reliable and valid in children and adolescents with FAPDs [60].

Avoidance and control behavior will be assessed by the IBS-BRQ–Child-adapted short version with 11 items, which is an adapted version of the IBS-BRQ for adults [36]. Items are rated on a 7-point scale from 0 “never” to 6 “always,” with scores ranging from 0 to 66, where higher scores indicate more avoidance. It has been validated for children and adolescents with FAPDs [60].

Illness perception will be assessed by the Brief Illness Perception Questionnaire [61,62], which is a 9-item questionnaire where 8 items are answered on an 11-point scale, and 1 item is an open-ended question. The total score range is 0-80, with higher scores indicating more severe illness perception.

Illness worries will be assessed by the Childhood Illness Attitude Scale with 11 items from the fear factor [63]. The questionnaire is developed and validated for children and adolescents. Items are answered on a 3-point scale from 0 “never” to 2 “most of the time,” with a total score range from 0 to 22, and higher scores indicate more illness worries.

Pain acceptance will be assessed by 2 items from the CPAQ-A8 [37]. One regarding pain willingness and one regarding activity engagement. They are both answered on a 5-point scale from 0 “never true” to 4 “always true,” the item on pain willingness is reversed scored, and higher scores then indicate higher pain acceptance.

Other Measures

Parents will provide information about school absence (hours last month) for children (aged 8-12 years) and about their work absence (days past month). Adolescents will provide information about their own school absence (hours last month).

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Adverse events will be assessed by adolescents and parents of children using a binary (yes or no) question and an open-ended question to describe the potential event in detail.

Treatment satisfaction will be assessed by the Modified Experience of Service Questionnaire [64], which is a 13-item questionnaire with 10 items scored from "not true" to "certainly true" and 3 free-text items. The total score range is 0-20 with higher scores indicating a better experience with the treatment.

Sample Sizes

According to research design standards [65], a minimum of 3 replications are recommended in a SCED study (substudy 1). However, to achieve sufficient power for randomization tests, a higher number of potential randomizations is recommended [66]. The number of randomizations is influenced by both the number of participants and the number of possible starting points; hence, guided by Levin et al [67], we chose 6 participants in each group.

For substudy 2, we based our power analysis on potential differences in cognitive bias and interoception between cases and healthy controls on a previous similar study on cognitive bias in children and adolescents [40] and studies on interoceptive accuracy in adults with functional disorders [68-69]. Based on these study findings, calculations show that in order to detect a minimum effect size of 0.5 (Cohen *d*), 60 patients and 100 healthy controls are required for the cognitive bias outcome, and a minimum of 51 patients and 51 healthy controls for the interoception outcome to achieve 80% power at an α level of .05. The subsequent analysis of the possible impact of treatment on these 2 factors is more explorative and therefore no a priori power calculation is provided. The same concerns the last study on parental factors (substudy 3) as possible effect moderators. However, here the sample size is the largest possible, comprised of parents from substudies 1 and 2.

Data Collection and Management

The DSQ, the BY-GIS task, and questionnaires are set up in REDCap (Research Electronic data capture; Vanderbilt University) [70], hosted by Aarhus University, and distributed through SMS text message or email. REDCap is a secure, web-based software platform designed to facilitate data capture for research studies.

For the DSQ (substudy 1), a text message reminder will automatically be sent through REDCap 2 hours after the initial SMS text message. If the DSQ is not completed 2 days in a row, a research assistant will contact the family by phone. For the BY-GIS task (substudy 2) and the extensive questionnaire (substudy 3), REDCap will generate automatic email reminders 24, 48, and 72 hours after the initial email if they are not completed. If there is no response after 7 days, a research assistant will contact the family by phone.

The interoception task in substudy 2 will take place at the Center of Functionally Integrative Neuroscience at Aarhus University Hospital in a behavioral testing room, and data will be stored in REDCap.

Data Analyses

In substudy 1, visual inspection analyses will be applied to demonstrate the effect of the intervention on all outcomes [71]. In addition, within-case effect size measurements will be calculated using Tau-U [72] and between-case effect sizes will be determined using hierarchical linear regression models to account for the serial dependency of data [73]. A randomization test will be applied to test differences in means for the baseline versus treatment, and baseline versus follow-up periods, respectively [74].

In substudy 2, participants' descriptions reported in the recall phase of the BY-GIS task will be coded to their corresponding word or picture and category presented in the encoding phase (eg, picture-description "children and cake" coded as the birthday picture within the fun category). Coding for the first 20% of participants will be conducted by 2 independent raters (ESN and EB-N). If the consensus rating exceeds 90%, 1 rater will code the remaining cases independently. A third and experienced rater (TBG) may be consulted to resolve potential disagreements. Baseline data will be analyzed descriptively and compared with (1) data from a healthy control group who performed the same experimental test [38], and (2) end-of-treatment data, exploring potential differences in the outcomes from the encoding, recall, and recognition phases using *t* tests or nonparametric tests, depending on data variability in the samples.

Baseline measures of interoceptive performance and metacognitive measures will be analyzed descriptively and compared with (1) measures from a healthy control group and (2) end-of-treatment measures, using *t* tests or nonparametric tests, depending on data variability in the samples.

In substudy 3, the potential moderation of parental factors on treatment adherence (number of completed modules) and main measure (gastrointestinal symptoms) for children or adolescents will be investigated using negative binomial regression and linear mixed models, respectively, adjusting for baseline parental distress, illness worries, and illness behavior, respectively.

In addition, the potential effect of treatment on these parental factors and all other child or adolescent measures will be analyzed using linear mixed regression models.

An experienced statistician will provide statistical support for all analyses.

Ethical Considerations

The study will be conducted according to the guidelines of the Declaration of Helsinki. The study was approved by The Central Denmark Region Committees on Health Research Ethics (record 1-10-72-277-21, 1-10-72-80-22, and 1-10-72-142-22).

Written informed consent will be obtained from parents and adolescents (≥15 years) whereas children and adolescents (<15 years) will only give oral consent.

Children and adolescents will be compensated with a gift card (value 150 DKK [US $21.13]) for the first time participating in the interoception study. No other compensation will be provided.

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Results

Recruitment of participants began in June 2022. Substudy 1 is finalized and expected to be published in 2025. Recruitment for substudies 2 and 3 is ongoing. By November 2024, 45 children and 24 adolescents have been included. Due to a skewed distribution in referrals, with a predominance of referrals on children, we continue to include children and adolescents until we have reached 30 adolescents. Inclusion is expected to be completed by January 2025 and data collection in March 2025.

Discussion

Principal Findings

With this study, we aim to explore previously sparsely investigated areas of ICBT for children and adolescents with FAPDs related to both child or adolescent and parental factors. This includes examining the detailed trajectory of effect, the presence of and potential changes in cognitive biases, and interoceptive inaccuracy after treatment, as well as investigating the potential role of parental distress, illness worries, and behavior as effect moderators.

Previous studies have demonstrated the effectiveness of Swedish ICBT programs in reducing abdominal symptoms and improving the quality of life in children and adolescents with FAPDs. Mediation analyses have shown that positive changes in symptom-specific avoidance behavior and fear mediate the treatment effects [17,18,27,29]. However, the detailed trajectory of treatment effects—specifically when and how possible changes occur during treatment for individual patients—remains unknown, and this will be investigated in substudy 1. This research could provide new insights into the mechanisms of change underlying treatment effects and could be clinically valuable for both therapists and patients.

To the best of our knowledge, this study is one of the first to assess cognitive biases and the ability to sense and interpret signals from the body (ie, interoception) in this patient group in comparison with healthy controls as well as to explore potential changes in these factors after treatment with CBT. Both factors are suggested to play a vital role in the predictive processing model, explaining the pathophysiology of FAPDs [11]. However, so far, they have mainly been studied in adults with various functional disorders [40,68-69,75-78]. By uncovering more knowledge about these factors, the results can potentially be used to further refine already established treatments. For example, this could involve adding biofeedback to train interoceptive accuracy or enhancing exposure exercises addressing specific cognitive biases that lead to fearful responses to gastro-related sensations and avoidance behavior.

Parental worries and anxious behaviors toward the child or adolescent's symptoms can impact the overall well-being of the child or adolescent. These factors are suggested to be part of the complex pathophysiology of FAPDs [9,20,21,48] and are therefore important to investigate further. Parental emotional distress has been found to negatively moderate the effect of ICBT for adolescents with chronic pain [79,80], whereby high levels of parental emotional distress lead to less improvement in disability for the adolescent. However, it is currently unknown how the level of parental distress impacts the effects of the ICBT programs for young patients with FAPDs [29,81]. A specific type of parental emotional distress is health anxiety by proxy, which is a recently described clinical phenomenon characterized by parents' excessive and distressing worries and rumination about their child's health, often involving fears of serious diseases being overlooked by medical professionals [82,83]. This fear may lead to frequent medical visits and investigations of the child [84]. In this study, we will use the newly developed HAPYS questionnaire [46,47] to assess parental health anxiety by proxy. To our knowledge, this is the first systematic examination of this specific type of parental emotional distress in parents of children and adolescents with FAPDs. Such type of parental anxiety may especially lead to symptom-related protective and monitoring behaviors, which are suggested to play a crucial role in the development, maintenance, and even aggravation of the child's FAPD and related health care visits [48-50]. The Swedish ICBT has been shown to effectively reduce such maladaptive parental behavior in both children and adolescents [28,29]. Still, the impact of parental emotional distress, particularly illness worries and related behavioral responses, on the effect of ICBT in children is less well-investigated [85] and no studies have yet been conducted specifically in relation to adolescents. This is why, in this study, we will explore parental distress, illness worries, and behaviors before and after ICBT and examine how these factors impact treatment adherence and treatment effects in both children and adolescents. By uncovering more knowledge about these parental factors, we aim to gain a better understanding of family dynamics and identify potentially important parental characteristics to focus on during treatment, thereby further improving its effectiveness.

The study has some limitations. In substudy 1, the generalizability of SCED study results has traditionally been questioned due to the low number of participants. However, our study adheres to guidelines that include multiple data points across different phases, randomization of the length of the baseline phase, and replication across several participants, thereby optimizing generalizability. Furthermore, participants are expected to answer daily questions for an extended period, which could induce some fatigue in responding and potentially affect reliability. Still, the inclusion of several close data points increases precision in analyses and helps buffer against occasional data loss. In addition, the setup was tested on 4 prestudy patients, who reported that the daily questionnaire was easy and quick to answer.

In substudy 2, we use the BY-GIS task, which is newly developed and has not been previously tested in patients. However, the task is developed based on well-known paradigms and previous tests, and it has already been tested in a sample of 96 healthy age-matched controls with good usability [38]. The interoception HRD measures participants' ability to sense their pulse, which is not directly related to gut sensations but falls within the broader perspective of interoception. However, studies in adults suggest altered interoceptive accuracy across different diagnoses of functional disorders and chronic pain,

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which indicates that there may be a general hypersensitivity to inner sensations in this patient group as well [86]. Since this study is one of the first to investigate interoceptive accuracy in children and adolescents with FAPDs, we believe it is still valuable to use this well-known and widely used interoception measure.

Substudy 3 is an open pilot trial without a control group for comparison which means conclusions regarding the clinical effect of the treatment should be interpreted with caution. However, the substudy is explorative and primarily aims to investigate new and additional modifiable treatment targets on a parental level.

Conclusion

In conclusion, this study is expected to provide new and important information about the process of the effect of ICBT, increase our understanding of modifiable treatment targets within the framework of predictive processing in children and adolescents with FAPDs, and shed light on parental factors that are important for the child's treatment adherence and effect. Overall, this research can guide the further development of even more effective psychological treatments for one of the most prevalent chronic pain disorders in children and adolescents.

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Authors' Contributions

Conceptualization, methodology, and writing—review and editing were contributed by ESN, KHK, EB-N, TBG, ML, LF, MB, and CUR. Writing—Original Draft Preparation was contributed by ESN. Supervision was handled by KHK, TBG, ML, LF, MB, and CUR. Project administration was managed by ESN, EB-N, KHK, and CUR. Funding acquisition was handled by ESN, LF, and CUR. All authors have read and agreed on the published version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

BY-GIS: biases in youth toward gastrointestinal-related stimuli
CBT: cognitive behavioral therapy
CPAQ-A8: Chronic Pain Acceptance Questionnaire – Adolescent Short Form
DSQ: daily short questionnaire
FAP-NOS: functional abdominal pain not otherwise specified
FAPD: Functional abdominal pain disorder
FPS-R: Faces Pain Rating Scale – revised
HAPYS: The Health Anxiety by Proxy Scale
HRD: heart rate discrimination
IBS: irritable bowel syndrome
IBS-BRQ: irritable bowel syndrome behavioral response questionnaire
ICBT: internet-delivered cognitive behavioral therapy
ICD-10: International Statistical Classification of Diseases, Tenth Revision
IgA: Immunoglobulin A
PedsQL: Pediatric Quality of Life Inventory
REDCap: Research Electronic Data Capture
SCAS-S: Spence Children Anxiety Scale – Short
SCED: single case experimental design study
SCRIBE: Single-Case Reporting guideline In BEhavioural interventions
SOL: Stop, observe, let go
SPIRIT: Standard Protocol Items Recommendations for Interventional Trials
TSH: thyroid stimulating hormone
VSI: Visceral Sensitivity Index
VSI-C: Visceral Sensitivity Index-Children

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Protocol

Co-Designing a Consumer-Focused Digital Reporting Health Platform to Improve Adverse Medicine Event Reporting: Protocol for a Multimethod Research Project (the ReMedi Project)

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Abstract

Background: Adverse medicine events (AMEs) are unintended effects that occur following administration of medicines. Up to 70% of AMEs are not reported to, and hence remain undetected by, health care professionals and only 6% of AMEs are reported to regulators. Increased reporting by consumers, health care professionals, and pharmaceutical companies to medicine regulatory authorities is needed to increase the safety of medicines.

Objective: We describe a project that aims to co-design a digital reporting platform to improve detection and management of AMEs by consumers and health care professionals and improve reporting to regulators.

Methods: The project will be conducted in 3 phases and uses a co-design methodology that prioritizes equity in designing with stakeholders. Our project is guided by the Consolidated Framework for Implementation Research. In phase 1, we will engage with 3 stakeholder groups—consumers, health care professionals, and regulators—to define digital platform development standards. We will conduct a series of individual interviews, focus group discussions, and co-design workshops with the stakeholder groups. In phase 2, we will work with a software developer and user interaction design experts to prototype, test, and develop the digital reporting platform based on findings from phase 1. In phase 3, we will implement and trial the digital reporting platform in South

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Australia through general practices and pharmacies. Consumers who have recently started using medicines new to them will be recruited to use the digital reporting platform to report any apparent, suspected, or possible AMEs since starting the new medicine. Process and outcome evaluations will be conducted to assess the implementation process and to determine whether the new platform has increased AME detection and reporting.

Results: This project, initiated in 2023, will run until 2026. Phase 1 will result in persona profiles and user journey maps that define the standards for the user-friendly platform and interactive data visualization tool or dashboard that will be developed and further improved in phase 2. Finally, phase 3 will provide insights of the implemented platform regarding its impact on AME detection, management, and reporting. Findings will be published progressively as we complete the different phases of the project.

Conclusions: This project adopts a co-design methodology to develop a new digital reporting platform for AME detection and reporting, considering the perspectives and lived experience of stakeholders and addressing their requirements throughout the entire process. The overarching goal of the project is to leverage the potential of both consumers and technology to address the existing challenges of underdetection and underreporting of AMEs to health care professionals and regulators. The project potentially will improve individual patient safety and generate new data for regulatory purposes related to medicine safety and effectiveness.

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KEYWORDS

adverse drug events; drug-related side effects and adverse reactions; adverse drug reaction reporting systems; pharmacovigilance; digital health; medication safety; co-design; qualitative research, user-centered design

Introduction

Adverse medicine events (AMEs), also known as adverse drug events, are unintended effects that occur following administration of a medicine and include adverse reactions and harm from medication errors [1]. AMEs are common and result in patient harm. In Australia, an estimated 1.2 million people reportedly experienced an AME within a 6-month period [2]. While AMEs can occur in anyone, people with chronic conditions and older people are particularly vulnerable to and are most affected by AMEs. For example, 1 in 5 hospital admissions of older adults in Australia is due to AME [2-4]. According to a 2022 estimate, medicine-related hospital admissions, including instances of noncompliance, overdose, and AME, incur an estimated annual cost of Aus $1.4 billion (US $870 million) in Australia, with AME being the most prevalent contributing factor [2,5]. Early detection and management of AMEs are crucial to preventing avoidable harms such as medicine-related falls, hospitalizations, and deaths. However, findings from surveys and reviews of consumer medical records conducted internationally suggest that many consumers do not disclose their AMEs unless prompted to do so. Consequently, up to 70% of AMEs are undetected by health care professionals [6,7], emphasizing the need for proactive interventions to identify and resolve AMEs.

AMEs are also underreported to medicine regulatory authorities (“regulators”), making it difficult to understand how medicines affect consumers. Spontaneous reporting of AMEs is the most common mechanism of safety surveillance worldwide after a medicine has been introduced to the market [8]. Spontaneous reporting of AMEs by consumers, health care professionals, and pharmaceutical companies is vital for regulators to identify potential medicine safety signals [9] and—when relevant—mandate necessary changes, such as updating product labels or withdrawing medicines from the market. A major challenge, however, is the very low AME reporting rate; as evidenced by a systematic review of 37 studies from 12 countries, only an estimated 6% of AMEs experienced by patients were reported [10].

Consumers often detect AMEs before their health care professionals notice them [11], and, where patient engagement is implemented, consumer self-report of AMEs alerts regulators to new and previously unknown reactions prior to health professional reports [12,13]. In Australia, however, the number of reports to regulators from consumers is disproportionately low compared with those made by health care professionals and pharmaceutical manufacturers [14], partly because of consumers’ limited awareness of the reporting system and perceived absence of benefits of reporting [15]. The AME reporting system, developed by the medicine regulatory body, the therapeutic goods administration (TGA) [14], has seen limited consumer uptake in Australia. Furthermore, there is currently no Australian-specific AME reporting platform co-designed with consumers. To address this gap, we developed a prototype system in a small pilot project comprising both Android and iOS apps and a public-facing website for consumers to report any AMEs they experienced [16]. The system was shown to be user-friendly. However, the development involved limited stakeholder engagement and participation (3 consumers) due to the inherent nature of a small pilot project.

Building on this pilot project, the current project aims to co-design with stakeholders (consumers, health care professionals, and regulators) a digital reporting platform to improve AME detection, management, and reporting. The ultimate goal of this project is to empower consumers to actively detect, manage, and report AMEs, fostering a collaborative approach with their health care professionals, and at the same time improve AME reporting to the TGA.

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Methods

Study Design

The project is being conducted in 3 phases (Figure 1) from 2023 to 2026 and uses a co-design methodology that prioritizes designing equitably with all stakeholders [17]. Co-design methodology focuses on generating and reflecting on data related to people's lived experiences and engaging participants in action to enhance the quality of their lives. Co-design facilitates collaboration among stakeholders to address challenges within sociotechnical systems and daily services [18,19]. It uses design-based strategies to collect qualitative data around users' experience and the interests of the stakeholders providing services to those users to foster dialogue for mutual insights. Using a range of research methods including stakeholder workshops, focus group discussions, and interviews, co-design aims to describe, categorize, question, and evaluate the needs, experiences, opinions, interests, decisions, and behaviors of stakeholders, ensuring equity through structured reflection. This project builds on the findings of our pilot project [16], using the pilot's prototype as the foundation for developing the co-design activities.

This project builds on the findings of our pilot project [16], engaging stakeholders in phase 1 and advancing to the development and validation of the platform in phase 2. The pilot's prototype serves as a foundation for developing the co-design activities. Our project is guided by the Consolidated Framework for Implementation Research, which considers 5 domains for effective intervention development and implementation: innovation, outer setting, inner setting, individuals, and implementation process [20]. The innovation domain includes the construct's trialability and evidence base, which we addressed in our pilot work [16] and systematic review [21]. We will consider constructs in each domain that influence use of our platform by consumers including innovation, complexity and usability, consumer needs and preferences, feedback, design, and engagement [20,22-24].

Figure 1. Key activities in each phase of the project. AME: adverse medicine event; GP: general practitioner.

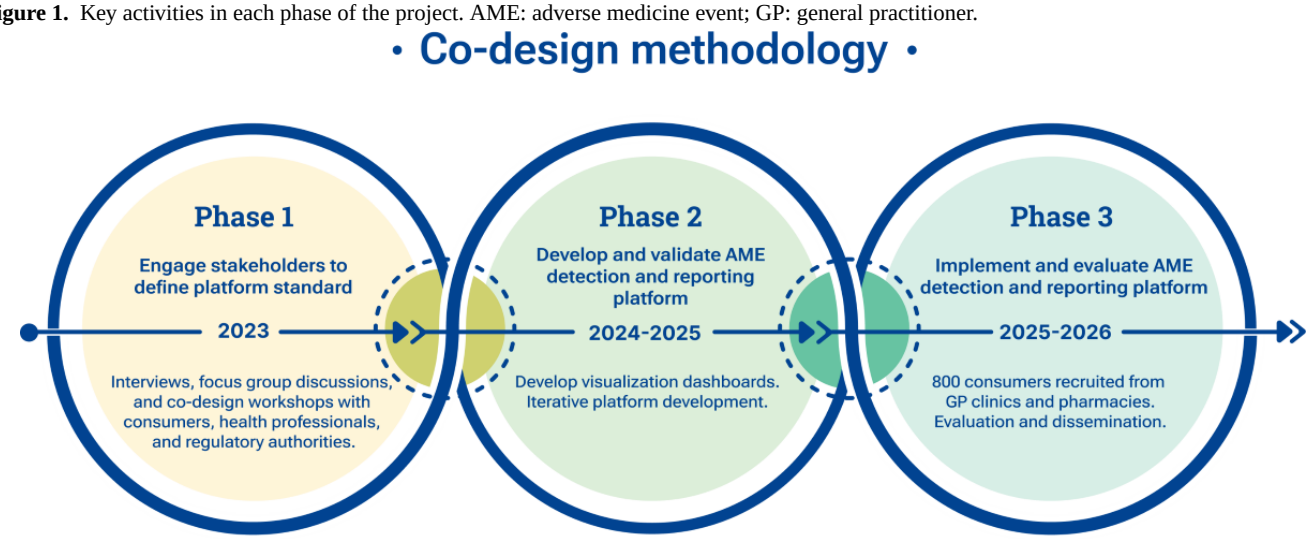

Phase 1: Engage With Stakeholders to Define Platform Development Standards

Phase 1 involves interviews, focus groups discussions, and co-design workshops with 3 specific stakeholder groups: consumers, health care professionals, and regulators (Table 1). Consumers eligible for inclusion must be 18 years of age or older, take regular medications or have previously experienced an adverse event from any medication, and own a smartphone or tablet. Health care professionals must be practicing as medical doctors, pharmacists, or nurses in Australia, and regulators will be eligible if they are involved in the postmarketing assessment of safety information for human medicinal products within Australia. Individuals will be excluded if they cannot speak, read, or write in English, or do not provide informed consent.

We will use purposeful sampling to recruit consumers with broad demographic variation to ensure that they represent consumers across different ages and social groups, levels of education and experience, and who have a range of health conditions and use a range of medications to ensure that our platform meets the needs of diverse groups of people. In addition, health care professionals and personnel who work for the medicine regulators will be recruited. All participants will be asked to participate in all 3 activities: semistructured interviews, focus group discussions, and co-design workshops. Attrition is natural in longitudinal projects such as this, and we will mitigate this by recruiting additional participants.

The interviews, focus group discussions, and co-design workshops will be conducted face-to-face where possible and audio- or video-recorded where participants agree. If participants are located interstate from the researchers or prefer to engage remotely for convenience, interviews, focus group discussions, and co-design workshops will be conducted on the web. When preferences differ, separate face-to-face and web-based workshops will be organized to accommodate participants' preferred formats. All recordings will be transcribed verbatim, manually coded inductively, and analyzed thematically in ATLAS.ti software (ATLAS.ti Scientific Software Development GmbH) [25]. Using the Capability, Opportunity, Motivation, Behavior (COM-B) model [26], a well-established model for analyzing and modifying behaviors, the themes identified will inform the recognition of barriers and facilitators to adopting a

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digital platform for reporting AMEs. The themes will also be used to highlight key design features essential to meeting the needs and preferences of each of the stakeholder group. Based on these analyses, persona profiles (which will be used to summarize the identified needs, priorities, motivations, goals, and challenges of each user archetype) and user journey maps [27] (which will be used to visualize and document participants' discussions of the likely experience personas might have during the process of reporting or reviewing AMEs as they move through the system) will be developed which will be used to guide subsequent phases of the project.

Table 1. Description of the different activities in phase 1 of the project.

Activity	Number	Aim	Duration	Outcome
Individual semistructured interviews	Ten to fifteen consumers; 10 health care professionals and regulators.	• To understand their experience with, or perspectives toward medicine use and the current AME[a]-reporting process in Australia. • To enable participants to offer their ideas and insights in confidence without the possible influence of bias from other participants.	Approximately 60 minutes per interview.	Findings will be used to develop personas that will then be discussed in focus group discussions to determine their accuracy and thoroughness as exemplar of user groups.
Focus groups discussions	Two focus-group discussions with each of the 3 stakeholder groups.	• To consider and define the respective needs, priorities, and motivations the personas—developed based on the findings from the interviews—might have for reporting an AME and to define the reporting goals for the platform.	Each stakeholder focus group discussion will run for 2 hours.	Outcomes from the discussions will inform the development and delivery of the co-design workshops.
Co-design workshops	Three co-design workshops held for the same stakeholders collectively.	• To employ the co-designed user personas to build a user journey map as a means to evaluate the processes of AME detection, management, and reporting, generate and agree on notional platform content and feature set to guide its subsequent development.	Each co-design workshop will last 3-4 hours and will contain multiple activities, each varying in duration but capped at 60 minutes. Regular breaks will be incorporated between activities to maintain engagement and focus.	The workshops will result in user journey maps which will be used to visualize and document participants' discussions of the likely experience personas might have during the process of reporting or reviewing AMEs as they move through the system.

[a]AME: adverse medicine event.

Phase 2: Develop the Platform and Interactive Data Visualization Tool

The second phase of the project focuses on the development of the platform. First, we will work with a software developer and user interaction designers to develop the underlying relational structure that received data from users might have, how the data function in terms of reporting, and what principle features a front-end user experience might have for gathering them (phase 2a—platform development). At a minimum, the project aims to achieve a fully functioning web-based reporting platform, a mobile app, or both, based on findings from phase 1. It will include a fully refined user interface and database integration and search function to operate with the TGA's Database of Adverse Event Notifications [28]. To ensure equity across stakeholder interests, we will continue to adhere to co-design principles throughout this phase by inviting consumers, health care professionals, and regulators to participate in this process. The platform development will undergo cycles of iteration and review where stakeholders will test, compare, and contribute to decision-making on the content, form, and function of the platform through each iteration. We will perform the iterative cycles with stakeholders until no new issues are identified with the platform. We anticipate that the process will require up to 5 cycles before saturation and a deployable outcome is achieved. Stakeholders recruited in phase 1 will be invited to participate in this process, and additional participants will be invited to compensate for any attrition.

Next, as part of our communication and engagement strategy, we will develop an interactive data visualization tool or dashboard to translate and disseminate the data collected to the public, health care professionals, and regulators (phase 2b—development of interactive data visualization tool). The visualization tool will be implemented with back-end integration in the digital reporting platform and developed collaboratively through 2 co-design workshops with 8 stakeholders. The visualization tool will be configured to allow both consumers and their health care professionals to access the data they provided, obtain information on the medicines they are taking,

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and compare their experience with those reported by other consumers taking the same medicines. A separate visualization tool will be developed for use by regulators and will include further levels of configuration necessary for them to examine data relative to their decision-making. All consumer reports will be reviewed by study investigators (clinicians) for causality assessment (ie, likelihood that the medicine caused the observed AME) using the Naranjo probability scale [29]. The causality assessment will be done to determine whether the platform has collected all the information needed for a causality assessment.

Phase 3: Digital Platform Implementation and Evaluation

In the third phase of the project, we will implement the new platform in general practices and pharmacies in South Australia and assess its impact for (1) increasing AME detection, (2) improving AME management, and (3) increasing AME reporting and enhancing existing TGA workflows.

A quasi-experimental study will be conducted to involve consumers who have recently begun taking new medicines. This is because most AMEs tend to occur within 4 weeks of patients commencing new medications [30]. Depending on results from phases 1 and 2, criteria for further inclusion may be specified (eg, consumers initiating medicines with a black triangle warning). Eligible consumers will be identified initially by general practices and pharmacies applying the inclusion or exclusion criteria to their software (eg, Doctors Control Panel software [Doctors Control Panel Software Pty Ltd] [31] and dispensing software used in the pharmacies). Eligible consumers will then be approached by a dedicated research assistant via phone, text message, or email to assess their eligibility, discuss the details of the project, answer any questions, and facilitate the process of obtaining informed consent from interested individuals. We will seek consent to send information reported by consumers to their health care professionals and regulators (ie, the TGA). Consumers will then be prompted to use the platform to report whether they have experienced any suspected or possible AME. Consumers will access the platform either by downloading the mobile app or by visiting the website. Where the consumer has consented, a report will be sent electronically to their general practitioner and pharmacist to enable targeted assessment for managing the AMEs. For those who provided consent, consumer reports will also be submitted to the TGA. Subsequent prompts to use the platform will be sent to the consumers via automated text messages. The frequency of sending the text messages will be determined based on co-design workshops with stakeholder groups. Consumers will be given a summary report of their data and access to the interactive data visualization tool (Figure 2).

Based on interventions to improve AME reporting [32], which report a relative risk of 2.04 (57% in intervention group vs 28% in controls), α value (significance level: rejecting the null hypothesis when it is actually true) of .05, and power of 80%, a total of 80 consumers experiencing and reporting AME is needed. Assuming that 20% of consumers starting medicines experience an AME [33] and half of the consumers will report their AMEs with targeted prompts from the research team [34], we aim to recruit 800 people for phase 3. The sample size was calculated based on Statistical Power Analysis using R [R Foundation for Statistical Computing] [35]. Initial database analysis in one of our participating clinics with 8 full-time equivalent general practitioners indicated that each general practitioner prescribes a medicine that is new to the patient for about 40 people per month (320 per month for the practice), supporting the feasibility of recruitment of 800 participants within 6 months.

To assess whether the platform improved AME detection, interrupted time series analysis will be used to determine the proportion of AME detected before and post platform implementation in the general practices. A random sample of up to 1000 patient records in the participating general practices will be manually reviewed by nurses at the practices to determine the number of AMEs detected up to 3 months prior to platform implementation. Furthermore, we will describe the number of AME reports submitted to the TGA by our study participants post platform implementation.

Finally, we will conduct 2 focus group discussions with the project team and stakeholders to evaluate the implementation process (what works, where, and why) [20], the acceptability of, and satisfaction with the platform. Questions related to the implementation process will be adopted from the Consolidated Framework for Implementation Research interview guide tool [20]. The focus group discussions will be audio-recorded, transcribed, and analyzed using thematic analysis [25].

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Figure 2. Flowchart for platform implementation in Australia. GP: general practitioner; TGA: therapeutic goods administration.

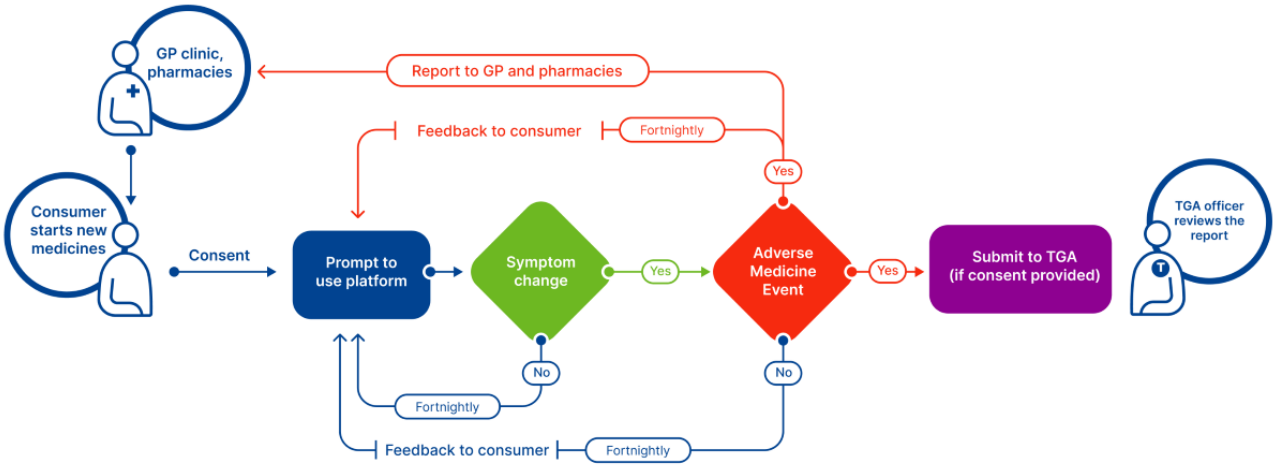

Ethical Considerations

Ethics approval for phases 1 and 2 has been received from the University of South Australia human research ethics committee (application ID 204984). Ethics approval will be sought from the same committee prior to starting phase 3. Informed consent will be sought from all participants. All data obtained during the project will be deidentified. Participants in any phase of the project will receive compensation at an hourly rate, provided as either a gift voucher or a direct bank transfer in Australian dollars (Aus $). Compensation rates, approved by the human research ethics committee, are set at Aus $35 (US $21.85) per hour for consumers, Aus $200 (US $124.88) per hour for medical doctors, and Aus $100 (US $62.44) per hour for pharmacists and nurses. Furthermore, participants attending in person will receive a transportation allowance of Aus $30 (US $18.73). No compensation will be provided to regulators, as they are prohibited from accepting it.

Results

This project is initiated in 2023 and will run until 2026. Phase 1 will result in persona profiles and user journey maps that define the standards for the user-friendly web-based communication platform and interactive data visualization tool or dashboard. This platform will be further developed and improved in phase 2. The platform will contain fully refined user interface features, an icon system for nonverbal communication, and integration with TGA's Database of Adverse Event Notifications to support the reporting of AMEs by consumers and health care professionals. The final phase—phase 3—will provide insights of the implemented platform regarding its impact on AME detection, management, and reporting. Altogether, the efforts will result in a platform through which consumers can report AMEs to their general practitioners and pharmacists and TGA. We will publish findings progressively as we complete our analyses. In addition to the traditional research outputs (journal articles and conference papers), the designers on our project team will develop a series of nontraditional research outcomes including the dissemination of visual outcomes in the form of a public exhibition, either on the web or in person. We will organize public displays of the visual works at multiple venues in Australia to increase awareness and discussions about the importance of detecting, managing, and reporting AMEs. We will promote the exhibitions and project findings through our teams' respective institutions' media platforms.

Discussion

Expected Findings and Implications

Medicine safety is complex and requires well-developed systems, strategies, and processes to keep consumers safe. Effective systems and strategies for AME detection, management, and reporting are crucial to ensure that medicines are used safely and effectively. However, AME reporting by consumers remains low [14]. Instead, consumers were generally more likely to report AMEs to doctors or pharmacists [36], potentially stemming from inadequate or lacking systems that enable the proactive detection and management of AMEs. Our project will bring these 2 aspects together to build what we hypothesize to be a single, readily available solution that integrates AME detection and management by consumers in consultation with their general practitioners and pharmacists and which also potentially benefits AME reporting to regulators. As such, our project aims to serve both patient-level clinical needs and population-level regulatory needs on medication safety issues.

The level of end user involvement during the development phase of digital interventions that are implemented in practice is unclear. Despite the development of numerous digital interventions to improve medicine management and safety, the minimal engagement of end users in this process and a failure to meet their needs adequately result in the low adoption of these interventions in practice [37]. For instance, the implementation of GuildCare (GuildLink), an AME surveillance system designed for Australian community pharmacists, was introduced in 2014. While the initial year saw a notable increase in AME reporting rates to the TGA, the subsequent year saw a decline, hinting at challenges in maintaining sustained adoption [38]. Factors influencing the adoption and ongoing use of digital health technologies include cost, simplicity of language, ease of use, design, scientific evidence base, motivation, and perceived value by end users [22-24]. To effectively tackle the challenges related to fulfilling the requirements of stakeholders

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and overcoming low adoption rates, our project takes a unique approach by grounding it in a multidisciplinary ideology from its outset. This includes collaborating with experts from various disciplines including medicine safety, co-design, user-experience design, communication design, psychology, engagement, and cybersecurity to address fundamental issues that predict successful implementation of the system in practice. This partnership, grounded in a co-design methodology, also represents one of the first instances where a digital intervention for AMEs is coproduced with consumers, health care professionals, and the regulators. The approach seeks to ensure that the digital intervention directly addresses the needs of the 3 stakeholder groups, thereby increasing the likelihood of adoption in practice and ensuring its long-term sustainability.

AME reporting by consumers has the potential to improve the safety of medicines. In a previous study conducted in Australia, despite acknowledging limited awareness, consumers expressed a positive attitude toward AME reporting [15]. The perceived lack of benefits for the reporting consumer, however, was recognized as a barrier to the reporting process [15]. The significance of our proposed platform lies in its potential to incorporate consumers' voices into their medicine and health care journey, enabling consumers to report AMEs to their health care professionals and to the regulators. If successfully implemented, the proposed platform has the potential to result in an increase in the proportion of consumer AME reports submitted to the TGA, which currently accounts for only 3.4% of the total reports submitted to the TGA [39].

There has been a decline in the percentage of AME reports from doctors in Australia, decreasing from 28% in 2003 to 4% in 2016 [36]. The potential increase in participation by consumers through use of our proposed platform may contribute to increased identification of safety signals. By streamlining the AME reporting process to the TGA, our platform has the potential to contribute to more timely detection and verification of potential medicine safety signals. This initiative addresses a national [40] and global health priority [41] and addresses 2 components of the Australia's National Strategy for Quality Use of Medicines: monitoring outcomes and improving people's ability to solve problems related to medicines, such as negative effects.

The introduction of a visualization tool as part of the platform has the potential to enhance end user interaction and participation in research and may facilitate early and effective communication of safety issues to relevant stakeholders. The development of interactive data visualization tools marks a creative initiative to enhance communication and transparency between consumers and regulators. While visualization tools for conveying important public health issues have become common, especially during the Covid-19 pandemic, they frequently lack transparency in describing the development process, fail to engage end users in design and development, and leave uncertainty about whether they adequately meet the needs of those end users [42]. Our user-centric co-design methodology for this project has the potential to ensure that the visualization tools effectively meet the diverse needs of consumers, health care professionals, and regulators alike.

Limitations

First, the success of our digital reporting platform will ultimately rely on the level of user engagement and participation. Robust stakeholder engagement strategies, including co-design workshops and ongoing collaboration, do not guarantee user uptake and continued use. Factors beyond our control, such as accessibility to devices, individual motivation and preferences, and previous negative experiences with reporting, may influence the level to which consumers actively engage in this new digital platform. The introduction of any new system, service, or technology is frequently considered an additional burden or challenge when implemented in practice. However, our early engagement strategy with stakeholders, from phase 1, is designed to potentially mitigate some of this resistance and to increase the chances of adoption. Second, the reliance on interrupted time series analysis for outcome evaluation introduces potential confounding factors that may not be fully accounted. Third, the small number of consumers recruited in phase 3 means that we will not be able to determine whether the platform had an overall effect on the number of consumer reports to the TGA, or whether the reports from our platform helped generate new or different medicine safety signals. Another potential limitation is that phase 3 will be conducted in South Australia, which may restrict the generalizability of findings to the broader Australian population or internationally. However, this limitation will be mitigated by incorporating insights from participants across multiple states in Australia during phases 1 and 2. Finally, certain processes in our project rely on interim review or support from members of the research team. These workflows and processes will require revision and adaptation when implemented in clinical practice.

Conclusions

This paper describes our co-design project that will actively involve key stakeholders in the development and evaluation of a new digital platform for AME detection, management, and reporting, with a central focus on consumers. The use of a co-design methodology ensures the incorporation of the perspectives and requirements from consumers, health care professionals, and regulators—a crucial element for fostering the adoption and sustainability of the intervention. The project harnesses the potential of both consumers and technology to address the existing challenges in underdetection and reporting of AMEs to health care professionals and regulators. The overarching goal is to enable consumers to actively participate in medication safety-related matters, thus enhancing the quality of their lives, influencing clinical decisions related to their health, and contributing to overall medicine safety.

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Authors' Contributions

EAG, CT, MT, STdeV, AQA, LKE, OF, PYC, KKRC, TLL, and RL contributed to the conception and design of the project. EAG and RL drafted the manuscript. All authors revised the manuscript critically for important intellectual content and provided final approval to the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AME: adverse medicine event
COM-B: Capability, Opportunity, Motivation, Behavior
TGA: therapeutic goods administration

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Protocol

A Live Video Resiliency Dyadic Intervention for Persons With Dementia and Their Care-Partners Early After Diagnosis: Protocol for Open Pilot of Resilient Together for Dementia

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Abstract

Background: Alzheimer disease and related dementias (ADRDs) are increasingly common progressive conditions that have a substantial impact on individuals and their primary care partners—together described as a *dyad*. The stressors experienced by dyad members at around the time of ADRD diagnosis commonly produce clinically elevated emotional distress (ie, depression and anxiety symptoms), which can become chronic and negatively impact health, relationships, and the overall quality of life. Dyads commonly report unmet needs for early support to address these challenges early after diagnosis.

Objective: This study is part of a larger study that has the primary objective to develop, adapt, and establish the feasibility of Resilient Together for Dementia (RT-ADRD), a novel dyadic skills-based intervention aimed at preventing chronic emotional distress early after diagnosis. The present study protocol describes an open pilot of the RT-ADRD intervention. This study will allow the study team to gather feedback on intervention components, administration of study measures, issues within general protocol, and perceptions about live video interventions prior to a larger feasibility trial.

Methods: All study procedures will be conducted on the web (via phone and health care system–supported videoconferencing) to optimize accessibility, inclusion, and representativeness. Eligible dyads will include couples (up to N=10) referred from Mount Sinai Hospital (MSH) clinics within 3 months of an ADRD diagnosis. Dyads will be referred by their diagnosing clinicians (eg, neurologists, geriatricians, and neuropsychologists) and screened for eligibility. Eligible dyads will have at least one member who exhibits clinically elevated emotional distress and will demonstrate capacity to consent to research participation on a standardized assessment. Consenting dyads will complete baseline assessments of emotional distress, quality of life, relationship

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functioning, and resiliency skills. Dyads will then participate in 6 weekly RT-ADRD sessions together (30-60 minutes each). After the conclusion of the intervention, dyad members will complete posttest assessments with similar measures as the pretest. Finally, dyads will participate together in a single 60-minute exit interview to gather information on intervention content and procedures to refine the intervention before a pilot feasibility trial.

Results: This study has been approved by the MSH institutional review board and is registered on ClinicalTrials.gov (NCT06421545). We anticipate that the study will be completed by late 2024.

Conclusions: We will use these results to administer changes and develop procedures for a pilot feasibility trial of RT-ADRD relative to a minimally enhanced control condition. Our study will allow us to gather comprehensive information on proposed RT-ADRD procedures and content and the best ways of delivering prevention-focused interventions to reduce the potential for chronic emotional distress stemming from ADRDs.

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KEYWORDS

dementia; dyad; emotional distress; intervention; diagnosis; telehealth; resilient; dyadic intervention; care-partner; Alzheimer's disease; ADRD; psychosocial; depression

Introduction

Background

Alzheimer disease and Alzheimer disease-related dementias (ADRDs) are conditions characterized by progressive declines in memory, language, behavior, and personality and produce early symptoms that include increased forgetfulness, communication challenges, and loss of recognition of places, time, and routines [1-3]. These early symptoms tend to worsen over time and undermine the independence, health, and well-being of persons living with ADRDs and their family care partners, many of whom are romantic or spousal partners [4-6]. Because both individuals and their partners (often referred to as "the second patient") experience life disruptions stemming from ADRD symptoms that amplify stress, role changes, and relationship strain [6,7], both individuals and their romantic partners require early support [8]. This need is ever more pressing; by 2030, it is expected that 75 million individuals will be living with ADRD worldwide [5].

In the time following the onset of ADRD symptoms and particularly after receiving a formal diagnosis, many individuals (23%-53%) and their care partners (35%-50%) experience clinically elevated emotional distress (ie, depression and anxiety symptoms) [9-13]. These elevated rates are not surprising given the poor prognosis and lack of disease-modifying interventions for ADRDs, limited resources to assist with early challenges, difficulties engaging in social support, and changes to established roles and responsibilities (eg, caretaking) [14-16]. Early emotional distress is an important intervention target in dyads facing ADRDs for several reasons. First, distress is *interdependent* (ie, correlated and bidirectionally influenced) within dyads. Second, untreated distress is likely to become chronic, and chronic emotional distress is difficult to treat and linked to the deterioration of dyads' physical and mental health, relationship quality, and quality of life [9,14,17,18]. Third, distress interferes with dyads' ability to effectively communicate and cope with early challenges linked to ADRDs, which can impact long-term adjustment [9,14].

Early psychosocial interventions may help individuals with ADRDs and their care partners adjust to challenges and plan collaboratively for the future, which can alleviate distress and maintain overall relationship quality and well-being [8]. Existing interventions for early or moderate-stage ADRDs primarily target family care partners, and several interventions demonstrate lasting improvements in depression symptoms and quality of life [5]. Dyads commonly express strong preferences to participate in interventions together, and dyadic interventions in the first few years of ADRD diagnosis demonstrate promise in reducing dyads' emotional distress as well as neuropsychiatric symptoms expressed by the person living with ADRD [19]. Interventions have historically ignored the "window of opportunity" to meaningfully include persons with ADRDs in interventions shortly after diagnosis, limiting their potential to assist in collaborative treatment and planning before symptoms progress [20-22]. Currently, there are no dyadic psychosocial interventions that prioritize delivery in the first weeks and months after diagnosis to promote dyadic adjustment to ADRDs [20,23-25].

Dyadic interventions may be a more effective, efficient, and economical avenue for promoting positive adjustment to ADRDs for individuals and their care partners earlier in the course of the illness [24,26]. Our team has developed successful dyadic interventions to prevent distress following medical adversity, including Recovering Together, a 6-session dyadic resiliency intervention that addresses emotional distress in patients and informal care partners shortly after neurointensive care unit admission for acute neurological conditions [27,28]. Recovering Together program uses interpersonal theories of adjustment aimed toward preventing chronic stress and transdiagnostic resiliency skills that we expect could also serve as mechanistic treatment targets for other neurological conditions such as ADRDs [29-37]. We then leveraged the NIH (National Institutes of Health) Stage Model for intervention development and in-depth interviews with ADRD clinician experts and dyads (Figure 1) to inform the development of a similar intervention to address early challenges linked to ADRDs [38,39].

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Figure 1. Iterative Development of RT-ADRD (Resilient Together for Dementia).

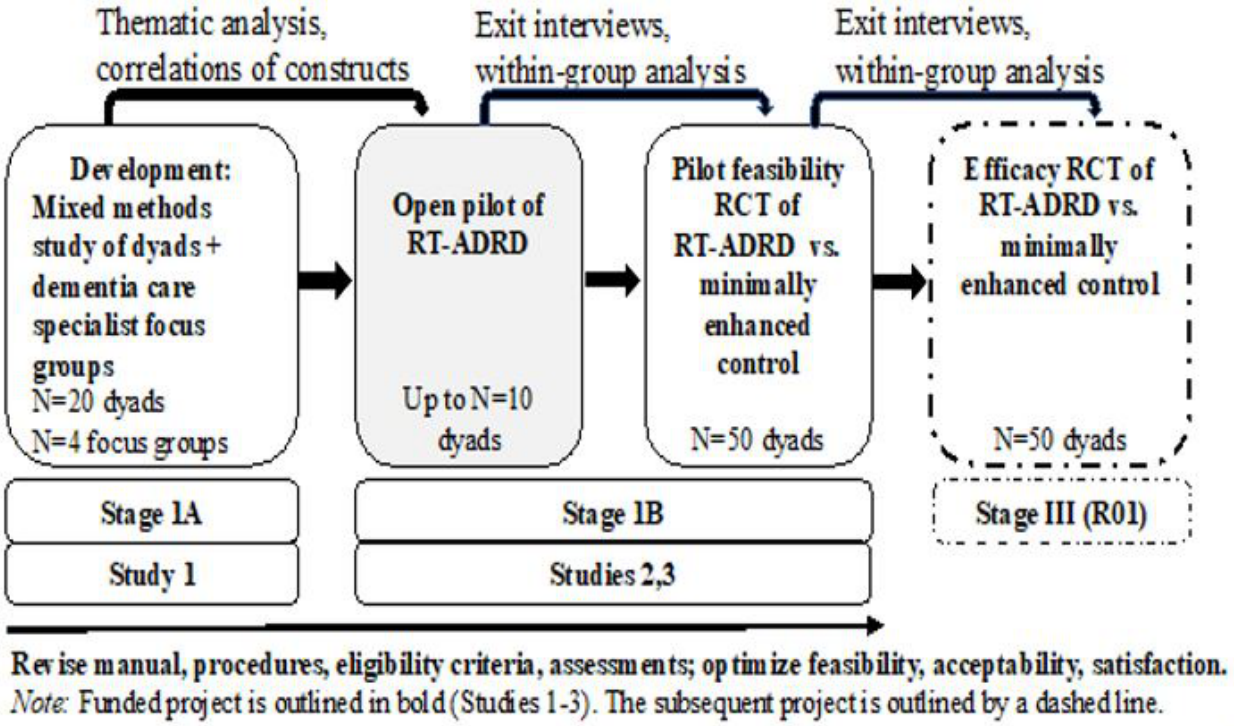

This Study

This study protocol is part of a larger 5-year study that aims to use the prior research, methodology, program content, and procedures of the Recovering Together program as a basis for developing the novel Resilient Together for Dementia (RT-ADRD). Our primary objective is to describe the protocol for the open pilot study of RT-ADRD that will inform a subsequent pilot feasibility trial of the program relative to a control condition (NIH Stage Model Stage 1a). In this study, we aim to gather comprehensive information from dyads regarding the feasibility of assessment, feedback on the intervention components, applicability of study measures, and to identify potential issues prior to the feasibility trial.

Methods

Ethical Considerations

This open pilot study was approved by the Icahn School of Medicine at Mount Sinai Independent Review Board (23-01360) and is registered on ClinicalTrials.gov (NCT06421545). Participants will provide electronic consent to participate via the REDCap (Research Electronic Data Capture; Vanderbilt University) HIPAA (Health Insurance Portability and Accountability Act)-compliant web-based application using a hospital-approved e-consent feature. Prospective participants will be given ample time to review the contents of the consent form as well as speak with the study coordinator who will provide detailed information about the study and answer any questions. The participants will also be reminded that they may decline to participate and can discontinue participation at any time. Participants will be given a copy of the consent form and will be invited to ask questions about their participation at any point over the course of the study. The identity of the participants will not be revealed in the presentation or publication of any results from this project. To protect confidentiality, all data will be deidentified and only identifiable by subject codes. Participants will be individually compensated US $80 for completion of the pre- and posttest assessments, for a total of US $160 per dyad at the end of the program.

Study Design

We will conduct an open pilot of RT-ADRD dyadic intervention involving dyads comprising (1) individuals with a recent ADRD diagnosis and (2) their spousal or romantic care partners, with a target recruitment of up to N=10 dyads, or 20 total participants. This study is designed to gather data that can be used to revise the intervention before a larger pilot feasibility trial.

Inclusion and Exclusion Criteria

Eligible participants will be adult dyads who are partners that currently live together and are willing to participate in the RT-ADRD intervention that are (1) English speaking, (2) patient with newly diagnosed (within 3 months) with an ADRD diagnosis after age 65 years (determined by medical chart review and provider referral), (3) patient with cognitive assessment scores and symptoms consistent with early-stage ADRD, as determined by Clinical Dementia Rating scale scores of 0.5 (very mild) or 1.0 (mild dementia) and Montreal Cognitive Assessment (MoCA) scores of 17-25, obtained via a review of medical records (if patients do not have cognitive assessment scores available, we will administer the MoCA to confirm eligibility), (4) either partner demonstrates clinically elevated emotional distress, as determined by Hospital Anxiety and Depression Scale [40], subscale scores >8 or Geriatric Depression Scale [41], scores > 5, and (5) both partners demonstrate the ability to understand study and research protocol, as determined by the University of California Brief Assessment of Capacity to Consent [42], >12. Individuals will

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not be eligible for the study if (1) either partner has a co-occurring terminal illness, and (2) patient was diagnosed with forms of dementia with clinical profiles that would preclude participation (eg, highly symptomatic Frontotemporal Dementia–behavioral variant), as determined by the treatment team.

Study Procedures

Dyads will be recruited from the Mount Sinai Departments of Neurology, Geriatrics and Palliative Medicine, and the hospital system's broader dementia clinical care infrastructure. We will circulate information via flyers, presentations, and word-of-mouth referrals, and dyads can be self-referred or be referred by their treating dementia care providers. The study team will present the aims to all staff at the clinics to explain the purpose of the study, potential benefits to participants, and discuss best ways to facilitate referrals. The study team obtained a waiver of informed consent for the purpose of eligibility screening and will also review electronic medical records of patients treated in relevant clinics to inform providers of potential eligibility prior to diagnostic disclosure visits. All recruitment, screening, and consent procedures will be performed remotely via telephone, electronic survey through REDCap, email, and over a live video using health care system–supported videoconferencing.

Treating providers will obtain permission from the dyad to be contacted by the study team. If self-referred, interested dyads will also have the option to respond to a brief survey via QR code or URL to a secure REDCap platform listed on the distributed study flyers. The study team will contact interested participants via telephone to schedule a telephone or live video call with the study research assistant, who will describe the study to potential participants and conduct screening for eligibility (including capacity to consent). If either dyad member is deemed ineligible based on screening criteria, the study team will provide dyad with a comprehensive list of resources containing local and national resources and document ineligibility in REDCap. If eligible and interested in participating, individuals will complete consent procedures by indicating verbal consent and documenting electronic consent a secure password-protected REDCap platform.

After enrollment, participants will be sent a baseline survey via a secure REDCap link to assess demographics, emotional distress, resiliency factors, and relationship functioning. Participants can also complete assessments via health care system–supported videoconferencing with the help of a trained research assistant. Once the dyad has completed the baseline survey, a member of the research team will schedule the first of 6 RT-ADRD treatment sessions together led by a PhD-level clinical psychologist with expertise in conducting dyadic interventions (SB). In advance of the treatment session, the dyad will be sent copy of the treatment manual to review the skills that will be taught during the 6-week treatment program. Each session will be audio recorded for the purpose of manual refinement. After completing treatment, dyad members will complete a similar set of surveys at posttest. Finally, they will participate in a single 60-minute exit interview together to gather comprehensive feedback on the material to further refine the intervention. Each dyad member will be compensated US $80 for completion of the pre- and posttest assessments, for a total of US $160 per dyad at the end of the program.

RT-ADRD Intervention Content

The RT-ADRD intervention will have 6 weekly live video treatment sessions lasting 30-60 minutes each delivered over health care system–supported videoconferencing; in-person and hybrid session options will be available as well, according to dyad preference. The content and procedures were developed by adapting the Recovering Together dyadic resiliency intervention for neurointensive care unit admitted dyads [27], and then revised using feedback from interviews with dementia care specialists [38], and from dyads interviewed after ADRD diagnosis [39]. Sessions for RT-ADRD contain content and training in resiliency skills that are particularly relevant after ADRD diagnosis for patients and their care partners. RT-ADRD was designed to include individual and interpersonal coping skills that are *transdiagnostic* (ie, relevant across mental and physical health conditions) and drawn from prominent evidence-based therapy approaches (eg, mindfulness, Dialectical Behavior Therapy, and Cognitive Behavioral Therapy). The sessions emphasize ways of using skills to cope with the common challenges experienced early after dementia diagnosis and focus on navigating challenges as a dyadic unit Dyads will also receive links with downloadable recordings of exercises for home practice of skills. The sessions are modular in nature, and dyads will choose 6 modules from a selection of 8 possible modules. The 8 modules are presented in Table 1.

Table 1. Sessions' outlines for the Resilient Together for Dementia (RT-ADRD) program.

Sessions	RT-ADRD topics	Content and skills (all sessions include home-practice of skills)
1	Being in the Here and Now	Deep breathing, mindfulness, and 24-hour block
2	Complex and Conflicting Experiences	Dialectics, mindfulness meditation, and open stress communication
3	Current and Future Challenges	Distress spiral, hands as worries, and acceptance and change
4	Planning and Coping Ahead	Cope ahead, cultivating routines, and coping as a team
5	Difficult Topics	Clarifying goals, effective communication, and relationship repair
6	Relationship Changes	Navigating support and defining roles
7	The Uncertain Future	Goal setting and coping plan
8	Accepting Changes and Making Meaning	Reflection for meaning making

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Assessments

After consent, both dyad members will independently complete a pretest survey via a secure REDCap link (~30 minutes each) sent by a research coordinator. If needed, participants will also have the option of completing surveys with the assistance of a trained research coordinator via the videoconferencing "Share Screen" tool. The survey will include validated measures to gather information on hypothesized mechanisms of intervention, intervention targets, and treatment moderators, consistent with the overall conceptual model (Figure 2). The primary intervention targets (Table 2, secondary outcomes) are individuals' emotional distress, relationship quality, and quality of life, which were selected based on their interdependence within dyads and the link of emotional distress to long-term mental and physical health outcomes and relationship functioning [9,14,17,18]. The hypothesized intervention mechanisms (Table 2; described further below) are transdiagnostic resiliency skills that demonstrated links to the same intervention targets in studies of prior dyadic interventions [27]. Following completion of the treatment sessions, dyads will complete a similar posttest survey in REDCap. Responses will be used to compare scores to population norms, examine interrelations among constructs, and inform procedures and the tailoring of RT-ADRD. The primary outcomes for this trial are feasibility and acceptability. In addition, we will use the 6-item Credibility and Expectancy Questionnaire [43] to assess treatment credibility at baseline. We will also use the 3-item Client Satisfaction Questionnaire [44] to assess satisfaction with RT-ADRD at posttest. We will gather comprehensive qualitative feedback on these benchmarks and report detailed information on study screening, enrollment, and intervention deliveries via health care system–supported videoconferencing or in person, to refine feasibility and acceptability benchmarks prior to further testing. A description of study measures is provided below (Table 2).

Figure 2. RT-ADRD Conceptual Model.

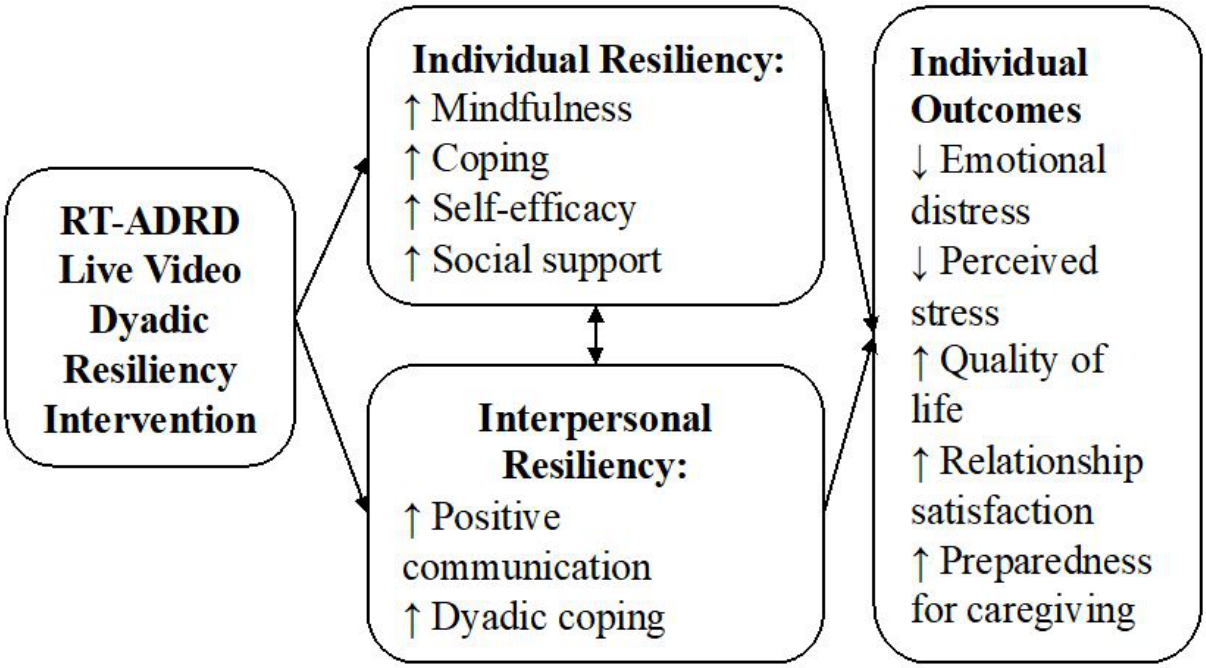

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Table 2. Assessment measures.

Construct	Description	Base	Post
Primary outcomes			
Feasibility	• Procedures: suitability and practicality of RT-ADRD[a] and procedures; qualitative feedback from exit interviews • Screening: proportion of dyads who screen eligible of those who undergo screening • Recruitment and Consent: proportion of dyads who are approached and agree to participate in the intervention • Engagement: proportion of dyads who are enrolled and complete 4 out of 6 sessions • Assessment: proportion of individuals who are enrolled and complete baseline and post-test assessments	X	X X X X
Acceptability	• Credibility and Expectancy Questionnaire (6 items)—assess how credible dyads perceive RT-ADRD • Client Satisfaction Questionnaire (3 items)—a measure of satisfaction with RT-ADRD • Qualitative feedback from exit interviews	*X*	*X* *X*
Covariates			
Demographics	• Review of medical records and participant self-report: age, sex and gender, race and ethnicity, education, and income		
Clinical Characteristics	• Review of medical records and participant self-report: type of ADRDb diagnosis, time since diagnosis, and cognitive tests	X	
Secondary Outcomes			
Emotional Distress	• Hospital Depression and Anxiety Scale (14 items)—a measure of emotional distress (anxiety and depression subscales) Geriatric Depression Scale (15 items)—a measure of depression symptoms	X X	X X
Perceived Stress	• Perceived Stress Scale (4 items)—a measure of perceived stress	X	X
Quality of Life	• WHO Quality of Life-Short Form (26 items)—a measure of quality of life	X	X
Relationship Satisfaction	• Couples Satisfaction Inventory (16 items)—a measure of couple relationship satisfaction	X	X
Preparedness for Caregiving (Care partners only)	• Preparedness for Caregiving Scale (8 items)- readiness for caregiving in relation to spouse	X	X
Intervention Mechanisms			
Mindfulness	• Cognitive and Affective Mindfulness-Scale (12 items)—a measure of mindfulness skills	X	X
Coping	• Brief COPE (28 items)—a measure of adaptive and maladaptive coping strategies	X	X
Self-efficacy	• General Self-Efficacy scale-6 (6 items)—a measure of self-efficacy	X	X
Social Support	• Social Support Questionnaire, Short Form—Revised (12 items)—a measure of satisfaction with social support	X	X
Interpersonal Communication and Coping	• Dyadic Relationship Scale (10 items—patients, 11 items—caregivers)—a measure of positive and negative dyadic interactions • Dyadic Coping Inventory (9 items)—a measure of dyadic stress management	X X	X X

Covariates

We will collect demographic information on participants' gender, age, race, ethnicity, marital status, relationship length, education level (number of years in school), employment (status, occupation, and income), and mental health history. We will also collect ADRD clinical characteristics via electronic medical records, including the type of diagnosis, age at diagnosis, and date of diagnosis.

Secondary Outcomes

Overview

We will use the 14-item Hospital Anxiety and Depression Scale (HADS) [40] total score to assess emotional distress once at

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baseline, and again at the completion of the program. We will examine the 7-item depression and anxiety subscales of the HADS separately (HADS-D and HADS-A, respectively). Scores range from 0 to 21, where a score >7 indicates significant depression or anxiety. We will also use the 15-item Geriatric Depression Scale–Short Form [41], to assess depression symptoms over the past week. Scores range from 0 to 15, with scores ≥5 suggesting the presence of clinically elevated depression symptoms. We will assess perceived stress over the past month using the Perceived Stress Scale [45]. Scores range from 0 to 16, with higher scores indicating greater perceived stress. To assess perceived quality of life, we will use the 26-item brief World Health Organization Quality of Life assessment [46], which captures quality of life across 4 subscales (physical health, psychological, social relationships, and environment). The first 2 items provide a global assessment of quality of life, and the subscale scores are calculated by summing items and transforming scores to a 0 to 100-point interval, with higher scores indicating a greater perceived quality of life. To assess relationship satisfaction, we will use the 16-item Couple Satisfaction Index [47]. Total scores range from 0 to 81, with higher scores indicating greater relationship satisfaction. Finally, for spousal care partners we will use the 8-item Preparedness for Caregiving Scale (9) to evaluate readiness for caregiving in relation to their spouse. Total scores range from 0 to 32, with higher scores indicating greater preparedness for caregiving.

Treatment Mechanisms

We selected treatment mechanisms assessing individual and dyadic coping and relationship functioning based on our hypothesized mechanisms underlying changes in proposed outcomes (ie, emotional distress, quality of life). We will use the 12-item Cognitive and Affective Mindfulness Scale, Revised [48], to assess mindfulness. Total scores range from 12 to 48, with higher scores indicating greater engagement in mindfulness practices. We will use the 28-item Brief Coping Orientation to Problems Experienced (Brief COPE) [49], to measure ways of individually coping with stressful events. The Brief COPE includes three subscales that assess coping styles: (1) problem-focused (8 items), (2) emotional-focused (12 items), and (3) avoidant coping (8 items). Scores for each subscale are calculated by taking the mean of all items, with higher scores indicating greater use of that coping style. We will assess perceived self-efficacy with the 10-item General Self-Efficacy Scale [50]. Total scores range from 10 to 40, with higher scores indicating greater perceived self-efficacy. We will use the 12-item brief Social Support Questionnaire (SSQR) [51] to assess social support availability and satisfaction. The SSQR consists of 2 subscales: support network availability (SSQR-N) and overall satisfaction (SSQR-S). Each item assesses support availability and satisfaction in separate parts; participants will be asked to indicate (1) how many people they can count on for various types of support and (2) how satisfied they are with the support. The SSQR-N subscale composite is calculated by taking the mean of all items. For the SSQR-S subscale, total scores are calculated by adding subscale items and range from 6 to 36, with higher scores indicating greater social support satisfaction. To assess the perceptions of dyadic stress management, we will use the items from the Dyadic Coping Inventory [52,53] subscales: common dyadic coping and negative dyadic coping. The common dyadic coping subscale includes 5 items that assess dyads' ability to cope with problems together and search for solutions. Scores range from 5 to 25, with higher scores indicating greater perceptions of the dyad's use of common coping. Negative dyadic coping will also be assessed using the Dyadic Coping Inventory (4 items). Scores range from 4 to 20, with higher scores indicating greater perceptions of the dyads using negative dyadic coping. In addition, we will assess dyadic relationship strain in the context of caregiving using the dyadic strain subscale of the Dyadic Relationship Scale (DRS) [54], which has a 10-item-Patient version and an 11-item Caregiver version. Subscale scores range from 1 to 10 and 1 to 11 for the DRS-Patient and DRS-Caregiver, respectively, with higher scores indicating greater relationship strain.

Exit Interviews

At the conclusion of the intervention sessions, dyads will participate together in a single 60-minute exit interview over health care system–supported videoconferencing to gather information on session content and procedures to refine intervention methods prior to the feasibility trial. Topics will include: what was most and least helpful about the intervention, topics or skills that were not included that might be helpful, whether additional sessions would be preferred, perceptions of skills, comfort with participating in sessions together, and barriers and facilitators of engagement in RT-ADRD procedures and the intervention. A trained research assistant will complete the interviews using an interview guide (see Supplemental Materials). As part of the interview, the research assistant will also capture observations within session domains, important quotes, and other important notes using a rapid data analysis template.

Data Analysis

Feasibility-related measures will be assessed and compared to our prior dyadic intervention studies [27] using proportions at the individual-level on feasibility markers outlined in Table 2, as well as qualitative feedback from exit interviews. Acceptability will be evaluated with the percentage of individuals with scores above the midpoint on self-report questionnaires (Table 2), as well as feedback from exit interviews. Given our primary goal of establishing feasibility and acceptability, this open pilot was not powered to statistically evaluate signal of improvement in quantitative outcomes. However, we will examine preliminary effectiveness of the secondary outcomes using estimated treatment effects for each measure. We will also assess the relationship among treatment mechanisms and secondary outcomes using bivariate correlations, focusing on whether the direction of the association is consistent with our conceptual model. Qualitative data obtained from exit interview transcripts will be analyzed using a rapid data analysis approach to thematic analysis [55]. We will use overarching themes surrounding feasibility markers and participant suggestions to further refine the intervention.

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Results

This study was supported by a grant from the National Institute on Aging (1K23AG075188-02) to SB. It was approved by the institutional review board of the Mount Sinai Hospital in April 2024. Recruitment began in April 2024 and will continue through August 2024. Data collection and analysis is anticipated to be complete by August 2024.

Discussion

Anticipated Findings

ADRDs are conditions that are increasingly common among the aging population and have considerable negative impacts on individuals living with ADRD and their spousal care partners [5]. Currently, these dyads have few resources to assist them in navigating early challenges together and adjusting positively to the diagnosis and symptoms [24,25]. Dyads describe an interest in participating in interventions together early after ADRD diagnosis to assist in navigating support and adjusting to symptoms [8]; however, no such interventions exist. Adapting existing interventions has the potential to be effective and efficient in addressing dyads' challenges to promote dyadic adjustment [27,28], and aid in preventing chronic individual and interpersonal stress. Thus, the RT-ADRD program is a timely potential solution to unmet needs reported by dyads at the time of ADRD diagnosis. The present study aims to refine RT-ADRD, a novel dyadic resiliency intervention for dyads at risk of chronic emotional distress early after ADRD diagnoses that includes individual and interpersonal resiliency training for both dyad members simultaneously to promote adjustment to ADRD.

The larger plan to develop and revise RT-ADRD is guided by the NIH Stage Model for behavioral intervention development [56]. This protocol provides the framework of our open pilot trial of RT-ADRD, stage 1B of the development of RT-ADRD. The intervention is novel and flexible, providing live video delivery of treatment sessions to maximize feasibility and adherence, while also providing the option of in-person sessions upon request. We will use the open pilot results to refine the program and inform the subsequent stage—a larger feasibility trial of RT-ADRD relative to an educational control condition (target N=60 dyads).

Limitations

Currently, we are only conducting the intervention in English and with couple dyads. This results in important limitations for non–English speakers and for other caregiving dyads commonly facing ADRDs (eg, parent-child dyads). We plan to address these limitations with parallel studies and in subsequent trials by creating a version of the program in Spanish using established guidelines for linguistic adaptation. We also plan to conduct additional qualitative studies to identify adaptations needed to address a range of caregiving dyads.

Conclusions

The results from this open pilot trial will be used to inform the development of Resilient Together for Dementia, a dyadic resiliency program for those living with ADRDs and their romantic or spousal care partners. Our study will provide quantitative and qualitative data that we will use to refine the current iteration of the program. We will then test the refined intervention in a larger feasibility trial relative to an educational control condition.

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Data Availability

Data collection and analysis instruments are available in the Multimedia Appendices. The datasets generated during and/or analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

BD is a Consultant for Acadia, Alector, Arkuda, Biogen, Cervomed, Eisai, Genentech, Ilios, Lilly, Merck, and Quanterix. BD receives royalties from Cambridge University Press, Elsevier, and Oxford University Press.

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Abbreviations

ADRD: Alzheimer disease and related dementia
Brief COPE: Brief Coping Orientation to Problems Experienced
DRS: Dyadic Relationship Scale
HADS: Hospital Anxiety and Depression Scale
HIPAA: Health Insurance Portability and Accountability Act
MoCA: Montreal Cognitive Assessment
NIH: National Institutes of Health
REDCap: Research Electronic Data Capture
RT-ADRD: Resilient Together for Dementia
SSQR: Social Support Questionnaire
SSQR-N: Social Support Questionnaire-network availability
SSQR-S: Social Support Questionnaire-overall satisfaction

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Protocol

Evaluation of the Feasibility of Transfusing Leukocyte Depletion Filter–Processed Intraoperative Cell Salvage Blood in Metastatic Spine Tumor Surgery: Protocol for a Non–Randomized Study

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Abstract

Background: Metastatic spine tumor surgery (MSTS) is often complex and extensive leading to significant blood loss. Allogeneic blood transfusion (ABT) is the mainstay of blood replenishment but with immune-mediated postoperative complications. Alternative blood management techniques (salvaged blood transfusion [SBT]) allow us to overcome such complications. Despite widespread use of intraoperative cell salvage (IOCS) in oncological and nononcological surgical procedures, surgeons remain reluctant to use IOCS in MSTS.

Objective: This study aims to analyze safety of IOCS-leukocyte depletion filter (LDF)–processed blood transfusion for patients undergoing MSTS by assessing clinical outcomes—disease progression: tumor progression and overall survival. This study evaluates whether reinfusion of IOCS-LDF–processed blood reduces ABT rates in patients undergoing MSTS by sorting patients undergoing MSTS who require ABT into patients who consent to receive or not receive SBT.

Methods: We aim to recruit a minimum of 90 patients—30 patients for SBT, 30 patients for ABT, and 30 patients with no blood transfusion. SBT and ABT form the 2 experimental arms, whereas no blood transfusion forms the control cohort. Available patient data will be reviewed to determine tumor burden secondary to metastasis and postoperative survival and disease progression, improvement in pain, and neurological and ambulatory status. Data collected will be studied postoperatively at 3, 6, 12, 24, 36, and 48 months or until demise, whichever occurs first. Outcomes of the experimental groups will be compared with those of the control group. Outcomes will be analyzed using 1-way ANOVA and Fisher exact test. The Kaplan-Meier curve and a log-rank test will be used to study overall survival. A multivariate and competing risk analysis will be used to study the association between blood transfusion type and tumor progression. All statistical analyses will be done using Stata Special Edition 14.0 (StataCorp LP).

Results: This is the largest clinical study on use of IOCS in MSTS from various primary malignancies to date. It will provide significant clinical evidence regarding the safety and applicability of IOCS in MSTS. It will help reduce use of ABT, improving overall blood management of patients undergoing MSTS. A limitation of this study is that not all patients undergoing MSTS will survive for the follow-up period (4 years), theoretically leading to underreporting of disease progression. Study commenced in 2016 and patient recruitment continued till 2019. As of September 2019, we have collected operative data on 140 patients. However, the 2-year outcomes of about 40.0% (56/140) of patients are in the process of collection. The study is aimed to be published in the years 2023-2024.

Conclusions: Results will be disseminated via peer-reviewed publications, paving the way for future studies.

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KEYWORDS

blood transfusion; autologous blood transfusion; operative blood salvage; leukocyte reduction filtration; intraoperative blood cell salvage; extramedullary spinal cord compression; metastases; tumors; leukocytes

Introduction

Background

The skeletal system is the third most common site of metastases, and cadaveric studies show that spinal metastases can be found in 30% to 90% of patients who die of cancer [1,2]. Surgery for metastatic spine disease (MSD) is complex, often requiring wide resection and extensive reconstruction leading to significant blood loss [1,2]. Emergency surgical treatment is often indicated for spinal cord compression with actual or impending paralysis or for spinal instability with severe pain that reduces the quality of life and mobility [3].

Typical blood loss in a patient undergoing tumor decompression and instrumentation in the thoracic and lumbar spine is about 1500 mL, and this requires an average of 3 units of packed red blood cells [4,5]. This blood loss is currently replenished by allogeneic blood transfusion (ABT) across the world, placing a significant burden on the already limited blood bank resources [6,7]. On the contrary, there is increasing evidence of the deleterious effects of ABT. Many studies have shown an increased incidence of postoperative infections [8] and promotion of tumor growth [8,9], which is thought to occur secondary to immunosuppression and other transfusion reactions.

Despite evidence describing multiple postoperative complications related to ABT [10,11], it remains to be the mainstay of blood replenishment in patients with heavy intraoperative blood loss [12]. These are immune-mediated complications and commonly affect the lungs (eg, transfusion-related acute lung injury) [13,14], wound healing [15-17], and survival duration [11,16]. This has prompted efforts to decrease reliance on ABT and to increase the utilization of alternatives, such as autologous predonation or intraoperative cell salvage (IOCS). Autologous predonation may not always be possible in metastatic spine tumor surgery (MSTS) because of suboptimal patient status, medical comorbidities, and in cases where emergency surgery is indicated.

Patient blood management is an evidence-based, patient-tailored approach aimed at reducing the need for ABT and its associated risks [18]. Patient blood management has both preoperative and perioperative components. Preoperative techniques include patient optimization via cessation of antiplatelet and anticoagulant medications [19,20] and anemia management [18]. Perioperative management comprises achieving surgical hemostasis, reinfusion of intraoperatively salvaged blood, the use of erythropoietic agents, and hemostatic drugs such as tranexamic acid. Randomized [21,22] and nonrandomized [23] studies on the use of IOCS in nononcological surgical procedures indicate that salvaged blood transfusion (SBT) significantly reduces the need for ABT [21-23]. Despite extensive use of SBT in orthopedic, trauma, and cardiac surgical procedures [24], the concern of reinfusion of tumor cells leading to disease progression persists [25-27]. The initial lack of literary evidence on the safety of SBT in oncological surgical procedures has made oncological surgeons reluctant to use SBT in MSTS [25-27].

This reluctance dates to an American Medical Council report from 1986, which stated that SBT was not suitable for use in tumor surgery [28]. This was in turn based on a case report from 1975 where tumor cells were found in salvaged blood [29]. There were concerns that tumor manipulation and resection would result in the spillage of tumor cells into the surgical field [30], which would lead to further metastasis if reinfused via SBT. Recent evidence indicates that circulating tumor cells (CTCs), which are shed by the primary tumor [31], are the most likely cause of tumor metastasis in oncological patients. CTCs have been shown to be eliminated by the reticular endothelial system [32], once they fail to metastasize (unable to complete the process of metastasis). Other CTCs may undergo cellular apoptosis after being retained in the capillary bed or the bone marrow [32]. These host defense mechanisms can prevent metastasis by reducing the metastatic ability of the vast majority of CTCs [33]. Consequently, one can ask, “Can SBT with a limited load of damaged malignant tumor cells cause tumor metastasis and disease progression?”

Investigation on the use of salvaged blood in MSTS started with a systematic review that we published [34]. It was envisaged that there is a place for salvaged blood in MSTS, provided the safety of IOCS in MSTS is established by the following steps. Our first step was to establish *basic cellular evidence* that there are no viable tumor cells in the salvaged blood. Second, we aimed to *quantify the number of tumor cells in the salvaged blood*, if any, and to demonstrate that the CTCs in the patient’s own blood are far more than those present in the salvaged blood. Our proposed *final phase* of study was to provide *clinical evidence* that SBT is safe for use in oncological surgical procedures, without increasing the risk of disease progression or tumor recurrence or resulting in poorer prognosis [32].

Our working hypothesis for the preclinical phase of this study was that the blood salvaged from patients undergoing MSTS does not contain viable tumor cells, and even if it did, viable tumor cells in the salvaged blood would be significantly lower than the number of CTCs present in the patient’s own blood at any given point in time. Therefore, there should be no increase in the risk of disease progression, in terms of further tumor dissemination, decreased survival, or increased tumor recurrence.

To test this hypothesis, we first conducted a study that analyzed the morphology and structural integrity of the tumor cells present in the patient’s circulation, operative field, and pre- and postfiltration samples of the salvaged blood [24,35]. Using the cell block technique, salvaged blood in the pre- and postfiltration samples was shown to mostly comprise cytoplasmic debris with no viable nuclei [24,25], thereby establishing the safety of IOCS in oncological surgery [36]. This is also supported by evidence from other studies [37] stating that upon passing through the

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IOCS system, 62% of tumor cells were destroyed, whereas the remaining 38% were morphologically altered.

Using flow cytometric studies, we then compared the number of CTCs present in the patient's own blood with that in salvaged blood [38]. We found that salvaged blood contained a significantly lower number of CTCs than those present in the patient's circulation [38]. Furthermore, we provided corroborative evidence that tumor cells passing through IOCS become nonviable and therefore cannot form new metastatic lesions [36]. We were able to demonstrate that CTCs lost the ability to develop into new metastatic lesions after passing through the IOCS apparatus, even without the use of leukocyte depletion filters (LDFs) [36]. LDFs are used to prevent leukocyte-mediated adverse reactions and have applications in both transplant surgery and treatment of hematological conditions [39]. LDFs are used for filtrating blood and have been proven to have the capability to remove tumor cells from the filtrate [38].

Currently, there is ample evidence in the literature for the clinical safety of salvaged blood used in oncological surgical procedures, including gastrointestinal [40], gynecological [41-43], hepatobiliary [40,44-46], and urological [47-54] surgical procedures (Multimedia Appendix 1 [55-64]). Although patients who received SBT required significantly lower amounts of allogeneic blood, their survival rates [44,49,51,52] and disease progression remained comparable with those who did not receive SBT [42,46,54,65]. Patients who received SBT had lower or similar rates of recurrence compared with the control cohort [47,49,51,53].

Despite the validity of the abovementioned literature, there still is hesitation to use IOCS in MSTS [34]. This can be addressed only by using a clinical study. Hence, we have designed this study to analyze the clinical use of IOCS in patients undergoing MSTS.

Objectives

Primary Objectives

This study aims to investigate the following clinical outcomes: disease progression, in terms of tumor progression (increase in size of existing metastatic lesions with or without the appearance of new metastasis), and the overall survival (OS) in patients who receive *IOCS in combination with LDF* (IOCS-LDF)–processed blood during MSTS. Therefore, this study aims to refute the prevailing conception that cell salvage should be avoided in MSTS owing to concerns of tumor dissemination.

Secondary Objectives

The secondary objectives of the study are to investigate whether reinfusion of IOCS-LDF–processed blood can reduce ABT rates in patients undergoing MSTS. We will also compare the length of stay and overall complication rate of patients who receive salvaged blood and those who receive ABT or no blood transfusion (NBT).

Hypothesis

The working hypotheses of this study are as follows:

1. Reinfusion of IOCS-LDF–processed blood of patients undergoing MSTS does not increase the risk of disease progression, in terms of tumor progression (increase in size of existing metastatic lesions with or without the appearance of new metastasis) and OS.
2. Patients receiving IOCS-LDF blood transfusion require less ABT.
3. Patients receiving IOCS-LDF blood transfusion will experience fewer overall complications and shorter length of stay than patients receiving ABT.

Methods

Recruitment

This study aims to recruit a minimum of 90 patients of whom 30 will receive SBT (with or with no allogeneic blood), 30 will undergo ABT, and the remaining 30 will have NBT. From our experience of treating patients with tumor, there are likely to be very few patients who receive only SBT. The majority of patients receiving SBT are likely to receive both SBT and ABT in various proportions. SBT and ABT form the 2 experimental arms, whereas patients with NBT form the control cohort. We will compare the number of patients receiving only SBT with those receiving ABT, if the sample sizes are sufficient.

Patients will be selected from specialist outpatient spine clinics or inpatient wards. These patients may be referred from an inpatient medical oncology team for management, especially in the setting of MSD with cord compression resulting in symptoms such as pain or neurology. A thorough examination of clinical history, physical examination, and review of imaging will be done, and appropriate patient management options will be discussed by the attending orthopedic surgeon. During the enrollment period, whenever a spine surgeon has obtained surgical consent for MSTS in patients with MSD, the principal investigator (NK) will be informed either by a telephone call or by text messaging.

The *research assistant* who is on-site at the National University Hospital during office hours or any member of the research team who is available will interview the patient. During this interview, the interviewer will confirm whether the inclusion criteria are fully met. The study will be explained to suitable subjects, including the advantages as well as possible intra- and postoperative risks of the reinfusion of salvaged blood. A copy of the *patient information sheet and consent form* will be provided to the patient, detailing the recruitment procedures, our objectives, hypotheses, and background information, and any queries will be addressed. Subsequently, written informed consent will be obtained from the patient.

Blood transfusion details will be collected from anesthetists immediately after the operation. Depending on the type of blood transfusion done during the surgery, that is, ABT only or SBT with or with no ABT or NBT, the patient will be categorized into the appropriate study cohort. All patients undergoing MSTS will receive tranexamic acid as an intravenous bolus before induction of anesthesia as per the department protocol, with subsequent top-up dosages every 4 hours during MSTS. If excessive blood loss is expected during surgery, such as in a

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separation surgery, continuous infusion of tranexamic acid is given to the patient.

Postoperatively, all subjects will be followed up individually by their operating surgeons, as per the standard of care at the National University Hospital. No additional patient follow-up sessions by the research team will be required. Clinical data and patient outcomes will be accessed via the computerized patient support system and EPIC system at monthly intervals. All available radiological data and clinical notes from the patients' follow-up by their treating surgeons or physicians will be reviewed by the research team. This is to determine the postoperative outcomes such as survival and disease progression. The collected data will be analyzed postoperatively at 3, 6, 12, 24, 36, and 48 months. The data collection and follow-up of available records will continue over a period of 4 years postoperatively or until the patient's demise, whichever occurs first. The collected outcomes of the 2 experimental groups (patients who received SBT with or without ABT) will be compared with those of the control group (patients who received NBT) as well as with the available historical data from the literature.

Statistical Analysis

We have defined *disease progression* as the increase in the size of an existing metastatic lesion or the appearance of a new lesion in the lung, liver, or the spinal column, which can be visualized by using radiological imaging.

Demographic and clinical characteristics of patients will be summarized using mean (SD) values for continuous variables with approximately normal distribution, median (IQR) values for continuous variables with skewed distribution, and frequency (percentage) for categorical variables. A 1-way ANOVA will be used to compare the mean of a normally distributed variable across the 3 blood transfusion groups, whereas a Kruskal-Wallis rank test will be used for the comparison of medians. A Fisher exact test will be implemented for categorical variables accounting for potential small frequencies.

The association between individual characteristics and OS will be studied by using the Kaplan-Meier curve and a log-rank test. The crude hazard ratio and its 95% CI will be used to measure the association between individual characteristics and OS and will be calculated based on their original definitions. Multivariate Cox proportional hazard regression will then be used to adjust for statistically significant confounders for the relationship between the type of blood transfusion and OS. The proportional hazards assumption will be tested after the final model is obtained.

The association between the type of blood transfusion and tumor progression will be investigated by the competing risks analysis, taking death without tumor progression as the competing event. First, cumulative incidence curves of the 3 blood transfusion groups will be plotted nonparametrically, and then we will model the relation via a subdistribution hazard regression model. The measure of association will be quantified by the crude subdistribution hazard ratio; its 95% CI and *P* value will be analyzed in a univariate analysis. Subsequently, a multivariate analysis will be used to adjust for potential confounders. All statistical analyses will be done using Stata Special Edition 14.0 (StataCorp LP). The statistical tests will be assumed to be 2-sided, with the conventional 5% significance level.

Analysis of Primary Outcome Measures

We intend to compare the proportion of patients with MSTS requiring blood transfusion and the amount of ABT required. The primary analysis will be based on the intention-to-treat principle. A Fisher exact test will be used to compare the 2 arms. The exact 95% CI will also be calculated for the difference in the ABT rate between the 2 arms.

Analysis of Secondary Outcome Measures

The progression of disease will be assessed using the internationally accepted Response Evaluation Criteria in Solid Tumors (version 1.1) [66,67]. Disease progression is defined as at least a 20% increase in the sum of the diameters of measurable target lesions (eg, lymph nodes and bone metastases with soft tissue components), unequivocal progression of nontarget lesions (eg, malignant ascites or pleural effusions), or the appearance of 1 or more new metastatic lesions.

Computed tomography of chest or abdomen and pelvis will be used to assess metastases in the lymph nodes, lung, liver, or any abdominal organ, all of which can be visualized adequately. Magnetic resonance imaging of whole spine and nuclear medicine bone will also be performed because of their increased sensitivity in detecting early new spinal or skeletal metastases [68]. A lesion identified in a follow-up study in an anatomical location that is not present at baseline is considered a new lesion and will indicate disease progression.

The OS rate will be defined as the proportion of patients who survive until the end of the study period. Median survival times and 95% CI will be estimated using Kaplan-Meier curves for experimental and control groups. The median OS times will be compared using a log-rank test. The survival rate at 6 months after surgery will also be estimated using Kaplan-Meier curves.

Ethical Considerations

The domain-specific review board of the National Healthcare Group, Singapore (reference numbers: 2014/00065 and 2022/00866), has granted ethical approval for this study. Written informed consent regarding participation in this research study and receiving SBT will be obtained from each patient before the patient is recruited for the study. Data have been anonymized and deidentified. No compensation was provided to patients for this study.

Results

This study has been funded by the National Medical Research Council of Singapore in November 2016 and approved by domain-specific review board of the National Health Group in April 2016.

Data were collected from November 2016 to present (as of submission date of manuscript). Numbers recruited into study, as of submission of the manuscript, were 140. The status of data analysis and expected results are expected to be published in the years 2023-2024, when the information is available.

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Discussion

Study Findings

This is the largest prospective clinical study on the use of IOCS in MSTS from a variety of primary malignancies. It will provide significant clinical evidence regarding the safety and applicability of IOCS in MSTS. The clinical safety of the use of IOCS has been established in oncological surgical procedures involving gastrointestinal [40], gynecological [41-43], hepatobiliary [40,44-46,55-57], and urological [47-54,58-62] specialties (Multimedia Appendix 1). However, the use of IOCS has neither been studied nor practiced regularly in metastatic musculoskeletal tumor surgeries (MMTSs). This may be because of the skepticism among surgeons about the safety of SBT in MMTSs, despite the presence of substantial supporting evidence in other surgical specialties in the field of oncology [40-54,63,64]. Amidst all the apprehension regarding IOCS, a retrospective comparative review has shown that SBT indeed reduces the need for postoperative ABT [69]. More recently, the use of SBT has been studied prospectively, demonstrating its safety for IOCS in MSTS [70]. Nonetheless, these studies did not have a comparative arm and had a small sample size.

This prospective clinical study is founded on substantiating evidence that salvaged blood is free from viable tumor cells, proven in our earlier methodical basic sciences approach [32,38]. We aim to study the OS, as well as tumor progression in MSTS patients through analysis of their various outcome measures. The results from this approach will help debunk the prevailing myth that IOCS contributes to disease progression either in the form of new metastasis or in the form of an increase in the size of the index lesion.

Limitations

The limitation of this study is that not all patients undergoing MSTS will survive for the total follow-up period of 4 years, thereby theoretically leading to potential underreporting of disease progression. The sheer number of possible primary tumors in MSD also inevitably leads to heterogeneity, which can be overcome through propensity score–matching analysis.

Broader Implications

Through the reporting of our analysis, this study will help reduce the use of ABT, reduce the burden on blood banks, and improve the overall blood management of patients with MSTS. This improvement in blood management will prevail even with the improvement of surgical techniques in the management of MSTS, that is, introduction of minimally invasive surgery techniques and the regular use of navigation. This is because the 2 techniques mentioned earlier will reduce blood loss during the steps of spinal instrumentation but are unlikely to have any effect on blood loss while performing decompression. Decompression and separation surgery presently still form a major component of MSTS and will continue to do so, resulting in significant bleeding that requires replenishment potentially in the form of SBT.

In this protocol, we have proposed a prospective observational nonrandomized study design as the ethical appropriateness of blinding or randomizing these patients is a key concern in our region and country. Blinding or randomization of patients with MSD could be deemed unethical, especially among patients who may not agree to receive SBT or ABT as this will limit the blood transfusion type applicable for them. This could be attributed to the current lack of clinical evidence that SBT does not lead to disease progression or shortened survival among patients undergoing MSTS who receive SBT. With this research proposal, we aim to highlight the safety profile of SBT, together with a design protocol applicable for use in patients with MSD. Future research, such as propensity-matched studies, can be done to further validate the outcomes from our current protocol.

Conclusions

We surmise that the results of our proposed study design will pave the way for future randomized studies on the use of IOCS in MSTS and MMTSs, given that the granting bodies and their reviewers would be more open to considering funding for such studies.

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Data Availability

All data generated or analyzed during this study will be included in published manuscripts and their supplementary information files.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Key papers evaluating the use of intraoperative cell salvage in various cancer surgeries.
[DOCX File , 39 KB - resprot_v14i1e54609_app1.docx]

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Abbreviations

ABT: allogeneic blood transfusion
CTC: circulating tumor cell
IOCS: intraoperative cell salvage
LDF: leukocyte depletion filter
MMTS: metastatic musculoskeletal tumor surgery
MSD: metastatic spine disease
MSTS: metastatic spine tumor surgery
NBT: no blood transfusion
OS: overall survival
SBT: salvaged blood transfusion

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Protocol

Clinical Characteristics of Virologically Confirmed Respiratory Syncytial Virus in English Primary Care: Protocol for an Observational Study of Acute Respiratory Infection

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Abstract

Background: There are gaps in our understanding of the clinical characteristics and disease burden of the respiratory syncytial virus (RSV) among community-dwelling adults. This is in part due to a lack of routine testing at the point of care. More data would enhance our assessment of the need for an RSV vaccination program for adults in the United Kingdom.

Objective: This study aimed to implement point-of-care-testing (POCT) in primary care to describe the incidence, clinical presentation, risk factors, and economic burden of RSV among adults presenting with acute respiratory infection.

Methods: We are recruiting up to 3600 patients from at least 21 practices across England to participate in the Royal College of General Practitioners Research Surveillance Centre. Practices are selected if they undertake reference virology sampling for the Royal College of General Practitioners Research Surveillance Centre and had previous experience with respiratory illness studies. Any adult, ≥40 years old, presenting with acute respiratory infection with onset ≤10 days, but without RSV within the past 28 days, will be eligible to participate. We will estimate the incidence proportion of RSV, describe the clinical features, and risk factors of patients with RSV infection, and measure the economic burden of RSV infection.

Results: A total of 25 practices across different English health administrative regions expressed interest and were recruited to participate. We have created and tested an educational program to deploy POCT for RSV in primary care. In addition to using the POCT device, we provide suggestions about how to integrate POCT into primary care workflow and templates for high-quality data recording of diagnosis, symptoms, and signs. In the 2023-2024 winter RSV detection in the sentinel network grew between

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October and late November. According to data from the UK Health Security Agency, the peak RSV swab positivity was in International Standards Organization week 48, 2023. Data collection remains ongoing, and results from the subset of practices participating in this study are not yet available.

Conclusions: This study will provide data on the RSV incidence in the community as well as rapid information to inform sentinel surveillance and vaccination programs. This information could potentially improve clinical decision-making.

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KEYWORDS

infectious diseases; primary care; sentinel surveillance; point-of-care system; virologically; respiratory syncytial virus; acute respiratory infection; clinical characteristics; community dwelling; adult; vaccination; programme; united kingdom; incidence; elderly

Introduction

Background

Respiratory syncytial virus (RSV) infection in adults is reported to be a substantial burden to health care systems globally [1]. A recent systematic review of the disease burden of RSV in older adults in the United Kingdom reported an average of 175,070 primary care physician episodes and 7915 deaths per season attributed to RSV, equivalent to 1946 primary care physician episodes per 100,000 population and 88 deaths per 100,000 population older than 65 years of age [2,3]. Another meta-analysis reported that RSV caused 4.66% (95% CI 3.34-6.48) of symptomatic respiratory infections in annual studies and 7.80% (95% CI 5.77-10.45) in seasonal studies among adults older than 60 years [4].

However, RSV is not widely recognized as a cause of respiratory infections in adults as its clinical manifestations are often nonspecific [5-10]. Among those with predisposing factors, such as older age, weakened immune systems, or underlying cardiopulmonary conditions, RSV can increase the risk of developing serious acute lower respiratory tract infection (LRTI), cardiovascular sequela, and exacerbation of underlying conditions, all of which are associated with a significant risk of hospitalization and mortality [5,6,11].

Current guidelines do not recommend rapid diagnostic testing for respiratory viruses in primary care in England [12,13] and a recent scoping review showed the paucity of literature on studies of RSV tests in specific populations and settings [14] despite the difficulty of clinical diagnosis and the availability of a number of highly accurate point-of-care tests (POCT) platforms for RSV in the National Health Service (NHS) [9,15]. Recent studies have estimated that limited routine clinical testing can result in more than 100-fold underestimation of RSV incidence in laboratory surveillance studies [16]. RSV disease burden is of considerable interest because of the development of new vaccines and monoclonal therapies [17-19]. The UK's Joint Committee on Vaccination and Immunization advised that an immunization program for RSV be established for older adults aged 75 years and older [17]. More precise contemporary data to estimate the incidence of RSV in the community and understand the clinical and economic burden of RSV infection in adults would assist in planning any new RSV vaccination program.

Deployed at scale, POCT for RSV has the potential to address the gaps in our knowledge about incidence, clinical presentation, and disease burden.

Aim and Objectives

The aim of the Observational Study of Acute Respiratory Infection (ObservatARI) study is to deploy POCT in primary care clinics to provide data about the incidence, clinical presentation, risk factors, and economic burden of virologically confirmed RSV among older adults presenting with acute respiratory infection (ARI).

Our primary objective is to calculate the incidence proportion of virologically confirmed RSV among adults aged ≥40 years, in a primary care-based sentinel surveillance cohort overall and by age, sex, and subgroups of interest.

Secondary objectives include (1) examining the population-level incidence of RSV, (2) the incidence of RSV-LRTI, (3) use of secondary care, (4) clinical profile, and (5) comparison of clinical and economic burden in cases with and without RSV. Prespecified subgroups (sample size permitting) include age and sex.

Methods

Coordinating Center

The coordinating center for this study was the Nuffield Department of Primary Care Health Sciences, University of Oxford, Oxford, United Kingdom.

Study Design

The ObservatARI study is ongoing, taking place between November 2023 and November 2024. It is nested within the English national sentinel network, the Oxford-Royal College of General Practitioners (RCGP) Research and Surveillance Centre (RSC), at the Nuffield Department of Primary Care, University of Oxford. This network of over 2000 primary care providers in England, referred to as general practices, is the primary care infectious disease surveillance network for England recruited to be representative of the English population [20]. It has been providing weekly data for over 57 years and is used to monitor trends in infectious disease and investigate real-world vaccine and treatment effectiveness [21].

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All practices that contribute data to the RSC are eligible to participate in the ObservatARI study. We will prioritize those practices that currently undertake reference virology sampling for the sentinel network and have previous experience with undertaking respiratory illness studies, including POCT studies. In order to ensure geographic representation, up to 3 practices in each English health region (East of England, London, Midlands, North East, Yorkshire, North West, and South East and South West) have been selected to participate in the study [22]. These sites will receive training on the appropriate use of the POCT device from the manufacturer, which will be documented on a training log. Provision of the POCT device to these sentinel surveillance sites will allow for the collection of data on RSV, which is not routinely tested as part of usual care.

Figure 1 shows the cohort entry date of recruited patients is the date the POCT swab is taken and will serve as the study index date. Baseline covariates are assessed in the period of up to 5 years before cohort entry, and the precise lookback period will vary depending on the variable of interest.

Figure 1. ObservatARI study design. ARI: acute respiratory infection; RSV: Research Surveillance Centre, POCT: point-of-care-testing. The study time period was from November 2023 to November 2024. *Lookback for baseline covariates will vary by variable using windows established by existing sentinel surveillance efforts. **Patients censored due to death or disenrollment from the clinic.

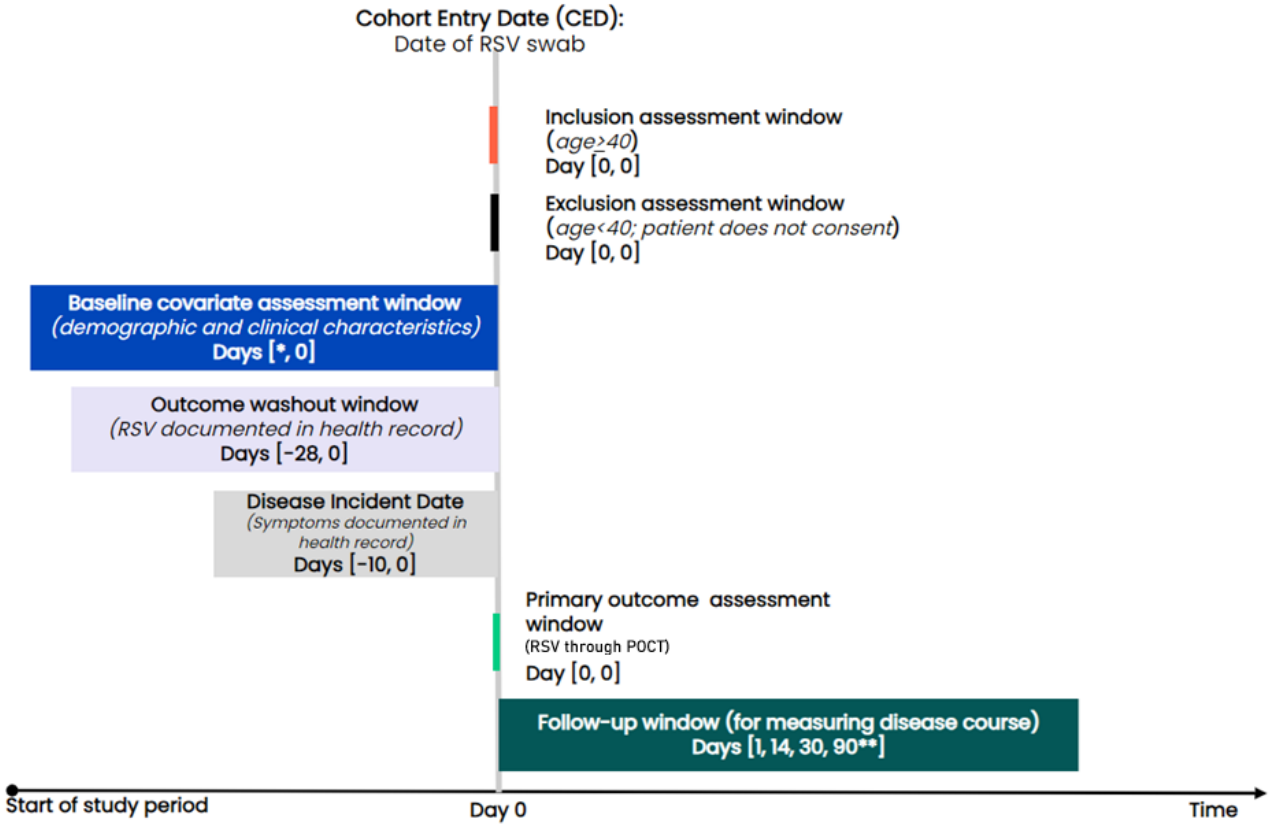

We will follow-up enrolled patients for up to 14 days, 30 days, and 90 days for secondary outcomes of interest, such as clinical outcomes and health service usage. This information will be presented according to the test result from POCT (ie, RSV-positive and RSV-negative).

Case Definition of Eligible Patients

Fully registered primary care patients, of study practices, who present with ARI, with its onset in the last 10 days (including index date), where illness is not due to another plausible diagnosis, are eligible for enrollment in the ObservatARI study. These are the same criteria currently used by the UK Health Security Agency (UKHSA) sentinel surveillance system [23].

Sampling and Data Collection

We are undertaking opportunistic virology sampling [24], with potential participants being identified from fully registered patients and temporarily registered patients who present to the participating study practices with respiratory symptoms described in the case definition.

ObservatARI practices are advised to take 2 swabs, and 1 nasopharyngeal swab for testing using the Cepheid POCT analyzer. Nasopharyngeal swab samples have been studied and validated for the detection and quantification of respiratory viruses and are considered more accurate for RSV than nasal swabs [15,25,26]. The second one is a nasal swab for testing using the UKHSA National Virology Reference Laboratory as per Oxford-RCGP RSC's standard practice [23].

Eligible patients are approached by their practice receive an explanation about the study and are asked for consent to take part when they present for a face-to-face consultation at the practice. Patients are informed that they are free to withdraw from the study at any time without giving any reason and without their legal rights being affected. Study participants will not receive compensation for taking part in this study.

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After obtaining consent using a form with a prepopulated study number, the primary care physician or research nurse will take the virology swabs [25,26]. The nasopharyngeal swab is inoculated in a test kit and tested using the POCT analyzer as soon as possible after being taken. Only the patient study number is entered into the POCT machine.

We are using the Cepheid GeneXpert Xpress CoV-2, Flu, RSV plus POCT analyzer for this study. This multiplex polymerase chain reaction system tests for SARS CoV-2, influenza A, influenza B, and RSV. It has demonstrated excellent performance comparable to gold-standard laboratory assays with a sensitivity for RSV of 0.979 (95% CI 0.889-0.996) and specificity of 1.000 (95% CI 0.981-1.000) [27]. It has Conformité Européenne marking in the European Union. In the United States, it is approved by the US Food and Drug Administration and it is also waived for use by the Clinical Laboratory Improvement Amendments for rapid RSV testing. This study will not assess the accuracy of the POCT analyzer but will use the machine for its approved purpose.

The clinician is also asked to enter the following date of onset of four symptoms in the patient's computerized medical record (CMR): (1) the presence or absence of fever because of infection, (2) cough (and if coughing is productive), (3) sore throat, and (4) shortness of breath or wheezing. In addition, the following four signs will be recorded in the CMR: (1) measured temperature (ear or tympanic preferred) ≥38 °C for fever, (2) peripheral oxygen saturation, (3) pulse rate >90 beats per minute for tachycardia, and (4) respiratory rate >20 breaths per minute for tachypnoea (Textbox 1). After the POCT analyzer has finished, the clinician is asked to code the result into the patient's CMR.

To facilitate the standardized collection of symptoms, signs, and POCT or laboratory results for the study, we have developed data entry templates for study practices using either the Egton Medical Information Systems or The Phoenix Partnership computerized medical systems available to participating practices (Figure 2). This allows clinicians in study practices to record respiratory symptoms and signs, and study consent, through dropdown menus and tick boxes. The results of POCT testing and reference laboratory testing will also be entered using these templates. The information from the templates is automatically entered into the patient's CMR as a relevant Systemized Nomenclature of Medicine Clinical Terms, which will be extracted for data analysis as part of this study.

Textbox 1. Key data on symptoms and signs of acute respiratory infection.

Symptoms data

- Presence or absence of fever because of infection
- Cough (and if coughing is productive)
- Sore throat
- Shortness of breath or wheezing

Signs data

- Measured temperature (ear or tympanic preferred) ≥38 °C for fever
- Peripheral oxygen saturation
- Pulse rate >90 beats per minute for tachycardia
- Respiratory rate >20 breaths per minute for tachypnea

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Figure 2. Sample ObservatARI data collection form. ARI: acute respiratory infection; RCGP: Royal College of General Practitioners; RSC: Research Surveillance Centre.

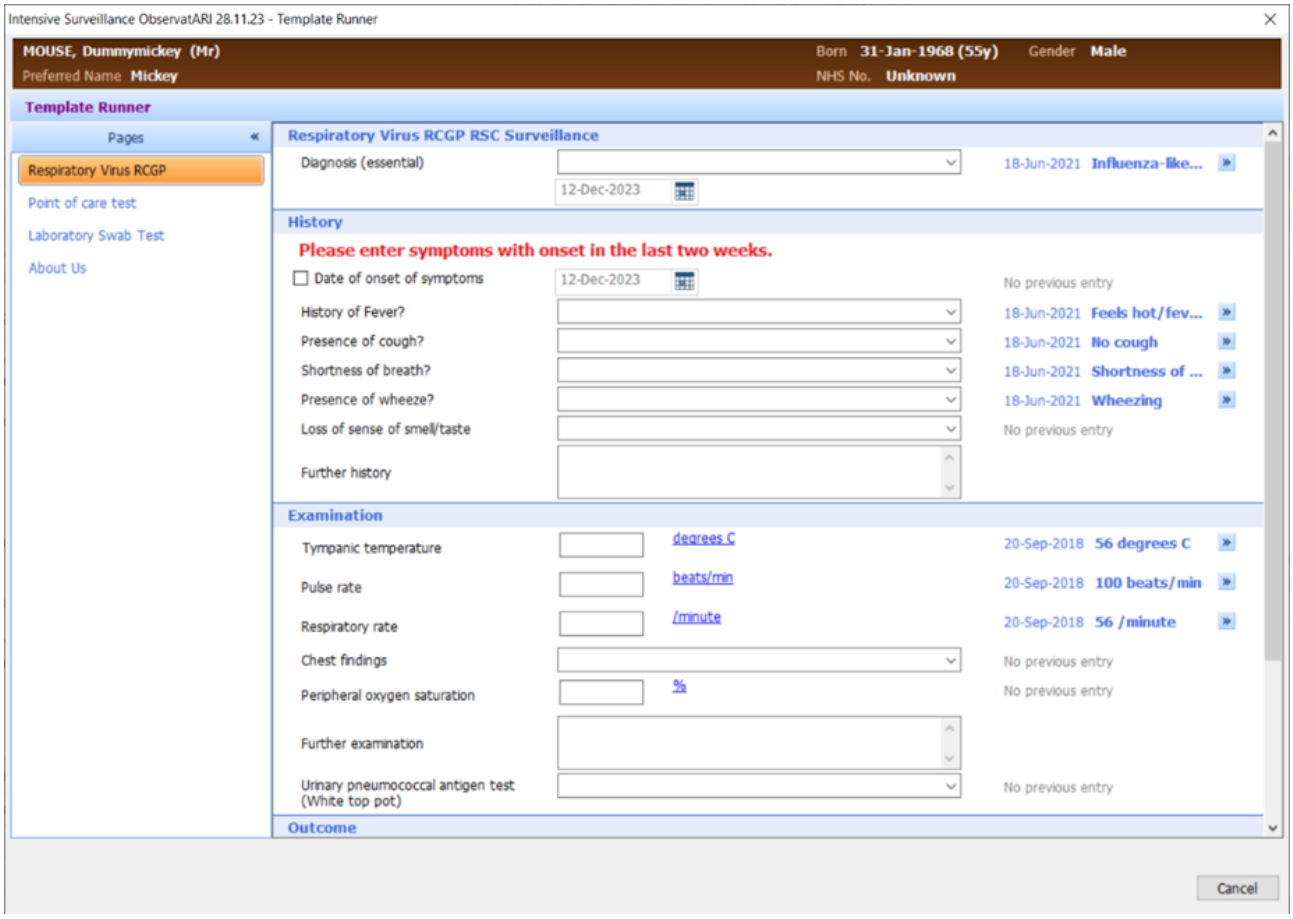

Data Sources

The Oxford-RCGP Clinical Informatics Digital Hub (ORCHID) trusted research environment will house the data required for this study.

We will use a pseudonymized NHS number to allow the linkage of ObservatARI data to national datasets. With appropriate approval, these data assets are held within the ORCHID trusted research environment. Data assets used for this study are as follows.

The primary virology diagnosis will be from POCT data collected from participating ObservatARI practices.

Supplemental data on test positivity will be available approximately a week later from the UKHSA reference laboratory data. In the event of a discrepancy between the POCT and UKHSA reference laboratory data, the POCT test will be selected as the main result with the proportion of discrepant results reported.

In addition, virology data from UKHSA virology sampling during the study period will be accessed to augment data obtained from POCT.

Pseudonymized patient data are also linked to UKHSA National Virology Reference Laboratory data results. NHS England national data collection provides access to hospitalization, intensive care unit admission, mortality, and other national datasets.

Hospital Episode Statistics (HES) is the transformed data, initially part of the Commissioning Data Set, covering patients attending accident and emergency units, admitted for treatment, or attending outpatient clinics at NHS hospitals in England, including details about length of stay and Health Care Resource Groups (HRGs) to enable health economic analysis. HRG consists of patient events that have been judged to consume a similar level of resource, which can be linked to an appropriate NHS tariff. Statistical controls have been applied to HES products. Data on cost will be extracted from HES using HRG. Health care resource use data during hospital admissions are not granularly available and, therefore, HRG codes will need to be used as a proxy for costing.

Emergency Care Data Set collects data from accident and emergency departments.

Civil Registrations include information including date, place, and certificated cause of death from the Office for National Statistics.

Data derived from primary and secondary care encounters are recorded using the Systemized Nomenclature of Medicine-Clinical Terms and *ICD-10* (*International Statistical Classification of Diseases, Tenth Revision*) codes, respectively [28]. The clinical concepts captured include diagnoses, therapy, test results, and other data [29]. Patient medical records in UK general practice have been computerized since the late 1990s, with pay-for-performance incentives introduced in 2004 for chronic disease management [30].

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Sample Size Calculation

Up to 3600 POCT swabs will be taken from consented, volunteer patients registered with the 21 ObservatARI general practices. Based upon the annual disease prevalence of 6% and reported sensitivity of 0.979 (95% CI 0.889-0.996) and specificity of 1.000 (95% CI 0.981-1.000) [27], we estimated the number of participants with and without RSV that would test positive and negative with the POCT if we sampled 3600 with ARI (Table 1).

Table 1. Expected counts (±95% CIs) for respiratory syncytial virus (RSV).

	RSV, expected count (95% CI)	No RSV, expected count (95% CI)	Total, n
Positive POCT[a]	211 (192-215)	0 (0-64)	211
Negative POCT	5 (1-24)	3384 (3320-3384)	3389
Total	216	3384	3600

[a]POCT: point-of-care-testing.

Given our estimates of prevalence, sensitivity, specificity, and the total available number of swabs in 21 practices in one season, we would expect to observe approximately 211 POCT true-positive RSV cases, which is sufficient to meet our primary objective of estimating the incidence proportion of POCT confirmed RSV.

We performed additional sensitivity analyses, keeping constant the number of swabs and prevalence of RSV, but assuming lower values of POCT sensitivity (90% and 80%) and estimated that 194 and 173 true-positive RSV cases would be detected, respectively. With smaller RSV case counts, SE of the incidence proportion (primary objective) would remain very similar and precise enough to generate meaningful inferences.

We have previously found that RCGP RSC practices using a POCT to diagnose respiratory viruses collect on average 6 swabs per practice per week over the winter season [31]. Thus, for our study in 21 practices over 12 months, we estimate that the target of 3600 swabs would be achievable.

Covariate Ascertainment

Tables 2 and 3 show the covariates we will use for this study which are known to be associated with the incidence and severity of respiratory syncytial virus [32].

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Table 2. Covariates associated with the incidence and severity of the respiratory syncytial virus.

Covariate	Categories
Age	• As whole years • 5-year increments (broader 10-year age bands may be considered)
Sex	• Male or female
Ethnicity	• White, Asian, Black, other, or mixed
Region	• Divided into areas served by an integrated care system
Urban or rural designation	• Urban or rural
Household composition	• Divided into categories 1, 2, 3, 4-5, 6-10, 11, or more
Socioeconomic status will be measured using the index of multiple deprivation [32]	• Quintiles from 1 (most deprived), 2, 3, 4, and 5 (least deprived)
BMI	• Obese or not obese (BMI ≥ or <30), • Also stratified as <18.5, 18.5-24.9, 25.0-29.9, 30.0-39.9, 40.0, or more)
Smoking status	• Current smoker, previous smoker, or nonsmoker
Cambridge Multi-Morbidity Score	• Quartiles • No comorbidities, 1, 2, 3, 4, or more comorbidities
Comorbidities known to relate to increased risk of severe respiratory illness, or suboptimal vaccine response, or vaccine contraindication	• Chronic respiratory disease • Chronic obstructive pulmonary disease • Chronic heart failure • Chronic heart disease and vascular disease • Chronic kidney disease • Chronic liver disease • Chronic neurological disease • Diabetes mellitus • Severe mental illness • Morbid obesity • Asplenia, or dysfunction of the spleen, immunosuppression due to disease, or treatment
Vaccination status within the season	• Influenza vaccination • COVID-19 vaccination • Pneumococcal vaccination

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Table 3. Covariates and categories.

Covariates	Categories
Age	• As whole years • 5-year increments (broader 10-year age bands may be considered)
Sex	• Male or female
Ethnicity	• White, Asian, Black, other, or mixed
Region	• Divided into areas served by an integrated care system
Urban/rural designation	• Urban or rural
Household composition	• Divided into categories 1, 2, 3, 4-5, 6-10, 11, or more
Socioeconomic status will be measured using the index of multiple deprivation [32]	• Quintiles from 1 (most deprived), 2, 3, 4, 5 (least deprived)
BMI	• Obese or not obese (BMI ≥ or <30) • Also stratified as <18.5, 18.5-24.9, 25-29.9, 30-39.9, 40, or more)
Smoking status	• Current smoker, previous smoker, or nonsmoker
Cambridge Multi-Morbidity Score	• Quartiles • No comorbidities, 1, 2, 3, 4, or more comorbidities
Comorbidities known to relate to increased risk of severe respiratory illness or suboptimal vaccine response or vaccine contraindication	• Chronic respiratory disease • Chronic obstructive pulmonary disease • Chronic heart failure • Chronic heart disease and vascular disease • Chronic kidney disease • Chronic liver disease • Chronic neurological disease • Diabetes mellitus • Severe mental illness • Morbid obesity • Asplenia or dysfunction of the spleen, immunosuppression due to disease, or treatment
Vaccination status within the season	• Influenza vaccination • COVID-19 vaccination • Pneumococcal vaccination

Statistical Analyses

For the primary objective, the incidence proportion of virologically confirmed RSV will be calculated as the number of swabs testing positive for RSV in the POCT, divided by the number of people fully registered at all 21 sites each month. Exact 95% CIs will be estimated using the Wilson method [33]. We will also calculate percent positivity as the number of positive cases divided by the number swabbed. Estimates will be presented overall and by key demographic and patient characteristics as defined above. Incidence proportions will be calculated by time (eg, moving average and monthly) depending on the sample size.

To approximate the response rate, and investigate potential selection bias, and external validity, we will compare the characteristics of patients for whom a swab was taken, with those who are ≥40 years presenting with an ARI code in the participating practices, and in the whole RSC network, respectively. This analysis will be restricted to the same study period.

For secondary objective 1, the incidence proportions (and 95% CI) estimated from the primary objective will be standardized (using the direct method) to the UK general population based on age or sex distribution [34].

For secondary objective 2, incidence proportions (and 95% CI) of RSV-LRTI will be calculated by dividing the number of cases meeting each of the three case definitions by the number of people at risk, for example, in a subgroup of interest.

For secondary objective 3, descriptive statistics (mean [SD], median [IQR], range [minimum and maximum], frequency [percentage]) will be used to describe the patient's clinical features at presentation, for all patients and RSV-positive patients (eg, signs and symptoms; Textbox 1). For reference, the same information will be presented for patients with ARI who test negative for RSV. We will adjust for variables that are hypothesized to lead to the development of symptoms as well

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as RSV positivity. Crude and adjusted odds ratios and 95% CIs indicating the association between these variables and testing positive for RSV (vs testing negative) will be presented.

For secondary objective 4, descriptive statistics will be used to describe the patient covariates listed in Table 2. These covariate characteristics will be examined among all patients, with the information presented according to POCT status (ie, RSV-positive and RSV-negative). As in secondary objective 3, logistic regression will be used to estimate crude and adjusted odds ratios.

For secondary objective 5, the clinical and economic burden of RSV will be assessed by comparing the number of health care visits (eg, visits to the general practitioner, hospitalization, and intensive care unit visits), medication use (eg, antiviral and antimicrobial therapy), receipt of ventilation and supplemental oxygen use up to 6 months after the swab. Additional outcomes of interest will include primary care costs, prescription costs, medical test costs, and secondary care costs.

Our approach to the analysis will depend on the type of outcome variable. For instance, cumulative health care resource costs covering primary and secondary health care services for the cohorts will be calculated for each patient by attaching unit costs to each service encounter. This will enable us to present initial estimates of the costs associated with health care usage across each group in terms of means, SD, median, IQR, minimum, and maximum. We will examine the distribution of the health care costs to identify outliers. This information will be presented according to POCT status (ie, RSV-positive and RSV-negative) and further, by the subgroup of interest. These steps will ensure that we fully comprehend the nature of the cost data [35].

Ethical Considerations

Data for the study are held on dedicated secure servers within the ORCHID TRE. The Research Group's secure network is sited behind a firewall within the University's network. Only staff members or associated members of the Research Group who have been appropriately trained and approved by the Head of Department can access the data from secure workstations or secure laptops with encrypted drives. All staff members of the Research Group working within the team base work from secure workstations or secure laptops with encrypted drives within the Research Group's secure network. The staff of the study sponsor will be provided with aggregate-level study data only. A risk assessment of the physical security of the Research Group's offices and server room has been conducted by the Building and Facilities Manager, the Faculty IT Service Manager, and the Research Group's Information Governance Lead. The University is compliant with the Data Protection Act and UK General Data Protection Regulation and has systems for technical and organizational controls for information security, including a University-level Information Security and Governance Group, chaired by the University Senior Information Risk Owner. The Research Group's private network has its own system-level security policy and is tested for vulnerabilities annually.

Study practices are given a stipend to cover the costs of training staff members and hosting the study. A small remuneration is also provided to practices for each POCT swab and reference laboratory virology sample taken to cover the additional time taken during each consultation to undertake swabbing for this study. Patients are not remunerated for taking part in this study.

The study received ethical approval for England and Wales from the Health Research Authority and Health and Care Research Wales on September 14, 2023 (Integrated Research Application System project ID: 329790, south central Oxford A Research Ethics Committee reference number 23/SC/0320).

The study and data extract were approved by the ORCHID Caldicott Guardian, the Primary Care Hosted Research Data sets Independent Scientific Committee of the Nuffield Department of Primary Care Sciences at the University of Oxford on November 7, 2023 (application reference PD-0030-2023).

Protocol Amendments

Important protocol amendments will be referred to the English National Research Ethics Committees for ethical approval. Once approved, it will be communicated directly with the recruiting study practices. The amended protocol will be shared with all relevant parties, for example, investigators and clinical research networks in a timely manner.

Results

We have received expressions of interest from 25 practices and have purposively recruited 21 practices from across the English health administrative regions.

In the 2023-2024 winter season, RSV detection in the sentinel network grew between October and late November. According to data from the UKHSA, the peak RSV swab positivity was in International Organization for Standardization week 48, 2023 (Figure 3 [36]). Data collection remains ongoing, and results from the subset of practices participating in this study are not yet available.

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Figure 3. The UK Health Security Agency virology swabbing positivity in 2023-2024 [36].

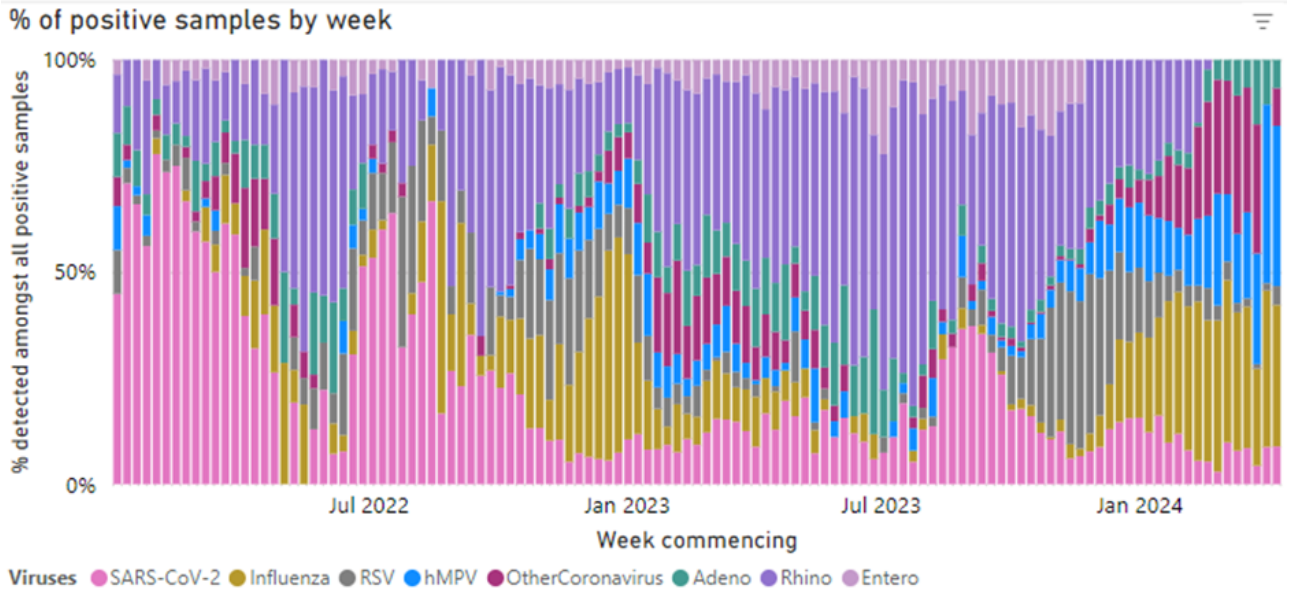

Discussion

Anticipated Findings

This study will generate contemporary data about the clinical presentation and disease burden of RSV among middle-aged and older adults in the community. Our primary outcome is the incidence of virologically confirmed, symptomatic, RSV infection presenting to primary care providers in England.

This study has a number of limitations. First, even with a sampling of 3600 eligible patients with ARI, it is expected that this study will only yield approximately 200 positive cases of RSV with the POCT. While this would be enough to estimate the incidence of RSV cases presenting to primary care with sufficient precision, the low number of cases could impact the number of covariates that we can adjust for in secondary objectives, as well as the estimation of ORs for categories with low frequencies (eg, underweight BMI category) and our ability to conduct subgroup analysis.

Second, there is inherent variation in clinical assessment and, thus, the decision to swab an eligible participant and exclude anyone with an illness due to another plausible diagnosis may potentially introduce bias. To minimize this variation, we will have robust site training available at the start of the study and throughout for new members of staff. We will also quantify any individual selection bias by comparing the characteristics of eligible swabbed and unsampled patients in POCT practices.

Third, a limitation of our opportunistic sampling strategy is that we will sample both fully registered and temporarily registered patients from study practices with eligible symptoms. Temporarily registered patients may include people at increased risk of infection or severe consequences of infection as well as people with less available information in their medical records such as refugee populations. We will quantify the effect this may have by comparing the characteristics of fully registered and temporarily registered patients in POCT practices.

Fourth, the study practices are not randomly selected so the results from the POCT surveillance cohort will not generalize beyond the selected clinics. To quantify any practice selection bias, we will compare the characteristics of patients for whom a swab was taken, with those presenting with an ARI code in the 21 participating practices, and in the whole RCGP RSC network, respectively.

Finally, the use of nasopharyngeal sampling is invasive and uncomfortable for the patient and it requires a trained provider to perform the collection. This may negatively impact the sensitivity of POCT in this older adult population, potentially biasing incidence estimates downwards. However, nasopharyngeal swabs have been validated for the detection and quantification of respiratory viruses [25,26]. They are considered the most accurate method for sampling RSV and practices in the Oxford-RCGP RSC sentinel network have many years of experience with undertaking nasopharyngeal swabs as part of national virological respiratory disease surveillance, which should reduce this risk [21,25,26]. In addition, where the virus has progressed lower in the respiratory tract, a nasopharyngeal swab may not detect these cases and a sputum sample may be required.

The limitations of the study must be considered in the context of its strengths. First, the study is nested within the English sentinel network, which includes participating practices that have developed expertise in identifying respiratory infections for the past 5 decades [21] and have a robust reporting infrastructure that supports rapid, accurate respiratory disease surveillance.

Second, the study uses a robust reverse transcription-polymerase chain reaction multiplex POCT platform that is rapid, accurate, cost-effective, simple to use, and reliable, and will provide viral positivity results for RSV, influenza, and SARS-CoV-2.

Third, the study leverages the NHS data system and a broader network of virology testing within the sentinel surveillance network to expand the breadth of the dataset (eg, clinical, economic, and humanistic variables) and ensure broader

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applicability of findings. Thus, we will have the opportunity to leverage the broader dataset of laboratory results and other data from patients from outside the 21 clinical sites in the analysis as needed.

Conclusion

We have started to deploy POCT for RSV in primary care and believe that if done at scale, POCT may provide data on the RSV incidence in the community as well as rapid information to inform sentinel surveillance. This information may also provide data to inform decisions about the benefits of a UK-wide RSV vaccination program for the adult population.

Acknowledgments

We would like to thank participating practices for sharing data and patients and their carers for volunteering to participate in this study. Magentus and Egton Medical Information Systems for their collaboration with pseudonymized data extraction.

Moderna funded and sponsored this study, and reviewed and proposed edits to the study protocol and study documents before submission for ethics approval and peer review publication.

Data Availability

The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request and with permission of RCGP RSC [37].

Conflicts of Interest

SdL is the director of the Oxford RCGP Research and Surveillance Centre. Through his university he has received funding for vaccine-related research from AstraZeneca, GlaxoSmithKline (GSK), Sanofi, Seqirus, and Takeda; he has been a member of advisory boards for AstraZeneca, Sanofi, and Seqirus. UH has undertaken continuing professional development podcasts funded by Seqirus and has been a member of advisory boards for Jansen. JR, ABA, CAP, OB, MD, AE, TL, and DM are employees and/or potential owners of Moderna stock.

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Abbreviations

ARI: acute respiratory infections
CMR: computerized medical record
HES: hospital episode statistics
HRG: health care resource groups
ICD-10: International Statistical Classification of Diseases, Tenth Revision
LRTI: lower respiratory tract infection
NHS: National Health Service
ORCHID: Oxford-RCGP Clinical Informatics Digital Hub
POCT: point-of-care test
RCGP: Oxford-Royal College of General Practitioners
RSC: Research and Surveillance Centre
RSV: respiratory syncytial virus
UKHSA: UK Health Security Agency

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Protocol

Use of Machine Learning to Predict Individual Postprandial Glycemic Responses to Food Among Individuals With Type 2 Diabetes in India: Protocol for a Prospective Cohort Study

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Abstract

Background: Type 2 diabetes (T2D) is a leading cause of premature morbidity and mortality globally and affects more than 100 million people in the world's most populous country, India. Nutrition is a critical and evidence-based component of effective blood glucose control and most dietary advice emphasizes carbohydrate and calorie reduction. Emerging global evidence demonstrates marked interindividual differences in postprandial glucose response (PPGR) although no such data exists in India and previous studies have primarily evaluated PPGR variation in individuals without diabetes.

Objective: This prospective cohort study seeks to characterize the PPGR variability among individuals with diabetes living in India and to identify factors associated with these differences.

Methods: Adults with T2D and a hemoglobin A_{1c} of ≥7 are being enrolled from 14 sites around India. Participants wear a continuous glucose monitor, eat a series of standardized meals, and record all free-living foods, activities, and medication use for a 14-day period. The study's primary outcome is PPGR, calculated as the incremental area under the curve 2 hours after each logged meal.

Results: Data collection commenced in May 2022, and the results will be ready for publication by September 2025. Results from our study will generate data to facilitate the creation of machine learning models to predict individual PPGR responses and to facilitate the prescription of personalized diets for individuals with T2D.

Conclusions: This study will provide the first large scale examination variability in blood glucose responses to food in India and will be among the first to estimate PPGR variability for individuals with T2D in any jurisdiction.

Trial Registration: Clinical Trials Registry-India CTRI/2022/02/040619; https://tinyurl.com/mrywf6bf

International Registered Report Identifier (IRRID): DERR1-10.2196/59308

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KEYWORDS

diabetes; T2DM; diabetes management; food responsiveness; postprandial glucose response; food intake; diet logs; dietary intake; machine learning

Introduction

Type 2 diabetes mellitus (T2D) is the leading cause of chronic kidney disease, end-stage renal disease, blindness, and nontraumatic amputation; it also substantially increases the risk of myocardial infarction, stroke, and heart failure [1]. Its prevalence is particularly high in India, which is now the most populous country in the world. As of 2023, more than 100 million people living in India have diabetes, representing more than 11% of the population and an additional 136 million have

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prediabetes [2]. These numbers are anticipated to continue to grow rapidly. The lifetime risk of T2D among 20-year-olds who are obese and living in India is estimated to be more than 86% [3]. The rising prevalence of this condition in India is believed to be the result of changing diets, increasingly sedentary occupations, lower levels of physical activity in the context of urbanization, and rapidly increasing rates of obesity [4].

These trends are particularly concerning because of important differences between the presentation and consequences in T2D among individuals of South Asian origin compared with other racial and ethnic groups. These differences, which often referred to as the "Indian Phenotype" or "South Asian Phenotype" [5-7], are characterized by the onset of T2D at a younger age and substantially lower BMI than people of other races and ethnicities [8-10]. Individuals of Indian origin have higher levels of insulin resistance (and for longer periods of time) and premature beta-cell failure [7]. They are more likely to develop the fatal complications of T2D, most notably heart disease [7]. These features are thought to result from a mix of lifestyle, epigenetics, and fetal programming factors [7,11,12].

The fundamental goal of diabetes management is to maintain near-normal glucose levels. A variety of self-management behaviors, in particular adherence to diet and regular exercise, are central to this goal. An extensive body of evidence demonstrates that aiding patients with T2D with self-management behaviors is associated with improvements in a wide range of outcomes including knowledge, self-care behaviors, weight, quality of life, hemoglobin A_{1c} (HbA_{1c}), all-cause mortality, and health care costs [13,14].

Guidelines recommend that nutritional guidance be personalized based on nutritional status, lifestyle, and metabolic goals [15]. Despite this, most dietary advice for individuals with T2D remains generic emphasizing reductions in calories and minimization of carbohydrates [16]. However, there are marked interindividual responses in postprandial glucose response (PPGR) [17]. A study conducted in Israel found substantial PPGR variability to standardized meals for individuals without diabetes [18]. Similar data has been generated in the United Kingdom, the United States, and China [19-21].

There have been no studies characterizing food responsiveness among individuals living in India and virtually no published data, from any judication, in the variability in PPGR for individuals with T2D [22]. Given the unique Indian diabetes phenotype and differences between Indian and western diets, in specific much higher rates of carbohydrate consumption overall [23] and the centrality of white rice and refined wheat [24], there are very likely to be differences in blood glucose responses to food and exercise in India than observed elsewhere, just as there have been in Indians' responses to diabetes medications [25]. Accordingly, the goal of this study is to characterize and identify factors associated the variability in PPGR among individuals with T2D in India.

Methods

This prospective cohort study seeks to evaluate the relationship between PPGR and self-management activities including diet, exercise, and other daily routines, for individuals with T2D in India (Figure 1).

Figure 1. Overall study design.

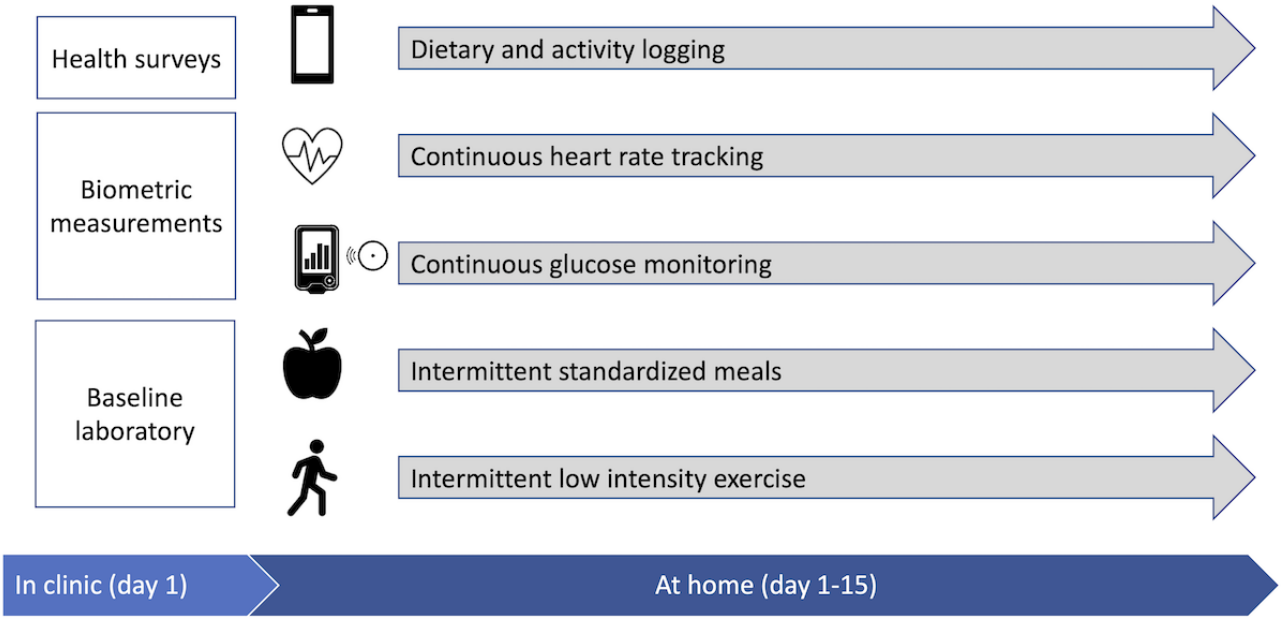

Study Setting

This trial is being conducted at 14 outpatient clinics in geographically distinct regions across India with population sizes ranging from 1.2 to 34 million. Sites were identified and managed by IQVIA, a multinational contract research organization, and were included if they specialized in the care of individuals with diabetes, had an established research infrastructure for the conduct of diabetes-related studies including a site principal investigator who is a diabetologist (with clinical training in endocrinology or internal medicine), a local ethics committee to provide study oversight, and a sufficient volume of potentially eligible patients. Study enrollment began in May 2022.

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Eligible Participants and Enrollment

The study population consists of adults with diabetes and suboptimal disease control, classified as HbA_{1c} ≥7. Complete inclusion and exclusion criteria are summarized in Textbox 1.

Textbox 1. Eligibility criteria required for participants to be enrolled in the study.

Inclusion criteria

- Age ≥ 18 and <75 years.
- Physician-diagnosed type 2 diabetes treated with ≥1 oral hypoglycemic agents
- Hemoglobin A_{1c}≥ 7.0% recorded within the past 30 days.
- Mobile phone capable of running protocol-specified apps.
- Functional English literacy.

Exclusion criteria

- Unable or unwilling to provide informed consent or comply with the study-specified procedures.
- Current use of prandial insulin including a continuous insulin infusion pump.
- Currently pregnant or planning to become pregnant.
- Estimated life expectancy of ≤12 months.
- Active cancer.
- Myocardial infarction or stroke in the last 6 months.
- Receiving or planned to initiate dialysis for end-stage renal disease.
- Receiving oral or intravenous steroids.
- Any contraindication to using a continuous glucose monitor.

Potentially eligible patients are identified from clinic records and are invited to attend an in-person screening visit at which time eligibility is confirmed and written informed consent obtained. Consenting patients are asked to provide sociodemographic and medical information (specifically, age, sex, predominant diet, health conditions, family history, and current medications) and to complete baseline surveys including the World Health Organization's STEPwise Approach to Non-Communicable Disease Risk Factor Surveillance (STEPS) survey [26], World Health Organization-Five Well-Being Index (WHO-5) [27]. Diabetes Distress Scale [28], Wilson Adherence Scale [29], and the Pittsburgh Sleep Quality Index [30].

Biometric data including blood pressure, heart rate, weight, height, and body measurements at the upper arm, thigh, calf, waist, and hips, are collected by study coordinators at each site. Finally, enrolled participants provide blood samples including a complete blood count, HbA_{1c}, blood electrolytes, creatinine, cholesterol, as well as urinalysis.

After completing baseline assessments, participants are fitted with an Abbott Freestyle Libre continuous glucose monitors (CGM) sensor on their upper, nondominant arm and are provided with a Xiaomi Mi Band Smart Wristband (heart rate monitor) and a Roche Accu-Chek glucometer with testing supplies, and dietary supplements to be consumed with their standardized meals (refer to Follow-up Procedures section). Study-specific apps are downloaded on to the participants' smartphones to allow them to log dietary intake and synchronize their continuous glucose and heart rate monitors. As a back-up, participants are given a paper dietary logbook and a Freestyle Libre CGM reader with which to collect protocol-specified data.

Follow-Up Procedures

Participants are followed for 14 days. They are instructed to wear the CGM and heart rate monitor. The heart rate monitor is to be always worn, including during sleep, and only removed for recharging. Participants are also asked to check their capillary glucose on days 2 through 6 before breakfast and dinner.

Participants log their full dietary intake using the study app or logbook over the 14-day study period, including all standardized test meals and free-living foods (including snacks), beverages (including water), and medications. Participants also log all exercise.

Participants are required to consume protocol-specified meals and to perform light activity, as described in Table 1. The standardized meals consist of vegetarian breakfast foods which participants are to prepare in their homes.

The meals vary in their proportion of carbohydrate, fiber, protein, and fat (refer to Table 2).

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Table 1. Meal schedule during the at-home study period.

Day and timing	Meal type
1	
Breakfast	Fasting
Lunch	As desired
Dinner	As desired
2	
Breakfast	Perceived healthy meal
Lunch	Post meal exercise
Dinner	Typical mixed protein with dinner
3	
Breakfast	Fiber supplement with standardized test meal
Lunch	Premeal exercise
Dinner	Alternative mixed protein with dinner
4	
Breakfast	Fiber supplement before standardized test meal
Lunch	As desired
Dinner	As desired
5	
Breakfast	Protein supplement with standardized test meal
Lunch	As desired
Dinner	Alternative mixed protein with dinner
6	
Breakfast	Protein supplement before standardized test meal
Lunch	Added fiber with lunch
Dinner	Alternative mixed protein with added protein
7	
Breakfast	Regular breakfast
Lunch	Added fruit
Dinner	Cooled carbohydrate
8	
Breakfast	Regular breakfast with added protein
Lunch	Added fruit with protein
Dinner	Regular carbohydrate
9	
Breakfast	Protein followed by carbohydrate
Lunch	Water 30 minutes before lunch
Dinner	As desired
10	
Breakfast	Standardized test meal
Lunch	As desired including dessert
Dinner	Protein followed by carbohydrates and vegetables
11	
Breakfast	Standardized test meal with postmeal exercise

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Day and timing	Meal type
Lunch	As desired including desert and cinnamon
Dinner	Vegetables followed by protein then carbohydrates
12	
Breakfast	Standardized test meal with postmeal exercise
Lunch	As desired
Dinner	As desired finishing eating by 8 PM
13	
Breakfast	Water before late breakfast + postmeal exercise
Lunch	Low glycemic index lunch
Dinner	Low glycemic index dinner + finish dinner by 8 PM + exercise after meal
14	
Breakfast	Water before late breakfast + exercise after meal
Lunch	Low glycemic index lunch + exercise after meal
Dinner	Low glycemic index dinner + finish dinner by 8 PM + exercise after meal

Table 2. Nutritional composition of standardized test meals.

Meal characteristics	Meal type		
	Carbohydrate	Added fiber	Added protein
Example meal	2 aloo parathas with curd	2 aloo parathas with curd + fiber supplement	2 aloo parathas with curd + protein supplement
Energy (kcal)	474.4	506.4	594.4
Carbohydrate (g)	61.5	64.1	62.9
Fat (g)	12.5	12.5	14.6
Protein (g)	7.7	7.8	31.9
Fiber (g)	8.3	21.9	8.3
Carbohydrate (% energy)	51.9	50.6	42.3
Fat (% energy)	23.8	22.3	22.1
Protein (% energy)	6.46	6.05	21.4

Participants are instructed to fast for a minimum of 8 hours before and 3 hours after consuming the standardized breakfast meal; during these fasting periods, limit exercise and drink only still (not sparkling) water, tea, or coffee in moderation; and eat the meal, in its entirety, within 20 minutes. After completing the postmeal fasting period on standardized test meal days, participants may consume other foods as they normally would unless there are other meal modifications specified by the protocol later the same day.

On other days, participants are asked to consume normal foods with protocol-specified constraints. For example, on different days, participants vary the types of mixed protein (eg, different types of lentils with or without added protein), ordering with the type of foods consumed (eg, protein before carbohydrate vs protein with carbohydrate), consume water before their meal, go for a walk after eating, or eat what they perceive to be a healthy meal. Where applicable, participants are given several options as to which of their usual foods are acceptable for each protocol specified food modification.

During the follow-up period, participants are contacted by phone and text messages to ensure protocol compliance. For participants using the study-specific smartphone apps, a web dashboard is used to monitor the completeness of dietary logging and CGM scanning, with outreach to participants initiated when missing data is detected. Participants using paper logs and a CGM reader, and therefore for whom no dashboard information is available, are contacted daily to ask about protocol compliance. Ad hoc midstudy visits are used to further ensure accurate data collection. If the outreach identifies a problem with a CGM (ie, it was damaged, fell off, or malfunctioned), study staff provide a replacement within 24 hours during which time participants are asked to pause their meal protocol and restart once their CGM has been reapplied and recalibrated. If a test meal was not consumed as intended, participants are provided with the option to repeat the meal.

On day 15, participants are asked to remove their CGM. If need be, study staff help record or correct missing or inaccurate food, activity, and medication data.

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Statistical Analysis Plan

The study's primary outcome is PPGR. Following the Wolever and Jenkins method [31], as adapted by Zeevi et al [18], Mendes-Soares et al [20], and Berry et al [32], logged meal times and continuous glucose measurements will be used to calculate the incremental area under the curve. Before conducting analyses, meals logged less than 30 minutes apart will be merged and meals logged within 90 minutes of other meals will be removed. Meals that are very small (<15 g and <70 calories), very large (>1 kg), with implausibly low PPGR values (ie, a PPGR < 5 mg/dL·h after consuming ≥ 40 g of carbohydrates), that are incompletely logged, and which are consumed in the first and last 12 hours of the CGM connection will also be removed. To reduce noise, the median of all glucose values from the 30-minute period before the meal will be taken as the initial glucose level, above which the incremental area will be calculated. Meals that had incomplete glucose measurements in the time window of 30 minutes before and 2 hours after the logged mealtime will be filtered out.

Descriptive statistics will be used to plot the range of PPGRs responses to standardized test meals as well as the correlation between PPGR and the nutritional composition of the logged meals (ie, carbohydrates, fat, and protein).

A machine learning predictor will be developed based on stochastic gradient boosting regression (XGBoost, version 2.2.1; The XG Boost Contributors) [33] using the XGBRegressor class. PPGR will be predicted as the sum of predictions from thousands of decision trees. Trees will be inferred sequentially, with each trained on the residual of all previous trees. The features incorporated in each tree are selected by an inference procedure from features representing meal content (ie, calorie, protein, carbohydrate, and fiber content), meal timing, baseline demographics (ie, age, sex, predominant diet, health conditions, family history, and current medications), baseline survey results (ie, WHO STEPS, WHO-5, Diabetes Distress School, Wilson Adherence Scale, and Pittsburgh Sleep Quality), baseline biometric values (ie, blood pressure, heart rate, weight, height, and body measurements at the upper arm, thigh, calf, waist, and hips), baseline laboratory values (complete blood count, HbA_{1c}, blood electrolytes, creatinine, cholesterol, and urinalysis), as well as CGM, heart rate, and activity data.

Performance will be assessed by holding out 30% of the sample and using 5-fold cross-validation in which cross-validation participants are divided into 5 groups, the model will be trained on the other 4 parts. Random datasets of the same size as the original will be sampled with replacement from the original dataset, and the entire training and validation process will be repeated. The performance will be measured by the ability to accurately predict meals reported by the held-out participants. Prediction results will be aggregated, and Pearson product moment correlation with the measured PPGRs will be reported. The SE for the calculated performance will be assessed using at least a thousand iterations of bootstrapping until the errors stabilize. Model discrimination will be assessed using a binary cut-point for PPGR, set at the 50th percentile of all observed PPGR values, plotting a receiver operating characteristic curve (ROC) and then calculating the area under the ROC.

Sample Size Considerations

A total of 1050 individuals will be targeted for recruitment. Assuming a 5% loss to follow-up, this corresponds to 1000 evaluable individuals at the end of the study. The study has been designed to predict postprandial glucose responses based on individual characteristics and 1000 participants followed for 14-days will result more than 4 million glucose readings (assuming glucose readings from the CGMs every 5 minutes) and 42,000 meals (assuming 3 meals per participant per day). This volume of data will also provide more than 80% power to detect correlations of a magnitude of r=0.13 (R^2=0.02) with P<.005. We will also be sufficiently powered to detect effects of r=0.17 (R^2=0.03, ie, explaining 2.7% of interindividual variation) with P<.001, that is, accounting for 5000 independent hypothesis tests.

Ethical Considerations

This study was approved by the following ethics committees at all institutions enrolling patients: SShrey Hospital Institutional Ethics Committee (DHINDIA_2021_01A04), Inamdar Multispecialty Hospital Ethics Committee (DHINDIA_2021_01A04), Neelima Hospitals Institutional Ethics Committee (DHINDIA_2021_01A04), Jaipur National University Institutional Ethics Committee (JNUIMSRC/IEC/2022/06), Maharaja Agrasen Hospital Institutional Ethics Committee EP/F-174), Ganesh Shankar Vidyarthi Memorial Medical College Ethics Committee (EC/72/March/2022), Mar Augustine Golden Jubilee Hospital Institutional Ethics Committee (DHINDIA_2021_01A04), Medisys Clinisearch Ethical Review Board, Dayanand Medical College and Hospital Drug Trials Ethics Committee (DMCH/DTEC/2020/1242), Chennai Meenakshi Multispecialty Hospital Ethics Committee (CMMHEC/22/02), Sparsh Hospital Institutional Ethics Committee (ZZA78309), Medical College of Kolkata Institutional Ethics Committee (MC/KOL/IEC/SPON/1296/03/22), Ethics Committee Downtown Hospital, and CHL-Hospitals Integrity Ethics Committee.

Results

Data collection commenced in May 2022, and the results will be ready for publication by October 2025. Results from our study will generate data to facilitate the creation of machine learning models to predict individual PPGR responses and to facilitate the prescription of personalized diets for individuals with T2D.

Discussion

Study Implications

This study will provide the first large scale examination of variability in blood glucose responses to food in India and will be among the first to estimate PPGR variability for individuals with T2D in any jurisdiction. We hypothesize that there will be substantial interindividual variability in PPGR and that, based on the data collected from this study, machine learning models will be able to accurately predict individual PPGR responses.

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This will facilitate the prescription of truly personalized diets for individuals with T2D.

These results will be particularly important in the context of the rapidly rising prevalence of T2D in India [34]. Along with medications and physical activity, diet is a key tenant of effective blood glucose control [15]. Like in other jurisdictions, guidelines call for individualization of meal planning, which is sometimes referred to as "Medical Nutritional Therapy." Despite this, personalization of dietary plans are generally based upon broad constructs like age, activity level, health status, and preferences, and, for all patients, tend to emphasize overall calorie reductions and minimization of carbohydrate [16]. especially added sugars and refined grains, in favor of the consumption of nonstarchy vegetables and foods that are high in protein [35].

However, emerging data demonstrates that there are marked interindividual responses to food [17], attributed to differences in physical activity [36], gut microbiome [18,19,37], and genetics [38], including in variations in skeletal glucose transporters related to insulin resistance [39]. For example, a study conducted in the United States among nondiabetic individuals with a mean BMI of 27 found PPGR to a standardized meal of bagel and cream cheese ranged from 6 to 94 mg/dL·h [20]. A similar study conducted in Israel enrolled nondiabetic individuals of whom 3-quarters had a BMI ≥ 25 and found mean PPGR to bread and butter of 44 mg/dL·h but the bottom decile had responses of ≤ 15 mg/dL·h and the top decile has responses ≥ 79 mg/dL·h [18]. Similar data have been generated for individual without diabetes in the United Kingdom and the United States [19,20], and for individuals with type 1 diabetes in Israel [40].

There is exceptionally limited data for variability in PPGR for individuals with T2D in the peer-reviewed although it is highly likely that such variability exists [22]. The primary goal of our study is to fill this void and to generate an India-specific machine-learning models on the basis of which PPGR can be predicted with high accuracy for T2D. Similar models have been built in other jurisdictions. For example, a machine learning algorithm trained on CGM data, dietary, activity, anthropometrics, and gut microbiota for nondiabetic individuals in Israel was much more accurate at predicting PPGR than generic models based on the carbohydrate content or the amount of calories in a meal [18]. A separate US-based study had similar findings [20].

Among individuals with diabetes, a study in the Netherlands that included a small number of individuals with T2D along with individuals with prediabetes and normal glucose metabolism, a machine learning model based on CGM data was highly accurate in predicting future glucose values but this study did not specifically evaluate the ability to predict PPGR [41]. A US study of 1000 patients of whom 1-quarter had T2D found that a machine learning model trained on CGM, HRM data and food logs was highly accurate at predicting PPGR but this study has, to our knowledge, only been published in abstract form [22]. These studies have all relied on CGM data to make their predictions. While these devices are increasingly used, practice guidelines do not recommend their long-term use for most individuals with T2D [42]. Accordingly, a key goal of our study will be to explore the ability to predict PPGR response without reliance on CGM data or with very limited blood glucose data from patients.

Limitations

There are several limitations to our approach. Our approach is purposely pragmatic and is intended to simulate real-world circumstances for individuals with T2D living in India. Similar to studies conducted in other jurisdictions, we rely on self-reported dietary and activity information. And, while we are auditing patient logs on an ongoing basis, there may nevertheless be issues with protocol adherence that may undermine the accuracy of the data we collect. Participants are being recruited from clinics, predominantly caring for individuals with diabetes, are required to have functional English literacy and a cellphone capable of running study specific devices. Thus, our results may not be fully generalizable to patients who do not fulfill these criteria. Finally, some of the enrollment has overlapped with the COVID-19 pandemic, which may have influenced access to health care, dietary practices, and glucose control for individuals with T2D.

Conclusion

In conclusion, this study will provide the first large scale examination variability in blood glucose responses to food in India and will be among the first to estimate PPGR variability for individuals with T2D in any jurisdiction. Results from our study will generate data to facilitate the creation of machine learning models to predict individual PPGR responses and to ultimately facilitate the prescription of truly personalized diets for individuals with T2D.

Acknowledgments

The authors wish to thank the site investigators and patients participating in the study as well as IQVIA for their assistance identifying study sites and overseeing the study conduct. This work is supported by Decipher Health, Inc.

Data Availability

The datasets generated during and analyzed during this study are not publicly available as they will be used for commercial application. Data may be available on reasonable request after executing appropriate data use and licensing agreements.

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Authors' Contributions

All authors meet International Committee of Medical Journal Editors (ICMJE) criteria. NKC had overall responsibility for the study design and drafted the trial protocol and manuscript. MM is the co-principal investigator, had overall responsibility for the study design, and helped draft the study protocol and manuscript. SP and JS contributed meaningfully to study design and implementation as well as the manuscript. All authors contributed to the refinement of the study protocol and approved the final manuscript.

Conflicts of Interest

NKC and JS receive consulting fees and hold equity in Decipher Health. SP is an employee of Decipher Health. MM is an employee and holds equity in Decipher Health.

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Abbreviations

CGM: continuous glucose monitor
HbA_{1c}: hemoglobin A1c
PPGR: postprandial glucose response
ROC: receiver operating characteristic
STEPS: STEPwise Approach to Non-Communicable Disease Risk Factor Surveillance
T2D: type 2 diabetes mellitus
WHO-5: World Health Organization-Five Well-Being Index

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Protocol

Digital Home-Based Self-Monitoring System for People with Heart Failure: Protocol for Development of SmartHeart and Evaluation of Feasibility and Acceptability

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Abstract

Background: Heart failure (HF) is a chronic, progressive condition where the heart cannot pump enough blood to meet the body's needs. In addition to the daily challenges that HF poses, acute exacerbations can lead to costly hospitalizations and increased mortality. High health care costs and the burden of HF have led to the emerging application of new technologies to support people living with HF to stay well while living in the community. However, many digital solutions have not involved consumers and health care professionals in their design, leading to poor adoption. The SmartHeart project aimed to codevelop a smart health ecosystem to support the early detection of HF deterioration and encourage self-care, potentially preventing hospitalizations.

Objective: This study aims to provide an overview of the SmartHeart project by describing our approach to designing the SmartHeart system, outlining its features, and describing the planned pilot study to determine the feasibility of the system.

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Methods: We used the Integrate, Design, Assess, and Share (IDEAS) framework to guide the development of the SmartHeart system, involving users (people with HF and their caregivers) and stakeholders (health care providers involved in the management of HF) in its design. SmartHeart is a complete remote heart health monitoring and automated feedback delivery system. It includes 2 user interfaces for patients: an Amazon Alexa conversational agent and a smartphone app. The system collects physiological, symptom, and behavioral data through wireless sensors and self-reports from users. These data are processed and analyzed to provide personalized health insights, self-care support, and alerts in case of health deterioration. The system also includes a web-based user interface for health care professionals, allowing them to access data, send messages to users, and receive notifications about potential health deterioration. A single-arm, multicenter pilot trial (N=20) is planned to determine the feasibility and acceptability of SmartHeart before evaluation through a randomized controlled trial. The primary outcome will be a description of the study's feasibility (recruitment, attrition, engagement, and changes in self-care).

Results: The SmartHeart study started in January 2021 on procurement of funding. Recruitment for the pilot trial started in August 2024 and will be completed by March 2025. We have currently enrolled 12 participants. Follow-up of all participants will be completed by the end of May 2025.

Conclusions: We have co-designed and developed a complete remote heart health monitoring and automated feedback delivery system for the early detection of HF deterioration and prevention of HF-related hospitalizations. The next step is a pilot study, which will provide valuable information on feasibility and preliminary effects to inform a larger evaluation trial. SmartHeart has the potential to augment existing health services and help people with HF stay well while living in the community.

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KEYWORDS

smart home; health; chronic conditions; digital health; technology; behavior change; wearables; methodological considerations

Introduction

Burden of Heart Failure and Importance of Self-Care

Heart failure (HF) is a complex life-threatening syndrome associated with high mortality and morbidity, poor quality of life, diminished functional capacity, and substantial health care burden [1,2]. HF affects over 64 million people worldwide [1]. People with HF experience debilitating symptoms, including shortness of breath and fatigue, which significantly impact their daily activities and quality of life [3]. Beyond these persistent daily challenges, individuals experience acute exacerbations, that frequently necessitate hospitalization [4]. These hospitalizations are strongly correlated with increased mortality. In Australia, data indicates that individuals experiencing acute HF exacerbations requiring hospitalization face a 50% reduction in their remaining life expectancy (10 years for those aged 65-75 years) [5]. Research suggests that two-thirds of HF-related hospital admissions could be prevented by enhanced coordination of postacute care and improved self-care [3]. Self-care refers to the process of maintaining health through health promotion and preventive practice [3]. While international guidelines make self-care integral for HF management, people find managing their condition while living in the community difficult, and adherence to clinical guidelines is poor [3].

Toward a Smart Health Ecosystem

There is an urgent need for new scalable models of person-centered health care in which care for long-term conditions such as HF shifts from the clinic to the home [6]. The COVID-19 pandemic was a catalyst for swift, wholesale change to the way we view and provide health care; there has been a significant increase in the use of telehealth and online care services, increased acceptance of digital health technologies by the medical community and the public, and broader recognition of the need to embrace digital health approaches to create a resilient health care system [6]. However, despite the potential for digital health to improve HF management [7], previous approaches to designing digital health interventions have largely failed to include patients and clinicians [8]. This can lead to lower levels of program adoption by users and increased dissatisfaction, stress, and nonadherence [9].

We previously argued for a smart health ecosystem, a holistic approach to support people living with long-term conditions that incorporate sensing, processing, and communication technologies [7]. Such an ecosystem uses a comprehensive network of internet-connected sensors (referred to as the Internet of Things) to collect data about the patient in the home [10,11] and processes these data to provide near–real-time individualized monitoring. It also uses predictive models to anticipate the need for medical intervention (eg, when detecting warning signs of decompensation) and support with self-care activities. While many of these discrete technologies exist, we bring them all together into a single system (named SmartHeart) to support people to better manage their HF at home and in the community. It is proposed that such a system can help maintain health outcomes, improve quality of life, promote independence, and reduce carer burden [12,13].

In this article, we present an overview of the SmartHeart project and describe its design and development approach. We provide a detailed description of the SmartHeart system and outline the planned pilot study to evaluate its feasibility and acceptability.

Methods

SmartHeart Project

To guide the SmartHeart project, we used the Integrate, Design, Assess, and Share (IDEAS) framework [14]. The IDEAS

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framework is an intervention-specific framework for the development of digital interventions, fitting the nature of our proposed intervention [15]. Moreover, the framework combines behavioral theory with design thinking, which are complementary perspectives that can promote the acceptance and adoption of an intervention [15]. The IDEAS framework proposes ten steps: (1) empathize with target users, (2) specify target behavior, (3) ground in behavioral theory, (4) ideate implementation strategies, (5) prototype potential products, (6) gather user feedback, (7) build a minimum viable product, (8) pilot potential efficacy and usability, (9) evaluate efficacy in a randomized controlled trial (RCT), and (10) share intervention and findings [14]. In addressing steps 1-7 of the IDEAS framework, we undertook a range of studies to co-design and develop the SmartHeart system. As part of step 7, build a minimum viable product, we undertook an additional alpha- and beta-testing phase. The methods and results of these studies are briefly described in this article and the development studies are reported in full elsewhere [16,17]. The protocol for step 8 of the IDEAS framework, pilot potential efficacy and usability, is presented later in this article and will inform the design of a larger hybrid RCT to assess the effectiveness and implementation of SmartHeart, which we hope will guide subsequent delivery at scale. Figure 1 presents the phases of the overall SmartHeart project.

Figure 1. Phases of the SmartHeart project.

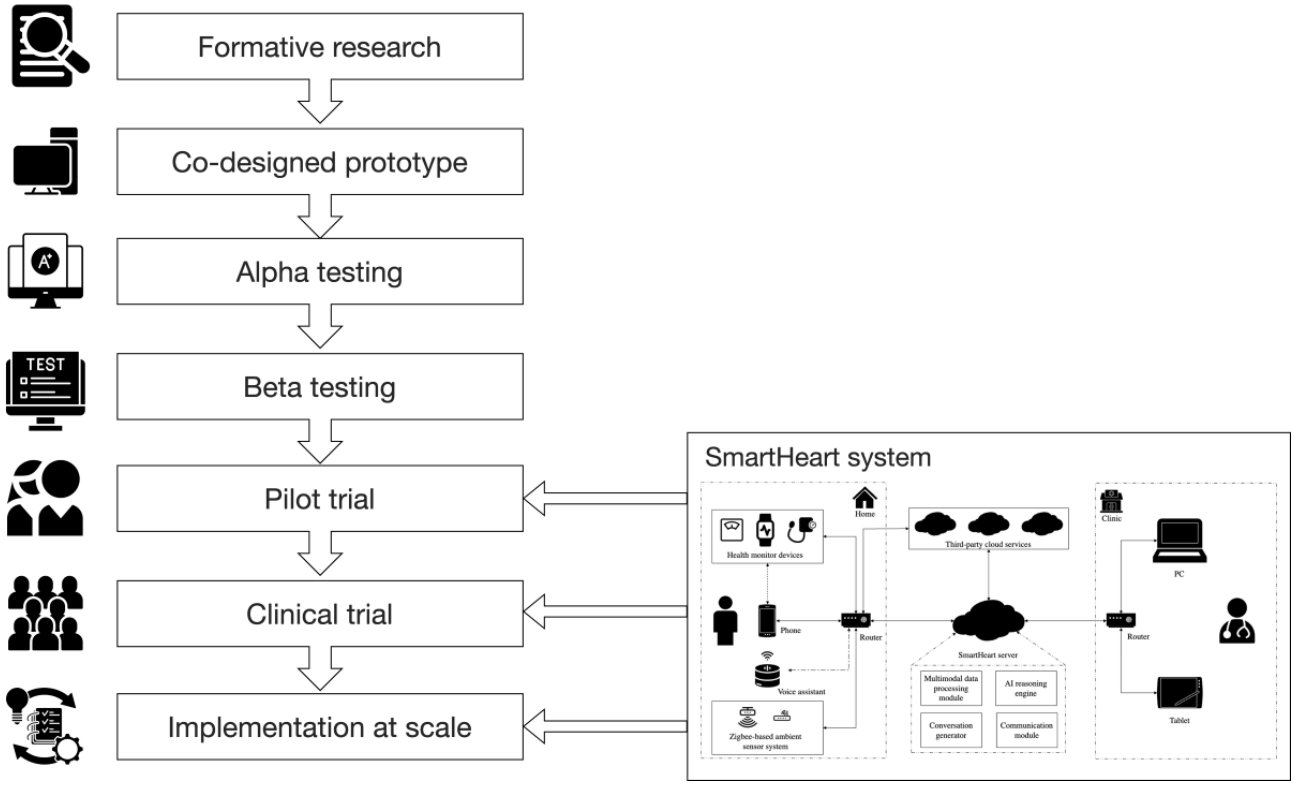

Approach to Designing the SmartHeart System

As part of the formative research phase, we conducted a scoping review of existing smart health ecosystems to support people with HF [18]. This study allowed us to identify data collection, personalization, behavior change, patient-facing, and mode of delivery features of similar interventions (refer to Figure 2). These features provided us with initial ideas for the SmartHeart system.

Then, we sought to better understand the lived experiences of individuals with HF in the community and the self-care strategies they used. This involved conducting in-depth interviews with individuals living with HF (n=9) [17]. Following this, we explored potential components and features for SmartHeart from the user perspective through workshops with individuals living with HF (n=16) and their caregivers (n=4) [16]. To identify consensus-based recommendations for potential intervention features, we used the Delphi method with 15 health care providers with experience caring for people with HF (eg, general practitioners (GP), cardiologists, nurses, pharmacists, and physiotherapists) [19]. We also conducted in-depth interviews with health care providers (n=9) [20].

Building upon these findings, we refined the SmartHeart prototype through a series of co-design workshops. Specifically, we conducted 4 co-design workshops with health care providers (n=15) to gain insight into how the system would work in practice and to refine the initial prototype [16]. Subsequently, 2 further co-design workshops were conducted with people with HF (n=6) to inform the user-facing app features, and optimize the overall design look, feel, and navigation logic.

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Figure 2. Intervention features identified in the scoping review.

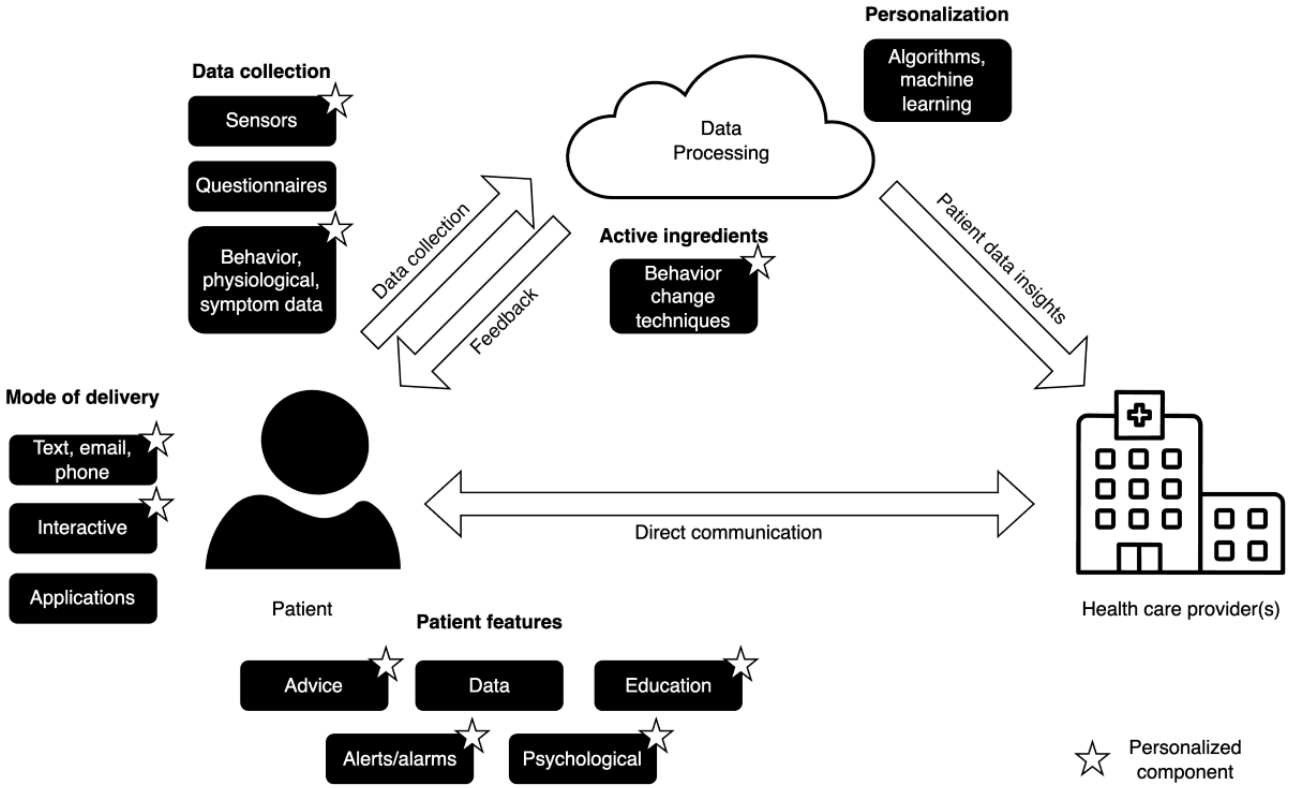

On completion of the SmartHeart prototype, we conducted alpha testing to evaluate the system's core functionalities, user interface, and performance under controlled conditions. For alpha-testing, four members of the research and development team used the system for 6 weeks, which allowed us to assess the system's responsiveness and identify and resolve any technical issues. Then, beta testing was undertaken to assess the system's responsiveness, data accuracy, and user experience. For beta testing, 5 people with HF used the prototype system for 4 weeks. Participant feedback from this testing was used to improve system onboarding, app performance, and data visualization.

SmartHeart System

In undertaking the design and development process outlined above, we developed the SmartHeart system (herein, SmartHeart), a smart health ecosystem to support the early detection of HF deterioration and prompt action by users with the aim of preventing HF-related hospitalizations. SmartHeart comprises components for patients (and their caregivers) and healthcare providers (ie, cardiologists, HF nurse practitioners, or other nurses).

Patient Components

User interface: Patients and caregivers interact with SmartHeart through an Amazon Alexa Echo Show 8 (second generation), featuring an 8-inch HD touchscreen, which serves as the primary user interface and conversational agent (Figure 3). In addition, a bespoke smartphone app (Figure 4), offers an alternative interface when Amazon Alexa is not available, such as when users are away from home. Amazon Alexa was selected based on access, ease of deployment, and programmability. In its current form, Amazon Alexa can facilitate interaction with people in their own language (currently 9 languages available). The smartphone app also supports multiple languages (for initial testing, we have included Hindi and Mandarin) and time zones.

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Figure 3. Screenshots of SmartHeart conversational agent.

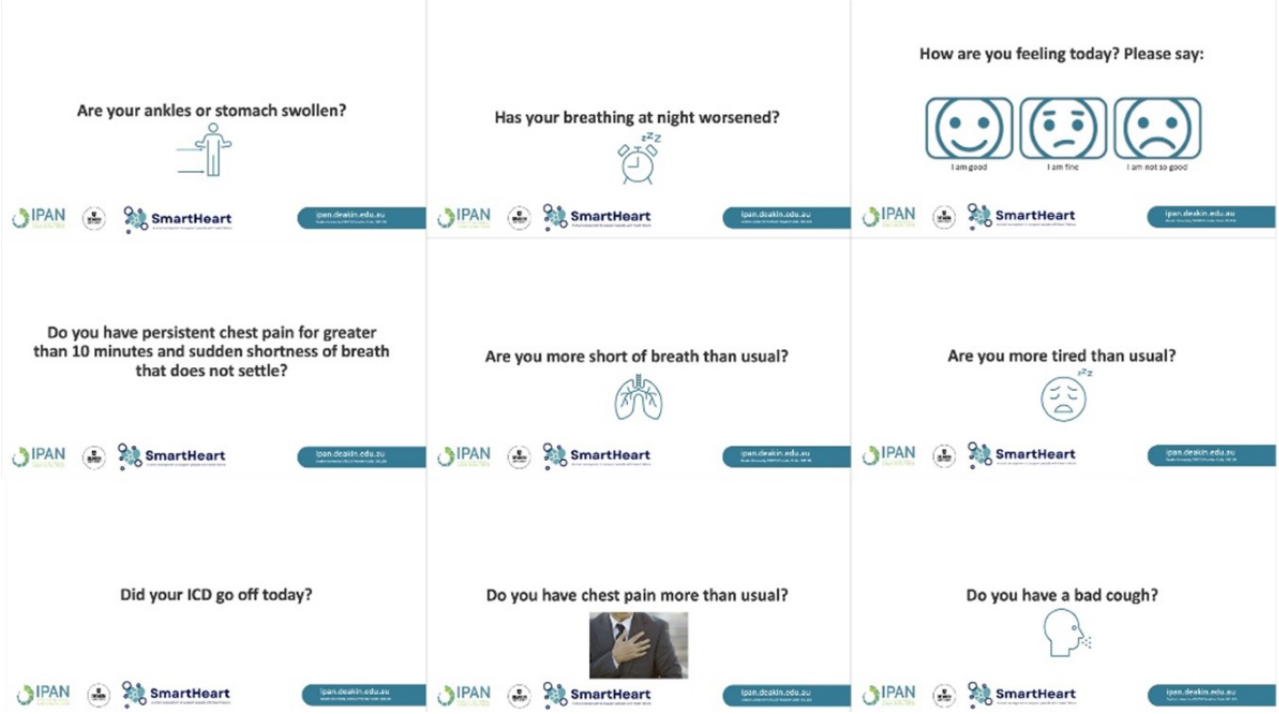

Figure 4. Screenshots of the SmartHeart app.

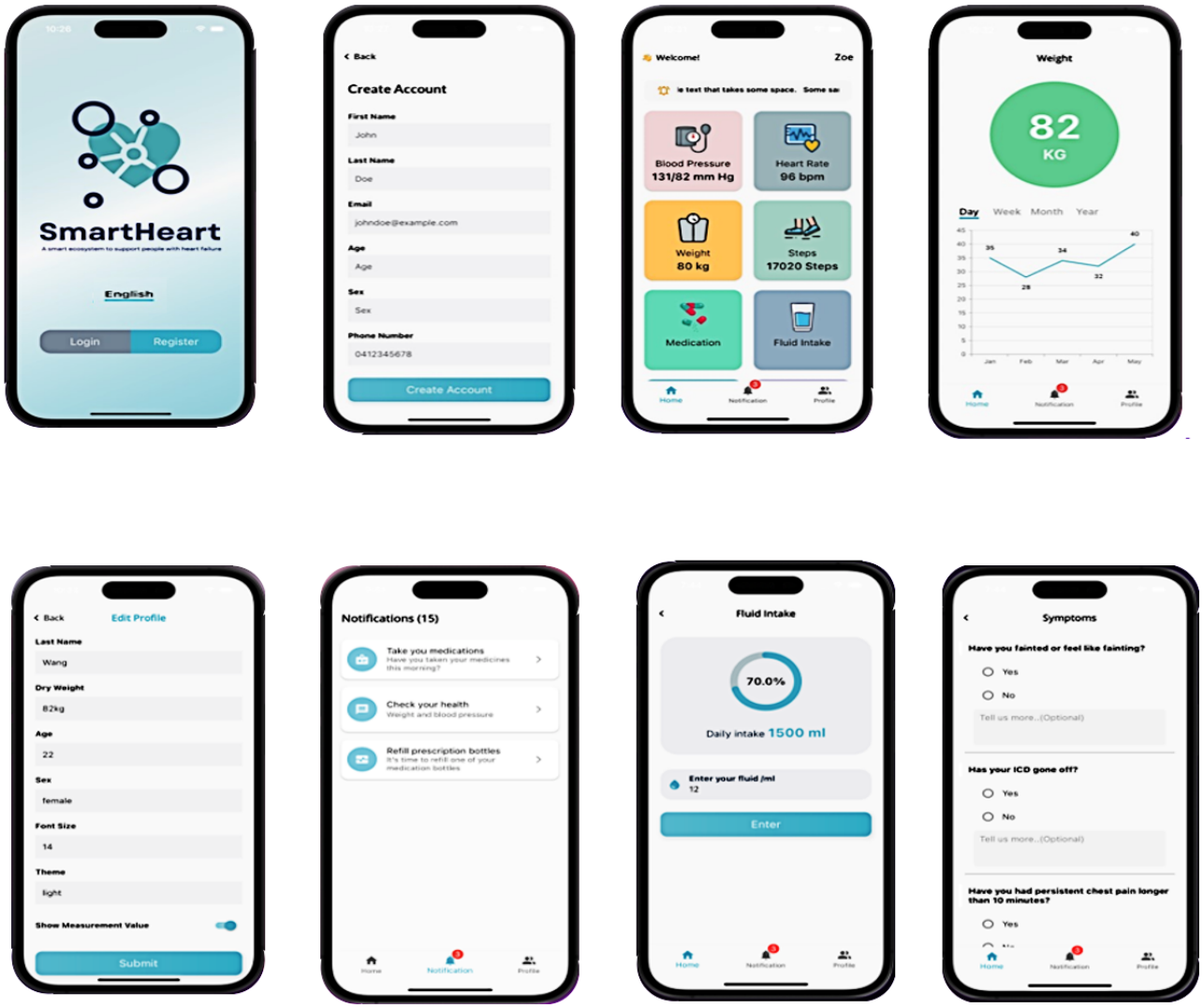

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Data Collection

SmartHeart will collect physiological, symptom, and behavioral data through wireless sensors and self-reports. The sensors included and the parameters they measure are outlined in Table 1. Users can also self-report symptoms at any time through the Amazon Alexa or smartphone app. Amazon Alexa will also periodically check in with users through timed ecological momentary assessments to gather feedback on symptoms [21]. The symptom questions are based on current practice, which involves people with HF completing a paper and pencil diary on standard symptoms (eg, shortness of breath, dizziness, cough).

To collect data on medication use, we use a proxy measure of medication access, as measured through a Philips Hue infrared motion sensor placed at the site of medication storage (eg, cupboard, drawer). This sensor will timestamp potential medication access. This approach was adopted to account for the heterogeneity of medications taken and strategies used by participants in managing their medications [16,17]. The pilot study described below will allow us to determine the feasibility of this approach. The motion sensor is connected to the Philip hub using Zigbee, a low-power wireless mesh network for connected devices. The Philips hub handles data transmission to the cloud.

Table 1. Wireless sensors and parameters measured.

Sensor	Parameter
Withings blood pressure monitor connects wireless blood pressure monitor	Blood pressure
Samsung Galaxy Watch Pro 5	Heart rate; activity levels (including physical activity, inactivity, and activities of daily living)
Withing's Body Smart Bluetooth scales	Weight
Phillips Hue infrared motion sensors	Medication access (as a proxy for medication use)

Support Features

The SmartHeart system offers a wide range of features aimed at supporting the early detection of HF deterioration and encouraging proactive self-care.

Through Amazon Alexa, users can access educational materials on topics such as healthy eating and heart health, and a home-based physical activity program. They can also set their own reminders for tasks such as taking medication, monitoring weight and blood pressure, monitoring mood, and attending health care appointments. Health data are presented to users in the form of graphs and charts, allowing them to track and self-monitor their health over time.

SmartHeart delivers alert messages according to a matrix of possible outcome states from all combinations of sensor and symptom measurements and a corresponding rule set to define conversational agent actions. We developed the matrix based on previous work [22], but it was modified to align with the Australian HF Guidelines [2]. Alert messages and actions associated with each outcome state were validated during a face-to-face user panel workshop with health professionals (cardiologists, HF nurses, physiotherapists) at 3 hospitals (Royal Brisbane and Women's Hospital, Bendigo Hospital, and Austin Hospital). For example, combinations of blood pressure, weight gain, and symptoms corresponding to a critical or urgent outcome state (Figure 5) will notify patients via the conversational agent (or smartphone app) to seek immediate medical support and prompt a text message to HF nurses to review data via the health care provider interface.

The numbers represented in Figure 5 are various patient alert messages (see Table 2).

Based on HF guidelines [2] and previous text messaging research in heart disease [23], we also developed a package of self-care support comprising data-driven and nondata-driven messages. In response to sensor data and self-reported symptoms, users will receive educational support and prompts to modify key self-care activities. For example, if the combinations of blood pressure, weight, heart rate, and symptoms correspond to a normal outcome state (Figure 5) users would receive personalized HF education. Alternatively, if low physical activity levels and high fluid intake were recorded, SmartHeart would prompt users to reduce fluid intake and increase their step count. This educational support and prompts will be delivered by the conversational agent or smartphone app.

In addition, users will receive regular unidirectional push notifications through the SmartHeart app only. These push notifications, delivered twice a week (1 message per day on Monday and Friday) are not data-driven and aim to encourage users to take their medication, eat a healthy diet (eg, low salt), manage their fluid intake, participate in physical activity, and reduce sedentary behavior (Textbox 1). Content for these nondata-driven notifications was adapted from our previous interventions [24,25]. Participants can opt in or out of receiving push notifications by toggling this feature on or off through the smartphone app.

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Figure 5. Matrix of outcome states from possible combinations of measurements. The numbers represented in Figure 5 are various patient alert messages (refer to Table 2). Ab: abnormal; BP: blood pressure; HR: heart rate; N/A: not applicable; N: normal.

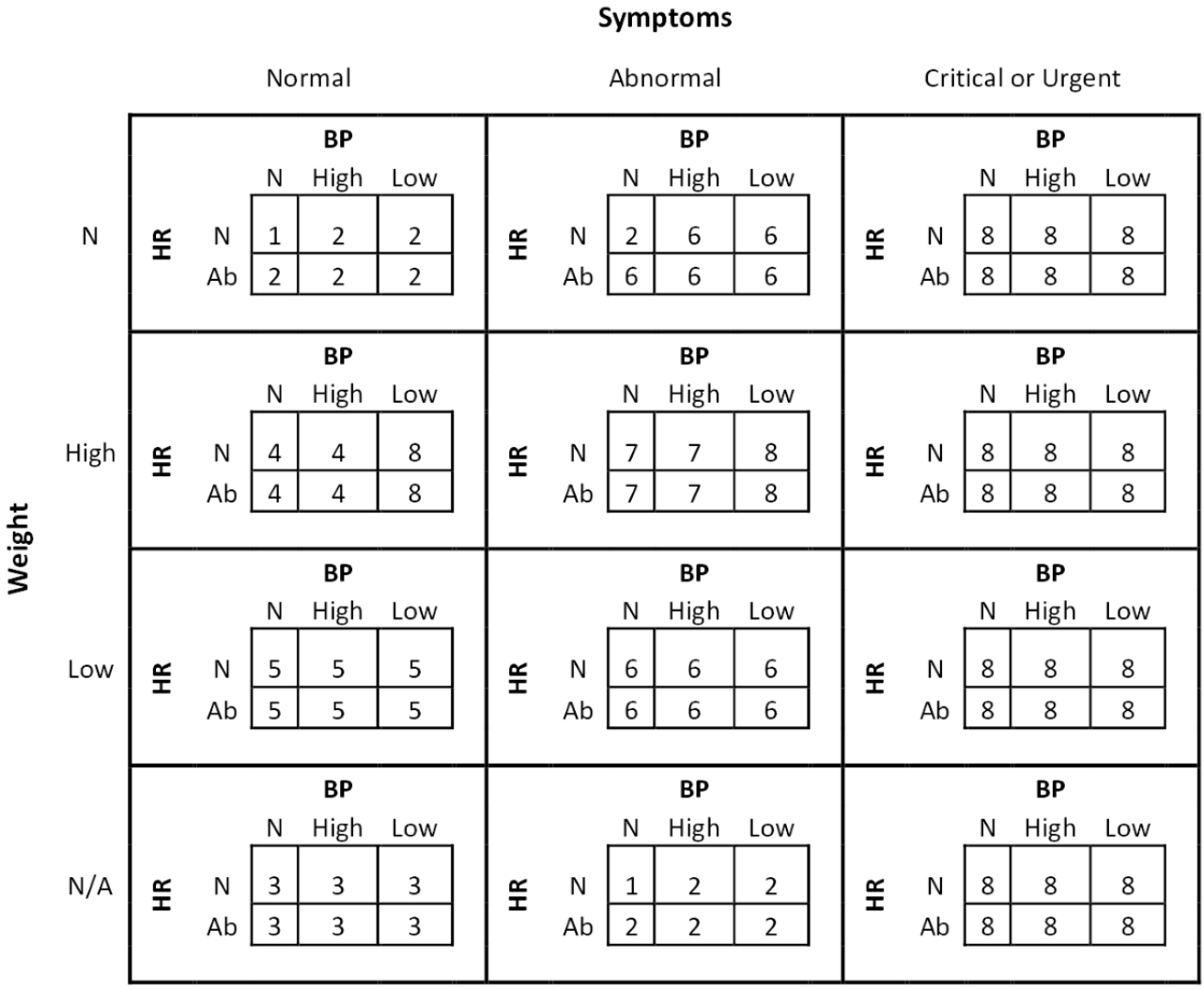

Table 2. Examples of alert messages provided through SmartHeart.

Message number	Example message
1	“Your measurements are fine today”
2-3	“If you feel worse later today, use the system to record your symptoms”
4-5	“Contact your Heart Failure Nurse or General Practitioner (GP). Follow doctor’s orders. Restrict salt and fluids.”
6-7	“Contact your GP now or go to the emergency department if you feel you should. Follow doctor’s orders. Restrict salt and fluids”
8	“Call 000 now”

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Textbox 1. Examples of regular SmartHeart unidirectional push notifications by category.

Health

- How much time do you spend sitting every day? Decreasing the amount of time you spend sitting can improve your heart health, even if you engage in regular exercise.
- Although physical activity is useful for heart health, taking the first step can be the biggest challenge. Choose a physical activity that you like, anything that makes you more active.
- Think about barriers that can stop you from being active. Choose an activity that is more fun. Some people find it useful to invite a friend or a family member to join their daily exercise.

Medication adherence

- Encountering obstacles with your medication regimen? You don't need to tackle these challenges by yourself. Your doctor is there to provide assistance.
- Consistently taking your medications is essential for effectively managing your heart condition and preserving the associated benefits.
- Consistently adhering to your medication regimen is essential in managing your condition. If you believe you're having side effects, it's crucial to discuss it with your doctor. They could recommend a different medication that suits you more effectively.

Refill prescription bottles

- Running out of your medication could lead to a few days without it, but this is a preventable situation. Stay prepared by marking your next prescription refill date on your calendar or setting a reminder on your mobile phone.
- Ensuring the continuous availability of your medications is a crucial measure, so be certain you're aware of the upcoming refill date. Incorporating a calendar reminder can be a valuable prompt when required.
- Think about where it would be most suitable for you to store extra medications as a backup strategy.

Health Care Provider Components

Health care providers (ie, cardiologists, HF nurse practitioners, or other nurses) access the SmartHeart web-based user interface to register participants, review health data, and view notifications patients have received. If necessary, and according to clinical practice, health care providers will contact patients directly by telephone (Figure 6).

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Figure 6. Health care provider interface.

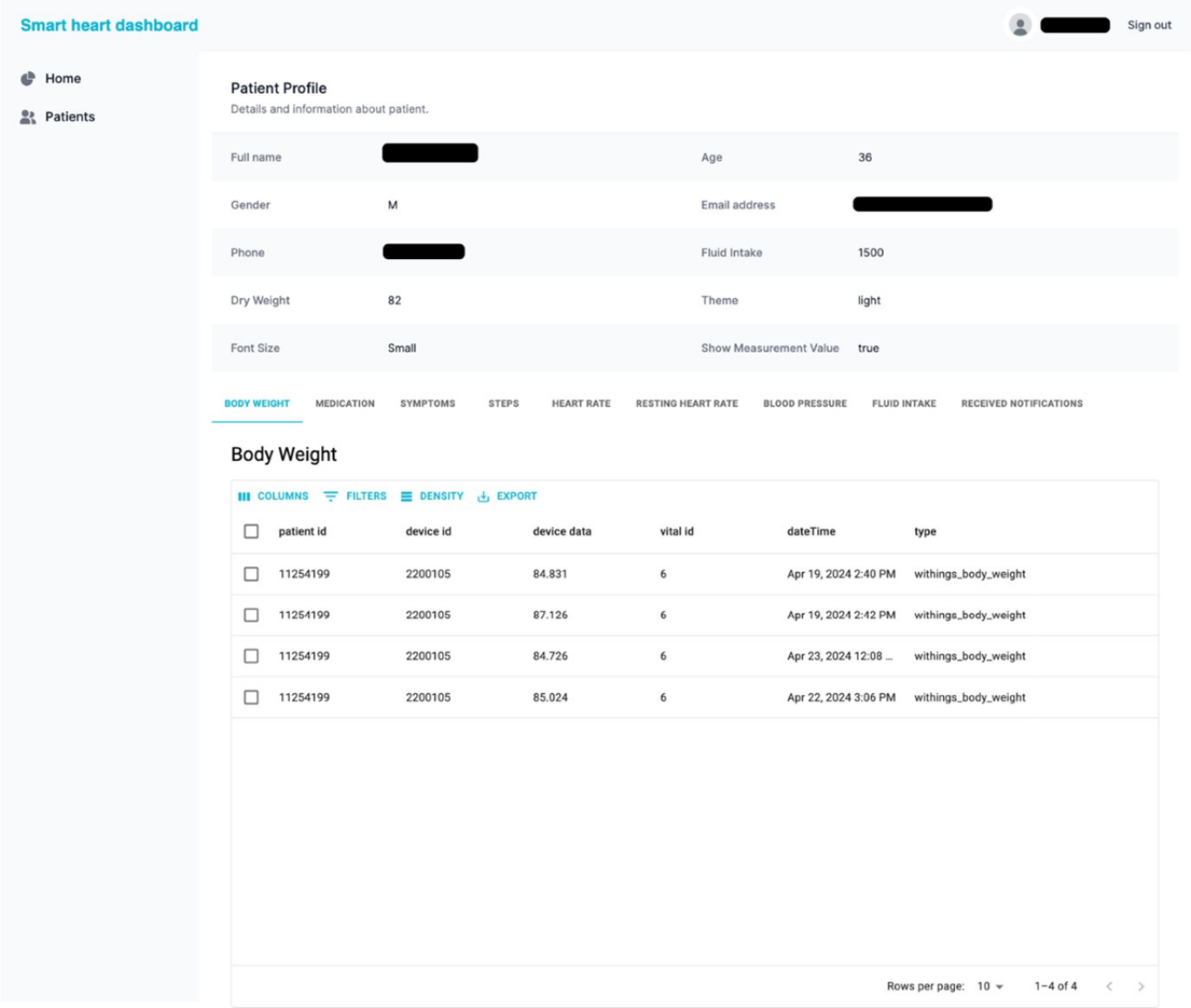

System Architecture and Functions

Cloud-to-cloud integration connects and transmits users' data from third-party (sensor vendor) clouds to the SmartHeart data processing server (Figure 7). This server processes multimodal data (ie, health monitoring device data and self-reported symptoms), and makes logical inferences to generate personalized recommendations for the users in different formats (ie, conversation and report). It also handles all data transmissions between end users and clinicians. Data collected through SmartHeart are stored in a secure cloud-based server hosted in Australia. All data capture, storage, and transmission are secured using state-of-the-art encryption technologies according to Health Insurance Portability and Accountability Act requirements.

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Figure 7. SmartHeart system architecture. AI: artificial intelligence.

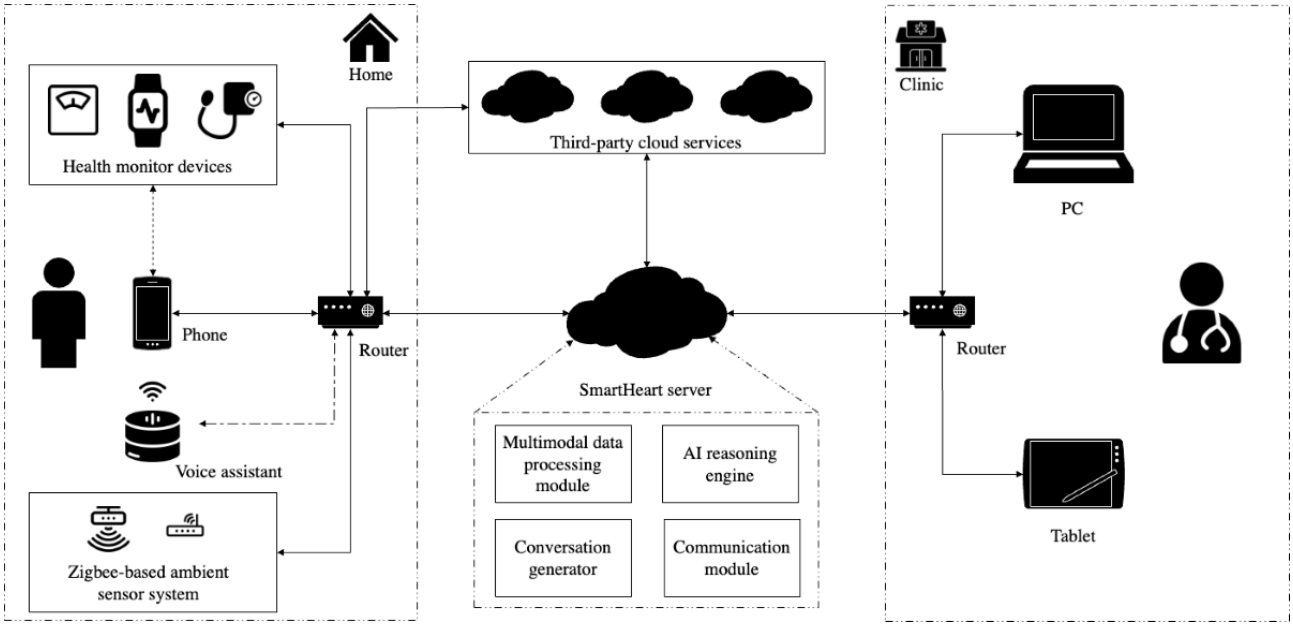

SmartHeart Pilot Study Protocol

Objectives

This pilot study aims to assess the feasibility and acceptability of SmartHeart and inform the design of a larger hybrid RCT to assess effectiveness and implementation outcomes.

Sample Size

The sample size for pilot feasibility studies should be based on practical considerations including participant flow, budgetary constraints, and the number of participants needed to reasonably evaluate feasibility goals [26]. For this study we aim to recruit a total of 20 participants, which will be sufficient to determine the feasibility of delivering SmartHeart, allowing for exploration of participant feedback regarding acceptability, usability, and uptake.

Participants and Eligibility Criteria

Participants will be 20 adults (aged 18 years or more) with a documented clinical diagnosis of HF, outpatients at the time of recruitment, with access to the internet, and able to read and understand the English language (for informed consent purposes) will be eligible. SmartHeart support is available in multiple languages, so people for whom English is not a first language can use it. Individuals will be excluded if they have difficulty communicating with study personnel or a conversational agent due to speech or untreated hearing problems; are planning to be away from home for ≥4 weeks during the intervention; have progressive neurological disorders including Parkinson Disease and multiple sclerosis; have schizophrenia or bipolar disorder; have renal disease requiring dialysis; have any other disorder of such severity that life expectancy is less than 12 months; or have any cognitive or physical impairment or disability that in the opinion of either the participants' GP or specialist, or the study investigators would result in the participant having difficulty interacting with SmartHeart without support.

Recruitment Process

Participants will be identified by clinical staff at the 2 participating sites (Austin Health and Bendigo Health in Victoria). Research nurses at study sites will identify eligible individuals before hospital discharge and through outpatient cardiac clinics. Nurses will provide potential participants with information and consent forms and refer interested individuals to the research team. Approximately one week after the provision of study information, a researcher will confirm interest, answer questions, and schedule a baseline assessment if individuals indicate an interest in consent.

Procedures

SmartHeart will be installed in participants' homes and demonstrated by a trained researcher. Written, verbal, and audio-visual support will be provided to help participants engage with the system. A loan phone (Android) will be provided free of charge to those who do not own one. With the help of SmartHeart, participants will be asked to record daily measurements of weight and blood pressure and answer questions about their symptoms. All participants will have access to their usual cardiology and general practice care throughout the course of the study.

For this study, HF nurses will have access to the clinician portal through which they can review participants' data, including notifications. HF nurses will receive email notifications to alert them of potential changes to the participants' HF condition. Australian HF guidelines and best practices will be followed when responding to notifications. HF nurses will be available to review sensed data and respond to notifications during their working hours; however, SmartHeart will alert participants to contact their GP as first contact.

Data Collection

Data will be collected at baseline and the end of the 8-week intervention period using self-reported questionnaires and qualitative interviews (refer to Table 3 for an overview).

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In addition, to the items in Table 3, a qualitative researcher will conduct one-to-one in-depth interviews with all participants, their caregivers (if applicable), and health care providers involved in the delivery of SmartHeart. Interviews will be based on the UK National Institute for Health and Care Excellence (NICE) Evidence framework for digital health technologies [27] and will address acceptability, demand, practicality, frequency of monitoring, burden to participants, potential of provoking anxiety, scenarios in which the program would be best employed, compliance with functional components, facilitators, and barriers to participation.

Table 3. Summary of outcome measures.

Items	Description or tool used to measure the item	Baseline	During intervention	Postintervention (8 weeks)
Recruitment and attrition	Study recruitment will be recorded by a trained research assistant and will include the total number of participants referred to the study, numbers who agree to participants, and those who enroll in SmartHeart. The research assistant will also record the number of participants that complete the study as a measure of attrition.	✓	✓	✓
Engagement	System use logs will be collected through the SmartHeart system and will provide data on the frequency of use of SmartHeart features. These will not require user input.	__[a]	✓	—
Weight	Withings Body Smart Bluetooth scales	✓	✓	—
Physical activity	Samsung Galaxy Watch Pro 5	—	✓	—
Heart rate	Samsung Galaxy Watch Pro 5	—	✓	—
Blood pressure	Withings blood pressure monitor Connect wireless blood pressure monitor	—	✓	—
Symptoms	Self-reported HF symptoms through the SmartHeart app	—	✓	—
Self-care	Self-Care of Heart Failure Index [28], version 6 [29]	✓	—	✓
Usability	System Usability Scale [30]	—	—	✓
Health-related quality of life	European Quality of Life 5D 5-level questionnaire [31]; Minnesota Living With Heart Failure Questionnaire [32]	✓	—	✓
Medication adherence	Philips Hue Infrared Motion Sensor (proxy); Medication Adherence Rating Scale [33]	✓	✓	✓
Hospitalization	Data provided by sites or study nurses.	—	✓	✓

[a]Not applicable.

Self-Report Measures

Self-Care will be assessed using the Self-Care Heart Failure Index (SCHFI) [28], version 6 [29]. The SCHFI comprises 22 items and collects data on 3 domains (self-care maintenance, management, and confidence). Scores can be summed, but this is discouraged by the authors of the SCHFI. They recommend that the scales (maintenance, management, confidence) be used individually. Each scale is standardized to a score of 100. A score of ≥70 can be used as the cut-point to judge self-care adequacy, although evidence is provided that benefit occurs at even lower levels of self-care [29]. The reliability and validity of this measure have been well documented [29].

The System Usability Scale (SUS) comprises 10 items (each question with a Likert scale ranging from strongly agree to strongly disagree) and was designed as a "quick and dirty" measure of the usability of either hardware or software or both by end users' system [30]. Five questions are positively framed, and 5 questions are negatively framed. The process for computing an SUS score is as follows: (1) subtract 1 from the user's Likert ratings for odd-numbered items or questions, (2) subtract the user's Likert ratings from 5 for even-numbered items, (3) each item score will range from 0 to 4, and (4) sum the numbers and multiply the total by 2.5. This calculation will provide a range of possible SUS scores from 0 to 100.

Previous research has shown that a mean score of 68 is a useful benchmark [34].

Health-related quality of life will be measured using the European Quality of Life 5D 5-level (EQ-5D-5L) questionnaire [31] and the HF-specific Minnesota Living With Heart Failure Questionnaire (MLWHFQ) [32].

The EQ-5D-5L comprises 5Ds: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. Each dimension has 5 levels: no problems, slight problems, moderate problems, severe problems, and extreme problems. Participants are asked to indicate their health state by ticking the box next to the most appropriate statement in each of the 5Ds. This

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decision results in a 1-digit number that expresses the level selected for that dimension. The digits for the 5Ds can be combined into a 5-digit number that describes the patient's health state. It also includes a visual analog scale that captures the participant's self-rated health. This can be used as a quantitative measure of health outcomes that reflects the participant's own judgment. The EQ-5D-5L has demonstrated excellent psychometric properties across a broad range of populations and health conditions [35].

The MLWHFQ is a 21-item multidimensional questionnaire designed to assess the health-related quality of life of people with HF in adults across physical, socioeconomic, and emotional or psychological dimensions. It is scored through a 6-point Likert scale (0-5), with a sum of item responses for total and dimension scores. The MLWHFQ has very good psychometric properties [36].

The Medication Adherence Rating Scale [33] is a 10 - item self - report adherence scale that assesses both intentional ("I avoid using it if I can") and nonintentional medication nonadherence ("I forget to use it"). Psychometric properties are well established [37]. Scores range from 0-10 with higher scores indicating better attitudes toward medication.

Feasibility Outcomes

To inform decisions to progress to a definitive trial, there must be evidence of achieving key criteria for recruitment, engagement, self-care, and attrition. For this, the criteria in Textbox 2 will be used. These criteria were not based on published data but were developed following expert discussion with the chief investigator team, which comprised 2 cardiologists, an HF nurse specialist, 2 public health researchers, 2 exercise physiologists, one computer scientist, a health economist, and a biostatistician.

Textbox 2. Feasibility criteria and metrics.

Green: If all four green criteria are met, we will consider the study feasible (unless there is a clear indication from the qualitative interviews and our experience that would improve the study)

- At least 80% of the target sample size is recruited within 3 months.
- At least 50% of participants engaged with SmartHeart.
- At least 60% of participants maintained or improved their Self-Care of Heart Failure Index score.
- Attrition ≤20%. A rule of thumb states that >20% attrition poses threats to study validity [38].

Amber: If one or more of our amber criteria are met, we will consider the study as likely feasible but will consider the results of the feedback from the qualitative interviews and our experience to improve whichever criteria are not at the "green light" level before considering a full trial.

- 50%-79% of the target sample size is recruited within 3 months.
- 35%-49% of participants engaged with SmartHeart.
- 45%-59% of participants maintained or improved their Self-Care of Heart Failure Index score.
- Attrition 20.1%-35%.

Red: If one or more red criteria are met, we would consider the study as likely not feasible with the current protocol.

- <50% of the target sample size is recruited within 3 months.
- <35% of participants engaged with SmartHeart.
- <45% of participants maintained or improved their Self-Care of Heart Failure Index score.
- Attrition >35%.

Analysis

Descriptive statistics (mean and SD for continuous data, N and percentage for categorical) will be presented for all quantitative primary and secondary (eg, self-care behaviors, Health-Related Quality of Life) outcomes and will be the primary form of analysis. The EQ-5D-5L questionnaire will be scored using the Australian value set [39]. Within a person, cross-correlation matrices will also be generated [40].

Interviews will be audio-recorded and transcribed. We will use framework analysis to analyze the interviews, using predefined categories according to the NICE Evidence framework for digital health technologies [27].

Ethical Considerations

The study received ethical approval from the Deakin University Human Research Ethics Committee (HREC/76317/MH-202). A participant information sheet and consent form will be sent to participants during the baseline assessment. Written informed consent will be obtained at the baseline assessment before data collection.

Results

The SmartHeart project, including the proposed pilot study, received funding from the National Health and Medical and Research Council grant (grant number 2018698) and commenced in January 2021. This study was conducted in collaboration with health and academic partners in the states of Victoria and Queensland, Australia. Recruitment for the pilot

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trial started in August 2024 and will be completed by March 2025. We have currently enrolled 12 participants. Follow-up of all participants will be completed by the end of May 2025. Once analysis from the pilot study has been completed, we will submit the findings for publication.

Discussion

Principal Findings

This article reports on the formative development of the SmartHeart system, a smart health ecosystem with advanced telemonitoring and behavioral support, offering a comprehensive, integrated, and coordinated approach to HF management. We also outline a protocol for piloting SmartHeart to inform a future RCT.

Consistent with the need to integrate consumers in health research [41], we have undertaken extensive user-centered design and engagement with end users. A comprehensive program of research, following the IDEAS framework was used in developing SmartHeart. Reflecting on the design and development process, we benefited greatly from using the IDEAS framework. Our formative work involving a scoping review, stakeholder interviews, and a Delphi survey was important for ideation and informing the prototype features and functions. Co-design workshops were critical in identifying the needs of users and health care providers. We hypothesize that this will likely maximize the acceptability, engagement, and usability of the SmartHeart system. However, the downside to this co-design approach was the much longer development timeframes to achieve the SmartHeart prototype.

SmartHeart incorporates a conversational agent (Amazon Alexa). With ongoing development, conversational agents have evolved into digital systems that aid the delivery of health interventions for individuals at the places most convenient for them. Using voice to interact with these agents is a more natural user interface than traditional mouse, keyboard, or touch interfaces, which may lower barriers to entry for many people, especially older adults, those culturally and linguistically diverse, and people with low literacy [42]. We also provide access to SmartHeart in multiple languages, increasing the accessibility of support to those who speak languages other than English. Furthermore, in Australia, SmartHeart could have a significant impact by providing greater access to health care, especially in high-priority rural and regional areas.

There are some limitations of the current system that warrant consideration. First, the system is currently Android-based; however, we offer participants an Android phone for the duration of the study, and we are developing an iOS version for future use. Second, the Samsung Galaxy watch used to collect data from participants is also only compatible with the Android system. Our future plans are to support most off-the-shelf smartwatches in the market, including Fitbit (Google; iOS and Android), Apple Watch (iOS), and Garmin. Third and finally, we use a cloud-to-cloud approach, which can be problematic when third-party providers (eg, Withings) provide updates affecting data capture. Our team will check and maintain the system on a regular basis to ensure all components are up to date, helping to mitigate this issue.

A risk mitigation strategy plan was developed for the funding application that supported this project. A key risk is the slow recruitment of participants. Our current recruitment strategy includes recruitment from participating partner hospital sites; however, we will mitigate risk by also recruiting from community HF support groups, general practices, and online through social media. The small number of participants may also be a risk as this may not be sufficient to inform feasibility; however, we have indicated in our ethics application that we may extend recruitment to mitigate this risk. Data security is another risk, which will be addressed by ensuring all data are anonymized, and data storage meets Melbourne and Deakin's Research Conduct Policy and the Research Data and Primary Materials Management Procedure. As mentioned earlier, all data will be stored securely on password-protected servers and in accordance with ethical procedures. Finally, because participants are required to provide consent in English, it is possible that the benefit of SmartHeart being available in different languages will not be realized. The requirement for consent in English is based on logistics; we do not have a resource to pay for interpreters; however, most participants in Australia for whom English is not a first language can read English for consent purposes.

The SmartHeart system has significant potential for future expansion and enhancement. While our current prototype uses desktop smart speakers, the integration of conversational agents on mobile devices (eg, phones, tablets, smartwatches) could extend the system's reach beyond the home environment. Furthermore, we are exploring the integration of generative artificial intelligence to enhance user engagement through more natural dialogue and personalized responses, leveraging a curated guideline-based database and retrieved augmented generation techniques. While the project's initial focus targets people living with HF, the system's architecture supports broad applicability to other long-term conditions. This versatility will be particularly beneficial for the increasing number of people managing more than one long-term condition. The system's adaptability is enhanced by the fact that challenges associated with HF significantly overlap with other health conditions, such as other cardiovascular conditions, chronic obstructive pulmonary disease, and diabetes, making the core functionality transferable. Potential adaptations include customizing symptom questionnaires for one or more conditions, implementing different wireless sensors, and refining the algorithms and support messages.

The next step is to assess the feasibility of this version of the SmartHeart system with both people with HF and health care providers. A pilot study will provide valuable information on feasibility and preliminary effects, which will inform the design of a larger proposed RCT. If clinical and cost-effectiveness are subsequently demonstrated, SmartHeart could augment existing health care services to support people with HF to stay well living in the community and living independently. The primary benefit of this solution is to empower people with HF to be more actively engaged in self-care and realize the unfulfilled potential for digital health to transform health care delivery. If proven

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feasible, it could improve clinical outcomes (hospital admissions, self-care, health-related quality of life) and reduce the cost burden of the health care system. The SmartHeart concept aligns with recent calls for a health care shift from clinics to the home, with digital health support [6] and a recent European Society of Cardiology position statement [43] to address key elements of digital health implementation.

Conclusion

The SmartHeart system represents a promising, user-centered approach to HF management through advanced telemonitoring and behavioral support, with significant potential for expansion to other chronic conditions. Future research, including a pilot study and larger RCT, will be crucial in assessing its feasibility, effectiveness, and impact on both clinical outcomes and health care costs.

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We would like to acknowledge all participants who have contributed to the development of SmartHeart as well as the clinical sites who have provided input on the study to date and will help with recruitment for the proposed pilot study.

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Data Availability

The datasets generated and analyzed in this study will be made available upon publication of the principal findings.

Authors' Contributions

RM led the conceptualization of this study, procured funding, and provided oversight for the whole study. RN, PJ, and RD led the formative and co-design work. YZ oversaw architecture development. YJ, RV, and RM led the software conceptualization and development. RM wrote the original draft. All authors provided feedback and edits on several revisions of the manuscript and gave final approval before submission. No artificial intelligence was used to support any portion of the manuscript creation.

Conflicts of Interest

None declared.

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Abbreviations

EQ-5D-5L questionnaire: European Quality of Life 5-Dimension 5-Level questionnaire
GP: general practitioner
HF: heart failure
IDEAS: Integrate, Design, Assess, and Share
MLWHFQ: Minnesota Living With Heart Failure Questionnaire
NICE: UK National Institute for Health and Care Excellence
RCT: randomized controlled trial
SCHFI: Self-Care of Heart Failure Index
SUS: System Usability Scale

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Protocol

Adolescent Youth Survey on HIV Prevention and Sexual Health Education in Alabama: Protocol for a Web-Based Survey With Fraud Protection Study

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Abstract

Background: In Alabama, the undiagnosed HIV rate is over 20%; youth and young adults, particularly those who identify as sexual and gender minority individuals, are at elevated risk for HIV acquisition and are the only demographic group in the United States with rising rates of new infections. Adolescence is a period marked by exploration, risk taking, and learning, making comprehensive sexual health education a high-priority prevention strategy for HIV and sexually transmitted infections. However, in Alabama, school-based sexual health and HIV prevention education is strictly regulated and does not address the unique needs of sexual and gender minority teenagers.

Objective: To understand knowledge gaps related to sexual health, HIV prevention, and pre-exposure prophylaxis (PrEP), we conducted the Alabama Youth Survey with individuals aged 14-17 years. In the survey, we also evaluated young sexual and gender minority individuals' preferences related to prevention modalities and trusted sources of health information.

Methods: Between September 2023 and March 2024, we conducted a web-based survey with 14- to 17-year-olds who are assigned male at birth, are sexually attracted to male youth, and lived in Alabama. Half of the study's participants were recruited through community partners, the Magic City Acceptance Academy and Magic City Acceptance Center. The other half were recruited on the web via social media. A 7-step fraud and bot detection protocol was implemented and applied to web-based recruitment to reduce the likelihood of collecting false information. Once data are ready, we will compute frequencies for each measure and construct summary scores of scales, such as HIV and PrEP knowledge, to determine internal consistency. Using multivariable logistic regression, we will examine associations between personal characteristics of survey respondents and key constructs using SPSS 29 (IBM Corp) or SAS 9.4 (SAS Institute).

Results: Analyses are ongoing (N=206) and will conclude in June 2025. Preliminary results include a sample mean age of 16.21 (SD 0.88) years; about a quarter identified as transgender or gender nonconforming, with 6% stating their gender as a transgender woman. A total of 30% self-reported their race as African American or Black; 12% were Hispanic or Latinx. More than half reported being sexually active in the past 6 months. Primary data analyses will be completed in mid-2025. If findings are promising, results will be used as preliminary data to support the development of an intervention to address knowledge gaps and prevention preferences.

Conclusions: If the study is successful, it will yield information on HIV knowledge, PrEP awareness, PrEP preferences, and related outcomes among sexual and gender minority teenagers in Alabama, an underserved, hard-to-reach, but also high-priority population for public health efforts to Ending the HIV Epidemic.

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KEYWORDS

HIV knowledge; PrEP; pre-exposure prophylaxis; adolescents; teenagers; transgender; MSM; men who have sex with men; south; bot protection; bots; fraud protection; survey protocol

Introduction

Background

In Alabama, the undiagnosed HIV rate is over 20%; youth and young adults, particularly those who identify as sexual and gender minority individuals, are at elevated risk for HIV acquisition and are the only demographic group in the United States with rising rates of new infections [1,2]. Adolescence is a period marked by exploration, risk taking, and learning [3], making comprehensive sexual health education, typically delivered in school systems, a high-priority prevention strategy for HIV and sexually transmitted infections [4,5]. However, in Alabama, school-based sexual health education is strictly regulated [6]; school-based sexual health education must adopt an abstinence orientation, and HIV prevention is typically discussed within the context of heterosexual marriage [7,8]. In response to these structural limitations, community-based organizations have developed their own sexual health and HIV prevention education programs [9]. However, their content is typically delivered inconsistently, relies on funding availability, and is offered only to youth engaged in services. In 2019, pre-exposure prophylaxis (PrEP) was established as safe and effective in preventing HIV among adolescent-aged men who have sex with men (MSM), and the US Food and Drug Administration approved PrEP for individuals weighing at least 77 pounds (~34.9 kg), thereby making it available to adolescents [10,11]. Nevertheless, prescribing PrEP to adolescents remains under ideal levels [12]. Potentially, due to the lack of comprehensive HIV prevention and sexual health education in Alabama schools, there are high rates of HIV among sexual and gender minority youth and low rates of PrEP uptake. This leads to unanswered questions about what adolescents know or do not know about HIV and sexually transmitted infections (STIs) and about characteristics of their psychosocial profile, which may influence the acceptance of PrEP. Furthermore, new PrEP modalities are being developed, and clinicians and researchers alike are interested in learning about what PrEP options may be more acceptable to adolescents.

While the National Institutes of Health–funded Adolescent Medicine Trials Network for HIV/AIDS Interventions and HIV Prevention Trials Network have supported studies that assess PrEP preferences among sexual and gender minority adolescents and young adults [13,14], the age range usually begins at 15 or 16 years, with few studies enrolling as young as 14 years, even though sexual debut is thought to be younger in MSM as compared to the public [15]. There also continues to be a need to examine PrEP preferences of sexual and gender minority adolescents in the southern United States, where stigma related to HIV, sexual orientation, and gender identity is high and resources are limited [16,17]. Some research on adolescent knowledge and preferences related to HIV prevention has been conducted in the region [18,19]; however, studies more often occur with adolescents' support persons, including guardians and providers, rather than the adolescents themselves and occur in clinical settings. Web-based surveys offer adolescents a comfortable and confidential way to share their essential opinions without feeling judged, especially since they heavily rely on digital technologies to build their social networks, receive social support, and obtain health information [5,20-22]. Engaging sexual and gender minority adolescents in research to understand their HIV and STI prevention is critical to reducing rates of HIV transmission but is challenging to do, making this protocol a high public health priority project.

While increasing PrEP uptake among young sexual and gender minorities is urgently warranted [23], and federal and local agencies are supporting behavioral interventions to reach this group [24], adolescent sexual and gender minority individuals will not engage in HIV biomedical prevention if (1) they do not know about PrEP, (2) PrEP options are not acceptable for their developmental period, or (3) they do not understand their risk [25-27]. There is an unmet need to deliver tailored HIV prevention for diverse sexual and gender minority youth, built upon adolescents' existing knowledge and preferences [28,29]. To understand existing knowledge gaps and specifically address them via intervention, we conducted the Alabama Youth Survey to evaluate 14- to 17-year-old sexual and gender minority individuals' preferences and knowledge related to HIV prevention, PrEP, and STIs. The aim of this study was to elucidate knowledge, beliefs, and preferences related to HIV and STI prevention from sexual and gender minority adolescents in Alabama through a web-based survey to inform future intervention development. Because this study is exploratory, no hypotheses are proposed.

Objectives

In this study, we aim to elucidate knowledge, beliefs, and preferences related to HIV and STI knowledge and prevention among sexual and gender minority adolescents in Alabama through a web-based survey to inform future intervention development. If this study yields informative results, we will develop or adapt digital health intervention modules [30,31], a preferred and effective modality for reaching youth to address PrEP uptake while considering preferences and levels of knowledge.

Methods

Ethical Considerations

All study materials and procedures were reviewed and approved by the University of Alabama at Birmingham Institutional Review Board (IRB; IRB-300009255) and the Florida State University IRB (STUDY00003480). Informed assent was collected digitally from all study participants before data collection. Potential participants were informed of the purpose of the survey and anonymity, confidentiality, and voluntary

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principles before responding. We received parental waivers from both reviewing IRBs due to the precarious situation of many sexual and gender minority youth in Alabama. Still, an information sheet for parents was made available. Participation in the study was voluntary. Study data have been deidentified and stored on a secure server. Study participants received an incentive of a US $35 digital gift card.

Eligibility Criteria

All potential participants completed a web-based screening survey via Qualtrics to verify their eligibility. To be eligible for the study, potential participants must have been 14-17 years old, assigned male at birth, report sexual attraction to men, and live in Alabama. MSM, transgender women, and genderqueer individuals were eligible if they met the aforementioned criteria.

Recruitment

We partnered with three local agencies for this study. The Magic City Acceptance Academy is the only trauma-informed charter school for LGBTQIA+ (lesbian, gay, bisexual, transgender, intersex, queer/questioning, asexual) individuals in the US Deep South. Magic City Acceptance Academy recruitment was supplemented by recruitment from the Magic City Acceptance Center [32,33]. While both agencies are independent, they have ties to leadership and are connected to Birmingham AIDS Outreach [8,34]. About half of our sample was recruited in person from these sites. The other half was recruited on the web via social media through targeted advertisements on Facebook, Instagram, and Snapchat. Adolescents could access the survey via QR codes linked to an eligibility screener. Eligible individuals were automatically redirected to the Alabama Youth Survey.

Bot Detection and Data Protection

Fraudulent data and fake responses are commonplace in web-based surveys, especially when a monetary incentive is provided. Examples of data fraud include bad actors, such as eligible individuals who submit surveys multiple times for multiple incentives, ineligible individuals who lie to meet eligibility criteria, and programmed bots. Since half of our sample was recruited on the web, we used extensive screening protocols, including (1) requiring the answering of youth-focused qualitative questions that require a typed response that would indicate residence, such as “What’s your favorite local restaurant?” and “What’s your favorite television show?” during screening [15]; (2) embedding multiple reCAPTCHAs throughout with review of Qualtrics bot detection; (3) requiring a US-based IP address; (4) locking surveys to disallow multiple submissions from the same IP address or device; (5) requiring all eligible respondents to provide an in-state phone number, which was then pinged for SMS text messaging verification before sharing the survey link—while many people have out-of-state area codes, this is much less likely for 14- to 17-year-old adolescents; (6) checking that all linked surveys were completed sequentially; and (7) using Zoom (Zoom Video Communications)–based verification audits when data seemed suspicious. Suspicious activities or indicators included but were not limited to submitting more than two surveys back to back, surveys received from the same small town in Alabama, and using an AOL or Yahoo (Yahoo Inc) email address. We also changed the survey links weekly to avoid improper circulation. These procedures were completed for all participants who were recruited on the web to ensure data integrity.

Adolescent Youth Survey

The Adolescent Youth Survey was developed and implemented following the CHERRIES (Checklist for Reporting Results of Internet E-Surveys) checklist [35]. The web-based survey was programmed in Qualtrics to collect data on HIV knowledge, perceived HIV risk, actual HIV risk, PrEP knowledge, preferences related to PrEP modalities, stigmas, and characteristics that are known to be related to HIV prevention among sexual and gender minority individuals. Some constructs were explicitly developed for this study, such as PrEP modality preference, while in other cases, we used validated scales. The measures are shown in Table 1 below. The question order was not randomized. Questions were adaptive, and questions that were not applicable were not presented. For example, if a participant was not sexually active, questions about using protection during sexual intercourse were not presented. Respondents were allowed to go “back” in the survey. However, they could not adjust their responses after pressing the final submit. We aimed to recruit 200 participants and were able to recruit a total of 206 participants between September 2023 and March 2024 via a convenience sample that was shared by those recruited via the Magic City Acceptance Academy, the Magic City Acceptance Center, and the web.

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Table 1. Measures collected

Construct	Description or examples	Questions, n
Demographics	Age, gender, sex, race, ethnicity, sexual orientation, residence in Alabama, parental education, and income	10
HIV risk and prevention	Sexually active [36,37], injectable substance use, on PrEP[a], and previous STI[b] diagnosis [38]	10
HIV knowledge	HIV-KQ-18[c] [39]	18
STI knowledge	STI Knowledge Scale [40]	27
Medication experience and preferences	Oral pills, shots, suppositories, patches, etc	13
PrEP familiarity	Seen commercials, types of PrEP, and PrEP brands	6
PrEP awareness	PrEP-COL[d] Scale [41]	10
PrEP preferences	PrEP modalities, PrEP delivery locations, etc	20
Trusted sources	Types of information sources and people	24
Stigma	IHP-R[e] [42] and Everyday Discrimination Scale [43]	14
Depression	PHQ-8[f] [44]	8
Resilience	MOS Social Support Survey [45], GSE[g] [46]	29

[a]PrEP: pre-exposure prophylaxis.
[b]STI: sexually transmitted infection.
[c]HIV-KQ-18: HIV knowledge questionnaire.
[d]PrEP-COL: PrEP Columbia Scale
[e]IHP-R: Revised Internalized Homophobia Scale.
[f]PHQ-8: Personal Health Questionnaire Depression Scale.
[g]GSE: General Self-Efficacy Scale.

Pilot Testing

Study team members aged 20-24 years pilot-tested the survey multiple times to assess its completion time. It was determined to be about 20-25 minutes, depending on how slowly one reads the questions and the time to consider response options. We then pilot-tested the survey with the first 10 respondents and found similar completion metrics, with no complaints or concerns reported.

Data Storage and Analysis

Encrypted data are saved on a Florida State University server with password protection. The database and associated data structures were developed before survey distribution and were not adjusted during the protocol. We asked participants to voluntarily provide emails and cell phone numbers to facilitate the provision of incentives. These personal data were only known to the incentive processors and were kept separate from survey responses. During data collection, we examined data quality weekly (eg, missing data, assessment of distributional assumptions, and identification of outliers) and will do so before statistical analysis is conducted. As a pilot study, missing scale data will not be estimated. Once data are ready, we will compute frequencies for each measure and for each scale to assess variability and internal reliability. We will construct summary scores of scales, such as HIV and PrEP knowledge, to determine if these have adequate internal consistency (Cronbach $\alpha \geq 0.70$) [47]. Using multivariable logistic regression, we will examine associations between the personal characteristics of survey respondents and key constructs. We will use SPSS 29 (IBM Corp) or SAS 9.4 (SAS Institute) for quantitative analyses.

Results

While this study was approved in 2021, data collection began in September 2023 and concluded in March 2024. Since the survey was open, the system could not record the number of unique visitors; thus, a formal response rate cannot be calculated. Data analysis is underway and will conclude in June 2025. The sample included 206 participants aged 14-17 years with a mean age of 16.21 (SD 0.88) years; about a quarter identified as transgender or gender nonconforming, with 6% explicitly stating their gender as a transgender woman. A total of 30% self-reported their race as African American or Black; 12% were Hispanic or Latinx. About half of them reported being sexually active in the past 6 months.

Discussion

Principal Findings

In this study, we aim to elucidate knowledge, beliefs, and preferences related to HIV and STI prevention among sexual and gender minority adolescents in Alabama through a web-based survey to inform future intervention development. If this study yields informative results, data could inform the adaptation or creation of a sexual health and HIV prevention intervention for sexual and gender minority adolescents who

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live in southern states, where school-based sexual health education may be unavailable or strictly limited.

While hypotheses were not proposed, based on preliminary analyses and the extant literature, we anticipate finding low levels of knowledge and high levels of poor mental health outcomes. Little is known about PrEP modality preference in this population, so we cannot anticipate findings related to this topic. Findings will provide intervention targets (eg, PrEP education) and the needed dose; very low knowledge will necessitate more significant emphasis on PrEP education. When recruiting on the web, we encountered an enormous amount of fraud and ultimately needed to implement SMS text messaging verification, wherein eligible participants would only be routed to the survey after their unique phone number, with in-state area code, was verified. Even after verification, since Google phone numbers can be created, we audited suspicious submissions, such as surveys that were completed too quickly. A total of 10% of web-recruited submissions were audited via a Zoom call with a trained study coordinator. The web-based survey and fraud detection strategies were feasible; however, completing this survey with data protection and scientific integrity was much more costly and time-intensive than expected. For future web-based survey studies, we recommend implementing SMS text messaging verification at study onset with a random audit of 20% of records. Audits should include a video call (preferred) or a voice call (acceptable). Email verification, while simple, was not reliable, likely due to the ease of creating email accounts.

As noted in the *Introduction*, little is known about 14- to 17-year-olds' knowledge, beliefs, and preferences related to HIV and STI prevention in the United States; thus, comparison to other studies is challenging. Recent research on these topics has been conducted in global settings with mixed findings [48-50]. A unique feature of our survey study is the assessment of PrEP modality preference, including options currently in clinical trials or may be available outside of the United States. Findings on modality preference have the potential to inform clinical care and how providers offer PrEP to sexual and gender minority adolescents.

While the study team was meticulous in bot detection and other fraud measures, some participants did not receive face-to-face interaction, and thus, those recruited on the web may be different from participants recruited from our local community partners. Second, the study may be susceptible to desirability bias, especially from participants recruited via in-person venues. While our sample is large for sexual and gender minority adolescents, a larger sample would increase generalizability. Some domains would have been valuable to assess, such as living circumstances and previous experiences with adverse life events; however, in pilot testing, adolescents felt the survey could not be lengthened.

Conclusions

If the study is successful, we will yield information on HIV knowledge, PrEP awareness, PrEP preferences, and related outcomes among sexual and gender minority teenagers in Alabama, an underserved, hard-to-reach, but also high-priority population for public health efforts to Ending the HIV Epidemic. Data can inform the development of a culturally appropriate (for southern contexts, to be adolescent-friendly) and modular HIV prevention intervention, targeting behavior change related to HIV prevention for sexual and gender minority adolescents, that can be seamlessly integrated into amenable community settings in the southern United States.

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Data Availability

Data are available upon reasonable request through this study's lead author (HB).

Authors' Contributions

HB is the principal investigator and lead author of the study and is involved in all aspects of the study from conceptualization and funding acquisition to writing. IY is the lead statistician and led the formal analysis. JB led data collection efforts with the support of CLB and AJ. JB, CLB, and AJ were involved with project administration and writing the original draft.

Conflicts of Interest

None declared.

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Abbreviations

IRB: institutional review board
LGBTQIA+: lesbian, gay, bisexual, transgender, intersex, queer/questioning, asexual
MSM: men who have sex with men
PrEP: pre-exposure prophylaxis
STI: sexually transmitted infection

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Protocol

Detecting Freezing of Gait in Parkinson Disease Using Multiple Wearable Sensors Sets During Various Walking Tasks Relative to Medication Conditions (DetectFoG): Protocol for a Prospective Cohort Study

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Abstract

Background: Freezing of gait (FoG) is one of the most disabling symptoms of Parkinson disease (PD). Detecting and monitoring episodes of FoG are important in the medical follow-up of patients to assess disease progression and functional impact and to adjust treatment accordingly. Although several questionnaires exist, they lack objectivity. Using wearable sensors such as inertial measurement units (IMUs) to detect FoG episodes offers greater objectivity and accuracy. There is no consensus on the number and location of IMU, type of algorithm, and method of triggering and scoring the FoG episodes.

Objective: The objective of this study is to investigate the use of multiple wearable sensors sets to detect FoG in patients with PD during various walking tasks under different medication conditions.

Methods: This single-center, prospective cohort study (DetectFoG) will include 18 patients with PD. Patients will be fitted with 7 IMUs and will walk a freezing-provoking path under different tasks—“single task,” “dual motor task,” or “dual cognitive task”—and medical conditions corresponding to levodopa medication (“on” or “off”). Passages will be videotaped, and 2 movement disorder specialists will identify FoG episodes in the videos. The accuracy, sensitivity, specificity, positive predictive value, and negative predictive value of the most effective combination of wearable sensors for detecting FoG episodes will be studied.

Results: The study is currently in the data collection phase, having commenced recruitment in February 2024. Once all data have been gathered, the data analysis will commence. As of August 2024, 3 patients have been recruited. It is anticipated that the results will be published by the end of 2025.

Conclusions: Detecting FoG episodes in various medical and clinical settings would provide a more comprehensive understanding of this phenomenon. Furthermore, it would enable reliable and objective monitoring of the progression of this symptom based on treatments and the natural course of the disease. This could serve as an objective tool for monitoring patients and assessing the severity and frequency of FoG.

Trial Registration: Clinicaltrials.gov NCT05822258; https://www.clinicaltrials.gov/study/NCT05822258

International Registered Report Identifier (IRRID): DERR1-10.2196/58612

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KEYWORDS

Parkinson; detection; freezing of gait; sensor; wearable; freezing; walk; neurodegenerative; movement

Introduction

Affecting more than 8.5 million people worldwide in 2019, Parkinson disease (PD) is the second most common neurodegenerative disease [1]. PD is diagnosed using criteria from the UK Parkinson's Disease Society Brain Bank [2] and is defined by the cardinal symptoms of tremor, bradykinesia, rigidity, and postural instability, along with other motor and nonmotor symptoms [3].

Among the various motor symptoms, freezing of gait (FoG), defined as a "brief and episodic absence or marked reduction in the forward progression of the feet despite the intention to walk" [4], is one of the most disabling symptoms of PD. In advanced and severe forms of PD, FoG occurs in 50% to 80% of cases [5]. FoG is correlated with PD severity and disease duration [6]. It increases the risk of falls [7] and loss of independence and affects patients' quality of life [8].

The detection of FoG episodes is an important issue for patient follow-up and treatment adjustment. Various subjective and objective methods can be used to assess these symptoms. Daily completion of a motor diary by the patient is one possibility for assessing these symptoms, but it relies on the patient's subjective judgment and is often discontinued after a few days or is not feasible in the presence of cognitive impairment [9]. Objective scores with predefined exercises (eg, double spot walking, 180° turning, etc) are available to assess FoG episodes during medical consultations; however, these exercises do not always trigger FoG episodes due to several reasons. First, the phenomenon known as the "white coat effect," whereby patients may perform differently in the presence of medical professionals, can alter their natural response and reduce the likelihood of FoG episodes [10]. Second, the structured nature of clinical assessments often causes a switch from automatic to goal-directed pathways, reducing the occurrence of FoG episodes, which typically occurs in more automatic walking scenarios [11]. Finally, the predefined exercises are constrained by time, unfamiliarity, and the artificiality of the clinical environment, which can influence patients' natural gait patterns. Thus, they fail to provide accurate information on the frequency and severity of FoG episodes in daily life [11]. One potential alternative method involves videotaping patients in different contexts and conducting a postscored examination, considered the gold standard, although this approach demands time and expertise [11].

To overcome these limitations, wearable sensors, such as electromyographs, electroencephalography electrodes, or inertial measurement units (IMUs), provide a solution for automatic FoG detection. The combination of accelerometer and gyroscopes data from an IMU seems to be the most widely used solution with high performance (sensitivity: 86%; specificity: 92.9% [12]). This compact sensor is easy to install and allows FoG assessment both in clinical practice and during daily living [9,13].

Despite numerous studies and literature reviews on the use of these wearable sensors for FoG detection, there is as yet no consensus in the literature on the optimal methodology for their use. It is likely that this discrepancy stems from the inherent variability in the protocols used. Indeed, there is considerable heterogeneity in the protocols for triggering [11] (medical condition: "on" or "off" levodopa treatment; freezing-provoking path; and dual-task conditions). In fact, there are few studies that directly compare FoG episodes in "on" and "off" conditions with small cohorts and a low number of participants [11,12,14]. Furthermore, many locations including feet, shin or ankle, thigh, and pelvis have been investigated [15]. The use of multiple sensors provides a more detailed and holistic view of the patient's movements, enabling the capture of subtle changes that may not be detectable with a single sensor [15]. An IMU is cost-effective and straightforward to wear, rendering it suitable for both laboratory evaluation and daily use. Even if patients prefer to wear sensors solely at the wrist, such as a stopwatch, or conceal them beneath clothing at the ankle or on a belt (lower back), as demonstrated by O'Day et al [15], the placement of sensors on multiple body parts could enhance the robustness of FoG detection across various walking tasks and different FoG subtypes. Furthermore, examining FoG under dual-task conditions provides a more comprehensive understanding of how cognitive load impacts freezing episodes, which only a few studies have addressed [16-20]. Finally, several other variables may confound the study, including the wide age range of cohorts (aged 7-118 years) and the diverse range of FoG episodes (50-1110) [21-23]. Therefore, this study is innovative as it stands out for its ability to replicate findings across various conditions, particularly the medical condition. Furthermore, it explores the effects of dual-task scenarios and optimal sensor placement in a larger cohort than those found in the literature, significantly enhancing our understanding of the underlying mechanisms. These multiple dimensions provide a more nuanced and robust perspective, allowing for better generalization of the results and improving practical applications in medical settings.

Regardless of the wearable sensors used or the freezing protocol, the accuracy of detection is sensitive to the type of algorithm [9,11,12,23]. Yet, the algorithms used to detect FoG episodes are controversial, especially for real-time detection. The threshold method provides a straightforward approach to the implementation and interpretation of algorithms. In this context, the freezing index—defined as the ratio between the power bands of freezing (3-8 Hz) and locomotion (0.5-3 Hz)—is the most commonly used feature in threshold-based algorithms [9,11,12,23]. This single feature accurately detects many FoG episodes (sensitivity: 84.3%; specificity: 78.4% [24]), but detection fails when no motion is observed and voluntary stops may be mistakenly classified as FoG [17]. Adding multiple indices can enhance algorithm performance, but it also increases complexity and the difficulty of tuning thresholds [25,26]. To address these limitations, machine learning (ML) algorithms have been developed to improve FoG detection performance. Indeed, ML algorithms could better fit the model to increase the accuracy of the models; this is a subfield of artificial

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intelligence that gives an algorithm the ability to learn without being explicitly programmed [12]. Among the various ML algorithms, support vector machine, multilayer perceptron, and ensemble classifiers (eg, random forest or AdaBoost) have proven to be the most efficient. Determining the best ML algorithm is challenging due to the highly heterogeneous nature of the training data. A limitation of ML algorithms is that training the model and processing the data can require high computational cost. Fortunately, advances in computer technology now offer the possibility of early or real-time detection with ML models [12].

The primary objective is to assess the accuracy of the optimal combination of wearable sensors for detecting FoG episodes in patients with PD. The secondary objectives of this study include measuring the specificity, sensitivity, positive predictive value (PPV), and negative predictive value (NPV) of the optimal combination of wearable sensors for detecting FoG episodes. Regarding the setup, we also aim to compare its performance (accuracy, sensitivity, specificity, PPV, and NPV) across various clinical and medical conditions.

Methods

Study Design and Participants

This study is a single-center, prospective cohort trial (DetectFoG) involving patients with PD with FoG at the University Hospital of Rennes. Patients will be recruited from the neurology department of University Hospital of Rennes during their visit to the neurologist. This study aims to include a total of 18 patients. To mitigate potential issues such as withdrawal of consent, absence of FoG during neurologist annotation, loss of follow-up (failure to attend the second visit), or inability to complete the required number of passages (fewer than 6), initially, 20 patients will be enrolled. Participants experiencing any of these issues will be excluded from the study.

Inclusion criteria will include patients older than 18 years diagnosed with PD according to the UK Brain Bank criteria. Patients must self-report as freezers, scoring between 1 and 3 on question 13 of the Movement Disorder Society-Unified Parkinson's Disease Rating Scale (MDS-UPDRS) II [27], and be capable of walking 30 m without assistance to complete the freezing-provoking path. Exclusion criteria will apply to patients scoring less than 20 out of 30 on the Montreal Cognitive Assessment [28] who are unable to give informed consent and those with neurological, orthopedic, or rheumatic comorbidities that could impact gait and ability.

Ethical Considerations

The study design was approved by the ethical committee of Ile de France III (23.01067.000298-MS01) on October 1, 2023. All data collection will adhere to applicable guidelines and regulations. Participants will provide informed consent before enrolling in the study.

Protocol

After verifying the inclusion and exclusion criteria, the neurologist will notify the principal investigator (KJ). The principal investigator will then contact the patients to provide comprehensive and understandable information about the study's objectives, as well as their right to refuse participation or withdraw at any time. If the patients consent and sign the consent form, they will participate in 2 visits separated by 2 weeks (±7 days), encompassing both "on" and "off" phases of levodopa treatment (Figure 1).

Figure 1. Timeline of study. IMU: inertial measurement unit.

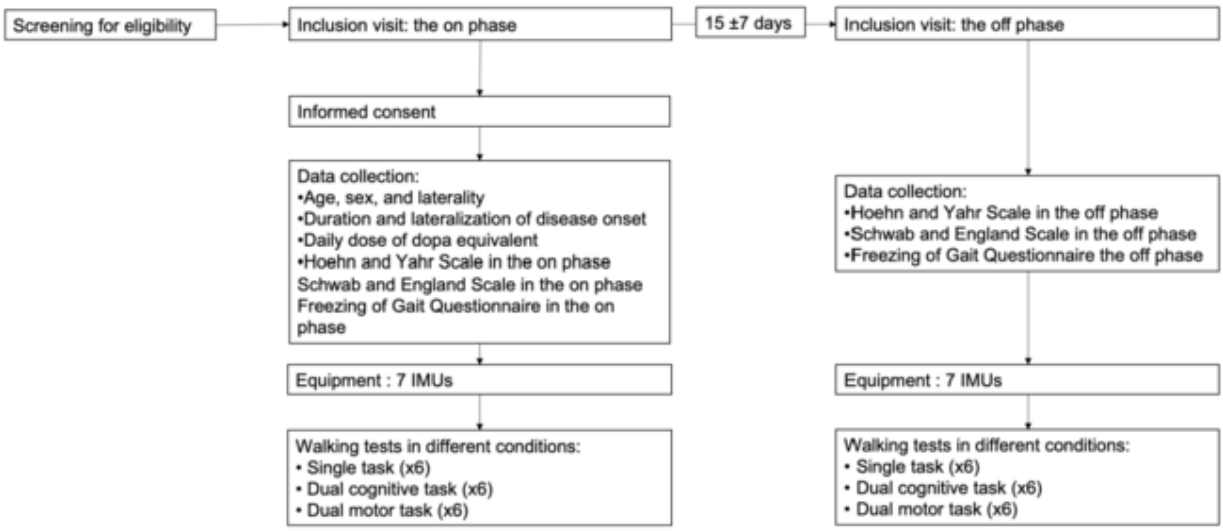

For organizational purposes, the first visit (inclusion visit) will occur during the "on" phase of levodopa medication, while the second visit (follow-up visit) will be during the "off" phase. During the "on" phase, patients will be assessed when oral treatment maximally improves dopa-sensitive PD symptoms (best "on" state, typically 1-2 hours after ingestion). This state will be determined based on patients' subjective assessment, similar to their daily motor self-assessments (home diaries), which has been established as reliable in various studies [29-31]. Assessment during the "off" phase will occur after 12 hours without treatment, preferably in the morning before the first levodopa dose.

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During each visit, participants will walk on a freezing-provoking path at a comfortable speed under 3 different clinical conditions (single task [ST], dual cognitive task [DCT], and dual motor task [DMT]). The Pardoel freezing-provoking path, known to induce FoG episodes [32], includes standing up, walking with a slalom (left and right turns), navigating a narrow passage with a 180° turn, and returning straight, with 2 designated stops—one chosen by the patient and another in front of a chair (Figure 2).

Figure 2. Freezing-inducing path (adapted from Pardoel et al [32], which is published under Creative Commons Attribution 4.0 International License [33]).

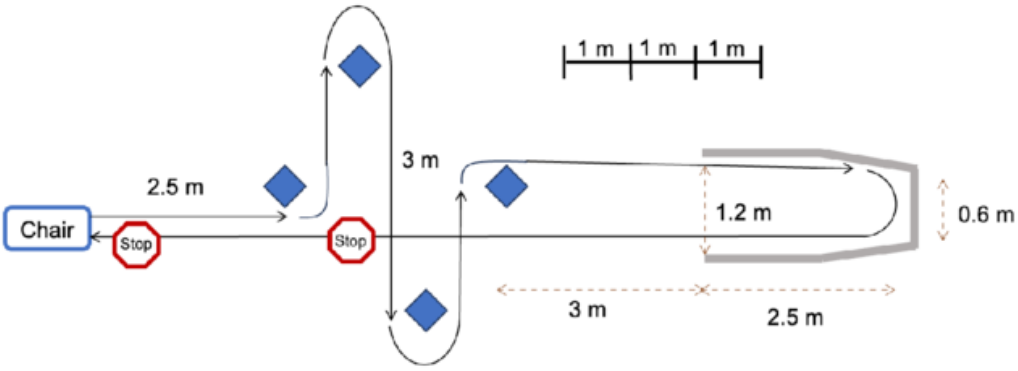

Participants will undergo testing under different dual-task conditions, which are recognized for promoting FoG episodes [32]. The DMT involves walking with a ball on a tray within a drawn circle, keeping the ball centered. The DCT requires participants to generate as many words as possible starting with a specified letter. Each participant will complete a maximum of 6 blocks, with each block consisting of the 3 conditions (ST, DCT, and DMT), resulting in a total of 18 trials (6 blocks × 3 conditions per block). The sequence of conditions within each block will be randomized to mitigate any order effects. This protocol accommodates varying endurance levels among patients; some may complete each block quickly with few or no FoG episodes, while others may take longer due to frequent tremors that consume energy. This flexible approach ensures that the study is comprehensive and respects each patient's physical limitations. However, participants who complete fewer than 2 blocks (6 trials) will be excluded from the analysis to ensure adequate data collection.

Data Collection (and Preprocessing)

Clinical Data

Various patient data are collected, including age, sex, laterality of symptoms, duration of PD, lateralization of symptom onset, daily dose of levodopa equivalent, MDS-UPDRS III score [27], Freezing of Gait Questionnaire (FoGQ; "on" and "off" phases) [34], Hoehn and Yahr Scale ("on" and "off" phases) [35], and Schwab and England Scale ("on" and "off" phases) [36]. The FoGQ is used to assess the characteristics of FoG. The Hoehn and Yahr Scale and the Schwab and England Scale serve as tools for the overall evaluation of patients with PD: the former to gauge disease severity and the latter to evaluate daily life impact, functional status, and level of dependence.

FoG Measurement

IMU Measurements

Patients will wear the Trigno Avanci IMU (Delsys; Figure 3), which includes a triaxial accelerometer, gyroscope, and magnetometer. Data will be transmitted via Bluetooth and collected using the Delsys application programing interface and then transferred to QTM 2020 software (Qualisys). The software manages recording at a sampling frequency of 148.15 Hz and synchronizes with cameras. While this sampling frequency is higher than that in some studies, it has been previously used, similar to the approach taken by Camps et al [37]. This frequency is selected to ensure that all nuances associated with FoG, particularly micromovements, are captured. IMU data will also undergo windowing with a 2-second window length and a 0.4-second shift. A trained operator will position the sensors manually, aligning them with anatomical axes. Seven IMUs will be placed as follows: 1 on each thigh (lateral side, upper third), 1 on each fibula (upper third), 1 on each foot (below the lateral malleolus), and 1 at lumbar level (L5).

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Figure 3. Inertial measurement unit placements. 1: Thighs (side, upper third); 2: fibulas (upper third); 3: foot (below lateral malleolus); 4: Lumbar (L5 level).

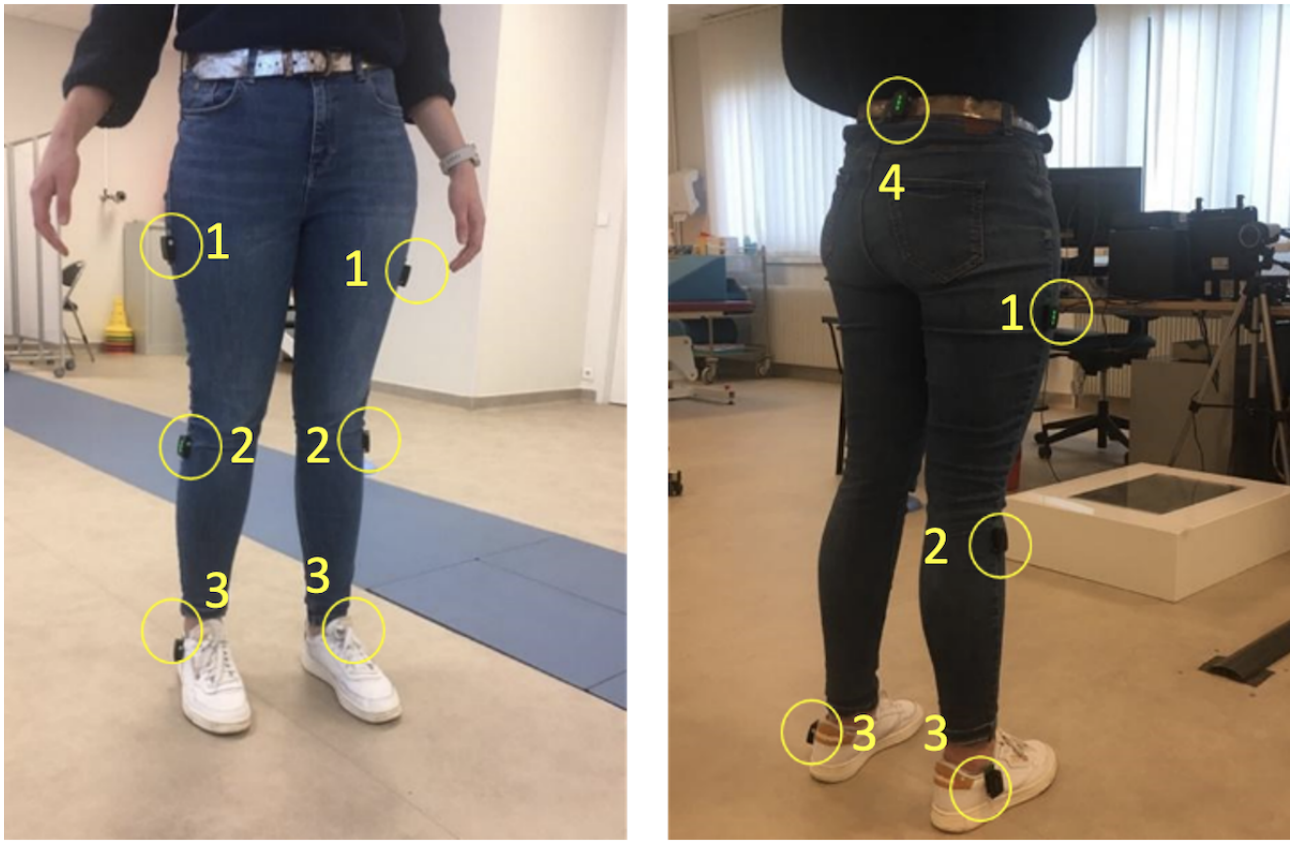

Video Recording and Window Labeling

During each visit, and during trials designed to induce freezing episodes, patients will be recorded using 14 synchronized Miqus M3 cameras (Qualisys). These cameras will record at a resolution of 1824 × 1088 pixels with a frequency of 25 Hz. FoG episodes will be identified from the videos by 2 movement disorders specialists (FL and SD) independently using QTM 2020 software (Qualisys). The start of a freezing episode is defined as "the moment when the stepping foot does not leave the ground despite a clear intention to step," and the end is defined as "the moment when the stepping foot begins or resumes an effective step" [32]. In cases where there is disagreement about the presence of a FoG episode, the specialists will discuss and reach a consensus. Following the methodology of Pardoel et al [32], the data timeline will be segmented into 2-second windows with a 0.4-second shift between windows (80% overlap). Windows will be labeled as "FoG window" when the entire window corresponds to a period of FoG. Windows not meeting this criterion, either during periods without FoG or during transitions between FoG episodes and non-FoG periods, will be labeled as "no-FoG window." The relative duration of FoG will be assessed by calculating the ratio of FoG windows to the total number of windows. This ratio provides a measure of the freezing time while accounting for the window labeling method used. To ensure comparability with other studies and to mitigate the effect of varying labeling methods across research [32,38], we will also calculate the total number of FoG episodes and the cumulative freezing time based on onset and end events, categorized by task type, session, and patient. This approach will facilitate meaningful comparisons with existing literature on FoG detection methodologies.

Data Management

All data are securely stored in a dedicated folder on a local server with restricted access limited to the research team. Patient's clinical information (such as age, sex, laterality of symptoms, duration of PD, lateralization of symptom onset, daily dose of levodopa equivalent, FoGQ score, Hoehn and Yahr Scale rating, Schwab and England Scale assessment, and MDS-UPDRS III score) along with study results (videos and IMU data) are collected and controlled by the University Hospital of Rennes. A database containing video data is duplicated for each expert responsible for labeling FoG episodes. Time annotations will be exported as events in C3D files along with IMU data before the windowing process, contributing to a final database used for subsequent data analysis. This structured approach ensures the integrity and confidentiality of patient data while facilitating precise event annotation and thorough analysis of collected data.

Data Analysis

Features Extractions

Each window of data will undergo normalization to achieve zero mean and unit variance. Our study distinguishes itself through an exhaustive exploration of features aimed at identifying FoG episodes. From each window, signal features will be extracted from both the time and frequency domains. A comprehensive array of features will be included, such as the number, duration, and length of acceleration or angular velocity

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reversals, kurtosis, and skewness [14]. Furthermore, we will incorporate metrics such as the magnitude of mean and SD of signals, as well as specific metrics related to smoothness such as spectral arc length measure [39] and the freezing ratio [40]. Nonlinear modeling features, such as sample entropy or Lyapunov exponent, which quantify gait regularity and complexity, will also be used [41]. Furthermore, measures of inter- and intralimb coordination will be integrated to highlight specific limb dynamics during FoG episodes. Feature selection will be conducted using Relief-F, chosen for its suitability in our application over methods such as minimum redundancy maximum relevance ranking [20]. This approach ensures that the selected features are highly relevant to distinguishing FoG episodes, thereby optimizing the accuracy and effectiveness of our analysis.

Model Training

The top-ranked features identified through Relief-F will be used in a decision tree (DT) model for classifying windows of data. The DT model will be tested using 5 and 10 decision splits and with various sets of top-ranked features ranging from 5 to 20. The performance of the DT model will be evaluated using metrics such as accuracy, sensitivity, specificity, PPV, and NPV. The model's performance will be determined based on the classification of each window as true positive (TP), true negative (TN), false positive (FP), or false negative (FN), comparing the model's classifications with the experts' identification of FoG episodes on video recordings (Figure 4).

Figure 4. Segmentation on true negatives (TNs), true positives (TPs), false negatives (FNs), and false positives (FPs) for each second according to the experts and the model.

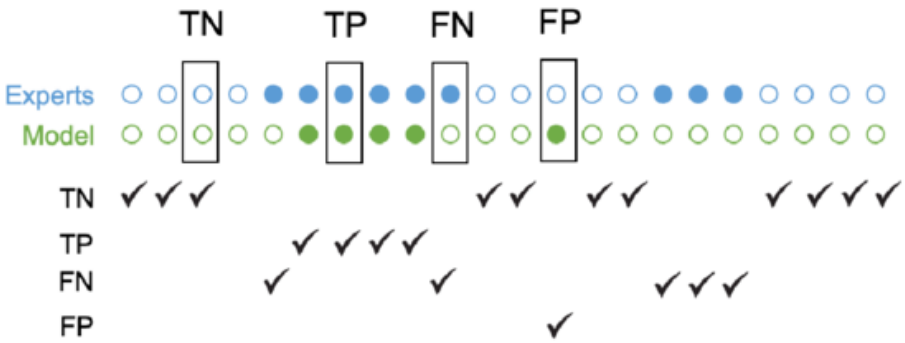

The agreement between the model and experts regarding FoG or non-FoG periods will be assessed as follows:

- TP: A FoG period correctly identified by both the experts and the model
- TN: A non-FoG period correctly identified by both the experts and the model
- FP: A FoG period incorrectly identified by the model but not by the experts
- FN: A FoG period incorrectly identified by the experts but not by the model

Performance scores will be calculated using the following equations:

Model Validation

The model validation will use the leave-one-subject-out (LOSO) cross-validation technique to assess its performance across participants and accommodate the considerable variability between participants. While some studies [20,42] advocate for the leave-one-freezer-out (LOFO) cross-validation technique to avoid overrepresentation of patients without FoG in training and validation sets, our study focuses on participants who have experienced at least 1 episode of FoG during their initial visit. Consequently, each patient will have FoG episodes, making the LOSO approach more suitable for our validation process.

Statistical Analysis

Clinical data of the participants will be presented as means (SD) or medians with IQRs for continuous data, depending on their distribution. Categorical data will be reported as counts (with percentages within parentheses).

Primary Outcome

The main objective of our study is to identify the most relevant features and locations of wearable sensors for detecting FoG episodes. The Relief-F technique will rank features extracted from data collected by all sensor segments. The top-ranked features across all subjects will indicate the most critical sensors for detecting FoG episodes, and these features will be used in model training and validation. The LOSO method will be used for validation, and accuracy will be computed for each subject. Furthermore, Relief-F analysis will be conducted individually for each subject to potentially reveal redundancy in the top-ranked features across subjects. Feature extraction, selection, model training, and validation will be implemented using Python 3.0 (PythonLabs) scripts.

Secondary Outcomes

We will investigate the differences in model performance across various conditions to propose recommendations for interpreting the model. Accuracy, sensitivity, and specificity will be evaluated using a mixed-effects model with fixed effects for patients and random effects for the type of condition (ST, DCT, and DMT) and medication state ("on" and "off").

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Results

The study is currently in the data collection phase, with recruitment starting in February 2024. Once all data have been gathered, data analysis will commence. As of August 2024, 3 patients have been recruited. We anticipate publishing the results by the end of 2025. The results of this study will be presented at scientific events and published in scientific journals.

Discussion

Strengths and Limitations of This Study

The aim of this study is to assess the accuracy of the most effective combination of wearable sensors in detecting FoG in patients with PD. This setup has been developed following an extensive literature review and clinical evaluation of patients.

To date, consensus on sensor placement remains elusive, necessitating a detailed examination of individual and collective placements [15]. The model used will incorporate a broad array of features from both temporal and frequency domains documented in the literature to maximize accuracy. Moreover, this model will undergo testing on a sizable cohort of patients (n=18), each completing 18 passages on a designated freezing-inducing path, yielding a comprehensive data set. Furthermore, the model will be evaluated on a path known to provoke FoG under different medical ("on" and "off" levodopa medication) and clinical (ST, DMT, and DCT) conditions [32]. This evaluation aims to simulate various walking tasks akin to daily life and assess their potential to induce or alleviate FoG, particularly in dual-task scenarios. Several datasets are available, some with restricted accessibility. Multimedia Appendix 1 outlines several pertinent and comparable datasets. Our dataset's strength lies in its incorporation of multiple sensor placements across varied medication states and task complexities, including cognitive dual tasks. This dataset will be openly accessible or supplied on request, fostering research and collaboration in the field.

One limitation of this study is its reliance on a controlled environment. Despite efforts to simulate ecological tasks that mimic everyday challenges and tend to provoke gait freezes (FoG) under dual-task conditions, it is crucial to acknowledge that the study is conducted under controlled conditions. For future research, conducting tests in real-life settings over prolonged periods would be advantageous. This approach could facilitate the accumulation of larger datasets across diverse situations, thereby enhancing our understanding of FoG in more complex real-world scenarios.

Perspectives

The miniaturization of sensors is unlocking new opportunities for monitoring patients with PD, particularly in detecting episodes of FoG. Extending this capability across all medical and clinical settings would offer a more comprehensive understanding of this phenomenon, which remains incompletely understood. Moreover, it would facilitate dependable and objective monitoring of symptom progression, influenced by treatments and the disease's natural trajectory. This could serve as an objective tool for patient monitoring, assessing both the severity and frequency of FoG.

Objective evaluation is crucial for identifying suitable medical and nonmedical treatments, including rehabilitation or deep brain stimulation [43]. Research has underscored the significance of personalized treatment tailored to individual patient needs and circumstances [44]. Real-time detection facilitates the integration of FoG episode identification with external stimuli, such as sensory, auditory, or visual cues, offering a significant opportunity to mitigate FoG episodes [45].

Conclusions

This study aims to enhance the detection of FoG in patients with PD through the use of multiple wearable sensors. By evaluating various sensor placements and the accuracy of detection algorithms, the study aims to determine the most effective combination of wearable sensors for detecting FoG episodes. Despite the study being conducted in a controlled laboratory environment rather than real-life settings, the findings are expected to significantly advance understanding and monitoring of FoG. The anticipated results will provide crucial insights into optimal sensor configurations and detection methodologies, ultimately supporting the development of more precise and personalized treatment strategies for patients with PD. Publication of these results by the end of 2025 will contribute valuable data to ongoing efforts aimed at improving patient care and enhancing quality of life for individuals affected by PD.

Acknowledgments

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Data Availability

No data are currently available, but the results of the trial will be disseminated either with all the accompanying dataset or on request from the authors.

Authors' Contributions

All authors contributed to designing the experimental protocol. KJ oversaw ethics and dissemination aspects. SC, AD, FB, and KJ will carry out the study. SD and FL will identify FoG episodes from the videos. SC will be responsible for developing and validating the setup. SC, AD, KJ, and IB will analyze the data, and KJ, SC, and IB will interpret the findings. All authors will participate in writing the paper. Finally, all authors have reviewed and approved the final version of the protocol.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Comparative overview of datasets for freezing-of-gait evaluation.
[DOCX File , 21 KB - resprot_v14i1e58612_app1.docx]

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Abbreviations

DCT: dual cognitive task
DMT: dual motor task
DT: decision tree
FN: false negative
FoG: freezing of gait
FoGQ: Freezing of Gait Questionnaire
FP: false positive
IMU: inertial measurement unit
LOFO: leave-one-freezer-out
LOSO: leave-one-subject-out
MDS-UPDRS: Movement Disorder Society-Unified Parkinson’s Disease Rating Scale
ML: machine learning
NPV: negative predictive value
PD: Parkinson disease
PPV: positive predictive value
ST: single task
TF: true negative
TN: true positive

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Protocol

A Digital Behavior Change Intervention for Health Promotion for Adults in Midlife: Protocol for a Multidimensional Assessment Study

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Abstract

Background: To support lifelong health promotion and disease prevention, Santé publique France studied the methodology for building a social marketing scheme with a digital intervention targeting middle-aged adults, specifically socioeconomically disadvantaged groups. The digital intervention aims to encourage people aged 40-55 years to look after their health in the short and medium terms by adopting small actions relating to 8 health determinants: nutrition, physical activity, smoking, alcohol, stress, cognitive health, sleep, and environmental health. In the long term, the intervention intends to prevent frailty and reduce the burden of multimorbidities in older age, particularly for lower socioeconomic groups.

Objective: This study aims to measure behavior changes among registered users of the future website. The protocol assesses the impact of the website based on users' implementation of small actions relating to the 8 health determinants. Specifically, it intends to evaluate the website's performance in terms of engaging a specific population, triggering behavior change, raising awareness about a multifactorial approach to health, and encouraging user interaction with the website's resources.

Methods: The methodology is based on clinical assessments developed alongside the website according to the functionalities offered to registered users in their personalized space. The assessment tool design draws on logic models for digital interventions, and their consistency for digital applications is verified. The target audience is clearly defined from the outset. The protocol sets out a 3-step assessment: upon registration, after 3 weeks of use, and after 10 weeks of use (end of assessment). Users are divided into 2 groups (socioeconomically disadvantaged users and others) to characterize differences and make corrections. The protocol uses a mixed assessment approach based on website traffic and user login data. Specific and identifiable behavior changes are documented by monitoring the same individuals from T0 to T2, using verbatim comments to classify them into profiles and conducting semistructured individual interviews with a sample of users.

Results: The protocol creates a multidimensional assessment of digital intervention, showing that during a given timeline, interactions with users can reveal their capabilities, opportunities, and motivations to adopt healthy lifestyles. The protocol's principles were integrated into the development of a personal account to assess users' behavior changes. Given the delayed launch of the website, no recruitment or effects analysis of the protocol took place.

Conclusions: As no multidimensional assessment protocol is currently available for digital behavior change interventions, our methods reveal that the different framework stages can strengthen the effect measurement, consolidate the choice of assumptions used within the logic model and steer the digital intervention toward action while reducing the burden of information. The suitability of the assessment protocol remains to be evaluated given the delayed launch of the website.

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KEYWORDS

digital behavior change intervention; assessment protocol; middle-aged adults; health promotion; user account; mixed assessments; health information technologies

Introduction

Background

Today, expert consensus recommends that people should strengthen disease prevention actions from the age of 40 years [1-3] to avoid loss of independence due to the accumulation of chronic diseases. Different studies show a correlation between the number of healthy behaviors (physical activity, diet, stop smoking, and reduction of alcohol consumption) and healthy aging. Santé publique France has been working on the planning stages of a social marketing scheme that includes a digital behavior change intervention. The digital intervention was designed in tandem with its assessment protocol in the hope that engineering feedback would improve its applicability. An overview of the literature on the assessment of digital tools for health promotion and disease prevention found proven evidence for the following: (1) the added value of a multidimensional assessment of a digital intervention [4,5], (2) the challenge of distinguishing between effect measurement and implementation measurement [6] since "a crucial implication of explicitly recognizing the distinction between engagement with the technological and behavioral aspects of the intervention is that intervention usage alone cannot be taken as a valid indicator of engagement" [7], (3) the importance of being able to qualify the maintenance of a target behavior over time [8], and (4) the absence, to our knowledge, of a mixed quantitative and qualitative assessment protocol [4,9-11].

It was precisely this gap that prompted the drafting of this assessment protocol for a nonclinical intervention. We explored the literature on assessments in the fields of medicine and medical informatics as a basis for consolidating some of our following methodological choices.

- The framework stages to develop an assessment protocol: preliminary diagram, study design, operationalization of the methods, project schedule, execution, and conclusion [12-14].
- The lesson that an evaluable result consists of the internet user's loyalty to the logic models used and not the loyalty necessary for a program to be effective [15]: "The distinction in digital health evaluation from traditional evaluation is that there is not always a need to evaluate health outcomes as direct effects of the digital health intervention" [13].
- The decision to document the initial impact of an intervention as well as its additional impact compared to existing digital interventions by Santé publique France [13].
- The decision to take into account the unexpected effects of health IT [16].

Digital Intervention for Behavior Change in Midlife

Based on a holistic and person-centered approach, the digital intervention provides information on the main risk factors for health, taking into account the barriers to and drivers for adopting healthy behaviors as well as the specific living conditions and environments of those aged 40-55 years. This digital intervention is based on the quantified self to support behavior transformation [17,18]. The design of the intervention is explained in a separate study (under review) that illustrates the complementary nature of the theories used in relation to the targeted behavior changes. To become familiar with the user and guide them toward behavior changes, the initial access to the site requires them to fill out a questionnaire on their lifestyle habits, which generates personalized feedback according to a traffic light system in order to introduce recommendations for protective behaviors. At this stage, the user has the option of downloading their report with an overview of the feedback in the form of a table. The next click opens a feed page with action cards and studies that the user can "like," save to their account, and use to navigate further around the site. The personal account is designed as a self-coaching tool intended to support motivation, increase the power to act, and help the user understand health as an interaction between several health determinants applying to all life areas (Table 1).

Table 1. Personalized space of the digital intervention with the available resources and functionalities.

Sections of the personalized space	Resources or functionalities available
Home page	The following items are displayed as a dashboard: answers to the "lifestyle habits" questionnaire, feedback in a traffic light system, feed page with action cards and study pages that can be liked, and liked actions and study pages following website navigation.
My favorite content and goals	A list of liked actions automatically categorized by determinants—users have total freedom to use drag-and-drop to modify the layout according to their needs (eg, from the easiest to the most difficult; based on a time frame) and to delete or add material; and a list of liked studies automatically categorized by determinant—users have total freedom to use drag-and-drop to modify the layout according to their needs (eg, from the easiest to the most difficult; based on a time frame) and delete or add more.
My assessment	An option to repeat the "lifestyle habits" questionnaire to see how habits have changed with the traffic lights and feed page being updated and a history of previous questionnaires is displayed.
My successes	A list of actions that have become everyday behavior.

As no gold standard questionnaire on lifestyle habits is available, the present one is a concatenation of different examples taken from the literature and pretested with a target group of midlife adults during a qualitative study.

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The personalized space for registered users was leveraged to form the basis of the assessment as the users' actions could be tracked via the content management system. The assessment could then be carried out continuously or in waves.

Conceptual Framework: Intervention Model

The first step was to identify the causes of the problem, shown in the "causal model of the problem" in Figure 1 [19], then to translate them into an objective in the "theoretical logic" part and finally to deduce the output and intervention objectives (operational logic model), leading to 3 evaluable working hypotheses.

Figure 1. Modeling the social marketing scheme to support the adoption of healthy lifestyles in midlife (adapted from Brousselle et al [19]). COM-B: capacities, opportunities, motivations-behavior.

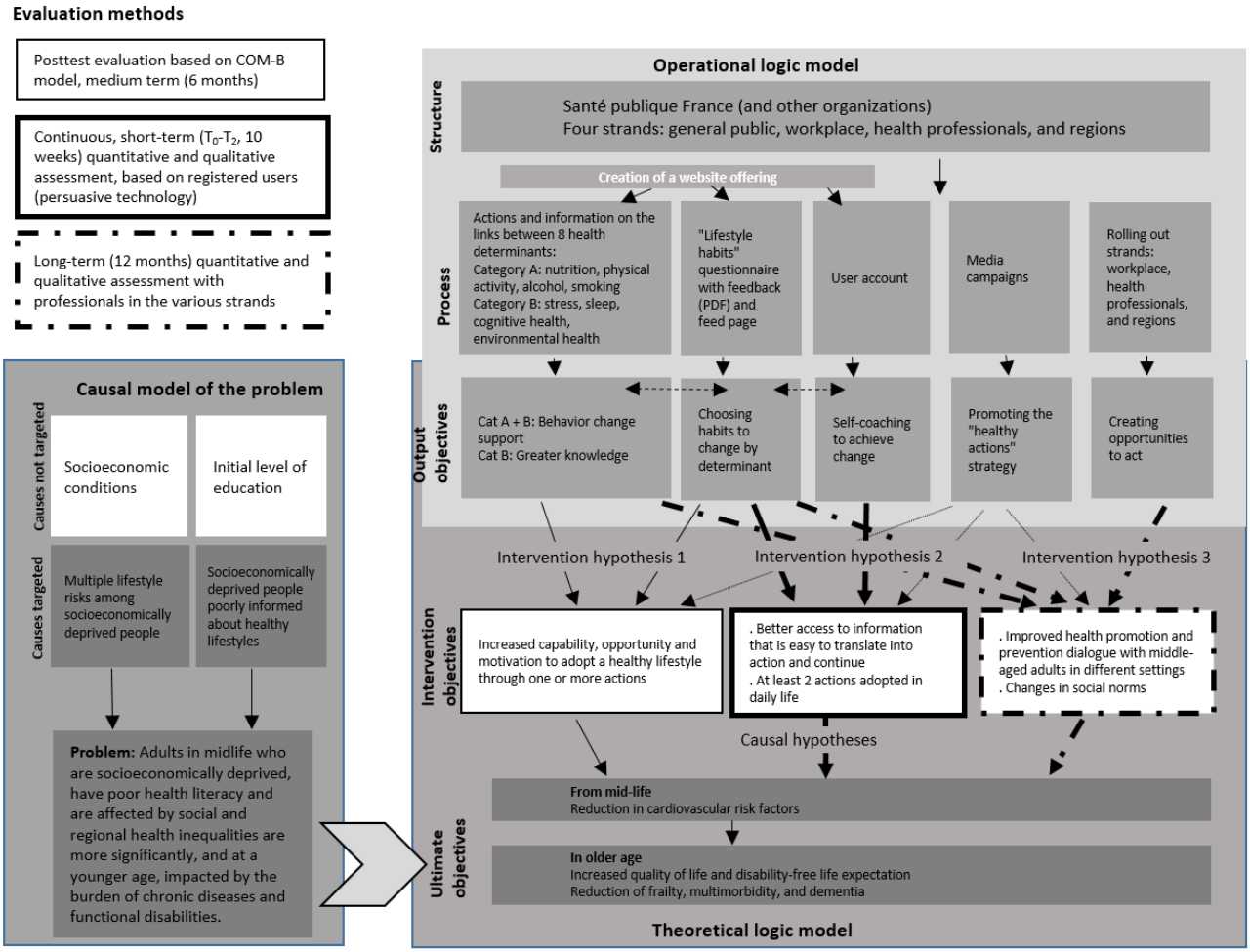

The protocol aims to assess the impact of the website based on the small actions triggered among users to the different health determinants. Specifically, it is intended to evaluate the website's performance in terms of the following objectives: (1) engaging a specific population, (2) triggering behavior change, (3) raising awareness about a multifactorial approach to health, and (4) encouraging user interaction with the website's resources. The paper describes the methods and their relevant limits when constructing an assessment protocol for digital interventions. It questions the value of digital self-assessment and the time frame necessary to evaluate the adoption of healthy lifestyles, as no expert consensus is available on this topic. Finally, the article explores how behavior change models can strengthen the effect measurement of an assessment protocol.

Methods

Objectives of the Digital Intervention

The effect of the intervention on protective behaviors in midlife is communicated through 8 health determinants: diet, physical activity, smoking, alcohol, stress, sleep, cognitive health, and environmental health. The digital intervention is intended to help people aged 40-55 years, and in particular, socioeconomically disadvantaged people to (1) adopt multifactorial preventive actions in their daily lives; (2) increase their knowledge about lesser known determinants (stress, sleep, cognitive health, and environmental health); (3) support dialogue with health care professionals; and (4) develop psychosocial skills, especially the ability to resist social pressure.

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Theory of Assessment of a Digital Intervention

The 3-pronged approach of "perceive, prepare, act," resulting from existing digital behavior change interventions [8,20], correlates with the functionalities of the website—questionnaire, actions, personalized space—designed using the behavior change techniques of capacities, opportunities, motivations-behavior (COM-B) [21].

Table 2 shows the indicators that can be used to answer the assessment questions.

- The mechanisms and factors that influence the choice of one or more actions and contribute to whether they are adopted are shown in "1. goals and planning—perceive, prepare, and act" as well as in the column "prepare" when a user likes one or more actions.
- The influence of personalized space on the adoption of actions (preferably multifactorial) and on the self-assessment of lifestyle habits can be understood on the basis of the items listed in the "act" column.
- The factors likely to influence target users' perception of their chosen health-promoting action are reflected in the fact that the questionnaire is repeated (2.4) and that behaviors are practiced, repeated, and changed (from 8.1 to 8.4).

Table 2. Transposing the BCT[a] of COM-B[b] onto the digital behavior change intervention context: perceive, prepare, and act.

COM-B	Digital behavior change intervention [8]		
	Perceive (website + questionnaire)	Prepare (actions)	Act (personalized space)
1. Goals and planning	1.6. Discrepancy between current behavior and goal (questionnaire)	1.1. Goal setting (behavior) 1.4. Planning behavior	1.5. Review behavior goals (increase practice) 1.6. Discrepancy between current behavior and goal (doing the action) 1.7. Review outcome goal(s) 1.9. Commitment (to be done, etc.)
2. Feedback and monitoring	2.2. Feedback on behavior (questionnaire)	__[c]	2.3. Self-monitoring of behavior 2.4. Monitoring of behavior outcomes (redo the questionnaire)
3. Social support	3.1. Social support (unspecified; internet resources) 3.2. Social support (practical) 3.3. Social support (emotional)	—	—
4. Shaping knowledge	4.2. Information about antecedents	4.1. Instruction on how to accomplish a behavior	—
5. Natural consequences	5.1. Information about health consequences 5.2. Salience of consequences 5.5. Anticipated regret	—	—
6. Comparison of behavior	6.2. Social comparison	6.1. Demonstration of the behavior	—
7. Associations	7.8. Associative learning (favorable environment and multifactorial approach)	—	7.1. Prompts or cues
8. Repetition and substitution	—	8.3. Habit formation	8.1. Behavioral practice or rehearsal 8.2. Behavior substitution 8.3. Habit formation 8.4. Habit reversal
9. Comparison of outcomes	9.1. Credible sources 9.3. Comparative imagining of future outcomes	—	—
10. Reward and threat		—	10.4. Social reward
11. Regulation	11.3. Conserving mental resources	—	—
13. Identity	13.1. Identification of self as role model	—	—
15. Self-belief		—	15.3. Focus on past success

[a]BCT: behavior change technique.

[b]COM-B: capacities, opportunities, motivations-behavior.

[c]Not applicable.

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The typology of a target user, as described earlier in the objectives, can be combined with the indicators of the perception, preparation, and action stages to complete an assessment in advance.

Mixed Assessment Protocol

Three evaluative questions emerge concerning the personalized account and, by extension, the website.

- What mechanisms and factors influence the choice of one or more actions and contribute to the user adopting them?
- What influence does personalized space have on the adoption of actions that are preferably multifactorial and on the self-assessment of lifestyle habits?
- What factors are likely to influence target users' perception of their chosen health-promoting action?

Our protocol combining quantitative and qualitative assessment is based on data collected from the personalized space, which was designed with the objective of "outsourced self-regulation" [17], supplemented by additional questionnaires and individual interviews. The mixed assessment evaluates behavior changes made at different time points in the data collection process rather than the increase in quality of life and disability-free life expectancy. As mentioned earlier, the evaluable result is the user's loyalty to the logic models used [13] and not the loyalty necessary for a program to be effective [15]. Kelders et al [22] described the typical components through an analysis of 83 digital interventions: modular, updated once a week, use of persuasive technologies, and potential to interact with the communicator and peers [23].

The features of an assessment protocol are as follows.

- Before the digital intervention is launched: it supports the design and modeling of digital intervention.
    - Once launched, (1) it checks whether the users of the personalized space are between the ages of 40 and 55 years, whether they are socioeconomically deprived, and whether they have a low level of literacy; (2) it creates typologies of registered users; (3) it measures the effects (ie, changes in the behavior of registered users) through evaluable criteria and indicators such as adopting and maintaining a new healthy behavior, increased knowledge, improved psychosocial skills, and improved health variables [6,24]; and (4) it continually improves the website and personalized space to support the desire to change behavior in midlife [18,25].

Recording unexpected effects [16] sheds light on the adjustments needed in order to continually improve the intervention. Several hypotheses for these have been formulated: (1) the questionnaire does not engage users or it is never repeated; (2) the initial request does not correspond to the determinant that the user is "coached" on in their personalized space; (3) a highly disparate choice of actions makes it difficult or even impossible to implement them (no actions are adopted); and (4) actions are liked without a time objective being set.

Assessment Objectives

As stated above, the intention was to split the individuals included in the assessment into 2 groups. The 7 measurement objectives presented below apply to both groups. A detailed description of the objectives is given in Multimedia Appendix 1.

- Objective 1: To assess whether the user's profile matches the purpose of the site, namely, to reach socioeconomically disadvantaged people with a low level of health literacy and aged between 40 and 55 years at T0.
- Objective 2: To record lifestyle habits that deviate to some extent from public health recommendations at T0, T1, and T2.
- Objective 3: To record liked actions and articles while distinguishing actions in category A (change in behavior: diet, physical activity, smoking, and alcohol—additional contribution compared to other Santé publique France social marketing schemes) from those in category B (greater knowledge: sleep, stress, cognitive health, and environmental health—initial contribution given the absence of other Santé publique France resources). The assumption made is that the user chooses actions for category A and study pages for category B. Data are collected at T0, T1, and T2.
- Objective 4: To assess willingness to change behavior at T0.
- Objective 5: To assess the evolution of the behavior change between T0 to T1 and T1 to T2; to assess the frequency and routine nature of actions at T1 and T2.
- Objective 6: To assess re-engagement at T2.
- Objective 7: To assess lapsed connection to the personalized space before T1 and before T2 [26].

Assessment Time Frame

A digital behavior change intervention consists of several stages with a total average duration of approximately 10 weeks [8], although there is no consensus between experts over the time frame. Engagement with the digital intervention involves registering to create an account with a personalized space and then signaling preparation for behavior change (phase 1), followed by the adoption of 1 or 2 actions (phase 2), and a phase of lapsed activity on the site (phase 3). Reengagement with the intervention (phase 4) is prompted by the need to solve a problem, renew motivation, identify a new action, and so on. [7]. Split into 3 evaluable phases—T0, T1, and T2 (respectively phases 1, 2, and 4 according to Yardley et al [7], in Table 3). The expected results and collection methods are presented in Table 3. It is based on the assessment work of the VERB™ campaign (in normal type) [27], the lessons learned on health information-seeking behaviors (in italics) [28], the theory of small actions (in bold) [29], and digital behavior change interventions (in bold and italics) [7].

Table 2 presents the interaction between perceiving, preparing, and acting, which can be repeated randomly at the 3 assessment intervals set out in Table 3.

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Table 3. Timing of the assessment process, evaluable results, and assessment indicators: engagement with physical activity.

Action verbs	Actions	Outcomes	Assessment or indicators
Phase 1 (T0): use of the digital intervention			
To be aware of and to understand	Campaign	—[a]	Quantitative posttest evaluation of social media campaigns
To access	*Information*	—	—
To engage with	**Information**	**Site log-in and completion of the questionnaire**	**Log-in data (quantitative)**
To choose	***A small target behavior***	***Actions or liked content pages, account created in the subscriber space, and healthy lifestyles***	***Interaction with the site and subscriber space data (quantitative and qualitative)***
Phase 2 (T1): use of the digital intervention and engaging with behavioral change			
To change in	—	Subjective norms, beliefs, self-efficacy, and perceived behavioral control	Qualitative data: questionnaires, verbatim comments, and individual interview
To use	*Information*	—	—
To intend to do	Physical activity	—	—
To engage with	**Behavior changes**	**Site log-ins and actions in the subscriber space**	**Qualitative and quantitative data from the subscriber space**
To choose	***A small target behavior and a concatenation of smaller goals***	***Actions or liked content pages and healthy lifestyles***	***Interaction with the site and subscriber space data (quantitative and qualitative)***
Phase 3: engaging with behavioral change			
—	—	—	—
Phase 4 (T2): use of the digital intervention and engaging with behavioral change			
To commit to and to maintain	Physical activity	Health outcomes	Log-in data (quantitative); interaction with the site and subscriber space data (quantitative and qualitative); and qualitative data: questionnaires, verbatim comments, and individual interview
To make	*Physical activity*	*Empowerment/ locus of control, satisfaction, activities of daily living, and health outcomes*	—
To choose	**A new small target behavior**	**Liked, validated actions**	—
To re-engage with	***Information if needed***	***Site log-ins and actions in the subscriber space***	—

[a]Not applicable.

Furthermore, it is particularly important to determine (1) T1 (changes related to subjective norms, beliefs, self-efficacy, and perceived control of behavior), (2) T2 (level of empowerment, degree of satisfaction, activities of daily living, and self-reported health outcomes), and (3) between T0 and T1 and then between T1 and T2, there are 4 reasons for lapsing—forgetting, having a technical problem, permanently giving up on self-quantification, and suspending usage—but these do not necessarily mean that the adopted action has been abandoned [26].

Assessment Methods From T0 to T2

As detailed in Figure 2 [30], the assessment of the digital intervention at T0, T1, and T2 is intended to be explanatory, combining a quantitative and qualitative approach based on recording for both groups of users: (1) log-in data for the site and user account with personalized space, (2) data relating to specific and identifiable behavior changes by monitoring registered users from T0 to T2 via the content management system, (3) verbatim statements from users for classification into user profile; and (4) information about capabilities, opportunities and motivations via semistructured individual interviews with a sample of users.

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Figure 2. Assessment methods from T0 to T2 (adapted from Trottier et al [30]).

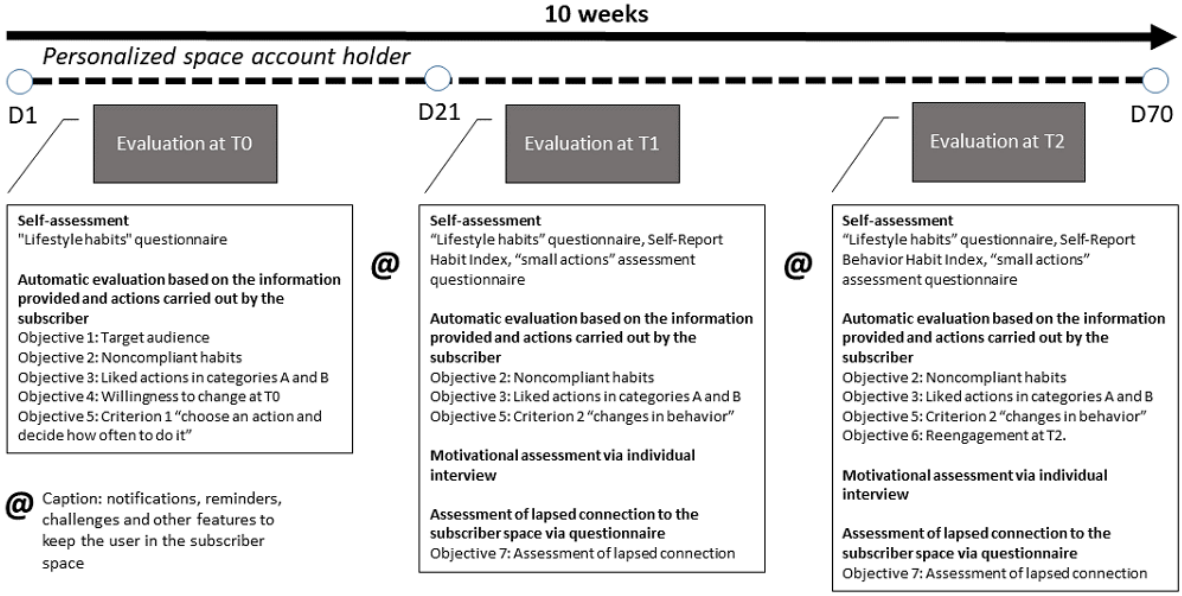

Self-Assessment at T0, T1, and T2

The "lifestyle habits" questionnaire is the basis of the initial self-assessment at T0, then again at T1 to visualize the changes that have taken place and finally at T2 to identify developments (Table 4). Other suggested tools at T1 are the Self-Report Habit Index [31] to assess the power of the "frequency" factor for the action performed most often and the "small actions" assessment questionnaire. At T2, the Self-Report Behavior Habit Index is intended to show whether the behavior has become routine, supplemented by the "small actions" assessment questionnaire.

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Table 4. Expected outcomes and measurement tools of the assessment protocol [32].

Objective	Domains	Measures	Source	Time frame	Measuring or recording tools
First results					
2. Lifestyle habits	Lifestyle habits more or less comply with public health recommendations	Results of lifestyle habits questionnaire	Server log files	T0, T1, and T2	"Lifestyle habits" questionnaire
3. Liked actions and articles	Adopting categories A and B actions related to one or more health determinants	Classification of actions by the user (including verbatim comments)	Server log files	T1, T2	Classification of actions
3. Liked actions and articles: multiple health factors	Understanding that health depends on multiple factors	Classification of actions by the user (including verbatim comments)	Server log files	T1, T2	Classification of actions
4. Willingness to change behavior	Statement of wanting to change a behavior	Classification of actions by the user (including verbatim comments)	Server log files	T0	"Lifestyle habits" questionnaire and Lapsing assessment questionnaire
5. Evolution of behavior change	Change in one or more lifestyle habits	Lifestyle habits questionnaire is repeated with one or more lifestyle habits changing	Server log files	T1, T2	"Lifestyle habits" questionnaire and classification of actions
5. SRHI[a]	Frequency of performing action	Self-assessment by SRHI	Server log files	T1	SRHI
5. SRBHI[b]	Extent to which action has become routine	Self-assessment using SRBHI	Server log files	T2	SRBHI
6. Re-engagement	Assess re-engagement	Classification of actions by the user (including verbatim comments); self-assessment by SRBHI	Server log files	T2	Classification of actions
7. Lapsed connection	Assess lapsed connection to the personalized space	Results of the assessment questionnaire on lapsed connection	By email	Before T1 and before T2	Lapsing assessment questionnaire
Mediators					
Effectiveness of mediator	Self-efficacy	Sense of personal efficacy [33]	Individual interview by group 1 and group 2 profile type	T1	Sense of personal efficacy scale
Effectiveness of mediator	Motivation	Situational motivation [34]	Individual interview by group 1 and group 2 profile type	T2	Situational motivation scale
Effectiveness of mediator	Capability, opportunity, and motivation	Information provided by the user through the individual interview	Individual interview by group 1 and group 2 profile type	T1, T2	Interview guide
Effectiveness of mediator	Frequency of personalized space log-in	Quantitative analysis of the user journey	Server log files	Continuous	Number of log-ins, liked actions and articles, incorporated or abandoned actions; time spent logged in; and interconnection between the determinants
Other results					
1. User profile	Biographical data	Categorized into group 1 or group 2: age, profession, level of health literacy, and absence of chronic disease	Results of lifestyle habits questionnaire and results of the "small actions" assessment questionnaire	T0	"Lifestyle habits" questionnaire and "Small actions" assessment questionnaire

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Objective	Domains	Measures	Source	Time frame	Measuring or recording tools
1. User profile	Relationship between initial contribution (category B) and additional contribution (category A)	Personalized space: liked actions and studies	Server log files	T0-T2	Number of liked actions and articles by category
1. User profile	Any difference in behaviors between group 1 and group 2	Processing quantitative and qualitative data provided by registered users	Server log files	T1, T2	"Lifestyle habits" questionnaire, "Small actions" assessment questionnaire, and individual interview
1. User profile	Rate of lapsed activity in the personalized space	Lack of log-ins to the personalized space	Server log files	T0–T2	Number of log-ins between T0 and T2 and Lapsing assessment questionnaire

[a]SRHI: Self-Report Habit Index.

[b]SRBHI: Self-Report Behavior Habit Index.

To further support the objectives mentioned earlier, an automatic assessment at T0, T1, and T2 retrieves the information provided and actions carried out by the user.

The aim of the semistructured individual interview at T1 and T2 by groups 1 and 2 profile type and sampling is to reveal the impact of the capabilities, opportunities, and motivations on behavior change by combining the methodology of the COM-B, the theoretical domains framework [35] and the tiny habits theory. Taking a human-machine interaction perspective, it is very difficult to determine whether the choice of an action is based on conscious or unconscious motivation [8].

The assessment of lapsed connection to the personalized space before T1 and before T2 will be carried out via a questionnaire sent by email to the concerned users. The objective is to identify the reasons for the lack of use (with the aim of continually developing the personalized space) and the number of actions maintained without logging in.

Objectives 2, 4, and 5 make it possible to assess any unexpected effects: (1) the questionnaire is not the draw for the user or is never repeated (meaning that the user cannot view their progress in the personalized space; objective 2); (2) actions are liked, but no goal is set (objective 4); (3) a highly disparate choice of actions makes it difficult or even impossible to implement them (no actions are adopted; objective 5, criterion 1); and (4) the initial request differs from the action that the user is "coached" on in the personalized space (objective 5, criterion 2).

Assessment Population

The internet users, included in the assessment will be between the ages of 40 and 55 years, have registered to create an account on the website with a personalized space, and have carried out actions in their space during the 3 assessment stages: T0 (date of personal account creation), T1 (3 weeks after creation), and T2 (10 weeks after creation) (see Figure 3). Users will be divided into 2 groups. Group 1 will include socioeconomically deprived people and group 2 all other users. Each group will then be subdivided based on the "motivations," "capabilities," and "opportunities" expressed. By characterizing users into these 2 socioeconomic groups, the diversity of behaviors can be questioned, and corrections can be made to support group 1. Classification into group 1 will be based on 2 conditions: belonging to the lower socioprofessional categories and having a level of health literacy below 3.39 on domain 8 of the French Health Literacy Questionnaire [36].

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Figure 3. Assessment diagram.

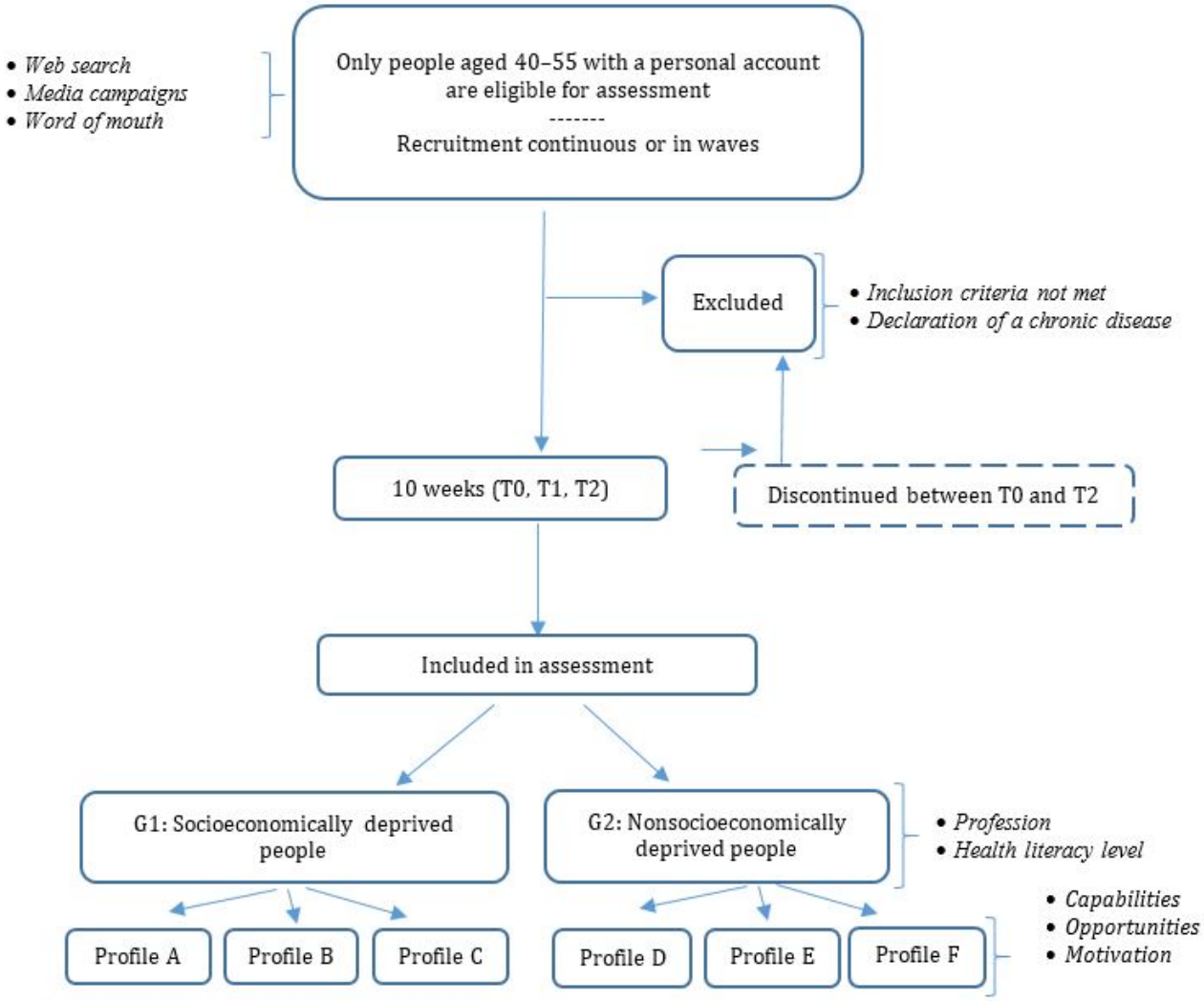

When people create their personal account, in accordance with the General Data Protection Regulation in force in Europe, registered users will need to consent to the use of their quantitative and qualitative data for study purposes and agree to be contacted as part of the assessment. No sensitive medical data will be recorded, and the data from the content management system will be separated from the information collected through the personalized space. The digital security officer at Santé publique France verified the compliance of this data management approach with French data protection regulations (Commission nationale de l'informatique et des libertés).

The protocol currently allows testing in a given context and on a regional scale, for example.

Results

This first version of the protocol responds to the objective to create a multidimensional assessment of a digital intervention based on the statement that during a given timeline, interactions with users aged 40-55 years can reveal their capabilities, opportunities, and motivations to adopt healthy lifestyles.

The assessment protocol based on the interactions with users in their personalized space of the digital behavior change intervention includes the evaluation of the following.

- Increased capability, opportunity, and motivation to adopt a healthy lifestyle through one or more actions.
- Improved access to information that is easy to translate into actions and to continue.
- At least 2 actions adopted in everyday life.

However, the protocol cannot evaluate improved health promotion and disease prevention dialogue with adults in midlife in different settings or assess changes in social norms.

As the construction of the website is currently delayed, no recruitment or effects analysis of the protocol could take place. The creation of a steering committee was abandoned.

Discussion

Expected Findings

As mentioned above, the protocol assesses the impact of the website based on the small behavior changes that it triggers among users in relation to different health determinants. The protocol has four aims: (1) engaging a specific population, (2)

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triggering behavior change, (3) raising awareness about a multifactorial approach to health, and (4) encouraging user interaction with the website's resources. The research takes an interest in challenging the time frame necessary to evaluate the adoption of healthy lifestyles. It focuses on how the usage of behavior change models (COM-B) combined with the techniques of digital behavior change interventions [8] can strengthen the effect measurement of an assessment protocol. The assessment protocol is based on typical digital functionalities such as a user account, self-evaluation of healthy lifestyles (questionnaire), and feedback to engage people with behavior change. It fosters a continuous short-term evaluation of digital behavior change interventions.

Main Results

This appears to be the first assessment protocol for digital health promotion interventions. It documents the potential of the digital intervention in various respects, supporting it on the basis of the chosen models that led to the design of the personalized space and contributing to its continued development both in terms of its technical features and written content. The mixed assessment method delivers a granular analysis that sheds light on the effectiveness and even the efficiency of the website through its personalized space. To our knowledge, our assessment protocol for a digital personalized space, designed with the aim of changing health promotion and disease prevention behaviors, is the first of its kind in the sense that it goes beyond the measurement of the implementation and expressly targets the measuring effect. According to literature reviews, the effects in question will be behavioral change, greater knowledge, improved psychosocial skills, development of a support network, and improved health variables [6]. The protocol cannot be likened to assessments in investigational designs such as randomized controlled trials, which have been dismissed by some experts as unsuitable by some experts due to the complexity of health promotion interventions. The open design is considered effective "for the institutions that set it up and its flexibility matches the characteristics of health promotion interventions" [6].

Limitations

The breadth of the mixed assessment may make the process of interpreting the lessons learned more complex if the power of each item of "collectible" information proves to be insufficient. The absence of an expert consensus on the duration necessary for behavior change to occur throws into question the time frame of 70 days. The weakness of the protocol relates to the lack of real application given that the launch of the website is delayed.

Conclusions

Drafting an assessment protocol is a significant aid in the design of a digital intervention. This makes it possible to consolidate the choice of hypotheses for constructing the logical models used and the objectives targeted. A protocol helps to steer the digital intervention toward the action and regularly checks that it meets the needs of its target audience. The assessment protocol meets the SMART (specific, measurable, achievable, relevant, and time-bound) criteria.

The research presented here will impact digital interventions in health promotion and disease prevention. As the protocol demonstrates, both the implementation and effects can be assessed. Health promotion and disease prevention stakeholders may prefer an assessment of the program, but this is rarely carried out. Without assessments, a digital intervention can claim to be "evidence-inspired," although, with assessments, it is closer to "evidence-based."

Conflicts of Interest

None declared.

Multimedia Appendix 1
Detailed presentation of the 7 objectives of the assessment.
[DOCX File , 26 KB - resprot_v14i1e60559_app1.docx]

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Abbreviations

COM-B: capacities, opportunities, motivations-behaviors
SMART: specific, measurable, achievable, relevant, time-bound

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Protocol

Developing and Evaluating an Interactive, Case-Based, Web-Based Active Learning Tool for Primary Care Physicians (Community Fracture Capture Learning Hub): Protocol for an Acceptability and Engagement Study

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Abstract

Background: The lack of osteoporosis treatment initiation after fragility fractures is a significant gap, especially in primary care. It is unclear whether barriers for primary care physicians (PCPs) arise from uncertainty about investigations, treatment initiation, or medication side effects. Key questions remain about whether active learning platforms improve treatment initiation rates better than passive methods and how PCP demographics affect learning outcomes. With PCPs increasingly using web-based platforms for continuing professional development due to time constraints and heavy workloads, an interactive community fracture capture (CFC) tool may serve as an effective alternative to in-person learning. Our CFC pilot study tested this new program's design and content, showing promising potential.

Objective: We aim to evaluate the interactive, case-based, web-based CFC Learning Hub, examining user acceptance and engagement with the platform, focusing on participants' interactions, satisfaction levels, and overall experience.

Methods: Participating PCPs are recruited through Praxhub, a web-based medical education platform, and provide electronic consent for data use after deidentification. They have been allocated into small groups (12-20 members) and join the CFC Learning Hub, a secure web-based community. This hub includes a web-based discussion forum with participant-contributed case studies and a knowledge repository. Over the 6-week program, participants will receive weekly modules with instructions, resources, discussion threads, and quizzes, along with interactive discussions moderated by experienced PCPs and physicians. The platform also hosts web-based surveys that, in combination with platform analytics, allow assessment of baseline knowledge gaps, level of activity or engagement, and improvements following the course completion. This study protocol demonstrates the creation and proposed evaluation of the CFC Learning Hub, featuring an interactive, case-based, small-group web-based learning platform equipped with flexibly scheduled, tailored modules to address the fracture treatment gap within the community. Both qualitative (via thematic analysis) and quantitative (by using 2-tailed paired *t* tests, Wilcoxon signed rank tests, and multivariable regression

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analysis) analyses will be used to assess levels of engagement and acceptance and changes in PCPs' knowledge and confidence after engagement with the CFC Learning Hub.

Results: Recruitment of participants started in May 2022. Data collection, analysis, and reporting will be completed following the completion of four 6-week cycles of the program.

Conclusions: The study described in this protocol will provide important insights into the function and effectiveness of the CFC Learning Hub. This information will guide the expansion of the program. This initiative offers a simple digital solution for promoting current bone health practices tailored to PCPs' needs and thereafter to expand the rollout of the e-learning hub and implementation of fracture liaison models at a primary care level in Australia and elsewhere. Future applications may extend to other clinical areas and professions.

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KEYWORDS

community-based fracture capture bone hub; osteoporosis; virtual communities of practice; continuing professional development; primary care physicians; web-based learning platform; case-based education

Introduction

Osteoporosis: A Growing Global and National Concern and the Unmet Challenges in Fracture Prevention and Management

Osteoporosis affects around 200 million people globally, resulting in more than 8.9 million fractures each year, equivalent to 1 fracture every 3 seconds worldwide [1]. Furthermore, this disease burden is projected to increase dramatically in the coming decades as the global population is aging [2]. By the year 2050, the global occurrence of hip fractures is estimated to rise by 310% for men and 240% for women, compared with 1990 rates [3]. In Australia, osteoporosis incurred a societal cost of Aus $2.6 billion (~US $1.638 billion) in 2022 [2]. Despite the alarming increase in the prevalence of osteoporosis and the morbidity, mortality, and economic costs associated with low-trauma fractures in the aging population [4-6], there remains a substantial deficit in the implementation of effective interventions to prevent fragility fractures [7-9]. Despite the presence of effective diagnostic tools (eg, dual-energy x-ray absorptiometry [DXA]), fracture risk assessment tools (eg, FRAX) [10], and medications known to mitigate fracture risk, a substantial treatment gap exists in osteoporosis care, with only about 20% to 30% of individuals who sustain fragility fractures receiving guidelines-based care [2,11]. International and Australian data have unequivocally demonstrated the cost-effectiveness of hospital-based fracture liaison services (FLS) in secondary fracture prevention to address this treatment gap among patients presenting with low-trauma fractures, including in our own institution [12,13]. However, many patients with low-trauma fractures that may not require tertiary care (eg, vertebra, radius, and others) are investigated and managed purely at the primary care level and therefore may escape hospital-based services [14]. Furthermore, a recent survey of the International Osteoporosis Foundation Capture the Fracture program also noted a relative paucity of FLS centers in Australia [2]. The probability of initiation of osteoporosis medication following hip fracture within 12 months after discharge has been falling, despite these patients having the highest risk for imminent refracture [15,16]. The same investigation gap exists in primary fracture prevention among primary care physicians (PCPs); since 2016, there has been a plateau in subsidized bone density requests for Australians older than 70 years, despite the rapidly aging population [9,12,14,17].

Adapting Fracture Prevention Models: The Urgent Need for Improved Primary Care Strategies

A rational approach to improving fracture prevention outcomes in the community setting would be to adapt the hospital-based model of care at the primary care level. However, unlike the hospital-based FLS that depends on the coordinator to facilitate investigations and clinic appointments, community-based fracture capture relies solely on PCPs to detect, investigate, and treat osteoporosis [18]. Despite compelling evidence for efficacious treatments to manage osteoporosis in primary care, and in particular the initiation of therapies to minimize the likelihood of refracture, the application of evidence and guidelines into clinical practice, particularly by PCPs, remains unacceptably low in Australia and many other countries such as the United States, Malaysia, Singapore, Germany, France, and Canada [9,19-24]. Consequently, many Australians are not receiving optimal, timely care in the community. For example, despite being eligible for osteoporosis-related investigations (eg, DXA) and antiresorptive therapies (eg, denosumab and bisphosphonates), a large proportion of Australians are neglected in this respect. While the hospital FLS model focuses on secondary fracture prevention with the motto of "Stopping at One Fracture," the additional focus among PCPs should be primary fracture prevention with the aim of "Stopping the First Fracture" [25].

Empowering PCPs: A Novel Approach to Bridging the Osteoporosis Treatment Gap Through Live, Interactive Learning Hubs

PCPs are faced with enormous challenges in daily practice to deal with multiple chronic health conditions, their sequelae, and comorbidities within a limited consultation time. Despite this, PCPs are required to continuously extend their knowledge to ensure that evidence-based practice is applied to their patients [26,27]. PCPs are increasingly seeking information on the web for their continuing professional development (CPD) [28-31], which is a viable alternative to face-to-face learning that

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potentially can be managed in their own time [32]. Hence, incorporating social media technologies for CPD has become a commonplace mechanism encouraging PCP learning in web-based group settings [29,33,34]. Including our Community Fracture Capture (CFC) Learning Hub pilot study, only a few recent studies have investigated the ability of web-based learning activities to mitigate the crisis in osteoporosis care by providing education, leveraging the scarce resources of the health care system, and enabling practitioners to offer better and more accessible skeletal health care locally and at a lower cost [35,36]. Our investigation of challenges PCPs face in using virtual communities of practice (VCoPs) for continuing medical education emphasizes the importance of trust building, efficient time management, and collaborative learning among health care professionals in building efficacious VCoPs [37]. We therefore aim to address the community osteoporosis treatment gap using a novel, live, and interactive CFC Learning Hub that provides a health VCoP to facilitate knowledge transfer to overcome barriers to osteoporosis recognition and management.

Although this program incorporates some elements typical of conventional courses, its distinctive combination of features and the unparalleled extent of flexible engagement opportunities set it apart. This uniqueness underscores our rationale for the study and the importance of conducting a formal research evaluation to fully assess its operational features, effectiveness, and potential impact on participants. Building on the feasibility study results, we aimed to create a more advanced version of the CFC Learning Hub with enhanced features. Therefore, this study aims to develop the CFC Learning Hub, an interactive web-based platform with case-based modules to improve fracture treatment among Australian PCPs and assess the impact of the CFC training model, while also examining the relationship between PCP demographics, clinical experiences, and knowledge gaps in treatment.

Methods

Study Context

The general design, development, and content planning for the interactive, patient-focused CFC Learning Hub have already been piloted to a small group of PCPs with favorable feedback and demonstrating excellent metric properties [35]. The CFC Learning Hub will be built from lessons learned from this feasibility study with the aim of enhancing PCPs' awareness and competence in caring for patients with osteoporosis. The hub was conceived, designed, and developed by an interdisciplinary team of experts, comprising specialist physicians with expertise in osteoporosis and bone health, experienced PCPs, information technology and data science experts, and a project manager. It took time and resources for specialists to discuss and agree on major decisions for the program. Therefore, the timing and resource for such projects require appropriate support because of the need to understand terms, expectations, deliverables, and measurables across disciplines. The project team, situated in Melbourne, Australia, drew on its learning, teaching, and clinical experience to define the following important design criteria for PCP participants and elements in the project:

1. Practicing PCPs registered for the training have been provided with case studies and asked to provide their own case study with anonymized patients to encourage engagement.
2. There is interactive engagement between all parties involved.
3. Experienced PCP peers lead the group as facilitators, with guidance where needed by specialist "advisors," promoting case discussions and guiding discussion of content according to its relevance and importance.
4. There is a minimum time commitment required for the award of CPD credits for participation.

Importantly, the CFC Learning Hub format is flexible in terms of the timing of participants' input. Comments can be posted and discussions can be viewed at any time of the day, in order to accommodate participants' workload and personal commitments. This learning platform provides an alternative to attending an on-site lecture or a webinar wherein a specific time slot needs to be set aside for attendance including discussion. The CFC Learning Hub will be driven by three principles: (1) sound learning pedagogy that is aimed at changing attitudes and behavior, supported by clear assessment structures; (2) learning analytics at the back end of the CFC Learning Hub to understand the development of the participants through studying their web-based participation in the discussion forum; and (3) usable and accessible features of the hub to ensure maximization of uptake of the system.

Education Platform

Education has been delivered via Praxhub [38], an Australian-based web-based platform for health care professionals to access CPD resources from leading health care organizations. At the time of publishing this paper, Praxhub is used by thousands of health care professionals from more than 150 countries and aggregate education from more than 50 health care organizations. The CFC Learning Hub represents a departure from the main model of webinars and web-based learning modules for PCPs on a wider scale by including a range of increased opportunities for engagement and interactions with the participants.

The Praxhub platform allows for "groups" to be set up, in which participants can join and each week's education modules can be hosted and made available to the participants. Before starting the CFC cycles, an early decision was made to make each of the groups "private"—meaning that only those participants invited into that group would have access to the modules and visibility of that group's activity (ie, conversations within the discussion thread). It was considered important to quarantine the activity within the group from the remainder of Praxhub's membership to create a more supportive and encouraging environment for individual participation. By extension, it was considered that a public group, in which conversations could be viewed by the broader Praxhub membership of health care professionals, may have the propensity to limit conversations (ie, active engagement) due to concern about criticism or professional judgement, as well as to avoid redundant discussions.

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After assignment of participants to a designated private group, they attended an approximately 1-hour orientation session, conducted via a Zoom (Zoom Video Communications, Inc) meeting, to familiarize them with navigating the group and accessing the modules. Participants were informed by email (with a link in the email) of the availability of a new module each week. Within each module, participants were provided video or written instructions of the activities to be completed in that week, additional resources or materials to download and read, and a facilitated discussion thread in which to post questions to the specialists or PCP coordinator. The composition of each module is shown in Table 1. A weekly quiz was also made available for participants to probe their understanding of the week's materials.

An additional consideration in selecting Praxhub as the system to deliver the CFC Learning Hub program was its robust data collection. While Praxhub strictly uses these data to enhance the user experience and report completions of CPD activities on the platform, in accordance with its privacy policy, participant consent was provided to Praxhub for the limited disclosure of their deidentified data for the purposes of this study (see the *Data Collection* and *Ethical Considerations* sections).

The research measured various user-system interaction points to allow us to quantify the participants' engagement with the education program. These included dates and times (particularly time of day) when participants engaged with the education modules, whether videos were viewed or materials were downloaded, their engagement with other participants and the PCP coordinator and specialists via the discussion thread, and the responses to weekly quizzes.

These data were reviewed each week during the program to monitor participant-level engagement and at the end of each 6-week cycle to construct and understand how the participants engaged with the education and determine the performance in the program against the overall objectives.

Table 1. A summary of Community Fracture Capture Bone Hub 6-week content design.

Characteristic	Week 1	Week 2	Week 3	Week 4	Week 5	Week 6
Cases	Live webinar + 1× case	1× case	2× case	2× case	2× case	Live webinar + 1× case
Hot topics	Osteoporosis introduction and investigation	Assessment of risk factors	Osteoporosis effects	Treatment and side effects	Treatment failure	Difficult osteoporosis cases
Surveys	Premodule survey	N/A[a]	N/A	N/A	N/A	Postmodule survey
Quizzes	N/A	1×	1×	1×	1×	N/A

[a]N/A: not applicable.

Education Program

The CFC Learning Hub is a web-based resource center for case studies, related resources to support PCP learning, and a web-based community discussion forum. Once enrolled, participants are required to watch a mandatory familiarization program to learn the function and capability of the hub and to submit 1 or 2 patient cases for discussion. Facilitators and specialist advisers will filter and select case studies that enable coverage of a syllabus of topics predetermined by members of the project team for this CPD course. Facilitators ensure that the posted case studies are anonymized and contain suitable, high-quality content for discussion. Each CFC Learning Hub cycle is scheduled for 6 weeks and comprises three main learning pillars: (1) osteoporosis investigation and treatment initiation, (2) treatment maintenance and monitoring, and (3) troubleshooting treatment side effects and treatment failure. In some cycles, a short video presentation will be delivered by a bone specialist to introduce the theme of that week. Participants will be exposed to a range of case studies over these modules and have access to resources to facilitate learning and novel paradigms of thinking about osteoporosis to address the treatment gap. In addition, there will be opportunities for peer-to-peer interactions and learning; the experience is enhanced and personalized by discussing difficulties that registrants encounter in their very own deidentified submitted cases. The CFC Learning Hub platform has two resources for PCP interactions: (1) a web-based knowledge repository (the "Knowledge Hub") containing prepopulated evidence-based research papers, guidelines, position statements, and other resources relevant to that week's topic curated by our team's subject matter experts, and (2) a web-based social network forum (the "discussion forum") where PCPs can freely post web-based comments including questions for discussion posted by facilitators; case studies as a way to encourage PCPs to learn and share their knowledge based on shared experiences and relevance to their immediate clinical practice; and topical discussions as either hot topics deemed relevant for PCPs, posted by our osteoporosis specialists, or other topics that were open for a wider discussion (ie, introductions (facilitators and PCPs introduce themselves) and burning questions (PCPs and facilitators post inquiries on osteoporosis; these will focus on significant issues arising during a group's participation). The platform's topical discussions section includes (1) diabetes and bone health, (2) atypical femoral fracture, (3) when to consider changing an osteoporosis therapy, (4) how to get the most from your patients' bone density testing, (5) an "Introduction" topic for all users to introduce themselves, and (6) a facility for PCP participants to post inquiries based on seeking specific information about osteoporosis. Facilitators can also raise questions to promote discussion. These inquiries are organized under the term, "Burning Questions." The Knowledge Hub will act as an accessible knowledge repository for all users at any time. It will be a dynamic source of information, being expanded

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and adapted in response to participants' learning needs. Participating PCPs will complete 4 knowledge quizzes (1 quiz in each of weeks 2-5) and a questionnaire regarding osteoporosis caseload and demographics, confidence in case finding, investigations and treatment initiation, and barriers to osteoporosis case finding, investigations, and treatment initiation. The knowledge assessed will be in accordance with The Royal Australian College of General Practitioners (RACGP) and the Healthy Bones Australia (formerly Osteoporosis Australia) Osteoporosis Management and Fracture Prevention Guideline 2024 [39], a position statement developed by national experts to provide PCPs with clear guidance concerning the identification, investigation, and treatment of persons at risk for fragility fractures. In addition, pre- and postparticipation multiple-choice questions will be used for testing to assess knowledge transfer, change in confidence, and behavior (Table 1). The forum will be highly interactive (active learning) and case based and is supported by the RACGP and the Australian College of Rural and Remote Medicine approving the award of CPD points or hours to their fellows for active participation in the CFC Learning Hub (RACGP: 40 CPD points [2020-2022 triennium] and 12 activity hours [2023-2025 triennium], and Australian College of Rural and Remote Medicine: 8 Professional Development Program hours [February 23, 2020 framework] and 12 activity hours [2023-2025 framework]).

Description of the Platform, Setting, Recruitment, and Participants

Platform

Praxhub has developed a web-based community (web and mobile apps) to support the delivery and distribution of medical education. It is free of charge for doctors to register and their credentials are validated against the government-held register of doctors. Praxhub already has a preexisting large network of registered PCPs in Australia and has been recruiting participants through their web page and internal member communication system.

The invitation to participate in the CFC Learning Hub will be distributed via PCPs professional bodies and using the existing pool of PCPs registered with Praxhub. Interested PCPs will contact the project manager, after which they will be screened for eligibility to participate in the program and subsequently enrolled if they satisfy the selection criteria and consent to participate in the project, approving to take part in the 6-week web-based educational program, answer pre- and postparticipation surveys, and allow the CFC Learning Hub to use their data for auditing and research purposes.

Once registered, all participants will be allocated to a private group, through which they can access the topical presentations, cases, and discussion forums. Participants and facilitators will have a profile, which shows their professional qualifications, experience, practice location, awards, and achievements, in accordance with the information that is required for the program, in addition to a profile picture (avatar) for personalization and easy identification. Participants will be able to engage in case studies and discussion topics and access and post comments, text, images, links to videos, and documents at their convenience.

The aim is to enroll 12-16 PCPs to participate per CFC Learning Hub cycle, and participants can drop in and out based on their interest in the content and their availability.

PCPs will be eligible to participate in the program if they (1) are a medical practitioner currently active in general practice in Australia, (2) submit at least 1 (preferably 2) suitable case studies with discussion or learning points from their own clinical experience that include patients at risk or those with prevalent osteoporosis, and (3) have web access.

PCPs will be excluded if they are unable to commit at least 6 hours to the anticipated time required to meet appropriate CPD guidelines.

Measures

Data related to sessions and activities of participants in the CFC Learning Hub will be collected for all cycles. Our primary focus, at this stage of the project, is detecting participation patterns to characterize the interactions of participating PCPs with the platform and specifically with respect to osteoporosis investigation and treatment initiation, learning, and knowledge-sharing behaviors related to participation and engagement in the CFC Learning Hub.

We will define the following terms from Praxhub analytics:

1. A session includes all user-related activities from initial logging in to logging out of the CFC Learning Hub. All activities made between the logging in and out activities will be grouped within a session.
2. An activity includes downloading of content, viewing posts and content, and posting comments.

Measuring sessions and activities will discover participants' full active and passive engagement with the web-based system, which can be used to help measure the success of the platform (eg, high-session count means PCPs are frequently logging in, undertaking 1 or more activities, and then logging out). PCPs can actively engage through posting in a case study or topical discussion, while they can also engage passively via browsing and watching a brief video presentation in a case study or topical discussion. Initially, in the Knowledge Hub, we anticipate that PCP participation is likely mainly to be passive as PCPs browse the Knowledge Hub database. In addition, PCPs can actively engage with the Knowledge Hub by posting comments or queries. In measuring discussion forum use, the usage behavior for each case study and topical discussion will be assessed. For each case study and topical discussion, usage is measured from the creation date (on a Monday of each cycle's week) until the end of the cycle).

Interactive Learning Hub

Once the 6-week program commences, the weekly content for 1 or more topics, along with a short video presentation on some topics (cycles 3 and 4), delivered by senior PCP and bone specialists to introduce the theme of that week, will be released by the moderators at a predefined scheduled time. This is communicated to participants via customized electronic

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correspondence allowing them to access and discuss. The content of these weekly modules is based on and selected from the following topics:

1. What is osteoporosis and why is it important?
2. Prevention strategies for osteoporosis and secondary fracture.
3. Who is at risk? Tools for assessing fracture risk.
4. Application in primary care.
5. The roles of allied health professionals—practice nurse, physiotherapist, and dietitian.
6. Physical activity and exercise: benefits and risks, beliefs about exercise.
7. Osteoporosis diagnosis and further evaluation. Appropriate initial workup.
8. DXA: Applications. What are its strengths and limitations?
9. Treatment: Approach to the choice of treatment and initiation of specific osteoporosis therapy.
10. Engaging patients in shared decision-making.
11. Calcium and vitamin D: Primary therapy and adjunctive therapy.
12. Monitoring for safety and effectiveness of therapy.
13. Recognizing and managing treatment "failure."
14. Issues with long-term therapy and "treatment holidays"?
15. Osteonecrosis of the jaw and atypical fractures associated with treatment.
16. Why are patients being missed?

The hub will direct participants to resources and organizational websites in line with the week's topic and case study. Along with the release of the educational resources, a relevant case study will be presented for discussion. Interactive and flexible discussion throughout the week will take place on predefined discussion boards within the CFC Learning Hub and will be moderated by PCP facilitators and experienced physicians.

Moderators and Data Gathering

Moderators will access the discussion boards during each topic discussion to monitor and participate in discussion at least once daily during each cycle. The time and way in which participants engage with the site will be quantitatively monitored throughout the duration of participation in the Learning Hub. Specifically, data that will be collected include (1) total number of discussion posts by each participant; (2) individual response time for each new discussion board opened on the web-based forum; (3) number of users who have actively participated in individual discussion board on the web-based forum; (4) the average time to reach a final resolution in each discussion on the web-based forum; (5) the accrued time that each participant spends logged onto the learning hub; (6) the total time that each participant spends on the web-based forum and individual pages on the learning hub, (7) the number of times internal and external websites are visited by each participant from the learning hub links; and (8) the overall popularity of web-based forums, as measured by number of page views, downloads, comments, rating, and followers of individual posts.

Data Collection

Sample Size and Justification

The aim is to enroll 12-16 PCPs to participate per CFC Learning Hub cycle. A relatively small number of participants in a VCoP (ie, 12-20) who are learning and seeking knowledge is desirable as participants are likely more incentivized to be an active rather than passive user [40-44]. For example, the study by Barnett et al [41] reported that PCPs felt less isolated and more motivated to exchange knowledge after joining a small VCoP for their family physician training.

Qualitative Analysis

The qualitative analysis will aim to (1) identify common themes related to barriers and facilitators of web-based learning, PCP perceptions, and attitudes toward the program, and (2) examine barriers to effective detection and management of osteoporosis in general practices in Australia (ie, PCPs using a virtual space for their specific learning needs rather than physical seminars).

To achieve this, the relational content analysis will be undertaken [45,46]. More specifically, 2 researchers within the team will inductively identify codes independently in the first instance. In this initial step, researchers will use both semantic (capturing explicit and obvious meanings of the text) and latent (capturing tone, intention, and underlying assumptions) coding approaches to explore a wider range of codes. Subsequently, in the second phase, the 2 researchers will discuss and debate on the codes to assess for patterns that coalesce around key themes. The codes are then presented as subthemes of the themes that are identified. Finally, all data will then be counted against the list of subthemes to explore how strongly each subtheme is represented in the dataset by a single researcher and a random sample will be validated by a senior researcher.

Due to the innovative nature of the e-learning hub, themes will be created from participants' transcriptions and validated through rigorously evaluating past and current initiatives made in this area (if any) in the literature. As the program progresses, we will seek to make necessary adjustments to the design and content of the e-learning hub.

The results of thematic analysis will be reported using a top to bottom approach with main (high level) themes reported first, following the subthemes emerged. All results will be supported by exemplary or representative quotes provided by participants.

We will also try to understand the differences in aforementioned areas based on PCPs' years of experience and level of web-based activity (subject to diverse participation and data availability). Overall, feedback by participants will be used to reevaluate and redesign the e-learning hub in terms of navigating and searching for relevant content for PCPs learning needs. The qualitative analysis will aim to identify common themes related to barriers and facilitators of web-based learning, PCP perceptions, and attitudes toward the program. We will also try to understand the differences in aforementioned areas based on PCPs' years of experience and level of web-based activity (subject to diverse participation and data availability). Due to the innovative nature of the e-learning hub, themes will be created from participants' transcriptions and validated through rigorously evaluating past

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and current initiatives made in this area (if any) in the literature. As the program progresses, we will seek to make necessary adjustments to the design and content of the e-learning hub. Overall, feedback by participants will be used to reevaluate and redesign the e-learning hub in terms of navigating and searching for relevant content for PCPs' learning needs.

Quantitative Analysis

The data from all cycles will be analyzed separately and combined. The between-cycle differences in participants demographic data (ie, years in practice) and level of activity, including time spent on the platform, number of various resources accessed during the training, and number of modules or education activities they have participated in, will be assessed using Kruskal-Wallis test. Changes in participants' level of knowledge, measured using the proportion of correct responses provided to pre- and posteducation quizzes, will be assessed using either 2-tailed paired *t* tests or Wilcoxon signed rank tests, whereas multivariable regression analysis will be used to examine factors associated with levels of change in knowledge and confidence, while controlling for PCPs' experience, level of participation in the program, and baseline level of knowledge or confidence. Other potential confounders will be considered, subject to the data availability and sufficient power. The level of significance for the quantitative analysis is set at $\alpha < .05$.

Ethical Considerations

The Melbourne Health Human Research ethics committee approved this project (site reference 2016.24), adhering to institutional ethical review processes for research involving human participants. Electronic consent from PCP participants who joined the CFC Learning Hub was obtained to use their deidentified data for research and auditing purposes. The electronic consent process included a waiver of consent for case study patients, whose anonymized information was also used in the project. The data collection and management of electronic consent were carried out using Praxhub tools, ensuring appropriate safeguards for privacy and confidentiality. The data used in this study were fully anonymized to protect participant identities. No compensation was provided to participants in this program.

Results

Recruitment of participants started in May 2022 through initial contacts with PCP members on the Praxhub platform. The recruitment continued until August 2023. The expected quantitative and qualitative data on outcomes are currently being collected and their analysis will be available in early 2025.

Discussion

Overview

We hypothesize that (1) the CFC Learning Hub can provide a novel, peer-to-peer learning experience, offering up-to-date knowledge of primary and secondary fracture prevention strategies among a diverse range of PCPs, and (2) the improved confidence and motivation to investigate and treat osteoporosis, gained via interactive live web-based discussion among PCP peers and bone expert facilitators, can be quantified using predefined analytics tools.

International and Australian studies clearly establish the cost-effectiveness of hospital-based FLS for secondary fracture prevention, aiming to bridge the treatment gap for patients with low-trauma fractures [12,47]. Nevertheless, a considerable number of patients with low-trauma fractures receive investigation and management solely or predominantly from PCPs, potentially bypassing hospital-based services, or alternatively, they receive their ongoing care from their regular PCPs once acute fracture care is provided by hospital services [48]. Therefore, it is imperative for PCPs to maintain currency with fracture prevention protocols and primary care service delivery models. The translation and application of evidence and guidelines for osteoporosis management in primary care, particularly by PCPs, are unacceptably low internationally including in Australia, leading to underdiagnosis, underinvestigation, and undertreatment of osteoporosis in many countries [12,47,49-52]. Furthermore, a significant number of Australians are not receiving timely and appropriate management in primary care, as evidenced by the lack of access to osteoporosis-related investigations and therapies despite eligibility for such interventions [27,48,53]. An Australian review of 88,000 postmenopausal women attending PCPs found that 29% (20,248/69,358) of the targeted cohort had sustained at least 1 osteoporotic fracture, yet less than one-third of these women with fractures were receiving specific treatment for osteoporosis and 7% (3825/57,088) of these women were taking calcium alone [14]. Another Australian study reported that 76% (87/109) of men who had sustained an incident fracture remained untreated for osteoporosis 12 months after sustaining the fracture, despite being eligible for osteoporosis treatment [27]. These studies indicate that PCPs in Australia need additional resources to support primary care management of fragility fractures. Our education modules target the knowledge gaps specifically to address the issues of osteoporosis underdiagnosis and undertreatment and the need for timely and appropriate osteoporosis management.

Regarding the sufficiency of medical resources to cope with osteoporosis-related health issues, a recent paper presenting system dynamics modeling of the potential impact on fracture care of increasing hospital-based FLS demonstrated the probable inadequacy of these services to cope with the predicted fracture burden in years to come [54]. These observations underline the critical need to upgrade such care in the community, which inevitably will require high levels of PCP involvement. These analyses add emphasis to the need for effective education programs in this field.

Comparison With Prior Work

PCPs encounter substantial daily challenges in providing optimal care for patients with various chronic health conditions, necessitating the application of evidence-based treatment approaches to enable the best outcomes [35,37]. Therefore, VCoPs for CPD may represent suitable alternatives for PCPs, being primary health care providers, to overcome barriers they encounter such as time constraints to accessing educational activities and a preference for face-to-face learning. Our

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collaborative group explored the challenges faced by PCPs in using VCoPs for their CPD, identifying seven themes crucial for designing and sustaining effective VCoPs: (1) low trust and risk perception, (2) patient information sharing, (3) timely responses, (4) relevant website access, (5) individual learning styles, (6) communication gaps between PCPs and specialists, and (7) the need for diversity and interactivity [37]. Following that exploratory study, few studies aimed to design virtual, interactive, and PCP-targeted bone health programs. In the United States, the Bone Health Tele Extension for Community Health Care Outcomes (TeleECHO) program [55] was proposed as one strategy that aimed at improving PCPs' knowledge related to treatment gaps in osteoporosis care, using real-time videoconferencing to mentor health care professionals in rural and underserved communities [36]. In that study, 263 health care professionals from various countries participated over 21 months, showing substantial improvement in self-confidence across 20 domains of osteoporosis care with the TeleECHO intervention and addressing the osteoporosis treatment gap through enhanced education and knowledge-sharing among health care professionals. Quantitative and qualitative assessments were made of participating PCPs' experience in our pilot program, which was developed because PCPs from different demographics might differ in their knowledge gap. Evidently, this CFC Learning Hub provided an innovative and interactive educational web-based tool to assist with increasing PCPs' knowledge of osteoporosis management models and in turn the application of these guidelines to improve patient care [35]. The pilot program revealed the hot topics (eg, about osteoporosis, risk assessment of osteoporosis, and treatment and prevention strategies) that triggered the most discussion, indicating lack of confidence or knowledge gaps in these areas that are addressed in our current learning modules to ensure more widespread distribution of this knowledge. In our published pilot program of the CFC platform, PCPs were engaged in practice-based, web-based learning where they discussed their own cases with peer facilitators and specialist advisors [35]. In that program, our prototype CFC Learning Hub recruited 7 PCPs, as a convenience sample of PCPs interested in bone health topics, and it included 2 key components: a web-based discussion forum and a knowledge repository (the Knowledge Hub). The discussion forum contained anonymized case studies (contributed by PCP participants) and topical discussions (topics that were not case studies). Using 2 complementary tools (Google Analytics and Igloo Statistical Tool), we characterized individual participating PCPs' engagement with the hub. The discussion included questions from participants directly to the facilitators regarding management dilemmas: this is a more practical tool to deliver knowledge than traditional questionnaires and quizzes. We measured the PCP participants' behavior by quantifying the number of web-based sessions attended by the participants, activities undertaken within these web-based sessions, written posts made per learning topic, and their time spent per topic. We calculated time spent in both active and passive engagement for each topic. The baseline questionnaire highlighted the knowledge gaps and the facilitators, specifically directed discussion to address these gaps during the hot topic discussions. This project draws on findings from the pilot study and insights gained from implementing assessment tools to expand the CFC Learning Hub.

Strengths and Limitations of the Program

Our educational program is positioned to deliver distinct outcomes compared with traditional face-to-face lectures and stand-alone, web-based webinars, offering PCPs time flexibility and leveraging the advantages of peer-to-peer and PCP-to-specialist interactions through web-based posts. It anticipates a departure from the traditional unidirectional nature of lectures by placing a strong emphasis on cultivating an interactive learning environment characterized by introspection and peer-to-peer discourse. This approach is designed to encourage participants to engage in more profound cognitive processing of the material, thereby fostering a nuanced comprehension. The integration of peer-to-peer discussions is a pivotal departure from conventional methods, establishing a collaborative and nonjudgmental forum for the exchange of insights, diverse perspectives, and shared learning experiences. This departure from traditional modes of education is anticipated to enhance the program's efficacy, providing a more profound and enriching educational encounter for participants due to its multifaceted nature. Osteoporosis presents diverse challenges across age groups and between sexes, requiring tailored approaches in primary and secondary fracture prevention. The absence of a universal solution adds complexity, necessitating nuanced insights for specific cohorts, such as those undergoing oncological treatment, relying on glucocorticoids, or in the posttransplant phase. With various modalities such as pharmaceutical interventions, over-the-counter supplements, and exercise-based strategies, the program's interactive and case-based nature is anticipated to align aptly with the intricate landscape of osteoporosis management, fostering a deeper understanding of this complex medical domain. For instance, our successful pilot study showcased the effectiveness of the program's innovative approaches in tracing the path from engagement to practice change as recognized by obtaining CPD accreditation for the activity, thereby affirming the rationale for informing a larger study with a specific focus on creating and facilitating more practice-based topics for PCP participants [35].

The limitations of this study include transferability of this work beyond Australia since there is a shift toward community-based rather than hospital-based fracture prevention programs, and PCPs are encouraged to develop subspecialty interests in chronic condition such as osteoporosis. This in-depth subspecialty education might be beyond the scope of PCPs elsewhere in the world. The success of this approach is dependent on PCPs' motivation to incorporate osteoporosis care into their workflow when it might be easier to refer to specialists. Personalized peer-to-peer discussion is more expensive to deliver per participant than traditional webinars and lectures and therefore might not be sustainable.

Principal Findings

The main contribution of this protocol paper is a detailed description of how to conduct and analyze co-design, interactive, peer-to-peer PCP learning activities to develop a digital collaborative environment that promotes up-to-date bone health practice among PCPs. The program platform has capacity and

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agility to improve and adjust in real time based on participants number and needs.

The CFC Learning Hub will provide insights into the barriers to community-based osteoporosis identification and treatment initiation from the PCP perspective, as well as the effectiveness of a VCoP facilitated through an innovative web-based platform, along with methods for evaluating participation. The barriers identified might differ depending on region of practice and the experience level of the PCP. The pre- and postparticipation surveys permit quantification of knowledge and confidence gained. If successful, the CFC Learning Hub can be expanded to specifically target rural areas where interactive knowledge transfer and delivery can be logistically challenging.

Conclusions

There is an urgent need to address the treatment gap in osteoporosis care, particularly within primary care settings where PCPs play a central role. The identified challenges, such as low trust of web-based content, patient information sharing, timely responses, and communication gaps, underscore the importance of tailored educational interventions such as the CFC Learning Hub. The pilot program's success in engaging PCPs and addressing knowledge gaps suggests the potential of the CFC Learning Hub program and its innovative, web-based tools in improving osteoporosis management and patient care within primary care settings.

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Data Availability

The datasets generated during and analyzed during this study are available from the corresponding author on reasonable request, once the relevant findings have been published.

Authors' Contributions

AMF, CC, RA, SC, and JDW contributed to study conceptualization, writing of the original draft, and project administration; AMF, CC, RA, SC, SS, CJY, RB, SP, LC, and JDW contributed to the methodology and investigation; JDW, CC, RA, RB, CYJ, SC, and LC contributed to conducting the learning sessions; SS contributed to providing regular liaison with Praxhub; AG, AMF, CC, RA, SC, and JDW contributed to the data curation; and JDW, CC, and SC contributed to study supervision. All authors have read, provided feedback, and agreed to the final version of the manuscript for publication.

Conflicts of Interest

None declared.

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Abbreviations

ACRRM: The Australian College of Rural and Remote Medicine
CFC: community fracture capture
CPD: continuing professional development
DXA: dual-energy x-ray absorptiometry
FLS: fracture liaison services
PCP: primary care physician
RACGP: The Royal Australian College of General Practitioners
TeleECHO: Tele Extension for Community Health Care Outcomes
VCoP: virtual community of practice

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Protocol

Identifying, Engaging, and Supporting Care Partners in Clinical Settings: Protocol for a Patient Portal–Based Intervention

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Abstract

Background: In the United States, the landscape of unpaid care delivery is both challenging and complex, with millions of individuals undertaking the vital role of helping families (broadly defined) manage their health care and well-being. This includes 48 million caregivers of adults, 42 million of whom are caregivers of adults aged 50 years or older. These family care partners provide critical and often daily support for tasks such as dressing and bathing, as well as managing medications, medical equipment, appointments, and follow-up care plans.

Objective: This study aimed to implement a novel patient portal–based intervention to identify, engage, and support care partners in clinical settings.

Methods: The project team collaborated with 3 health care organizations (6 primary care practices in total) to design and implement a patient portal–based intervention. Three days in advance of a visit, patients were invited to log on to their patient portal account and answer a brief questionnaire as part of the routine electronic check-in process asking them to (1) identify themselves as the patient or someone answering for the patient, (2) report major life changes, (3) set the agenda for the upcoming visit, and (4) report on care partner responsibilities. Respondents' answers to this brief questionnaire were available to providers ahead of the visit. Patients with care partner responsibilities, as well as care partners answering the questionnaire on behalf of patients, were provided a link to the ARCHANGELS Caregiver Intensity Index to measure the intensity of their caregiving role and motivate care partners to connect with suggested state and local resources.

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Results: The intervention was launched in September 2022 at Organization A. Organization B launched in May 2023 in one clinic and June 2023 in the other. In focus groups, staff and clinicians reported that the intervention was easy to implement and did not cause workflow disruption. At 6 months post implementation, across both organizations, a total of 22,152 patients had received questionnaires and 13,825 (62.4%) had submitted completed questionnaires. Full data will be reported at the completion of the intervention period.

Conclusions: Early results suggest that the intervention could be an easily scalable and adaptable method of identifying and supporting care partners in clinical settings.

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KEYWORDS

patient portal; previsit questionnaire; caregivers; care partners; questionnaires; support; engagement

Introduction

Caregiving in the United States

In the United States, the landscape of unpaid care delivery is both challenging and complex. Millions of individuals undertake the vital role of helping someone else manage their health care and well-being. This includes 48 million caregivers of adults, 42 million of whom are caregivers of adults aged 50 years or older [1]. Family (broadly defined) care partners provide critical and often daily support for tasks such as dressing and bathing, as well as managing medications, medical equipment, appointments, and follow-up care plans [2-4]. The role of a care partner can be fulfilling as well as challenging. Many care partners report a sense of purpose and fulfillment related to the care they provide, and some research suggests that caregiving has a protective health effect [5-8]. Other studies suggest that having caregiving responsibilities can also be correlated with poorer mental and physical health, finding substantial rates of chronic illness and poorer mental health over time [9-13].

Surveys of care partners taken during the COVID-19 pandemic noted particularly high levels of stress and adverse mental health symptoms, including anxiety, depression, and suicidality [10-12], possibly due to the reduced availability of services related to social distancing and closures by home care services and caregiver respite services [13]. A survey of more than 10,000 US adults conducted between late 2020 and early 2021 revealed significant mental health issues. A total of 70% of all care partners reported experiencing at least one adverse mental health symptom such as anxiety, depression, or suicidal thoughts, in comparison to 32% of respondents with no care partner responsibilities [10]. While the pandemic represented an extraordinary challenge to care partners, surveys conducted before the pandemic also found significantly higher rates of adverse mental health conditions among this population [14,15].

Providing care partners with psychosocial support has been shown to help both care partners and their care recipients [16,17]. However, identifying care partners and linking them to services remains challenging [18]. While care partners frequently interact with the health care system on behalf of patients, they often lack a way to access support for themselves [19,20]. A visit to a care recipient's health care provider rarely includes a discussion of care partner stress. As well, adding time to discuss caregiving responsibilities and available resources to an already busy clinical visit is often not feasible [21]. Identifying care partners (both patients who are care partners and care partners of patients) before or during clinical visits and connecting them to resources, without adding to clinical work, could be beneficial to patients, care partners, and clinicians.

Use of Patient Portals

Electronic health records (EHRs) and secure patient portals offer a ready opportunity to identify care partners in need of services. Most health care providers use EHRs and have online patient portals through which their patients can access their medical information, message their clinicians, renew prescriptions, schedule appointments, and more [22]. Previsit questionnaires, administered through the patient portal in preparation for a visit, have become more commonplace [23]. These questionnaires can provide an opportunity for clinicians to learn more about patient needs and concerns before a visit [24]. In addition to previsit data collection, portals offer the opportunity for interventions and the provision of resources outside of the clinic visit [25]. Studies suggest that portal-based interventions can lead to improvements in psycho-behavioral outcomes, such as health knowledge, self-efficacy, and decision-making [25,26]. While these benefits are typically focused on patients' reported health care needs, they can also be extended to other aspects of patients' lives, including their caregiving responsibilities.

Here we report on a multisite intervention designed to implement a method of identifying, engaging, and supporting care partners in office-based clinical settings using the patient portal. Specifically, we sought to create a model of care that identified care partners through a previsit questionnaire ahead of their own health care appointments, engaged them through the incorporation of their self-reported visit concerns and priorities into the questionnaire data, and activated them to understand their caregiver intensity and connect with resources without requiring additional action from the care team. We report here on the intervention design and interim feasibility data. The intervention took place for 1 year and the interim data were gathered at 6 months.

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Methods

Intervention Components

Caregiver Intensity Index

The ARCHANGELS Caregiver Intensity Index (CII) [27] is designed as a self-assessment instrument of caregiver intensity across multiple dimensions. Individuals who complete the CII are provided with a numeric score between 0 and 100, a color (clear: low intensity; yellow: moderate intensity; and red: high intensity), and the top two drivers and top two buffers of their caregiver intensity. Those completing the CII are then directed to a microsite with resources specific to their needs and the community in which the patient receives care. The project team collaborated with each implementing site to ensure that the resource page was comprehensive.

In-Clinic Materials

Each participating site was provided with in-clinic posters, wallet-sized handouts (referred to as “Care Cards”), and tip sheets for clinicians and staff. The posters and Care Cards included scannable QR codes that linked patients to the CII. These QR codes were specific to each site and modality, which allowed tracking of how resources were accessed (whether via poster, Care Card, after-visit summary, or previsit questionnaire). The tip sheets for clinicians and staff contained information on how to talk with patients about caregiving responsibilities and how to find patients’ completed questionnaires in the EHR.

Previsit Questionnaire

The team at Organization A convened regularly with the project team to draft and refine the previsit questionnaire, adapting a previously tested questionnaire [24] with input from clinic staff and clinicians as well as feedback from patient and family advisors in the organization’s Patient and Family Advisory Council. The final previsit questionnaire was also tested at Organizations B and C.

The final previsit questionnaire, to be sent to all patients aged 18+ years with an upcoming visit (except those whose upcoming visits were Medicare annual wellness visits, annual physicals, or telehealth visits), comprised the following items (see Multimedia Appendix 1 for complete survey branching logic and the exact wording of the questions): (1) Identification: respondents were prompted to specify if they were the patient or were completing the previsit questionnaire on the patient's behalf (either as a designated portal proxy or by logging in as the patient; note: if someone other than the patient is filling out the questionnaire, they are answering the questions for the patient, not for themselves). (2) Life changes notification: respondents were asked to communicate significant life changes since their last clinic visit. (3) Visit agenda-setting: respondents were asked to identify the one or two most important things they wished to discuss at the upcoming visit. (4) Care partner responsibilities: respondents were asked if they had caregiving duties and to share for whom they provided care. (5) Receipt of care partner support: respondents were prompted to indicate if they received help managing their health and health care from another person. (6) Caregiver intensity index: respondents reporting caregiving responsibilities were given a link to the CII and provided with an opportunity to report their color and score in the previsit questionnaire. Those who answered the previsit questionnaire on behalf of the patient were given the CII link but were not given the option of sharing their score (Figure 1).

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Figure 1. Previsit questionnaire flowchart.

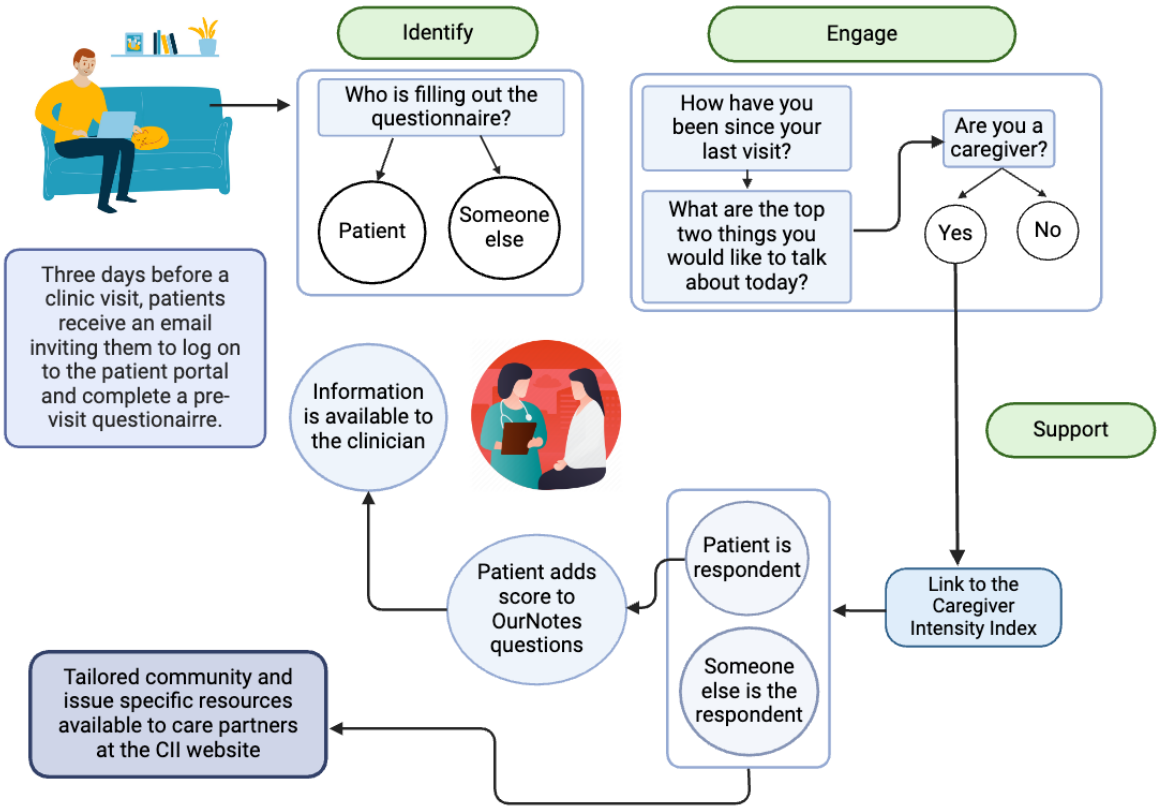

We integrated previsit questions into the EHR for testing, assessing both the patient-facing interface within the patient portal and the corresponding view for clinic staff and clinicians upon submission of responses.

EHR Macros

Two macros were developed: 1 for clinicians to incorporate information about the CII in the patient visit summary and another enabling clinicians to integrate questionnaire responses into their notes.

Education for Clinicians and Staff

Before implementation, the project team conducted sessions with staff and clinicians from participating practices to demonstrate how to access the previsit questionnaire within the EHR, identify workflow adjustments, and provide an overview of the in-clinic materials. The project was approved by the institutional review boards at all project sites.

Stakeholder Input

The project team met with staff and clinicians at each participating site at 3 and 6 months, both in person and virtually. These meetings were held to identify and address implementation issues, provide ongoing education and support to clinic staff and clinicians, and surface feedback and concerns about the initiative.

Plans for Statistical Analysis

Upon the intervention period's completion at all sites, we will summarize the study participants' demographics, their usage of the CII, and the Caregiver Intensity scores. To compare the characteristics between groups, we will use the chi-square test or Fisher exact test for categorical variables and the Student *t* test for continuous variables. Multivariable regression models will be used to explore the associations between the Caregiver Intensity score and patient demographic factors. We will also use qualitative analytic methods to identify key themes and subthemes in the free-text responses. All statistical analyses will be performed using SAS software (version 9.4; SAS Institute Inc).

Ethical Considerations

The protocol was approved and deemed exempt from full review by the institutional review boards at Beth Israel Deaconess Medical Center (IRB protocol # 2021P000928) and the University of Michigan (IRB protocol # HUM00225451). Per the exempt status of the intervention, informed consent was not required. Patients were informed about their right to opt out of the intervention in the invitation email. All data will be deidentified in the analytic data file. No personally identifying information will be included in the analytic file. Participants were not compensated.

Results

We engaged 3 health care organizations to collaborate on the design and implementation of the intervention (Figure 1). The first site (Organization A) is a prominent academic medical center network in the Northeast. Within this network, we partnered with three clinics situated in suburban areas outside

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a major metropolitan hub. Our second partner (Organization B) is a large academic medical center based in the Midwest. Within this center, we collaborated with two primary care clinics: a general internal medicine practice and a combined general internal medicine and pediatrics practice. Our third partner organization (Organization C) is a nonprofit health care entity serving primarily urban communities in the Northeast. The clinic associated with this organization predominantly serves low-income and racially diverse populations.

Two of these organizations are situated within regions commonly supported by the Ralph C Wilson Jr Foundation (the project funder), namely western New York and southeastern Michigan. The selection of the third site was based on existing strong professional relationships between project team members and the organization's leadership, coupled with the organization's keen interest in participating. Characteristics of participating health care organizations are shown in Table 1.

Table 1. Site characteristics.

Characteristics	Organization A	Organization B	Organization C
Total number of clinicians	• Clinic 1: n=2 • Clinic 2: n=6 • Clinic 3: n=5	• Clinic 1: n=22 • Clinic 2: n=20	2
Total number of clinic staff	• Clinic 1: n=17 • Clinic 2: n=13 • Clinic 3: n=15	__[a]	11
Clinic location	• Clinic 1: suburban • Clinic 2: suburban • Clinic 3: suburban	• Clinic 1: mixed • Clinic 2: mixed	Urban
Organizational payer mix, %			
Medicaid	14	28	57
Medicare	10	30	21
Private commercial insurance	72	40	20
Uninsured	2	2	1
Other unknown	3	—	—

[a]Not applicable.

Each organization established a dedicated work group that convened regularly with the research team (Table 2). These groups consisted of clinical champions, clinic leadership, project managers, and information technology staff. All partner organizations use the same electronic health record system.

Table 2. Organizational workgroups.

Collaborators	Organization A	Organization B	Organization C
Clinical champion	✓	✓	
Project manager		✓	
EHR[a] medical director	✓		
EHR team member	✓	✓	✓
Director of grants and program management			✓
Chief innovation officer	✓		
Social worker			✓
Practice administrator			✓

[a]EHR: electronic health record.

Organization A launched the intervention on September 30, 2022, and Organization B launched on May 17, 2023, in one clinic and June 1, 2023, in the other. Organization C was not successful in implementing the previsit questionnaire in their EHR and withdrew from the initiative. This was due to a mix of factors, including the lack of a clinical champion, the low usage of the patient portal among its patients combined with a higher reliance on paper documents by staff, and varied methods across clinics and staff as to if and how questionnaires submitted from the portal are identified and reviewed ahead of visits.

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Adult patients at least 18 years of age were eligible to participate in the initiative. As shown in Figure 1, patients with a patient portal account and with an upcoming clinic visit were sent an invitation through the patient portal, 3 days ahead of a visit, to complete the previsit questionnaire. All visit types were included in the initiative with the exception of Medicare annual wellness visits, annual physicals, and telehealth visits. Annual wellness visits and physicals were excluded by request at participating sites because patients were already asked to complete a substantial number of questionnaires before those visits. Telehealth visits were excluded due to clinician concern that asking patients to fill out the previsit questionnaire would serve as a barrier to the telehealth login process and cause a delay in care. As shown in Figure 1, all the information provided by patients, or by others on patients' behalf, through the previsit questionnaire was available to clinicians in the EHR. Patients and care partners who did not complete the previsit questionnaire could access the CII through QR codes on the in-clinic materials (eg, care cards, posters, or the after-visit summary).

At the 3- and 6-month check-ins, clinic staff and clinicians reported few challenges with implementing the intervention. The primary challenge was learning to access patients' previsit questionnaire responses in the clinician and staff EHR view. Clinic staff and clinicians reported that some patients expressed appreciation for the opportunity to share and discuss their caregiving responsibilities. Further, they reported that few patients complained about being asked to fill out the previsit questionnaire. Clinic staff and providers said they felt better prepared to discuss care partner responsibilities with patients because they had resources to offer. Based on clinician and staff concerns with lengthy patient responses to the life changes and agenda-setting questions, the project team made minor wording changes to those questions and instituted character limits on the free text responses (see final questionnaire in Appendix). Finally, staff reported minimal disruption to workflows after adjustments to reduce the character limits of agenda-setting questions.

At 6 months post implementation, 25,611 surveys were assigned to 13,299 patients at Organization A and 16,265 questionnaires to 8853 patients at Organization B. At Organization A, 7076 questionnaires were received from 5350 patients. At Organization B, 6749 questionnaires were received from 4982 patients. Because the previsit questionnaire was tied to clinical visits, patients with multiple visits during the observation period received more than one invitation to complete a previsit questionnaire (Table 3).

Data for the full intervention period will be published in a future paper.

Table 3. Questionnaires assigned and submitted.

Disposition of questionnaires	Organization A	Organization B
Number of questionnaires assigned to patients, n	25,611	16,265
Number of questionnaires submitted by patients, n/n (%)	7076/25,611 (27.6)	6749/16,265 (41.5)
Number of patients assigned at least one questionnaire, n	13,299	8853
Number of patients submitted at least one questionnaire, n/n (%)	5350/13,299 (40.2)	4982/8853 (56.3)

Discussion

Principal Findings

We report on the rationale, development, and early uptake from the first 6 months of implementing a practice-based intervention aimed at identifying, engaging, and supporting care partners in office-based clinical settings using the patient portal. Early results from this work suggest that the intervention is acceptable to clinicians and staff and simple to implement. While we did not directly ask patients and care partners about their willingness to complete the previsit questionnaire, our robust response rate suggests that the intervention is feasible for patients and that it is possible to identify care partners before or during a clinical visit and connect them to resources.

To our knowledge, our intervention represents the first systematic attempt to identify, engage, and support care partners in clinical settings through a previsit questionnaire. Previous work focused on identifying patients' visit priorities using a similar methodology and found much lower rates of patient uptake than our preliminary findings suggest [24]. Understanding the extent to which the local clinical environments and patient populations affected implementation will be a critical area of focus for the final evaluation [28]. Our preliminary findings suggest that patients were generally receptive to completing the previsit questionnaire through the patient portal. The usage of previsit questionnaires is becoming more prevalent for assessing Social Determinants of Health and identifying resources or referrals that may benefit patients [29]. Incorporating caregiver-related responsibilities within Social Determinants of Health assessment efforts could also merit attention as a strategy for raising awareness of caregiver needs and integrating care partner identification and support within care delivery if our findings hold in the final evaluation.

While the role of a care partner can be fulfilling, it can also be fraught with numerous challenges, leading to elevated rates of mental and physical health issues among care partners [28]. Identifying care partners is a first step in understanding their capacity and needs, and in facilitating access to appropriate resources. Doing so within care delivery enables clinicians to become aware of caregiving responsibilities; however, busy clinical practices may struggle to address these needs. By providing resources outside of the clinical visit, our intervention could help to support caregivers, clinicians, and staff. Staff reported minimal burdens and disruptions to their workflow and the intervention was relatively simple to implement.

Our protocol has several limitations that should be noted. First, while the protocol includes in-office materials for patients and clinicians, patients must have access to the internet in order to

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take the CII and explore the resources offered. This requirement may exclude a subset of patients with lower digital literacy. Future efforts could explore the possibility of, for example, text-based options using mobile devices. Second, our protocol is implemented in 5 primary care practices associated with academic medical centers. These centers may have resources for implementation that are not available in community-based practices. Finally, our protocol was designed for and implemented in health care organizations with the same commercially available EHR system. Implementing in other EHR systems may require adjustments to the protocol.

In the final 6 months of the project, we will monitor whether staff continue to report minimal workflow disruptions, whether patient feedback remains predominantly positive or neutral, or if there is an increase in complaints. If current results hold, and we find that patients with caregiving responsibilities are using the CII, this portal-based intervention could be a scalable and adaptable method of identifying, engaging, and supporting patients and their care partners in clinical settings. Should that be the case, we will widely disseminate our findings through the peer-reviewed and gray literature, as well as develop and disseminate "how-to" toolkits for primary care practices. Further studies focused on implementation in a larger number of diverse settings, by patient population, electronic medical record vendor, types of care delivery organizations, and geographic regions, will also be important as we seek to engage and support care partners through the health care system.

Conclusion

Millions of adults help another person with their health and care, and their needs are often unidentified and unmet. Despite the impact of caregiving responsibilities on physical and mental health, often their own health care providers do not know about their responsibilities. The early assessment of this unique pilot seeking to identify care partners through previsit questionnaires and in-office materials indicates that this low-burden effort may be an effective tool for identifying and supporting care partners. Future analyses of data from the full one-year pilot will give a more complete picture of the results and the possibility of adapting and scaling this intervention beyond the individual clinics involved in the study.

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Data Availability

The datasets generated during and analyzed during this study are not publicly available per the requirements of the participating organizations to maintain strict confidentiality and disclosure standards for patent data obtained during the course of routine care. For this reason, the data are also not available from the corresponding author.

Authors' Contributions

CMD contributed to conceptualization, methodology, investigation, formal analysis, writing-original draft, and writing-review and editing. DW contributed to methodology, investigation, formal analysis, writing-original draft, and writing-review and editing. ZD assisted with formal analysis, writing-original draft, and writing-review and editing. AD contributed to conceptualization, writing-original draft, and writing-review and editing. IH handled investigation, writing-original draft, and writing-review and editing. JA contributed to methodology, investigation, writing-original draft, and writing-review and editing. AC assisted with methodology, investigation, formal analysis, writing-original draft, and writing-review and editing. NC contributed to methodology, investigation, writing-original draft, and writing-review and editing. JM assisted with methodology, investigation, writing-original draft, and writing-review and editing. JN handled methodology, investigation, writing-original draft, and writing-review and editing. KO'D assisted with methodology, writing-original draft, and writing-review and editing. CW contributed to methodology, investigation, writing-review and editing. SSW assisted with methodology, investigation, formal analysis, writing-original draft, and writing-review and editing. JY contributed to investigation, formal analysis, and writing-review and editing. JLW assisted with methodology, writing-review and editing. The sponsor recruited Organization C.

Conflicts of Interest

AD and SSW are the cofounders of ARCHANGELS. ARCHANGELS sells services designed to support care partners, including the use of the CII. AC is employed by ARCHANGELS. AD is a member of the BIDMC trustee advisory board.

Multimedia Appendix 1
Previsit questionnaire.
[DOCX File , 16 KB - resprot_v14i1e66708_app1.docx]

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Abbreviations

CII: Caregiver Intensity Index
EHR: electronic health record

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Protocol

Using the Community Resilience Model and Project ECHO to Build Resiliency in Direct Support Professionals: Protocol for a Longitudinal Survey

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Abstract

Background: Individuals with intellectual disabilities or autism spectrum disorder (ID/A) sometimes require supportive services from direct support professionals (DSPs). The supportive care provided to individuals with ID/A by DSPs can vary from assistance with daily living activities to navigating society. The COVID-19 pandemic not only exacerbated poor outcomes for individuals with ID/A but also for DSPs, who report experiencing burnout in the aftermath of the pandemic. DSPs are critical to providing much-needed support to individuals with ID/A.

Objective: The goal of this study is to evaluate the impact of the community resilience model on DSP burnout and neurodivergent client outcomes using the Project ECHO (Extension for Community Healthcare Outcomes) telementoring platform as a dissemination tool.

Methods: This protocol leverages community resilience theory and telementoring through the Project ECHO model to foster resilience in DSPs and their neurodiverse client population. ECHO participants' resilience behaviors will be evaluated via surveys including the Connor Davison Resilience Scale and the WHO-5 Well-Being Index. These surveys will be administered preprogram, at the end of the 8-week ECHO program, and 90 days after the ECHO program's completion. Pre-post relationships will be assessed using generalized estimating equations. The main outcomes will be self-reported changes in knowledge, self-efficacy, and resilience.

Results: All ECHO program cohorts and follow-up data collection have concluded, with 131 survey participants. The project team is currently analyzing and interpreting the data. We anticipate having all data analyzed and interpreted by February 2025.

Conclusions: DSPs provide critical services to individuals with ID/A. By providing skills in resiliency via the ECHO model, participants will be able to apply resiliency to their own professional lives while fostering resilience within their neurodiverse client base, leading to increased positive outcomes for both groups.

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KEYWORDS

neurodiversity; community resilience model; Project ECHO; direct support professionals; autism; telementoring; methods and feasibility; resiliency; intellectual disabilities; ASD; autism spectrum disorder; DSP; supportive care; community resilience; burnout; resilience; neurodivergent client; neurodevelopmental disorders; evidence-based knowledge

Introduction

Intellectual disabilities and autism spectrum disorder (ID/A) are lifelong, complex neurodevelopmental disorders characterized by social, cognitive, and adaptive skill deficits [1,2]. These skill deficits vary in levels of severity for each individual with ID/A and may require supportive care [2]. Direct support professionals (DSPs) provide supportive care to individuals with ID/A in the form of community integration, including employment navigation, assistance with daily living activities, and advocacy [3].

Individuals with ID/A are especially vulnerable to trauma and may struggle more to identify and implement successful coping strategies. Pairing this with undereducation in recognizing and responding to trauma among the service provider community creates a significant gap in services available to individuals with ID/A. Stress responses in individuals, including those with ID/A, can be moderated by factors that increase resilience. Resilience is defined as a process of interactive adaptation that facilitates coping in the face of adversity linked with a person's neurological and psychological makeup and socioecological contexts [4]. Fostering resilience for both service providers and individuals with ID/A can enhance their adaptive stress responses across all domains of functioning. Currently, there are limited resources in the community that can adequately address building resiliency, specifically in this population.

Prior to the COVID-19 pandemic, DSPs were already in the midst of a workforce crisis long characterized by low wages, training challenges, and high turnover rates [5]. However, DSPs working with those in the ID/A community reported experiencing lower quality of life and even higher percentages of burnout during the COVID-19 pandemic [6,7]. Evidence suggests that the COVID-19 pandemic exacerbated already-existing support system weaknesses, resulting in the displacement of DSPs that strained an already short-staffed workforce, increased hours worked by those not displaced, and worsened work-life quality [6,8]. These issues, compounded by the complexity of providing supportive care for this population during a global public health crisis, presented the need for resilience training and improved support for DSPs. Resiliency is associated with the achievement of life satisfaction, positive well-being, competent functioning, and improved quality of life after experiencing stressors or adversity [9]. Therefore, fostering resilient behaviors in DSPs as well as their neurodivergent clients is critical to strengthening and empowering neurodivergent individuals and creating more inclusive neurodiverse communities.

To better support individuals with ID/A, DSPs require new and advanced knowledge and skills to provide best-practice care. Providing training and resources in resiliency-building skills would allow DSPs to assist these often-overlooked populations while also providing DSPs with the tools needed to navigate post–COVID-19 working conditions. Further, it is well-known that individuals with ID/A who receive services and support from DSPs experience better personal outcomes, especially when the same DSP is engaged over time [10]. Identifying training and supportive opportunities for DSPs that improve DSP resilience, improve the health and resilience among the ID/A community, and improve the well-being and retention of the DSPs could significantly improve care for adults with ID/A. Unfortunately, current resources and supports that address building resiliency for DSPs are limited. In response to this service gap and the COVID-19 pandemic, Project ECHO (Extension for Community Healthcare Outcomes) at Penn State College of Medicine developed the "Fostering Resilience for Neurodiverse Communities ECHO" program for professionals serving neurodivergent individuals. The goal of this program is to share strategies to build resilience and better support those in their care to address trauma and stress needs as they reintegrate following the COVID-19 pandemic. These strategies were intentionally designed to have wide application so that service professionals could also benefit. The intent was to create resources and strategies that the neurodivergent clients and their service providers could use together in an embrace of more inclusive neurodiverse community building. This protocol aims to detail the Fostering Resilience for Neurodiverse Communities ECHO program conduction, curriculum, data collection, and planned outcomes analysis to facilitate further use of the ECHO model with other audiences, including those supporting neurodiverse populations. Our program's intended outcome is to invoke positive change in the knowledge, confidence, and resiliency of DSPs after participation in the ECHO program.

Methods

Project ECHO

The Fostering Resilience for Neurodiverse Communities ECHO program used the ECHO platform to provide DSPs with evidence-based knowledge and skills to best support their neurodiverse clients in building resiliency following the COVID-19 pandemic. Project ECHO is an evidence-based educational model with the power to rapidly transfer knowledge and exponentially increase capacity to deliver best-practice care to underserved populations [11-18]. The ECHO model's "all teach, all learn" approach is the infrastructure for knowledge-sharing in underserved communities around the world. The heart of the ECHO model is its hub-and-spoke knowledge-sharing networks, led by expert specialist teams (hub), mentoring multiple DSPs (spokes) via teleconferencing (Figure 1). The ECHO model is not "telemedicine" where specialists assume the care of the client; rather it is a guided model aimed at practice improvement, in which DSPs retain responsibility for clients, and operate with increasing independence as skills, confidence, and self-efficacy grow. Unlike traditional learning, Project ECHO facilitates rapid dissemination of knowledge and increased capacity to deliver

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best-practice care by utilizing case-based, collaborative learning to support the discussion of learners' challenges and barriers to guideline implementation.

The ECHO model has 4 core principles: (1) use technology to leverage scarce resources; (2) share best practices to reduce disparities; (3) use case-based learning to master complexity; and (4) monitor outcomes to ensure benefit. DSPs and other professionals (spokes) who serve neurodiverse populations participated in weekly web-based ECHO sessions with a multidisciplinary specialty team at Penn State College of Medicine (hub) with behavioral health, psychiatry, and community resource expertise. Project ECHO used Zoom, a user-friendly, Health Insurance Portability and Accountability Act–compliant, cloud-based software application for video conferencing.

Figure 1. The ECHO (Extension for Community Healthcare Outcomes) hub-and-spoke learning model.

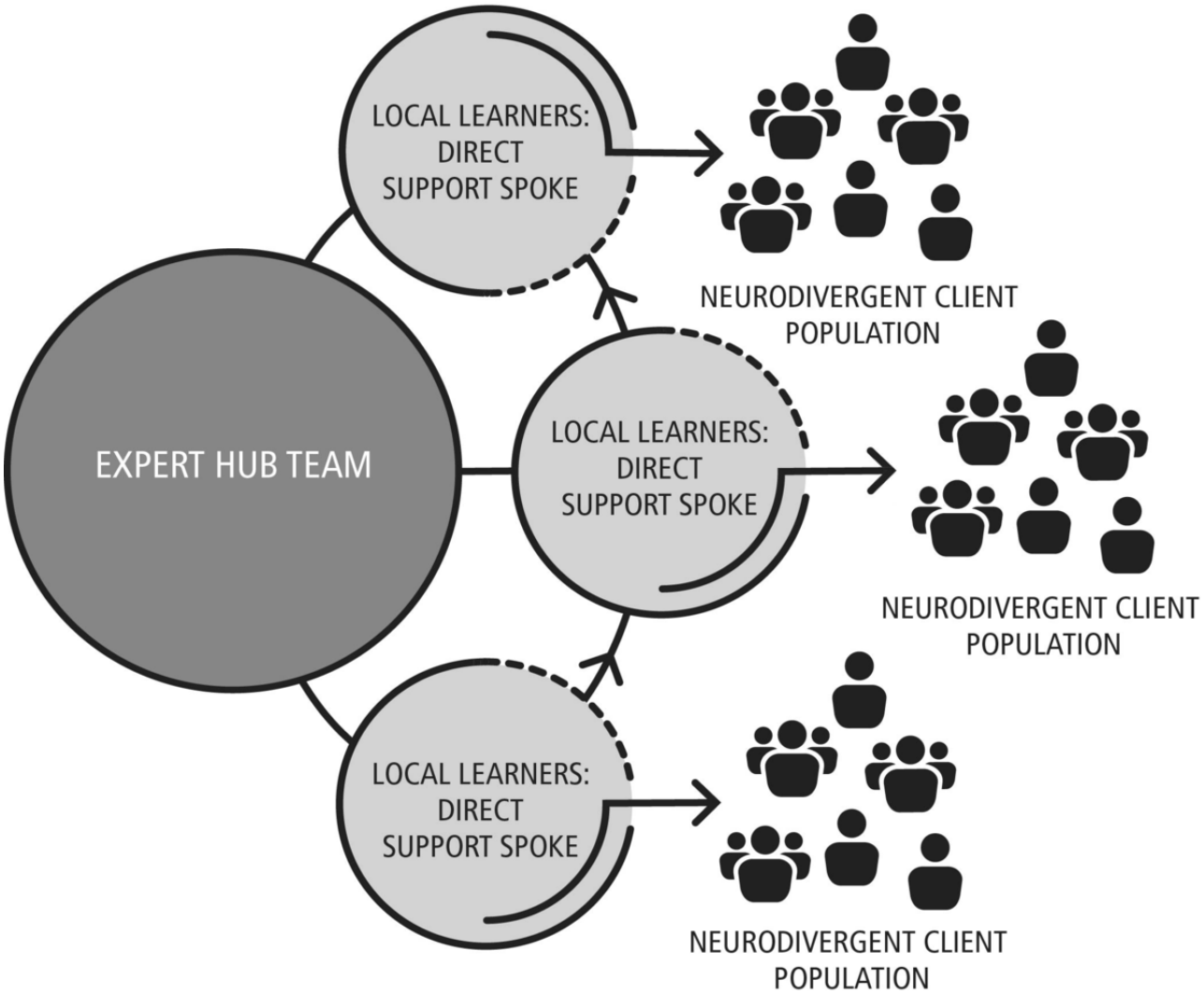

ECHO sessions featured presentations of deidentified client cases by DSPs and team members and brief lectures by specialists. The ECHO specialists and DSPs collaborated to discuss the case and develop recommendations for the DSP and the client. The hub team provided technical assistance and training on resilience building and facilitated the discussion of cases provided by spokes. Together, hub experts collaborated with spoke participants to share knowledge, expertise, best practices, and experiences while discussing deidentified cases and developing recommendations. Over time, spoke participants developed expertise while also engaging in a wider community of learners. Spoke participants were empowered to address the difficulties faced by their clients in their communities. As a result, ID/A clients gained access to best practices and resources through DSP participation in the ECHO sessions.

The Fostering Resilience for Neurodiverse Communities ECHO hub team consisted of multidisciplinary experts who provide care to neurodiverse patients. This team included the Clinical Director and Associate Clinical Director of the Division of Autism Services at Penn State Health Milton S. Hershey Medical Center, a psychologist with experience in behavioral health, a board-certified psychiatric nurse practitioner, a licensed clinical social worker, and a board-certified behavior analyst. Additionally, the expert specialist team also consisted of a neurodivergent self-advocate to provide a client perspective and expertise to case discussions. The project team included a project manager, education specialist, and program director from Project ECHO at Penn State College of Medicine who support the day-to-day operations of the ECHO model.

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Proposed Approach: Community Resilience Model

This protocol details the use of the community resilience model (CRM) to train DSPs to foster resilience in themselves as well as their neurodiverse clients, including individuals with ID/A, through the Project ECHO platform [19]. The overarching objective of the Fostering Resilience for Neurodiverse Communities ECHO series was to teach the skills of the CRM to professionals who serve neurodiverse clients to promote psychological flexibility in themselves and their clients.

The CRM is a community-based approach for coping with acute and chronic stress states [19]. It is a sensory-focused approach aimed at increasing mental well-being and greater resilience, which has been successfully used in diverse populations and settings, including front-line health workers at the height of the COVID-19 pandemic [20,21]. Its neurobiological basis is aimed at down-regulating stress responses in the body through a skills-based approach that has wide applicability. CRM is a community-based approach where community members not only help themselves but also support others within their social networks. CRM aims to create "resiliency-focused communities," an approach well suited for the intended outcomes of this project [19].

Using CRM, the hub team developed a curriculum addressing trauma, stress, anxiety, improving resilience, and more. A portion of the Fostering Resilience for Neurodiverse Communities ECHO curriculum promoted using the iChill App to teach the CRM through a set of self-help skills [22]. Participants registered for one cohort of the Fostering Resilience for Neurodiverse Communities ECHO program. Each ECHO cohort consisted of 8 weekly 75-minute ECHO sessions. A comprehensive list of topics can be found in Table 1. Goals aligned with the approach are found in Textbox 1.

Table 1. Fostering resilience for neurodiverse communities ECHO[a] series topics.

Session	Didactic topic
1	What is trauma? Traumatic stress, expressions of trauma, and trauma responses
2	Anxiety: Intolerance of uncertainty
3	What is resilience? Introduction to CRM[b]: why is it important? Resilience zone and widening the zone
4	Resilience skills I: Tracking, resourcing, and grounding
5	Resilience skills II: Gesturing, shift and stay, help now!
6	Crisis risk reduction and safety considerations
7	Adapting skills for those with brain differences
8	Fostering community reengagement

[a]ECHO: Extension for Community Healthcare Outcomes.

[b]CRM: community resilience model.

Textbox 1. Intended programmatic goals.

1. Increased awareness and better recognition of trauma issues related directly to the COVID-19 pandemic and past trauma issues that have been exacerbated by it
2. Better understanding of the community resilience model and the importance of developing greater resiliency for both providers and neurodivergent clients
3. Ability to guide direct support professionals and other team members into effective use of available resources to better meet the needs of the individuals they are supporting

Participants and Recruitment

Participants for this program were DSPs and those supervising DSPs who participated in Fostering Resilience in Neurodiverse Communities ECHO sessions. Within Pennsylvania, DSPs directly supporting neurodivergent individuals, as well as direct supervisors of DSPs, were recruited through targeted email listservs. An informative recruitment flyer was disseminated directly to DSPs through the Pennsylvania Department of Human Services' Office of Developmental Programs. The project team also leveraged social media platforms through the autism services, resources, education, and training network to promote the ECHO program.

The initial recruitment survey was distributed via flyer with a public-facing survey link. However, participants were screened after entering basic demographic or contact information, at which point study staff would invite eligible participants to complete questionnaires. Screening criteria included those employed currently as a DSP or as a direct supervisor of DSPs. Once approved by study staff, participants received surveys via email with personalized links, ensuring that all surveys except for the initial recruitment survey were not publicly available. After completion of all preprogram surveys, participants were invited to participate in ECHO sessions.

Survey Administration

All surveys were hosted electronically and, aside from the public recruitment survey, were only accessible via email. Project data were collected and managed using REDCap (Research Electronic Data Capture), developed by Vanderbilt University

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and hosted at Penn State Health Milton S. Hershey Medical Center and Penn State College of Medicine, which was supported by Penn State Clinical and Translational Science Institute. REDCap is a secure, web-based application designed to support data capture for research studies [23].

Survey responses were collected across multiple cohorts from August 2022 to August 2024. Initial survey completion was mandatory for participation in the ECHO series, but completion of session evaluations, final program surveys, and follow-up surveys was voluntary.

Survey questions were not randomized and were displayed on a single page per survey. Adaptive questioning was utilized in every survey to minimize survey fatigue. Participants did have the ability to review and change answers before submitting each survey.

Participants answered several demographics (eg, geographic location) and professional questions (eg, credentials, job title, provider type). Participants were also asked about their experience in providing care to neurodiverse populations and how the acuity of care provided to their neurodivergent clients has changed throughout the COVID-19 pandemic. Participants completed several educational evaluations at baseline and postprogram to measure programmatic impact.

The recruitment survey contained 36 questions. The preseries assessment, which was only administered to participants who were screened as eligible for participation by study staff, contained 59 questions. The session evaluations were completed after every ECHO session and contained 14 questions. The final program evaluation contained 83 questions. The 90-day follow-up survey contained 35 questions.

Response Rates

Survey view rates were not available for this study. Study staff closely monitored response rates. The public recruitment survey was closed once at least 40 eligible participants were enrolled. Study staff screened for eligibility as participants completed the surveys. Additionally, study staff monitored the completion of preprogram questionnaires to ensure that only those who completed the preprogram questionnaires were invited to join the ECHO sessions. Session evaluations, final program evaluations (n=66), and follow-up evaluations (n=51) were also closely monitored by study staff to ensure completion and data integrity.

Questionnaire Development

Upon registering for a Fostering Resilience for Neurodiverse Communities ECHO cohort, participants answered several demographics (eg, geographic location) and professional questions (eg, credentials, job title, provider type). Participants were asked about their experience in providing care to neurodiverse populations and how the acuity of care provided to their neurodivergent clients has changed through the COVID-19 pandemic.

Participant self-efficacy was measured at baseline and postprogram using adapted versions of measures identified in the literature [22,24]. Respondents completed each item with their respective level of confidence on several items on a 5-point Likert scale ranging from “not confident” to “highly confident.” Next, participants rated their respective level of confidence on a 6-point Likert scale, ranging from “no confidence” to “highly confident” [21,23]. In postprogram evaluation, participants self-reported changes in clinical knowledge and the application and dissemination of knowledge learned from the Fostering Resilience for Neurodiverse Communities ECHO series. This was measured using a series of questions using a 5-point Likert scale, ranging from “strongly disagree” to “strongly agree,” and included “I applied or shared knowledge learned in ECHO sessions to the neurodiverse clients who have ID/A support,” “I applied or shared knowledge learned in ECHO sessions to the direct support professional I supervise,” “I applied or shared knowledge learned in ECHO sessions with my colleagues in similar roles as mine,” “I applied or shared knowledge learned in ECHO sessions with my supervisors and/or agency management team,” and more.

The Connor-Davison Resilience Scale [25] and the WHO-5 Well-Being Index [26] were used to determine the impact on participant resiliency. Participants were asked to report the use of CRM skills. Additionally, participants’ use of the iChill app [22] that is promoted through the ECHO series is explored through a sequence of questions including, “do you use the iChill app on your phone or tablet,” “if yes, how often do you use it,” and “how helpful is the app?” Participants also responded to several questions related to their experience and satisfaction with the Fostering Resilience for Neurodiverse Communities ECHO series.

Planned Data Analysis

All variables will be summarized using descriptive statistics to assess their distributions and missing data. Pre versus post, pre versus 90-day follow-up, and post versus 90-day follow-up comparisons will be made for all outcome variables. For binary and ordinal (5-category Likert scale) categorical outcomes, we will use binomial or ordinal generalized estimating equation models, which account for the correlation between multiple observations made on each subject over time, to estimate odds ratios between the time points. The magnitude and direction of the odds ratios will allow us to assess the effect size of any significant changes over time. The *P* values for odds ratios that relate to the comparisons between time points, which generally will be all 3 possible comparisons, will be adjusted for multiple comparisons using the Tukey method for each outcome variable. This will maintain a familywise error rate of 0.05. Using this approach will also allow us to include any significant covariates in the model for adjustment if necessary. A sensitivity analysis will be applied to the ordinal outcome variables using quantile regression of the median by using the difference between the outcome responses for each pair of time points as the outcome variable in the model. This will also allow us to adjust for any covariates and use the same Tukey method of adjustment for multiple comparisons. All analyses will be performed using SAS software (version 9.4; IBM Corp) developed by the SAS Institute.

Ethical Considerations

Approval for this project was obtained from the Penn State Institutional Review Board at the Penn State College of

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Medicine in Hershey, Pennsylvania (STUDY00018204). Our program was given a not-human subjects research determination because it did not meet the definition of human subject research as defined in 45 CFR 46.102(e) and (l). This determination was made because the intention of this protocol is to assess and improve ECHO processes rather than contribute to generalizable knowledge. Because our program was determined to be a quality improvement activity, consent from ECHO participants was not required. The project data were only accessible to project staff. Participant data were deidentified and aggregated by ECHO staff before use in reporting and analysis.

Monetary incentives were provided for follow-up survey completion for September 2022, January 2023, and April 2023 cohorts only. Monetary incentives were based on the number of surveys completed: completion of at least 7 of 8 session evaluations: US $200; completion of only the 90-day follow-up survey: US $25; and completion of at least 7 of 8 session evaluations AND completion of the 90-day follow-up survey: US $225.

Reporting Guidelines

We used the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) [24].

Results

The ECHO cohorts ran from September 2022 to May 2024, with final follow-up survey data collection occurring in August 2024. There were 131 unique participants who attended ECHO sessions across the 6 cohorts. Participants were DSPs or supervisors of DSPs located in Pennsylvania, although 2 participants indicated that they were from other states (New Jersey and Oregon). Participants were from rural (n=35) and urban (n=94) counties, while other participant rurality is unknown (n=2). Data analysis is planned to be concluded by January 2025.

Discussion

The COVID-19 pandemic has shed further light on the pressing need to provide neurodiverse populations with the skills and resources necessary to successfully navigate society and the ongoing workforce crisis impacting the DSPs serving these populations. In response to the need presented to equip DSPs with resilience-building tools for themselves and their neurodivergent clients, Project ECHO at Penn State College of Medicine launched the Fostering Resilience for Neurodiverse Communities ECHO series. This ECHO series trains DSPs in ways to foster resilience in their neurodivergent clients and themselves. We anticipate that DSPs participating in the ECHO program will report feeling more confident and resilient in their roles.

The CRM has been implemented in other audiences, including health care professionals such as nurses, and it was found that brief resiliency trainings using CRMs for nurses resulted in improved well-being and resiliency among participants [25]. Additionally, the Project ECHO model has been used in resiliency training for first responders, resulting in increased confidence in resiliency skills [26]. The application of the CRM paired with the Project ECHO model for DSPs outlined in this protocol is a novel approach to resiliency training. Other applications of the CRM occur over shorter periods, with one training session lasting 3 hours [21,25]. The application of the CRM in this protocol will give DSPs tools to apply CRM principles in 75-minute ECHO sessions, held once per week over 8 weeks, leveraging active learning, engagement, and community-building, which defines the Project ECHO model. While our study is innovative and comprehensive, it is not without limitations. We rely on self-reported measures of knowledge acquisition, self-efficacy, resiliency building, and satisfaction, potentially resulting in self-report bias of over or underreporting a change in the above-mentioned outcomes. Other less biased outcome measures include supervisor-reported questionnaires, usage data of the iChill application, and retention rates of DSPs, which can be incorporated into future studies.

The Fostering Resilience for Neurodiverse Communities ECHO program introduces a unique opportunity for the application of resilience-building strategies across a variety of contexts to individuals who can apply them directly to their work and in real time. Common themes already identified within the ongoing ECHO program indicate the need for more trauma-informed training among DSPs and other professionals who serve neurodiverse populations, particularly in underserved and marginalized communities. We anticipate this training will result in increased self-efficacy, improved well-being, and expanded application of resiliency skills for DSPs and their neurodiverse clients.

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Authors' Contributions

KPL contributed to supervision, investigation, and writing – review and editing; LLF contributed to writing – original draft, writing – reviewing and editing, project administration, and data curation; SC contributed to writing – reviewing and editing; JML contributed to project administration, conceptualization, resources, and writing – reviewing and editing; EL contributed to methodology and formal analysis; MM contributed to conceptualization, methodology, funding acquisition, supervision, and writing – reviewing and editing; and JLK contributed to supervision and writing – reviewing and editing.

Conflicts of Interest

None declared.

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Abbreviations

CRM: community resilience model
DSPs: direct support professionals
ECHO: Extension for Community Healthcare Outcomes
ID/A: intellectual disabilities and autism spectrum disorders
REDCap: Research Electronic Data Capture

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Protocol

Integrating Ambient In-Home Sensor Data and Electronic Health Record Data for the Prediction of Outcomes in Amyotrophic Lateral Sclerosis: Protocol for an Exploratory Feasibility Study

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Abstract

Background: Amyotrophic lateral sclerosis (ALS) leads to rapid physiological and functional decline before causing untimely death. Current best-practice approaches to interdisciplinary care are unable to provide adequate monitoring of patients' health. Passive in-home sensor systems enable 24×7 health monitoring. Combining sensor data with outcomes extracted from the electronic health record (EHR) through a supervised machine learning algorithm may enable health care providers to predict and ultimately slow decline among people living with ALS.

Objective: This study aims to describe a federated approach to assimilating sensor and EHR data in a machine learning algorithm to predict decline among people living with ALS.

Methods: Sensor systems have been continuously deployed in the homes of 4 participants for up to 330 days. Sensors include bed, gait, and motion sensors. Sensor data are subjected to a multidimensional streaming clustering algorithm to detect changes in health status. Specific health outcomes are identified in the EHR and extracted via the REDCap (Research Electronic Data Capture; Vanderbilt University) Fast Healthcare Interoperability Resource directly into a secure database.

Results: As of this writing (fall 2024), machine learning algorithms are currently in development to predict those health outcomes from sensor-detected changes in health status. This methodology paper presents preliminary results from one participant as a proof of concept. The participant experienced several notable changes in activity, fluctuations in heart rate and respiration rate, and reductions in gait speed. Data collection will continue through 2025 with a growing sample.

Conclusions: The system described in this paper enables tracking the health status of people living with ALS at unprecedented levels of granularity. Combined with tightly integrated EHR data, we anticipate building predictive models that can identify opportunities for health care services before adverse events occur. We anticipate that this system will improve and extend the lives of people living with ALS.

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KEYWORDS

amyotrophic lateral sclerosis; machine learning; precision health; ALS; health monitoring; electronic health record; EHR; federated approach; in-home sensor data

Introduction

Amyotrophic lateral sclerosis (ALS) is a rapidly progressing neurodegenerative disorder that usually leads to death within 3 years of symptom onset and within 2 years from diagnosis [1]. The sequence and rate of ALS progression can vary widely depending on the phenotype, age at onset, and diagnostic delay [2,3]. Pharmacological developments (eg, Riluzole and Radicava) can slow disease progression, but the result is always premature death, typically due to respiratory failure, pneumonia, or heart failure [4,5].

Treatment in a specialized, multidisciplinary ALS clinic is among the strongest predictors of quality of life and prolonged survival among people with ALS [6]. In the United States, these clinics take the form of ALS Association Certified Treatment Centers of Excellence, which, by definition, must include a multidisciplinary team with treatment standards based on the American Academy of Neurology Practice Parameters [6,7]. Even in this best-case treatment setting, though, weeks or months may pass between clinic visits. Rapid physiological and functional declines between visits mean that a person with ALS can be hospitalized or deceased before the care team is aware of their change in status. The time between clinic visits represents a critical gap in the multidisciplinary care of people with ALS. A reliable, noninvasive system for passively detecting physiological and functional decline between visits would give the multidisciplinary team unprecedented ability to predict outcomes and, more importantly, make near–real-time treatment recommendations to counteract disease progression, prolong independence, and maintain quality of life. Rates of respiratory decline and lower extremity functional decline, in particular, are reliable prognostic indicators for ALS survival time [1]. In addition to pharmacological options, targeted nonpharmacologic interventions can reduce perceived fatigue, improve manual dexterity, prevent falls, promote myriad cognitive improvements, and preserve the overall quality of life among those living with ALS [8]. These interventions, enabled by early detection of decline, are most effective when delivered in the context of multidisciplinary programs, resulting in longer survival and higher quality of life [6,9].

To monitor the decline, members of the research team have developed a passive, in-home, sensor-based system for monitoring physiological biomarkers and functional status through a combination of hydraulic bed sensors, motion sensors, and privacy-preserving depth sensors [10]. The system can reliably capture pulse, respiration rate, bed restlessness, room activity, gait speed, stride length, and falls. It has been deployed in more than 300 senior housing units and private homes throughout the midwestern United States since 2005. The system was developed and tested in two phases with support from the National Institutes of Health (National Institute of Nursing Research 1R21NR011197-01, Rantz, principal investigator). The first phase was retrospective [11-13], reviewing 3 years of significant health events from previous study participants. Parameters deemed important for an aging-in-place population include increasing or decreasing bed restlessness, pulse, respiration, time in bed, increasing bathroom activity, and decreasing general activity and time away from home [10,14-16]. Previous iterations of the system have been described extensively elsewhere [17,18]. The current iteration is a closed-source implementation purchased from Foresite Healthcare and maintained by the research team.

Our previous work makes clear that it is possible to detect and track very early signs of health changes using passive in-home sensing. In some cases, the onset of clinical declines may be detected before patients are aware of changes [18-20]. The system captures a variety of important biomarkers and functional data, including the key variables for predicting decline among people with ALS. The purpose of this work is to adapt the existing sensor system to predict physiological and functional decline in people living with ALS. This approach relies on a myriad of multimodal data, including robust sensor signals and structured electronic health record (EHR) data from distinct platforms. Here, we describe a necessarily federated approach to combining these distinct data types into a single dataset for the generation of the prediction algorithm. We hypothesize that this approach is feasible.

Methods

Design

The goal of the parent study is to adapt the existing sensor-based alert system to facilitate early detection of physiological and functional declines among people living with ALS. To this end, the study considers three hypotheses: (1) the enhanced sensor system is feasible for collecting biometric data and health outcomes from people living with ALS; (2) enhanced sensor system data, processed through an unsupervised machine learning approach, may enable early detection of health status changes among people living with ALS; and (3) changes in health status detected by the multidimensional streaming clustering approach can predict adverse health outcomes, including pneumonia, hospitalization, and death among people living with ALS.

This paper specifically addresses the methodology for hypothesis 1, testing the feasibility of the federated collection, storage, and analysis of data from the sensor system and EHR. Data collection is scheduled to continue through December 2025, and interim findings are reported in the *Results* section below. Full results of this process will be reported elsewhere upon completion of the study.

Recruitment

Participants are recruited from the ALS Association Certified Treatment Center of Excellence at University of Missouri Health Care. Inclusion criteria are age 18 years or older, a clinical diagnosis of ALS by a qualified neurologist as documented in the EHR, home zip code within 100 miles of the clinic, and

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either the presence of a live-in caregiver (eg, spouse or adult child) or a Montreal Cognitive Assessment (MoCA) score >22. Recruiting coordinators are allowed to omit scoring individual MoCA items if, in their clinical judgment, response difficulties are due to speech or motor deficits resulting from ALS, rather than cognitive impairment. ALS genotype and phenotype, enrollment in clinical trials, and any other treatments are not considered inclusion or exclusion criteria.

Sensor System

We use three types of in-home sensors: hydraulic bed mats, thermal depth sensors, and motion tags, to monitor participant health. The sensor systems function effectively regardless of lighting conditions, providing a noninvasive, passive way to monitor participant health. The bed sensor is installed beneath the participant's mattress, where signals are best captured during rest. It uses a hydraulic pressure transducer to gather composite ballistocardiogram signals, which are deconvolved into components of sleep restlessness, respiration rate, and pulse. Ballistocardiogram signals are a mechanical measure of blood flow produced by cardiac activity, analogous to electrocardiogram signal patterns. The composite signals are partitioned into their respective components using signal-filtering algorithms. The ballistocardiogram component is subjected to a sixth-order bandpass filter with a 0.7-10 Hz cutoff. The respiration component is subjected to a sixth-order low-pass filter with a 0.7 Hz cutoff. Instances of heightened bed restlessness appear in the signal data as periods marked by higher amplitude and increased noise.

A wall-mounted thermal depth sensor generates a series of depth images, where each pixel corresponds to a coordinate measurement within the scene [17]. The depth images contain 3D point-cloud coordinates of the participant during walks. Validated algorithms extract gait parameters from these depth images. Gait parameters for stride time, stride length, walking speed, and participant height are derived from the point cloud silhouettes. To overcome the limitations posed by the sensor's field of view, which can be potentially occluded by furniture or other objects, a centroid-based gait parameter estimation technique has been developed. This approach permits the collection of additional gait parameters, such as gait bounce, trunk sway, asymmetry, and entropy across all 3 axes (X, Y, and Z), as well as the XY diagonal with partial leg occlusion during stride. In addition to gait parameters, a standardized Timed Up and Go fall risk assessment score is computed from the average in-home walking speed, as captured by the depth sensor [17]. In the event of a detected fall, the depth sensor performs a dual function: sending an immediate alert to designated contacts and generating a short video clip of the fall event for subsequent investigation or diagnosis.

Passive infrared motion sensors are deployed using the ZigBee (Connectivity Standards Alliance) protocol, a high-level radio communication protocol designed for low-power wireless data transmission. The motion sensors are installed in key locations such as the bathroom, bedroom, living room, kitchen, and front door to capture room-level activity. Abnormal activity in these spaces, based on the time of day or night, may suggest potential health issues, such as a urinary tract infection or the onset of cognitive decline. As the motion sensors detect movement in infrared light, they are effective at identifying activity regardless of lighting conditions. In addition to motion counts, we calculate room activity density, represented as the number of motion events within a unit of time for a respective sensor, providing an overall level of activity for each room.

The system has been tested in a multiresidential environment and can handle the presence of visitors, distinguishing them from residents based on gait patterns [18]. In a commitment to maintain privacy and comply with HIPAA (Health Insurance Portability and Accountability Act) standards, all data collected from these sensors are anonymized and time stamped with a study-specific participant identifier, which is used to deterministically link with sensor data. The data are stored in a secure AWS instance.

EHR Data Integration

We leveraged the REDCap (Research Electronic Data Capture; Vanderbilt University) Fast Healthcare Interoperability Resource (FHIR) interface to extract participants' most recent clinical information directly from the backend Oracle Health EHRs Database system of University of Missouri Health [21-23]. The REDCap FHIR interface enables interoperability with EHR systems, allowing real-time data extraction. By leveraging the FHIR interface, we can extract relevant data elements, such as laboratory results, vital signs, and clinical assessments, to populate the registry with up-to-date information. To ensure data accuracy and completeness, we map the extracted EHR data to the corresponding REDCap data fields using standardized terminologies, such as *ICD-9-CM* (*International Classification of Diseases, Ninth Revision, Clinical Modification*), *ICD-10* (*International Statistical Classification of Diseases and Related Health Problems 10th Revision*), LOINC (Logical Observation Identifiers Names and Codes), SNOMED CT (Systematized Medical Nomenclature for Medicine–Clinical Terminology), and RxNorm. This mapping process facilitates seamless data integration and enables efficient data retrieval for further analysis. Once the EHR data are extracted and mapped to REDCap data fields, the data are stored in the REDCap database. REDCap provides a secure and user-friendly platform for managing research data, allowing researchers to more easily access clinical information on people with ALS. However, the current FHIR interface does not support real-time extraction of unstructured notes, which were manually extracted and uploaded into the same REDCap project, along with an additional outcome ascertainment form for collecting monthly evaluations of the ALS Functional Rating Scale-Revised (ALSFRS-R). All EHR data collected into REDCap are anonymized and time stamped, with a study-specific participant identifier created to deterministically link with sensor data.

Data Management Plan

The extracted EHR data from REDCap and sensor data are loaded into a single study-designated cloud storage via Secure Shell File Transfer Protocol or Transport Layer Security 1.2 Protocol, hosted on a HIPAA-compliant, cloud-based data enclave. Data are integrated and analyzed via the self-service "Analytic Workbench," hosted within the same data enclave. Uninterrupted monitoring of accesses and activities occurs on

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the study database following established best practices that have been implemented at the system level. Researchers' access details are required to be reviewed on an annual basis according to current data use protocols. Access to the study database is restricted to the study period, plus an additional 5 years after the end of the study period, to facilitate subsequent requests to validate and reuse the database for future analyses and retrospective projects [24].

Data Analysis

Sensor Feature Engineering

We will test the preliminary efficacy of the expanded sensor platform for detecting changes in health status among people living with ALS. The Center for Eldercare and Rehabilitation Technology has previously developed a multidimensional streaming clustering algorithm that can simultaneously monitor all of the inputs of the existing sensor platform and detect cumulative deviations from expected patterns. The multidimensional streaming clustering approach applies principal components analysis and t-distributed stochastic neighbor embedding to identify the "normal" relationships between multiple biometric variables. The change in each variable over time can be treated as a vector, and those vectors can effectively be summed to produce a single vector leading to a single point in feature space. The point represents the patient's cumulative health status for the day, and the vector indicates day-to-day changes in that overall health status. When tracked over time, these changes reveal a cluster of expected behavior. The cluster is defined not only by its central mean value but also by the degree of typicality of the values. Typicality is an indicator of the consistency within the cluster, comparable with SD. Importantly, those clusters remain relatively stable and identifiable within a given period. Potential alterations in function can then be identified by retrospectively tracing the daily point trajectory as it approaches or leaves the cluster boundary. This deviation from typicality is often a warning sign of health decline caused by injury or illness. Outliers indicate potential moments of acute health decline, triggering a warning to health care staff. This same approach will be leveraged using expanded sensor platform data (including input from the Garmin 245 wearable sensor) to generate and monitor clusters of baseline data for people with ALS.

To establish the preliminary efficacy of the system, we will follow the methods demonstrated by Wu et al [25]. We will retrospectively compare outlier points to any adverse health outcome indicators from the EHR to explore whether detected outliers occurred in the period immediately preceding adverse health outcomes. This process begins with an exploratory visual analysis conducted by the Center for Eldercare and Rehabilitation Technology and Clinical Teams. We can then bin outliers into true and false positives and bin adverse health events into caught and missed events, establishing the sensitivity and specificity of the outliers as alerts to health status change. These results will achieve two important goals. First, they will answer the preliminary efficacy question, providing our first indication of whether this system can potentially detect health status changes in people living with ALS. We will also investigate the associations between the outliers and ALSFRS-R score changes and irregularities.

Early Detection Modeling

We will develop multiple state-of-the-art machine learning models (including but not limited to regularized logistic regression, least absolute shrinkage and selection operator, support vector machine [26], random forest [27], gradient boosting, and deep neural networks [28]) to achieve optimal performance for predicting future ALSFRS-R scores. Machine learning approaches broadly involve three phases: training, validation, and testing. In the training phase of a supervised learning approach, investigators define the relevant predictors (eg, biometric sensor data and outlier warnings) and outcomes (eg, ALSFRS-R score change, EHR indicators of pneumonia, hospitalization, and death) of interest. The system feeds the predictors and outcomes into a recurrent neural network first to extract sequential features, and then each of the identified algorithms creates a predictive model that can subsequently predict outcomes in novel datasets. We will perform the training phase on the first 12 months of retrospective sensor and EHR data. When the training and validation phases involve continuous collection of data from a single or growing dataset, the holdout method suggests a 2:1 ratio of training to validation data. Therefore, we will complete the validation phase with the final 6 months of prospective data collection. In the validation phase, inputs (eg, biometric data, gait, and sleep) are fed into the model and predicted outputs (eg, adverse health outcomes) are compared to real-world outcomes (eg, EHR outcome indicators of pneumonia, hospitalization, and death) [29]. Validation tests are then conducted for both traditional sensitivity and specificity, as well as for overfitting of the model. The validation phase allows us to fine-tune the relative weights of each factor in the model, improving its predictive validity. The optimal predictive model will be selected based on testing accuracy.

Ethical Considerations

This study was approved by the University of Missouri Institutional Review Board (project number 2084262) and the U.S. Army Medical Research and Development Command (USMRDC) Office of Human Research Oversight (log number E03062.1a). All participants provided informed consent. Sensor data are deidentified on the device before transmission to the REDCap database. EHR data are deidentified in the REDCap FHIR process before transmission to the REDCap database. Participants are not compensated.

Results

User Statistics

A total of 4 participants have been recruited (Table 1). None of the 4 participants required accommodations to complete the MoCA. Preliminary data from participant 1 are summarized in the preliminary analysis below (Figures 1-4). Specific dates of diagnosis and enrollment are not provided, as they could be combined with general geographic information to effectively deidentify participants with a rare condition. Sensor feature engineering and early detection modeling, based on all 4 participants, will be analyzed and reported in 2025.

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Examples of monitoring results are shown in Figures 1-4, all scaled to the identical period from September 11 to December 29, 2023.

Figure 1 depicts motion density in the home, with the most motion detected during a prolonged family visit in November and considerable time spent out of the home around the December holidays (black boxes).

Figure 2 illustrates the number of movements detected in different rooms of the home, featuring spikes in time spent in bed (tall yellow lines) and confirming several nights spent outside the home in December (absence of yellow and red lines).

Figure 3 displays in-bed respiration rate (bottom purple plot) and four techniques for estimating pulse rate: energy [30] in brown, Hilbert transform [31] in red, k-means clustering [32] in black, and windowed peak-to-peak deviation [33] in blue.

Figure 4 depicts, from top to bottom, average gait speed, stride length, and stride time. Notably, reductions in average gait speed are indicated by orange lines on December 3 and 10, 2023. These represent system-generated alerts. The December 3, 2023, alert reads:

> *Walking Speed Decrease: The average walking speed of 91.4 cm/s observed during the current 7-day period ending on 12/03/2023 is 3.4 cm/s (3.6%) lower than the average walking speed of 94.8 cm/s observed during the 7-day baseline period which ended on 11/26/2023.*

Table 1. Participant characteristics.

Characteristics	Participant			
	1	2	3	4
Age (years)	62	70	55	45
Sex	Male	Male	Male	Male
Race	White	White	White	White
Days since Dx[a] at enrollment, n	617	41	24	56
Initial ALSFRS-R[b] composite score	31	20	38	27
Deceased	No	Yes	No	No
Days of data collected, n	330	48	86	59

[a]Dx: diagnosis.

[b]ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised.

Figure 1. Whole home movement data density by hour from September 11 to December 29, 2023.

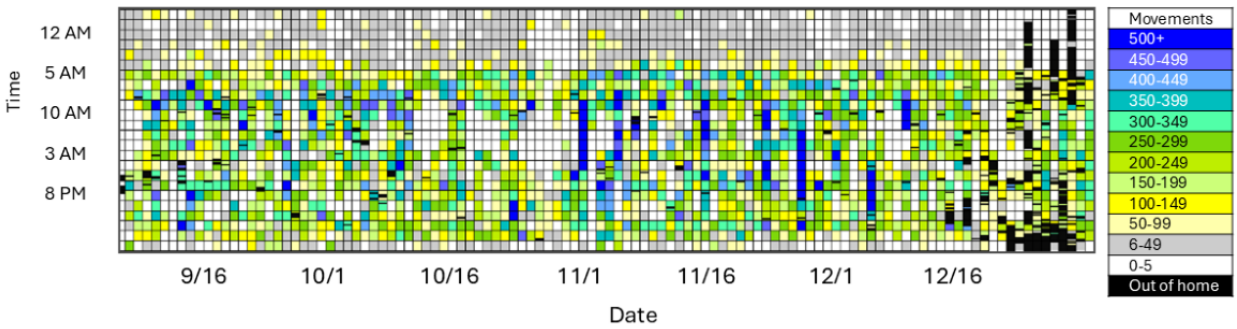

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Figure 2. Per-room movement detections over 24-hour periods from September 11 to December 29, 2023. Red: bathroom; yellow: bedroom; green: front door; lavender: kitchen; purple: living room.

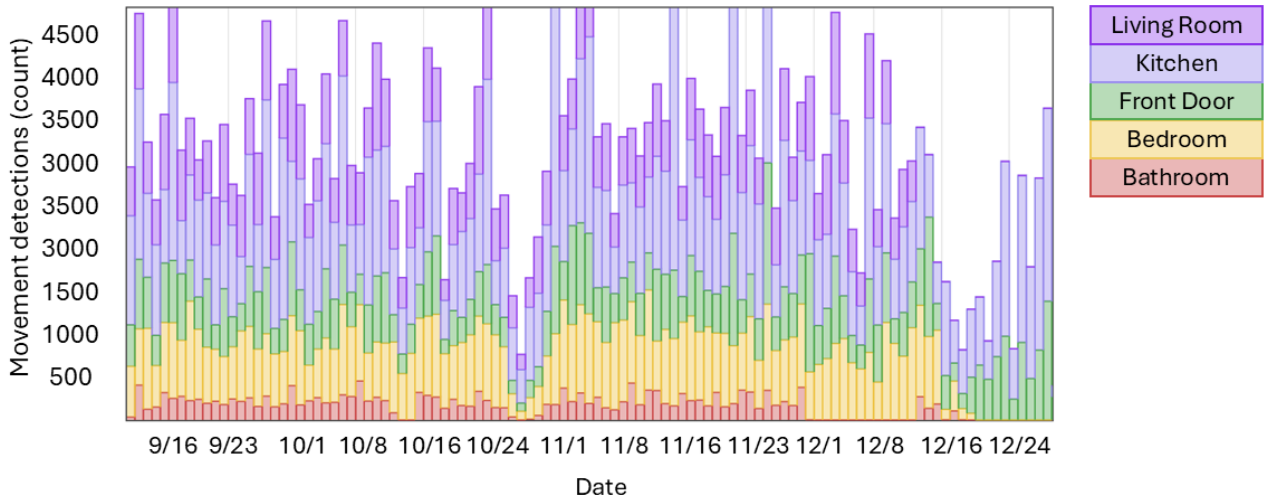

Figure 3. Heart rate and respiration rate by day from September 11 to December 29, 2023. Brown: energy; red: Hilbert transform; black: K-means clustering; blue: windowed peak-to-peak deviation; purple: respiration rate.

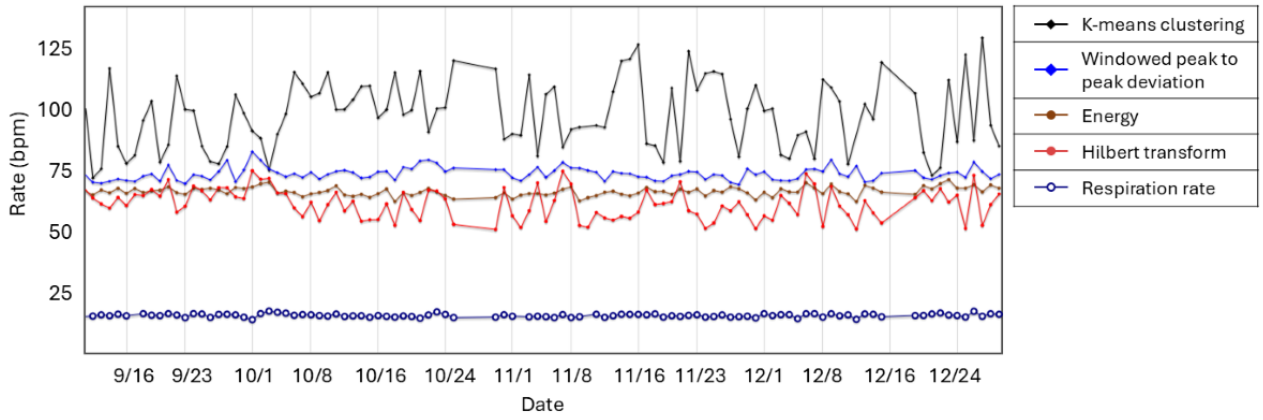

Figure 4. Gait data by date from September 11 to December 29, 2023. Light green: stride length (cm); dark green: average speed (cm/s); yellow: stride time (s); orange: system-generated gait alerts.

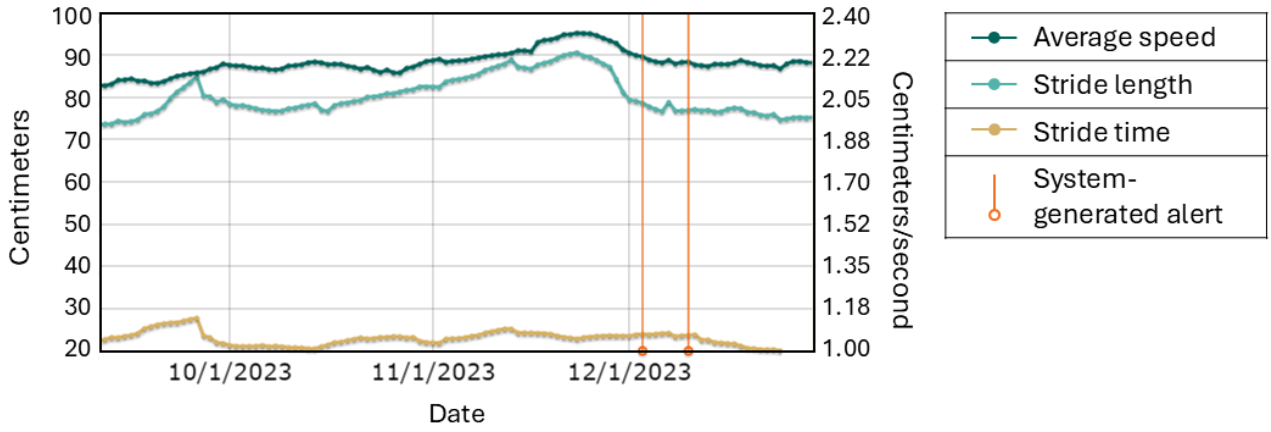

Evaluation Outcomes

As of this writing (fall 2024), sensor feature engineering is underway, and early detection modeling will be reported upon completion. The timeline of this work-in-progress is provided in Figure 5.

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Figure 5. Timeline. “1” indicates the phase of work presented in this paper.

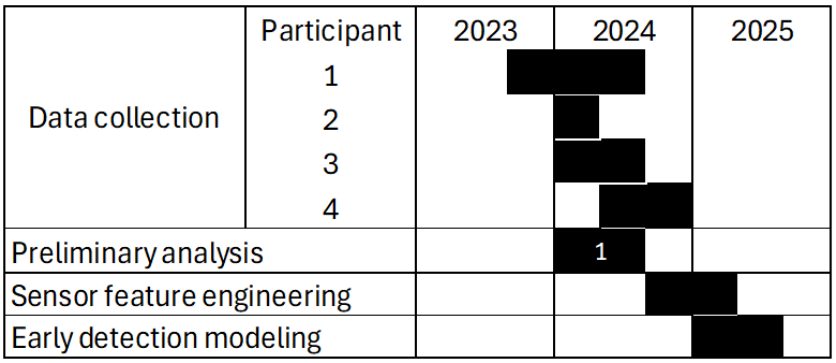

Discussion

Preliminary Results

This paper describes a federated approach to the collection of in-home sensor data and the extraction of EHR data to create predictive models of health status change in people living with ALS. This approach is feasible for collecting both biometric data and health outcomes from people living with ALS. The sensors are nonintrusive and privacy preserving by design, making them acceptable to participants. Similarly, the FHIR process is nonintrusive and ensures timely, secure extraction of records for machine learning purposes.

In the next phase of this work, we will process the data using both supervised and unsupervised machine learning approaches to detect health status changes and predict adverse health outcomes, including pneumonia, hospitalization, and death among people living with ALS. We anticipate that the results generated by this protocol will inform subsequent clinical trials for the prediction of ALS progression, providing guidance for interventions and their optimal timing.

Impact

This work represents a novel application of a remote sensor monitoring platform that has been previously validated in other settings and populations, such as stroke and independent living. This approach has tremendous potential in ALS, where progression is often rapid and, until now, unpredictable. It allows us to capture around-the-clock health state parameters, including during the critical late stages of decline. The system may provide important insight into physiological changes in late-stage ALS and suggest new intervention strategies to slow the rate of decline throughout the course of the disease.

Limitations

We anticipate several challenges during the course of this study. The sensor data are limited to physiological measures, gait parameters, and household-level motion activity, which may not adequately capture the full spectrum of deficits observed in ALS and are reported through clinical evaluations such as the ALSFRS-R. Recruitment has been lower than projected, which could reduce our ability to develop a reliable predictive model. Even if the sample size meets projections, there remains concern regarding whether the sample will be representative of the larger population of people living with ALS due to the geographic limitations of our single-site study. Our sampling frame results in a sample that is disproportionately White and non-Hispanic. This is an inherently criterion-referenced, single-subject approach, where each patient’s biometric indicators are evaluated only in terms of deviation from their own established historical norms. In contrast, hypothesis 3 will involve creating a predictive model based on historical data. A model built from a homogeneous sample may overfit the characteristics of that sample. Overfitting occurs when relatively few outcome events are represented in the data, thus overweighting their contribution to the model. As a result, the model becomes tuned to detect cases that match the original training phase cases but cannot adapt to novel cases that differ from the training cases. As such, our initial model may not perform as well with people with ALS from non-White and Hispanic backgrounds, including Black people with ALS, who are known to receive later diagnoses and have faster rates of decline [34]. Our validation phase will recognize the limited diversity available in our sample. Importantly, we will design the initial model to evolve with additional data.

Future Work

The project described in this paper will conclude in 2025. The authors have secured additional funding from the ALS Association (24-AT-722) to develop models to predict ALSFRS-R scores from sensor data and develop sensor-derived clinical alerts. That multisite project will provide a more diverse sampling frame to improve representation in the model. Future plans include clinical trials to establish the efficacy and effectiveness of this approach for delaying adverse outcomes.

Conclusions

This study will provide important new insights into the progression of ALS at a previously impossible level of granularity. The federated system described in this paper will facilitate the development of predictive algorithms for illness, falls, hospitalization, and death. This approach has the potential to transform the clinical assessment workflow through the implementation of decision-support predictive analytics, enabling more proactive and personalized care strategies. By integrating sensor-informed care for clinicians and caregivers, we hope that this work may lay the foundation for clinical trials to intervene ahead of adverse outcomes with the goal of extending and improving the quality of life of people living with ALS.

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Acknowledgments

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Data Availability

The datasets generated and analyzed during this study are available from the corresponding author on reasonable request. This paper adheres to the Guidelines and Checklist for the Reporting on Digital Health Implementations (iCHECK-DH) checklist, a copy of which is available from the corresponding author upon reasonable request [35].

Authors' Contributions

WEJ contributed to the conceptualization, funding acquisition, investigation, methodology, project administration, resources, supervision, visualization, writing of the original draft, and review and editing. NM contributed to data curation, formal analysis, investigation, methodology, software, validation, visualization, writing of the original draft, and review and editing. XS contributed to data curation, formal analysis, funding acquisition, investigation, methodology, resources, supervision, validation, and writing of the original draft. MP contributed to the conceptualization, funding acquisition, methodology, supervision, and writing of the original draft. ASMM contributed to the conceptualization, funding acquisition, methodology, resources, supervision, and writing of the original draft. JHE contributed to data curation, investigation, and project administration. VJ contributed to funding acquisition, project administration, and resources. MS contributed to conceptualization, funding acquisition, methodology, resources, and supervision.

Conflicts of Interest

The University of Missouri and MS have minority ownership stakes in Foresite Healthcare, which produces the sensor platform. MS also serves on the Advisory Board of Foresite Healthcare. These conflicts are managed by the University of Missouri Conflict of Interest Committee to ensure objective research conduct.

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Abbreviations

ALS: amyotrophic lateral sclerosis
ALSFRS-R: Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised
EHR: electronic health record
FHIR: Fast Healthcare Interoperability Resource
HIPAA: Health Insurance Portability and Accountability Act
ICD-9-CM: *International Classification of Diseases, Ninth Revision, Clinical Modification*
ICD-10: *International Statistical Classification of Diseases and Related Health Problems, 10th Revision*
LOINC: Logical Observation Identifiers Names and Codes
MoCA: Montreal Cognitive Assessment
REDCap: Research Electronic Data Capture
SNOMED CT: Systematized Medical Nomenclature for Medicine–Clinical Terminology

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Protocol

Contactless Sleep Monitoring for the Detection of Exacerbations in People With Chronic Obstructive Pulmonary Disease: Protocol for a Longitudinal Observational Study

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Abstract

Background: Exacerbations of chronic obstructive pulmonary disease (COPD) are one of the main causes of mortality, and early detection of exacerbations is thus essential. Telemedicine solutions have shown promising results for the detection of exacerbations in COPD and have increasingly been used. However, the effect of telemedicine is divergent. According to several studies, respiration rate (RR) increases before, during, and after an exacerbation and the change is measurable with several contactless devices. Despite this, RR is rarely measured, and telemedicine solutions only use wearable devices for measuring RR, even though wearable respiratory monitoring devices have been associated with certain drawbacks. Contactless devices are often used during sleep, as measurements conducted during sleep minimize the risk of disturbance from physical activities. However, the potential of measuring RR and heart rate (HR) during sleep for the detection of exacerbations in COPD remains unclear.

Objective: The aim of this observational study is to investigate whether contactless measurement of RR, HR, and sleep stages can be used to detect exacerbations in people with COPD.

Methods: An observational study including 50 participants with COPD will be conducted. The participants reside in Aalborg municipality, located in the North Denmark Region. Participants will use a contactless monitor (Sleepiz One+) near their bed during sleep for a period of 4 months. After data collection, descriptive statistics will be used to identify any extremes or variations in RR, HR, or sleep stages in the nights preceding an exacerbation. Correlation analysis will be performed to evaluate the relationship between the number of exacerbations and extremes or variations in RR, HR, or sleep stages. Finally, qualitative interviews will be conducted with 12 participants to explore their experiences of sleeping with the monitor nearby.

Results: Recruitment started at the end of April 2024. A total of 12 participants have been recruited, and the remaining participants are expected to be recruited during March and April 2025. Six out of 12 participants have completed the data collection and qualitative interview stages. Overall data collection is expected to be completed by September 2025. The results are expected to provide insight into the potential for identifying extremes or variations in RR, HR, or sleep stages in the days preceding an exacerbation. Additionally, the results are expected to assess the correlation between the number of exacerbations and extremes or variations in RR, HR, and sleep stages.

Conclusions: The findings from this study may clarify the possibility of using a contactless monitor to detect exacerbations in COPD. Furthermore, the results may have the potential to improve the ability to predict exacerbations in the future.

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KEYWORDS

disease exacerbation; chronic obstructive pulmonary disease; contactless measurements; sleep monitoring systems; heart rate measurement; respiration rate measurement; radar technology; health literacy; patient remote monitoring

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Introduction

Chronic obstructive pulmonary disease (COPD) poses a global health challenge. In 2019, around 212 million people were diagnosed with COPD, and it was the third leading cause of death with approximately 3.3 million deaths [1,2]. COPD is associated with significant economic costs, which increase with the progression of the disease [1]. In the European Union, the direct expenses related to respiratory diseases are estimated to comprise approximately 6% of the total annual health care expenditures, with COPD accounting for 56% of respiratory disease expenditures [1].

Exacerbations in COPD are characterized by exacerbation of shortness of breath and/or coughing with increased sputum over a period of <14 days. These escalating symptoms may be accompanied by rapid breathing and/or rapid pulse [1,3]. Frequent exacerbations are associated with reduced quality of life (QoL), increased risk of rehospitalization, and higher mortality rates compared to fewer exacerbations [4]. Hence, it is essential to prevent exacerbations.

Timely treatment of exacerbation reduces the risk of hospitalization and increases QoL [5,6]. Identification of the first symptoms of exacerbations is therefore essential to initiate early treatment. For early detection of exacerbations, telemedicine solutions are increasingly used, which seem to have a positive effect on QoL and hospital admissions [7,8]. However, the effectiveness of telemedicine solutions in preventing exacerbations is not convincing, and the results are generally divergent, indicating the need for further research [7-11].

In telemedicine, monitoring of physiological parameters is widely used for early detection of exacerbations. Primarily, oxygen saturation and heart rate (HR) are measured and used for detection of exacerbations [11-14]. However, the telemedicine solutions are generally based on studies with a low methodological quality, highlighting the need for robust, well-designed clinical trials [14].

According to several studies, both respiration rate (RR) and HR increase before, during, and after an exacerbation [15-17]. Despite measurement of RR being more effective than HR for early detection of exacerbation, only a few telemedicine solutions include measurements of RR [11-14]. The lack of RR measurement may possibly be attributed to the general challenge of measuring RR over an extended time period at home [18]. Moreover, respiratory monitoring equipment has been associated with certain drawbacks such as discomfort and difficulty in use [19]. Overall, the usability of respiratory monitoring systems is sparsely investigated [18].

Various contactless devices are capable of measuring RR [20], including contactless radar-based monitors [21,22]. Existing telemedicine solutions only use wearable devices for RR measurements [19,23-25], even though it seems possible to measure a change in RR during exacerbation using contactless devices [26]. Contactless devices enable free movement and eliminate the discomfort associated with wearable devices. Discomfort can hinder measurement over an extended time period [22,27,28], and contactless devices are therefore increasingly used for measurements of physiological parameters [29]. However, contactless devices require the user to be near the device and are therefore often used for overnight measurements, where the user remains close to the device for an extended time period [20]. During sleep measurement, it is essential that the equipment is contactless to minimize the impact on sleep quality [30]. Sleep monitoring minimizes the risk of measurements being influenced by factors such as physical activity. Several contactless devices are capable of measuring both RR and HR [20-22]. To the best of our knowledge, no previous studies have conducted frequent contactless measurement of RR and HR during sleep for detecting exacerbations in people with COPD.

The overall objective of the study is to investigate whether physiological variables such as RR, HR, and sleep stages can be used to detect exacerbations in people with COPD. This study is based on the hypothesis that data from frequent measurement of RR and HR during sleep can be used to detect exacerbations in COPD. Ultimately, these data may improve the prediction of exacerbations in COPD.

Methods

Study Design

This study is a longitudinal observational study and is expected to run from April 2024 to September 2025 [31,32]. This study will recruit participants from the Danish telemedicine service, TeleCare Nord (TCN), which is part of routine care in the North Denmark Region [33]. The telemedicine service includes measurements of oxygen saturation, pulse, blood pressure, weight, and patient-reported outcomes once a week [34].

Eligibility Criteria

Inclusion Criteria

People aged ≥18 years with a diagnosis of COPD will be included in the study, and both men and women are qualified. Moreover, people residing in the Aalborg Municipality will be deemed eligible to participate.

Exclusion Criteria

The exclusion criteria are the inability to complete questionnaires, pregnancy, nursing, electronic implants, and children or pets sleeping in the same bed as the participants, as it can disturb the measurements.

Recruitment

For the observational study, 50 participants will be recruited from Northern Jutland, Denmark. Initially, recruitment is conducted by specialized COPD community nurses (or a related clinician; Figure 1). The specialized COPD nurse gives a short introduction to the trial and in case of someone is interested in participating, a researcher from Aalborg University (AAU) will send a participant information letter by mail. Hereafter, the participants are contacted by a researcher from AAU who will provide further information about the study. If the individual is interested in participating, a consent form and questionnaires regarding baseline information will be sent by mail.

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Figure 1. The study procedure from recruitment until the end of the study. AAU: Aalborg University; COPD: chronic obstructive pulmonary disease.

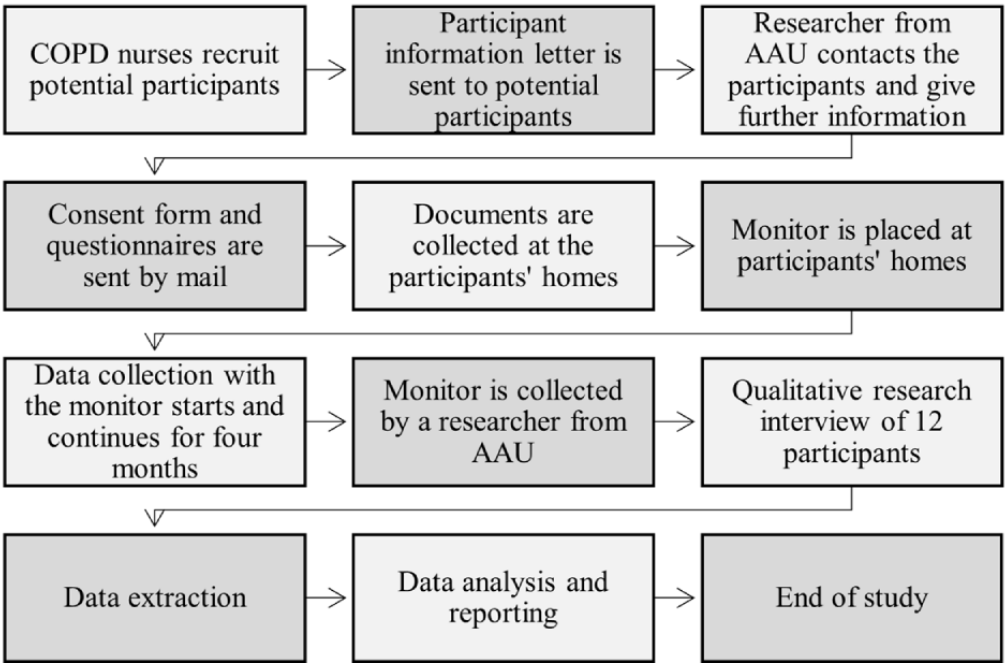

Study Setting

After the participants have received and completed the questionnaires and consent forms, a researcher from AAU will collect the documents at the participants' homes. Subsequently, a contactless radar-based monitor (Sleepiz One+) will be placed near the participants' bed. The monitor measures RR, HR, and sleep stages, including rapid-eye-movement sleep, light sleep, and deep sleep. The participants are asked to take measurements throughout the study period. The monitor measures changes in distance originating from breathing activity and heart contractions by using Doppler radar. These distance changes are analyzed using signal processing algorithms to extract RR and HR every fifth second.

The monitor is positioned on a stand 5-10 cm above mattress level, 40-50 cm from the participant pointing to the lower part of the chest. The monitor measures the participant during sleep and only measures the person who is positioned closest to the monitor. Therefore, the participants will be instructed to stay closest to the monitor during sleep, since it would disrupt the measurements if partners were sleeping closest to the monitor. Furthermore, participants will be instructed to turn on the monitor before going to sleep and turn it off upon waking throughout the entire study to ensure consistent data collection. This approach also prevents the monitor from recording data from partners who may go to bed earlier or stay in bed longer than the participants.

Neither the nurses nor the participants will have access to the data from the monitor during the study. Data from the monitor are solely used retrospectively to investigate whether it is possible to identify changes in RR, HR, or sleep stages preceding exacerbations. After the researcher from AAU had placed the monitor at the right position and ensured that the monitor works, data collection was carried out for 4 months.

The data will automatically be transmitted through Wi-Fi to a web application connected to the monitor, enabling data extraction. This web application allows users to view and analyze data collected by the contactless monitor. Participants will be registered as users in the web system by a researcher from AAU, who will also connect a monitor to each individual participant.

The questionnaires will be used to explore health status and health literacy. The health status involves baseline information (gender, age, civil status, educational level, deployment, years since COPD diagnosis, smoking status, and comorbidities), the COPD Assessment Test (CAT) [35], the Medical Research Council (MRC) dyspnea score [36], and The European Health Literacy Survey Questionnaire (HLS-EU-Q16) [37,38]. Additionally, the Danish Short Test of Functional Health Literacy in Adults (DS-TOFHLA) [39] questionnaire will be distributed to assess health literacy.

In cases of missing data for more than 2 consecutive nights, the participants will be contacted by a researcher from AAU by telephone to clarify the underlying reason and resolve that. Once data collection for 4 months (±10 nights) is completed, the monitor is collected by a researcher from AAU.

Data will be extracted from the web application connected to the monitor, TCN, and the National Patient Registry to determine the number and dates of exacerbations. Exacerbations are defined as hospitalizations caused by COPD or self-initiated treatment with antibiotics and/or steroids [40]. To obtain the exact dates of exacerbations, hospitalizations related to COPD will be extracted from the National Patient Registry. Similarly, to determine the dates of exacerbations related to self-initiated treatment, participants are already registering their use of antibiotics and steroids as part of TCN. If self-initiated treatment is registered, a researcher from AAU will contact the COPD nurse to obtain information about when the treatment began, thereby obtaining the exact date of the exacerbation.

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User Experience

A total of 12 participants will be asked to participate in a qualitative research interview, focusing on the experience and acceptance of sleeping with the monitor nearby over an extended period. The number of informants for the qualitative research interviews is expected to be sufficient, as data saturation is typically achieved with 12 participants [41]. However, the final number of informants may vary slightly, depending on when data saturation is achieved. To explore the participants' perspectives on using the monitor, the qualitative research interview will be supplemented with the System Usability Scale (SUS) [42] to gather additional information regarding the usability of the system.

Interviews and surveys will be conducted after participants have used the monitor for at least 2 months, allowing them to gain a more realistic understanding of the long-term use.

Data collected during the interviews will be analyzed using the thematic analysis approach developed by Liamputtong [43] and Braun and Clarke [44]. The SUS score will be calculated in accordance with the guidelines presented by Lewis and Sauro [45]. The scores will be analyzed descriptively by using statistical tools in Excel (Microsoft 365 MSO; version 2406, build 16.0.17726.20222).

Statistical Analysis

Overall, the data analysis will include descriptive statistics and logistic regression. Descriptive statistics will be used to calculate mean, SD, and variance for RR, HR, and the time spent in different sleep stages. Logistic regression is particularly relevant when working with binary outcomes to calculate the probability of an event occurring based on one or more independent variables. Since this study investigates whether changes in physiological parameters occur in the nights preceding an exacerbation, logistic regression is an appropriate method for analysis. Logistic regression will be used to calculate the probability of developing an exacerbation based on the descriptives derived from RR, HR, and sleep stages as independent variables. Odds ratios based on logistic regression and the F statistic ($P<.05$) will determine whether each descriptive is independently associated with developing an exacerbation. Furthermore, correlations between the descriptives will be examined.

Sample Size

A sample size of 40 participants will provide 90% power to demonstrate a significant correlation coefficient of 0.5 between the number of exacerbations and extremes or variations in RR, HR, and sleep stages. Considering a presumed dropout rate of 25%, based on previous findings in a study among people affiliated with TCN (ClinicalTrials.gov NCT05218525), 50 participants need to be recruited in this study.

Ethical Considerations

The study has been approved by the Regional Ethical Committee for Medical Research in the North Denmark Region (N-20230072). The study will be performed in accordance with the tenets of Helsinki Declaration [31] and the principles of Good Clinical Practice. Written consent will be obtained from each participant after detailed verbal and written information about the study has been given and will be obtained before inclusion in the study [31]. Data will be anonymized and stored securely in compliance with the Danish Data Protection Rules [32]. The protocol will not be modified unless a new approval from the Regional Ethical Committee is obtained. The participants will not be provided with any compensation for their participation. There are no expected risks associated with participation in the trial. There is no increased risk of exacerbations, as the participants are not exposed to any interventions that could contribute to the development of exacerbations in COPD.

Results

The study received final approval from the Regional Ethical Committee for Medical Research in the North Denmark Region on April 10, 2024 (N-20230072). In April 2024, the first participant information letter was sent by mail to the initial potential participants. The first participant was recruited in May 2024. A total of 12 participants have been recruited so far. Six out of 12 participants have been completed. These participants have also participated in qualitative research interviews at the end. The delivery of the remaining monitors has been delayed and is expected to be underway in March and April 2025. The remaining participants will be recruited once the delayed monitors are received. Data collection will begin as participants are recruited. The first participant completed the data collection stage at the beginning of October 2024 and the last participant is expected to complete this stage by September 2025.

Discussion

Anticipated Findings

The main finding of this study is presumed to be a new way to detect COPD exacerbations using contactless sleep monitoring. The study aims to provide knowledge regarding the possibility of detecting COPD exacerbations through frequent measurements of RR, HR, and sleep stages collected by using a contactless monitor during sleep. If the study proves that exacerbations can be detected by contactless measurements, the results have the potential to improve the ability to predict exacerbations in the future. Predicting exacerbations enables the possibility of initiating early treatment, which is expected to reduce hospitalizations and increase the quality of life among people with COPD.

Additionally, the study is also expected to provide knowledge regarding the experience of using the monitor more permanently. This is considered valuable knowledge about the potential of the monitor, as users' experience and acceptance are important to consider when developing and implementing new technologies [46,47].

An expected strength of this study is the high frequency of measurements conducted over an extended time period. To our knowledge, no previous studies have monitored RR by a contactless monitor with a high frequency of measurements over an extended time period in people with COPD. However, continuous data collection can be crucial in this study because

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missing data from the nights preceding an exacerbation can reduce the ability to detect exacerbations, as symptoms primarily change a few days prior to onset [48]. While the recommendation to turn the monitor on/off throughout the entire project period is expected to meet the participants' needs regarding privacy in the bedroom, this recommendation can also increase the risk of missing data. Therefore, it is important to be aware of missing data throughout the study period.

Another expected strength is that the measurements are conducted during sleep without physically touching the participants. This is expected to eliminate the discomfort associated with wearable equipment. Moreover, conducting measurements during sleep reduces the risk of data being influenced by factors like physical activity, which can be challenging to control when people perform the measurements at home during the day on their own. Øverst på formularen

This study may be limited by the risk of observing too few exacerbations during the project period. To address this, most participants will collect data during the winter, when exacerbations are more frequent. However, participants will also collect data at different times of the year, and thus across different seasons, which will help increase the generalizability of the results. Additionally, to mitigate this potential limitation, exacerbations of varying severities will be included to increase the likelihood of capturing exacerbations. This approach was also chosen because it is of interest to examine whether it is possible to detect changes or patterns in the days preceding different severities of exacerbations. The study has the potential to improve the ability to detect COPD exacerbations and thereby initiate early treatment to reduce hospitalization.

Dissemination Plans

The results are expected to be published in international scientific journals. All results will be reported anonymously. The results will be published irrespective of whether they are positive, negative, or inconclusive. The authorship will be admitted to persons who have participated to the design, interpretation, conduct, and reporting of the trial. The results will also be communicated to participants who have indicated that they wish to be informed.

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Data Availability

Data will not be made publicly available as the study participants have not consented and their data fall under General Data Protection Regulation regulations.

Authors' Contributions

Conceptualization and methodology: JE, TK, OH, and SH
Writing—original draft: JE
Writing—review, editing, and finalization:TK, OH, and SH

Conflicts of Interest

None declared.

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Abbreviations

AAU: Aalborg University

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CAT: COPD Assessment Test
COPD: Chronic obstructive pulmonary disease
DS-TOFHLA: Danish Short Test of Functional Health Literacy in Adults
HLS-EU-Q16: The European Health Literacy Survey Questionnaire
HR: Heart rate
MRC: Medical Research Council dyspnea score
QoL: Quality of life
RR: Respiration rate
TCN: TeleCare Nord

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Protocol

A Multicomponent Strategy to Improve HIV Pre-Exposure Prophylaxis in a Southern US Jail: Protocol for a Type 3 Hybrid Implementation-Effectiveness Trial

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Abstract

Background: Pre-exposure prophylaxis (PrEP) is an effective approach for preventing HIV infection, but it is underutilized by populations who may benefit the most, including people living in the Southern United States and those involved in the criminal legal (CL) system. Improving the access and use of PrEP for these groups could decrease HIV-related health disparities. Beyond individual outcomes, HIV prevention for CL-involved people can have a significant public health impact on HIV incidence due to a high turnover between jails and the community.

Objective: We will develop, implement, and evaluate a multicomponent PrEP implementation strategy for the Dallas County Jail (DCJ) to increase the initiation of this HIV-preventive intervention for CL-involved individuals.

Methods: This is a type 3 hybrid implementation-effectiveness study that takes a combined approach by assessing the implementation of a strategy to identify candidates for PrEP at the DCJ and linking them to PrEP providers upon community re-entry while also gathering information about clinical outcomes. The approach is guided by the EPIS (exploration, preparation, implementation, sustainment) framework. Initial formative work (exploration) involves qualitative interviews of diverse key stakeholders to identify factors that may influence linkage to PrEP after jail release. These findings will undergo rapid qualitative analysis (preparation) to inform the adaptation of a multicomponent jail PrEP implementation strategy protocol. This approach, which will include an electronic health record (EHR) prediction model and integration of a PrEP patient navigator into the jail health team, will allow medical providers and the navigator at the DCJ to engage individuals most likely to benefit in shared decision-making about PrEP and navigate them to community PrEP care (implementation) in a process that begins before release from jail and ends with successful care linkage. Regular quantitative and qualitative evaluations of this approach will allow for ongoing stakeholder input, refinement of the implementation strategy, and maintenance of the program (sustainment).

Results: Findings from 26 qualitative interviews (9 formerly incarcerated individuals, 9 county jail staff, and 8 employees of community organizations) have been obtained, analyzed, and mapped to an implementation strategy formalized in a jail PrEP protocol. An HIV risk prediction model based on EHR data to identify individuals most likely to benefit from PrEP has been

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developed and internally validated and is ready to be deployed. We anticipate the availability of preliminary study findings in 2026.

Conclusions: This study will provide key insights into the feasibility and effectiveness of a PrEP implementation strategy among people at increased risk of HIV acquisition in an urban jail in Southern United States. This practical and scalable strategy can be used as a model for other urban jails to address HIV-related inequities.

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KEYWORDS

pre-exposure prophylaxis; PrEP; HIV; HIV prevention; jail; incarceration; health disparity; electronic health records; EHR; southern United States

Introduction

It was estimated that there were 31,200 new HIV infections across the United States in 2021 [1], with a disproportionately high percentage of new diagnoses occurring in the South [2]. New HIV infections disproportionately affect men who have sex with men (MSM) and Black and Hispanic populations [3]. HIV prevention with pre-exposure prophylaxis (PrEP) can reduce the risk of HIV acquisition by 99% [4,5], but its public health impact depends on connecting populations at risk of HIV to PrEP care and continuing care over time [6-9]. Uptake of PrEP is increasing among White MSM on the east and west coasts but remains limited in minority groups in the South [10-12] where HIV incidence is the highest [13]. The PrEP-to-need ratio, defined as the number of PrEP users divided by new HIV diagnoses [14], is lower in the South than in any other region, particularly among racial and ethnic minorities, further highlighting inequitable access [15].

To decrease HIV incidence, there is a need to improve PrEP use in populations most heavily impacted by HIV. Launched in 2019, the federal *Ending the HIV Epidemic* (EHE) initiative provides an evidence-based framework for decreasing HIV incidence in the United States by 90% by 2030 [16]. The EHE initiative identifies that a critical component of epidemic control is to focus prevention efforts on geographic hotspots, including the 48 counties with the highest incidence, which are disproportionately in the Southern United States, and 7 states with major rural HIV epidemics. Active multisector partnerships among local public health departments, health care facilities, academic institutions, and community organizations are pivotal to achieving the EHE initiative's goal [8,17].

Dallas County in Texas is one of the largest HIV hotspots in the South, with high rates of new HIV infections and major racial and ethnic disparities in HIV incidence and access to preventive services. In 2021, Dallas County had one of the highest rates of persons newly diagnosed with HIV at 38 per 100,000 population, compared to the national incidence of 11.5 per 100,000 population [18]. The rate of new HIV diagnoses was even higher for Black individuals in the county, at 72 per 100,000 population [19]. Despite the dense HIV epidemic in Dallas County, only 25% of the estimated number of people with indications for PrEP were prescribed it in 2023 [3]. Barriers include high rates of uninsurance and poverty [20,21], medical mistrust and stigma [22,23], low HIV risk perception [15], and high rates of incarceration [24].

About 1 in 7 people with HIV pass through US jails and prisons each year, making the justice system a potentially high-impact setting for HIV testing and prevention [25]. In Texas, the Department of Justice estimated in 2021 that 1.4% of the prison population is living with HIV, which is 4 to 5 times greater than the prevalence in the general US population [26]. Individuals in the criminal legal (CL) system, including those who are in jail, in prison, or under community supervision (ie, probation and parole), also remain at disproportionate risk for HIV infection due to higher rates of sexually transmitted infections (STIs) [27], condomless sex [28,29], transactional sex [30], shared injection drug use equipment [31], dissolution of primary intimate partnerships [32], and broader socioeconomic barriers to medical care (eg, unemployment and homelessness) [33]. Opt-out HIV testing in jails is feasible and can identify many new infections while avoiding the burden of requesting a test among patients [34]. Testing uptake when offered in a nonjudgmental opt-out manner is 80% to 95% [35-37] and should be followed by linking incarcerated individuals to appropriate HIV treatment or preventive care [38-42]. Yet, despite recommendations for the practice of opt-out HIV testing by the Centers for Disease Control and Prevention (CDC), only about a third of US jails offer opt-out HIV testing [43].

Given that most individuals spend less than a month in jail and often cycle multiple times between incarceration and the community [44], there is a high potential public health impact of HIV prevention strategies in jails. Barriers to PrEP implementation in jails exist at several ecological levels and include limited knowledge of PrEP among those likely to benefit and their providers [45,46], lower perceived than actual risk of HIV [47,48], and distrust of institutions [49]. The timing of HIV prevention interventions is also significant, with the transition to living in the community being a particularly pivotal period when HIV transmission–risk behavior is increased and other personal needs take priority during community re-entry [50,51]. For these reasons, effective PrEP implementation strategies in jails may require multiple components to be successful [52-54]. For example, interventions at the individual level have included supporting HIV prevention after incarceration through a mobile app with customized wellness goals and incentives [55]. Building on evidence from CL-involved people with HIV transitioning to the community, peer education and patient navigation are being explored as

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approaches to improving HIV prevention [56-59]. At the dyadic level, patient-provider shared decision-making around PrEP, which has been used in the community, is also being applied in correctional settings [60-63]. The objective of our study is to assess specific needs and recommended strategies and use these findings to develop, implement, and evaluate a multicomponent PrEP implementation strategy for the Dallas County Jail (DCJ), which is the 8th largest jail in the nation and located in an HIV hotspot [64].

Methods

Study Setting

The DCJ is the main jail facility for Dallas County, with 51,000 incarcerated individuals per year (86% men, 48% Black, and 30% Hispanic) and approximately 275 individuals entering and leaving the jail daily. The mean length of stay is 45 days, and 11% of people transfer to prison [65]. Parkland Health, a teaching hospital for UT Southwestern Medical Center, provides health care services at the jail for approximately 6200 patients monthly. Health care for individuals experiencing incarceration is paid for by Dallas County.

Of over 12,000 HIV/STI tests performed each year at the DCJ, there are approximately 50 to 100 new HIV diagnoses (personal communication by Dr Barry-Lewis Harris, April 2024) and high STI positivity (5% syphilis, 5% gonorrhea, and 11% chlamydia) [35,66], which is a recommended indication for PrEP use. The approach to HIV testing at the DCJ is a combination of opt-in and opt-out. All persons entering the jail complete a nursing intake questionnaire to review medical history, receive the option for HIV/STI testing (opt-in), and, for men, indicate if they want to be in separate housing for MSM as a safety precaution. All individuals who undergo blood draws are offered opt-out HIV testing. Individuals with negative HIV test results are not routinely counseled about the results, and few, if any, receive information about PrEP. Currently, new initiation of PrEP is not permitted at the DCJ, and thus, the study will focus on linkage to PrEP after release.

Study Design

This is a type 3 hybrid implementation-effectiveness study, which takes a combined approach in assessing implementation while also gathering information about clinical outcomes associated with implementation [67]. We will track established implementation outcomes (eg, feasibility, acceptability, and penetration), effectiveness (eg, attending PrEP visits and new HIV/STI diagnoses), and sustainability, including integration into routine processes at collaborating agencies and duration of any positive effects in care processes and outcomes. We will use the EPIS (exploration, preparation, implementation, sustainment) framework [53,54] to guide our efforts to identify and address performance gaps in DCJ PrEP care. Although originally developed for public service sectors, the EPIS framework has since been widely applied in health care, including in jails [54]. As shown across the top portion of Figure 1, our key study concepts and activities reflect EPIS framework components.

Figure 1. Conceptual socioecological model of pre-exposure prophylaxis (PrEP) implementation for criminal legal–involved people. EHR: electronic health record.

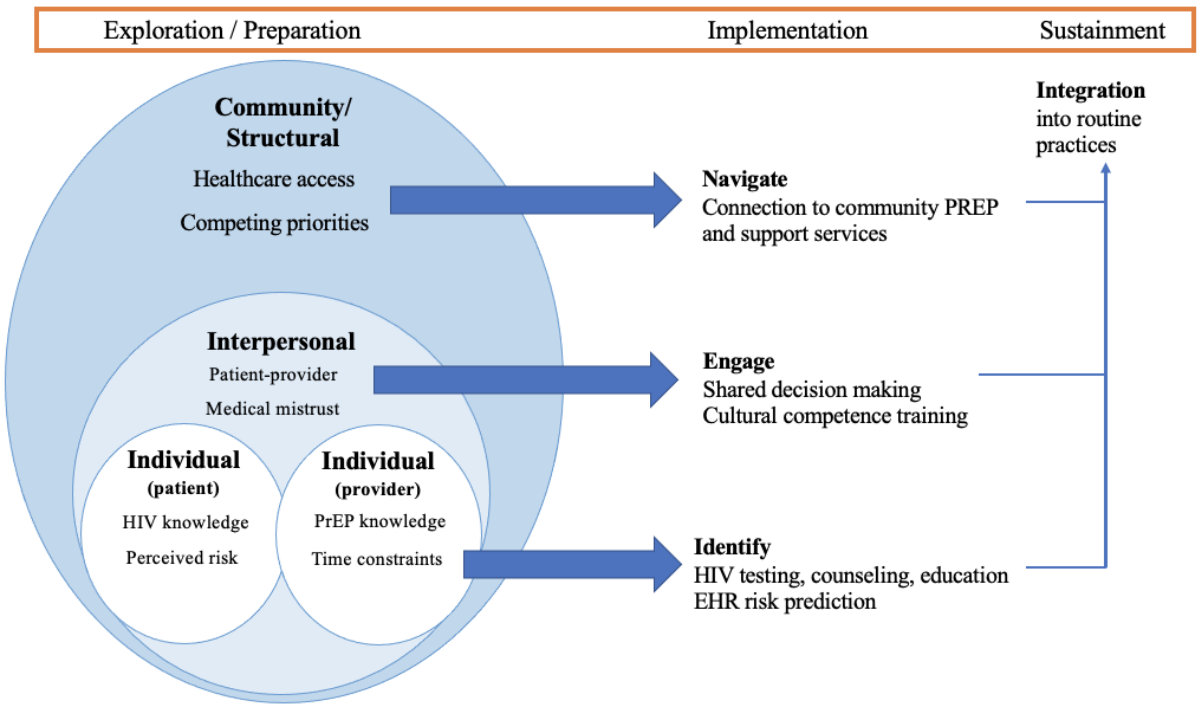

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Study Aims

Aim 1: Exploration

Using the socioecological model as a conceptual model [68], we will identify and describe specific individual, interpersonal, and community/structural factors that influence PrEP implementation through qualitative interviews and focus groups with key stakeholders in the jail and Dallas community (Figure 1).

Participant Characteristics and Recruitment

Participants will be individuals aged 18 years or older who are medical providers or administrators in the DCJ or in the surrounding community, people formerly incarcerated in the DCJ, representatives of community-based organizations serving those affected by HIV or with criminal justice involvement, and members of the public health department. Of note, due to restrictions on recording individuals at the DCJ and due to the benefit of addressing the postincarceration transition, the individuals we recruit will be formerly incarcerated rather than currently incarcerated. Formerly incarcerated individuals will be referred by their health care providers in community clinics or can self-refer in response to Institutional Review Board (IRB)-approved flyers posted in community-based service organizations. Health care professionals will be recruited at routine staff meetings and via email invitations. Administrators will be contacted about participation via email or personal contact from members of the study team.

Data Collection

We will conduct 20 to 30 semistructured interviews, which, based on our previous work, should be sufficient to reach saturation (ie, the point at which no new information is being uncovered through additional interviews). Individual interviews are preferred for formerly incarcerated individuals, jail staff, and members of community organizations due to the sensitive nature of questions and the convenience of scheduling.

Separately, we will also conduct a focus group with 10 to 12 members of the HIV/AIDS Re-Entry Coalition (HARC) in Dallas County during one of their quarterly teleconferenced meetings. The HARC is a group comprised of individuals from diverse community organizations who regularly collaborate to enhance the delivery of health and supportive services to individuals who have been recently released from incarceration. Feedback is especially valuable from these group discussions given the breadth and length of experience of the members. Lastly, we will conduct 2 focus groups during a summit event in which we will invite PrEP-providing organizations to compare their experiences and challenges in providing PrEP and related services amid the dynamic funding landscape and to assess opportunities for collaboration.

Semistructured interview and focus group guides will be tailored to each target group, and topics will reflect the range of factors relevant to PrEP implementation across different socioecological levels, as shown in Figure 1. All participants will also be asked to provide feedback on how to adapt and optimize the components of our implementation strategy for local populations, settings, resources, and norms. All interviews and focus groups will be audio recorded and conducted by research staff experienced in qualitative methods.

Data Analysis

We will conduct both a rapid qualitative analysis during data collection and a systematic thematic analysis when all data have been collected. The purpose of the rapid analysis is to promote consistent data capture, facilitate communication among the members of the research team about findings, and monitor progress toward saturation [69]. The thematic analysis will systematically categorize patterns in findings across interviews within a group (eg, patients) and across groups (eg, patients, jail providers, and health care leaders), using iterative thematic analysis in accordance with best practice techniques [70,71]. All data will be managed in NVivo 12.0 (QSR International). The study's principal investigators in conjunction with a study co-investigator who is an established qualitative methodologist will jointly develop a thematic codebook based on a review of the rapid analysis data and 20% of the interview fieldnotes, with codes mapped to the socioecological model presented as part of Figure 1. Trained research staff will double-code all interview transcripts, resolving discrepancies through discussion and conferring with the qualitative co-investigator as needed. A synthesis of the major findings will be presented to stakeholder groups to confirm appropriateness [72].

Aim 2: Preparation

In aim 2, our qualitative findings from aim 1 will inform the refinement of a multicomponent PrEP implementation strategy for CL-involved individuals. We will adapt and hone approaches to identify incarcerated people at increased risk for HIV using electronic health record (EHR) clinical decision support tools and patient-reported data to prompt providers to conduct HIV/STI tests and discuss PrEP with those most likely to benefit; engage CL-involved individuals in shared decision-making about PrEP using adaptations of previously developed patient decision aids; and navigate these individuals to existing PrEP services in the Dallas area after release.

Datasets to Identify Individuals at Increased Risk for HIV

The Parkland Center for Clinical Innovation (PCCI) has developed and validated an automated matching algorithm to extract data from the DCJ EHR (PEARL) and match it to data from Parkland's EHR (Epic) from 2010 to the present. Records will be matched based on multiple variables, including patient name, preferred name, date of birth, gender, sex assigned at birth, race or ethnicity, and social security number as available. We will exclude any individuals younger than 18 years. Individuals may have multiple encounters in both the jail and Parkland EHRs due to repeat jail incarcerations or medical visits, and these data will be incorporated as summary variables (eg, number of prior episodes of gonorrhea) with statistical adjustments for repeated measures in an individual. This combined dataset will provide rich data for identifying PrEP candidates and allow us to develop an HIV prediction model. This component of the study will involve the collection of existing data and the development of tools and protocols, and therefore, a waiver of consent will be obtained. Furthermore, matching of records using the identifiers above will be performed behind the firewall of the PCCI, and all datasets will

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be deidentified prior to sharing with the rest of the research team.

Validation of the HIV Risk Prediction Model

We will use our prior models for predicting incident HIV [73,74] to identify candidate variables for our HIV prediction model. Subsequently, the use of temporal validation will assess how well our model will perform prospectively, dividing our dataset into a derivation dataset (2015-2021) and a validation dataset (2022-present). We will train our model to predict incident HIV diagnoses, defined as positive HIV screening and confirmatory tests or new HIV diagnosis codes without prior evidence of HIV in the EHR [73-75]. We will have ample data on new HIV diagnoses to train our models, as Parkland has a robust HIV testing program and diagnoses more new cases of HIV than any other entity in Dallas [76]. Jail EHR data may be more limited in scope because the jail generally provides short-term episodic care. However, given high recidivism rates [77], many incarcerated individuals will have multiple data points in the jail EHR to inform HIV risk prediction, including data on prior HIV/STI testing and substance use.

We will compare the performance of parsimonious versus full models in the validation dataset based on their ability to discriminate between patients with and those without incident HIV using the C-statistic or area under the receiver operator characteristic curve and the Hosmer-Lemeshow goodness of fit test. Additionally, we will use multiple complementary approaches for estimating HIV risk to capture the greatest number of individuals with indications for PrEP. This will include anyone who identifies as transgender, requests MSM housing, has had a recent STI, or opts-in for HIV/STI testing, in addition to those flagged by our EHR model. We will compare EHR models against these criteria to measure the added value of each approach (eg, number of individuals identified by our model as likely to benefit from PrEP who are missed by patient-reported data and vice versa).

Protocol Development

In conjunction with our risk prediction model, the findings from our aim 1 stakeholder interviews will directly inform our protocol for identifying persons who are at increased risk for HIV and likely to benefit from PrEP. This will include elements, such as which practitioners receive EHR alerts about potential PrEP candidates and the content of staff trainings for collecting and acting on patient-reported data and EHR alerts. We will select a final process for identifying candidates for PrEP discussions based on sensitivity (ie, missing as few persons at increased risk as possible), feasibility, and efficiency, while taking into account priorities identified by stakeholders in aim 1.

A key consideration for sexual health discussions in the jail setting is privacy. Feedback in aim 1 will inform how and where these discussions will take place. Providers may also desire additional training in assessing sexual risk, as knowledge of PrEP among correctional nursing staff and clinical providers is vital for successful implementation [78]. Furthermore, the approach to incarcerated individuals about sensitive topics, such as sexual health and substance use, will be informed by best practices, including having these screenings conducted one-on-one by medical staff and partnering with community-based organizations [79]. Any paper materials given to patients will be adapted to the American Medical Association's recommended 6th grade reading level and worded to avoid disclosing the health status.

Navigation for Individuals Likely to Benefit From PrEP

Individuals who are identified as being at increased risk for HIV and who test negative for HIV will be considered PrEP candidates. We will develop a PrEP decision-support tool to be used with the diverse populations present in the jail, informed by stakeholders' preferences from aim 1. This will include presenting information on sexual health and HIV prevention for multiple populations (eg, transgender people and cisgender women), local details on HIV epidemiology, and ways to afford and access PrEP. Individuals identified as PrEP candidates will meet with medical providers or navigators (depending on stakeholders' preferences) to review HIV prevention options and our patient decision-support tool. Patients will be informed that they will not be charged for these visits, as for all care related to communicable diseases in the DCJ. At this visit, the provider or navigator will assess the patient's knowledge of and interest in PrEP. Together with the patient, they will work through the decision-support tool. If the patient plans to pursue PrEP care after incarceration, the navigator will initiate the navigation protocol.

PrEP Care Navigation and Linkage Following Release

Those interested in PrEP will receive intensive navigation that includes both in-person and electronic referrals. Similar to existing navigation protocols (eg, for hepatitis C [80]), the navigator will initiate this process while the individual is still in jail. The navigator will obtain detailed patient contact information, identify and address the patient's health priorities and potential barriers to care, and create a personalized step-by-step process for accessing PrEP services after release. Patients will also be able to contact the navigator after jail release directly by phone or SMS text messaging.

Multiple PrEP providers in the Dallas community employ peer outreach workers who accompany patients to their PrEP visits. We will work with these providers to develop a protocol for seamless hand-off from the jail-based navigator to the community-based peer. For electronic referrals, we will integrate stakeholders' preferences for details regarding the transfer of information to community PrEP sites, including what information to communicate, how to communicate, and the timing of communication. Findings from our aim 1 qualitative data will help us pinpoint solutions to barriers or competing priorities to PrEP that patients identify. In some cases, we anticipate that multiple referrals will be necessary for patients to successfully access PrEP.

Aim 3: Implementation and Sustainment

In aim 3, we will deploy our multicomponent strategy at the DCJ and assess its impact on implementation and clinical outcomes for PrEP, as specified in Table 1.

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Table 1. Quantitative implementation outcomes, metrics, timing, and data source.

Hybrid type 3 domain and outcome	Metrics (among patients with high risk)	Timing (month range)	Data source[a]
Implementation			
Feasibility	HIV/STI[b] testing offered	1-24	EHR[c], navigator
Feasibility	PrEP[d] discussions offered	1-24	EHR, navigator
Feasibility	Shared decision-making tool offered	1-24	EHR, navigator
Feasibility	PrEP navigation visits offered	1-24	EHR, navigator
Feasibility	PrEP referrals offered	1-24	Navigator
Penetration	Providers discuss/refer for PrEP	1-24	EHR, navigator
Acceptability	HIV/STI testing completed	1-24	EHR
Acceptability	PrEP discussions completed	1-24	EHR, navigator
Acceptability	Shared decision-making tool used	1-24	EHR, navigator
Acceptability	PrEP navigation visits completed	1-24	EHR, navigator
Acceptability	PrEP referral completed	1-24	Navigator
Effectiveness			
PrEP	PrEP visits in the community	1-24	Navigator
PrEP	PrEP prescription	1-24	Navigator
PrEP	PrEP use at 3 months	1-24	Navigator
HIV/STI	New HIV/STI diagnoses	1-24	EHR
Sustainment			
All	Reassess all study outcomes	25-30	All

[a]Qualitative assessments (3 times per year) complement quantitative metrics for all outcomes.

[b]STI: sexually transmitted infection.

[c]EHR: electronic health record.

[d]PrEP: pre-exposure prophylaxis.

Training of DCJ Staff

The project principal investigators will conduct a 2-session interactive group training for frontline DCJ practitioners to introduce our PrEP implementation strategy. Session 1 will be adapted from trainings on culturally competent sexual health care, HIV, and PrEP [81], including clinical indications for PrEP and barriers and facilitators to its adoption in the jail and local community. Session 2 will introduce the rationale and practical aspects of using patient-reported and EHR data to identify PrEP candidates, as our prior qualitative work suggests that providers are more likely to trust, adopt, and use HIV risk assessment tools if they understand how they work [82]. The session will also review how providers and navigators can engage patients in the shared decision-making process and will include demos of PrEP decision-support tools. Lastly, session 2 will cover PrEP navigation processes, including PrEP resources in Dallas County, and navigation protocols. Postsession evaluations will be conducted for rating quality and usefulness.

Steps for Strategy Implementation

Our strategy will include the following detailed steps that can be visualized as part of the continuum (Figure 2): (1) identify, (2) engage, and (3) navigate.

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Figure 2. Intervention steps in the jail-to-community continuum. DCJ: Dallas County Jail; EHR: electronic health record; PrEP: pre-exposure prophylaxis; STI: sexually transmitted infection.

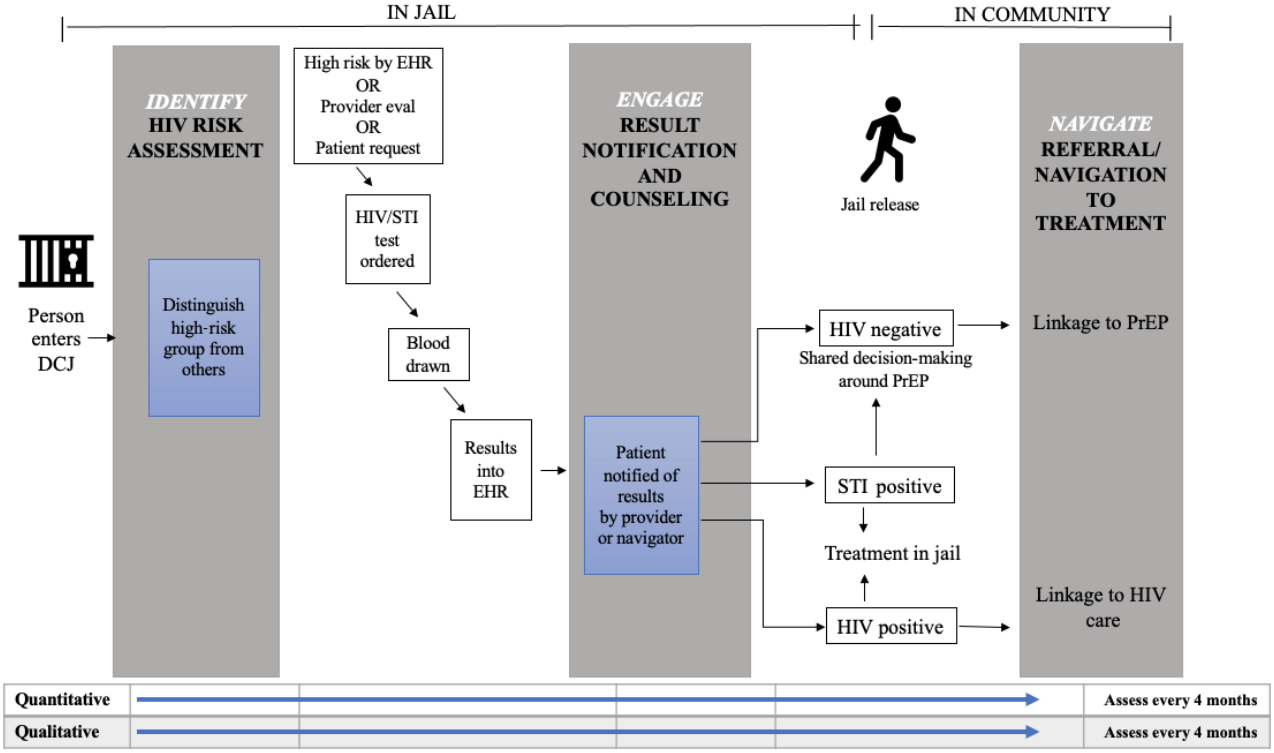

In the "identify" step, when individuals enter the jail, a jail EHR record will be created (or an existing record will be opened for those with prior DCJ incarceration). Our automated algorithm will match the jail EHR to the Parkland EHR and generate an individual HIV risk score. For people with predicted HIV risk above a prespecified threshold that maximizes sensitivity without causing alert fatigue among providers, an automated prompt will appear in the jail EHR for providers to discuss PrEP and order HIV/STI testing. As illustrated in Figure 2, providers will also be prompted to order HIV/STI tests for any patients who report risk factors at intake or during a clinical assessment (eg, transgender identity and requests to be housed with MSM) or who request testing directly. Prompts will persist until orders are completed as a "nudge," a behavioral economic intervention to maximize ordering [83], and results are entered into the EHR.

In the "engage" step, positive HIV tests will prompt referrals to the jail HIV clinic for rapid initiation of antiretroviral therapy according to the current practice, and STIs will be treated based on CDC guidelines [84]. Persons with negative HIV tests will meet one-on-one with a provider or PrEP navigator and receive counseling informed by our PrEP decision-support tool. The navigator we hire will be experienced in working with CL-involved people. Counseling will be person-centered and culturally tailored, with positive sexual health framing.

In the "navigate" step, for patients interested in PrEP, the navigator will review a list of PrEP clinic locations and assist with selecting a provider. Once an individual is released from the DCJ, the navigator will facilitate PrEP linkage by contacting that individual (by phone or SMS text messaging) and providing personalized care navigation. A hotline will be available for released individuals to call for assistance with PrEP referrals. The navigator will continue to follow referred patients for 3 months after any PrEP initiations, recording these contacts and clinical outcomes in REDCap, a secure online data capture system [85].

For this aim of the study, the patient navigator will obtain verbal consent from patients to proceed with a discussion on sexual health and to contact them after release from jail. The navigator will use a script to inform patients about the goals of the project, including the metrics to be collected, and reinforce that the meeting with the navigator is voluntary and will not affect the legal status of the patients.

We will track quantitative and qualitative metrics related to our implementation strategy during a 24-month period of iterative assessment and refinement. Our study metrics map directly to the EPIS framework at key steps in the PrEP care continuum (Figure 2). As shown in Table 1, we will assess quantitative effects, including the number of patients who attend a community PrEP visit, initiate PrEP, and persist with PrEP use for ≥3 months, which is a robust HIV prevention outcome [7]. We will track the rates of new and previously known HIV diagnoses and STIs in the DCJ through EHR chart review.

Feasibility

Feasibility refers to the extent to which a practice change can be successfully used or carried out within a specific setting [86]. We define feasibility as >65% of eligible patients being offered HIV/STI testing and one or more PrEP discussions, our patient PrEP decision-support tool, a PrEP navigation visit, or a PrEP referral in jail.

Penetration

Penetration refers to the extent to which a practice is integrated within a specific setting [86]. For this metric, we will track the

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proportion of providers who discuss PrEP or refer to a navigator for at least one eligible patient.

Acceptability

Acceptability refers to the perception among setting stakeholders that a practice is agreeable, palatable, or satisfactory [86]. We will calculate the proportions of patients who accept offers for one or more HIV testing, STI testing, PrEP discussion, navigator contact, or PrEP referral, with acceptance of >80% of test offers and >65% of discussion offers considered acceptable based on prior studies [35,87-89]. We will evaluate differences in feasibility and acceptability among patients by age, sex, gender identity, and race or ethnicity to identify imbalances in the offering and uptake of testing and referrals.

Effectiveness Regarding PrEP Outcomes

Additionally, on a monthly basis, we will measure the proportion of individuals who test negative for HIV, the proportion of this subgroup who receive notifications of their HIV test results, and the proportion of all those tested who are candidates for PrEP based on US Public Health Service practice guidelines for PrEP [90].

Among these PrEP candidates, we will assess how many are released to the community and how many are successfully contacted by the jail navigator after release. We will track the proportion of candidates attending ≥1 PrEP visit after jail release, the proportion prescribed PrEP, and the proportion using PrEP at 3 months after initiation (using direct patient assessments by the navigator). We will complete a run chart, which we will adapt from quality improvement methodologies [91], to evaluate trends in the PrEP care cascade [92] on a monthly basis during the 24-month intervention period and the additional 6-month sustainment period.

Effectiveness Regarding New HIV/STI Diagnoses

We will also track STIs and new and previously known HIV diagnoses in the jail among priority groups and the general jail population. STI positivity will be calculated as positive tests per the total number of tests completed. New HIV diagnosis rates will be calculated as confirmed positive test results in persons without a prior diagnosis of HIV per the total number of tests completed within a given time period. We will use an interrupted time series analysis using monthly data points to compare rates during the 24 months before and 24 months after our intervention is implemented. Our primary analysis will involve a comparison of the longitudinal rates before and after the intervention, and a mixed effects model for interrupted time series will be used as a secondary analysis. We will conduct linear regression analyses to determine if there is a significant difference in new HIV diagnosis rates before and after the intervention.

Sustainment

Sustainability refers to the extent to which a new practice is maintained or institutionalized within a setting's ongoing operations [86]. We will assess how well the strategy components are maintained as part of existing jail processes for 6 months after the formal 24-month study period, including tracking retention in PrEP care for up to 6 months (through navigator follow-up). Our research team includes dissemination consultants, who are medical providers working in jails in Austin, TX; Chicago, IL; and Boston, MA, and who will offer input on refining our strategy components for ongoing use at the DCJ and the potential transfer and integration into other jail settings.

For PrEP linkage, current rates of linkage are essentially zero. Thus, in lieu of a pre/post comparison, we will report the proportion of patients linked to PrEP care during the implementation period with 95% CIs. Power analysis is performed for the interrupted time series analysis of monthly HIV positivity rates, assessing the difference in the mean between the 24 months before and after implementation. Over the preimplementation period, an anticipated 250 tests will be performed monthly with 3 new HIV diagnoses per month. In the postimplementation period, of 500 HIV tests per month, an increase to 9 new diagnoses per month is anticipated due to the focus on individuals identified by the prediction model as being at increased HIV risk. Furthermore, we assume a correlation of 0.2 among monthly observations. Based on a mixed effects Poisson regression model, we can detect the difference in the mean HIV-positive rate between the 2 periods with >80% power at a 2-sided type I error of 0.05. We will also perform subgroup analyses, comparing testing rates by sex, age group, and race or ethnicity.

Evaluation of Qualitative Effects

We will also evaluate the qualitative effects of our implementation strategy through structured observations and discussions at the DCJ to assess changes (positive or negative) in knowledge and opinions of PrEP, workflow, and cross-agency collaboration in line with Dallas County's goal of a coordinated HIV response [93]. Observations will be conducted by individuals with postgraduate training in qualitative methods who have undergone additional training with the DCJ and Parkland Health and who are approved to conduct observations under the protocol approved by the IRB at UT Southwestern Medical Center. Observations will be focused on specific interactions pertinent to the research questions (eg, between the navigator and person soon to be released). Qualitative data on effectiveness and implementation outcomes will be rapidly analyzed in real-time using structured analysis of field notes from observations and discussions. The resulting iterative findings will be presented to a study advisory panel every 4 months to assess evolving attitudes and practices surrounding HIV testing and PrEP (ie, acceptability), gather perceptions of feasibility and penetration of the intervention, and solicit feedback about the ways to improve outcomes.

Ethical Considerations

Each aim of the study has undergone a separate review of procedures and protocols by the UT Southwestern Medical Center IRB, with details of human subject protection outlined in the protocol by aim. This IRB has a prisoner representative, and all IRB-approved protocols were reviewed by Parkland Health and approved by the DCJ correctional health leadership before beginning study activities. To date, the IRB has approved the protocols for aim 1 (STU 2021-0763) and aim 2 (STU 2021-1172). In addition, the Office of Human Research

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Protection has reviewed and approved the inclusion of prisoners in human subject research for the overall study protocol in 2022.

For all participants in focus groups and individual interviews in aim 1, the research team has obtained verbal consent. To ensure informed consent, researchers also provided information about the nature and purpose of the study, confidentiality and privacy, HIPAA (Health Insurance Portability and Accountability Act) regulations, potential risks, discomforts and benefits of participation, and the option not to participate or start then stop participating in the interview at any time. In addition, stakeholders were encouraged to contact the study team at any time with questions or concerns they may have about the study. Eligible participants (ie, individuals not employed by UT Southwestern or Parkland Health according to institutional policy) were paid US $25 as compensation for their time for each interview or focus group attended.

Regarding EHR usage for aim 2, all study data were collected from existing EHRs, including medical intake forms at the DCJ and EHRs from Parkland Health and Hospital Systems, to identify potentially eligible subjects for the research. Records were matched based on multiple variables, including patient name, preferred name, date of birth, gender, biological sex, race or ethnicity, and social security number, as available. The medical record data include data collected as part of the medical intake process at the jail and routine clinical care at the jail and Parkland, including demographics, information from clinical encounters, prescription information, laboratory tests and results, and billing information. For those who did not receive medical care or treatment at Parkland Health, only data from the jail EHR were used. There was no additional direct collection of specimens, records, or data from subjects, and the IRB approval allowed secondary analysis without additional consent to identify research subjects and build the prediction model.

Data are not deidentified, as individuals meeting the basic eligibility criteria will be contacted by the researchers for recruitment into the study. No additional research procedures or continued access to identifiable private information will occur until after subjects have given valid consent to participate in the research study. The risk of this activity is minimal to the subjects because the information collected will be limited only to information allowing researchers to determine eligibility for the study and contact information. Only the minimum information necessary to determine eligibility will be recorded. Researchers have been granted access to the medical record data by the institutions and will protect the data they use and record for this activity according to institutional and HIPAA standards for protecting privacy and maintaining confidentiality. If the subjects identified decline participation in the research, the data collected will not become part of the research data. If subjects agree to participate in the research, the identifiable data collected will become part of the subjects' research records and will be stored according to the research confidentiality plan. Because of the nature of the detailed inclusion criteria, it is not feasible for researchers to advertise and screen for eligible subjects. The Office of Human Research Protection highlights this as an acceptable activity to waive informed consent to permit investigators to obtain and record identifiable private information for the purposes of identifying potential subjects [94].

Results

The study was funded by the National Institute of Mental Health in April 2022. Progress has been made on various aims to date. Qualitative interviews have been completed with 26 individuals, including 9 formerly incarcerated individuals, 9 county jail staff, and 9 employees of community organizations (1 individual was both a formerly incarcerated individual and an employee of a community organization). A focus group with 10 additional individuals has also been conducted. All interviews have been transcribed, coded, and analyzed, and a manuscript highlighting the key themes is in progress.

In addition, summaries of field notes for each interview have been organized into key barriers; facilitators; suggested approaches to overcome barriers; resources needed to overcome barriers; and specific strategies to improve risk assessment, HIV testing, sexual health or PrEP education during incarceration, and postrelease linkage to PrEP. Findings from these interviews have been applied to formulate a jail PrEP implementation protocol using rapid qualitative analysis.

An HIV risk prediction model based on jail EHR data to identify individuals most likely to benefit from PrEP has been developed using records from 33,458 individuals who have undergone HIV testing in jail. This model has been optimized using machine learning, has been internally validated, and is ready to be deployed. Future exercises will include integration with health system EHR data from Parkland Hospital and comparisons to parsimonious models, which will guide the iterative development of the model. We anticipate that preliminary study findings on the implementation and effectiveness of the jail PrEP implementation strategy will be available in 2026.

Discussion

Expected Results

We anticipate that the implementation of the multicomponent strategy will promote robust linkage to PrEP care for many individuals at risk for HIV, which currently does not occur at the DCJ. Moreover, we expect to identify a higher number of new HIV infections and STIs than in the 2 years prior to implementation. Our final product will be a well-integrated sustainable multicomponent PrEP implementation strategy that starts upon jail entry and ends with linkage to community-based HIV prevention, which can address major HIV-related inequities for CL-involved populations.

Potential Limitations and Alternative Approaches

In the process of refining the implementation strategy in our second aim, EHR models may be hampered by limited or missing data. We will minimize the missingness of EHR data by combining jail and Parkland data and extending this dataset over a 10-year timespan. We will explore the use of the missingness of EHR variables (which may be a proxy for not being engaged in primary care) as indicators to understand the

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effect on model performance. If model performance is suboptimal, we will rely primarily on patient-reported data to identify HIV risk. For EHR alerts, we will proactively address potential alert fatigue [95] by employing rigorous user-centered design principles [96]. We will also train providers on how to respond to alerts about HIV risk, as providers may be unaccustomed to these.

Delays in the generation of electronic HIV risk scores could result in the identification of individuals likely to benefit from PrEP after their release from jail. If this occurs, we expect to identify many of these individuals using patient-reported data. However, the model we have developed will generate scores on day 3 of each person's incarceration, which will mitigate delays. We will also generate future EHR prompts for HIV/STI testing and PrEP if the patient returns to jail, and the navigator will contact the patient to encourage HIV testing and PrEP evaluations with community providers. Though patients may decline visits to discuss PrEP, we will maximize patient interest by training staff to present PrEP in a positive, discreet, and patient-centered manner and will offer our decision-support tool for patients to review independently. Since barriers, such as medical mistrust, transportation, and anticipated stigma, may limit patients' access to PrEP, we will hire and train a navigator who is able to build rapport with diverse populations, use principles of trauma-informed care [97-99], and teach at many education levels. Additionally, we will access existing resources, such as care coordination, offered by community partners.

Study Impact

Despite these possible limitations, this project will generate a valuable approach to prevent HIV in the disproportionately burdened population of CL-involved individuals in the Southern United States. As these individuals often have fragmented health care and may not be reached with approaches targeting primary care or STI clinics [100], our multicomponent implementation strategy has the potential to efficiently reach many persons likely to benefit from PrEP in a nontraditional but well-defined setting with rapid turnover to the larger community. Future projects will focus on adapting this strategy for dissemination to other urban jails, including those represented by our dissemination consultants, in HIV hotspots nationally to maximize its impact on the HIV epidemic for underserved minority communities.

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Conflicts of Interest

AEN has received research funding from Gilead Sciences. DK has participated in research with funding from Gilead Sciences and Merck to his institution, has received personal funds from UpToDate, Inc and Medscape to develop medical education content on HIV prevention, and has received funds from PrEP4All for travel to an advisory conference.

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Abbreviations

CDC: Centers for Disease Control and Prevention
CL: criminal legal
DCJ: Dallas County Jail
EHE: Ending the HIV Epidemic
EHR: electronic health record
EPIS: exploration, preparation, implementation, sustainment
HARC: HIV/AIDS Re-Entry Coalition
HIPAA: Health Insurance Portability and Accountability Act
IRB: Institutional Review Board
MSM: men who have sex with men
PCCI: Parkland Center for Clinical Innovation
PrEP: pre-exposure prophylaxis
STI: sexually transmitted infection

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Protocol

Developing and Implementing Provider-Training and Evidence-Based Tools to Support Pre-exposure Prophylaxis (PrEP) Decision-Making and Increase PrEP Adherence Among Young Men Who Have Sex With Men: Protocol for the PrEP Choice Longitudinal Cohort Study

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Abstract

Background: Despite the availability of highly effective HIV pre-exposure prophylaxis (PrEP), uptake and adherence to PrEP among young men who have sex with men (YMSM) remains low, limiting its impact on the prevention of HIV infection. Strategies that incorporate an array of prevention options and provide YMSM and their providers with tailored education and support tools, including tools to support shared decision-making, are needed.

Objective: The goals of the Centers for Disease Control and Prevention (CDC)–funded PrEP Choice study include the development and deployment of CDC guideline–consistent PrEP provider training and the implementation of evidence-based provider- and client-facing PrEP education and support tools. Under this initiative, the CDC funded 2 research projects, Florida State University (the Expanding PrEP in Communities of Color [EPICC] project), and Columbia University (the mChoice project).

Methods: Providers from both projects will complete the PrEP Choice online training, which was developed to educate providers on PrEP options and how to engage clients in open discussions around sexual health and PrEP options. EPICC project providers will also attend online tailored motivational interviewing (TMI) training sessions, and mChoice project providers will view a training video on cultural competency and humility in PrEP care. Following training, each project will enroll a cohort of 400 participants receiving care from study providers and follow them for 12-18 months. Participants will complete online surveys every 3 months and provide biomarkers to assess PrEP adherence. Electronic health record (EHR) data will be collected every 6 months to provide additional information on clinic attendance, PrEP prescriptions, and HIV/sexually transmitted infection (STI) testing. Each project will provide cohort participants with a unique digital health tool to support the PrEP choice and ongoing adherence. The study will assess the effectiveness of training and educational and support tools in practice and the critical factors associated with the successful uptake of and adherence to PrEP by participants. The study will also monitor patterns of PrEP use among YMSM, including types of PrEP and switching between types.

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Results: Formative work to develop and prepare the tools for implementation was completed in 2023. The EPICC project began provider training in early 2024, and the mChoice project began in spring 2024. Cohort enrollment for both projects began after provider training began.

Conclusions: Given the changing PrEP landscape, implementation of provider education and tools to maximize uptake and adherence is needed. By delivering culturally competent and interactive provider training on PrEP options, the study will help providers counsel and guide participants on the effective and safe use of PrEP. The digital health tools created will support participant adherence to help them optimize PrEP benefits. Through the cohort design, the PrEP Choice study will provide real-world data about PrEP use that will be critical for informing future guidelines and tools.

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KEYWORDS

pre-exposure prophylaxis; PrEP; PrEP cohort; young men who have sex with men; YMSM; digital health; evidence-based tools; motivational interviewing

Introduction

Background

Young gay, bisexual, and other young men who have sex with men (YMSM) are the population most affected by HIV in the United States. Among all HIV infections diagnosed in 2021, 67% were found in MSM [1]. Racial and ethnic disparities persist in HIV diagnoses among MSM, with 36% of diagnoses among Black or African American (Black) MSM and 33% among Hispanic or Latino (Hispanic) MSM, compared with 25% among White MSM, despite smaller overall populations of Black and Hispanic MSM compared with those of White MSM. HIV can be prevented with the use of HIV pre-exposure prophylaxis, or PrEP [2]. The US Food and Drug Administration has approved the use of 3 antiretroviral drugs for PrEP by MSM: oral emtricitabine and tenofovir disoproxil fumarate (F/TDF) in 2012, followed by the availability of generic F/TDF in 2021; oral emtricitabine and tenofovir alafenamide (F/TAF) in 2018; and long-acting injectable cabotegravir (CAB-LA) in 2021. Clinical trials of sexual event-driven PrEP regimens or 2-1-1 PrEP using F/TDF have demonstrated it to be highly effective for HIV prevention among MSM [3,4]. These options provide MSM with choices about their preferred PrEP regimen; however, little is known about the PrEP choices men make, their switching between PrEP options, and the reasons for these decisions.

PrEP coverage continues to increase markedly among men [5]. However, findings from analyses of limited race and ethnicity data for PrEP users suggest racial and ethnic disparities exist in coverage. These PrEP use disparities are especially concerning in the context of large racial and ethnic disparities in HIV diagnoses, because men who might most benefit from PrEP are not being prescribed it, and among those prescribed, adherence remains suboptimal [6-9]. To accomplish the goals of the "Ending the HIV Epidemic in the US" initiative to reduce new HIV diagnoses by 90% by 2030, increase PrEP coverage to 50% of individuals with indications, and achieve health equity [10], it is imperative to overcome racial and ethnic disparities in PrEP use.

The implementation of effective interventions is needed to increase PrEP initiation, adherence, and persistence among YMSM. YMSM need tailored education with autonomy-supportive communication related to the growing array of PrEP options, and providers who serve these clients also need education and clinical decision-making support. Implementation of resources that discuss all PrEP options and emphasize shared clinical decision-making have the potential to enhance PrEP outcomes among YMSM, including PrEP initiation, adherence, and persistence [11]. Increased understanding of PrEP use patterns, including switching among PrEP options, is needed to optimally support lifetime HIV prevention among YMSM. Using evidence-based PrEP care as a guide, provider and patient education and support tools have been developed to assist in the provision of PrEP care. Evidence-based provider and patient education and support tools (EBTs) are available but are not being routinely used in clinical settings to increase PrEP screening, counseling, initiation, adherence, and persistence by YMSM [2,12,13]. To date, there has been a lack of research on the impact that existing informational materials have on PrEP provision or how tailoring these materials to meet the needs of providers and YMSM from diverse backgrounds could enhance their effects. Further, although EBTs for both providers and YMSM are available, these resources do not acknowledge or incorporate information about a growing arsenal of prevention products nor do they maximize opportunities to engage in a shared decision-making process about these products [14,15].

Provider education can support clinicians to provide recommended PrEP services and to maintain up-to-date knowledge of PrEP options. Patient education using adapted EBTs can help men understand how PrEP can support their sexual health and learn about the PrEP options available to them. Adherence and persistence support tools, such as user-friendly apps, can support men prescribed PrEP to take their medication as directed and to continue to use it for as long as they can benefit from its protection. Increased understanding of PrEP use patterns, including switching among PrEP options, is needed to optimally support YMSM to use PrEP that is appropriate for them at various times in their lives.

Aims and Objectives

The goals of the Center for Disease Control and Prevention (CDC)–funded study, known as the PrEP Choice study, include the development and deployment of CDC guideline–consistent

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PrEP provider training and the implementation of evidence-based provider- and participant-facing PrEP education and support tools [13,16]. PrEP support tools include innovative, customized mobile apps. The study will also conduct a longitudinal assessment of YMSM who are initiating or persisting with PrEP to understand their preferences for PrEP modalities and changes in PrEP use over the course of the study. The study will assess the implementation context, assess the effectiveness of provider training and EBTs in practice, and analyze the critical factors associated with successful uptake of and adherence to PrEP by participants enrolled in the study.

Under this initiative, the CDC funded 2 research projects, at Florida State University (the Expanding PrEP in Communities of Color [EPICC] project) and at Columbia University (the mChoice project). The PrEP Choice study is a 5-year initiative; funding began on September 30, 2021. In this paper, we discussed both EPICC and mChoice Studies, as they are supported under the same funding announcement, use the same PrEP training modules, use similar instruments for their longitudinal cohorts, share the same eligibility criteria, and incorporate digital health tools.

Through these 2 studies, we will test the effectiveness of provider training to increase provider knowledge of and comfort with PrEP modalities in clinical practice; evaluate the feasibility and acceptability of implementing provider training; describe the barriers and facilitators impacting the implementation of new PrEP modalities in clinical practice; test the effectiveness of provider training and digital tools to increase PrEP adherence and persistence among YMSM; and describe real-world PrEP use, including factors influencing the selection and change of PrEP regimens.

Methods

Ethical Considerations

This works follows a protocol reviewed and accepted by the Institutional Review Boards of Florida State University (approval number 00003623) and Columbia University (approval number AAAT8812). Participants will provide informed consent prior to beginning any study activities. The consent form includes standard consent sections describing the purpose of the study, the procedures to be followed, and the risks and benefits of participation. The consent form went through multiple reviews by team members to ensure the language was sufficiently simple. A certificate of confidentiality was obtained from the CDC. All data and records will be stored on password-protected servers. No identifiable data will be published.

EPICC project providers will be compensated US $50 for completing the pretraining survey; US $50 for completing online PrEP training modules, tailored motivational interviewing (TMI) training sessions, the posttraining survey, and the first standard patient interaction; and US $50 for the 3-month posttraining standard patient interaction. Cohort participants will be compensated US $50 for the baseline survey and app download, US $50 for an optional onboarding visit, US $25 for the 3-month follow-up survey, US $50 for the 6-month follow-up survey, US $25 for the 9-month follow-up survey, US $50 for the 12-month follow-up survey, US $25 for the 15-month follow-up survey, and US $50 for the 18-month follow-up survey. For home-based dried blood spot (DBS) collection, cohort participants will be compensated US $50 for the baseline, 6-month, and 12-month collections and US $75 for the 18-month collection. A US $50 bonus will be provided to participants who complete the first 3 collections. Participants who complete the exit interviews will be compensated US $50. Providers who complete focus group discussions will be compensated US $75.

mChoice project providers who complete the pre- and postassessment will be compensated US $50. Providers who complete an in-depth interview will be compensated US $100. Cohort participants will be compensated US $40 for the baseline survey and app download, US $45 for the 3-month follow-up survey, US $55 for the 6-month follow-up survey, US $60 for the 9-month follow-up survey, US $70 for the 12-month follow-up survey, and US $80 for the 18-month follow up survey. Cohort participants who complete an in-depth interview will be compensated US $35. Providers who complete an in-depth interview will be compensated US $100.

Study Design

The EPICC project includes 2 distinct aims. Aim 1 includes provider training. Providers will be trained on the use of education tools adapted in the formative work and the process of screening, counseling, initiation, and follow-up with clients interested in or already taking PrEP through our PrEP training modules and will complete TMI training. The effectiveness of the training will be measured quantitatively. Aim 2 is a longitudinal cohort study designed to test the newly adapted education tools through a hybrid type 2 effectiveness implementation cohort to assess PrEP uptake and adherence to PrEP among YMSM and provider provision of PrEP and competence with education tools to increase PrEP services. Aim 2 will include a mixed methods analysis. Figure 1 provides an overview of the EPICC project's design. Formative work can be found elsewhere [17].

The mChoice project includes 3 aims. Aim 1 of the mChoice project is to conduct a hybrid type 2 trial testing the effectiveness of the mChoice clinical intervention to increase PrEP adherence and persistence among YMSM using PrEP. Aim 2 is to conduct in-depth interviews to assess multilevel factors at the patient level associated with selection of a PrEP regimen and switching patterns. Aim 3 is to provide training to health care providers to improve knowledge of PrEP clinical recommendations and enhance provider communication. Figure 2 provides an overview of the mChoice project design. Formative work findings can be found elsewhere [18].

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Figure 1. EPICC project design. EPICC: Expanding Pre-Exposure Prophylaxis (PrEP) in Communities of Color; YMSM: young men who have sex with men.

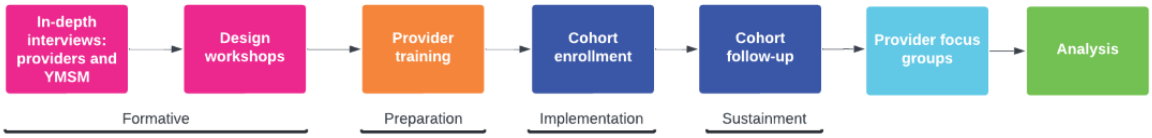

Figure 2. mChoice project design.

Data Collection

Every 6 months, study sites (EPICC and mChoice) will complete a clinic assessment that will include information around PrEP prescriptions issued, clinic services, financial assistance, and PrEP support services. This information will be collected prior to the provider training and will continue for the duration of the study to assess implementation efficacy. There will be a clinic assessment baseline and final, which is completed at the beginning of data collection and at the end and a shorter clinic assessment every 6 months. These assessments will capture data on clinic demographics, PrEP uptake and follow-up and provision of HIV and PrEP education.

The EPICC project's aim 1 provider training consists of the completion of surveys prior to and after training components. Providers are rated on their use of TMI during standard patient interactions immediately after training and three months post training. Aim 2 data collection will occur using surveys every three months, project app paradata, and exit interviews. Additionally, we will conduct focus group discussions with providers at the end of the longitudinal cohort.

The mChoice project's aim 1 data collection will occur using surveys every three months, and project app paradata. Aim 2 data collection will occur using in-depth interviews with a subsample from aim 1. The mChoice project's aim 3 provider training consists of the completion of surveys prior to and after training components and an interview following completion of the training.

Provider Training

Each project will enroll participants for both provider training and the cohort from unique study sites. Figure 3 includes a map of each project's enrollment sites.

The EPICC project team developed online PrEP training modules to educate providers on currently available PrEP options and how to engage clients in open discussions around sexual health and PrEP options. The goal of these open discussions between providers and clients is to encourage shared decision-making on PrEP options. The flexible and interactive modules were created using the Easygenerator online authoring tool, which allows learners to complete their assigned courses over multiple sessions at any time. The interactive features used throughout the modules are designed to keep providers engaged. Some of these features include checks for understanding, embedded videos, and links to external content. Each module also contains at least 1 case-based scenario. These scenarios are based on real-world interactions that study team providers experience during interactions with clients.

The EPICC project team developed these modules using a variety of content sources, including CDC-produced guidelines and materials, research papers, and expert guidance. In addition to modules covering PrEP regimens, we also included modules on the need for PrEP, PrEP screening and startup, postexposure prophylaxis (PEP), and PrEP adherence and persistence. The modules were refined to their final form through an iterative feedback process with subject matter experts within the EPICC project team. Both EPICC and mChoice project teams will use these modules in their respective provider training. Table 1 lists the titles and brief descriptions of each module.

Figure 4 includes screenshots of content within the modules that highlight interactive elements used throughout the course. The video image shown is from "Let's Talk About Sexual Health" [19] produced by the CDC and BeSmartBeWell.com.

In the EPICC project, after completing the online PrEP training modules, providers will attend live, online TMI training sessions led by a member of the motivational interviewing (MI) network of trainers. The training has been split into distinct training modules: (1) introduction to TMI and PrEP choice; (2) TMI spirit, cultural humility, antiracism, and stigma reduction; (3) managing counter change talk and discord with empathy and autonomy support; and (4) eliciting and motivation for PrEP. There will be 2 training sessions lasting approximately 3 hours conducted virtually over 2 days. The training uses videos of

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PrEP providers demonstrating TMI integrated with antiracism and cultural humility that were created specifically for this study. The workshops are structured with cooperative learning activities, video examples, and behavioral skill acquisition steps (modeling, verbal and behavioral rehearsal, feedback). After the live, online training is completed, providers will complete a 15-minute standard patient interaction assessment, where a member of the study team will act as a client and the provider will attempt to use TMI techniques during their interaction. The conversation will be coded by a study team member using the MI Coach Rating Scale [20], and a feedback report will be generated and sent to the provider. The report will include strengths and areas for improvement, with video links featuring skills identified as areas for improvement. Three months after completing the TMI training sessions, providers will complete an additional standard patient interaction assessment with the same feedback format. Providers will also complete a brief survey prior to starting the online modules, which will include demographics; PrEP familiarity and attitudes; and PrEP use and future intentions. Providers will complete another survey after the TMI training sessions are over, which will include similar questions to the first survey to assess for change after completing online modules and TMI training.

After completing the online PrEP training modules, providers in the mChoice project will watch a 10-minute video on cultural competency and humility in PrEP care training developed specifically for this study. This module consists of an introduction to cultural competency and humility and exemplifies how these concepts are key components to PrEP care. Like the EPICC project team, sources for the video include information from CDC guidelines, CDC-produced materials, and peer-reviewed journal–cited research papers. For example, the CDC's 5Ps approach to gathering sexual history is highlighted as a critical step in the context of PrEP care. More information about the 5Ps approach can be found on the CDC's website [21]. Useful tips, such as using layperson's terms that are also anatomically correct, making eye contact, and not appearing to be in a hurry, are mentioned throughout. Simultaneously, this module emphasizes the importance of making clients feel comfortable and respected and allowing the client to guide the conversation. This module aims to inform providers about how to best interact with clients and demonstrate racial and ethnic diversity among clients through the use of dynamic graphics. The module also provides training to facilitate provider-client communication so that there can be effective shared decision-making. It will be included in the PrEP Choice provider series launched through Easygenerator.

Figure 3. Map of EPICC and mChoice project enrollment sites. EPICC: Expanding Pre-Exposure Prophylaxis (PrEP) in Communities of Color.

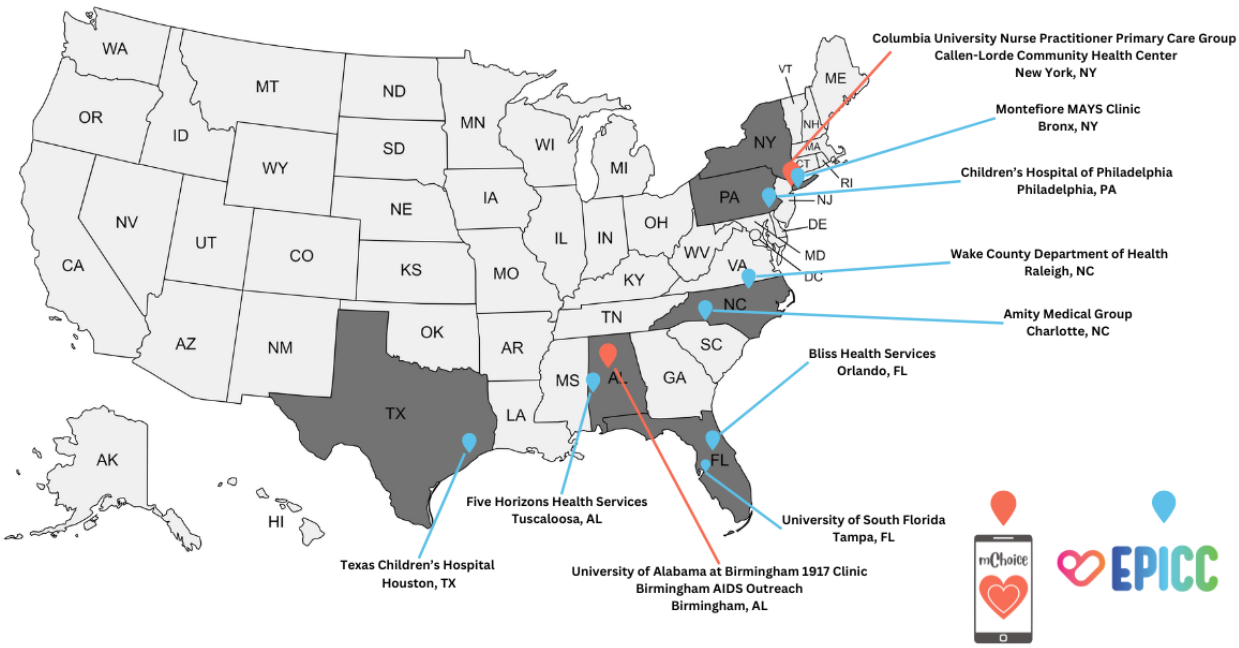

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Table 1. Online PrEP[a] training module titles and topics used in EPICC[b] and mChoice Studies.

Module title	Topics covered
Module 1: Why Do We Need PrEP?	HIV epidemic in the United States, the EHE plan, PrEP update in the United States, and PrEP efficacy and effectiveness
Module 2: Who and Why for PrEP	PrEP guideline changes, PrEP screening, and HIV testing recommendations
Module 3: What Is PEP and Who Should Get It?	PEP screening, prescribing, and monitoring
Module 4: Considerations in Choosing Among Oral PrEP Options	Oral PrEP regimens, oral PrEP initiation and follow-up, 2-1-1 or on-demand PrEP, and oral PrEP side effects
Module 5: Considerations in Prescribing and Monitoring Injectable PrEP	Injectable PrEP initiation, follow-up, adherence, side effects, and future PrEP modalities
Module 6: Maximizing PrEP Adherence and Persistence	Adherence counseling components, PrEP implementation, and cost considerations

[a]PrEP: pre-exposure prophylaxis.

[b]EPICC: Expanding PrEP in Communities of Color.

Figure 4. Screenshots and descriptions of interactive content within online PrEP modules used in EPICC and mChoice provider training.

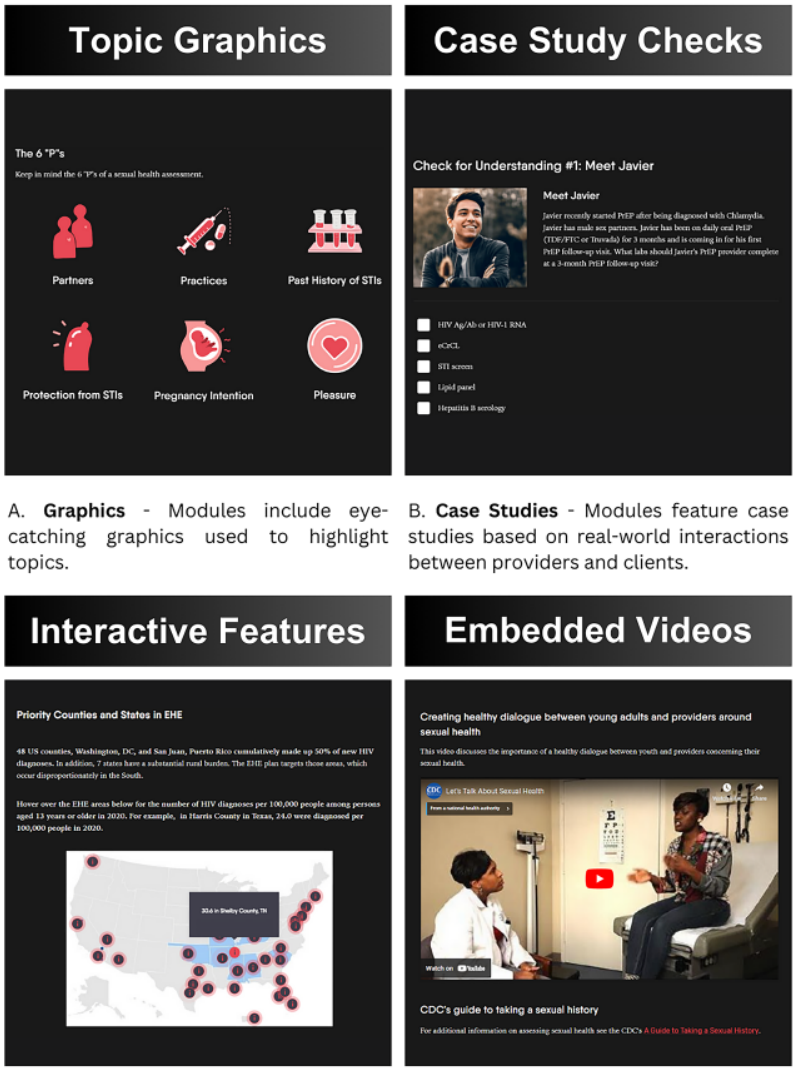

A. **Graphics** - Modules include eye-catching graphics used to highlight topics.

B. **Case Studies** - Modules feature case studies based on real-world interactions between providers and clients.

C. **Interactive Content** - Modules feature interactive content to encourage engagement. This image demonstrates a feature where learners hover over a hot spot to view additional relevant information .

D. **Embedded Videos** - Modules contain embedded videos that summarize key concepts.

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Longitudinal Cohort

Both EPICC and mChoice projects will enroll a cohort of 400 participants. Study participation will range from 12-18 months, depending on the study enrollment date. Eligibility criteria include (1) age 18-39 years, (2) the male sex, (3) ever had sex (as a top or a bottom, insertive or receptive) with a person who has a penis, (4) have an active prescription for PrEP (including both new prescriptions at baseline or refills), (5) receive care at 1 of the participating study sites, (6) provide a mailing address within the 50 states where packages can be received, (7) have daily smartphone access, and (8) be fluent in written and spoken English or Spanish. Cohort participants will be recruited by the clinic staff during scheduled visits, through study advertisements placed in clinic waiting rooms, or through study advertisements on social media platforms.

Each project team builds off prior work to adapt their unique digital health tools poised to support PrEP choice and ongoing adherence. The EPICC project builds from the HealthMpowerment (HMP) intervention. HMP is a theory-based status app designed to provide health and wellness information and resources relevant to young people via a mobile optimized platform. HMP was created based on the Integrated Behavioral Model [22-24]. HMP is flexible and easy to adapt for specific populations and health topics. The EPICC project's version of HMP includes resources most relevant for our study population. The mChoice app was created based on the Information System Research framework and builds on formative work to develop a PrEP adherence and monitoring app [25-27]. The mChoice app was built in collaboration with Compliance Meds Technologies (CMT) CleverCap. CMT is an mHealth technology solutions provider that develops adaptable technology to promote health. The CleverCap app is linked to a CleverCap device, which is an electronic pill bottle that records when the cap opens and closes and tracks medication adherence. The CleverCap app was customized to the needs of the mChoice project to support PrEP adherence among YMSM. It offers PrEP resources, such as 2 client-facing PrEP training modules created by the study team and a sexual activity log. It can be programmed for the use of participants who are taking any of the 3 PrEP regimens: oral (daily or event driven) or injectable. Table 2 lists the features of each project's mobile app.

Table 2. Description of EPICC[a] and mChoice digital health support tools.

Feature	EPICC	mChoice
Resources	Educational content across a range of health topics, as well as support for app engagement and behavior change through information and skill building	Participant-facing PrEP training modules, links to the CDC[b] website
Adherence support	Medication tracker to support oral, injectable, or event-driven PrEP adherence	Electronic adherence monitoring through the use of the CleverCap app and device
Sexual behavior tracking	Sexual activity log	Sexual activity log
Connection to care	"Ask the Expert" feature to allow providers to anonymously answer user questions and connect users to resources	Chat function to communicate with the study team
Engagement features	Gamification with badges and avatars earned for completing activities	Adherence statistics for participants taking oral daily PrEP
Integrations with test kits	Yes	N/A[c]

[a]EPICC: Expanding Pre-Exposure Prophylaxis (PrEP) in Communities of Color.

[b]CDC: Centers for Disease Control and Prevention.

[c]N/A: not applicable.

Cohort Procedures

Participants will complete a computer-assisted self-interview (CASI) every 3 months while in the study. Surveys will be hosted on REDCap. EPICC surveys will be distributed through emails and links available within the study app. mChoice surveys will be completed at study sites on a tablet. The surveys will address various topics related to PrEP care engagement, PrEP usage, and PrEP adherence, as well as sociodemographics and risk factors related to PrEP adherence (Table S1 in Multimedia Appendix 1) [7,28-38].

EPICC project participants will complete a home-based DBS collection kit every 6 months while in the study to assess for levels of tenofovir-diphosphate (TFV-DP) and emtricitabine-triphosphate (FTC-TP). Additionally, EPICC project participants can attend an optional virtual onboarding visit with a member of the study team to review key features of the study app and DBS collection instructions. mChoice project participants who report using PrEP containing TFV and FTC will provide a urine sample of 15-30 mL at each visit to measure adherence. After the visit, the staff will use the urine sample for a rapid strip test to interpret adherence results. The staff will upload a picture of the test results to REDCap to send to the lab so that they can perform quality control checks. Participants' urine samples will be used for 2 separate tests: one that measures TFV levels and another that measures FTC levels. Throughout the study period, participants (EPICC and mChoice) will be asked to track their PrEP adherence and sexual behavior in study mobile applications. Electronic health record (EHR) data (EPICC and mChoice Studies) will be collected every 6 months during the study period; variables will include PrEP prescription information, HIV testing, sexually transmitted infection (STI) testing, and results. Clinic site staff will complete medical record abstraction (MRA) using participants' EHRs

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every 6 months while in the study. MRA will collect information about PrEP prescriptions, STI testing and results, and HIV testing and results. Table S1 in Multimedia Appendix 1 includes cohort measures.

A subset of EPICC project participants will also complete exit interviews. Questions will focus on understanding factors that influenced participants' selection of PrEP regimens, changes, or discontinuations; perceptions of the counseling they received by providers at PrEP initiation and follow-up; and the receipt of tools or materials that influenced their choice and feasibility/acceptability of the HMP app. The mChoice project team will similarly conduct in-depth interviews with a subset of participants following completion of the intervention to explore experiences with PrEP, reasons for PrEP choices, and impressions of the mChoice intervention.

Postcohort Provider Focus Group Discussions and Interviews

After the cohort is completed, the EPICC project team will conduct 6 virtual focus groups with PrEP providers, clinic staff, and study staff. The purpose of the focus groups will be to gather feedback on overall perceptions of the barriers and facilitators to education tool implementation within their clinical site. Prior to participating in the focus groups, participants will complete a survey that will collect their demographics, whether the provider can prescribe PrEP, and how long the provider has worked at their current clinic.

The mChoice project team will conduct in-depth interviews with participating providers following completion of the PrEP training modules and assessments. The research staff will ask participants about the implementation of the mChoice intervention, any long-term effects of the intervention, opinions of the provider training modules, and recommendations for future implementation of the mChoice intervention.

Primary Outcome Measures

The primary outcome for provider training is PrEP familiarity, PrEP beliefs, and intentions to use PrEP measured at pre- and posttraining. The primary outcome for the cohort is PrEP adherence. For the EPICC project, adherence outcomes will be measured by using blood and will be tailored for oral PrEP modality (daily or 2-1-1) and categorized as protective (1) or not protective (0). The protective level of PrEP in the blood is defined as ≥4 doses taken per week, and the not-protective level is defined as <4 doses taken per week. Adherence outcomes for participants on CAB-LA will be determined by the timely administration of injections. The timely administration of the second injection is defined as within +/–1 week of the target date and within +/–2 weeks of the target date for subsequent injections. For the mChoice project, adherence outcomes, as measured by using urine, will be assessed by testing TFV and FTC levels in urine specimens collected from participants who report daily use of PrEP containing TFV and FTC. The mChoice project will also measure adherence by electronic medication monitoring via the CleverCap device, EHR data, and self-report.

Secondary Outcome Measures

Secondary outcomes for provider training include the feasibility and acceptability of implementing provider training and barriers and facilitators impacting the implementation of new PrEP modalities in clinical practice measured through participant responses during the provider focus group discussions that will occur at the end of the cohort follow-up. The EPICC project cohort's secondary outcome is persistence measures and will be based on (1) the participant's self-report of currently taking PrEP (daily or 2-1-1) or having received the last shot of CAB-LA and (2) the participant having an active prescription for PrEP based on study records or drug levels associated with use within a 1-month window at 6 months, 12 months, and 18 months postenrollment. mChoice secondary outcomes will consist of sexual risk behaviors, HIV status, substance use, and outcomes by the initial PrEP regimen, as reported through follow-up assessments and EHR data.

Statistical Analysis

Specific statistical analyses will be performed for the different projects. Next, we describe the EPICC and mChoice project analysis plans separately.

The EPICC Project

Sample Size and Power Calculations

The sample size for this study was determined based on feasibility after considering the intended analyses and multiple parameter estimates. With 400 participants, the minimum detectable difference in the PrEP adherence and persistence rates was 5.6%, assuming 15% loss to follow-up and a reference rate of 20%, at 0.80 power with a 1-sided test and 0.05 type I error. For baseline to postintervention analyses, simulation-based results indicated the minimum detectable difference from a baseline rate of 20% was approximately 9% (odds ratio 1.6), assuming again 15% loss to follow-up, at 0.80 power with a 1-sided test and 0.05 type I error [39].

Analysis Plan

Baseline participant characteristics will be described for the entire sample and disaggregated by regimen, site/region, ethnicity, level of HIV risk perception, substance use, PrEP experience (naive vs familiar), partner relationship status, and the other variables of interest included in Table S1 in Multimedia Appendix 1.

To determine any differences in discontinuation and nonadherence, we will use Cox proportional hazards to analyze (1) time to first discontinuation and (2) time to first nonadherence by regimen using PrEP adherence measures. To incorporate observations after the first discontinuation or after the first nonadherence, including allowing for the possibility of restarting on PrEP after discontinuation and for periods of nonadherence followed by a period of adherence, we will use a multilevel survival model by including a frailty term in the model to allow analysis of recurrent events [40]. We will follow the same analytic strategy for other dichotomous primary and secondary effectiveness and implementation outcomes. For the composite measure of number of prescriptions (primary implementation outcome), we will fit a multilevel linear or a

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generalized linear regression model, again using all the time point data available to assess the strength of the associations between the composite measure for the number of prescriptions and the predictor variables. To examine the trajectories of regimens, we will use generalized linear mixed models (GLMMs) and a survival model to assess the time to each regimen switch.

Provider Training

Mean scores for the pre- and postadministration of PrEP knowledge items, as well as the mean scores for motivational interviewing familiarity and comfort, will be evaluated for significance of difference using the nonparametric Wilcoxon signed-rank test for hypothesis testing of repeated measurements on a single sample [41].

The mChoice Project

Sample Size and Power Calculations

Sample size estimation was based on the number of individuals required in order to detect an odds ratio of 1.7 or greater, based on a previous intervention study [42], in the primary outcome measures (PrEP adherence and persistence) before and after the intervention. We used a GLMM [43] with 80% power and a 2-sided test of .05 significance. We estimated the power and sample size by simulating responses based on the following assumptions: 20% attrition postintervention follow-up, an intraclass correlation coefficient of 0.2 across sites, and correlations in the range of 0.3-0.6 of participants' outcomes at different time points [43]. With these conditions, a sample size of 400 was needed [43].

Primary Outcome

A GLMM, also called an individual growth model and a multilevel model, with an appropriate link function will be used to compare the pre- and postintervention difference for each outcome. The GLMM allows different trajectories for each participant, and this method is appropriate to compare outcome changes after the implementation of the intervention, with the control of baseline values. Analyses will be conducted for the full sample and by study location (New York City and Birmingham) separately [44].

Secondary Outcomes

Similar GLMMs will be used for analyzing secondary outcomes. We will conduct a multigroup comparison in pre- and postintervention differences (the difference-in-difference analysis) using a GLMM by adding the group variable and the group × intervention status interaction (pre- and postintervention) in the GLMM described before. Because the PrEP regimen cannot be randomized, we will use the propensity score method [45] to reduce the between-group bias. We will also examine factors that are associated with the length of time that participants take to change their regimens or associated with the instantaneous rate of change of regimen. Since we will know the date of change of the PrEP regimen (from the EHR data), we will apply a Cox proportion hazard ratio model with time-varying covariates (eg, sexual activity, insurance, side effect) to examine the time to change the regimen.

Provider Training

Mean scale scores for the pre- and postadministration of PrEP knowledge items, as well as the mean time with PrEP patients, will be evaluated for significance of differences using the nonparametric Wilcoxon signed-rank test for hypothesis testing of repeated measurements on a single sample [41]. Categorical data for assessing differences in the proportion of participants in agreement with individual items before and after participating in the knowledge module will be analyzed using the McNemar test of marginal homogeneity [41].

Results

The EPICC project formative work to develop evidence-based tools (Maragh-Bass et al, unpublished data, March 2025) was completed in April 2023 [17]. Provider training enrollment began in January 2024 and was completed in August 2024. Cohort enrollment began in April 2024. As of October 2024, 40 participants were enrolled in the EPICC project cohort. Cohort enrollment is expected to be completed in September 2025, with the final results anticipated in early 2027. Provider focus groups are expected to begin in April 2026, with the final results expected in early 2027.

The mChoice project formative work to develop and evaluate evidence-based tools was completed in January 2024 (Kay et al, unpublished data, March 2025) [18,46]. Provider training enrollment began in June 2024 and is ongoing. Cohort enrollment began in July 2024. As of October 2024, 18 participants were enrolled in the mChoice project cohort. Cohort enrollment is expected to be completed in July 2025. The final results are expected in late 2027.

Discussion

Overview

Posttraining, we anticipate providers will increase competence in using EBTs and providing PrEP support services. We also anticipate participants in the cohort will increase PrEP adherence and persistence. Given the changing PrEP landscape and the availability of new options and formulations, the implementation of provider education and tools to maximize uptake and adherence within their patient populations is needed. By delivering culturally competent and interactive provider training on PrEP options, the study will help providers counsel and guide participants on the effective and safe use of PrEP. The digital health tools created will support participant adherence and help them optimize the prevention benefits of their chosen PrEP regimen. Through the longitudinal, cohort design, the PrEP Choice study will provide real-world data about PrEP use that will be critical for informing future guidelines and tools.

Limitations

This research is limited in its design as a cohort study and not a randomized controlled trial. However, early work to harmonize measures and outcomes across the 2 projects is expected to allow for informative descriptions and the possibility for both pooled and separate analyses, as well as comparison across the entire study. Although multiple study sites across the United

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States are included, PrEP Choice is not a nationally representative study and results will not be generalizable.

Conclusion

A multitude of efforts exist to make PrEP more available for people at risk for acquiring HIV infection, especially YMSM. Activities to increase PrEP uptake need to be accompanied by research that assesses its real-world use and identifies strategies to support and maximize its benefits. In addition to improving our understanding of how those at increased risk for acquiring HIV infection use PrEP, the PrEP Choice study will support the design and testing of informed interventions to support PrEP users' adherence and persistence, in addition to initiation.

Acknowledgments

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The content is solely the responsibility of the authors and does not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

Data Availability

The datasets generated and analyzed during this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

All authors contributed to the study design and paper development.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Cohort measures for the Expanding Pre-Exposure Prophylaxis (PrEP) in Communities of Color (EPICC) and mChoice Studies. [DOCX File , 25 KB - resprot_v14i1e64186_app1.docx]

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Abbreviations

CAB-LA: long-acting injectable cabotegravir
CASI: computer-assisted self-interview
CDC: Centers for Disease Control and Prevention
CMT: Compliance Meds Technologies
DBS: dried blood spot
EBT: evidence-based provider and patient education and support tool
EHR: electronic health record
EPICC: Expanding Pre-Exposure Prophylaxis (PrEP) in Communities of Color
F/TAF: tenofovir alafenamide
FTC: emtricitabine
FTC-TP: emtricitabine-triphosphate
F/TDF: tenofovir disoproxil fumarate
GLMM: generalized linear mixed model
HMP: HealthMpowerment
MI: motivational interviewing
MRA: medical record abstraction
MSM: men who have sex with men
PEP: postexposure prophylaxis

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PrEP: pre-exposure prophylaxis
STI: sexually transmitted infection
TFV: tenofovir
TFV-DP: tenofovir-diphosphate
TMI: tailored motivational interviewing
YMSM: young men who have sex with men

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Protocol

Clinical Safety of Pudilan Xiaoyan Oral Liquid for the Treatment of Upper Respiratory Tract Infection in the Real World: Protocol for a Prospective, Observational, Registry Study

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Abstract

Background: *Pudilan Xiaoyan* oral liquid (PDL) is a proprietary Chinese medicine preparation widely used for upper respiratory tract infection, known for its significant therapeutic effects. However, the safety profiles reported in several observational studies vary, and these studies primarily focus on efficacy rather than specifically addressing safety concerns, thus representing inadequate safety monitoring.

Objective: This study aimed to investigate the incidence of adverse drug reactions (ADRs) associated with PDL and explore the factors contributing to these reactions.

Methods: The study is a prospective, observational, multicenter, hospital-based surveillance study. A total of 17 hospitals from China are involved. The study is expected to enroll a large sample of 10,000 patients aged between 18 and 80 years with upper respiratory tract infection who were prescribed PDL. The patients' data, including demographics, medical history, diagnostic information, medication details, adverse events, and laboratory test results, will be monitored. The occurrence of ADRs will be recorded. The primary outcome is the incidence of ADR. Secondary outcomes are the ratio of patients whose body temperature return to the normal range (cases of body temperature normalization and the duration for achieving normal body temperature within a 3-day period will be documented) and changes in liver and kidney function (occurrence of drug-induced liver injury and acute kidney injury). Descriptive analyses will be performed for the primary and secondary outcomes. A cohort, nested, case-control study design will be used. If one patient has an ADR, then 4 patients without ADRs will be matched as the control group according to gender, age within 5 years, drug batch, and other factors, at a ratio of 1∶4 to compare the symptoms related to ADRs. The differences of ADR incidence among the possible influencing factors will be compared separately to find the factors with large differences. Then, synthetic minority oversampling technique and group least absolute shrinkage and selection operator methods will be used to identify factors influencing the occurrence of ADRs. Finally, propensity scoring methods will be used to control for confounding variables. The progress of each subcenter will be closely monitored, and the incidence of ADR will be systematically calculated. Furthermore, the characteristics and influencing factors of ADR will be analyzed, along with an investigation into its geographical distribution.

Results: The study began on July 17, 2019. Due to the limited number of eligible patients, missed follow-ups, and the huge clinical burden caused by public health events in 2019, the final case will be enrolled on August 30, 2025.

Conclusions: This study will obtain safety results of PDL in the real world and provide guidance on the clinical safety of traditional Chinese medicine formulations.

Trial Registration: ClinicalTrials.gov NCT04031651; https://clinicaltrials.gov/study/NCT04031651

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International Registered Report Identifier (IRRID): DERR1-10.2196/65789

(JMIR Res Protoc 2025;14:e65789) doi:10.2196/65789

KEYWORDS

Pudilan Xiaoyan oral liquid; PDL; upper respiratory tract infection; URTI; registry; adverse drug reaction

Introduction

Upper respiratory tract infection (URTI) involves inflammation of the respiratory mucosa from the nose to the lower respiratory tract; it causes localized symptoms that constitute several overlapping syndromes: pharyngitis, common cold, sinusitis, and bronchitis [1]. Bacterial or viral infections may be the cause of URTI, but antibiotics are recommended only for the former [1]. It is a self-limiting viral infection [2]. Currently, considering the treatment of symptoms for URTI and anti-infective therapy [3], the efficacy remains unsatisfactory with notable adverse reactions [4]. *Pudilan Xiaoyan* oral liquid (PDL) is a Chinese patent medicine, collected in the *Chinese Pharmacopoeia*. It has been widely used for URTI and has obtained good curative effect [5,6]. It contains drugs such as *Scutellaria baicalensis*, *Corydalis bungeana*, *Taraxacum mongolicum*, and *Isatis indigotica* [7]. All four herbs have the traditional Chinese medicine effects of removing heat and toxic materials, cooling blood, and reducing swelling. Besides, they also have anti-inflammatory, analgesic, antibacterial, and other biological effects [8]. Despite the efficacy of PDL, it is also necessary to monitor its safety.

In terms of safety, among the biological mechanisms of PDL, *S baicalensis*, *C bungeana*, *T mongolicum*, and *I indigotica* have been identified as herbs with low toxicity. The aforementioned drugs, however effective, are associated with gastrointestinal adverse reactions due to their bitter cold properties. Additionally, *S baicalensis* exhibits limited embryotoxicity and hepatotoxicity and can induce allergic reactions leading to vesicular eruptions [9]. *T mongolicum* primarily contributes to reversible toxicity targeting red blood cells [10], while *I indigotica* possesses nephrotoxic properties and may impose a burden on the urinary system with prolonged use [11]. The formulation of *C bungeana* contains certain hepatotoxic effects [12]. Therefore, it is necessary to investigate the safety of PDL since it is composed of the aforementioned herbal groups.

Monitoring the unintended effects of a drug (pharmacovigilance or drug safety) is crucial due to limited knowledge of rare or late-stage side effects upon market release of new drugs [13,14]. In recent years, numerous related studies have reported the clinical efficacy of PDL; however, there were few independent safety studies on it, most of which were small scale and exhibited significant variations in reported safety outcomes across different studies [15-18], resulting in inadequate understanding of its safety monitoring. In summary, published safety data on adverse effects of PDL therapy were insufficient, thereby impeding the use of standardized recommendations that are necessary for ensuring drug safety.

Although Chinese patent medicine generally exhibits a low incidence of adverse reactions, the evidence pyramid classification derived from effectiveness evaluations primarily considers randomized controlled trials as high-level evidence. However, this classification standard may not fully meet the evidence requirements for postmarketing drug safety evaluation due to limitations such as short intervention courses or small sample sizes, often resulting in an inability to detect ADRs and differences between groups. For the above reasons, this study intends to adopt a large-scale, multicenter, long-term, noninterventional, observational study design to comprehensively analyze and report on the occurrence of adverse events (AEs) [19].

The mechanism of kidney metabolism and excretion of various drugs and toxins is an important cause of drug nephrotoxicity [20], while studies have shown that most of the AEs related to the urinary system were from treatment with PDL [21]. It can be seen that the kidney damage caused by PDL needs further investigation. As hepatic function plays an essential role in drug metabolism [22], clinical studies are necessary to determine the characteristics of PDL-related hepatotoxicity. Additionally, the influencing factors of other PDL-related adverse reactions are still unclear and may be related to the inherent characteristics of the drug itself, improper usage and dosage, improper combination, repeated administration, or use without indications, which need further investigation and study. Furthermore, a comprehensive study regarding the adverse effects associated with PDL use in patients is imperative to optimize the risk-benefit ratio and alleviate strain on limited health care resources.

Methods

Research Design

This is a prospective, observational, multicenter, hospital-intensive monitoring, and continuous registry study. We used the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist when writing our report [23]. The study flowchart is shown in Figure 1.

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Figure 1. Study flowchart. ADR: adverse drug reaction; CRF:case report form; PDL: Pudilan xiaoyan oral liquid.

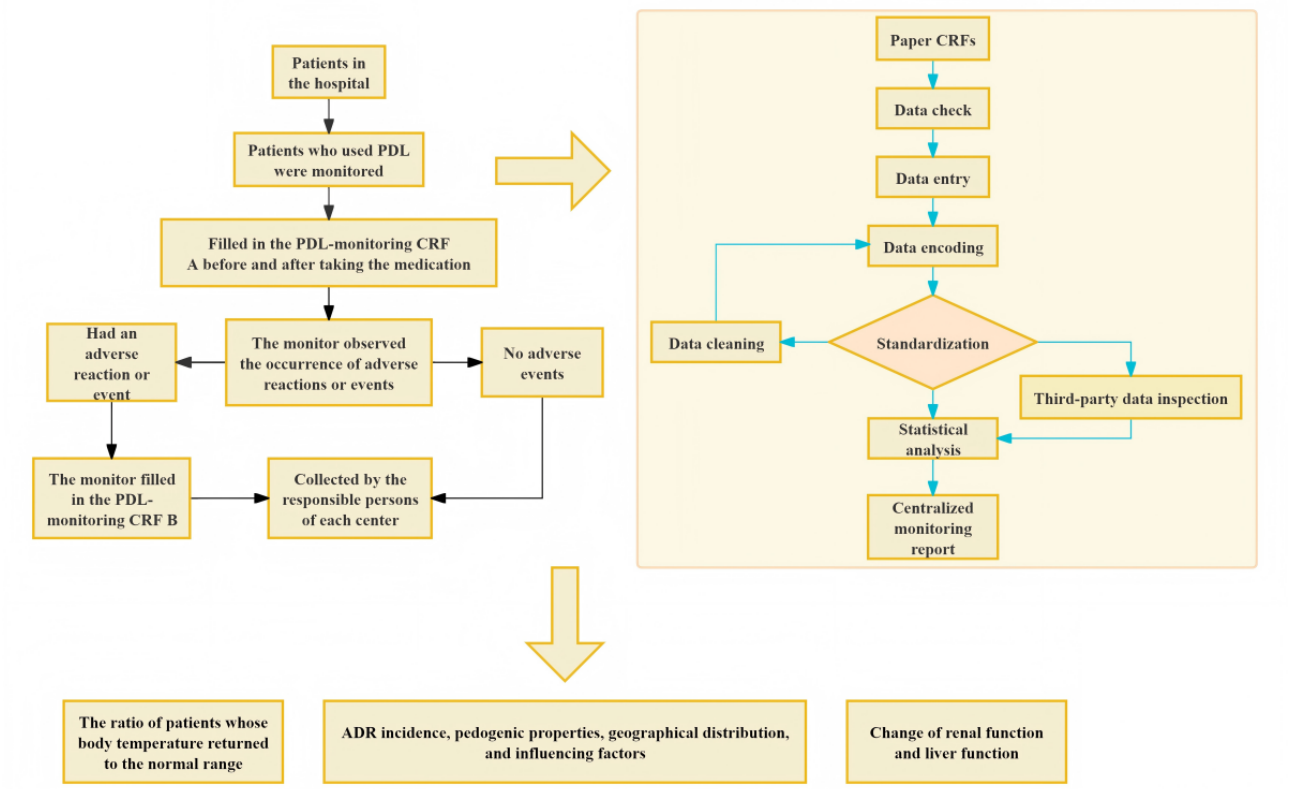

Organization

A total of 17 hospitals in China are involved in this study: Xiyuan Hospital of China Academy of Chinese Medical Sciences, the First Hospital of Hunan University of Chinese Medicine, Nantong Hospital of Traditional Chinese Medicine, Shenxian People's Hospital, the Second People's Hospital of Liaocheng, He Xian Memorial Affiliated Hospital of Southern Medical University(Panyu Maternal And Child Care Service Centre Of Guangzhou), Harbin Traditional Chinese Medicine Hospital, Affiliated Hospital of Yangzhou University (Yangzhou First People's Hospital), Friendliness Hospital Yangzhou, Xuzhou Central Hospital, Peixian People's Hospital, Affiliated Hospital of Liaoning University of Chinese Medicine, Affiliated Hospital of Shandong University of Chinese Medicine (Shandong Province Hospital of Chinese Medicine), the First Bethune Hospital of Jilin University, the First Affiliated Hospital of Anhui University of Chinese Medicine, Yantaishan Hospital, and Taizhou Traditional Chinese Medicine Hospital. Figure 2 shows their specific locations.

Figure 2. The geographical location of the 17 hospitals in China involved in this study.Light blue represents North China, light pink represents Central China and light green represents South China.

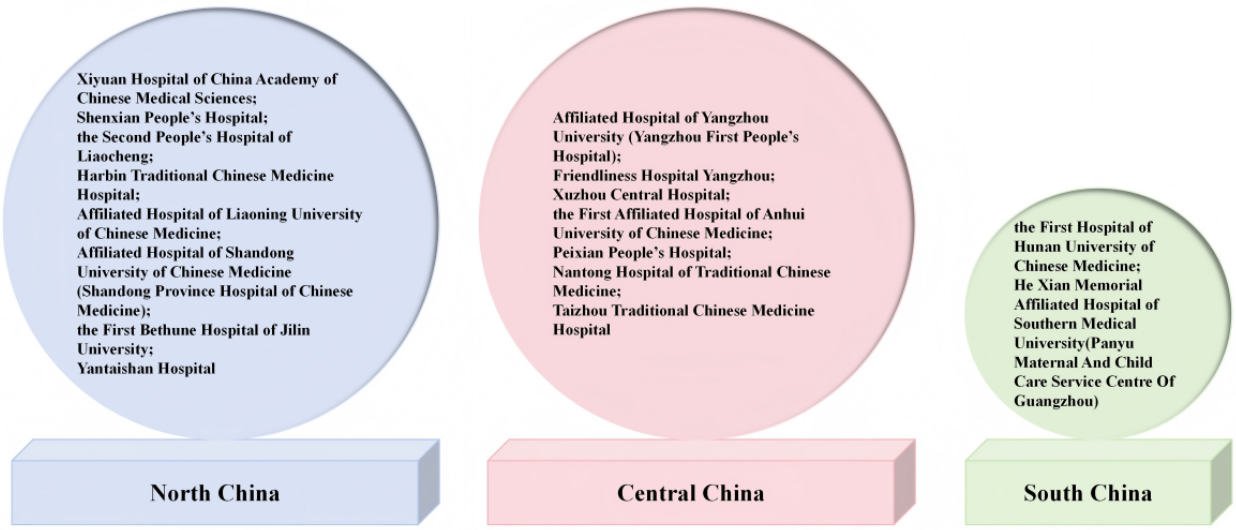

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Sample Size

In accordance with the requirements of the *Guide to Key Drug Monitoring for Manufacturing Enterprises* [24], and referring to the 2013 *Technical Specifications for Intensive Hospital Safety Monitoring of Post-Marketing Chinese Medicine* [25], the "rule of threes" was used for sample size calculation, which states that "if no specific event is observed in X existing cases, there is a 95% likelihood that the occurrence rate of such an event is ≤3/X." Based on the detection rate of rare ADRs (1/10,000 to 1/1000), it is estimated that 3000 cases would need to be collected. However, due to the low probability of ADR occurrences investigated in this study, actual monitoring will be extended to 10,000 cases.

Monitoring Time and Follow-Up

Patients are monitored throughout the medication period in the hospital. The treatment duration of PDL for URTI ranges from 3 to 14 days. This study will include a follow-up period of 7 days after the completion of observation treatment [26], aiming to assess the drug's long-term efficacy and observe any delayed ADRs. The follow-up will be conducted either through face-to-face meetings or via telephone communication. We will use systematic methods and reminders to schedule appointments with patients.

Criteria

The inclusion and exclusion criteria are reported in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Patients with upper respiratory tract infection (URTI) who are administered

  Pudilan Xiaoyan

  oral liquid; the diagnostic criteria for URTI are based on the disease code J06.900 of the

  International Classification of Diseases, 11th Revision
- Aged between 18 and 80 years

Exclusion criteria

- Lactating women, pregnant women, those planning to become pregnant, patients with psychiatric conditions, and others

Instructions for Taking Medicine

In the respiratory and emergency departments of the hospitals under surveillance, the medication of PDL is observed for those aged 18-80 years who strictly follow the prescribing instructions: taking PDL 10 mL at a time, 3 times a day. During hospitalization, the patient must take PDL at least once. The patients will be visited and checked before and after taking the medicine.

Monitoring Content and Data Administration

Monitoring Patient Data, Demographic Information, Diagnosis, Complications, and Medication Information

A collaborative monitoring approach involving doctors, nurses, and pharmacists will be used in this study. They will receive relevant training in surveillance knowledge.

Basic Information Form for Administering PDL

The researchers will record the AE information collected during the study period into the safety monitoring case report form (CRF). All patients will be required to complete CRF A (PDL basic information form). If the monitored patient experiences an ADR or AE during the medication period, the monitor will need to fill out CRF B. We will check the monitoring data; enter, encode, standardize, and clean the data; and then conduct a third-party data inspection. Any discrepancies in the data will be addressed by two data administrators who will resolve them after independently verifying the original CRFs.

Interpretation of ADR Causality

In this study, AEs, ADRs, and serious ADRs will be judged according to the *Administrative Measures on Reporting and Monitoring for Adverse Drug Reaction* issued by the Ministry of Health in 2011 [27]. The evaluation of ADRs follows a 3-level decision-making process, comprising initial reporting by clinical practitioners, assessment by the Expert Committee for ADR Monitoring at the surveillance center, and final determination by panel of senior domestic experts. Based on established assessment criteria, the causal relationship between AEs and PDL will be evaluated according to five key parameters: (1) temporal plausibility, (2) consistency with known mechanisms of action or established adverse reaction profiles, (3) positive dechallenge response, (4) positive rechallenge response, and (5) exclusion of alternative explanations. The correlation between AE and PDL will be divided into six grades: positive, probable, possible, possibly unrelated, to be evaluated, and unable to be evaluated. Those judged to be the first three grades will be classified as ADRs, those judged to be "possibly unrelated" will be classified as AEs, and those judged as "to be evaluated" or "unable to be evaluated" should be rejudged in combination with the original monitoring data. We will conduct thorough evaluations to ultimately confirm the incidence of ADRs associated with PDL. This approach helps to minimize potential biases associated with patient self-reporting and variations in medical practices across different centers. The occurrence characteristics and processes of ADRs will be meticulously documented, with particular emphasis on the timing of ADR onset, the

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implementation time of intervention measures for ADRs, and the termination time of ADRs.

Quality Control of ADRs

Each monitoring subcenter will formulate the first-level, quality-control rules and quality-control list according to the content of the monitoring program. The information system of each monitoring unit will be reviewed to ensure that the clinical study data are authentic and traceable. The implementation of the study will adhere to the research protocol and standard operating procedures in order to ensure the authenticity and reliability of the research data. The data collected are presented in Table 1.

Table 1. Basic information form for administering Pudilan Xiaoyan oral liquid[a].

Basic information	Before taking the medicine	After taking the medicine		
		7 days	14 days	21 days
Age	✓			
Sex	✓			
Smoking history	✓			
Occupation	✓			
Expense category[b]	✓			
Pathways to admission	✓			
Drinking alcohol	✓			
Western medicine diagnosis	✓			
Traditional Chinese medicine diagnosis	✓			
Past medical history	✓			
Personal history of allergies	✓			
Allergic manifestation	✓			
Previous other adverse drug reactions or events	✓			
Main drug combination: Western medicine, antibiotics, antipyretic analgesia, proprietary Chinese medicine, or other drugs		✓	✓	✓
Blood routine before and after treatment, white blood cell count, granulocyte, routine urine examination, liver function, renal function, ECG[c] (test sheet within 30 days before treatment), C-reaction protein, influenza virus detection, pathogen detection, and other tests	✓	✓	✓	✓
Adverse reaction occurrence (yes or no)		✓	✓	✓

[a]Patients are visited and examined before and after taking the medication.

[b]Expense category refers to the classification of expenses, such as out-of-pocket (self-funded) costs, expenses covered by medical insurance, and other payment types. It helps in understanding how different types of expenses are categorized based on their funding source or payment method.

[c]ECG: electrocardiogram.

Outcome Measures

Primary Outcome Measure: Incidence of ADRs

The incidence of ADRs is the primary outcome measure, and we will identify factors that contributed to the occurrence of ADRs. The incidence of ADR will be primarily categorized in accordance with the criteria proposed by the Committee of International Organization of Medical Sciences: very common (≥10%), common (1%-10%, including 1%), occasional (0.1%-1%, including 0.1%), rare (0.01%-0.1%, including 0.01%), and very rare (<0.01%) [28], as well as according to the classification of ADR symptoms by the World Health Organization (WHO) [29]. The WHO classification of organs and systems involved in ADRs will also be referenced [30]. The incidence characteristics and regional distribution will be subsequently analyzed, while concurrently investigating the influencing factors (Table 2).

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Table 2. Centralized monitoring results of Pudilan Xiaoyan oral liquid in the registered hospitals.

Monitoring result	Description
Categorization	• The ADR[a] was categorized based on general, novel, and severe classifications • The classification was based on the organs and systems affected by the ADR • The symptoms of the ADR were classified
ADR incidence	• The specific event features of each ADR included the incidence rates of various categories and whether they are infrequent or exceptionally rare
Pedogenic properties	• Occurrence characteristics of ADRs specific to each category
Geographical distribution	• The distribution of ADRs is primarily observed in North China, Central China, South China • Each region exhibits distinct characteristics of ADRs
Influencing factors	• Days of medication, age, drug combination, etc

[a]ADR: adverse drug reaction.

Secondary Outcome Measures

The Ratio of Patients Whose Body Temperature Returned to the Normal Range

The cases of body temperature normalization and the duration for achieving normal body temperature within a 3-day period will be documented. The body temperature will be recorded prior to medication, on the first day after medication, and on the second and third days after medication. Daily measurements will be conducted by professional nurses using mercury thermometers. The time of normal body temperature restoration is defined as when the body temperature drops below 37.3 °C after the initial medication administration, with no recurrence observed within a 24-hour period. Thus, the ratio of normalization represented the percentage of cases in which individuals return to a normal body temperature within the total number of cases in the group.

Change in Liver Function

We will observe liver function in at least 3000 patients before and after medication. Liver function indexes will include alanine transaminase (ALT) and aspartate transaminase. To observe whether the above liver function indexes appear abnormal after medication, we will use the 2011 International Association for Severe Adverse Reactions–recommended biochemical diagnostic criteria for drug-induced liver injury [31]. Drug-induced liver injury is defined as meeting one of the following conditions:

1. ALT ≥5× upper limit of normal (ULN);
2. Alkaline phosphatase ≥2×ULN, especially with 5’-nucleotidase or γ-glutamyl transpeptidase elevation, excluding alkaline phosphatase elevation caused by other diseases; or
3. ALT ≥3×ULN and total bilirubin ≥2×ULN.

Change in Renal Function

We will observation renal function in at least 3000 patients before and after medication. The renal function indexes will include creatinine and blood urea nitrogen. To observe whether the above renal function indexes appear abnormal after medication, the diagnostic criteria for acute kidney injury will be defined based on the Kidney Disease: Improving Global Outcomes serum creatinine criteria [32] (at least 50% increase in creatinine within 7 days or a 26.5 μmol/L increase within 48 h).

The time frame for all four result items is 7 days (Table 2).

Statistical Analysis

Data review and cleaning work will take the paper monitoring form as the original record, delete redundant and repetitive parts, supplement missing data, modify wrong values, and report about abnormal values. The basic characteristics of the patients will be included. Descriptive analyses will be performed for the primary and secondary outcomes. SPSS Statistics 26 software (IBM Corp) will be used for descriptive analysis. Data conforming to a normal distribution will be described by means and SDs, and those conforming to a skewed distribution will be described by median, minimum, maximum, and IQR scores. Categorical data will be described by frequencies and percentages. A cohort, nested, case-control study will be used. If 1 patient has an ADR, then 4 patients without ADRs will be matched as the control group according to gender, age with 5 years, drug batch, and other factors, at a ratio of 1∶4 to compare the symptoms related to adverse reactions. In addition, the risk factors of adverse reactions will be analyzed. First, the differences of ADR incidence among the possible influencing factors will be compared separately to find the factors with large differences. Then, synthetic minority oversampling technique and group least absolute shrinkage and selection operator methods will be used to identify factors influencing the occurrence of ADRs, while propensity scoring methods will be used to control for confounding variables.

Ethical Considerations

This monitoring scheme is implemented after the approval of the Ethics Committee of Xiyuan Hospital of China Academy of Chinese Medical Sciences (ethics batch: 2019XL009-1). Patient data included in the analysis were approved by the institutional review committee of each participating agency. Informed patients in this study were exempt from signing the consent application. In addition, the data will be kept confidential, and the researchers who participate in the data

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inquiry will need to submit the corresponding application, to ensure that no individual participant or user can be identified in any images in the paper or supplementary materials.

Results

The first case was included on July 17, 2019. Due to the limited number of eligible patients, missed follow-ups, and the huge clinical burden caused by public health events in 2019, the final case will be enrolled on August 30, 2025.

Discussion

Summary

The practice of traditional Chinese medicine in China spans over 2000 years and has consistently garnered high regard for its precise therapeutic efficacy, minimal adverse effects, and cost-effectiveness [33]. As a proprietary Chinese medicine preparation already on the market, PDL had outstanding efficacy in treating URTI [5]. The action mechanism of PDL has been extensively used in clinical practice. However, it is important to acknowledge that there are no completely safe drugs, and every drug administration carries inherent risks. Therefore, the objective of this study was to closely monitor the safety profile of PDL.

The therapeutic safety of PDL is currently being overlooked during the course of disease treatment. Early identification and a better understanding of its adverse reactions will enhance the drug safety profile of PDL and mitigate the therapeutic costs associated with such reactions.

This study is a continuous registry, hospital-intensive monitoring study. Hospital-intensive monitoring allows the evaluation of efficacy and safety in diverse populations under real-world conditions, including sensitive populations that may not be included in premarketing clinical trials, such as pregnant women, ethnic minority groups, older adult patients, children, patients with multiple comorbidities, and those taking multiple medications. The limitation of centralized monitoring in registry hospitals is that it may underestimate the impact of ADRs, as health care professionals may prioritize serious adverse reactions and overlook general adverse reactions. However, this study will implement a 3-level, quality-control approach, using a professional electronic data management system to mitigate missing and misreported data occurrences and ensure the validity and authenticity of the collected information [19].

There are numerous pathological conditions that contribute to drug-induced acute kidney injury, among which the nephrotoxicity of drugs stands as a preventable factor. Enhancing our comprehension of drug safety aids in mitigating the risk associated with drug-induced acute kidney injury. Furthermore, apart from the inherent nephrotoxicity of drugs themselves, administering potentially nephrotoxic medications in high doses or over prolonged treatment durations amplifies the likelihood of renal damage. Additionally, concomitant administration of multiple drugs can synergistically induce nephrotoxicity and consequently lead to kidney injury. Therefore, studying the kidney injury factors of PDL forms the basis for preventing adverse reactions. The Chinese medicine preparation PDL can also induce hepatotoxicity, leading to drug-induced liver damage, which may occur at both therapeutic and overdose doses. This can be attributed to either direct intrinsic hepatotoxicity of the drug or specific (unpredictable) liver toxicity [34], which needs to be further observed and explored.

The monitoring and evaluation of the safety of proprietary Chinese medicine preparations, along with the acquisition of authentic drug safety information, can complement drug instructions, promptly grasp the latest research advancements in related medications, guide their clinical application, and enhance the safety and efficacy of their clinical use.

Conclusions

This study will obtain the safety results of PDL in real-world, clinical applications. Furthermore, monitoring and evaluating the safety of proprietary Chinese medicine preparation is instrumental in providing further clinical guidance on drug use.

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Data Availability

Since this is a protocol, data are not yet available, and information not included in this paper will be provided by the corresponding author upon completion of the trial.

Authors' Contributions

MW and LW prepared the study and the first version of the manuscript. RC participated in the design of the trial. FL collected the information needed for the performance of this trial in each center. ZW, XC, and YL performed a critical revision of the manuscript. YX and LW are responsible for all aspects of the study, including the preparation of the grant application, securing funding, data analysis, and interpretation and preparation of the final manuscript for publication. All of the authors discussed,

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read, and revised the manuscript and gave final approval for the publication of this study protocol. The sponsor of this protocol is China Academy of Chinese Medical Sciences, and the responsible party is YX.

Conflicts of Interest

None declared.

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Abbreviations

ADR: adverse drug reaction
AE: adverse event
ALT: alanine transaminase
CRF: case report form
PDL: Pudilan Xiaoyan oral liquid
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
ULN: upper limit of normal
URTI: upper respiratory tract infection
WHO: World Health Organization

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Protocol

Tailoring a Skills-Based Serostatus Disclosure Intervention for Transgender Women in South Africa: Protocol for a Usability and Feasibility Study

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Abstract

Background: Transgender women have few interventions to support their HIV prevention and treatment outcomes in South Africa. Further, increased focus should be on intervention development that will reduce HIV transmission within HIV-discordant partnerships, especially for transgender women who navigate gender, sexuality, and relationship stigma. The Speaking Out and Allying Relationships (SOAR) intervention has been developed for sexual minority men to address these outcomes in South Africa. It is a behavioral intervention that is delivered in groups via videoconference to develop coping skills to manage HIV-related stress, assist with disclosure to partners, and establish and maintain safer sex practices with partners. Tailoring SOAR may be feasible for transgender women to support their HIV care while reducing transmission within their relationships.

Objective: This study aims to (1) adapt SOAR for transgender women and test its usability, then (2) assess its feasibility.

Methods: To achieve aim 1, we will use a human-centered design approach to tailor the existing SOAR intervention for transgender women. Interviews and a survey will be administered to transgender women (N=15) to assess intervention preferences. Findings will be used to tailor content like roleplays, scenarios, and media to align with transgender women's lived experiences navigating HIV and relationships. Afterward, we will conduct a usability test with 7 (47%) of the 15 participants to determine intervention understanding and satisfaction. Participants will be transgender women living with HIV and in a relationship with a man who has unknown HIV status or is HIV-negative. All participants will be recruited using community-based approaches. In aim 2, we will examine SOAR feasibility using a 1-arm pilot study. Transgender women (N=20) will be recruited using aim 1 methods and eligibility criteria, with participants completing feasibility surveys and interviews, as well as behavioral and biomedical assessments.

Results: Intervention adaptation began in May 2023 with interviews. Feasibility pilot testing was conducted with 14 transgender women, with study completion in January 2025.

Conclusions: Transgender women need more intervention options that engage their relationships since these can present barriers to HIV treatment outcomes like hindering viral suppression in South Africa. Delivering an existing yet tailored intervention via videoconference expands its reach to transgender women and allows them to engage with others and learn new skills in a secure setting like their homes. SOAR has the potential to improve relationship dynamics and reduce violence, which will in turn enhance HIV treatment and prevention engagement.

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KEYWORDS

transgender women; intervention development; relationships; HIV treatment; South Africa; mobile phones, smartphones; skills-based; serostatus disclosure; HIV; HIV prevention; transgender; treatment outcomes; transmission; HIV-discordant partnerships; behavioral intervention; safe sex; human-centered design; viral suppression; Speaking Out and Allying Relationships; LGBTQ2S; LGBTQ; 2SILGBTQ

Introduction

Background

HIV infections among transgender women are 2.2 higher than gay, bisexual, and other men who have sex with men in sub-Saharan Africa due to syndemics consisting of stigma and discrimination that perpetuate violence and victimization, limiting access to HIV prevention and treatment [1-4]. In South Africa, the HIV incidence for transgender women is 31 cases per 100-person years, with studies showing limited pre-exposure prophylaxis (PrEP) and antiretroviral therapy (ART) access and adherence. Based on other African studies, only an estimated 25% of transgender women are virally suppressed [5-7]. HIV prevalence among transgender women in South Africa mirrors the realities that they share with their peers in other Global South settings, with a 52% mean prevalence documented in 3 South African cities [8]. Transgender women's health and safety remain compromised in South Africa, inhibiting their ability to engage in HIV services to lower transmission risk and improve their overall wellness, and compounding these health outcomes are poor relationship dynamics.

Being in an unhealthy or imbalanced relationship for transgender women can lower their HIV testing behaviors and increase rates of condomless anal intercourse with partners to create trust and intimacy [9-13]. Fear of partner rejection or loss and intimate partner violence may lead transgender women to limit or halt ART use to conceal their serostatus from partners [14-16]. Further, studies increasingly show that transgender women experience negative outcomes of relationship stigma (when partners fear being romantically associated with someone who is stigmatized), which in turn has hindered their ability to discuss HIV treatment with them [15,17]. Although studies with transgender women in South Africa are limited, in the United States, relationship dynamics for transgender women influence HIV risk, in the same ways they do for cisgender women and sexual minority men [17-21]. Additional factors hindering HIV prevention and treatment discussions that transgender may have with a partner include living with them, drug use, alcohol use, education level, and low self-efficacy to use condoms [18]. In sum, cisheteronormative social structures and power dynamics have been shown to result in increased marginalization, increased susceptibility to intimate partner violence, and increased risk of mental issues among transgender women, all hindering HIV prevention and treatment [22-24].

Further, transgender women are less likely to disclose their HIV status to other transgender women and sexual minority men within their social networks, increasing social isolation [25-27]. Only after being out of care and developing AIDS-related illnesses do transgender women disclose their HIV status to an immediate family member in order to secure support for their treatment, but this disclosure does not extend to partners [25,27]. Given a history of HIV care marginalization and discrimination, transgender women often possess inaccurate knowledge and skills in discussing with partners how PrEP and ART adherence, including "undetectable is untransmissible" (U=U) messaging, can work together to reduce transmission and in turn support relationship health [14-16]. Thus, transgender women have ongoing HIV-related stress without the skills to manage this stress and their disclosure to partners and others for support.

The benefits of social and partner support are significant for transgender women. Studies show that transgender women in committed relationships are less likely to engage in HIV-related high-risk behaviors, with researchers suggesting that relationship stability and emotional support lead to more consistent condom use and improved HIV prevention and treatment overall [28-30]. Specifically, higher relationship satisfaction, trust, and commitment were protective factors against HIV transmission among transgender women [17,31]. Additionally, 1 randomized controlled trial found that a social support group intervention further reinforced relationship-related protective behaviors among transgender women [32]. Therefore, a relationship-focused HIV intervention may support treatment and prevention outcomes for transgender women and their partners while garnering the support of family members earlier in their treatment journey.

To address this gap in interventions for transgender women living with HIV in South Africa, the aim of our study is to tailor our existing intervention, Speaking Out and Allying Relationships (SOAR) intervention, with them and then conduct a 1-arm pilot study to assess intervention feasibility in Eastern Cape, South Africa. Specifically, we will tailor SOAR and assess usability for content understandability and satisfaction (aim 1), and then evaluate its feasibility to include retention and any changes in behavioral and biomedical measures (aim 2). We hypothesize that participants will find SOAR feasible, acceptable, and safe to inform a larger efficacy study.

Our SOAR intervention is based on Healthy Relationships (HR), a 5-session, group-based evidence-based intervention to develop individual HIV disclosure risk assessment and safer sexual behavior skills with partners that have demonstrated efficacy in these outcomes in a range of settings [33,34]. The core elements of SOAR are to: (1) develop coping skills to manage HIV-related stress and sexually risky situations; (2) enhance decision-making skills for HIV disclosure to partners; and (3) establish and maintain safer sex practices with partners. The HR intervention was identified based on our preliminary research with sexual minority men and transgender women in South Africa [35]. Additionally, through this preliminary research, we demonstrated that transgender women are willing to complete HIV-related group work and have an interest in mHealth tools, like videoconference modalities, to learn skills in HIV treatment management and disclosure for support

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[36,37]. Moreover, harnessing high use rates of smartphones by transgender women for intervention delivery is feasible in South Africa [20,38]. Increased evidence shows that transgender women access web-based social networking sites and use SMS for social networking through mobile and smartphone technologies, creating the potential to tag on ART adherence interventions [39,40]. In our research, we found that HIV-positive sexual minority men and transgender women regularly use videoconferencing to support community networking across rural and urban settings, with 2-hour conversation events focused on HIV, sexuality, and gender [37]. Further, mHealth tools (SMS, chat rooms, and web-based video group interventions) for HIV prevention and treatment in South Africa are part of the national strategic plan [41]. As in the original HR, our SOAR intervention integrates media, scenarios, and roleplays for skill development, and these reflect the experience of South African sexual minority men living with HIV and in relationships. In addition to the standard 5 sessions, we include three 30-minute booster sessions to review action plans over 3 months.

Theoretical Framework

Social cognitive theory serves as the framework for the intervention, which posits that cognition, behavior, and environment interact and influence health outcomes, like HIV risk reduction, disclosure, prevention, and ART adherence. SOAR aims to enhance coping skills for HIV-related stress, self-regulation of disclosure to include risk assessment, treatment, and prevention, and build self-efficacy in healthy behaviors and communication within relationships. Further, the intervention will provide a platform for participants to strengthen coping skills that will support and empower gender affirmation within relationship dynamics that may be experiencing stigma or risk of violence, or desire for improved relationship communication. Within the social cognitive theory model, the intervention will incorporate components such as HIV risk reduction education, treatment education including U=U, HIV prevention strategies like PrEP, and gender affirmation within the context of HIV. Skill-building activities for HIV communication and disclosure risk assessment will be conducted in a confidential group setting. By helping individuals plan for safe sex and consider HIV communication and disclosure to partners, the intervention aims to support ART adherence, empower participants with a sense of agency, and reduce negative feelings associated with their HIV status and internalized HIV stigma.

Our proposed tailoring of SOAR for transgender women is based on high interest to participate among those who attended community outreach activities for recruitment of sexual minority men as part of the original intervention. If this tailoring shows promise of feasibility, then we will conduct a larger randomized controlled trial to assess efficacy and implementation with local agencies that service sexual and gender minority communities in South Africa.

Methods

Study Design Overview

The study will use a 2-fold approach, beginning with intervention tailoring and usability assessment (aim 1) and then a 1-arm pilot study of the intervention (aim 2) to evaluate feasibility. Prior to study initiation, a study coordinator will be hired and trained in study procedures and the SOAR intervention and its delivery approach. The coordinator will be a member of the sexual and gender minority community in Eastern Cape and have a history of HIV program work. Coordinator training will include a review of sexual and gender minority health with a focus on HIV treatment and prevention barriers and facilitators for transgender women, gender-affirming care such as hormone replacement therapy, and relationship dynamics influencing HIV care. Additionally, the coordinator will complete training in good clinical practice and ethics and study procedures including data collection. Finally, the coordinator will be trained in the SOAR intervention which will include both didactic and simulation sessions until competency has been achieved. The study coordinator will conduct all study procedures with mentoring provided by the research team.

Tailoring SOAR for Transgender Women

In aim 1, we will tailor SOAR by using a human-centered design approach. First, we will assess transgender women's preferences and confirm their relationship dynamics regarding HIV. Then, we will evaluate the functionality of the intervention in a videoconference format (Zoom, Qumu Corp), and usability by gauging participants' understanding and satisfaction with the SOAR intervention.

The study will be conducted in Buffalo City Municipality, Eastern Cape, South Africa. In this setting, there is a 46% HIV prevalence among transgender women who live in both urban and rural areas [8]. We will recruit transgender women (N=15) living with HIV and in a relationship for more than a month. Recruitment activities will be conducted by study staff at community events focused on transgender women and sexual and gender minorities. Study staff are members of the sexual and gender minority community and allies, and all completed LGBTQ competency training. Interested participants will be provided study explanation and invited to answer questions in the screening survey. Eligible participants will complete written informed consent in the language of their choosing (eg, isiXhosa, Afrikaans, English). The consent form will outline confidentiality and protections of participant information if they are interested in participating in the study. All participants will receive travel reimbursement and refreshments to complete study procedures.

Preference Assessment and Integration

To assess transgender women's preferences for the intervention, we will conduct in-depth interviews (IDIs). These interviews will delve into influences on HIV treatment including support and relationship dynamics, and gather feedback regarding various aspects of the intervention, including format and delivery. A semistructured question guide will ask questions in four domains: (1) HIV prevention and treatment knowledge;

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(2) relationship scenarios involving HIV disclosure and support for role-play development; (3) videoconference delivery preferences; and (4) positive representation of transgender persons in media (web-based, television, and movies) to show during the sessions. Each interview will be 60 minutes long, conducted in the local language (isiXhosa), transcribed verbatim, and translated for analysis. Findings from the analysis will be used to tailor SOAR to the contextual factors influential in HIV treatment and status disclosure for transgender women and to ensure representation of their empowering voices in the roleplays and videos to support skill building.

Usability Testing

Usability testing will involve 2 tasks: pretesting and IDIs with participants. We will recruit 7 (50%) racially and relationship-length diverse transgender women participants from step 1 for pretesting. The pretesting phase will span 5 weeks, with 2-hour sessions each week. At week 8, 3 weeks after the last session, a group check-in session will be conducted via Zoom. Participants will receive SMS reminders for each session and the Zoom session link. All sessions will be completed together to foster positive group dynamics and will include a set of group rules for this purpose, and to protect the confidentiality of participants and their contributions during the sessions. The interventionist will monitor participant engagement throughout the pretesting and follow up with any missed sessions. Participants will provide their smartphone numbers for session reminders, self-assessment, action plans, and partner referrals delivered through Research Electronic Data Capture (REDCap; Vanderbilt University). The sessions and group check-in will be video-recorded for analysis, and participants will receive a data plan to facilitate their participation. After the pretesting phase, IDIs will be conducted with racially and relationship-length diverse participants over Zoom. The interviews will cover 6 usability domains for SOAR, including session functionality, timeliness and appropriateness, clarity of content delivery, document clarity and management, incomplete sessions, and technical transitions between sessions. The individual interviews in isiXhosa are expected to last approximately 50 minutes. Audio recordings of the interviews will be transcribed and translated into English for further analysis.

Data Analysis

To understand SOAR preferences and usability, interview transcripts will be cleaned and confirmed for accuracy before being uploaded into the qualitative data management program, Dedoose, where data will be coded and categorized [42,43]. First, the research team will separately analyze each transcript using predefined codes and open coding, and then discuss coding to confirm alignment and coding distinctions in order to clarify codes [16]. Second, using a thematic approach [44], researchers will analyze the coded transcripts to identify SOAR preferences and usability themes as an iterative process. An additional comparative analysis based on age was conducted to identify any distinctions [44-46]. These discrepancies will be resolved by agreement during research team discussions.

Evaluating the Feasibility of SOAR for Transgender Women

After SOAR has been tailored, in aim 2, we will conduct a pilot study of the intervention using a 1-arm design to determine feasibility, acceptability, willingness, and safety for transgender women (SOAR study design; Figure 1). Also, we will collect data on ART adherence (viral load) and relationship communication to establish a preliminary understanding of outcomes and implementation of measures in a larger study.

We will recruit transgender women (N=20) living with HIV and suboptimally adherent to ART (missed at 2 doses over 2 weeks), to complete the intervention. Additionally, participants must have been in a romantic relationship with a man for more than 1 month and live in Eastern Cape. For screening, participants will complete a rapid HIV viral load test to confirm HIV status.

There will be 5 participants per group for a total of 4 groups. All participants will be recruited and screened into the study by the trained study coordinator, and all recruitment activities will occur at transgender community–focused events. During the consent process, participants will be provided a general overview of the study and informed about the number of study sessions and expected behavioral and biomedical data collection procedures. As in aim 1, all participants will receive a travel reimbursement and refreshments.

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Figure 1. SOAR study design. ART: antiretroviral therapy; SOAR: Speaking Out and Allying Relationships; STI: sexually transmitted infection; VL: HIV viral load.

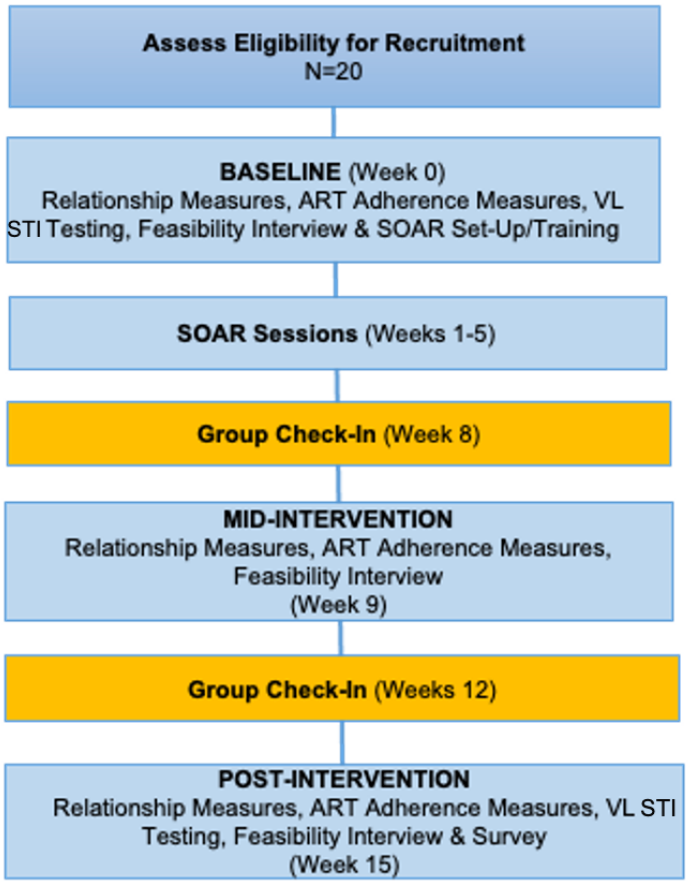

Procedures

Overview

Once enrolled, participants will complete a behavioral survey on REDCap. These measures cover HIV, sexuality, relationship stigma and discrimination, communication in relationships, and HIV prevention and treatment behaviors [47-53]. They will also complete syphilis testing using a rapid diagnostic test (Abbott Determine Syphilis TP), blood draw for HIV viral load, and urine collection for *Chlamydia trachomatis* and *Neisseria gonorrhea* testing. All measures will be administered by study staff.

Afterward, participants will receive training in Zoom, and their smartphones will be assessed and set up for Zoom compatibility. Participants will be notified that they will receive an SMS reminder 12 hours before each session, and then 1 hour before each session, they will receive an SMS with the Zoom link for that session. Also, participants will be informed that during the intervention they will be asked to complete an action plan, and they will receive a partner referral letter via SMS or in paper form (their choice) at the start of the study and can request the letter throughout the study. The referral letter describes the availability of local HIV and mental health services. Each participant will be informed that they will complete 1 SOAR session per week for 5 weeks with 2 check-in sessions afterward.

Group Check-Ins

All participants will be invited to attend group check-ins (n=2) via Zoom. The check-in dates and times will be provided during the last session with connection details (eg, Zoom link) sent via SMS to their mobile devices. Participants will be informed that they will receive a reminder about each check-in session 12 hours before and then 1 hour beforehand.

Each session and group check-in will be conducted by the study coordinator and a research assistant who is trained in the intervention.

Retention Procedures

All participants will be given a card with the study phone number to contact the interventionist if their phone number changes or if they have technical difficulties during the session (the card will not contain information that identifies their participation in the study). The interventionist will phone participants after a missed study visit and SMS each participant monthly to confirm smartphone numbers to support retention.

Measures and Data Analysis

We will use the same measures as outlined in the parent study to include feasibility, behavioral outcomes for ART adherence and relationship communication, and HIV viral load.

Feasibility

The assessment of feasibility encompasses four domains: feasibility [54], acceptability [55], willingness [56], and safety

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[57]. Feasibility pertains to the ability to successfully recruit and retain participants, as well as facilitate message exchange and engagement in group sessions [54]. Acceptability refers to participants' preferences and satisfaction with different components of the intervention [55]. Willingness relates to participants' interest in enrolling in a longer study and their likelihood of recommending the intervention to others [56]. Safety focuses on ensuring the confidentiality and security of participant data and communication both within and outside the intervention.[57]

We will assess feasibility using surveys and interviews. The Self-Intervention Evaluation Form and the Client Satisfaction Questionnaire will be administered to evaluate the acceptability [58,59]. A study-specific Likert scale survey will also be developed to assess feasibility, willingness, and safety [60]. This survey will gauge participants' perceived ability to exchange messages, participate in group sessions and check-ins (feasibility), their likelihood of enrolling in a longer study or referring other transgender women (willingness), their willingness to provide referral letters to partners, and their perception of the intervention's confidentiality and security (safety). Also, we will conduct 30-minute interviews with purposively all participants, and these will be conducted at baseline, midintervention, and postintervention [61]. Feasibility will be evaluated by examining participants' attitudes toward various aspects of the intervention, such as video-group interactions, referral letters, and their perceived changes in self-management of ART, HIV risk, and HIV disclosure [62]. Acceptability will be assessed by examining participants' preferences and satisfaction with specific intervention components and the intervention as a whole [62]. Willingness will be measured by assessing participants' willingness to use the intervention consistently from start to finish, their openness to using the intervention in different contexts, and their likelihood of recommending the intervention to others [62]. Safety will be examined by evaluating participants' perceived levels of discomfort with different intervention components and their perceptions of personal safety and the risk of unwanted disclosures [57].

Relationship, ART Adherence, and Biomedical Measures

In this study, we will assess the feasibility of collecting behavioral and biomedical measures and provide a preliminary understanding of outcomes. The SOAR intervention is designed to provide transgender women skills in assessing disclosure and related risks, and association communication skills to discuss HIV with partners. We will administer surveys for relationship satisfaction [63] and communication [64], HIV disclosure [65], and HIV treatment adherence [66] Also, we will assess HIV viral load using whole blood. All measures will be administered at baseline through follow-up.

All data will be analyzed using similar procedures as outlined in aim 1 of this study.

Participants

For both study aims, all transgender women will be over the age of 18 years, be in a relationship for more than a month, own a smartphone, be comfortable with group discussions about HIV, and be HIV-positive with confirmatory testing using OraQuick (OraSure Technologies) during screening. We will enroll with racial diversity to ensure the representation of multiple voices. Our relationship criteria require participants to have a self-reported romantic or emotionally connected partnership with another individual of any sex or gender, and partners must be either HIV-negative or of unknown status. Additionally, all participants need to live in Eastern Cape and suboptimally adhere to their HIV treatment [66].

Ethical Considerations

For this study, aim 1 procedures have been reviewed and approved by the University of Cape Town Review Board (FWA00001938) with reliance on the institutional review board at Arizona State University (STUDY00014539). For aim 2, the study procedures were reviewed and approved by the University of Pretoria Review Board (189/2022) with reliance on Arizona State University (16397). All participants completed written informed consent. All participants will complete written informed consent and will receive R150 (around US $10) as travel reimbursement for completing the study activities and an R150 (around US $10) data plan to support their session attendance. All data will be anonymized when reported.

Results

Staff hiring and intervention tailoring began in May 2023 and were completed in November 2023. During this time, interviews were completed and we identified preferences for the integration of gender-affirming care and South African transgender women's voices (eg, videos) into SOAR sessions. Feasibility pilot testing started in January 2024 and was completed in January 2025. At this time, there are 14 participants who have completed 1-5 SOAR sessions. Primary feasibility results will be used to inform further adaptation and a clinical trial.

Discussion

Expected Findings

The SOAR intervention for transgender women is responsive to South African clinical guidelines for HIV care and addresses barriers to HIV disclosure management and treatment with partners [67]. Specifically, recent clinical guidelines outline a recommendation to deploy mHealth tools for treatment support, as these may allow transgender women to navigate perceived and enacted stigma and discrimination more easily when seeking clinic care [15,16]. Given the established smartphone use in South Africa, and among transgender women, harnessing these tools in HIV interventions is feasible [68]. However, few mHealth HIV interventions have been designed and tested for transgender women [4].

SOAR leverages videoconferencing and group format for delivery. Both modes of delivery have been shown to be highly effective in other settings [69,70], and more research is needed to determine its feasibility with transgender women in South Africa. Further, SOAR has the potential to improve skill-building for HIV status disclosure management that may in turn garner needed support from partners and improve HIV treatment adherence. If partner disclosure and support are not

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feasible, then SOAR provides participants with coping skills to manage HIV treatment and identification of other support systems for care.

Given that transgender women have some of the highest HIV incidence rates in South Africa and globally [4], it is imperative that we develop more intervention options based on their lived experiences. Integrating mHealth tools into these interventions can empower participants, as it allows them to control engagement based on their safety and needs. If SOAR is feasible as videoconference delivery for transgender women, then we will propose an efficacy study of the intervention to understand the impact on HIV viral load and quality of life. The intervention has the potential to build relationship skills around HIV treatment for transgender women and their partners who are consistently left behind in the HIV response.

Limitations

The one potential study limitation is smartphone ownership or access. Specifically, although smartphone use is high in South Africa, device costs may be prohibitive for some participants. To facilitate participation such that we have representation of transgender women across socioeconomic standing, we will provide smartphones for participants to borrow, or they may access a tablet with headphones at a community site to attend the sessions.

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Authors' Contributions

The study was conceptualized and designed by JD. CB completed data acquisition with data analysis and interpretation by JD, SN, CB, RPP, and LLAVDM. The writing was completed by JD, SN, and SPP with review and revision by JD, LLAVDM, SPP, RPP, CB, and SN. All authors approve and are accountable for the manuscript content.

Conflicts of Interest

None declared.

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Abbreviations

ART: antiretroviral therapy
HR: Healthy Relationships
IDI: in-depth interview
PrEP: pre-exposure prophylaxis
REDCap: Research Electronic Data Capture
SOAR: Speaking Out and Allying Relationships

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Protocol

Lung Cancer Screening in Family Members and Peers of Patients With Lung Cancer: Protocol for a Prospective Cohort Study

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Abstract

Background: Low-dose computed tomography (LDCT) screening is promising for the early detection of lung cancer (LC) and the reduction of LC-related mortality. Despite the implementation of LC screening programs worldwide, recruitment is challenging. While recruitment for LC screening is based on physician referrals and mass advertising, novel recruitment strategies are needed to improve the enrollment of high-risk individuals into LC screening.

Objective: We aim to identify whether patients with LC can act as advocates to enroll their family members and close contacts into LC screening and whether this strategy increases screening uptake at the population level.

Methods: We designed a prospective cohort study comprising 2 cohorts constituted between June 2023 and January 2024 with a prospective follow-up of 18 months. Patients with LC (cohort 1) are approached at clinics of the McGill University Health Centre, educated on tools for communicating with family members and close contacts about the benefits of LC screening, and invited to refer their close ones. Referred individuals (cohort 2) are directed to this study's web-based questionnaire to assess their LC risk score with the PLCOm2012 (Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial) prediction model. Individuals meeting the eligibility criteria for LC screening (PLCOm2012 score ≥2% and aged 55-74 years) are directed toward the Quebec LC screening program. Data collected include sociodemographic characteristics, health literacy and smoking status (all participants), patient activation (cohort 1), perceived risk of LC, and generalized anxiety at baseline and at 28 days (cohort 2). LDCT completion within 18 months from referral is assessed from health records. Focus groups will identify the barriers and facilitators in the uptake of LC screening and preventative behaviors based on perceived genetic and clinical LC risks. The primary outcomes are the number of referred participants per survivor of LC and the mean risk of LC of the referred population based on PLCOm2012 scores. The secondary outcomes are the proportion of (1) participants eligible for LC screening; (2) participants eligible for screening who complete LDCT screening within 18 months of referral from a survivor of LC; (3) participants showing interest in genetic testing to inform LC risk; and (4) participants showing interest in a smoking cessation program. Multivariable logistic regression will identify the predictive factors of being referred for LC screening. PLCOm2012 scores will be compared for referred participants and controls from the provincial LC screening program.

Results: Overall, 25 survivors of LC and 84 close contacts were enrolled from June 2023 to January 2024, with followed up through July 2025. The results are expected by the end of 2025.

Conclusions: We describe an approach to LC screening referral, leveraging patients with LC as advocates to increase screening awareness and uptake among their family and peers.

Trial Registration: ClinicalTrials.gov NCT05645731; https://clinicaltrials.gov/ct2/show/NCT05645731

International Registered Report Identifier (IRRID): DERR1-10.2196/58529

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KEYWORDS

lung cancer; low-dose CT; chest tomography; lung cancer screening; patient advocacy; early detection of cancer; referral and consultation; cohort study; patient empowerment; patient experience

Introduction

Background

Almost three-quarters of lung cancers (LCs) are diagnosed at stages III and IV with poor overall survival [1,2]. LC remains the cancer with the highest mortality rate, with high rates of comorbidities also [3,4]. The projected increase of LC burden in Canada calls for improving its early detection and preventative strategies [5]. Low-dose computed tomography (LDCT) screening of high-risk individuals is promising for early detection and reduction of LC-related mortality [6]. With more than 50,000 high-risk individuals enrolled, the pioneering National Lung Screening Trial has shown a 20% reduction in LC-related mortality with LDCT screening compared to standard chest radiography [7]. Evidence supporting this screening strategy was further supported by the NELSON (Nederlands-Leuvens Longkanker Screenings Onderzoek Trial), Pan-Canadian Early Detection of Lung Cancer Study, and UK Lung Cancer Screening Trial [8,9], leading to recommendations for screening high-risk individuals and the implementation of LC screening programs in North America and Europe [10].

The efficiency of LC screening programs relies on the optimization of the risk-benefit ratio and ensuring high participation rates within individuals with a higher risk of LC. Efforts to improve screening uptake within these groups are necessary as the preliminary uptake rates from pilot programs in the United States, Canada, and Europe were suboptimal, with only 4% to 13% of eligible individuals enrolling in LC screening [11,12]. Recent scoping reviews identified the barriers to LC screening uptake, with the most important barriers being the lack of awareness of screening programs, perceived smoking-related stigma, socioeconomic difficulties, and fear of receiving a cancer diagnosis. Furthermore, individuals facing these barriers have concomitantly higher risk of LC [13,14]. For example, in Canada, the highest rates of LC are clustered among individuals living in rural areas with lower socioeconomic status, who also have lower access to screening programs for those geographical and socioeconomic reasons [15,16]. Strategies to reach those most socially disadvantaged groups are thus imperative to guarantee the efficiency of LC screening.

Survivors of LC are empowered with valuable knowledge on their disease's trajectory, from diagnosis to treatment. By sharing their stories within their communities, they can empower other individuals in similar health states. Due to a combination of both genetic and shared risk factors such as smoking or exposure to radon, individuals with a first-degree relative with a history of LC have a 2- to 3-fold higher risk of LC compared to the general population [17]. In a qualitative study, among individuals eligible for LDCT screening per the US Preventative Services Task Force, Roth et al [18] demonstrated that having friends or family members being treated for LC was a major motivator for being screened themselves.

So far, no previous studies have examined the impact of using survivors of LC as sources of education and referral for peers and family members who may be eligible for screening. We hypothesize that survivors of LC would be willing to refer family members or peers to LC screening, leading to a positive impact on the uptake of both the preventative and screening behaviors of the referred population. This study thus aims to determine the feasibility and acceptability of referral to LC screening through patients with LC referring their close ones to LC screening and to assess the early impact of this novel recruitment strategy on the uptake of LC screening and the patients' outcomes.

Objectives

We aim (1) to examine if patients with LC are willing to refer family members or close contacts to LC screening and if referral is associated with increased patient activation; (2) to examine if targeted enrollment of family members or close contacts of patients with LC for LC screening leads to increased engagement of individuals at higher risk of LC compared to referral through usual care; and (3) to examine the barriers and facilitators on the uptake of preventative strategies and LC screening, based on perceived genetic and clinical LC risks.

Methods

Study Design

This is a prospective cohort study of 2 separate cohorts.

Participants Eligibility and Recruitment

Cohort 1

The first cohort includes biopsy-proven patients with LC aged older than 18 years at various stages in their disease trajectory, including those undergoing clinical surveillance. Participants in cohort 1 are recruited into this study either through discussion with trained research staff approaching them in the clinical settings or through posters or pamphlets available for viewing in the waiting areas of the clinics. The clinical settings where participants are recruited include the thoracic surgery clinic, pulmonary oncology clinic, pulmonary procedural suites, and chemotherapy infusion centers located at the McGill University Health Centre, one of the largest university hospitals in Montreal, Canada. Recruitment discussions and materials invite these patients to access this study's website [19]. The web page section directed at participants in cohort 1 (Figure 1A) includes educational material on the rationale for LC screening and the methods on how to approach and discuss LC screening with peers and family members.

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Figure 1. Screenshot of the web page for survivors of lung cancer and their close contacts. LC: lung cancer.

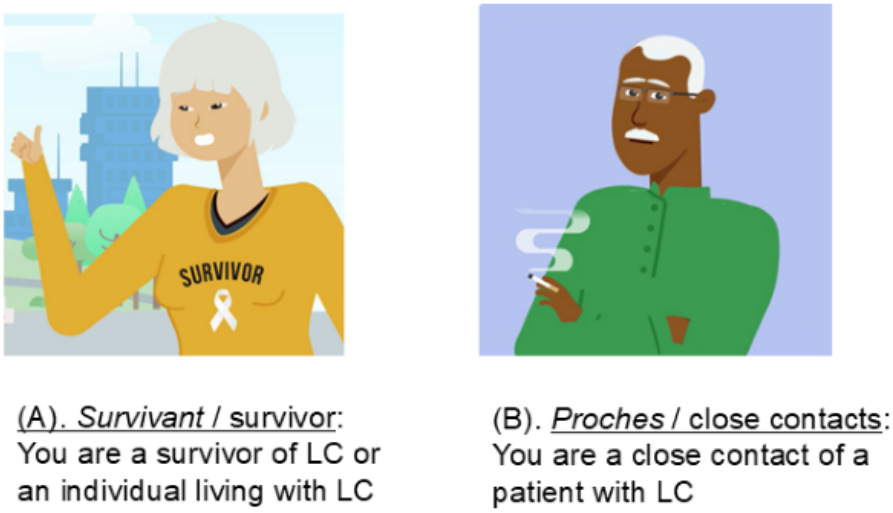

Patients interested can consent and enroll through this study's website using digital or paper forms. Participants are invited to provide contact information (email or phone number) for the close ones they wish to refer for inclusion in the second cohort of our study. They are also advised to inform their close contacts that they shared their details with the research team and that their informed consent will be mandatory before participation.

Cohort 2

The second cohort includes participants being referred for inclusion into our study by the participants of cohort 1. Referred participants should be aged older than 18 years. Individuals with a personal history of LC are excluded. Referred participants are contacted by our research team through emails, phone calls, or through a recruitment pamphlet mailed for those without internet access. Participants are encouraged to access our study's website [19]. The web page section directed at cohort 2 (Figure 1B) provides general information on LC, its epidemiology, information on LC screening programs and the risk-based eligibility, and information on risk mitigation strategies such as smoking cessation and home radon testing. The enrollment of referred participants is also carried out with a submittable digital form available on this study's website. Participants lacking the digital literacy to enroll by themselves are contacted by the research team to enroll over the phone or through mailed material.

Once enrolled, participants have their 6-year risk of LC estimated with the PLCOm2012 (Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial) risk model [20]. The risk prediction PLCOm2012 model has been extensively validated in previous studies [21,22]. The PLCOm2012 model has also shown adequate properties to discriminate patients with LC in a large cohort of Quebec smokers [23]. Moreover, data from the International Lung Screening Trial have shown that the PLCOm2012 model was more efficient compared to the US Preventative Services Task Force 2013 criteria to identify high-risk individuals to enroll into LC screening programs [24]. Participants who meet the eligibility criteria for the provincial LC screening program (ie, aged between 55 and 74 years and PLCOm2012 score ≥2%) are directed toward the provincial LC screening program to complete LDCT.

Website and Educational Material

This study's website [19] and educational material were developed based on 3 main pillars: accessibility, comprehensibility, and inclusivity. First, we succinctly presented information to account for the health literacy level of the targeted population. Individuals at high risk of LC and with lower education levels are significantly less likely to enroll for LC screening and engage in harm-reduction programs [25], underlining the importance of presenting information comprehensible for all. This study's website content was developed in collaboration with current patients with LC with written material created to be comprehensible at a 5th-grade reading level and above. Second, audiovisual contents are more easily comprehensible and with lower decisional conflict when used as a patient decision aid compared to information presented in textual format [26]. The audiovisual format is also more inclusive of participants with very low literacy. In collaboration with the digital media company Tactica Interactive [27], videos were produced to include the textual information of the website in audiovisual format. Lastly, for participants interested in enrolling in this study but lacking the digital literacy to enroll by themselves, information is provided on this study's website to contact this study's research staff (email address and telephone number).

Outcomes

The primary and secondary outcomes are summarized in Table 1.

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Table 1. Study outcomes.

Outcomes	Methods
Primary outcomes	
Number of referred participants per individuals with LC[a] (survivors of LC)	• Questionnaire: cohort 1
Mean risk of LC in the referred population	• Questionnaire: cohort 2 • PLCOm2012 model
Secondary outcomes	
Proportion of participants eligible for the Quebec provincial LC screening program	• Questionnaire: cohort 2 • PLCOm2012 model
Proportion of participants eligible for screening who complete LDCT[b] screening within 18 months from referral	• Provincial health data
Proportion of participants who demonstrate interest in undergoing genetic testing to inform their LC risk	• Questionnaire: cohort 2
Proportion of individuals who demonstrate interest in a smoking cessation program among referred participants who are current smokers	• Questionnaire: cohort 2
Barriers and facilitators in the uptake of LC screening and preventative strategies, based on perceived LC risk	• Focus groups: cohort 1 and cohort 2
Number of visitors on the study's website for referred participants	• Google analytics data

[a]LC: lung cancer.

[b]LDCT: low-dose chest tomography.

Data Collection

Overview

Data are collected using the REDCap (Research Electronic Data Capture; Vanderbilt University) platform [28]. Participants are sent links to complete the web-based questionnaires.

Baseline data collected for all participants include sociodemographic characteristics (age, sex, education level, and ethnicity), health literacy, and smoking status. Health literacy is assessed with the 3-item Brief Health Literacy Screen [29] questions: "How often do you have someone help you read hospital materials?" "How confident are you filling out medical forms by yourself?" and "How often do you have problems learning about your condition because of difficulty understanding written information?" rated on 5-point Likert scales.

Cohort 1

For participants with LC (cohort 1), the phase of LC trajectory (investigative, treatment, or surveillance), tumor stage, performance status (as defined per Eastern Cooperative Oncology Group performance status grading), and their relationship to the referred participants are collected. The degree of self-empowerment they experienced by referring peers and family members for LC screening is assessed using the 13-item Patient Activation Measure (PAM) questionnaire [30]. The 13-item PAM questionnaire is a validated instrument to measure patient knowledge, skills, beliefs, and confidence for self-managing health. Patient activation stands as an important pillar of patient-centered care [31], and evidence has shown that being engaged and active in one's own care is linked to better outcomes [32]. For each participant with LC, the number of unique web page visits is quantified using Google Analytics, and the number of referrals per participant with LC is collected. For participants who refer family members only, supplementary questions are asked to explore the potential barriers: "I don't feel comfortable speaking with friends or close contacts about their health"; "I did not want my friends or close contact who smoke or used to smoke feel judged about their smoking"; "I did not want my friends to worry about their risk of LC"; "Speaking about LC screening and/or LC in general brings up negative emotions for me"; "I don't see or speak with my friends or close contacts very often"; and "This study did not help me feel more comfortable discussing the potential benefits of LC screening."

Cohort 2

For referred participants (cohort 2), the web-based questionnaire collects their known personal history of chronic obstructive pulmonary disease, prior exposure to radon or asbestos, smoking habits, and nicotine dependence using the Fagerström Tolerance questionnaire [33]. Data are used to calculate their PLCOm2012 six-year LC risk. The perceived risk of developing LC is assessed by asking "Compared with others your age, what do you think your chances are of being diagnosed with LC during your lifetime?" rated on a 5-point Likert scale. We also assess whether referred participants believe their risk is high or low due to genetics or smoking exposure and which they think is more important in increasing their lifetime LC risk. Generalized anxiety is assessed at baseline using the General Anxiety Disorder 7-item questionnaire (GAD-7) [34], and a question asks if they believe their anxiety is associated with their perceived risk of LC. We repeat the GAD-7 at 28 days after enrollment to assess the impact of the LC screening risk assessment on anxiety levels. Patients will be asked to give their

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consent to access their provincial health records within the 18 months following their enrollment in this study. Extracted data will consist of whether these participants underwent LC screening via LDCT within 18 months after enrollment. No data about the results of the LDCT imaging will be extracted.

Both Cohorts

Focus groups are conducted to explore the perceptions of LC risk (perceptions of genetic risk based on polygenic scores vs perceptions of clinical risk based on PLCOm2012 scores) and their associations with engagement in LC screening and preventative behaviors (such as smoking cessation, radon measurement, and remediation). Qualitative questionnaires and clinical scenarios are presented to this study's participants of both cohorts to explore these themes and elucidate the most prevalent barriers and facilitators toward engagement in preventative behaviors and screening programs. Focus groups will be audio visually recorded and transcribed in verbatims.

Statistical Analysis

Quantitative Analysis

Participants with LC who refer at least one peer for participation will be compared to those who did not refer a peer for participation. To identify the predictive factors of referral, multivariable logistic regression will be used, adjusting for age, sex, educational attainment, health literacy, PAM score, and phase of LC trajectory. The dependent variable in the logistic regression will be referral by patients with LC. Using logistic regression, we will also examine if increased patient with LC activation is associated with increased odds of referral. Chi-square tests and 2-tailed *t* tests will be used for comparisons of categorical and continuous variables.

Referred participants who are eligible for LC screening will be considered as cases. A control group will be selected from patients who were either self-referred or referred by their primary care physician to the Quebec LC screening program and matched by age (1:1). To determine if participants in cohort 2 have a higher risk of LC than the controls, the mean PLCOm2012 scores will be compared using 2-tailed *t* tests in our cohort and in the Quebec LC screening program. The predictive factors of being eligible for LC screening and whether being referred by survivors of LC is associated with increased odds of being eligible will be examined using multivariable logistic regression. We will account for clustering among individuals referred by the same family member using a random effect model.

Spearman coefficients will be calculated to assess the correlations between the actual risk and the perceived risk of LC. Kruskal-Wallis tests will be used to compare actual and perceived risks of LC with different levels of anxiety. Odds ratios and their 95% CIs will be reported. All statistical analyses will be conducted using R (version 4.2.0; R Foundation for Statistical Computing).

Qualitative Analysis

Focus groups consisting of both cohorts will be conducted. For referred participants, the association between their perceived risk of LC based on both their genetic perceptions of risk and their actual clinical risk of LC and undertaking preventative behaviors and screening will be explored.

First, focus groups consisting of both cohorts will be audiovisually recorded and transcribed in verbatims. Responses will be labeled with descriptive codes by 2 independent analysts using NVivo (Lumivero). Interrater agreement and κ coefficients will be calculated to assess intercoder reliability and consensus reached through comparison and discussion within the panel group. The second stage will involve constant comparison, where codes and their content are compared across interviews to discern common and divergent themes. In the final stage, the data will be organized by searching for patterns, variations, and relationships between themes to characterize the entire dataset.

Sample Size

Preliminary data from the provincial LC screening program indicate that 40% of patients either referred to the program by their primary care physician or via self-referral meet the eligibility criteria for LC screening. The McGill University Health Centre receives approximately 800 new patients with LC annually, and the provincial LC screening program receives around 100 referrals each month. With a sample size of 194 referred participants, we will be able to detect a 20% difference in the rates of referral, with a power of 80% and an α value of .05.

Ethical Considerations

This study has been approved by the McGill University Health Centre's Research Ethics Board (MP-37-2023-9041). All participants will provide their informed consent before participation and will be informed that they can withdraw from this study at any time. Informed consent is obtained in either the English or French language through (1) internet-based web forms, (2) phone calls with trained research staff, or (3) completing consent forms in person when approached in one of this study's clinics. To ensure participants fully understand this study's goals when they enroll, three simple comprehension questions are asked being: (1) if this study involves medications (false), (2) if participants will be asked to complete questionnaires (true), and (3) whether they will be asked to refer family and friends (true). If participants have any questions or concerns regarding this study, they can contact our research team via telephone or email at any time (contact information is available on this study's website, pamphlets, and posters).

The REDCap platform used to collect data conforms to the General Data Protection Regulation and Canadian privacy legal and security standards. Access to the REDCap platform is secured with private log-ins and 2-factor authentication. The REDCap database is securely hosted on the Research Institute of the McGill University Health Centre server. No information will be released to unauthorized third parties without prior written approval of the participant except as necessary for monitoring by public health authorities or our institutional research board. Participants will not receive compensation for their enrollment in this study. Those participating in focus groups will be reimbursed on an hourly basis by the Research Institute of the McGill University Health Centre.

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Results

Enrollment in the cohorts was conducted from June 2023 to January 2024, with participants being followed up through July 2025. Overall, we have enrolled 25 survivors of LC who have referred 84 of their close contacts to this study. The results of this study are expected to be reported at the end of 2025 through publications in peer-reviewed journals and presentations at relevant national and international conferences.

Discussion

Principal Findings

This paper describes the protocol of a pilot study examining the acceptability, feasibility, and impact of an innovative strategy of referral using patients with LC as advocates to increase the uptake of LC screening among individuals with high risks of LC. Increasing the uptake of LC screening for high-risk individuals is crucial as early detection of LC with LDCT has proved effective in reducing LC-related mortality by 20% and all-cause mortality by 7% [9]. LC screening with LDCT presents unique barriers that hamper the implementation and efficiency of these programs at the population level. In our study, survivors of LC receive education aimed at increasing awareness and enrollment in LC screening programs. We postulate that encouraging survivors of LC to empower and refer their close ones can not only have a positive effect on uptake rates for LC screening but can also improve patient activation and the psychosocial and clinical outcomes of patients with LC themselves.

LC is clustered among individuals with lower socioeconomic status who often also reside in rural areas [15,16,35,36]. The low screening uptake within these subpopulations has been well-established through prior LC screening programs [37]. Determining eligibility for screening is unique to LC screening and requires more extensive shared decision-making discussions between provider and patient compared to other cancer screening programs. As a result, primary care physicians need to dedicate a significant portion of a clinical visit to an LC screening discussion, which can be time-consuming. These subpopulations often face limited access to health care services while concomitantly having a high burden of clinical comorbidities. Thus, health care visits are both limited in frequency and in time as the other comorbidities may require further investigation. A recent study has shown that 67% of primary care physicians would not engage in LC screening discussions if they expected that the discussion would exceed 8 minutes [38]. Placing the referral burden entirely on primary care physicians appears to be unrealistic. These subpopulations with a higher risk of LC may benefit from this approach of encouraging survivors of LC to raise awareness within their social networks and reduce the burden placed on the providers servicing these groups.

As opposed to other cancer screening programs, such as those for breast, colon, and cervical cancers, there is a robust causal association between LC and “self-inflicted” behaviors in individuals at high risk [39]. This perceived smoking-related stigma has a negative psychosocial impact on high-risk patients, leading to self-blame, guilt, and hesitance in discussing their risk of LC with health care professionals and peers [40]. Smoking-related stigma impacts the patient-provider relationships as patients who smoke tobacco are often hesitant to provide an accurate disclosure of their smoking status to their provider and often demonstrate avoidance to discuss topics such as smoking cessation and investigations for ongoing respiratory symptoms. Prior evidence has also consistently shown that this smoking-related stigma leads to delays in seeking medical evaluation when experiencing the presenting symptoms of LC and limits patient involvement in treatment and survivorship care [41]. In turn, this smoking-related perceived stigma leads to hesitancy in seeking enrollment into LC screening programs. Ali et al [42] explored the barriers among high-risk individuals from enrolling in the UK Lung Cancer Screening Trial and determined that current smokers were significantly less likely to enroll in LC screening than exsmokers or never smokers. Compared to nonsmokers, current smokers were more fatalistic and less likely to consider LDCT for LC screening and also less likely to believe early detection would improve their chances of survival [43]. When exploring methods to mitigate the burden of smoking-related stigma, it emerges that current smokers experience the most empathy and can express their emotions more comfortably within support groups made up of other current smokers with similar “lived experiences” [44]. Using preexisting relationships as a forum for open communication and advocacy can therefore be fruitful. Perceived risk of LC can be an important motivator to help balance the negative effects of both practical and emotional barriers and engage in LC screening programs. Interestingly, the perceived risk of LC was positively correlated to the estimated risk of LC in participants from the Pan-Canadian Early Detection of Lung Cancer Study [45]. Furthermore, the perceived risk assessment of LC was associated with higher self-referrals, implying that encouraging individuals to both acknowledge and assess their own perceived risk of LC can be a significant motivator to enroll in screening programs. Using preexisting interpersonal relationships between survivors of LC and close contacts can be fruitful in establishing a forum of open communication to share lived experiences.

This study also aims to show that empowering survivors of LC to engage and motivate close contacts in LC screening and harm-reduction initiatives may have a positive impact on their own clinical outcomes and survivorship. In a recent qualitative study among survivors of LC, the concept of “passing it on”—referring to survivors’ experience with becoming and acting as educators for others—was identified as an important way to address their personal perception of the stigma of LC [46]. Survivors of LC placed significant value on the need to share their stories with their communities, to help family members learn about LC and navigate the health care system. In engaging in a conversation with close contacts regarding LC, they can express how the disease impacted their own well-being from the psychosocial stressors it placed on their mental health, the consequences on their interpersonal relationships, or the physical problems they face daily. Expressing these emotions to their social network may help them feel heard and understood, and in turn, their social network may be more aware and caring of the survivor’s well-being and needs.

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Limitations

This study should be interpreted considering the following limitations. First, the recruitment is conducted in clinical settings based on patients receiving in-person care, either through approaching patients with LC directly or via self-referral to our study's website after viewing study-related posters or pamphlets in the waiting areas of clinics. Patients who receive telemedicine follow-up care (such as teleconsultations with health providers and real-time counseling) are then less likely to enroll in this study. This recruitment strategy may introduce a selection bias with a selection of participants in better health states who can participate in this study, living closer to this study's urban health care center, or with a larger social network that supports them in their travel to this study's site. However, this bias appears limited as telehealth for LC care remains marginal at our institution, as also stated in a review of telehealth in LC during the COVID-19 pandemic [47].

Second, when potential participants are approached in person or view our study's recruitment material in the clinics, those accompanying them are exposed to the same discussion and material. Therefore, the referred cohort may be biased to preferentially include the first-degree relatives of survivors of LC as these are the close contacts most likely to accompany patients to their clinical appointments. Friends or more distant relatives of survivors of LC may ultimately be underrepresented in the referred cohort.

To finish, this study is conducted among a cohort of residents in Quebec, where public health care expenses are covered for citizens. The generalizability of the results is limited to similar populations and health care systems, and caution is needed when generalizing results to other Canadian provinces or countries.

Future Directions

Primary care health providers and mass advertising are the current methods of recruitment to LC screening programs. In Canada and the United States, most participants who are eligible for LC screening are being referred to screening programs by a health provider. Barriers related to health care services access then limit the uptake of LC screening, notably in Canada, where approximately 15% of patients are unattached to a regular primary care provider [48]. This lack of providers per population is even worse in Quebec and is expected to worsen with the current population ageing. Developing new strategies to identify and enroll high-risk individuals into LC screening programs is crucial to ensure the success of implementing those programs and, in the end, to improve the patients' outcomes.

Conclusion

Early diagnosis of LC can improve survival rates, and strategies are needed to engage high-risk individuals in LC screening. We believe that patient advocacy has an important value and could be harnessed to identify high-risk individuals to participate in LC screening. Patients with LC have a unique role to play as advocates, and by sharing their lived experience, they could improve the motivation and engagement in LC screening and preventative strategies for their close ones. This study will provide evidence on the feasibility, acceptability, and early impact of this novel referral strategy. The results will be of interest for public health programs and policies, as well as for clinicians, patients facing LC, and their close ones.

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Conflicts of Interest

None declared.

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Abbreviations

GAD-7: General Anxiety Disorder 7-item questionnaire
LC: lung cancer
LDCT: low-dose computed tomography
NELSON: Nederlands-Leuvens Longkanker Screenings Onderzoek Trial
PAM: Patient Activation Measure
PLCOm2012: Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial
REDCap: Research Electronic Data Capture

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Protocol

Assessment and Intervention for Diabetes Distress in Primary Care Using Clinical and Technological Interventions: Protocol for a Single-Arm Pilot Trial

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Abstract

Background: Diabetes distress (DD) is a common emotional response to living with diabetes. If not addressed, DD can have negative impacts on diabetes management, including the progression to mental health conditions such as depression and anxiety. Routine screening and treatment for DD is recommended, with primary care being an ideal setting given that the majority of people with diabetes receive their diabetes care from primary care providers. However, consistent screening of DD does not routinely occur in primary care settings. Research is needed to understand how to effectively and feasibly integrate DD screening and treatment into routine diabetes care.

Objective: This study aims to (1) design and implement individualized technology-supported DD workflows, (2) evaluate the primary outcome of determining the acceptability and feasibility of integrating technology-based workflows to provide treatment for DD, and (3) evaluate the secondary outcomes of changes in DD, depression, and anxiety (baseline, 3 months, and 6 months) in patients receiving screening and personalized treatment.

Methods: In total, 30 English and Spanish-speaking primary care patients with either type 1 or type 2 diabetes will receive screening for DD during clinical visits and subsequent support from an artificial intelligence (AI)–based health care chatbot with interactive tailored messaging. In addition, the use of electronic consultation with a specialist or referral to a behavioral health provider could occur depending on the severity and source of DD. The use of electronic consultations allows providers convenient and timely asynchronous access to a range of specialty care providers. Health outcomes will be measured through changes in validated screening measures for DD, depression, and anxiety. Digital outcomes will be measured through surveys assessing user experience with technology and system usability, and by system performance data. Qualitative data on acceptability and satisfaction with the clinical workflows and technological interventions will be collected through interviews with patients and clinical providers. Descriptive statistics will summarize quantitative outcome measures and responses to closed-ended survey items, and rapid thematic and content analysis will be conducted on open-ended survey and interview data.

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Results: Workflows for screening and treating DD have been approved and clinical staff have received training on the process. Electronic surveys for screening measure collection have been created. Data from visit screeners will be entered into the electronic medical record during the medical appointment. Recruitment will begin late June-July 2024.

Conclusions: This study is expected to demonstrate the feasibility and acceptability of integrating individualized workflows for DD into primary care. Improving clinical and digital interventions for addressing DD in primary care can provide alternative care options for busy clinical providers. This study is intended to deliver whole-person diabetes care to people with diabetes within a primary care setting.

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KEYWORDS

diabetes care; diabetes distress; primary care; healthcare chatbot; artificial intelligence; eConsult; care pathways; clinical workflows

Introduction

Backgrounds

In the United States, diabetes is the eighth leading cause of death [1], with an estimated 38 million people living with diabetes [1]. This chronic condition requires consistent care for effective management to help avoid poor health outcomes [2]. In fact, it is estimated that people with diabetes spend over 8000 hours per year managing their diabetes outside of medical settings [3]. Diabetes distress (DD) is the disruptive and demanding emotional response to these daily demands of living with diabetes [4]. This emotional burden associated with diabetes is pervasive, with one in 4 people experiencing severe DD [4]. DD is associated with negative impacts on engagement in self-care and self-management behaviors, medication adherence, and exacerbation of mental health conditions [5].

Accordingly, the American Diabetes Association recommends that diabetes care be delivered by an interdisciplinary team with a person-centered approach [6] and that it includes regular screening for and monitoring of DD in routine diabetes care for people with diabetes with treatment for DD to be provided by practitioners with specific training to address DD [5]. In addition, a recent white paper by the National Committee for Quality Assurance suggested having a variety of pathways to tailor DD treatment for individuals who screen positive for DD by involving relevant health care professionals and care modalities [7]. Yet, in everyday clinical settings, DD is infrequently identified and only a small number of people with diabetes are asked about how diabetes affects their life by their health care professionals [8]. As primary care is where most people receive their diabetes care, it is a crucial setting within which to assess and address DD [9,10]. However, there remains a lack of consistent screening for DD within primary care, which likely contributes to the emotional burden of diabetes going undetected and untreated [4,11]. Thus, even though DD is highly prevalent and there exist well-validated measures to assess for DD, there is a significant knowledge gap in best practices for implementing DD screening and treatment interventions systematically in primary care. Intervention studies specifically aimed to treat DD have largely been conducted in specialty care settings and not in primary care [5]. Further, among health care providers there remain a lack of awareness of DD and a shortage of trained health care providers who feel adequately equipped to assess for DD and intervene when a patient is experiencing DD [12]. Consequently, there is a clear need to develop scalable and feasible workflows and interventions that can be easily incorporated into primary care settings. Implementing assessment and treatment for DD is a crucial part of incorporating the psychological and emotional aspects of living with diabetes into routine diabetes care. It is part of intentionally incorporating the often-forgotten about psychological and emotional aspects of diabetes care that comprise whole-person care.

Clinical decision support systems (CDSS) have proven effective in prompting providers to deliver recommended care [13]. In general, CDSS improves health care delivery through the use of technology to enhance clinical decision-making, sometimes even using data and observations that are normally unobtainable by providers alone [14]. Clinical decision support technology leverages electronic health records (EHRs), medical knowledge databases, and algorithms to provide patient-specific recommendations, thus enabling providers to make more informed decisions [15]. Benefits can include a reduction in medical errors, enhanced patient safety, improved decision-making, and scalability [15]. The recent integration of artificial intelligence (AI) into health care technology has led to the classification of CDSS as either knowledge-based systems using traditional technology frameworks, or nonknowledge-based systems to indicate the use of AI to transform data into information for the user [16]. Recent reviews of studies that focus on the implementation of nonknowledge-based CDSS in diabetes care have demonstrated significant improvements in patients' blood glucose, blood pressure, and lipid profiles in 71%, 67%, and 38% of the studies, respectively [16]. Technology-based referrals to specialty care electronic consultation (eConsults) have been shown to successfully augment and support care provided in the primary care setting without requiring patients to leave their medical home. Curated health chatbots are an interactive, patient-focused approach to providing patients with important information in an empathic manner at the time of need and point of inquiry, without requiring appointments or waiting for return calls from highly burdened health care professionals. While CDSS can promote diabetes care by facilitating patient self-management, it is hoped that further emerging technology will allow for more efficient and effective management for many people living with diabetes [16].

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Research examining the treatment of DD indicates that when DD is specifically targeted that it can be improved, which is important given that DD is known to worsen over time if it is not addressed [17]. eHealth interventions providing support for DD have shown promising results. For instance, a systematic review and meta-analysis concluded that eHealth interventions were effective at significantly reducing DD and that these reductions occurred across a range of different eHealth interventions (eg, telehealth, web-based, and mobile health) [18]. While the eHealth interventions were found to reduce DD, the authors of the meta-analysis indicate the results be interpreted with caution because of the low number of studies included in the review [18]. Additional research delivering DD interventions through flexible and affordable eHealth avenues requires further exploration. This study is intended to build upon previous research suggesting that digital interventions could provide an avenue for treating DD.

Objective and Aims

The primary objective of this study is to assess the feasibility and accessibility of using health IT integrated into primary care workflows to improve screening and treatment for DD. This project will examine the technical and operational feasibility, patient and provider experience, and behavioral health outcomes of a new technology-supported workflow to conduct screening for DD and provide follow-up treatment by a multidisciplinary team in a primary care setting.

The aims of this pilot study are to (1) design and implement individualized technology-supported DD workflows, (2) evaluate the acceptability and integration of technology-based workflows to provide treatment for DD, and (3) evaluate the change in DD (baseline, 3 months, and 6 months) in patients receiving screening and personalized treatment for it. Symptoms of anxiety and depression will also be evaluated. The primary outcome of this study is to determine the feasibility and acceptability of integrating individualized workflows for DD into primary care.

Methods

Intervention Implementation Process

Preimplementation

The principal investigator (PI) conducted a 1-hour practice-level training session for clinical team members including primary care practitioners, medical assistants, administrative staff, and behavioral health providers. The training topics included an orientation to DD, person-first language when working with people with diabetes, a review of the DD screeners, and a brief introduction on how to support patients experiencing DD. This training was informed by expertise from clinical experts on DD. The training also reviewed the clinical workflow for this study and provided the opportunity for staff and providers to ask questions about the protocol.

Implementation

Patients will complete informed consent to participate in the research study. After being consented, they will attend a scheduled diabetes-specific visit with their primary care physician (PCP). The workflow for the diabetes-specific visit is presented in Figure 1. At clinic check-in, front desk staff or a medical assistant (MA) will provide the patient with the appropriate assessment to complete based on their diagnosis, either the Type 1 Diabetes Distress Assessment System (T1-DDAS) [19] or the Type 2 Diabetes Distress Assessment System (T2-DDAS) [20]. Clinic staff will also provide the patient with the Patient Health Questionnaire-9 (PHQ-9) [21] to assess for symptoms of depression and the Generalized Anxiety Disorder-7 Scale (GAD-7) [22] to assess for symptoms of anxiety. The PHQ-9 and GAD-7 questionnaires are already part of the rooming process and thus not an addition to the established workflow. During the visit rooming process, the MA will enter the results of the screeners (eg, PHQ-9, GAD-7, T1-DDAS, or T2-DDAS) into the flowsheets in the EHR. The EHR used in this study is Epic. Refer to Table 1 for measure descriptions.

Figure 1. Primary care diabetes distress screening and treatment workflow. AI: artificial intelligence; eConsult: electronic consultation; MA: medical assistant; PCP: primary care physician.

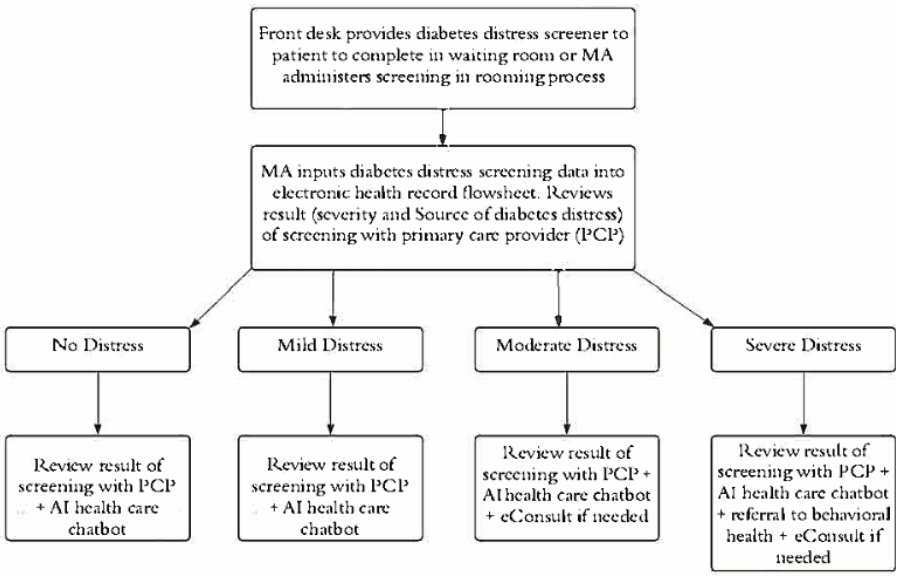

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Table 1. Diabetes distress pilot study measures.

Measure	Description	Collection time points
T1-DDAS[a] [19]	• 30 items; 5-point Likert scale. • Assesses the emotional impact of living with type 1 diabetes. Determines the severity and Source of DD[b]. The sources of DD indicate which aspects of living with type 1 diabetes are creating challenges. • The T1-DDAS was validated with adults with type 1 diabetes and has adequate internal consistency on the Core Scale (α=0.95) and Source Scales (α range=0.53-0.88).	• Baseline (at initial clinic visit) • 3 months post screening • 6 months post screening
T2-DDAS[c] [20]	• 29 items; 5-point Likert scale. • Assesses the emotional impact of living with type 2 diabetes. Determines the severity and source of DD. The Sources of DD indicate which aspects of living with type 2 diabetes are creating challenges. • The T2-DDAS was validated on people with type 2 diabetes including both insulin and noninsulin users. Adequate reliability for the Core scale was demonstrated by alpha statistics for noninsulin users (α=0.94) and insulin users (α=0.95). The Core Scale has statistically significant construct validity with the 7 Source Scale criterion variables (all, P<.001).	• Baseline (at initial clinic visit) • 3 months post screening • 6 months post screening
PHQ-9[d] [21]	• 9 items; 4-point Likert scale. • Brief screener assessing symptoms of depression. Amongst a primary care population, the internal reliability was excellent (Cronbach α=0.89) [21]. • The PHQ-8[e] omits question 9 on the PHQ-9, which asks respondents about thoughts of self-harm or death.	• Baseline (at initial clinic visit) • 3 months post screening • 6 months post screening
GAD-7[f] [22]	• 7 items; 4-point Likert scale. • Brief screener assessing symptoms of anxiety. The reliability of the weighted scoring of the items on the GAD-7 has been estimated at 0.91 with internal consistency estimated at 0.92.	• Baseline (at initial clinic visit) • 3 months post screening • 6 months post screening
UMUX-lite[g] [23]	• 2 items; 7-point Likert scale. • Brief measure assessing participant's experience of technology (ie, AI[h] chatbot). Internal reliability estimates for the UMUX-lite range from 0.81-0.87).	• 3 months post screening
System Usability Scale [24]	• 10 items; 5-point Likert scale. • Brief measure assessing the usability of the technology (ie, AI chatbot). Research demonstrates an average reliability using coefficient alpha to be 0.91. Concurrent validity ratings range from 0.22 to 0.96.	• 3 months post screening
Technology Use Assessment [25]	• A 12-item survey assessing user's comfort with and routine use of technology in daily life.	• Baseline (at initial clinic visit) • 3 months post screening
Practice demographics	• Clinic data (ie, number of patients with diabetes, clinical staff, and roles).	• Baseline
AI Chatbot System Performance Metrics	• Engagement and operational metrics recording during the period of system use.	• 3 months post screening
eConsult[i] System Performance Metrics	• Operational metrics recorded during system use from study-specific standardized templates, including the number of patients receiving eConsults, which specialists were eConsulted, what were the consult questions, the time to respond by the specialist, and did the patient follow up with the specialist if referred.	• 3 months post screening • 6 months post screening
Patient demographics	• Includes age, race, ethnicity, gender, sexual orientation, health care insurance type, and comorbid medical diagnoses if applicable.	• Baseline
Qualitative data-clinical staff	• Semistructured interview and survey questions. • Questions assessing experience implementing new workflows and screening patients for DD from clinical staff. A trained qualitative researcher will conduct interviews over the phone or video call according to the semistructured interview guide.	• 3 months post screening

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Measure	Description	Collection time points
Qualitative data-patients	• Semistructured interview and survey questions. • Questions assessing participants' experience of being screened for DD, using an AI chatbot, and being referred to targeted providers using eConsults. A trained qualitative researcher will conduct interviews over the phone or video call according to the semistructured interview guide.	• 3 months post screening
Diabetes Distress Provider Time Survey	• Survey form tracking the types of tasks and amount of time spent on tasks related to workflow.	• Primary care physician completes following each participant encounter.

[a]T1-DDAS: Type 1 Diabetes Distress Assessment System.

[b]DD: diabetes distress.

[c]T2-DDAS: Type 2 Diabetes Distress Assessment System.

[d]PHQ-9: Patient Health Questionnaire-9.

[e]PHQ-8: Patient Health Questionnaire-8.

[f]GAD-7: Generalized Anxiety Disorder-7 Scale.

[g]UMUX-lite: Usability Metric for User Experience-lite.

[h]AI: artificial intelligence.

[i]eConsult: electronic consultation.

If there is a negative screen on the T1-DDAS or T2-DDAS, the MA will communicate this to the PCP. The PCP will then provide validation and encouragement based on the skills they learned in the team training. The patient and provider will then collaboratively determine which aspects of DD the patient would like to start to receive information and guidance on from the AI chatbot. Even though the patient is not currently experiencing DD, it is theorized that receiving coping skills and other information from the chatbot will help mitigate future distress. The PCP will send these identified areas through the EHR to the research team so they can send push notification from the AI chatbot to the patient's cell phone in these specific areas.

If there is a positive screen on the T1-DDAS or T2-DDAS, the MA will communicate the severity and source of DD to the PCP. On the T1-DDAS there are 10 sources of distress including financial worries, interpersonal challenges, management difficulties, shame, hypoglycemia concerns, health care quality, lack of diabetes resources, technology challenges, burden to others, and worries about complications [19]. The T2-DDAS indicates specific areas or sources of distress that people with type 2 diabetes may experience [20]. On the T2-DDAS there are 7 sources of distress including hypoglycemia, long-term health, health care provider, interpersonal issues, shame or stigma, health care access, and management demands [20]. The research team has developed specific content areas for sources of distress for both the T1-DDAS and T2-DDAS meant to provide targeted and individualized material to support the needs of patients delivered through the AI chatbot. The study design for levels of DD is the same for type 1 and type 2 diabetes. There are three levels of distress on the T1-DDAS and T2-DDAS: (1) little or no distress, (2) moderate, and (3) high. The levels and source of distress will guide clinical decision-making and intervention pathways that are selected. For each level of distress, the PCP will provide validation and support to patients based on skills they learned during the team training. For little to no distress on the T1-DDAS or T2-DDAS, the PCP will discuss the top 3 sources of distress with the patient and the patient will then obtain a push notification on their cell phone from the AI chatbot on these specific areas. For moderate levels of DD on the T1-DDAS or T2-DDAS, the provider will discuss the main sources of distress with the patient and determine if an eConsult or referral might be indicated based on the needs of the patient in addition to the AI chatbot. An eConsult to the following specialists can include endocrinology, clinical pharmacy, social work or care management, diabetes education, and behavioral health. All these specialty providers are available in the primary care practice where this study will occur. For high levels of DD on the T1-DDAS or T2-DDAS, the PCP will collaboratively determine which areas of distress would be more relevant for the patient to receive from the AI chatbot and determine if an eConsult to any of the above-stated specialties would be indicated and then subsequently discuss and provide a referral to behavioral health if needed. Integrating eConsults into the treatment process allows the PCP to ask a specific clinically oriented question about their patient and obtain an asynchronous response from the specialist. Thus, allowing for shared care decisions between the PCP and specialist without having to refer the patient to an in-person appointment and leading to a possible delay in care [26].

AI Chatbot Intervention

All patient participants, regardless of whether they have DD or the severity of the DD, will be enrolled to receive text messages from the AI chatbot. The AI chatbot will provide education on DD, normalization of DD, suggestions for solution-focused coping strategies, and information provision on patient resources and support. For patients not reporting symptoms of DD, chatbot messaging will be seen as a preventative measure to provide information and build awareness of DD should this arise in the future. For patients reporting DD, the AI chatbot will be seen as a resource to provide suggestions for coping strategies connecting to local support resources and psychoeducational material. Following a collaborative discussion with their PCP on the sources of DD that they would like to receive support on, they will obtain a push notification with the top 3 identified areas of distress. Following this initial conversation, the AI

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chatbot will deliver a 12-week curriculum on topics specifically related to DD and the sources of DD (for either the T1-DDAS or T2-DDAS). Participants will receive 3 scheduled text messages on the curriculum content per week throughout the 12 weeks to their cell phone. In between scheduled messages, participants can initiate interaction with the AI chatbot through the text message chain if they choose. Development of the AI chatbot content was overseen and reviewed by DD expert consultants. Participants will not receive messages on topics unrelated to DD or content that was not developed and approved by the study team. In other words, participants will not receive content that is generated by the system or off-topic.

The technology will facilitate error-free delivery of messages via text to user cell phones using an AI chatbot that deploys natural language processing for highly precise communications. We will maximize chatbot precision so that users are more often sent a response from our system that matches the intent of their query. Specifically, we have developed and categorized anticipated "intents"—that is, the specific topics we believe people want to learn or ask about DD and self-management, along with 25-50 variations on ways to ask each question. Question variations allow the system to have enough initial data to learn how to interpret user questions, tolerate misspellings, and recognize the underlying intent of each question. When the system cannot match a response to the question intent, it reverts to a fixed choice (called a "pick list") of responses, for example, "I think you are asking about one of these topics: (1) Cost of diabetes medicine, (2) Cost of treatment, (3) Where to find medications near me. Please type the number corresponding to the topic you wish to explore or try your question again." We rely on data augmentation techniques to create and continuously update a robust library of questions and question variations that the system draws on to generate precise and consistent responses to user queries. We do this through "lemmatization" and "stemming," both processes that group the different inflected forms and stems of a word so they can be analyzed as a single item (eg, runs, run, and running are all forms of the word "run" and thus "run" is the lemma, or root, for all these words). After doing this preprocess work on our prototype dataset, we use Multinomial Naïve Bayes, Linear SVC, and multiclass regression algorithms to anticipate prediction accuracy in correctly matching a response to a question.

eConsult Intervention

The EHR-embedded eConsult system provides a streamlined and timely consultative process that has been shown to improve the quadruple aim-related outcomes and to enhance communication and coordination of care between primary care providers and specialists regarding specific patient areas of concern [27]. The PCP sends a focused question with relevant subjective and objective patient information to a specialist through the eConsult system. The specialist then reviews pertinent information from the EHR and responds to the PCP with guidance and care support with recommendations regarding diagnosis, treatment, and follow-up plans.

Following the patient-specific interaction with the PCP in the diabetes-specific visit, an eConsult with different specialties (indicated above) will be placed through the EHR. The eConsult system is already an established part of routine clinical care since it is embedded in the EHR. eConsults will be used to assist with clinical decision-making and obtaining specialized knowledge and support from various health care professionals based on the specific source of DD. If the patient requires additional support, the eConsult system will allow for a conversion to an in-person or telemedicine visit with the needed specialty.

Poststudy Intervention

Poststudy time point 1 (3 months following initial screening): the research assistant (RA) will send patients a link to complete the screening measures through the patient portal. The screening measures completed at 3 months post screening will assess for DD, symptoms of depression and anxiety, and technology use (refer to Table 1). Outside the clinical setting, the PHQ-8 will be administered instead of the PHQ-9 [28]. The technology measures include the Usability Metric for User Experience-lite (UMUX-lite) [23], System Usability Scale (SUS) [24], technology use assessment, AI chatbot system performance metrics, and eConsult system performance metrics. Qualitative data will be collected at 3 months post screening. Table 1 includes the measures and time points for data collection. The RA will call each patient to conduct a semistructured interview and ask survey questions if patients have not completed surveys electronically within 1 week. The qualitative interview will include questions about participating in screening for DD, experience with the AI health care chatbot and being referred to specialty providers through eConsults. Further, the RA will obtain qualitative data through semistructured interviews and survey questions with 6 clinical staff and both primary care providers who participated in the study. The questions for health care staff or providers will assess their time spent and experience implementing workflows that screen for DD and offer treatment options through provider support, AI health care chatbot, and eConsults.

Poststudy time point 2 (6 months following initial clinic visit): the RA will send patients a link to complete the screening measures through the patient portal at the 6-month time point. The screening measures completed at the 6-month time point are included in Table 1. If patients do not complete the surveys electronically within 1 week, the RA will call to follow up and administer surveys via phone.

Study Design

We propose a pilot clinical trial to be conducted at a suburban multidisciplinary family medicine practice in an academic medical setting. The study is designed to provide feasibility and acceptability data for the development of DD-based screening and treatment using digital and clinical interventions.

Participants

Up to 30 adult English- or Spanish-speaking patient participants with a diagnosis of type 1 diabetes or type 2 diabetes who receive their diabetes care from 2 PCPs at the primary care practice will be enrolled in the study. For Spanish-speaking participants, Qualified medical interpreters are used for translation services that are provided at no cost at the clinic. Qualified medical interpreters are part of routine medical

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services. A sample size of 30 is the minimum generally recommended if the underlying population is expected to have a normal distribution [29]. It is also double the minimum recommended number of persons to be included in human factors and usability testing for medical devices, which allows for loss to follow-up or nonparticipation by some individuals in data collection activities [30].

Clinic staff engaged in the new workflows for DD will also be invited to participate in surveys and interviews about their experience with the technology-supported intervention following the completion of the study. Inclusion and exclusion criteria are mentioned in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Age at time of consent 18-89 years;
- Diagnosed with type 1 or type 2 diabetes;
- Patient at the primary care clinic;
- Able to understand English or Spanish;
- Willing and able to sign the informed consent form;
- Willing to be contacted by the study team through the patient portal, phone, or text to complete study measures;
- Ability to reliably send and receive text messages.

Exclusion criteria

- Participation in another study that might interfere with participation in this study;
- Unable to follow the study procedures for the duration of the study or is deemed unacceptable to participate in the study per principal investigator judgment;
- Participant or participant's immediate family member is an employee of the health care chatbot company providing services for the study;
- Planning to move in the next 6 months;
- Planning to change primary care practices in the next 6 months.

Data Collection and Outcome Measures

Both qualitative and quantitative methods will be used to assess study outcomes at the patient level, practice level, and technology system level. Patient-level health outcomes include DD, depression, and anxiety measured at baseline, 3 months, and 6 months using the T1-DDAS or T2-DDAS, PHQ-8, and GAD-7. The T1-DDAS was selected to be used in this study because it is the most updated and comprehensive assessment tool for determining DD in people with type 1 diabetes. The T2-DDAS was used as a measure because it is the most comprehensive and contemporary survey tool to determine DD among people with type 2 diabetes. The PHQ-9 and GAD-7 are commonly used brief screeners in primary care [21,22]. User experience with technology will be assessed through the administration of the UMUX-lite at 3 months, the SUS at 3 months, and a technology use assessment at baseline and 3 months. The SUS is widely adopted as a reliable measure of usability across technology types and in a variety of populations. The UMUX-lite represents a user experience-focused usability measure that has proven to correlate well with the SUS in overall usability and is appropriate for use with health technologies. The technology use assessment was previously developed by a member of the research team for use in discerning technology adoption and use patterns with primary care patients [25]. In addition, qualitative data from interviews and responses to open-ended survey items will be collected from practice staff, PCPs, and patients to determine the acceptability and feasibility of implementing screening and technology-supported treatment for DD. Interviews will be conducted by a trained qualitative analyst according to a semistructured interview guide, recorded and transcribed using artificially intelligent transcription software (Otter.ai), with human adjudication of transcripts to avoid error (refer to Multimedia Appendices 1 and 2 for interview guides). Positive experiences with the digital interventions will be determined by participant responses to the qualitative interview questions. Further, PCPs will complete the DD Provider Time Survey to track activities and time spent on workflow tasks. Acceptability with the eConsults will be evaluated by standard data collection protocols in the EHR. eConsult data will capture the patient-specific inquiries and requests from PCPs and responses given by specialists. AI chatbot performance data will be collected from the chatbot system and used to evaluate engagement with the AI chatbot according to the People at the Center for Mobile Application Design framework [31]. Table 1 lists the measures to be collected for this study in detail.

A number of the validated measures have existing published versions in both English and Spanish including the T1-DDAS, T2-DDAS, PHQ-8, and GAD-7. For outcomes measures including the UMUX-lite, SUS, and the technology use assessment that did not have an available version in Spanish, we had a system-verified language translator assist in translating these materials from English into Spanish.

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Data Analysis

Quantitative Data Analysis

The study team will use standard statistical packages (eg, R [R Foundation for Statistical Computing]) to conduct data analysis. Descriptive statistics (means, SD, frequency distributions, and proportions) will be used to summarize baseline patient characteristics, clinical and behavioral outcomes, and other quantitative outcome measures and responses to closed-ended survey items. As a feasibility study, it is not powered for inferential analyses or power analyses, but the results are expected to inform future work. Based on results from similar studies, a 60% (18/30) threshold will be used to determine technical and operational feasibility and user acceptability, that is, 60% (18/30) of participants remain engaged with the technology solutions throughout the duration of the study, and 60% (18/30) of participants report positive experiences and satisfaction levels with the program overall [32]. The study has been planned to minimize the amount of missing data overall and thus anticipates the use of maximum likelihood methods to estimate missing values for statistical analysis. We will use this data to calculate an effect size to power a larger study.

Qualitative Data Analysis

This study's acceptance is determined by patient and health care provider user experience through interviews, clinical team member feedback, and responses to user experience surveys. An overall positive rating on tailored survey items or positive themes identified from qualitative data represents acceptability for this study. The program will be deemed acceptable among participants overall if 60% (18/30) or more of participants report positive ratings and themes. Qualitative analysis of open-ended survey data and interview data will be conducted using rapid thematic and content analysis to assess user experience by identifying and exploring common topics and themes that emerge from participants' responses. The rapid analysis will be informed by the Consolidated Framework for Implementation Research and will use a dual-read approach and matrix classification method with 2 reviewers, who will discuss classification decisions to achieve consensus [33]. Enough participants are included in the planned sample size to ensure qualitative analyses will reach thematic saturation overall.

Ethical Considerations

Approval and Study Consent

This study has been approved by the Colorado Multiple Institutional Review Board (protocol #24-0186). The PI and primary care providers will assemble a patient list from the Diabetes Registry in the EHR and send this to the RA. The RA will outreach to potential participants via the patient portal in the electronic medical record, by email, and by phone using scripted language to invite patients to participate. As part of enrollment, the patient will opt-in to receive text messages from the AI chatbot. If a patient declines to participate, this will be documented for evaluation purposes so that the same patient is not reapproached in association with a future scheduled clinic visit. If the patient expresses interest in participating, the research team will complete informed consent and study enrollment before a future clinic visit. As part of the consent process, patients will agree to a chart audit by the research assistant within 4 weeks of their initial visit to ensure all initial measures are completed.

Safety and Potential Risks

The procedures used in the proposed research study pose no greater than minimal risks to patients and practices involved in the study. The AI chatbot is a nongenerative system meaning that it does not independently develop content. The primary clinical team has generated the content and reviewed it with expert consultants on DD. Further, no Protected Health Information is requested from patient participants or sent from the AI chatbot. The AI chatbot operates on HIPAA (Health Insurance Portability and Accountability Act)-compliant infrastructure under a business associate agreement between the health care system where this study is taking place and the AI chatbot company. During the course of this study, patients could experience worsening of their symptoms of DD as a result of interacting with the AI chatbot and discussing the emotional and psychological aspects of diabetes with their medical provider. However, we do not expect that these are likely risks for patients participating in the study in part because messages provided by the chatbot have been prewritten and approved by clinicians and the chatbot is not using in-the-moment generative AI technologies to respond, such that it cannot create separate content or go off-script. If these concerns arise through a review of messages and chatbot interactions or as reported by patients, the PI will review and refer as appropriate to other health care providers for follow-up. The clinic where this study will take place has fully staffed behavioral health providers integrated into the practice who will be available to discuss any concerns that providers and patients may experience.

Compensation

Patient participants will receive a small financial incentive at 2 separate time points. They will receive two US $25 gift cards (totaling US $50). The first US $25 gift card will be given after enrollment in the study and completing the first set of surveys. The second US $25 gift card will be given after completing the 3-month postscreening questionnaires. Providers will receive no direct financial incentive. The primary care clinic where this study will take place will receive a financial incentive for participating in and attending the team training.

Results

Implementation Status

The PI met with clinic leadership to describe the project and obtained buy-in from the team. Workflows were developed that outline study design and patient flow (refer to Figure 1). The PI conducted a team training with the clinic where this study will take place as well as met with the PCPs that will be participating in this study to provide education and training on DD, an overview of validated measures for DD (eg, T1-DDAS and T2-DDAS) and conversational tools that can be used to support people with diabetes and DD.

T1-DDAS and T2-DDAS scoring were incorporated into the EHR through an EHR build. The PI collaborated with the EHR administrative team on requesting the 2 DD measures be

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incorporated into the EHR. This was done during the annual optimization and training period, namely the Epic Sprint program [34]. This program is intended to improve the users' experience of the EHR and assist with updates and requests. The DD measures were built into the EHR as flowsheets so that data could be entered and scored in the EHR.

Chatbot content specific to DD was developed with assistance from 2 leading diabetes psychologists with expertise in DD. The AI chatbot was field tested by the primary research team and the project was reviewed with patients with diabetes through a patient advisory committee including 8 members and feedback was incorporated in refinements of the chatbot content. Key feedback that was incorporated included the frequency of chatbot messages and the time of day that chatbot messages would be sent. The primary research team field-tested the chatbot by sending and receiving text messages to their cellular phones and documented any errors, challenges, or missing content that they experienced. This information was reviewed and discussed with the chatbot vendor and incorporated into the chatbot analytics and content library. The field testing and feedback process was repeated twice.

Recruitment Status

Patient recruitment is anticipated to begin during late June-July 2024. Recruitment will likely take place through January 2025.

Data Collection Timeline

We anticipate that data collection will be completed by July 2025.

Research Status

Institutional review board approval was obtained on March 15, 2024. We have signed contracts with RAs that will be performing the duties of providing outreach to eligible patients, obtaining informed consent from patient participants, and administering screening tools at the 3-month postscreening and 6-month postscreening time points. In addition, RAs will ensure that data collection from patient screeners is complete and documented appropriately. Following 3 months post screening, research assistants will conduct the semistructured interviews and administer the survey questions to both patients and clinical staff. At the 6-month study time point, the primary team will send the remaining screeners to patient-participants. The primary research team has been meeting weekly since November 2023 to develop the research plan and discuss project tasks.

Technology Status

Licensing agreements and institutional risk assessment approval for the AI chatbot were obtained before patient recruitment. The AI chatbot was initially beta-tested by the primary research team and patients with diabetes to determine if messages could be delivered on a schedule and if the system could get replies back. The beta test revealed that additional content related to suicidality and "hating having diabetes" was needed, more training on the model to correctly match intents to the content library was needed, and that more of the intents had existing content in the chatbot library but that improving the link to these was still needed. The clinical research team developed content related to suicidality including providing crisis resources and directions to seek emergency services if needed. The introductory chatbot disclosure message was reviewed and indicated that the chatbot is not a replacement for medical treatment and to contact 911 for medical emergencies. Before the study launch, the primary research team retested the chatbot system to ensure that the updates had been completed.

eConsults are an active clinical care option for PCPs at our institution, fully integrated into the EHR and in use by over 28 specialties [35]. As a result, they are a readily usable aspect of this study. For our study, specialists available by eConsults will include behavioral health, social work, care management, diabetes education, pharmacy, and endocrinology.

T1-DDAS and T2-DDAS were created and incorporated into the EHR as flowsheets. The PHQ-9 and GAD-7 are already embedded in the EHR. The results of the DD screeners will be able to be pulled into visit documentation, facilitating care coordination with eConsulted providers. In addition, flowsheet data can be tracked over time and will be easily accessible for providers to review during and after patient visits.

The chatbot performance metrics will be monitored throughout the course of this study and evaluation of the chatbot functionality is part of the feasibility. The study team will monitor for communication failures and in the event of longer-term impact will contact participants directly.

Funding Status

Funding for this study was secured from the Peer Mentored Care Collaborative in January 2024. The duration of the funding was 1 year.

Discussion

Expected Findings

This pilot study is expected to demonstrate the acceptability and feasibility of implementing screening and treatment for DD in a primary care clinic. Through this study, workflows will be developed and implemented to screen for DD at a diabetes-specific visit. Following screening for DD, patients will engage in a clinical conversation with their PCP about the results of the screening measure. A tiered approach will be used to determine the type of intervention that is suggested to the patient. All patients (regardless of DD screening result) will receive access to the AI chatbot. Patients might also receive an eConsult with another health care specialist (eg, social work, clinical pharmacy, care management, behavioral health, endocrinology, and diabetes educator) to support the specific Source of DD. If levels of DD are in the high range, patients may also receive a referral to a behavioral health provider.

We anticipate that the use of technological interventions such as the AI chatbot and eConsults will be experienced positively by participants. It is expected that participants will view the AI chatbot as beneficial to their diabetes care and will find it easy to use. The semistructured interviews will specifically request feedback on participant experience using the AI chatbot. The use of eConsults will allow PCPs to increase collaborative communication among the interdisciplinary team and provide participants with additional specialty services if needed. Having

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increased coordination among their primary care team will likely be seen as beneficial and helpful to participants. Existing research indicates that specifically targeting DD for intervention has positive benefits on the severity of distress [17]. Further, eHealth interventions for DD have been shown to be effective for improving diabetes-related distress [18].

This study is expected to increase provider and staff awareness and knowledge of screening for and intervening with DD through team and provider training. The training will provide opportunities for learning important psychological and emotional aspects of patients with diabetes that often go overlooked in clinical care. Clinical conversations focusing on the emotional side of living with diabetes are expected to be a new experience for patients in this study. While this might be a new type of clinical interaction, obtaining validation, normalization, reassurance, and empathy from their medical provider will likely be seen as a helpful and rewarding experience. Living with diabetes is a challenging undertaking that under the best of situations requires nuanced interventions from providers and constant attention and monitoring on behalf of patients and their caregivers. Having a supportive environment to discuss challenging lived experiences is intended to improve the emotional burden of diabetes. This finding is anticipated given that emerging evidence suggests that how health care members speak to people with diabetes can impact the development or exacerbation of DD [12].

Even though DD has become increasingly viewed as an important aspect of diabetes care, there remains limited data on treatment approaches. Current literature points to the importance of addressing DD but interventions specifically focused on DD are needed [36]. Most studies do not examine DD as a primary outcome but deliver interventions focused on managing diabetes more broadly [36,37]. This study will provide interventions that are meant to target DD specifically. The primary research team intends to continue pursuing funding opportunities to conduct larger studies in DD assessment and treatment in primary care settings. Future research would expand the assessment and treatment of DD to entire practices involving the whole care team to provide consistency in whole-person diabetes care delivery.

DD significantly impacts clinical, behavioral, and psychosocial outcomes in people living with diabetes. The majority of people with diabetes receive their diabetes care in primary care. However, assessment and treating DD do not routinely occur in primary care settings. The use of several interventions, including supportive dialogue with PCPs, an AI chatbot, and eConsults, will assist in delivering individualized treatment and support for DD without contributing to increased workload for primary care practices. Learning how to provide screening and treatment for DD in primary care settings is crucial to improving the care of people living with diabetes. Health care systems should cultivate environments that promote open discussions about emotional health. This may include training staff to establish a welcoming atmosphere, integrating whole-person considerations into standard assessments, and ensuring that patients feel at ease when sharing their experiences. Embedding the assessment and treatment for DD within primary care workflows is intended to invite providers and patients to consider the broader impact of living with diabetes.

Limitations and Challenges

Given the current state of rapid evolution for AI technologies and associated policies governing AI use in practice, obtaining institutional approval to use AI chatbot technology as part of patient care requires an extensive review process. While health care technology continues to be seen as a scalable and feasible form of care delivery, administrative barriers can make implementation and usage challenging. Overcoming some of these barriers will likely contribute to increased uptake of technology.

Potential barriers to the implementation of new interventions into primary care practices can include lack of leadership buy-in, lack of communication regarding the rationale for the intervention to all practice staff and providers, and workflow barriers. We have thoughtfully approached each of these barriers through our preimplementation work highlighted above, including practice-level training. The PI also met with clinic and health system leadership before the start of the study to secure support for the project. In addition, the study was designed to seamlessly integrate into already existing practice workflows that were being used for depression and anxiety screening. The integration of DD measures into the EHR was intended to further reduce implementation barriers.

Potential barriers to implementing our protocol in other primary care settings include differing resources. Access to eConsults is not universal and alternative protocols would need to be developed depending on practice settings. Furthermore, not all clinics have integrated behavioral health teams easily accessible. It is likely that providers and staff in other primary care settings may also require training on the diagnosis of DD given its emerging status within the spectrum of care for patients with diabetes. The results of this study could help inform what resources (eg, personnel and training) would be needed to successfully integrate DD assessment and treatment into diverse primary care practices.

A potential limitation of eConsult use is the increased, noncompensated workload on primary care providers, who must act on the e-consultant's recommendations for each patient. Primary care is a fast-paced setting that is often stretched for resources, staffing, and time. Further, primary care is a diverse setting with varied access and structures to care delivery. Consequently, it is unlikely that a single approach or method of care is appropriate in all primary care settings. With significant variability in primary care, interventions need to have adequate flexibility to have a chance to be incorporated successfully into this care environment. Feasibility studies offer an opportunity to determine if interventions can be flexibly disseminated into primary care in a scalable fashion. For the AI chatbot, we anticipate a limitation to be the imperfect matching of responses to participant questions. We are mitigating this limitation by setting expectations upfront with participants and using the dataset to iteratively improve chatbot responses over time with use. We chose this curated content route versus an open generative AI approach to minimize potential risks from chatbot hallucination or inaccurate responses.

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Given that this is a feasibility study with a small sample size, and we are not powered for inferential analyses, the results of this study will not be generalizable. However, the results of this study will be used as preliminary data for a larger trial.

Conclusions

Creating and disseminating workflows for screening and treating DD in primary care is an important component for delivering whole-person diabetes care. The use of an AI chatbot to deliver individualized treatment and support for DD and eConsults providing additional specialty support are expected to help increase support and treatment for DD without contributing to an increased workload for primary care practices. This study is intended to help us begin to understand how to implement DD screening and treatment in primary care settings in a scalable and real-world manner.

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during this study.

Authors' Contributions

MK, TKO, and SLM conceptualized the study. EK and JFG were involved in the dissemination of the project. DS and JFT supervised the project and provided feedback. AS assisted with a literature search and adding content to the manuscript. MK drafted the manuscript and designed the figure and table. All authors reviewed and approved the final version of the manuscript.

Conflicts of Interest

TKO has received funding through the University of Colorado for work related to diabetes technology but has no COI related to DD, eConsults, or the use of an AI chatbot. SK has received research money for diabetes technology but no COI regarding diabetes distress.

Multimedia Appendix 1
In-depth interview with patients.
[DOCX File , 35 KB - resprot_v14i1e62916_app1.docx]

Multimedia Appendix 2
In-depth interview with providers/staff.
[DOCX File , 35 KB - resprot_v14i1e62916_app2.docx]

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Abbreviations

AI: artificial intelligence
CDSS: clinical decision support systems
DD: diabetes distress
eConsult: electronic consultation
EHR: electronic health record
GAD-7: Generalized Anxiety Disorder-7 Scale
HIPAA: Health Insurance Portability and Accountability Act
MA: medical assistant
PCP: primary care physician
PHQ-9: Patient Health Questionnaire
PI: principal investigator
RA: research assistant
SUS: System Usability Scale
T1-DDAS: Type 1 Diabetes Distress Assessment System
T2-DDAS: Type 2 Diabetes Distress Assessment System
UMUX-lite: Usability Metric for User Experience-lite

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Protocol

Integrating Virtual Reality, Neurofeedback, and Cognitive Behavioral Therapy for Auditory Verbal Hallucinations (Hybrid): Protocol of a Pilot, Unblinded, Single-Arm Interventional Study

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Abstract

Background: Current treatments for schizophrenia and other psychotic disorders have limited efficacy, with high rates of nonresponse to “gold standard” treatments. New approaches are therefore urgently required.

Objective: The aims of this pilot study are to investigate the feasibility, acceptability, safety, and usability of Hybrid treatment (primary aim); and to explore Hybrid’s treatment efficacy and engagement of treatment targets (secondary aim). The primary aim will be assessed via face-to-face user experience surveys on a (self-assessed) 5-point Likert scale (and qualitative open-ended questions) examining: (1) acceptability, (2) helpfulness, (3) engagement, and (4) perceived safety. We will also examine consent and completion rates, and the number of sessions attended. Our threshold for moving on to efficacy trials will be at least 70% of our participants to rate 3 and above (which corresponds to agree or strongly agree) that the intervention package was acceptable, feasible, and safe. The secondary aims will be assessed by observing whether individuals achieve self-directed modulation of high-β neurophysiological activity (neural target) and progression upwards through the VR-based exposure hierarchy (psychological target), and by assessing symptom change scores. This study developed a new treatment approach for auditory verbal hallucinations, a major symptom of psychotic disorders, that integrates advances in psychological therapy (cognitive behavioral therapy for psychosis), technology (virtual reality, VR), and neuroscience (electroencephalography-based neurofeedback).

Methods: Hybrid takes a “symptom capture” approach using individually tailored VR-based exposure exercises. Participants (N=10) will receive the intervention package weekly over 12 face-to-face sessions. Here, participants will be progressively exposed to symptom triggers and develop methods of downregulating neural activity associated with these symptoms (neurofeedback component) while concurrently receiving clinician-delivered cognitive behavioral therapy for psychosis.

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Results: As of February 2025, Hybrid has commenced (unblinded) recruitment activities from Orygen clinical services in Northwestern Melbourne, Australia. A total of 75 individuals have been approached and 64 individuals have been prescreened (41 individuals were deemed eligible, 15 individuals were ineligible, and 8 individuals declined or did not respond to contact attempts) and 5 individuals have been included in the study. Of the 5 individuals who have commenced the Hybrid treatment, 4 are actively engaged in the program and 1 individual has withdrawn. We expect recruitment to conclude in July 2025 and for the results to be published in 2026.

Conclusions: The Hybrid study is piloting a novel approach that has the potential to address the shortcomings of current treatments for psychotic symptoms. If there is favorable evidence for the acceptability, feasibility, safety and usability of Hybrid, the study team will move on to efficacy trials.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12624000357550; https://tinyurl.com/24ey8hpy

International Registered Report Identifier (IRRID): PRR1-10.2196/63405

(JMIR Res Protoc 2025;14:e63405) doi:10.2196/63405

KEYWORDS

psychosis; first episode psychosis; schizophrenia; virtual reality; neurofeedback; EEG; auditory verbal hallucinations; voices; cognitive behavior therapy; youth mental health; pilot study; paracusias; paracusis; treatment; medication; psychotic disorder; efficacy; neuroscience; psychology; hybrid; adolescent; Australia

Introduction

Overview

Psychosis is the distinguishing feature of schizophrenia spectrum disorders and a frequent manifestation of mood and substance use disorders [1]. It is characterized by alterations in thoughts and perceptions, often taking the form of positive symptoms such as delusions, hallucinations [2], and disorganized thinking [3], as well as negative symptoms such as blunted affect, poverty of speech, and withdrawal from social and occupational activities [4]. First episode psychosis (FEP) onset most commonly occurs in late adolescence and early adulthood [5], with auditory verbal hallucinations (AVHs) being the most prevalent type of positive symptom reported in this clinical population (≈80%) [6,7]. AVHs are typically characterized by hearing voices that are perceived as distinct from the person's own thoughts. Such experiences are often a cause of significant distress and disruption to daily functioning [8], making AVHs an important target for treatment. Furthermore, evidence supports the benefits of early intervention following the first onset of psychotic symptoms with the duration of untreated psychosis (ie, the time between first psychotic symptoms to antipsychotic treatment) consistently predicting poorer long-term outcomes in longitudinal studies [9,10].

Current Treatments for Psychosis

Current treatment recommendations for psychosis include antipsychotic medications, psychosocial support, and psychological treatment, specifically, cognitive behavioral therapy for psychosis (CBTp) [11-13]. Unfortunately, all currently available treatments are only moderately effective. First, the efficacy of antipsychotic medication for the treatment of positive symptoms of psychosis is not optimal. For example, while commonly prescribed antipsychotics can be significantly more effective than placebo, these medications are accompanied by side effects such as weight gain, sedation, and extrapyramidal symptoms which lead to high incidences of patient nonadherence [2]. A 2019 meta-analysis including 16 randomized controlled trials of antipsychotics and >6200 patients with schizophrenia found that 38% (n=2364) of patients met the criteria for nonresponse and two-thirds showed only "minimal improvement" [14]. Second, the effect sizes for psychological treatments, such as CBTp, tend to be small (≈0.4) and limited in long-term efficacy [2]. Both pharmacological and psychological interventions have higher rates of nonresponse [14] and disengagement [15] in patients with earlier onset of illness highlighting the importance of targeting FEP populations and developing effective and reliable treatments for early intervention. New treatment development, both pharmacological and psychological, is therefore urgently required.

"Cold Cognitions"

One of the limitations of psychological therapies such as CBTp may be that they tend to rely on abstract self-reflection (or "cold cognitions") which can be detached from the actual in vivo experience of symptoms (or "hot cognitions") [16]. This limitation may be particularly relevant for young people in the early stages of psychotic disorder, many of whom find it challenging to engage in this form of self-reflective therapy [17]. Borrowing from the "symptom capture" approach used in other mental disorders, the effectiveness of CBTp may be improved if it is applied while the symptom is actively occurring [18] and collaboratively addressing the symptom that has been activated. The benefit of actively eliciting "hot" cognitions has been demonstrated in the treatment of anxiety disorders and obsessive-compulsive disorder (OCD) [19]. In these disorders, "exposure and response prevention" (ERP) is a key feature of gold-standard psychological treatment [20]. This therapeutic approach involves actively eliciting a degree of anxiety by exposing the patient to symptom triggers and addressing the cognitive and behavioral reactions together with the therapist. Once a degree of mastery and tolerance has been achieved over a low-level, anxiety-inducing trigger, the patient and therapist collaboratively proceed to higher levels of an exposure hierarchy.

Virtual Reality

One advance in technology that may help anchor treatment to the in vivo experience of symptoms is virtual reality (VR). VR

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is an interactive computer-generated experience in which the user wears a headset that immerses them in a simulated environment. The VR system is able to create sensory illusions that mimic reality and elicit brain and behavioral responses that parallel those that occur in the real world [21]. VR environments have been found to be useful in the treatment of mental disorders such as social anxiety (for review see Chard and van Zalk [22]), phobias (for review see Kothgassner et al [23]), posttraumatic stress disorder (PTSD; for review see Maples-Keller et al [24]), and as a treatment of psychotic symptoms such as paranoia [25] (see Valmaggia et al [26] for review). Similar to cognitive behavioral therapy (CBT) for anxiety and OCD, this therapeutic technique is founded on exposure principles, where a person is presented with feared, anxiety-provoking, or symptom-inducing stimuli in a graded manner within a controlled environment to enable them to gradually develop strategies to cope when triggers arise in the course of daily life. VR studies for PTSD have found that immersion (ie, a subjective sense of presence in the VR environment) and personalization of the VR environment (ie, tailoring the VR environment to the person's specific and idiosyncratic triggers) may lead to better outcomes, as therapy is more likely to generalize to real-world situations [27]. Indeed, a meta-analysis of VR-assisted exposure therapy for anxiety disorders showed a large overall effect size for VR exposure therapy compared with (mostly waitlist) control conditions (Cohen d=1.11, SE 0.15, 95% CI 0.82-1.39) [28]. Furthermore, research on the use of VR for psychosis treatment has indicated the approach can be feasible, acceptable, and effective for improving some symptoms including positive symptoms such as paranoia and hallucinations [29].

For the specific treatment of AVHs, the small number of VR trials to date have all involved avatar therapy, a related approach that involves the creation of a computerized, audio-visual avatar that mimics the hallucinated voices normally experienced by participants, either on a computer screen [30] or using a head-mounted display [31,32]. During these sessions, the participant is supported by the therapist to engage in a dialogue with the created personalized avatar and to develop strategies to respond to the voices. At the same time, the avatar voice and expressions are gradually adjusted from their normal content/tone (eg, abusive) to be friendly and supportive, controlled by the therapist [33]. A 2020 meta-analysis showed favorable results for avatar therapy in patients with schizophrenia compared with supportive counseling on measures of mental state, level of insight, and quality of life [34]. However, while avatar therapy involves artificially recreating an analog AVH experience, the use of the VR environment to elicit symptoms naturally (as is used in traditional ERP treatments) has not yet been explored.

Neurofeedback

Another technological advance, neurofeedback, has proven useful in the treatment of a number of disorders and has shown promising results for psychotic symptoms [35,36]. Neurofeedback is a technique in which individuals use a brain-computer interface to control their own brain activity by receiving real-time feedback on their neural activity. Neurofeedback has most commonly been provided via electroencephalography (EEG) or real-time functional magnetic resonance imaging (rtfMRI). In an example of EEG neurofeedback, individuals receive real-time information on their brain activity, often presented as a bar graph, where the height of the bar represents the power of oscillatory activity in a given frequency band (eg, α or β) measured in terms of power (ie, amplitude squared). This visual display allows participants to try to gain control over their brain activity by manipulating the visual feedback. Participants are typically provided with directions or mental techniques to control their brain activity, are encouraged to apply and adapt their own strategies, and to use the visual feedback display as a guide [37].

The ability of healthy individuals to manipulate their neural activity using neurofeedback has repeatedly been demonstrated [38-40] and is suggested to have positive impacts on cognitive and emotional domains, including the improvement of working memory [40], intelligence [38], and identification of emotional prosody [41]. This has led to neurofeedback's clinical application to a range of psychiatric or neurological disorders, with meta-analyses reporting benefits for attention deficit hyperactivity disorder [42], depression [43], PTSD [44], subclinical OCD [45], and epilepsy [46]. The findings in patients with medication-resistant epilepsy are particularly striking, with neurofeedback demonstrating efficacy in averting seizures once patients learn to anticipate their onset, and with a transfer effect evident even years later [42,46].

The use of neurofeedback in psychotic disorders is increasing in popularity, with a small number of studies published to date (for review see [36]). All studies have found that patients with schizophrenia were able to self-regulate their neural activity, although evidence for a transfer effect (that is, the ability of participants to employ the strategies they have learned during neurofeedback to control their neural activity in the absence of neurofeedback) has yet to be clearly demonstrated. A particularly promising study using rtfMRI indicated a transfer effect for patients with schizophrenia with treatment-refractory AVH after a 2-week training period [47]. Interestingly, the posttraining increase in functional connectivity between brain regions associated with AVH (the left superior temporal gyrus and inferior prefrontal gyrus) was associated with a reduction in AVH symptoms over the training period. As Nan et al [48], recently concluded, "these positive outcomes suggest that such intensive neurofeedback training may provide new insight into the treatment of schizophrenia and thus deserves further study to fully examine its scope."

While rtfMRI-based neurofeedback (like that used in the aforementioned study) can be costly and uncomfortable (due to the space restrictions), EEG-based neurofeedback offers the benefits of portability, cost-effectiveness, and higher patient acceptability. EEG has the further advantage of capturing oscillatory dynamics associated with neural functioning, which cannot be detected using functional MRI owing to the slow temporal latency of the hemodynamic response [49,50]. For patients with FEP, studies on EEG frequency bands (α: 8 to 12 Hz; β: 13 to 30 Hz; θ: 4 to 7 Hz; δ: 0.5 to 4 Hz; low γ: 30 to 50 Hz; and high γ: 50 to 90 Hz) have reported several abnormalities across all 6 bands [51]. Oscillations in the high β band range (approximately 18-30 Hz) are associated with autonomic nervous system hyperarousal and anxiety, which are recognized

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as one of the most common subjective features of AVH [52,53]. Previous studies have found that reducing high β band activity (and hyperarousal) is associated with a decrease in psychotic symptoms in patients with schizophrenia, including AVH [48,54,55]. Thus, the use of EEG-based neurofeedback targeting high β band activity represents an important target for the treatment of AVH.

The Hybrid Study

This study, Hybrid, will investigate the potential of a novel treatment approach to AVH in young people with FEP that, if successful, could be incorporated into an individual's broader health care program. Our integrative model combines psychological therapy (CBTp), new immersive technologies (VR), and neuroscience (neurofeedback) in an individualized symptom capture (or ERP) treatment approach. The term "Hybrid" is used to reflect the integrated approach of treatment where each element has been selected to strengthen the effectiveness of the treatment regime as a whole.

A pilot study is required to investigate the following aims: (1) to determine whether Hybrid is feasible, acceptable, and safe; (2) to examine participants' experience of the intervention package and whether it can be modified to increase probability of clinical utility; (3) to explore if there is a signal of clinical benefit in response to Hybrid treatment; and (4) to examine whether Hybrid engages specific neural (modulating high β band activity) and psychological (moving up a symptom-eliciting exposure hierarchy) targets (proof of concept). Hybrid will be an unblinded, single-arm intervention study.

Methods

Participants

Ten participants with a diagnosed FEP will be recruited via telephone from Orygen's Early Psychosis Prevention and Intervention Centre, headspace youth mental health services, and the Orygen Clinical Trials Unit database which serve the Northern and Western suburbs of Melbourne, Australia. Help-seeking participants with FEP from the community will also be recruited. Recruitment will involve phone calls, email, and SMS contact with potential participants. Participants will receive a manually initiated reminder SMS or phone call the day before participation sent by the study clinician or research assistant.

Inclusion Criteria

The inclusion criteria are as follows:

- Aged 15-26 years inclusive.
- Sufficient fluency in English to engage in psychological therapy with an English-speaking therapist, and to understand the study assessments.
- Ability to give informed consent and adhere to study procedures. Parental or guardian consent will be obtained for participants younger than 18 years.
- Psychotic threshold AVH in lifetime as measured by the Comprehensive Assessment of At Risk Mental States (5 or 6 on the severity and ≥4 on frequency for longer than 1 week [56]).
- A rating in the past year of ≥1 on the Psychotic Symptom Rating Scales hallucinations scale [57], corresponding to voices occurring at least once/week. The purpose of this is to ensure that participants with reasonably frequent hallucinations are included in the study, as the experience of symptoms during Hybrid sessions will optimize the study's test of outcomes of interest.

Exclusion Criteria

The exclusion criteria are as follows:

- Documented history of head injury, seizures, or other significant neurological illness.
- Documented history of intellectual disability.
- Visual impairment precluding the ability to view VR scenarios.

Ethical Considerations

Ethics approval for Hybrid has been obtained from The Royal Melbourne Health Human Research Ethics Committee (number 2022.116). This study has ethics approval via the Melbourne Health Human Research Ethics Committee (HREC/76936/MH-2022) for research involving humans and access to patient medical records and information. Participants (or their caregiver/guardian if younger than 18 years) must provide informed consent to participate in the Hybrid treatment. Participants are free to withdraw at any time, with the knowledge that doing so has no impact on their routine treatment. All data from the study is deidentified and only the study investigators have access to this information. This means that each participant's data will have a unique code which only the study team members will have access to. Each participant will be reimbursed AUD $50 (US $31.72) per research interview visit as well as AUD $20 (US $12.69) per EEG recording session.

Data Management and Imputation Strategy

To address attrition or missing values, we will code these as "N/A." The current follow-up protocol is designed to maximize data collection; however, if the missing data are substantial, we will apply multiple imputation methods.

Key Components of the Hybrid Treatment Model

Psychological Therapy

The CBTp approach used in Hybrid relies on hierarchical exposure principles in order to trigger cognitive and affective reactions that occur while experiencing symptoms, that is, "hot cognitions" during symptom activation [58]. As outlined above, this approach may maximize the impact of psychological therapy, as has been observed in other disorders.

Virtual Reality

The VR paradigm that will be used to elicit AVH is inspired by Stinson et al [59] who used a real-world setting comprising computer-generated characters of both sexes and several ethnicities and background sounds simulating the environment. Our VR approach is based on the CBTp framework, beginning with developing a shared understanding (functional analysis) between the participant and therapist of the antecedents of

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hallucinatory episodes (eg, presence of other people and lack of meaningful activity) and habitual responses to them (eg, talking back to voices, avoidance). The participant and therapist will then select a template scenario from preexisting VR environments (eg, supermarket and bedroom) developed in consultation with a small group of current and previous service users. Various aspects of the VR environment will be modified to personalize it for the antecedents the individual has identified and to create a hierarchy of symptom-provoking situations. These will include such aspects as the number of people present, proximity and gaze intensity of people, context (interpersonal interaction, indoors, outdoors, time of day or night), sounds, and the presence or absence of "safety strategies" to manage symptoms (eg, mobile phone). For each participant, there will be 5 scaled variants of the personalized scene graded on a 0-100 scale of subjective distress (ranging between 0 and 20 [low], 21 and 40 [moderate], 41 and 60 [high], 61 and 80 [very high], and 81 and 100 [severe]). There are a number of benefits of the VR approach. (1) It provides a controlled environment that can be stopped at any moment, which is not always feasible in real-life exposure settings. (2) It can be designed in a manner that is highly personalized to the individual, which may maximize therapeutic potential. (3) It is a treatment approach that may be particularly suited to young people, given its engaging and interactive nature. (4) It is becoming increasingly feasible for translation into clinical services, given the dramatic reduction in the cost of VR equipment and the fact that VR devices are becoming increasingly portable.

Neurofeedback

EEG will be used to provide real-time neurofeedback to participants while experiencing AVH.

EEG will be acquired using the Muse Headband 2 attached to the Oculus Rift S VR headset. The Muse Headband 2 acquires EEG via 4 electrodes placed over the prefrontal (forehead) and temporal-parietal areas of the brain (electrodes AF7, AF8, TP9, TP10 in the traditional 10-20 electrode system) and collects data at a sampling rate of 500 Hz (with a fifth reference electrode in the position of FPz). The Muse device has been shown to yield frequency-based components of the EEG signal comparable to the research-grade EEG system Biosemi Active Two with the additional benefit of live-streaming capabilities and neurofeedback integration [60]. In Hybrid, the neural target will be the neurophysiological activity associated with autonomic nervous system hyperarousal, specifically, power in the high β range (18-30 Hz) as discussed above (see below for further details).

Intervention Design

Hybrid consists of a Preparation phase (face-to-face, approximately 2 weeks) followed by an implementation phase (12 weekly face-to-face sessions based on previous VR study designs [31,61-63]). Figure 1 shows a visual representation of the Hybrid intervention design and Figure 2 presents the schedule of assessments.

Figure 1. Hybrid design. CBT: cognitive behavioral therapy; VR: virtual reality.

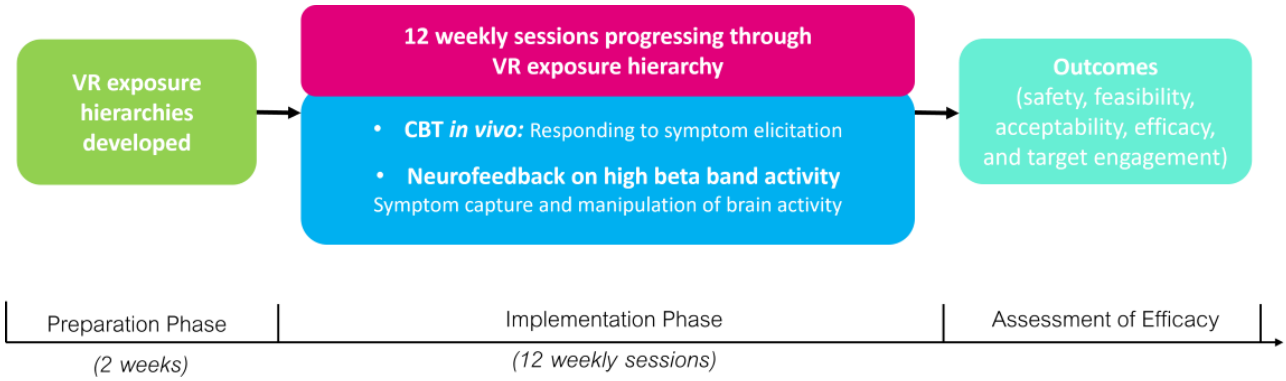

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Figure 2. Hybrid schedule of assessments. BPRS: Brief Psychiatric Rating Scale; CAARMS: Comprehensive Assessment of At Risk Mental States; PANSS: Positive and Negative Syndrome Scale; PSAI: Pilot Study Assessment Instrument; PSYRATS: Psychotic Symptom Rating Scales; SCID-V: Structured Clinical Interview for the DSM-V; SOFAS: Social and Occupational Functioning Assessment Scale.

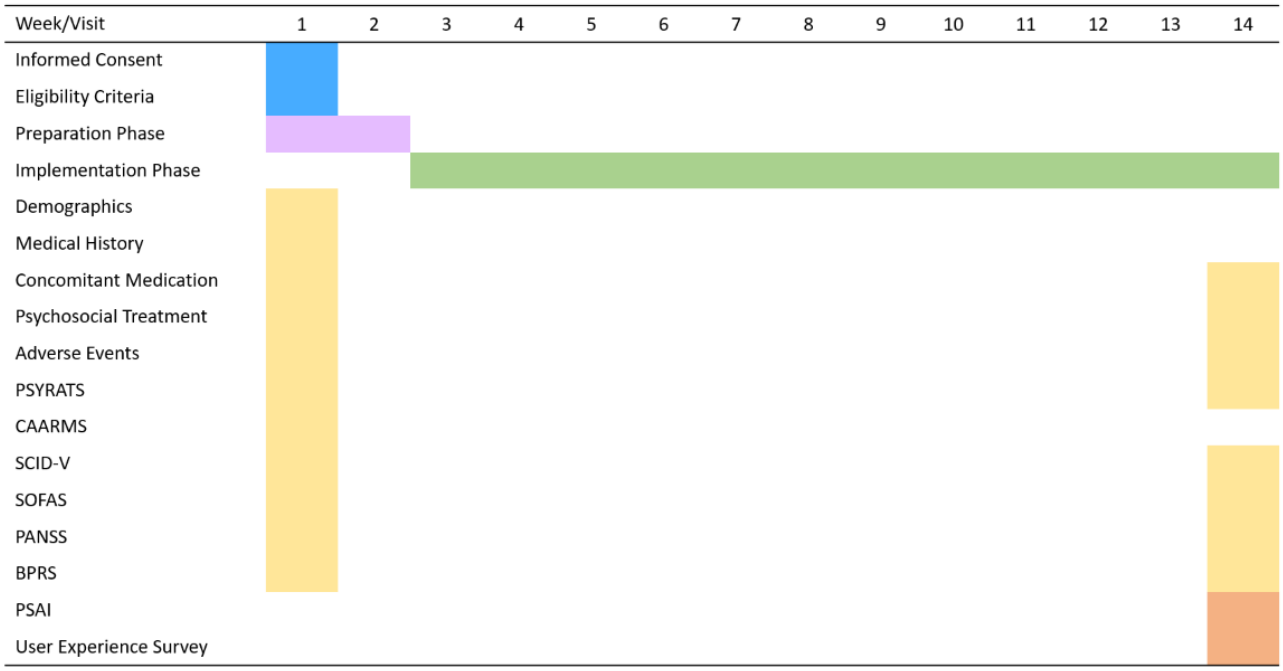

Note: All visits will have a window of ±14 days to maximise participant ability to take part in each visit

Preparation Phase (Weeks 1-2) Development of the VR Exposure Environment

The preparation of the VR exposure hierarchy will be embedded within a CBT framework by using an adaptation of the standard CBT for voices approach [64]. As mentioned above, the participant and therapist will develop a hierarchy of VR environments personalized for the antecedents identified as symptom-provoking. An example of a VR exposure hierarchy is provided in Figure 3. In developing this hierarchy, the participants will rate the degree of subjective immersion ("presence") they felt in the VR environment using the Immersive Technology Centre-Sense of Presence Inventory [65], a widely used measure in this field. VR environments will only be used if they are rated as inspiring at least "moderate presence," as this has been found to increase therapeutic effectiveness [27]. Once the VR exposure hierarchies have been developed, participants will commence the implementation phase.

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Figure 3. Hybrid VR exposure hierarchy example: Shopping Centre template. Example of VR hierarchy exposure levels (left) based on the shopping center template. The participant is exposed to the exposure environments via the VR headset while concurrently speaking with their therapist (cognitive behavioral therapy for psychosis) and receiving neurofeedback of high β band activity via a visual display of a thermometer (right). VR: virtual reality.

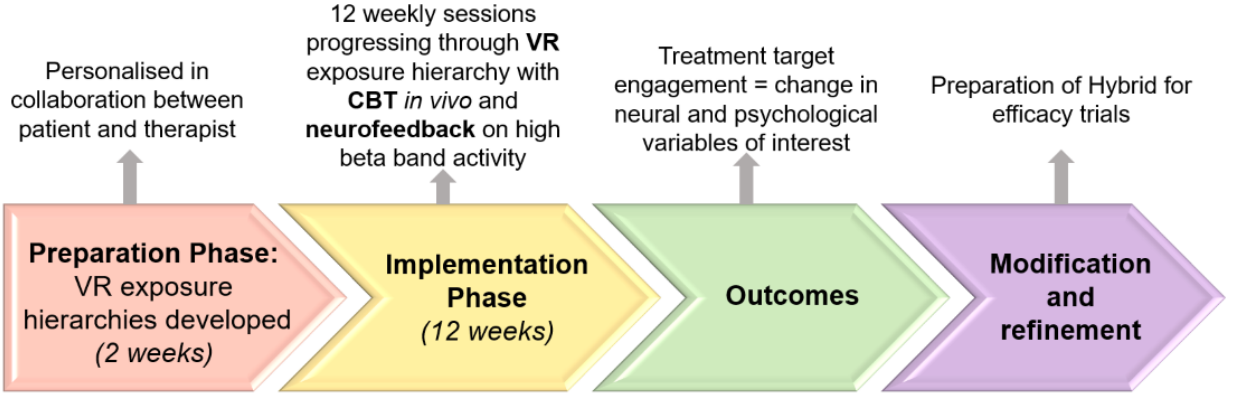

#	Exposure Level	Subjective Distress	VR Environment
5	81-100	Maximum	Crowded shopping center, critical gazes, indistinct noises
4	61-80	Very High	Crowded shopping center, people passing by, looking occasionally
3	41-60	High	Interaction with cashier at checkout, people heard in the distance
2	21-40	Moderate	Walking in supermarket aisles, passing people, supermarket music playing
1	0-20	Low	Leaving shopping center, in car park, nobody around

Implementation Phase (Weeks 3-14)

The implementation phase will consist of weekly sessions delivered over a 12-week period (SD 14 days, Figure 2) and consists of the following two components: (1) CBT in vivo (in response to the VR exposure) and (2) neurofeedback simultaneously presented to the participant via the VR device. The VR apps and sessions can only be accessed by the clinician and administered in person. During these weekly sessions, the therapist will be able to view the VR scenario (via an external monitor) and the neurofeedback thermometer, hear the auditory input, and provide guided assistance to the individual.

Cognitive Behavioral Therapy in Vivo (in Response to VR Exposure)

The participant will start at the lowest level of their exposure hierarchy and progressively work up the hierarchy over the course of the sessions. The standard approach in ERP interventions will be adopted, which is to achieve a reduction in subjective units of distress to 30/100 before progressing to the next step in the hierarchy. While the participant is exposed to the symptom-eliciting VR scenario, they will engage in CBTp with their therapist (the participant will be wearing "open backed" headphones, allowing them to hear the therapist as well as sounds coming from the VR environment). The CBT will be standard, manualized CBT for voices [64,66,67] dealing with the "hot" cognition reactions elicited by the VR scenario. Key elements include reassurance regarding lack of threat, challenging appraisals of AVH (eg, their perceived power, threat, or dominance; reducing submissive or reactive behaviors), actively responding to AVH, and developing a sense of control over AVH by attempting to delay or reduce their volume or distract from them with a variety of strategies (eg, humming and visualization). Sessions will last 30-45 minutes and will be stopped at any point if requested by the participant.

Neurofeedback Simultaneously Presented to Participant Via the VR Device

While the participant is being exposed to the VR scenarios and engaging in CBT with a therapist, they will receive visual neurofeedback of electrophysiological activity (power) in the high β band (18-30 Hz) range as measured via EEG. The neurofeedback will be provided to the participant via a single visual image of a thermometer in the corner of the VR scene (ranging from 0 to 100 "degrees"). The temperature of this thermometer is based on the individual's "baseline" neural activity within the high β band range which is measured at the start of each session prior to entering the VR scenario. The thermometer will increase in "temperature" if high β band power increases. The therapist will inform participants that this thermometer is a visual representation of their current stress levels which will give them a real-time objective indication of how their brains are reacting to the Hybrid therapy. Participants will be instructed to keep their eyes open (so as to remain exposed to the VR scenarios) and to keep the thermometer below the 50-degree reading (ie, "half way"; regulating their neural activity in the desired direction) as an additional motivating goal. In keeping with other neurofeedback studies [18], they will be instructed to devise their own strategy for modulating this neural activity but will be informed that they can discuss different strategies with their therapist. If the thermometer measurement is maintained in the lower half ≥50% of the session time, participants will be made aware of the success of their

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efforts as positive reinforcement at the end of each of their weekly sessions.

Integration of Multiple Technologies in One Innovative Treatment Package

Combining the treatment components in Hybrid will engage multiple treatment targets and possible pathogenic mechanisms (psychological, neurophysiological, and neurobiological) simultaneously. There is also likely to be a synergistic effect through the interaction of the individual treatment components that will make the package more than the sum of its parts. To illustrate, the real-time neurofeedback provided to participants and therapists in response to the VR exposure exercises will feed into the content of the CBT therapy, because the participant and therapist will be able to discuss the direct impact the exposure exercises are having in an immediate, non-retrospective fashion. This preserves the benefits of dealing with "hot" cognitive and affective reactions. In turn, the CBT will assist the young person in developing strategies for modulating their neural activity in response to the VR exposure exercises. Moreover, the neurofeedback will dynamically reinforce and boost the effect of CBT via participants being able to see in real time that the CBT is helping change their brain activity. This will create a salient and durable learning experience, contributing to a "real world" transfer effect and motivating the use of CBT skills in the absence of neurofeedback. This tridirectional impact of the treatment components—the way the individual items work together—will amplify their individual contribution to therapeutic gain.

Measures

Primary Outcomes

Feasibility and Acceptability of the Hybrid Model

A Pilot Study Assessment Instrument developed by Orygen researchers based on the user experience approach will assess (1) acceptability, (2) helpfulness, (3) engagement, and (4) perceived safety. Items are rated on a self-assessed 5-point Likert scale. Acceptability and feasibility will also be determined by assessing consent and completion rates, the number of sessions attended, the number of dropouts, and completion rates of measures. A high rate of elicited AVH is required to facilitate "hot" cognitions so that the symptoms are targeted directly rather than through abstract self-reflection.

Safety of the Hybrid Model

Safety will be assessed by recording adverse events or serious adverse events.

Usability of the Hybrid Model

Assessing the experience and usability of the VR environments was conducted using the user experience survey, a specifically adapted 18-item questionnaire from other Orygen VR studies for this study. This measure will be completed at the end of the Hybrid intervention (week 14 of the study). At this point, participants will also complete a semistructured interview about their experience of the intervention and suggestions for modifications to the treatment package.

Threshold of the Hybrid Model

Our decision to move on to efficacy trials will be based on the user experience survey, which uses a 5-point Likert scale. We will require at least 70% of our participants to rate 3 and above (which corresponds to agree or strongly agree) that the intervention package was acceptable, feasible, and safe.

Secondary Outcomes

Auditory Verbal Hallucinations

The hallucinations scale of the Psychotic Symptom Rating Scales will be used to assess changes in AVH severity, frequency, and distress.

General Psychopathology

The Brief Psychiatric Rating Scale [68], Structured Clinical Interview for the *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) [69], Social and Occupational Functioning Assessment Scale (SOFAS) [70], and the Positive and Negative Syndrome Scale (PANSS) [71] will be used to assess change in general psychopathology and symptoms.

Psychological Treatment Target

The highest level in exposure hierarchies was achieved in each session. For each participant, the final target score of each of these measures will be the average over the 12 implementation phase sessions.

Neuropsychological Treatment Target

This will be operationalized as the difference (ie, change) between the first half and the second half of the VR exposure exercises in average power of high β band activity. A mean score will be used for analysis and will be given by the average change in ratings over the sessions attended.

Planned Analyses

As this study is a pilot study designed to generate initial data to guide future research, a power calculation has not been conducted. A sample size of 10 participants is consistent with similar proof-of-concept and pilot studies [44,48].

Primary Analyses

Means and SDs of acceptability, feasibility, safety, and usability measures and the percentage of participants showing different levels of ratings on the Pilot Study Assessment Instrument will be reported. Thematic analysis of the semistructured interviews will also be conducted. The number of adverse events and serious adverse events will be reported and reviewed.

Secondary Analyses

Clinical Efficacy

Effect sizes, paired *t* tests and Wilcoxon analysis of clinical rating changes before and after the intervention will be computed, which will inform future efficacy trials.

Target Scores

Means, SDs, and 95% CIs of neural (average β band power) and psychological (exposure hierarchy level) target scores will be reported. The magnitude of the changes in both scores will reflect the degree of target engagement achieved. A mean score

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will be used for analysis and will be given by the average change over the first half (mean of weeks 3 to 8) and second half (mean of weeks 9 to 14) of the sessions attended.

Further Analyses

Whether greater engagement of neural and psychological targets is associated with greater change in clinical measures will also be explored. This finding would indicate a treatment mechanism that could be systematically tested in future studies.

Results

As of February 2025, Hybrid has commenced (unblinded) recruitment activities from Orygen clinical services in Northwestern Melbourne, Australia. A total of 75 individuals have been approached and 64 individuals have been prescreened (41 individuals deemed eligible, 15 individuals ineligible, and 8 individuals declined or did not respond to contact attempts). Of the 41 individuals who were prescreened as eligible, 9 individuals consented (16 individuals declined and 8 individuals did not respond) and 5 individuals have been included in the study. Of the 5 individuals who have commenced the Hybrid treatment, 4 individuals are actively engaged in the program and 1 individual has withdrawn. The demographic information for these 5 participants are as follows: aged 21 to 27 (mean 24, SD 2) years; 5 male sex at birth consisting of gender identity of 2 cisgender males, 1 transgender male, 1 nonbinary, and 1 questioning their gender. We expect recruitment to conclude in July 2025 and for the results to be published in 2026.

Discussion

Anticipated Findings

Hybrid introduces a new treatment approach that integrates CBTp with VR and neurofeedback. This integration of treatment components may augment each individual element in such a way that it maximizes the impact of each individual component. We anticipate that this will produce durable skill-building and a “real world” transfer effect that motivates the use of Hybrid strategies in everyday life. In addition, individuals should see a reduction in AVH distress, severity, and frequency as evidenced by symptom change scores at the end of the treatment package.

We predict that Hybrid will be successful in achieving this based on the fact that the treatment package will be as follows. (1) Engaging and acceptable: previous studies have shown that young people in the early stages of psychosis find neurophysiological assessments highly acceptable and the neurofeedback and VR components of Hybrid leverage “gamification” [72,73] (ie, using game design and mechanics to encourage active participation) in the treatment of mental disorders. (2) Easily implementable given the increasingly affordable and portable nature of the tools used in the Hybrid intervention (EEG and VR). (3) Empowering: young people develop self-directed control over their symptoms, as opposed to being an “object” of treatment, which is often how other treatment approaches, such as pharmacotherapy, are experienced [74]. As has been recognized [75] previously, neurofeedback can be a means of “taking back control” of the brain by promoting strategies to manage symptoms that come “from the inside” and can be used at any point in the course of everyday life. (4) Focused on individual symptoms rather than diagnostic categories. This is in keeping with the current trend in psychiatric research away from disorder-bound approaches toward transdiagnostic and symptom-based risk factors [76,77]. Therefore, Hybrid could represent a breakthrough in clinical research for effective treatments for psychosis and, if successful, would significantly improve clinical outcomes in young people with AVH.

In terms of study limitations, we highlight that our use of the PANSS and SOFAS as measures of symptoms and functioning may be suboptimal for fine-grained assessment of symptomatology (such as for the negative symptoms) and function. We note that the main aim of this study is to assess the feasibility and acceptability of the Hybrid treatment and we plan to include additional, more fine-grained measures in future studies. We chose to use the PANSS and SOFAS based on many previous studies in early psychosis populations using these measures and increasing our comparability to previous research [70,71]. Second, our clinical assessments are structured to minimize the burden on the individual, therefore, certain features which may be of significance (eg, past history of trauma or eating disorders) were not assessed, but may affect responsiveness to the Hybrid treatment. In subsequent trials, a more thorough assessment of psychopathology may be included to address this. Finally, by virtue of design, we cannot make inferences about any other symptoms associated with psychosis (eg, paranoia and disorganized thinking) as we were targeting AVH in these efficacy trials. Future studies could expand to target other psychotic symptoms.

Conclusion

This pilot study aims to demonstrate the safety, feasibility, and acceptability, as well as establish proof of concept for Hybrid treatment. This initial study will provide valuable information as to whether the Hybrid treatment protocol could be modified and whether moving on to efficacy trials is indicated.

Acknowledgments

We would like to thank Tamar Wong for his significant contribution to the VR component of the Hybrid study. We also extend our gratitude to Hybrid research participants. The study is funded by an NHMRC Investigator Grant (2026484) awarded to BN.

Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

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Authors' Contributions

JS contributed to writing the original draft, project administration, conceptualization, supervision, and investigation. ER was responsible for reviewing and editing the manuscript. MA-J, IB, ID, SL, JL, NT, AT, GW, and SW were involved in conceptualization, with IB also contributing to manuscript review and editing. LB and JL provided supervision. ID contributed to the methodology. CE and BM handled project administration, with BM also involved in investigation and manuscript review. HPY conducted a formal analysis. BN contributed to conceptualization, manuscript review, and editing, and secured funding.

Conflicts of Interest

None declared.

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Abbreviations

AVH: auditory verbal hallucination
CBT: cognitive behavioral therapy
CBTp: cognitive behavioral therapy for psychosis
DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)
EEG: electroencephalography
ERP: exposure and response prevention
FEP: first episode psychosis
OCD: obsessive-compulsive disorder
PANSS: Positive and Negative Syndrome Scale
PTSD: posttraumatic stress disorder
rtfMRI: real-time functional magnetic resonance imaging
SOFAS: Social and Occupational Functioning Assessment Scale
VR: virtual reality

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Protocol

Assessing Patient-Reported Satisfaction With Care and Documentation Time in Primary Care Through AI-Driven Automatic Clinical Note Generation: Protocol for a Proof-of-Concept Study

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Abstract

Background: Relisten is an artificial intelligence (AI)–based software developed by Recog Analytics that improves patient care by facilitating more natural interactions between health care professionals and patients. This tool extracts relevant information from recorded conversations, structuring it in the medical record, and sending it to the Health Information System after the professional's approval. This approach allows professionals to focus on the patient without the need to perform clinical documentation tasks.

Objective: This study aims to evaluate patient-reported satisfaction and perceived quality of care, assess health care professionals' satisfaction with the care provided, and measure the time spent on entering records into the electronic medical record using this AI-powered solution.

Methods: This proof-of-concept (PoC) study is conducted as a multicenter trial with the participation of several health care professionals (nurses and physicians) in primary care centers (CAPs). The key outcome measures include (1) patient-reported quality of care (evaluated through anonymous surveys), (2) health care professionals' satisfaction with the care provided (assessed through surveys and structured interviews), and (3) time saved on clinical documentation (determined by comparing the time spent manually writing notes versus reviewing and correcting AI-generated notes). Statistical analyses will be performed for each

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objective, using independent sample comparison tests according to normality evaluated with the Kolmogorov-Smirnov test and Lilliefors correction. Stratified statistical tests will also be performed to consider the variance between professionals.

Results: The protocol has been developed using the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist. Recruitment began in July 2024, and as of November 2024, a total of 318 patients have been enrolled. Recruitment is expected to be completed by March 2025. Data analysis will take place between April and May 2025, with results expected to be published in June 2025.

Conclusions: We expect an improvement in the perceived quality of care reported by patients and a significant reduction in the time spent taking clinical notes, with a saving of at least 30 seconds per visit. Although a high quality of the notes generated is expected, it is uncertain whether a significant improvement over the control group, which is already expected to have high-quality notes, will be demonstrated.

Trial Registration: ClinicalTrials.gov NCT06618092; https://clinicaltrials.gov/study/NCT06618092

International Registered Report Identifier (IRRID): DERR1-10.2196/66232

(JMIR Res Protoc 2025;14:e66232) doi:10.2196/66232

KEYWORDS

primary health care; patient satisfaction; artificial intelligence; medical records systems; computerized; patient-centered care

Introduction

Background

In the medical field, medical record writing is an essential task that requires time and accuracy on the part of health care professionals. The medical record, which includes the patient's medical history, any symptoms they have had, treatments performed, and other relevant details, is a critical component in making appropriate medical decisions and ongoing patient follow-up [1].

In the modern health care context, there has been a transition to the digitization of these records, giving rise to the concept of the electronic medical record (EMR). An EMR is the electronic representation of a patient's medical record, created and maintained by health care professionals. This digital approach has not only revolutionized the way medical information is stored and accessed but has also improved the efficiency of medical care by facilitating the retrieval of relevant data at the point of care [2,3]. EMRs provide a centralized platform for medical information management, allowing for more accurate tracking and more coordinated care [4].

Traditionally, health care professionals have spent a significant amount of time writing medical records [5], which can affect the efficiency and quality of care they provide. This manual task is not only time-consuming but can also lead to documentation errors, omissions, or inconsistencies in the information recorded. A descriptive study published in the *Annals of Internal Medicine* in 2020 conducted a detailed assessment of the amount of time doctors spent using EMRs during outpatient visits. In this study, which included comparisons of 1482 doctors, it was found that doctors were actively using EMRs for 43% of the total time they were online [6]. It has also been shown that all this can contribute to an increase in burnout among professionals [7,8].

In recent years, the field of artificial intelligence (AI) has experienced significant advances in natural language processing and speech recognition [9,10]. These advances have enabled the creation of automated tools and systems that can accurately and efficiently transform speech into text. In the health care setting, this technology has the potential to streamline and improve the writing of medical records, freeing up time for professionals to focus on direct patient care [11,12]. However, this technology was necessary but not sufficient, and it was not until the advent of generative AI that a key part of the process could be completed to obtain sufficient quality for practical use [13,14].

Another important aspect is the issue of data privacy and security [15]. The implementation of AI systems in clinical practice must comply with strict regulations regarding the protection of patient health data. This includes ensuring the security of data transmission and storage, as well as compliance with data privacy regulations, and the General Data Protection Regulation [16]. In the case of AI use, these requirements must go further, given the additional risks of training models with data in health care, which in the worst cases can result in data hacking or the inclusion of strong biases in the algorithms [17,18].

Several companies and academic institutions have developed prototypes and pilot systems for the automated writing of medical records from the doctor-patient conversation in English (Nuance DAX, Amazon HealthScribe). These tools use advanced algorithms and AI models trained on large amounts of clinical data to extract and record relevant information [19].

Relisten

In this context, the Spanish company Recog Analytics has developed Relisten [20], an automated clinical note-writing system designed to handle real-world consultations, supporting multiple languages and offering integration with EMRs.

Through a natural conversation between the health care professional and the patient, this AI-powered tool uses recordings to extract relevant fields corresponding to key sections of the medical history in a structured way and then send them to the Health Information System (after correction and approval by the health care professional). A detailed description of the algorithm's architecture can be found in

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Multimedia Appendix 1, providing technical insights into its design and functionality.

Methods

Study Objectives

This study has the following objectives: (1) to evaluate the perceived quality of care reported by patients with the use of an AI-powered solution in the consultation, measured through anonymous satisfaction questionnaires at the end of each consultation (Multimedia Appendix 2); (2) to assess the satisfaction of health care personnel with the care provided in consultations, measured using an anonymous satisfaction survey at the end of the study (Multimedia Appendix 3) and a structured interview; and (3) to assess the time spent by health care personnel on entering records in the EMR, measured by statistical tests comparing consultations with and without the tool.

Overview, Design, and Hypotheses of Study

A proof-of-concept (PoC) analysis will be carried out in the context of a multicenter study, where several health professionals (nurses and physicians) from different primary care centers (CAPs) will use the AI-powered tool in consultations (under informed consent of the patient) and will survey patients and the professionals themselves.

The project is structured in three main phases: (1) preparation: this includes the demonstration and initial training of the participating professionals, the preparation of the technological infrastructure (microphones), and the coordination for carrying out the surveys, with an approximate duration of 2 weeks; (2) development: this consists of the use of an AI-powered solution during consultations, as well as data collection, including audios, clinical notes, and survey results, lasting approximately 20 weeks; and (3) data analysis and presentation of results: this phase involves the processing and analysis of the data collected, followed by the presentation of the results obtained, and lasts approximately 2 weeks.

The measurement of the objectives will be carried out using the following methods: (1) perceived quality of care as reported by patients using an anonymous patient survey after each consultation, in a patient-blinded study (patients are not told beforehand whether the AI-powered tool has been used in the consultation; this fact is outlined by a graphic mark in the surveys in which the tool has been used); (2) satisfaction of health care personnel: an anonymous survey will be conducted at the end of the study. This will qualitatively evaluate the tool's impact on consultations, focusing on aspects such as its general usefulness, ease of use, the quality of notes generated, its perceived ability to improve attention during consultations, and the extent to which it saves time. In addition, the study will incorporate structured interviews with primary care health care professionals (nurses and physicians) to explore their experiences with the tool in depth. The interviews will include questions about the above concepts, as well as at least an additional request to the health care professional to identify limitations and improvements to the tool. (3) Time spent entering information into the EMR. To determine the magnitude of savings, 2 measurements taken during the PoC will be compared: the time the health care professional spends typing in the consultation and the time the health care professional spends reviewing and correcting notes generated by the AI-powered tool.

Figure 1 facilitates the visualization of the development of the study in consultations.

Figure 1. Steps involved in the study workflow.

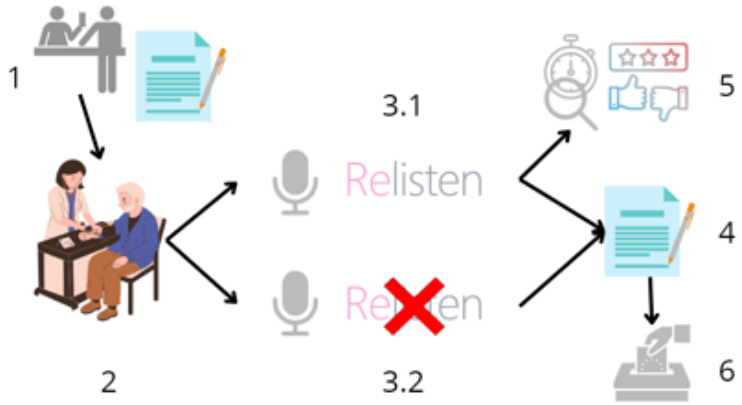

The steps mentioned in Figure 1 include:

1. Patient consent at reception: the patient arrives at the CAP and is attended to at the reception desk, where he or she is given the information sheet and the informed consent form, which he/she will return signed if he/she agrees to participate in the study.
2. Consultation begins: the patient arrives for consultation and the doctor confirms their participation.
3. (3.1) Use of Relisten: the consultation is carried out, alternating between consecutive patients (simple randomization). Recording and using the AI-powered tool to provide full patient care. In this mode, the health professional does not take notes during the consultation and proceeds to step 5.
4. (3.2) Standard documentation: recording it and writing it at the same time in the electronic record as usual. In this mode the AI-powered tool is only used as a consultation recorder to calculate the typing time of the health care professional, using these consultations as a control group.

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5. Note review or writing: the doctor hands the survey to the patient and says goodbye.
6. Satisfaction surveys: the doctor reviews the notes generated by the AI-powered tool, recording the time required for that task directly on the tool's website, copies and pastes them into the electronic record, and rates the notes generated by the tool for that consultation.
7. Anonymous survey submission: the patient deposits the completed survey anonymously in the box provided.

The study team hypothesizes that the use of an AI-powered tool improves the perceived quality of care by allowing health care professionals to spend more time interacting directly with patients and less time on clinical documentation. This translates into more patient-centered care and a measurable improvement in both patient and staff satisfaction.

Setting of the Study

The study population will be made up of patients who are visited in person at CAPs in Catalonia, both in emergency and control consultations, whose professionals (nurses and physicians) participate in the study. The participating primary care centers are CAP Amposta, CAP Centelles, CAP Artés, CAP Sallent, CAP Súria, and the Consorci d'Atenció Primària de Salut Barcelona Esquerra.

Given the nature of the tool and its applicability to most of the practice settings, there will be no previous selection of patients, but any patient who comes for consultation with the professionals participating in the study will be eligible.

Participants eligible for inclusion in the study must have provided written informed consent, be involved in face-to-face medical or nursing consultations conducted in Catalan or Spanish, and be aged 18 years or older.

Participants will be excluded from the study if they are unable to understand the nature of the study, lack fluency in Catalan or Spanish, do not provide consent to be recorded, or if any technical issues, such as internet service downtime, compromise the recording process.

The study included patients in unscheduled visits (emergency), first visits (with history taking), and follow-up for chronic disease.

The SPIRIT guidelines were followed when designing the research (Multimedia Appendix 4) [21].

Sample Size and Randomization

To calculate the sample size, the 2 objectives that require such calculation are considered:

1. For the patient satisfaction surveys, proposed on a Likert scale from 1 to 5, we are faced with the problem of comparing independent samples. Assuming normality in the difference of the samples (a hypothesis that will be verified during the statistical tests), the formula for the determination of the required sample size is the following:

   Where Z_α and Z_β represent the Z-table values for confidence level and test power, respectively, sigma is the SD of the (estimated) differences, and d is the effect size to be measured. For this study, standard values for α=.05 (95% confidence) and β=.8 (80% test strength) are selected, σ=1 is estimated as an extreme case to ensure that the results will be statistically significant, and d=0.25, as the minimum improvement we want to demonstrate. The result is n=395.21 for each group, so we set the number of patients to be analyzed to 400 with the AI-powered tool and 400 without the tool.
2. For time-saving, applying a similar procedure with the same standard values, σ=90 seconds and d=30 seconds, we obtain n=111.15 for each group, so we set the number of consultations to be analyzed to 120 with the AI-powered tool and 120 without the tool.

   Since the groups are the same and there is no interconnection between the measurement of both objectives, it is possible to use the same consultations for both, and therefore the total number of patients required will be the larger of the two above, resulting in n=800 (400 patients with the AI-powered tool and 400 without the tool). The randomization was carried out in a simple format, given the sufficient sample size and the fact that the aim is to validate the hypotheses at a general level, although for information purposes the study also shows intermediate results stratified by type of consultation (first or follow-up) or by a health professional.

Data Collection

The data collection process involves the following:

1. Satisfaction surveys completed by patients at the end of the consultation (with the AI-powered tool as a test and without the tool as a control). The survey will be given to the patient on paper by the health professional inside the doctor's office at the end of the visit. They will be collected anonymously in a box upon exiting the office, in a visible and accessible place. This involves single-blinded data collection (the patient does not know whether the AI-powered tool is being used, although the health care professional does). These questionnaires will be available in Catalan and Spanish.
2. Quality surveys at the end of each consultation by health care professionals, on a scale of 0-10 with the possibility of including open-ended comments, will be carried out directly through the AI-powered tool's digital platform. These questionnaires will be available in Catalan and Spanish.
3. Satisfaction surveys completed by health care professionals at the end of the study, as well as interviews to better understand the impact and limitations in a qualitative manner.
4. Recordings of conversations between the patient and health care professional (Recog will delete the recordings at the end of the study).

These items align with study objectives and are detailed in the Multimedia Appendices 2 and 3.

Qualitative data will be collected using open-ended survey surveys for patients and health care professionals and structured interviews with professionals. These data will be analyzed using thematic analysis.

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The study variables are mentioned in Textbox 1.

Textbox 1. Study variables.

Independent variables

- Indicator of whether the artificial intelligence (AI)–powered solution has been used in the consultation (no typing during the consultation; yes or no)
- Identifier of the health care professional involved (user code stored in the AI-powered tool)

Dependent variables

- Results for each survey question, on a scale of 1-5.
- Time saved during consultations is measured by comparing the writing time in the 2 scenarios: one where doctors manually write notes during the consultation (non–AI-powered audios) and another where they review and correct notes generated by the AI-powered tool. For the non–AI-powered audios, investigators listen to the recordings and measure the exact time the professional spends writing. In AI-assisted consultations, the doctors use the platform to time their note corrections. By comparing these two measurements, the study aims to quantify the time-savings offered by the AI-powered tool, with each recording being analyzed individually for accuracy. This has been chosen because other forms of measurement (such as automatically measuring silences) may introduce greater biases (silences due to circumstances other than note taking) than human interpretation. Although logically it is not a perfect measure either, the savings impact is expected to be sufficiently significant for these random errors to have a very small impact in relative terms.

  In addition, health care professionals are asked to include, through the AI-powered tool's digital platform, possibly relevant comments about the consultation they have just carried out, such as when a consultation has been carried out in multiple languages, with one participant speaking in Spanish and another in Catalan.

Statistical Analysis

The main hypotheses of the study focus on evaluating the reported quality of care and saving time in the writing of clinical notes. To assess the improvement in reported quality of care, the normality of the sample will be checked using the Kolmogorov-Smirnov test with Lilliefors correction. Student *t* test for independent samples will be applied in the case of normality, or an equivalent nonparametric test otherwise. Key survey items, including patient-reported satisfaction with time spent, the attention received, and perceived care quality, as well as health care professional satisfaction with reduced administrative burden, ease of use, and note quality, will be analyzed to test for significant differences.

In terms of time savings, 2 aspects will be measured separately: the relative time (in percentage) that the professional spends writing notes during the consultation without using the AI-powered solution, and the relative time that the doctor spends reviewing the notes generated by the tool. Similarly, the normality of the sample will be checked using the Kolmogorov-Smirnov test with Lilliefors correction, and the Student *t* test or its nonparametric equivalent will be applied as appropriate.

Since the sample is not randomized, a sensitivity analysis will be conducted to account for potential selection bias. All statistical analyses will be performed using RStudio, considering a confidence level of 95% and a statistical power of 80%.

Confidentiality

In this study, confidentiality will be rigorously protected by several procedures. The patient surveys, which will be conducted anonymously upon exiting the consultation, will be transcribed by the Recog staff into a Microsoft Excel file for subsequent analysis, without any identifying data. The audios collected during the consultations will be automatically stored in the AI-powered tool platform, guaranteeing their security by storing them in the S3 (Simple Storage Service) service of Amazon Web Services, with controlled access, encryption, and without identifiers that allow patients to be identified. The professionals' comments will be stored in Amazon Web Services DynamoDB tables, also with controlled access, thus ensuring the confidentiality of all the information collected.

In no case is the objective of the study to train the algorithm with the data obtained, since the algorithm is already trained. The models applied are speech-to-text models, originally trained on multilingual datasets [22] and a large language model trained on generic datasets in multiple languages, public and private, not specified by the model developer. Notes are written in the project and no medical analysis is being performed by AI. The initial tests have shown the correct capability of the complete software for this task, which we seek to validate more extensively with this project. The initial stages of the algorithm use machine learning techniques, such as advanced speech-to-text models for transcription. The subsequent steps, including structuring the extracted information into relevant clinical fields, rely on a combination of rule-based processes, predefined templates, and generative AI models.

Ethical Considerations

This study was approved by the University Institute for Primary Care Research Jordi Gol Health Care Ethics Committee (Code 3/286-P). The research adhered to institutional guidelines for studies involving human subjects, including those requiring the recording of patient interactions and subsequent analysis. Written informed consent will be obtained from all participants before their inclusion in the study. Participation was entirely voluntary. No monetary or material compensation was provided to participants. All participants will complete a written informed consent. Upon arrival at the CAP, the Admissions administration staff will offer the patient the chance to participate in the study. The participant will be given the information sheet attached to the informed consent form, where he or she will be informed

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about the purpose of the study and the handling of the data. If the patient authorizes his or her participation, he or she must complete and sign the informed consent form and give it to the clinical professional with whom the consultation is to take place.

Results

This study was preregistered on ClinicalTrials.org. Recruitment began in July 2024, and as of November 2024, a total of 318 patients have been enrolled at participating CAPs. The recruitment process is proceeding more slowly than expected and to ensure sufficient sample size the recruitment period has been extended until March 2025. This adjustment enables comprehensive data collection without compromising the study's objectives.

Discussion

Principal Findings

The implementation of AI-based technologies in health care has been a topic of growing interest in the last decade. These technologies promise to improve the efficiency and quality of health care, but their adoption depends largely on empirical evidence to support their benefits.

This study seeks to contribute to that evidence base by evaluating a specific tool that has the potential to alleviate one of the main sources of administrative burden for health care professionals: the writing of clinical notes. By freeing up time that would otherwise be spent on administrative tasks, an AI-powered tool could enable health care professionals to focus more on direct patient care, thereby improving the quality of care.

The results of the project will serve to validate the usefulness of an AI-powered solution in daily practice, from the perspectives of improving the perceived quality of care and saving professionals' time, which could amount to more than an hour a day that could be invested in attending to more patients, promoting adherence with the same patients, or other value-added tasks.

If the result of the study is favorable, the tool is technically prepared to be integrated with IT systems, is scalable to thousands of queries in parallel and has been designed from the ground up with absolute priority to data security and privacy (the tool deletes queries minutes after processing to avoid being a target for cyberattacks; it is not a database, just a processor). It is therefore considered that its implementation may be feasible, the first step being to validate its capabilities in this study.

While our study is one of the first to evaluate the use of an automated clinical note-writing system based on AI algorithms in day-to-day clinical consultations in primary care, previous research has explored similar technologies in other medical specialties. For example, a 2024 study assessed the accuracy of AI-generated clinical notes using ChatGPT-4 (OpenAI), finding that such tools can produce notes comparable in quality to those taken by physicians [23]. In another study, the Permanente Medical Group (United States) implemented AI scribes for more than 10,000 physicians and found that this technology reduced documentation time, improved doctor-patient interactions, and achieved high satisfaction among both patients and physicians [24].

Limitations of the Study

One of the main limitations of this study is that the sample is not randomized, which may introduce selection bias. To address this, a sensitivity analysis will be performed to ensure that any potential bias is minimized. Related to the sample size, while substantial for a PoC study with 800 participants, may still be considered relatively small.

Another important limitation is the variability introduced by the participation of different health professionals, who can generate a significant variance in the results obtained, both in patient satisfaction and in the time saved in the consultation. Although patients were blinded to the use of the tool, their reported satisfaction may still be influenced by other factors such as the health care professional's behavior or consultation dynamics. To mitigate this effect, it has been decided to involve a reasonable number of professionals, seeking a balance between reducing variance and avoiding an excessive burden on participants, although this will still be a limiting factor.

Another possible bias is in the measurement of time saved. This is calculated as the difference between the time spent on a consultation without the AI-powered tool to write the notes and the time needed to review the notes generated by the tool in another consultation. However, there will always be an inherent bias, as it is not possible to reproduce the same consultation exactly, and the professional's previous knowledge may influence how quick they are in carrying it out. In addition, the measurement of the time the professional spends writing may not be completely accurate. In addition, while we assess the time spent on writing clinical notes, another potential limitation lies in the time spent reviewing the notes generated by the tool. This measurement may be influenced by external factors, such as interruptions (eg, being called to the door, receiving phone calls, etc), which could result in prolonged review times without the actual time being spent on reviewing the notes. The start and end points of the review period are based on when the professional clicks "start review" and "finish review," but interruptions could lead to inaccurate time recordings. In addition, another limitation is the risk that doctors rely too much on AI-generated notes without thoroughly reviewing them, which could lead to inaccuracies. Although doctors are instructed to verify the notes as soon as possible following the consultation to avoid this, individual differences in review diligence could have an impact on the results. Despite these challenges, an analysis of these errors has been performed and it has been concluded that their impact will be significantly lower than the effects that are intended to be measured, so the results, with the proposed sample, can be considered valid. However, if any extreme values are identified during the analysis, they will be excluded.

Conclusion

We anticipate that patients participating in the study will perceive an improvement in the quality of care they receive and

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that there will be a significant reduction in the time spent taking clinical notes. Although we expect the generated notes to be of high quality, it remains uncertain whether a significant improvement over the control group, which is already expected to have high-quality notes, will be demonstrated. Ultimately, this proof-of-concept study seeks to explore the potential benefits of integrating AI in primary care settings.

Acknowledgments

We thank all the primary care centers that participated in this study, as well as the health care professionals and patients who volunteered. We would also like to thank the Recog Analytics technical team for their ongoing support during the development and implementation of Relisten. This project has had no external funding except for the development of the tool by the company Recog Analytics.

Data Availability

The datasets used and/or analyzed during the current study will be available from the corresponding author on reasonable request.

Authors' Contributions

JV-A, CA, and DHH made significant contributions to the methodology, investigation, and writing (original draft and review & editing of the work). They also supervised and validated the project. AC, ES-F, MLB, CFP, IM, RA, OC, RF, JA, CM, MMM, MG, and SN critically reviewed the manuscript, ensuring accuracy, clarity, and intellectual rigor, and approved the final version for publication, participating in writing and validation. AG coordinated and supervised the project, critically reviewing the intellectual content, approving the final published version, and participated in project administration and supervision.

Conflicts of Interest

CA, DHH, and ACC are employees of Recog Analytics, the company that developed Relisten. While the study was funded by Recog Analytics, to minimize potential bias, the analysis of the results will be conducted independently by authors not affiliated with the company. We have a collaboration agreement with Recog Analytics for this research project. This agreement ensures compliance with data privacy regulations, prohibits fine-tuning of the algorithm using study data, and mandates the deletion of all temporary data immediately after processing. The tool is used solely for research purposes and its inclusion in this study is based on its potential to support primary care professionals by reducing administrative burden and improving workflow efficiency.

Multimedia Appendix 1
Algorithm Architecture.
[DOCX File , 101 KB - resprot_v14i1e66232_app1.docx]

Multimedia Appendix 2
Health Professional Satisfaction Survey.
[DOCX File , 20 KB - resprot_v14i1e66232_app2.docx]

Multimedia Appendix 3
Patient Satisfaction Survey.
[DOCX File , 17 KB - resprot_v14i1e66232_app3.docx]

Multimedia Appendix 4
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 86 KB - resprot_v14i1e66232_app4.pdf]

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Abbreviations

AI: artificial intelligence
CAP: primary care center
EMR: electronic medical record
PoC: proof of concept
S3: Simple Storage Service
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

A Reminder App to Optimize Bladder Filling During Radiotherapy for Patients With Prostate Cancer (REFILL-PAC): Protocol for a Prospective Trial

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Abstract

Background: Many patients with nonmetastatic prostate cancer receive radiotherapy, which may be associated with acute cystitis, particularly if the volume of the urinary bladder is small. Three studies showed bladder volumes <200 ml or <180 ml to be associated with increased urinary toxicity. Therefore, it is important to maintain bladder volumes greater than 200 ml during as many radiation fractions as possible. Several studies investigated drinking protocols, where patients were asked to drink a certain amount of water prior to radiotherapy sessions. This may require considerable discipline from the patients, who are predominantly older adults. Adherence to a drinking protocol may be facilitated by a mobile app that reminds patients to drink water prior to each radiation session. This study investigates the effect of such an app on bladder filling status in patients with prostate cancer undergoing external beam radiotherapy (EBRT) alone.

Objective: The primary goal of this study is to evaluate the impact of an app that reminds patients irradiated for prostate cancer to drink 300 ml of water prior to each radiotherapy session on the number of fractions with bladder volumes <200 ml during the radiotherapy course.

Methods: This ongoing phase 2 aims to recruit 28 patients treated with EBRT alone for nonmetastatic prostate cancer. Radiotherapy will be administered using normo-fractionation, with doses ranging from 70 to 80 Gy in 35 to 40 fractions of 2 Gy, preferably with volumetric-modulated arc therapy (VMAT). Treatment volumes include the prostate with or without the seminal vesicles.

Results: Recruitment for this trial will start in March 2025 and is planned to be completed in October 2026. The study is scheduled to conclude in December 2026.

Conclusions: This trial is the first to evaluate the impact of a reminder app on the number of radiotherapy fractions with bladder volumes <200 ml in patients undergoing irradiation for localized prostate cancer.

Trial Registration: Clinicaltrials.gov NCT06653751; https://clinicaltrials.gov/show/NCT06653751

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KEYWORDS

prostate cancer; external beam radiation therapy; radiation toxicity; bladder filling; mobile app

Introduction

Prostate cancer is one of the most common solid malignancies worldwide [1]. Most patients with nonmetastatic disease receive either prostatectomy or radiotherapy. Radiotherapy is often performed with normo-fractionated (5 × 2 Gy per week) external beam radiotherapy (EBRT) alone or EBRT plus a high-dose-rate brachytherapy boost [2]. For normo-fractionated EBRT alone, the recommended total dose is between 74 and 80 Gy, corresponding to 37 to 40 fractions of 2 Gy [2]. Prostate cancer radiotherapy may be associated with significant acute urinary toxicity such as cystitis, particularly if the volume of the urinary bladder is small. A total of 3 studies showed that bladder volumes <200 ml or <180 ml, respectively, were associated with increased acute or late urinary toxicity [3-5]. In a retrospective study by Pisani et al [3], which included 280 patients treated with EBRT for prostate cancer, bladder filling (volumes <200 ml vs ≥200 ml) was an independent predictor of grade ≥2 acute urinary toxicity. A prospective study by Pinkawa et al [4] assessed the quality of life in 80 patients irradiated for prostate cancer at different time points. At follow-up between 6 and 10 weeks after radiotherapy, pain with urination was reported less frequently by patients with an initial bladder volume of ≥180 ml compared to <180 ml. In another prospective study from Germany, 193 patients received training via a biofeedback mechanism to achieve a bladder volume between 200 and 300 ml at each radiation session [5]. The results showed that reproducible bladder volumes >180 ml were associated with a significant decrease in grade ≥2 acute urinary toxicity. In another study, a planned bladder volume >200 ml and daily filling between 82% and 113% were associated with reduced intrafraction motion of the prostate [6]. Moreover, in the study by Smith et al [7], optimal bladder dose constraints were missed more frequently if the bladder volumes were <200 ml. Therefore, it is important to maintain bladder volumes >200 ml at as many radiation fractions as possible.

In a recent study by our group that investigated the bladder volumes at each of the first 35 radiation fractions in 72 patients receiving EBRT alone, the mean and median numbers of radiation fractions with bladder volumes <200 ml were 17.8 (SD 12) and 16.5 (IQR 7.5-29.5) fractions, respectively [8]. On the other hand, in a subgroup of 37 patients with a bladder volume of at least 200 ml before the start of the radiotherapy course, the mean and median numbers of radiation fraction with bladder volumes <200 ml were only 9.4 (SD 8.3) and 8 (IQR 2-16), respectively. The mean and median were significantly higher in the subgroup of 35 patients with bladder volumes <200 ml, at 26.7 (SD SD 8.5) and 30 (IQR 22-34), respectively. Therefore, there is a medical need for improvement, especially in the latter subgroup.

Several studies have investigated the role of drinking protocols [5-7,9-17]. Patients were asked to drink a certain amount of water prior to computed tomography (CT) simulation and radiotherapy sessions. In these studies, the amount of water ranged between 200 and 600 ml, and the time interval until the CT simulation or radiation session was between 30 and 60 minutes [5-7,9-17]. However, drinking a certain amount of water at a specific point in time may require considerable discipline from patients, who are predominantly older adults. These considerations led to the idea of developing a mobile app that reminds patients to drink a certain amount of water prior to each radiation session. The idea of testing a reminder app in this context was based on our experience with such an app during our previous Interreg project NorDigHealth [18,19].

This study investigates the number of radiation fractions with bladder volumes <200 ml in a prospective cohort of patients using a reminder app. Additionally, it evaluates whether the use of the reminder app significantly reduces the proportion of radiation fractions with bladder volumes <200 ml compared to a historical control group without app support. After several ethical discussions, we decided to compare the cohort of the single-arm phase 2 trial to an appropriate historical control group after careful matching rather than performing a randomized phase 3 trial. Since the responsible individuals at the contributing centers were confident that the reminder app would improve bladder filling in the phase 2 cohort, they deemed it unethical to withhold the app from approximately 50% of the patients participating in a randomized phase 3 trial. The main goal of this prospective phase 2 study is to evaluate the impact of a reminder app on the number of fractions with bladder volumes <200 ml during radiotherapy in patients irradiated for prostate cancer. The app reminds the patients to drink 300 ml of water 45 minutes prior to each radiotherapy session. The primary end point is the number of radiation fractions with bladder volumes <200 ml after 35 fractions of radiotherapy. Additionally, the following end points will be evaluated: (1) the number of radiation fractions with bladder volumes <200 ml at the end of radiotherapy, (2) patient satisfaction with the reminder app, and (3) the impact of the reminder app on the use of health technology.

Methods

Trial Design and Duration

This is a single-arm prospective study performed in 1 university hospital, 2 academic teaching hospitals, and 1 private practice. It will investigate the effect of a reminder app on the number of radiation fractions with bladder volumes <200 ml during a course of radiotherapy for the treatment of prostate cancer compared to a historical control group [8]. The control group is considered appropriate for comparison with this study cohort, as these patients were treated very recently (in 2022 or 2023)

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with external beam radiotherapy alone in 3 of the 5 centers participating in this study. The control group underwent a cone beam computed tomography (CBCT) session prior to each radiation fraction, enabling bladder volume assessment with the same level of precision as in this study. To ensure comparability of the total number of fractions administered in the prospective study with those in the historical control group, the primary end point is restricted to the first 35 fractions administered. The recruitment of all 28 patients is planned to be completed within 20 months. The follow-up period will end directly after the radiotherapy course, which is scheduled to take 7 to 8 weeks. This equals a total running time of 22 months for the study. In accordance with the previous study assessing the number of radiation fractions with bladder volumes <200 ml during a course of radiotherapy for treating prostate cancer, the following characteristics will be recorded to allow adequate comparison with the historical control group: (1) bladder volume at CT simulation, (2) BMI, (3) age, (4) prostate volume prior to radiotherapy, (5) Karnofsky performance score, (6) risk group of prostate cancer, and (7) antihormonal therapy [8]. All patients in the phase 2 cohort and the historical control group must have a bladder volume <200 ml at CT simulation.

Patient Selection

This trial will be performed in patients with prostate cancer receiving definitive normo-fractionated radiotherapy. Patients will be adequately informed about their diagnosis and the nature, significance, and scope of the trial. Patients will only be included after completing the pretherapy evaluation, meeting all inclusion criteria, and not meeting any exclusion criteria (Textbox 1).

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria:

- Histologically proven prostate cancer
- Indication for definitive normo-fractionated radiotherapy
- Possession of and ability to use a smartphone
- Bladder volume at computed tomography (CT) simulation <200 ml
- Age ≥18 years
- Written informed consent
- Capacity of the patient to consent

Exclusion criteria:

- Radiotherapy of pelvic lymph nodes
- Expected noncompliance

Patient Interventions

For all patients, radiotherapy will be administered using normo-fractionation with 70 to 80 Gy in 35 to 40 fractions of 2 Gy, given 5 days per week (overall treatment time 7-8 weeks), preferably with volumetric-modulated arc therapy (VMAT) [2]. Treatment volumes include the prostate with or without the seminal vesicles.

Radiotherapy for prostate cancer may be associated with acute side effects, including dermatitis, cystitis, proctitis, diarrhea, and fatigue. If grade 3 toxicity occurs according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5, radiotherapy may be delayed for a maximum of 7 days without consequences [20]. If it is delayed for more than 7 days, participation in the study will be terminated, and the coordinating investigator must be informed.

Patients may receive concurrent systemic agents as part of their anticancer treatment, regardless of their participation in this trial [2]. These agents will be indicated and prescribed by treating medical oncologists or urologists outside this trial.

The following parameters will be recorded prior to the start of radiotherapy: medical history including micturition disorders, medication including anticancer treatment, physical examination, age, body height and weight, Karnofsky performance score, bladder volume and prostate volume at CT simulation, tumor stage, histology, Gleason score, prostate-specific antigen, risk group, planned radiation dose and dose per fraction, number of fractions, radiation boost, treatment volume, radiation technique, experience with smartphones, and need for support regarding the use of the reminder app. Throughout the trial, bladder volumes will be assessed by staff members prior to the radiotherapy course (based on CT simulation) and before each radiation fraction using CBCT. Adverse events will be assessed on an ongoing basis according to CTCAE version 5 [20]. At the end of the radiotherapy course, patients will be asked to complete a questionnaire assessing their satisfaction with the reminder app and the impact of its use on their attitude toward health technology.

Safety Management

An adverse event is any event experienced by a patient or participant in a clinical trial that does not necessarily have a causal relationship with the treatment. It can include any adverse or inadvertent occurrence (including notable laboratory findings), symptom, or illness that occurs during the treatment period, regardless of whether there is a causal relationship. Existing illnesses that deteriorate during the trial should also be reported as adverse events. Events covered by the documentation for concomitant diseases and radiation-related

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acute toxicities of Grade ≤2 do not have to be additionally documented as adverse events. Serious adverse events are those that fulfill one of the following criteria at any dose level: lethal, life-threatening, requiring hospitalization or extent of a hospital stay, permanent or significant disability, birth defects or malformations, any medically significant event, or any event necessitating surgery to prevent one of the aforementioned concomitant illnesses. Hospitalization should be defined as necessary for treating the adverse event. Hospital stays that are part of the treatment outlined in the protocol or due to a planned, elective operation are not classified as serious adverse events. Likewise, an elective hospitalization to facilitate the trial process does not count as a serious adverse event.

Sample Size Calculation

The primary goal of this study is to assess the impact of an app that reminds patients irradiated for prostate cancer to drink water before each radiotherapy session on the number of fractions with bladder volumes <200 ml during the radiotherapy course. This study also aims to demonstrate that this number is lower than without using an app (historical control group). To allow for a skewed distribution of the primary end point, the Wilcoxon-Mann-Whitney test will be applied for confirmatory statistical analysis. Sample size calculation is based on the article by Noether [21]. In the external historical control group consisting of 35 patients, the mean number of radiation fractions with bladder volumes less than 200 ml was 26.7 (SD 8.5), and the median number was 30 (IQR 22-34). A decrease in this mean value by roughly 30% (to 18.7 fractions) is considered clinically relevant. For illustrative purposes, translating this decrease into a nonparametric effect size framework (assuming normal distribution) leads to a probability of roughly 0.25 that the number of fractions <200 ml with the reminder app will be larger than without the app. Based on this effect size, a sample size of 25 patients in the prospective trial is required for comparison with the historical control group to ensure 90% power to reach statistical significance with a 2-sided Wilcoxon-Mann-Whitney U test and a 5% significance level. Assuming that roughly 10% of the enrolled patients will not be eligible for the primary analysis as they received less than 35 fractions, a total of 28 patients should be enrolled.

Statistical Analyses

All data recorded in the case report forms describing the study population, efficacy, safety, and quality of life will be analyzed descriptively. Categorical data will be presented in contingency tables with frequencies and percentages and 95% CIs. Continuous data will be summarized with at least the following: frequency (n), median, quartiles, mean, SD (standard error), minimum, and maximum. The number of participants with protocol deviations during the study and listings describing the deviations will be provided. Chi-square tests will be used to compare percentages in a 2 × 2 contingency table, replaced by the Fisher exact test if the expected frequency in at least 1 cell of the associated table is less than 5. Stratified 2 × 2 contingency tables will be analyzed using Cochran-Mantel-Haenszel tests. Logistic regression models serve as multivariable methods for binary end point data. A comparison of ordinal variables between treatment arms will be performed using the asymptotic Wilcoxon-Mann-Whitney test, replaced by its exact version in case of ordinal categories with a small number of categories and/or sparse data within categories. Any shift in the location of quantitative variables between study groups will be performed using the Wilcoxon-Mann-Whitney tests. All patients who start the radiotherapy and provide data on the primary end point will be analyzed (full analysis set). The data analysis will be performed according to the statistical analysis plan, which will be finalized prior to database lock and any statistical analysis.

The primary study end point is defined as the number of radiation fractions with bladder volumes less than 200 ml after 35 fractions of radiotherapy. Descriptive measures of location and dispersion will be used to describe the results of the prospective study. The impact of patient characteristics on the primary end point will be assessed by Wilcoxon 2-sample tests. These characteristics include age (<75 vs ≥75 years), Karnofsky performance score (70-80 vs 90-100), BMI (<30 vs ≥30=obesity), prostate volume prior to radiotherapy (<60 vs ≥60 mL), risk group of prostate cancer (low to intermediate vs high), and antihormonal therapy prior to and/or during the course of radiotherapy (no vs yes). For confirmatory analysis, the prospective study will be compared with the historical control group through a 2-sided Wilcoxon-Mann-Whitney 2-sample test and a significance level of 5%. A high degree of comparability is expected between the prospective trial cohort and the retrospective patient data set. However, potential heterogeneity among the study populations will be identified by comparing patient characteristics with Wilcoxon-Mann-Whitney tests. Homogeneity will be assumed if all resulting P values are above 20%. Any factor indicating a tendency toward heterogeneity (ie, $P<.20$) will be included in a multivariable count data Poisson regression model with the number of radiation fractions with bladder volumes <200 ml as a dependent variable and the respective factors and binary factor (prospective study vs historical control) as the independent variables. If there is evidence of overdispersion, the Poisson model will be replaced by a negative binomial model.

Additionally, secondary end points will be subjected to statistical analysis. Since no comparison with historical data is possible, these analyses will focus on descriptive statistical analysis only. Patient satisfaction results will be used to decide whether the app needs modifications. In the case of a dissatisfaction rate >20%, app modifications will be made. If the app has a dissatisfaction rate >40%, it will be considered not useful.

Ethical Considerations

The examinations to be carried out as part of this trial are all considered standard procedures. There are no additional laboratory investigations or X-rays to be done, or any other examinations that could be potentially burdensome for the patient. The trial protocol was approved by the ethics committee of the University of Lübeck, Germany (file 2024-519), and the trial has been registered at Clinicaltrials.gov (NCT06653751). Prior to inclusion in the trial, each patient will be fully informed about its contents and procedures. If the patient has received the necessary information and the investigator is sure that the patient has understood this information, they will be asked to provide their consent via signature. The patient will receive a

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copy of their information and the signed informed consent forms. The investigator will also inform the patient that they have the right to withdraw consent to participate in the trial at any time and without providing any reasons. Patients will be informed that the data collected as part of the trial will be documented anonymously and then forwarded for scientific evaluation.

The trial will be conducted in accordance with the principles laid out in the Declaration of Helsinki. Data will be collected in accordance with the regulations set out in the Data Protection Act. All findings from the clinical trial will be stored on electronic data storage devices and treated with utmost confidentiality. Organizational measures have been taken to prevent the data from being sent to unauthorized people. Patients will only be identified via their individual patient numbers throughout the entire documentation and evaluation phase, and any identifiable data will not be used.

For the personal activation of the app for each study participant, Nextlabel OHG will receive the participant's e-mail address. To ensure the protection of all e-mail addresses, a contract has been signed between the Sponsor (University Medical Center Schleswig-Holstein) and Nextlabel OHG. The contract includes an approved data protection concept. Nextlabel will not have access to any patient data that are not pseudonymized. Amendments to the study protocol may only be implemented if approved by the responsible ethics committees. Only the coordinating principal investigator may carry out such changes. However, all coinvestigators will contact the coordinating principal investigator if modifications are deemed necessary. If any changes are made to the study protocol, all investigators will be informed after ethics committee approval, and the notice must be confirmed.

Data Management and Monitoring

All data relating to patients will be recorded pseudonymously. Each patient will be identifiable only by their unique patient number, date of birth, and sex. A patient identification list will only be kept in the relevant trial centers and will not be forwarded to the sponsor. Data collection will be done using the study-specific data documentation forms that must be filled in using a ballpoint pen. Fountain pens or pencils will not be used. If corrections need to be made, we will cross the error out once with a straight line, enter the correct information next to it, and note the date and/or reason for correction. Comments will be made if data fields cannot be filled in because of missing information. The forms will be filled in as soon as possible and submitted to the checker for review, signed, dated, and forwarded to the study management team.

The original versions of all key trial documents, including the documentation sheets, will be kept at the trial headquarters (ie, the sponsor responsible for the trial) for a minimum of 10 years after the final report.

The principal investigator/head of the trial center will keep all administrative documents (ie, written correspondence with the ethics committee, regulatory authorities, trial management, and trial headquarters), the patient identification list, the signed informed consent forms, copies of the documentation sheets, and general trial documentation (ie, protocol and amendments) for the aforementioned time period. Original patient data will also be kept for the length of time stipulated for the trial centers but not for less than 10 years.

Clinical on-site monitoring at the German sites will be conducted according to good clinical practices and written standard operating procedures to ensure the patients' rights and safety are upheld, along with the reliability of the trial results. For initiation, trial sites will be visited onsite by a clinical research associate. During the trial, sites will be visited at regular intervals depending on the recruitment rate and data quality. Informed consent and defined key data will be checked for all patients. Medical files will be screened for adverse and serious adverse events. Patients' questionnaires will be checked. All trial-specific monitoring activities will be defined before starting the trial and documented in writing (monitoring manual). The sites in other countries will be monitored according to the corresponding national regulations in their own responsibility. No regular audits are planned. However, to ensure the correct execution of the study, audits may be conducted if necessary. Because this study is not linked to the German Medicinal Products Act, no inspections of higher federal authorities are scheduled. A data monitoring committee is not required since patients in this trial will receive standard treatment.

Results

This phase 2 trial investigates the number of radiation fractions with bladder volumes <200 ml in a prospective cohort of patients using a reminder app. In addition, this study evaluates whether the use of the app leads to a significant reduction of the proportion of fractions with bladder volumes <200 ml when compared to a historical control group without app support. The reminder app was developed by the professional company Nextlabel OHG from Lübeck, Germany. It reminds the patients to drink 300 ml of water 45 minutes prior to each radiation session. The time to be reminded can be set by the patients for each radiation session to consider potential changes in schedule (eg, due to maintenance of the linear accelerator). The patients must confirm their water intake and receive a puzzle piece as a reward. Prior to its use in the REFILL-PAC (Reminder App to Optimize Bladder Filling During Radiotherapy for Patients With Prostate Cancer) trial, the app was tested by 30 healthy volunteers to assess its functionality and practicability and to identify and solve relevant issues prior to the start of the trial. Recruitment for this trial will start in March 2025 and is planned to be completed in October 2026. Termination of the entire study (28 patients) is scheduled for December 2026. The expected results will be available at the beginning of 2027. The REFILL-PAC trial did not receive any specific funding. It is part of the Interreg Deutschland-Danmark project Health Advancing Technologies for the Elderly (HeAT) funded by the European Regional Development Fund (01-1-23 2).

Discussion

Expected Results

It is expected that the use of the reminder app will reduce the mean number of radiation fractions with bladder volumes <200

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ml by approximately 30% from 26.7 (of 35 fractions) found in the historical control group to 18.7 fractions in patients with a bladder volume <200 ml at CT simulation [8]. A sample size of 25 patients is required for the phase 2 cohort to achieve a power of 90% for statistical significance and a 5% significance level.

Study Limitations

Although appropriate matching will be conducted based on 7 patient- and tumor-related characteristics, the risk of a hidden selection bias cannot be entirely excluded due to the retrospective nature of the data obtained from the control group. Moreover, the fact that patients in the phase 2 cohort must possess a smartphone and be able to use the app may lead to a selection bias. These limitations must be considered when the results of the comparative part of this study will be available and distributed.

Comparison With Prior Work

Radiotherapy for prostate cancer may be associated with significant urinary toxicity such as cystitis, particularly if the volume of the urinary bladder is <200 ml at the time of irradiation. Findings from 3 previous studies highlight the importance of patients drinking a sufficient amount of water each day before irradiation to achieve a bladder volume of <180 ml or, preferably, ≥200 ml [3-5]. To ensure appropriate bladder filling, protocols asking the patients to drink water before CT simulation and/or each radiation fraction have been investigated [5,6,8-17]. In the corresponding studies, the amount of water ranged between 200 and 600 ml, with a waiting period of 30 to 60 minutes before CT simulation or the radiation. However, bladder volumes during the radiotherapy course varied considerably, and adherence to the drinking protocols was suboptimal. This raises the question of whether an app reminding patients before each radiation session of the required water intake could improve adherence to the prescribed drinking protocol.

Dissemination Plan

The coordinating principal investigator will work toward a comprehensive internal and external dissemination of the study results. The coordinating principal investigator, biostatisticians, and staff members of the center will prepare a report regardless of whether the study concludes as planned or is terminated early.

The scientific results will be published in an international, peer-reviewed journal. Additionally, the results will be presented at meetings and symposia. Reports and publications related to the study must be coordinated with the statistician to avoid misinterpretations. Conclusions must be statistically validated and approved by the statistician. The study acronym REFILL-PAC will be used in all publications.

Conclusion

This phase 2 trial is the first study that investigates the impact of a reminder app on the number of radiation fractions with bladder volumes less than 200 ml in patients treated with normo-fractionated radiotherapy alone for localized prostate cancer. The hypothesis is that using the app will significantly reduce the number of fractions below 200 ml compared to a historical control group of patients who underwent normo-fractionated radiotherapy without app support. If the reminder app proves effective, it may contribute to a decrease in urinary toxicity.

Acknowledgments

The REFILL-PAC (Reminder App to Optimize Bladder Filling During Radiotherapy for Patients With Prostate Cancer) trial is part of the Interreg Deutschland-Danmark project Health Advancing Technologies for the Elderly (HeAT), which is funded by the European Regional Development Fund (01-1-23 2). The trial sponsor is the University Medical Center Schleswig-Holstein, Germany. Neither the funding body nor the sponsor has any role in the study conception, data handling, or article writing.

Data Availability

Further information regarding the REFILL-PAC (Reminder App to Optimize Bladder Filling During Radiotherapy for Patients With Prostate Cancer) trial is available at Clinicaltrials.gov (NCT06653751).

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 247 KB - resprot_v14i1e68179_app1.pdf]

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Abbreviations

CBCT: cone beam computed tomography
CT: computed tomography
CTCAE: Common Terminology Criteria for Adverse Events
EBRT: external beam radiotherapy
HeAT: Health Advancing Technologies for the Elderly
REFILL-PAC: Reminder App to Optimize Bladder Filling During Radiotherapy for Patients With Prostate Cancer
VMAT: volumetric-modulated arc therapy

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Protocol

Designing eHealth Interventions for Pediatric Emergency Departments: Protocol for a Usability Testing Study With Youth, Parent, and Clinician Participants

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Abstract

Background: Usability tests provide important insight into user preferences, functional issues, and differences between target groups for health interventions and products. However, there is limited guidance on how to adapt the usability testing approach for a youth audience, especially for digital health interventions.

Objective: This protocol paper outlines a novel approach for conducting usability tests with a diverse audience of youth, parents, and clinicians in the development of 2 digital health tools for the pediatric emergency department (ED) setting.

Methods: This paper outlines a protocol for usability testing as part of a broader study aimed at co-designing ED discharge communication tools with youth, parents, and clinicians. The broader study involved co-designing 2 digital tools: one for asthma and one for concussions. A multimethods approach to usability testing was used to assess the functionality of these tools through 2 rounds of testing. A mix of youth, parents, and ED clinicians were invited to participate in each round of usability testing. Participants were asked to provide feedback on the tools through quantitative surveys and open-ended qualitative questions. The usability testing approach was adapted to suit each target group, such as including a youth in the data collection process, to enhance the quality of the data. The severity of usability problems was analyzed following the first round of testing, and each tool was refined based on this feedback. The second round of usability tests involved collecting both qualitative and quantitative feedback on the revised tools.

Results: All usability data have been collected and are being analyzed. Outcomes will be disseminated through a subsequent publication. Results will include demographic characteristics from each user group from both rounds of testing, severity of usability scores, qualitative and quantitative feedback, and differences in test outcomes between each target group.

Conclusions: This paper provides novel guidance for conducting usability tests with youth participants when designing digital health tools. By using a comprehensive co-design and usability testing approach, we anticipate that final tools will be highly relevant to the end users and will lead to better uptake and patient outcomes when pilot-tested in future studies. The outlined approach may be adapted to different health care contexts for other youth participants. Further research should continue to explore ways to design usability tests that are suitable for youth audiences, as there is still a significant gap in the literature around this topic.

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KEYWORDS

eHealth intervention; emergency department; usability testing; youth; health services; parents; pediatric; digital health tools; mixed methods; quantitative surveys

Introduction

The International Organization for Standardization describes usability as "the extent to which a system, product or service can be used by specified users to achieve specified goals with effectiveness, efficiency and satisfaction in a specified context of use" [1]. Usability testing is a method in which a product is evaluated by users as they perform tasks, and may include formative or summative testing [2]. Usability testing is considered a cornerstone of user-centered design, valuable for capturing user preferences, to identify any functional issues and determine differences between how certain demographic groups use a product or tool [3]. This information is helpful for both designers and researchers who want to ensure that a product suits the needs of the end user.

In the context of eHealth (ie, digital health tools and health information technologies), applying methods and approaches to usability testing could improve the design and implementation of new interventions. This includes digital tools such as mobile apps, kiosks, virtual care, and electronic health records [4]. The World Health Organization recognizes eHealth interventions as a global priority, as part of the 2020-2025 global strategy on digital health, to create more efficient and effective health care systems [5]. Despite this global health priority setting, it is unclear how often eHealth interventions undergo usability testing prior to implementation. One systematic review reported limited or poor-quality usability testing of electronic health records prior to implementation [6], while another review of 104 eHealth interventions reported that only 38% of them included an aspect of usability testing [4]. Often, eHealth researchers rely on industry-focused protocols, which may lack transferability to complex health care contexts. To evolve the rigor and field of usability testing in the development of eHealth interventions, more diverse testing protocols applied in specific health contexts (eg, emergency departments [EDs]), for specific populations (eg, youth, their caregivers, and clinicians), or for specific types of eHealth interventions (ie, websites versus kiosks) are needed.

Further, eHealth researchers should develop usability protocols that are developmentally appropriate for the target users (ie, age and condition) and relevant to the specific context (ie, hospital or outpatient clinic) where they may be deployed. A scoping review by Maramba et al [7] identified 133 studies where usability testing informed the development of eHealth interventions. However, no studies in the review reported on the usability testing of eHealth interventions in the ED setting, and despite 9 studies being related to child health [7], only 2 studies included youth (aged 14-21 years) as usability testing participants [8,9]. This represents a significant research-to-practice gap as youth and their parents (eg, parents, caregivers, and/or legal guardians) are typically early adopters of eHealth interventions, and their insights could benefit broader adoption. Health services researchers need guidance on how to conduct or adapt usability tests to ensure that end users are appropriately involved in design. The aim of this protocol paper is to describe a youth-, parent-, and clinician-focused approach to usability testing of 2 eHealth interventions for pediatric EDs. This paper will highlight key testing session logistics, considerations for test user eligibility, testing activities and scenarios, adaptations for youth test users, and approaches to synthesizing multimethods usability data.

Methods

Study Design

This protocol paper describes one component of the emergency department discharge communication strategies (EDUCATE) study, which aimed to evaluate a co-design method for discharge communication tools for use in the pediatric ED [10]. Based on methodological guidance from Barnum [2] and calls for a more comprehensive approach to usability testing, as reported in previous literature [6], a multimethods approach including quantitative (ie, surveys and severity scoring) and qualitative (ie, open-ended interviews) data was used. Using a multimethods approach allowed us to view usability data from different lenses, with count and frequency data from surveys and experiential data from qualitative sources. The protocol was designed to support remote synchronous usability testing. Remote, synchronous usability testing has previously been shown to be as effective as in-person usability testing for eHealth interventions among both adults and youth [11]. Formative usability testing was used, where tools were evaluated through 2 iterative cycles with a small number of participants [2] to identify any errors prior to implementation. The Template for Intervention Description and Replication (TIDieR) checklist was used to guide the reporting of this protocol paper [12] (Multimedia Appendix 1).

Ethical Considerations

The study received ethical approval from the institutional review board at IWK Health (#1024004). All participants provided written informed consent prior to each usability test. Additional consent was obtained from a research team member whose image is included in the study materials. Following each usability test, participants received a unique identifier, and their data remained anonymous and confidential. Upon completion of the usability test, all participants received a CAD $30 (US $20.96) gift voucher as a reimbursement for their time.

Tool Development

During the first phase of the EDUCATE study, 2 electronic discharge communication tools were co-designed by parents, youth, and ED clinicians (ie, nurses and physicians) [13]. A full description of the co-design process will be published in a future publication and is briefly described here. Two co-design teams were established, one for asthma and one for concussion, and met 8 times over a 2-year period between 2020 and 2022. Each co-design team worked together to develop an interactive web-based tool that would address a key discharge

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communication issue for youth and families visiting the ED. One tool was co-designed to help parents and youth decide whether to visit the ED during an asthma attack, while the second tool was co-designed to help parents and youth navigate the postconcussion recovery journey after leaving the ED. Two user design experts integrated the co-design teams' ideas into 2 digital tools, which were then assessed for usability.

Usability Testing Steps

The usability testing process involved four steps, based on usability testing literature [2]: (1) defining the user profiles, (2) the think-aloud process, (3) task-based scenarios, and (4) refining and retesting. Each usability test was facilitated by a researcher trained in mixed and multimethods health services research (MS). Previous literature shows that usability tests often use one approach (ie, quantitative, qualitative, or heuristic methods) to collect usability data, but few use multiple methods [7]. Therefore, a combination of quantitative and qualitative methods was used to gather comprehensive usability data and to identify as many usability issues as possible. The usability tests included a combination of quantitative self-report survey questions, qualitative think-aloud processes, observations, and open-ended interview questions, and were planned to last approximately 60 minutes. This protocol paper focuses on the usability testing process, while more details on recruitment, study setting, and outcome data will be reported in a future publication. Table 1 and the following section describes each of the four usability steps in detail, including how each step was adapted for each target population (ie, youth, parents, and ED clinicians).

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Table 1. Overview of the usability testing process including each step and corresponding component of the usability test.

Step and item	Goal
Usability step 1: defining the user profiles	
Presession	
Screening questionnaire	• Determine eligibility for the usability test
Informed consent	• Gain written informed consent
Round 1 (total session time: 60 minutes)	
Opening script (5 minutes)	• Describe the study and provide an overview of tasks • Allow participants to ask questions
Demographic survey (5 minutes)	• Gather demographics, health care usage, and computer skills data
Usability step 2: think-aloud process—overview of the "think-aloud" process (5 minutes)	• Describe the think-aloud process • Go through 1 live example of the think-aloud process, using a familiar website (all participants) • Share a prerecorded video of the think-aloud process with a youth participant (youth participants only)
Usability step 3: task-based scenarios	
Task 1: first impressions (20 minutes)	• Gather initial thoughts about the tool • Complete a word desirability activity
Task 2: scenario-based activities (×2; 15 minutes)	• Gather qualitative and quantitative metrics related to specific tasks, designed to capture the main functions of the tool
Gibson survey (5 minutes)	• Gather additional quantitative usability testing data
Thank you and closing remarks (5 minutes)	• Thank participants for joining • Discuss compensation and next steps
Postsession	
Quantitative data analysis	• Gather time to complete tasks, number and frequency of errors, usability severity scores, and satisfaction data
Qualitative data analysis	• Gather qualitative feedback about usability issues and satisfaction with the tool
Usability step 4: refining and retesting	
Presession	
Screening questionnaire	• Determine eligibility for the usability test
Informed consent	• Gain digital e-consent
Round 2	
Demographic survey	• Gather demographic details about participants prior to testing
Posttask questionnaire	• Gather quantitative and qualitative usability and satisfaction data on a refined version of the tool through an asynchronous, remote usability test with a new group of end users

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Step 1: Defining the User Profiles

Overview

Barnum [2] proposes that defining the user profile is an important first step in usability testing. As our tools were codeveloped by and for ED clinicians, parents, and youth, these 3 target groups were chosen as the user profiles. For this study, youth included any individual aged between 12 and 19 years who had visited the ED for either asthma or concussion in the past year. Parent users included any adult (>18 years) who visited the ED with their child for asthma or concussion presentations in the past year, and the clinician profile included any nurse or physician employed in a pediatric ED setting. Nielsen and Landauer [14] argue that 85% of usability issues could be identified with as few as 5 participants, and Barnum [2] proposes that formative usability testing is better suited to a smaller number of participants. Therefore, we aimed to include 2 to 3 participants from each user group (youth, parents, ED nurses, and ED physicians) for each tool across 2 study sites for a proposed sample of 16 to 24 participants from each site in each round of usability testing (Figure 1).

Figure 1. Overview of the expected number of usability testing participants to be recruited from each site for each round of testing for each tool.

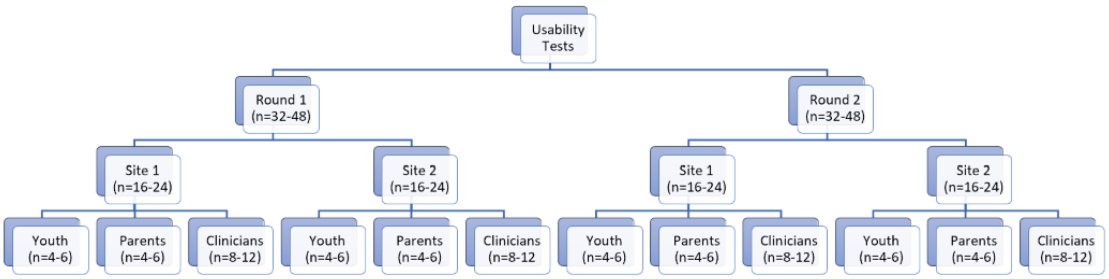

Eligibility and Pretest Survey

To determine eligibility, a screening survey was administered to interested participants through the REDCap (Research Electronic Data Capture; Vanderbilt University) platform [15]. Since participants would be testing a digital tool, it was important to screen for health literacy level and access to a computer with audio/video capabilities. To assess health literacy level, the REDCap survey included branching so that parents would be directed to the METER health literacy test [16], which is shown to be a quick and valid measurement of health literacy level among adults. Youth were directed to the Health Literacy Assessment Tool 8 test [17], a quick, feasible and accurate health literacy assessment tool for youth [1]. Clinicians did not have to complete a health literacy test. The screening survey can be found in Multimedia Appendix 2. Participants provided written informed consent and agreed on a day and time to complete a test session with the facilitator (MS).

Test Session Setup

Participants joined the session remotely via the Zoom (Zoom Video Communications) using their own computer and webcam. The facilitator provided a brief overview of the study and allowed participants to ask questions to ensure that they understood the expectations of the usability test. The facilitator described that the aim of the usability test was to find problems with the tool and assured participants that their skills and abilities were not being evaluated. This was important to create a safe testing space, particularly for youth participants. Participants were then asked to complete a demographic questionnaire on REDCap prior to the start of the test. The facilitator shared a link to the survey and allowed the participant to complete the test in real time to ensure higher completion rate. Sessions were video recorded.

Step 2: the Think-Aloud Process

The think-aloud process involves participants talking through their thought process as they complete a task or solve a problem [18]. This approach is common in usability tests of eHealth interventions [6,7] and is valuable for understanding participants' decision-making processes rather than strictly observing their behaviors [19,20]. Following the completion of the demographic survey, and immediately prior to the start of the usability test, the facilitator explained to participants how to use a think-aloud approach during the usability test. A mock example was used, which involved navigating a popular Canadian departmental store's website so that test users could become familiar with the think-aloud process in a web-based environment they recognized. While it was important to demonstrate the think-aloud process with all participants, the co-design team suggested that a second think-aloud example featuring a youth should be modeled for youth participants prior to their usability test. Therefore, a youth member of the co-design team created a 1-minute video of themselves using the think-aloud process to find their way on a popular theme park's map (Figure 2). This was played for all youth participants prior to the start of the usability test. Examples of the think-aloud process were shared with the co-design teams and refined based on their feedback prior to starting the usability tests with participants.

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Figure 2. A screen capture of the youth-led think-aloud example.

Step 3: Task-Based Scenarios

Overview

Once participants confirmed that they were comfortable with the think-aloud process, the facilitator started video-recording the usability testing session. The facilitator used a variety of techniques to fully evaluate the usability of the eHealth intervention by adapting traditional usability methods for the end user population (ie, youth, parents, or clinicians). Before sharing a link to the tool, the facilitator shared a link to a web-based Microsoft Word document to guide the user through tasks and included visual prompts to support the scenario-based exercises. This approach was used to eliminate the need for alternating screen sharing by the facilitator and participant and to reduce complexity in the remote testing environment [21]. Six documents were developed, based on the 6 unique user groups (ie, youth with asthma, their parents, and their clinicians; and youth with concussions, their parents, and their clinicians).

Task 1: First Impressions

The first task in the usability test was designed to gather participants' first impressions of the tool. This crucial step in usability testing can quickly determine whether users like or dislike a tool in about 80% of cases [2]. After opening the tool, users were invited to click around, using the think-aloud process to describe their initial reactions to the tool. The facilitator used open-ended prompts to encourage verbalizations of what the participant was thinking; these included the following: "What are your first impressions of the tool?" "What do you think the purpose of the tool is?" Participants were then asked to choose 5-10 words from an adapted list of 118 desirability reaction words of Benedeck and Miner [22]. For usability tests, the Nielsen Norman Group [23] suggests adapting the original list to include approximately 25 words that are appropriate for the user interface being evaluated, with at least 40% of chosen words having a negative connotation. This activity aimed to gather additional user satisfaction data while helping participants, particularly youth, feel more comfortable about sharing their honest thoughts about the tool. This approach has been successfully used in previous usability tests [24]. The list of desirability words can be found in Multimedia Appendix 3.

Task 2: Scenario-Based Questions

Next, participants were presented with a scenario relevant to their user identity (ie, youth, parent, or clinician) and medical condition (ie, asthma or concussion). Each scenario was designed by a research team member (MS) based on the user's persona, as outlined by Quesenbery and Brooks [25]. This involved crafting a situation with the user as the main character where they must achieve a specific goal by using the eHealth intervention being tested. The facilitator used a visual guide and a predetermined script to describe a scenario and then ask participants to complete 2 tasks. The tasks were designed to walk participants through key features of the tool so that additional navigation and usability errors could be easily identified. Participants were asked to use the think-aloud process to describe their thoughts and decisions as they completed each task. Participants were asked open-ended questions about the scenario-based activities, such as the following: "How did you find using the tool to complete that task?" "Is there anything you would change about the tool to make that task easier?" The user-specific tasks are outlined in Multimedia Appendix 4.

Global Feedback

Following the scenario-based tasks, participants were asked open-ended questions about the tool, such as the following: "Is there anything else you would change about the tool to make it better?" "On what device/format would you most likely use this tool if you were to use it in the future?" Quantitative data about

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the functionality and satisfaction of the tool were captured through a REDCap survey, which was administered to participants at the end of the usability test. The facilitator shared a link to the survey using the chat feature of the web-based meeting platform and waited until participants completed the task in real time, to ensure a high completion rate. This posttest was adapted from a survey by Gibson et al [26], which is a validated tool for collecting patient and provider satisfaction data on educational resources. The survey by Gibson et al [26] aims to gather information on visual appeal, functionality, content, and intended use. Branching was used to direct participants to the correct survey in REDCap, as the youth survey also included a question to understand the impact of seeing a youth-led example of the think-aloud process. The posttest surveys adapted from Gibson et al [26] can be found in Multimedia Appendix 5 [26].

Step 4: Refining and Retesting

Following each usability testing session, the video recording was uploaded to a secure, password-protected internet server. Four coders (MS, JC, AG, LW) watched the videos and independently scored the usability issues using a combination of Nielsen's [27] scoring system and qualitative analysis. The Nielsen scoring system for severity of usability issues is based on a 5-point scale, ranging from 0 (no usability problem) to 4 (catastrophic usability problem) [27]. Nielsen [27] proposes 3 factors associated with a usability issue: frequency of the problem, impact of the problem, and persistence of the problem. If an eHealth intervention is evaluated to include only minor usability issues (score of 0-2), then the tool may be released without further refinement, while an eHealth intervention with major or catastrophic issues (score of 3-4) should undergo alterations before another round of testing and/or public release [27]. Each coder scored the recorded usability sessions using a deductive approach, following Nielson's [27] scoring system. A numerical value and descriptive details were entered into an Excel (Microsoft Corp) sheet to explain the reasoning underlying each score. Coders then met to discuss their scores and reach a consensus on final severity scores for each usability test.

In conjunction with Nielson's [27] severity scoring step, each reviewer made notes about users' open-ended responses or comments during the usability session. For example, if users described their dislike of a certain feature of the eHealth intervention, the reviewer documented this during the qualitative analysis. Directed content analysis was used to understand the qualitative data and identify the most reported user issues [28]. This type of qualitative analysis allows for a deeper interpretation of qualitative data, often informed by a theory or previous research, and allows for the quantification of the data [28]. In this study, the quantitative findings informed the qualitative data analysis and allowed researchers to calculate the number of user issues with additional context. Following qualitative analysis and severity scoring of each usability test, a description of the most severe usability issues and a list of proposed changes was sent to the design team. The developers then refined the tools by addressing severe usability issues and the most common cosmetic concerns.

The refined tools were brought to each co-design team for further input before undergoing a second round of usability testing with another sample of target users. As the first round aimed to identify catastrophic usability issues, the second round was intended to identify additional, minor issues. This second round of usability testing involved a modified, remote, asynchronous approach to capture any additional usability issues in the tools. As the first round aimed to identify catastrophic usability issues, the second round was intended to identify additional minor issues. Therefore, a modified approach was used to quickly gather usability information without placing unnecessary burden on participants. To capture remote usability data, images and video clips were embedded in a new REDCap survey to demonstrate the main functions and features of the tools (Figure 3). Participants then completed posttask questionnaires using a Likert scale, informed by Nielson's [27] methods, with additional free-text boxes to capture qualitative data. Basic demographic questions were also included in the survey.

The final version of each tool was then presented to the co-design team members for their thoughts. Each team made final decisions about what refinements should be incorporated into each tool, signaling the end of the usability testing process.

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Figure 3. Example of an embedded video clip, along with posttask questions from the asthma tool.

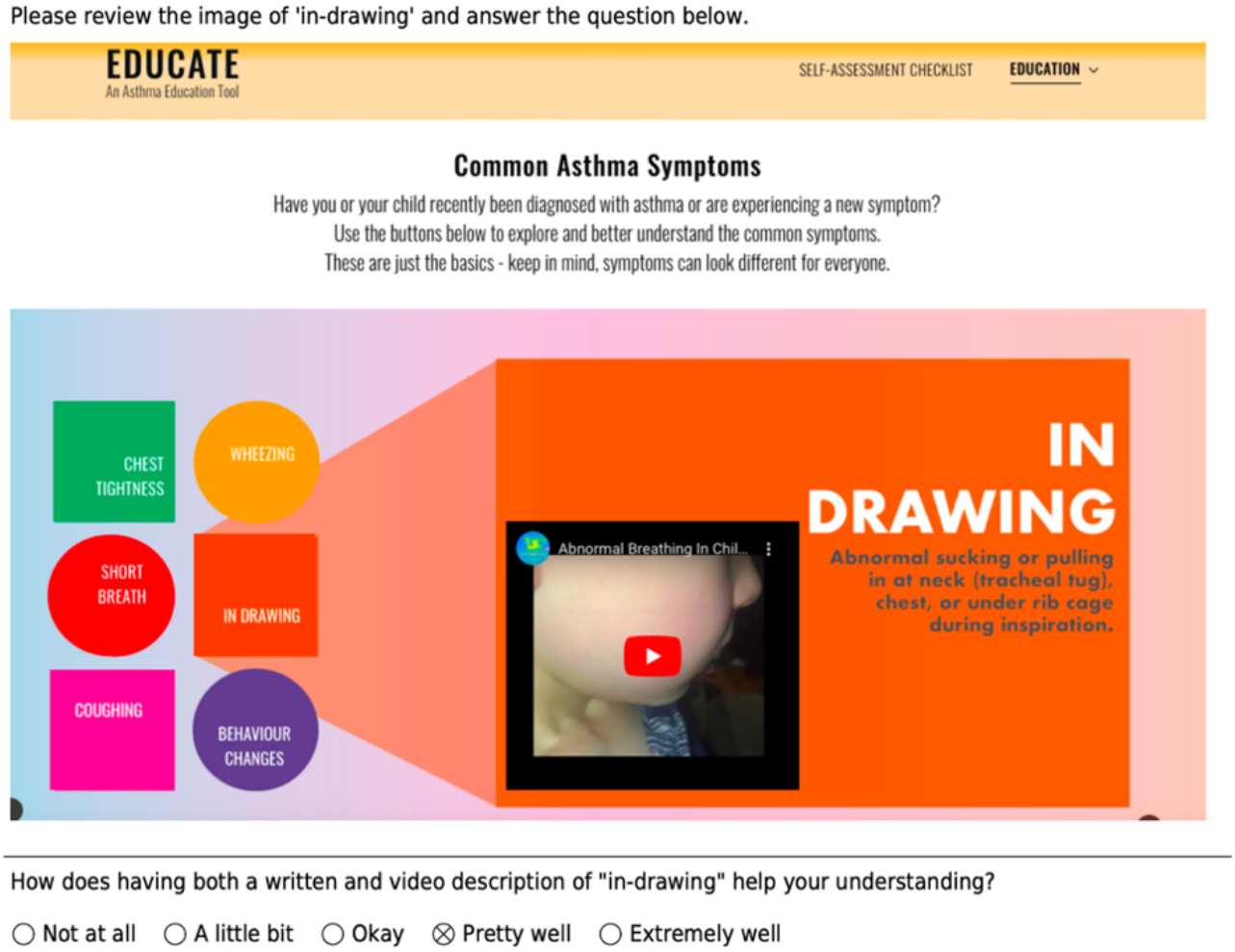

Results

The first round of usability testing was conducted between December 2021 and July 2022, while the second round of testing was conducted between November 2022 and March 2023. Data analysis of round 1 took place in July and August 2022 and informed the second round of testing. The final results from both rounds of usability testing will be shared in a future publication. Outcome data will include an overview of severity of usability scores from round 1, qualitative feedback on tool usability and satisfaction from rounds 1 and 2 of testing, and demographic details about study participants. Details about the changes made between rounds 1 and 2 of usability testing will also be presented and may include changes such as button size or location, colors, and new navigation pathways. We will describe any observations related to user characteristics and feedback and identify opportunities for future usability testing and implementation.

Discussion

Anticipated Findings

This paper addresses an important gap in the academic usability literature by detailing a co-designed approach to usability testing that was adapted for youth, parents, and clinicians. In particular, this paper describes multiple adaptations that were made to the testing procedures to address developmental stages and comfort levels of youth participants. These adaptations included modeling the think-aloud technique by other youth, allowing for a test-and-try before initiating the recording, screening for the appropriate level of health literacy so participants would be able to complete tasks, using multiple methods for soliciting feedback (self-report survey, observation, and interviews) so participants had varied opportunities to express opinions and suggestions, keeping testing sessions brief and accessible offsite (ie, via Zoom), keeping the sessions short (<60 minutes), using branching logic in data collection methods so participants only accessed information relevant to them, and including less cognitively demanding activities (eg, word desirability activity) to solicit feedback. By applying these approaches to usability testing, it is anticipated that the feedback will be highly relevant, leading to a more user-centered product. We expect that the first round of usability testing will lead to several changes to the tools, while the second round may result in fewer or more minor changes. By using a co-design approach and bringing the usability feedback to each co-design team for further consideration, the next step of piloting the 2 tools in ED settings will lead to positive uptake and outcomes. Previous studies have indicated the benefits of using a co-design approach to engage more end users [29]. However, few usability studies tend to include the youth perspective, even when they are the target

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audience [7]; hence, we expect this paper to be a significant and beneficial contribution to the usability literature.

Strengths and Limitations

While this paper provides a comprehensive overview of an approach to usability testing for youth, there are several limitations to consider. Due to the remote nature of the usability tests, participants require internet and computer access. Further, among individuals who do complete a remote usability test, the differences in home environments and technical equipment may affect the quality of the testing process [21]. Future work may focus on offering technical support or request a specific technology setup, as these concerns may have limited participation for some individuals, particularly those from lower socioeconomic backgrounds. Additionally, while it is not a requirement to speak English as a first language to participate in the study, the digital tools were only designed in English, and therefore non–English speakers may be unable to complete the usability tests. Although a small sample of participants is needed to identify most usability issues, a small sample may reduce the generalizability of the findings, which may be seen as a limitation. We have future research planned to mitigate both of these concerns by co-designing multilingual digital tools with broader populations to ensure that the specific needs of clinicians, parents, and youth from varied backgrounds are met. Finally, while the findings of the usability tests may not be generalizable to a non-ED health care context or for individuals presenting with medical conditions apart from concussion and asthma, the techniques used to engage youth may be applied to any usability testing setting.

Key Recommendations and Conclusion

Youth provide valuable perspectives into eHealth intervention designs and therefore should be included in the usability process; however, there is a significant gap in the literature around usability testing with youth in health services. Therefore, researchers may find the methods used in this paper helpful for guiding usability tests with youth participants in other health care contexts. Further outcome data are needed to determine what works well in youth-based usability studies, some of which will be shared through a future publication presenting the outcomes of the detailed approach.

Acknowledgments

We would like to acknowledge the members of each co-design team who designed the digital health tools assessed through usability testing.

Data Availability

The datasets generated during this study are not publicly available because the results have not yet been analyzed but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
TIDieR (Template for Intervention Description and Replication) reporting guidelines.
[DOCX File , 495 KB - resprot_v14i1e64350_app1.docx]

Multimedia Appendix 2
Screening survey for usability participants.
[DOCX File , 209 KB - resprot_v14i1e64350_app2.docx]

Multimedia Appendix 3
The list of desirability words.
[DOCX File , 14 KB - resprot_v14i1e64350_app3.docx]

Multimedia Appendix 4
An overview of the user-specific tasks.
[DOCX File , 20 KB - resprot_v14i1e64350_app4.docx]

Multimedia Appendix 5
Posttest surveys adapted from Gibson et al [27].
[DOCX File , 279 KB - resprot_v14i1e64350_app5.docx]

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Abbreviations

ED: emergency department
EDUCATE: emergency department discharge communication strategies
REDCap: Research Electronic Data Capture
TIDieR: Template for Intervention Description and Replication

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Protocol

iCogCA to Promote Cognitive Health Through Digital Group Interventions for Individuals Living With a Schizophrenia Spectrum Disorder: Protocol for a Nonrandomized Concurrent Controlled Trial

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Abstract

Background: Cognitive impairments are a key aspect of schizophrenia spectrum disorders (SSDs), significantly affecting clinical and functional outcomes. The COVID-19 pandemic has heightened concerns about mental health services and cognitive stimulation opportunities. Despite evidence-based interventions like action-based cognitive remediation (ABCR) and metacognitive training (MCT), a research-to-practice gap exists in their application across mental health settings.

Objective: The iCogCA study aims to address this gap by implementing digital ABCR and MCT through a national Canadian collaborative effort using digital psychological interventions to enhance cognitive health in SSDs.

Methods: The study involves 5 Canadian sites, with mental health care practitioners trained digitally through the E-Cog platform, which was developed by our research group. Over 2.5 years, participants with SSDs will undergo pre- and postintervention assessments for clinical symptoms, cognition, and functioning. Each site will run groups annually for both ABCR and MCT, totaling ~390 participants. A nonrandomized concurrent controlled design will assess effectiveness design, in which one intervention (eg, ABCR) acts as the active control for the other (eg, MCT) and vice versa, comparing cognitive and clinical outcomes between the interventions using generalized linear mixed effect modeling. Implementation strategy evaluation will consider the digital

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platform's efficacy for mental health care practitioners' training, contextual factors influencing implementation, and sustainability, using descriptive statistics for quantitative data and thematic analysis for qualitative data.

Results: A pilot pragmatic trial has been conducted previously at the Montreal site, evaluating 3 early implementation outcomes: acceptability, feasibility, and engagement. Patient and therapist acceptability was deemed as high and feasible (21/28, 75% of recruited service users completed therapy, rated feasible by therapists). Technology did not appear to significantly impede program participation. Therapist-rated levels of engagement were also satisfactory. In the ongoing study, recruitment is underway (114 participants recruited as of winter 2024), and intervention groups have been conducted at all sites, with therapists receiving training via the E-Cog learning platform (32 enrolled as of winter 2024).

Conclusions: At least 3 significant innovations will stem from this project. First, this national effort represents a catalyst for the use of digital technologies to increase the adoption of evidence-based interventions and will provide important results on the effectiveness of digitally delivered ABCR and MCT. Second, the results of the implementation component of this study will generate the expertise needed to inform the implementation of similar initiatives. Third, the proposed study will introduce and validate our platform to train and supervise mental health care practitioners to deliver these interventions, which will then be made accessible to the broader mental health community.

Trial Registration: ClinicalTrials.gov NCT05661448; https://clinicaltrials.gov/study/NCT05661448

International Registered Report Identifier (IRRID): DERR1-10.2196/63269

(JMIR Res Protoc 2025;14:e63269) doi:10.2196/63269

KEYWORDS

schizophrenia spectrum disorders; digital technology; cognitive health; cognitive remediation; metacognitive training; schizophrenia; digital group interventions

Introduction

Background

Schizophrenia and related psychoses present debilitating challenges, imposing an enormous burden on individuals, families, and communities [1,2] and are characterized by symptom recurrence, social deterioration, and cognitive impairments [3-8]. Most affected individuals experience persistent positive (eg, hallucinations and delusions) and negative symptoms (eg, amotivation, avolition, and reduced expressivity), alongside notable cognitive challenges like difficulties in verbal memory, executive functions, and attention. In addition to these impairments are cognitive distortions [9], affecting reasoning and information processing and, collectively, represent a core feature of schizophrenia, impacting clinical and functional recovery [10-13]. Thus, addressing overall cognitive health in schizophrenia is crucial. Over the past 25 years, advancements in psychological interventions, including cognitive remediation (CR) and metacognitive training (MCT), have shown promise for the treatment of schizophrenia spectrum disorders (SSDs). Both CR and MCT have been found to enhance cognitive functioning and decrease cognitive biases [14,15].

Cognitive Health Interventions in Schizophrenia: State of the Evidence and Delivery Format

Meta-analyses affirm the effectiveness of CR in enhancing cognition [14,16,17] and MCT in addressing cognitive biases [15,18]. Notably, various mental health practitioners with an understanding of cognitive processes can be trained to provide these interventions, providing flexibility in service delivery [19-21]. Delivered in a group format, these interventions enable practitioners to reach multiple service users simultaneously [20]. Research indicates the feasibility of using technology for remote cognitive assessment and psychological interventions, as individuals with psychosis express interest and willingness to engage with digital mental health services [22-24] and find this mode of communication more satisfying and less challenging than observed in the general population [25].

Preliminary Work on Remote Delivery of Cognitive Health Interventions

Our preliminary work investigated the remote delivery of action-based cognitive remediation (ABCR) and MCT [26]. ABCR is a distinct form of CR, which integrates the traditional cognitive training techniques of CR with simulated workplace scenarios and goal setting [27]. This work involved evaluating 3 crucial early implementation outcomes: acceptability, appropriateness, and feasibility for both patients and therapists. Across 6 cohorts (3 ABCR and 3 MCT) conducted within Montreal, patients expressed high acceptability, with overall satisfaction for expectations and perception of progress. The interventions demonstrated feasibility; 36 participants completed therapy, attending an average of 10 MCT sessions and 12 ABCR sessions.

Using recently developed measures [28], therapists also reported excellent acceptability, appropriateness, and feasibility of the interventions [26]. Several facilitators and barriers to delivering these digital interventions were also identified. Barriers comprised patients' clinical status (eg, more severe symptomatology and medication side effects), interaction issues (eg, lack of involvement and decreased accountability), technological challenges (eg, access to devices and the internet), program elements (eg, language options), and scheduling conflicts. On the other hand, facilitators included patients' motivation to learn, therapist characteristics (eg, warmth and proper training), financial support for internet connectivity, program support (eg, education on interventions and ice breakers), and logistical adjustments (eg, offering evening sessions and forming smaller groups).

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Objectives

Having established the acceptability, appropriateness, and feasibility of our digital interventions that collectively represent the early stages of implementation, the next step is to examine how the proposed digital strategies promote the uptake of these interventions across mental health care settings. A major challenge with evidence-based psychosocial interventions is that very few are subsequently tested in effectiveness or implementation trials and thus have little impact on population health [29]. The field of implementation science has emerged over the last 20 years, promoting strategies to adopt and integrate evidence-based interventions and change practice patterns within specific settings. Implementation frameworks, such as the Consolidated Framework for Implementation Research (CFIR) [30], provide the roadmap and tools to achieve this. To test this implementation strategy, we propose a study spanning 5 different mental health care sites across Canada. In collaboration with partners and knowledge users, we will conduct a hybrid effectiveness-implementation trial and create a bilingual digital learning platform (English and French) to ensure the long-term use of these digital interventions nationwide. The first objective of this study is to investigate the clinical effectiveness of the digital modality of ABCR and MCT. The second objective of the study is to investigate the implementation strategy involving (1) the contextual factors influencing the digital delivery of cognitive health interventions [31], (2) the effectiveness of a digital learning platform (E-Cog) to train mental health practitioners, and (3) the sustainability of the maintenance of these interventions within current clinical settings.

Methods

Study Design

A hybrid effectiveness-implementation trial [32-34] relying on digital technology will be used. The effectiveness component involves assessing the outcomes of these interventions, while the implementation component focuses on conducting the research in a way that emulates the naturalistic clinical setting. This design is ideal for transferring evidence-based behavioral interventions into real care environments [32-35], as it confirms clinical effectiveness while targeting necessary procedures to deliver and sustain such interventions in real-world care settings. A nonrandomized concurrent controlled design will be used to assess clinical effectiveness where one intervention acts as the active control for the other. The nonrandomized concurrent controlled design was selected, as it eases access to the preferred intervention by service users, overcoming the challenges of randomizing participants in real care settings and facilitating recruitment.

Study Setting

This study takes place across 5 sites providing care to those with psychotic disorders across Canada. These sites include the Centre intégré universitaire de santé et de services sociaux (CIUSSS) de l'Ouest-de l'Ile de Montréal, Royal Ottawa Health Care Group, Kingston Health Sciences Centre, Ontario Shores Centre for Mental Health Sciences in Toronto, and Vancouver Coastal Health. We will recruit 390 service users across the 5 sites.

Selection Criteria

Inclusion criteria include 18 years of age or older; diagnosis of affective or nonaffective psychosis or related disorder; followed and treated by a clinician at one of the services mentioned earlier; considered symptomatically stable and capable of using the digital platforms and participating in intervention groups, as judged by their primary clinicians; access to a private space to ensure group confidentiality; and provision of emergency contact and consent to allow researchers to contact their clinician or emergency services in the event of an emergency during study procedures. Most criteria are present for the safety of the group and participants. Exclusion criteria include intellectual disability, hospitalization at the time of recruitment, inability to speak or read English or French, and high suicide risk as per evaluation. We will recruit 4-6 mental health practitioners per site who will complete training on the E-Cog training platform to deliver the 2 cognitive health interventions. Practitioners will be eligible if they have a background in psychology, social work, nursing, or any other health-related training.

Recruitment

Recruitment for this study uses a multimodal communication strategy designed to effectively reach potential participants. This strategy includes displaying informational flyers on hospital television screens, distributing email newsletters to health care employees, and presenting intervention details to case managers to facilitate referrals. Additionally, recruitment materials will be posted in clinic waiting rooms. n example of the recruitment pamphlet is provided in Multimedia Appendix 1. Health care team members can refer eligible participants or obtain consent for the research team to make direct contact. Participants are permitted to be engaged in other psychological or psychosocial interventions while participating in our study. Data on whether they are currently receiving other interventions will be collected.

Ethical Considerations

This study has been approved by the respective research ethics boards (REBs) of the 5 mental health sites and their partner institutions. The study will be conducted in Montreal (CIUSSS de l'Ouest-de l'Ile de Montréal; REB 2023-561) [36], Ottawa (Royal Ottawa Health Care Group; REB 2022034) [37], Kingston (Kingston Health Sciences Center; REB 6037321) [38], Toronto (Ontario Shores Centre for Mental Health Sciences; REB 38116) [39], and Vancouver (Vancouver Coastal Health; REB H22-02300) [40]. The research adheres to the principles outlined in the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans and complies with Canadian legal requirements for scientific research involving human participants, including the Privacy Act and applicable clinical trial regulations [41]. Participants provide informed consent through a comprehensive process that includes a detailed explanation of the study's objectives, procedures, potential risks and benefits, and their rights as research participants, in accordance with the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans guidelines. This process will involve both written documentation and verbal discussion, and participants will be informed of their right to withdraw from the study at any time without consequence to their ongoing care. Particular attention will be given to ensure

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an understanding of these processes among individuals with SSDs. All collected data will be deidentified using unique participant codes, with personal identifiers stored separately in encrypted files accessible only to authorized research personnel. In terms of compensation, participants will receive monetary remuneration for each completed assessment measure, with a standardized gift card amount of US $18 per assessment session or focus group. This compensation structure ensures fair and consistent reimbursement for participants' time and effort while maintaining ethical standards for human participant research. The compensation details will be clearly communicated to participants during the informed consent process to ensure transparency and avoid undue influence on participation decisions.

Measures

To assess the effectiveness of the 2 digital cognitive health interventions (objective 1), primary outcomes will encompass quantitative measures of cognitive function for ABCR and cognitive biases for MCT. These outcomes were selected in alignment with the primary targets for each intervention and primary outcomes assessed in the past ABCR and MCT studies. To capture the full extent of these outcomes, both objective and self-report measures were selected. The collection of these primary outcomes will be prioritized. Secondary outcomes for both interventions will include clinical and functional measures. Propensity score matching will consider background characteristics such as sociodemographic variables, illness duration, medication dosage, length and nature of prior treatment, and subjective reports of cognitive capacity and biases. To promote data quality, research staff will partake in centralized interrater reliability sessions every 6 months. To evaluate the implementation strategy (objective 2), a combination of quantitative and qualitative data will be gathered. Refer to Table 1 for a breakdown of the data types to be collected, organized by objectives, time points, and stakeholders.

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Table 1. Summary of the type of data to be collected as a function of objectives, time points, and stakeholders.

Objectives or data type and measures	Measurement time points	Stakeholder groups
1. Effectiveness (quantitative)		
Cognitive tests or tasks: • Brief version of the CANTAB[a] computerized battery (Intra-Extra Dimensional Set Shift, Stocking of Cambridge, and Spatial Working Memory)[b] [42] • Wechsler Memory Scale (Logical Memory Subscale)[b] [43] • Cognitive bias against disconfirmatory evidence story[b] [44] • Jumping to conclusions (Beads)[b] [45] Subjective cognition: • Subjective Scale to Investigate Cognition in Schizophrenia (Brief)[b] [46] • Cognitive Motivation Scaleb [47] • Davos Assessment of Cognitive Biases Scale[b] [48] Symptoms: • Positive and Negative Syndrome Scale-6 [49] • Brief Negative Symptom Scale [50] • Psychotic Symptom Rating Scales [51] Psychosocial: • Self-Esteem Rating Scale—Short Form [52] • Overall Emotional and Social Loneliness Scale [53] • Short Warwick-Edinburg Mental Well-Being Scale [54] • Questionnaire About the Process of Recovery [55] • Basic Psychological Need Satisfaction and Frustration Scale [56] • Autonomous-Controlled Motivation for Intervention Questionnaire [57] • Personal and Social Performance [58]	• Preintervention • Postintervention • 3-month follow-up	Service users
Intervention: • Health Care Climate Questionnaire [59] • Autonomous-Controlled Motivation for Intervention Questionnaire [57] • MMI[c] Cognitive Training Questionnaire [60] • Satisfaction With Therapy (STQ[d]) [61] • Time spent on cognitive drill exercises (ABCR[e]) • Last log in (iCog platform)	• Midintervention	Service users
2. Implementation (quantitative and qualitative)		
Evaluation of E-Cog platform: • Number of practitioners invited to participate in the E-Cog training • Number of practitioners agreeing to participate in E-Cog training • Reasons for nonparticipation or participation • Number of practitioners not agreeing to participate in E-Cog training • Total number of attendees participating in all of the training modules • Total number of attendees per session or module • Semistructured interview (health care practitioners)	• Preintervention • During intervention	Health care practitioners and service users
Evaluation of factors influencing the implementation of the 2 digital interventions: • E-Therapy Attitudes and Process Questionnaire—Therapist Version [62] • Semistructured interview (service users and health care practitioners)	• Postintervention (8-12 and 24-30 months after the 2 interventions are implemented)	Health care practitioners and service users
Sustainability: • Program Sustainability Assessment Tool [63] • Monitoring of the intervention offer after an effectiveness trial at each site	• Postintervention	Health care practitioners and service users

[a]CANTAB: Cambridge Neuropsychological Test Automated Battery.

[b]Denotes primary outcomes in the study.

[c]MMI: MUSIC Model of Academic Motivation Inventory.

[d]STQ: Satisfaction Therapy Questionnaire.

[e]ABCR: action-based cognitive remediation.

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Cognitive Health Interventions

Interventions will be delivered through a secure videoconference platform. Network-connected tablets will be provided as necessary for the trial duration. ABCR [27,64] sessions consist of computer-based cognitive training activities (Brain Training Pro; 60%), teaching of problem-solving strategies (20%), and transfer activities (20%). Transfer activities include discussing and role-playing how cognitive skills are applied in everyday life and teaching potential strategies for overcoming cognitive challenges. ABCR targets include processing speed, attention, memory, executive functions, and social cognition, which are all commonly impaired in psychosis [12]. ABCR will be delivered in 16 sessions lasting 1.5 hours each over an 8-week period. MCT targets cognitive biases and errors in judgment underlying delusions using the theoretical foundations of cognitive behavioral therapy [65]. Sessions consist of discussions and activities aimed at increasing participants' awareness of distortions and expanding their current problem-solving strategies. MCT will be delivered in 12 sessions lasting 45-60 minutes each over 6 weeks.

Both interventions will be offered at all sites. Depending on the site, interventions will either be offered concurrently or in sequence. Intervention group allocation follows a personalized, participant-centered approach. Potential participants will meet individually with the research coordinator at their site, who will provide a comprehensive overview of both interventions. Together, they will collaboratively determine which intervention best aligns with the participant's personal goals and preferences. To maximize participant benefit and engagement, individuals will have the opportunity to complete the alternative intervention after finishing their initial chosen intervention. This flexible approach ensures that participants can potentially benefit from both interventions.

To improve adherence, participants will be contacted prior to each session with reminders. If participants miss several sessions in a row, therapists or a research assistant will contact them to confirm their interest in continuing the intervention and discuss any barriers to their participation. If any adverse reactions occur during the trial, participant involvement in our study may be discontinued after a discussion with the research team. Finally, to improve and track treatment adherence, sessions will be audio recorded, and 2 sessions from each of the ABCR and MCT groups will be randomly selected for review by 2 experienced facilitators using the treatment integrity assessment tool.

Training Platform

E-Cog training platform [66] is a digital platform providing training certifications for ABCR and MCT interventions developed by our group following the analyze, design, develop, implement, and evaluate model for the design of digital learning platforms [67]. Each training certification includes three training modules: (1) impact of cognitive impairments in psychosis and an introduction to remediation strategies (2 hours), (2) technological tools for digital mental health (1 hour), and (3) theoretical foundations and practical delivery of ABCR (~9 hours) or MCT (~12 hours). After obtaining the training certification, mental health practitioners participate in weekly supervision by a dedicated experienced trainer using a secure videoconferencing software. Screenshots from the training platform can be found in the multimedia appendices (Multimedia Appendices 2-4).

Involvement of Individuals With Lived Experience

Peer support workers have been involved at different stages of the project. The pilot study, which informed this study, involved 2 peer support workers in the project committee. In this study, our peer support worker has been providing continuous consultation, which has led to changes throughout the study (eg, adapting intervention materials). Our peer support worker will also be involved in the intervention groups and will be coconducting the service user qualitative interviews.

Statistical Analysis

Power

Monte Carlo simulations computed in R (R Foundation for Statistical Computing) were used to estimate the required sample size for our proposed models. Our analyses, based on simulated data, suggest that a total sample size of 300 provides enough statistical power (up to 90%) to detect anticipated effect sizes on primary outcomes of cognitive capacity and cognitive bias based on values from our group and those reported in the literature (CR: d=0.50 and MCT: g=0.27) [9,20,27,31]. The attrition rate for our digital groups has been approximately 20%; we will nonetheless conservatively adjust for an attrition rate of 30%. When considering the propensity score, this results in a requirement of 390 participants. Comparable studies using the same interventions and statistical methods in in-person settings have included similar sample sizes as those proposed at our individual sites [68,69]. Further, this sample size will allow us to detect anticipated effect sizes on secondary outcomes related to symptomatology (CR: d=0.28 and MCT: g=0.38) [70,71] and functioning (CR: d=0.36-0.51 and MCT: d=0.37) [31,71,72]. We also anticipate that the proposed sample size will be adequate to explore sex- and gender-related differences using subgroup analyses of 2 (male and female) and 4 (men, women, nonbinary, and other) groups, respectively.

Data Analysis

Data related to the analysis of objective 1, focusing on clinical effectiveness, will be compared between both interventions. Primary and secondary outcomes will be compared between the 2 interventions, using one as the active control for the other. First, propensity score matching will be used to identify a subset of participants who will comprise the active control group that is equivalent to the intervention group on background variables (sociodemographic variables, illness duration, medication dosage, length and nature of prior treatment as well as subjective reports of cognitive capacity and cognitive biases). Then, Z-standardized outcome data will be compared between the groups with generalized linear mixed effect modeling techniques using R software. Factors of interest will include fixed time (pre, post, and follow-up), fixed treatment (ABCR and MCT), fixed time and treatment interaction (time*treatment), random site (CIUSSS de l'Ouest-de l'Ile de Montréal, the Royal's Institute in Ottawa, Kingston Health Sciences Centre, Ontario Shores Centre for Mental Health Sciences in Toronto, and Vancouver Coastal Health), random intercepts (participants'

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ID), and random slopes (participant*time). Age, illness duration, medication dosage, length, and nature of prior psychological treatment will also be included as fixed covariates. This procedure will be done twice, with the active control group subset using propensity score matching. This approach ensures that participants are not counted twice and is an integral part of the propensity score matching procedure. Statistically, performing the procedure twice helps to validate the robustness of the matching process without introducing bias, as each participant is only included once in each comparison. Specifically, the procedure will be as follows: (1) ABCR as the intervention and MCT as the active control and (2) MCT as the intervention and ABCR as the active control. Missing data pattern will be assessed for whether it is missing completely at random, missing at random, or not at random [73]. If data are missing at random, multiple imputation will be applied [74]; if data are missing not at random, then the robustness of the primary analyses will be evaluated through sensitivity analyses.

Analyses for all implementation objectives will be executed using descriptive statistics for quantitative data and thematic analysis for qualitative data, following Braun and Clarke's [75] interpretive descriptive approach. This method emphasizes the researcher's active role in the analytical process, allowing for a nuanced understanding of themes such as facilitators and barriers to implementation, identified from CFIR semistructured interviews. Investigator triangulation will be used, with 3 independent raters conducting iterative qualitative analyses until a consensus (≥80%) is reached. A convergent quantitative-qualitative mixed methods design [76] will facilitate a comprehensive comparison of results from quantitative and qualitative analyses, aiming to develop a holistic understanding of factors influencing implementation. Side-by-side comparison tables will support this analytical process and engage implementation teams in interpretation. To ensure reflexivity, member checks will be conducted with participants to validate findings, ensuring that their perspectives and interpretations are accurately represented and that any potential biases in the researcher's analysis are addressed. This methodological framework is designed to uphold rigorous standards in qualitative research while ensuring that the findings are credible, dependable, and relevant to broader contexts. All qualitative analyses will be done using NVivo (version 15; Lumivero).

Results

A pilot pragmatic trial [26] has been conducted previously at the Montreal site, where 6 cohorts (3 ABCR and 3 MCT) were run, evaluating 3 early implementation outcomes: acceptability, feasibility, and engagement. Of the 28 participants attending at least 1 session, 21 completed more than half of the sessions. All completers reported a positive experience with therapy, 2 of 3 were not bothered by the remote setting, and 16 trusted the confidentiality of the information shared. Technology did not appear to significantly impede program participation. Therapist-rated levels of engagement were also satisfactory [26].

This study was approved by the institutional review board by September 2023. From September 2022 to January 2023 staff training was conducted across all 5 sites. Intervention materials including intervention manuals and digital portals began in June 2022 and continued until November 2023. Therapist training began on the E-Cog learning platform in April 2023 and is ongoing. All sites began recruitment in 2023 and have run cohorts of MCT and ABCR in their respective regions. Quantitative data collection occurs prior to and following the intervention group and is ongoing, qualitative data collection for implementation assessment began in summer 2024 and is ongoing. As of winter 2024, a total of 114 participants have been recruited and 32 therapists are enrolled in the E-Cog training platform with 25 therapists having completed the training. The updated project timeline can be accessed for those who create free accounts on the iCogCA Hub web page [77].

Discussion

Overview

This study aims to address the crucial clinical needs of individuals with SSD by evaluating the feasibility and effectiveness of delivering cognitive health interventions through a digital platform. We hypothesize that these interventions will yield positive outcomes in terms of accessibility, engagement, symptom reduction, and cognitive functioning.

Principal Findings and Comparison to Prior Work

The objectives of this study are 2-fold, focusing on both service users and mental health care providers. The first objective aims to assess the effectiveness of digital cognitive health interventions in enhancing accessibility and engagement for individuals with SSD. If proven effective, these interventions may provide an evidence-based framework for other service providers providing care for individuals with psychotic disorders and could be adapted for other populations receiving mental health services where these interventions show similar efficacy (eg, mood disorders) [78,79]. Objective 2 aims to identify facilitators and barriers to digital delivery and a digital training platform for clinicians. We anticipate that this study will introduce and validate our platform to train and supervise mental health care practitioners to deliver these interventions, which will then be made accessible to the broader mental health community. Further, these findings will furnish crucial information for the implementation of digital health technologies to improve access to psychosocial therapies for optimized care. These findings will be used to guide the implementation of similar projects across Canada. Notably, New York State has already fully integrated CR into its psychiatric care systems [80], and parallel efforts are underway in Australia [81] and the United Kingdom [82]. Collaborating with a National Steering and Implementation Committee, we will test our set of tools based on the CFIR and make them accessible to the mental health community. Site-specific implementation committees, which include patient partners, will assist with the local implementation of our cognitive health interventions.

Strengths and Limitations

This proposed national collaborative effort serves as a catalyst for leveraging digital technology to enhance the adoption of evidence-based psychosocial interventions. This study has

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several strengths. The first is the implementation across multiple Canadian sites, which enhances the generalizability of our findings. Second, we also aim to engage a broad pool of participants, both service users and mental health practitioners, by using digital technology to provide the intervention and training. Encouragingly, previous studies have demonstrated that a significant portion of those with severe mental illnesses appear to have the required technological access and ability to join, participate, and benefit from digital services [83,84]. We have also a planned comprehensive collection of quantitative and qualitative data. Our data collection plan involves service users and mental health practitioners at multiple time points, allowing us to answer our research questions in a multifaceted manner. Finally, we have engaged with diverse stakeholders throughout various stages of the study, including those with lived experiences, clinicians, researchers, and managers.

Some limitations of our study include the nonrandomized concurrent controlled design, which raises concerns about potential group differences. However, we will address this by statistically controlling for measurable background characteristics. Second, although we aim to engage a broader population by providing services using a digital format, we acknowledge that there could be variability to technology access. We have planned to provide tablets and internet to service users without access to technology. For service users or health care providers unfamiliar with technology, we will also offer orientation sessions to help them become comfortable with the digital format. Next, the recruitment of therapists within a research setting may not reflect therapists involved in nonresearch settings. In addition, although we have taken great care in selecting instruments that have been validated in our population and available in both English and French, some limitations may still exist with the instruments chosen. For instance, ceiling effects have been observed in the Cambridge Neuropsychological Test Automated Battery cognitive test. Finally, there may exist differences across 5 sites in training experiences and implementation fidelity. We plan to attend to this by standardizing training and fidelity checks conducted across all sites.

Conclusions

In summary, this project aims to address pressing clinical needs related to cognitive impairments and biases in SSDs. By leveraging digital technologies, it aims to facilitate the adoption of evidence-based interventions within clinical settings, support future implementation of similar initiatives, and validate an adaptable platform designed for widespread use.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are not publicly available due to ongoing data collection but are available from the corresponding author on reasonable request.

Authors' Contributions

CA-Y and HT were responsible for writing the original draft and conducting investigations. They will also handle future formal analysis. MB, SG, KML, ET, and GS developed the conceptual framework and methodologies and participated in writing and reviewing the manuscript. AES contributed to the visualization and also engaged in manuscript review and editing. CRB, MM, SM, MP, and TSW contributed to conceptualization and methodology, provided resources, and reviewed and edited the manuscript. ML played a multifaceted role including conceptualization, methodology development, drafting and reviewing the manuscript, as well as overseeing the project administration and securing funding. DR-C was involved in conceptualization, methodology development, writing the original draft, and reviewing the manuscript, in addition to supervising the entire project. All authors reviewed the final manuscript.

Conflicts of Interest

This project is carried out in collaboration with the company SBT, which provides licenses for the Happy Neuron platform. ML reports grants from Roche Canada, grants from Otsuka Lundbeck Alliance, and personal fees from Boehringer Ingelheim, Janssen, Lundbeck Canada, and Otsuka Canada outside the submitted work. SG has received financial compensation for consulting services from Boehringer Ingelheim outside the submitted work. MB has received consulting fees from Boehringer Ingelheim. KML reports consulting fees from Otsuka Canada, Lundbeck Canada, and Boehringer Ingelheim. SM has received consultant fees from

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Boehringer and ROVI and is developer of metacognitive training. DR-C reports consultations fees from Otsuka Canada Pharmaceutical, outside the submitted work. All other authors declare no conflicts of interest.

Multimedia Appendix 1
Example of iCogCA recruitment pamphlet.
[PNG File , 1033 KB - resprot_v14i1e63269_app1.png]

Multimedia Appendix 2
E-Cog training platform home page.
[PNG File , 383 KB - resprot_v14i1e63269_app2.png]

Multimedia Appendix 3
E-Cog training platform action-based cognitive remediation introduction page.
[PNG File , 821 KB - resprot_v14i1e63269_app3.png]

Multimedia Appendix 4
E-Cog training platform metacognitive training introduction page.
[PNG File , 539 KB - resprot_v14i1e63269_app4.png]

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Abbreviations

ABCR: action-based cognitive remediation
CFIR: Consolidated Framework for Implementation Research
CIUSSS: Centre intégré universitaire de santé et de services sociaux
CR: cognitive remediation
MCT: metacognitive training
REB: research ethics board
SSD: schizophrenia spectrum disorder

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Protocol

Evaluating a Web-Based Application to Facilitate Family-School-Health Care Collaboration for Children With Neurodevelopmental Disorders in Inclusive Settings: Protocol for a Nonrandomized Trial

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Abstract

Background: An individual education plan (IEP) is a key element in the support of the schooling of children with special educational needs or disabilities. The IEP process requires effective communication and strong partnership between families, school staff, and health care practitioners. However, these stakeholders often report their collaboration as limited and difficult to maintain, leading to difficulties in implementing and monitoring the child's IEP.

Objective: This paper aims to describe the study protocol used to evaluate a technological tool (CoEd application) aiming at fostering communication and collaboration between family, school, and health care in the context of inclusive education.

Methods: This protocol describes a longitudinal, nonrandomized controlled trial, with baseline, 3 month, and 6-month follow-up assessments. The intervention consisted of using the web-based CoEd application for 3 months to 6 months. This application is composed of a child's file in which stakeholders of the support team can share information about the child's profile, skills, aids and adaptations, and daily events. The control group is asked to function as usual to support the child in inclusive settings. To be eligible, a support team must be composed of at least two stakeholders, including at least one of the parents. Additionally, the pupil had to be aged between 10 years and 16 years, enrolled in secondary school, be taught in mainstream settings, and have an established or ongoing diagnosis of autism spectrum disorder, attention-deficit/hyperactivity disorder, or intellectual disability (IQ<70). Primary outcome measures cover stakeholders' relationships, self-efficacy, and attitudes toward inclusive education, while secondary outcome measures are related to stakeholders' burden and quality of life, as well as children's school well-being and quality of life. We plan to analyze data using ANCOVA to investigate pre-post and group effects, with a technological skills questionnaire as the covariate.

Results: After screening for eligibility, 157 participants were recruited in 37 support teams, composed of at least one parent and one professional (school, health care). In September 2023, after the baseline assessment, the remaining 127 participants were allocated to the CoEd intervention (13 teams; n=82) or control condition (11 teams; n=45).

Conclusions: We expect that the CoEd application will improve the quality of interpersonal relationships in children's IEP teams (research question [RQ]1), will show benefits for the child (RQ2), and improve the well-being of the child and the stakeholders (RQ3). Thanks to the participatory design, we also expect that the CoEd application will elicit a good user experience (RQ4). The results from this study could have several implications for educational technology research, as it is the first to investigate the impacts of a technological tool on co-educational processes.

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KEYWORDS

neurodevelopmental disorders; coeducation; whole-school approach; family-professional partnership; web application; inclusive education; family-school-health care

Introduction

Background

There is a growing body of literature on the benefits of using educational technologies to support children with special educational needs or disabilities (SEND) and, notably, those due to neurodevelopmental disorders (NDD; eg, [1-4]). Most of these technologies target students as their primary users, forgetting the social environment that has to work together to support the children in their educational project. This study aims to conduct a field study to assess the effectiveness of an interactive web application (namely, the CoEd application) for fostering collaboration between family, school, and health care practitioners.

In several countries, a key element in the support of the child's schooling is the individual education plan (IEP), which defines their needs and gathers information on aids and adaptations that can be implemented to help them attain their full potential. IEP structures differ by country, but the core process emphasizes a robust partnership among families, school staff, and health care professionals, with regular meetings and a deep understanding of the child's profile and progress [5,6]. Effective communication between teachers and parents is universally recognized as a cornerstone of a child's education [6,7]. The ability of parents to share pertinent information about their child's disabilities, strengths, and weaknesses significantly enhances educators' awareness and enables them to tailor their pedagogical approaches [8]. Furthermore, parental involvement in the educational process has far-reaching implications, encompassing the holistic development and well-being of children with SEND. It serves as the bedrock for fostering a culture of productive family-school collaboration and cultivating a supportive school environment [9,10]. For students grappling with complex disorders such as autism spectrum disorder (ASD), the synergy of collaboration between parents and educators paves the way for improved academic performance, smoother integration, and enhanced social adaptation [11]. In a broader context, collaboration between parents and educators emerges as a catalyst for positive outcomes, benefiting students across the spectrum of educational needs [12]. Despite all of this, studies on the IEP process consistently underscore the pronounced discord between stakeholders' aspirations for effective teamwork and the actual communication and collaboration practices in place [12-17]. This paradox is particularly evident in the experiences of parents, teachers, and educators who frequently encounter obstacles ranging from resource constraints to training deficits, communication impediments, intercoordination challenges, and intricate administrative processes [12,18-22]. These challenges are not unique to inclusive education of children with NDD and extend to other areas such as patient care [23,24].

Within the continuum of collaborative practices in inclusive education, 3 progressive levels can be delineated: cooperation, coordination, and collaboration [25]. As elucidated by Larivée et al [26], elevation in the school-family-community collaboration level correlates with mutual recognition of expertise, bidirectional communication, shared responsibilities, and the spirit of reciprocity.

Several theoretical models of collaborative practices within the framework of IEPs have been proposed. These models may pivot around the child, exemplified by the "Whole School, Whole Community, Whole Child" model [27,28], or emphasize the dynamics of partnerships between stakeholders, as exemplified by the Sunshine model [29]. Other models are grounded in the objectives of IEPs, as demonstrated by polycentric approaches based on the child's life project [30]. Additionally, some models embrace a multidimensional perspective typified by the Holistic School Care Coordination System Model [31,32].

The proliferation of these models underscores the pivotal role of educational systems in facilitating interactions between educators and families. This entails the provision of guidelines and recommendations for effective collaboration, alongside the allocation of critical resources encompassing time, physical infrastructure, and financial support [19,20]. Among the envisaged solutions, harnessing digital technologies emerges as a promising avenue to support continuous communication for efficient stakeholder collaboration [33,34].

Prior Work

Maintaining communication and collaboration within the extended team for IEPs is challenging due to various communication channels like emails and phone calls. Despite digital advancements, tools often prioritize one-to-one communication over team-based sharing. Additionally, the lack of trackability in one-to-one exchanges hampers information flow within the team. To the best of our knowledge, very few digital tools are designed to help stakeholders with team-based information sharing, communication, and collaboration in the follow-up of the IEP and of the child's schooling and development [35]. Many proposed devices in this field lack maturity, either due to an inadequate design that does not consider user needs, resulting in usability issues, or because participatory design methods were used without subsequent effectiveness studies conducted to standard methodological levels for producing evidence (for a review, see [35]). An example of that is illustrated by the CoEd application, which provides a web application with functionalities aiming at fostering information sharing, communication, and collaboration in IEP and with the support team [36]. Through participatory methods, the CoEd application was designed based on stakeholders' needs and iterative design steps for eliciting good

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user experience, usability, and utility (see [36] for the design process).

Aims

We propose to conduct a field study aiming to evaluate the impact of using the CoEd web application on 3 outcomes. First, we hypothesized that the CoEd application will improve communication and relationships between stakeholders (family, school, and health care practitioners), as well as their attitudes toward school inclusion, and increase each stakeholder's perceived self-efficacy (research question [RQ]1). Second, we hypothesized a beneficial effect of using CoEd on the child in terms of behavioral or academic functioning (RQ2). Third, we expect that using CoEd results in a better quality of life for both the stakeholders and the children (RQ3). Finally, as it is crucial when evaluating technology to verify that it is both effective and usable [37], we added measures related to the user experience of participants. Thanks to the participatory design, we expected that the CoEd application will elicit a good user experience (RQ4).

The paper follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines for reporting study protocols [38]. The SPIRIT checklist for this paper is provided in Multimedia Appendix 1.

Methods

Ethical Considerations

The ethics committee (Comité Opérationnel d'Évaluation des Risques Légaux et Éthiques [COERLE]) of the French National Institute of Informatics and Mathematics (Inria) approved the study protocol (application number 2022-08).

As the study protocol implies the management of health-related data, the CoEd app is hosted and managed on a secured server at Inria as if CoEd's data are medical data, in respect of the General Data Protection Regulation (GDPR). Additionally, the study protocol and data management processes were approved by the National Commission of Informatics and Liberty and by the Inria Security Homologation committee (application number 13953). All participants were informed about the study and gave written informed consent.

Study Overview

We designed a longitudinal, nonrandomized controlled trial to evaluate the impact of the CoEd application developed by our team [36]. We enrolled teams monitoring the school or social inclusion of secondary school pupils with NDD (between 10 years and 16 years old). These teams were recruited throughout France via email communication with schools, school districts, special education advisors, academic inspectors specializing in Special Education, and associations supporting families of children with NDD. Field partners of the project, namely the Nouvelle-Aquitaine academy, Autism Resources Center, and Association pour la Réadaptation et l'Intégration, were also engaged in the recruitment process and encouraged participation in their networks. We also put out calls for participants on digital social networks. Parents, teachers, and health care professionals were asked to complete a questionnaire to check the inclusion criteria. When the participant and child were eligible, all the members of the follow-up team were contacted, and the study was presented to them. Once participation was confirmed, individual participants received a consent form. They were given a week to return the completed form, with researchers available to address any questions during this period.

Whether they were in the control or experimental condition, they had to complete a baseline assessment and a 3-month follow-up assessment, and if they were willing to continue participating, they would complete a 6-month follow-up assessment (Figure 1).

Figure 1. Timeline of the field study according to the group conditions and the number of school terms (3 months for each term) for study participation.

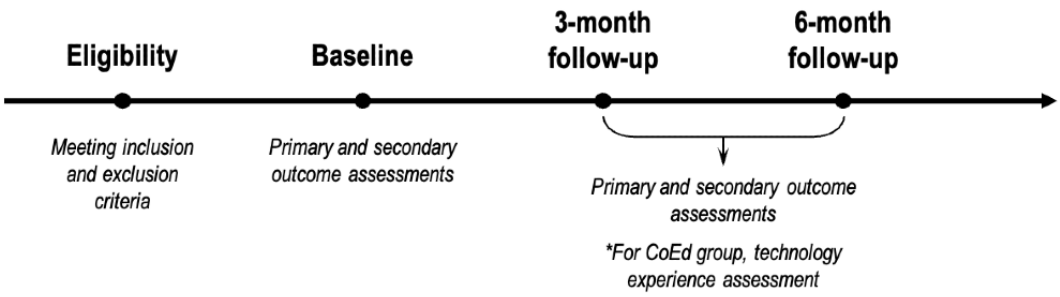

Eligibility Criteria

To participate, a support team had to consist of at least two stakeholders, including at least one of the parents. Additionally, the pupil had to be aged between 10 years and 16 years, enrolled in secondary school, be taught in mainstream settings, and have a diagnosis of ASD, attention-deficit/hyperactivity disorder, or intellectual disability (IQ<70). The pupil needed either an established diagnosis or to be undergoing a multidisciplinary intervention for diagnosis.

Allocation and Blinding

In this quasi-experimental trial, the group allocation was not randomized. Group allocation was carried out as participants were recruited according to eligibility criteria, taking care to balance groups in terms of team size. A nonrandomized procedure was chosen because we recruited participants as volunteers arose who had a complete team. As the control group did not use the CoEd application and functioned as usual whereas the experimental group was asked to use the CoEd application and needed secure access to the web-based application, it was not possible to conduct a double-blind study.

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Outcome Measures

Selection of Outcome Measures

Outcome measures were chosen from the researchers' hypotheses and participatory decision-making. In 2 focus groups, parents, teachers, and health care professionals discussed the CoEd application's potential impact and evaluation criteria (Multimedia Appendix 2). Participants reviewed preselected indicators and suggested new measures, especially concerning quality of life and caregiver burden, for the field study. As a result, the primary outcomes include 3 main dimensions (ie, stakeholders' relationships, perceived individual efficacy, and attitudes toward school inclusion). To this end, parents, teachers, and health care professionals completed a series of common or specific questionnaires (Table 1). The secondary outcomes include measures for stakeholders (burden and quality of life) and for the children (quality of life, school well-being, and school inclusion perception; Table 1). Additionally, a measurement of technology experience that covers technology skills and CoEd experience was included for the intervention group (Table 1). Although some questionnaires had a validated French version, others did not. In the latter case, as we are French native speakers, we translated them in collaboration with native English speakers. The scales used are presented in Table 1.

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Table 1. Description of the assessment batteries to address the targeted (primary and secondary) outcomes and technology experience of participants.

Outcomes, dimension, and subdimension	Questionnaire	Respondent			
		Child	Parent	Teacher	Professionals
Primary outcomes (stakeholders)					
Relationship					
Parent-teacher	Parent-Teacher Relationship Scale II[a]	—[b]	X	X	—
Therapeutic or interprofessional	Helping Alliance Questionnaire	—	X	X	X
Perceived educational efficacy					
Self-efficacy	Basic Psychological Need: Satisfaction and Frustration scale	—	X	X	X
Achievement of educational goals	Goal Attainment Scale	—	X	X	X
Attitudes toward school inclusion					
Teachers	Multidimensional Attitudes Towards Inclusive Education Scale	—	—	X	—
Parents	Attitudes Toward Inclusion/Mainstream[a]	—	X	—	—
Secondary outcomes (stakeholders)					
Burden					
Family burden	Caregiver Strain Questionnaire	—	X	—	—
Adult burden	Zarit Inventory Short Form	—	—	X	X
Burnout	Maslach Burn-out Inventory[a]	—	X	X	X
Quality of life					
Adult	WHOQOL-Bref	—	X	X	X
Family	Beach Center Family Quality of Life (FQOL)	—	X	—	—
Secondary outcomes (children)					
School life					
Child's quality of life	Pediatric Quality of Life Inventory (PedsQL)	X	X	—	—
School well-being	Multidimensional Students' Life Satisfaction Scale (MSLSS)	X	—	—	—
School inclusion	Individual school perception	X	—	—	—
Technology experience[c]					
Technology skills					
Computer skills	Computer Usage Questionnaire	—	X	X	X
CoEd application experience					
Subjective user experience	User Experience Questionnaire, short version and Technology-based Experience of Need Satisfaction (TENS)[a]	—	X	X	X
Objective user experience	The uses and usages of the CoEd application are quantified with the following indicators across periods of 3 months or 6 months: (1) number of times the application is opened and (2) number of exchanged posts	—	X	X	X

[a]Translated in French by the authors.

[b]Not applicable.

[c]Intervention group only.

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Primary Outcomes

Perception of Stakeholders' Relationships

Parents and teachers completed the Parent-Teacher Relationship Scale [39], which consists of a 24-item questionnaire measured on a 5-point Likert scale (1=strongly disagree to 5=strongly agree) assessing the 2 dimensions joining and communication-to-other, including their feeling of affiliation and support; the dependability and availability of both parties; shared expectations; and beliefs about the child and each other, their communication, and their sharing of information and emotions. To assess the relationship with medical-social professionals, the Helping Alliance Questionnaire [40] was completed by parents, teachers, and health care practitioners. The Helping Alliance Questionnaire initially evaluated the therapeutic alliance through the 2 dimensions perceived helpfulness and collaboration, but it was adapted to the purpose of the study. Two versions were used: a 13-item parent form and an 11-item professional form, both using a 6-point Likert scale (1=totally disagree to 5=totally agree).

Perceived Individual Efficacy

The feeling of self-determination was measured using the French version of the Basic Psychological Need Satisfaction and Frustration Scale [41], which assesses satisfaction and frustration with the 3 basic psychological needs: competence, affiliation, and autonomy. This 24-item scale using a 5-point Likert scale (1=Completely False to 5=Completely True) provides a proxy of general individual efficacy. A version of the Goal Attainment Scale [42] adapted by our team was proposed. Initially, parents and professionals were asked to independently specify 2 to 5 school, social, or behavioral goals for the young individual, along with their current level, desired level, difficulty, and importance. At the end of the experimentation, the goal was recalled, and the adults were asked to assess the level of goal attainment. This adapted version of the Goal Attainment Scale provides a probe of (individual) educational efficacy.

Attitudes Toward Inclusive Education

The parents' attitudes toward inclusive education was measured using the Attitudes Toward Inclusion/Mainstream scale [43]. This questionnaire, consisting of 18 items that are rated on a 5-point Likert scale (1=strongly agree to 5=strongly disagree), assesses the overall attitude of parents toward the inclusion of students with disabilities in mainstream schools, including 4 dimensions (benefits factor, satisfaction with special education, teacher ability and inclusion support, child rights). The Multidimensional Attitudes Towards Inclusive Education Scale [44] was selected to evaluate teachers' attitudes toward the inclusion of students with disabilities in mainstream schools. It consists of 18 items assessed using a 6-point Likert scale (1=strongly disagree to 6=strongly agree) and measuring 3 dimensions (cognitive, affective, behavioral).

Secondary Outcomes

Perception of Caregiver Burden

Parents and professionals completed the Zarit Burden Inventory Short Form [45,46], which consists of 12 items assessing the individual perception of their burden. Each item is scored between 1 point and 5 points (1=never to 5=almost always), and the total score is the sum of all item scores. The higher the score is, the higher the burden is, with the following cut-offs: no to mild burden (0-10), mild to moderate burden (10-20), and high burden (>20). For parents, the assessment was completed with the Caregiver Strain Questionnaire [47] to evaluate the familial burden through 21 items using a 5-point Likert scale (1=not at all to 5=very much) and 3 dimensions (objective burden, internalized subjective burden, and externalized subjective burden). The Caregiver Strain Questionnaire has been specifically validated with families of children with disabilities, including NDD or ASD. For professionals, the level of burnout was assessed using the French version of the Maslach Burnout Inventory [48], a 22-item scale using a 7-point Likert scale (1=never to 7=every day) that evaluates emotional exhaustion, depersonalization in relationships with others, and a sense of reduced personal accomplishment in one's work.

Stakeholders' Quality of Life

Parents and professionals completed the WHOQOL-BREF [49], a 26-item scale using a 5-point Likert scale (1=Very Low, Very Dissatisfied, Not at all, Very Difficult, Never to 5=Very High, Very Satisfied, Extremely, Very Easily, All the Time) recommended by the World Health Organization to assess individuals' quality of life based on 4 dimensions (physical health, psychological health, social relationships, environment). The quality of life of the family was assessed using the Beach Center Family Quality of Life scale [50], adapted into French by Rivard et al [51]. This scale, consisting of 25 items using a 5-point Likert scale (1=Slightly Important, Very Dissatisfied to 5=Very Important, Very Satisfied), measures 5 dimensions of family quality of life: family interactions, parenting, emotional well-being, physical and material well-being, and disability-related support.

Child's Quality of Life

The pupil's quality of life was assessed using the Pediatric Quality of Life Inventory [52]. The Pediatric Quality of Life Inventory is composed of 23 items using a 5-point Likert scale (0=never to 4=almost always) assessing children's physical, emotional, social, and school functioning through self-report (completed by children) and proxy report (completed by parents).

Child's Perception of School Life

The student's sense of school inclusion was evaluated using the single-item inclusion scale by Aron et al [53], which measures 7 levels of the sense of inclusion and has been adapted to assess the sense of inclusion in both the school and peer group contexts. School satisfaction was evaluated using an 8-item subscale that uses a 7-point Likert scale (1=strongly disagree to 7=strongly agree) derived from the French adaptation of the Multidimensional Students' Life Satisfaction Scale [54,55].

Measurement of Technology Experience (Experimental Group Only)

To assess the potential effect of prior technology skills on the use of CoEd, parents and professionals completed the Computer Usage Questionnaire [56] that consists of a self-reported measure of 18 questions asking for the frequency (5-point scale

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ranging from never to very often) of different computer activities and software usage.

To address the specific user experience with the CoEd application, the User Experience Questionnaire short form [57] was selected as the measurement. It uses a 7-point Likert scale (–3=fully agree with negative term to +3=fully agree with positive term) of subjective perceptions of users in terms of both the hedonic and pragmatic dimensions toward a given product and according to a benchmark for digital products. The Technology-based Experience of Need Satisfaction-Interface [58] is related to the self-determination theory framework for assessment and uses a 5-point Likert scale (1=Do Not Agree to 5=Strongly Agree) to assess basic psychological need (autonomy, competence, relatedness) satisfaction through the interaction with the interface or system. Satisfaction of these needs is arguably associated with sustained engagement with a technology.

Complementary to the subjective measures, direct measures of CoEd use and usage are collected through active interactions (log data) with this web application, in particular the number of times the app was opened and the number of exchanged posts (Table 1).

Presentation of the CoEd Technology

Specific to the French school context, the CoEd application (Figure 2) is accessible through a web browser and allows users to view and edit one or multiple student files. Users need to be registered by the administrator and can log in with an email and password. Roles—parent, teacher, or external professional—are assigned during registration, offering equal file access rights. A designated moderator role, open to any team member by consensus, is suggested for content moderation.

Figure 2. Screenshots of different tabs from the CoEd app.

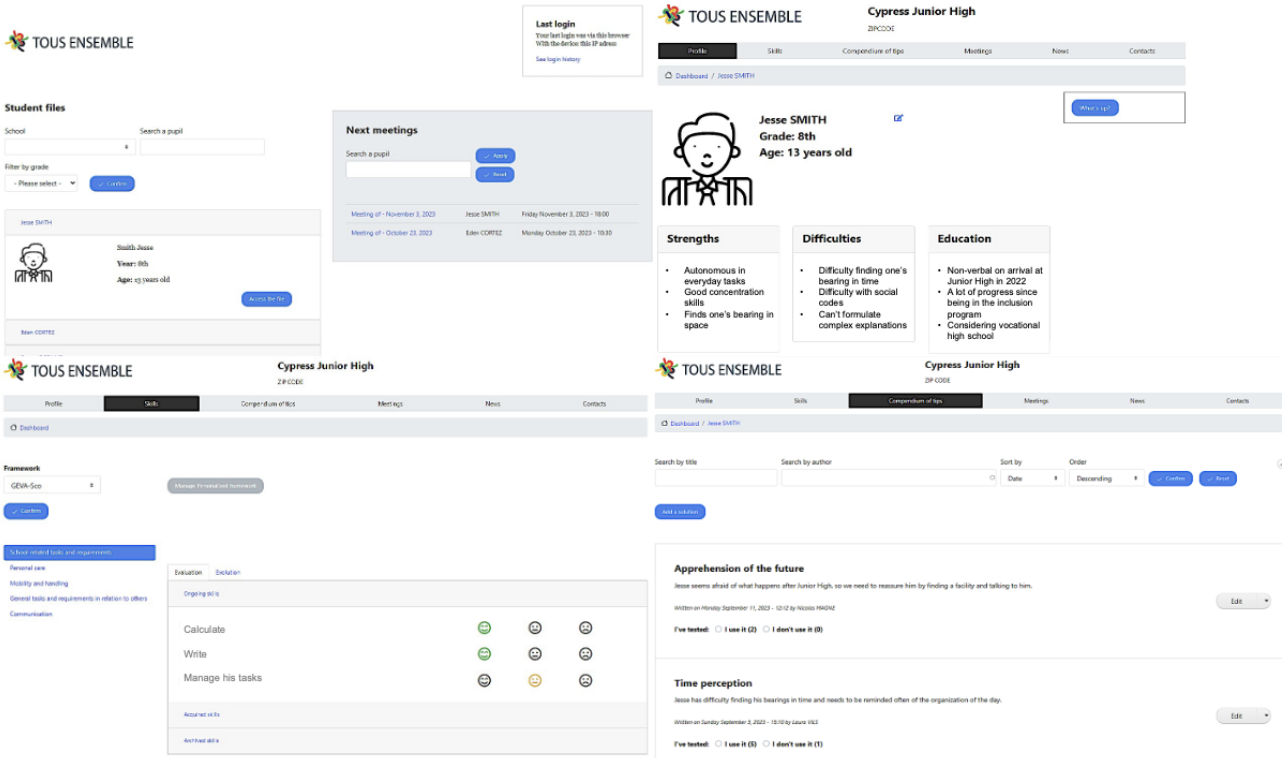

Once logged in, the user can access the student's file, which consists of 6 tabs: profile, skills, meetings, compendium of tips, news, contacts.

As an identity card, the profile provides key main information to know about the child. A “What’s up?” block allows users to be informed of new content in the folder.

The skills section allows users to review the child’s skill assessment. Two skill referentials are provided: (1) a formal IEP evaluation (ie, Geva-Sco scale for French IEP) and (2) a custom skill referential, where users can determine the categories and skills they wish to assess according to the child’s profile.

The meetings tab allows user awareness of past and upcoming meetings about the child. This section also provides an interface to automatically generate reports about past meetings in PDF format, which are accessible by all users.

On the compendium of tips tab, users can share tips, aids, and adjustments that they successfully used with the child in particular situations. They can receive feedback from the other team members.

The news section is dedicated to punctual and rapid information sharing, such as daily events or feedback and particular events.

On the contacts tab, all team members related to the child’s folder are identified, including their role in the team and contact information.

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Procedure

When the participants were assigned to the CoEd intervention condition, the researchers created the child's page and the users' logins on the CoEd application. The participants may provide initial general information to be put on the child's page by the researchers. At the beginning of the study and after collecting baseline measures, the participants of the CoEd intervention condition received a user manual and video tutorials to help them handle the application, and additional training could be provided by the researchers if needed. Once the study began, the participants were asked to use the application at least once a week but were free to use it as often as they wanted.

The participants from the control group did not receive any intervention and were asked to function as usual.

All questionnaires were administered through online forms. Every participant received an identification number, which was used to anonymize the data collected. At the date of measurement (baseline, 3-month follow-up, 6-month follow-up), participants were instructed by mail to complete the questionnaires. The data collection was monitored by the researchers, and the participants who did not answer were reminded once a week by mail or phone. If participants remained unreachable for more than 6 weeks, they were labeled as "lost" and excluded from the trial.

The data collected through forms and the CoEd application were stored on a secure server at the Inria research center and anonymized using participants' identification numbers. Only researchers working on the project are authorized to consult the collected data.

Statistical Analysis

Power

We did not find previous studies assessing the impact of a digital device on IEP teams' relationships and communication in order to perform a power analysis. However, some behavioral interventions with the same target were published and reported moderate effect sizes. Thus, we based our power analysis on an effect size of d=0.600.

Planned Statistical Analyses

We plan to conduct pre-post mean comparison analysis on primary (RQ1) and secondary outcomes (RQ2 and RQ3) to assess within and between-team effects of the intervention. We will conduct within-team analyses using 1-way ANCOVA to compare pre and postintervention differences separately for each team's experimental and control groups. This approach helps identify specific changes within teams and assesses differential effects between groups. Additionally, a between-team analysis will treat all participants as a single population, using repeated-measures ANCOVAs or linear regression analyses to examine the overall intervention effect across teams. This global analysis disregards team distinctions to assess the intervention's overall impact. In addition, using ANCOVA will allow us to control for potential bias coming from the variability in technological skills (Computer Usage Questionnaire; see Table 1) as well as any variable that may compromise the homogeneity across groups. Missing data will result in the exclusion of related observations, and dropouts will be monitored to explore the reasons.

By combining these methods, we aim to provide a comprehensive evaluation of the psychological intervention's effectiveness, considering both within-team variation and overall effects.

To assess the user experience (RQ4), only the participants of the CoEd intervention condition answered the user experience questionnaire. These data will be analyzed through descriptive statistics and compared with questionnaire-related benchmarks.

Results

The study was funded in 2021 with public funds from Conseil Régional d'Aquitaine and the Fondation International pour la Recherche Appliquée au Handicap (FIRAH), Klesia, and Comité National Coordination Action Handicap (CCAH).

Figure 3 shows the flowchart of the recruitment process. We initially recruited 37 eligible teams who were allocated to either the experimental or control group, which resulted in a sample size of 157 participants (2-7 people per team). At baseline, 31 individuals did not complete the questionnaires, leading to the exclusion of 11 teams due to incomplete data. In September 2023, the recruitment ended with 13 teams participating in the experimental condition (n=82) and 11 teams in the control condition (n=45). The experimental group is larger than the control group due to the nature of our action-research approach. Participants and partners expressed a strong preference for being included in the intervention to benefit from the CoEd app, viewing control group assignment negatively. To address this while maintaining rigorous assessment, we included more participants in the experimental group, ensuring sufficient data for analysis and respecting the ethical considerations of action research.

At the end of data collection (June 2024), a total of 59 individuals had dropped out: They stopped responding to the questionnaires and did not reply to our follow-up attempts. Consequently, there were 89 remaining participants at the 3-month follow-up and 67 participants at the 6-month follow-up. Data cleaning and analysis began in March 2025, and results are expected by June 2025. We anticipate that the findings may be ready for publication by the end of 2025, although this timeline remains provisional.

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Figure 3. Flowchart of participant recruitment.

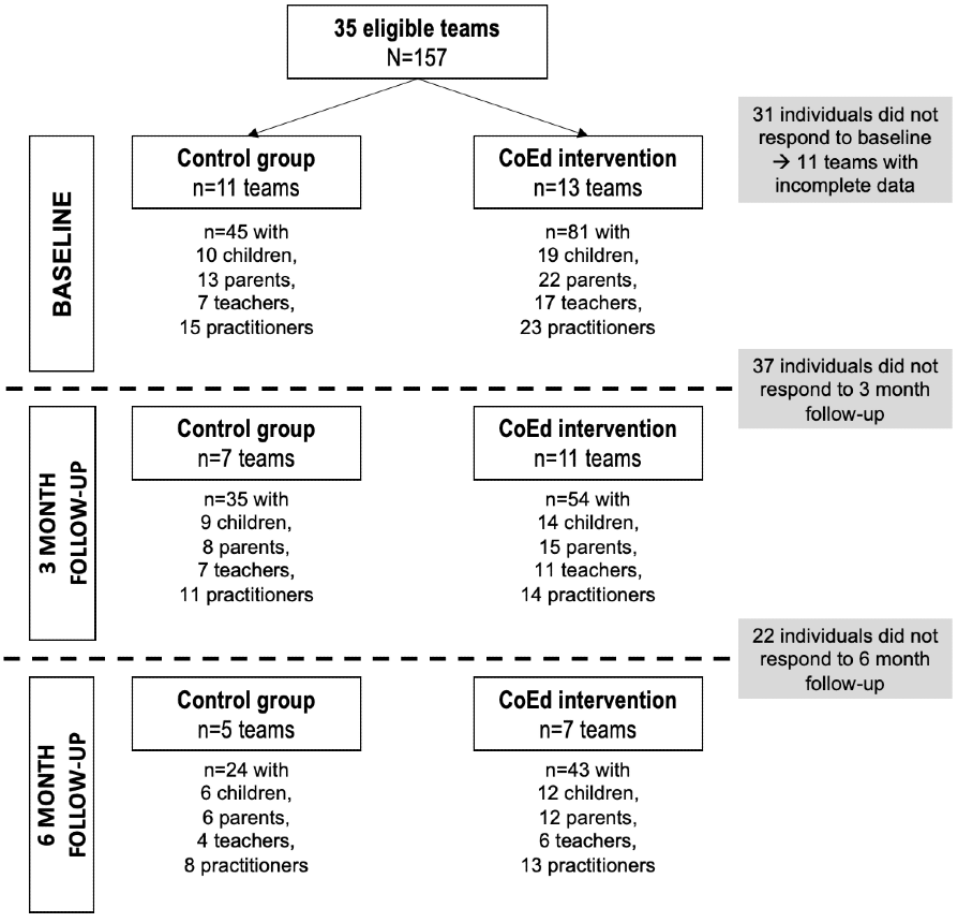

Discussion

Expected Results and Comparison With Prior Work

This research protocol was developed to empirically evaluate the impact of a digital technology solution on collaborative relationships among stakeholders in inclusive education. Conducting a field study with a quasi-experimental protocol will provide true empirical support of the technology's utility and effectiveness for fostering stakeholder collaboration. Through the targeted primary outcomes, we particularly expect an improvement in the quality of interpersonal relationships as well as more congruent cross-stakeholder attitudes toward school inclusion while empowering each stakeholder in their capabilities to achieve their own goals as educator and to support child in their IEP (RQ1). We also expect a beneficial effect of using the CoEd application on child-related outcomes (RQ2) and on the quality of life of stakeholders and children (RQ3).

Meyer et al [35] identified 6 digital projects and a strategy using an existing social network, all at different development stages. Of these projects, 3 used participatory design, 4 conducted needs analyses, and 3 were field-tested. However, none included a control group nor aimed to evaluate the impact on school inclusion, IEPs, stakeholder interactions, or health and well-being dimensions. From this review, it becomes evident that conducting quasi-experimental field studies and involving a substantial number of educational teams and various stakeholders will be an essential contribution. Building on this, our protocol seeks to provide robust evidence for a digital co-education tool designed with user-centered design methods and approaching a gold standard methodology.

Strengths and Limitations

The CoEd application has already completed all the design and user testing in order to reach the step of empirical evidence thanks to this study (see [36] for the design study). Furthermore, our field study included evaluations that cover more broadly other critical indicators for co-educators, such as their mental health using the burden and quality of life assessments. There is strong evidence of the great influence of perceived self-efficacy on a person's well-being [59,60]. Hence, we will be able to explore the links between the primary outcomes (interpersonal relationships, attitudes toward school inclusion, and self-efficacy) and some health measures. For the children, the collaboration benefits from technology could promote, by the bounds effect, their sense of school inclusion, school-life satisfaction, and overall well-being through an effect on parent-teacher relationships and collaboration between stakeholders [6,7,61-63]. This technology could also facilitate the implementation of IEPs by leveraging each stakeholder's expertise [6,8] and, as a result, increasing the educational achievement (academic and social objectives) for each child.

Additionally, the log data from the CoEd application will provide insights on its actual usage across time and the targeted primary outcomes. For instance, RQs could address the traditional dilemma between quality and quantity of exchanged

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information, or content analyses could even document interpersonal tensions and their potential relation with a degraded partnership in the team and vice versa.

For the intervention group using the CoEd application, we are collecting data on usability, technology acceptance, and usage factors. This assessment is of great importance in studies examining the impacts of technology-based interventions, as usability and effectiveness are intrinsically related, and is part of most studies evaluating this kind of intervention [37].

These secondary indicators address the needs of project stakeholders (inclusive school policymakers, school organizations, teachers, practitioners, parents, and children with SEND) for successful participatory achievements and pave the way for innovative research, such as exploring relationships between CoEd acceptance and effectiveness in inclusive school environments. Most of the participants of this study are people who did not participate in the design steps of the project. Therefore, the bias from "being both designer and evaluator" is limited, and the results from this study will provide insight on the efficacy of using a citizen science approach in the domain of inclusive education. This study combines a traditional top-down approach (ie, expectations relative to specific primary criteria for a prescriptive purpose) with a bottom-up approach driven by the field expertise of the main stakeholders of school inclusion. As a reminder, the study outcomes have been cobuilt thanks to focus group methods involving actual stakeholders as well as researchers in the field (see Multimedia Appendix 2 for details about the focus group sessions). This citizen science approach (albeit risky) contributes to bridging science and practice, facilitating rapid societal impact, and emerging new research issues [64,65]. The results from this study could also contribute to documenting the effectiveness of citizen science and participatory design methods in designing innovative technologies tailored to the specific needs of people, especially in health and disability domains [24,65,66].

From our combined approaches, the study consortium encountered a few issues that reinforced the study-related challenges, especially with children with SEND and with a technology-based intervention. First, major challenges were related to the quasi-experimental study design in which the CoEd intervention condition is compared with a control condition where there are fewer teams. We paid great attention to matching the 2 groups with respect to the factors known for influencing the primary outcomes as well as possible. These factors include the size of the team, demographic factors, and the SEND of the child. Nonetheless, we are aware that such a matching method does not neutralize possible biases related to differences in the group size. We plan to explore the impact of any variable that is not matched between groups to investigate its impact on the intervention's effect. A second study challenge was the great variability in the participants' technological skills in the CoEd condition. Indeed, computer skills and prior experience with technology will necessarily influence the experience with using a digital tool and, in turn, modulate the intervention's effects. We set up a standardized training phase for the use of CoEd application according to training use scenarios and provided both written and video tutorials to help people handle the CoEd application. In addition, the questionnaire on technological skills will be used as a covariable to explore the impact of this interindividual variability on the intervention's effects. Another study challenge was associated with the increasing digitalization of schools, whether in teaching, student support, or parental involvement. Since the COVID-19 pandemic, this digitalization has significantly increased, especially in the field of education [67]. However, the extensive digitalization during the COVID-19 pandemic brought issues related to digital anxiety and data protection [68], increased screen time, and the effects on well-being and interpersonal relationships [69-71]. In this project, these themes were central during design and development steps, as it involved processing data concerning children with NDD. This point was addressed during the participatory design steps and proved to be a very important one for future users [36]. During the development steps, we made data security a priority, so that users can use the system with complete confidence (compliance with regulations, security certification). Finally, the last challenge our research had to confront was related to the context of digital development in France. The French government has introduced a new digital tool to bridge the gap between decision-making bodies for educational obligations and resources allocated for the implementation of an IEP and schools. This deployment has led teachers to increase digital data input on academic difficulties and IEP accommodations. However, this deployment has caused confusion with CoEd and could lead some teachers to limit their participation, as some data would need to be entered both in CoEd and the governmental digital tool. However, there are important differences between the CoEd application and the governmental tool: The latter is more oriented toward archiving aims and digitalization of the IEP, while the CoEd application promotes free sharing of experiential knowledge from each stakeholder, which indirectly contributes to IEP implementation and follow-up. In addition, the CoEd application allows stakeholders to communicate with each other about daily events, which is not covered by the governmental tool. In this context, the CoEd application can be viewed as an aid for following IEP objectives and to better support the use of the governmental app through complementary features.

Despite all these challenges, the outcomes of the CoEd study will yield significant insights on the benefits of a digital collaborative tool for teaching students with SEND. It will also yield some insights on the communication factors influencing the health of stakeholders and children. The study will also inform the feasibility of technology-based personalization of IEP and will likely teach some useful lessons for future technology-based field studies regarding empowering stakeholders to teach children with SEND.

Dissemination Plan

Results from our study will be disseminated via scientific publications and conferences. In addition, as we previously included decision-makers of the French public policy of inclusive schooling in the CoEd design phases, we made sure that the solution is ethically, technologically, and financially sustainable in the public services. This will provide a solid foundation for a business model in case there is a startup to market the technology.

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A second perspective is to explore the feasibility of disseminating the CoEd application outside of the French frontiers, by scaling up in other countries. However, there are cultural and structural differences between countries, particularly regarding inclusive education. This international dissemination will necessitate an additional needs analysis and adaptations to the application for the specific context of other countries [72]. A first step will be to explore the feasibility of disseminating the application in French-speaking countries with a similar cultural background (eg, Belgium), thereafter moving to wider internationalization with other European countries. This internationalization strategy is certainly ambitious and will necessitate a new needs analysis and adaptations of the CoEd application.

Conclusion and Future Directions

Although further research is needed, the findings of the CoEd project will provide the first real evidence-based study in the field of educational technology for social environments supporting children with SEND with their IEPs.

To move the robustness of the evidence forward, it will be necessary to consider conducting a trial using strict randomized controlled trial methods. In the same vein, the question of a large-scale intervention exists. As also mentioned, our ecosystemic and participatory approach has led us to work directly with the key stakeholders in inclusive education in order to both design an upstream CoEd application and evaluate it downstream. Consequently, a scaling up in other countries for the evaluation of the CoEd application will be required for better proof of the interest for an interactive web application for a co-education process.

Acknowledgments

We would like to thank all the members of this project: first, the participants and second, all the professionals linked to the project (eg, engineers, technicians, techno-clinicians) as well as the structures and organizations that allowed the project to be conducted (French School Academy of Bordeaux-New Aquitania in France) and Aurélien Dumez, Computer Security Officer and Engineer at the Inria (National French Institute of Informatics and Mathematics) center of the University of Bordeaux who supervised all the computer development required for the CoEd solution and notably its conformity to General Data Protection Regulation (GDPR) and European standards for ethical research with a digital tool.

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Data Availability

Upon study completion, the data sets generated during or analyzed during this study will be available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT checklist for this study.
[DOC File , 120 KB - resprot_v14i1e63378_app1.doc]

Multimedia Appendix 2
Description of Focus group for selecting study outcomes.
[DOCX File , 23 KB - resprot_v14i1e63378_app2.docx]

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Abbreviations

ASD: autism spectrum disorder
CCAH: Comité National Coordination Action Handicap
COERLE: Comité Opérationnel d'Évaluation des Risques Légaux et Éthiques
FIRAH: Fondation Internationale pour la Recherche Appliquée au Handicap
GDPR: General Data Protection Regulation
IEP: individual education plan
Inria: French National Institute of Informatics and Mathematics
NDD: neurodevelopmental disorders
RQ: research question
SEND: special educational needs or disabilities
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Locomotive Syndrome Digital Therapeutics Provided via a Smartphone App: Protocol for a Single-Group Trial

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Abstract

Background: Locomotive syndrome (LS) is a condition in which muscle weakness and reduced motor function due to musculoskeletal disorders cause reduced mobility and physical function. In Japan, musculoskeletal disorders are the most frequent reason for requiring home support or nursing care, and the prevention and amelioration of LS are thus being emphasized. However, it is difficult for older people to make a habit of exercise therapy, which is the mainstay of LS treatment. We investigated whether digital therapy could (1) lead to behavioral change in older people and (2) prevent or improve LS in older people.

Objective: We sought to determine whether digital therapeutics (DTx) are useful for the prevention and amelioration of LS in older people, and we assessed the effects of DTx on the participants' exercise awareness and motor function.

Methods: We conducted a multicenter, prospective, longitudinal, nonrandomized, single-group study of Japanese adults aged ≥40 years who were eligible for LS checks. Each participant underwent an 8-week locomotion training (LT) intervention, and their subjective and objective motor abilities and motor awareness were objectively assessed at the following time points: baseline (before the start of the DTx), interim (4 weeks after the start of the DTx), and end (8 weeks after the start of the DTx). We evaluated the participants' objective motor function using the timed up and go (TUG) test, and we compare the results using a 3-way ANOVA with the TUG test at the 3 evaluation time points as the dependent variable. The results of the 25-question Geriatric Locomotive Function Scale, which is a subjective measure of motor function, and the results of the Behavioural Regulation in Exercise Questionnaire 3, which assesses motor awareness, were also evaluated using an ANOVA in the same way as the TUG test. The significance level was set at .05 / 3 = .0167 after Bonferroni correction.

Results: As of April 2025, this study had enrolled 47 participants, and complete data had been gathered from 45 participants for the proposed analysis. Study participation was ongoing as of April 2025.

Conclusions: The study cohort will be used as a basis for further observational and intervention studies. This research could lead to more efficient use of medical resources and a reduction in financial and medical burdens on individuals and the economy, and it could support the prevention and amelioration of LS and the establishment of exercise habits among older people.

Trial Registration: University Hospital Medical Information Network Clinical Trials Registry UMIN000053922; https://center6.umin.ac.jp/cgi-open-bin/ctr_e/ctr_view.cgi?recptno=R000061550

International Registered Report Identifier (IRRID): DERR1-10.2196/70163

(JMIR Res Protoc 2025;14:e70163) doi:10.2196/70163

KEYWORDS

locomotive syndrome; locomotion training; digital therapeutic; TUG; 25-Geriatric Locomotive Function Scale; BREQ-3; behavioral change; support application

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Introduction

Background and Rationale

The Japanese Orthopaedic Association (JOA) issued its first guidelines regarding locomotive syndrome (LS) in 2007 [1]. Locomotive syndrome refers to a condition in which a musculoskeletal disorder results in muscle weakness and motor weakness, leading to reduced mobility and physical function [1]. The development of LS causes a decline in healthy life expectancy and can lead to individuals becoming bedridden and requiring long-term care [2]. In Japan, motor system disorders are the most frequent reason for requiring assistance at home or nursing care, accounting for 24.8% of all cases [3]. The JOA recommends the early detection of motor function decline by conducting LS checks (LSCs), in part to prevent the future need for assistance or care [4]. The JOA also advocates locomotion training (LT), which involves standing on one leg and squatting, to prevent and ameliorate LS [5].

Guidelines for assessing the risk of LS were developed in 2015 [6]; these defined stage 1 LS as the early stage of motor decline and stage 2 LS as advanced motor decline. In 2020, stage 3 LS was added, defined as a state of progressive decline in mobility and difficulty in social participation [7]. The risk of developing LS is assessed based on three items: (1) a stand-up test, (2) a 2-step test, and (3) the 25-question Geriatric Locomotive Function Scale (GLFS-25) [5].

Japan has one of the world's most prominent aging populations, and the burden of health care for the oldest segment of Japan's population on the country's insurance system continues to increase [8]. It is also necessary to consider how to make the most effective use of limited medical resources. The prevention and amelioration of LS are considered important as countermeasures against motor system disorders. Exercises such as LT are effective for preventing and ameliorating LS [5], but it is difficult for many older adults to start or continue an exercise routine. As one solution, we advocate an approach to the prevention and improvement of LS in older people based on using technological devices to promote behavioral change.

Technology is used in the medical field for electronic medical records, telemedicine, and surgical robots; in addition to this, mobile devices are used for medical procedures and support, which is called mobile health (mHealth) [9]. Digital therapeutics (DTx) are an area of mHealth that is receiving particular attention [10]. A variety of apps have been approved by insurance as DTx, including diabetes and hypertension self-management apps and smoking cessation support apps [11-13]. However, DTx for musculoskeletal diseases have not been approved for insurance coverage. Although some apps have functions such as step counting and exercise management, they are not scientifically supported. We have created a smartphone app for older people who have no exercise habits and whose physical functions have declined. The smartphone app has functions that support the implementation of 2 types of LT, using video and audio, and when participants carry out LT, the implementation status is recorded not only on the target person's smartphone, but also on the health care provider's smartphone. The advantage of this system is that health care providers can check the progress of LT remotely, and the patient can feel that they are exercising with the support of health care providers. We are conducting this study to determine whether the use of DTx can lead to behavioral change in older people and prevent or improve LS.

Objectives

The study's primary aim is to determine whether the use of a smartphone app (ie, DTx) can prevent or ameliorate LS in older people: the outcomes are exercise awareness as assessed by the Behavioural Regulation in Exercise Questionnaire 3 (BREQ-3) and motor function as assessed by the GLFS-25 and timed up and go (TUG) test. In this study, participants who were unable to perform the stand-up test or 2-step test due to hip or knee pain were excluded from the measurement items. The research questions are as follows: (1) Can older people use DTx to proactively change their exercise habits with the help of their health care providers? (2) Are changes in exercise habits in older people associated with changes in motor awareness and function?

Our main and secondary study hypotheses are that (1) continued LT with DTx will prevent or improve LS in older adults and (2) well-established exercise habits will improve these individuals' motor awareness and function.

Methods

Participants and Study Setting

We plan to recruit a minimum of 50 participants aged ≥40 years who are eligible for LSCs [14] at any of 3 general hospitals (Bange-Kosei General Hospital, Southern Tohoku General Hospital, and Minami-Soma City General Hospital) that perform orthopedic surgery. The target minimum numbers of participants is 25 at Bange-Kosei General Hospital, 15 at Southern Tohoku General Hospital, and 10 at Minami-Soma City General Hospital. The overall recruitment target is based on the minimum sample size necessary to complete the intended analysis, taking omissions into account.

The study's inclusion criteria are as follows: participants aged ≥40 years who generally have lower-extremity muscle weakness [15] and who have visited 1 of the 3 abovementioned hospitals for an LSC, which are scored as follows: 1 point if the individual cannot put on a sock on one foot; 2 points if they stumble in their house; 3 points if they need a handrail to climb stairs; 4 points if they have difficulty using a vacuum cleaner at home; 5 points if they have difficulty carrying parcels weighing >2 kg; 6 points if they have difficulty walking continuously for >15 minutes; and 7 points if they cannot cross a crosswalk with a green light. Additional inclusion criteria are scoring ≥3 points on the Mini-Cog cognitive functional assessment [16,17], having access to the smartphone app, and being able to provide informed consent for study participation. The exclusion criterion was difficulty using smartphone apps due to cognitive decline or visual or hearing impairment.

Study Design

This trial is a multicenter, prospective, longitudinal, nonrandomized, single-group study of Japanese adults aged ≥40

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years with applicable LSC results. The design includes 3 evaluation time points: baseline (0 weeks, ie, before the initiation of DTx), an interim evaluation (4 weeks after DTx initiation), and a final evaluation (8 weeks after DTx initiation).

An investigation of DTx that was designed to reduce anxiety about recurrence in postoperative breast cancer patients included a baseline assessment before the DTx intervention, an interim assessment after 4 weeks of intervention, and a final assessment after 8 weeks of intervention [18]. Previous studies have shown that 6 weeks of balance exercise intervention and 2 months of body weight–bearing exercise can improve lower limb muscle strength, balance ability, and walking speed in older people [19,20]. We and other research groups thus consider 4-week and 8-week postintervention assessment time points as appropriate for this type of study.

We registered the trial with the University Hospital Medical Information Network Clinical Trials Registry (UMIN000053922; receipt number R000061550). The date of approval was March 22, 2024.

Procedures

Recruitment

Participants will be recruited from among patients attending the collaborating hospitals. All 3 recruitment sites follow the same recruitment plan. Recruitment will continue until the target number of cases is achieved, with a 1-year time limit. At the end of a regular outpatient clinic session, a participant who meets all of the eligibility criteria and wishes to participate in the study will be provided with a description of the study, a questionnaire, and an evaluation sheet, and they will be asked to give their written informed consent to participate in the study. The need for follow-up and written consent for future contact will also be explained. The candidate participants are also informed that they can withdraw their consent or participation at any time if they so desire.

Intervention

The smartphone app used in this study is a newly prototyped app developed for this research study. We will provide smartphones equipped with a communication environment and downloaded apps in advance, which will be lent to the participants (Figure 1). The participants will be instructed to refrain from using the smartphone for any purpose other than use of the relevant smartphone app.

Figure 1. Implementation schema for the locomotive training (LT) app used in this study. The physician in charge will provide a smartphone onto which the LT app has been downloaded to the patient. The patients perform the LT at home, and the app's implementation data are stored in the database and saved in the cloud. Through the cloud, the physician can check the participant's LT implementation remotely.

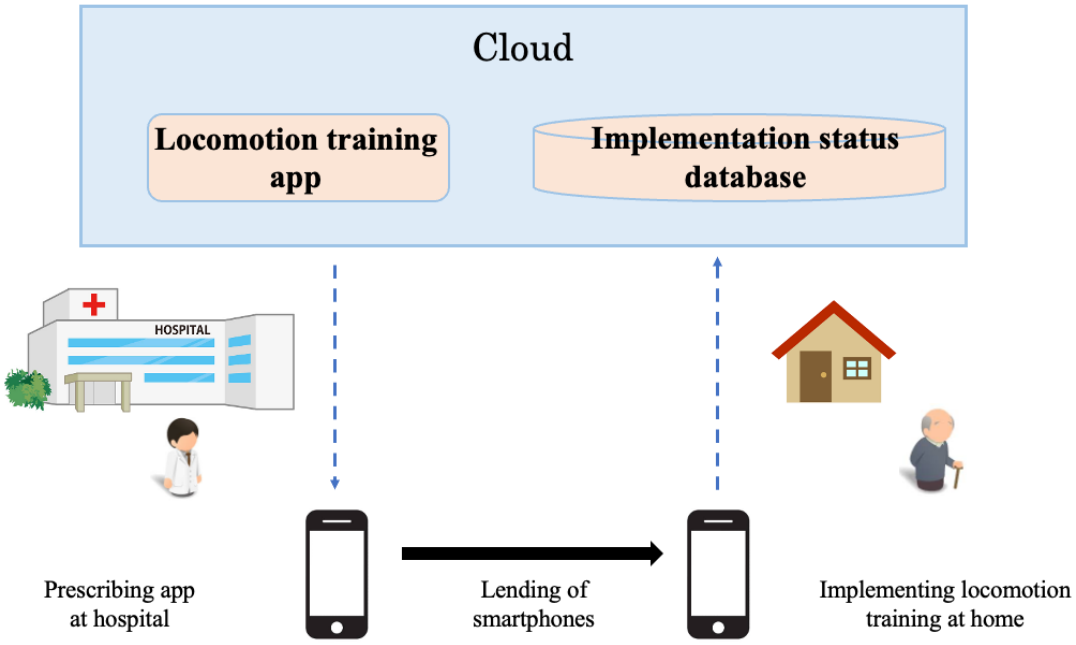

Each participant will be scheduled for LT intervention every day for 8 weeks. The LT application is simple to use and is set up so that by touching the screen, a voice announcement is played and the user can perform 2 LT programs: the 1-leg stand program and the squat program. A single LT session consists of a program of 60 seconds of standing on one leg and 5 squats, with each exercise repeated 3 times. For participants with weak legs and backs who find it difficult to do the regular LT, it is recommended that they stand on one leg while supporting their body with their hands and fingers on a desk, or that they sit on a chair and stand up by putting their hands on a desk instead of doing squats. In addition, for participants with particularly weak legs and backs, each LT repetition could also be reduced to 1 time instead of 3 times [5]. Sustainable goals are set for each

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individual for LT continuity. After completion of the LT, the participant touches the screen to check the record of the LT, not only on the participant's but also on his or her physician's smartphone (Figure 2).

Figure 2. Screenshots of the app used in this study. The app for patients has a simple design to help them perform the locomotive training (LT). The app for physicians allows them to check a patient's LT status based on the ID for that patient. The number of days with LT is displayed on the same screen for both the patient and the physician.

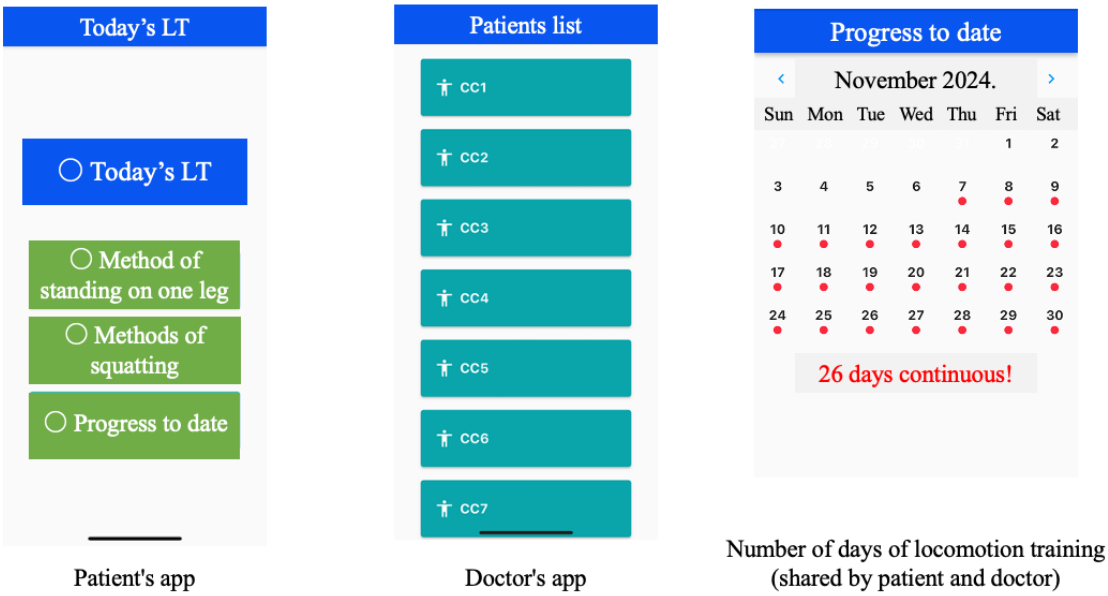

Outcomes

Timeline

The timetable of enrollment, interventions, and assessments is displayed in Table 1, including the quantitative self-reported outcomes and TUG results at the baseline, interim, and final evaluations. Demographic and clinical information will be obtained from the participants' electronic medical records at baseline and will include their date of birth, gender, BMI, medical history, and disease or diseases causing LS.

Table 1. Timetable and evaluation items.

Item	Baseline	4 weeks after DTx[a] initiation	8 weeks after DTx initiation
Patient consent	✓		
Patient background	✓		
Timed up and go test	✓	✓	✓
25-question Geriatric Locomotive Function Scale	✓	✓	✓
Behavioural Regulation in Exercise Questionnaire 3	✓	✓	✓
Days with locomotion training		✓	✓

[a]DTx: digital therapeutics.

Primary Outcome

The primary outcome is TUG test values before and after the DTx intervention. The TUG test is widely used in clinical practice as an outcome measure to assess mobility, fall risk, and dynamic balance in adults, and it can assess objective mobility [21,22]. Furthermore, previous research has shown that patients with LS have significantly longer TUG times than control groups [23]. In patients with rheumatoid arthritis, TUG values are significantly shortened and physical function is improved by continuing LT [24]. We determined that TUG is a useful indicator of the effects of LT for participants with LS.

Secondary Outcomes

Secondary outcomes are the participants' GFLS-25 and BREQ-3 scores. The GFLS-25 is a self-report questionnaire used to assess difficulties and impairments in daily activities related to LS and can be used to assess subjective mobility [5-7]. The BREQ-3 assesses motivation for exercise with 18 questions in 6 areas: intrinsic motivation, integrative adjustment, identification adjustment, incorporative adjustment, external adjustment, and demotivation [25]. The BREQ-3 is used in this study to assess changes in attitudes toward exercise before and after the DTx intervention.

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Other Clinical Outcomes

We will evaluate the numbers of days LT was performed at 4 weeks and 8 weeks after the intervention, as recorded in the smartphone app.

Statistical Methods and Sample Size

The primary outcome of this study, TUG test values, will be measured repeatedly in the same participants at 0 weeks before the DTx intervention and 4 and 8 weeks after the intervention. These data will be compared with an ANOVA, with the TUG score as the dependent variable. The secondary outcomes, GLFS-25 and BREQ-3 scores obtained at the 3 time points, will also be compared with an ANOVA. The significance level will be set at .05 / 3 = .0167 with Bonferroni correction.

The minimal clinically important difference in the TUG test for patients with degenerative disc disease has been reported to be 3.4 (SD 5.0) [26]. Considering this finding, we set the minimal clinically important difference at 3 for this investigation. The required sample size was calculated using G*power (Heinrich-Heine-Universität Düsseldorf) [27]. We selected the corresponding *t* test, and we calculated the effect size as 0.6 based on a mean difference of 3.0 and an SD of difference of 5.0. Assuming that α is .05 and power $(1 - \beta)$ is .80, the required sample size was estimated to be 24. We set the target number of cases for this study at 50, taking into account that the SD might be smaller than in previous studies, some participants might drop out, and other factors.

Randomization and Blinding

This is a nonrandomized (unblinded) study and will use a single group. All participants will serve as their own controls; data from all participants before the DTx intervention will be used and compared with the data from after the DTx intervention. The planned statistical methods will add strength to the study's conclusions.

Data Monitoring and Adverse Event Reporting

The risk of adverse events from participation in DTx is very low. We are thus not establishing a data monitoring committee, and no interim analyses are planned to identify risks.

The principal investigator will (1) report the progress of the study without delay to the ethics review committee on an annual basis, (2) monitor adverse events related to the procedures and group program, and (3) discuss any necessary protocol amendments. If a member of the research team becomes aware of the occurrence of a serious adverse event, they will promptly report it to the research director, who will promptly report it to the principal investigator. If the principal investigator determines that the serious adverse event was unanticipated and is unable to be ruled out as being causally related to this study, he will promptly report it to the head of the research institution.

Ethical Considerations

The Fukushima Medical University Ethics Review Committee provided ethical approval for this study (REC 2023-196). All study methods follow the relevant guidelines and regulations, and written informed consent will be obtained from participants. The study's main results will be published in a peer-reviewed scientific journal and submitted for presentation at clinical and scientific meetings and conferences. The principal investigator will oversee the publication and presentation of the study results, including the determination of authorship. Participants will be asked if they would like to be informed about the study's main results, and those who express interest and provide contact information will be provided this information as soon as it becomes available. Data will be deidentified and participant information will be protected. Although no monetary rewards or other compensation will be provided to those participating in the research, in the event of an adverse event, we will respond promptly and provide compensation while consulting with the ethics committee.

Participants' data will be entered into a password-protected electronic file that will be kept on a secure computer by the principal investigator. Coding sheets with identifiable participant information will be stored on a secure computer as password-protected electronic files. Hard copies of consent forms and research documents will be stored in a locked filing cabinet at the research site.

Results

Trial enrollment began in April 2024 and will initially continue until at least April 2025. As of April 2025, 47 had participants agreed to be evaluated, 47 participants had completed the interim evaluation, and there were complete data sets from 45 participants for the proposed analysis. The data analysis has not yet been conducted.

Discussion

To our knowledge, this is the first trial to evaluate the effectiveness of DTx in preventing and ameliorating LS and changing the exercise behavior of older people. Although it is limited by its single-group design, the study has the strength that it evaluates the effectiveness of DTx in routine practice. External validity is also strengthened by the that fact that the practice sites are spread across 3 general hospitals and target communities with different sociodemographic characteristics.

A randomized design was not feasible, as the intervention is offered in routine practice [28], thus limiting causal conclusions. However, a randomized control study of approximately 200 participants per group in collaboration with local authorities has been proposed to strengthen this study. This is intended to improve the quality of the study by assessing in greater detail the impact of DTx on behavioral change and the prevention and amelioration of LS in older adults.

We are concerned that participants with low exercise awareness and low technology literacy may have difficulty participating in this study. However, for patients who are highly conscious of exercise but find it difficult to continue exercising on their own, or who are anxious about the content of the exercise, an advantage of the study is that they can exercise according to a set protocol with the cooperation of health care providers.

Notably, DTx enables the online assessment of the participants' engagement in LT and facilitates feedback in routine practice.

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DTx is less burdensome for medical practitioners and more motivating for the participants as it creates an environment in which the participant is continuously supported by a physician. This research promises not only to lead to more efficient use of health care resources and reduced human and financial burdens, it may also lay the groundwork for more rapid implementation of DTx in real-world clinical practice, depending on the results. Nevertheless, a randomized controlled study based on our results will be required in order for DTx to gain insurance coverage in Japan, which calls for adequate funding and the cooperation of local authorities. If successful, the study will support the prevention and amelioration of LS and the establishment of better exercise habits among older adults.

Acknowledgments

We thank the hospital department heads for collecting the patient data and the study participants for their time and effort. This study is funded by a grant from the Japanese Orthopaedic Association (JOA-Subsidized Science Project Research 2022-1).

Data Availability

The datasets generated during and analyzed in this study will be made available from the corresponding author on reasonable request.

Authors' Contributions

TS and YM developed the evaluation method, participated in the study's conception and design, obtained ethical approval, and wrote the manuscript. Both authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

BREQ-3: Behavioural Regulation in Exercise Questionnaire 3
DTx: digital therapeutics
GLFS-25: the 25-question Geriatric Locomotive Function Scale
JOA: Japanese Orthopaedic Association
LS: locomotive syndrome
LSC: locomotive syndrome check
LT: locomotion training
mHealth: mobile health
TUG: timed up and go

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Protocol

Technical Requirements, Design, and Automation Process for a Statewide Registry-Based Tailored Text Messaging System: Protocol for a Longitudinal Observational Study

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Abstract

Background: Tailored text messaging is a low-cost mobile health intervention approach shown to effectively improve self-care behaviors and clinical outcomes for patients with chronic cardiometabolic conditions. Given the ubiquitous nature of mobile phones, text messages have the potential to reach a large audience. However, automating and disseminating tailored text messages to large populations at low cost presents major logistical challenges that serve as barriers to implementation.

Objective: This study aimed to describe the protocol for a longitudinal observational study designed to assess the feasibility of an innovative approach for automating and disseminating personalized and tailored text messages to large populations at risk of cardiovascular events using a low-cost registry-based tailored text messaging system known as the Heart Health Messages (HHM) program. Further, it describes the technical requirements, architectural design, automation process, and challenges associated with program implementation.

Methods: Patients at high risk of cardiovascular diseases are identified using a statewide population health registry known as the Tennessee Population Data Network. Tailored invitation messages and enrollment surveys are sent to eligible patients via Twilio. Upon completion of the receipt of consent and enrollment forms, participants receive tailored text messages from a library of generic messages based on participant-selected frequency of message delivery (daily or every other day). In addition, participants receive monthly text-based check-in survey messages designed to assess intervention adherence and improvement in self-care. Participants are also sent quarterly follow-up surveys to update enrollment information and preferences. All enrolled participants will receive tailored text messages for a 12-month intervention period.

Results: Since the start of the program, 18,974 patients from 2 major health systems have met the inclusion criteria and were eligible for the HHM program. A total of 3 phases of HHM 1.0 have been implemented so far, reaching 225 eligible patients in phase 1, a total of 5288 patients in phase 2, and 13,461 patients in phase 3, with an enrollment of approximately 2% (n=4/225), 3% (n=137/5228), and 3% (n=350/13461), respectively. Efforts are underway to implement strategies in collaboration with the health systems to enhance the HHM program rollout and patient participation.

Conclusions: The HHM program is a low-cost tailored text messaging intervention set for broader dissemination and potential replication. The program has the capacity to improve outcomes for people with chronic medical conditions.

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KEYWORDS

text messaging; clinical informatics; chronic disease; telehealth; telemedicine; electronic health records

Introduction

Background

The dramatic increase in the prevalence of obesity-associated chronic conditions, including hyperlipidemia, diabetes, and cardiovascular disease in the United States [1,2], demands a strong clinical and public health response. Given their low costs and high dissemination potential, mobile health interventions hold promise for promoting behavioral change and improving outcomes for patients with chronic conditions. Tailored motivational text messages have particular promise as extensive research demonstrates their effectiveness in encouraging healthy eating, physical activity, weight loss, management of chronic diseases, and medication adherence [3-8]. Motivational health-related text messages are text messages designed to support and encourage people to change specific health behaviors, such as healthy eating, exercising, or quitting smoking [9,10]. Tailored text message automation and dissemination to large populations at low cost remains logistically difficult. Many research groups have used population health registries to track and address gaps in care for people with diabetes and other cardiovascular conditions [11-13]. However, to our knowledge, no organizations have used registry-based data to populate a tailored motivational text messaging system.

This study describes the protocol for an innovative approach for automating and disseminating tailored text messages to large populations at low cost through a registry-based tailored text messaging system known as the Heart Health Messages (HHM) program. The HHM uses both patient input and a statewide population health registry [14] to tailor and personalize health-related text messages to patients identified at high risk for cardiovascular events. The HHM program is being made available to primary care practices through the Tennessee Heart Health Network (TN-HHN), a statewide quality improvement cooperative which seeks to implement evidence-based patient-centered interventions to improve cardiovascular care [15]. The current pilot study assesses the feasibility of the HHM program's innovative approach for automating and disseminating personalized and tailored text messages to large populations with or at risk of cardiovascular disease across Tennessee.

Research Context and Early Development of the HHM Program

The HHM program is a theory-based tailored text messaging platform initially developed for the Patient-Centered Outcomes Research Institute-funded Management of Diabetes in Everyday Life (MODEL) Study, a pragmatic randomized trial comparing the effectiveness of motivational text messaging with health coaching and educational materials for African American patients with uncontrolled diabetes [16,17]. The message library was created using patient-centered design with input from health behavior research, motivational interviewing, and patient experts. Messages focused on improving self-care behaviors related to healthy eating, exercise, and medication adherence were tailored using patient enrollment survey responses and periodic text message check-ins and were delivered using manual processes [18].

Our earlier research demonstrated that the MODEL Study tailored motivational text messaging program was highly effective in improving healthy eating and physical activity self-care behaviors for patients with or at high risk of cardiovascular disease. For example, MODEL patients who received both a health education toolkit and motivational text messages reported a significantly greater increase in the number of days following a healthful eating plan, with an average increase of 1.36 days per week (95% CI 1.07-1.64), compared with those who received only the health education toolkit who saw an average increase of 0.67 days per week (95% CI 0.30-1.04). Patients randomized to the motivational text messages intervention also significantly improved their blood sugar control. In addition, tailored text messages were found to be more effective in improving physical activity among suburban or rural populations compared with patients who received the education toolkit alone [17,19].

In preparation for the TN-HHN initiative, our regional population health data registry [14] was expanded statewide as the Tennessee Population Data Network (TN-POPnet) to support practice-level quality reporting, outcome tracking, and the HHM program [20]. The new HHM text messaging system sought to modify the MODEL motivational text messaging program to reduce dependence on the enrollment survey, increase the use of registry electronic health record data for tailoring, and automate the tailoring process and delivery of motivational text messages for statewide scaling and dissemination. The current pilot study also seeks to describe the process of scaling and automating the MODEL motivational text messaging program as a statewide registry-based tailored text messaging system and the technical requirements, architectural design, automation process, and challenges associated with program implementation.

Methods

Study Design

The HMM Pilot Study is a pragmatic pilot feasibility study that uses a prospective cross-sectional design with repeated measures (ie, longitudinal observational) to assess the participation experience of successive waves of participants recruited over time in the setting of evolving HHM program recruitment strategies informed by previous experience using a

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Plan-Do-Study-Act (PDSA) framework for continuous quality improvement [21]. Reporting for the HHM program description was based on the TIDieR (Template for Intervention Description and Replication) checklist. (Multimedia Appendix 1) [22].

Study Setting

The initial piloting of the HHM program is being conducted in 2 major nonprofit health systems participating in the TN-HHN, including 1 regional safety net hospital system and 3 of its outpatient clinics and 1 large federally qualified health center with 7 major outpatient locations, in Memphis, Shelby County of West Tennessee.

Participants and Eligibility Criteria

The HHM pilot study included all adults meeting one or more of the following criteria placing them at increased risk of cardiovascular disease; (1) diagnosis of one or more of the following conditions: obesity, diabetes, prediabetes, hypertension, hyperlipidemia, arrhythmia, and congestive heart failure requiring one or more prescription medication; (2) heart attack, hospitalization for chest pain, or stroke in the past 6 months; and (3) cardiac bypass surgery or cardiac catheterization. Patients were excluded if pregnant or currently taking medication for cancer, HIV, or viral hepatitis.

Recruitment Procedures

Patients meeting the above inclusion criteria at high risk for cardiovascular events were identified using electronic health record data in the TN-POPnet. The eligibility criteria are applied to all adults seen in participating health system outpatient clinics within the past year. Patient identifiers were collected and used to send personalized invitation messages and enrollment surveys to all those meeting eligibility criteria.

Heart Health Messages Program Technical Requirements

Before starting development, the following HHM program technical requirements and their proposed solutions were identified.

Secure Relational Database

The HHM required a secure relational database that meets the 1996 HIPAA (Health Insurance Portability and Accountability Act) requirements (ie, is HIPAA-compliant). TN-POPnet data, including direct patient identifiers, demographics, diagnoses, and laboratory values, were already housed in a fully HIPAA-compliant Oracle database. The database also includes patient-reported data, text message stems, schedule tables, and procedures and functions for tailoring and delivering text messages.

Secure Web-Based Application

The HHM required a HIPAA-compliant web-based application to capture patient-reported message preferences and health goals, beliefs, attitudes, and self-care motivation and activities [18]. Since REDCap (Research Electronic Data Capture; Vanderbilt University) [23] was used for MODEL, this platform was selected for HHM candidate consent and enrollment survey data collection and will be used for research purposes in program evaluation. Previous research studies have used REDCap for data capture and storage [24,25], and its compliance with HIPAA regulations have also been well described [23,26].

Short Messaging Service Gateway

The HHM required a HIPAA-compliant SMS gateway capable of sending text messages and receiving participant responses to periodic check-in messages. Based on extensive vetting of alternatives, Twilio (Twilio Inc) was selected as the SMS gateway and customer engagement communication platform [27].

Application Program Interface Services

The HHM required application program interface (API) services to connect and integrate REDCap, Twilio, and the Oracle Database. Since these applications all require use of representational state transfer (REST) API services, we used REST API services to query, monitor, tailor, and deliver personalized text messages [28].

Development of HHM Content and Features

Key HHM program content and features were adapted from the MODEL program system [18], including a text message library and a REDCap web-based data capture system, however, all features required additional development to suit the HHM program. Several alternative vendors were considered for each feature. Twilio was selected as the SMS gateway due to its ease-of-use API and Studio Flow tools. We initially considered Python (Python Software Foundation), MySQL (Oracle Corporation), and PHP (Zend Technologies) for text message personalization and tailoring but selected Oracle Procedural Language and SQL due to its ready integration into Oracle using Oracle Application Express. Existing MODEL program text message stems were then migrated into the HHM schema of the TN-POPnet Oracle database (Figure 1). Example stems are shown in Table 1.

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Figure 1. Heart health messages program architectural design. API: application program interface; HHM: heart health messages; REDCap: Research Electronic Data Capture; REST: representational state transfer; TN-POPnet: Tennessee population health data network.

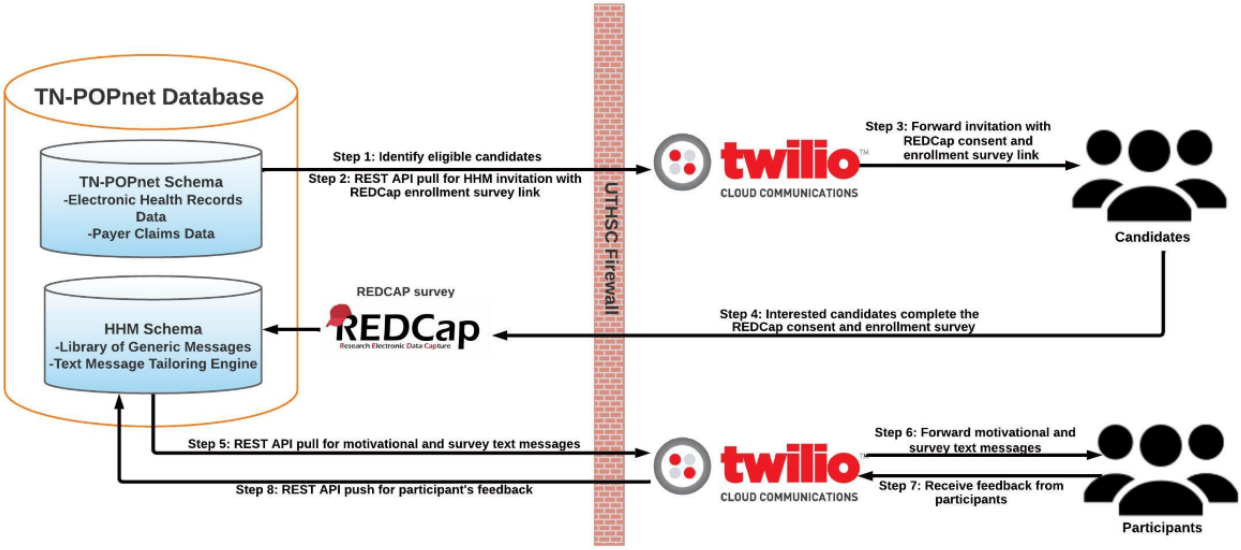

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Table 1. Example message stems used for the heart health messages program.

	Example message stems (ie, without personalization)
Healthy eating focus	
Frame	
Education	• {First name}, grocery shopping tip: most fresh food is located along the walls of grocery stores. Try buying most of your food from these locations • {First name}, before you buy any food, read its label. It has important info that will help you choose what foods are best for your blood sugar
Goal setting	• {First name}, controlling diabetes can be challenging but there is a lot in your control, like reaching for your goal of healthy eating each day • {First name}, eating healthier is a challenge for anyone but your health depends on it. Make eating healthy a goal and better health will be your reward
Motivation	• {First name}, believing in the power of healthy foods is a winning attitude when you have diabetes. Turn that attitude into action and eat well all day • {First name}, not everything about diabetes is easy. Eating healthy is a good first step in managing your care
Exercise focus	
Frame	
Education	• First name}, now that you have a workout goal, think about why you chose it. Thinking about why you exercise will make it easier to do each day • {First name}, we know you are busy. But every step counts so do as much exercise as you can each day and add more time little by little
Goal setting	• {First name}, you are on the way to being able to handle your diabetes. You may not be there yet, but every day you follow your exercise plan you get closer • {First name}, taking a friend along for your workouts is a great way to stay healthy together and keep you on track to reach your physical activity goal
Motivation	• {First name}, the hardest step is the first one. Once you get going on your physical activity plan each step you take will be easier. Start today! • {First name}, handling your diabetes does not always happen overnight. Hang in there and follow your exercise plan, you wll be able to handle it better soon
Medication messages	
Frame	
Education	• {First name}, with {health condition} you have a higher risk of dying due to pneumonia. Talk with your doctor about whether you should get vaccinated. • {First name}, every time you buy an over-the-counter medication be sure to check with your pharmacist, so you know it is safe to use with your {health condition} drugs.
Goal setting	• {First name}, you may not believe it yet but you can take care of your {health condition}. Something to do each day to show it: meet your goal of taking your medications. • {First name}, taking care of your {health condition} and taking your medicine can be tough, but you can do it. Ask your doctor about resources that may help you.
Motivation	• {First name}, taking {#_of_prescribed_medications} medications is certainly a challenge. Know that each one is helping you improve your overall quality of life. • {First name}, thinking you can meet the challenges of your {health condition} head on is a powerful attitude. Stay strong and keep up with your entire treatment.
Heart health focus	
Frame	
Education	• {First name}, {health condition} tends to lower your “good” cholesterol which means you need to stick to your treatment plan to help your body stay healthy. • {First name}, trying to control {health condition} can be stressful. Do not let it get your down. Stick with your plan and the results will help with the stress.

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	Example message stems (ie, without personalization)
Goal setting	• {First name}, having {health condition} is nothing to be embarrassed about- it is just like any other condition that requires managing. Focus on you and your goals. • {First name}, {health condition} can lead to poor blood flow in your legs. Having goals like eating well, exercising, and taking your medications will help prevent this.
Goal progress[a]	• {First name}, your blood pressure is looking better, which means you are on the path toward even better health! • {First name}, your "bad" cholesterol is on its way down! Keep sticking with your treatment plan and even better results on are the way • {First name}, you are at a healthy weight for your height. Maintaining a healthy weight goes a long way to keep your heart healthy, too
Motivation	• {First name}, we know that handling {health condition} is time consuming. Once it becomes habit I bet you'll see that it will just fit right in with your lifestyle. • {First name}, treating {health condition} takes a team, including friends and family. Maybe they can make changes with you? Just ask. Their help can go a long way.

[a]"Goal Progress" messages are tailored based on positive or negative changes in blood pressure, BMI, or cholesterol values.

MODEL schedule tables for sending messages based on participant message preferences (eg, for each combination of focus, frame, and frequency) were adapted for patients with and those without diabetes and migrated to the HHM schema. As shown in Table 1, the message stem, "focus," represents the health behaviors participants would like to prioritize, such as healthy eating, physical activity, or medication adherence. The frame refers to the content and tone of the messages, which can be educational, motivational, or goal-oriented. The frequency determines the options for message delivery, including once a day or once every other day. Variables from REDCap enrollment and quarterly follow-up surveys were linked to the text message library in the HHM schema using APIs. Text-based monthly check-in surveys are initiated, and valid text responses are collected through Twilio Studio Flow and sent to the HHM schema through a HTTP request.

Architectural Design of the HHM Program

HHM functionality requires electronic health records and patient-reported data collection, data analysis, message tailoring, and message delivery processes. The HHM program's modular design allows each component to function independently and govern a specific system activity (Figure 1).

The HHM automated text messaging system relies on the TN-POPnet database (Figure 1). In step 1, SQL scripts apply predefined eligibility criteria to identify eligible patient candidates in TN-POPnet. In step 2, candidate identifiers (name, cell phone number, zip code, date of birth, and clinic information) are collected (REST API pull) from the TN-POPnet to personalize both invitation messages and enrollment surveys. Enrollment surveys are personalized by automatically feeding candidate information into the HHM schema using an SQL query to reduce candidate data entry time. In step 3, individualized invitation messages to the HHM program including a REDCap consent and enrollment survey link are forwarded to candidates' mobile phones via Twilio. In step 4, interested candidates follow the REDCap link to consent, fill out the enrollment survey, and receive the HHM welcome message. Nonconsenting candidates automatically stop getting text messages and are given the option to receive another invitation in the future. Consenting candidates can also text "STOP" to halt further messages. In the case of no response, eligible candidates are resent the REDCap link to the HHM program after 2 days from the initial invitation, and this process is repeated after another 2 days. After that, participants will no longer receive an invitation. Consent forms and enrollment on the survey data are stored in REDCap and API-pulled into the HHM schema. In step 5, messages are tailored using the TN-POPnet registry data as well as data from the enrollment surveys. The HHM Schema makes an HTTP request to Twilio to prepare for sending tailored text messages and surveys.

In step 6, participants are forwarded tailored text messages from a library of generic messages via Twilio based on the selected frequency of message delivery (daily or every other day). Also, participants receive monthly text-based check-in survey messages (Textbox 1) designed to assess adherence and improvement in self-care based on participant-selected focus. Furthermore, participants are sent REDCap links to quarterly follow-up surveys to update enrollment information and focus, frame, and frequency preferences.

Textbox 1. Example monthly survey conversation between the heart health messages program and an anonymous participant (Jane).

HHM: Jane, on how many of the last 7 days did you follow a healthy eating plan? Please REPLY with a number from 0 to 7.

Jane: Five

HHM: Sorry, we do not recognize the value of the answer. Please try again.

HHM: Jane, on how many of the last 7 days did you follow a healthy eating plan? Please REPLY with a number from 0 to 7.

Jane: 5

HHM: Thank you, you have completed the survey!

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In steps 7 and 8, participant responses from the monthly check-in surveys and quarterly follow-up surveys are sent to the HHM schema via an API Push. Each combination of focus, frame, and frequency (n=27) has 3 buckets (A, B, and C) in which the majority of messages pertain to the participant's selected focus, mixed with messages from the other 2 focus areas, with decreasing percentage of messages from nonselected foci, as described in our formative work [18]. Participants are changed to a different bucket (ie, mix of messages) when participant responses to the monthly check-in survey differ from their baseline enrollment surveys. Participants continue to receive messages from the same bucket for the next month when their responses are unchanged. Responses from the quarterly follow-up surveys are also used to update enrollment information, as discussed in step 5. If participants do not complete quarterly follow-up surveys or choose to remain in the same focus as the last quarter, they receive another combination of their previous quarter's preference, referred to as an "instance." The timing at which tailored text messages and all surveys are sent is controlled by the Oracle Job Scheduler module. Interested candidates complete the HHM program over a 12-month period or depending on the agreement with the patients' health system or primary care practice.

Patient-Centered Design of the HHM Program

Throughout, HHM development was informed heavily by patient-centered design principles [29] to enhance patient experience of the HHM program (Figure 2). Before formal piloting of the system, we received feedback on system usability from 23 physicians and staff members volunteers, including some individuals with similar demographics and educational background to the target population. Feedback was used to make changes in system properties to improve user experience, including (1) shortening the enrollment survey to reduce respondent burden, (2) revising the consent form to use more patient-friendly language, (3) updating the invitation message to be more engaging, and (4) redesigning the enrollment workflow by dividing it into 2parts: a separate consent process followed by the baseline survey.

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Figure 2. Patient experience flowchart illustrating the chronology of participant interactions with the heart health messages program. REDCap: Research Electronic Data Capture.

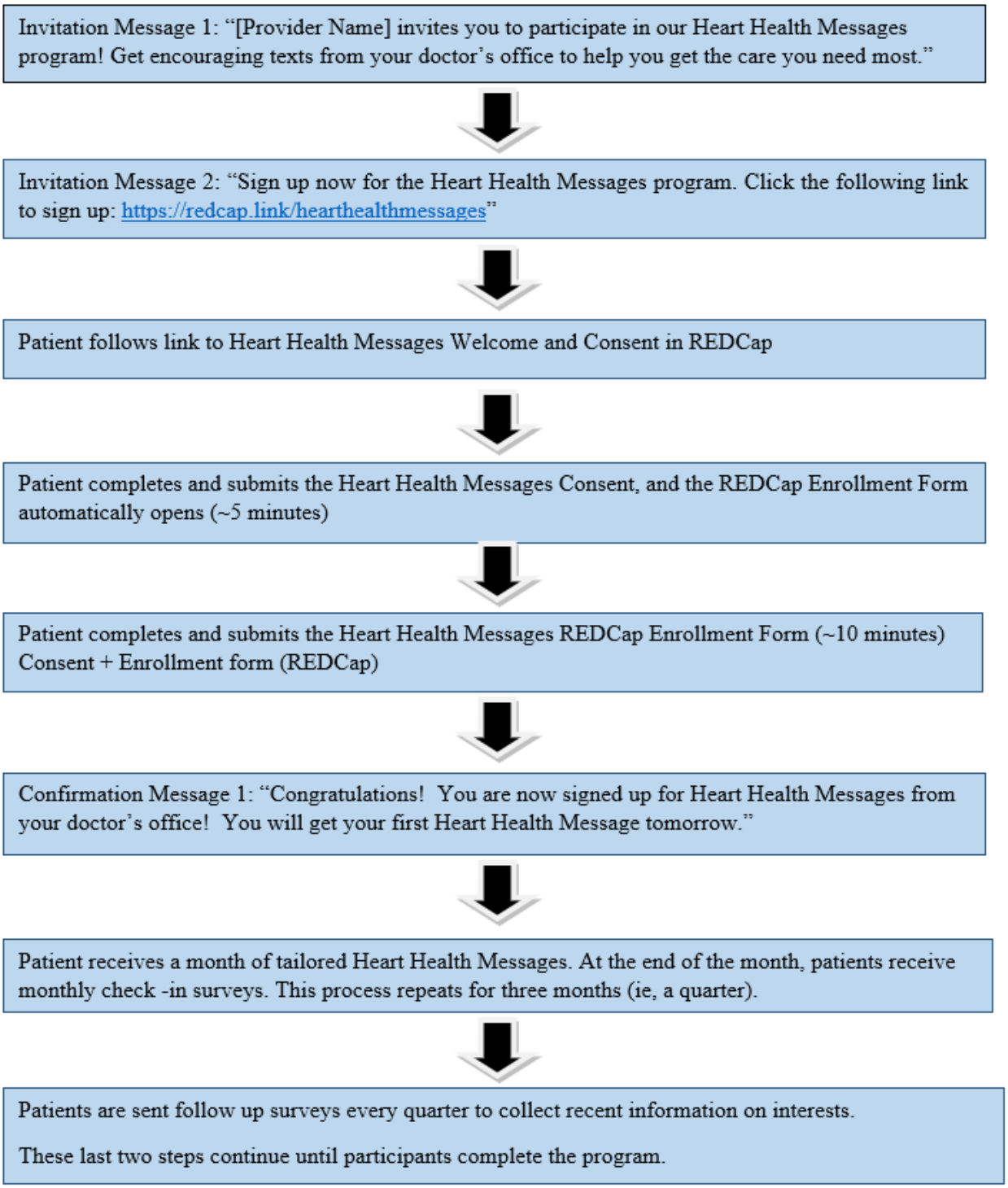

Outcomes

The current ongoing pilot study process evaluation for all participating health systems and practices includes ongoing assessment of the number and proportion of (1) eligible patients consented, enrolled, and with incomplete enrollment tracking completed signups on a monthly basis for a 3-month sign-up period until outreach efforts are completed; (2) enrolled patients responding (ie, engaged) to monthly text-based check-in surveys; and (3) participant retention rates at 3 and 6 months.

The long-term HHM program outcomes evaluation will use a quasi-experimental study design using a difference-in-differences methodology and non-enrolled matched controls to evaluate the impact of the HHM program on major health outcomes including systolic and diastolic blood pressure, hemoglobin A_{1c}, cholesterol, and BMI. The

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Difference-in-Differences approach is considered the most reliable advanced statistical method for program evaluation and assessment of the impact of non-randomized interventions, especially in primary health care settings [30,31]. The TN-POPnet registry, where patient and program measures and metrics are recorded, will also substantially support and facilitate the planned outcomes evaluation.

Ethical Considerations

This study was approved by the institutional review board at the University of Tennessee Health Sciences Center (No. 21-08392-NHSR). All participants provided informed consent before their enrollment in the HHM program, and this consent was stored in our Secure Web-based Application REDCap. Patient participation was completely voluntary, and no compensation was involved.

Results

So far, 18,974 patients in the 2 major health systems participating in the TN-HHN were eligible and included in the pilot study of the automated registry-based version of the tailored text messaging system (HHM 1.0). Eligible candidates will receive between approximately 212 and 428 messages based on selected message preference at enrollment. These messages cost US $0.008 each, and the estimated cost of sending a tailored text message per patient via Twilio for 12 months ranges from US $1.70 to US $3.42.

Table 2 shows the baseline results from the initial pilot cohort of HHM 1.0. In phase 1 (November 16-20, 2022), 225 eligible patients were sent invitation messages. Approximately 2% (4/225) completed the HHM consent and baseline survey following receipt of a text message invitation alone. In phase 2 (March 2-6, 2023), 5288 eligible patients were contacted, and approximately 3% (137/5228) responded and completed the HHM consent and enrollment survey**.** In phase 3 (September 22-26, 2023), invitations were sent to an additional 13,461 eligible patients and a 3% (350/13461) enrollment rate was observed. All consented and enrolled participants will receive tailored text messages for a 12-month period. Efforts are underway to implement strategies in collaboration with health systems to enhance the HHM program rollout and patient participation.

Table 2. Preliminary results from the initial pilot cohort of heart health messages 1.0 patients.

	Eligible and invited patients, n
First phase of piloting (n=225)	
Did not respond to consent survey	218
Did not respond to consent survey, stopped	0
Completed consent survey, did not consent	2
Completed consent survey, consented, did not complete baseline	1
Completed consent survey, consented, stopped	0
Consented, completed baseline survey, set to receive messages	4
Second phase of piloting (n=5288)	
Did not respond to consent survey	4679
Did not respond to consent survey, stopped	131
Completed consent survey, did not consent	13
Completed consent survey, consented, did not complete baseline	327
Completed consent survey, consented, stopped	1
Consented, completed baseline survey, set to receive messages	137
Third phase of piloting (n=13,461)	
Did not respond to consent survey	12,536
Did not respond to consent survey, stopped	0
Completed consent survey, did not consent	34
Completed consent survey, consented, did not complete baseline	540
Completed consent survey, consented, stopped	1
Consented, completed baseline survey, set to receive messages	350

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Discussion

Anticipated Findings

The HHM program approach for using data from a statewide population health registry (ie, TN-POPnet) as well as patient input to tailor and personalize health-related text messages is highly innovative. To our knowledge, the HHM approach to registry-based message tailoring has not been previously described. This approach allows health systems to send tailored and personalized messages to large populations of patients at high risk for cardiovascular disease at a significantly lower cost compared with alternative interventions such as in-person counseling, traditional mail, or phone calls. These alternative traditional methods are usually more expensive and require intensive manpower labor [32-34] compared with the tailored text messaging approach, which is more cost-effective and scalable [35], particularly in rural and underserved populations where access to care is limited [36]. Another key strength of the HHM is its patient-centeredness. The HHM message library was established using a patient-centered design with critical input from health behaviors literature and feedback from patient experts [29]. HHM program participants are enabled to select and prioritize their own health goals (ie, healthy eating, physical activity, or medication adherence) at enrollment, and they can update enrollment information and focus, frame, and frequency preferences of incoming text messages during quarterly follow-up surveys. Further, participants are assessed monthly for program adherence and improvements in self-care. An additional strength of the HHM program is its ability to provide personalized and tailored progress feedback for some health outcome metrics (eg, blood pressure, cholesterol, and BMI) if they prioritize receiving "Goal Progress" messages, either at initial enrolment or at follow-up. Finally, the HHM is evidence-based; the nonautomated version of the text messaging program has already been tested and evaluated in the real world and demonstrated to change health behaviors in patients at increased risk for cardiovascular events **[17,19,37].**

The low participation rate seen in HHM 1.0 is consistent with other research demonstrating an average of approximately 3% response rates for unsolicited text messages [38]. However, previous research has also demonstrated that participation rates in similar text messaging programs can reach 20% or more with more intensive recruitment supported by the physician and other primary care team members [39]. The low enrollment rates observed could negatively impact the cost-effectiveness of the program as a large amount of text messages are sent to a relatively small number of participants, which could affect the overall cost-benefit ratio of the program. Although the cost of text messages is low, at US $0.008 each, the fixed administrative costs could potentially make it difficult for current participating health systems to invest significant resources unless higher program enrollment and effectiveness can be achieved. To increase participation rates and program effectiveness, we are implementing several strategies, including distributing posters, flyers, and patient letters and providing staff members support to encourage patient sign-ups at participating health systems. These strategies ensure the program reaches its full potential with respect to cost-effectiveness and improving patient health outcomes. Further piloting will focus on deploying this service to additional TN-HHN primary care practices serving eligible patients with or at risk of chronic disease across Tennessee. In accordance with Agile implementation methodology principles, ongoing piloting of the HHM program in new health systems and practices will be guided by the experience of initial pilot study participants [40].

Other states and organizations considering the use of a population health registry to tailor and send motivational text messages must also pay particular attention to patient privacy requirements. Despite strict HIPAA requirements regarding the transmission of Patient Health Information (PHI) via text messages, some bulk messaging services that claim to be HIPAA-compliant fail to provide secure connections outside their networks [41]. Moreover, US regulations regarding electronic communication through mobile technologies like SMS have no specific technological requirements regarding SMS security, which means any platform can be used to communicate with patients as long as it upholds a high level of patient security and privacy [42]. Thus, substantial due diligence is required to ensure the safe transmission of PHI via text message to ensure optimal security. Our HHM system's technical and design requirements and architecture were carefully selected to ensure full HIPAA compliance while maintaining patient data confidentiality and security. Specifically, all PHI is stored in a HIPAA-compliant Oracle database-TN-POPnet database. REDCap, a secure web-based application designed for research purposes, was selected and used to collect consent and enrollment information. For messaging services, we selected Twilio (Twilio Inc), a HIPAA-compliant SMS gateway, to securely manage patient communication and protect patient data. In addition, we obtained consent from each patient before their enrollment into the program, and participants were thoroughly informed of the risks associated with transmitting PHI via text messages.

Technical Challenges and Limitations

While developing the HHM program, we experienced some technical challenges and limitations. First, while the length of the enrollment survey was necessary for the proper tailoring of motivational text messages, it also served as a barrier to patient participation. We attempted to rectify this by reducing the length of the enrollment survey, but this still potentially served as a hurdle to enrollment. Future text messaging platforms should ideally seek to rely on EHR data and other data sources rather than requiring a lengthy survey to be filled out by patients or participants.

Second, there were technical difficulties with moving information in the MODEL program to our automated HHM program. While the medication table was relatively straightforward, the expansion of HHM to include more medical conditions increased complexity. Several MODEL stems explicitly dealt with diabetes, so these had to be changed to be more general or replaced with another stem from the same focus and frame.

Third, it is also possible that the use of outdated or incomplete registry data could present potential risks to patients, such as encouraging adherence to medications that have recently been

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discontinued. However, the HHM program sought to minimize these risks through the use of as close to real-time updates of its underlying TN-POPnet registry system. Fourth, the HHM system's reliance on patient self-reporting during enrollment and follow-up surveys could impact the accuracy and reliability of the tailored messages sent to participants. However, the results obtained from the HHM system's real-world experience in the MODEL program indicate a positive effect on health behaviors. Therefore, these potential accuracy and reliability issues might not have clinical significance. Fifth, some invitation messages were blocked by Twilio (ie, the carrier) as potential spam. Further program iterations will seek to overcome this difficulty through broad registration of the campaign. This means that the HHM program will be registered as an application-to-person Campaign with Twilio. Finally, scaling the HHM program across multiple health systems presents challenges, primarily related to the need for practice participation and data sharing with a third party. To address these challenges, we merged all data into a common data model (TN-POPnet database), which facilitates seamless integration and collaboration among participating practices. This also enables data standardization.

Conclusion

The HHM program provides an innovative and low-cost solution for sending personalized and tailored motivational text messages on behalf of their primary care provider to patients at risk for cardiovascular events. The HHM approach for using both a statewide population health registry and patient input to tailor and personalize health-related text messages to patients at highest risk has high potential for broader dissemination and replication. The patient-centered design and architecture of HHM lends itself to program scalability and ongoing refinement to improve its cultural tailoring and incorporation of additional modules to address additional self-care behaviors linked to improved outcomes for people with common chronic conditions. The HHM Program also demonstrates the utility of statewide population health registries like the TN-POPnet, and how they can provide a strong foundation for the low-cost delivery of essential population health services that can enhance the management and outcomes of care for chronic conditions, particularly for underserved or low-resource communities. Studies are needed to further assess the impact of registry-tailored motivational text messaging on overall health care expenditures and support its implementation and dissemination in states nationwide.

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Data Availability

The datasets generated or analyzed during this study are not publicly available due to privacy concerns but are available from the corresponding author on reasonable request.

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Authors' Contributions

All authors have made substantial contributions to this pilot study. JB, JG, and JC designed the HHM program. DO, JC, AP, AK, UK, JG, and JB contributed to the initial drafting of the work. DO, JC, SS, AM, SM, and JB critically reviewed the work for important intellectual content prior to submission. All authors have reviewed the final version to be published.

Conflicts of Interest

JG is an employee of GlaxoSmithKline. All other authors have no competing interests to declare.

Multimedia Appendix 1
TIDieR (Template for Intervention Description and Replication) checklist.
[PDF File (Adobe PDF File), 836 KB - resprot_v14i1e62874_app1.pdf]

Multimedia Appendix 2
Example of motivational health-related text messages sent to participants, tailored to their selected “focus” and “frame”.
[PNG File , 133 KB - resprot_v14i1e62874_app2.png]

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Abbreviations

API: Application Program Interface
HHM: Heart Health Messages
HIPAA: Health Insurance Portability and Accountability Act
MODEL: Management of Diabetes in Everyday Life
PDSA: Plan-Do-Study-Act
PHI: Patient Health Information
REDCap: Research Electronic Data Capture
REST: Representational State Transfer
TIDieR: Template for Intervention Description and Replication
TN-HHN: Tennessee Heart Health Network
TN-POPnet: Tennessee Population Data Network

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Protocol

Preventing Premature Pre-Exposure Prophylaxis Discontinuation and Sexually Transmitted Infections Among Men Who Have Sex With Men (Project PEACH): Protocol for a Prospective Cohort Study

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Abstract

Background: There is an ongoing syndemic of HIV and sexually transmitted infections (STIs) in the United States, particularly among men who have sex with men (MSM). We have increasingly effective and diverse measures of prevention, including various types of pre-exposure prophylaxis (PrEP) for HIV prevention and doxycycline postexposure prophylaxis (doxyPEP) for STI prevention. As options expand, we need to understand how to use a combination of these strategies and other supports for MSM to best curb the syndemic.

Objective: We designed a patient-preference trial to understand patient preferences for PrEP and doxyPEP, how preferences may change over time, and methods for preventing premature discontinuation of PrEP.

Methods: We enrolled HIV-negative MSM in metropolitan Atlanta, Georgia. Participants could elect to take PrEP (daily or on-demand), doxyPEP, both, or neither, along with app-based support to evaluate for risk factors of discontinuation or behavioral changes that might affect their choice of prevention methods. Participants were able to switch prevention methods at any time. Oral PrEP and doxyPEP users are currently being offered quarterly in-person or at-home HIV, syphilis, gonorrhea, and chlamydia testing along with opportunities for motivational interviewing.

Results: We enrolled individuals from November 2021 to September 2023. Among 240 participants, the median age was 30 (IQR 25-35), 63% (n=150) self-identified as non-Hispanic Black, and 69% (n=166) were insured. Most participants (n=144, 60%) elected to take daily PrEP plus doxyPEP, with a smaller proportion taking on-demand PrEP plus doxyPEP (n=34, 14%) or daily PrEP without doxyPEP (n=33, 14%).

Conclusions: We designed an ongoing study to evaluate the preferences for PrEP and doxyPEP among MSM in metropolitan Atlanta. Enrollment was completed in 22 months and included a diverse cohort of MSM that will be followed longitudinally to evaluate prevention preferences over time. At baseline, most participants preferred to take a combination of daily PrEP and doxyPEP for HIV and STI prevention.

Trial Registration: Clinicaltrials.gov NCT05072093; https://clinicaltrials.gov/study/NCT05072093

International Registered Report Identifier (IRRID): DERR1-10.2196/56096

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(JMIR Res Protoc 2025;14:e56096) doi:10.2196/56096

KEYWORDS

PrEP; doxyPEP; HIV; sexually transmitted infections; men who have sex with men; pre-exposure prophylaxis; United States; prevention; syndemic; patient preferences; app-based; cohort study

Introduction

The US HIV epidemic continues to disproportionately impact men who have sex with men (MSM), who comprise 2% of the US population but account for about two-thirds of all new HIV diagnoses in the United States [1]. Epidemic modeling studies [2-4], our National HIV/AIDS Prevention Strategy [5], and the Centers for Disease Control and Prevention (CDC) Ending the HIV Epidemic initiative [6] all emphasize the critical role of pre-exposure prophylaxis (PrEP) in the national HIV prevention response. PrEP use is rising among men. Despite this, current estimates of coverage of PrEP among PrEP-eligible MSM fall short of the sustained 30%-50% coverage of PrEP among MSM that would be required to produce substantial decreases in new HIV infections [2,3]. PrEP use also varies widely geographically and by race. For example, in 2021, about 30% of PrEP-eligible men reported ever using PrEP in their lifetime [7]; in Ending the HIV Epidemic priority jurisdictions in metropolitan Atlanta, Georgia, less than 19% of PrEP-eligible MSM took PrEP [8].

Increasing rates of sexually transmitted infection (STI) diagnoses, independent of and concurrent with higher PrEP use [9], lead to concerns that men using PrEP may abandon condom use, contributing to greater increases in STIs among all MSM. Recent data from the CDC has shown a rise of 459% in the rate of cases of syphilis, 132% for chlamydia, and 96% for gonorrhea over the last 20 years [10], and although data from 2020 and 2021 may have been impacted by limitations of testing during the COVID-19 epidemic, there has overall been a steady increased rate of these STIs. The Southern United States has the highest rates of chlamydia and gonorrhea, and second highest rates of syphilis when compared to the West, Midwest, and Northeast, and rates of chlamydia and gonorrhea are highest in people who identify as Black or African American [10]. The recent introduction of postexposure prophylaxis with doxycycline (doxyPEP) to prevent STIs, which can decrease the risk of incident chlamydia, syphilis, and gonorrhea by up to 89%, 87%, and 55%, respectively [11], has been an encouraging prevention tool. The CDC recently released guidelines for the use of doxyPEP with a particular focus on offering it to MSM and TGW who have been diagnosed with an STI in the previous 12 months [12].

The syndemic of HIV and STIs is inherently intertwined given the shared mode of transmission, similar sociodemographic and structural risk factors, and as STIs can increase the risk of acquiring HIV [13]. Multiple prior studies have found that men on PrEP are more likely to discontinue taking PrEP after being diagnosed with an STI [14,15]; the exact reasons for this are unknown but thought to potentially be related to the change in sexual behaviors (eg, participants on PrEP noted they were engaged in more risky behaviors and thus had more STIs, so chose to discontinue it) and a marker of adherence to medical interventions. Given effective methods for the prevention of both HIV and STIs, they must be framed as a syndemic to provide comprehensive, patient-centered sexual health services to best support patients [16,17]. There are few data on PrEP uptake and persistence by PrEP modality and how preferences might change over time. In a sample of US MSM, on-demand PrEP was ranked as the most preferred mode of PrEP among nine possible routes of PrEP administration, and men reported statistically significantly higher intention to use on-demand oral PrEP than to use daily oral PrEP [18]. With the introduction of injectables and other forms of long-acting PrEP, more recent studies have shown that this may be an even more appealing option for individuals [19-21]. Many prior studies of PrEP have focused on recruiting individuals to start PrEP, but few have developed systems to mitigate PrEP discontinuations and prevent STI infections for MSM on PrEP.

The holistic focus relates importantly to implementation strategies because the barriers to persisting on PrEP are both structural (eg, distance to provider for follow-up visits, health insurance, and reimbursement mechanisms) and socio-relational (eg, attitudes of friends and family, relationship status, and perception of vulnerability to HIV) [22-25]. The barriers to starting PrEP (eg, lack of awareness of PrEP, barriers to care entry, stigma, and doubts about the efficacy or safety of PrEP) are not the same as the barriers to PrEP persistence (eg, lapse of insurance or assistance programs, difficulties with long-term adherence, changing sexual partners, frequency or networks, negative influence of friends or family, and concerns about new STIs) [26]. With the increasingly widespread availability of multiple modalities of PrEP, as well as doxyPEP as a novel method for STI prevention, it will be important to determine patient preferences in the combination of these prevention methods to best support services for individuals to prevent incident HIV and STIs.

We designed the Parrying the Pitfalls of PrEP: Preventing Premature PrEP Discontinuation and STIs Among MSM (Project PEACH) to offer a combination of sexual health prevention interventions. We recruited MSM without HIV living in metropolitan Atlanta, offered a bundle of sexual health prevention interventions, including multiple PrEP options and doxyPEP, and provided adherence and retention support through a mobile app and motivational interviewing. The purpose of Project PEACH is to understand which combination of sexual health interventions MSM will choose to use, how these might change over time, and to evaluate the determinants of PrEP persistence.

Methods

Design

Project PEACH is a prospective, observational cohort of 240 people assigned male sex at birth who have sex with other men (MSM) living in metropolitan Atlanta, Georgia. Recruitment

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of the cohort took place from November 2021 to September 2023. Participants are followed for 2 years with study assessments at baseline and months 4, 7, 12, 19, and 24. Study inclusion and exclusion criteria are shown in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Assigned male sex at birth
- Self-identification as a cisgender male
- Aged 18-45 years
- Lives in the metropolitan Atlanta area and not planning to move out of the area in the next 2 years
- Had at least one male anal sex partner in the 12 months before the baseline interview
- Able to complete survey instruments in English
- Provide 2 or more means of contact
- Own a cell phone with data service and willing to download and use a health-related study app

Exclusion criteria

- Positive HIV screening test at baseline visit
- Enrolled in another HIV prevention clinical trial

All participants were offered daily PrEP with tenofovir disoproxil fumarate (TDF) 300 mg/emtricitabine (FTC) 200 mg unless the participant had underlying chronic kidney disease with a creatinine clearance <50 mL/min or other contraindication for TDF/FTC per clinician review, in which case the participant was offered daily tenofovir alafenamide 25 mg/FTC 200 mg. All participants were also offered STI PEP with doxycycline 200 mg to be taken no longer than 72 hours after condomless sex. Participants who elected to use STI PEP were dispensed enough doxycycline to allow up to three weekly doses, but refills were readily available to participants if requested. If a participant was not interested in daily PrEP or planned to discontinue daily PrEP, they were offered on-demand PrEP. On-demand PrEP was offered with TDF/FTC and participants were directed to take two pills 2-24 hours before sex and to take an additional pill 24 hours after the first pill and a final dose 24 hours after that ("2-1-1"). TDF/FTC and tenofovir alafenamide/FTC prescriptions were provided for use at local pharmacies and navigation for insurance approvals and patient assistance plans for uninsured participants or participants with copays were provided. We amended our study protocol in May 2022 when injectable PrEP with cabotegravir became locally available. Patients were offered this option through local partner community organizations by providing them with information about clinics and instructing them to make an appointment, although injectable PrEP remained difficult to access throughout the study period. Participants were able to elect to start PrEP or STI PEP or change PrEP modality at each survey visit (months 4, 7, 12, and 19) or at any time through the study app.

All participants were provided with the study's mobile SMaRT (Study Management and Retention Toolkit) phone app to support early identification of risks for PrEP discontinuation and offer alternative prevention methods, to identify any side effects from medications, to provide information about STI PEP and document use patterns of on-demand PrEP and STI PEP, and to support easy linkage to support services for PrEP counseling and addressing concerns or questions about STI PEP. Participants are able to complete monthly (daily PrEP and injectable PrEP users) and weekly (on-demand PrEP, STI PEP, and first 2 weeks for daily PrEP users) short surveys within the SMaRT app, which also provides links to web-based study assessments at months 4, 7, 12, 19, and 24.

Recruitment, Enrollment, and Retention

Participant recruitment was conducted through multiple sources. We used a modified venue-day-time screening approach using data from past studies to prioritize venues with historically high numbers of MSM who were HIV-negative [27,28]. We offered a US $5 incentive to take the study screener at in-person recruitment events. We used dating apps and social media with targeted advertisements to adult MSM in Atlanta and offered US $20 incentives to current study participants who shared our institutional review board (IRB)–approved study ads on their social media. Our initial recruitment plan was to exclude participants already on PrEP, but given limitations in enrollment during the COVID-19 pandemic, we expanded eligibility in May 2022 to include participants currently prescribed PrEP. NIH recruitment goals were set to include ≥70% of participants who identify as a racial or ethnic minority, including ≥10% of all participants identifying as Hispanic.

Participants who were eligible for the study based on the initial screening questionnaire were scheduled for an enrollment (baseline) visit at the community-based Programs, Research, & Innovation in Sexual Minority Health (PRISM) Health Research Clinic. This clinical site is located 1.5 blocks from public transportation, and ride-share services were provided to participants with limited transportation opportunities or long commutes. The enrollment visit consisted of an informed consent process, a computer-assisted self-interview behavioral survey, HIV and STI testing, training on using the study app, and a counseling session to include pre- and posttest HIV prevention information and a discussion about PrEP and STI PEP options. Participants who completed an enrollment visit

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were compensated US $125 regardless of whether they subsequently participated in the study. Participants with a positive HIV screening test at baseline or any point during the study were linked to HIV care.

To maximize retention, we used several strategies. We hired a study staff member dedicated exclusively to retention who collaborated with the study team to promote retention among participants. The SMaRT mobile app was customized for this study to allow participants to schedule, reschedule, receive reminders of, and cancel study appointments; communicate securely with study staff; and update contact information from within the Health Insurance Portability and Accountability Act (HIPAA)-compliant app. Participants were reminded about their follow-up visits through the app messaging system or their preferred means of contact both 3 days and 1 day before the scheduled follow-up date. We also sent reminders for surveys up to one week prior and up to 20 days after the target date through the SMaRT app. If we lost contact with participants (missed surveys or appointments and were nonresponsive to contact requests), we obtained consent to use for-fee public-use databases (eg, Lexis-Nexis) to locate participants; this has been used by us in previous studies to relocate participants who were lost to follow-up [29,30]. For participants who could not be contacted, after IRB approval, staff first attempted to contact emergency contacts, and if unsuccessful, attempted to link the identities of participants to registries of known decedents using a statewide data set (vital records) and a nationwide data set (National Death Index).

Study Procedures

All participants who elected to use oral PrEP or STI PEP received brief weekly surveys for the first two weeks after starting medications, with a US $5 incentive provided for each survey. After this period, daily PrEP and injectable PrEP users received monthly short surveys to assess risk for discontinuation (US $10 incentive for each survey) whereas participants who opted for on-demand PrEP or STI PEP continued to receive weekly short surveys (US $5 incentive for each survey). All participants were sent computer-assisted self-interview surveys at months 4, 7, 12, 19, and 24, and encouraged to attend in-person follow-up visits at 12 and 24 months (US $40 at 4, 7, and 19 months; US $100 at 12/24-month survey and study visit) and additional telehealth or in-clinic visits if the risk for PrEP discontinuation was identified by surveys. Daily or on-demand PrEP users or STI PEP users had the option for in-person or home-testing for HIV/STIs every 3 months for clinical monitoring of their medication use. For injectable PrEP users, all clinical monitoring was done outside the study by a local provider of the participants' choosing.

Motivational Interviewing

Risk factors for discontinuing PrEP were developed using data from a previous cohort of MSM in Atlanta (Textbox 2) [14,31,32]. When a participant reported any of these risk factors for discontinuing PrEP on a monthly survey, they were invited to schedule a discussion with a peer navigator with the intention of identifying possible risks for PrEP discontinuation, minimizing discontinuation of PrEP, or offering another prevention option. Triage sessions were client-centered, using an approach grounded in motivational interviewing. By focusing on the last time that the client was confident about being on PrEP (eg, think back to when you were taking your medication every day, what was going on in your life? Where were you living? Who were you dating?), the peer navigators were able to better understand the holistic context of the current risk factor. Based on this comprehensive understanding of needs and the monthly screening data, trained peer navigators used motivational interviewing tools to help participants problem-solve based on the needs identified and worked with them to develop a plan to address those concerns while maintaining PrEP, if appropriate. Clinical concerns (eg, side effects) were referred to a PrEP clinician for discussion.

Textbox 2. Risk factors for discontinuing pre-exposure prophylaxis (PrEP).

- Issues with remembering to take PrEP
- Stigma (ie, judgment from friends or family)
- The side effects made me feel bad
- Did not want to take a pill every day
- Did not think I was at risk anymore (decrease in risky behavior)
- Having sex less frequently
- Change in sex partner
- Time conflict
- Increase in risk behavior
- Housing issues
- Cannabis use
- Depression
- Anxiety
- Had bad experiences (eg, clinic not open at convenient times)
- Too much going on in my life right now

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Laboratory Specimens

Laboratory testing was done at the research clinic or remotely by the participant at home using self-collection specimen methods and differed by prevention method choice as described in Table 1. Clinical monitoring of injectable PrEP use was done by the local provider who administered the medication. Any positive HIV/STI test results were provided to participants over the phone by a study staff member who could refer participants to study-paid treatment for STI infections at a local community-based health clinic, or to participant-paid treatment through a provider of their choosing. Negative test results were delivered through the HIPPA-compliant study app. To minimize bias in self-report data on substance use, we collected urine drug screening in our on-site clinical laboratory improvement amendments-waived laboratory at baseline, 12, and 24 months using the Ten Panel Integrated EZ Split Key Cup Drug Test. We attempted to examine Neisseria gonorrhoeae resistance patterns among men who acquired the infection during follow-up by having them return for Neisseria gonorrhoeae culture prior to treatment with compensation of US $100; however, we discontinued this when none of the isolates grew in culture.

Table 1. Study design of testing and surveys by group.

Test or survey type	Group of participants		
	If elect daily oral PrEP[a]	If elect daily oral PrEP or injectable PrEP	If elect on-demand PrEP or doxyPEP[b]
HIV Ag/Ab, RPR[c], urine/throat/rectal GC[d]/CT[e] PCR[f,g,h,i]	Baseline and every 12 months	Baseline and every 12 months	Baseline and every 3 months
Web-based computer-assisted self-interview surveys	Months 4, 7, 12, 19, and 24	Months 4, 7, 12, 19, and 24	Months 4, 7, 12, 19, and 24
Serum creatinine	Baseline and every 12 months	N/A[j]	N/A
Hepatitis B surface antigen	Baseline	N/A	N/A
Survey of PrEP discontinuation risk	N/A	Monthly	N/A
Survey of PrEP use and discontinuation risk	N/A	N/A	Weekly

[a]PrEP: pre-exposure prophylaxis.

[b]doxyPEP: doxycycline postexposure prophylaxis.

[c]RPR: rapid plasma reagin.

[d]GC: *Neisseria gonorrheae*.

[e]CT: *Chlamydia trachomatis*.

[f]PCR: polymerase chain reaction.

[g]HIV Ag/Ab screening done in-person via INSTI (a clinical laboratory improvement amendment-waived HIV rapid test); if positive or indeterminate or if someone was initiating PrEP/ sexually transmitted infection PrEP, we sent a blood sample to Quest for commercial fourth-generation HIV testing. If HIV Ag/Ab screening was done remotely, patients collected a dried blood spot card and were sent to a laboratory for fourth-generation HIV testing specifically for dried blood spot protocol.

[h]Participants self-collected pharyngeal, urine, and rectal samples for *N gonorrhea* (GC) and *C trachomatis* (CT) using Abbott Real Time GC/CT assay.

[i]Serum samples for a US Food and Drug Administration–approved syphilis RPR test were either collected in-person at the clinic by a phlebotomist or remotely via participant fingerstick blood sample. If RPR is reactive on home tests, participants were asked to come to the clinic to have an RPR titer drawn.

[j]N/A: Not applicable.

Planned Analyses

In Table 2, we have outlined the proposed analyses for this study. We will evaluate the rate of PrEP uptake, rate of doxyPEP uptake, rate of PrEP discontinuation, rate of doxyPEP discontinuation, and rate of incident STI and HIV diagnoses by prevention choice. We will describe use patterns of PrEP modality and STI PEP over the study period including changes in use. We will also describe the proportion of participants who initially chose each method of PrEP and the proportion who switched method of PrEP during the study period. We will describe the utilization of various support systems offered. Finally, we will compare incident STI diagnoses (gonorrhea, chlamydia, syphilis) at 12 and 24 months in this cohort to a historical control group to evaluate the effect of STI PEP.

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Table 2. Proposed outcome measures and planned analyses.

Outcome measure	Planned analyses
PrEP[a] uptake	• Descriptive analysis—prevalence
DoxyPEP[b] uptake	• Descriptive analysis—prevalence
PrEP discontinuation	• Proportion of PrEP users discontinuing, by group • Time to discontinuation by Cox Proportional Hazards model (if sufficient events for analysis)
DoxyPEP discontinuation	• Proportion of doxyPEP users discontinuing, by group • Time to discontinuation by Cox Proportional Hazards model (if sufficient events for analysis)
Change in STI[c] prevention modality	• Descriptive analysis with alluvial plots or heat maps
Utilization of support systems (eg, motivational interviewing and application)	• Descriptive analysis—prevalence
Time to incident HIV diagnoses	• Cox proportional hazards model
Time to incident chlamydia diagnoses[d]	• Cox proportional hazards model
Time to incident gonorrhea diagnoses[d]	• Cox proportional hazards model
Time to incident syphilis diagnoses[d]	• Cox proportional hazards model

[a]PrEP: pre-exposure prophylaxis.

[b]DoxyPEP: doxycycline postexposure prophylaxis.

[c]STI: sexually transmitted infection.

[d]Plan to compare incident STI diagnoses at 12 and 24 months to historical Atlanta data over the same time period using a denominator of men who have sex with men.

Ethical Considerations

The study was approved by the Emory IRB (STUDY00000608). Informed consent was provided by participants at the time of enrollment and participants were given the option to opt out of the study at any time. The data obtained were all anonymized using a unique patient identifier number. Participants were compensated for their time as outlined above.

Results

The study was approved by the Emory University IRB in May 2021 and launched in September 2021. Of the 1299 people who completed electronic screening, 525 people were eligible for the study (Figure 1). We enrolled 240 men in Atlanta, Georgia, over the course of 21 months from November 2021 through September 2023. Median age was 30 (IQR 25-35), 63% (n=150) self-identified as non-Hispanic Black, 12% (n=29) as Hispanic, 19% (n=46) as White, and 6% (n=15) as Other. A total of 31% (n=74) were uninsured at baseline (Table 3).

Laboratory measurements at baseline are shown in Table 4. Treponemal antibody results are presented below, which could represent past or current infection. For primary analysis, cases of syphilis will be individually adjudicated.

At first visit, 57% (n=136) elected for daily PrEP and STI PEP, 14% (n=34) on-demand PrEP and STI PEP, 13% (n=31) daily PrEP only, 7% (n=17) STI PEP only, 4% (n=9) on-demand PrEP only, 3% (n=8) injectable PrEP and STI PEP, 2% (n=5) app only, and 1% (n=2) injectable PrEP only (Figure 2). Of note, although injectable PrEP was offered through the study starting in May 2022, the first date that a study participant received injectable PrEP was March 2023.

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Figure 1. Flowchart of participants included in the analysis and reasons for exclusion at each step in the enrollment process. This was an adaptive design, patient preference trial in which men who have sex with men in Atlanta, Georgia from 2021 to 2023 were able to choose a combination of HIV PrEP and STI postexposure prophylaxis (doxyPEP) that was best for their needs. Individuals who completed electronic screening but were ineligible for the study could have been excluded for multiple reasons. doxyPEP: doxycycline postexposure prophylaxis; PrEP: pre-exposure prophylaxis; STI: sexually transmitted infection.

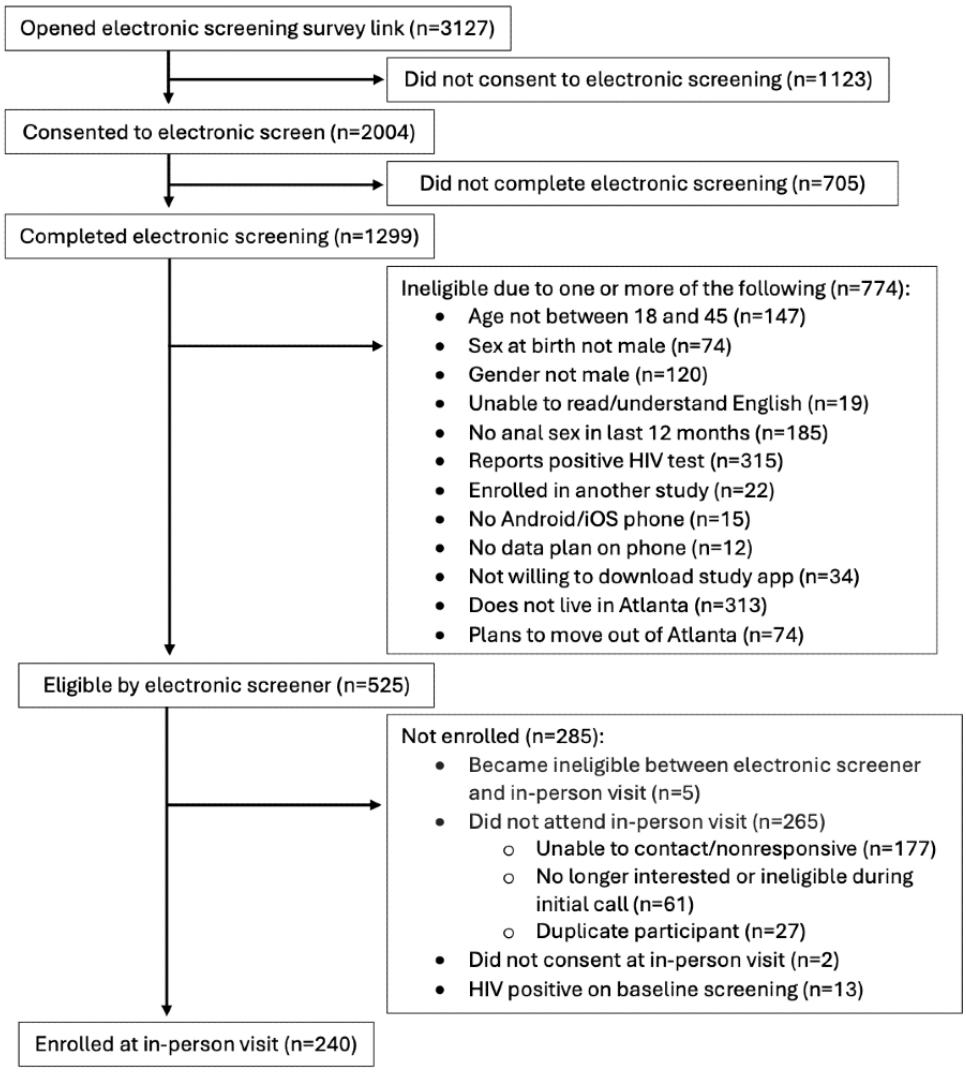

Table 3. Baseline demographics of participants.

Participant characteristics	Total participants (n=240)	PrEP[a] + DoxyPEP[b] (n=177)	PrEP only (n=42)	DoxyPEP only (n=16)	App only (n=5)
Age (years), median (IQR)	30 (25-35)	31 (25-35)	29 (24-33)	32 (28-37)	24 (23-28)
Race/ethnicity, n (%)					
Black, non-Hispanic	150 (63)	108 (61)	28 (67)	12 (75)	2 (40)
Hispanic	29 (12)	22 (13)	4 (9)	1 (6)	2 (40)
White, non-Hispanic	46 (19)	34 (19)	8 (19)	3 (19)	1 (20)
Other	15 (6)	13 (7)	2 (5)	0 (0)	0 (0)
Insured, n (%)	166 (69)	120 (68)	33 (79)	9 (56)	4 (80)

[a]PrEP: pre-exposure prophylaxis.

[b]DoxyPEP: doxycycline postexposure prophylaxis.

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Table 4. Baseline laboratory data of participants.

Baseline participant laboratory measurement	Total participants (N=240), n (%)
Hepatitis B surface antigen-positive	0 (0)
Creatinine clearance <60 mL/min	2 (0.4)
Chlamydia PCR[a] test positive	
Pharyngeal	5 (2)
Rectal	12 (5)
Urine	8 (3)
Gonorrhea PCR test positive	
Pharyngeal	8 (3)
Rectal	12 (5)
Urine	1 (0.4)
Syphilis test results	
Treponemal antibody positive[b]	41 (17)

[a]PCR: polymerase chain reaction.
[b]Indicates past or current infection.

Figure 2. Choices at enrollment of type of PrEP and doxyPEP. A majority of participants (n=144, 60%) preferred to use both daily PrEP and doxyPEP together. The next most common choices were either daily PrEP alone or on-demand PrEP with doxyPEP. The above proportions are to scale and are across all categories. Proportions do not add up to 100% due to rounding. doxyPEP: doxycycline postexposure prophylaxis; PrEP: pre-exposure prophylaxis.

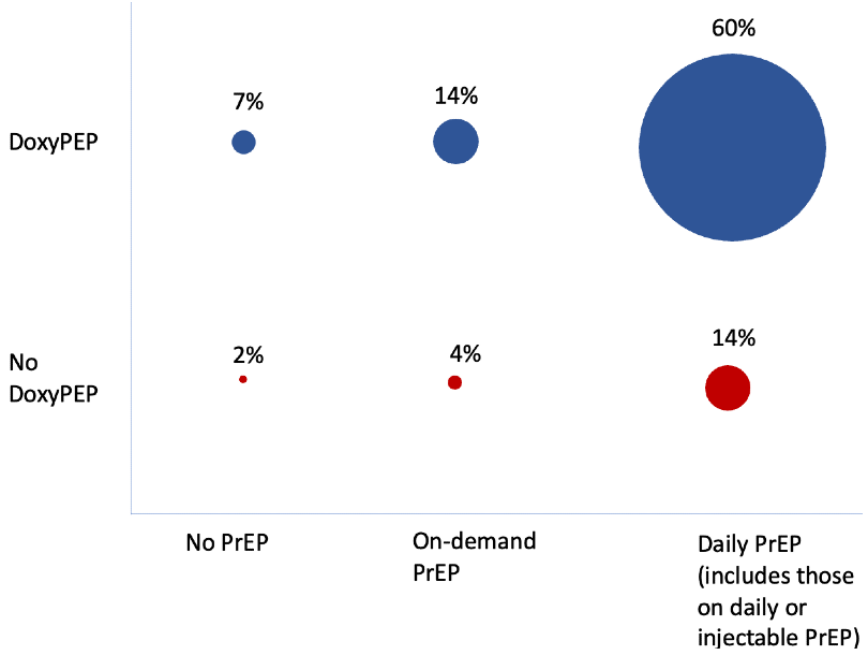

Discussion

Principal Findings

Given the ongoing HIV and STI syndemic, there is a great need to leverage available tools to help prevent these infections. We designed this study to investigate the preference for HIV and STI prevention strategies and support mechanisms among MSM in Atlanta, Georgia. After the enrollment of 240 men, we found that their initial choice of prevention was typically daily PrEP combined with doxyPEP. Of all prevention methods, combining PrEP with doxyPEP was more desirable than doxyPEP alone. To our knowledge, this is the first study to evaluate the preference for a combination of PrEP and doxyPEP. Participants will be followed longitudinally for 24 months to evaluate the persistence of these prevention interventions and changes in preferences over time. Strengths of this study include that we have recruited a racially and ethnically diverse cohort of participants with two-year longitudinal follow-up, and its novel design to evaluate how patient preferences change over time.

In several prior studies of preference for PrEP modality, individuals have prioritized PrEP effectiveness and low-cost options; as more long-acting PrEP options become available,

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recent studies have demonstrated that this is often desirable, but that preference for long-acting PrEP may differ between groups [21,33,34]. During enrollment in this study, long-acting injectable PrEP with cabotegravir was approved in the United States for HIV prevention. Although we incorporated this change into our study protocol, there were delays in clinics being able to offer this option to patients, leading to a few participants selecting this as their initial choice. Given this, although it appeared very few people chose injectable PrEP initially, this is likely not representative of true choices given the initial lack of availability. We anticipate that individuals may change their preferences for using PrEP and STI prevention methods based on factors like sexual practices and that motivational interviewing through this study can assist participants persist or reengage in using prevention methods.

Limitations

There are a few limitations to this study. Although initial results suggest a preference for daily oral PrEP combined with doxyPEP, injectable PrEP was not yet available at the time of enrollment for most individuals; this preference may be different in the era of injectable PrEP. Individuals were eligible for the study only if they lived in metropolitan Atlanta, so conclusions from this study may be different for populations in different geographic areas. Although the study was open to all individuals regardless of insurance status, nearly 70% of participants were insured, which may have affected the choice of STI prevention method. Given that this is an observational study, there is potential for unmeasured bias.

Conclusions

We plan to evaluate the preferences of combination PrEP and doxyPEP over the course of 2 years and describe trends including changes in use over time. We also plan to evaluate the impact of support tools like motivational imaging on the persistence of sexual health prevention methods. Bundling PrEP and doxyPEP in a way to be most desirable and acceptable to MSM, along with determining what support tools augment persistence, will be imperative to curb the HIV and STI syndemic, which is particularly pronounced in the southern United States. We plan to present the findings of our work at community advisory board meetings, community-oriented presentations, and through peer-reviewed publications, with the goal of ensuring patients are supported in choosing a combination of sexual health prevention methods that are best for their needs.

Acknowledgments

We are grateful to the Project PEACH participants for the time and data they have contributed to this study. We are thankful for our community partnerships that have been able to provide injectable PrEP for patients. Funding for PSS and CFK was provided by the National Institute of Mental Health (R01MH122341) and Emory CFAR (P30AI050409); funding for AA was provided by the National Institute of Allergy and Infectious Diseases (T32AI157855).

Data Availability

The data sets generated during or analyzed during this study will be available after publication of the primary results from the corresponding author on reasonable request with an executed data use agreement.

Authors' Contributions

AA wrote the original draft and contributed to data visualization. DSC, CAD, EVG, GBH, and RM-B assisted with data curation. OK assisted with formal data analysis and validation. CFK and PSS conceptualized the project, acquired funding, created the methodology, and supervised. AA, DSC, CAD, EVG, GBH, RM-B, OK, RV, CFK, and PSS assisted with the review and editing of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CDC: Centers for Disease Control and Prevention
doxyPEP: doxycycline postexposure prophylaxis
FTC: emtricitabine
IRB: institutional review board
MSM: men who have sex with men
PrEP: pre-exposure prophylaxis
SMaRT: Study Management and Retention Toolkit
STI: sexually transmitted infection
TDF: tenofovir disoproxil fumarate

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Protocol

Vital Sign and Biochemical Data Collection Using Non-contact Photoplethysmography and the Comestai Mobile Health App: Protocol for an Observational Study

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Abstract

Background: Early detection of vital sign changes is key to recognizing patient deterioration promptly, enabling timely interventions and potentially preventing adverse outcomes.

Objective: In this study, vital parameters (heart rate, respiratory rate, oxygen saturation, and blood pressure) will be measured using the Comestai app to confirm the accuracy of photoplethysmography methods compared to standard clinical practice devices, analyzing a large and diverse population. In addition, the app will facilitate big data collection to enhance the algorithm's performance in measuring hemoglobin, glycated hemoglobin, and total cholesterol.

Methods: A total of 3000 participants will be consecutively enrolled to achieve the objectives of this study. In all patients, personal data, medical condition, and treatment overview will be recorded. The "by face" method for remote photoplethysmography vital sign data collection involves recording participants' faces using the front camera of a mobile device (iOS or Android) for approximately 1.5 minutes. Simultaneously, vital signs will be continuously collected for about 1.5 minutes using the reference devices alongside data collected via the Comestai app; biochemical results will also be recorded. The accuracy of the app measurements compared to the reference devices and standard tests will be assessed for all parameters. CIs will be calculated using the bootstrap method. The proposed approach's effectiveness will be evaluated using various quality criteria, including the mean error, SD, mean absolute error, root mean square error, and mean absolute percentage error. The correlation between measurements obtained using the app and reference devices and standard tests will be evaluated using the Pearson correlation coefficient. Agreement between pairs of measurements (app vs reference devices and standard tests) will be represented using Bland-Altman plots. Sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and likelihood ratios will be calculated to determine the ability of the new app to accurately measure vital signs.

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Results: Data collection began in June 2024. As of March 25, 2025, we have recruited 1200 participants. The outcomes of the study are expected at the end of 2025. The analysis plan involves verifying and validating the parameters collected from mobile devices via the app, reference devices, and prescheduled blood tests, along with patient demographic data.

Conclusions: Our study will enhance and support the accuracy of data on vital sign detection through PPG, also introducing measurements of biochemical risk indicators. The evaluation of a large population will allow for continuous improvement in the performance and accuracy of artificial intelligence algorithms, reducing errors. Expanding research on mobile health solutions like Comestai can support preventive care by validating their effectiveness as screening tools and guiding future health care technology developments.

Trial Registration: ClinicalTrials.gov NCT06427564; https://clinicaltrials.gov/study/NCT06427564

(JMIR Res Protoc 2025;14:e65229) doi:10.2196/65229

KEYWORDS

biochemical data; mHealth; mobile app; non-contact photoplethysmography; detection; Comestai; data accuracy; monitoring; vital sign measurement; screening

Introduction

In recent decades, there has been an increasing focus on self-monitoring apps in primary care, which, with the advent of new technologies, have become more convenient and accessible for patients [1-3].

The use of mobile health (mHealth) apps is undeniably a valuable tool for enabling self-monitoring and health care interventions [4,5]. Specifically, the advancement of noncontact techniques for monitoring human vital signs holds significant potential to enhance patient care across various settings [6,7].

By enabling easier and more convenient monitoring, these techniques can mitigate serious health issues and improve patient outcomes, particularly benefiting individuals who cannot or prefer not to visit traditional health care settings. Vital signs are objective measures of the essential physiological functions of a living organism and they are the critical starting steps in any clinical evaluation.

Early detection of changes in vital signs typically correlates with faster identification of changes in the patient's health status and the escalation of care if necessary [8]. Alterations in vital signs preceding clinical deterioration are well documented, and the early identification of preventable outcomes is crucial for timely intervention [8]. Logically, the more frequently vital signs are measured, the quicker clinical deterioration can be detected.

The app named Comestai is a noninvasive and easy-to-use tool that enables the measurement of different vital parameters. The app allows users to simultaneously measure vital parameters such as heart rate (HR), respiratory rate (RR), oxygen saturation (SpO_2), blood pressure (BP), hemoglobin (Hb), and glycated hemoglobin A_{1c} (HbA_{1c}) using the photoplethysmographic method with the front camera of a mobile device.

Photoplethysmography is a practical method for noncontact vital sign measurement using a red-green-blue (RGB) camera that has been recently introduced [6,9]. Photoplethysmography uses a transducer that emits infrared light from an LED into the dermis. The adjacent photodetector measures the backscattered light, which is then represented as a line tracing. The intensity of the backscattered light changes with the volume of red blood cells in the dermal capillaries [9]. Photoplethysmography captures color change signals collected from various regions of the face, correlating the estimated magnitudes of red cell aggregation influenced by blood perfusion with the reflected light intensity in each region. By comparing variations in the averaged color signals, the camera-based signal-to-noise ratio estimates are enhanced.

As reported by [10,11], photoplethysmography has shown promising results in measuring vital signs and could be a valuable tool for the early detection and screening of cardiovascular, respiratory, and metabolic conditions. These interventions could be crucial in combating noncommunicable chronic diseases (NCDs) [12]. Furthermore, literature data on the use of photoplethysmography for vital sign detection usually refer to controlled clinical settings. Larger, more diverse populations need to be included to ensure accuracy across various demographics and health conditions [10,12,13].

In this study, vital parameters will be measured using the Comestai app to confirm the accuracy of photoplethysmography methods compared to standard clinical practice devices, analyzing a large and diverse population. In addition, the app will facilitate big data collection to enhance the algorithm's performance in measuring Hb, HbA_{1c}, and total cholesterol. The results will be useful to determine whether this user-friendly mobile app achieves adequate accuracy and can be adopted to enhance self-monitoring of health status and detect early health deterioration. A secondary result will be the collection of raw data that can be used to train the algorithm to detect other vitals.

Methods

Recruitment

The objectives of this study will be achieved by recruiting 3000 participants from the outpatient clinic of ASST-Fatebenefratelli-Sacco, Buzzi Children's Hospital, and IRCCS MultiMedica in Milan, Italy. All participants who meet the inclusion criteria and provide consent to participate will be enrolled consecutively. Recruitment will take place from June 2024 to September 2025.

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Eligibility Criteria

Participants eligible for inclusion in the study must meet the criteria in Textbox 1.

In addition to the above criteria, 70% of the target population should include adult participants meeting at least one of the conditions in Textbox 2. Family history of diabetes or hypertension will also be investigated.

The procedures and evaluations in Textbox 3 will be performed during screening to enroll eligible participants.

Characterizing aspects will be noted, such as scars, piercings, beards, glasses, or the use of facial products, sunscreen cream, or nail polish. Furthermore, current pregnancy will be reported.

The flowchart of the process is schematized in Figure 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Must demonstrate the ability to comprehend and provide written informed consent.
- Male or female participants aged ≥16 and ≤65 years.
- Must be willing and able to adhere to study procedures.

Exclusion criteria

Participants will be excluded if they meet any of the following conditions:

- Compromised circulation, injury, or physical abnormalities affecting fingers, hands, ears, forehead/skull, or other regions of interest essential for study testing.
- The presence of tattoos in the optical path hinders the assessment of necessary regions of interest.
- Severe allergies to standard adhesives, latex, or other materials used in medical sensors for measuring vital signs.
- Medical conditions that, in the investigator's opinion, prevent the conduct of study assessments.
- Considered unfit for participation by the investigator.

Textbox 2. Additional inclusion criteria.

1. Prediabetes or diabetes with glycated hemoglobin (HbA_{1c}) levels between 5.7% and 13%:
   - 30% of participants with HbA_{1c} 5.7%-6.4%.
   - 30% of participants with HbA_{1c} >6.4%.
2. Hypertension with systolic measurements exceeding 130 mm Hg:
   - 40% of participants with systolic blood pressure >130 mm Hg.
   - 20% of participants with systolic blood pressure >160 mm Hg.
3. Total cholesterol:
   - 40% of participants with levels >200 mg/dL and/or low-density lipoprotein cholesterol >130 mg/dL.
4. Atrial fibrillation (~1% prevalence).
5. Smokers, constituting approximately 20%-30% of the study cohort.

Textbox 3. Procedures and evaluations.

- Obtain participant consent and, if agreed, additional consent for a blood sample.
- Review eligibility: assess eligibility as described in the inclusion and exclusion criteria.
- Record the participants' medical and medication history: each medical problem encountered is classified into the sector of the body involved and for each of these, the starting date and the drugs used for treatment are indicated.
- Record participant demographics, including date of birth, age, smoking, and alcohol drinking habits.
- Record body characteristics including height, weight (BMI will be calculated as a person's weight in kilograms divided by the square of height in meters), and skin tone using the Fitzpatrick scale
- Interview the patient about his feelings in the last 2 weeks and if he has suffered from problems such as anxiety, nervousness, lack of control, loss of interest in doing things, or depression.

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Figure 1. Process flowchart.

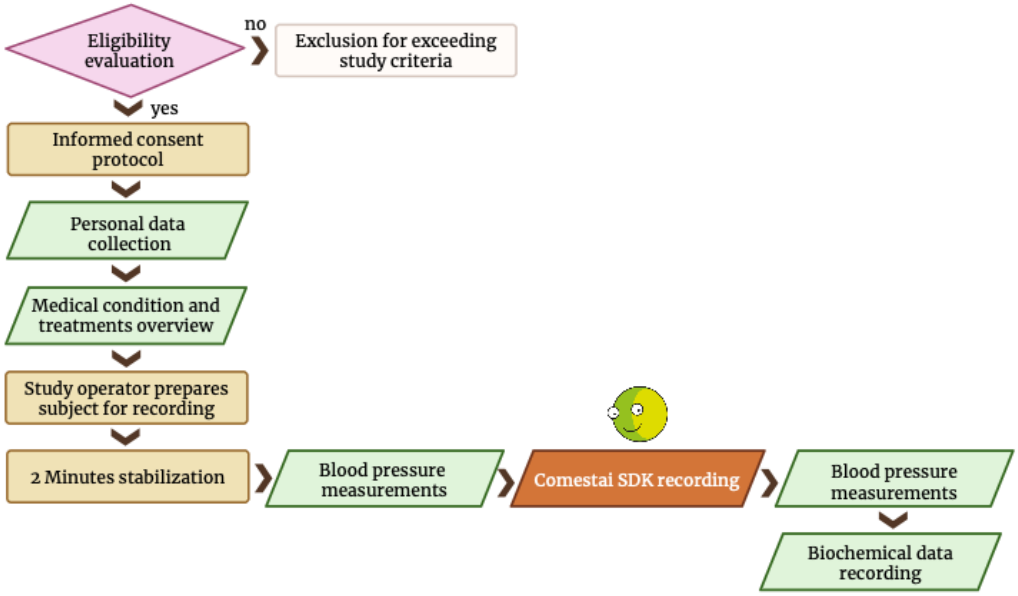

Technology

Comestai is a mobile app that leverages a combination of signal processing and artificial intelligence (AI) technologies, along with a proprietary mathematical backend server, to analyze the skin of the upper cheek region through a smartphone's front camera (iOS or Android).

The Comestai app captures video images using signal processing AI technologies and analyzes the data using photoplethysmography techniques (Figure 2) [9,14-16]. This approach provides real-time measurements of physiological parameters, including SpO_2, HR, PR, and RR, and biochemical parameters Hb, HbA_{1c}, and total cholesterol. Unlike other apps, the app uses a novel technology that extracts ambient light RGB signals from face videos in real time, eliminating the need for cloud servers or an internet connection.

Figure 2. Remote photoplethysmography from facial videos. RGB: red-green-blue.

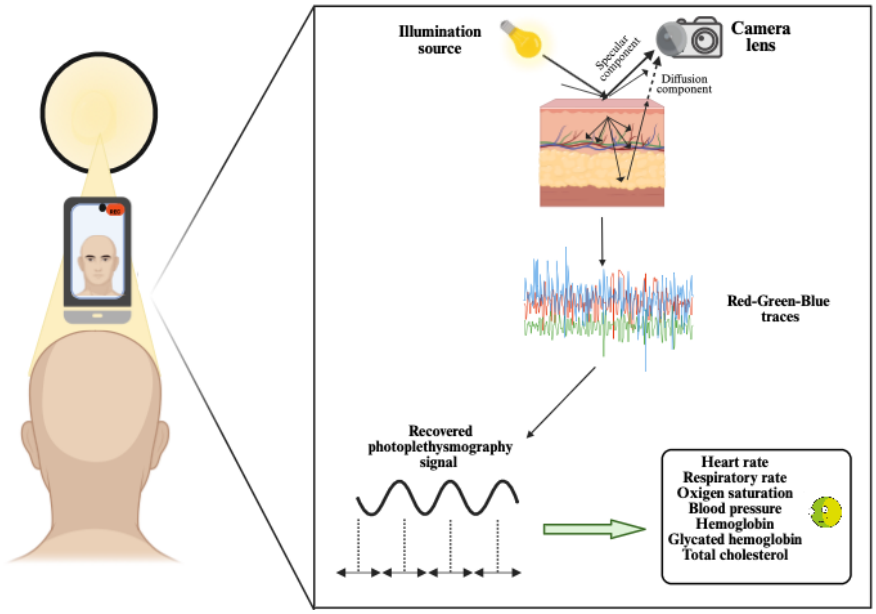

Equipment for Data Collection

For vital signs data collection using the Comestai app, the study staff will use the following mobile phones for remote photoplethysmography "by face" measurements:

1. Face—iPhone 13 Pro (10 bit) and Samsung Galaxy S21 Ultra
2. A total of 2 additional phones will be used remotely—Android phone (recorder remote for initiating measurements from a distance) and iPhone (Masimo app for collecting data from the Masimo finger sensor).
3. Other necessary equipment includes phone stands (2 per measurement room).

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In addition to the equipment for vital signs data collection using the Comestai app, reference devices will be used to measure the participant's vital signs for comparative purposes.

Vital Sign Data Collection Using the Comestai App and Reference Devices

The study personnel will gather vital signs data in a designated room equipped with the following amenities: a table, a chair with a headrest and arm support, a white wall for participants to sit against, stable Wi-Fi, power sockets, and adequate lighting (if the room lacks sufficient illumination, one Theralite lamp per room will be necessary).

Vital signs data will be gathered using the Comestai app through the "by face" method and with the reference devices detailed in Table 1.

Table 1. Reference devices for measuring vital signs.

Device	Saturation of oxygen	Pulse rate	Respiratory rate	Blood pressure
Withings BPM Connect				✓
Masimo mightySat Rx	✓	✓	✓	
Polar Verity Sense		✓		

Specifically, as reported in Figure 3, the measurement procedure flow will be as follows: first, The participant should sit for 2 minutes for stabilization with references connected. Second, baseline distance will be set at approximately 25 cm (closest as possible). Third, we will measure BP twice (if systolic ±10 and/or diastolic ±5, we will make a third measurement), waiting 1 minute in between the 2. Fourth, we will make 1 recording with each device. Fifth, we will measure BP twice (if systolic ±10 and/or diastolic ±5 make a third measurement).

Figure 3. Measurement procedure flow.

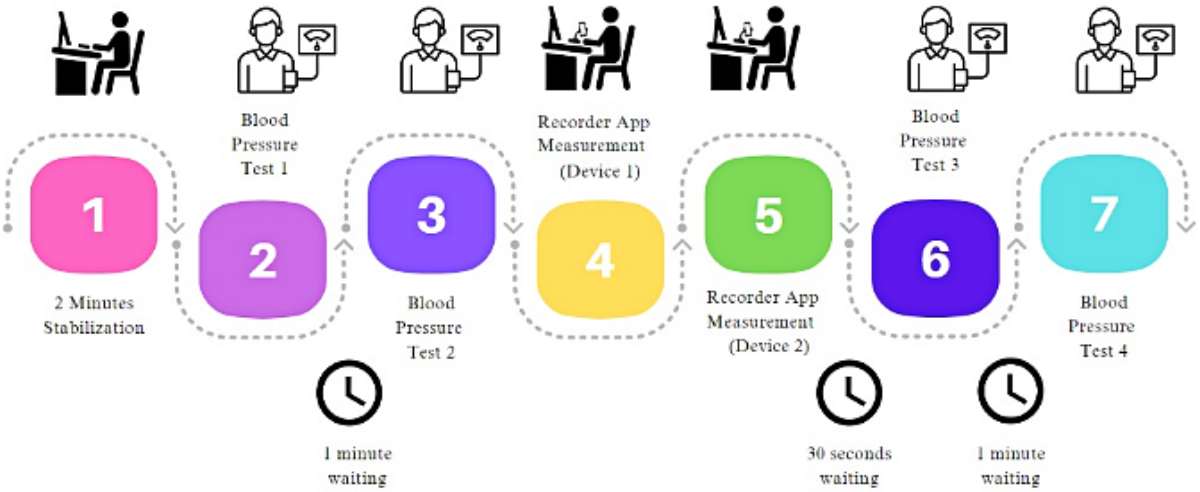

The "by face" method for remote photoplethysmography vital signs data collection involves recording participants' faces using the front camera of mobile devices (iOS and Android) for approximately 1.5 minutes.

During "by face" data collection, participants will be seated comfortably, facing a screen at approximately 25 cm, with their faces fully visible (without wearing masks, hats, or any facial accessories). Participants are required to maintain stable breathing and minimal movement and to gaze directly at the camera throughout the data collection process.

Simultaneously, vital signs data (SpO_2, RR, BP, and PR) will be continuously collected for about 1.5 minutes using the reference devices alongside data collected via the Comestai app.

BP measurements will be taken using the reference devices before and immediately after data collection with the Comestai app.

Data Collection and Management

Data from the investigational device will be collected by trained staff members. Vital signs data obtained using the app and reference data will be stored on a secured cloud. The app will be activated only when the cell phone is offline, ensuring that no information is stored in the Comestai cloud. Consequently, the company will not have access to any data collected during the tests.

In addition, the app will be deleted after use to prevent any data from being uploaded into the system. Data collected using the reference devices will be stored without any identifiable participant information and will only be identifiable using the participant identification number provided during screening.

The raw data of participants' vital signs will be locked, encrypted, and accessible only to the study center team. Raw data can be processed only after unlocking the files to calculate the final measured results.

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The coordinator center (Buzzi Children's Hospital) will be responsible for securely storing the data in a locked and secured location. The Endocrinology Unit of ASST-Fatebenefratelli-Sacco and Buzzi Children's Hospital will handle data entry and ensure data quality.

This study will be conducted in compliance with the Good Clinical Practice guidelines, including the archiving of essential documents.

No medical decisions will be made based on the data obtained from the Comestai app, reference devices, or blood sample results.

Clinical Data Cleaning and Validation

Clinical data for the study will be meticulously organized, easily accessible, and thoroughly cleaned both throughout and after the study concludes (post data lock). Activities in clinical data management encompass data collection and entry, tracking electronic case report form (eCRF) usage, database design, data validation, and database locking.

As previously outlined, the eCRF will serve as the primary tool for capturing clinical data. The data fields within the eCRF are clearly defined and maintain consistency throughout. The eCRF is designed to be succinct, intuitive, and user-friendly.

Database edit checks will be conducted to identify discrepancies in the data, which could stem from inconsistent entries, missing data points, range discrepancies, or deviations from the study protocol. Any incomplete discrepancies will be addressed by site investigators. Continuous quality control measures for data processing will be implemented at regular intervals throughout the study duration.

Criteria for Data Collection and Study Interruption

Temporal interruption of vital signs data collection using the app may occur in the following cases:

- Technical issues with the investigational and/or reference devices
- The study may be interrupted for the following reasons:
  - Breach of participant confidentiality.
  - Decision by the principal investigator or institutional ethics committee.
  - The investigators may also decide to terminate the study early if sufficient data has been collected for algorithm improvement.

Statistical Analysis

Numerical variables will be presented as minimum and maximum values, means, SDs, medians, and quartiles. Categorical variables will be presented as absolute and relative frequencies.

The accuracy of the app measurements compared to the reference devices and standard tests will be assessed for all parameters. CIs will be calculated using the bootstrap method. Participants with abnormal adverse events (defined as 3 SDs or more above the mean) and those with invalid reference device values will be excluded from the analysis.

In order to provide a more comprehensive view of the model's performance, the proposed approach's effectiveness was evaluated using various quality criteria, including the mean error, SD, mean absolute error, root mean square error, and mean absolute percentage error. The correlation between measurements obtained using the app and those from reference devices and standard tests will be evaluated using the Pearson correlation coefficient. The agreement between the 2 sets of measurements (app vs reference devices/standard tests) will be represented using Bland-Altman plots. Sensitivity, specificity, positive predictive value, negative predictive value, accuracy, and likelihood ratios will be calculated to determine the ability of the new app to accurately measure vital signs.

Sample Size Estimation

Considering the average values of pressure/saturation/HR among a general population with a sample of 3000 participants, there will be a power exceeding 95% for all evaluated parameters in a 2-sided test with a *P* value of .05 if the discrepancy between the 2 measurement methods is as reported in Table 2.

Table 2. Expected error level of the measurements.

Vital	Range	Unit of measurement	Error level
Pulse rate	50-180	BPM[a]	RMSE[b] ≤3
Respiratory rate	8-30	BrPM[c]	RMSE ≤3
Blood pressure systolic	80-180	mm Hg	MAE[d] ≤15
Blood pressure diastolic	50-120	mm Hg	MAE ≤10

[a]BPM: beats per minute.

[b]RMSE: root mean square error.

[c]BrPM: breaths per minute.

[d]MAE: mean absolute error.

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Known Potential Risks and Benefits of the Investigational Device

Potential Risks

No adverse device effects are expected from the Comestai app, and there are no contraindications for its use in the study population. However, unforeseeable risks related to the data collection process may arise.

One such risk is the potential breach of participant confidentiality due to improper data storage. In order to mitigate this, vital signs data will be securely stored on Comestai's cloud. Videos of faces obtained using the "by face" method will be anonymized, and recognized only by the participant identification number assigned during screening. The raw vital signs data will be locked, encrypted, and accessible solely by the study center team. Processing of this data will only occur once the files are unlocked.

Potential Benefits

Participants in this study will not receive direct benefits. However, the data gathered may aid in the advancement of the Comestai noninvasive software app for monitoring vital signs. Progress in this area has the potential to enhance patient care quality and reduce labor time and costs within the health care system.

Advances in this field may improve the quality of care provided to patients and save labor time and costs for the health care system.

Ethics Approval

The study was approved by the ethics committee (Comitato Etico Territoriale Lombardia 1, Milano, Italy, approval code CET 98-2024). The study will be conducted according to the Declaration of Helsinki guidelines, international guidelines, and current clinical trial laws.

All participants will give their written consent after being fully informed about the study. For individuals younger than 18 years, both legal guardians' written consent and assent by adolescents themselves will be collected.

Data will be collected and stored securely to maintain confidentiality, with only authorized personnel having access to identifiable information.

The study protocol was registered in ClinicalTrials.gov (NCT06427564). If modifications in the original protocol are required, additional amendments will be demanded by the Ethics Committee. In this scenario, the approved related information will be updated on ClinicalTrials.gov.

The authors followed the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines for study protocol reporting (Multimedia Appendix 1) to ensure greater scientific rigor. Written informed consent will be obtained from all participants, and data collection will be performed by a trained research team.

Consent will be requested for the use of the blood sample results (complete blood count, HbA_{1c}, lipid profile, glucose, and creatinine). Consenting to view the biochemical data is optional. A participant who chooses not to provide their biochemical results will still be eligible to participate and complete the recordings.

Results

Data collection began in June 2024. As of March 25, 2025, we have recruited 1200 participants. The outcomes of the study are expected at the end of 2025. The analysis plan involves verifying and validating the parameters collected from mobile devices via the app, reference devices, and prescheduled blood tests, along with patient demographic data.

Discussion

Principal Findings

The project aims to report whether this user-friendly mobile app supports a high level of accuracy in monitoring SpO_2, RR, BP, and PR, demonstrating the same reliability in detecting Hb, HbA_{1c}, and total cholesterol. Enhancing algorithm performance and achieving a high level of accuracy will be crucial in assessing whether the app can be adopted to improve self-monitoring of health status. This, in turn, could enhance the screening for early abnormalities in vital signs and biochemical parameters.

Strengths and Limitations

Today's health care industry embraces technological innovations to provide better personalized health care services to the public [17]. Mobile-based solutions and apps are one such revolutionary and trending innovation that facilitates enhanced patient care management and efficient diagnosis. They are increasingly reliant on wireless technologies as they evolve [17]. Applications of mHealth typically include the use of mobile devices in the collection of health and clinical data, the provision of health information to practitioners, researchers, and patients, the real-time monitoring of patients; vital signs, and the direct delivery of care (via mobile telemedicine).

In an mHealth context, the advancement of noncontact methods to monitor human vital signs holds substantial promise for enhancing patient care across various environments [6].

A recently proposed RGB camera–based method for noncontact vital sign measurement using photoplethysmography has been identified as an interesting tool for recording vital signs. Photoplethysmography is also used by the Comestai app to assess various vital functions, including SpO_2, RR, BP, and PR [10]. Initial research into photoplethysmography shows promising outcomes; however, scientific evidence regarding the accuracy and benefits of digital health apps that measure vital signs remains limited and somewhat controversial. Many photoplethysmography studies are still susceptible to errors [18-20], with the majority involving only small sample sizes.

In our protocol, we will recruit a large population (3000 participants) to ensure accuracy across various demographics and health conditions, including also pathological conditions. The use of a large population will also help reduce errors in the results, improving the reliability of the tool. Thorough analysis

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and classification of these signals are essential for the development of affordable and user-friendly PPG-based tools across a wide range of applications [10].

While there is an increasing number of articles and research on SpO_2, RR, BP, and PR monitoring using PPG, a limited number of available publications on advancements related to biochemical parameter estimation are reported [10]. Comestai offers the possibility to monitor Hb, $HbA_{1c,}$ and cholesterol concurrently with other parameters, thereby broadening its application possibilities in health care services.

Although the protocol included participants with diseases such as hypertension, prediabetes and diabetes, dyslipidemia, and atrial fibrillation to assess the tool's accuracy even in the presence of pathological values, conducting the study in a controlled setting can be considered a limitation. Its application in real-life scenarios may present challenges that were not accounted for.

Future Research

As suggested by the World Health Organization (WHO), it is important to disseminate medical procedures and health programs based on mHealth [21]. Mobile apps have become increasingly popular among professionals and individuals involved in the health care sector, with a variety of mHealth apps developed to improve health care facilities for all kinds of patients [22,23]

Specifically, mobile apps can play a vital role in screening, leading to the early detection of vital sign alterations, which is useful for alerting individuals and their caregivers to access medical care services and design and implement treatment plans. Screening is considered a crucial player in addressing chronic noncommunicable diseases (NCDs), which are responsible for nearly 70% of all deaths worldwide [12,24,25].

According to the WHO [12], NCDs cause 41 million deaths each year. This burden is expected to grow over the next decade, with NCD deaths projected to reach 52 million by 2030. Cardiovascular diseases are the leading cause of NCD deaths, accounting for 17.9 million fatalities annually. They are followed by chronic respiratory diseases (4.1 million) and diabetes (2.0 million, including kidney disease deaths linked to diabetes). Early detection and screening are vital strategies in combating NCDs. Disease screening detects diseases early, often before symptoms appear, through tests, examinations, or other rapid procedures [26]. This early detection enables effective prevention or treatment of identified diseases through timely medical intervention for those at risk [27].

Despite screening being recognized as the gateway to care, routine NCD screening at community and health facilities remains challenging due to limited capacity within health systems. A screening tool must be simple, valid, reliable, quick to administer, cost-effective, and user-friendly [23]. According to reports, photoplethysmography wearables have significant potential for estimating the risk of cardiovascular diseases [28], predicting suspected sleep apnea [29,30], and helping in the clinical diagnosis of hypertension [31] and diabetes. This potential can be harnessed through app solutions.

Recent reviews have assessed the role of apps in aiding self-management and transition among chronically ill young people, enhancing the lifestyles of chronic patients, and improving lifestyle in NCDs [32]. As reported by Moses et al [27], regardless of a country's economic status, there has been a rise in mobile cellular subscriptions per hundred people in developing nations, mobile app solutions may provide equitable health care solutions without barriers.

Conclusion

Our study will enhance and support the accuracy of data on vital sign detection through PPG, also introducing measurements of biochemical risk indicators. The evaluation of a large population will allow for continuous improvement in the performance and accuracy of AI algorithms, reducing errors. Expanding research opportunities to evaluate mHealth solutions as effective and dependable screening tools is useful for preventive strategies, reducing the burden of NCDs [27]. App solutions, such as Comestai, may present new opportunities and challenges related to technology use in the health care sector, offering insights and guiding future research directions.

Acknowledgments

The authors thank Comestai S.p.A. for providing the Comestai app and all materials used for the protocol free of charge for the entire duration of the project. This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors. All authors have approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Data Availability

The data that will support the findings of this study will be derived from participants' record data. All data generated or analyzed during this study will be included in the published article and its supplementary information files.

Authors' Contributions

GV, POA, and VC contributed to conceptualization and supervision. LL, EC, DB, SB, FL, CCFB, RFEP, and MX conducted the investigation. GV, POA, LL, EC, DB, SB, FL, MX, CCFB, RFEP, PF, SMDP, and VC developed the methodology. GV and VC handled project administration. LL, EC, DB, SB, FL, and VC were involved in writing (original draft). GV, POA, PF, SMDP, and VC were responsible for writing (review and editing).

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Conflicts of Interest

POA and SDP are co-founders of Comestai S.p.A

Multimedia Appendix 1
SPIRIT checklist.
[PDF File (Adobe PDF File), 71 KB - resprot_v14i1e65229_app1.pdf]

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Abbreviations

AI: artificial intelligence
BP: blood pressure
eCRF: electronic case report form
HbA_{1c}: glycated hemoglobin
HR: heart rate
mHealth: mobile health
NCD: noncommunicable disease
RGB: red-green-blue
RR: respiratory rate
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SpO_2: oxygen saturation
WHO: World Health Organization

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Protocol

Exposure to and Engagement With Digital Psychoeducational Content and Community Related to Maternal Mental Health by Perinatal Persons and Mothers: Protocol for a Web-Based Survey With Optional Follow-Up

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Abstract

Background: Leveraging digital platforms may be an effective strategy for connecting perinatal persons and mothers with evidence-based information and support related to maternal mental health and peers. Momwell is a mom-centered model of care that provides psychoeducational content through several digital platforms, including social media, a podcast, and a blog. The aims of this project were to describe how perinatal persons and mothers engage with Momwell's psychoeducational content and community; describe the perceived benefits of exposure to and engagement with content and community; examine associations between engagement with digital psychoeducational content and maternal mental health, parenting attitudes, and interparental relationships; and examine changes in mental health and parenting attitudes and concurrent engagement with Momwell's digital psychoeducational content and community over 2 to 3 months.

Objective: This paper aims to describe the design of a study of perinatal persons and mothers who are exposed to or engage with Momwell's psychoeducational content and community and describe sample characteristics.

Methods: Adults who engaged with Momwell on any of their digital platforms were recruited to complete a web-based survey in July 2023 to September 2023. Participants completed either a longer or shorter survey. Participants who provided permission to be recontacted were invited to complete a second survey 2 to 3 months later. The surveys included validated psychological measures, study-specific quantitative questions, and open-ended questions that assessed participant demographics, exposure to and engagement with Momwell's psychoeducational content and community, maternal mental health, parenting relationships, parenting self-efficacy, and additional psychosocial and health measures. We outline planned analyses to achieve the aims of the project.

Results: Data collection occurred from July 2023 to September 2023 (N=584). A subset of participants completed the optional second survey in October 2023 to December 2023 (N=246). Participants were >99% mothers (582/584, 99.7%); 45.5% (266/584) perinatal (59/584, 10.1% pregnant; 210/584, 36% post partum); and, on average, aged 32.4 (SD 3.9) years. In total, 59.1% (345/584) were from the United States, 35.6% (208/584) were from Canada, and 5.3% (31/584) were from other countries. The vast majority (552/584, 94.5%) followed Momwell on Instagram, 44.2% (258/584) listened to the Momwell podcast, and 41.1%

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(240/584) received their newsletter. Most participants had been exposed to Momwell's psychoeducational content for at least 6 months across the different platforms (range 16/36, 44% on TikTok to 480/552, 87% on Instagram).

Conclusions: Data from this study will provide insights into how pregnant persons and mothers use digital psychoeducational content and peer communities to support their mental health throughout the perinatal period and into the early years of motherhood. Leveraging digital platforms to disseminate evidence-based digital psychoeducational content related to maternal mental health and connect peers has the potential to change how we care for perinatal persons and mothers.

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KEYWORDS

social media; podcasts; blogs; perinatal mental health; maternal mental health; digital health; engagement

Introduction

Background

Depression and anxiety are common during pregnancy and the postpartum period, yet many struggling with their mental health do not seek mental health care [1,2]. Mothers often feel pressure to achieve socially constructed ideals of motherhood and struggle to balance life roles and responsibilities, which together can negatively impact their mental health [2,3]. Prevention, screening, and treatment of perinatal mental health problems are critical given the long-lasting impact that perinatal mental health can have on mothers, children, and families. Several meta-analyses and systematic reviews have shown that psychosocial, psychological, and psychoeducational interventions can improve mood and reduce the risk of depression among perinatal persons [4-6] and parents of young children [7]. A recent meta-analysis found that peer support interventions are efficacious for preventing or managing perinatal and postpartum depression [8]. Specifically, information and support from peers via phone can prevent postpartum depression in high-risk women [9], and online asynchronous support groups can also reduce depressive symptoms during the perinatal period [10].

Leveraging digital platforms such as social media and podcasts may be an effective strategy for overcoming barriers to seeking mental health care and connecting perinatal persons and mothers with evidence-based information and peer support related to maternal mental health [11]. Most women of childbearing age and mothers use social media, including those in Canada [12] and the United States [13-15], and many turn to their online networks for support and information about diverse health and parenting topics [16,17]. In addition, 67% of adults in the United States aged 18 to 39 years and 58% of those aged 30 to 49 years listen to podcasts [18]. Connecting with other perinatal persons or mothers online can decrease feelings of isolation, provide a safe space to discuss mental health without feeling judged or stigmatized, and increase parenting confidence [19,20]. Given the ever-expanding opportunities for psychoeducation and peer support available via social media and other digital platforms such as podcasts, content disseminated via these digital platforms has the potential to reach millions for widespread impact on perinatal and maternal mental health. However, little is known about how perinatal persons and mothers consume and engage with psychoeducational content disseminated through digital platforms and how this psychoeducational content and peer interactions impact perinatal and maternal mental health. There is an ongoing need to understand how people access and use digital mental health resources focused on perinatal and parenting populations. We conducted a web-based survey of adults exposed to or who engage with Momwell via social media or other digital platforms to address this gap.

Objectives

The overarching aims of this project are to (1) describe how perinatal persons and mothers engage with Momwell's psychoeducational content and community; (2) describe the perceived benefits of exposure to and engagement with Momwell's psychoeducational content and community; (3) examine associations between engagement with digital psychoeducational content and maternal mental health, parenting attitudes, and interparental relationships; and (4) examine changes in mental health and parenting attitudes and concurrent engagement with Momwell's digital psychoeducational content and community over 2 to 3 months. In this paper, we describe the design of the study and the characteristics of the sample. As most women of childbearing age and mothers in the United States and Canada use social media [12-15] and listen to podcasts [18], there is great potential for wide dissemination of relevant and impactful evidenced-based psychoeducational content that can support maternal mental health.

Methods

Overview

We recruited a convenience sample of adults exposed to or who engage with Momwell via social media or other digital platforms to complete a web-based survey. We invited participants who provided permission for us to recontact them to complete a second survey 2 to 3 months later.

Ethical Considerations

The University of Connecticut Institutional Review Board approved this study (protocol X23-0344). Individuals were recruited to participate in 1 of 2 cohorts (cohort 1 and cohort 2); participants in cohort 2 completed shorter surveys at both time points. Before completing the survey, participants were shown a cohort-specific information sheet and provided with an opportunity to download a PDF of the information sheet. Participants consented to the research study electronically before completing their survey. We stored study data on

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password-protected research drives. Only appropriate research staff had access to study data on Qualtrics (Qualtrics LLC), REDCap (Research Electronic Data Capture; Vanderbilt University), or research drives. Cohort 1 participants who completed at least 80% of the survey received a gift card (US $15 or CAD $20 [US $14.47-$15.35 over course of study]). Cohort 2 participants who completed at least 80% of the survey were entered into a gift card lottery. One in every 30 participants was randomly selected to receive a gift card (US $60 or CAD $80 [US $57.88-$61.40 over course of study]). Cohort 1 participants who completed at least 80% of the optional second survey received a gift card (US $15 or CAD $20 [US $14.47-$15.35 over course of study]), and cohort 2 participants who completed at least 80% of their survey were entered into a gift card lottery in which 1 in 30 participants was randomly selected to receive a gift card (US $60 or CAD $80 [US $57.88-$61.40 over course of study]).

Recruitment and Eligibility Screening

From July 2023 to September 2023, we recruited adults who followed Momwell on any of their social media platforms, listened to their podcast, read their blog, or received their email newsletter. Founded and led by Erica Djossa, a registered psychotherapist based in Ontario, Canada, Momwell offers a mom-centered model of care that seeks to educate, empower, and support mothers. Momwell offers individual telehealth psychotherapy to clients in Canada and the United States and self-paced virtual workshops and courses led by Ms Djossa and her team of licensed psychotherapists. In addition to these for-fee services, Momwell provides evidence-based psychoeducational content about motherhood, parenting, and maternal mental health to the public without cost through their social media feeds (Instagram, Facebook, and TikTok), weekly podcast, and blog with posts corresponding to the podcast episodes. A weekly email newsletter alerts readers to new podcast episodes and blog posts and provides other updates, including new workshop and course offerings. In this study, we focused on exposure to and engagement with the Momwell psychoeducational content and community via their social media feeds, podcast, blog, and email newsletter (ie, resources freely available to the public).

The Momwell team posted recruitment messages that included a link to an eligibility screener via Qualtrics. Recruitment messages were posted as public social media posts and Instagram stories. On Instagram, interested individuals could comment “STUDY” to be sent a link to the eligibility screener via direct message. An advertisement was included in a Momwell podcast in mid-July 2023. In addition, a message about the study was included in Momwell’s weekly email newsletter. These recruitment messages included a link to the eligibility screener; this eligibility screener could be considered an open survey in that any individual with the link could complete the screener. Inclusion criteria for both cohorts included age of ≥18 years, following or engagement with Momwell on at least one of their digital platforms (eg, Instagram, Facebook, Facebook group, TikTok, podcast, blog, or email newsletters), comfort participating in the study in English, and ability and willingness to provide informed consent. To participate in cohort 1, individuals additionally had to be (1) a perinatal person (eg, currently pregnant or within 12 months post partum) or mother (eg, identifying as the mother of at least one child aged <18 years who lived with them at least part time) and (2) currently living in Canada or the United States. As part of the eligibility screener, respondents indicated whether they had a preference for completing the longer or shorter survey (or had no preference); participants who expressed preference for the shorter survey were all invited to complete it.

As some recruitment messages were posted publicly, we recognized the potential for attracting the attention of bots or individuals trying to participate under false pretenses to receive the gift card incentive [21-24]. As recommended [23,24], we used a multifaceted strategy to ensure that enrolled participants were truly eligible, including Qualtrics bot and fraud detection features, checking for duplicate respondents (eg, email and IP address), and checking the consistency of the information (eg, specific recruitment link clicked on vs where the respondent reported they had heard about the study). Individuals whose responses to the eligibility screener suggested that they were a bot or fraudulent were not invited to complete the survey.

Data Collection

Eligible individuals were emailed personal invitations to complete a web-based survey via Qualtrics. Individuals who did not respond to the invitation were sent a reminder 1 day later. Nonresponders were sent 2 additional invitations a few weeks later. Participants who partially completed the survey were sent a reminder email with a new survey link. The survey included both quantitative and open-ended questions. The survey for cohort 1 participants was designed to take 30 to 45 minutes to complete (median 52, IQR 36-95 minutes among those who completed at least 80% of the survey). The survey for cohort 2 participants was a shortened version of the cohort 1 survey comprising a subset of questions and scales. It was designed to take 15 to 20 minutes to complete (median 29, IQR 21-45 minutes among those who completed at least 80% of the survey).

We reviewed participants’ responses and survey metadata to detect likely fraudulent respondents who were not detected at eligibility screening (eg, discrepancies between metadata and survey responses and discrepancies between data provided in the eligibility screener and survey). As recommended [23,24], we conducted additional data quality checks at this phase of data collection; we reviewed the surveys for patterns of responses indicating inattentiveness or fraudulent responses (eg, completing the survey in less than half the median time for that cohort; straight-lined psychological measures with reversed items; failure of an attention-check item; or missing, extremely brief, or nonsensical responses to open-ended questions). We contacted participants with multiple flags via phone or email to clarify their responses or ask them to provide responses to the open-ended survey questions. Individuals whom we could not reach or who provided conflicting responses were excluded. Our final analytic sample includes participants who completed at least 80% of their survey who were not excluded during the data quality review.

The final question in the survey asked participants for permission to contact them about future research studies, specifically, a second survey approximately 2 months later.

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Participants who responded affirmatively were invited to complete an optional second survey 2 to 3 months later (October 2023-December 2023). Study procedures (eg, survey invitations, reminders, and consent process) were the same as procedures for the main survey. Survey response review was also similar to that of the main survey; we additionally compared consistency of responses between the 2 surveys (eg, pregnancy or postpartum status of participants who were pregnant when they completed the main survey). Similar to the main survey, the second surveys were designed to take 30 to 45 minutes (cohort 1; median duration 34, IQR 24-62 minutes among those who completed at least 80% of the survey) or 15 to 20 minutes (cohort 2; median duration 12, IQR 9-22 minutes among those who completed at least 80% of the survey).

To ensure that participants had opportunities to be exposed to and engage with content related to perinatal mental health, the Momwell content development team created and published 3 psychoeducational posts specifically related to perinatal mental health per week for 16 weeks beginning at the start of recruitment for the main survey.

Measures

Overview

The surveys included a rich set of validated psychological measures, study-specific quantitative questions, and open-ended questions that assessed exposure to and engagement with Momwell's psychoeducational content and community, maternal mental health, parenting relationships, parenting self-efficacy, and other participant characteristics and behaviors. The measures are described in the following sections and in Table 1. The study team tested the surveys, including survey logic before recruitment and data collection. The number of questions asked of each participant varied depending on their responses to previous questions (eg, only participants who followed Momwell on Instagram were asked questions about their exposure to and engagement with Momwell content on Instagram). Participants were not able to go back to previous survey pages once submitted (ie, the back button on the survey was disabled).

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Table 1. Measures assessed by cohort and time point.

Measure	Main survey		Optional second survey	
	Cohort 1	Cohort 2	Cohort 1	Cohort 2
Exposure to and engagement with the Momwell psychoeducational content and community				
Exposure to and engagement with the Momwell content and community	✓	✓	✓	✓
Perceived impact of Momwell content	✓	✓	✓	✓
Suggestions to increase engagement and desired topics for future posts or podcast episodes	✓	✓		
Mental health				
PHQ-8[a] [25,26]	✓	✓	✓	✓
GAD-7[b] [27]	✓	✓	✓	✓
PSS-10[c] [28]	✓	✓	✓	✓
Parenting support and self-efficacy				
PPSS[d] [29]	✓		✓	
BCRS[e] [30]	✓		✓	
PSOC[f] [31]	✓		✓	
Additional psychological measures				
TIPI[g] [32]	✓	✓		
GHSQ[h] [33,34]	✓		✓	
MHLS[i] [35]	✓		✓	
Brief COPE[j] [36]	✓		✓	
INCOM[k] [37-39]	✓		✓	
SCS-SF[l] [40,41]	✓		✓	
ULS-8[m] [42,43]	✓		✓	
Additional participant characteristics				
General social media use and digital health literacy	✓	✓		
Demographics and household composition	✓	✓	✓	✓
Health and health behaviors	✓	✓	✓	✓
Health care use	✓	✓	✓	✓

[a]PHQ-8: 8-item Patient Health Questionnaire.
[b]GAD-7: 7-item Generalized Anxiety Disorder scale.
[c]PSS-10: 10-item Perceived Stress Scale.
[d]PPSS: Postpartum Partner Support Scale.
[e]BCRS: Brief Coparenting Relationship Scale.
[f]PSOC: Parenting Sense of Competence Scale.
[g]TIPI: Ten-Item Personality Inventory.
[h]GHSQ: General Help-Seeking Questionnaire.
[i]MHLS: Mental Health Literacy Scale.
[j]COPE: Coping Orientation to Problems Experienced.
[k]INCOM: Iowa-Netherlands Comparison Orientation Measure.
[l]SCS-SF: Self-Compassion Scale–Short Form.
[m]ULS-8: University of California, Los Angeles, Loneliness Scale.

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Exposure to and Engagement With Momwell's Psychoeducational Content and Community

As part of the eligibility screener, main survey, and second survey, participants were asked a variety of questions about their exposure to and engagement with Momwell's psychoeducational content and community to capture different dimensions of exposure and engagement, including duration, frequency, and depth of active engagement (Table 1).

In the eligibility screener, participants were asked whether they listened to the Momwell podcast; followed Momwell on Instagram, Facebook, or TikTok; were members of the Momwell Community Facebook group; followed the Momwell blog; or received the Momwell email newsletters. From this, we categorized participants as social media followers (ie, followed Momwell on Instagram, Facebook, or TikTok or were members of the Momwell Facebook group) or not. We also categorized whether participants listened to the Momwell podcast or read the Momwell blog as both these platforms provide a deeper dive into psychoeducational topics and blog posts are published that correspond to each podcast episode.

Those reporting exposure to content on each platform were asked how recently they had started consuming content from that platform ("within the past 7 days," "at least 7 days ago but less than 3 months ago," "at least 3 months ago but less than 6 months ago," "at least 6 months ago but less than 12 months ago," and "at least 12 months ago"). As Momwell rebranded themselves as "Momwell" from "Happy as a Mother" in January 2023, we prompted participants to include involvement with "Happy as a Mother." To capture duration of exposure to Momwell content, we calculated the longest duration of exposure on any platform (ie, how long ago they had joined via their first digital platform). We also calculated how recently they had joined a new platform.

For each platform, participants reported how often they engaged in specific ways applicable to that platform within the previous 4 weeks (or since they had started following Momwell on that platform if more recently than 4 weeks before) on a 4-item Likert scale ("every day," "3+ times per week but not every day," "1-2 times," and "not at all"). Activities included passive exposure to content (eg, reading posts, watching videos, listening to podcast, and reading the blog) and more active and visible forms of engagement (eg, liking, reacting, and replying to posts).

Participants who completed the second survey who did not report exposure to Momwell content on a particular platform at eligibility screening were asked about exposure to Momwell content on that platform during the second survey. Existing and new users of each platform were then asked the same questions about their exposure to and engagement with the Momwell content and community since they completed the main survey (eg, "since you completed the first survey in August 2023").

In the main survey, participants were asked several questions related to their perceived impact of Momwell content on their lives. First, they were asked the following: "What Momwell social media post, blog post, or podcast has had the biggest impact on your life? How did it impact you?" In the second survey, they were asked similar open-ended questions about the perceived impact of Momwell content but specific to each platform. In both surveys, participants were also asked whether they had taken several actions as a result of their exposure to Momwell content (eg, "talked with a doctor or health care professional about something you heard in the Momwell podcast or saw on a social media post"). In the main survey, participants reported the extent to which they agreed with several statements about changes since joining the Momwell community (eg, "I feel more aware of the signs and symptoms of mental health conditions or I feel more confident in my approach to parenting"). In the main survey, participants were also asked what would help them engage more with the Momwell community and what topics or content they would like to see more of from Momwell.

While our primary interest was in exposure to and engagement with the free psychoeducational content and peer community provided by Momwell through their social media feeds, podcast, and blog, we also asked participants about paid services available from Momwell. Specifically, we asked participants who had joined the Momwell community >7 days before whether they had ever purchased a guided journal or other self-paced tool from Momwell, enrolled in a Momwell workshop or course, or enrolled in therapy (in person or remote) with a Momwell therapist. From the responses, we calculated the proportion who had purchased any paid services.

Mental Health

Our main measures of maternal mental health are depression, anxiety, and perceived stress. Participants in both cohorts were asked to complete these measures in the main and second surveys (Table 1). Depressive symptoms were assessed using the 8-item Patient Health Questionnaire [25,26]. This scale asks participants to indicate on a 4-point scale how often they have been bothered by various depressive symptoms in the past 2 weeks. Response options include "Not at all," "Several days," "More than half the days," and "Nearly every day." Responses are summed to obtain a total score ranging from 0 to 24, with a greater score indicating greater reported depressive symptoms. Internal consistency was acceptable, with Cronbach α=0.85 in the main survey and Cronbach α=0.86 in the second survey compared to the original measure (Cronbach α=0.86-0.89 across samples) [25].

Symptoms of anxiety were assessed using the 7-item Generalized Anxiety Disorder scale [27]. Participants are asked to report how often they have been bothered by symptoms of anxiety over the past 2 weeks. Response options include "Not at all," "Several days," "More than half the days," and "Nearly every day." Responses are summed to obtain a total score ranging from 0 to 21, with a greater score indicating higher symptoms of anxiety. Internal consistency was acceptable, with Cronbach α=0.91 in the main survey and Cronbach α=0.90 in the second survey compared to the original measure (Cronbach α=0.92) [27]. Participants also reported whether they had ever been diagnosed with depression or anxiety during pregnancy, the postpartum period, or a nonperinatal period of life. Participants reporting a history of depression (or anxiety) were asked whether they currently had depression (or anxiety).

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Participants who scored ≥10 on the 8-item Patient Health Questionnaire or 7-item Generalized Anxiety Disorder or who endorsed feeling as if they were currently experiencing depression or anxiety were flagged and shown a message noting that they might be experiencing some feelings of depression (or anxiety depending on which was flagged); encouraging them to connect with a mental health care professional for assessment, support, and therapy if appropriate; and noting that their primary care provider, obstetrician, or gynecologist may also be a good resource for support or to help them connect with a mental health care professional. Participants were then offered the option of downloading a PDF mental health resource guide developed by the research team (options for participants from the United States, Canada, and other countries). Participants were asked whether they wanted a copy of the guide sent to them via email, and research staff emailed a copy of the appropriate mental health guide to participants who answered affirmatively.

The 10-item Perceived Stress Scale [28] was used to assess perceived stress during the past 2 weeks. Participants selected how often they experienced the feelings and thoughts presented in the items via response options ranging from "Never" to "Very often." Responses are summed to obtain a total score with a range from 0 to 40, with a higher score indicating higher perceived stress. Internal consistency was acceptable, with Cronbach α=0.88 in the main survey and Cronbach α=0.88 in the second survey compared to the original measure (Cronbach α=0.78) [28].

Parenting Support and Self-Efficacy

Participants in cohort 1 completed a set of measures related to parenting support and self-efficacy (Table 1). We first asked participants with children whether they had a parenting partner (ie, a partner who assisted the participant with parenting, with a note that, for many people, their parenting partner is their spouse or the child's other parent).

Participants who reported having a parenting partner completed a modified version of the Postpartum Partner Support Scale [29], a validated 20-item measure that assesses support provided by their husband or partner. To better represent a variety of partnerships and family structures, we modified the Postpartum Partner Support Scale to replace "him" (ie, husband) with "my partner." We also modified questions to refer to "our children" rather than "our baby." Responses are summed to obtain a total score with a range from 20 to 80, with higher scores indicating higher parenting support. Internal consistency was acceptable, with Cronbach α=0.95 in the main survey and Cronbach α=0.96 in the second survey compared to the original measure (Cronbach α=0.96) [29].

Participants who reported a parenting partner completed a modified version of the 14-item Brief Coparenting Relationship Scale [30] to assess interparental relationships. We modified the phrasing of the items and measure instructions to refer to "child(ren)" versus "child" to better reflect families of various sizes. Responses are averaged, with scores ranging from 0 to 6 and higher scores indicating a more positive relationship with the parenting partner. Internal consistency was acceptable, with Cronbach α=0.90 in the main survey and Cronbach α=0.91 in the second survey compared to the original measure (Cronbach α=0.81-0.89 across different samples) [30].

Perceived parenting competence was assessed using a modified version of the 16-item Parenting Sense of Competence Scale (PSOC) [31]. We modified the language of the PSOC to replace the words "mother" and "father" in items with "parent," as well as to replace "child" with "children." The PSOC is composed of 2 subscales, efficacy and satisfaction, which combined produce an overall score representing parenting self-esteem. The overall PSOC score is reflective of 16 items, with a range from 16 to 96 and higher scores indicating greater sense of overall parenting self-esteem. The satisfaction subscale comprises 9 items, with scores ranging from 9 to 54. Higher scores indicate higher levels of parenting satisfaction. The efficacy subscale is assessed using 7 items, with scores ranging from 7 to 42 and higher scores indicating more parenting efficacy. Internal consistency was acceptable for the overall score and both subscales, with Cronbach α=0.80 for the overall score, Cronbach α=0.77 for the satisfaction subscale, and Cronbach α=0.76 for the efficacy subscale in the main survey and Cronbach α=0.83 for the overall score, Cronbach α=0.77 for the satisfaction subscale, and Cronbach α=0.83 for the efficacy subscale in the second survey compared to the original measure (Cronbach α=0.79 for the overall score, Cronbach α=0.76 for the satisfaction subscale, and Cronbach α=0.76 for the efficacy subscale) [31].

Additional Psychological Measures

We included several additional psychological measures to provide data for secondary analyses (Table 1). As part of the main survey, participants in both cohorts completed the Ten-Item Personality Inventory [32], which assesses the personality traits extraversion, agreeableness, conscientiousness, emotional stability, and openness to experience. Participants in cohort 1 completed several additional measures as part of the main and second surveys (Table 1). Participants completed a modified General Help-Seeking Questionnaire [33,34], which asked individuals to rate how likely they would be to seek help from various sources (eg, partner or spouse and mental health professional) if they were experiencing sadness, low mood, irritability, and other depressive symptoms. Knowledge of mental health conditions and mental health literacy were assessed using a subset of questions from the Mental Health Literacy Scale [35]. Given the interests of this study (perinatal mental health vs general mental health or illness), we included items assessing knowledge of generalized anxiety disorder and major depressive disorder, the connection between sleep and mood, information seeking related to perinatal depression, and general attitudes toward people with perinatal depression (stigma).

Participants completed the Iowa-Netherlands Comparison Orientation Measure [37-39], which is designed to assess frequency of social comparisons. We modified the measure stem to ask about comparisons with "other mothers" rather than "other people" to assess the tendency to make social comparisons to other mothers. Participants completed the short form version of the Self-Compassion Scale [40,41], a validated questionnaire measuring self-compassion via 6 subscales.

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Feelings of loneliness were ascertained using the short-form Revised University of California at Los Angeles Loneliness Scale [42,43]. Finally, participants completed the Brief Coping Orientation to Problems Experienced [36], which assesses 14 coping strategies: self-distraction, active coping, denial, substance use, use of emotional support, use of instrumental support, behavioral disengagement, venting, positive reframing, planning, humor, acceptance, religion, and self-blame.

General Social Media Use and Digital Health Literacy

Participants reported their use of social media generally, including whether they had accounts on different platforms (ie, Instagram, Facebook, or TikTok); how often they engaged with various platforms in different ways (eg, posting a video); and whether they followed social media accounts related to motherhood or parenting, mental health, or another health topic. Participants were also asked whether they subscribed to or regularly listened to podcasts (other than Momwell). We modified 2 items from the eHealth Literacy Scale [44] to assess perceived skill and confidence using social media to access health information: “I have the skills I need to evaluate health information I see on social media” and “I feel confident in using health information from social media to make health decisions for me or my family.” Response options ranged from “Strongly Disagree (1)” to “Strongly Agree (5).” As a brief screener of health literacy, participants were asked how confident they were filling out medical forms by themselves [45].

Demographic Characteristics, Health Behaviors, and Health Care Use

Participants reported demographic characteristics, including country and state or province of residence, urbanicity of their city or town of residence, gender, sex assigned at birth, and sexual orientation [46]. Race and ethnicity were assessed via an open-ended question (ie, “How would you describe your racial and ethnic background?”). Participants living in the United States and Canada were also asked to indicate their racial and ethnic background by choosing all that applied from a standardized list corresponding to each country. Participants from the United States were also asked whether they considered themselves Hispanic or Latino (yes or no). Participants also reported whether they self-identified as someone who was a visible minority [47]. Participants also reported educational level, employment status, family structure, the number of children living in the home at least part time, and the ages of those children. In the second survey, participants were asked about current pregnancy (including gestational age); whether they had given birth to a baby in the past 12 months; and, if yes, how many months before they had given birth. Financial strain was assessed by asking participants to identify how difficult it had been for them, in the past 30 days, to pay for usual household expenses (eg, food, rent, car payments, or medical expenses) [48]. Participants reported their current employment status by selecting one of the following options: “working full-time,” “working part-time,” “working but currently on parental leave,” “stay-at-home parent or homemaker,” “unemployed,” “student,” and “other.” Given the small number of participants who endorsed each of these categories, we collapsed “unemployed,” “student,” and “other” into 1 category. Participants completed the Hunger Vital Sign [49], a validated 2-item food insecurity screening tool based on the US Household Food Security Survey Module. Participants reported whether, in the past 12 months, they had ever worried about food running out due to financial hardship and whether there was ever not enough money to get more food when food did run out. Participants who answered either of the 2 items with “often true” or “sometimes true” (vs “never”) were considered to be at risk of experiencing food insecurity [49]. Participants who completed the second survey reported employment status, food security, financial strain, and changes to the household structure occurring since completing the main survey. To put any changes in mental health in context, as part of the second survey, we asked participants to report whether they had experienced various life events since the first survey (eg, spouse or partner dying, getting divorced or separated, becoming pregnant, giving birth, or adopting a child). Life events were adapted from the Holmes-Rahe Life Stress Inventory [50]; we added “gave birth or adopted a child.” Participants who reported one or more potentially stressful life events were asked to rate how stressful that time was for them on a Likert scale from “not at all stressful” to “extremely stressful.”

Participants were asked questions about their health, health behaviors, and health care use. Participants self-reported their height and weight and whether they had any physical or mental health conditions requiring frequent medical visits (and, if so, what conditions). Participants answered questions regarding diet, alcohol consumption, tobacco use, physical activity, and sleep. To assess diet quality, participants completed the 8-item Starting The Conversation dietary screener [51]. Participants reported how many days per week they consumed at least one alcoholic beverage, the number of alcoholic drinks per day they consumed, and the frequency of binge drinking. Participants also reported ever use and current use of cigarettes and e-cigarettes. Participants reported frequency and duration of moderate or greater-intensity physical activity in the past 4 weeks. To assess quality of sleep in the previous 4 weeks, participants completed a subset of questions from the Pittsburgh Sleep Quality Index [52] related to sleep duration and self-rated sleep quality. Participants first reported via free response how many hours they slept at night. Participants were then asked to rate their quality of sleep, with possible answer options of “very bad,” “fairly bad,” “fairly good,” and “very good.” Mothers were also asked how often in the past 4 weeks a child had disrupted their sleep. Participants reported any physical or mental health care services accessed via in-person visits, telehealth visits, phone call, email, or online patient portal in the past 6 months. In the second survey, participants were asked about new medical diagnoses, health care use, and sleep.

Statistical Analysis

The eligibility screener and surveys were administered in Qualtrics. We used REDCap for participant tracking [53]. Analyses were conducted in SAS (version 9.4; SAS Institute). We described recruitment and enrollment. As recommended when reporting the results of a web-based survey [54], we calculated the participation rate as the number consented divided by the number invited to participate and the completion rate as the number who completed the survey (ie, up to the last page)

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divided by the number consented for both the main and optional second surveys. We described the characteristics of the participants in our final sample overall and by study cohort. We compared participant characteristics and exposure to Momwell's content on different platforms in relation to whether participants completed the second survey using chi-square tests for categorical variables, Wilcoxon rank sum tests for poor physical and mental health days, and *t* tests (2-tailed) for other continuous variables.

Planned Analyses

The aims of this project are to (1) describe how perinatal persons and mothers engage with psychoeducational content and community; (2) describe the perceived benefits of exposure to and engagement with psychoeducational content and community; (3) examine associations between engagement with digital psychoeducational content and maternal mental health, parenting attitudes, and interparental relationships; and (4) examine changes in mental health and parenting attitudes and concurrent engagement with digital psychoeducational content and community over 2 to 3 months. We have several planned analyses corresponding to these aims; we will report the results in future publications.

First, we will describe how perinatal persons and mothers engage with psychoeducational content and community. We will describe exposure to Momwell's psychoeducational content and engagement with the Momwell community over the past 4 weeks using frequencies and percentages. Engagement metrics include duration of exposure (<6 months, ≥6 but <12 months, and at least 12 months); frequency of exposure to content on any digital platform (not at all in the past 4 weeks, 1-2 times, ≥3 times but not daily, and daily); and how often participants listened to the podcast, read the blog, read posts, watched videos on social media, liked or reacted to social media content, and replied to social media content (not at all in the past 4 weeks, 1-2 times, ≥3 times but not daily, and daily).

Second, we will describe the perceived benefits of exposure to and engagement with the content and community. We will report participants' degree of agreement with statements about changes in their lives since joining the Momwell community using frequencies and percentages. As participants who joined the Momwell community in the past 7 days were not asked these questions, the analyses will not include these participants. We will conduct sensitivity analyses of the item about perceived impact on partner or coparent communication including only participants who reported that their children lived with 2 parents in the same household and mothers in cohort 1 who reported that they had a parenting partner. We will conduct content analyses [55] of responses to open-ended questions on the main and second survey about what Momwell social media post, blog post, or podcast episode had the biggest impact on participants' lives.

Third, we will examine associations between engagement with digital psychoeducational content and maternal mental health, parenting attitudes, and interparental relationships. We will summarize measures of depressive symptoms, anxiety symptoms, parenting efficacy and satisfaction, and interpersonal relations using means and SDs overall and in relation to engagement metrics. We will compare these outcomes in relation to engagement metrics using crude and adjusted linear regression models. Potential confounders will include sociodemographic, household, and health-related characteristics. Analyses of parenting attitudes and interparental relationships will be limited to participants in cohort 1 as only these participants completed these measures.

Fourth, we will examine changes in mental health and parenting attitudes and concurrent engagement with digital psychoeducational content and community over 2 to 3 months. We will calculate changes in mental health and parenting outcomes from the main survey to the second survey among participants who completed both surveys. We will compare changes in these outcomes in relation to engagement metrics reported on the second survey using crude and adjusted linear regression models. Potential confounders will include sociodemographic, household, and health-related characteristics. Analyses of changes in parenting attitudes and interparental relationships will be limited to participants in cohort 1.

Results

Recruitment and Data Collection

Participant flow during recruitment and data collection is shown in Figure 1. Recruitment, eligibility screening, and completion of the main survey took place from July 2023 to September 2023. Of the 6706 eligibility screeners, 690 (10.3%) were incomplete, 131 (2%) were screened as ineligible, 313 (4.7%) were eligible but did not provide their email address, and 4175 (62.3%) were excluded during quality review (n=707, 16.9% with duplicate email addresses; n=1746, 41.8% with nonsense email addresses; and n=2052, 49.1% with conflicting information regarding digital platform engagement or recruitment source); we invited 1397 (20.8%) to participate. The participation rate (ie, the number consented divided by the number invited to participate) for the main survey was 56.4% (788/1397), and the completion rate (ie, the number who completed the survey up to the last page divided by the number consented) was 81.5% (642/788). Our final analytic sample comprised 584 perinatal persons and mothers who completed the main survey (ie, at least 80% of the questions) and were not removed during quality review (n=298, 51% in cohort 1 and n=286, 49% in cohort 2; Figure 1). Of these 584 participants, 532 (91.1%) were invited to complete an optional second survey 2 to 3 months later, from October 2023 to December 2023. For the optional second survey, the participation rate was 54.7% (291/532), and the completion rate was 83.8% (244/291). Our final analytic sample for the optional second survey was 246 participants who completed it (ie, at least 80% of the questions) and were not removed during quality review (n=149, 60.6% in cohort 1 and n=97, 39.4% in cohort 2; Figure 1).

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Figure 1. Participant flow during recruitment and data collection.

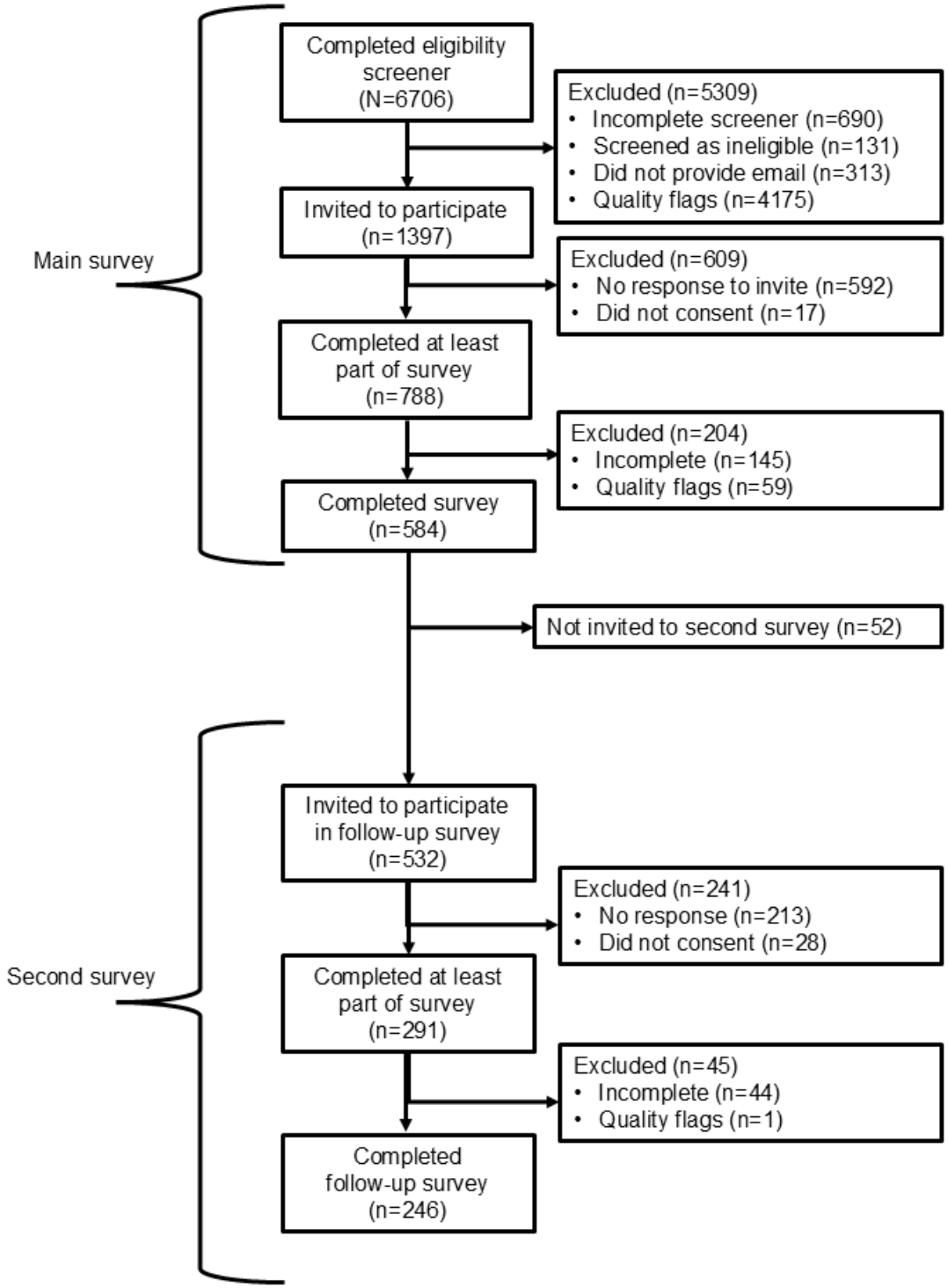

Sample Characteristics

In total, 0.3% (1/286) of the participants in cohort 2 indicated that they would prefer not to report their gender; all other participants identified as female. The characteristics of the sample, overall and by study cohort, are shown in Table 2. All but 2 participants (582/584, 99.7%) were mothers (the remaining 2/584, 0.3% were pregnant but did not identify as mothers). Almost all participants in cohort 1 (291/296, 98.3%) reported that they had a parenting partner; 97.6% (283/290) of parenting partners were the participants' spouses or committed partners who lived in same household. A total of 10.8% (31/286) of cohort 2 resided in countries other than the United States and Canada, including the United Kingdom (6/286, 2.1%), Australia (5/286, 1.7%), Japan (2/286, 0.7%), and 18 other countries (1/286, 0.3% each).

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Table 2. Characteristics of the sample overall and by study cohort (N=584).

	Overall (n=584)	Cohort 1 (n=298)	Cohort 2 (n=286)
Identified as mothers, n (%)	582 (99.7)	296 (99.3)	286 (100)
Children aged 0-5 y	563 (96.4)	285 (95.6)	278 (97.2)
Children aged 6-12 y	99 (17)	57 (19.1)	42 (14.7)
Children aged 13-17 y	22 (3.8)	10 (3.4)	12 (4.2)
Perinatal status, n (%)	266 (45.5)	150 (50.3)	116 (40.6)
Currently pregnant	59 (10.1)	32 (10.7)	27 (9.4)
Currently post partum	210 (36)	120 (40.3)	90 (31.5)
Age (y), mean (SD)	34.2 (3.9)	34.4 (3.9)	34.1 (3.8)
Country of residence, n (%)			
Canada	208 (35.6)	116 (38.9)	92 (32.2)
United States	345 (59.1)	182 (61.1)	163 (57)
Another country	31 (5.3)	0 (0)	31 (10.8)
Identified as a visible minority, n (%)	77 (13.2)[a]	39 (13.1)	38 (13.3)[b]
Urbanicity of residence, n (%)			
Large city	150 (25.8)[c]	83 (27.9)[d]	67 (23.5)[b]
Suburb near a large city	212 (36.4)[c]	104 (35)[d]	108 (37.9)[b]
Small city or town	157 (27)[c]	74 (24.9)[d]	83 (29.1)[b]
Rural area	63 (10.8)[c]	36 (12.1)[d]	27 (9.5)[b]
Educational level, n (%)			
Lower than bachelor's degree	76 (13)	38 (12.8)	38 (13.3)
Bachelor's (4-year university degree)	255 (43.7)	122 (40.9)	133 (46.5)
Graduate degree	253 (43.3)	138 (46.3)	115 (40.2)
Employment status, n (%)			
Working full time	284 (48.6)	138 (46.3)	146 (51.1)
Working part time	91 (15.6)	50 (16.8)	41 (14.3)
Working but currently on leave	74 (12.7)	40 (13.4)	34 (11.9)
Stay-at-home mother	105 (18)	54 (18.1)	51 (17.8)
Other employment status	30 (5.1)	16 (5.4)	14 (4.9)
Difficulty paying for basic expenses, n (%)			
Not at all difficult	333 (57.1)[a]	163 (54.9)[d]	170 (59.4)
A little difficult	170 (29.2)[a]	86 (29)[d]	84 (29.4)
Somewhat or very difficult	80 (13.7)[a]	48 (16.2)[d]	32 (11.2)
Food insecurity, n (%)	63 (10.8)	34 (11.4)	29 (10.1)
Impaired health literacy, n (%)	95 (16.3)[c]	48 (16.1)	47 (16.5)[e]
Had physical or mental health conditions that required regular medical visits, n (%)	151 (25.9)[c]	85 (28.5)	66 (23.2)[e]
Days in the previous 4 weeks when physical health was not good, median (IQR)	0 (0-3)	0 (0-3)	0 (0-3)
Days in the previous 4 weeks when mental health was not good, median (IQR)	5 (2-10)	4 (2-8)	5 (2-10)
Social media and podcast use, n (%)			
Instagram	569 (97.4)	287 (96.3)	282 (98.6)
Facebook	516 (88.4)	266 (89.3)	250 (87.4)

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	Overall (n=584)	Cohort 1 (n=298)	Cohort 2 (n=286)
TikTok	139 (24)[f]	64 (21.5)[d]	75 (26.6)[g]
Podcasts	312 (53.7)[h]	162 (54.7)[i]	150 (52.6)[b]

[a]n=583.
[b]n=285.
[c]n=582.
[d]n=297.
[e]n=284.
[f]n=579.
[g]n=282.
[h]n=581.
[i]n=296.

Exposure to Momwell's Psychoeducational Content and Community

Most of the sample (552/584, 94.5%) reported that they followed Momwell on Instagram (Table 3). Approximately 4 in 10 participants listened to the Momwell podcast (258/584, 44.2%) and received the email newsletter (240/584, 41.1%). Smaller proportions followed Momwell on Facebook (89/584, 15.2%) or TikTok (36/584, 6.2%), were a part of the Momwell Facebook group (41/584, 7%), or read the blog (156/584, 26.7%; Table 3). The largest subgroup—a third (193/584, 33%)—followed Momwell on Instagram and did not connect on any other digital platform. Other common combinations of platforms included Instagram and podcast (66/584, 11.3%); Instagram, podcast, and email newsletters (57/584, 9.8%); Instagram and email newsletters (41/584, 7%); and Instagram, podcast, blog, and email newsletters (36/584, 6.2%).

Table 3. Exposure to the Momwell psychoeducational content and community by digital platform and survey cohort (N=584).

	Overall, n (%)	Cohort 1 (n=298), n (%)	Cohort 2 (n=286), n (%)
Instagram	552 (94.5)	275 (92.3)	277 (96.9)
Facebook	89 (15.2)	46 (15.4)	43 (15)
Facebook group	41 (7)	19 (6.4)	22 (7.7)
TikTok	36 (6.2)	18 (6)	18 (6.3)
Podcast	258 (44.2)	129 (43.3)	129 (45.1)
Blog	156 (26.7)	76 (25.5)	80 (28)
Email newsletter	240 (41.1)	127 (42.6)	113 (39.5)

Most had been exposed to the Momwell psychoeducational content and community on each digital platform for at least 6 months: 87% (480/552) on Instagram, 81% (72/89) on Facebook, 66% (27/41) on the Facebook group, 44% (16/36) on TikTok, 59.7% (154/258) via the podcast, 65.4% (102/156) on the blog, and 84.2% (202/240) via the email newsletters. Most of the sample (433/584, 74.1%) had been following Momwell on at least one digital platform for at least 12 months, and 34.9% (204/584) had started following Momwell on a new digital platform within the previous 6 months. Nearly all participants (568/584, 97.3%) followed Momwell on at least one social media platform, and 54.5% (318/584) listened to the Momwell podcast or read their blog. A total of 30% (175/584) were exposed to Momwell content on any platform daily, and 52.4% (306/584) were exposed to content ≥3 times per week but not daily. A quarter of participants (140/563, 24.9% [n=4 missing] who had joined the Momwell community >7 days before) had obtained paid services from Momwell—6% (34/564) had purchased a guided journal or other self-paced tool from Momwell, 16.3% (92/566) had enrolled in a Momwell workshop or course, and 10.4% (59/567) had enrolled in therapy with a Momwell therapist.

Characteristics of Participants Who Completed the Optional Second Survey

Participant characteristics and exposure to Momwell content on different digital platforms were largely similar among participants who completed just the main survey compared to those who also completed the second survey (P>.05 in all cases). Participants who completed the second survey were more likely to have chronic health conditions (75/246, 30.5% vs 76/336, 22.6%; P=.03) and more likely to read the Momwell blog (82/246, 33.3% vs 74/338, 21.9%; P=.002) than participants who did not complete the second survey. Country of residence also differed by completion of the optional second survey (102/246, 41.5% from Canada; 136/246, 55.3% from the United States; and 8/246, 3.3% from other countries among those who completed the second survey vs 106/338, 31.4% from Canada; 209/338, 61.8% from the United States; and 23/338, 6.8% from other countries among those who did not complete the second survey; P=.01).

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Discussion

Principal Findings

The overall goal of this study is to understand how mothers and the perinatal population consume and engage with digital psychoeducational content and the peer community and how it impacts their mental health and parenting. In this paper, we describe the study design, including recruitment procedures, characteristics of the sample, and participants' exposure to maternal mental health psychoeducational content on different digital platforms. We also outline planned analyses corresponding to the overall aims of the project.

While we recruited a cohort of nearly 600 pregnant persons and mothers, we encountered challenges during recruitment, particularly related to fraudulent and low-quality responses. Bots and fraudulent respondents are becoming more and more of a problem when recruiting participants online, particularly when using public recruitment links and recruiting for studies that provide participants with a monetary incentive for completing a survey [21-24]. As some of our recruitment messages were posted publicly, we recognized the potential for attracting the attention of bots or individuals trying to participate under false pretenses—and, indeed, we experienced significant interest in our study from suspicious actors (human or bots), with several hundred respondents with duplicate email addresses; >1800 with nonsense email addresses; and >2000 with conflicting information in terms of location, digital platform engagement, or recruitment source. Bot and fraud detection features of survey administration platforms such as Qualtrics and REDCap provide a starting point, but researchers must go further to verify the eligibility and quality of respondents. As recommended [23,24], we used a multifaceted, multistage strategy. We separated eligibility screening from the survey and only sent individual survey invitations to individuals who passed our reviews. We compared information collected through multiple methods (eg, recruitment source reported by participants vs recorded by Qualtrics) and the consistency of information provided by participants (eg, ages of children). Our strategy for identifying low-quality or inattentive respondents included an attention-check question, reviewing responses to open-ended survey questions, and checking for straight-lining when completing psychological measures [23,24]. We also phrased eligibility questions to reduce the chance that respondents could guess the "right" (ie, eligible) response. We followed up with participants with inconsistent information on the survey via phone or email to clarify information. While it is possible that we excluded some eligible individuals, our quality control procedures were designed to prevent bots or fraudulent participants from taking part in our study. Researchers who are recruiting samples online using public survey links are encouraged to develop and implement similar procedures for preventing and detecting bot and fraudulent respondents. For additional discussion and specific recommendations, researchers are encouraged to read the work by Walker et al [23] and Wang et al [24], especially their table 1 and tables 2 and 4, respectively.

Another recruitment challenge was related to which members of the Momwell community volunteered to participate in this study. We had originally intended to invite only new followers or subscribers (ie, those who had started following Momwell in the previous 7 days) to complete the optional second survey to explore engagement and concurrent changes in mental health and parenting self-efficacy soon after becoming exposed to Momwell's psychoeducational content and community. However, only 42 eligible respondents reported joining Momwell within the previous 7 days (of whom n=15, 36% completed the main survey)—perhaps a result of algorithmic biases regarding which followers were more likely to see our recruitment messages [56,57] and which followers were interested in sharing their experiences with us. Therefore, we pivoted our design to invite any participants to complete the second survey.

In total, 13.2% (77/584) of our sample identified as a visible minority compared to 31% of women aged 25 to 64 years in Canada [58]; 48% of birthing persons in the United States identify as a race or ethnicity other than non-Hispanic White [59]. In our sample, food insecurity was reported by 10.8% (63/584), which is similar to food insecurity among households with children and married couples in the United States (11%) [60] but lower than the proportion among women aged 25 to 44 years in Canada (20%) [61]. Our sample was more likely to have a bachelor's degree or higher education (508/584, 87%) than birthing persons in the United States (36%) [59] and women aged 25 to 34 years born in Canada (40%) [62]. However, in the United States, use of Instagram and Facebook is higher among women with higher levels of education (34% of those with at most a high school education, 58% of those with some college education or an associate's degree, and 52% of those with a bachelor's degree or higher education for Instagram and 71%, 84%, and 82%, respectively, for Facebook) [14]. Similarly, listening to podcasts is more common among adults in the United States with higher levels of education (59% of those with at most a high school education, 64% of those with some college education or an associate's degree, and 79% of those with a bachelor's degree or higher education among adults aged 18-29 years and 44%, 58%, and 70%, respectively, among adults aged 30-49 years) [18]. Whether these differences are a function of the demographics of the Momwell community or due to which Momwell followers volunteered to participate in this study is unknown. Future studies could estimate this by including engagement with digital platforms generally and with specific communities (such as Momwell) in population-based studies of perinatal persons and mothers. Future studies could also use specific strategies to recruit a more diverse sample.

Limitations

This study has additional limitations worth noting. First, our sample is composed of perinatal persons and mothers who volunteered to participate in this study and, thus, likely does not represent all individuals who consume Momwell content. Specifically, more engaged followers (eg, those who regularly comment on or like Instagram posts) are more likely to have seen our recruitment messages in their social media feeds [56,57], and those who regularly read the weekly email newsletters or listen to the podcast are more likely to have seen

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our recruitment messages disseminated through these communication channels. Followers or community members who feel more connected with the community or perceive higher benefit may have been more likely to volunteer to share their experiences, and thus, perceived impacts may overrepresent community members who perceive a greater positive impact on their lives and well-being. Another limitation is the proportion of participants who chose to complete the optional second survey (149/298, 50% of those who completed the longer survey and 97/286, 33.9% of those who completed the shorter survey). The lower response rate for participants who completed the shorter survey may be in part due to the incentive structure as these participants were entered into a lottery with 1 in 30 selected to receive a gift card. However, demographic characteristics and exposure to Momwell content on different digital platforms were overall quite similar among participants who completed just the main survey compared to those who also completed the second survey.

Conclusions

In this paper, we describe the design and methods of this study and the characteristics of pregnant persons and mothers exposed to or who engage with Momwell's psychoeducational content and community. In future papers, we will describe how perinatal persons and mothers engage with Momwell's psychoeducational content and community; perinatal persons' and mothers' perceived impacts of this content and peer interactions; associations between exposure to and engagement with digital psychoeducational content and maternal mental health, parenting attitudes, and interparental relationships; and concurrent engagement over 2 to 3 months and changes in mental health and parenting attitudes. Beyond these planned analyses, we hope that these data can provide additional insights into the health and well-being of pregnant persons and mothers. We have shared a deidentified public use dataset with a subset of the data collected (variables omitted to protect participant confidentiality) [63], and researchers interested in collaborating with our research team are encouraged to email the first author.

Maternal mental health is critically important, and understanding how individuals, clinicians, and health systems can leverage digital platforms to disseminate evidence-based digital psychoeducational content and connect perinatal persons and mothers with mental health care professionals and peers has the potential to change how we care for individuals during these life phases. As most women of childbearing age and mothers in the United States and Canada use social media [12-15] and listen to podcasts [18], there is great potential for wide dissemination of relevant and impactful evidence-based psychoeducational content that can support maternal mental health. We have designed this study to provide insights into how perinatal persons and mothers leverage digital psychoeducational content and communities to support their mental health during pregnancy, the postpartum period, and the early years of motherhood.

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Data Availability

A deidentified dataset with a subset of the data collected (variables omitted to protect participant confidentiality) is available in the Open Inter-university Consortium for Political and Social Research repository [63]. Researchers interested in collaborating with our research team are encouraged to email the first author.

Authors' Contributions

MEW contributed to conceptualization, data curation, formal analysis, funding acquisition, investigation, methodology, results interpretation, project administration, software, resources, writing (original draft, review, and editing), and supervision. KEM-S contributed to investigation, methodology, data curation, results interpretation, writing (original draft, review, and editing). CMF contributed to investigation, methodology, data curation, results interpretation, and writing (original draft, review, and editing). SB contributed to data curation, visualization, results interpretation, and writing (original draft, review, and editing). AP contributed to data curation, results interpretation, and writing (review and editing). OS contributed to data curation, results interpretation, and writing (review and editing). SAG contributed to data curation, results interpretation, and writing (review and editing). CLD contributed to conceptualization, methodology, results interpretation, and writing (review and editing). .

Conflicts of Interest

None declared.

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Abbreviations

PSOC: Parenting Sense of Competence Scale
REDCap: Research Electronic Data Capture

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Protocol

Assessing a Digital Tool to Screen and Educate Survivors of Domestic Violence on Affordable Housing Programs in New York City: Protocol for a Mixed Methods Feasibility Study

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Abstract

Background: Extant research has long documented the association between domestic violence and homelessness. Yet, there appear to be few interventions to address the housing needs of survivors of domestic violence, and none on a digital platform.

Objective: Our primary objective is to determine the feasibility of a full-scale intervention trial of a web-based tool that screens and educates survivors of domestic violence on affordable housing programs in New York City. Our secondary objectives are to assess the perceived usability and acceptability of the tool.

Methods: The study will take place in a community-based domestic violence center in New York City. Treatment will consist of study participants not using (SC) or using (SC+) the tool, in or outside of private meetings with a case manager to discuss housing and other benefits. The frequency of the meetings will vary depending on the participant's needs. The study will measure changes in housing knowledge, housing self-efficacy, and staff trust through two electronic surveys, administered at times 0 and 2 weeks. Following a historical cohort control group design, we will sequentially recruit participants, starting with SC and followed by SC+. After data collection for SC+ ends, we will invite staff from the partner site to individual, web-based interviews to share their experiences of and recommendations for implementing the tool.

Results: Recruitment for the SC arm commenced in March 2022 and was completed in April 2023. After a year, 23 participants completed the study: 75 were screened, 44 were deemed eligible, 35 enrolled, and in the end, 23 participants completed baseline and follow-up surveys. Given the length of time it took to recruit for SC and the limited time overall that we had for the study, the study team decided to follow an expedited recruitment timeline for SC+. Recruitment for SC+ commenced in January 2024 and is anticipated to end by May 2024. Recruitment for the staff interviews will take place in June 2024. We expect to complete the study and be ready to compile the results by the end of June 2024.

Conclusions: The protocol describes a feasibility study that can inform future research on housing or digital tools for a similar study population. Data from the study will also be used to inform revisions to the tool.

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KEYWORDS

domestic violence; intimate partner violence; homelessness; housing; feasibility study; digital intervention; digital solution

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Introduction

Background

Survivors of domestic violence (survivors) in the United States are at heightened risk of homelessness [1,2]. Homelessness refers to a state in which an individual does not have a fixed place to stay or is living in a place unsuitable for human habitation [3]. In New York City, more than 2 in 5, or 41%, of families entering the City's homeless shelter system, run by the Department of Homeless Services (DHS), have attributed their homelessness to domestic violence [4]. Short-term emergency shelters, specifically for domestic violence in New York City, offer survivors much critical aid; however, one study found that one-quarter of survivors exiting from emergency shelters moved directly into DHS shelters [5]. Presently, over 86,000 individuals are served by DHS shelters on a given day [6], up from prepandemic estimates that hovered closer to 60,000 [4]. Against a backdrop of about 600 domestic violence–related calls to the New York Police Department a day [7], the numbers, alone, underscore the significance of homelessness and domestic violence in New York City. The research team of this feasibility study thus purposively selected New York City as the study setting given its disproportionate need.

Remarkably, considering the sheer magnitude of domestic violence and its bidirectional relationship with homelessness in the United States and New York City, few housing solutions have been designed to specifically address the housing needs of survivors of domestic violence. The few solutions that follow, however, show promise.

Temporary Housing

Two common forms of temporary housing are emergency shelters and transitional housing. Emergency shelters are a type of homeless shelter allocated for use by survivors of domestic violence. In New York City, emergency shelters provide survivors with a temporary place of stay, for 90 days initially, with a possible extension of up to 180 days [8]. Transitional housing in New York City, likewise, offers survivors a temporary place of stay, for up to 2 years in facility-based or scattered-site programs. In facility-based programs, survivors reside in the same building; whereas in scattered-site programs, survivors receive rental subsidies to live in apartment sites scattered throughout the community or in their current homes if the abuser has vacated the home [9].

While little research to the best of our knowledge exists on temporary housing's housing outcomes, prior research in the United States does suggest that emergency shelters and transitional housing lead to positive safety outcomes for survivors [10,11]. According to Messing et al [10], female survivors who left their perpetrators for emergency shelter experienced significantly less abuse during the follow-up period of 8 months than female survivors who did not seek emergency shelter. Findings from another study indicated that a longer shelter stay led to a lower degree of repeat abuse in the initial 6 months following a survivor's exit from the shelter [11]. Although these studies did not take place in New York City, we can infer from their findings that emergency shelters and transitional housing can contribute to promising safety outcomes for survivors in New York City.

Permanent Supportive Housing

Permanent supportive housing (PSH) programs offer individuals and families a government-subsidized place of stay, for which tenants typically contribute one-third of their income to rent [12], along with a broad range of support services to help tenants with their clinical and nonclinical needs [13]. In the United States, PSH's benefits have included reductions in emergency and hospital use and substance use, and fewer encounters with the criminal justice system [14]. While PSH programs are available to and accessed by survivors in New York City, many have not been designed specifically for the needs of survivors. Many PSH programs, for instance, do not include safety planning, a critical strategy for survivors leaving their abusers [9].

Housing First (HF) [15] is a type of PSH program that prioritizes rapid housing placement. The HF model hypothesizes that helping someone obtain stable housing first will facilitate their subsequent ability to address other concerns; hence, HF programs seek to connect tenants with permanent, independent housing first, prior to addressing other issues [15,16]. Based on HF's successes with adults with mental illness and substance abuse issues, agencies across the United States are now exploring adaptations of HF for domestic violence. One such successful adaptation has been the Washington State Domestic Violence Housing First Program (DVHF) [16]. Designed with survivors' needs in mind, the DVHF includes safety planning, as well as various support services, including home security and lock changes, counseling, career training, and legal services. Initial results have been promising. In the inaugural cohort of four agencies, the DVHF saw 89% of survivors retain, that is, maintain or obtain permanent housing by the end of the 18-month study period, as compared with one-third at the start of the study [17]; similarly, in the second cohort of nine agencies, the DVHF saw 88% of survivors retain housing by the end of the 36-month study period, as compared with about half at the start of the study [18]. In addition, DVHF in both studies led to increases in survivor-reported independence and positive shifts in needs and priorities [17,18].

Presently, there are no HF programs in New York City tailored for survivors of domestic violence. However, the promising performance of DVHF programs in states like Washington offers encouragement for their adoption in places like New York City.

Rapid Rehousing and Flexible Funding

Besides DVHF, rapid rehousing and flexible funding are two other promising innovative models. Rapid rehousing refers to an approach consisting of an intensive housing placement effort including housing identification, a time-limited subsidy, and additional education and support to retain housing. Flexible funding refers to an approach in which domestic violence agencies may grant survivors discretionary funding for basic needs, like changing locks, moving, storage, or security deposits.

While research on these newer approaches has been sparse, a few published studies have supported their potential in helping survivors access and retain housing in the United States. In one

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study, 94% of survivors in an urban city who were about to lose housing at the start of the study reported positive housing outcomes just 6 months after receiving flexible funding [19]. A rapid rehousing pilot, moreover, found that, in comparison with participants given standard shelter services, rapid rehousing participants saw a reduction in the length of shelter stay and recidivism back to shelter [20]. While we are not aware of any peer-reviewed program evaluations in New York City, rapid rehousing and flexible funding both saw upticks in use among New York City–based domestic violence agencies during the COVID-19 pandemic [21,22].

Gaps to Be Addressed

Currently, when a survivor asks their case manager, "What are my housing options?" and "What am I eligible for?" the case manager would typically collect information about the survivor, manually determine which options would work best and are available, explain the options to the survivor, and then apply for each option with the survivor. The process is arduous and could take a few months. In parallel, the survivor may receive different information from different sources, further complicating the process and leading the survivor to feel overwhelmed.

While the existing housing solutions, albeit sparse, have shown promise, there appears to be no digital solution that survivors can use to address their housing needs. This is especially salient given most adults (90%) in the United States, regardless of socioeconomic status, have smartphones, and more than half with browsing capability [23,24]. Digital solutions furthermore have served as promising complements to traditional services like counseling and advocacy [25-27]. Thus, there is an opportunity to develop a digital tool to address the housing needs of survivors.

Description of the Tool

Knowing the above, the study team collaborated with a coalition of domestic violence housing specialists in New York City to create a web-based tool that both screens and educates survivors on affordable housing programs in New York City. Grounded in the process of empowerment [28], the digital tool strives to address survivors' barriers to housing knowledge while building survivors' self-efficacy to achieve their housing goals. Taking only a few minutes, the tool starts by collecting survivors' household size, income, and living situation, and ends by generating curated matches of housing programs based on the survivors' information (Figure 1). The tool gives the survivor the agency to determine and learn about their options, without the case manager serving as the sole gatekeeper of information. Because it is one tool, the survivor and case manager also reference the same information, thereby, standardizing the process and freeing up the case manager and survivor to focus on applying for housing programs.

It is important to note that the tool neither guarantees the survivor's access to housing programs nor addresses every housing need of every survivor. Still, the tool introduces survivors to relevant, available housing programs, all from the convenience of their phones. The tool also serves survivors and nonsurvivors alike. Its content on housing programs is broadly relevant to anyone keen to determine their eligibility for affordable housing programs in New York City.

For this feasibility study, the study team will test the concept of the tool with a convenience sample of survivors served by a community-based domestic violence center (site) in New York City. The site serves a wide range of clients and is particularly attentive to the needs of survivors with disabilities.

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Figure 1. Snapshots of tool.

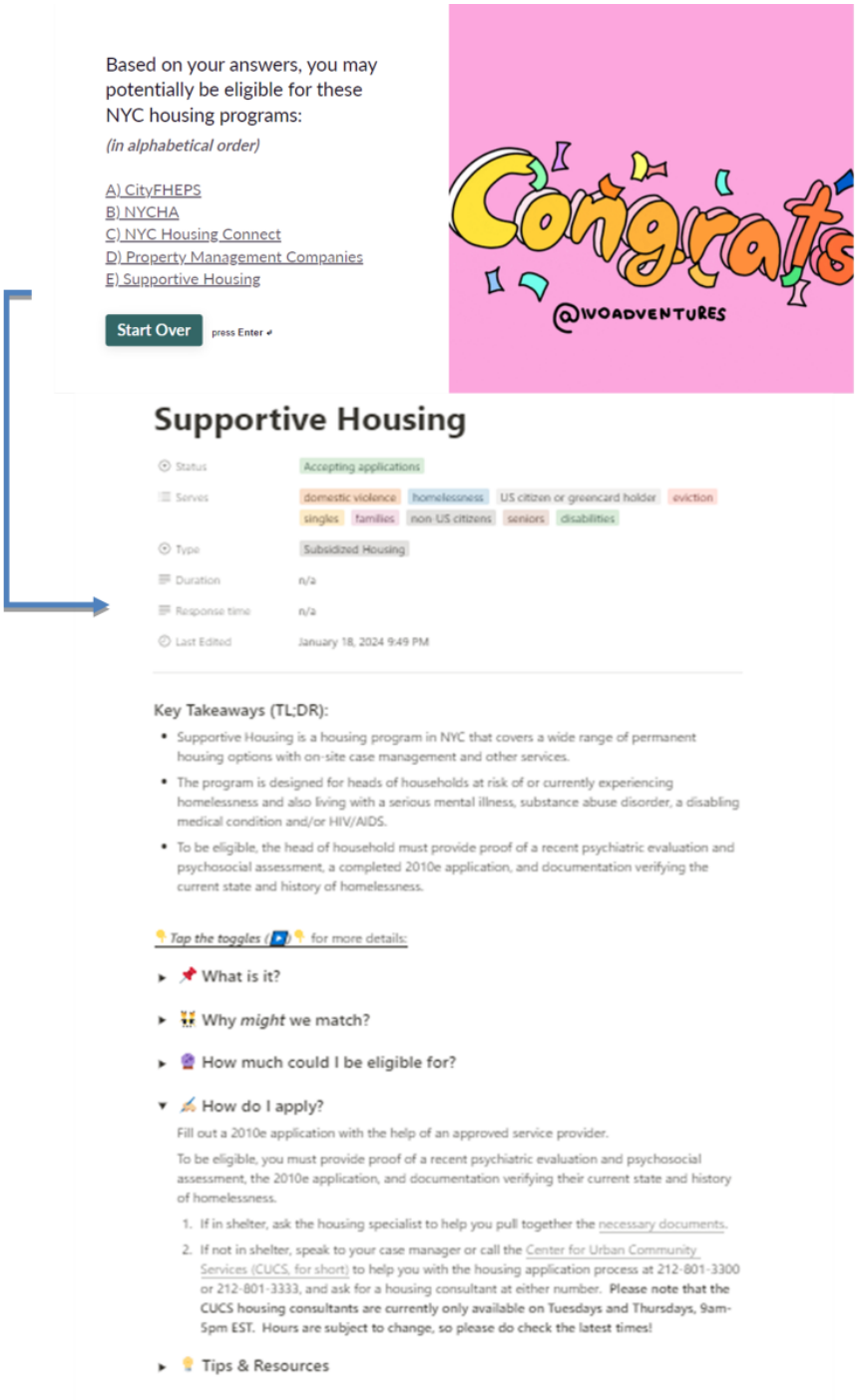

This Study

This paper presents the protocol for testing the concept of the tool in a community-based domestic violence center. The feasibility study aims to determine whether implementing a web-based tool in this setting is possible; and whether the delivery of housing information through a digital tool could show promise of increasing survivors' housing knowledge, housing self-efficacy, or trust in staff. In this paper, we use the terms "full-scale" or "large-scale" trials to denote next-phase trials that will be fully powered to measure impact. This study will compare the intervention with a control condition of no intervention use. We hypothesize that the intervention group will report greater increases in at least one of the primary outcomes: housing knowledge, housing self-efficacy, and staff trust, relative to the control condition. We also hypothesize that most survivors using the intervention will rate the tool as usable and acceptable.

Research Questions

Through this study protocol, we are seeking to answer the following research questions: (1) What is the initial treatment effect of SC+ (standard care plus), as compared to SC (standard care), on survivors' housing knowledge, housing self-efficacy, and staff trust? (2) What is the estimated sample size needed for a full-scale intervention trial? What is the estimated timeline needed to reach this sample size? (3) Are the expected rates of recruitment and retention achieved? (4) Are the study's

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processes and instruments feasible for a full-scale intervention trial? and (5) Is the tool acceptable and usable by survivors and staff?

Methods

Study Design

The study will use a quasi-experimental, mixed methods design to assess the feasibility, usability, and acceptability of the tool (Multimedia Appendix 1). There will be two treatment groups: no use of the tool (standard care only, SC) and use of the tool (standard care plus, SC+). Survivors mostly come to the site through the organization's crisis hotline. A survivor calls the hotline for help, and if deemed appropriate, the site makes an appointment for an intake interview to determine the survivor's needs, including housing. Subsequently, a case manager is assigned to meet with the survivor. For new clients, the meetings normally take place twice a week during their first month. In these meetings, the case manager helps the survivor apply for a myriad of benefits, including housing programs if housing has been identified as a need. The meeting frequency then lessens as the survivor's needs are met. SC will consist of no tool use, in or outside of the case manager meetings. SC+ will consist of tool use, in or outside of the case manager meetings. To ensure access to the tool regardless of whether a meeting is scheduled during the study period, the study team will email all SC+ participants a link to the tool for their self-use.

Following a historical cohort control group design, the study team will recruit participants into each arm, sequentially. We will recruit SC participants first. After all SC participants have completed their follow-up surveys, SC+ recruitment will begin. The SC and SC+ study groups will engage in two data collection points: one baseline survey prior to the housing meeting and one follow-up survey 2 weeks after completion of the baseline survey, each anticipated to take up to 30 minutes to complete. Study participants will be given a 1-week grace period to complete each survey. During SC+, the study team will email the tool to all enrolled participants following the completion of their first survey.

After SC+, we will engage five staff participants (key informants) in 60-minute individual interviews through a web conferencing platform like Zoom (Zoom Communications, Inc) about their experiences using the tool. The staff serve as decision-makers who can influence whether the tool will be used after the study. Thus, their perspectives are critical for understanding how to successfully implement the tool in the partner site and similar settings. Only 5 of the 12 staff met the eligibility criteria, which were determined in consultation with the partner site. We will not engage survivors in interviews to mitigate potential research fatigue [29]. We will, however, ask survivor participants about their experiences using the tool in the SC+ follow-up survey.

The study team had initially considered a randomized controlled trial (RCT) but selected a quasi-experimental, historical cohort design for several reasons. First, randomizing at the participant level, as in an RCT, was not feasible. Randomizing participants would have required the case managers to know the participant's enrollment status and arm assignment to introduce the tool to the appropriate person. This lack of concealment could have produced differential treatment by the case managers based on the participant's enrollment status. Second, we anticipated that tracking each participant's arm assignment in an RCT would have added to the staff's already limited capacities, a concern that the site also shared. Third and final, there was the concern that SC+ participants could interact with SC participants and share the tool, further confounding the results. Fortunately, the current historical cohort control group design mitigates the above risks. In the current design, case managers deliver SC, followed by SC+, regardless of whether a participant enrolls, thereby reducing any potential administrative burden on the staff. While the case managers are not entirely blinded to the participants' enrollment status and arm assignment, the current design reduces the risk by emailing participants directly with the intervention link. If a participant mentions the link to the case manager, then the case manager will know that they have signed up for SC+. Otherwise, case managers will not know and will be encouraged to share the tool with all clients. Furthermore, the tool will only be accessible to participants during the SC+ arm, hence removing the possibility of participants interacting with the tool during the SC arm. To mitigate ethical concerns over one group and not the other receiving the tool, all SC participants will receive access to the tool after the SC+ arm completes data collection. Thus, while the study team had considered an RCT, the quasi-experimental, historical cohort control group design ultimately allowed the study team and partner site greater logistical flexibility, decreased administrative burden, and lower risk of confounding.

Study Population

The partner site, a community-based domestic violence program based in New York City, provides domestic violence and sexual assault counseling, case management, legal services, occupational therapy, and support groups for any survivor of domestic violence and is particularly attuned to the needs of survivors who are D/deaf or Hard of Hearing or have a disability [30]. Based on the last set of data collected by the site in 2021, the partner site, on average, served 171 new and existing clients per month. About 26% (n=45) of clients were new to the program each month. Of those who disclosed their information to the site, 84% (109/130) identified as a cisgender woman, and 15% (19/130) as a cisgender man. The majority identified as either Black (48/114, 42%) or Latino/a/x (32/114, 28%). None chose to disclose their employment status, but more than half (76/151) reported being on some form of public assistance. Finally, 52% (66/128) of clients reported a mental health disability, 18% (23/128) reported a sensory disability (ie, blindness or deafness), 17% (22/128) a physical disability, 10% (13/128) a medical condition, and 3% (4/128) a cognitive disability. The site has three full-time case managers, who cover a wide range of survivor needs including housing, and a full-time program director and assistant director who oversee the case managers.

Eligibility Criteria

Survivors, or participants, will be eligible for study inclusion if they consent to participate; are seeking assistance from the

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site at the time of joining the study; are at least 18 years old; have access to a device with web-browsing capability (eg, smartphone, tablet, or the site's computers); are looking for housing; have a safe email account, with "safe" being interpreted as the survivor sees fit; can read English without assistance from others including translation or interpretation assistance; and have not participated in the study before. Staff, or key informants, will be eligible for inclusion in the study if they give oral consent to participate, are at least 18 years old, and bear the title or responsibilities of "case manager" or "director." We expect to recruit five key informants.

Procedures

The two sequential study arms will follow the same procedures, differing only in treatment (Figure 2). In each arm, the program director will send a mass email about the study to their clients with the recruitment flyer and screening form link. The case managers may also refer prospective participants to the study in their individual meetings. If the prospective participant is interested, they will answer questions on a digital form to determine whether they meet the inclusion criteria. If the prospective participant meets all the inclusion criteria, the form will automatically collect their contact information, which will then trigger a digital consent form that will be emailed to the participant. If the prospective participant wishes to join the study after reading the consent form, they will click yes to proceed to the baseline survey. As we are waiving the collection of a signature to protect the participant's confidentiality, clicking yes will constitute the participant's consent to join the study. Should the participant proceed, they will receive the baseline survey immediately and a follow-up survey 2 weeks later, both by email. Each survey will be active for 1 week, and up to 3 email reminders will be sent to the participant during the 1-week grace period if the survey remains incomplete. If the participant completes the follow-up survey during the grace period, they will receive an additional email upon completion with the answer key to the knowledge quiz.

Figure 2. Participant flow. SC: standard care only; SC+: standard care plus.

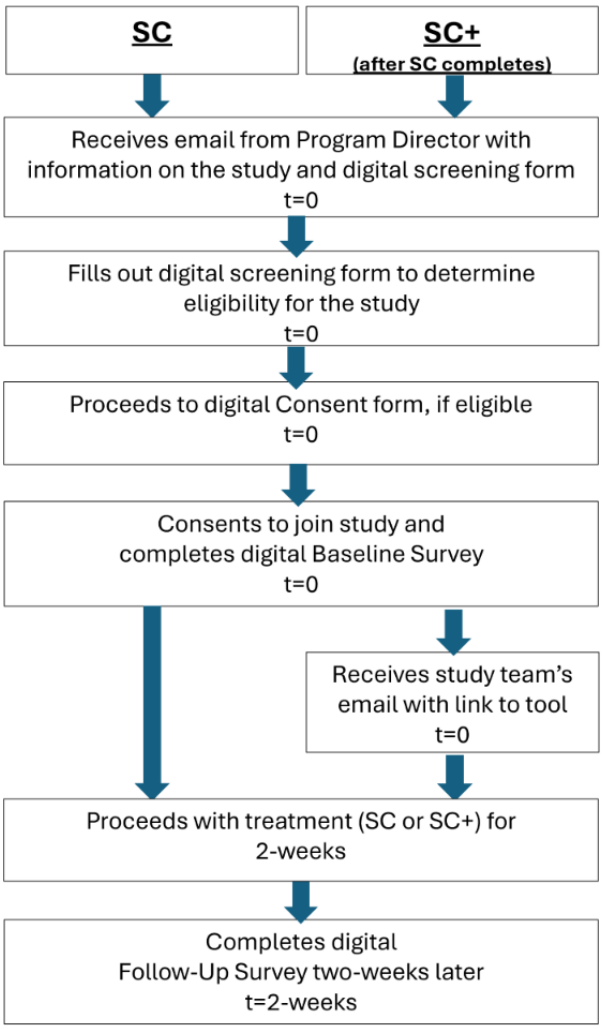

During the 2-week period between the baseline and follow-up surveys, the participant will receive services as usual in the SC arm and services plus the tool in the SC+ arm. Regardless of whether a participant completes the surveys, the site will continue to provide services to the participant. In the SC+ arm, the study team will email the participant a link to the tool to use over the 2-week treatment period. The case manager will also share the tool in their individual meetings with SC+ participants. If there happens to be no meeting during a participant's enrollment in the study, the participant can still access the tool through the study team's email.

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For each completed survey, the participant will receive a US $10 Visa eGift card via email for a potential total of US $20 for two completed surveys. Study data will be collected and managed using REDCap (Research Electronic Data Capture; Vanderbilt University) electronic data capture tools hosted at Johns Hopkins University [31,32]. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for data integration and interoperability with external sources.

Outcome Measures

Overview

For all measures (Table 1), the time frame will be the current point-in-time at which the participant is answering the survey. It is important to note that the measures do not presently pertain to specific types of disabilities, thereby potentially limiting our ability to relate the findings to participants with disabilities. Still, the measures and subsequent findings can be used to inform future studies engaging survivors of domestic violence, generally, and serve as a base for the inclusion of questions specific to survivors with disabilities.

Table 1. Research questions, outcome measures, and time of data collection.

	Research question	Audience		Time and method of data collection		
		Survivor	Staff	Baseline survey	Follow-up survey	Individual interview
1	What is the initial treatment effect of SC+[a], as compared to SC[b], on survivors' housing knowledge, housing self-efficacy, and staff trust?	✓		✓	✓	
2	What is the estimated sample size needed for a full intervention trial? What is the estimated timeline needed to achieve the full intervention trial sample size?	✓				
3	Are the expected rates of recruitment and retention achieved?	✓				
4	Are the study's processes and instruments feasible for a full intervention trial?	✓		✓	✓	✓
5	Is the tool acceptable and usable by survivors and staff?	✓	✓		✓	✓

[a]SC+: standard care plus.

[b]SC: standard care only.

Sociodemographics

The study will collect sociodemographic information from participants at baseline. Variables include age, gender, income, length of time with the site, prior or current domestic violence exposure, housing status, and experiences of housing instability in the last 6 months.

Housing Knowledge

As no known prior studies have measured housing knowledge, we will assess whether the tool improves survivors' knowledge of housing options through a 10-item Housing Knowledge Quiz developed for this study (Table 2). Questions like "Which housing program is a lottery of affordable housing apartments in New York City?" will ask survivors about affordable housing programs in New York City and program eligibility criteria, with each question carrying a 1-point weight for a possible summed score range of 0 to 10.

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Table 2. Housing knowledge quiz.

Question	Answer choices
1. Jane is a survivor of domestic violence in shelter. She and her two children plan to move out of shelter to an apartment. What is Jane's household size?	1,2,3
2. "Affordable housing" means that you pay about one-third or less of your income on rent.	True, False
3. Eligibility for New York City housing programs can depend on your...	Household size, Income amount, Citizenship or residency status, Current living situation, Whether you have children or are expecting children, Disability, All of the above
4. Which housing program is a lottery of affordable housing apartments in New York City?	FHEPS[a], Housing Connect, Property Management Companies, Do Not Know. Please select one answer.
5. Which housing program lists apartment openings, reviews housing applications, and takes payment?	FHEPS, Housing Connect, Property Management Companies, Do Not Know. Please select one answer.
6. Which housing program is a type of rental assistance paid directly by the government to the landlord? The amount of rental assistance will vary by one's income and household size.	FHEPS, Housing Connect, Property Management Companies, Do Not Know. Please select one answer.
7. DHS[b] shelter provides a time-limited stay only for households of domestic violence.	True, False
8. Supportive housing is a type of permanent housing that also includes services like case management, medical, and psychiatric help.	True, False
9. Who may be eligible for SSI[c] benefits?	Individuals or couples who are 65 years or older, blind, or disabled, with limited income and resources, Children who are disabled or blind, with limited income and resources, All of the above, None of the above
10. What is the name of a property management company that manages affordable and low-income housing in New York City?	Reliant Realty, Insignia, Barrier Free Living, Urban Resource Institute. Please select one answer.

[a]FHEPS: family homelessness and eviction prevention supplement.

[b]DHS: Department of Homeless Services.

[c]SSI: supplemental security income.

Housing Self-Efficacy

According to social cognitive theory, the stronger one's self-efficacy, the higher the goals one sets and the more favorable the outcomes one expects, and vice versa [33]. In Cattaneo and Chapman's [28] empowerment process model, likewise, self-efficacy drives the rest of the components: power-oriented goals, knowledge, competence, action, and impact. To measure whether the tool improves survivors' abilities to achieve their housing goals, we have constructed a 10-item Housing Self-Efficacy Likert scale (Table 3), adapted from three existing scales to incorporate housing: the Generalized Self-Efficacy Scale [34], the Financial Self-Efficacy Scale [35], and the Scale of Economic Self-Efficacy [36]. The questions have been constructed using 4 response categories, from 1=strongly disagree to 4=strongly agree. Participants will be asked to rate their level of agreement on questions such as "I can always manage to solve difficult housing problems if I try hard enough" and "If I experience housing trouble, I can usually think of a solution." To balance the potential "forced-choice" nature of the four categories, a "does not apply" option has also been added.

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Table 3. Housing self-efficacy scale.

No.	Item
1	I can always manage to solve difficult housing problems if I try hard enough.
2	If I have a housing problem, I can find ways to get what I need.
3	It is easy for me to stick to and accomplish my housing goals.
4	I am confident that I could deal efficiently with unexpected housing events.
5	Thanks to my resourcefulness, I know how to handle unforeseen housing situations.
6	I can solve most housing problems if I invest the necessary effort.
7	I can remain calm when facing housing difficulties because I can rely on my abilities.
8	When I am confronted with a housing problem, I can usually find several solutions.
9	If I experience housing trouble, I can usually think of a solution.
10	No matter what housing problem comes my way, I am usually able to handle it.

Staff Trust

Trust is defined as an individual's expectation that their needs will be met without any harm [37]. When developing the tool, the coalition of housing specialists continually expressed an interest in knowing how the tool would affect survivor trust in staff. For them, they hoped the tool could validate and explain the staff's housing advice to survivors. An abundance of research further illustrates the importance of trust in service delivery. Patient trust in health care settings, for instance, has been correlated with patient satisfaction and continuity of care [38-41]. While several valid, reliable scales have been designed to measure trust in service delivery [38,42,43], no trust scale quite captures the uncertainty of the emergency shelter context or the often-volatile relationship between staff and survivors. The 10-item Trust in Community Health Workers (CHWs) Scale [37]was thus adapted to measure survivors' perceptions of staff trustworthiness, particularly of their case managers. CHWs in low- and middle-income countries are comparable to case managers in domestic violence agencies in that both typically work with vulnerable groups in resource-constrained, emergency settings. We adapted the Trust in CHWs Scale then, not only for its validity and reliability but also for its applicability to an emergency setting, like that of a domestic violence center. Like the Housing Self-Efficacy Scale, the resulting Staff Trust Scale (Table 4) will use 4 response categories, from 1=strongly disagree to 4=strongly agree, along with a "does not apply" category for additional scenarios. Sample questions include, "My case manager tells me everything I need to know when dealing with my housing problems" and "In my opinion, my case manager is committed to providing me with the best care possible."

Table 4. Staff Trust Scale.

No.	Item
1	My case manager tells me everything I need to know when dealing with my housing problems.
2	My case manager knows as much as they can about finding housing.
3	My case manager takes enough time with me during our housing meetings.
4	My case manager keeps what we discuss confidential or private from others at [agency name].
5	In my opinion, my case manager is committed to providing me with the best care possible.
6	My case manager is an excellent listener.
7	I feel better emotionally after talking to my case manager.
8	My case manager treats me with respect.
9	My case manager has my best interest at heart.
10	My case manager makes me feel like I am worthy of their time.

Sample Size, Recruitment and Retention Rates, and Timeline

We will estimate the desired sample size for a full-scale trial based on the effect sizes achieved in this study in the housing knowledge, housing self-efficacy, and staff trust variables. Both the rates of recruitment and retention will be measured quantitatively; the recruitment rate will be defined as the number of participants who enroll divided by the total number of participants recruited, while the retention rate will be defined as the number of participants who complete the follow-up survey divided by the number of participants who complete the baseline survey. Finally, the timeline, or the time it takes to recruit participants, will be recorded to give a benchmark for the full-scale intervention trial.

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Large-Scale Trial Feasibility

To determine the feasibility of a full-scale trial, we will look at response rates, ease of implementation, and outcome appropriateness, as well as learn how participants respond to the instruments. The response rate on the surveys will serve as a proxy of instrument feasibility and will be calculated as the number of items answered on a survey divided by the total number of survey questions. A "does not apply" answer will count as an item nonresponse, or unanswered. If a 75% response rate or higher is achieved, then the instrument will be deemed feasible. A list of the questions that were answered versus unanswered will also be compiled to improve the instruments.

Ease of implementation, on the other hand, will be measured solely in the key informant interviews. Staff will be asked open-ended questions on their experiences with participant recruitment and use of the tool, for example, "What were some facilitators or challenges to recruiting participants?" "...to the use of the tool in your meetings?"

Perceived outcome appropriateness, finally, will be measured qualitatively through questions on the SC+ follow-up survey and informant interviews on whether housing knowledge, self-efficacy, and staff trust were appropriate to measure for the tool, as well as whether participants recommended other outcomes to measure.

Acceptability and Usability of the Tool

To understand the survivors' and staff's experiences of using the tool, we will collect data from the survivors through surveys (Table 5) and the staff through interviews (Textbox 1).

Table 5. Perceived Usability Scale.

	Items
1	The tool is easy to use.
2	I had no trouble seeing the information in the tool.
3	The information in the tool is easy to understand.
4	The information in the tool is relevant to me.
5	I found the tool hard to use.

The survivors' and staff's intent to continue use and perceived effect will serve as proxies of the tool's acceptability. In the follow-up survey to the SC+ group of survivors, intent to continue use will be measured by participants' responses to the statements, "I plan to continue using the tool," and "I would recommend the tool to others in a similar situation as me," based on their tool use from the prior 2 weeks. For each statement, participants will also have an opportunity to elaborate on their answer with the open-ended question "Why?" Similarly, in the key informant interviews, staff will be presented with open-ended questions: "How likely are you to continue using the tool or recommend the tool to other case managers beyond the feasibility study? Why or why not?" To gauge the perceived effect, staff will be encouraged to identify changes in their workloads, relationships with survivors, and the survivors' housing search approach after using the tool with questions like, "How does using the tool impact your or your staff's workload? Do you have examples?" and "Have you noticed changes in your relationship with survivors as a result of using the tool?"

Perceived usability, on the other hand, will be measured through 5 items in the SC+ follow-up survey to survivors, as well as open-ended interview questions to the staff on navigation and content relevance. The 5-item measure to survivors was adapted from a 16-item Likert scale used to evaluate the bMORESafeapp [25] and has a response set ranging from 1=strongly disagree to 4=strongly agree, with a "does not apply" category for additional scenarios. Only five items of the original 16-item Likert scale measured general app usability. The remaining 11 items were specific to features found only in the bMORESafeapp.

Finally, the staff will be asked for their input on the future dissemination of the tool within the partner site and to other agencies through open-ended questions, like "How could the tool be used by others (eg, housing specialists, case managers, social workers, lawyers, real estate brokers, and other domestic violence advocates)?"

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Textbox 1. Key informant interview guide (outcome and questions).

Introduction

- Tell me about yourself.
- How long have you worked at the partner site?
- What is your role at the site? What does that entail?
- What are you most proud of in your work?

Intent to continue use (acceptability)

- How likely are you to continue using the tool with clients beyond the feasibility study? Why or why not? Scale of 1-4, 1=strongly disagree, 4=strongly agree.
- How likely are you to recommend the tool to other case managers beyond the feasibility study? Why or why not? Scale of 1-4, 1=strongly disagree, 4=strongly agree.

Perceived effect (acceptability)

- How has using the tool impacted your or the staff's workload? Do you have examples?
- Was there something that you learned from the tool that you think is valuable to your work? To your relationship with clients?
- Have you noticed any changes in your or the staff's relationship with clients as a result of using the tool?
- Have you noticed any changes in how clients have approached their housing search as a result of using the tool?

Ease of implementation (implementation)

- What were some facilitators or challenges to recruiting participants?
- What were some facilitators or challenges to the use of the tool in your meetings? (eg, leadership support, internet stability, tech comfort, meeting duration, and client disinterest)

Outcome appropriateness (implementation)

- Were the outcomes of knowledge, self-efficacy, and staff trust appropriate for the tool?
- Would you add other outcomes to consider? If so, what would they be, and why?

Perceived usability

- Can you describe how (easy or difficult) it was to navigate the tool? See the information in the tool? Guide clients on how to use the tool?
- How relevant was the information presented by the tool to your discussions with clients?
- Did any of the content help start a conversation? Why or why not?
- How would you explain the tool to a client? To another staff member?

Dissemination

- What suggestions do you have for disseminating the tool to staff and clients in the rest of the organization? Other agencies?
- How could the tool be used by others (eg, housing specialists, case managers, social workers, lawyers, real estate brokers, and other domestic violence advocates)? Probe: Who else could use the tool? Could it be used to build capacity (eg, training) or standardize information sharing?

Feasibility Criteria

As recommended by Thabane et al [44], we established formal Stop or Go criteria to evaluate the success of the feasibility study. A Stop outcome states that the subsequent large-scale trial is not feasible, while a Go outcome means that the study can continue, with or without modifications [44]. The outcomes will be determined after assessing the study data. We will stop if (1) no positive change approaching significance in any of the primary outcomes in SC+: survivors' housing knowledge, housing self-efficacy, or staff trust, relative to SC, is observed; or (2) survivors, on average, do not intend to continue the use of the tool, as measured by scores of 2=Disagree or 1=Strongly Disagree on the Likert scale. Criteria #1 and #2 will help us determine whether SC+ shows promise of a positive effect and acceptability (as determined by intent to use) to warrant a subsequent intervention trial to a larger group. If either Stop criterion is met, then the full-scale study is not feasible.

If both Stop criteria are not met, then we can move to a Go, that is, continue to a large-scale trial. Modifications will be needed if (1) 75% or more of the questions in the survey are left unanswered, (2) 75% or more of potential survivor participants do not join the study, or (3) less than 95% of enrolled survivors do not complete both the baseline and follow-up surveys. This retention rate is informed by the retention rates of the web-based myPlan evaluation, which hovered around 94% at 6 months and 93% at 12 months [27]. The Go criteria will help us determine

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whether the study could enroll and engage sizable participation, as illustrated by the rates of recruitment, retention, and response.

Statistical Analysis

Multiple linear regression models will be used to test the difference-in-difference in means of housing knowledge, housing self-efficacy, and staff trust. The inclusion of independent variables in the models will be determined by prior tests assessing whether any significant differences exist in outcome variables by demographic and moderating variables. The outcomes of interest will also be input as independent variables to determine the association between housing knowledge, housing self-efficacy, and staff trust.

Sample size, the rates of recruitment, retention, and response, and timeline will be recorded. Ease of implementation and outcome appropriateness will be collected through open-ended questions in individual interviews with the key informants, while acceptability and perceived usability will be collected through a mix of Likert scale and open-ended questions in the surveys and interviews.

To analyze the qualitative data, the written answers from the participant surveys and the transcripts from the key informant interviews will be inductively coded using a constant comparative method. Two coders will separately code the transcripts and then compare and iterate for agreement. Interrater reliability will be calculated as the number of codes in agreement, in proportion to the total number of codes [45]. We will iterate our codes until we achieve a minimum 80% agreement on 95% of our code set [45].

Ethical Considerations

The study received approval from the Johns Hopkins Bloomberg School of Public Health Institutional Review Board (18116). To minimize the risk of a confidentiality breach of the participant's personally identifiable information, we closely followed the World Health Organization [46] guidelines on domestic violence research, which includes the use of unique study identification numbers for participants. Consent will be collected in two ways. First, a participant clicking yes on the consent form to continue to the baseline survey will constitute consent. The study will not obtain participant signatures to protect confidentiality. Participants will receive US $10 for each completed survey, US $20 total, in e-gift cards. Second, the study will ask for oral consent from the key informants at the start of their interviews. Key informants will receive a US $20 e-gift card for participating in the individual interviews.

Results

Recruitment for the SC arm began in March 2022 and completed in April 2023. Of the prospective participants, 75 participants were screened, 44 participants were deemed eligible, 35 participants were enrolled (ie, consented to the study), and 23 participants completed both baseline and follow-up surveys. Initially, we had sought to attain 50 completed surveys, 25 in each arm. However, the recruitment timeline for SC took longer than anticipated, and the enrollment numbers were lower than expected. Following 1 year of recruitment for SC that resulted in 23 completed surveys, we sought to expedite the recruitment timeline for SC+. Recruitment for the SC+ arm started in January 2024 and is anticipated to end by May 2024. After SC+ arm recruitment ends, we plan to recruit, conduct, and complete the key informant interviews in June 2024. We subsequently expect to complete the study and be ready to analyze the results by the end of June 2024.

Discussion

Hypothesized Findings

Among the results, we anticipate that SC+ will show a positive change relative to SC on at least one of the primary outcomes: survivors' housing knowledge, housing self-efficacy, or staff trust. While the change may or may not be statistically significant, we are looking for the direction of change as an indication of possible future change in a large-scale trial. We also expect that most survivors in the SC+ group will deem the tool usable and acceptable. Overall, we anticipate achieving a Go outcome on feasibility for subsequent testing, likely with modifications to processes such as recruitment and retention.

Comparisons to Prior Work

Only a handful of digital (mobile and nonmobile) solutions address the needs of survivors of domestic violence. In the United States, these solutions fall into three main categories. First is an educational and practical assistance category in which solutions educate users on domestic violence, engage users in safety planning, and connect users to resources, that is, myPlan, Aspire News, and bMORESafe [25-27]. Second is an emergency assistance category in which solutions alert survivors' preprogrammed networks of the need for help, that is, bSafe, Kinetic Global (formerly Lifeline Response), and Circle of 6 [24-26]. Third and less common is a documentation category that empowers survivors with the capability of storing evidence of the abuse for later use. The National Network to End Domestic Violence had previously launched DocuSAFE for this purpose, but unfortunately, as of October 2023, the app is no longer functioning [47,48].

Regardless of category, studies of digital domestic violence solutions have demonstrated promising outcomes, particularly in addressing the safety planning needs of survivors [25-27]. The myPlan safety planning app, for instance, has been associated with reductions in intimate partner violence experience and risk of suicide [26]. Moreover, the app's predecessor, the myPlan website, has been shown to increase survivors' knowledge and perceived helpfulness of safety behaviors [27]. Survivors using the website were also more likely to have left their abusers than survivors who did not use the myPlan website over the 1-year study period [27]. All things said, none of these digital interventions address the housing needs of survivors. To the best of our knowledge, this will be the first time a digital housing tool for survivors of domestic violence will have been developed or studied in the United States.

Limitations

Among the study's limitations, first, the case managers will not be entirely blinded to the participants in the SC+ group. Case managers will be encouraged to use the tool with all survivors

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regardless of their enrollment status. However, if a survivor receives the tool from the study team and informs their case manager, then the case manager will know that the survivor has enrolled in the study, thereby potentially leading to differential treatment of survivors. Still, participants will not know of their arm assignments, thereby minimizing the risk of such knowledge influencing participant outcomes. Second, the specificity of the study's setting in a community-based domestic violence center that helps survivors with disabilities, in New York City, may limit the applicability of results to other settings. Nevertheless, we believe that domestic violence and disability organizations in other urban areas could still gain from the findings and lessons of this study.

Future Directions

Considerations

When implementing the SC arm, the study team encountered several delays with data collection that have been highlighted here for future consideration.

To start with, the study was conducted during the pandemic, at a time when nonprofits, like the partner site, were experiencing significant labor shortages and funding constraints [49,50]. At the same time, demand for services continued to increase, leading more nonprofits to report a decrease in their ability to provide services [51]. As such, the study's data collection efforts often inadvertently competed with the staff's full workload. In turn, the crisis context of domestic violence work also may have prevented the staff from fully participating in the study as they had hoped.

Further delaying data collection were unanticipated enrollment issues. Halfway through SC recruitment, we discovered about half of the SC participants were not truly eligible for the study. We infer that some participants had forwarded the study information to friends and family, who then falsely answered the screening questions to participate in the study. While we subsequently removed those faulty participants, we also extended the SC recruitment timeline to make up for the loss.

Finally, the study team had not accounted for the time it would take to obtain the appropriate site approvals, nor had we prepared for an unexpected change in case management systems.

Recommendations

Regardless of the issues we may have encountered, we continue to advocate for research in community settings. Community-placed research, such as this study, allows researchers unparalleled insight into the operations of community settings, which would only strengthen researchers' efforts to effect sustainable change. Thus, to help researchers prepare for work in similar settings, we offer a few recommendations from our experience.

First, outline a partnership agreement with the community partner before any research begins. The agreement will delineate the expectations of time, resources, and approvals and will ensure that all parties have a shared understanding of and buy-in for the research study. We did not engage in a partnership agreement for this study.

Second, ensure that you have champions with some decision-making authority within the partner site to advocate for your partnership.

Third, even with the right champions as we had, maintain regular communication with the partner site to proactively preempt or address any issues as they arise. For instance, as in our case, the study team could have suggested actively comparing the participants' emails sooner to prevent false participants.

Fourth, recognize how the crisis context of a community-based domestic violence organization may impact participation in the study. There is a growing body of evidence that calls for researchers to be aware of the multilevel forms of trauma existing within gender-based violence organizations and how the trauma may present itself [52]. This trauma may show up as last-minute meeting changes to address survivors' crises or secondary trauma from direct service provision [52].

Finally, be ready to adapt. Following our observations with the SC arm, for instance, we subsequently adapted and shortened the recruitment timeline for the SC+ arm.

Conclusions

While some of the issues, like the crisis context, will remain unavoidable, we can proactively take steps to ensure the successful implementation of future research within similar community settings. Future researchers could consider using community-based participatory research (CBPR) approaches, for instance, to guide their transition from conducting community-placed to community-based research. Central to CBPR is the equitable involvement of community stakeholders and researchers in all steps of the research [53,54]. Equitable involvement can look like shared decision-making, expertise, and ownership at each step by both the academic and community partners [53,54]. While other approaches exist, CBPR has gained much attention for its association with positive health outcomes for communities [54,55]. Still, little is known about the organizational capacity to support these outcomes [54,55], and we would remind researchers to be mindful of the capacity required to build a successful CBPR. Considerations aside, through this protocol, we aspire to encourage more research at the intersection of domestic violence, housing, and technology.

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Data Availability

The datasets generated or analyzed during this study are not publicly available due to the sensitive nature of the study but are available from the corresponding author upon reasonable request.

Authors' Contributions

All authors have been involved in reviewing the protocol. JKT wrote the protocol, and MRK revised and approved it before submission. All authors have approved the final version.

Conflicts of Interest

JKT's contribution to this publication was as a member of the Board of Directors of the partner site. This arrangement was reviewed and approved by Johns Hopkins University in accordance with its conflicts of interest policies.

Multimedia Appendix 1
Presentation of the feasibility study.
[PDF File (Adobe PDF File), 480 KB - resprot_v14i1e63162_app1.pdf]

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Abbreviations

CBPR: community-based participatory research
CHW: community health worker
DHS: Department of Homeless Services
DVHF: Domestic Violence Housing First Program
HF: Housing First
PSH: permanent supportive housing

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RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SC: standard care
SC+: Standard care plus

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Protocol

Development of a Risk Score to Aid With the Diagnosis of Infections After Spinal Cord Injury: Protocol for a Retrospective Cohort Study

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Abstract

Background: Patients with spinal cord injury (SCI) who develop urinary tract infection (UTI) present differently than the non-SCI population. UTIs can cause loss of quality of life and even lead to life-threatening complications including urosepsis. Challenges in SCI management include distinguishing symptomatic UTI from asymptomatic bacteriuria (ASB), which occurs often in patients with SCI, and the lack of standardization in UTI diagnosis in SCI.

Objective: This study aims to set the foundation for the development of a risk score to improve diagnostic accuracy of UTI after SCI.

Methods: This study will use data from the Veterans Health Administration Corporate Data Warehouse from national outpatient clinics. It will use 2 approaches: (1) a case-control study comparing frequency-matched healthy SCI cases (n=2000) with healthy non-SCI controls (n=2000) to establish a physiologic baseline for vital sign and lab measurements after SCI and (2) a retrospective cohort study of patients with SCI (n=400) to determine the positive predictive value of the baseline vital signs and lab measurements found in step 1, from which a threshold for clinically meaningful UTI after SCI will be established.

Results: The study was funded in May 2023, and initial data extraction started in early 2024 and is expected to be completed in 2026. Data extraction, analysis, and results for aim 1 were completed as of manuscript submission. For aim 1, we hypothesize that SCI will be associated with lower temperature, heart rate, and systolic blood pressure when compared with non-SCI controls. SCI will also be associated with higher baseline levels of pyuria and peripheral white blood cells when compared with non-SCI controls. Data extraction for aim 2 will begin in year 1, and analysis and results will be completed in year 2. For aim 2, we hypothesize that pyuria, heart rate, and temperature measurements will have a high positive predictive value for clinically meaningful UTI.

Conclusions: Once complete, this study will be the basis for our future work developing a risk score to aid with the diagnosis of UTI after SCI and prevent antibiotic overuse in patients with SCI.

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KEYWORDS

spinal cord injury; neurogenic bladder; asymptomatic bacteriuria; positive predictive value; risk assessment; diagnosis; SCI; risk score; urinary tract infection; UTI; quality of life; complication; urosepsis; management; vital sign; retrospective; cohort; physiology; bladder health; bladder; urinary tract; infection

Introduction

Urinary Tract Infection After Spinal Cord Injury

After spinal cord injury (SCI), urinary tract infection (UTI) poses significant economic burden and interruption to quality of life [1]. UTI, including catheter-associated UTI (CAUTI), is a common and costly medical complication after SCI [1]. Our research team and others have found that diseases of the genitourinary tract, of which a large proportion are UTI or CAUTI, are among the most common reasons for emergency room and inpatient visits, with septicemia being one of the leading causes of death for persons with SCI [1,2]. UTI and CAUTI are the focus of multiple quality improvement campaigns, with many hospitals and health care facilities setting their sights on "Getting to Zero" [3]. Some of the impetus for preventing CAUTIs has been attributed to the change in the Centers for Medicare and Medicaid reimbursement policy in 2008 [4], which provided hospitals financial incentive to prevent CAUTIs as an important component of hospital quality metrics [5].

Contrary to common belief, walking after SCI is not among the most important indicators of quality of life, but adequate control of bladder function (including minimizing the disruption of UTI or CAUTI) is [6-8]. Therefore, providers, patients, and hospital systems all have a vested interest in accurately identifying this burdensome condition. For simplification, UTI will be used throughout this paper to represent UTI and CAUTI in this population.

UTI Versus Asymptomatic Bacteria

Distinguishing UTI from asymptomatic bacteria (ASB) after SCI is challenging, often leading to antibiotic overuse and its harms. The rate of ASB, also defined as bacteriuria in the absence of signs or symptoms of infection, in persons with SCI is very high due to how common bladder instrumentation is in this patient population and does not require antibiotic treatment [9]. For many clinicians, however, translating ASB and UTI treatment guidelines to the bedside proves difficult when faced with a "positive" urinalysis or urine culture result [10,11]. In a pilot study, our research team demonstrated that a positive urine culture led to 35% of ASB cases being treated with unnecessary antibiotics in the SCI population [12]. Overtreatment of ASB promotes the development of multidrug-resistant organisms and *Clostridioides difficile* infections, both of which occur frequently in the SCI population [13-16].

Accurately distinguishing between UTI and ASB based on clinical practice guidelines is cognitively taxing in the non-SCI population; the challenge is even greater for accurately diagnosing UTI in persons with SCI [17]. Persons with SCI often do not present with typical infection signs and symptoms (ie, dysuria, suprapubic pain, urinary frequency) due to lack of sensation and bladder management strategy. The Infectious Diseases Society of America (IDSA) guidelines include SCI-specific signs and symptoms such as increased spasticity and autonomic dysreflexia [18] in their decision algorithms for UTI diagnosis [19], but limited evidence on the sensitivity and specificity of these symptoms exists.

Patients and providers alike have difficulty determining which signs and symptoms arise from UTI. Several studies have shown that patients with SCI are often inaccurate when identifying when an UTI is present, with an accuracy rate between 61% and 66% [20,21]. Okamoto et al [22] performed a qualitative study of intermittent catheterization users to understand their views of signs and symptoms of UTI, finding that users had difficulty distinguishing UTI symptoms from symptoms of their comorbidities. Our research team recently completed a mixed methods analysis exploring Veterans Health Administration (VHA) SCI providers' knowledge and attitudes toward distinguishing ASB from UTI with nearly one-third of all participants endorsing non-IDSA guideline–recommended triggers for obtaining a urine culture (ie, change in urine color, cloudiness, or odor) [23]. The type of organism identified on culture drove unnecessary antibiotic use; 57% would treat ASB if caused by extended-spectrum beta-lactamase *Escherichia coli* [23]. Interview analysis identified how the limited recall of clinical practice guidelines for ASB and UTI content among SCI providers was a potential barrier to their use [23].

An antibiotic stewardship program is defined as "a multidisciplinary activity that includes appropriate selection, dosing, route, and duration of antimicrobial therapy" [24]. The Centers for Disease Control and Prevention has called for immediate, nationwide improvements in infection control and antibiotic prescribing to prevent increasing drug-resistant infections [25]. The United Nations recently convened a general assembly to address the global concern of antibiotic resistance, the fourth instance of such a high-level meeting for a health issue since its inception [26]. Therefore, a risk score that improves the accuracy of UTI diagnosis and minimizes the overtreatment of ASB would be a high-value stewardship tool in the SCI population.

Impact of Cardiovascular and Immunologic Changes

Quantification of the impact of cardiovascular and immunologic changes on vital signs and routine laboratory tests is a knowledge gap. The pathophysiology of autonomic nervous system changes leading to cardiovascular abnormalities after SCI have been well described [27,28], but there is little information quantifying the degree of change or expected values for vital sign readings in the SCI population. Disruption of the sympathetic nervous system in cervical and high thoracic level injuries leads to vasodilation and orthostatic hypotension, risk of autonomic dysreflexia, bradycardia, and impaired thermoregulation [28]. In order to develop an accurate diagnostic tool to identify severe UTI, having a better sense of the expected

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values of vital sign readings for the various neurologic levels of SCI is crucial.

Numerous authors have described the multi-organ dysfunction and systemic inflammation present after SCI. The genitourinary tract is especially affected due to the development of neurogenic bladder, kidney damage, and UTI [29,30]. SCI-induced immune depression is thought to be caused, in part, by disruption of the autonomic nervous system [31]. There is emerging evidence that episodes of autonomic dysreflexia also contribute to immune suppression after SCI [32]. In summary, what is normal for a person with SCI, in terms of vital signs and routine lab results, may differ at baseline from similar signs and laboratory measurements in the non-SCI population. Determining whether derangements in vital signs and lab tests in a person with SCI are indicative of UTI requires that we first establish what is normal in persons with SCI.

Identifying Baseline Physiologic Measurements

The impact of SCI on baseline vital sign and laboratory values has not been determined or measured systematically once the patient is beyond the acute injury. Most of the baseline physiologic measurements used to diagnosis abnormality in SCI are extrapolations from the non-SCI population [32,33]. Quantifying the normal values in chronic SCI will help investigators answer further questions about the autonomic and immunologic influences of SCI and its impact on diagnosing UTI after SCI.

Framework for Identifying Clinically Meaningful Infections

This study draws on established concepts of identifying and stratifying disease severity and infection requiring hospitalization. The Acute Physiology and Chronic Health Evaluation-II (APACHE-II) score uses a point score based on the initial values of 12 routine physiologic measurements, age, and previous health status to provide a general measure of the severity of disease. The score can also be tracked over time to predict mortality. Vital sign values such as temperature, heart rate, and respiratory rate and laboratory values such as white blood count and serum creatinine are given points depending on whether they are in the high abnormal or low abnormal range [34]. As described, however, physiologic ranges for these measurements after SCI have not been established.

To bridge this gap in the literature, this study aims to (1) establish physiological baseline vital sign measurements after SCI and (2) determine the positive predictive value (PPV) of those baseline vital signs and lab measurements and to create a threshold for clinically meaningful UTI after SCI.

Methods

Rationale

Figure 1 provides the rationale for each aim proposed in this study, as well as how the work of this study will guide further research. The aims build upon, but are not dependent on, each other and will support the robust development of a risk score to help make the diagnosis of UTI after SCI more objective.

Figure 1. Building the foundation toward the objective diagnosis of urinary tract infection after spinal cord injury (SCI; ODUS) risk score.

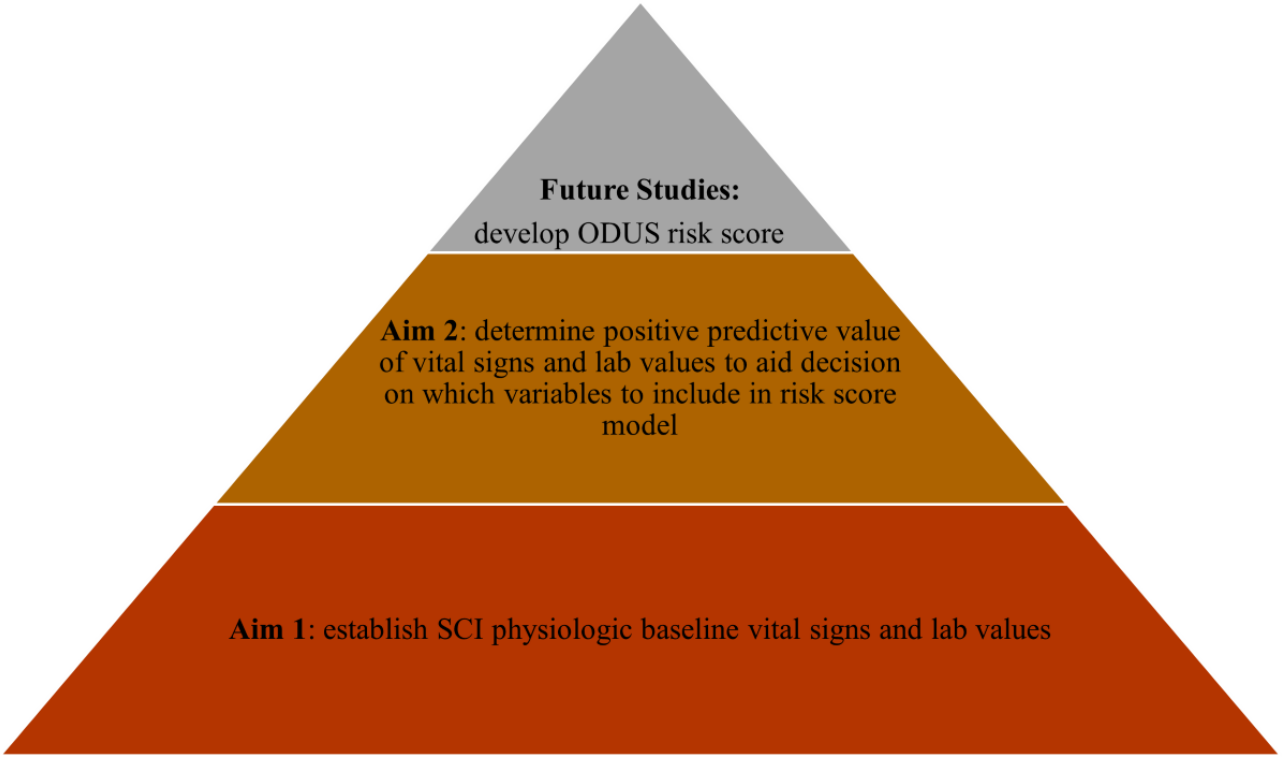

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Aim 1 Data Extraction (Year 1)

Data will be extracted from the national Veterans Health Administration (VHA) Spinal Cord Injuries & Disorders (SCI/D) Registry (SCIDR) and VHA Corporate Data Warehouse (CDW) from 2018 through 2019 to establish the physiologic baseline for vital sign and lab measurements after SCI. SCIDR is a large SCI/D registry used as a case identification platform for VHA patients that can directly be linked to CDW and all other VHA health care data [35]. CDW is a national repository that includes clinical and administrative data from VHA. Data are stored in a relational database (ie, data are grouped into several domains that are structured to recognize relations among the stored information) and are updated on a continual basis [36]. We will use data from these domains within CDW to obtain the vital signs and laboratory values listed in Table 1. Urinalysis tests are done routinely with healthy veterans with SCI due to national guidelines [37] and not infrequently with other veterans within Veterans Affairs (VA) due to the high incidence of genitourinary concerns [38]. Sociodemographic data including age, race, ethnicity, neurologic level of injury, sex, and medical comorbidities will be used to construct a Deyo comorbidity index.

Table 1. Vital sign and laboratory values to be examined.

Outcome variable name	Type of variable	Comments
Vital signs		
Systolic blood pressure	Continuous	This is found in the CDW[a] Outpatient Vital Sign Domain.
Diastolic blood pressure	Continuous	This is found in the CDW Outpatient Vital Sign Domain.
Heart rate	Continuous	This is found in the CDW Outpatient Vital Sign Domain.
Temperature	Continuous	This is found in the CDW Outpatient Vital Sign Domain.
Respiratory rate	Continuous	This is found in the CDW Outpatient Vital Sign Domain.
Urinalysis results		
White blood cell count	Continuous	This is found in the CDW Micro Domain.
Red blood cell count	Continuous	This is found in the CDW Micro Domain.
pH	Continuous	This is found in the CDW Micro Domain.
Nitrites	Categorical (present/absent)	This is found in the CDW Micro Domain.
Leukocyte esterase	Categorical (present/absent)	This is found in the CDW Micro Domain.
Peripheral blood results		
White blood cell count	Continuous	This is found in the CDW Outpatient Lab Domain.
Hemoglobin	Continuous	This is found in the CDW Outpatient Lab Domain.
Platelets	Continuous	This is found in the CDW Outpatient Lab Domain.
Creatinine	Continuous	This is found in the CDW Outpatient Lab Domain.
Blood urea nitrogen	Continuous	This is found in the CDW Outpatient Lab Domain.
Glucose	Continuous	This is found in the CDW Outpatient Lab Domain.

[a]CDW: Corporate Data Warehouse.

Aim 1 Approach

We used a case-control retrospective study design. We included healthy Veterans with SCI (cases: n=2000) as well as healthy Veterans without SCI (controls: n=2000), seen in the outpatient clinic setting in 2018 and 2019. The cases and controls were randomly sampled and frequency matched based on the variables listed in Table 2. Cases and controls were excluded if the encounter has any International Classification of Diseases, Tenth Revision (ICD-10) code for an infectious disease (see Multimedia Appendix 1). Cases were adults aged 18 years and older with an SCI diagnosis confirmed via the SCIDR registry plus the presence of an SCI/D Annual Exam. Controls were adults without an SCI diagnosis confirmed by ensuring they were not on the SCID Annual Exam Reports. This study will conform to all STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for a case-control study and will report the required information accordingly.

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Table 2. Variables for frequency matching of cases and controls.

Variable name	Type of variable	Comments
Age	Continuous	This is found in the CDW[a] Age domain.
Sex	Categorical (male/female)	This is found in the CDW Sex domain, and we oversampled female SCI[b] cases to reflect the general population.
Race	Categorical (white/Black/other)	This is the convention we have used in previous studies based on the typical distribution of the study population.
Ethnicity	Categorical (Hispanic/not Hispanic)	This is found with the domains.
Deyo comorbidity index	Continuous	This is generated by using medical comorbidities extracted from CDW domains.

[a]CDW: Corporate Data Warehouse.

[b]SCI: spinal cord injury.

Aim 1 Statistical Analysis

The primary exposure is SCI and categorical. Descriptive statistics for each group will be calculated, including mean and SD (continuous variables) and frequency counts and percentages (categorical variables). Depending on the distribution, *t* tests or Mann-Whitney *U* tests will be used to compare the means of continuous variables of the cases to those of the controls. Chi-square tests will be used to compare categorical variables between cases and controls. Each laboratory variable will be regressed on a dummy variable indicating group membership (SCI vs non-SCI) along with potential confounding variables including age, gender, race/ethnicity, and neurologic level of injury for the cases (ie, tetraplegia and paraplegia), and standard model assessment practices (eg, examination of residuals) will be used to ensure assumptions are met and the logistic regression model is appropriate [39]. Each regression model will serve 2 purposes: (1) A test of the group membership indicator will assess group differences between patients with SCI and control patients, and (2) using marginal effects analysis, population marginal means and their confidence intervals will be derived from the models to serve as covariate-adjusted estimates for normed values among patients with SCI [40]. Marginal effects make logistic regression analysis results more easily understood, by expressing the change in probability that the outcome occurs as the risk factor changes by 1 unit while holding all the other explanatory variables constant [40].

There are numerous methods to determine a minimal clinically important difference (MCID), and each method has its pros and cons [41]. We will use the distribution-based method for our study, because it considers measurement error, is readily implemented, and is easy for others to understand. There is no golden criterion to judge MCID by distribution method so far. Based on work by Kallogjeri et al [42], we will use these definitions for MCID: 0.2 SD as a small difference, effects around 0.5 SD as moderate, and effects as large as 0.8 SD or larger as large differences.

With the anticipated sample size drawn from CDW, we expect 80% with an effect size of 2% after accounting for variance explained by as many as 10 confounding variables and an α of .05. This is in accordance with the commonly cited guideline for a small effect size [43].

Aim 2 Data Extraction (Year 1-2)

Data for Aim 2 will also be extracted from CDW outpatient encounters from 2018 to 2019 to determine the PPV of the physiologic vital sign and lab measurements for clinically meaningful UTI after SCI. SCI diagnosis will again be confirmed using the SCIDR Registry. The same variables will be extracted from CDW domains as listed in Table 1. In addition, urine culture results, signs and symptoms of UTI, and bladder management strategies (ie, spontaneous voiding, indwelling catheters-intraurethral, intermittent catheterization) will be extracted from CDW through in-depth chart review by 2 members of our study team. Basic demographic and comorbid conditions will also be extracted from CDW as described in Aim 1.

Aim 2 Approach

We will use a retrospective cohort study design. The cohort will include a national random sample of Veterans with SCI seen in the outpatient setting (n=400). Through chart review of the electronic health record, each eligible encounter will be classified as having ASB, having a UTI, having neither, or indeterminate using a validated algorithm developed by our team and previously used in this patient population; it showed high reliability between expert and nonexpert clinicians when the algorithm was used [17,44]. The algorithm incorporates IDSA guidelines for UTI symptomatology in SCI as well as the IDSA recommended interpretation of culture results based on the organisms per mL reported on the urine culture [44]. The first step of the validated algorithm is to determine the presence of signs or symptoms of UTI, which our team will determine through examination of the electronic medical record. We will continue to follow the algorithm by referring to encounters during the study time period until a final classification is assigned for each person in the cohort. This study will conform to all STROBE guidelines for a cohort study and will report the required information accordingly.

Aim 2 Statistical Analysis

Using the moderate MCID of vital sign and laboratory values determined from Aim 1, the PPV will be calculated as the ratio of the proportion of all those screened who meet the criteria for UTI and a positive test (ie, moderate MCID value for blood pressure and heart rate) to the proportion of all those screened who have a positive test. A similar analysis method was used

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by Massa et al [20] to determine predicative signs and symptoms of UTI after SCI. The 95% CIs of the PPV will be calculated using a binomial distribution.

The sample size was calculated using a 30% expected prevalence of UTI and a 0.05 precision.

Ethical Considerations

This study has institutional review board approval, which covers secondary analysis without additional consent from Baylor College of Medicine (H-50481) and the Veterans Health Administration (22A07.H). An informed consent waiver was approved by the institutional review board, as data will be deidentified upon extraction to protect patient privacy.

Results

Study Progress

This study was funded in May 2023, with initial data extraction starting in early 2024 and expected completion in 2026. Data extraction, analysis, and results for the 4000 records (cases: n=2000; controls: n=2000) for Aim 1 were completed upon submission of this manuscript. Data extraction for Aim 2 began in year 1, and analysis and results will continue in year 2.

Dissemination Plan

Plans for dissemination include presentation of results at SCI and Physical Medicine and Rehabilitation conferences, sharing findings with the Paralyzed Veterans of America and local Veterans Engagement Board, and sharing results with VA SCI team members through cyber seminars.

Discussion

Principal Considerations and Anticipated Results

There is a pressing need for more targeted and efficient diagnosis and management of UTIs in the SCI population. SCI-specific tools and protocols can be invaluable for achieving better patient outcomes, reducing unnecessary antibiotic treatments, and improving the overall quality of life for these patients. There is not currently a standardized risk score for identifying UTIs in the SCI patient population, which this study aims to address.

Aim 1 Anticipated Results

We anticipate that mean blood pressure, heart rate, temperature, serum creatinine levels, and hemoglobin levels will be lower in the SCI cases than in the non-SCI controls. Mean serum white blood count, glucose levels, and urine white blood cells will be higher in the SCI cases than in the non-SCI controls.

Aim 1 Potential Pitfalls and Alternative Approaches

Extracting and refining data from relational databases can be challenging, but our entire study team has experience with doing so. The principal investigator, who is also the data analyst, for this proposal has been extracting SCI-specific data for her current career development award; over 7000 SCI cases have been identified with the desired values. Because of the large number of SCI cases, we will be able to oversample for women and minorities to overcome the limitations of the VA SCI population (largely male and white) to make our sample more representative of the general population. The CDW database results will be validated by chart review of 100 cases and 100 controls for accuracy.

Even if no difference is found in vital sign and lab measurements for people with SCI compared with non-SCI controls, this will be a valuable contribution to the field of knowledge, and Aim 2 can still proceed with a solid foundation on this knowledge.

Aim 2 Anticipated Results

The PPVs of moderately MCID pyuria, systolic blood pressure, and temperature will be high for UTI after SCI.

Aim 2 Potential Pitfalls and Alternative Approaches

By using a nationwide sample, we will have an abundance of SCI cases, allowing us to oversample for women and minorities to overcome the limitations of the VA SCI population (largely male and white) in order to make our sample more representative of the general population. By taking this rigorous approach, we will ensure that the variables with the highest PPV will be included in the development of the risk score.

Comparison With Previous Work

Although previous work looked at and showed fever and autonomic dysreflexia having high sensitivity (99%) for UTI in the SCI patient population [20], this study will look more closely at specific lab values and vitals, such as urine and serum white blood cells in a much larger patient population. This study aims to first establish baseline labs including various urine and blood serum markers and vitals after SCI injuries, such as temperature and heart rate. The study then will create an objective risk score to better help differentiate between ASB and UTI in the SCI patient population.

Current Limitations

The VA SCI population will not be fully representative of the entire patient population with SCI injuries. There will also be limitations inherent to use of the electronic health record data [45]. The accuracy and reliability of the encounter data are reliant on the diligence of the clinician or health care professional imputing the information. However, any human error in data input would likely be random and not systematic in nature, resulting in only a dilution of our study findings. As further limitations arise in our study, we aim to address them.

Conclusion

This study will provide the foundation for our future work of developing a risk score to help improve accuracy of the diagnosis of clinically meaningful UTI after SCI. This work in turn will help guide antibiotic use in the SCI patient population, providing much needed stewardship in this vulnerable population and preventing antibiotic overuse in this population.

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Acknowledgments

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Data Availability

Data sharing is not applicable to this article as no data sets were generated nor analyzed during this study.

Authors' Contributions

FS acquired the funding. FS and BT conceptualized that study. LG was responsible for the methodology. FS and JP wrote the original draft of the manuscript. All authors reviewed and edited the manuscript draft.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Exclusion ICD-10 Codes for Infectious Diseases.
[DOCX File , 16 KB - resprot_v14i1e52610_app1.docx]

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Abbreviations

APACHE-II: Acute Physiology and Chronic Health Evaluation-II
ASB: asymptomatic bacteria
CAUTI: catheter-associated urinary tract infection
CDW: corporate data warehouse
ICD-10: International Classification of Diseases, Tenth Revision
IDSA: Infectious Diseases Society of America
MCID: minimal clinically important difference
PPV: positive predictive value
SCI: spinal cord injury
SCI/D: Spinal Cord Injuries & Disorders
SCIDR: Spinal Cord Injuries & Disorders Registry
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
UTI: urinary tract infection
VHA: Veterans Health Administration

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Protocol

Telenursing Health Education and Lifestyle Modification Among Patients With Diabetes in Bangladesh: Protocol for a Pilot Study With a Quasi-experimental Pre- and Postintervention Design

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Abstract

Background: The global burden of chronic diseases is increasing and becoming a public health issue throughout the world. The use of telenursing is increasing significantly during and after the COVID-19 pandemic to treat and prevent chronic diseases. Telenursing is growing in many countries to reduce health care costs, increase the number of aging and chronically ill populations, and increase health care coverage to distant, rural, small, or sporadically populated regions. Among its many benefits, telenursing may help to solve increasing shortages of nurses, reduce distances, save travel time, and keep patients out of the hospital.

Objective: The objective of this study is to apply the self-management telenursing program and telenursing system developed by the researchers to Bangladesh and to evaluate its feasibility and efficacy (improved diabetes control in participants).

Methods: This is a pilot, quasi-experimental pre- and post-intervention study. Diabetes patients who will attend the Grameen Primary Health Centers (PHCs) in Bangladesh will be enrolled between September 2024 and August 2025. We include patients who have been diagnosed with type 2 diabetes, both sexes, ages 18-75 years old, all types of treatment, willing to participate and give us consent. We exclude patients who have been diagnosed with gestational diabetes, diabetes as a secondary cause, complication of chronic kidney disease (CKD) stage 5, Hemoglobin A1c (HbA_{1c}) is less than 7% for the past 1 year with CKD stage 1 or 2, no complications or complications with good control, having enough knowledge (had education before) and implemented good practice regarding diabetes management assessed by the research nurses, and disabled persons who need other person's support for daily living. The sample size was calculated and found 70. Written informed consent will be obtained from all the participants. The study protocol got approval from the National Research Ethics Committee of the Bangladesh Medical Research Council (BMRC/NREC/2022-2025/336) on September 08, 2024. The outcome of this study is to evaluate the effects of telenursing intervention by controlling HbA_{1c}.

Results: The project was funded in 2024. The enrollment of the participants started on October 26, 2024, and the required sample (n=70) enrollment was completed in February 2025. Data analysis will be started after completion of data collection and results will be expected to be submitted for publication in 2026.

Conclusions: Diabetic patients will acquire disease-specific management skills. Setting and monitoring goals ensures the continuation of the desired behavior and gives the patients control over their lifestyle. After developing self-management skills, patients assess their lab data and lifestyles including diet, and understand their condition so that they can work with their physiological data by acquiring knowledge of both the disease and self-care. By making self-supported decisions, the patients will be able to manage their diet, exercise, and medication.

Trial Registration: ClinicalTrials.gov NCT06632652; https://clinicaltrials.gov/study/NCT06632652

International Registered Report Identifier (IRRID): DERR1-10.2196/71849

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(JMIR Res Protoc 2025;14:e71849) doi:10.2196/71849

KEYWORDS

telenursing; health education; lifestyle modification; diabetic patients; Bangladesh

Introduction

Background

The global burden of noncommunicable diseases (NCDs) is increasing and becoming a public health issue throughout the world [1]. Globally, diabetes caused 1.6 million deaths and 47% of all deaths before the age of 70 years in 2021. Diabetes increases the risk of death from kidney and cardiovascular diseases [2]. The prevalence of diabetes has been increasing over the last few decades in all countries and is considered a global epidemic [3], more quickly in low- and middle-income (LMICs) countries than in high-income countries. Moreover, diabetic treatment coverage was the lowest in the low- and middle-income range in 2022 [4]. It is alarming that an estimated half of the global people (49.7%) living with diabetes remain undiagnosed [5]. Diabetes has acute complications including ketoacidosis, hypoglycemia, or hyperglycemia. Chronic complications are macroangiopathy, retinopathy, nephropathy, neuropathy, and diabetic foot. Patients with diabetes are vulnerable to infections, myopathy, osteoporosis, arthropathies, and liver damage [6]. Patients with diabetes may be able to prevent or delay diabetic health problems by maintaining a healthy lifestyle, taking medicine regularly, and controlling blood glucose levels [7].

The use of telenursing is increasing significantly during and after the COVID-19 pandemic to treat and prevent chronic diseases [8]. As a field, it is part of telemedicine and has many points of contact with other medical and nonmedical applications, such as telediagnosis, teleconsultation, and telemonitoring. The field, however, is still being developed as the information on telenursing is not comprehensive enough [9].

Telenursing has been adopted by many developed and developing countries. It reduces health care costs and increases the coverage of health care to outreach, rural, small, or sporadically populated regions [10]. It is useful for the increasing number of aging and chronically ill populations [11]. Among its many benefits, telenursing may help solve increasing shortages of nurses [12]; to reduce distances and save travel time and keep patients out of hospital [10]. A greater degree of job satisfaction has been registered among telenurses [13]. Continuous glucose monitoring (CGM) in patients with diabetes by integrating diagnostic devices for 24-hour real-time data transmission [14] and IBM Watson Health for personalized lifestyle optimization can help to identify and prevent the early appearance of diseases. It allows rural patients to receive personalized, high-quality care and improves health care access and outcomes [15].

Diabetes in Bangladesh

The prevalence of diabetes was 9.2% (male: 8.8%, female: 9.6%) and prediabetes was 13.3% (male: 13%, female: 13.6%) in 2017. Among the patients, only 30.4% had controlled diabetes, 35.2% took treatment regularly and 61.5% were not aware of their diabetic condition. The factors related to getting diabetes were increasing age, overweight, and hypertension. The proportional mortality was 3% from diabetes of total death in all ages. In Bangladesh, 17% population was overweight (male: 14.4%, female: 19.6%), 3.3% were obese (male: 2%, female: 4.6%), and 25.1% had physical inactivity (male: 9.2%, female: 41.3%), those are the related risk factors for diabetes [16]. For the national response to diabetes, Bangladesh has an operational policy, strategy, and action plan for controlling diabetes and reducing physical inactivity, but not for reducing overweight and obesity. There are evidence-based national diabetes guidelines available, but not fully implemented. There are no set standard criteria for referral of patients from primary care to higher levels of care. In the primary care facilities, there are only blood glucose measurements and urine strips for glucose and ketone measurements generally available, but no facilities for insulin, metformin, sulphonylurea, oral glucose tolerance test, hemoglobin A_{1c} (HbA_{1c}) test, dilated fundus examination, retinal photocoagulation, foot vibration perception by tuning fork, renal replacement therapy by dialysis, foot vascular status by Doppler, renal replacement therapy by transplantation in 2016 [17].

As there are no standard criteria for referring patients from primary care to a higher level of care, we will facilitate the patients to acquire self-management skills to understand the risk factors for diabetic complications and seek treatment in referral hospitals as necessary. They can attend referral hospitals to prevent diabetic complications by doing HbA_{1c} tests, dilated fundus examinations, retinal photocoagulation, foot vibration perception by tuning fork, renal replacement therapy by dialysis and transplantation, and also foot vascular status by Doppler.

Study Objectives

General Objective

To apply the self-management telenursing program and telenursing system developed by the researchers to Bangladesh to evaluate its feasibility and efficacy (improved diabetes control in participants)

Specific Objectives

- To control patients' diabetic condition by measuring HbA_{1c}.
- By having them acquire self-management behaviors and increase their self-efficacy, to minimize the risk of arising diabetic complications.
- To see the feasibility and barriers to implementing telenursing among patients with diabetes in Bangladesh.

Research Questions

Whether implementing a health education program will improve diabetic patient outcomes or not and will be operational and acceptable by the patients and health care professionals in Bangladesh.

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Hypothesis

1. The diabetes self-management program developed by the researchers cannot improve the participants' management of their diabetes (avoid aggravation, develop complications, and hospitalization) (H_0) or can improve the participants' management of their diabetes (H_1).
2. Is the telenursing system developed by the researchers operational in Bangladesh? Can the system be used by health care personnel (nurses) and patients? What are the obstacles and challenges, if any, in using the system?
3. Is the diabetes self-management program developed by researchers acceptable to health care providers and patients? How about engagement? Will the program be continued (will there be dropouts)? If so, what are the reasons?

Methods

Design and Period

A pilot study with a quasi-experimental pre- and postintervention design will be implemented. As we will try to explore the participants' characteristics, we want to conduct a pilot study to see the feasibility of this project among these participants. We plan to conduct quasi-experimental pre- and postintervention design, as we found in this setting randomization; case-control is rather difficult. Therefore, we will enroll the participants and collect baseline data and then we will educate them, and after 6 months we will evaluate them and compare the baseline (pretest) and the endline (posttest) data of individual participants. We set 6 months, as a previous study showed that a patient's behavioral modification requires at least 6 months of intervention [18]. The study duration will be 1 year after getting approval from the Ethical Committee.

Study Participants

The participants are people with diabetes, who take services from Grameen primary health centers (PHCs). We use 2 PHCs from Sahorail and Jamshahat of Manikganj District in Bangladesh.

Inclusion Criteria

The inclusion criteria are as follows:

- Having been diagnosed with type 2 diabetes
- Being of either sex
- Being 18-75 years
- Having a smartphone or mobile phone
- Willingness to participate and give us consent

Exclusion Criteria

The exclusion criteria are as follows:

- Patients who have been diagnosed as type 1 and gestational diabetes
- Patients whose diabetes are secondary causes
- Patients who have complications of chronic kidney disease (CKD) stage 5
- Patients whose HbA_{1c} has been less than 7% for the past 1 year with CKD stage 1 or 2, with no complications or complications with good control, have enough knowledge (had education before) and implemented good practice regarding diabetes management assessed by the research nurses (hereafter "the nurses")
- Disabled persons who need other people's support for daily living

Sampling Technique

We will use a purposive sampling technique to select the participants. Patients who meet the eligibility criteria will be introduced by physicians at the PHCs, and the nurses will contact them at the PHC and obtain their consent.

Sample Size

We calculated the sample size using G*Power software (version 3.1.9.7; Heinrich-Heine-University). As this is a pilot study, we set an effect size of 0.39 considering the differences between 2 dependent matched pair means of HbA_{1c} from a previous study [19], with a level of significance of 5%, and 80% power, the total sample size is calculated at 54. As patients have many options to discontinue the study (consent, withdraw, migration, change the health care facilities based on the disease severity, complications, hospitalization, etc), we consider a 30% dropout (16 participants) for this study. Therefore, the total sample size is estimated to be 70 (Textbox 1).

Textbox 1. Output of software after generating sample size calculation.

Effect size dz = 0.39

α err prob = 0.05

Input: Tail(s) = 2

Power (1-β err prob) = 0.80

Output: Noncentrality parameter δ = 2.8659030

Critical *t*= 2.0057460

Df = 53

Total sample size = 54

Actual power = 0.8033525

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Method of Data Collection Procedures

The principal investigator (PI) and co-investigators (telenurses) received training in telenursing such as communication and behavior modification techniques, and self-management skills on diabetes including blood sugar control and foot care. They will receive study-specific training from other coinvestigators and one diabetic consultant on data collection such as how to collect data and what type of tool has to be used during data collection. The patients who will attend the PHCs and telenurses will identify the patients with diabetes by checking the patient's blood test report. They will check the participants' eligibility criteria (inclusion and exclusion criteria) and obtain written informed consent. It will be ensured that there will be no risk in disclosing the information.

They will educate patients using an investigator-developed "Education Booklet" at the PHCs. The booklet will be given to the patients after receiving consent and health education will be provided at the time as scheduled (Multimedia Appendices 1 and 2). The data will be collected within a 6-month study period using:

1. "Initial assessment sheet" developed by the investigators. It will be filled out once by the telenurses in the PHCs to assess the patient's initial condition and to set the goals for their behavior change. This contains sociodemographic, clinical history, and lifestyle.
2. "Self-monitoring book" developed by the investigators (Multimedia Appendix 3). Patients will complete their daily life activities including their laboratory investigation reports at home. The telenurses will educate and guide them on how to fill it over telecommunication. This contains daily practice goals (eg, energy intake, salt, exercise, ideal weight), laboratory data record (eg HbA_{1c}, fasting blood sugar [FBS] or random blood sugar [RBS], lipid profile, and renal function), foot care (monthly check), daily recording (RBS if needed, blood pressure, medication intake, daily goal achievement of diet and exercise) and behavior change goals (monthly).
3. "Diabetes management self-efficacy scale" developed by Bijl et al [20] and has 20 items with a 5-point Likert scale from 1-5. The scores range from 20 to 100, a higher point indicates better self-efficacy.
4. The "Lifestyle behavior questionnaire" developed by the investigators has 6 items with a 6-point Likert scale from 0 to 5, a higher point indicates a better lifestyle. This is asked every month to check their behavior by the telenurse.
5. "Patient Satisfaction" on tele-education and prepared materials developed by the investigators. It has 6-item with a 6-point Likert Scale, and higher indicates more satisfaction.
6. A "Monthly outcome checklist" was developed by the investigators (Multimedia Appendix 4). The telenurses interview patients monthly asking about education material use, goal attainment, and complication management. The engagement rate and follow-up rate also will be counted every month by the telenurses.

All of the above except Diabetes management self-efficacy scale (number 3), was reviewed by the investigator team with the telenursing, diabetes, and chronic care nursing specialists for validity.

Data on all complications of diabetes will be asked of the patients by the investigators and check the accuracy of the information from the records.

Research Collaboration Framework

We will use the telenursing model with the collaboration of the Hiroshima University telenursing center and the Nursing Research Center of Grameen Caledonian College of Nursing (GCCN) (Figure 1).

Figure 1. Research collaboration framework.

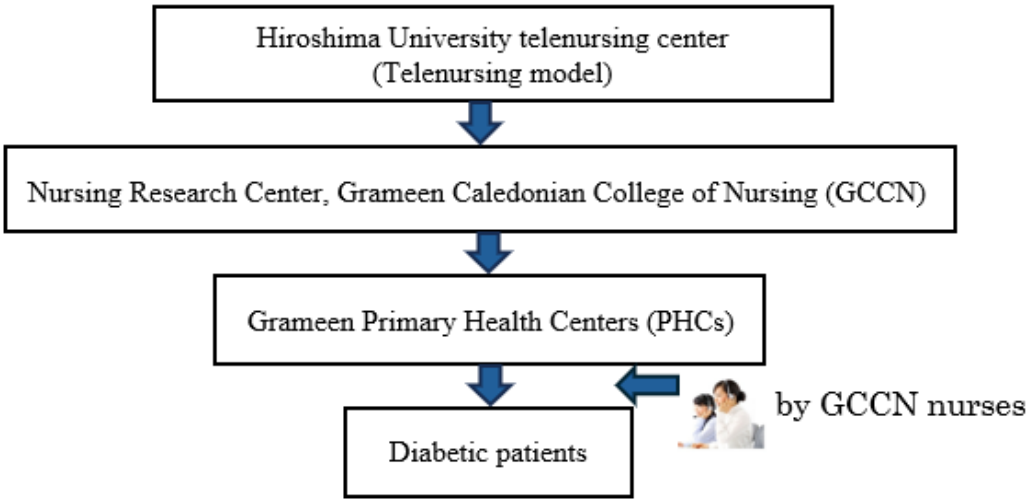

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Intervention

Operational Definition of Self-Management and Structure of the Self-Management Program

The focus of this program is the acquisition of self-management skills, operationally defined in Figure 2. First, the patients analyze their laboratory data and lifestyles including diet, and understand their condition so that they can work with their physiological data by acquiring knowledge of both the disease and self-care. By making self-supported decisions, the patients can manage their diet, exercise, and medication. They also acquire disease-specific management skills. Setting goals and then monitoring them ensures the continuation of the desired behavior and gives the patients control over their lifestyle [19].

Figure 2. Structure of the self-management program.

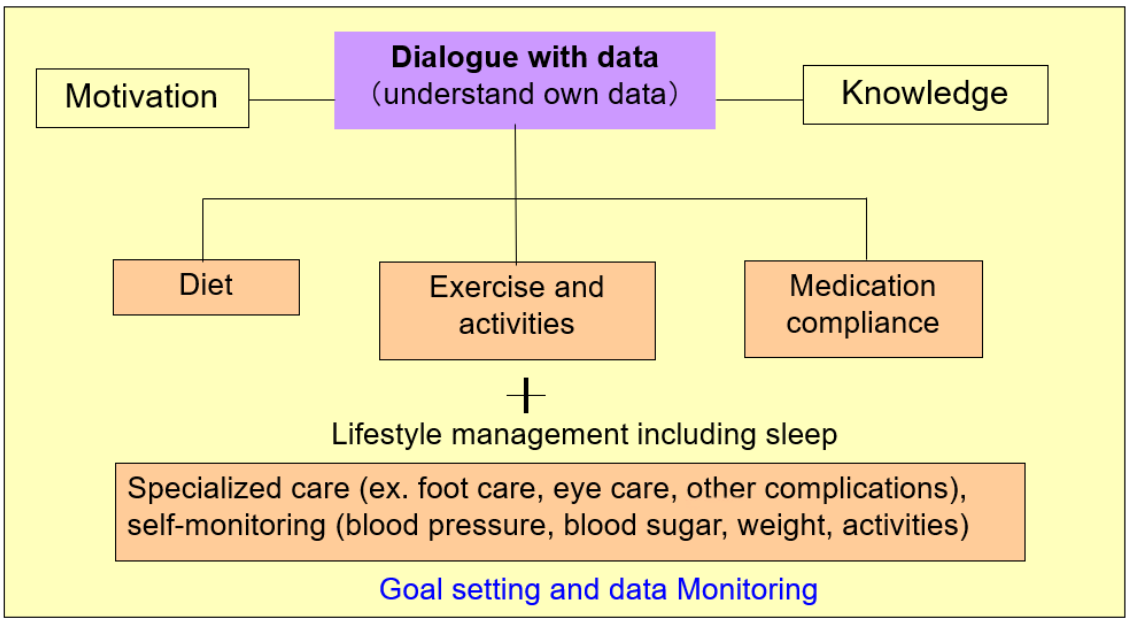

Process of Providing Education

Figure 3 shows the 6-month program process. Because of the pilot study, we set a program for 6 months.

Right after the nurses obtain consent from participants, the nurses conduct the initial assessment using an "Initial assessment sheet" and provide educational materials ("Education booklet" and "Daily monitoring notebook"). If needed, a weight machine, BP machine, medication box, salt measurement spoon, foot care set (monofilament, mirror, nail cutter, nail file, and socks), and eye check chart will be provided. If needed, a blood glucose meter is rented to the patients.

Group education (1 group of less than 20 patients) will be provided at the PHC by the nurses on the scheduled date (1 group education is set for 2 hours).

One week after the group session, telephone calls from the nurses (telenursing education) will be provided weekly on the first month, then biweekly from the second month to the six month. The nurses will contact patients periodically over the telephone, smartphone, or tablet and follow-up on their regular dietary behavior, physical activities, and medicine compliance. They will check clinical examination and laboratory test reports, self-monitoring data, and behavior changes.

Figure 3. The 6-month program process.

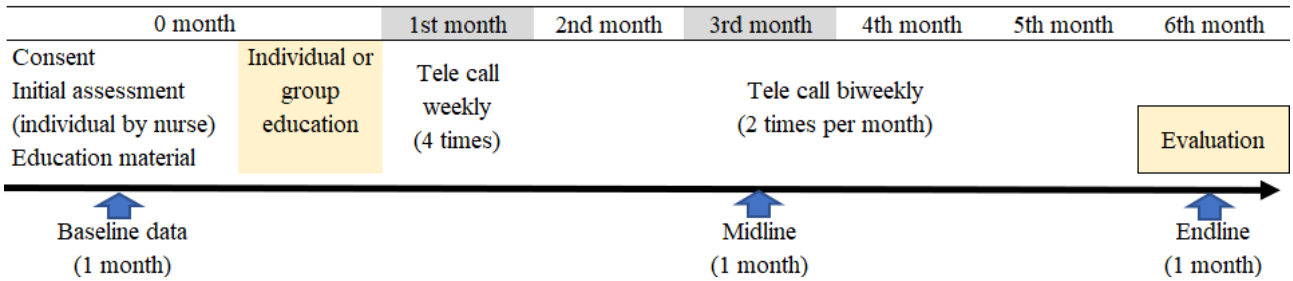

In the third month, patients are requested to visit the PHC for regular follow-up by physician and laboratory test. In the sixth month group evaluation for 1 hour and endline data will be collected by the nurses at the PHC.

Patients will start implementing diabetes management right after group education. Each patient will develop monthly goal settings (behavior change plan) related to their diabetes management, daily practice them, and record the results every day in the self-monitoring notebook. The nurses call each patient on the scheduled day, ask about his or her behavior changes and monitor data, then make "step-up goals" for the next month. In addition, based on his or her knowledge and practice level, the nurses provide education using the education booklet. Patients and nurses repeat these activities for 6 months.

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Outcomes and Data Collection Schedule

Since this is a pilot study, we set various indicators (Multimedia Appendix 5). The primary outcome is set as a change in HbA_{1c}. As the secondary outcomes, we set various evaluation indicators. The data collection schedule is also set in Multimedia Appendix 5.

Sociodemographic data, clinical history, and lifestyle are taken at the initial assessment (Initial assessment sheet). Satisfaction is measured by the Likert scale (Satisfaction scale). Achievement of monthly goals is measured by percentage. Behavior change is measured by the researcher-developed scale (Lifestyle behavior questionnaire). Self-efficacy is measured by the Diabetes Management Self-Efficacy Scale.

Qualitative data will be interviewed, described, or recorded when it occurs. Engagement and follow-up rate, education material used, complication management, and "patients who have achieved HbA_{1c} in recommended level" will be counted. Cost-effectiveness will be calculated.

Statistical Analysis

Descriptive statistics will be expressed as frequencies and percentages for categorical variables and mean with SD or median with quantile, distribution, and range for the continuous variables. To compare the categorical variables between pre- and postdata, the chi-square test will be performed. To compare feasibility and efficacy (pre and post), continuous variables will be compared by paired *t* test or one-way ANOVA for the normally distributed and or McNemar test or Wilcoxon signed-rank sum test for the not normally distributed variables after checking the data normality. Qualitative data will be described and categorized if necessary. Statistical significance will be set as <0.05. Data will be analyzed using IBM SPSS Statistics for Windows, Version 25.0 (IBM Corp).

Ethical Considerations

This study was approved by the institutional review board of the Bangladesh Medical Research Council (BMRC/NREC/2022-2025/336). The researcher will explain the consent procedures including the purpose, procedure, confidentiality, right to withdraw from the study, risk, and benefits, and will obtain written informed consent (ICFs) individually from all the participants. To maintain privacy and confidentiality, data will be collected anonymously. The data will be stored on two password-protected computer sets in the GCCN research room. After deleting all personal identifying information, anonymized data will be used for data analysis, so that research participants will not be identified. To participate in this study, we will not provide any money to the participants. We will provide all the treatments free of cost. As there is no risk or minimum risk to participate in this study, therefore, we will not provide any compassion to participate in this study. We ensure that identifiable features of research participants in any images of the manuscript or supplementary material will not be visible.

Interpretation

Data will be cleaned, organized, and verified by investigators as well as checking for any missing data or error data. Then analyze, interpret the findings, conclude, recommend dissemination, and further publication.

Training of the Study Nurses

The study nurses received overseas telenursing training on materials development and telenursing services. They have regular oriented sessions about the telenursing research activities with the investigators before the study initiation. They have been receiving protocol-specific hands-on training on how to collect data to perform procedures about self-care and behavioral changes.

Procedure for Maintaining Confidentiality

This research will be conducted in accordance with the "Declaration of Helsinki (2013)" by the World Medical Association. This research will be conducted in compliance with the ethical guidelines set forth by the institutional review board of the Bangladesh Medical Research Council (BMRC). The IRB ensures that the human participants are protected through the study. Before enrolling in this study, we will get written informed consent from the participants. Furthermore, we will keep confidentiality maintain through the research process. The researchers of our study will take all necessary steps to ensure the anonymity of the participants. The shared information will not be identified. We will keep all medical information, description of treatment, and results of the laboratory tests confidential, under lock and key, and only our key research staff will have access to this information. The regular monitoring and evaluation system will be conducted to ensure the implementation of preventative measures, or any other potential risk arising during the study. All the study-related information will be kept under lock and key in a secure data store. An appropriate password-based login mechanism would be used to prevent unauthorized access to the server. The collected information would only be visible to authorized research team leaders on a need basis.

No identifiable information would be published anywhere.

Reasons for Termination of the Study

The study would be terminated based on the following reasons:

1. Unpredicted ethical concerns that could not be adequately addressed.
2. Unexpected negative events or any harm to participants.
3. Insufficient participant enrollment
4. Financial barriers that could affect the feasibility of the study.

Discontinuation of Research

The PI will consider whether to continue the research if any of the following applies:

1. When the ethics review committee has given instructions to change the implementation plan, it is deemed difficult to accept such instructions.
2. When facts or information that undermine the ethical validity or scientific rationality of the research are obtained.
3. When facts or information that undermine the appropriateness of the implementation of the research or the credibility the research results are obtained.

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Quality Assurance, Control, and Data Monitoring

The study quality will be assured and controlled by the PI and other investigators. Data will be collected by the trained research nurses. The participants' names will be coded by a unique ID number, and the data will be recorded with the IDs to maintain confidentiality. The data will be cross-checked among the research team. Data will be entered by the nurses. If any discrepancy is found, it will be corrected before data entry. A weekly meeting will be held among the research team to discuss the study and resolve if there will be any study-related confusion.

Results

The project was funded in 2024. The enrollment of the participants started on October 26, 2024, and as of February 2025, all the participants (N=70) were enrolled. Data analysis will be started after the completion of follow-up data collection and the first results are expected to be submitted for publication in 2026 if all information is available.

Discussion

Principal Findings

The results of the research will be disseminated in international scientific conferences and will be published in the *International Science Citation Index (SCI) Journals*. If the results show significance, we will share them with the policymakers, stakeholders, and the research community to implement such interventions in the government and private hospitals. Patients with diabetes will benefit, and it will reduce morbidity and mortality and will reduce patients' and national economic burden. To control diabetes, health education and lifestyle changes such as food habits, exercise, and medication adherence are imperative. By doing this research, we can improve quality of life by controlling diabetes and preventing complications and death. In this way, we can also decrease the number of hospital visits and admissions and economic burden. This study will increase patients' health literacy so that they can share their health knowledge with their peers and in the community. The study findings may assist us in the future implementation of telenursing interventions with a large sample size for determining factors that influence the quality of life among patients with diabetes.

Future Perspectives

By implementing this pilot study, we would like to see the feasibility and significance of this study. We can understand the potential barriers to use the telenursing system. Based on this study, we can revise the methodology and use multiple sites to make further research more effective. If we find our disease management program is effective, we can scale up this program throughout the country. Moreover, government and other nongovernment and private organizations can adopt this program and integrate into the existing health care system of Bangladesh. We can establish a public-private partnership incorporating all the stakeholders to develop a sustainable telenursing system [21].

Limitations

This study has certain limitations. As we use a purposive sampling technique for selecting the study sites and participants, it causes selection bias. This is a pre- and poststudy design, not using any control group, and thus no causal inferences could be made. We will use appropriate statistics to understand associations in outcome measures to minimize biases [22]. We use 2 rural PHCs from one district; therefore, our findings cannot be generalized for the population of the whole country. Some of the enrolled patients may not understand and follow the study procedures, so we can arrange group education via video conference to minimize this.

Facilities Available

GCCN has 76 different PHCs throughout Bangladesh. PHC receives patients with diabetes. They also have laboratory facilities to diagnose patients with diabetes. In this study, we have trained investigators and diabetic consultants who will conduct research activities and will provide consultancy. All the data will be entered into a password-protected computer and documents will be kept in the cabinet with a lock and key. Telecommunication will be conducted using smartphones.

Conclusions

By participating in this study, patients with diabetes will acquire disease-specific self-management skills and can manage a healthy lifestyle and prevent complication.

Acknowledgments

The authors would like to thank all the respected personnel of Grameen Primary Health Centers, the diabetes specialist, and patients for their kind patience and willful participation in this study. The study is funded by the restricted grants of Hiroshima University, Japan.

Data Availability

The datasets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

MM, KATMEH, and NSN performed supervision. MM, LM, ARM, and KATMEH performed data curation. LM, ARM, and NSN performed the investigation and methodology. MM also contributed to methodology and handled funding acquisition. MM and NSN handled project administration. MM and NSN managed resources. KATMEH managed software. MM and KATMEH

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conducted validation. MM and KATMEH performed visualization. KATMEH wrote the original draft. All authors contributed to the conceptualization, writing–review and editing, and approval of the submitted manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Education booklet.
[DOCX File , 285 KB - resprot_v14i1e71849_app1.docx]

Multimedia Appendix 2
Education Booklet_Bengali.
[PDF File (Adobe PDF File), 5100 KB - resprot_v14i1e71849_app2.pdf]

Multimedia Appendix 3
Self-monitoring Book.
[PDF File (Adobe PDF File), 651 KB - resprot_v14i1e71849_app3.pdf]

Multimedia Appendix 4
Outcome checklist.
[DOCX File , 20 KB - resprot_v14i1e71849_app4.docx]

Multimedia Appendix 5
The outcome table and data collection schedule.
[DOCX File , 19 KB - resprot_v14i1e71849_app5.docx]

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Abbreviations

BMRC: Bangladesh Medical Research Council
CGM: continuous glucose monitoring
CKD: chronic kidney disease
FBS: fasting blood sugar
GCCN: Grameen Caledonian College of Nursing
HbA_{1c}: hemoglobin A_{1c}
ICF: informed consent
LMIC: low- and middle-income country
NCD: noncommunicable disease
PHC: Primary Health Center
PI: principal investigator
RBS: random blood sugar

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Protocol

Integration of Digital Phenotyping and Genomics for Dry Eye Disease: Protocol for a Prospective Cohort Study

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Abstract

Background: Dry eye disease (DED) is a common ocular condition with diverse and heterogeneous symptoms. Current treatment standards of DED include the post facto management of associated symptoms through topical eye drops. However, there is a need for predictive, preventive, personalized, and participatory medicine. The DryEyeRhythm mobile health app enables real-time data collection on environmental, lifestyle, host, and digital factors in a patient's daily environment. Combining these data with genetic information from biobanks could enhance our understanding of individual variations and facilitate the development of personalized treatment strategies for DED.

Objective: This study aims to integrate digital data from the DryEyeRhythm smartphone app with the Tohoku Medical Megabank database to create a comprehensive database that elucidates the interplay between multifactorial factors and the onset and progression of DED.

Methods: This prospective observational cohort study will include 1200 participants for the discovery stage and 1000 participants for the replication stage, all of whom have data available in the Tohoku Medical Megabank database. Participants will be recruited

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from the Community Support Center of Sendai, Miyagi Prefecture, Japan. Participant enrollment for the discovery stage was conducted from August 1, 2021, to June 30, 2022, and the replication stage will be conducted from August 31, 2024, to March 31, 2026. Participants will provide demographic data, medical history, lifestyle information, DED symptoms, and maximum blink interval measurements at baseline and after 30 days using the DryEyeRhythm smartphone app. Upon scanning a registration code, each participant's cohort ID from the Tohoku Medical Megabank database will be linked to their smartphone app, enabling data integration between the Tohoku Medical Megabank and DryEyeRhythm database. The primary outcome will assess the association between genetic polymorphisms and DED using a genome-wide association study. Secondary outcomes will explore associations between DED and various factors, including sociodemographic characteristics, lifestyle habits, medical history, biospecimen analyses (eg, blood and urine), and physiological measurements (eg, height, weight, and eye examination results). Associations will be evaluated using logistic regression analysis, adjusting for potential confounding factors.

Results: The discovery stage of participant enrollment was conducted from August 1, 2021, to June 30, 2022. The replication stage will take place from August 31, 2024, to March 31, 2026. Data analysis is expected to be completed by September 2026, with results reported by March 2027.

Conclusions: This study highlights the potential of smartphone apps in advancing biobank research and deepening the understanding of multifactorial DED, paving the way for personalized treatment strategies in the future.

International Registered Report Identifier (IRRID): DERR1-10.2196/67862

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KEYWORDS

dry eye syndrome; dry eye disease; mobile health; smartphone; biobank; ocular surface; digital health; genome-wide association study

Introduction

Dry eye disease (DED) is one of the most diagnosed ocular conditions, with an estimated prevalence of 5%-50% [1]. It is associated with several recent global trends, including an aging population, a digitalized society, and cultural changes related to the COVID-19 pandemic [2-4]. The economic burden caused by the negative impact of DED on quality of life and vision is estimated at US $3.84 billion in the United States [5]. Patients with DED present with a highly heterogeneous range of symptoms, including dryness, photophobia, eye fatigue, and decreased visual acuity [6-8]. This situation presents a diagnostic challenge for clinicians, as several DED symptoms are nonspecific, resulting in a substantial number of patients being undiagnosed and untreated [9].

The progression of DED to severe stages, as observed in cases of Sjögren syndrome, graft-versus-host disease, and Stevens-Johnson syndrome, can lead to the development of corneal epithelial disorders that are refractory to existing therapies. Consequently, patients may experience severe pain, infectious keratitis, corneal perforations, and vision loss due to corneal neovascularization [10]. Current standards for DED treatment involve the post-facto management of associated symptoms using topical eye drops. However, no definitive cure exists for this chronic condition, which often affects individuals throughout their lives. Therefore, clinicians should actively implement preventive and predictive medicine strategies to prevent the onset and progression of DED. These strategies involve identifying risk factors and exploring new biomarkers to assist providers in anticipating disease progression [6-8].

From a pathophysiological perspective, DED is considered a multifactorial disease that disrupts tear film layer homeostasis [11]. Its onset and progression arise from the interplay of various factors, which are broadly divided into 3 categories: lifestyle factors (diet, cigarette use, physical activity, on-screen time, and contact lens use), environmental factors (humidity, pollen level, and particulate matter 2.5), and host factors (age, sex, presence of collagen diseases, family medical history, and genetic predispositions) [1]. Therefore, improving the current understanding and treatment of DED requires a comprehensive assessment of each patient's health status. Several clinicians recommend effective strategies for preventive, predictive, personalized, and participatory medicine (P4 medicine). These strategies include a holistic review of associated factors using personalized digital data on lifestyle patterns and digital phenotypes obtained through mobile health (mHealth) apps and integrating mHealth data with comprehensive biomedical data, such as genomic composition and DED-related laboratory findings [1,12].

mHealth, as defined by the World Health Organization, refers to a broad range of "medical and public health practice supported by mobile devices, such as mobile phones, patient monitoring devices, personal digital assistants, and other wireless devices" [13]. Recent advancements in portable smart devices have accelerated global efforts to implement mHealth in clinical practice [14]. Compared with existing electronic medical record software or epidemiologic studies, mHealth-based studies facilitate the collection of personal longitudinal health data, such as daily symptoms and lifestyle factors, with minimal intrusion. They also provide access to different types of comprehensive digital data, including those from embedded biosensors and real-time environmental information available online [6-9,15]. mHealth enables the collection of longitudinal, high-frequency, real-time, and remote data for clinicians and researchers. In addition, it supports bidirectional participatory medicine, allowing users and participants to provide active feedback [16]. Informed consent for research participation can be obtained digitally, reducing

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access barriers and increasing outreach to traditionally secluded populations [17].

To facilitate the implementation of P4 medicine, we launched DryEyeRhythm, an in-house mHealth app for DED research, in 2016 and 2020 for iOS and Android, respectively. To date, DryEyeRhythm has enrolled over 55,000 participants who have provided comprehensive real-world data, including subjective symptoms, digital information, lifestyle factors, environmental status, and biosensor data [7,9,15,17-20]. For our digital cohort studies on DED variability and heterogeneity, the DryEyeRhythm app has been pivotal in monitoring digital data, lifestyle factors, environmental data, and symptom changes that reflect participants' daily life and activity patterns.

A study based on the TwinsUK registry cohort [21] indicated that several chronic pain syndromes, including DED, demonstrated genetic heritability. A follow-up metabolome study revealed several metabolites associated with DED. Multiple gene loci are hypothesized to influence the onset and progression of DED, with several gene polymorphisms playing a crucial role in DED pathogenesis [22-39]. Polymorphisms in the estrogen receptor α and vitamin D receptor gene *APA-1* (rs7975232) have been associated with an increased prevalence of DED in several ethnic groups [22-24,28]. However, as of December 2023, no comprehensive reports on the genetic factors underlying DED heritability from genome-wide association studies (GWAS) have been published. Although numerous genetic factors contribute to DED heritability, the lack of GWAS limits the understanding of gene loci associated with DED onset and progression, hindering the provision of personalized medicine.

The Tohoku Medical Megabank (TMM) project was established in 2012 to support the reconstruction of areas affected by the Great East Japan Earthquake, promote the health of affected populations, and provide personalized and preventive medicine [40]. Collaborating with the Tohoku University and Iwate TMM Organizations in Miyagi and Iwate Prefectures, respectively, a 3-generation cohort study involving 150,000 local participants was conducted. The collected medical samples and data have established a foundation for a large-scale biobank [40-42].

This study conducts an add-on study to integrate DED-related personalized digital data, such as lifestyle factors and activity patterns, with the existing TMM databases by providing the DryEyeRhythm app to the participants of TMM cohort studies. These TMM databases include genomics, epidemiologic data, medical history, medical sample analyses, and physiological function testing results. Ultimately, we seek to establish a novel, comprehensive database for DED to elucidate the interplay between environmental factors, lifestyle choices, host factors, gene loci, and polymorphism traits that contribute to the onset and progression of DED, as well as to identify new DED subtypes through stratification techniques.

Methods

The TMM Project

As part of the TMM project, an integrated biobank was established based on the TMM Community-Based Cohort Study (TMM CommCohort Study) and TMM Birth and Three-Generation Cohort Study (TMM BirThree Cohort Study). The study design and recruitment methods have been described previously [40-42]. Briefly, the TMM CommCohort Study began in May 2013 and recruited 80,000 residents of the Miyagi and Iwate Prefecture in Japan. Participants responded to questionnaire items regarding sociodemographic factors, lifestyle habits, and medical history; provided biospecimens, such as blood and urine; and underwent physiological measurements, such as height, weight, and eye examinations [41-43]. The TMM BirThree Cohort Study commenced in July 2013 and recruited 70,000 residents (approximately 40,000 adults) of the Miyagi Prefecture. The survey items were nearly identical to those used in the TMM CommCohort Study [40-42]. The 2 cohort studies conducted follow-up surveys, including mailed questionnaires and repeated health examinations at community support centers in Miyagi Prefecture and satellites in Iwate Prefecture. Individual clinical and genomic data were incorporated into the TMM database (dbTMM) [42].

DryEyeRhythm Smartphone App

DryEyeRhythm, a free smartphone app for DED surveys and research, was launched in Japan in November 2016 and in the United States in April 2018 [15]. DryEyeRhythm collected electronic informed consent from all users. As illustrated in Figure 1A, participants provide demographic information, medical and lifestyle histories, and disease-specific questionnaire results for DED (Figure 1B, the Japanese version of the Ocular Surface Disease Index [J-OSDI]) [19,44], results of a depression rating scale results (Zung Self-rating Depression Scale [SDS]) [45], and work productivity details (Table S1 in Multimedia Appendix 1). Furthermore, DryEyeRhythm is equipped with functionality to measure the blink rate and maximum blink interval (MBI) of participants using smartphone cameras (Figure 1C) [7,20,46]. Collected data are automatically stored on the dedicated data server of the DryEyeRhythm smartphone app.

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Figure 1. Screenshots of the DryEyeRhythm app. (A) Screenshot of the DryEyeRhythm test results. (B) screenshot of the DryEyeRhythm app–based J-OSDI. (C) Screenshot of the DryEyeRhythm exam menu. J-OSDI: Japanese version of the Ocular Surface Disease Index.

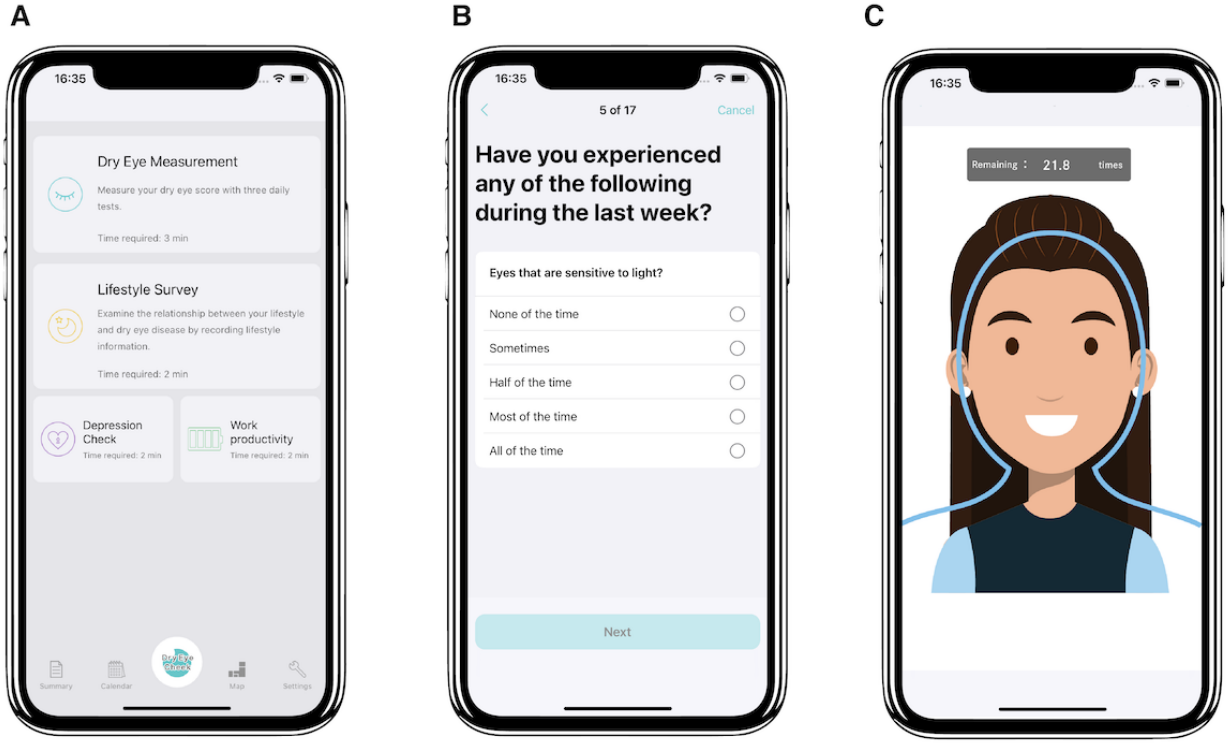

Study Design and Participants

This study was designed as a prospective observational add-on cohort study (Figure 2). Eligible participants were aged ≥20 years at the time of providing informed consent, participated in the TMM CommCohort Study or TMM BirThree Cohort Study, and conducted a follow-up survey at the Community Support Center of Sendai. A key inclusion criterion was that participants could use their smartphones. Participants were excluded if they did not have or use a smartphone or if their advice did not meet the operating system requirements (iOS 13.0 or later for iPhones; Android 8.0 or later for Android phones). Participants could withdraw their consent at any time before completing the second survey.

Figure 2. Schematic overview of the study design and participants.

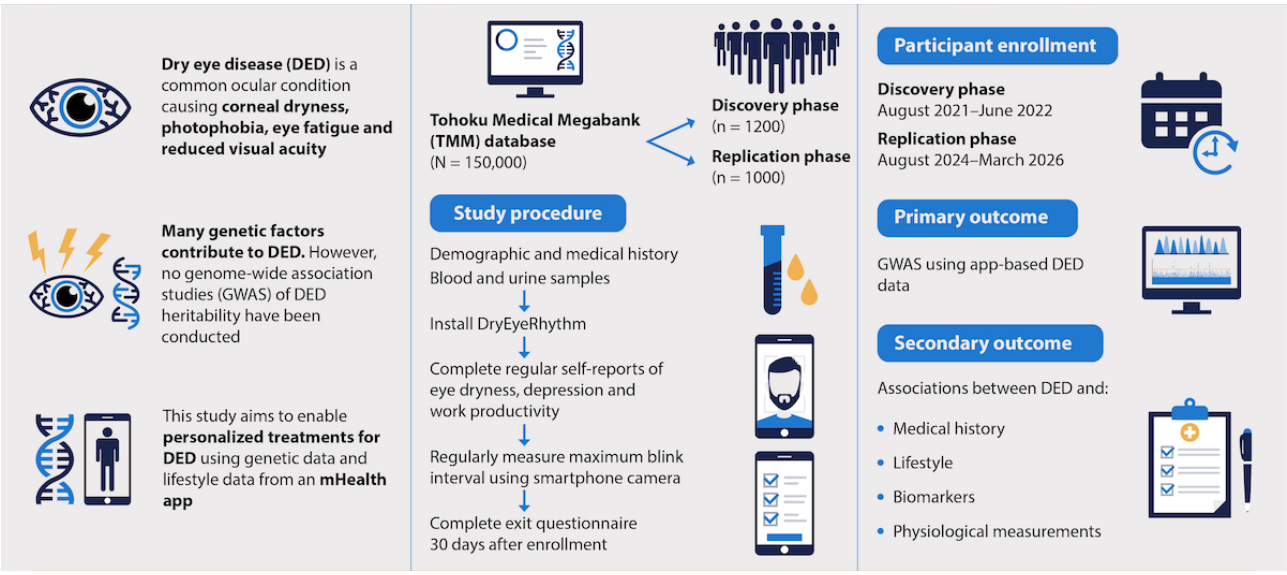

We aim to recruit participants at the Community Support Center of Sendai in Miyagi Prefecture, Japan, by distributing brochures when they present for health surveys. Those interested in the study have been and will be recruited. Study recruitment will occur between March 2021 and March 2026. Participants enrolled between March 2021 and June 2022 were included in the discovery stage cohort, whereas those enrolled between August 2024 and March 2026 will be included in the replication stage cohort. Participants will download and activate the DryEyeRhythm app [15] when they are recruited, and the cohort ID assigned to each participant will be scanned using a smartphone camera to connect the cohort ID to the app. The

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participants will be required to review the study description and provide electronic informed consent by DryEyeRhythm. The DryEyeRhythm survey can be completed anywhere; however, participants who complete the survey at the Community Support Center of Sendai can receive assistance from genome medical research coordinators if they have questions regarding the survey.

Study Procedures

Figure 3 shows a flowchart of the study. Participants visiting the Community Support Center of Sendai for health surveys and providing consent will complete questionnaires on sociodemographic factors, lifestyle habits, and medical history. They will also undergo blood and urine collection, physiological measurements, and eye examinations. Subsequently, participants will install the DryEyeRhythm app on their smartphones. They will then provide data through DryEyeRhythm (Figure 1A) regarding their demographic characteristics, medical and lifestyle histories, DED symptoms based on the J-OSDI (Figure 1B), depression symptoms based on the SDS, work productivity, and app-based blink rate and MBI (Figure 1C) measurements through the smartphone camera. After 30 days, participants who receive a notification requesting a second round of data submission will provide another round of information on DED symptoms based on the same criteria as the first round using DryEyeRhythm. Participants who do not submit the second-round data will receive a reminder through a phone call.

Figure 3. Flowchart of this study. J-OSDI: Japanese version of the Ocular Surface Disease Index; SDS: Zung Self-rating Depression Scale.

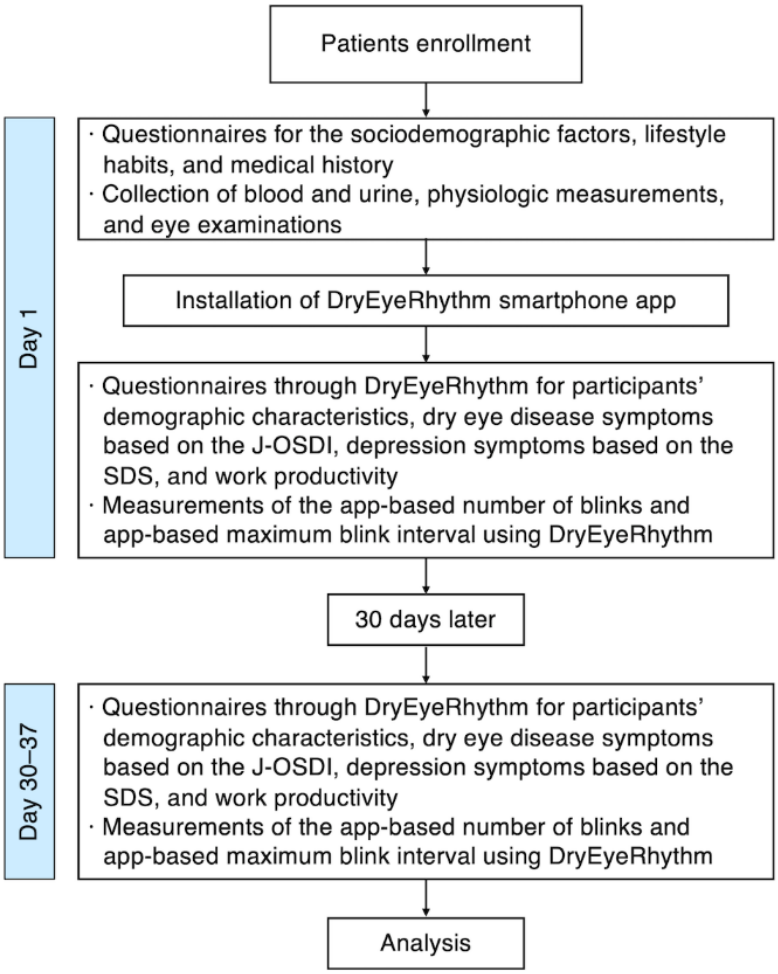

DED Diagnosis

Subjective symptoms of DED will be assessed using the 12-item J-OSDI questionnaire with 3 subscales: ocular symptoms, visual functioning, and environmental triggers [47]. Each response will be recorded on a 5-point scale (0="None of the time" to 4="All of the time" [4]), with "N/A" for questions not applicable to the user. The J-OSDI total score will be reported on a 100-point scale to determine the severity of DED symptoms (0-12, normal; 13-22, mild; 23-33, moderate; and 33-100, severe). The app-based J-OSDI has been validated in Japanese [44]. In this study, subjective symptoms of DED will be evaluated using the DryEyeRhythm-based (app-based) J-OSDI (Figure 1B). The app-based J-OSDI has been validated and compared with the paper-based J-OSDI in a previous study [19].

The MBI is defined as the duration the participants could keep their eyes open [46]. MBI is positively correlated with tear film breakup time (TFBUT) [48]. In this study, the app-based MBI measured using DryEyeRhythm (Figure 1C) will be used for diagnosing DED. A previous study has demonstrated that the app-based MBI is a valid and reliable substitute measurement compared with the slit-lamp-based MBI [20].

We defined app-based DED as an app-based J-OSDI total score of ≥ 13 points and app-based MBI of ≤ 12.4 seconds [48]. The app-based diagnostic method has been validated as a simple

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and noninvasive screening test for DED in previous studies [17,48]. The sensitivity, specificity, and area under the curve values for the app-based diagnostic method were 50%, 95%, and 0.91, respectively.

GWAS for the Primary Outcome

Genotyping of participants and data imputations will be completed using TMM, as previously described [49]. Individuals will be excluded from the analysis if they have a low call rate (<0.95), deviate from the mean of the major population by more than 4 SDs in genotyping principal component (PC) 1 and PC2, a medical history of Parkinson disease, or lack phenotypic and covariate data such as age, sex, and PCs. Variants will be excluded if they have a low call rate (<0.99), low Hardy-Weinberg equilibrium exact test P value ($P<1\times10^{-6}$), low minor allele frequency (<0.01), or low imputation quality ($R^2<0.3$). The target outcome will be app-based DED. A stringent threshold of $P<5\times10^{-8}$ will denote genome-wide significance, minimizing false positives associated with multiple testing, and a suggestive threshold of $P<1\times10^{-5}$ to indicate potential associations that warrant further investigation. Only variants reaching the threshold ($P<5\times10^{-5}$) during the discovery stage will be selected for the replication stage. Logistic regression will be applied to binary outcomes, adjusting for confounding factors (such as age, sex, and PCs) using well-validated GWAS tools, including Plink2 [50].

Secondary Outcome

The secondary outcomes of this study will include the association between app-based DED and patients' sociodemographic factors, lifestyle habits, medical history, biospecimens such as blood and urine, and physiological measurements such as height, weight, and eye examination results [41-43]. These associations will be evaluated using logistic regression analysis and adjusted for confounding factors. A significance level of $P<.05$ will be used.

Sample Size Calculation

This study's sample size was calculated using the web-based tool Genetic Association Study Power Calculator [51]. The rs1143634 polymorphism in IL1B was selected as a candidate single-nucleotide polymorphism based on previous associations with non-Sjögren DED, with an odds ratio of 3.337 [26]. The minor allele frequency for rs1143634 was 0.047, based on data from the Japanese Multi Omics Reference Panel [52]. The prevalence of DED in the target population was estimated to be 30% [53], with a significance level of $P<5\times10$. The sample size was calculated to achieve an 80% statistical power, assuming 2000 participants (600 cases and 1400 controls, with a 30:70 case-control ratio).

As shown in Figure 4, the statistical power increased as the relative risk approached ≥1.9. The odds ratio can be used as an approximation of the relative risk. With an odds ratio of 3.337 for rs1143634, the sample size was deemed adequate for detecting associations based on the effect size observed in a previous study [26]. The sample size was increased by 10% to account for potential exclusions, resulting in a final recruitment target of 2200 participants. Of these, 1200 participants were included in the discovery stage, and 1000 participants will be included in the replication stage.

Figure 4. Statistical power analysis.

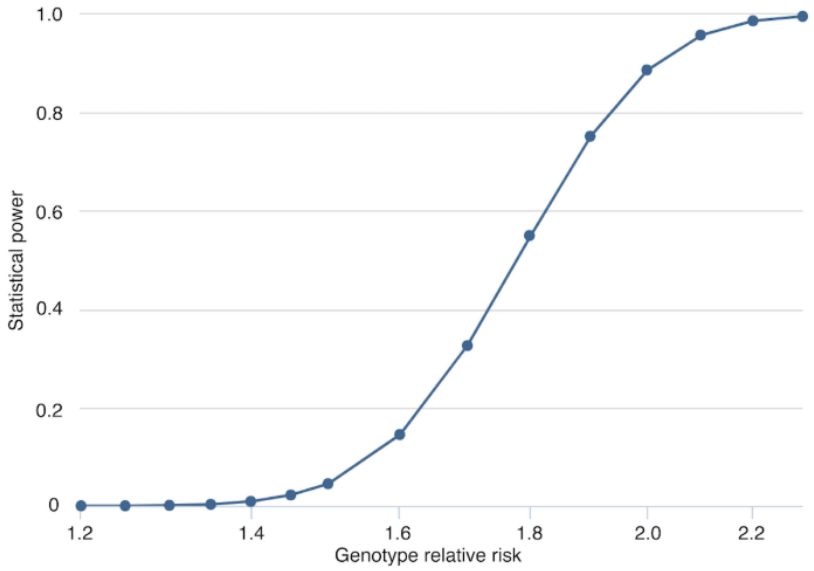

Statistical Analyses

The initial data selection for the DryEyeRhythm dataset collected will be conducted for each cohort ID. If the dataset contains complete data (data without missing values), the first available dataset will be used as the initial dataset. If only incomplete data are registered, the first incomplete dataset will be used as the initial dataset. If complete data are registered on or after 30 days and before 37 days from the initial dataset, the first dataset among them will be used as the second dataset. If only incomplete data are registered within this period, the first dataset among them will be used as the second dataset. The demographic characteristics of the participants will be analyzed as the input values of the initial data. The month of a participant's inclusion will be defined as the month when their initial data are recorded. The ophthalmic data analyzed in this

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study will be measured at the time of recruitment for the TMM CommCohort Study and TMM BirThree Cohort Study and stored in the dbTMM [40-42].

Continuous variables will be presented as median (IQR) values and categorical variables as percentages. The Mann-Whitney *U* test will be used for continuous variables, and the chi-square test for categorical variables. All analyses will be conducted with a significance level of .05 using a 2-sided test. The associations between app-based DED and factors stored in the dbTMM and measured through DryEyeRhythm will be evaluated using the logistic regression analysis. This model will incorporate participants' characteristics (such as age, gender, height, weight, and medical history), lifestyle factors, environmental factors (including residential environment), and ophthalmic examination results as variables to calculate fully adjusted odds ratios, accounting for various confounding factors. All data will be analyzed using Stata (version 18.0; StataCorp) and R (version 4.2.1; R Foundation for Statistical Computing).

Ethical Considerations

This study was approved by the Ethics Committee of the Tohoku University TMM Organization (approval number: 2023-4-188; September 10, 2023, version 1), the Independent Ethics Committee of Juntendo University Faculty of Medicine, and the Ethics Committee of Iwate Medical University, adhering to the principles outlined in the tenets of the Declaration of Helsinki. The research protocol was reviewed by the Ethics Committee of the Tohoku University TMM Organization on behalf of multiple institutions. All participants will provide informed consent upon visiting the Community Support Center, Sendai, Miyagi, Japan. In addition, electronic informed consent will be obtained upon the first activation of the DryEyeRhythm smartphone app. The consent process includes approval for the use of data from the Tohoku Medical Megabank database. To ensure participants' confidentiality, all data will be anonymized, with participants identified using a cohort ID that prevents personal identification. Participants will receive an honorarium of 500 Yen (US $3.50) per survey (up to a maximum of 1000 Yen [US $7]) for completing the DryEyeRhythm surveys.

Results

Participant enrollment for the discovery stage was performed from August 1, 2021, to June 30, 2022. Enrollment for the replication stage will be performed from August 31, 2024, to March 31, 2026. Data analysis will be completed by September 2026, and results will be reported by March 2027.

Discussion

Implementing the principles of P4 medicine through cross-hierarchical analyses, which include comprehensive and personalized digital health and genomic datasets, may be crucial for preventing the onset or progression of highly multifactorial DED. By integrating DryEyeRhythm, our mHealth app for DED research, with the TMM project, we establish a comprehensive database for DED that integrates genomic data from the biobank with multifaceted datasets (ie, lifestyle, biosensor records, and demographics) collected through our app. Using this robust dataset, we identify new gene loci and polymorphisms associated with DED pathogenesis and progression, as well as new DED subtypes and their characteristics through stratification strategies. This approach can also be extended to other fields of medicine, providing insights into the underlying pathophysiology of various multifactorial diseases.

We conducted a systematic review using PubMed and Embase for all research articles published until April 15, 2024, using the search terms "(dry eye) AND ((genome) OR (polymorphism) OR (SNP) OR (variant) OR (locus) OR (loci) (mutation))." This systematic review did not identify any existing publications that collected real-world, daily DED-related health data, such as lifestyle patterns, environmental status, biosensor inputs, or subjective symptoms using mHealth technology. However, we identified 20 reports on gene mutations or polymorphisms associated with DED onset and severity [22-39,54,55]. No studies have conducted GWAS to identify loci associated with DED. Therefore, the proposed approach marks the first attempt to create a holistic database for DED using genomic and digital health data. This integration may reveal unknown aspects of DED regarding its variability, heterogeneity, and implementation of P4 medicine. In addition, we highlight the new use and value of biobanks in global health care research communities through this initiative, eventually promoting the incorporation of genomic studies into standard clinical practice.

The add-on portion of this study will be conducted through DryEyeRhythm to provide DED diagnostic support [15]. The diagnostic criteria for DED in Japan include positive subjective symptoms on the DED-specific symptom questionnaire and decreased TFBUT [44,56]. To meet these criteria, DryEyeRhythm first administers the J-OSDI questionnaire through its app interface [17,46,48]. Instead of directly measuring TFBUT, the app measures the MBI of the participants, which is positively correlated with TFBUT [17,46,48]. Our previous studies on the comeasurement of the app-based J-OSDI total score and MBI demonstrated sufficient validity, reliability, and equivalence to the traditional diagnostic standard [19,20]. Regarding diagnostic performance, the positive and negative predictive values were reported to be 91.3% and 69.1%, respectively [17]. Furthermore, using data collected through DryEyeRhythm, we developed and tested an original stratification algorithm that identified 7 DED subtypes based on subjective symptoms [7]. In this study, we applied the above stratification technique to better detect DED subtypes and understand DED pathophysiology by identifying the digital phenotypic characteristics of each cluster.

Another crucial aspect of this protocol is the cross-hierarchical analysis using real-time, day-to-day digital data and lifestyle factors, which are difficult to capture in traditional cohort studies involving established biobanks [6,7,9,15]. Typically, biobanks require participants to visit facilities or send samples directly for collection. Conversely, mHealth offers the advantage of nonintrusive, longitudinal data collection, closely reflecting real-world data as facility-attained data are readily affected by undesired variables (such as white-coat syndrome and masked hypertension) [57]. Such data characteristics that closely resemble real-world data can be particularly crucial for perfecting the future implementation of P4 medicine [57]. For

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DED, day-to-day health data can be important as they are associated with daily activities and factors immeasurable in a facility setting, such as on-screen time and living environment. With the use of common smart devices and attached sensors, clinicians and researchers can access the data above. Objective data points, including DED questionnaire scores and biosensor data, can reduce barriers to access and cost, as mHealth apps can be operated by users without requiring specialized examination tools or personnel [17,19,20,58]. Physical and biological specimens such as genomic samples, secretions, or hair will still be crucial but with a shift toward using mailed specimens, allowing for a study cohort without geographic limitations to populations near specific research centers. Cohort studies in Western countries where participants provided consent through a smartphone app and physical specimens through the mail have been reported [59,60]. Although no similar attempts have been made in ophthalmology, DryEyeRhythm could serve as a platform to recruit cohorts similarly and expand the use of existing and prospective biobanks.

Our protocol has some limitations, consistent with those identified in previous studies using smartphone apps [9,15]. First, this study may be prone to recall bias due to the reliance on self-administered questionnaires, which may lead to an overestimation of DED prevalence in the community. On the other hand, in evaluating subjective symptoms of DED, self-reported questionnaires, such as the J-OSDI questionnaire, are commonly used in standard clinical DED diagnostic methods [56]. Therefore, the impact of using a self-reported questionnaire for subjective DED symptoms on the study results is likely minimal. Second, selection bias may occur, as individuals concerned about DED prevalence and those with previous symptoms may be more likely to participate due to the voluntary registration process. In addition, older adults or those lacking access to smart devices will have difficulty participating in this study. This study will target participants of the TMM CommCohort Study and the TMM BirThree Cohort Study, which geographically restricts the pool of participants. The limitations in the geographical and demographic representativeness of the sample may introduce bias and affect the generalizability of the study results. Third, this study will diagnose DED using app-based J-OSDI and MBI metrics without conducting clinical examinations, such as TFBUT, the Schirmer test, osmolality measurements, and ocular surface staining [9,11,46]. The difference in this method may affect the study results. However, this app-based DED diagnostic method has been validated for reliability and validity against the standard DED diagnostic method, which uses the paper-based J-OSDI questionnaire and TFBUT [17,56]. The positive predictive and negative predictive values of the app-based DED assessment were 91.3% and 69.1%, respectively, with an area under the curve of 0.91. Therefore, the effect of differences in the method of diagnosis of DED on the results of this study is likely minimal.

In conclusion, by establishing a comprehensive database for DED that integrates existing medical biobank data with highly personalized and holistic mHealth data, this study may discover a new biobank value and contribute to the implementation of genomics in clinical practice.

Acknowledgments

The authors thank Medical Logue and InnoJin for developing the DryEyeRhythm smartphone app and genome medical research coordinators and administrative assistants at the Community Support Center of Sendai. This research was supported in part by the Tohoku Medical Megabank Project (Tohoku University) from MEXT (Tohoku Medical Megabank Organization), the Japan Agency for Medical Research and Development (AMED; grant number JP21tm0124005 [Tohoku Medical Megabank Organization]), BioBank-Construction and Utilization Biobank for Genomic Medicine Realization: B-Cure from AMED (grant number JP21tm0424601), Japan Society for the Promotion of Science KAKENHI grants (20KK0207 [TI], 20K23168 [AMI], 21K17311 [AMI], 21K20998 [AE], 22K16983 [AE], 23K16364 [AMI], 23K18406 [TI], and 24K19796 [AE]), Japan Science and Technology Agency FOREST program (24012732 [TI]), Kondou Kinen Medical Foundation, Medical Research Encouragement Prize 2020 [TI], Charitable Trust Fund for Ophthalmic Research in Commemoration of Santen Pharmaceutical's Founder 2020 [TI], Nishikawa Medical Foundation, Medical Research Encouragement Prize 2020 [TI], the OTC Self- Medication Promotion Foundation [TI and YO], Takeda Science Foundation 2022 [TI], and Research Grants in the Natural Sciences 2024, The Mitsubishi Foundation. The sponsors had no role in the design or performance of the study, data collection and management, analysis and interpretation of the data, preparation, review, or approval of the manuscript, or in the decision to submit the manuscript for publication.

Data Availability

All data are available in the main text. The code supporting the findings of this study will be made available from the corresponding author upon reasonable request. Data processing and analysis will be performed using STATA version 18.0.

Authors' Contributions

KN, YA, and TI had complete access to all data in this study and took responsibility for the integrity of the data and the accuracy of the data analysis. KN, YA, and TI managed the study concept and design. KN, YA, NF, SO, AS, AU, YS, YOY, FN, JS, TN, SN, MT, TK, RS, AH, SK, AE, AMI, MN, AM, SN, and TI handled acquisition, analysis, or interpretation of data. KN, JS, AY, and TI managed the drafting of the manuscript. KN, JS, AM, SN, and TI conducted critical revision of the manuscript for important intellectual content. AMI, AE, and TI obtained funding. KN, YA, AMI, and TI conducted statistical analysis. NF, SO, AS, AU,

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AM, SN, and TI handled administrative, technical, or material support. NF, SO, AS, AM, SN, and TI contributed to supervision. All authors read and approved of the final manuscript.

Conflicts of Interest

The DryEyeRhythm smartphone app was developed by Juntendo University (Tokyo, Japan) and InnoJin (Tokyo, Japan). TI is the owner of InnoJin. KN and AMI reported receiving personal fees from InnoJin. SN reports grants from Kowa, Mitsubishi Tanabe Pharma Corp, Alcon Japan, Santen Pharmaceutical, Machida Endoscope, Wakamoto Pharmaceutical, Bayer Yakuhin, Senju Pharmaceutical, Nippon Boehringer Ingelheim, Chugai Pharmaceutical, Hoya Corp, and Novartis Pharma KK, outside the submitted work. TI reports nonfinancial support from Lion Corporation and Sony Network Communication; grants from Johnson & Johnson Vision Care, Yuimedi, ROHTO Pharmaceutical, Kobayashi Pharmaceutical, and Kandenko; and personal fees from Santen Pharmaceutical and InnoJin, outside the submitted work.

Multimedia Appendix 1
DryEyeRhythm questions.
[PDF File (Adobe PDF File), 1121 KB - resprot_v14i1e67862_app1.pdf]

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Abbreviations

dbTMM: database Tohoku Medical Megabank
DED: dry eye disease
GWAS: genome-wide association studies
J-OSDI: Japanese version of the Ocular Surface Disease Index
MBI: maximum blink interval
mHealth: mobile health
PC: principal component
P4 medicine: predictive, preventive, personalized, and participatory medicine
SDS: Zung Self-rating Depression Scale
TFBUT: tear film breakup time
TMM: Tohoku Medical Megabank
TMM BirThree Cohort: TMM Birth and Three-Generation Cohort Study
TMM CommCohort: TMM Community-Based Cohort Study

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Protocol

Jaw Bone Density in Chronic Areca Nut Chewers and Nonchewers Using Digital Panoramic Radiography Indices as a Screening Tool for Osteoporosis: Protocol for a Comparative Evaluation

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Abstract

Background: Jaw bone density can be altered due to various factors including aging, bone pathologies, hormonal levels, medications affecting bone density, and undue stress posed by parafunctional and adverse habits. Of these factors, chronic areca nut chewing, which creates a heavy load on jaw bones, is a commonly encountered adverse habit in patients. Digital panoramic radiography (OPG) indices are an easy and cost-effective method to evaluate jaw bone density. Index values can also be used as a screening tool for osteoporosis.

Objective: This study aims to compare and evaluate jaw bone density in chronic areca nut chewers and nonchewers using OPG indices as a screening tool for osteoporosis.

Methods: Patients aged 20 years to 40 years reporting to the Department of Oral Medicine and Radiology with and without a history of chronic areca nut chewing will be recruited. OPG will be collected for all recruited patients. The mandibular cortical index, panoramic mandibular index, gonial index, antegonial index, antegoinal notch depth, and mental index will be calculated.

Results: The values of these indices will be used to assess and compare osteoporosis in chronic areca nut chewers and nonchewers. Data will be entered and displayed in a tabular format, and correlations between osteoporosis and OPG index values will be determined. The study did not receive any external funding. Recruitment is expected to begin in summer 2025, and publication of the results is expected to occur in late 2026.

Conclusions: Evaluation of jaw bone density in chronic areca nut chewers using OPG indices might prove to be a feasible and cost-effective technique for assessing osteoporotic bone changes. Although the gold standard modality is dual x-ray absorptiometry, its cost and availability create challenges for use in the general population. As osteoporosis of jaw bones does not usually present with symptoms, patients can be made aware of it using the findings from this evaluation. Hence, it will ultimately aid in early detection and prompt interventions, thereby halting disease progress.

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KEYWORDS

areca nut; digital panoramic radiography; jaw bone density; osteoporosis; bone mineral density

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Introduction

Maxillary and mandibular jaw bones have different densities. Mandibular bone is more dense and compact than maxillary bone, which is cancellous bone. Alteration in bone density can occur due to aging, diseases affecting bone, and altered hormonal levels, especially in peri- and postmenopausal women. Osteoporosis, which affects bone density, is a common finding in women older than 40 years. It can also be seen in men with various diseases affecting the bones or taking medications that affect bone mineral density (BMD). The risk of osteoporosis increases with age and can have deleterious effect on the body. Early detection of this condition may help to halt progression and offer prompt treatment to the patients.

One of the reasons for altered jaw bone density is the amount and frequency of functional load (load posed on the mandibular bone due to continuous masticatory movement) to which it is subjected [1]. A continuous heavy masticatory load attributed to a continuous grinding action, such as when chewing areca nut, poses a risk of altered jaw bone density. This can be due to various reasons like bone remodeling in response to increased masticatory load and toxic elements leaching out of areca nut. Studies have been performed to evaluate jaw bone density in bruxers and nonbruxers, and the results revealed increased cortical thickening (ie, increased jaw bone density), which is a reaction to a continuous load applied to the bone [1].

India is a country where habits like areca nut chewing, use of tobacco in either smoked or smokeless forms, and alcohol consumption are extremely prevalent, especially among young adults. The effect of smoking on BMD has already been proven in many previous studies. Areca nut chewing increases the masticatory load on the jaw bones in the same manner as that seen in patients with bruxism. Furthermore, studies have revealed a decrease in vitamin D levels in chronic areca nut chewers, which in turn can affect the density of jaw bones [2]. This shows that areca nut chewing might alter the density of the jaw bones. Hence, the effect of areca nut chewing on bone density remains controversial.

Digital panoramic radiography (OPG) is a widely used imaging modality for primary screening in clinical practice. It has several significant advantages including feasibilty, ease of acquisition, being cost effective, a low radiation dose, and ability to depict the dentition as well as jaw bones together. Several indices studied on OPG are helpful for evaluating jaw bone density. The measurements are easy to perform and understand. Hence, the overall benefits of OPG make it a beneficial tool for evaluation of jaw bone density [3].

There is a paucity of studies related to jaw bone density in chronic areca nut chewers using OPG indices and evaluating the efficacy of OPG as a screening tool for osteoporosis [4].

Hence, the purpose of this study is to compare and evaluate jaw bone density in chronic areca nut chewers using panoramic radiographs and to detect the efficacy of the same as a screening tool for the detection of underlying undiagnosed osteoporosis.

Methods

Ethical Considerations

The study received approval from the Institutional Ethics Committee (IEC number DMIHER(DU)/IEC/2023/1203) of Datta Meghe Institute of Higher Education and Research, Sawangi (Meghe), Wardha.

Informed consent was obtained from all participants involved in the study. The data collected will not include any identifiable information. Patients will benefit from education on the adverse effects of areca nut chewing on jaw bone density and receive proper counseling to cease chewing. They will receive no other compensation.

Participants

This prospective, observational, case control study will be conducted with patients aged 20 years to 40 years visiting the Department of Oral Medicine and Radiology with a chronic history of areca nut chewing. The patients will be divided into 2 groups: Group A (patients without a history of chronic areca nut chewing; control group) and Group B (patients with a chronic history of areca nut chewing; study group). The inclusion criteria are patients aged between 20 years and 40 years, dentulous patients with a chronic history of areca nut chewing, and dentulous patients with a complete set of dentition except the third molars. The exclusion criteria are patients with a history of smoking, alcohol consumption, or drug use; with any systemic disease affecting the bone; having undergone chemoradiotherapy for any reason; taking medications affecting bone density; with congenital anomalies, malignancy, or disorders of jaw bones; with a jaw bone fracture; with a history of a surgical intervention involving jaw bones; with a history of orthodontic treatment; with periodontal diseases; and with a history of bruxism.

Sample Size

Participants will be divided into 2 equal groups. The sample size was calculated using N=B/C, where $C=(E/S)^2$, $B=(Z_\alpha + Z_\beta)^2$, Z_α is the standard normal deviation for α (1.9600), and Z_β is the standard normal deviation for β (0.06745). C was 0.2500, and B was 6.9403, resulting in an N of 27.7614 for each group. Therefore, N was rounded up to the next highest integer to give a group size of 70.

Methodology

Eligible patients reporting to the Department of Oral Medicine and Radiology and who are willing to participate in the study will be recruited. Each patient's previous medical history will be collected to rule out systemic disease affecting jaw bone density, history of medications affecting the bone, and history of pathology affecting the jaw bones. Each patient's previous dental history will be collected to rule out a history of orthodontic treatment or periodontal diseases. A detailed history of habits, including type, duration, and frequency, will be collected from each patient. A thorough clinical examination will be conducted to rule out missing teeth, root pieces, or impacted teeth. All patients will be undergo a panoramic radiographic examination using standard parameters.

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Evaluation of jaw bone density will be based on the OPG indices as shown in Figures 1-5 [5,6]. The reference values for mandibular cortical index (MCI) and panoramic mandibular index (PMI) for normal, osteoporotic, and osteopenic bone that will be used are shown in Table 1 [7].

Figure 1. Graphic and radiographic representation for the calculation of the (B) mandibular cortical index and (C) mental index.

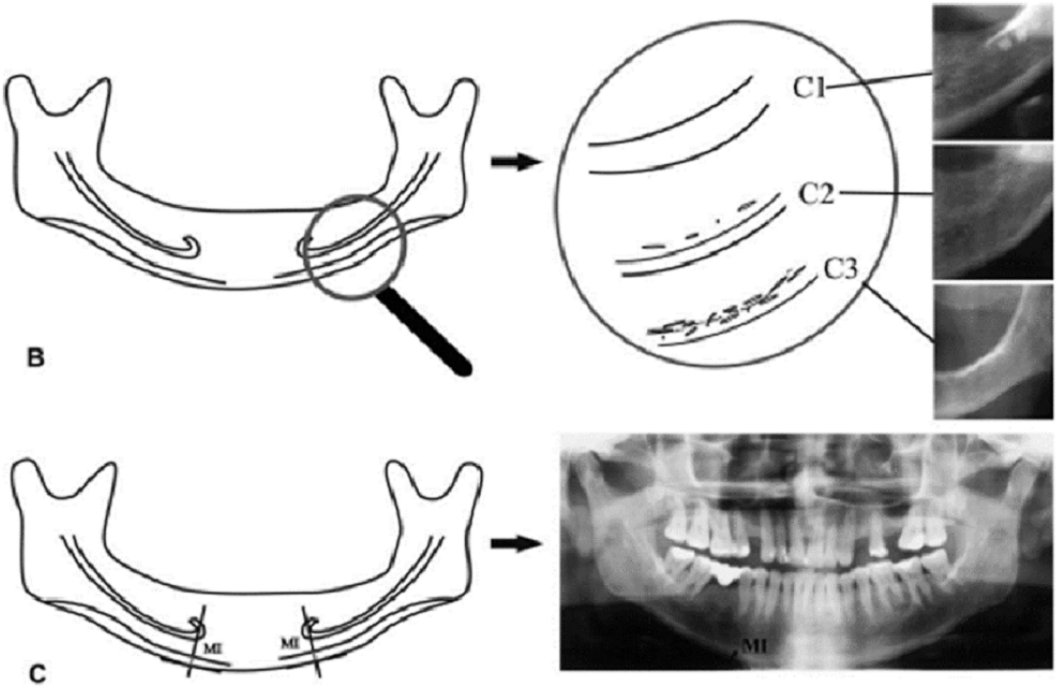

Figure 2. Graphic and radiographic representation for calculations of the panoramic mandibular index (width B/width C) and gonial index (width D).

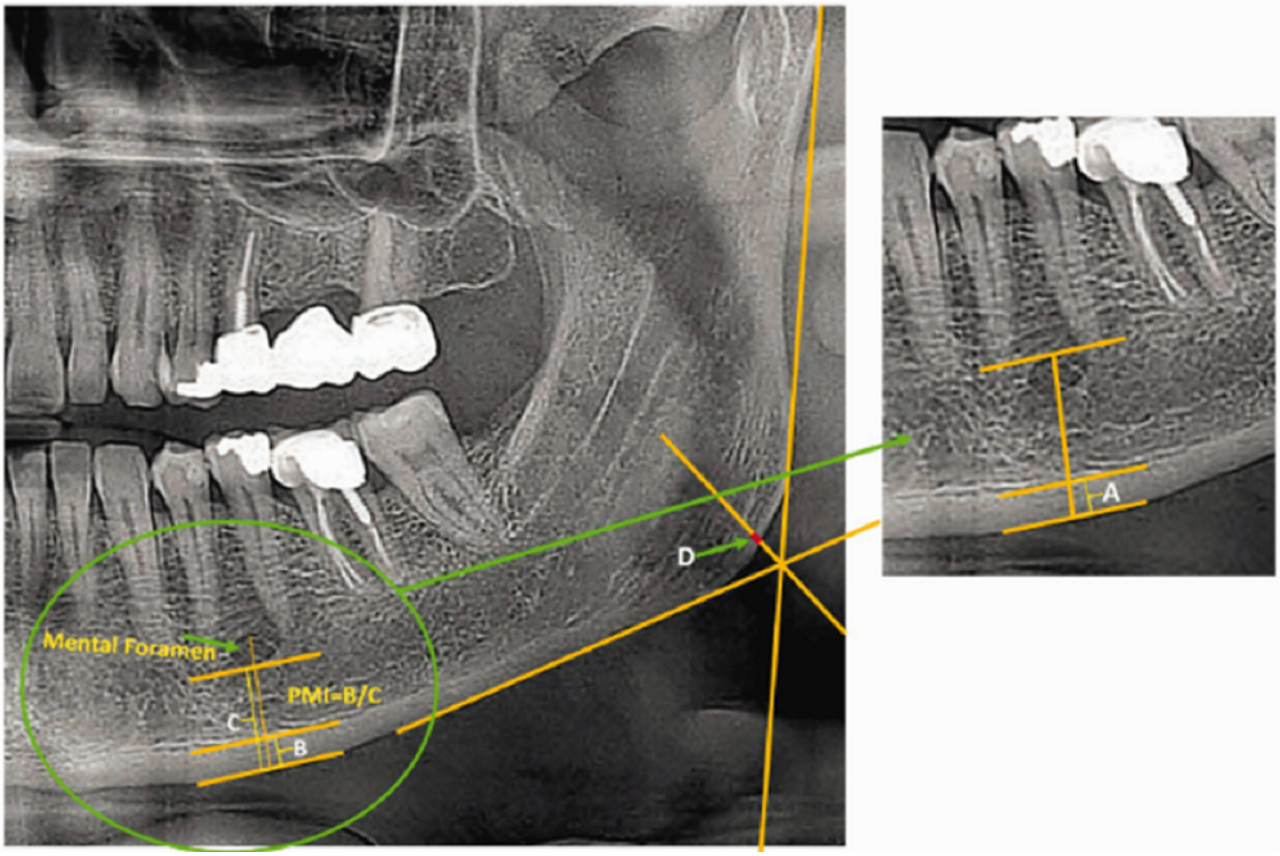

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Figure 3. Radiographic representation of the determination of the antigonial index.

Figure 4. Graphic and radiographic representation for calculation of the gonial index: the length of “e” in mm.

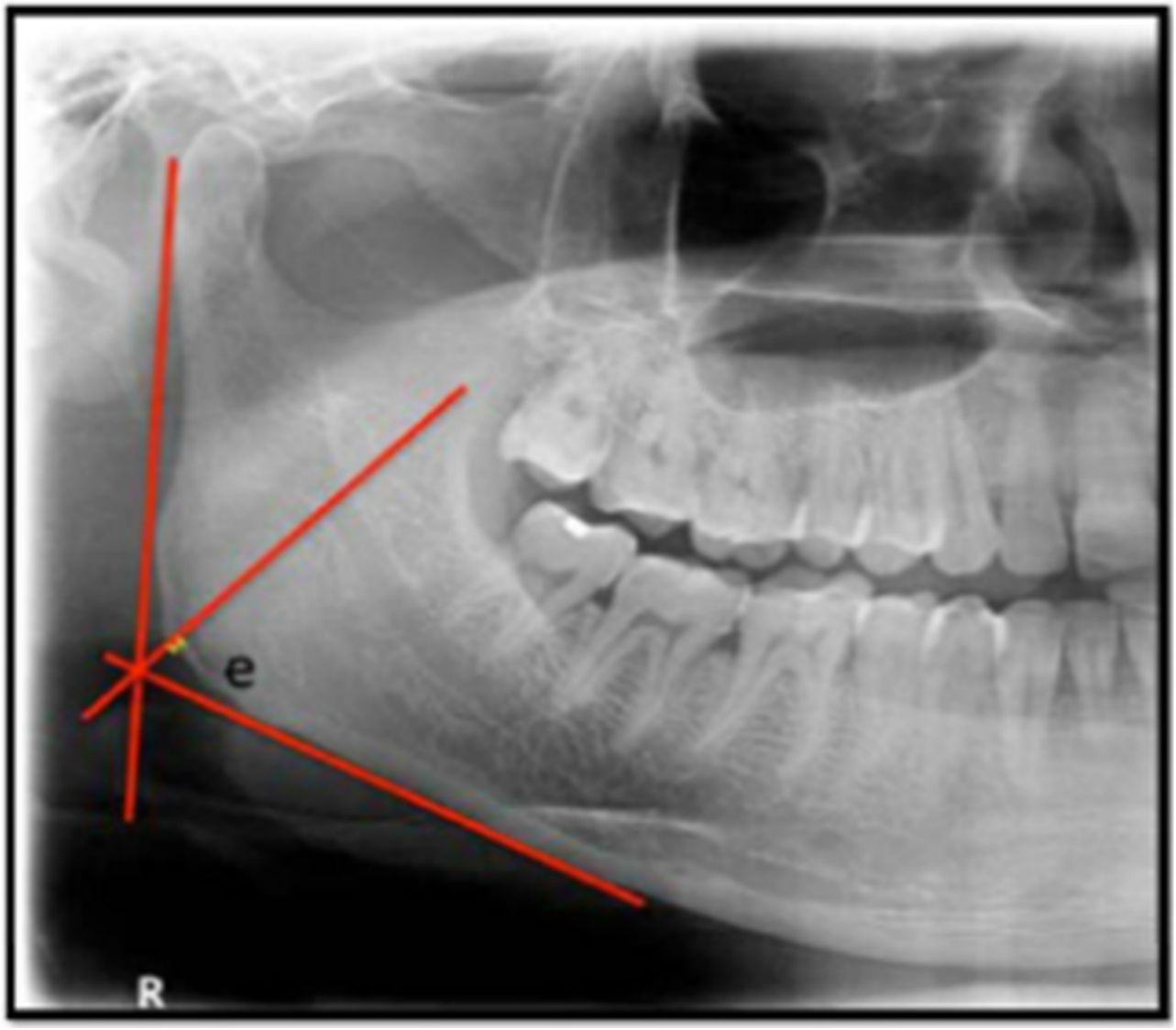

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Figure 5. Graphic and radiographic representation for the calculation of the antegonial notch depth, which is calculated by measuring the depth of the notch from the line drawn tangent to the inferior border of the mandible.

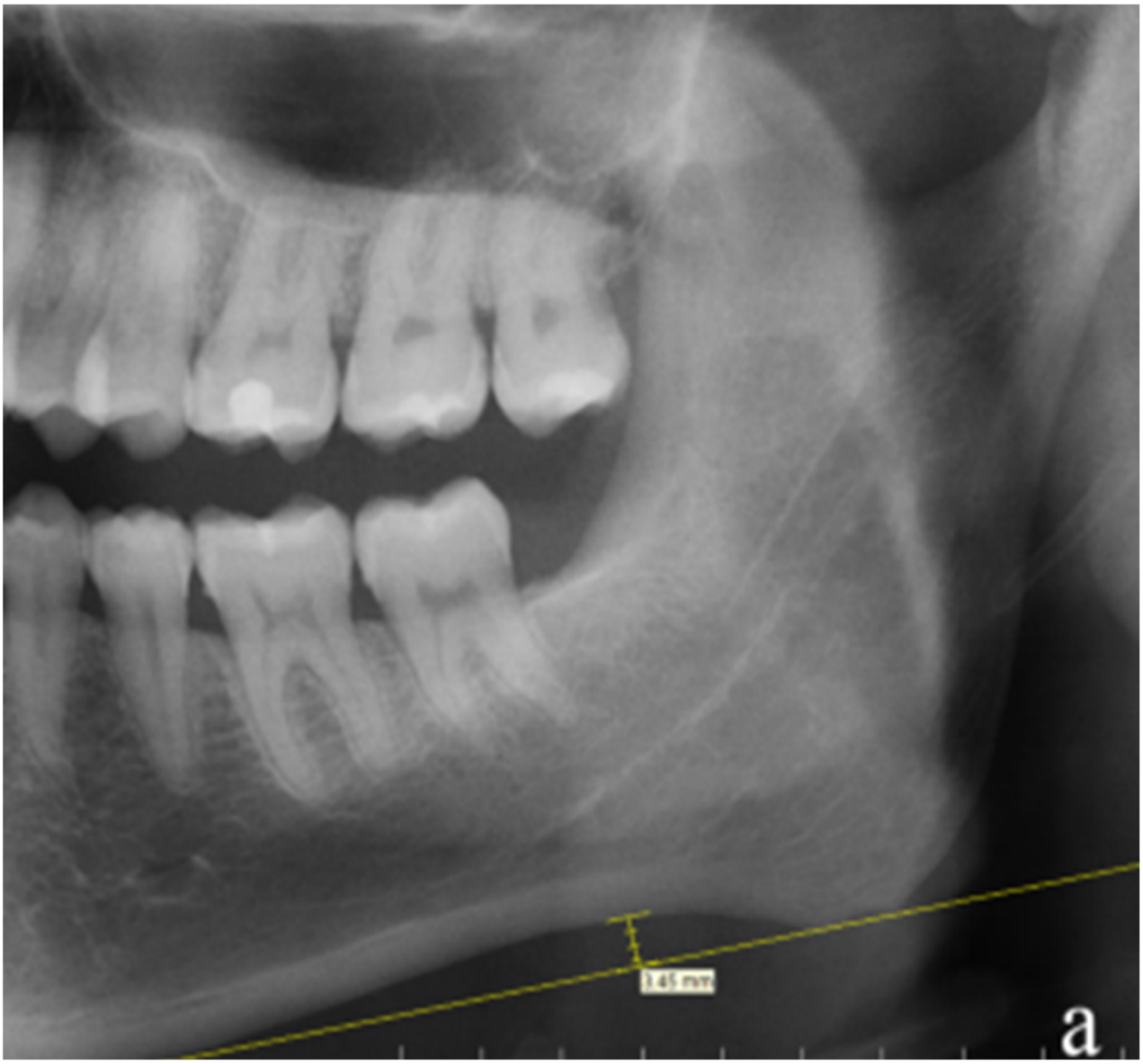

Table 1. Reference values for digital panoramic radiography indices to evaluate osteoporosis.

Bone density	Scores for the orthopatomogram indices	
	Mandibular cortical index	Panoramic mandibular index
Normal	4.56	0.33
Osteoporotic	3.39	0.24
Osteopenic	3.97	0.28

Statistical Analysis

Reference values for MCI and PMI will be correlated with the OPG index values to determine the patients' osteoporosis status.

Results

The study did not receive any external funding. Recruitment is expected to begin in summer 2025, and results are expected to be published in late 2026.

The results from the analyses based on the values of OPG indices will be displayed in tabular form similar to that shown in Tables 2 and 3.

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Table 2. Example representation of how the values of the digital panoramic radiography indices in the control group and study group will be reported.

Study group	Digital panoramic radiography indices					
	MCI[a]	PMI[b]	AI[c]	GI[d]	AND[e]	MI[f]
Control group	__[g]	—	—	—	—	—
Study group	—	—	—	—	—	—

[a]MCI: mandibular cortex index.
[b]PMI: panoramic mandibular index.
[c]AI: antegonial index.
[d]GI: gonial index.
[e]AND: antegonial notch depth.
[f]MI: mental index.
[g]Placeholder.

Table 3. Example representation of how bone quality based on the digital panoramic radiography indices in the control and study groups will be reported.

Study group	Calculated MCI[a] value	Calculated PMI[b] value	Status of bone after correlation of calculated values of MCI with reference values	Status of bone after correlation of calculated values of PMI with reference values
Control group	__[c]	—	—	—
Study group	—	—	—	—

[a]MCI: mandibular cortex index.
[b]PMI: panoramic mandibular index.
[c]Placeholder.

Discussion

Background

Chronic areca nut chewing is thought to decrease jaw bone density. Multiple reasons have been discussed, including remodeling of bone and toxic elements leaching out due to chronic areca nut chewing. A few studies, however, have suggested an increase in bone density due to chronic areca nut chewing. Hence, this study will aid with establishing more clarity over this dispute. As areca nut is a hard substance, the chronic masticatory actions associated with chewing areca nut should lead to increased jaw bone density; however, due to a decrease in vitamin D levels, there could be a negative impact on jaw bone density. As osteoporosis is asymptomatic, it is frequently overlooked and goes undiagnosed. Dual x-ray absorptiometry examinations are currently the gold standard for diagnosing osteoporosis based on BMD. However, “a large portion of the Indian elderly population cannot access this diagnostic modality due to its high cost and limited availability” [8]. In order to diagnose oral problems, dentists frequently use radiography in their daily work. The focus of recent studies has been on whether radiographic changes in the jaws might serve as a reliable, early osteoporosis diagnosis tool [8].

Comparison With Prior Work

Bajoria et al [9] conducted a study to measure radiomorphometric indices in OPG to find interrelationships between the indices and age and sex. In the study, 23 patients were randomly selected to be examined. The results revealed that the MCI, PMI, mental index, and antigonial index can be effectively measured on OPG and could be used to determine osteoporosis. All indices were statistically significantly correlated with osteoporosis in both the younger and older age groups. All indices were lower in women than men [9]. Similarly, Suman and Redhu [10] conducted a study to assess relationships between BMD and radiomorphometric indices using panoramic radiography in tobacco users, and the authors concluded that tobacco had a detrimental effect on BMD as revealed by the MCI, PMI, and MI. Palaskar et al [11] conducted a study to assess relationships between personal habits like tobacco chewing, areca nut chewing, alcohol consumption, and BMD in Indian adult men aged 20 years to 60 years using OPG. They concluded that OPG indices, especially the antegonial index, were negatively affected in men with the personal adverse habits of interest. This radiography technique is readily available and reasonably priced. Dental practitioners might be the first to notice abnormalities in the mandible and make the necessary referrals because OPG is a standard diagnostic technique in the office [11].

Temur et al [12] evaluated the effect of anti-epileptic drugs (AEDs) on trabecular and mandibular cortical bone. The case group’s fractal dimension (FD) of the mandibular body and angle and mandibular cortical width were substantially lower than those of the control group ($P<.001$). Compared with second-generation medications, first- and third-generation AEDs were associated with reduced FD values in the ramus and angle ($P\leq.011$). Users of first- and second-generation AEDs had lower mandibular FDs than users of third-generation drugs ($P=.017$). Although PMI increased with more than 1 year of AED use ($P\leq.02$), drug use for at least 1 year was associated with

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considerably lower values for all FDs and mandibular cortical widths and more class 3 MCI assessments than short-duration use. Sex and age had no discernible impact [12]. A study was conducted by Önsüren and Temur [13] to examine the effects of likely sleep and awake bruxism on the mandibular trabecular bone structure in pediatric patients with bruxism using fractal analysis, OPG, and radiomorphometric measures. It concluded that bruxism can alter mandibular trabecular bone in children and teenagers. Just like in adult dentistry, fractal analysis can be used as a supplemental technique to identify the mandibular trabecular variations of patients with bruxism in pediatric dentistry [13]. Geçkil and Temur [7] investigated the effect of two different bisphosphonate types on bone using dental panoramic radiographs and compared these findings with those from a healthy cohort. This study demonstrated that changes in cortical bone structure are significantly influenced by the kind of bisphosphonate and the length of medication usage. It appears that bisphosphonates have a long-lasting effect on bone since these effects are persistent and unaffected by the amount of time that has passed since the last dose [7].

Strengths

It is possible to screen using OPG indices because a history of smoking, drinking, and eating betel nut products may be regarded as a risk factor for the development of osteoporosis [14]. Evaluation of bone density in chronic betel nut chewers has not yet been assessed and compared with bone density in nonchewers. Although the literature includes some studies in which bone density was altered in areca nut chewers, the scarcity of the same leads to the need for further research in this field [5]. Hence, this study will aid with assessing bone density in chronic areca nut chewers and help with educating patients about the condition, thereby aiding with appropriate treatment approaches and halting the progression of the same.

Limitations

The study will use OPG indices to evaluate jaw bone density; however, the indices cannot be compared with the gold standard dual x-ray absorptiometry to establish the efficacy of the OPG for determining jaw bone density due to unreliable patient compliance, high cost, and limited availability of dual x-ray absorptiometry.

Conclusion

This study hypothesizes that smoking, areca nut, and alcohol consumption negatively impact mandibular bone density based on the existing literature, which suggests reductions in MCI, PMI, mental index, and antegonial index. Although a few studies have demonstrated increased bone density, the majority reflected a reduction. Dentists can detect these changes through routine panoramic radiography examinations and identify patients at risk for osteoporosis at an early stage. A reduction in jawbone density is a significant risk factor for implant placement, prosthetic planning, and periodontal treatments. Therefore, dental implant placement and prosthetic planning should be approached more cautiously in patients with decreased bone density.

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Authors' Contributions

Conceptualization: AT, SD
Data curation: AT
Formal analysis: AT
Investigation: AT
Methodology: AT
Project administration: SD
Resources: AT
Software: SD
Supervision: SD
Validation: AT, SD
Visualization: AT, SD
Writing – original draft: AT, SD
Writing – review and editing: AT, SD

Conflicts of Interest

None declared.

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Abbreviations

AED: anti-epileptic drug
BMD: bone mineral density
FD: fractal dimension
MCI: mandibular cortical index
OPG: digital panoramic radiography
PMI: panoramic mandibular index

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Protocol

Web-Based Nursing Intervention to Promote Physical Activity Among Older Adults After Coronary Revascularization: Protocol for Mixed Method Pilot Study

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Abstract

Background: Given the high prevalence of coronary heart disease among older adults and aging populations, there is a need for secondary prevention interventions to help older adults become more physically active. Web-based interventions could be considered for this purpose, knowing that internet use is growing rapidly among older adults. In addition, since older adults would appreciate developing a trusting relationship with a nurse, web-based interventions should include this support, which is not widely observed in the literature.

Objective: This study aims to evaluate a web-based nursing intervention aimed at promoting physical activity in people 65 years and older with coronary heart disease.

Methods: A web-based nursing intervention was developed according to the Intervention Mapping framework in collaboration with a team of health care professionals (n=5) and based on the needs of older adults (n=10). The 7-week intervention (1 session per week) aims to support older adults living with coronary artery disease in resuming, maintaining, or increasing their level of physical activity after coronary bypass surgery or percutaneous coronary intervention. The intervention offers educational content on coronary heart disease and physical activity, suggestions for physical activity, reflective activities, case histories of older adults who have experienced different journeys, an electronic physical activity diary to track progress, and support from a nurse through feedback to increase knowledge, motivation, and sense of self-efficacy. The preliminary effects and impacts of the intervention will be assessed through a mixed method pilot study with a sequential explanatory design. First, a single-group pre-post test will be used to assess the intervention's preliminary effects on physical activity (electronic journal), quality of life (36-Item Short Form Health Survey version 2), knowledge (quiz), motivation, and self-efficacy (visual analog scale) of 30 older adults living with coronary heart disease, as well as the feasibility of the intervention. Second, a descriptive qualitative design will use semistructured interviews to assess the intervention's impacts as perceived by 8-12 older adults and its acceptability. Quantitative data on the effects of the intervention will be integrated with the collection and analysis of qualitative data to assess the impact perceived by older adults, using matrices. Nonparametric statistics and a thematic analysis will be produced. A joint display will be used to integrate mixed data.

Results: The results of this study will provide insight into the preliminary evaluation of a web-based nursing intervention to support older adults living with coronary heart disease as they increase their physical activity levels. The recruitment commenced in June 2024, and data collection should be completed by June 2025.

Conclusions: With the potential to promote older adults' health, this study could guide the development of new interventions to meet the needs of an aging population.

Trial Registration: ClinicalTrials.gov NCT06197347; https://clinicaltrials.gov/study/NCT06197347

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International Registered Report Identifier (IRRID): DERR1-10.2196/67678

(JMIR Res Protoc 2025;14:e67678) doi:10.2196/67678

KEYWORDS

older adults; web-based intervention; coronary heart disease; elder; elderly; older people; physical activities; physical exercise; exercises; exercising; digital; digital health; digital technology; digital interventions; nursing role; nurses; nursing; coronary; cardiology; heart disease

Introduction

Background

Coronary heart disease (CHD) is increasingly prevalent among older adults [1]. While aging contributes to CHD due to arterial stiffness and fatty plaque buildup, secondary prevention strategies, including lifestyle modifications such as increased physical activity, can improve survival and quality of life in this population [2-4]. Increasing physical activity is a core component of secondary prevention, and one of the most important habits to change due to its direct association with a reduced risk of complications and mortality associated with CHD [5-8]. Physical activity has many benefits for the health of older adults, such as improving quality of life [2,9]. Furthermore, such individuals consider an improved quality of life as a priority recovery goal following a coronary event [10,11].

In this regard, secondary prevention interventions have been shown to help promote healthy lifestyles in people with CHD, especially after cardiac revascularization (ie, coronary bypass surgery or percutaneous coronary intervention) [2,9]. However, these interventions, such as cardiac rehabilitation (CR) programs, are underused [12], especially by older adults [13,14], partly due to accessibility issues [15] and their lack of adaptation to aging-related challenges such as comorbidities, frailty, or physical limitations [13]. Given the paucity of literature on the needs of older adults for secondary prevention of CHD after cardiac revascularization, it is essential to explore this subject to develop new accessible interventions that are suitable for this population.

Home-based secondary prevention interventions offer a promising alternative to traditional CR programs, showing comparable benefits in promoting healthy lifestyle habits [16,17]. However, their implementation faces barriers such as high costs [9] and limited human and financial resources in the health care system [18]. The COVID-19 pandemic has further highlighted the need for innovative remote interventions to ensure continued support for older adults [19].

Advances in eHealth technologies (ie, the delivery of health care and services using information and communication technologies, including the web) are resulting in increased use [20]. Web-based interventions can be defined as care or treatments aimed at promoting behavior change and delivered, via a web browser, over the internet through various technological tools such as computers, tablets, and smartphones [20]. Web-based interventions could be considered as a means to support older adults with CHD in their adoption of healthy lifestyle behaviors because of their accessibility and flexibility of use [21], and considering that use of the internet among older adults has increased significantly in recent years [22]. In Canada and the United States, nearly 80% of older adults used the internet in 2022, compared with 73% in 2020 [23,24]. Several web-based interventions are available in the literature, but these are aimed at a population of all ages and none have been developed specifically for older adults [25,26]. Older adults may have distinct secondary prevention needs compared with younger adults (eg, information they want, how they should manage their complex condition, and strategies to maintain their various physical capacities) [27,28] because of the heterogeneous changes that occur with aging (eg, decreased functional capacity, comorbidities, and frailty) [29,30]. Several authors argue that web-based secondary prevention interventions should be developed to address the challenges associated with aging and to respond to the individualized needs of older adults [3,31]. Web-based secondary prevention interventions for people with CHD tend to be tailored rather than individualized to needs [32] and often lack interaction with health care professionals [33,34], factors that are critical for sustained engagement [35,36]. This situation calls for new studies.

Nurses could be well-suited to support older adults through web-based interventions, given the key role they play in managing chronic diseases, including CHD, promoting health and supporting healthy lifestyle habits [37,38]. Their strong interpersonal skills, highly valued by older adults [35,39,40], further reinforce their suitability for this role. Furthermore, their involvement in the secondary prevention of CHD is well-known in the literature [41,42]. To promote behavior change, web-based interventions should also be designed to address key factors influencing the target population, such as motivation and self-efficacy [43,44]. Older adults with CHD can have little motivation to change, low confidence in their ability to become active because of diminished physical abilities related to age [10,45], and may be poorly informed about the benefits of secondary prevention [45,46]. Despite this evidence, no existing web-based intervention has been specifically designed for this population while integrating nursing support. This study aims to address this gap by developing a web-based nursing intervention individualized to the needs of older adults with CHD and that aims to sustain their knowledge, motivation, and self-efficacy toward physical activity.

Aim and Research Questions

The purpose of this study is to evaluate a web-based nursing intervention to support older adults living with CHD in engaging in physical activity. This study aims to answer the following questions:

- Primary research question

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- What is the acceptability (content, structure, and usefulness) and feasibility (recruitment, retention, adherence, and fidelity) of a web-based nursing intervention to support older adults living with CHD in engaging in physical activity?

- Secondary research questions
  - What are the preliminary effects of the web-based nursing intervention on the physical activity level and quality of life of older adults living with CHD?
  - What are the qualitative impacts of the web-based nursing intervention as perceived by older adults on their physical activity level, quality of life, motivation, knowledge, and self-efficacy?
  - How do the qualitative findings on perceived impacts from older adults post intervention complement and illustrate the preliminary quantitative effects of a web-based nursing intervention developed for this population?

Methods

This protocol is registered on ClinicalTrials.gov (NCT16197347). Figure 1 summarizes the protocol steps.

Figure 1. Summary of research protocol. CHD: coronary heart disease.

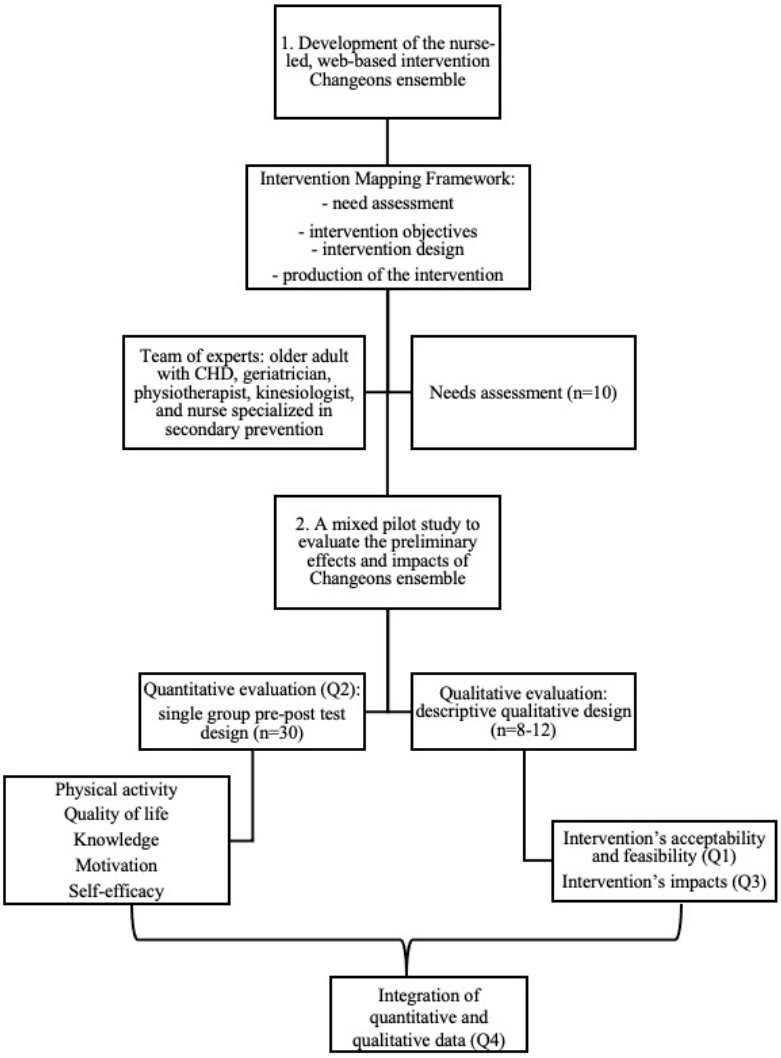

Intervention

The nurse-led web-based intervention, named "*Changeons ensemble*," was designed to support older adults living with CHD who have recently undergone cardiac revascularization in engaging in physical activity. The intervention was developed by the student researcher (AL), her supervisor (VD), and a team of experts (ie, older adult with CHD, geriatrician, physiotherapist, kinesiologist, and nurse specialized in secondary prevention), following the Intervention Mapping approach [44], which includes a needs assessment of older adults living with CHD who have recently undergone cardiac revascularization (n=10). The Intervention Mapping framework is relevant to this study, as it offers a model for intervention development in health promotion that includes all the decision-making steps for intervention planning [44]. Using this framework enabled a systematic approach to intervention development based as much on data collected from a population as on empirical data.

The intervention is based on the Information-Motivation-Behavioral skills (IMB) model. The IMB model posits that an individual with the necessary information and a high level of motivation can apply behavioral skills (ie, self-efficacy) to achieve behavior change [47]. This

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model has been selected because it can be used to act on the factors that seem most likely to influence the behavior of older adults, such as knowledge, motivation, and self-efficacy [45], as these factors converge with the constructs of the model. Figure 2, which was adapted with the authors' permission [48], presents the IMB model and the relationships between the constructs.

Figure 2. Information-Motivation-Behavioral skills (IMB) model adapted for use in this study.

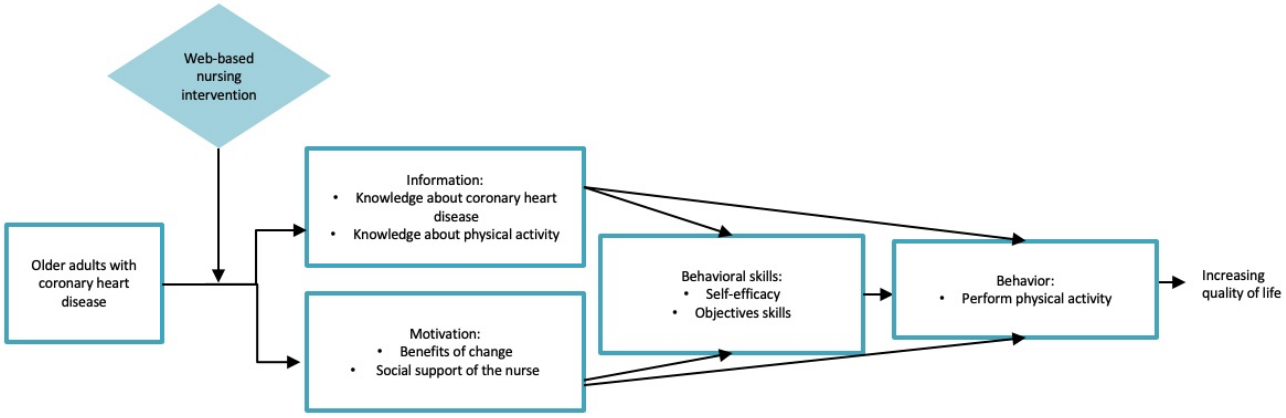

Through the intervention, information on physical activity and CHD, such as recommendations, benefits, and impacts, is provided to increase older adults' knowledge. The intervention aims to bring out the person's motivation by providing the support of a nurse and by exploring and reinforcing the benefits of change. Vicarious experience, verbal persuasion, and reinforcement of past and current successes are strategies used within the intervention to promote self-efficacy [49].

The team of experts was consulted to provide feedback on the intervention's content based on their area of expertise. The older adult with CHD offered his opinion on the usefulness and relevance of the intervention's content and components to be consistent with the needs of the target population. The geriatrician's contribution was to ensure that the intervention was aligned with the various challenges that can arise with aging, while the physiotherapist offered his expertise on functional limitations and physical activity. The kinesiologist's role was to validate the examples of suggested exercises for participants, ensuring they were safe in relation to CHD. The nurse ensured that the content was in line with clinical guidelines for older adults living with CHD.

Changeons ensemble is a 7-week, nurse-led, web-based intervention that includes educational content (eg, recommendations on physical activity and CHD), reflexive activities (eg, identifying motivation for physical activity), case stories (eg, different pathways of older adults living with CHD who engage in physical activity), physical activity suggestions (eg, instructions and images of cardiovascular or balance exercises), forums (eg, ask questions and exchange with peers), goal planning (eg, a target to be reached each week, with an action plan to achieve it), and an electronic physical activity diary. With a new session available every week, participants log in with a username and password on a secure Moodle (Martin Dougiamas) platform, accessible 24/7 at a time convenient to them. The intervention proposes an initial meeting in person, via videoconference, or by phone with the nurse to foster the older adult's commitment to the intervention and help build a relationship of trust [40,50]. Every week, the nurse supports participants through the web-based intervention by monitoring their progress, providing asynchronous written feedback by responding to their answers to reflective activities, and facilitating discussions and answering questions on the forum. In this role, the nurse aims to value participants, empower their abilities, bring out their motivations, highlight their progress, and offer advice and encouragement to promote physical activity, quality of life, knowledge, motivation, and self-efficacy. An email reminder is sent to participants after 1 week of inactivity on the platform.

Given the variability in activity levels within this population, the intervention focuses on promoting regular physical activity and reducing postrevascularization barriers rather than prescribing a specific type, duration, or intensity of exercise. We rely on individual support from the nurse and the reinforcement of knowledge, motivation, and a sense of self-efficacy to encourage physical activity, according to each older adult's physical and health condition.

The intervention was designed with patient-partner and user-friendly principles tailored to older adults, including a simple navigation system, large print and icons, and color contrast. The nurse provides technological support to participants, including explaining how the platform works and assisting them with any difficulties they may encounter. Step-by-step written instructions are provided for additional support.

The Consolidated Standards of Reporting Trials eHealth CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) was applied to ensure that all the aspects of the web-based intervention have been reported [20] and is available in Multimedia Appendix 1.

Design

A pilot study with an explanatory sequential mixed design (quantitative→qualitative) [51,52] will be conducted to evaluate the intervention's preliminary effects and impacts. The mixed sequential explanatory design implies that a quantitative method is followed by a qualitative one [51,52]. Therefore, the

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quantitative method for evaluating the preliminary effects of the intervention will be carried out first, followed by the qualitative method for evaluating the benefits perceived by older adults as a result of the intervention.

Quantitative Component

For the quantitative component, a single-group pre-post test design will be used to evaluate quantitatively the preliminary effects of the intervention on physical activity level, quality of life, motivation, knowledge, and self-efficacy. This quantitative component is presented according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist [53], presented in Multimedia Appendix 2.

Qualitative Component

For the qualitative component, a descriptive qualitative approach will be used to assess the acceptability and feasibility of the intervention, as well as its impact, as perceived by the older adults on their level of physical activity, quality of life, knowledge, motivation, and self-efficacy. The COREQ (Consolidated Criteria for Reporting Qualitative Research) checklist is presented in Multimedia Appendix 3 and will ensure that the qualitative portion of the study is explicitly reported [54].

Setting and Sample

Participants will be recruited in the cardiac units of a French-language university hospital in Montreal (Canada). The intervention will be delivered on the open-source learning platform Moodle [55].

Quantitative Component

To assess the preliminary effects of the intervention, we will seek to enroll 30 older adults living with CHD. According to some authors, 30 participants are sufficient for a pilot study [56,57], and this sample size is found in similar studies [58,59]. Given that we are interested in a vulnerable clientele that has a low participation rate in CR programs [14] and in research projects in general [60], we anticipate some challenges in terms of both recruitment and retention of participants. As the primary aim of this study is to explore preliminary effects, acceptability, and feasibility, a larger sample size was not deemed necessary at this stage.

Older adults will be recruited by the student researcher by convenience sampling during their hospitalization for coronary bypass graft surgery or a percutaneous coronary intervention. The first author (AL) will screen each patient's record to verify eligibility and then meet with the eligible patients to evaluate their interest in participating in the project after their hospitalization. Eligibility criteria for participation in this study will be (1) 65 years or older; (2) agreement to participate in the study within 3 months post hospitalization for a coronary bypass graft surgery or 1 month for a percutaneous coronary intervention; (3) no concurrent involvement in an intervention designed to increase their level of physical activity (eg, a CR program, consultation with physical activity expert) during their participation in the project; (4) fluency in French, spoken and written; (5) access to a computer or a tablet connected to the internet; and (6) no cognitive impairments according to the patient record (ie, decreased or impaired complex attention, executive functions, learning abilities, memory, or social skills). Recruitment will take place from June 2024 to June 2025.

Qualitative Component

We will contact the 30 older adults who took part in the intervention by phone to invite them to participate in the qualitative evaluation, with the goal of recruiting 8-12 participants. As suggested by several authors [61,62], we estimate that we will need 8-12 participants to reach data saturation regarding their perceptions of the intervention's impacts and its acceptability. Since the study requires a long-term commitment from the participants, we may not be able to reach the desired number of participants for the qualitative analysis. These results will form part of the assessment of the project's feasibility.

Data Collection

The data collection period is planned from June 2024 to June 2025. Table 1 summarizes the study variables and measures, which are discussed in detail in this section.

Electronic physical activity diary inspired by the IPAQ [63].

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Table 1. Summary of study variables and measurements.

Study variable	Data collection tool	
	Quantitative component	Qualitative component
Sociodemographic data	Self-administered questionnaire	Self-administered questionnaire
Intervention's acceptability	—[a]	Semistructured interviews with questions on appreciation of the intervention's content and structure
Intervention's feasibility	—	Logbook with data (%) on recruitment, retention, adherence, and fidelity to the intervention
Physical activity	Electronic physical activity diary inspired by the IPAQ[b] [63]	Semistructured interview
Quality of life	SF-36v2[c] questionnaire: 36 items with 3-, 5- and 6-point Likert scales [64,65]	Semistructured interview
Knowledge	Quiz consisting of 5 multiple-choice questions	Semistructured interview
Motivation	Visual analog 10-point Likert scale	Semistructured interview
Self-efficacy	Visual analog 10-point Likert scale	Semistructured interview

[a]Not applicable.

[b]IPAQ: International Physical Activity Questionnaire.

[c]SF-36v2: 36-Item Short Form Health Survey version 2.

Quantitative Component

For the quantitative component, we will assess the preliminary effects of the intervention on the participants' physical activity level, quality of life, knowledge, motivation, and self-efficacy (question 2). For sociodemographic data, a questionnaire will be completed by the participants at T1 (preintervention).

Physical Activity

Participants' physical activity level will be measured at T1 and T2 (postintervention) via an electronic physical activity diary completed by the participants on the platform. A self-reported physical activity diary has been shown to be easy to administer, well accepted, and more practical than other objective assessments of physical activity, such as accelerometers [66,67]. In this study, the electronic diary was inspired by the French version of the International Physical Activity Questionnaire (IPAQ) [68], by assessing physical activity over the last 7 days (type of physical activity and duration). It enables participants to self-monitor their physical activity each week by entering the type and duration of physical activity performed.

Quality of Life

The French Canadian version of a quality-of-life questionnaire (36-Item Short Form Health Survey version 2 [SF-36v2] [65]) will be completed by participants at T1 and T2 via LimeSurvey (Jason Cleeland). This questionnaire has 36 items to answer on 3-, 5-, and 6-point Likert scales, with a higher score indicating a better quality of life. It covers eight concepts: physical functioning, bodily pain, role limitations due to physical health problems, role limitations due to personal or emotional problems, emotional well-being, social functioning, energy, fatigue, and general health perceptions. The SF-36v2 is a revised and improved version of the SF-36 [69]. The SF-36v2 has good psychometric properties with internal consistency reliability ranging from 0.83 to 0.95, test-retest reliability ranging from 0.64 to 0.86, and median correlations of items to their scales ranging from 0.612 and 0.87 [69].

Knowledge

Participants' level of knowledge will be assessed through a quiz to be developed by the research team according to the content of the intervention. The quiz will include 5 multiple-choice questions about physical activity (eg, Which of these answers are benefits of engaging in physical activity?) and will be completed by participants at T1 and T2 via LimeSurvey.

Motivation

Participants' motivation will be assessed at T1 and T2 by auto-captured data on the platform with a visual analog 10-point Likert scale (ie, How important is it for you to increase your physical activity level? 0=somewhat important and 10=extremely important). Visual analog scales are useful for assessing change in individuals over time in a way that is comparable to more traditional Likert-type scales [70,71]. Visual analog scales have been used in several studies to rate subjective feelings about motivation, as they lacked valid rating scales [72-74].

Self-Efficacy

As for motivation, participants' self-efficacy level will also be assessed at T1 and T2 by auto-captured data on the platform using a visual analog 10-point Likert scale (ie, If you decided to increase your level of physical activity, how confident would you be in your ability to succeed? 0=somewhat confident and 10=extremely confident). Visual analog scales have been shown in several studies to be a valid method that allows individuals to visually estimate their sense of self-efficacy [75,76].

Feasibility

The following feasibility parameters will be assessed: (1) recruitment (ie, the proportion of eligible patients who agree to participate in the study), (2) retention (ie, the proportion of

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participants who complete the intervention), (3) adherence (the proportion of sessions and activities completed), and (4) fidelity to the intervention (ie, the difference between the planned and delivered intervention). Due to anticipated recruitment challenges and because the refusal rate during recruitment of older adults generally varies from 20% to 50% [77], we consider it feasible to achieve a recruitment rate of 70% for the desired sample size (n=21 older adults) in the given recruitment time (ie, 1 year). Of this number, we will aim to obtain a retention rate of 75% of the participants for completion of the intervention and data collection (n=16 older adults), considering that a retention rate of about 70%-80% is observed in similar studies of web-based interventions with populations of older adults [36,78,79].

Qualitative Component

For the qualitative component, we will assess the acceptability (question 1) and the impacts (question 3) of the intervention. Semistructured interviews will be conducted 1 week post intervention (T2) by a Master's student, a member of the research team who is unbiased and trained in conducting interviews. The interview guide was developed to address research questions 1 and 3. The acceptability questions were drafted on the basis of the characteristics of an intervention as outlined by Sidani and Braden [80], that is, structure and content. The impact questions were designed to assess the qualitative impact on the various outcomes of the study (ie, physical activity level, quality of life, knowledge, motivation, and self-efficacy). The interviews will last approximately 30 minutes and will be conducted by phone. Acceptability will be assessed through data collected on the intervention's structure (ie, delivery mode, number of sessions, frequency, and duration) and content (ie, information and activities proposed) to determine whether participants found the intervention appropriate to their situation and relevant in supporting their engagement in physical activity [81]. During the interviews, we will also evaluate the impacts of the intervention, as perceived by the participants, on their physical activity level, quality of life, knowledge, motivation, and self-efficacy (eg, Have you noticed any changes since participating in the *Changeons ensemble* intervention? If so, please tell us about the changes in your physical activity level). The interview guide was pretested with the patient-partner who contributed to the development of the intervention.

Data Integration (Mixed Component)

For a mixed explanatory sequential design study, some authors propose developing a joint display (refer to Figure 3 for an example). Joint display allows for the presentation of integrated quantitative data (eg, statistical) and qualitative data (eg, verbatim) [82]. In this study, quantitative data on the effects of the intervention will be integrated into the qualitative results [51] of the older adults' perceptions of the impacts of the intervention. The quantitative results will be integrated into the qualitative results to illustrate how the quantitative effects of the intervention can be connected to the qualitative impacts on physical activity level, quality of life, knowledge, motivation, and feelings of self-efficacy (question 4). To this end, we will follow the four steps proposed by Johnson, Grove, and Clarke [83], which are (1) listing, that is, listing data in the quantitative data (statistics) or the qualitative data (verbatims or categories) column; (2) matching, that is, matching quantitative data with qualitative data based on their similarity, patterns, or parallels; (3) checking, that is, verify whether the data are matched correctly; and (4) pillar building, that is, comparing and contrasting the findings from the last steps to build proposals based on patterns and insights in the integration themes column, to help clarify connections between the data.

Figure 3. Example of joint display.

Quantitative data	Quantitative categories	Integration themes	Qualitative categories	Qualitative data
Quality of life score (T1-T2)	Increased quality of life	Improved quality of life following the intervention	Feel better	Verbatim of the older adult's perceptions of the impacts of the intervention (eg, "*The intervention helped me to feel better,*" participant X).

Analysis

The sample will be described using descriptive statistics (eg, mean, SD, percentage, and frequency). Descriptive statistics will also be used to compare, between pre- and postintervention, participants' level of physical activity, knowledge, motivation, and self-efficacy as well as feasibility data. The Wilcoxon signed rank test will be performed to compare the results from the SF-36v2 questionnaire. Statistical analyses will be performed using QualityMetric's PRO CoRE system [84]. Semistructured interviews will be recorded and transcribed verbatim, and a thematic analysis [85] will be performed using MAXQDA Analytics Pro (VERBI Software GmbH) 2022. The data will be analyzed by the student researcher (AL) and validated by her supervisor (VD). Themes and subthemes will be identified from the verbatim transcripts and then grouped according to

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their complementarity, similarity, recurrence, or divergence to form salient thematic clusters. The links between these themes will be further explored to create thematic groupings, and a thematic tree will be developed in the form of a diagram [85].

Ethical Considerations

This study was approved by the ethics committee of the Centre hospitalier de l'Université de Montréal (23.237) and the Science and Health Research Ethics Committee of Université de Montréal (2024-5351). Written informed consent will be obtained from the participants. The data will be anonymized and stored on a secure server at the research center of the Centre hospitalier de l'Université de Montréal.

Results

This study will provide a preliminary evaluation of the acceptability, feasibility, impacts, and effects of a web-based nursing intervention for older adults after coronary revascularization. Findings will offer insights into recruitment, retention, and adherence, as well as participants' perceived impacts regarding physical activity, motivation, self-efficacy, and quality of life. The recruitment commenced in June 2024, and data collection is expected to be completed by June 2025. As of April 2025, we enrolled 20 participants. Results will inform the refinement of the intervention for future studies. Table 2 shows the SPIRIT flow diagram of the study.

Table 2. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) flow diagram: schedule of enrolment, interventions, and assessment procedures.

Timepoint	Enrolment (–t1)	Preintervention (t1)	Postintervention (t2)
Enrollment			
Recruitment poster	✓		
Eligibility screen	✓		
Informed consent	✓		
Interventions			
"Changeons ensemble" intervention		✓	✓
Assessments			
Physical activity level		✓	✓
Quality of life		✓	✓
Knowledge		✓	✓
Motivation		✓	✓
Self-efficacy		✓	✓

Discussion

Implications for Practice and Research

This paper describes the protocol of a study aimed at evaluating a web-based nursing intervention to promote physical activity among older adults with CHD. To our knowledge, this is the first study to propose a nurse-led web-based intervention developed according to the needs of older adults with CHD. This study has important implications for both practice and research.

In terms of practice, the intervention has the potential to promote physical activity and quality of life among older adults with CHD, as well as increase their knowledge, motivation, and sense of self-efficacy. This nurse-led intervention, specifically developed with and for older adults with CHD, could potentially respond to the needs of a sub-group of the population that is often excluded from secondary prevention programs. In terms of the research, this study will generate knowledge about the acceptability and feasibility of this intervention, which could lead to its evaluation on a larger scale and guide further studies in this area. By providing the support of a nurse despite the web-based mode of delivery, this study will generate more knowledge on the role played by nurses in supporting the adoption of healthy lifestyle habits via the web, what has been little studied. However, we believe that this intervention modality may allow nurses to follow older adults than they would in a face-to-face intervention.

Limitations

This study has certain limitations. First, the design for the quantitative evaluation of the intervention (ie, a single-group pre-post test) implies the absence of a control group. This means that we will not be able to eliminate the influence of confounding variables. For example, our results may be influenced by our participants' social support networks and digital literacy, which could affect the study's internal validity. Second, since we are proposing a convenience sampling method and participants may have a high level of digital literacy, the participants we recruit may not be representative of the senior population. As a result, we will not be able to generalize the results, but they will provide new knowledge on the acceptability and feasibility of the intervention, as well as its preliminary effects and impacts on older adults. To encourage the participation of older people with various levels of digital literacy, we made sure to develop an intervention that is easy for older adults to use. Among other things, we incorporated the comments of a patient-partner and took into account factors that may facilitate the use of web-based interventions by older

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adults (eg, large print and icons, color contrast, simple navigation, etc). In addition, an initial meeting with the nurse (face-to-face, via videoconference, or by phone) will help participants understand how the platform works, making it easier to use. Support will be provided by the nurse throughout the intervention to address any difficulties experienced with technology. Finally, another limitation of this study is the self-reported data, including physical activity levels recorded via an electronic diary. While this approach allows participants to document their activity in a flexible and accessible manner, it is subject to potential recall and social desirability biases. Future studies may consider integrating objective measurement tools (eg, fitness tracker) to complement self-reported measures.

Conclusion

The global COVID-19 pandemic and the increasing use of the internet by older adults suggest an urgent need to develop new models of care that can be accessed remotely. Such interventions should be capable of being individualized to the varying needs and preferences of older adults with CHD [31]. To facilitate the engagement of older adults in these types of interventions, a relationship of trust with a professional, such as a nurse, would appear to be essential [35,50]. We highly encourage researchers to continue developing and evaluating interventions that promote the health of older adults with CHD.

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Authors' Contributions

AL contributed to the conceptualization, investigation, and writing the original draft. VD contributed to the conceptualization, supervision, validation, and writing through review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT-EHEALTH (v 1.6.1).
[PDF File (Adobe PDF File), 398 KB - resprot_v14i1e67678_app1.pdf]

Multimedia Appendix 2
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOC File , 123 KB - resprot_v14i1e67678_app2.doc]

Multimedia Appendix 3
COREQ (Consolidated Criteria for Reporting Qualitative Research) checklist.
[DOCX File , 26 KB - resprot_v14i1e67678_app3.docx]

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Abbreviations

CHD: coronary heart disease
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials eHealth
COREQ: Consolidated Criteria for Reporting Qualitative Research
CR: cardiac rehabilitation
IMB: Information-Motivation-Behavioral
IPAQ: International Physical Activity Questionnaire
SF-36v2: 36-Item Short Form Health Survey version 2
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Training and Assessing Teamwork in Interprofessional Virtual Reality–Based Simulation Using the TeamSTEPPS Framework: Protocol for Randomized Pre-Post Intervention Study

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Abstract

Background: Interprofessional teamwork is essential for patient outcomes in emergency medicine; yet, effective training in this area is scarce. Virtual reality (VR) provides a promising, resource-efficient solution for simulating emergency scenarios and facilitating interprofessional collaboration. While VR-based training has shown benefits for medical skill and knowledge acquisition, assessing teamwork within such environments remains a challenge due to the lack of validated measurement tools. Existing teamwork assessment instruments, developed for physical simulations, may not fully apply to VR due to differences in communication modalities, interaction mechanics, and observer perspectives.

Objective: This study aims to adapt and validate the TeamSTEPPS framework to assess teamwork in VR-based training. Subsequently, these adapted instruments will enable the investigation of whether interprofessional teamwork can be successfully trained in VR scenarios.

Methods: Prior to the study, measurement instruments for subjective (Teamwork Perceptions Questionnaire) and objective teamwork quality (Team Performance Observation Tool, TPOT) will be adapted and validated for use in VR scenarios. Validation of the adapted version of the Team Performance Observation Tool includes expert consensus via a modified Delphi method as well as validity and reliability testing using recorded VR teamwork sessions. The study itself is designed as a prospective pre-post study with a planned enrollment of 65 nursing and 65 medical students working in randomly assigned interprofessional teams. On 3 timepoints (day 1, day 8, and day 15), participants engage in a VR scenario simulating 1 out of 3 different emergency medical conditions (esophageal variceal bleeding, exacerbated chronic obstructive pulmonary disease, and atrial fibrillation due to urinary tract infection). As an intervention, a structured training video on successful teamwork according to the TeamSTEPPS concept is shown on day 8 immediately before the second VR scenario. Teamwork is assessed objectively with the adapted version of the Team Performance Observation Tool and subjectively with the adapted Teamwork Perceptions Questionnaire. Medical performance will be recorded automatically by the VR software based on the medical measures conducted by the team.

Results: As of May 2024, a total of 28 interprofessional teams have been enrolled. Data analysis will begin in late 2025.

Conclusions: This study addresses the challenge of adapting teamwork assessment tools to VR environments and may provide insights into the potential of VR-based training for improving interprofessional collaboration in medical education. Future research could include a control group to measure the effects of team training more rigorously or use more enhanced technologies (eg, natural language processing) to capture the full range of teamwork behavior.

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KEYWORDS

interprofessional teamwork; medical education; TeamSTEPPS; Team Performance Observation Tool; team training; Teamwork Perceptions Questionnaire; virtual reality

Introduction

Interprofessional teamwork plays a crucial role in affecting patient outcomes in emergency medical contexts [1,2]. However, interprofessional team training is uncommon both in undergraduate medical education and in professional practice [3,4]. This is particularly due to the high personnel and resource requirements for effective team training [5,6]. Virtual reality (VR)–based training environments are playing an increasing role in emergency medicine, facilitating the widespread and effective learning of medical content, and may also enable interprofessional team collaboration training in the future [7]. The improvement in medical performance through such training is measured using various parameters such as checklists or "time to action" [8-11]. Some VR programs already allow for automated result recording [10], which could support examiners in complex practical examination settings in the future.

In contrast to capturing medical knowledge or performance, there are currently no validated tools for measuring (interprofessional) team collaboration in VR-based environments. For conventional physical simulation–based training, numerous tools exist to objectively capture various aspects of teamwork [12,13]. These are often based on Crew Resource Management or similar principles. However, these evaluation criteria cannot be fully transferred to VR scenarios for several reasons: Currently, team-capable VR training environments vary significantly in their level of functionality. For instance, considerable differences exist in how verbal interaction with virtual patients is represented (either through menu-based options or speech recognition [14]) and how haptic measures are depicted (solely via VR controllers [15,16] or additional haptic devices [8]). The ways teamwork is represented in VR environments (verbal communication, handing over objects, as well as briefing and debriefing) also may differ and nonverbal communication skills such as facial expressions and nuanced gestures are largely missing among current VR-based avatars. Finally, it is crucial to provide evaluators with a sufficient view of the actions and verbal communication in the VR scenario—whether as participants wearing a VR headset or through visualizing the participants' perspectives on a computer screen. These challenges may explain why the quality of teamwork in VR-based environments has barely been measured so far. While technical hurdles are increasingly being overcome through advances in hardware and software, assessment tools for team collaboration in virtual settings still need to be adapted and validated.

A well-validated framework that includes educational content and both subjective and objective tools for assessing teamwork in physical simulations is the TeamSTEPPS framework [17]. In its current version (3.0), it covers 5 dimensions: team structure, communication, leadership, situation monitoring, and mutual support, and provides both subjective and objective evaluation metrics. The objective metric, the Team Performance Observation Tool (TPOT), has been significantly enhanced in terms of test-retest and interrater reliability through the inclusion of behavioral anchors compared to the original version [18]. In a recently published comparison of the most promising team performance assessment tools for evaluating longitudinal training, the TPOT was rated the most comprehensive tool and showed the second-best interrater reliability [19]. The associated questionnaire for subjective team member perceptions, the Teamwork Perceptions Questionnaire (T-TPQ), is also well-researched and validated [20]. While other assessment tools may outperform in specific criteria [12], the TeamSTEPPS concept is well suited for studies assessing comprehensive learning outcomes in simulations due to its alignment between teaching and assessment tools.

This study aims to adapt and validate objective and subjective assessment tools for the facets of teamwork that meet the requirements of VR-based environments, using the TeamSTEPPS measurement instruments. In the planned prospective study, these assessment tools will be used to measure the objective quality and the subjective perceptions of teamwork longitudinally (before, immediately after, and 1 week after completing a VR-based team training). In addition, the medical performance of the teams will be assessed based on the medical actions taken. The hypotheses derived from this are as follows:

- H1: A VR-adapted TPOT (vTPOT) supplemented with behavioral anchors demonstrates good item characteristics (concurrent validity, interrater reliability, and internal consistency) for the various facets of teamwork compared to the original version.
- H2: VR-based team training leads to a sustainable objective improvement in all facets of teamwork performance in interprofessional teams (as measured with the vTPOT).
- H3: VR-based team training leads to sustainable subjective improvement in all facets of teamwork perceptions in interprofessional teams (as measured with an adapted T-TPQ).
- H4: The increasing quality of teamwork is associated with an improvement in treatment quality, represented by the automatically recorded percentage of correctly performed medical actions.

Methods

Apparatus

STEP-VR (version 1.0; ThreeDee GmbH, Munich, Germany) will be used as the VR simulation of complex emergencies, which represents a joint development between a 3D visualization company and the University Hospital of Würzburg. The version includes multiuser functionality, allowing the selection of an

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avatar with typical nursing or medical attire and multiple stylized faces (Figure 1).

The VR hardware setup for this study includes 2 OMEN by HP 17-ck0075ng Laptops (chipset: Intel Core i7-11800H; graphics adapter: NVIDIA GeForce RTX 3070 Laptop GPU [8 GB GDDR6 dedicated]) and 2 Oculus Quest III VR head-mounted displays (HMDs). The equipment enables STEP-VR to run at a constant framerate of over 60 frames per second on "high quality" display settings of the HMD.

Figure 1. Top left: participants with the virtual reality head-mounted display and image transmission to a monitor (background) for the study staff. Top right: interaction of stylized avatars in the first-person perspective. Bottom left: final evaluation after the simulation with an assessment of medical performance. Bottom right: overview showing stylized avatars and a virtual patient.

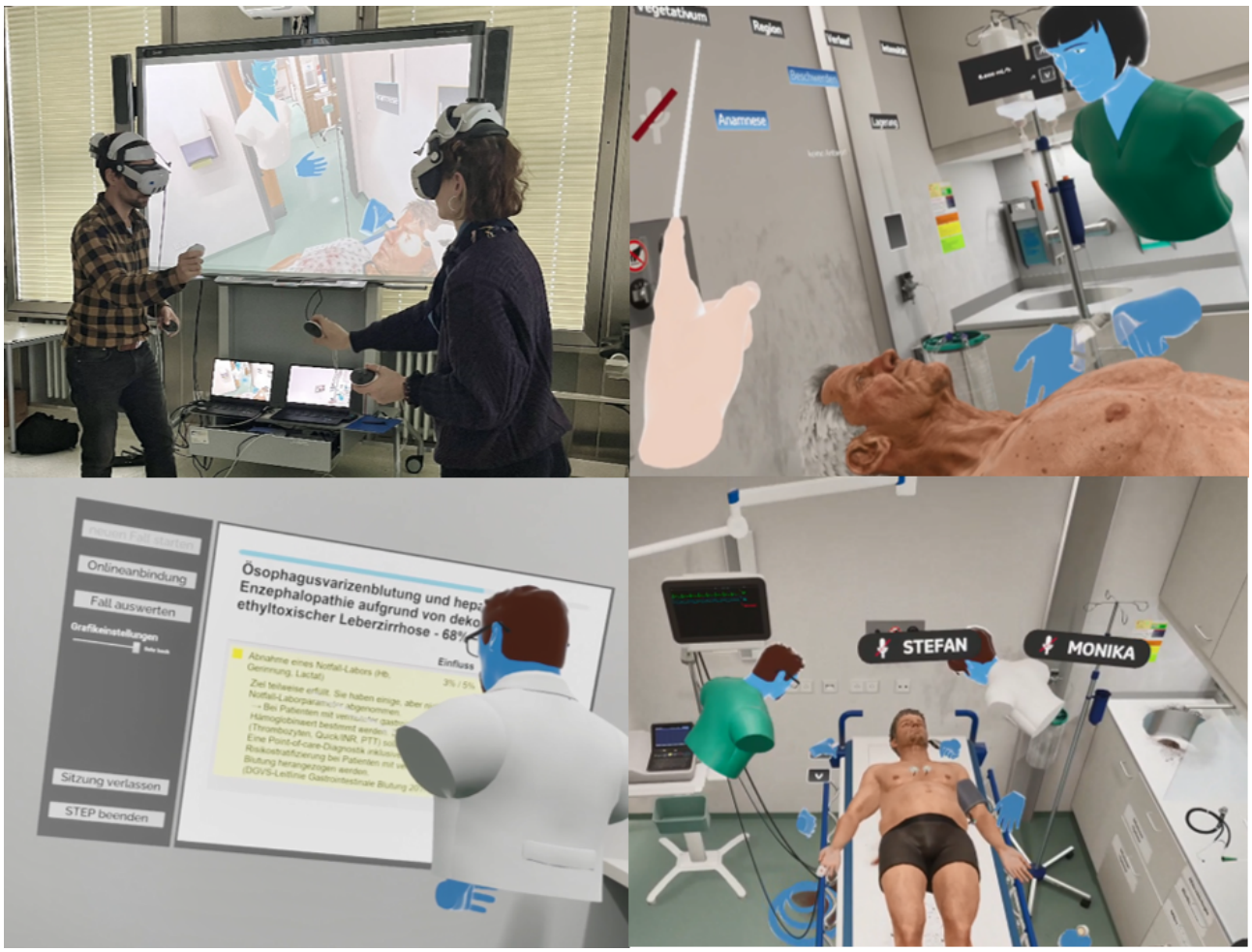

Adaptation and Validation of the Measurement Instruments for Teamwork Quality

Adaptation and Validation of the TPOT for VR-Based Scenarios

The original version of the TPOT includes 25 items to assess 5 facets of teamwork: team structure, communication, leadership, situational awareness, and mutual support. Compared to traditional, in-person team training, the novel context of VR-based interactions, as well as the small team size of 2 people, make adjustments necessary. To ensure content validity, respective changes will be proposed by 4 experts—a certified TeamSTEPPS expert (HP), a specialist in internal medicine and medical education (TM), an intensive care nurse with additional specialization in medical education (JM), and the study coordinator (ML, a skills lab tutor with special training and 2 years of experience in undergraduate medical education)—independently and implemented after thorough joint discussion. In the next step, a modified Delphi method will be applied. Experienced doctors or nurses with either additional qualifications in medical education, specialization in emergency medicine or emergency nursing, or extensive experience in conducting team training form the expert panel. These experts will be asked to rate the appropriateness and applicability of items within the novel context of VR-based interactions [21].

To investigate the concurrent validity between the original TPOT and vTPOT, subsequently, 6 video recordings of teamwork in virtual reality scenarios will be evaluated by multiple raters using both instruments, and the correlation will be calculated overall and for each facet of teamwork. The interrater reliability for the vTPOT, as well as the internal consistency, will also be calculated from this analysis.

Adaptation and Validation of the T-TPQ for VR-Based Scenarios

The 35-item self-report tool T-TPQ developed by TeamSTEPPS, uses 5-point Likert scales to measure staff perceptions of Team

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Structure, Team Leadership, Situation Monitoring, Mutual Support, and Communication. These 5 facets of teamwork correspond to those described in the above-mentioned TPOT. The 5-point Likert scale ranges from 5="strongly agree" to 1="strongly disagree." All items of the T-TPQ were translated into German.

For the identification of inappropriate items of the T-TPQ, quantitative and qualitative methods will be applied. In the first step, as part of a pilot study, all participants initially answered the 35 items of the original T-TPQ. Following this, internal consistency is calculated and items that strongly deviate from the responses to other items will be identified.

In the second step, an additional response option, "not applicable," will be integrated into the T-TPQ for all items. Also, within the pilot study, participants will be asked to explain why they had rated an item as "not applicable." Exclusion of inappropriate items will be made based on these analyses.

Study Design

A prospective preintervention-postintervention study will be conducted between May 2024 and June 2025. Teams consisting of 1 nursing and 1 medical student will complete 3 different interprofessional VR-based scenarios on 3 dates. These teams will be newly randomized for each session.

Three scenarios, each lasting about 30 minutes, will be completed by all participants in random order on different dates: (1) esophageal variceal bleeding due to ethyl-toxic liver cirrhosis, (2) exacerbated chronic obstructive pulmonary disease, and (3) tachycardic atrial fibrillation due to complicated urinary tract infection. The contents of the scenarios and indicated medical actions are listed in Table S1 in Multimedia Appendix 1 and were already described in detail elsewhere [16,22]. Participants can communicate via voice-over IP and interact with each other through avatars during the scenarios (eg, handing over equipment or demonstrating findings on a screen). The type and order of medical actions and teamwork elements are not predetermined and can be independently structured by the team members (eg, briefing and mid-discussion). After the scenario, a detailed guideline-based evaluation of the medical actions and an overview of the physiological course of the disease can serve as the basis for debriefing.

On the first date (day 1), informed consent will be obtained. A tutorial will follow to familiarize participants with VR hardware and software. The first scenario will be completed without specific prior team training (pre-test). On the second date (day 8), a training video on successful teamwork including practical recommendations will be shown (approximately 30 min). The content of the training video is based on the official TeamSTEPPS guidelines [17] and has been adapted by the authors of the study to fit the specific context (limited time and VR setting). In addition, video examples were shown to demonstrate how certain team interactions (particularly for performing "Check-Backs," "Huddles," giving feedback, and applying the "Two-Challenge Rule") can be implemented in VR. Then, the second scenario will be completed (post test). A total of 7 days later (day 15), without additional training, the third and final scenario will be completed (retention test). Figure 2 provides an overview of the study design and data collection.

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Figure 2. Overview of the data collection process. vTPOT: Team performance observation tool adapted for virtual reality scenarios. T-TPQ: TeamSTEPPS T-TPQ; VR: virtual reality.

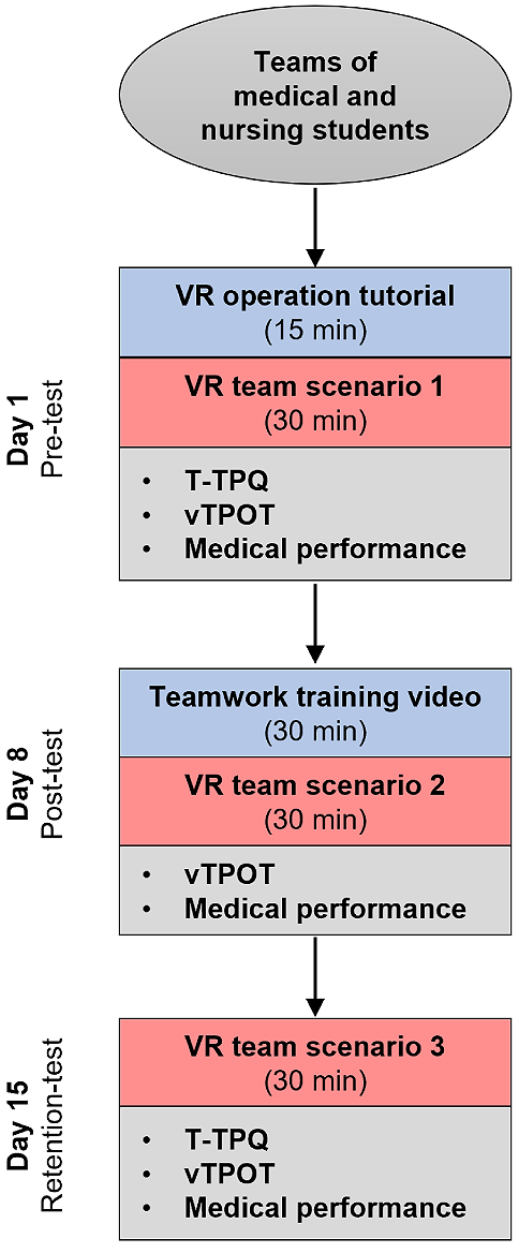

Participants

Overview

All regularly enrolled nursing students in their second-third year of training and all medical students in their 8th-10th semester at the University Hospital of Würzburg are eligible to participate. Participants of the study will provide written informed consent after being detailed on the study conditions. Inclusion criteria and exclusion criteria are listed in Textbox 1.

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Textbox 1. Eligibility criteria.

Inclusion criteria

- Regularly enrolled nursing students in their second or third year of training or medical students in their eighth to tenth semester
- Signed informed consent provided
- 18 years of age

Exclusion criteria

- Known epilepsy
- Known severe motion sickness

Sample Size Calculation

Since the team tandems are reassembled in a new, randomized form at each session a sample size estimation for 3 repeated measures timepoints could not be computed. Instead, we had to assume 3 independent groups. A between-groups ANOVA with an α level of 5%, a power of 80%, and assuming a large effect size, indicated that approximately 65 team tandems would be required, resulting in a total of 130 participants.

Measurement Instruments

Measures of Teamwork Quality

Both measures of teamwork quality are based on the TeamSTEPPS framework and include items related to the 5 facets of team structure, communication, leadership, situation monitoring, and mutual support. Details on the adaptation and validation process are provided in the corresponding section.

Objective teamwork will be measured through first-person video recordings of the VR sessions, which will be analyzed using the adapted version of the TPOT (vTPOT). This tool will evaluate observable behaviors and team interactions based on predefined teamwork criteria.

Subjective teamwork will be assessed using the adapted version of the T-TPQ completed by the participants after the first and third VR scenarios, focusing on their perceptions of teamwork quality.

Automatically Recorded Medical Performance Score

After each scenario, both team members can view and discuss the final evaluation together. All medical tasks specific to each scenario are assessed and it is recorded whether they were fully completed, partially completed, or not completed at all. The checklists for each scenario had been previously established by the authors based on guidelines from professional societies [23-25]. It was already ensured as part of a pilot study, that the automated final evaluation—in comparison with a manual checklist—accurately recorded all measures [10]. Importantly, when recording the tasks, the VR software does not differ whether they were carried out by medical or nursing staff. Based on that, a percentage score of medical performance for each team is generated.

Ethical Considerations

The local institutional review and ethics board judged the project as not representing medical or epidemiological research on human participants and as such adopted a simplified assessment protocol. The project was approved without any reservation (proposal 20240422-01). Students will be informed about the study and their participation is voluntary. Written informed consent is obtained in printed form from all participants, who are also provided with information on data processing for the analysis and the publication of results. Contact details are supplied for participants wishing to withdraw their consent to data processing. The decision to participate or not has no consequences on the students' academic progress. Survey data from the questionnaires are collected anonymously using the EvaSys platform. Data are processed and stored in accordance with local data protection laws. A €30 (approximately US $33.40) book voucher will be handed to the participants upon completion of day 3.

Statistical Analysis

Test quality criteria of vTPOT will be assessed as follows: For concurrent validity, Pearson correlations will be calculated. Interrater reliability of the vTPOT will be calculated using Cohen Kappa to quantify the agreement between the assessments of the independent reviewers. Internal consistency of the vTPOT will be assessed by using Cronbach α. A value exceeding 0.7 will be considered acceptable, and greater than 0.8 as good. Considering the results of objective team performance, subjective teamwork perception, medical performance scores, and descriptive statistics including mean and SD will be calculated and presented in the format of mean and SD. Pearson correlations will be calculated to capture relationships between the results of different measurement instruments. The Shapiro-Wilk test is used to check for normal distribution. In case of a violation of the normality assumption, nonparametric tests (Wilcoxon rank test for group differences and Spearman test for correlations) are used. The calculations and generation of figures will be performed using GraphPad Prism (Version 10.1.2; GraphPad Software Inc).

Results

This study received ethics approval in April 2024. As of May 2024, the enrollment of participants is ongoing and currently (March 2025) has 28 enrolled interprofessional teams. Data collection and analysis will be complete in December 2025.

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Discussion

Strengths and Limitations

This study leverages advanced VR technology to enhance interprofessional team training in medical education, allowing participants to engage in immersive, high-fidelity scenarios that closely mimic real-life emergency situations. A key strength lies in the use of an established VR-based training program (STEP-VR) that has been implemented in curricular teaching at several locations in Germany since 2020 and has already been evaluated in various teaching and examination settings. In terms of teamwork, the well-researched and validated measurement instruments of the TeamSTEPPS framework are used as a foundation, which is optimally aligned with teamwork training. The adaptation and validation are carried out in a rigorous selection process together with experts from all involved professions. Thus, the results will provide both objective and subjective insights into the improvement of teamwork skills. In addition, the study's relatively large sample size and inclusion of participants from different cohorts within nursing and medical programs offer a comprehensive view of the potential impact of VR-based training on interprofessional teams.

Despite these strengths, there are several limitations to consider. First, the absence of a control group limits our ability to definitively attribute improvements in teamwork to the VR-based training intervention alone. The pre-post design allows for intragroup comparisons, but the lack of a parallel group experiencing conventional training or no training reduces the robustness of our findings. In particular, regarding the subjectively perceived quality of teamwork, an anticipated treatment effect of uncertain magnitude could arise due to the lack of a control group. To mitigate this, we reassemble the teams for each session. While an effect due to mere repetition is also conceivable for the objective measurements of teamwork quality, it is less likely, as most TeamSTEPPS concepts (eg, check-backs, the Two-Challenge Rule) are unlikely to be learned intuitively. Moreover, the intervention (the training video on successful teamwork) is significantly shorter than typical training sessions from the TeamSTEPPS framework and may not achieve a sufficient effect. However, with regard to future application, it seemed important to find a training concept that could be applied both in academic studies and within the tightly scheduled clinical routine. In addition, the study is conducted at a single institution, which may restrict the generalizability of the results to other educational contexts or healthcare systems. Finally, another limitation stems from the voluntary nature of participant enrollment. It is possible that those opting to participate may already have a positive attitude toward teamwork or technology, potentially introducing a selection bias.

Challenges

One of the main challenges in this study is the adaptation of the TPOT and T-TPQ to VR environments. VR scenarios differ from traditional simulation in their representation of communication and interaction, as some elements (eg, natural communication with patients and their relatives) may be missing and others (eg, nonverbal cues and nuanced interpersonal behaviors) are often not as effectively captured in virtual environments. To address this, the vTPOT has been developed, but further validation will be necessary to confirm its reliability and validity in virtual settings. In addition, the need for evaluators to accurately observe and assess participant actions in a VR scenario poses a challenge. Ensuring a clear and comprehensive view of participant behaviors, both in real-time and via recordings, will be crucial for the consistent and objective application of the vTPOT. Finally, recruiting participants could prove challenging, as the curricula of the different study programs vary significantly and include shift work during practical placements.

Future Implications

To address some of the study's limitations, future research could incorporate a control group receiving traditional team training or no intervention, allowing for a more rigorous comparison of the effectiveness of VR-based training. A multicenter approach could also increase the generalizability of the findings by including participants from different educational institutions and health care settings. Moreover, future studies could explore the integration of more sophisticated haptic devices and natural language processing to enhance the realism of the VR environment and better capture the full range of teamwork behaviors. As VR technology continues to advance, it will be essential to continuously refine the tools used for teamwork assessment to ensure they remain aligned with the evolving capabilities of the technology.

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No generative artificial intelligence was used in the writing of this manuscript.

Data Availability

The datasets generated during and analyzed during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

ML contributed to the conceptualization and will conduct the investigation and data curation. JM contributed to the conceptualization of the study and is involved in the recruitment of nursing participants. HP serves as the TeamSTEPPS expert, responsible for the adaptation of the questionnaires and the training of additional study personnel as raters. JB assisted in conceptualization of the study and will perform statistical analysis. SK also contributed to the conceptualization and participated in the writing, review,

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and editing of the manuscript. TM was responsible for the conceptualization of the study, funding acquisition, supervision of the execution and data analysis, and writing the original draft for this research protocol.

Conflicts of Interest

TM was involved in the software development process of STEP-VR.

Multimedia Appendix 1
Medical actions to be performed during the virtual reality scenarios.
[DOCX File , 16 KB - resprot_v14i1e68705_app1.docx]

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Abbreviations

HMD: head-mounted display
TPOT: Team Performance Observation Tool
T-TPQ: Teamwork Perceptions Questionnaire
VR: virtual reality
vTPOT: adapted version of the TPOT

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Protocol

Implementation and Evaluation of a Best Practice Advisory to Reduce Inequities in Technology Use for People With Type 1 Diabetes: Protocol for a Mixed Methods, Nonrandomized Controlled Trial

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Abstract

Background: Continuous advancements in diabetes technologies have improved self-management for people with type 1 diabetes. Continuous glucose monitoring and automated insulin delivery systems have enhanced the quality of life and glycemic outcomes while reducing severe hypoglycemia and diabetes ketoacidosis hospitalizations. Despite these benefits, racial inequities in the use of advanced diabetes technology (ADT) persist.

Objective: This study aims to develop and evaluate a best practice advisory (BPA) within the electronic medical record (EMR) to reduce racial and ethnic disparities in ADT use. We hypothesize that an EMR-based BPA designed to standardize the prescribing of ADTs will minimize racial and ethnic disparities in ADT adoption or progression in use among pediatric and adult people with type 1 diabetes.

Methods: The Best Practice Advisories to Reduce Inequities in Technology Use (BPA-TECH) study will use a nonrandomized matched pair intervention design. Phase 1 will use qualitative methods to develop and refine the BPA, including focus groups and surveys of health care providers and people with type 1 diabetes or their caregivers. Phase 2 will evaluate the effectiveness of the BPA through a controlled before-after study of people with type 1 diabetes seen at 7 T1D Exchange Quality Improvement Collaborative (T1DX-QI) centers, with control people with type 1 diabetes matched from nonintervention T1DX-QI centers. The baseline and postintervention periods will be the 12 months before and 12 months after deployment of the BPA at the intervention

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centers, respectively. Eligibility criteria include people with type 1 diabetes aged ≥2 years with an EMR diagnosis of T1D during the baseline period. The primary outcome is the progression in ADT use from the baseline to postintervention periods.

Results: This 3-year study began in July 2024, with data collection from key stakeholders for phase 1 qualitative research beginning in August 2024. For phase 2, we estimate approximately 3000 eligible non-Hispanic Black and Hispanic people with type 1 diabetes at the intervention centers and 15,000 matched controls. Data on ADT use, glycated hemoglobin (HbA_{1c}), severe hypoglycemic events, and diabetes ketoacidosis events will be collected via the T1DX-QI coordinating center. The study is powered to detect a between-group difference of 15% in the proportion of patients in the intervention and control groups in meeting the primary endpoint. We anticipate the completion of this study by May 2027.

Conclusions: The BPA-TECH study aims to leverage health IT to address racial and ethnic disparities in ADT use among people with type 1 diabetes. By standardizing the approach to ADT prescribing for people with type 1 diabetes, the BPA-TECH has the potential to promote equity in diabetes management and improve clinical outcomes. The outcomes of this study will inform future efforts to reduce health care disparities.

Trial Registration: ClinicalTrials.gov NCT06931275; https://clinicaltrials.gov/search?term=NCT06931275

International Registered Report Identifier (IRRID): DERR1-10.2196/71038

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KEYWORDS

equity; disparities; continuous glucose monitor; automated insulin delivery system; insulin pump; type 1 diabetes; best practice advisory; practice advisory; clinical decision support

Introduction

Over the past decade, continuous advancements in diabetes technologies have helped to ease the burden of diabetes self-management for people with type 1 diabetes (T1D). Continuous glucose monitors (CGM) and automated insulin delivery (AID) systems have not only led to improved quality of life but also better glycemic outcomes and reduced incidence of hospitalizations for severe hypoglycemia and diabetic ketoacidosis (DKA) [1,2]. Given these clinical benefits, the American Diabetes Association now recommends that CGM be considered the standard of care for all people with T1D and that AID systems be recommended to people with T1D who are capable of safely using them [3].

Despite proven clinical benefits, racial inequities in the use of advanced diabetes technologies (ADTs), such as AID systems and CGMs, persist in both children and adults with diabetes [4-8]. Compared with Non-Hispanic White people with T1D, Non-Hispanic Black people with T1D have 1.5% higher glycated hemoglobin (HbA_{1c}) levels on average [9] and are more than 3 times as likely to be hospitalized for hypoglycemia or DKA [10,11], yet they are half as likely to be using ADTs [12].

Factors contributing to these disparities include individual barriers like cost concerns, insertion pain, and alarm anxiety [13-16], as well as provider-level barriers such as insufficient knowledge, bias, and clinical decision-making criteria that do not align with current guidelines [17-19]. System-level barriers include insurance coverage issues and complicated processes for obtaining devices [20,21]. For example, a recent 7-year study at a large academic medical center found significantly lower rates of CGM discussions and use among Black people with T1D compared with their White counterparts, even after adjusting for various other factors [6]. In addition, a study by the T1D Exchange Quality Improvement Collaborative(T1DX-QI) highlighted the presence of implicit racial bias in approximately one-third of endocrinologists when prescribing ADTs [19].

Health IT (HIT) has the potential to address racial inequities in the prescribing and use of ADTs. HIT tools within the electronic medical record (EMR) include computerized provider order entry, clinical decision support (CDS) systems, patient communication portals, population health tools, and data warehouse tools among others. Recommendations for using HIT to reduce racial disparities include the standardized collection and use of race and ethnicity data, identifying inequities, tailoring quality improvement efforts, developing CDS systems for areas with significant disparities, and including input from racial and ethnic minorities in developing HIT tools [22]. CDS systems have been demonstrated to reduce racial disparities for multiple clinical conditions, including venous thromboembolism prophylaxis [23], chronic disease management [24-26], and HIV screening [27]. For example, a CDS intervention in people with heart failure led to a significant increase in referrals and guideline-recommended testing for non-Hispanic Black and Hispanic patients [28]. Compared with manual approaches, computer-based CDS systems are more effective in improving clinical practice and patient outcomes [29,30]. Evidence supports the success of CDS tools in diabetes management, where automated recommendations have led to improved glycemic outcomes and better adherence to clinical guidelines.

This Best Practice Advisories to Reduce Inequities in Technology Use (“BPA-TECH”) study will develop and evaluate a best practice advisory (BPA), an informatics alert, aimed at reducing disparities in ADT use among people with T1D. To the best of our knowledge, no CDS systems have been specifically developed or evaluated to address disparities in T1D technology use in a multicenter study. This gap is significant given the substantial evidence demonstrating the magnitude of this disparity and its adverse impact on clinical outcomes. We hypothesize that an EMR-based BPA designed

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to standardize the approach to people with T1D selection and prescribing of ADTs will minimize racial disparities in ADT use and progression among pediatric and adult people with T1D. We propose testing this hypothesis through a nonrandomized matched-pair intervention study, assessing a center-wide intervention among 7 clinical centers participating in the T1DX-QI.

Methods

Overall Study Design

This BPA-TECH study will use mixed methods and nonrandomized controlled trial designs (ie, controlled before-after study) to implement and evaluate a BPA aimed at reducing inequities in the use of ADTs among children and adults with T1D. Phase 1 will be a qualitative mixed methods study to develop, implement, and refine the BPA. Phase 2 will be a prospective nonrandomized matched pair intervention design to evaluate the effectiveness of the BPAs in promoting prescribing and thus patient use of ADTs. The study organizing committee will be represented jointly by principal investigators in the T1DX-QI coordinating center and Johns Hopkins University, while the T1DX-QI will be responsible for the data management and analysis. We adhered to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (Multimedia Appendix 1) in the development of this study protocol and all items from the World Health Organization Trial registration dataset are included [31,32]. Protocol amendments will be communicated during monthly meetings between the organizing committee and the participating clinical sites, and updates will be posted on ClinicalTrials.gov. The timeline for this 3-year study is shown in Figure 1.

Figure 1. Best practice advisory development and implementation process. AID: automated insulin delivery; BPA: best practice advisory; CGM: continuous glucose monitoring.

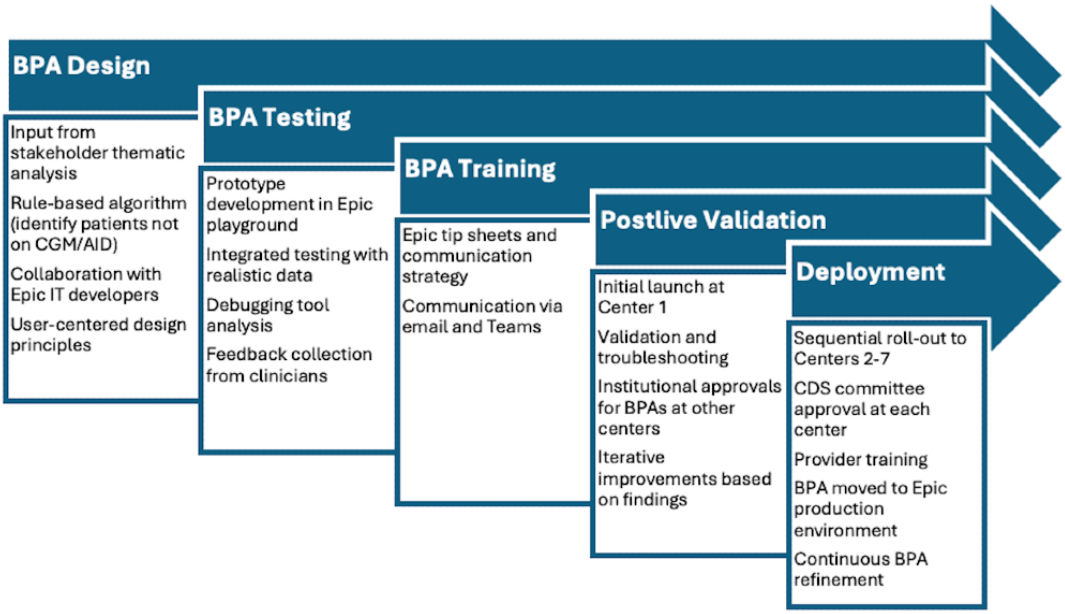

Study Setting

In 2016, through financial support from the Leona M. and Harry B. Helmsley Charitable Trust, T1D Exchange established the T1DX-QI, which initially included 10 diabetes and endocrinology centers focused on population health by advancing quality improvement, health equity, and real-world studies. The network has since expanded to include 62 T1D and 20 type 2 diabetes (T2D) centers, along with partners in primary care.

T1DX-QI manages more than 10 multicenter projects annually, with 4-10 centers participating per project, and has expanded its scope to include equitable access to diabetes technology and devices for both T1D and T2D populations.

In phase 1 of the study, we will recruit health care providers specializing in diabetes management from academic hospitals affiliated with the T1DX-QI. People with T1D or their caregivers will be recruited from the T1DX online registry, which includes individuals across the United States who may receive care in community clinics or academic hospitals. Phase 2 of the study will also encompass participating clinical sites affiliated with the T1DX-QI, specifically academic medical centers.

Phase 1: Implementation

Stakeholder Input

During the qualitative phase of this study, we will use electronic surveys and conduct focus group sessions and structured interviews of (1) pediatric and adult endocrinology and diabetes health care providers from centers who are part of the T1DX-QI and (2) people with T1D and their caregivers. The objective of the qualitative phase of this research study is to solicit stakeholder input regarding the perceived utility, design, functionality, benefits, and potential challenges of a BPA targeting increased ADT prescribing for people with T1D. We will use the Agency for Healthcare Research and Quality (AHRQ) “Five Rights” for effective CDS [33] (Table 1) and the T1D Exchange Health Equity Framework as guiding frameworks [34].

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For the health care providers, 8 focus groups will be conducted with a multidisciplinary group of providers (approximately 3 to 5 participants per focus group) selected from centers participating in the T1DX-QI collaborative to understand systems barriers to incorporating a BPA, criteria that would trigger the BPA, and reasons for deciding not to prescribe ADTs to patients. The focus group guide is provided in Multimedia Appendix 2. Eligible participants will be physicians, advanced practice providers, certified diabetes care and education specialists, and nurses who are involved in the care of patients with T1D and have expertise in the management of ADTs along with IT specialists involved in the development of BPAs. An incentive of US $150 remuneration will be provided to focus group participants. In addition, 4 questions related to the proposed BPA were sent to all participating centers in the T1DX-QI as part of their annual survey (Multimedia Appendix 3).

Table 1. Agency for Health Care Research and Quality 5 rights of effective clinical decision support frameworks to guide electronic surveys and focus group sessions.

Five rights of clinical decision support	Provider	Patients
Right information	• How to translate ADA[a] standards of care for • CGM[b] and insulin pumps into prompt and alert? • Reason device not offered or declined?	• What information would be helpful to you in making a decision about using ADT[c]? • Reasons device declined?
Right person	• Who should receive the prompt? Endocrinologist or diabetes advanced practice provider? Primary care physician?	• Who should receive the information about technology (patient only, parent, primary care physician)?
Right intervention format	• Define BPA[d] inputs	• MyChart notification?
Right channel	• Order entry • Progress note template • Level of service (closing chart) • Health maintenance or care gap	• MyChart notification • Previsit questionnaire • Postvisit questionnaire
Right timing	• Previsit charting • During encounter • When closing encounter • How often? Once, 3 months, 6 months, 12 months?	• Before visit? • After visit? • How often? Once, 3 months, 6 months, 12 months?

[a]ADA: American Diabetes Association.

[b]CGM: continuous glucose monitoring.

[c]ADT: advanced diabetes technology.

[d]BPA: best practice advisory.

All participating intervention centers currently use the Epic EMR system; therefore, focus group sessions will also be guided by Epic's CDS setup and support guide as a reference to inform the questions for the focus group session and qualitative interviews. It is important to note that EHR systems often use varying terminology to describe CDS alerts. For instance, the Epic EMR vendor recently renamed its "Best Practice Advisory" to "Our Practice Advisory." To maintain consistency throughout this study, we will use the term "BPA" to refer to CDS alerts.

For people with T1D and caregivers, we will administer a 20-item Qualtrics questionnaire on the T1D Exchange Online Registry, which is accessed by approximately 19,000 caregivers or individuals with T1D who have consented to be contacted about additional studies. People with T1D or caregiver survey (Multimedia Appendix 4) will address (1) the perceived need for the BPA, (2) benefits and concerns, (3) relevant information and communication approaches, (4) the importance of person-centered care, and (5) user interface and alerts. The goal is to survey approximately 50 caregivers of youth with T1D and 50 adults with T1D. Participants completing the electronic survey will be offered the opportunity to participate in a follow-up structured interview.

We will conduct structured interviews with approximately 10 caregivers of youth with T1D and 10 adults with T1D to capture people with T1D perspectives on BPAs related to ADTs (Multimedia Appendix 5). For both the interviews and survey, we will recruit a representative sample of 50% non-Hispanic Black and Hispanic people with T1D. Participants will receive a US $100 payment for time remuneration.

All focus group sessions for both health care providers and people with T1D or their caregivers will be conducted by T1DX-QI staff trained in qualitative interviewing. Focus group sessions will be audio-recorded, transcribed, and exported into NVivo software (NVivo version 13, Lumivero) for data organization and management and will continue until thematic saturation is reached. Focus group guides may be iteratively adapted based on insights gathered during the sessions.

Intervention Centers

A total of 7 T1DX-QI clinical centers, consisting of pediatric and adult diabetes specialty clinics in the United States (Table

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2), will participate in both the development and implementation of the BPA. A 7-item Qualtrics survey was distributed to all clinical centers within T1DX-QI to gather information on their EMR systems, capacity to develop automated alerts for CGMs and AIDs, IT capacity and commitment to the project, anticipated EMR freezes or delays during the planned intervention period, typical timeline for EMR changes at the institution, and previous experience building BPAs. Based on these responses, centers were selected to ensure geographical representation of the United States and a balance of pediatric and adult centers, with priority given to clinical centers using Epic EMR and demonstrating capacity, interest, and commitment to the project.

Table 2. Intervention clinical centers.

Intervention center	Clinical center	Geographical region	Pediatric or adult
1	Johns Hopkins	Mid-Atlantic	Pediatric and adult
2	Hassenfeld Children's NYU[a]	Northeast	Pediatric
3	Upstate Medical University	Northeast	Adult
4	Nationwide Children's	Midwest	Pediatric
5	Grady Memorial	Southeast	Adult
6	University of Texas Southwestern	Southwest	Pediatric
7	Seattle Children's Hospital	Northwest	Pediatric

[a]NYU: New York University.

Each center will have a designated principal investigator who will participate in monthly meetings with the organizing committee. Johns Hopkins University, which includes both pediatric and adult diabetes centers, will be the primary center for the development of the BPA. This center will oversee prototype development, testing, and postlive validation.

BPA Development

The BPA development phase of this study will encompass several stages: design, testing, training, postlive validation, deployment, and ongoing refinement (Figure 1).

BPA Design

Using a rule-based algorithm, the EMR-based BPA will be designed to recommend ADT prescriptions for people with T1D not already using an AID system, and this would also encompass an alert for people not using CGM (and thus not using AID). The specific functionality of the BPA will be guided by the thematic analysis of the stakeholder input obtained in phase 1. The function will generate a BPA if a patient is not using an AID system and will suggest to the provider to discuss and prescribe technologies for using an AID system.

The BPA design will be led by the study organizing committee with direct involvement and support from Epic IT analysts and developers at Johns Hopkins University. Iterative feedback will be obtained from the principal investigators at each of the participating intervention centers during the prototype development. Table 3 outlines the key considerations for the design team. Throughout the design process, Norman's user-centered design principles will be applied to ensure the BPA is intuitive, user-friendly, and meets the needs of all stakeholders [35].

Table 3. Key considerations for best practice advisory (BPA) design team.

Consideration	Descriptions
Stakeholder input	Incorporate thematic analysis of feedback from patients, caregivers, and health care providers.
Algorithm rules	Define criteria for triggering the BPA based on patient EMR[a] data.
Workflow integration	Ensure BPA integrates seamlessly into the provider's workflow.
Iterative testing	Conduct iterative testing and refinement based on feedback from pilot implementations.
Setting and restrictions	Consider the setting (ambulatory, inpatient, both) and specific locations such as endocrinology clinics, primary care clinics, or health-system wide.
Location in Epic	Determine the BPA's location in Epic, such as Windows, BPA Navigator, or Flag in Storyboard.
Active versus passive	Decide between active (windows that appear in the user's Epic workflow) and passive (appear within assigned locations that fit into the end user's workflow) BPAs.
Clinician action	Specify actions clinicians can take, such as placing orders or referrals.
Triggering messages	Determine language in the BPA, including potential references to practice guidelines, explain the reason for the BPA, and suggest actions to be taken.
Iterative testing	Conduct iterative testing and refinement based on feedback from pilot implementations.

[a]EMR: electronic medical record.

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BPA Testing

After a prototype BPA is developed, the testing phase will involve incorporating the BPA into integrated testing scripts in the Epic sandbox environment. The prototype BPA will be tested thoroughly in an environment using realistic data. A debugging tool will test specific cases in the BPA builder before actual deployment. Site principal investigators will be asked to provide direct oral or written feedback about the usability of the BPA and will be encouraged to suggest improvements.

BPA Training

Minimal provider training is expected as BPAs are widely used in the EMR. However, Epic tip sheets and a communication strategy will be developed by each of the intervention centers to facilitate the training process. Communication methods may include email and Microsoft Teams posts to ensure that all relevant staff are informed and prepared to use the BPA effectively.

Postlive Validation

Initially, the BPA will be launched at Center 1 (Johns Hopkins University) to allow for an in-depth assessment and troubleshooting of any potential issues before wider deployment. This initial launch will involve a thorough 90-day validation phase, during which the functionality and impact of the BPA will be closely monitored and evaluated. During this validation phase, any issues or inefficiencies identified will be addressed and rectified. In addition, during this period, the intervention centers will begin the process of obtaining local institutional approval for the BPA. This approach ensures that the BPA is fully optimized before it is implemented at the remaining 6 intervention centers (centers 2-7).

Deployment

Following the successful completion of the validation phase at Johns Hopkins University, the BPA will be rolled out sequentially to the other intervention centers. Each institution has a CDS committee that approves new builds, and this approval process will be factored into the timeline (Figure 2). Each of the participating intervention centers has already received letters of support from institutional IT leadership; therefore, we do not anticipate any approval barriers. To ensure that each intervention center is prepared to launch the BPA at the same time, the organizing committee will recommend that the approval process for the build occur at least 90 days before the planned launch. This staged deployment strategy minimizes the risk of widespread issues and allows for iterative improvements based on real-world feedback. Once the study team has ensured that the target providers at the other 6 participating centers have received requisite training, the BPA will be moved into the Epic production environment, which will correspond to the start of the intervention phase of the study.

After deployment, we will monitor adherence to the BPA using SlicerDicer, an analytics tool integrated within Epic. This tool enables us to track the frequency of BPA activations, the acknowledgment reasons selected by clinicians, and the subsequent actions taken. SlicerDicer allows for the creation of custom reports and dashboards that visualize compliance trends over time and facilitates in-depth analysis of specific instances of noncompliance. These insights will be used to generate feedback reports for clinicians, enabling clinical leaders to compare provider compliance rates against their peers and internal benchmarks. This approach aims to encourage adherence to BPAs and foster a culture of continuous quality improvement.

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Figure 2. Study timeline. ADT: advanced diabetes technology; BPA: best practice advisory; IRBL institutional review board; QI: quality improvement; T1D: type 1 diabetes.

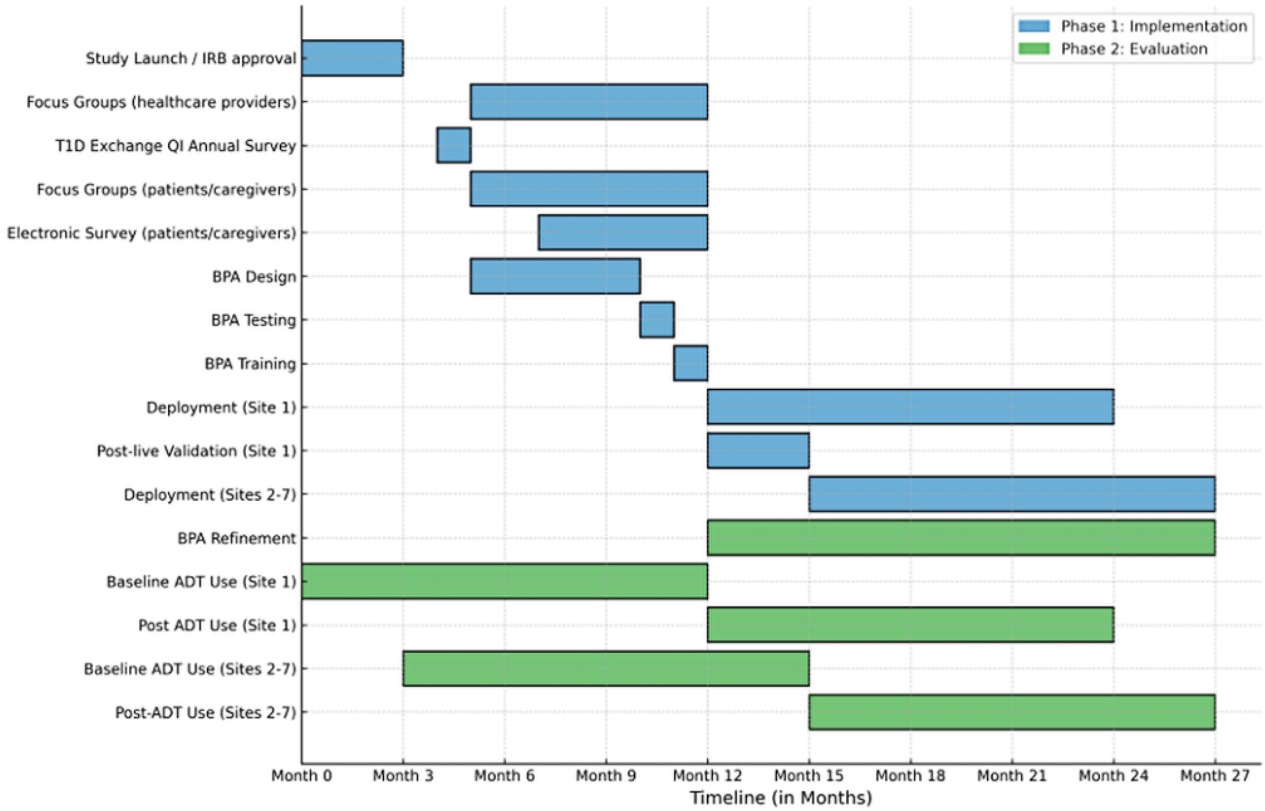

Refinement

Feedback from the providers at the 7 participating centers will be collected following the implementation of the BPA and periodically during the 12-month assessment period. This feedback will be used to refine the BPA in an iterative fashion.

Phase 2: Evaluation (Study Design)

Using a nonrandomized matched pair-intervention design (ie, controlled before-after study), we will compare the use of ADT following the BPA intervention among non-Hispanic Black and Hispanic people with T1D at 7 participating T1DX-QI centers. These will be matched with control non-Hispanic Black and Hispanic people with T1D at nonintervention T1DX-QI centers over a 12-month period. Both control and intervention centers have completed the EMR data mapping to the T1DX-QI, allowing for consistent outcome assessment across both groups. The study will consist of 2 distinct periods:

1. Baseline period (before): 12 months before deployment of the BPA at the intervention centers.
2. Implementation period (after): 12 months after the deployment of the BPA at the intervention centers.

The before-after matched-pair intervention design allows for a real-world assessment of the BPA's impact on ADT use while controlling for key confounders. Comparing ADT prescribing before and after BPA implementation within intervention sites and using matched controls from nonintervention centers, the design also accounts for site-specific prescribing patterns and secular trends. This quasi-experimental approach is practical for an EMR-based intervention and minimizes selection bias by matching key clinical and demographic variables.

Eligibility Criteria

Inclusion and exclusion criteria are listed in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Age ≥2 years
- A diagnosis of type 1 diabetes (determined using *ICD-10* [*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision*] diagnosis codes [E10.X] and other various discrete data elements, such as flowsheet rows, as mapped by clinical centers to the Type 1 Diabetes Exchange Quality Improvement Collaborative database).
- Receiving care at one of the seven intervention centers or a matched control center in the Type 1 Diabetes Exchange Quality Improvement Collaborative.
- Patients with at least one clinical encounter (in-person or video visit) in both the baseline and follow-up periods.
- Not prescribed an automated insulin delivery system (patients prescribed only continuous glucose monitoring are eligible, provided they are not prescribed an automated insulin delivery system).

Exclusion criteria

- People with type 1 diabetes already using an automated insulin delivery at baseline.
- Pregnant patients.
- People with type 1 diabetes receiving end-stage kidney disease dialysis.
- People with type 1 diabetes using hydroxyurea.

Intervention Group

People with T1D meeting the eligibility criteria at one of the 7 intervention centers where the BPAs are deployed will be assigned to the intervention group. We estimate that there are approximately 11,496 eligible people with T1D in the intervention centers.

Control Group

Matched control people with T1D will be selected from the pool of nonintervention clinical centers sharing EMR data with the T1DX-QI coordinating center with over 80,000 people with T1D data available in the database.

To accurately match people with T1D between the intervention and control groups, we will identify and include a comprehensive set of covariates that may influence the likelihood of receiving the BPA. These covariates will include both patient-level and clinical center-level characteristics. Patient-level characteristics will include demographics (age, sex, race, and ethnicity), socioeconomic status (insurance type and zip code–based income), and clinical characteristics (duration of diabetes, comorbidities, HbA_{1c} levels, etc). Clinical center-level characteristics will include clinic size and resources (number of people with T1D seen annually, number and type of clinical full-time equivalents, geographic location, patient population demographics, and historical usage rates of CGMs and AID systems. Intervention and control groups will be matched using the propensity score method.

Before propensity score matching, any missing baseline covariate data will be imputed using predictive modeling techniques. Multiple imputation by chained equations will be used to generate multiple complete datasets, which will then be averaged to create a single dataset for the matching process. This approach ensures that the imputed values are based on observed data, maintaining the integrity and representativeness of the dataset.

Propensity scores will be estimated using logistic regression, where the outcome variable is the likelihood of receiving the BPA intervention. The model will include the identified patient-level and clinical center–level covariates as predictors. The estimated propensity score represents the predicted probability that a given patient would receive the BPA based on their covariate profile. Patients in the intervention group will be matched to patients in the control group using a 1:4 matching ratio. Nearest neighbor matching without replacement will be used, ensuring that each control patient is only matched once. The matching process will aim to minimize the distance between propensity scores of matched pairs, thus creating comparable groups. The quality of the matching process will be assessed by comparing the distribution of covariates between the matched intervention and control groups. Standardized mean differences will be calculated for each covariate to ensure balance, with a standardized mean difference of less than 0.1 indicating adequate balance. In addition, a visual inspection of propensity score distributions before and after matching will be conducted to confirm the success of the matching process.

To assess the robustness of the results, sensitivity analyses will be performed using different matching algorithms (eg, caliper matching and kernel matching) and varying the matching ratio (eg, 1:3). In addition, the impact of imputation on the results will be examined by comparing outcomes using datasets with and without imputed values.

For nonstatic matching variables (eg, laboratory results), the last available result in the baseline period of 12 months before the BPA deployment date in the intervention centers will be used.

Primary Outcome

The primary outcome will be progression in ADT use (as documented in the EMR) during the 12-month study period. For both intervention and control centers, a participant's baseline ADT status will be ascertained in the 12-month period before deployment of the BPA intervention. The primary outcome will

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be defined as positive for an individual if any of the following transitions from the baseline period to the implementation period occur with respect to ADT:

1. No CGM → CGM.
2. No AID → AID.

The T1DX-QI database includes variables that will be used to evaluate the study outcome (eg, medication list and flowsheet data). We have extensively published on the T1DX-QI data source and its validation, and have used the database for several real-world studies [36-42].

Adverse Events

It is not anticipated that the intervention will pose any additional risk of harm to people with T1D, particularly given the established benefits of AIDs and CGMs in enhancing glycemic control and reducing the risk of hypoglycemia. Nevertheless, the study will closely monitor rates of serious hypoglycemic events and DKA events, using existing data mapped from control and intervention sites to the T1DX-QI database. These rates will be compared between the intervention and control sites to ensure that there are no unexpected or unintended consequences of the intervention on adverse glycemic outcomes.

Statistical Analysis

Data Collection

Currently, more than 102,000 people with T1D have EMR data in the T1DX-QI database. Mapped outcome data include ADT use, HbA_{1c}, severe hypoglycemic events, and DKA events, and are automatically transmitted to the T1DX-QI database monthly. Data from all intervention and control sites will be analyzed by the T1DX-QI data coordinating center. All data are anonymized and deidentified to ensure patient privacy. Protected health information is in the form of a limited dataset, which includes dates but excludes any direct identifiers. Medical record numbers are never shared with T1DX. Unique identifiers are created by the hospitals and shared with T1DX for the purpose of longitudinal (encounter-level) data analysis. Results are aggregated, and no encounter-level data are published, further safeguarding participant confidentiality. The data monitoring committee will be composed of the principal investigators from JHU and T1DX-QI, along with biostatisticians, and will operate independently from the sponsor. Members of the data monitoring committee will have access to the final trial dataset.

Power

This study is powered to detect a between-group difference of 15% in the proportion of patients in the intervention and control groups meeting the primary endpoint. The matched-pair control assessment of 15% progression in ADT use is estimated from T1DX-QI data over a previous 12-month period. The largest sample size necessary for 90% power if the absolute difference in the proportion of ADT progression is only 5% (relative increase of 25%) is 589 matched pairs. If possible, we will attempt to match intervention to control patients in a 1:2 fashion with 2 matched controls per intervention patient. An interim analysis of the intervention group event rate may be conducted to inform whether additional matched pairs are needed.

Analysis

Phase 1

For survey data, Likert scale responses will be coded numerically for qualitative analysis. Descriptive statistics will be calculated to summarize the data, and differences between groups (ie, based on demographic variables) will be explored. For the structured interviews and focus groups, a thematic approach will be used to identify, analyze, and report patterns with the qualitative data. NVivo software will be used, which provides features for coding, organizing, and visualizing data [43]. Both deductive and inductive coding methodologies will be used to link similar codes to broader themes based on significant phrases, concepts, and ideas present in the transcripts [44]. Themes will be reviewed and refined through discussions among the research team to ensure consistency and reliability.

Phase 2

The primary outcome will evaluate the impact of the BPA intervention on patients' progression of ADT use using a generalized linear mixed model to account for matched pairs and random center effects. The model will be adjusted for the number of encounters and other possible confounders not already matched.

The secondary outcome analyses will compare differences in ADT use between non-White and White people with T1D in the intervention and control groups. Additional secondary and exploratory outcomes will be assessed using the appropriate statistical model for the outcome adjusting for patient- and center-level confounders. Exploratory analysis assessing pediatric and adult centers separately will be performed.

In cases where ADT is not prescribed by the provider, we will explore the reasons why, and why the diabetes technology was not offered or accepted by patients. We will quantify the BPA responses as provider-led or patient-led reasons for not advancing ADT use. We will perform multivariable logistic regression analysis to evaluate whether patient characteristics (demographics, race, ethnicity, diabetes characteristics, and complications) are associated with the reasons that technologies are not offered or declined.

Ethical Considerations

This intervention study was registered on ClinicalTrials.gov (NCT06931275) and received approval from the WCG institutional review board on April 26, 2024 (institutional review board approval number 45614667). For the qualitative research proposed in phase 1 of the study, oral informed consent will be obtained from all participants (patients, caregivers, and health care providers) for the focus groups and interviews, and written informed consent will be obtained from all participants (patients, caregivers, and health care providers) for the surveys. However, due to the nature of this implementation study, informed consent cannot be obtained from participants during the observation phase (phase 2), which will evaluate the impact of a before-and-after design on clinical outcomes.

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Results

The BPA-TECH study funding was finalized in April 2024. Data collection for the phase 1 qualitative component of this study began in August 2024 and is expected to be completed around July 2025. Phase 2 will commence with the deployment of the BPA, followed by a 12-month evaluation period that is expected to conclude around July 2026. We estimate evaluating data from 3000 eligible people with T1D across the 7 clinical centers and 15,000 possible matched controls across 41 centers.

Discussion

Principal Findings

The overarching goal of this study will be to promote the use of ADT and enhance health equity in ADT use for diabetes management in people with T1D. While previous research has illustrated the many barriers and racial disparities in ADT use, the focus of this initiative is to develop a comprehensive and evidence-based solution using HIT to address and mitigate ongoing disparities in ADT use and outcomes. We expect that clinical centers implementing the BPA will demonstrate higher rates of progression to ADT use compared with matched controlled sites, as well as a smaller gap in the use of these technologies between White and non-White patients.

In a 2-phased approach, this protocol aims to develop a BPA with input from key stakeholders, and then evaluate the effectiveness of the BPA in reducing disparities in ADT use among people with T1D. The goal of this intervention is to increase the progression of ADT use overall, while reducing health disparities and improving outcomes in all people with T1D. In addition, reasons for not prescribing ADT in response to the BPA will be collected. If successful, the build for this BPA can be disseminated to other hospital systems for implementation to improve outcomes on a larger scale.

To our knowledge, this is one of the first studies to develop and use a CDS initiative in the EMR to promote equitable discussion and prescribing of ADT in people with T1D. In addition, to increase the generalizability of our findings, a diverse sample of People with T1D will be included from multiple centers across the United States to account for geographical and systems-level (ie, state-level and insurance-based) variabilities.

Previous initiatives to improve the use of diabetes technologies in people with T1D have focused on patient-level interventions. Early initiation of CGM soon after diagnosis of T1D, and point-of-care CGM placement and education during routine diabetes care visits have led to increased uptake of CGM and improved glycemic outcomes [45-47]. A current randomized control trial deploying a diabetes navigator will determine if the help of a technology liaison can improve uptake and sustained use of ADT in people with T1D [48].

The use of a BPA as a CDS tool in this protocol serves as an intervention at both the provider and system level, enabling greater scalability to create lasting improvements in ADT uptake and glycemic outcomes. There is previous evidence supporting the successful implementation of computer-based decision support in diabetes care [49-51]. One cluster randomized clinical trial consisting of 14 primary care centers (66 primary care physicians and 697 patients with T2D on insulin therapy) in Madrid, Spain successfully implemented a computer application designed to help primary care physicians make decisions about insulin therapy [52]. The design of the algorithm included the recommendation to change the insulin dose and the insulin regimen when necessary. The people receiving care at the 7 centers randomly assigned to use the algorithm had a significant reduction in HbA_{1c} compared with the people at the 7 centers in the control group [52]. Another meta-analysis of 70 randomized controlled trials assessing the critical features of CDS systems that improve clinical practice highlighted 4 initiatives strongly associated with a successful center decision support system: (1) CDS provided automatically as part of clinical workflow, (2) CDS delivered at the time and location of decision-making, (3) actionable recommendations provided such as prescriptions, and (4) computer-based [53]. In this protocol, the BPA is designed to incorporate these 4 critical features and thus we expect to see improvement in ADT uptake at the intervention sites.

This study leverages the T1DX-QI consortium, which has a robust quality improvement and health equity framework to evaluate the impact of an EMR-based BPA on ADT use and racial disparities. By implementing the intervention at 7 motivated sites with strong research and QI expertise, and strong IT infrastructure, the study ensures effective troubleshooting and optimization of the BPA. This real-world, multicenter approach enhances generalizability and supports the potential for scalability to other centers if successful. In addition, integrating health equity principles strengthens the study's ability to assess disparities and inform broader systemic improvements in diabetes care.

Although this study is limited to centers using the Epic EMR system to streamline the development of the BPAs, the BPA prototypes developed in this study could be adapted for other EMR systems in the future. Further, this study is limited to centers participating in the T1DX-QI, where there is likely to be greater motivation to improve outcomes and close care gaps, and thus findings may not be generalizable to all centers providing diabetes care. However, the use of BPAs allows standardization of practice and can serve as an equalizer across different practices.

Dissemination of Findings

The findings will be published in diabetes, health technology, and health equity–focused medical journals, and will be presented at major national and international conferences. Patient-friendly summaries will be developed and shared with patients and caregivers, while educational materials and training programs will be created for health care providers to facilitate clinical implementation on a larger scale. Authorship eligibility for publications resulting from this study will adhere to the International Committee of Medical Journal Editors (ICMJE) guidelines [54].

Conclusions

The research approach outlined in this protocol aims to leverage health IT to reduce racial disparities in prescribing and use of

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ADTs, thereby promoting equity, improving disease management, and enhancing outcomes in people with T1D.

Acknowledgments

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during this study.

Authors' Contributions

NM, RMW, NR, and OE contributed to conceptualization. ST assisted with data curation. ST handled formal analysis. NM, RMW, NR, and OE contributed to funding acquisition. NM, RMW, OE, and ST assisted with methodology. NM, RMW, NR, OE, TW, and EO handled project administration. NR contributed to resources. NR, ST, and EO assisted with software. NM, RMW, and OE contributed to supervision. ST assisted with validation. NM, RMW, and OE handled visualization. NM and RMW contributed writing—original draft.

Conflicts of Interest

RMW receives research grants from Novo Nordisk, Lilly and Sanofi as the site PI of a clinical trial, unrelated to this work. OE receives research grants from Medtronic Diabetes, Sanofi, Tandem, Vertex, Lexicon,Eli Lilly, Abbott through his organization T1D Exchange. He is on the advisory board for Sanofi and Medtronic Diabetes. RSW participates in multicenter clinical trials, through her institution, sponsored by Tandem, Insulet, Eli Lilly, Amgen, MannKind, Diasome, and has received devices from DexCom at reduced cost for clinical research. Research support to Emory University from Insulet was received by GD. NM and MG have no relevant financial disclosures.

Multimedia Appendix 1
SPIRIT checklist.
[DOC File , 123 KB - resprot_v14i1e71038_app1.doc]

Multimedia Appendix 2
Focus group session guide for health care providers.
[DOCX File , 30 KB - resprot_v14i1e71038_app2.docx]

Multimedia Appendix 3
2024 Type 1 Diabetes Exchange Quality Improvement Collaborative Annual Center Survey questions related to the proposed best practice advisory.
[PDF File (Adobe PDF File), 350 KB - resprot_v14i1e71038_app3.pdf]

Multimedia Appendix 4
Electronic survey for people with type 1 diabetes and their caregivers.
[DOCX File , 48 KB - resprot_v14i1e71038_app4.docx]

Multimedia Appendix 5
Focus group session guide for people with type 1 diabetes and their caregivers.
[DOCX File , 50 KB - resprot_v14i1e71038_app5.docx]

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Multimedia Appendix 6
ChatGPT prompts used to generate figures.
[DOCX File , 17 KB - resprot_v14i1e71038_app6.docx]

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Abbreviations

ADT: advanced diabetes technology
AHRQ: Agency for Healthcare Research and Quality
AID: automated insulin delivery
BPA: best practice advisory
BPA-TECH: Best Practice Advisories to Reduce Inequities in Technology Use
CDS: clinical decision support
CGM: continuous glucose monitoring
DKA: diabetic ketoacidosis
EMR: electronic medical record
HbA_{1c}: glycated hemoglobin
HIT: health IT
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
T1D: type 1 diabetes
T2D: type 2 diabetes

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T1DX-QI: Type 1 Diabetes Exchange Quality Improvement Collaborative

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Protocol

Personalizing mHealth Interventions for Occupational Stress: Protocol for a Randomized Pilot Study

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Abstract

Background: Occupational stress is associated with detrimental consequences that are addressed by mobile health (mHealth) solutions. Previous developments of apps for occupational stress have not yet fully exploited the potential of multilevel diagnostics through the integration of wearable sensors for interventions. Personalizing mHealth approaches in terms of intervention time and content, which requires the use of artificial intelligence, is the next logical developmental step. The "Relax" approach developed a corresponding prototype of an app-wearable system, which will be evaluated for effectiveness in terms of stress reduction and usability.

Objective: This study protocol describes an evaluation study used to test the effectiveness and usability of the Relax approach.

Methods: The evaluation study was designed as a 2-arm randomized trial with 2 phases, each with a 3-week intervention period. In both phases, employees were required to use the app to record daily stress and to wear a wearable sensor to measure heart rate variability. The app offered interventions based on algorithms, which altered the probability of their selection after learning from the data, thereby personalizing the user experience. In the second phase of the study, the sample was divided into 2 groups, varying the degree of personalization of the app. To analyze effectiveness, a 2-factorial mixed within-between design will be applied to compare the outcomes between both groups as well as in a pre-post comparison. In addition, exploratory analyses of the usability of the approach are planned.

Results: The study was conducted during the spring and summer of 2024, with a total of 46 participants enrolled, and is ready for data analysis.

Conclusions: The Relax approach, including a number of factors related to personalization that have not yet been incorporated into mHealth in current research, will provide new insights into the next steps of advanced mHealth solutions. Limitations of the study design, such as the lack of a control group and the sample representativity, have to be addressed.

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KEYWORDS

mHealth; occupational stress; personalized apps; multilevel diagnostics; just-in-time adaptive intervention; artificial intelligence

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Introduction

Occupational Stress

For employees, work has the potential to be the most significant source of stress in their life. The working environment, which is often characterized by deadlines, role requirements, uncertainties, and time constraints, can be particularly stressful [1]. When stress is perceived as matching one's abilities and motivations optimally, it can be referred to as "eustress" or a "flow experience" [2] and is characterized by positive emotions and high performance [3]. The term "distress," which will henceforth be referred to simply as "stress," describes the harmful type of stress that cannot be easily managed by the individual. Chronic work-related stress has been demonstrated to have detrimental impacts on an individual's emotional well-being and overall quality of life [4]. Loss of energy and efficiency, mental and physical strains, and absence from work owing to burnout or other forms of mental health impairments are common consequences of unaddressed stress [5-7]. The study by Nekoei et al [8] recorded the suspected economic costs attributable to burnout as >2% of the national labor income, which demonstrates a continuous increase in workloads and speaks of an "epidemic of burnout" [9] affecting all fields of occupation, although some of them, such as health care, school education, or geriatric care, are particularly affected [10,11].

The provision of health care for working people with regard to stress-related burdens remains fragmented. The study by Molek-Winiarska and Molek-Kozakowska [12] showed that less than half of the organizations they had addressed committed to provide stress management support for their employees. In recent years, there has been a notable increase in interest in digital health solutions [13]. The COVID-19 pandemic, which placed many employees in unanticipated stressful work conditions, has demonstrated the urgent need for person-centered health care in the occupational setting, which can be effectively delivered by digital means [14]. The domain of mobile health (mHealth) addresses this type of individual health care, wherein mobile apps are used to facilitate cost-efficient and low-threshold access to effective interventions [15]. As the smartphone can serve as a constant companion during working hours [16], the provision of close health support via smartphone apps is particularly advantageous.

A plethora of mHealth apps addressing work stress are available in commercial sectors, as well as in scientifically based products [17-19]. The apps in question are highly diverse and exhibit considerable variation in their efficacy. Most apps concentrate on microinterventions derived from cognitive behavioral therapy (CBT), encompassing relaxation techniques, meditation, psychoeducation, and cognitive methods [17-19]. It may take many trial-and-error attempts for an employee to select a suitable approach [20]. An offer from the employer themself would be a logical and straightforward solution, particularly given the individualized nature of work stress, which can vary considerably depending on the specific workplace context. Given the continued tendency to regard mental health issues as a taboo subject in professional contexts [21], it is evident that mHealth apps for occupational stress are typically addressed at the individual level through the use of the employee's personal smartphone rather than through the direct involvement of the employer. However, these apps must be tailored to the specific needs of the individual employee in terms of the stress-inducing circumstances and modes of coping and intervention without being set up by the employer. Therefore, the customizability of the app is important in developing an mHealth app for individual occupational stress.

Personalized mHealth for Work Stress

The relevance of personalized apps that provide interventions for occupational stress is emerging [22,23]. On the one hand, personalization can be achieved simply through the input of personal data, which is then processed by the apps to customize interventions. To illustrate, a user may personalize the app using demographic data or specify the notification behavior for the intervention offer [24,25]. In addition to developments in the area of personal input and settings, there have also been significant advances in recent years in the field of combining apps with more advanced diagnostic measurement tools. The technical advancements in the domain of mobile sensors, or "wearables" for short, have opened up the opportunity for unobtrusive measurement of individuals' current conditions through the use of wearable devices [26,27]. In the realm of stress diagnostics and interventions, this is particularly advantageous, as it enables the unobtrusive determination of heart rate variability (HRV), which is defined as a significant and practical physiological indicator of stress, although not the only one [28,29].

A multilevel diagnostic approach, which incorporates subjective input and objective sensor data, can facilitate the development of mHealth solutions for occupational stress management [17,26]. Such solutions are personalized on the basis of real-time data, a process referred to as "just-in-time adaptive interventions" (JITAIs) [30]. In this context, both the timing of the intervention and the content of the intervention are adapted to the situation and individual and therefore are necessarily linked to real-time data from the individual [31]. The necessity for the integration of multilevel data, coupled with the considerable volumes of data amassed through the integration of apps and wearables, necessitates the involvement of algorithms and learning agents in the background [32]. The development of artificial intelligence (AI) has led to its adoption in numerous domains of human-machine interaction, with the objective of enhancing user experience and personalizing processes [33]. In addition to smart technology such as voice assistants, the deployment of AI in health care apps could pave the way for the development of personal health assistants.

Recent Developments and Research

This approach to health assistants is still in its infancy in terms of research and product development. General mHealth interventions with unobtrusive wearables are on the horizon, and their effectiveness has already been confirmed by several studies [34,35]. However, there is still a lack of attention being paid to the specific field of occupational stress [26,36]. Some approaches focus on safety systems that use wearables to monitor physical risks such as temperature and analyze physical stress but do not take mental stress into account [37]. Other

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approaches that explicitly examine mental stress have yielded the development of numerous systems designed exclusively for monitoring one's own stress levels [27]. These systems lack the capacity for active interaction, such as the implementation of interventions. A recent review of the literature reveals that although mobile apps and wearable devices for mental stress interventions are also being developed, in most cases, they are based on either one or the other tool [26]. Combinations of both tools, in which the evaluated data are dynamically integrated, remain a barely addressed approach.

mHealth biofeedback apps provide an opportunity for such interactions, thus facilitating personalized mHealth interventions for occupational stress. In this approach, some developments have used real-time sensor data to feed into the app, which then provides the user with feedback on their stress levels [38]. When such measurements and feedback are coupled with breathing interventions, users have the ability to influence their heart rate through controlled or guided breathing [22,39-41]. Such interaction with the app allows for personalized data processing and can be seen as a basic form of individualization. There was only one approach that offered other CBT interventions in addition to biofeedback units for work stress, but these did not use the sensor data [22], which means that the full potential of continuous condition monitoring is not realized. Another way to personalize interventions is to use personal (sensor) data to determine the content of the intervention, a module, or the timing of the intervention, according to the JITAI concept. This idea was realized in the approach by Winslow et al [42], where CBT interventions were selected according to previous stress indications and conceptualized in the studies by Clarke et al [43] and Luštrek et al [44].

When developing such approaches, it is important to consider their real-world applicability as potential health companions in the everyday lives of their users. The feasibility of such apps goes beyond the technical capabilities and is closely related to usability factors. A review of the literature on mHealth usability shows that privacy is a particularly important concern for mHealth users [45,46]. This is evidenced by the fact that users express discomfort with the digital storage of sensitive health data, such as cardiac data or irregularities, within nontransparent commercial products [47]. A lack of motivation to integrate mHealth approaches into personal routines could be a consequence. Motivation, acceptance, and adherence issues are recognized as challenges in the development of mHealth [48,49]. In addition, although developed for the general population, highly educated, younger, or middle-aged individuals might access and adopt them more frequently, thus showing another challenge in the development of usable systems [50].

The "Relax" Approach

The "Relax" approach involves the development of a system for multilevel diagnostics of occupational stress, with the aim of using these data to personalize interventions. This approach addresses the shortcomings of existing developments in the domain of personalized mHealth for work stress and extends the status quo by gathering a broad range of data for an AI-driven system to identify the most personally appropriate interventions from a diverse pool of contemporary CBT and health approaches.

The system combines a smartphone app for monitoring both direct and indirect subjective stress-related data, as well as dispositional personal data, and wearable devices for the assessment of cardiovascular indications of stress. The subjective data were multilayered, with dispositional and demographic characteristics serving as the basis for an individual profile for further personalization, as well as continuous data about current experiences that the AI would use to gain insight into the individual's daily life. The data obtained from the sensors covered the area of objective stress measurement. The agent, trained with personal and stress-related data, was not only to determine the timing of an app-delivered intervention on an individual basis. In addition, the agent should select an individually tailored intervention that is as appropriate as possible at this predetermined point in time. Thus, the Relax project was planned to address the research on the development of JITAIs in mHealth for occupational stress in an advanced way. The concept of this approach, with its complexity and AI-driven personalization in the context of psychological support for work stress, addresses the existing gap in the field.

However, at the time of the evaluation, the system had not yet reached the final stage of development, that is, not all planned technical functions had been integrated. Regarding just-in-time quality, the functionality of the trigger system was limited to the essential function of triggering an intervention at a predetermined threshold of personal stress. This intervention has its adaptive quality in that the participants had to navigate through a predefined decision algorithm, in the form of a decision tree, when a stress event was detected to be offered an appropriate intervention in terms of situational fit. The specific probability of selection could be influenced and thus personalized by the participants through feedback ratings.

The pathways of the tree were represented by a series of successive questions about the experience of the current stress event. These were answered personally, resulting in increasingly specialized questions until, at the end, an intervention was delivered that was suitable for the input. The possible interventions from the repertoire were not exclusive per pathway, allowing for a wide range of interventions per pathway with different probabilities. The system decided which single intervention to offer the user based on the probabilities. The probabilities could be influenced by how the participants rated the intervention after it had been presented. Consequently, following a sufficient period of use, the probabilities of the interventions should be strongly modified on an individual basis, thereby reflecting the personal preferences for the interventions that are perceived to be personally most effective.

Research Questions

This study aims to evaluate the prototype developed to date. The central research question of this evaluation is the effectiveness of the prototype in terms of the amount of stress reduction achieved by the participants. It is hypothesized that the greater the degree of personalization offered, the greater the reduction in stress. In addition, it was expected that all individuals would more or less experience an overall reduction

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in stress as a result of using the prototype. In addition to effectiveness, questions of usability and feasibility were addressed because of the pilot nature of the project approach and the research stage of the prototype at the time of the study. No hypotheses were formulated here, as the corresponding data were collected for exploratory purposes.

Methods

Study Design

The study used a 2-arm randomized controlled design, comprising 2 experimental groups with varying levels of intervention. In a field design, participants applied the intervention in their natural (occupational) environment. Two 3-week study periods were conducted, with all participants receiving the same intervention in the first 3-week phase (P1) and, after a 3-week break, being allocated to 1 of 2 groups in the second 3-week phase (P2). This resulted in a within-subject comparison in the pre-post design as well as between-subject comparisons between both experimental groups. The within-subject design consisted of the collection of time series data enabled by the continuous daily measurement of variables. Subjective data on experiences and stress levels were collected daily in the morning and evening, as well as at least twice during the day, via the app. Continuous physiological data were also collected via wearing a sensor. In contrast, the between-subject design comprised 3 measurement points: before P1 (T1), between P1 and P2 (T2), and after P2 (T3). At these times, web-based questionnaires about chronic stress and various usability aspects of the wearable app system were submitted via a web-based survey platform. The break was used to improve the mobile app based on user feedback, split the participants into the experimental groups, train the models for automated stress detection based on the HRV and questionnaire data recorded in P1, and implement the weight adjustment mechanisms for personalized intervention delivery.

Ethical Considerations

The study design and conditions were initially approved in advance by the Ethics Committee of the University of Salzburg (EK-GZ 25/2023). Following minor alterations to the study design, including adjustments to the study duration, study period, the exclusion of a second sensor, and the reduction of the number of participants, an amendment was approved by the same committee (EK-GZ 25/2023 amendment). After data collection, a preregistration for hypothesis testing was performed (osf.io/myrd9). Due to the unpredictable nature of the study and the technical adjustments required during implementation, prospective preregistration was not performed.

Before completing the screening questionnaire, respondents were informed of the purpose of the data collection in order to provide informed consent. Those who were screened positively were informed of the acceptance of their registration via the email address they had provided. Those who were screened negatively were informed of the exclusion immediately after the screening. After the conclusion of the registration period, the final registration confirmations were sent out to all individuals included in the optimally balanced sample. Subsequently, the positions of those who had dropped out before the commencement of the study were filled by new participants until shortly before the study began. The identities of the participants were pseudonymized before the collection of study data. Participants were provided with an individual, reproducible code comprising questions on personal characteristics that could not be traced back [51]. The identity was only traceable by means of a coding list, which was kept by the study management and was only consulted in serious technical cases, dropouts or when checking whether the level of participation was sufficient to apply for the proposed compensation. Interested individuals were informed about the financial compensation worth €180 (US $204.86) (including the value in kind of retaining the study sensor). They could opt out at any point without negative consequences.

Study Participants

The sample consisted of individuals who were of legal age and employed. Participants were required to possess a smartphone with a minimum Android operating system (version 7.0). In advance of the study, participants were required to demonstrate a sufficient level of knowledge of the German language, equivalent to that of a native speaker, as well as normal or corrected-to-normal eyesight. To be eligible for inclusion in the study, participants were asked to indicate that they had sufficient time to use the app daily during the study period, including having the opportunity to use the app every 3 to 4 hours. In addition, participants were only eligible if they had a regular working day that was not interrupted by holidays, significant changes in employment status, or travel during the study period.

Individuals who met the following criteria were excluded from the study: those with irregular work routines during the study period (eg, irregular night shifts), cardiovascular diseases, or atypical menstrual cycle complaints in women, those with upcoming medical interventions during the study period, and those with a diagnosed severe mental disorder or undergoing psychotherapy or psychopharmacotherapy. Inclusion and exclusion criteria were clarified by self-report unless the information was obviously evaluable. There were no restrictions regarding the location of participants in German-speaking countries or their occupational fields. The participants were able to communicate with the study team via online correspondence, including email and telephone.

Sample Size

The optimal sample size for the central analysis of main effects was calculated using an a priori power analysis with G*Power (version 3.1) [52]. With an α value of .05, a power of $1-\beta=0.80$, and a desired effect size of Cohen $d=0.5$, this resulted in a recommended sample size of 31. The sample size was increased in the study to the maximum number of participants that could be financed, which was 50 individuals. This resulted in a maximum of 25 (50%) individuals per experimental group.

Recruitment

The ad hoc sample was constituted by recruiting potential participants via a variety of parallel channels. The recruitment process was centered on a study website that advertised participation and provided access to the study registration portal. First, precommitted companies were contacted and reminded

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of their participation. These companies were provided with the necessary information and access data for the registration portal for their employees. In addition to the previously committed companies, further companies were contacted and selected ad hoc from web-based registers. The professional network of the members of the study team was also addressed. Moreover, the public was made aware of the study through the dissemination of flyers in public spaces and on social and traditional media platforms. These flyers were placed in locations frequented by the public, including public areas and local businesses, as well as distributed via direct mail in the region of Salzburg and neighboring German towns. Dedicated social media accounts were set up on Facebook (Meta Platforms, Inc) and Instagram (Meta Platforms, Inc), which used public relations strategies that extended beyond the dissemination of study-related information, such as sharing posts on general information on stress management, to achieve a broader reach. The study accounts were used to contact relevant social media groups, including those of employees and individuals with an interest in research or stress. In addition, individuals who regularly posted on work-related topics were also contacted. Similarly, articles on the Relax project were published in traditional regional and national newspapers with a specific reference to the study.

The registration portal directed respondents to a web-based screening that inquired about the inclusion and exclusion criteria, as well as basic demographic data, including age, gender, and current employment sector. The collection of demographic data was undertaken to ensure the resulting sample was representative of the target population.

Randomization

The randomization process was conducted midway through the study, following the scheduled break. No data from P1 were used to balance the randomization in any way. The participants were randomly assigned to the groups *local* and *global*. For the group *local*, the intervention weight matrix was primarily affected by participants' own ratings, while the ratings of all participants affected the weights for the group *global*. The group *local* was regarded as the group with greater personalization than the group *global*, given that the personalization in question was based on the individual inputs.

The participants were not informed of their group allocation, which meant that they were considered blinded. As the randomization was conducted by a separate subgroup of the study team from those involved in the study itself and the data analysis, the latter 2 parts of the study can also be described as double blinded. The evaluation of the data in pseudonymized form further enhanced this aspect of independence.

App Intervention

The intervention consisted of the use of the system of the Relax app and the wearable sensor developed in the Relax project. The participants were encouraged to use the system daily in P1 and P2. To accommodate the planned technical adjustments that will be made throughout the course of the study, all participants will be required to commence the study and complete the phases simultaneously.

The Relax app was developed based on a predefined mock design at the kickoff of the Relax project. This design was crafted with future projects in mind, ensuring long-term usability for data collection across several subsequent studies. The data management plan adhered to the European Union regulations. Bluetooth Low Energy (Bluetooth SIG) facilitated communication between the device and the phone, while REST interfaces enabled data exchange between the phone and the database.

The app interface consisted of several areas: the dashboard, the questionnaires, the interventions, calendar page, support page, user information, and an overview of the sensor data (provided in P2). In the dashboard, participants could check the status of the connection and synchronization of the sensor and monitor their study's progress. For the questionnaires, profile and daily questionnaires were available. The profile questionnaires consisted of a series of 7 diagnostic measurements about living and working conditions, technological competence, work-related and everyday stressors, risk factors, resources, coping strategies, and consequences of stress. The profile data were designed to be administered in the first week of P1 to serve as a source of personal information for personalizing the interventions in subsequent weeks of the study. However, due to technical barriers, this information could not be used for further personalization.

The daily questionnaires consisted of morning and evening questionnaires and interval questionnaires during the day. The morning questionnaires included items on the quality of sleep during the previous night, current state and experiences and expected stress for the day. The evening questionnaire included questions about chronic stress, the current state and experiences, and summarized experiences of the day. The interval questionnaires asked about the current state and experiences and the state and experiences at the time of the last stressful event, if any. Participants were required to complete the morning and evening questionnaires and at least 2 interval questionnaires each day. They received daily reminders for the morning and evening questionnaires. The interval questionnaires were to be completed approximately 4 hours apart at the latest. This interval ensured that the questionnaires could be completed smoothly, even on participants' busy working days. Participants were reminded several times a day to complete the interval questionnaires: twice in P1 (noon and 3 PM) and 3 times in P2 (11 AM, 2 PM, and 5 PM).

In addition to the daily use of the app, the sensor was to be worn to record physiological stress. The Polar Verity Sense (VS; Polar Electro OY), a wristband photoplethysmography sensor with an integrated inertial measurement unit from which various HRV parameters can be derived, was used for this purpose. The sensor was to be worn day and night in P1 and P2. Participants were instructed to take a maximum of two 30-minute breaks per day to avoid overstimulation and recharge the battery. It was possible to limit the duration of use individually if they felt uncomfortable, for example, to take it off at night. None of the participants took up this offer.

From the second week of the study in P1, interventions were triggered on the basis of individual stress information. On the

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one hand, a trigger was immediately released when (very) high stress was subjectively noted within the daily questionnaires. On the other hand, a trigger was released from objective sensor data. Multiple HRV metrics were calculated from measured sensor data based on 5-minute intervals. A stress intervention was triggered if (1) both the root mean square of successive differences (RMSSD) and the low frequency (LF) to high frequency (HF) ratio exceeded a predefined absolute threshold (deceded for RMSSD; exceeded for LF/HF ratio), (2) both metrics were among the 25% most significant values for the individual within a 24-hour window, and (3) both conditions held for 2 consecutive 5-minute time intervals.

From the trigger, a notification displayed in each area of the app provided access to the decision tree, which used various questions about the circumstances of the current stress experience to offer the optimal individual intervention. The main areas of the decision tree were external stressors, internal stressors, and indirect stress-related areas. For external stressors, the focus was on a dichotomy between occupational and other stressors, while for other stressors, it was noted that the Relax project only addressed occupational stress, so the participants were redirected to the top level of the decision tree. Internal stressors were divided into amplifiers, emotions, reactions, and resilience. The peripheral areas were divided into prevention and further information. All of these areas were further specified by the participants through up to 4 levels of predefined pathways. At the end of each path, there were several possible interventions.

The possible interventions were weighted differently depending on the end point of the pathway. The weights ranged from 0 to 1, with a higher weight increasing the likelihood of allocation. In the preliminary stages of the project, the initial weights were set according to the expert opinion of the development team. After P1, the initial weights for intervention selection were adapted based on all available user interactions. Popular intervention for a specific context received increased weights, thus a higher probability of being chosen in the subsequent context. Within P2, the weights of these mappings were adapted instantly for each intervention feedback.

The choice of intervention was made automatically by the system on the basis of the random weighted selection. At each node of the pathway, participants had the opportunity to immediately choose the weighted random selection of an intervention.

The 179 interventions were drawn from various areas of CBT, including psychoeducation, skills and attitude training, and relaxation and health habits. The interventions were designed as microinterventions that could be completed in a short period so that they could be easily integrated into everyday work life. Presentation formats varied across interventions depending on their applicability. These included simple text or tables with information, task prompts with a description and call to action, assisted tasks where participants received automated live instructions or otherwise interacted live with the app, or open prompts where participants were given an open field for response and self-reflection. In addition, there were pseudochats where participants were guided through automated educational chat transcripts, audio, or video content. At the end of an intervention presentation, the intervention could be rated. These ratings changed the initial weights of the intervention accordingly. Over time, this resulted in an individualized weight pattern of possible interventions for each person. For economic reasons, the system could not reach the stage at which interventions were offered fully automatically, so participants used the decision tree to receive interventions until the end of the study. Multimedia Appendix 1 illustrates the intervention areas and their subtypes in relation to their initial probability of occurrence with respect to the various stressor types within the decision tree. This higher probability is represented by the presence of an initial weight >0.5 (range from 0.0 to 1.0). In addition, Multimedia Appendix 1 depicts the presentation formats applied to these intervention areas and subtypes, as well as their quantities.

The level of individualization of interventions in the respective experimental group was characterized by a variation in automatic individualization with regard to the interventions offered by the learning agent. Due to intentionally high α values during the adjustment of the intervention weight matrix, the *local* group had the possibility of significantly influencing their intervention delivery within 3 weeks, while the group *global* would only perceive minor changes. α-local describes the extent to which a rating changed the weight of an intervention for a single user. For the group *global*, it was set to 1.0 (no change to the user's own weight), and for the group *local*, it was set to 2.1. The weights were adapted using the following formula: new_weight=old_weight * (alpha_local^old_weight). α-global describes the extent to which a rating changed the weight of an intervention for all users. It was set to 21 for both groups. The weights were adapted using the following formula: new_weight=old_weight *(alpha_global^(old_weight/number_of_users)).

Data entry was continuously monitored by the study team throughout the weeks. Participants were encouraged to continue their engagement through regular emails from the study team. It was expected that a general increase in adherence would be achieved as these messages were sent to all participants equally. If technical problems occurred, they were addressed individually via the app and generally via email. It is assumed that such individual correspondences would not add to the overall bias of the user experience since the individual disruption was already a bias, which is not uncommon in pilot studies. In P1, an update of the app was offered in the second week, which solved the technical problems that had arisen up to that point. Participants were given support to reinstall the app, and a self-help guide for the most common technical problems was offered. During the break between P1 and P2, additional technical difficulties were overcome by the study team, and when feasible and relevant, the participants' input thus far was considered. Following this adaptation of the system in accordance with feedback, a graphical overview of the sensor data was made available in P2. This enabled the participants to maintain awareness of the data and its evolution over time.

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Data Collection

Overview

Data for the study were collected from 2 sources: the mandatory app and wearable sensor data collected as part of the Relax approach and instruments implemented specifically for the study.

Items for the primary and secondary outcomes from established instruments were translated into German where necessary. Table 1 shows an overview of all outcomes, and Table 2 shows the data collection during the course of the study.

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Table 1. Primary and secondary outcomes and their measurement conditions.

Outcome	Subscales	Design of measurement	Instrument	Item format	Example item
Primary					
Momentary emotional state	Arousal, valence	Daily EMA[a] (morning, interval)	Internally created scale	7-point Likert scale	"My current mood is:"
Emotional state of last stress event	Arousal, valence	Daily EMA (interval)	Internally created scale	7-point Likert scale	"My mood was:"
Chronic stress	Lack of satisfaction, high demand, loss of control, ability to recover, and negative emotions	Daily EMA (interval)	Selected items from CSSS[b] [53] and LKCS[c] [54]	7-point Likert scale	"I couldn't relax today."
Work-related distress	Relationship, personal accountability, work-life balance, and workload	Pre-post online	VEDAS[d] [55], online	6-point Likert scale	"Dealing with ambiguous or 'delicate' situations."[e]
Work-related eustress	Relationship, personal accountability, work-life-balance, and workload	Pre-post online	VEDAS [55], online	6-point Likert scale	"Dealing with ambiguous or 'delicate' situations."[e]
Satisfaction	Overall satisfaction, workday adaptability, exertion due to EMA, and exertion due to sensor handling	Pre-post online	CSAT[f] [56], internally extended), online	5-point Likert scale	"How would you rate your overall satisfaction with Relax?"
Usability	—	Pre-post online	SUS[g] [57], online	5-point Likert scale	"I found using the Relax app unnecessarily complicated."
HRV[h]	SDRR[i], RMSDD[j], and LF[k]/HF[l]	Continuously	Polar VS[m]	Passive	—[n]
Secondary					
Momentary activity	Environment (work or private), type of activity (if work: routine or extraordinary, if private: duty or leisure), physical exertion, mental exertion, and social activity	Daily EMA (interval)	Internally created scale	Dichotomous, 7-point Likert scale, single choice, open (text)	"Is work time right now?"
Activity of last stress event	Physical exertion, mental exertion	Daily EMA (interval)	Internally created scale	7-point Likert scale	"My physical exertion was:"
Expected stress	—	Daily EMA (morning)	Internally created scale	7-point Likert scale	"I expect for today:"
Subjective sleep quality	Subjective restfulness, sleep disruptions	Daily EMA (morning)	Internally created scale	7-point Likert scale, dichotomous, open (numeric)	"My sleep was:"
Summarized emotional state	Arousal, valence	Daily EMA (evening)	Internally created scale	7-point Likert scale	"My general mood throughout the day was:"
Summarized well-being	—	Daily EMA (evening)	Internally created scale	7-point Likert scale	"I felt overall today:"
Summarized activity	Environment (work/private), type of activity (if work: routine/extraordinary; if private: duty/leisure), physical exertion, and mental exertion	Daily EMA (evening)	Internally created scale	Dichotomous, 7-point Likert scale	"Has today been a workday?"
User feedback	Sensor handling, favorite function, requests on functionality, and general feedback	Pre-post online	Internally created scale	Open (text)	"What were your favorite features of the Relax app?"
Acceptable price	Optimal price, indifference price, marginal cheapness, marginal expensiveness	Pre-post online	PSM[o] [58]	Open (numeric)	"At what price would the product on a monthly subscription basis be too expensive for you to buy it?"

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Outcome	Subscales	Design of measurement	Instrument	Item format	Example item
Physical arousal	Mean HR[p] and mean RR[q]	Continuously	Polar VS	Passive	—

[a]EMA: Ecological Momentary Assessment.
[b]CSSS: Chronic Stress Screening Scale.
[c]LKCS: Leipzig Screening Questionnaire on Chronic Stress.
[d]VEDAS: Valencia Eustress-Distress Appraisal Scale.
[e]In the VEDAS, the same items were presented twice, once with a eustress framing of the instruction and once with a distress framing.
[f]CSAT: customer satisfaction score.
[g]SUS: System Usability Scale.
[h]HRV: heart rate variability.
[i]SDRR: SD of r-r-intervals.
[j]RMSSD: root mean square of successive differences.
[k]LF: low frequency.
[l]HF: high frequency.
[m]VS: Verity Sense. The same items were presented twice, once with a eustress framing of the instruction and once with a distress framing.
[n]Not applicable.
[o]PSM: price sensitivity meter.
[p]HR: heart rate.
[q]RR: r-r-intervals.

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Table 2. Study schedule of enrollment, interventions, and assessments, according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [59].

Time point	Study period					
	Enrollment	Preallocation		Allocation	Postallocation	
	T0[a]	T1[b]	P1[c]	T2[d]	P2[e]	T3[f]
Enrollment						
Eligibility screen	✓					
Informed consent	✓					
App installation	✓					
Allocation				✓		
Interventions						
App use			✓		✓	
Sensor use			✓		✓	
Microinterventions			✓		✓	
Assessments						
VEDAS[g]		✓		✓		✓
HRV[h]			✓		✓	
Profile			✓			
EMA[i] (morning, interval, and evening)			✓		✓	
CSAT[j], SUS[k], PSM[l], and feedback				✓		✓

[a]T0: baseline.
[b]T1: before P1.
[c]P1: first 3-week phase.
[d]T2: between P1 and P2.
[e]P2: second 3-week phase.
[f]T3: after P2.
[g]VEDAS: Valencia Eustress-Distress Appraisal Scale.
[h]HRV: heart rate variability.
[i]EMA: ecological momentary assessment.
[j]CSAT: customer satisfaction score. The CSAT was expanded with 3 additional items.
[k]SUS: System Usability Scale.
[l]PSM: price sensitivity meter.

Primary Outcomes

First, primary outcomes were the emotional state over the course of the study and self-reported experience of chronic stress. On the one hand, levels of emotional states and stress were recorded daily using the ecological momentary assessment (EMA) technique. The data obtained from the daily subjective interval, morning, and evening interval questionnaires were used as a diagnostic tool. These questionnaires were developed internally, with established psychometric instruments used in certain cases. A team of experts was responsible for selecting the items for the internally developed instruments, some of which were commonly used items for the topics in question. Emotional state was assessed on the basis of the 2 dimensions: arousal and valence. In the interval questionnaire, in addition to the current state experienced at the time of entry, the state at a possible last stress event was also recorded in a similar manner.

The experience of chronic stress was evaluated using the evening questionnaire, which included items from the Chronic Stress Screening Scale [53] and the Leipzig Screening Questionnaire on Chronic Stress [54]. The Chronic Stress Screening Scale items assessed feelings of lack of satisfaction and high demands, while the Leipzig Screening Questionnaire on Chronic Stress items focused on experiences of loss of control, inability to recover, and negative emotions. The EMA questionnaires were each scored on a 7-point Likert scale. Conversely, chronic stress was evaluated using the Valencia Eustress-Distress Appraisal Scale [55] at the following time points after P1 and P2 in the web-based questionnaire. The questionnaire was used to distinguish between work-related distress and eustress, as well as to evaluate the subscales of relationship, personal accountability, work-life balance, and workload. A 6-point Likert scale was used in line with the original instrument.

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Second, the physiological stress parameters, as measured by the Polar VS sensor, were recorded as primary outcomes. Similarly, the continuous data from the app use were used as an outcome. The stress parameters were HRV variables: SD of r-r-intervals, which is a direct measure of HRV; RMSSD, which is a measure of the parasympathetic recovery capacity; and LF/HF, which is the ratio of the balance between the sympathetic and parasympathetic nervous systems in favor of the latter.

Third, the level of satisfaction was assessed using the web-based questionnaire administered after P1 and P2. In this instance, the customer satisfaction score [56] was expanded with 3 supplementary items that were specifically designed to assess satisfaction and effort with the Relax approach. The items included ratings for overall satisfaction, workday adaptability, exertion due to EMA, and exertion due to sensor handling. The participants were required to indicate their level of agreement with the statements on a 5-point Likert scale.

Fourth, the System Usability Scale [57] was used to assess usability in the web-based questionnaire at P1 and P2. The items that were specifically reformulated for the Relax approach were collected using a 5-point Likert scale.

Secondary Outcomes

The interval questionnaire also included items on the momentary activities at the time of entry and the last stress event. The daily morning questionnaires for participants in P1 and P2 included additional items pertaining to expected stress levels for the day, as well as perceived restfulness of sleep from the previous night and the frequency and duration of sleep disruptions. The evening questionnaires inquired about the summarized emotional state along with well-being and the summarized activities of the previous day.

In addition to the quantitative survey, which was used as the primary outcome measure, satisfaction was also assessed using qualitative items. A total of 4 questions with an open item format were included in the survey to elicit feedback on the use of the app and the wearable device, as well as any suggestions or comments the participants might have. Finally, participants' price acceptance was measured in the web-based questionnaire using the price sensitivity meter [58].

Within the displayed daily questionnaires, plain text fields allowed participants to report stressful events and special circumstances from the day. These responses were catalogued by the backend service and stored in the web-based database. However, they were not automatically analyzed by the system at this early stage of app development. Future research may explore automated analysis of stress-related text responses.

Data Management

To prevent loss of the sensor data and ensure continuous 24/7 recording without gaps, a specialized workflow was designed for the app. All data were first stored locally on the VS system. Whenever a Bluetooth connection to the Android phone was established, a secure bulk transfer of all saved files was initiated, with a watchdog mechanism ensuring complete data reception. Once transferred to the phone, the data remained stored locally until an internet connection became available, at which point it was uploaded to the database in a similar manner as the Bluetooth transfer. If any data loss was detected, the entire file transfer process was restarted. Low battery charging problems had an inbuilt early detection system to prevent writing corrupted files on both systems.

The subjective data, pseudonymized using the self-generated code, were transferred to SPSS (version 29; IBM Corp) for data analysis. Means were calculated for all scales and then statistically analyzed. For the web-based questionnaires at T1, T2, and T3, exclusive values were created for the scales. The continuous daily data from P1 and P2 were transformed into weekly means for progression analysis. The broad time span of 1 week was intended to compensate for any missing data that were expected with complex EMA data collection integrated into daily life [60]. In addition, the general adherence to possible EMA entries and wearable data will be taken into account in the following statistical analysis. The records of individuals with at least >80% missing data will be excluded from the calculations. Data are available on reasonable request.

Statistical Analysis

To statistically analyze the central evaluation questions of the prototype developed in the Relax project in terms of its efficacy in reducing stress in the workplace, different models will be constructed. First, the difference between the groups and thus the degree of individualization by the app will be determined. Second, the pre-post design will be used to ascertain whether the individuals exhibited a reduction in stress over time. These 2 approaches will use all stress-relevant outcomes to make assertions about the work stress of the individuals, namely the emotional states, self-reports on chronic stress as well as distress and eustress, and the physiological parameters. Linear mixed models will be used for the effectiveness analyses.

To address the usability and feasibility of the prototype, the data obtained from the satisfaction and usability scales will be used. These will also be analyzed between the groups and in the pre-post design. Exploratory analyses will test the secondary outcomes for possible effects. Additional moderation and mediation analyses will be possible here, in which the variables from the demographic and profile surveys could also be used. It is anticipated that the qualitative data from the user feedback will provide information about the specific background of the participants' usability ratings.

Results

The study was completed in the summer of 2024, and the statistical analyses are ready to be carried out. Data collection has reached a sample size of 46. Publication of the results is expected in the summer or fall of 2025.

Discussion

Anticipated Findings

The objective of the evaluation study of the prototype from the Relax project is to assess the effectiveness of the system, as well as its feasibility and usability. It is expected that the Relax approach will demonstrate stress reduction in working

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individuals according to comparable approaches in the field of mHealth for work stress [17]. However, this system occupies a distinctive position in the current research landscape, offering mHealth interventions in accordance with the concept of JITAIs, delivered at the optimal time and with content tailored to the individual for work stress management. Thus, it addresses the next step in development possibilities for current approaches that only focus on personalized interaction in individual interventions, such as biofeedback [22,39-41], or only make a rudimentary individualized module selection based on personal data [42]. The ability of a constantly learning app to select the optimal intervention for a given situation and individual from a pool of >100 interventions represents the potential of an AI-controlled mHealth app for occupational stress.

It is anticipated that, due to the pilot nature of the study, the results will be primarily dominated by the feasibility and usability aspects of the user experience. It should be noted that the app at the time of evaluation was in a raw version, which will inevitably result in a user experience that is not yet smooth. Furthermore, the Relax approach integrates a number of innovative design and development decisions, each of which represents a significant advancement in the field of mHealth for work stress [23,25]. The approach incorporates several novel elements, including AI-driven personalization, the implementation of the JITAI concept in both temporal and content aspects, and the incorporation of a multitude of potential interventions and continuous data input by the user. The results of the evaluation may provide insights into these aspects individually or generate new research questions regarding the design of advanced mHealth personalization and usability.

A special case is that, due to the individual personalization, the user experience may vary considerably from one individual to another, which can be challenging for an evaluation on a group basis. The fact that virtually every user could create a different experience in terms of the quantity and timing of the interventions can result in heterogeneous outcomes. Such heterogeneous results are desirable in analyses where individual personalization is a means to a general end, such as stress reduction or satisfaction with the app. In such cases, personalization must necessarily be heterogeneous due to the heterogeneity of personal stress experiences. However, such a heterogeneous user experience could lead to the app being perceived as unusable, for example, by users who experience little stress and therefore little interaction with the app.

Limitations

The study design reveals some limitations in the significance of the results that are still to be analyzed. First, the pilot nature of the study permits only an initial impression of the effectiveness of the developed system in terms of stress reduction in an individual context. The absence of a control group without interventional procedure precludes certainty that any effects are undoubtedly attributable to the intervention. It is possible that the potential effects on stress reduction during the study period may be influenced by factors unrelated to the intervention. Consequently, a subsequent investigative study using a controlled design is imperative to clarify the causes of any effects.

Furthermore, the unspecified ad hoc sample represents a limitation. No distinction was made between professions and sectors, which means that user experiences can vary considerably not only due to individual characteristics and stress levels but also due to the specificities of individual everyday working lives. These can partly determine the degree of interaction with the app due to varying degrees of availability of the individual for using the app during working hours. It is therefore anticipated that adherence may vary considerably among individuals who are not able to adhere to the app use instructions and are unable to wear the wearable device continuously. The small sample size will not allow for subgroup analysis, as a highly variable sample is expected in this regard. However, it is also expected that the personalization approach of the app will adapt to the highly heterogenous work lives and still create the optimal experience for each individual user.

Another limitation of this study is that data collection was conducted exclusively on Android devices. This decision was driven by technical constraints, including iOS restrictions on background data access and sensor use, as well as the greater flexibility of Android for research applications. In addition, cost considerations and the higher prevalence of Android devices compared to iOS devices within our target population influenced this choice [61].

Technical challenges and adjustments, both planned and unplanned, can influence the behavior of the data. Technical issues may result in the absence of data recording during specific intervals or the occurrence of transmission errors. These factors have the potential to significantly distort use patterns and the overall picture of an individual's stress levels. Further studies should incorporate a more advanced version of the prototype, informed by the feedback obtained in this study, with the objective of enhancing its usability and resilience to anticipated technical and adherence issues.

Conclusions

The Relax approach provides a new perspective on how personalized elements can be incorporated into mHealth solutions, paving the way for more tailored and effective interventions according to the JITAI concept. This pilot study aims to test the developed system. The initial findings from this study will offer further insight into the feasibility of the system, as well as its preliminary effectiveness. However, there are several limitations to the study design that need to be considered, including the absence of a control group, concerns regarding the representativeness of the sample, and anticipated technical interference with data quality. Addressing these limitations is crucial for ensuring the robustness and generalizability of the results in future research.

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Authors' Contributions

Conceptualization: MP (lead), ARL (equal), BK (equal), CS (equal), OJ (equal), and MS-T (supporting)
Data curation: CS (lead), BK (equal), and OJ (equal)
Funding acquisition: MP (lead), ARL (equal), BK (equal), and OJ (equal)
Investigation: BK (lead), ARL (supporting), and OJ (supporting)
Methodology: BK (lead), OJ (supporting), and CS (supporting)

Conflicts of Interest

None declared.

Multimedia Appendix 1
Relationships between intervention areas, subtypes, initial weights, and presentation formats.
[DOCX File , 48 KB - resprot_v14i1e68012_app1.docx]

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Abbreviations

AI: artificial intelligence
CBT: cognitive behavioral therapy
EMA: ecological momentary assessment
HF: high frequency

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HRV: heart rate variability
JITAI: just-in-time adaptive intervention
LF: low frequency
mHealth: mobile health
RMSSD: root mean square of successive differences
VS: Verity Sense

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Protocol

Screening and Risk Analysis of Atrial Fibrillation After Radiotherapy for Breast Cancer: Protocol for the Cross-Sectional Cohort Study “Watch Your Heart (WATCH)”

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Abstract

Background: Atrial fibrillation (AF) after radiotherapy (RT) in patients with breast cancer (BC) is a relatively new and understudied topic. AF can increase the risk of stroke and other serious cardiovascular complications, compromising patients’ quality of life and survival. Screening of AF, both asymptomatic and symptomatic forms, is therefore essential for optimal management.

Objective: The aim of the Watch Your Heart After Radiotherapy for Breast Cancer (WATCH) study is to assess the incidence of AF (symptomatic or asymptomatic) occurring throughout a 5-year follow-up after RT and to investigate whether cardiac radiation exposure is associated with the occurrence of such events.

Methods: WATCH is a cohort study that will include 200 patients over 65 years old, treated with RT for BC 5 years before inclusion and without a history of AF. Cross-sectional screening for AF at the time of the scheduled 5-year post-RT visit will be conducted by recording data from a Withings ScanWatch smartwatch for 1 month, confirmed by an electrocardiogram (ECG), and validated by a physician. In addition, a transthoracic echocardiography (TTE) will be performed, providing a comprehensive assessment of cardiac structures, and allowing us to investigate the underlying etiology and assess the risk of complications. Patients’ medical records will provide retrospective information about the timing and risk factors for the occurrence of AF and other arrhythmias and cardiac diseases during the 5 years following RT. The development of deep learning algorithms for autosegmentation analysis of potentially critical substructures for the occurrence of AF, including cardiac chambers, the sinoatrial node, the atrioventricular node, coronary arteries, and pulmonary veins (PVs), will produce dosimetry linked to previous RT treatment for all contoured structures.

Results: Enrollment started in October 2023 and will continue until mid-2026 to include 200 patients, which will ensure an 80% statistical power to detect a significant difference in AF incidence around 15% for the group of patients moderately exposed (<75th percentile of the mean heart radiation dose) and 25% for the group of patients highly exposed (>75th percentile of the mean heart radiation dose). The results are expected by the end of 2026.

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Conclusions: This study will contribute to generating new knowledge on AF after RT for BC and help considering the inclusion of AF screening into routine clinical practice for these patients. Identifying the dose-risk associations would improve RT delivery protocols to limit the occurrence of different forms of AF and, if necessary, initiate appropriate treatment.

Trial Registration: ClinicalTrials.gov NCT06073509; clinicaltrials.gov/study/NCT06073509?id=NCT06073509&rank=1.

International Registered Report Identifier (IRRID): DERR1-10.2196/67875

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KEYWORDS

breast cancer; radiotherapy; atrial fibrillation; smartwatch; arrhythmia; cardiac dosimetry

Introduction

Background

Breast cancer (BC) is the most common cancer in women [1]. Early screening and advances in treatment, including surgery, chemotherapy, hormone therapy, and targeted therapies, have significantly improved survival rates. Radiotherapy (RT) plays a crucial role in BC management by reducing the risk of local recurrence and improving overall survival, particularly following breast-conserving surgery [2]. Despite its efficacy, RT for BC can induce adverse effects on the heart, particularly when the heart is near the radiation field. Cardiac complications can include coronary artery disease, pericarditis, valvular heart disease, and myocardial infarction [3-5]. Emerging evidence also indicates a risk of atrial fibrillation (AF) in patients with BC that may manifest months to years after treatment [6,7]. AF is a common cardiac arrhythmia characterized by an irregular and often rapid heart rate [8,9] that can eventually lead to conditions with significant health impacts (stroke, heart failure, dementia) [10-12]. AF screening is challenging, further compounded by its frequent asymptomatic nature, which has often gone undetected in retrospective noninterventional studies. It is therefore crucial to further investigate the risk of AF in patients with BC as it may compromise the quality of life and survival of patients.

Atrial Fibrillation in Patients With Breast Cancer

Cancer patients have an increased risk for developing AF, varying according to cancer type and stage [7] and medical treatments for cancer [13]. It has been suggested that patients with BC may also not be exempt from AF risk, but results between studies are conflicting. A recent study based on the Medicare database showed that the incidence of AF is significantly higher in patients following the year of the diagnosis of BC compared to a control population without cancer (3.3% vs 1.6%, $P<.05$) [6]. With longer follow-up, several retrospective studies have indicated higher AF rates in patients with BC compared to the noncancer population [14-21], but these results were not confirmed in a Danish cohort [22], a US case-control study [23], and a meta-analysis [19]. The impact of age could explain such discrepancies between studies, as illustrated in a large cohort study using the National Inpatient Sample database in the United States based on 40,030,380 adults' hospitalization for cancer, where patients with BC aged >80 years had an increased risk of AF [24]. Similar results were observed in a systematic review and meta-analysis that found that older patients (age ≥65 years) with BC have a 4.5 times' higher incidence of AF than younger patients with BC (8.6% vs 1.9%) [18]. Other important factors could impact the risk of AF in patients with BC, such as the medical treatments for cancer, including thoracic surgery, chemotherapy, endocrine therapy, or RT [25]. The effects of surgery and chemotherapy on AF risk have been widely studied, but few studies have documented the risk of AF after RT.

Indeed, some scarce studies have specifically analyzed the link between AF and RT for BC. In 2 studies, RT was associated with a significantly increased risk of AF when compared to a control population without cancer (relative risk [RR] 1.82, 95% CI 1.07-3.08) [26]; hazard ratio [HR] 1.25, 95% CI 1.05-1.48 [27]). However, in a US cohort study, the risk of AF was not significantly higher in patients treated with RT compared to the general population [28].

Screening of Atrial Fibrillation: A Challenge

Most of the aforementioned studies were retrospective and based on medical records and hospitalization for identification of AF events and thus presented the limitation of potential undercapture of events, which is a concern for AF, as explained next.

AF is the most common arrhythmia, which affects 1% of the general population and about 10%-20% of individuals aged 80 years or more. The definitive method for diagnosing AF is through visual inspection of an electrocardiogram (ECG). Although an irregular pulse might suggest the possibility of AF, an ECG is essential to confirm the diagnosis. Although persistent AF is easily detected, other forms are hard to diagnose despite symptoms. This is due to the paroxysmal nature of many types of AF that might disappear on the way to the hospital for a 12-lead ECG evaluation. Holter monitoring might fail to detect paroxysmal AF if it does not occur on the day of examination. Moreover, AF may be asymptomatic [29], and the challenge in early screening of AF is compounded by its often asymptomatic nature, as approximately one-third of individuals with this form of arrhythmia are unaware of its presence [30]. This has led to the concept of silent AF, which describes subclinical, asymptomatic episodes of paroxysmal AF.

To overcome these limitations of 12-lead ECG and Holter monitoring, advancements in wearable technology have led to the development of smartwatches with integrated ECGs (30-second single-lead electrocardiogram [SL-ECG] recording), which allows continuous monitoring of cardiac activity and can help identify silent AF episodes that might be missed during a single evaluation [31-33]. The effectiveness and reliability of

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ECG smartwatches for the screening of AF has been demonstrated in several studies (sensitivity 55%-97.3%, specificity 60%-98.2% [31,34-36]), in particular for silent or paroxysmal AF, by measuring continuous cardiac frequency and SL-ECG [37-39]. Moreover, ECGs generated by smartwatches are considered effective and noninferior to ECG/composite 12-lead ECG/Holter/patch monitoring for AF screening [40,41], even if validation of the diagnosis through manual interpretation by a physician is required [39]. Regarding the adherence rate of smartwatch wearing in individuals over 65 years, the PulseWatch trial showed a decrease after 1 month (baseline: 73%; day 30: 63%; $P<.05$) [42], illustrating the limitations of a long period (>1 month) of follow-up with smartwatches in the frame of an AF-screening campaign.

Recently, the European Heart Rhythm Association published recommendations on the use of digital devices to detect and manage AF [43]. It concluded that systematic screening using intermittent ECGs may be beneficial to detect AF in individuals aged >65 years with comorbidities increasing the risk of stroke. RT has been shown to increase the risk of cardiovascular and cerebrovascular diseases [4,44] in patients with BC. It may thus be important to consider AF screening for patients who have undergone RT for BC, due to their increased risk of cardiovascular complications. The interest and feasibility of opportunistic screening for AF in women treated with RT for BC have never been investigated.

Relationship Between Cardiac Exposure to Radiation and Atrial Fibrillation Among Patients With Breast Cancer

Women treated with RT for BC present clinical characteristics at baseline that may induce a higher risk of cardiac events independent of irradiation, and it is consequently crucial to consider cardiac dosimetry to better understand the potential association between RT and the occurrence of AF and then establish a causality link. The association between the mean heart radiation dose and AF risk have been poorly investigated. The Northern Ireland Cardiac Health Events After Radiotherapy (NI-HEART) Study of patients with lung cancer found a dose-response relationship with HR=1.75 (95% CI 1.03-2.97) [45]. For BC, a similar association with the mean heart radiation dose was observed, with HR=1.23 (95% CI 1.15-1.32) [46]. However, radiation exposure of the heart during RT is not homogeneous, and the mean heart radiation dose is often not relevant to evaluate cardiac substructure RT doses [47] that may be more relevant to evaluate associations with AF. Some studies have begun to explore the dosimetry of cardiac substructures, and recent data have demonstrated associations between cardiac substructure radiation doses and specific cardiac events or mortality in patients. In a cohort that included 238 patients with esophageal cancer treated with RT, increasing the mean left atrial radiation dose was associated with AF risk (with 30% for every 10 Gray increase) [48]. In the field of arrhythmias and conduction disorders, this was observed for the right atrium and the sinoatrial node and the risk of conduction disorders in patients with BC [49-51]. In the case of AF, the arrhythmogenic tissue is often located in the pulmonary veins (PVs), but these structures are not yet considered organs at risk during RT planning, despite a potential relevant association, as suggested in the NI-HEART Study, which investigated the PV radiation dose and the risk of AF in patients with lung cancer following RT. Dose metrics for both the left (V55) and the right (V10) PVs were associated with the incidence of new AF (HR 1.02, 95% CI 1.00-1.03, $P=.005$, and HR 1.01, 95% CI 1.00-1.02, $P=.033$, respectively) [52]. Further research is needed to accurately assess the radiation doses absorbed by some of these substructures and to determine whether the exposure of certain potentially critical structures can better predict the risk of cardiac arrhythmias, particularly AF, in patients with BC. Indeed, identifying critical substructures for AF in women undergoing RT for BC and demonstrating the dose-risk relationship could thus improve RT delivery protocols to limit the occurrence of these arrhythmias.

Manual contouring in radiation treatment planning is time-consuming, requiring meticulous effort to ensure precise delineation of volumes. In recent years, artificial intelligence (AI), particularly deep learning–based autosegmentation models, has emerged to mitigate this workload. These models are used for contouring organs at risk, offering significant improvements in consistency and efficiency, and substantially reducing the time required [53]. However, such deep learning autosegmentation models are scarce or inexistant for specific cardiac substructures, such as conduction nodes [54] or PVs [55], and remain to be developed.

Study Rationale

Studies on AF and its potential link with RT for BC are relatively limited and have several limitations: the probable undercapture of AF events, particularly in the case of silent AF; the lack of details on the identification or diagnosis of AF; and the lack of precise dose metrics data for cardiac substructures.

In the population of patients with BC treated with RT, asymptomatic forms of AF are often missed in retrospective data collection, which typically identifies only symptomatic cases. Our study hypothesizes that at the time of the last follow-up visit (ie, 5 years post–breast RT by an oncologist), an opportunistic single-timepoint screening combining the use of a smartwatch and a cardiological evaluation, including an ECG and an echocardiogram, could help identify these asymptomatic cases. This would facilitate the management and potential treatment of these patients and increase the completeness of identifying incident cases potentially associated with RT.

Cardiac irradiation related to RT for BC can lead to an increased risk of cardiovascular diseases a few months to several years after treatment. However, precise data for AF, to establish a potential dose-response relationship, are sparse. Our study hypothesizes that the risk of AF could be associated with the radiation dose absorbed by critical cardiac substructures.

Objectives

In this context and to explore these hypotheses, we will implement the Watch Your Heart After Radiotherapy for Breast Cancer (WATCH) cohort study combining a retrospective design and cross-sectional screening, which aims to investigate AF,

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including asymptomatic forms, that has occurred in patients with BC during 5 years following RT.

The *primary objective* of the study is to assess the incidence of symptomatic or asymptomatic AF occurring throughout a 5-year follow-up after RT and to identify nonradiation and radiation risk factors for the occurrence of such events.

The *secondary objectives* are as follows:

- Perform a dosimetry evaluation of radiation doses absorbed in the heart and cardiac substructures (chambers, conduction nodes, coronary arteries, PVs) based on autosegmentation models developed with deep learning algorithms.
- Investigate whether the risk of AF is associated with cardiac irradiation characterized by these absorbed radiation doses.
- Assess the incidence of other arrythmias or cardiac diseases throughout the 5-year follow-up after RT and analyze these risks according to the level of cardiac irradiation.
- Evaluate the satisfaction and usability of the smartwatch with an integrated ECG in patients with BC.

Methods

Study Design

WATCH is a cohort study implemented as a retrospective and cross-sectional study [56] that will include female patients with left- and right-sided BC treated with postoperative RT after primary breast-conserving surgery. A cross-sectional collection at least 5 years after RT at the time of the last follow-up visit with the oncologist will be performed through smartwatch screening and a cardiology consultation (ECG and echocardiography) for AF screening. This 5-year post-RT timepoint for cross-sectional analysis has been chosen for 2 main reasons: first, to catch an opportunity of the last follow-up consultation with the oncologist to present the study to the patients and, second, a delay of 5 years post-RT appeared relevant to detect AF in patients with BC treated with RT, as observed in our previous work [49]. The retrospective collection of information will be based on questionnaires delivered to the patients to complete and checked against medical records. Figure 1 shows the study design.

Figure 1. WATCH study design. AF: atrial fibrillation; BC: breast cancer; ECG: electrocardiogram; RT: radiotherapy; SL-ECG: single-lead electrocardiogram; WATCH: Watch Your Heart After Radiotherapy for Breast Cancer.

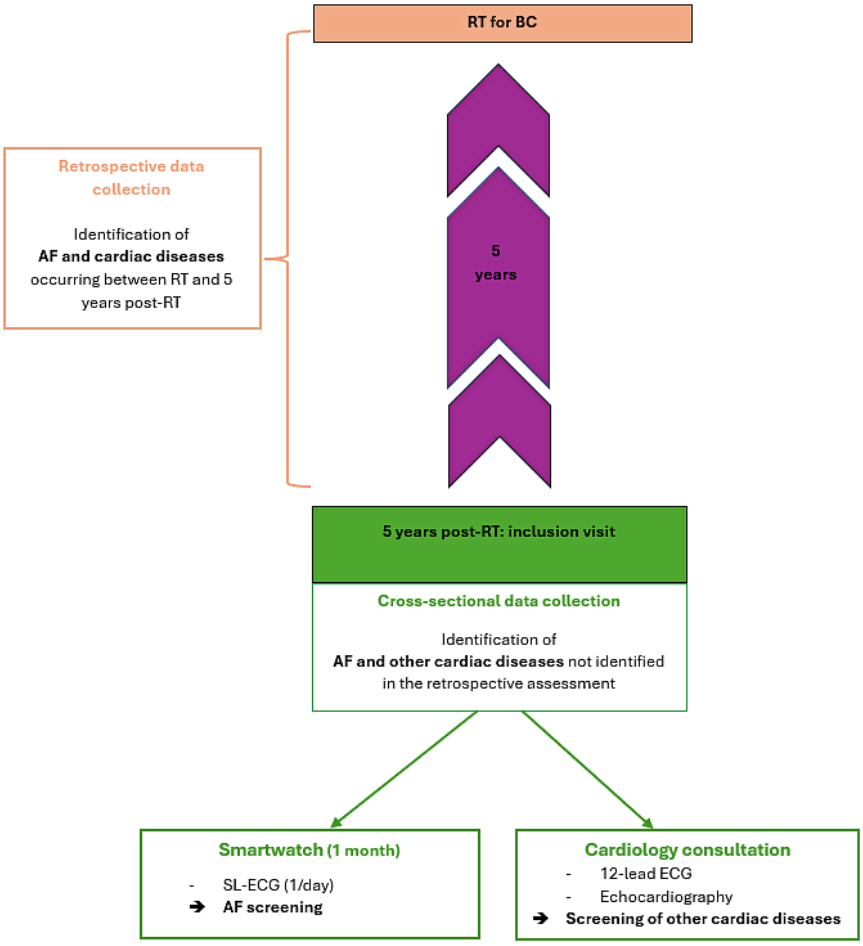

The study was registered with ClinicalTrials (NCT06073509) on September 10, 2023.

Ethics Approval

This study will be conducted in accordance with the Declaration of Helsinki (amended at the 64th World Medical Association General Assembly, Fortaleza, Brazil, October 2013) and the principles of Good Clinical Practice and the Medical Research Involving Human Subjects Act (WMO). This project aims to evaluate a medical device or a device used for nonmedical purposes and is framed by Regulation (EU) 2017/745 on medical devices (MDR). This study received ethical approval from the

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French Southwest Committee for Protection of Persons and from the National Agency for Medical and Health Products Safety (IDRCB number 2023-A01622-43). Participants enrolled in the study will provide written informed consent. To ensure privacy and confidentiality, all data collected in this study are de-identified prior to analysis, with no personally identifiable information retained.

Study Population

In this study, we plan to include 200 female patients with unilateral BC, aged over 65 years old at inclusion and treated at least 5 years ago with postoperative modern photon-based RT after surgery. For this study, we will focus on patients aged >65 years, as recommended by the European Heart Rhythm Association [43], which concluded that systematic screening using intermittent ECG may be beneficial to detect AF in individuals aged >65 years with comorbidities increasing the risk of stroke. Patients with a history of cancer or AF before RT or with recurrent cancer (BC or other) after RT will be excluded. Inclusion and exclusion criteria are summarized in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria:

- Women surgically treated for left or right breast cancer (BC) and for whom adjuvant treatment is radiotherapy (RT), with irradiation of the breast or chest wall irradiation and possibly ganglion chains
- Adjuvant RT performed between 5 years before enrollment
- A 5-year post-RT follow-up oncologist consultation performed in one of the investigating centers
- Age 65 years or more at enrollment
- Owning a smartphone and able to understand and use digital tools alone or with the help of a caregiver
- Consented to a connected follow-up
- Affiliated with a social security system or equivalent
- Volunteering to participate in the study and providing signed informed consent

Exclusion criteria:

- History of cancer before RT for BC
- History of atrial fibrillation (AF) before RT for BC
- Recurrent cancer (BC or other) after RT for BC

Recruitment and Study Procedures

Patients will be enrolled at the Clinique Pasteur in Toulouse and at the François Baclesse Center for Cancer Control/Caen University Hospital in Normandy. Until now, enrollment has begun only at the Clinique Pasteur.

Before Inclusion

Potential participants undergo prescreening by the oncologist during their final post-RT follow-up consultation (approximately 5 years after RT) to ensure eligibility. This is performed before any study procedure is conducted. The participants are enrolled formally only after they sign the informed consent form at the inclusion visit.

Inclusion Visit

Participants complete a medical questionnaire to provide information about their medical history prior to RT and all treatments and cardiovascular diseases that may have occurred since the end of RT (see details in the *Data Collection* section). The participants then receive the *Withings ScanWatch* (Withings SA) smartwatch, and they install the Withings HeathMate app on their smartphone to continuously record their cardiac activity and register ECGs. The watches are purchased by the Authority for Nuclear Safety and Radiation Protection (ASNR), the study sponsor. The choice of Withings ScanWatch was based on several reasons. Many smartwatches integrated with ECG recording currently meet the European Conformity (CE) standards. A recently published study [31] concluded that all evaluated devices have high diagnostic accuracy. An inclusion criterion for the WATCH Study specifies that patients must own a smartphone, with no restrictions on the smartphone brand. An analysis of the user manuals of the different watches led us to choose Withings ScanWatch, as it is the only one compatible with all smartphone brands. Moreover, feedback from the cardiologists involved in the study was positive regarding this smartwatch: accurate ECG recordings, quite simple for patients to use, and good battery life. It should be noted that there was no conflict of interest among the investigators in the choice of Withings ScanWatch.

The functions of the smartwatch and its application are explained to the participants. They are required to wear the loaned smartwatch for 1 month and record an ECG at least once per day or when the smartwatch automatically detects an abnormal heart rhythm and suggests that the user record an ECG.

Screening Visit

One month after the inclusion visit, all recorded smartwatch-based ECG data are emailed as a PDF file by the patients to the study cardiologists. To prevent data collection failure due to elderly adults' unfamiliarity with smartphone usage, especially when sending an email with a PDF file attached, practice time is scheduled during the screening visit

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with clinical researchers (practice for 1 hour). During this visit, if necessary, patients can be accompanied by their caregivers, who will be able to transfer the PDF files. The patients complete a questionnaire to evaluate their satisfaction with and the usability of the smartwatch integrated with ECG recording, reset the smartwatch, and return it. The smartwatch is then loaned to another patient enrolled in the study. Finally, a cardiology consultation including a 12-lead ECG completed with transthoracic echocardiography (TTE), providing a comprehensive assessment of cardiac structures and functions, is performed (see details in the *Data Collection* section). Criteria for diagnosing asymptomatic AF and AF using instruments and auxiliary examinations in this study will follow the most recent guidelines for AF management [57].

Data Collection

Cancer, Treatment, and Medical History Before and After RT

Information about cancer and its treatment (surgery, chemotherapy, RT, hormonotherapy) are collected through hospital medical records. The retrospective collection of information, which aims to identify cardiovascular diseases prior to RT and those that occurred between RT and 5 years post-RT, is based on medical questionnaires filled by the patients and checked against their medical records (see Textbox S1 in Multimedia Appendix 1).

Cardiac Examinations

The cross-sectional data collection, which aims to identify AF and other cardiac diseases at 5 years post-RT, not previously identified in the retrospective data collection, is based on screening for cardiac diseases. This screening is conducted by recording data from the Withings ScanWatch smartwatch, confirmed by an ECG, and validated by a cardiologist. In addition to AF screening, a 12-lead ECG and a TTE are performed (see Textbox S2 in Multimedia Appendix 1). Patient satisfaction with and usability of the smartwatch are assessed using a satisfaction survey [58] and the System Usability Scale (SUS) score [59] (see Textbox S3 in Multimedia Appendix 1).

Cardiac Dosimetry

For cardiac dosimetry, autosegmentation algorithms are being developed based on AI/deep learning to assess the radiation dose to potentially critical substructures for the occurrence of AF (whole heart, cardiac chambers, sinoatrial node, atrioventricular node, coronary arteries, PVs). These algorithms will use convolutional neural networks trained on large datasets of annotated computed tomography (CT) images to identify and contour cardiac substructures with high precision. Specifically, the model used in this study will be trained and validated using a dataset of CT images annotated by expert radiation oncologists and cardiologists to ensure anatomical accuracy and reproducibility [47,50]. Validation metrics, such as the Dice similarity coefficient (DSC), the Hausdorff distance, and the mean surface distance, will be used to evaluate the model's performance against expert contours.

For each patient included in the WATCH cohort, CT images are collected with Digital Imaging and Communications in Medicine (DICOM) data. These CT images will be contoured with our deep learning segmentation tool to provide mean radiation doses and dose-volume histograms for all critical cardiac substructures. The application of AI in this study will allow for reproducible, time-efficient, and standardized dosimetry, addressing interobserver variability associated with manual contouring. Furthermore, the algorithms will be tested for robustness across different scanner models and imaging protocols to ensure generalizability. Nevertheless, manual review and correction by experienced clinicians will be performed for a subset of cases to further verify segmentation accuracy and consistency, aligning with the best practices for incorporating AI in clinical research.

Outcome Measurement

Primary Outcome

The difference in the occurrence of AF (questionnaire + SL-ECG based) throughout the 5-year follow-up after RT according to heart exposure (moderate or low exposure: <75th percentile of radiation dose distribution for the whole heart; and high exposure: ≥75th percentile of radiation dose distribution) will be measured as the primary outcome of interest for this study.

Secondary Outcomes

As mentioned before, the secondary outcomes are:

- Cardiac substructure dosimetry (cardiac chambers, conduction nodes, coronary arteries, and PVs)
- Association between AF occurrence and cardiac substructure dosimetry
- Occurrence of other arrythmias and conduction disorders (12-lead ECG based) throughout the 5-year follow-up after RT
- Occurrence of other cardiac dysfunction, cardiomyopathies, and valvular heart diseases (TTE based) throughout the 5-year follow-up after RT
- Association between other arrythmias and conduction disorders or other cardiac diseases, and cardiac substructure dosimetry
- Patient satisfaction score using the Lickert scale and usability score using the SUS

Sample Size Calculation

The calculation of the required sample size was conducted within the framework of an exploratory study. The required number of patients was set to 200 based on a statistical power of 80% with a type I error rate of 5% and theoretical percentages of AF incidence of 10% for the group of patients considered moderately exposed (<75th percentile of the average heart radiation dose distribution) and 25% for the group of patients considered highly exposed (>75th percentile of the average heart radiation dose distribution) [60]. We plan to include these 200 patients in approximately 30 months.

Planned Statistical Analysis

We will summarize the baseline data (description of the cancer and treatments, history of cardiovascular diseases, cardiac dosimetry) using descriptive statistics: means (SDs) will be used for continuous data with a normal distribution, medians (IQRs) for skewed data, and percentages for categorical data.

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Continuous data will be compared between cases and noncases of AF using the *t* test or the Wilcoxon Mann-Whitney test, and categorical variables will be compared using the chi-square test. All tests will be bilateral, with α=5%.

The estimation of the incidence of AF and other cardiovascular pathologies occurring in the 5 years following RT will be carried out based on data collected during the cardiology consultation (SL-ECG screening, 12-lead ECG, and echocardiography) and the medical questionnaire. A univariate analysis using regression models will identify the risk factors associated with the studied cardiovascular pathologies, other than cardiac radiation exposure (ie, individual and medical characteristics). Subsequently, only variables with $P<.20$ will be retained for multivariable analyses [61]. Estimations of the risk of AF and other cardiovascular diseases according to cardiac radiation doses will be performed using regression models adjusted for the risk factors identified in the univariate analysis. To limit issues in the multivariate analysis due to correlation between dosimetry parameters, each dosimetry parameter will be analyzed separately. Analysis will be performed using the data analysis and statistical software SAS version 9.4.

Results

The study was funded in October 2023 and is still in progress. Enrollment and data collection began in October 2023, and we aim to cover 200 patients by mid-2026. A second inclusion center is planned to be opened by mid-2025. Data analysis will start in June 2026, and the results are expected by the end of 2026.

Discussion

Summary

This study protocol aims to evaluate the risk of AF in patients with BC who have undergone RT, addressing a critical gap in understanding cardiovascular complications of BC treatment. AF is a common arrhythmia with potential to cause severe complications, and its risk may be heightened by the incidental cardiac radiation exposure during RT for BC. Given the increasing survival rates in patients with BC, assessing long-term cardiovascular outcomes has become essential for optimizing post-treatment care.

Several studies have investigated the association between RT for BC and AF [6,26,62]; however, these studies have not provided precise dosimetry data for cardiac substructures, and it remains unclear whether this association is causative or whether cancer and AF just share the same pathophysiologic mechanisms. Our study aims to enhance our understanding of how radiation dose distribution across specific cardiac regions correlates with AF incidence. Our study's approach involves detailed dosimetry analysis of cardiac substructures using deep learning–based autosegmentation, including the left and right atria, the left and right ventricles, coronary arteries, the conduction system, and PVs. This precision in quantifying radiation doses received by these areas will allow for a more granular assessment of radiation exposure and its impact on AF risk, distinguishing our study from studies that have evaluated whole-heart doses [26]. Univariate and multivariable regression analyses will be used to isolate the effects of these localized radiation doses, while adjusting for confounding factors, such as age, comorbidities, and chemotherapy. This will provide an understanding of the dose-response association and help identify high-risk cardiac regions.

With a retrospective design, previous studies that have investigated AF occurrence in patients with BC may have undercaptured AF events, particularly in the case of silent AF. Traditional methods, such as standard ECGs and echocardiography, have proven efficacy in detecting AF but often lack continuous monitoring capability essential for capturing transient AF episodes. Smartwatches, equipped with SL-ECG recording, offer a promising adjunct, providing continuous real-time data on heart rhythm. To investigate AF incidence over 5 years post-RT, our study combines retrospective patient-reported outcomes and cross-sectional screening based on smartwatches, in addition to traditional diagnostic methods (ECG and echocardiography). Patient questionnaires capture symptoms and medical history, offering a broader context for interpreting cardiovascular health and identifying potential noncardiac factors influencing AF risk. ECG and echocardiography will provide objective data on cardiac rhythm disturbances and structural and functional cardiac abnormalities. More particularly, in patients with AF, echocardiography will allow us to investigate the underlying etiology and assess the risk of complications, while patients' medical records will provide information about the timing and risk factors for the occurrence of AF and other arrhythmias/conduction disorders during the 5 years following RT. This multimodal approach will allow for a comprehensive understanding of AF development in the context of radiation exposure and patient-specific factors.

Limitations

However, this study presents several limitations. First, the sample size is relatively small, which, although suitable for an exploratory analysis, will limit the generalizability of our findings. Future studies should incorporate larger cohorts to enhance the statistical power and validity of the results. Due to the inclusion criteria, which selected only patients aged more than 65 years and who own and are able to use multiple digital tools (smartphone, smartwatch, email) or at least be assisted by a caregiver, our estimates of AF at the scale of our population will not be applicable to all patients with BC. However, results on the association between cardiac radiation exposure and AF will not be biased by such potential selection bias. Moreover, this exploratory study does not intend to provide exhaustive figures of AF in all patients with BC who are >65 years old, but it will compare AF between high- and low-cardiac-exposure groups. Selection bias, if any, will not be impacted by the cardiac radiation exposure level of patients. Thus, our study should not provide biased results regarding the potential association between cardiac radiation exposure and AF risk. Second, the study population is limited to older adults, potentially overlooking age-related variability in radiation-induced AF risk. Expanding the research to include a broader age range will provide a more comprehensive understanding of the age-dependent effects. Third, for

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retrospective collection of medical data, some patients may provide incomplete information, resulting in missing data. However, this issue will be limited by additional collection of missing data based on medical records. Last, the follow-up period is limited to 5 years and AF screening performed 5 years after RT. Missed screening of AF should be limited by a combination of retrospective and cross-sectional design. The retrospective part will allow us to collect data on the occurrence of AF based on patients' questionnaires and medical records for a duration of 5 years post-RT. In cross-sectional screening 5 years after RT, patients will wear their smartwatch for a duration of 1 month. This duration will not avoid missed screening for patients with AF that would not occur during this period. Moreover, this duration and opportunistic single-timepoint screening may not fully capture the long-term incidence of AF or the shorter effects post-RT, suggesting the need for both shorter-term and extended follow-up in future investigations to better understand the timing and progression of AF posttreatment.

Conclusion

To conclude, this study will refine our understanding of radiation-induced AF after RT, a topic almost absent from the European Society of Cardiology (ESC) guidelines on cardio-oncology [63]. Given the relatively high incidence rate of AF from a certain age in the general population, identifying increased AF risk linked to RT could result in a significant number of RT-attributable cases. Detecting silent AF may necessitate medical/preventive management for certain patients to limit the risk of stroke. The use of smartwatches has never been studied in a specific population, such as patients treated with RT for BC. This study will evaluate the interest of patients and cardiologists in this type of connected tool within this population. The results of this project could provide recommendations for primary and secondary prevention strategies to limit RT sequelae and improve patients' quality of life.

Acknowledgments

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Data Availability

The datasets generated and analyzed during this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Medical questionnaire: list of items; cardiology consultation: list of items; and questionnaire to evaluate patient satisfaction with and usability of the smartwatch integrated with electrocardiogram (ECG) recording.
[DOCX File , 25 KB - resprot_v14i1e67875_app1.docx]

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Abbreviations

AF: atrial fibrillation
AI: artificial intelligence
BC: breast cancer
CT: computed tomography

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ECG: electrocardiogram
HR: hazard ratio
NI-HEART: Northern Ireland Cardiac Health Events After Radiotherapy
PV: pulmonary vein
PV: pulmonary vein
RT: radiotherapy
SL-ECG: single-lead electrocardiogram
SUS: System Usability Scale
TTE: transthoracic echocardiography
WATCH: Watch Your Heart After Radiotherapy for Breast Cancer

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Protocol

Insight inTo Stress and POOping on Work TIME (ITS POO TIME): Protocol for a Web-Based, Cross-Sectional Study

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Abstract

Background: Long occupational working hours and shift work are common in high-, middle-, and lower-income economies. Bowel movement frequency and stool form in occupational settings may be important markers of stressful working conditions as well as diurnal gut microbiota action, gastrointestinal discomfort, and disorders of gut-brain interaction (DGBI). Characterizing DGBI in shift and nonshift workers could help identify the impact of diurnal work patterns on workers' physical and mental health, including anxiety related to bowel movements.

Objective: This study aims to outline the Insight inTo Stress and POOping on work TIME (ITS POO TIME) protocol describing a web-based multimethods research project on DGBI, stool form and frequency, psychological factors, sleep, diet, and anxiety related to bowel movements in occupational settings by comparison to residential settings.

Methods: Study 1 comprises a web-based convenience sampling survey to acquire quantitative data from adults who are engaged in paid employment. We seek to assess occupational characteristics, organizational factors, as well as standardized questionnaires for stool form, DGBI assessed based on Rome-IV criteria, sleep, diet, bowel movement anxiety (ie, parcopresis), and distress. Study 2 is a qualitative study that asks open-ended questions about respondents' attitudes to defecation at work. Analyses for study 1 will explore rates of DGBI in shift versus nonshift workers and explore how occupational characteristics are associated with occupational bowel movement stool form and frequency. With regards to distress and parcopresis, study 1 will analyze how parcopresis, distress, and contamination fears are associated with stool form and frequency in occupational settings compared with residential settings. Study 1 is designed to have 90% power to detect a 5% difference in DGBI prevalence between groups at α=.05 based on the conservative estimate of 15% DGBI prevalence in shift workers and 10% DGBI prevalence in nonshift workers, with a final sample of 1967 required. Study 2 qualitative data will be analyzed using inductive thematic analysis to identify themes concerning feelings and attitudes about bowel movements in occupational settings.

Results: The findings of ITS POO TIME will elicit important information on what factors are associated with bowel movements and stool form and frequency in occupational settings and identify associations pertinent to occupational health. Data collection commenced in January 2019 and finished enrollment in December 2023. Study 1 obtained 1872 responses and fell short of the desired sample size. Study 2 received 337 responses, and the primary results are expected to be published in 2025 and the qualitative results published in 2026.

Conclusions: The results of the research described in this research protocol will have direct implications for industry, employers, and policy makers concerning DGBI, stress, and worker health.

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KEYWORDS

disorders of gut-brain interaction; gastrointestinal disease; irritable bowel syndrome; shift work; anxiety; occupational health; occupational stress; parcopresis; social anxiety disorder; mixed-methods

Introduction

Extended occupational hours including paid and unpaid overtime as well as shift work during the biological night are an increasingly vital and common component of the labor force in global economies. The number of shift workers alone is estimated at 22 million in the United States [1]. Long work hours and shift work may lead to disrupted circadian rhythms [2], change in hormonal metabolism [3], change in diet [4,5], and irregular timing of eating [6] as a direct consequence of being exposed to artificial light at night [7,8]. The influence of diurnal rhythms on gut microbiota [9,10], patterns of food intake, and satiety [11], is being increasingly recognized as important to worker health. Direct health consequences include upregulated inflammatory response and metabolic disease [10,12], obesity [13], gastrointestinal diseases, and disorders of gut-brain interaction (DGBI) [14]. This research predominantly relates to the latter aspect of gastrointestinal health, specifically, DGBI such as irritable bowel syndrome and related symptoms as they are among the most common health complaints of shift workers [15]. Other DGBI can be categorized as esophageal (eg, functional heartburn), gastroduodenal (eg, functional dyspepsia), bowel (eg, functional diarrhea), centrally mediated disorders of gastrointestinal pain, gallbladder and sphincter of Oddi disorders (eg, functional gallbladder disorder), anorectal disorders (eg, fecal incontinence), as well as childhood functional gastrointestinal disorders.

A higher prevalence of gastrointestinal diseases, DGBI, and related symptoms documented among shift workers than among their nonshift worker peers include *Helicobacter pylori* infection [16,17], duodenal ulcer [18], irritable bowel syndrome [19-21], constipation [22,23], diarrhea, abdominal bloating, gastroesophageal reflux, and regurgitation [23]. A high prevalence of gastrointestinal disease and DGBI is reported in diverse shift work samples such as Iranian petrochemical workers [24], US air traffic controllers [25], German resident physicians [26], Indian restaurant workers [27], Danish fishermen [28], and merchant sailors [29]. High gastrointestinal disease and DGBI rates among nurse shift workers alone were reported in Brazil [30], South Korea [21], Iran [23], Iceland [31], Poland [22], and Turkey [32]. Collective findings raise the likelihood that shift work, regardless of occupation or location, is associated with DGBI. However, most research to date is merely descriptive of gastrointestinal symptom correlates in different occupational settings, and despite this, our understanding of putative associations remains incomplete.

One aspect of gastrointestinal disease and DGBI risk in shift workers that has not been examined comprehensively is the association between gastrointestinal symptoms and defecation routines in occupational settings. Changes in defecation patterns during shift work could be an important marker of diurnal gut microbiota action, gastrointestinal discomfort, or an early indicator for DGBI [33]. Indeed, shift workers may face high job demands as well as limited access to toilets and toilet breaks in addition to the abovementioned diurnal changes [34]. A parallel body of research in school settings offers insights into the impact of restricting access to toilets and voiding behaviors [35-37]. A survey of 791 school teachers suggested that teachers restricted their fluid intake to limit the number of toilet breaks and this was associated with a higher likelihood of experiencing urinary tract infections [37]. Similarly, school students reported behavioral strategies including limiting food and water intake to mitigate the need to use school toilets [38]. Students have also reported avoiding bowel movements at school due to a lack of privacy and perceptions of uncleanliness [38-40]. The ratio of toilets to users has also been identified as a factor in toilet use among students and workers, with privacy and uncleanliness again cited as reasons for toilet avoidance behaviors [35,39]. Despite these findings, there is a very limited understanding of whether such avoidances persist into adulthood and whether toilet access impacts worker attitudes and defecation behaviors in occupational settings. To the best of our knowledge, no study has investigated symptoms of DGBI, occupational toilet characteristics, and attitudes to defecation in occupational settings in shift and nonshift workers.

A second aspect of the association between shift work and gastrointestinal health that remains unclear is the role of psychosocial factors such as stress. Occupational health policies typically focus on biological, chemical, physical, and ergonomic factors, paying less attention to the psychosocial well-being of their workers [12,41,42]. To date, research on the interplay between shift work and gastrointestinal symptoms has largely neglected psychosocial factors. This approach belies prior reports linking shift work with depression [43-45], suicidal ideation [45], burnout [46], workplace conflict [30], poorer decision-making [47,48], workplace accidents [12], and disruption to life outside work [49]. Similarly, psychosocial factors like stress are implicated in DGBI such as irritable bowel syndrome [50-56]. The collective findings raise the possibility that stress is a contributing factor in the association between shift work and adverse gastrointestinal symptoms such as those characterizing DGBI.

Indeed, the term stress is rather nebulous, and therefore it is imperative to further explore different stressors that may include general distress, anxiety, and even voiding-specific stressors. Specifically, diagnostic descriptors of social anxiety disorder refer to “bladder shyness” and difficulties using public bathrooms [57]. More specifically, parcopresis is a term used to describe anxiety surrounding one’s own bowel movements in public restrooms because of an overwhelming fear of perceived scrutiny [58]. Given that prior research indicates approximately 85% of students avoid defecating at high school [59], it remains unknown whether such avoidance behaviors and social concerns persist into adulthood and occupational

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settings. Elucidating defecation avoidance behaviors in adult workers is imperative because such avoidances may have harmful secondary consequences to gastrointestinal health. Unfortunately, less empirical data exist concerning parcopresis by comparison to social anxiety disorder in general as well as paruresis, that is, the difficulty or inability to initiate or sustain micturition [60]. Conceptual models of social anxiety applied to parcopresis and paruresis [61] support the direct contribution to symptom severity from the components of the extended bivalent fear of evaluation model [62]; fear of negative and positive evaluation, concerns of social reprisal, and dysfunctional attitudes [63]. Parcopresis was also associated with toilet avoidance more commonly than contamination fears (17% vs 3%) underscoring that social anxiety processes were responsible for toilet avoidance behaviors [64]. Further empirical data on parcopresis could help improve understanding of this condition contextualized against socio-occupational toileting norms. Specifically, it is unclear if parcopresis symptoms are heightened in restrooms used by work colleagues where perceived social scrutiny could foreseeably be higher. Most research to date investigates toilet behaviors in public restrooms that are largely used by strangers and not work colleagues. To the best of our knowledge, neither social anxiety nor parcopresis has been examined in relation to bowel habits in occupational settings.

The Insight inTo Stress and POOping on Work TIME (ITS POO TIME) study's main aim is to comprehensively describe the prevalence of probable DGBI in shift- and nonshift workers, estimate the prevalence of parcopresis in adult workers, and examine the impact and characteristics of residential and occupational bowel movements. A secondary aim is to explore the role of pertinent covariates including sleep, diet, and psychosocial stress while also collecting data on relevant occupational characteristics. A qualitative study aims to identify attitudes to bowel movements in occupational settings.

Methods

Study 1

Recruitment

The quantitative study uses a cross-sectional survey and convenience sampling design, hosted on the SurveyMonkey electronic platform (Symphony Technology Group). Participants are recruited via advertising at The University of Adelaide Medical School, The University of New England (UNE) Faculty of Health, as well as investigator promotional interviews with national radio and free-to-air television stations, and organizations representing occupations with shift work (Nursing Times) or known toileting restrictions (NSW Teachers Federation). The study adheres to the principles of the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) [65] and is reported in Multimedia Appendix 1.

Ethical Considerations

This study was approved by the Human Research Ethics Committees of the University of Adelaide (H-2018-235) and UNE (HE18-300). Study participants provided informed consent and could opt out of the study at any time by closing their browser window. All submitted data was anonymized and deidentified and respondents did not receive any compensation for their participation.

Respondents reporting any concerns to the questions pertaining to gastrointestinal health are provided with referral information for national health care services and recommendations to consult their primary care provider in the first instance. Participants reporting any concerns relating to mental health are provided with 24-hour emergency and general mental health support services.

Statistical Analysis

Study 1 is designed to have 90% power to detect a 5% difference in DGBI prevalence between groups at α=.05 (1-sided) based on the conservative estimate of 15% DGBI prevalence in shift workers and 10% DGBI prevalence in nonshift workers [15]. The study aimed to recruit 2500 persons based on the anticipated sampling of 25% shift workers and 75% nonshift workers, allowing for 25% incomplete responses in the study, with a final sample of 1967 required.

Hypothesis 1: There will be higher levels in occupational stool form indicating looser stools when compared with residential stools.

Hypothesis 2: Shift workers will have increased odds for DGBI compared with persons not engaged in shift work.

Hypothesis 3: Higher anxiety and distress scores will be observed in persons with DGBI.

Hypothesis 4: Higher parcopresis anxiety symptoms will be more strongly associated with bowel movement form in occupational settings than occupational characteristics.

To assess hypothesis 1, a paired-sample test will be used to evaluate the change between residential and occupational stool types rated on the Bristol Stool Chart. To assess hypothesis 2, analyses will use logistic regression showing the odds ratios and 95% CIs for any probable DGBI (binary outcome) in shift workers in comparison with their nonshift working counterparts using nonadjusted, minimally adjusted (sociodemographic factors), and adjusted for occupational factors such as perceived toilet break adequacy and other self-reported measures including distress. To assess hypothesis 3, a 1-way ANOVA will examine if higher anxiety and distress scores are observed in persons with DGBI compared with their non-DGBI counterparts, using nonadjusted, minimally adjusted models (sociodemographic factors), and models fully adjusted for occupational factors. To assess hypothesis 4, multivariable regression will assess the association between occupational bowel movement type (outcome) and parcopresis (predictor) and occupational factors (predictors), adjusted for other self-reported measures including contamination fears. Occupational factors include toilet break adequacy, number of toilets, and toilet subtype, perceived adequacy of toilet breaks.

Eligibility

Inclusion criteria were individuals aged ≥18 years who self-identify as having paid employment in a part-time or full-time capacity in any work role in any organization, or

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self-employed, or undertaking paid training (eg, apprentice and internist).

Exclusion criteria were individuals who were retired, had a volunteer role, had unpaid work placement, were working from home office (eg, during COVID-19 lockdowns), were working in a sheltered workshop due to intellectual disability or developmental disorder, had no access to the internet to complete the survey, and were unable to visually rate one's own stool.

Measures

Demographic and Occupational Data Collected

General descriptive information included age, gender, occupation, industry, years of employment in current job, household income, shift work type, the number of employees at each workplace, number of toilets at the place of employment, type of toilet (gender-specific, gender-neutral, or shared), cubicle within larger toilet room or enclosed blocks, and perceived adequacy of toilet breaks. We will also quantify how often respondents report defecating in occupational and residential settings.

Medical History

Self-report questions (dichotomized, yes or no) ask about the past history of gastrointestinal surgery, gastrointestinal cancer, urological surgery, urological cancer, spine surgery, use of laxatives, and use of antidiarrhea drugs. This serves as the prescreener before administering comprehensive questions pertaining to gastrointestinal health and DGBI.

Shift Work

We will use reference values for melatonin and the biological night (9 PM-7 AM) as proposed by Arendt and the UK Labour Force Survey [66] to classify workers using their self-reported typical start and end work times as shift work or nonshift work.

Gastrointestinal Disorders

The primary outcome of interest is the prevalence of probable DGBI measured by the Rome IV Diagnostic Questionnaire (R4DQ) [67]. The R4DQ was designed to measure esophageal disorders, gastroduodenal disorders, bowel disorders, centrally mediated disorders of gastrointestinal pain, gall bladder and sphincter of Oddi disorders, and anorectal disorders, as well as two domains not relevant to the proposed project (excluded: childhood functional disorders in neonates or toddlers or children or adolescents). The questionnaire asks respondents a series of questions about gastrointestinal symptoms over the past 6 months, and between 26 to 86 questions are asked in total depending on R4DQ skip pattern logic that we implemented for ITS POO TIME. It takes respondents approximately 15 minutes to complete the R4DQ. Validation studies with the R4DQ [67] indicate high receiver operating characteristic specificity for the detection of any irritable bowel syndrome, functional dyspepsia, and functional constipation (specificity 97.1%, 93.3%, and 93.6%, respectively). However, the sensitivity for detection of DGBI's was low irrespective of whether disorders were mutually exclusive (<63%) or when disorders were permitted to overlap (73%) [67]. In Australia, the R4DQ was successfully administered via the web to 2036 Australians as part of a study on the global prevalence of DGBI [68].

Stool Form and Frequency

Using the Bristol Stool Chart [69], participants were asked to identify the form and frequency of their most recent stool. There are 7 options on the Bristol Stool Chart, with 2 categories indicative of constipation, two categories indicative of normal bowel movements, and 3 categories indicative of diarrhea or urgency. The Bristol Stool Chart was adapted here to ask respondents to rate their most recent stool in the occupational setting, where we obtained information about toilet design. A modified Bristol Stool Chart was also asked for respondents to rate their most recent residential stool. Other bowel habit questions were adapted from the Taiwan Teacher Bladder Survey that asked participants about the adequacy of toilet breaks and frequency of toilet behaviors [36].

Sleep

The 8-item Sleep Condition Indicator (SCI) asks respondents about their concerns about getting to sleep, remaining asleep, sleep quality, daytime personal functioning, daytime performance, duration of sleep problem, nights per week having a sleep problem, and extent troubled by poor sleep. The SCI has high internal consistency ($\alpha \geq .86$) and convergent validity with other sleep measures [70].

Diet

General food frequency was quantified by an abbreviated Food Frequency Questionnaire (FFQ). Abbreviated FFQs are common in epidemiological surveys when diet is not the key variable of interest. We selected 10 items from the 2008/2009 New Zealand nutrition survey that asks about the frequency of eating fruit (servings per day), vegetables (servings per day), wholemeal or whole grain foods, soft drinks, alcohol (standard units), cake sweet or chocolate biscuits, processed meats, red meat, low or reduced fat foods, take away foods [71].

Parcopresis

Several scales exist for anxiety related to urinary voiding; however, only one exists for anxiety related to bowel movements. Toilet anxiety in relation to bowel movements was quantified by the 8-item parcopresis subscale of the Shy Bladder and Bowel Scale [72]. The questionnaire was explicitly designed to assess toilet anxiety in adults and consists of 2 subscales, one for urinary voiding and one for bowel voiding. A validation study of the Shy Bladder and Bowel Scale was performed in psychology students (n=387) and general population groups (n=334), which supported the proposed 8-item 2-factor structure as well as favorable content, concurrent, and test-retest validity [72]. The scale asks respondents a series of questions about their toilet behaviors on a Likert-type scale from "none of the time," "a little of the time," "some of the time," "most of the time," and "all of the time." Higher scores are indicative of higher parcopresis.

Social Anxiety

Social anxiety was quantified with 3 items from the abbreviated Social Phobia Inventory (Mini-SPIN) [73]. The Mini-SPIN items are "Fear of embarrassment causes me to avoid doing

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things or speaking to people," "I avoid activities in which I am the centre of attention," and "Being embarrassed or looking stupid are among my worst fears." Respondents rate each item on a Likert-type scale from "not at all," "a little bit," "somewhat," "very much," and "extremely." The Mini-SPIN was evaluated in 344 persons in a 2-stage psychiatric assessment, which showed that a cutoff score of ≥6 demonstrated high sensitivity (88.7%), specificity (90%), and negative predictive value (98.5%), supporting its utility as a screening tool for social anxiety disorder.

Contamination Fears

Fear of contamination was quantified with 3 items comprising the contamination subscale of the Obsessive-Compulsive Inventory-Revised as validated by Huppert et al [74]. The subscale items are "I find it difficult to touch an object when I know it has been touched by strangers or certain people," "I sometimes have to wash or clean myself simply because I feel contaminated," and "I wash my hands more often and longer than necessary." Respondents rate each item on a Likert-type scale from; "not at all," "a little," "moderately," "a lot," and "extremely."

Distress

General distress is measured with the Kessler Psychological Distress Scale (K10) [75]. The 10-item questionnaire asks about general psychological distress in the previous month. Respondents rate each of the 10 symptoms on a Likert scale from 1 "none of the time" to 5 "all of the time." The K10 is commonly used in epidemiological surveys and normative data exist for the Australian general population [76]. Scores range from 10 to 50, with cutoff scores of 10 to 15, 16 to 29, and ≥30 indicative of low, medium, and high risk for a probable mood or anxiety disorder.

Study 2

Recruitment

Study 2 is a distinct study hosted on Qualtrics and was advertised concurrently with study 1, and it was possible to participate in both or just study 1 or study 2. Advertising was performed through the UNE Faculty of Health research participant pool. UNE typically attracts students characterized as older adult learners retraining for a new career who are engaged in part- or full-time work in addition to their university studies.

Ethical Considerations

Study 2 was approved by the Human Research Ethics Committee of UNE (HE19–198). The study is anonymous, and participants can withdraw at any time. Any potentially identifying information (eg, name of the workplace) will be removed from any publication of results or data sharing.

Methods and Analysis

The study will be conducted in line with the well-recognized quality principles for qualitative research outlined by Tracy [77], including rigor and sincerity. For example, we will aim to provide sufficient, abundant, appropriate, and complex data to ensure rigor. To achieve this, data analysis will be iterative and conducted by multiple authors. Doing so enables peer discussion and reflection in order to engage with reflexive considerations and manage researcher subjectivity and theoretical assumptions [78]. Ongoing engagement with the data through the analysis further enables reflexivity to be explored and considered. To achieve sincerity, we will provide a reflexivity statement about the relevant background details of our team so that the reader can judge how these may have impacted on our approach to the work, including the way that we have interpreted the data. Ongoing review of analysis and the coded data by multiple authors will also take place to support analytic rigor and trustworthiness by ensuring that analysis provides a clear and coherent representation of the data, with trustworthiness and openness also supported by the presentation of detailed extracts in publications from the study.

Qualitative data will be analyzed using an inductive thematic analysis at the latent level from a realist epistemology perspective [79]. Thematic analysis can be viable on open-ended survey questions, and data will be coded across the dataset, rather than by individual questions, to ensure breadth and depth of patterns across the entirety of the data [76]. Study analysis will expand on study 1 results regarding workplace parcopresis by further outlining attitudes and experiences of defecation in the workplace. Data will be read and reread to gain familiarity. Initial coding of data will be undertaken, with similar codes grouped together. Coding will be conducted across the entire dataset rather than individual items, as recommended for qualitative online survey research [80]. In the next stage of analysis, data for each code will be collated and reviewed in depth, with a view to exploring patterns and themes in the data. Preliminary themes and the generated codes will be reviewed by other authors. In an iterative process, overarching themes and subthemes will be reviewed and refined to ensure coherence and distinctiveness, so that they provide a comprehensive representation of the data.

The quantitative (study 1) and qualitative data (study 2) will be analyzed separately. Due to the deidentified nature of the study, it is not possible to determine if a respondent participated in both studies or not. Thus, an integrated analysis of the 2 datasets (eg, outliers and typical instances from the quantitative findings) cannot be performed. Study 2 will build on the results of study 1 by providing in-depth insight into experiences around defecation at work to complement quantitative findings.

Power

While it is not possible to ascertain the power of qualitative research, and some coherently argue against such a quantitative approach to inductive thematic analysis [81], nonetheless, a number of factors can guide what constitutes a sufficient sample. Data saturation (ie, the point at which no new themes or ideas are identified) is a common method of determining a sufficient sample [82]. In research designs that use free-response qualitative surveys, a median sample size of 75 has previously been identified as required for reaching saturation [82]. Therefore, a minimum sample of 75 is sought.

Eligibility

The eligibility was the same as specified for study 1 above.

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Measures

Study 2 collates descriptive information pertaining to age and employment status. Respondents are asked a series of 12 questions, some with probes, each with a separate free-text box without a response character limit. Specific questions used in the survey are displayed in Figure 1.

Figure 1. Questions regarding attitudes, patterns, behaviors, and strategies used at a respondent's place of employment.

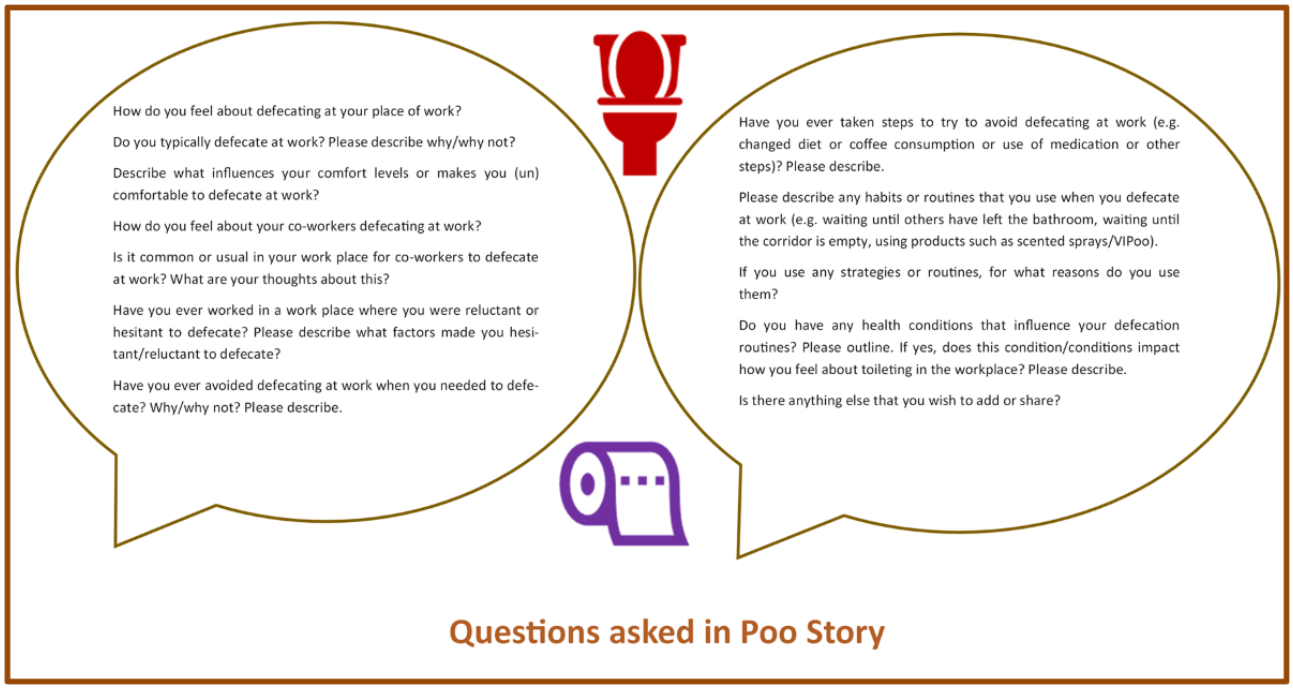

Results

Description of Sample 1

Study 1 commenced enrollment in January 2019 and finished enrollment in December 2023. The analyses to answer the study's hypotheses will commence after the publication of the protocol, expected in the first quarter of 2025. Thematic analyses are expected to occur in the second half of 2025. From 2113 persons who read the study information sheet, 241 were ineligible for the following reasons; withdrawing consent (n=5), not answering any questions (n=131) and not completing the assessment of bowel or psychosocial factors (n=105) leaving an analytical sample of 1872 persons and estimated 88.6% completion rate (Table 1). It should be noted that a further 95 persons did not rate their work or home stool type on the Bristol Stool Form and Frequency chart but had sufficient data for occupational and residential bowel movement frequency.

The sample was comprised predominantly of women (1413/1872, 75.5%), and the average (SD) age was 34.5 (SD 11.3) years. Approximately 29.5% (552/1872) of respondents had a household income above the Australian median income. However, 3.5% (66/1872) of respondents' work was outside of Australia, and, in total, workers in 27 countries completed the study, most commonly from Australia and New Zealand (1788/1872, 95.5% of the sample).

The occupational characteristics of study 1 indicate that most respondents were engaged in full-time employment (962/1872, 51.4%), with work hours mostly between 31 and 45 hours per week (897/1872, 47.9%; Table 2). Employees had been in their current place of employment for an average 7.7 (SD 8.1) years. The majority of respondents were not engaged in shift work or working during the biological night (1264/1872,67.5%) with the remaining 32.5% (608/1872) engaged in some form of shift work. A total of 19.7% (369/1872) of respondents were classified as working during the biological night.

A graphical display of respondents at home and occupational bowel movements (Figure 2) indicates that type 3 (like a sausage but with cracks in its surface) and type 4 (like a sausage or snake, smooth and soft) bowel movements were the most common, irrespective of location.

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Table 1. Descriptive information of ITS POO TIME (Insight inTo Stress and POOping on work TIME) study 1.

Descriptive information	Completed study (N=1872)[a]
Age (years)[b], mean (SD), IQR	34.5 (11.3), 26-42
Gender, n (%)	
Women	1413 (75.5)
Men	449 (24.0)
Nonbinary and other gender identities	10 (0.5)
Household income (Aus $), n (%)	
0-50,000 (US $34,390)	428 (22.9)
50,000-100,000 (US $34,390-69,880)	631 (33.7)
100,000-150,000 (US $69,880-104,820)	413 (22.1)
> 150,000 (US $104,820)	400 (21.4)
Region where working, n (%)	
Australia and New Zealand	1787 (95.5)
Europe	40 (2.1)
North America	17 (0.9)
South America	12 (0.6)
Africa and Middle East	6 (0.3)

[a]Data presented as n (%) unless otherwise specified.

[b]Data presented as mean (SD) followed by IQR.

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Table 2. Employment characteristics of ITS POO TIME (Insight inTo Stress and POOping on work TIME) study 1.

Employment characteristics	Completed study (N=1754)[a]
Employment status, n (%)	
Full-time	962 (51.4)
Part-time	491 (26.2)
Self-employed	114 (6.1)
Casual	305 (16.3)
Work hours per week, n (%)	
0-15	243 (13)
16-30	488 (26.1)
31-45	897 (47.9)
46-60	207 (11.1)
>60	37 (2)
Years in current employment, mean (SD), IQR	7.7 (8.1), IQR 2-11
Number of employees at workplace, n (%)	
Sole (self-employed)	117 (6.3)
Small ≤10	363 (19.4)
Medium 11 to 50	555 (29.6)
Moderate 51 to 100	274 (14.6)
Large 101 to 1000	347 (18.5)
Very large ≥ 10,001	216 (11.5)
Work during the biological night, n (%)	
9 PM to 4 AM	199 (10.6)
4 AM to 7 AM	146 (7.8)
Commute time to employment (mins), n (%)	
≤15	833 (44.5)
16-30	553 (29.5)
31-60	374 (20.0)
>61	112 (6.0)

[a]Data presented as n (%).

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Figure 2. A histogram depicts the frequency of different types of stool selected by participants for the most recent home (panel A) and work (panel B) bowel movement. Participants selected the most appropriate response using a visual representation and description of the Bristol Stool Form Chart.

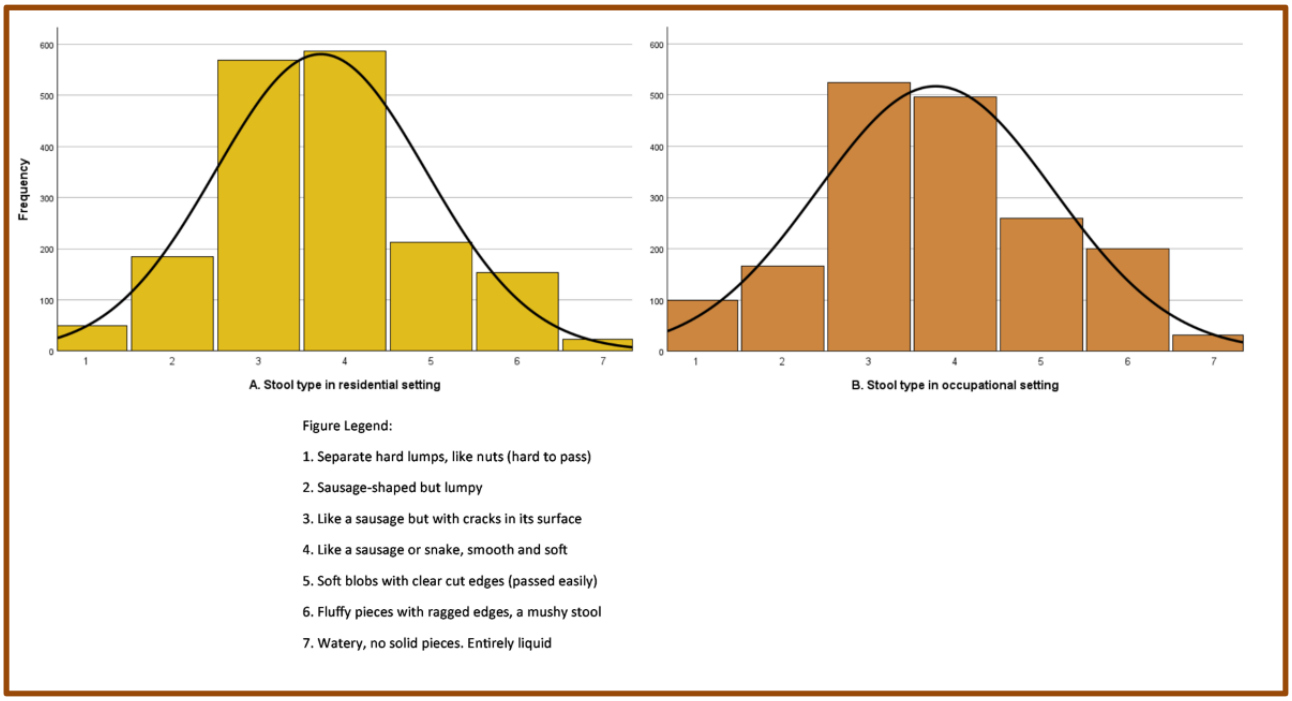

Description of Sample 2

Study 2 commenced enrollment in December 2019 and finished enrollment in September 2020. A total of 346 persons commenced the study. Of those who responded to study 2, 3 did not provide consent and were excluded, 8 persons did not respond to any of the open-ended questions, and 1 person provided part responses to some of the open-ended questions. Due to the qualitative nature of the analysis, any completed data will be retained for thematic analysis, resulting in a final analytical sample of 337 for study 2. The average age was 34 (SD 10.49) years. Of the analytical sample, 49.6% (167/337) worked full time, 34.7% (117/337) were engaged in part-time work, and 10.1% (34/337) undertook shift work, while 0.9% (3/337) worked both full-time and a part-time job, and 4.7% (16/337) did not specify their employment type.

Discussion

Principal Results

This will be the first research project known to the authors with the specific aim of assessing bowel movement anxieties and DGBI in shift and nonshift workers. The qualitative study aims to identify attitudes to bowel movements in occupational settings as well as patterns, behaviors, and strategies used to mitigate embarrassment, fear, or parcopresis. The research study is pivotal in providing further information regarding the prevalence of parcopresis and its relationship to occupational toileting avoidance as well as gastrointestinal health in a range of employees, including shift and nonshift workers.

Limitations

ITS POO TIME is limited in scope to persons with employment, meaning that the findings may not generalize readily to persons engaged in nonpaid internships, persons studying, or those with carer responsibilities. A related limitation is that we have restricted the research focus to bowel movements in occupational settings when parcopresis applies more generally to the use of any public restroom. It remains unknown and a limitation of ITS POO TIME whether parcopresistic fears of embarrassment are amplified around known persons such as work colleagues compared with strangers.

In the interests of brevity, the assessment battery is limited to subsets of more exhaustive questionnaires. Indeed, we have adopted brief measures and subscales for key constructs in our study pertaining to social anxiety, contamination fears, and parcopresis. With regards to the latter, although this construct is commonly comorbid with paruresis, our study has not assessed paruresis. More than 50% of persons with this condition report limiting their occupation because of paruresis [83]. This may have a significant impact on the research findings and although there are known gender differences in paruresis [60], it remains unclear whether gender differences hold in parcopresis. The study 1 sample is overly representative of female gender respondents which may lead to biases in planned comparisons across genders, while study 2 did not collate information on gender. A possible explanation for the overrepresentation of female gender respondents could relate to oversampling from specific occupations characterized by shift work (eg, nurses) and toileting restrictions (eg, school teachers). Another limitation is that there are potential selection biases and response biases and we were unable to reach the prespecified power calculation. This study did not reach the target sample as stipulated in the power calculation due to larger survey response attrition than anticipated combined with an institutional change in ethics and recruitment procedures, resulting in a need to close the study after 4 years. Consequently, the results will result in less than 90% power to detect a difference in DGBI between shift work groups.

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Conclusions

There is a known paucity of empirical data concerning parcopresis [60]. This project will offer novel insights into occupational, behavioral, and psychosocial factors associated with gastrointestinal health and identify if there are differences between residential and occupational toileting frequency and voiding behaviors. The results of the studies projected in this research protocol will have direct implications for industry, employers, and policy makers concerning functional gastrointestinal diseases, stress, and worker health.

Acknowledgments

No generative artificial intelligence was used in the production of this paper.

Data Availability

Data generated or analyzed during this study are subject to an embargo of 12 months from the publication date of the article. Once the embargo expires the data will be available upon reasonable request from the corresponding author on reasonable request, for noncommercial purposes, and without breaching participant confidentiality.

Authors' Contributions

PT and SC were responsible for conceptualization, project administration, and supervision. PT was responsible for data curation, formal analysis, visualization, and writing the original draft. PT, SC, GW, SM, AV, AM-W, and DT were responsible for the methodology and review and editing the protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Checklist for Reporting Results of Internet E-Surveys (CHERRIES).
[DOCX File , 21 KB - resprot_v14i1e58655_app1.docx]

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Abbreviations

CHERRIES: Checklist for Reporting Results of Internet E-Surveys
DGBI: disorders of gut-brain interactions

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FFQ: Food Frequency Questionnaire
ITS POO TIME: Insight inTo Stress and POOping on work TIME
K10: Kessler Psychological Distress Scale
Mini-SPIN: Mini-Social Phobia Inventory
R4DQ: Rome IV Diagnostic Questionnaire
SCI: Sleep Condition Indicator
UNE: University of New England

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Protocol

Home Monitoring in Interstitial Lung Disease: Protocol for a Real-World Observational Study

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Abstract

Background: Interstitial lung diseases (ILDs), a group of parenchymal lung disorders, present with varying degrees of inflammation and fibrosis, which lead to symptoms such as progressive breathlessness, impaired quality of life (QoL), and reduced life expectancy. Patients with ILD can experience a sudden worsening of their condition, known as an acute exacerbation, which is associated with inappropriate hospital admissions, concomitant National Health Service (NHS) costs, impaired QoL, and high mortality. The heterogeneity of ILDs, the unpredictability of acute exacerbations, and significant variation in disease progression and response to treatment present numerous management challenges. Standard care typically involves 3-6 monthly hospital outpatient visits to monitor disease and assess response to treatment. Home monitoring with remote review of spirometry, pulse oximetry, and patient-reported measures offers an alternative approach to in-person clinic review and laboratory-based physiological measurements. Clinical trials indicate home monitoring of patients with ILD is acceptable, and results correlate with laboratory-based pulmonary function tests (PFTs). The impact of implementing home monitoring for patients with ILD in a real-world setting is not well understood.

Objective: We aim to evaluate the safety, effectiveness, and acceptability of home monitoring with standard care in the management of patients with ILD.

Methods: This study has been registered as a quality improvement project at Guy's and St Thomas' NHS Foundation Trust (reference 13660) and Royal Devon University Healthcare NHS Foundation Trust (reference 24-1378). The project has been co-designed by the steering group, including clinicians, researchers, technology partners, a patient advocacy charity, and patients diagnosed with ILD. Patients who meet the inclusion criteria will be provided a handheld spirometer, pulse oximeter, and access to patientMpower, an electronic health app, on their smart devices and followed up for 12 months. All participants will be asked to complete at least once weekly home spirometry and pulse oximetry measurements and 3 monthly patient-reported measures, including outcome, engagement, and experience measures, using the patientMpower app. Results will be available to the clinicians in real time and used to monitor disease progression, symptoms, and QoL, and to assess treatment response.

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Results: This study was funded by NHS Digital in September 2021. Patient recruitment and data collection started in March 2022. By January 2024, 186 patients were enrolled. All patients will have home monitoring for at least 12 months. Results are expected to be published at the end of 2025.

Conclusions: We hypothesize home monitoring will be safe, effective and acceptable for patients with ILD and result in a 50% reduction in routine laboratory-based pulmonary function tests and in-person clinic consultations.

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KEYWORDS

remote monitoring; interstitial lung disease; spirometry; real-world; multicenter; observational study; home monitoring

Introduction

Interstitial Lung Disease

Interstitial lung diseases (ILDs), a group of parenchymal lung disorders, present with varying degrees of inflammation and fibrosis [1]. Idiopathic pulmonary fibrosis (IPF) is the archetypal, invariably progressive, fibrotic lung disease characterized by a decline in lung function, worsening breathlessness, impaired quality of life (QoL), and reduced life expectancy [2,3]. Other ILD subtypes may develop into a progressive fibrotic phenotype despite conventional therapies and are described as progressive pulmonary fibrosis (PPF) [4]. Shared mechanistic and clinical features have been identified between PPF and IPF such as worsening respiratory symptoms, decline in lung function, and premature mortality [5-12]. The heterogeneity of ILDs, the unpredictability of acute exacerbations, and significant variation in disease progression and response to treatment present numerous challenges in diagnosis and management.

The gold standard for ILD diagnosis requires a multidisciplinary team, preferably an interdisciplinary team, an approach where experts, including respiratory physicians, rheumatologists, thoracic radiologists, pathologists, and ILD specialist nurses, review clinical symptoms, exposure history, serology, and radiology [4]. Frequent monitoring, including assessment of symptoms, functional capacity, and physiological measurements, is recommended to enable the identification of disease progression, assess response to treatment, and inform ongoing management [4,13]. The frequency of follow-up is determined by the severity of disease progression, deterioration in QoL, and available resources [4,14]. In-person clinic review often places a significant physical burden on patients due to exertional breathlessness, oxygen dependency, infection risk, work commitments, and the need for carer support. In the United Kingdom, many patients travel long distances with inadequate transport provision to reach ILD specialist services. Consequences include delayed follow-up and increased costs to the patient, the National Health Service (NHS), and the environment [15].

Home Monitoring

Clinical trials have demonstrated that home spirometry is acceptable to patients with ILD [16-18]. Home spirometry correlates with clinical spirometry and is thought to be effective in detecting disease progression in patients with ILD [19,20]. The widespread increase in societal digitization, including smartphone utilization, has enabled the development of digital care pathways. The COVID-19 pandemic further accelerated the utilization of home monitoring devices, such as pulse oximeters, to support admission avoidance or early discharge from the hospital, shifting the emphasis to supporting the delivery of care closer to home [21,22]. Home monitoring of patients with ILD is not yet part of standard care, despite its perceived utility. This may be due to organizational factors, clinician workload, funding, patient factors including the ability to adopt digital technology, perceived risk to psychological well-being, and concerns regarding the correlation of home and laboratory-based pulmonary function tests (PFTs) [18,23,24].

Home monitoring, including spirometry, pulse oximetry, and patient-reported measures (PRMs), with remote review offers an alternative approach to in-person clinic review and laboratory-based PFTs for patients with ILD. It has the potential to support early identification of disease progression or acute exacerbation, assess response to treatment, enhance QoL, and alleviate health care burden [23]. Evidence of the long-term safety, effectiveness, and acceptability of home monitoring, including assessment of the impact on clinical outcomes, resource use, and patient satisfaction is needed to optimize this approach to patient care. We aim to assess if home monitoring is safe, effective, and acceptable for patients with ILD when offered in addition to standard care. We hypothesize home monitoring will lead to a 50% reduction in routine laboratory-based PFTs and in-person clinic consultations.

Methods

Study Design

This study has been co-designed using the ObsQual (Observational and Qualitative Study Protocol Reporting) checklist with a steering group of clinicians, researchers, technology partners, a patient advocacy charity, and patients with ILD [25]. All participants will be offered a portable handheld Spirobank Smart MIR spirometer and Nonin 3230 Bluetooth pulse oximeter. These will be linked to patientMpower, an electronic health app, downloaded to the patient's smart device. The recruiting clinician will counsel the patient, provide written information, and gain informed patient consent. Trained clinicians will provide patient training on the use of the home spirometer, pulse oximeter, and completion of PRMs, in person or virtually.

Patients will be asked to record spirometry and pulse oximetry measurements at least once weekly, and a series of PRMs at

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baseline and at months 3, 6, 9, and 12. These include the idiopathic pulmonary fibrosis patient-reported outcome measure (IPF-PROM), modified Medical Research Council dyspnea scale (mMRC), EQ-5D-5L, cough severity visual analog scales (VAS),Global Rating of Change Questionnaire (GRCQ), 9-item Patient Health Questionnaire (PHQ-9), 7-item General Anxiety Disorder (GAD-7), and experience and engagement measures, including Porter-Novelli, a home spirometry satisfaction questionnaire (SpiroQ), and the interstitial lung disease patient-reported experience measure (modified from the rheumatoid arthritis patient-reported experience measure) [26-34]. These PRMs have been used and validated in IPF and PPF populations, except for SpiroQ, which was co-designed with the steering group to support us in measuring patient satisfaction with home monitoring. EQ-5D-5L is a health utility measure that will enable health economic evaluation [35]. The timeline of measurements is demonstrated in Figure 1. All data recorded via the app will be visible to the patient and the clinicians in real-time via a secure browser-based portal.

Figure 1. Interstitial lung disease supported self-management schematic. PFTs included FVC, forced expiratory volume, diffusing capacity of the lungs for carbon monoxide, carbon monoxide transfer coefficient, and partial pressure of oxygen in the alveoli. PRMs include idiopathic pulmonary fibrosis patient-reported outcome measure, modified Medical Research Council dyspnea score, EQ-5D-5L, cough visual analogue scale, Global Rate of Change Questionnaire, SpiroQ (home spirometry satisfaction questionnaire), 9-item Patient Health Questionnaire, 7-item General Anxiety Disorder, Porter-Novelli, and modified patient-reported experience measure for patients with rheumatoid arthritis. 6MWT: 6-minute walk test; CPI: composite physiologic index; FVC: forced vital capacity; GAP: gender-age-physiology; HCP: health care professional; HRCT: high-resolution computed tomography; MDT: multidisciplinary team; PFT: pulmonary function test; PRM: patient-reported measure.

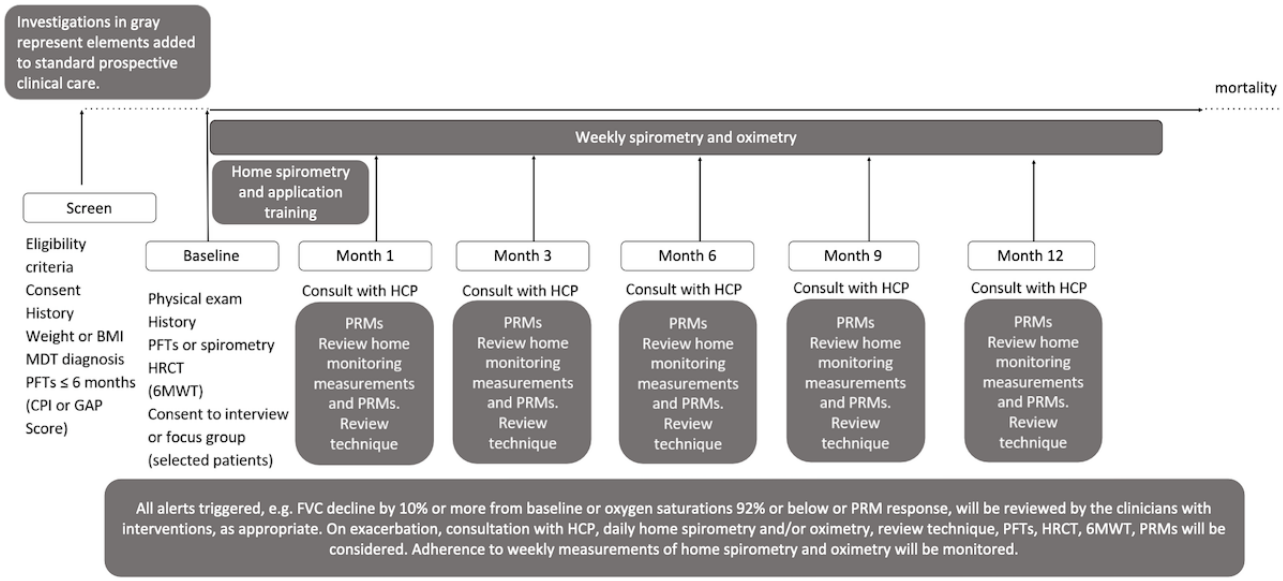

The registering clinician will be responsible for setting thresholds for a ≥10% decline in absolute forced vital capacity (FVC) and oxygen saturation <94%, according to the individual's baseline measurement [34]. If measurements fall below the threshold, alerts will be sent to the clinical team via the browser-based portal. The clinical team will review daily alerts during weekday working hours (Monday to Friday, 9 AM-5 PM). Each review will consider measurements, quality of the measurements, trends, changes from baseline, and contributing factors. Patients may require follow-up telephone or in-person clinic assessment to guide management decisions, for example, with repeat high-resolution computed tomography (HRCT), 6-minute walk test, long-term oxygen therapy assessment, and laboratory-based PFTs. Patients will continue to receive standard care as per their local clinical protocols.

Setting

Patients will be recruited from ILD specialist clinics at Guy's and St Thomas' NHS Foundation Trust (GSTT) and Royal Devon University Healthcare NHS Foundation Trust (RDU), from March 2022 to January 2023. All patients will have 12 months of home monitoring. Alerts will be managed by ILD specialist clinicians at each site. All clinical data will be collected on the browser-based portal and in an electronic case report form within secure Microsoft Office software only accessible to participating clinicians.

Participants

A total of 200 patients will be recruited from 2 ILD specialist services in the United Kingdom to achieve robust and comprehensive insights from a diverse patient population. Adhering to the inclusion and exclusion criteria, ILD specialist clinicians will recruit adults aged 18 years and older, with a tertiary center multidisciplinary diagnosis of ILD confirmed by HRCT and expectation of variability in progression. Patients will need to be able to perform spirometry and achieve a baseline FVC >45% predicted value within 6 months of recruitment. They will need access and the ability to use a smart device with internet and email. A budget will be available to provide smart devices and internet connectivity to patients who do not have access. Patients will need to be able to communicate with the team, understand written instructions, and complete PRMs. Patients will not be able to participate if they have a life expectancy of less than 6 months determined by clinical judgment, contraindications to spirometry as per Association for Respiratory Technology and Physiology guidelines, upper or lower respiratory tract infection within 4 weeks, acute

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exacerbation within 4 weeks, and active cancer diagnosis or life-limiting malignancy [36].

All patients will have 3 monthly virtual reviews with an ILD specialist clinician. Home monitoring measurements will be reviewed. Patients will be asked to report any upper or lower respiratory tract infections, acute exacerbations, accident and emergency presentations, or hospital admissions in the previous 3 months. Responses will be documented on the browser-based portal and electronic case report form. Daily alerts will be reviewed and addressed by the clinical team. Alert management will be documented on the browser-based portal and electronic case report form. Patients who miss weekly measurements for 3 weeks or choose to withdraw from home monitoring will be contacted, and the reason for stopping will be documented on the browser-based portal.

Variables

The variables to be measured and how they will be measured are outlined in Table 1.

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Table 1. Outcome measures.

	Measurement tools
Primary outcome measures	
Potential to detect disease progression, acute exacerbation, or response to treatments enabling prompt review of patients and access to appropriate therapies compared with standard care	Browser-based portal: • Number of patients with ≥5%-10% decline in FVC[a] • Time to ≥5%-10% decline in FVC • Number of patients diagnosed with progressive pulmonary fibrosis who become eligible for antifibrotic treatment • PRM[b] changes in score • Number of patients who start or change their prescription for oxygen therapy • Time to titrate or start oxygen therapy Electronic case report form: • Number of acute exacerbations and how they were managed • Interventions made (type and number)
Impact on the number of in-person clinic consultations with ILD[c] clinicians compared with standard care	Electronic case report form: (data comparison with 2019 to 2020): • Number of F2F[d] consultations • Number of telephone consultations • Number of video consultations
Impact on the number of laboratory-based pulmonary function tests compared with standard care	Electronic case report form (data comparison with 2019 to 2020): • Number of F2F consultations • Number of telephone consultations • Number of video consultations
Real-world patient acceptability of home monitoring program, including spirometry, oximetry, and PRMs	Browser-based portal: • Frequency of patient recording of key measurements (eg, spirometry, pulse oximetry, PRMs) • Duration (minutes) of regular patient engagement with the application • Patient engagement and experience measure ratings Electronic case report form: • Patients not eligible or declined participation and reason
Secondary outcome measures	
Impact on clinician time and experience compared to standard care	Browser-based portal: • Clinician time spent on the browser-based portal Electronic case report form: • Time taken to address each alert
Correlation of PRMs with patient symptoms	Electronic case report form: • Review symptoms and measurements every 3 months
Number of patient requests for technical support	Browser-based portal: • Number and length of unique interactions with the technical team
Impact on the number of ILD-related hospital admissions and duration of inpatient stay	Electronic case report form: • Review admissions every 3 months
Impact on patient access to ILD specialized services	Browser-based portal: • Completion of PRMs Electronic case report form (data comparison with defined standard care, eg, 3-4 per year, and 2019 to 2020): • Number of interactions with the ILD team
Correlation between home monitoring and patient satisfaction	Browser-based portal: • PRMs • Duration and frequency of patient app use

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	Measurement tools
Impact on travel costs to the patient, NHS[e], and environment	Electronic case report form: • Postcode and usual mode of travel at registration • Cost of mode of transport (car mileage 45p per mile) • Dependent on carer support

[a]FVC: forced vital capacity.

[b]PRM: patient-reported measure.

[c]ILD: interstitial lung disease.

[d]F2F: face-to-face.

[e]NHS: National Health Service.

Bias

We will reduce bias by recruiting patients from a diverse geographical patient population across 2 ILD specialist services in the south of England. Patients will be recruited from the ILD specialist clinics using a randomized approach. In addition, we will undertake sensitivity analyses to account for potential biases and uncertainties, ensuring the robustness of the findings.

Study Size

The sample size for this study is pragmatic, based on local populations within the clinical service and feasibility within financial constraints.

Quantitative Variables

Statistical analysis will include patient demographic data, including age, gender, ethnic background, smoking status, occupation and geographical location, measurements and PRM responses, number and type of alerts and interventions, number and mode of clinic consultations, and investigations.

Statistical Methods

A data management standard operating protocol will be co-developed considering the range and variation in data types. The steering group will meet fortnightly to check data for quality and consistency. Missing data will be identified, inconsistencies resolved, and data completed where possible. All end points will be summarized for descriptive statistics display. Values will be expressed as mean (SD) or median and range. Comparison of baseline home and hospital spirometry will use the Bland-Altman method. The rate of FVC change will be calculated using all available values using linear regression analysis without imputation of missing values. The rate of change in FVC will be presented as the percentage change relative to baseline values. For home-based spirometry, the baseline value will be calculated according to the mean of the values obtained at baseline and week 2. Survival analyses will be analyzed using Kaplan-Meier plots if we are defining disease progression as death or a >10% decline in home-based FVC at 12 months. A P value of <.05 will be considered statistically significant.

Ethical Considerations

The study design and protocol have been registered and peer-reviewed as a quality improvement project in the 2 participating centers (GSTT reference 13660 and RDU reference 24-1378), as per local Trust policies. All patients will provide informed consent to participate in home monitoring and be included in data analysis. All patients will be able to opt out at any time and return to standard care. No remuneration will be offered as home monitoring is being offered in addition to standard care. Data will be stored for the duration of the project and for 8 years after the end. All data will be handled in accordance with the Data Protection Act 2018. A data processing agreement is in place at both Trusts to support this data being shared under the Data Protection Act. All data will be anonymized and grouped for presentation and publication.

Results

This study was funded by NHS Digital in September 2021. Patient recruitment and data collection started in March 2022. By January 2024, we recruited 186 patients. All patients will have home monitoring for at least 12 months. Data analysis is ongoing, and results are expected to be published at the end of 2025. No significant safety concerns are anticipated with any measurements carried out as part of this study. In the case of adverse events, the established clinical safety procedures, investigation protocols, and reporting guidelines for each Trust will be adhered to, ensuring thorough and consistent management in accordance with established guidelines. The approach to care outlined in this protocol signifies a potentially pivotal moment in the transformation of health care delivery to patients with ILD.

Discussion

Previous Work

The incidence and prevalence of PPF and IPF are increasing [37,38]. A recent real-world study suggested that up to 20% of patients treated for PPF had advanced disease [37]. This is associated with productivity loss, increased health care costs, and reduced QoL [39]. Detecting and treating acute exacerbations early is likely to positively impact health care resource consumption, and direct or indirect costs, and enable informed choice relating to the place of death. Previous studies have demonstrated good adherence and feasibility of home monitoring in ILD, in clinical trial settings, and when observed in study populations [16,17,20,40-43]. A systematic review found that home monitoring presented an opportunity for early detection of disease progression or acute exacerbation [18]. The COVID-19 pandemic accelerated the utilization of home monitoring and supporting delivery of care closer to home [21,22].

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Principal Findings

We hypothesize that the findings of this study will demonstrate that home monitoring is safe, effective, and acceptable to patients with ILD, in a real-world setting. The results will provide the evidence required to inform the adoption of home monitoring for ILD clinical care and a digital care pathway. In addition to the primary outcomes, this study may inform a health economic evaluation and the impact of digital and health literacy on adherence. This study will also investigate differences in terms of patient characteristics and demographics in 2 diverse regions of the United Kingdom. We anticipate this research will provide valuable evidence to inform the development of guidelines relating to digital care pathways for patients with IPF and PPF, and decision-making by policy makers and integrated care boards.

Strengths and Limitations

The strengths of this study include the implementation of home monitoring in a real-world setting, across 2 NHS Trusts with diverse geographical and socioeconomic patient representation. Home monitoring will include spirometry, oximetry, and PRMs to assess changes in patient symptoms, disease, and response to treatment. We will undertake long-term home monitoring of a chronic lung condition compared to short-term acute virtual wards. The limitations of this study include real-world practice, which may lead to inconsistencies in data collection across the 2 NHS sites.

Future Directions

This study will inform the adoption of home monitoring in ILD, a long-term chronic condition, in the NHS. It will identify the knowledge gaps and barriers to implementing home monitoring in real-world practice. We anticipate that further research questions will arise, informing future work.

Dissemination

Our findings will be disseminated through communications of results to participants, people living with fibrotic lung disease, and their stakeholders, including caregivers, health care professionals, and the scientific community. Specific activities include dissemination through publication, including at national and international respiratory conferences and open-access peer-reviewed publication of findings. Further, we will communicate our findings through the internet and social networks associated with our patient charity and technology partners.

Conclusion

Despite limitations, home monitoring offers an opportunity to deliver personalized, home-centered care. Multimodal care delivery is required to meet the needs of this patient population, and digital care may lead to improved engagement with health care, adherence to treatment, and improved QoL.

Acknowledgments

We would like to thank and acknowledge the contributions of the late Rod Webb, a member of the steering group, and members of the wider patient community whose expertise and insight, through their lived experience, helped shape the design and delivery of this protocol.

Data Availability

All data generated or analyzed during this study will be included in the published article (and its supplementary information files), where possible.

Authors' Contributions

MN, MG, and AW contributed to the conceptualization of the study and completed funding acquisition. MN, JD, SL, and JM performed an investigation. WA represented the patient advocacy charity. ES handled the project administration. MG, AW, and AMR managed supervision. MN and RB wrote the original draft. All authors performed the methodology and development of the protocol. All authors participated in editing, reviewing, and approval of the final version of the manuscript.

Conflicts of Interest

RB is an employee of patientMpower Ltd. CE is a shareholder and advisor of patientMpower Ltd.

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Abbreviations

FVC: forced vital capacity
GSTT: Guy's and St Thomas' NHS Foundation Trust
ILD: interstitial lung disease
IPF: idiopathic pulmonary fibrosis
NHS: National Health Service
ObsQual: Observational and Qualitative Study Protocol Reporting

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PFT: pulmonary function test
PPF: progressive pulmonary fibrosis
PRM: patient-reported measure
QoL: quality of life
RDU: Royal Devon University

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Protocol

Assessing Community and Social Media Influence to Increase Influenza Vaccine Uptake among Youth in Soweto, South Africa (The Bambisana Study): Protocol for a Mixed Methods Pretest-Posttest Intervention Study

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Abstract

Background: Seasonal influenza has an estimated global reach of 3-5 million infections, with 290,000-650,000 influenza-related deaths yearly. Despite its efficacy in reducing morbidity and mortality, influenza vaccination rates remain low globally and in South Africa. Youth between the ages of 18 and 34 years are not prioritized for influenza vaccines although influenza surveillance in South Africa shows that individuals aged 19-44 years present the highest asymptomatic episodes and the lowest medically attended illness. This creates an opportunity to investigate if and how vaccine demand can be created in the absence of clear imperatives to vaccinate. The study tests the effectiveness of tailored, context-specific education, and community engagement, including community and social media to increase influenza vaccination uptake. Tailored, context-specific education, community engagement, reliable vaccine supply, and free, localized access are all critical for improving perceptions of, increasing confidence in, and motivating the uptake of vaccination.

Objective: This study will explore strategies to increase influenza vaccine uptake amongst economically marginalized youth aged 18-34 years in Soweto (South-Western Townships), South Africa, where influenza vaccines are not universally accessible through the public health system for this age group.

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Methods: The Bambisana Study uses an innovative approach, including community influencers and social media to increase the uptake of influenza vaccines through designing and testing an integrated communications strategy targeted at economically marginalized youth in Soweto, South Africa. The study uses a mixed methods pretest-posttest intervention design to test the effects of the interventions. The intervention will consist of the following components: (1) social media campaign, (2) microinfluencers on and offline, and (3) nonsocial media focused, offline microinfluencer-led engagement within communities. Quantitative data will be collected using a randomized household sample pre- and posttests, and clinic surveys with vaccinees and clinic attendees who declined vaccination. Focus group discussions (FGDs) will be conducted pre- and post intervention with participants aged ≥18 years, and 20 key informant interviews (KIIs) will be conducted with key influencers including religious leaders, traditional healers, and youth leaders. FGDs and KIIs will be audio-recorded and transcribed into English for analysis using framework thematic analysis, and quantitative data analyses will be conducted using SAS Enterprise (Guide 7.15; SAS Institute).

Results: This study was funded in December 2022, with recruitment having started in May 2023. As of May 2024, all data collection is complete, with data analyses and preparation of peer-reviewed publications in progress. The first results are expected to be submitted for publication in November 2024.

Conclusions: Enhancing perceptions of, bolstering confidence in, and fostering uptake of vaccination relies heavily on the efficacy of yearly influenza vaccination initiatives, personalized education tailored to specific contexts, active community involvement, consistent vaccine availability, and easily accessible, cost-free distribution channels at the local level.

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KEYWORDS

influenza; vaccines; vaccine confidence; youth; South Africa; social media

Introduction

Globally, seasonal influenza causes an estimated 3-5 million infections, and 290,000-650,000 deaths annually [1,2]. Estimates for the influenza burden of disease are limited in Africa; however, hospitalization and mortality are higher in low- and middle-income countries (LMICs) than in high-income countries [3,4]. In South Africa, an estimated 6,000-11,000 people die from influenza every year, with approximately half of these deaths in older individuals, and people living with HIV [5]. Seasonal outbreaks of influenza pose challenges to the health care system, leading to increased hospitalizations, outpatient visits, and strain on health care resources [6]. Vulnerable populations, including the older individuals, young children, pregnant women, and individuals with underlying medical conditions are at the highest risk of severe infection [7].

While nonpharmaceutical interventions can play a role in decreasing influenza infections, vaccination is deemed pragmatic and endorsed by the World Health Organization (WHO) as the recommended method for preventing seasonal influenza [1]. Overall, vaccine efficacy to prevent influenza infection ranges from 40% to 60%, with higher vaccine efficacy (82%) in reducing severe illness and hospitalization [8,9]. Therefore, the influenza vaccine is especially recommended for those who have chronic illnesses, those who are pregnant, and older individuals [10-12]. Influenza vaccination campaigns typically prioritize these groups during the influenza vaccination season [7,13]. However, an investigation into the seasonal influenza burden in urban and rural areas in South Africa showed that children younger than 12 years and those aged 19 and 44 years have an elevated risk of acquiring seasonal influenza [14]. Whilst severe disease is less likely, vaccinating younger adults has the added indirect benefit of providing herd immunity to the family and communities [15,16]. Furthermore, vaccination offers potential economic benefits related to the out-of-pocket expenses incurred by patients to treat influenza-related symptoms. An estimated annual cost of US $111.3 million is incurred by the government, while out-of-pocket costs incurred by the patient were reported to be US $40.7 million [17]. Individuals are at risk of financial loss due to absence from work and missed opportunities for those who are self-employed [18]. Despite recommendations, seasonal influenza vaccine uptake in the most vulnerable groups is low in LMICs, including South Africa [19]. Accessibility, lack of knowledge, and risk perception have been cited as the most significant barriers to vaccination in South Africa [20].

Despite the demonstrated effectiveness of vaccines in significantly reducing morbidity and mortality of affected individuals, youth are less proactive in health care–seeking behaviors due to low-risk perception and are not necessarily encouraged to vaccinate for influenza and other infectious diseases [9,21-23]. For COVID-19, youth were not initially prioritized for vaccination rollout, yet they might have been in contact with vulnerable populations [24,25]. In addition, evidence suggests that low vaccination rates are in part due to low health care–seeking behaviors among youth. Health care–seeking behaviors are the actions involved in achieving and maintaining a healthy condition [26,27]. Various factors, both individual and related to health care providers, can influence young people's health care–seeking behaviors [28].

Targeted health promotion interventions can increase health care–seeking behaviors and uptake of vaccination [29]. Influenza surveillance shows that individuals aged 19-44 years present the highest asymptomatic episodes and the lowest medically attended illness [14,30]. Studies undertaken in sub-Saharan Africa have shown that leveraging community involvement in immunization programs positively contributes to vaccine

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confidence and uptake [31,32]. In the case of HIV, for example, awareness campaigns to lower the burden of HIV and AIDS epidemics in Southern African countries have proven vital in reducing the rise of the disease [33]. The use of television series to promote positive sexual health and prevent HIV effectively engaged the youth by challenging old models of education [34]. The use of social media campaigns has also been increasingly used to promote behavior change [35,36] while sparking debate, especially when considering the abundance of false and misinformation [37]. It is vital to consider the significance of social media to improve vaccine uptake in LMICs.

Promoting health care through various platforms and to youth in LMICs may improve vaccination uptake. Therefore, as part of the Bambisana Project, which includes a diverse and multidisciplinary team comprising social and behavioral scientists, biostatisticians, population health surveillance specialists, health communications researchers, community influence and engagement practitioners, and marketing and communication strategists, we aim to:

1. Evaluate the impact of influencers online, offline, and in collaboration, on influenza vaccine uptake, with a specific focus on young people, and assess the additional value added by social media engagement.
2. Design and implement an integrated communications strategy centered around community influencers and social media to increase the uptake of influenza vaccines, particularly among younger populations who are likely unemployed, partially or informally employed, and living in Soweto (South-Western Townships), South Africa.
3. Explore motivations and barriers to health priorities, and to influenza vaccination, through the use of microinfluencers both online and offline in Soweto, South Africa.

The outcomes of the project will include increased influenza vaccination rates at the local health care clinics linked to campaign interventions, alongside an improved attitude toward the importance of vaccination in the target audience—this will be assessed using the Vaccine Confidence Index scale [38] and measured against the most recent Vaccine Confidence Index data from South Africa [39]. In addition, the project will provide important health systems-strengthening recommendations, which could potentially be implemented within the current infrastructure.

Methods

Research Design

The primary research aim uses a prospective mixed methods study design, including qualitative and quantitative data collection, to assess the effects of community and social media interventions to increase influenza vaccine uptake among youth in Soweto, South Africa. During the intervention phase, surveys will be conducted among potential participants attending study clinics who accepted or declined influenza vaccination.

Study Setting

The study will be conducted in Soweto, which is a congregation of 29 townships within the Johannesburg Metropolis in South Africa [40]. Soweto is one of the poorest areas of Johannesburg with high rates of youth unemployment which is at 46.3% among the 15- to 34-year age group [41].

Sampling

The Bambisana Project leverages the Soweto Health and Demographic Surveillance System, led by Wits Vaccines and Infectious Diseases Analytics Research Unit since 2017 and part of the Child Health and Mortality Prevention Surveillance Programme. The Soweto Health and Demographic Surveillance System has been providing access to longitudinal health and demographic data for specific enumerated areas of Soweto and the South of Johannesburg, since 2017 [42]. The study population includes young adults aged 18-34 years from four Health Demographic Surveillance System (HDSS) economically marginalized and geographically distinct Soweto communities namely Phiri, Senaoane, and Mapetla, Mofolo and Meadowlands, Thulani, and neighboring Thembelihle. Adults (18 y and older), living in these clusters or accessing clinic services in the following five study clinics: Senaoane Clinic, Mofolo Community Health Centre, Meadowlands Zone 2 Clinic, Siphumlile Clinic, and Thembelihle Clinic are deemed eligible for the study. Table 1 below shows the population of HDSS communities that will comprise our study clusters while Figure 1 presents the study design.

Table 1. Health and Demographic Surveillance System (HDSS) cluster summary data.

Cluster number	Communities	Total population	Youth 18-34 years	Number of households with youth	Total number of households
Cluster 1	Mofolo and Meadowlands	20,986	5824	3478	5912
Cluster 2	Phiri, Senaoane and Mapetla	23,805	6801	4037	6626
Cluster 3	Thulani	23,711	6848	4072	6262
Cluster 4	Thembelihle	19,449	5648	3831	6586

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Figure 1. Project timeline: data points and study design. Flu: influenza; FGD: focus group discussion.

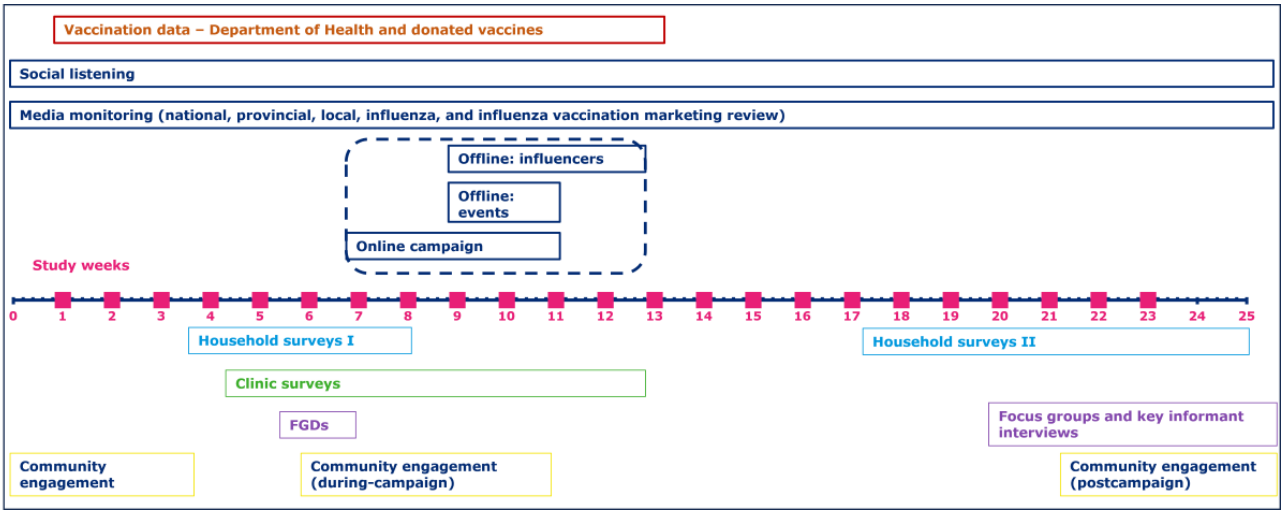

Community Engagement

The Bambisana (an isiZulu word, which means to work together) study leverages active, long-standing, dynamic community-level relationships and partnerships in accessing community insights at the household and local clinic level. The Wits Vaccines and Infectious Diseases Analytics social behavioral sciences team has longstanding relationships through Community Advisory Boards (CAB) and extensive community engagement in support of health research objectives throughout Soweto. CAB members are individuals residing in the HDSS-enumerated areas, who have been identified as active citizens in their communities. There are standing quarterly CAB meetings with the study team and members; however, these often increase in relation to shifting project activities. Consultations span project development, implementation, and community feedback sessions at the end of data collection, analysis, and interpretation.

Formative Qualitative Data Collection

The qualitative component includes 16 focus group discussions (FGDs) stratified by age group (18-24 y and 25-34 y), sex (male and female) and community (2 per cluster). These approaches aim to gather contextual data essential for understanding the factors influencing young people's decisions regarding influenza vaccination, including both motivators and barriers.

Study staff will purposively select and recruit young people for FGDs and key stakeholders from the community for key informant interviews (KIIs). FGD recruitment will be iterative until data saturation is achieved [43]. All study participants will be recruited through the CAB members who work with HDSS communities. Trained and experienced qualitative researchers fluent in local languages spoken in Soweto and Thembelihle (including isiZulu and Sesotho) will conduct the qualitative research using the participants' language of choice. The FGDs (16 FGDs; 8-12 participants per FGD) and KIIs (20; 10 male and 10 female participants) will be audio-recorded after written informed consent is obtained.

Intervention

The intervention will be delivered through a public health messaging campaign in targeted clusters or "subplaces" in Soweto, leveraging microinfluencers to provide information and motivate positive attitudes toward vaccination without a mandate in currently unvaccinated populations. The aim of the campaign is to create a behavioral change action: to go to your local clinic to get vaccinated. This has the secondary aim of highlighting the extent to which such intervention might be possible on wider issues of public health in the future. Secondary to this is the desire to investigate the value-add of social media targeting wider forms of engagement, such as that which occurs in communities offline.

The campaign will be timed with points when the clinic is well-supplied and prepared for such a public drive. The project will mitigate the risk of potential vaccine shortages by making vaccine donations to partner clinics. The study will center around the 2023 national influenza vaccination drive. Vaccines are generally provided in a very short and sporadic supply to the local community clinics, so supplying vaccines is also a part of the objective to make a community-level impact as part of the project.

The implementation of the intervention will be guided by information obtained after conducting community engagement discussions, which would be used to design the messaging and communication strategy. Surveys will be administered before, during, and following the communication interventions to establish baseline, midline, and end-line measures for evaluating the intervention's impact. This will help assess the effectiveness of four distinct approaches aimed at boosting influenza vaccine uptake among youth across clinics in four diverse HDSS clusters.

1. Standard of care: Vaccine made available with standard government promotional activity without support from the project (ie, based on standard government drive).
2. Social media: Social media campaign pushed to the target audience to highlight availability and drive to get vaccinated.
3. Microinfluencers on and offline: The social media campaign will be amplified through a coordinated effort by microinfluencers in their online and offline networks.
4. Offline microinfluencers: Nonsocial media focused; offline microinfluencer-led engagement within communities.

The intervention components are detailed below:

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1. Social media campaign to highlight availability and drive to get vaccinated pushed to the target audience (18-34 y) in 4 distinct geographic areas. Using Meta platforms Facebook and Instagram, along with other relevant social media channels identified through community engagement and marketing insights, we will disseminate information through static images, carousel posts, and video posts to promote the availability of, education around, and motivation to get vaccinated. Paid advertising on Meta will target people aged 18-34 years in two of the four distinct geographic study clusters.

2. Microinfluencers on and offline: the social media campaign will be amplified through a coordinated effort by microinfluencers in their online and offline networks. We will use community influencers—people with traditional influence such as community leaders, religious leaders, elders, and key business leaders—to amplify our social media campaign. They will engage their online and offline networks in coordination with our social media campaign to promote vaccine availability and encourage vaccination.

3. Nonsocial media offline microinfluencers: nonsocial media focused; offline microinfluence led engagement within communities. In these communities, our community influencers will focus only on offline engagement and will be specifically instructed to not do anything on social media. Using interpersonal conversations, and small-scale community events to share the importance of vaccines, they will encourage people to get vaccinated.

Quantitative Data Collection

Quantitative data collection will include five survey data points as outlined below.

All surveys will be developed using the REDCap (Research Electronic Data Capture; Vanderbilt University) software, a computer-assisted survey platform with built-in data encryption [44]. All surveys will be completed using dedicated study tablets, which means participants will not be required to use their internet data. In addition, we will use a data-free survey completion option. The survey links will also be sent to participants who wish to complete the surveys on their own devices. There will be no data costs for participants for completing the assessments. Participants will be reimbursed ZAR 50 (US $3) in airtime toward their time.

Household surveys include 2-time points of data collection, a pre- and posttest design, as described below.

Sampling

Households were chosen through a simple random sampling method, and eligible participants were enrolled as follows: a minimum of 800 adult men and women aged 18 years and older, with 400 designated for the pretest and 400 for the posttest. At least 100 households with index participants aged 18-34 years will be approached per community. Nonindex participants include other adults in the households who are aged 18-34, 35-49, and 50 years and older who will also be invited to complete surveys.

Pre- and Posttest Surveys

Using a random sample of households having youth participants (18-34 y) generated from the HDSS database, adults will be approached in their households to complete a 15-minute online pretest assessment survey (Multimedia Appendix 1) to measure: sociodemographics (age, gender, food security, and potential loss of income), knowledge of influenza vaccines and benefits, health beliefs, and sources of health information (social media, television, radio, friends, and family), and vaccine confidence [45]. The same households will be invited to participate in the posttest household survey (Multimedia Appendix 2). The posttest household survey will be conducted after the study campaign intervention.

Clinic survey data collection with vaccinees (Multimedia Appendix 3) and those who declined vaccination (Multimedia Appendix 4) are described below.

All adults (older than 18 years) who received an influenza vaccination will be approached; as such, numbers may vary as this depends on who elects to vaccinate. However, a total of at least 400 (n=100 per community) youth (aged 18-34 y) participants who go to the intervention clinics will be purposively approached to complete a postvaccination assessment. The study team will work closely with health care workers at public health clinics in the study communities. Health care workers will refer patients after having received the influenza vaccine, on-site at the clinics. These participants will be invited to complete a brief survey using the same measures as specified for the pretest survey. The data will be covered as part of the project expenses. There will be no data costs for participants to complete the assessments. Participants will be reimbursed ZAR 50 (US $3) in airtime toward their time.

Additional measures will assess motivations for influenza vaccines, where participants heard about this or other drives for the influenza vaccination, if participants had seen any online messaging driving them to get the influenza vaccine or been exposed to specific community engagement activities, and whether it had influenced their decision to vaccinate, and online impressions, for example, video views rates (dependent on final campaign strategy and media mix) and their impact on vaccinations in that region. The uptake of influenza vaccines will be tracked in the 4 clusters across the study period.

Clinic attendees who decline vaccination will also be approached to complete surveys. These participants will be aged 18 years and older. Health care workers will refer patients who were offered vaccination as part of their clinic attendance but who declined vaccination. Those participants who agree to participate will be invited to complete a brief survey to understand the reasons for declining vaccination. The survey measures will include: if and where participants heard about this drive for the influenza vaccination, if participants had seen any online messaging driving them to get the influenza vaccine or been exposed to specific community engagement activities, and whether it had influenced their decision to vaccinate.

As with all the surveys, the data costs will be covered as part of the project expenses. There will be no data costs to

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participants for completing the assessments. Participants will be reimbursed ZAR 50 (US $3) airtime toward their time.

Qualitative Evaluation

Additional FGDs (Multimedia Appendix 5), including 10-12 participants per FGD, will be conducted: 8 midway through the intervention (during vaccination season) and 8 post intervention. These FGDs will be mixed gender and will be stratified by age group (18-24, 25-34 y), and community (2 per cluster). Key informant interviews (KIIs; n=20; Multimedia Appendix 6) with key influencers including, religious leaders, traditional healers, and youth leaders, as well as other influencers that would be identified through community engagement and communications activities.

Data Analysis

Qualitative Data Preparation and Analysis Plan

FGDs and KII recordings will be transcribed verbatim and translated into English for analysis. Transcripts will be analyzed using a framework analysis approach. Framework thematic analysis provides a highly systematic method of categorizing and organizing data according to key themes, concepts, and emergent categories in grids or matrices [46]. Coding will follow a combined approach, ie, both deductive based on our hypothesized themes and inductive (data-driven) to allow for emerging themes. Priori coding based on the interview guide questions will be used to generate an initial coding framework [47]. After developing the initial coding framework, 2 researchers will read through 2 transcripts independently and code them line by line, to identify patterns and themes in the data [47]. This will allow us to further refine the domains and categorize the codes into themes and subthemes. Codes will then be captured using Dedoose, a qualitative data analysis software, and each transcript will be coded in Dedoose by at least 2 researchers and assessed for consistency in the coding of the first 5 transcripts [48]. The research team will convene to review the initial codes and apply general categories that will make up the analytic framework. Any coding disagreements will be discussed until an agreement is reached. This will allow for the finalization of the codebook, which will then be applied to the remaining transcripts. Rigor will be ensured through peer debriefing, triangulation with quantitative data, and member-check presentations with key stakeholders [49].

Statistical Analysis Plan

We will use descriptive statistics to describe study variables including knowledge of influenza vaccines, experiences with influenza vaccines, stigma, and vaccine confidence. Reliability assessments using the Cronbach alpha test will be evaluated for scale measures. Scales with poor reliability scores will be calibrated using factor analysis. Data will be analyzed overall and stratified by community. Frequencies will be determined for categorical measures whereas means (SD) and medians (IQR) will be determined for continuous measures. Pairwise comparisons of categorical measures between communities will be evaluated by the chi-square or Fisher exact test as appropriate. Similarly, pairwise continuous measures will be analyzed by the 2-sample *t* test, if satisfying normality distribution conditions or the Wilcoxon Mann-Whitney test, if nonnormally distributed. Normality will be assessed by the Shapiro-Wilks method. Drivers of knowledge, stigma, and experiences of influenza vaccines will be determined by logistic regression for binary outcomes and linear regression for continuous outcomes. Multivariable analysis will be carried out to adjust for potential confounders. Model fit statistics will be assessed on all multivariable regression models to ensure the validity of the findings. Data analyses will be conducted using SAS Enterprise (Guide 7.15; SAS Institute) [50].

Bias Correction

While the study is designed to focus on four relatively distinct geographic areas, due to the nature of social media and health care–seeking behaviors in the broader community of Soweto, it is possible that members from the intervention communities may interact with those not receiving the intervention. While potential interaction cannot be prevented entirely, research questions for all participants will include questions about exposure to intervention components and other potentially similar national or localized campaigns. In addition, a phased delivery of the interventions to ensure the offline intervention is not biased by the online intervention should help mitigate this.

It is also possible that those exposed to the interventions may seek to be vaccinated in clinics that are not included in the study's geographically defined target areas. An effort will be made to collaborate with the Department of Health to broadly understand influenza vaccinations during the campaign season, in broader Soweto and areas where residents typically seek health care. Vaccine and vaccination sentiments broadly in Soweto and South Africa will also be tracked during the course of the project for context and monitoring of potential risk.

Ethical Considerations

All research procedures were approved by the University of the Witwatersrand Human Research Ethics Committee (Medical; M230254) and the local Department of Health. Participants will be reimbursed ZAR 50 (US $3) airtime for survey completion and ZAR 150 (US $8) for the FGDs and the KIIs. This study will be conducted in accordance with the World Medical Association Declaration of Helsinki's ethical principles for research involving human subjects and will align with the guidelines of the Protection of Personal Information Act (POPIA) 4 of 2013. A copy of the information leaflet detailing the nature and processes involved in the study will be given to the participants. Written informed consent will be obtained from participants before participation, and audio recording of KIIs and FGDs. All information about participants will be confidential and protected, and data dissemination will not include any identifiable information.

Results

As of May 2024, all data collection is complete, with data analyses and preparation of peer-reviewed publications in progress. The results will encompass qualitative analysis of factors influencing influenza vaccine uptake, a pretest-posttest evaluation of interventions, and campaign intervention methodology along with a longitudinal household investigation

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of changes in perceptions and attitudes toward influenza vaccination. The first results are expected to be submitted for publication by November 2024.

Discussion

Principal Findings

This study will provide critical insights for improving the effectiveness of influenza vaccination campaigns in South Africa. Leveraging micro- and nanoinfluencers on social media, and collaboration with community influencers has been proven to reach and motivate target groups with low vaccine uptake [51]. This study will provide valuable insights into the use of microinfluencers online and offline to reach economically marginalized communities to make positive health decisions where the personal risk perception from not doing so is low in the absence of any mandated reasons to do so. It will also provide an assessment of the differing impact of campaign approaches and the value of the amplification of voices into online social networks for health outcomes.

Dissemination Plan

Knowledge dissemination will include clear research into action goals through community-based gatherings and activations, radio, and social media–driven activities to key audiences. A strongly connected dissemination platform will be developed by starting with key partners attending an initial study planning meeting, including collaborators, scientists, health policy makers, and representatives from local groups and CAB to recruitment sites. A dedicated website will promote the study and health awareness. A results dissemination group comprising youth CABs and stakeholders will develop knowledge dissemination material for sharing with study participants, stakeholders, and the wider community. Results will be disseminated through press releases, community meetings, social media, and the website. This will be accompanied by scientific presentations to academia, fellow practitioners, and policy makers, publications in open-access peer-reviewed journals, and national and international meetings. Results dissemination meetings will be convened for all study communities and the CAB.

Conclusions

Enhancing perceptions of, bolstering confidence in, and fostering uptake of vaccination relies heavily on the efficacy of yearly influenza vaccination initiatives, personalized education tailored to specific contexts, active community involvement, consistent vaccine availability, and easily accessible, cost-free distribution channels at the local level.

Acknowledgments

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The content and findings reported/illustrated are the sole deduction, view, and responsibility of the authors and do not reflect the official position and sentiments of the Vaccine Confidence Fund and the SAMRC.

Data Availability

The datasets generated/analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

JD contributed to conceptualization, investigation, methodology, resources, supervision, validation, and writing—original draft. CH was involved in conceptualization, investigation, funding acquisition, methodology, project administration, resources, supervision, visualization, writing—original draft. GT, TM, MM, and KG handled investigation, project administration, writing—review & editing. SV performed investigation, validation, writing—review & editing. NM, SM, IG, and EG were involved in conceptualization, methodology, writing—review & editing. PA handled methodology, writing—review & editing. KO was responsible for investigation; writing—review & editing. HJL managed conceptualization, methodology, validation, writing—review & editing. ZD contributed to resources, supervision; writing—review & editing.

Conflicts of Interest

HJL has received research funding from GSK and Merck.

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Multimedia Appendix 1
Household pretest survey.
[PDF File (Adobe PDF File), 202 KB - resprot_v14i1e60481_app1.pdf]

Multimedia Appendix 2
Household posttest survey.
[PDF File (Adobe PDF File), 311 KB - resprot_v14i1e60481_app2.pdf]

Multimedia Appendix 3
Clinic (vaccinated) survey.
[PDF File (Adobe PDF File), 76 KB - resprot_v14i1e60481_app3.pdf]

Multimedia Appendix 4
Clinic (unvaccinated) survey.
[PDF File (Adobe PDF File), 203 KB - resprot_v14i1e60481_app4.pdf]

Multimedia Appendix 5
Semistructured interview guide for focus group discussions.
[DOCX File , 64 KB - resprot_v14i1e60481_app5.docx]

Multimedia Appendix 6
Semistructured interview guide for key informant interviews.
[DOCX File , 66 KB - resprot_v14i1e60481_app6.docx]

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Abbreviations

CAB: Community Advisory Board
FGD: focus group discussion
HDSS: Health and Demographic Surveillance System
KII: key informant interview
LMIC: low- and middle-income country
POPIA: Protection of Personal Information Act
REDCap: Research Electronic Data Capture
Soweto: South-Western Township
WHO: World Health Organization

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Protocol

Strengthening Immunization Data: Protocol for the Evaluation of an Electronic Immunization Register

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Abstract

Background: Electronic immunization registers (EIRs) can strengthen immunization systems and, if used effectively, can lead to greater efficiency and improvements in vaccination coverage. Several low- and middle-income countries introduced EIRs for COVID-19 vaccination and are now integrating them for routine immunization.

Objective: This study aims to describe the protocol used to evaluate the implementation of an EIR in the Lao People's Democratic Republic in 2022. In addition, it seeks to identify opportunities to improve implementation, scale-up, and sustainability in the country.

Methods: To evaluate the implementation of the EIR in the Lao People's Democratic Republic, we will (1) map the EIR workflow process, (2) examine EIR user and stakeholder perspectives, and (3) assess the EIR data quality. Data will be collected and analyzed through a mixed methods approach. This evaluation will involve a document review, observation of workflows in health facilities, health facility user surveys, key informant interviews with decision makers, and an assessment of immunization data quality. This protocol details the methods for each of these components. The evidence generated will be triangulated to identify the strengths and weaknesses of the early implementation phase of the EIR, facilitators of and barriers to the implementation, and whether the introduction of the EIR has improved immunization data processes and quality compared with paper-based processes.

Results: Data collection took place between April 2024 and August 2024. Data analysis is currently ongoing, with results expected to be shared with study stakeholders in October 2024.

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Conclusions: This early evaluation will contribute to developing a road map for the nationwide strengthening and sustainability of the EIR based on challenges and lessons learned, potentially streamlining further implementation efforts and enabling more effective use of the EIR. This paper presents a methodology for evaluating EIR implementation that can be replicated in other low- and middle-income countries implementing EIRs.

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KEYWORDS

electronic immunization register; evaluation; process evaluation; digital technology; vaccination coverage; health system strengthening; mixed methods; data quality

Introduction

Background

Vaccines are a highly effective public health intervention, with childhood vaccination programs estimated to have prevented as many as 154 million deaths over the past 50 years [1]. Despite significant improvements in coverage of routine immunization over the past 2 decades, there have been challenges in recent years, as evident from the coverage of the third dose of diphtheria-tetanus-pertussis (DTP) vaccine plateauing at approximately 86% [2]. Coverage of other childhood vaccines has increased over time, but many vaccines remain underused [3]. Widespread disruptions to routine immunization programs during the COVID-19 pandemic and consequent declines in coverage [4,5] meant an additional 5 million children missed receiving a single dose of DTP vaccine in 2021 [4]. Urgent recovery efforts are needed to prevent an estimated 49,000 excess deaths by 2030 [6,7].

Global immunization actors such as the World Health Organization (WHO), United Nations Children's Fund (UNICEF), and the World Bank have promoted the implementation of digital tools for health, which include electronic immunization registers (EIRs), to improve vaccine uptake and management of immunization programs and to strengthen health systems [8,9]. An EIR is a confidential, computerized, population-based routine system used to capture, store, access, and share individual-level data on vaccine doses administered (Multimedia Appendix 1) [10]. An EIR is a component of a comprehensive health information system that consolidates individualized immunization information for various purposes, such as vaccine coverage monitoring, safety monitoring, and supply management [11] (Table 1). EIRs have the potential to improve vaccination coverage by enhancing the monitoring of individuals' immunization status, automating the tracking and recalling of defaulters, identifying health care providers with lower performance, and providing decision support for immunization [12-14]. In addition, EIRs can reduce costs to the health system [15,16]. From a policy and governance perspective, EIRs allow countries to identify coverage gaps and inequities at the national, subnational, and local levels, facilitating evidence-based decision-making and developing targeted initiatives to address gaps [17]. The use of EIRs aligns with a key priority of the Immunization Agenda 2030 (IA2030), the strategy guiding improvements in immunization programs globally, to use high-quality data to track progress and inform decision-making at all levels of the health system [18]. Furthermore, when EIRs are linked with other data as part of the broader immunization information system, they can strengthen safety monitoring and be used to conduct vaccine effectiveness studies in almost real time [19-26].

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Table 1. Definitions of terms.

Term	Definitions	Characteristics
EIR[a]	It is a confidential, computerized, population-based routine system to capture, store, access, share, and consolidate individual-level data on each vaccination. Immunizations are recorded directly into an electronic system. Immunization actors at other levels of the health system (ie, district, province, and national) can directly access the data.	• At a minimum, a register typically includes an individual identification number or code, names, date of birth or age, sex or gender and information on the vaccine administered (vaccine type and brand and date of administration) and the vaccine administration itself (date and facility or health care provider). • Data are recorded and stored electronically (online or offline) rather than on paper[b]. • Ideally, registration occurs as close as possible, in time and place, to the vaccination act itself. • Individuals may be identified using a unique identifier (eg, a national identification number, biometrics, or a combination of personal information). • Data for each individual (improving population denominator data quality). • It is accessible at all levels of the health system[b]. • Data aggregation and visualization are automated, with aggregation by various factors (eg, age, sex, geographical region, and other factors for which data are captured) possible with relative ease[b]. • Facilities can conduct timely individualized follow-up for vaccination[b]. • It includes processes for data security and patient confidentiality[b]. • Linkage, interoperability, and integration with other immunization, health, and civil registry information systems are possible[b]. • It can allow individuals to access their vaccination history and generate a record of their vaccinations.
Paper-based immunization systems	These are paper-based individual-level records of vaccinations administered to a defined target population. Immunizations are typically recorded in a paper-based register held by the health facility where the vaccine was administered. A vaccination card or other home-based record or tickler files (a systematic way of organizing vaccination cards to enable follow-up of children due for vaccination) may also be used to record the immunization. Health workers use tally sheets to count and consolidate the number of vaccines administered over a given time (usually a month) and then report to the district, provincial, or other subnational level office. Subnational offices compile multiple reports and report up to the health system, until they reach the national office.	• Data are recorded manually, that is, typically with pen and paper. • Typically, individual-level data are accessible only by health facilities. • These systems might rely on updated information or data from child health records. • Data aggregation is manually completed by health workers recording the number of vaccines administered on a tally sheet, often for reporting purposes. Only limited information is captured, typically the number of specific types of vaccines administered by age group and gender. • Data visualization is limited; aggregated data are typically recorded in a monthly summary form after being counted manually from tally sheets. • Individualized follow-up (recall) may be challenging, and it requires staff to manually review handwritten registers, as the data are not easy to retrieve. • Data may be recorded in multiple registers over the years, and it is a manual, labor-intensive process that is prone to errors. There is also a risk of loss of data from being physically displaced or fading ink. • Linkage or interoperability with other data systems is not possible.
Immunization registry system	It encompasses the entirety of the ecosystem of processes, resources, regulations, technology, and infrastructure needed to support the use of an EIR to enable improved efficiency and improved vaccination coverage.	• It includes all health system structures necessary for an effective EIR, such as human resource capacity, IT and digital infrastructure, financial resources, governance and policy framework, and mechanisms for effective data use and evidence-based decision-making.
Immunization information system	It is a comprehensive health information system (encompassing multiple information sources) that consolidates individualized immunization information for various purposes, including, but not limited to, vaccine coverage monitoring, safety monitoring, supply management, and disease surveillance.	• Individual-level information on vaccination and vaccination events is available. • It encompasses all systems involved in capturing vaccine uptake, calculating vaccination coverage, monitoring adverse events, conducting public health surveillance of vaccine-preventable diseases, managing vaccine and related commodity supply and stock, and potentially tracking the behavioral and social drivers of vaccination. • Individual systems may be interoperable or linked to support functions, such as safety monitoring, stock management, disease surveillance, or outbreak response, and with civil registry systems, other health information systems, and other population-based data systems to enable detailed vaccine effectiveness and safety analyses in specific populations. • It may include a communication platform that allows for targeted communication with health care professionals and the public. • It links to other electronic technologies, such as decision support systems for health care providers (eg, automated alerts to physicians for vaccination catch-up).

[a]EIR: electronic immunization register.

[b]These are essential features of EIRs based on information extracted from multiple sources [11,27-32].

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There is a growing body of evidence that EIRs can strengthen immunization programs in low- and middle-income countries (LMICs) by enabling greater data use [33,34]. A 2015 EIR evaluation in a province of Vietnam found that full vaccination coverage of children aged <1 year improved from 75.4% to 81.7% following the province-wide introduction of the EIR along with an SMS text message reminder system and to 99.2% one year after the intervention [35]. In Pakistan, an EIR with decision support and SMS text message reminders, supplemented by health worker attendance logging and a web-based dashboard, increased polio vaccination coverage from 12% in May 2019 to 97% in December 2019 [36]. However, the attribution of improvements in coverage directly to EIRs is problematic, and several studies have failed to detect an effect or an impact [37-39]. Moreover, little is known about the level of investment needed for the establishment and ongoing maintenance of EIRs in relation to the benefits achieved.

The unprecedented scale and speed at which COVID-19 vaccination programs were rolled out prompted several LMICs to implement EIRs for the first time. While many of these systems were designed for COVID-19 vaccination and were frequently motivated by the need for vaccine certificates and monitoring coverage, the positive experiences have encouraged countries to invest in efforts to integrate and scale up EIRs into routine immunization programs [7,40]. Well-designed evaluations at critical time points are necessary to ensure robust implementation, assess the usefulness of the system in guiding policy and practice, monitor coverage, and help prioritize allocation of resources. Few EIR evaluations have been conducted to date [41], and there are limited assessment protocols that are context specific and co-designed with key stakeholders and technical experts. Moreover, while there are standard methodologies to evaluate public health surveillance systems [42], systematic frameworks or approaches to evaluate EIRs, particularly in LMICs, are lacking [43].

Immunization in the Lao People's Democratic Republic and Implementation of an EIR

The national immunization program of the Lao People's Democratic Republic (Lao PDR) provides funded vaccination for 12 vaccine-preventable diseases. The vaccines are as follows: Bacillus Calmette–Guérin vaccine; hepatitis B vaccine; oral poliovirus vaccine; inactivated poliovirus vaccine; the pentavalent vaccine containing diphtheria, pertussis, tetanus, hepatitis B, and *Haemophilus influenzae type B*; pneumococcal conjugate vaccine; measles-rubella vaccine; Japanese encephalitis vaccine; tetanus-diphtheria vaccine; seasonal influenza vaccine; and human papillomavirus vaccine (Multimedia Appendix 2).

Despite significant investment into immunization programs in the Lao PDR, the COVID-19 pandemic impacted routine vaccination coverage with significant declines in 2020 and 2021. The estimated coverage of DTP3 and the first dose of measles-containing vaccine in 2022 was 92% and 82%, respectively [44]. Challenges to the immunization program include identification of unvaccinated (zero-dose children) and partially vaccinated children, the need to reduce dropout rates between doses, improving vaccination timeliness, sustainable delivery of immunization services in hard-to-reach communities, timely recording and reporting of immunization data, challenges in attaining appropriate denominators, and the accuracy of coverage estimates [45].

Currently, the Lao PDR immunization information system uses a combination of paper-based and digital systems. Since 2015, the Lao PDR Ministry of Health (MoH) has used the District Health Information Software 2 (DHIS2), an open-source digital health information management system, to manage information on malaria, tuberculosis, HIV, and the immunization program. Vaccination coverage statistics were generated from this system using aggregated data collected from health facilities, limiting the ability to appropriately evaluate the immunization program's performance and identify where vaccination coverage is low. This limitation also affects the measurement of key indicators, such as dropout rates, which require individual-level data for accurate estimation.

During the COVID-19 pandemic, the Lao PDR the Maternal Child Health Centre (MCHC) of the MoH established a custom EIR comprising of an individualized immunization system using the DHIS2 Tracker software to capture individual COVID-19 vaccination data nationally. This system was designed to be used in tandem with DHIS2 as a health information management system [46]. On the basis of the lessons and experiences learnt from the development and implementation of the COVID-19 Vaccination Registry, a separate EIR for childhood immunization targeting children aged <5 years was developed. This EIR was piloted in November 2022 in a district hospital in the capital city and subsequently rolled out across 2 provinces between May 2023 and August 2023. As of January 2024, health workers in all 18 provinces had received training on the use of the EIR. Currently, the system only captures vaccination data for children aged ≤5 years. Through this transition phase, health facilities are required to use both the EIR and the traditional paper-based form for recording and reporting purposes at fixed and outreach immunization clinics.

Rationale and Aims

Early and ongoing evaluations provide valuable insights into the current strengths and challenges of the system, its implementation, and barriers to and facilitators of the successful transition from an aggregated paper-based system to a digital system. Information arising from evaluation can be used by decision makers to address challenges during the early stages of implementation of the EIR. The data can inform system-related updates and address human resource needs and requirements to make the system sustainable.

This study aimed to conduct an evaluation of the Lao PDR EIR for childhood immunization to identify opportunities for improving and strengthening its implementation, scale-up, and sustainability. The specific objectives were as follows:

1. To describe and map the components and workflow processes of the immunization registry system
2. To examine the perspectives of those involved in implementing and using the system, namely health system decision makers and health workers at health facilities, to determine the extent to which the system is fit for purpose

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3. To assess the quality of the data captured in the EIR
4. To examine the barriers to and enablers of implementation and long-term use of the system.

This pilot study was designed to provide recommendations to the Lao PDR MoH and inform EIR implementation and scale-up.

Methods

Conceptual Framework

This evaluation is underpinned by the theory of change approach, which theorizes that the implementation and use of an EIR can lead to improved immunization outcomes. A theory of change for supporting data-informed decision-making for immunization programs, arising from a realist review of interventions aimed at improving the use of immunization data, has been adopted for this evaluation [33]. This theory of change hypothesizes that effective implementation of an EIR will translate into improved data use, which, in turn, will drive demand for data quality and access, building a culture of data use to drive decision-making at all levels of the system. In the longer term, increased data use is expected to lead to improvements in vaccination coverage and reductions in the burden of vaccine-preventable disease.

However, this theory of change may be erroneously interpreted as a linear, organic process following the introduction of an EIR, while, in reality, the environment within which the EIR is implemented affects its success or failure. The IA2030 Data Action Theory of Change Framework partly reconciles this and identifies digital tools as 1 of the 5 building blocks needed to improve the availability and fit-for-purpose data, increasing data use in decision-making and resulting in improved program outcomes [47]. The other four blocks include (1) establishing a continuous cycle of assessment and quality improvement, (2) having clearly defined governance processes and policies for data collection and use, (3) empowering health workers to use data for decision-making, and (4) documenting ways to improve data and its use [47]. While more holistic, the IA2030 Data Action Theory of Change Framework depicts the EIR as one of several inputs rather than as a health system-strengthening intervention that is implemented within an evolving environment. The IA2030 Data Action Theory of Change Framework and the theory of change framework developed by Osterman et al [33] have both been adopted as underpinning conceptual frameworks in this evaluation.

In this study, we will examine the “immunization registry system,” which incorporates the EIR and the ecosystem surrounding it. The term “EIR” refers to the computer-based tool used to capture, store, access, and share individual-level data on vaccine doses administered [27]. The immunization registry system encompasses the entirety of the processes, resources, regulations, technology, and infrastructure needed to support the use of an EIR, enabling improved efficiency and improved vaccination coverage (Table 1). Mapping of the Lao PDR immunization registry system was first performed through a document review using the Pan American Health Organization criteria for EIR evaluation [43].

For primary data collection, we adapted a recently published framework for the evaluation of EIRs and electronic logistics management systems (Figure 1) [28]. This approach focuses on the design and function of the tool, its implementation, the contextual factors affecting implementation (ie, the ecosystem), and the impact and sustainability of the tool. The framework incorporates the EIR’s impact on immunization service delivery and its financial sustainability and viability as outcomes. However, it is important to note that achieving these outcomes may take many years, and while an EIR is a critical tool, much like a “vector,” implementation of an EIR is unlikely to realize these benefits without addressing other reasons for poor uptake of vaccination. As the Lao PDR EIR has only recently been implemented, our evaluation focuses on the uptake and use of the EIR, particularly its acceptance and use by decision makers and health workers.

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Figure 1. Framework for the evaluation of the Lao People's Democratic Republic electronic immunization register (adapted from report published by the Bocconi School of Management [28]).

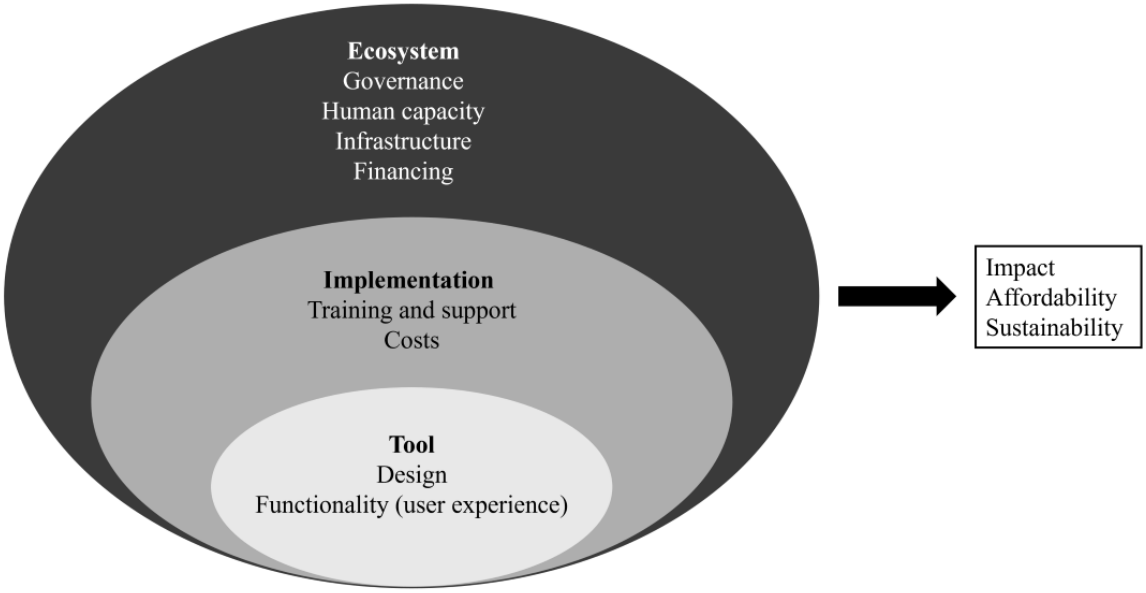

Study Design and Data Collection

Overview

We will use quantitative and qualitative research methods to (1) map the Lao PDR immunization registry system components and workflows, (2) examine the EIR stakeholder perspectives, and (3) assess EIR data quality. The evaluation methods and data collection tools were informed by a review of the key literature on the use and evaluation of EIRs, in addition to evaluation protocols shared by experts working in the field. This mixed methods approach will be sequential and iterative, whereby the outcomes of one component will inform subsequent elements of the study (Figure 2).

Figure 2. Outputs from each study component and contribution to the summary of findings from this process evaluation of the Lao People's Democratic Republic electronic immunization register (EIR).

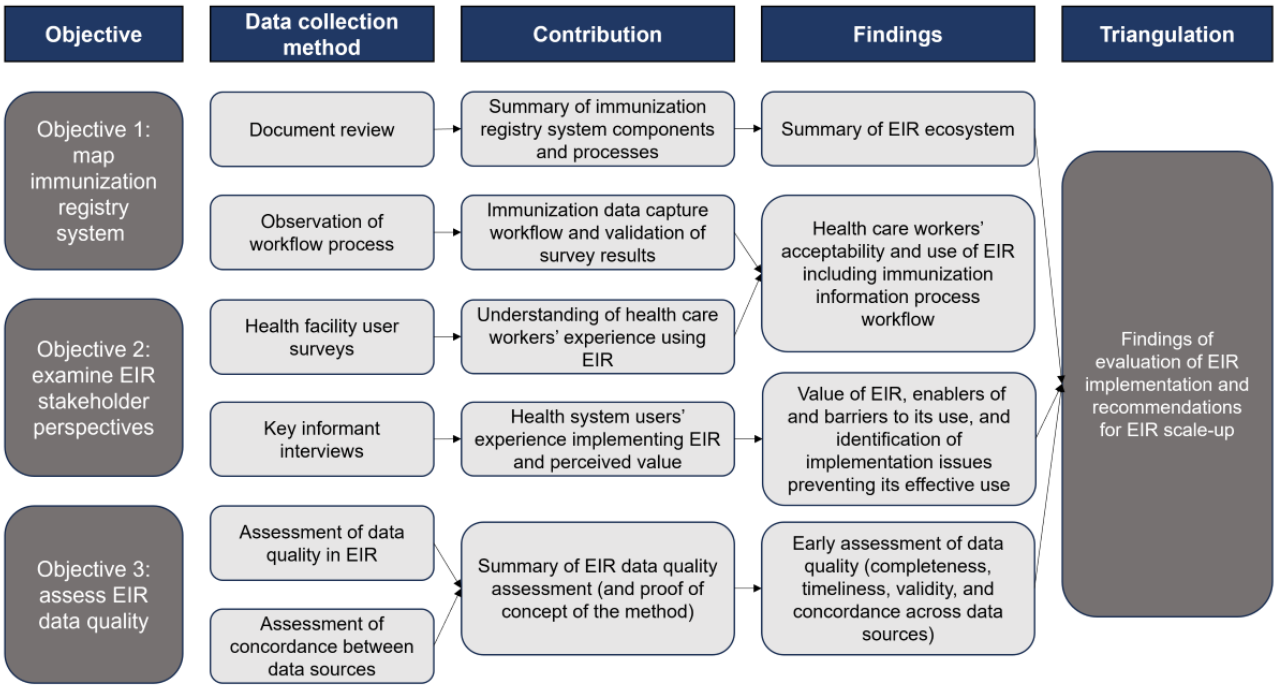

Data collection methods will involve (1) a document review, (2) observation of workflows in health facilities, (3) health facility user surveys, (4) key informant interviews with decision makers, and (5) an assessment of immunization data quality (Table 2).

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Table 2. Summary of data collection methods, target population, and analysis methods for this evaluation.

Activity	Target population	Sample strategy and size	Analysis
Document review	Documents pertaining to the performance and operation of the Lao PDR[a] EIR[b]	• N/A[c]	• Narrative synthesis based on the criteria by PAHO[d] for EIR evaluation [44]
Observation of the workflow process	Health facilities providing immunization services	• 4 purposively selected health facilities	• Narrative summary and validation of health facility surveys
Health facility surveys	Health facility immunization providers	• 24 randomly selected community health facilities and 2 purposively selected large hospitals (26 facilities in total)	• Descriptive statistics summarizing quantitative and qualitative data
Key informant interviews	Decision makers and implementing partners at the Lao PDR Ministry of Health and other partner agencies working in immunization and digital system teams at the national and subnational levels	• 12 to 14 purposively selected participants	• Thematic analysis
Data quality assessment	All health facilities using the EIR during the agreed period of analysis	• 4 purposively selected health facilities (concordance) • Cohort of children who were born in 2023 and have their records available in the EIR (selected data and immunization quality indicators)	• Metrics to quantify the concordance of data in the EIR compared to existing methods of data capture • Metrics to quantify the completeness, timeliness, and validity of the data in the EIR

[a]Lao PDR: Lao People's Democratic Republic.

[b]EIR: electronic immunization register.

[c]N/A: not applicable.

[d]PAHO: Pan American Health Organization.

Method 1: Document Review

We will search for peer-reviewed publications, gray literature, and internal government documents that pertain to the performance and operation of the Lao PDR EIR, the national immunization program, the health system, or the governance of health and immunization systems. Documents detailing policies and procedures (eg, organizational charts, immunization agenda goals or strategies, recent evaluations of immunization system, regulatory frameworks, and standard operating procedures), regulations, national immunization technical advisory group's recommendations, immunization schedules and indicators, technical reports and guidance documents, digital and paper-based tools, and educational resources will be considered for inclusion. We will extract data based on the criteria for EIR system evaluation developed by the Pan American Health Organization [30], with domains, including system scope, normative and legal context, system architecture, maintainability and sustainability, human resources, modules included in the system, and functionalities.

Method 2: Observation of the Vaccination Workflow

We will undertake health facility visits in 4 purposively selected sites to observe the vaccination process and how these intersect with data capture, entry, and reporting. This activity will be a proof of concept, conducted in a high-performing and a low-performing district based on their vaccination coverage and as advised by local in-country stakeholders. This activity is designed to support an accurate understanding of data capture and process flow, provide further context to variability between health facilities and service types, and provide validation of other data collected. A data enumerator with experience in clinical practice, including immunization, will observe how data are recorded by health facility workers during 3 vaccination encounters at each facility. Observations will be recorded using a site observation tool (Multimedia Appendix 3) and will capture a mix of quantitative and qualitative (free text) items.

Method 3: Health Facility User Surveys

We will examine the perspectives of EIR users at health facilities using a cross-sectional survey adapted from existing tools (Multimedia Appendix 4; Pan American Health Organization, unpublished report, May 2025). Survey questions are structured into six key domains: (1) process, (2) infrastructure, (3) data management and use, (4) workforce, (5) user satisfaction with the EIR, and (6) user perception of EIR data quality. The user satisfaction tool covers the user's perceptions of the ease of using the EIR, its efficiency compared with paper-based methods, data security, impact on immunization service delivery, and overall satisfaction with the EIR. The tool measuring users' perception of information quality covers the user's satisfaction with the accuracy, completeness, timeliness, ease of access, and usefulness of data in the EIR. We iteratively tested and revised the survey instrument based on feedback, then translated it into Lao, where it was tested by technical expert native speakers. We will conduct a pilot of the survey at 2 to 3 health facilities

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to test the tools and make final adjustments to the data collection tools. Data from the pilot study will be included in the final dataset. Trained data enumerators with experience in immunization and surveys will administer the survey using the REDCap (Research Electronic Data Capture; Vanderbilt University) system. The REDCap mobile app was selected for this study as it can support secure offline data capture on mobile devices, critical for data collection in remote areas with poor internet connectivity [48,49].

Method 4: Key Informant Interviews

There is a lack of consensus on how to quantitatively measure data use for immunization, with indicators generally being poorly defined, lacking specificity, and failing to capture the complexity involved in assessing the extent to which data are used. At present, a qualitative approach is more appropriate to understand facilitators of and barriers to the implementation, how data are used, and how the ecosystem and digital tool impact data use. We will use a semistructured interview guide informed by previously published literature and protocols provided by content experts (Pan American Health Organization, unpublished report, May 2025) [50]. The interview guide will cover seven domains: (1) overall perceived net benefits of the EIR, (2) implementation process of the EIR, (3) impact of the EIR on the national immunization program, (4) impact of the EIR on decision-making, (5) the cost of implementing the EIR, (6) linkage and interoperability with other health data systems to support program evaluation, and (7) investment in the EIR. This will evolve based on findings from user surveys. In total, 2 to 3 members of the study's advisory group from the Lao PDR will translate and pilot the tool in Lao. Interviews will be reviewed by the study team in real time for quality assurance and to ensure that interviews continue until saturation is reached. Thematic analysis will be used to interpret and report patterns within the data.

Method 5: Assessment of Immunization Data Quality

A comprehensive assessment of immunization data quality typically involves an audit of paper and electronic records. This activity can be resource intensive and is challenging when records are missing or difficult to retrieve, such as paper-based records and child home-based documentation. Nonetheless, a data quality assessment offers a powerful way to quantify the impact of introducing digital tools and demonstrate improvement in the short term. A comprehensive audit of immunization records across all facilities included in this study is not feasible; however, we will conduct a targeted audit to test the proof of concept, drawing on several established audit methods.

First, we will assess data concordance, that is, agreement of different sources of immunization data (refer to the data concordance tool in Multimedia Appendix 5). This will be undertaken in 4 purposively selected health facilities, with 1 site including the district-level hospital. Data enumerators will collect aggregate data on selected indicators (hepatitis B birth dose, DTP-containing vaccine [pentavalent vaccine] dose 1, and measles-containing vaccine dose 1) over a 3-month period. Counts will be compared across paper-based health facility registers, monthly reports, and EIR records.

In addition, we will obtain an EIR dataset and assess the data quality of the records of the cohort of children born in 2023. We will use indicators from existing frameworks (Pan American Health Organization, unpublished report, May 2025) [51] to assess the data quality dimensions of completeness (absence of missing data), timeliness (recorded within a specific time frame), and validity (absence of errors).

Study Location, Sampling, and Study Participants

This study will be conducted in Vientiane capital and Vientiane province, where the EIR was first implemented in 2022. We purposively selected 1 district hospital in Vientiane capital and the provincial hospital in Vientiane province. In addition, a target of 50% of all health facilities will be selected while still capturing a sufficiently large number that would provide critical data. We will randomly select 24 (39%) of the 61 health facilities in Vientiane province, including both health centers and district hospitals. To do so, we will apply stratified random sampling proportionate to the number of health facilities in each district to identify a sample of health facilities to survey. To reduce selection bias and ensure a geographically representative sample, we will use random sampling proportional to population size, ensuring that health facilities from all districts are included. At each health facility, any health worker who vaccinates or uses the EIR to collect or review immunization data will be targeted for recruitment.

We will select 4 (15%) of the 26 sites for the site observation and data quality assessment components of this study. We will purposively select these sites to capture diverse data from different health facilities. We will use coverage estimates from 2023, using data from the aggregated DHIS2 database, to identify districts with high and low vaccination coverage, selecting 2 facilities each from a high- and low-performing district. We will only select sites that provide outreach services to allow us to assess whether data quality differs by fixed or outreach services. Local study investigators and technical advisors will provide advice and guidance on the selection of facilities.

For face-to-face key informant interviews, we will aim to recruit 12 to 14 stakeholders. Stakeholders will be purposively selected by the study team and the technical advisory group for inclusion in the study. Stakeholders will represent different functions and roles in the health system, with knowledge of the roles in immunization program planning and decision-making, including members of the country's National Immunization Technical Advisory Group [52]. Stakeholders will also include those involved in implementing the EIR, such as individuals at the subnational level. In case of unavailability, stakeholders will be asked if there are others who may be able to contribute to the study (ie, snowballing). We will also interview stakeholders from key partner organizations, such as the WHO; UNICEF; and Gavi, the Vaccine Alliance, who are involved in using immunization data for programmatic and monitoring purposes.

An in-country coordinator was recruited to the study team to better facilitate recruitment and participation. The in-country coordinator will seek permission from each of the relevant provincial and district health center staff members from the preselected health centers and key informants before

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commencing study activities. Prior permission to attend the health facility and collect data from the site will be obtained from the immunization lead at the MCHC at the MoH. Consent will be sought from both the health worker being surveyed and the person in charge of supervising routine vaccine activities or the person in charge of immunization data management. All individual participants will be provided with a participant information sheet in English or Lao before the survey or interview, with written consent collected at the time of the survey.

Study Management and Conduct

Governance and Study Monitoring

A technical advisory group comprising experts from the MCHC, the department of finance and planning of the MoH, the WHO Country Office, UNICEF, and the University of Health Sciences of the Lao PDR was invited to provide advice and guidance on the design of the evaluation. The advisory group includes in-country representatives who are involved in the implementation, training, monitoring, and maintenance of the EIR. All study materials will be reviewed by the advisory group to ensure they are context appropriate.

Data Management

Health facility surveys, on-site workflow observations, and key informant interviews will be conducted in Lao by local research team members who have knowledge of the national health and immunization system of Lao PDR. All data enumerators will receive training before data collection. Training sessions will be developed and delivered by study coordinators with expertise in quantitative and qualitative research methods. Training topics will include public health research methods, research ethics, interview techniques, data collection and management, and troubleshooting of data collection tools.

Survey data will be captured digitally in the REDCap mobile app. Interviews will be digitally recorded and then transcribed by native language speakers. Workflow observation and immunization data from records held at health facilities will be captured on paper and later transcribed into a secure digital format. All records will be held securely by the local study team for at least 5 years.

Data Quality

All data collection tools will be pilot-tested before the start of fieldwork. During fieldwork, survey and observation data will be monitored daily for gaps, inconsistencies, and clarity of free-text responses. This real-time feedback between data enumerators and field coordinators will support timely modification of the data collection tools, troubleshooting, correction and clarification of data, and additional training of data enumerators as required.

All data obtained from the EIR, including both individual and aggregated data on vaccination coverage, will be deidentified before acquisition. While some analysis may be completed at the health-facility level, caution will be taken to ensure that reporting of facility-level results does not adversely impact the facilities or any individual's reputation or standing with local organizations in the Lao PDR. Therefore, results by individual facility may not be published; however, summary findings on factors associated with improved data quality or workflows will be reported.

Ethical Considerations

The ethical conduct of this study was reviewed and approved by the Lao PDR MoH Institutional Review Board (National Ethics Committee for Health Research; submission ID 2023.71) and the University of Sydney Human Research Committee (protocol 2024/038). Protocol amendments will be reviewed by both ethics committees. Participants will be provided with a participant information sheet and asked to give written informed consent, with the option of opting out at any time. Data will be anonymized and deidentified. No compensation will be provided for participants.

Outcomes and Analysis

Findings from study components will be separately analyzed and then triangulated to develop a summary of the immunization registry system with a focus on EIR operations and integration with other key systems.

The document review will provide contextual background for analyzing the study findings, including information about process workflows and the health and digital environment in which the EIR is being implemented. Both the health facility user surveys and data quality assessment will be quantitatively analyzed, with results reported as descriptive statistics. For the user experience and perspectives from the survey, we will report on current practices with regard to recording immunization data, enablers of and barriers to using the EIR, and user perceptions of and satisfaction with the EIR. Survey results will be reported as counts and proportions with 95% CIs for each survey item (eg, the number and proportion of respondents who were very satisfied, satisfied, unsatisfied, and very unsatisfied with the completeness of EIR data). Findings from the site observations will be narratively summarized and used to verify findings from the survey and document review.

Key informant interviews will be transcribed into Lao and translated into English for thematic analysis, with themes identified inductively. Themes will be discussed with the research team and modified until an agreement is reached.

For the data quality assessment, we will assess data for the following:

- Completeness of EIR records, that is, absence of missing records or data elements (eg, proportion of records in the EIR with missing date of birth) and completeness of the EIR (eg, proportion of births registered in the EIR)
- Timeliness, that is, data are recorded within predefined time frames (eg, proportion of vaccination events recorded within 3 days of vaccination as per standard operating procedures)
- Validity, that is, data are accurate and do not contain errors (eg, the proportion of records with the date of vaccination before the date of birth)
- Concordance, that is, agreement of different sources of immunization (eg, the number of hepatitis B birth dose vaccinations recorded in the health facility report, district level report, and EIR for a given month).

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Subgroup analysis will include sex, location, and service type (particularly fixed vs outreach services). Summary statistics from the data quality assessment will be reported as counts or proportions.

We will triangulate the results across the 5 study components using the framework derived inductively based on themes from the key informant interviews. Key findings and their interpretation from each study component will be mapped and tabulated by theme and then compared across each theme to identify convergent and divergent findings. Through this process, we will identify the strengths and weaknesses of EIR implementation; the facilitators of and barriers to implementation; and whether the introduction of the EIR has improved immunization data flow, processes, and quality compared with paper-based processes. This will then be used to codevelop recommendations, in collaboration with the Lao PDR MoH, on how the nationwide scale-up of the EIR can be implemented more effectively.

Results

Overview

Participant recruitment for this study began in April 2024 and concluded in July 2024. We surveyed workers at 26 health facilities and interviewed 18 key informants. We collected data on administered vaccinations from 4 sites for our assessment of data concordance concurrently during the health facility surveys and subsequently obtained data from the EIR for the 2023 birth cohort in August 2024. Data analysis is currently ongoing.

Dissemination

Results will be shared with key stakeholders, including the Lao PDR MoH and study funders, before public dissemination. Study findings will be presented and collaboratively reviewed with the advisory group and key stakeholders from the Lao PDR during a result dissemination meeting in October 2024. The meeting will be used to review and draft recommendations for improving the nationwide enhancement of the EIR. After finalizing the results, we will summarize our findings in a formal report, brief the MoH, and prepare the manuscript for submissions to peer-reviewed publications. Results will be shared with the key stakeholders, including all study participants and external organizations.

Discussion

Anticipated Findings

The shift from manual methods of data collection and reporting to electronic methods offers opportunities to improve the quality, availability, and use of immunization data, leading to greater accountability and ownership of data [33,53-55]. The use of the health management information system DHIS2 in Nigeria allowed users at different levels of the health system to track progress toward goals in real time, understand areas of poor immunization performance, and provide appropriate support to improve performance [55]. Cost savings, driven largely by reductions in the amount of time spent by health workers on immunization reporting due to the use of an EIR, have been reported in Tanzania and Zambia. Additional savings were attributed to improved vaccine management (eg, fewer trips for vaccine resupply) and reduced printing costs [16]. Health workers in facilities in Tanzania reported saving >70 hours each year that they could allocate to patient care [56]. Increased data visibility led to improved practices for ensuring data quality, resulting in fewer errors and greater data completeness [56].

While there are clear benefits of implementing EIRs, the shift from paper-based systems to digitized immunization information systems poses new challenges surrounding implementation, uptake, and sustainability [16,57]. In the Lao PDR, the switch to digitized systems, such as DHIS2, has been underway for the last decade and is still ongoing [58]. EIR implementation is resource intensive, and poor implementation can result in a waste of resources. For example, the proliferation of noninteroperable platforms used to collect and manage data in West Africa during the 2014 to 2016 Ebola virus crisis resulted in siloed and duplicated information systems that were detached from national systems [59]. Limited workforce capacity to manage and use the data and technical constraints, such as unreliable electricity, battery life, and network coverage, led to several tools being abandoned after the acute crisis [59]. This led to a waste of time and financial resources as well as missed opportunities for strengthening the health system. Similar challenges were identified in the implementation of an EIR in Tanzania, where workforce capacity constraints on both time and technical competencies; the use of other electronic systems in parallel with the EIR; and infrastructural challenges, such as inadequate computing equipment, internet, and electricity outages, hindered the implementation and use of the EIR [60]. At present, the Lao EIR is not used for automated reminders for caregivers, but this is an area to be explored in the future.

Similar to other health system strengthening initiatives, the impacts of new interventions (technological or other) are often realized several years after their implementation and are difficult to attribute to the technology, given the other system factors that also affect the outcome of improved vaccination coverage. Furthermore, there is a false perception that the implementation of a digital innovation alone is sufficient to bring about improvements in vaccination coverage, but this is not the case. EIRs can only be an effective health system strengthening tool if the information system works synchronously, with an appropriate enabling health digital environment including infrastructure and regulatory framework; ongoing resourcing including human, financial, and technological investments; strong leadership to advocate for their implementation, procedures, and use; and ongoing monitoring and evaluation [61]. Achieving EIR scale and sustainability requires time, investment, and adaptations based on the local context [10]. Often, there can be challenges with user experience resulting in compromised data quality and incompleteness, which, if persistent and not addressed early on, can compromise the benefits of the system [62]. In the absence of process evaluations of the implementation of EIRs, it is likely that problems with implementation will go undetected and unaddressed and only be acknowledged when the expected benefits of EIRs are not realized. Thus, process evaluations of the initial rollout and

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scale-up help to mitigate such issues and are vital to inform the next stages of rollout. In this paper, we present a detailed protocol to assess the early stages of implementation of an EIR in a low-resource setting.

Limitations

This pilot study has some limitations. This study will be conducted in only 1 province in the Lao PDR (Vientiane province) and will not be representative of the country-wide implementation. Therefore, our evaluation may fail to identify challenges in and barriers to implementation that may be present in other provinces or health facilities. However, identifying the key enablers of and barriers to EIR implementation even in this setting will help inform national scale-up and implementation by highlighting issues that may hinder implementation. This study endeavors to identify contextual factors that affect the functionalities of the EIR rather than providing a statistical representation of an entire province or country. While evaluations can be time and resource intensive, they should be conducted regularly to ensure optimal use of the system and identify opportunities for improvement.

As this is a pilot of a new protocol and approach, and outcomes of interest were not previously measured, a sample size for the health survey could not be estimated. The health facility survey may be subject to desirability bias [63], as younger health care workers might be more inclined to favor new technologies but might not always feel comfortable providing honest feedback. However, using independent enumerators with a strong background in immunization, who are trained in interviewing and rapport building, will help minimize some of these biases. Furthermore, we used purposive sampling for key informant interviews, observation, and data quality assessments, which may introduce selection bias. Due to the small sample size in this study, we were unable to compare high-performing and low-performing districts; however, such a comparison may be useful for future research. To minimize this bias, we will include a variety of stakeholders in the interviews and continue data collection until saturation is reached. Similarly, with workflow observations, there may be some observer bias; however, by maintaining distance and building a relationship of trust ahead of the interview, we will aim to minimize any influences [64]. We will also build strong relationships with in-country partners and stakeholders by establishing a technical advisory group, holding regular meetings and communication, and ensuring local communities receive all necessary information to make informed decisions to participate. For the data quality assessments, we have attempted to minimize bias by purposefully selecting 2 of the 4 sites from the low-performing districts. In addition, the hierarchical nature of the health system and reluctance to speak openly with people perceived to be in positions of authority may lead to falsely optimistic results. To mitigate this, data enumerators will be trained to build trust and rapport with participants and conduct data collection in a private location to minimize interference from others. In line with the aforementioned frameworks, it is important to acknowledge that EIR implementation is influenced by many additional health system factors, including funding, digital health infrastructure, and health literacy, which were beyond the scope of this evaluation. Despite these limitations, our protocol provides a standardized approach to evaluate EIRs in different settings.

Conclusions

Similar robust evaluations are rarely documented and tend to focus on their findings, and guidance on how to conduct such evaluations is scarce in the literature. As a result, the findings of similar evaluations in the literature are highly varied and are often focused on a narrow aspect of the EIR. Only few studies adopt a holistic, system-wide approach. By publishing our protocol, we hope to provide countries and researchers with a standardized approach, data collection tools, and indicators that can be adapted and applied in other low-resource settings, including many of the countries that have implemented COVID-19 EIRs and are looking to integrate them for routine immunization. While the context will vary, we use the best practice research methods that are feasible to implement and can be replicated across settings. Using a standardized methodology can enable comparability of performance across different settings, keeping in mind the contextual factors.

As EIR implementation is a multiyear process, extending over 10 years, and even well-established EIRs in high-income settings constantly evolve, a single process evaluation is insufficient to ensure an effective EIR. Evaluation must be ongoing and ideally incorporated as part of the monitoring and evaluation for immunization programs.

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Authors' Contributions

MS conceptualized the study, led the funding application, designed the protocol, and drafted the manuscript. CP designed the protocol and drafted the manuscript. GS designed the protocol and critically revised the manuscript. ML drafted the manuscript and coordinated project implementation. AT, NC, MT, and PG made significant contributions to the study design and critically

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revised the manuscript. KP, YP, SN, DB, and NB contributed to the study design and reviewed the manuscript. MC and MCD-H contributed to the study design and tools and critically revised the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Comparison of electronic immunization registries versus traditional systems.
[DOCX File , 131 KB - resprot_v14i1e65663_app1.docx]

Multimedia Appendix 2
Lao People's Democratic Republic National Childhood Immunization Schedule, 2024.
[DOCX File , 32 KB - resprot_v14i1e65663_app2.docx]

Multimedia Appendix 3
Data collection tool for observation of immunization data workflow at health facilities.
[DOCX File , 35 KB - resprot_v14i1e65663_app3.docx]

Multimedia Appendix 4
Data collection tool for the survey of health workers at health facilities.
[DOCX File , 53 KB - resprot_v14i1e65663_app4.docx]

Multimedia Appendix 5
Data collection tool for assessment of concordance of immunization data in the electronic immunization register compared with alternative paper-based data sources.
[DOCX File , 33 KB - resprot_v14i1e65663_app5.docx]

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Abbreviations

DHIS2: District Health Information Software 2
DTP: diphtheria-tetanus-pertussis
EIR: electronic immunization register
IA2030: Immunization Agenda 2030
Lao PDR: Lao People's Democratic Republic
LMIC: low- and middle-income country
MCHC: Maternal Child Health Centre
MoH: Ministry of Health
REDCap: Research Electronic Data Capture
UNICEF: United Nations Children's Fund
WHO: World Health Organization

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Protocol

Risk Factors for Serious Bacterial Infections Among Young Infants With Hypothermia: Protocol for a Multicenter, Retrospective Case-Control Study

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Abstract

Background: Hypothermia in young infants presenting to the emergency department (ED) may indicate a serious bacterial infection (SBI) such as a urinary tract infection, bacteremia, or bacterial meningitis. Improved understanding of the epidemiology of SBI in infants with hypothermia and the development of prediction models can help avoid unnecessary invasive procedures and antimicrobial exposure.

Objective: The aim of the study is to (1) describe the epidemiology of SBI and herpes simplex virus (HSV) among infants with hypothermia, (2) assess the role of biomarkers in predicting SBI, and (3) derive and internally validate a multivariable predictive model for SBI among infants with hypothermia.

Methods: The study is being conducted through the Pediatric Emergency Medicine Collaborative Research Committee as a retrospective nested case-control study. We will include infants with hypothermia (rectal temperature<36.5 °C) presenting to 1 of 28 pediatric EDs in the United States between January 1, 2013, and December 31, 2022. Exclusion criteria will include (1) fever in the ED or prior to ED arrival, (2) transfer from another health care facility, (3) technology dependence, (4) trauma, (5) skin and soft tissue infections, and (6) presentation in cardiac arrest. The primary outcomes will be culture-confirmed SBI (objectives 1-3) and HSV-positivity (objective 1). The analytic approach for each objective will be (1) to use descriptive statistics to summarize the epidemiology of SBI and HSV and clinical outcomes, (2) to compare biomarker parameters of infants with and without SBI and determine optimal cutoff values using a receiver operator characteristic curve, and (3) to develop a multivariable predictive model using penalized mixed effects logistic regression within a 1:3 case-control sample among infants in the cohort who had a blood culture obtained.

Results: Data collection for this study is ongoing, with a collection of data from 21 hospitals at the time of protocol submission. Of 16 sites evaluated in preliminary analysis (n=45,673), the median age is 25 (IQR 6-52) days, and 24,182 (52.9%) are male. In total, 340 (0.7%) infants have an SBI, of whom 103 had bacteremia or meningitis. Mortality occurred in 7 (2.1%; 95% CI 0.9%-4.3%).

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Conclusions: We will use a consensus-based outcome measure for SBI with an established data acquisition pathway. We will use a multicenter sample from US children's hospitals, using a consensus-based outcome measure for SBI and a case-control approach to evaluate outcomes to improve the management of young infants with hypothermia in the ED.

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KEYWORDS

hypothermia; serious bacterial infection; urinary tract infection; UTI; bacteremia; bacterial meningitis; herpes simplex virus; noninfectious pathologies; environmental factors; pediatrics; infants; neonatal; infectious diseases; bacterial infection; herpes

Introduction

Globally, neonatal sepsis is estimated to occur in nearly 3000 cases per 100,000 live births, with an estimated mortality rate of 18% [1]. While abnormalities of temperature (including fever or hypothermia) are understood to be a risk factor for sepsis [2,3], the specific association of hypothermia with high-risk infections is poorly characterized. Hypothermia among young infants presenting to the emergency department (ED) may be a sign of a serious bacterial infection (SBI), which includes urinary tract infection (UTI), bacteremia, or bacterial meningitis [4,5]. Prior study suggests that hypothermia may also occur in disseminated herpes simplex virus (HSV) infection [6-8]. However, infants more frequently present with hypothermia due to noninfectious pathologies or secondary to environmental factors [9,10]. The etiology of hypothermia in the setting of sepsis is likely multifactorial, with some preclinical studies suggesting an advantageous role for hypothermia as compared to fever in rats with severe endotoxemia [11]. It remains unclear what percentage of infants with hypothermia are ill-appearing or have other relevant findings on examination. Prior work has provided limited data with respect to SBI among young infants with hypothermia. These studies, performed from single centers or from administrative datasets, have identified that SBIs occur in 1%-8% of young infants with hypothermia [5,6,9,12-15].

In contrast to young infants with fever [16,17], infants presenting to the ED with hypothermia lack prospectively derived evidence to guide care. In the absence of robust evidence-based consensus and guidelines to assist clinicians, substantial variability exists in the care provided for these infants, as demonstrated in one large survey of 1231 ED clinicians [18]. This is further challenged by the lack of a consistent definition for hypothermia, which varies from 36.0 °C to <36.5 °C [5,6,15]. Many infants with hypothermia are managed similarly to young infants with fever [18], but this approach has not been fully studied. There is wide variability in the performance of cerebrospinal fluid (CSF) testing (14%-70%), obtaining blood for inflammatory markers (8%-88%) and empirical antibiotic use (56%-92%) [19]. These data also suggested an increasing reliance on the use of inflammatory markers to guide decision-making, including C-reactive protein (CRP) and procalcitonin [19]. Nevertheless, prior work has demonstrated associations of clinical factors with the presence of bacterial infections among infants with hypothermia, including age [4,6], temperature [4,14], persistence of hypothermia [5], laboratory measures [4-6], and examination factors [9,12]. A well-performing prediction model to predict SBI is currently lacking.

Improved data are required to evaluate the prevalence of SBI among young infants with hypothermia and to construct a predictive model for this outcome. This will help identify infants at very low risk for SBI in whom invasive procedures and unnecessary antimicrobial exposure can be avoided. This study therefore has the following three objectives: (1) to describe the epidemiology and prevalence of SBI and HSV among young infants (≤90 days) presenting to the ED with hypothermia, (2) to evaluate the role of biomarkers in the prediction of SBI among young infants, and to derive and internally validate a prediction rule for SBI among young infants presenting to the ED with hypothermia.

Methods

Overview

We will perform a multicenter study of infants with hypothermia in the ED using the Pediatric Emergency Medicine Collaborative Research Committee (PEM CRC) to characterize infants with SBI and HSV and to compare infants with hypothermia with and without SBI. The PEM CRC offers a framework for multicenter investigations, supporting and facilitating the development of valuable and rigorous collaborative research in pediatric emergency medicine. PEM CRC plays a crucial role in developing high-quality protocols and identifying interested coinvestigators across its member sites. The PEM CRC has established a centralized data center at Texas Children's Hospital, Baylor College of Medicine (BCM). This center offers data collection support services, including front-end logic checks for electronic data sheets, high-speed automated data sheet scanning, and database creation, encryption, and processing, and has conducted several important studies focused on topics relevant to the care of uncommon, but clinically important, conditions that occur in children presenting to the acute care setting [20-23]. We will include infants ≤90 days with a blood culture performed and who presented to a contributing hospital with a rectal temperature of <36.5 °C in the ED over a 10-year period. We will use a case-control approach. BCM will serve as the data coordinating center. A graphical summary of the study protocol is provided in Figure 1.

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Figure 1. Overall flowchart of study protocol. ED: emergency department; PI: principal investigator; REDCap: Research Electronic Data Capture; SBI: serious bacterial infection.

Approaches

Objective 1 Approach

We will construct a large, retrospective, multicenter dataset assembled from at least 25 participating hospitals to identify the frequency of presentation of hypothermia across participating hospitals, the incidence of SBI and HSV, types of SBI, the underlying bacteriology of SBI, and clinical outcomes of infants with SBI, including in-hospital mortality. We will describe secondary outcomes of infants to describe diagnoses and evaluate clinical outcomes of hospitalization, length of stay, use of the intensive care unit, diagnoses, and unscheduled return visits to the ED following ED discharge.

Objective 2 Approach

We will analyze infants with hypothermia who do and who do not have SBI to identify the predictive value of frequently performed tests and calculate ideal cutoffs for these tests to maximize their diagnostic value. As an exploratory component of this aim, we will additionally investigate the role of newer tests of inflammation for SBI in this population, including CRP and procalcitonin.

Objective 3 Approach

We will construct a prediction model using a multicenter dataset. We will use penalized multivariable logistic regression to develop a full model and bootstrapped backward selection models to develop a parsimonious reduced model. A prediction rule for infants with hypothermia will allow for the identification of infants at low risk of SBI. The identification of historical, clinical, and laboratory risk factors would facilitate real-time risk stratification and identification of a low-risk group. The performance and reporting of this prediction model will adhere to the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis guideline [24].

Inclusion Criteria

Infants ≤90 days of age presenting to the ED of a participating pediatric ED with hypothermia, defined as a minimum rectal temperature of <36.5 °C in the ED over a 10-year period (January 1, 2013, to December 31, 2022). The <36.5 °C criterion is determined based on preliminary work performed by the investigators [14] and uses the World Health Organization criteria to define hypothermia in neonates [25]. We will allow participating sites that are unable to provide data from 2011 to contribute data due to varying adoption of EHR systems across these hospital systems [23].

Exclusion Criteria

The exclusion criteria are as follows:

1. Fever in the ED or prior to ED arrival. Fever is recognized as a risk factor for SBI among young infants presenting to the ED [4]. Infants with fever should be managed according to national guidelines recommending routine testing for infants with fever on ED arrival. We will use a threshold for fever (rectal temperature ≥38.0 °C) used by the American Academy of Pediatrics in a clinical practice guideline published for the evaluation of this condition [26].
2. Transfer from another health care facility. It is difficult to accurately assess or obtain assessment or laboratory data present at the time of initial outside health care facility evaluation; as such, we exclude infants who were transferred to a study site from a different ED or hospital.
3. Technology dependence. We will identify infants with technology dependence (eg, ventriculoperitoneal shunts) using the ICD-10 (International Statistical Classification of Diseases, Tenth Revision) procedure and diagnosis codes documented for the patient during any prior encounter within the hospital electronic health record (EHR) system. These will be identified using the technology dependence flag of the pediatric chronic complex condition algorithm [27].
4. Trauma. Hypothermia can occur in the setting of traumatic injury, including child abuse [28]. Children with an encounter-level diagnosis consistent with trauma will be excluded using
ICD-10
codes from a validated injury diagnosis framework [29].
5. Skin and soft tissue infections. Children with skin and soft tissue infections frequently demonstrate a clinically apparent source of infection at the time of presentation. While these are known to occur among young infants with fever [30], the incidence of skin and soft tissue infections among infants with hypothermia is unknown. These infections will be identified using the encounter-level ICD-10 codes L030, L031, L032, L033, L038, and L039 [31].
6. Presentation in cardiac arrest. Children may be hypothermic because they are present in a perimortem state. We will specifically exclude children who present to the ED in cardiac arrest or postmortem state. These will be identified by finding all infants who received cardiopulmonary resuscitation during their hospitalization, had a diagnosis code consistent with cardiac arrest, or had in-ED or in-hospital mortality. This process is intended to be sensitive to identify all potential encounters with cardiac arrest. We will ask each site principal investigator (PI) to manually

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review these cases to identify those presented in cardiac arrest or for whom resuscitative efforts were not attempted.

As our inclusion period includes the period of time prior to the adoption of *ICD-10* in the United States, we will crosswalk the *ICD-9* (*International Classification of Diseases, Ninth Revision*) diagnosis codes using generalized equivalence mappings, a resource developed by the US Centers for Medicare & Medicaid Services that provides forward and backward mappings between the diagnosis coding systems [32].

Case Ascertainment and Initial Data Upload

The EHR will be queried each participating ED to identify eligible age (≤90 days) encounters from 2013 to 2022 with at least 1 documented episode of hypothermia during the ED encounter. Due to the large volume of records anticipated to be identified at each site (varying between 1500 and 3000 encounters on initial efforts from 7 hospitals), data collection will proceed through 2 phases to maximize the efficiency of manual chart review and avoid the collection of unnecessary data. First, we will use a standardized data collection of all variables that can be ascertained from the EHR through computerized queries. This will include (1) demographic details such as age, race, ethnicity, and sex, and administrative data (payor status, year, and season of visitation); (2) medical history, ED chief complaints, multiple temperature measurements throughout the visit, and heart rate and blood pressure data; (3) laboratory test results, including complete blood counts (CBCs), metabolic panels, and tests for viral and bacterial pathogens (including the results of urine, blood, and CSF culture, results from urinalysis and urine dipstick testing, and results from HSV testing); (4) results from chest radiography, if performed; (5) medication administrations (antipyretics, antibiotics, and antiviral medications); (6) ED outcomes and details of hospitalization such as neonatal or pediatric intensive care unit admissions; (7) follow-up information on any return visits (>7 days); and (8) diagnosis and procedure codes for the index encounter and all prior encounters. Considering race and ethnicity and social constructs, we will collect these data acknowledging the limitations in how these data may be reported in a retrospective study and that the means of reporting may vary by institution and over time (eg, self-reported vs determined by registration staff). These data will be reported descriptively. We will not incorporate race or ethnicity in prediction models. To minimize duplication of efforts and maximize homogeneity with data collection procedures across sites, we will promote the sharing of Structured Query Language queries using Epic and Cerner platforms across participating sites. Data will be uploaded from the EHR via a secure, HIPAA (Health Insurance Portability and Accountability Act)-compliant REDCap (Research Electronic Data Capture; Vanderbilt University) database hosted at BCM using a data upload. Data from each site will undergo quality assurance by the study team to ensure that the uploaded data from each site is free from systemic errors.

Case Matching and Manual Data Extraction

Trained study-site PIs will abstract variables from the EHR and enter them into a secure, HIPAA-compliant REDCap database hosted at BCM. The initial upload of patient data will include data for all encounters meeting minimum inclusion criteria (age ≤90 days presenting to the ED of a participating pediatric ED with at least 1 episode of a temperature <36.5 °C during the ED encounter). Exclusions will then be applied using the methodology described earlier. Outcome data with respect to SBI and HSV will be defined by the author team using a priori defined criteria (described in the Outcome Definitions section). Cases will be identified by querying each hospital's EHR system or microbiology laboratory in the ED during the study period to identify infants ≤90 days with SBI. Controls will include infants with a minimum rectal temperature of <36.5 °C in the ED who had a blood culture performed and with no SBI identified. We will perform 3:1 nested matching of controls to cases based on site and proximity of the date of the encounter. Among encounters where blood cultures were obtained after antibiotic administration (which may be ascertained during manual chart review), cases or controls deemed ineligible will be replaced, and case-control matching will be reperformed within that subgroup. As prior work suggests that only some infants with hypothermia have a blood culture performed, the inclusion of only those infants with a culture performed will allow for the construction of models for infants for whom a clinician may have a suspicion for SBI.

After matching cases and controls, we will provide the record numbers of these selected cases to each of the site PIs. Site PIs will manually review each encounter to ensure whether it fulfills the inclusion criteria and does not meet any exclusion criteria. If cases or controls are found to meet exclusion criteria based on manual review, new assignments for these will be provided based on the next eligible matched control based on the proximity of the encounter. Site PIs will manually abstract the following variables: (1) birth history and relevant past medical history, including gestational age, birthweight, and maternal history (including history of group B *Streptococcus* positivity, maternal fever, and use of peripartum antibiotics), admission to the neonatal intensive care unit, presence of significant medical conditions diagnosed previous to the index ED encounter, immunization status, prior treatment for hyperbilirubinemia, and sick contacts in the home; (2) presenting history (history of seizure, apnea, abnormal behavioral or lethargy, cough, congestion, vomiting, diarrhea, alteration in feeding, decreased feeding, concern for environmental exposure, presence of reported hypothermia prior to ED arrival, lowest temperature prior to ED arrival, and mode of temperature assessment); and (3) physical examination data including (a) general ill-appearance (sick, toxic, inconsolable, or meningismus), (b) poor perfusion (shock, decreased pulses, cyanotic, and pale or ashen colored), (c) mental status changes (somnolence, lethargy, and altered), (d) sunken or full fontanelle, and (e) presence of respiratory distress, apnea, cyanosis, congested, seizure, clinical bronchiolitis, jaundice, or rash on examination. Historical and physical examination findings will be categorized as present or received or absent or not received based on documentation in the EHR. Variables categorized as either undocumented or missing based on the criteria in the manual of operations.

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Compliance

All data abstractors will undergo web-based training via teleconferences and have access to a detailed manual of operation at each site. Regular updates to monitor study progress and address questions throughout the chart review process during each phase of data collection will be conducted. The REDCap database will be established according to best practices, including data validation and strategies to minimize missing data, ensuring precise data capture. Additionally, we will conduct routine monitoring and compliance reviews of the database to maintain data accuracy during the study.

Outcome Definitions

Our primary outcome of interest is culture-confirmed SBI, defined as positive blood, urine, or CSF cultures [33-35]. Classification for pathogenic versus contaminant bacteria (from false positive cultures) will be determined based on established criteria for the classification of suspected pathogens published by the Pediatric Emergency Care Applied Research Network [36]. Indeterminate cases will be reviewed by the investigator team (which includes a specialist in pediatric infectious disease; ATC). UTI will be defined as the growth of ≥10,000 colony forming units/mL of a pathogen in urine culture plus an abnormal urinalysis (defined as the presence of leukocyte esterase, nitrites, or >5 white blood cells per high-power field on urine microscopy) [37]. We will use SBI as our outcome of interest instead of invasive bacterial infection (IBI; defined as bacteremia or bacterial meningitis and which is a preferred definition in the literature pertaining to infants with fever [26]), given the relative rarity of IBIs in previous publications and our pilot work (~2%). Cases that remain ambiguous will be reviewed by the investigator team (which includes a specialist in pediatric infectious disease; ATC), blinded to the context of relevant study predictors. We will plan an a priori sensitivity analysis limited only to infants with IBI, wherein we assess the performance of the SBI-based predictive model when using this alternative outcome. This 2-tiered approach has been previously applied to research on young infants with fever [16]. We will evaluate return visits within 7 days. For any return visits, we will review testing performed to identify potential missed cases of SBI. Our secondary outcome of interest will be HSV infection. HSV will be identified by the presence of a positive polymerase chain reaction or culture from any source [23].

Predictors and Subgroups

We have selected candidate predictors based on a review of prior literature [4,5,9,12,15,16,38] and following discussion among members of the study team. For each predictor, we will seek to ensure that data elements can be reliably and accurately extracted from the EHR. A list of candidate predictors that we will study is provided in Table 1.

Table 1. Candidate predictors for the development of a multivariable model for serious bacterial infection.

Category	Candidate predictors
Past history	Gestational age, birthweight, small for gestational age status, previous use of antibiotics, previous neonatal intensive care unit hospitalization, maternal history of fever, peripartum antibiotics, group B *Streptococcus* colonization
Demographics	Age, sex, season
Presenting history	Hypothermia prior to emergency department arrival, seizure, apnea, abnormal behavior, cough, congestion, vomiting, diarrhea feeding changes, environmental exposure
Vital signs	Minimum and maximum temperature, persistent hypothermia on multiple temperature assessments, systolic blood pressure, respiratory rate, heart rate
Physical examination	Ill appearance, compromised perfusion, mental status changes, fontanelle changes, respiratory distress, apnea, seizure, congestion, jaundice, rash
Laboratory assessment	Components of complete blood count, procalcitonin, C-reactive protein, urinalysis, results of respiratory pathogen testing

Analyses

Objective 1: Epidemiology of SBI and HSV

We will describe the epidemiology of SBI and HSV among infants with hypothermia prior to the selection of controls and stratify infants into groups of UTI, bacteremia without meningitis, and bacterial meningitis (with or without bacteremia). We will calculate the percentage of infants having each outcome among the overall cohort of infants with hypothermia and among the cohort of infants who had a blood culture. We will also characterize important clinical outcomes, including the proportion of infants hospitalized following their ED visit and in-hospital mortality, and describe variation in care among the included study sites.

Objective 2: Role of Biomarkers in the Prediction of SBI

We will calculate descriptive statistics and use the Wilcoxon rank-sum test to compare parameters among infants with and without SBI. We will evaluate the individual role of continuous laboratory predictors (including components of the CBC such as the white blood count, absolute neutrophil count, band count, and platelets) for an outcome of SBI. For these predictors, we will determine optimal cutoff values by identifying the optimal point on the receiver operator characteristic curve (as defined by the Youden index) and derive test characteristics based on the optimal cutoffs. The area under the receiver operator characteristic curve will be the empirical determinant of whether predictors are related to the likelihood of occurrence of SBI.

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Objective 3: Derivation and Internal Validation of a Prediction Rule

We will construct a multivariable predictive model using penalized mixed effects logistic regression to identify predictors associated with SBI. We will calculate adjusted odds ratios with 95% CIs to quantify the magnitude of the association between each predictor and the outcome, considering the study site and matched group as random effects. For continuous predictors (such as age or values of blood tests), we will evaluate three approaches: (1) retaining the variable as a continuous linear predictor, (2) classifying them as categorical variables based on optimally selected points on the receiver operator characteristic curve, or (3) exploring nonlinear or nonbinary categorical effects by applying restricted cubic splines.

After the construction of the full predictive model, we will use bootstrap backward selection to develop a more parsimonious model involving fewer predictors most related to the occurrence of SBI [39]. We will assess the performance of our model using calibration metrics [40,41] and use bootstrapping for internal validation. We will report metrics of the diagnostic accuracy (sensitivity, specificity, and positive and negative likelihood ratios) of our study sample at differing decision thresholds. We will develop a risk score to best identify children who are at risk of SBI by assigning point values to included predictors to develop an easily usable point-based scoring system [38].

We will assess the performance of the predictive model by its discrimination and calibration. Discrimination will be measured by calculation of the concordance index [42] and the area under the receiver operator characteristic of the predicted probabilities of SBI generated by the models. Calibration will be evaluated by plotting the observed smoothed proportions of SBI against the predicted proportions over the observed range of predicted probabilities and by calculating the Hosmer-Lemeshow statistic [43]. We will perform bootstrap resampling to calculate indices of overfitting and overoptimism to evaluate if the model is tailored to the specific study cohort and therefore not generalizable [39]. Statistical analyses will be conducted using R (version 4.3.2; R Foundation for Statistical Computing).

Missing Data

As with all retrospective chart reviews, there is a risk of encountering missing or inaccurately documented data. We will implement clear definitions and provide detailed instructions for data extraction and interpretation, with a particular focus on subjective data points. Additionally, we will analyze the factors associated with such missingness. These measures will help reinforce the assumption that the missing data are missing at random, thus enhancing the robustness of the study findings. We will evaluate complete case versus multiple imputation-based approaches for missing data for data elements that are missing in <20% of cases. Data missing in excess of this proportion will be excluded from multivariable modeling.

Sample Size

We estimate identifying 41,250 infants with hypothermia in the proposed study from 25 sites over 10 years. We expect that at least 825 (2%) will have an SBI, resulting in a 95% CI width for the prevalence estimate of ±0.14%. Of these, approximately 25% (n=205) will have an IBI [5,6,14]. Greater than 80% of patients with hypothermia who have a blood culture also have a CBC performed [44]. From our sample of 41,250 infants anticipated from objective 1, we estimate that 25% (approximately n=10,310) will have a blood culture performed; and of these, 8250 will additionally have a CBC. As an exploratory component of this aim, we will evaluate inflammatory markers (specifically, CRP and procalcitonin). Prior work suggests that the use of these biomarkers is increasing over time, with 30% of patients with procalcitonin and 39.6% with CRP in 2019 [19]. Projected from our pilot data, we expect to have 650 patients with procalcitonin from our study, of whom 65 will have an SBI.

For our third objective, we anticipate having a sufficiently large sample size for the development of robust multivariable models. Under the 3:1 case-control design, the proportion of individuals with SBI in the dataset will be fixed at 0.25. Assuming 825 patients with SBI from objective 1, we estimate that the concordance index for the model will have a maximal CI half-width of 2.3%. At the expected model concordance index of roughly 0.80, the CI half-width will be 1.8%, which represents substantial precision in estimating the model's quality of fit [45].

Ethical Considerations

This study involves the review of medical records for patients. Institutional review board (IRB) approval as exempt from the requirements of informed consent has been obtained from the Ann & Robert H. Lurie Children's Hospital of Chicago (IRB #2023-5779) and the 26 other participating hospitals (Table 2). Data use agreements have been established between all hospitals and BCM. All data uploaded into the REDCap repository are deidentified. No compensation is provided to participants. Adverse events, including breaches of confidentiality, will be reported to the local IRBs of Ann & Robert H. Lurie Children's Hospital of Chicago.

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Table 2. List of included sites.

Hospital name	City
Ann & Robert H. Lurie Children's Hospital of Chicago	Chicago, IL
Boston Children's Hospital	Boston, MA
Children's Healthcare of Atlanta	Atlanta, GA
Children's Hospital Colorado	Aurora, CO
Children's Hospital Los Angeles	Los Angeles, CA
Children's Hospital of Orange County	Orange, CA
Children's Hospital of Philadelphia	Philadelphia, PA
Children's Medical Center Dallas, UT Southwestern Medical Center	Dallas, TX
Children's Mercy Kansas City	Kansas City, MO
Children's Minnesota	Minneapolis and St Paul, MN
Cincinnati Children's Hospital Medical Center	Cincinnati, OH
Hasbro Children's Hospital	Providence, RI
Johns Hopkins Children's Center	Baltimore, MD
Medical College of Wisconsin, Children's Wisconsin	Milwaukee, WI
MUSC Shawn Jenkins Children's Hospital	Charleston, SC
Nemours Children's Health	Wilmington, DE
Norton Children's Hospital, University of Louisville	Louisville, KY
Primary Children's Hospital	Salt Lake City, UT
Rady Children's Hospital-San Diego	San Diego, CA
Texas Children's Hospital, Baylor College of Medicine	Houston, TX
UH Rainbow Babies & Children's Hospital, Cleveland Medical Center	Cleveland, OH
UMass Memorial Children's Medical Center, University of Massachusetts Medical School	Worcester, MA
University of Florida Health Shands Children's Hospital	Gainesville, FL
University of Michigan Health C.S. Mott Children's Hospital	Ann Arbor, MI
UPMC Children's Hospital of Pittsburgh	Pittsburgh, PA
Weill Cornell Medical Center	New York, NY
Yale New Haven Children's Hospital, Yale School of Medicine	New Haven, CT

Results

Initial site recruitment included coinvestigators and clinicians with relevant research experience and strong engagement with the study question. As of May 1, 2025, 27 sites have been included in the study, with data uploaded to a central REDCap repository from 23 sites, with 62,771 records prior to the application of exclusion criteria. Currently, we have reviewed data from 16 sites, encompassing 45,673 infants (median age 25, IQR 6-52 days), with 9361 (20.5%) receiving blood cultures, 9120 (20%) urine cultures, and 4470 (10.4%) CSF cultures. UTIs were identified in 253 (0.6%) infants and bacteremia or meningitis in 103 (0.2%), with most IBIs being isolated bacteremia. *Escherichia coli* was the most common pathogen, and mortality among infants with SBI was 7 (2.1%), primarily among those with bacteremia or bacterial meningitis. We intend to complete data submission using automated EHR criteria by June 2025, with manual chart review completed by December 2025. We expect to submit the main study findings for publication within 9 months following the final data analysis.

Discussion

Overview

This study aims to identify risk factors for SBIs among young infants with hypothermia and to develop a predictive model to inform clinical decision-making. We hypothesize that a subset of infants with hypothermia, particularly those with specific clinical and laboratory features, are at increased risk for SBI and that a multivariable model can reliably stratify this risk. By leveraging a large multicenter dataset, we anticipate that our findings will support more targeted evaluation and management strategies for this vulnerable population.

Principal Findings

Using a large, multicenter sample of infants presenting to the ED with hypothermia, this study will characterize the

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epidemiology of SBI and HSV and assess the diagnostic value of biomarkers in the prediction of SBI. This work will culminate in a statistical model to determine the risk of SBI among this patient population using clinical and laboratory factors and facilitate the development of a parsimonious model.

Limitations

First, preliminary research suggests that not all infants with hypothermia receive testing for SBI in EDs and that the proportion who do receive testing varies based on the criteria used to define hypothermia [15,19,44,46]. However, this is of limited impact, as our model will allow physicians to risk-stratify children for SBI on the subset of patients for whom diagnostic testing may be considered due to a suspicion of SBI. To further investigate this potential bias, we will compare demographics among children who are tested and who are not tested for SBI. A second limitation pertains to missing data; some infants may not have documentation of relevant risk factors or data required to calculate outcomes. We will evaluate both complete case versus selective multiple imputation-based approaches for missing data, acknowledging that missingness may be related to clinical decisions, such as ordering blood tests. Third, we plan to construct a parsimonious model that is generalizable (ie, both reproducible and transportable) to best serve the needs of clinicians who manage infants with hypothermia in the ED. We will assess the internal validity of the model using bootstrap resampling techniques, from which we will derive overoptimism indexes for various measures of model fit, including the concordance index [47].

Although this will be the largest sample of infants with hypothermia in the ED, our findings may not be completely representative of the prevalence of SBI among these patients because most participating institutions are academic institutions and pediatric hospitals; therefore, the findings may not be generalizable to different care settings. However, the PEM CRC represents geographic and socioeconomically diverse areas, and we would not expect that a systematic bias would be introduced.

Comparisons With Prior Work

The majority of prior work has been limited to single-center data and therefore is of limited generalizability [6,9,12]. Limitations of prior multicenter work include small sample size, incorporation of infants with fever within the study sample, inclusion of infants with hypothermia during their hospitalization (and not only the ED stay, where management options differ) [4,5], and lack of internal validation. We will build upon these prior studies by providing a larger, analytically robust approach to identify risk factors for SBI in this population. The proposed study will be significantly larger, focused on the initial ED presentation and decision-making, and represent a more diverse population than prior studies. It will address a continued knowledge gap in the care of young infants.

Future Directions

The findings from this study allow for additional research that will potentially allow for the implementation of real-time risk calculation for the presence of serious infections among infants with hypothermia. Our preliminary results (which corroborate with other work [14]) suggest that SBIs occur infrequently but are associated with high mortality, heightening challenges in risk stratification in this population. Future steps may therefore be intended to safely facilitate a reduction in low-value testing. Following the completion of this study, we will seek to externally validate and implement the model via clinical decision support systems and guidelines, reducing both overtreatment in low-risk infants and health care variability, thus improving care standardization and reducing the incidence of low-value care. This will potentially lower health care costs, decrease antibiotic exposure and unnecessary hospitalization, and alleviate the emotional and financial burden on families. At the study's conclusion, dissemination efforts will involve broad participation from key partners in pediatrics, emergency medicine, hospital medicine, primary care pediatrics, infectious disease, and dissemination or implementation science.

Conclusions

We aim to address the critical gap in evidence-based guidance for managing hypothermia in young infants presenting to the ED. By leveraging a large, multicenter dataset, we will delineate the epidemiology of SBI and HSV in this vulnerable population, evaluate the predictive value of biomarkers, and develop a clinically useful prediction model to stratify the risk of SBI. Our findings are expected to enhance patient care by reducing unnecessary invasive procedures and antibiotic exposure. If a robust model is developed and validated externally, these results will contribute to more standardized and evidence-based care, potentially reducing health care costs and the burden on families. Despite limitations such as variability in testing and the generalizability of the findings to nonacademic settings, this research marks a significant advancement in understanding and managing hypothermia in young infants.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are not publicly available due to institutional data use agreements and restrictions but are available from the corresponding author on reasonable request. The study's results will be published in peer-reviewed journals and shared through conference presentations and web-based education platforms.

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Authors' Contributions

SR conceived of the study. SR, ATC, AJR, and PA initiated the study design and are the grant holders. DL provided statistical expertise in clinical trial design. All authors contributed to the refinement of the study protocol and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

BCM: Baylor College of Medicine
CBC: complete blood count
CRP: C-reactive protein
CSF: cerebrospinal fluid
ED: emergency department
EHR: electronic health record
HIPAA: Health Insurance Portability and Accountability Act
HSV: herpes simplex virus
IBI: invasive bacterial infection
ICD-9: International Classification of Diseases, Ninth Revision
ICD-10: International Statistical Classification of Diseases, Tenth Revision
IRB: institutional review board
PEM CRC: Pediatric Emergency Medicine Collaborative Research Committee
PI: principal investigator
REDCap: Research Electronic Data Capture
SBI: serious bacterial infection
UTI: urinary tract infection

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Protocol

Comparing the Accuracy of Different Wearable Activity Monitors in Patients With Lung Cancer and Providing Initial Recommendations: Protocol for a Pilot Validation Study

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Abstract

Background: Wearable activity monitors (WAMs) provide insights into physical activity (PA) and are widely used in behavioral interventions and cancer survivorship research. However, validation studies of wearable devices in populations with cancer are scarce, and existing studies using activity monitors in patients with cancer lack standardization. This gap is particularly significant in patients with lung cancer (LC), who often experience unique mobility challenges and gait impairments that may affect device accuracy. This study addresses this gap by validating the Fitbit Charge 6, ActiGraph LEAP, and activPAL3 micro in patients with LC in both laboratory and free-living conditions and developing a standardized framework for assessing wearable devices in populations with cancer and impaired mobility.

Objective: This study aims to validate and compare the accuracy of consumer-grade (Fitbit Charge 6) and research-grade (activPAL3 micro and ActiGraph LEAP) WAMs in patients with LC under both laboratory and free-living conditions. Moreover, this protocol aims to establish standardized procedures that can be adapted for validating current and future generations of wearable devices while accounting for disease-specific factors that may impact measurement accuracy.

Methods: In total, 15 adults diagnosed with LC (stages 1-4) will participate in laboratory and free-living protocols, wearing Fitbit Charge 6, activPAL3 micro, and ActiGraph LEAP devices simultaneously. The laboratory protocol will consist of a series of structured activities, including variable-time walking trials, sitting and standing tests, posture changes, and gait speed assessments. Activities will be video recorded for validation. In the free-living protocol, participants will wear the devices continuously for 7

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days except during water-based activities. WAM-based outcome measures will include step count; time spent at light, moderate, and vigorous PA intensity levels; posture; and posture changes (only the activPAL3 micro measured posture). Validated survey instruments will be administered both before and after WAM data collection to control for potential confounding factors that may influence movement patterns and device accuracy. Laboratory-based validity measures will compare WAM data to video-recorded observations. Sensitivity, specificity, positive predictive value, and agreement will also be determined. Free-living agreement between devices will be assessed using Bland-Altman plots, intraclass correlation analysis, and 95% limits of agreement.

Results: Data collection is ongoing, with 11 participants enrolled and 7 (64%) having completed both in-laboratory and free-living protocols. On average, enrolled participants are aged 63.0 (SD 7.8; range 50.0-73.0) years, with 8 (73%) participants being women. Participant enrollment is expected to conclude in mid-2025, and initial findings are expected to be disseminated by the end of 2025.

Conclusions: This is the first study that validates WAM accuracy for populations with LC while providing comprehensive recommendations for future validation studies. This study will provide critical insights into the accuracy and reliability of WAMs for assessing PA in LC survivors, which are essential for interpreting clinical research and informing future interventions.

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KEYWORDS

physical activity monitoring; wearable devices; validation study; lung cancer; consumer technology; Fitbit; ActiGraph; activPAL3 micro; cancer survivorship; digital health

Introduction

Background

Lung cancer (LC) is the most diagnosed cancer worldwide (with approximately >2.5 million new cases in 2022) and the leading cause of death due to cancer (with an estimated 1.8 million deaths in 2022) [1]. In the United States alone, there are an estimated 384,000 LC survivors, and as early detection methods improve, that number is rapidly increasing [2]. Although treatments are quickly improving, patients still experience debilitating disease–related symptoms, such as cough, chest pain, fatigue, and depression. However, new studies have shown that moderate exercise during LC treatment can lead to significant improvements in fatigue, anxiety, stress, self-esteem, cardiovascular fitness, muscle strength, gastrointestinal side effects, breathing, cancer recurrence, and overall mortality [3,4].

In recent years, wearable devices, such as fitness trackers, watches, and mobile sensors, have become increasingly popular. User penetration rates of fitness trackers are expected to reach 13.4% by 2029, and fitness tracker–derived measurements are being incorporated more frequently into patient health records [5,6]. The well-established benefits of physical activity (PA) on cancer outcomes have prompted researchers and clinicians to explore new methods for monitoring and managing patient health. Consumer-grade and research-grade wearable devices are increasingly being investigated as tools to track PA, heart rate, and cardiorespiratory fitness in patients with cancer [7]. These devices offer the potential for more comprehensive and continuous health monitoring, which could lead to improved management strategies and better outcomes for individuals undergoing cancer treatment [8]. Wearable devices are also often used to implement (eg, process measures, feedback, and goal setting) and evaluate PA interventions [9]. Implementation feasibility is essential when considering wearable devices in cancer care. Miyaji et al [10] demonstrated high adherence rates (90% of the patients used wearable activity monitors [WAMs] as instructed for >70% of the observation period) among both patients with gastrointestinal cancer and patients with LC using commercially available WAMs over a 28-day study, confirming their clinical feasibility. Similarly, Gupta et al [11] reported high adherence rates (96% of the patients used WAMs as instructed for >50% of the observation period) among patients with cancer using WAMs over a 12-week longitudinal study. Consequently, assessing health behaviors, such as PA and sedentary behavior (SB), using wearable devices in an individual's free-living environment provides widespread opportunities for public health–related research and clinical applications.

Wearable devices such as the consumer-grade Fitbit Charge (Google LLC) and the research-grade activPAL3 micro (PAL Technologies) and ActiGraph GT3X have been extensively studied and validated against criterion measures, such as indirect calorimetry, validated research-grade devices, direct observation (DO), video analysis, and polysomnography (ie, a diagnostic test for sleep disorders), in healthy adult populations [12-15]. However, unlike healthy populations, patients with cancer (and particularly patients with LC) frequently experience respiratory-, balance-, and mobility-related impairments that alter typical movement patterns and present unique challenges when conducting studies using activity monitor–derived outcome measures [16]. These challenges are particularly evident in gait speed, as patients with cancer often exhibit significantly slower walking velocities compared to healthy adults, and the accuracy of most activity monitors has been shown to decrease substantially at slower walking speeds [17]. Moreover, physiological and behavioral differences, cancer treatment side effects, adherence issues in wearing activity monitors, and environmental factors may all impact wearable devices' accuracy and reliability.

Objectives

Despite the increasing use of research-grade and consumer-grade wearable devices for PA tracking in patients with cancer and

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the known challenges with their use in this population, validation studies are scarce, and none have specifically examined device accuracy in patients with LC. Moreover, studies using wearable activity monitoring devices in populations with cancer show significant heterogeneity in their protocols [18,19], and there are a few published protocol papers to guide researchers toward standardization. This lack of standardized validation procedures makes it challenging to compare results across studies and establish evidence-based recommendations for device selection and implementation in clinical practice. Therefore, this paper aims to describe a comprehensive protocol for validating both research-grade and consumer-grade WAMs in patients with LC, incorporating both laboratory and free-living conditions to provide a more complete understanding of device performance in patients with LC. In addition, this paper provides recommendations and considerations for future PA validation studies of wearables in similarly affected populations.

Methods

Study Design

The validation protocol will contain (1) in-laboratory and (2) free-living environment components. The purpose of the in-laboratory protocol will be to assess the validity and reliability of 2 research-grade activity monitors, namely activPAL3 micro and ActiGraph LEAP, and 1 consumer-grade device, Fitbit Charge 6, by comparing them to the gold-standard DO [20]. In addition, the purpose of the free-living protocol will be to evaluate the validity and reliability of the Fitbit Charge 6 compared to the criterion measures from 2 research-grade devices (ActiGraph LEAP and activPAL3 micro).

A series of surveys and self-report assessments will be administered to evaluate potential confounding variables due to stress, health-related quality of life (HRQoL), PA, sleep, symptom burden, and user-reported acceptability of the devices being validated.

Participants and Recruitment

On the basis of previous work, our target is to enroll 15 participants for the study [20,21]. Our sample size of 15 participants aligns with similar validation studies of activity monitors [22,23]. Despite this relatively small number of individuals, the study design generates a robust dataset through multiple observations per participant. Each participant contributes hundreds to thousands of daily steps, numerous walking trials, static posture tasks, and posture changes. In addition, each person provides 7 full days of free-living data (exceeding 100 h per person). Given the challenges in recruiting patients with LC, this approach creates a statistically efficient dataset that is adequate for validation purposes. Inclusion criteria are participants aged between 18 and 89 years; a diagnosis of stages 1-4 of LC; the ability to speak, read, and understand English; the ability to engage in PA; and having access to email. Exclusion criteria are pregnancy or plans to become pregnant and administration of adjunct therapy within 7 days of the baseline laboratory visit. Therapies, such as oral tyrosine kinase inhibitors (TKIs) and hormonal therapies will be permitted during the study period, given that both treatments are administered continuously and are very commonly administered treatments for patients with cancer [24,25]. The administration of adjunct therapy before or during the collection of activity monitor–derived data will be included as an exclusion criterion due to the high levels of fatigue experienced immediately after treatment in patients with cancer [26].

The recruitment process began in May 2024, and enrollment is still ongoing. Initially, clinical oncologists will identify prospective participants at The Ohio State University Wexner Medical Center. The clinical oncology team will provide flyers with a brief description of the study to the patients (Multimedia Appendix 1) and will forward patient medical record number information to the research staff upon initial indications of interest.

Subsequently, research staff will verify age and previous diagnosis information via patient chart records in the Epic electronic medical record. Once verified, the contact information will be obtained from Epic patient chart records, and research staff will attempt to contact the participants via a phone call or the messaging system built into MyChart Epic. Research staff will try to contact patients 3 times at precisely 1-week intervals. If participants confirm their willingness to participate, a brief telephone interview will be administered (Multimedia Appendix 2) to screen patients for adherence to the inclusion criteria before obtaining consent (Multimedia Appendix 3) and enrolling participants in the study.

Devices and Associated Software

Consumer-Grade Devices and Software

The Fitbit Charge 6 was chosen for validation because of its widespread popularity, low cost, ease of use, and detailed metrics tracking on a minute-by-minute basis. It is important to note that access to minute-level data collected by Fitbit is not available via a web portal or an app and is only available via an application programming interface (API). There are 2 approaches commonly used to access Fitbit data. The first approach is to use a verified third-party vendor such as Fitabase [27] to manage data collection. The second approach (which will be used in this study) is to create a custom software solution that accesses the Fitbit API (Multimedia Appendix 4). Fitbit uses the OAuth 2.0 authorization framework to grant access to user data [28]. In addition, the Fitbit device requires a mobile phone running iOS (Apple Inc) or Android (Google LLC) for real-time data collection. Participants will be encouraged to use their own devices; however, iPhone 13 (Apple, Inc) devices will be provided to those individuals who do not possess mobile phones.

Research-Grade WAMs and Software

For Fitbit validation in the free-living environment, activPAL3 micro and ActiGraph LEAP will be used as the standard research-grade devices for comparison [29]. activPAL3 micro is a thigh-worn monitor with a 14-day battery life and is shown to have strong agreement with the previous generation of ActiGraph GT3X [30]. Proprietary software PALconnect (PAL Technologies) will be used to initialize the devices and download data upon study completion (PALbatch). The ActiGraph LEAP is one of the most comprehensive and accurate research-grade activity monitors currently available, with

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support for monitoring measures related to PA (eg, step count and minutes of moderate-intensity activity), heart function (eg, heart rate and heart rate variability), and sleep (eg, total sleep time), as well as support for additional measures forthcoming. Proprietary software CentrePoint (ActiGraph LLC) will be used to initialize the devices and download data upon study completion. ActiGraph is easily removable by participants and requires recharging at approximately the 4-day mark when using photoplethysmography features, so both activPAL3 micro and ActiGraph will be used to ensure sufficient data collection for free-living validation. For validation in the laboratory environment, a handheld Sony FX30 digital cinema camera will be used to record participants and compare wearable device outcome measures against gold-standard researcher-labeled video data. Outcome measures from the Fitbit, activPAL3 micro, and ActiGraph devices will all be compared against the researcher-labeled video data. Before participant use, all devices will undergo battery life assessment and functional testing through a 7-day "simulated protocol" conducted by research staff to minimize the risk of device malfunction-related issues, such as incomplete data collection, missing data due to dropped data points, sensor-related impairments leading to unrealistic results (eg, very high activity), excessive noise in the data, etc. This testing protocol will help minimize data quality issues during the actual study period.

Data Collection and Timeline

Overview

The data collection procedure and timeline are shown in Figure 1. Upon enrollment in this study, participants will be emailed a series of surveys to complete before the in-laboratory visit (refer to the Baseline Procedures and Assessments section). Participants will then be scheduled for a 2-hour in-laboratory visit to complete the in-laboratory protocol and receive the activity monitoring devices (refer to the Laboratory Measurement Procedures and Assessments section). Upon completion of the in-laboratory protocol, participants will then be released to their respective free-living environments to further validate the consumer-grade Fitbit device for 7 days, not including the day of the in-laboratory protocol (refer to the Free-Living Measurement Procedures section). Wearable device data collection will take place over 8 days for each participant. Finally, after participants have completed the free-living protocol, they will be sent an email with additional surveys to complete, which will conclude their participation in the study (refer to the Post–Free-Living Survey Procedures section).

Figure 1. Data collection procedure. SPPB: Short Physical Performance Battery.

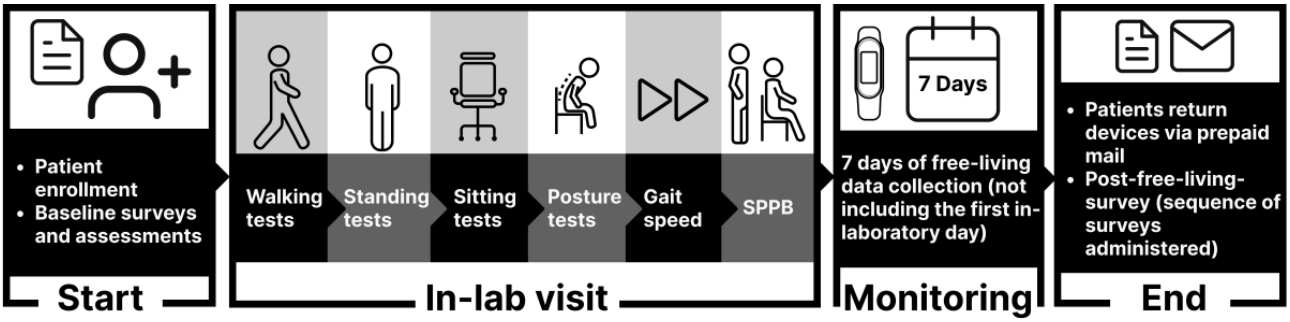

Baseline Procedures and Assessments

Overview

After obtaining patient consent, participants will first be emailed a set of baseline surveys to complete before in-laboratory data collection. Participants will be allowed to complete the surveys before their in-laboratory portion or during the visit. Participants will be permitted to complete the initial set of surveys at home, as allowing participants to complete surveys at home reduces the time required to complete the in-laboratory portion of the protocol. This will be especially beneficial for patients with cancer, who often experience fatigue and might find the lengthy in-laboratory measurement protocol challenging.

Instruments and Surveys Administered

Demographic information that will be collected includes full legal name, address, phone number, email, date of birth, ethnicity, race, and sex. Study participants will complete several validated questionnaires to assess quality of life and stress as follows: the Functional Assessment for Cancer Therapy–General 7 (FACT-G7) [31], EQ-5D-5L [32], the Functional Status Assessment [33], and the Perceived Stress Scale [34].

Laboratory Measurement Procedures and Assessments

Overview

After the baseline surveys are completed, participants will be scheduled for an in-laboratory visit. Before scheduling the visit, a research staff member will screen the participant's electronic medical record (Epic) to ensure that this visit will be scheduled at least 7 days after the last administration of adjunct therapy; however, oral TKIs and hormonal therapies will be permitted.

Previsit Preparation

One day before the laboratory visit, a laboratory-administered Fitbit account will be created for use with the Fitbit devices, and the device will be linked to the custom laboratory-developed Fitbit app to provide real-time API access to the data. The full protocol for API key linkage is available in Multimedia Appendix 4. Although some studies have permitted participants to create their own personal Fitbit accounts, laboratory-administered accounts will be used in this study for data security purposes.

Upon commencement of study data collection, the activPAL3 micro and the ActiGraph firmware will be frozen. Previous studies have indicated that firmware updates can create

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statistically significant differences in measurements within actigraphy devices [35]. Freezing the firmware reduces variation from firmware-specific differences within the study. Unfortunately, Fitbit does not currently permit firmware freezing.

Device Initialization, Application, and Synchronization

After arriving for the in-laboratory protocol, participants' height and weight will be measured and recorded in REDCap (Research Electronic Data Capture; Vanderbilt University), a secure electronic database. Afterward, research staff will download the custom Fitbit app onto the participant's mobile device and pair the Fitbit via Bluetooth with the mobile device. During this initialization period, one important but overlooked consideration is ensuring that the participant's device's time setting is correctly matched with the computer's time zone used to initialize ActiGraph and activPAL3 micro, and that automatic updates of time zones are disabled. The free-living protocol requires synchronizing time settings among all 3 devices for accurate validation.

Then, ActiGraph LEAP will be initialized before applying it to the participant using a laboratory computer via CentrePoint software, and the sampling frequency will be set to 32 Hz. Although higher frequencies are available, 32 Hz will be used, as higher sampling rates dramatically reduce battery life, and the 32 Hz frequency has been shown to be sufficient for accurate measurement of PA [36]. With the 32 Hz sampling frequency, we found during testing that the device lasted between 4 and 7 days of continuous wear (using the photoplethysmography sensor significantly reduced battery life). The activPAL3 micro will also be initialized at a sampling rate of 20 Hz to maximize battery life and most closely mirror settings from the ActiGraph.

After initialization, a video recording will be initiated using the Sony FX30 camera. To make it easier for the research team to match the timing of the video recording to the 3 activity monitors, we will record all 3 devices being vigorously shaken by hand, and the exact time (including seconds) of the initialization step will be recorded in REDCap. If the video recording is interrupted (eg, the battery dies and the memory is full) before completion of the in-laboratory protocol, the synchronization step will be repeated.

After initialization, Fitbit and ActiGraph will be attached to the same nondominant wrist via straps provided by the device's company. Both devices will be placed on the same wrist to minimize variation from left versus right arm movement during PA. Finally, activPAL3 micro will be attached to the midline anterior aspect of the participant's right upper thigh using an adhesive waterproof Tegaderm dressing (3M; Figure 2) in concordance with the device instructions and previous studies [37-39].

Figure 2. Placement of the Fitbit Charge 6, activPAL3 micro, and ActiGraph LEAP.

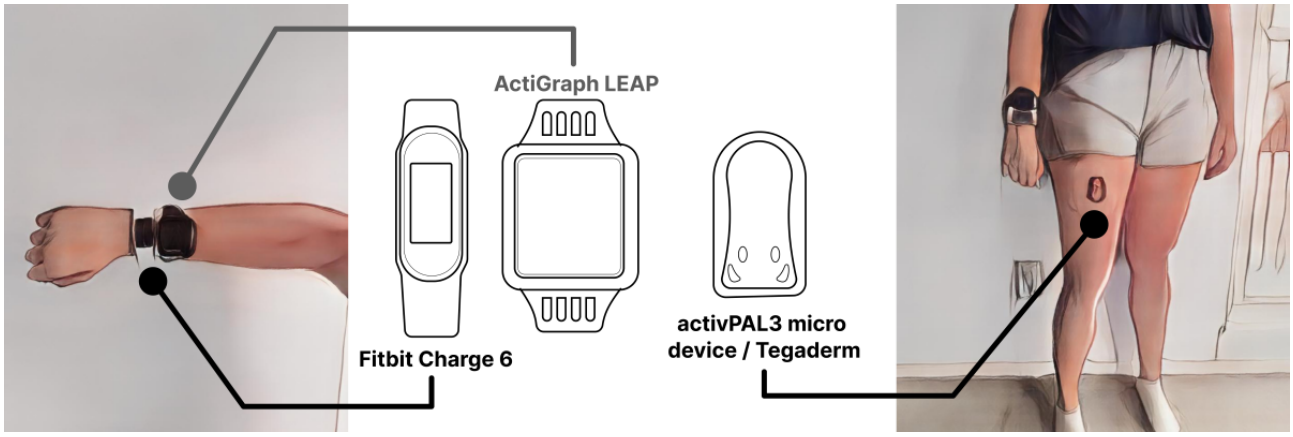

Movement and Posture Change Assessments

Following device placement, a battery of tests will be administered (Figure 3) that aligns with validated protocols from previous wearable device studies [20,21].

First, a series of variable-time walking tests will be administered. A 10 m walking track will be prepared and marked (Figure 4A). Participants will be instructed to walk for 5 seconds (repeated 3 times), then for 15 seconds (repeated 3 times), and then for 30 seconds (repeated 3 times) for 9 trials (Figure 4B). Step counts from the Fitbit device will be recorded at the beginning and end of each trial. If participants reach the end of the 10 m track, they will be instructed to turn around and continue walking in the opposite direction.

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Figure 3. In-laboratory data collection. SPPB: Short Physical Performance Battery.

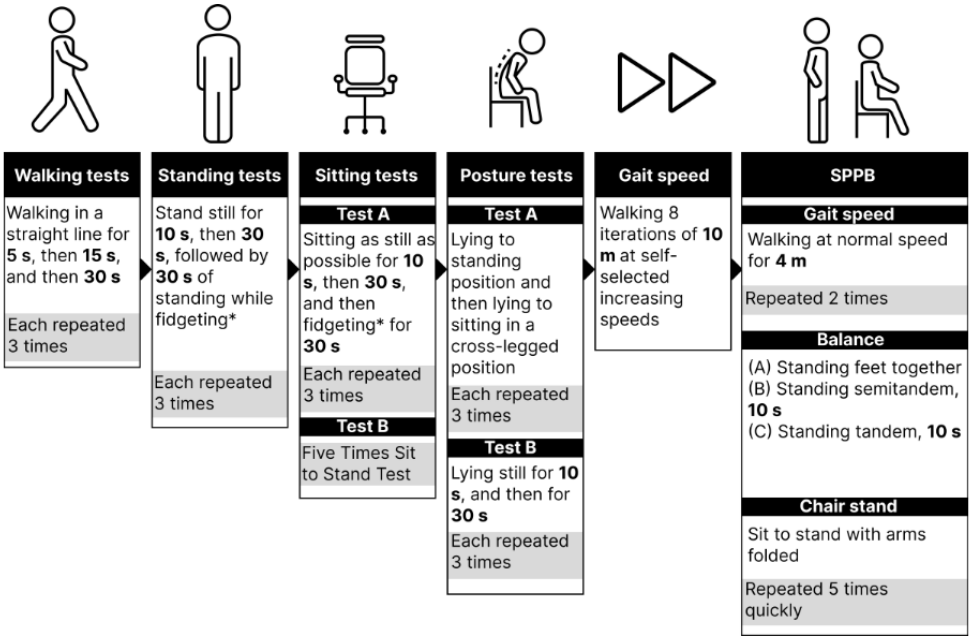

Figure 4. Various data collection setups.

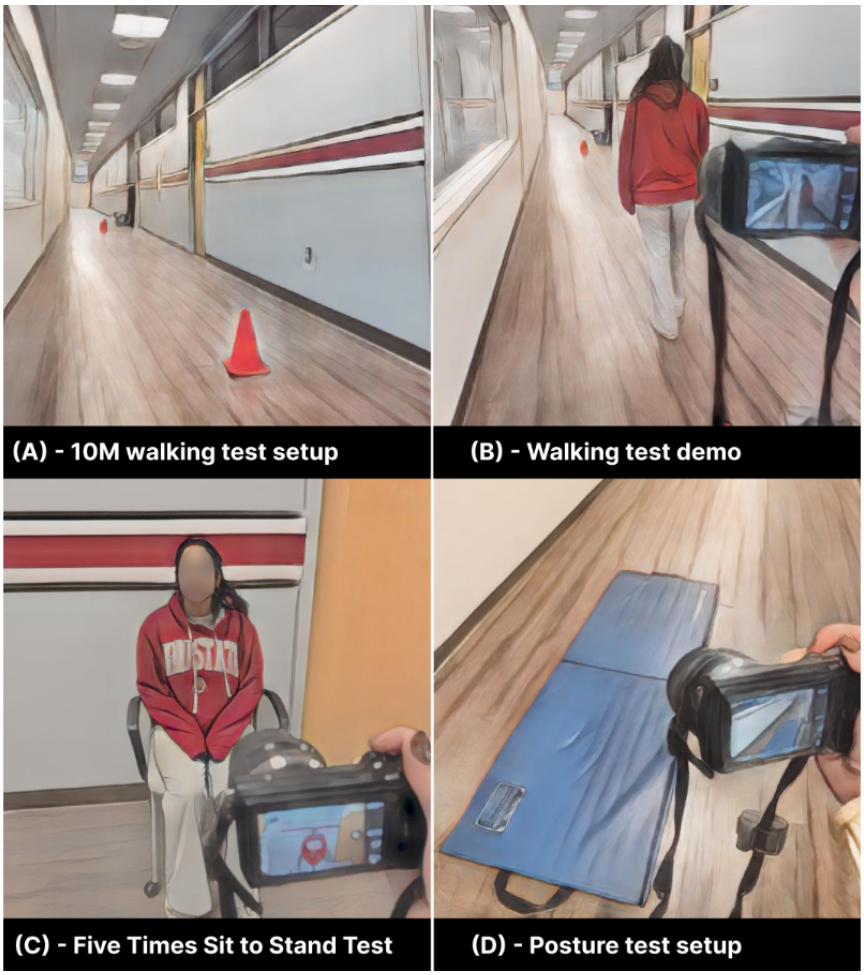

Next, a series of variable-time standing and sitting tests will be administered. First, participants will be instructed to stand as still as possible for 10 seconds (3 trials) and then for 30 seconds (3 trials). Then, the participants will be asked to stand while fidgeting for 30 seconds (3 trials). Following the standing tests, the procedure will be repeated with the participant seated in a chair. The participant will be told to sit as still as possible for 10 seconds (3 trials) and then 30 seconds (3 trials). Then, the participants will be asked to sit while fidgeting for 30 seconds (3 trials).

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After the variable-time standing and sitting tests, the five times sit to stand test will be administered. Participants will be instructed to sit in a chair with their backs against the back of the chair (Figure 4C). They will be instructed to cross their arms across their chest, repeatedly stand, and sit for 5 iterations. The time when the participants achieve the standing position on the fifth repetition will be recorded. This test assesses functional lower extremity strength, transitional movements, balance, and fall risk [40].

Following the Five Times Sit to Stand tests, a series of posture change tests will be administered. A thick cushioned mat will be used to alleviate participant burden during this portion of the test to increase participant comfort (Figure 4D). First, participants will be instructed to lie flat on their backs and change their posture to a standing position in any way they can (3 trials). Second, participants will be instructed to lie flat on their backs and change their posture to a cross-legged sitting position in any way they can (3 trials). Third, participants will be instructed to lie as still as possible, flat on their backs, for a 10-second interval (3 trials). Fourth, participants will be instructed to lie as still as possible, flat on their backs, for 30 seconds (3 trials).

Upon the conclusion of the posture change tests, a 10 m gait speed test will be conducted to test the reliability and accuracy of step count measurements at varying walking speeds. Participants will be instructed to walk the length of a 10 m marked walking track at 8 self-selected speeds. Participants will be instructed to walk at the slowest speed during the first trial and gradually speed up in each subsequent trial, with the eighth trial representing the fastest speed. Step counts will be manually recorded from the Fitbit device before and after each of the 8 trials. The final assessment conducted is the Short Physical Performance Battery. The Short Physical Performance Battery is a widely used battery of tests and examinations to assess balance, gait, strength, endurance, and overall lower extremity function [41]. The test examines the ability to stand with feet together side-by-side, in semitandem, and tandem positions; the time to walk 10 m; and the time to rise from a chair and return to the seated position 5 times.

Free-Living Measurement Procedures

Overview

After the in-laboratory protocol, participants will be instructed to wear the Fitbit Charge 6, ActiGraph LEAP, and activPAL3 micro for 7 continuous days (not including the day of the in-laboratory visit) to validate the Fitbit Charge 6 measurements in a free-living environment.

Wear Protocol

In total, 7 days and nights for data collection were chosen, given that previous studies have routinely demonstrated that a 7-day monitoring period provides enough days to achieve a daily intraclass correlation of >80% while capturing both weekday and weekend behavior [42]. Participants will be instructed to always wear the activPAL3 micro and to remove the Fitbit Charge 6 and ActiGraph LEAP when bathing and swimming (but to keep the devices on while showering). Notably, the Fitbit Charge 6 and ActiGraph LEAP do not retain charge for the entire 7-day period. Therefore, patients will be instructed to remove the 2 devices upon depletion of charge and to charge each device for 1 hour. Moreover, the activPAL3 micro does not suffer from such battery-life complications.

Monitor Attachment and Participant Instructions

Participants will be instructed on proper wear and application techniques for each device when attached during the in-laboratory protocol. Before leaving the facility, participants will also be given detailed wear instructions (Multimedia Appendix 5). The instruction sheet details the charging and wear information, as well as the contact information of study researchers, to minimize participant burden. The instruction sheet also contains contact information for the research team in the case of adverse events. Furthermore, the activPAL3 micro requires the use of adhesives to stay attached to the participant, and 4 sets of replacement Tegaderm adhesive patches will be provided to each participant. Notably, previous studies have indicated that participants (and particularly those with more sensitive skin, as may be seen in patients with cancer) may experience contact dermatitis from the Tegaderm adhesive used to attach the device [43]. To proactively address potential skin sensitivity issues, kinesiology tape will be provided to participants as a supplemental alternative adhesive option alongside the Tegaderm patches. Providing an alternative method of wearing devices increases wear compliance and reduces participant discomfort during the free-living protocol. Chargers will be provided for both the Fitbit Charge 6 and ActiGraph LEAP.

Finally, in addition to wear instructions, chargers, and replacement Tegaderm and kinesiology tape, participants will also be provided with a sleep and nonwear log to record all periods of sleep and periods when any of the devices are removed (Multimedia Appendix 6). This log will help verify valid periods of wear time during the free-living period.

Post–Free Living Protocol Survey Procedures

Overview

Upon conclusion of the 7-day free-living protocol, a series of surveys will be emailed to the participant to evaluate the participant's HRQoL, sleep, symptom burden, and acceptability of the Fitbit Charge 6. These instruments were selected to collect self-reported data corresponding to the period during which participants wore the activity monitor. The collected data will then be used to analyze the relationship among HRQoL, symptom burden, sleep quality, and accelerometry-determined PA. Furthermore, sensitivity analyses will be conducted using these data to assess the impact of these factors on the validity and reliability of the Fitbit device. After completion of the surveys, participants will be instructed to mail the 3 devices back to the laboratory using a provided prepaid envelope. Upon receipt of the devices, a US $60 electronic Amazon gift card will be emailed to the participant as compensation for study participation.

Instruments and Surveys Administered

Study participants will complete several validated questionnaires: the FACT-G7 [31], the International Physical Activity Questionnaire–Short Form [44], the Epworth Sleepiness

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Scale [45], the Pittsburgh Sleep Quality Index [46], the Patient-Reported Outcomes Measurement Information System-29 (version 2.0) [47], and a 31-item technology acceptance survey adapted by Fioranzato et al [48] from Puri et al [49]. These questionnaires were chosen to describe the population and control for potential confounders (eg, symptom burden) that may impact our results.

Outcome Measures

The primary outcome measures that will be evaluated from the activity monitors are step count; posture and posture changes (activPAL3 micro only); and time spent in light, moderate, and vigorous PA. In the in-laboratory protocol, step count and active time from all 3 devices will be assessed against gold-standard video-recorded manual counting. The posture classification and posture change measurements of activPAL3 micro will similarly be validated against gold-standard video-recorded manual classification (as only the activPAL3 micro records posture and posture changes). In the free-living protocol, measurements of step count and time spent in PA intensities (light, moderate, and vigorous) from the Fitbit will be validated against those recorded by the ActiGraph LEAP and activPAL3 micro.

To account for potential confounding effects, a series of survey-measured outcome measures will also be collected. Before wearable-device data collection, HRQoL will be evaluated across multiple domains. Cancer-related symptoms and concerns, with emphasis on fatigue and ability to enjoy life, will be assessed using the FACT-G7 [31]. General HRQoL will be measured across 5 dimensions (mobility, self-care, usual activities, pain and discomfort, and anxiety and depression) using the EQ-5D-5L [32]. Physical, psychological, social, and role functions will be evaluated using the Functional Status Assessment, a modified version of the Functional Status Questionnaire [33]. Perceived stress levels will be measured using the Perceived Stress Scale, which categorizes stress as low (0-13), moderate (14-26), or high (27-40) based on experiences over the previous month [34]. These measures were included because previous research has shown that HRQoL and mental state can influence movement patterns, potentially affecting activity monitor assessments [50-52].

After the conclusion of the free-living portion of the study, HRQoL will be remeasured using the FACT-G7 survey [31]. PA levels and SB, including time spent sitting, walking, and in various activity intensities, will be assessed using the International Physical Activity Questionnaire–Short Form [44]. Sleep parameters will be evaluated using 2 instruments: the Epworth Sleepiness Scale, which measures general daytime sleepiness, and the Pittsburgh Sleep Quality Index, which generates scores for 7 sleep-related domains (quality, latency, duration, efficiency, disturbances, medication use, and daytime dysfunction) and a global sleep quality score [45,46]. The Patient-Reported Outcomes Measurement Information System-29 will be used to assess overall symptom burden across 8 domains: physical function, anxiety, depression, fatigue, sleep disturbance, social role participation, pain interference, and pain intensity [47]. Wearable tracker acceptance will be evaluated across 6 key dimensions: perceived usefulness, perceived ease of use, privacy concerns, perceived risks, facilitating conditions, and equipment characteristics, using a validated survey adapted for older adult populations [48].

Data Processing and Quality Control

Immediately upon the receipt of the devices, preliminary data quality control checks will be conducted to ensure that no technical issues resulted in missing or rogue data during the laboratory-based or free living–based data collections as well as proper wear compliance for each device during the field-based data collection. The ActiGraph and activPAL3 micro acceleration data will be checked to determine if the devices are being worn correctly or upside down (as inversion interferes with posture detection), and data will be corrected, when necessary, by inverting them. This is important to note, given that once the data are inverted, they cannot be fed back into the proprietary analysis program and will need to be analyzed using an algorithm developed in-house. Wear compliance will be determined through different approaches across devices. The ActiGraph and activPAL3 micro wear time will be assessed using validated movement-based algorithms [53,54]. Because the Fitbit device does not provide epoch-level activity count data, wear time will be determined using the availability of photoplethysmography heart rate readings, consistent with previous studies [55].

Video data will be considered the gold standard for all laboratory-based validation analysis. For each activity performed by participants in the laboratory, a trained human rater from the research team will manually determine and count each step taken. For movement and posture classification, video data will be organized into 1-second windows for comparison to ActiGraph and activPAL3 micro measures and classified by the human rater as either “active” or “static,” and also as “upright,” “sitting,” “lying down,” or “postural transitions.” Fidgeting while sitting and standing will be categorized as an activity by the rater. The human rater will also manually determine step counts for each activity from the video data.

Similar to the video data classification, accelerometer data from the ActiGraph and activPAL3 micro devices will be organized into 1-second windows. One-minute epochs are the shortest epoch lengths for which the Fitbit data are available to us, and there is no standardized method of human rater classification of activity from video data in 1-minute epochs for activities that last only a small number of seconds. Therefore, the ActiGraph will be used as the criterion measure to evaluate the reliability and validity of the Fitbit device to identify movement and activity intensity levels. Fitbit step counts will be counted by a study team member by manually recording the step counts recorded on the device interface at the start and end of each activity. This will allow us to directly evaluate the agreement of step count measures from all 3 devices to the gold standard video data.

Statistical Analysis

We will evaluate the validity and reliability of each of the 3 devices following the Food and Drug Administration’s guidance on patient-reported outcome (PRO) measurement instruments as outlined in the study by Byrom et al [56]: (1) content validity,

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(2) reliability assessment, (3) criterion validity, and (4) ability to detect change.

Content Validity

How useful and meaningful these devices are to the patients will be evaluated based on evidence from the peer-reviewed literature, in addition to insights from the wearable tracker acceptance survey administered to patients upon completion of our study.

Reliability Assessment

During in-laboratory data collection, intradevice reliability will be assessed by comparing ActiGraph and activPAL3 micro device agreement with the gold standard video data across repeated trials by each participant. For the Fitbit device, intradevice reliability will be assessed by comparing Fitbit agreement with the ActiGraph across repeated trials by each participant. Interdevice reliability will be assessed using the Bland-Altman method and intraclass correlation analyses to compare (1) the total time spent in each posture or movement type as determined by both the accelerometers and video observation [26], (2) the Fitbit and ActiGraph devices' estimations of movement and different activity intensity levels in 1-minute epochs, and (3) step counts as determined by all 3 devices and video observation. Limits of agreement from the Bland-Altman plots will be used as an additional indicator of reliability in addition to intraclass correlation.

During free-living data collection, interdevice reliability of the Fitbit for measures of active time, step count, and time spent in different activity intensity levels will be compared to the ActiGraph and activPAL3 micro devices using Bland-Altman analyses and intraclass correlation analyses.

In-Laboratory Criterion Validity Assessment

The validity of the ActiGraph and activPAL3 micro devices to properly identify different postures and movement will be assessed with agreement (calculated using the Bland-Altman method), sensitivity, specificity, and positive predictive value (PPV) using video data as the gold-standard criterion measure. Sensitivity will describe the percentage of an observation category that is correctly detected by the accelerometers or the ratio of true positives to the sum of true positives and false negatives. Specificity will describe the percentage of observations not belonging to a category that are correctly identified as not belonging or the ratio of true negatives to the sum of true negatives and false positives. PPV will provide the percentage of true positives that is identified when compared to the total number of true positives and false positives determined by the accelerometers. Validity of the Fitbit device to properly identify movement in 1-minute epochs will be assessed with agreement, sensitivity, specificity, and PPV against 2-criterion measures: active time classification in 1-minute epochs from ActiGraph and activPAL3 micro. ActiGraph and activPAL3 micro step counts will be validated against the steps counted manually from the video data for each participant. Agreement, sensitivity, and PPV will be used to assess the research-grade activity monitors' abilities to accurately detect steps. As mentioned earlier, Fitbit step counts will be evaluated for accuracy against the video data by agreement only, as the validity of each individual step cannot be determined due to the available data granularity.

Moreover, 95% limits of agreement and CIs will be used to determine if there are significant differences in reliability and validity measures among all devices in both the in-laboratory and free-living data collections. In the Bland-Altman plots, systematic error is present if the mean is >0 or <0. Systematic error is considered significant if both repeatability coefficients are on the same side of 0. Linear regression analyses will be used to identify any existing proportional bias.

Ability to Detect Change

While a full evaluation of the ability to detect change in outcome measures is out of scope for this study due to the cross-sectional study design, we will calculate the SE of measurement for all intradevice or interdevice assessments. This will inform the ability to detect a minimal detectable change.

Ethical Considerations

The Ohio State University Cancer Institutional Review Board reviewed and provided initial approval on January 4, 2024 (2023C0190). All participants will provide informed consent before participating in this study. Informed consent materials will be provided in both digital and printed mediums (if requested) and in both written and verbal formats. Informed consent will review, in detail, the study design, components of the study, study duration, right to withdraw from the study, potential risks of participation, protection against risk, and the rights of human research participants. This process will also include the signing of the HIPAA (Health Insurance Portability and Accountability Act) waiver, permitting researchers to review and screen medical records. All patient-identifying information will be kept secure in REDCap. All research data will be anonymized and stored in encrypted Ohio State University Wexner Medical Center–managed hard drives to ensure the highest level of data security and privacy protection. Fitbit API keys will be stored in the laboratory on a single, encrypted machine. For access to Fitbit API data, a custom software solution will be used that only stores API access keys on a local machine. Upon receipt of the devices, a US $60 electronic Amazon gift card will be emailed to the participant as compensation for study participation.

Results

Data collection is still ongoing. In total, 11 participants have enrolled in the study as of December 2024, with both in-laboratory and free-living data collection completed for 7 (64%) participants. On average, the enrolled participants are aged 63.0 (SD 7.8, range 50.0-73.0) years. Moreover, 8 (73%) participants are women. Data analysis is being conducted simultaneously with ongoing participant enrollment. Participant enrollment is expected to conclude in 2025, and the first reported findings are expected to be disseminated by the end of 2025.

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Discussion

Summary of Validation Process

This study follows a comprehensive validation protocol designed to assess the accuracy and reliability of both commercial (Fitbit Charge 6) and research-grade activity monitors (activPAL3 micro and ActiGraph LEAP) in LC survivors. The process is divided into two main components: (1) an in-laboratory protocol and (2) a free-living environment protocol.

For the in-laboratory protocol, participants will be fitted with the Fitbit Charge 6, activPAL3 micro, and ActiGraph LEAP and will perform a series of controlled tasks, including walking, sitting, standing, and posture changes. Each task's outcomes, such as movement, step counts, and postural transitions, as recorded by the research-grade devices, and step counts, as recorded by the Fitbit devices, will be compared to DO (gold standard). This validates the devices' accuracy in a controlled setting. Following the in-laboratory session, the free-living environment protocol will involve participants wearing the Fitbit Charge 6, activPAL3 micro, and ActiGraph LEAP continuously for 7 days in their daily environments. The Fitbit's output (eg, activity intensity levels) will be compared to research-grade monitors to assess validity in the laboratory and the free-living environment.

Challenges in Validation for LC Survivors

Disease- and treatment-related symptoms of LC can influence PA levels in patients. Patients with LC frequently experience debilitating disease-related symptoms, including dyspnea (shortness of breath), cough, fatigue, anxiety, depression, insomnia, muscle wasting, loss of appetite, and pain [57], all of which could impact their ability to engage in PA. To accommodate for the physiologic challenges (eg, reduced pulmonary function) and symptoms inherent to LC, patients might adopt a sedentary lifestyle, which could further contribute to a decrease in cardiorespiratory failure and poorer symptom control, often coined as the "dyspnea-inactivity vicious circle" [58]. These symptoms are exacerbated during and after treatments such as chemotherapy and surgery, further limiting activity levels. Thus, LC survivors spend most of their waking days in sedentary pursuits. When they engage in PA, it is predominantly light-intensity PA (LIPA), with very little time spent in moderate-to-vigorous PA (MVPA), as measured in a previous study using a waist-worn ActiGraph GT3X+ [59]. D'Silva et al [59] objectively assessed SB and PA levels in LC survivors and found that LC survivors spent 9.8 hours per day in sedentary pursuits, 4.1 hours per day in LIPA, and only 14 minutes per day in MVPA. They found that time spent in LIPA was positively associated and sedentary time was significantly and inversely associated with HRQoL and fatigue. However, PA prescriptions for improving symptom burden are based on MVPA [60]. Given the detrimental effects that LC and related treatments have on survivors' HRQoL, identifying ways to enhance the HRQoL and reduce symptom burden in LC survivors is essential. Using commercial activity monitors is one way that we can start advancing our understanding of how varying PA patterns can influence health outcomes. Thus, there is a need to understand the accuracy and reliability of these devices to capture SB, LIPA, and MVPA levels in LC survivors to advance our understanding of the impact of physical behaviors on PROs.

Recommendations and Considerations for Validation Studies of Activity Monitors

This section, informed by findings from the ongoing study, summarizes recommendations and considerations for validation studies of activity monitors (Textbox 1).

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Textbox 1. Recommendations and considerations.

Validation protocol recommendations

- Use research-grade (activPAL3 micro and ActiGraph LEAP) and commercial (Fitbit Charge 6) monitors for cross validation in the laboratory and free-living environments.
- Use multiple research-grade devices (activPAL3 micro and ActiGraph LEAP) if feasible to ensure sufficient data collection during free-living validation.
- Direct observation in the laboratory should serve as the gold standard for validating physical activity (PA) measurements.
- Surveys should be administered to evaluate potential psychosocial and physiological confounders impacting PA behaviors.
- Provide participants with the ability to complete survey instruments at home to reduce the burden during in-laboratory visits.

Data management and software recommendations

- Use third-party tools or custom software to manage data.
- Store application programming interface keys on local, secure machines to minimize the risk of data breaches, or use a secure third-party Fitbit data access vendor such as Fitabase.
- Create laboratory-administered accounts when using consumer-grade activity monitors to minimize the risk of data breaches.
- Freeze firmware on research-grade devices to prevent inconsistencies from software updates.
- Adjust sampling rates for devices based on the length of the free-living observation period.
- Test all devices and software before launching the study.

Participant enrollment recommendations

- Recruit 30% more participants to account for noncompliance and data collection errors.
- Partner with medical professionals to understand disease- and treatment-related factors that could impact the behavior being evaluated (eg, PA) and to support recruitment efforts.

Device handling and wear recommendations

- Synchronize devices' time settings for accurate data matching and log this using a secure electronic database (eg, REDCap [Research Electronic Data Capture; Vanderbilt University]).
- Minimize variation caused by body placement by placing all monitors in identical locations (eg, dominant vs nondominant wrist) when feasible.
- Provide participants with sleep and nonwear logs to validate sleep-based metrics and periods of nonwear.
- Evaluate additional environmental factors impacting the device's performance (eg, temperatures).
- Provide a prestamped envelope to reduce participant burden once the data collection is complete, and provide additional tape to seal the envelope to avoid loss of devices in transit.
- Permit participants to wear water-resistant devices while showering to reduce the burden.

Participant comfort recommendations

- Demonstrate how to properly use (eg, wear and charge) the wearable and provide instructions to reduce any negative experiences (eg, confusion and anxiety).
- When applicable, provide alternative adhesives (eg, kinesiology tape instead of Tegaderm) for participants to increase comfort and improve device wear compliance.

Statistical recommendations

- Perform preliminary checks on data for compliance and wear accuracy during (if possible) and immediately after receiving the devices.
- Consider extending the data collection period from 7 days to 10 days. This would provide more variability in daily activity patterns, especially capturing potential differences between weekdays and weekends.
- After data collection, follow up with participants to debrief about their experience wearing the devices, focusing on any difficulties encountered.

When designing validation protocols for activity monitors, a combination of research-grade devices such as the activPAL3 micro and ActiGraph LEAP, along with commercially available devices such as the Fitbit Charge 6, should be used to ensure robust cross validation in both controlled laboratory settings and free-living environments. DO is often considered the gold standard for assessing the accuracy of WAMs due to its accuracy and objectivity and should be implemented whenever possible [20]. It allows researchers to record PA behaviors, such as steps, distance, or activity duration, with high fidelity and without relying on potentially flawed device algorithms or self-reported data. Unlike wearables, DO is independent of biases caused by

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sensor misalignment, body size, skin tone, or activity type. It also provides rich contextual information about activities, such as intensity, posture, and transitions, which devices may not fully or accurately capture. However, DO has limitations, including being labor intensive, requiring considerable time and resources, and being restricted to controlled settings or small sample sizes. There is also potential for observer bias if strict protocols are not followed. Because of these challenges, many validation studies (such as ours) combine DO with other methods, such as accelerometer-based measures, video analysis, or doubly labeled water, to comprehensively evaluate wearable performance. In addition, to improve the data quality, the activities chosen for the in-laboratory protocol must represent those that occur in the real-world environment for the population being studied, as accuracy is influenced by shorter task segments and slower and higher gait velocities. Moreover, some validation studies use treadmills during the in-laboratory procedures, which may impede individuals from walking naturally and at their normal walking speed. As stated in the Free-Living Measurement Procedures section, many psychosocial and physiological factors may confound PA levels and the ability of the device to capture information accurately, such as mental and physical PROs (eg, fatigue and pain). Thus, researchers should administer surveys to participants to assess potential. We recommend allowing participants to complete these before or after the appointment to reduce the burden during the in-laboratory visit.

From a data management perspective, using third-party tools or custom software to handle device data is advisable, ensuring that API keys are stored securely on local machines to minimize the risk of data breaches. At the same time, researchers should aim to maintain consistency by freezing the firmware on research-grade devices to avoid measurement variability caused by software updates. To promote interoperability, common standards for storing mobile health data, such as Fast Healthcare Interoperability Resources, Health Level 7, and open mobile health schemas, should be used to enable consistent data exchange and integration across platforms and systems [61]. Finally, one of the most important practices is to test all devices thoroughly before the study commences.

Regarding participant recruitment, we recommend planning for the possibility of having to enroll 30% more participants than initially required to account for potential noncompliance and data collection errors. Collaborating with medical professionals will (1) enhance recruitment and (2) provide insights into disease- and treatment-related factors that may influence PA behaviors, ultimately impacting the device's ability to capture physical behaviors. Recruitment could be enhanced by leveraging the patient–health care provider relationship by having the health care provider present the study to the patient during their encounters. In addition, the health care provider can help prescreen participants given their understanding of participants' eligibility related to personal (eg, age, sex, and willingness to participate in the research study) and clinical factors (eg, ability to walk independently and disease status), which can reduce the number of eligibility screen fails and burden on the research team.

Proper device handling is crucial; synchronizing time settings across devices and documenting this information in a secure electronic database (such as REDCap) ensures accurate data matching. Multiple research-grade monitors should be considered for free-living conditions to guarantee continuous data collection, especially given battery limitations. Batteries can be limited by the participant's baseline activity levels or the use of an activity monitor (eg, tracking activities and scrolling through its features). Cold temperatures can also diminish battery function, so it is essential to consider this depending on the geography and season where these monitors are being used. Participants should be provided with sleep and nonwear logs to help validate metrics related to sleep and periods of nonwear, and additional factors, such as environmental conditions, should also be evaluated for their impact on device performance. For water-resistant devices, we recommend allowing participants to shower while wearing the devices, as this simplifies wear instructions and reduces participant burden.

Finally, participant comfort must be prioritized to improve compliance. For example, to improve the chances that the participant adheres to the wear protocol, we have found that it is important to provide participants with clear demonstrations on how to wear and charge the devices and provide alternative adhesives (eg, kinesiology tape in addition to Tegaderm) to minimize discomfort and align with their preferences (ie, Tegaderm can create a waterproof barrier that allows users to wear the devices during activities involving water). Statistically, researchers should perform preliminary checks on the data for compliance and wear accuracy, both during the study and immediately after receiving the devices. Extending the data collection period from 7 to 10 days can also capture more variability in daily activity patterns, especially distinguishing differences between weekdays and weekends. Pre–data collection reminders about the appointment as well as reminding them of key activities (eg, returning the device and survey completion) can improve participant compliance. Post–data collection follow-up with participants could also be beneficial, allowing an additional opportunity to gather feedback on their experience with the devices, address any issues encountered during the study, and review the monitor wear log.

Integration and Impact of Commercial Activity Monitors in Health Care and Patient Management

The integration of commercial activity monitors into health care holds significant promise, particularly in enhancing patient outcomes and supporting the long-term management of chronic conditions such as cancer. Commercial wearables such as Fitbit and other accelerometer-based devices have demonstrated their potential in monitoring PA, circadian rhythm, sleep, and other vital health metrics, providing real-time patient and clinician data. In cancer care, including clinical trials, wearables are increasingly being used to monitor and support the delivery of PA interventions aimed at improving health outcomes (eg, HRQoL) during and after treatment, as shown by studies across cancer sites (ie, breast, gastrointestinal, lung, and gynecologic) [62]. These devices provide increased accessibility, ease of use, and the ability to gather health data outside clinical settings in near real time.

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One notable advantage of commercial wearables is their ability to seamlessly integrate into patients' daily lives, offering a nonintrusive and ecologically valid approach to monitoring activity and other health metrics. These data can be used to tailor interventions, improve patient adherence to exercise regimes, enhance symptom tracking, and detect adverse events related to the disease and treatment [62,63]. Electronic health record (EHR) systems such as Epic already incorporate wearable data through API integrations, allowing clinicians to view patient-generated digital health data. This capability enhances the continuity of care by providing a comprehensive view of patient health, particularly between clinical visits [5]. In addition, insurance companies such as United Healthcare and Humana incentivize the use of wearables by offering rewards and health-tracking programs that integrate wearable data into personal health records. These initiatives promote proactive health management, encouraging patients to engage with their health data and use them to inform daily health behaviors [5]. In addition, the potential to link wearable data with PROs and leverage machine learning approaches enables a more holistic view of a patient's health, offering predictive insights that extend beyond PA patterns to include mental health and HRQoL [62,63].

However, several considerations must be made when using wearables in health care. One challenge is adherence, as adherence rates vary widely across studies, with patients sometimes wearing devices inconsistently [62,64,65]. This inconsistency can skew data and make it difficult to draw accurate conclusions about a patient's health over time. Therefore, it is important to standardize what is considered a valid day for PA measures, often denoted as at least 10 hours of wear per day [64]. The variability in measurement accuracy across different devices presents a notable limitation, particularly for complex metrics such as MVPA. The reliability of MVPA data is crucial, as it is the foundation of the Physical Activity Guidelines for Americans and is directly linked to health outcomes [66]. Depending on the device (brand, model, and firmware) and population, studies have shown variable accuracy in tracking activity in free-living conditions between commercial monitors and research-grade devices in PA metrics such as step counts and moderate-to-vigorous activity (often overestimated in those with mobility issues) [64,65,67,68]. Therefore, while commercial wearables offer a promising tool for monitoring patient health, standardized data collection and interpretation protocols are needed to ensure their reliability in clinical settings.

The future of commercial wearables in health care largely depends on their seamless integration into broader health systems, mainly by incorporating wearable data into EHRs. As EHRs evolve, the ability to merge real-time data from wearables with clinical records could provide clinicians with continuous, detailed insights into a patient's health status, enabling more personalized care and timely interventions (eg, to support unmet needs) [5,69]. This integration is especially promising in oncology, where wearables are explored in clinical trials to monitor treatment-related outcomes and improve patient management. Studies have shown a growing interest in using wearables to track PA, circadian rhythms, and other health metrics in patients with cancer undergoing treatment [62,63]. As technology continues to evolve, commercial wearables have the potential to significantly contribute to the move toward precision medicine by collecting real-world, continuous data that can be used to tailor clinical care and interventions.

Study Protocol Strengths and Limitations

This study presents several strengths. Building on previous research [20,21], this protocol addresses inconsistencies in metrics, wear time, and definitions of valid data by providing extensive supplementary materials, including API code, wear instructions, nonwear logs, and consent forms, to promote standardization and reproducibility. A key feature of the study is its combination of laboratory-based validation, using DO as the gold standard, with assessments in real-world, free-living conditions. This dual approach enhances the reliability and applicability of the findings. In addition, the study focuses on LC survivors, a high-prevalence but underresearched population, recognizing their unique challenges. Rigorous methods, such as freezing firmware and software updates, are used to minimize measurement variability, and this protocol includes tracking nonwear periods to ensure comprehensive data collection and insights into wear compliance. Despite its strengths, this study also has limitations. It does not evaluate device accuracy during active cancer treatments, such as chemotherapy or radiation therapy, with the exception of specific cases, such as TKIs, which may miss crucial activity changes during these periods. While the study duration is standard, it is relatively short, limiting the assessment of device reliability and ability to detect change as well as participant compliance over longer periods in real-world conditions. Furthermore, the findings may be influenced by environmental and contextual factors, such as temperature, humidity, and daily routines, which were not thoroughly examined.

Conclusions

This paper provides a comprehensive protocol for validating consumer-grade and research-grade WAMs in LC survivors, addressing a critical gap in the literature. By combining rigorous laboratory-based assessments with real-world, free-living evaluations, this protocol highlights the strengths and limitations of these devices in capturing PA and SBs in a uniquely vulnerable population. The inclusion of LC survivors underscores the importance of tailoring validation methods to the specific needs and challenges of underrepresented groups in health research. While this study offers valuable insights into wearable device performance, further research is needed to explore device reliability over extended periods, during active cancer treatments, and under diverse environmental conditions. These findings provide a foundation for future studies aiming to standardize validation protocols and advance the integration of wearable technologies in oncology care, ultimately supporting improved health outcomes for cancer survivors.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist based on the SPIRIT guidelines is available in Multimedia Appendix 7.

Authors' Contributions

RMB conceived the study idea, interpreted data, wrote and revised the manuscript, provided funding, and supervised the project. RS conceived the study idea, conducted data and statistical analysis, wrote the software used in the study, assisted with patient enrollment, and wrote and revised the manuscript. CJP conceived the study idea, enrolled patients, and wrote and revised the manuscript. MKT conceived the study idea, assisted with patient enrollment, assisted with data interpretation, and wrote and revised the manuscript. ZLC, CMH, JY, PW, FJP, EDP, and VL participated in scientific discussions and wrote and revised the manuscript. EF conceived the study idea, conducted data and statistical analysis, interpreted data, wrote and revised the manuscript, and supervised the project. RMB serves as the corresponding author. All authors reviewed and approved the final version of the manuscript.

Conflicts of Interest

EDP is a multiple principal investigator of grants to the institution not related to this work from Genentech, Pfizer, AstraZeneca, and Guardent Health and is on advisory boards for GSK and Merck. All other authors declare no conflicts of interest.

Multimedia Appendix 1
Study material used.
[DOCX File , 692 KB - resprot_v14i1e70472_app1.docx]

Multimedia Appendix 2
Telephone interview and script.
[DOCX File , 20 KB - resprot_v14i1e70472_app2.docx]

Multimedia Appendix 3
Consent documentation.
[DOCX File , 29 KB - resprot_v14i1e70472_app3.docx]

Multimedia Appendix 4
Fitbit application workflow.
[DOCX File , 917 KB - resprot_v14i1e70472_app4.docx]

Multimedia Appendix 5
Activity monitor wear instructions.
[DOCX File , 212 KB - resprot_v14i1e70472_app5.docx]

Multimedia Appendix 6
Sleep and nonwear diary.
[DOCX File , 22 KB - resprot_v14i1e70472_app6.docx]

Multimedia Appendix 7
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOC File , 139 KB - resprot_v14i1e70472_app7.doc]

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Abbreviations

API: application programming interface
DO: direct observation
EHR: electronic health record
FACT-G7: Functional Assessment for Cancer Therapy–General 7
HIPAA: Health Insurance Portability and Accountability Act
HRQoL: health-related quality of life
LC: lung cancer
LIPA: light-intensity physical activity
MVPA: moderate-to-vigorous physical activity
PA: physical activity
PPV: positive predictive value
PRO: patient-reported outcome
REDCap: Research Electronic Data Capture
SB: sedentary behavior
TKI: tyrosine kinase inhibitor
WAM: wearable activity monitor

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Protocol

Technology Effects and Child Health: Wellness Impact and Social Effects (TECHWISE): Protocol for a Prospective, Observational, Real-World Study

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Abstract

Background: There has been controversy over the extent to which technology use in general—and social media exposure specifically—may be associated with adverse youth mental health outcomes. To date, studies have generally been small and exploratory, relying on youth self-reports to characterize technology and social media use patterns. The goal of this study is to explore the associations between objectively collected data, gathered through a commercially available app, and youth mental health outcomes.

Objective: The broad goal of this study is to characterize the association between objectively measured technology/social media use and a range of mental health–related outcomes. Three specific aims will be initially addressed. First, we aim to quantify the association between objectively measured smartphone use and measures of well-being. Second, we aim to differentiate types of engagement—specifically, the types of content consumed versus the overall time spent on the device—and examine their association with outcomes. Third, we aim to identify moderating factors, such as age, gender, and socioeconomic status, that might influence these relationships. A secondary broad objective of this research is to establish a freely available data resource that can be accessed by qualified investigators to address a much wider range of questions in the future.

Methods: Up to 1000 male, female, and nonbinary youth aged 8-17 years (inclusive), along with their primary caregivers, will be enrolled in the study. Youth participants must have their own dedicated iOS- or Android-based smartphone or tablet, and both they and their parents must be willing and able to download and install the data collection app on their devices. The study is open to all US-based participants who meet these 2 criteria. Following electronic consent (eConsent), participants and their caregivers will complete a range of baseline measures electronically, including assessments of psychiatric and social functioning, as well as measures of loneliness, digital stress, and disordered eating. Caregivers will be asked to provide information on the participant's health and mental health history. Youth and caregivers will then complete a similar battery of assessments 1, 2, and 3 months after baseline. Youth participants will also respond to daily questions about their mood, stress, physical activity, and sleep. Both youth and their caregivers will be compensated for completing measures at each time point. The data collection app gathers a wide range of daily data from the participant's device, including temporal patterns of use, the number and frequency of various app usage, social interactions within apps, and keystroke data. A variety of analytic methods will be used to address key questions related to how technology and social media use are associated with mental health and wellness outcomes.

Results: Enrollment for this study began on November 13, 2024. As of May 20, 2025, a total of 106 participants and their caregivers had consented to participate and provided baseline data. An additional 203 children and parents have consented and are currently undergoing eligibility verification and enrollment. Initial data analysis is anticipated to begin in late autumn 2025 or winter 2026, with the expected publication of initial findings in spring 2026.

Conclusions: This study will be among the largest to date to collect both objective device usage data and validated, clinically relevant outcome measures. In accordance with our data-sharing policies, any qualified investigator will be able to access the study data, provided appropriate steps are followed.

Trial Registration: ClinicalTrials.gov NCT06664944; https://clinicaltrials.gov/ct2/show/NCT06664944

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International Registered Report Identifier (IRRID): DERR1-10.2196/69358

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KEYWORDS

youth; adolescence; social media; mental health; technology use

Introduction

Over the past 15 years, there has been a dramatic rise in technology use among children and adolescents, particularly following the introduction of smartphones [1]. Nearly 95% of adolescents report using social media [2]. By age 17, the vast majority of youth in the United States have access to a smartphone and report spending hours on it daily. Nearly 50% say they are on social media and other smartphone-based apps "nearly constantly" [3].

Concurrent with these changing patterns of technology use by young people, there has been widespread concern about increases in youth mental health problems, including self-harm/self-injurious behavior, rates of mood and anxiety problems, and self-reported loneliness. Even in the decade preceding the onset of the COVID-19 pandemic, high school students reported increases in feelings of sadness and hopelessness, along with higher rates of suicidal ideation and behavior [4]. Since 2020, there is considerable evidence that rates of mental health challenges among youth, such as depressive and anxiety symptoms and self-harm, have continued to rise. The scope of these challenges prompted both the US Surgeon General and the American Academies of Pediatrics and Child and Adolescent Psychiatry to issue proclamations calling for a range of measures to address the problems [5,6]. Yet, more than 3 years later, there is little evidence that rates of mental health challenges among youth are abating.

Given the temporal congruence between the rise of technology and social media use and the reported increases in youth mental health challenges, much research and public discussion have centered on how these trends may be related. The link between social media use in particular and adverse mental health outcomes has drawn national attention, including a US Congressional hearing with the chief executive officers of the top social media companies [7], and 2 additional reports from the US Surgeon General specifically highlighting potential harms of social media use on youth mental health [8,9]. Most recently, the Governor of California signed a bill banning social media apps from sending notifications during school hours and late at night, and is considering a bill that would require a mental health warning label on social media apps [10].

Despite the highly publicized concern over the link between tech/social media use and mental health outcomes in young people, the published evidence is mixed. Many studies report associations between social media use and mental health problems [11-13], while others find weak or no relationship—or even a positive link [14-16]. One reason for these mixed findings is almost certainly that the relationship between smartphone use and mental health outcomes is not straightforward. A myriad of person-centered factors (eg, age, sex/gender identity, preexisting mental health condition, reward sensitivity), content exposure (eg, inappropriate material, cyberbullying), and nondevice activities (eg, in-person connection, physical activity) can influence the links between smartphone use and mental health outcomes [17,18].

One common feature of studies examining the mental health impacts of smartphone or social media use on young people is the nature of data collection. The literature in this area typically relies on self-reports of usage patterns by youth themselves or their caregivers [19]. However, the correlation between self-reported social media use and objectively derived use (from the devices themselves) is modest. For example, a meta-analysis of 47 studies found a correlation of 0.35 between self-reported and objectively measured social media use [20]. Given the limitations of data collection in previous studies, there is general agreement—both in the published literature and in reports from the Surgeon General and other public sources—on the need for more objective data to better understand how technology and social media use may influence mental health outcomes in young people.

The overall goal of this longitudinal, observational study is to examine the association between youth technology and social media use and mental health outcomes, including mental health and wellness, physical activity, digital stress, and loneliness, as well as daily ratings of mood, stress, and sleep. Our initial analysis, described in this protocol, will focus on 3 primary aims. First, we aim to quantify the association between objectively measured smartphone use and measures of well-being. Second, we aim to differentiate types of engagement—specifically, the types of content consumed versus the overall time spent on the device—and their associations with outcomes. Third, we aim to identify moderating factors, such as age, gender, and socioeconomic status, that might influence these relationships.

A second broad goal of this research is to establish a data set that can be used by a wide range of investigators to address a variety of questions over time. The specific aims outlined above represent our initial priorities for data analysis, but our study design will support the exploration of a myriad of additional questions.

This research will extend previous work in 3 important ways. First, device usage data will be collected using a commercially available product (the Aura app), which provides an objective measurement of a wide range of youth digital activity, including patterns of time spent on various apps throughout the day and overnight, social interactions, messages sent across platforms, and derived sentiment from outgoing messages. Second, rather than examining the relationship between device usage and mental health outcomes solely at the population level, we will leverage the unique combination of objective smartphone data

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and daily subjective well-being measures to adopt an idiographic approach. This allows us to use individuals as their own baselines, capturing within-person changes in smartphone use to predict corresponding shifts in well-being over time. Third, the granularity of the data will allow us to identify distinct usage patterns across children and adolescents. By including person-centered factors (eg, age, gender, and race/ethnicity) alongside both device usage and off-device behaviors, the data could help uncover protective and moderating effects within broader behavioral trends. These refined approaches—leveraging both the depth and breadth of objective and subjective data on smartphone use and well-being—aim to clarify this controversial topic and provide a foundation for a wide range of subsequent research, clinical interventions, and policy development.

Methods

Ethics Approval

The study is approved by the WCG IRB Copernicus Group Institutional Review Board (study approval number 20243405; approval date: September 25, 2024) and has been registered on ClinicalTrials.gov (identifier NCT06664944). Informed consent and assent will be obtained from all eligible participants. Copies of the institutional review board approval notification, as well as the current versions of the parent consent and child assent forms, are included in Multimedia Appendices 1 and 2, respectively. Although the data for this study are not deidentified, all study-related data (eg, outcome measures, app data) will be stored separately from any identifying information for each participant. Individual-level participant data will not be disclosed in any subsequent manuscript or presentation. Participants will receive US $200 per child and US $100 per parent/caregiver for completing all aspects of the research study, for a total compensation of US $300. In addition, active participants who enroll and complete the baseline assessments are eligible to receive a US $25 bonus for each successful participant referral—up to 10 additional eligible participants who consent, enroll, and complete baseline assessments. This referral program is limited to 10 referrals, for a maximum of US $250 per participating dyad.

Study Design

This is a prospective, observational study. Figure 1 provides a schematic of the study, including participant incentives.

Figure 1. TECHWISE (Technology Effects and Child Health: Wellness Impact and Social Effects) study schematic. EDC: electronic data capture.

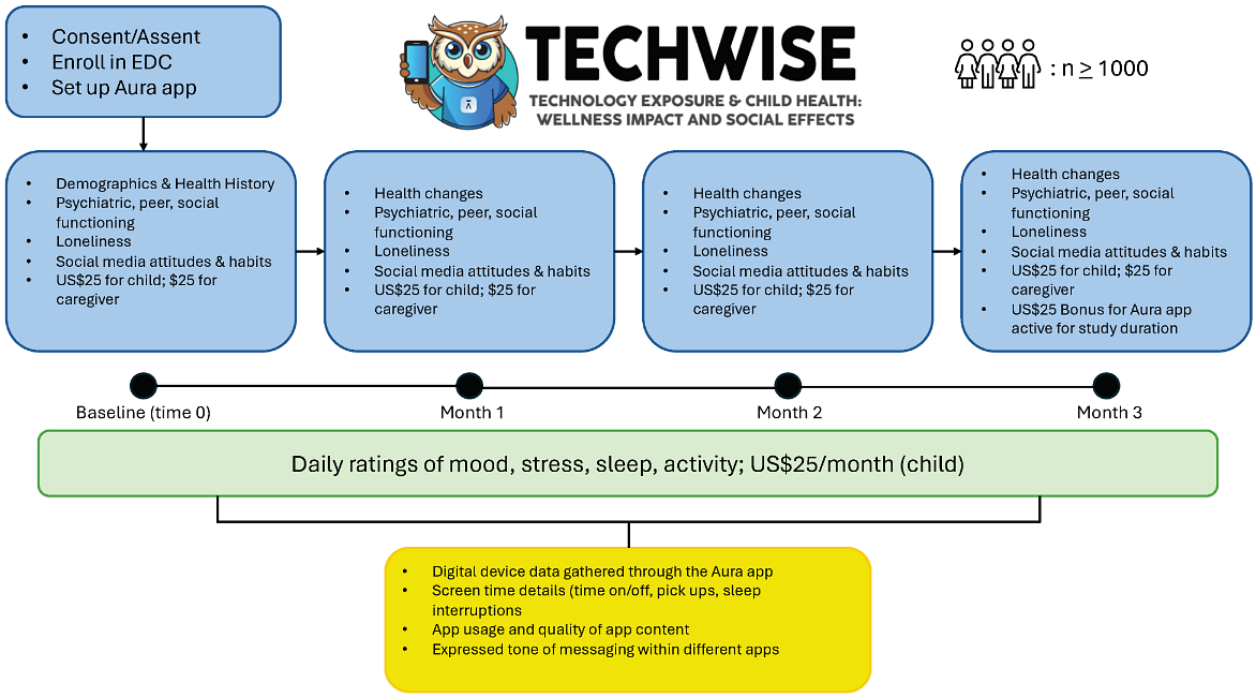

Setting

The study will be conducted completely remotely in the United States.

Participants

The initial enrollment goal for this study is 1000 participants; however, depending on the pace of enrollment, a larger sample may be recruited. Data analysis is expected to begin in the spring or early summer of 2025.

Participants for this prospective cohort study must meet the following eligibility criteria:

- Child participants will be male, female, or nonbinary individuals between the ages of 8 and 17 years (inclusive).
- A parent or authorized legal guardian must be willing to provide informed consent, and the child must be willing to provide assent.
- Both the parent/authorized legal guardian and the child must own a mobile device that either already has the Aura app installed or is capable of installing and running the Aura app and the appropriate parental control features.
    - The parent/authorized legal guardian and child must be willing for the child to use a dedicated device for

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the duration of the study (ie, the device cannot be shared with a sibling or other family member).
    - Multiple children from the same family may be eligible to participate, provided that each enrolled child uses a dedicated device, is able to complete outcome assessments independently, and the parent/authorized legal guardian is able to complete assessments for each enrolled child.
- Both the parent/authorized legal guardian and the child must be willing to share data collected through the Aura app and related device apps.
- The consented parent/authorized legal guardian and child must maintain active Aura accounts throughout their study participation (ie, they must activate the appropriate features and keep them enabled for the duration of the study).
- The consented parent/authorized legal guardian and child must be able to follow written and verbal instructions in English, as assessed by the principal investigator or study coordinator.
- The consented parent/authorized legal guardian and child must be able to comply with all testing and study requirements.

Participants will be excluded if they do not meet all of the above inclusion criteria or if they have any medical conditions or social circumstances that, in the opinion of the investigator, may confound study data or assessments. This exclusion criterion is included to address unforeseen circumstances that could impact a participant's ability to complete assessments or result in atypical device use, potentially leading to misleading data. Any exclusions under this criterion will be reported with the study results.

Study Recruitment

Given the remote nature of the study, any US-based participant/caregiver dyad who meets the eligibility criteria can enroll via the study landing page [21]. Active recruitment of participants and their parents/caregivers will be conducted virtually across the United States, with efforts focused on enrolling a representative and thus generalizable sample of youth and their parents with respect to race/ethnicity, geographic location, and socioeconomic status. We will monitor enrollment periodically and adjust recruitment efforts as needed to maximize generalizability. Details on the sample demographics and potential limitations related to generalizability will be reported in subsequent papers and presentations. Specific recruitment sources to be used include the following: (1) social media advertisements; (2) current Aura customer base; (3) other selected media activity and announcements (Aura-sponsored marketing activities, Aura Parent Community site (Digital Parenthood [22]), which is free and open to the public; (4) schools/parent-teacher association partnerships; (5) partnerships with academic researchers; and (6) word of mouth.

Study Enrollment

Interested parents/caregivers and their children will be directed to the study landing page [21]. The landing page will provide detailed information about study participation and enrollment procedures. It will also prominently display the eligibility criteria to help parents/caregivers and children determine their interest and eligibility for the study.

If they affirm eligibility and interest, they will be directed to an electronic consent (eConsent)/assent page. All data collection, including eConsent/assent, will be conducted using a commercially available electronic data capture system (OpenClinica; OpenClinica, LLC). Participants will be enrolled fully remotely (direct-to-participant) and monitored by the central principal investigator (SHK).

Once participants and caregivers assent/consent to participate in the study, they will be prompted to schedule an online visit with the study team (using Google Calendar [Google LLC] and Zoom [Zoom Communications, Inc]) to complete enrollment. This virtual visit will allow study staff and participants to complete the following 4 tasks to verify eligibility and confirm that inclusion criteria have been met: (1) verify parent/caregiver identity; (2) review and countersign consent/assent forms; (3) set up the Aura app on parent and child participant devices; and (4) confirm participants' preferred methods of contact for study measures. Participants who are unable to schedule a live session will have the option to verify their identity and complete the Aura app setup remotely (ie, by uploading a picture of identification and other materials for identity verification, and sending screenshots of the successfully installed Aura app). Study staff will also be available to answer any questions about study objectives and activities during the remote session or via email or phone.

Participants and their caregivers will receive free Aura app subscriptions for the duration of the study. Current Aura users will be credited with 3 months of subscription time on their accounts.

Parents/caregivers and child participants will also be compensated for completing study-related activities. The total possible compensation over the duration of the study will be US $200 for child participants and US $100 for caregiver participants, amounting to US $300 per caregiver-child dyad. Participants will receive payment for each completed task (see Table 1). Active participants will also be offered an optional US $25 referral bonus, payable to the referring parent, for each new eligible parent-child dyad they refer who subsequently enrolls and completes baseline assessments.

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Table 1. Summary of participant incentives.

Activity/incentive trigger	Participant	Amount[a]	Timing	Requirement
Baseline forms	Caregiver	US $25	Baseline	Timely completion within the assessment window
Baseline forms	Child	US $25	Baseline	Timely completion within the assessment window
Monthly forms	Caregiver	US $25/month	Months 1, 2, and 3	Timely completion within the assessment window
Monthly forms	Child	US $25/month	Months 1, 2, and 3	Timely completion within the assessment window
Daily ratings	Child	US $25/month	Months 1, 2, and 3	20 or more ratings completed within the month
Maintain active Aura App	Child	US $25	End of the study	App remains active on their device throughout the entire study duration
Maximum total (tasks)	Caregiver	US $100	Study duration	All required tasks complete
Maximum total (tasks)	Child	US $200	Study duration	All required tasks complete
Maximum total per dyad	Both	US $300	Study duration	All required tasks complete

[a]Additional referral bonus: US $25 per referred dyad that enrolls and completes baseline, up to 10 referrals, for a maximum of US $250.

Participant Withdrawal or Discontinuation

Participants are free to withdraw from the study at any time, for any reason, without prejudice. They will be provided with a study email address and phone number to communicate their decision to discontinue participation.

Participants who are withdrawn or discontinued after enrollment will be sent an exit survey. Those who are ineligible to enroll will receive an email explanation.

Study Procedures

Baseline and Follow-Up Visits (Months 1, 2, and 3)

Following the enrollment visit, baseline assessments will be sent electronically to participants via their preferred method of contact (email or SMS text message; Table 2). Participants and caregivers will receive email or SMS text message prompts to complete online surveys as outlined below. In general, assessments will be completed monthly. Beginning at baseline, child participants will receive daily email or SMS text message prompts to rate their mood, stress, sleep, and physical activity.

Baseline data collection includes (1) sociodemographic information about the child (eg, age, gender, race, ethnicity, education status, individual education plans, school technology and phone policies, and Zip code); (2) sociodemographic information about the caregiver (eg, age, date of birth, for study compensation eligibility, gender, race, ethnicity, highest education completed, and annual income); (3) medical history for the child (eg, current/past mental health diagnoses, current/past other health diagnoses, prescribed medications, over-the-counter medications, current/past other treatments, and behavioral habits [exercise/activity level, nicotine use, alcohol use, caffeine use, and sleep]); and (4) general ("How did you hear about us?" and "If referred, who referred you?")

Outcome assessments at baseline include Kiddie Computerized Adaptive Testing (K-CAT), The EPOCH Measure of Adolescent Well-Being, The University of California, Los Angeles (UCLA) Revised Loneliness Scale, The Eating Disorder Screen for Primary Care, The Digital Stress Scale (DSS), The Child & Adolescent Social and Adaptive Functioning Scale, The Adolescent Sleep Wake Scale, The World Health Organization (WHO)-5 Well-Being Index, The K6 Psychological Distress Screening questions, The Social Media Screening Questionnaire/HEADS-4 (Home, Education/Employment, Activities, Drugs/Substances, Sexuality, Safety, Suicide/Mental Health, Social Media/Screen Use)—Child version, The Social Media Screening Questionnaire/HEADS-4—Caregiver version, The Social Media Use Scale, and The Child Safety and Well-Being Survey.

The following assessments will be administered monthly after baseline: K-CAT; The EPOCH Measure of Adolescent Well-Being; The UCLA Revised Loneliness Scale; The DSS; The Child & Adolescent Social and Adaptive Functioning Scale; The Adolescent Sleep Wake Scale; The WHO-5 Well-Being Index; The K6 Psychological Distress Screening questions; and changes in health status (new diagnoses, new treatments [medication or otherwise], hospitalizations/emergency department/urgent care visits).

The following measures will be completed at 3 months after baseline: The Eating Disorders Screen for Primary Care, The Social Media Screening Questionnaire—Child version, The Social Media Screening Questionnaire—Caregiver version, The Social Media Use Scale, and The Child Safety and Well-Being Survey.

Measures will be sent electronically via SMS text message or email with unique participant links directing caregivers and participants to the dedicated study site for completion, except for the K-CAT, which will be completed on the Adaptive Testing Technologies platform.

At each monthly time point, parent participants will be asked to verify that the Aura app is active and running on both their device and the child participant's device. Additionally, the parent will respond to a single 5-point Likert scale question assessing the child's receptivity to having the Aura app on their device.

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Table 2. Schedule of assessments.

Schedule	Baseline	Month 1	Month 2	Month 3
eConsent	Parent/caregiver, child	N/A[a]	N/A	N/A
Identity verification and Aura app setup on parent and child participant devices	Parent/caregiver and child	Parent/caregiver and child	Parent/caregiver and child	Parent/caregiver and child
Demographics/health/medical history	Parent/caregiver	N/A	N/A	N/A
Medical/treatment change	N/A	Parent/caregiver	Parent/caregiver	Parent/caregiver
The K-CAT[b] battery	Parent/caregiver and child	Parent/caregiver and child	Parent/caregiver and child	Parent/caregiver and child
The EPOCH[c] Measure of Adolescent Well-Being	Child	Child	Child	Child
The UCLA[d] Loneliness Scale Version 3	Child	Child	Child	Child
The Eating Disorders Screen for Primary Care	Child	N/A	N/A	Child
The Digital Stress Scale	Child	Child	Child	Child
The Child and Adolescent Social Adaptive Functioning Scale	Child	Child	Child	Child
The Adolescent Sleep Wake Scale	Child	Child	Child	Child
The WHO[e]-5 Well-Being Index	Child	Child	Child	Child
The K6 Psychological Distress Screening questions	Child	Child	Child	Child
The Social Media Use Screening Questions	Parent/caregiver and child	N/A	N/A	Parent/caregiver and child
The Social Media Use Scale	Child	N/A	N/A	Child
The Child Safety and Well-Being Survey	Parent/caregiver	N/A	N/A	Parent/caregiver
The daily report (day 0, daily)	Child	Child	Child	Child

[a]N/A: not applicable.

[b]K-CAT: Kiddie Computerized Adaptive Testing.

[c]EPOCH: Engagement, Perseverance, Optimism, Connectedness, Happiness.

[d]UCLA: University of California, Los Angeles.

[e]WHO: World Health Organization.

Participant Enrollment and Engagement Support

Participants will receive ongoing communication throughout the enrollment process and at each study time point to provide support. During enrollment and baseline assessments, participants will receive email or SMS text message reminders from the Technology Effects and Child Health: Wellness Impact and Social Effects (TECHWISE) study team regarding parent/child consents, the virtual enrollment visit, baseline surveys, K-CAT paired interviews, and daily ratings for child participants. Throughout the study, the TECHWISE study team will update a community page to provide news, research updates, and study support to enrolled participants. Additionally, the team will distribute a monthly newsletter to maintain participant engagement and keep communication channels open.

Participants may use Google Calendar, Zoom, and the TECHWISE study team email to schedule 1-on-1 support throughout the study. Additionally, parent participants will receive a study tracker at each monthly time point, listing the study activities for both parent and child participants.

Digital Activity Data Collection

The Aura product (current version 3.34.2) is a consumer-focused digital security app available to any smartphone user with iOS (Apple Inc) or Android (Google LLC) operating systems. When activated as part of the Family Plan subscription (used in this study), the app continuously monitors and collects data on a child's smartphone or tablet device usage. The data gathered include, but are not limited to, the following: time spent on the device; specific app usage patterns (including which app, total time, time of day used, etc); contact information (individuals with whom the child interacts through a range of apps and messaging platforms); content consumption (viewing history, search history, etc); and keystroke data (including overall sentiment).

As product updates and releases occur throughout the study, participants and their parents/caregivers will continue participation using the latest version operating on their devices. The commercially available version of the app is used for all data collection in this study, with no modifications. The app's Privacy Policy and Terms of Service are included in Multimedia Appendix 3.

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Outcome Measures

Demographic/Medical History

This form, completed by parents at enrollment, captures a range of information about the child participant, including age, race/ethnicity, sex/gender identity, family composition, household income, school/educational status, and medical/mental health history (including diagnoses and treatment). Additionally, information about family mental health history is collected.

Medical/Treatment Change

This form, completed by parents/caregivers at months 1-3, inquires about any changes in medical status or treatment over the past month, including inpatient/outpatient visits and changes in medication or other treatments.

The Kiddie Computerized Adaptive Testing (K-CAT)

The K-CAT is a suite of measures validated for assessing depression, anxiety, mania, attention-deficit/hyperactivity disorder, conduct disorder, oppositional defiant disorder, and posttraumatic stress disorder. It is the children's version of computer adaptive testing (CAT) based on multidimensional item response theory. The K-CAT includes both child self-report and parent ratings. The initial item responses are used to determine a provisional estimate of the child's standing on the measured trait, which is then used for subsequent item selection. Item Response Theory is a statistical theory and associated methodology that relates a series of item responses (binary, ordinal, or nominal) to 1 or more latent variables (eg, depression). The K-CAT has been validated against semistructured research interviews for youth aged 7-17 years. The full K-CAT takes an average of 7.56 minutes to complete for the child portion and 5.03 minutes for the caregiver portion [23].

The EPOCH Measure of Adolescent Well-Being

The EPOCH Measure of Adolescent Well-Being assesses 5 positive psychological characteristics: Engagement, Perseverance, Optimism, Connectedness, and Happiness. It extends Seligman's PERMA (Positive Emotion, Engagement, Relationships, Meaning, and Accomplishment/Achievement) theory to adolescents, aiming to identify traits that influence well-being in adulthood. The measure consists of 20 items, validated through factor analysis, and has demonstrated good reliability and validity across multiple samples. Respondents rate statements on a 5-point scale, with findings supporting its stability and predictive validity. The EPOCH takes an average of 5 minutes to complete [24].

The UCLA Loneliness Scale Version 3

The UCLA Loneliness Scale Version 3 is a psychometrically valid self-report measure of loneliness and social isolation. It is a 20-item inventory that uses a 4-point rating scale (1=never to 4=always) to assess how often a person feels disconnected from others. The scale includes 10 reverse-coded items. The measure is highly reliable, demonstrating strong internal consistency and test-retest reliability over a 1-year period [25]. It has been validated for use with teens and adults and takes approximately 3-5 minutes to complete.

The Eating Disorders Screen for Primary Care

The Eating Disorders Screen for Primary Care is a brief, 5-item questionnaire recommended for use in primary care settings and published by the National Eating Disorders Collaboration. Each item is answered with a "yes" or "no" response, and a "yes" response to any item is considered indicative of risk for disordered eating [26].

The Digital Stress Scale

The DSS assesses the stress individuals may experience when engaging with social media. Item content is based on a theoretical model of the negative effects of social media use, as well as insights from focus groups. The DSS consists of a 24-item inventory using a 5-point Likert-type scale across 5 factors: Approval Anxiety, Availability Stress, Connection Overload, Fear of Missing Out, and Online Vigilance. The DSS was developed from a preliminary theoretical model of digital stress [27] and validated through exploratory and confirmatory factor analyses [28,29]. It takes an average of 5 minutes to complete.

The Child and Adolescent Social and Adaptive Functioning Scale

The Children and Adolescent Social and Adaptive Functioning Scale (CASAFS) was designed to assess the social functioning of young people across 4 domains: school performance, peer relationships, family relationships, and home duties/self-care. The CASAFS is a self-report inventory consisting of 24 items that evaluate social functioning, defined as the degree to which individuals fulfill various roles in their lives. The CASAFS comprises 4 subscales that examine functioning in the 4 key social role areas relevant to children and adolescents. Six items were selected to reflect each of the 4 dimensions of social functioning. Participants are asked to respond to each social functioning item using a 4-point scale: 1 (never), 2 (sometimes), 3 (often), and 4 (always). Family relationship items include a fifth scoring category: "Does not apply to me." The questionnaire was designed so that the 1-4 ratings on the CASAFS could be summed across the 24 items to provide a total social functioning score ranging from 24 to 96, with higher scores reflecting a greater level of social functioning. Similarly, subscale scores can be calculated, with each ranging from 6 to 24. The internal consistency and 12-month test-retest reliability of the total scale were acceptable. A significant negative correlation was found between the CASAFS and a measure of depressive symptoms, indicating that high levels of social functioning are associated with low levels of depression. The assessment is validated for children aged 10-17 years and is estimated to take 8-10 minutes to complete [30].

The Adolescent Sleep Wake Scale

The Adolescent Sleep Wake Scale is a measure of behavioral sleep problems widely used in general adolescent populations and, more recently, in adolescents with specific comorbidities such as depression and chronic pain. The Adolescent Sleep Wake Scale is a 28-item measure scored on a 6-point rating scale that assesses sleep quality across 5 subscales: going to bed, falling asleep, awakening, reinitiating sleep, and returning to wakefulness, with adequate psychometric reliability [31].

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The measure is validated for 12-18-year-old adolescents to self-report monthly and takes less than 10 minutes to complete.

The WHO-5 Well-Being Index

The WHO-5 is a short questionnaire consisting of 5 noninvasive questions that measure respondents' well-being. The scale has adequate validity as a screening tool for depression and as an outcome measure in clinical trials. A systematic review of the literature on the WHO-5, conducted in accordance with PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines, yielded 213 articles. The review demonstrated that the WHO-5 has adequate validity and is a sensitive and specific screening tool for depression [32].

The K6 Psychological Distress Screening Questions

The K6 is a 6-item screening scale for psychological distress. It was developed, along with the K10, for the redesigned US National Health Interview Survey. The K6 demonstrates good precision in the 90th to 99th percentile range of the population distribution and consistent psychometric properties across major sociodemographic groups. The K6 has a strong ability to discriminate between the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition cases and noncases, making it suitable for use in general-purpose health surveys [33].

The Social Media Screening Questionnaire (Child and Caregiver Versions)

These questions are based on a series developed to systematically assess social media use and misuse in primary care and are recommended by The American Academy of Pediatrics Center of Excellence for Social Media and Youth Mental Health [34]. They extend the HEADS-4 survey, which guides the assessment of Home, Education, Activities, and Drugs in primary care. For the purposes of this study, these screening questions have been adapted to gather information from caregivers. The questions address which apps youth use, the amount of time spent online daily, whether respondents believe the youth spends too much time online, whether social media use impacts self-confidence, and whether the youth has directly experienced cyberbullying or sexual exploitation.

The Social Media Use Scale

The Social Media Use Scale is a questionnaire used to measure individuals' social media use. It includes 22 items divided into 5 dimensions: social interaction, entertainment, information seeking, convenience, and social comparison [35]. The Social Media Use Scale is valid for individuals aged 12-30 years and takes 3-6 minutes to complete.

The Child Safety and Well-Being Survey

The Child Safety and Well-Being survey is a 9-question tool used to gather parent or legal guardian perspectives on their child's technology use, app use, and online safety and well-being. This survey is consistently used across Aura studies on family and child digital media use.

Daily Mood, Stress, and Sleep Report

Daily ratings of mood, stress, sleep, and physical activity will be completed by the child. For mood, stress, and sleep, a 0-100 sliding visual analog scale with descriptive anchor points will be used, where lower ratings reflect poorer mood, higher stress, or worse sleep. For the physical activity rating, participants will choose from a 5-point scale reflecting how much activity they engaged in over the past 24 hours: none, 0-30 minutes, 30 minutes to 1 hour, 1-2 hours, and more than 2 hours. At the end of each week, the daily report will include 3 questions asking the child to reflect on mood, stress, sleep, and physical activity over the course of the week.

Statistical Considerations

Specific Aims

Three specific aims will be initially addressed in this work (Textbox 1).

Textbox 1. Specific aims.

1. Quantify the association

   Determine the strength and direction of associations between objectively measured smartphone use (eg, total screen time, frequency of use, specific app engagement) and self-reported well-being measures (eg, Kiddie Computerized Adaptive Testing [K-CAT], World Health Organization-5 Well-being Index [WHO-5]).

2. Differentiate engagement types

   Evaluate whether distinct aspects of smartphone engagement—specifically, the types of content consumed versus overall time spent on the device—show differential associations with well-being outcomes.

3. Identify moderating factors

   Investigate the extent to which key person-centered characteristics, including age, gender identity, and socioeconomic status, moderate the relationships observed between smartphone usage and well-being.

Statistical Analysis: Specific Objectives

Elastic Net Regression Modeling

We will employ penalized regression models to predict baseline self-report outcomes for well-being and mental health. Specifically, for each of the following outcome measures—the World Health Organization-5 Well-being Index (WHO-5) total score, the EPOCH Measure of Adolescent Well-Being total score, the K-CAT Depression Scale total score, and the UCLA Loneliness Scale total score—we will train an Elastic Net regression model using device usage features as predictors. To identify statistically significant predictors for each outcome, we will examine the coefficient estimates of the final trained model. Features with nonzero coefficients after Elastic Net

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regularization will be considered important predictors and explored further in post hoc analyses.

This approach will enable us to identify which specific aspects of smartphone usage are most strongly and statistically significantly associated with self-reported measures of well-being and mental health at baseline, directly addressing specific aim 1. Furthermore, by examining the patterns of significant predictors across the different outcome variables, we can gain insights into whether time- or content-based engagement metrics are differentially associated with well-being, contributing to specific aim 2. Additionally, by including potential moderators, we can begin to address specific aim 3.

The Elastic Net is a linear regression model that combines the penalties of both Lasso (L1) and Ridge (L2) methods. This approach is especially well-suited for data sets with many potentially correlated predictors, as it simultaneously performs variable selection—shrinking coefficients of irrelevant predictors to zero—and manages multicollinearity.

We consider an initial set of 21 features derived from device usage within the first 2 weeks of the study, proximate to the baseline outcome measures. Given the richness of the device usage data, there is no clear upper limit to the number of features that could be developed. However, 21 features were selected based on initial interest, divided between time-on-device metrics and content-specific engagement, in line with specific aim 2. Additional features such as age, gender identity, household income, and racial and ethnic background will be included to address specific aim 3.

Time on device features are (1) total daily screen time, (2) total daytime screen time, (3) length of screen time sessions, (4) number of problematic screen time sessions (2 or more consecutive hours), (5) length of breaks from device usage, (6) number of breaks from device usage, (7) total nighttime screen time, (8) frequency of late-night usage, (9) duration of usage (session lengths), (10) total opportunity for sleep (time offline in the sleep window), and (11) consistency in their nighttime device schedule.

Content-based features include (1) proportion of time spent on 6 categories, namely, social, social generative artificial intelligence (AI), gaming, generative AI, educational, and productivity; (2) frequency of using apps; (3) percentage of time with social AI experience for human-AI interactions; (4) number of messages sent on social platforms; and (5) ratio of consumptive versus interactive social interactions.

For each outcome variable, the Elastic Net model will be trained using 10-fold cross-validation. This robust method partitions the data into 10 equally sized folds. The model is trained on 9 folds and evaluated on the remaining fold, repeating the process 10 times so that each fold serves as the validation set once. This procedure provides a reliable estimate of the model's generalization performance and helps mitigate overfitting. During cross-validation, we will systematically sweep across a grid of Elastic Net hyperparameters: the mixing parameter (α), which controls the balance between L1 and L2 penalties (ranging from 0 to 1), and the regularization strength (λ), which scales the overall penalty. The optimal hyperparameters will be selected based on the mean squared error performance across the 10 validation folds. After identifying these optimal values through cross-validation, the Elastic Net model will be retrained on the entire data set. The resulting model will provide coefficient estimates for each of the 21 device usage features and other moderating features (age, gender identity, etc) in predicting the respective well-being or mental health outcome. To test for moderation, these additional features and their interaction terms will be included as independent variables in the Elastic Net model during fitting. Variables with nonzero coefficients will be considered significant, and their effects on the dependent variables (scores from the WHO-5, EPOCH, K-CAT, etc) will be further investigated by comparing models with and without these moderating factors.

Analysis Populations

The primary analysis population will include all participants enrolled in the registry who complete their baseline assessments and have at least 10 days of device usage data within a 14-day period (ie, up to 4 days of missing data within those 2 weeks). Additional analyses may be conducted on subgroups defined by baseline sociodemographic or clinical characteristics, technology use patterns (eg, high-frequency users, social media users), time of enrollment, and other factors.

Sample Size

The initial target enrollment for the study is 1000 participants with complete data for baseline and months 1-3. While we aim to explore a wide range of outcomes related to digital device usage and mental health, our initial analysis will focus on the specific aims outlined above.

To assess the appropriateness of this sample size for powering the planned analyses, we consider our initial set of 21 features. For a multiple regression model (of which Elastic Net is an extension), assuming a moderate effect size (R^2=0.13, Cohen f^2=0.15) between a well-being measure and 21 device usage–based predictors, a sample size of 160 participants is required to achieve 80% power. Our goal in enrolling additional participants in this ongoing study is to enable more fine-grained analyses of other research questions and to provide a resource for qualified investigators to explore a wider range of analyses (see the "Data Sharing" section).

Additional Possible Analytic Approaches

Beyond the specific aims noted above, the study design supports a wide range of questions related to the association between device usage and outcomes in youth. This section provides an overview of the general approach to statistical analyses—both quantitative and qualitative—that may be used to analyze the collected data. Given the exploratory, observational nature of the study, the data will allow for a wide range of questions to be addressed. Specific procedures will vary depending on the aims and data used in future publications.

The broad goal of this study is to characterize the association between objectively measured technology and social media use and a range of mental health–related outcomes. The initial specific objectives of the study are as follows:

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- To identify objectively measured patterns of technology and social media use in children and adolescents, and to assess whether important individual differences in use patterns over time exist based on various variables. These variables include, but are not limited to, age, sex/gender identity, race/ethnicity, geographic location, and presence of existing mental health diagnoses or treatment.
- To examine bivariate associations between technology use features and mental wellness and mental health outcomes.
- To develop preliminary predictive models using technology use and smartphone-derived parameters to predict point-in-time mental health outcomes, as well as changes over time.

Possible Analyses for Objective 1

We aim to identify objectively measured patterns of technology and social media use in children and adolescents, and to assess whether significant individual differences in use patterns over time exist based on various variables.

A range of descriptive analyses will be used to characterize the sociodemographic and other characteristics of the study population. For continuous variables, measures will include mean and SD, as well as median, minimum, maximum, and IQR, as appropriate. Categorical variables will be summarized using counts and percentages. To explore changes in the profile of participants entering the study over time, results may be stratified by enrollment date, and grouped by calendar month, quarter, or year. We will also examine patterns of technology and social media usage as a function of sociodemographic variables (age, sex/gender, etc). Additional analyses (eg, ANOVA, paired *t* tests) may be used to examine differences in usage patterns over time, both within and between participants.

Possible Analyses for Objective 2: Examining Bivariate Associations Between Technology Use Features and Mental Wellness and Mental Health Outcomes

Given the wide range of variables derived from the Aura app and the number of assessments collected, all analyses will be considered exploratory. As an initial step toward this objective, we will conduct simple bivariate analyses between technology use variables and mental health outcomes. Example questions include, but are not limited to, the following:

- Is the total device usage time measured at baseline associated with mental health outcomes, such as higher probabilities of mental health conditions, as measured by the K-CAT?
- Do baseline psychological distress (measured by the K6) or well-being (measured by the WHO-5) predict patterns of technology and social media use over time?
- Are temporal patterns of device usage (eg, increased evening or late-night use) associated with sleep or physical activity outcome measures?
- Does digital stress (measured by the DSS) mediate the relationship between device usage and mental health outcomes?

As more participants enroll over time, we will progressively be able to address more complex questions regarding device usage and changes in mental health–related outcomes. Examples of time-related outcomes we may measure include, but are not limited to, the following:

- Are there relationships between variability in daily mood, stress, or sleep and daily patterns of device usage?
- Do broad changes in device usage over weeks or months lead to changes in mental health–related outcomes (positive or negative), or vice versa?
- Are changes in health care utilization (medical events, changes in ongoing treatment, etc) associated with changes in device usage over time?

Possible Analyses for Objective 3: To Develop Preliminary Predictive Models Using Technology Use and Smartphone-Derived Parameters to Predict Point-in-Time Mental Health Outcomes, As Well As Changes Over Time

A wide range of analytic techniques will be used to develop and evaluate predictive models aimed at determining whether mental health–related outcomes and their changes over time can be reliably predicted from device usage data. Predictive modeling methods will start with standard statistical approaches (eg, multiple regression) and expand to include nonlinear techniques such as random forests and gradient-boosted regression. With up to daily sampling of some outcomes (mood, stress, and sleep) over a 3-month period and a sample size of 1000 participants, it will also be feasible to train neural network or deep learning models, including temporal models such as long short-term memory neural networks. Example tasks for these prediction models include, but are not limited to, the following:

Do patterns or changes in device-mediated social interactions predict the presence or severity of loneliness?

- Are specific patterns in keyboard data (eg, particular search terms, SMS text messaging sentiment) predictive of changes in mood or anxiety outcomes?
- Are patterns of keyboard activity associated with daily self-reports of mood, stress, or anxiety?
- Can patterns of device usage predict changes in health care utilization over time?

Results

The Checklist for Reporting Results of Internet E-Surveys (CHERRIES) has been included as Multimedia Appendix 4. Enrollment for this study began on November 13, 2024. As of May 20, 2025, a total of 106 participants and their caregivers have consented to participate and provided baseline data. An additional 203 children and parents have consented and are currently undergoing eligibility verification and enrollment. The anticipated date for initial data analysis is late autumn 2025 or winter 2026, with the expected publication of the initial analyses in spring 2026.

Discussion

Anticipated Findings

Despite public interest and academic research on smartphone usage and well-being in youth, critical gaps remain in the literature regarding (1) the scale of real-world data; (2) access

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to ethically gathered, objective smartphone usage data; and (3) the ability to combine large-scale objective data with validated outcomes to longitudinally assess the association between smartphone use and mental health and well-being.

Together, the strengths of this study design include:

- The ability to recruit a large and diverse sample size through a fully remote and virtual study.
- The ability to ethically collect a wide range of objective smartphone usage data longitudinally from participants who have provided informed consent/assent.
- The ability to combine daily subjective measures of well-being and displacement with objective measures of device usage.

We anticipate that the findings from this study will show that device usage in youth is associated with both positive and negative aspects of mental well-being, depending on the specific usage patterns analyzed (eg, time-based vs content-based) and person-centered factors (eg, age, race, gender). As such, this study design has the potential to clarify some of the inconsistencies previously reported in the literature. For example, while some studies have found associations between excessive social media use and adverse mental health outcomes, such as increased depression and anxiety, others have reported weak or null effects, or even positive associations, such as increased social connectedness [11,36-38].

Therefore, this study presents a unique opportunity to provide real-world insights into the complex relationships between smartphone usage and youth mental health and well-being.

Despite the potential strengths of this research, there are limitations that need to be considered. First, the requirement that youth participants own their own devices may limit the representativeness and generalizability of the sample. This concern is somewhat mitigated by reports indicating that the majority of children aged 11 years and older own a phone, with ownership rates increasing through the teen years and over time [3,39,40]. A second limitation that may affect the generalizability of the findings is that children's device usage could change as a result of app installation. For instance, parents may choose to implement time limits or content filters, which could restrict the applicability of the results to youth who use their devices without such restrictions. Additionally, given the remote nature of the study, we are unable to verify whether the device on which the app is installed for data collection is, in fact, the child's primary device. We ask parents and children to attest to this during the consent/assent process; however, we do not independently verify it. As such, this may also affect the generalizability or reliability of the findings. Finally, it should be noted that all authors of this protocol are full-time employees of the study sponsor, Aura, and no independent researchers were involved in the development or implementation of the study. Other tools are available for researchers to gather similar device usage data from youth smartphone or tablet activity—for example, the Effortless Assessment Research System (EARS) [41]—which has been used in previous studies [42,43].

Dissemination Plans and Future Directions

In addition to the stated goals of the overall study, an objective of publishing this protocol is to provide detailed information about the study design, allowing subsequent peer-reviewed papers and conference presentations to reference it as a source. Beyond the primary analyses described in this manuscript, the collected data will enable a wide range of additional questions and analyses. As described in the "Data Availability" section, the data set will be made freely available to qualified investigators who clearly articulate their research questions and analytical approaches, and who enter into an appropriate Data Use Agreement to ensure participant confidentiality, data security, and integrity.

Given the strong need for data on this important topic, this study is well-positioned to provide valuable new insights into the association between child device usage and mental well-being outcomes.

Data Availability

Data gathered in this study will be made freely available to qualified researchers from academic institutions, provided that appropriate data sharing and usage agreements are executed. Inquiries about data access can be directed to the primary author (SHK; scott@aura.com) or to KG (karen.goetz@aura.com). Alternatively, interested investigators may complete an online form to request access to the TECHWISE data.

Authors' Contributions

All authors contributed to the conceptualization, writing, editing, and methodology of this study. SHK was primarily responsible for funding acquisition and supervision, while KG led project administration.

Conflicts of Interest

SHK, JF, KG, and SAB are full-time employees of Aura and hold equity options. As the sponsor of this study, Aura employed all authors involved in the development of this protocol; no independent or unaffiliated researchers contributed.

Multimedia Appendix 1
Institutional review board-approved consent form.
[DOCX File , 40 KB - resprot_v14i1e69358_app1.docx]

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Multimedia Appendix 2
Institutional review board-approved assent form.
[DOCX File , 25 KB - resprot_v14i1e69358_app2.docx]

Multimedia Appendix 3
Sponsor privacy policy and terms and conditions for app usage.
[PDF File (Adobe PDF File), 362 KB - resprot_v14i1e69358_app3.pdf]

Multimedia Appendix 4
The Checklist for Reporting Results of Internet E-Surveys (CHERRIES) for internet-based studies.
[PDF File (Adobe PDF File), 61 KB - resprot_v14i1e69358_app4.pdf]

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Abbreviations

AI: artificial intelligence
CASAFS: Children and Adolescent Social and Adaptive Functioning Scale
DSS: Digital Stress Scale
eConsent: electronic consent
HEADS-4: Home, Education/Employment, Activities, Drugs/Substances, Sexuality, Safety, Suicide/Mental Health, Social Media/Screen Use
K-CAT: Kiddie Computerized Adaptive Testing
PERMA: Positive Emotion, Engagement, Relationships, Meaning, and Accomplishment/Achievement
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
TECHWISE: Technology Effects and Child Health: Wellness Impact and Social Effects
UCLA: University of California, Los Angeles
WHO: World Health Organization

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Protocol

Suicide Risk Screening in Jails: Protocol for a Pilot Study Leveraging the Mental Health Research Network Algorithm and Health Care Data

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Abstract

Background: Suicide in local jails occurs at a higher rate than in the general population, requiring improvements to risk screening methods. Current suicide risk screening practices in jails are insufficient: They are commonly not conducted using validated screening instruments, not collected by clinically trained professionals, and unlikely to capture honest responses due to the chaotic nature of booking areas. Therefore, new technologies could improve such practices. Several studies have indicated that machine learning (ML) models considerably improve accuracy and have positive predictive value in detecting suicide risk compared with practice as usual (PAU). This study will use administrative data and ML modeling to improve suicide risk detection at jail booking.

Objective: This study is primarily focused on gathering preliminary information about the feasibility and practicality of using administrative data and ML modeling for suicide risk detection but also incorporates elements of hypothesis testing pertaining to clinical outcomes.

Methods: The study uniquely contributes to our understanding of suicide risk by further validating an existing ML model developed and previously validated by the Mental Health Research Network using Medicaid outpatient health care claims data. This validation uses complete claims data on a sample of approximately 6000 individuals booked into 2 diverse jails in a midwestern state. This model validation uses 313 unique demographic and clinical characteristics from 5 years of historical health care data. It detects suicide risk in jails and postrelease by using merged jail, Medicaid, and vital records data. The study will use jail administrative data for September 1, 2021, through February 28, 2022; Medicaid records data for September 1, 2016, through March 31, 2023; and vital records data for March 1, 2022, through March 31, 2023.

Results: First, the algorithm will be validated on the data gathered for the jail sample using the C-statistic and area under the receiver operating characteristic curve. Second, the resulting model will be compared with the jails' suicide identification PAU to assess risk and detection of identified suicide attempts and deaths from intake through 120 days and 13 months after jail release. The funding timeline for this project is August 1, 2022, through July 31, 2025. The algorithm's predictions and actual event incidence will be linked and validated in the spring of 2025, with results ready for publication in the fall of 2025.

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Conclusions: The study will also investigate implementation factors, such as feasibility, acceptability, and appropriateness, to optimize jail uptake. Interview data on the implementation factors will be gathered in the summer of 2025, with expected dissemination in 2026. We hypothesize that a combination of intake screening PAU and the ML model will be the optimal approach, in that the combination will be more accurate and can have practical application in this context.

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KEYWORDS

suicide; suicide prevention; health risk behaviors; machine learning; jails

Introduction

Suicide Risk in Jails and Standard Screening Procedures

The most recent available data indicate that suicide is the leading cause of death among those incarcerated in jails, and the suicide rate among those detained in jails is approximately 4 times greater than those in the public [1,2]. Long-term trends suggest that suicide has been the leading cause of in-jail deaths from 2006 to 2016 following steady increases in suicide mortality since 2000, and it accounted for nearly 30% of all in-jail deaths in 2019 [3]. A period of incarceration is also associated with suicide mortality postrelease, as evidence indicates that the risk of suicide doubles after jail release [4].

Few jails effectively screen for suicide risk at jail booking. Due to the fast-paced booking process, most jails use nonstandardized, self-report, or single-item measures that can lack cultural sensitivity or are inappropriate for this setting [5,6]. Given that many jail booking areas are not private, individuals may be less forthcoming in reporting suicidal ideation to jail staff. Current suicide risk identification practices are insufficient given the impracticability of having clinically trained professionals conduct adequate assessments at booking. These deficiencies in suicide risk screening in jail settings exemplify the need to improve risk detection. Improved suicide risk identification could reduce the persistent missingness of behavioral health data in jail facilities [7] while mitigating the adverse impacts that suicide has on detainees, families, jail staff, and the community [8].

Machine Learning for Suicide Risk Screening

Machine learning is the basis for suicide risk identification models. Several studies have indicated that machine learning models considerably improve accuracy and have positive predictive value in detecting risk of suicide compared with practice as usual (PAU) [9-11]. Suicide risk identification via machine learning detection has already been applied in health care systems [9,12], psychiatric care [11], and cross-sectional [13,14] and longitudinal [15,16] study designs focused on suicide risk identification, with earlier estimates of suicide attempt and death accuracy ranging from the high 0.80s to low 0.90s, meaning predictions are accurate nearly 90% of the time [10]. Further, a recent systematic review of machine learning that was applied to predict suicide among psychiatric patients reported that predictive accuracy was reliably above 0.70—with 14 studies between 0.80 and 0.90 and 11 studies above 0.90 [11]. The systematic review by Pigoni et al [11] and meta-analysis by Ehtemam et al [9] demonstrated that the strongest associations of suicide included prior suicide attempts and behaviors [17,18] and diagnosis of major depressive disorder or borderline personality disorder, as well as historical psychiatric hospitalizations [11].

The Mental Health Research Network (MHRN) developed and validated a suicide risk identification machine learning model that detects suicide attempt and death risk based on historical health and insurer (including Medicaid) data [19]. Among a general population sample, the MHRN model has shown effectiveness at identifying increased risk for suicide attempts and deaths using general and behavioral health records and claims data across 7 health care systems [19] and from claims data alone [20]. The MHRN model generates a suicide risk score that can be used to alert health personnel to the possibility of heightened suicide risk and prompt further screening and service provision.

The MHRN model gathers 313 unique factors such as demographic and clinical characteristics from 5 years of historical health care data. The MHRN model outperformed other suicide screens and machine learning models with a C-statistic, area under the receiver operating characteristic (ROC) curve, of 0.853 (95% CI 0.849-0.857) compared with the Recovery Engagement and Coordination for Health-Veterans Enhanced Treatment (REACH VET) model, which has a C-statistic of 0.761 (95% CI 0.751-0.771) [21], with the top 5% of risk scores identifying over 43% of suicide attempts or deaths 90 days following a health care visit. The MHRN model includes a comprehensive set of clinical indicators, is intended to be used at the point of encounter, and shows promising results for improved suicide risk identification among a sample of the general population. A similar identification process for incarcerated individuals, available at jail booking, could help detect those at risk for in-jail and postrelease suicide attempts and deaths. Because there is no standardized process for identification of suicide risk across jails, an objective data-driven risk indicator would greatly enhance such screening.

Study Aims

Our protocol includes 3 interrelated aims. The first unique contribution this study makes to suicide risk identification is that it validates the MHRN model using retrospective data from approximately 6000 individuals booked into 2 geographically and demographically diverse jails in a midwestern state to assess model generalizability. Jail administration data will be linked with historic (ie, prebooking) Medicaid claims data so the MHRN model can generate suicide risk scores. Since Medicaid

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is the insurer for 73% of the jail population in the study's state [22], most of the jail population will be included in the analysis. The second aim seeks to compare the accuracy of the MHRN flag at identifying risk of suicide attempt and death to current suicide risk identification PAU over 120 days and 13 months from initial jail booking among individuals who have been released from jail. This involves merging jail records and prospective Medicaid, pharmacy, and vital records data to examine if the MHRN model improved suicide risk detection in jails and postrelease as compared with the jails' PAU. The research team hypothesizes that the MHRN model will be validated as an effective screening tool to detect risk for suicide attempts and deaths as evidenced by a C-statistic (area under the ROC curve) of at least 0.75 and a positive predictive value that exceeds the base rate of suicide attempts and deaths through 13 months postbooking [23]. The pilot testing is included in the third aim, which will evaluate implementation outcomes related to integrating the MHRN model in jails.

This pilot project benefits from having a substantive sample size that will allow for an evaluation of the implementation of the MHRN model in jails and to conduct hypothesis testing on select clinical outcomes. For instance, if the MHRN model improves jails' PAU, increased opportunities to connect individuals at risk of suicide with interventions to reduce suicide attempts and deaths in jail and postrelease will be created. The research team hypothesizes that more individuals with subsequent suicide attempts or deaths will be identified by the model or a combination of the model and screening versus screening only.

Methods

Overview

Two participating jails will provide data on booking and suicide risk identification PAU results for their jail population over a 6-month period (September 1, 2021, through February 28, 2022). To assess suicide risk, the MHRN model will be applied to 5 years of Medicaid encounter data prior to jail booking (September 1, 2016, through August 31, 2021). We will compare the accuracy of the MHRN model, the jail's screening PAU at identifying suicide attempts, and deaths in jail and over 13 months after jail release using Medicaid and pharmacy data for suicide attempts and vital records data for suicide deaths (both sources [Medicaid and pharmacy data] as well as vital records data: March 1, 2022, through March 31, 2023).

Ethical Considerations

The study was approved by the Wayne State University institutional review board (#22064717). Informed consent was waived because there is no more than minimal risk to the participants, participation in the study will not adversely affect their rights and welfare beyond data privacy and confidentiality, and the study could not practicably be carried out without the waiver. Data use agreements were legally established between the research team and entities providing personal identifiable information (PII). The final data set will be linked together using PII, and once verified, all PII will be destroyed. All data will be maintained on an encrypted and secure cloud server (Microsoft OneDrive) that only allows access to a small number of research team members.

Analytic Focus

National Center for Health and Justice Integration for Suicide Prevention (NCHATS) research studies are grounded in application of data analytic approaches to identify individuals at risk for suicide across different intercepts of the sequential intercept model [24]. This project focuses on suicide risk detection during incarceration, whereas other NCHATS projects focus on suicide risk detection and prevention before and after incarceration.

Jail County Sites

Two county jails are participating in the study. Jails were selected based on their varying geographic settings and jail populations. County A is a metropolitan-sized county on the west side of the state with a population of approximately 670,000 people. The jail has 1285 beds and booked 24,000 individuals in 2019. County B, on the east side of the state, is an urban county, with over 370,000 people. The jail had 404 beds and 8300 bookings in 2019. These jails vary in screening methods for suicide risk at jail booking, which reflects variability nationally. County A uses several scripted questions about current and past suicide ideation or attempts, and County B uses several scripted questions and a truncated version of the Columbia Suicide Severity Rating Scale [25].

The 2 jail populations vary demographically. County A is just under one-half White (46.5%), while County B is less White (39.4%). County A has a smaller proportion of men (71.4%) than County B (76.4%). Both jail populations are similar in age, with County A having 51.3% of people 31 years or older and County B with 51.5%. Medicaid is the insurer for 96% of people in jail in County A and 78% of people in jail in County B. Prior studies show varying rates of mental health needs, assessed by a modified cutoff score on the Kessler-6 [26], with County A (21.5%) reporting higher proportions than County B (16.8%). According to the Bureau of Justice Statistics [27], the average jail length of stay nationally was 33 days in 2021, an increase of 5 days from the previous year (28 days in 2020).

Data Sources and Assessments

Jail Data

Jail data will include admission and discharge dates and jail medical records, including results from the suicide identification PAU (positive or negative), intervention or referral related to suicide risk, veteran status, and information on suicide attempts or deaths while in jail. To determine if a death occurred within the jail, the research team will use jail admissions and discharge dates and date of death from vital records data to determine if the death occurred inside the facility. Self-injury vital record deaths that occur within 24 hours of jail discharge will be considered an in-custody suicide, accounting for jail to hospital transfer.

Community Health and Death Data

So that individuals can be matched across data sets, the research team will provide identifiers to the state's Department of Health and Human Services, which oversees Medicaid, pharmacy, and

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vital records data. To account for the average time spent in jail, the postrelease period will be extended to 120 days and 13 months, as opposed to 90 days and 12 months [19]. Physical and behavioral health Medicaid encounter data and pharmacy data include date of service between September 1, 2016, and March 31, 2023; current procedural terminology code; procedure code; diagnosis-related groups code; national drug code; medication class, generic name, dose; medication provider; medication days of supply and fill dates; member ID type; quantity of service and length of stay; transactional control number; national provider ID; diagnosis code and sequence; encounter or provider type; zip code; census tract; and member-months. Identifiers such as date of birth and first and last name will be needed for record linkage purposes. The research team will use the MHRN model definition for suicide attempt, which includes International Classification of Diseases, Tenth Revision (ICD-10) diagnosis of suicide attempt (example codes: suicide attempt [T14.91]; self-inflicted injury/poisoning due to asphyxiation [T71.X]) as measured using Medicaid encounter data. Vital records data requested consists of the following variables recorded from March 1, 2022, through March 31, 2023: state and county of occurrence; state, county, and zip code of residence; census tract; date of death; age; sex; race; marital status; autopsy; underlying cause of death code (Code800); related cause of death; if the case was referred to the medical examiner and the certifier of the death record; place and manner of death; and the decedent's first and last name and birth date. An ICD-10 diagnosis of self-inflicted injury (codes X60-X84) or injury/poisoning with undetermined intent (codes Y10-Y34) will be used to capture suicide deaths from the vital records data. To ensure the accuracy of the match and determine missingness, the research team will conduct intense data cleaning on these sources, removing individuals not found in Medicaid data. If individuals are not found in the vital records data, it is assumed death did not occur since these are official records. Table 1 outlines the key identification methods and post-year outcomes, along with corresponding data sources.

Table 1. Key measures and data sources.

Key measures	Source
Suicide risk identification method	
Model (5th-10th percentile groups)	Medicaid data
Practice as usual (PAU)	Jail data
Suicide behavior outcomes (1 year after jail)	
Suicide deaths	Vital records
Suicide attempts	Medicaid data, jail incident reports

Results

Study Status

This study is funded by the National Institute of Mental Health to NCHATS. The funding timeline for this project is August 1, 2022, through July 31, 2025. The algorithm's predictions and actual event incidence will be linked and validated in the spring of 2025, with results ready for publication in the fall of 2025.

Quantitative Data Analysis

This study will determine if the model is successful at identifying suicide attempts and deaths during and after jail detention. Assessment of drops in predicted probability for every 1% increment between 5% and 10% will inform the creation of a cutoff percentile for this population. Univariate analyses for identifying suicide outcomes from intake through 120 days and 13 months after jail release will include 3 suicide risk identification methods: (1) model only, (2) PAU only, and (3) model and PAU. Risk identification methods will be compared within each jail separately and in both jails together. Frequencies of suicide risk identification will be summarized, and associations between identification method and suicide outcomes will be examined using chi-squared analyses. Predictive validity of risk identification methods for assessing suicide attempts and deaths (separately and combined) will be calculated using ordinal logistic regression models. Adjusted odds ratios and their 95% confidence intervals will be estimated. Nonindependence of observations within jails will be considered using robust standard errors that account for the intracluster correlation. A secondary set of analyses will also include suicide attempts reported within jails. Moderation analyses will explore whether MHRN and PAU accuracy vary by sex; race or ethnicity; past suicide attempt; past behavioral health treatment; county; the Area Deprivation Index, which reflects income, education, employment, and housing quality; Mental Health Professional Shortage Area score; and per capita incarceration.

The model will be validated using SAS (SAS Institute). SAS will return the predicted probabilities and percentile groupings across the sample. The same percentile groups used in the MRHN study will be used for analysis in this pilot (5th percentile), with expansion to higher test levels (10th percentile) to allow state-level partners and jail staff to assess any gains that could be made at each 1% interval in probable scores (Figure 1) [19].

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Figure 1. Analysis model. Pred. prob.: predictive probability.

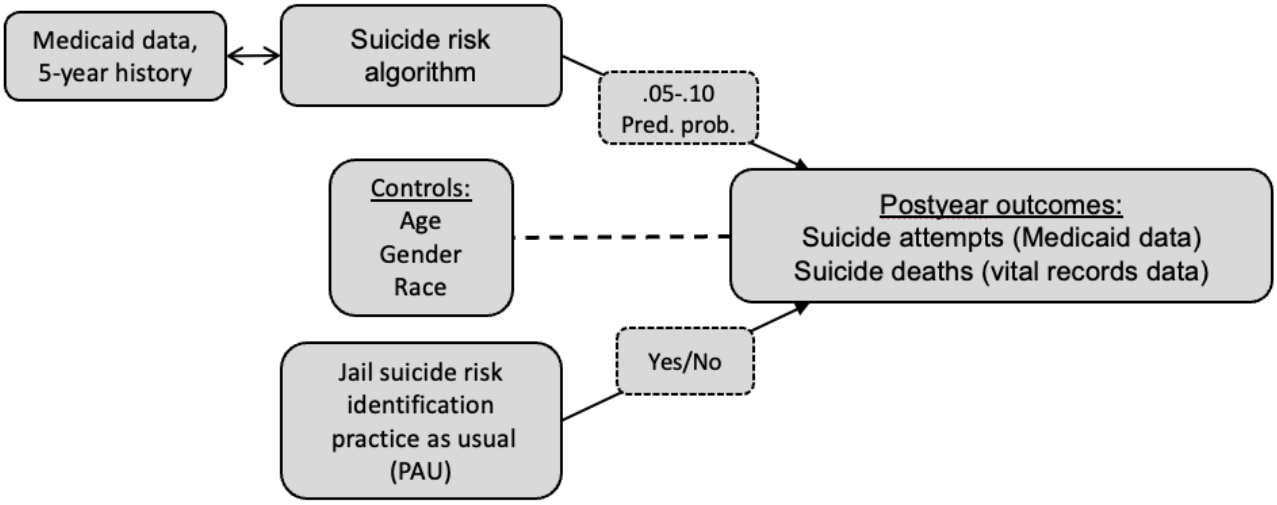

Cost Analysis

To facilitate replication, the study team will track the hours spent negotiating access to the linkable data sets, programming the linkage and scoring, and developing a user interface appropriate to the jail setting. Costs for these 3 tasks will be reported and include salaries, fringe benefits, overhead, and any other direct costs (eg, for data storage).

Administrator Interviews

Through semistructured interviews with state-level administrators involved in the health and jail data linkage study and jail staff across both jail sites, the research team will assess the facilitators and barriers of utilizing the MHRN model as a suicide risk flag. These interviews will assess the jails' information technology and software capacity for and barriers to embedding the MHRN model at jail booking as well as institutional policies, procedures, and practices that hinder or facilitate future implementation of the MHRN model in jails. Guided by the Institute for Healthcare Improvement Framework for Going to Full Scale [28], broad and jail-specific implementation factors of acceptability, feasibility, and appropriateness will be assessed per the Acceptability of Intervention Measure, Intervention Appropriateness Measure, and Feasibility of Intervention Measure [29]. This information will be used to design potential implementation approaches for future testing.

Qualitative Analyses

All interviews will be audio-recorded and transcribed and analyzed by multiple coders using a grounded theory approach to understand facilitators and barriers to implementation through a content-analytic matrix and by jail staff role through role-ordered matrix [30,31]. Findings will be used in the creation of a data integration tool kit that will provide summarized recommendations to state and jail partners on what is needed to efficiently and effectively implement the MHRN model into the jails' systems. The tool kit will also include recommended actions needed to respond to suicide risk in jails.

Discussion

Overview

This article describes a research protocol for validating a community suicide risk identification machine learning model with jail populations by comparing the model with other validated instruments and screening practices to improve data surveillance and treatment linkage for a highly vulnerable population. By integrating data across general health, behavioral health, and criminal-legal systems, providers could leverage an existing high-performing suicide risk model to detect risk of suicide in a novel jail population [19]. Using data linkage to ensure access to critical and life-saving information at jail booking would greatly increase the probability of appropriate intervention. The implications of improved suicide risk detection for clinical and community impacts would be clear: (1) greater justification for enhancing mental health care in carceral settings, (2) reduced harm on communities by preventing suicide exposure (eg, community impact on jail staff, other incarcerated individuals, and families), and (3) improved efficiency for processing behavioral health data and reduced likelihood for missing key information. These benefits would contribute to the potential scalability of implementing suicide risk identification model technology. Although this is a complicated endeavor, marked by information technology infrastructure and data sharing legality challenges, authors and state-level officials in the study state are engaged in ongoing efforts to better integrate community and jail health data. Key considerations for these ongoing efforts to link data sources and apply the algorithm are the data privacy and security measures needed to protect sensitive behavioral health and criminal-legal data from this vulnerable population. The highest standards of protection will be adopted to assure that no future harm from data breaches occurs (ie, identity theft, financial losses).

More accurate and efficient ways of identifying vulnerable individuals at high risk of suicide and rapidly connecting them to treatment are needed. This project attempts to fill this gap using an automated, algorithmic screening tool that has demonstrated effectiveness in prior medical settings [19]. Should

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the MHRN model prove to be a stronger alternative to jails' PAU or to improve accuracy when combined with the PAU, the next steps will be to understand how it might be replicated in other areas. Project implementation analyses will identify implementation facilitators and develop strategies to address potential implementation barriers, such as limited medical health care in carceral settings [32], wide-ranging variations in service quality in carceral settings [33], and mental health stigma [34]. We anticipate that additional potential barriers to implementation identified in other research, such as ethical, technological (eg, data quality, data access), liability and regulatory (eg, responsibility for outcomes and decisions), and workforce (eg, training and willingness) [35], may be relevant to this study.

Although this study is intended to validate the MHRN model in a new clinical population, there are limitations to consider. Only 2 jails from one midwestern state will be used for validation: one in a metropolitan area and the other in an urban area. Given that no jail in a rural community will be represented in the validation, the results may not be generalizable to that geographic context. Rural validation would be desirable if the urban validation is successful. In addition, limitations exist in the data sources used for our outcome variables of suicide attempt and death. Like in the initial validation, this validation restricted its nonfatal event detection to Medicaid claims data; thus, attempts were missed during periods when the person was uninsured, was insured by another payer, or received care that was not billed (eg, from a community mental health center or the Veterans Administration). Despite these limitations, this study will close the main gap in MHRN model validation in the Medicaid population. If the model validates there, the most pressing validation need remaining is to assess MHRN accuracy in a higher income group of privately insured people.

Conclusion

There is a growing interest in using machine learning to detect suicide risk, and through this study, this promising methodology will be applied to an incarcerated population. Machine learning to detect suicide risk among incarcerated individuals holds promise for improving the identification and prevention of suicide. However, it is important to rigorously validate machine learning algorithms and carefully consider the potential advantages of use before they are widely implemented. This project will (1) accomplish this important next step, validating the models overall and by sex, race and ethnicity, and other important moderators, and (2) explore implementation strategies to be tested in future trials, should tested algorithms prove effective.

Acknowledgments

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Generative artificial intelligence tools were not used in generating this manuscript.

Data Availability

The data sets generated during this study are not publicly available due to privacy and confidentiality concerns but are available from the author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

MHRN: Mental Health Research Network
NCHATS: National Center for Health and Justice Integration for Suicide Prevention
PAU: practice as usual
PII: personal identifiable information
REACH-VET: Recovery Engagement and Coordination for Health-Veterans Enhanced Treatment
ROC: receiver operating characteristic

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Protocol

Development of a Cohesive Predictive Model for Substance Use Disorder Rehabilitation Using Passive Digital Biomarkers, Psychological Assessments, and Automated Facial Emotion Recognition: Protocol for a Prospective Cohort Study

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Abstract

Background: Substance use disorder (SUD) involves excessive substance consumption and persistent reward-seeking behaviors, leading to serious physical, cognitive, and social consequences. This disorder is a global health crisis tied to increased mortality, unemployment, and reduced quality of life. Altered brain connectivity, circadian rhythms, and dopaminergic pathways contribute to sleep disorders, anxiety, and stress, which worsen SUD severity and relapse. Factors like trauma and socioeconomic disadvantages heighten risk. Digital health technologies, including wearables and machine learning, show promise for diagnosis, monitoring, and intervention, from relapse prediction to early detection of comorbidities. With high relapse rates and younger patient cases, these innovations could enhance the treatment outcomes of SUD.

Objective: The objective of this study is to develop and validate a predictive model with machine learning for the duration of therapy and the rehabilitation or relapse in patients with SUD, using digital physiological measurements, psychological profiles, automatic facial emotion recognition, and the emotional state during craving.

Methods: The study will be conducted with adult male patients with SUD at a rehabilitation center and control volunteers. Participants will undergo a self-reported demographic and psychological assessment, a clinician-administered craving and emotional reaction test, and will also be monitored using a smartwatch. SUD participants will be monitored for a total of 18 months (6 months during rehabilitation, an additional 12 months post discharge), and control participants for a total of 6 months. All participants will be reassessed at the sixth month of monitoring. The collected data will then be used to train models with a neural network, which will then be validated against other models and compared with other algorithms. Demographic, psychological, digital biomarkers, and craving profiles will be created, correlations will be analyzed, and they will be compared with controls to generate a digital phenotype of SUD. When the model achieves adequate validity (area under the curve of ≥0.80), a graphic user interface will then be designed for clinical use.

Results: The study is supported by the Program for the Improvement of Working Conditions for Members of the SNII and SNCA (PROSNII U006EST), and APPAC-VII-CUCS-2025 for Article Publication Fees, from the University of Guadalajara. The research protocol was approved by the University of Guadalajara (reference CI-01225) in January 2025. Recruitment of patients with SUD and control participants will take place from January 2025 through January 2027.

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Conclusions: As shown in recent studies, accessible and affordable wearables, like commercial smartwatches, combined with psychological, demographic, and emotional state data, used with a machine learning predictive model, may be able to be used as tools to enhance SUD rehabilitation and prevent relapse.

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KEYWORDS

digital biomarker; predictive model; substance use disorder; machine learning; facial emotion recognition; digital phenotype; digital health; wearable; data model; real-time monitoring

Introduction

Substance user disorder (SUD) is characterized by the excessive consumption of a substance, persevering and repetitive conducts of reward-seeking and reinforcing, regardless of the harmful physical, cognitive, behavioral, and social consequences. The disturbances created by SUD are related to alterations in brain connectivity, even after successful remission of substance use [1].

Worldwide, SUD is considered a multidimensional and critical health crisis phenomenon, connected with an increase in mortality, development of diseases, reduction of safety, increase in unemployment rates, and reduction of quality of life [2].

Research has suggested a link between the alteration of circadian rhythms and SUD in its earlier stages, that in time, due to the alteration of dopaminergic and glutamatergic pathways [3], results in sleep disorders. The development of these has been found to be a pivotal factor in the progression, severity, and relapse of SUD. These findings confirm a bidirectional relationship between SUD and sleep disorders [4-6].

Increased levels of anxiety and stress have also been associated with SUD, specifically in the abstinence and craving stages of the addiction cycle [7-12]. Anxiety and stress have also been related to an increase in heart rate, sweating, oxygenation levels, and atypical patterns of physical activity, all of which have been found in SUD [13-17].

In addition to physiological biomarkers, psychological evaluation has identified critical changes in executive function, decreased emotional regulation, and heightened levels of anxiety and depression [18-22]. Furthermore, environmental factors have been recognized to increase the risk of developing this disorder, like adverse experiences during childhood, violent or traumatic events, and disadvantageous economic conditions [23-29].

The first studies using digital technologies in mental health disorders were done on patients with major depressive disorder (MDD) through ecological moment assessment questionnaires through mobile devices, increasing a better treatment adherence [30-33]. After this study, various researches have been carried out, using varying methodologies and with objectives going from early diagnosis to prognosis of various complex pathologies, such as Alzheimer disease and major neurocognitive disorders some of the areas, where wearables and virtual reality have been used, allowing to observe cognitive decline and behavioral patterns [34-39].

Machine learning (ML) has also been used as a tool for the diagnosis of anxiety disorders with the use of speaking patterns, gaming activities, and self-reports [40-49]. It has also allowed researchers to measure the severity and variability of that disorder in varying environments through wearables, allowing remote intervention and through simulations [30,48,50-52]. It has also been used in predictive models for early depression diagnosis through smartphone use, severity, and progression through physical activity, sleep, and social interaction data [53-61]. In addition, ML models (MLM) have been trained to detect relapse in MDD and risk of suicide [62-64]. Similarly, it has been used to predict the start of a psychotic episode 5 days before it by using patterns of movement and sleep disturbance [63,65].

With a 60% relapse rate, an average of 5 recovery attempts required for full remission, and a growing number of new patients with SUD presenting at younger ages [2], this disorder represents a significant opportunity for digital health technologies. These tools, often used in managing cognitive and mood disorders commonly comorbid with SUD, have the potential to enhance treatment effectiveness and reduce relapse rates.

This study aims to integrate physiological, behavioral, and psychological data through digital technologies to develop comprehensive digital profiles of individuals with SUD. These profiles will be analyzed using ML tools to identify clinically relevant patterns. The resulting models are intended to serve as complementary tools in clinical practice, supporting treatment decisions, improving prognostic accuracy, and facilitating the monitoring of patients in remission.

Methods

Goal and Objectives

The purpose of this study is to develop and validate a predictive model of substance use relapse or rehabilitation with ML in patients with SUD. This will be through using digital physiological measurements (digital biomarkers), demographic and psychological profiles, automatic facial emotion recognition, and the emotional state during craving (ESDC).

Study Design

This study adopts a prospective cohort design, using data collected from nontraditional experimental groups to develop a MLM aimed at predicting clinical outcomes in the rehabilitation or relapse of patients with substance use disorders. The model will rely on comparative analyses between groups,

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identifying patterns in physiological, psychological, and emotional reactivity data to enhance predictive accuracy.

No interventions will be implemented in either group as part of this study, ensuring that all collected data reflect naturalistic conditions and minimizes external influence on the observed outcomes.

Participant Identification and Randomization

Participants in both groups will be randomly assigned a unique identification number, which will be used throughout the study to ensure anonymity and meet the inclusion criterion of randomization. Psychological assessments conducted at the rehabilitation center will be conducted through self-reported questionnaires, administered in a traditional pen-and-paper format, overseen by the institution's psychologists, who will use only the assigned ID numbers during the digitization of all data. Control participants will complete all psychological tests in a self-reported computer-based format, using their ID numbers, which will be randomly assigned at the start of the monitoring period.

A secondary randomization process will be conducted to create k-clusters of data before training the ML algorithm. This step will also include the selection of test data for verification purposes, ensuring robust validation of the model.

Blinding

Due to the nature of this study, neither the participants nor the first group of research staff will be blinded to group assignments. However, the group allocation of participant ID clusters will remain concealed from the second group of researchers. This second group will be responsible for data management, training the ML algorithm with the predictive model, and conducting validation, verification, and testing of the highest-performing models.

Timeline

This study will include 2 types of observations: continuous passive monitoring and active surveys conducted at specific time points. Passive monitoring will occur continuously for 6 months in both groups, followed by an additional year for participants with SUD after their discharge from the treatment facility. Active surveys will be conducted at three time points: (1) baseline session or baseline, (2) 3 months after baseline, and (3) 6 months after baseline.

For digital monitoring purposes, smart bands provided to participants will be synchronized with a smartphone at the baseline session. Psychological assessment will be conducted within the first 15 days after baseline. Retesting will take place during the 15 days prior to the 6 months after baseline. Emotional reactions to cravings will be assessed at two points: (1) 3 months after baseline and (2) at 6 months after baseline (Figures 1A-1F).

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Figure 1. Timeline of experimental procedures. (A) Demographic and psychological assessment, a battery of interviews and tests will be applied at 2 timepoints. (B) Digital measurements with the smart band Xiaomi Redmi Smart Band 8, starting on day one for controls, and after the first month of treatment for substance use disorder. (C) Evaluation of the emotional state during craving halfway through the digital monitoring period (third month), and at the end of it. (D) Data preprocessing is required for all 3 data sources. (E) Training in a machine learning predictive model in neural networks. (F) creation of a graphic user interface for clinical use.

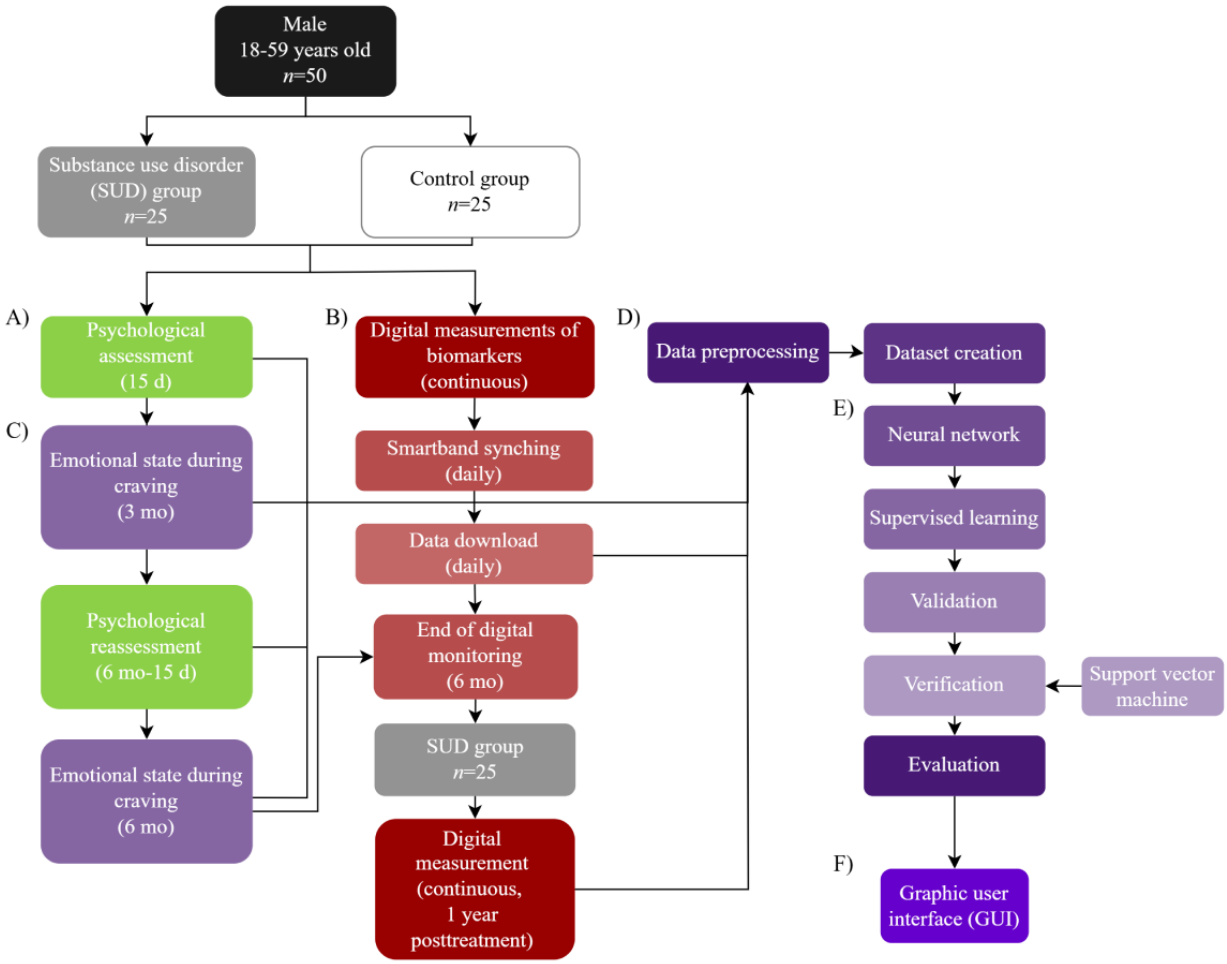

Participants and Study Setting

Sample Size

The minimum sample size was determined using Epidat 4.2 software (Xunta de Galicia), following the equation for estimating the comparison between independent means. The calculation was based on data reported by Rykov et al [30], in a study where patients were screened using wearable devices, and (MLMs were applied (Textbox 1).

Textbox 1. Sample characteristics.

- Variance: distinct
- Standardized mean difference=2.54
- Expected SD of population 1=1.6
- Expected SD of population 2=3.21
- Ratio between sample sizes=1
- CI=95%
- Statistical power=80%

In addition, based on the rule of one-to-ten for artificial neural network (ANN) models suggested by Kavzoglu and Mather [31], in which a sample should be at least 10-100 times the numbers of independent variables (4 in this study, based on the 4 suggested profiles), a sample of 40-400 participants was obtained. Therefore, a minimum sample size of 25 was determined for each group. Participants will be recruited within 2 years of the beginning of the study, aiming for recruitment greater than 25 per group.

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Recruitment

Participants for the SUD group will be recruited from a male-only, age-restricted inpatient drug rehabilitation facility in Cajititlán, Mexico. Eligibility criteria include being male, aged 18-59 years, and actively participating in a therapeutic community treatment program for SUD, with a cognitive behavioral therapy approach. Furthermore, candidates must undergo their first rehabilitation attempt within this specific program and be under medication management for any possible mental health comorbidity diagnosed with the Mini International Neuropsychiatric Interview (MINI) or physical disease. Finally, participants are required to review the privacy and safety terms and provide informed consent before joining the study. Smartwatches will be synchronized with a community smartphone by the personnel of the rehabilitation center, in accordance with the restricted access to smartphones.

Control Participants

Control group participants will be recruited through an open call for volunteers in the ZMG area, restricting the sampling to similar sex and age characteristics of the patients from the rehabilitation facility. To be eligible, individuals must be male, aged 18-59 years, have no history of SUD, either diagnosed or self-reported, with no current use of substances, excluding caffeine. They must review and agree to the privacy and safety terms, as well as the requirements for active participation. In addition, participants are required to commit to a six-month study period, synchronize and upload their data weekly, and attend scheduled meetings with the research team. In case an individual is interested in participating in the study, but does not have access to a personal smartphone, a device will be provided.

Exclusion Criteria

The exclusion criteria have been established for both groups equally. Individuals with physical conditions that significantly affect mobility, impede the use of a smart band or the registry of facial expressions, such as facial (eg, craniofacial abnormalities, facial nerve palsies, or severe neurological conditions) or neurological disorders, are ineligible. In addition, patients with a history of heart conditions, breathing issues, as well as significant vision and hearing impairment will be excluded, as these conditions might affect the measurements.

Withdrawal Criteria

Participants will be withdrawn from the study under the following circumstances: failure to use or misuse of the smart band for more than 5 consecutive days or exceeding 20% of the six-month period will result in the cessation of monitoring, with participants being notified, the device retrieved, and the data discarded. Relapse in substance use for the SUD group or the onset of addictive behavior for controls will also lead to immediate withdrawal; if the exact timing of such behavior cannot be determined, the corresponding data will be excluded. Finally, participants who voluntarily drop out of the study or request the removal of their data will be withdrawn, and their data will be discarded.

Study Setting

Participants will be evaluated in person at the key time points outlined in Figure 1 by health care professionals trained in conducting clinical interviews, administering psychological tests, and assessing the ESDC. For patients with SUD, assessments will take place in a designated area within the rehabilitation treatment facility, ensuring both privacy and comfort. Control group participants will be assessed at the University Center of Health Sciences, University of Guadalajara, in Guadalajara, Mexico, by trained health professionals.

Passive monitoring of biological and digital measurements using a smart band will be conducted for at least 22 hours per day, allowing a threshold of 2.4 hours (20%) of lost daily data, 7 days a week. Participants will be required to wear the device during sleep. Participants' physiological activity will be recorded during various activities and across diverse locations.

Data Collection, Storage, and Protection

Digital measurements will be downloaded from a Xiaomi account as a password-protected zip file. The csv files containing data from the linked devices will be processed and coded before being securely stored for future use. Clinical data will be entered into the database under a unique study ID number, either directly from source materials or from the instruments used for assessment.

In compliance with ISO (International Organization for Standardization)/IEC (International Electrotechnical Commission) 29100 guidelines and the General Data Protection Regulation (GDPR) [66,67], all data will be stored in encrypted storage units housed within the Department of Neuroscience at CUCS, University of Guadalajara. In addition, all files will be backed up on an encrypted cloud system hosted by the University of Guadalajara servers. During the study, access to these databases will be restricted to authorized study staff with the necessary training and permissions, ensuring the privacy and confidentiality of participants.

Instruments

The study instruments that will be used in this protocol to measure each assessment category referred to in the timeline (Figure 1), are presented in Table 1.

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Table 1. Study instruments.

Instrument	Period				
	Baseline	3 Months	6 Months	18 Months	Continuous
Wearable: Xiaomi Redmi Smart Band 8[a]	✓	✓	✓	✓[b]	✓
Demographic survey[c]	✓				
The Adverse Childhood Experiences Assessment (ACEs)[d]	✓				
The University of Rhode Island Change Assessment Scale (URICA)[d]	✓				
The Alcohol, Smoking and Substance Involvement Screening Test (ASSIST)[d]	✓				
The Beck Depression Inventory (BDI-II)[d]	✓				
The Beck Anxiety Inventory (BAI-II)[d]	✓				
The Pittsburgh Sleep Quality Index (PSQI)[d]	✓		✓	✓[b]	
Wechsler Adult Intelligence Scale IV (WAIS-IV): Digit Span and Letter-Number Sequencing subscales[d]	✓		✓		
Emotional Pictures Database (EmoMadrid)[e]		✓	✓		
Mannheimer Craving Scale (MaCS)[e]	✓	✓	✓		
Automatic facial emotion recognition software (FER)[e]		✓	✓		

[a]Digital measurement of biomarkers.
[b]Substance use disorder group only.
[c]Demographic assessment.
[d]Psychological assessments.
[e]Emotional state during craving assessment.

Digital Measurement of Biomarkers

The Xiaomi Redmi Smart Band 8 will be worn on the user's nondominant hand, positioned 2 cm below the wrist bone and secured at a comfortable level, as instructed by the user manual. The device will be worn for a minimum of 22 hours per day, allowing for an anticipated loss of up to 2 hours of data due to activities such as recharging the device, synchronization with a smartphone, showering, and other routine tasks.

Physiological data, including heart rate (HR), peripheral capillary oxygen saturation, physical activity, stress, and sleep, will be collected using the device's shortest available measurement intervals. Data will capture periods of both high and low activity, during self-reported exercise, regular physical activity, and rest, and will identify any abnormalities in activity patterns.

Data synchronization, which facilitates upload to the associated Xiaomi account, will occur every 72 hours for all participants during the 6- or 18-month study period, as applicable. This data will be downloaded, preprocessed, and stored securely on an encrypted external hard drive and the institution's server for access by authorized research staff within 48 hours (Figures 2A-2E). Participants will receive a reminder notification if synchronization is not completed within 5 days.

Raw data will be used to compute digital the physiological features proposed in a MLM study by Rykov et al, [30] (Table 2).

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Figure 2. Scheme of smart band data retrieval. (A) Data from the smart band Xiaomi Redmi Smart Band 8 via Bluetooth to the smartwatch it's been linked to for synchronization. (B) Through the Xiaomi app Mi Fitness, the data of the monitored period will be uploaded to the account's cloud to be downloaded by the researchers. (C) Raw data will be extracted, labeled, and preprocessed. (D) All data will be saved in an assigned encrypted server, property of Universidad de Guadalajara. (E) Alternatively, a second copy will be done on an encrypted external hard drive.

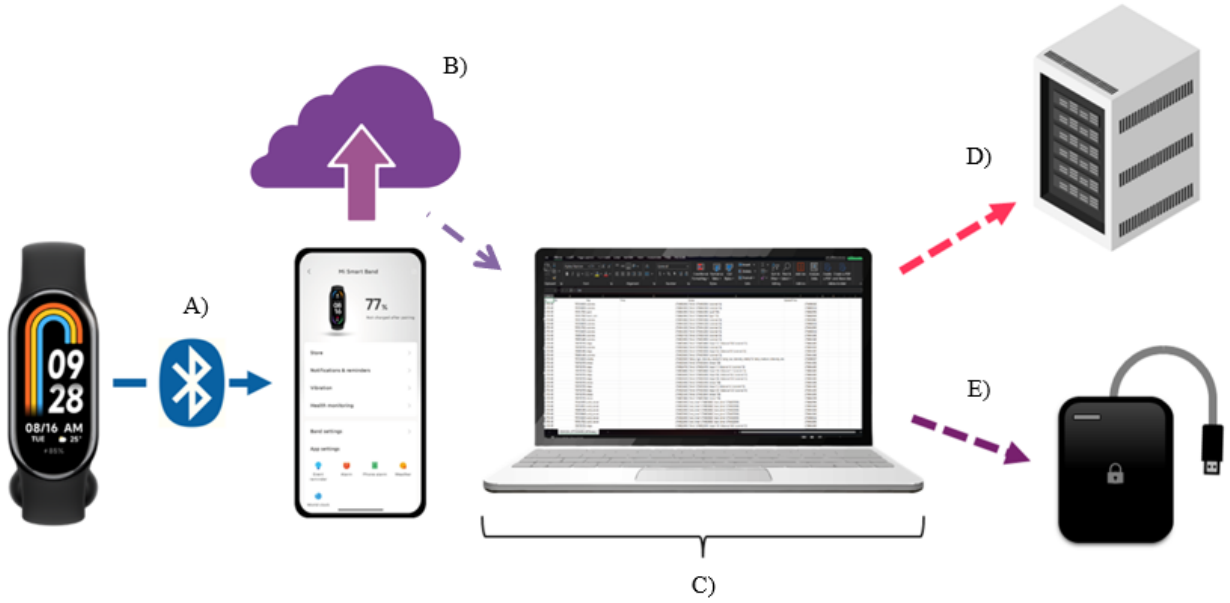

Table 2. Summary of raw measurements and physiological features.

	Raw data	Physiological features
Physical activity	Calories, steps, vitality, and time standing up	Daily footsteps, sedentary time, light physical activity, moderate physical activity, and vigorous physical activity
Heart rate (HR)	Beats per minute (BPM), maximum and minimum BPM, and single measure	HR resting HR, daytime HR, nighttime HR, HR delta, and HR root-mean-square successive differences
Sleep	Type of sleep, wake-up time, bedtime, and awake	Coefficient variance, time in bed, total sleeping time, sleep efficiency, sleep onset latency, waking after sleep onset, and sleep midpoint
Rhythm	Activity peaks	Circadian rhythm: COSINOR and nonparametric measurements
Oxygenation	SpO_2[a] during daytime, single measures of SpO_2, and sleep time SpO_2	—[b]
Stress	Stress level and single stress measurements	—

[a]SpO_2 : peripheral capillary oxygen saturation.
[b]Not available.

Demographic and Psychological Assessment

Demographic information, such as age, place of birth, education, occupation, civil status, household income, housing characteristics, as well as medical and family history, will be collected at baseline. A form will be filled in by the participant, assistance from the trained research staff will be provided if it is required.

The psychological tests will be administered at baseline within the first 15 days of participation. A battery of self-report questionnaires has been chosen to assess for a history of childhood trauma (Adverse Childhood Experiences Assessment [ACEs]) [68], the presence of depression or depressive symptoms (Beck Depression Inventory [BDI-II]) [69], anxiety and stress (Beck Anxiety Inventory [BAI-II]) [70], sleep disorders (Pittsburgh Sleep Quality Index [PSQI]) [71], and short-term memory (Wechsler Adult Intelligence Scale IV [WAIS-IV] subtests: Digit Span and Letter-Number Sequencing) [72]. Substance use–specific tests will aim to determine the type of substance, frequency and quantity of used drugs (Alcohol, Smoking and Substance Involvement Screening Test [ASSIST]) [73], level of substance craving (Mannheimer Craving Scale [MaCS]) [74], as well as the stage or frame of mind of the individual starting the therapeutic process (University of Rhode Island Change Assessment Scale [URICA]) [75].

To obtain a comparative measurement after treatment, depression, anxiety and stress, sleep disorders, short-term memory, stage of change and craving, will be reevaluated within fifteen days before the sixth month period of digital tracking ends (Figure 3).

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Figure 3. Flowchart of the psychological test battery. WAIS-IV: Wechsler Adult Intelligence Scale IV;.

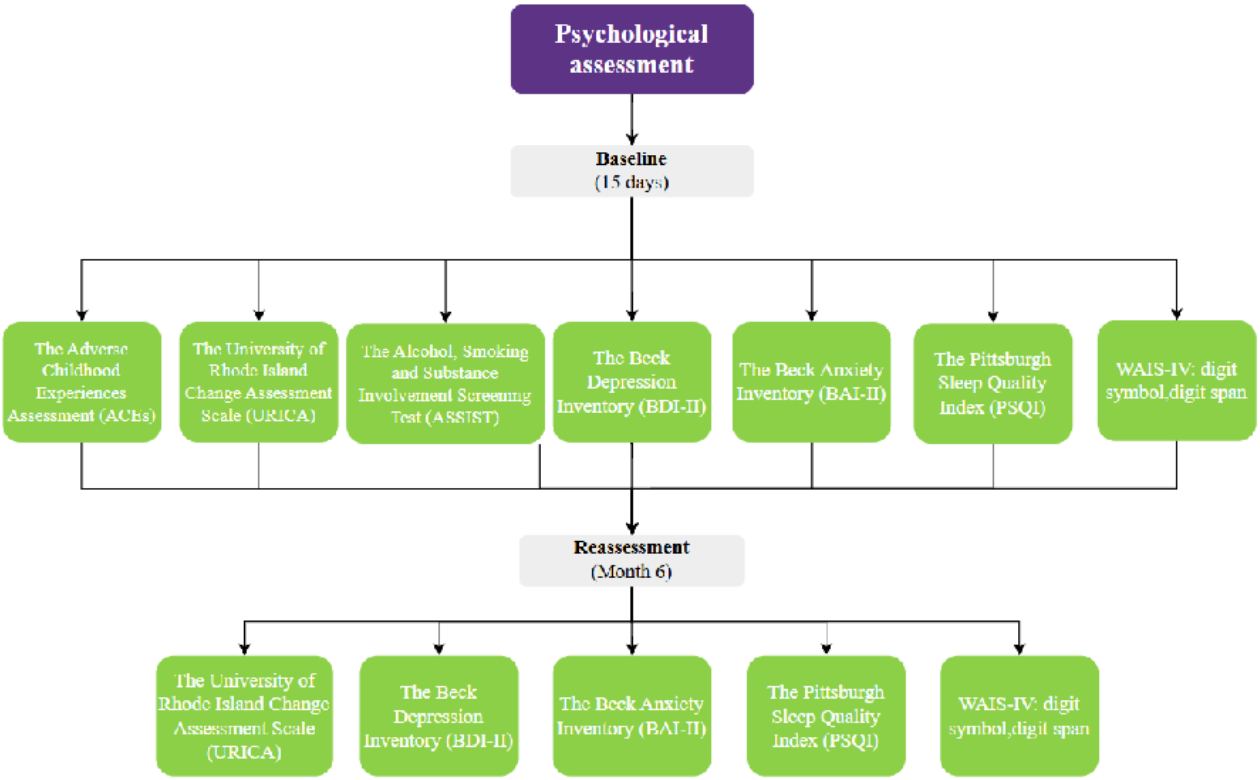

Emotional State During Craving

Given the significance of craving in SUD, a profile of the ESDC will be developed. Participants will be shown images from the Emotional Picture Database (EmoMadrid), designed by CEACO, which will be used as stimuli to elicit an emotional response [76]. Participants will be recorded all throughout the test, and Facial Emotion Recognition (FER) software. Software will provide an objective, real-time measure of participants' emotional expressions, which we will analyze in conjunction with their self-reported "Emotional State during Craving" data. The FER software is a personal script written in python, which automatically detects emotions by analyzing changes of facial expression of dataset that consists of 48×48 pixel grayscale images (32,298 images) of faces (FER-2013). Craving levels will be measured both before and after the test.

An experimental setup will be arranged to ensure optimal conditions for the test. This setup will include a white screen for image projection, an HD camera for recording the participant, and a controlled environment with low lighting and sound insulation to minimize distractions. A trained researcher will administer the test in this environment.

At the start of the experiment the FER software will be activated and participants will respond to items 9 to 11 of the MaCs scale (Table 1), which assesses craving-related anxiety levels, the effort required to resist urges, and impulses to consume substances. Following this brief questionnaire, the instructions for the experiment will be presented both visually and verbally to ensure the participant's full understanding.

A modified version of the protocol has been designed to suit the characteristics of the study population. Fifty images have been selected and categorized as positive, negative, neutral, or substance-use-related. These images have been further customized to align with the substance use profile of the participant group. Each image will be displayed for 1 second, after which participants will score it based on valence and activation. Once a score is provided, the next image will be shown. The procedure will be divided into 2 sets of 25 images, with a 30-second rest period between sets.

After the image presentation, participants will be reassessed using the same 3 MaCs scale items. In addition, they will be asked whether they experienced any changes in their emotional state after viewing the images and to provide a qualitative description of any observed shift (Figures 4A-4D).

All data obtained from the FER analysis, MaCS EMA, the EmoMadrid emotional response assessment and physiological data obtained by the smart band, will be used to observe the relationship between exposure to emotional and substance use visual stimuli, emotional response and craving.

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Figure 4. Flowchart of emotional reaction to craving assessment. Steps of the brief craving assessment, in addition to a modified version of the emotional pictures database for valence and activation, including a sample of the chosen images of each category. (A) Positive images (n=15). (B) Negative images (n=16). (C) Neutral images (n=10). (D) Substance use-related images (n=9).

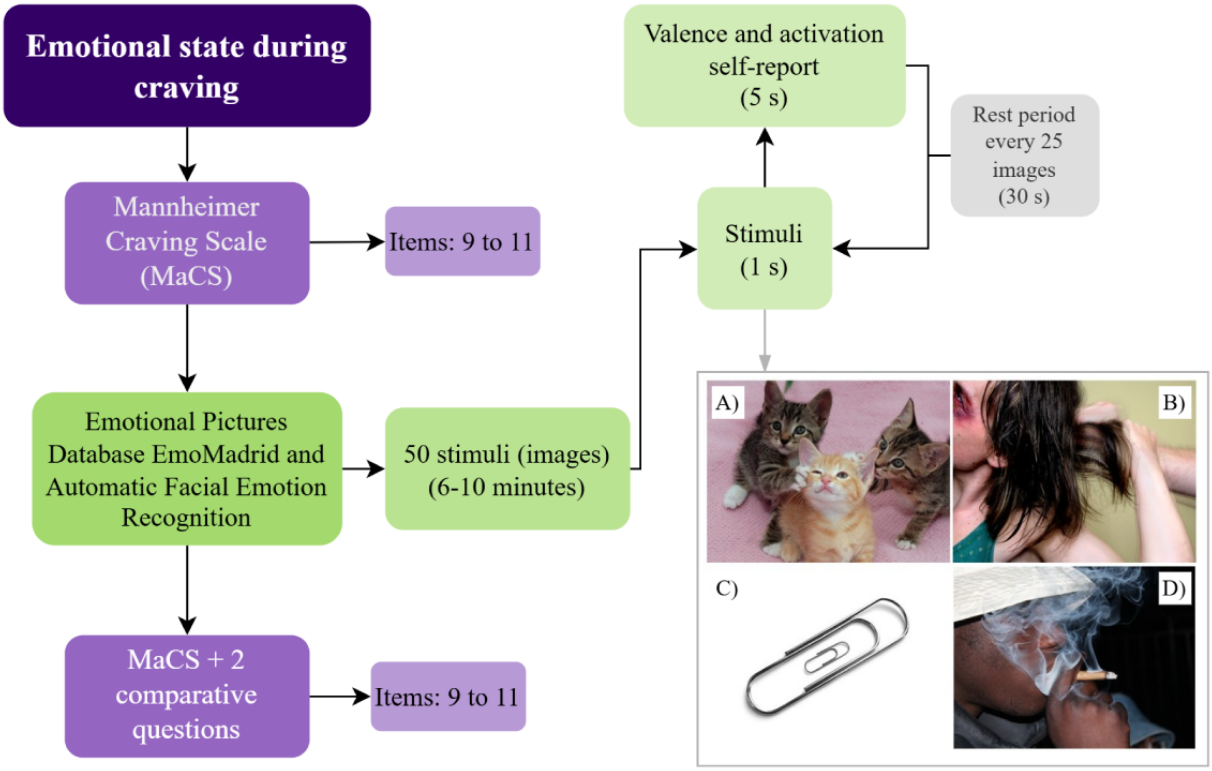

Statistical Analysis

Statistical analysis will be conducted using R-Studio IDE (version 4.3.1; Posit PBC), Prism GraphPad (version 9, GraphPad Software Inc), and MATLAB (version R2025a, MathWorks Inc). A descriptive analysis of normality (Shapiro-Wilkin normality test) means and medians, SD and error, variance (ANOVA or Kruskal-Wallis tests) will be performed. Correlation analyses (Spearman or Pearson) will be conducted to gain a preliminary understanding of the interactions between variables, as well as using time series analysis descriptive models to identify patterns, trends and cycles of activities by participants, and by groups. MATLAB will be used for advanced data processing and visualization, ensuring robust and comprehensive analysis.

Data Exclusion

Missing data will be addressed through imputation. If more than 20% of daily data samples are missing, they will be excluded. For missing data below this threshold, linear interpolation and neighbor mean imputation (k-nearest neighbor) will be applied during preprocessing using MATLAB.

The quality of data collected from the smart band will be assessed by correlating heart rate at randomly selected timestamps with oxygen saturation, activity levels, self-reported exercise, and sleep type during sleep hours. If atypical correlations are identified, 10 data points before and after the anomaly, along with 5 additional randomly chosen timestamps, will be reviewed. A day with more than 20% of faulty measurements will be excluded from the dataset.

Data will also be excluded in cases of device misuse, such as exchanging the device with other participants or nonparticipants, switching the wearing side without prior notice, or removing the device for more than 5 hours without informing the research team.

If the total sum of missing and excluded data exceeds 20% of the 6-month period, the participant's data will be removed from the study. Finally, for SUD participants, any measurements obtained during periods of substance use will be excluded, and their participation in the study will be terminated.

MLMs

Predictive MLMs for classification and regression will be designed, trained, and tested following the methodology outlined by Luo and colleagues [77] in their Guidelines for Developing and Reporting Machine Learning Predictive Models in Biomedical Research.

Data Preprocessing

Databases and labeling will initially be managed using Microsoft Excel (version 2412), after which MATLAB (version 2025a, MathWorks, Inc) will be used for data preprocessing. This process will include data cleaning and preparation to ensure the dataset is suitable for ML training.

Feature selection will be done following a filter methodology after correlation analysis to assess the correlation with the target

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and statistical measures. All data obtained through the wearable device, psychological assessment and ESDC will be scaled through a *z*-score standardization for dimensionality reduction and integration across all modality.

The data will be divided into training, validation, and test datasets using a k-fold cross-validation approach. The dataset will be split into k folds, with 2 folds randomly selected: one for validation and another for testing. The remaining k-2 folds will be used for training. The number of folds will vary depending on the specific model, enabling a broader experimental variance and improved model evaluation.

Algorithms

Modeling will be conducted using MATLAB, with ANN serving as the base algorithm. Additional algorithms, including decision trees, random forests, and support vector machines, will be used for validation. This multialgorithm approach will facilitate a comprehensive comparison of predictive accuracy across various models.

Output

The primary objective of this study is to develop a MLM capable of predicting clinical outcomes in patients. To achieve this, the data will be segmented and classified into 5 categories (Figure 5). Around 2 of these categories will correspond to the first layer, which pertains to the duration of the therapeutic process, while the remaining 3 will focus on the latency of relapse, if any.

Figure 5. Model's possible outputs. These categories will be used as output labels of the predictive model and will allow the evaluation of the patterns detected from the input.

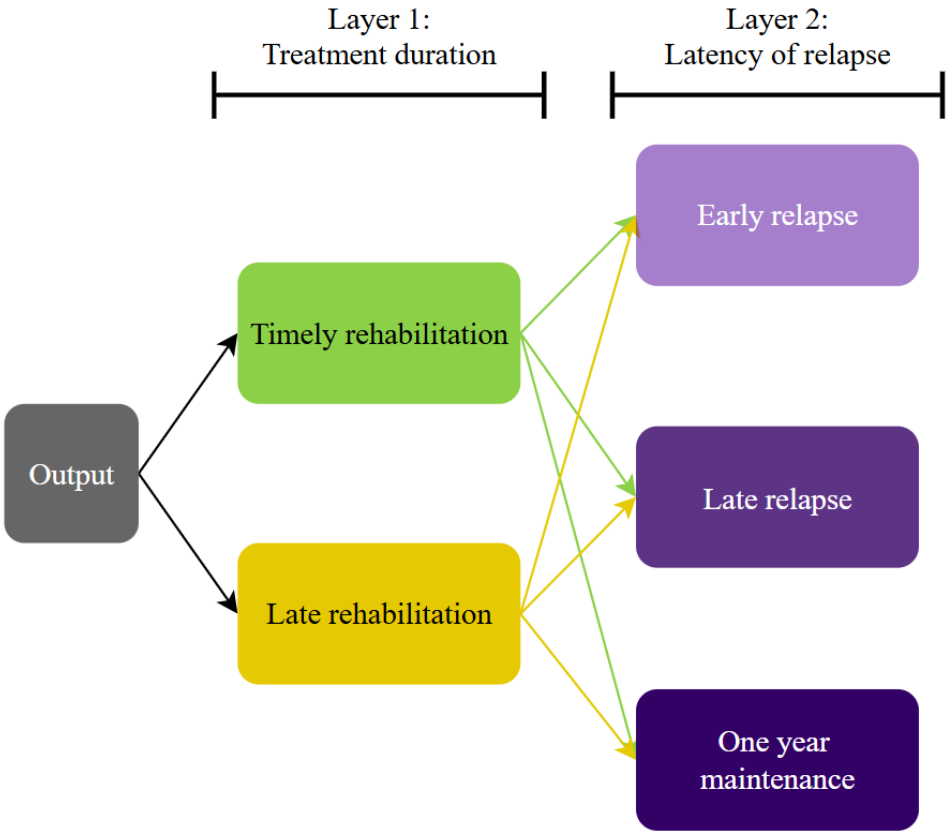

For the duration of the therapeutic process, the following labels will be used:

1. Timely rehabilitation: patients with SUD who complete the rehabilitation protocol within 7 months.
2. Late rehabilitation: patients with SUD who complete the protocol in 7 months or longer.

Regarding relapse latency, the labels will include the following:

1. Early relapse: substance use occurring within the first 6 months post discharge.
2. Late relapse: substance use occurring after 6 months but before the completion of 18 months post discharge.
3. One-year maintenance: patients who have abstained from substance use at the end of the 18-month postrecovery period.

Validation and Verification

All models and algorithms will undergo validation, verification, and testing using MATLAB's tools for model evaluation and hyperparameter optimization. These processes will assess precision, performance, and recall metrics. Optimal model performance will be defined by achieving an area under the curve (AUC) of ≥0.80 and F2 score of ≥0.8.

The output categories will serve as benchmarks to evaluate the validity, reliability, and precision of the models. The validation dataset will be used to perform initial comparisons both within

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individual models of each algorithm and across different algorithms, replicating models with distinct architectures to refine performance.

For model verification, the test dataset will be used to determine final AUC and F2 scores. This final evaluation will confirm the models' effectiveness as ML tools for predicting rehabilitation outcomes and informing clinical decision-making.

Outcomes

Profiles

A total of 4 distinct subprofiles will be generated based on the results of the statistical analysis: (1) demographic, (2) psychological, (3) craving, and (4) digital biomarkers. These profiles will subsequently be integrated to create digital phenotypes for individuals with SUD.

Predictive Model

A predictive model will be developed to distinguish between healthy individuals and patients with SUD. In addition, the model will predict the duration of a rehabilitation therapeutic program and the length of sobriety adherence for individuals rehabilitated using the center's methodology. A minimum performance threshold of AUC≥0.8 and F2≥0.8 has been established to evaluate the model as fully functional.

Graphical User Interface

As an outcome of this study, a graphical user interface will be developed using MATLAB to enable practical application of the predictive tool within the rehabilitation center where this research is being conducted. The graphical user interface will facilitate clinical use of the model and allow for further training and refinement, expanding its potential utility in similar settings.

Ethical Considerations

This study has been approved by the Research, Ethics in Research and Biosafety committees of the Centro Universitario de Ciencias de la Salud, Universidad de Guadalajara (registry number 25-06; approval ID CI01225). This certifies that the research protocol adheres to the principles outlined in the Declaration of Helsinki of ethical research involving human participants, with a satisfactory quality and relevancy of the research.

Candidates will be provided with detailed materials in both written and digital formats for review before confirming their participation. All participants will be provided with an informed consent reviewed by the previously mentioned committees, signed by the participant, researchers, and two witnesses. Participants have the right to withdraw their consent at any time and may request the removal of their data from the study, in compliance with the Federal Law on Personal Data Protection and Article 16 of the Federal Constitution of the United States of Mexico [78,79].

All identifying participant information will be anonymized through a numeric ID system. Subsequently, the obtained data will be securely stored, either locked in a filing cabinet or in encrypted digital files and retained for a minimum of 5 years before being destroyed, as required by the Official Mexican Norm for Clinical Files (NOM-004-SSA3-2012) [80]. This information will only be accessible for purposes related to contact by the research group.

Participation in this study is entirely voluntary, and no financial incentives will be provided for joining or continuing in the study.

Results

The study is supported by the Program for the Improvement of Working Conditions for Members of the SNII and SNCA (PROSNII U006EST), and APPAC-VII-CUCS-2025 for Article Publication Fees, from the University of Guadalajara. The research protocol was approved by the University of Guadalajara (reference CI-01225) in January 2025. Recruitment of patients with SUD and control participants will take place from January 2025 through January 2027. As of June 2025, we have enrolled 35 participants, 18 patients with SUD and 17 controls. Data obtained from the device, as well as psychological and demographic data at baseline assessments and at 3 months are at the labeling and preprocessing stage of the data analysis. Results are expected to be published by the summer of 2028.

Discussion

Principal Findings

This study aims to evaluate the viability and efficacy of a predictive model designed to estimate the duration of a rehabilitation process and predict the likelihood of early, late, or no relapse in substance use, based on the digital phenotype of SUD. The hypothesis posits that an AUC of ≥0.80 and F2 of ≥0.8 will demonstrate that data collected from an affordable commercial smart band, demographic questionnaires, psychological tests included in the institution's base protocol, and the proposed use of FER combined with valence and emotional activation scoring during craving episodes can effectively support the creation of this predictive model.

The potential of this project is supported by several premises. Wearable devices have become increasingly accessible and seamlessly integrated into daily life. As of January 2024, GSMA Intelligence reported 125.4 million cellular connections in Mexico, and GWI estimated that 31% of internet users aged 16-56 years use a smartwatch or smart band [81]. Considering that the device used in this study is among the most affordable commercial smart bands and compatible with any mobile operating system, the development of a viable predictive model could introduce this tool as a complementary aid in SUD rehabilitation, enhancing the effectiveness of treatment strategies.

Wearable devices and MLM have been successfully applied to various mental health conditions. For example, passive physiological activity measurements and MLMs have distinguished depressive patients from healthy controls by correlating variations in circadian rhythms, nocturnal HR, and higher depression test scores [30]. Similarly, MLMs using passive data have predicted depressive, manic, or hypomanic episodes in patients with bipolar disorder (BD) by identifying sleep disturbances, circadian rhythm changes, and physical activity variations [82]. Furthermore, facial emotion recognition

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combined with MLMs has been used to diagnose and predict alexithymia with an AUC of 0.80 [83]. In the context of SUD, MLMs have demonstrated potential by evaluating participant engagement, correlating stress and craving during recovery, and providing insights into treatment outcomes [84].

Psychological assessments remain a cornerstone for diagnosing and quantifying symptom severity in SUD, projecting recovery trajectories, and supporting research protocols. The psychological tests included in this study have been previously validated in SUD research, translated into Spanish, and recommended for clinical and diagnostic use [85-90]. Despite potential biases in self-reports, these tools have also been engaged in mental disorders such as schizophrenia and mood disorders like major depression and BD to develop MLMs and support symptom monitoring through digital technologies [30,46,60,91-96].

Digital tools for long-term symptom monitoring and clinical support during remission have been widely accepted in studies involving high-risk populations. For example, US veterans at risk of suicide provided valuable data on physiological activity and behavioral patterns surrounding suicide attempts through digital monitoring [64]. Similarly, high levels of acceptance have been observed among patients with BD, schizophrenia, anxiety, and major neurocognitive disorders, highlighting the feasibility of using such technologies in mental health research and clinical practice [34,37,56,60,93,97-102].

Limitations and Considerations

This study is subject to several limitations and potential risks of bias that must be acknowledged. Participants will be selected through convenience sampling of patients with SUD in a rehabilitation facility, limiting participation to cisgender male individuals between 18 and 59 years of age in both groups, therefore limiting the generalizability of results. The experimental status will be disclosed to them beforehand as well. This awareness could influence self-reporting in psychological tests and responses during exposure to visual stimuli related to substance use, potentially introducing bias.

While the Xiaomi Redmi Smart Band 8 has been selected for its cost efficiency and suitability for future clinical applications in rehabilitation centers, its sensors may have higher measurement errors compared to research-grade devices. Studies have indicated that similar consumer-grade devices generally exhibit lower precision. However, this trade-off is justified by the need to prioritize accessibility and scalability in clinical settings.

To identify events of physical activity, such as exercise, and atypical behavior, this study will rely in self-reporting through the app included in the Xiaomi Smart Band 8 device in the control group. Activity of participants with SUD will also be assessed by classifying their behavior according to the fixed schedule at the rehabilitation facility. Data will be clustered time-wise according to the time of the day and the reported activity accordingly, to reduce possible noise created by this variability. Since these events will rely on self-reported activities, a margin of error might be present in the observations in this time window.

Data clustering by groups before final testing introduces a potential risk that research staff may infer group assignments prematurely, which could influence the interpretation of results. The reliability of data used for training the models also depends on participants' proper use of the device and the accuracy of self-reported information, both of which carry inherent risks of bias that may impact outcomes.

The characteristics of the data and the results of ML training, validation, and verification may affect the algorithm's performance. There is a possibility that the baseline algorithm designed for this project might not achieve the desired accuracy or generalizability, based on the participants recruited by the cutoff time of recruitment. In addition, the possibility of an algorithm better suited for smaller sample sizes could be considered at a later stage of this study based on the available data.

To address these risks, the study will follow established guidelines for developing and reporting ML predictive models in biomedical research [103]. These guidelines provide a comprehensive framework for reporting in research articles and outline structured steps for model development, aiming to reduce bias and ensure robustness in predictive modeling [77].

Conclusion

As shown in recent studies, accessible and affordable wearables, like commercial smartwatches, combined with psychological, demographic, and emotional state data, used with a ML predictive model, may be able to be used as tools to enhance SUD rehabilitation and prevent relapse.

Acknowledgments

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Authors' Contributions

DFQ performed conceptualization, formal analysis, software management, and supervision. APGP performed data curation, investigation, methodology, visualization, and contributed to writing the original draft and review and editing. KMP contributed to investigation, visualization, and writing—review and editing. JGE and SL were responsible for funding acquisition and provided resources. DEMF and SL handled project administration. DEMF also contributed to supervision.

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Conflicts of Interest

None declared.

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Abbreviations

ACE: Adverse Childhood Experiences Assessment
ANN: artificial neural network
ASSIST: Alcohol, Smoking and Substance Involvement Screening Test
AUC: area under the curve
BAI-II: Beck Anxiety Inventory
BD: bipolar disorder
BDI-II: Beck Depression Inventory
EmoMadrid: Emotional Pictures Database
ESDC: emotional state during craving
FER: facial emotion recognition
GDPR: General Data Protection Regulation
HR: heart rate

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IEC: International Electrotechnical Commission
ISO: International Organization for Standardization
MaCS: Mannheimer Craving Scale
MDD: major depressive disorder
MINI: Mini International Neuropsychiatric Interview
ML: machine learning
MLM: machine learning model
PSQI: Pittsburgh Sleep Quality Index
SUD: substance use disorder
URICA: University of Rhode Island Change Assessment Scale
WAIS-IV: Wechsler Adult Intelligence Scale IV

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Protocol

The Effects of a Smartphone App (Feelee) to Enhance Adolescents' Emotion Regulation Skills in a Forensic Outpatient Setting: Protocol for a Multiple Single-Case Experimental Design

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Abstract

Background: Difficulties in emotion regulation are a significant contributing factor to delinquent behavior in adolescence. These adolescents struggle with recognizing, comprehending, and controlling emotions, which impedes the effectiveness of current forensic treatments. In addition, forensic care often faces challenges regarding treatment engagement due to a lack of motivation and difficulties building an alliance between clients and caregivers. The use of Feelee, an app that collects and displays active and passive data, is promising to support adolescents in obtaining more insight into their emotion regulation abilities. Furthermore, the integration of smartphone apps, like Feelee, offers new perspectives to increase adolescents' engagement and adherence to treatment.

Objective: This study presents the research protocol for evaluating the initial effects of the Feelee app on emotion regulation among adolescents in the forensic outpatient setting. The Feelee app integrates with treatment as usual, and the multiple single-case experimental design methodology is discussed in detail.

Methods: A multiple single-case experimental ABA design was applied to examine the initial effectiveness of Feelee. A total of 24 participants from 2 forensic outpatient care centers completed a 2-week baseline (phase A1), 4-week intervention (phase B), and a 2-week follow-up (phase A2). The primary outcome, emotional regulation, is measured daily using self-reports via the smartphone. Secondary outcomes, including emotional differentiation, insight and self-reflection, emotional awareness, and treatment-related factors such as motivation and therapeutic alliance, are assessed through questionnaires administered at preintervention, postintervention, and follow-up points. Quantitative analyses follow single-case experimental design methods, including visual analysis of individual trajectories, standardized mean difference permutation distance tests, and Cohen *d* at the group level. A 95% CI is calculated per participant to assess change reliability. Secondary outcomes are analyzed using the Reliable Change Index. Qualitative follow-up interviews are analyzed using thematic analysis at both the individual and group levels.

Results: Data collection started in June 2023 and was completed in January 2025. By the time of final manuscript submission, 89 participants had been recruited and 24 had enrolled in the study. Study results will be published in peer-reviewed journals and presented at national and international conferences throughout 2025

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Conclusions: This study aims to evaluate the effectiveness of the Feelee app in enhancing emotion regulation skills. By using a multiple single-case experimental ABA design, we will get a first insight into the addition of Feelee to treatment as usual in the forensic outpatient setting. Study strengths include the low-threshold addition, ecological validity, and the use of both quantitative and qualitative research methods. Further implications for clinical practice are discussed.

Trial Registration: Central Committee on Research Involving Human Subjects NL-OMON54390; https://onderzoekmetmensen.nl/en/trial/54390 and ClinicalTrials.gov NCT06509360; https://clinicaltrials.gov/study/NCT06509360

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KEYWORDS

emotion regulation problems; emotional awareness; delinquent behavior; forensic treatment; treatment motivation; smartphone apps; digital phenotyping; single case experimental design; protocol; adolescent; teenager; mHealth; app

Introduction

Background

Delinquent behavior in adolescence is associated with the existence of emotion regulation problems [1,2]. As stated in the risk-need-responsibility (RNR) model, these problems arise from various adverse childhood conditions and experiences such as problems in the household (eg, experience of parental divorce, violence, or parental mental illness) or different types of maltreatment (eg, abuse or neglect). The RNR model suggests that adolescents facing these challenges are at a higher risk of engaging in delinquent behavior compared with their typically developing peers [3-6]. Multiple studies show that these harmful experiences negatively impact adolescents' emotional development [5,7,8]. In particular for emotion regulation, adolescents experience difficulties with recognizing and controlling emotions, culminating in impulsive or aggressive behavior, which increases the risk of showing delinquent behavior [9,10]. Emotion regulation problems affect a variety of negative outcomes such as conflicts at home, school dropouts, or delinquency [11-14]. This highlights the importance of effective emotion-oriented treatments for adolescents to support their emotional regulation abilities and prevent them from future delinquent behavior.

In forensic outpatient youth care, treatment as usual (TAU) consists of both family- and individual-based therapy aimed at addressing the future risk of delinquent behavior. These TAU programs typically integrate elements from cognitive behavioral therapy and regulation skills training, focusing on enhancing cognitive and emotional skills to improve behavioral regulation [15,16]. Although TAU programs are widely considered as evidence-based interventions for prevention and rehabilitation, the effectiveness of these approaches in the forensic outpatient setting has yielded mixed results. For example, multiple meta-analysis found small to moderate effects for family-based treatments results for family-based treatments for the reduction of delinquent or disruptive behavioral problems among adolescents [17-20]. In addition, meta-analyses have shown mixed results on the efficacy of psychosocial and individually oriented cognitive behavioral therapy treatments for reducing disruptive and aggressive behaviors in adolescents. These mixed outcomes can be attributed to differences in the research design, small sample sizes, and limited research on individual treatments in this context [16,21].

The mixed results of TAU programs in the forensic outpatient setting can be attributed to the characteristics of adolescents within this population. A contributing factor is the adolescent's limited emotional understanding. According to the RNR model, effective interventions should be tailored to adolescents' risk levels for recidivism, as well as their learning styles and cognitive capabilities [22,23]. However, current TAU requires adolescents to recognize and reflect on their emotions in order to gain insight into their (delinquent) behavior [24,25]. This approach does not align with the cognitive capability of adolescents, who often encounter significant difficulties in maintaining emotional awareness and regulating cognitive responses [26-28]. Additionally, emotion-focused interventions are typically restricted to the treatment setting, neglecting adolescents' emotional experiences in their everyday lives [29]. This restricted approach hinders a comprehensive understanding of adolescents' emotional and behavioral patterns, which is critical for accurately assessing and improving their emotion regulation capacities [26,29,30].

Another factor that impedes the effectiveness of forensic outpatient TAU is the lack of motivation and difficulties in building an alliance between adolescents and caregivers, which leads to low engagement and poor adherence to treatment. Among the forensic population, the rates of no-shows and early treatment dropout are notably high: 21.7% among young offenders in sociotherapeutic settings and 57.7% among juvenile inpatient treatments [31]. Additionally, no-show and dropout rates are higher among younger individuals [32]. In most cases, clients have less insight into their problems, a different view of their needs, and are skeptical about the benefits of treatment [33,34]. Establishing a lasting treatment alliance is also challenging due to adverse life events and previous unsuccessful treatment experiences [35]. Noncompletion of treatment significantly increases the risk of recidivism [36]. Consequently, there is a need for supportive tools that align with the perceptions of adolescents in the forensic outpatient setting, in order to enhance their engagement and adherence to TAU [36,37].

The integration of digital phenotyping into TAU could support the enhancement of adolescent emotion regulation skills and increase engagement in forensic outpatient settings. Digital phenotyping involves moment-by-moment quantification through the use of data sources on digital devices (eg, smartphones or smartwatches) to better understand humans'

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traits, behavior, and functioning [38,39]. This includes both active data, which requires a short action from the user, and passive data, collected through sensors on the device without requiring a user action [39-41]. Studies have shown promising results regarding the integration of digital phenotyping into clinical practice [42-45]. In treatment, the objectively measured data collected from smartphones provide valuable insights into adolescents' real-life functioning, including daily emotions and behavioral patterns [45-48]. Furthermore, the use of wearables as part of digital phenotyping enhances adolescents' self-management, thereby increasing their engagement in treatment [49]. Therefore, integrating digital phenotyping in TAU offers new opportunities to address emotion regulation and motivation problems in the forensic setting.

Feelee is a new smartphone app that leverages digital phenotyping to enhance emotion regulation skills. The app connects digital diary entries by means of emojis (active data) with movement and sleep time (passive data) to provide users with accessible insights into their emotions and behavior. Emojis which include pictographs of faces, objects, and symbols, have been shown to effectively communicate emotions, mood, and physical states [48]. Users are notified 3 times a day (8 AM, 12 AM, and 8 PM, but the times can be adjusted) to enter an emoji. Along with the emoji, users are asked to reflect on 3 questions: "How come you feel this way?" "What are you doing?" and "Who are you with?" Feelee asks to reflect for a moment on the specified emoji. In addition to these active data inputs, Feelee combines the emoji data with passive data on users' movement and sleep. Poor movement and sleep quality in adolescence are associated with negative emotions and mood disturbances [50-52]. Furthermore, monitored changes in movement and sleep patterns are a strong indicator of the risk of emotion regulation problems [44,53,54]. By combining active emoji and passive behavioral data, Feelee offers valuable insights into adolescents' daily emotional and behavioral functioning, as well as potential risk patterns in emotion regulation. The low-threshold approach of the app, along with its focus on enhancing emotional regulation skills, makes it a promising transdiagnostic tool for supporting current TAU in forensic outpatient care.

The integration of Feelee into TAU in the forensic outpatient setting can be valuable in 3 aspects of enhancing emotion regulation skills: emotional recognition, reflection, and the development of strategies to manage emotional impulses. First, Feelee facilitates emotional recognition by using preselected emojis, which encourage users to identify and differentiate their emotional states. In TAU, discussions surrounding these emoji selections further support this process, helping adolescents improve their ability to recognize and articulate their emotions [55-58]. This approach also contributes to the development of reflective skills, as both the reflective questions posed by Feelee and the subsequent discussions in TAU further train adolescents' emotional reflection capacities. Additionally, the weekly overview provided by Feelee, which includes both emoji data and passive behavioral data (eg, physical activity and sleep patterns), supports clinicians and adolescents in identifying patterns and discussing them during treatment sessions. By training individual reflective skills, adolescents gain better insight into their emotional and behavioral functioning (such as physical activities and hours of sleep), which are important aspects of emotion regulation [29,59]. These reflective insights support the development of strategies to manage emotional impulses [60]. Furthermore, enhanced insights into emotional functioning contribute to a better understanding and control of emotional and physical cues, which is considered indicative of improved emotion regulation [60].

Besides emotion regulation, the integration of smartphone apps, like Feelee, offers new perspectives to increase adolescents' engagement and adherence to treatment. For example, the use of Feelee in treatment better aligns with adolescents' contemporary interests in digital devices than the usual paperwork (eg, questionnaires or emotion journals) used in mental health care [61]. For adolescents, it is more appealing to be engaged with personalized real-time data that is presented in a visual way [62,63]. Furthermore, the integration of Feelee in treatments contributes to more shared goals, tasks, and decision-making processes, which positively affect the therapeutic alliance [64]. Beyond treatment, Feelee offers opportunities to motivate self-management behaviors by lowering barriers for adolescents to practice emotion regulation skills outside the treatment [48,65]. Hence, Feelee can positively contribute to the adolescents' motivation and therapeutic alliance, leading to increased engagement and adherence to treatment.

Study Aims

Given the potential of digital phenotyping to address the need for emotion-focused interventions for adolescents in forensic settings, we previously conducted a feasibility and usability study with a research version of Feelee in addition to TAU [58]. Feedback from participating adolescents and clinicians was incorporated into the development of a new version of the Feelee app. The aim of this article is to provide a detailed description of a multiple single-case experimental design (SCED). The primary objective of this research project is to explore the initial effectiveness of a new version of the Feelee app in addition to TAU to enhance emotion regulation skills. By conducting a SCED, we aim to explore individual changes and between-participant differences on 3 aspects of emotion regulation: recognizing reflection, and the ability to manage emotional impulses. We hypothesize that adolescents will show improvements in the 3 aspects of emotion regulation through the combined use of the Feelee app in TAU; however, we do expect differences in the strength of these improvements between participants.

Secondary objectives include examining the underlying mechanisms through which the Feelee app, as an adjunct to TAU, facilitates the development of emotional differentiation, self-reflection, insight, and emotional awareness. In this context, we also aim to assess the interindividual variability in the effects of the app. We hypothesize that the extent to which the Feelee app contributes to these 3 aspects of emotion regulation will differ across participants. Additionally, we aim to investigate how the use of Feelee to TAU influences shared-goal, decision-making, and self-management within treatment. We hypothesize that the integration of Feelee into TAU will

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positively affect both treatment alliance and treatment motivation.

The fourth and final objective is to gain an in-depth understanding of the experiences of both adolescents and clinicians using the Feelee app, as well as its application in treatment. We expect that both adolescents and clinicians will respond positively to the use of the Feelee app and will provide valuable recommendations for its further development and integration into treatment.

Methods

Study Design

In this study, we apply a multiple single-case experimental ABA design across single participants [66-68]. The multiple ABA-design is a SCED method used to evaluate the effectiveness of an intervention at the individual level [68]. Unlike group-based comparison methods, such as randomized controlled trials (RCTs), which compare outcomes across different groups, we conduct repeated measurements within the same individual under varying conditions [69]. For ABA-designs, repeated measurements are conducted in the absence (A) and presence (B) of an intervention [67,68,70]. This approach allows participants to serve as their own controls [68,69]. Performing a SCED, such as an ABA design, is particularly effective for identifying causal relationships between an intervention (independent variable) and changes in the outcome measures (dependent variables) [69]. Moreover, SCED is an idiographic research method, enabling the tailoring of interventions to the unique needs of participants during the study [71,72]. This makes SCED especially suited for small, heterogeneous populations, where recruiting large numbers of participants can be challenging and time-consuming. This study aims to examine the effects of Feelee in forensic care, which can be characterized as a hard-to-reach study population, making this study design highly suitable. Additionally, the intensive study of a small population in a clinical setting contributes to a better understanding of the potential effects of the intervention within the variability of individuals in the clinical setting [73].

Participants follow a 2-week baseline phase, 4-week intervention phase, and a 2-week follow-up phase. The inclusion of a baseline phase and the absence of randomization are due to practical considerations related to the hard-to-reach population in this study and the limited effectiveness of randomization for ensuring reliability in this case. Therefore, the phases are kept as short as possible to minimize potential dropout. Primary outcome measurements are taken daily throughout the baseline (phase A1), intervention (phase B), and follow-up phase (phase A2), using the smartphone app M-path. Secondary outcomes are measured at pre-(T0), post-(T1), and short-term follow-up measurements (T2). Additionally, qualitative data collection occurs at T2 and T3. The total research period, from the start of the baseline until the final measurement of the follow-up phase, lasts approximately 8 weeks per participant. A short-term follow-up measurement is taken 3 months after T3. An overview of the study design is presented in Figure 1.

Figure 1. Overview of the study design. Daily repeated measure starts immediately after T0. T1 is conducted on the first day following the 4-week intervention phase. T2 takes place after 2-week follow-up. T3 is conducted 3-months after T2. A(1): baseline; A(2): follow-up; B: Intervention; D: daily questionnaires; I: semistructured interviews; T0: premeasurement; T1: postmeasurement; T2: follow-up measurement; T3: 3-months follow-up measurement.

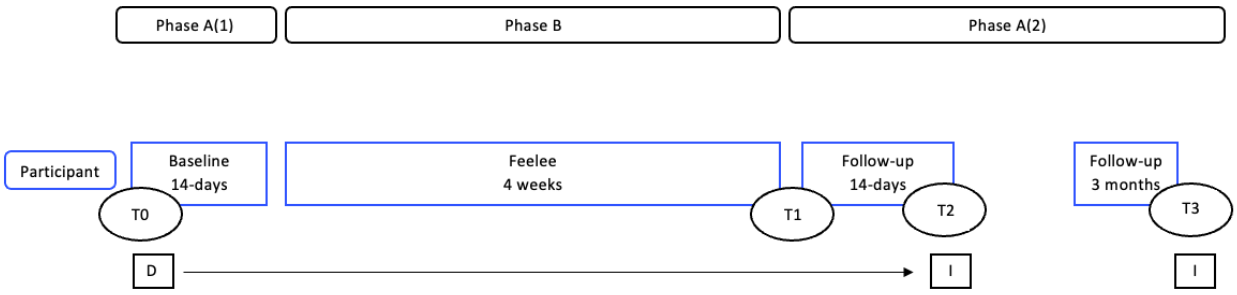

Participants

Participants are recruited among clients from forensic outpatient teams at Levvel and Inforsa. Both organizations provide mental health care and support for residents of the metropolitan region of Amsterdam. These clients are referred for treatment by a probation officer or general practitioner due to concerns about delinquent behavior and recidivism. The population at Inforsa is slightly older (age 16-27 years) than at Levvel (age 15-21 years). Clients from Inforsa typically have a longer criminal justice history, and most have already been treated in the adult criminal justice system. Since the goal of the Feelee app is transdiagnostic and it can integrate into TAU with minimal barriers and low risks, no distinction is made between types of treatment for participants. However, clinicians are trained to assess the appropriateness of the Feelee app for potential participants, based on the following inclusion and exclusion criteria: (1) aged between 12 and 23 years, (2) at the moment of study in treatment at Levvel or Inforsa, (3) expected to be in treatment for at least 3 more months, (4) own an IOS or Android operating smartphone and (5) have a basic understanding of smartphone use. Exclusion criteria include (1) serious psychiatric conditions, such as psychosis or high risk of suicide, (2) insufficient understanding of the spoken and written Dutch language, and (3) not owning a smartphone.

Sample Size

The SCED research standards require studies to make at least 3 attempts to demonstrate an intervention effect. Additionally, each phase must include a minimum of 5 data points to effectively demonstrate an effect [70,74]. This means that at least 3 participants must complete a minimum of 5 measurements during the 2-week baseline, 4-week intervention, and 2-week follow-up phase to fulfill these requirements.

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Therefore, to gain a better understanding of individual differences and enable within- and between-participants comparisons, at least 9 to 10 participants will be included in the data analyses [67].

In addition to the SCED research requirements, the considerable risk for treatment attrition in the forensic population must also be considered. Studies on adolescents' outpatient mental health care report attrition rates ranging between 28% and 75% [75]. For the forensic population, a meta-analysis on juvenile inpatient treatments shows that dropout rates can go up to 60% [31,32]. To account for a potential 60% attrition rate and to ensure the inclusion of at least 9 participants for demonstrating intervention effects and conducting within- and between-participant analysis, a total of 24 participants will be included in this study.

Procedures

First, all adolescents in the caseload at the forensic outpatient teams are screened by clinicians. During this screening process, the clinician makes an initial informed assessment of whether the adolescent is eligible to participate in the study. All clinicians are thoroughly briefed about the study design and population in advance (see also section: Feelee training). Additionally, clinicians can always consult the first author or independent experts if they are uncertain about whether to approach an adolescent for the study. This screening method is necessary due to the high risk of nonresponse in the study population. When an adolescent is deemed eligible, the clinician briefly introduces the study to the adolescent. An information handout about the Feelee app and the study will be available for this purpose. If the adolescent meets these criteria and agrees to participate, the researcher arranges an informed consent appointment. During this appointment, the researcher explained the Feelee app and study procedures. The inclusion and exclusion criteria are reviewed again to confirm the adolescent's eligibility. If the adolescent meets the criteria and agrees to participate, informed consent is signed. If the adolescent is under 16 years old, parental or legal guardian consent is also required, and they need to sign the informed consent form.

After the informed consent procedure, premeasurement is conducted. Following this, daily measurements are set up by installing a data collection app (M-path) on the adolescent's smartphone. The researcher explains how to use the app and tests it directly. From that moment, adolescents receive a daily notification from the app to complete the measurement within a set time frame. The daily measurement continues throughout the 2-week baseline phase, the following 4-week intervention phase, until the last day of the 2-week follow-up phase. After the 2-week baseline phase, participants start using the Feelee app. The researcher provides them with the login details. From then on, participants select an emoji at least once a day (active data) and allow the app to collect data on their daily steps and hours of sleep per day through sensors (passive data). The clinician reviews the Feelee data during weekly treatment sessions. After the 4-week intervention phase, participants uninstall the Feelee app from their smartphones. Additionally, the researcher schedules an appointment for the postmeasurement. During the 2-week follow-up phase, participants continue completing the daily questionnaire but no longer use the Feelee app. anymore. Thereafter, an appointment is scheduled for the follow-up measurement and semistructured interview. To minimize the effort for participants, both the follow-up measurement and the semistructured interview are conducted in a single appointment. The researcher also arranges a final appointment with the clinician for an interview. Once these steps are completed, the study period closes. Three months after the study ends, participants are asked if they are willing to participate in the 3-month follow-up. If they agree, the researcher schedules the 3-month follow-up measurement and interview.

Participants receive compensation for each completed questionnaire and submitted emoji. The researcher and participant agree in advance on how often participants want to receive an update about the compensation. Additionally, the researcher, participant, and clinician make agreements about the contact moments during the study. The frequency of these contact moments is kept as consistent as possible among participants. However, it may vary slightly between participants, for example, to encourage the daily measurements. All contact moments are logged to track variations, which will be considered during the analysis.

Feelee App Use

The use of the Feelee app in this study is twofold. First, participants use the app independently, submitting at least one emoji each day and granting Feelee permission to read data on the number of steps and hours of sleep. After each emoji submission, participants receive advice that could positively influence emotions in daily life or a question to reflect on emotions and behavior. Furthermore, Feelee provides a weekly overview of the submitted emoji and collected behavioral data that can be viewed at any time (Figure 2).

Second, the weekly overview is discussed during weekly individual TAU sessions. In this process, clinicians follow a number of steps that contribute to the adolescents' emotional understanding [58]. Step 1 involves emotion recognition. Clinicians select one emoji from the weekly overview and ask the participant questions in order to feel and recognize the emoji in their body. Step 2 focuses on reflection. When submitting an emoji, Feelee forces participants to reflect on their emoji with a few short questions. In this step, participants and clinicians review the answers together and discuss them further. The most important aspect of this step is that participants can recall which circumstances in their daily lives may have influenced their emotions. Step 3 involves understanding patterns in emotions. In this step, clinicians analyze the Feelee data to identify patterns, such as whether certain emojis are linked to specific days of the week, activities, or social contacts. These questions help participants gain insight into the contextual and behavioral factors that may influence their emotions. Last, step 4 involves examining patterns in activity and sleep data alongside the emojis. Both participants and clinicians explore how the activity and sleep data might influence the emojis selected by the participant.

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Figure 2. Screenshots from the Feelee app.

Feelee Training

All clinicians in the participating teams complete a 2-day training session conducted by the first author, developed in collaboration with the third and fourth authors. On day 1, clinicians receive background information on the development of the Feelee app and study objectives. Between the first and second day of training is at least 14 days, during which clinicians are instructed to use the Feelee app by themselves. On day 2, clinicians exchange their experiences with the app and receive guidance on how to integrate Feelee and its data into treatment. This includes instructions on interpreting the app's data as well as identifying and addressing relevant patterns. These instructions are informed by the Feelee manual, specifically developed for the forensic population, which is distributed to clinicians during the training. Clinicians also participate in a role-play exercise based on the manual, providing them with an opportunity to practice using the Feelee data in a clinical context. Additionally, clinicians are briefed on the participant selection criteria, ensuring they understand the process for identifying eligible participants and the potential risks associated with participation in the study. Throughout the research period, clinicians received ongoing guidance through different contact moments with the first author. To assess adherence to the Feelee manual and study protocol, clinicians complete a brief questionnaire following each treatment session during the intervention phase.

Measures

Primary Outcome Measure

Assessment

The primary outcome measure is collected daily through a short self-report questionnaire on the adolescents' smartphones. Participants received a notification on their smartphones after 3 PM to complete the questionnaire before the end of the day.

Emotion Regulation

Emotion regulation is measured using a short composite questionnaire comprising items from the Difficulties in Emotional Regulation Scale (DERS-36) and Regulation of Emotion Systems Survey for Ecological Momentary Assessment [76-78]. The questionnaire includes 2 items from the DERS-36 that focus on recognizing and managing emotions, adapted for daily use. Answers to the DERS-36 can be given by a 5-point Likert-scale from "strongly disagree" to "strongly agree" [77]. Additionally, 4 items from the Regulation of Emotion Systems Survey for Ecological Momentary Assessment, representing rumination, reappraisal, distraction, and suppression, are included to capture the various aspects of emotion regulation strategies. Answers can be given from 0="not at all" to 10="very much" [78].

Secondary Outcome Measures

Assessment

The secondary outcome measures include the potential working mechanisms of the Feelee app (emotional differentiation, reflection, and awareness), as well as treatment-related factors such as motivation and alliance. These measures are collected at pre-(T0), post-(T1), and follow up-(T2) measurements.

Emotional Differentiation

Emotional differentiation is measured using the Positive and Negative Affect Schedule [79]. The Positive and Negative Affect Schedule asks participants to rate 20 items of prewritten emotions, including 10 positive and 10 negative emotions, presented in random order. The items are scored on a Likert scale ranging from "Very slightly/not at all" to "Extremely." Both the positive affection and negative affection scales demonstrate high reliability [79].

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Emotional Reflection

Emotional reflection is assessed using the Self-reflection and Insight Scale for Youth (SRIS-Y) [80]. The SRIS-Y is a 17-item self-report questionnaire, answered on a 6-point Likert scale ranging from "disagree strongly" to "agree strongly." The instrument consists of 2 subscales, self-reflection and insight, which provide separate subscores. The original adult version has been shown to be a reliable and valid measure of self-reflection and insight [81], and the SRIS-Y is considered a reliable tool for measuring these constructs in adolescents [80].

Emotional Awareness

Emotional awareness is measured by the Multidimensional Assessment of Interceptive Awareness [82]. The Multidimensional Assessment of Interceptive Awareness includes 32 items across 8 different subscales: noticing, not-distracting, not-worrying, attention regulation, emotional awareness, self-regulation, body-listening, and trusting. Answers can be given on a 6-point Likert scale ranging from "never" to "always." To minimize the questionnaire length, only the Emotional awareness subscale is used, which demonstrates good reliability [82].

Treatment Motivation

To measure the participant's motivation for treatment, the Dutch Adolescent Treatment Motivation Questionnaire (ATMQ) is used [83]. The ATMQ consists of 11 self-report items rated on a 3-point Likert scale, including "not true," "kind of true," and "true." Overall, the ATMQ demonstrates good reliability [83].

Treatment Alliance

Treatment alliance is assessed using an abbreviated Dutch translation of the Working Alliance Inventory (WAV-12) [84]. The questionnaire includes versions for youth, parents, mentors, and family therapists, with only the youth version used in this study. The WAV-12 consists of 12 self-report items rated on a 5-point Likert scale from "rarely or never" to "always." Higher scores on this questionnaire indicate a stronger working alliance between the client and clinician. The Dutch version of the WAV-12 showed high reliability [84].

Other Study Parameters

Sociodemographic Parameters

The following social demographic information is collected: age, sex, native country, language, second language (optional), education level, ethnicity, living situation, marital status of parents, and possible experiences with delinquent behavior. The information is gathered through a demographic questionnaire developed by the researchers. Furthermore, background information about the treatment process, such as diagnostic background and treatment history, is obtained from file information provided by the clinician.

Treatment Integrity

Treatment integrity is intended to briefly capture the use of the Feelee app during treatment sessions. It is measured through a short questionnaire completed by the clinician after each weekly treatment session during the intervention phase (phase B). The questionnaire includes 4 short questions regarding the availability of data in the Feelee app and whether these data were discussed during the treatment session.

Feelee App Parameters

The following study parameters are derived from the use of Feelee app during the 4-week intervention phase.

Emotional Well-Being

Emotional well-being is measured by active monitoring. During the intervention phase, participants complete a short emoji questionnaire in the Feelee app once a day. The selected emojis are presented in a weekly overview in the Feelee app.

Physical Activity

Insight into physical activity is obtained through passive monitoring, with data read from the health app (Google Fit for Android, Health app for IOS) by the Feelee app. Physical activity is measured by the number of steps taken each day, tracked by a pedometer on a smartphone. The Feelee app provides a weekly overview of the daily step count, displayed alongside the selected emoji.

Sleep Activity

Sleep activity is also monitored passively through data collected by the health app. It is measured by the reported bedtime in combination with screen time and movement (via the pedometer). The Feelee app provides a weekly overview of the hours of sleep per night, displayed both with and without the associated emojis.

Evaluation

Assessment

During the follow-up phase, both quantitative and qualitative evaluations are conducted to assess overall experiences regarding the Feelee app and the use of the smartphone app during treatment.

Evaluation Feelee App

To evaluate the Feelee app, we first conduct 2 short questionnaires: the Twente Engagement with eHealth Technologies Scales [85] and the System Usability Scale [86]. The Twente Engagement with eHealth Technologies Scale consists of 9 items about engagement, of which 3 assess behavioral engagement, 3 assess cognitive engagement, and 3 assess affective engagement. Answers are given on a 5-point Likert scale from "strongly disagree" to "strongly agree." The overall questionnaire shows good reliability [85]. In addition, the System Usability Scale is used as a quick tool to measure the usability of Feelee. A total of 10 items can be answered on a 5-point Likert scale from "strongly disagree" to "strongly agree" [86]. The questionnaire also shows good reliability [87].

To get an in-depth understanding of the use of Feelee, semistructured interviews with both adolescents and clinicians are conducted. The interviews focus on experiences regarding emotional skills and changes in treatment-related factors (motivation and treatment alliance). Adolescents and clinicians are asked about possible changes during treatment sessions and whether these changes may be attributed to the use of Feelee.

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The interviews provide opportunities to get a deeper insight into the adolescents' and clinicians' experiences, as well as feedback for further improvements in the use of the Feelee app.

Evaluation Smartphone Use in Treatment

In addition to the evaluation of the Feelee app, questions are added to the interviews about the general use of smartphone apps and smartphone data in treatments. Adolescents and clinicians are asked to reflect on their experiences regarding the use of smartphones in treatment and whether they liked working with them. Further, special attention is paid to the use of smartphone data (active and passive) during the treatment session.

Figure 3 and Table 1 present an overview of all measurements and data collection moments.

Figure 3. Overview data collection moments. ATMQ: adolescent treatment motivation questionnaire; DERS: Difficulties in Emotion Regulation Scale; MAIA: multidimensional assessment of interceptive awareness; PANAS: Positive and Negative Affect Schedule; RESS-EMA: Regulation of Emotion Systems Survey for Ecological Momentary Assessment; SRIS-Y: Self-reflection Insight Scale for Youth; SUS: System Usability Scale; TWEETS: Twente Engagement with eHealth Technologies Scale; WAV-12: Working Alliance Inventory.

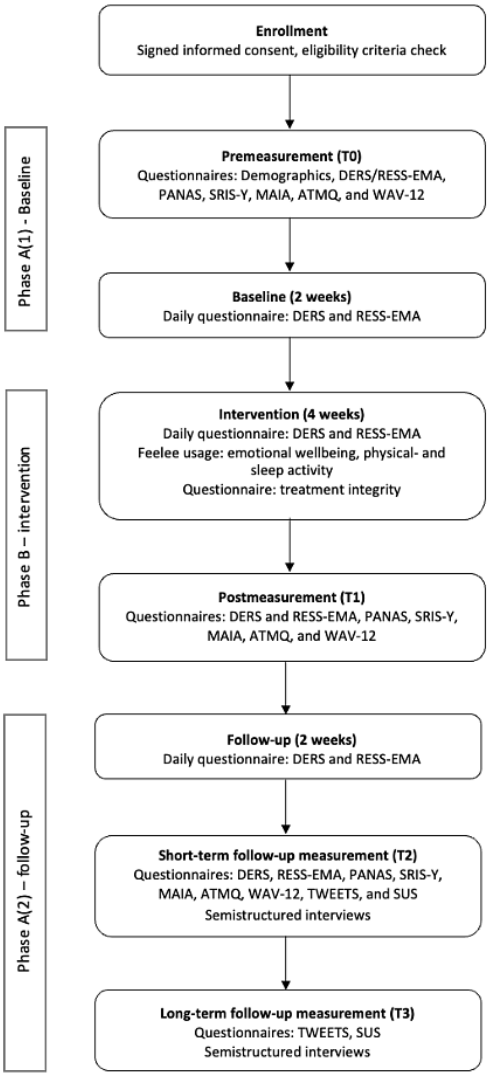

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Table 1. Overview variables, measurements, and informants.

Variable	Measure	Measuring point	Informant
Primary outcome			
Emotion regulation	DERS[a], RESS-EMA[b]	Daily questionnaire	Adolescent
Secondary outcomes			
Emotional differentiation	PANAS[c]	T0, T1, and T2	Adolescent
Emotional reflection	SRIS-Y[d]	T0, T1, and T2	Adolescent
Emotional awareness	MAIA[e]	T0, T1, and T2	Adolescent
Treatment motivation	ATMQ[f]	T0, T1, and T2	Adolescent
Treatment alliance	WAV-12[g]	T0, T1, and T2	Adolescent
Other study outcomes			
Demographics	Demographic questionnaire	T0	Adolescent
Diagnostic and treatment history	File information	T0	Clinician
Emotional wellbeing	Feelee app	Intervention phase	Adolescent
Physical activity	Feelee app	Intervention phase	Adolescent
Sleep activity	Feelee app	Intervention phase	Adolescent
Treatment integrity	Questionnaire	Intervention phase	Clinician
Evaluation Feelee app	TWEETS[h], SUS[i], and semistructured interviews	T2 and T3	Adolescents and clinician
Evaluation smartphone use	Semistructured interviews	T2 and T3	Adolescent

[a]DERS: Difficulties in Emotion Regulation Scale.
[b]RESS-EMA: Regulation of Emotion Systems Survey for Ecological Momentary Assessment.
[c]PANAS: Positive and Negative Affect Schedule.
[d]SRIS-Y: Self-reflection and Insight Scale for Youth.
[e]MAIA: Multidimensional Assessment of Interceptive Awareness.
[f]ATMQ: Adolescent Treatment Motivation Questionnaire.
[g]WAV-12: Working Alliance Inventory.
[h]TWEETS: Twente Engagement with eHealth Technologies Scale.
[i]SUS: System Usability Scale.

Analysis

The primary outcome measure, emotion regulation, is assessed daily through a self-report questionnaire completed on the participants' smartphones. As prescribed by SCED-methods, results are analyzed using visual analyses [68,74]. For this purpose, the hypotheses for each item are plotted visually, mapping the expected direction and strength of change between phases. Graphical visualizations are conducted at both the within-individual participant and between-participant levels. Through visual inspection, the degree of spread between the daily measurements, the potential rate of change across all phases, and the degree of change regarding the hypothesis are examined for each participant individually. To assess the reliability of potential changes, a 95% CI is calculated for each participant using standard errors of difference. For each item, a standardized mean difference permutation distance test is performed for both each participant and the group level, with a P value of <.05 considered significant. [88]. At the group level, we also perform a Cohen d test. If necessary, additional analyses related to the SCED-procedure will be conducted

The secondary outcome measures are collected during pre-(T0), post (T1), and follow-up measurements (T2 and T3) and semistructured interviews during both follow-up measurements. For the quantitative data, each data point is analyzed by computing a Reliable Change Index (RCI) [89]. The RCI is used to assess whether the observed change in an individual's score is statistically significant and exceeds the potential measurement error. A change is considered reliable if the RCI meets the criteria of >1.96. The RCI scores of participants are compared with the results from the primary outcome.

For the qualitative data, interviews are recorded and transcribed. The anonymous transcripts are then analyzed at both the individual and group levels. At the individual level, the analysis aims to identify explanations underpinning each participant's quantitative results. At the group level, recurring themes and shared experiences across participants are examined to identify overarching patterns. For both levels of analysis, reflexive thematic analysis [90] is performed using MAXQDA [91]. The coding process begins with an initial phase at the individual level, where codes are defined based on participants' quantitative

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data, including experienced effects on the emotion variables, treatment factors, and evaluation of Feelee app use. These codes are iteratively refined and expanded following a thorough review of the transcript from both the participant and the involved clinician. Subsequently, a separate coding phase is conducted at the group level to systematically identify patterns and themes across participants. All transcripts are independently coded by 2 researchers. After each round of data analysis, discussions are held to ensure consensus on the identified codes for individual participants and consistency in the identification of group-level themes. To enhance transparency and maintain methodological rigor, each researcher keeps a logbook documenting the analysis process.

Ethical Considerations

This study was approved in April 2023 by the independent Medical Ethical Committee of Vrije Universiteit Medical Center (reference number: 2022.0398). Since this study involves clinical research that includes the smartphone in treatment, the Medical Device Regulation is applicable [92]. Therefore, in addition to the ethical aspects, the study is also reviewed on the technical functioning and safety. No participants younger than 12 years were included in this study. During informed consent, adolescents give explicit permission for the audio recording of interviews and for the collection of both active and passive data by the Feelee app. Audio recordings are used to produce deidentified transcripts of the interviews and are permanently deleted immediately after transcription. Both the recordings and transcripts are securely stored on an encrypted hard drive within the research department. Further details on data handling and storage, including those related to the Feelee app, are provided in the section "Confidentiality of Data." Participants received a gift voucher of up to €33 (US $38.66) as compensation for their contribution, depending on their level of engagement with both the questionnaires and the daily emoji submissions in the Feelee app. This manuscript does not contain any identifiable images or data related to participants. Further implementation of the study proceeds according to the principles of the World Medical Association Declaration of Helsinki, the Medical Research Involving Human Subjects Act, and guidelines of the Medical Device Regulation [93].

Confidentiality of Data

Handling and storage of data are done in accordance with the General Data Protection Regulation. Furthermore, a data protection impact assessment and confidentiality, integrity, and availability are performed in collaboration with the privacy officer from Amsterdam UMC to identify potential risks and measures for data collection and storage. Study data, including questionnaires and interviews, are collected by researchers from the Department of Child and Adolescent Psychiatry at the Amsterdam UMC. All data are collected and stored under a unique participant ID number. For the daily questionnaire, data are stored in a protected folder from the M-Path app on the participant's smartphone. This folder is only accessible by M-Path. Furthermore, the storage data in M-Path consists only of bytes, which means the content of the data is not visible. At the end of the study, the M-Path data are exported to the participant folder that is kept on the secure disk of the study project in the department. Data from the other questionnaires are collected and stored on the Castor Electronic Data Capture database. During the intervention, participants use the Feelee app. Since users of Feelee normally log in with their private email addresses, participants in this study will receive a unique email address and password. In this way, Feelee's data from participants remains unidentified. Data from Feelee is stored on a secure server managed by a professional ISO 27001 qualified hosting organization. At the end of the study, a data export of the Feelee data is conducted to match participants' Feelee data with the participants' measurements in the intervention phase. Last, interviews are recorded by a recording device. After the transcript of these recordings is completed, the recordings are deleted. In accordance with the guidance from the Board of Directors of the Amsterdam UMC, research data and analyses are stored for 15 years after finishing the research project.

Results

Data collection started in June 2023 and was completed in January 2025. At the time of final manuscript submission, 89 participants had been recruited, 24 had enrolled, and 15 had been retained in the study. Data analysis started after the final data collection had been completed. Study results will be published in scientific peer-reviewed journals and presented during international and national conferences. The study has been registered at the medical ethics committee of the Vrije Universiteit Medical Center, the Netherlands (2022.0398/NL78889.029.21) and at the ClinicalTrials.gov registry (NCT06509360)

Discussion

Study Aims

While current treatments in the forensic outpatient setting are often limited by providing sufficient insight into daily emotion and behavioral functioning, as well as motivating and engaging adolescents for treatment, Feelee offers new opportunities to meet these challenges [48,58]. In this study, we elaborated the protocol of the SCED study in order to conduct an initial exploration of the effectiveness of Feelee in forensic outpatient TAU. By using both quantitative and qualitative methods, we are able to get an in-depth understanding of the individual effectiveness and experiences of Feelee in a clinical setting. Thereby, we aim to conduct an adequate and effective innovative tool to support the treatment of adolescents with emotion regulation problems.

Strengths and Challenges

The study has multiple strengths. First, in order to explore the initial effects, a SCED will be applied instead of more traditional group comparison designs, such as an RCT. Besides the practical advantages (eg, less time-consuming and more cost-efficacy), SCED provides higher internal validity than traditional group comparison designs [68,74]. Throughout a SCED baseline, it is possible to collect a large amount of individual and contextual information within the entire study process while respecting the personal variability of each participant [74]. Additionally, it is

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possible to include the real-time monitored data from Feelee to increase the number of observations that capture a more accurate presentation of the outcomes on the individual level [94]. This provides a lot of insights about the individual trajectory of the intervention for each participant, which allows us to get an in-depth understanding of the circumstances under which Feelee could be supportive in their treatment. Second, through the use of repeated measurement within and beyond treatment sessions, we are able to get insight into the real-life circumstances of the use of Feelee in addition to treatment. This provides a unique insight into the specific needs of participants, allowing better-tailored care [95]. Furthermore, these insights contribute to strengthening the ecological validity of the study [67,71,96]. Last, the use of Feelee has been applied and studied in TAU, which means participation in this study is known for its low threshold. Therefore, participating in the study poses a minor risk and burden for participants.

In addition to the strengths, this study also faces several potential challenges. First, as described in this study, treatments in the forensic setting are typified by a high number of nonresponses and dropouts [31,32]. Despite several measures being taken (eg, keeping the study design and questionnaires as short as possible), nonresponse and dropout will still be conceivable. Therefore, the research team will try to facilitate the participants as much as possible. This may include scheduling appointments at the participant's treatment location, but also staying in touch with participants during the study by sending reminders for appointments or questionnaires. Second, another issue related to the risk of nonresponse is the potential for selection bias. Participants are recruited through preselection by the researchers in consultation with the involved clinicians. This approach risks excluding adolescents who are less motivated for treatment and belong to a higher risk group for recidivism. Therefore, the training for clinicians emphasized the potential risk of selection bias. In addition, researchers will continue to emphasize the risk in the discussions with clinicians to ensure appropriate considerations will be made during recruitment. Third, this study makes use of validated self-report questionnaires, which potentially causes the risk of social desirability bias. However, a mixed method approach will be applied to combine the qualitative outcomes with quantitative results. This triangulation contributes to the interpretation of the study results and reduces the limitations of self-reporting. Last, Feelee is a new innovative tool that is still in the development phase, meaning the potential risks and benefits have yet to be fully established. As such, during clinician training, particular attention is given to the potential risks associated with participant involvement in this study, ensuring these factors are carefully considered during participant selection. Moreover, studying the integration of Feelee in treatment requires a cautious and precise research approach. Therefore, the use of a SCED rather than an RCT is particularly suitable at this stage of development and research [66,67].

Implications for Practice

Feelee is a new innovative smartphone app that could be valuable in improving adolescent emotion regulation skills and contribute positively to treatment motivation and alliance. The study will demonstrate that, while observing medical-ethical and privacy standards, it is possible to safely use smartphone data in treatment. This contributes to new insights and perspectives in data-driven treatment. In addition, the description of the study protocol will show the possibilities of clinical research for adolescents with delinquent behavior, a population known to be hard to reach. Consequently, this population is often overlooked in research due to the high dropout risk. However, these adolescents, in particular, would benefit from new innovations that better suit their perspectives and interests. Conducting a SCED instead of an RCT contributes to the flexibility required for this population and the achievability of the required sample size. This study shows possibilities for conducting innovative research in difficult clinical environments. As such, the study contributes to new insights in science and clinical practice.

Conclusions

To date, the development and research of smartphone apps for the forensic population remains limited. The apps that are available are often developed and designed for adults [97], or additional wearables (such as smartwatches) are needed for app use [98]. With respect to improving emotion regulation skills, apps are often limited to tracking daily emotions. In contrast, Feelee tracks and displays both emotions and behavior aspects (eg, movement and sleep). Additionally, the Feelee app is designed for use on smartphones without the need for other wearables, increasing its user-friendliness and accessibility.

So far, only feasibility and usability studies using a research version of the Feelee app have been published [48,58]. However, no empirical research has been conducted to explore the effectiveness of Feelee in clinical treatment. This study will be the first that will explore the value of Feelee in enhancing emotion regulation skills in the treatment of delinquent behavior. Results will contribute to the further development and design of follow-up studies of Feelee in treatment.

Acknowledgments

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Data Availability

The datasets generated or analyzed during the study, for which this protocol is described, will be available from the corresponding author upon reasonable request, once the research and data analyses have been completed.

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Authors' Contributions

MMLL conceptualized and designed the final study protocol. LvD and TMvdP were major reviewers. RB and AP reviewed the final study protocol. MMLL wrote the manuscript. All authors (LvD, TMvdP, RB, and AP) read, edited, and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ATMQ: adolescent treatment motivation questionnaire
DERS: Difficulties in Emotion Regulation Scale
RCI: Reliable Change Index
RCT: randomized controlled trial
RNR: risk-need-responsibility
SCED: single-case experimental design
SRIS-Y: self-reflection insight scale for youth
TAU: treatment as usual
WAV-12: working alliance inventory

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Protocol

Remote Monitoring by ViQtor Upon Implementation on a Surgical Department (REQUEST-Trial): Protocol for a Prospective Implementation Study

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Abstract

Background: Continuous monitoring of patients' vital signs is critical for early detection of postoperative complications. Traditional manual monitoring by nursing staff is time-consuming and provides only intermittent data. Wearable devices offer continuous monitoring capabilities, potentially enhancing early warning systems, reducing nurse workload, and facilitating earlier patient discharge. However, research on their implementation and effectiveness in clinical settings remains limited.

Objective: This study aims to evaluate the implementation and feasibility of continuous monitoring using photoplethysmography sensor technology (a viQtor device) in a surgical ward. We will also assess the impact on nursing workload and the usability of this workflow.

Methods: The REQUEST (Remote Monitoring by viQtor Upon Implementation on a Surgical Department) study is a prospective observational implementation study conducted over 8 months in a surgical ward. The vital signs of 500 postoperative patients will be continuously monitored using the viQtor device, which measures heart rate, respiratory rate, and oxygen saturation. The study consists of 2 phases: an initial period with manual spot checks, followed by a phase using the wearable device as the primary monitoring tool. Outcomes include the Integrated Workload Scale for nursing workload and a framework evaluating acceptability, feasibility, adoption, and sustainability. Data collection involves device performance metrics, questionnaires (the Evidence-Based Practice Attitude Scale and the System Usability Scale), and thematic analysis of focus groups.

Results: Staff training was completed in October 2024, and full implementation is ongoing. Preliminary findings, including data on usability and workload, are expected by July 2025.

Conclusions: This study will provide insight into the practical implementation of continuous vital sign monitoring in surgical care. The findings may support future adoption of wearable technology in clinical workflows.

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KEYWORDS

monitoring; vital signs; early warning system; implementation; wearable device; workload

Introduction

The health care sector is currently undergoing a significant transformation, with increasing emphasis on integrating smart technologies to enhance patient safety and clinical efficiency. A central innovation in this shift is the use of wearable monitoring devices in hospitals, particularly for patients recovering from major abdominal surgery. These procedures

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are associated with a high risk of serious adverse events, which could lead to preventable harm if early signs of clinical deterioration—often evident in vital sign changes—go unnoticed [1].

Current early warning systems are based on intermittent manual assessments of vital signs, and the Early Warning Score (EWS), typically performed three times daily. However, research indicates that deterioration in vital parameters often precedes clinical events by several hours. One study found that in approximately 60% of patients who experienced postoperative complications, changes in vital signs had already occurred but were not recognized in time due to the limited frequency of monitoring [2].

Efforts have been made to improve the EWS, such as the development of the Modified Early Warning Score (MEWS), which incorporates oxygen saturation [3,4]. While these adaptations have increased the sophistication of monitoring, the overall predictive value of these systems remains limited [2,5]. Moreover, variation in EWS methodologies and inconsistent validation have raised concerns about reliability in daily clinical practice [6].

Advancements in wearable technology offer a promising alternative. These devices provide real-time, continuous monitoring of vital signs, enabling earlier detection of clinical deterioration and potentially more timely intervention [4,7-9]. In addition, continuous monitoring may reduce the burden of manual assessments on nursing staff. Despite the potential benefits, widespread implementation of wearables in clinical settings remains uncommon. Most studies to date have focused on technical performance, while few have explored how such devices are adopted and integrated into routine care.

Successfully introducing wearable monitoring systems requires attention not only to the technology itself but also to the clinical environment, the needs and attitudes of health care professionals, and the sustainability of new workflows. This study therefore follows the revised Medical Research Council framework for evaluating complex interventions [10], which emphasizes the role of context, stakeholder engagement, and real-world feasibility.

The objective of this study is to evaluate the implementation and feasibility of continuous vital sign monitoring using the viQtor wearable device in a surgical ward. In doing so, the study aims to assess the device's usability, its impact on nursing workload, and how effectively it can be embedded in standard clinical practice.

Methods

Setting

This prospective implementation study with retrospective data analysis (the REQUEST [Remote Monitoring by viQtor Upon Implementation on a Surgical Department] trial) will be conducted at a large teaching hospital. All adult patients (aged 18 years and older) admitted to the surgical department for elective procedures will be eligible for inclusion, provided they meet our inclusion criteria and provide informed consent. Patients unable to wear the device or unwilling to participate will be excluded.

The viQtor device, developed by SMARTCARE, was selected due to its proven capability for autonomous, continuous monitoring and its established structure for seamless data transfer into the electronic health record (EHR). The device is CE (Conformité Européenne)-certified and transmits data every minute via a cellular network without the need for any hub. Each vital sign—heart rate, respiratory rate, and peripheral oxygen saturation (SpO_2)—is updated every minute, with data being transferred to the EHR. The device provides median values from the last 4 hours for each vital sign, which means that the system aggregates data over that period to ensure stability in measurements. In the event of missing data, the system generates flags to indicate the absence of readings, and data imputation strategies will be applied. By using clinical-grade photoplethysmography sensor technology, the device allows accurate tracking of heart rate, respiratory rate, and SpO_2. Although the device can also measure skin temperature, this parameter will not be used in this study. The solution comprises a device with a charger and an armband. The device is worn on the upper arm under clothing and is applied upon admission (Figure 1).

Figure 1. The viQtor device placed on the upper arm.

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Implementation Phase

Implementation of the device as the new standard of care for monitoring will be executed in 2 distinct phases to ensure a thorough evaluation and implementation of this monitoring system (Table 1).

During phase 1 (the initial phase; months 1-3), patients will continue to receive the current standard of care, which involves manual spot checks and MEWS measurements by nursing staff. Concurrently, all health care staff will receive training on the application, data interpretation, and protocol adherence concerning the solution to optimize the infrastructure before its implementation.

Following phase 1 (in month 4; the evaluation and validation period), the preimplementation phase will be evaluated. Predictive accuracy will be evaluated by comparing device data against clinical outcomes such as complications, intensive care unit transfers, or MEWS-triggered interventions using area under the receiver operating characteristic curve analysis.

In phase 2 (months 5-8), the wearable will become the primary tool for patient monitoring, supplemented by manual spot checks by nurses as needed. This phase aims to evaluate the integration into standard care.

During the whole study, every minute data are securely stored. During phase 2 of the study, 6 times a day, median values of the previous 4-hour window will be uploaded to the EHR. In case of signal loss or low-quality readings, the system generates flags, allowing for assessment of signal-to-noise ratio (SNR).

Table 1. Psychometric properties and statistical analysis.

Objective	Instrument	Variable	Statistical test	Achievement criteria
Fidelity	SUS[a]	Continuous	Unpaired *t* test or Mann-Whitney *U* test	Fidelity achieved when protocol adherence is ≥95%
Acceptance	SC[b]/day	Continuous	Descriptive statistics	Acceptance achieved when ≥75% of nurses use the device regularly
Acceptance	SC/patient	Continuous	Descriptive statistics	Acceptance achieved when ≥75% of nurses use the device regularly
Acceptance	IWS[c]	Ordinal	1-way ANOVA	Acceptance achieved when ≥75% of nurses use the device regularly
Adoption	EBPAS[d]	Continuous	Repeated measures ANOVA	Adoption achieved when device use exceeds 70% by clinical staff
Appropriateness	SNR[e]	Continuous	Descriptive statistics	Adoption achieved when device use exceeds 70% by clinical staff
Appropriateness	ADE[f]	Continuous	Descriptive statistics	Appropriateness achieved with minimal ADEs
Feasibility	Thematic analysis	Nominal	Braun and Clarke [11] thematic analysis	Feasibility achieved when 80% of clinicians can successfully implement the device
Time efficiency	Time measurement	Continuous	Descriptive statistics	Time efficiency achieved when nurses' time spent on monitoring decreases by ≥20%
Predictive accuracy	MEWS[g] and CREWS[h]	Nominal	AUROC[i]	Predictive accuracy achieved when AUROC ≥0.80

[a]SUS: System Usability Scale.
[b]SC: spot check.
[c]IWS: Integrated Workload Scale.
[d]EBPAS: Evidence Based Practice Attitude Scale.
[e]SNR: signal-to-noise ratio.
[f]ADE: adverse device event.
[g]MEWS: Modified Early Warning Score.
[h]CREWS: Continuous Remote Early Warning Score.
[i]AUROC: area under the receiver operating characteristic curve.

Outcomes

The primary objective of this study is to evaluate the implementation of a new wearable on the surgical ward at Catharina Hospital Eindhoven. This will be achieved by assessing its usability, degree of implementation, and the workload for nursing staff. The primary outcome will be acceptability, specifically evaluating workload as measured by the Integrated Workload Scale (IWS). The IWS is a comprehensive tool that provides multidimensional descriptions and gradations of workload, ranging from "not demanding" to "work too demanding" on a 9-point Likert scale. This scale is suitable for both periodic assessment and real-time monitoring of tasks, with measurements conducted throughout the entire study period.

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For secondary outcomes, the study will apply the framework of the taxonomy of implementation outcomes of Proctor et al [12], focusing on adoption, feasibility, appropriateness, predictive accuracy, and technical feasibility. Adoption will be measured by the Evidence-Based Practice Attitude Scale and the System Usability Scale, along with the amount of spot checks conducted in addition to the standard monitoring.

Feasibility will be evaluated by determining the extent to which health care employees can successfully implement the device, and by measuring the time required to perform and process manual spot checks or digital monitoring checks. Appropriateness will be assessed by examining the SNR and counting the number of (suspected) adverse events that occur during or result from the use of the wearable.

Additionally, the predictive accuracy for early detection of health deterioration and postoperative complications among patients will be evaluated through focus group discussions. Technical feasibility will involve analyzing the availability of data on the web platform, including monitoring time and the types and quantities of algorithm artifacts, such as low-quality data during the monitoring of photoplethysmography values.

Approximately 70 nurses from the surgical ward will participate in the study and complete the IWS. In addition, 10 nurses and 5 physicians will voluntarily join focus groups to conduct an in-depth evaluation of the new implementation. These focus groups, which will be established prior to the study's commencement, will meet 3 times during the study period to discuss the progress of the study and share their experiences with the implementation. A structured analysis of fidelity, feasibility, and acceptability will be conducted by the focus group, and this information will be processed and objectified using a thematic analysis devised by Braun and Clarke [11].

Statistical Analysis

Quantitative data will be analyzed using IBM SPSS Statistics (version 26.0). Descriptive statistics will be used to summarize categorical data (frequencies and percentages) and continuous variables (means and SD or medians and IQRs, depending on the distribution). Normality will be assessed using the Shapiro-Wilk test. Group comparisons will be made using *t* tests, ANOVA, Mann-Whitney *U*, or chi-square tests where appropriate. For repeated measures, linear mixed models or repeated measures ANOVA will be used. Qualitative data from focus groups will be coded and thematically analyzed following Braun and Clarke's [11] approach.

Ethical Considerations

This study involves human participants and has been approved by Medical Research Ethics Committees United (reference number W24.065). Written informed consent to participate will be obtained from all participants prior to inclusion in the study.

All data collected will be pseudonymized before analysis to protect participants' privacy. Personal identifiers will be replaced with unique study codes, and the key linking codes to participant identities will be stored separately in a secure, access-restricted location. Only authorized study personnel will have access to this information.

Participants will not receive any financial compensation or other incentives for participation in this study. Participation is voluntary, and participants may withdraw at any time without any consequences for their care.

Results

Staff training was completed in October 2024, and full implementation is ongoing. Up to 150 participants intend to be enrolled in the study. Preliminary findings, including data on usability and workload, are expected by July 2025 (see details in Table 2).

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Table 2. Measurement timetable for psychometric properties.

Objective	Instrument	0[a]	1	2	3	4 (evaluation/validation)	5	6	7	8 (evaluation/validation)
Fidelity	SUS[b]						Q[c]			Q
Acceptance	SC[d]/day				AD[e]					AD
Acceptance	SC/patient				AD					AD
Acceptance	IWS[f]	Q			Q		Q	Q	Q	Q
Adoption	EBPAS[g]	Q			Q				Q	Q
Appropriateness	SNR[h]									AD
Appropriateness	ADE[i]									AD
Feasibility	Thematic analysis				FG[j]			FG		FG
Time efficiency	Time measurement		M[k]	M	M		M	M	M	M
Predictive accuracy	MEWS[l] and CREWS[m]		M	M	M	AD and M	AD (and M)	AD (and M)	AD	AD

[a]Numbers 0-8 represent the study months, starting from baseline (month 0) through to month 8.
[b]SUS: System Usability Scale.
[c]Q: questionnaire.
[d]SC: spot check.
[e]AD: administered data.
[f]IWS: Integrated Workload Scale.
[g]EBPAS: Evidence Based Practice Attitude Scale.
[h]SNR: signal-to-noise ratio.
[i]ADE: adverse device event.
[j]FG: focus group.
[k]M: manual measurement.
[l]MEWS: Modified Early Warning Score.
[m]CREWS: Continuous Remote Early Warning Score.

Discussion

This study is expected to demonstrate that the implementation of continuous vital sign monitoring using the viQtor wearable device is feasible within a surgical ward setting. We anticipate that this technology will be perceived as acceptable and usable by health care professionals, and that its integration may contribute to a measurable reduction in perceived nursing workload. Importantly, by including continuous SpO_2 monitoring, the system may offer added clinical value in identifying early signs of postoperative deterioration.

While earlier studies have assessed the technical accuracy of wearable monitoring devices, relatively few have focused on their integration into clinical workflows. For instance, Breteler et al [8] validated a similar system in high-risk surgical patients, but implementation outcomes such as usability or staff adoption were not the focus. Bellomo et al [7] also examined automated advisory systems, but their routine use in general hospital wards remains uncommon.

Our study distinguishes itself by applying a structured implementation framework, specifically the revised Medical Research Council guidance [10] and the taxonomy of implementation outcomes of Proctor et al [12]. This approach allows us to assess whether the device not only works but also can be realistically adopted in daily practice.

A notable addition in our protocol is the continuous monitoring of SpO_2 , a parameter that was lacking in earlier studies such as those involving a Healthdot device. Since respiratory complications are among the more frequent and severe postoperative issues, continuous SpO_2 tracking may enhance the early recognition of patient decline [4,6,13].

The study's multidisciplinary design, combining clinical, technical, and implementation expertise could be seen as a strength. The use of validated instruments—including the IWS [14], Evidence-Based Practice Attitude Scale [12], and the System Usability Scale—ensures a structured and multidimensional evaluation.

Limitations of this study can be expected as well. As a single-center trial focusing on patients undergoing elective surgery, its findings may not be directly generalizable to other hospital departments or to emergency or critical care populations. Additionally, while the viQtor device captures data at regular intervals, data loss or reduced signal quality could occur. These technical aspects will be explored through SNR

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analysis and artifact tracking. If implementation proves successful, the findings may support broader deployment across other wards or institutions. Future research could explore postdischarge remote monitoring or the integration of wearable data into clinical decision support systems, possibly enhanced by predictive algorithms.

Results will be shared internally within the hospital through clinical meetings and departmental presentations. Externally, we plan to present findings at national conferences and submit our results to peer-reviewed journals. Data will be made available upon reasonable request, and the implementation protocol may serve as a blueprint for similar projects in other hospitals.

Acknowledgments

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Data Availability

The datasets used and/or analyzed during this study are available from the corresponding author on reasonable request. All data generated or analyzed during this study are included in this published article.

Feasibility will be assessed based on the proportion of eligible patients enrolled, device adherence rates, and completeness of data collection. Acceptability will be evaluated through surveys and interviews with health care professionals and patients regarding their experiences with the new device.

Authors' Contributions

Conceptualization: SWN
Methodology: RAB, EJ, and SWN
Formal analysis: RAB and SWN
Data curation: SWN
Writing—original draft: SWN and RAB
Writing—review and editing: SWN, RAB, and EJ

Conflicts of Interest

None declared.

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Abbreviations

CE: Conformité Européenne
EHR: electronic health record
EWS: Early Warning Score
IWS: Integrated Workload Scale
MEWS: Modified Early Warning Score
REQUEST: Remote Monitoring by viQtor Upon Implementation on a Surgical Department
SNR: signal-to-noise ratio
SpO_2 : peripheral oxygen saturation

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Protocol

Measuring Stress, Socialization, and Smoking Behaviors Among Lesbian, Gay, Bisexual, Transgender, Queer, and Other Sexual and Gender Minority Adolescents (the Puff Break Research Study): Protocol for a Ecological Momentary Assessment Study

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Abstract

Background: Adolescent tobacco and nicotine use is a major public health concern, with lesbian, gay, bisexual, transgender, queer, and other sexual and gender minority (LGBTQ+) adolescents showing disproportionately high use compared to their heterosexual and cisgender peers. Research suggests factors such as socialization, stress, mood, and craving exacerbate tobacco and nicotine use. However, there is a dearth of knowledge of how these factors influence tobacco, nicotine, and cannabis use among LGBTQ+ adolescents in general and particularly on a momentary basis.

Objective: This study aims to use ecological momentary assessment (EMA) to assess real-time predictors of tobacco, nicotine, and cannabis product use among LGBTQ+ adolescents.

Methods: The Puff Break protocol was adapted from existing EMA protocols, key informant recommendations, LGBTQ+ adolescent perspectives, and insights from community members. Recruitment occurred through multiple channels, with high recruitment results via social media. Eligible participants were aged 14 to 19 years; self-identified as LGBTQ+; and used tobacco, nicotine, or cannabis products at least once in the past 30 days. The EMA pilot began with a 1.5-hour in-person or remote meeting where participants completed a timeline follow-back assessment for tobacco and nicotine use, salivary cotinine assessment, baseline survey, and EMA protocol training. Then, participants completed a 2-week EMA trial during which they received 1- to 2-minute surveys 5 times a day. Within a week of completing the EMA trial, participants concluded with an exit survey and exit interview.

Results: Funded in July 2022, the Puff Break study conducted EMA data collection between August 2023 and November 2024, recruiting a sample of 50 participants. Analyses evaluating the feasibility and acceptability of the Puff Break EMA protocol will be completed by July 2025. Multilevel modeling techniques to estimate both contemporaneous and lagged associations among stress, socialization, and craving (exposures) and smoking (outcomes—combustible cigarette, smokeless product, e-cigarette, and cannabis use) are expected to be completed by November 2025. Finally, qualitative thematic analyses to identify robust tailoring variables, intervention options, and decision rules to support future just-in-time-adaptive intervention development are expected to be completed by May 2026.

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Conclusions: Puff Break is an innovative EMA protocol developed to capture factors influencing tobacco, nicotine, and cannabis use among LGBTQ+ youth. Despite some inherent limitations to the EMA design, the Puff Break protocol has the potential to inform the development of a just-in-time-adaptive intervention to reduce tobacco, nicotine, and cannabis use among LGBTQ+ adolescents.

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KEYWORDS

telemedicine; mobile app; vaping; cigarette smoking; cannabis; nicotine; smoking; sexual and gender minority adolescents

Introduction

Background

Adolescent and young adult tobacco and nicotine use continues to be a major public health concern. The 2024 National Youth Tobacco Survey found that 8.1% of all middle and high school youths surveyed reported current use of tobacco products, with 2.8% of students reporting combustible cigarette use, while 5.9% of middle school students and 7.8% of high school students reported current e-cigarette use [1]. While rates of e-cigarette use declined from the previous year, demonstrating the success of public health efforts and policy regulations to prevent or reduce use among youth (eg, warning labels, and drug and tobacco policies to regulate sales and access) [2,3], 38.4% of the students using e-cigarettes reported frequent use (at least 20 out of 30 days) and 26.3% reported daily use [4]. Similar studies, such as Monitoring the Future, also highlight that, in 2024, 9% of 8th graders, 12.7% of 10th graders, and 19.5% of 12th graders reported using any nicotine products [5]. Adolescent and young adult users of e-cigarettes have an elevated likelihood of initiating combustible cigarette use [6,7] and using e-cigarettes in conjunction with other tobacco products (cigars, and smokeless tobacco) [8-10], thus increasing their risk for nicotine dependence.

Early prevention of tobacco use in all forms is paramount. It is particularly imperative to target research and prevention efforts toward subpopulations who are at elevated risk for both smoking and tobacco-related disease and negative consequences, such as lesbian, gay, bisexual, transgender, queer, and other sexual and gender minority (LGBTQ+) adolescents [11,12]. Starting in adolescence, LGBTQ+ populations are at substantially elevated risk for combustible tobacco and e-cigarette use compared to heterosexual and cisgender populations [13,14]. Data from the California Healthy Kids Survey (CHKS) shows that middle and high school LGBTQ+ students report a 1% to 2% higher prevalence of past 30-day current use of combustible cigarettes relative to their heterosexual peers, and high school transgender students report a 6% to 7% higher prevalence of past 30-day current use of combustible cigarettes relative to their cisgender peers [15]. Similarly, middle and high school LGBTQ+ students report a 2% to 5% higher prevalence of past 30-day current use of e-cigarettes relative to their heterosexual peers, and high school transgender students report a 7% higher prevalence of past 30-day current use of e-cigarettes relative to their cisgender peers [15]. Furthermore, an analysis of CHKS data revealed that transgender middle and high school students of color had up to 6.0 greater odds of using e-cigarettes or vape products in the last 30 days relative to their cisgender peers of the same race and ethnicity [16]. Similar studies using nationally representative and longitudinal cohort data also highlight increased prevalence and odds of tobacco and nicotine use among LGBTQ+ adolescents relative to their heterosexual and cisgender peers [17,18]. While the overall prevalence of combustible cigarettes and e-cigarette use is decreasing among LGBTQ+ adolescents, addressing nicotine and tobacco dependence and addiction is still an important health priority [19].

Beyond typical risk factors for smoking in adolescence (eg, mood, craving, risk perceptions and expectancies, exposure to tobacco-related media, and being around peers who smoke) [20-22], sexual orientation and gender disparities in smoking may be further elevated due to daily minority stress and LGBTQ+-specific socialization experiences. Minority stress theory [23-25] posits that LGBTQ+ populations experience excess stress due to exposure to various forms of prejudice, discrimination, and internalized stigma, which results in adverse mental and physical health (eg, anxiety and depression) and maladaptive coping behaviors (eg, smoking and vaping). Elevated rates of smoking have been associated with high degrees of sexuality- and gender-based mistreatment. In their analysis of CHKS data, Coulter et al [26] found that sexual and gender minority middle and high school students reported substantially higher rates of sexuality- and gender-based harassment than their heterosexual and cisgender peers. The combined effect of sexuality- and gender-based harassment led to significantly higher tobacco and e-cigarette use compared to when each type of harassment was evaluated separately [26].

In addition to stress-related factors, LGBTQ+ individuals may be more likely to smoke due to socialization factors, such as perceived norms that promote tobacco use [27,28]. For instance, a review by Simons-Morton and Farhat [27] found that peer group homogeneity (eg, adolescents with friends who smoke are more likely to smoke themselves), peer influence (eg, best friends who smoke), and crowd affiliation (eg, group membership) predict adolescent smoking behaviors. In a similar light, research by Garcia et al [29] found that adolescents were 7 times more likely to have ever used an e-cigarette if their close friends also used e-cigarettes. Furthermore, studies by Hinds et al [28] indicated that sexual minority young adults are more accepting of cigarette-related norms compared to their heterosexual peers [28,29]. These findings allude to the need to explore how peer group norms may influence tobacco and nicotine product use among LGBTQ+ adolescents.

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The contributions of minority stress processes and socialization factors on LGBTQ+ youth smoking have been primarily studied via retrospective surveys [28,30], limiting understanding of the real-time impacts of minority stress and socialization effects on smoking behaviors during the developmental period when sexual orientation and gender disparities in smoking emerge. Minority stress experiences [31,32] and exposure to peer norms [27-29] that influence smoking are common daily events. These events shape contemporaneous and future smoking, requiring methods that enable intensive time-series analyses to examine the contributions of these factors to LGBTQ+ adolescent smoking behaviors. Therefore, a deeper understanding of these real-time impacts is crucial for developing effective interventions.

Ecological momentary assessment (EMA) is a moment-to-moment data collection method that can detect real-time relationships between experiences with exposures, such as stress, sociocontextual cues, psychological states, and changes in behavioral outcomes [33], such as tobacco, nicotine, and cannabis product use. EMA research has examined the contributions of minority stress and socialization factors to smoking among LGBTQ+ adult populations [34-36]. For example, Livingston et al [32] found that for every unit increase in stress, there was a 3-fold increase in reports of smoking among LGBTQ+ young adults in the same observation period. EMA research by Nguyen et al [34] also identified sociocontextual and environmental influences (eg, being around other smokers and socializing in bars) as unique risk factors for smoking. However, the study was constrained to only the adult LGBTQ+ population. Identifying age-appropriate sociocontextual and environmental risk (and protective) factors for LGBTQ+ adolescents warrants additional research.

EMA methodologies have been used to measure exposure to tobacco-related media among adolescent students with high rates of retention and participation, demonstrating their potential acceptability and feasibility among this adolescent population [21]. Furthermore, EMA can be adapted for dynamic interventions (eg, just-in-time adaptive interventions [JITAIs]), enabling researchers to both measure substance use behavior and quickly implement interventions in response to triggers for behavior [37]. With limited EMA studies on tobacco and nicotine use among LGBTQ+ adolescents, significant gaps remain in understanding specifically how minority stress and socialization factors jointly contribute to these behaviors at the individual level in real time among LGBTQ+ youth. Delineating such processes could contribute to the development of secondary prevention approaches to reduce current tobacco, nicotine, and cannabis use and promote positive health behaviors (eg, salubrious coping strategies) in response to underlying behavioral determinants.

This Study

The Puff Break Research Study, further referred to as Puff Break, is a 2-phase EMA pilot designed to characterize the momentary associations among general stress, minority stress, socialization, and other evidence-based predictors of tobacco, nicotine, and cannabis product use (eg, mood, craving) among LGBTQ+ adolescents aged 14 to 19 years. In phase 1, Puff Break aimed to use key informant interviews with subject matter experts and LGBTQ+ adolescent interview data to adapt an existing adult EMA protocol to validly and reliably measure minority stress exposure, smoking socialization, and smoking and vaping behavior among LGBTQ+ adolescents. In phase 2, via the adapted EMA protocol, we will assess the acceptability and feasibility of real-time measurement of minority stress; smoking socialization; and tobacco, nicotine, and cannabis product use behaviors in a sample of 50 LGBTQ+ identified adolescents (aged 14-19) who reported combustible cigarette or e-cigarette use. This paper describes the phase 2 protocol.

Methods

Ethical Considerations

All study procedures were reviewed and approved by the San Diego State University Human Research Protection Program's Institutional Review Board (HS-2022-0101).

Puff Break used Tango gift cards to remunerate participants, as Tango gift cards offer a wide variety of redeemable merchants and branded gift cards. Participants received US $25 for completing the baseline survey and US $25 for completing the exit survey and interview. Remuneration during the EMA trial was commensurate with the completion rate of the assessment, in which participants received an additional US $50 for a <50% survey completion rate, US $100 for ≥50% and ≤80%, or an additional US $125 for >80%. The total remuneration a participant could receive ranged from US $100 to US $175. The remuneration schedule is consistent with previous EMA research of similar duration with adolescent samples [38,39]. Participants who attended a meeting in person were given an additional US $40 for transportation reimbursement. Thus, participants who attended both the onboarding and exit meetings in person received an additional US $80.

Study Development

Phase 1 of the project included the development of the EMA protocol, adapted from other existing protocols for measuring antecedents and correlates of smoking behaviors among LGBTQ+ young adults [32,34,36] and other existing protocols for measuring antecedents and correlates of smoking behaviors among LGBTQ+ young adults. To ensure the acceptability, feasibility, and appropriateness of phase 2 of the Puff Break protocol, we first established a participatory planning group, consisting of 5 leaders within the local county health department and nonprofit organizations focused on serving LGBTQ+ youth, to consult on their expertise related to the goals of the project. In addition, we conducted semistructured interviews with 7 key informant subject matter experts and 10 LGBTQ+ adolescents, 90% (9/10) of whom reported tobacco, nicotine, and cannabis use. Insights from these interviews led to iterative adaptations (eg, measurement selection, preferences for response formats, momentary sampling response schedule, and flexibility of scheduling due to work or school conflicts), contributing to the development of the phase 2 protocol described in this paper.

The phase 2 protocol was programmed into the mobile EMA (mEMA) software ilumivu [40]. Figure 1 [34,41-45] displays the domains of the final adapted EMA protocol used to assess stress, socialization, and other pertinent factors in relation to

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tobacco or nicotine product use among LGBTQ+ adolescents. A detailed list of measures included in the EMA protocol is provided in Multimedia Appendix 1 [41,46-56] and Multimedia Appendix 2 [34,41-43,46,55,57-61]. Both in-person and remote protocols to train participants on EMA procedures and complete onboarding and exit assessments were developed to make the study as accessible as possible for participants. Unless otherwise noted, study components were identical for the in-person and remote versions of Puff Break.

Figure 1. Puff Break ecological momentary assessment (EMA) protocol domains [34,41-45]. Participants reported on the domains of mood, stress, safety, support, and craving in the present moment and the domains of product use, other product use, and socialization in both the present moment and retrospectively. Minority stress and media exposure were reported retrospectively. LGBTQ+: lesbian, gay, bisexual, transgender, queer, and other sexual and gender minority.

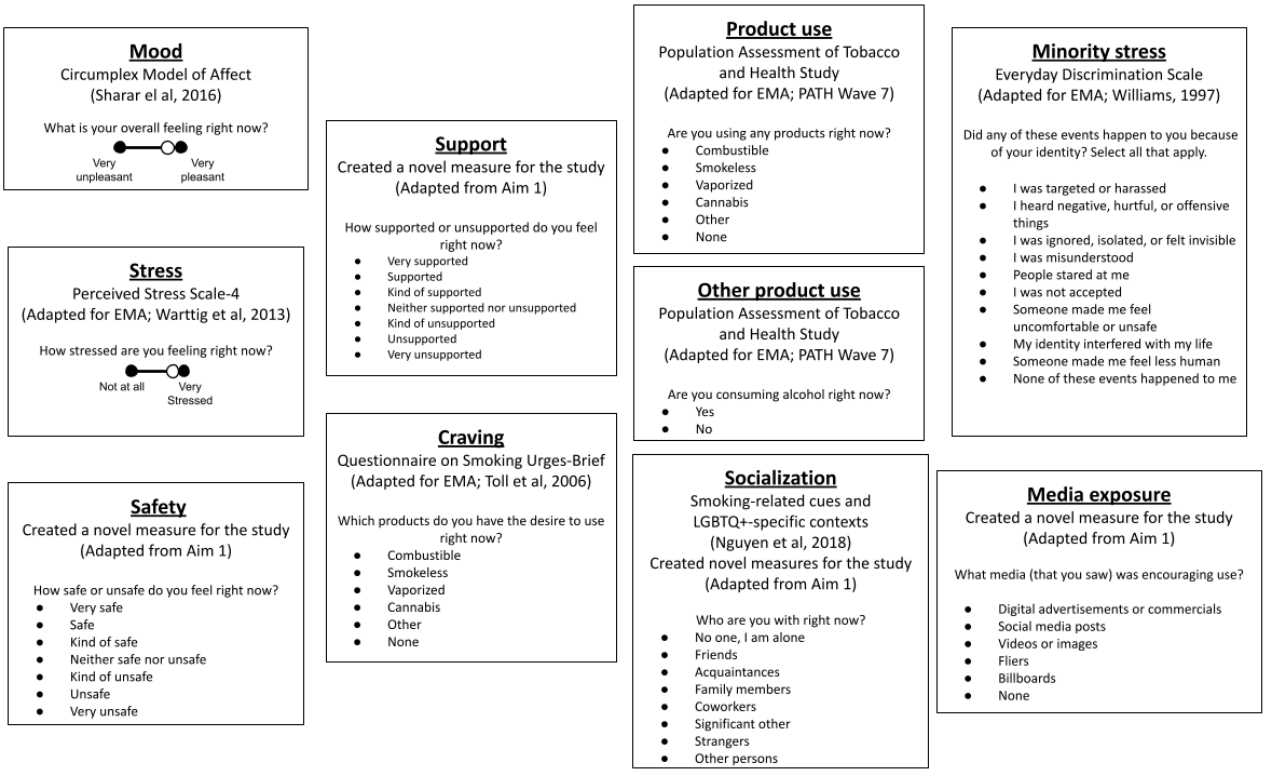

Recruitment Efforts

Overview

To pilot the adapted EMA protocol, we recruited 50 LGBTQ+ adolescents with different sexual orientations and gender identities between August 2023 and November 2024. Participants were recruited using multiple methods, including distributing flyers, tabling at local youth and LGBTQ+ community events, presenting to community and academic partners, participant snowball sampling, and social media posts.

Flyers

Seven flyers were developed by the Puff Break team to appeal to different social identities of LGBTQ+ adolescents, with a brief description of Puff Break and a QR code to the screener survey. On the basis of previous experiences engaging LGBTQ+ adolescents in research and recommendations from the participatory planning group, flyers were posted in local university settings (eg, the student union, student housing office, and the campus LGBTQ+ center) and local community centers or storefronts (eg, youth LGBTQ+ drop-in centers, libraries, and coffee shops) that served or were accessed by youth.

Community Events and Presentations

The Puff Break team conducted 8 presentations to community and academic partners and 3 tabling events where staff shared information regarding the study and shared flyers with potentially eligible participants.

Referrals

Enrolled participants provided recommendations on potential peers who might be eligible and interested in joining the study.

Social Media

Using the social media platforms Facebook and Instagram (Meta Platforms, Inc), advertisement campaigns were created and configured to target specific age groups and demographics. Advertisement campaigns were reconfigured iteratively to target specific participants, such as updating advertisement artwork to appeal to younger audiences and expanding the campaign's geographic radius to reach additional communities of color disproportionately impacted by tobacco and nicotine use. As social media platforms, such as Facebook and Instagram, do not allow researchers to target specific demographic groups, especially minors, we also attached relevant keywords to appeal to our target population. Available keywords relevant to LGBTQ+ culture (eg, Pose, Charlie XCX, Love, Simon, and gender) were attached to the campaign. The advertisements

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consisted of 1 of the 7 flyers, along with a short statement in the textbox of the advertisement's post that encouraged participation in the study. A link to the screener survey was provided for participants to submit their responses for determining eligibility. Each week, a Puff Break team member manually edited the campaign to run a new advertisement cycle. After comparing views and click rates across weekdays and weekends, the team chose to run advertisements every Thursday through Sunday, and the advertisement costs varied from US $25 to US $75, in total, per advertisement life cycle.

Screener Survey

The following inclusion criteria were set based on previous EMA studies on youth smoking behavior [22,65]: (1) individuals who reported current tobacco, nicotine, or cannabis product use (ie, any use in the past 30 days); (2) individuals who were aged between 14 to 19 years old; (3) individuals who self-identified as LGBTQ+; and (4) individuals who had daily access to a personal smartphone. The screener survey collected respondents' contact and demographic information (age, residence, race, ethnicity, sex, gender identity, and sexual orientation). The survey also included 13 questions assessing the past month and daily product use. Participants were first asked if they had used any of the following products within the past 30 days: combustible cigarette, cigar, cigarillo, bidi, hookah, e-cigarette, chewing tobacco, snus, snuff, nicotine lozenges, nicotine patches, nicotine gum, cannabis, and other. If they responded yes to using any of the products, additional follow-up questions were asked, adapted from the Population Assessment of Tobacco and Health study, Wave 7 [41]. However, a more detailed assessment of recent product use was captured for those who enrolled in the study at the onboarding meeting (refer to Timeline Follow Back Assessment section). Finally, participants were asked to choose a potential date for onboarding into the study, provided they met the eligibility criteria. Participants who reported using combustible or vaporized products at least 5 times per day on a typical day were prioritized for enrollment, but this level of use was not an eligibility requirement.

Pilot Study Components

The overall study components included an in-person or remote onboarding meeting, a 2-week EMA trial, and an in-person or remote exit meeting (Figure 2). Except when noted, in-person and remote protocols were identical.

Figure 2. The Puff Break study schedule. The Exit Meeting occurred as soon as Day 15 and as late as Day 21 due to participant scheduling availability. Zoom or text check-ins were scheduled at any time between Day 1 and Day 14, only if participants did not submit any surveys within 48 hours. Check-in communication methods depended on participant preference.

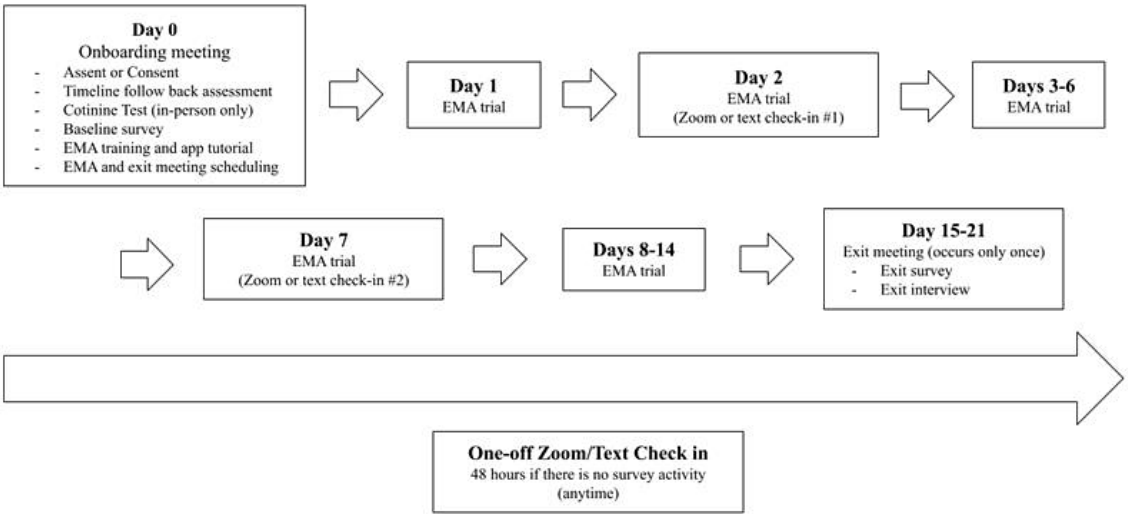

Onboarding Meeting

Overview

Once participants completed the screening form and were deemed eligible, they were invited to enroll into Puff Break at an in-person or remote onboarding meeting with a study research assistant. Participants were contacted 24 hours before the onboarding meeting to confirm participation. The onboarding meeting consisted of the following: (1) consent or assent, (2) a 2-week timeline follow-back assessment, (3) salivary cotinine test using NicoTest test strips (in-person protocol only), (4) baseline survey, (5) training on the EMA protocol, and (6) tutorial on how to use the EMA app (mEMA powered by ilumivu). Participants were also asked to schedule 2 check-in meetings during their EMA trial as well as their final exit meeting.

Identity Verification

Before consent or assent, participants were asked to verify their identity via a state-issued driver's license, a school-based ID, or a passport. Identity verification was used to ensure the participant matched their screener survey responses, as some online screeners were populated with disingenuous responses or completed by bots. Participants who used a preferred name or had a gender expression different from that on their ID were included in the study. Participants who were unable to verify their identity were offered an opportunity to reschedule the meeting when identification was possible. For remote onboarding, participants were instructed to turn their cameras on and show their IDs via camera to verify their identity. To ensure participant confidentiality and comfort during the Zoom (Zoom Communications, Inc) meeting, participants were encouraged to sit in a private, indoor place where they would

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not be disturbed; wear headphones; and have their computer facing a wall.

Assent and Consent Form

During the assent (for participants aged 14-17 years old) and consent (for participants aged >18 years old) process, the study research assistant reviewed the form with the participant and answered any questions the participant had. For in-person meetings, the participants signed and dated a physical copy of the assent or consent form that was then signed by a Puff Break research assistant as a witness. For remote onboarding, the assent and consent forms were integrated into a Qualtrics (Qualtrics International Inc) survey, which was provided to the participants via the Zoom chat feature. Once the form was reviewed, the participants typed their full name and date in the survey's respective textboxes, along with the name of the Puff Break research assistant who was with them before submitting the survey. The Puff Break research assistant confirmed receipt of the signed assent or consent form before proceeding with the onboarding meeting. Due to the potential risk of "outing" LGBTQ+ youth and disclosing unknown youth-smoking behaviors to their parents and guardians, a waiver of parental consent was authorized by the San Diego State University Institutional Review Board.

Timeline Follow-Back Assessment

The 2-week timeline follow-up assessment assessed the participants' product use over the past 2 weeks before their onboarding meeting. The measure was adapted from the timeline follow back questions asked in the Population Assessment of Tobacco and Health Wave 7 Youth and Parent questionnaire [41]. The Puff Break research assistant shared a document with pictures of each product (ie, combustible cigarette, cigar, cigarillo, bidi, hookah, e-cigarette, chewing tobacco, snus, snuff, lozenges, nicotine patches, nicotine gums, cannabis, and other) with the participant to reference when answering each question. Product-by-product, the Puff Break research assistant asked if the participant had used the product within the 2-week period. If the participant said "yes" to using a product, they were asked to specify which day or days within the 2-week period they used the product. As the specific day or days were determined on the calendar, the Puff Break research assistant privately filled out the assessment via a Qualtrics matrix. The matrix consisted of the date of onboarding; the various tobacco, nicotine, and cannabis products of interest; and checkbox response options inclusive of the following: has not used, used today, 1 day ago, 2 days ago, 3 days ago, 4 days ago, 5 days ago, 6 days ago, 7 days ago, 8 days ago, 9 days ago, 10 days ago, 11 days ago, 12 days ago, 13 days ago, and 14 days ago. Once the matrix was populated, the Puff Break research assistant verbally confirmed all the participants' answers before submitting the survey.

Salivary Cotinine Test

For biochemical validation of self-reported tobacco and nicotine use, we measured cotinine levels using the NicoTest Extra-Sensitive Nicotine Saliva 30 ng Test Kit [62] that required participants to submit a saliva sample to be pipetted on a test strip. Participants were instructed to drink 8 ounces of water and wait approximately 10 minutes, as indicated in the manufacturer's instructions, before submitting the saliva sample. Once the results were ready (approximately in 5 min), the Puff Break research assistant privately recorded the test result via a Qualtrics survey. If the first NicoTest result was invalid, a second test was repeated. If the second test was invalid, it was excluded from the study. The NicoTest was excluded for remote participants.

Baseline Survey

The baseline survey was administered via Qualtrics, where the participants self-reported their responses on a study-provided iPad (Apple Inc). The baseline survey consisted of several blocks of detailed questions (eg, demographics, past product use [lifetime and 30 days], past cannabis-specific use, minority stress assessment, socialization, product purchasing, marketing, social media exposure, motivations to use products, product dependency, and mood). Details of the baseline measure are shown in Multimedia Appendix 1.

EMA Training and EMA App Tutorial

The EMA training and EMA app tutorial were combined into 1 slide deck presented to the participant by a Puff Break research assistant. The EMA training consisted of the origins of EMA, general descriptions of the EMA survey question blocks, the safety and security of the mEMA app, how to report product use, the daily survey schedule, and the schedule of the entire Puff Break protocol. For the tutorial, the Puff Break research assistant instructed the participant on how to download the app, helped them select the optimal settings for their mobile device, and showed them where to access their surveys within the app. Participants were also shown how to update the app and were provided with a test survey to practice answering questions.

EMA and Exit Scheduling

Once the participant completed the EMA app tutorial, 2 check-ins with the Puff Break research team were scheduled for the second and seventh days of the EMA trial. Participants were also offered to adjust their survey schedule by an hour per survey if they had known scheduling conflicts (eg, class or work). For example, a participant could delay their 9 AM survey to 10 AM or prompt their 6 PM survey to 5 PM. Even with these adjustments, participants still had a minimum of 2 hours scheduled in between each survey. The Puff Break study staff also used this time to schedule the participants' final exit meeting, no later than 1 to 2 weeks after their 2-week EMA trial participation ended.

EMA Trial and Measures

The 2-week EMA trial consisted of 5 surveys, approximately 1 to 2 minutes in length, delivered to the participant's mEMA app between 8:30 AM and 9:30 PM, on a 2- or 3-hour cycle, depending on their survey schedule. Using the administrative functions of mEMA's web-based account manager, the survey delivery time was randomly generated, within 30 minutes before or after the standard delivery times of the 5 surveys (9 AM, 12 PM, 3 PM, 6 PM, and 9 PM). Therefore, a 9 AM survey could be delivered as early as 8:30 AM and as late as 9:30 AM. Participants had 60 minutes to submit their survey upon delivery. Participants were informed of their survey delivery via an initial push notification, with 2 additional push notifications prompted 15 and 30 minutes after their survey was delivered, if the survey

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was not yet complete. All 5 surveys were also programmed into Qualtrics to be used as a backup in case there were technical difficulties with the mEMA app; however, the Puff Break team never used this backup option during the pilot.

As displayed in Figure 1, the question blocks consisted of the following: (1) current mood; (2) current stress, current safety, and support; (3) products currently used; (4) products currently craved; (5) other substances currently used; and (6) current social environment. Retrospectively, participants were also asked about the following: (1) products used since the last survey, (2) other products used since the last survey, (3) experiences of minority stress, (4) the past social environment, and (5) product-related media they had seen. Each survey's responses were uploaded to Puff Break's ilumivu cloud. No survey responses were saved on participants' mobile devices. EMA measures can be found in Multimedia Appendix 2.

Two check-ins were conducted with each participant on the second and seventh day of the EMA trial via Zoom or text, depending on the participant's preference. A Puff Break research assistant would ask the participant 2 questions: "How is the study going for you so far?" and "Are there any challenges you are experiencing in the study?" If a participant stated that they experienced a challenge, the Puff Break research assistant probed on how they resolved the challenge or helped the participant resolve it. Finally, the Puff Break research assistant would inform the participants of their current retention rate and encourage them to complete as many surveys as possible with the time remaining in the study. Participants were reminded that they could contact the Puff Break staff during working hours if they needed assistance. If a participant did not submit any surveys within a 48-hour period, a Zoom meeting was scheduled to check in with the participant and ensure they were still able and willing to participate in the study. No participant withdrew or was dismissed from the study prematurely.

Exit Meeting

Overview

At the end of the 2-week EMA period, participants attended a final exit meeting to conclude their participation in the study. The exit meeting consisted of the following: (1) a second NicoTest, (2) an exit survey, and (3) a semistructured interview. Participants were contacted 24 hours before the exit meeting to confirm participation. Exit meetings were held either in person or remotely via Zoom. If participants attended the meeting in person, the NicoTest was offered, using the same guidelines as the onboarding meeting. If participants attended remotely, the NicoTest was excluded from their meeting. Participants then completed a 10- to 15-minute exit survey as well as a 60-minute semistructured exit interview.

Exit Survey

The exit survey used both open- and closed-ended survey questions to gather feedback on participants' experience with the EMA, including the following: (1) satisfaction with the process, (2) the perceived burden of participation in the study, (3) their preferred reporting methods, and (4) and reflections on administrative support (training and technical support). Seven open-ended questions were adapted from the study team's adult EMA protocol, which included questions such as "What did you like or dislike about the EMA method?" and "What procedures were difficult to complete, confusing, or required additional support?" Closed and open-ended questions assessed the EMA protocol's acceptability and feasibility. Acceptability was operationalized as the perception among LGBTQ+ adolescents that the Puff Break protocol was appealing, favorable, or satisfactory. Feasibility was operationalized as the extent to which the Puff Break protocol could be successfully implemented among the target population. Measures were adapted from the 12-item Acceptability of Intervention Measure (AIM), Intervention Appropriateness Measure (IAM), and Feasibility of Intervention Measure (FIM) [63]. Each component of the assessment consists of 4 items specific to each domain, measuring the extent to which the participant believes an evidence-based practice is acceptable, appropriate, and feasible. These measures are intended to be as pragmatic as possible and were adapted to the context of Puff Break. The AIM, IAM, and FIM are measured via a 5-point Likert scale where 1 indicates completely disagree and 5 indicates completely agree. In addition, participants completed the 6-item Mobile Application Rating Scale app-specific subscale, which aims to assess the perceived impact of an app on the user's knowledge, attitudes, and intentions to change as well as the likelihood of actual change in the target health behavior [64,66]. Questions were adapted to fit the context of the Puff Break. Each of the 6 items is measured using a 5-point Likert scale (1=strongly disagree to 5=strongly agree).

Exit Interview

The final activity for Puff Break included a 60-minute semistructured interview, with approximately 15 questions wherein participants reflected on their tobacco and nicotine or cannabis product use during the 2-week EMA trial, provided additional feedback on the Puff Break protocol, and provided feedback on how to best disseminate a future mEMA intervention aimed at monitoring and reducing tobacco and nicotine or cannabis product use among this target demographic. The first 8 questions were specific to the EMA responses submitted by the participants. The Puff Break team generated a series of bar charts depicting trends in tobacco, nicotine, and cannabis product use by day of the week and time of day for the participant being interviewed. Each participant was asked to confirm the different products they reported using during the EMA trial and to describe what happened during the given day or time windows that may have affected their product use. Participants were also asked to think about what would have stopped them from using tobacco and nicotine products during those moments. In addition, participants were asked to reflect on their tobacco, nicotine, and cannabis product use depending on their social environments (eg, where they were or who they were with), stressors experienced, and cravings. The next 7 questions were informed by the Reach, Effectiveness, Adoption, Implementation, and Maintenance framework by Glasgow et al [67] to understand how a future EMA mobile intervention aimed at monitoring and reducing tobacco, nicotine, and cannabis product use could effectively be disseminated to, reached by, and implemented with LGBTQ+ adolescents. To assess *reach*, participants were asked to think about how to

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increase the likelihood that LGBTQ+ adolescents would download an app such as Puff Break (eg, where the app should be advertised and types of messaging [negative or positive] used to advertise the app). *Effectiveness* and *implementation* were assessed by asking participants to reflect on how an app such as Puff Break could affect their ability to monitor their tobacco, nicotine, and cannabis product use; what would motivate them to download an app such as Puff Break; and what features would be needed in the app to increase its effectiveness (eg, trackers, data visualizations, and motivational messages). For *adoption*, participants were asked if they have ever been screened for or advised to quit tobacco and nicotine products, who they would want to hear about this type of app from (eg, friends, family, and trusted individuals), and when would be an ideal time to learn about an app such as Puff Break once developed. Finally, we assessed *maintenance* by asking participants to think about what would motivate them to continue using the app (eg, what makes an app easy or difficult to use).

Data Management

Quantitative

Responses from participants were downloaded from cloud storage to an encrypted, password-protected server accessible only to the research team and manually reviewed and cleaned. After the data were cleaned, they were merged into the existing database and deidentified. While EMA data had a unique user ID within the mEMA program, they were also merged using their participant IDs. A private cloud storage folder that stored a separate key file for participant names, ID numbers, and consent and assent forms was only accessible to project leadership.

Qualitative

Exit meeting audio files (from Zoom or in-person recordings) were transcribed verbatim. After transcription, the study team reviewed transcripts against audio files for accuracy, and the audio files were deleted. Transcripts from participant exit meetings were stored on the Puff Break team's restricted, password-protected drive. Participants' and interviewers' names as well as any identifiable information stated by the participant (school name, city names, others' names, employer's name, etc), were redacted from the transcript.

Data Analysis

Demographics

Demographic characteristics of our sample populations will be reported using descriptive statistics.

Acceptability and Feasibility

The primary analysis for this pilot will be conducted to determine the acceptability and feasibility of the EMA protocol. To determine acceptability, we will conduct a descriptive analysis of the mean survey scores according to the AIM measure [63]. Qualitative content analysis of open-ended response feedback from the exit survey and thematic analysis from participant interviews will also be conducted to assess protocol acceptability.

To determine feasibility, we will conduct a descriptive analysis of sample characteristics and compliance data (ie, number of participants who meet the recommended threshold of completing 80% of the scheduled assessments) along with mean survey scores according to the FIM measure [63]. We will also conduct a content analysis of the open-response feedback from the exit survey and a qualitative analysis of participant interview testimonials regarding protocol feasibility. In addition, we plan to conduct a descriptive analysis of the protocol's appropriateness using the IAM [63] along with analyzing mean survey scores from the Mobile Application Rating Scale app-specific [64,66] subscale to understand the protocol's perceived impact on user's knowledge, attitudes, and intentions to use a protocol such as Puff Break to monitor their tobacco, nicotine, and cannabis product use.

Associations Among Stress, Socialization, and Smoking

The sample size for the pilot was set to power analyses to detect small to moderate associations among measures of stress, socialization, and smoking outcomes in the EMA data. To maximize power for the calculation of reliability (eg, intraclass correlations), validity, and detection of associations between exposures and outcomes, analysis of EMA data will be conducted at the level of participant observations. Each participant is expected to provide up to 5 assessments per day for 2 weeks (ie, if a participant completed all 5 assessments per day for 2 weeks, then 70 participant observations multiplied by 50 participants will be equal to 3500 participant observations). Using previous effect estimates of the association between minority stress exposures from an EMA study of LGBTQ+ young adults [34,35], we determined that 50 EMA participants with 14 measurement occasions (ie, 1 per day; n=700 participant observations) would provide adequate power (80%) to detect at least a 1.2-unit increase in the odds of smoking. We will investigate missing data on exposures, covariates, and outcomes by summarizing the degree of missing on each variable and potential patterns of missing (eg, by participants and across variables) using data visualization techniques in R software (version 4.3.3; R Foundation for Statistical Computing). Finally, we will use appropriate approaches to handling missing data, such as multiple imputation, based on patterns of missing data observed and consider sensitivity analysis to evaluate robustness of findings against different plausible missing mechanisms (eg, missing at random and missing not at random) [68]. Participant observation data will be analyzed using multilevel modeling techniques to account for the correlated structure (ie, repeated measures within individuals). We will estimate both contemporaneous and lagged associations between stress and socialization (exposures) and smoking (outcome—combustible cigarette and e-cigarette use). Models with and without adjustment for baseline measures (stress and socialization and demographics) and potential covariates (mood, craving, and expectancies, level of nicotine dependence, and other forms of tobacco use and couse behaviors [eg, cannabis]) will be conducted.

Intervention Development

Qualitative thematic analysis from the exit interviews will be used to identify overarching themes related to states of

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vulnerability or opportunity (ie, internal or contextual states when someone may be susceptible to engage in smoking behavior or positive health behavior change) and identify robust tailoring variables (ie, individual-level information that can be used to individualize when and how to intervene, eg, sexual orientation and gender identity), intervention options (ie, possible actions or treatments that can be delivered at decision points, eg, playing a game on the phone to avoid smoking) [69], and decision rules (which intervention option to offer, given the tailoring variables, and when) [37,70]. These data will support future JITAI intervention development. Analysis of qualitative data will further guide the exploration of quantitative data to examine specific antecedents and correlates of smoking behavior to support future JITAI intervention development.

Results

Funded in July 2022, Puff Break conducted EMA data collection between August 2023 and November 2024. During the data collection period, we recruited a total sample of 50 participants. Analyses are currently underway. We anticipate completing analyses evaluating the acceptability and feasibility of the Puff Break EMA protocol by July 2025. Multilevel models to estimate both contemporaneous and lagged associations among stress, socialization, and craving (exposures) and smoking (outcomes—combustible cigarette, smokeless product, e-cigarette, and cannabis use) are expected to be completed by November 2025. Finally, qualitative thematic analyses to identify robust tailoring variables, intervention options, and decision rules to support future JITAI development are expected to be completed by May 2026.

Discussion

Anticipated Findings

Puff Break is an EMA protocol developed through an iterative process incorporating existing EMA protocols, key informant insights, and perspectives from LGBTQ+ adolescents and community members. This protocol aimed to measure a range of factors influencing tobacco, nicotine, and cannabis use behaviors among LGBTQ+ youth on a momentary basis. Participants were onboarded into the study in person or remotely and completed the Puff Break protocol using flexible momentary sampling schedules. The brief Puff Break assessments were bolstered by an in-depth baseline assessment, an exit survey, and an exit interview, all of which provide the research team with additional opportunities to contextualize and validate EMA data. The quantitative and qualitative data collected from Puff Break have great potential to inform the development of JITAIs to reduce tobacco, nicotine, and cannabis use among LGBTQ+ youth.

Limitations

There are some inherent limitations in the design of the Puff Break protocol. First, the small sample size may limit our ability to detect individual-level tailoring variables (eg, sexual orientation or gender-specific patterns in response) that could be meaningful for JITAI development. Second, while EMA assessments can generate numerous observations per participant, capturing time, state, and context factors that contribute to real-time and lagged tobacco, nicotine, and cannabis use, the brevity of EMA, by design, may overlook key exposures or modifying factors of product use. To account for these potential limitations, Puff Break used exit interviews to carefully review snapshots of each participant's response data that enabled participants to further contextualize factors that influenced their tobacco, nicotine, and cannabis use.

Conclusions

If Puff Break is deemed acceptable and feasible by LGBTQ+ youth participants and is able to support identification of robust exposures linked to tobacco, nicotine, and cannabis use, this protocol has great potential to serve as the basis for the development of a JITAI to reduce tobacco, nicotine, and cannabis use. With such results, we will seek funding to adapt Puff Break from an observational tool into an ecological momentary intervention. However, if analyses indicate that Puff Break did not measure robust exposures linked to tobacco, nicotine, and cannabis use among LGBTQ+ youth nor generate enough substantive information to inform JITAI development, we will further adapt the Puff Break protocol until sufficient evidence is collected.

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Data Availability

The datasets generated or analyzed during this study are not publicly available due to organizational policies but are available from the corresponding author on reasonable request.

Authors' Contributions

LS contributed to the investigation of the study, writing the original draft, and reviewing and editing the manuscript. DK contributed to project administration, investigation, software use, writing the original draft, and reviewing and editing the manuscript. JH

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contributed to conceptualization, funding acquisition, methodology, and reviewing and editing the manuscript. AJB contributed to conceptualization, funding acquisition, methodology, and reviewing and editing the manuscript. MM contributed to conceptualization, funding acquisition, methodology, and reviewing and editing the manuscript. HJJ contributed to conceptualization, funding acquisition, methodology, and reviewing and editing the manuscript. ACL contributed to investigation and reviewing and editing the manuscript. JPC contributed to conceptualization, funding acquisition, methodology, project administration, investigation, supervision, writing the original draft, and reviewing and editing the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Baseline survey measures and adaptations (when applicable) in the Puff Break study.
[DOCX File , 1944 KB - resprot_v14i1e71927_app1.docx]

Multimedia Appendix 2
EMA survey measures and adaptations (when applicable) in the Puff Break study.
[DOCX File , 39 KB - resprot_v14i1e71927_app2.docx]

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Abbreviations

AIM: Acceptability of Intervention Measure
CHKS: California Healthy Kids Survey
EMA: ecological momentary assessment
FIM: Feasibility of Intervention Measure
IAM: Intervention Appropriateness Measure
JITAI: just-in-time adaptive intervention
LGBTQ+: lesbian, gay, bisexual, transgender, queer, and other sexual and gender minority
mEMA: mobile ecological momentary assessment

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Protocol

Identifying Psychosocial, Self-Management, and Health Profiles Among Women With Chronic Pain Who Have Experienced Intimate Partner Violence and Those Who Have Not: Protocol for a 2-Phase Qualitative and Cross-Sectional Study Using AI Techniques

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Abstract

Background: Women who experience intimate partner violence (IPV) are more likely to develop disabling chronic pain (CP). However, there is little information on what it means to live with CP while being exposed to IPV. In addition, despite well-established risk and protective factors for CP and its health outcomes, there are no data on whether these factors differ in women who have experienced IPV compared to those who have not.

Objective: Our aims are to understand the meaning and implications of living with CP for women who have experienced IPV compared to women with CP alone and to identify possible differences in risk and protective factors as well as health outcomes.

Methods: We have designed 2 studies to be conducted in 2 phases. The first phase will involve a qualitative study with a descriptive and exploratory design. Individual semistructured interviews will be conducted with at least 10 women with CP alone and with 10 women with CP who have experienced IPV. Reflexive thematic analysis will be used to examine participants' experiences, meanings, and realities. In the second phase, a cross-sectional study will be conducted with women with CP affected by IPV, including those currently experiencing IPV and those with past exposure to IPV, as well as women with CP who have never experienced IPV. A total of 359 women will complete various scales assessing risk and protective factors (eg, pain-related worrying and activity patterns) and health outcomes (eg, legal and illegal drug use and health care use). Data analysis will involve inferential statistics and machine learning.

Results: As of May 2025, we had contacted relevant associations to present the project and begin recruiting voluntary participants. We have conducted the pilot study to assure the adequacy of the questionnaire and usability or technical functionality of the web-based platform. The results are expected to be published starting in January 2026.

Conclusions: This research addresses two urgent needs in pain research identified by the European Pain Federation: (1) expanding knowledge on CP management in relation to contextual factors; and (2) identifying specific psychosocial, self-management, and

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health profiles among women with CP who have experienced IPV and those who have not. This could provide valuable insights for personalizing pain management treatments. In addition, the findings may help identify women experiencing IPV who present to health care settings.

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KEYWORDS

chronic pain; intimate partner violence against women; treatment; risk factors; profiles; qualitative study; quantitative study; artificial intelligence; AI

Introduction

Background

Chronic pain (CP) is defined as pain that persists beyond the normal tissue healing period, typically lasting approximately 3 months. It is a major health concern affecting approximately 30% of people worldwide [1]. CP is more prevalent and burdensome among populations experiencing vulnerability, including women, older adults, children, individuals from racial or ethnic minority groups, and those from lower socioeconomic backgrounds [2,3]. In Europe, the economic burden of CP could reach up to €300 billion annually (US $343 billion) [4].

There is broad consensus that understanding and treating CP requires a biopsychosocial approach. Beyond biological and physiological factors, psychological, social, and life experiences play a crucial role in the development, exacerbation, and persistence of pain [5-7]. Notably, CP is a well-documented consequence of another public health problem, intimate partner violence (IPV) against women, as demonstrated by controlled studies in both population-based and clinical samples [8-11].

IPV against women is a gender-based issue [12-14] that encompasses physical, psychological, or sexual violence perpetrated by some men against their female partners [15]. Today, IPV against women remains a widespread epidemic, affecting at least 30% of women worldwide [16]. It has severe health and social consequences [17] and imposes an economic cost of €174 billion (US $199 billion) per year on the European Union [18].

Compared to women who have not experienced violence, those exposed to IPV against women report a higher prevalence of fibromyalgia, abdominal pain, genitourinary tract pain, pelvic and genital pain, headaches (including migraines), and back and neck pain [19-22]. A study conducted with 108 male and female patients with CP attending a rehabilitation center found that 56% had a current or past history of IPV, with more than 80% being women. Nearly 30% had experienced IPV within the previous year [23].

Other studies have shown that those who have experienced IPV and are living with sickle cell disease are 5 times more likely to report CP than those who have never experienced IPV [24]. In addition, they are nearly twice as likely to develop fibromyalgia and chronic fatigue syndrome [25]. A recent systematic review and meta-analysis found strong and consistent associations between women who have experienced violence—whether by a partner or others—and CP conditions [26]. Furthermore, IPV against women is often linked to disabling pain [8,23,27]. Survivors with disabilities are more likely to report generalized CP than those with other disabling health conditions [28], and more than one-third continue to experience a high level of pain-related disability long after ending the abusive relationship [29].

Women who have experienced IPV also frequently use medication to alleviate pain [30]; for example, individuals with sickle cell disease who have experienced interpersonal violence are more than 6 times as likely to use opiate-based medications daily compared to those without a history of violence exposure [24].

Given the increased likelihood of those with exposure to IPV against women developing disabling CP and experiencing worse health outcomes [23,24,28,30]—even after leaving a violent relationship [29]—it is possible that experiencing (or having experienced) IPV against women influences the risk and protective factors involved in the development and maintenance of disabling CP differently. While previous studies have examined factors that predict or contribute to CP in those with exposure to violence [31,32], to our knowledge, no comparative studies have explored whether the underlying factors of CP differ based on a history of interpersonal violence.

Gathering this information is crucial for early detection and tailored treatment strategies for CP management in women who have experienced IPV as well as those who have not. Some researchers suggest that women with CP who are experiencing IPV may require more holistic care and support [26]. In addition, there is a need to better understand the daily experience of women living with CP while currently experiencing IPV compared to that of women who experience CP without a history of experiencing violence. However, no studies on this topic were found in the reviewed literature. In fact, the intersection of CP and IPV against women as interrelated phenomena has received little research attention [23].

Goals of This Study

This research project has 2 general objectives and 6 specific aims.

First, we seek to understand the meaning and implications of living with CP for women experiencing IPV compared to those with CP alone. From this point forward, the term “women with CP alone” will refer to women who have never experienced any form of psychological, physical, or sexual violence at any stage of their lives, whether perpetrated by an intimate partner or another known or unknown individual. We include other forms

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of violence beyond IPV against women because they may also influence CP management and health outcomes [31].

More specifically, by comparing women with CP and exposure to IPV to women with CP alone, we aim to (1) examine how CP affects their daily lives, (2) identify the impact that CP may have on their intimate relationship and vice versa, (3) understand how they self-manage CP, and (4) describe their experiences with health systems.

Second, we aim to determine whether women with CP alone, women with CP who are currently experiencing IPV, and women with CP who have a past history of IPV present distinct profiles based on risk and protective factors for disabling CP and health outcomes. If differences exist, we will also (5) identify the factors that best explain these profiles and (6) detect more specific subprofiles within each group.

Ultimately, the findings will be used to develop assessment and intervention guidelines for health and social service professionals.

Risk and Protective Factors

Overview

The scientific literature has identified well-known risk and protective factors for disabling CP. The most widely studied have been individual factors [5,33] that are "the result of historical and ongoing interactions between genetic, epigenetic, and environmental conditions, which are embedded in and shaped by multilevel social factors" [34].

However, the role of interpersonal factors—such as experiencing IPV against women versus not experiencing it—in shaping these "individual" factors is often overlooked, despite evidence recognizing interpersonal relationships as both a risk and a protective factor for pain-related dysfunction [33,35]. In the following subsections, we provide a brief overview of some of the most relevant risk and protective factors for CP and health outcomes identified in the scientific literature.

Gender Norms and Identity

Biological differences partially explain sex-related variations in pain perception; however, psychosocial factors such as gender norms also play a significant role. Gender norms influence differences between men and women in pain sensitivity, pain tolerance, pain expression, and coping mechanisms [36-39]. These norms shape gender identity, which refers to an individual's social and psychological self-conception as a man or a woman [40].

A recent clinical study pointed out that gender identity, rather than genetic sex, may play a more significant role in shaping pain perception [41]. Clinical studies have found that feminine traits correlate with pain sensitivity and can predict the development of CP in men [42,43]. In addition, traits associated with femininity, such as servility or subordination, have been linked to greater disability in individuals with CP [44]. More recently, a study based on machine learning modeling identified a strong association between agreeableness and fibromyalgia [6].

Education and Socioeconomic Background

Research highlights socioeconomic factors—such as income, occupation, wealth, and education—as primary contributors to a wide range of health outcomes [45], including perceived pain and CP management [5,46]. In fact, socioeconomic status is inversely related to both the prevalence and severity of CP, as well as higher levels of disability [47,48].

Regarding education, having spent less time in education can influence pain in various ways, including through exposure to environmental stressors, work history, and health literacy [46]. Education level has also been linked to the overall burden on health care systems [49].

Ethnicity or Racialized and Minoritized Groups

Through social learning, children acquire the specific cultural meanings attached to pain, which is influenced by ethnicity [50,51]. Ethnicity impacts various aspects of pain experiences, such as pain expression, remedies, when to ask for help, and perceptions of health care systems and illness behaviors [52]; for example, children learn when it is appropriate to share pain experiences with family members and caregivers [53,54].

Studies in the United States and Europe have shown differences across ethnic and cultural groups (eg, American, British, Latinx, and South Asian) in self-reported pain intensity and coping styles [55-60]. In addition, there is increasing evidence that racism negatively affects pain perception and pain management [61-63].

Pain Worrying (Pain Catastrophizing)

Pain catastrophizing, now referred to as pain worrying [64], is considered one of the strongest predictors and correlates to negative pain experiences [65-69]. The higher the levels of pain worrying, the greater the intensity, severity, and emotional distress related to pain [65,70,71]. Pain worrying is also associated with a greater need for medical advice and increased health care use [72], as well as higher levels of disability [73]. It is a key factor in explaining variability in pain experiences [67] and is commonly used as a criterion to assess changes in cognition, making it an important component in interventions aimed at reducing pain and improving functioning [74]. The fear-avoidance model, one of the most accepted theories on CP, suggests that pain worrying mediates the relationship between pain and disability [75].

Pain-Related Self-Efficacy

Self-efficacy refers to an individual's belief in their ability to organize and execute the necessary actions to achieve specific goals in a given situation [76]. For individuals with CP, self-efficacy is related to their belief in their ability to perform activities despite pain—referred to as pain-related self-efficacy [77]. Regardless of pain severity, improvements in pain-related self-efficacy are associated with reductions in disability [78]. Moreover, a previous meta-analysis found that pain-related self-efficacy negatively correlated with impairment, affective distress, and pain severity [79].

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Traumatic Events

The scientific literature has strongly linked posttraumatic stress disorder (PTSD), particularly as a result of childhood trauma, to CP [23,80]. The comorbidity between PTSD and CP health issues ranges from 10% to 50% [81]. According to some studies, when CP coexists with PTSD, the pain tends to be more severe and causes greater distress, higher levels of interference, and more disability compared to cases of CP without a history of trauma [82]. PTSD is also a highly prevalent consequence of IPV against women, affecting 31% to 84.4% of women experiencing IPV [83], with similar rates found in more recent studies [84].

Receipt of Informal Social Support

Social support refers to the resources provided through both informal and formal relationships [85]. There is growing research on how social factors, particularly social support, influence pain experiences [86-88]. Informal social support is especially valued by patients with CP [89,90]. Within a person's social context, spouses or partners can play a critical role in CP management as either risk or protective factors. They can promote autonomy by encouraging positive behaviors [91] or foster dependence by reinforcing disabling pain behaviors through overprotectiveness [91-93] or negative responses such as hostility and criticism [93,94]. However, negative responses are more likely to worsen pain intensity, disability, and pain behaviors when they occur in the context of low marital satisfaction [95,96].

Activity Patterns

Studies have identified 3 general activity patterns that affect the quality of life and CP adjustment: pacing, avoidance, and persistence [97]. These general activity patterns can be divided into more specific ones depending on the person's goals [98,99]. However, to simplify, pacing generally involves breaking down daily activities into smaller, more manageable tasks and distributing them throughout the day. Pacing is used in clinical contexts to reduce avoidance and excessive persistence. There is strong empirical evidence that avoidance and excessive persistence contribute to worsened CP outcomes, including poorer psychological and physical functioning, increased pain [97,100], and difficulties in performing daily activities, leading to more global disability [101,102]. Avoidance is a strategy aimed at minimizing pain escalation by reducing engagement in physical activities. In cases of highly disabling CP, avoiding physical activity is common [103]. Conversely, the persistence pattern involves continuing to perform tasks despite pain, aiming to increase productivity by "ignoring" the pain [97].

Exercising

Exercising is a key component of the multidisciplinary treatments in CP, offering significant benefits beyond musculoskeletal health. It has been shown to reduce pain intensity and fatigue as well as improve physical function, psychological well-being, and overall quality of life [104,105]. Its benefits for CP go beyond just musculoskeletal health [106,107]. In fact, several studies have shown that exercise ameliorates pain even if the person's strength, flexibility, or endurance does not improve [107,108]. It could be that physical exercise has analgesic effects [109].

CP Outcomes

How individuals manage CP can have deep and long-lasting effects on their quality of life. Effective management can minimize pain, reduce physician visits, empower patients to participate in treatment decisions, and provide a sense of control over their lives [110-114]. By contrast, poor CP management can negatively impact socialization, reduce participation in social events, and decrease independence, leading to isolation [115,116]. It can also increase vulnerability to suicide and suicidal ideation [110] as well as contribute to the misuse of both licit and illicit drugs—such as alcohol, marijuana, or heroin—for pain relief [117-119], which, in turn, further strains health systems. Pain is one of the primary reasons for medical consultations worldwide, accounting for 22% of visits [120,121]. People with CP visit their general practitioner twice as often as those without CP [122], and they are more likely to use emergency services and unscheduled care [123,124]. In Spain, CP is the second most common reason for primary care consultations, with >50% of visits related to this condition [125].

Methods

This research project is expected to last 3 years and will be conducted in 2 phases: the first phase will involve a qualitative study (general aim 1, study 1), and the second phase will involve a quantitative cross-sectional study (general aim 2, study 2). Before commencing the studies, the web-based closed questionnaires to be completed by participants will be piloted with a sample of 10 women to address any issues related to content, usability, or technical functionality of the web-based platform used to design the questionnaires.

Ethical Considerations

Approval has been obtained from the ethics committee of Miguel Hernández University (DCC.ANR.240227) and the Public Health Ethics Committee for Research of the Foundation for the Promotion of Health and Biomedical Research of the Valencian Community (CEI-SP 20240531/05/P).

Ethical requirements will be consistent across both studies. All participants will receive a letter with a description of the study and of the individual interview content and questionnaires that they will have to fill in depending on the study in which they participate. There will not be any incentive for participation.

For the qualitative phase (phase 1), participants will sign an informed consent form, which clearly states that participation is voluntary and that they can withdraw at any time. Before the interviews, they will have to complete a web-based questionnaire to check whether they meet the inclusion criteria. Participants will submit their informed consent to a designated professional at the relevant health center, unit, or association, who will assign a code to each participant and will also be responsible for ensuring the correct completion of the web-based questionnaires with the corresponding code. Participants who do not meet the inclusion criteria will have their questionnaires deleted, and the informed consent forms for nonparticipants will be discarded by the professionals. Participants who meet the inclusion criteria

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will be interviewed. Interviews will be audio recorded for analysis purposes and erased afterward. The informed consent forms will be securely handed over by the professionals to the principal investigator in a sealed envelope. The professionals will also schedule the interview date and communicate the participant's code number to the research team, ensuring that the interview and questionnaire data match. The research team will not have access to any personal identifying information, such as names.

For the quantitative phase (phase 2), participants will fill in anonymous web-based questionnaires, as outlined in the informed consent form. For security reasons, participants must complete the questionnaire at the center they attend. Allowing them to complete it at home could put them at risk because their aggressors could see their responses. Participants will submit their informed consent to a designated professional at the relevant health center, unit, or association. This professional will have a list of codes. They will have to assign one to each participant (unknown to them) and will have to enter it so that each participant can start or pick up the questionnaire where they left off the last time. The professional will collect all informed consent forms and submit them to the principal investigator in a sealed envelope. Throughout the study, the research team will not have access to any personal identifying information.

In both studies, the web-based closed questionnaires will be designed using LimeSurvey, a private platform that meets security standards and data protection regulations. The responses will be stored in a database under the supervision of one of the collaborating universities. Before commencing the studies, the questionnaires will be piloted with a sample of 10 women to address any issues related to content, usability, or technical functionality of the web-based platform.

Phase 1: Qualitative Study (General Aim 1, Specific Objectives 1 to 4)

Overview

We will use a qualitative approach with a descriptive and exploratory design, conducting individual semistructured interviews. Focus groups are not considered due to the necessity of maintaining the anonymity of those experiencing IPV against women. The results of this phase will allow us to incorporate any additional relevant factors or health outcomes into the study's second phase.

Participants

The study will be conducted in the province of Alicante in Spain. To detect possible differences, interviews will be conducted with 2 groups: first, adult women with CP who are currently experiencing IPV (group 1) and, second, women with CP who are in a partner relationship and have never experienced IPV or any other form of violence, as defined earlier (group 2).

We will initially interview 10 women from each group, progressively increasing the number of interviews until theme saturation is reached [126]. Both groups will include women with varying sociodemographic characteristics, levels of disabling pain, and trauma symptoms. However, the diversity between the 2 groups will be balanced, ensuring that both groups include equal numbers of women with disabling pain and those without.

Procedure

First, we will reach out to the organizations through which we plan to access both groups and request their collaboration. To contact women who have experienced or are experiencing IPV and women with CP, we will consult associations and support centers for IPV against women, CP associations, CP units, and primary health care centers. These organizations will be asked to inform their patients about the project and encourage their participation.

Eligible candidates will be required to complete a series of questionnaires (refer to the Instruments subsection) to determine whether they meet the inclusion and exclusion criteria. The data from those who do not meet the criteria will be discarded. Those who qualify will proceed to complete additional questionnaires. The answers from these questionnaires will help us form the 2 groups while ensuring diversity based on age, racial background, and degree of disabling CP.

The inclusion criteria for both groups will be as follows: (1) women aged ≥18 years, (2) in a heterosexual intimate relationship for at least 1 year (as per Spanish law, IPV against women pertains to violence perpetrated by male intimate partners) [15], and (3) living with a CP condition highly prevalent in women and among those who have experienced IPV against women (eg, fibromyalgia, abdominal pain, genitourinary tract pain, pelvic and genital pain, headaches [including migraines], back and neck pain, and chronic fatigue syndrome) [19-22]. Women belonging to group 1 will, in addition, have to be currently experiencing IPV.

The exclusion criterion for group 2 will be having previously experienced IPV against women or any other form of violence because this may affect their current intimate relationships. The exclusion criterion for both groups will be experiencing oncological pain.

Interviews

A member of the research team will be in charge of conducting individual semistructured interviews. For security reasons, the interviews will be carried out at the locations where participants were recruited. Each interview is expected to last approximately 1 hour. The questions that will be posed to both samples are as follows:

- What does "living with CP" mean to you?
- How do you manage CP in your daily life?
- Have your self-management strategies changed over time? If yes, how?
- What role does your partner play with regard to your CP?
- Does CP affect your relationship? If yes, how?
- Does your partner use your health condition against you? If yes, can you provide examples?
- Does your relationship affect your CP? If yes, how?
- What is your experience with the health system?
- What is your relationship with medication?

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Instruments

The variables and instruments that will be used, organized by purpose, are summarized in Table 1 and described in the subsections that follow.

Table 1. Variables and instruments used in study 1, organized by purpose.

Variable	Questionnaire	Control purposes[a]	Data analysis
Chronic pain	Ad hoc question	✓	
Sociodemographic characteristics	Ad hoc questionnaire	✓	✓
IPV[b] against women	European Union Agency for Fundamental Rights study on violence against women survey inventory	✓	✓
Possible traumatic events experienced	Adapted version of Life Events Checklist for DSM-5	✓	
Disabling chronic pain	GCPS-R[c]		✓
Severity of PTSD[d] symptoms	EGS-R[e]		✓

[a]We include compliance with the inclusion and exclusion criteria.

[b]IPV: intimate partner violence.

[c]GCPS-R: Graded Chronic Pain Scale Revised.

[d]PTSD: posttraumatic stress disorder.

eEGS-R: Escala de Gravedad de Síntomas Revisada (Posttraumatic Stress Disorder Symptom Severity Scale-Revised [according to Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition criteria]).

Screening for Compliance With Inclusion and Exclusion Criteria

CP and Type

To distinguish participants with acute pain from those with CP, they will first be asked how long they have been experiencing pain. Participants will also select the type of CP they experience, such as fibromyalgia, from a provided list.

Sociodemographic Characteristics

Participants will have to indicate their age, sex at birth, gender identification, racial and ethnic identity, sexual orientation, and relationship status (whether currently in a relationship and for how long).

IPV Against Women: European Union Agency for Fundamental Rights Study on Violence Against Women Survey Inventory

Participants will complete an inventory [127] consisting of 32 items that assess various forms of violence exerted by a partner: 11 items on physical violence, 4 on sexual violence, and 17 on emotional and psychological violence. Participants will respond with the frequency of each type of violence (0=*never*, 1=*once*, and 2=*more than once*) and specify whether the violence was inflicted by a past or current partner, including the duration of the violent relationship. A woman will be classified as experiencing current IPV or having experienced past IPV if she reports experiencing any item more than once from the same partner.

Possible Traumatic Events Experienced: Adapted Version of Life Events Checklist for DSM-5

The original version of this checklist [128] contains 17 items referring to different stressful events. Participants will have to mark whether they have experienced, witnessed, or learned about each event; whether it was part of their job; or whether it does not apply to them. The adapted version will rephrase the items on physical and sexual assault (items 6 to 9) into a single item: exposure to "psychological, physical, and/or sexual violence or abuse at any stage of your life by a known or unknown person other than an intimate partner."

The purpose of using this instrument is helping to control for any external traumatic events (eg, natural disasters) that may influence pain experiences different from experiencing IPV.

Configuration for Diverse Groups and for Data Analysis Purposes

Additional Sociodemographic Characteristics

Both groups of participants will need to complete a questionnaire detailing their nationality, years of education, profession, annual household and personal incomes, relationship satisfaction, and the number of children. This information will help in differentiating the groups and understanding various factors that may impact pain experiences. Regarding pain characteristics, participants will report on pain location, severity, diagnosis, and the time since they were diagnosed with CP.

IPV Against Women: European Union Agency for Fundamental Rights Study on Violence Against Women Survey Inventory

This inventory [127] will be used to assess the severity of violence experienced by participants, based on the total score obtained, with a maximum possible score of 64 points. The severity of the violence will be classified into 3 categories—low, moderate, and high—determined by calculating percentiles. This inventory is available in multiple European languages, including Spanish.

Disabling CP: Graded CP Scale Revised

For assessing disabling CP, the Graded Chronic Pain Scale Revised [129] will be used. This scale consists of 5 items, each rated on a scale ranging from 0 to 10, and provides a simple and valid method for classifying CP as mild, bothersome, or high impact. Those who, on items 1 and 2, report that in the

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past 3 months, their pain has limited their life activities or work on most days or every day will be classified as grade 3 (high-impact CP). Those who score ≥12 on items 3 to 5 will be classified as grade 2 (bothersome CP); and those who score <12, with no high-impact pain, will be categorized as grade 1 (mild CP). The Graded Chronic Pain Scale Revised has demonstrated good concurrent validity.

Severity of PTSD Symptoms: PTSD Symptom Severity Scale-Revised

This instrument [130] consists of 21 items related to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* diagnostic criteria: 5 to re-experiencing symptoms, 3 to behavioral and cognitive avoidance symptoms, 7 to cognitive disturbances and negative mood, and 6 to symptoms of increased psychophysiological arousal and reactivity. The responses are rated on a 3 points Likert- type scale ranging from 0 to 3 points according to symptom frequency and intensity. When a person scores at least 2 points in an item, the symptom to which the item refers to is considered present. The overall scale ranges from 0 to 63 points. The instrument has shown high internal consistency, good discriminant and concurrent validity and diagnostic efficacy in a large sample of Spanish women who have mostly experience IPV.

Data Analysis

The verbatim interview transcripts will undergo inductive reflexive thematic analysis, a foundational and flexible qualitative method that allows researchers to identify, analyze, and report themes or patterns in data [131,132]. In this study, the focus will be on understanding participants' experiences, meanings, and realities.

Two researchers trained in reflexive thematic analysis will collaborate using the process established by Braun and Clarke [131,132]. The process begins with data familiarization, where the researchers review the material and take initial notes. Next, they will systematically code the data, group similar codes, and produce initial themes based on the collated data. These themes will then be developed and revised through an iterative process. The final stage involves refining, defining, and naming the themes before writing the report. Inductive coding will be carried out using NVivo 10 software (Lumivero).

To ensure the quality of the analysis, several procedures will be implemented throughout the research. This will include ensuring that the research question aligns with the methodological decisions (ie, methodological coherence) and selecting participants who can provide the most relevant and insightful information. Data analysis will be an iterative process, allowing ideas to evolve and be confirmed with the data. In addition, the research team will work closely together to develop interpretations and concepts that best capture the phenomenon under investigation.

Phase 2: Quantitative Study (General Aim 2, Specific Objectives 5 and 6)

Phase 2 of the research will focus on a cross-sectional quantitative study aimed at examining the differences between 3 groups of women.

Participants

The reference population will include heterosexual women aged ≥18 years living in the province of Alicante. To detect possible differences in profiles, the study will be carried out in 3 groups of women: those who have CP and have never experienced IPV or any other type of violence (group 1), those who have CP and are currently experiencing IPV (group 2), or those who have CP and have a past history of IPV (group 3). It is important to note that the effects of violence may continue to impact individuals long after the relationship ends, and this study aims to identify risk and protective factors, as well as health outcomes, to support detection and intervention efforts.

Sample Size Calculation

To calculate the sample size, the prevalence of the pain-avoidance activity pattern was used, which is typically present in cases of highly disabling CP [102]. Specifically, we considered several factors: first, the expected prevalence ratio assumed to be 2.0 between individuals with CP who are exposed to IPV against women and those who are not. Second, we estimated the prevalence of the pain-avoidance activity pattern within the study population, assuming it to be approximately 20%. While a previous study found that 40.4% of patients with fibromyalgia exhibited this pattern [133], we decided to use a more conservative estimate, given that the prevalence of this behavior is likely lower among the broader population of patients with CP. Finally, we accounted for the expected prevalence of IPV exposure among women with CP, estimated at 30% based on findings from earlier research [23].

We have defined the risk level α as 5% and the study power as 90%. The program used for size calculation was a macro, !NSize, for SPSS Statistics [134]. On the basis of these parameters, the required sample size consists of 359 women with CP: 193 (53.8%) with CP alone, 83 (23.1%) with CP and a current history of IPV, and 83 (23.1%) with CP and a past history of IPV.

Procedure

We will access the sample through the same channels as in phase 1. First, we will explain the benefits of the project to the organizations and request their support in encouraging their patients to participate. The directors of these organizations will receive the link to the web-based questionnaire, which will then be distributed to patients who, for security reasons, can only complete the questionnaire at the respective facilities.

Participants willing to participate will have to complete a web-based questionnaire. The first page will outline the objectives of the study, and the second page will ask participants to confirm whether they meet the inclusion criteria, as described in the phase 1 Procedure subsection. Specifically, participants must be women aged ≥18 years and must have been living with one of the identified types of CP for at least 3 months.

Participants will have 1 month to complete the questionnaire. During this period, answers will be saved in the system to allow participants to complete the questionnaire on different occasions; however, as stated, the professionals at the centers will need to activate the survey links. Survey links are deactivated to prevent

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respondents from completing the questionnaires outside of the designated locations. The data will be automatically stored in a database, and the progress of sample collection will be monitored weekly to ensure that each group reaches the necessary sample size.

Variables and Instruments

The variables and instruments that will be used, organized by purpose, are summarized in Table 2 and described in the subsections that follow. Some response scales will be alternated to identify biases in participants' responses.

Table 2. Variables and instruments used in study 2, organized by purpose.

Variable	Questionnaire	Control purposes[a]	Data analysis
Chronic pain	1 screening item	✓	
Sociodemographic characteristics	Ad hoc questionnaire	✓	✓
Access to the study	Ad hoc question	✓	
IPV[b] against women	European Union Agency for Fundamental Rights study on violence against women survey inventory		✓
Possible traumatic events experienced	Adapted version of Life Events Checklist for DSM-5	✓	✓
Disabling chronic pain	GCPS-R[c]		✓
Severity of PTSD[d] symptoms	EGS-R[e]		✓
Gender norms and gender identity	CFNI-45[f]		✓
Activity patterns	APS[g]		✓
Exercising	IPAQ[h]		✓
Pain worrying (pain catastrophizing)	PCS[i]		✓
Pain-related self-efficacy	CPSS[j]		✓
Informal social support	ISSADI-PAIN[k]		✓
Health related quality of life	MOS SF-12[l]		✓
Physical functioning	BPI- SF[m]		
Anxiety and depression	HADS[n]		✓
Suicide attempts and thoughts	Ad hoc questionnaire		✓
Medication use and illegal drug use	Ad hoc questionnaire		✓
Health service use	Ad hoc questionnaire		✓

[a]We include compliance with the inclusion and exclusion criteria.
[b]IPV: intimate partner violence.
[c]GCPS-R: Graded Chronic Pain Scale Revised.
[d]PTSD: posttraumatic stress disorder.
[e]EGS-R: Escala de Gravedad de Síntomas Revisada (Posttraumatic Stress Disorder Symptom Severity Scale-Revised)
[f]CFNI-45: Conformity to Feminine Norms Inventory-45.
[g]APS: Activity Patterns Scale.
[h]IPAQ: International Physical Activity Questionnaire.
[i]PCS: Pain Catastrophizing Scale.
[j]CPSS: Chronic Pain Self-Efficacy Scale.
[k]ISSADI-PAIN: Informal Social Support for Autonomy and Dependence in Pain Inventory.
[l]MOS SF-12: Medical Outcomes Study Short-Form Health Survey-12.
[m]BPI-SF: Brief Pain Inventory–Short Form.
[n]HADS: Hospital Anxiety and Depression Scale.

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Variables and Instruments for Control Purposes

Screening for CP and Type and Sociodemographic Characteristics

These variables are described in detail in the phase 1 CP and Type and Sociodemographic Characteristics subsections.

Access to the Study

Participants will have to indicate how they accessed the study (associations and support centers for IPV against women, CP associations, CP units, or primary health care centers).

Variables and Instruments for Risk and Protective Factors

Sociodemographic Characteristics

Age, belonging to a minority group (yes or no), years of education, annual household and personal incomes (categorized as €0 to €19,000; €20,000 to €40,000; and >€40,000; 1€=US $1.14), relationship status (single, partnered, or married), relationship duration (years), relationship satisfaction (10-point scale), CP diagnosis (yes or no), and time since CP diagnosis (years).

Gender Norms and Identity

Gender norms and identity will be measured using the Conformity to Feminine Norms Inventory-45 [135,136]. The Spanish-adapted version of the inventory [137] consists of 23 items rated on a 4-point response scale ranging from 0=*strongly disagree* to 3=*strongly agree*. The inventory includes 7 subscales: care for children, invest in appearance, domestic, romantic relationship, nice in relationships, thinness, and modesty. It is designed to assess the degree to which women conform to traditional femininity norms as reflected in their behaviors, feelings, and thoughts. Higher scores on this inventory indicate a greater adherence to these traditional femininity norms. The Conformity to Feminine Norms Inventory- has demonstrated good psychometric properties, making it a reliable measure for evaluating conformity to feminine norms.

IPV Against Women: European Union Inquiry; Possible Traumatic Events Experienced: Adapted Version of Life Events Checklist for DSM-5; Disabling CP: Graded CP Scale Revised; Severity of PTSD Symptoms: Posttraumatic Stress Disorder Symptom Severity Scale-Revised

These scales have been described in study 1. With regard to the IPV against women questionnaire, participants will have to indicate whether they are currently experiencing such situations or have experienced them in the past and for how long. In addition, those women who have experienced IPV in the past will be asked how long they have lived free from violence.

Activity Patterns: Activity Patterns Scale

Overview

The 3 activity patterns—pacing, avoidance, and persistence—can serve different goals and have varying impacts on health outcomes. To measure these patterns, we will use the Activity Patterns Scale [138]. This scale consists of 8 subscales, each with 3 items, for a total of 24 items. The subscales include pain avoidance, activity avoidance, task-contingent persistence, excessive persistence, pain-contingent persistence, pacing to increase activity levels, pacing to conserve energy for valued activities, and pacing to reduce pain. Participants will rate how well each statement applies to them on a 5-point scale ranging from 0=*not at all* to 4=*always*. Higher scores in a subscale indicate a stronger tendency to display the corresponding activity pattern. The instrument demonstrates adequate reliability as well as structural, convergent, and criteria validity. It has been specifically developed for use with the Spanish population [138].

Exercising: International Physical Activity Questionnaire

Although some studies advocate the use of objective measures of physical activity and physical exercise [139], the International Physical Activity Questionnaire (IPAQ) [140] allows the collection of detailed information on physical activity performance comparable to that collected with objective measures such as pedometers [141]. The short, self-administered version of the IPAQ focuses on the past 7 days and consists of 7 items that estimate the time spent on moderate to vigorous physical activity, such as walking, bicycling, or heavy lifting, in at least 10-minute bouts over the week. This version provides a continuous score reflecting the minutes of physical activity performed, with higher scores indicating greater physical activity. The IPAQ presents good psychometric properties and is available in Spanish [140].

Pain Worrying (Pain Catastrophizing): Pain Catastrophizing Scale

This scale [142] contains 13 items that are rated on a 5-point scale ranging from 0=*not at all* to 4=*all the time*. It assesses the 3 components of catastrophizing: rumination, magnification, and helplessness. The total score ranges from 0 to 52 points. Higher scores reflect higher levels of catastrophic thoughts. The Spanish version [143] presents strong psychometric properties.

Pain-Related Self-Efficacy: CP Self-Efficacy Scale

This specific scale [144] for patients with CP helps measure perceived self-efficacy and capability to manage pain consequences. It is composed of 22 items structured across 3 factors: self-efficacy to control pain, self-efficacy for physical functioning, and self-efficacy for symptom control. It is a well-known instrument that has been validated with the Spanish population with good psychometric properties [145]. In the Spanish version items are rated from 0=*I think I am totally incapable* to 10=*I think I am totally capable*, with a higher score suggesting higher self-efficacy in a specific factor or in the overall measure of self-efficacy.

Informal Social Support: Informal Social Support for Autonomy and Dependence in Pain Inventory

This instrument [146] consists of 11 items designed to measure both emotional and instrumental social support in relation to promoting functional autonomy or addressing functional dependence. Participants are asked to rate how frequently their family members have provided support when they were in pain.

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In our case we specifically ask on the support they receive from their intimate partners. Only women currently in a relationship will be required to complete this section. Responses are provided on a Likert scale ranging from 1=*not at all frequent* to 5=*extremely frequent*. Higher scores indicate that participants perceive more frequent support for functional autonomy or dependence. This instrument has demonstrated validity and reliability in its original form and has been validated with the Spanish population [146].

Variables and Instruments for Health Outcomes

Health-Related Quality of Life: Short-Form Health Survey-12

This tool [147] consists of 12 items that measure both positive and negative health states across 8 health concepts (physical functioning, role limitations because of physical health problems, bodily pain, general health, vitality, social functioning, role limitations because of emotional problems, and mental health). It offers 2 physical and mental health summary measures. The responses are based on Likert scales ranging from 3 to 5 points. This questionnaire has been validated for use with the Spanish population [148].

Physical Functioning: Brief Pain Inventory–Short Form

The Brief Pain Inventory–Short Form [149] assesses pain severity and pain interference. The latter includes 7 items that assess pain's impact on various areas of life (general activity, mood, ability to walk, work, social relationships, sleep, and the ability to enjoy activities), which participants rate on a 10-point scale (maximum score=70). For the purpose of evaluating physical functioning, items related to general activity, ability to walk, and ability to work will be selected, with a maximum score of 30. This instrument has been validated for use with the Spanish population [150].

Anxiety and Depression: Hospital Anxiety and Depression Scale

This scale [151] includes 2 subscales, one for anxiety and one for depression, each with 7 items and a 4-point response scale ranging from 0=*no presence or minimum presence* to 3=*maximum presence*. The scale assesses emotional distress in patients with chronic conditions, focusing on the cognitive and behavioral symptoms of anxiety and depression. The recommended cutoff scores for possible cases are 8 for both subscales, with scores of >10 indicating probable cases. This scale has been widely validated across multiple countries, including Spain, and demonstrates strong psychometric properties [152].

Suicide Attempts and Thoughts: Ad Hoc Questionnaire

Participants will be asked whether they have ever considered committing suicide (yes or no); how frequently they have had such thoughts (never, rarely, sometimes, often, or always); and the number of suicide attempts, if any.

Medication Use and Illegal Drug Use: Ad Hoc Questionnaire

Participants will be asked to indicate the types of analgesics prescribed for their CP condition and their adherence to the prescribed medication regimen. They will be asked if they are taking the medication as prescribed, not taking it at all, or taking it in lesser or greater amounts. The questionnaire will also inquire about the use of nonprescribed medications and the consumption of other legal (eg, alcohol) and illegal drugs (eg, marijuana) for pain management. In addition, participants will be asked about other prescribed medications they may be taking and the purposes for which these medications are used.

Health Service Use: Ad Hoc Questionnaire

Participants will be asked about the frequency of visits to their general practitioner. Specifically, they will be asked how many times per month they visit their general practitioner, with the following response options: none, only when needing medication prescriptions or check-ups, at least once a month, or ≥2 times per month.

Data Analysis

Inferential statistics help researchers draw conclusions about populations based on sample data, providing insights into social phenomena [153]. Machine learning, as a subset of artificial intelligence (AI) techniques, analyzes large datasets to identify patterns and make predictions [154]. These methods are transformative in gender studies, uncovering patterns in gender-related data and deepening the understanding of social inequalities and biases [155]. These methods have been successfully applied to areas such as forecasting gender-based violence, further demonstrating their relevance in social sciences [156].

Exploratory data analysis (EDA) will be crucial in examining CP and its connection to past or current IPV against women. EDA uses techniques such as scatterplots, clustering algorithms, and principal component analysis to investigate multidimensional datasets [157]. Scatterplots help identify correlations between sociodemographic variables, clustering algorithms reveal subgroups within the population, and principal component analysis reduces dimensionality to uncover latent factors such as the relationship between gender identity and social support [158]. The use of EDA will allow us to detect groups and subgroups at a glance by creating subclusters, that is, more specific profiles in each of the groups.

Inferential statistical methods will be applied to differentiate between women with CP alone and those with CP who have experienced IPV in the past or are currently experiencing IPV. Hypothesis testing, estimation, and prediction techniques will be used to make comparisons, with visual tools such as boxplots for examining variable distributions across groups. We will use 2-tailed *t* tests and ANOVA to compare means across groups [159].

Feature ranking techniques will help identify the most relevant variables for accurate classification. Methods such as information gain, gain ratio, Gini index, and relief will determine the importance of features such as education, socioeconomic

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status, pain level, and social support [160]. This feature ranking will help prioritize the most influential factors affecting each group, including those based on country distribution.

Machine learning classifiers, including random forest, decision trees, adaptive boosting, gradient boosting, and support vector machines, will be applied to classify data. The process will involve training, validation, and testing phases, with hyperparameter tuning during validation. K-fold cross-validation will be used to evaluate the model's performance, using training, validation, and testing phases across different folds [161]. The model's performance will be assessed using metrics such as precision, recall, F_1-score, and receiver operating characteristic curves [162].

Feature importance evaluation will identify which variables most significantly influence the model's predictions. This analysis, combined with explanatory models such as Shapley additive explanations, will provide further insights into how features impact classification outcomes [163]. These methods are widely used in gender studies to uncover social patterns and inequalities. By combining Shapley additive explanations values with EDA, we aim to pinpoint the most significant factors that explain different profiles in the data [164].

Data analysis will be conducted using Python (Python Software Foundation), with libraries such as *pandas* (for data manipulation), *NumPy* (for numerical operations), *scikit-learn* (for machine learning), and the combination of *matplotlib* and *seaborn* (for visualization). This suite of tools provides an efficient framework for inferential statistical analysis and exploratory data. Comparable analysis could also be performed using R (R Foundation for Statistical Computing), which presents similar usability for data study. R comes with *tidyverse*—a package that merges *dplyr* and *ggplot2* for visualizing data—and *caret* for building predictive models. Similar software such as MATLAB (The MathWorks, Inc) also allows for wider functionality for statistical computing and algorithm development.

Results

As of May 2025, we had contacted relevant associations to present the project and begin recruiting voluntary participants. We have conducted the pilot study to assure the adequacy of the questionnaire and usability or technical functionality of the web-based platform. The results are expected to be published starting in January 2026. The study timeline is presented in Table 3.

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Table 3. Study timeline.

Year, study phases, and tasks	Months											
	1	2	3	4	5	6	7	8	9	10	11	12
Year 1												
Phase 1												
Identification of and contact with associations and support centers for IPV[a] against women, CP[b] associations, CP units, and primary health care centers to present the projects and request their collaboration for phase 1 and phase 2	✓	✓										
Development of semistructured interview guide			✓									
Conducting interviews				✓	✓							
Transferring data						✓						
Data analysis							✓		✓			
Writing articles and communications									✓	✓	✓	✓
Year 2												
Phase 2												
Contact with associations and support centers for IPV against women, CP associations, CP units, and primary health care centers to initiate participation in phase 2	✓	✓										
Design of web-based questionnaire	✓	✓										
Questionnaire piloting and inclusion of changes			✓									
Supervision of questionnaire completion				✓	✓	✓	✓		✓	✓	✓	✓
Year 3												
Data analysis	✓	✓	✓									
Writing articles and communications				✓	✓	✓	✓		✓	✓	✓	✓
Develop assessment and intervention guidelines									✓	✓	✓	

[a]IPV: intimate partner violence.

[b]CP: chronic pain.

Discussion

Summary

This project has 2 main aims. The first is to acquire knowledge on the meaning and implications of living with CP for women experiencing IPV compared to those with CP alone. In this regard, we hypothesize that (1) women who experience any form of IPV (psychological, physical, or sexual) will report a greater daily impact of CP on their functionality than those with CP alone; (2) compared to the latter, the former will report a stronger bidirectional relationship between CP and intimate relationship dynamics as well as worse health outcomes (ie, episodes of violence will increase CP symptomatology and vice versa), with such a negative cycle being more prevalent; and (3) CP management and experiences with the health system will be better among women with CP alone. Hypotheses 1 and 3 are based on the fact that some authors have highlighted that the impact of IPV against women on the health of those affected adds to CP [31]. This could impair their ability to self-manage CP, leading to increased medication use and more frequent visits to health centers [165]. We believe that this result will be independent of the type of violence experienced because studies have shown that psychological violence alone can negatively impact CP severity and disability [166,167].

Regarding our second hypothesis, we expect that aggressors will present more hostility and criticism toward their partners' health conditions as a way to undermine them, increase dependence, and control them, considering violence as an instrumental component [165]. We also expect that periods of violence will be linked to an increase in CP symptomatology. However, in women with CP alone, their partners will likely promote autonomy by encouraging and reinforcing healthy behaviors or promote dependence by maintaining disabling pain behaviors through solicitousness. In this group of women, even if hostile responses can also be present sometimes, their impact on CP will be less significant because they need to take place in a context of low marital satisfaction [95,96], and we assume that levels of marital satisfaction will be higher among women with CP alone. In addition, we expect that periods with an increase in CP symptomology will be more related to external stressors than to the relationship itself.

Second, we aim to identify whether women with CP alone, those with CP and currently experiencing IPV, and those with CP and

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a past history of IPV present different profiles based on risk and protective factors for (disabling) CP and health outcomes. We hypothesize that women with CP and current or past experiences of IPV will show higher levels of disabling pain, more excessive persistence or avoidance activity patterns, lower levels of exercise, worse pain-related self-efficacy, greater pain worrying, informal social support that fosters dependence, lower levels of physical functioning, greater anxiety and depression, poorer medication management, increased illegal drug use, more suicidal thoughts and attempts, and a higher frequency of health system use. This hypothesis is based on previous findings indicating higher levels of disabling pain in women experiencing IPV compared to those with CP alone, as well as higher levels of suicidal thoughts, addiction issues, and greater use of health services compared to the general female population [23,165]. These characteristics will likely worsen in the presence of PTSD [82]. In addition, because pain-related self-efficacy and pain worrying have been linked to CP [65-69,78], we expect these factors to most effectively account for the profiles of women with a current or past history of IPV, along with informal social support, for the aforementioned reasons.

Moreover, because AI techniques go beyond traditional inferential statistics, it can identify patterns and relationships between variables that might remain undetected by the human eye. AI may uncover specific profiles within different groups of women, revealing how factors such as educational background, traditional feminine roles, ethnicity, and the duration of violence intersect with CP-related variables; for example, it could be that the pattern of excessive persistence is more common in women who are in the initial stages of the relationship and that they may seek to conform to traditional gender roles in an effort to meet their aggressors' expectations. AI's ability to process large datasets could lead to new insights and advances in understanding pain, its management, and its relationship with other concurrent psychosocial factors.

Limitations

This study is not without limitations. One of the main challenges is the high number of participants required for the quantitative study. To mitigate this issue, we will contact primary health care centers, associations and support centers for IPV against women, CP associations, and CP units across the province of Alicante. A second limitation is the use of nonprobability sampling, which may introduce bias. However, this research aims to provide a preliminary understanding of the co-occurrence of these 2 significant health issues; to the best of our knowledge, it will be the first to do so with a large sample using AI. A third limitation concerns the number of questionnaires that need to be completed in the second study. To address this, participants' responses will be saved, and they will be given ample time to complete all questionnaires. In addition, the order of presentation will be randomized to reduce the likelihood that the same questionnaires are consistently left unanswered. We hope this will result in a similar number of responses across all questionnaires. To further encourage questionnaire completion, we will ask the center directors and professionals to remind participants about the importance of answering all questions.

A fourth limitation is the focus on only individual and relational factors. While community and societal factors also influence CP and its disabling effects [168], the primary aim of this study is to enhance the detection and treatment of CP in health care settings by personalizing care. Therefore, the focus is placed on individual and relational factors. Finally, not all scales have been validated with Spanish samples. Validating several scales has high costs and is time consuming, but we will conduct translation and back-translation procedures and test the instruments directly with the population. Moreover, the study will only be conducted in the province of Alicante. However, if profiles are identified, we plan to extend the second study to other Spanish regions as well as other countries while controlling for other macrovariables (eg, free access to the health system) to analyze the commonalities and differences in the profiles. If minimal or no differences are found, the profiles could be largely explained by the experience of IPV against women, and recommendations could be generalized to similar countries.

Conclusions

In 2023, the European Pain Federation identified 7 key areas of focus in pain research [169], two of which are central to our study: (1) understanding and addressing comorbidities that complicate management and recovery; and (2) personalizing pain management because current treatments remain uniform, regardless of factors such as gender, age, lifestyle, or overall health. Our research directly addresses both areas. First, we tackle 2 closely related yet under-studied health issues: CP and IPV against women. As Craner et al [23] have noted, most research on traumatic events and CP has concentrated on childhood trauma and posttraumatic stress symptoms, with limited attention given to IPV against women. Second, our study aims to identify profiles based on risk factors and health outcomes, which could enhance detection and help design more personalized treatments.

In addition, our study could indirectly have a positive impact on costs and contribute to achieving the United Nations' Sustainable Development Goals. Both CP and IPV against women have significant consequences for individuals and societies, with economic costs of at least €300 billion and €172 billion, respectively (US $343 billion and US $197 billion) [4,18]. These high costs primarily stem from frequent primary health care consultations, diagnostic procedures, medication, therapies (eg, psychology, occupational therapy, infiltrations, or surgery), hospitalizations, and loss of work productivity. As a result, both health issues severely affect productivity and the health care system [121,170], threatening human capital and hindering progress toward the United Nations' Sustainable Development Goals. We believe that by improving the detection of IPV against women associated with CP and tailoring treatments to the identified risk factors and health outcomes, our study can help reduce costs and advance progress toward achieving the United Nations' Sustainable Development Goals. Effective self-management could alleviate the burden that CP places on the health care system and reduce its economic costs [171,172].

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Data Availability

Data sharing is not applicable to this paper as no datasets were generated or analyzed during this study. However, when generated, the datasets as well as the interview guide (phase 1) will be available from the corresponding author on reasonable request.

Authors' Contributions

AN-R contributed to the conceptualization and design of the project and wrote the draft. SB, MAP-M, and LP-A contributed to the conceptualization and design of the project and reviewed the manuscript. SL-R contributed to the conceptualization and design of the project (quantitative phase) and reviewed the manuscript. AS-P contributed to the conceptualization and design of the project (quantitative phase). VAF-P contributed to the conceptualization and design of the project. IR-R contributed to the conceptualization and design of the project (quantitative phase—artificial intelligence). PH-G contributed to the conceptualization and design of the project (qualitative phase).

Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
CP: chronic pain
EDA: exploratory data analysis
IPAQ: International Physical Activity Questionnaire
IPV: intimate partner violence
PTSD: posttraumatic stress disorder

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Protocol

The Cost-Effectiveness of Adding Helicobacter Pylori Screening to the National Gastric Cancer Screening Program in Korea: Protocol for a Cost-Effectiveness Modeling Study

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Abstract

Background: In Korea, the National Cancer Screening Program (NCSP) was implemented in 1999 and provides biennial endoscopy for adults aged ≥40 years. The NCSP has contributed to the early detection of gastric cancer and reduction of associated mortality in Korea. *Helicobacter pylori* is the main cause of gastric cancer. Screening for and eradication of *H pylori* reduces the incidence and mortality of gastric cancer. Previous studies have reported that screening for *H pylori* is a cost-saving intervention that can significantly decrease gastric cancer burden in areas with a high prevalence of *H pylori* infection. However, no study has examined whether incorporating *H pylori* screening into national endoscopic screening is cost effective.

Objective: This study aims to evaluate the cost-effectiveness of incorporating *H pylori* screening into Korea's National Gastric Cancer Screening Program.

Methods: We have developed a Markov model to compare two strategies: (1) endoscopy screening every 2 years starting at the age of 40 years (conventional screening), and (2) *H pylori* screening at the age of 40 years followed by continuous endoscopy screening every 2 years. We will also conduct a comparative analysis by varying the age at which the *H pylori* screening is performed. The primary outcome is the incremental cost-utility ratio (ICUR), calculated by dividing the incremental cost by the incremental quality-adjusted life-years (QALYs) between the two strategies. A probabilistic sensitivity analysis will be performed to test the uncertainty of the cost-effectiveness results. A sensitivity analysis will identify the most influential variables for cost-effectiveness.

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Results: The primary outcome parameter is the cost-effectiveness of adding *H pylori* testing to the current NCSP, which is expressed as the ICUR. Costs and utilities are discounted at an annual rate of 4.5%. The ICUR threshold is set at KRW 50 million (US $36,719), which is the South Korean gross domestic product per capita. This research has been funded by a Patient-Centered Clinical Research Coordinating Center grant from the Ministry of Health & Welfare, Republic of Korea (grant RS-2024-00398474). This study will analyze and synthesize previously published information and is thus exempt from institutional review board approval. Data collection started in June 2024 and was completed in May 2025. Study results will be published in peer-reviewed journals and presented at national and international conferences throughout 2025.

Conclusions: We will examine whether introducing *H pylori* testing and eradication therapy into the NCSP is a more cost-effective strategy for reducing gastric cancer risk than conventional endoscopy-based screening. Our study also examines the optimal age for *H pylori* screening, as well as the optimal screening frequency.

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KEYWORDS

eradication; gastric cancer; Helicobacter pylori; primary prevention; screening

Introduction

Helicobacter pylori infection is associated with peptic ulcers, marginal zone B-cell lymphoma of the mucosa-associated lymphoid tissue type, and gastric cancer [1]. South Korea has the highest global incidence rate of gastric cancer and a high prevalence of *H pylori* [2,3]. The prognosis of cancer is closely related to its stage at the time of the first diagnosis. Therefore, early detection is crucial to avoid death. Endoscopic screening reduces the risk of gastric cancer mortality by 40% [4]. Furthermore, early gastric cancer patients have a high chance of improving their long-term quality of life through treatments such as endoscopic mucosal resection or endoscopic submucosal dissection [5]. Therefore, early detection with an effective screening strategy is crucial in high-incidence countries such as Korea. To prevent this high incidence of serious severity or death, the Korean government implemented the National Cancer Screening Program (NCSP) in 2002 and currently facilitates adults aged ≥40 years to undergo upper gastrointestinal series or endoscopy as primary gastric cancer screening every 2 years [6]. The optimal frequency for gastric cancer screening is still debated, and it is unclear whether tailoring screening intervals according to an individual's gastric cancer risk may outperform the current NCSP approach of repeating endoscopy every 2 years.

Eradication of *H pylori* is associated with a 52% reduction in gastric cancer incidence and a 38% reduction in mortality [7]. *H pylori* screening and eradication have been reported to be associated with significant cost savings and health impacts for gastric cancer prevention [8]. A recent study reported that nationwide endoscopy screening is not cost-effective and that cost-effectiveness can be improved when *H pylori* eradication is performed only in high-risk groups [9]. For many years, South Korea and Japan have implemented nationwide programs to screen for gastric cancer. A recent study reported that South Korea's NCSP has apparent benefits for decreasing gastric cancer mortality and upper gastrointestinal disease mortality [10]. This study aims to determine whether adding *H pylori* screening to the current NCSP in South Korea would result in greater benefits in terms of cost compared to endoscopic screening alone.

Methods

Model Design

We constructed a Markov model to perform a cost-effectiveness analysis to evaluate the economic benefits of incorporating *H pylori* testing and eradication therapy into the existing endoscopy-based NCSP. Markov models can track long-term progression of diseases with complex progression, such as cancer, so they are widely used in studies to predict long-term follow-up cost-effectiveness for chronic diseases [11].

We referenced a previously published Markov model for the economic evaluation of gastric cancer screening in Korea, modifying it to focus on *H pylori* infection [12]. Therefore, the cancer screening–related data input into the model were based on the cancer screening and registration data in Korea as used in Bae et al [12]. Other epidemiological indicators were reviewed by multiple expert review meetings to use real-world data as much as possible. This study is being conducted with reference to the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) framework (Multimedia Appendix 1).

The two main strategies being compared for cost-effectiveness are (1) a strategy in which individuals undergo endoscopy every 2 years starting at the age of 40 years (conventional screening), and (2) a strategy in which individuals receive both endoscopy and *H pylori* testing with eradication therapy at the age of 40 years followed by continuous endoscopy thereafter. Furthermore, we will conduct a comparative analysis by varying the age at which *H pylori* screening is performed.

The Markov simulation model was constructed for a hypothetical population starting at 40 years, with cycles repeated until death or up to a maximum age of 120 years, for a total of 81 cycles; 1 cycle indicates 1 year. The main outcome presents the estimated cumulative costs and quality-adjusted life-years (QALYs) for a person's entire life cycle. At the beginning of the cohort, individuals are categorized as either noninfected or infected with *H pylori*, and those who successfully undergo eradication therapy transition to the eradicated state. Reinfection is possible even in the eradicated state, and it is assumed that natural eradication does not occur and that infection is only

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eradicated by treatment. In all states, individuals may transition to either early or advanced gastric cancer. Upon cancer onset, patients remain in a cancer-cured state after a 5-year follow-up period. Figure 1 shows the Markov model. This study aims to verify whether introducing *H pylori* testing and eradication therapy is cost-effective, and to determine whether it reduces the risk of developing early gastric cancer compared to conventional screening.

Figure 1. Markov model based on Helicobacter pylori and gastric cancer natural history. AGC: advanced gastric cancer; EGC: early gastric cancer; Erad: eradicated; F/U: follow/up; GC: gastric cancer; HP: Helicobacter pylori.

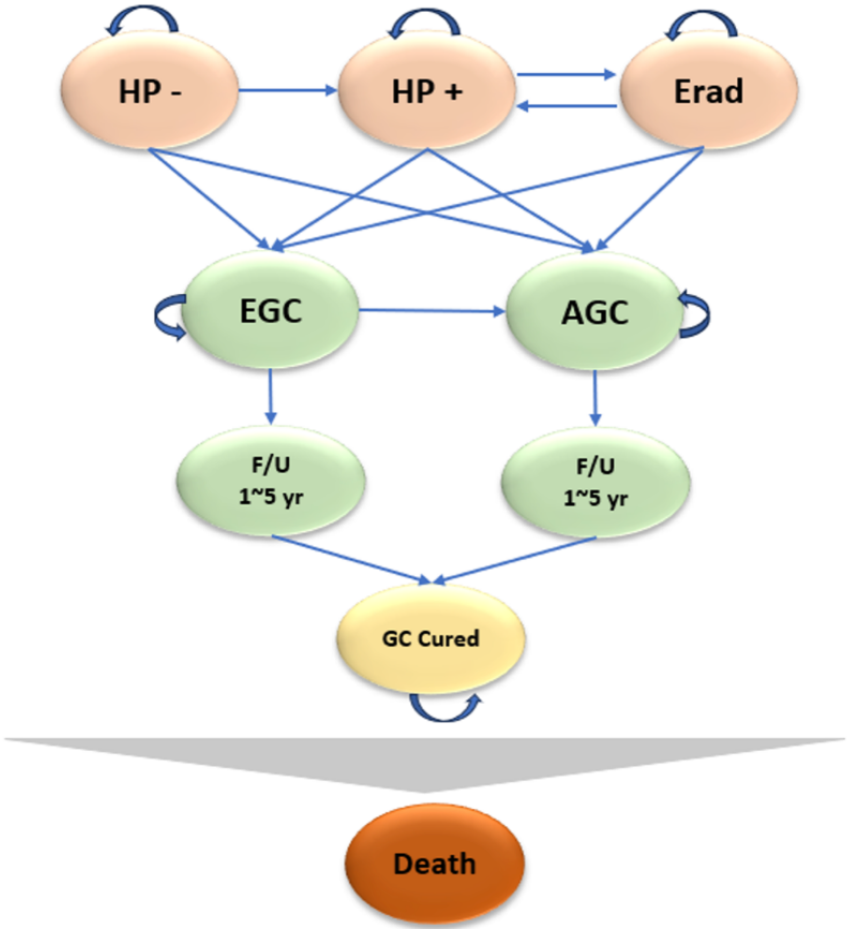

Parameters

In this study, the parameters required for the model are categorized as related to epidemiology, cost, or screening. Epidemiological parameters include the prevalence of *H pylori* infection, annual infection rate, reinfection rate, probability of progression to cancer, and mortality rate (among the general population and patients with cancer), which can be obtained from sources such as the National Health Insurance Service (NHIS) database, national statistics, and prior studies [3,13-20]. Cost parameters include the costs associated with *H pylori* testing and eradication therapy (such as biopsy costs and medication costs), the cost of endoscopy screening, and the cost of cancer treatment. Following the economic evaluation guideline of the Health Insurance Review and Assessment Service, we take a health care system perspective, so only direct costs, excluding transportation and caregiving expenses, are considered. Cost data are obtained through the National Health Insurance Medical Service Benefit Costs, the price by main ingredient of pharmaceutical products, and the NCSP guidelines [21]. Finally, the screening parameters include the rate of *H pylori* testing and rate of eradication therapy if the test result is positive, which is assumed to be 100%. The sensitivity and specificity of the *H pylori* testing and eradication success rates are derived from prior studies [22-25]. The endoscopy screening rate, sensitivity, and specificity are obtained from a combined dataset of the Central Cancer Registry Database and the National Cancer Screening Database of the NHIS. A list of these parameters is presented in Table 1.

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Table 1. Model parameters.

Parameter	Base case	Sensitivity analysis	Reference
Epidemiological parameters, %			
H pylori prevalence rate (from age 40-49 years)	41.5	±10	[3]
Transition rate from *H pylori* negative to *H pylori* positive	0.4	0.3-0.5	[13]
Transition rate from *H pylori* negative to EGC[a]	0.14	0.11-0.17	[14]
Transition rate from *H pylori* negative to AGC[b]	0.073	0.06-0.086	[15]
Risk ratio of cancer incidence w/wo *H pylori* infection	1.69	1.29-2.22	[16]
Transition rate from "eradicated" to *H pylori* positive	4.3	1.7-6.9	[17]
Transition rate from EGC to AGC	29.67	±10	[18]
Annual mortality rate for EGC patients	0.66	0.4-0.99	[19]
Annual mortality rate for AGC patients	Age 40-59: 12.3; age 60-79: 15.3; age ≥80: 22.1	__[c]	[20]
Utility weights, %			
H pylori infected	0.857	SD 0.22	[26]
EGC patients	0.773	SD 0.26	[26]
AGC patients	0.589	SD 0.26	[26]
Examination parameters, %			
H pylori test sensitivity	90	85-95	[22-24]
H pylori test specificity	98	96-100	[22-24]
H pylori eradication success rate	76	64-91.4	[25]
Cost parameters, KRW (1 KRW = US $0.00073)			
H pylori test cost	83,006	±10	Health insurance benefits
H pylori eradication cost	131,490	±10	Health insurance benefits
Endoscopy screening cost	118,867	—	[21]
Sedation cost	50,000	38,771-72,500	HIRA[d] open data

[a]EGC: early gastric cancer.
[b]AGC: advanced gastric cancer.
[c]Not applicable.
[d]HIRA: Health Insurance Review and Assessment.

H Pylori Screening

An individual receives a rapid urea test at the age of 40 years during endoscopy as part of the NCSP. The patient receives eradication therapy if the urease test results are positive. The eradication regimen consists of a clarithromycin-based triple therapy regimen (twice-daily doses of 40 mg esomeprazole, 1 g amoxicillin, and 500 mg clarithromycin) for 14 days.

Outcomes

The main outcome of this study is the incremental cost-utility ratio (ICUR). This is calculated by dividing the incremental cost between the two strategies by incremental utility, represented by the QALYs accumulated over all cycles for each strategy. The utility weight for each health state is aggregated to determine the QALYs, with utility weights for the general population obtained from the National Health and Nutrition Examination Survey Database and those for *H pylori*–infected individuals and cancer patients obtained from a prior study [26].

Uncertainty and Scenario Analysis

A probabilistic sensitivity analysis will be performed to test the uncertainty of the cost-effectiveness results. This involves running the Markov simulation 100,000 times to verify the consistency and robustness of the results. Additionally, a one-way sensitivity analysis will be conducted to identify the variables that have the most significant impact on the results, observing how the cost-effectiveness outcome changes when the values of these variables vary within a specific range.

In the base-case analysis, the *H pylori* testing and eradication therapy implementation rates are assumed to be 100%. However, when these rates vary, the cost-effectiveness of different scenarios can be compared. Therefore, the analysis identifies which scenario, with specific values for testing and eradication therapy implementation rates, is the most cost-effective.

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Ethical Considerations

This study will analyze and synthesize previously published data and is therefore exempt from institutional review board approval from the National Cancer Center.

Results

The primary outcome parameters are the cumulative costs (in KRW) and QALYs for each strategy. A strategy with higher QALYs indicates higher effectiveness; however, if a strategy leads to cost overloads, it cannot be considered cost-effective. The ICUR predicts the cost-effectiveness of a strategy of adding *H pylori* testing and eradication versus the current strategy of endoscopic cancer screening. The ICUR should be within an advanced threshold set to confirm the cost-effectiveness of a certain strategy. Notably, according to the World Health Organization recommendation to evaluate pharmacoeconomics, for an ICUR <1-fold gross domestic product (GDP) per capita, the increased cost is completely worth it and very cost-effective; for an ICUR >1-fold and <3-fold GDP per capita, the increased cost is acceptable and cost-effective. In Korea, a study reported that the average amount of willingness-to-pay for gaining 1 QALY was KRW 30,500,000 (US $22,398) for the overall severity of health conditions (including mild, moderate, and severe) [27]. Therefore, this will be used as the threshold in this study. Costs and utilities will be discounted at an annual rate of 4.5%, with a range of 3% to 6%, for the sensitivity analysis.

In addition, a tornado diagram will be presented to depict the changes in certain variables that influence the results, and a cost-effectiveness acceptability curve will be drawn to confirm the uncertainty of cost-effectiveness with 100,000 simulations. This research has been funded by a Patient-Centered Clinical Research Coordinating Center grant from the Ministry of Health & Welfare, Republic of Korea. Data collection started in June 2024 and was completed in May 2025. The results of this study will be disseminated through publication in a peer-reviewed scientific journal. In addition, the findings will be presented at relevant national and international conferences throughout 2025. Our results will also be shared with government health care directors to facilitate changes in government health policies.

Discussion

Principal Findings

This study aims to provide evidence for the cost-effectiveness of integrating *H pylori* screening into the NCSP to reduce gastric cancer risk. We are planning to determine the most cost-effective methods of *H pylori* screening based on age at screening and the frequency of screening. We expect that our study will also identify factors that contribute to improving cost-effectiveness in the National Gastric Cancer Screening Program. The anticipated findings of our study have the potential to significantly impact gastric cancer screening programs. By examining the cost-effectiveness of *H pylori* screening, we aim to highlight the importance of *H pylori* in preventing gastric cancer. This should lead to a paradigm shift in gastric cancer screening programs, from early detection to primary prevention.

There are expected limitations to our study, such as the age at *H pylori* screening. As the purpose of our study is to incorporate *H pylori* screening into the nationwide gastric cancer screening program, we will examine the cost-effectiveness of screening starting from the age of 40 years, which is when the NCSP begins. Future studies are needed to determine whether early screening for *H pylori* is more cost-effective. Stratified screening based on the risk of gastric cancer development will not be examined in our study due to the lack of data on this topic. We plan to examine whether extending the endoscopic screening interval is cost-effective in patients who have received eradication therapy.

Our cost-effectiveness analysis represents a crucial step toward understanding and promoting the most effective method for gastric cancer screening. We expect to provide evidence for the effectiveness of *H pylori* screening for gastric cancer prevention. The results of our study could serve as a valuable reference for the development of gastric cancer screening programs in other countries.

Conclusion

We plan to examine whether introducing *H pylori* testing and eradication therapy into the NCSP is a more cost-effective strategy than conventional endoscopy-based cancer screening for reducing the risk of gastric cancer. Our study will also examine the optimal age for *H pylori* screening as well as the optimal screening frequency for *H pylori*.

Acknowledgments

This research was supported by a grant of Patient-Centered Clinical Research Coordinating Center (PACEN) funded by the Ministry of Health & Welfare, Republic of Korea (grant number: RS-2024-00398474). We appreciate the contributions of Dr. Mina Suh, whose guidance and insights supported this study.

Data Availability

This study will analyze and synthesize previously published information. Data sharing does not apply to this study because no datasets will be generated or analyzed. The data and references included in the development of the Markov model are presented in Table 1.

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Authors' Contributions

JGK and MS designed the study and are responsible for the overall content as guarantors. SB and JSK analyzed the data and created the figure. All other authors participated in the acquisition and interpretation of the data. SB and JSK drafted the manuscript and all authors critically revised it. All authors approved the manuscript for publication and agreed to be accountable for this work.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CHEERS checklist.
[PDF File (Adobe PDF File), 402 KB - resprot_v14i1e72228_app1.pdf]

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Abbreviations

CHEERS: Consolidated Health Economic Evaluation Reporting Standard
ICUR: incremental cost-utility ratio
NCSP: National Cancer Screening Program
NHIS: National Health Insurance Service
QALY: quality-adjusted life-year

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Protocol

A Human-Centered Approach for a Student Mental Health and Well-Being Mobile App: Protocol for Development, Implementation, and Evaluation

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Abstract

Background: The rising prevalence of mental health concerns among students is prompting universities to explore innovative solutions to support student well-being. This paper describes the protocol for the development, implementation, and evaluation of a mobile app designed to address the mental health and wellness needs of students. This project employs a student-centered approach, partnering with students from the initial needs analysis through to the final design and implementation stages.

Objective: The app aims to increase the use of campus resources that address student mental health and wellness by improving the awareness of these resources through user-designated preferences that are established on the initial use of the app and then iteratively refined as it is used. The app is linked to the campus student's electronic health record so that health and wellness services can be coordinated and enhanced and the student journey to and through care become more seamless. The long-term objective is to leverage data from both the app and electronic health record to improve individual and population health for the entire campus.

Methods: At the beginning of the project, a comprehensive logic model was created to outline the core inputs, activities, outputs, outcomes, and long-term impacts that were desired for the app. The model emphasized the integration of the app within existing campus mental health and wellness services and its potential to foster a culture of well-being across the university community. An evaluation plan was developed that incorporates both quantitative and qualitative methods through biannual assessments to track trends and app impact across campus in addition to feasibility, acceptability, and usability as well as its reach, effectiveness, and sustainability. Validated measures such as the Patient Health Questionnaire and Generalized Anxiety Disorder scale were selected to track changes in mental health and wellness, while custom surveys and analytics will gauge user engagement and satisfaction. New students, including freshmen, transfers, and first-year medical students, are invited to participate after giving informed consent. They receive compensation for their involvement in both quantitative and qualitative assessments.

Results: As of March 2025, we have collected over 600 survey responses from freshmen, transfer, and medical students. A second survey round and additional focus groups are planned for April to May 2025. No analyses have been conducted yet. The

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findings from this project have the potential to inform similar efforts at other institutions and contribute to the broader field of digital mental health innovation and the development of well-being interventions tailored for young people.

Conclusions: By leveraging digital technology and actively engaging students in supporting their well-being, this initiative represents an innovative user-centered approach to improve mental health and wellness support on university campuses.

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KEYWORDS

student-centered; well-being application; student mental health; student wellness; university well-being

Introduction

Students in higher education are tasked with navigating a major life transition that can be incredibly challenging as they move away from home, manage higher academic demands, navigate new social environments, and take on more personal responsibilities for their daily lives [1,2]. These changes can lead to high levels of stress and the onset or exacerbation of mental health issues [3].

Research has shown that university students experience high rates of mental health concerns and reduced well-being. In a 2024 National College Health Assessment survey of 103,639 students at 154 institutions, over 20% of the undergraduate and 15% of the graduate student respondents reported experiencing serious psychological distress. Anxiety and depression are the most prevalent problems, with over 35% of the undergraduate and 33% of the graduate students reporting having anxiety, and over 26% of the undergraduate and 25% of the graduate students reporting depression as chronic conditions [4]. Other studies globally have reported similar rates of common mental health concerns among university students, including anxiety, depression, eating disorders, substance abuse, and self-harm/suicidal ideation [5-8]. Further, there is evidence that the COVID-19 pandemic and associated social restrictions and campus closures amplified these rates [9].

Concerningly, many students who are struggling do not seek help. Estimates suggest that only around 30%-40% of the university students with mental health needs actually receive treatment [7,10]. There are many barriers to accessing mental health and wellness services, including stigma, lack of awareness of available resources, financial constraints, and difficulty navigating the complex health care systems [11]. Even for those who do seek help, mental health and wellness resources in many university campuses are often overburdened and insufficient to meet student needs [12]. Counseling centers frequently report long waitlists, limited session caps, and inadequate funding and staffing [13]. These resource constraints make it challenging for counseling centers to provide high-quality, comprehensive care.

Addressing the mental health and well-being crisis on university campuses requires a multifaceted approach [14]. In addition to increasing staffing for on-campus counseling, colleges should also focus on implementing evidence-based prevention and early intervention programs. This could include initiatives to reduce stigma, educate students on mental health and wellness, and teach coping strategies [15]. Strengthening connections between campus mental health and wellness services and local health care providers in the community can also help expand care available to students. Digital technologies embedded into care pathways is a recognized sustainable way forward to build capacity for student well-being and mental health support and improve transition to and through support resources and services.

Ultimately, addressing student mental health and well-being is crucial not only for individual well-being but also for academic success and long-term outcomes [16]. By taking steps to better support the mental health and wellness needs of university students, institutions can foster healthier and more resilient campus communities.

In recognition of the growing mental health and wellness crisis among university students, many institutions of higher education have implemented programs and initiatives aimed at supporting student well-being. These efforts have ranged from expanding on-campus counseling services to implementing mental health and wellness education and prevention initiatives. One approach has been to increase the resources and staff available at university counseling centers. Many universities have hired additional counselors, psychologists, and psychiatrists to expand their clinical capacity and reduce long waitlists [13]. Some have also extended hours of operation or established satellite locations to improve accessibility. However, the demand for services often continues to outpace available resources, limiting the impact of these expansions. Moreover, students who utilize on-campus counseling and wellness services have improved mental health and well-being and academic outcomes, but the overall impact on the broader campus population has been more limited, with persistent unmet needs and disparities in both utilizing the available services and access to care [17].

Colleges have also worked to destigmatize mental health issues and encourage students to seek help when needed. Awareness campaigns, gatekeeper trainings, and peer-to-peer support programs have been employed to foster a more open dialogue around mental health on campus [7]. Although these initiatives have shown some promise in reducing stigma, evidences of their effects on the actual utilization of services have been mixed.

Beyond clinical services, many institutions have implemented upstream prevention and early intervention programs. These have included efforts to promote stress management, healthy coping strategies, and emotional regulation skills through workshops, courses, and web-based modules [15,18]. Some colleges integrate mental health and wellness screenings into routine health checkups to facilitate early identification and

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treatment of issues, but there is limited published evidence of the effectiveness of these initiatives.

Moving forward, a comprehensive, public health-informed approach will likely be needed to truly address the mental health and wellness crisis affecting university students. This could involve better integrating campus mental health and wellness services with on and off-campus health care providers, expanding preventive programming, and working to change campus cultures and norms around mental health and wellness. Sustained institutional commitment and investment will be crucial to the success of these efforts.

In recent years, approaches that link digital mental health interventions with wellness services have emerged as a promising approach to expand access and use of support services for university students [19-21]. These web-based and app-based tools offer a variety of self-guided well-being interventions, teletherapy services, and mental health education resources that can complement traditional in-person counseling [22].

The rapid growth of digital solutions has been driven in part by their potential to overcome key barriers that prevent students from seeking help, such as perceived stigma, time constraints, and transportation challenges [23]. Many digital platforms allow users to access services discreetly and conveniently from their own devices [24]. Studies have also found that students may be more willing to engage with mental health and wellness support delivered via technology compared to traditional in-person therapy [21].

Evaluations of digital mental health interventions and well-being programs geared toward university populations have generally found positive outcomes. For example, a meta-analysis of internet-based cognitive behavioral therapy interventions for anxiety among university students showed significant reductions in symptom severity compared to control groups [18]. Other research has linked the use of mental health and wellness apps to improve symptoms of depression, stress, and disordered eating among students [25].

However, the success of digital intervention tools has been tempered by some important challenges. Uptake and sustained engagement with these programs is often low, with many students downloading apps but then failing to use them regularly [24,26]. Concerns about data privacy and security with digital platforms limit the appeal for some users, and the recent proliferation of mental health and wellness apps has resulted in a crowded and unregulated market, making it difficult for students to identify high-quality, evidence-based options. Finally, the lack of interfaces that enable data exchange between these tools and campus health and counseling services hinders the ability to provide a continuum of care for students [21].

Moreover, Patrick et al [27] argue that traditional research methods and approaches to digital health interventions overall are inadequate for the increasingly data-rich environment of digital health. They propose an “agile science” approach that emphasizes rapid iteration, ongoing computational modeling, and iterative personalization that dynamically address the complexity inherent in human existence. This approach allows researchers and interventionists to move beyond static, descriptive theories toward dynamic, predictive models that can drive more effective and sustainable digital health solutions.

Therefore, moving forward, a more strategic and coordinated approach is needed that integrates digital mental health innovation with health and wellness services on university campuses to maximize the impact and more holistically address the well-being needs of student. To accomplish this, in January 2023, the Joan and Irwin Jacobs Center for Health Innovation at University of California San Diego (UCSD) Health, in partnership with UCSD’s Campus Health and Wellness program, began to develop an app and the supporting information technology platform, branded as Willo. This paper describes the approach taken to develop Willo and then focuses on the plan for implementation and evaluation.

Methods

This protocol is reported in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 statement [28] (Multimedia Appendix 1).

User-Centered Design Process

From its inception, the development of Willo was in co-partnership with students, recognizing that students would be their primary users and beneficiaries. The project team collaborated with students throughout the design process to ensure that the final product would be tailored to their specific needs, preferences, and challenges.

The process began with a comprehensive gap analysis, where students from diverse backgrounds were invited to participate in focus groups and individual interviews (Multimedia Appendix 2). These sessions explored students’ mental health and wellness needs, the challenges they face in accessing support, and the gaps they perceive in existing campus services. Students shared their experiences managing stress, symptoms of anxiety and depression, along with other wellness concerns, providing valuable insights into the priority need areas for additional support and informing and shaping the app’s features and overall value proposition.

As the design process progressed, students continued to play an active central role in refining the app’s features and functionality. Through surveys, usability testing sessions, and design workshops, students provided feedback on various prototypes and concepts. They helped prioritize the features that would be the most useful and likely to be used regularly, such as mood tracking, guided meditation exercises, or anonymous peer-support forums. Students also offered insights into potential barriers to app usage, such as concerns about privacy or stigma, which informed the development of user-friendly interfaces and confidentiality measures. By maintaining this student-centered approach throughout the design process, the team ensured that the resulting app would be not only evidence-based by using state-of-the-art privacy and technological features and evidence-based content but highly relevant and appealing to its intended user base. This student-centered methodology fostered trust and transparency while enabling rapid, iterative refinement of the platform through continuous end-user feedback and contributions.

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Design Process

We conducted iterative co-design studies with students and key stakeholders involved in student well-being, including care providers, clinical staff, and university administrators, to identify the critical challenges affecting student well-being. A recurrent theme across these sessions was the absence of a personalized, regularly updated medium through which students could effectively engage with available university resources. Although a range of services existed, participants emphasized the need for an integrated system to support continuous search, discovery, and engagement. In response, we conceptualized a resource aggregator that could centralize both static resources (eg, physical centers, institutional services) and dynamic offerings (eg, events) organized by the core dimensions of wellness and relevant thematic tags. These tags served as the foundation for tailoring resource recommendations to individual student needs and preferences. Figure 1 illustrates the Willow app interface screens.

Figure 1. Willo app. From left to right: onboarding interface, main home screen, search and exploration interface, and a detailed view of an individual event or resource.

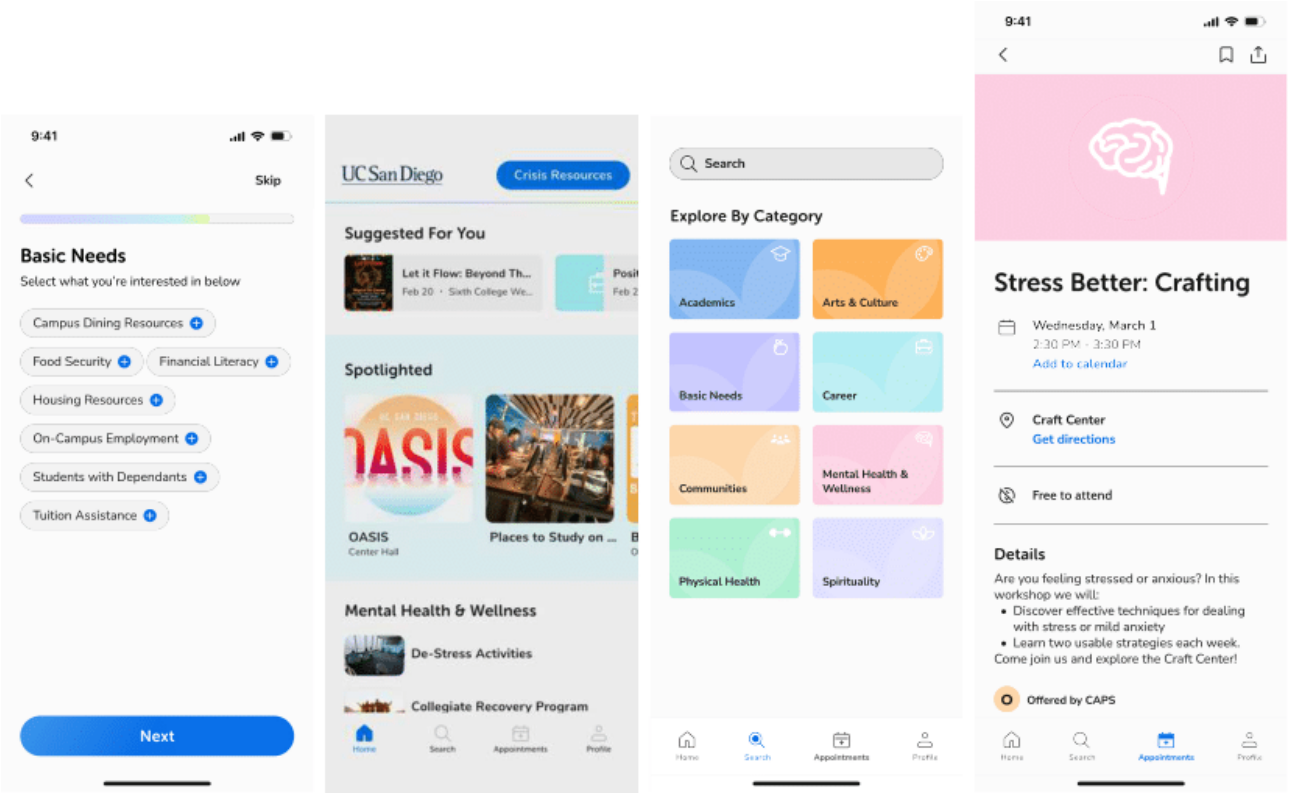

Logic Model

Based on the best practices in program evaluation in public health [29], our process of evaluation began with the development of a logic model that established the key inputs, activities, outputs, and outcomes associated with the implementation and evaluation of our student mental health and wellness mobile app. A scientific advisory committee composed of students with lived experience, experts in student health and well-being, medicine, psychology, digital interventions, public health, and health services evaluation, was formed to provide input to the app development team on each component of the model and to recommend measurable outcomes for each that would help determine the effectiveness and feasibility of the app. The logic model highlights the multifaceted approach needed to drive positive impacts at both the individual and institutional level. The short, intermediate, and long-term outcomes reflect the iterative and sustained nature of effecting meaningful change in campus mental health and well-being (Figure 2).

The advisory committee also made recommendations about the resources and assets necessary for the successful implementation of the project. These inputs included funding from university administration and external grants and interdisciplinary stakeholders, including clinical psychologists, student health clinicians, computer and data scientists, and user experience designers. Further partnerships with campus counseling centers and other student support services and access to university student population and data were identified as critical.

The essential actions and processes that have been undertaken to achieve the project's goals are to conduct user research and needs assessment with university students, design and develop a mobile app prototype with evidence-based features, implement pilot testing and iterative improvements based on user feedback, and promote app availability and usage through campus-wide marketing and education.

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Figure 2. Logic model. ACTRI: Altman Clinical and Translational Research Institute; CAPS: Counseling and Psychological Services; H&W: Health and Wellness; R&D: Research and Development; UC: University of California; UCSD: University of California San Diego.

Situation	Inputs	Outputs		Outcomes		
		Activities	Products	Short-term	Medium-term	Long-term
High prevalence of mental health and well-being problems Limited resources for individual psychological counseling Lack of awareness of the variety of resources and support available Suboptimal campus culture of health and wellness	Funding from State of California for 3-year project focused on innovative approaches that, if successful, can scale to other campuses statewide Broad stakeholder support and collaboration from UCSD Health and all key UCSD campus resources, including CAPS and Student Health and Wellbeing High engagement of UCSD students Scientific input from UCSD faculty & researchers (Schools of Medicine, Public Health, Engineering, and the ACTRI) Resources for *software, app, and platform* development	Environmental scan of issues Interview all campus stakeholders & synthesize findings Multiple rounds of human-centered design workshops & focus groups to obtain input on requirements Develop *firm* roadmap for development of version 1.0 and *draft* roadmap for subsequent versions. Contract for Willo developer Develop evaluation plan Develop plan for long-term sustainability of Willo	Iterative pilot tests of Willo Beta versions and use of results to improve it Launch Willo version 1.0 Outreach & education for CAPS and Campus H&W providers to ensure familiarity with Willo Marketing program for Willo to UCSD students Baseline measures conducted Pilot test of additional and more granular measures of success Operationalize plan for long-term sustainability of Willo	Increase in awareness of the Willo app (a measure of marketing success) Initial use of the Willo app (a measure of adoption) Referral to the Willo app by CAPS & H&W providers (a measure of professional acceptance) Evidence of Willo use for at least one month (a measure of retention) Indicators of continued development of Willo roadmap and milestones	Increase in awareness of the Willo app Initial use of the Willo app Referral to the Willo app by CAPS & H&W Evidence of use of Willo for at least 1 month, 3 months, 6 months Reductions in key indicators of mental health distress Increases in measures of campus health and wellness Indicators of continued development of Willo roadmap and milestones	Reduction in prevalence of psychological problems and stress, including suicides Increased levels of awareness and utilization of the variety of resources and support available Improved indicators of a campus culture of health and wellness Plan for long-term sustainability to support continued deployment and improvement of Willo

Goals	Concurrent Areas of Effort	
Reduce rate of suicides and episodes of preventable serious mental illness Optimize the use of existing counseling and other mental health and wellness resources Increase awareness of and access to support services Improve collective health and wellness	***Engage subpopulations of interest*** (eg, medical students) in separate but related interventions as resources permit. To the extent possible, these efforts will be articulated with core Willo efforts ***Conduct pilot tests of data collection from wearables and passive sensing*** to evaluate its utility for including in the Willo predictive analytics that support early interventions and prevention	As the Willo app is rolled out and iteratively evaluated, stakeholders will engage in campus-wide efforts to ***develop and implement policy and environmental changes*** that support campus health and wellness ***Explore partnerships*** with other UC campuses and/or Universities that support Willo R&D and its evaluation (eg, cost/benefits of Willo)

The immediate, tangible output of the project activities will include a fully functional mobile app for student mental health and wellness support, an increased awareness and utilization of campus mental health and well-being resources, and outreach and education for campus service providers to familiarize them with the app. The committee made recommendations about the following short-term, intermediate, and long-term changes to be assessed as a result of the project and how these lead to broader systemic change.

1. The short-term outcomes include improved mental health and wellness literacy and help-seeking attitudes among students, increased engagement with evidence-based self-management strategies, and enhanced feelings of social connectedness and reduced isolation.
2. Intermediate outcomes include reduced symptoms of anxiety, depression, and other common mental health issues and increased utilization of the app and on-campus counseling and support services.
3. Long-term outcomes are expected to be a positive shift in the campus culture around mental health and well-being; sustainable adoption and integration of the app through students; and improved overall student health, satisfaction, and success outcomes.
4. The broader systemic changes that the project aims to contribute to over time would be a healthier and more resilient university student population, leading to reduced mental health–related costs and productivity losses for universities.

The committee emphasized the importance of viewing this logic model as a dynamic framework, subject to refinement and adaptation, as new evidence emerges and the project evolves. They also stressed the need for rigorous evaluation at each stage

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to ensure that the project is meeting its intended goals and to inform continuous improvement efforts.

Evaluation Plan

Using the logic model as a foundation, the advisory committee and development team identified key areas that required evaluation. They prioritized metrics that would provide actionable insights for improving the app and its integration into existing campus mental health and wellness services. Drawing on their collective expertise, the committee discussed various data collection methods. They aimed for a mixed methods approach to capture both quantitative and qualitative data, ensuring a comprehensive evaluation. Moreover, recognizing the evolving nature of digital health interventions, the committee built in mechanisms for ongoing review and refinement of both the app and the evaluation process itself.

Throughout this process, the committee emphasized the importance of flexibility and adaptability, acknowledging that the evaluation plan may need to be adjusted as the project progresses and new insights emerge. They also stressed the need for ongoing communication and collaboration among all stakeholders involved in the implementation and evaluation of the student mental health and wellness app. The evaluation questions that could address important outcomes are listed below.

1. To what extent does the use of the mobile app lead to reductions in symptoms of anxiety, depression, and other common mental health issues among students?
2. How many students download and actively use the app on a regular basis? What user characteristics or engagement patterns are associated with better outcomes?
3. How well is the app integrated with campus counseling, health, and other support services? What are the facilitators and barriers to this integration?
4. What are the key lessons learned from implementing the app, and what modifications or additional support are needed to sustain and scale the program in the long term?

Data collection methods will include pre-post surveys of app users to assess changes in knowledge regarding campus resources, presence and severity of mental health symptoms, emotional self-awareness, stigma and other barriers to care, confidence in and degree of help-seeking behaviors, and overall app usage data (downloads, login frequency, feature engagement). We also plan to conduct interviews and focus groups with app users, campus mental health staff, and other relevant stakeholders.

For continuous quality improvement, we plan to regularly review the evaluation results with the project team to identify the areas for app refinement and programmatic enhancements and use data to secure continued funding and support for sustaining and scaling the app-based program.

This evaluation plan (Table 1) outlines a mixed methods approach to assess the student mental health and wellness app project on multiple levels—individual student outcomes, community reach and usage, operational feasibility, and long-term sustainability. The plan emphasizes the importance of utilizing evaluation findings to drive ongoing improvement and broader dissemination of effective practices. Rigorous data collection, analysis, and reporting will be critical to demonstrating the value of this initiative to university stakeholders and external partners.

The evaluation team designed a process to evaluate cohorts of the students biannually. This process enables the team to monitor trends and changes at the population level across campus and assess the outreach, effectiveness, and impact of the app. In the first cohort, students who are new to the campus (ie, freshman, transfer, and first-year medical students) will be invited to enroll in the assessments. They will be required to provide informed consent before participating and will be compensated for their time and engagement in the quantitative and qualitative assessments (Multimedia Appendix 3).

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Table 1. A summary of the evaluation plan for the mental health and wellness app (Willow).

Evaluation domains	Outcomes	Key performance indicators	Data sources and collection method
Campus services awareness, accessibility, and utilization	Improving access to mental health resources, improved efficiency of use of resources for individual psychological counseling, referral to the app by counseling and psychological services & health and wellness providers, improved utilization of on-campus services	Satisfaction, in-app services usage, Counseling and Psychological Services usage, effectiveness and relevance of the app, utilization of campus services	App analytics, in-app rating systems, in-app surveys and questionnaires, focus groups; interviews with counseling and psychological services & health and wellness providers
Student mental health	Reducing stigma, increasing peer support, improving mental health, improving emotional self-awareness, decreasing loneliness	Trend of improved score in mental health surveys, loneliness score, social connectedness on campus	App analytics, in-app surveys and questionnaires, focus groups
Serious mental illness	Detecting and predicting serious mental illness	Detect serious mental illness	App analytics, in-app surveys, and questionnaires
Student engagement and provider engagement	Increasing engagement with the app, increased use of features and services provided by the app, increased levels of awareness and utilization of the variety of resources and support available	Adoption rates, number of users, frequency of use, duration of use sessions, referral rates from providers	App analytics, in-app surveys and questionnaires, focus groups (students/providers)
App/platform usability and effectiveness	Continued development of app roadmap and milestones, plan for long-term sustainability to support continued deployment and improvement of the app	Daily, weekly, monthly active users, satisfaction rates, acceptability, and user-friendliness scores	In-app rating systems, in-app surveys and questionnaires to collect feedback, focus groups

Ethical Considerations

This evaluation plan, which is described in more detail below, is approved by the UCSD institutional review board (approval 810254). Data will be collected using unique participant ID numbers that are based on the order of completion and will not be connected to any identifiable information about individual users. The app contains a digital consent form that participants complete before starting study activities. They receive an emailed copy and can access a video walk-through of the consent process. With rolling recruitment, participants can take time to decide and consult with the study team. Focus group members receive individual consent forms after eligibility confirmation. All consent forms are stored on a secure UCSD server accessible only to approved study coordinators. The consent mentions that participants can opt out at any time, and their deidentified data might be used for other studies without their consent. Participants have the opportunity to earn a maximum of US $25 per quarter for completing the surveys. Participants who take part in the focus groups will receive US $60. All incentives will be in the form of digitally delivered Amazon gift cards.

Process and Participants

A marketing campaign was initiated to advertise the Willo app across the campus during the first quarter of the academic year 2024-2025. The campaign included multiple channels to reach out to students so that they can download and start using the app. Participants who agree to join the research portion of the app launch will provide electronic consent within the app. All participants will be asked to complete web-based assessments through Qualtrics at baseline fall quarter of 2024 and spring quarter of 2025. Additionally, we will conduct 6 focus groups each consisting of 10 students to gather qualitative data about their feedback and experience with the app. If participants consent, they may be contacted up to twice per calendar year until graduation or departure from UCSD.

Measures

Metrics

Metrics to assess the evaluation domains are described below in more detail. We will use several tools and methodologies to collect data, including web-based surveys and in-app data for quantitative and focus groups and interviews for qualitative data. We based much of our approach on that used by the U-Flourish program [1,5] particularly in areas such as the longitudinal assessment of student well-being and the importance of a whole-campus approach to mental health. This collaboration helped us select a suite of evaluation measures that was not only scientifically validated but also of proven use in a large number of college students. This will also enable us to compare some of our findings to others in the U-Flourish network.

Surveys and Questionnaires

Validated mental health screening tools (eg, Generalized Anxiety Disorder Scale-7 items, Patient Health Questionnaire-8 items) and health behavior tools (eg, Sleep Condition Indicator-8 items, College Student Subjective Well-being Questionnaire) to measure changes in symptoms over time will be administered (Table 2). We also plan to include custom survey questions to gather user feedback and measure help-seeking behaviors such as their knowledge and interest of student resources and activities.

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Table 2. List of questionnaires used in the evaluation of the app.

Label	Measure
Resources	Knowledge and Usage of Student Resources
GADS-7	Generalized Anxiety Disorder Scale-7 items
PHQ-8	Patient Health Questionnaire-8 items
WEMWBS-7	Warwick-Edinburgh Mental Wellbeing Scale-7 items
SCI-8	Sleep Condition Indicator-8 items
CSSWQ	College Student Subjective Wellbeing Questionnaire
ULS 4	UCLA Loneliness Scale-4 items
PSS-4	Perceived Stress Scale-4 items
SCOFF	Eating Disorder Diagnostic Scale
GBS	General Belongingness Scale
SCS-SF	Self-Compassion Scale-Short Form
RRS-B	Ruminative Response Scale-Brooding subscale
BCC	Barriers to Care Checklist
BACE-3	Barriers to Care Evaluation
CECA	Childhood Experiences of Care and Abuse
GLTEQ	Godin Leisure-Time Exercise Questionnaire
MSCS	Mindful Self-Care Scale-Mindful Relaxation Subscale
DERS-18	Difficulties in Emotional Regulation Scale

App Usage Analytics

At the aggregate level, measures such as weekly and monthly active users, average session duration, and most accessed resources will be tracked to monitor overall app engagement. For each individual user, the app will track their activities such as clicks, pages/resources browsed, events liked, and searched queries. These interactions will also be contextualized by individual app usage sessions. These metrics will help the app learn more about user preferences in general as well as their behaviors with respect to time and further allow the system to define and execute just-in-time adaptive interventions in the future by using varied notifications.

Interviews and Focus Groups

We plan to conduct semistructured interviews and focus groups with app users to gather qualitative feedback on their experiences and to understand the barriers, motivations, and perceptions about the app.

Data Analysis and Interpretation

Quantitative Analyses

Quantitative data will be analyzed using appropriate statistical software (SPSS or similar) to determine if users are gaining knowledge about the featured services and resources and if the services and resources that are being highlighted are matching with the desires of the target populations.

To assess changes in mental health and wellness outcomes within and between cohorts over time, we will conduct repeated measures analysis of variance and mixed-effects modeling. These approaches are well-suited for analyzing longitudinal data with repeated observations per participant. The primary dependent variables will include standardized scores from validated instruments measuring mental health and well-being. Independent variables will include cohort membership, time (semester), usage of the Willo app, and engagement with university support services. Interaction terms (eg, time × app usage) will be included to assess potential moderating effects.

A power analysis was conducted using a conservative estimate of small-to-moderate effect sizes, consistent with those commonly reported in similar longitudinal mental health studies. With 850 participants per cohort and repeated measurements across 8 time points, the study is adequately powered (≥80%) to detect meaningful changes in outcomes over time and between groups, assuming an α level of .05.

Qualitative Analyses

We will employ Rapid Qualitative Analysis drawing on the structured and pragmatic methodology [30,31], which is particularly well-suited to applied health and implementation research settings where timely yet rigorous analysis is needed. Rapid Qualitative Analysis involves structured data reduction by using summary templates and matrix-based analysis to support both cross-case comparison and theme identification while maintaining methodological transparency and feasibility. To enhance trustworthiness, we will implement the following strategies.

1. Credibility: analyst triangulation and regular team-based discussions will be used to verify interpretations.
2. Dependability: a documented audit trail will capture analytic decisions and changes throughout the study.

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3. Confirmability: independent checks of data summaries will ensure interpretive consistency.
4. Transferability: contextual information will be included to support the applicability of findings beyond the sample.

We will incorporate reflexivity throughout the analytic process, as recommended in reflexive approaches to qualitative research. Analysts will document positionality, and the team will engage in critical discussions about how their perspectives shape interpretation. In doing so, we also align with the call for "knowing practice" [32] in thematic analysis—owning our theoretical stance, making reflexive choices explicit, and avoiding the uncritical mixing of incompatible analytic paradigms.

Results

As of March 2025, we are in the process of data collection. Preliminary data that have been collected include >600 responses to surveys from freshman, undergraduate transfer, and medical students. A second round of survey assessments to measure change is expected in April to May 2025. We have also conducted 2 focus groups with undergraduate freshman to date. Two focus groups with undergraduate transfer students and one with medical students are planned for April-May 2025. No data analyses have been performed as of yet. These data will be the baseline for the metrics used, and we plan to repeat the data collection with every cohort biannually.

Discussion

The rising prevalence of mental health challenges among college students underscores the critical importance of addressing student mental health and wellness in higher education settings [33]. This project's multifaceted approach, combining digital technology, user-centered design, and evidence-based interventions, represents a promising step toward improving access to mental health resources and support for university students.

By leveraging mobile app technology and potentially incorporating artificial intelligence–driven features, this initiative aligns with the increasingly tech-savvy nature of today's student population. Knowing the rapid evolution of digital technologies, we tried to emphasize iterative modeling and personalized interventions in this app to effectively address student's wellness challenges [27]. As digital natives, current and incoming university students are likely to find app-based mental health support more approachable and accessible than traditional services alone. This technological approach not only meets students where they are but also has the potential to reduce the stigma associated with seeking help—a significant barrier to mental health care utilization among young adults [34].

A key rationale for the potential effectiveness of this app lies in its ability to address one of the most critical barriers to student mental health support: timely access to resources and information. By providing a readily accessible platform that offers immediate information about available resources and services, the app has the potential to bridge the gap between students' needs and appropriate support systems. This proactive approach is supported by research indicating that timely access to mental health resources is associated with better academic performance, higher retention rates, and improved mental health outcomes and overall well-being among university students [35,36].

The user-centered design process employed in this project is a key strength, ensuring that the final product is tailored to the specific needs and preferences of university students. By involving students at every stage, from the initial gap analysis to feature selection and usability testing, the app is more likely to resonate with its intended users and achieve higher engagement rates. This approach aligns with best practices in digital health intervention development and increases the likelihood of the app's effectiveness and sustained use [37,38].

The integration of the mental health app with the campus student electronic medical record represents a significant advancement in coordinated care for college students. This linkage allows for a more comprehensive and holistic approach to student health and wellness, enabling seamless coordination between digital interventions and traditional health care services. The long-term objective of leveraging data from both the app and electronic medical record to improve individual and population health for the entire campus is particularly promising. This data integration could enable sophisticated predictive analytics and population health management strategies, allowing for the early identification of at-risk students and the development of targeted preventive interventions [39].

The potential for scalability to other college campuses is another significant aspect of this project. By designing the app with scalability in mind, there is an opportunity to extend its reach and impact across different student populations, potentially benefiting hundreds of thousands of students. This scalability also offers the possibility of gathering large-scale data on student mental health trends and intervention effectiveness, which could inform future research and policy decisions [40].

The interdisciplinary nature of the project, bringing together expertise from software engineering, public health, mental health and wellness, and design, is a testament to the complex, multifaceted nature of student mental health and well-being challenges. This collaborative approach ensures that the app is not only technologically sound but also grounded in public health principles and current best practices in mental health and wellness care. The data generated from this project could serve as a rich resource for researchers across these disciplines, potentially spurring new collaborations and lines of inquiry. For example, public health researchers might collaborate with artificial intelligence specialists to develop predictive models for mental health trends on university campuses.

It should be noted that, as with any digital health intervention, issues of data privacy, security, and ethical use of artificial intelligence (if implemented) must be carefully considered and addressed [41]. Ongoing evaluation and refinement of the app based on user feedback and outcome data will be crucial to ensuring its long-term effectiveness and relevance.

In conclusion, this project represents an innovative, student-centered approach to addressing the pressing issue of

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college student mental health. By combining technological innovation with evidence-based practices and interdisciplinary collaboration, it has the potential to significantly improve access to mental health support for university students. As the project moves forward, continued emphasis on user engagement, privacy protection, and integration with existing campus services will be key to its success and potential for broader impact across the University of California system and other institutions of higher education [42].

We plan to disseminate the findings and lessons learned from this project through peer-reviewed publications and multimedia channels, including social media, news, university websites, and conference presentations.

Acknowledgments

We would like to thank Dr Colin Depp and Dr Eric Granholm for their contributions as scientific advisory board members. Finally, we thank the many University of California San Diego students who contributed their time and effort to the design process for Willo. Funding by the State of California and Clinical and Translational Science Award UL1TR001442 supported this work.

Data Availability

Data sharing is not applicable to this study, as no data sets were generated or analyzed during this study.

Authors' Contributions

Conceptualization: MG (lead), KP (equal)
Data curation: DW
Formal analysis: DW (lead), MG (supporting)
Funding acquisition: CAL
Investigation and methodology: MG, DW, KP
Project administration: NM (lead), KP (supporting)
Resources: AD, NW, HR, BF, MSB, AI
Supervision: KP, CAL, KS
Validation: NW, MSB, AI, HR, BF, AD
Visualization: MG (lead), KP (supporting)
Writing – original draft: MG (lead), DW (supporting), KP (supporting)
Writing – review & editing: MG (lead), KP (supporting), DW (supporting)

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist for protocols.
[PDF File (Adobe PDF File), 122 KB - resprot_v14i1e68368_app1.pdf]

Multimedia Appendix 2
Focus group interview guideline.
[DOCX File , 18 KB - resprot_v14i1e68368_app2.docx]

Multimedia Appendix 3
Consent form.
[PDF File (Adobe PDF File), 977 KB - resprot_v14i1e68368_app3.pdf]

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Abbreviations

SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
UCSD: University of California San Diego

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Protocol

Epidemiology and Impact of Staff Training in Controlling Complications Related to Central Venous Catheters in 4 Intensive Care Units in a French University Hospital: Protocol of a Prospective, Quasi-Experimental, Before-After Study

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Abstract

Background: Central venous catheters (CVCs) are essential tools in the management of critically ill patients in intensive care units (ICUs). However, their use is associated with several preventable complications, including central line–associated bloodstream infections (CLABSIs), catheter-related thrombosis, and mechanical events (eg, occlusion and rupture). Despite the availability of evidence-based guidelines from the French Society of Hospital Hygiene for CVC insertion and maintenance, adherence variability persists across health care settings, contributing to prolonged hospitalization, increased morbidity and mortality, and even increased health care costs. In 2022, an audit conducted at Edouard Herriot Hospital (Hospices Civils de Lyon, Lyon, France) revealed a degree of variation in adherence to current protocols. Specific deficits were noted in practices such as hand hygiene, flushing procedures, and aseptic techniques, among others.

Objective: This study aims to (1) evaluate the effectiveness of a multifaceted educational intervention in improving health care workers' adherence to national CVC management guidelines; (2) assess changes in complication rates (CLABSIs, thrombosis, and mechanical events) and patient outcomes (readmissions and mortality); and (3) identify factors associated with CVC-related complications through multivariate analysis.

Methods: We are conducting a prospective, quasi-experimental, before-after study in 4 adult ICUs at a French university hospital. The protocol includes preintervention and postintervention audits using a digital tool to capture real-time compliance data, as well as standardized educational sessions based on French Society of Hospital Hygiene recommendations. The intervention consists of face-to-face training, posters, and digital reminders, all delivered by the same team to ensure consistency. Clinical data include demographics, comorbidities, CVC type and duration of use, administered medications, and complications. All patients with CVCs, including centrally inserted catheters (jugular or subclavian), femoral lines, and peripherally inserted central catheters, are eligible. The primary outcome is the incidence rate of CVC-related complications per 1000 catheter-days. Secondary outcomes include rates of hospital readmission, ICU and in-hospital mortality, and the degree of improvement in guideline adherence across participating units.

Results: As of submission, 640 patients have been included in the study. Data collection remains ongoing. Data entry and final statistical analyses are expected to be completed in the third quarter of 2025.

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Conclusions: By combining audits, education, and feedback, this study will provide key insights into the effectiveness of education-based interventions for improving CVC-related practices in critical care settings. It may serve as a scalable model for enhancing patient safety and care quality in ICU settings. Results will be disseminated through peer-reviewed publications and international conferences.

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KEYWORDS

audit; central venous catheter; complications; education; guidelines; practices; training

Introduction

Central venous catheters (CVCs) are essential tools in the care of critically ill patients in intensive care units (ICUs), providing vital vascular access for hemodynamic monitoring, administration of medications, and nutritional support. Despite their significant benefits, their use is associated with significant risks, including mechanical issues (eg, occlusion, rupture, and malposition), catheter-related thrombosis, and infectious complications such as central line-associated bloodstream infection (CLABSI). Among these, CLABSIs remain a persistent and significant concern for health care workers (HCWs) in ICUs, contributing to prolonged hospital stays, increased health care costs, and higher mortality rates [1].

Over the past decade, substantial progress has been made in reducing CLABSI rates through evidence-based guidelines and prevention bundles—including proper hand hygiene, full barrier precautions during insertion, use of alcohol-based antiseptics, optimal site selection, prevention of port line occlusions, and daily reassessment of catheter necessity [2,3]. However, despite these advancements, CLABSI continues to pose a serious concern. Its incidence varies depending on patient populations and health care settings, with estimates ranging from 0.5 to 5 per 1000 catheter-days [4]. In our institution, surveillance data collected between 2017 and 2022 show a mean CLABSI incidence of 3.11 per 1000 CVC-days. A peak was observed in 2021, reaching 5.1 CLABSIs per 1000 CVC-days, likely reflecting the impact of the COVID-19 pandemic. Although our average rate is lower than reported in a recent multinational, prospective study (4.82 CLABSIs per 1000 CVC-days) [5]. This variability underlines the need for targeted interventions to reinforce guideline adherence and reduce preventable complications.

Clinical guidelines are intended to support HCWs in delivering evidence-based care, but implementation is often inconsistent. The growing volume of recommendations, coupled with the complexity of ICU care and the evolving severity of patient conditions, complicates adherence. Furthermore, variability in practice both within and between institutions can significantly impact care quality. To better understand local practices, an audit was conducted in 2022 at Edouard Herriot Hospital (Hospices Civils de Lyon, Lyon, France) in collaboration with Becton, Dickinson and Company (BD). This audit revealed variability in adherence to established CVC management protocols. While over 70% of observations followed recommended practices—such as the use of gauze and alcohol-based antiseptics for line handling and appropriate catheter flushing—key areas, such as hand hygiene, flushing techniques, and aseptic measures, were suboptimal [6]. These findings underscored the need for targeted interventions to improve compliance.

Educational interventions have been shown to enhance HCWs' knowledge, improve practices, and reduce complication rates [7,8]. Combining audits with targeted training can help bridge the gap between knowledge and bedside practice [9]. Moreover, bundling key evidence-based guidelines into practical, point-of-care tools has proven effective in improving adherence and reducing preventable complications [10].

In response to the audit findings, we developed a structured intervention that integrates audits and education to improve professional competencies and reduce the incidence of CVC-related complications.

The primary objective of this study is to evaluate the impact of an educational program on adherence to national CVC management recommendations issued by the French Society of Hospital Hygiene (SF2H). Secondary objectives include assessing whether improved adherence results in reduced CVC-related complications (including CLABSI, catheter-related thrombosis mechanical complications, readmissions related to CVC use, and associated mortality), and identifying risk factors associated with such complications, taking into account both clinical variables and observed care practices.

Methods

Ethical Considerations

The study participants' personal information will be gathered and handled exclusively on the legal basis established by the applicable regulations, in line with Lyon University hospitals' public service missions. Participants are provided with an information letter outlining the study's objectives and follow-up procedures.

The research protocol was approved by the Institutional Ethical Board (reference number 2024 06 27 20). Additionally, the Comité National de l'Informatique et des Libertés of Hospices Civils de Lyon has granted approval for the study under reference number 23-115.

Study Site

The study is being conducted in the 4 ICU wards of Edouard Herriot Hospital, a university hospital in Lyon, France.

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Study Design

This is a prospective, quasi-experimental, before-after study combining audits, interventions, and clinical data. Figure 1 summarizes the study stages and timeline.

All consecutive patients with a CVC aged 18 years or older, hospitalized for at least 48 hours in 1 of the 4 ICU units of the hospital, and affiliated with the French national health insurance system were eligible. Recruitment occurred between February 27 and December 31, 2024. Patients with hemodynamic instability, receiving palliative care, or unable to engage in the information process independently or via a representative were excluded.

For this study, CVC refers to all central venous access devices, including centrally inserted central catheters (which may be jugular or subclavian), femoral inserted central catheters, and peripherally inserted central catheters, as per nomenclature endorsed by the World Congress on Vascular Access/Global Vascular Access Network and the European Society of Anesthesiology [11,12].

Figure 1. Study design of a prospective before-after study conducted in the 4 intensive care units of Edouard Herriot Hospital, Lyon, France. Audits were performed using Becton Dickinson Signature Solutions. The intervention was an educational program. The second audit was completed after a washout period of 2-3 months following the last session of the educational intervention. The follow-up was 30 days per central venous catheter to track complications (eg, central line–associated bloodstream infections, catheter-related thrombosis, mechanical damage, readmission for central venous catheter–related complications, and related death).

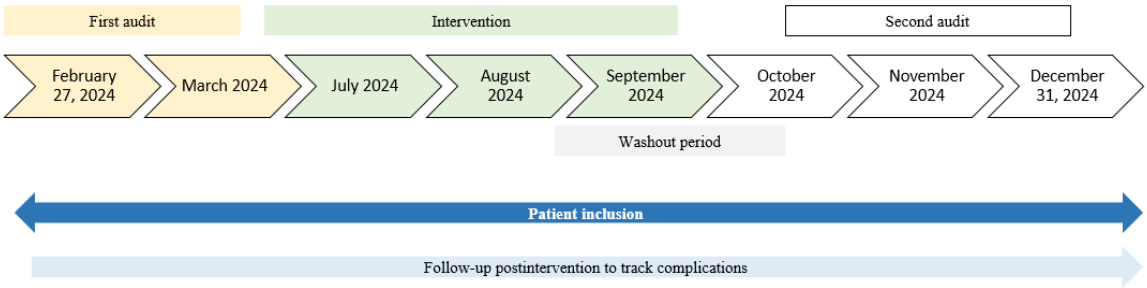

Study Procedures

Audits

A standardized auditing tool was developed based on SF2H recommendations [13-15]. The questionnaire includes approximately 100 items covering hand hygiene; skin antisepsis; CVC insertion, maintenance, and removal; and documentation. It also collects data on HCWs' professional education and clinical experience, which are considered potential factors influencing adherence to recommended practices. The main structure of the observation framework is detailed in Figure 2.

Figure 2. Structure of the observation framework used in the study. The audit tool followed the guidelines set by the French Society of Hospital Hygiene. CVC: central venous catheter; HCW: health care worker.

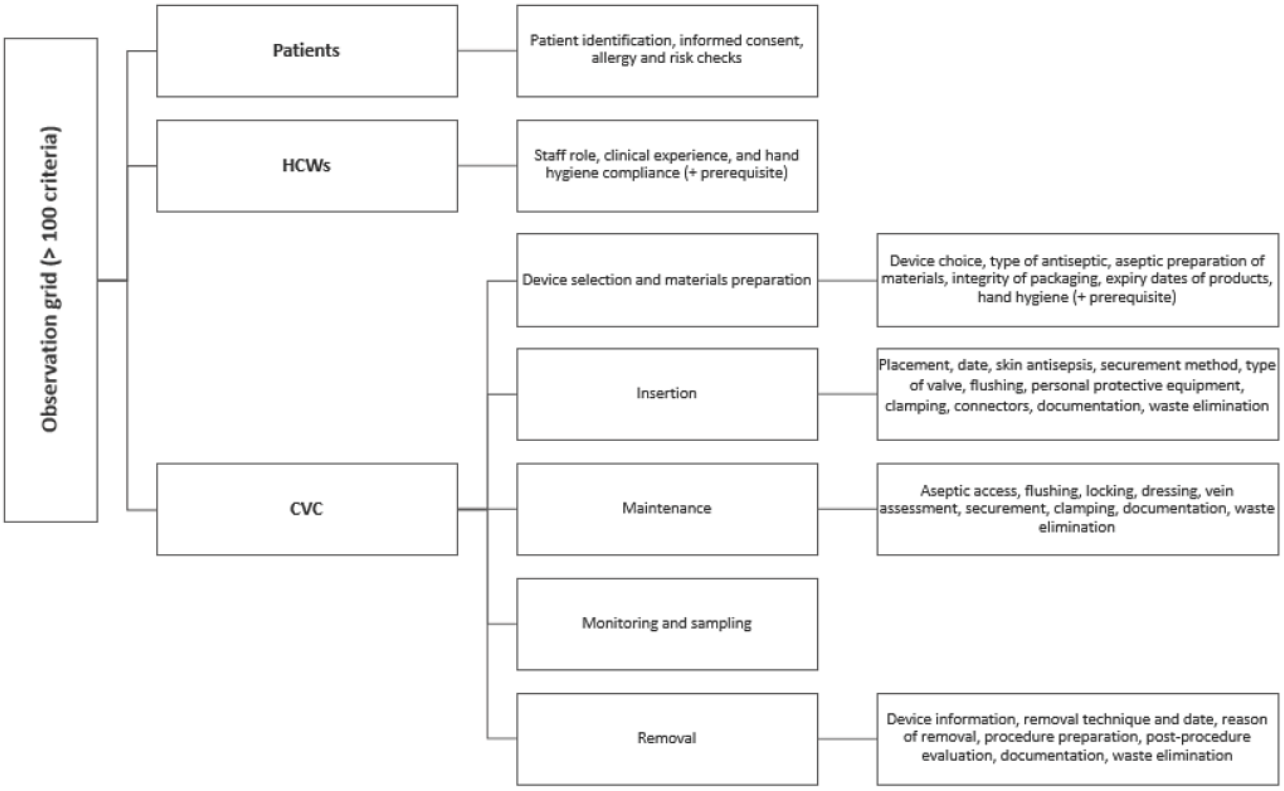

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Audit observations were recorded using Signature Solutions, a digital tool developed by BD which captures real-time bedside practices [6]. Observations were recorded offline via secure tablets and uploaded for analysis by the hospital team.

Two audits were planned in this study: 1 before and 1 after the educational intervention. All analyses will be conducted independently by the research team without any BD involvement to maintain objectivity and scientific integrity.

Intervention (Educational Program)

The intervention included face-to-face exchange sessions, departmental poster displays, and electronic communications. Content focused on essential aspects of CVC management (eg, insertion procedures, drug administration, line handling, verification of reflux and tract patency, and timely removal of unnecessary catheters). Infection prevention measures were emphasized, including proper hand hygiene, disinfection protocols (including the type and formulation of antiseptic), vascular line handling, flushing techniques (including syringe type, volume, and method), use of personal protective equipment, and the application of full barrier precautions.

Training sessions were standardized and delivered by the same team across all ICUs to ensure consistency. Posters summarizing key practices were displayed uniformly in all ICUs, and digital reminders were sent via institutional communication channels.

To clarify the contents and objectives of this intervention, Table 1 summarizes the key points of the SF2H recommendations that were integrated into the training.

Table 1. Summary of French Society of Hospital Hygiene (SF2H) recommendations integrated into the educational intervention [14,15].

Theme	Main recommendations from the SF2H
Hand hygiene	Perform hand hygiene using alcohol-based hand rub before and after all catheter-related procedures.
Skin antisepsis	Use alcohol-based chlorhexidine (2%) for skin disinfection before insertion and during dressing changes.
Insertion technique	Apply barrier precautions.
Flushing procedures	Use single-use syringes; flush with sterile saline (minimum 10 mL) using the pulsating technique.
Manipulation of lines	Disinfect catheter hubs with alcohol-based antiseptic before any access.
Dressing and maintenance	Use sterile transparent dressings; change every 7 days or sooner if soiled or detached.
Catheter removal	Remove as soon as it is no longer clinically necessary (daily reassessment required).

Data Collection

Following verification of inclusion criteria, enrollment occurred upon CVC insertion or upon ICU admission for patients with preexisting inserted CVCs. A standardized questionnaire captured demographics, comorbidities as defined by *International Classification of Diseases, Tenth Revision* codes, information on hospital stay, total number of catheters on admission and during the stay in the ICU, products administered by CVC, CVC details (type, date and site of insertion, dressing, securement, and connectors). Data on antibiotics (molecule and duration) will be fully collected. Patients were monitored until discharge, death, or withdrawal. Those discharged with a CVC were contacted every 15 days until CVC removal or the conclusion of the study to determine whether complications occurred in the interim within 30 days of inclusion. No additional testing was requested for the purpose of this study.

Data collection is ongoing and will be completed during the second quarter of 2025.

Data Entry

Clinical data were recorded on paper in specific clinical record folders. Epi Info (US Centers for Disease Control and Prevention) will be used to create a digital survey for data entry. Different tables with data obtained upon admission, during the hospital stay, or at follow-up will be created. For each table, a unique key will be used to link with the main questionnaire. Data entry was planned for June 2025.

Data Management and Handling of Missing Data

All data will be reviewed for completeness and consistency. In the case of incomplete data, records with missing fields will be reported. Audit data had minimal missingness due to real-time entry. In contrast, loss to follow-up may occur in the clinical cohort, particularly among patients discharged with a CVC. These cases will be recorded, and reasons for the loss to follow-up will be documented when available. If the rate of missing data is nonnegligible, sensitivity analyses will be conducted to evaluate the potential impact on outcomes.

Data Curation

All data will be stored in the hospital's information systems and will be accessible exclusively to investigators. No data will be shared with BD. Data retention complies with French regulations.

Outcomes

Primary Clinical Outcome

The primary outcome is the incidence of CVC-related complications before and after the educational intervention. The overall complication rate is the number of associated complications per catheter-day that occurred during its use.

Complications are defined as follows:

- CLABSI is defined as a laboratory-confirmed bloodstream infection occurring in a patient who had a CVC in place for at least 48 hours prior to the onset of infection, with no other apparent source except the catheter. When catheter

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removal is performed, the catheter tip is used to support the diagnosis whenever available.

- CVC-related thrombosis is defined by clinical (eg, swelling, pain, and redness) and radiologic findings.
- Mechanical complications are defined as obstruction, occlusion, breakage, migration, or dislodgment (accidental withdrawal) of the catheter. Ruptures requiring replacement are also counted.

Secondary Clinical Outcomes

Postdischarge consultations and rehospitalizations related to CVCs within 30 days were tracked.

Primary Educational Outcome

The overall improvement in compliance with the national recommendations of the SF2H following the intervention will be evaluated. Scores will be calculated at the ICU level rather than on an individual basis.

Statistical Analysis

Descriptive and bivariate analyses will be conducted. Data will be reported as frequencies (%) for categorical data or means (SD) for continuous data. The normality of continuous variables will be checked. Comparisons will use appropriate tests (chi-square, Fisher, *t* test, Mann-Whitney).

Epidemiological, clinical, and microbiological data will be described and interpreted independently. Participants will be categorized into different groups according to their status with respect to end points (ie, complications or not).

Poisson regression will estimate incidence rate ratios and 95% CIs for complication incidence rates. Multivariate regression models (logistic, Cox, or Poisson) will be used to identify factors significantly associated with complications.

The data will be analyzed using the program SPSS (version 21; IBM Corporation).

The complete results are expected in the third quarter of 2025.

Results

Among the 812 patients admitted to the participating wards as of December 2024, 640 met the inclusion criteria and were enrolled in the study. Data collection is ongoing. Once completed, data entry and verification will be performed, followed by statistical analyses scheduled for the third quarter of 2025.

Discussion

This study protocol presents a quasi-experimental, prospective before-after design aimed at evaluating the effectiveness of a multifaceted educational intervention to improve adherence to national guidelines for CVC management in ICUs. We anticipate that the implementation of a targeted training program delivered consistently across participating ICUs will lead to measurable improvements in adherence to evidence-based practices and a corresponding reduction in CVC-related complications, such as CLABSI, catheter-related thrombosis, and mechanical issues.

Previous studies have shown that well-structured and context-specific educational programs can bridge the gap between clinical guidelines and bedside practice [8,9,16]. Building on this, our study combines real-time audits and feedback, standardized educational content, and multimodal communication strategies. Unlike single-center initiatives, our study is implemented across 4 ICUs within a large university hospital, providing a broader view of practice variability and revealing the significant deviations from best practices—particularly concerning hand hygiene and flushing technique—highlighting the need for a structured intervention [6].

A recent review supports the view that improving adherence to clinical guidelines necessitates a multifaceted approach addressing both psychological and practical barriers. Effective interventions typically include education and feedback [17].

Despite advancement in clinical protocols, managing CVC-related complications remains a significant challenge. By integrating audits, targeted education, and reminders of best practices, this study aims to reduce practice variability and promote the consistent application of national guidelines, ultimately improving patient outcomes. We hope this initiative will serve as a reproducible model for other institutions seeking to improve care quality and reduce catheter-associated risks.

A key strength of this study is its pragmatic, real-world design. The educational sessions are delivered by the same team using standardized materials across all participating ICUs, ensuring consistent content. Real-time bedside audits further strengthen data reliability by minimizing missing data and allowing objective assessment of clinical practices. Additionally, the protocol includes an extended follow-up period of 30 days per catheter, allowing for comprehensive monitoring for catheter-related complications beyond the ICU setting. This includes complications arising after ward transfer or hospital discharge, providing a more accurate estimation of complication rates.

However, several limitations must be acknowledged. First, no formal sample size or power calculation was performed. The number of patients and audit observations was determined based on feasibility and expected ICU admissions. Approximately 50 audit observations per ICU were planned, covering CVC insertion, maintenance, and removal practices. In addition, a 10-month patient inclusion period was chosen to ensure sufficient volume for robust preintervention and postintervention comparisons. While the absence of formal power estimation is a limitation, the expected sample size and data collection strategy should provide sufficient statistical power to support meaningful analyses and conclusions.

Second, the study excludes patients in palliative care or with hemodynamic instability. This choice was based on both ethical and methodological considerations. Under French research regulations, informed nonopposition is required for participation; in practice, obtaining this from end-of-life or critically unstable patients is often challenging or inappropriate. Furthermore, these patients may follow atypical care pathways that could introduce bias in the evaluation of adherence to standard catheter care protocols. We therefore focused on patients whose clinical

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condition allowed for the consistent application and assessment of best practices.

Future research could explore the adaptation of this intervention to other hospital departments or high-risk patients. Additional components, such as e-learning modules or behavior change models, may further enhance the intervention's effectiveness and sustainability.

Results from this study will be disseminated through publication in a peer-reviewed journal and presentations at national and international conferences on infection control and critical care. Feedback will also be shared with ICU teams and hospital leadership to support ongoing quality improvement initiatives.

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Authors' Contributions

All authors meet standard criteria for authorship. NK contributed to the conception of this project, drafting of the manuscript, and data acquisition. A-CL and LA participated in patient recruitment and revision of the manuscript. EK participated in elaboration of the questionnaire, patient recruitment, and data collection. PV participated in study conception and revision of the manuscript. All authors approved the final version of the manuscript and assure that it is not being considered for publication elsewhere.

Conflicts of Interest

None declared.

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Abbreviations

BD: Becton, Dickinson and Company
CLABSI: central line–associated bloodstream infection
CVC: central venous catheter
HCW: health care worker
ICU: intensive care unit
SF2H: French Society of Hospital Hygiene

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Protocol

Developing an AI Governance Framework for Safe and Responsible AI in Health Care Organizations: Protocol for a Multimethod Study

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Abstract

Background: Artificial intelligence (AI) has the potential to improve health care delivery through enhanced diagnostics, streamlined operations, and predictive analytics. However, health care organizations face substantial challenges in implementing AI safely and responsibly. This is due to regulatory complexity, ethical considerations, and a lack of practical governance frameworks. While many theoretical frameworks exist, few have been tested or adapted for real-world application in health care settings.

Objective: This study aims to develop and validate a practical AI governance framework to support the safe and responsible use of AI in health care organizations. The specific objectives are to identify governance requirements for AI in health care, examine existing AI governance processes and best practices, codevelop an AI governance framework to meet the needs of health care organizations, and test and refine the framework through real-world application.

Methods: A multimethod research design will be used, comprising four key stages: (1) a scoping review and document analysis to identify governance needs and current processes, (2) in-depth interviews with health care stakeholders as well as national and international AI governance experts, (3) development of a draft AI governance framework through a synthesis of findings, and (4) validation and refinement of the framework through stakeholder workshops and application to case studies of AI tools. Data will be analyzed using qualitative methods informed by grounded theory.

Results: The project received funding in October 2023. Ethics approval was obtained from the Alfred Health Human Research Ethics Committee (project 171/24) and the Macquarie University Human Research Ethics Committee (project 16508). Data collection commenced in April 2024, with the scoping review and document analysis being finalized. As of March 2025, a total of 43 interviews have been completed. The final AI governance framework is expected to be completed and ready for dissemination by June 2025.

Conclusions: This study will deliver a comprehensive AI governance framework co-designed with health care stakeholders to address real-world challenges in AI oversight. The framework will offer practical guidance to support health care organizations in adopting AI technologies safely, ethically, and in alignment with regulatory requirements. Outcomes from this study will inform local and international discussions on AI governance and promote the responsible integration of AI in health systems.

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KEYWORDS

artificial intelligence; governance; health care; oversight; patient safety; ethics; framework

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Introduction

Background

Artificial Intelligence (AI) technologies have the potential to transform health care by improving standards of care and addressing global challenges such as rising costs, staff shortages, and increasing patient complexity [1-4]. AI applications span both clinical and nonclinical tasks, including predicting patient care needs, assisting with diagnosis, and optimizing administrative processes [5]. Despite these benefits and technological advancements, adoption within health care organizations remains slow [6]. Compared to some other industries, health care is subject to significant regulation to ensure patient safety [7], and ethical considerations such as data privacy, transparency, and equity, which may limit adoption [8].

Governance at the organizational level is critical to ensure AI is implemented safely and responsibly. However, there is little practical guidance for governing AI development, implementation, and use in health care [9,10]. While numerous theoretical frameworks exist, these often focus on broad ethical principles such as fairness, transparency, and accountability but lack actionable strategies for health care organizations to adopt. This gap leaves organizations without clear mechanisms to assess AI risks, ensure compliance with regulatory standards, or integrate AI into clinical and operational workflows safely [8]. Most existing frameworks have not been designed for real-world application within complex health care environments. Few have been systematically tested or implemented, meaning there is limited evidence on their effectiveness in practice. Additionally, little is known about how key stakeholders such as health care professionals, patients, administrators, and AI developers perceive AI governance challenges or what governance mechanisms would best support responsible AI adoption [11]. Without a structured and adaptable governance framework, AI technologies may be deployed without sufficient oversight, leading to potential safety, ethical, and legal concerns.

Emerging evidence highlights safety concerns associated with AI and their impact on patient care, emphasizing the need for adequate governance to ensure a whole-of-system approach to safe AI implementation [12]. Effective governance at the organizational level is required to ensure that AI tools are effectively integrated into the IT infrastructure, as they are highly reliant on data from other clinical information systems [10]. For instance, data quality and requirements for any accompanying changes to the electronic medical record and other supporting clinical information systems need to be assessed to ensure data provided to the AI tools is fit for purpose and its output is accurately displayed to users. There is also a need to ensure that AI tools are integrated with the clinical workflow, with users aware of their intended use and trained to use them safely. Recent incidents of patient data being shared with the industry for AI training [13,14], along with evidence of hospitals deploying AI without adequate local evaluation for bias [15], also highlight the urgency for more stringent and consumer-centered AI governance.

The evolution of AI further necessitates a governance approach that can accommodate emerging technologies such as generative AI, AI-enabled clinical decision support systems, and automated administrative processes [16]. With the likelihood that AI capabilities will continue to progress, it is foreseeable that so will the potential risks, which will require governance approaches that are dynamic, iterative, and responsive to these technological and regulatory changes [17].

Health care must also consider organizational factors not addressed in broad conceptual frameworks, such as financial constraints, organizational culture, and commercialization [18]. Ongoing technological advancements and growing public awareness further necessitate governance strategies that adapt to emerging challenges. For example, the proliferation of generative AI, including AI scribes, has led to the development of new guidelines to address associated risks [19-21]. This study seeks to bridge these gaps by developing an AI governance framework tailored to the needs of health care delivery organizations, ensuring that AI innovations can be integrated safely and responsibly while maximizing their benefits for patient care and system efficiency [22].

Aim

This study aims to develop and test an AI governance framework to enhance organizational oversight of AI applications in health care delivery.

Objectives

To achieve the aim of the study, there are four specific objectives:

1. Identify governance requirements for AI applications in health care delivery organizations
2. Examine existing AI governance processes and current best practices for AI governance
3. Codevelop an AI governance framework to meet the needs of health care organizations
4. Test and refine the AI governance framework by applying it to exemplar AI tools

Output

We will produce a comprehensive AI governance framework for a health care delivery organization.

Methods

Study Setting

This study will be conducted within a major Australian public health care organization that delivers care to a catchment of over 770,000 residents in Melbourne's inner south. The organization operates across three hospital campuses, including a major tertiary and quaternary referral hospital that provides specialized care for patients who are critically ill. The other campuses focus on community-based health care, offering services in rehabilitation, geriatric medicine, general medicine, and aged mental health. Additionally, the organization delivers statewide and national health care services to patients across Victoria and Australia [23]. As a large and diverse health care provider, this setting offers a robust environment for developing

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and testing an AI governance framework for real-world application in health care. While the organization already has established AI-driven initiatives and governance structures supporting patient safety and digital health, there is currently no standardized AI governance framework tailored to its varied operational needs.

Study Design

We will adopt an exploratory multimethod approach [24] to develop and test an AI governance framework for the safe and responsible use of AI in health care delivery organizations. The structure of the study will comprise four stages that are directly linked to the study objectives: understanding governance needs through a scoping review and document analysis, gathering stakeholder insights on AI governance via in-depth interviews, codeveloping the AI governance framework through a synthesis of findings, and validating and refining the framework through stakeholder workshops and AI case studies (Figure 1).

Figure 1. Study process diagram. AI: artificial intelligence.

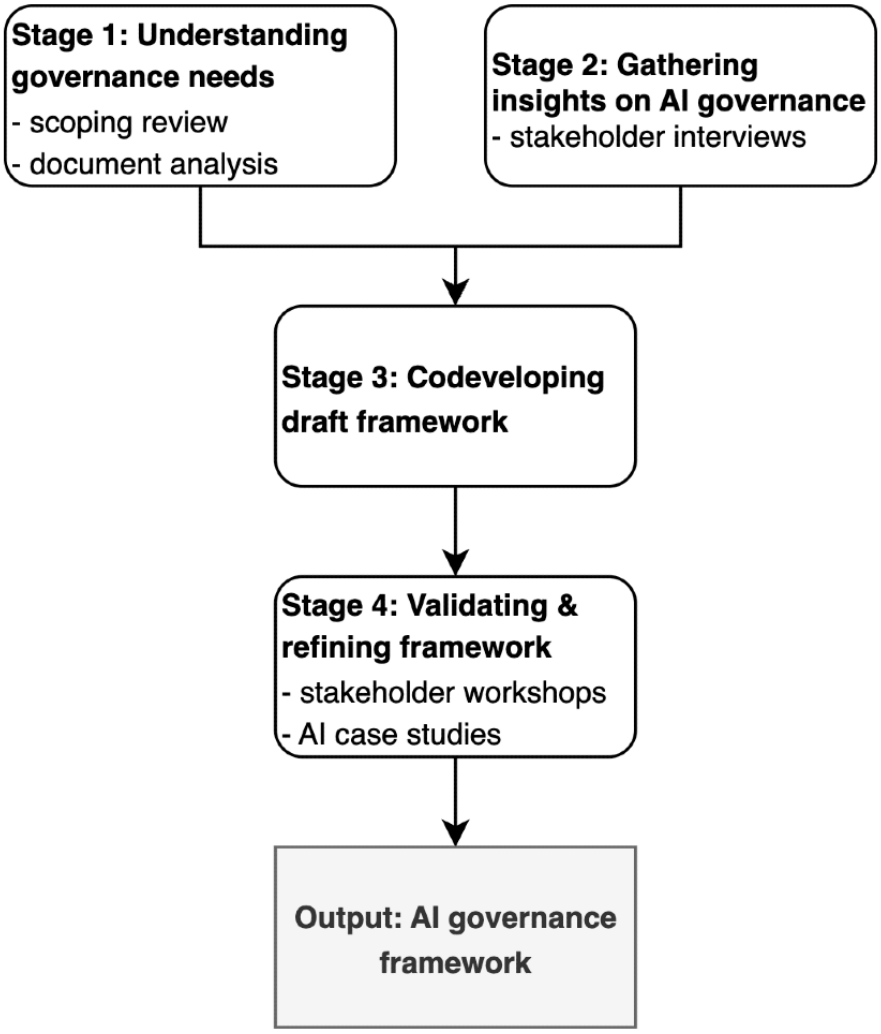

Given the evolving nature of AI governance within health care organizations, we have developed a comprehensive research strategy that draws on existing methodologies for investigating emerging technologies [25,26], evaluating complex systems [27], and ensuring stakeholder engagement in governance development [28]. This qualitative study will be designed in accordance with COREQ (Consolidated Criteria for Reporting Qualitative Research) [29]. The final output of the study is to produce a practical and actionable AI governance framework that addresses key challenges in AI oversight at the organizational level. The research will run concurrently to enable insights from one stage to inform other stages iteratively. The four research stages are detailed in the following sections.

Stage 1: Understanding Governance Needs

Scoping Review

Published literature about approaches to AI governance at an organizational level will be reviewed. Given the volume of literature published in this domain, only frameworks that are specific to health care will be reviewed [30]. The search strategy will be designed to address study site requirements, including governance approaches for AI tools with a clear intended purpose (eg, AI-enabled medical devices).

The following electronic databases will be searched: MEDLINE, Embase, and Scopus. These databases were selected based on consultation with a Macquarie University research librarian. A search will also be conducted on Google Scholar and Google

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search, where the first 200 results will be included for review. This is based on guidance around the use of Google for searching for gray literature [31]. Reference lists of key papers will be hand-searched for additional peer-reviewed and gray literature. Appropriate search strings will be developed by linking concept clusters relating to each component of the question (AI, governance and implementation, and a health care setting) with Boolean operators "AND" and "OR." Search results will be imported into Covidence where a two-stage review process (title and abstract screening, followed by full-text review) will be conducted by two independent reviewers. Data will be extracted into Excel (Version 16.98; Microsoft Corporation).

Document Analysis

To ensure the AI governance framework aligns with the current state of governance processes at the study sites, a document analysis will be conducted to map current processes. This will involve a systematic review of relevant internal policies, governance documents, and procedural guidelines. This will help establish a baseline of governance structures to ensure that the AI framework does not replicate existing or previously established governance processes and to identify strengths and gaps in current governance approaches.

Stage 2: Gathering Stakeholder Insights on AI Governance

Overview

In-depth semistructured interviews will be conducted with two key groups: health care staff and national and international experts in AI governance, policy, health care, AI, and patient safety. A purposive sampling technique will be used to identify key informants from both groups. A snowballing technique will also be used, allowing participants to refer other relevant informants for involvement in the study. Semistructured interview guides will be developed based on a review of the existing literature and input from the multidisciplinary project team. Members of the project team have recognized experience in health care, qualitative research, and AI safety and governance. Around 25-30 interviews (a total of 50-60) from both groups are expected to provide thematic saturation (where no new themes are identified). Key informants who agree to participate will be interviewed via online videoconferencing or in person, with audio recording. Audio files will be deidentified and professionally transcribed by a secure transcription service. Two investigators will independently analyze and code the interviews using open coding techniques based on grounded theory. A grounded theory approach will be applied as it provides a methodology and procedure for collecting and analyzing data and conceptualizing the results [32].

Health Care Stakeholder Interviews

We will recruit a diverse range of health care stakeholders to gain their perceptions on how to effectively govern the safe and responsible use of AI. The interviews will initially include informants from the board of directors and executive leadership, clinicians undertaking AI projects, clinical trial managers, and representatives from ethics and research governance offices, as well as clinical governance, risk, research, clinical operations, medical services, hospital liaison, legal, and consumer representatives. During the interviews, participants will be asked about current approaches to governance and processes to manage the safe and responsible application of AI in health care and barriers to adoption. In addition to health care stakeholder interviews, dedicated consumer consultation will be incorporated into the framework's development process. To do this, we will engage the Australian Institute of Health Innovation Consumer Engagement Panel, which supports person-centered research. The panel will provide their perspectives on governance priorities through review sessions. Feedback from these sessions will be analyzed using a grounded theory coding approach and integrated alongside other stakeholder data to inform the development of the AI governance framework.

National and International Expert Interviews

We will examine current practices for governing AI in health care. Experts will include participants from academia (ethics, governance, digital health, technology, AI), government, health care administration, clinical settings, and professional health care associations. Participants will be asked about current approaches to AI governance in health care and will be invited to share any documentation about governing AI as well as tools or templates used to support AI governance processes.

Stage 3: Codeveloping a Draft AI Governance Framework

Findings from the scoping review, document analysis, and stakeholder interviews will be synthesized to develop a draft AI governance framework tailored to the needs of health care organizations. A grounded theory approach will guide the synthesis of findings across the scoping review, document analysis, and stakeholder interviews. Data from each source will be open coded to identify key concepts, which will then be compared and integrated through constant comparative analysis [33]. Emerging categories will be iteratively refined to develop the framework structure to reflect insights from stages 1 and 2.

The framework will outline pathways for integrating AI governance within existing clinical and operational workflows. To do this, the draft framework components will be mapped against current clinical governance, digital health, risk management, quality improvement processes, etc. Here, potential points of alignment and areas requiring modification will be identified. To address challenges such as organizational resistance, workflow incompatibilities, and training needs, the framework will include implementation recommendations outlining strategies for change management, staff education, and stakeholder engagement, informed by stakeholder insights.

During this phase, the framework will be designed to apply to different types of AI applications, including emerging technologies such as large language models and generative AI. A stratified governance approach based on the type of AI application and risk profile will be considered to address common and emerging risks, such as explainability challenges, hallucinations, etc, where identified. Additionally, specific governance components will be developed based on study findings to ensure the framework remains applicable across evolving AI technologies. The draft AI governance framework

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developed in this stage will be tested and validated in stage 4 through stakeholder workshops and AI case studies.

Stage 4: Validating and Refining the Draft AI Governance Framework

Stakeholder Workshops

Stakeholder workshops will be conducted to refine and validate the AI governance framework with key stakeholders from the health care organization. Stakeholder workshops will be structured using facilitated discussion and scenario-based exercises focused on the practical application of the draft framework. The number of workshops and participants will be determined in consultation with the study site's project team to ensure appropriate representation of clinical, operational, and governance stakeholders. Detailed notes will be taken during the workshops, which will be analyzed using a grounded theory approach to identify key themes and areas for framework refinement. Insights from the workshops will be incorporated iteratively to improve the framework's practicality, ease of use, and alignment with organizational needs.

Testing the Draft Framework on Case Studies

The draft governance framework will be applied to exemplar AI tools from the study site to determine whether it provides adequate oversight. We will select 3-5 AI tools that are representative of the different pathways by which health care organizations acquire and use AI tools, including in-house development, codevelopment with external partners, and procurement of external AI tools. Selection criteria for case studies will also include representation of both clinical and administrative applications, diversity in levels of autonomy (eg, assistive vs decision support) [1], and variation in associated risk profiles. Tools will be selected in consultation with the study site's project team to ensure relevance and alignment with the organization's operational and clinical priorities. To evaluate the framework's usability and adaptability, a think aloud protocol will be used during pilot testing [34]. Participants will talk through their experience as they apply the framework to the AI tool in real time, providing insights into its effectiveness and identifying areas for improvement in the checklist. These findings will inform iterative refinement of the framework to enhance its applicability across diverse implementation contexts.

We will also assess the extent to which the AI framework will continue to be fit for purpose for current and next-generation AI technologies. Findings from these case studies and stages 1-3 will help identify gaps to refine the AI governance framework. The framework will be evaluated during this study based on its perceived usability, completeness, relevance to risk management and regulatory requirements, and stakeholder acceptance. This will be assessed with feedback collected during the stakeholder workshops and case study pilots.

Results

This study received funding in October 2023 from the Digital Health Cooperative Research Centre, Alfred Health, and Macquarie University. Ethics approval was granted by the Macquarie University Human Research Ethics Committee (project 16508) in December 2023 and Alfred Health Human Research Ethics Committee (project 171/24) in February 2024. Data collection commenced in April 2024 and is progressing as planned.

As of March 2025, the scoping review and document analysis (stage 1) are underway, with preliminary findings identifying key themes in existing AI governance frameworks and internal governance structures at the study site. Interviews with health care stakeholders and AI governance experts (stage 2) are complete (n=43), and the thematic analysis has commenced. Case study selection for framework testing has been finalized in consultation with the study site. The final AI governance framework is anticipated to be finalized and disseminated by June 2025.

Discussion

Study Significance and Strengths

This study will generate critical insights into AI governance by developing and validating a framework for the safe and responsible integration of AI in health care. By addressing the gap in practical guidance for governance at the health care organizational level, this study will provide actionable strategies for managing AI tools in both research and operations. Its multimethod approach will ensure a comprehensive understanding of AI governance by integrating findings from a scoping review, stakeholder engagement, and case studies. This methodology will support the development of a governance framework that is both theoretically grounded and practically applicable.

A key strength of this study is the inclusion of diverse stakeholder perspectives, ensuring that governance recommendations are aligned with real-world requirements. By systematically developing an AI governance framework, this study will provide evidence-based recommendations for improving oversight of AI tools in health care delivery. It will ensure that organizational policy supports safe and responsible AI and complies with legislation (eg, data privacy, consumer law, and cybersecurity) and relevant AI ethics frameworks. The findings will contribute to international discussions on AI governance and support the development of governance that balances adaptability with patient safety and ethical considerations.

Limitations

Despite the strengths of this study, its limitations should be acknowledged. The study is currently limited to one Australian health care organization, which may limit the generalizability of the AI governance framework to other settings with different regulatory environments, organizational structures, or levels of technical maturity. While stakeholder interviews will include international participants, the findings may still reflect context-specific challenges rather than universal governance solutions. This also means that the successful integration of the framework into existing structures and organizational cultures may vary depending on local governance systems, staff engagement, and available training resources. Furthermore, while the framework is being developed at a large metropolitan

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health care organization, limiting generalizability, it is being designed to be adaptable to support its application in diverse health care settings (eg, regional hospitals, resource-limited settings). However, further research will be needed to evaluate the framework's scalability and effectiveness across diverse health care environments.

Additionally, the study focuses on governance at the health care organizational level, which may not account for broader policy, legislative, or technological changes that might impact AI adoption in health care. The rapid progress of AI technologies such as generative AI presents challenges in ensuring the framework remains adaptable and relevant over time. While the iterative design of this study allows for ongoing updates, future research will be needed to assess the long-term sustainability and adaptability of the framework as AI capabilities continue to evolve.

Future Directions

This study will provide an AI governance framework specifically designed for health care organizations; however, further research will be needed to ensure its long-term applicability and scalability within dynamic health care contexts. Future studies should focus on implementing and evaluating the framework's effectiveness across a broader range of health care organizations, including regional and rural health services, to assess its adaptability in diverse settings. Expanding the research to include international case studies will also provide comparative insights into how different regulatory and health care systems approach AI governance. Further research, including longitudinal follow-up studies, will be critical to track the sustained impact of AI governance frameworks on patient safety, operational efficiency, and clinician trust over time. This includes researching how governance processes develop alongside emerging AI technologies and regulatory changes as well as the long-term effectiveness and sustainability of the AI governance framework itself. This research should evaluate real-world outcomes such as long-term adoption, compliance improvement, and risk reduction.

Conclusions

This study will develop and validate an AI governance framework to support the safe and responsible use of AI in health care. By integrating a multimethod approach, the study will provide practical guidance on AI oversight at the organizational level, addressing gaps in existing governance structures. Findings will contribute to international discussions on AI governance, ensuring that AI technologies are adopted in a way that prioritizes patient safety, ethical considerations, and regulatory compliance. The iterative nature of this research will enable the framework to adapt to evolving AI capabilities and organizational needs, providing a foundation for robust governance strategies in health care.

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Data Availability

The datasets generated during this study will not be made publicly available for privacy reasons, but requests to the corresponding author will be considered on a case-by-case basis.

Authors' Contributions

FM and EC conceptualized the study. FM, SF, and AW designed and are conducting the study. SF, AW, and FM drafted the manuscript with input from all authors. All authors provided revisions for intellectual content. All authors have approved the final manuscript.

Conflicts of Interest

SS and EP are employees of Alfred Health and participated in the project steering committee but were not involved in data collection, analysis, or interpretation. Their involvement in recruitment was limited to forwarding the study invitation to potential participants. SS participated in the board and chief executive officer interviews. SF, AW, FM, and EC have no professional or personal affiliation with Alfred Health.

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Abbreviations

AI: artificial intelligence
COREQ: Consolidated Criteria for Reporting Qualitative Research

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Protocol

Evaluation of Free-Living Motor Symptoms in Patients With Parkinson Disease Through Smartwatches: Protocol for Defining Digital Biomarkers

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Abstract

Background: Monitoring motor symptoms in patients with Parkinson disease (PD) presents significant challenges due to the complex nature of symptom progression, variations in medication responses, and the fluctuations that can occur throughout the day. Traditional neurological visits provide only a limited perspective of a patient's overall condition, with challenges in achieving accurate and objective assessments of symptoms. To bridge this gap, extended monitoring in nonclinical settings could play a critical role in personalizing treatments and improving their efficacy. Wearable devices have emerged as potential tools for assessing PD symptom severity; however, studies integrating both in-clinic and free-living conditions, as well as multiday monitoring, remain scarce. Defining digital biomarkers that provide valuable insights into motor symptoms could enable comprehensive monitoring and tracking of PD in various contexts, facilitating more precise medication adjustments and the implementation of advanced therapeutic strategies.

Objective: This study aims to collect a dataset to support the proposal and definition of digital biomarkers of PD motor symptoms using wearable devices. Data will be collected both in a supervised setting and continuously in a remote, free-living context during participants' normal daily activities; the study will include patients with PD and healthy controls. The goal is to identify reliable digital biomarkers that can effectively distinguish patients with PD from healthy controls and classify disease severity in both supervised and unsupervised free-living environments.

Methods: This paper outlines a protocol for an observational case-control study aimed at assessing motor symptoms in patients with PD using a smartwatch. The smartwatch will record accelerometer, gyroscope, and physical activity data. Participants will be instructed to perform a series of exercises guided via a smartphone. Measurements will be collected in 2 settings: a supervised clinical environment, with motor symptoms assessments conducted at the beginning and end of the study, and in an unsupervised free-living context for 1 week. In both settings, participants will be required to wear the smartwatch while performing the same set of exercises. In their daily routine, participants will be required to wear the smartwatch continuously throughout the day, removing it only at night for charging.

Results: Participant recruitment and data collection started in December 2024 and will continue until spring 2025. The study aims to enroll 20 participants with PD and 20 healthy controls.

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Conclusions: It is anticipated that the generation of a dataset of accelerometer and gyroscope signal data recorded from patients with PD at various stages of the disease, alongside data from a control group, will enable robust comparative and impactful analyses. In addition, the study seeks to develop analytical techniques capable of tracking PD symptoms in real-life scenarios, both in everyday settings and clinical environments.

Trial Registration: ClinicalTrials.gov NCT06817772; https://clinicaltrials.gov/study/NCT06817772

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KEYWORDS

movement analysis; wearable devices; home monitoring; health indicator; smart health care

Introduction

Background

In the context of an increasingly aging society characterized by an inverted population pyramid, the treatment and management of neurodegenerative diseases represent an important challenge. In 2013, the World Health Organization recognized neurodegenerative diseases as “a global health problem that must be addressed without delay for humanitarian, social, and economic reasons” [1].

Parkinson disease (PD) exemplifies this issue, with the number of individuals affected rising by 250% between 1990 and 2015 [2]. In Spain, a new case of PD is diagnosed approximately every 45 minutes, with 15% of these cases occurring in individuals aged < 45 years [3]. PD is a progressive neurodegenerative disorder characterized by the selective degeneration of dopaminergic neurons in the substantia nigra pars compacta, which supports the corticosubcortical network, which facilitates limbic, associative, cognitive, and motor functions [4]. In early stages, PD often exhibits nonmotor dysfunctions, including impairments in working memory, executive function, attention, visuospatial capacity, and semantic fluency, which may eventually progress to dementia [5].

In advanced stages, motor symptoms (such as tremor, bradykinesia, postural instability, and rigidity) and nonmotor symptoms (including cognitive decline, mood disorders, sleep disturbances, and autonomic dysfunction) become more pronounced, significantly affecting patients’ quality of life [6,7].

Currently, there is no cure for PD. Treatment strategies typically involve pharmacological and surgical interventions, often complemented by nonpharmacological therapies [8]. Pharmacological treatments focus on restoring dopamine levels to preserve motor function for as long as possible [9]. While effective in managing hypokinesia (loss of movement) and tremor, these therapies remain beneficial within a therapeutic window of 5 to 10 years, after which 50% to 80% of patients develop dyskinesias (involuntary muscle movements). In addition, certain patients exhibit resistance to these treatments [10].

Nonpharmacological interventions are crucial for enhancing patients’ quality of life [11]. These include traditional treatments such as physical exercise, physiotherapy, occupational therapy, or cognitive training, among others [12-14]. Experimental approaches, including noninvasive neurostimulation techniques such as transcranial direct current stimulation [15], are also being explored for their potential to improve symptom management.

The diagnosis of PD is primarily clinical, relying on a detailed anamnesis based on information from the patient and their family, combined with a physical examination [16]. These consultations are used to conduct clinical assessments, adjust medications, and prescribe exercises or therapies. Several clinical scales support this process, with the Movement Disorder Society-Unified Parkinson’s Disease Rating Scale (MDS-UPDRS) [17] being the most widely used. However, the time allocated per patient during these visits is limited [18]. Reflecting this constraint, numerous resources, including guidelines, websites, and individualized workshops, have been developed to help patients and caregivers prepare effectively for their neurologist appointments [19-22].

Recent studies have highlighted the suboptimal accuracy of clinical diagnoses for PD, as the techniques are inadequate for capturing the nuanced and fluctuating nature of PD symptoms, which can vary significantly throughout the day [23]. Clinical assessments, conducted infrequently during brief consultations, fail to provide a comprehensive understanding of patients’ conditions in their everyday lives [24]. This limitation underscores the need for continuous monitoring tools to complement periodic clinical evaluations.

To enhance diagnostic resources for objective monitoring, digital health technologies, particularly wearable devices, offer significant potential for optimizing health management [25]. These technologies can serve as complementary clinical tools, supporting tasks such as early diagnosis and the objective monitoring of PD symptoms over time [26]. Wearable devices provide a discreet and user-friendly solution that not only reduces the burden on patients to remember and manually record information about their symptoms but also offers systematically organized data on symptom evolution [27]. This can be achieved by using digital biomarkers [28], which enable the objective assessment of disease progression and the impact of treatments or therapeutic interventions in chronic conditions such as PD.

BioClite Project

BioClite (Digital Biomarkers for the Assessment of Motor Status in Parkinson’s Disease Patients With Clinical and Therapeutic Application) is a project funded by the Ministry of Science and Innovation of Spain (No. PID2021-123708OB-I00) that aims to enhance PD monitoring using wearable technology.

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The BioClite project responds to the growing need for objective assessment tools to improve the management and long-term monitoring of PD using wearable devices, specifically smartwatches. By using this technology, the project aims to improve the accessibility of medical care and eliminate physical barriers between patients and health care providers.

Prior studies have used wearable devices to assess motor symptoms. In the study by Samà et al [29], bradykinesia severity was evaluated using a waist-worn device; in the study by Di Lazzaro et al [30], several wearable devices were used to assess several MDS-UPDRS tasks; Coates et al [31] focused on gait parameters using an inertial measurement unit placed on the lower back; and in the study by Antonini et al [32], multiple motor symptoms were assessed using a commercially available wearable device. According to a review on wearable devices for PD monitoring [28], the most commonly used wearables incorporate inertial measurement units, such as accelerometers and gyroscopes, typically embedded in smartwatches, wristbands, or worn on the lower back or ankles.

However, previous technology-based approaches have presented several limitations. Many required bulky or intrusive equipment, limiting their practicality for long-term or home-based use. Others were constrained to controlled environments, reducing ecological validity and overlooking symptom fluctuations in daily life. Furthermore, user compliance was often hindered by complex device management or lack of feedback. Importantly, some earlier systems did not sufficiently address data privacy concerns, raising potential risks regarding the handling of sensitive personal information, particularly when combined with the use of artificial intelligence models [33].

This study advances this field by implementing a dual-monitoring approach: guided exercises conducted in controlled environments, where participants perform specific tasks to capture motor patterns associated with PD, and free-living activities, where data are collected from participants in uncontrolled environments during their daily routines outside of clinical or laboratory settings without direct supervision and under natural conditions.

One of the daily-life activities is egg beating, an activity often identified by patients with PD as one that made them aware of their condition; this activity is performed under both supervised and unsupervised conditions. This approach not only allows for direct comparison between clinical and real-world data but also introduces an ecological, patient-centered perspective that is largely absent from previous research, which has typically relied on standardized clinical tasks. By including free-living monitoring, this methodology allows for continuous data collection without interrupting patients' everyday activities, providing a more natural and unobtrusive experience compared to traditional methods.

Data labeling plays a crucial role in the project and is carried out using 2 main methods: algorithmic tagging, where custom-designed algorithms automatically analyze collected signals to identify significant motor events, and the use of external beacons and markers to link time points with contextual information, improving the accuracy of the tagging process. The combination of these approaches can support the collection of a comprehensive, annotated dataset that supports the development of algorithms for PD detection, status prediction, and personalized therapeutic strategies.

Through the collection of motor activity data, primarily in real-world environments, the project aims to develop digital biomarkers that provide valuable insights into PD symptoms, particularly tremors and bradykinesia. The protocol detailed in this paper describes a study designed to leverage digital biomarkers for PD detection, with the objective of distinguishing patients with PD from healthy individuals and enabling early-stage disease assessment. This approach allows continuous monitoring of symptoms and evaluation of therapeutic effects, thereby supporting personalized treatment strategies and improving the management of the disease.

The BioClite project contributes to more precise symptom tracking and the advancement of wearable technology in PD management by enabling continuous and unobtrusive monitoring, ultimately enhancing patient care and advancing scientific research in the field.

Methods

Inclusion and Exclusion Criteria

For the PD cohort, the main inclusion criterion is a diagnosis of PD based on the United Kingdom Brain Bank criteria. All participants in this group were recruited from Asociación Parkinson Madrid (APM), ensuring access to a well-defined population actively engaged in PD care and support.

To ensure a representative sample, efforts will be made to achieve a gender balance across the study population. In addition, participants must meet an age requirement ranging from 45 to 80 years, reflecting the study's focus on middle-aged and older populations typically affected by PD [34].

The control participants are not selected based on strict age alignment with the PD patients, as both groups are recruited and analyzed concurrently. Instead, efforts will be made to ensure that the 2 groups exhibit comparable means and SDs with respect to age, such as pairing the recruitment of healthy controls with that of participants with PD or dividing participants into smaller age groups (eg, 55-60, 61-65 years) and ensuring a similar number of healthy controls and participants with PD within each group.

While this design choice may introduce variability, age will be included as a covariate in statistical analyses to account for its potential impact on the results. In addition, prioritizing inclusivity over strict matching allows a broader understanding of how the proposed biomarkers may generalize across diverse populations.

The common inclusion criteria established for participants with PD and control groups are as follows:

- Wear the study devices on the hand most affected by the condition and dominant (for patients with PD) or the dominant hand (for controls). In both cases, this should be the hand primarily used in the free-living activities.

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- Be capable of performing prescribed exercises independently.
- Maintain daily functioning without dependence on caregivers.

Specific inclusion and exclusion criteria for the PD group have been designed to enhance better representative of the sample, given that the study focuses on the detection and initial stages of the disease, as participants with advanced PD often exhibit evident motor symptoms that are more readily identifiable; however, they may also experience impairments that could limit the feasibility or effectiveness of wearable monitoring technologies [35]:

- Eligible participants must have minimal or mild disease severity, defined by a Hoehn and Yahr scale score of ≤2.5.
- Participants must not experience motor symptom fluctuations throughout the day.
- Individuals who have undergone deep brain stimulation, used dopamine infusion pumps, or have conditions mimicking PD symptoms (eg, progressive supranuclear palsy, Lewy body dementia, multiple system atrophy, or other parkinsonian syndromes) are excluded.

Recruitment Process

The recruitment of new participants begins with an initial contact, conducted either in person or by telephone, during which a concise overview of the study's purpose and procedures is provided. If the prospective participant expresses interest and meets the inclusion criteria, they are invited to proceed with the next steps.

For participants in the PD group, an appointment is arranged at the APM, while control group participants attend a meeting at the Escuela Técnica Superior de Ingenieros Industriales at Universidad Politécnica de Madrid. During these sessions, the study's objectives, procedures, and expectations are thoroughly explained to ensure participants have a comprehensive understanding of their role and responsibilities.

To formalize their participation, individuals are asked to review and sign an informed consent form in compliance with ethical guidelines and regulatory standards.

Study Design

This study comprises 1 week of free-living monitoring of 20 participants with PD and 20 healthy control participants. The proposed number of participants in this study is comparable to those found in the literature for defining biomarkers in PD (mean 15, SD 6.8 patients with PD) [28,31,36-39] or for monitoring PD motor symptoms (mean 15.4, SD 4.5 patients with PD) [29,40-45]. Small samples are common in exploratory research with wearable sensors, particularly in populations considered vulnerable and hard to recruit such as individuals with PD. Such studies are important for early validation of methods and identifying key trends to inform future research. While the sample size limits detailed subgroup analyses, it is adequate for assessing general patterns and methodological feasibility. All participants will undergo the same experimental protocol, which includes the following:

- A baseline assessment to establish initial measures
- A 1-week period of unsupervised free-living activity monitoring to capture naturalistic data
- A final evaluation to reassess clinically and compare with baseline results

The study schema is illustrated in Figure 1, providing an overview of the structured protocol and its key phases.

Figure 1. Overview of the experimental protocol of the study.

Participants will engage in a series of standardized exercises and a structured free-living activity conducted at home. The findings from this study will establish a foundation for future research focused exclusively on assessing free-living activities without requiring patients to perform any predetermined tasks.

Upon recruitment, each participant begins the experimental protocol with a meeting at APM (for the PD group) or at the Escuela Técnica Superior de Ingenieros Industriales at Universidad Politécnica de Madrid (for the control group). During this visit, a baseline assessment of the participant's motor symptoms is conducted using the Monipar set of exercises [46]. This set comprises 8 tasks specifically designed to evaluate various motor symptoms of PD.

Seven of these exercises are adapted from the MDS-UPDRS III scale: resting tremor amplitude (item 3.17), postural tremor of the hands (item 3.15), finger tapping (item 3.4), hand movements (item 3.5), pronation-supination movements of the hands (item 3.6), arising from a chair (item 3.9), and gait (item 3.10). The eighth exercise, proposed by the research team, complements the evaluation by addressing additional motor symptoms. These tasks are routinely used by neurologists in

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clinical settings, and participants are generally familiar with their performance, ensuring ease of implementation.

For the PD group, a specialized PD physiotherapist performs all the assessments using the MDS-UPDRS III scale to ensure consistency and reliability across participants.

In addition, to facilitate the transition from controlled clinical assessments to unsupervised free-living conditions, participants are required to perform a specific free-living activity. This activity involves beating eggs for 1 minute, a common daily task familiar to most individuals. The repetitive nature of this activity makes it particularly useful for evaluating bradykinesia [47,48] under free-living conditions. The selection of this activity was informed by consultations with nurse practitioners, patients, and therapists, all of whom stated its potential relevance and significance for assessing bradykinesia.

Following the baseline evaluation, participants proceed with the study in free-living, unsupervised conditions, maintaining their normal daily routines. They are required to wear the smartwatch throughout the day for 1 week, removing it only at night for charging. Vanmechelen et al [49] revealed that some participants feel discomfort using wearable devices, particularly at night, due to concerns about privacy and intrusion into daily life.

The smartwatch records accelerometer and gyroscope data during a designated 4-hour period each day. This recording window, determined by the participants at the study's outset, accommodates their individual schedules and availability. Participants are expected to perform a series of tasks within this defined period, which will remain consistent throughout the 7 days of the study.

In the 4-hour recording period, each participant is asked to perform the Monipar exercises daily under free-living conditions and without supervision. Participants are encouraged to complete the full set of exercises each day, ideally at the same hour of the day.

Completing this set of exercises takes approximately 7 to 8 minutes daily, which does not significantly disrupt patients' daily lives. Incorporating them as a routine task facilitates easier recall and adherence. In addition, participants will be required to perform the specific free-living activity of beating eggs for 1 minute each day. So, the participants will need to set aside 10 minutes each day to perform these 2 tasks.

In prior clinic-based studies [46], participants reported that they did not perceive the daily performance of these exercises as tedious or repetitive. However, modifications were implemented in the duration of each exercise to mitigate fatigue and to provide users with the flexibility to choose when to complete them. This adjustment is intended to enhance user compliance without compromising data quality.

In addition, participants will complete a daily paper questionnaire to help contextualize the 4-hour recorded sensor data. This questionnaire captures the timing of key activities such as breakfast, lunch, and dinner; rest periods (useful for assessing resting tremors); and medication intake. Participants are also encouraged to include any relevant comments for each day, such as forgetting to wear the smartwatch or if the device was completely discharged.

As participants are required to wear the smartwatch throughout the day, their physical activities, such as walking, running, or cycling, are automatically recorded and labeled by the device using its built-in apps [50]. Physical activities are characterized by step count, distance covered, and calories burned during each session. This automatic labeling allows any physical activity that occurs during the designated 4-hour signal recording period to correlate with the acquired accelerometer and gyroscope data, enhancing the contextual understanding of the recorded measurements.

After 1 week of free-living monitoring, participants return to APM for a final evaluation, conducted in the same manner as the baseline assessment. This includes performing the Monipar exercises under the guidance of the PD physiotherapist (for the PD group); completing the specific free-living activity; and filling out a questionnaire to assess the comfort and usability of the smartwatch, report any issues encountered, and provide additional observations or feedback.

Devices Used in the Study

This study uses 2 different types of devices: a smartwatch (Samsung Galaxy Watch5) and a smartphone (Samsung Galaxy A14). The smartwatch serves as the primary measuring tool, responsible for recording all generated data throughout the study. In contrast, the smartphone is used to display instructions and label the proposed activities.

Figure 2 illustrates the devices used in this study. The home screen of the smartphone displays 2 distinct icons representing the apps participants will use to complete the activities. A contact telephone number is displayed on the wallpaper (blurred for privacy purposes). In addition, the smartwatch screen is intentionally designed to display only essential information, such as the time, date, and battery status, to ensure user-friendliness and minimize distractions for participants.

The smartwatch incorporates an LSM6DS0 module, integrating a 3-axis digital gyroscope and a 3-axis digital accelerometer, which facilitate the recording of both acceleration and angular velocity. The smartwatch configuration was set to prevent the collection of unnecessary data, such as location, audio, or video, to ensure data relevance and privacy.

Sensor's data are captured using an Android Wear OS custom app developed by the research team, configured to acquire data at a sampling rate of 50 Hz from each sensor. This frequency was chosen because it is well suited for analyzing PD motor symptoms, which typically occur within the 0 to 20 Hz range [51].

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Figure 2. Devices used in this study: smartphone (left) and smartwatch (right).

In addition, this custom app facilitates the scheduling of accelerometer and gyroscope signal recordings. In this study, a period of 4 hours per day is chosen for the free-living monitoring week. Continuous recording throughout the day is avoided for 2 primary reasons: to preserve participants' privacy—because certain activities could be inferred from these sensor data—and to minimize battery consumption. With these considerations, data from the accelerometer and gyroscope are recorded for a duration of 4 hours, during which the participants must perform the proposed activities.

In addition, the smartwatch is responsible for collecting data related to the physical activity performed by each participant all day, obtained from the smartwatch's dedicated apps.

In contrast, the smartphone functions as a user interface, facilitating participants' execution of both the Monipar activity and the specific free-living activity. This was achieved through 2 dedicated apps designed to display and playback the instructions necessary for performing these tasks effectively.

While the apps were identical in functionality, each was designated for a specific task—one for the Monipar activity and the other for the specific free-living activity. This differentiation served 2 purposes: providing participants with the flexibility to perform each activity at their convenience and accommodating the additional preparation required for the specific free-living activity.

The smartphone synchronizes with the smartwatch; tags each activity performed; and, upon completion of the study with each participant, integrates the data recorded by the smartwatch with these labels. This process ensures accurate data labeling, aligning the sensor measurements with the corresponding activities for subsequent analysis.

The smartphone is set up to prevent the collection of unwanted data, such as location, audio, or video. In addition, participants are restricted from making calls or accessing apps unrelated to the study. To address potential participant inquiries, the phone number of a researcher is set as the device's wallpaper.

Figure 3 illustrates the interface of the Monipar app, while Figure 4 depicts the layout of the app for the specific free-living activity.

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Figure 3. Interface of the app related to the Monipar activity: start screen (left) and activity screen (right).

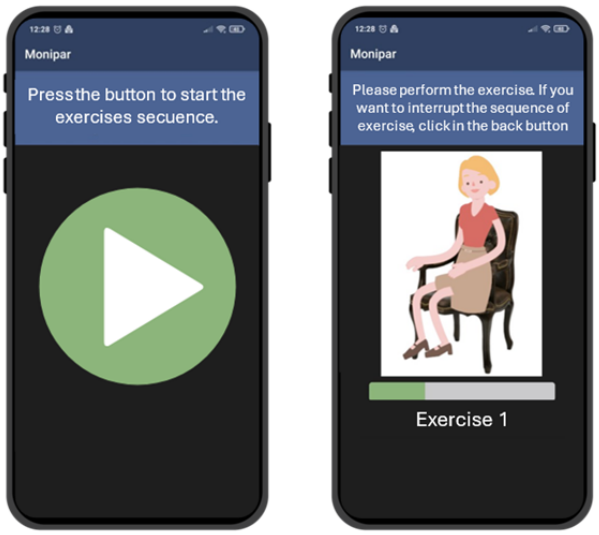

Figure 4. Interface of the app related to the specific free-living activity: start screen (left) and activity screen (right).

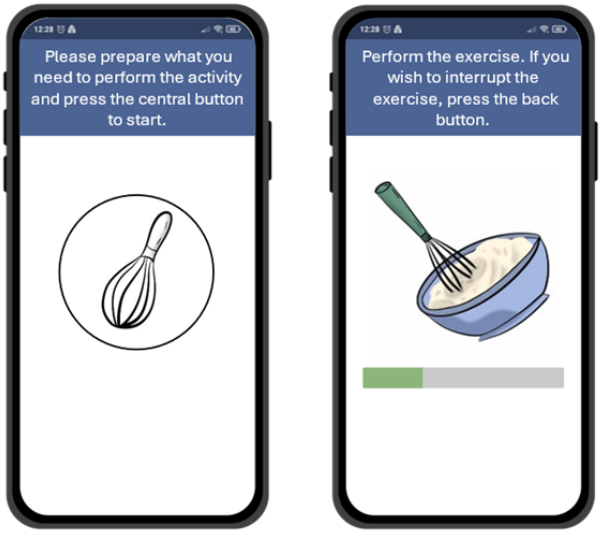

Data Collection

The proposed system is designed for dual functionality, allowing use in both supervised clinical settings and unsupervised daily-life scenarios. Although all devices involved operate independently, they are temporally synchronized via Bluetooth, ensuring simultaneous data collection and seamless integration of information from multiple sources.

The smartwatch serves as the primary device for recording data, while the smartphone facilitates the capture of time stamps for activity labeling. Data extraction and processing will occur after the study using a desktop computer. Figure 5 illustrates the architecture of the data acquisition system during and after the study.

The smartwatch worn by the participant acquires data from the accelerometer and gyroscope sensors for a duration of 4 hours each day. The data are recorded at a frequency of 50 Hz and stored in a text file in the device memory. Once the specified recording period is completed, the text file is saved in a compressed format (zip), and the original text file is deleted. This compression is done to prevent the risk of memory saturation on the device, as text files take up approximately 4 times the space of compressed files. This ensures that all daily data files are saved and stored on the device without any issues. These compressed files remain on the smartwatch until the device is retrieved at the final study visit.

Physical activity data will be collected using the device's built-in apps, temporarily stored on the watch, and periodically transmitted via Bluetooth to the smartphone. The smartphone then retains this information until the study concludes.

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Figure 5. Structure of the data acquisition system.

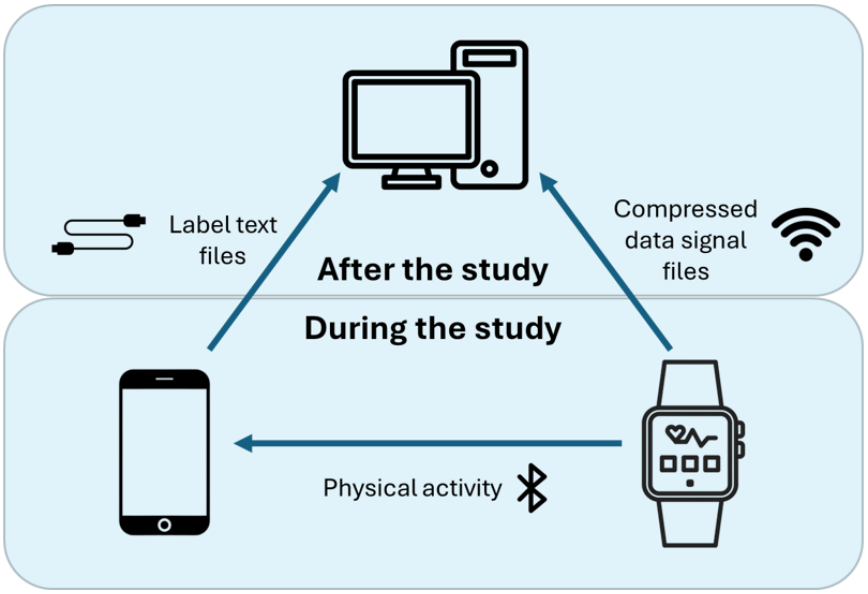

The smartphone also generates text files containing time stamps that indicate the start and end of each exercise performed. As the exercises are tracked using 2 different apps, 2 separate label files are generated each day: one corresponding to the 8 exercises of the Monipar sequence and the other to the specific free-living activity. These text files are stored on the smartphone until the end of the study.

Upon completion of the study and the return of the devices by the participants, the collected data are extracted. The extraction process differs based on the type of wearable device, though in both cases, it requires the use of a computer. For the smartphone, text files containing the temporary labels are extracted via a direct cable connection to the computer. Conversely, for the smartwatch, the compressed data files from the inertial sensors are retrieved over a Wi-Fi connection, ensuring that both the watch and the computer are connected to the same network.

Data Analysis

The resulting database from the data collection campaign will comprise signals from the 3 axes of the smartwatch's accelerometer and gyroscope. These data will be divided into 3 distinct parts. First, it will include the evaluation of the sequence of 8 Monipar exercises, conducted both in supervised and labeled conditions following the MDS-UPDRS III scale, as well as in unsupervised free-living conditions. Second, it will encompass the performance of the specific free-living exercise, 1 minute of beating eggs, performed under supervised conditions at the association and under unsupervised free-living conditions. Finally, the database will contain the daily recording of 4 hours of free-living activity, accompanied by the physical activities performed during the day and participant-completed notebooks detailing activities such as eating, resting, and taking medication.

A comprehensive data analysis will be proposed to identify appropriate indicators and validate their effectiveness. Various scenarios will be proposed based on the collected data, providing insights into the potential applicability of these biomarkers in diverse clinical and therapeutic contexts.

A set of biomarkers will be defined for the identification of patients with PD by comparing their data with those of healthy participants. Another collection of biomarkers will be calculated to predict MDS-UPDRS scores in patients with PD using the labeled sessions, enabling a more detailed understanding of the relationship between the recorded signals and clinical evaluations.

In addition, a comparative analysis will be undertaken using the previous or new biomarkers between measurements collected in supervised clinical contexts and those recorded in unsupervised, free-living conditions. Similarly, the validity and performance of the proposed biomarkers will be examined across different age groups, given the motor variability present among various age ranges. This will help determine the consistency and reliability of the data across different contexts. Furthermore, the study will explore the correlation between the specific free-living exercise, which is strongly linked to bradykinesia, and the MDS-UPDRS exercises of the Monipar sequence. This correlation will be examined for both data collected at the APM and at the participants' homes, providing insights into how specific activities reflect the motor symptoms in patients with PD across diverse settings.

To define these potential biomarkers, data analysis methods are developed and organized according to a data analysis workflow. As the entire database is based on the triaxial accelerometer and gyroscope signal, the pipeline will be applied to the whole database. Figure 6 shows the proposed pipeline. All data analysis will be conducted using Python (Python Software Foundation) and MATLAB (MathWorks).

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Figure 6. Data analysis pipeline.

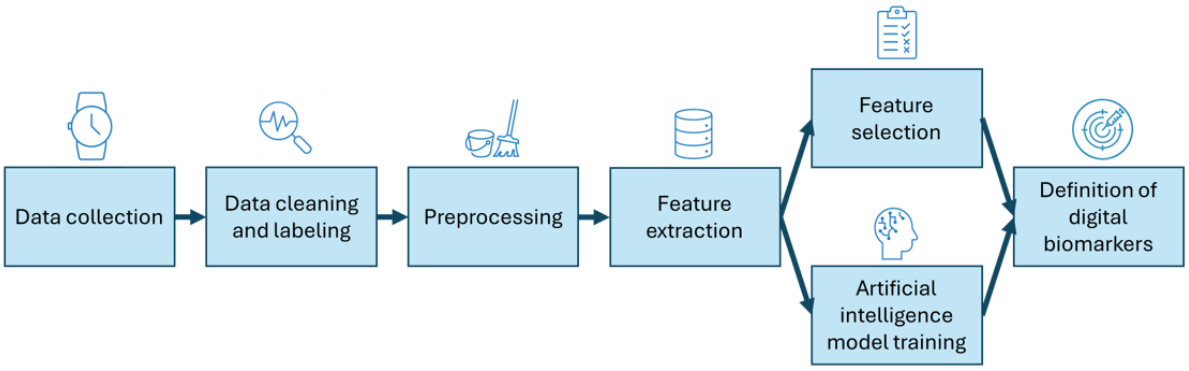

First, the correct recording and collection of the expected data for each participant will be verified to ensure that all records are properly saved and stored. Once confirmed, the data will be labeled by combining the signals collected from the smartwatch with the activity tags generated by the smartphone. The 8 exercises of the Monipar sequence and the forced free-living activity will be tagged, with automatic tagging enabled by the synchronization between the 2 devices. However, a manual check will be conducted to ensure the accuracy of the start and end times for each tagged activity.

An individual analysis will be conducted for each participant's data collected in unsupervised, free-living conditions to assess the reliability and trustworthiness of the signals. Although all participants will receive the same clear and standardized instructions, this step helps ensure that variations in guidance do not impact performance. To achieve this, the signals recorded in a supervised setting—reviewed by at least 4 experts (including a physiotherapist specialized in MDS-UPDRS and 3 other researchers or engineers to ensure correct exercise performance)—will be used as a reference for comparison with those recorded during free-living conditions. This will be done both for the set of exercises of the Monipar sequence and for the forced free-living activity.

Participants with corrupted, incomplete, or inaccurate data will be considered for inclusion only if they possess a complete supervised recording and at least half of the expected unsupervised data, ensuring sufficient data quality for reliable analysis.

The sessions conducted at the beginning and end of the study for the PD group will also be labeled, as these recordings are accompanied by evaluations performed using the MDS-UPDRS by a physiotherapist specialized in PD. It is crucial to highlight that the initial and final MDS-UPDRS assessments are performed by the same evaluator, who will evaluate each of the MDS-UPDRS exercises performed. This introduces 2 sources of subjectivity: one related to the evaluator's individual judgment and the other inherent to the interpretation and use of the MDS-UPDRS scale, which is subjective by nature. To mitigate this potential bias, the evaluator had undergone standardized training procedures before assessments, and intrarater reliability will be monitored throughout the study to ensure consistency in scoring. These scores serve as the reference label for assessing the participant's current condition and can be used to categorize individuals into groups based on the intensity of motor symptoms.

Once the data have been labeled, a preprocessing step will take place. During this phase, various actions will be performed depending on the specific analysis objectives. These actions include combining the 3 signals from each sensor using the Euclidean norm; applying filters (eg, low-pass, high-pass, or band-pass) to isolate specific frequency ranges; segmenting the signal into windows with or without overlap; resampling the signal to a different frequency; or transforming the time-domain signal into the frequency domain, for example. These preprocessing steps aim to prepare the data for further analysis, ensuring that the signals are in the optimal format for extracting meaningful insights.

Following the preprocessing phase, feature extraction will be conducted to identify and compile characteristics from the processed signals for further analysis. This process transforms raw data into a structured set of measurable attributes or features, facilitating analysis or modeling. The goal of this step is to reduce data complexity while preserving its most relevant and informative aspects. Extracted features may encompass statistical properties of the signals, such as mean, SD, or range, in both time and frequency domains [49]. In addition, they may be derived from mathematical computations or based on biomechanical analyses of the movements performed, targeting specific motor symptoms, including resting tremors, bradykinesia, or gait abnormalities.

Depending on the amount of extracted features, it may be beneficial to reduce their number, as a manageable and well-defined set of characteristics is essential for establishing reliable biomarkers.

Statistical and probabilistic analyses will be performed using the proposed features to identify potential biomarkers that correlate with the various PD symptoms being studied. These biomarkers may be consistent across all symptoms or distinct for each symptom, as well as for different activities.

Furthermore, artificial intelligence classification models will be developed using the proposed features. Given the medical context of this study case, it is crucial that the models are interpretable and explainable. To achieve this, machine learning algorithms such as random forests or decision trees will be used, as these models can be subjected to explainable artificial intelligence techniques. In addition, deep learning models will

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be incorporated to enhance the predictions made by the machine learning models. The most relevant features will be extracted from the models to identify digital biomarkers for motor symptoms of PD.

The evaluation of the classification models will be assessed through a confusion matrix, alongside metrics such as sensitivity, specificity, or accuracy. Other performance measures, such as the area under the receiver operating characteristic curve, could be considered to offer a more thorough evaluation of the model's effectiveness.

In unsupervised measurements conducted at participants' homes, the MDS-UPDRS score determined in the clinical setting can be used as a benchmark to evaluate its alignment with the results obtained from these unsupervised measurements. However, considering the intrinsic subjective nature of MDS-UPDRS labeling, unsupervised learning methods, such as association rules or clustering algorithms, will also be explored to analyze the assessment of the exercises performed to uncover data-driven patterns. This approach aims to provide a complementary perspective and reduce reliance on subjective evaluations.

In addition, the 4-hour period of free-living activity, recorded alongside the patient's self-reported medication intake times, will be analyzed to assess the relationship between medication administration and the patient's condition during the period of inertial signal recording. This analysis will involve segmenting the free-living activity data into periods before and after medication intake and comparing the evolution of the inertial signal and defined biomarkers during these periods.

All relevant features, both before and after model training, will be examined and used to define the biomarkers. These biomarkers will serve several purposes: differentiating patients with PD from healthy participants, assessing the MDS-UPDRS stage in both supervised and free-living conditions, and evaluating the ability of free-living activities to correlate with the disease stage of each patient. In addition, these biomarkers will help elucidate the relationship between the MDS-UPDRS assessment and free-living motor activities and assess the impact of surgical and therapeutic treatments and interventions on motor performance.

Technical Support

At the beginning of their participation in the study, each participant receives a detailed set of instructions designed to facilitate understanding and adherence during the week of free-living monitoring. These instructions primarily consist of image-based guidelines to ensure clarity and ease of comprehension. These visual instructions are provided to each participant in printed form for convenient reference throughout the study. In addition, participants are given the phone number of a research team member, which is prominently displayed on their smartphone wallpaper and included in the instruction materials, allowing them to reach out with any questions or concerns during the study.

In addition, as participants in the PD group are members of the APM, they will receive personalized follow-up regarding their participation in the study. For individuals with whom in-person contact will not be possible, phone calls will be made—upon request—to remind them of specific aspects of the study. Furthermore, the final evaluation questionnaire will include a question regarding the participants' willingness to receive further follow-up through alerts or calls. Once data collection is complete, a detailed analysis of each participant's actual follow-up will be conducted to assess adherence to the study protocol.

Ethical Considerations

The study protocol was approved by the ethics committee of the Universidad Politécnica de Madrid (reference numbers: BDPLEDEMDP-IPG-HUMANOS-20231030; BDPLEDEMDP-IPG-DATOS-20231030). The ethical guidelines established clear procedures and responsibilities for managing data protection before the processing of any personal data, ensuring full compliance with legal regulations and adherence to best practices in research. Personal data, including participants' names and contact details, will be recorded on paper and securely managed by the designated data controller for the project. The data controller will pseudo-anonymize these records by substituting identifiable information with an alphanumeric code, according to the Spanish data protection agency.

This unique code will be used to log all other participant information, such as gender, age, educational level, profession, handedness, clinical data, and additional comments, into the project's digital database. Researchers will have access only to this anonymized digital database and not to the original paper records containing identifiable information.

In addition, the database will include sensor data collected through a custom app developed by the research team, as well as health indicators obtained via smartwatch and smartphone apps. Tam et al [52] noted that many remote monitoring devices lack official medical certifications, raising questions about the validity and security of the collected data. However, the smartwatch used in this study has received several approvals from the United States Food and Drug Administration or the Conformité Européenne Marking for its use for functionalities such as sleep apnea detection and electrocardiogram monitoring.

To set up these devices, nonpersonal user accounts will be established, which will collect only physical attributes, such as height and weight, necessary for the accurate measurement of participants' physical activity. Similarly, the devices will be configured to avoid the collection of GPS data, audio, video, images, or any other personal information that could potentially compromise individual privacy. These measures ensure the secure and ethical handling of sensitive participant data throughout the study.

Although previous studies have highlighted a lack of consensus among patients regarding data ownership and access, suggesting shortcomings in the communication and understanding of informed consent procedures [52], in this study, all participants will be thoroughly informed about the study details before their participation begins. Written informed consent will be obtained from each participant in accordance with Good Clinical Practice guidelines and International Conference on Harmonization standards. Furthermore, each participant will be provided with a copy of the signed consent form to allow them to review the

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terms at any time, thereby reinforcing transparency and autonomy in the data collection process.

Participation in this study is completely voluntary. Participants can withdraw at any time without providing a reason, and their decision will not affect the quality of care or services they receive from the organization. Upon withdrawal, any data previously collected from the individual will be excluded from the analysis, and no replacement participants will be recruited.

Results

Recruitment for the study commenced in December 2024 and will continue until spring 2025. The findings from this study are anticipated to be published by late 2025 or early 2026. Furthermore, the results will be disseminated to national and international patient organizations, as well as shared with the public. The database generated will be published at European public repositories.

Discussion

Anticipated Findings

This paper presents the research protocol for the BioClite project at APM, a study focused on monitoring PD using smartphones and smartwatch sensors. The study aims to compile a dataset comprising 20 participants with PD and 20 healthy controls for assessing motor symptoms in individuals diagnosed with PD. The ultimate goal of the study is to facilitate the definition of digital biomarkers for assessing motor symptoms in patients with PD.

In recent years, the use of technologies such as smartphones [53], smartwatches [46], and other wearable sensors [32,54] for monitoring PD has garnered increasing attention. Furthermore, advancements in computational capabilities have enabled the development of algorithms capable of recognizing complex movements and patterns [25]. These developments highlight the considerable potential of portable solutions to effectively monitor PD and provide valuable insights into its progression and management.

The high variability in motor symptoms associated with PD necessitates the evolution toward continuous patient monitoring. In consequence, the BioClite study aims to bridge this gap by transitioning from controlled clinical assessments to follow-up in nonsupervised free-living environments, as high variability in motor symptoms associated with PD necessitates the evolution toward continuous patient monitoring.

This approach involves evaluating participants through the MDS-UPDRS exercise sequence and the specific free-living activity of beating eggs by analyzing accelerometer and gyroscope signals from a commercial smartwatch. These activities are performed in both supervised clinical settings and unsupervised free-living conditions. Although the inclusion of structured tasks introduces a semisupervised element, it achieves a necessary balance between methodological standardization and validity for initiating the transition to free-living contexts. This dual approach ensures a comprehensive assessment of motor symptoms under controlled conditions and in participants' daily lives.

The proposed biomarkers will be designed for app in both supervised clinical context and unsupervised free-living environments, enabling neurologists and PD specialists to evaluate symptoms and monitor their progression across both contexts.

Limitations

Despite its potential, the study has several limitations. The data collection period is limited to a week, which may not fully capture the long-term variability of symptoms in PD. In addition, the inclusion of unsupervised data introduces potential biases. Although efforts are made to standardize data collection (eg, tagging activities and monitoring data quality), variations in how participants perform tasks in a free-living environment cannot be fully controlled. Advanced signal processing techniques and robust filtering methods will be explored to mitigate these effects.

Another challenge relates to participant adherence. Not all participants may complete the entire protocol or provide the expected volume and quality of data. Variations in motivation, cognitive impairment, or practical barriers (eg, technical issues) could reduce the completeness of the dataset. Personalized follow-up and automated reminders will be used to improve adherence.

Future research will focus on exploring the use of this technology in long-term study periods to assess the potential use of the defined digital biomarkers for continuous and free-living monitoring between clinical visits. Moreover, the approach developed here can be adapted for use in clinical trials and therapeutic monitoring. Integration into digital health platforms may support large-scale longitudinal studies and personalized medicine approaches in PD.

Both the anonymized dataset and the results of the study will be made publicly available, supporting transparency, reproducibility, and further research in the field of PD digital health.

Conclusions

This study represents an important first step toward the implementation of free-living monitoring for PD. It provides evidence that a simplified protocol, combining structured and daily-life tasks, can be used to detect PD and monitor motor symptoms in real-world conditions. The proposed methodology may support the detection of PD, as well as the evaluation of disease progression and therapeutic effects. The development of digital biomarkers from these data could substantially improve the clinical management of PD.

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Acknowledgments

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Authors' Contributions

CPF, MCC, LS, and I Pavón contributed to the conceptualization of the study. Data curation was carried out by CPF, MCC, and MG. Formal analysis was performed by CPF, MCC, and MM. I Pavón secured funding for the project. Methodology was developed by CPF, MCC, and I Pavón. Project administration was managed by JCMC and I Pavón. I Pavón also contributed to resource provision and supervision. Visualization was handled by CPF and I Pavón. The original draft was written by CPF, MCC, MM, LS, and I Pavón. CPF, MCC, LS, GDA, MG, MM, I Pareés, JCMC, and I Pavón were involved in reviewing and editing the manuscript. All authors have read and agreed to the published version of the manuscript. During the preparation of this work, the authors used DeepAI [55] to assist with stylistic editing. Following the use of this tool, the authors thoroughly reviewed and revised the content and assumed full responsibility for the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

APM: Asociación Parkinson Madrid
BioClite: Digital Biomarkers for the Assessment of Motor Status in Parkinson's Disease Patients With Clinical and Therapeutic Application
MDS-UPDRS: Movement Disorder Society-Unified Parkinson's Disease Rating Scale
PD: Parkinson disease

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Protocol

Assessing Clinical Impressions of Early Warning Score Integration With the Rapid Response Team: Protocol for a Prospective Cohort Study

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Abstract

Background: The use of early warning scores (EWSs), which integrate real-time vital sign monitoring, can help rapid response teams (RRTs) proactively identify patients at risk of deterioration. However, existing EWSs demonstrate limited evidence for the reduction of clinically important adverse events. The Visensia Safety Index (VSI) is an EWS that combines heart rate, blood pressure, temperature, oxygen saturation, and respiration rate vital sign information to generate a VSI acuity score ranging from 0, signifying the lowest risk of deterioration, to 5, signifying highest risk of deterioration. Continuous monitoring of the risk of deterioration, with alerts triggered by a score of 3.0 or greater, prompts medical attention.

Objective: This protocol outlines the methodology for assessing the feasibility of combining a portable continuous vital sign monitoring system (Masimo Root Monitor) with VSI monitoring to evaluate patients at high risk of acute deterioration at The Ottawa Hospital (TOH).

Methods: This 2-phase, prospective cohort study will be conducted at TOH. Patient participants will include adults (≥18 years) with high-risk conditions, such as those undergoing high-risk elective surgery, malignant hematology or oncology patients, and those admitted with infections. Exclusion criteria include patients receiving comfort care or those in specialized units requiring higher-level monitoring. Eligible patients will be monitored using the VSI with alerts to trigger rapid response team evaluation. In tandem, health care workers including physicians, nurses, and research staff who are involved in patient care and monitoring will be recruited for semistructured interviews. These interviews will explore health care providers' clinical impressions of the VSI as an EWS to identify barriers and enablers to implementation using the Consolidated Framework for Implementation

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Research. Interviews will assess impressions of the monitoring technology, clinical workflow challenges, and perceptions of implementation. Data analysis will involve directed content analysis of interview transcripts to identify barriers and drivers for successful implementation. Furthermore, the feasibility of the VSI will be assessed by evaluating the proportion of continuous data successfully collected and transmitted, the timeliness of VSI-triggered alerts and their communication to the RRT team, the regular updating of the predictive tool, the rate of reported VSI-triggered events, and the completion rates of study-related tasks by research and clinical staff.

Results: As of April 2025, we can report that enrollment is complete, and analysis of the results is ongoing. Interviews are still being transcribed and analyzed. We anticipate submission for publication of the results of the study by the summer of 2025.

Conclusions: The execution of this prospective, mixed methods feasibility study requires a multidisciplinary effort. The study uses continuous vital sign monitoring, combined with prediction of deterioration risk, used to activate the RRT. Evaluating the feasibility and clinical impressions of this trial implementation is the first step in exploring monitoring-based predictive decision support.

Trial Registration: ClinicalTrials.gov NCT05108376; https://clinicaltrials.gov/study/NCT05108376

International Registered Report Identifier (IRRID): DERR1-10.2196/65360

(JMIR Res Protoc 2025;14:e65360) doi:10.2196/65360

KEYWORDS

early warning score; Visensia safety index; rapid response team; intensive care unit; critical care; resuscitation

Introduction

Many hospitals have adopted rapid response teams (RRTs) that often include registered nurses (RNs), respiratory therapists, and physicians who provide urgent critical care expertise to assist with managing unstable patients outside of the intensive care unit (ICU) [1,2]. Early warning scores (EWSs) incorporate routinely collected data such as vital signs or laboratory results to provide a systematic, evidence-based approach for identifying vulnerable patients for assessment before a critical deterioration event [3]. Although numerous EWSs exist, many are based on a single vital sign, thereby relying on a single vital sign crossing a static threshold without accounting for trends over time or the interplay between multiple physiologic changes. For example, tools like the National Early Warning Score or Between-the-Flags primarily use fixed criteria to detect abnormalities, which can result in low sensitivity and missed detection of complex deterioration events [4]. This is in line with the traditional and current metric for monitoring deterioration with vital signs often monitored intermittently, with abnormal values flagged manually or through basic thresholds in electronic medical records [5,6]. However, this approach can delay the identification of clinical deterioration, as it may not account for trends over time or the combined significance of multiple vital sign abnormalities [6,7]. Importantly, delayed detection of patient deterioration has been associated with adverse outcomes, including higher rates of ICU admission, prolonged hospital stays, cardiac arrest, and mortality [8,9]. Recent evaluations of single vital sign–based EWS tools like the Queensland Adult-Deterioration-Detection-System and the electronic Cardiac Arrest Risk Triage Score (eCART) highlight variability in predictive accuracy, with eCART demonstrating superior sensitivity but also higher alerting rates, which can overwhelm clinical workflows [10]. Additionally, while EWS and RRT systems are widely implemented, evidence of their effectiveness in reducing hospital mortality, unplanned ICU admissions, and other adverse outcomes remains limited and of low certainty, underscoring the need for standardized outcome measures and improved methodologies in future studies [11].

In contrast to relying solely on a single vital sign for cues of deterioration, OBS Medical's Visensia Safety Index (VSI) is an EWS that uses physiological monitoring software and machine learning to identify the likelihood of deterioration that may lead to cardiac or respiratory arrest [3,5]. As depicted in Figure 1, the VSI is a continuous measure that combines 5 vital signs—heart rate, blood pressure, temperature, oxygen saturation, and respiratory rate—into a single acuity score ranging from 0 (lowest risk) to 5 (highest risk). This score is recalculated in near real-time, with updates occurring at one-minute intervals as new vital sign data are collected. A score of 3.0, or a predetermined threshold determined based on clinical context, or greater represents a critical threshold, suggesting a significant risk of clinical deterioration and prompting an alert to the RRT [4]. The dynamic nature of the VSI allows for continuous monitoring of patient stability and early identification of deterioration trends, enabling timely interventions. Unlike traditional Early Warning Scores, VSI dynamically integrates multiple parameters into a single metric, enabling earlier and more precise detection of deterioration trends. While all five vital signs contribute to the VSI calculation, the system can operate with a minimum of three input parameters, ensuring functionality even when some data are unavailable. This capability makes VSI particularly robust for continuous patient monitoring in dynamic clinical environments.

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Figure 1. An infographic showing the patient setup for this study. Image created on BioRender. SpO2: oxygen saturation; VSI: Visensia Safety Index.

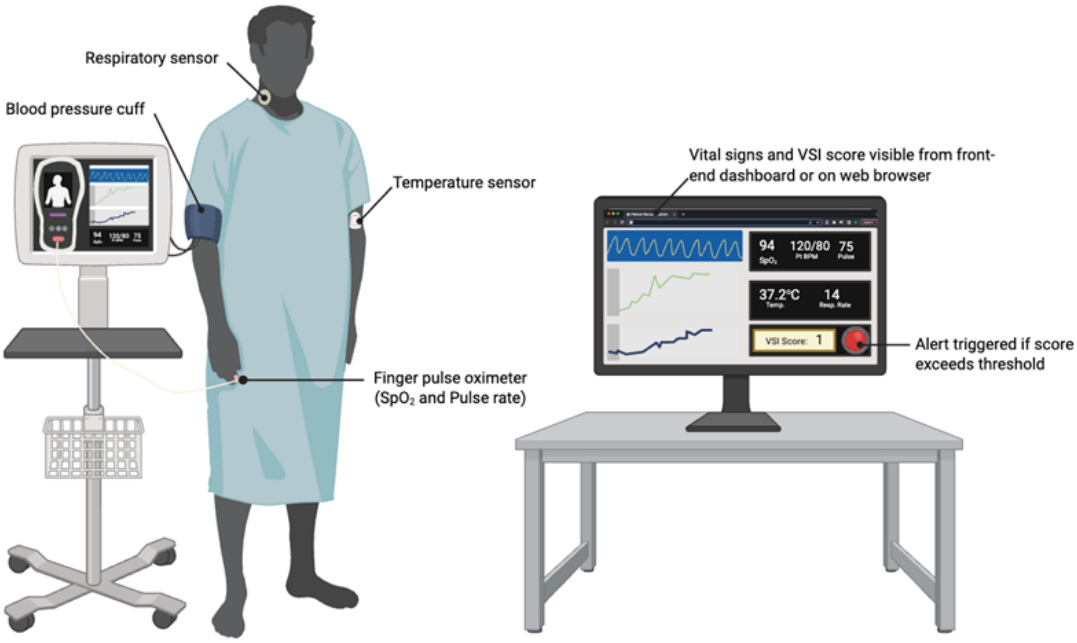

A retrospective cohort study of 168 patients found that 95% of the episodes of severe physiological abnormalities were identified by the VSI system and deemed valid, defined as requiring a change in clinical management [12]. A 3-phase prospective study was implemented for validation at the University of Pittsburgh Medical Centre, which included a continuous collection of cardiorespiratory variables in a non-ICU patient population [13]. Patients monitored with VSI had a statistically significant shorter average duration of any instability, shorter average duration of physiological instability, and fewer episodes of serious and persistent instability [13]. While continuous monitoring likely contributes to these outcomes, the VSI integrates multiple physiological parameters into a single predictive score, enabling earlier identification of deterioration trends compared to traditional EWS. By providing a more comprehensive and dynamic view of patient stability, VSI facilitates timely clinical interventions that may not occur with traditional monitoring systems alone [4].

A recent retrospective cohort study at The Ottawa Hospital (TOH) compared outcomes for patients who would have had an EWS alert, triggered by VSI or the National Early Warning Systems 2 (NEWS2), prior to RRT activation to patients without an EWS alert [14]. It was found that an EWS would have identified earlier deterioration for over half of the patients; however, clinical impact requires interventional study. While both the VSI and NEWS2 may have contributed to the favorable findings of early deterioration detection, EWS like NEWS2 have limitations in sensitivities, underscoring the need for more dynamic tools like VSI to improve early detection in real-world settings [5,15].

Studies involving multiparameter EWS, like the VSI, have shown promise in identifying patient deterioration earlier than clinical judgment alone, much of the existing work has been limited to proof-of-concept or validation studies, which do not address the complexities of real-world implementation. The integration of such tools into hospital workflows remains challenging due to the numerous moving parts required for successful adoption, including technical barriers, clinician buy-in, and alignment with existing clinical processes. These barriers underscore the critical need for feasibility studies that evaluate not only whether the system can be implemented within a hospital context, but also how its integration could be improved by incorporating feedback from healthcare providers. This study offers a protocol designed to address these gaps by taking a focused approach to feasibility: assessing the practicality of implementation at a single institution and identifying key barriers and enablers to facilitate smoother adoption at other sites.

The objectives of this study are to evaluate the initial clinical impressions and feasibility of using a portable monitoring system with a VSI trigger. More specifically, feasibility will be assessed by examining the proportion of continuous data successfully collected and transmitted, the frequency and timeliness of VSI-triggered alerts, the regular updating of the predictive tool, and the completion rates of study-related tasks. Clinical impressions will be explored through qualitative interviews with physicians, nurses, and research staff, focusing on barriers and enablers to implementation, perceived strengths and limitations of the system, and its integration into clinical workflows (Table 1). Overall, this protocol paper seeks to outline the methodology for evaluating the feasibility of integrating a portable continuous monitoring system using the

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VSI and exploring clinical impressions of its implementation to identify barriers, enablers, and potential clinical impact.

Table 1. Description of the study's primary objectives of feasibility and impact as well as how each will be evaluated and monitored.

Evaluation component	Objective	Objective description	Evaluation of objective
Evaluation	Feasibility	Evaluate the practicality of continuous data collection, continuous data feeding, regular updating of the predictive tool, and communication with the RRT[a].	This study will be considered "technically feasible" if 80% of (a) continuous data are collected, (b) continuous data are fed to the predictive tool, (c) the time the predictive tool is updated on a regular basis, and (d) of triggers are reported to the RRT team.
Evaluation	Barriers and enablers to implementation	Perform a qualitative analysis of physicians, nurses, and research personnel regarding impressions of the predictive tool, perceived strengths and limitations, and perceived enablers and barriers to effective usage.	Physician, nurse, and research personnel opinions regarding impressions of the predictive tool, perceived strengths and limitations, and perceived enablers and barriers to effective usage will be evaluated through theory-driven postencounter interviews.
Impressions	Clinical impact	Compare the predictive performance of the VSI trigger to clinical gestalt.	Clinical impact will be assessed by the patient acuity rating [15], and performance measures including sensitivity, specificity, positive predictive value, and negative predictive value.

[a]RRT: rapid response team.

Methods

Overview

This study uses a mixed methods design to comprehensively evaluate the feasibility of implementing a portable continuous monitoring system with VSI-triggered alerts. The quantitative component focuses on assessing feasibility outcomes, such as data collection and transmission rates, VSI alert timeliness, and completion rates of study tasks. The qualitative component involves semistructured interviews with healthcare providers to explore their clinical impressions, including barriers, enablers, and perceptions of usability and integration into workflows. Together, these complementary approaches aim to provide a holistic understanding of the implementation process.

Study Setting

This study will be conducted at both the Civic Campus and the General Campus of TOH. Each campus has a tertiary-level, mixed medical-surgical ICU with a 32-bed capacity that uses the same RRT activation criteria and institutional database, although each caters to a different patient population. Specifically, patients at the General are typically from the hematology, medical oncology, and thoracic surgery wards, whereas those from the Civic are trauma, neurology, neurosurgery, or vascular cases.

The criteria for RRT activation were defined as concerns relating to the airway, consciousness, cardiovascular system, or other markers of deterioration as deemed by clinical discretion. Data for the RRT database will be prospectively gathered by the responding RN using a standardized data collection form at the time of patient assessment.

Eligibility Criteria

Selection criteria for patient participants and VSI users who will participate in the subsequent semistructured interviews are outlined in Table 2. The study population will include patients outside of units with high-level monitoring, such as ICUs, as these areas already have continuous vital sign monitoring systems in place. Eligible participants will be adult patients (≥18 years) admitted to general medical or surgical wards across the two hospital campuses, which each have mixed medical-surgical ICUs with 32 beds. Patients categorized as "Category 1–Full Care" will be included as they will have no limitations on critical care interventions. Patients with "Category II, III, and IV" statuses are excluded due to goals of care that prioritize comfort or limited interventions, which do not align with the proactive monitoring and management strategies being evaluated in this study (Table 2).

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Table 2. Inclusion and exclusion criteria for patients and clinicians.

Criteria	Inclusion	Exclusion

Patient participants	• Adult patients (≥18 years of age) designated for the most aggressive levels of potential intervention (Category 1 status–Full Care) belonging to any of the following:
	  • Patients who have undergone high-risk elective surgery.
	  • Malignant hematology or oncology patients at high risk for deterioration.
	  • Patients with infections admitted from the Emergency Department to the ward.
	  • Other high-risk patients determined at the discretion of RRT[a] physicians with agreement from the patient's MRP[b].
		• Patients admitted to a unit with higher-level monitoring, including the Neurological Acute Assessment Unit, Acute Monitoring Area, Trauma Step-Down, or Intensive Care Unit.
		• Patients in Category II, which includes full care except for CPR[c], Category III which includes full care except respiratory or hemodynamic life support, or CPR or category IV status, which is focused solely on Comfort Care.

Visensia Safety Index users	• Physicians, RNs[d], and research personnel who consent to participate in an interview and are the enrolled patients: • RRT physician or ward physician. • RRT RN or ward RN. • Research personnel.	• Physicians, RNs, or research personnel unable to complete the interview in English.

[a]RRT: rapid response team.
[b]MRP: most responsible physician.
[c]CPR: cardiopulmonary resuscitation.
[d]RN: registered nurse.

Design

This study uses a prospective, mixed methods feasibility design. The enrollment and monitoring involve the patient's most responsible physician, and members of the RRT including physicians, RNs, or respiratory therapists. Eligible patients will be identified based on the inclusion criteria listed in Table 2 and approached for potential consent. During the initial interaction, research staff will discuss the study protocol, review eligibility criteria, and assess willingness to participate. Written consent will be obtained from patients prior to initiating monitoring, A study summary is depicted in Figure 2 highlighting the study timeline and steps followed in this study.

Figure 2. Visual overview of study timeline and design with emphasis on overlap in study timeline with semistructured interviews beginning 3 months after patient enrollment. RRT: Rapid Response Team.

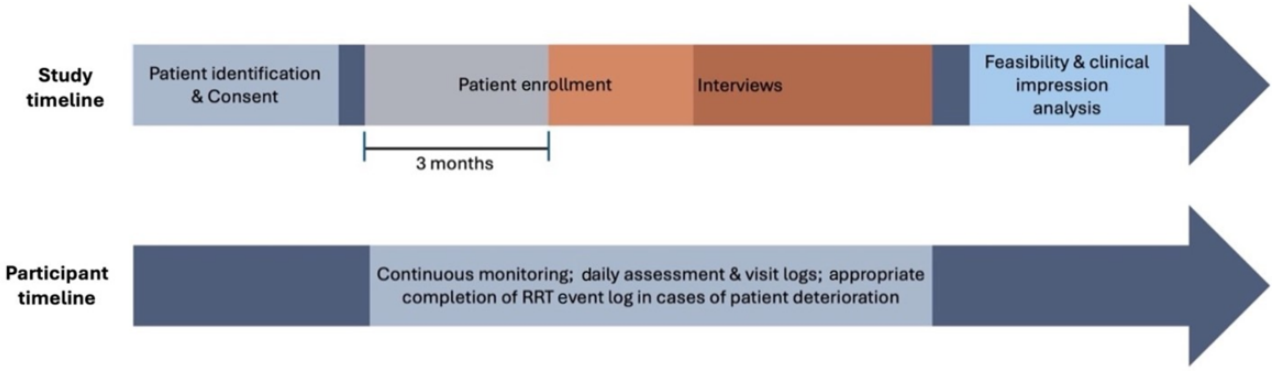

Monitoring

After enrollment, the patient will be connected to a vital sign monitor (VSM). The Masimo Root monitor, a portable continuous monitoring device that integrates multiple physiological parameters, including oxygen saturation, pulse rate, and respiration rate, will be used in this study. For this study, the device is equipped with a continuous monitoring license, which allows it to perform uninterrupted data collection and enable the calculation of VSI scores. This ensures seamless monitoring and timely alert generation for high-risk patients. Research staff or the RRT RN will ensure that the patient's data output is visible at the RRT monitoring station set up in the ICU. The monitoring system will send vital signs data to the VSI vital sign platform (VSP) server, which will process the data and calculate the VSI score, which will appear at a monitoring station set up in the ICU. VSI notifications will also be available on a mobile device carried by RRT members.

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Of the 5 vital signs monitored, a minimum of 3 are required by the VSI to calculate a patient's acuity score. To ensure accuracy, all components measuring vital signs must be appropriately connected to the patient and the VSM. As depicted in Figure 1, for the Masimo Root monitor, the patient has (1) a temperature sensor patched above the cubital fossa, (2) a finger pulse oximeter measuring oxygen saturation and pulse rate on the index finger, (3) a blood pressure cuff on either arm that intermittently inflates, and (4) a respiratory sensor placed to enable auscultation of breathing laterally to the thyroid cartilage. The RRT physician and RN can view and monitor all enrolled patients and their VSI index via the VSP front-end dashboard, which can be accessed via a standard web browser or approved mobile devices. For the Masimo VSM, viewing acuity scores across devices is only possible if the VSM is connected to a local Wi-Fi network. A visual setup of the study can be seen in Figure 1.

Patient and Study Team Timeline

Once the patient is on continuous monitoring, the following will be completed on a daily basis:

1. The patient is clinically assessed in person by the RRT, as per the standard of care for patients on the RRT roster. These assessments will include a clinical evaluation of the patient's condition, a review of vital sign trends, and any alerts generated by the VSI.
2. The RRT RN completes the Daily RRT visit log to capture the opinion of deterioration risk for the ward and RRT staff and the status of VSI monitoring. This includes the nurse's assessment of the patient's risk of deterioration based on clinical judgment, observations of vital sign trends, and any relevant changes in the patient's condition.
3. The RRT RN completes the RRT event log for any calls to the RRT for patients.
4. The research coordinator completes the patient's case report form, capturing demographic data as well as any deterioration events and outcomes.

Response Team Activation

The RRT RN will clinically assess a patient on the inpatient ward if an RRT call is (1) activated traditionally at the clinical discretion of the MRP team or RN or (2) activated by the VSI trigger. Importantly, VSI does not directly lead to clinical decision-making. Clinical decision-making will depend upon the assessment by the practitioners on the RRT.

In this study, the VSI critical threshold is defined as ≥3.0, which is an indication to practitioners of potential deterioration, defined as being a rapid and negative decline in monitored vital signs that require clinical monitoring or intervention. When the VSI reaches ≥ 3.0, the RRT is signaled for activation. This threshold may be changed during the study to balance sensitivity and specificity appropriate to the target population and clinical context. Adjustments will be made based on real-time observations of system performance and clinical relevance, aiming to ensure optimal detection of deterioration while minimizing false alerts. Any changes to the threshold will apply to all enrolled patients to maintain consistency.

The RRT RN will call or visit the ward to discuss the patient's potential deterioration if a VSI alert is triggered. If erroneous or artefactual data are suspected, the bedside and RRT RNs will troubleshoot the monitoring issue with support from research staff as required. If deterioration is suspected, an RRT member will visit the patient and initiate a formal RRT call if warranted. Patient participation in the study will be complete when continuous monitoring is no longer required, following a minimum of 48 hours and up to a maximum of 10 days. Patients will be followed via their electronic medical records until hospital discharge. Importantly, the maximum monitoring period of 10 days was determined based on the study's data storage and management capabilities, as this is a pilot study to evaluate the feasibility of using VSI acuity scores. Monitoring duration for each patient will be decided collaboratively by the research team and clinical staff, considering the patient's clinical condition and study requirements. A future study could evaluate the long-term use of VSI scores beyond this threshold to assess its utility.

Interviews

Incorporating a portable continuous monitoring system with a VSI trigger into practice constitutes a complex intervention [7,9]. Therefore, we will conduct postimplementation semistructured interviews with involved physicians, RNs, and research personnel members of the RRT and wards where the portable continuous monitoring with VSI trigger is implemented. Importantly, despite not being part of the clinical team, research personnel were involved in setting up the study, including backend management of the VSI acuity score generation and ensuring proper functionality of the monitoring systems used in the study. Their expertise with the technical aspects of the VSI system and its integration into workflows makes their insights valuable in evaluating the ease of implementation and identifying potential barriers or enablers. Including them in interviews allows for a comprehensive assessment of the implementation process from both technical and clinical perspectives.

Interviews will be 30 to 45 minutes in anticipated length and structured using the Consolidated Framework for Implementation Research (CFIR) [16-18]. This framework describes the range of the barriers and drivers to the effective implementation of complex interventions at multiple levels and among many stakeholders; it has been used in health care settings to evaluate the implementation of innovations [17,19,20]. We will select CFIR constructs relevant to the current implementation collaboratively with the research team. We will develop questions relevant to each selected construct to explore the range of barriers and drivers to using the Masimo monitoring and VSI trigger–induced alerts and evaluate health care providers' intentions to use such EWS in clinical practice. The guide will be pilot-tested for length, clarity, and comprehensiveness and revised as needed.

Potential interviewees will be identified by the research team and emailed an initial invitation and consent form to participate, with up to 2 email reminders. Verbal consent will be obtained at the time of the interview. Interviews will be divided into 2 sections. Section 1 will include background and demographic

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questions. Section 2 will assess potential barriers and drivers to using the monitoring and alerts according to the CFIR, with particular attention to (1) questions about the monitoring itself and how it compares to current processes, (2) environmental issues around resources and the setting in which the monitoring is being used, (3) the individuals involved in the implementation and other colleagues that may assist with or impede use, and (4) the implementation process itself including the implementation context and the adaptability of the innovation and setting. We will also ask about goals for use, and beliefs about outcomes related to monitoring use (see Multimedia Appendix 1 for the full interview guide including related CFIR constructs). Interviews will be audiotaped and transcribed, and field notes taken during the interview. All physicians, RNs, and research personnel who participate in an interview will receive a token of appreciation for their time and expertise.

Sample Size

The sample size is based on a convenience sample obtainable with the currently available resources. The target feasibility metrics for this study are depicted in Table 1. Projected enrollment is 1-2 new patients per week at both centers for a total of 70 patients over a 10-month period. The sample size of 70 patients was selected to ensure sufficient variability in patient characteristics and clinical scenarios to evaluate feasibility outcomes, including the proportion of continuous data successfully collected and transmitted, VSI alert timeliness, and completion rates of study-related tasks.

Approximately 10-15 physicians, and 10-15 nurses, from both the RRT and ward will be interviewed alongside 2-4 research personnel who are involved in the care of patients enrolled in the clinical implementation portion of this study. Purposive sampling will include consideration of all patient subgroups listed in the inclusion criteria to ensure respondents are from a variety of clinical backgrounds. The interview sample size estimates are based on previous work around theme saturation using theory-informed interviews [21].

Data Management

The output of VSI is comprised of two components: (1) the first produces a real-time risk score based on the patient's own vital signs to ultimately send alerts to clinicians and (2) a user interface with all patients and their acuity continuously displayed and updated. The system has current US Food and Drug Administration (FDA) and Conformité Européenne (CE) clearance.

The VSI is a software application consisting of both a software backend hosted on a hospital server and a front-end dashboard accessible via a web browser. It is backed by two databases: a low-volume database storing the configuration information and a high-volume database storing anonymized vital sign information. Data are fed into the VSP by means of Health Level 7 (HL7), version 2. Feeds communicated once every minute provide a good balance between data storage requirements and data usefulness. They will be correlated to the same anonymous identification number as the vital sign data.

Several options exist for the anonymization of HL7 data from patients, depending on the hospital infrastructure. In this study, the anonymization will be performed on the VSP server via the installation of Mirth Connect before sending the data to the VSP. The VSP's own database (anonymized vital signs) would be accessible by the sponsor (for study management purposes); however, the mapping table between study IDs and Protected Health Information/Personally Identifiable Information would only be accessible by the study data custodian.

Safety Reporting

Any safety issues related to the VSI will be addressed by the study co-principal investigators and study sponsor, OBS Medical. RRT RNs and physicians can bring any safety concerns to the RRT leads, who will communicate these to the study co–principal investigators. Concerns will be discussed and addressed on the same day. All safety issues will also be communicated to OBS Medical. Clinical issues will be addressed by the study co–principal investigators and technical issues will be addressed by OBS Medical. All safety issues will additionally be reviewed during the next monthly steering committee meeting.

All adverse device effects need to be assessed by the site investigator for severity, seriousness, expectedness, and causality/relatedness. The site investigator is required to report serious adverse events or serious adverse device effects to Health Canada and the Regulatory Correspondent within 72 hours of discovery. This includes cases in which the incident relates to the improper functioning or failure of the device or serious deterioration or death of the patient participant. It is expected that any serious untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users, or other persons, whether related to the investigational medical device, will be reported.

Study Management

A steering committee comprised of all investigators will meet monthly to discuss the study's progress. This committee includes representatives from TOH leaders from information services, biomedical engineering, research coordinators, and investigators. Concerns raised by any staff will be evaluated monthly to guide changes to the protocol in an ongoing fashion. Interim results from interviews will be reviewed at every second meeting.

Data Analysis

Table 3 outlines the statistical analysis that will be conducted to evaluate the study objectives.

The study will collect both quantitative and qualitative data to address its objectives. The results evaluated will include outcomes listed in Textbox 1.

Descriptive statistics will summarize feasibility outcomes. Categorical variables will be presented as counts and percentages, and continuous variables as means and SDs (if normally distributed) or medians and interquartile ranges (if nonnormally distributed).

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Table 3. Summary of statistical analysis.

Outcome domain	Objective	Statistical analysis
Evaluation	Feasibility	• Representation of categorical variables as counts and percentages. • Representation of continuous variables with either (1) means with SDs if a normal distribution is followed, or (2) medians with interquartile ranges if a non-normal distribution is followed.
Evaluation	Clinical impressions	• Interview transcripts will be examined to identify barriers and enablers for the implementation of a VSI[a] trigger using content-directed coding into CFIR[b] constructs [8,9]. • Additional inductive analysis of quotations within CFIR constructs for interpretation, with themes being periodically examined for revision, combination, and deletion as needed [12]. • All transcripts will be double coded by 2 independent researchers meeting for consensus regularly.
Impressions	Clinical impact	• Calculation of sensitivity and specificity with respect to the ability of the VSI score to predict intensive care unit admissions. • Analysis of practitioner's initial impressions of the system as well as challenges and benefits to its use.

[a]VSI: Visensia safety index.

[b]CFIR: Consolidated Framework for Implementation Research.

Textbox 1. Feasibility outcomes.

Feasibility outcomes

- The proportion of continuous data successfully collected, transmitted, and analyzed using the Visensia Safety Index (VSI) system.
- The frequency and timeliness of VSI-triggered alerts and rapid response team activations.
- Completion rates for study-related tasks, including data logging, daily assessments, and interviews.
- Technical barriers encountered during system implementation and integration.

Ethical Considerations

This study was approved by the Ottawa Health Science Network Research Ethics Board (OHSN-REB; protocol ID number 20210667-01). Written informed consent will be obtained from all participants, including patient participants and health care providers involved in interviews. Participants will have the ability to withdraw from the study at any time without any consequences. Privacy and confidentiality will be maintained by anonymizing all collected data, including interview transcripts, and storing data securely on encrypted servers accessible only to authorized study personnel.

Clinical Impressions

Semistructured interviews with physicians, nurses, and research personnel will explore perceived barriers and enablers to implementing the VSI-triggered system. Directed content analysis into CFIR constructs will be used to identify barriers and drivers to use the monitoring and alerts in practice [17,18]. Coding according to CFIR allows for implementation-related barriers and drivers to be categorized into a widely understood and clearly defined series of constructs that can be acted upon for improved innovation uptake. For further interpretability of results, we will develop themes within identified CFIR constructs inductively, during consensus meetings between coders. Two reviewers will code all transcripts independently, meeting for consensus to agree on initial and new themes and revise, combine, and delete themes collaboratively.

We will take a reflexive approach to analysis, taking into consideration team members' subjectivity to shape our qualitative methods and conclusions [22]. By having implementation experts from a separate department conduct the interviews we avoid power dynamics that could affect how interviewees respond and remain objective through coding and analysis. Coders have several years of experience in implementation science and qualitative methods and will meet with the wider study team regularly to ensure clinical relevance and credibility of results by involving a diverse team while maintaining objectivity. In using the CFIR framework to guide interviews and coding, we limit the influence of any one individual, while still capitalizing on the experience and expertise of the study team by enhancing the interpretability and applicability of CFIR constructs with inductively developed themes within the constructs. We have also considered methodological reflexivity in adding more general questions about any other issues and general inquiries about the overall impressions of the technology, which are also reflected in our coding plan, ensuring we do not limit responses and theme generation to only include CFIR constructs. Qualitative results will be analyzed alongside the quantitative feasibility data in designing future implementation plans.

Predictive Performance

The predictive performance of the VSI-triggered alerts will be compared to clinical gestalt using sensitivity, specificity, positive predictive value, and negative predictive value. Quantitative data will be analyzed using statistical software, and subgroup analyses will account for variability across patient populations and clinical settings [21].

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Integration and Safety Reporting

Observations of system usage, including technical or clinical safety concerns, will be documented and analyzed. These findings will inform recommendations for future refinements to the monitoring system and its clinical deployment.

Results

As of April 2025, we can report that enrolment is complete, and analysis is ongoing of the results. Interviews are still being transcribed and analyzed. We anticipate submission for publication of the results of the study by the Summer of 2025.

Discussion

Overview

This study aims to evaluate a trial implementation of a protocol to integrate continuous vital sign monitoring, predictive risk assessment for patient deterioration, and RRT activation. This initial implementation of the Masimo Root Monitor with OBS Medical's VSI lays the groundwork for future developments in the field. By evaluating the feasibility of this integrated approach, we aim to participate in the early adoption of artificial intelligence in clinical decision support systems in acute and critical care environments [23]. However, the logistical challenges of collating real-time multidimensional data streams are noted to be a common limitation often ignored during initial validation efforts [23]—an important consideration that this feasibility study is intentionally designed to evaluate. We hypothesize that the integration of the VSI with a portable continuous monitoring system will demonstrate feasibility in clinical workflows and provide valuable insights into its potential to enhance early detection of patient deterioration, streamline RRT activations, and improve clinical decision-making processes.

Comparison to Prior Work

Prior studies, including proof-of-concept work and retrospective analyses have demonstrated the potential of VSI, to identify patient deterioration earlier than traditional methods [3]. Notably, a three-phase prospective study at the University of Pittsburgh Medical Centre showed that integrating continuous monitoring with VSI reduced instability duration and improved patient outcomes [3,4]. However, these studies focused on validation, while this protocol emphasizes feasibility and implementation within real-world workflows at a Canadian tertiary care hospital.

Anticipated Strengths and Limitations

This study's strengths include its use of a mixed methods design, allowing for a comprehensive evaluation of both quantitative feasibility metrics and qualitative clinical impressions. Including a diverse, multidisciplinary team, who meet regularly to discuss study progress, share insights, and document decisions and challenges throughout the study process will improve the credibility, transferability, dependability, and confirmability of results. The use of the CFIR ensures a structured approach to understanding the barriers and enablers of implementation.

A notable limitation is that this study evaluates the feasibility of integrating the VSI within a continuous monitoring system to enhance RRT workflows; however, it does not isolate the independent effects of continuous monitoring, which may itself contribute to improved outcomes or operational efficiencies. Future studies will be required to differentiate the impact of continuous monitoring alone from the added value provided by predictive tools like VSI.

While conducting this study, we anticipate learning from individual patient deployments, particularly in addressing technical requirements and troubleshooting potential issues in integrating the VSI trigger with vital sign monitoring. For instance, as depicted in Figure 1, an acoustic respiratory sensor will be used in this study which requires adequate placement and limited environmental interference (patient talking and vibrations) to be registered and used in the calculation of a VSI acuity score. Moreover, the VSM must be connected to the hospital's Wi-Fi to sync a patient's real-time recorded vitals and their respective VSI to the VSP front-end dashboard that can be viewed by ward or RRT staff via a web browser. Training of research personnel, RRT, and ward staff on the use and maintenance of the VSM with a VSI trigger will allow for an eased integration and use of the system. Another anticipated limitation includes, despite its proof-of-concept work in the early phases of evaluating VSI feasibility and identifying barriers and enablers to implementation, practitioners involved in the care of patients in the study must appreciate that the VSI score must be contextualized by understanding the magnitude and trend of the index as well as the clinical context. We will evaluate clinicians' experience of the monitoring and alerts in this study.

Health care provider perspectives regarding the clinical usefulness and utility of the VSI-based trigger will be evaluated during the semistructured interview portion of this study. It is well-known that the "black-box" nature of algorithms may limit acceptance by the medical community, especially when incongruent with clinical intuition [23]. As such, efforts to measure what matters most to patients and clinicians using evaluation frameworks from implementation science may be particularly valuable [24]. Due to the interdisciplinary nature of implementing such a device, a comprehensive framework is required to understand the barriers and enablers of its use, ways in which it can improve the efficiency and workflow of allied health care professionals within the team, identify necessary behavioral changes to overcome obstacles, and enhance the effectiveness of outcome measurement and comprehension. Such results can be achieved by following CFIR, a meta-theoretical framework that helps practitioners evaluate the implementation process and understand key factors that can impact implementation success. Using CFIR will allow the research team to design a comprehensive implementation plan to minimize barriers and leverage drivers for the integration of the VSI-based alerts and related monitoring more broadly into practice.

A multidisciplinary research team is essential to enable clinical and technical feasibility. The implementation of a VSM with a VSI trigger requires a coordinated effort by research personnel, external partnering agencies, physicians, RNs, and respiratory

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therapists part of RRTs and on the wards. As such, it is vital for all involved members to become familiar with the technical requirements of the portable VSM being used, the predictive algorithm of the VSI, the data management platform, and the VSP dashboard. Moreover, practitioners must be knowledgeable and trained in evaluating VSI-related clinical information on a daily basis with appropriate logging and reporting in the case of deterioration events.

Future Studies

Following the completion of this feasibility study, subsequent research should focus on refining the integration of the VSI into routine clinical workflows. This includes assessing its impact on patient outcomes, such as reducing ICU admissions and preventing adverse events, through a larger interventional trial. Additionally, studies could explore the scalability of this system across hospital settings, including resource-limited environments, and investigate the incorporation of advanced machine learning algorithms to enhance predictive accuracy. Long-term evaluations should also examine cost-effectiveness and sustainability to support widespread adoption.

Conclusion

This study protocol outlines a mixed methods approach to evaluate the feasibility and clinical impressions of integrating continuous VSM with the VSI for early detection of patient deterioration and rapid response team activation. By combining prospective data collection with theory-informed qualitative interviews, this study aims to identify key implementation barriers and enablers within real-world hospital workflows. Findings from this feasibility study will inform the design of future interventional trials and guide the broader integration of predictive monitoring systems into acute care settings.

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Data Availability

Data sharing is not applicable as no datasets were generated or analyzed during the current study. As this manuscript outlines a study protocol, no datasets were generated or analyzed at this stage.

Authors' Contributions

AT and AS drafted the preliminary study protocol. The remaining authors (JB, NH, JH, IW, RP, KK, KH, KT, JH, D Kosevic, D Kubelik, KB, CH, NS, BH, JAK, JP, CB) provided expertise and edits to the final draft. RR drafted the initial protocol manuscript. AS contributed to the overall research supervision, as well as further editing and review

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guide.
[DOCX File , 513 KB - resprot_v14i1e65360_app1.docx]

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Abbreviations

CE: Conformité Européenne
CFIR: Consolidated Framework for Implementation Research
eCART: Cardiac Arrest Risk Triage Score
EWS: Early Warning Score
FDA: US Food and Drug Administration

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HL7: Health Level 7
ICU: intensive care unit
NEWS2: National Early Warning Systems 2
RN: registered nurse
RRT: rapid response team
TOH: The Ottawa Hospital
VSI: Visensia Safety Index
VSM: vital sign monitor
VSP: vital signs platform

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Protocol

Data Collection for Automatic Depression Identification in Spanish Speakers Using Deep Learning Algorithms: Protocol for a Case-Control Study

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Abstract

Background: Depression is a mental health condition that affects millions of people worldwide. Although common, it remains difficult to diagnose due to its heterogeneous symptomatology. Mental health questionnaires are currently the most used assessment method to screen depression; these, however, have a subjective nature due to their dependence on patients' self-assessments. Researchers have been interested in finding an accurate way of identifying depression through an objective biomarker. Recent developments in neural networks and deep learning have enabled the possibility of classifying depression through the computational analysis of voice recordings. However, this approach is heavily dependent on the availability of datasets to train and test deep learning models, and these are scarce. There are also very few languages available. This study proposes a protocol for the collection of a new dataset for deep learning research on voice depression classification, featuring Spanish speakers, professional and smartphone microphones, and a high-quality recording standard.

Objective: This work aims to create a high-quality voice depression dataset by recording Spanish speakers with a professional microphone and strict audio quality standards. The data are captured by a smartphone microphone as well for further research in the use of smartphone recordings for deep learning depression classification.

Methods: Our methodology involves the strategic collection of depressed and nondepressed voice recordings. A minimum participation of 60 subjects was established and 2 health centers were selected to gather data. A total of 3 types of data are collected: voice recordings, depression labels (using the Patient Health Questionnaire-9), and additional data that could potentially influence speech. Recordings are captured with professional-grade and smartphone microphones simultaneously to ensure versatility and practical applicability. Several considerations and guidelines are described to ensure high audio quality and avoid potential bias in deep learning research.

Results: This data collection effort immediately enables new research topics on depression classification. Some potential uses include deep learning research on Spanish speakers, an evaluation of the impact of audio quality on developing audio classification models, and an evaluation of the applicability of voice depression classification technology on smartphone apps.

Conclusions: This research marks a significant step toward the objective and automated classification of depression in voice recordings. By focusing on the underrepresented demographic of Spanish speakers, the inclusion of smartphone recordings, and addressing the current data limitations in audio quality, this study lays the groundwork for future advancements in deep learning–driven mental health diagnosis.

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KEYWORDS

automated depression diagnosis; deep learning for audio analysis; depression binary classification; depression Spanish language dataset; high-quality and smartphone audio recordings; high-quality audio data

Introduction

Background

Depression is a mental health disease that affects around 5% of the world's population; nonetheless, it can go as high as 7% in some countries [1,2]. Despite being a common disease, depression goes frequently undiagnosed or misdiagnosed, preventing affected people from getting the psychological treatment they need [3]. Detecting depression can be difficult, due to a variety of reasons. First, the 2 most common depression symptoms tend to be low energy and sleeping problems, which can be easily found in individuals without depression [1]. Second, although there are many symptoms associated with depression, the patients rarely present all of them, and the combination of symptoms can vary greatly. Fried and Neese [4] (2015) found that only 1.24% of patients showed the most common combination of symptoms. Third, according to the American Psychiatric Association, it is especially difficult to evaluate depression symptoms when they occur in an individual who also has a general medical condition [5]. This is why many professionals seek to use complementary tools in the diagnostic process. Nowadays, most depression diagnosis is done through validated health questionnaires such as the Patient Health Questionnaire (PHQ-9) and the Beck Depression Inventory (BDI-II). However, these diagnostic methods are based on patient self-reports which are influenced by their attitude, expressiveness, and familiarity with the questionnaire [6]. Besides, many people who present depression report not relating to any of the symptoms presented by the questionnaires [1]. This has made researchers interested in finding an alternative and more objective method to identify depression symptoms. Recent research has shown that the computational analysis of speech recordings can be a useful way of identifying depression symptoms objectively. The best algorithms up to this date can perform binary classification with F_1-scores of around 85% [7,8]. This has been made possible by the recent progress in the field of neural networks and deep learning. However, neural networks are heavily dependent on the availability of labeled training data and depression datasets are scarce [6,9].

Related Work

The dataset we built in this work, called D3TEC (TEC de Monterrey's Depression Detection Dataset), stands out for providing 2 new types of data previously unavailable in voice depression classification: Spanish recordings and simultaneous recordings using both professional and smartphone microphones. Moreover, audio quality standards are higher than most publicly available voice depression datasets.

As of now, most research on automated depression classification using voice recordings has been done using the Distress Analysis Interview Corpus/Wizard-of-Oz Dataset (DAIC-WOZ dataset), which contains only English-spoken recordings, and there has been very little research in other languages [6,10]. The scarcity of non-English datasets, as noted by Wu et al [6], is one of the most important roadblocks in developing speech depression classification models. The D3TEC dataset addressed this issue by providing a collection of high-quality recordings in Spanish.

This work is also the first to record participants with both a professional and a smartphone microphone simultaneously. This enables researchers to evaluate the effect of the recording device when training deep learning models for voice depression classification. As shown in Table 1, D3TEC is the only publicly available dataset to feature smartphone recordings as well. This is important as smartphone research makes technology developments much more scalable.

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Table 1. Comparison of different datasets used for mental health disorders detection and classification, based on audio recordings and different languages.

Dataset	Language	Audio format	Microphone	Label	Size	Year
D3TEC[a]	Spanish	WAV 44.1 kHz, 24 bits	Shure SM27 (condenser mic) and iPhoneSE2020	PHQ-9[b]	62 subjects, 1674 recordings	2024
DAIC-WOZ[c]	English	WAV 16 kHz, 16 bits	Lapel mic (unspecified)	PHQ-8[d]	189 subjects, 189 recordings	2014
AVEC[e] 2013	German	WAV 41 kHz, 16 bits	Headset mic (unspecified)	BDI-II[f]	84 subjects, 150 recordings	2013
AVEC 2014	German	AAC 128 kbps (compressed)	Headset mic (unspecified)	BDI-II	84 subjects, 300 recordings	2014
MODMA[g]	Chinese	WAV 44.1 kHz, 24 bits	Neumann TLM102	BDI-II	52 subjects, 1508 recordings	2020

[a]D3TEC: TEC de Monterrey's Depression Detection Dataset

[b]PHQ-9: Patient Health Questionnaire-9.

[c]DAIC-WOZ: Distress Analysis Interview Corpus/Wizard-of-Oz Dataset.

[d]PHQ-8: Patient Health Questionnaire-8.

[e]AVEC: Audio/Visual Emotion Challenge Dataset.

[f]BDI-II: Beck Depression Inventory.

[g]MODMA: Multi-modal Open Dataset for Mental Disorder Analysis.

Finally, the D3TEC dataset also stands out for its high-quality recording standards. Of all the public datasets on depression classification, D3TEC and MODMA (Multi-modal Open Dataset for Mental Disorder Analysis) are the only datasets that feature audios recorded to a professional quality standard, taking CD audio quality as the baseline (44.1 kHz, 16 bits) [11]. These are the only datasets that specify the microphone model used for recording as well.

Although this work is focused on audio analysis, it is important to note there are other biomarkers that can be used for automated depression classification. A very interesting research area is based on electroencephalography data analysis using machine learning techniques. A lot of progress has been made, achieving promising results. In the studies conducted by Soni et al [12,13], authors use electroencephalography to analyze brain signals for depression detection. They propose a method for automatic feature extraction by first constructing a graph where the nodes represent the subjects in the dataset and edge weights are obtained using the Euclidean distance, which reflects the relationship between them. The results show that the proposed method detects depression with an accuracy of 0.933. Although these are impressive results, our approach is different as we are focusing on voice analysis rather than electroencephalography signals analysis. We believe that creating a new dataset based on audio recordings is more feasible, low-cost, scalable, and ubiquitous compared to building an electroencephalography-based dataset.

Problem Definition

Arguably, the most important requirement to build a high-performance deep learning model is to have a large amount of quality training data. Few depression datasets include voice recordings and even fewer are openly available. There are 4 main voice depression datasets available upon request. The most relevant of these is the DAIC-WOZ [10], collected in English; it features 189 recordings from the same number of participants. In addition, AVEC (Audio/Visual Emotion Challenge Dataset) 2013 [14] and AVEC 2014 [15], both featuring 84 German language speakers, contain 150 and 300 recordings, respectively. Finally, the MODMA [11] dataset, which contains data in Chinese, features 1508 recordings from 52 different subjects.

As noted by Wu et al [6] (2022), the scarce availability of datasets is one of the main roadblocks for research in voice depression classification, and currently available data have some important problems and limitations. We can point out 4 main issues:

1. Language barrier: datasets are available in very few languages. An English-spoken dataset should not be used in training if the intended purpose of the model is to identify depression in another language. To the best of our knowledge, there is no voice depression dataset in Spanish available for download.
2. Low audio quality standards: audio-quality recording standards have been neglected in most datasets. Almost none follow the basic CD quality standard of 44.1 kHz, which is the minimum required to capture the whole range of human hearing with no aliasing according to the Nyquist–Shannon theorem [16,17]. Besides that, no dataset specifies the characteristics of the room in which the recording took place or if all the recordings were collected in the same room. This might lead to a potential bias if recordings of both classes were done in different rooms (ie, recording participants with depression in a clinic and those with depression in an office or studio) as room acoustics have a significant impact on voice recordings [18]. Finally, most datasets do not report either the specific microphone used on the recordings or the signal flow (microphone, preamp, and analog-to-digital or digital-to-analog conversion) used to capture the audio, which directly affects the frequency response and sonic characteristics of the captured recording.
3. Class imbalance: as it is easier to find participants without depression, most datasets present a class imbalance. This

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means that both classes (depression and nondepression) have a different number of samples. This needs to be addressed during development to prevent the model from being biased toward the majority class [19,20].

4. Scarce smartphone research: most datasets have data collected in what can be inferred to be controlled environments, although the specific sonic characteristics of these environments are vaguely specified. Aiming to implement this technology in mobile apps, the effect of using a smartphone microphone instead of a professional one remains unknown. There is only 1 depression dataset that includes smartphone recordings called SH2, but it was collected privately by Sonde Health researchers, and it is not publicly available [21].

Objectives

The present protocol gives guidelines for the collection of a new dataset that aims to address current issues in data availability for depression classification research, specifically: lack of language variety, low audio quality controls, and scarcity of data recorded with smartphone microphones. Although this work focuses on collecting data from Spanish speakers, this research protocol's guidelines could be used to collect data in other languages as well.

The D3TEC dataset is designed with 3 main objectives in mind:

1. Spanish language: there is little language variety in current depression datasets. We focus on collecting data in Spanish, which has been an underrepresented language in voice depression classification.
2. High audio quality: audio is captured with studio-grade quality standards. This includes a low-noise environment, professional-grade recording equipment, a large diaphragm condenser microphone (Shure SM-27), and a high-quality recording format (44.1 kHz, 24 bits). In addition, potential sources of bias are controlled, including room acoustics.
3. Additional smartphone recordings: all professional recordings are also simultaneously captured by a smartphone microphone (iPhone SE2020). This provides data that can be used to evaluate the performance of deep learning models in depression classification when using smartphone recordings during training.

This data collection protocol is proposed by a multidisciplinary team that includes a professional audio engineer, 2 clinical psychologists, and 2 computer science researchers.

Methods

Participants

In deep learning, having a large dataset is desirable. However, as depression is a sensitive subject, it is not easy to include people with depression symptoms as research participants, thus depression datasets tend to be small [6]. We aimed at capturing recordings of at least 60 people, this number was established using other available depression datasets as a reference [11,14,15]. A total of 62 subjects are included in the final data collection. Data were collected in 2 different health centers, Tecnológico de Monterrey's Centro de Bienestar Estudiantil (ITESM) and Centro Académico de Atención en Bienestar Integral (CAABI). The former gives mental health care to active ITESM students. The latter was established by the TEC Salud Foundation in San Gilberto, a low-income county in Santa Catarina, Nuevo León. Its goal is to give health care and psychological therapy at an affordable cost.

The inclusion criteria are the following: age between 18 and 65 years; live in Nuevo León, Mexico; enrolled in one of the health centers either as an active ITESM student or as an active patient at CAABI. Exclusion criteria are: engaged in illicit drug consumption in the past 2 weeks; adapting to a new psychiatric medicine that has been prescribed less than 1 month ago.

We established a relationship with each health center where patients are invited to participate in the voice recording session before or after their psychological appointment. An incentive of 200 MXN is offered to each participant as compensation for their time and participation in the study. This amount approximately equals US $12 in 2024.

Data Collection

We collected 3 different kinds of data. The 2 most important ones are voice recordings and the depression screening questionnaire called PHQ-9 which is used to label the data [20]. In addition, we collected data on variables that could potentially affect the way a person speaks. The PHQ-9 scores encoded as binary values are the outcomes that are meant to be used as prediction labels in a machine learning model. It is important to note that the predictors in this case would only be the voice recordings; the additional demographic variables were collected only for control and data balance purposes.

Participants are asked to record their voices performing a variety of tasks prompted by a slideshow presentation. These include 3 categories: open questions, text fragments, and image descriptions as suggested by Wu et al (2022) [6]. Subjects are asked to aim for 30-second answers to each one of the 27 prompts. The recording tasks and time frame are established with the future goal of implementing the technology on a smartphone app. The prompts used on the slideshow presentation can be easily implemented on a mobile application, contrary to interactive interviews used on the DAIC-WOZ [10].

Each of the tasks has a different emotional valence. Positive valence refers to a prompt that makes the participant think of something positive. Neutral and negative valence evoke these emotions, respectively. An example of an open question used for each emotional valence is stated as follows:

1. What or who motivates you? Why? (Positive)
2. Describe your morning routine. (Neutral)
3. Which things make you angry? (Negative)

After the recording process, the participant is asked to fill out the PHQ-9 questionnaire. This is a depression screening test that includes 9 questions. Each question inquires about 1 symptom related to depression and the person must rate it on a scale from 0 to 3 according to how many times they have experienced that symptom in the last 2 weeks. Each audio is labeled with the obtained PHQ-9 score, which ranges from 0 to 27. A higher score indicates a higher presence of depression symptoms. Each audio is also labeled with a binary value of 0

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(nondepressed class) when the PHQ-9 score is less than 10, and with a value of 1 (depressed class), when the PHQ-9 score is greater than or equal to 10.

The PHQ-9 cutoff score of 10 has been validated in numerous studies and is considered to effectively identify moderate to severe depression, ensuring those who need further mental health evaluation are identified while reducing false positives. It is important to note that the choice of cutoff score can affect the balance between missing cases of depression (false negatives) and incorrectly identifying individuals who do not have depression (false positives). Therefore, the choice of a cutoff score often depends on the screening's goals and the context in which the screening tool is used [22,23].

Finally, we also collected some additional data. Although not intended to be used as a label or inclusion or exclusion criteria, we considered it important to collect data that could potentially affect the way a person speaks. Therefore, if a deep learning model trained using this dataset classifies data in an unexpected way, these variables can be analyzed to identify a potential cause of bias. The additional control variables are shown in Table 2.

Table 2. Additional control data.

Variable	Value	Reason to collect
Age (years)	18-65	Biological aging of vocal tract
Sex (biological)	Male or female	Biological differences on vocal tract
Place of residence	City, State, Country	Influence on accent
Place of birth	City, State, Country	Influence on accent
Social class	Working, middle, or upper[a] class	Influence on accent
Data collection center	ITESM[b] or CAABI[c]	Potential influence on accent. Influence on room acoustics
Medicine	Current medication or none	Potential influence on speech or mood
Physical health condition	Current health condition or none	Potential influence on speech
Mental health condition	Current diagnosis or not available	If a formal diagnosis exists, it is relevant

[a]Social class data were assigned according to average household monthly income in Mexican pesos. We used 13,000 MXN (~US $758) for the working class, 23,000 MXN (~US $1341) for the middle class, and 78,000 MXN (~US $4548) for the upper class which is the average for each social class in Mexico according to data provided by Instituto Nacional de Estadística y Geografía [24].

[b]ITESM: Tecnológico de Monterrey's Centro de Bienestar Estudiantil.

[c]CAABI: Centro Académico de Atención en Bienestar Integral.

Audio Recordings and Quality Standards

A total of 27 audios are recorded by each subject. These audios are collected simultaneously by a professional microphone and a smartphone microphone. This is meant to be used by researchers to evaluate how audio quality affects deep learning–based models' performance in depression classification.

The purpose of high-quality recordings is to collect audio with the highest amount of information possible. Even if most humans cannot differentiate between uncompressed (WAV and AIFF) and compressed (MP3, OGG, FLAC, etc) audio formats, there is a significant difference in the amount of information present in each format. A file size comparison is shown in Table 3. These sizes are calculated by transforming a 44.1 kHz, 24-bit WAV into different formats using iZotope RX format and Cloudconvert. It clearly shows how a 44.1 kHz, 24-bit WAV file can have up to 15 times more data than a compressed 128 kbps AAC file.

Table 3. File size of 1-minute WAV files recorded with different sample rate and bit depth parameters before and after file compression.

Sample rate	Bit depth	File size (uncompressed)	File size (mp3, 320 kbps)	File size (AAC 128 kbps)
44.1 kHz	24 bits	15.9 MB[q]	2.4 MB	0.96 MB
44.1 kHz	16 bits	10.6 MB	2.4 MB	0.96 MB
41 kHz	16 bits	9.8 MB[b]	2.4 MB	0.96 MB[c]
16 kHz	24 bits	5.8 MB	1.2 MB	0.96 MB
16 kHz	16 bits	3.8 MB[d]	1.2 MB	0.96 MB

[a]MODMA (Multi-modal Open Dataset for Mental Disorder Analysis dataset).

[b]AVEC (Audio/Visual Emotion Challenge Dataset) 2013 dataset.

[c]AVEC 2014 dataset.

[d]DAIC-WOZ (Distress Analysis Interview Corpus/Wizard-of-Oz Dataset) dataset.

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Currently, no study compares the effect of audio quality on the performance of deep learning–based models for depression classification. The only reason to capture audio with lower quality is to save digital space, but this decision should not be taken if the effect of reducing quality is unknown. Higher-quality audio can be converted into lower-quality formats; therefore, capturing audio to a high-quality standard is desirable, as this renders audio with more information and allows researchers to change the audio format and run experiments considering different audio qualities.

The high-quality audio section of the D3TEC dataset was recorded with a high audio quality standard. A sample rate of 44.1 kHz is established since it is the minimum needed to represent the whole audible frequency spectrum while avoiding aliasing [17]. Although using 16 bits is standard CD quality, the higher bit-depth standard of 24 bits is chosen since it allows for more dynamic range. The complete recording parameters of the D3TEC dataset are shown in Textbox 1.

Textbox 1. Hardware, software, and recording parameters for the high-quality audios of the Dataset for the Detection of Depression of Tecnológico de Monterrey dataset.

Recording parameters

- Sample rate: 44.1 kHz
- Bit depth: 24 bits
- Stereo or mono: mono

Hardware

- Microphone: Shure SM27 (large diaphragm condenser)
- Analog-to-digital interface: AVID Fast track duo

Software

- DAW: Logic Pro X

Other

- Mouth distance from microphone at 20 cm, approximately.
- No pop filter used.
- All recordings share the same gain configuration. The interface's gain knob is marked at 6/10. Gain level is established moderately to avoid clipping considering that voice volume varies from person to person.
- RT60 time on both recording centers is less than 1 second.

The purpose of recordings using a smartphone is for researchers to be able to evaluate the performance of deep learning–based models when a smartphone is used instead of a professional microphone. The goal of these recordings is to make them representative of a real case scenario in which a person records their voice with their smartphone in a quiet room. All audios are recorded on an iPhone SE2020 using the Apple Voice Memos application with a sample rate of 48 kHz in the compressed format M4A, which is the default audio format of the app. The smartphone is placed on a desk in front of the subject at approximately the same distance the professional microphone is placed. Audios are afterward converted to a WAV format of 44.1 kHz, 24 bits for processing; however, converting low-quality audio to a higher-quality format does not add new information. Therefore, these audios should be considered M4A, even if converted to WAV for practical purposes.

For binary classification, a neural network-based model must be able to correctly classify data into one of 2 classes: depression and no-depression. Broadly speaking, the model accomplishes this by learning common patterns present in each class that make both classes different. A bias occurs when the model classifies the data, taking as a common pattern something that the developer did not intend or anticipate. For example, if a model is meant to train in and classify a dataset of circles and squares, but all circles are red and all squares are blue, one cannot assume that the model learned the pattern that separates a circle from a square. It could be the case that the model learned to classify according to color, not shape.

The same applies to audio. The voice of the person is not the only factor at play, many other factors affect the way an audio recording sounds. For example, room acoustics, microphone, audio interface, preamp, sample rate, bit-depth, audio format, and gain staging. Say for example that a data collector decided to record participants with depression in a clinic with concrete walls and people without depression in a studio with wooden walls. A model trained with these data might present a bias caused by the room acoustics, incorrectly classifying voices recorded in concrete-walled rooms as depressed.

For the D3TEC dataset, we undertook several measures to avoid potential bias in audio recordings. We used the same room at each data collection center with the same microphone placement. All audios are recorded with the same 2 microphones simultaneously, Shure SM-27 and iPhone SE 2020. For every recording, we used the same audio interface (AVID Fast Track Duo) and the same channel, preamp, and gain level. Finally,

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we used Logic Pro X software for professional audio and the Voice Memos App for smartphone audio.

Ethical Considerations

This research protocol has been approved by the Institutional Research Ethics Committee of Tecnológico de Monterrey (protocol code CA EIC-2407-03; Multimedia Appendix 1). All participants provided written informed consent after being briefed about the study's goals and were informed about the ability to opt out of the process at any stage of the protocol (Multimedia Appendix 2). All audio recordings and collected data were anonymized and deidentified to comply with ethical and personal data privacy requirements. An incentive equivalent to US $12 in 2024 was offered to each participant as compensation for their time and participation in the study. The ethics committee approval and informed consent forms can be found in the Multimedia Appendices 1 and 2.

Results

This section presents the final collected dataset. The main demographic information of the D3TEC dataset is displayed in Tables S1 and S2 in Multimedia Appendix 3, which contain the suggested training and testing set, respectively. The full dataset including audio and every collected variable can be found in IEEE DataPort [25].

The variables included in Tables S1 and S2 in Multimedia Appendix 3 are described as follows. ID refers to a unique code given to each participant, which is used instead of their name for anonymization purposes. PHQ-9 is the depression screening score as obtained in the PHQ-9 questionnaire. A Boolean value, PHQ-9 binary for depression, is included using a score of 10 as the cutoff value. Demographic information is included such as age, biological sex, and place of residence. Social class is recorded based on the monthly household income of each participant and classified into lower, middle, or upper class using the INEGI scale for social class quantification [24]. Finally, the medicine variable indicates if the participant was taking medication at the time of the recording session. These include any kind of medication, psychiatric and nonpsychiatric.

The D3TEC dataset includes audio recordings from 62 participants, recording 27 audios each, which equals 1674 voice recordings. The dataset is split into suggested training and test sets. The training set has 79% of the dataset while the remaining 21% is designated as the test set. However, researchers can decide on alternative approaches for splitting the data according to their needs.

Discussion

Overview

The protocol to create the D3TEC dataset was carefully designed to address the current limitations of data availability for deep learning research in voice depression classification, which include limited language diversity, low audio quality standards, class imbalance, and scarcity of audio data collected through smartphones. We undertook the following actions during the data-gathering process, to guarantee the quality of the resulting dataset. First, the D3TEC dataset contains audio samples in Spanish, a language that has been largely underrepresented in voice depression classification. Second, every audio was collected with a professional, studio-grade microphone in a noiseless environment. Moreover, several measures were taken to avoid potential bias by controlling room acoustics and recording parameters. Third, in our dataset, the nondepressed class is 53% and the depressed class is 47%, indicative of a reduced class imbalance, especially when compared to the DAIC-WOZ dataset, where the class imbalance is a concern [10]. Finally, alongside the professional microphone, every audio was simultaneously recorded with a smartphone, providing data that enables researchers to evaluate the feasibility of deploying voice depression classification models in mobile apps. It is worth mentioning that the D3TEC dataset is publicly available and can be downloaded through IEEE DataPort (Multimedia Appendix 3).

As noted by Wu et al [6], one of the most important roadblocks preventing the development of automated depression recognition technology is the scarcity of data collected for this purpose. Our work is focused not only on recording voice data of individuals with depression, but also on providing data with characteristics that are not present in currently available datasets. Therefore, the D3TEC dataset is expected to open new research paths in automated depression classification. First, the inclusion of recordings in Spanish enables the development of robust deep learning models that can identify depression in Spanish-speaking populations; this language has been largely underrepresented in currently available datasets including DAIC-WOZ, MODMA, and AVEC [10,11,14]. Second, the inclusion of recordings in the dataset, captured simultaneously with professional and smartphone microphones, allows for a comparative analysis of device impact on model performance. These dual-format data are expected to enable research focused on the development of deep learning depression classification models that can be deployed in mobile apps. Therefore, the technology will be scalable, available, and usable in real-world applications. Third, the high audio-quality standards of the dataset, which include controlled room acoustics and recording parameters, are anticipated to minimize biases often present in voice data. It is worth noting that the most popular datasets shown in Table 1, present lower audio quality standards than the D3TEC; only MODMA was recorded with comparable recording quality [11]. Finally, the inclusion of additional control variables allows for potential demographic-induced bias identification. All these attributes are expected to significantly reduce overfitting problems when developing deep learning classification models for automated depression identification.

We are providing the research community with a new dataset developed with high-quality standards, regarding room ambiance and recording parameters. The selection of the Spanish language alleviates the current shortage of datasets in this language, considering that Spanish is the second most spoken native language in the world, with almost 500 million people [26]. The implication of this is a higher coverage of the number of people that potentially will benefit from any health-monitoring application resulting from forthcoming research. We hypothesize that new deep learning models trained and tested on this dataset

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will benefit from a reduced bias and overfitting; therefore, performance metrics, such as F_1-score, precision, and recall will be more reliable. In addition, our goal is to assess the effect of audio quality on the performance of deep learning–based models for depression classification. The number of participants in the dataset, 62, is very competitive compared to the other datasets found in the literature. The resulting balance between classes, depressed/not-depressed, is also a very positive property. We are currently working on the development of deep learning models trained and tested on the D3TEC dataset to prove the validity of our hypothesis.

Limitations

In the following paragraphs, we discuss the limitations and strengths of the presented dataset and potential issues that should be considered when using it. The main limitations discussed are label quality, the potential influence of prescribed medication, and biological sex imbalance.

The most important information for each data entry is whether the audio comes from a participant with or without depression. In this dataset, that ground truth is based on the PHQ-9 questionnaire, which is a screening tool that has proven valuable in identifying depression and can be self-administered [23]. Although it performs well when compared to other questionnaires, the PHQ-9 is only a screening tool and it cannot be used on its own to determine if a subject is, in fact, depressed. That diagnosis can only be given by a clinical psychologist, which usually takes several sessions. Although the original idea was to label subjects using a clinical diagnosis, this proved to be impractical, expensive, and time-consuming. It would take at least 3 sessions to diagnose a potential participant in each of the health centers used for data collection. Thus, to collect more recordings in a shorter time frame, we chose to label them with the PHQ-9. It is important to recall that this label is not as good as a clinical diagnosis.

Regarding the potential influence of prescribed medication, some of the participants who scored high on the PHQ-9 questionnaire were also taking antidepressant medication, such as sertraline and fluoxetine. These medications are meant to reduce depression symptoms. This could have a negative impact on data collection since a person's score on the PHQ-9 could be affected by the medication. Other datasets took their participants off medication 2 weeks before recording; however, this approach represents a medical risk for the participant's emotional well-being, therefore we decided not to follow it [11]. In our case, we decided to collect the variable, hence it can be traced back, in case we suspect bias due to medication.

The dataset currently presents a slight class imbalance. The nondepressed class is 53% and the depressed class is 47%. The presence of class imbalance is common in depression datasets, but this needs to be considered when using the data for deep learning research [6,19]. On top of the class imbalance, the dataset presents a biological sex imbalance: 58% of participants are female and 42% male. This imbalance must be considered when splitting the data into training and testing sets for deep learning research.

Although we worked with 2 different data collection centers, most audio recordings were made at ITESM and only 9 participants were recorded at CAABI. When working with the dataset, removing the 9 audios from CAABI for deep learning experimentation might be beneficial in some applications, as this removes an additional recording space and demographic population that could introduce noise in the results. The decision whether to use the CAABI recordings or not must be taken by each researcher using this dataset according to the goals of their research. For identification purposes, a CAABI participant ID starts with 0 and an ITESM participant ID starts with 1.

Conclusions

This research outlines a thorough protocol for creating a dataset of depression voice recordings for deep learning research, with 3 novel characteristics: it has a high audio quality standard, it features Spanish speakers, and it collects data simultaneously using professional and mobile devices; hence, overcoming main issues on current voice datasets for depression classification.

Some of the research areas enabled by this new dataset are binary and multiclass depression classification of Spanish speakers. Also, it allows for a clear assessment of the impact of audio and microphone quality on the performance of depression classification models. This is of great relevance, since evaluating if there is a statistically significant difference in training these models with mobile collected data, opens the door for a lower cost, more flexible and scalable data-gathering process. Furthermore, it will make wearable-based applications more feasible.

Prior research, mainly performed on the DAIC-WOZ dataset, shows that the computational analysis of voice recordings can be a useful way of identifying depression, with performance as high as an F_1-score of 85% in the best algorithms. The development of new deep learning models trained and tested on datasets created with high-quality standards paves the path for new practical and research applications in voice depression classification, assuring better performance metrics, such as F_1-score, precision, and recall.

As the process of collecting new datasets continues, the prospects of creating an objective, accessible, and noninvasive tool for screening depression become increasingly tangible. Future research is meant to expand upon these foundations, exploring the integration of this technology into clinical practices and the potential for its application across different languages and cultural contexts.

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contributions, which were crucial in facilitating our research. We sincerely appreciate the cooperation and assistance of all parties involved.

Authors' Contributions

LFB performed data curation and investigation; supervision of the work was led by JAC-C and LAT. LFB, DA-DL, and FPH-M were in charge of providing all resources. LFB wrote the original draft of the manuscript. JAC-C, LAT, and LFB contributed to the final review and editing of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Ethics committee approval.
[PDF File (Adobe PDF File), 53 KB - resprot_v14i1e60439_app1.pdf]

Multimedia Appendix 2
Informed consent form.
[PDF File (Adobe PDF File), 138 KB - resprot_v14i1e60439_app2.pdf]

Multimedia Appendix 3
Tables describing the D3TEC (Dataset for Depression Detection of Tecnológico de Monterrey) dataset structure as published in IEEE Dataport.
[DOCX File , 21 KB - resprot_v14i1e60439_app3.docx]

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Abbreviations

AVEC: Audio/Visual Emotion Challenge Dataset
BDI-II: Beck Depression Inventory
CAABI: Centro Académico de Atención en Bienestar Integral
D3TEC: TEC de Monterrey's Depression Detection Dataset
DAIC-WOZ: Distress Analysis Interview Corpus/Wizard-of-Oz Dataset
ITESM: Tecnológico de Monterrey
MODMA: Multi-modal Open Dataset for Mental Disorder Analysis
PHQ-9: Patient Health Questionnaire

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Protocol

A Chatbot-Based Version of a World Health Organization–Validated Intervention (Self-Help Plus) for Stress Management in Pregnant Women: Protocol for a Usability Study

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Abstract

Background: Pregnancy is a complex period involving significant physical, mental, and social changes in a woman's life, affecting her psychological well-being. According to the literature, anxiety, stress, and depression are common symptoms among pregnant women. Promoting a healthy lifestyle with a focus on mental health is essential. In this context, digital solutions such as coaches on smartphones are emerging as valuable tools to support the psychological well-being of pregnant women without existing disorders.

Objective: This study aims to present the research protocol of a pilot study designed as a proof-of-concept investigation. The study evaluates the feasibility, acceptability, and utility of an acceptance and commitment therapy–based stress management mobile app. The primary objective is to explore the feasibility of using a coach, ALBA (A Well-Being Assistant), developed within the TreC Ricerca app, to promote women's psychological well-being during pregnancy through 5 sessions based on acceptance and commitment therapy. The pre- and postintervention effects on psychological well-being will also be explored as a secondary objective, serving as a proxy for the potential impact of the intervention.

Methods: The study serves as a proof-of-concept investigation, where a small sample size (N=50) is deemed adequate to fulfill the study's objectives. Participant recruitment will be conducted among pregnant women affiliated with the pregnancy care services of the Azienda Provinciale per i Servizi Sanitari di Trento, using a convenience sampling approach. ALBA will interact with the participating women for 6 weeks, between the 14th and 26th weeks of gestation. Specifically, there will be 1 session per week, which the woman can choose, to allow more flexibility regarding her needs, supplemented by ALBA-supported exercises to be performed between sessions. This study adopts a mixed methods approach, combining quantitative and qualitative data collection and analysis. Usability and engagement are assessed using the System Usability Scale, Chatbot Usability Questionnaire, User Engagement Scale-Short Form, and the User Mobile Rating Scale. Moreover, other quantitative outcome measures include levels of stress, anxiety, depression, emotional regulation, psychological flexibility, coping strategies, self-efficacy, and overall

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well-being, along with qualitative data from semistructured interviews. Finally, the analysis of the data gathered in this study will primarily adopt descriptive statistics and a text mining approach, focused on evaluating the attainment of the study objectives and changes over experimental time.

Results: The psychoeducational approach aims to yield notable outcomes regarding the usability and engagement of women with ALBA. Furthermore, an anticipated enhancement in psychological well-being and quality of life is expected.

Conclusions: Existing literature indicates a preference among women in the perinatal period for online support, highlighting the potential of digital interventions to address barriers related to social stigma and seeking assistance. In this context, ALBA emerges as a valuable resource, providing consistent psychoeducational support for women throughout pregnancy.

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KEYWORDS

stress management; promoting well-being; pregnancy; eHealth; mobile health; mHealth; mobile apps; development; usability; user-centered design; chatbot; multifaceted; woman; transformations; well-being; psychological health; healthy lifestyle; digital solutions; psychological

Introduction

Overview

Despite the increasing awareness of mental health issues and concerted efforts, a significant proportion of individuals with poor mental well-being do not receive prevention actions or appropriate care [1,2]. This treatment gap is influenced by various factors, including financial constraints, limited availability of services, and societal stigma, particularly for populations susceptible to stressful situations [3,4], including pregnancy.

The pregnancy period is characterized by essential transformations in the woman, with relevant impact on her physical, mental, and social well-being. How a woman adapts to these changes can affect her quality of life (QoL) and psychological well-being. The literature highlights that various psychological symptoms can be commonly experienced during pregnancy, ranging from anxiety, stress, and depression [5-9].

To date, psychoeducational interventions that promote women's psychological well-being during pregnancy are scarce and tend to focus primarily on subgroups of women with psychiatric symptomatology, such as perinatal depressive disorder [5,10]. Evidence of the effectiveness of psychological interventions targeting pregnant women is increasing [11], but access to support services still presents several challenges. A considerable proportion of women face geographic barriers, with specialized centers often far from their homes [12,13]. In addition, a shortage of qualified staff, such as psychologists, further limits access to specialized care [12,13]. The stigma associated with mental health problems can also prevent women from seeking psychological support in these circumstances [12,13].

The overall strategy adopted by the World Health Organization (WHO) for mental health promotion is based on principles of inclusiveness and scalability for the public and susceptible populations [14]. WHO promotes inclusive mental health by aligning with human rights, ensuring cultural sensitivity, engaging diverse stakeholders, providing accessible and tailored services, and addressing social determinants to reduce disparities [15]. Within this framework, special attention is paid to the potential role of digital technologies in promoting psychological well-being, as it can be an optimal solution [16]; women can access it from anywhere and at any time, thus remaining flexible to their needs and reducing barriers related to service availability, social stigma, and seeking help [17].

The study described in this protocol is in line with WHO strategies and aims to assess the acceptability and feasibility of an intervention delivered through digital tools to promote psychological well-being. To the best of our knowledge, the intervention, originally validated by WHO and named Self-Help Plus (SH+), has never been used on this study's target population, pregnant women.

SH+ is a low-intensity intervention developed by a multidisciplinary and international working group [18-20]. This type of intervention is usually designed to be transdiagnostic, easily adaptable in different settings, deliverable by nonspecialists, and based on sound evidence-based psychological principles embedded in a self-help approach (guided or unguided). This approach has already been validated in various target populations such as health care workers, migrants, and refugees to promote psychological well-being and clinical interventions, demonstrating general levels of acceptability and potential effectiveness [20]. A first attempt was made to make the protocol web-based within the RESPOND (Improving the Preparedness of Health Systems to Reduce Mental Health and Psychosocial Concerns Resulting From the COVID-19 Pandemic) project, but the involvement of a human person, in the role of helper, was still necessary [21].

Cognitive behavioral therapy techniques, particularly those referring to third-generation therapy, are shown to be more suitable than other psychotherapeutic approaches to be transferred into low-intensity interventions delivered by nontraditional methods, such as eHealth applications. SH+ is based on the principles of acceptance and commitment therapy (ACT), a third-wave form of cognitive behavioral therapy [22,23], and is divided into 5 chapters that address 5 strategies for managing stress and promoting psychological well-being. The five chapters, later translated into sessions, are as follows: (1) grounding (mindfulness), (2) unhooking (defusion), (3)

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acting on your values (values-based behavioral activation), (4) being kind (gratitude), and (5) making room (acceptance).

In this study, "acceptability" refers to participants' perceived appropriateness, satisfaction, and willingness to engage with the digital intervention, as captured through self-report measures of user experience (UX) and user engagement (UE), as well as through semistructured interviews. "Feasibility" is defined as the extent to which the digital delivery of the SH+ intervention can be successfully implemented in the target population, considering aspects such as ease of access, completion rates, and usability. Both constructs are aligned with widely accepted definitions in the implementation science literature [24,25].

In conclusion, this study protocol aims to make the virtual coach, ALBA (A Well-Being Assistant), platform (described in the following paragraphs) available to women by evaluating the acceptability and feasibility of delivering SH+ through an assistant created to deliver psychoeducational sessions through dialogues, video, audio, and images (ie, the 5 chapters of SH+), as well as representing a virtual coach who guides the user in carrying out assigned exercises and tasks to be done independently between sessions. Moreover, we acknowledge that not all individuals who give birth identify as women, and that the more inclusive term would be "birthing person." However, because most cases involve women, we have chosen to use the term *women* in this context. When specifically referring to birthing persons, appropriate linguistic and content-related considerations will be applied. Nevertheless, future replications of this intervention may be revised to ensure greater inclusivity.

Goal of the Study and Research Questions

Overview

This study is positioned within the design and development cycle of the obesity-related behavioral intervention trials (ORBIT) model [26], specifically the refine phase. It involves delivering material based on SH+ in text, audio, and video formats by a virtual coach (ie, a digital assistant, identified as ALBA) implemented within the TreC Ricerca (TreC Research) app.

This intervention is embedded into the framework of behavior change interventions [27], which aim to enable women to acquire adaptive strategies to improve or maintain their psychological well-being. It should be noted that the term intervention in this context is used to identify a tool (in this case, the virtual coach) that will periodically be offered in a predefined (ie, rule-based), structured, and ordered manner, as informational material that has been structured and reviewed by psychological professionals.

This intervention has been developed and implemented for research purposes. The final goal is to validate the digital health intervention targeting women's psychological well-being during pregnancy by helping them manage stressful situations more effectively through modules based on the principles of ACT.

Primary Objectives

The primary objectives of this proof-of-concept study described in this protocol paper are as follows: (1) to exploratively investigate through self-report standardized questionnaires UX and UE, that is, women's experience and engagement when interacting with the TreC Ricerca app and the virtual coach, ALBA, (refer to the Step 3: Participation section for detailed description of questionnaires) and (2) to assess the women's UE with ALBA and the app through semistructured interviews and investigate their feelings and overall experience during the intervention.

Secondary Objective

The secondary objective is to assess the level of pre-post psychological well-being through administered self-report questionnaires at the beginning and the end of the intervention.

This represents a preliminary exploration of the potential impact of the intervention by assessing changes in psychological well-being through post self-report questionnaires administered at the beginning and end of the intervention. Although this does not constitute an efficacy evaluation per se, it aligns with the *refine* phase of the ORBIT model, where early signals of potential effectiveness may be explored alongside feasibility and acceptability. This preliminary assessment aims to inform the design of future pilot or randomized controlled trials.

ALBA Intervention

Overview

The virtual coach, ALBA, will deliver an intervention based on ACT techniques to promote QoL and perceived psychological well-being and manage stressful situations for pregnant women. The module is self-administered and available for both Android (Google LLC) and iOS devices (Apple Inc). All the contents of the dialogues were developed by a group of researchers affiliated with the Digital Health Research of the Bruno Kessler Foundation of Trento (Fondazione Bruno Kessler, Trento [FBK]) and psychologists from the Istituto Pavoniano Artigianelli with specific communication skills, based on the SH+ manual [28]. Subsequently, materials have been revised by a psychologist from the psychology operating unit of the Azienda Provinciale per i Servizi Sanitari di Trento (Provincial Health Services Authority of Trento; APSS). The dialogues, videos, and audio tracks were developed using an educational approach, rather than an emergency management approach. In addition, the structuring of the material and delivery methods was supervised by professionals from the WHO Center for Research in Mental Health at the University of Verona, who have already carried out implementation and validation studies of SH+ nationally and internationally.

To ensure the best possible adaptation of the intervention to our target sample, we previously conducted a co-design study based on guidelines of a previous step of the ORBIT model [26]. This process involved domain experts, such as psychologists, SH+ experts, communication and usability experts, and a small sample of new mothers and clinicians (midwives and gynecologists). For further details, please refer to our previous study [29].

Technological Tools

The technological component of the study is based on TreC. This platform allows citizens of the Autonomous Province of

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Trento to access, manage, and share information on their health and well-being [30]. TreC stands for *cartella clinica del cittadino* (citizen's medical record) and is a reliable and well-tested platform designed to be a "system of systems" rather than a simple data hub. The central pillar of the TreC platform is the role of the citizen or as the manager of their health-related data, as in the case of a personal health record. TreC is designed with a flexible architecture, which enables the collection and management of heterogeneous data and allows the development and use of further subsystems to provide additional and specific functions.

This research project uses an additional module of the TreC platform, TreC Ricerca. The app can be downloaded via a specific link sent directly to participants. Authentication should be carried out via 2-factor authentication (one-time password code), which is secure and General Data Protection Regulation–compliant.

SH+ Sessions

SH+ intervention lasts 6 weeks, with 1 session of approximately 40 per week, which can be divided into 2 subsessions of 20 minutes each. Figure 1 shows a graphical representation of the conversational protocol delivered to women and its chronological structure.

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Figure 1. Graphical representation of the conversational protocol delivered to women and its chronological structure. COPE-NVI-25: Coping Orientation to the Problems Experienced–New Italian Version (25-item); ERQ: Emotion Regulation Questionnaire; GHQ: General Health Questionnaire; GSE: General Self-Efficacy Scale; ITA BUS B: Italian version of the Chatbot Usability Scale (version B); K10: Kessler Psychological Distress Scale; MPFI: Multidimensional Psychological Flexibility Inventory; PSS: Perceived Stress Scale; SF-36: 36-Item Short Form Health Survey; SH+: Self-Help Plus; SUS: System Usability Scale; UES-SF: User Engagement Scale-Short Form; uMARS: User Mobile Application Rating Scale; UX: user experience.

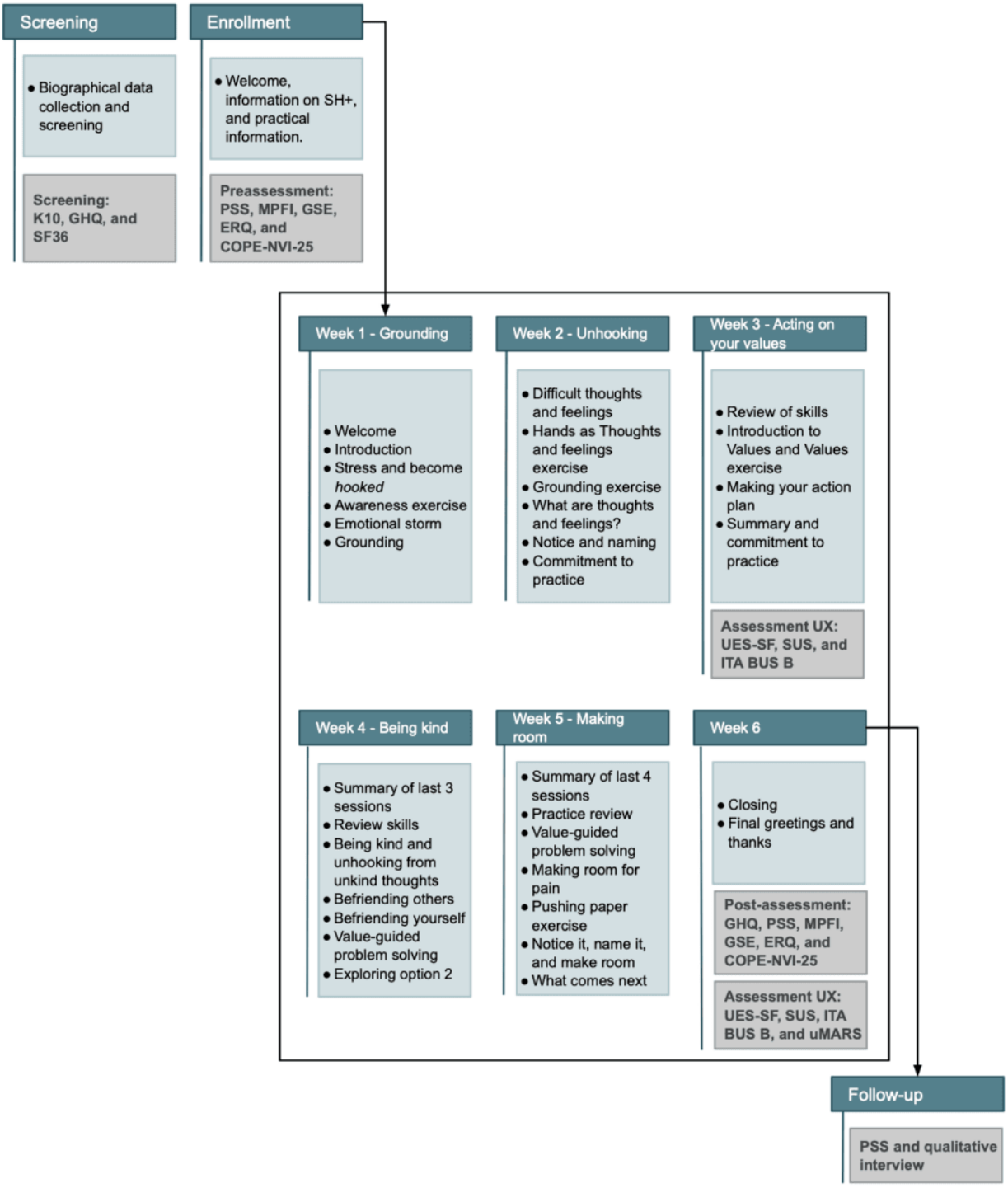

This intervention aims to enable women to acquire healthy coping strategies in stressful situations to promote psychological well-being during and after pregnancy.

The intervention was developed by referring to the SH+ program and adapting it to a psychoeducational course delivered via a virtual coach (refer to Figure 2 for some examples). The contents are presented through a gradual path that will enable the woman to become aware of herself and the present moment, accept and normalize internal states, cope with stress, and perceive an increase in her psychological well-being. In addition, the woman will be asked to perform tasks independently and fill out her diary daily.

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Figure 2. Mockups of the coach, ALBA (A Well-Being Assistant), within the TreC Ricerca app with some of its different sections.

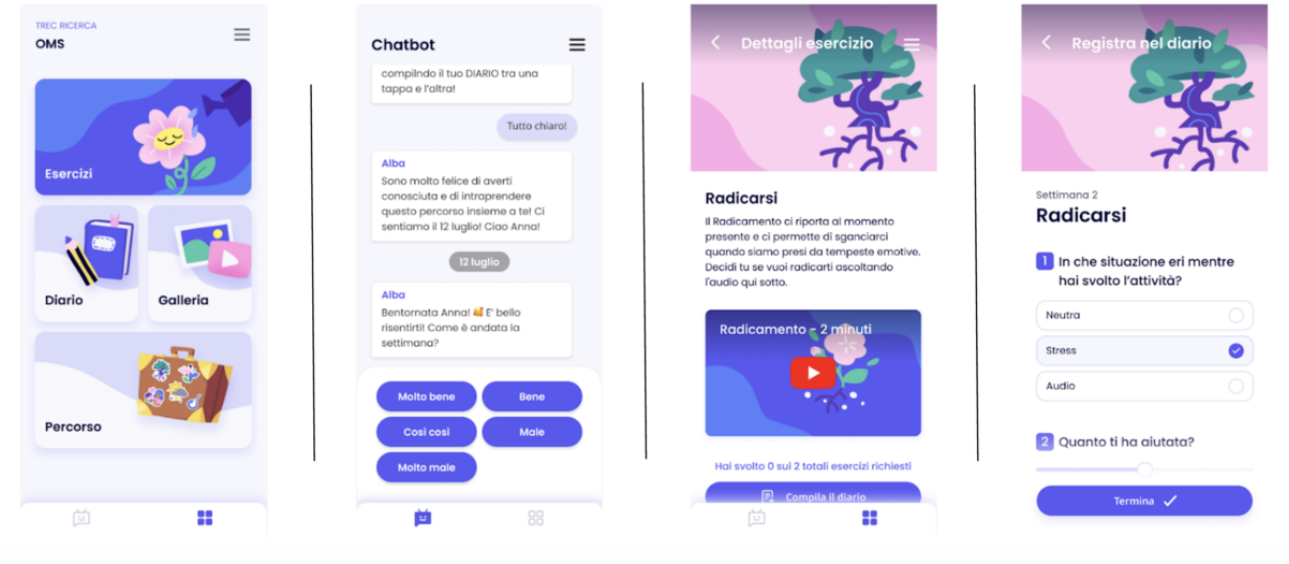

Methods

Design and Study Plan

ALBA is designed to interact with pregnant women for 6 weeks, starting between weeks 14 and 26 of pregnancy. This period was chosen because the risk of miscarriage was much lower [31], a factor that could, of course, affect stress levels [32]. This will also ensure that we can complete the study before the due date of the participants. Weekly sessions are followed by the virtual coach's instructions to independently perform some simple exercises and fill in the personal diary. The woman can choose the best day and time to interact with ALBA and perform exercises.

At the beginning of the pathway, ALBA will administer 6 self-report questionnaires, described in the Data Collection section, to establish a baseline for the examined psychological variables. After the data collection phase, the module will be administered, and its contents will be presented in different formats (ie, text, images, audio, and video).

An additional round of questionnaire administration is foreseen at the end of the intervention to assess potential changes in terms of psychological well-being and QoL perceived by the women. Four questionnaires will be administered to assess usability. To ensure the collection of all the necessary data, reminders were scheduled to complete the questionnaires 24, 48, and 72 hours after the first request. However, at present, there are no reminders for session completion.

Two months after giving birth, women from whom consent has been obtained will be invited to a semistructured interview to discuss their experience using ALBA and the app and to collect a more in-depth understanding of their experiences during the psychoeducational process. The 2-month postpartum period was chosen for both organizational convenience and methodological considerations. The expert group identified this timeframe to find a balance between scientific appropriateness and practical arrangements of the interviews, avoiding a prolonged span after the end of the intervention while ensuring that interviews with the participants were not conducted too close to the week of childbirth. The underlying assumption is that the period immediately following childbirth may be a logistically and emotionally complex time for the family, with a particular focus on the mother's availability and experience.

Participant Recruitment and Withdrawal

Recruitment will occur within the group of pregnant women between the 14th and 26th weeks of gestation attending the pregnancy care services of the APSS in Trentino.

Midwives from the APSS hospital and territorial service were involved in the study to identify women potentially eligible to participate.

The inclusion and exclusion criteria for women to participate in the study are provided in Textbox 1.

Figure 3 shows a flowchart of the research project procedure.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

1. Be pregnant
2. Be in a gestational state between the 14th and the 26th week
3. Be aged ≥18 years
4. Have a smartphone with internet access, be able to download the app, and be able to use it
5. Be a resident of the Autonomous Province of Trento
6. Know and understand the Italian language
7. Have a stress level score, as measured by the Kessler Psychological Distress Scale, between 15.9 and 29.9
8. Have a general well-being score, as measured by the General Health Questionnaire, ≥3
9. Obtain a score on the Mental Health scale of the 36-Item Short Form Health Survey between 30 and 80.

Exclusion criteria

1. Patients unable to provide informed consent, which is a prerequisite for participation in the study
2. Inadequate understanding of the Italian language
3. Substance addiction or in recovery for 1 year
4. Suicidal tendencies
5. Depression or other psychiatric diagnoses
6. Women undergoing medically assisted procreation (due to the increased risk of anxiety and depressive states, ascertained in the literature)
7. Already being placed, followed, or taken care of on a psychological or psychotherapeutic path at the time of recruitment

Figure 3. Flowchart of the research project procedure. ALBA: A Well-Being Assistant.

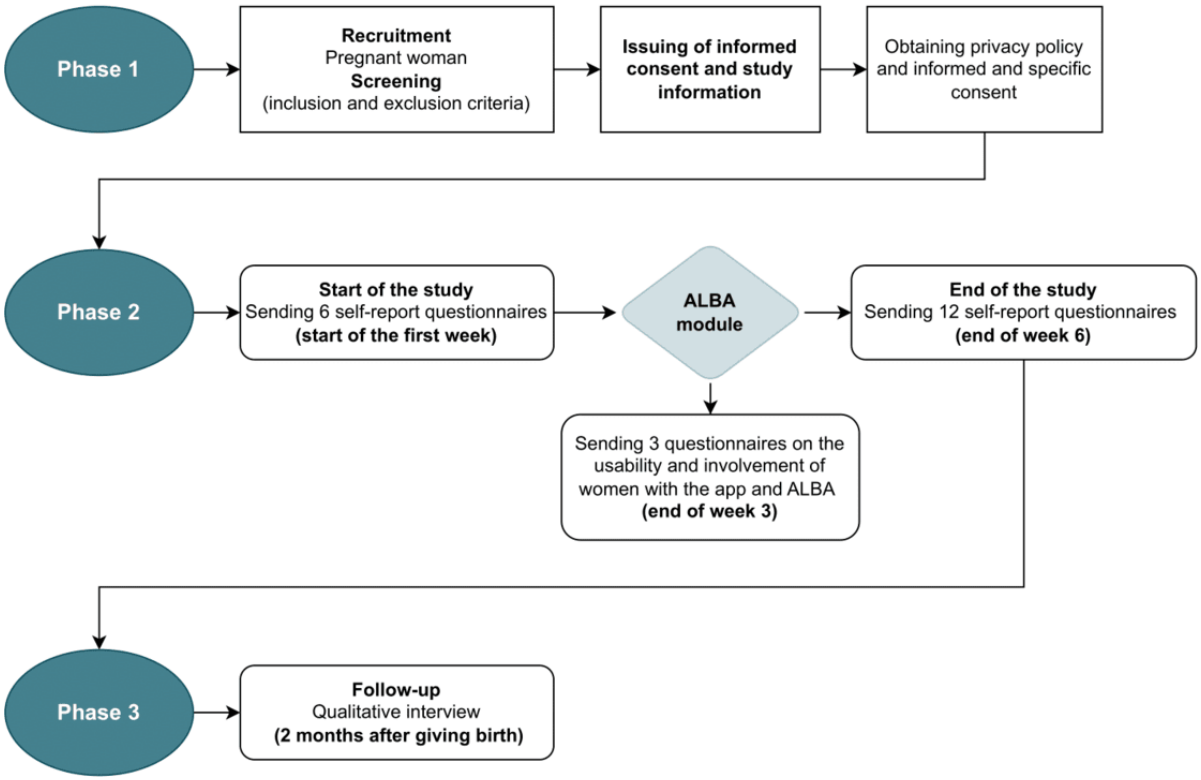

Sample Size

This research project is designed as a proof-of-concept study, where a limited sample is sufficient to achieve the intended aims. It was calculated that if nonparametric statistics are conducted (assuming the distribution is not normal), the sample should consist of 24 pregnant women with Bonferroni correction

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(α=.025). The sample size and power for nonparametric tests (Kruskal-Wallis and Wilcoxon post hoc tests) were calculated according to method reported by Noether [33]. If parametric statistics are conducted (assuming the normal distribution), the sample should consist of 41 pregnant women with Bonferroni correction (α=.025). The sample calculation was further confirmed with the

Power Analysis and Sample Size (NCSS LLC) and Stata (StataCorp LLC) programs, for which the resulting numerosity is 41 participants, assuming null hypothesis (Ho):d=d0, alternative hypothesis (Ha):d≠d0, and considering as study parameters α=.025; mean of group 1 (ma1): 0.000; power: 0.800; mean of group 2 (ma2): 1.000; delta (difference of means, delta): 0.500; expected difference (da): 1.000; and SD of difference (sd_d): 2.000.

Thus, by a power level set at 0.80, a significance level of .025, and considering a 20% potential dropout rate, an estimated 50 pregnant women are needed for recruitment to conduct the study.

Ethical Considerations

The ethics committee of the APSS approved this study (17241). This study was approved by the ethics committee of the APSS (17241). Recruited women who meet the inclusion criteria and consent to participate will be enrolled in the research. Participants are enrolled voluntarily and do not receive any form of compensation. Their data are pseudonymized using unique codes, and all analyses will be conducted on aggregated data, ensuring that no individual can be identified or traced.

All women who decide to participate in the study will be asked to sign an informed consent form at the time of enrollment after a careful explanation of the project; its aims; how the data will be collected, managed, and processed; the level of involvement required; and the duration of the research, as well as any confidentiality issues. The woman will also be informed of the possibility of quitting the study at any time she wishes without any explanation and that this option would not impact the quality of care or interfere with her course of treatment.

The study will be explained partially by the midwives. In addition, a video recorded by the research team explaining the study, the purpose, and the woman's involvement in simple, understandable words will also be available. The participants will be informed of the study's results through the app.

Regarding data protection, a privacy policy will be provided according to articles 13 and 14 of the Regulation EU 2016/679 of the General Data Protection Regulation, explaining the purposes and legal grounds of the data processing, how the personal data will be collected, their categories, how it will be managed, including the data retention period, the obligations of the data controllers, and the rights of the participants who provide data. Personal data are processed for specific research purposes within the scope of public interest tasks of the data controllers. Informed, freely given, voluntary, and explicit consent will be collected regarding the processing of particular categories of personal data (ie, data concerning health and self-reported behavioral habits in the area of lifestyle health). Moreover, specific consent will be requested regarding the possibility of contacting the participant via telephone to conduct the research interviews.

All data collected will be kept confidential and managed by authorized persons. Data necessary for evaluating the study objectives will be pseudoanonymized before processing. Copies of the study information and the privacy policy will be issued to the participant and will always be available in a dedicated section of the app.

The study manager will produce a research report and report the data responsibly and consistently. Personal data will neither be disclosed nor disseminated except in anonymized or aggregated form for publishing purposes. The publication of data from this study will take place independent of the results obtained. The transmission or dissemination of the data, through scientific journals and presentations at congresses, conferences, and seminars, will take place exclusively in anonymous form using only aggregated data that prevents any identification of the participants, even indirectly. This sharing is expected within 1 year after the conclusion of the study.

Study Outcomes

Primary Outcome

The primary outcomes are UX and UE. They will be assessed using 4 questionnaires, namely the User Engagement Scale-Short Form (UES-SF) [34], the System Usability Scale (SUS) [35], the Italian version of the Chatbot Usability Scale (version B; ITA BUS B) [36], and the User Mobile Application Rating Scale (uMARS) [37], which will be administered at different time slots throughout the study, in particular at the end of the week 3 and at the end of the study (ie, week 6).

The end points that will be measured are the scores of the individual items of the questionnaires (UES-SF, SUS, ITA BUS B, and uMARS), the average score of the questionnaires, and the difference between the average score values of the individual questionnaires at different survey times.

UX refers to the overall perceptions and responses that arise from interacting with a product or system, with reference to aspects such as usability, aesthetics, and functionality [38]. UE describes the user's cognitive, emotional, and behavioral involvement during this interaction [39]. The chosen instruments capture complementary dimensions of UX and UE, including usability, aesthetics, engagement, and satisfaction (for detailed description, refer to Step 3: Participation section). These were selected due to their widespread validation and adaptation in human-computer interaction [40] and their focused use for mobile health app evaluation [41], particularly for chatbot evaluation [36]. Their dimensions are theoretically linked to constructs from cognitive psychology [42] and UX design [43], offering a deep understanding of how users interact emotionally and cognitively with digital products [35,44].

The evaluation of the experience of using the app and the virtual coach (ALBA) and the use of the intervention itself will also be assessed through the semistructured interviews conducted 2 months after childbirth. In this case, qualitative data will be collected to enrich the information related to the primary outcome.

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The platform adopted for the intervention allows for recording activity logs, enabling proper mapping of patients' actions and experiences. This covers a range of logs, assessing whether the patient is appropriately exposed to the intervention protocol while recording use patterns (eg, session execution time, number of accesses, and use patterns of different features). Among the variables considered are any missed sessions or interruptions. These data will be correlated with acceptability scores during the analysis phase. In case a patient does not complete activities and fails to fill in specific questionnaires (leading to data missing), particular pieces of information on patients' experiences and platform use will be collected during the scheduled postintervention interview sessions.

Secondary Outcome

The variable expressing the "psychological well-being" outcome will be assessed by administering 6 self-report questionnaires at the beginning (ie, week 0) and the end (ie, week 6) of the module (refer to Table 1 for a detailed overview of the questionnaire adopted). The end points that will be measured are as follows: a score of the individual items of the questionnaires, the average score of the questionnaires, and the difference between the average score values of the individual questionnaires in the 2 survey times.

Table 1. Summary of the questionnaires administered and their timing.

Questionnaires	Screening	At the beginning of the study (week 0)	At the end of week 3	At the end of the study (week 6)	Follow-up (2 months after birth)
K10[a]	✓				
GHQ[b]	✓			✓	
SF36[c]	✓				
PSS[d]		✓		✓	✓
MPFI[e]		✓		✓	
GSE[f]		✓		✓	
ERQ[g]		✓		✓	
COPE-NVI-25[h]		✓		✓	
UES-SF[i]			✓	✓[j]	
SUS[k]			✓	✓[j]	
ITA BUS B[l]			✓	✓[j]	
uMARS[m]				✓[j]	
Qualitative interview					✓

[a]K10: Kessler Psychological Distress Scale.
[b]GHQ: General Health Questionnaire.
[c]SF36: 36-Item Short Form Health Survey.
[d]PSS: Perceived Stress Scale.
[e]MPFI: Multidimensional Psychological Flexibility Inventory.
[f]GSE: General Self-Efficacy Scale.
[g]ERQ: Emotion Regulation Questionnaire.
[h]COPE-NVI-25: Coping Orientation to the Problems Experienced–New Italian Version (25-item).
[i]UES-SF: User Engagement Scale-Short Form.
[j]These usability questionnaires will be administered the following day, so as not to burden the participant during completion.
[k]SUS: System Usability Scale.
[l]ITA BUS B: Italian version of the Chatbot Usability Scale (version B).
[m]uMARS: User Mobile Application Rating Scale.

These psychological instruments were selected for their widespread validation and adaptation in clinical and psychological research, as well as their relevance for assessing various aspects of mental health and coping in the context of digital health interventions. For example, the Kessler Psychological Distress Scale (K10) is a widely used screening tool for psychological distress, with strong validity across cultures, including Italian culture [45,46]. Furthermore, the Multidimensional Psychological Flexibility Inventory (MPFI) and the Perceived Stress Scale (PSS) are highly relevant for examining psychological flexibility and perceived stress, 2 critical constructs for understanding emotional and behavioral responses in mobile health contexts [47-49], (for detailed

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description of all questionnaires, refer to Step 3: Participation section).

In the framework of this study, these tools are adopted to assess early signals of potential effectiveness of the intervention while assessing UX and UE.

Data Collection

Step 1: Data Collection

The first phase of participant recruitment will take place in collaboration with midwives. In this first phase, the clinical professionals will collect and send the sociodemographic data and email addresses of possible participants (ie, those women who meet inclusion criteria 1 to 6 and have no exclusion criteria) to the FBK researchers, after obtaining informed consent and explaining the study, its purposes, and the need for verification of the characteristics required by inclusion criteria 7 to 9.

Midwives will collect sociodemographic data using a prestructured form. Each woman will be assigned a unique alphanumeric code. The sociodemographic data collection form and the data collected during the study will be stored separately. In addition, data will be pseudonymized to ensure confidentiality.

The parameters requested from pregnant women will be (1) date of birth, (2) expected date of delivery, (3) educational level, (4) occupation, (5) marital status, (6) the number of pregnancies and deliveries, and (7) partner's occupation, if any.

Step 2: Screening

To fulfill the verification of inclusion criteria 7 to 9, the researchers will contact the participants via email and administer the screening questionnaires in Table 1 via the LimeSurvey platform [50]. This platform complies with current data protection requirements and regulations. After the results of the screening questionnaires and the different sociodemographic inclusion criteria have been processed, the women will be contacted again. The following scenarios will open up. First, the participant does not meet the inclusion criteria by manifesting a markedly positive psychological well-being status (stress level, as measured by the K10, <15.9; a general well-being score, as measured by the General Health Questionnaire (GHQ), <3; and a well-being level >80 on the "mental health" scale of the 36-Item Short Form Health Survey (SF-36). In this case, the woman may not be enrolled in the study, and the reasons for exclusion and the results obtained on the screening questionnaires will be returned by the research psychologists only upon the participant's request. Second, the participant does not meet the inclusion criteria by manifesting a markedly negative psychological well-being status (stress level measured by the K10>29.9 and obtaining a well-being level <30 on the "mental health" scale of the SF-36). Even in the latter case, the woman may not be enrolled in the study, and the reasons for exclusion from the study and the results obtained on the screening questionnaires will be returned by the research psychologists only upon the participant's request. In addition, indications of territorial services to which to turn for problems that have arisen will be appropriately provided, again only at the participant's request. This is so that a structured and agreed system of possible access to a territorial service of qualified psychological support can be suggested to the woman concerned, who will provide intake when appropriate. Third, the participant meets the inclusion criteria and is enrolled in the study.

Step 3: Participation

Overview

Women who meet the inclusion criteria and provide consent to participate in the study are enrolled in the study. All women who decide to participate in the study will be asked to sign an informed consent after a careful explanation of the study, as described in the Participant Recruitment and Withdrawal section.

Participants will also be asked if they would like to take part in a qualitative interview 2 months after delivery. In case of positive feedback, their telephone number will be collected to facilitate future contact and follow-up interviews. Women who provide consent to this interview will be sent (again via the app) a questionnaire 1 month after the expected date of delivery in which the following will be asked: (1) actual date of delivery, (2) type of delivery, (3) sex of baby, (4) name of baby, (5) mode of breastfeeding, and (6) date and time when the woman wishes to be contacted for the interview.

As shown in Table 1, the psychoeducational intervention involves completing self-report questionnaires delivered at the beginning, during, and at the end of the interaction with ALBA, in addition to the initial screening phase. Completing the instruments takes about 20 minutes. Specifically, 5 questionnaires will be administered at the beginning and 6 at the end of the intervention to investigate stress, self-efficacy, emotional regulation, psychological flexibility, coping strategies, and psychological well-being. None of these questionnaires has diagnostic purposes, so they will not be used to make diagnoses of psychopathology but only to collect descriptive data. Women with psychopathology will be excluded a priori from participation in the study (as defined in the Participant Recruitment and Withdrawal section). Four questionnaires will be delivered during the course to assess the usability and engagement of the woman with the app and ALBA. Specifically, usability questionnaires will be offered at the end of weeks 3 and 6 (ie, the end of the study).

A detailed description of each instrument that will be administered is presented in subsequent sections.

The Coping Orientation to Problems Experienced (COPE) [51] is a shortened version of the COPE Inventory, designed to assess various coping strategies individuals use to deal with stress. This 25-item questionnaire explores strategies, such as active coping, planning, and acceptance, providing a complex picture of an individual's coping behavior. It uses a Likert scale from 1 (never do it) to 4 (do it often), with a minimum score of 25 points and a maximum of 100. Foà et al [52] translated and validated the questionnaire in Italian, showing good psychometric characteristics.

The Emotion Regulation Questionnaire [53] is a 10-item scale designed to measure the tendency to use 2 emotional regulation strategies as cognitive reappraisal and expressive suppression. Respondents answer each item on a 7-point Likert-type scale

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ranging from 1 (strongly disagree) to 7 (strongly agree). Balzarotti [54] translated and validated the questionnaire in Italian, showing good psychometric characteristics. In this study, Cronbach α was 0.81 for cognitive reappraisal and 0.84 for expressive suppression.

The GHQ is a self-assessment instrument designed to identify mental health disorders and monitor general psychological well-being. Developed by Goldberg and Blackwell [55], the GHQ is widely used in clinical, research, and public health settings. The 12 items of the questionnaire are formulated to investigate how the individual has been feeling recently, with reference to psychological symptoms (such as anxiety and depression), ability to cope with everyday situations, sleep disturbances, and somatic symptoms. The response is based on a 4-point Likert scale, ranging from "much better than usual" to "much worse than usual" with a maximum score of 36. Fontanesi et al [56] translated and validated the questionnaire in Italian, showing good psychometric characteristics.

The General Self-Efficacy Scale (GSE) [57] is a psychometric instrument designed to assess an individual's general perception of self-efficacy, that is, confidence in one's ability to organize and perform the actions necessary to handle potentially stressful or difficult situations. It consists of 10 statements on which respondents must express their level of agreement on a Likert scale ranging from 1 (not true for me) to 4 (exactly true for me). Items on the scale explore various aspects of self-efficacy, such as problem-solving ability, overcoming obstacles, and handling unexpected situations. The total score, obtained by summing the scores of all items, reflects the individual's overall perceived level of self-efficacy and can range from 10 to 40. The GSE scale was translated into 28 languages. Scholz et al [58] examined the instrument's psychometric properties in 25 countries, concluding that the construct of perceived self-efficacy is international and that the GSE is an equivalent measure across different cultures. Cronbach α ranged from 0.79 to 0.90. The Italian adaptation of the GSE scale was developed by Sibilia et al [59].

The K10 is a widely used screening instrument to measure psychological distress. Developed by Kessler et al [45], the K10 is a short questionnaire consisting of 10 items that investigate the frequency of psychological symptoms experienced by the individual in the past month, such as nervousness, sadness, fatigue, and feelings of hopelessness. Each question is scored on a 5-point scale, ranging from "not at all" to "all the time." Total scores can range from a low of 10 to a high of 50, with higher scores indicating a higher level of psychological distress. The Transcultural Mental Health Center also makes available the validated version of this questionnaire in Italian [46].

The MPFI [47] is an assessment tool that measures psychological flexibility on several dimensions. It investigates how people adapt their thoughts and behaviors in response to changing situations and challenges. The MPFI focuses on various aspects of psychological flexibility, including openness to experiences, present-moment awareness, and value-driven action. The 12 dimensions of flexibility and inflexibility (according to the hexaflex model) are assessed through 60 Likert scale items from 1 to 6. The Italian adaptation of the MPFI scale was developed by Landi et al [48].

The PSS [49] is a self-report questionnaire used to measure perceived stress. Specifically, it aims to determine the degree to which situations are perceived as stressful in a person's daily life. Ten 5-point Likert scale questions investigate thoughts or feelings one has had in the past month about certain events, such as how often one has felt unable to control important things in one's life. The Italian version of the PSS-10, translated by Andrea Fossati and obtained from the Carnegie Mellon University website [60], was used.

The SF-36 [61] is the most widely used instrument for measuring general health status. It includes 8 scales: physical functioning (10 items), limitations due to physical health (4 items), pain (2 items), perception of general health (5 items), energy and fatigue (4 items), social activities (2 items), limitations due to emotional problems (3 items), and emotional well-being (4 items). The 36th item differentially assesses the change in health status (2 item) from the previous year. For each dimension, question scores are coded, summed, and transformed into a scale ranging from 0 (worst possible health status) to 100 (best possible health status). The SF-36 has been used in large population studies and in many different clinical conditions, showing excellent psychometric properties. It has been translated and validated in several languages, including Italian [62].

The ITA BUS B [36] is designed to assess users' ease of use, effectiveness, and satisfaction in interacting with chatbots. This tool is structured around 11 items that cover various aspects of the UX with chatbots, aiming to provide an in-depth, multidimensional assessment of their usability. The items involve responses on a 5-point Likert scale, where 1 equals "strongly disagree" and 5 equals "strongly agree," thus scoring from 11 to 55.

The SUS [63] is a quick and reliable tool for assessing system usability. It consists of 10 items with Likert-type responses from 1 to 5. The questionnaire, developed by Brooke [35], provides an overall score that reflects the ease of use and applicability of a system or product. This score can range from 10 to 50. A document with printable SUS questions is available online [63,64].

The UES-SF [34] is a short self-report questionnaire to assess UE with a digital solution. This measure includes 12 items based on a 5-point Likert scale, ranging from 1 (strongly disagree) to 5 (strongly agree). The questionnaire consists of 4 factors: (1) focused attention, which indicates the feeling of being immersed in the interaction; (2) perceived usability, which is the negative effect experienced due to the interaction and the effort expended; (3) aesthetic attractiveness, which represents the graphical and visual appeal to a digital solution; and (4) the reinforcement factor (reward). The latter is a single factor that includes duration, which evaluates the overall success of the interaction; novelty, which examines the general interest related to the interaction with a digital solution; and, finally, the perceived engagement factor, which evaluates the overall enjoyment of the interaction. This questionnaire was not available in Italian

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and was, therefore, translated through the back translation procedure.

The uMARS [65] is a tool for assessing the quality and functionality of mobile apps. It is characterized by a 20-item measure that includes 4 objective quality subscales (engagement, functionality, aesthetics, and information quality) and 1 subjective quality subscale rated on a 5-point Likert scale, ranging from 1 (poor) to 5 (excellent). The total and subscales scores have very high coefficients (0.90 and 0.78-0.80, respectively). The scale has also been validated in the Italian context [66].

Qualitative Interview

A chartered psychologist (SR) from FBK will conduct the interviews. The interviews are structured with ad hoc items to purposively capture specific characteristics of the study and participants' experiences [67]. They will be carried out 2 months after the delivery, last approximately 20 minutes, are subject to the woman's consent, and will be audio-recorded to allow subsequent analysis.

The platform adopted for the intervention allows for recording activity logs, enabling proper mapping of patients' actions and experiences. This covers a range of logs, assessing whether the patient is appropriately exposed to the intervention protocol while recording use patterns (eg, session execution time, number of accesses, and use patterns of different features). Among the variables considered are any missed sessions or interruptions. These data will be correlated with acceptability scores during the analysis phase. In case a patient does not complete activities and fails to fill in specific questionnaires (leading to data missing), particular information on patients' experiences and platform use will be collected during the scheduled postintervention interview sessions.

Data Analysis

Quantitative Analysis

Statistical data processing will be conducted using the software R (version 4.0.0; R Foundation for Statistical Computing), SPSS Statistics (IBM Corp), and Stata (version 17; StataCorp LLC).

Categorical variables will be summarized through absolute and percentage frequency distributions, and quantitative variables through appropriate centrality and variability indices.

Descriptive analyses will be calculated for both psychological variables (stress level, anxiety level, depression level, emotional regulation, psychological flexibility, coping strategies, well-being, and QoL) and variables on usability (UX) and UE. These analyses will be performed on the variables analyzed at the beginning, during, and at the end of the interaction with ALBA.

The relationships between variables will be analyzed mainly through ad hoc statistical tests, such as the chi-square test, Fisher exact test, 2-tailed *t* test for paired data, Wilcoxon nonparametric tests, and the sign test (based on assessment of compliance with assumptions), to understand the differences between the beginning and the end of the course in the same study sample with respect to the variables under investigation.

In addition, univariate logistic or multinomial regression models will be presented. Finally, to eliminate possible confounders, multiple regression models will be proposed in which the effects of the explanatory variables on the outcome variables will be adjusted for possible confounders. For each analysis, statistical significance will be found with a P value of $\leq .05$. It is also planned to use McNemar test [68] and Cochran Q [69] to evaluate paired qualitative data.

Qualitative Analysis

For the analysis of the semistructured interviews, a text mining approach [67] will be used to extract the responses that appear repeatedly in the interviews. To support the analysis, specific software tools, such as NVivo (version 14; Lumivero), could be adopted [70]. The analysis will involve identifying frequently occurring words or phrases to explore dominant lexical patterns. Sentiment and polarity will also be assessed by classifying the emotional tone of texts as positive, negative, or neutral. In addition, meaningful excerpts (quotes) will be extracted, and all results will be interpreted in the context of the relevant literature. The interviews will be conducted regarding the women's experience of using ALBA and how they felt throughout the process (Multimedia Appendix 1).

Results

Recent literature underscores a growing interest in interventions based on ACT, primarily due to their demonstrated effectiveness in alleviating anxiety, depression, and fear of cancer recurrence, as well as in enhancing psychological flexibility and overall QoL. Core ACT techniques, such as mindfulness and cognitive defusion, support the management of anxiety and depressive symptoms by promoting emotional regulation and stress management through acceptance-based approaches. In addition, by encouraging value-driven actions, ACT is expected to foster improvements in well-being and life satisfaction. In line with these goals, this study includes key psychological variables—psychological flexibility (MPFI), self-efficacy (GSE), coping strategies (COPE) New Italian Version, 25-item), and emotion regulation (Emotion Regulation Questionnaire) as predictors, to provide a comprehensive assessment of ACT's impact during different phases of oncological treatment.

From a technical perspective, collaboration with computer science experts will continue throughout the study to ensure the app's structure and design are optimized. We have drawn on previous internal usability evaluations and a co-design study [24] to guide the app's development and refine its features ahead of this pilot phase. During implementation, any new technical issues, such as bugs or glitches, will be monitored and addressed in real time. The primary objective of this feasibility study is to identify and resolve any usability challenges before advancing to a larger-scale trial. Its findings will guide future decisions about scaling the intervention or launching a more extensive efficacy study.

Key benchmarks for evaluating feasibility will include UE, retention and dropout rates, significant improvements in psychological measures (as mentioned earlier), and feedback on the app's acceptability and usability. These data will be

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gathered through self-report questionnaires and technical assessments such as bug tracking. Should these benchmarks be achieved, the study will move toward a broader trial. Moreover, results from this phase will inform potential refinements to both the intervention and study design, ensuring they align more closely with the needs of the target population in terms of content, UX, and delivery methods.

Preliminary data analysis is scheduled for early October 2025, while final results will be available at the end of the study (first half of 2026). The results will be published within 1 year after the study's conclusion.

Discussion

Anticipated Findings

This study aims to investigate and evaluate women's experience and engagement with the TreC Ricerca app and the virtual coach dedicated to the stress intervention (ALBA) and assess the level of pre-post psychological well-being.

First, we expect to collect relevant feedback and suggestions from the women to improve the structure of the intervention, making it more engaging and improving the interaction. Second, we intend to find differences in terms of improved pre-post psychological well-being. However, we are aware that this change may not be related to the intervention itself and that the evaluation of effectiveness will be carried out through a randomized clinical trial at a later stage.

All results will be reported and adequately discussed through a comparison with the relevant literature.

Limitations

This study has several limitations that should be considered and resolved during the implementation of future studies. As mentioned earlier, it is crucial to consider that this study does not aim to evaluate the effectiveness of the intervention, which is why a control group is not planned. It will be crucial to involve a control group to assess the actual effectiveness in a randomized controlled trial. In addition, this study involves several pregnant women from the Autonomous Province of Trento, Italy. It would be interesting to extend the study to women from other regions in Italy as well.

It is important to emphasize that ALBA might be a valuable technological support in providing regular psychoeducational services for women during pregnancy. Moreover, the literature has shown that women during the perinatal period indicated a preference for online support, suggesting that the implementation of digital interventions can overcome barriers to social stigma and seeking help [71,72]. Finally, it is crucial to remember that this technological support (ALBA and TreC Ricerca app) is not a substitute for clinical and medical pathways and in-life medical support; instead, it is an additional element in promoting psychological well-being and healthy lifestyles during pregnancy.

If the results of this study are positive, we expect that, after evaluating its effectiveness, the intervention could be made available as a tool to support the psychological well-being of pregnant women.

Conclusions

Existing literature indicates a preference for online support among women in the perinatal period, highlighting the potential of digital interventions to address barriers related to social stigma and seeking assistance. In this context, ALBA emerges as a possible valuable resource, providing consistent psychoeducational support for women throughout the course of pregnancy.

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This publication reflects only the views of the authors. The Italian Ministry of Health is not responsible for any use that may be made of the information it contains.

Data Availability

The datasets generated and analyzed during this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Questions posed to participants attending the evaluation.
[DOCX File , 8 KB - resprot_v14i1e53891_app1.docx]

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Abbreviations

ACT: acceptance and commitment therapy
ALBA: A Well-Being Assistant
APSS: Azienda Provinciale per i Servizi Sanitari di Trento (Provincial Health Services Authority of Trento)
COPE: Coping Orientation to Problems Experienced
FBK: Fondazione Bruno Kessler (Bruno Kessler Foundation)
GHQ: General Health Questionnaire
GSE: General Self-Efficacy Scale
ITA BUS B: Italian version of the Chatbot Usability Scale (version B)
K10: Kessler Psychological Distress Scale
MPFI: Multidimensional Psychological Flexibility Inventory
ORBIT: obesity-related behavioral intervention trial
PSS: Perceived Stress Scale
QoL: quality of life
RESPOND: Improving the Preparedness of Health Systems to Reduce Mental Health and Psychosocial Concerns Resulting From the COVID-19 Pandemic
SF-36: 36-Item Short Form Health Survey
SH+: Self-Help Plus
SUS: System Usability Scale
TreC Ricerca: Trec Research
UE: user engagement
UES-SF: User Engagement Scale-Short Form
uMARS: User Mobile Application Rating Scale
UX: user experience
WHO: World Health Organization

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Protocol

A Dashboard for Managing an Ecosystem and People With Dementia: Protocol for a Healthy Ageing Ecosystem for People With Dementia (HAAL) International Feasibility Pilot Study

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Abstract

Background: Dementia is a syndrome characterized by a wide spectrum of symptoms and needs. There is no cure for this syndrome, which represents a major challenge to society in terms of quality of life for those affected and in terms of workload and stress burden for those who take care of them.

Objective: The Healthy Ageing Ecosystem for People With Dementia (HAAL) aimed to improve the quality of life of both people with dementia and their formal caregivers (FCs) and informal caregivers (ICs) by providing a personalized set of devices to the person with dementia, along with a dashboard designed for caregivers to monitor and manage the older person.

Methods: The HAAL platform comprises a dashboard that integrates, aggregates, and analyzes heterogeneous data gathered from an ecosystem of devices designed for and tested with people with dementia. The study was designed as a technical feasibility pilot to test the HAAL ecosystem in 3 countries: Italy, Taiwan, and the Netherlands, where older people with initial, moderate, and severe dementia were enrolled, respectively. The study was run in 2 stages: the alpha and beta pilot studies aimed to test the second and third prototypes of the platform, respectively.

Results: The alpha test was conducted from March to May 2023, involving 41 end users, of which 13 were people with dementia, 13 were ICs, and 15 were FCs. The beta test was conducted from September 2023 to February 2024, involving 83 end users, of which 26 were people with dementia, 20 were ICs, and 37 were FCs. The results have been elaborated and are supposed to be published by 2026.

Conclusions: The HAAL pilot study was an innovative feasibility study whose primary objectives were to assess reduction in care load for FCs, stress relief for FCs and ICs, and improvement in the perceived quality of life for ICs and people with dementia. The study also evaluated the usability and the acceptance of the platform. Preliminary analyses of the results showed that the HAAL platform partially relieved caregivers' stress and that the quality of life of people with dementia did not worsen over the test period.

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KEYWORDS

older people; dementia; dashboard; technology for older adults; digital health; eHealth; innovation in health care

Introduction

Background

Dementia is a chronic neurodegenerative syndrome characterized by deficits in cognitive functions, associated with the loss of daily function and with mental and behavioral disorders. The number of people living with dementia worldwide is about 50 million, and it is thought to become 152 million by 2050 [1]. In Europe, there were 7.7 million cases in 2001 that are expected to double by 2040 [2]. In Taiwan, the trend is even worse: the number of people diagnosed with dementia is expected to double every 20 years, exceeding 0.6 million in 2050 [3]. Neuropsychiatric symptoms such as apathy, social withdrawal, disinhibition, agitation, psychosis, and wandering are a source of stress and negatively affect the quality of life of both the person with dementia and their caregiver [4]. There is no cure for Alzheimer disease, although psychosocial interventions have been shown to be effective in improving the quality of life and psychological well-being of people with dementia [5-8]; moreover, they are considered the treatment of choice for the management of psychological and behavioral disorders [9,10]. Neurocognitive disorders, in particular, dementia, represent a major challenge for society. Efforts to reduce the burden for caregivers, as well as for society at large, are imperative. Nordberg et al [11] showed that the amount of informal care received by people with dementia is as much as 6 times greater than formal care, with supervision constituting the largest proportion of the total informal care provided. Older people generally report higher preferences for their home over other living arrangements, and from the societal point of view, this can contribute to the burden of care, for example, for their families. Dementia caregivers are at high risk of care burden, anxiety, and stress, which exposes them to a higher rate of mortality compared with noncaregivers (Vitaliano et al [12]). Thus, promoting ageing in place for people with dementia should not constitute a strategy to shift the burden of care from the formal care services to the informal caregivers (ICs). Instead, efforts should focus on reducing caregiver stress. Part of the difficulties and stress related to caregiving might be prevented by new information and communication technologies and by developing innovative support services for these people [13,14]. This corresponds closely with the recent European strategy on long-term care [14] as well as the recent Horizon 2020 Work Programme [15], both emphasizing the key role of novel information and communication technology systems in supporting the independent living of older people, as a complement to support from other persons. Previous large-scale evaluations, such as the Whole Demonstrator System in the United Kingdom [16], did not include patients with cognitive impairment, even if, for instance, Alzheimer disease is among the most burdensome diseases for the European Society [17]. These data have the potential to inform regional and national policy makers, allowing the introduction of innovative and cost-effective interventions in order to reduce the burden of Alzheimer disease on public finances and single families.

The HAAL Project

The Healthy Ageing Ecosystem for People With Dementia (HAAL) project (AAL-2020-7-229-CP, funded by the European Commission) aimed to develop an ecosystem where smart care technologies are embedded in a unique and innovative platform able to support older people ranging from early to late dementia and their caregivers. The services that were developed in HAAL can support people with dementia to stay longer in their own residences with some degree of independence, supporting the final aim of decreasing the workload of caregivers, while improving the quality of care. The project aims to achieve this goal through 4 main actions: care assistance, monitoring, notification, and prevention. Care assistance is provided by supporting the independence of people with dementia on a daily basis and maintaining their well-being. In practice, it is provided through reminders of daily activities, cognitive and physical stimulation, communication with ICs and formal caregivers (FCs), and an alert button for emergency cases. Monitoring is meant for collecting behavioral data continuously to support remote monitoring of people with dementia, in order to provide more targeted care based on data patterns. The information includes lifestyle patterns of activeness, falling status, location, quality of sleep, and performance for rehabilitating exercises of people with dementia.

The notification service sends real-time notifications to caregivers in case of behavioral deviation. The alarm is triggered by data provided through the monitoring device, which could recognize the lifestyle patterns of the users. Behavioral deviation also includes delayed medication and languishes, while emergency cases include falling, wandering, and a patient getting lost. Finally, HAAL invests in prevention to avoid undesirable accidents or irreversible deterioration. This service runs in parallel with the alarm by using longitudinal behavioral data to predict the risk of falling, getting lost, dementia progression, and other frailty symptoms.

The HAAL project stood out from traditional ambient assisted living systems by integrating a customizable, artificial intelligence–driven ecosystem that actively supports both people with dementia and their caregivers. Unlike conventional ambient assisted living solutions, which rely on passive monitoring, HAAL leverages predictive analytics to detect behavioral deviations and cognitive decline patterns over time, allowing for early interventions before critical issues arise. Traditional systems primarily focused on reactive alerts, but HAAL not only offered real-time monitoring but also provided proactive, data-driven insights to help caregivers anticipate risks and adjust care strategies accordingly. Furthermore, while past solutions often followed a one-size-fits-all model, HAAL ensures highly personalized care, dynamically adapting assistive technologies to the specific stage of dementia so that support evolves with the user's changing needs. In fact, many existing platforms lacked flexibility, whereas HAAL is scalable and modular, integrating different smart devices as required to provide a seamless transition from early to advanced dementia care.

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Goal of the Study

This paper presents the HAAL field trial, a feasibility study whose primary objectives were to assess the stress relief at work for FCs and ICs, the improvement in the perceived quality of life for ICs and persons with dementia, the reduction in care load for the FCs, and the increased cost-effectiveness of the HAAL solution in comparison with the available services. Secondarily, the study aimed to assess the usability and acceptance of the HAAL platform for both people with dementia and caregivers. The purpose of this project was to present and share with the scientific community the HAAL innovative ecosystem and the related field trial protocol for testing it worldwide (Italy, the Netherlands, and Taiwan) with caregivers and people with dementia in real scenarios.

Methods

The HAAL Platform

The HAAL platform, presented in this section, is comprises 6 smart technologies designed for people affected by dementia (an interactive game for cognitive training, a social robot, a GPS-tracking system, a lifestyle-monitoring system, an alarm system, and a smart mattress) and 1 dashboard—consisting of a web app—to be installed on a tablet or PC. Since people with dementia start losing the ability to comprehend some digital interactions (social robots and interactive games) in the transition from early to middle dementia, each user benefits from a combination of such devices, according to their own needs. The dashboard, which is used by the IC, receives, analyzes, and shows data acquired and processed by those devices through machine learning (ML) algorithms to detect and determine the health status of people with dementia. In particular, unsupervised algorithms (k-means) were adopted to highlight the deviation of people with dementia from standard behavior, while supervised algorithms were applied to describe and predict the behavior of people with dementia. The first prototype of the platform has been preliminarily tested in the laboratory by Morresi et al [18] and then underwent the usability test successfully [19]. Then, subsequent prototypes 2 and 3 were developed to be tested in the alpha and beta stages of experimentation, respectively. The alpha prototype was developed on the basis of integrated fictitious data, used for formative evaluation with the goal of studying the overall experience, usability, acceptability, and attitude toward the system over a short time period to collect feedback from end users. The beta prototype was a version of the system intended for market launch that includes ML algorithms to predict various aspects of the well-being of people with dementia such as the previous version but refined through data collected during the alpha testing stage of the project. In summary, while the alpha prototype was trained with simulated data, the beta prototype implemented ML algorithms with real data. In addition to that, much of the feedback received at the end of the alpha stage was translated into technical requirements and implemented in the subsequent beta version to improve the usability, acceptability, and efficiency of the platform. Figure 1 shows the platform architecture.

Figure 1. Healthy Ageing Ecosystem for People With Dementia (HAAL) platform. IADL: instrumental activities of daily living.

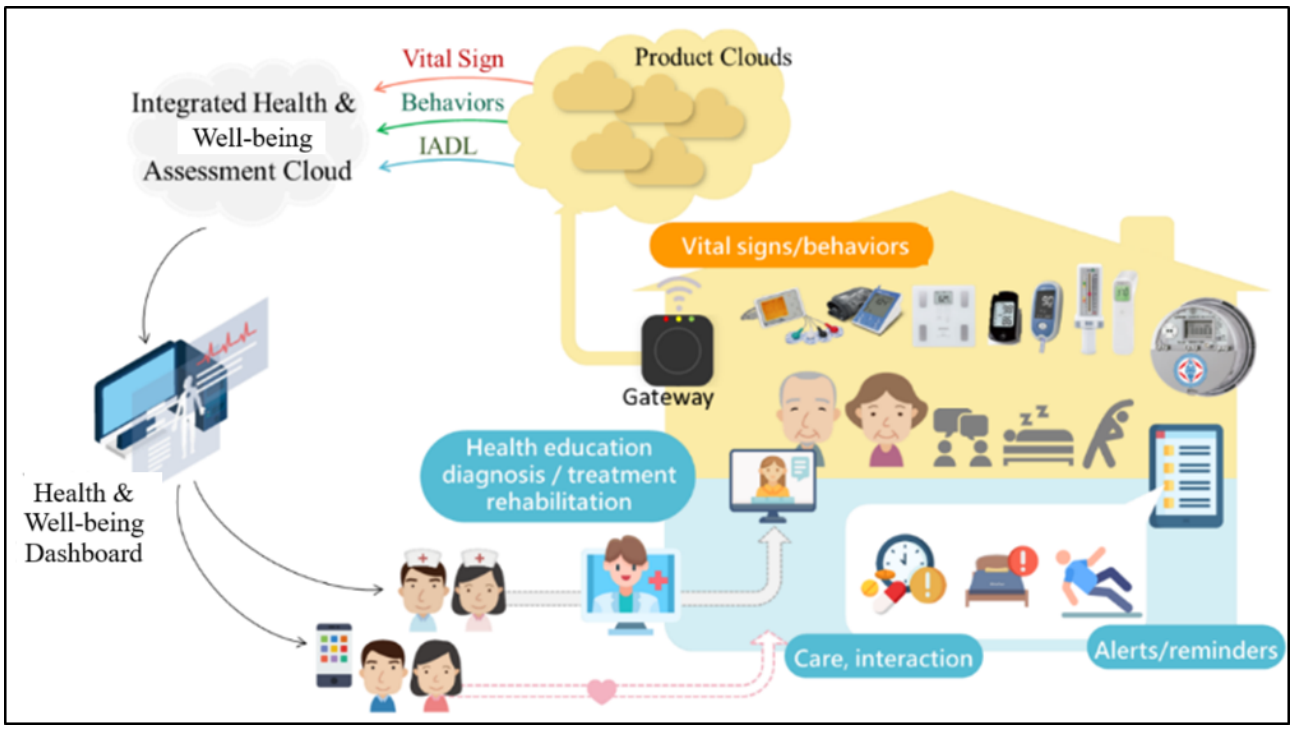

WhizToys

WhizToys, displayed in Figure 2, is 9 lightweight, portable motion-sensing floor tiles arranged to form a 3 × 3 square. They can be connected to a television to display game instructions on the screen. The game combines physical activity and cognitive training. The game is considered a serious gaming gym that can be personalized. This could prevent cognitive function decline or slow down the progression of the mild cognitive impairment stage. Older adults could participate in different cognitive games, such as music, numbers, colors, and

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spelling, simply by walking and stepping on tiles. In addition to providing multisensory stimulation such as visual, light, and sound, the app also allows caregivers to choose a game type and difficulty level. The app also provides individual user accounts and stores the game results in the cloud for subsequent evaluation and analysis. Basically, the input variables include people's movement and their background information such as age and gender. The primary output of the WhizToys game app includes steps, total playtime for a game, memory time for the memory-training games, frequency of use, correction rate of the game, length of steps, and time of the timed up and go results. The app also provides individual user accounts and stores the game results in the cloud for subsequent evaluation and analysis.

Figure 2. WhizToys.

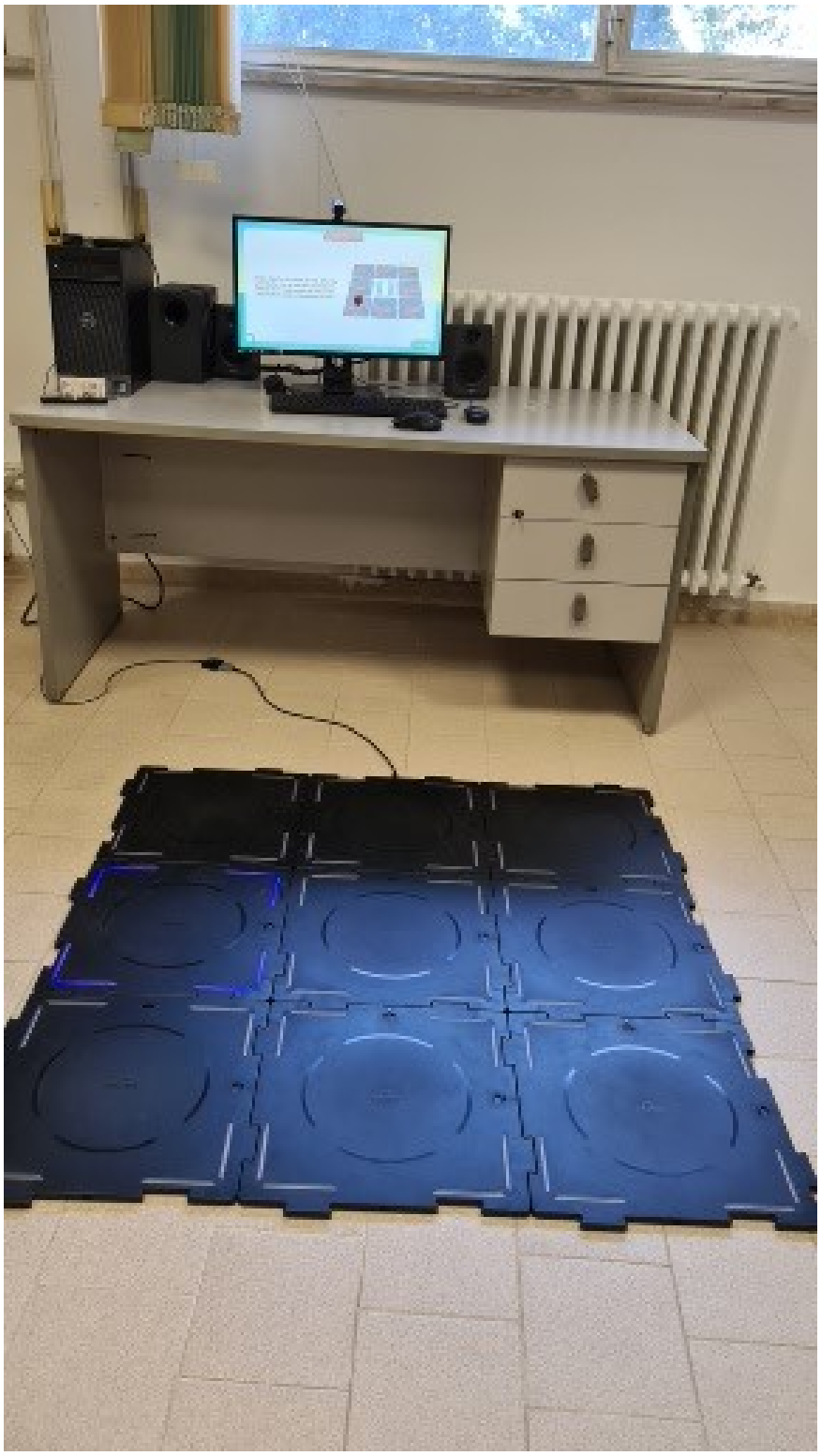

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Tinybots

Tinybots, displayed in Figure 3, is a small social robot named Tessa, able to provide verbal guidance to older adults on daily activities. Tessa has her own speaker and microphone to communicate with the user and is able to understand yes/no answers. Tessa helps people with orientation by giving personal reminders, suggesting activities, or providing instructions for certain tasks. Tessa helps people get active again by providing spoken suggestions and by playing personal music. In fact, caregivers can schedule the tasks and personalize the spoken messages and instructions spoken by Tessa, which helps people with dementia to structure their days. ICs use a simple web app to write messages for Tessa and schedule these messages at specific times.

Figure 3. Tinybots and its web application.

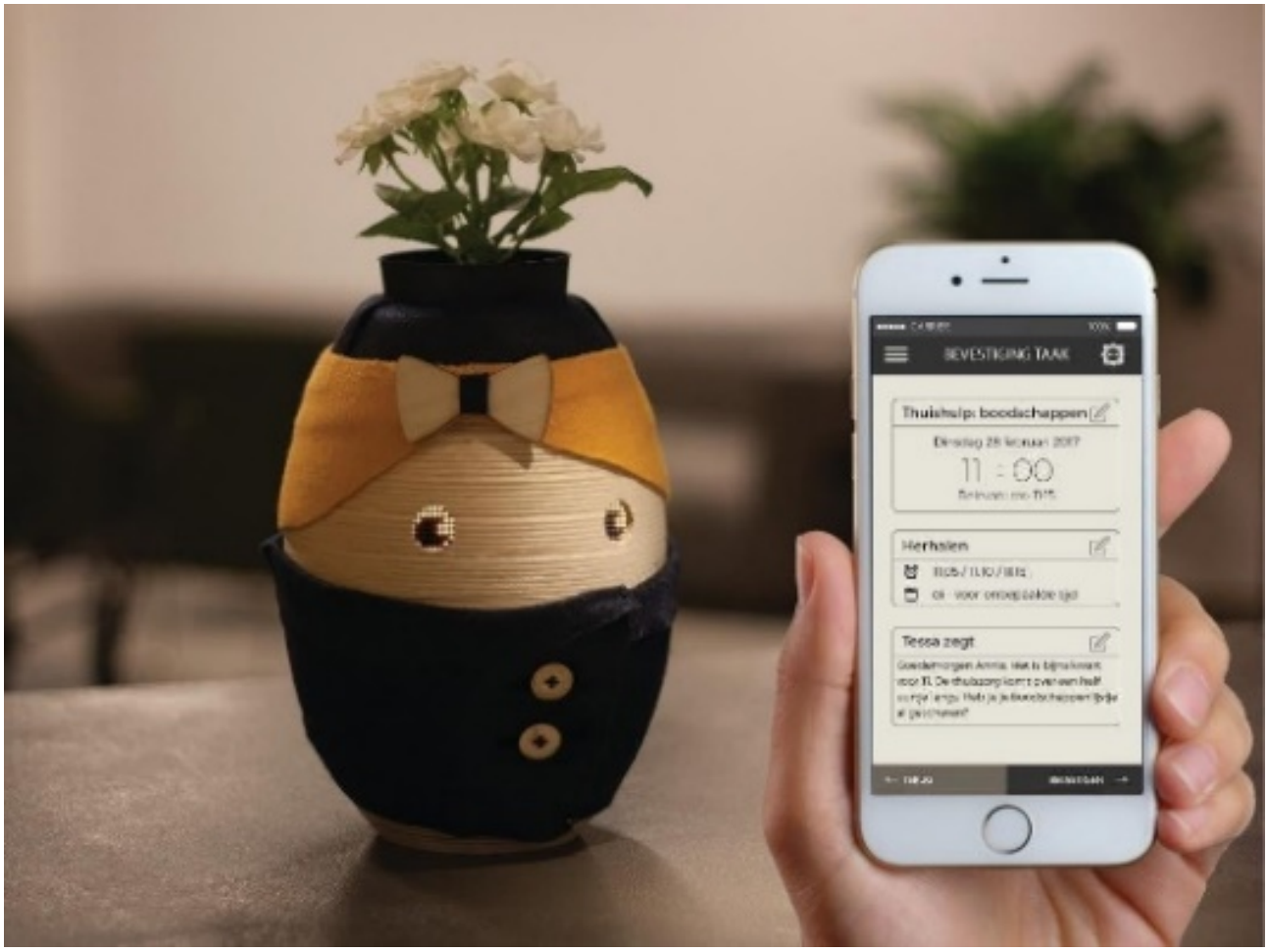

Kompy Pico

Kompy Pico, displayed in Figure 4, is a GPS tracker that can be used to localize or call someone and to set a geofence. It is a personal device that the user can wear as a necklace, attach to a belt, or keep in a pocket, and it has a GPS, Bluetooth, and Wi-Fi. The device is precise in determining the location both in indoor and outdoor locations. Kompy Pico provides direct communication between the people with dementia and the IC, which can be called through the alarm button. The caregiver receives the alarm notification directly on the mobile app Mopas, available on both Google Play and Apple Store. As soon as the alarm goes off, the exact position of the people with dementia is sent to the caregiver. The caregiver can set a “safe zone,” which is a specific area outside of which the user is not expected to be and therefore the alarm can be sent. All the activities of the people with dementia for the last 60 days can be tracked and logged in the app.

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Figure 4. Kompy Pico.

Sensara

Sensara HomeCare has 8 wireless sensors that can be installed in toilets or bathrooms, kitchens, exit doors, halls, and living rooms to monitor older persons' daily activities (Figure 5). The sensors are unobtrusive, battery operated, and privacy friendly. Due to smart (self-learning) algorithm design, the system automatically supports all possible customer lifestyles. After 2 weeks of use, the algorithm is able to distinguish the person's daily activities and set a baseline behavior. Sensara informs the FCs and ICs via a smartphone app if something goes wrong. When caregivers want to zoom in on trends, they can see how things are going in the long run. Otherwise, they can check on what is going on in the present on the events list.

Figure 5. Sensara.

CogvisAI

CogvisAI, displayed in Figure 6, is a medium-sized sensor to be mounted on a wall of a room that makes use of 3D smart sensors to analyze behavior. Based on these data, an alarm can be sent in critical situations: when an inhabitant leaves the space or falls. Furthermore, it can be sensed if someone is in the bed or not. CogvisAI mainly focuses on the later stage of dementia, in which older adults have a problem wandering or falling. Furthermore, the device is coupled to a specific account from which the IC can see the status of the device and settings for which detections a notification should be sent to whom.

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Figure 6. CogvisAI.

WhizPad

WhizPad is a comfortable mattress made with temperature-sensitive pressure-relieving foam to prevent pressure ulcers (Figure 7). WhizPad is a thin mattress pad made of memory foam and conductive textile materials. WhizPad counts more than 30 sensing areas installed, which provide an on/off signal, which means that whenever they are activated, they provide a binary output (on = sensor is activated, off = sensor is not activated). Data coming from pressure sensors are processed and fed into an ML algorithm for posture identification of the patient. Given the event algorithms implemented in a bedside data processor, the pressure signals collected by WhizPad can be used to detect on/off bed, sleep posture, movement counts, and respiration rate. Integrated with information and communication systems, caregivers can maintain awareness of older adults' daily activities and needs by using their mobile devices to access the WhizPad for real-time monitoring and a historical data record of bed-related activities, as well as receiving service reminders and alerts for abnormal events.

Figure 7. WhizPad.

Dashboard

The core of the HAAL project is the development of the dashboard, which focuses on the well-being of people with dementia. In fact, the dashboard integrates heterogeneous data from the abovementioned smart care products and is processed by an ML algorithm. The dashboard primarily focuses on descriptive analyses with relatively low complexity and a low level of automation. The indices provided by the smart care products are categorized into "vital sign indices," "behavior indices," and "instrumental activities daily living indices." Based on public standards (ie, set by World Health Organization) and personal patterns (established by everyday measurements), the assessment algorithm ranks the indices into 4 levels: great, normal, attention, and abnormal. The final status is marked as the worst level among all 4 statuses. Notably, each profile has

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4 statuses: high urgency (need action at that time), low urgency (may need attention), offline (adopted devices are not working or connected), and normal (no detected deviation). These statuses are shown in 4 colors: red, orange, blue, and green, respectively. Besides, the deviations or accidents require action from FCs. Each situation contains 3 levels of response status: requiring (need responding), attending (when a caregiver responds), and being already attended (when a caregiver marks the situation as safe). The second branch for medical workers would focus on giving a quick overview of several clients and urgent notifications. The dashboard is designed to be displayed on a television or a personal working computer. The notification is sent to a working mobile phone. The health and response statuses are consistent with the first branch. Figures 7-11 show various screens of the dashboard to understand what the caregiver can see and do on it. The caregiver, through the menu "List of Clients" (shown in Figure 8), has an overview of clients whom he or she is caring for. Moreover, there are data about age, weight, level of dementia, and location of the patient.

Figure 8. Healthy Ageing Ecosystem for People With Dementia (HAAL) dashboard home page: lists of patients followed by a caregiver.

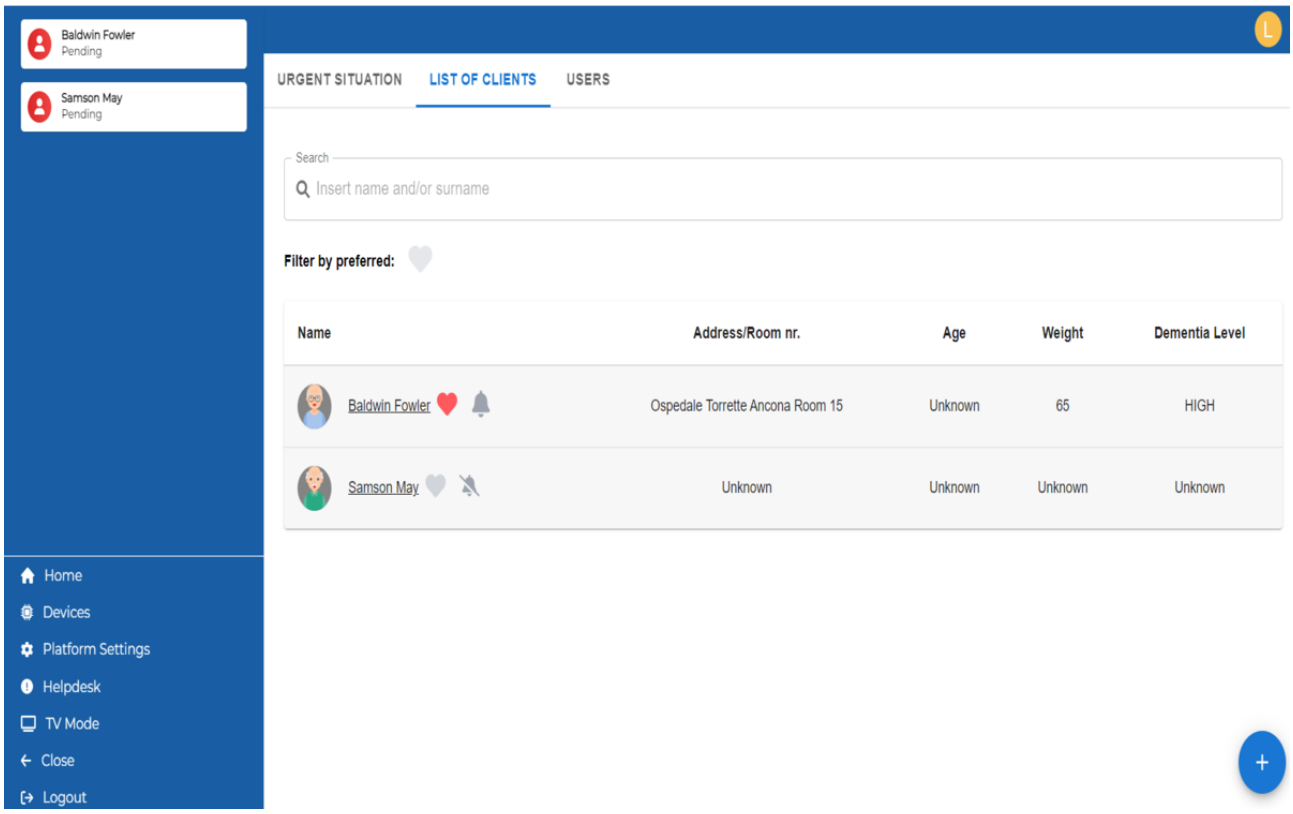

Then, the caregiver can select 1 single patient and get an overview of its situation, coded by color and dimension of the following aspects: physical status, sleep activity, cognitive status, and general well-being, as shown in Figure 9. In the same screen (Figure 9), the caregiver has information about pending situations, general notes (that are added by the caregiver), and emergency contacts of the patient.

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Figure 9. Healthy Ageing Ecosystem for People With Dementia (HAAL) dashboard. General overview of a single patient's status: quality of physical status, sleep activity, cognitive status, and general well-being.

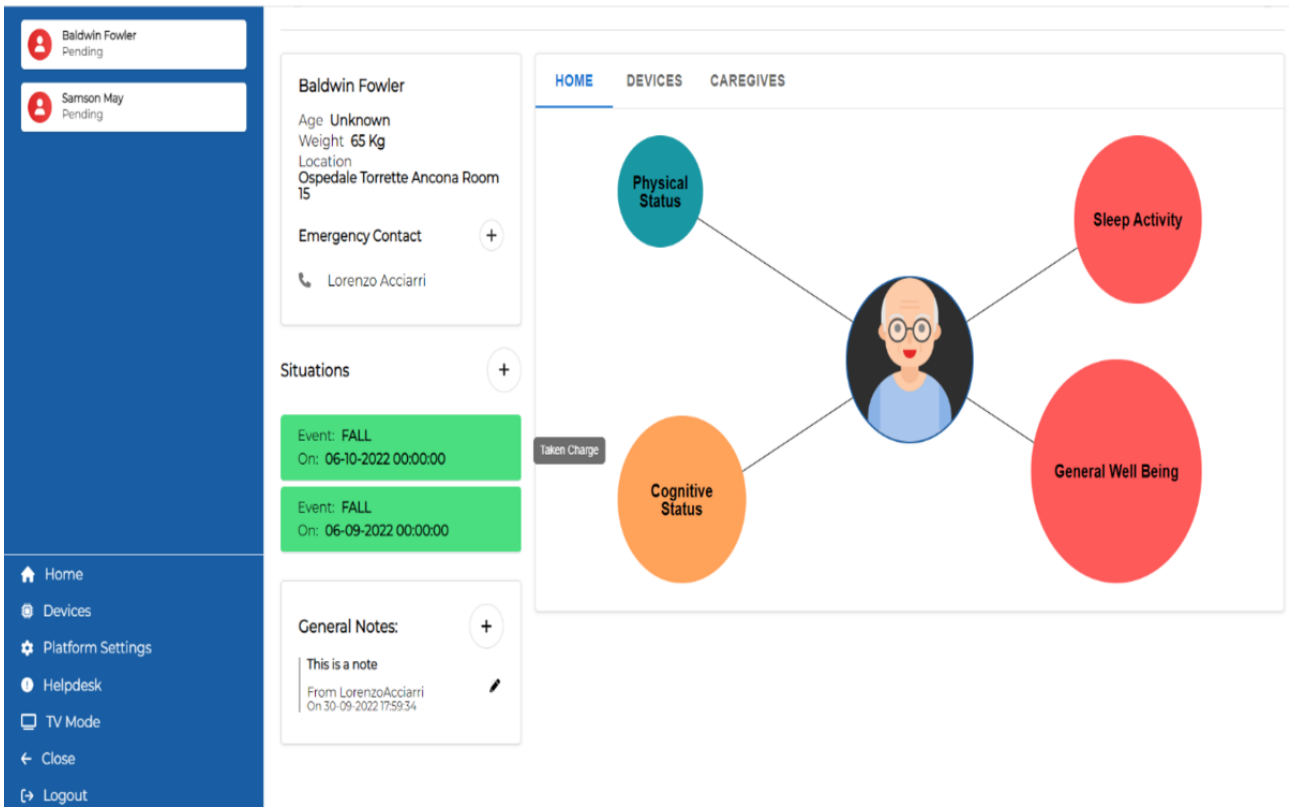

In the "Situations" window, shown in Figure 10, the caregiver can view who requires intervention. In this case, all the situations were already taken in charge (in fact, the situations are shown in green). The kind of situation is written in the column "situation," and the location and connection status are shown.

Figure 10. Healthy Ageing Ecosystem for People With Dementia (HAAL) dashboard. Overview of situations occurred to a patient.

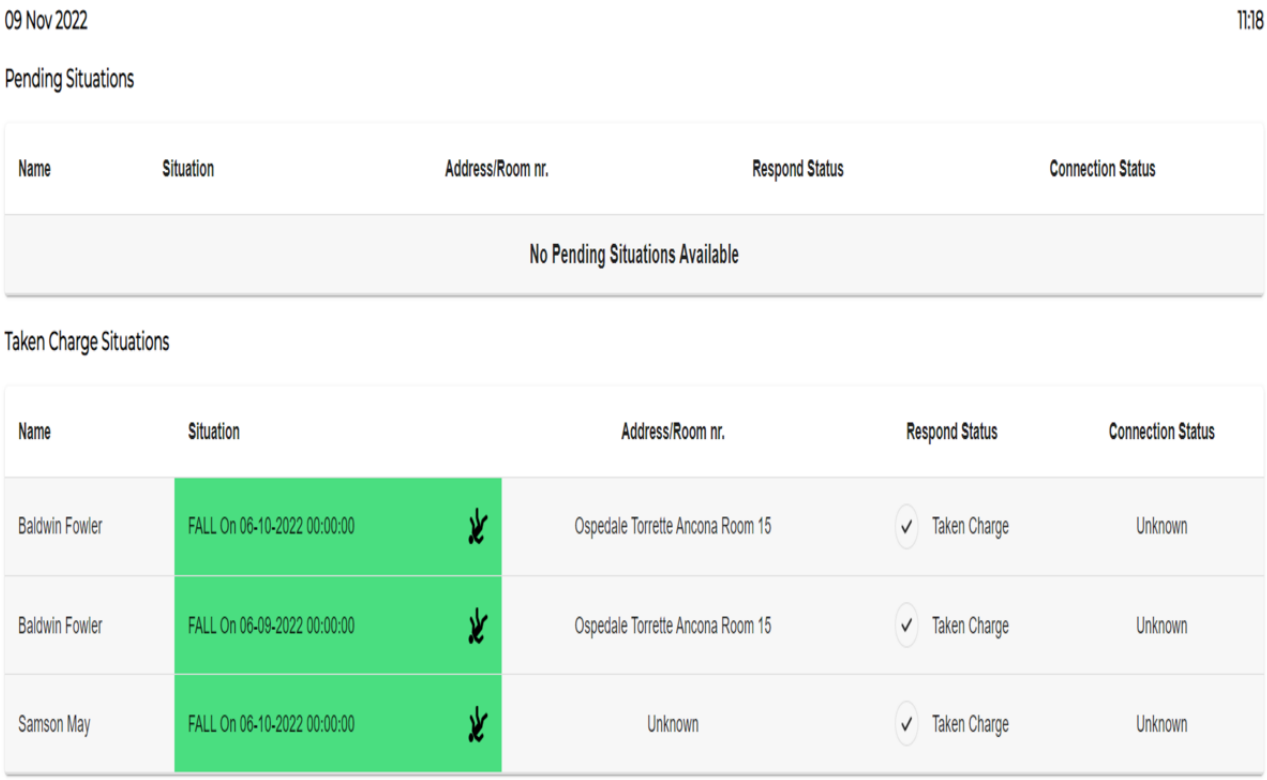

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In the device menu, displayed in Figure 11, it is possible to see which devices are used by the patient. The color (given by the round of the device) codes the level of alert related to each device. In Figure 11, the analysis of data collected by WhizPad is alarming (red), whereas there is a warning related to Sensara, and no problem from the GPS tracker.

Then, the caregiver can explore a single device to get insights about the collected and analyzed data. In Figure 12, an analysis of data collected by WhizPad is shown.

Figure 11. Healthy Ageing Ecosystem for People With Dementia (HAAL) dashboard. Overview of installed devices used of a patient.

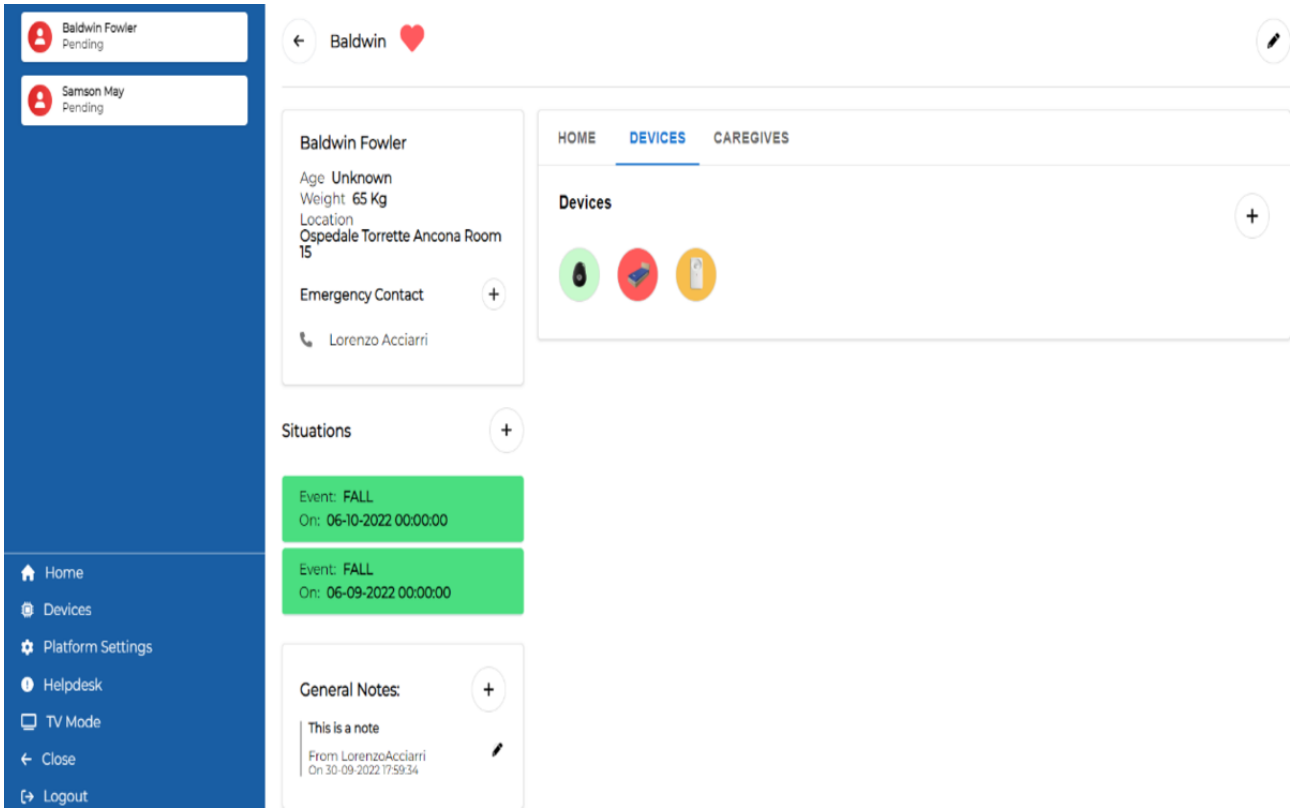

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Figure 12. Healthy Ageing Ecosystem for People With Dementia (HAAL) dashboard. Focus on data analysis of a device: measurement of sleep quality by WhizPad.

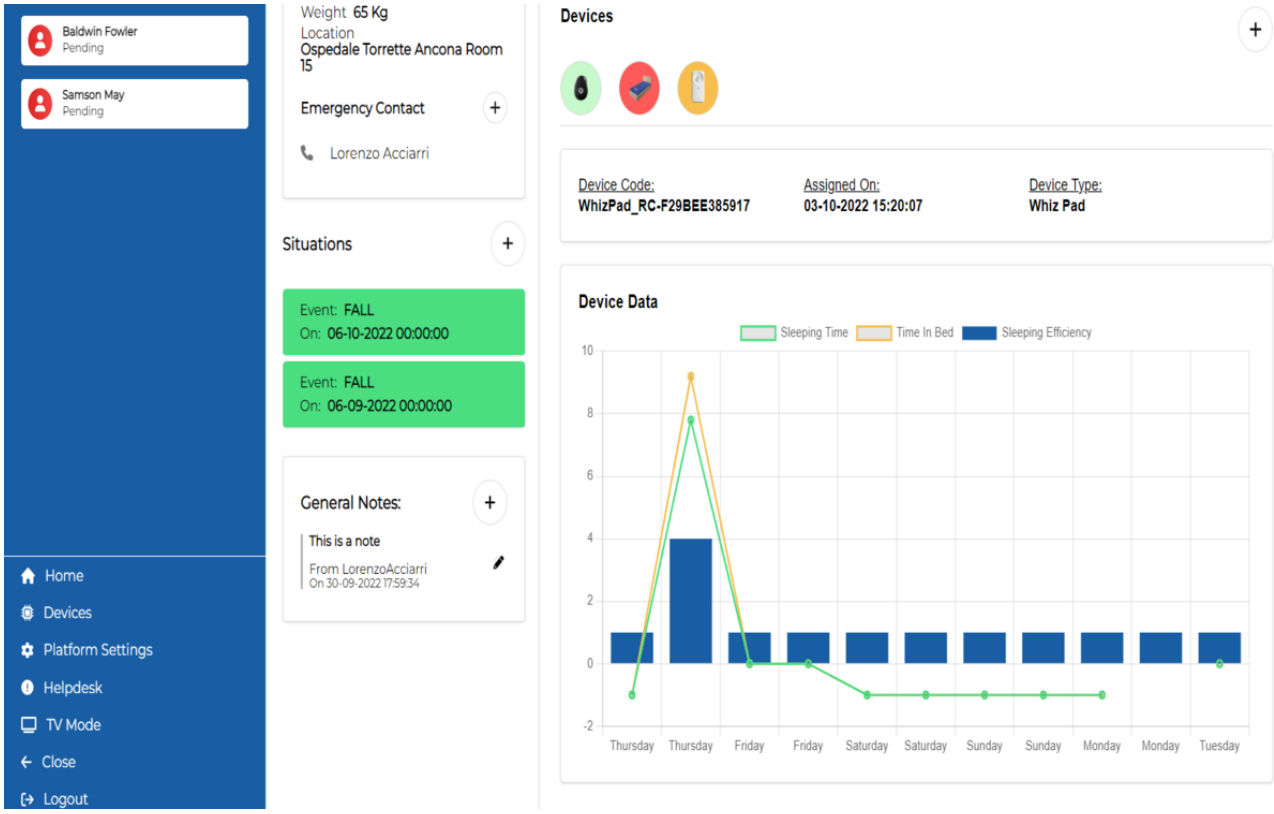

The Field Trial

The field trial was conducted as an uncontrolled longitudinal study, with a before and after design where the observations are made on a series of enrolled individuals, receiving the intervention described in this section with no control group, with data collected before and after the installation and use of the technical solution. The uncontrolled longitudinal design was chosen to assess the practical implementation, usability, and preliminary effectiveness of the HAAL platform, although it might introduce selection bias, measurement bias, and confounding variables. The field trial was also conducted in 2 stages—alpha and beta—where prototypes 2 and 3 of the HAAL dashboard were tested, respectively. Both phases were run in the same way in terms of duration and activities carried out, as well as interviews. The field trial procedure was divided into 4 different phases after the recruitment of the participants: baseline evaluation (T1), first evaluation (T2), second evaluation (T3), and final evaluation (T4), with the aim of collecting data as described in Textbox 1. Given the study's reliance on consistent participation from people with dementia and their caregivers, data dropouts were anticipated and addressed by design. In fact, as the study involves 4 evaluation phases, partial data could still be collected and analyzed even if a participant dropped out. The same principle stands for qualitative data. However, to prevent dropout and make the participants feel involved in the study, they were contacted frequently (eg, every 2 weeks) by research personnel and supported promptly any time they needed technical support. In any case, even dropouts, accompanied by justification, constitute useful feedback in a feasibility study in order to understand the weaknesses of the solution to be improved.

Textbox 1. Field trial phases.

- Recruitment phase: the recruitment protocol included general information on the subjects, in particular, health status and cognitive condition. The information was collected with the help of the caregiver or family member, if needed.
- Baseline evaluation consisted of the first real contact with the users and their families, before the start of the field trial.
- First evaluation (after 1 month of use): the aim of this phase is to analyze the usability and acceptability of the system, after a short period of use. The evaluation of the system usability was conducted adopting qualitative and quantitative techniques.
- Second evaluation (after 2 months of use): the aim of this phase is to analyze the usability and acceptability of the system, after a short period of use. The evaluation of the system usability was conducted adopting qualitative and quantitative techniques.
- Final evaluation (after 3 months of use): the aim of this phase is to collect useful information on the whole benefits perceived by the users after a meaningful period of use of the system. The final evaluation was conducted after the system deinstallation to detect and analyze the impact of the system in the daily life of the older people and their family and to gain knowledge on older adults' technology acceptance and usability issues and provide methodological approach for further studies in the field.

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Recruitment

In the dementia care context for HAAL, 3 groups of end users were involved, such as people with dementia, ICs, and FCs. People with dementia vary between mild cognitive impairment and severe stages of dementia. This intellectual deterioration can be measured using the Global Deterioration Scale, which defines 7 cognitive decline stages and 4 stages of dementia [20]. As this was a pilot study on the feasibility of using the technology, the sample size was not calculated. However, similar studies [21,22] were taken as reference points and, above all, the analysis of Billingham et al [23], which shows that in feasibility pilot studies, net of great variability, an average of 30-36 participants are included. For these reasons, it was decided to recruit 45 participants in the alpha test and 90 participants in the beta test, that is, 15 and 30 triads, respectively, equally divided among the 3 pilot sites.

In Italy, the end users were recruited from the neurology unit and Alzheimer assessment unit (Memory Clinic) of the Italian National Institute of Health and Science on Aging (IRCCS INRCA). The research team had the opportunity to meet the families of patients with dementia and to present them with the project and the modalities of possible participation. Researchers at Vilans—a private organization for digital health—recruited participants via the care organization Livio, established in the Enschede region, in the Netherlands. In Taiwan, 2 research institutes actively participated in the HAAL field trials. The Yuan Ze University recruited participants at Bianciao Veteran Dementia Nursing Home, while the National Cheng Kung University recruited the end users from day care centers established by Schuhe Social Welfare Foundation.

Older People With Dementia

Once the informed consent was obtained in duplicate, the compliance with the criteria of inclusion and exclusion of the study was verified, and the baseline evaluation was carried out with the questionnaires and clinical trials provided by the study design. The inclusion and exclusion criteria are reported in Textbox 2.

Textbox 2. Inclusion and exclusion criteria for people with dementia.

Inclusion criteria

- Aged 65 years and older.
- Capacity to consent.
- Score at the Global Deterioration Scale (GDS) as follows: GDS 2-4 (group A), GDS 5 (group B), and GDS 6-7 (group C).
- Have both an informal and a formal caregiver to support in carrying out the main daily activities.
- Healthy sight and hearing.

Exclusion criteria

- Active implantable medical device incorporated.
- Failure to meet the inclusion criteria.
- Concomitant participation in other studies.
- Lack of written informed consent.
- Lack of informal caregiver.
- Sight and hearing not intact.

Informal Caregiver

ICs are mostly family members or daily references of the people with dementia. Connections between ICs and clients are private and not via a care organization. ICs are usually concerned about the well-being of the people with dementia, and they provide emotional or practical support regularly. Although it is easier to live near the people with dementia, ICs did not necessarily need to live close to the people with dementia. ICs were included in the HAAL project since they play an important role in the daily life of the people with dementia. Moreover, the ICs can fulfill caring tasks to reduce the burden of FCs. A good collaboration between IC and FC is needed, as the IC can be the link between the client and the FC.

The inclusion and exclusion criteria are reported in Textbox 3.

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Textbox 3. Inclusion and exclusion criteria for informal caregivers.

Inclusion criteria

- Being the informal caregiver of a person with cognitive impairment or dementia in stage, following the Global Deterioration Scale groups.
- Availability of time to participate.
- Visiting the assisted person at least 2 times a week or living with him or her.

Exclusion criteria

- Active implantable medical device incorporated.
- Lack of familiarity with apps and minimal digital literacy.
- Failure to meet the inclusion criteria.
- Concomitant participation in other studies.
- Lack of written informed consent.

Formal Caregivers

Care professionals or FCs are professionally responsible for dementia care. They are trusted agents for people with dementia and have direct contact with older adults and provide care when needed. In Italy, the FCs are a case manager, neurologist, psychotherapist, occupational therapist, and nurse. The case manager is responsible for the organization. The neurologist is a specialized medical doctor who diagnoses the disease and prescribes the treatment. The psychotherapist leads the intervention, whereas the nurses and the occupational therapists act as assistants. These professionals may be especially found in day care, but they are available in residential home care as well. People at a severe stage of dementia are suggested to move to a care home.

In the Netherlands, the FCs are case managers or nurses. In other words, they are local district nurses, and case managers have a specialization in dementia care. Nurses are responsible for nondiagnosed seniors, while case managers would be assigned for the diagnosis of people with dementia and take part in long-term care provision. They will provide home care in the early and middle stages of dementia until the person needs more intensive professional care for daily tasks. Then, in the severe stage, the case managers would suggest the transition to a care home to receive professional caregiving.

In Taiwan, the care of people with dementia is first evaluated by the case managers of the long-term care management centers supervised by Ministry of Health and Welfare. The case managers are well-trained physicians, physical therapists, occupational therapists, nurses, and social workers. After the assessment, the case managers will arrange related follow-up care services for people with dementia. The follow-up care services include home care, day care centers, institutional care, group homes, psychiatric wards for older adults, institutional respite services, and so forth (Textbox 4).

Textbox 4. Inclusion and exclusion criteria for formal caregiver.

Inclusion criteria

- Being the formal caregiver of a person with cognitive impairment or dementia in stage, following the Global Deterioration Scale groups.
- Availability of time to participate.
- Work experience of at least 4 years in the field.

Exclusion criteria

- Failure to meet the inclusion criteria.
- Concomitant participation in other studies.
- Lack of written informed consent.

Outcomes

The field trials aimed to assess the feasibility of implementing the HAAL platform in the assistance of people with dementia at any stage. For this reason, the primary interest was to assess the impact of the HAAL platform on caregivers' workload and end users' quality of life, as described in Textbox 5. Then, the field trials also focused on the usability and cost-effectiveness of the HAAL solution, as shown in Textbox 6.

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Textbox 5. Primary outcomes of the study.

- Reduction of the care load of the formal caregiver (FC) and the informal caregiver (IC) through Zarit Burden Interview [24].
- FC's and IC's decrease in stress and anxiety through the General Anxiety Disorder-7 [25].
- Improvement in the perceived quality of life for IC and person with dementia through EQ-5D [26].

Textbox 6. Secondary outcomes of the study.

- Usability of the platform for formal caregiver and informal caregiver through System Usability Scale [27] and semistructured interview.
- Increased cost-effectiveness of the Healthy Ageing Ecosystem for People With Dementia (HAAL) solution in comparison with the available services through semistructured interview.

For these reasons, the protocol included study-specific questions on demographics, attitudes toward and acceptance of the HAAL platform technology, and questions regarding demands and cost. All scales used are validated in the pilot sites' languages and suitable for administration to the patients recruited in the study. Tables 1-Tables 4 summarize different tools adopted with each end user group in all the phases of the study.

Table 1. Tools and dimensions for the people with dementia protocol at stages 2-4 of the Global Deterioration Scale.

Dimension and tool	R[a]	T1[b]	T2[c]	T3[d]	T4[e]
Cognitive status: GDS[f] [20]	✓				✓
Sociodemographics: ad hoc questions		✓			
eHealth literacy: eHEALS[g] [28]		✓			
Attitude toward technology: ATDPA-E[h] [29]		✓			
Quality of life: EQ-5D [26]		✓	VAS[i]	VAS	✓
Usability					
SUS[j]		✓	✓	✓	✓
Ad hoc questions			✓		✓
Desirability cards			✓		✓
Acceptability: ad hoc questions					✓

[a]R: recruitment.
[b]T1: baseline.
[c]T2: first evaluation.
[d]T3: second evaluation.
[e]T4: final evaluation.
[f]GDS: Geriatric Depression Scale.
[g]eHEALS: eHealth Literacy Scale.
[h]ATDPA-E: Assistive Technology Device Predisposition Assessment, Scale E.
[i]VAS: Visual Analogue Scale.
[j]SUS: System Usability Scale.

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Table 2. Tools and dimensions for the people with dementia protocol at stages 5 and 6-7 of the Global Deterioration Scale.

Dimension	Tool	R[a]	T1[b]	T2[c]	T3[d]	T4[e]
Cognitive status	GDS[f] [20]	✓				✓
Sociodemographics	Ad hoc questions		✓			
Quality of life	EQ-5D [26]		VAS[g]	VAS	VAS	VAS
Usability	Ad hoc questions			✓		✓
Acceptability	Ad hoc questions					✓

[a]R: recruitment.
[b]T1: baseline.
[c]T2: first evaluation.
[d]T3: second evaluation.
[e]T4: final evaluation.
[f]GDS: Geriatric Depression Scale.
[g]VAS: Visual Analogue Scale.

Table 3. Tools and dimensions of the informal caregiver protocol.

Dimension and tool	R[a]	T1[b]	T2[c]	T3[d]	T4[e]
Sociodemographics: ad hoc questions	✓	✓			
eHealth literacy: eHEALS[f] [28]		✓			
Attitude toward technology: ATDPA-E[g] [29]		✓			✓
Social support: Lubben Scale [30]		✓			
Quality of life: EQ-5D [26]		✓	VAS[h]	VAS	✓
Caregiver burden: Zarit Burden Interview [24]		✓	✓	✓	✓
Anxiety and stress: GAD-7[i] [25]		✓	✓	✓	✓
Usability					
SUS[j] [27]			✓		✓
Ad hoc questions			✓		✓
Desirability cards			✓		✓
Acceptability: ad hoc questions					✓
Demand and cost information: ad hoc questions					✓

[a]R: recruitment.
[b]T1: baseline.
[c]T2: first evaluation.
[d]T3: second evaluation.
[e]T4: final evaluation.
[f]eHEALS: eHealth Literacy Scale.
[g]ATDPA-E: Assistive Technology Device Predisposition Assessment, Scale E.
[h]VAS: Visual Analogue Scale.
[i]GAD-7: 7-item Generalized Anxiety Disorder.
[j]SUS: System Usability Scale.

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Table 4. Tools and dimensions of the formal caregiver protocol.

Dimension and tool	R[a]	T1[b]	T2[c]	T3[d]	T4[e]
Sociodemographics: ad hoc questions	✓	✓			
eHealth literacy: eHEALS[f] [28]		✓			
Attitude toward technology: ATDPA-E[g] [29]		✓			✓
Quality of life: EQ-5D [26]		✓	VAS[h]	VAS	✓
Caregiver burden: Zarit Burden Interview [24]		✓	✓	✓	✓
Anxiety and stress: GAD-7[i] [25]		✓	✓	✓	✓
Usability					
SUS[j] [27]			✓	✓	✓
Ad hoc questions			✓		✓
Desirability cards			✓		✓
Acceptability: ad hoc questions					✓
Demand and cost information: ad hoc questions					✓

[a]R: recruitment.
[b]T1: baseline.
[c]T2: first evaluation.
[d]T3: second evaluation.
[e]T4: final evaluation.
[f]eHEALS: eHealth Literacy Scale.
[g]ATDPA-E: Assistive Technology Device Predisposition Assessment, Scale E.
[h]VAS: Visual Analogue Scale.
[i]GAD-7: 7-item Generalized Anxiety Disorder.
[j]SUS: System Usability Scale.

Statistical Analysis

The first step of the data analysis dealt with the description of the sample. Continuous variables were reported as either mean and SD or median and IQR on the basis of their distribution (assessed using Kolmogorov-Smirnov test). Categorical variables were expressed as an absolute number and percentage. Mann-Whitney *U* tests (for nonnormal distribution), or chi-square tests (normal or nonnormal), were used to compare the independent and dependent variables between the preconditions and postconditions, in addition to simple descriptive statistics (means, medians, and SDs as appropriate).

To verify the achievement of the primary end point (ie, caregivers' burden), subscales of the Zarit Burden Interview questionnaire were calculated. Means and SD or medians and IQRs of the scores were reported according to their distribution. Correlation coefficients (Pearson for normally distributed variables and Spearman for nonnormally distributed variables) of the subscales with the other rating scales at each stage of the study and with the main characteristics of the subjects were calculated to check for potential determinants of higher acceptability, as a secondary end point of the project.

Ethical Considerations

The study was approved in all the 3 pilot countries: by the ethics committee of the IRCCS INRCA in Italy (3750/2023), in the Netherlands (NW2023-13), and by the institutional review board of the National Cheng Kung University Hospital in Taiwan (B-ER-112-026). The study protocol was registered on ClinicalTrials.gov (NCT06307197).

The principles of the Declaration of Helsinki [31] and Good Clinical Practice guidelines were adhered to. All participants in this study provided written informed consent, but the acquisition of informed consent from people with dementia is a long-debated issue. Although dementia leads to cognitive decline, a diagnosis alone does not imply loss of decision-making capacity. Legal capacity remains unless formally revoked, and people with dementia may retain decision-making skills for a long time. While executive functions deteriorate progressively, early-stage patients may still comprehend simplified consent forms and express preferences aligned with their values. Informed consent requires full understanding and voluntary decision-making. Every effort was made to respect residual autonomy, adapting information to cognitive abilities and facilitating communication. The will of people with dementia took precedence over family input, and consent was continuously monitored throughout the study. Participants could withdraw at any time without consequences. If a participant could not provide valid consent, a legally designated representative will be involved, but the individual's willingness to participate will still be considered under a "double consent" approach. The study ensured informed decision-making while prioritizing the well-being of participants.

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Personal data collected during the trial were handled and stored in accordance with the General Data Protection Regulation, the European law on privacy. For this purpose, data were anonymized at the end of the study. Use of the study data was and will be controlled by the principal investigator (RB). All data and documentation related to the trial are stored in accordance with applicable regulatory requirements, and access to the data is restricted to authorized study personnel.

The equipment needed electric power. However, all devices were of low power consumption. Some of them (tablet, mobile router, and Kompy Pico) are rechargeable. The user was informed on how much electric power is supposed to be consumed in relation to the set of devices. No refund to the end user was given for participating or power consumption.

Results

The recruitment started in November 2022 and continued until April 2023. The alpha test was conducted from March 2023 to May 2023 involving 41 end users, of which 13 were people with dementia, 13 were ICs, and 15 were FCs. The beta test was conducted from September 2023 to February 2024 involving 83 end users, of which 26 were people with dementia, 20 were ICs, and 37 were FCs. The recruited end users are reported in Table 4 grouped by their category, phase of study, and country.

The efficacy of the HAAL ecosystem will be demonstrated in a separate publication expected to be published by 2026. The HAAL ecosystem, successfully updated from prototype 2 to prototype 3, showed promising results. The use of the system did not negatively impact the caregivers' burden; in some cases, the stress lowered instead. This positive outcome was coherent with the usability, which received positive scores from the end users. As regards the quality of life of people with dementia, the level remained stable through the period of testing, given that the pathological condition was considered a very positive result. Table 5 shows the end users recruited in all pilot countries in both test stages.

Table 5. End users recruited for the field trials in the 3 pilot sites.

	Italy, n		The Netherlands, n		Taiwan, n	
	Alpha	Beta	Alpha	Beta	Alpha	Beta
People with dementia, n	3	7	5	9	5	10
GDS[a] 2-4	None	None	None	None	5	10
GDS 5	3	7	None	None	None	None
GDS 6-7	None	None	5	9	None	None
IC[b]	3	7	5	3	5	10
FC[c]	5	9	5	18	5	10
Total	13	23	15	30	15	30

[a]GDS: Global Deterioration Scale.

[b]IC: informal caregiver.

[c]FC: formal caregiver.

Discussion

The preliminary findings from the HAAL feasibility study suggest promising trends regarding the usability, acceptance, and potential benefits of the platform for both people with dementia and their caregivers. The system was tested across multiple pilot sites, providing insights into caregiver burden, stress management, and user interaction with assistive technologies. Results indicate that the HAAL ecosystem was generally well received, with variations in usability perceptions across different user groups and settings. Caregivers reported engagement with the platform and its components, while qualitative feedback highlighted areas for improvement in usability and system integration. Additionally, the study provided valuable learnings on user adaptation to the technology over time. The study design allowed for testing the solution for a relatively long period (3 months) and to exploit feedback coming from the alpha phase to improve the prototype that is then tested in the beta phase. The same process has been done previously through a usability test in which professional workers tested the dashboard prototype 1 [19]. Thus, this protocol applied to prototypes 2 and 3 of the HAAL dashboard. The iterative user-centered design has characterized all the HAAL project stages, starting from cocreation with end users (both primary, ie, FC, and secondary, ie, people with dementia) till the presented tests. The main challenges of this study were represented by the cultural and health care systems differences among the 3 pilot sites and 2 continents. The HAAL platform was ambitious as it aimed to work for managing people of any degree of dementia in different care settings. For these reasons, and given the low number of end users recruited, it has been decided to recruit only 1 category of people with dementia in each pilot site. In fact, this methodology allowed for the reduction of the number of variables to consider in data analysis.

The HAAL platform is designed to be scalable through the use of Amazon Web Services, which allows it to manage a large number of devices and users. Integrating different devices and heterogeneous systems is a key challenge of the HAAL project, which took a modular and flexible approach, offering application programming interfaces to enable partners to natively integrate with the ecosystem. Regarding off-the-shelf products, specific

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software integration microservices were developed. This heterogeneity requires device-specific normalization of information, linking each device to a specific client at a specific time interval. In addition, the lack of event standardization and the difficulty in monitoring the proper connection of devices are further limitations to interoperability. Although the HAAL platform was designed with scalability and interoperability features, its practical implementation presented challenges related to device heterogeneity and the need for customization. Future efforts should focus on standardization, reliable data collection, and integration of user feedback to overcome these limitations. In fact, several technological devices are available on the market and tested for this target group; however, very few ecosystems are in place and used by health care facilities, institutions, or systems. In this regard, the challenge was to embed and aggregate different technologies to provide quick and intuitive information that can effectively support caregivers in managing people with dementia, relieving their stress partially. Moreover, the need extends beyond mere access to information; it encompasses the development of comprehensive support systems that cater to the dynamic needs of caregivers and people with dementia alike. These systems must go beyond the provision of basic information and extend to offering personalized guidance, respite services, and community resources. Using the user-centered design approach, with input from caregivers throughout the development process, the design team worked to make the dashboard as usable as possible. End users received a brief lesson on how to use the dashboard along with a handbook. The aim of this approach was to avoid frustration and additional burden to the care of people with dementia. Moreover, the measurement of technological skills (Assistive Technology Device Predisposition Assessment) and digital health literacy (eHealth Literacy Scale), along with usability (System Usability Scale), acceptability (Unified Theory of Acceptance and Use of Technology), and burden (Zarit Burden Interview), allows us to assess whether additional burden due to learning and using a new dashboard depended on the caregiver's digital and health literacy. By fostering a collaborative environment where caregivers feel empowered and supported, these initiatives not only enhance the quality of care provided but also contribute to the overall well-being of both caregivers and care recipients. Within this framework, the main objective of the HAAL project is to assess the stress relief at work for FCs and ICs and the improvement in the perceived quality of life for ICs and persons with dementia.

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Data Availability

Data are not available to share due to Department of Veterans Affairs and ethical retractions; however, annotation instructions and vocabulary are available upon request..

Conflicts of Interest

None declared.

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Abbreviations

FC: formal caregiver
HAAL: Healthy Ageing Ecosystem for People With Dementia
IC: informal caregiver
IRCCS INRCA: Italian National Institute of Health and Science on Aging
ML: machine learning

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Protocol

Effectiveness and Cost-Effectiveness of Using a Social Robot in Residential Care for Individuals With Challenges in Daily Structure and Planning: Protocol for a Multiple-Baseline Single Case Trial and Health Economic Evaluation

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Abstract

Background: A substantial number of individuals in disability care experience challenges with daily structure and planning and require 24-7 support. The use of a social robot might decrease their need for support from care professionals, leading to improved well-being of individuals with disabilities and increased work engagement for care professionals.

Objective: This paper presents the research protocol for an effectiveness study and a health economic evaluation from a societal perspective on the use of a social robot by individuals experiencing challenges with daily structure and planning who are living in long-term disability care facilities in the Netherlands.

Methods: We will assess the effectiveness of social robot care in reducing the level of support provided by care professionals in a multiple-baseline single case study. In total, 30 participants will be randomly allocated to 1 of 4 clusters, determining the baseline length (2, 3, 4, or 5 weeks) of a 13-week study period, and a 2-week follow-up will be conducted 6 months after participants start using the robot. During baseline, participants will receive care as usual. After baseline, participants will use the robot as part of their care plan. For each participant, 3 to 5 personal goals will be formulated, and attainment of these goals will be evaluated weekly. A health economic evaluation from a societal perspective will be performed to assess the cost-effectiveness.

Results: This study was funded in July 2023. As of October 2024, we enrolled 29 participants. Data collection is planned to be finished in the third quarter of 2025. Data analysis will be performed from the second quarter of 2025. Results will be published in peer-reviewed journals and presented at international conferences in 2026.

Conclusions: We will provide insights into the effectiveness and cost-effectiveness of social robot care for individuals living in Dutch residential care facilities, aimed at enabling them to live more independently, reducing pressure on Dutch care professionals in times of growing staff shortages in long-term care, and allowing care facilities to make informed decisions about implementing such a technology.

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KEYWORDS

assistive technology; social robot; executive dysfunction; independence; effectiveness; health economic evaluation; cost of illness

Introduction

Background

In residential disability care, clients (from here on referred to as individuals) rely on care professionals for lifelong support and care. Many of them experience difficulties in facing the complex challenges of daily life, such as managing time, overseeing household tasks, or remembering important information. These challenges are often linked to executive dysfunctions, also known as higher-level cognitive dysfunctions (eg, planning, performing goal-directed tasks, procrastination, attention, taking initiative, and limited time management) [1]. Such dysfunctions are common for individuals with neurodevelopmental disorders (eg, autism spectrum disorder), brain injuries (eg, acquired brain injury), or intellectual disabilities [2,3]. Therefore, these individuals need support in regaining daily structure. In the Netherlands, the size of this group was estimated to be 2 million people in 2024, based on estimates from various publications [4-6]. Approximately 84,000 of them live in a long-term care facility where they receive residential care [7]. Care professionals provide essential support by offering reminders, answering questions, motivating task initiation, giving hints as to where to begin, and engaging in activities together. The individuals are dependent on this external support and may struggle to live independently and participate in everyday life, which in turn impacts their emotional well-being and overall quality of life [8].

Assistive technology holds great potential to offer support to individuals experiencing problems with daily structure and planning in their daily functioning [2]. It may compensate for the gap between a person's capacity and their everyday life challenges [9], thereby decreasing a person's dependence on the support of others [10-12]. Moreover, assistive technology offers opportunities to tailor the support to the person's exact needs, particularly in situations where support provided by care professionals may be limited, insufficient, or unwanted. Systematic review of the literature shows that technology offering functions such as calendars and reminder alarms can improve memory and execution of tasks [13]. However, Brandt et al [13] conclude that further research on the effectiveness and cost-effectiveness of such technologies is warranted. In line with this, the Dutch Ministry of Health, Welfare, and Sport has emphasized the importance of evaluating the impact of innovative technologies in disability care settings to ensure that they are both effective and financially sustainable [14]. Effectiveness studies measure the level of beneficial effect of interventions in "real-world" settings [15,16]. An explorative study [17] found that a social robot that speaks out verbal instructions and reminders at a preset time can support individuals with acquired brain injury, autism spectrum disorder, and mild intellectual disability in remembering and executing daily tasks more independently. This social robot is already widely used in residential care in the Netherlands, particularly in older adult care. In addition, 28 Dutch disability care organizations have reported using this robot in a recent survey of used technology in Dutch long-term disability care [18]. However, both the effectiveness and cost-effectiveness of using a social robot in care are still unknown.

Aims

We aim to evaluate the effectiveness and cost-effectiveness of using a social robot in Dutch residential disability care for individuals experiencing challenges with daily structure and planning.

We will compare care involving a social robot (CiSR) to care as usual (CAU). The study consists of 2 parts, each with its own focus and research questions (RQs; Textbox 1).

Textbox 1. Research questions (RQs).

Effectiveness study

RQ1: What is the effectiveness of compare care involving a social robot (CiSR) on the support provided by professional caregivers (frequency or duration) compared to care as usual (CAU)?

RQ2: Does the potential effectiveness of CiSR persist at follow-up?

RQ3: Which individual goals are set to be achieved by CiSR, and are these goals attained?

RQ4: What is the effectiveness of CiSR on the well-being of individuals with challenges in daily structure and planning?

RQ5: How does CiSR affect the work engagement of care professionals?

Economic evaluation

RQ6: What is the cost-effectiveness of CiSR, assessed by a model-based economic evaluation?

Methods

This paper presents the research protocol according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guideline [19].

Study Design

A multiple baseline single case study will be conducted in everyday care practice. Multiple baseline single case studies are based on the principle that evidence of a causal effect can be strengthened by assigning participants to baselines of varying lengths. The staggered introduction of the intervention helps to

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rule out alternative explanations such as maturation or testing and session experience [20].

The study period consists of 3 phases (within 13 weeks) and a follow-up phase (Figure 1, Textbox 2, and Table 1). The number and timing of clusters is based on power calculations while considering the practical feasibility. The intervention does not allow for blinding within the trial.

Figure 1. Study planning overview. CAU: care as usual; CiSR: care involving a social robot.

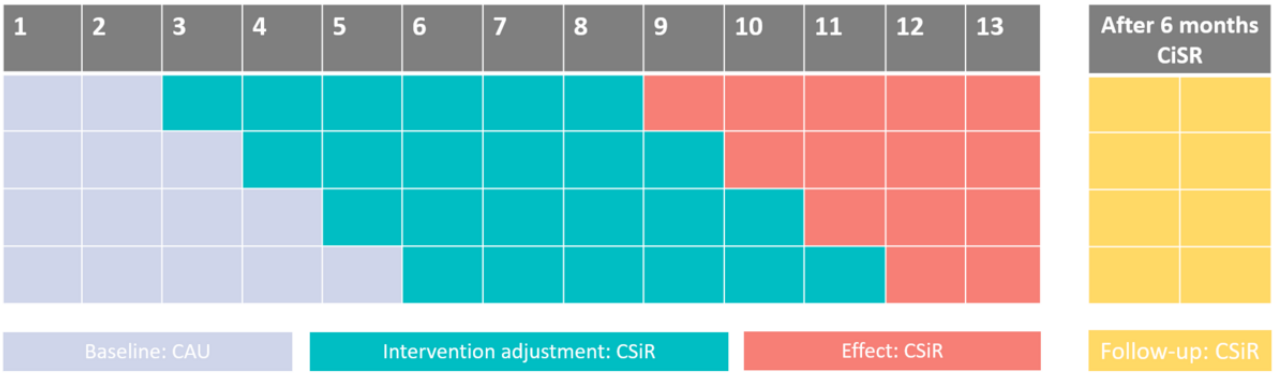

Textbox 2. Summary of the study period.

- Baseline phase: participants will be randomly allocated to 1 of 4 baseline lengths (2, 3, 4, and 5 weeks, respectively), resulting in 4 different clusters. In the baseline phase, participants will receive care as usual.
- Intervention adjustment phase: a 6-week phase in which each participant starts to receive compare care involving a social robot (CiSR), that is, using and adjusting to the social robot.
- Effect measurement phase: this period varies in length based on the cluster to which the participant is assigned, from 2 to 5 weeks. Participants will continue CiSR.
- Follow-up phase: to observe whether the results are maintained while participants continue CiSR, a follow-up measurement will take place 6 months after the start of the intervention adjustment phase.

Table 1. Study planning.

Cluster	Baseline	Intervention	Effect	Follow-up
1	2 weeks of CAU[a]	6 weeks of CiSR[b]	5 weeks of CiSR	Weeks 34-35
2	3 weeks of CAU	6 weeks of CiSR	4 weeks of CiSR	Weeks 35-36
3	4 weeks of CAU	6 weeks of CiSR	3 weeks of CiSR	Weeks 36-37
4	5 weeks of CAU	6 weeks of CiSR	2 weeks of CiSR	Weeks 37-38

[a]CAU: care as usual.

[b]CiSR: care involving a social robot.

Ethical Considerations

This study was approved by the Ethics Review Board Tilburg School of Social and Behavioral Sciences of Tilburg University (TSB_RP1461) and was exempted from ethics approval by the Medical Ethical Review Committee of Radboudumc, Nijmegen (2023-16798). Both the participants and care professionals will be provided with verbal and written information about the study, and their informed consent will be obtained before randomization. To promote full participation in the project, residential care organizations will receive a financial contribution for the research activities, up to a maximum amount of €10,000 (US $10.845,69; currency rate as per October 18, 2024) when different targets are met (such as enrolling 10 participants and completing data collection). Individuals participating in the study will receive no financial compensation. Pseudonymized data will be stored at a secure site with limited access and separated from personal data, such as names. The World Health Organization trial registration dataset is presented in Multimedia Appendix 1.

Recruitment

Participants: Care Organizations

Individuals with challenges in daily structure and planning will be recruited from 3 Dutch residential disability care organizations. Facilities will have to meet the criteria detailed in Textbox 3.

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Textbox 3. Inclusion criteria for care organizations.

- Have an intention to sustainably implement the social robot
- Have an IT infrastructure to support the use of the social robot
- Show commitment to implementation and participation in the research, characterized by the following:
  - release funding for the purchase of the social robot
  - provide human resources for implementation and training
  - provide a project leader to coordinate the project

Participants: Individuals With Challenges in Daily Structure and Planning

Individuals will be eligible for inclusion in the study if they meet the predefined inclusion and exclusion criteria, as detailed in Textbox 4.

One coresearcher is recruited from each of the 3 participating care organizations. A coresearcher is an individual who receives care within the context of this care organization and can represent the perspective of the participants. The 3 coresearchers are each coupled with a researcher and will function as a duo. The duos will receive training on how to collaborate and perform coresearch. During the study, coresearch activities will be logged, and the impact of the coresearcher's involvement on the participants will be evaluated.

Textbox 4. Inclusion and exclusion criteria for individuals with challenges in daily structure and planning.

Inclusion criteria

- Aged ≥18 years (no upper age limit)
- Currently receive residential care
- Struggle with daily structure and planning, for example, have trouble remembering appointments and activities, or require assistance to initiate them
- Capable of understanding and following verbal instructions
- Possess the cognitive capacity to set 3 to 5 personalized goals with the help of a care professional and are motivated to work on these goals with the support of the social robot; these are goals for which the participant usually receives daily or weekly support by a care professional at the start of the study
- Supported by motivated care professionals to guide them in using the social robot

Exclusion criteria

- Prone to convert stress into physical aggressiveness
- Overly sensitive to stimuli

Procedure

Overview

The SEAR (Screened, Eligible, Approached, Randomized) framework [21 will be used to systematically monitor and report the recruitment of participnats, according to the CONSORT (Consolidated Standards of Reporting Trials) extension for N-of-1 flowchart [22.

Eligible participants will receive an information letter about the study. The purpose of the research will be explained in a conversation and questions will be answered. The participant and care professional will be given sufficient time to consider the information. When they decide to participate in the study, participants will be asked to sign an informed consent form.

Randomization

The researcher (KNvD) will randomly assign each location within the participating care organizations to a cluster. Due to practical considerations, randomization will be applied at the location level rather than the participant level, as this ensures a consistent and manageable implementation for the care team. This cluster determines the duration of the baseline length (2, 3, 4, or 5 weeks). The first 4 locations will be randomly assigned to one of the 4 clusters using a random sequence generator. Subsequent locations will be assigned to the cluster with the fewest participants at that moment. If multiple clusters have the same number of participants, a random sequence generator will be used to decide the assignment. The risk of unequal exposure to external influences is limited due to the initial randomization of the first 4 locations and the balanced allocation strategy of the following locations, which aims to maintain the balance between the clusters.

Start of the Study Period

Within each participating care organization, the research period for all locations will begin simultaneously.

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Intervention: CiSR

Social Robot (Tessa)

In this study, the social robot Tessa will be used to support the participants. Tessa was developed by Tinybots [23] and was originally designed with and for people with dementia. Tessa is a small wooden egg or flowerpot-shaped robot with amber LED-lit eyes, simulating eye contact and responsiveness. Tessa needs a connection to the power network and the internet via WiFi, MiFi, or cable. The social robot helps support daily structure by providing reminders and suggestions for activities. Tessa does not engage in complex conversations but offers a friendly and predictable presence in the home. From a central location in the user's home, with a default female voice, Tessa pronounces upcoming appointments or tasks from the user's day program, with repeated reminders, if necessary. The content of these messages is programmed via a web app, that can be accessed from a smartphone, tablet, or PC, functioning like a simple digital calendar. The app allows users—whether the participant, a care professional, or a family member—to personalize messages, adapting the robot's communication to the user's preferences. In this study, the care professional decides on the contents, timing, and frequency of these messages in consultation with the participant. Tessa can either give a reminder or ask a question that can be answered by the user with "yes" or "no." Depending on the participant's response, the social robot responds with a preprogrammed message and may give an additional reminder for the task. For example, Tessa asking the user to take a shower in the morning could be programmed with the following message: "Good morning! Did you take a shower?" If the user replies with "yes," Tessa's response could be programmed as "Good job, champ!" and if the user answers "no," Tessa's reaction could be programmed as "Hop in the shower, and start your day fresh!" The yes or no answers are logged and can be viewed in the web app, enabling the care professional to check task completion without having to ask the client directly.

Each participant will tailor the use of the social robot to their own goals. Before the start of the study, the type, frequency, and duration of support provided by the care professionals, specifically regarding daily structure and planning, will be assessed. In consultation with the care professional, 3 to 5 goals will be selected to work on with the support of the social robot. These can involve (1) activities of daily living (such as brushing teeth, shaving, drinking enough water, and getting up and going to bed on time); (2) household activities (such as doing the dishes, cleaning, changing the bed, and making a shopping list); and (3) planning (such as being ready for an appointment on time or being aware of the daily schedule).

Evaluation of Selected Goals by Goal Attainment Scaling Method Once a Week

The selected goals will be formulated using the goal attainment scaling (GAS) method [24]. Setting goals to work on with the support of the social robot is considered an integral part of the intervention and will be evaluated weekly from the start of the intervention adjustment phase. The GAS method is an individualized evaluation method to evaluate the progress of treatment goals, with goals being set according to the SMART (specific, measurable, achievable, relevant, and time-bound) principles and evaluated on a 5-point scale. Therefore, even when the goals of the participants are not similar, the progress on these goals is scored in a similar way. The GAS method is a valid and reliable method [25]. If the participants find it overwhelming to work on all goals simultaneously, a realistic, stepwise schedule will be created.

Training of Care Professionals

To integrate the social robot into the care process, care professionals need to be trained through a demonstration and guided practice in using the technology. This will be carried out during a training session, in which an implementation expert will install the social robot together with the care professional or the care team. After this, the care professional will introduce the social robot to the participant. Besides learning how to use the technology, care professionals will need to change their working routines, as the social robot will handle reminders that they previously provided. Thus, they will need to deimplement CAU for these specific goals. This will be discussed with the care professionals during weekly phone calls.

The social robot will be integrated into the care process, with the research team monitoring its implementation by logging and resolving support requests related to Tessa. During weekly phone calls with the care professionals, a researcher will check whether they have encountered any prevailing problems and directly help to solve these problems (eg, technical problems, problems with programming the messages, and communication issues between the various parties involved).

Components of CAU

During the baseline phase, the participant will receive CAU from care professionals. The care for individuals with challenges in structure and daily planning usually consists of several components, as described in Textbox 5.

Textbox 5. Components of usual care for individuals with challenges in structure and daily planning.

- Visual aid: the care professional provides instructions on paper or in digital format
- Hints: the care professional provides verbal instructions before the participant performs an activity
- Supervision: the care professional checks and provides general instructions during or after the performance of an activity
- Verbal instructions: the participant performs an activity while the care professional instructs the participant on what to do
- Demonstration: the care professional shows how to perform the activity, which the participant then replicates
- Doing tasks together: the care professional provides physical assistance or takes over part of the activity, while the participant performs the rest
- Taking over: the care professional performs the entire activity on behalf of the participant, who is not required to be involved.

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Measures

The study uses mixed methods, yielding quantitative as well as qualitative data, to answer the RQs.

Effectiveness Study

Primary Outcome

The primary outcome variable is the support provided by care professionals to the participant per week. These support moments will be registered daily in a "support diary" for each participant throughout the research period. Each day, the care professionals involved in the support of the participant will log the frequency and duration of each support moment provided to the participant during their shift. On the basis of the intake information provided by the care professionals, the diaries will be standardized and personalized by prefilling the typical daily prevalent types of support relevant to each participant. In this way, the caregivers only need to log frequency and duration of these predefined types of support and provide content descriptions only in cases of nonroutine support. To ensure consistency, the care professionals will receive detailed instructions on how to fill in the diaries by a standardized procedure, which includes participation of the researchers in team meetings and a "test week" before the study period to practice diary logging. Throughout the study, the researcher will hold weekly meetings with a designated care professional at each location to monitor compliance. In addition, to assess interrater reliability of the diary entries, on-site observations will be performed by the researchers.

Secondary Outcomes

Content of Support Provided by the Care Professionals

The care professionals will log the content of the support they provided to the participants in the support diary. During weekly calls with the care professional, a researcher will also inquire whether there are changes in the content of the provided support and what these changes are.

Well-Being of the Participants

The Personal Wellbeing Index–Intellectual Disability will be used to measure well-being. The scale is designed specifically for individuals who have an intellectual disability or other form of cognitive impairment and is considered a state-of-the-art instrument to measure subjective well-being in this population with acceptable psychometric properties [26]. It measures 8 domains of quality of life: life satisfaction, standard of living, health, life achievement, personal relationships, personal safety, community-connectedness, and future security. The Personal Wellbeing Index–Intellectual Disability will be administered 5 times (once every study phase; twice during the intervention adjustment phase).

The 10-item version of the Psychosocial Impact of Assistive Device Scale-Adults measures the psychosocial impact of CiSR, on items such as happiness, independence, self-esteem, and sense of control [27]. The systematic review performed by Atigossou et al [27] supports the use of the 10-item version of the Psychosocial Impact of Assistive Device Scale-Adults and states that it has overall good psychometric properties.

Both questionnaires will be filled in as part of an in-depth interview. During this interview, participants will also be asked about their experiences with the social robot and its added value, with questions such as "What do you find most helpful about Tessa?" or "What would you miss the most if Tessa would be no longer available to you?" The interviews will be guided by a specific topic list, which is available upon request from the corresponding author.

Perception of Work by the Care Professionals

To measure work engagement, the care professionals and involved care teams will be asked to complete a short questionnaire, consisting of eight 5-point Likert scale questions, such as "Working with the social robot brings me more enjoyment in my work" or "Working with the social robot helps me save time."

Complementary in-depth interviews with care professionals will be held to explore their experiences with the implementation of the social robot and how it affects their work engagement. In addition, care professionals will be asked about the perceived added value of CiSR for each client and how it influences the support provided to this participant, with questions such as "How do you perceive the impact of using Tessa on the participant's progress toward their personal goal?" or "How do you incorporate the use of Tessa into the support you provide to the participant?" The interviews will be guided by a specific topic list, which is available upon request from the corresponding author.

Economic Evaluation

Medical Consumption and Productivity Cost

Together with the intervention costs, such as the purchase of the social robot and subscription costs, medical consumption and productivity costs will be considered. To measure the medical consumption and productivity costs, a questionnaire containing relevant items from the iMTA Medical Cost Questionnaire and iMTA Assessment Productivity Cost Questionnaire will be conducted at baseline, effect, and follow-up [28,29]. These questionnaires are commonly used to study cost-effectiveness and can be adjusted by selecting relevant items.

Quality of Life

To measure the participants' quality of life, the Icepop Capability Measure for Adults (ICECAP-A) will be administered [30,31]. The use of this questionnaire is advised when performing a cost-effectiveness study [32]. The ICECAP-A contains 5 items measuring stability, attachment, autonomy, achievement, and enjoyment.

Table 2 shows an overview of the measurements.

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Table 2. Study measurements overview.

Measurement	Baseline	Intervention adjustment	Effect	Follow-up	Used to answer RQ[a]
Daily registration of support (diary)[b]	✓	✓	✓	✓	RQ1 and RQ2
Weekly evaluation of goals (GAS[c])[b]		✓	✓	✓	RQ3
Interview: well-being (PWI-ID[d])[b]	✓	✓	✓	✓	RQ4
Interview: psychosocial impact (PIADS-10[e])[f]			✓	✓	RQ4
Interview: added value of CiSR[f,g]			✓	✓	RQ4
Interview: work engagement and added value of CiSR[h]			✓	✓	RQ3, RQ4, and RQ5
Questionnaire: work engagement[h]			✓	✓	RQ5
Questionnaire: medical consumption and productivity cost (iMCQ[i]+iPCQ[j])[b]	✓		✓	✓	RQ6 and RQ7
Questionnaire: quality of life (ICECAP-A[k])[b]	✓		✓	✓	RQ6 and RQ7

[a]RQ: research question.
[b]Information on individuals with challenges in daily structure and planning, provided by the care professional.
[c]GAS: goal attainment scaling.
[d]PWI-ID: Personal Wellbeing Index–Intellectual Disability.
[e]PIADS-10: 10-item Psychosocial Impact of Assistive Devices Scale.
[f]Information on individuals with challenges in daily structure and planning provided by the individuals themselves.
[g]CiSR: care involving a social robot.
[h]Information on care professional.
[i]iMCQ: iMTA Assessment Medical Consumption Questionnaire.
[j]iPCQ: iMTA Assessment Productivity Cost Questionnaire.
[k]ICECAP-A: Icepop Capability Measure for Adults.

Analysis

Power

Due to the staggered design, power was determined through simulation using the R (R Foundation for Statistical Computing) packages simstudy and lme [33]. For a varying number of participants, 1000 datasets reflecting the staggered design were generated, all assuming a normally distributed outcome variable, a correlation between consecutive weeks of Pearson r=0.8, and a final effect of Cohen d=0.5 between the baseline phase and the first week of the effect phase (increasing linearly in 6 weeks). With 24 participants, a significant intervention effect (P<.05) was observed in 80.3% (803/1000) of cases, between the measurements from the baseline phase and those from the effect phase. Assuming 22% dropout (based on the study by van Dam et al [17]), the study is adequately powered when a total of 24 + (0.22 × 24) = 30 participants are included.

Effectiveness Study

Primary outcome data will be analyzed using a multilevel model (R, version 4.0+; package lme4) to investigate whether there is a significant difference between the level of professional care support moments (frequency or duration) per week in the baseline phase and the effect phase. The dependent continuous variable is the frequency and duration of professional care support moments per week. We will analyze all professional care support moments provided, as well as a selection of the specific professional care support moments connected to the goals for which the social robot is deployed.

The independent binary variable is the moment of measurement (baseline phase or effect phase). Because there are multiple measurements per participant at both phases, the model will contain a random intercept for participants. Time will be included in the model as a covariate. Measurements are consequently averaged and compared within participants per phase. Following the intention-to-treat principle, all participants will be included in the analysis, regardless of whether the participant has used the social robot in all weeks during the intervention adjustment phase and effect phase. Because multilevel models handle missing values well, no imputation is needed [34]. Quantitative secondary outcome data will be analyzed similarly. To assess the robustness of the primary outcome, additional per-protocol analyses and completers analyses will be performed as sensitivity analyses.

Clinical relevance will be determined per participant. Here, two conditions must be met as follows: (1) a Reliable Change Index of >1.96 for the level of support provided by care professionals [35] and (2) with CiSR, the participant progresses in carrying out the selected activities independently (GAS score of ≥+1 for at least one goal).

The follow-up data will be used to determine how many participants continue to receive CiSR, whether the effect is

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sustained in these participants, and what reasons there are to discontinue CiSR.

As recommended by recent single-case intervention research design standards [36], visual analysis will be conducted on the primary outcome. For each participant, data will be presented graphically to compare and interpret changes in patterns, level, and slope within and between different phases (baseline, intervention adjustment, effect, and follow-up). Using the contextual data collected for each case during the study period, we will qualitatively explore and report missing data patterns and discuss their implications for the robustness of the findings.

Qualitative data will be coded and analyzed thematically using Atlas.ti (version 8.4.20; Lumivero, LLC).

Health Economic Evaluation

A model-based economic evaluation with a follow-up time equal to the life span of the social robot will be performed. This study will be reported by following the Consolidated Health Economic Evaluation Reporting Standards 2022 guidelines for reporting economic evaluations in health care [37]. This study will also follow the Dutch guideline for health economic evaluations [32].

If the collected data suffices, the cost-effectiveness of CiSR will be examined by a model-based economic evaluation. For this, a Markov model, following the established guidelines [32,38], will be developed. Costs and effects will be modeled for 5 years with cycles of 3 months. The sources for transition opportunities, effects, and cost data will be the effect study, scientific literature, and expert opinions. Cost estimates from the Dutch costing manual will be used as a reference. For costs and health outcomes that occur after 1 year, a 3% discount rate to future costs and a 1.5% discount rate to future health outcomes will be applied [32]. Cost prices will be expressed in euros based on the cost prices in 2024 (index year). If necessary, the existing cost prices will be updated to those in 2024 using the consumer price index available from Statistics Netherlands. Outcomes will be incremental cost-effectiveness ratios using societal costs and effects (the costs per reduced number of support moments), or incremental cost-utility ratios expressed in costs per quality-adjusted life years (QALYs). The QALYs will be calculated for the utilities obtained by the ICECAP-A [39].

For the analyses, R (version 4.0+; package lme4) will be used. Missing measurements will be handled using multiple imputations. Resource use and costs will be reported in means, SDs, and 95% CIs. Costs and outcomes will be measured at the baseline (CAU) and the effect and follow-up phases (CiSR). Baseline adjustments will be made if needed. Deterministic and probabilistic sensitivity analyses will be performed. Cost-effectiveness planes will be constructed by plotting the (bootstrapped) cost-effectiveness and cost-utility pairs. The likelihood that CiSR is a cost-effective option compared to CAU will be illustrated using a cost-effectiveness acceptability curve, which demonstrates the probability of an intervention being cost-effective for a given threshold. This represents the amount that society is willing to pay to gain one unit of effect. The willingness-to-pay threshold for the costs per reduced number of support moments is unknown, while the willingness-to-pay for a QALY varies across and within countries. In the Netherlands, the Health Council of the Netherlands estimated the QALY threshold between €20.000 and €80.000 (1=US $1.083; currency rate as per October 18, 2024) depending on the level of severity of the disease [40].

If, in practice, it appears that the data are of insufficient quality, making it impossible to create a model, the costs and effects will be described with a cost-consequence analysis.

Results

This project received approval for funding on July 13, 2023, by ZonMw, the Netherlands Organization for Health Research and Development (project 10310012210009). The funding period is 30 months.

Data collection from 30 individuals living in residential disability care organizations and the care professionals who provide them support will yield insights into the effectiveness and cost-effectiveness of CiSR. By October 2024, we had enrolled 29 participants. Data collection is planned to be finished in the third quarter of 2025. Data analysis will be performed from the second quarter of 2025. Results will be published in peer-reviewed journals and presented at international conferences in 2026.

Discussion

Expected Findings

We expect to demonstrate that the sustainable and person-oriented implementation of a social robot in residential care for individuals with challenges in structure and daily planning will reduce the level of support provided by care professionals. As participants become more independent, the need for support is likely to decrease. This increased independence is anticipated to improve the well-being of participants and the work engagement of care professionals.

In an era of increasing strain on care systems due to rising health care demands and staff shortages, the integration of technology holds substantial promise for improving quality of care. Technology enables more personalized care and might empower individuals to maintain independence in their daily routines, while reducing the need for constant human supervision and support. This may not only improve the quality of life for individuals but also allow care professionals to focus on more complex tasks and meaningful interactions with clients.

Thorough research on the effects, added value, and costs will provide funding bodies and policy makers in long-term care organizations with the necessary information to make informed decisions about implementing technology such as the social robot used in this study. By leveraging these innovations, we can create a more sustainable, effective, and compassionate care system that meets the needs of both individuals and care professionals.

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Strengths and Limitations

We describe the first adequately powered study that investigates the effectiveness and cost-effectiveness of using a social robot in daily residential care practice for individuals experiencing challenges with daily structure and planning. This study will give insight into the characteristics of participants for whom CiSR is successful by combining statistical and visual analysis and considering clinical relevance.

Single-case experimental designs (SCEDs) are increasingly used in behavioral research and provide a clear framework for establishing causal relationships between interventions and outcomes. SCEDs are particularly useful in applied settings and allow researchers to conduct a thorough examination of an individual's response to an intervention in their daily setting [41]. While enabling analysis of data on a group level due to the multiple baseline design, the design of this study involves frequent measurements for each participant, providing valuable insights into individual effects as well. The use of 4 clusters enhances the internal validity by controlling for potential confounding variables [42]. Given the large variation in support needs regarding daily structure and planning (nature, frequency, and severity) between participants, SCED enables a personalized approach essential to investigating the effectiveness of CiSR [43]. Although personal goals are formulated for each participant, our multiple baseline SCED enables adequate comparison of results between individuals and the application of findings to daily care practice [44]. While the results of group studies may not always apply to individuals, especially in the field of long-term care, SCED focuses on studying how individuals respond to an intervention. This can help understand how to apply the same intervention in the care and support for people with similar conditions [45]. Therefore, with the use of SCED methodology —which allows for an in-depth analysis of individual responses and the identification of causal relationships— findings can be meaningfully interpreted beyond the specific setting [46]. When compared to randomized clinical trials, SCEDs are often questioned for their lack of generalizability. In this study, generalizability is increased by 30 systematic replications (the same intervention, ie, CiSR, with different participants' characteristics and settings) [47]. This study takes place in a Dutch residential care context. However, given the use of SCED methodology, we anticipate that the findings will be transferable to individuals with similar challenges in residential care settings in other countries.

This study will generate many data points, quantitatively by daily registrations by care professionals, and supported by qualitative data. Here, a potential limitation could be that care professionals might not be able to provide all the expected data due to their heavy workload. This could potentially lead to missing data points. To prevent missing data, we will invest in frequent personal contact with the care professionals involved and take early joint action to offer creative solutions in case of problems arising with the completion of the diaries.

The reason for residential care locations to participate in this study is the desire to sustainably implement and use a social robot. To determine the effectiveness of CiSR, adequate implementation of the social robot in daily care practice by care professionals is essential. The research team will actively stimulate the actual adjustment of work processes to the use of the social robot by investing in weekly contact with the care professionals.

Another strength of this study is the collaboration with coresearchers, which is expected to enable the collection of richer data and a better understanding of the participants and their settings [48].

Finally, this study includes longer-term follow-up assessments, enabling the examination of the sustainable use of the social robot as a part of daily care practice and the maintenance of its potential effects for individuals experiencing challenges with daily structure and planning.

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Data Availability

The datasets generated or analyzed during this study will not be made publicly available due to the vulnerable position of the participants. However, they will be made available from the corresponding author upon reasonable request.

Authors' Contributions

KNvD and MFMG drafted the manuscript. KNvD was involved in finalizing the research instruments and will execute and manage the study under the supervision of MFMG and BB. NMS advised on the study design. GAPGvM advised on the economic evaluations. WdH contributed to the statistical analyses. BB, MFMG, GAPGvM, and WdH conceived the study design. All authors reviewed the manuscript for critical content and approved the final version.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
The World Health Organization trial registration dataset.
[DOCX File , 22 KB - resprot_v14i1e67841_app1.docx]

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Abbreviations

CAU: care as usual
CONSORT: Consolidated Standards of Reporting Trials
CiSR: care involvinv a social robot
GAS: goal attainment scaling
ICECAP-A: Icepop Capability Measure for Adults
QALY: quality-adjusted life year
RQ: research question
SCED: single-case experimental design
SEAR: screened, eligible, approached, randomize
SMART: specific, measurable, achievable, relevant, and time-bound

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Protocol

Optimizing Cardiovascular Risk Management in Primary Care Using a Personalized eCoach Solution Enhanced by an Artificial Intelligence–Driven Clinical Prediction Model: Protocol from the Coronary Artery Disease Risk Estimation and Early Detection Consortium

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Abstract

Background: Atherosclerotic cardiovascular disease poses a heavy burden on the population's health and health care costs. Identifying apparently healthy individuals at risk of developing cardiovascular diseases using clinical prediction models raises awareness, facilitates shared decision-making, and supports tailored management of disease prevention. In the CARRIER project, a personalized cardiovascular risk management (CVRM) eCoach approach is cocreated, in which identified individuals receive education, guidance, and monitoring to prevent atherosclerotic cardiovascular disease through existing interventions. In this approach, an artificial intelligence–driven clinical prediction model calculates the 10-year risk for atherosclerotic cardiovascular disease, which supports informed decision-making.

Objective: This study aims to assess the effectiveness of our CVRM eCoach approach through a 10-year risk calculation of atherosclerotic cardiovascular disease, including risk factors contributing to this risk.

Methods: This pretest-posttest interventional study provides the CVRM eCoach approach for 6 months to 100 apparently healthy individuals eligible for CVRM. The CVRM eCoach approach is a multicomponent eHealth solution, including a clinical prediction under intervention model that not only calculates the 10-year risk of cardiovascular disease through conventional risk factors (smoking, blood pressure, and lipid profile) and individual characteristics (age, gender, socioeconomic status, physical activity, and diet) but also calculates how the risk changes after hypothetical lifestyle or medical interventions. The CVRM eCoach approach includes features that encourage behavior change. Most of these features include goal setting, decision cards to help decide on an intervention, intervention monitoring, remote communication, and education, all accessible from one dashboard. A

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practice nurse or physician consults the individuals after risk calculation with the clinical prediction model and uses behavior change features, such as the decision cards, to support shared decision-making. Data are primarily collected via the eCoach, after which the 10-year risk for atherosclerotic cardiovascular disease and its components are analyzed using paired-sample analyses.

Results: Recruitment began in March 2024 and will continue until 100 participants have been recruited, which is expected in 2025.

Conclusions: We anticipate that our CVRM eCoach approach will be valuable in the primary prevention setting. During the crucial initial first months of habit formation, factors such as education, regular check-ups via the eCoach, and clear risk communication could support individuals in sustaining their medical or lifestyle interventions. We hypothesize that there will be a slight to moderate reduction in the 10-year risk of atherosclerotic cardiovascular disease, which over time will lead to significant health improvements on a larger scale.

Trial Registration: CCMO NL84584.096.23; https://onderzoekmetmensen.nl/nl/trial/56578

(JMIR Res Protoc 2025;14:e66068) doi:10.2196/66068

KEYWORDS

atherosclerotic cardiovascular disease; disease management; cardiovascular risk management; digital health; clinical prediction model; artificial intelligence; medical informatics; cardiovascular; primary care; risk management; AI-driven; prediction model; atherosclerosis; costs; cardiovascular disease; effectiveness; eCoach

Introduction

Atherosclerotic cardiovascular disease (ASCVD) imposes a significant burden on both the general population and health care expenditure [1]. The risk of ASCVD is strongly associated with demographic factors such as age and sex, in conjunction with conventional risk factors such as hypertension [2], hypercholesterolemia [3], and smoking status [4]. Furthermore, nonconventional risk factors, including socioeconomic status [5], as well as lifestyle factors such as diet [6] and physical activity [7], are pivotal in the progression of ASCVD. Adhering to lifestyle recommendations substantially reduces the risk of ASCVD [8]. Nonetheless, the prevalence of modifiable risk factors remains alarmingly high [1].

Cardiovascular risk management (CVRM) aims to mitigate the impact of ASCVD at various levels, namely in individuals, specific groups with elevated risk, or at a population level. In the Netherlands, CVRM is commonly conducted in a general practitioner's (GP's) office and largely managed by practice nurses. The target population is apparently healthy individuals who are at heightened risk for ASCVD due to the presence of risk factors but without established ASCVD or diabetes mellitus. According to international guidelines, CVRM initiates with a personalized risk assessment to estimate the likelihood of future cardiovascular events [9,10]. Clinical prediction models (CPMs), such as the Framingham model [11] and the SCORE2 (Systematic Coronary Risk Evaluation 2) Working Group and European Society of Cardiology Cardiovascular Risk Collaboration algorithms [12,13], assist in risk assessment by estimating individualized risks for future cardiovascular events as well as the impact of lowering these risk factors. However, lifestyle factors, such as physical activity and dietary habits, are not yet included.

The Dutch CARRIER (Coronary Artery Disease: Risk Estimations and Interventions for Prevention and Early Detection) consortium is dedicated to reducing the burden of ASCVD by empowering apparently healthy individuals to adopt healthier lifestyles and mitigate their cardiovascular risk [14]. The consortium's objectives include (1) addressing ethical and legal requirements for the use of data from different sources for the CPM; (2) creating a CPM that incorporates both conventional and specific, attainable nonconventional risk factors; (3) cocreating with health care professionals and patients to realize a personalized artificial intelligence–driven eHealth solution (eCoach) in the CVRM health care plan; and (4) evaluating the effectiveness of this eHealth solution in primary care settings. This personalized eHealth solution is designed to visualize estimated risk, support shared decision-making, provide guidance on interventions, and monitor adherence to medical and lifestyle interventions.

Our primary aim is to assess the effectiveness of our CVRM eCoach approach in the primary prevention of ASCVD. Additionally, our study will qualitatively evaluate the CVRM eCoach approach with a 1-time semistructured interview with a selection of the participants and the practice nurses. The primary endpoint of the trial is the change in calculated 10-year ASCVD risk and its risk-contributing risk factors 6 months into the CVRM eCoach approach. Secondary endpoints encompass health-related quality of life, user experience, and health care satisfaction through questionnaires.

Methods

Study Design

This trial adopts a multicenter, pretest-posttest interventional design. Commencing in April 2024, the study will continue until the completion of recruitment, anticipated to occur in 2025. Recruitment will take place across at least 4 GPs' offices and 2 hospitals situated in the southern region of the Netherlands. Potential participants are recruited from a pool of individuals registered at the participating GPs' offices, who are routinely invited to see the practice nurse as part of the primary prevention of ASCVD. Potential participants are also recruited at the cardiac emergency department or outpatient clinic at the hospital, in case no ASCVD is diagnosed. Approval of the study was obtained from the Medical Ethics Committee

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Zuyderland-Zuyd (02/02/2024, NL84584.096.23, METCZ20230114).

Study Population

The study population comprises apparently healthy individuals (without a history of diabetes mellitus or ASCVD), aged 40-70 years, who are eligible for CVRM at the GPs' offices or hospitals. Individuals eligible for CVRM have modifiable risk factors (eg, smoking, hypercholesterolemia, or hypertension) that elevate the risk of ASCVD and are then routinely invited and treated per the Dutch guidelines for CVRM [15]. Eligible individuals must be Dutch-speaking and possess hardware such as a smartphone, computer, or tablet with internet access, along with adequate digital literacy to operate these devices. Exclusion criteria include language barriers preventing sufficient Dutch comprehension and physical, psychiatric, or neurological conditions that hinder completion of study procedures. In addition to the apparently healthy individuals, practice nurses involved in the study are considered part of the study population, as their experiences with using the eCoach will also be included in the qualitative data collection.

Recruitment

Individuals with an upcoming CVRM consultation at their GP's office will undergo eligibility screening by the practice nurse. Eligible individuals will receive a preliminary contact by phone, preferably 2 weeks before their scheduled appointment. Individuals at the cardiac emergency department or outpatient clinic will undergo eligibility screening by their treating physician. Individuals screened from the hospital will have their CVRM consultation with one of the physicians from the hospital affiliated with the study (refer to Figure 1 for the study flowchart). Those expressing interest in participation will receive detailed study information from the research team. Upon obtaining written informed consent, eligible individuals will be enrolled in the trial and given login credentials to the eCoach.

Figure 1. Flowchart of the study and the cardiovascular risk management eCoach approach. CVRM: cardiovascular risk management.

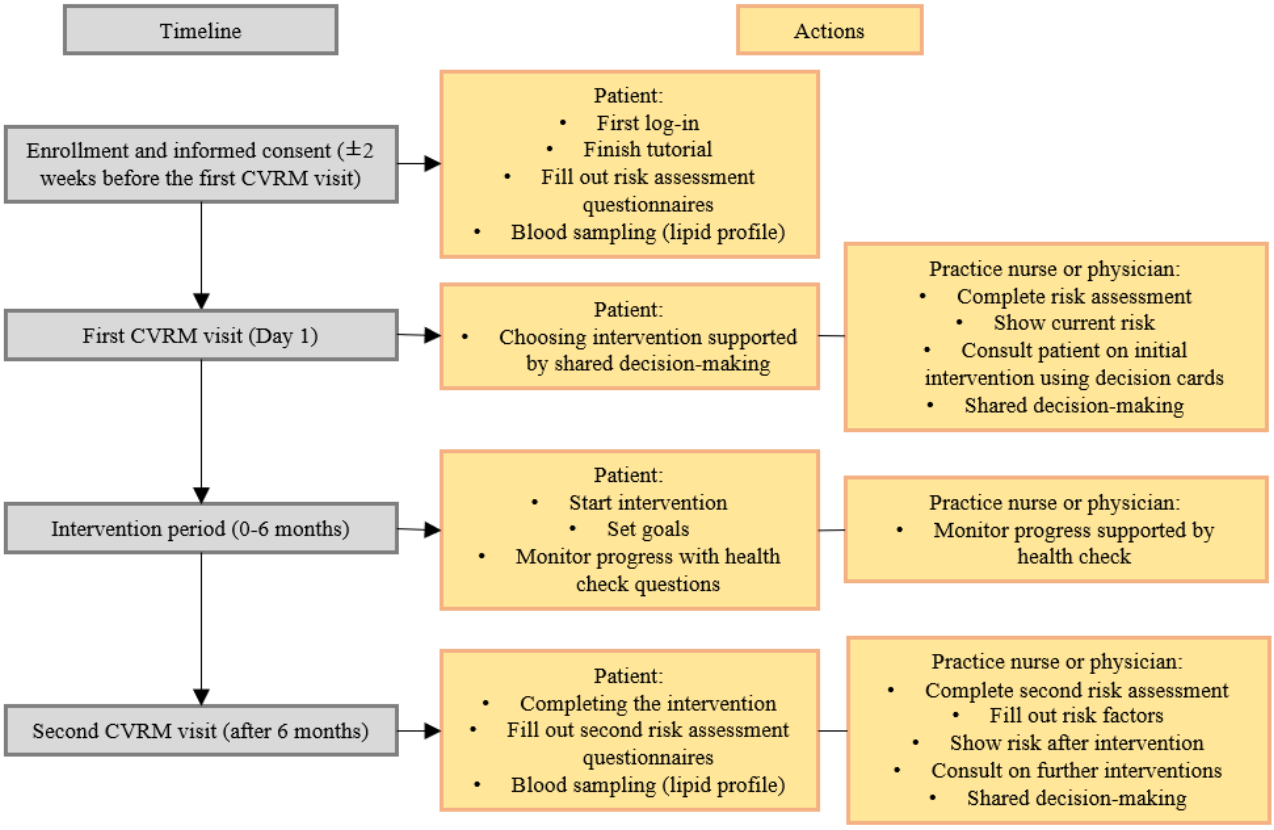

The CVRM eCoach Approach

The eCoach is accessible via smartphone, tablet, or desktop computer. Each participant has their own account and platform interconnected to a separate platform accessible to their practice nurse or physician. In these platforms, participants and practice nurses or physicians can perform the actions as described in the remainder of this section and in Figure 1. A built-in tutorial guides the participant through the platform's functionalities, and they complete their part of the first risk assessment. This includes information known to the participant, which includes age, gender, zip code for socioeconomic status [16], smoking status, physical activity measured via the Community Healthy Activities Model Program for Seniors (CHAMPS) questionnaire [17], and dietary intake measured via the Eetscore Food Frequency Questionnaire (FFQ) [18].

At the first CVRM visit, the practice nurse or physician completes the risk assessment by filling out the blood pressure measurement and lipid profile into the eCoach, along with blood pressure medication and lipid-lowering medication. Once completed, the CPM computes the 10-year ASCVD risk, which is graphically depicted in the eCoach dashboard (Figure 2). A drop-down menu is available for each risk factor, allowing participants and practice nurses to interactively view the

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estimated impact of any interventions, which are displayed as "risk after intervention." Adjustments can be made for the variables smoking status, blood pressure, low-density lipoprotein cholesterol levels, physical activity, and dietary habits. After risk assessment, the practice nurse and participant can use the "decision cards" offering various lifestyle or medical intervention options to achieve desired goals (eg, smoking cessation assistance from a specialized nurse; Figure 3). Each decision card offers seven attributes of information, which include (1) a short description of the intervention, (2) the group size, (3) the (online) location, (4) the duration, (5) the costs (if any), (6) the necessity for a referral, and (7) a link to provide the first step toward starting the intervention. All interventions are part of routine or existing care, with the eCoach primarily aimed at creating awareness, inciting action, facilitating shared decision-making, monitoring progress, and promoting adherence.

Figure 2. Risk calculation menu (translated from Dutch to English; enlarged and simplified for readability). The risk profile indicates the current (left drop-down menus) and potential risk (right drop-down menus) of atherosclerotic cardiovascular disease, which allows risk comparison after potential targets are achieved. LDL: low-density lipoprotein.

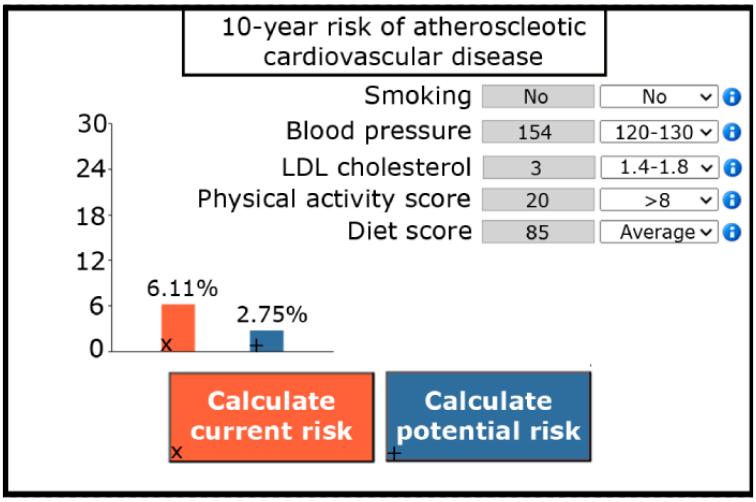

Figure 3. Decision cards (translated from Dutch to English; enlarged for readability). The figure shows an example of a decision card that displays four available smoking cessation interventions. Other decision cards include physical activity, healthy diet, blood pressure, and lipid profile. GP: general practitioner.

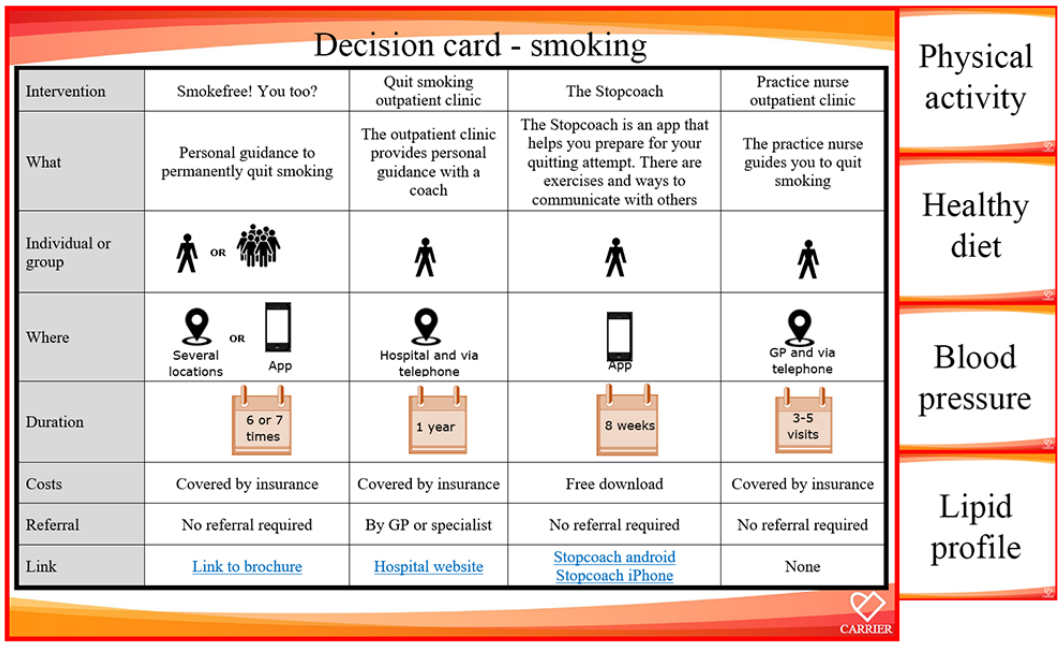

After the initial CVRM visit, participants can use the eCoach to track the evolution of their lifestyle or medical interventions. The eCoach prompts participants with simple weekly inquiries. Examples of inquiries include asking the participant if they picked up their medication (if applicable) or visited the website for their chosen intervention (if applicable). Practice nurses can review responses, which are color-coded as red (requires attention), orange (may require attention), or green (requires no attention). This facilitates early detection of potential challenges the participant faces for their intervention. Practice nurses can encourage participants, when necessary, on the non–content-related aspects of the intervention (eg, remind them

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to pick up medication or visit the website of the chosen intervention).

Participants can navigate through the eCoach using the menu, depicted with simple symbols at the bottom of the screen (Figure 4). The task menu displays incomplete tasks, including health check questions, educational materials disseminated by the practice nurse, and goals formulated by the participant. The goals menu features short-term and long-term goals, along with previously accomplished objectives. The messaging feature enables participants to communicate with the practice nurse, and vice versa. Practice nurses have the additional capability to broadcast messages to all their participants, such as promoting local health events or sharing informative papers on cardiovascular health. Risk factor statuses are represented on a sliding scale for participants in the eCoach, representing progress compared with previous measurements. The sliders turn green to denote improvement and red to indicate deterioration. Using the concept of shared decision-making between the participant and caregiver, an intervention domain and corresponding strategy can be selected to contribute to ASCVD risk reduction.

Figure 4. Screenshots of the eCoach (translated from Dutch to English; enlarged for readability). The icons in the bottom row menu, from left to right, represent (1) tasks, (2) goals, (3) dashboard (including risk factors), (4) messages, (5) education, and (6) settings.

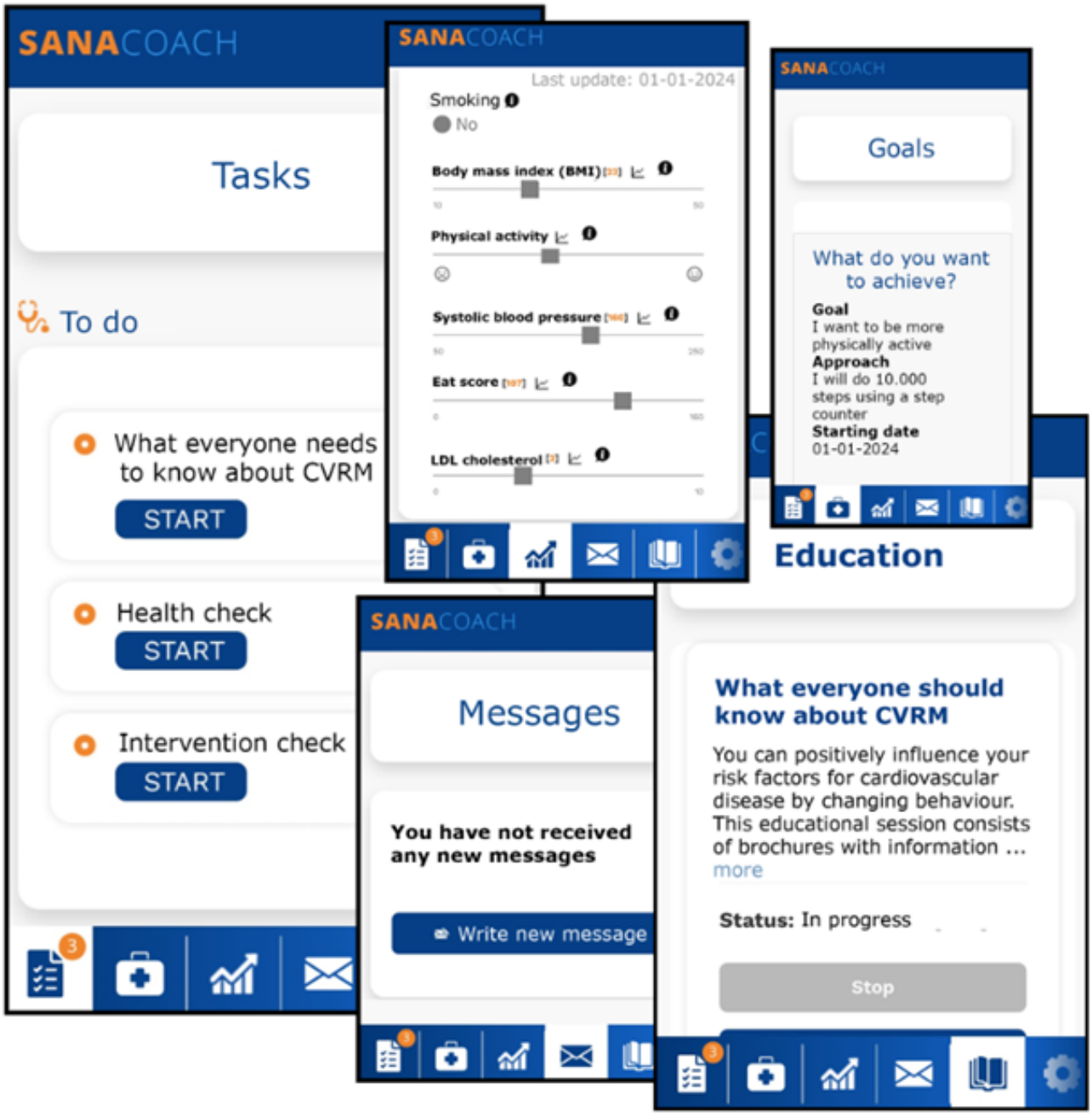

Around 6 months into the CVRM eCoach approach, participants undergo a second and last CVRM visit, during which the practice nurse provides consultation on the progress of their 10-year cardiovascular risk profile. This involves a risk reassessment identical to the first visit.

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Clinical Prediction Model

We developed the CPM [19] that estimates baseline 10-year ASCVD risk based on a set of conventional risk factors, individual characteristics, and medication. The complete list of predictors of the baseline risk model is age, gender, socioeconomic status, systolic blood pressure, use of blood pressure medication, total cholesterol, high-density lipoprotein (HDLs), use of lipid-modifying agents, smoking status, moderate to vigorous physical activity (as measured using the CHAMPS questionnaire [17]), and diet (using the Eetscore FFQ [20]). In addition, the model is a prediction under an intervention model [21] that can estimate the effect of combinations of hypothetical lifestyle interventions such as lowering high blood pressure and increasing exercise.

We used the concordance index (C-index) to assess the discriminative performance of the model, which we internally validated using 10-fold cross-validation. The resulting model based on a complete case analysis using the follow-up data available at the time of development achieved a mean C-index of 75.7 (95% CI 65.8-85.6) in the validation sets.

We developed competing risk models using the Fine and Gray [22] method with data from the Maastricht Study [23], a population-based cohort study including approximately 9000 individuals. To create the ASCVD outcome and the competing risk outcome (eg, mortality due to a different cause), we enriched the data from the Maastricht Study with data from Statistics Netherlands and hospitalization data from the Dutch Hospital Data Foundation [24-27]. To estimate the effect of lifestyle interventions, the parametric g-formula, as described by Hernán and Robins [28], was used. Variable selection was driven by expert consensus on relevant confounders, predictors, and the lifestyle interventions targeted by the CARRIER project (eg, smoking cessation, physical exercise, and diet).

In terms of the effect of lifestyle interventions estimated by our model, the hazard ratios (HRs) for smoking cessation and diet improvement were in line with published literature. Our model estimated an HR of 0.47 linked to smoking cessation. A meta-analysis by Mons et al [29] reported an HR of 2.07 (comparing current smokers to never-smokers), which is inversely comparable with the HR in our model. Our model estimated an HR of 0.96 for diet improvement with an increase of 1 SD in the Dutch Healthy Diet Index, equal to the HR of 0.96 estimated by Struijk et al [30]. However, the effect of physical activity estimated by our model was negligible. This might be due to measurement errors related to self-reported physical activity compared with actual physical activity. To address this, we used the HR published by Ramakrishnan et al [31] on a study using accelerometer-measured physical activity on UK Biobank participants. In addition, our model included an HR of 0.80 for each 10-mmHg systolic blood pressure reduction [32] and an HR of 0.79 for each 1 mmol/L reduction in low-density lipoprotein [33]. This is in line with the risk estimation applications supported by the European Society of Cardiology (U-Prevent).

Measurements

Quantitative data are collected via online questionnaires, blood sampling, and physical examinations at baseline (T0), 3 months (T1), and 6 months (T2) after baseline. The primary outcome includes the change in estimated 10-year ASCVD risk 6 months after using the CVRM eCoach approach as measured by the CPM. The CPM includes age (years), sex (male or female), socioeconomic status, lipid profile (HDL and total cholesterol), blood pressure (in mmHg), lipid-lowering and blood pressure–lowering medication (yes or no), smoking status (current or ex or never), physical activity as measured with the CHAMPS (moderate to vigorous physical activity in hrs/wk) [17], and dietary status (0-160 score) according to the Eetscore FFQ [18,20].

Secondary outcomes encompass the presence of cardiovascular risk factors (smoking, hypertension, hypercholesterolemia, physical activity, and diet) that are used for the CARRIER CPM, health-related quality of life measured with the EQ-5D-5L [34], and usability as measured with the system usability scale [35]. In addition to relevant demographics at baseline, such as living situation (single or living together, with or without children, with or without partner), highest education achieved (eg, primary school, high school, and university), and working status (retired or unemployed or employed + hours worked per week), two 6-item questionnaires are sent out to participants to test digital literacy and satisfaction with health care.

Moreover, qualitative data regarding usability and feasibility are gathered after completing the 6-month follow-up, for which participants and practice nurses are requested to participate in a 1-time interview to evaluate the CVRM eCoach approach. The topics of the interview include (1) the CPM and risk prediction, (2) communication features, (3) user interface, (4) content, (5) time consumption, and (6) health awareness. Interviews will be audio-recorded, and answers to the questions will be annotated fully, clustered, and reported within the previously mentioned topics. We will be using a thematic analysis approach [36].

Sample Size Calculation

Previous research [37] showed a treatment effect of –2.7 (95% CI –3.3 to –2.2) on the 10-year risk of ASCVD in high-risk participants using mobile technology and smart devices in addition to usual care treatment. The risk score before and after treatment with the mobile technology and smart devices was 14.6 (95% CI 9.5-21.2) and 13.4 (95% CI 8.6-18.2). However, differences exist as our study focuses on primary prevention with likely lower-risk participants (<10% 10-year ASCVD risk) and a more comprehensive risk model including modifiable factors such as diet and physical activity. We assume an SD of 4.5 for the treatment effect and a precision or margin of error of 1. The sample size is calculated using the formula shown in , where z is the z score (1.96) associated with the chosen 95% CI, σ is the estimated SD (4.5), and E is the margin of error. This results in a sample calculation of 78 participants, adjusted to 100 to account for potential missing data, with replacements considered for early dropouts.

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Statistical Analysis

Descriptive statistics will be used to report baseline characteristics. A paired sample *t* test will be performed for at least the 10-year ASCVD risk, assuming normality. Individual components, including systolic blood pressure, use of blood pressure medication, total cholesterol, HDL, use of lipid-modifying agents, smoking status, and moderate to vigorous physical activity, will be evaluated using the McNemar test for dichotomous outcomes and the paired sample *t* test for continuous variables. An ANOVA analysis will be performed at least on the Eetscore FFQ results and CHAMPS questionnaire results. A *P* value of .05 or less will be considered significant in all analyses.

Ethical Considerations

The Medical Ethics Committee Zuyderland-Zuyd has approved the study protocol before the start of the study (METC20230114). All participants are required to sign informed consent before participating in the study. Data are de-identified. Participants will be reimbursed for travelling costs.

Results

Recruitment began in March 2024 and will continue until 100 participants have been recruited, which is expected in 2025. A full overview of the study can be found in Figure 5.

Figure 5. Study overview for the cardiovascular risk management eCoach approach. ASCVD: atherosclerotic cardiovascular disease; CHAMPS: Community Healthy Activities Model Program for Seniors; FFQ: Food Frequency Questionnaire; CVRM: cardiovascular risk management.

Study period	Enrollment	Allocation	Postallocation	Closeout
Timepoint	−2 weeks	Day 1	0-6 months	6 months
Enrollment				
Eligibility screen	✓			
Informed consent	✓			
First log-in to eCoach	✓	✓		
Allocation		✓		
Assessments				
10-year risk score of ASCVD		✓		✓
CHAMPS questionnaire		✓	✓	✓
Eetscore FFQ		✓	✓	✓
Interventions				
Lifestyle or medical intervention, not part of, but supported by the CVRM eCoach approach		✓	✓	✓
Questionnaires				
Digital literacy questionnaire		✓		
EQ-5D-5L questionnaire		✓		✓
System usability scale				✓
Satisfaction with health care				✓
Other				
Experiences with eCoach use				✓

Discussion

Principal Findings

This manuscript outlines the study protocol for a multicenter, pretest-posttest interventional trial investigating the impact of our CVRM eCoach approach on reducing the estimated 10-year ASCVD risk in apparently healthy individuals. The eCoach was developed through a cocreation process involving participants, caregivers, health care providers, eHealth developers, and researchers. This collaborative approach aimed to tailor the intervention to align with the individual needs and preferences of participants while also considering the daily practices of involving primary prevention. The final personalized eCoach includes several key features: (1) a risk assessment based on a newly developed CPM that incorporates personalized risk factors and lifestyle variables, (2) a dashboard that visualizes

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personalized risk and facilitates risk communication by showing both current risk and potential reductions through hypothetical interventions, (3) intervention decision cards to help participants and health care providers in selecting interventions tailored to the participant's specific characteristics, and (4) an adherence monitoring to track participant's compliance with the selected interventions.

The CPM has been developed by the CARRIER consortium on data from the Maastricht Study, enriched by data from Statistics Netherlands and hospitalization data from the Dutch Hospital Data Foundation [24-27]. By using artificial intelligence, the model is constructed to estimate ASCVD risk in apparently healthy individuals [14] and trained on data from a cohort of Dutch patients enrolled in the Maastricht Study, a local cohort study [23]. In selecting variables for the CPM, we prioritized those that are readily available or easily obtainable during routine CVRM visits. Therefore, this model incorporates not only conventional risk factors but also publicly available socioeconomic data through the participant's zip code [16], along with data on physical activity and dietary habits, using validated questionnaires (even though these might be prone to recall and social desirability biases). By integrating lifestyle factors into the models and dashboard, we aim to improve the precision of risk estimation while also highlighting potential risk reduction for participants and encouraging greater adherence to recommended lifestyle goals. To ensure feasibility in primary care settings, we chose not to include data from advanced imaging techniques such as coronary imaging [13,38,39] or additional laboratory measurements such as proteomes [40] and lipoprotein a [13], despite their known potential to improve risk estimation. Future steps for the CPM include model validation, model comparison to established risk models (eg, SCORE2), and a model impact analysis. In an ideal situation, data from existing users allows for the model to be updated as well.

The dashboard with personalized risks needs to create awareness and incite action. Effective risk communication is pivotal in prevention, as it bridges the gap between medical knowledge and public understanding. This involves conveying the actual meaning of personalized risks (being more personalized but still only risks that may not be realized), the urgency to change lifestyle behavior (even if figures seem to be rather small), and showing potential benefits (that are relevant to the individual participant). A combination of different communication formats, for example, percentages and visuals, is advisable [41]. In this case, the dashboard can be used as a starting point for the conversation. Essential is conveying the information meeting the needs of the target population [42] to improve health literacy. Tailoring communication strategies to account for an individual's cultural, social, and educational background might further enhance receptivity and adherence to preventive measures.

Numerous medical and lifestyle interventions are available to reduce the risk of ASCVD; yet, many individuals are unaware of their options or lack sufficient knowledge about the pros and cons of each alternative. This often results in uninformed decisions that do not align with the individual's circumstances and needs [43]. A personalized care approach can help health care professionals guide apparently healthy individuals in choosing and adhering to suitable lifestyle interventions [44]. Decision support tools, such as patient decision aids and decision cards [45], are emphasized when discussing available treatment alternatives. These tools provide balanced and neutral information on relevant options, helping patients make informed health care decisions. Decision aids provide in-depth information and support complex decision-making processes with detailed explanations and interactive features. In contrast, decision cards are typically concise and visually straightforward, often presented on a single card, and function as a quick-reference tool for specific choices or actions. In the CVRM eCoach approach, 5 decision aid cards were integrated for the key intervention domains, including smoking, physical activity, diet, blood pressure, and lipid profile. These cards were created by the study team, tested with end users, and customized to fit our regional health care context.

Achieving durable behavior change is essential for reducing the risk of future cardiovascular diseases. Our study incorporated several behavior change techniques to promote long-term adherence, including self-monitoring, performance feedback, goal setting, information on the consequences of behaviors, and guidance on how to perform the desired behaviors [46]. Research suggests that combining eHealth interventions with face-to-face contact can significantly enhance adherence [47]. To further support adherence, our practice nurses and physicians are available throughout the 6-month follow-up period to provide monitoring, support, and answers to any questions participants may have.

What Do We Expect to Learn From This Study?

The primary outcome of this study is the change in estimated 10-year ASCVD risk from baseline to 6 months after the initiation of the eCoach solution. While the ultimate goal is to reduce actual ASCVD events, such outcomes require long-term follow-up, which was not feasible at this stage. Therefore, our focus is on reducing the estimated risk, with the expectation that this reduction will ultimately translate into a decrease in actual events, an increase in community health, and a decrease in health care costs on a population level [48]. Moreover, we aim to address individual risk factors, enhance health-related quality of life, assess user experience, and evaluate health care satisfaction. Insights gained from these latter 2 endpoints may provide valuable feedback for refining future CVRM decision-making processes for interventions tailored to this population.

Future Perspectives

In light of constrained financial and human resources, innovative solutions are increasingly imperative to augment our health care services [49,50]. Future CPMs may be fully integrated with hospital electronic health records and automatically extract relevant data from them, as well as wearable devices, integrating longitudinal laboratory results, vital signs, physical activity levels, socioeconomic factors, and environmental variables. This comprehensive data collection has the potential to enhance the early detection of individuals at risk for ASCVD.

High-risk individuals will receive personalized lifestyle advice to mitigate their risk. When medication is necessary for risk

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reduction, patients will be referred to health care professionals for further discussion and guidance. This process will be supported by eHealth technologies and fully integrated patient decision aids, tailored to individual patient characteristics for CVRM. To monitor chosen interventions, wearable devices will be used to gather unique patient information about lifestyle, ensuring assessment and adjustment of personalized health strategies.

The CARRIER consortium is actively developing data infrastructures and ethical and legal frameworks for responsible data handling in health care. We envision a future in health care that is data-driven and bolstered by digital health solutions.

Conclusion

The CARRIER consortium is actively developing data infrastructures, as well as ethical and legal frameworks, for responsible data handling in health care. We envision a data-driven future in health care, supported by digital health solutions.

Acknowledgments

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Data Availability

The datasets are generated during the study. Once completed, they can be obtained from the corresponding author upon reasonable request.

Authors' Contributions

RVM and BS are the lead authors. RVM, BS, and LH drafted the first version of this manuscript. RVM, BS, JV, and LH conceptualized the study. AD, AvH, IB, and MS obtained funding for the study. IB conceptualized the clinical prediction model, and AB performed this analysis.

Conflicts of Interest

AD is the founder, a stockholder, and an employee of Medical Data Works B.V. AvH received unrestricted grants from Abbott Vascular, Medtronic, Boehringer Ingelheim.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOC File , 123 KB - resprot_v14i1e66068_app1.doc]

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Abbreviations

ASCVD: atherosclerotic cardiovascular disease
CARRIER: Coronary Artery disease: Risk estimations and Interventions for prevention and Early detection
CHAMPS: Community Healthy Activities Model Program for Seniors
CPM: clinical prediction model
CVRM: cardiovascular risk management
FFQ: Food Frequency Questionnaire
GP: general practitioner
HDL: high-density lipoprotein
HR: hazard ratio
SCORE2: Systematic Coronary Risk Evaluation 2

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Protocol

Effects of Acute Time-Restricted Eating on Inflammation in Individuals With Psoriasis: Protocol for a Case-Control, Prospective Study

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Abstract

Background: Psoriasis is a chronic inflammatory disease associated with multiple comorbidities, including metabolic syndrome and cardiovascular disease. Although specific dietary interventions, such as intermittent fasting and caloric restriction, have been shown to ameliorate inflammation and promote weight loss, the effect of these interventions independent of weight loss remains unclear. Time-restricted eating (TRE), a type of intermittent fasting, limits the daily eating window to a fixed number of hours. Recent studies suggest TRE may improve immune function in individuals with metabolic syndrome and cardiovascular risk factors. A crucial advantage of TRE over other investigated dietary restriction strategies is its reported high adherence rate, making it a more feasible intervention for long-term use. Therefore, exploring the effects of TRE on metabolic and immunological parameters in psoriasis is warranted.

Objective: This study was designed to evaluate the effects of short-term, isocaloric TRE, independent of weight loss, on immune cell function and serum metabolite profiles of volunteers with mild-to-moderate psoriasis compared to healthy individuals.

Methods: This case-control, prospective study was performed on 10 healthy male participants and 10 age-, BMI-, and sex-matched individuals with mild-to-moderate psoriasis. All individuals with psoriasis had stable disease and were being treated with topical therapies without any exposure to immunomodulatory biologics. This study was conducted at the National Institutes of Health Clinical Center. Immune profiles, glucose handling, energy expenditure, and participants' weights were assessed at baseline and after 3 days of TRE following a daily 6-hour eating window and 18-hour fast.

Results: The trial commenced in June 2021 and was completed in February 2023. A total of 20 participants were enrolled—10 with mild-to-moderate psoriasis and 10 age-, BMI-, and sex-matched healthy individuals. As of the time of manuscript submission, data processing is ongoing. Multiomic datasets, including gene expression, surface and intracellular protein levels, and metabolite profiles, are being generated from peripheral blood mononuclear cells, $CD4^+$-enriched T-cells, and serum samples. The integrated bioinformatics analyses will be reported once the data analysis is completed.

Conclusions: This clinical protocol was designed to characterize the effects of short term (3-day) TRE on psoriasis, independent of weight loss, by comparing immune cell regulatory responses between healthy individuals and those with psoriasis. More

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specifically, we aim to map the molecular pathways activated by TRE and assess how they affect immune cell composition, activation, and metabolism. Additionally, components of the metabolic response to isocaloric TRE are being explored. Insights into how dietary interventions impact metabolism and the immune system will enhance our understanding of the pathogenesis of psoriasis and may reveal new therapeutic avenues for managing this inflammatory condition.

Trial Registration: ClinicalTrials.gov NCT04728165; https://clinicaltrials.gov/study/NCT04728165

(JMIR Res Protoc 2025;14:e74999) doi:10.2196/74999

KEYWORDS

psoriasis; calorie restriction; intermittent fasting; time-restricted eating; immunoregulation; immunometabolism

Introduction

Psoriasis is a chronic inflammatory skin disease that affects approximately 2%-3% of the US population. Beyond its skin and joint manifestations, psoriasis predisposes individuals to premature cardiovascular comorbidities, primarily due to immune activation and systemic, inflammation-induced atherosclerosis.[1] Skin-initiated immune activation through nonprofessional immune cells, including keratinocytes and fibroblasts, initiates and amplifies both innate and adaptive immune responses. These responses include the activation of monocytes and macrophages, neutrophils and their subsets (including low-density granulocytes), as well as effector T- cells (predominantly T_H1 and T_H17 subsets). These immune cells exacerbate local disease and propagate systemic sterile inflammation. The centrality of immune activation in psoriasis is reinforced by the therapeutic efficacy of targeted therapies, such as anti-TNF and anti-IL-17 treatments, which aim to modulate these immune responses [2,3].

The contribution of excess calorie consumption to the pathogenesis of psoriasis has been long debated. However, epidemiological and meta-analytic data support the notion that the incidence of obesity is higher in individuals with psoriasis and that the severity of psoriasis is positively correlated with an increased incidence of obesity [4]. The role of calorie excess in the pathophysiology of psoriasis is further strengthened by studies demonstrating the beneficial effects of calorie restriction on disease activity [5,6]. Taken together, these data suggest that calorie intake may play a significant role in the pathophysiology of psoriasis and that dietary restriction interventions may contribute to disease amelioration by modulating inflammatory pathways.

Various dietary interventions, including prolonged fasting [7,8], intermittent fasting, fasting mimetic dietary supplementation, and calorie restriction per se, have all been shown to confer anti-inflammatory effects through mechanisms that are not yet fully understood [9]. The underlying biological mechanisms are complex, as the duration of fasting may act as an independent mediator, distinct from the effects of calorie restriction on inflammation. Moreover, distinguishing cell-mediated anti-inflammatory effects from other aspects of dietary interventions, such as changes in glucose sensitivity or weight loss, remains challenging.

Previously, we showed that a single 24-hour fast is sufficient to blunt inflammation in monocytes and $CD4^+$ T cells [7,8,10]. In contract, the direct assessment of inflammatory markers in time-restricted eating (TRE), which involved an 8-hour feeding window and 16-hour fast, showed modest effects on some markers (eg, reductions in circulating cytokine levels of TNFa and IL-1b, but not IL-6 and hs-CRP) [11]. In this context, we opted to test a more vigorous TRE protocol comprising a 6-hour eating window and 18-hour fast to assess the effects of this dietary intervention on immunoregulation.

To explore these mechanisms, we designed an acute exploratory study to examine the immune and metabolic responses to an isocaloric, short-term (3-day) TRE regimen consisting of a 6-hour eating window and an 18-hour fasting period in both healthy individuals and individuals with psoriasis. The primary outcome of this study was to phenotype circulating immune cells in both cohorts before and after TRE, focusing on the composition and activation status of peripheral blood mononuclear cells (PBMCs), T-cell subsets (specifically T_H1 and T_H17), and other immune mediators implicated in psoriasis pathogenesis. In parallel, the interplay of metabolic changes will be assessed by quantifying glucose control, weight changes, and energy expenditure.

We aimed to investigate the impact of short-term TRE in individuals with mild-to-moderate psoriasis compared with healthy individuals. We hypothesized that a 6-hour eating window followed by an 18-hour fast for 3 consecutive days would lead to changes in serum metabolites and immune cell composition, activation status, and cellular metabolism independent of glucose control and energy expenditure. Hence, this study aims to provide mechanistic evidence of how TRE ameliorates inflammation, offering insight into its benefits for psoriasis management and evaluating whether these effects are independent of weight loss. Furthermore, this initial limited study may serve as a proof-of-principle for future longitudinal investigations into the role of TRE in inflammatory conditions, including psoriasis and other related disorders.

Methods

Study Design

This study explored the immunometabolic features of a calorie restriction intervention by comparing the effect of TRE (6-hour eating window/18-hour fast) to a more conventional dietary regimen (12-hour eating window/12-hour fast). The conventional regimen was defined as the baseline for this study. Data were collected from individuals with mild-to-moderate psoriasis and from age-matched (within 10 years) and BMI-matched (within 5 kg/m^2) healthy individuals. This is a small, acute TRE,

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case-control study where only male participants were enrolled to eliminate the confounding variable of menstrual cycle phases on low-grade inflammation and insulin sensitivity [12].

Participants were screened with a medical history and medicine review, physical exam, blood tests, skin examination, nutritional evaluation, and resting energy expenditure measurements. Study participants were admitted as inpatients to the Metabolic Clinical Research Unit at the National Institutes of Health (NIH) Clinical Center, where they stayed in individual rooms for 5 days. The first and final 23 hours were spent in metabolic chambers to measure baseline and TRE effects on energy expenditure.

Study Intervention

The study was designed to explore the effects of TRE using a 6-hour eating window and an 18-hour fasting window. Participants followed a weight-maintaining balanced diet to meet 100% of their daily caloric needs throughout the inpatient visit. All foods and beverages were consumed in their rooms during designated hours of the day. On day 0, participants ate during a typical 12-hour window from 8 AM to 8 PM and then fasted from 8 PM to 8 AM the following day. From days 1-4, participants consumed all calories within a 6-hour eating window (8 AM to 2 PM), followed by an 18-hour fast. Meals were provided at 8 AM, 10:30 AM, and 1:30 PM, with participants given 30 minutes to consume each meal. Throughout the study, participants consumed a eucaloric diet consisting of 50% carbohydrate, 35% fat, and 15% protein. Each meal provided 33% of the participant's estimated daily energy requirements. Energy needs for the study diet were calculated based on the resting energy expenditure measured at the screening visit and an activity factor of 60%. Participants had access to water throughout the study intervention.

Blood samples for immune and metabolic measurements were taken via intravenous catheter on day 1 and day 4. Participants wore a continuous glucose monitor (CGM) throughout the 5-day inpatient stay. Liquid mixed meal tests (MMTs) were conducted on day 1 (baseline) and day 4 (after 3 days of TRE). On MMT days, participants consumed a liquid meal for breakfast.

Ethical Considerations

This study has been registered on Clinicaltrials.gov (NCT04728165). This study was approved by the National Institutes of Health Institutional Review Board (000149H). Informed consent was obtained both verbally as well as in writing prior to participation in the study. The data was deidentified by excluding the main identifying elements such as name, address, date of birth, phone number, email, medical record number, institutional identification number, and social security number. Participants received an identification code, according to the order of inclusion in the study. The participants were informed about the possibility of withdrawing at any time, without loss of their treatment at the institution. Additionally, participants were informed about the voluntary nature of their participation. Participants received financial compensation for their time and inconvenience of procedures due to no direct benefit for their inclusion in the study.

Primary Objective

The primary objective of this study was to evaluate the response to TRE in individuals with psoriasis compared to age-, sex-, and BMI-matched healthy individuals. The primary outcome was the change in IL-17 secretion from activated $CD4^+$ T cells at baseline and the end of the study in both groups.

Secondary Objectives

The secondary objectives of this study were to compare the broader impact of TRE on immune cell regulatory pathways and immunometabolism. Additionally, we aimed to evaluate whether TRE modifies 24-hour glucose flux and glycemic excursions during meal tests. Energy expenditure was also compared at baseline and following 3 days of TRE. These measurements were taken over a 23-hour period in a metabolic chamber. Finally, the change in weight over the acute isocaloric study was determined.

Recruitment and Eligibility

A total of 10 male participants aged 18 to 80 years with mild-to-moderate active psoriasis (measured using the psoriasis area and severity index score) were enrolled in the study. Ten age-matched (within 10 years) and BMI-matched (within 5 kg/m^2) healthy individuals were also enrolled as the control group. The inclusion and exclusion criteria are outlined in Textbox 1.

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Textbox 1. Inclusion and exclusion eligibility criteria for study participation.

Inclusion criteria:

- Men aged 18 to 80 years with mild-to-moderate active psoriasis, as determined using the psoriasis area and severity index score.
- Age-matched (within 10 years) and BMI-matched (within 5 kg/m^2) healthy men for inclusion in the control group.
- Individuals able to provide informed consent.
- Individuals willing and able to participate in the study procedures.

Exclusion criteria:

- A psoriasis area and severity index score above 12.
- Individuals who received treatment with systemic biologic immune modifying agents within the last 2 months.
- Individuals currently receiving treatment for allergies or other inflammatory diseases.
- Individuals who have taken vitamin B or tryptophan supplementation within 2 weeks of participation.
- Individuals unwilling or unable to provide informed consent.
- Individuals with a known history of type 1 or 2 diabetes mellitus or other metabolic conditions that would interfere with study parameters, including chronic kidney disease, chronic liver disease, or history of hypoglycemia.
- Individuals using medications that would interfere with the study parameters, including antihyperglycemic medications, systemic steroids, adrenergic-stimulating agents, or other medications known to affect sleep, circadian rhythms, or metabolism.
- Individuals with caffeine consumption in excess of three 8 oz cups per day.
- Individuals exposed to factors affecting circadian rhythm, such as overnight shift work, irregular sleep or eating schedules, or regularly fasting for more than 15 hours per day.
- Individuals who have regularly used tobacco products within the last 3 months.
- Individuals consuming more than 3 servings of alcohol per day.
- Individuals engagement in competitive sports training.
- Individuals with moderate to severe claustrophobia.
- Individuals with unstable weight (ie, with more than a 5% change in body weight in the last 3 months).
- Individuals with food allergies or intolerances or dietary patterns that would prohibit consumption of the study diet or mixed meal test.

Study Interventions

The participants were required to fast for 12 hours prior to the screening visit, during which fasting energy expenditure was measured using the ventilated hood technique. This assessment was used to calculate isocaloric diets for each individual, which they followed during the conventional and TRE regimens.

On admission to the metabolic unit on day 0, a CGM was placed following an initial breakfast meal. Total energy expenditure was determined using indirect calorimetry during a 23-hour stay in the respiratory chamber. Participants entered the respiratory chamber after breakfast on day 0 and day 4. At 8 AM on day 1, blood samples were drawn for the immune parameter studies. Following this, participants underwent a MMT at breakfast after completing the conventional regimen (day 1) to measure metabolic hormones and serum metabolites.

Participants then initiated the isocaloric TRE regimen for 3 days. On day 3, after breakfast, they entered the respiratory chamber again for a 23-hour analysis to assess the potential metabolic effects of the TRE protocol. On the following morning (day 4), blood samples were drawn at 8 AM for immune parameter studies after completing the third 18-hour fast. While still in the respiratory chamber, participants underwent a final MMT to assess the metabolic features of TRE. The study was completed once participants exited the chamber. The schematic of the study is shown in Figure 1.

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Figure 1. Schematic of the clinical study. CGM: continuous glucose monitoring; MMT: mixed meal test; TRE: time-restricted eating.

Summary of Tests and Calculations

Anthropometrics

Participants' weights and heights were measured on day 0. Daily weight measurements were subsequently obtained from day 1 to day 4.

Metabolic Cart

Resting energy exposure was measured to assess basal energy requirements for designing the eucaloric diets for each study participant. Measurements were performed in the morning after a 12-hour fast using indirect calorimetry with the ventilated hood technique with a metabolic cart (Parvomedics, Murray, UT) [13].

Mixed Meal Test

After a 12-hour (day 0) and 16-hour (day 4) overnight fast, 1 intravenous catheter was placed in each arm for blood draws upon arrival in the morning. A liquid meal (Boost Plus) was provided to meet 33% of the estimated daily calorie requirements. Blood samples were obtained after 0, 10, 20, 30, 40, 50, 60, 90, and 120 minutes to measure plasma glucose, serum insulin and C-peptide, and triglyceride concentrations [14].

Respiratory Chamber

Total body energy expenditure was assessed in an in-room metabolic respiratory chamber over 23 hours beginning on day 0 and day 3 [15]. In this isolation chamber, resting and sleeping energy expenditure, the thermic effect of food [16], and the energy cost of physical activity can be assessed [17]. Blood samples were obtained through an isolette system, allowing direct nursing contact with the participant. Telemetry and a nurse call were available to ensure participant safety. A 24-hour urine specimen was collected while in the chamber to measure changes in urea and nitrogen levels. A random urine creatine sample was also collected.

Respiratory chamber measurement periods were approximately23 hours, and the data were extrapolated to represent 24-hour periods by assuming the mean of the measured periods accurately represented the full 24-hour period. The formula used to calculate energy expenditure was as follows: energy expenditure (kcal) = $3.88 \times VO_2 - 0.32$ L/g × Kexcr (g) + $1.08 \times VCO_2 - 1.57 \times N$. VO_2 and VCO_2 are the volumes of oxygen consumed and carbon dioxide produced, respectively, in liters. Kexcr refers to ketones excreted in grams. N refers to the 24-hour urinary nitrogen excretion in grams.

Sleeping energy expenditure was determined as the lowest energy expenditure over a continuous 180-minute period between midnight and 6 AM.

The ratio of VCO_2 to VO_2 is termed the respiratory exchange ratio and reflects the relative oxidation of macronutrients (carbohydrates, fats, and protein). Changes in the respiratory exchange ratio from waking hours to the fasted sleeping period were used to quantify metabolic flexibility during each feeding schedule [14].

Continuous Glucose Monitoring

Participants wore FDA-approved CGMs during their inpatient admission. The devices recorded real-time serum glucose levels approximately every 5 minutes. The system consisted of a small sensor, transmitter, and handheld receiver (roughly the size of a pager). The sensor was inserted with a small introducer needle that was retracted after subcutaneously inserting the sensor. The transmitter, attached to the sensor, sent the measured glucose readings to the receiver. The data stored in the receiver was uploaded to a server for future analyses. To compare the change in 24-hour glycemic profiles, glucose data from day 0 at noon will be compared to data from day 4. A CGM R package was used to calculate active wear time, wear days, percent wear days, and glycemic metrics, including average blood glucose, time in range, SD, coefficient of variation, and mean amplitude glucose excursion [18,19].

Metabolic Analyses

Fasting concentrations of glucose, insulin, C-peptide, and triglycerides were measured in serum using the Roche Cobas 6000 analyzer (Roche Diagnostics). Hemoglobin A1c was measured using the HPLC D10 instrument (Bio-Rad).

PBMC Multiomic Analysis

TRE-mediated changes in immune cells will be assessed using high-throughput single-cell modalities. Transcriptomic and immunophenotype changes will be quantified using single cell RNA-sequencing (scRNA-seq) combined with cellular indexing of transcriptomes and epitopes sequencing (CITE-seq). Changes in cellular metabolism will be assessed using cytometry by time-of-flight (CyTOF) to quantify levels of metabolic enzymes and regulatory proteins [20]. This approach has been successfully performed in similarly modest-sized human studies [21]. The integration of these datasets will enable an

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unprecedented, granular analysis of immune cells before and after TRE in both healthy individuals and patients with psoriasis. Downstream analyses will be performed to generate hypotheses that may be tested through ex vivo studies [8,22] or inform the design of future larger and longer-term prospective studies.

Outcome Measures

The primary outcome was quantification of IL-17 secretion from T cell receptor–activated CD4+ T cells isolated from samples collected on day 1 and day 4. The delta (change) in IL-17 secretion was compared using a 2-tailed paired *t* test. IL-17 secretion in response to TRE was compared between the 2 cohorts using a 2-tailed, 2-sample *t* test in each study group.

The collected samples will also allow hypothesis generation to understand the molecular mechanisms underlying changes in IL-17 secretion. To this end, PBMC transcriptomic and protein-level changes will be quantified using high-throughput multimodal platforms, including scRNA-seq, CITE-seq, and CyTOF. A broad range of downstream analyses will be performed to uncover immunophenotypes, cellular states, enriched signaling pathways, and intercellular communication. More specifically, clustering and cell type annotation will allow the identification of distinct cell populations based on gene and protein expression profiles. Differential gene expression analysis will elucidate significant expression changes pre- and post-TRE. Gene set enrichment analysis will be used to evaluate the enrichment of specific pathways or biological processes. Cell-to-cell communication inference tools will identify putative ligand-receptor interactions driving immune responses. Moreover, multimodal integration will permit the cross-validation of cell types using both gene and protein expression data and link transcriptional programs to functional immune phenotypes.

We will implement statistical correction tools across all data types to address the risk of false discoveries due to multiple hypothesis testing. This will include false discovery rate adjustment using the Benjamini-Hochberg method.

For phenotypic data, including glucose levels and metabolic rates, comparisons within groups were conducted using paired 2-tailed *t* tests, and between-group comparisons were performed using unpaired 2-tailed *t* tests. A *P* value of <.05 was considered statistically significant.

Sample Size Calculations and Statistical Analyses

There are no published data on TRE in either healthy individuals or individuals with psoriasis on which to base calculations for the number of participants required to uncover distinct effects on IL-17 cytokine release. Hence, to justify our sample size and facilitate power calculations for 10 participants per group, we referred to data from a previous fasting study in which isolated $CD4^+$ T cells were analyzed in 13 healthy individuals at the NIH Clinical Center (ClinicalTrials.gov NCT02719899). In that study, the mean and SD for the paired refed-fasting differences in IL-17 release were 187.1 pg/ml and 398.79 pg/ml, respectively [8].

For the primary objective, our computations for change from baseline IL-17 secretion in patients with psoriasis assumed the SD from the aforementioned fasting study. Using a 2-tailed paired *t* test with α=.05 and n=10, we estimated 80% power to detect a clinically significant change of 396.36 pg/ml or greater. To compare the change in IL-17 secretion between healthy participants and patients with psoriasis, we assumed a 187.1 pg/ml change from baseline in controls (the value observed in the fasting study). With a 2-tailed paired *t* test with α=.05 and n=10 for the 1:1 matched participants, the study would have 85% power to detect a 209.26 pg/ml (396.36 pg/ml – 187.1 pg/ml) or greater difference between the psoriasis and control groups in IL-17 secretion from baseline. For these computations, we assumed a SD of 199.4 pg/ml for the paired differences in IL-17 secretion from baseline between matched patients with psoriasis and healthy participants (half the SD for the controls in the fasting study).

Therefore, we requested approval to enroll up to 15 healthy individuals and 15 individuals with mild-to-moderate psoriasis for this initial study, with the goal of having at least 10 participants complete the study in each group. The effect of TRE will be assessed within each group and the response to TRE will be assessed between groups.

All other analyses will be exploratory, and the analytical approaches are briefly described in the Outcome Measures section above.

Dissemination of Project Findings

The findings of this study will be disseminated through various channels to reach a diverse audience. To engage the dermatology clinical community, we aim to share our results at international and national congresses focusing on dermatology and psoriasis. Additionally, our findings will be disseminated to the scientific communities focused on immunology and metabolism by publishing our findings in peer-reviewed journals germane to those fields. We seek to engage the patient community through potential collaborations with the National Psoriasis Foundation and via a laypeople summary of the findings. Finally, we want to reach the general public by communicating the key results through social media platforms.

Results

Patients were enrolled in the study between June 2021 and February 2023. PBMC scRNA-seq, CITE-seq, and CyTOF were performed in 2024. Data analysis is currently being performed concurrently with flow cytometry and $CD4^+$ T cell metabolomics. We aim to publish and share our findings by 2026.

Discussion

In psoriasis, the major circulating immune cell lineages operational in the disease pathophysiology include neutrophils, low-density granulocytes, monocytes, and $CD4^+$ T cells [23-25]. This study was designed to explore the gene regulatory and metabolic pathways altered in most of these cells, except for neutrophils, which are excluded in the polymorphonuclear cell fraction isolation protocol. Including a control group will allow us to evaluate whether the immune effects of TRE are more

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pronounced in an inflammatory disease cohort compared to individuals without baseline inflammation.

The primary outcome of this study, aimed at determining T_H17 immune responsiveness through IL-17 secretion, was performed in negatively selected T cell receptor–activated $CD4^+$ T cells. As the samples were paired (baseline and post-TRE), these $CD4^+$ T cells were also analyzed for changes in intracellular and serum steady-state metabolite levels. This analysis will help characterize whether TRE evokes systemic metabolite changes that influence $CD4^+$ T cell signaling and provide insights into how TRE modulates intracellular metabolic pathways.

From an unbiased discovery perspective, data from high-throughput multimodal technologies, including scRNA-seq, CITE-seq, CyTOF, and flow cytometry, will be analyzed and integrated [26] to explore the effects of TRE in both healthy individuals and individuals with psoriasis. These analyses will offer crucial hypothesis-generating insights into how TRE exerts anti-inflammatory effects across different immune cell populations in PBMCs.

Finally, this initial study was designed to evaluate whether the effects of weight loss or glucose sensitivity can be dissociated from the direct immunomodulatory effects of TRE. The robustness of the eucaloric study design will be determined by changes in weight, continuous glucose monitoring, and energy expenditure, as measured by indirect calorimetry.

The limitations of this study arise in part from its small sample sizes and its short duration (3 days of TRE). This design is intended to generate hypotheses about immunoregulation independent of caloric load that can be further explored in more targeted and larger studies. Another limitation of the small study size was the restriction of this protocol to men to alleviate adding the variable of hormonal changes during the menstrual cycle. This is obviously a significant constraint when considering the generalizability of findings to women, and this will need to be addressed in a larger, longer-term follow up study.

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Authors' Contributions

SRA contributed to conceptualization, investigation, methodology, writing the original draft, and review. KH reviewed and edited all sections of this paper. RDH supported the provision of resources. STC, GPT, NAM, ABC, RJB, and KYC were involved in the metabolic phenotyping analysis of the study. LCC contributed to data management and analytic planning. MNS was the principal investigator responsible for the conception, overall design, and conducting of this trial. MNS was also principally responsible for developing the intervention content and reviewed all sections of this paper. MNS, STC, and AJC contributed to conceptualization, formal analysis, funding acquisition, investigation, methodology, supervision, and writing.

Conflicts of Interest

LCC has received grants or research support from Abbvie, Amgen, Janssen, and UCB; has worked as a paid consultant for AbbVie, Amgen, Bristol Myers Squibb, Eli Lilly, Enlivex, Janssen, Moonlake, Novartis, Pfizer, Takeda, and UCB; and has been paid as a speaker by AbbVie, Amgen, Eli Lilly, Janssen, Novartis, Pfizer, and UCB.

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Abbreviations

CGM: continuous glucose monitor
CITE-seq: cellular indexing of transcriptomes and epitopes sequencing
CyTOF: cytometry by time-of-flight
MMT: mixed meal test
NIH: National Institutes of Health
PBMC: peripheral blood mononuclear cell
scRNA-seq: single cell RNA-sequencing

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Protocol

Association Between Refrigerator Openings and Protein Intake After Hospitalization for Heart Failure Decompensation: Protocol for a Prospective Cohort Pilot Study

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Abstract

Background: Sarcopenia, characterized by loss of muscle mass, reduced strength, and increasing frailty, is common in older adults and is often the result of underlying diseases such as advanced stages of heart failure (HF). Protein intake is crucial for maintaining muscle mass and strength. However, older adults typically consume less protein compared to younger individuals. It has recently been shown that the time of the first refrigerator opening in the morning, indicated by a door sensor, may be correlated with frailty in older individuals living alone.

Objective: The aim of this study is to determine whether the time of the first refrigerator opening in the morning can serve as a potential indicator of protein intake in older patients (age ≥70 years) after hospitalization for HF decompensation over a period of 6 months.

Methods: This is a substudy of a prospective interventional cohort study that aims to identify changes in digital biomarkers derived from an ambient sensor system, which may support the early detection of HF decompensation. In this substudy, the frequency and timing of refrigerator door openings in participants' homes will be measured. To assess associations between protein intake and refrigerator openings, dietary intake will be evaluated using 24-hour dietary recalls at 3 different timepoints: at 1, 3, and 6 months after hospital discharge. All 24-hour dietary recalls will be conducted by trained dietitians in face-to-face interviews on weekdays. The primary outcome of this study will be the correlation between protein intake and the time (in minutes after midnight) of the first refrigerator door opening at each of the 3 assessment points.

Results: The study is currently in the data collection phase. Recruitment began in February 2024. Data analysis will begin after all data have been collected. As of manuscript submission, 12 patients have been recruited. Results are expected to be published by the end of 2025.

Conclusions: Considering that protein-rich foods are typically stored in the refrigerator, the relationship between frailty and refrigerator usage may be a relevant indicator for nutritional assessment, particularly regarding protein intake. In addition, sarcopenia and frailty may also be linked to protein distribution across meals. This study will explore whether monitoring

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refrigerator openings can serve as a simple method for identifying increased risk of frailty and sarcopenia. Early detection through such monitoring could facilitate timely interventions and potentially reduce the risk of these conditions.

Trial Registration: ClinicalTrials.gov NCT06126848; https://clinicaltrials.gov/study/NCT06126848

International Registered Report Identifier (IRRID): DERR1-10.2196/66299

(JMIR Res Protoc 2025;14:e66299) doi:10.2196/66299

KEYWORDS

ambient sensor system; digital health; older people; muscle mass; muscle strength; nutrition assessment; protein intake

Introduction

The population of older people is increasing significantly around the world, including in Switzerland [1]. With higher life expectancy and increasing age, the risk of diseases characterized by a decline in muscle mass is also rising [2,3]. Loss of muscle mass and strength is associated with an increased risk of mobility impairment, fractures, prolonged hospitalization, hospital readmission, reduced quality of life, morbidity, and mortality [2,4-6]. These conditions arise due to a combination of reduced food intake, increased nutrient requirements, metabolic changes, sepsis, trauma, aging, and physical inactivity [4]. The interplay between malnutrition, sarcopenia, and frailty in older people has already been demonstrated in many studies [7-10]. A systematic review and meta-analysis has shown that about half of hospitalized older adults suffer from 2 or even 3 of these diseases or precursors [3].

Furthermore, sarcopenia and frailty are often the result of other underlying diseases such as chronic heart failure (HF). The prevalence of sarcopenia has been found to be 55% (95% CI 43-66) in hospitalized patients with HF and 26% (95% CI 16-37) in nonhospitalized patients [11]. Additionally, 79% of patients with HF are frail. This, in turn, may be associated with reduced quality of life and poor prognosis [12]. Overall, diet quality is associated with the risk of frailty, and poor intake is adversely related to muscle mass and strength [13,14]. Nutritional status is, therefore, also a crucial risk factor for the development and prognosis of HF.

Due to the high prevalence of sarcopenia and frailty in patients with HF, more attention should be paid to protein intake as an important influencing nutritional factor [14-16]. To achieve this, the protein intake of patients with HF in the home environment must first be assessed. Ideally, simple, valid instruments should be used for this purpose. Common screening tools such as the Mini Nutritional Assessment (MNA) are insufficient to recognize people with low energy and protein intakes [17]. Currently, a number of screening and assessment tools are available [18]; however, the assessments with these tools are very time-consuming for long-term monitoring at home and therefore not very feasible for application in HF patients' everyday lives.

Digitalization can offer new possibilities that allow patients with HF living at home to be monitored easily and regularly. It has been shown that a sensor system using interaction-free, contactless, and inexpensive sensors is suitable for long-term monitoring of physical activity, sleep, and door openings, including the refrigerator door in the homes of older people living alone [19]. Considering that protein-rich foods (such as meat, meat products, fish, milk, and dairy products) are typically stored in the refrigerator, the relationship between frailty and use of the refrigerator door could be an important indicator for nutritional status in terms of protein intake. Furthermore, sarcopenia and resulting frailty may also be linked to protein distribution across meals. To date, very few studies have investigated this. A study among older women in the Nurses' Health Study indicates that consuming at least 30 g of protein over 2 or more meals could be more effective for maintaining muscle mass and physical performance compared with eating a single high-protein meal [20]. In addition, 2 recent studies in older populations indicate that skipping breakfast increases the risk of frailty [21,22]. A Japanese survey (n=2468) showed a correlation between breakfast habits and frailty in older people aged 75 and over. Breakfast skippers generally had lower food intake and poorer nutrient density than daily breakfast consumers. The multivariable-adjusted odds ratio (95% CI) of breakfast skippers for frailty was 1.62 (1.04-2.52; P=.032) in one model (adjusted for age, sex, body mass index, and living alone) [22].

The use of refrigerator openings (eg, the first door opening of the day or frequency) as indicators for increased risk of sarcopenia and frailty would provide an easy monitoring opportunity. In this context, the study by Schütz et al has shown that the time of the first refrigerator opening in the morning indicated by a door sensor at the refrigerator may correlate with frailty in older single living persons [19]. Notably, approximately one-third of older people in Switzerland live alone [23], emphasizing the relevance of such monitoring approaches. Prior studies have also shown that living alone increases the odds of falling among community-dwelling older adults [24-26]. With such simple assessment tools, interventions could be initiated at an early stage to reduce the risk of these diseases. This, in turn, would have a positive impact on the quality of life of those affected and could also help to reduce health care costs.

As a part of prospective interventional cohort study (for details refer to study protocol of Vögeli et al [27]), a substudy will be conducted with the aim of evaluating the sensitivity and specificity of the time of the first refrigerator opening in the morning as a potential indicator for protein intake in older patients after hospitalization for HF decompensation over a period of 6 months.

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Methods

Study Design and Participants

In this prospective cohort pilot study, 24 consecutive patients living alone at their homes who were hospitalized for HF decompensation at 2 secondary care hospitals (Solothurner Spitäler AG) in Olten and Solothurn, Switzerland, will be included.

The inclusion criteria are current hospitalization for HF decompensation, age≥70 years, left ventricular ejection fraction <50% and treatment with diuretics, New York Heart Association class II or III, living alone, willingness to participate with informed consent, and agreement to attend follow-up visits at the hospital at 3 and 6 months. Exclusion criteria include major depression (9-item Patient Health Questionnaire [PHQ-9] score >9) or being on hemodialysis. In addition, patients with a left ventricular assist device, or those who had undergone coronary revascularization or cardiac resynchronization therapy implantation within 28 days before the index event of HF decompensation, or have been scheduled for such interventions, are excluded from the study.

Assessment

Baseline Assessment

The baseline parameters that will be evaluated at hospital entry have been previously described [27].

Dietary Assessment

For dietary assessment, food intake will be measured using the 24-hour dietary recall. The 24-hour dietary recall is an open-ended, retrospective dietary assessment method. It aims to record as much detailed information as possible about all foods and drinks consumed by the respondent in the previous 24 hours or the day before [28]. In this study, 24-hour dietary recalls are conducted at 3 different timepoints, at 1 month (optional), 3, and 6 months after hospital discharge. The first 24-hour dietary recall at 1 month is optional, as—unlike the assessments at 3 and 6 months—it cannot be coordinated with a routine follow-up hospital visit. Conducting this assessment would require an additional clinic or home visit, which was deemed burdensome for participants. To reduce participant burden and support adherence, this timepoint was made optional. All 24-hour dietary recalls will be conducted on weekdays by trained dietitians in face-to-face interviews. As the main drawback of this method is the forgetfulness of the participants, the 24-hour dietary recalls will be conducted by using the Automated Multiple-Pass Method (AMPM), as described elsewhere [29]. The AMPM uses multiple memory cues with standardized wording to elicit recall of all possible foods. Before the start of the 24-hour dietary recall, it will be recorded whether the day surveyed reflected a usual day in terms of diet or whether it was an unusual day. A usual day is defined as a day on which the participant ate according to their usual habits and routines, reflecting habitual dietary intake. This terminology was chosen to emphasize the importance of capturing habitual intake patterns. Conversely, an unusual day is determined based on the participant's own judgment and refers to any day they perceive as not representative of their usual intake. Examples will be provided to participants, for example, holidays, celebrations, excursions, acute illness, or other events that may have significantly altered their eating behavior. The amount of consumed food will be estimated using the photo book of the National Nutrition Survey in Switzerland (menuCH) [30] (Multimedia Appendix 1). The conversion of the estimated amounts into weights will follow the menuCH photo book manuals and commercially available packaging sizes in Switzerland. All conversions will be performed by experienced dietitians. Protein intake in grams (g) and energy intake in kilocalories (kcal) will be calculated using nut.s nutritional software (version 1.33.10 - 2022.08.26; dato Denkwerkzeuge) based on the 24-hour dietary recalls. The nutritional database used in nut.s is adapted for the evaluation of Swiss food products.

Anthropometric Measurements

Anthropometric measurements include body height, body weight, and BMI. Weight is measured using a clinically validated and calibrated scale. Participants must remove heavy clothing (eg, jackets and jumpers) and shoes. Weight is recorded to the nearest 0.1 kg. Height is measured using a calibrated stadiometer. The measurement is taken in an upright position with the feet on a hard surface. The heels, buttocks, shoulders, and the back of the head touch the wall, and the arms are placed at the sides. Height is recorded to the nearest 0.1 cm. BMI is calculated by dividing body weight in kilograms by height in meters squared. Measurements will be taken at 1 month (optional), 3, and 6 months after hospital discharge, each time following the 24-hour dietary recall.

Mini Nutritional Assessment Short Form

Screening for malnutrition or risk of malnutrition will be carried out at 1 month (optional), 3, and 6 months after hospital discharge, using the Mini Nutritional Assessment Short Form (MNA-SF). The MNA-SF, consisting of 6 questions, is cost-effective, simple, and suitable for use in hospitals and therefore fulfills the requirements for a screening instrument, which can be used to identify existing malnutrition or the risk of malnutrition in older people [31]. The MNA-SF includes questions on mobility, psychological stress, or acute illness and neuropsychological problems, which increase the risk of malnutrition but do not directly detect malnutrition. The MNA-SF is therefore particularly suitable if the screening aims to detect malnutrition as early as possible [32].

Handgrip Strength

There is strong evidence for a correlation between reduced handgrip strength (HGS) and poor nutritional status, increased mortality, complication rates, and hospital length of stay [33-36]. Therefore, HGS will be measured 1 month (optional), 3, and 6 months after hospital discharge, using a dynamometer as follows: participants sitting in a chair with the elbow joint bent 90 degrees. On request, the dynamometer is squeezed as firmly as possible. First, the nondominant hand and then the dominant hand will be tested 3 times each. The highest value for each hand is entered into the database.

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Refrigerator Door Sensors

The refrigerator at the patient's home will be equipped with a door sensor recording the opening and closing events of the fridge door. This sensor consists of a small magnet fixed on the door and a sensor with a reed relay attached to the frame. When the door opens or closes, the sensor immediately sends this information to a base unit through an encrypted radio frequency protocol continuously with a resolution of 1 second. The base unit collects the data and sends it to the cloud in real time using the Global System of Mobile Communication networks. The duration of each refrigerator opening is calculated as the time difference between the opening and closing events. The system has been described in detail in the main study, where the sensor system is used to collect digital markers beyond refrigerator openings with the aim of evaluating the system's potential to detect HF decompensation [27]. The integration of the magnetic refrigerator door sensor into the sensor system to detect refrigerator openings represents a minor extension to the overall setup. The high reliability of the ambient sensor system, with extremely low susceptibility of the sensor and the transmission system, has been shown previously [27]. The refrigerator door sensors will be installed at the patient's home within 1 week after hospital discharge. Frequency and timing of refrigerator openings are collected over a 6-month period after hospital discharge. The assessment during the study is shown in Figure 1.

Figure 1. Assessments during the substudy.

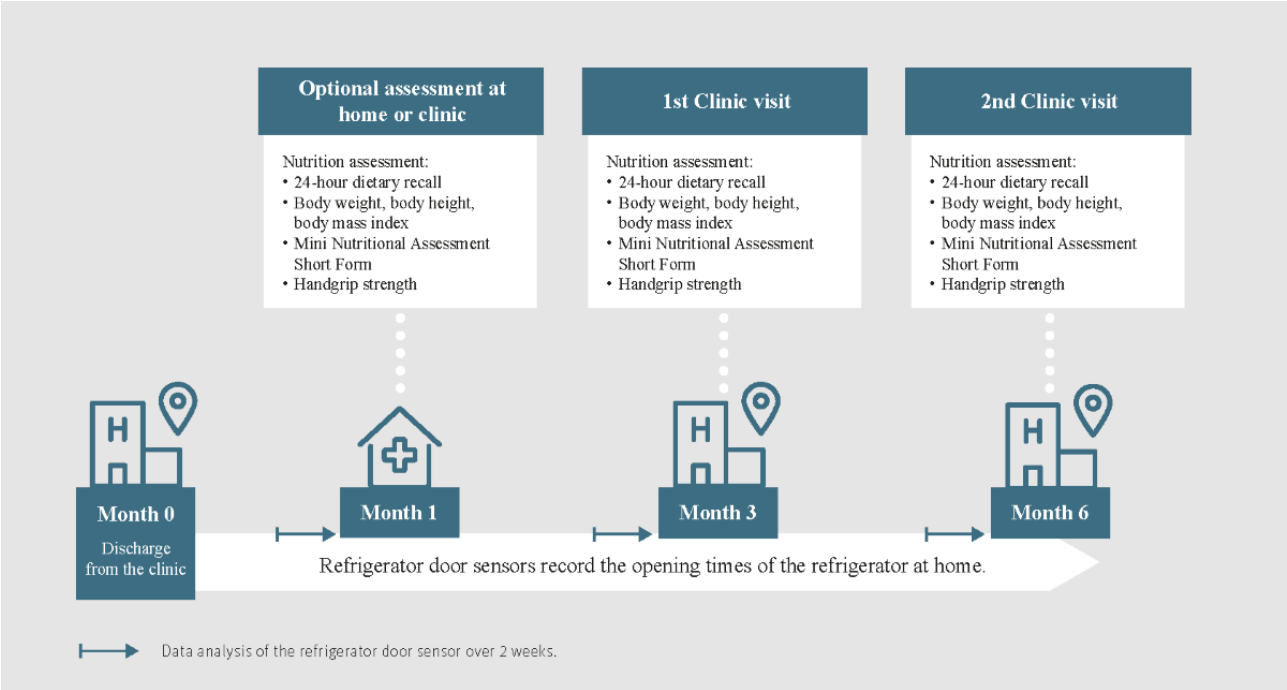

Statistical Analysis

We will compute the cross-sectional correlations between protein intake (g) and first refrigerator door opening after midnight in minutes (RDmin) at the start (1 month) and at 3 and 6 months (primary outcome). Further, quantities of interest are the correlation between protein intake (g) and refrigerator opening frequency per day (RDfreq), between energy intake (kcal) and RDmin and RDfreq, between (risk of) malnutrition (score) and RDmin and RDfreq, and between HGS (kg) and RDmin and RDfreq. From the time series of refrigerator opening time after midnight in minutes over the period of 6 months, we will create 3 time windows, each window representing the 2-week period prior to each nutrition assessment (Figure 1). For each window, a mean RDmin measurement will be calculated, resulting in 3 RDmin measurements, 3 RDfreq, and 3 measurements of protein intake (g) and energy intake (kcal) from the 24-hour dietary recalls, 3 measurements of malnutrition and HGS (after 1, 3, and 6 months). We will estimate the cross-sectional associations between RDmin and RDfreq and protein intake (g), energy intake (kcal), (risk of) malnutrition (score), and HGS (kg) at 1, 3, and 6 months to quantify the correlation and to assess the stability of this correlation over time. We will compute Spearman correlation coefficients with corresponding 95% CIs.

Ethical Considerations

The study will be conducted in accordance with the principles of the Declaration of Helsinki, the International Council for Harmonisation–Good Clinical Practice (ICH-GCP) Guideline, and the Human Research Act after protocol approval by the regional ethics committee (Ethikkommission Nordwestschweiz: BASEC-ID 2023-02138). Patients will provide written informed consent for the main and the substudy. Data will be collected by specially trained research staff and entered into a password-protected data environment. Each patient will be assigned a study-specific patient identification number (PID). For statistical analysis, datasets will be merged using the PID as an identifier. Upon completion of data collection, including follow-up, patient data will be coded using the PID, and the database will be locked. Coding using the PID will be done at the earliest time point after completion of follow-up data collection. Data generation, transmission, storage, and analysis of health-related personal data will comply with current Swiss

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legal requirements for data protection and will be performed according to the Human Research Ordinance Art. 5. Health-related personal data captured during this study will remain strictly confidential and will not be disclosed to third parties. Participants will be reimbursed for travel expenses for hospital follow-up visits. No costs will be incurred by participants for taking part in the study.

Results

The study is in the collection phase. Study recruitment started in February 2024. Data analysis is scheduled to start after all data are collected. As of June 2025, 12 patients have been recruited. Results are expected to be published by the end of 2025.

Discussion

What Does the Study Offer?

Because overall diet quality is associated with the risk of frailty, and insufficient protein intake leads to loss of muscle mass and strength [13,14], more attention should be paid to healthy nutrition and adequate protein intake in patients with HF. Although results from other studies suggest that patients with HF may benefit from a high-protein diet, conclusive evidence from prospective controlled clinical trials, particularly in relation to mortality, is scarce. Individual studies, such as a randomized double-blind pilot study in 29 patients with HF, have shown improvements in quality of life after 18 weeks on a high-calorie, high-protein diet [37]. However, most studies on protein intake are observational and have been conducted in the general population [38], while limited data are available for patients with HF. Simpler and more innovative tools for collecting information on protein intake in patients with HF could reduce the burden of long-term home monitoring. Furthermore, such tools may help minimize recall bias, which is particularly problematic in older adults when using retrospective dietary assessment methods. Refrigerator openings could represent such a tool, both in terms of the first opening of the day and overall frequency. For example, a late first refrigerator opening after midnight may be indicative of skipping breakfast. In general, little is known about the nutritional status of older people who skip breakfast, and there are contradictory results regarding meal frequency and frailty [39,40].

To the best of our knowledge, this is the first prospective study investigating the use of refrigerator openings as a potential indicator of protein intake. The use of the refrigerator openings in relation to frailty and sarcopenia would allow easy monitoring. Interventions could be initiated at an early stage and thereby reduce disease progression.

Limitations

This study has several limitations. First, the patterns of refrigerator openings—regarding time of day and frequency—may be subject to great variations, and the use of single values or combinations of values will require both internal and external validation. Second, the study is limited to patients who live alone. This complicates the generalizability of the results to other populations with HF. The small sample size is based on experience from a previous study, including a similar patient population with hospitalization for HF decompensation. At present, no prior data are available to support a formal power calculation. Third, to verify the accuracy of the refrigerator openings in assessing the protein intake, results must be compared with a standard reference method. This is done in this study with a 24-hour recall. As a retrospective method, it also has weaknesses, in particular, recall bias or unusual eating days. For this reason, at least two 24-hour dietary recalls per person are carried out.

Conclusions

This study aims to provide new insight into the relation between refrigerator openings and nutritional intake, particularly protein intake. It is hypothesized that monitoring refrigerator openings within the framework of an ambient sensor system may help identify patients at risk for malnutrition and, as a result, for muscle mass and strength loss. Such identification of insufficient, and particularly protein-deficient, diets could enable simple monitoring and timely intervention to prevent or at least delay sarcopenia and frailty. This, in turn, may improve quality of life and potentially reduce health care costs. In addition, this low-effort monitoring approach could be of interest for other target groups.

Acknowledgments

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Data Availability

The datasets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

KH, FSB, and HS have designed the substudy. BV, NA, and HS are responsible for the overall study. HK and SF are responsible for collecting the data. AM designed the analyses and will conduct them. HK, SF, and HS wrote the first and subsequent versions of the manuscript. All authors have read and approved the final manuscript. HK has final responsibility for the content of this manuscript.

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Conflicts of Interest

PB works for DomoHealth, one of the manufacturers of the sensor system used in the study.

Multimedia Appendix 1
Examples from the photo book of the national nutrition survey in Switzerland (menuCH).
[PDF File (Adobe PDF File), 419 KB - resprot_v14i1e66299_app1.pdf]

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Abbreviations

AMPM: Automated Multiple-Pass Method
HF: heart failure
HGS: hand grip strength
ICH-GCP: International Council for Harmonisation–Good Clinical Practice
menuCH: National Nutrition Survey Switzerland
MNA: Mini Nutritional Assessment

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MNA-SF: Mini Nutritional Assessment Short Form
PHQ-9: 9-item Patient Health Questionnaire
PID: patient identification number
RDfreq: refrigerator door opening frequencies per day
RDmin: refrigerator door opening after midnight in minutes

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Protocol

Chatbot-Based Version of a World Health Organization–Validated Intervention for Stress Management in Patients With Breast Cancer (Self-Help Plus): Protocol for a Pilot Feasibility Study

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Abstract

Background: Emerging digital tools play an innovative and key role in supporting women's psychological well-being throughout the different stages and challenges of cancer. The development and adoption of digital interventions, including chatbots and virtual coaches within smartphone apps, are increasingly recognized as valuable resources for enhancing women's mental health.

Objective: The aim of this paper is to present the research protocol for a pilot study designed as a proof-of-concept investigation. The study evaluates the feasibility, acceptability, and perceived utility of a mobile app delivering an acceptance and commitment therapy–based stress management intervention. The intervention is delivered through ALBA (A Well-Being Assistant), a virtual coach embedded within the TreC (an acronym for *cartella clinica del cittadino*, meaning "citizen's electronic health record") research platform—a mobile health ecosystem designed to support research and digital health interventions. ALBA guides users through 5 coaching sessions tailored for women undergoing breast cancer (BC) treatment. The chatbot-delivered app is an adaptation of Self-Help Plus, a World Health Organization (WHO)–validated stress management intervention, and is provided in text, audio, and video formats. The intervention's potential impact on participants' psychological well-being is also explored.

Methods: A convenience sample size of 50 participants will be identified to meet the study's objectives. Participants will be recruited using a convenience sampling approach from women receiving care at the Breast Unit of the Azienda Provinciale per Servizi Sanitari di Trento. ALBA will interact with the participants for 6 weeks. Specifically, there will be 1 coaching session per week, followed by weekly assigned acceptance and commitment therapy exercises to be performed between sessions.

Results: The app is expected to demonstrate high usability and engagement, aligning with the WHO Self-Help Plus protocol. Improvements in psychological well-being and quality of life are anticipated. Data from this pilot will be analyzed using both quantitative and qualitative methods, with a focus on assessing feasibility, acceptability, and perceived utility and usability in supporting women during BC treatment.

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Conclusions: Existing literature indicates a promising role for new technologies in delivering validated mental health interventions, highlighting the potential of digital interventions to address barriers related to social stigma and seeking assistance. This pilot is expected to provide valuable insights on the potential acceptability and usefulness of providing consistent mobile health psychoeducational support to women throughout the course of BC.

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KEYWORDS

stress management; psychological well-being; breast cancer; eHealth; mobile health; mHealth; mobile apps; development; usability; user-centered design; artificial intelligence; AI

Introduction

Overview

A growing need for psychological support is emerging among the general population, and this need increases even more if we consider populations exposed to stressful situations [1,2]. Emerging scientific literature highlights that psychological vulnerability is often linked to specific periods along the disease trajectory, such as those experienced by women with breast cancer (BC). On the one hand, psychological distress, including stress, anxiety, and depression, often accompanies pathologies such as BC [3]. On the other hand, having a more positive attitude contributes to disease management and recovery, highlighting the importance of addressing mental health issues on physical aspects while taking charge [4,5]. Therefore, improving the mental well-being of women dealing with BC could be an effective way to enhance their overall health. In this sense, evidence of the effectiveness of psychological interventions aimed at women with BC is increasing [6,7], but access to support services still presents several challenges. Many women face geographical barriers, with specialist centers often located far from their homes. Furthermore, the shortage of qualified personnel, such as psychologists, limits access to specialist care. The stigma associated with mental health problems can also prevent women from seeking psychological support in these circumstances [8,9].

Within this framework, there is a recent focus on the potential contributions of digital technologies in fostering psychological well-being, recognizing their capability to provide an optimal solution to reduce barriers [10] and enhance patient empowerment [11].

Indeed, the World Health Organization (WHO) has implemented a comprehensive mental health strategy grounded in principles of inclusivity and scalability, which also incorporates the use of digital technologies [12,13]. The study described in this protocol is part of the panorama of WHO's strategies, and it aims to evaluate the acceptability and feasibility of an intervention delivered via digital tools to promote psychological well-being. In particular, this intervention, initially validated by WHO itself and called Self-Help Plus (SH+) [14-16], has never been used on the target population of this study, women with BC. SH+ is a low-intensity and transdiagnostic intervention that is easily adaptable in different contexts, delivered by nonspecialist operators, and has solid evidence-based psychological principles inserted in a self-help approach. This approach has already been validated with various populations considered vulnerable, such as migrants, refugees, and health care workers, both to promote psychological well-being and for clinical intervention purposes, demonstrating general acceptability and potential effectiveness [16,17]. The first attempt was made to make the protocol web based within the RESPOND (preparedness of health systems to reduce mental health and psychosocial concerns resulting from the COVID-19 pandemic) project, but the involvement of a human person, in the role of a helper, was still necessary [18].

Cognitive behavioral therapy (CBT) techniques, and in particular those referring to third-generation therapy, are shown to be more suitable than other psychotherapeutic approaches to be transferred into low-intensity interventions delivered by nontraditional methods such as eHealth applications [19]. SH+ is based on the principles of acceptance and commitment therapy (ACT), a third-wave form of CBT [20,21], and is divided into 5 chapters that address 5 strategies for managing stress and promoting psychological well-being. The five chapters, later translated into sessions, are (1) grounding (mindfulness), (2) unhooking (defusion), (3) acting on your values (values-based behavioral activation), (4) being kind (gratitude), and (5) making room (acceptance).

This Study

Overview

Our study is placed within the design and development cycle of the Obesity-Related Behavioral Intervention Trials (ORBIT) model [22], specifically in phase 2a, "refine." It involves providing material based on SH+ intervention in text, audio, and video format by a virtual coach (ie, a digital chatbot assistant, identified as ALBA [A Well-Being Assistant]) implemented within the TreC (an acronym for *cartella clinica del cittadino*, meaning "citizen's electronic health record") research app (a platform or app purposively designed to enable the delivery of several types of mobile health [mHealth] features). It could be stated that this study is innovative for 2 main reasons. First, it involves the digitalization of an intervention that was originally delivered in person and in group settings [14,15]. The ALBA chatbot version is designed to be more accessible and tailored to the individual, functioning without the presence of a helper, unlike in the RESPOND project [17,18], and includes chatbot-guided activity completion between sessions, which differs from the group session delivery format. Therefore, it is essential to evaluate how effectively this new format achieves these goals. Second, this study introduces

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a novel focus on a population consisting exclusively of female individuals and those considered medically vulnerable, which represents a significant new factor in evaluating the feasibility, acceptability, and efficacy outcomes. The proof-of-concept (POC) study, described in this research protocol, aims to test both the transferability and acceptability of the digitalized intervention from the original, context-specific in-person format (refer to the Primary Objective section), as well as to assess its initial efficacy on the targeted psychological variables in this newly defined population (refer to the Secondary Objective section).

ALBA Intervention

ALBA is an intervention based on ACT techniques; it aims to promote the quality of life and enhance stress-coping skills in women with BC through a psychoeducational approach. The module is self-administered and available for both Android (Google LLC) and iOS (Apple Inc) devices. All the contents of the dialogues were developed by a group of researchers belonging to the Digital Health Research of the Bruno Kessler Foundation of Trento and psychologists belonging to the Pavoniano Artigianelli Institute with specific skills in the communication field starting from the SH+ manual [23] and subsequently reviewed by a psychologist manager of the psychology operational unit of the Provincial Health Services Authority of Trento (Azienda Provinciale per i Servizi Sanitari di Trento). The dialogues, videos, and audio tracks were developed according to educational logic. Furthermore, the structuring of the material and the delivery methods were supervised by professionals from the WHO Center for Research in Mental Health of the University of Verona, who have already carried out implementation studies and validation of SH+ at national and international levels.

To ensure the best possible adaptation of the intervention to our target sample, we previously conducted a co-design study based on guidelines of a previous step of the ORBIT model [22]. This process involved domain experts, such as psychologists, SH+ experts, and communication and usability experts, and a small sample of women with BC and oncological clinicians. For further details, please refer to our previous study [24].

Technological Tools

This intervention is part of a behavior change framework [25] aimed at supporting women's psychological well-being. The term "intervention" refers to the virtual coach, the chatbot ALBA, which delivers structured, rule-based informational content reviewed by psychological professionals. ALBA functions as a tool for information delivery, not as a conversational agent, as it does not engage in real-time, dynamic interactions. While it collects and transmits data, it is primarily a chatbot for eHealth interventions. ALBA is developed for research purposes to validate the digital health version of SH+ focused on ACT practices for women with BC.

ALBA, the technological component of this study, is built upon the general TreC platform, a public mHealth platform enabling residents of the Autonomous Province of Trento (North Italy) to access, manage, and share their health and well-being information. TreC is a robust and reliable platform designed as a "system of systems" rather than merely a data repository [26]. Indeed, its flexible architecture allows for collecting and managing diverse data types and supports developing and integrating additional subsystems to offer specific functions. A key feature of TreC is empowering users to manage their health-related data, functioning as a personal health record.

Within this general platform, a specific mHealth ecosystem has been designed to support research and digital health interventions, called TreC research ("Trec Ricerca" in Italian; Figure 1). This module is available for free download as a mobile app to all women diagnosed with BC. Authentication is required via the secure, General Data Protection Regulation–compliant national identification system (Sistema Pubblico di Identità Digitale).

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Figure 1. Graphical representation of the TreC (an acronym for cartella clinica del cittadino, meaning "citizen's electronic health record") research platform, which incorporates the ALBA (A Well-Being Assistant) chatbot and illustrates its interactions with the database and users. SH+: Self-Help Plus.

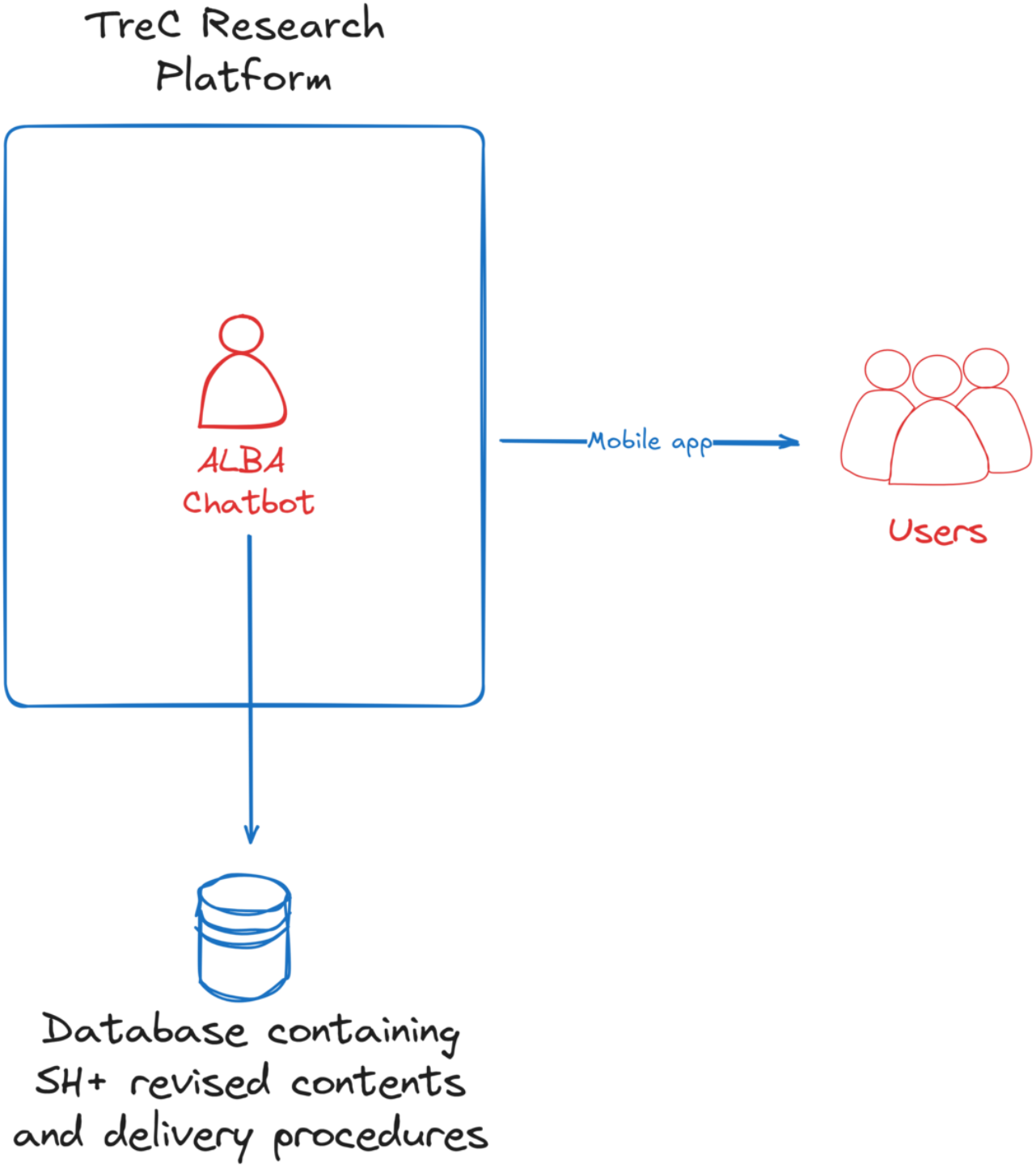

SH+ Sessions

The intervention spans a total duration of 6 weeks. For each week, a session of approximately 40 minutes is delivered, while this can be divided into two 20-minute subsessions according to users' preferences. Phase 3, represented in Figure 2, provides a graphical depiction of the conversational protocol delivered to the participants and its chronological structure. The intervention's contents are presented through a gradual process designed to progressively increase the participant's self-awareness and mindfulness-oriented skills, including accepting and normalizing internal states, managing stress, and enhancing psychological well-being. Participants are also required to complete tasks and fill in a dedicated e-diary. The program is structured into 5 main coaching sessions, following the operational chapters of the SH+ manual, each addressing a specific strategy for managing stress and promoting psychological well-being, which are the main aims of the intervention. These 5 modules, translated into weekly e-sessions, are grounding (mindfulness), unhooking (defusion), acting on

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your values (values-based behavioral activation), being kind (gratitude), and making room (acceptance; phase 3 in Figure 2).

Figure 2. Graphical representation of the conversational protocol delivered to users and its chronological structure. COPE-NVI-25: Coping Orientation to the Problems Experienced; ERQ: Emotion Regulation Questionnaire; GHQ: General Health Questionnaire; GSE: General Self-Efficacy Scale; ITA BUS B: Italian Chatbot Usability Scale, version B; K-10: Kessler Psychological Distress Scale; MPFI: Multidimensional Psychological Flexibility Inventory; PSS: Perceived Stress Scale; SF-36: Short Form Health Survey 36; SUS: System Usability Scale; UES-SF: User Engagement Scale-Short Form; uMARS: User Mobile Application Rating Scale.

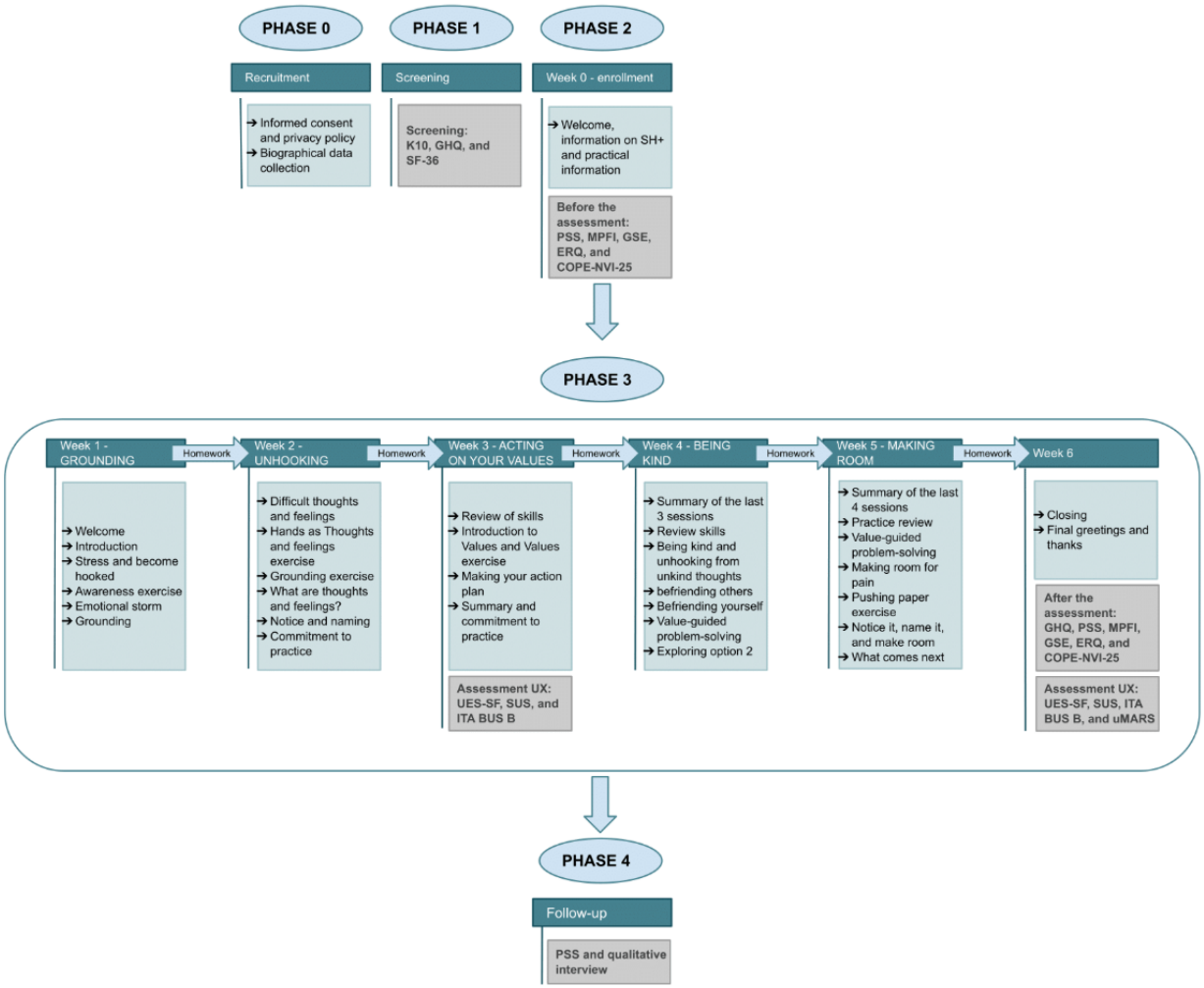

Goal of the Study and Research Questions

Overview

Therefore, this protocol paper aims to describe the POC developed to deploy the ALBA app to women with a BC diagnosis. The POC aims to evaluate the acceptability and feasibility of delivering SH+ through ALBA, a platform designed to provide ACT-based psychoeducational sessions. ALBA supports users in completing exercises and tasks assigned between coaching sessions and periodically delivers structured information—curated by professional psychologists—in audio, text, and video formats. This material is independently accessed and managed by users. The virtual coach serves as an information transmission tool, while the app also administers questionnaires and manages data collection.

This behavioral change intervention [25] aims to empower women with adaptive strategies for managing stress. Studying its feasibility can represent a first step to evaluate the possibility of including a digital service to support and promote psychological well-being in the context of stepped care for women in the BC pathway.

Primary Objective

The main objective of the POC study is to evaluate how women experience the chatbot-based version of the WHO-validated intervention SH+. It aims to assess the following areas: (1) the user experience (UX) and the usability of the virtual coach, ALBA, installed in the TreC research app environment and (2) how users felt during the intervention, using ALBA, as reported through semistructured interviews. The IT evaluation of the TreC research app itself will be presented in another study.

Secondary Objective

The secondary goal is to assess the efficacy of the intervention on women's psychological well-being through the administration of self-report pretest-posttest and follow-up questionnaires.

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Methods

Design and Study Plan

The study is articulated in 4 main phases depicted in Figure 2 and extensively described in the Data Collection section.

Phase 0: Recruitment

This phase will take place at the hospital's Breast Unit, and it will be carried out by the health professionals of the Breast Unit (physicians and case manager nurses).

Phase 1: Screening

The screening phase is carried out by psychologists, and subsequent included participants are given access to the TreC research app.

Phase 2: Enrollment at Week 0

At the beginning of the path, ALBA will administer 5 self-report questionnaires to establish the baseline level of the examined variables (preassessment questionnaires). The participant can choose the best day and time to interact with ALBA (first interaction with ALBA).

Phase 3: Intervention Delivery From Week 1 to Week 5

Specifically, there is 1 psychoeducational session per week, and the contents will be presented in different formats (text, images, audio, and video tracks). Moreover, ALBA provides users with instructions on how to carry out simple exercises and fill in a personal diary. The questionnaires will be further administered by ALBA at the end of the course (at week 6) to verify whether participants have perceived a change in terms of psychological well-being and quality of life. In total, 4 questionnaires will be administered to evaluate usability and UX (weeks 3 and 6).

Phase 4: Follow-Up

Four months after the conclusion of exposure to SH+ intervention, women who have given consent will be invited to participate in a semistructured interview to investigate their experience of using ALBA and the TreC research app to understand how the women felt during the intervention. In addition, the long-term effects of stress will be collected by administering a follow-up questionnaire.

Participant Recruitment and Withdrawal

Overview

The study will take place in the Province of Trento (North Italy), where approximately 5000 women have or have had a diagnosis of BC, with almost 500 new cases every year [27]. In January 2018, the Breast Unit was established in the Province of Trento. It represents an innovative organizational model that merges various professionals, structures, and services transversally to make it more effective and homogeneous and coordinates the clinical path of patients with BC.

Recruitment will target women diagnosed with BC who are enrolled in the Breast Unit program, with additional support from local voluntary associations where possible. A convenience sampling approach will be used. Textbox 1 [14,17,28-30] outlines the study's inclusion and exclusion criteria.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Have a diagnosis of stage 0, I, II, or III breast cancer (BC)
- Be a female patient under the care of the Breast Unit
- Be aged ≥18 years (Italian legal age)
- Have a smartphone with internet access and the ability to download the app and be able to use it
- Be a resident of the Autonomous Province of Trento
- Know and understand the Italian language
- Have a moderate level of psychological distress, defined by a score between 15.9 and 29.9 on the Kessler Psychological Distress Scale, with higher scores indicating more severe distress [28]. This range aligns with the inclusion thresholds used in World Health Organization (WHO) studies using the RESPOND protocol [17].
- Have a general well-being score of ≥3 on the General Health Questionnaire, consistent with the inclusion criterion used in World Health Organization studies using the Self Health Plus protocol [14].
- Obtain a score between 30 and 80 (cutoffs identified based on the literature on the Short Form Health Survey 36 [SF-36] instrument in patients diagnosed with BC [29,30]) on the "Mental health" scale of the SF-36 questionnaire.

Exclusion criteria

- Patients unable to provide informed consent (prerequisite for participation in the study)
- Inadequate understanding of the Italian language
- Patients aged >75 years
- Women with metastatic BC (stage IV), those in the metastatic phase, receiving palliative care, or with a life expectancy of <1 year
- Obtain a score <30 on the "Bodily Pain" scale of the SF-36, indicating severe pain levels [29,30]
- Suicidal tendencies, depression, or other psychiatric diagnoses
- Already receiving psychological or psychotherapeutic care at the time of recruitment

Health professionals at the Breast Unit will verify the inclusion and exclusion criteria related to the sociodemographic data (phase 0), while psychologists will assess the psychological screening data (phase 1).

Participants will be required to sign an informed consent form during recruitment (phase 0), following a comprehensive explanation of the project, its objectives, data collection, management, processing procedures, the required level of involvement, the study duration, and confidentiality matters. They will be informed that they can withdraw from the study at any time without providing a reason and that doing so will not affect the quality of their care or interfere with their treatment. Informed consent must be given freely and in writing, accompanied by a data processing authorization form, before joining the study. Participants must provide written informed consent. They will also receive a privacy policy statement explaining how their personal data will be processed during the study and must provide explicit consent for its use. Copies of the informed consent and privacy forms will be provided to participants and available in a dedicated section of the app.

To promote participant engagement and retention throughout the 6-week intervention, specific features were designed to sustain interest and minimize dropout, such as incorporating gamification elements, providing regular feedback or progress tracking, scheduling personalized reminders, and offering small recognition for continued participation. No monetary compensation was provided.

Sample Size

This research project is designed as a POC study, where a limited sample is sufficient to achieve the intended aims. On the basis of calculation assuming a nonnormal distribution and using nonparametric statistics, a sample of 24 women with BC diagnoses is sufficient when applying a Bonferroni-corrected significance level (α=.025) to control for type I error and multiple comparisons. Nevertheless, to validate this estimate, the sample calculation was run with the Power Analysis and Sample Size 2021 (NCSS, LLC) and Stata (StataCorp LLC) programs. The resulting sample size is 41 participants, based on the following assumptions: a significance level (α) of .025, statistical power of 0.80 (to ensure sufficient sensitivity to type 2 error), a mean difference between groups (eg, pre- and postintervention questionnaires) of 1.00, an expected effect size (δ) of 0.50, and an SD of 2.00.

The chosen effect size (Cohen d=0.50) reflects a moderate change [31], which is consistent with previous digital mental health interventions in populations with psychological disorders [32]. This approach aligns with recommended practices in early-stage mHealth research, where the focus is on identifying potential signals of efficacy rather than definitive effect estimates [22]. Therefore, considering a 20% possible dropout [33], 50 women were estimated to need to be recruited to carry out the study. This approach is also coherent with previous studies adopting this type of methodology in the field of mHealth.

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Study Outcomes

Primary Outcomes

The primary outcomes are UX and usability. They will be assessed using 4 questionnaires, namely, the User Engagement Scale-Short Form (UES-SF) [34], the System Usability Scale (SUS) [35], the Italian Chatbot Usability Scale, version B (ITA BUS B) [36], and the User Mobile Application Rating Scale (uMARS) [37]. They will be administered at different time slots throughout the study, in particular, at the end of week 3 (UES-SF, SUS, and ITA BUS B) and at the end of the study (week 6: UES-SF, SUS,; ITA BUS B, and uMARS; Textbox 2).

Textbox 2. Summary of the questionnaires administered and their timing.

Screening

- Kessler Psychological Distress Scale (K10)
- General Health Questionnaire (GHQ)
- Short Form Health Survey 36 (SF-36)

At the beginning of the study (week 0)

- Perceived Stress Scale (PSS)
- Multidimensional Psychological Flexibility Inventory (MPFI)
- General Self-Efficacy Scale (GSE)
- Emotion Regulation Questionnaire (ERQ)
- Coping Orientation to Problems Experienced - New Italian Version 25 (COPE-NVI-25)

At the end of week 3

- User Engagement Scale-Short Form (UES-SF)
- System Usability Scale (SUS)
- Italian Chatbot Usability Scale, version B (ITA BUS B)

At the end of the study (week 6)

- GHQ
- PSS
- MPFI
- GSE
- ERQ
- COPE-NVI-25
- UES-SF (this will be administered the following day so as not to burden the participant during completion)
- SUS (this will be administered the following day so as not to burden the participant during completion)
- ITA BUS B (this will be administered the following day so as not to burden the participant during completion)
- User Mobile Application Rating Scale (uMARS; this will be administered the following day so as not to burden the participant during completion)

Follow-up (4 months after the conclusion)

- PSS
- Qualitative interview

The end points to be measured include the scores of individual questionnaire items, the average scores of the questionnaires, and the differences between average scores of the questionnaires at various survey times. In addition, the participants' experiences with the app and interactions with ALBA, as well as their use of the intervention, will be evaluated through semistructured interviews conducted 4 months after the study concludes. These interviews will collect qualitative data to supplement the primary outcome information.

Secondary Outcomes

The variables expressing the psychological well-being outcomes will be assessed by administering self-report questionnaires at the beginning (screening and week 0) and at the end (week 6) of the intervention (Textbox 2 provides a detailed overview of the questionnaire adopted). The end points to be measured include the scores of individual questionnaire items, the average scores of the questionnaires, and the differences between the average scores of the questionnaires at 2 survey times. In

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addition, the Perceived Stress Scale (PSS) [38] will be administered during a follow-up conducted 4 months after the study's conclusion.

Both the clinical and usability tests will yield within-subject and between-subject comparison results.

Data Collection

The data collection process will take place in all the phases of the research, starting with recruitment and ending with follow-up.

Phase 0: Recruitment

Sociodemographic data collection will be carried out by the health professionals at the Breast Unit (physicians and case manager nurses) using a prestructured form. After informed consent is obtained, each form will be assigned a unique alphanumeric code. The parameters requested from participants will be (1) date of birth, (2) oncological disease history (ie, date of first cancer diagnosis, date of tumor removal surgery, date of any other interventions carried out or planned, and date of last neoadjuvant or adjuvant chemotherapy or radiotherapy treatment or if still ongoing), (3) maximum education grade, (4) employment, (5) marital status, and (6) current or previous experience of psychological support (exclusion criterion 7 verification).

Phase 1: Screening

To fulfill the verification of the inclusion criteria from 7 to 9 and the exclusion criteria 5 and 6, the researchers will administer the screening questionnaires through LimeSurvey (LimeSurvey GmbH; Textbox 2).

After processing the results of the screening questionnaires and the various sociodemographic inclusion criteria, the women will be contacted again, and the following scenarios will open.

First, the participant does not meet the inclusion criteria due to demonstrating a markedly positive state of psychological well-being, as indicated by a stress level <15.9 on the Kessler Psychological Distress Scale (K-10) [28], a general well-being score <3 on the General Health Questionnaire (GHQ) [39], and a general well-being score >80 on the "Mental Health" scale of the Short Form Health Survey 36 (SF-36) [29]. In such cases, the women will not be enrolled in the study, and the reasons for exclusion will be shared along with the screening questionnaire results, but upon the participant's request.

Second, the participant does not meet the inclusion criteria due to exhibiting a markedly negative state of psychological well-being or signs of psychopathology, as indicated by a score <30 on mental health scale of the SF-36 and a K-10 score >29.9. In addition, in the second case, the participant will not be able to be enrolled in the study, and the reasons for exclusion from the study will be returned, and only upon request of the participant will the results obtained from the screening questionnaires be returned. Furthermore, indications of local services to contact for problems will be appropriately provided. This is to provide the participant with a structured and agreed system of referral to a qualified support service and taking charge where appropriate.

Third, the participant meets the inclusion criteria. In this case, the participant is enrolled in the study. The participant will also be asked if they would like to participate in a qualitative interview and in compiling a last questionnaire about stress 4 months after delivery. In case of positive feedback, the telephone number will be collected to facilitate contacts and follow-up interviews.

Phases 2 and 3: Enrollment and Participation

Overview

To properly assess included participants' experience during the psychoeducational pathway, some questionnaires were adopted and delivered at the beginning (phase 2), during, and at the end of the interaction with ALBA (phase 3), as shown in Textbox 2.

Specifically, 5 questionnaires will be administered at the beginning (week 0) and at the end of the intervention (week 6) together with the initial screening questionnaires, which aim to investigate stress level, self-efficacy, emotional regulation, psychological flexibility, coping strategies, well-being, and level of psychological well-being. None of these questionnaires has diagnostic purposes. Therefore, they will not be used to diagnose psychopathology but only to collect descriptive data.

Four more questionnaires will be sent during the process to analyze the usability and involvement of the participant with the app and with the virtual coach, ALBA. Specifically, the usability and UX questionnaires will be administered at the end of week 3 (3 questionnaires) and week 6 (4 questionnaires).

A detailed description of each instrument that will be administered is presented in the subsequent sections.

UX and Usability Evaluation

The ITA BUS B [36] is a tool designed to evaluate the ease of use, effectiveness, and user satisfaction in interacting with the chatbot. While it is commonly used with artificial intelligence (AI)–powered chatbots, it is also applicable to other types of chatbot systems [36,40,41]. The 11 items are rated on a 5-point Likert scale, where 1 means "strongly disagree" and 5 means "strongly agree," resulting in a total score ranging from 11 to 55. The areas investigated are as follows: perceived accessibility to chatbot functions, perceived quality of chatbot, perceived quality of conversation and information provided, perceived privacy and security, and time response.

SUS [35] is a quick and reliable tool for evaluating the usability of systems. Consisting of 10 items with Likert-type answers from 1 ("strongly agree") to 5 ("strongly disagree"), the questionnaire provides a global score that reflects the ease of use and applicability of a system or product. The SUS yields a single number representing a composite measure of the overall usability of the system being studied, with a global score that can range from 0 to 100, depending on the degree of agreement with sentences such as "I found the system very cumbersome to use."

UES-SF [34] measures user engagement with digital technology. Consisting of 12 items, the scale offers a quick but practical assessment of user engagement. Each item is rated on a 5-point

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Likert scale ranging from 1 (“strongly disagree”) to 5 (“strongly agree”), yielding a total score between 12 and 60. The questionnaire consists of four factors: (1) focused attention, which indicates the feeling of being immersed in the interaction; (2) perceived usability, which is the negative effect experienced due to the interaction and the effort expended; (3) aesthetic attractiveness, which represents the graphical and visual appeal of a digital solution; and (4) the reinforcement factor (reward). The latter is a single factor that includes duration, which evaluates the overall success of the interaction; novelty, which examines the general interest related to the interaction with a digital solution; and the perceived engagement factor, which evaluates the overall enjoyment of the interaction. As the questionnaire was not available in Italian, it was translated using the back-translation procedure. The 4 scales show good internal reliability, as follows: focused attention (ω=0.82), perceived usability (ω=0.86), aesthetic attraction (ω=0.84), and reinforcement (ω=0.81).

uMARS [37] is a tool for evaluating the quality of mobile apps. It provides a 20-item measure that includes 4 objective quality subscales—engagement, functionality, esthetics, and information quality—and 1 subjective quality subscale. One further subscale, consisting of 6 items, is added to measure users’ perceived impact of the evaluated app. This allows participants to obtain an in-depth and multidimensional evaluation of the quality of mobile apps. Each item offers answers on a Likert scale from 1 to 5, with 1 corresponding to “insufficient” and 5 to “excellent.”

Psychological Assessment

The Coping Orientation to Problems Experienced - New Italian Version 25 (COPE-NVI-25) [42] is a shortened version of the Coping Orientation to Problems Experienced Inventory, designed to evaluate different coping strategies individuals use to deal with stress. This 25-item questionnaire explores strategies such as active coping, planning, and acceptance, providing a complex picture of an individual’s coping behavior. Specifically, 5 dimensions are examined: problem orientation, transcendent orientation, positive attitudes, social support, and avoidance strategies. These dimensions are assessed using a Likert scale ranging from 1 (“I never do it”) to 4 (“I often do it”), resulting in a total score between 25 and 100.

The Emotion Regulation Questionnaire [43] is a tool that evaluates 2 main emotion regulation strategies: expressive suppression and cognitive reappraisal. The questionnaire includes 10 items, with responses on a Likert scale from 1 (“strongly disagree”) to 7 (“strongly agree”), and is used to understand how individuals control and modify their emotional reactions in various contexts. On the basis of the answers, the score can vary from 10 to 70. Balzarotti et al [44] translated and validated the questionnaire in Italian, showing good psychometric characteristics.

GHQ-12 [39] is a self-assessment tool designed to identify mental health disorders and to monitor general psychological well-being. Because of its brevity, GHQ-12 has become one of the most widely used tools for detecting psychological distress. GHQ is widely used in clinical, research, and public health settings. The 12 items of the questionnaire are formulated to investigate how the individual has felt recently concerning psychological symptoms (such as anxiety and depression), ability to cope with daily situations, sleep disorders, and somatic symptoms. The response is based on a 4-point Likert scale, ranging from “not at all” to “much more than usual,” with a maximum score of 36.

The General Self-Efficacy Scale (GSE) [45] is a psychometric tool designed to evaluate an individual’s general perception of self-efficacy, that is, confidence in organizing and executing the actions necessary to manage potentially stressful or difficult situations. The GSE consists of 10 statements on which respondents must express their level of agreement on a Likert scale ranging from 1 (“not at all true”) to 4 (“exactly true”). The scale items explore various aspects of self-efficacy, such as the ability to solve problems, overcome obstacles, and handle unexpected situations. The total score, obtained by adding the scores of all the items, reflects the general level of self-efficacy perceived by the individual and can vary from 10 to 40, with a higher score indicating more self-efficacy.

K-10 [28] is a widely used screening tool to measure psychological distress. The K-10 is a short questionnaire composed of 10 items that investigate the frequency of psychological symptoms experienced by the individual in the last month, such as nervousness, sadness, tiredness, and feelings of hopelessness, for example, “During the last 30 days, about how often did you feel tired out for no good reason?” Each question is rated on a 5-point scale, ranging from “none of the time” to “all of the time.” Total scores range from 10 to 50, with higher scores indicating greater psychological distress (scores ≥30 suggest a high likelihood of a severe mental disorder).

The Multidimensional Psychological Flexibility Inventory (MPFI) [46] is a tool designed to assess psychological flexibility across multiple dimensions. It investigates how people adapt their thoughts and behaviors in response to changing situations and challenges. The MPFI focuses on various aspects of psychological flexibility. In particular, there are 6 scales for flexibility (acceptance, present moment awareness, self as context, defusion, values, and committed action) and 6 scales for inflexibility (experiential avoidance, lack of contact with the present moment, self as content, fusion, lack of contact with values, and inaction), according to the Hexaflex model [46]. For each of these dimensions, there are 5 items with responses ranging from 1 (“never true”) to 6 (“always true”).

PSS is a self-report questionnaire used to measure perceived stress. In particular, the objective is to determine the degree to which situations are perceived as stressful in a person’s daily life. Using 10 items rated on a 5-point Likert scale, this tool assesses participants’ thoughts and feelings over the past month regarding specific events, such as how often they felt unable to control important aspects of their lives. For each item, participants indicate the frequency on a scale from 0 (“never”) to 4 (“very often”).

SF-36 [29] is the most widely used general health measurement tool. It is a questionnaire divided into 8 sections: physical functioning (10 items), limitations due to physical health (4 items), limitations due to emotional problems (3 items), energy

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and fatigue (4 items), emotional well-being (5 items), social activities (2 items), pain (2 items), and perception of general health (36 items). For each dimension, the scores of the questions are coded, summed, and transformed into a scale ranging from 0 (worst health state) to 100 (best health state).

The platform adopted for the intervention allows for the recording of activity logs, enabling proper mapping of patients' actions and experiences. This covers a range of logs, assessing whether the participant is properly exposed to the intervention protocol while recording use patterns (eg, session execution time, number of accesses, and use patterns of different features). Included among the variables considered are any missed sessions or interruptions. These data will be correlated with acceptability scores during the analysis phase. If a patient does not complete activities and fails to fill in specific questionnaires (leading to missing data), specific information on patients' experiences and platform use will be collected during the scheduled postintervention interview sessions.

Phase 4: Follow-Up

The follow-up interview will be carried out 4 months after the conclusion of the SH+ process; will last approximately 20 minutes; and, subject to the patient's consent, will be audio-recorded to allow subsequent analysis. The interviews are structured with ad hoc items specifically designed to capture key characteristics of the study and participants' experiences. They are conducted by psychologists from the design team. During the qualitative interview, the patient will also be asked if someone supported them during the intervention, how easy it was to carry out the exercises, and general personal perceptions about the usability and real-world application of this app. Interviews will be conducted 4 months after the end of the intervention and will last approximately 20 minutes.

Privacy and Data Management

At the time of recruitment, privacy documentation is available in line with Articles 13 and 14 of EU Regulation 2016/679 (General Data Protection Regulation), with specific focus on purposes and legal grounds of data processing, including information on how the personal data will be collected, the types of personal data collected, how the data will be managed, the retention period, the responsibilities of data controllers, and the rights of data subjects. Personal data are processed for specific research purposes within the scope of public interest tasks of the data controllers. Informed, freely given, voluntary, and explicit consent regarding the processing of special personal data (ie, data concerning health and data on self-reported behavioral habits in the area of lifestyle health) will be collected. Moreover, specific consent will be collected on the possibility of contacting the data subject via telephone to conduct research interviews. All data collected will be kept confidential, and data necessary for evaluating the study objectives will be pseudoanonymized before processing.

Access to personal or sensitive data is strictly limited to authorized IT specialists solely for the purpose of platform maintenance and in accordance with standard operating procedures and data protection protocols. App developers and platform hosts do not access personal or sensitive user data for any other purpose.

Copies of the information on the study and of the privacy policy will be issued to the participant and made available in a dedicated section of the app.

The study manager produces a report on the research and ensures that the data are reported responsibly and consistently. Personal data will neither be disclosed nor disseminated, except in anonymized or aggregated form for publication purposes. The transmission or dissemination of the data will take place exclusively in anonymous form, using only aggregated data that prevent any direct or indirect identification of the participants.

Data Analysis

Overview

Preliminary data analysis is scheduled for early November 2024, while the final results will be available at the end of the study. The publication of the results will take place within 1 year after the conclusion of the study. Given the potential for dropout, which is commonly observed in digital interventions, and the sensitive nature of our sample population, missing data will be carefully addressed during the analysis phase. Where appropriate, multiple imputation methods will be applied to account for missing values and reduce potential bias. In addition, participants who drop out or fail to complete the follow-up assessments will be included in the analysis using an intention-to-treat approach, wherever feasible.

Quantitative Analysis

Statistical data processing will be conducted using the software R (version 4.0.0; R Foundation for Statistical Computing) [47], SPSS (IBM Corp) statistics [48], Stata (version 17) [49], and Jeffreys's Amazing Statistics Program [50].

Categorical variables will be summarized using absolute frequencies and percentage distributions, while quantitative variables will be summarized using specific measures of central tendency and variability. Descriptive analyses will cover psychological variables (stress level, anxiety level, depression level, emotional regulation, psychological flexibility, coping strategies, well-being, and health status) as well as UX and usability variables. Relationships between variables will be analyzed primarily using ad hoc statistical tests, including the chi-square test, Fisher exact test, paired *t* test, Wilcoxon signed rank test, and sign test, depending on the assumptions met. These tests will help identify differences between the beginning and end of the course within the same study sample for the variables under investigation. In addition, univariate logistic or multinomial regression models will be presented. To account for potential confounding factors, multiple regression models will be proposed, adjusting the effects of explanatory variables on outcome variables for possible confounders. Statistical significance will be found for each analysis with a P value $\leq .05$. The McNemar test [51] and Cochran Q test [52] will also be used to evaluate paired qualitative data.

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Qualitative Analysis

A qualitative analysis will be conducted using a combination of text mining techniques and thematic analysis. With regard to the analysis of the final semistructured interviews, the text mining approach [53] will be used to extract the answers that appear repeatedly from the interviews that will be conducted with respect to the women's experience of interacting with ALBA and with respect to how they felt during the study participation. In particular, frequencies will be analyzed by identifying recurring words or phrases and exploring the dominant lexicon. Classifying texts according to emotional tone (positive, negative, and neutral) will also allow us to analyze sentiment and polarity. This is very useful for analyzing feedback, reviews, and opinions [54]. The specific software or tools to support this analysis (eg, NVivo [55]; Lumivero) are currently being evaluated. The final selection will be based on their ability to efficiently code and interpret open-ended responses, ensuring alignment with the study's objectives and methodological framework.

Finally, significant segments (quotes) will also be extracted, and then, all results will be interpreted in the light of the literature.

Ethical Considerations

This study received approval from the ethics committee of the Provincial Health Services Authority of Trento (Azienda Provinciale per i Servizi Sanitari di Trento; A985; July 17, 2024). At recruitment, all women who voluntarily choose to participate will be asked to sign an informed consent form after receiving a thorough explanation of the study, its objectives, the level of involvement required, the duration of the research, and all ethical issues related to confidentiality. While the health professionals of the Breast Unit will provide part of the explanation, a video recorded by the research team will also be available, clearly detailing the study; its purpose; and the participants' involvement in simple, understandable terms. The participants will be informed of the study's results through the app. Data will be pseudonymized and used only in aggregate form for research purposes. Participation is voluntary, and no compensation will be provided.

Results

The literature highlights the growing interest in ACT-based interventions due to their efficacy in reducing anxiety, depression, and fear of recurrence and enhancing psychological flexibility and quality of life in patients with cancer [56]. ACT techniques, such as mindfulness and cognitive defusion, help manage anxiety and depressive symptoms, improve emotional regulation, and facilitate better stress management due to acceptance principles. Moreover, we expect an enhanced quality of life because through value-based actions, users could improve their overall well-being and life satisfaction. Consequently, we intend to incorporate variables such as psychological flexibility (MPFI), self-efficacy (GSE), coping strategies (COPE-NVI-25), and emotion regulation (Emotion Regulation Questionnaire) as predictors to our results. These variables are crucial for understanding the association between the ACT protocol and health outcomes, ensuring a comprehensive analysis of ACT's efficacy across different phases of cancer treatment.

From a technical standpoint, collaboration with computer science experts will continue throughout the study to ensure the app is properly designed and maintained. We referred to internal usability studies and the previous co-design paper [24] as key examples to evaluate and refine the app's functionalities before this pilot phase, but all new technical issues, such as bugs and glitches, will be monitored online throughout the development of the chatbot. This study aimed to identify and address any technical usability challenges before proceeding with a larger-scale trial. In other words, the findings from this feasibility study will inform decisions about scaling up the intervention or proceeding to a larger efficacy trial. Fundamental benchmarks will be based on key outcomes such as participant engagement rates, retention and dropout rates, significant changes in psychological variables (as mentioned earlier), and outcomes related to the acceptability and usability of the ALBA app, as measured by self-report questionnaires, along with the app's functionality, including bug tracking. If these benchmarks are met, consideration will be given to moving forward with a larger, more definitive trial to assess the intervention's efficacy. In addition, potential modifications to the intervention or trial design will be discussed, based on the results of this feasibility study, ensuring that the next phase could be better tailored to the needs of the target population in terms of content, functionality, and delivery methods.

Discussion

Anticipated Findings and Comparison to Previous Work

This POC study's results can provide valuable data about the use, acceptance, and efficacy of this psychoeducational support for patients with BC receiving care through the Breast Unit. Previous studies indicated that patients diagnosed with BC found this form of support well accepted [57,58], suggesting that digital interventions can help address barriers related to social stigma and help seeking in patients with cancer, while also effectively enhancing patients' psychological well-being.

The app examined in this study features personalized health plans tailored to users' unique needs, which can lead to improved adherence to self-help treatment protocol and better health outcomes, particularly in terms of reduced stress, anxiety, and depression levels. Furthermore, the capacity for progress monitoring allows for timely interventions, which are crucial for also managing chronic conditions effectively [59]. The psychoeducational resources integrated into our app could promote health literacy and patient engagement among individuals with BC, empowering them to actively participate in their health management [60]; this is achieved through the innovative, interactive, and technology-driven delivery of ACT techniques.

Indeed, ALBA, as a basic and easily deliverable tool, could be offered to patients with BC in cases of mild to moderate psychological distress within a stepped care framework. This approach positions the ALBA app as a form of psychological

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first aid that allows a more efficient allocation of clinical resources, such as specialized psycho-oncological support, prioritized for more severe or urgent cases [61]. In this way, the intervention can serve as a widely accessible and user-friendly option, particularly for patients who may be hesitant to seek traditional psychological support or who are placed on waiting lists due to the mild nature of their distress.

Summing up, mHealth apps, such as the one described in this paper, offer promising advantages, such as increased accessibility, scalability, cost-effectiveness, and potential to reduce stigma around mental health care [10-12]. However, they are also accompanied by significant challenges. Key concerns include data privacy and security, limited regulatory oversight, and variability in clinical effectiveness, especially in the absence of robust evidence and standardized evaluation methods [11,12,24,57]. Although these tools may support self-management and extend care to underserved populations, they often rely on users' technological literacy and self-discipline, limiting their usability and adherence over time [10,62]. Tools, such as uMARS [37], have been developed to assess app quality, yet a persistent gap remains in validating content and ensuring sustained engagement. Moreover, overreliance on such interventions may reduce face-to-face interactions with health care professionals, potentially weakening the therapeutic alliance and care continuity. This concern is particularly relevant for populations considered vulnerable, including older adults and individuals with low digital literacy, who may experience reduced access or engagement [63]. Indeed, the digital divide remains a significant issue, as only some have access to or are proficient with digital technologies, which can exacerbate disparities in health care access [64]. Furthermore, issues such as reduced personalization, risk of self-diagnosis, and a lack of integration with traditional clinical pathways raise questions about their long-term safety [57,62]. Therefore, digital health solutions such as ALBA should be implemented as complementary to, rather than substitutes for, human-delivered care, ensuring that personal support and professional guidance remain accessible and central to the care pathway [62]. This aspect, including organizational implications of these technologies in terms of health care delivery, could be explored in future studies.

Finally, we plan to implement AI capabilities in ALBA in the future. The usability and UX questionnaires—particularly those used in this study, along with the psychological assessments—will play an important role in supporting the validation process and ensuring the system's continuous improvement. It is important to note that ALBA and TreC research are not intended to replace clinical or medical support but rather to complement them by promoting psychological well-being and healthy lifestyles during BC care, including in cases where AI is integrated.

Strengths, Limitations, and Future Directions

One of the strengths of this study protocol is the involvement of experts from various disciplines related to oncology and psycho-oncology, as well as experts of SH+ working for WHO, in the design phase. This multidisciplinary collaboration not only enhances the protection of the interests of patients with BC but also ensures a more comprehensive and well-rounded perspective in the codevelopment of the intervention [65]. Another major strength is integrating the study within a structured behavioral intervention design framework, specifically the ORBIT model [22]. This approach adds methodological rigor and scientific validity to the intervention's development and the subsequent testing phases. Second, adhering to a standardized framework facilitates comparisons with previous literature, ensures replicability, and enables a more robust evaluation of the intervention's effectiveness. Positioned after the co-design phase [24,65], this POC study provides an initial assessment of the app's usability and potential efficacy. However, it does not explore how ACT-based psychoeducation affects other important issues for patients with BC, such as body image, sexual quality of life, chronic fatigue, or dyadic adjustment following surgery [66,67]. A limitation of this study is the absence of a control group, which limits the ability to draw comparative conclusions. Future research should consider more robust designs, including larger randomized controlled trials. Moreover, although age was accounted for in the inclusion criteria, we acknowledge that digital literacy is a distinct and equally relevant factor influencing participants' ability to engage with digital mental health tools. Future studies will consider incorporating specific assessment tools, such as the eHealth Literacy Scale [68], to evaluate participants' comfort with and proficiency in using digital technologies at the time of recruitment. Finally, the limitation of using self-report tests and the inherent lack of control, in our case, of the social desirability bias, is typical of psychological intervention protocols. Because this is a POC study with voluntary participation in a clinical setting, we believe, however, that if the study is replicated in the future as a clinical trial or expanded, it will be important to consider this factor. For instance, it could be useful to use response evaluation tools that focus on indirect evaluation methodologies, such as the Implicit Association Test [69], or scales specifically targeting social desirability, such as the Marlowe - Crowne Social Desirability Scale [70]. Finally, within the broader framework of the ALBA study, a dissemination project is planned. This will cover both the Italian national and regional territories where the app will be tested, involving clinical stakeholders, hospitals, and support services. The plan also includes outreach to the wider scientific community through participation in conferences and publication in scientific journals, aiming to promote the use of digital mental health interventions, highlighting their strengths and weaknesses, and engaging sector experts in potential multicultural replications of our study.

Conclusions

The preliminary results from the previous ALBA co-design study and results from the scientific literature suggest that delivering consistent psychoeducational CBT support via mHealth solutions may be both acceptable and potentially useful for women undergoing BC treatment. Therefore, the POC study's findings illustrated in this protocol paper could contribute to the growing body of evidence supporting the use of digital technologies in mental health care. In particular, these findings could offer valuable insights into the usability, acceptance, and effectiveness digital mental health interventions

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in promoting psychological well-being among populations that face barriers and typically have limited access to psychological support.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

VF and AF are the chief investigators and are responsible for the study design and execution and the decision to submit the manuscript for publication. The study design was conceived and approved by VF, SR, LG, SS, and AF. VF and SR wrote the protocol manuscript with approval from all authors and developed the statistical analysis plan. LG, LP, and SP were involved in the drafting of the research protocol, ensuring adherence to the requirements of the local ethics committee, and the processing of personal data in compliance with General Data Protection Regulation regulations. All the authors have critically reviewed the manuscript for important intellectual content and have read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

ACT: acceptance and commitment therapy
AI: artificial intelligence
ALBA: A Well-Being Assistant
BC: breast cancer
CBT: cognitive behavioral therapy
COPE-NVI-25: Coping Orientation to Problems Experienced - New Italian Version 25
GHQ: General Health Questionnaire
GSE: General Self-Efficacy Scale
ITA BUS B: Italian Chatbot Usability Scale, version B
K-10: Kessler Psychological Distress Scale
mHealth: mobile health
MPFI: Multidimensional Psychological Flexibility Inventory
ORBIT: Obesity-Related Behavioral Intervention Trials
POC: proof-of-concept
PSS: Perceived Stress Scale
RESPOND: preparedness of health systems to reduce mental health and psychosocial concerns resulting from the COVID-19 pandemic
SH+: Self-Help Plus
SF-36: Short Form Health Survey 36
SUS: System Usability Scale
TreC: cartella clinica del cittadino; ("citizen's electronic health record")
UES-SF: User Engagement Scale-Short Form
uMARS: User Mobile Application Rating Scale
UX: user experience
WHO: World Health Organization

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Protocol

A Teleneuropsychological Battery for Assessing Older Panamanian Adults: Protocol for a Cross-Sectional Pilot Feasibility Study

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Abstract

Background: Evidence has shown that teleneuropsychology is a crucial tool in the assessment and treatment of individuals with limited access to in-person health services. Nevertheless, studies in Latin America are scarce, and there is a pressing need for studies that test the feasibility of teleneuropsychology and contribute to the development and validation of tools and models, as well as the establishment of normative data for the diverse populations of the region.

Objective: This study aims to conduct the first pilot study in Central America to assess the feasibility of a teleneuropsychology protocol and to generate normative data for a Panamanian sample.

Methods: This is a cross-sectional, descriptive, community-based study derived from the Development and Validation of Teleneuropsychology Normative Data for Older Adults in Florida (FLOAT) study. The study's final sample will include 150 participants (aged ≥50 years). Participants will undergo initial screening to determine their eligibility and will be included if they have a basic understanding of and access to technological devices such as telephones, tablets, or computers; are free of cognitive impairment or serious health conditions; and provide informed consent. Participants will complete 2 questionnaires to determine if they can continue in the study. Participants who are eligible will be assessed with a teleneuropsychology cognitive battery and will answer questionnaires via a REDCap (Research Electronic Data Capture) link.

Results: Feasibility will be assessed based on an analysis of the tools, funding, expertise, and resources needed to conduct neuropsychological assessments. So far, the study has proven feasible as researchers have been able to obtain a REDCap license and all other material necessary to carry out assessments. As of November 11, 2024, a total of 67 participants aged ≥50 (mean 62.2, SD 7.6) years had been assessed with questionnaires and a complete cognitive test battery. Sociodemographic and clinical characteristics show that participants on average had 16.7 (SD 1.9) years of formal education. A satisfaction questionnaire revealed that most participants were satisfied (22/67, 33%) or very satisfied (39/67, 58%) with the teleneuropsychological assessment, and most participants (58/67, 86%) would recommend this study to others. We expect to assess a similar number of women and men as well as different age groups with the teleneuropsychology battery. We plan to generate normative data for Panamanian adults aged >50 years.

Conclusions: This study may point to the need to use assessment methods that are convenient and efficient for older adult populations and that can be used as substitutes for in-person evaluations. Although it is a viable approach, expanding the sample size is essential to generate reliable normative data. This is an unprecedented area of research in the country and the Central American region.

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KEYWORDS

cognition; older adults; telehealth; teleneuropsychology; protocol; Hispanic population

Introduction

Background

Teleneuropsychology refers to the use of audiovisual technologies for remote neuropsychological assessments and interventions [1]. Specialty psychological services, namely, neuropsychological assessments, seek to integrate digital tools into conventional practice, combining traditional in-person measures for rich clinical observations with novel digital or remote assessments that allow for more precise quantification of behavioral patterns [2]. Teleneuropsychology requires the use of various tests and tools to evaluate a person's current cognitive and emotional status. This service usually requires patients to visit assessment sites and undergo clinical interviews and neuropsychological testing. Nevertheless, health emergencies such as the COVID-19 pandemic hindered in-person visits, prompting mental health professionals to adopt remote evaluations or teleneuropsychological assessments as an alternate method. The Inter Organizational Practice Committee created new guidelines for the practice of teleneuropsychology during the pandemic [3,4] to aid with some of the difficulties that are common in teleneuropsychology, such as uncontrolled conditions of in-home assessments [5]. In Latin America, recommendations on the use of teleneuropsychology emerged during the pandemic, with a lack of normative data for various countries [3]. However, teleneuropsychology did not arise solely as a response to health emergencies. Before the COVID-19 pandemic, guidelines for remote testing had been created by the American Psychological Association and Joint Task Force for the Development of Teleneuropsychology Guidelines for Psychologists [6]. These guidelines were developed to address ethical and methodological challenges associated with internet-based assessments, such as limited confidentiality and security risks when using the internet. One key recommendation was to incorporate ethical limitations into the informed consent process, providing participants with a clear and thorough explanation of the unique aspects of teleneuropsychology assessments [7]. Moreover, historically, studies have explored the validity and feasibility of remote care, initially through telephone and later through videoconferences.

Teleneuropsychology: How It Came to Be and Its Development Before the COVID-19 Pandemic

Teleneuropsychology's origins date back to the 1980s, when telephones were used for patient follow-up and cognitive health assessments. By then, widespread telephone use in US households facilitated telephonic data collection, particularly in primary care for consultations and surveys. In the 1990s, telephones were used for follow-ups with patients and screenings to detect dementia in older adults [8] as they function as a cost-effective alternative to in-person surveys [9]. In this period, there was an initial exploration of the feasibility of videoconferencing for cognitive evaluations in older adults [10,11] and an ongoing development and validation of remote tests [12-21]. Telephone screening tools, such as the modified Telephone Interview for Cognitive Status (TICS-M) and the Mini-Mental Status Examination, offer benefits such as rapid administration and cost-effectiveness, making them suitable for large-scale epidemiological studies [22]. These tools can also help minimize dropout rates in longitudinal studies and overcome geographical barriers [23]. Older adults, who may have mobility issues or reduced motivation, often respond well to telephone assessments, enabling "cognitive triage" and follow-ups in hard-to-reach populations [24]. However, the effectiveness of telephone assessments largely depends on the design of the screening instruments [25]. In this context, videoconferencing presents several limitations, including the inability to assess praxis or visuospatial abilities [26], limited use of visual stimuli, and the examiner's restricted ability to directly observe behavior in an uncontrolled environment [27]. In addition, communication challenges arising from hearing loss or cognitive decline further complicate the assessment process [28].

Since the early 21st century, research has explored the feasibility of teleneuropsychological assessments. Studies have shown no significant performance differences between videoconference and face-to-face assessments, demonstrating its feasibility and potential utility [27-31]. Furthermore, teleneuropsychology has not hindered clinical intervention or rapport building [29,30]. Diagnostic agreement between on-site and videoconference screenings for neurocognitive disorders has also been confirmed [32,33]. Likewise, teleneuropsychological assessments have shown to be feasible in different clinical settings, such as assessment of survivors of stroke [34]. Acceptability [35] and satisfaction [36] with teleneuropsychology have been documented, including assessments designed for use in Latin populations [37] and other underrepresented populations [38].

State of Teleneuropsychology During COVID-19: Uses, Validation, and Research

Before the pandemic, a survey revealed that approximately one-fourth of professionals, primarily from the United States, used teleneuropsychology for clinical interviews and interventions [39]. This highlighted the underuse of teleneuropsychology, which was largely due to lack of reimbursement from Medicare and private insurance [40]. Challenges such as limited access to technology, inability to perform hands-on assessments, and reduced behavioral observation opportunities also hindered its adoption [41]. However, lockdowns increased the need for recommendations and research, leading to greater use of teleneuropsychology among practitioners [5,42-44]. Research during the COVID-19 pandemic underscored the necessity for further investigation into teleneuropsychology and its limitations. Individuals with

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lower incomes often lacked access to necessary technology [45,46]. In addition, participants' computer literacy skills were frequently inadequate, and there was a scarcity of research on teleneuropsychology's application in home health care [33,47-49].

Research in teleneuropsychology, especially concerning culturally diverse populations, has progressed following the declaration of the end of the COVID-19 pandemic [50-52]. Notably, neuropsychologists have reported significant use of this work method [53]. In addition, new tools such as the Tele-Global Examination of Mental State [54] and Tele Executive Function for children [55] have shown promising results.

Studies on validity have shown that standardized cognitive tests used in teleneuropsychology retain their psychometric properties and yield results comparable to in-person administration [56]. Similarly, research shows that teleneuropsychology assessments are reliable, as they often show stable results when repeated over time, indicating reliability in tracking cognitive performance [57]. In addition, remote assessments allow for broader participation while maintaining standardized administration protocols through platforms such as Zoom (Zoom Video Communications), REDCap (Research Electronic Data Capture; Vanderbilt University), and other secure testing software [5].

Teleneuropsychology in Latin America: Research and Practice

Until 2021, no studies on teleneuropsychology had been reported in Latin America [41]. However, from 2021 to date, 8 studies have been documented regarding the use of teleneuropsychology in 4 countries in the region. Most of the studies are descriptive, and only 1 is a randomized controlled trial. In 38% of the studies, a satisfaction survey was included. In half of the studies, teleneuropsychology was used to evaluate participants, and in 1 study, telerehabilitation was performed. Results indicated good acceptance of teleneuropsychology as an assessment or rehabilitation modality by both participants and professionals [49,58,59]. Key benefits included reducing the stress of traveling to evaluation sites, increased accessibility to remote areas, increased comfort of home assessments [45,60], continued access during social distancing, and reduced COVID-19 risk [59]. Moreover, challenges noted by practitioners included patients' unfamiliarity with technology; lack of environmental control; and insufficient access to technological resources, including internet connectivity [46].

These studies represent a significant initial progress in Latin America, revealing insights into the experiences of neuropsychology professionals in the region. Although Mexico and Argentina are middle-income countries, they face findings and challenges similar to those observed in high-income nations. Moreover, proposals for clinically applicable models are beginning to emerge in Latin America [61]. However, normative data in the region are scarce, a phenomenon not unique to the teleneuropsychology, and precedes the COVID-19 pandemic as a recurrent issue in Latin America clinical practice [62]. There is a pressing need for studies that test the feasibility of teleneuropsychology and contribute to the development of tools, models, and validations and the establishment of normative data for the diverse populations of the region.

The objective of this study is to conduct the first pilot study in Central America to assess the feasibility of a teleneuropsychology protocol and to generate normative data for a Panamanian sample. The specific objectives of the study are to (1) administer a teleneuropsychological assessment to a Panamanian sample of participants identified as having a low risk of developing dementia, (2) generate normative teleneuropsychological data from a Latin American sample in Panama to compare with a Hispanic sample in the United States, (3) compare performance on teleneuropsychological tests across different gender and age groups, and (4) assess the sample's level of satisfaction with the administration of the teleneuropsychological evaluation battery using a standardized scale.

Methods

Participants

The protocol of this study is adapted from the Development and Validation of Teleneuropsychology Normative Data for Older Adults in Florida (FLOAT) [63], a study being conducted at the University of Florida with the aim of validating a battery in a healthy sample of older adults with low risk of developing Alzheimer disease and related dementias (ADRD). This study is cross-sectional, descriptive, and community based. As of November 11, 2024, we have recruited 67 (44%) out of 150 participants, all aged ≥50 years and residing in Panama. Details of participants invited to participate, recruited, and assessed are shown in Figure 1.

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Figure 1. Flowchart of participants included and excluded in the study. EDS: Escala de Satisfacción; TICS-M: modified Telephone Interview for Cognitive Status.

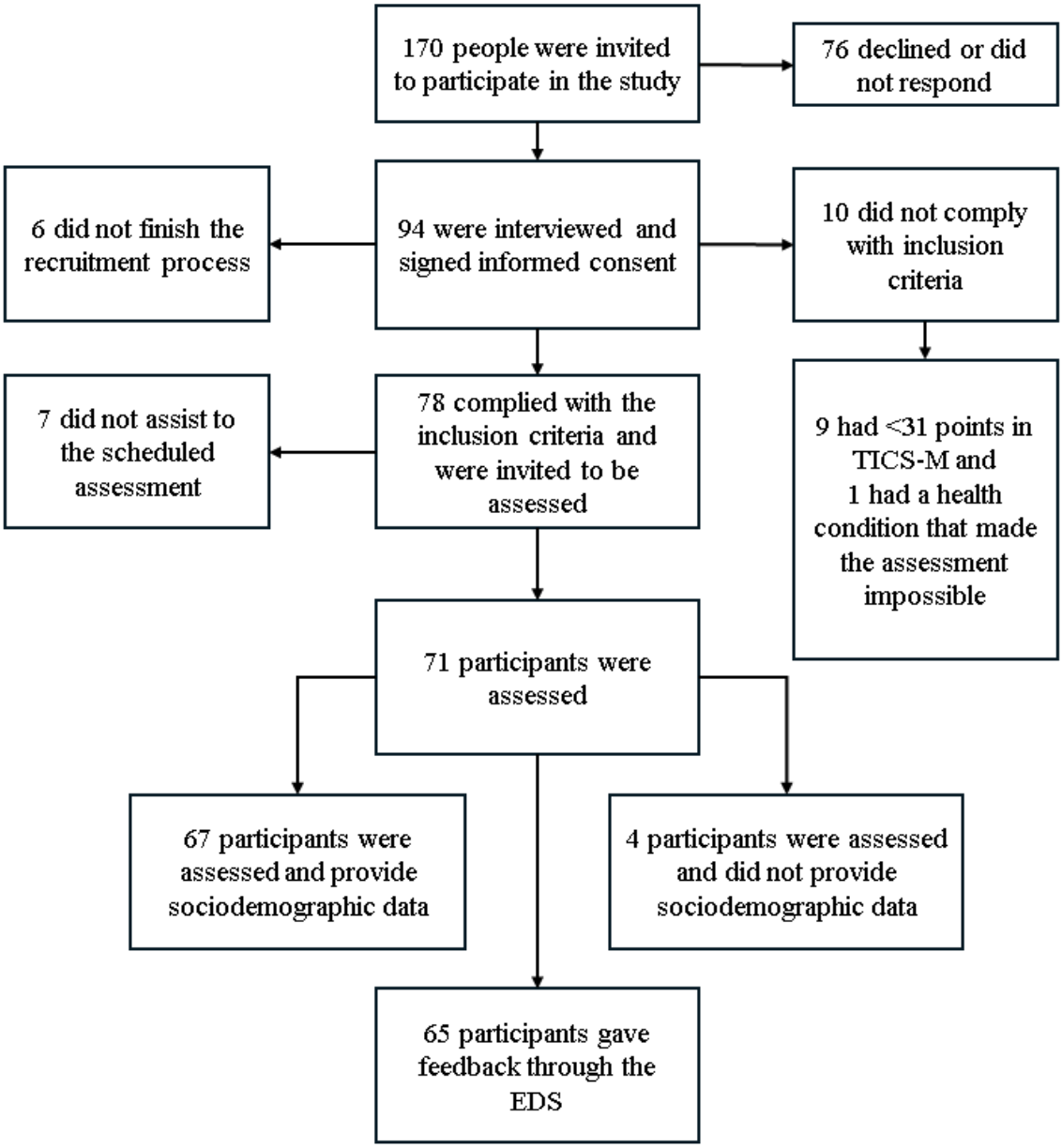

Eligibility Criteria

Participant eligibility criteria are presented in Textbox 1.

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Textbox 1. Participant eligibility criteria.

Inclusion criteria

- Are aged ≥50 years at the time of enrollment
- Have a basic understanding and control of technological devices
- Have access to a phone, tablet, or computer
- Have signed informed consent
- Are available to assist to all the program visits included in the study
- Has no cognitive impairment at the time of enrollment
- Has no conditions that limit or prevent them from completing the neuropsychological evaluation (ie, blindness, analphabetism, and severe physical limitations)

Exclusion criteria

- A diagnosis of Alzheimer disease and related dementias or other neurological disorders that affect cognitive functioning
- A history or diagnosis of a severe psychiatric disease (ie, schizophrenia)
- Evidence of cognitive impairment (modified Telephone Interview for Cognitive Status <31)
- No access to internet
- Lack of access to a smartphone with a webcam for videoconference
- Ongoing participation in another clinical study or the intention to participate in another study

Recruitment

Potential participants are recruited from the community in Panama through social media advertisements, flyers in community centers, and newspaper announcements. Individuals living outside the city are also encouraged to participate due to the availability of remote testing. The research team, which includes the principal investigator, research assistants, and trained psychology students, supervised by senior scientists, assist in recruitment and data collection. Participant recruitment process is displayed in Figure 2.

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Figure 2. Flowchart of the recruitment process. TICS-M: modified Telephone Interview for Cognitive Status; NACC: National Alzheimer's Coordinating Center.

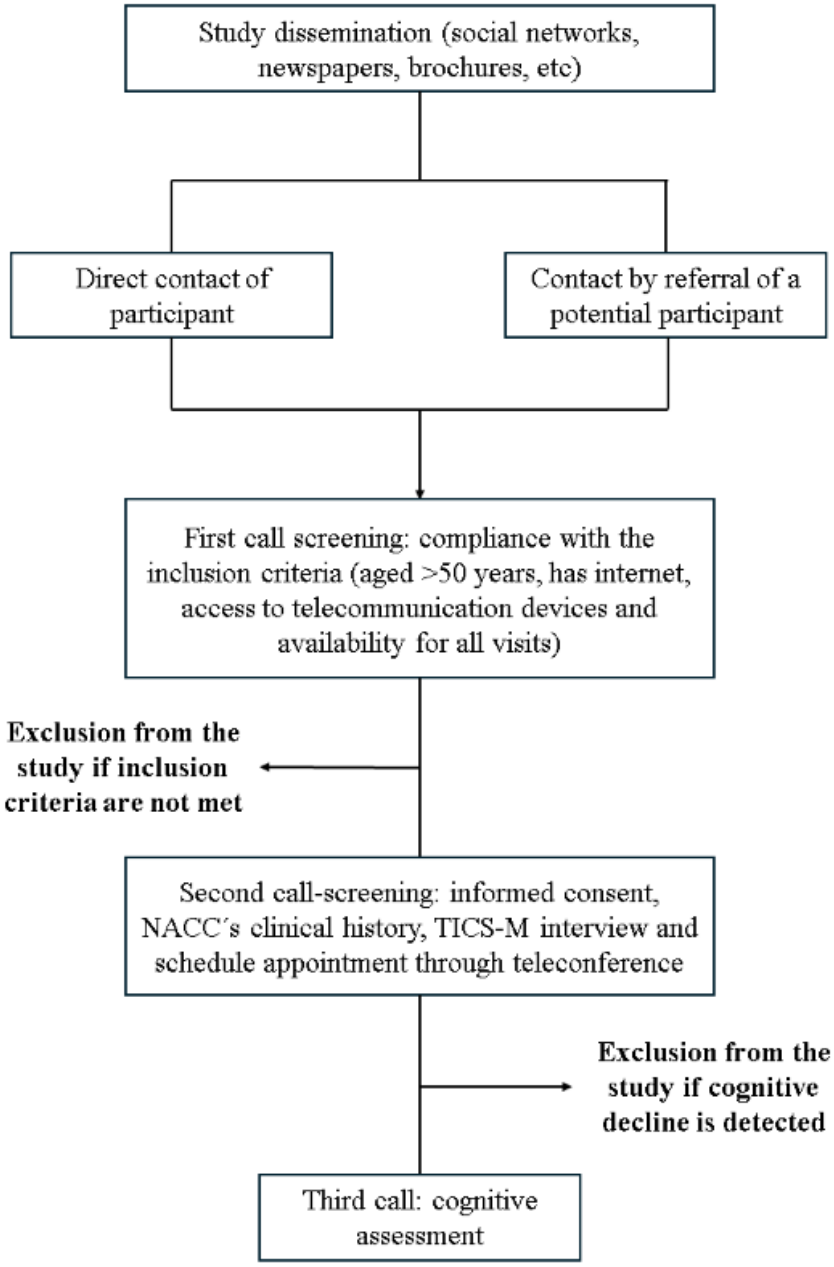

Procedure

Participants undergo an initial screening to determine their eligibility. Those who meet the inclusion criteria and agree to participate will provide telephone-informed consent. Following this, participants complete 2 questionnaires: an adapted Spanish version of the modified TICS-M and the National Alzheimer's Coordinating Center (NACC) Health Questionnaire. These assessments help identify any underlying neurological diseases or uncontrolled medical conditions that may impact cognition, such as depression or bipolar disorder. The screening aims to (1) confirm that the participant does not have cognitive impairment (eg, mild cognitive impairment or dementia) and (2) ensure that they have the cognitive capacity to provide informed consent. Participants scoring ≤31 points in TICS-M, indicating mild cognitive impairment or dementia, are excluded from the study. Those who do not meet the eligibility criteria are thanked for their time, and the assessment is discontinued.

Eligible participants receive a link to complete the questionnaires and surveys via email using the REDCap platform, an online platform designed for data collection and storage [64]. This process takes approximately 30 minutes. Later, a member of the research team schedules a 2-hour block for the teleneuropsychological assessment with ≥1 breaks if requested by the participants. A team member assists participants in setting up the videoconferencing technology. Before beginning the study, research staff reviews the informed consent document with the participant and addresses any questions.

REDCap is used to capture and store participant data, while Zoom facilitates the administration of neurocognitive tests. The screen-sharing feature is used to display test stimuli. For tasks

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requiring a scored motor component (eg, figure drawing), participants are asked to hold their drawings up to the camera, and a screenshot is taken for later scoring. These screenshots do not include any identifying information about the participants. Captured images are stored in the participant's REDCap dataset for future analysis. During the assessment, 2 computers are used: a laptop and a touchscreen device, both of which project visual stimuli via the screen-sharing function. These stimuli are displayed in PowerPoint, and data collection is conducted in REDCap throughout the assessment.

Measures

Overview

Following the FLOAT protocol, this study uses an open-access battery in Spanish that is part of the Uniform Data Set version 3 (UDSv3), comprising longitudinal data collected since 2005 at the National Institute of Aging funded Alzheimer's Disease Research Centers (NACC, 2023). All measures in this study have been adapted for use with REDCap. In addition, several questionnaires, including the Health History, Functional Activity Index, Geriatric Depression Scale (GDS), and Demographic Information, have been modified to be completed directly by participants.

The evaluation process lasts approximately 3 hours, which includes 30 minutes for informed consent and screening measures, 30 minutes for participant-completed questionnaires via the REDCap platform, and approximately 2 hours for teleneuropsychological testing.

Screening Measures

The TICS-M [65] is administered in a Spanish version to screen for mild cognitive impairment. TICS-M measures domains such as orientation, verbal memory, attention, working memory, or abstraction and has no visual stimuli. Cognitive impairment is established at ≤31 points. This cutoff was used to determine which individuals could participate. Certain items have been modified to better suit the Panamanian context, such as replacing the question "Who is the president of the United States?" with "Who is the president of Panama?" In addition, the NACC Health History [66] measure is used to evaluate the participant's general health history, helping to identify potential neurodegenerative diseases or other risk factors that may disqualify them from participation in the research.

Questionnaires

These questionnaires were obtained in the Spanish versions. Participants fill out these questionnaires online using a REDCap link provided by the study team.

The NACC-Demographics questionnaire [66] has been adapted to better suit the Panamanian population by modifying relevant questions and removing those that are not applicable, such as enquiries about the last digits of the zip code or the Alzheimer's Disease Research Center. To assess symptoms of depression, the Spanish version of the GDS [67] is included, consisting of 30 yes or no questions completed via a REDCap form. If a participant scores >20 on the GDS, the study team contacts them to enquire about suicidal ideation. The Functional Activity Index [66] is used to evaluate an individual's ability to perform daily activities, which may decline due to neurodegenerative processes. In addition, the Teleneuropsychological Assessment Satisfaction Scale provides participants with an opportunity to give feedback on various aspects of the assessment, including satisfaction, the use of Zoom and REDCap, instructions, advantages, difficulties, recommendations, and overall time.

Teleneuropsychological Tests

A variety of cognitive assessments are used to evaluate different cognitive domains. The Montreal Cognitive Assessment [68] is administered in an adapted Spanish version, serving as a cognitive screening tool that measures visuospatial skills, naming, verbal memory, working memory, attention, language, abstraction, and orientation. Verbal memory is further assessed using the Craft Story test [69], in which participants listen to a semantically related story and recall it both immediately and after a 20-minute interval, aiming to maintain the original phrasing. Similarly, the Rey Verbal Learning Test [70] requires participants to learn a list of 15 words through repeated exposure. After 5 trials, an interference list is introduced, and after a 20- to 30-minute delay, participants attempt to recall the original list, evaluating both immediate and delayed memory recall, as well as word recognition.

Visual memory and visuoconstruction skills are measured through the Benson Complex Figure test [71], where participants first copy a complex figure and then recall and recognize it after 10 minutes. Naming ability is assessed using the Multilingual Naming Test [72], in which participants observe and name figures, receiving semantic or phonemic cues if needed. The Digit Span Test [73] evaluates attention and working memory by having participants repeat a sequence of numbers in both forward and backward order, with increasing difficulty. Verbal phonological fluency [74] is assessed through a task where participants must generate as many words as possible starting with a given letter within a set time (excluding names, numbers, or repeated words). In the semantic fluency task [74], participants generate words belonging to a specific category, such as animals, vegetables, or fruits.

Executive function is measured using the Wisconsin Card Sorting Test-64 [75], a computer-based assessment where participants match cards according to rules they must infer, with alternative verbal response options available if they cannot control the screen. In addition, the Oral Trail Making Test is also used to measure executive functions. Divided in part A and part B, participants are first asked to count from 1 to 25 as fast as they can (part A). Later, they are requested to alternate between numbers and letters from 1 to 13 (part B). On both occasions, the time to finish, errors, and correct answers are recorded [76].

The Boston Naming Test [77], using a 15-item version from the Mayo Older Americans Normative Studies, presents participants with images to name, offering semantic or phonemic cues if necessary. Speeded information processing is evaluated using the oral version of the Symbol Digit Modality Test [78], in which a PowerPoint slide is displayed while responses are recorded in REDCap. Finally, premorbid intelligence is assessed with the Word Accentuation Test Chicago [79], where

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participants read a list of words and attempt to place the correct accentuation.

Statistical Analyses

Neuropsychological test results will be analyzed using multivariate statistical methods. We will perform initial data analyses with chi-square and ANOVA tests to observe distribution across age groups or other groups of interest. We will obtain raw scores of each test as well as composites of cognitive domains to conduct further analyses per test and per cognitive domain. Comparisons will be made regarding sex and age groups. Student *t* test will be applied to examine differences in performance between sexes and within age groups (the sample will be divided in 3 groups: aged 51-59 years, 60-69 years, and >70 years). Multivariable regression analyses will be performed to assess linear relationships between age, years of education, or other (ie, income) variables and cognition. Once we have assessed and ruled out potential interaction effects influencing participant performance, we will proceed with an in-depth analysis of normative data stratified by age, sex, and education level. Test scores will be standardized into *z* scores based on the mean and SD of the respective group, and these *z* scores will be subsequently converted into normative scores for each assessment. Cases with incomplete data will be excluded from analyses via listwise deletion.

Ethical Considerations

The study protocol was approved by the Research Bioethics Committee of Universidad Santa María La Antigua (CBI-USMA; 2022-P004). Informed consent is read to participants via phone call. After verbal confirmation of acceptance to participate in the study, participants get a Google Forms link were they formally accept to be part of the study and attach an image of their personal sign. Once they finish filling the forms, they are assigned a unique code.

All data collected will be saved in a password-protected database. Only authorized research personnel will have access to this database. If a participant chooses to withdraw from the study, the data collected before their withdrawal will still be included in the analysis. Data collected on REDCap are identified with a specific number to protect the identity of the participant.

Some estimated harms that could be caused by this type of evaluations include fatigue, stress, or anxiety while either responding to the questionnaires or performing the neuropsychological tests. However, we expect minimal harm to our participants. If the participant needs it, the evaluation is rescheduled. Participants are informed that they are free to withdraw from the research study at any time. As exclusion criteria indicates eligibility for participating is based on participants not having a diagnosis of ADRD or other neurological disorders that affect cognitive functioning, all participants contacted and included in the study are cognitively healthy. Nevertheless, if a participant with a diagnosis of ADRD contacts the research team, researchers will refer them to a neurologist.

Data Management

All data, including consent, will be added to a REDCap database that has all the measures obtained in this study. To ensure high-data quality collection, scoring of the tests is reviewed by 2 different evaluators at the end of the testing. This is done to improve interrater reliability in test scoring. All evaluators have been trained using the same tools and in a standardized environment to minimize variability in score interpretation. Test scoring instructions are followed precisely.

Dissemination Policy

Results from this research will be published, shared, and presented at national and international conferences, science events, and high-impact journals. At the end of the study, participants will be given a summary of their results that will give them an insight of their cognitive status. The report will be divided in different cognitive domains, including “below average,” “average,” and “above average” to identify the participant’s cognitive level when compared with other peers of the same age range, sex, and education.

Results

Preliminary General Characteristics of the Sample

The demographic and clinical characteristics of the sample are summarized in Tables 1 and 2. Participants were mostly female (53/67, 79%) and were on average aged 62.2 (SD 7.6) years. Participants on average had 16.7 (SD 1.9) years of formal education. Most participants have a partner (44/67, 66%). Participants reported few cardiovascular, cerebrovascular, and psychiatric illnesses. Nevertheless, the most common chronic illness is hypertension (22/67, 33%), followed by hypercholesterolemia (19/67, 28%). Most participants identify as White (31/67, 46%) or other (20/67, 30%). Participants showed a high degree of functional independence in performing basic and instrumental activities of daily living. On average, participants had 1.5 (SD 1.8) symptoms of depression.

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Table 1. Protocol measures for teleneuropsychology assessment.

Measure	Description
Screening measures	
TICS-M[a]	Measures domains such as orientation, verbal memory, attention, working memory, or abstraction and has no visual stimuli; cognitive impairment is established at ≤31 points
NACC[b] Health History	Evaluates general health history, identifying potential neurodegenerative diseases or other risk factors that may disqualify participants in the research
Questionnaires	
NACC-Demographics Questionnaire	Addresses topics of age, sex, education, independence, type of housing, and civil status, among others.
GDS[c]	Consists of 30 yes or no questions completed via a REDCap[d] form; if a participant scores >20 on the GDS, the study team enquires about suicidal ideation
The Functional Activity Index	Evaluates an individual's ability to perform daily activities
Teleneuropsychological tests	
Montreal Cognitive Assessment	Cognitive screening tool that measures visuospatial skills, naming, verbal memory, working memory, attention, language, abstraction, and orientation
Craft Story Test	Short- and long-term verbal memory are measured with a related story
Rey Auditory Verbal Learning Test	Short- and long-term verbal memory are measured with a 15-word list
Benson Complex Figure	Short- and long-term visual memory and visuoconstruction are measured with a complex figure
Multilingual Naming Test	30-item test that measures naming ability
The Digit Span Test	Working memory and attention abilities are measured with series of numbers repeated in a forward and backward order
Verbal Fluency	Verbal phonological fluency is assessed by generating as many words as possible beginning with a specific letter (F, A, S, and M) in 1 min each
Category Fluency	Semantic fluency is assessed by generating as many words as possible from a specific category (animals, vegetables, and fruits) in 1 min each
Wisconsin Card Sorting Test-64	Executive function is measured by having the participant match cards according to certain rules (color, figure, and number of figures in card)
Boston Naming Test	15-item test that measures naming ability
Symbol Digit Modality Test	Speeded information processing is assessed by associating numbers with symbols as fast as possible in 90 seconds
Word Accentuation Test Chicago	Participants read a list of words and attempt to place the correct accentuation, measuring premorbid intelligence
Feasibility	
Teleneuropsychological Assessment Satisfaction Scale	Provides participants with an opportunity to give feedback on various aspects of the assessment, including satisfaction, the use of Zoom and REDCap, instructions, advantages, difficulties, recommendations, and overall time

[a]TICS-M: modified Telephone Interview for Cognitive Status.

[b]NACC: National Alzheimer's Coordinating Center.

[c]GDS: Geriatric Depression Scale.

[d]REDCap: Research Electronic Data Capture.

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Table 2. Demographic and clinical characteristics of the study participants (n=67).

Variable	Participants
Age (y), mean (SD)	62.2 (7.6)
Sex, n (%)	
Female	53 (79.1)
Race, n (%)	
Afro-Panamanian or Black	11 (16.4)
Asian	1 (1.5)
Indigenous people	2 (3.0)
White	31 (46.3)
Unknown	2 (3.0)
Other	20 (29.9)
Marital status, n (%)	
Partnered	44 (65.7)
Not partnered	23 (34.3)
Education (y), mean (SD)	16.7 (1.9)
Years smoking, mean (SD)	15.3 (12.4)
Age at smoking cessation (years), mean (SD)	36.7
Diabetes (yes), n (%)	6 (9)
Hypertension (yes), n (%)	22 (32.8)
Hypercholesterolemia (yes), n (%)	19 (28.4)
Thyroid disease (yes), n (%)	13 (19.4)
Arthritis (yes), n (%)	9 (13.4)
Number of cardiovascular disease, mean (SD)	0.25 (0.8)
Number of cerebrovascular illnesses, mean (SD)	0.15 (0.5)
Number of medical conditions, mean (SD)	1.1 (1.0)
Number of sleep-related illnesses, mean (SD)	0.33 (0.6)
Number of psychiatric diseases, mean (SD)	0.33 (0.8)
Depression (yes), n (%)	11 (16.4)
Anxiety (yes), n (%)	7 (10.4)
Geriatric depression symptoms, mean (SD)	1.5 (1.8)
Functionality Index, mean (SD)	0.5 (0.8)

Expected Outcomes for Assessing Feasibility

Feasibility will be assessed based on an analysis of the tools, funding, expertise, and resources needed to conduct neuropsychological assessments. Likewise, the Teleneuropsychological Assessment Satisfaction Scale will assess feasibility through the satisfaction of the sample with the teleneuropsychology assessment. The Teleneuropsychological Assessment Satisfaction Scale provides participants with an opportunity to give feedback on various aspects of the assessment, including satisfaction, the use of Zoom and REDCap, instructions, advantages, difficulties, recommendations, and overall time.

So far, the Teleneuropsychological Assessment Satisfaction Scale (Multimedia Appendix 1) has shown that most participants (39/67, 58%) were very satisfied with the teleneuropsychological assessment, while high levels of satisfaction were found with other elements of the assessment, such as the use of the Zoom platform (47/67, 70%), the evaluator (57/67, 85%), or the REDCap platform (33/67, 49%). All participants reported instructions were clear. Most participants (49/67, 73%) were satisfied with being able to do the evaluation from home. Two-thirds of participants (44/67, 66%) reported that they were able to use electronic equipment, such as computers, phones, or tablets. Most participants (37/67, 55%) would recommend a teleneuropsychological assessment to others.

Although most of the sample (53/67, 79%) reported no difficulties at all, main limitations that were stated by participants were internet connection (8/67, 12%), space in which the assessment took place (8/67, 12%), and electronic

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equipment used (5/67, 7%). Other barriers (12/67, 18%) included the long duration of the assessment, confusing wording in questionnaires, problems with sound, interruptions, difficulties with the assessment materials, problems with the Zoom platform, availability for the assessment, lack of light, and complaints regarding their own abilities.

Expected Outcomes for Creating Normative Data

In line with the FLOAT study [63], percentile ranks for each test's raw scores will be calculated from cumulative frequency distributions and then normalized to a distribution with a mean of 10 and an SD of 3 (ie, scaled scores). These normalized scores will then be entered into a stepwise regression, including sex (male and female), education, and different age groups. Predictors contributing <5% of additional variance in the normalized scores will be retained for further regression-based adjustments.

Discussion

Principal Findings

This paper describes the protocol of a pilot study designed to assess the feasibility of conducting teleneuropsychological cognitive assessments in adults aged ≥50 years. Teleneuropsychology is a technology-based practice that includes collecting patient data using multiple assessment modalities. So far, we have successfully assessed 67 participants with a complete teleneuropsychology evaluation. Our results indicate that our sample is comparable to those in other studies in terms of age [34,38], education level [80,81], and the distribution of men and women [40], characteristics that might contribute to the validity of our design in future analyses.

Moreover, feasibility could also be demonstrated through the successful use of various technological platforms in the assessments, including REDCap and Zoom. This approach to teleneuropsychological assessments has been recommended in other studies [5] and aligns with guidelines established before and during the COVID-19 pandemic [1,7]. To date, very few studies in Panama have used REDCap to capture and store clinical data; nevertheless, this is the first time it is used for neuropsychological assessments, making this an unprecedented study. REDCap has been widely used and recommended for teleneuropsychology studies across various regions worldwide [3,82], as data can only be accessed with a password and server administrator permissions, making the platform ideal for securely storing the collected information [83]. REDCap stands as a viable platform that could be part of the regular clinical practice, ensuring the security, conservation, and confidentiality of gathered data. Likewise, using Zoom as the platform for the assessment is a notable strength, as it has been effectively used in other similar studies [48,84].

In addition, current participant satisfaction has been assessed, revealing that most respondents (39/67, 58%) were highly satisfied with the remote assessment. This aligns with findings from previous studies on participant satisfaction [35,36,42,85]. Key positive aspects highlighted by participants included the use of electronic equipment, the convenience of conducting assessments from home, and the quality of interaction and communication with evaluators. These findings reinforce the strengths of teleneuropsychology identified in another research [41].

Limitations

So far, participants reported difficulties primarily related to electronic equipment, internet connectivity, and the environment in which the assessment took place. These limitations are common challenges associated with teleneuropsychology [86,87], and as participants completed the assessment at home, these factors were beyond the assessor's control. We expect other participants assessed to encounter technological difficulties. The use of REDCap presents both strengths and limitations. On the one hand, this platform ensures secure and confidential storage of test and questionnaire data, as it is only accessible to those connected to the research institution's server. On the other hand, because the server hosting REDCap is owned by the institution, both the researcher and the participant must have access to the server to use the platform.

Other limitations include the use of convenience sampling for recruitment, which hinders the inclusion of a diverse sample. This resulted in participants with a high level of education and a medium to high socioeconomic level that are not representative of the population. We will actively aim to recruit participants that come from different backgrounds and diverse socioeconomic levels.

Strengths

The study's strengths include the innovative teleneuropsychology assessment format, which involved both the participant and assessor being at home, creating a teleneuropsychology "home-to-home" format, an approach that has been validated but not extensively studied [33,42,60,88,89]. This is of particular interest given that the use of teleneuropsychology home-to-home neuropsychological testing by mental health professionals has been reported in the Latin American region; however, no specific studies documenting this modality have been published to date [59], making this study one of the few to explore this method.

The application of the assessment battery enabled the collection of specific data from the Panamanian population, paving the way for the development of normative data for tests conducted remotely. This aims to address a significant limitation in the region, where standardized tests have not been adapted to the populations of these countries [90-93].

While some participants reported challenges related to connection issues, the assessment environment, and the equipment used, it is important to note that these difficulties were experienced by only a minority of the sample. In addition, specific issues related to the questionnaires emerged; participants noted that the wording and timing of the questions were not favorable. In contrast, the overall timing of the evaluation itself was well received by participants.

Conclusions

Teleneuropsychology has gained ground in the field of psychology, offering new spaces and opportunities for professionals, patients, and participants. Ongoing research is

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essential to bring clarity to the clinical practice of those using these alternatives. Drawing on lessons learned before, during, and after the pandemic, many professionals have adopted models that combine elements of remote and traditional face-to-face care, giving rise to hybrid neuropsychology [94]. In Latin America, further research is essential, particularly studies aimed at developing instruments, models, and validations and establishing normative data for diverse populations in the region.

This study represents the first pilot investigation in Central America aimed at assessing the feasibility of a teleneuropsychology protocol and establishing normative data for a Panamanian sample. By administering cognitive assessments to individuals at low risk of developing dementia, we aim to generate data that can be compared with Hispanic samples from the United States, contributing to a broader understanding of cognitive performance across diverse populations. In addition, evaluating participant satisfaction with the teleneuropsychological evaluation process provides valuable insights into its acceptability and usability. Furthermore, analyzing performance differences across gender and age groups will help identify potential demographic influences on test outcomes. Ultimately, this research will contribute to the validation of remote cognitive assessments in Latin America, supporting their use as reliable and accessible tools for neuropsychological evaluation.

We recommend expanding the sample to establish normative data for older adults in Panama. This will require strengthening participant recruitment efforts across diverse regions of the country to maximize the accessibility and advantages of teleneuropsychology. Likewise, this study can be replicated to use teleneuropsychology assessments with other age ranges and populations, such as children, adolescents, and middle-aged adults. In addition, it is imperative to conduct a similar study with individuals with mild cognitive impairment to explore applications in neurodegenerative conditions such as Alzheimer and Parkinson disease. Finally, in studies such as ours, we recommend incorporating medical records in future studies to confirm participants' health status, aligning with best practices used in research worldwide.

Acknowledgments

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Data Availability

Results from this study will be available upon completion and publication of the primary findings, upon reasonable request and with appropriate ethics approvals and data use agreements.

Authors' Contributions

LS wrote the manuscript. AP-L and DO conceived, managed, and coordinated the study. DO oversaw funding acquisition. GBB conducted the analyses. All authors read and wrote sections of the manuscript. All authors reviewed and approved the submitted version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Satisfaction with the teleneuropsychological assessment.
[DOCX File , 17 KB - resprot_v14i1e68520_app1.docx]

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Abbreviations

ADRD: Alzheimer disease and related dementias
FLOAT: Development and Validation of Teleneuropsychology Normative Data for Older Adults in Florida
GDS: Geriatric Depression Scale
NACC: National Alzheimer's Coordinating Center
REDCap: Research Electronic Data Capture
TICS-M: modified Telephone Interview for Cognitive Status

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Protocol

Identifying Firearm Violence Exposure in Primary Care Clinical Notes: Protocol for Developing a National Language Processing Text Classifier

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Abstract

Background: Structured data codes capture acute bodily injury from firearm violence but do not necessarily describe follow-up care from bodily injury and secondary exposure to firearm violence (eg, witnessing a shooting, being threatened by a firearm, or losing a loved one to gun violence and injury from firearms) even though such exposure is associated with many short- and long-term health impacts. Clinical notes from electronic health records (EHRs) often contain data not otherwise captured in structured data fields and can be categorized using natural language processing (NLP).

Objective: This study protocol outlines the steps being taken to develop an NLP text classifier for determination of exposure to firearm violence (both primary and secondary exposure) from ambulatory primary care and behavioral health EHR clinical notes for persons aged ≥5 years.

Methods: The study will use unstructured data from clinical notes taken between 2012 and 2022 from OCHIN, a multistate network of community health organizations using a single instance of Epic EHR. We describe the process of developing a labeled dataset for supervised NLP development that includes establishing a lexicon (words related to firearm violence) to identify potentially relevant notes, followed by a review of text extracted from a sample of these notes. We then describe the process of building, training, and evaluating candidate machine learning, neural network, and large language model NLP text classifiers. From this, a final NLP model is chosen then evaluated on a new set of randomly selected notes. An engaged stakeholder advisory committee will provide input and guidance on methods and results to identify and address potential biases in the NLP text classifiers.

Results: The study was funded in September 2023. Study activities have been ongoing through July 2025 and we are currently evaluating NLP text classifiers. We expect that the final model will be selected by August 2025 and we will publish results of NLP model development and the final model performance in 2026.

Conclusions: This work describes the development of a novel NLP text classifier to identify exposure to firearm violence in ambulatory primary care and behavioral health clinical notes. The NLP model developed in this study may lead to increased ascertainment of patients with exposure, laying the groundwork for understanding the long-term impacts and outcomes of firearm violence exposure and presenting opportunities for improved patient care.

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KEYWORDS

firearm violence; firearm injury; natural language processing, electronic health records; text classifier

Introduction

Background

As injury and death by firearm continues to increase in the United States, so too does secondary exposure to firearm violence (witnessing a shooting, being threatened by a firearm, or the injury or death of a loved one or acquaintance by gun violence). It is estimated that 3 million US children are exposed to firearm violence each year and that 54% of all US adults have experienced firearm violence [1,2]. Primary and secondary exposure can lead to adverse social, emotional, physical, and behavioral health impacts [1,3-6]. Despite the high prevalence of exposure to firearm violence, structured data (eg, diagnostic codes) on firearm violence is largely limited to acute primary exposure (ie, direct injury or death) and there are no International Classification of Diseases (ICD) codes that specifically capture follow-up care from injury or exposure without injury. As a result, most firearm violence research is conducted using acute injury data from hospitals, emergency departments, or death data and is therefore limited to individuals who sustained acute physical injury [7].

Comprehensive data from ambulatory care settings (primary and behavioral health care) are needed to better understand the short- and long-term impacts associated with firearm violence exposure [7-9]. ICD-10 diagnosis codes now exist to document adverse socioeconomic and community circumstances, but these codes are used infrequently across health systems and there is no specific code documenting secondary exposure to gun violence [10,11]. Another opportunity to identify this exposure in clinical settings is through the development and use of custom data collection instruments, such as a trauma history "SmartForm" described in prior work [12]. While these documentation practices show promise, they remain inconsistently available and underused.

Another promising emerging source of data is electronic health record (EHR) clinical notes [13]. Clinical notes include relevant medical care notes that are needed for comprehensive, longitudinal patient health care. Accessing unstructured clinical data using advanced natural language processing (NLP) methods has demonstrated utility in similar types of firearm and trauma research, yet the application of these methods to outpatient settings remains largely unexplored [13-17]. Early work using a keyword search of firearm violence terms identified that exposure to firearm violence is available in unstructured data in ambulatory care settings [18]. This finding provided rationale for developing an NLP text classifier to identify cases of firearm violence exposure documented in clinical notes.

This protocol describes the development of an NLP text classifier to identify firearm violence exposure in primary care and behavioral health care clinical notes. Ambulatory clinics providing primary and behavioral health care offer a novel source of data on firearm violence, particularly exposures that may not have resulted in acute emergency care, hospital encounters, or death. The rich contextual information (eg, patient social history and comorbidities) contained in primary care and behavioral health clinical notes presents an opportunity to expand our understanding of the short- and long-term adverse effects of firearm violence exposure [19-21]. The addition of data from this novel source, combined with learnings from more established data sources on firearm injury and death, could greatly expand our understanding of risks and outcomes associated with exposure [7,22].

Objective

This research protocol describes the development of a stakeholder-informed NLP model to identify patients with exposure to firearm violence using clinical notes from a large, multistate network of ambulatory health care centers by classifying text as indicative as exposure to firearm violence or not.

Methods

Study Aims and Design

This protocol describes the development of a stakeholder-informed NLP text classifier to identify patients with firearm violence exposure documented in unstructured clinical notes during a primary care or behavioral health care encounter. The current study builds on pilot work that confirmed the presence of unstructured data in clinical notes that included firearm violence keywords that had contextual meaning of exposure [18]. Study findings, when available, will be reported following guidance for reporting machine learning model development in biomedical research [23].

Setting

The data used in this study come from OCHIN, a multistate network of community health organizations using a single instance of Epic EHR [24]. OCHIN is a nonprofit health care innovation center that offers a fully hosted, highly customized instance of Epic practice management and EHR solutions at over 2000 health care delivery sites across 40 states. OCHIN member health organizations provide health care services to patients in low-resource settings, regardless of their ability to pay. We will access clinical notes from unstructured records in natural language serving as a record of treatment, diagnoses, and clinical progress from ambulatory primary care and behavioral health care encounters to patients aged ≥5 years at encounter from January 1, 2012, to December 31, 2022. These chart notes will be used to develop an NLP model that will classify the note text as representative of firearm violence exposure or not.

Ethics Approval

OCHIN community health organizations, as part of their contract with OCHIN, authorize OCHIN to create limited datasets of member information for certain research activities consistent with applicable law and aligning with best practices of research, including institutional review board oversight of study activities.

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This study was reviewed and deemed exempt by the Norwich University Institutional Review Board. Only research staff who are OCHIN employees have access to clinical notes, and efforts were made to remove direct patient identifiers prior to review.

Data Source

Data for NLP model development will be identified by searching for keyword phrases in clinical notes for study-eligible patient encounters. We define study-eligible patient encounters as those occurring between January 1, 2012, and December 31, 2022, with patients who were aged ≥5 years on their date of encounter (4,024,926 patients). This study period aligns with the date range of EHR data availability at the time of study start. The age restriction was imposed to reduce the number of "false positive" firearm exposure measures resulting from screening for household gun ownership commonly assessed in early childhood encounters [25]. We further restricted eligible ambulatory encounters to those categorized as either primary or behavioral health, using a previously defined algorithm (31,801,530 encounters) [26].

Stakeholder Advisory Committee

The NLP model development will be guided by an 8- to 10-person stakeholder advisory committee (SAC), a multidisciplinary group of individuals who will review methods, provide guidance on testing and evaluation, participate in interpreting and disseminating study findings, and evaluate the social and ethical merits for ongoing study and model deployment. SAC members include people with lived experience of firearm violence exposure, clinicians, researchers, clinical informaticists, and data scientists.

Development of the SAC will be conducted during the first 3 months of the study. SAC members will meet monthly, alternating between synchronous and asynchronous meeting formats, to guide study activities and will be compensated for their time (the mean compensation will be $185 per hour). Due to the dynamic nature of the research activities and the novel application of a SAC for NLP development around firearm violence, the ongoing contribution of SAC members after lexicon development and review (see below) will continue to evolve as study activities progress. We anticipate that SAC members will participate in interpreting research findings and provide ongoing input into the applicability of the model in clinical practice.

Dataset Development

During pilot work, a list of keywords informed by MacPhaul et al [13] was applied to a set of notes for patients with known exposure to firearm violence. A random sample of 30 notes from each of 3 text string search categories (broad, gun-only, and shooting) were reviewed to contextualize how keywords are used in clinical notes and to identify lexicon refinements (eg, remove preset template EHR phrases and add keywords[18]). Among the 90 notes reviewed, 13 (14%) were determined to be true "cases," while all other notes did not indicate exposure to or injury from firearm violence.

In this study, the lexicon (Multimedia Appendix 1) was expanded to include additional terms used by Chew et al [27] and will be used to extract a random sample of 5000 clinical notes that contain keywords for review. Applying a case rate of 14%, we anticipate that 700 of these clinical notes will indicate exposure to firearm violence. The study team worked together to develop a case note selection decision guide to clarify inclusion and exclusion criteria and reduce variation among study team annotators (Multimedia Appendix 2). The guide defines a case as "primary or secondary exposure to firearm violence as a direct witness of firearm violence or the acute aftermath." The decision guide clarifies that cases will include any mention in the clinical note of gun threats (primary or secondary) experienced by a patient. In addition, cases include mention of retained bullets in the body, sequalae from firearm violence, patients brandishing or perpetrating crime with a gun, or self-inflicted gunshot wounds. Following pilot methods, the sample of clinical notes will be posted as a shared Microsoft Excel document for review. Study team members independently review notes for keywords and contextualize the meaning of the note as case or noncase, copying over relevant sentences that informed their decision into the document. When case status is not apparent from the clinical note even though it contains lexicon words, the reviewer will indicate in an electronic comment that additional review and adjudication is needed. An additional 2 study team reviewers will review the clinical note, document their assessment, and the 3 reviewers will subsequently meet to make a determination. If additional input is needed for categorization the study team will involve the clinician informaticists on the study team, one of whom is a primary care physician and the other a behavioral health clinician. If needed, the decision guide will be updated iteratively by the study team. Counts of total notes available, the prevalence of keywords, and the prevalence of firearm violence–indicative notes will be recorded and detailed in future publications.

The study team will also engage the SAC to review keywords and suggest additional terms. These terms will be evaluated for inclusion into the lexicon by performing a keyword search to identify potentially related notes, followed by a review of a sample (up to 30 per term, if available in notes) of these notes. Terms that identify at least one note indicative of firearm violence exposure will be added to the lexicon. Engaging stakeholders is an important approach for incorporating broad community perspectives in developing and applying NLP and other artificial intelligence in health care, reducing bias and improving applicability [28-30].

NLP Text Classifier Development

The adjudicated notes will become the labeled dataset for training and testing our NLP text classifier. The study team will use Python (Python Software Foundation) to build the NLP text classifier. The output of our classifier will result in a new structured data variable that identifies exposure to firearm violence from behavioral health or primary care encounters in ambulatory settings.

The NLP text classifier will be trained as follows:

1. The dataset, containing chart notes and the adjudicated label, will be randomly separated into training and test sets using an 80% to 20% train-test split, stratified by label.

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2. The study team will use the training set to train several baseline machine learning (ML) and neural network (NN) classifiers available in the *scikit-learn* Python library [31] and Tensorflow platform [32] with Keras application programming interface [33], respectively, implemented with their default values.
   - Baseline ML models will consist of a pipeline with a vectorizer and classifier. The vectorizer will be a term frequency inverse document frequency [34] implemented via *scikit-learn's* TfidfVectorizer. ML classifiers will include random forest, multinomial naïve Bayes, gradient boosting, and LightGBM, implemented using *scikit-learn* and the LightGBM library [35].
   - Baseline NN models will use a tokenizer with a 1000-word vocabulary fit, and transformed sequences will be padded to 95% of the maximum sequence length. A sequential model consisting of an embedding layer with dimension 100, a model layer, and a dense layer with sigmoid activation will be compiled using an Adam optimizer, binary cross entropy loss, 50 epochs, a batch size of 64, and a validation split of 0.20. Model layers will be either recurrent neural network, long short-term memory, or gated recurrent unit with 64 units.
3. Performance of baseline models will be measured by evaluation on the held-out test set using metrics such as precision, recall, specificity, and the F_1-score (in future work, we would instead use cross-validation on the training set to assess baseline model performance to avoid data leakage).
4. The ML and NN baseline models with the higher evaluation metrics on the held-out test set will then be tuned for model hyperparameters, architecture (NN), learning parameters (NN), and threshold.
   - Tuning of the ML model will use BayesSearchCV from the *scikit-optimize* library [31] using the vectorizer-classifier pipeline with cross validation and 60 iterations and scored using average precision. The model with the best parameters will be fit on the training and validation data and then the optimal threshold will be determined using sckikit-learn's TunedThresholdClassifierCV with cross validation and the F_1-score.
   - Tuning of the NN model will use a text vectorization layer with tunable max_tokens and output_sequence_length; an embedding layer with tunable output_dim; a tunable number of NN layers each followed by a dropout layer with a tunable number of units, activation function, and dropout rate; and lastly, a dense layer with sigmoid activation. The model will be compiled using an Adam optimizer and binary cross entropy loss. The model will be fit with a tunable batch size. The training set will be split into training and validation sets and the BayesianOptimization tuner will be used to tune hyperparameters using 60 trials with 3 executions per trial, an objective of maximizing the average precision score, 100 epochs, and early stopping with patience=2. The model with the best parameters will again be fit on all the training data for 100 epochs, and the epoch with the maximum average precision score on the validation split will be assigned as the optimal number of epochs. The model with the best parameters will be fit on the training and validation data using this optimal number of epochs. The optimal threshold will be determined using cross validation and the F_1-score.
5. An open-source large language model, clinicalBERT [36], will be fine-tuned using the training and validation sets and the Transformers [37] and Datasets [38] libraries from HuggingFace to produce another NLP text classifier. The learning rate, batch size, and number of epochs will be tuned manually, using initial values of 0.00005, 16, and 5, respectively.
6. Evaluation of the tuned models and the clinicalBERT model will be done by assessing evaluation metrics of model predictions on the held-out test set; assessing evaluation metrics of model predictions on the held-out test set across subpopulations defined by age, sex, and race or ethnicity, and the intersection of these subpopulations; reviewing and discussing the performance of tuned and clinicalBERT models with the SAC.
7. Documentation of model performance and suggestions for any preprocessing, inprocessing, or postprocessing methods that should be pursued to mitigate any observed biases in the predictions of tuned or clinicalBERT models on the test set will be carried out.
8. One of the tuned models or the clinicalBERT model will be selected as our final NLP model, using the criteria in step 6.
9. Evidence of the validity of the final NLP model will be collected. We will do this by applying a keyword search to extract text excerpts from 1,000,000 randomly selected novel notes not previously adjudicated or used. From preliminary data pulls, we estimate that approximately 3% (n=30,000) of notes will have a keyword. Our final NLP model will be applied to these text excerpts, and a random sample of these (n=1000) will be adjudicated to give evidence as to the validity of the model. Adjudication will follow the same process described in the Dataset Development section above.

Addressing Ethics, Equity, and Bias in Model Development

The study team is approaching development of the NLP text classifier with a lens toward minimizing biases that may emerge [39-41]. Our primary strategy to address bias in model development is through the engagement of a SAC throughout the study. SAC members will participate in discussions about the use of an NLP-based classifier in a clinical context. Discussions with SAC members on the implications of false positives and false negatives at both the patient level and research findings level will help guide how potential NLP models will be evaluated (ie, which metrics are of higher importance). The SAC will be asked to consider bias based on patient characteristics and provider practices as well as

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algorithmic bias. Inclusion of SAC-suggested terms indicative of firearm violence and considerations of model performance across subpopulations are key evaluative characteristics for considering, identifying, and then mitigating potential biases in a universal firearm violence NLP algorithm. For additional diversity in input, our research team will meet with OCHIN's primary care and behavioral health clinical workgroups, attended by clinical leaders from member health organizations during the study start up (Year 1, quarter 1).

Potential biases in our training data include missing patients where firearm violence exposure is not present in a clinical note, possibly due to care received outside the health center, variation in provider care, or documentation practices, and patients who do not self-report exposure. These biases are inherent to all EHR-based research, and generalizability should be interpreted in light of the convenience-based, albeit large, nature of the dataset used [42,43] Our data come from primarily low-resource populations but it is not necessarily representative of all subgroups or individuals most likely to experience exposure to firearm violence. Likewise, we do not have reliable data on many variables in which model bias may exist (eg, gender).

There is the possibility of annotation bias during adjudication of text excerpts from clinical notes, even with our experienced team members. To minimize this bias, the study team developed a case note selection decision guide to support review by different study team members. We did not assess inter-rater reliability but would recommend this be performed in future projects.

We will attempt to identify potential model bias by calculating model performance across subpopulations of sex, age, race and ethnicity, and the intersections of these subpopulations (ie, group fairness) as these are protected attributes that are reliably documented in our data. We will provide this information to the SAC for further consideration along with discussions of stereotypical bias that can occur by evaluating models over such groups, under-representation bias due to low numbers in some subgroups, and possible mitigation strategies.

There may be other types of biases present in an NLP model that require more in-depth analysis to identify and mitigate. Such analyses include counterfactual evaluation (eg, replacing pronouns), adversarial testing, checking for bias in word embeddings, and evaluating model bias on an external dataset. However, due to the short duration of this study that spans lexicon development to the evaluation of NLP models, and without the intent to put this model in production at the end of this study, we leave these advanced and necessary bias identification methods to future work. If we do identify any biases in this study, we will document and provide transparency to these biases. We do not foresee time to effectively mitigate all potential biases within this study period. If there are identified biases and time left in our study period, we will consider and use appropriate mitigation strategies, which will most likely involve postprocessing mitigation techniques such as calibration and threshold adjustment given time constraints.

Results

The AIM-AHEAD Impact of Gun Violence Exposure on Health was funded on October 1, 2023, for a 2-year period.

NLP Model Development

Data acquisition started in February 2024 and was completed in April 2024, with >85 million primary care and behavioral health notes from >7 million patients. The study team extracted text from a random sample of 5000 notes with at least 1 firearm violence term for review and adjudication between March 2024 and May 2024. The first NLP template for baseline models was run in July 2024. Model development will continue throughout the study period to identify the best performing model for potential deployment. We expect that the final model will be selected by August 2025, and we will publish results of NLP model development and the final model performance in 2026.

Stakeholder Advisory Committee

The SAC was established during the first 3 months of the study in 2023 and includes 12 members: 5 community advocates or patients with lived experience; 1 physician; 2 clinician researchers; 2 clinical informaticists; and 2 data scientists with firearm violence data and research experience. The SAC will continue to meet monthly for the duration of the study. SAC contribution includes providing guidance on lexicon development, review of NLP performance, and application of NLP model in clinical practice [30].

Discussion

While exposure to firearm violence is common, identification of this experience is rare in structured ambulatory EHR data, particularly for secondary exposure that does not result in acute bodily injury. This study will be the first to develop an NLP text classifier to identify firearm violence exposure in clinical notes. We expect the NLP model developed in this study will be able to increase ascertainment of primary care and behavioral health patients with exposure to firearm violence; these findings will lay the groundwork for understanding the long-term impacts and outcomes of firearm violence exposure and present opportunities for improved patient care. Engagement with OCHIN network providers throughout the study will facilitate integration of results with clinical care and documentation practices. NLP has been used in other contexts to identify processes poorly captured by ICD codes; we expect that our work will also be able to identify patterns of exposure not otherwise captured in patient EHRs [44-46].

Because of the novelty of applying NLP to clinical notes for this purpose, we intentionally kept our approach open-ended and did not define a precise taxonomy or operational definition for firearm violence exposure, nor will we attempt to delineate between different types of exposure (eg, witnessing a community event versus direct personal threat). This is a limitation and presents important opportunities for future study and refinement. On the other hand, clinical notes are unlikely to represent a comprehensive picture of firearm violence exposure, and documentation is likely biased by provider practices and patient characteristics [43]. The value of identifying patients with

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exposure to firearm violence is to alert providers to the potential health care and support needs of such patients, to expand our knowledge of health sequalae following firearm violence, and to more fully frame the public health burden of firearm violence. Future work would benefit from collating clinical note–based NLP models with other sources of firearm violence exposure information—such as ICD-10 codes, personal and family history, and trauma screening—documented within and across clinical settings.

Additional limitations include the exclusion of clinical notes from children younger than 5 years, which limits generalizability, and the lack of more recent data, which may yield differential documentation patterns in structured or unstructured data. These limitations may be addressed in future studies.

Ultimately, addressing the epidemic of gun violence in the US and understanding the long-term impacts of exposure will require more comprehensive data. The NLP model developed through this work represents one aspect of this unmet need [7-10].

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Data Availability

Because chart notes contain protected health information, raw data for this study are not accessible to researchers outside of OCHIN. Model natural language processing code is available upon request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Firearm keywords.
[DOCX File , 20 KB - resprot_v14i1e76681_app1.docx]

Multimedia Appendix 2
Case note selection decision guide.
[DOCX File , 21 KB - resprot_v14i1e76681_app2.docx]

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Abbreviations

ADVANCE: Accelerating Data Value Across a National Community Health Center
EHR: electronic health record
ICD: International Classification of Diseases
ML: machine learning
NLP: natural language processing
NN: neural network
SAC: stakeholder advisory committee

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Protocol

Addressing Safety, Quality, and Cost of Care Through a Telehealth Outpatient Transitional Care Model: Protocol for a Pragmatic Randomized Controlled Trial

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Abstract

Background: People with multimorbidity have complex health care needs, resulting in high health service use, hospital readmission rates, and support needs. To prevent unnecessary hospital readmissions, effective coordination during the transition from hospital to primary care is essential; the transitional care model (TCM) is an effective approach to achieve this. This study will adapt the TCM, focusing on a nurse-led telehealth-based follow-up transition coordination service to enhance continuity between hospital and primary care, aiming to reduce unnecessary hospital readmissions and improve patient transitions.

Objective: This study aims to assess the impact of a TCM on 3-month readmission rates in people with multimorbidity after discharge in an Australian context. Other objectives include evaluating the rate of re-presentation to hospital and overall length of hospital stay within 1, 6, and 12 months of discharge from the index admission; conducting a cost analysis of the transitional service model of care; evaluating the patient experience with the transition service; assessing patients' symptom burden before and after transitional support service intervention; and evaluating patients' quality of life, self-efficacy, and symptom management before and after intervention.

Methods: The study design is a multicenter, pragmatic randomized controlled trial of patients with multimorbidity; therefore, real-world clinical practices, and operations will be the considerations within the research design elements. A mixed methods approach using quantitative and qualitative data collection methods will be used. The study setting incorporates 2 hospitals, initially commencing at the Queen Elizabeth Hospital (a 355-bed acute and subacute teaching hospital) and then at the Royal Adelaide Hospital (an 880-bed acute care teaching hospital), both located within the Central Adelaide Local Health Network, South Australia. We will include 3 to 6 medical units and wards. The intervention will focus on nurse-led transition assessment and care planning and telehealth transition coordination support for people with multimorbidity for 6 to 10 weeks following hospital discharge.

Results: This project received ethics approval (17554) on June 29, 2023, and was registered with the Australian New Zealand Clinical Trials Registry on February 15, 2024 (12624000142538). The study commenced on July 1, 2023; data collection started in February 2024 and was completed on March 31, 2025. Finalized results are expected in March 2026.

Conclusions: The Central Adelaide Local Health Network currently lacks a process to assess or manage readmission risks for people with multimorbidity, despite evidence linking transitional care to reduced rehospitalizations. Our feasibility study highlighted the effectiveness of a transition coordinator role in supporting patients' return to home and community. Progressing this work,

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an adapted TCM, with telehealth-based follow-up and home and health care support, will enhance continuity between hospital and primary care, aiming to reduce unnecessary readmissions and improve patient transitions.

Trial Registration: Australian New Zealand Clinical Trials Registry (ANZCTR) ACTRN12624000142538; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=383721

International Registered Report Identifier (IRRID): DERR1-10.2196/71847

(JMIR Res Protoc 2025;14:e71847) doi:10.2196/71847

KEYWORDS

transitional care model; multimorbidity; primary care; secondary care; nurse led

Introduction

Background

Multimorbidity, the presence of 2 or more chronic conditions, is common and becomes more common with increasing age [1]. It is estimated that 8% of Australians (9.7 million people) had 2 or more chronic disease conditions in 2022. This ranged from 11% of people aged between 0 and 14 years to 79% of people aged ≥85 years [2]. Due to increasing life expectancy and improvements in health care, the prevalence of multimorbidity is rising [3,4]. People with multimorbidity have health outcomes characterized by functional decline, decreased quality of life, and increased mortality [5]. Multimorbidity is also costly for health systems and society due to associations with high patient readmission rates [1], high health care use [6,7], and decreased productivity [8-10]. Historically, the health system has been underpinned and strengthened by the primacy of the single disease model of illness [4,11]. However, there is consensus that the single disease model is unsuitable for people with multimorbidity; a coordinated model of transitional care at the primary and secondary health care interface is required to reduce health service use, hospital readmission, and care fragmentation and support positive patient experiences [4,12].

Several transition interventions have been trialed to reduce high short-term readmission rates [13,14]; however, no discrete intervention or bundle of interventions has been found to reliably reduce rehospitalization. Beneficial interventions for patients with multimorbidity include transition coaches, home visits, and postdischarge telephone calls. However, these patients also often take multiple medications (polypharmacy) and are frequently readmitted due to medication-related issues [15,16]. Depression and anxiety are also common in this group and can lead to poorer health outcomes [17,18]. To address these challenges, interventions such as home medication reviews and mental health care plans may improve overall care for patients with multimorbidity. Nonetheless, services required by people with multimorbidity go beyond their needs in relation to polypharmacy management. Services need to support continuity of care, including multifaceted, time-limited transitional care and multiple health and social service supports and coordination [19,20].

Many services that were previously only provided face-to-face or through outpatient services have successfully, after the COVID-19 pandemic, transitioned to a telehealth service [21]. Still, issues with telehealth delivery persist, including device and internet capabilities at the end of the consumer, the unfamiliarity of the user interface, and uncertainty regarding the cost-effectiveness at the end of the provider [21,22].

Although intensive interventions, including multidisciplinary care and home visits, have been shown to reduce short-term readmissions, they may not be cost-effective in all settings and are difficult to implement across an organization. Low-intensity interventions, such as phone calls, are easy to implement; however, they have not been shown to impact readmission rates by themselves [23]. What is needed is a low-cost intervention that combines multiple interventions into a coordinated package, which can be delivered without requiring face-to-face or outpatient consultations and which, if successful, can be readily spread across an organization.

The transitional care model (TCM) is a nurse-led multidisciplinary model of care developed at the University of Pennsylvania [24]. It focuses on improving the transition of older adults with complex health needs from hospital to home, aiming to reduce hospital readmissions, improve overall patient outcomes, and demonstrate lower overall health care costs by providing comprehensive coordinated care during the critical period following hospital discharge [19,25,26]. Through personalized care coordination, comprehensive assessments (including risk of readmission), ongoing time-limited follow-up, nursing care, and interventions, the TCM has proven effective in enhancing patient care quality while lowering health care costs [26].

To date, there is no evidence that the TCM has been implemented or adapted for implementation within the Australian health care system. However, related transitional care interventions have been trialed. An umbrella review by Berthelsen et al [27], which synthesized findings from 59 randomized controlled trials and 3 quasi-experimental studies relating to key components of the TCM, included 5 systematic reviews conducted in Australia. In these reviews, 5 Australian studies were identified. However, these studies were not direct implementations of the TCM.

The Australian studies included the following: (1) evaluations of general practitioner (GP) involvement in discharge planning to reduce emergency service use [28,29]; (2) a care coordination intervention not based on the TCM [30]; (3) several occupational therapy–focused interventions [31]; and (4) a study related to residential care management [32]. Berthelsen et al [27] also refer to broader evidence regarding GP engagement in transitional care, citing studies such as Allen et al [33], Manderson et al [34], Morkisch et al [19], and Parker et al [35].

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In addition, Australia has implemented various care coordination programs, such as Planned Care for Better Health [36] and the inTouch Residential Aged Care Facility Pathway [37], although these initiatives are not based on the TCM. Other programs related to hospital discharge, such as those reported by Courtney et al [38], also diverge from the TCM framework.

A recent feasibility study examined a nurse-led transition care coordinator role designed to improve the quality of transitional care for individuals with multimorbidity at risk of hospital readmission [39]. The study was successful, providing evidence of the role's acceptability, feasibility, fidelity, and sustainability from both patients and staff in the Australian context. Results highlighted a gap in local health service provision, whereby there was no current process for assessing or managing the risk of readmission for people with multimorbidity, despite international evidence linking effective transitional care to reduced rehospitalization rates [39]. In addition, the study showed that the participants demonstrated significant support needs during the transition period, suggesting that a crucial shift is needed from traditional discharge planning to more tailored transition planning and care coordination for people with multimorbidity [39].

Australia does not have the TCM embedded within its acute care services. This is significant because transition coordination between the primary and secondary health care sectors has been shown to decrease hospital readmissions and increase primary health care use [40]. This study is being implemented at 2 acute hospital sites, both located within the Central Adelaide Local Health Network (CALHN), South Australia; the purpose of the study is to implement an adapted nurse-led TCM to minimize unnecessary hospital readmissions and emergency department presentations for people with multimorbidity [12].

Aim and Objectives

The aim of this study is to develop and test an adapted nurse-led transition model of care to optimally support people living with multimorbidity after hospital discharge via telehealth and ensure continuity of care between the secondary (acute) and primary health care sectors to minimize direct contact with hospital services.

The objectives of this study are as follows:

- To implement an adapted nurse-led TCM intervention
- To assess the intervention's impact on the rate of re-presentation to the hospital (emergency department or hospital admission) within 3 months of discharge from the index admission
- To quantify the rate of re-presentation to hospital (emergency department or hospital admission) within 1, 6, and 12 months of discharge from the index admission
- To calculate a cost analysis of the transition service model of care
- To evaluate the participants' symptom burden, self-efficacy, quality of life, and experience of continuity of care in relation to the intervention

Hypothesis

We hypothesize that the provision of a nurse-led transition support service (after hospital discharge) for patients with multimorbidity will decrease the short-term hospital readmission rate for this patient cohort.

Methods

Ethical Considerations

This project received ethics approval on June 29, 2023, from the CALHN Human Research Ethics Committee (17554). It was registered with the Australian New Zealand Clinical Trials Registry on February 15, 2024 (12624000142538). Written informed consent will be obtained from all participants to ensure that they understand the study requirements, risks, and benefits. If potential participants accept an invitation to participate in the study, they will be provided with a participant information sheet and consent form for consideration. They will then be approached 24 hours later to confirm their willingness to participate. The study commenced on July 1, 2023; data collection started in February 2024 and was completed on March 31, 2025. Finalized results are expected in March 2026.

Design and Setting

This study is a multicenter pragmatic randomized controlled trial (pRCT) of patients with multimorbidity for deployment at 2 acute hospital sites, initially commencing at The Queen Elizabeth Hospital (a 355-bed acute and subacute teaching hospital) and then at The Royal Adelaide Hospital (an 880-bed acute care teaching hospital), both located within the CALHN, South Australia. Between 3 and 6 medical units or wards will be included per site. This pRCT uses a mixed methods (quantitative and qualitative data collection) approach.

Data Collection

The pRCT will use a mixed methods approach to data collection, primarily quantitative with a qualitative descriptive component. Data will be gathered through validated patient assessment and transition instruments (Table 1), electronic medical record reviews, phone call support and monitoring, and interviews.

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Table 1. Data collection instruments, characteristics, and analysis methods.

Instrument	Number of items and response options	Analysis method
Community Assessment Risk Screen [41,42]	Three items (ranging 0-9): 0-3 (low risk); 4-9 (high risk)	Quantitative
Customized transition nursing assessment [43]	A total of 28 summary items	Quantitative and qualitative: open-ended narrative comments from participants
EQ-5D-3L health questionnaire [44]	Five dimensions: mobility, self-care, usual activities, pain or discomfort, and anxiety or depression and patient's self-rated health on a vertical visual analog scale	Quantitative and qualitative: open-ended narrative comments from participants
Patient Continuity of Care Questionnaire (short) [45]	A total of 12 items	Quantitative and qualitative: open-ended narrative comments from participants
Barthel Index [46]	A scale describing 10 tasks scored according to the amount of time or assistance required by the patient; total score from 0 to 100, with lower scores representing greater nursing dependency	Quantitative
Edmonton Frailty Scale [47,48]	A scale sampling 10 domains, where the maximum score is 17, representing the highest level of frailty	Quantitative
Kessler Psychological Distress Scale [49]	A 10-Item measure designed to assess nonspecific psychological distress	Quantitative
Malnutrition Universal Screening Tool [50]	Three independent criteria are assessed: BMI score, weight loss score, and acute disease effect score; all scores are added, where 0 indicates low risk, 1 indicates medium risk, and a score of 2≥ indicates high risk	Quantitative
General Self-Efficacy Scale [51]	A 10-item scale for a self-rated measurement of self-efficacy; total score between 10 and 40, with higher scores indicating higher self-efficacy	Quantitative and qualitative: open-ended narrative comments from participants
Edmonton Symptom Assessment System [52]	Measures symptom burden of chronic disease and has evolved into an 11-point numeric rating scale, ranging from 0 (no symptom) to 10 (worst possible)	Quantitative

As no suitable preexisting tools were available, customized instruments were developed in REDCap (Research Electronic Data Capture; Vanderbilt University) to capture transition assessment data, medical record readmission data, and phone call monitoring data [53]. Table 1 provides an overview of the validated data collection instruments, their key characteristics, and the planned analysis. All 10 instruments will collect quantitative data, with 4 also incorporating qualitative data.

Throughout the study, researchers and Supporting Transitions and Referrals nurses (STARnurses; recruited to support transitions and referrals) will prioritize patient sensitivity, build rapport, and minimize participant burden.

Qualitative Data Analysis

Thematic analysis, following the methodology by Braun and Clarke [54], will be used to categorize, analyze, and synthesize data from interviews and qualitative survey responses. Up to 15 interviews will be conducted or until thematic saturation is achieved.

Interview tools, including 12 open-ended questions, will be designed, piloted, and validated by us before data collection. All interviews will be audio recorded and transcribed using artificial intelligence transcription software, with transcriptions reviewed and validated by participants. Once finalized, transcripts will be uploaded to NVivo (Lumivero) software for coding and analysis. To protect confidentiality, all personal and identifiable information will be removed, and participants will be assigned pseudonyms (numerical IDs).

Each transcript will be systematically reviewed and coded, followed by an inductive categorization process. To support theme development, transcripts and categorized data will be read multiple times, allowing for the identification of emerging themes within the categories.

Statistical Analysis

An intention-to-treat approach will be used. Linear regression analyses will be conducted to estimate the effects of the intervention on primary and secondary outcomes. A fixed effects model will be used to account for stratification at the hospital and unit levels. Sensitivity analyses will be performed to assess the robustness of the findings. Table 2 presents the alignment of data analysis with primary and secondary study outcomes.

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Table 2. Primary and secondary outcomes—measurement and statistical analysis.

Outcome	Data source, measurement, and analysis
Primary	
The percentage of patients having hospital re-presentation (emergency department presentation with or without hospital admission) within 3 months of discharge from the index admission	• Re-presentation data available from the electronic medical record • Statistical analysis: comparison of proportions between treatment and control groups and time to re-presentation analysis using the log-rank test with the method of Kaplan-Meier [55]
Secondary	
Health care use	
The rate of hospital re-presentation within 1, 6, and 12 months of discharge from the index admission	• Readmission data available from electronic medical record • Rate defined as the number of re-presentations over a unit of time (eg, 1 y) • Statistical analysis: nonparametric comparison of rates of re-presentation between treatment and control groups
Overall length of hospital stay within 1, 3, 6, and 12 months of discharge from the index admission	• Readmission data available from electronic medical record • Defined as the cumulative number of days spent in hospital over a unit of time (eg, d/y) • Statistical analysis: nonparametric comparison of rates of re-presentation between treatment and control groups
Cost of transition service	• Economic benefits of the intervention will be confirmed through a comparison of subsequent rehospitalization costs in the treatment and control groups
Model of care and patient outcomes	
Patient-reported symptom burden	• ESAS[a] [52] (nonparametric comparison of responses between treatment and control groups)
Patient symptom management and self-efficacy	• ESAS [52] • GSE[b] [51] (nonparametric comparison of responses between treatment and control groups)
Quality of life	• EQ-5D-3L health questionnaire [44]
Patient experience, satisfaction, and perceived continuity of care	• PCCQ[c] (short) [45] (nonparametric comparison of responses between treatment and control groups)
Organization of care	
Implementation of components of the TCM[d]	• Economic benefits: cost calculations of comparison between control and intervention hospital readmissions from the index admission • Includes TCM intervention cost compared with usual care cost
Implementation of the transition action plan for all patients	• Customized transition action plan developed

[a]ESAS: Edmonton Symptom Assessment System.

[b]GSE: General Self-Efficacy Scale.

[c]PCCQ: Patient Continuity of Care Questionnaire.

[d]TCM: transitional care model.

Sample Size Estimation and Justification

We anticipate that the enrollment of approximately 200 patients over 15 months will be feasible and provide a sufficient sample size to achieve the primary outcome, with the anticipated baseline readmission rate in the control group and absolute reduction in the intervention group (Table 3). Enrollment commenced in February 2024 and was completed on March 31, 2025. Given that the primary end point will be derived from health information systems in South Australia and that the study has an intention-to-treat approach, there will be a need to consider a larger sample size, taking into account withdrawals, dropouts, or loss to follow-ups.

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Table 3. Sample size per group by baseline readmission rate and absolute reduction in readmission with 80% power (α=.05).

Absolute reduction in readmission rate in the intervention group (%)	Baseline readmission rate in the control group at 3 mo, n		
	35%	40%	45%
15	136	150	160
20	70	79	86
25	40	47	52

Randomization

The randomization will occur at the individual level. The participants will be randomized 1:1, with stratification at the ward or unit level to intervention or control, using REDCap, a secure, web-based software platform designed to support data capture for research studies [53].

Control

Participants in the control group will receive usual care, which is defined as the "usual follow-up services" planned while the patient is in hospital, before discharge. Transition care is not implemented after discharge from the hospital (usual care). Usual services are planned or initiated while the participant is in the hospital in preparation for discharge, but provision of these services is not followed up by the STARnurses.

Eligibility Criteria

The eligible population includes individuals aged ≥18 years with multimorbidity who fulfill all inclusion criteria and do not meet any of the exclusion criteria. For the purposes of the inclusion criteria, multimorbidity is defined as the coexistence of 2 or more chronic conditions [56] (Textbox 1).

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Inpatients (ward or emergency department)
- Sufficient cognitive function and English language skills to provide informed consent and complete assessments
- Ability to engage in telehealth
- A history of either diabetes with cardiovascular disease or comorbidity in minimum 3 of the following illness domains:
  - Diabetes—type 1 or type 2
  - Cardiovascular disease—symptomatic atherosclerotic disease (ischemic heart disease, cerebrovascular disease, peripheral vascular disease, symptomatic valvular heart disease, or atrial fibrillation)
  - Chronic cardiac failure
  - Psychiatric illness, including mood or anxiety disorders
  - Respiratory disease, including chronic obstructive pulmonary disease, asthma, or interstitial lung disease
  - Kidney disease resulting in chronic renal impairment, with creatinine clearance ≤30 mL/min
  - Current malignant neoplasm

Exclusion criteria

- Patients living in or likely to be discharged to a high-level residential care facility for older adults
- Patients enrolled in a comprehensive management program upon discharge, for example, a formal rehabilitation program, rehabilitation in the home, heart failure outreach service, chronic obstructive pulmonary disease pulmonary rehabilitation, hospital in the home, or receiving disability or community psychiatric services, including care coordination
- Patients followed up through other local health network services providing community outreach, such as patients who are homeless
- Patients with a current history of illicit drug or alcohol dependence, which may interfere with their ability to engage with the program
- Patients with palliative intent and likely to have a life expectancy of <6 mo
- Patients due for elective readmission within 2 wk of current hospital discharge
- Insufficient cognitive function or English language skills to provide informed consent and complete assessments
- Patients who are found to have been in hospital for >3 wk during the index admission and are not transitional patients

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Identification and Recruitment of Participants

Several procedures to identify and recruit participants for the trial intervention have been incorporated into the study design.

Nursing, medical, pharmacy, and allied health leads and managers; ward staff; and patient flow and bed management meetings will be attended by the research leads and STARnurses to brief staff and explain all aspects of the research and introduce the STARnurses and their role. Emails and flyers will be sent by the research leads to medical, nursing, pharmacy, and allied health leads as well as relevant clinical staff.

Study criteria will be entered into the local electronic medical record to produce a trial list of potential participants. The STARnurses will review the list daily and follow up with relevant treating clinicians. Daily rounds will be conducted at trial wards, and nursing staff will liaise with medical staff to identify patients. Huddles will be attended, and nursing staff will liaise with medical staff to identify patients.

The patient's clinical team will be consulted first, and if permission is granted, a research team member will then approach the patient. They will be invited to participate in the study, and if they accept, they will be provided with a participant information sheet and consent form for consideration. The patient will then be approached 24 hours later to confirm their willingness to participate. Individual randomization using REDCap will take place following informed written consent [53].

It is acknowledged that participants who provide consent will have multimorbidity and may even be frail, and the collaboration with their multidisciplinary team will be an integral component of the intervention. Therefore, balancing the participant's agency and self-efficacy and capability with their anxiety and hesitancy will require ongoing discussion between the participant and team members, along with their support.

Intervention

The intervention involves establishing a transition coordination service led by nursing transition coordinators, who will support transitions and referrals, known as STARnurses. The intervention consists of 4 key phases.

The first phase involves in-hospital screening in which "risk of readmission" screening is conducted during the hospital stay, using the Community Assessment Risk Screen tool [41,42]. Patients who meet the inclusion criteria are invited to participate in the study.

The second phase involves in-hospital baseline assessment, transition planning, and participant goal setting (following participant research and information discussion, acceptance to participate, and consent procedure complete). A detailed inpatient baseline and transition assessment is performed to collaboratively develop personalized goals and a transition action plan. Researchers will use the following tools to assess participants' transition needs: customized transition nursing assessment [43], Barthel Index [46], Edmonton Frailty Scale [47,48], Kessler Psychological Distress Scale [49], Malnutrition Universal Screening Tool scale [50], and General Self-Efficacy Scale [51]. The participant's GP or practice nurse will be contacted and receive the transition action plan before the participant's hospital discharge.

The third phase is posthospital discharge transition coordination. Participants will receive transitional care coordination, with phone calls or telehealth follow-up in the first 48 hours following discharge and then weekly and fortnightly (Figure 1).

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Figure 1. Interventions aligned with time points (TPs) of data collection and phone calls. ESAS-r: Edmonton Symptom Assessment System–Revised; TAP: transition action plan.

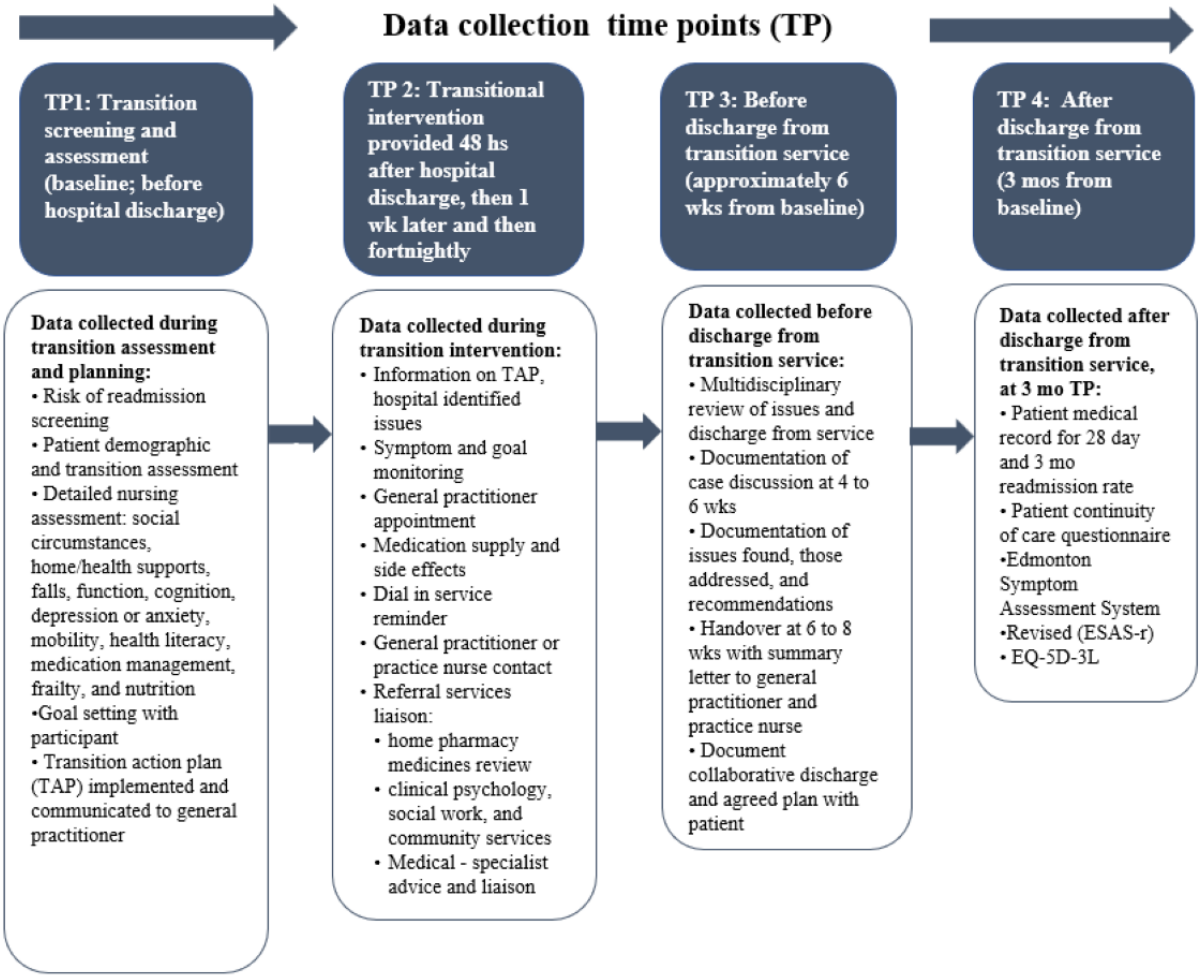

The fourth phase involves handover to primary care. A multidisciplinary case discussion will occur approximately 4 weeks after discharge in preparation for handover to the GP or practice nurse and other specialist providers. The STARnurse will have a final consultation with the patient after the multidisciplinary case discussion (6-10 wk after discharge) to inform the patient of any outcomes or actions. Handover and written communication are provided to the GP or practice nurse to ensure the participant is stable in the community, and if not stable, follow-up care is required.

In this study, a key adaptation of the TCM is replacing the advanced practice registered nurse home visits with STARnurse telehealth or telephone follow-up. This follow-up is provided according to the intervention protocol (Figure 1). The feasibility of the STARnurse and transition coordinator role and the associated transition service was previously evaluated in an earlier feasibility study [24].

Results

This project received ethics approval (17554) on June 29, 2023, and it was registered with the Australian New Zealand Clinical Trials Registry on February 15, 2024 (12624000142538). This study commenced on July 1, 2023, with data collection commencing in February 2024; data collection was completed on March 31, 2025. Finalized results are expected in March 2026.

Discussion

Anticipated Findings

The primary outcome of this research is decreasing the rate of hospital readmission within 3 months of discharge from the index admission in people with multimorbidity. In a prospective, quasi-experimental TCM study (N=172), improvements in all health status and quality of life measures were observed after intervention compared to before the intervention, and a significant decrease in total number of readmissions (TCM: 45 readmissions vs control: 60 readmissions; $P<.041$) and total hospital days (TCM: 252 d vs control: 351 d; $P<.032$) were observed at 3 months [57].

The secondary outcomes include the cost analysis of the transition service model of care. In a previous study, cost savings were demonstrated in relation to appropriate implementation of the TCM, whereby it was associated with a short-term decrease of US $439 per patient per month in total health care costs at 3 months and cumulative per-patient savings of US $2170 at 1 year ($P<.037$). In a cost comparison study in which the post–acute care costs of 3 care management interventions for hospitalized older adults with cognitive impairment and

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their family caregivers were compared (N202), the TCM had significantly lower costs than 2 other comparable care management interventions and has been associated with an estimated net savings of US $2972 per individual at 6 months [26].

People with multimorbidity are readmitted to the hospital more, spend more time seeking health care, and often receive fragmented care. When they are discharged from the hospital, they are often readmitted due to poor health care team communication, uncoordinated follow-ups, and not knowing whom to contact when they have symptoms. Supporting these patients as they transition to the community after hospital discharge with an adapted nurse-led TCM intervention will assist them to resume their normal lives more quickly and prevent unnecessary hospital contact.

This study is informed by TCM evidence and an earlier feasibility study [12,39]. Consequently, it represents an additional and focused investigation into a discrete and known area of health service provision. This focus has allowed researchers to refine the intervention to a practical and effective modality. The method responds to previously encountered challenges and locates the participant and their health care team at its center. It is anticipated that patients' awareness of this approach will encourage their health care agency in a goal-directed and beneficial manner. The previous research was at a single large acute hospital; the sample size was small; and the design omitted the use of comparator groups. These parameters have been addressed in this study, enabling future generalizability of the findings.

Limitations

Although the power of the research has been addressed through an appropriate cohort number, the 2 hospitals included in this study remain within the same local health network, which could emerge as a limitation later. At this point, an adapted nurse-led TCM is being trialed, posing infidelity to the original model; in addition, people with cognitive impairment have been excluded. However, this research is considered part of an overall plan to eventually embed the transition care model as standard care within the health system; consequently, each research project builds on demonstrated evidence.

Health sectors use diverse electronic record and patient data systems, which can lead to challenges with access and consistency. To address these challenges, this study is a pragmatic one, emphasizing relationship building [46] and fostering regular, consistent communication among the multidisciplinary team, the participants and significant others, and the health sectors as integral components of the nursing interventions.

Conclusions

In this research, the role of the STARnurses is key, which spans the hospital, multidisciplinary teams, and the primary health care setting. Their collaborative role enables patient-centered care that is tailored to participants' transition goals; it needs to empower them in the management of their own care. Evidence is clear that the TCM has a positive impact on reducing readmission rates through its enhanced care coordination and the management of patients in transition from the acute to the primary health care sector. However, the South Australian local health networks currently lack a structured process to evaluate the risk of hospital readmission at the time of discharge, even though readmissions among patients with multimorbidity are both costly and potentially avoidable. This research offers the opportunity to enhance continuity of care, minimize unnecessary rehospitalizations, significantly decrease overall health care use, and improve quality of life for people with multimorbidity. It also represents a significant opportunity to transform health care delivery, emphasizing a shift from discharge planning to an integrated model of transition planning and care.

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Data Availability

The datasets generated or analyzed during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

KD contributed to the literature search, study design, and drafting the initial manuscript and its revised versions. SS, ME, and GS significantly contributed to the study design and also contributed to the literature search and drafting and reviewing the initial manuscript and its revised versions. NM significantly contributed to drafting the initial manuscript, and LD contributed to the preparation and revision of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CALHN: Central Adelaide Local Health Network
GP: general practitioner
pRCT: pragmatic randomized controlled trial
STARnurse: Supporting Transitions and Referrals nurse
TCM: transitional care model

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Protocol

Real-Time Exposure to Alcohol Content in Digital Media in Adolescents: Protocol for a Multiburst Ecological Momentary Assessment Study

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Abstract

Background: Digital media frequently contains positive portrayals of alcohol content, which has been shown to be associated with alcohol-related cognitions and behaviors. Because youth are heavy media consumers and have access to unsupervised, repeat viewing of media content on their personal mobile devices, it is critical to understand the frequency of encountering alcohol content in adolescents' daily lives and how adolescents engage with the content.

Objective: This paper outlines the study protocol for examining adolescents' exposure to alcohol-related content in digital media within their natural environments.

Methods: Adolescents (N=302; 31.8% boys, 16.2% nonbinary, 51.3% girls; 25.8% Asian, 3.6% American Indian, 21.5% Black, 4.6% other, 52% White, 25.8% Hispanic or Latinx; mean age 16.21, SD 0.77 y) enrolled in high school were recruited through social media to participate in a prospective study involving bursts of ecological momentary assessment (EMA) reports coupled with longer surveys. We conducted group orientation sessions via videoconference and online surveys, followed by a 21-day EMA period that included scheduled reports across 4 daily time blocks, as well as self-initiated reports on media exposure. Reports of alcohol content exposure included details about the platform, level of engagement, source characteristics, beliefs and perceived norms about the content, the viewing context, and whether the content was sponsored or branded. The participants submitted exposures to alcohol content as an image (screenshot or photo) or text description to be objectively coded. The participants completed a weekly online survey assessing alcohol use and related cognitions. EMA reports will be merged with coded image and text entries and with data from baseline, weekly, and follow-up surveys. Self-reported alcohol exposure will be explored descriptively, and differences in exposure tested across subgroups. Event-level data will be compared with random prompt data to examine differences at times of exposure versus nonexposure. Prospective associations between media alcohol content exposure and alcohol use will be explored over 1-week and 4-month time frames. Mediation of the association between media alcohol exposure and drinking will be tested to explore putative mechanisms.

Results: EMA data collection took place from February 2022 to August 2023. Data management and preliminary analysis are ongoing. Preliminary data were disseminated through conference presentations in 2024-2025 and manuscripts are ongoing with full results anticipated to be published in 2025-2026.

Conclusions: By characterizing adolescents' real-world exposure to alcohol content in the media, the study provides critical information to develop and implement interventions to target youth behavior that are well suited to delivery via mobile devices. Next steps are to conduct focus groups to understand participants' lived experience of exposure to media alcohol content and

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reactions to proposed intervention targets. This study and subsequent qualitative work will launch a program of research to counter the effects of alcohol-related media exposure as experienced by adolescents in an effort to minimize underage alcohol involvement.

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KEYWORDS

media; entertainment; social; exposure; adolescent; alcohol use; ecological momentary assessment; passive

Introduction

Background

Initiation of alcohol use typically occurs well before the legal drinking age [1-3], which is concerning as early use is associated with short- and long-term adverse outcomes, including acute and prolonged neurobiological impairments [4-6]. The importance of the environment in shaping early drinking behavior is increasingly recognized, with adolescents highly susceptible to the socializing influences of peers and prevailing generational norms [7-10]. Media represents one particularly important contextual influence for adolescents. Youth are heavy media consumers [11], and personal mobile devices such as smartphones and tablets offer youth ease of unsupervised, repeat viewing of personalized media content.

Digital media, which encompasses social media, new media, and entertainment media such as television, movies, and music, frequently contains positive portrayals of alcohol content. Entertainment media features images of and references to alcohol, associating alcohol use with social, sexual, and financial success, with little depiction of the hazards of drinking [12,13]. The digital media environment has rapidly evolved over the past 15 years, and alcohol content is pervasive on social media and YouTube. These platforms are highly interactive, allowing for user engagement through exchange and manipulation of information [14-18]. Youth self-report high exposure to alcohol content in digital media [19-21]. Notably, rigorous review studies have concluded that exposure to media alcohol content is consistently associated with increased risk of early initiation and progression of underage drinking [22-24]. Etiological research on the mechanisms underlying the association between media exposure and drinking points to cognitive and social mechanisms, including perceived norms [25,26], cognitions (expectancies [27,28] and drinker prototypes [29]), identity [30], and attitudes (favorability [31] and evaluative conditioning [32,33]).

Despite this etiological research, virtually no information is available about in vivo exposure to media alcohol content. Understanding the frequency of encountering alcohol content in adolescents' daily lives and how adolescents engage with the content is critical for efforts to reduce exposure. Determining how such exposure influences a person is important for mitigating the impact of the exposure. This study seeks to understand when, where, and how much teenagers are exposed to alcohol content in digital media and its influence on attitudes, cognitions, and behavior. Study outcomes will address gaps in the literature, focusing on several limitations in earlier research: the focus on a single aspect of media exposure (eg, social media), assessment of primarily passive exposures through screen media, use of primarily retrospective self-reports of media exposure and behavior, and coarse time frames of assessment.

Our study focuses on older adolescents. Younger teenagers tend to have little experience with alcohol, report low intention to drink, and perceive negative consequences of drinking, with a shift to positive beliefs occurring toward later adolescence [34,35]. The link between media exposure and social norms also may be tenuous at younger ages, when fewer youth have friends or same-age peers who consume alcohol. Thus, there may be limited variability in drinking cognitions and peer norms in young adolescents, as documented in our own work [36,37]. Older adolescents may be well suited to an intervention that provides tools for countering effects of exposure to media alcohol content, as content may be more relevant, perceived norms and cognitions may be more modifiable, skills can be practiced as alcohol is available and consumed, and this age accesses new media continually and with little supervision.

The first aim of the project is to quantify and characterize in vivo exposure to alcohol content in digital media, including entertainment media (film, television, and popular music), social media, and YouTube, in terms of frequency and duration, medium and format, and context. The second aim is to examine prospective associations between exposure to alcohol media content and alcohol involvement (willingness, use, heavy use, and problems) across short- and longer-term time frames. Aim 3 identifies putative mechanisms of these associations, including perceived norms, cognition (expectancies and drinker prototypes), and identity (personal and social). The study's multiple-burst longitudinal design will permit direct comparison of cognitions, norms, and context at moments of exposure versus nonexposure to media alcohol content and will provide important information regarding timing and directionality (or bidirectionality) of influence between exposure to media alcohol content and youth alcohol use.

Objectives

This paper describes the protocol for a study that examines exposure to digital media alcohol content in the natural environment among adolescents (aged between 15 and 18 years). The project involves 3 bursts of ecological momentary assessment (EMA) reports coupled with longer surveys of broader content. The participants were also asked to submit exposures to alcohol content in the media in the form of an image (eg, screenshot and photo) or text description to be objectively coded. The study is the first in vivo, EMA investigation of exposure to alcohol content in the media that considers a wide array of entertainment and digital media.

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Methods

Design

Adolescents (N=302) currently enrolled in high school were recruited through social media to participate in an EMA study with three 21-day bursts of daily EMA assessments separated by 4-month intervals (Figure 1). Following a baseline session, EMA reports were coupled with weekly 7-day timeline follow-back (TLFB) assessments during the bursts.

In addition, 2 follow-up surveys were administered preceding each burst (Figure 2). The measurement burst design [38,39] combines a longitudinal panel design with experience sampling methods and permits investigation of processes in both short term and long term.

Figure 1. Multiple cohort multiburst study design to examine exposure to alcohol content in the media among adolescents in the United States.

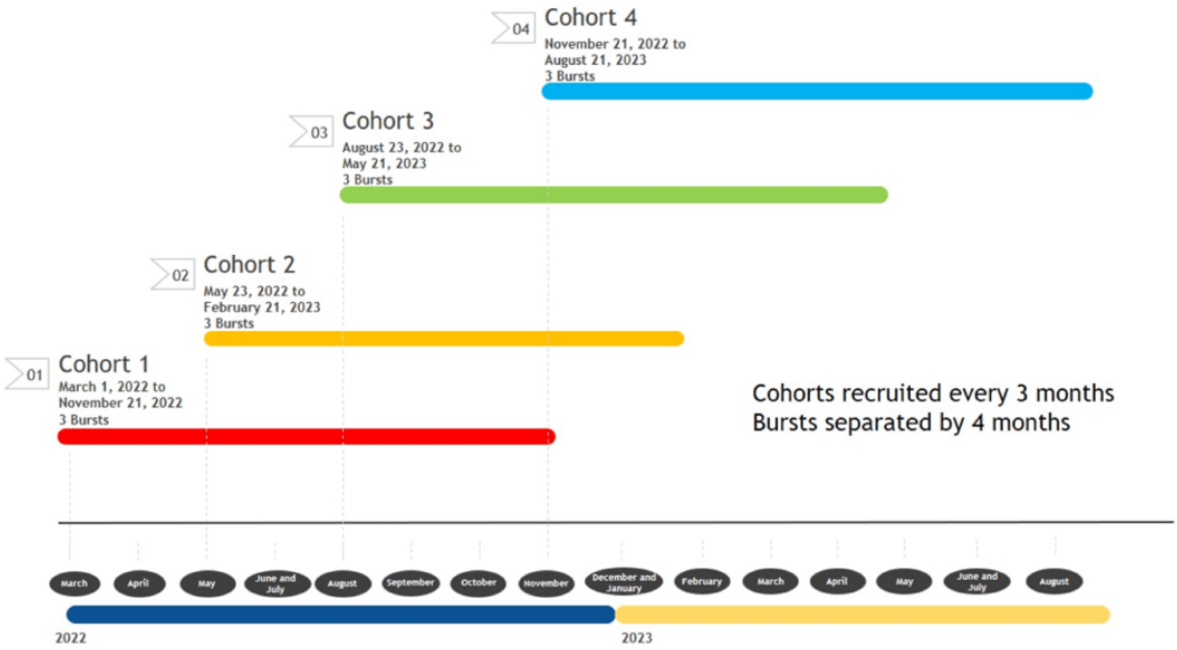

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Figure 2. Visual timeline of study procedures.

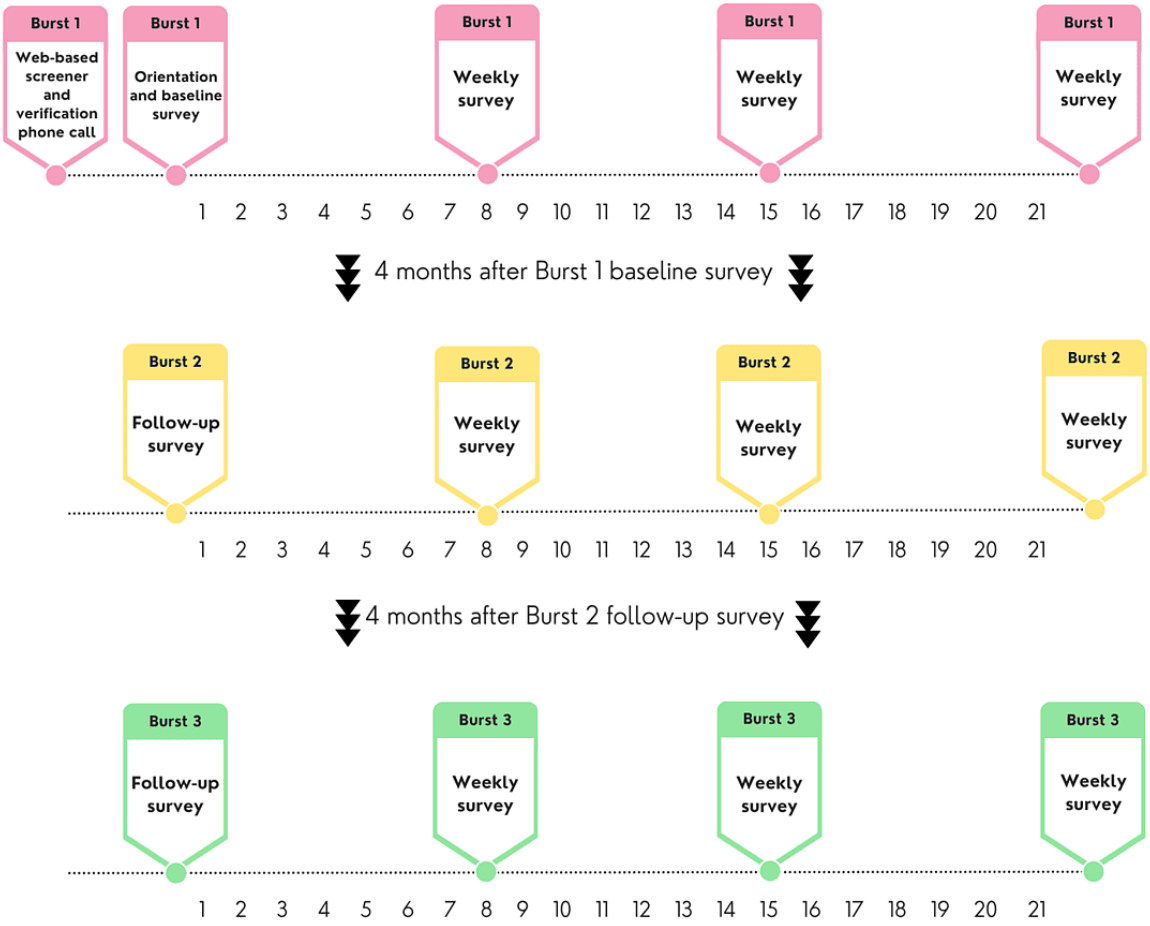

The participants completed a group orientation session conducted over Zoom (Zoom Communications, Inc) where study procedures were explained and the study smartphone app was installed. Before the orientation, the participants completed self-report measures in Qualtrics (Qualtrics International Inc). EMA reporting began for each cohort of participants from 1 to 12 days following their orientation session. Each day during the study, the participants used the study smartphone app to report on exposure to alcohol content in the media and responded to a series of items assessing type of media, reaction to the content, and attitudes and cognitions about the content. The participants also used the app to submit images or text descriptions of the content, which were subsequently content coded by the research team.

Youth Advisory Board

We formed a youth advisory board (YAB) of high school students in the southern New England area to obtain youth perspectives to (1) understand adolescent experiences encountering alcohol content in the media and (2) obtain specific input on study methods to make our study relevant and engaging to present-day high school youth. We recruited youth who could share and reflect the diverse perspectives of the community by involving students with variation in age, gender, racial and ethnic group, school, and region. The YAB contributed to the development of our recruitment and retention strategies and provided input on the study protocol and assessment battery. The YAB members received an annual honorarium of US $100, distributed in 2 payments of US $50 every 6 months. We informed members that they had to attend at least 4 of 6 meetings to receive the full honorarium. From the application process, it seemed that most members also had an intrinsic interest in belonging to the group and offering their perspectives. Further information about the YAB and associated methods will be presented in a separate forthcoming paper.

Participants

We recruited 302 eligible participants into 4 cohorts enrolled in the winter, spring, summer, and fall of 2022. Splitting up enrollment into multiple cohorts enhanced feasibility by reducing burden on research staff. It also permits examination of seasonality separately from testing effects. We will attend to seasonality as we anticipated potential seasonal differences in response rates, alcohol use, and access to media and electronic devices. Although there is a paucity of literature examining seasonal patterns in adolescent compliance with daily surveys, we expected that response rates might differ over summer months as compared to the school-year assessments. For some youth, response rates might be expected to be higher during the summer due to fewer responsibilities and a less structured environment; for others, response rates may be lower due to travel or structured summer activities. We also anticipated that

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participants would have greater access to social and entertainment media during the summer months, which is a time for relaxation, exploration, and social connection. Finally, the literature indicates seasonal variation in alcohol consumption, at least in college students and adults. Higher rates of alcohol use are seen during times of holidays and summertime [40-43], with 1 study documenting prominent peaks in daily drinking corresponding to summertime and holiday weeks known to be associated with heavy consumption over a 2-year period [44].

Participant inclusion and exclusion criteria included (1) being aged between 15 and 18 years, (2) currently enrolled in high school (9th through 12th grades), (3) able to read simple English, (4) owned a smartphone (iPhone [Apple, Inc] or Android [Google LLC]), and (5) lived in the United States (verified via phone call by a research assistant [RA]). In addition, we only included youth who had consumed alcohol or had at least 1 close friend who drank alcohol, to ensure participants had some familiarity with alcohol while capturing a range of drinking experiences. We limited our sample to adolescents enrolled in high school to ensure similarity in context, as the environment in a high school can vastly differ from the middle school environment or the environment following high school, which spans workforce entry through 4-year college enrollment.

Figure 3 presents a flow diagram of participant screening and enrollment. During the recruitment phase, 3530 people completed our screening questionnaire on the online survey platform Qualtrics. Of those, 1535 (43.5%) participants were eligible to continue the enrollment process, including 16 of 33 (48%) participants who were aged exactly 18 years and who completed the consent form. The remainder of eligible participants were younger than 18 years and were asked to complete a brief contact form (859/1502, 57.2% respondents), following which parental permission was sought. A total of 512 parental consent forms were returned, with 508 parents agreeing to their child's participation; of these, 452 (89%) also returned assent forms to participate. The students lost following the assent or consent completion were either nonresponsive to our subsequent attempts to reach them by phone to confirm orientation or were withdrawn because we could not verify their identities. Ultimately, 305 students enrolled in the study, meaning they provided consent or assent, attended a study orientation, and completed a baseline survey. A total of 3 individuals withdrew themselves from the study at days 1, 6, and 8, respectively, and are not counted in the final analytic sample. The 302 active participants were enrolled in 4 cohorts, 3 months apart (C1: n=56, 18.5% participants; C2: n=101, 33.4% participants; C3: n=103, 34.1% participants; and C4: n=42, 13.9% participants). In the final sample, 63.9% (193/302) of participants reported being assigned female at birth; gender distribution was reported as follows: 4.6% (1/302) nonbinary, 5.3% (16/302) gender nonconforming, 32.7% (99/302) boys (cis- or trans-), 52.6% (159/302) girls (cis- or trans-), and 4.6% (14/302) other. Our first 2 cohorts were predominately composed of participants assigned female at birth, consistent with other contemporaneous research that uses social media platforms for recruitment. For recruitment of the third and fourth cohorts, we sought to enroll more youth who were assigned male at birth through targeted social media advertisements; our final sample was still skewed toward youth who were assigned female at birth but with diversity in gender identity. Mean age was 16.21 (SD 0.77) years, and 1.3% (4/302) were in the 9th grade, 17.2% (52/302) were in the 10th grade, 44.0% (133/302) were in the 11th grade, and 37.4.% (113/302) were in the 12th grade. The sample exhibited racial and ethnic heterogeneity, with 25.8% (78/302) Asian, 3.6% (11/302) American Indian, 21.5% (65/302) Black, 5% (15 /302) other, and 52% (157/302) White; 25.8% (78/302) reported being Hispanic or Latinx, and 74.2% (224/302) reported being non-Hispanic or non-Latinx.

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Figure 3. Flow diagram of participant screening and enrollment through active participation. EMA: ecological momentary assessment.

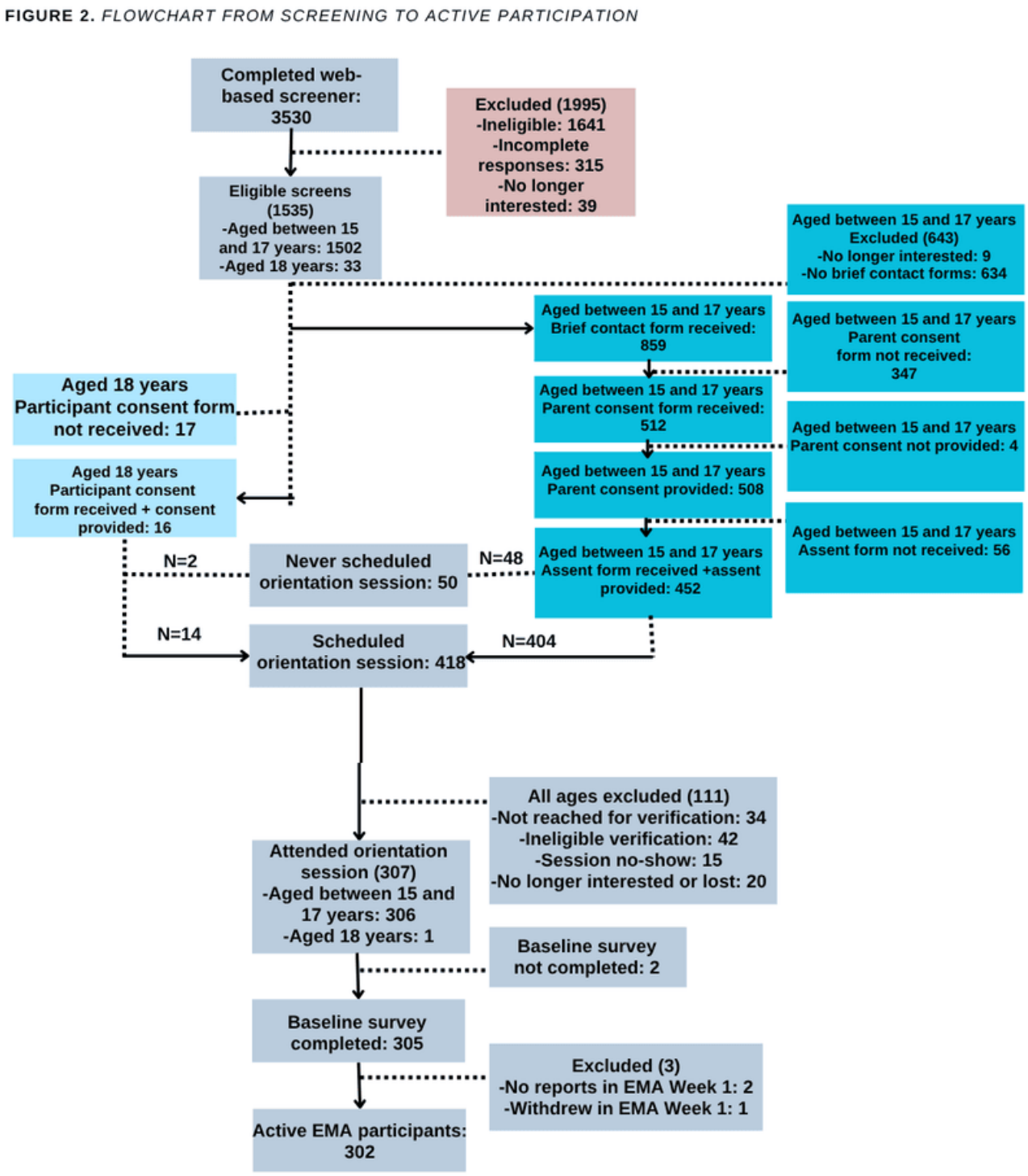

Procedures

Recruitment

We recruited adolescents from social media advertisements, including paid advertisements on Instagram (Meta Platforms, Inc) and Facebook (Meta Platforms, Inc) and posts by research team members on TikTok (ByteDance). Advertisements displayed different combinations of study aspects, including the study name (TEAM300) and logo; engaging phrases (eg, Join the squad!); language about compensation and online format; and relevant images of teenagers, alcohol content in media, and general media use (Figure 4 depicts illustrative advertisements). Advertisements promoted diversity and inclusion by featuring young people from a variety of racial and ethnic backgrounds, with specific visuals and text refined based on feedback from our YAB (refer to the subsequent sections). Study staff ultimately developed advertisements as both still and animated graphics to fit social media feed and story layouts.

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Figure 4. Examples of social media advertisements for recruitment.

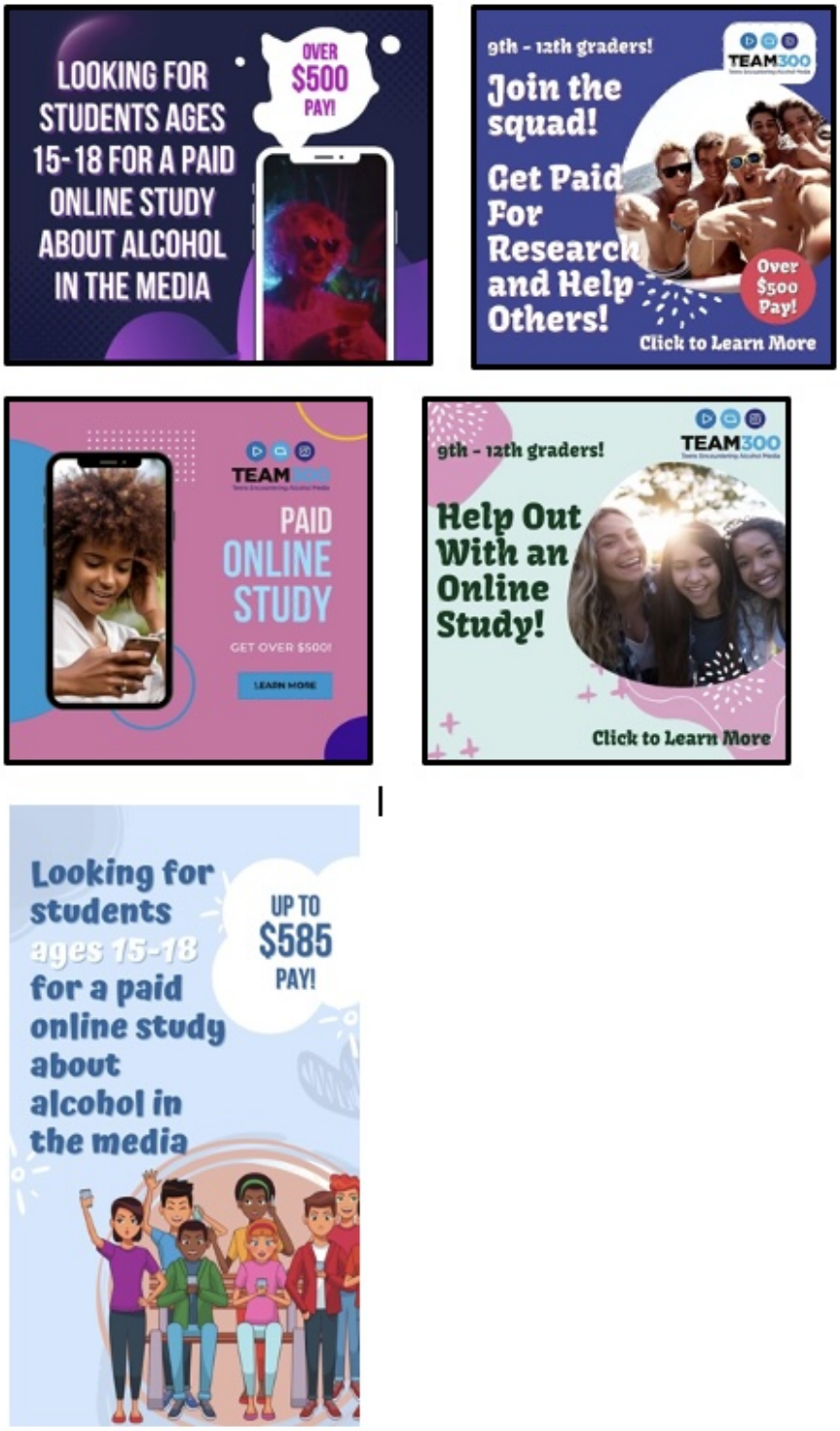

Clicking a digital study advertisement directed the individual to a study landing page in Qualtrics that provided basic information about the study, both in brief written and video format, as well as a link to our study website. Those interested in participating were directed to a 14-item anonymous screening survey that assessed basic eligibility criteria. We enabled various security features on Qualtrics (eg, ReCaptcha 2/3 and bot detection) to reduce instances of fraud.

After completing the screening survey, eligible adolescents who were aged 18 years continued directly to the online consent form. Those who consented then provided contact information. Eligible adolescents younger than 18 years provided contact information and subsequently received an email containing study information to be forwarded via email to their parent or legal guardian (hereafter referred to as parents) so that they could provide parental permission. The email contained a link to a Qualtrics landing page for parents, which provided a study

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overview, an informational video, links to the study website, and a link to the parental consent form. The project website contained a brief description of study procedures and compensation as well as 2 informational videos, 1 geared toward the participants and 1 geared toward parents. The research team, including our staff and YAB members from groups considered historically underrepresented, was featured on our study website. Two frequently asked questions sections were also provided on the website, 1 for adolescents and 1 for parents. The frequently asked questions responded to questions such as “Are there any risks to participating?” “Are you asking me to share anything on my phone or in my social media accounts?” and “What are you asking my child about?” All website materials were written at an 8th-grade reading level or lower. Parents were invited to contact research staff to answer any questions using the study contact information provided, or they could provide online consent for youth participation without additional information needed from project staff. There were no instances of parents reaching out to the team for additional study information before providing parental consent. Once parental permission was obtained within Qualtrics, the participant then received an email with a link to complete their own digital assent form.

Eligible participants who provided consent or assent (with documented parental consent) were directed to an online scheduling platform to select a 45-minute group orientation session. Once scheduled, an RA confirmed the orientation session appointment over the phone. During these calls, staff also confirmed the identities of the participants by asking the participants to confirm their contact information and state the name of their high school, verifying the high school location against the zip code previously given by the participant. We encountered approximately 40 nonlegitimate cases, including issues of contact information not matching previously submitted details, inaccurate high school names or locations, or inability to provide requested information.

Participant Orientation and Baseline Assessment

Orientation sessions were conducted via Zoom in groups ranging from 2 to 10 (median 4) participants. Orientations, which were delivered by RAs, incorporated a slide deck as a visual aid to reinforce study information. Our RAs were diverse across both gender and racial and ethnic groups. The slide layouts, content, and flow of topics were adjusted and refined across time via staff, peers, and YAB feedback, ultimately resulting in standardized orientation session content across cohorts. The presentation included general study elements such as study staff names and position titles, overall study aims, participation timelines, and compensation structure, as well as specific procedural elements such as screenshots of the daily phone app reports and weekly surveys that the participants would complete. Figure 5 shows sample orientation content presented using Canva slides. The goals of the orientation sessions were to promote participant study engagement and teach the participants (1) examples of references to alcohol that might be encountered in day-to-day use of media, (2) the different types of reports, (3) how to submit a self-initiated report about the different types of media content they noticed, (4) how to download and navigate the study app, and (5) how to identify each type of survey and corresponding submission details. The orientation sessions included built-in knowledge checks throughout to ensure that the participants fully comprehended the study protocol.

Figure 5. Representative screenshots containing participant instruction guide content.

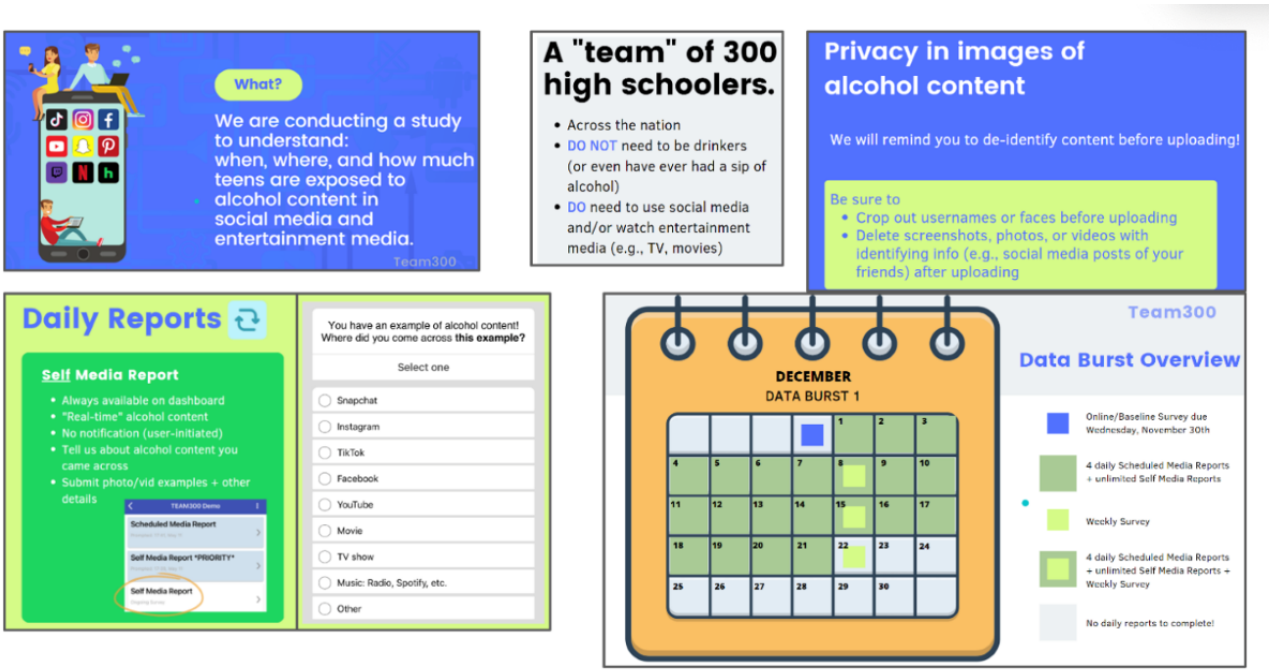

At the end of orientation, the RA assisted the participants in real time in downloading and logging into the EMA app, MetricWire (MetricWire, Inc), with their study-assigned (nonpersonal) emails and assisted in adjusting phone settings and permissions. Youth were instructed to keep their device with them at all times, except while at school and sleeping, and to ensure they were receiving notifications. They were also provided instructions to adjust notifications in MetricWire (eg,

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turn off or mute or silence notifications) if desired, such as while sleeping or during sports practice.

We asked the participants to keep their phone on and charged and not to change phone settings for the duration of the study. The participants were explicitly told that researchers were not taking any information from their phone or device, putting anything on their phone or device, or trying to change their behavior. We emphasized that the participants should not deviate from their normal activities to find alcohol content (Figure 6).

Figure 6. Representative screenshots containing orientation key reminders.

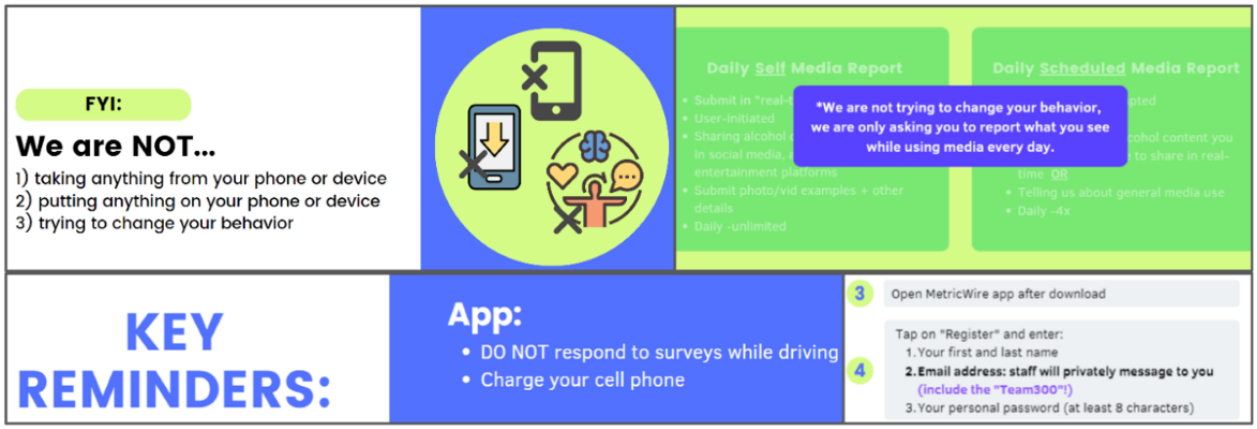

Smartphone use is highly prevalent in this age group and more evenly distributed across race, ethnicity, and household income levels than PCs (resulting in limited bias associated with access) [45]. Thus, we did not anticipate that participants would have any difficulty accessing the survey software. In focus groups conducted before this study [46,47] and in our YAB, we probed device ownership, text plans, and access to Wi-Fi as barriers to participation, and none of the participants indicated this as a concern. It is possible that potentially interested participants were dissuaded from enrolling upon learning that the study procedures involved frequent surveys administered on a smartphone; this might produce a small bias in our sample. We will assess this potential bias using a baseline survey item: “Do you have a data plan for your smartphone?” (response options: yes, unlimited data; yes, but limited data; and no, no data plan), along with indicators of disadvantage such as socioeconomic status, which is measured by free or reduced-cost lunch eligibility and parental education level. It is also worth noting that the digital divide may be less apparent in our study because surveys only require a few minutes of data per day. Following attendance of the orientation session, the participants were emailed a link to the Qualtrics baseline survey. This assessment was requested to be completed before the first day of EMA data collection and included a section where the participants were asked to rate their reasons for joining our study to use the participant’s rationale to personalize our reminder and outreach messages. (For any cohort that did not receive this section in the baseline survey, it was administered instead at their follow-up survey.)

Instructions for Reporting Alcohol Content

During orientation, the participants were provided with detailed and illustrated guidance on how to use the study app to report alcohol content that they observed. They were instructed to report each instance of alcohol content in media by initiating a survey continuously available on the study app’s dashboard.

To facilitate coding of alcohol content within the context of a movie, show, video, or song, we instructed the participants to enter a time stamp indicating exactly when the reference to alcohol occurred. When movies, shows, or videos had multiple references to alcohol, the participants were instructed to report on the most noticeable or important scene or example using a free-text entry item that accompanied the event-contingent report. For YouTube, we provided a field for the participants to paste a hyperlink, which could be used to obtain a static image. Finally, the participants were encouraged to submit a comment at the end of the report to describe additional scenes or any other notable information.

For participant reports of alcohol references in images, we similarly asked them to submit these images in event-contingent reports. We taught the participants how to deidentify an image by marking over or cropping out usernames or faces before submitting the image. We recommended that they delete any screenshots or photos with identifying information from their phone or gallery after submitting the report.

Before the start of EMA data collection, staff emailed the participants a participant instruction guide consisting of key reminders about participation rules and expectations (Figure 7). The participants were told that they could refer to this condensed guide at any point for clarification about study terms or survey details. Shortly before each subsequent data burst, staff again emailed the participants the link to the guide, encouraging them to review the information as a refresher of study protocols before starting the EMA portion again.

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Figure 7. Examples of participant instruction guide content.

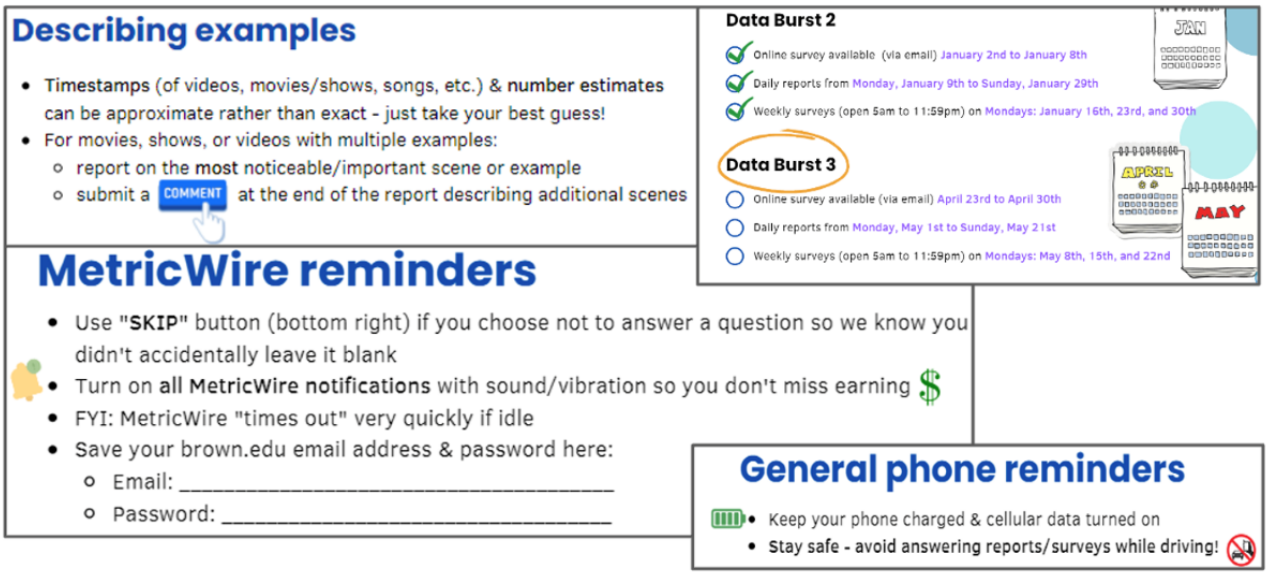

EMA Protocol

The first 3-week EMA phase began no more than 12 days after the orientation session. During this monitoring period, the participants completed 2 types of EMA reports on their own personal smartphone devices: scheduled reports (scheduled media reports) and self-initiated reports (self-media reports; Figure 8). The participants were prompted to complete scheduled reports during 4 intervals each day: 5 AM to 2 PM (morning), 2 PM to 5 PM (afternoon), 5 PM to 8 PM (evening), and 8 PM to 11 PM (night). These intervals were chosen to best align with adolescents' schedules, with the selection of a very early morning survey prompt informed by discussion with members of the YAB. The prompt for the morning report was delivered at 5 AM, and the survey stayed available on the app dashboard until 2 PM each day, with reminders issued at 8 AM and 12 PM if necessary. The participants were prompted to complete afternoon, evening, and night reports at random times within their respective time blocks. Access to each of those reports expired 1 hour after the initial notification.

Figure 8. Types of ecological momentary assessment reports, as explained to participants (as provided to participants in the instruction guide).

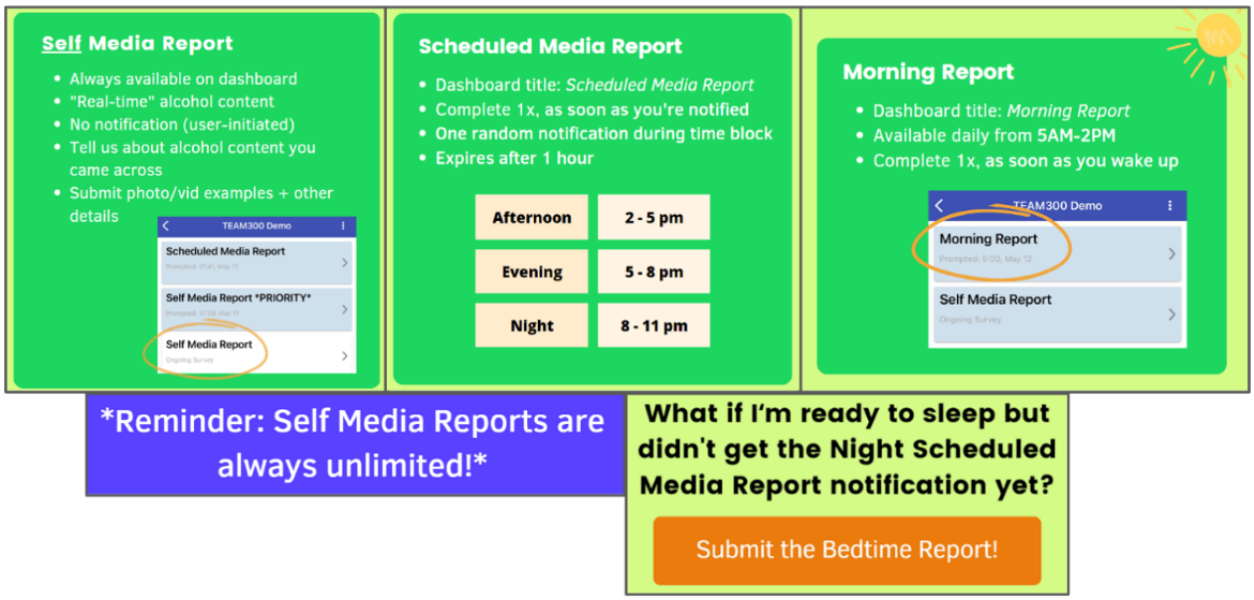

The participants could also complete a bedtime report, available from 8 PM to midnight, if they needed to go to sleep before receiving their prompt for the night report. These scheduled prompts assessed whether the participants had come across alcohol content in the media since their last submitted report. If the participants endorsed having any unreported alcohol content, they were asked whether it was one or multiple instances; for multiple exposures, they were instructed to think back on only the most recent instance of alcohol content when completing the subsequent set of questions. The participants who did not report encountering alcohol content were administered a set of general media questions that included

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self-reported media platform use and digital interactions unrelated to alcohol. This ensured that all the participants had the same opportunities to earn compensation based on survey compliance regardless of their daily alcohol content exposure.

Self-initiated media reports allowed youth to record exposure to media alcohol content in vivo. The participants initiated an assessment whenever they encountered an alcohol reference in the media. If the participants encountered >1 exposure in a time block, their first self-initiated media report fully assessed all alcohol media exposure content, including attitudes, cognitions, and context. Subsequent self-initiated media reports were abbreviated to reduce participant burden when submitting multiple exposures.

In all surveys, the participants were asked to share a screenshot, take a photo, type a text description, or include a link to a video. Images of alcohol content could be uploaded when submitting reports or taken within the app itself (videos uploads were also allowed). Youth were asked to describe the nature of the exposure, including the format or medium and source. They also indicated whether they reacted to the image (eg, like and comment). They also completed survey items assessing attitudes, cognitions (identification, liking, expectancies, and prototypes), and context related to the content. Abbreviated self-initiated media reports assessed only format or medium, source, and reaction. Measures and items are detailed in Table 1.

Table 1. Constructs assessed at the ecologic momentary assessment (EMA) report and weekly surveys.

	EMA (self-initiated or scheduled report)	Weekly
Exposure to alcohol-related content in media	• Platform or medium • Show, movie, or song name • Sponsored advertisement or marketing • Source of content • Character presence	• Frequency of exposure[a] • Platform or medium[a]
Engagement	• Like, emoji, comment, etc • Sharing of content	• Like, emoji, comment, etc[a]
Identification with character	• Want to be like the character, etc	—[b]
Prototypes (for content with characters)	• Character is popular, attractive, cool, immature, etc	—
Context	• Social context (alone or with others and in person or digitally interacting)	—
Exposure to other substance use content	• Cannabis use[c] • Cigarette smoking[c] • e-Cigarette use[c]	—
Attitudes	• I like or dislike content, disapprove or approve of content, etc	—
Perceived norms	• Teenagers their age like or dislike content, disapprove or approve of content, etc	• Descriptive norms (peer and close friend)[a]
Alcohol use	—	• Alcohol use, subjective effects, and problems[d] • Intention and willingness to drink[a] • Alcohol available or offered[a]
Substance use	—	• Cannabis use, cigarette smoking, and e-cigarette use • Willingness to use cannabis or e-cigarettes[a]
Affect	—	• Positive and negative affect[a]
Filler items	• Open-ended text	• Sleep[d] • Fun polls[a]

[a]Only assessed in the night or bedtime scheduled report.

[b]Not collected in this survey.

[c]Measured at the daily level via timeline follow-back.

[d]Measured at the weekly level.

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Weekly Surveys

At the end of each week during the EMA protocol, the participants received a link to complete an online survey (on days 8, 15, and 22 of each burst). Items assessed past-week exposure to alcohol content, perceived peer and friend norms about alcohol use, and affect. This was followed by a 7-day TLFB assessment, which captured daily alcohol and other substance use over the past week.

Follow-Up Surveys

Follow-up surveys were administered 1 week before each burst. These surveys were identical to the baseline, except they excluded stable sociodemographic information (eg, sex assigned at birth and race or ethnicity).

Retention Methods

Study personnel contacted the participants daily via text or email and as needed to check progress, encourage compliance, and address technical issues. In addition, we created study social media accounts and encouraged the participants to follow them as a means to promote engagement and a sense of study community. Posts included the results of weekly polls as well as other fun content. We also communicated with the participants in between data collection bursts, including text check-ins, emailing certificates of burst completion, and mailing study swag, and we implemented a weekly survey raffle to encourage compliance with the weekly survey. A companion paper describing techniques for and data on retention and compliance is currently being prepared for submission.

Ethical Considerations

Human Participant Protections

All procedures were approved by the Brown University institutional review board (protocol number 2009002813). Informed consent was obtained from the participants who were aged 18 years, and both parental consent and verbal assent was obtained for the participants who were younger than 18 years. Consenting materials were written at an 8th-grade reading level.

Methods to Maximize Confidentiality

We informed the participants during the orientation session that to protect data and prevent unauthorized access, study data were deidentified and stored in password-protected internal servers. We also encouraged the participants to ensure they enabled passwords to protect their phones and to exit out of the app and survey when complete. To protect against the risk that concerned parents might seek information from the study about their child, the consent and assent forms explained that we could not provide the parent with information that their child had given us.

Confidentiality of Image Content

Given that the participants could submit images that contained identifying information (eg, social media posts of friends), the participants were instructed to crop out usernames or faces and to cover or mark over faces and personal information. They were also told to delete screenshots or photos with identifying information from their phone and gallery after submitting the image.

Compensation

One of the keys to achieving high EMA response rates is designing compensation schedules that are linked to target response rates. The participants were coached to achieve a response rate of at least 3 reports (either prompted or self-initiated) per day. A complete day was defined as at least 1 report in 3 out of 4 time blocks (morning, afternoon, evening, and night or bedtime), and the participants were compensated US $5 per complete day. To encourage consistent responding, the participants could also earn a US $10 weekly bonus by having at least 6 complete days in a given week. In addition to EMA compensation, the participants could earn US $30 for completing both the baseline survey and the orientation session. They could also earn US $5 for each weekly survey completion and US $35 and US $40, respectively, for completing the first follow-up and second follow-up surveys. These incentives together meant that the participants could earn up to US $555 for participating. Level of compensation was commensurate to level of participant involvement and consistent with regional compensation norms for similar studies. All compensation was given in the form of Amazon e-gift cards. The compensation schedule was clearly delineated in the orientation materials and in the consent forms.

Measures

Overview

Tables 1 and 2 present an overview of study measures. Across all survey types, skip patterns, error checks, and validation features were built in to ensure high-quality data and minimize data entry errors. Items were programmed in MetricWire, which is a commercially available app with features that are appropriate for smartphone-based experience sampling and EMA research. MetricWire also allows the user to take photographs or videos from within the app and permits uploads of screenshots or saved photos from a user's phone.

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Table 2. Constructs assessed in the baseline and follow-up surveys.

Measure	Subscales or sample items	Source
Sociodemographic and academic factors	• Biological sex, gender, age, grade, racial and ethnic group, religious involvement, family household income, weight, and height • Academic performance (grade point average, missed classes, and hours studying) • Engagement	__[a]
Media use	• Media ownership and use, intensity of use (h/d), how social media makes them feel about themselves and others, and how social media makes them feel about alcohol content	Social media and technology survey
Exposure to alcohol content in the media	• Frequency of exposure to alcohol on each platform • Who posts alcohol content • Types of engagement with alcohol content • Personal alcohol posting behavior • Exposure to alcohol advertising	Pew Research Center [48], Wartella et al [49], and Roberts et al [50]
Media literacy	• Like content • Critical thinking about message source • Critical thinking about message content	Austin et al [51]
Online social identity	• Whether being a member of one's online social network is an important reflection of who they are	Pegg et al [52]
Parental monitoring of digital use	• Parental controls, check social media profiles and websites visited, take away privileges • Parents have talked with them about appropriate: online behavior toward others; content to share online; content to be viewing online; and content to be viewing, hearing, and reading in the media	Anderson [53]
Alcohol use	• Frequency of drinking and heavy drinking, typical number of drinks, subjective effects (high, drunk), availability of alcohol, age of initiation, first sip context, and shortened Rutgers Alcohol Problems Index	Adapted from National Institute on Alcohol Abuse and Alcoholism; Dawson [54], Rehm [55] and White and Labouvie [56]
Other substance use	• Frequency and types of cannabis, cigarettes, e-cigarettes, tobacco dependence, classes of illicit drugs, and (nonmedical) prescription drug use • Age of initiation for all substances used	Adapted from the National Youth Tobacco Survey [57] and Adolescent Brain Cognitive Development Study [58] and items adapted from Morean et al [59]
Peer norms	• Injunctive norms of close friends • Descriptive norms close friends and kids your age	Peer Passive Social Influence questionnaire and Wood et al [60,61]
Deviant peers	• My friends are very smart • My friends get into trouble with the police	Social development scale [58]
Peer orientation	• Willingness to sacrifice to be popular and have friends	Peer Orientation Scale [62]
Parental monitoring	• Knowledge of child activities (eg, Do your parents know what you do during your free time?)	9-item Parental Monitoring Questionnaire [63]
Affect	• Positive and negative affect	Positive and Negative Affect Schedule [64]
Anxiety	• Social anxiety	Adolescent Version of Social Anxiety Scale for Children [65]
Stress	• In the past month, please describe how often have you...felt that you were on top of things?	Perceived Stress Scale [66]
Life events	• Family moved; parents got divorced	Adverse Life Events and Resilience [67]

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Measure	Subscales or sample items	Source
Impulsive behavior	• Premeditation, sensation seeking, perseverance, and urgency (positive and negative)	UPPS-P Impulsive Behavior Scale [68]
Need for cognition	• I find satisfaction in deliberating hard and for long hours	Need for Cognition scale [69]
Motivation to seek out or approach fun activities	• I will often do things for no other reason than they might be fun	Behavioral Activation fun-seeking subscale [70]
Leisure boredom scale	• Leisure experience (awareness, boredom, challenge, and distress)	Leisure Boredom Scale [71]
Alcohol expectancies	• Affective, cognitive, and behavioral effects of alcohol use were assessed following the prompt: "How likely is it that the following would happen to someone your age if they had one or more alcoholic drinks?	Schell et al [72] and adapted from the Alcohol Expectancy Questionnaire—Adolescent
Drinking identity	• How much drinking plays a part in one's life (eg, drinking is a part of who I am)	Alcohol Self-Concept Scale [73]
Drinker prototypes	• How much does the word "POPULAR" describe your image of a typical high school student who chooses not to drink alcohol?	Adapted from a measure developed by Gerrard et al [74]
Explicit alcohol approach	• I would have liked to have a drink or two	Inclined/Indulgent subscale of Approach and Avoidance of Alcohol Questionnaire [75]
Family history of alcohol problems	• Did you ever wish that a parent would stop drinking?	6-item Children of Alcoholics Screening Test [76]

[a]Not applicable.

EMA Measures

For all reports of alcohol content in the media, the report first assessed the format or medium (all that apply): Snapchat, Instagram, TikTok, Facebook, YouTube, movie, TV show, music (eg, radio and Spotify), or other. For social media (Snapchat, Instagram, TikTok, and Facebook), we assessed who posted or shared the content, with the following response options: "sponsored ad/commercial that appeared," "company/brand I follow," "influencer/celebrity I follow," "friend or similar-aged family member I know well," "older friend or family member I know well," and "someone I know but not well." We also asked whether the content was posted publicly or privately and about who created the content, with the following response options: "same person who shared it," "company/brand I follow," "influencer/celebrity I follow," "friend or similar-aged family member I know well," "older friend or family member I know well," "someone I know but not well," and "someone I do not know/not sure." Participant engagement with the content was assessed, including "liked," "other reaction (eg, emoji)," "commented," "shared/posted publicly," "shared/posted privately," "saved it or added it to a list," "followed user/account or related group," "blocked or deleted the user/account," "clicked on an affiliated link," "discussed with someone else, in person," and "nothing (I kept scrolling)." If "shared/posted privately" was endorsed, we asked who they shared it with; response options were "close friend/best friend," "significant other (eg, boyfriend or girlfriend)," "friend/acquaintance," "peer (eg, classmate or coworker)," "adult family member," "sibling/cousin similar in age," and "other."

For music, we asked the participants the song name and artist in a text field. For YouTube videos, we asked the participants to enter the link (URL). We also asked whether the alcohol content was part of the YouTube video or in a sponsored ad/commercial that appeared before/during the video. Likewise, for movies and TV shows, we asked whether the alcohol content was part of the movie or show or in a sponsored ad/commercial that appeared. We also asked the participants to enter the name of the movie or show and time stamp (if known) in a text field.

For all types of content, we assessed whether there were people shown or described in the alcohol content. If there were multiple people, we asked the participant to think of the person who was most engaged with alcohol. If there were people shown, we asked who the person was with the following response options: "friend/peer," "celebrity/influencer," "somebody I did not know," and "other." We asked the participants to evaluate the person along 4 domains: I want to be like this person, I wish I could do what they do, I wish I could have as much fun as they have, and I felt like the person was similar to me; each item was rated on a scale from 1 (strongly disagree) to 7 (strongly agree). The participants rated their perceptions of the person's or character's (1) popularity, (2) attractiveness, (3) coolness, (4) immaturity, (5) confusion, and (6) self-centeredness (prototypes) [74] using a scale from 0 (not at all) to 3 (very). The participants reported on their own attitudes as well as beliefs about teenagers their age (perceived norms) with respect to the following domains: (1) content promotes or discourages alcohol drinking, (2) liking or disliking content, (3) disapproval or approval of the content, (4) content makes drinking seem better or worse than it really is, and (5) more or less likely to drink upon viewing

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content (response options: better, neutral, and worse). We also asked whether the creators of the content were intending to promote or discourage drinking.

We asked respondents whether they were with someone or others (in person) when they encountered the content and, if so, who it was: “alone,” “with a close friend or best friend,” “with a significant other (eg, boyfriend or girlfriend),” “with a friend or acquaintance,” “with a peer (classmate or coworker),” “with an adult family member,” and “with a sibling or cousin similar in age.” We also asked how many other people the respondent was digitally interacting with (such as texting, online messaging, video chat, etc) when they encountered the content and, if so, how many people (none, 1, 2 or 3, and ≥4). Finally, we asked whether the participant came across any examples of marijuana (weed and cannabis), e-cigarette use, or cigarette smoking that day (bedtime report only).

In total, the self-media report contained 32 items. The scheduled media reports contained 32 items if the participant endorsed encountering alcohol content. However, participants were shown only a subset of these items due to planned skip patterns (eg, if the participant endorsed YouTube, they were not shown the 6 items about other media types, and if the participant noted there were no people shown or described in the content, they were not shown the 3 items specific to people). The shortened versions of self-media reports contained 13 items, although again participants were only shown a subset of these items. If the participant did not endorse encountering alcohol content in the scheduled media report, they completed 6 items. Consequently, most reports took between 1 and 3 minutes.

Content Coding

Coding manuals were developed for both image and text submissions. We strove to make the coding systems similar to one another, as the participants were given the choice of whether to upload an image or to enter text for each digital media type (eg, taking a screenshot of a song or lyrics on Spotify and entering the name of the song or relevant lyrics into the text box). The participants were also provided an open-ended text box at the end of the survey where additional information could be entered (eg, describing a scene in a film for which a screenshot was provided). For the image coding, student coders underwent a rigorous training process to ensure interrater reliability and consensus. This involved 2 rounds of training with 10 coders (80 images) each. Interrater reliability of the training images was >90%. Codes with lower reliability (eg, social and sophistication) were redefined using advisory board input, and trainers were retrained. A companion paper describing the content coding process is currently being prepared for submission.

Weekly Measures

A 7-day TLFB assessment queried alcohol use, cigarette use, e-cigarette use, cannabis use, and sleep for each day, using an online TLFB [77]. We also assessed whether the participants experienced any of the following alcohol-related problems, which were a subset of items from the Rutgers Alcohol Problem Index [56]: hangover, nausea or vomiting, self-injury, driving after drinking, blackout, rude or aggressive behavior, and unwanted sex. Alcohol use and related consequences were assessed on a weekly rather than daily basis to separate the assessment of media alcohol content from the assessment of drinking behavior.

We assessed whether the participant had planned or intended to drink but did not, whether they were at a place where alcohol was available, and whether they were offered alcohol in the past week. We assessed willingness to drink alcohol, use marijuana or weed, and use an e-cigarette if offered by a friend or classmate using the following prompt: “If a friend or classmate offered you [substance], would you use it?” Response options ranged from 0 (definitely not) to 3 (definitely yes) [78]. We assessed descriptive norms for close friends (“How often do you think that your close friends drank alcohol in the past week?”) and peers (“How often do you think that the typical student in your grade drank alcohol in the past week?”); response options ranged from 0 (did not drink alcohol) to 4 (drank alcohol daily or nearly daily), adapted from a measure used by Wood et al [60] to reflect past-week use. Injunctive norms were assessed by asking how most of their close friends feel about kids drinking alcohol, getting drunk, using marijuana or weed, or using e-cigarettes; responses ranged from 1 (strongly disapprove) to 5 (strongly approve) [60]. We also assessed positive and negative affect (5 items each) using the Positive and Negative Affect Schedule [64]; responses ranged from 1 (very slightly or not at all) to 5 (extremely).

In addition, the participants reported whether they had seen any alcohol-related content in the past week (and if so, the media platform and whether they engaged with it), as well whether they came across any content that specifically referred to positive and negative consequences of drinking. Finally, we asked whether they had publicly or privately posted any text, images, or videos of alcohol in the past week.

Baseline and Follow-Up Survey Measures

At baseline and preceding each burst, a web-based survey assessed sociodemographics, media, alcohol consumption and related problems, other substance use, drinking context, and source of alcohol (Table 2 provides a list of all measures).

Data Management and Analysis Plan

The scheduled and self-initiated media reports were cleaned and merged by participant ID into a single database with all daily media reports. Coded image and text descriptions of media will be merged into the database when all coding is complete. The weekly survey provides variables for alcohol use at the level of the day (which can be merged with EMA data aggregated at the level of the day), at the level of the week (aggregated across 7 days), and at the level of the burst (aggregated across 21 days).

Models will include sex, age, and seasonality (dummy coded, summer as reference group) as controls. We will examine bivariate associations and test basic mean differences across subgroups and time with generalized linear models with the appropriate link function. Given concerns about spurious findings and replicability, primary analyses were planned a priori; secondary analytic analysis will be thoughtfully planned and based on a priori hypotheses. We will preregister analytic

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plans and hypotheses. We will control type 1 error by distinguishing primary and secondary measures, testing a priori hypothesized associations, and using ensemble-type tests.

To document adherence to the protocol, we will compute the proportion of reports completed overall, consistent with the broader literature [34,35]. We will also compute completion rates for each survey type (eg, morning and evening) and for each burst to identify trends (declines) in average compliance rates as the monitoring period progresses. We will calculate the proportion of reports completed each day and compute the number of participants who complete at least 1 report on a given day (which we anticipate will be high) as well as complete all reports in a day (which we expect to be moderate). We will also examine adherence with surveys required for compensation (≥3 completed surveys per day). Finally, we will examine the number of items completed and the amount of time (in min) from prompt signal to answering of prompt, consistent with recommendations in the field [79]. Inattention to survey content may be reflected by incomplete surveys or surveys completed excessively fast. We will examine correlates of noncompliance as a function of person-level characteristics (eg, gender and experience consuming alcohol) and within-person survey or day-level characteristics (eg, time of day [80]). We will test for a fatigue effect in reported exposure; if necessary, we will correct for this using inverse probability weights [31].

To quantify and characterize in vivo exposure to media alcohol content, proportions and means (SDs) will be computed to describe exposure frequency, duration, and format or medium. We will test group differences using parametric (correlations and regressions or general linear models) and nonparametric (chi-square) tests. We can also conduct latent class analysis to characterize different domains of media exposure. To examine differences between constructs at times of exposure versus nonexposure, we will compare event-level data versus random prompt data using multilevel models (MLMs), which account for clustering (events within person) and permit varying numbers of observations. Level 1 (L1) corresponds to within-person effects, including event-level and random assessments. Level 2 (L2) corresponds to between-person effects (eg, sex or L1 variables aggregated over time). L1 variables will be person centered, and L2 variables will be grand mean centered. Compositional effects are tested by aggregating the L1 variable. We will model bursts as a time-varying effect, as there are too few for a 3-level MLM.

To examine prospective associations between media alcohol content exposure and alcohol use, we will conduct MLM for short-term time frames. We will conduct cross-lagged panel models for longer-term time frames, including a 1-week time frame and a 4-month time frame. In the cross-lagged models, psychometric work will establish reliable latent variables for media exposure and alcohol involvement. We will control for key social influences on adolescent drinking, including close friend and peer norms about alcohol use and familial influences (eg, parental monitoring, parental communication and rules about alcohol use, and parental alcohol use), as assessed in weekly surveys and baseline and follow-up surveys.

To identify mechanisms of the association between media alcohol content exposure and drinking, we can test mediation by the putative mechanisms, predicting alcohol use at the burst level from event-level exposure. Mediation of event-level media exposure by an event-level mediator (eg, identification with the character) can be modeled. Alternately, mediation could be tested at the burst level, for example, by aggregating media content across the 21 days and using a mediator from a (preceding) follow-up survey. We will also control for relevant covariates, particularly when examining event-level prototypes and week-level social norms.

Analytic models will handle missing data under assumptions that data are missing at random using maximum likelihood estimation [81,82], including full information maximum likelihood, which is available in current software packages such as Mplus [83]. We will incorporate correlates of missingness to provide information for our model based on our findings from our examination of both person- and event-level correlates of noncompliance.

Results

This research received funding in September 2020. Following a qualitative phase of data collection, EMA data collection took place from February 2022 to August 2023. Data management is ongoing. Descriptive preliminary analyses are underway; however, hypothesis testing for the study aims has not yet begun. Preliminary data have been disseminated through conference presentations in 2024-2025 and manuscripts are currently ongoing with full results anticipated to be published in 2025 and 2026.

Discussion

Overview

This paper describes a fine-grained ecological protocol that addresses the fundamental question of how media alcohol content elevates underage drinking risk to optimally inform next steps in preventive media literacy intervention research. Existing media intervention programs are less equipped to handle new media, focusing on those in middle childhood and failing to engage adolescents (a group arguably at greatest need for intervention), and they do not target media as it is experienced in vivo on portable devices. By characterizing adolescents' real-world, in vivo exposure to alcohol content in the media, the study will generate essential insights to inform the development and implementation of digital interventions tailored for delivery via mobile devices.

Anticipated Findings

By querying exposure to alcohol content throughout the day, study findings will inform the nature of alcohol content, including platform (social media, YouTube, film, television, and music), source, and engagement. We expect to observe high rates of alcohol exposure in entertainment media and YouTube but anticipate that the degree of exposure in social media will vary as a function of source (eg, less alcohol content will be observed when the content is posted by same-age peers or friends relative to content posted by the alcohol industry or

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influencers). We also anticipate greater engagement when content is posted by peers or friends. Ancillary data from content-coded images and text descriptions will provide a highly rich representation of media content. At the same time, content coding of these data may prove to be challenging to do by hand and may necessitate artificial intelligence and machine learning approaches to fully capitalize on the data captured.

The study will assess youth appraisal of media content as it is encountered and thereby pinpoint momentary factors that may account for media's influence on drinking behavior. Cognitive mechanisms (expectancies and prototypes) are expected to vary as a function of exposure at a more proximal, momentary scale (and hence provide superior digital intervention targets) as compared to social mechanisms, which may require a cumulative or distal influence. Given the inherent limitations of conducting research in a constantly evolving area, such as entertainment and social media, there is value in shifting focus to the underlying mechanisms or processes (eg, targeting beliefs about alcohol content on a given platform rather than targeting time spent on that platform, given that the platform may change or be replaced over time). We attempted to keep abreast of recent advances in social media (eg, incorporating BeReal midway through the study), but it was difficult to do so in a systematic way.

The multiburst design permits testing of prospective bidirectional associations between exposure to media alcohol content and alcohol involvement across short- and longer-term time frames. Longitudinal data also will be used to test whether effects of exposure on alcohol cognitions, norms, and use are cumulative over platform and over time, consistent with the idea of a reinforcing effect of repeated exposure. The most effective approach to mitigating the influence of the media is to break the reciprocal cycle of media exposure leading to drinking, and vice versa, by reducing both the effects of media exposure on adolescent drinking and the extent to which at-risk adolescents seek out media content that normalizes and glamorizes alcohol use. Targeting constructs that are induced by in vivo media exposure at the time of exposure may be a highly effective strategy for breaking this cycle.

Next Steps

Although not described here, next steps are to conduct focus groups with a subset of the participants who completed the study to understand youth's lived experience of in vivo exposure to media alcohol content and to obtain their perceptions about the content, the effects of media exposure on them and their peers, and their reactions to proposed intervention targets. Both this study and the subsequent qualitative work will launch a program of research to counter the effects of alcohol-related media exposure as it is experienced in vivo by adolescents in an effort to minimize underage alcohol involvement.

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Data Availability

Data will be made available through the National Institute on Alcohol Abuse and Alcoholism Data Archive, a data repository housed within the National Institute of Mental Health Data Archive.

Authors' Contributions

Conceptualization: KJ (lead), JG (supporting), SC (supporting), TW (supporting), TJ (supporting)
Data curation: CD (lead), MR (equal)
Formal analysis: TJ (lead), MR (equal)
Funding acquisition: KJ
Investigation: CD
Methodology: KJ (lead), JG (supporting), SC (supporting), TW (supporting), TJ (supporting), CD (supporting)
Project administration: KJ (lead), CD (equal), JG (supporting), SC (supporting)
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Writing – original draft: KJ (lead), JG (supporting), SC (supporting), TW (supporting), CD (supporting)
Writing – review & editing: TJ (lead), MR (equal)

Conflicts of Interest

None declared.

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Abbreviations

EMA: ecological momentary assessment
MLM: multilevel model
RA: research assistant
TLFB: timeline follow-back
YAB: youth advisory board

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Protocol

Metastatic Breast Cancer mHealth App to Promote Patient-Provider Communication: Protocol for a Usability and Satisfaction Study

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Abstract

Background: With the availability of more advanced and effective treatments, life expectancy has improved among patients with metastatic breast cancer (MBC), but this makes communication with their medical oncologist more complex. Some patients struggle to learn about their therapeutic options and to understand and articulate their preferences. Mobile health (mHealth) apps can enhance patient-provider communication, playing a crucial role in the diagnosis, treatment, quality of life, and outcomes for patients living with MBC. Our team developed an app called My MBC Journey to focus on the collection of important information for patients with MBC between clinical encounters.

Objective: This study will evaluate the usability and satisfaction of My MBC Journey, a mobile app designed for MBC, to inform future modifications.

Methods: This mixed methods study will assess patient use and satisfaction with the My MBC Journey app to inform future app modifications and identify the barriers and facilitators to the app's use for enhancing patient-provider communication. We will recruit a prospective, cross-sectional convenience sample of 25 patients with MBC and a sample of 15 members of the care team (ie, caregivers, nurse navigators, and medical oncologists). Applying iterative, convergent mixed methods, we will conduct qualitative, semistructured interviews with the patients and care team members. We also will collect quantitative data on usability through app analytics and standardized questionnaires (ie, the Mobile Application Rating Scale, the Mobile Application Rating Scale user version, and the System Usability Scale). Qualitative interviews will be audio recorded and analyzed using NVivo software to identify mHealth implementation themes.

Results: The study's results will inform future app design modifications and gauge preliminary effect size in support of future evaluations of the app's efficacy in improving patient-provider communication.

Conclusions: Our long-term goal is to improve patient-provider communication by developing mHealth apps that empower patients to collect and share clinically relevant, patient-reported information in a timely manner.

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KEYWORDS

mHealth; breast cancer; patient-provider communication; usability study; mixed methods research; metastatic; mHealth app; patient-provider; communication; usability; protocol; mobile health; digital; technology; patient outcome; satisfaction; cross-sectional; semi-structured interview; design; modification

Introduction

Metastatic breast cancer (MBC) is late-stage breast cancer, where the disease has spread beyond the nearby lymph nodes to other sites such as the liver, lungs, bones, and brain [1,2]. Although men develop breast cancer, MBC most often affects women [3]. It is estimated that 168,000 women in the United States are living with MBC, and that number will likely grow to around 246,000 by 2030 [4,5]. Previously, treatment of MBC was nihilistic in nature, with a major goal of care being palliative. However, with the availability of more advanced and effective treatments, life expectancy has improved among patients with MBC, with over one third of patients now living 5 years beyond their diagnosis and some exceeding 15 years of survival [6,7].

Given the many therapeutic options now available, prolonging survival is a feasible goal for many individuals with MBC; however, it also makes communication with their medical oncologist more complex and essential to the treatment process [7]. Many patients struggle to identify and articulate their preferences for therapeutic options that may help them achieve their personal goals for living with cancer. Current guidelines from the National Comprehensive Care Network involve over 45 treatment regimens for MBC that include chemotherapy (single-agent or combination), hormonal therapy, and immunotherapy [8]. For patients receiving treatment beyond the recommended first-line therapies, the therapeutic combinations present many different toxicity considerations [9]. Beyond the number of potential therapeutic options, communication and decision-making between patients and their medical oncologists is increasingly complex due to competing medical comorbidities and acceptability of treatment toxicities. Patients want to participate in treatment conversations with their medical oncologists, but they often feel overwhelmed by the magnitude of treatment information and how it aligns with their personal goals [6,7]. Additionally, they may undervalue their own insights and are hesitant to ask questions about problematic side effects [6,7]. Patients also must balance the demands of their therapeutic program and its consequences with their health-related social needs, such as housing, food, transportation difficulties, and personal well-being [6,7,10].

Mobile health (mHealth) apps represent a potential tool to facilitate communication between the patient and the medical oncologist. These apps allow the patient to identify, record, and recall information about their well-being, personal goals, and toxicity preferences between clinical visits on their smartphone [11]. Given the high percentage of individuals with a mobile phone that they carry everywhere, the app could assist with recalling and sharing this information during the clinical encounter. Mobile apps also may reach a broader, more diverse patient population, including those who have historically experienced disparities in patient-centered care [11,12]. However, evidence on digital health interventions (DHIs) to improve patient provider communication is limited. A recent systematic review identified only 13 DHIs that targeted improvement of patient-provider communication in cancer care, with just 4 focused on breast cancer. None of these interventions involve delivery through a mHealth app [13]. Additionally, in 2023 we conducted a preliminary review of existing mHealth apps for breast cancer and identified only 1 for MBC that was available in the United States. Upon initial review, this app did not include functionality for a DHI focused on enhancing communication with the provider. In a subsequent review of this app in the fall of 2024, it was no longer available within the app store. With no apps available for patients with MBC in the United States, there is a clear need for continued, evidence-based development of mHealth apps for patients with MBC.

Our mHealth app, My MBC Journey, was designed to focus on the collection of important information to the patient with MBC between clinical encounters. Collection and organization of information important to the patient may help enhance self-efficacy and build confidence towards communication with the medical oncologist. To design an mHealth app for MBC, our team integrated evidence from qualitative interviews with a human change behavior theory to determine functionality that promotes a patient's understanding and communication about their health status. The development of My MBC Journey was based on social cognitive theory constructs of self-efficacy and self-regulation [14]. Besides providing the rationale behind the content and functions development process, it is possible to see social cognitive constructs associated with the design of specific resources, such as motivational and personalized messaging and alerts to help people manage their conditions [15,16]. Our app includes the following functionalities: 1) tracking physical, social, emotional, and functional well-being through patient reported outcomes (using the Functional Assessment of Cancer Therapy-Breast and European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer 23 instruments); 2) recording personal goals for activities of daily living and treatment preferences for symptom and side effect management; and 3) documenting details about problematic symptoms or side effects in a written, free-form manner. The app also can graphically display patient-reported outcomes (PROs) over the multiple dates where the patient has entered information, thereby demonstrating trends in improvement or decline. It also displays written free-form notes recorded over the same dates as the PROs on top of the graphical display of trends. This novel integration of trends in PROs displayed with the users' own comments on their health status may help the patient pinpoint how they are feeling at a specific time, thereby enabling more detailed recall and discussion of this information during the clinical encounter. Additionally, having the ability to log goals for activities of daily living and treatment preferences supports the patient in having this information readily available and may enhance their ability to

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discuss it during the clinical encounter. The app development process, including description of frameworks, screenshots, and functions, is described in depth in a forthcoming paper.

Effective use of mHealth apps as DHIs to improve patient-provider communication hinges on the end users' engagement with the app and willingness to enter information at a frequency that is clinically valuable. Therefore, as an initial step to app development, this study will evaluate usability and satisfaction with the mHealth app and its barriers and facilitators toward enhancing patient-provider communication. Our specific aims are to assess patient use and satisfaction with the My MBC Journey app to inform future app modifications and to identify the barriers and facilitators to the app's use for enhancing patient-provider communication.

Methods

Study Design

This study will use a prospective, convergent mixed methods design to assess the usability and satisfaction of an mHealth app for patients with MBC that was developed to promote patient-provider communication [17]. We will collect and integrate quantitative and qualitative outcomes on app use and satisfaction with functionality (aim 1). For Aim 2 we will use qualitative, personal interviews to identify barriers and facilitators of the app's use to determine how it may best be integrated into the clinical care setting to enhance patient-provider communication [18]. We will seek both the patients' and the care team members' perceptions. The results will inform modifications to our mobile app that will then be ready for future, iterative usability testing and eventual evaluation of the app's efficacy to enhance patient-provider communication (Figure 1).

Figure 1. Study design. MBC: metastatic breast cancer; mHealth: mobile health.

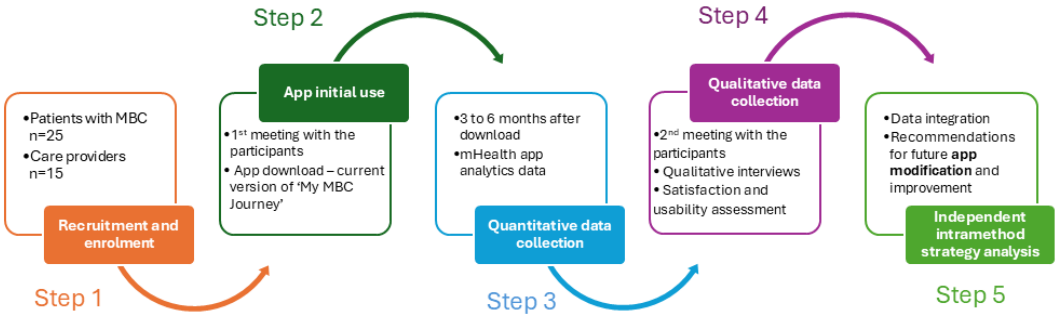

Participants and Recruitment

Patients with MBC and their care team members are eligible to participate in this study. Aim 1 will require a prospective, cross-sectional convenience sample of 25 participants with MBC. Aim 1's recruitment inclusion criteria are as follows: patients aged 19 years or older who are able to speak and read English, have clinically-documented MBC, possess a mobile device on which the mHealth app for MBC can be installed (Android or iOS operational systems), have a visit with their medical oncologist within the next 4 months, and are able to provide written informed consent. Exclusion criteria are participants who decide with their oncologist to enter hospice care. Similar criteria have been used in previous studies determining mobile apps' usability by patients with other diseases [19].

Aim 2 requires a prospective, cross-sectional convenience sample of care team members who provide oncologic care to the study participants recruited in aim 1. A sample of 15 care team members will be recruited. A breast cancer care team may consist of medical oncologists, nurse navigators, informal caregivers, radiation oncologists, psychiatrists, physiologists, nutritionists, social workers, and integrative therapists, among others [20]. In this study, eligible care members include medical oncologists, nurse navigators, and informal, patient caregivers because they are most likely to assist and engage with the patient during usage of the app, and hence, will experience how the apps' functionality potentially enhances or inhibits patient-provider communication at the point of care.

Our team will partner with the Buffet Cancer Center in Omaha, Nebraska, to register eligible participants over a 7-month period and follow them for at least 1 visit with their medical oncologist. Frequency of visits for patients with MBC is heterogenous, based upon disease severity such as whether it is in an acute or stable phase. Most patients within our setting see their medical oncologist every 3 to 6 months [19]. While this time window may cause different exposure length to the app, it is necessary to support collection of data regarding patients' perceptions about how the app functions to enhance patient-provider communication in aim 2. Potential patient participants will be informed of the study by their medical oncologist during a regular visit. The medical oncologist and research team will work to ensure diversity across clinical and demographic strata and mitigate sample bias to the extent possible. If the patient is willing to consider participation in the study, the oncologist will give the patient a flyer with written information that explains the study and provides contact information for further details. The contact, referred to hereafter as the study coordinator, will field inquiries (by phone call or text). For the participant who indicates a willingness to participate, the study coordinator will review the aspects of the study and obtain informed consent from the participant during the phone call or a web-based meeting. Once the participant provides informed consent by reviewing and electronically signing the consent form on

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Research Electronic Data Capture (REDCap) [21], the study coordinator will schedule a meeting to assist the participant in downloading and using the mobile app.

Care team members also will be recruited from within the Buffet Cancer Center. Medical oncologists and nurse navigators will be informed about the study through flyers posted within the cancer center and snowball recruitment. Informal caregivers will be recruited via nomination of a patient participant in the study, snowball recruitment, or through posted flyers of the study. Care team members may be part of a care team dyad but do not have to be part of that dyad to participate. For care team members who indicate a willingness to participate, the study coordinator will review the aspects of the study and obtain informed consent from the participant during the phone call or a web-based meeting. Once the care team member participant provides informed consent by reviewing and electronically signing the consent form on REDCap, the study coordinator will schedule a meeting to familiarize the care team member with the app and conduct a qualitative interview. Familiarization with the app will occur through demonstrating the major features of the app in a web-based testing environment. Additionally, care team members will be given time to navigate through the app at their own pace and ask questions about how the app works for the patient. During the same session, a study team member will conduct a qualitative interview.

Study Procedure (Data Collection of Outcomes)

Data collection of outcomes will occur in 2 ways: via the app and through in-person interviews (Table 1). Outcomes collected via the app include aggregated data analytics, such as how many times, on average, users went to a page and how long they spent on the page (aim 1a). During the in-person interviews, we will collect the qualitative outcomes and use the following standardized questionnaires to assess satisfaction and usability (aims 1b, 1c, 2a, 2b, and 2c): the Mobile Application Rating Scale (MARS) [22] with care team participants, the Mobile Application Rating Scale user version (uMARS) [23] with patient participants, and the System Usability Scale (SUS) [24,25] with both patients and care team members. The interviewer will provide an explanation about the standardized questionnaires used to measure satisfaction and usability, and they will be self-administered by the participants. Interview guide questions will be developed based on a matching integration strategy applied from a convergent mixed method research methodology [17] to gather more in-depth data about app use.

During the initial use of the app, the participant will provide the independent variables (questions about age, sex, race and ethnicity, education, marital status, income, health-related social needs, and whether they have ever used another health app); the study coordinator will be available to assist the participant as required. As participants use the app, we will obtain outcome measures for aim 1a. After the app use period is completed and the patients with MBC have a visit with the medical oncologist (approximately 4 months), our team will contact the participants (patient and care team member) to schedule the interviews and collect outcomes for aims 1b, 1c, 2a, 2b, and 2c, including, for example, completion of the standardized MARS, uMARS, and SUS questionnaires [22-25]. Interviews will be scheduled for 1 to 2 weeks following the patient's appointment with the oncologist depending on their availability. The care team members outcomes and independent variables (age, sex, and race and ethnicity) will also be collected during the interviews. Each interview will take up to 60 minutes, and with participant consent, will be audio recorded. The interviews will be conducted by a researcher with a clinical background and extensive experience in qualitative data collection and digital health evaluation. To avoid personal bias, the team member responsible for qualitative data collection will have no previous knowledge, contact, or work experience with the patients or care team members in any capacity.

The audio records will be transcribed using the support of NVivo software (Lumivero) for further analysis. Participants will receive a $30 gift card for participation.

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Table 1. Outcome measures.

Outcome	Source of data	Measures	When the outcome is collected
Aim 1: access patient use of the mHealth[a] app to inform future modifications using iterative, convergent mixed methods.			
1a. Identify the app functions used most often and to what extent	Quantitative data on mHealth app analytics	Events (number of times a page within the app was visited, amount of time participants remained there, and average views on a page per user) and duration (amount of time a patient-reported measure took to complete; assessed using the FACT-B[b] or EORTC QLQ-BR23[c])	As participants use the app after initial download.
1b. Assess patient perceptions of the app's aesthetics and content and their sustained engagement with the app	Qualitative personal interviews and quantitative survey questionnaires	Open-ended question prompts (10 items) and uMARS[d] (20 items)	Within 3 to 6 months after app download during a semistructured personal interview after a visit to a medical oncologist.
1c. Assess patients' satisfaction with the mobile app functionality	Qualitative personal interviews and quantitative survey questionnaires	Open-ended question prompts (10 items) and SUS[e] (10 items)	Within 3 to 6 months after app download during a semistructured personal interview after a visit to a medical oncologist.
Aim 2: assess the barriers and facilitators to app use for enhancing patient-provider communication.			
2a. Assess patient perceptions of app use to promote communication with their medical oncologist	Qualitative personal interviews	Open-ended question prompts (8 items)	Within 3 to 6 months after app download during a semistructured personal interview after a visit to a medical oncologist.
2b. Assess the care team members' perceptions of the app and ways in which it is useful to them in supporting the patient	Qualitative personal interviews	Open-ended question prompts (8 items)	Following interactions with the patients and app after download. Within 3 to 6 months after app download.
2c. Assess the care team members' satisfaction with functionality, their perceptions of the app's aesthetics and content, and their sustained engagement with the app	Quantitative survey questionnaires	MARS[f] (23 items) and SUS (10 items)	Within 3 to 6 months after app download.

[a]mHealth: mobile health.

[b]FACT-B: Functional Assessment of Cancer Therapy-Breast.

[c]EORTC QLQ-BR23: European Organization for the Research and Treatment of Cancer Quality of Life Questionnaire-Breast Cancer 23.

[d]uMARS: Mobile Application Rating Scale user version.

[e]SUS: System Usability Scale.

[f]MARS: Mobile Application Rating Scale.

Data Analysis

To analyze the outcomes related to the extent of the app's use (aim 1a) and the standardized questionnaires (aims 1b, 1c, and 2c), we will use descriptive statistics such as means, SDs, and tabulations. Specifically for the usability and satisfaction classification and rating, we will follow the recommendations for scoring of each instrument [22,23,25]. For the qualitative outcomes explored through the interviews, we will analyze the transcripts by applying content analysis [26] in 4 stages—decontextualization, recontextualization, categorization, and compilation—using the software NVivo. To avoid personal bias and to increase validity, after reviewing 2 transcripts, a codebook will be established independently by 2 researchers with expertise in qualitative analysis who will meet to garner consensus across the codebook and then apply it to a third transcript and discuss any further changes necessary. Upon project leader concordance with the codebook, the 2 investigators will analyze the remaining transcripts separately and then discuss their results to obtain consensus.

Our research team will apply the independent intramethod strategy from the convergent mixed methods design to analyze the outcomes of this mixed method study. With this strategy, the qualitative data analysis occurs independently of the quantitative data analysis, and then the findings from both are integrated to draw overarching interpretations and formulate recommendations for future mobile app modification [17] (Figure 1). Qualitative and quantitative data will be examined within a joint-display table to compare the similarities, differences, or contradictions [17]. Convergence of data between methods highlights areas for app modification or demonstrates that the app's development is satisfactory and usability testing is complete. In cases of discordance, both qualitative and quantitative data will be reanalyzed to resolve differences based

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on the social cognitive theory constructs used during app development and the usability and satisfaction objective quality items addressed in the MARS, uMARS, and SUS questionnaires.

Sample Size Consideration

Our feasibility test will apply the previously piloted methods to recruit 25 patients with MBC and a sample of 15 members of the care team (ie, caregivers, nurse navigators, and medical oncologists). This sample size is based on guidelines for behavioral treatment development research [27]. Our goal is to get reasonable estimates of the intervention's effect size for planning the needed sample size in future usability testing. Thus, we performed a power analysis in PASS 14 (NCSS Statistical Software) to calculate the CIs of the utility measure estimates.

The confidence level represents the proportion of CIs that would contain the population mean when constructed with the same parameters. A CI effectively measures estimation precision. Figure 2 shows the distance to the limit for sample sizes ranging from 5 to 40, demonstrating that increasing sample size enhances estimation. Distance from mean to limit refers to the distance between the confidence limits and the mean. For 2-sided intervals, this is also called precision, half-width, or margin of error. The target distance is the specified value entered into the procedure, while the actual distance is the value obtained. The population's SD measures its variability.

We calculated the sample size using the CI formula for 1 mean and generated numeric results for 2-sided CIs with an unknown SD. A sample size of 25 produces a 2-sided 95% CI with a distance from the mean to the limits of 0.41 when the estimated SD is 1 [28]. This sample size ensures that the actual distance to the limit is below the target distance, set at 0.5. The calculation also accounts for a 20% dropout rate. Figure 2 shows the distance to the limit for sample sizes ranging from 5 to 40, demonstrating that increasing the sample size enhances estimation.

For the care team members' sample, we selected to obtain a sample size of 15. This sample size should be sufficient to reach saturation of themes for barriers and facilitators of the app's functionality to inform app modifications for future useability testing for the care team as a whole. Future research will focus on cross comparisons between medical oncologists, nurse navigators, and informal caregivers.

Figure 2. Sample size determination based on the CI of the mean. CL: confidence level.

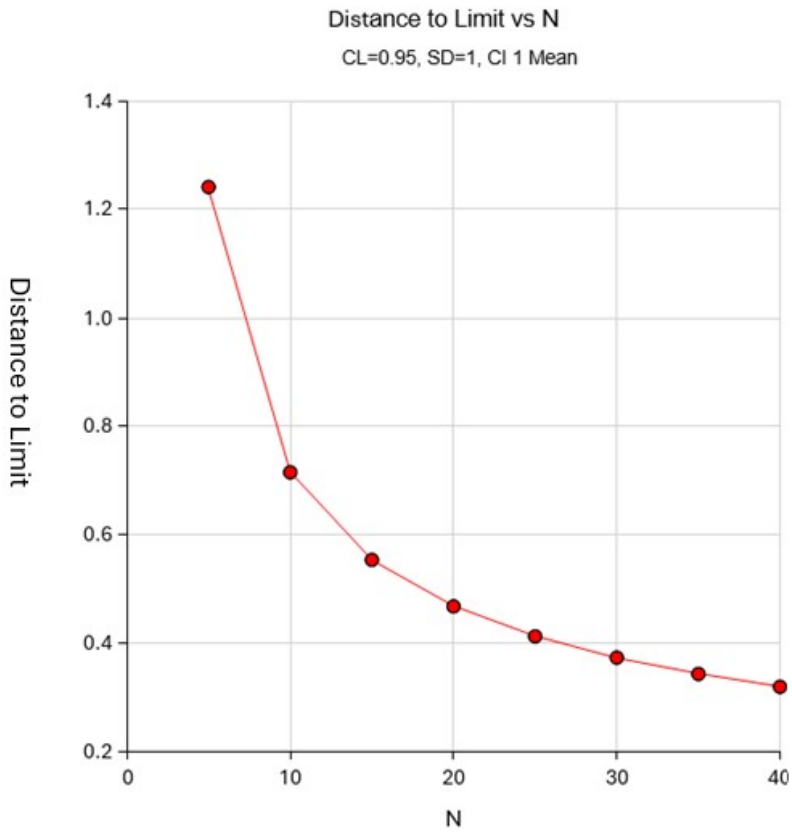

Data Management Plan

The data elements recorded through the mobile app will be stored in a secure, cloud-based server. The mobile app passes the data—identified only by the unique numeric identifier assigned to each participant—to a secure, cloud-based storage system that is accessible only by the study leads. All information in the secure cloud storage system is deidentified, as this study requires no names or personal identifiers of the participants to be collected. All interviews and other related data (such as the researcher's note) from the qualitative, semistructured interviews will be stored under the unique numeric participant identifier, allowing app-derived data and interview-derived data to be linkable. If the participant wishes to be compensated with the gift card, we will collect information on name and address solely for this purpose, and this list will not be linked to any of the data collected from the participant. We will keep the data for 7

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years in a secure shared folder accessible only to the study leads.

Ethical Considerations

The mobile app, My MBC Journey, was approved by the University of Nebraska Medical Center Information Technology security team for use. Our study is under review by the University of Nebraska Medical Center Institutional Review Board (#0791-23-EP). We will initiate the data collection process only after receiving IRB approval. We received financial support from the National Cancer Institute through an administrative supplement focused on digital health and patient-provider communication through a P30 grant awarded to Dr. Kenneth Cowan at the Fred and Pamela Buffet Cancer Center.

Results

We anticipate the enrolment of 40 participants (25 patients with MBC and 15 of their care team members). We expect to enroll the first participants by July 2026 and have 100% of planned enrolment recruited by July 2027. The target completion date of our primary endpoint data analysis is August 2027 and the results will be reported at ClinicalTrials.gov by March 3, 2028.

Discussion

Study Overview

Assessing the usability and satisfaction of the mHealth app, My MBC Journey, will allow us to identify future design modifications and assess the technology's efficacy through a randomized controlled trial. Our team's long-term goal is to improve patient-provider communication by developing mHealth apps that empower patients to collect and share clinically relevant, patient-reported information during the clinical visit. The iterative, convergent mixed methods design will provide us qualitative and quantitative data that, when integrated with outcomes from aims 1 and 2, will give us in-depth information on the perspectives of the patients and their care team members, which is essential to achieve better patient-provider communication.

This study is relevant because mobile app use may provide additional clinically relevant information related to patient self-monitoring and satisfaction, thereby activating them in their care and supporting more effective patient-provider communication. We anticipate that participants may also derive satisfaction from knowing their experience could help future patients and health care providers enhance communication. They may also derive satisfaction from helping create a mobile app to improve the quality of life and care for patients with MBC.

Methodological Limitations

This study will assess usability and satisfaction to track and design future modifications to the mHealth app, but we will not test the app's effectiveness at this point. Also, this version of the app is only for English speakers and those who can read, but we will seek diversity in the sample across important socioeconomic dimensions (eg, rural- and urban-residing participants). We understand that recruitment and retention of patients with this condition can be a challenge, and we will partner with oncologists to help enroll participants.

Methodological Strengths

We will conduct robust mixed methods research, applying the independent intramethod strategy [14] that is specifically designed and validated to evaluate the usability of mHealth apps. Standardized and internationally disseminated questionnaires help ensure the validity of the results, especially for the study's quantitative portion. Furthermore, our research team has expertise in qualitative analysis, which will allow us to approach the phenomenon and data integration in depth. The strong partnership between the investigators and the cancer center that is the study's setting is also a strength in that it can promote recruitment, enrollment, and participant retention. The results will allow us to improve our technology for use in an assessment of the app's efficacy in improving patient-provider communication through a randomized controlled trial as a next step.

Acknowledgments

The research team acknowledges funding support provided by the Fred and Pamela Buffett Cancer Center for the development of My MBC Journey. Funding was also provided by the National Cancer Institute through a P30 supplemental award. Additionally, the authors thank Grayston Stanton and Keegan Brown from NebDev, LLC for their information technology support in the deployment and maintenance of My MBC Journey.

Conflicts of Interest

MJC is the owner of Optimal Choice, a consulting business that develops digital health apps and health economics textbooks. RDH provides consulting services to Optimal Choice, LLC. RDH also is collaborating with MJC on the development of a mobile app for rheumatoid arthritis.

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Abbreviations

DHI: digital health intervention
MARS: Mobile Application Rating Scale
MBC: metastatic breast cancer
mHealth: mobile health
PRO: patient-reported outcome
REDCap: Research Electronic Data Capture
SUS: System Usability Scale
uMARS: Mobile Application Rating Scale user version

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Protocol

Crowdsourcing a Training Dataset of Question-and-Answer Pairs for AI-Enabled Health Information Tools on Sexually Transmitted Infections: Protocol for a Cross-Sectional Exploratory Survey Study

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Abstract

Background: Sexually transmitted infections are a significant public health concern, particularly in sub-Saharan Africa, where their prevalence remains high. Promoting awareness and reducing stigma are essential strategies for addressing this challenge, but those affected often have limited access to accurate and culturally appropriate health information. Therefore, innovative solutions are essential to enhance sexual health literacy and encourage informed health-seeking behaviors. Artificial intelligence (AI)–enabled tools, such as chatbots, have emerged as promising avenues for delivering accurate and accessible health information. However, their potential is constrained by the lack of contextualized datasets, which are crucial for ensuring their effectiveness and relevance to diverse populations.

Objective: This study aims to develop an open access, contextualized dataset of question-and-answer pairs on sexual health and sexually transmitted infections to support the development and training of digital and AI-enabled health information tools.

Methods: Using a crowdsourcing approach, questions are being collected from participants aged ≥15 years via online platforms, paper-based submissions, and in-person interactions at public events across sub-Saharan Africa. Each question will be anonymized and reviewed by medical professionals who will provide accurate, evidence-based answers. The dataset will then undergo processing, including cleaning and tagging for AI training, ensuring adherence to findability, accessibility, interoperability, and reusability principles. The final dataset will be published as open access.

Results: Data collection began on June 12, 2024, and is ongoing. The data collection process was piloted in Kigali, Rwanda, where 132 questions were collected. As of August 2025, the study had collected over 5620 question-and-answer pairs. The collected data are undergoing a simultaneous rigorous data processing phase in collaboration with health workers who provide evidence-based answers to the questions and new questions based on their experience in the clinic. The data cleaning and processing will enhance the utility of the data for AI applications.

Conclusions: The final dataset will be published as open access in 2025, contributing to the development of AI-driven health tools and promoting public health literacy.

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KEYWORDS

sexually transmitted infections; artificial intelligence; AI; health information; dataset; crowdsourcing

Introduction

Background

The burden of sexually transmitted infections (STIs) in sub-Saharan Africa (SSA) is high and increasing [1,2], accounting for approximately 40% of the global burden, with an incidence rate of 241 per 1000 among adults aged 15 to 49 years [3,4]. Challenges such as lack of awareness, stigma surrounding STIs, and poor access to medical care contribute to the high prevalence of STIs. As a key strategic action for primary prevention of STIs, the World Health Organization (WHO) recommends the provision of comprehensive, accurate, and culturally relevant information and education that promote sexual health and well-being [5]. Information, education, and counseling are effective approaches to improve health-seeking behavior in the context of STIs because people become better able to recognize the signs and symptoms of disease [6].

In recent years, internet access in Africa has been expanding rapidly due to improvements in infrastructure, including increased electricity availability, and the widespread adoption of digital technologies. The continent has seen significant growth in both internet connectivity and mobile phone use, creating opportunities for data-driven strategies and innovations [7]. This increasing access to the internet, combined with the rise of social media platforms, offers an opportunity to use these digital platforms to disseminate information about STIs on a large scale. With increased internet penetration, health care workers are more easily able to access technical STI resources [8], such as the Centers for Disease Control and Prevention, WHO, American Congress of Obstetricians and Gynecologists, and the Joint United Nations Programme on HIV/AIDS. When using the internet, the public, particularly adolescents and young adults, accesses STI information via social media platforms [9,10]. However, the information on these platforms may not be credible and may not have an adequate level of detail and risks, perpetuating myths and misconceptions about the subject [9,10].

Chatbots can understand and interact with human language through natural language processing, a branch of computer science and artificial intelligence (AI) that uses machine learning to help computers understand and communicate using human language [11]. There is emerging evidence that they are acceptable for use in public health. For example, a mixed methods study comprising interviews and surveys, conducted by Chang et al [12] in central Taiwan, found that users' attitudes and subjective norms were significantly and positively associated with their intentions to use medical chatbots. Their study pointed out that these conversational agents are viewed more favorably when they are perceived as reliable, and much clinical work is itself quite conversational. Their study also suggested that the use of chatbots was acceptable due to their accessibility and anonymity [12]. In addition, the study by Miles et al [13], conducted among adults in the United Kingdom, suggested that chatbot acceptability might be higher for stigmatized health issues. For illnesses that have a high level of perceived stigma, such as STIs, chatbots may offer greater anonymity than face-to-face consultations. This was highlighted by an increased willingness to disclose sensitive health information to chatbots in comparison to health care workers [13]. Research also shows that medical practitioners recommend chatbot use for the provision of medical information. In the United States, a study involving 100 general practitioners showed that more than half of the physicians (54%) agreed that health chatbots could help patients better manage their health and improve access to and timeliness of care [14].

Comparison With Prior Work

A review of 12 studies by Phiri and Munoriyarwa [15] emphasizes the opportunity that health chatbots present in Africa for making health information more accessible. Nonetheless, they and other authors frequently point to a common limitation that holds back this promise—not having enough quantity or quality of contextualized data to train the chatbots. Chatbots need to be trained with a knowledge base relevant to the subject area so that they can adequately respond to the queries of users. However, access to large datasets that have been adapted to the diverse linguistic, cultural, epidemiological, and socioeconomic realities of the African continent is a challenge [15,16]. DataKind UK [16] discusses the importance of "decolonizing" the data that AI is trained on so that it reflects the lived experiences of groups that are underrepresented in both the health and technology sectors. These datasets must include question and answer (Q&A) pairs that cover topics relevant to the potential users, accounting for factors such as local languages, including slang and colloquial expressions, particularly about sensitive subjects, such as sexual reproductive health (SRH). Generally, the terminology associated with sex and SRH tends to use population-specific words that change frequently and vary by age group, location, education level, and other social factors, with people often using it to discuss private or intimate matters, such as STIs. For example, male genitalia are generally referred to by different names such as penis, kettle [17], whopper [18], bazuka [19], etc in the south, east, and west African regions, respectively. The training datasets should also adapt to the users' varying educational levels and lived experiences.

The socioeconomic realities of the African continent mean that questions and advice on health care access may be different from higher-income settings. For example, in most resource-limited settings, STIs are treated through syndromic management. It is rare to undergo testing for individual STIs. Therefore, datasets must seek to give responses that balance what is on the ground in resource-limited settings as well as give information about best or newer practices that may exist elsewhere in high-income economies. This will ensure that the chatbots offer accessible, accurate, and empathetic responses.

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Rationale

To maximize applicability in the African setting, we propose crowdsourcing from populations across Africa. By using crowdsourcing, as recommended by Abhigna et al [20] and the Implementation Research and Innovation Support [21], this study ensures the inclusion of genuine, community-specific concerns, capturing the diverse linguistic and contextual nuances. Crowdsourcing is a shared computing method that taps into the collective knowledge and skills of people to solve problems that are difficult for computers but easily handled by humans, such as labeling data, speech recognition, and software development [22]. This approach has been found to be beneficial in AI because it enables the collection of large amounts of diverse data within a short period, which reduces bias and increases data richness [20,23].

While many datasets used by large language models or generative AI systems are not formally verified by medical professionals, the dataset we aim to construct will be carefully curated and validated by health care professionals to ensure its medical accuracy and reliability. This is crucial when dealing with sensitive topics, such as sexual health and STIs, where incorrect or misleading information could have serious consequences [24]. Crowdsourcing will allow us to gather authentic insights directly from the populations most affected [21], and by combining these crowdsourced data with expert validation, we ensure that the chatbot delivers accurate, medically sound information.

Study Objectives and End Points

Overall Aim

This study's general aim is to engage a wide range of people from across Africa to collect relevant context-specific questions about sexual health and use evidence-based medical knowledge to develop answers to the questions. Therefore, this will produce an open access, contextualized Q&A pair dataset on sexual health in English, which can be used to train AI-enabled health information tools.

Specific Objectives

The specific objectives of this study are as follows:

1. To collect at least 5000 contextualized English language questions on sexual health and STIs from the public through crowdsourcing via the internet and public events in SSA over a period of 6 months
2. To provide at least 2 accurate, evidence-based answer formats, based on the WHO guidelines, to each question collected on sexual health and STIs from the public in English in SSA
3. To process and curate the pairs into a training dataset for AI-enabled sexual health information tools
4. To provide the public with an open access, contextualized training dataset of Q&A pairs on sexual health and STIs in English

The dataset will be made available with a framework for adapting to different languages and contexts to be used in different geographic and sociodemographic settings across the continent.

Methods

Study Setting

This study will be conducted as part of a network activity for the Hub for Artificial Intelligence in Maternal, Sexual and Reproductive Health (HASH) [25]. As of January 2023, the HASH network is composed of 10 subgrantees from 7 African countries. These subgrantees are students, start-ups, and established organizations that won grants from HASH to research and develop AI innovations through a competitive request for applications. In total, 3 of these subgrantees are developing chatbots to relay information about sexual health, in particular STIs, in different settings in Ethiopia, Kenya, and Nigeria.

Study Design

This study is a cross-sectional exploratory survey.

Screening and Enrollment

There are various methods for recruiting participants in this study. Data collection will be done through crowdsourcing from members of the public, including but not limited to students, colleagues, and professionals aged ≥15 years from different locations and using different methods to ensure diversity in responses.

First, invitations for participants to contribute to crowdsourcing will be extended through advertisements via the internet media. The link to the online platform will be shared widely on the social media platforms of HASH and its partners and networks to attract as many participants and questions as possible.

Second, invitations will be extended through signposts and word of mouth at physical gatherings, such as relevant health or AI conferences, meetings, and other public events or locations. At physical public events or locations, a designated area with physicians will be set up for question collection and advertised by signposting and word of mouth. A link to the online platform will also be provided at the physical locations. For an informative and robust dataset, Q&A sessions from previously held SRH conferences will be added.

Participant Selection

The eligibility criteria designed to select participants for whom protocol treatment is considered appropriate are presented in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Must be aged ≥15 years
- Must be able to speak, write, and comprehend English
- Must be willing to give consent or assent for their questions on sexual health to be anonymously discussed, responded to, and shared publicly
- Must be willing and able to comply with the determined modes of crowdsourcing
- Evidence of personally signed informed consent or assent in the case of minors, indicating that the participant (or a legal representative) has been informed about all pertinent aspects of the study

Exclusion criteria

- People who are unable to read and write due to disability
- People with mental impairment or those experiencing serious health issues

The team will deploy various measures to ensure that only eligible participants will enroll in the study. First, data collection sites for physical recruitment will be at locations and gatherings where we are certain that there will be no participants aged <15 years and where the language of conduct is English (eg, academic conferences or English language workshops). Any non-English language questions were excluded from the dataset. In addition, while the link to the online platform was shared widely, even on forums that might include those outside our target population, the online consent form asked participants twice to confirm that they were aged >15 years.

There were no specific exclusion criteria or questions to determine the location and nationality of the contributor, as the recruitment strategies were designed to maximize African participation; however, if there was a small proportion of questions from non-African individuals, given that STIs are a global issue, we did not deem this to be a problem for the study.

Study Procedures

Overview

Participants will submit questions related to any aspect of sexual health, particularly STIs, through 3 modes: an online platform developed on Slido (Cisco) [26], a widely used tool that allows anonymous question submission and feedback; anonymous question submission on paper; or face-to-face interaction with a physician. A web link to the online platform will be shared with online communities for their submission.

At physical public events or locations, a designated area will be set up for question collection, and a link to the online platform will also be provided. A physician will be available to provide accurate answers to questions posed via the 3 modes. Figure 1 shows the Slido interface used for anonymous question submission and real-time interaction.

Figure 1. Slido interface.

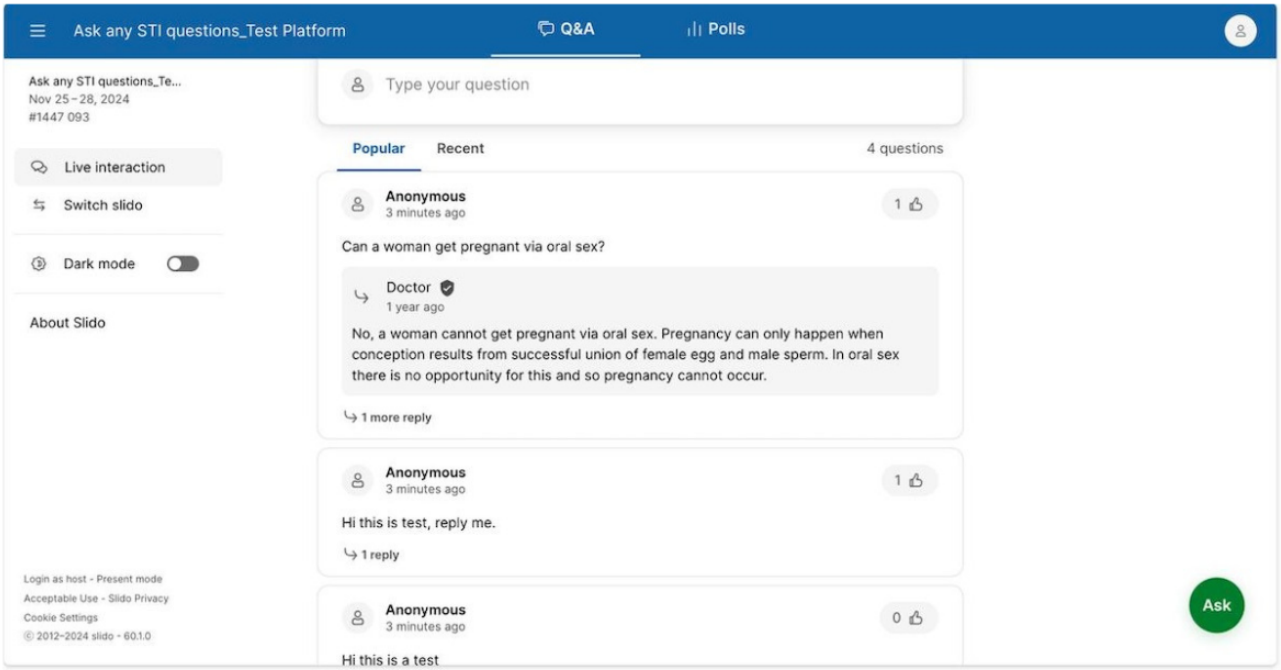

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Therefore, there will be no limit to the number of participants enrolled in the study to pose questions, how many questions a participant can pose, or the number of times a participant can engage to ask questions. All questions will be posed anonymously through the Slido platform, which ensures that the participants' identities are not captured when submitting questions. Slido will assign each participant "Anonymous" as their name, so their personal details remain confidential, creating an environment for open and honest participation. Figure 2 illustrates the study design.

Figure 2. Schematic of study design. Q&A: question and answer.

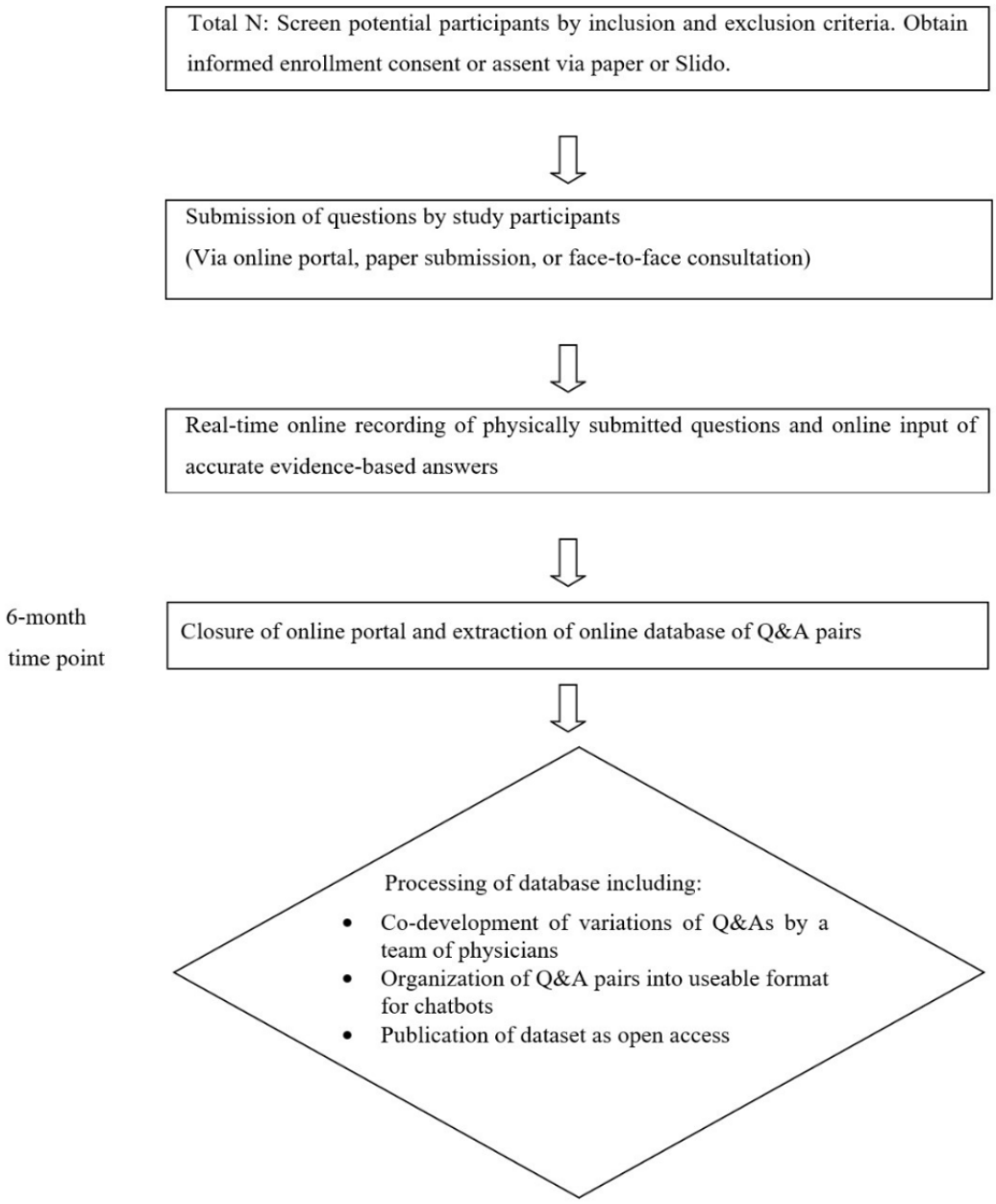

Study visits will be self-directed, allowing participants to engage with the data collection process at their convenience. After a participant provides informed consent or assent as the preliminary step, they are eligible to return as many times as they desire to their preferred data collection mode (ie, online platform, paper, or face-to-face consultation) to submit anonymous questions, check answers as provided by qualified health workers, or review other participants' anonymous Q&As. For centralization and consistency, all questions collected outside of the online platform will also be recorded on the platform. To promote health literacy, participants will be able to view Q&As submitted by them or other participants and contribute to discussions through "replies," which may stimulate further questions, enhancing learning. These "replies" are also an opportunity for clarification or to ask follow-up questions. This approach ensures that participants benefit not only from their own inquiries but also from the collective knowledge and experiences shared within the study.

There will be no follow-up of study participants, and all questions will be logged anonymously. From its launch, the online platform will be open to questions for 6 months. While participants will be able to interact with the online platform

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independently, there will be contact information on the platform and the informed consent and assent document through which participants can communicate with the study team in case of any challenges.

Withdrawal

Participants may withdraw from the study at any time at their own request, or they may be withdrawn at any time at the discretion of the investigator or sponsor for safety, behavioral reasons, or the inability of the participant to comply with the protocol-required procedures.

Because there are no follow-up visits, participant withdrawal will not necessitate an effort to contact the participant. The study team may retain and continue to use any data collected before such withdrawal of consent. However, should the participant wish to withdraw their question after submission, if they entered it directly onto the online platform, they are free to log back in and do so themselves. However, if their question was submitted on paper or through a face-to-face consultation, the participant should contact the study team and request withdrawal of their particular question.

Assessment of Safety

Safety monitoring for this study will focus on unanticipated problems involving risks to participants, including unanticipated problems that meet the definition of a serious adverse event.

Unanticipated Problems

Unanticipated problems involving risks to participants are defined as any incident, experience, or outcome that meets all the following criteria:

- Unexpected in terms of nature, severity, or frequency given the research procedures that are described in the protocol-related documents, such as the institutional review board (IRB)–approved research protocol and informed consent or assent document, and the characteristics of the participant population being studied
- Related or possibly related to participation in the research (possibly related means there is a reasonable possibility that the incident, experience, or outcome may have been caused by a procedure involved in the research)
- Suggests that the research places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized

Adverse Event Reporting

As this is an exploratory survey collecting anonymous questions about sexual health, we do not anticipate any adverse events.

Because this study does not test any investigational drug or intervention, and causality assessment is not applicable, any possible adverse events will also be reported to the IRB and the Uganda National Council of Science and Technology (UNCST) annually in aggregate.

The investigators will generate and submit annual reports summarizing these adverse events.

Data Processing

There will be no fixed participant sample size, but the study will aim to create a dataset of 5000 English Q&A pairs. There is no universally accepted minimum sample size for training AI models; AI training does not typically use conventional power calculations, but sample size adequacy in this context is contingent upon various criteria, including task complexity, label consistency, and model architecture. According to empirical studies in machine learning, larger, high-quality datasets improve model accuracy and generalization. The selection of 5000 questions will provide a diverse dataset and is feasible considering the time and resources of this study.

All submitted questions will be reviewed and answered collaboratively by a team of at least 3 health workers using evidence-based information from reputable medical sources, such as the WHO, Centers for Disease Control and Prevention, Medscape, and UpToDate, guaranteeing medical accuracy. For information that may be country specific, the physicians shall source responses from official governmental or nationally recognized documents. We will aim to recruit health workers from various cadres, such as physicians, reproductive health nurses, and counselors, as their different experiences and expertise can enrich the quality of the answers provided. Each answer will be deliberated and jointly agreed upon before being entered into the dataset. This study provides sexual health information in real time to participants as a service; therefore, any question posed will be documented and answered, either face-to-face or on the online platform. For purposes of the final dataset, where participants submitted questions that are only partially related to STIs, the data processing team will include broad themes, for example, “safe sex practices,” “myths and misconceptions,” and “education”; the physicians will answer partially related questions and include these in the final dataset. Responses will be provided in real time to the participants for those questions determined by the data processing team to be completely unrelated to STIs, and the questions will also be documented in our source documents, but they will not be included in the final dataset.

The health workers will also work closely with a data scientist to ensure that the dataset is suitable for training chatbots. For a chatbot developed using this dataset to have a wide range of understanding, it is necessary for its knowledge base to be as comprehensive as possible in terms of the various ways questions may be asked and the answers to those different variations. For example, the team will create some additional variations of question format, and for each question, there will be both short and long (more detailed) answers to support different questions that could be encountered by the chatbot. Hence, questions with the same meaning but different wording will be included.

When data collection is complete, the database of Q&A from the online portal will be extracted and processed into a training dataset that can be used for the development of AI-enabled information tools such as chatbots. This process will include labeling each data entry with relevant tags, called intents (eg, prevention, treatment, and symptoms), to facilitate easy retrieval of information. Each individual question with its relevant short

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answer and the same question with its relevant long answer will be considered as 2 Q&A pairs. All similar Q&A pairs will be grouped under one intent. The dataset will be in JSON format [27] to support interoperability with existing health IT systems via Fast Healthcare Interoperability Resources standard [28] and as recommended by the findability, accessibility, interoperability, and reusability (FAIR) data principles [29]. Data cleaning and annotation will also be done using OpenRefine to speed up these processes and ensure high-quality results.

Quality Control and Assurance

During the study, periodic monitoring will be conducted to ensure the study's adherence to the protocol and Good Clinical Practice (GCP) guidelines. In addition, the study site may be subject to independent audits and inspections by appropriate regulatory authorities, such as the IRB, from time to time.

Record Retention

The investigator has ultimate responsibility for the collection and reporting of all questions entered through the different data collection methods, that is, online, hard copy case report forms, and face-to-face consultations (source documents), and ensuring that they are accurate, authentic and original, attributable, complete, consistent, legible, timely (contemporaneous), enduring, and available when required. Any corrections to entries made in the source documents must be dated, initialized, and explained (if necessary) and should not obscure the original entry.

To enable evaluations and audits, the investigator agrees to keep records, including the identity of all participating patients (sufficient information to link records, eg, case report forms), all original signed informed consent or assent documents, copies of all safety reporting forms, source documents, detailed records of treatment disposition, and adequate documentation of relevant correspondence (eg, letters, meeting minutes, telephone calls, and reports).

Investigator records must be kept for as long as required by applicable local regulations (UNCST generally requires the records to be kept for a minimum of 5 years). When more than 1 requirement can be applied, records must be maintained for the longest period provided.

Protocol Deviations

A protocol deviation is any noncompliance with the clinical study protocol, GCP, or the manual of procedures requirements. Noncompliance may be on the part of the participant, investigator, or study staff. Because of deviations, corrective actions are to be developed by the study staff and implemented promptly.

All deviations from the protocol must be addressed in study participant source documents and promptly reported to the local IRB according to their requirements.

Ethical Considerations

Ethics approval has been obtained from the Infectious Diseases Institute Research Ethics Committee (2024-91) and the UNCST (HS5173ES). The study also obtained a waiver of parental consent for minors from the research ethics committee because even though the study posed minimal risk to participants, in the African cultural setting, parents may feel uncomfortable giving consent to their children being requested to ask questions regarding STIs. Therefore, participating minors will enroll with individual assent only.

This study will be conducted in accordance with legal and regulatory requirements as well as the general principles outlined in the International Ethical Guidelines for Biomedical Research Involving Human Participants [30] and the Declaration of Helsinki [31]. In addition, the study will be conducted as per the protocol, GCP guidelines, and applicable local regulatory requirements and laws. Participants will provide written informed consent or assent via online forms or hard copy forms. The record of consent or assent will be stored electronically for the online forms or via hard copy records for those participants who sign physically. All questions will be submitted anonymously, and parties will ensure the protection of participants' personal data and will not include participants' names on any forms, reports, publications, or disclosures, except where required legally. The informed consent or assent document used in this study and any changes made during the study will prospectively be approved by the IRB.

Participants will not receive any financial compensation for their participation, but they will benefit from receiving an accurate evidence-based answer to their question from a qualified health worker.

Data will be collected online, on paper, or through face-to-face consultations with physicians. Each participant will submit at least 1 question, and all questions will be recorded anonymously. Questions submitted via paper and face-to-face consultations will also be transcribed into the online platform for record purposes. Access to the online platform will be password protected and limited to only study staff with role-based access control (ie, admin, editor, and viewer) to ensure participant confidentiality and data integrity.

To protect privacy, both the online and physical consent forms advised study participants to carefully phrase their questions in a way that protected them and others. Where participants' questions contained personally identifiable information, the study team had moderation rights through the Slido platform to make edits to the questions to ensure anonymity. Hard copy consent or assent forms, handwritten questions, and any other source documents will be kept in locked cabinets. The online platform's database will be hosted in a secure cloud server owned by the Infectious Diseases Institute. Access to the database will be given to authorized personnel only (members of the immediate study team), and a log of authorized personnel will be stored in the trial master file.

Publication of Study Results

When the dataset is completed, in adherence to the FAIR principles [29], we shall use Harvard Dataverse to host the dataset. Harvard Dataverse is a free, self-service data repository open to all researchers from any discipline, both within and outside of the Harvard community, where researchers can share, archive, cite, access, and explore research data. Each Dataverse

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collection is a customizable collection of datasets (or a web-based repository) for organizing, managing, and showcasing datasets [32].

Results

Overview

Piloting of the process was done at the AfricAI conference in Kigali, Rwanda, held in 2023 [33]. The conference targeted participants from Africa's AI communities and ecosystems, but there are no specific demographic conference data. A QR code for Slido was generated and shared with participants at a booth and on fliers around the conference venue. Furthermore, the QR code was printed on small chocolates in the session rooms. These advertising efforts played a crucial role in raising awareness and expanding the reach of the pilot study, highlighting the value of sustained promotional strategies for maximizing participation. During this pilot, physicians were available on-site to answer questions in real time for those posing questions. The pilot study collected 132 questions from the conference over 3 days. Only 1 question was unclear and could not be answered. The physician responded on the online platform stating this. Another question was simply a greeting. All the remaining 130 questions were answered within 24 hours, and these were documented on the online portal. The question themes are categorized in Table 1.

Table 1. A table showing the categorization of questions collected through the pilot study (N=130).

Categorization of questions	Questions, n (%)
STI[a] transmission	19 (14.6)
STI signs and symptoms	13 (10.0)
STI testing and diagnosis	6 (4.6)
STI treatment	9 (6.9)
STI complications	1 (0.8)
STI prevention	1 (0.8)
Contraception	14 (10.8)
Relationship advice	21 (16.2)
Circumcision	2 (1.5)
Pregnancy	9 (6.9)
Menstruation	9 (6.9)
Morality	4 (3.1)
SRH[b] education	9 (6.9)
Vaccination	2 (1.5)
Other reproductive conditions	10 (7.7)
Menopause	1 (0.8)

[a]STI: sexually transmitted infection.

[b]SRH: sexual reproductive health.

Integration of Pilot Lessons and Current Progress

The pilot study revealed the need for a large, supportive team to actively engage with participants, answer questions promptly, and monitor the process. This team-based approach ensured that participants felt encouraged and supported throughout, and professionals could consult internally. The importance of real-time monitoring and support during data collection was also evident, as it enabled the resolution of any challenges encountered and ensured the smooth execution of the pilot study. Following the pilot study, full recruitment and data collection for this study began in June 2024 and will continue for 30 months. As of August 2025, the study had collected more than 5620 Q&A pairs (including the 132 questions from the pilot phase). The collected data are simultaneously undergoing a rigorous processing phase, which involves cleaning and tagging to facilitate their use in training AI tools. The data have been grouped into 8 STI areas comprising the common STI topics: general STIs, HIV, syphilis, gonorrhea, chlamydia, hepatitis B, trichomoniasis, and herpes simplex virus. The questions have been categorized into key themes, such as prevention, treatment, symptoms, and other subcategories, to enhance usability for AI-enabled health information systems. In total, 11 workshops have been held with health workers of various cadres, including physicians, nurses, counselors, and pharmacists, to develop accurate answers for each STI topic and category and add questions to the dataset based on their experience in the clinic.

Upon completion, the dataset will be hosted on the Harvard Dataverse open access repository [32], with publication planned for mid-2025. This effort aims to create a valuable resource for AI developers and public health initiatives, particularly in the African context.

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Discussion

Strengths

This study has several strengths that contribute to its innovation, reliability, and broader impact. It leverages an innovative crowdsourcing design to gather questions from a diverse and geographically dispersed participant pool, ensuring data diversity and relevance. This will allow the inclusion of real-world concerns, enhancing the cultural and contextual accuracy of the resulting dataset. The involvement of health workers of different cadres in the processing of the dataset will also ensure the medical accuracy of the answers to the questions collected. This aspect of collaborative expertise is a cornerstone of this study and will enhance the reliability and utility of the final dataset.

To maintain the accuracy and relevance over time, the dataset will undergo regular updates at least annually by a team of medical experts and a data scientist. Continuous feedback from participants and stakeholders will ensure that emerging topics and linguistic changes are also captured. This process will enable the dataset to evolve alongside medical knowledge and public health needs.

In addition, anonymity and privacy are emphasized, encouraging participants to share authentic and nuanced data on sensitive topics such as STIs without fear of judgment. The study will also publish its dataset as an open access resource, adhering to FAIR principles [29], which will support HASH subgrantees in their chatbot development and benefit the broader AI and public health community. Furthermore, this study offers a scalable model that can be adapted to other health domains or regions, leveraging the increasing internet penetration across Africa. Together, these strengths enhance the study's potential impact and utility.

Limitations

Despite its innovative approach, this study faces several limitations. Selection bias may arise as it excludes individuals without internet access, English literacy, or the confidence to ask questions about sexual health. In addition, this study does not have specific targets or sample size calculations for the different demographic groups. This could potentially limit the dataset's representativeness for marginalized populations and lead to overrepresentation of certain demographic groups. However, setting targets for each population group may also limit participation because there was no way to know how many questions could come from an individual or section of the population, and even then, some questions cut across population groups. Therefore, we chose to keep the data collection open and seek opportunities to collect data from different populations (eg, universities; conferences; and clinical settings, such as rural and urban health facilities) and then consider saturation (where no new questions are being received) as an indicator that we have collected most available questions. Finally, the regular updates that the study team will continually provide to the published dataset will also serve to incorporate any new questions that emerge later.

There is also a risk of misinterpretation as some questions may not fully capture the participants' intended concerns, leading to mismatched answers. This study's anonymous nature, while ensuring privacy, limits opportunities for clarification. Maintaining the sustainability of the dataset in the long run might require consistent funding and collaboration with public health organizations, which is an ongoing consideration.

The exclusive focus on English further narrows the scope, overlooking the unique concerns of non-English speakers. Although strides have been made recently, there remains a significant absence of datasets that are fine-tuned to the many forms of African speech and the continent's almost 2000 different languages. This is emphasized in studies by Javaid [23] and Ochieng and Awosiku [34]. The absence of such datasets in a key demographic region means that AI tools will perform comparatively poorly in this part of the world. This study aims to produce a training dataset for chatbots and other AI-enabled conversation agents. AI models require training before they can work, but this training requires a vast amount of data from multiple sources, including books, dictionaries, scientific papers, etc. At present, unfortunately, these resources are most commonly available in what are termed highly resourced languages, such as English, Chinese, French, etc. Most native African languages tend to be grouped under low-resourced languages, meaning they have relatively less data available for training AI models. However, the investigators are aware of the need to strengthen the presence of native African languages in the AI space.

The recruitment was done in Africa-based meetings or on African forums. While there may be non-African individuals accessing these events or online forums, due to the content of these forums, we can assume that they have significant knowledge of and interest in the African context. Therefore, their submitted questions would not introduce significant bias. Nonetheless, because of our emphasis on anonymity, this does remain an unintended weakness of our study.

Finally, the 6-month data collection window may not be sufficient to account for changes in public engagement over time, potentially affecting the comprehensiveness of the dataset. These limitations underscore areas for improvement in future iterations of the study.

Potential Risks and Benefits

Risks

Overall, this study is considered to have minimal risk of injury to participants. In addition, this study has been designed to provide multiple options for participants to ask questions, maintain privacy and anonymity, and minimize embarrassment and stigma.

However, there is a minor risk of unintended psychological triggers related to abuse, stigma, or trauma that may occur as participants engage with our study. We provide real-time answers from health workers, and these answers can provide guidance on where to seek help for health-related issues that a participant may be facing related to a particular question. If psychological distress is identified by the health worker, then this will be addressed, and the participant will be guided on where to seek help. We anticipate that through the informed consent process, participants who may experience psychological

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distress will assess their risk, and this will minimize enrollment of participants who may be triggered by the study. Where participants do eventually enroll, the option to withdraw at any time of psychological distress is made clear at the informed consent stage. However, this assessment of risk is left to the discretion of the participant should psychological distress occur. We also have a disclaimer in our online portal reminding participants of the option to seek medical advice in their local setting.

This dataset is designed to train a chatbot, but the content and the chatbot design must be contextualized to the local population it will be used with. This includes adaptation to local expressions and cultural nuances and review of questions for cultural sensitivity. Therefore, any chatbots using this dataset must be validated before use, and training with this dataset does not replace validation of any AI tools that are trained on it.

Benefits

The dataset on sexual health that will be developed through this study will be used to enrich the training data of the HASH subgrantees who are developing chatbots. This will enhance the ability of their chatbots to respond to various queries that will be presented during interaction with end users and therefore support these members of the HASH network in making their research successful.

In addition, because the dataset will be open access, it will be made available to all users who desire a training dataset for their AI-enabled information tools on sexual health. This will contribute toward solving a significant need for African AI developers, which is for large datasets. It will also contribute toward combating misinformation and improving public health literacy in Africa by increasing access to accurate medical information.

Finally, during the crowdsourcing process, participants will receive accurate medical answers to their questions and have access to other Q&As gathered through the crowdsourcing process. This will improve the knowledge of participants.

In constructing an English STI dataset, we are seeking to produce a dataset to support the development of AI tools based on the resources we currently have. However, the plan is that the HASH project will develop a framework so that this dataset can be contextualized for specific populations, including translation into other African languages and adaptation with cultural nuances and sensitivities for each group of target beneficiaries. We aim to have a Swahili version and at least 1 other language version of the dataset by early 2026.

Conclusions

This study represents a significant step toward developing accessible evidence-based health information tools, with the potential to increase literacy levels regarding STIs and improve health-seeking behaviors. The Q&A dataset from this study will enable the development of AI tools to address critical gaps in sexual health education, fostering informed decision-making. The open access nature of the dataset will encourage collaboration while providing a resource for researchers and developers worldwide.

The developed chatbots will need full contextualization, testing, and validation for the population they aim to serve. We also need to prioritize expanding linguistic diversity and accessibility of medical data, including evidence and guidelines, so that we can develop AI tools for underserved populations to ensure broader applicability and equity in health information dissemination.

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Authors' Contributions

Conceptualization: RP-R (lead), EO (supporting), and RLK (supporting)
Data curation: EO (lead) and HS (equal)
Formal analysis: HS (lead)
Funding acquisition: RP-R (lead)
Investigation: RP-R (lead), EO (equal), MB (equal), and HS (supporting)
Methodology: RP-R (lead) and EO (equal)
Project administration: EO (lead), HS (supporting), and CAK (supporting)
Resources: EO (lead) and CAK (equal)
Software: HS (lead) and CAK (equal)
Supervision: RP-R (lead), ABN (equal), and RLK (Supporting)
Validation: RP-R (lead) and ABN (equal)
Visualization: PKM (lead) and HS (equal)
Writing the original draft: EO (lead), RP-R (equal), PKM (equal), ABN (equal), and HS (supporting)

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Reviewing and editing the manuscript: EO (lead), PKM (equal), RP-R (equal), ABN (supporting), MB (supporting), RLK (supporting), CAK (supporting), and HS (supporting)

Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
FAIR: findability, accessibility, interoperability, and reusability
GCP: Good Clinical Practice
HASH: Hub for Artificial Intelligence in Maternal, Sexual and Reproductive Health
IRB: institutional review board
Q&A: question and answer
SRH: sexual reproductive health
SSA: sub-Saharan Africa
STI: sexually transmitted infection
UNCST: Uganda National Council of Science and Technology
WHO: World Health Organization

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Protocol

Association Between Household Livestock Ownership and Stunting in Children Younger Than 5 Years in Central Rural India: Protocol for a Case-Control Study

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Abstract

Background: In resource-constrained environments where malnutrition in children is common, people coexist closely with livestock. Undernutrition, which can result in stunting, wasting, and being underweight, is still a major public health issue for children in India. Livestock serves as a direct source of protein through animal-source foods such as meat, milk, and eggs, which significantly reduce undernutrition in children younger than 5 years. The association between livestock ownership and stunting in children has not been explored well in Maharashtra, India.

Objective: This study evaluates the relationship between stunting among children younger than 5 years in central India and livestock ownership by using the Tropical Livestock Unit (TLU) score.

Methods: A community-based, case-control study will be conducted for 12 months among 614 children aged 6-59 months in a few rural blocks of Wardha district, Maharashtra. A predesigned semistructured questionnaire will collect data from the informant (either parent). Anthropometric measurements will be plotted on World Health Organization (WHO) standard growth charts for *z* scores for stunting and wasting. TLU will be used to represent the livestock count of all species. The categorical variables (stunted and nonstunted) will be analyzed using the Fisher exact test to find significant associations between different risk factors. All confounding variables will be analyzed using multivariable logistic regression. Associated risks will be identified and tabulated using the odds ratio with confidence intervals.

Results: This study protocol will provide a comprehensive understanding of the associations of livestock ownership with childhood stunting and wasting among children aged 6-59 months in central rural India. This study will be conducted from October 2025 to September 2026. Currently, necessary approvals are obtained, and data collection is planned to begin from November 2025 to May 2026.

Conclusions: Our findings will show the prevalence of the current stunting, wasting, and underweight rates among Indian children younger than 5 years and the association of these rates with livestock ownership by using the TLU index. These results will be instrumental in building new public health policies, integrated programs, and nutritional interventions.

Trial Registration: Clinical Trials Registry – India CTRI/2024/05/066865; https://tinyurl.com/y3zvh5t7

International Registered Report Identifier (IRRID): PRR1-10.2196/66576

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KEYWORDS

stunting; wasting; livestock; tropical livestock unit; TLU; India; animal-source food; study protocol; case-control study

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Introduction

Stunting, which refers to low height/length for age, is usually a result of chronic undernutrition, often linked to poor socioeconomic conditions, maternal health, infant care, and children's nutrition. It restricts children from achieving maximum physical and cognitive capabilities [1]. In 2022, 149 million children younger than 5 years experienced stunted growth, which accounts for 22.3% of all children younger than 5 years globally [2]. More than a million child deaths are estimated annually due to stunting, which is defined as a height-for-age below minus 2 *z* scores of the median height-for-age in the World Health Organization (WHO) child growth standards [3]. Stunting and undernutrition continue to have a high prevalence globally.

In India, although there has been economic growth and significant decreases in child mortality rates, undernutrition and stunting are still prevalent [4]. For children, stunting, wasting, and underweight are crucial markers of their nutritional condition. Although wasting results from acute food scarcity and illness, stunting is due to recurring illnesses and long-term inadequate nutritional intake. Stunting has generally irreversible impacts on delayed motor development and decreased cognitive development. However, wasting is a major indicator of death and needs to be addressed right now. Underweight integrates weight for length/height and linear growth hindrance data [1].

One of the key priorities for the 2030 "Zero Hunger" Sustainable Development Goal is reducing stunting [5]. Stunting and wasting are also highlighted in the Global Hunger Index 2017 report, in which India ranked 100th [6]. The latest National Family Health Survey-5 (NFHS-5) was conducted in India from 2019 to 2021, which revealed that underweight, wasting, and stunting are common in Indian children younger than 5 years. The prevalence of underweight, wasting, and stunting according to NFHS-5 was 35.5%, 19.3%, and 32.1%, respectively [7]. This is undoubtedly lesser than that reported in the NFHS-4 study, which was performed between 2015 and 2016 [8]. The stunting and wasting rate for Maharashtra as per recent NFHS-5 (2019-2021) was 35.2% and 25.6%, respectively. As per NFHS-4 (2019-20) from the district fact sheet of Wardha, Maharashtra, the stunting rate for rural children younger than 5 years was 29.4%, and the wasting rate was 25.8% [9].

Agriculture, with its allied sectors such as animal husbandry and livestock production, is India's largest source of livelihood [10]. One integrated agricultural component that enhances household income, consumption, productivity, and food security is livestock [11]. Livestock provides protein directly through meat, milk, and eggs, known as animal-source food or indirectly by boosting the household income for food purchases [12]. Livestock ownership can improve the nutritional diversity and the quality of nutrition for households that own them, even though it may also raise the risk of environmental enteropathy, a condition linked to the loss of nutrients in the stomach, in children [13]. The Wardha district in Maharashtra is notable for its livestock and poultry farming, which is essential to the rural economy. According to the 20th livestock census, Wardha district recorded 489,836 animals, of which 344,875 are poultry and cattle units [14]. A few studies conducted in African nations have shown that owning more livestock can greatly boost the consumption of food items derived from animals and enhance nutritional outcomes [15,16]. Nonetheless, few studies [4,17] have been conducted in India to examine the relations between household livestock ownership and the stunting and nutritional status of children younger than 5 years. The tropical livestock unit (TLU), an index used in this study, is created by giving each animal a weight and merging all of the livestock characteristics for the household into a single variable [18]. Additionally, a dearth of studies [19] in Maharashtra examines the association between livestock ownership and stunting in children younger than 5 years. This study seeks to evaluate the relationship between stunting among children younger than 5 years in central rural India and livestock ownership by using the TLU index, considering existing research gaps.

Methods

Study Design, Participants, and Setting

This case-control study will be conducted in a community-based setting. It will be performed for 24 months in a few randomly selected villages from 8 rural blocks of Wardha district, located in central Maharashtra, by using a computerized method. Cases and controls will be proportionally allocated based on the number of children younger than 5 years and the stunting prevalence in each block. Permission for the interviews will be obtained from the authority/sarpanch of the respective villages. The list of children younger than 5 years of the selected blocks will be acquired from the respective Anganwadi Center of the village. For each case, 1 control will be recruited through simple random sampling. Informants will be briefed on the study's process and purpose. Participation will only be allowed after either parent gives written and informed consent. Data will be gathered using a semistructured questionnaire in English/Marathi via interviews. The questionnaire was developed and reviewed by field experts and will be validated through a pilot study (Multimedia Appendix 1). An infantometer/stadiometer will be used by the investigator to measure the length/height (in centimeters), and weighing scales will be used to measure the weight (in kilograms) of each child. The children's height and weight measurements will be compared to WHO 2006 standards based on age and gender to calculate the height-for-age *z* score and weight-for-height *z* score. Stunting and wasting are defined as falling below –2 SD of the WHO reference median. After plotting the measurements on the WHO growth charts, stunted and nonstunted children will be listed separately. All stunted children will be the cases in this study, and all nonstunted children will be the controls.

Ethical Considerations

This study received approval on January 31, 2024, from the Institutional Ethics Committee of Datta Meghe Institute of Higher Education and Research (DMIHER(DU)/IEC/2024/137) to ensure adherence to ethical guidelines, respect participant rights, and meet established standards. This study has been registered with the Clinical Trials Registry-India under registration CTRI/2024/05/066865. Participants will be provided with an informed consent form, clearly describing the study's

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aim, procedures, risks, benefits, and their right to opt out at any time. Consent for publication of data will be obtained and will be used for all analyses, including secondary analyses. We will confirm that the original consent and institutional review board approval explicitly cover the use of primary and secondary data. We ensure that the data collected will be fully anonymized, with no personally identifiable information retained or linked to any participant. As there are no interventions involved and as only a cross-sectional survey will be conducted in which the data will be collected via an interview and anthropometric measurements, participants will not be provided with any compensation in this study.

Inclusion and Exclusion Criteria

Cases will be defined as children who are stunted, reside in the study area, are aged 6 months to 5 years, with a mother or father as the caregiver, reside in a household with or without livestock, and are willing to participate and follow the requirements of the study. Controls will be defined as children who are not stunted, residents of the same study area, aged 6 months to 5 years, with a mother or father as the caregiver, who reside in a household with or without livestock, and are ready to participate and follow the requirements of the study. Children will be excluded from the study if they exhibit any obvious congenital defect, have a major medical condition, or need a prolonged hospital stay after birth. Those who have not lived in the Wardha district for at least the past 3 months and those presently involved in another study on animal husbandry will also be excluded.

Sample Size

The study will involve participants chosen based on specific inclusion and exclusion criteria. It will include all children younger than 5 years from the respective villages. Considering the overall number of children younger than 5 years in the Wardha rural area sample, the total population was 88,224 children [20].

Estimated sample size = n≥(NZ_(1-α⁄2)^2 p(1-p))/(d^2 (N-1)+Z_(1-α⁄2)^2 p(1-p)), where α (a)=.05; estimated proportion of children younger than 5 years who are stunted (height-for-age) *P*=.28 [9]; and estimation error (d) = 5% = 0.05. The minimal sample size calculated for this study will be 614, of which 307 are cases and 307 are controls, considering the ratio of case-control is 1:1.

Data Collection Tools and Methods

Villages from all 8 blocks of Wardha district will be randomly selected using a computer-based randomization method. A list of all children younger than 5 years will be collected from the Anganwadi Center of the respective villages. The children will be selected from the list according to the inclusion and exclusion criteria. The final list of the selected children of respective villages will be arranged according to the location and proximity of their homes, and the investigator will visit their homes for data collection and anthropometric measurements. Data will be collected using a semistructured questionnaire in English/Marathi. The questions will be asked to the informant (either of the parents). The questionnaire will contain questions related to the sociodemographic profile of the child, mother, and household; personal history of the child; livestock ownership; livestock management and disease; environment; and behavioral determinants such as Water, Sanitation, and Hygiene (WASH) (Multimedia Appendix 1). Following the interview, the child's height and weight will be measured. The digital weighing scale (Seca), pretested for accuracy, will be used to record weight with minimal clothing. Children up to the age of 2 years will have their length measured while lying on the horizontal measuring scale (Seca infantometer). Children older than 2 years will have their height measured with a stadiometer (Prestige). Height measurement will be conducted up to the nearest tenth of a centimeter. The child will have to stand on the scale barefoot, with heels together and shoulder blades, buttocks, and heels touching the vertical surface. The child's height will be measured by placing a headpiece on the top of their head while they are looking straight ahead and their arms are hanging naturally at their sides. To ensure anthropometric accuracy, the data collectors will undergo 3-day training and standardization sessions following WHO protocols. Technical errors of measurement will be calculated before the study and will be monitored periodically. There will also be regular supervisory visits, which will ensure consistency and interrater reliability. To reduce recall and selection biases, there will be validation assessments utilizing anthropometric data and health records. Moreover, data triangulation will be utilized by combining interviews, focus groups, and observations from the community.

To calculate the total number of livestock, a standardized unit must be used to represent the livestock counts for all species. A TLU is a standard unit that allows for the comparison of various species of varying sizes by using a common measure. Conversion equivalents of livestock into TLU are mentioned in Table 1 for households with livestock ownership [21].

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Table 1. Conversion equivalents of livestock into Tropical Livestock Unit [16].

Species (animal type)	Tropical Livestock Unit equivalent
Cattle (bull)	1.0
Cattle (cow/buffalo)	0.8
Cattle (calves)	0.2
Sheep/goats	0.1
Horses	0.8
Donkeys/mules	0.5
Poultry	0.01

Data Analysis

All the results will be calculated using RStudio software (version 4.3.2; Posit). The complete analysis dataset will consist of all study participants who have no missing data for any of the variables in the dataset. The study participants will be those individuals who meet the criteria for inclusion and exclusion. Baseline characteristics will be utilized to compile all the data, representing demographic variables with mean and standard deviation for continuous data and frequency and percentage for categorical data. The results will be examined for continuous data, which will be described using the minimum, maximum, average, standard deviation, standard error, and 95% CI for parametric data. The normality of the continuous outcome variables will be assessed initially with the Kolmogorov-Smirnov test at a 5% significance level ($P \leq .05$). If the data are not rejected, a nonparametric test will be used to determine significance; otherwise, it will be considered normal. The significant difference at the 5% level ($P \leq .05$) between stunted and nonstunted comparative groups will be determined using a 2-sided *t* test. Nonnormal data will be summarized using mean, median, and lower and upper quartiles for nonparametric testing and will be assessed for significance using the Mann-Whitney test. Categorical variables will be presented with frequency (n) and percentage value (%). The categorical variables (stunted and nonstunted) will be analyzed by Fisher exact test to find significant associations of different risk factors. All confounding variables will be analyzed using multivariable logistic regression. Associated risks will be investigated and tabulated using the odds ratio with a confidence interval. To understand the effects of multiple factors, confounding variables will be recognized and adjusted to understand the multiple factors that can influence the outcome (stunting). For the confounding effect, multivariable methods will be employed to estimate the association between exposure (livestock) and outcome (stunting), or the impact of one or more confounding factors such as WASH; wealth index of the household; episodes of illness; dietary habits; knowledge, attitude, and practices regarding livestock; and livestock diseases will be considered. Essentially, multivariable logistic regression will allow assessing the independent effect of each of the exposures.

Results

This study is expected to provide insights into whether there is an association between household livestock ownership (measured by TLU index) and the prevalence of childhood stunting and wasting in central rural India. This study will be conducted from October 2025 to September 2026. Currently, necessary approvals are obtained, and data collection is planned to begin from November 2025 to May 2026.

Discussion

Overview

The research aim of this study is to determine the association between stunting among children younger than 5 years and household livestock ownership in rural areas of central India, and if a one-health approach can contribute to and address this association.

According to Hossain and Khan [22], owning cattle in Bangladesh is substantially associated with a lower incidence of stunting. The beneficial impact of owning a domestic animal on the decrease in stunting in children implies that apart from nutritional interventions in Bangladesh, enhancing livestock output could also aid in enhancing the nutritional condition of children. To maximize the effect, integrated programs, including agricultural production and WASH, are needed. A small effect size may be owing to the lack of dietary diversity, livestock health, and productivity data as well as the complexity of the relationship, requiring further studies [22].

Another study by Gelli et al [23] showed that the size of the chicken flock, poultry husbandry, and household hygiene standards were all correlated with the occurrence of chicken feces. Higher height-for-age *z* scores were linked to improved water sources and more visibly clean children. Lower weight-for-height *z* scores were linked to the presence of chicken feces; no correlations were detected with the height-for-age *z* scores. They also concluded that increasing poultry production in environments where children and poultry coexist may raise nutrition-related risks for young children, and more livestock-focused WASH programs may act as a significant barrier to stopping the spread of pathogens from livestock to humans [23].

A systematic review by Muema et al [24] suggested that depending on the type of intervention and length of program/intervention implementation, different livestock interventions have different effects on stunting, wasting, and underweight. Hence, due to the heterogeneity in reporting metrics, they were unable to compute the pool estimates. They

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further suggested that more randomized controlled trials with uniform and comparable reporting criteria are therefore required to strengthen the body of information regarding the effects of nutrition-sensitive livestock interventions on child development outcomes because the quality of the available data is low. They concluded that improving dietary diversity was a result of nutrition-sensitive livestock interventions, which increased the consumption of animal-source food [24].

Mosites et al [25] incorporated monthly anthropometric measurements for children younger than 5 years into an ongoing linked human and animal surveillance cohort in Western Kenya. Using linear mixed models, they tested whether baseline household livestock ownership was related to baseline child height-for-age or prospective growth rate. This study did not find a relationship between owning higher numbers of household livestock and child baseline anthropometric measures or subsequent child linear growth outcomes. However, there was an indication that livestock disease was associated with some measures of diminished growth [25].

Limitations

Potential limitations that can impact the validity and reliability of the findings are as follows. Selection bias, the method of selecting cases and controls, may not accurately reflect the general population, leading to possible bias in the findings. Recall bias can be another limitation in this study, as this study will rely on the informant's recollection of livestock ownership and child health history. Failure to consider the confounding factors can misrepresent the true association, adding to the limitations. Inaccuracies in anthropometry measurements of children can affect the study findings. Our findings will be from a specific region in central rural India, which may not be generalized to other regions with different cultural, environmental, and economic settings.

Conclusions

There is a lack of studies in Maharashtra, India, which examine the relationship between livestock ownership and stunting in children younger than 5 years. Considering existing research gaps, this study aims to assess the relationship between stunting among children younger than 5 years in central rural India and livestock ownership by using the TLU index. It will determine the prevalence of the current stunting, wasting, and underweight among Indian children younger than 5 years. This study will offer insight into the correlations between stunting, wasting, and livestock ownership. This association will guide policymakers and program designers about the potential strategies to reduce stunting, such as promoting livestock ownership and ensuring that it provides nutritional benefits for children. This will be crucial in developing new public health policies, integrated programs, and nutritional interventions. It will also offer insights into how household resources (like livestock) are allocated and their impact on child nutrition and health, contributing to broader discussions about rural livelihoods and child development, particularly in a resource-constrained rural settings where understanding the determinants of child health is critical for developing effective interventions. It will help to generate hypotheses about the pathways through which livestock ownership might influence stunting, which can then be tested in future research such as cohort or interventional studies.

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Authors' Contributions

Conceptualization: PPT
Data curation: PPT
Formal analysis: PPT
Investigation: PPT, AG
Methodology: PPT, ZQ
Project administration: PPT, ZQ, AG, SC
Resources: PPT, AG
Supervision: ZQ, AG, SC
Validation: ZQ, AG, SC
Visualization: PPT, ZQ, AG, SC
Writing – original draft: PPT, ZQ, AG, SC
Writing – review & editing: PPT, ZQ, AG, SC

Conflicts of Interest

None declared.

Multimedia Appendix 1
Study questionnaire.
[DOCX File , 50 KB - resprot_v14i1e66576_app1.docx]

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Abbreviations

NFHS-5: National Family Health Survey
TLU: Tropical Livestock Unit
WASH: Water, Sanitation, and Hygiene
WHO: World Health Organization

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Protocol

Measuring 24-hour Movement Profiles During Pregnancy: Protocol for the 24MOVE Prospective Cohort Study

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Abstract

Background: Physical activity (PA) during the waking period and sleep during pregnancy may mitigate the increased risk for adverse pregnancy outcomes posed by gestational diabetes mellitus (GDM) and excessive gestational weight gain (GWG) in pregnant individuals with pre-pregnancy overweight and obesity. Recent studies have conceptualized PA, sedentary behavior, and sleep as part of a 24-hour movement framework; however, there is a gap in the knowledge about the relationship between 24-hour movement and pregnancy outcomes.

Objective: This paper describes the study protocol for the 24MOVE study, a prospective cohort study that examines associations between 24-hour movement profiles across pregnancy and maternal glucose tolerance, GWG, and infant birthweight.

Methods: Participants (N=306) were recruited from a large, integrated health care delivery system at 10 weeks' gestation. In early (10-12 weeks), mid- (20-22 weeks), and late (33-35 weeks) pregnancy, all eligible individuals with a pre-pregnancy BMI of ≥25 kg/m2 completed online surveys collecting information about sociodemographic characteristics and pregnancy symptoms and behaviors, including sleep quality. Participants concurrently wore a research-grade accelerometer for 24 hours per day for 7 consecutive days to capture movement, sedentary behavior, and sleep data. Data from accelerometry will be processed to create 24-hour movement profiles. Pregnancy outcomes will be ascertained from electronic health records (EHRs). We will use compositional data analysis (CoDA) methods, modeling associations of reallocations of time from one component behavior to another at various timepoints with outcomes.

Results: Recruitment began on March 19, 2023, and ended on September 11, 2024. Enrollment was completed on September 19, 2024. Data collection was completed in April 2025. Over an 18-month recruitment period, 2035 individuals were invited to participate, and of those, 306 (15%) eligible participants were enrolled in this study. The enrolled cohort had a median age of 33 (quintile 1 [Q1]-quintile 3 [Q3] 30-36) years and a median BMI of 28.8 (Q1-Q3 26.9-32.7) kg/m². Most participants had private insurance (n=266, 86.9%) and were multiparous (n=232, 75.8%). Analyses are in progress.

Conclusions: The 24MOVE study is designed to address gaps in our knowledge of the impact of 24-hour movement during pregnancy on maternal glucose metabolism, GWG, and other risk factors for childhood obesity, such as a high birthweight. Data from this study will also serve as a rich resource for future investigations of 24-hour movement profiles and behavior substitutions and other perinatal mental and physical health outcomes.

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KEYWORDS

24-hour movement; physical activity; sleep; pregnancy; sedentary behavior; obesity; gestational diabetes; maternal glucose tolerance; adverse pregnancy outcomes; infant birthweight

Introduction

A high maternal pre-pregnancy BMI, gestational diabetes mellitus (GDM), and excessive gestational weight gain (GWG; value above the Institute of Medicine recommendations [1]) are prevalent pregnancy conditions that contribute to an in utero environment of overnutrition, leading to significant short- and long-term health ramifications for pregnant people and their children, including increased risks for obesity and diabetes [2-11]. Pregnant individuals with both obesity and excessive GWG have the highest risks of adverse pregnancy outcomes [12], and their children are also at greater risk of childhood obesity [13-15] and a greater BMI [16] in adulthood compared to children exposed to a normal weight and GWG within recommendations in utero.

Physical activity (PA) during the waking period and sleep during pregnancy may mitigate the increased risk for adverse pregnancy and health outcomes posed by GDM and excessive GWG in pregnant individuals with a high pre-pregnancy BMI. When studied as individual behaviors, regular moderate- to vigorous-intensity PA during pregnancy, light-intensity PA, less sedentary behavior, and adequate sleep are associated with pregnancy-specific health benefits [17], including lowering the risk of GDM [18-25], abnormal glucose tolerance [26-29], and excessive GWG [30-36]. Moderate-to vigorous-intensity PA is also associated with a lower risk of large for gestational age (LGA) birthweight [37]. In addition, emerging evidence suggests that sleep regularity, including consistent timing of sleep and wake periods, may be important for optimal health outcomes in adults [38].

Given that PA, sedentary behavior, and sleep are interrelated behaviors in the context of a 24-hour day, recent studies have conceptualized these behaviors as part of a 24-hour movement framework [39,40]. Informed by associations of 24-hour movement profiles and individual component behaviors with physical and mental health outcomes in the general adult population, Canada [41] and Thailand [42] have released "24-Hour Movement Guidelines for Adults," and Australia is in the process of incorporating a 24-hour approach for their next set of "Physical Activity and Sedentary Guidelines for Adults" [43]. In the United States, the most recent PA guidelines [44] include the recommendation to "sit less, move more, implying that for individuals initiating or increasing PA, replacing sedentary behavior with PA is a beneficial behavior change. Recent research has also highlighted the importance of integrating 24-hour movement guidance with dietary recommendations to support more holistic public health strategies [45]. These recommendations recognize the importance of considering the balance of behaviors in the 24-hour day, as well as behavior change as a replacement of one behavior for another in the context of the 24-hour day, but do not provide specific guidelines during pregnancy, a time when behavior change is common.

Initial studies on 24-hour movement in pregnancy suggest behavior reallocations to maintain or increase moderate- to vigorous-intensity PA may be beneficial for reducing pregnancy-induced increases in cardiometabolic biomarkers [46,47], improving body composition [46,48], and improving cardiorespiratory fitness [48]. In addition, one study found that reallocating time from sleep or sedentary behavior to light-intensity PA in early pregnancy may be beneficial for improving body composition and cardiometabolic biomarkers in late pregnancy [46]. However, these studies have all been exploratory and focused on risk factors for adverse outcomes. Larger, more representative, and longitudinal studies designed to address research questions on 24-hour movement and pregnancy outcomes, rather than risk factors, are needed to guide recommendations in this population.

As previous studies have all been exploratory, the impact of 24-hour movement during pregnancy on maternal glucose metabolism, GWG, and LGA birthweight remains uncertain. To address crucial knowledge gaps, studies with concurrent measurement of sedentary behavior, PA, and sleep throughout pregnancy are essential for informing recommendations and interventions to promote a healthy 24-hour day during pregnancy and optimal pregnancy outcomes.

This paper describes the study protocol for the 24MOVE study, a prospective cohort study that seeks to fill these knowledge gaps by examining associations between 24-hour movement profiles across pregnancy and maternal glucose tolerance, GWG, and infant birthweight. The aims of this study are to (1) examine relationships of 24-hour movement profiles in early and midpregnancy with maternal glucose tolerance in midpregnancy; (2) examine relationships of 24-hour movement profiles in early, mid-, and late pregnancy with GWG, and (3) examine relationships of 24-hour movement profiles in early, mid-, and late pregnancy with infant birthweight.

Methods

Study Setting

This study is currently being conducted within Kaiser Permanente Northern California (KPNC), an integrated health care delivery system providing care for more than 66,000 pregnancies (40,000 live births) annually in Northern California. KPNC health plan members are covered by employer-sponsored insurance plans, the California Insurance Exchange, Medicare, and Medicaid. KPNC membership represents the diverse population of the Northern California region in terms of demographic, ethnic, and socioeconomic characteristics, except with respect to income, where members underrepresent the poor and the wealthy [49]. Leveraging the KPNC's electronic health records (EHRs), participants were identified and recruited from three KPNC medical centers: Oakland, Walnut Creek, and South Sacramento. The Oakland, Walnut Creek, and South Sacramento medical centers represent urban, suburban, and semirural regions

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across Northern California, providing a geographically and socioeconomically diverse sample.

Ethical Considerations

All study procedures were reviewed and approved by the KPNC Institutional Review Board (IRB approval number 1998165). Written informed consent was obtained from all participants prior to study enrollment, including consent for use of their data in future analyses. Participants were informed that participation was voluntary and that they could withdraw from the study at any time. All data used in this study were deidentified prior to analysis in order to protect participant privacy and confidentiality. No identifiable personal health information was used in analyses or shared outside the study team. Participants received compensation as follows:

- A US $75 gift card at each of the three study timepoints (early, mid-, and late pregnancy) after completing the study surveys and returning the accelerometer
- A US $25 gift card at each timepoint for completing three time-use and three diet surveys
- A US $20 gift card after completing the feedback survey at the late pregnancy timepoint

Overview of the Study Design

This prospective cohort study identified newly confirmed pregnancies among KPNC members with pre-pregnancy overweight or obesity through the KPNC's EHRs. Identified individuals were invited to participate in this study via letter and email invitations. Eligible participants who provided written informed consent completed surveys (copies of study surveys are available in Multimedia Appendix 1) wore an accelerometer on their nondominant wrist for 24 hours per day for 7 days and participated in daily short sleep surveys at three timepoints in pregnancy (early, mid-, and late). During select days of activity and sleep monitoring, participants received links for additional surveys on 24-hour time use and diet. At the late pregnancy timepoint, participants also received an additional survey asking for feedback on their experience in the study, including their motivation for participating, any problems or issues they experienced with any aspect of the study, and suggestions for future research questions that are important to them. Pregnancy outcomes were ascertained from the EHRs.

Recruitment

Eligible KPNC members at 10 weeks' gestation (10 weeks 0 days to 10 weeks 6 days) were identified weekly from the EHRs. Identified members received an invitation letter by mail, including a link to an online eligibility survey, administered via Research Electronic Data Capture (REDCap), to confirm eligibility for the study. After completing the eligibility survey, eligible individuals who chose to participate in the study proceeded to complete informed consent. In cases of nonresponse to the mailed letter invitation after a week, an email study invitation was sent from the study email address. If there was still no response to the email after a week, a research assistant followed up once by phone. Members who did not respond to any of these invitations were not contacted further. Those who initiated but did not complete the baseline survey received two reminders via email through REDCap (1 reminder per week) after initiating the survey. If the survey was not completed after the reminders were sent, the individual was not contacted further.

Eligibility Criteria

As summarized in Table 1, potential participants were identified using initial EHR criteria, and eligibility was confirmed with an online eligibility survey.

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Table 1. Eligibility criteria for the 24MOVE study.

Eligibility criterion	EHRs[a]	Eligibility survey
KPNC[b] membership	X[c]	X
Currently pregnant	X	X
Receiving care at Kaiser Permanente Oakland, South Sacramento, or the Walnut Creek Medical Center	X	—[d]
Singleton pregnancy	X	X
≤12 weeks' gestation (10 weeks 0 days to 12 weeks 6 days)	X	X
Age ≥18 years	X	X
Pre-pregnancy BMI ≥25 kg/m² (based on closest weight measured within 12 months prior to pregnancy)	X	—
No diabetes diagnosis in the 12 months before pregnancy	X[e]	X
Not currently on bed rest or activity restriction (to exclude those with extreme limitations on their PA[f])	—	X
No diagnosis or treatment of a sleep disorder in the 12 months before pregnancy (to exclude those with disrupted sleep patterns)	X[g]	X
No clinically significant insomnia symptoms (Insomnia Severity Index [50,51] <15, to exclude those with disrupted sleep patterns)	—	X

[a]EHR: electronic health record.

[b]KPNC: Kaiser Permanente Northern California.

[c]Applicable.

[d]Not applicable.

[e]Identified using the KPNC Diabetes Registry [52]

[f]PA: physical activity.

[g]Identified using International Classification of Diseases (ICD) codes F51 and G47.

Overview of Data Collection

At each of the three data collection timepoints—early pregnancy (10 weeks 0 days to 12 weeks 6 days), midpregnancy (20 weeks 0 days to 22 weeks 6 days), and late pregnancy (33 weeks 0 days to 35 weeks 6 days)—participants completed a set of surveys administered through REDCap (copies of study surveys are available in Multimedia Appendix 1), wore a Centrepoint Insight accelerometer (ActiGraph) on their nondominant wrist for 24 hours per day for 7 days, and participated in short daily sleep surveys. The surveys at each timepoint covered a broad range of topics, including PA levels, pregnancy-related symptoms, substance use, perceived social support, depressive and anxiety symptoms, perceived stress levels, quality of life, and sociodemographic characteristics (Table 2). At the early pregnancy timepoint, participants additionally reported whether it was their first pregnancy, the number of children currently residing with them, the birthdate of each child, their typical waking times on weekdays and weekends since the beginning of pregnancy, their gender identity, their racial and ethnic identities, educational attainment, the total annual household income, the number of individuals supported by this income, marital status, and wrist size. Participants' address and contact information were confirmed, by phone or as part of the online survey, at each study timepoint. After survey completion at each timepoint, accelerometers were mailed to participants, along with a prepaid return envelope. Participants were provided detailed written instructions on how to properly wear, care for, and return the accelerometer, including a frequently asked question (FAQ) section covering common concerns. Participants received a link to a Consensus Sleep Diary via a text message at their usual wake time (as indicated on the early pregnancy survey) for 7 consecutive days during the accelerometer wear period. If typical wake times were not provided by a participant, surveys were sent at 8:00 AM by default. On 3 random days during the 7-day period of accelerometer wear, participants received links via email for additional surveys for 24-hour recall of time use and diet. After delivery, maternal glucose tolerance–screening results, GWG, and infant birthweight will be abstracted from prenatal care and delivery records in the EHRs.

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Table 2. Overview of data collection at each study timepoint.

Measure	Instrument	Study data collection timepoint		
		Early pregnancy (10-12 weeks' gestation)	Midpregnancy (20-22 weeks' gestation)	Late pregnancy (33-35 weeks' gestation)
24-hour movements				
24-hour accelerometry	Centrepoint Insight watch	X[a] (7 consecutive days)	X (7 consecutive days)	X (7 consecutive days)
In-bed duration, sleep duration, sleep quality, napping	Consensus Sleep Diary [53]	X (7 consecutive days)	X (7 consecutive days)	X (7 consecutive days)
PA[b] and sedentary behavior	Modified PPAQ[c] [54]	X	X	X
Time use	ACT24[d] [55]	X (3 random days)	X (3 random days)	X (3 random days)
PA before pregnancy	Stanford Leisure-Time Activity Categorical Item (L-Cat) [56,57]	X	__[e]	—
Usual weekday/weekend wakeup times	—	X	—	—
Pregnancy symptoms and behaviors				
Nausea and vomiting	Modified PUQE[f] index [58]	X	X	X
Tobacco, alcohol, and marijuana use	—	X	X	X
Diet	ASA24[g] [59]	X (3 random days)	X (3 random days)	X (3 random days)
Mental health and social support during pregnancy				
Perceived social support	Multidimensional Scale of Perceived Social Support [60,61]	X	X	X
Perceived stress	PSS-10[h] [62]	X	X	X
Depressive symptoms	PHQ-8[i] [63]	X	X	X
Anxiety symptoms	GAD-7[j] [64]	X	X	X
Quality of life	QOL-GRAV[k] [65]	X	X	X
Sociodemographic characteristics				
Gravidity, number of children living with the participant, birthdates of those children	—	X	—	—
Gender identity	—	X	—	—
Racial and ethnic identities	—	X	—	—
Education	—	X	—	—
Employment status	—	X	X	X
Household income, number of people supported by this income	—	X	—	—
Marital status	—	X	—	—

[a]Applicable.
[b]PA: physical activity.
[c]PPAQ: Pregnancy Physical Activity Questionnaire.
[d]ACT24: Activities Collected over Time over 24 hours.
[e]Not applicable.
[f]PUQE: Pregnancy-Unique Quantification of Emesis and Nausea.
[g]ASA24: Automated Self-Administered 24-Hour Dietary Assessment.
[h]PSS-10: 10-item Perceived Stress Scale.
[i]PHQ-8: 8-item Patient Health Questionnaire.
[j]GAD-7: 7-item General Anxiety Disorder Scale.

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[k]QOL-GRAV: Quality of Life Gravidarum questionnaire.

Data Processing and Creation of 24-hour Movement Profiles Using Accelerometer Data

Accelerometer Wear Time

Raw accelerometer data will be sampled at 32 Hz, downloaded using the Centrepoint software platform (ActiGraph), and processed with R (R Foundation for Statistical Computing) [66]. Vector magnitude counts, summarized for each minute (60-second epoch) of data collection, will be extracted. Nonwear time will be identified using the Choi algorithm [67-69], where nonwear is defined as an interval of ≥90 consecutive minutes with 0 vector magnitude counts/minute, allowing up to 2 minutes of nonzero counts during the 30-minute window before or after that interval. Any nonzero vector magnitude counts (except within the allowed short intervals) will be considered wear time. Valid accelerometer data will be defined as ≥10 hours of waking wear time in a 24-hour period for ≥4 days.

Sleep Opportunity Period

The Tracy bed rest algorithm will be used to estimate sleep opportunity periods [70]. Uniaxial counts, summarized for each minute (60-second epoch) of data collection, will be extracted. Wear time will be divided into 60-minute time blocks; counts per minute will be averaged for each block. The algorithm, using a 4-step decision tree process, identifies transition times for getting in and out of bed, with thresholds of 400 counts per minute for getting in bed and 1500 counts per minute for getting out of bed. Minutes between identified in-bed and out-of-bed times will be classified as the sleep opportunity period and the remaining minutes as wake time. The duration of the sleep opportunity period for each 24-hour period will be calculated and averaged across valid days, with daily averages for sleep opportunity period duration considered as exposures in the 24-hour movement framework. Daytime naps will be separately reported via the Consensus Sleep Diary and will be considered as an additional component of 24-hour movement profiles in secondary analyses. We will also use self-reported measures of sleep quality from sleep diaries as potential effect modifiers in analyses.

Light-Intensity PA, Moderate- to Vigorous-Intensity PA, and Sedentary Behavior

We will use the 2-regression algorithms developed by Hibbing et al [71] to categorize the waking period by intensity. Raw acceleration data for each second of identified waking wear time (1-second epochs) will be extracted. Each 1-second epoch will be classified as sedentary or at least light-intensity PA. Sedentary 1-second epochs will be assigned a metabolic equivalent of task (MET) value of 1.25 METs. Epochs classified as light- or higher-intensity PA will be further categorized as continuous walk/run or intermittent activity, regression equations will predict a MET value for each 1-second epoch, and then MET values will be averaged over each minute. Minutes of waking wear time will then be classified as sedentary (≤1.5 METs), light intensity (1.6-2.9 METs), or moderate to vigorous intensity (≥3 METs). Daily averages for light-intensity PA duration, moderate- to vigorous-intensity PA duration, and sedentary behavior duration will be calculated by summing the times per day and averaging across valid days.

24-hour Movement Profiles

Participants' 24-hour movement profiles will be created by normalizing the sleep opportunity period, sedentary behavior, light-intensity PA, and moderate- to vigorous-intensity PA durations to a 24-hour period.

Survey Data: 24-hour Movement

Self-Reported PA and Sedentary Behavior

The self-reported PA and sedentary behavior levels of participants will be assessed using the Pregnancy Physical Activity Questionnaire (PPAQ) [54]. The PPAQ was developed based on commonly reported physical activities in pregnant women and is a validated tool for assessing PA levels during pregnancy [54]. We used a modified version of the PPAQ that expands on leisure time behaviors to include additional activities (eg, weightlifting, yoga/Pilates/stretching, and team sports). We will use the PPAQ to provide contextual information about activity domains to complement accelerometer data. In scoring, activities reported will be matched to their assigned MET values, which will then be summed across categories to calculate total MET-hours per week or day by intensity of behavior and by domain.

24-hour Time Use

The Activities Collected over Time over 24 hours (ACT24) [55] instrument will be used to collect detailed data on each participant's activities over the previous 24-hour day, including PA, sedentary behavior, and sleep. The ACT24 is a valid tool for accurately capturing time spent in the previous day's activities across multiple intensities and domains [55,72,73]. Data from the ACT24 will complement accelerometer data by providing contextual information on the types of activities and domains not captured by movement sensors alone.

Survey Data: Pregnancy Symptoms and Additional Behaviors

Pregnancy Nausea and Vomiting Symptoms

The modified Pregnancy-Unique Quantification of Emesis and Nausea (PUQE) index is a validated tool for measuring the severity of nausea and vomiting during pregnancy [58,74]. It assesses the frequency and intensity of nausea and vomiting and their impact on daily life. Responses are summed to obtain a total score ranging from 3 to 15, with a higher score indicating more severe nausea and vomiting symptoms during pregnancy.

Diet

The Automated Self-Administered 24-Hour Dietary Assessment (ASA24) is a web-based recall tool for collecting detailed dietary intake data over a 24-hour period that has been validated for estimating dietary intake in multiple populations [59,75,76]. The ASA24 generates comprehensive reports and analysis files on nutrient intake and food group consumption based on user inputs.

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Survey Data: Mental Health and Social Support During Pregnancy

Perceived Social Support

The Multidimensional Scale of Perceived Social Support [60,61] measures perceived support from family, friends, and significant others. It is a widely validated and reliable tool across various populations [60,61,77]. The scale consists of 12 questions scored on a 7-point Likert scale ranging from 1 (very strongly disagree) to 7 (very strongly agree). Scores are calculated for overall social support and within each subscale (family, friends, significant other). Calculated scores range from 1 to 7, with higher scores indicating greater perceived social support.

Perceived Stress

The 10-item Perceived Stress Scale (PSS-10) [62] is the most widely used psychological instrument for measuring the perception of stress and has been validated in diverse populations and in perinatal women [78]. Scores range from 0 to 40, with 14 or greater signifying moderate-to-severe perceived stress.

Depressive Symptoms

Depressive symptoms will be measured using the 8-item Patient Health Questionnaire (PHQ-8) [63]. The PHQ-8 has been validated in many studies as an instrument for screening for depression, with high sensitivity (>88%) and specificity (>88%) in obstetric patients [63,79]. The PHQ-8 is also a valid tool to establish depression severity and outcome [80]. The 8-question screener scores range from 0 to 24. A score of 1-4 suggests minimal depression; 5-9, mild depression; 10-14, moderate depression; 15-19, moderately severe depression; and 20-24, severe depression.

Anxiety Symptoms

The 7-item General Anxiety Disorder Scale (GAD-7) [64] has been validated in prenatal populations and will be used to measure anxiety symptoms [64,81]. Scores range from 0 to 21, and scores of 10-21 are categorized as clinically significant anxiety symptoms.

Pregnancy-Related Quality of Life

The Quality of Life Gravidarum questionnaire (QOL-GRAV) is a validated tool for assessing the well-being of pregnant women across physical, emotional, and social aspects [1,65]. Overall scores range from 15 to 35, with a lower score reflecting a higher quality of life during pregnancy.

Pregnancy Outcomes

Pregnancy outcomes, including glucose tolerance, GWG, and infant birthweight, will be identified from EHR data. The KPNC maintains a virtual data warehouse where data from EHRs are aggregated on a daily basis with rigorous quality control and standardization of data for consistency and accuracy across multiple data sources. Outcomes will be extracted from this database.

Maternal Glucose Tolerance

GDM screening at the KPNC consists of a 50 g glucose challenge test for all pregnant patients. If the glucose challenge test results are abnormal (≥140 mg/dL), a subsequent 100 g, 3-hour oral glucose tolerance test is administered. GDM will be diagnosed according to Carpenter-Coustan criteria [82]. Glucose tolerance–screening results and GDM diagnoses will be abstracted from the EHRs. Glucose challenge test results (continuous glucose levels and dichotomized as normal [<140 mg/dL] vs abnormal [≥140 mg/dL]) will be examined as outcomes in the main analyses. In exploratory analyses, we will examine the GDM diagnosis as an outcome.

Gestational Weight Gain

Weight measurements will be taken and recorded during each prenatal visit in the EHRs. The total GWG will be calculated as the difference between the final pregnancy weight predelivery (within 3 weeks of delivery) and the pre-pregnancy weight (the most recent clinically measured pre-pregnancy weight within 6 months before the last menstrual period or for women lacking a measured pre-pregnancy weight, the earliest clinically measured pregnancy weight before 10 weeks' gestation). We will use standardized GWG-for-gestational age charts to calculate GWG z-scores to account for the correlation between the GWG and the gestational age at delivery [83,84]. GWG z-scores will be used as continuous outcomes in the main analyses. The average weekly trimester-specific GWG for the second and third trimesters will also be calculated. The trimester-specific GWG will be categorized using Institute of Medicine recommendations (below, within, or above recommendations) [85]. We will examine the trimester-specific GWG as a continuous outcome, stratified by pre-pregnancy BMI category, and as a categorical outcome.

Infant Birthweight

The birthweight is measured at the time of delivery and recorded in the EHR. We will use gestational age data from the EHR in conjunction with national sex-specific birthweight curves to identify birthweight-for-gestational age z-scores and the LGA birthweight [86]. We will examine birthweight as a continuous outcome in the main analyses. In exploratory analyses, we will examine the LGA birthweight as an outcome.

Sample Size

Given a sample size of 300, there is sufficient power (0.80) to detect an additional 2.1%-2.4% in the proportion of variance in glucose-screening results, GWG, and birthweight explained by the duration of each behavior (sleep, sedentary behavior, light-intensity PA, or moderate- to vigorous-intensity PA) across the expected ranges in R^2 for a set of confounders (5%-20%; 15 confounders assumed, α=.05, *F*-test). In exploratory analyses, the minimum detectable relative risk of GDM, excessive GWG, and LGA per 1 SD increase in a component behavior is 1.70, 1.12, and 1.60, respectively (power=0.80, α=.05, 2-sided test).

Planned Statistical Analyses

We will use a compositional data analysis (CoDA) approach for all analyses. We will apply isometric log-ratio transformations to normalized 24-hour movement profiles (the proportion of the 24-hour day spent in the sleep opportunity period, sedentary behavior, light-intensity PA, and moderate- to vigorous-intensity PA) to obtain three transformed variables

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that capture the codependence and collinearity between these behaviors [87-89]. To examine how hypothetical behavior substitutions within the 24-hour day during pregnancy impact outcomes, we will use a compositional isotemporal substitution approach [90] to model the predicted change in pregnancy outcomes when reallocating up to 60 minutes of time from one component behavior to another at various timepoints. We will assess associations of hypothetical behavior substitutions in early and midpregnancy with glucose tolerance outcomes (aim 1); in early, mid-, and late pregnancy with GWG outcomes (aim 2); and in early, mid-, and late pregnancy with birthweight outcomes (aim 3).

We will use linear regression models to model relationships with continuous outcomes (glucose challenge test results, GWG, birthweight) and log-binomial regression models to model relationships with dichotomous outcomes (abnormal glucose challenge test results, GDM diagnosis, GWG above recommendations, LGA birthweight). All models will be adjusted for a priori–identified confounding variables (eg, maternal age, race and ethnicity, education, income, employment, pre-pregnancy BMI, parity, diet, depression and anxiety symptoms, stress, smoking and alcohol use, and severity of nausea and vomiting). We will assess potential multicollinearity using variance inflation factors and exclude covariates from the models, as necessary. Departures from linearity will be addressed by the addition of higher order (eg, quadratic) terms. Departures from model assumptions will be assessed via diagnostic plots of weighted residuals. Missing data will be assessed, and if necessary, missing data in covariates and outcomes will be handled using standard multiple imputation methods for longitudinal data analysis, namely multivariate imputation by chained equations (MICE), which has also been referred to as fully conditional specification (FCS).

Results

Study Timeline

Recruitment began on March 19, 2023, and ended on September 11, 2024. Enrollment was completed on September 19, 2024. Data collection was completed in April 2025.

Recruited Cohort

Over an 18-month recruitment period, we invited 2035 KPNC members to participate in this study (Figure 1). Responses to the invitation were received via recruitment emails (n=327, 16.1%), recruitment letters (n=64, 3.1%), and recruitment phone calls (n=43, 2.1%). Of those invited, 434 (21.3%) individuals completed the eligibility survey, and 376 (86.6%) met the eligibility criteria. The most prevalent reason for ineligibility was clinically significant insomnia symptoms (n=36, 8.3%). A total of 306 (81.4%) participants consented to participate in the study and were enrolled.

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Figure 1. Summary of recruitment for the 24MOVE study. In total, 2035 participants were invited to participate, 434 (21.3%) responded and completed an eligibility survey, 376 (86.6%) were eligible for the study, and 306 (81.4%) were enrolled. KPNC: Kaiser Permanente Northern California.

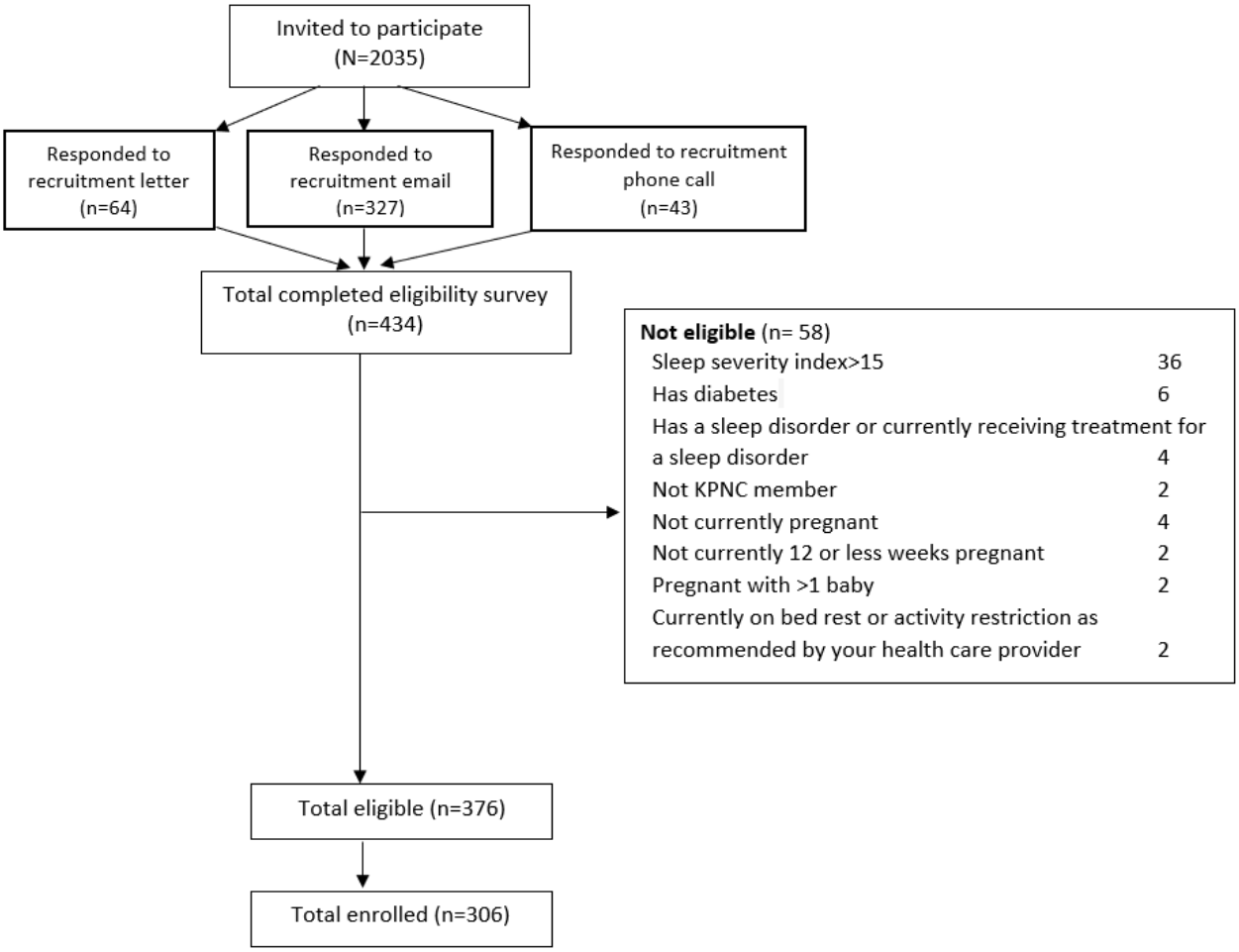

Enrolled participants had a median age of 33 (quintile 1 [Q1]-quintile 3 [Q3] 30-36) years with a median pre-pregnancy BMI of 28.8 (Q1-Q3 26.9-32.7) kg/m^2 (Tables 3 and 4). Among the 306 participants, 129 (42.2%) were non-Hispanic White, 61 (19.9%) were Hispanic, 48 (15.7%) were Asian, and 24 (7.8%) were non-Hispanic Black. Most participants had private insurance (n=266; 86.9%) and were multiparous (n=232; 75.8%). Pre-pregnancy anxiety and depression had a prevalence of 19%-22% (n=58-68), while hypertension and diabetes were uncommon (reported by 0-12, 0%-4%, participants). Comparing sociodemographic and pre-pregnancy health characteristics between invited participants and the subset that were eligible and enrolled in this study, the enrolled cohort underrepresented non-Hispanic Black, Asian, and Hispanic participants and those with Medicaid insurance compared to the invited group. Other characteristics (age, parity, and pre-pregnancy health) were similar between the invited and enrolled participants.

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Table 3. Comparison of sociodemographic characteristics between subsets of participants invited to the 24MOVE study.

Characteristics	Invited (N=2035)	Completed eligibility survey (n=434)	Eligible (n=376)	Enrolled (n=306)
Age (years), median (Q1[a]-Q3[b])	32 (28-35)	33 (30-36)	33 (30-36)	33 (30-36)
Race and ethnicity, n (%)				
Asian	424 (20.8)	70 (16.1)	61 (16.2)	50 (16.3)
Non-Hispanic Black	283 (13.9)	41 (9.4)	33 (8.8)	25 (8.2)
Hispanic	497 (24.4)	100 (23.0)	82 (21.8)	61 (19.9)
Multiracial	170 (8.4)	42 (9.7)	35 (9.3)	30 (9.8)
Non-Hispanic White	560 (27.5)	158 (36.4)	147 (39.1)	128 (41.8)
Other	63 (3.1)	12 (2.7)	9 (2.3)	4 (1.3)
Missing	38 (1.9)	11 (2.5)	9 (2.3)	8 (2.6)
Medicaid insurance, n (%)				
Insured	333 (16.4)	44 (10.1)	36 (9.6)	28 (9.2)
Missing	90 (4.4)	18 (4.1)	13 (3.5)	12 (3.9)
Nulliparous, n (%)				
Yes	316 (15.5)	67 (15.4)	58 (15.4)	45 (14.7)
Missing	145 (7.1)	34 (7.8)	32 (8.5)	27 (8.8)

[a]Q1: quintile 1.
[b]Q3: quintile 3.

Table 4. Comparison of pre-pregnancy health characteristics between subsets of participants invited to the 24MOVE study.

Characteristics	Invited (N=2035)	Completed eligibility survey (n=434)	Eligible (n=376)	Enrolled (n=306)
BMI (kg/m^2), median (Q1[a]-Q3[b])	30.4 (27.4-34.9)	29.2 (27.0-33.5)	29.1 (26.9-33.1)	28.8 (26.9-32.7)
Anxiety diagnosis, n (%)	396 (19.5)	101 (23.3)	89 (23.7)	68 (22.2)
Depression diagnosis, n (%)	339 (16.7)	88 (20.3)	72 (19.1)	57 (18.6)
Hypertension diagnosis, n (%)	95 (4.7)	19 (4.4)	15 (4.0)	12 (3.9)
Diabetes diagnosis, n (%)	11 (0.5)	2 (0.5)	1 (0.3)	1 (0.3)

[a]Q1: quintile 1.
[b]Q3: quintile 3.

Discussion

Summary

The 24MOVE study is designed to address gaps in our knowledge regarding the impact of 24-hour movement during pregnancy on maternal glucose metabolism, GWG, and other risk factors for childhood obesity, such as a high birthweight. Data from this study will serve as a rich resource for future investigations of 24-hour movement profiles and behavior substitutions and perinatal mental and physical health outcomes, in addition to the aims of this study. As a growing number of countries release "24-Hour Movement Guidelines for Adults," the results from this study will contribute to the body of literature that will guide future 24-hour movement guidelines for pregnant individuals.

Strengths and Limitations

Strengths of the 24MOVE study include prospective data collection using wearable devices and self-reported measures for all component behaviors during the 24-hour day at multiple timepoints across pregnancy, allowing for the assessment of the duration, intensity, and domain of PA and sedentary behavior and the duration and quality of sleep, including napping. In addition, all data collection is remote, and outcomes are ascertained from EHRs, decreasing the participant burden. Our planned statistical analysis approach using CoDA addresses limitations of conventional statistical approaches, including all mutually exclusive component behaviors of the 24-hour day [91-94]. We will also assess a variety of important confounders and covariates in our data collection and include them in analysis models, as well as assess and address missing data using statistical approaches to maximize available data.

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Several potential limitations should also be considered. Although more than 50% of our enrolled study cohort are participants from minoritized racial and ethnic groups, these groups are underrepresented compared to those invited to participate in the study. In addition, those with Medicaid insurance (a proxy for low income) are also underrepresented in the enrolled cohort. Our cohort may not be representative of pregnancies with pre-pregnancy overweight or obesity across the United States. We did not collect data on whether the pregnancy was planned, which may influence pregnancy-related behaviors and outcomes. Although we attempted to minimize the participant burden as much as possible by streamlining surveys and accelerometer protocols, there is a risk of participant fatigue due to multiple data collection modalities over the three timepoints of data collection. During follow-up data collection, we monitored participant engagement and loss to follow-up, amending study procedures to address identified issues if necessary. We will also carefully consider representativeness and loss to follow-up in our analyses and apply appropriate statistical methods to mitigate some of these concerns.

Dissemination of Results

Results from the 24MOVE study will be disseminated widely via publication in peer-reviewed journals and presentations at national and international conferences.

Conclusion

The 24MOVE study seeks to enhance our understanding of how 24-hour movement throughout pregnancy influences maternal glucose regulation, the GWG, and key risk factors for childhood obesity, including a high birthweight. Furthermore, the study will offer a comprehensive data resource for future research on movement patterns, behavioral changes, and associations with perinatal mental and physical health outcomes.

Acknowledgments

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Data Availability

Deidentified individual participant data and supporting documentation will be made publicly available in a data repository upon publication, in accordance with funder requirements. The code used for statistical analyses will be provided as a supplement to the published manuscript or made available in the same repository.

Authors' Contributions

ER led project administration, coordinated data collection, wrote the initial draft, and reviewed and edited the manuscript. AA handled data curation and reviewed and edited the manuscript. CPQ contributed to the methodology and reviewed and edited the manuscript. KPG, RM, LAA, and MMH contributed to conceptualization, funding acquisition, and reviewed and edited the manuscript. SEB led the study's conceptualization, methodology, supervision, and funding acquisition; contributed to writing the initial draft; and reviewed and edited the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
First trimester survey and feedback survey.
[PDF File (Adobe PDF File), 320 KB - resprot_v14i1e72828_app1.pdf]

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Abbreviations

ACT24: Activities Collected over Time over 24 hours
ASA24: Automated Self-Administered 24-hour Dietary Assessment
CoDA: compositional data analysis
EHR: electronic health record
GAD-7: 7-item Generalized Anxiety Disorder Scale
GDM: gestational diabetes mellitus
GWG: gestational weight gain
KPNC: Kaiser Permanente Northern California
LGA: large for gestational age
MET: metabolic equivalent of task
PA: physical activity
PHQ-8: 8-item Patient Health Questionnaire
PPAQ: Pregnancy Physical Activity Questionnaire
PSS-10: 10-item Perceived Stress Scale
PUQE: Pregnancy-Unique Quantification of Emesis and Nausea
Q1: quintile 1
Q3: quintile 3
QOL-GRAV: Quality of Life Gravidarum questionnaire
REDCap: Research Electronic Data Capture

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Protocol

Optimizing Digital Solutions to Improve Access to Comprehensive Primary Health Care Services in Remote Indigenous Communities: Protocol for a Participatory Action Research Project

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Abstract

Background: Aboriginal and Torres Strait Islander (Indigenous) peoples living in remote Australia experience a heavy burden of ill health and multiple barriers to accessing health care. Digital health technologies (DHTs) have the potential to help overcome some of these challenges and increase access to comprehensive primary health care (CPHC), thereby improving equity of health outcomes. However, little is known about the community and provider preferences for the use of digital technologies for improving health and wellness.

Objective: The study aims to co-design, implement, and evaluate how DHTs can improve access to CPHC in remote Indigenous communities in the Northern Territory (NT), Australia.

Methods: This multiphased project will take a participatory action research approach to co-design and optimize digital health solutions with local community members and health service staff in 2 communities. Our mixed methods approach will include pre- and postimplementation focus group discussions, interviews, quantitative analysis of CPHC utilization administrative data, and surveys administered by Indigenous community-based researchers to understand the use of digital devices and connectivity, eHealth literacy, preferences for different attributes of DHTs using best-worst scaling, and consumer satisfaction and experiences with DHT interventions. Priority DHTs will be selected for implementation based on consumer and health staff preferences. Focus group discussions and interview data will explore community and health service staff preferences, experiences, and satisfaction with implemented DHTs. A realist approach will be taken to identify how DHT interventions work, for whom, and in what circumstances, so that the understanding of why some interventions work while others do not is expanded. Economic analyses will be conducted to calculate the incremental costs and benefits of implemented DHT interventions. The scalability of digital health solutions will be tested in two additional communities. Project partners include key funding, service, and support agencies in the NT and nationally.

Results: As of November 2024, we have selected two implementation sites. Digital health initiatives are underway at the implementation sites, and evaluation activities are progressing. The initial findings from these sites have informed our scalability assessment in an additional two sites.

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Conclusions: Knowledge translation is integral to the study design, which involves partnering with consumers, CPHC service providers, and a range of key stakeholders to inform health service providers and policy makers about which DHTs work for which groups of consumers, and under what circumstances, to improve access to CPHC. This unique study will accommodate consumer and provider preferences regarding the use of DHTs to improve CPHC access and address the lack of knowledge about how to deploy digital solutions to best support CPHC in remote Indigenous Australia.

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KEYWORDS

Indigenous peoples; primary health care; digital health; telehealth; remote; access; participatory action research; co-design; Indigenous health

Introduction

Comprehensive primary health care (CPHC) is the delivery of essential health care services from the first point of contact, enabling equitable access to health and well-being for all residents in a community [1]. In the context of Australian Aboriginal Community Controlled Health Services (ACCHSs), CPHC has four domains for delivering core services: governance, clinical services, community health promotion and empowerment, and policy direction and partnerships [2]. In common with primary health care services, such as those delivered by Northern Territory (NT) Health, ACCHSs deliver a broad range of clinical services. However, ACCHSs have governance structures that support the expression of self-determination and offer services that include community development, advocacy to improve determinants of health that are outside the health system, and fostering partnerships to optimize action addressing those determinants. CPHC is characterized by the achievement of more equitable health outcomes in line with the Alma-Ata Declaration of 1978 on primary health care [3,4]. CPHC is also the most inclusive and cost-effective approach to delivering health care services and involves identifying local health needs and responding to health provision gaps [1]. Strong CPHC systems are therefore essential for optimizing health outcomes for high-needs, dispersed, and marginalized communities.

Remote Aboriginal and Torres Strait Islander (respectfully referred to as Indigenous throughout this protocol) Australians experience the heaviest burden of ill health and the highest rates of preventable hospital admissions and potentially avoidable deaths of all Australians [5]. Overall, Indigenous Australians have 2.3 times the burden of disease compared to the non-Indigenous population [5]. Responding adequately to this burden of disease and the associated need for CPHC in remote Indigenous communities of the NT is challenging [6]. The NT spans a large geographical area (1,347,791 km^2), all classified as rural or remote, and population density is sparse [7]. In Australia, geographical remoteness has been associated with long-standing health workforce issues, including poor supply, low retention, and high turnover, with associated adverse impacts on access to CPHC, especially continuity of care [8-11]. In addition, high proportions of nurses are employed on casual or short-term agency contracts [12]. On average, only 20% of remote area nurses and Aboriginal health practitioners (AHPs) remain working in the same clinic 12 months after commencing their employment [8,12,13]. While the use of temporary staff provides a short-term solution to address dire need, there are trade-offs regarding the skills and suitability of these staff, with consumers preferring to have their complex chronic conditions managed by health care professionals they know [8,9,12]. High mobility of remote populations is also a feature of remote communities and is a further barrier to continuity and access to care.

Digital health technologies (DHTs) such as telehealth, wearable devices, and mobile health apps can help to address barriers to CPHC for people living in remote Indigenous communities as well as support remote area health care professionals [6,14]. Telehealth has been shown to reduce the need to travel, decrease waiting periods to see a clinician, and improve continuity of care [15,16]. DHTs can also increase flexibility of employment and provide enhanced training opportunities for remote clinicians [17], thereby promoting workforce retention. DHTs may also improve communication between different service providers [17], which can improve coordination of health care, improve decision-making, and strengthen communications between specialists and primary health care providers. DHTs also have the potential to increase cultural security and minimize disparities in access to health care [18]. For instance, a recent systematic review reported that in some circumstances, Indigenous people may feel more comfortable using telehealth and thereby avoid embarrassment, which might arise from a face-to-face interaction with a health provider who lives in their community [19]. Nevertheless, Indigenous peoples are diverse and have different needs. For cultural safety to be in place, trusting and respectful relationships must first be created. Therefore, the vision of the NT Virtual Care Strategy [6] is that DHTs will facilitate improved access, result in greater choice for consumers, reduce travel time to get to appointments, and increase convenience for consumers.

Several studies have developed and applied digital tools such as apps and programs to promote health and wellness in rural and remote communities, but these are often not developed in collaboration with communities and, when they have been, are rarely evaluated [20,21]. In the NT, DHTs being used include telehealth (audio with video), electronic patient management information systems, and a range of mobile apps. However, despite existing use and the potential for more widespread adoption of DHTs, it is not well understood which DHTs might work well, how, and for whom to improve access to CPHC for remote Indigenous populations in the NT. While some health

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services in the NT have used DHTs to deliver CPHC and support follow-up of specialist care, DHTs generally remain underutilized and have neither been systematically implemented nor evaluated [20,21]. The use and type of DHTs in the NT have primarily been driven by providers' preferences [14], with limited focus on consumer preferences and experiences. Likewise, there is little evidence of consumer involvement in the design and delivery of health care using DHTs in remote Indigenous settings elsewhere in Australia, which stand to benefit most from this technology. In light of these important gaps, this research will co-design, implement, and evaluate the use of DHTs to strengthen the evidence about how DHTs can best support access to CPHC for remote Indigenous communities, considering consumer and remote health staff preferences. This protocol is reported in line with the iCHECK-DH (Guidelines and Checklist for the Reporting on Digital Health Implementations) reporting guideline, with some adaptations in subheadings [22].

Methods

Setting

This project is being conducted (July 2022-June 2025) in two remote Indigenous communities in the NT, where health care is provided by either NT Government-run health services or ACCHSs. Health services across the NT were invited to express their interest in participating in the project. A project advisory committee, consisting of key decision-makers from the NT and Commonwealth Health Departments, ACCHSs, and stakeholder partners, selected the sites based on community size, remoteness, location (Top End, Central Australia), health service delivery and governance model (government, ACCHS), and estimated readiness to engage with DHTs. This approach sought to maximize the opportunity to evaluate and compare the findings from diverse communities with different governance structures. The clinics in these communities are mostly staffed by remote area nurses, AHPs, and nonclinical administrative staff based in the community, with visiting (and sometimes telehealth) services provided by general practitioners, Allied Health Professionals, and various medical specialists. The NT has unique cultural, social, and language considerations, with 26.3% of the population identifying as Aboriginal or Torres Strait Islander (compared to 3.2% across Australia) [23]. In remote and very remote communities of the NT, more than 90% of the population identify as Aboriginal, and for many, English is not their first language [23]. The participating communities in our project meet this unique NT profile: they are small (<400 population), very remote, and have a predominantly Indigenous population. They face numerous health care delivery challenges and have differing usable technological infrastructure, such as the presence of a 4G mobile network, the presence of microwave, satellite, or cable internet, and the presence of community Wi-Fi.

Theoretical Frameworks

A participatory action research (PAR) methodology actively involves key stakeholders, including patients (consumers), health care providers, caregivers, and community members in the research process. This methodology emphasizes collaboration, shared decision-making, and engagement of those directly affected by the research [24,25]. The intention is that a network of participants who are actively engaged in the project can help bridge the gap between research and practice to create sustained system change.

We will apply three theoretical frameworks in the design, implementation, and evaluation of DHT solutions in the 2 communities. First, an overarching logic model (Figure 1 [26]) for CPHC will be used to provide a systematic approach for data collection across the different components of a CPHC system (context, inputs, enablers, outputs, and immediate, intermediate, and outcomes), and the contribution of each component will be monitored against relevant outcome measures [27].

Second, the six dimensions of the modified theory of access—acceptability, accommodation, affordability, accessibility, availability, and awareness (including digital health literacy)—will be used to evaluate the impact of DHTs in providing enhanced access to CPHC [28,29].

Third, a realist approach will be used to explore which DHTs work, for whom, and under what circumstances [30,31]. Realist evaluations go beyond simply determining whether an intervention is effective or not; they provide insight into underlying mechanisms and the context of causal relationships between interventions and outcomes.

This tri-part approach is likely to be especially useful to unpack the complex interplay of factors operating within remote and Indigenous health care environments [30,32].

Specific research questions include:

1. What technologies are available to support CPHC, including prevention and health promotion programs, in remote communities?
2. How can existing technologies be modified or enhanced to support CPHC, and what new technologies are needed?
3. What are the consumer and provider preferences for the use of digital technologies to support CPHC in remote communities?
4. How can technologies be used to promote access to care and support a holistic approach to social and emotional well-being in remote communities?
5. How can digital technologies support coordination of, and access to, CPHC in a highly mobile population, as well as collaboration between providers?
6. What skills are required for remote providers to use digital technologies to support CPHC in remote communities?
7. What is the impact of deploying different digital technologies to support CPHC on consumer and staff experiences in remote communities?
8. What are the potential cost consequences of deploying different digital technologies to support CPHC in remote communities?
9. How can the deployment of digital technologies improve the efficiency of CPHC in remote communities?

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Figure 1. An evidence-based logic model for sustainable comprehensive primary health care for small, rural, and remote communities. NT: Northern Territory; PHC: primary health care.

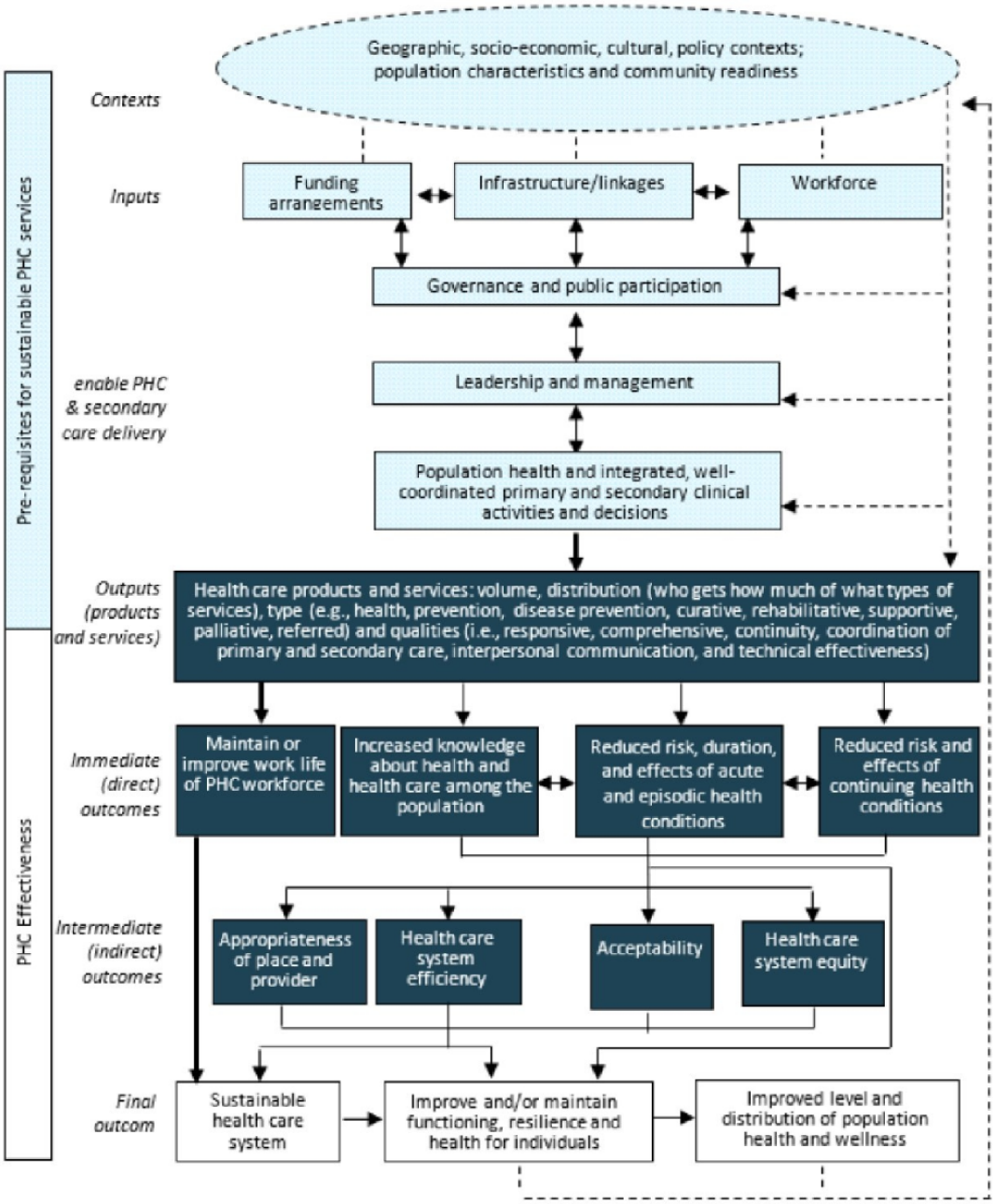

Project Co-Design, Implementation, and Evaluation

The project will be conducted in multiple phases, including investigation and co-design of DHTs with consumers and health service staff, iterative implementation of different DHTs in two community sites, and evaluation of these DHTs on consumer and staff experiences and access to CPHC (refer to Figure 1).

Preimplementation Activities and Co-Design of Digital Health Interventions

A desktop review will identify existing DHTs being applied in the NT and elsewhere that can be applied to support CPHC in remote Indigenous communities. A concurrent realist review will develop initial program theories about how and for whom DHTs affect access to CPHC in remote Indigenous communities [30,33]. Initial program theories developed from the existing literature will be refined using data collected from thought leader interviews (refer to the interview guide in Multimedia Appendix 1). Some of these theories may subsequently be tested during the evaluation phase (depending on preferences for DHTs to be implemented).

A technology-enabled patient journey map will be prepared and refined iteratively for use during interviews and community interactions. It will be a tool to assist with identifying the facilitators and barriers for remote residents accessing CPHC during different stages of their health care journey.

Initial community-engagement activities will entail consulting local elders in the two selected sites. This will inform the employment of local community-based Indigenous researchers. Elders will be consulted throughout the project. Male and female local community-based Indigenous researchers will be employed

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at each site. These researchers will be key to ensuring locally responsive and culturally appropriate data collection and for developing and maintaining relationships between the research team and local stakeholders [34]. Aboriginal researchers will actively participate in all stages of the project and all phases of the data lifecycle, including data tool creation, data collection, access analysis, co-design, analysis, interpretation of results, and dissemination of findings, including publications and presentations to key stakeholder groups.

Baseline data will be collected on general communities' views on the use of technology for health and wellness, digital health coverage [35], eHealth literacy [36], and consumer satisfaction with current use of telehealth to access health services and group health promotion sessions [37-39].

Qualitative semistructured interviews and focus group discussions (FGDs) with consumers and providers will be undertaken to explore preferences for DHTs and to inform the attributes of DHT interventions [40,41]. Community-based researchers will actively identify and recruit participants for FGDs and interviews. We will use a yarning method to conduct these FGDs and interviews. Discussions will be led by community-based Indigenous researchers to ensure that FGDs and interviews are conducted in a culturally safe way. The information obtained from the FGDs and interviews will be used to identify the key attributes of DHT interventions, which will inform the preimplementation quantitative survey. The survey will quantify the best and worst attributes of DHTs using best-worst scaling (BWS), digital technology coverage, eHealth literacy, and satisfaction of consumers who have used DHTs. The BWS will quantify consumer and local primary health care staff members' priorities for key attributes of DHTs and any differences in preferences among different groups of respondents. These findings will be used to further refine and target DHT development and implementation [41]. Local elders will be consulted at each stage of the project, ideally before employing local community-based Indigenous researchers and before each stage of the project.

Implementation

Information regarding the candidate DHTs identified during the co-design phase will be presented to the consumers, local health staff, and the leaders in government and community sectors. An integrated set of candidate DHTs will be implemented based on their feasibility and anticipated impact on access to CPHC. Interventions will be tailored to the local context using the PAR design approach led by community-based researchers who will support intervention implementation and lead the collection of feedback.

Evaluation

Postintervention data will be collected as the interventions are implemented and iteratively refined. We will use quantitative administrative data and qualitative data from interviews and FGDs with consumers and stakeholders about their experiences with DHTs in order to identify what works for whom, in what context, and by which mechanism [30].

An economic analysis will investigate the incremental costs of implementing DHTs and the associated benefits. The incremental resource use will be calculated based on different patterns of digital solution uptake in terms of additional resources required, and staff costs are based on assumptions around how many extra staff hours would be required per patient per unit of time. Whether a cost-effectiveness or cost-benefit analysis is conducted will be determined through consultations with key stakeholders.

Scalability Analysis

Scalability analyses will be conducted in two additional communities, using a previously published framework [42]. The objectives of such analysis will be to (1) identify core and adaptable features of implemented DHTs and (2) explore the feasibility of scaling DHTs to additional community sites, including cost implications. The scalability analysis will enable the evaluation team and participating organizations and their respective health boards to assess the suitability of the developed DHTs for scale and further implementation. This component will have strong translational implications.

Participants

Community partnership is an important aspect of this project. It is crucial to understand how remote communities experience access to CPHC and how DHTs may improve or deter their access to and experiences with health services. A total of 6 stakeholder groups were identified as crucial partners in this project (refer to Table 1 for details). Briefly, group 1 includes community leaders, group 2 includes consumers, and group 3 includes health service staff, health board members, and clinical and nonclinical staff at the participating sites. Likewise, group 4 includes project partner organization staff, group 5 includes technology provider organization staff, and group 6 includes other stakeholders and thought leaders. Participants must be aged 18 years or older and able to provide informed consent.

This is a multi-institutional collaboration that includes government and industry partners [43]. The key partners include the Digital Health Cooperative Research Centre, the Commonwealth Department of Health and Aged Care, the NT Government, the NT Primary Health Network (NTPHN), the Aboriginal Medical Services Alliances NT, Healthdirect, the Australian Digital Health Agency, the Menzies School of Health Research, and the University of Sydney. Representatives from each partner provide substantial research and industry input at all stages of the project.

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Table 1. Research participants, recruitment, and data collection methods for each phase of the project, evaluating the design and implementation of digital health technologies in two remote Indigenous communities of the Northern Territory, Australia.

Data source	Example participants	Sample	Recruitment method	Data collection method	Time
Primary data					
Workshops with remote NT[a] health service providers	GPs[b], allied health professionals, remote area nurses, and health service managers	60	Invitation; convenience sampling	Group discussions	Preimplementation
Group 1: community leaders at the two participating sites	Traditional owners, mayors, religious and cultural leaders, and local council board members	8	Purposive sampling via local contacts	Individual interviews	Co-design, implementation, and evaluation
Group 2: consumers at the two participating sites	Consumers (or their carers) who have used local health care services	100	Purposive sampling to ensure representativeness	Survey administered in person (digital technology coverage, best-worst scaling survey, consumer satisfaction, and eHealth literacy)	Co-design, implementation, and evaluation
Group 2: consumers at the two participating sites	Consumers (or their carers) who have used local health care services	40	Purposive sampling to ensure various perspectives are included	Individual interviews and focus group discussions	Co-design, implementation, and evaluation
Group 3: health service staff at the two participating sites	CEOs[c], managers, board members (where applicable), clinical staff (eg, doctors, remote area nurses, and Aboriginal health workers), and nonclinical staff (eg, drivers and administrative staff)	25	Purposive sampling from the local sites	Individual interviews and small group discussions	Co-design, implementation, and evaluation
Group 4: partner organization staff	NT health staff members and other partner organizations such as AMSANT[d] and NT PHN[e]	25	Purposive and snowball sampling	Workshop, small group discussion, individual interviews, and system usability surveys	Preimplementation
Group 5: technology provider organization staff (nonpartners)	Current staff of technology providers such as NBN Co[f] and Telstra	5	Purposive and snowball sampling	Meeting minutes and documents, interviews	Implementation
Group 6: other stakeholders and thought leaders	Staff at other remote clinics or those who have an in-depth understanding of the remote CPHC[g] context	25	Purposive and snowball sampling	Individual interviews and workshops	Preimplementation and co-design
Secondary data					
Comprehensive primary health service usage data	All consumers of participating health care services	All consumers	NT Health[h] and ACCHSs[i]	Clinic records and activity, CPHC service utilization data, hospitalization data, and patient travel data	Baseline and end-line (01/01/2022 to 02/28/2025)
Economic data	The key data source will be health personnel and technology-related costs.	All expenditure relevant to DHTs[j]	NT Health and ACCHSs	Expenditure and personnel data from participating institutions. Obtain data from NT Health for the participating clinic and from the ACCHSs	Baseline and end-line (01/01/2022 to 02/28/2025)

[a]NT: Northern Territory.

[b]GP: general practitioner.

[c]CEO: chief executive officer.

[d]AMSANT: Aboriginal Medical Services Alliances Northern Territory.

[e]NT PHN: Northern Territory Primary Health Network.

[f]NBN Co: National Broadband Network Company.

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[g]CPHC: comprehensive primary health care.

[h]NT Health: Northern Territory Department of Health.

[i]ACCHS: Aboriginal Community Controlled Health Services.

[j]DHT: digital health technology.

Data Collection

Table 1 provides a summary of data sources used at each stage as the project progresses.

Primary Data

Initial workshops and key informant interviews with thought leaders will be used to develop primary health care journey maps that depict how different DHTs are being used. Barriers and enablers of access to CPHC and the role of DHTs in improving access will be discussed to identify initial outcomes and mechanisms.

Interviews with stakeholders will be used to explore their perspectives on various barriers and enablers of access to CPHC and the role of DHTs in improving various aspects of access. Focus group discussions with consumers in the communities will explore key challenges and identify their preferences. A baseline survey, including the BWS survey, will collect data on DHT coverage, consumer experiences with DHT use [37,38], eHealth literacy [36], and consumers and health staff preferences for DHT implementation [40,41].

Once preferences of consumers and health care providers regarding DHTs are identified and feasible DHTs are implemented and optimized, focus group discussions, interviews, and surveys will be used to collect data about consumer use and satisfaction. This will be an iterative process and will inform scalability to other remote Indigenous communities.

Secondary Data

Secondary administrative data will be retrieved from multiple sources, including CPHC data at the two intervention sites, such as utilization data, hospitalization, and patient transport data. These analyses will complement scalability and economic analyses. Expenditure and personnel data (eg, workforce composition and supply) required for economic analyses will be obtained from the participating organizations. Further secondary data needs will be determined once the DHTs are prioritized (refer to Table 1).

Data Analysis

Qualitative Data

All interviews, focus group discussions, and workshops will be audio-recorded (if acceptable at the time) and transcribed; detailed field notes will also be used to inform analysis and understanding. Transcripts will be thematically analyzed [44,45] using a combined inductive and deductive approach and the six phases suggested by Braun and Clarke [45], that is, familiarizing with the data, initial coding and agreeing on codes, identifying themes, reviewing them, finalizing themes, and writing the results. The analysis will also be informed by realist approaches [30] to examine what works for whom and in which contexts. Data collection and analysis will be guided by multiple theoretical frameworks. For instance, the modified theory of access [28,29] will be used to identify the barriers faced by remote communities in accessing CPHC. The Systems Engineering Initiative for Patient Safety (SEIPS) framework will be used to identify system factors that influence how care is delivered in digitally enabled models of care and lead to better outcomes for patients and remote health service staff [46]. Due to the co-design nature and unique complexities of each digital health initiative, some flexibility remains in adapting theoretical frameworks specific to each initiative. Lumivero NVivo software will be used during data analysis to identify barriers and facilitators to DHT across different domains of access and the mechanisms by which interventions impact access to CPHC for different groups of consumers. Case studies will be used to understand what DHTs work (or do not) for CPHC in remote Indigenous communities, for whom, in what circumstances, and by what mechanism to improve access to health care [30,31].

A total of two community-based Indigenous researchers from each site will be involved throughout the project. They will accompany other experienced qualitative researchers to conduct each stage of data collection and analysis. Various data sources, such as consumer, provider, observation, and quantitative data, will be used to triangulate the findings. Multiple researchers will be involved in coding, refining, and summarizing data. Results will be shared with community members and the respective community-based researchers to validate the findings. The community engagement and data collection will happen over many months; therefore, trust building and longitudinal relationships are kept at the center of the data collection process.

The researchers come from diverse backgrounds, with expertise covering health services, clinical practice, remote care, digital health, human factors, and community engagement. The project leaders are non-Indigenous; however, they have spent significant time in the Indigenous health space. The community-based researchers will be the key bridge between the community and the rest of the project team. This will allow the non-Indigenous researchers to remain conscious of their viewpoints and biases and remain intentional to ensure the voice of participants is heard while interacting with the community, collecting and analyzing data, and presenting the findings. Findings of the study will be shared with key community stakeholders and community-based researchers to confirm that it aligns with the community's view.

Quantitative Data

Pre- and post-intervention data will be compared to investigate the changes in the use of primary health care services. Descriptive statistics using frequency tables and visualization, along with, where possible, univariate and multivariable regression analyses, will determine the association between the DHT interventions and revealed access to CPHC.

The economic analysis will present disaggregated incremental costs and consequences of different DHT uptakes relative to the status quo. In addition, changes in patient satisfaction and

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outcomes, use of primary care, hospitalizations, and patient transport will be assessed to determine the impact on incremental costs and outcomes of changing values of cost or outcome variables and alternative ways of delivering care.

Data Management

A central data repository of quantitative and qualitative data will be maintained on a secure university server. These data will also be stored on the university and health service organizations' password-protected computers of individual researchers who have ethical clearance to access these data during the study. Collaborators will ensure that their IT network infrastructure complies with Australian IT security standards and the General Data Protection Regulation.

Principles of Indigenous data sovereignty will be adhered to, including the involvement of Aboriginal people in all stages of data acquisition, use, and reuse.

Project Governance

This project is situated within the governance of the Strengthening Our Health System Strategy, an established collaboration of Aboriginal Medical Services Alliances NT Health (the state health department), and NT Primary Health Network. It focuses on crucial aspects of the NT Virtual Care Strategy [6] relating to improving equity, delivering culturally safe services, and providing support, resources, and guidance for staff about how and when digital health care is effectively provided. It is overseen by a Project Control Group and a Project Advisory Group, each having representation across all partner organizations and the Commonwealth Department of Health. Around 3 additional working groups (the research working group, project operational team, and technical working group) hold responsibilities for guiding research activities, ensuring smooth project delivery, and navigating technology issues in the implementation and adaptation of DHTs for CPHC in remote NT.

This implementation project has Indigenous leadership and representation, including as chief investigators, and at all stages, including design and implementation. This project also uses 1 male and 1 female community-based Indigenous researcher at each study site. The community-based researchers are mentored by experienced research team members and have been provided with training on ethical conduct in research, data collection, and analysis, and they provide reciprocal cultural mentoring for non-Indigenous research team members.

Knowledge Translation

Knowledge translation is an integrated feature of the project and is of particular interest to stakeholders and other partners in the project. The governance structure enables rapid feedback on project developments and outcomes. Sharing findings with stakeholders, health services, funders, and executive groups (eg, NT Health and the Commonwealth Department of Health) will be prioritized to inform the scalability and suitability of DHTs for CPHC in other remote Indigenous communities. Customized reports will be provided to each of the stakeholder groups and participating services. A one-page, plain-language report will also be distributed to the participating communities and all NT remote health services. The lead researchers and local community-based Indigenous researchers will present findings to key members of the community. Where necessary, Aboriginal community-based researchers will help interpret the findings in the local language. Dissemination will include peer-reviewed publications and presentations at conferences and professional workshops.

Ethical Considerations

The project was reviewed and approved by the Human Research Ethics Committee of the Northern Territory Department of Health and the Menzies School of Health Research (HREC approval no 2022-4275). Administrative approval was also obtained from the Research Governance Office, NT Health (EFILE2023/8720), and from the Boards of any participating ACCHS. Research project approval was also sought from the respective land councils, and appropriate travel and work permits were obtained for each site to support community-based research activities.

Results

As of November 2024, more than 70 consumers, 17 thought leaders, and 20 health care professionals have been interviewed to assess the feasibility of various digital health initiatives to improve access to health care in the two implementation sites. Researchers have spent more than 50 days at each implementation site. Several digital health initiatives have been co-designed and optimized, which include telehealth from the primary health care clinics to outpatient services, telehealth for aged care allied health services, an SMS text messaging program on selected topics identified by the community, and exploring the feasibility of teledentistry. An economic analysis is also underway to help inform the financial benefit (or loss) of the initiatives. Initial findings from these sites have informed scalability assessments in two additional sites. Data analysis is progressing. The findings will be reported in reports and peer-reviewed publications.

Discussion

Principal Findings

This project aims to optimize the use of DHTs to improve access to CPHC in remote Indigenous communities. DHTs, including telehealth, have been used ad hoc or as pilot projects rather than for mainstream ongoing health care delivery [47]. While there are promising findings from other studies in the NT [14,16], to the best of our knowledge, our project will be the first to co-design DHT interventions with consumers and remote health providers and to systematically evaluate the acceptability and effectiveness in remote Indigenous communities.

Key findings from this project will include community preferences and priorities for digital health, the co-design process of the digital health initiatives, and learnings from implementation and evaluation. The findings will provide evidence on the impact of digital health initiatives on access to health care and remote community and health provider experiences. Barriers and facilitators to implementing these

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initiatives will help inform learnings for future DHT implementations in remote communities.

The involvement of multiple stakeholders, including consumers, health service providers, technology partners, and policy and funding partners, is critical to improving the knowledge about and skills for using DHTs to provide CPHC in remote communities [24,48]. The use of one DHT (telehealth) to improve access to CPHC has been examined in remote NT, and it has been reported that the doctors were able to provide more clinical care because less of their time was consumed traveling to each community [14,16]. This project considers a broader range of DHTs, extending beyond telehealth to include, for example, SMS text messaging for appointment reminders, medication reminders, health promotion messages, community health portals, and use of the Australian Government's My Health Record. The intention is to improve access to CPHC, promote equity, and improve health outcomes in the two remote communities through improved continuity of care and fewer avoidable hospitalizations and patient transfers. Effective and acceptable CPHC also capitalizes and contributes to increased trust and long-term relationships with health service providers to increased cultural security, greater convenience in receiving health care, a reduction in health care disparities, and stronger community engagement in health management and well-being [6,14].

The economic analysis is unique, as previous studies have not reported such systematic evaluations. The virtual care strategy of NT Health [6] has reported that digital health has the potential to save AU $6.3 million (US $4.095 million) on annual travel costs and AU $950,000 (US $617,500) on the cost of appointment cancellations in the NT (1 AU$ =0.65 USD). However, these estimates are not based on community-based studies from the NT. Our economic evaluation intends to show the financial benefit at the local level for the clinic and patient, which will inform decision-making about implementing DHTs in CPHC.

Unintended consequences are not uncommon in the digital health space, and one such risk is the additional administrative and clinical workload that the resident staff may bear and the concern for burnout [17,47]. The co-design and PAR approach is expected to help identify such issues proactively and address them on time. For instance, additional workload needs to be accounted for when telehealth consultations with outpatient hospital services or health promotion sessions are offered in the community [49].

A second issue is managing the "digital divide" [50,51]. Cautious and informed DHT identification and implementation will minimize the impact of broad-stroke DHT interventions that widen the gap in access to CPHC experienced by disadvantaged populations who may not have digital devices, connectivity, or digital literacy or skills for such consultations [52,53]. The realist approach, by identifying how DHTs work and who needs support, why, and in what circumstances within the available provisions, adds further critically important information regarding approaches to DHT implementation in marginalized populations such as those living in remote Indigenous communities [30,31].

A third issue is managing perceptions that telehealth may be "a cheaper option" for CPHC in remote communities [10]. In an ideal situation, the same clinical staff would always be available face-to-face for consultations, but in many remote communities, this is not realistic due to high staff turnover, declining general practitioner training enrollments, vast geographical distribution of the smaller communities, and the inequitable distribution of resources [8,27,54]. This project will identify opportunities to implement DHTs that do not take away existing face-to-face services but rather complement and enhance CPHC in remote communities. The DHT interventions may be catalysts to improve health and well-being in remote Indigenous communities.

Limitations

There are important limitations to consider in this study. Due to the small remote community population sizes, the sample included in the studies will have limited statistical power but will have inclusive consideration for the remote communities. Poor digital connectivity and high staff turnover, including changes in the health service administration, are also beyond the control of our project team. The use of secondary administrative data that have not been collected for the express purpose of the study is likely to present additional challenges. For example, the ACCHSs and government health services use different patient information management systems, limiting the ability to link datasets and the comparability of data available at different sites. Despite its strengths, the PAR approach is time-consuming, needs additional efforts to focus on processes, and has the potential to lead to friction among the stakeholders due to competing priorities [24,25]. While it can be counterproductive if not handled with care and expertise, this has been accounted for in the project design and development strategies, which are founded on the considerable expertise of the research team. The credibility and local ownership offered by the PAR approach outweigh these limitations.

Conclusions

Digital innovations have affected every aspect of our lives. It is unlikely that the current health system and health service delivery can remain isolated from such a rapid proliferation of innovative DHTs. This project provides a unique opportunity to optimize and systematically evaluate key digital health interventions. It will also highlight why DHTs work for some but not for others, identifying risk groups to create appropriate supports within the community. Furthermore, the economic analysis will help the local health board and other stakeholders make an informed decision to adopt, refine, or reject DHTs in the future. In conclusion, the project has the potential to substantially improve access to CPHC services for the remote Indigenous communities of the NT. Such improved access will help improve the health outcomes of those living in remote communities.

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Authors' Contributions

VK led the conceptualization, formal analysis, methodology, project administration, and supervision of the study and drafted, reviewed, and edited the original manuscript. DR and ES contributed to the formal analysis, methodology, supervision, and reviewing and editing of the manuscript. NN, TS, KC, AP, SN, AH, TC, PB, and JW provided significant input in drafting, revising, and editing the protocol. TS, JW, and DR served as project leads and were responsible for funding acquisition, resource allocation, project administration, and supervision. SN and AH led the conceptualization and investigation of the economic evaluation and reviewed and edited the related content.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guide sample.
[DOCX File , 18 KB - resprot_v14i1e68892_app1.docx]

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Abbreviations

ACCHS: Aboriginal Community Controlled Health Service
AHP: Aboriginal health practitioner
BWS: best-worst scaling
CPHC: comprehensive primary health care
DHT: digital health technology
iCHECK-DH: Guidelines and Checklist for the Reporting on Digital Health Implementations
NT: Northern Territory
PAR: participatory action research
SEIPS: Systems Engineering Initiative for Patient Safety

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Protocol

AI-Based Algorithm to Detect Heart and Lung Disease From Acute Chest Computed Tomography Scans: Protocol for an Algorithm Development and Validation Study

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Abstract

Background: Dyspnea is a common cause of hospitalization, posing diagnostic challenges among older adult patients with multimorbid conditions. Chest computed tomography (CT) scans are increasingly used in patients with dyspnea and offer superior diagnostic accuracy over chest radiographs but face limited use due to a shortage of radiologists.

Objective: This study aims to develop and validate artificial intelligence (AI) algorithms to enable automatic analysis of acute CT scans and provide immediate feedback on the likelihood of pneumonia, pulmonary embolism, and cardiac decompensation. This protocol will focus on cardiac decompensation.

Methods: We designed a retrospective method development and validation study. This study has been approved by the Danish National Committee on Health Research Ethics (1575037). We extracted 4672 acute chest CT scans with corresponding radiological reports from the Copenhagen University Hospital–Bispebjerg and Frederiksberg, Denmark, from 2016 to 2021. The scans will be randomly split into training (2/3) and internal validation (1/3) sets. Development of the AI algorithm involves parameter tuning and feature selection using cross validation. Internal validation uses radiological reports as the ground truth, with algorithm-specific thresholds based on true positive and negative rates of 90% or greater for heart and lung diseases. The AI models will be validated in low-dose chest CT scans from consecutive patients admitted with acute dyspnea and in coronary CT angiography scans from patients with acute coronary syndrome.

Results: As of August 2025, CT data extraction has been completed. Algorithm development, including image segmentation and natural language processing, is ongoing. However, for pulmonary congestion, the algorithm development has been completed. Internal and external validation are planned, with overall validation expected to conclude in 2025 and the final results to be available in 2026.

Conclusions: The results are expected to enhance clinical decision-making by providing immediate, AI-driven insights from CT scans, which will be beneficial for both clinicians and patients.

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KEYWORDS

artificial intelligence; AI; computed tomography; machine learning; cardiac decompensation; dyspnea; acute care; diagnostic imaging

Introduction

Background

Dyspnea accounts for up to 15% of all acute hospital admissions [1], and patients with dyspnea are often older adults and have multimorbid conditions. Correctly diagnosing the cause of dyspnea as either heart or pulmonary disease in emergency settings can be challenging, and 20% of the patients with acute heart failure are initially misdiagnosed [2]. Chest radiographs have long been the primary diagnostic tool for acute dyspnea [2]. However, cardiac decompensation and signs of pneumonia are often overlooked on chest radiographs, especially in older adult patients with chronic lung disease [3]. In addition, many patients with acute dyspnea cannot stand while undergoing chest radiographs, which further limits their diagnostic value.

Chest computed tomography (CT) scans offer the highest standard of care modality for patients with comorbid conditions and emergent conditions, such as pulmonary embolism, aortic dissection, pneumothorax, and chest trauma. Moreover, the diagnostic use of CT imaging for patients with dyspnea has increased [4]. CT scans allow for fast image acquisition and depict anatomy in cross section and 3 dimensions, providing superior information compared to conventional chest radiographs on diseases in the pulmonary parenchyma, heart, and vessels [5]. In our previous work, we identified 5 characteristic CT signs that were strongly associated with acute heart failure in patients with dyspnea [6] and later demonstrated that CT was 4 times more likely than chest radiography to detect cardiac decompensation in the emergency department [7]. Building on these findings, we now aim to enable automatic detection of cardiac decompensation on CT.

With an expected increase in older adults and patients with comorbid conditions admitted with dyspnea, there will be a greater need for accurate and fast diagnostic methods in the emergency departments. Over the course of the last 2 decades, there has been a worldwide increase in the number of CT scans [4]. In combination with a shortage of radiologists, this limits the broad use of chest CT imaging for patients with acute dyspnea in the emergency setting [8]. Automated diagnostic tools have the potential to enhance radiological efficiency by expediting the assessment and triage of patients presenting with acute dyspnea, thereby streamlining workflow in acute care settings. Conditions, such as cardiac decompensation, pneumonia, and pulmonary embolism, require timely diagnosis and intervention to improve clinical outcomes [1,2,9], making them appropriate targets for such models.

While the potential of artificial intelligence (AI) to support physicians in acute care is substantial, several challenges are particularly relevant for patients with dyspnea. Older adults and populations with comorbid conditions may introduce demographic bias and limit generalizability across settings, and variations in CT protocols, scanner types, and image quality can affect feature representation. Furthermore, interpretability is essential to ensure clinical applicability. In this protocol, we outline strategies to address these challenges by including diverse training data and multiple CT protocols and planning model outputs that are clinically interpretable with validation as a central component.

Previous AI studies have mainly focused on detecting pneumonia and pulmonary embolism on chest CT scans [10-15]. To our knowledge, no previous work has addressed the automated identification of acute heart failure on chest CT. This study introduces an algorithm capable of detecting all 3 conditions in the acute setting.

Objectives

We hypothesize that AI algorithms can identify radiological conditions requiring urgent intervention with diagnostic accuracy comparable to current clinical radiology practice.

The aim of this protocol is to outline the framework for developing and validating AI algorithms to support this initiative. The proposed algorithms should be able to automatically analyze chest CT scans with the potential for providing immediate feedback on the likelihood of dyspnea-related diagnoses. The primary focus will be on cardiac decompensation, with the model also serving as a foundation for detecting pneumonia and pulmonary embolism.

Methods

Study Design

This is a retrospective study, including method development and validation (Figure 1).

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Figure 1. Overview of development and validation cohorts. We did not extract CT studies from participants from the FACTUAL study (year 2017-2019) or for patients below 18 years of age. CT: Computed Tomography; NSTE-ACS: non–ST-segment elevation acute coronary syndrome. Created with Biorender.

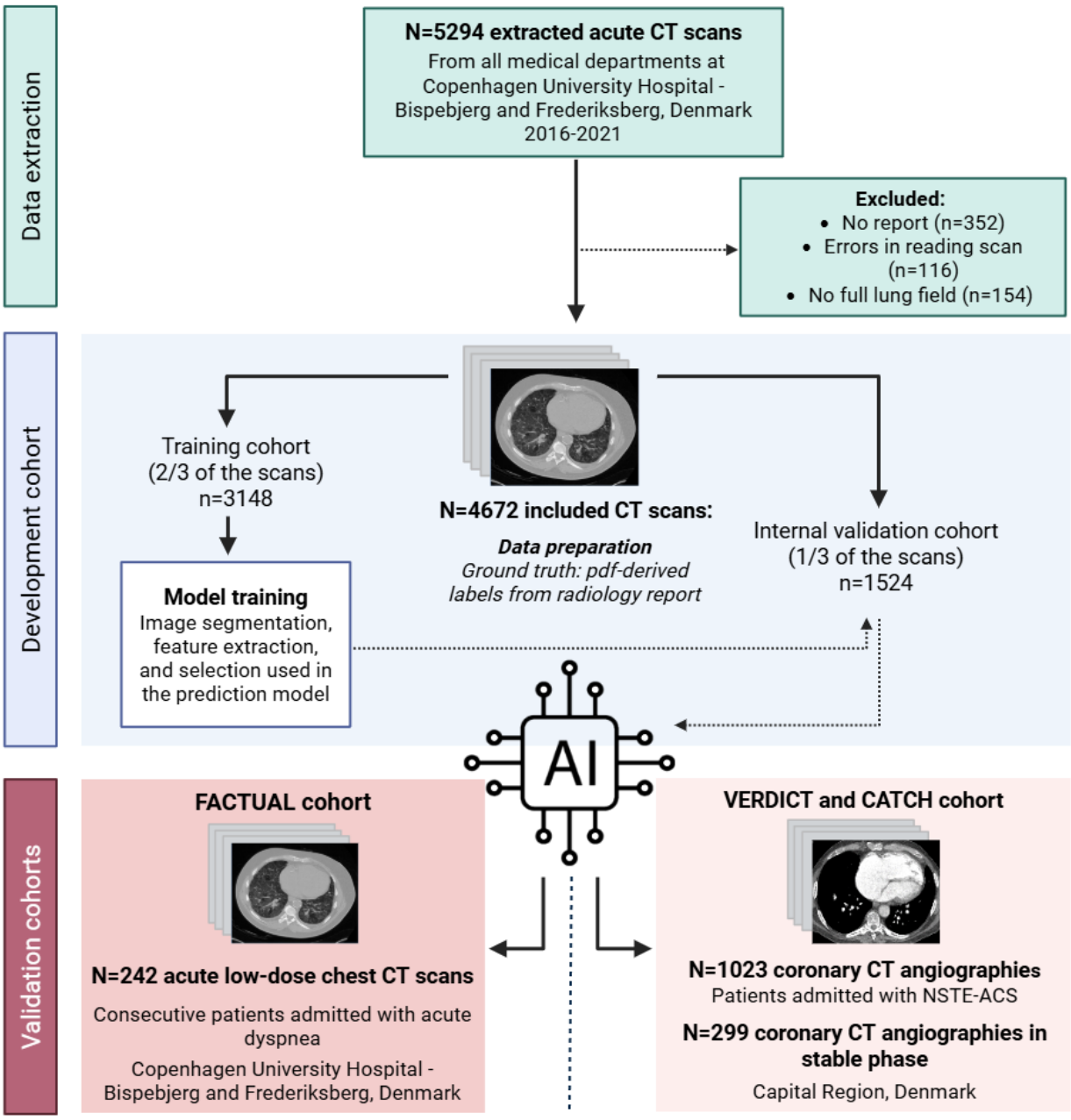

Training and Internal Validation Cohort

We extracted CT scans with accompanying radiological reports from all medical departments at the Copenhagen University Hospital–Bispebjerg and Frederiksberg Hospital, Denmark, conducted from January 1, 2016, to December 31, 2021. Consequently, 12,348 CT scans from 5111 studies of 4672 individual patients were extracted (Figure 1).

The scans originated from all medical wards ordering acute CT scans as standard diagnostic procedures. All types of CT scans (chest CT and abdominal scans, including the lungs) were included, encompassing various manufacturers, contrast-enhanced scans, noncontrast scans, low-dose protocols, and various imaging phases. Given the comprehensive inclusion of all acute chest CT examinations, the indications for these scans were broad and included assessments of chest pain, dyspnea, suspected pulmonary embolism, suspected pulmonary infection, suspected pneumothorax, or pleural effusion. We did not extract CT scans for patients aged 18 years or younger and participants in the Feasibility of Computer Tomography in Patients with Acute Decompensated Heart Failure (FACTUAL) study, as it served as a clinical validation cohort [7].

Development of the AI Algorithm

We will develop an individual AI algorithm for automatic interpretation of radiologic signs of cardiac decompensation on chest CT scans, but the algorithm will also serve as a foundation for pneumonia and pulmonary embolism. The model will be trained to detect each condition, pulmonary congestion,

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pneumonia, and pulmonary embolism, independently, using a multilabel approach with separate binary classifiers. This allows more than one condition to be identified in the same scan. The CT scans were extracted in pseudonymized form.

Participants will be randomly split on the participant level into training (2/3) and internal test data (1/3; Figure 1). This process will be carried out separately for each of the 3 diseases, creating distinct AI models for each. We will train boosted tree prediction models using volume, diameter, and density measurements from structures segmented in the CT images. The segmentations will be derived from TotalSegmentator, extreme gradient boosting, and in-house codes [16,17].

We do not expect substantial missing data, as all CT scans will be extracted retrospectively without patient consent. Extreme, noisy, or missing feature values, typically caused by segmentation errors, will be handled by allowing them as many splits as possible in the tree-based model. To develop the model, a three-step procedure will be applied for boosted trees models: (1) parameter tuning with all features, (2) feature selection by forward selection guided by internal feature importance measures of extreme gradient boosting, and (3) retuning with the selected features. Hyperparameter optimization will be conducted by grid search using the area under the receiver operating characteristic curve as the evaluation metric. Parameter tuning and feature selection will be performed on the training data with stratified 3-fold cross validation, defined at the participant level and kept consistent across all steps.

We will use grid search and forward feature selection to find the best parameters. To further assess performance and enhance model interpretability, results will be presented using Shapley Additive Explanations (SHAP) [18]. The overall impact of each feature will be illustrated with SHAP beeswarm and bar plots. SHAP waterfall plots will explain the contribution of individual features to specific predictions, supported by visual inspection of the corresponding segmentations. This analysis allows for the removal of features deemed clinically unimportant or redundant. To evaluate the AI algorithms, they will be qualitatively evaluated by visual inspection, including segmentations. We will qualitatively evaluate the AI algorithms and model predictions using receiver operating curve (ROC) curves and confusion matrices of the thresholded predictions. False positives and false negatives will be evaluated by chief physicians with a special interest in thorax radiology.

Ground Truth for Development and Validation of the AI Algorithm

The ground truth for the development and validation will be the radiological description of each CT scan, prepared by the on-call radiologist following standard clinical procedures. The on-call radiologists include both board-certified specialists and junior radiologists in training. All final assessments are supervised by a board-certified radiologist. All radiological reports are produced as part of routine clinical practice, and while variations in descriptions may occur due to specific clinical focuses of the scans, the regional standard reporting procedures ensure a consistent approach to assessing pathologies. These radiological findings will be extracted from the radiology reports (PDF) using a set of regular expressions for the selected diseases. The report clinical labels for cardiac decompensation may encompass terms such as pulmonary congestion, pulmonary edema, heart failure, and decompensation in the description of the radiologist. A subset of training data will be used to iteratively improve expressions. All reports containing these indicators, whether affirming or negating their presence, will be manually reviewed to correct any labeling errors. All labels will be reviewed for technical accuracy, with unclear cases assessed by project clinicians. False positives and negatives will be evaluated by chief physicians specializing in thoracic radiology.

Given the large volume of scans, manual review by an expert radiologist is impractical and resource intensive, but this approach maximizes the dataset, reflects real-world workflow, and mitigates risks to model validity.

Target Condition Distribution

Previous studies from Denmark have reported that acute heart failure accounts for approximately 6% of medical hospital admissions among adults [19], that the incidence of pneumonia requiring hospitalization was 442 per 100,000 person years in 2003 [20], and that the incidence of pulmonary embolism requiring hospitalization occurs at a rate of 64 per 100,000 adults annually [21]. Preliminary labeling of the development dataset shows a similar distribution, with 7% to 8% positive for cardiac decompensation, while labeling for pneumonia and pulmonary embolism is still ongoing.

Validation of the AI Algorithm

The AI algorithms will be internally validated using the area under the curve from ROC curves and confusion matrices. Optimal thresholds for the likelihood of heart and lung diseases will be obtained from the validation cohort and defined by a true positive rate and true negative rate of 90% or greater. These thresholds will be tested for the prediction of heart and lung diseases in the validation cohorts.

Validation in Chest CT Scans in the Clinical FACTUAL Cohort

The AI algorithm for not only cardiac decompensation but also pneumonia will be validated in a previously performed clinical prospective observational study. The study included 242 consecutive patients with dyspnea, who underwent acute low-dose, noncontrast, chest CT scans within 12 hours from admission (FACTUAL study [H-17000869]; Textbox 1) [7]. CT scans were acquired without contrast at low dose (<2 mSv) using a multislice scanner and standard lung and soft tissue reconstruction kernels. A firewall ensured that none of these patients were included in the AI development sets.

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Textbox 1. Inclusion and exclusion criteria for the FACTUAL, VERDICT (Very Early Versus Deferred Invasive Evaluation Using Computerized Tomography), and CATCH (Cardiac CT in the Treatment of Acute Chest Pain) studies.

Inclusion criteria for the FACTUAL study

- Aged >50 years
- Acute dyspnea, combined with at least 1 abnormal objective parameter supporting respiratory imbalance
  - Respiratory rate of more than 20 breaths per minute
  - Saturation below 95% (if known chronic obstructive pulmonary disease (COPD) below 92%)
  - Abnormal partial pressure of oxygen (pO2) or partial pressure of carbon dioxide (pCO2) in arterial blood
  - Objective signs of heart failure (ie, jugular vein distention, peripheral edema, orthopnea, and bilateral rales on auscultation)
  - Rhonchi or prolonged breathing on auscultation

Exclusion criteria for the FACTUAL study (none of the exclusion criteria must be met)

- All study examinations, including low-dose chest computed tomography (CT) scans, performed later than 12 hours after admission
- Patients who are unstable
  - Requiring ventilation (including noninvasive ventilation)
  - Requiring intensive care (inotropic treatment)
  - Requiring telemetry due to acute coronary syndrome
- Patients who refuse or cannot provide consent (ie, mental illness [eg, dementia] and language barriers)
- Patients without Danish citizenship
- Life expectancy <3 months (assessed by the emergency department physician)
- CT thorax already indicated (pulmonary embolism, aortic dissection, or aneurysm)
- Patients who are isolated (ie, vancomycin-resistant *Escherichia coli* and influenza)

Inclusion criteria for the VERDICT study

- Invasive coronary angiography clinically indicated and logistically possible within 12 hours from the non–ST-segment elevation acute coronary syndrome (NSTE-ACS) diagnosis
- Aged >18 years
- Clinical suspicion of ACS, combined with at least one of the following high-risk criteria:
  - Electrocardiogram (ECG) changes indicating new ischemia (new ST-segment depression, horizontal or downsloping ≥0.05 mV in 2 consecutive leads, and T-wave inversion >0.01 mV in 2 leads with prominent R-wave or R/S ratio >1)
  - An increase in coronary markers of ischemia (troponin)

Exclusion criteria for the VERDICT study (none of the exclusion criteria must be met)

- Pregnancy
- Patients who refused or could not provide consent
- Indication for acute invasive coronary angiography (very high-risk NSTE-ACS)
- Life expectancy <1 year
- Known intolerance to platelet inhibitors, heparin, or x-ray contrast that could not be remedied medically
- Previous coronary artery bypass grafting
- Creatinine >140 µmol/L
- Known atrial fibrillation
- Women aged <45 years were not considered eligible for coronary CT angiography

Inclusion criteria for the CATCH study

- Hospitalized with suspicion of NSTE-ACS
- Normal or nondiagnostic ECG findings

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- Normal troponins
- Discharged within 24 hours without recurrence of chest pain
- Clinical indication for further noninvasive, outpatient cardiac evaluation, evaluated by the treating physician

Exclusion criteria for the CATCH study (none of the exclusion criteria must be met)

- Aged <18 years
- New diagnostic ECG changes with ST-segment elevation or depression >0.5 mm or T-wave inversion >4 mm in ≥2 contiguous leads
- Women of childbearing age not using approved contraception
- Geographical residence or mental or physical conditions that could complicate follow-up
- Known allergy to iodinated contrast agents
- Serum creatinine >130 mg/L
- Abnormal chest radiography or blood test results that could explain chest pain
- Previous coronary artery bypass grafting
- Patients who refused or could not provide consent

The primary outcome is to validate the diagnosis of the AI algorithm in identifying the following: (1) normal CT images without treatment-requiring pulmonary changes, (2) radiological signs of cardiac decompensation, and (3) radiological infiltrates indicative of pneumonia.

The gold standard is the radiological evaluation of the CT images, which were analyzed in 2 ways:

1. Randomly analyzed by the on-call clinical radiologists according to clinical standards. The on-call radiologists had access to the medical journal, laboratory reports, and previous radiology images. The workflow is as follows: a radiology report is made by the on-call clinical radiologist and subsequently approved by a senior radiologist.
2. Two blinded, independent specialist thoracic radiologists evaluated every CT scan for distinct signs of heart and pulmonary diseases according to the Fleischner Society list [7,22].

Validation in Coronary CT Angiograms in the VERDICT and the CATCH Studies

Overview

We aim to calibrate and validate the AI algorithm for cardiac decompensation on coronary CT angiographies (CCTA) in the Very Early Versus Deferred Invasive Evaluation Using Computerized Tomography (VERDICT) trial and in the Cardiac CT in the Treatment of Acute Chest Pain (CATCH) trial.

VERDICT Study

The VERDICT study was a large-scale randomized-controlled trial conducted in the Capital Region, Denmark, that included 2147 patients with non–ST-segment elevation acute coronary syndrome (NSTE-ACS). Patients were randomized to invasive coronary angiography within 12 hours or standard invasive care within 48 to 72 hours. In a substudy, 1023 participants from both groups underwent CCTA before the invasive procedure (Textbox 1) [23]. CCTA was performed on 64- or 320-detector scanners, predominantly with prospective electrocardiogram-triggering and intravenous contrast injection [23].

CATCH Study

In a randomized, controlled trial, 299 patients with acute chest pain but normal electrocardiogram findings and troponin values were randomized to CCTA in a stable phase and 301 to standard care (Textbox 1) [24]. CCTA was performed on a 320-detector scanner with standard premedication and contrast protocols [24].

The primary purpose is to investigate whether the AI-generated label of cardiac decompensation will have an independent prognostic value to predict death and heart failure hospitalization within 3 years of follow-up. An automatic AI report of cardiac decompensation on CCTA may guide early heart failure treatment for patients with NSTE-ACS. This is beneficial, as the lung field of CCTA often is underused but can provide important complementary information about pulmonary diseases.

Ethical Considerations

This study is approved by the Danish National Committee on Health Research Ethics (1575037). All data used for algorithm development and validation were pseudonymized before research access.

The data were accessed for research purposes during the period from 2022 to 2023. We collected information on clinical indications for CT scans, radiographic diagnoses, and patient sex and age, with no other sensitive data obtained. Permission to use patient data was granted based on the determination that the study serves the public interest and only involves pseudonymized data. Therefore, the requirement for oral or written consent was waived. The validation cohorts were approved under separate ethical permissions and required written informed consent from all participants [7,23,24]. No compensation was provided to participants.

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Dissemination of Research Outcomes

Incidental findings are expected to be few due to the retrospective nature of the data collection as part of the clinical workflow; however, any findings identified during AI-assisted validation will be handled in accordance with the approved study protocol. Cases meeting predefined clinical significance criteria will be reviewed by a multidisciplinary safety committee and, if appropriate, communicated to the participant.

In terms of dissemination, the findings of this study are planned to be published in a high-impact, peer-reviewed journal and will be presented at international conferences, ensuring widespread dissemination and engagement with the broader scientific community (Multimedia Appendix 1). A separate technical methods article will be prepared and published independently. That methods article will provide a comprehensive and transparent description of the AI algorithm development, including data preprocessing, feature extraction, model training, and evaluation procedures (Multimedia Appendix 1).

Data Management

All data are pseudonymized and stored securely on encrypted institutional servers with restricted access. Data extraction and coding are performed using automated scripts, with quality control checks applied during preprocessing.

Statistical Analyses

In each validation cohort, the default thresholds obtained from the internal validation will be used to calculate the diagnostic ability of the AI algorithm to predict the prespecified heart and lung diseases. We will, for all diagnoses, calculate odds ratios, sensitivity, specificity, positive and negative predictive values, positive and negative likelihood ratios, and area under the curve from the ROC curves.

Power Calculation

To account for variations in scanner generations, we included chest CT scans from all medical departments at a large hospital from 2016 onward, yielding approximately 5000 scans. Our initial estimation suggested the need for access to at least 15,000 scans to develop an algorithm with high diagnostic accuracy, as we expected that not all extracted scans would be suitable for algorithm development. Factors such as multiple scans per patient, incomplete thoracic coverage, and preprocessing challenges reduced the number of usable scans. Furthermore, we anticipated a distribution of diagnoses among patients with dyspnea, including heart failure, pneumonia, and chronic obstructive pulmonary disease exacerbations [9]. Given these considerations, we expect that our dataset of 5000 scans will provide a sufficient foundation for reliable training and validation of the AI model.

Results

This is a retrospective study based on previously collected imaging data. As of August 2025, we have completed the extraction of CT scans and accompanying radiological reports. Natural language processing, CT segmentation, and the final stages of developing the AI algorithm are completed for pulmonary congestion but are still ongoing for the remaining conditions. The development and validation of the AI model constitute the main components of the study and are ongoing. Validation using 3 preexisting cohorts (FACTUAL, VERDICT, and CATCH) is planned (Multimedia Appendix 1). No new data collection or participant recruitment is planned, as all data have already been collected under previous ethics approvals.

A modified SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) schedule (Multimedia Appendix 1) outlines the timeline for key milestones, including algorithm development, internal validation, expert misclassification review, external validation in independent cohorts, and dissemination. We expect validation to conclude in late 2025, with final study results expected in 2026.

Discussion

Anticipated Findings

Overview

This study aims to develop and validate AI algorithms to automatically analyze chest CT scans and deliver instant feedback on the probability of dyspnea-related conditions. Our primary focus is on detecting cardiac decompensation while also laying the groundwork for assessing pneumonia and pulmonary embolism. To broadly test the algorithm, we evaluate the algorithm for cardiac decompensation in 3 different cohorts. The intended use of the algorithms is to assist in the detection of these conditions in a hospital setting, particularly in acutely admitted patients presenting with dyspnea. The algorithm is designed to support physicians, both radiologists and nonradiologists, by aiding in the early identification of critical findings while awaiting the final radiologic report. The AI model will provide interpretability through SHAP values for participant-level explanations, supported by visual inspection of segmentations and a numerical probability score for each detected disease. Its primary role will be to expedite early decision-making by highlighting relevant imaging features, potentially reducing time to diagnosis and treatment initiation. Optimizing the use of CT scans is crucial given their increasing prevalence. Currently, there is no standardized routine for describing cardiac decompensation on chest CT scans, presenting a gap that AI applications can fill.

AI Applications in Chest CT: Previous Evidence

CT scans are highly accurate for diagnosing cardiac decompensation and pulmonary diseases, often revealing subtle signs missed by chest radiographs [5,7]. Although CT scans involve higher radiation exposure, the advent of low-dose and ultra-low–dose chest CT scans has mitigated some of this concern while maintaining their diagnostic accuracy [25]. While it is unlikely to replace chest radiographs soon, CT imaging is frequently used when chest radiographs are inconclusive, especially in patients with undifferentiated dyspnea. It is important to address the upcoming challenges, including the shortage of radiologists and the need for AI assistance for nonradiologists. AI models can support physicians awaiting the final radiologic report and may alleviate radiologists' workload,

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as AI models have been shown to reduce radiology reporting times by up to 22% [26].

To our knowledge, no published research has designed AI algorithms specifically to detect radiologic signs of cardiac decompensation on chest CT scans. One study demonstrated that machine learning–based quantification of lung water could identify increases in extracellular lung water in patients with heart failure with preserved ejection fraction, even in the absence of symptoms [27]. Previous research has highlighted the effectiveness of AI in diagnosing pulmonary conditions, including lung nodules [10], COVID-19, and COVID-19–related pneumonia [11,12]. A recent review emphasized that AI models can quantitatively assess pneumonia severity using CT images [13]. However, existing studies on CT imaging have primarily focused on patients with COVID-19. Our study extends this application, providing new insights into the use of AI for diagnosing different types of pneumonia. Limited research exists on AI and the detection of pulmonary embolism. One study demonstrated superior sensitivity and negative predictive values of AI models for pulmonary embolism detection, thereby reducing the risk of missed diagnoses [14]. Another study showed that an AI model aids detection and prioritization of incidental pulmonary embolisms on CT scans, but it was conducted in oncology patients [15].

Our study will assess the diagnostic efficacy of AI models in a broad population of hospital patients undergoing acute chest CT scans and across multiple diagnostic categories. For future clinical applications, the performance of the AI algorithms must be examined across various cohorts to demonstrate reliable differentiation between patients with and without critical conditions. At this stage, considerations such as diagnostic performance, regulatory approval, and integration into clinical workflow remain essential factors to establish the true clinical utility of these AI models.

Mitigating Imaging Variability and Validation Thresholds

Differences in imaging protocols across cohorts, including variations in scanner type, reconstruction kernels, and acquisition parameters, may affect AI model performance. To address this, the algorithm will be developed using data from multiple manufacturers, image types, and reconstruction kernels, and it will include both contrast-enhanced and noncontrast scans. This approach is designed to minimize the impact of technical variability and improve generalizability across different clinical settings, reducing the risk of bias from scanner settings and acquisition protocols. Planned cross-cohort validation will further ensure the robustness of the algorithm.

The sensitivity and specificity thresholds of 90% or greater chosen for validation are ambitious, but they align with performance levels generally regarded as necessary for clinical decision support in acute care, where the consequences of false negatives and false positives can be substantial. Thus, these thresholds serve as a target for ensuring patient safety and diagnostic reliability. We acknowledge that achieving such levels may involve trade-offs, including impaired sensitivity-specificity balance or reduced generalizability due to increased model complexity. High false positive rates could burden clinicians with unnecessary alerts, while false negatives might delay diagnosis of critical conditions.

Strengths and Limitations

First, we use on-call radiological image descriptions as ground truth for developing and internally validating the AI algorithms. This is a limitation, as clinical reports may contain flaws or misdiagnoses, potentially compromising the accuracy of the AI algorithms. However, our approach allows for the algorithms to be easily trained on a large dataset and later be refined with higher-quality datasets as performance issues are identified in subsequent validations.

Second, the AI models are developed and will be validated on CT scans in the FACTUAL study, all obtained from the same university hospital in the Capital Region. While the diverse development cohort includes a broad range of acute chest CT scans, the FACTUAL cohort consists solely of low-dose, noncontrast chest CT scans from patients with dyspnea. To ensure independent validation in a clinical setting, FACTUAL data were strictly excluded from the development dataset. However, broader validation is necessary in diverse patient cohorts from other regions. We aim to extend validation to coronary CT angiography scans from the VERDICT and CATCH studies, which were acquired in different hospitals and time periods. However, these datasets lack radiological reports and primarily assess the algorithm's prognostic value. The validation will provide evidence of the algorithm's applicability in external cohorts, but we also underscore the need for further external validation using datasets with radiological ground truth.

Third, differences in imaging protocols across cohorts, such as variations in scanner type, reconstruction kernels, and acquisition parameters, may influence AI model performance in external cohorts. To mitigate these effects, the algorithm will be calibrated using normalization, data augmentation, and cross-cohort validation to ensure robustness. Such strategies are intended to minimize the impact of technical variability and enhance generalizability across different clinical settings, but site-specific biases need to be addressed in future cohorts.

Fourth, although the AI model will be trained on well-characterized cohorts, its future performance may be affected by variations in demographic, technical, and clinical factors outside the study setting. Demographic differences, such as age, sex, and comorbidities, could influence the appearance of the disease on CT scans. Technical factors, including scanner models, acquisition parameters, and image reconstruction methods, may alter feature representation and introduce site-specific biases. Clinical workflow differences, such as referral patterns or labeling practices, could further affect the distribution and definition of target conditions. These challenges are inherent to all nonmulticenter studies. Consequently, the algorithm will likely require further adaptation and validation before being deployed commercially or applied globally. To mitigate these issues, this protocol emphasizes standardized labeling procedures and the inclusion of diverse training data with multiple scanning protocols and scanner brands. In addition, external validation across diverse populations and imaging settings is needed to further strengthen the model.

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Successful clinical implementation will also require regulatory approval, user-friendly integration, and appropriate clinician engagement. If the developed AI model demonstrates satisfactory performance in the planned validation cohorts, subsequent work will examine how best to integrate it into routine clinical workflows; however, this is not encompassed by this protocol. Finally, potential risks of AI, including clinician overreliance and false negative results, must be carefully considered. AI outputs are intended to support, not replace, clinical judgment.

A strength of this study is that the AI algorithms will be developed in a cohort of undifferentiated patients from all medical departments ordering acute scans. We included diverse CT images conducted with different scan protocols, reconstruction kernels, and scanner models and vendors, both contrast and no contrast and low dose and high dose. The FACTUAL patient cohort for the validation is well validated, with comprehensive and detailed radiologic labels provided by 2 blinded thoracic expert radiologists.

Conclusions

In conclusion, this study will develop AI algorithms that enable automatic analyses of acute CT scans in adult patients for the detection of acute heart and lung diseases across several populations of patients who are acutely hospitalized. This work is a critical first step, establishing a methodology that can guide subsequent multicenter and international validation studies.

Acknowledgments

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Data Availability

Data sharing is not applicable to this article as no new datasets were generated or analyzed during this study protocol. The TotalSegmentator software and the boosted trees model implementation are publicly available. Upon publication of the study results, the source code for the AI algorithm will be made available in a public repository (GitHub).

Conflicts of Interest

OWN is currently employed at Novo Nordisk. MDB is partly funded by the Netherlands Organisation for Scientific Research (NWO) VICI project VI.C.182.042. MBA has received speaker honoraria from Philips, Siemens Healthineers, AstraZeneca, and Boehringer Ingelheim, and reports a departmental research agreement with Siemens Healthineers. All other authors declare no conflicts of interest.

Multimedia Appendix 1
Planned SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) study schedule.
[DOCX File , 16 KB - resprot_v14i1e77030_app1.docx]

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Abbreviations

AI: artificial intelligence
CATCH trial: Cardiac CT in the Treatment of Acute Chest Pain
CCTA: coronary computed tomography angiography
CT: computed tomography
FACTUAL trial: Feasibility of Computer Tomography in Patients with Acute Decompensated Heart Failure
NSTE-ACS: non−ST−segment elevation acute coronary syndrome
ROC: receiver operating curve
SHAP: Shapley Additive Explanations
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
VERDICT trial: Very Early Versus Deferred Invasive Evaluation Using Computerized Tomography

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Protocol

Efficacy and Safety of a Digital Tapering Intervention for Patients Prescribed Opioids After Surgery: Protocol for a Prospective Exploratory Cohort Study

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Abstract

Background: More than 300 million surgical procedures are performed worldwide each year, and opioids remain a primary approach for managing acute postoperative pain. Studies have demonstrated that a significant number of patients do not discontinue opioid treatment and continue to use opioids for months or even years after surgery. Tapering and management of prescription opioids is a well-known practice and is a part of the current clinical guidelines on safe prescribing. Every patient should receive thorough monitoring, education, and a tapering plan when prescribed opioids or receiving refills after a prolonged treatment. There are challenges associated with tapering, including close follow-up, patient education, clinician time, and withdrawal safety. The evolution of smartphone app use for follow-up has shown promising results in some fields of medicine, and patients are increasingly interested in this approach.

Objective: The objective of this study is to investigate the efficacy and safety of Prescriby services, comprising clinician management augmented with digital support, as a tapering intervention in patients after knee or hip replacement surgery.

Methods: Efficacy will be measured in tapers successfully completed, doses successfully lowered during tapering, number of active users, satisfaction with the intervention, and patients successfully remaining off opioid medication at 6 and 12 months after the intervention. Participant safety will be monitored by assessing adverse effects during tapering using the numeric pain rating scale to assess the severity of pain. Participants are recruited via referrals from orthopedic clinics and orthopedic departments in the hospital after surgery during the 6-month study period to the Prescriby clinic, where they will receive a personalized tapering treatment and follow-up with a clinical pharmacist. Despite the existence of numerous clinical guidelines on tapering off dependence-inducing medications, there is limited knowledge of the outcomes of such tapering.

Results: This study received funding in February 2024. Data collection for secondary outcomes started in November 2024 and ended in July 2025. Data collection for primary outcomes will start in June 2026 and finish in July 2026. As of manuscript submission in August 2025, 75 patients had been recruited into the study. Analysis of secondary data started in August 2025, and results will be published in the fourth quarter of 2025. Analysis of primary data will start in July 2026, and results will be published in the fourth quarter of 2026.

Conclusions: We anticipate that persistent opioid use in standard treatment could be somewhere in the range of 10% to 15%. We hypothesize that the intervention group will have a lower rate of persistent opioid use. With regard to the secondary outcomes, we estimate that more than 85% of the participants in intervention group will be able to taper completely off their opioid medication and anticipate a high degree of satisfaction with the intervention.

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(JMIR Res Protoc 2025;14:e72317) doi:10.2196/72317

KEYWORDS

medication adherence; medication therapy management; pain; pain management; general surgery; arthroplasty, replacement, knee; arthroplasty, replacement, hip; analgesics, opioid; oxycodone; drug tapering; deprescriptions

Introduction

Opioid Epidemic

The global increase in opioid use over the past decade has raised concerns, contributing to what is commonly referred to as the "opioid crisis" [1]. The opioid epidemic has been a long-standing battle. In the late 1990s, pharmaceutical companies advised the medical community that patients would not become addicted to opioid pain relievers. This led to increased prescription of opioids and widespread misuse of both prescription and illicit opioids before it became clear that these medications could indeed be highly addictive. Although prescription habits have since improved, the mistakes of the past continue to haunt us [2]. Opioid-related overdoses continue to rise, with an increasing number now related to heroin and illicitly manufactured fentanyl and fentanyl analogues [3]. Alarmingly, it has been shown that 75% of heroin users report that their first opioid was a prescription drug [4]. In 2019, there were 70,630 drug overdose deaths in the United States (21.6 deaths per million population), and over 70% of those deaths involved opioids [5]. While the European Union has fewer drug-induced deaths overall (14.8 deaths per million in the population aged 15 to 64 years), most of these deaths are also found to be driven by opioids—76% of recorded cases [6]. The economic burden of opioid use disorder (OUD) is immense, estimated to be approximately US $1.02 trillion in 2017 when taking into account fatal opioid overdoses, increased health care costs, and loss of productivity [7]. It is estimated that, for patients with OUD, health care costs are 8.7 times higher than for the average person. They are also 4 times more likely to end up in the emergency department and 12 times more likely to be admitted to hospital [8]. OUD and opioid dependence also affect workplaces. People with OUD do not show up for work for an average of 2.2 days per month, whereas the average person only misses an average of 0.8 days per month [8].

More than 300 million surgical procedures are performed worldwide each year, and opioids remain a primary approach for managing postoperative acute pain [9,10]. Studies have demonstrated that a significant number of patients do not discontinue opioid treatment and continue to use opioids for months or even years after surgery [10]. The percentage of patients who develop persistent opioid use (POU) depends on the definition of POU. One study found 29 different definitions of POU, and the patients who developed it ranged from 0.01% (10 patients fulfilled the definition criteria) to 14.7% (23,442 patients fulfilled the definition criteria) [11]. An Iceland-based study conducted on patients undergoing cardiac surgery found that 4.6% developed POU. When including all patients who filled an opioid prescription after surgery, that number rose to 10.1% [12]. Another study that looked at patients undergoing hand surgery with a cohort of 49% opioid-naïve patients found that 21% developed POU [13]. Both the Icelandic and hand surgery studies defined POU as filling at least one opioid prescription in the first 90 days postoperatively and then another one between 90 and 180 days postoperatively. One study also included patients who filled a prescription in the perioperative phase as part of their POU definition [12,13].

Opioid Management

Tapering and management of prescription opioids is a well-known practice and is a part of the current clinical guidelines on safe prescribing. Every patient should receive thorough monitoring, education, and a tapering plan when prescribed opioids or receiving refills after a prolonged treatment [14-16]. However, there are challenges associated with tapering. Creating tapering plans is a time-consuming process in which clinicians can spend 15 minutes or more on each plan. To contextualize this, take, for example, a general practitioner making up to 3 tapering plans a day. With time pressure and normalization of working overtime, reducing this to 2 minutes per plan generated could save the practitioner up to 40 minutes of work per day, adding up to 3.3 hours of work over the week. Given the time-consuming nature of the current method of developing tapering plans, one can see how this could influence a clinician's likelihood of even offering tapering to patients. This is especially relevant to high-volume prescribers. This increased efficiency may encourage wider implementation of tapering support in routine care.

Studies have shown that most medical doctors are so heavily burdened with documentation through electronic health record work and desk tasks that they cannot manage their daily duties [17]. Patients can develop physical tolerance to opioids quickly, which results in withdrawal syndrome if doses are not tapered; this, in turn, often prolongs the treatment [14,16]. After just a few weeks of opioid use, dependence can develop, where patients begin to rely on the medication not for its pain-relieving effects but due to an emerging addiction. Often, they are unaware of the dangerous progression they are facing. This can lead to the development of OUD [14]. When prescribing opioids after surgery, the total duration of opioid use is the strongest predictor of misuse. Each refill is associated with a 44% increase in the rate of misuse, and each additional week of use increases the risk of misuse by 20% [18]. According to the World Health Organization and the United Nations Office on Drugs and Crime, the largest risk factor regarding misuse of addictive drugs is the lack of education and understanding of their adverse effects. Other risk factors include easy access, naive social attitude toward these drugs, and poor prescribing habits [19,20]. Women are at higher risk of developing opioid addiction. On the other hand, men are much more likely to be prescribed opioids and represent 75% of opioid-related deaths [8,21].

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However, there are also factors that are associated with opioid tapering success. One study shows that some risk factors for developing opioid dependence and abuse are also associated with opioid tapering success. Comorbidities such as substance use disorder and anxiety, along with other notable factors such as young age (21-49 years), surgery in the previous year, and nonnarcotic analgesic medication use, increased the odds of patients successfully lowering their opioid dose by 50% in 1 year. There is limited information on this topic, but the available data present intriguing implications [22].

The Future of Follow-Up?

The evolution of follow-up through smartphone apps has shown promising results in other fields of medicine, such as cardiac rehabilitation and diabetes [23,24]. Furthermore, patients are increasingly interested in the idea of using smartphone apps for follow-up, and the recent COVID-19 pandemic has dramatically increased the use and acceptability of digital health solutions [25]. A review from 2020 looked at both the effectiveness and cost efficiency of telemedicine tools for various diseases and health problems [26]. In total, 40 of 53 reviews included in this umbrella review focused on effectiveness and used device- or app-based monitoring of patients, similar to what we propose in this protocol. There were 18 reviews focused on cost-effectiveness [26]. Most reported either (1) that the intervention was cost-effective or (2) that evidence was limited but pointed toward cost-effectiveness [26]. This is not enough to draw conclusions as the reviews were from different specialties of medicine. Just the possibility of lower costs regarding in-person meetings and hospitalizations, reduction in stigma, and a higher level of support emphasizes the justification for testing this intervention. It has also been found that telemedicine is superior or at least comparable to face-to-face communication in targeting lifestyle factors such as alcohol consumption, medication adherence, physical activity, and sleep habits [27-31]. The proposed project aims to address the challenge of reducing long-term opioid use after surgery, which is extremely important given the substantial volume of surgical procedures conducted worldwide.

Methods

Design

This protocol describes a prospective exploratory cohort study. The usual care procedure entails discharging patients after surgery with an opioid prescription, verbal instructions on how to taper opioid medication, and a printout of the tapering instructions upon request. The experimental procedures in this study are the referral to the Prescriby clinic alongside treatment and follow-up offered by a clinical pharmacist using the Prescriby application.

The primary target population for this study are patients undergoing surgery; surgeons; and other health care professionals involved in opioid prescription, management, and tapering. The patients are the main participants in this study and have a platform to voice their concerns or satisfaction in an exit interview at the conclusion of the intervention. The satisfaction of patients will be measured using a questionnaire at the intervention's conclusion. The surgeons and other health care professionals connected to the patients and the processes involved have the chance to contact Prescriby directly with their concerns or to express satisfaction.

Outcomes

The primary and secondary research questions that will be investigated are presented in Textbox 1.

Textbox 1. Primary and secondary research questions.

Primary research questions

- Do patients who completely tapered off opioids successfully sustain tapering of the opioid medication at 6 and 12 months after the intervention?
- Do the patients who partially tapered off opioids maintain their reduced dose at 6 and 12 months after the intervention?

Secondary research questions

- How many successful tapers off opioids are achieved with the intervention?
- How many participants reduce their opioid dose with the intervention?
- What percentage of users are active users (ie, those who completed at least 80% of data registrations during the intervention and underwent both the introduction and exit interviews)?
- Are the participants satisfied with the intervention?
- Do patients experience increased pain symptoms during the intervention?
- Do patients experience opioid withdrawal symptoms during the intervention?

Participants

All participants enrolled in this study have been referred to the Prescriby clinic from orthopedic clinics and the orthopedics department at Landspítali University Hospital after elective knee or hip replacement surgery. They must be prescribed opioids after surgery, own a smartphone, and be over the age of 18 years to be included in this study.

The exclusion criteria are (1) recent history of nonoral self-administration of narcotics, (2) recent history of attempted suicide, and (3) untreated mental illness.

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The exclusion criteria are the same as for the Prescriby clinic services in general. The clinic not only serves the orthopedics cohort but also offers services through primary health care for long-term users of benzodiazepines, opioids, and Z-drugs. We do not exclude oral or smoked illicit opioid users from our services but require these patients to receive care at the outpatient ward of the National Center of Addiction Medicine for assessment of their treatment options.

The criteria to stop the intervention are as follows: (1) 3 or more dose increases or continuations of the same dose, (2) the patient wanting to stop participation, (3) the patient being admitted to hospital, (4) the patient having to undergo another surgery, (5) the patient's adverse effects being deemed too serious through a clinician assessment, (6) the patient showing threatening behavior toward the clinician, and (7) an untreated medical condition (eg, endometriosis or mental illness) arising that contributes to pain and needs to be resolved before tapering. Justification for these criteria is the safety of the participants and the clinician.

Most of the criteria for stopping the intervention are connected to escalation of care or the transfer of care to other health care workers, where the responsibility for medication management is not in the hands of clinicians at the Prescriby clinic. Exceptions to this are if the patient wants to stop tapering treatment, in which case the patient can decide what type of health care to accept, or if they show threatening behavior toward the clinician, in which case the safety of the clinician is a priority.

There will not be any sampling; all patients who consent to participation will be included. The estimated number of participants will be between 150 and 200.

A comparison group will be included in the study. This group will be composed of all patients who undergo hip or knee replacement surgery in Iceland and who receive usual care during the same period as the intervention (eg, from approximately November 2024 to April 2025). The following surgery codes of the Icelandic version of the Nordic Medico-Statistical Committee Classification of Surgical Procedures will be used to identify this group: NFB (primary prosthetic replacement of hip joint) and NGB (primary prosthetic replacement of knee joint). The personal identification numbers from the intervention group will be removed from the comparison group.

Setting and Intervention

The intervention itself is the use of the Prescriby tapering software alongside clinician follow-up. A more detailed description of the clinic setting and the mobile phone app follow-up is provided in the following sections.

Prescriby Clinic and Service

The Prescriby clinic opened in collaboration with the National Center of Addiction Medicine and has 2 clinical pharmacists and a physician, hereafter referred to as the clinicians. The clinic serves different patient groups, one of which is patients who are prescribed postsurgical opioids.

The clinic receives its patients from a safe web-based referral form that has been distributed to Icelandic health care workers (eg, in orthopedics departments). A patient from the orthopedics department is referred to the clinic on the day they are discharged from the ward with their opioid prescription. They receive the same education as other patients and receive information on the starting dose of opioids to take at home. They are offered information on the Prescriby clinic and the study. The day after discharge, the patient undergoes an introduction interview over the phone with the Prescriby clinic. From this point on, the clinic handles prescription responsibility. The Prescriby clinician will offer information on the study, the terms of service, and the treatment and obtain consent using the relevant consent form (supplementary file available upon request). After this, the patient is onboarded to the Prescriby app, and follow-ups are scheduled. Before onboarding patients, the Prescriby clinicians receive training in the use of the Prescriby app, communication, and deprescribing care and follow-up of patients. The participants are offered support in the form of a phone number if they wish to contact a study investigator whom they can ask questions or obtain further information from about what they are consenting to. During onboarding, participants can optionally enter baseline characteristics such as age and gender. The clinician and patient talk about the tapering plan and implement a personalized one. Specifics on the tapering are input into the system, which includes medication, starting dose, and tapering treatment length. The system then generates a plan with a roughly even dose reduction corresponding to the available medication strength in Iceland. The clinician can then change the plan to their and their patient's desires before the plan is set up or at any point during the tapering progress. Finally, the clinician offers the patient a chance to ask questions about the service or the introduction interview. During the course of treatment, the clinician monitors the information input by the patient into the mobile phone app bidaily and adjusts follow-up if necessary. When a patient has finished or is close to finishing tapering services, the clinician books an exit interview with the patient.

The standard opioid tapering protocol from the orthopedics department for elective knee and hip replacement surgery is approximately 2 weeks, but this can be shorter or longer if needed. Most patients are started on 5-mg long-acting oxycodone tablets and are prescribed 5 to 10 mg twice daily. The standard care offered currently includes this prescription and an interview 6 to 8 weeks after surgery. Standard care is patient initiated, so if there is a problem (eg, severe pain or prescription problems), the patient has to contact the orthopedics or emergency department or primary care to solve it. The intervention described previously is more clinician initiated as the clinician monitors the data twice daily and simplifies the process after discharge from the orthopedics department and the clinic oversees the prescription for the opioid medication.

The Prescriby Application

The Prescriby application is designed to support patients when tapering off medication that can lead to dependence and addiction. It has 2 modules: the dashboard for the clinician and the mobile app for the patients. Images of these 2 modules can be found in Figures 1 and 2.

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The clinician-facing dashboard is viewed on a computer. The clinician can make new tapering plans on the onboarding screen, see their patients on the dashboard, and set up “flags” that make the patient a higher priority in follow-up. When onboarding patients onto the app, the clinician creates the patient profile using the patient’s social security number, phone number, and name. During onboarding, the clinician must set up a plan that can be adjusted later. The clinician can also send questionnaires to patients from the dashboard to the app that the patient will be prompted to fill out the next time they open the app.

The patient-facing app is used on a smartphone. The patient-facing app has an interface where the patient can register their adherence to the tapering plan and an interface where the patient can see the data that they have input. It also has a questionnaire section where the questionnaires that the clinician has opened up can be accessed to log symptoms. Patients can see an overview of the tapering plan and their progress on the app.

Figure 1. Clinician-facing module of the Prescriby application on the web browser.

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Figure 2. Patient-facing module of the Prescriby application on the mobile app.

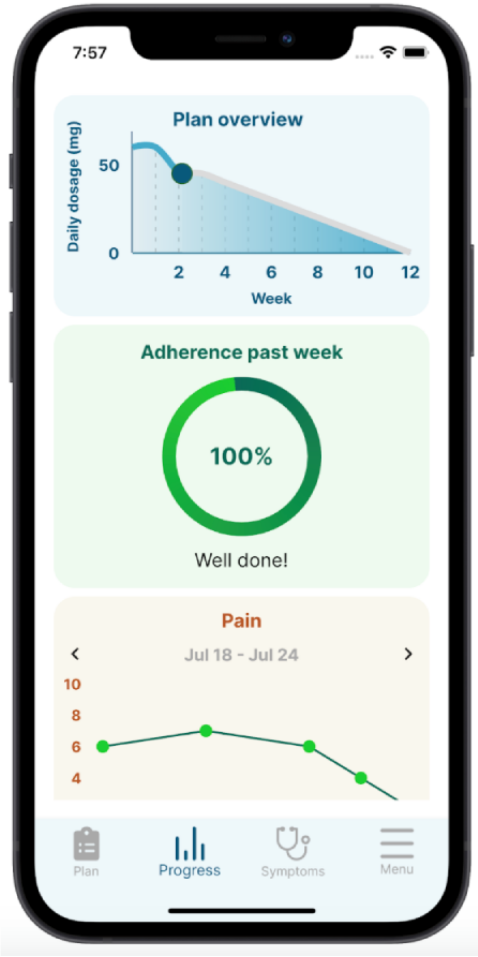

Collected Data and Covariates

Intervention Group

Data will be collected from the Prescriby application database and from the Prescription Medicines Database through the Directorate of Health of Iceland in the 6 and 12 months after surgery and intervention follow-up, which requires patient consent. All data will be encrypted to prevent personal identification. The dataset will be kept for 5 years after the last in a series of publications based on this study. This will allow the investigators to validate the results if requested. After 5 years, those data will be destroyed.

The data for the primary outcome measures will be extracted from the Prescription Medicines Database through the Directorate of Health of Iceland. The data for the secondary outcome measures will be extracted from the Prescriby database. Successful tapers are defined as instances in which the patient successfully tapers down and stops the medication. Reduction in opioid dose will be considered for those who did not stop the medication. These 2 outcomes will be assessed through a comparison from the start of the intervention to the end. Patients can optionally provide their gender and age. Participants will be asked about opioid use 3 months before surgery in the introduction interview.

The engagement metrics collected at the end of the intervention will be (1) active users (ie, those who completed at least 80% of data registrations during the intervention and underwent both the introduction and exit interviews) in numbers and percentages, (2) total active days in medians and IQRs, and (3) highly engaged users (ie, those who registered dosage at least 5 days a week) in numbers and percentages.

Experience and usability outcomes collected at the end of the intervention will be captured via the following statements: (1) “I would recommend this intervention to others,” (2) “The educational material was helpful,” (3) “The mobile application was user-friendly,” (4) “This intervention has improved my life and well-being,” and (5) “This intervention was better that the standard care currently offered” (the usual care procedure would be discharging patients after surgery with an opioid prescription, verbal instructions on how to taper opioid medication, and a printout of the taper upon request).

Answers are scored on a 7-point Likert scale ranging from 1 (“don’t agree at all”) to 7 (“very much agree”).

Data collection on subsequent opioid prescriptions will be conducted at 6 and 12 months after surgery. Data will only be collected on medication with the Anatomical Therapeutic Chemical (ATC) Classification System code N02A (opioids). Data on pain symptoms will be collected using the numeric pain rating scale for all patients, and data on opioid withdrawal symptoms will be collected using the Subjective Opiate Withdrawal Scale if needed. These data will be collected at the

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start of the intervention if needed, during the intervention, and at the end of the intervention.

Comparison Group

Data will be collected from the Prescription Medicines Database and Hospital Discharge Register through the Directorate of Health of Iceland in the 6 and 12 months after surgery. All data will be encrypted to prevent personal identification. The dataset will be kept for 5 years after the last in a series of publications based on this study if the investigators need to validate the results upon request and will then be destroyed. The comparison group will only be used to compare with the results of the primary outcomes of the intervention group, not the secondary outcomes.

The following data will be requested from the Directorate of Health of Iceland 6 and 12 months after the intervention for the comparison group: (1) age; (2) gender; (3) medication name of opioid, ATC code N02A, prescribed after surgery; (3) number of medication prescriptions with ATC code N02A down to the fifth level 6 months after surgery; (4) number of medication prescriptions with ATC code N02A down to the fifth level 12 months after surgery; (5) number of physicians who prescribe medication with ATC code N02A down to the fifth level 6 months after surgery; (6) number of physicians who prescribe medication with ATC code N02A down to the fifth level 12 months after surgery; and (7) *International Classification of Diseases* codes from Table 1.

These data on the comparison group will be gathered from the Directorate of Health of Iceland and using the surgery codes of the Icelandic version of the Nordic Medico-Statistical Committee Classification of Surgical Procedures, and all patients who have received Prescriby services will be removed from that list. From the Directorate of Health, we will obtain information on the same diagnoses found in Table 1 that we will have also collected from the intervention group. This will help us extract a comparison group with similar ages, genders, and comorbidities that affect physical function to those of our intervention group. Finally, we will also collect opioid prescription data on this comparison group and our intervention group through the Directorate of Health.

The results from the comparison group will be compared to the results from the intervention group. The results will be presented as the number of refills in that period and as the percentage of the comparison group that receives a refill. The results will be presented without personal identification.

Comparison of the baseline characteristics of age, gender, state of chronic opioid use before surgery, and comorbidities found in Table 1 and starting opioid dose will be conducted between the intervention and comparison groups. These characteristics will be shown in the proposed table on the demographics of the participants when the results are published.

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Table 1. Comorbidities that affect physical function; scoring; and their International Classification of Diseases, 10th Revision–Clinical Modification (ICD-10-CM) codes [32,33].

Comorbidity	*ICD-10-CM* codes	Are any of the *ICD-10-CM* codes present? (Yes=1; no=0)
Arthritis (rheumatoid and osteoarthritis)	M05[a], M06[a], M08.0[a], M08.2[a], M08.3, M08.4[a], M08.8[a], M08.9[a], M12.0[a], M15[a], M16[a], M17[a], M18[a], and M19[a]	
Osteoporosis	M80[a] and M81[a]	
Asthma	J45[a]	
Chronic respiratory disease (chronic obstructive pulmonary disease, chronic respiratory distress, or emphysema)	J43[a], J44[a], J47[a], J60, J61, J62[a], J63[a], J64, J65, J66[a], J67[a], J68.4, J70.1, J96.1[a], and J96.2[a]	
Angina	I20.1, I20.8, and I20.9	
Congestive heart failure or heart disease	I09.81, I24[a], I25.1[a], I25.3, I25.4[a], I25.5, I25.6, I25.7[a], I25.8[a], I25.9, and I50[a]	
Myocardial infarction	I21[a], I22[a], and I25.2	
Neurological disease	G04.1, G10, G11[a], G12[a], G20, G21[a], G25.4, G25.5, G30[a], G31.0[a], G31.1, G31.83, G31.84, G31.85, G31.89, G31.9, G32.81, G35, G36[a], G37[a], G40[a], G80[a], G81[a], G82[a], G83.0, G83.1[a], G83.2[a], G83.3[a], G83.5, G83.8[a], G83.9, and G93.1	
Stroke or transient ischemic attack	G45.0, G45.1, G45.2, G45.8, G45.9, G46.0, G46.1, G46.2, I60[a], I61[a], I63[a], I67.84[a], and I69[a]	
Peripheral vascular disease	I70.2[a], I70.3[a], I70.4[a], I70.5[a], I70.6[a], I70.7[a], I70.92, and I73.9	
Diabetes (type 1 or 2)	E08[a], E09[a], E10[a], E11[a], and E13[a]	
Upper gastrointestinal disease	K20[a], K21[a], K22.1[a], K22.7[a], K25[a], K26[a], K27[a], K28[a], and K29[a]	
Depression	F31[a], F32[a], F33[a], F34[a], and F39	
Anxiety or panic disorder	F40[a], F41[a], F42[a], and F43.1[a]	
Visual impairment	H54[a]	
Hearing impairment	H83.3[a], H90[a], and H91[a]	
Back disease (degenerative disc disease, spinal stenosis, or severe chronic back pain)	M08.1, M45.0, M45.4, M45.5, M45.6, M45.7, M45.8, M45.9, M46.4[a], M47.10, M47.14, M47.15, M47.16, M47.20, M47.24, M47.25, M47.26, M47.27, M47.28, M47.814, M47.815, M47.816, M47.817, M47.818, M47.819, M47.894, M47.895, M47.896, M47.897, M47.898, M47.899, M47.9, M48.00, M48.04, M48.05, M48.06, M48.07, M48.08, M51[a], M54.14, M54.15, M54.16, M54.17, M54.3[a], M54.4[a], and M96.1	
Obesity (BMI≥30 kg/m^2)	E66.0[a], E66.1, E66.2, E66.8, E66.9, Z68.3[a], and Z68.4[a]	

[a]All subclasses for the relevant *ICD-10-CM* code.

Timelines

Definitions of the data gathered can be found in the Collected Data and Covariates section.

The data gathered are shown in Table 2. The study timeline encompasses 20 months: a recruiting period for the first 6 months, the 6-month period after surgery on the 12-month mark, 12 months after surgery on the 18-month mark, analysis and data processing during months 18 and 19, and then the write-up period during month 20.

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Table 2. Patient-centered data gathering timeline.

	D0 (introductory interview; baseline)	D1 (follow-up and exit interview; 2-8 weeks)	D2 (6 months after surgery)	D3 (12 months after surgery)
Intervention group				
Consent	✓			
Starting dose	✓			
Age	✓			
Gender	✓			
Comorbidities		✓		
Opioid prescription data			✓	✓
Comparison group				
Starting dose			✓	
Age			✓	
Gender			✓	
Comorbidities			✓	
Opioid prescription data			✓	✓

Analysis

Descriptive statistics for background factors, age, gender, and comorbidities will be presented. Analysis of binomial variables related to the primary and secondary outcomes will be presented as a binomial proportion with Wald CIs, with the confidence level set to 95%.

Ordinal variables measured before and after the intervention will be analyzed using a paired Wilcoxon signed rank test, with significance level set at .05. An a priori power analysis was conducted for the primary dichotomous outcome assuming a 2-sided α level of .05, power of 0.80, and an anticipated prevalence of opioid prescriptions 12 months after surgery 5% to 10% in the study group compared to a presumed population incidence of 20%. To account for uncertainty in the expected incidence, the power analysis was repeated using anticipated incidences of 5% and 10%, and the larger resulting sample size was selected to ensure adequate power across a plausible range of scenarios [34,35]. A clinician involved in the intervention, data management, and follow-up will analyze the data. The plan for data management and analysis will be reviewed and validated by an external statistician. There is a possibility of publication bias, which is negated by the prospective registration of this study and a mandated publication of results regardless of whether they are positive or negative.

Ethical Considerations

The participants are informed of this during acquisition of consent with the clinician in the introduction interview. They have access to the investigator with questions and can at any time opt out of the research. The offer their consent with an electronic ID signature and the authors attest to maintaining privacy and confidentiality of the participants' data and identity. As this study is exploratory, requires handling of personal data, and seeks to improve existing practice, it requires the approval of a bioethics committee. The National Bioethics Committee of Iceland has given approval for a study using this protocol. This study has been given the registration number VSNb2024090010/03.01 and will be running from November 2024 to April 2026.

Results

This study was funded in February 2024. The results of this research will be published in a peer-reviewed journal. Data collection for the secondary outcomes started in November 2024 and ended in August 2025. Data collection for the primary outcomes will start in June 2026 and finish in July 2026. As of manuscript submission in August 2025, a total of 75 patients have been recruited into the study. Analysis of secondary data started in August 2025 and is expected to end in September 2025. Results will be published in the fourth quarter of 2025. Analysis of primary data will start in July 2026 and is expected to end in September 2026, and results will be published in the fourth quarter of 2026. The authors will apply to scientific publications to publish the results, estimated in September 2025 for the secondary results and in July 2026 to September 2026 for the primary results. Preliminary results will be presented as a poster at the European Geriatric Medicine Society congress in Reykjavík on September 24 to 26, 2025. If other opportunities arise, the results might be presented at other congresses. Disseminating the results through these channels allows for wider visibility and accessibility of the findings within the local medical community.

Discussion

Principal Findings and Comparison to Previous Work

It is difficult to estimate exactly how many patients could develop POU in the year after elective knee or hip surgery. The percentage of POU a year after surgery ranges from 0.01% to 21% depending on the definition of POU and surgery type [10-13]. We anticipate that the POU in standard treatment (the comparison group) could be somewhere in the range of 10% to

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15%. The hypothesis is that the intervention will produce a lower percentage of POU than what is observed in the comparison group. With regard to the secondary outcomes, we estimate that more than 85% of the patients in intervention group will be able to taper completely off their opioid medication and anticipate that the participants will be satisfied with the intervention.

Strengths and Limitations

A strength of this planned study is that it will address a gap in the current scientific knowledge base. The study itself will contribute to the ever-changing eHealth scene and will offer new insights into the field of postsurgery tapering and medication monitoring. The protocol and its research questions are feasible, interesting, novel, ethical, and relevant. It is especially relevant to the current hot topic in health sciences: the deprescribing of medications. The scientific benefit of conducting this exploratory research lies primarily in obtaining better evidence on the outcomes of tapering off dependence-inducing medications. Other strengths of this research are its replicability and transparency. The authors have provided a detailed protocol describing how the intervention itself works and how to implement it. The authors have also been transparent regarding each aspect of the service offered. The authors will also distribute their dataset for validation upon request.

This study involves comparison of standard treatment (a reactive patient-driven health care service) and an intervention in the form of a mixed patient- and a clinician-driven health care service with a higher level of support than that of standard treatment. The primary outcomes rely on prescription data for both the comparison and intervention groups. This could affect the outcomes as real medication intake may be over- or underestimated. The intervention and comparison groups have an observational cohort design without random assignment. This will increase the risk of selection bias and confounding, making it difficult to attribute outcomes in tapering success or opioid use directly to the intervention.

Future Directions

The team is looking at future research opportunities, the clinic setup, and tapering outcomes with other patient groups undergoing surgery and patients with chronic opioid use and expanding on benzodiazepine tapering. In these research opportunities, emphasis will be placed on research design that enables randomization to compare a group using the application alone as an intervention with a group with a similar level of support.

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The contributors associated with Prescriby LLC Team are as follows: Elísabet Jónsdóttir, Kjartan Þórsson, Árni Johnsen, and Farah McCrate. The contributors associated with Orthopedics Department Group are Dagrún Ása Ólafsdóttir, Matthías Örn Halldórsson, Magney Ósk Bragadóttir, Elías Þór Guðbrandsson, and Tómas Viðar Sverrisson. And the contributors associated with SÁÁ group are Ragnheiður Hulda Friðriksdóttir and Valgerður Rúnarsdóttir.

Authors' Contributions

ABB is the principal investigator and contributed to project administration. ABB, BEH and Kjartan Þórsson took part in the conceptualization process. Kjartan Þórsson was behind funding acquisitions. ABB, BEG and Árni Johnsen cooperated with the methodology compilation.

BEH, Elísabet Jónsdóttir, Ragnheiður Hulda Friðriksdóttir, Valgerður Rúnarsdóttir, Dagrún Ása Ólafsdóttir, Matthías Örn Halldórsson, Magney Ósk Bragadóttir, Elías Þór Guðbrandsson and Tómas Viðar Sverrisson all contributed to the protocol implementation.

BEH is the secondary investigator in charge of all writing in relation to publications.

ABB oversees the supervision of all areas of the protocol and research. Farah MacCrate and ABB review and edit all writing for this protocol and research.

Conflicts of Interest

BEH, Elísabet Jónsdóttir, and Kjartan Þórsson are employees of Prescriby LLC, the start-up company that owns the Prescriby smartphone app and the Prescriby clinic in Iceland. No conflicts of interest are present for ABB, the principal investigator, or for any persons at the Landspítali University Hospital or the National Center of Addiction Medicine (SÁÁ).

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Abbreviations

ATC: Anatomical Therapeutic Chemical
OUD: opioid use disorder
POU: persistent opioid use

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Protocol

A Dual In-Person and Remote Assessment Approach to Developing Digital End Points Relevant to Autism and Co-Occurring Conditions: Protocol for a Multisite Observational Study

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Abstract

Background: Research priorities for autistic people include developing effective interventions for the numerous challenges affecting their daily living, for example, mental health problems, sleep difficulties, and social well-being. However, clinical research progress is limited by a lack of validated objective measures that represent target outcomes for improvement. Digital technologies, including wearable devices and smartphone apps, provide opportunities to develop novel measures that may reflect everyday experience and complement key clinical assessments. However, little is known about the acceptability and feasibility of implementing digital data collection in this population.

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Objective: The primary objective of this study is to evaluate the usability, acceptability, adherence, and feasibility of a dual in-person and remote (ie, at-home) protocol. Secondarily, we aim to explore the properties of certain resulting data with a view to developing novel digital end points for key target outcomes, including social communication, sleep, and mental health.

Methods: Eligible autistic and nonautistic in the AIMS Longitudinal European Autism Project were invited to participate in a digitally augmented in-person Autism Diagnostic Observation Schedule-2 (ADOS-2) and a 28-day remote measurement (RM) protocol involving wearing a Fitbit device, downloading a passive smartphone data collection app, and using 2 active reporting apps.

Results: The first AIMS Longitudinal European Autism Project study participants were enrolled in September 2021 (in-person component) and March 2022 (RM component). To date, 190 participants have taken part in the digitally augmented ADOS-2 component, and 86 participants have been enrolled for the RM protocol. Recruitment is now complete with some RM data collection ongoing until August 2025. Data analysis has commenced, including qualitative framework analysis of feedback interview data coproduced with autism community members, exploration of acceptability and feasibility metrics, pipeline development for ADOS-2 speech analysis, and RM sleep measures.

Conclusions: This study lays important groundwork in understanding the acceptability and feasibility of in-person and remotely implemented digital measurement procedures to capture meaningful outcomes in domains important to improving everyday life for autistic people.

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KEYWORDS

autism; mental health; sleep; digital end points; remote measurement technology; wearables

Introduction

Background

Autism is a lifelong neurodevelopmental condition characterized by social communication differences, restricted or repetitive behaviors and interests, and differences in sensory experience [1]. Presentation across individuals is diverse and often complicated by co-occurring conditions, such as intellectual disability, attention-deficit/hyperactivity disorder (ADHD), mental health problems, epilepsy, and sleep difficulties [2]. Most autistic people face considerable challenges affecting numerous domains of everyday life, such as accessing health care, community activities, education, and employment [3]. Across studies consulting the autism community, major research priorities include enabling activities of daily living and enhancing quality of life by treating co-occurring conditions and alleviating difficulties associated with core characteristics (eg, providing training for social, vocational, and life skills and by making environments more autism friendly) [4]. However, progress in addressing these priorities is limited not only by the development of effective intervention and support strategies but also by the measurement tools available to capture desired changes in response to intervention [5-7].

Current Measurement

Self- or informant-report instruments and clinical observations or assessments form most outcome measures used in clinical autism research in domains such as social functioning [8], mental health [6], and ADHD [9]. Self-report measures are well-placed to capture real-world experiences and behavior. However, high rates of alexithymia and difficulties or differences in interpreting questionnaire items may present specific challenges for autistic people reporting on their own feelings and behaviors [10,11]. Parents, teachers, and other informants reporting on behaviors in different contexts share only modest variance, with characteristics such as parenting stress accounting for discrepancies [12,13]. When evaluating psychosocial treatment approaches, which play a key role in supporting autistic people and their families, findings may be impacted by difficulty in blinding informants involved in the treatment itself [14]. Finally, even where blinding is possible, self- or informant-report measures may show spontaneous improvement in the absence of treatment, which makes treatment effects more difficult to establish [15,16].

Assessments carried out by clinicians and researchers mitigate certain limitations; for example, in pharmacological trials targeting core autistic features (eg, social communication difficulties), placebo effects were lower for clinician versus caregiver ratings [16]. However, these are time-consuming and therefore costly to implement at scale. They may also be unrepresentative of everyday behavior or experiences because they are often conducted in unfamiliar settings that are potentially anxiety provoking and challenging for autistic people to access. Finally, whether self- or informant reported, such measures are often ordinal and limited in their effective resolution, compromising sensitivity [2] and inflating thresholds for detecting clinically meaningful results [17]. Given the profile of strengths and limitations of measurement options based on human judgment, many authors have called for the development of objective measurement tools to complement these.

Digital Measurement Opportunities

Table 1 summarizes potential areas in which digital technology could address the limitations of current measurement, as well as outlining potential challenges for measure development based on these, including those that may be particularly problematic in autism research. Smartphones and wearable devices, such as smartwatches, are widely used by the general population and are subject to commercial optimization; thus, their application in health research may benefit from already honed acceptability.

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They offer an array of passively collected data types (ie, not requiring user input), including physiological (eg, heart rate), lifestyle (eg, sleep and activity levels), and nearby environmental data (eg, light levels). These may provide more objective data indexing characteristics and symptoms of interest while reducing challenges associated with subjective reporting. Furthermore, their unobtrusiveness may reduce Hawthorne effects (ie, behavioral change due to being observed) [18]. Smartphones also provide the opportunity to collect active measures efficiently and repeatedly in everyday life (eg, collecting mood data via ecological momentary assessment) [19]. Although subjective, these data have high ecological validity and minimize recall effects. They provide context for objective data and enable investigation of fluctuation in subjective symptom levels. At the same time, modern analytical methods, such as machine learning, provide tools for efficiently extracting and identifying meaningful patterns in large datasets. Suitably large datasets are readily produced by wearables, as well as through video, audio, and natural language recording, and can now be processed much more efficiently than via traditional approaches such as manual coding. Together, such technology may enable efficient measurement with relatively low burden to participants and high ecological validity. Such characteristics hold particular promises for clinical research, in which symptom changes would ideally be tracked over time, and early detection of a subtle change may be valuable.

Table 1. Summary of current measurement limitations, opportunities for digital technology to address these, and potential challenges therein.

Domain	Limitation of current measurement	Opportunity for digital technology	Potential challenges
Meaningful capture of real-world outcomes	• Difficulties associated with self-reporting and recall effects • Observations and assessments are often conducted at discrete time points and in unfamiliar situations	• Reporting in the moment via smartphone may alleviate difficulty remembering thoughts, feelings, and behavior over weeks or months • Real-world, real-time data collection offers potential for high ecological validity	• Limits inclusion of certain groups, for example, those without a smartphone and those who find technology less accessible or trustworthy. Daily reporting for long periods may be burdensome. Both these points may disproportionately affect autistic individuals.
Measurement error and bias	• Susceptibility to attention or placebo effects; difficulty blinding informants in psychosocial intervention research	• Objective data capture possible via passive physiological and environmental sensors	• Subjectivity may still be present, for example, in analytic choices and model training. Models relying on neurotypical data may misclassify data from autistic individuals.
Scalability	• Observations and assessments by researchers or clinicians are expensive and time-consuming • Repeated and lengthy questionnaire administration may become burdensome	• Potentially highly scalable across individuals and over time • Passive data collection could reduce the burden of repeated or long-term data collection	• Wide variation in affordability of devices; many devices are inaccessible in lower-resource research settings. • Wearable device comfort and data privacy concerns associated with passive data collection may affect adherence and exclude certain groups, for example, those with sensory sensitivities.
Capture of differences	• Difficult for humans to detect subtle differences across or within people	• Digital sensors can capture fine-grained differences	• Processing and interpretation of large amounts of data is challenging, has an environmental impact, and often lacks validation against well-understood instruments.

For these reasons, digital measurement has drawn interest in diverse physical health applications, such as wearable sensors for monitoring recovery in oncology patients and patients who have had stroke [20,21], monitoring disease progression in Parkinson disease [22], and identifying epileptic seizures noninvasively [23]. Elsewhere, smartphone apps and wearable wristbands have been explored for use in predicting depression relapses [24,25]. In autism research specifically, several digital measurement systems have been developed. These include in-person autism diagnostics or brief conversation-based assessments using machine learning to quantify elements of social communication from videotaped interactions [26-29]. Similar techniques have also been applied remotely, including at-home attention and emotion analysis based on computer vision [30]. In the domain of sleep, objective monitoring via actigraphy has been applied relatively widely [31-33]. Integrating laboratory-based and wearable biosensors with a web-based and mobile app to collect objective and caregiver-report data, the Janssen Autism Knowledge Engine (JAKE) system [34] has been fruitful in exploring existing and novel measures relating to autism and co-occurring symptoms in the domains of sleep [35], prediction of diagnostic groups

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from multimodal biosensor data [36], and daily caregiver-reported mood and behavior [37]. Published research using the JAKE system has focused on a sample of caregivers and their autistic or nonautistic children, who are predominantly children or young adults of average intellectual ability. However, to our knowledge, a comprehensive system such as the JAKE system has not been developed to capture self-report and passive smartphone data alongside wearable and in-person assessment among autistic adolescent and adult smartphone users.

Furthermore, despite growing research interest, very little has been published on the acceptability, feasibility, and implementation challenges of digital assessments in autism (although important work on evidence-based practice for developing digital supports for autistic people has been published [38]). For the JAKE system, caregiver feedback was sought and showed encouraging findings in terms of usability and device comfort; however, the experiences of the autistic participants themselves were not directly captured. Autistic people's experiences of research supported by digital technology are likely to differ in several ways from those of other populations, as is the analysis and interpretation of the data yielded. First, sensory sensitivities may affect the comfort of wearable devices. This means that important data may be missing, for example, if people find a wristband uncomfortable to wear at night in a sleep study [39]. On the other hand, wristbands may be more widely tolerated than scalp electrodes such as those used in polysomnography [40] and innovation in the characterization of sleep from data acquired via wristbands (eg, actigraphy and pulse rate monitoring) may enable the inclusion of a wider proportion of the autistic population. Second, higher rates of intellectual disability may affect the usability of smartphone apps, and differences in communication and emotional literacy may affect the way in which objective data correspond to reported subjective experience. Third, analytical tools and pipelines developed in other populations may function differently in the autistic population. Care must be taken to anticipate potential neurotypical biases in the ways that features of speech, social interaction, and facial expressions are classified in machine learning tools trained in other populations.

Study Approaches and Target Domains

This study protocol comprises a dual in-person and remote approach to digital measure development in the domains of autistic characteristics (social communication and restricted or repetitive behaviors and interests) and selected co-occurring difficulties (mood, sleep, inattention, and hyperactivity). Our primary focus is on evaluating the acceptability and feasibility of the methods developed. Co-occurring domains were selected based on being (1) associated with everyday challenges, (2) highlighted by autistic people as important targets for improvement, and (3) putatively amenable to digital measurement. As depicted in Figure 1, we aim to enable the evaluation of a range of candidate data collection methods for their individual and combined potential in indexing these target domains.

Our in-person approach explores digital augmentation to the Autism Diagnostic Observation Schedule-2 (ADOS-2) [41], a widely used in-person observational assessment, a gold-standard instrument in informing autism diagnosis. The ADOS-2 has been used in clinical studies to evaluate intervention effects on social communication [42-44]. Its scoring system is designed to allow human administrators to differentiate reliably between several levels of intensity across a range of behaviors characteristic of autism. Because fine-grained discriminations are challenging for humans, this system may not be ideal for identifying subtle changes, for example, early response to an intervention [45]. Our digital augmentations to the ADOS-2 comprise video recording from 3 angles, audio recording for speech transcription, and a wearable wristband recording heart rate using photoplethysmography, electrodermal activity (EDA), and accelerometer data. These digital augmentations are intended to enable exploration of objective data to complement subjective observer ratings of social communication and repetitive and restricted behaviors and of the underlying autonomic demands of this assessment.

Existing research has shown autonomic correlates of outcomes of interest within the autistic population, such as social function [46], anxiety [47], and depression [48]. Such outcomes are among those that are both key sources of everyday distress and difficult to verbalize for many autistic people. Thus, there is an interest in discovering objective autonomic markers that may underlie states of subjective distress and may be sensitive to treatment response. The ADOS-2 provides a standardized series of presses mimicking everyday interpersonal interactions that present various challenges to autistic people. Therefore, it is well-placed for studying autonomic responses during such interactions.

We will also use a 28-day remote measurement (RM) period by using a commercial wearable device and both passive and active smartphone-based measures. Passive smartphone data collection will use an app that records data continuously from smartphone sensors (eg, motion sensors, GPS location, and Bluetooth connectivity) and logs (eg, app use and call and SMS logs). Such apps have contributed elsewhere to assessing mental health [49,50], and diverse aspects of social interaction and environment [51-53]; however, they have not been widely applied in autism. In this study, both active and passive approaches seek to understand trade-offs between data quality, acceptability to participants, and feasibility of implementation.

For both in-person and remote assessments, we developed our approach in a stepwise manner. First, autism community representatives were consulted to discuss potential opportunities and pitfalls for using candidate technologies in autistic populations, to select specific devices, to maximize procedural acceptability, and to identify potential facilitators and barriers for participation. Protocols were then piloted before implementation as part of the third time point of the AIMS Longitudinal European Autism Project (LEAP) [54,55]. As a large, well-characterized cohort comprising both autistic individuals and comparison individuals, data collection in LEAP enables a detailed understanding of participant characteristics that may affect acceptability and feasibility and how our measures relate to existing gold-standard and widely used conventional measures.

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Figure 1. Conceptual depiction of study approaches to exploring individual and combined potential for candidate data collection modes to index variance in domains of interest. Arrows represent potential indexing of domains of interest by data collection modes. For example, sleep disruption (blue arrows) may be indicated by a self-report sleep quality rating and also by several passive data sources. ADHD: attention-deficit/hyperactivity disorder; ADOS-2: Autism Diagnostic Observation Schedule-2; EDA: electrodermal activity; RRBI: restricted or repetitive behaviors and interests.

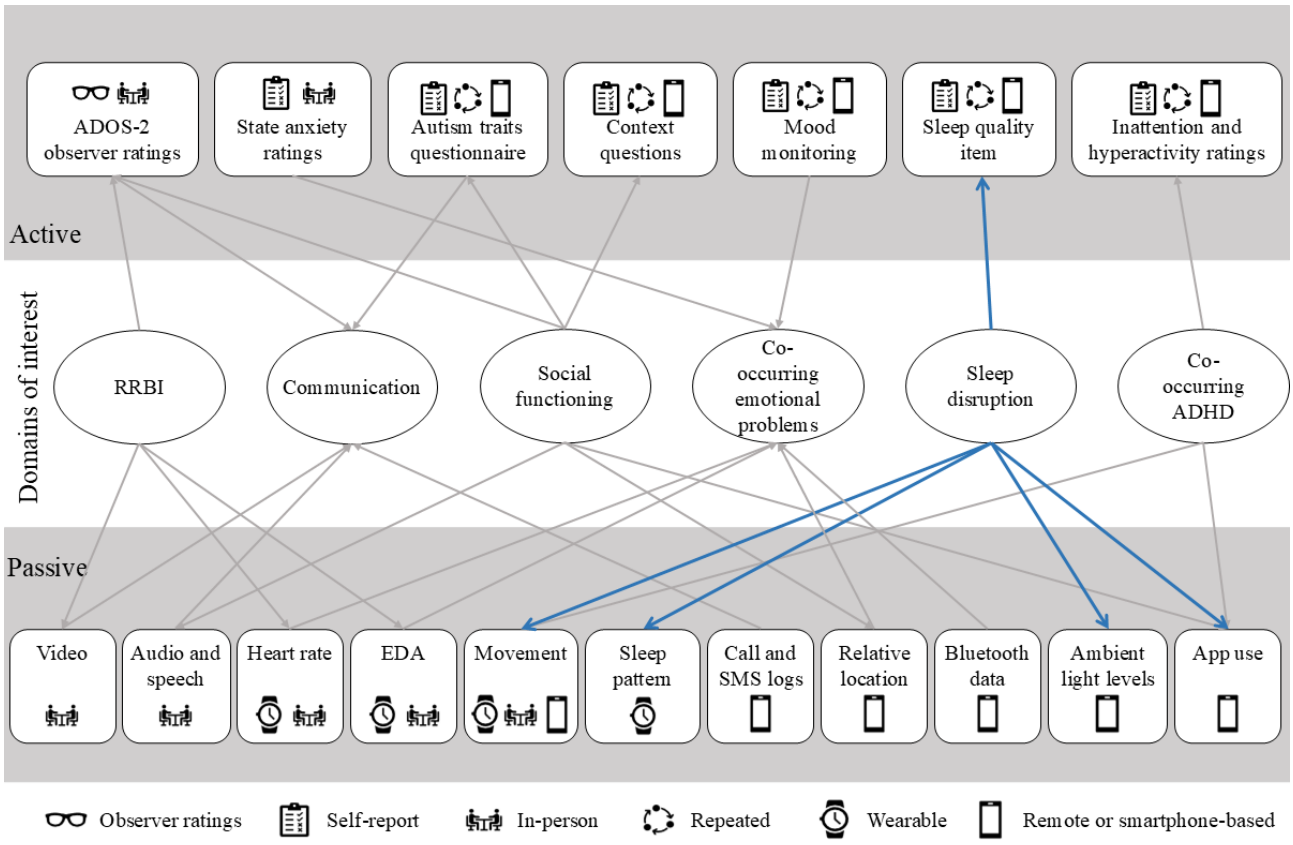

Study Objectives

The primary aim of this study is to evaluate, via quantitative and qualitative methods, the acceptability and feasibility of the measurement systems developed. Primary acceptability outcomes are uptake, adherence, completion rates for each component, and qualitative feedback on participant experience for RM. Primary feasibility outcomes are data availability and proportion of usable data relevant to each target domain. Secondarily, we aim to develop measures from the resulting data relevant to core autism characteristics (eg, social communication) and co-occurring conditions (eg, mental health and sleep problems). Finally, we aim to explore the resulting measures in terms of the association between subjective and objective measures and psychometric properties. In so doing, we hope to identify key candidate measures that show promising characteristics for further validation. This paper will describe the overall design, protocols for in-person and remote assessment, and key target analyses before discussing the potential impact, strengths, and limitations of our approaches.

Methods

Overall Design

Autism Community Involvement

In developing our protocol, we involved community representatives in a series of online focus groups aiming to explore community views on practical and ethical concerns regarding the use of digital technology in outcome measure development. Community views informed key elements of the protocol, such as study information processes, choice of wearable devices, and the interview schedule for qualitative feedback.

Participants

Data collection has been implemented primarily as part of the third (and, at the time of writing, most recent) time point of the LEAP study [54,55]. LEAP constitutes a large, well-characterized cohort recruited from centers across Europe: King's College London (KCL), University of Cambridge (UCAM), Radboud University Medical Centre, Nijmegen (RUMC), University Medical Centre, Utrecht, and Central Institute of Mental Health, Mannheim. At inception, LEAP included 437 autistic participants and 300 nonautistic participants aged between 6 and 30 years who have undergone repeated comprehensive phenotyping at 3 time points (T1: 2014-2017, T2: 2015-2017, and T3: 2020-2024). This includes gold-standard autism clinical profiling (ie, ADOS-2, Autism Diagnostic Interview-Revised, and Vineland Adaptive Behavior Scales); neurocognitive assessments; co-occurring symptom assessments; brain imaging; biochemical markers; and genomics. Participants with an IQ in the typical range were recruited in a 3:1 male-to-female ratio within age bands defined as (A) adult (aged between 18 and 30 y), (B) adolescent (aged between 12 and 17 y), and (C) child (aged between 6 and 11 y). Participants aged between 12 and 30 years with mild intellectual disability

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(IQ 50-74) were additionally recruited to a fourth schedule (D). The eligibility criteria for autistic participants were an existing clinical diagnosis according to the *DSM-IV* (*Diagnostic and Statistical Manual of Mental Disorders* [Fourth Edition]); *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]); or *ICD-10* (*International Statistical Classification of Diseases, Tenth Revision*) criteria.

Preliminary recruitment figures for LEAP T3 indicate that 225 autistic participants and 132 nonautistic participants took part across sites. A sample of 36 autistic participants and 44 nonautistic participants but with epilepsy (referred to as the LEAP epilepsy sample) was additionally recruited at KCL to complete the LEAP T3 protocol, including digital measures. All autistic participants in schedules A and B (ie, those aged ≥12 years) who were contactable at T3 at the KCL, UCAM, and RUMC sites (including University Medical Centre, Utrecht participants, who were seen at RUMC) were eligible to take part in our digitally augmented ADOS-2. In total, 30 nonautistic participants from across sites and schedules were also to be recruited. For RM, additional eligibility criteria were enrollment at KCL or UCAM (non-UK sites were not included because app translation was beyond our scope), independent use of an up-to-date Android (Google LLC) smartphone (version 8 or later), and willingness to try wearing the Fitbit Inspire 2 device as much as possible (day and night) for 28 days. There were no additional exclusion criteria to not meeting the inclusion criteria. We planned to only include Android users because our passive smartphone data collection app is only compatible with Android smartphones. Although we considered providing Android study phones to participants, we reasoned that these additional smartphones were unlikely to be used in a habitual manner and would thereby compromise ecological validity. Participants indicating interest but also a concern that they would find the Fitbit uncomfortable were invited to try to participate. It was emphasized that they would be free to discontinue wearing the Fitbit at any time or work with researchers to find a more comfortable strap. Finally, participants in schedule D were also eligible for each component, according to the same criteria, where it was felt that the protocol would be manageable within the context of overall demands presented by the wider LEAP T3 protocol and adequately understood for the purpose of providing informed consent. Participants in LEAP epilepsy were also invited to take part in both components according to the same criteria.

In addition to data collection in the LEAP sample, we recruited a volunteer sample of 25 nonautistic individuals or without known neurodevelopmental, neurological, mental health, or sleep conditions (RM comparison sample) to participate in an extended version of the RM component only. While data collection in LEAP and LEAP epilepsy is complete, data collection in our RM comparison sample is ongoing and will be completed in August 2025.

RADAR-Base Data Collection Platform

Both in-person and remote assessments use the RADAR-base platform for digital data collection and management [56]. The platform comprises the collection of multiple data sources, for example, passive and active data collection smartphone apps, as well as application programming interface integration for ingesting third-party (eg, Fitbit) data, secure data storage systems, and a management portal for linking data sources to participant identifying codes. The active RM technology (aRMT) app is a questionnaire administration app that allows a customizable schedule of questionnaires to be administered. The use of RADAR-base enables the secure collection and management of automatically time-stamped active and passive data for downstream analysis. The passive RM technology (pRMT) app [23,50] collects smartphone sensor data (eg, movement, relative location, light levels, and app use) as well as data from integrated wearable devices (eg, the Empatica E4 device used in this study).

In-Person Assessment

Procedure

The digitally augmented ADOS-2 is implemented in LEAP T3 as part of a 2-day in-person assessment visit. Cameras and a lapel microphone are set up before the participant enters the room (as depicted in Figure S2 in Multimedia Appendix 1 [27,28,49,57-75]). At the beginning of the assessment, participants are introduced to the Empatica E4 wristband and shown how to put it on their nondominant wrist. Video recording is then started on all cameras, and ceiling lights are switched off and on again as a synchronizing marker. The E4 is then turned on, and connection with the RADAR passive app is automatically established. Before starting the ADOS-2 assessment, participants complete a pencil-and-paper measure of state anxiety (detailed in subsequent sections). The ADOS-2 assessment is then administered according to standard protocol. Data collection started in September 2021, while certain social distancing and enhanced hygiene policies were still in place. We accommodated these via several adaptations to usual ADOS-2 procedures (summarized in Table S1 in Multimedia Appendix 1). The exact implementation for each "ADOS-2 informed assessment" was allowed to differ according to current site-specific policies and guidelines and was documented in case report files. For example, participants and administrators sat at a distance (eg, 2 m), clear masks were used, and certain ADOS-2 materials were adapted or removed. Between each ADOS-2 activity, the participants are asked to wave the wrist on which they were wearing the E4 to create an event marker. At the end of the assessment, recording is stopped, the E4 wristband is removed, and participants fill in the state anxiety measure again. Participants are also invited to wear the E4 wristband during a separate electroencephalography and eye-tracking task battery that forms part of the LEAP T3 visit. This acts as a comparison condition with lower social interaction demands.

Measures

Empatica E4

The Empatica E4 is a wrist-worn device that captures motion via accelerometer, heart rate via photoplethysmography, and EDA activity via electrodes on the device or via finger attachments (Figure S1 in Multimedia Appendix 1). Previous research has shown poor accuracy for wrist-worn EDA capture [57], and our own piloting demonstrates better capture using

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finger electrodes. Therefore, we use these unless participants find them uncomfortable, in which case we use the on-device electrodes. This option is provided primarily to maximize collection of photoplethysmography and motion data from the E4 and to explore acceptability of EDA electrode options in this context. This is because EDA readings differ across sites [76], and our protocol is not optimized for wrist placement (to date, all participants willing to wear the E4 were happy with finger placement). E4 data are ingested via the RADAR pRMT app installed on a study-owned compatible Android smartphone. The RADAR pRMT app is configured to pair automatically with the device via Bluetooth to ingest data. The Empatica E4 has been shown elsewhere to be well tolerated in naturalistic observation sessions involving autistic youth and to produce usable data for prediction of overt behavior from physiological data [77].

Video and Audio Recording

Video data are captured using commercially available high-definition video cameras, exporting at a minimum of 1920×1080-pixel resolution and 24 frames/second sampling rate, from three angles: (1) recording participant face from researcher perspective, (2) recording researcher face from participant perspective, and (3) recording the scene from observer perspective (camera setup is shown in Figure S2 in Multimedia Appendix 1). Cameras are mounted on tripods to minimize movement. The exact room setup varies across sites and sometimes within sites due to the use of different rooms and the constraints imposed by furniture size and layout. It is also not possible to standardize room acoustics and ambient lighting due to windows and differences in electrical lighting across rooms. In addition, the researcher wears a mobile lapel microphone to aid in distinguishing speakers (ie, researcher speech from participant speech).

Researcher Observational Ratings

The ADOS-2 [41] is a widely used gold-standard diagnostic instrument for autism in which a trained administrator leads a series of activities designed to elicit social interaction. The administrator assigns scores on numerous ordinal scales within domains, such as language and communication, reciprocal social interaction, and stereotyped behaviors and restricted interests. In this study, as per the LEAP protocol, we used modules 3 and 4 activity schedules, which were designed for individuals who are verbally fluent.

State Anxiety

The 6-item short form of the Spielberger State-Trait Anxiety Inventory state scale [78] comprises the 6 items exhibiting the highest item-remainder correlations in the full scale. The short form displays excellent correlation with full-scale scores ($r \geq 0.90$), and acceptable reliability and validity. Participants rate items (eg, I feel calm) on a 4-point scale between 1 (not at all) and 4 (very much) according to how they feel “right now.”

Remote Measurement

The RM System

Overview

The RM system comprises 4 components encompassing both active and passive data collection for a period of 28 days. This period was chosen pragmatically, considering the trade-off between gathering sufficient data to enable target analyses and acceptability to participants. Active data collection is via the RADAR aRMT app and MyJournE (Digital Marmalade) mood monitoring app. Passive data collection is via the RADAR pRMT app, Fitbit Inspire 2 wristband, and Fitbit app. Both active and passive data acquisition components are described in detail in subsequent sections. Figure 1 shows how multimodal data from the RM system map onto the domains of interest for measure development.

Active Components

We will use the RADAR aRMT primarily to administer our questionnaire schedule with prompts sent by push notification. The schedule includes a daily sleep quality item, biweekly attention items, and fortnightly social communication items (instruments detailed in subsequent sections). We will also use the aRMT to provide information about weekly progress, informing participants when each of the 4 weeks has been completed. Finally, at the end of the 28 days, system usability and user experience items will be administered to quantitatively capture participant satisfaction with the system. The schedule for the active components is summarized in Table S2 in Multimedia Appendix 1, and the instruments used are detailed in subsequent sections.

MyJournE is a mood monitoring app codesigned by young people [79] and researchers at KCL and developed by a UK-based software development company Digital Marmalade [80]. The app sends reminders via push notification twice per day for participants to complete the mood logs. These include a series of questions to efficiently capture context (eg, who a participant is with, where they are, and what they are doing), followed by a general happiness rating on a 5-point scale from very unhappy to very happy. This is followed by an implementation of the Positive and Negative Affect Scale (PANAS; refer to subsequent sections) in which each item is accompanied by a visualization of the emotion word involving a purple bean character (Figure S3 in Multimedia Appendix 1). Participants respond using a movable visual slider. Visual supports are commonly used by autistic people to aid in processing abstract concepts [81] and thus may contribute to acceptability, especially in the context of high rates of alexithymia among autistic individuals.

Passive Components

Fitbit Inspire 2 is a commercial fitness tracking device that records heart rate via photoplethysmography and motion via an accelerometer. It is lightweight, unobtrusive, and allows for a choice of strap material; thus, it is well-placed to cater for some degree of sensory sensitivity. Using proprietary algorithms, Fitbit provides heart rate, step count, and sleep staging data. Fitbit models manufactured after 2017 estimate time spent in 4 sleep stages (awake, light sleep, deep sleep, and rapid eye

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movement) using machine learning methods applied to motion and heart rate [82]. From this, sleep parameters such as total sleep time and wake after sleep onset may be derived [49].

The RADAR pRMT collects a variety of Android smartphone sensor data without the need for regular participant input. Specifically, these data include physical motion (eg, from the onboard accelerometer and gyroscope), ambient light levels, GPS location, number of Bluetooth-enabled devices in range, phone and app use data, and battery levels. GPS coordinates are offset by a random number for each participant to obscure the absolute location while preserving the relative location (ie, information about distance, duration, and direction of travel). In addition, for this project, we used a custom build of the app [83] that included functionality to access call and SMS logs including data on incoming and outgoing call duration, SMS length, and whether they were with a saved contact. These data are potentially relevant in capturing aspects of social functioning and, due to Google Play Store restrictions, are not included as standard in the app. No call or SMS content is recorded, and participants are able to freely grant or remove permissions for different data sources in the app settings.

Procedure

Given the novelty, complexity, and privacy considerations of RM data collection, our community representatives stressed the importance of a comprehensive information process with a clear description of which information is collected, how it is managed, and how it will be used. With this in mind, we developed an extended information and consent process. Eligible participants will be sent an email with attachments comprising the participant information sheet and a participant handbook (Multimedia Appendix 2). The participant handbook contains additional information on the types of data collected, particularly those that may feel more personal (eg, location and app use data), and how the data are pseudonymized, stored, and processed. Participants are also invited to a study information video call, which is typically scheduled at least 1 week after the email to allow time for reading the information documents. The call takes approximately 30 minutes, aims to run through the study information at a suitable pace, and allows time for questions. At the end of the call, participants who are happy to proceed are provided with a link to a web-based consent form, which they may complete as part of the call or in their own time. Consenting participants are invited to an enrollment video call approximately 1 week after the information call to allow for a Fitbit to be posted to their home.

The enrollment call takes approximately 1 hour and comprises app installation, setup, and Fitbit connection. The MyJournE app, RADAR active app, and the Fitbit app are installed from the Google Play Store whereas the custom RADAR passive app is installed from GitHub to the Android Application Package. Participants are given log-in details for each app and given a chance to explore the active data collection apps. The RADAR passive app requests access to several smartphone data sources. Participants are taken through these and reminded that they can control the data the app accesses by toggling permissions and are free to disallow access to any data source at any time if they feel uncomfortable. Finally, participants are taken through setting up their Fitbit device and pairing it with the app.

The 28-day data collection period starts the day after the enrollment call. Participants receive reminders to respond to the active components. A day 3 check-in is administered via video or phone call or email to check if the participant is happy with how the month is proceeding and to troubleshoot any issues. Researchers complete regular checks by accessing the RADAR-base platform to ensure data are coming in for each component (ie, Fitbit, pRMT app, aRMT app, and MyJournE). We contact the participant or relevant technical support teams for troubleshooting if any data component is not received or largely missing. For example, if data checks show that Fitbit data are missing, the participant is contacted to establish if the device is being worn or if there are syncing or charging issues. If the participants report that they are finding the device uncomfortable, an alternative strap is offered if it is felt that this may help. If data are missing from the smartphone apps, similar troubleshooting occurs, for example, to establish if notifications are being received or if the participant is simply finding it difficult to respond.

At the end of the 28 days, participants are notified to complete the user experience questionnaires via the RADAR aRMT. These questionnaires are available for 1 week, after which data are no longer collected via the aRMT app. Participants are also invited to complete a feedback interview during the week following completion. The feedback interview is conducted via a video call and lasts around 1 hour. It also includes questions eliciting participant opinions on the study information and enrollment processes, general experience and impact on daily life (including discussion of potential Hawthorne effects), Fitbit usability and comfort, active app scheduling, and passive data collection acceptability. Participants keep the Fitbit device at the end of the month and receive £20 (US $26.81) in Amazon vouchers for their time spent taking part in the feedback interview.

Measures

Autism Ratings

The Social Responsiveness Scale Short Form [84] is a questionnaire measure of autistic characteristics, particularly, in the social communication domain. It comprises 16 items derived from the full parent report version (65 items). The short form showed excellent reliability (α=.96) and substantial associations with social features of autism measured by gold-standard instruments (eg, Autism Diagnostic Interview-Revised Social subscale, r=0.48, and ADOS-2 module 4 Social Affect, r=0.49) [84]. In this study, it is administered as a self-report questionnaire on days 8 and 15 of the 28-day RM period.

Inattention and Hyperactivity Ratings

On the basis of a previous experience sampling study [85], we used a 4-item scale comprising 3 inattention items (eg, “I was easily distracted and could not concentrate over a longer period of time”) and 1 hyperactivity item (“I felt restless or fidgety”), based on *DSM-5* ADHD criteria. In a community sample of adolescents aged between 14 and 17 years, internal consistency

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for the inattention items was satisfactory (α=.67-.79) [85]. In this study, items are rated every 4 days on a scale from 0 (not at all) to 100 (all the time) using a movable slider.

Sleep Quality Ratings

The Single-item Sleep Quality Scale [86] is a simple measure of overall sleep quality rated on a ten-point scale. It shows a strong association with widely used questionnaire measures and was able to differentiate normal, borderline, and problem sleepers in a study of patients with depression [86]. In this study, participants are asked to rate their sleep quality for the night before each morning on a scale from 0 (terrible) to 100 (Excellent) using a moveable slider. The 0-100 scale was used for consistency with the inattention and hyperactivity items.

Mood Ratings

The PANAS is a widely used 20-item measure of positive and negative affect in which participants rate the intensity with which they are feeling each of 10 positive and 10 negative mood descriptors (eg, “enthusiastic” and “distressed”). Internal consistency for both scales was shown to be excellent (α=.84-.90) [87]. In the MyJournE app, items are rated according to the question “How appropriate is this word today?” using a 5-point movable slider scale ranging from “very slightly/not at all” to “extremely.”

User Experience Ratings

The System Usability Scale [88] is a 10-item usability questionnaire in which statements (eg, “I thought the system was easy to use”) are rated on a 5-point Likert scale from 1 (“strongly disagree”) to 5 (“strongly agree”). The scale has been demonstrated to have excellent internal consistency (α=.91) [89]. In this study, participants are notified via the RADAR aRMT app to complete the System Usability Scale based on their experience of the RM system *overall* (Fitbit and smartphone apps) on day 29 after enrollment. At the same time, participants were also notified to complete a separate user experience questionnaire with 7 items specific to the Fitbit and 10 items specific to the active questionnaire apps [90].

Ethical Considerations

Ethics approval was obtained for LEAP and LEAP epilepsy groups at KCL and UCAM from the London-Central and Queen Square Health Research Authority Research Ethics Committee (13/LO/1156) and at RUMC from the RUMC’s Medisch-Ethische Toetsingscommissie (2019-5942; NL72033.091.19). For the RM comparison group, KCL Research Ethics was obtained (LRS/DP-23/24-42359). Compliance with European and UK data protection policies was ensured by performing a data protection impact assessment in consultation with the KCL information compliance department and compliance teams at local sites. RM data are pseudonymized via a study identification code, and dummy Fitbit accounts are set up for participants, which are not linked to their personal information. Data acquired from the Fitbit and smartphone apps are automatically encrypted and uploaded to secure servers as part of the RADAR platform. Video and other identifiable data are kept separately on secure servers and shared across study sites for analysis purposes with explicit consent.

Planned Analyses

Overview

This protocol is primarily intended to support evaluation of the acceptability and feasibility of the range of candidate technologies and methods that it uses. Secondarily, it may provide rich, multimodal data supporting the exploration of a range of potentially meaningful outcome measures. The potential avenues for such exploration are numerous and dependent not only on the quality of the resulting data but also on available data processing tools and analytic approaches, which are expected to evolve rapidly. Therefore, in this paper we describe our primary analyses of acceptability and feasibility in detail and give only several examples of candidate outcome measure exploration planned in this study. The specifics of these secondary analyses are beyond the scope of this paper but will be presented in individual outputs. Our featured initial domains for outcome measure development are based on community priorities (eg, sleep and mental health) [91,92], tractability based on currently available analytic tools, and innovation in terms of building on existing work. Initial data processing plans are provided in Table S3 of Multimedia Appendix 1.

Acceptability and Feasibility

Overview

Acceptability and feasibility will be evaluated comprehensively via quantitative and qualitative analyses (Table 2). Uptake and completion rates will be calculated at the level of each system (ie, augmented ADOS-2 and RM protocols), whereas quantification of adherence, tolerance, and participant experience will differ according to subcomponents; for example, adherence to wearing the Fitbit is examined separately to adherence to questionnaire completion. Qualitative data, for example, reasons for declining to participate and for withdrawal will contribute to our understanding of quantitative information and, in the case of our RM protocol, will support a larger qualitative framework analysis of feedback interviews. Similarly, feasibility will be evaluated with reference to participant eligibility, data availability, and data quality and may be specific to each analytic approach. Limiting factors for the proportion of usable data will be identified; for example, establishing whether active RM data are missing due to technical failure (eg, notifications not sending) or nonresponse.

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Table 2. Planned metrics for acceptability and feasibility.

	In-person components (E4 and video recording)	Remote measurement components (Fitbit, pRMT[a], aRMT[b], and MJE[c])
Acceptability		
Uptake	Proportion consenting and reasons for decline	Proportion consenting and reasons for decline
Adherence and tolerance	E4 wear time and reasons for removal and requests for discontinuation of filming	Fitbit wear time and reasons for removal, pRMT app permissions granted, and aRMT and MJE response rates
Experience	STAI State-6[d] (before and after assessment)	Usability ratings (SUS[e] and UEQ[f]) and feedback interview (qualitative)
Completion	Proportion completing protocol and reasons for withdrawal	Proportion completing protocol and reasons for withdrawal
Feasibility		
Eligibility	Proportion eligible and reasons for ineligibility	Proportion eligible and reasons for ineligibility
Data availability	Missing data and reasons for missingness (eg, equipment malfunction)	Missing data; reasons for missingness (eg, hardware and software malfunction versus acceptability issue)
Data quality	Proportion of usable data for each analysis and reasons for low-quality data	Proportion of usable data for each analysis and reasons for low-quality data

[a]pRMT: passive remote measurement technology.

[b]aRMT active remote measurement technology.

[c]MJE: MyJournE app.

[d]STAI State-6: 6-item short form of the Spielberger State-Trait Anxiety Inventory.

[e]SUS: System Usability Scale.

[f]UEQ: User Experience Questionnaire.

Predictors of Acceptability and Feasibility

Predictors of certain acceptability and feasibility metrics will be explored. Primarily, differences between autistic and nonautistic groups will be examined for each metric with formal parametric and nonparametric statistical methods applied where possible. Age, cognitive ability, and adaptive ability will be assessed as predictors of uptake, adherence (wear time and active app response rates), usability ratings, and completion. We will also explore the association between Fitbit wear time and the tactile sensitivity subscale of the Short Sensory Profile [93] completed by participants as part of the main LEAP study.

Planned Exploration of Candidate Outcome Measures

Digitally Augmented ADOS-2 Data

Audiovisual data from ADOS-2 will be processed using machine learning–based tools, assisted by researcher annotation of key behaviors. We will explore associations between resulting features extracted from the audiovisual data and observer-assigned scores in key domains. In so doing, we will explore the performance of existing speech and video processing tools and the suitability of extracted features for quantifying clinically relevant characteristics via more objective, precise, automatically generated scores. Note that it is not our intention to use these data to explore diagnostic classification approaches as has been done elsewhere. Our focus is on developing tools to quantify characteristics that may be used to understand heterogeneity within clinical classification and to evaluate interventions. For example, drawing on previously published pipelines [58], our speech data will be processed using open-source, automated diarization, transcription, and conversation analysis tools such as pyannoteAI Audio [59], OpenAI Whisper [60], and ConvoKit [61], respectively (Table S3 in Multimedia Appendix 1). Resulting features (eg, number of conversational turns and the length of participant and researcher utterances) will be tested for association with ADOS-2 language and communication codes indicating the amount and nature of social speech and reciprocal social interaction codes for the frequency and quality of social initiation and response. Such associations will be tested using conventional regression-based statistical analyses.

In addition, we will explore the ability of machine learning and computer vision tools to identify instances of verbal and nonverbal behaviors relevant to ADOS-2 scoring algorithms. For example, drawing on existing work identifying and classifying stereotyped movements from ADOS-2 data in children [62], we will explore the feasibility of applying such methods to our adolescent and adult data, as well as assessing the utility of integrating E4 motion and psychophysiological data to refine classification.

Using Empatica E4 photoplethysmography and EDA data, we plan to develop pipelines for investigating autonomic arousal in the context of the ADOS-2 assessment. Data will undergo quality control procedures (eg, [63,94]) and processing (Table S3 in Multimedia Appendix 1). Tasks will be demarcated using event markers generated via hand waves. Key tasks of interest within the ADOS-2 will be identified, that is, those hypothesized to have high (presenting a story from a cartoon and discussing emotions) versus low (completing a puzzle and describing a

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picture) psychosocial demand for autistic people. Within each relevant task, heart rate, heart rate variability, and EDA features will be calculated, applying and testing existing pipelines [95,96]. Derived indices of autonomic arousal will then be compared across conditions within participants. If data are of sufficient quality and power, linear mixed effects models (LMEMs) will investigate group differences in autonomic response to psychosocial demand [47]. Association of autonomic responses with subjective state anxiety scores from the beginning and end of the assessment will also be explored.

RM Data

Overview

Using RM data, we will focus on exploring objective, multimodal indices from passive data in several key domains (sleep, mental health, and social functioning) and investigate their associations with corresponding self-report data. Due to the relatively short observation period and lack of planned intervention during that time, this exploration will focus on between-subject analyses as opposed to within-subject change over time. Given the hierarchical data structures produced by repeated measurement, associations will be investigated using LMEMs. These account for dependent data points flexibly, with minimal loss of power [97].

Missing Data

Given the challenges associated with collecting data remotely, we anticipate missing data due to varying participant engagement levels, device issues, or network connectivity. We will draw on published research establishing feature-specific guidance on acceptable levels of missing data to determine data eligibility for further analysis [98]. Where possible, we will use multiple imputation to account for missing values (eg, where certain modalities have some missing values for a participant in a multimodal analysis). Coupled with this, LMEMs allow for retention of cases with missing observations and are compatible with certain maximum likelihood–based estimation procedures [99]. Multiple imputation– and maximum likelihood–based approaches are considered unbiased where data are missing at random [100]. The plausibility of this assumption will be assessed on a case-by-case basis and be addressed where necessary, for example, using sensitivity analyses.

Sleep

As well as drawing on Fitbit-provided sleep staging data, we will incorporate passive smartphone data, such as light levels, phone motion, and app use, to derive objective indices of sleep architecture. This novel approach is intended to improve accuracy in differentiating periods of sleep versus wakefulness. In particular, we will target sleep parameters identified commonly as disrupted in autistic youth and adults, for example, sleep onset latency, wake after sleep onset, sleep efficiency, and percentage of rapid eye movement sleep [33,101]. We will test the associations between these objective parameters and daily subjective sleep quality ratings using LMEMs. In addition, we will use cluster analysis to identify more homogeneous, objectively recorded sleep patterns.

Mental Health

Drawing on existing research into smartphone sensor-based indicators of mental health, for example, from location and activity data, phone and app use patterns, and call and SMS logs [102], we plan to test currently available tools and procedures for feature extraction and assessment of correspondence between passive data and subjective positive and negative affect as reported in the PANAS, administered via the MyJournE app (eg, [103]). We will also explore associations between extracted features and mental health measures collected as part of the LEAP questionnaire battery (ie, the Beck Depression Inventory [104] and Beck Anxiety Inventory [105]) and reported diagnoses.

Social Functioning

Finally, we plan to use similar methods to explore aspects of everyday social functioning and environments that may be indexed in our passive RM data. Our data offer an opportunity to explore objective indices of social functioning and environment in everyday life in relation to subjective reports of social communication, social activities, and mood. We will adapt pipelines developed in other populations to index various aspects of social functioning, including social activity [106], “sociability” (comprising communication and social exploration domains) [51], and loneliness [52], from multimodal data (including duration, frequency, and diversity of telephone calls, Bluetooth connectivity, GPS location, and smartphone screen interactions). We aim to develop similar multimodal indices that may be referenced against subjective measures, such as the Vineland Adaptive Behavior Scales, Social Responsiveness Scale Short Form, and the MyJournE context questions (eg, “Who are you with?”).

Results

Following ethics approvals documented earlier, the first participant was enrolled for the digitally augmented ADOS-2 component on September 11, 2021, and for the RM component on March 3, 2022. Data collection within the LEAP and LEAP epilepsy samples is complete as of October 2024. In the digitally augmented ADOS-2 component, 190 participants took part (LEAP: n=167, 87.9% and LEAP epilepsy: n=23, 12.1%). In the RM component, 86 participants have been enrolled (LEAP: n=47, 55%, LEAP epilepsy: n=14, 16%, and RM comparison: n=25, 29%). In the RM comparison group, data will be collected in an ongoing manner until August 2025.

Several planned analyses are underway. In our primary outcome domains of acceptability and feasibility, qualitative framework analysis coproduced with community members is in its final stages and will contribute to a key planned mixed methods publication on the acceptability and feasibility of RM. This publication will also outline work with autism community members during initial stages and the impact on the protocol. Quantitative acceptability and feasibility analyses contributing to this publication are also underway; for example, we have explored adherence to Fitbit wearing and the active questionnaire schedule. Elsewhere, we have developed working pipelines for analysis of ADOS-2 speech data and RM sleep data.

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Discussion

Study Contributions

Autistic people face diverse and complex challenges in daily lives that are difficult to quantify using conventional techniques. Measuring treatment response in a scalable, precise, and unbiased manner is particularly problematic, and a lack of tools available to do this has impeded progress in evaluating autism-specific interventions for such challenges. Development of better measurement tools for quality of life, mental health, social well-being, and sleep was among the top 5 priorities identified by autistic adults and other stakeholders in the study by Benevides et al [91]. Digital technology offers an array of compelling opportunities to measure more objectively, with lower burden and greater ecological validity. This study protocol was designed with input from autism community representatives to develop and evaluate acceptable digital measures relevant to priority outcomes. Our dual in-person and remote approach enables us to develop an understanding of how such measures may relate to and potentially complement each other in the context of a range of study designs. If demonstrated to be adequately acceptable and feasible, the measures explored in this study could be used to enhance understanding of everyday challenges for autistic people. They could support clinical research by providing outcome measures that are specific and responsive to small changes in meaningful outcomes.

Most existing studies applying digital technology to challenges in the diagnosis and management of autism are aimed at proof-of-concept and have relatively small sample sizes [107]. Understanding generated from this study of digital acceptability and feasibility could facilitate the application of digital measures at scale and assist implementation of digital supports for autistic people, for example, app-based mental health interventions [108] and wearable devices that may help autistic people to understand and communicate their emotions [109] or predict maladaptive behaviors [77].

Potential Strengths and Limitations

Data collection in the LEAP study is well positioned for achieving these aims. The sample is already well characterized, meaning that factors potentially associated with acceptability and feasibility may be thoroughly investigated. LEAP includes high-quality measures of autism clinical characteristics, intellectual ability, and co-occurring symptoms, factors that may influence participant uptake and experience of digital measures. Certain candidate measures may also be validated against robust conventional measures in domains of interest, for example, gold-standard autism assessments and well-validated questionnaire instruments. For other novel measures, we do not incorporate a reference standard. In the domain of sleep, polysomnography is not included because its feasibility for implementation outside of clinical settings is problematic and its representativeness in capturing everyday sleep is unclear. However, we do incorporate a daily subjective sleep quality measure, which is an important clinical end point.

For the RM component, instruments were selected to build a system that maximizes acceptability and accessibility (within the context of independent smartphone users). Accordingly, we selected very brief active measures to minimize participant daily time burden and interference with everyday life. We also selected Fitbit Inspire 2 as our wearable device of choice, given its widespread use in the broader population, unobtrusive design, and affordability. However, this approach comes with challenges in terms of data quality and analytic potential. Both wearable devices use photoplethysmography to estimate heart rate, rather than obtaining direct measures via electrocardiography. Use of Fitbit also necessitates relying on proprietary algorithms for heart rate, step count, and sleep pattern, which limits flexibility in analysis. On the other hand, Fitbit provides ready-to-use processed data with established performance against gold-standard measures [82,110,111]. Across studies, recent-generation Fitbit models have been shown to have high sensitivity (0.95-0.96) in identifying sleep epochs, lower specificity (0.58-0.69), and a tendency to underestimate sleep onset latency [82]. Despite efforts to maximize the acceptability of remote data collection, some level of noncompliance is expected, and understanding factors associated with these forms a primary area of investigation for this study.

Another limitation is that the focus on independent smartphone users is likely to exclude many participants with intellectual disabilities, a group forming a considerable proportion of autistic people [112]. Our hope is that the current research may identify promising candidate measures that could be adapted for populations with ID. Indeed, enhancing our understanding of how objective, passive measures relate to subjective experience may pave the way for the development of novel measures of internal states, such as anxiety, which do not require explicit self-report [113]. Similarly, our inclusion criterion of "willingness to try to wear the Fitbit Inspire 2 as much as possible for 28 days" may exclude participants with particular sensitivity to touch. However, our selection of the Fitbit Inspire 2 was largely based on discussion with autistic community members who advised us that selecting a lightweight device with a choice of strap material may minimize exclusion of those with sensory sensitivities and support adherence. Furthermore, our explicit inclusion of questions on device comfort in the feedback interview is intended to advance understanding of the factors that may influence adherence to wearing such a device for autistic participants in research studies.

More generally, our sample is primarily derived from LEAP, a volunteer sample that has been further selected based on eligibility criteria mentioned earlier. This limits the generalizability of the current findings to the wider, highly heterogeneous autistic population. However, it is hoped that responding to acceptability and feasibility challenges highlighted by this study will inform future research that may be more widely applicable. In turn, highly precise, objective, digital end points may ultimately contribute to identifying subgroups of the autistic population that may reflect different mechanisms underpinning challenges and different responses to intervention.

Data privacy is another important issue raised in our community involvement activities and those of others [114]. Digital technology is powerful in the sense that large quantities of data capturing potentially sensitive features are generated with low effort and awareness. Research has shown that most owners of smart devices are willing or would consider sharing their digital

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data for health research purposes [115]. However, for certain others, this constitutes an uncomfortable invasion of privacy. In the general population, acceptability may depend on how data are used (eg, for the good of the public), managed (eg, using anonymization procedures), and with whom they are shared [116]. This study has the potential to provide insight into the circumstances under which such data collection is acceptable for autistic people and how to communicate effectively about data use and sharing.

Finally, although this is an observational study, our RM procedures may cause people to change aspects of daily living, introducing Hawthorne effects. For example, use of the Fitbit for its intended purpose as a fitness tracker may lead to changes in activity levels and sleep habits, and knowledge that app use is recorded may cause a participant to change app use habits. Because a putative advantage of digital measurement (particularly, passive and objective measures) is a reduction in potential observation or attention effects in the context of clinical trials, it is important to investigate these during measure development. Therefore, we ask specifically about perceived behavioral changes in our qualitative interview. However, quantitative investigation of within-subject variance over time is out of scope in our study due to the relatively short observation period. Future studies may wish to draw on platforms providing the capability to blind participants from on-device information and app-based dashboards showing summarized data (eg, Oura Ring [117]).

Conclusions

Despite the range of potential challenges in digital measure development, particularly in the field of autism research, identification and understanding of these are incorporated as key aims of this study. Our collection of both quantitative and qualitative data on acceptability will allow a more thorough understanding of factors influencing uptake, adherence, completion, and, importantly, experience of the protocol. Careful consideration of the acceptability and feasibility of candidate measurement techniques, alongside extracting and validating meaningful indices of outcomes important to community stakeholders, is essential in developing measures that live up to the potential afforded by digital innovation.

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Authors' Contributions

IY, CC, EL, JB, DM, RD, and ES were responsible for the conceptualization. IY, CB, ARC, PC, HS, YR, and ZR were responsible for data curation. ARC, NC, AF, and RD were responsible for the formal analysis. EL, JB, DM, RD, and ES were responsible for the funding acquisition. IY, CB, and ARC were responsible for the investigation. IY, ARC, BO, PC, HS, YR, ZR, J Dineley, J Downs, CC, NC, AF, RD, and ES were responsible for the methodology. J Downs, EL, JB, DM, RD, and ES were responsible for resources. IY, CB, ARC, BO, AF, EL, JB, DM, RD, and ES were responsible for the project administration. ARC, PC, HS, YR, ZR, J Downs, AF, and RD were responsible for software. J Downs, NC, AF, RD, and ES were responsible for supervision. IY was responsible for writing the original draft. All the authors were responsible for writing—reviewing and editing.

Conflicts of Interest

RD is the director of CogStack Ltd and Onsentia Ltd. CC is a full-time employee of Shionogi, Inc. AF has shares in Google, which acquired Fitbit. All other authors declare no conflicts of interest.

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Multimedia Appendix 1
Additional tables and figures comprising Autism Diagnostic Observation Schedule-2 (ADOS-2) pandemic–related adaptations, schedule of events for the 28-day Mobile Measures Month, Empatica E4 device set-up, videocamera and lapel microphone set-up for the ADOS-2, screenshots from the MyJournE app, and additional detail on proposed data processing for passive data collection modalities.
[DOCX File , 789 KB - resprot_v14i1e71145_app1.docx]

Multimedia Appendix 2
Participant handbook for the remote measurement component.
[PDF File (Adobe PDF File), 1368 KB - resprot_v14i1e71145_app2.pdf]

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Abbreviations

ADHD: attention-deficit/hyperactivity disorder
ADOS-2: Autism Diagnostic Observation Schedule-2
aRMT: active remote measurement technology
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)
DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)
EDA: electrodermal activity
ICD-10: International Statistical Classification of Diseases, Tenth Revision

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JAKE: Janssen Autism Knowledge Engine
KCL: King's College London
LEAP: AIMS Longitudinal European Autism Project
LMEM: linear mixed effects model
PANAS: Positive and Negative Affect Scale
pRMT: passive remote measurement technology
RM: remote measurement
RUMC: Radboud University Medical Centre, Nijmegen
UCAM: University of Cambridge

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Protocol

Quantifying Maternal Health Using Digital Phenotyping: Protocol for a Longitudinal Observational Study

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Abstract

Background: We present a digital phenotyping protocol designed to continuously and objectively measure behavioral, physiological, and contextual data during pregnancy and the postpartum period using passive sensing from Garmin smartwatches and smartphones, along with active ecological momentary assessments (EMAs). This novel protocol uniquely adapts to the unpredictable timing of childbirth, spanning from the third trimester through 6 weeks post partum, to accurately capture critical temporal changes and maternal-infant outcomes. By providing high-frequency real-time data, this methodology offers comprehensive insights into pregnancy-related behaviors and physiological processes, overcoming the limitations of traditional retrospective self-report methods.

Objective: We aim to develop a protocol for longitudinal data collection supporting digital phenotyping that is optimized for pregnancy and the postpartum period. This protocol leverages the pregnant population's heightened interest in health and tracking. It aims to minimize the burden on the participants, increase retention, and assess the value of wearables compared to smartphones to determine the appropriate data collection methods.

Methods: Data will be collected from 30 nulliparous participants from the start of the third trimester through 6 weeks post partum. This protocol uses 3 distinct 1-time surveys, alongside daily and weekly EMAs, to capture real-time maternal experience data. Passive maternal data—such as activity, vitals, sleep, and location—are collected via smartphones and Garmin smartwatches. Participants are expected to log data about the newborn after delivery through the mobile app Huckleberry. This protocol was developed in collaboration with the Northeastern University Sath Laboratory, which focuses on digital phenotyping and longitudinal data collection, and the Tufts Medical Center's obstetrics and gynecology department, which has expertise in working with the pregnant population.

Results: This study was funded in August 2024. Data collection is projected to run from October 2025 to July 2026. As of September 2025, the study has been approved, and recruitment and data collection are to begin. The results are expected to be published by August 2026. We plan to assess the retention rates, survey and EMA completion rates, wear time of the smartwatch without intervention, and data volume logged in the Huckleberry app. In addition, we will perform digital phenotyping to determine whether the data collected during pregnancy can be used to predict breastfeeding outcomes, delivery outcomes, and maternal-infant well-being.

Conclusions: This protocol integrates the use of digital phenotyping in pregnancy and postpartum research, providing a novel method for capturing real-time indicators of maternal well-being. It will determine the expected rates of data completion and appropriate sample size using a power analysis for a more extensive future study. By integrating smartphone and wearable sensor

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data, this protocol has the potential to transform the way maternal health clinical interventions are designed and implemented in the future.

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KEYWORDS

digital phenotyping; longitudinal data; pregnancy; smartwatch; smartphone; ecological momentary assessment

Introduction

Background

We present a digital phenotyping protocol specifically designed for pregnant populations using smartphones and Garmin smartwatches to continuously measure behavioral, physiological, and contextual data. Our design addresses the inherent challenges posed by pregnancy, including a nonfixed study duration and unpredictable delivery-triggered phase transition, by spanning from the third trimester through 6 weeks post partum. This protocol also takes into account the engagement-burden tradeoff with data collection and increased physiological variability during pregnancy through various data streams and development specifically for digital phenotyping, which is the in situ quantification of an individual's phenotype using data from their digital devices, such as smartphones and wearable sensors [1]. This approach allows for the continuous objective measurement of behavior, physiology, and environmental context in someone's everyday life, offering a detailed understanding at the individual level [1]. Data in this study are collected both passively via automatic sensing from ubiquitous devices and actively through ecological momentary assessments (EMAs), which are brief surveys completed by participants in their everyday environments. By overcoming the limitations associated with retrospective self-report methods, this approach allows for a more comprehensive understanding of pregnancy-related behaviors, physiological processes, and maternal and infant outcomes.

Conventional analytical techniques that rely on retrospective self-reporting can be affected by recall bias and thus fail to capture critical temporal changes [1]. In contrast, digital phenotyping uses high-frequency real-time data [1]. Previous perinatal digital phenotyping studies, such as the Mom2B study [2] and the Postpartum Mothers Mobile Study [3], have shown the feasibility of smartphone-based prediction of outcomes, EMA for post partum and breastfeeding, and mobile tracking of maternal health. Although the Mom2B study relied primarily on smartphone data, our protocol extends this work by integrating synchronized wearable data and multiple app-based platforms. We also adapted EMAs from the study by Demirci and Bogen [4] on primiparous women and the combination of EMA and smartphone data from the Postpartum Mothers Mobile Study [3]. By continuously and objectively capturing behavioral and physiological data, our protocol provides robust insights into the complex interactions influencing maternal and infant health outcomes. This comprehensive approach can significantly enhance our understanding of the pregnancy and postpartum experience. In addition, by collecting a multitude of data that adapts after participants deliver, we can understand participants' behavior in a more comprehensive way than digital phenotyping studies that stay the same during different stages of pregnancy or the postpartum period.

Nonfixed Study Duration

The first challenge that this protocol must address is the nonfixed study duration.

The duration of an individual's pregnancy is highly variable, and in clinical practice, the estimated due date (EDD) is 40 weeks of gestational age [5]. In the Early Pregnancy Study [6], even after excluding pregnancies affected by complications or preterm births, the variation in human gestational length was 37 days. Only approximately 5% of people deliver on their assigned 40-week gestational age EDD, and 66% deliver within 7 days of their EDD [5]. The variability in delivery timing means that although the duration of the third trimester is defined as 12 weeks, beginning at 28 weeks of gestation and culminating at 40 weeks of gestation [7], many people will have a third trimester that is shorter or longer. The duration of the third trimester can range from less than 1 week, if the baby is delivered at 29 weeks, to approximately 14 weeks. For example, a participant delivering at 30 weeks 0 days gestation would have 2 weeks of data collected in the third trimester and 6 weeks of data collected in the postpartum period for a total of 8 weeks. Conversely, a participant delivering at 41 weeks and 6 days of gestation would have 14 weeks of data collected in the third trimester and 6 weeks of data collected in the postpartum period for a total of 20 weeks. The nonfixed third-trimester study duration creates a challenge, as compensation in a study is typically for a set amount of time. In addition, data storage amounts cannot be pre-estimated, and research apps typically need to know the study duration before commencement. In addition, to best understand pregnancy, EMA questions need to transition from prenatal-focused questions to postpartum-focused questions. Given these inherent biometric challenges, we developed a protocol that adapts to both longer and shorter study durations.

Unpredictable Delivery-Triggered Phase Transition

The variance in the third-trimester duration for participants creates the challenge of an unpredictable delivery-triggered phase transition, which is the change in EMA questions that occurs because of the participant delivering their baby. We collect data in 2 phases, antepartum third trimester and postpartum period, which are segmented by delivery. There is no way to know for certain exactly when the baby will be delivered, and the delivery date will be different for each participant. There will be a discrepancy between the EDD (40 weeks) and the actual delivery date, and between the actual delivery date and the date on which the research team becomes

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aware that the participant's pregnancy has ended. This may lead to a delay when the postpartum EMA questions are triggered. The unpredictable delivery-triggered phase transition will also lead to some participants providing a different amount of data before and after delivery, with participants who have a longer third trimester providing a greater amount of data before delivery. This variability introduces complexity when developing a longitudinal data collection protocol aimed at capturing critical behavioral and physiological changes during pregnancy, the puerperium, and the postpartum condition. The protocol must account for transitioning from prenatal data collection streams to the postpartum data collection streams in a way that can be implemented variably after delivery without leading to delays in postpartum data collection.

Engagement-Burden Tradeoff

This protocol aims to investigate the engagement-burden tradeoff. Research data suggest that pregnancy is a health care state associated with high rates of engagement with online searches. One study reported that 90% of pregnant individuals obtained supplemental health care information online [8]. In addition, 50% of pregnant individuals installed a health-tracking app on their phones during pregnancy [9]. This provides a unique opportunity to leverage this increased engagement to collect more data than is typically collected from other populations. However, we must balance this opportunity with minimizing the burden on the participant while still emphasizing increased engagement. Previous studies have prioritized minimizing the burden on participants by including only 1 detection device, collecting fewer data streams, or implementing either passive or active data collection, and not both simultaneously. This protocol must leverage the opportunity for increased data collection while also incorporating multiple touchpoints with clinicians and the use of apps and devices that participants are familiar with.

Vulnerable Population

The pregnant population is vulnerable and experiences increased physiological, psychological, and social variability [10,11]. Several physiological and potentially pathophysiological changes occur during pregnancy [12,13]. Subjective data regarding these changes are collected with surveys at multiple points throughout the pregnancy and after delivery. To address the vulnerability of pregnant participants, this protocol must have questions tailored to and validated for the pregnant population and not make assumptions about the participants. Objective physiological data are obtained via passive sensing with a wearable device.

Many previous digital phenotyping studies investigating pregnancy have focused exclusively on the postpartum or perinatal period or have used the same protocol for both phases [2-4]. By focusing exclusively on 1 period, key changes that occur between the pregnancy and postpartum periods are missed. In addition, these protocols did not need to account for the uncertainty in delivery timing or adjust their protocol during the postpartum period due to having 1 consistent protocol or focusing on 1 period [2-4]. In contrast, our protocol uniquely spans the duration of each participant's third trimester and resumes immediately during the postpartum period for 6 weeks of new data collection. Our protocol supports digital phenotyping by combining passive data collection from Garmin smartwatches and participant smartphones with active labeling through EMAs. Over an approximate 18-week period, from the third trimester through the 6-week postpartum period, we continuously track behaviors and physiological data relevant to pregnancy outcomes, such as delivery, newborn feeding practices, and mental health and well-being.

Methods

Study Design

This protocol collects data passively through a smartphone (Beiwe app [14]) and smartwatch (Labfront application [15]). It collects data prospectively and actively through participant survey completion, EMAs, and participant data logging in the Huckleberry app [16]. The use of the Beiwe app addresses the nonfixed study duration for EMAs and smartphone data by allowing flexibility in study length. The use of the Labfront application for smartwatch collection also allows for flexibility in the length of the study. The unpredictable delivery-triggered phase transition is also managed by the Beiwe app, as the platform allows us to trigger a change in EMAs after delivery. The engagement-burden tradeoff is addressed by adding more active data collection through EMAs and having participants log data in the Huckleberry app. We allow participants to log their data into the Huckleberry app whenever it is convenient for them and balance the burden of EMAs by implementing this only once a day. Finally, to ensure that the protocol is pertinent for this population with increased physiological variability, we have reviewed and adapted all 350 survey questions and 14 unique EMA questions. In addition, we incorporate all study visits with in-person medical appointments and have clinicians and doulas on staff to help with any situation that may arise (Figure 1).

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Figure 1. Overview of the study procedure and timeline. EMA: ecological momentary assessment.

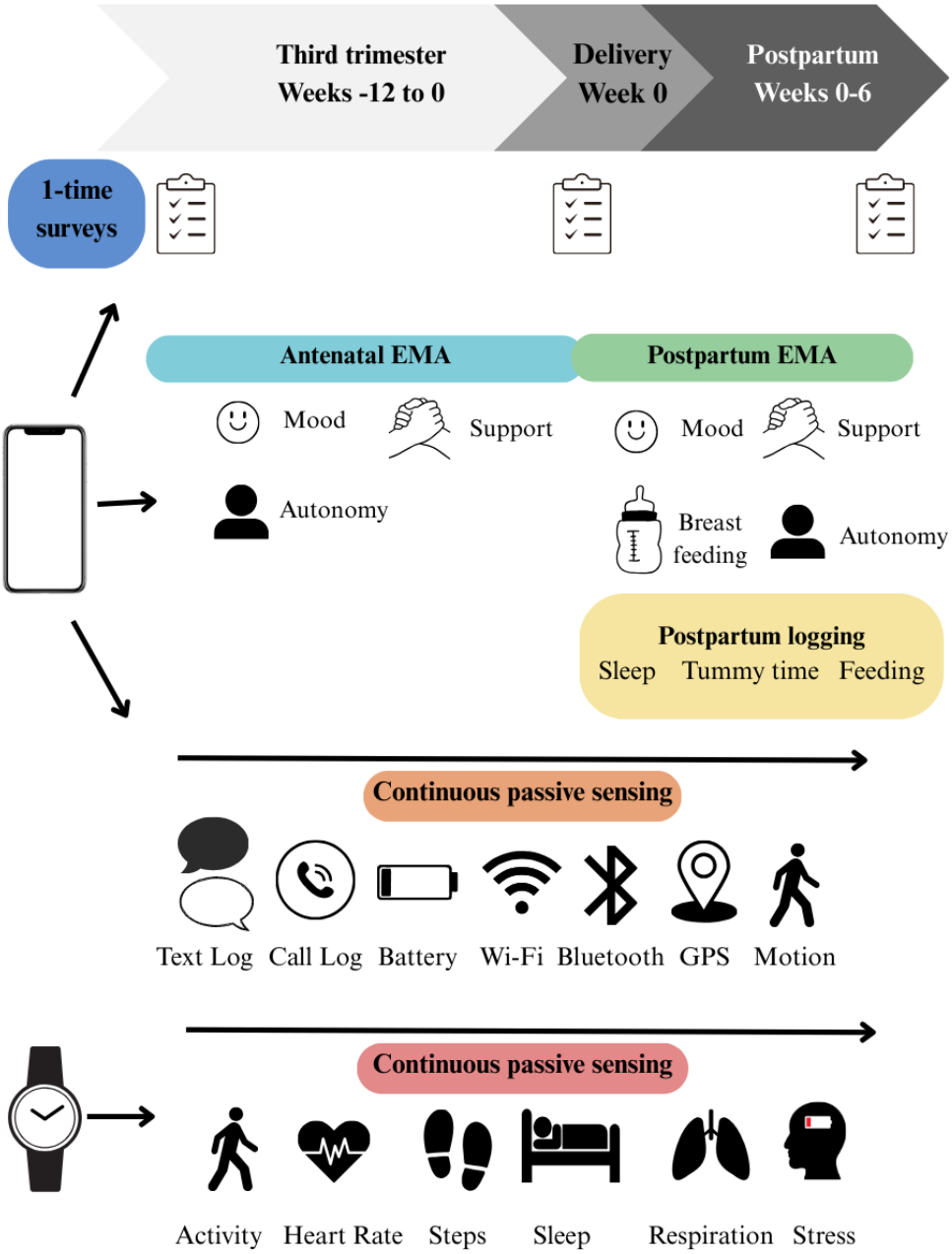

Participants

An initial cohort of approximately 30 nulliparous (females who have never given birth to a living child) participants will have data collected from the start of their third trimester through the 6-week postpartum period. A starting point of 30 participants was selected to ensure fair compensation. The inclusion criteria are that the participants should (1) be pregnant, (2) be between 14 and 28 weeks of gestation, (3) be nulliparous, (4) be aged ≥18 years, (5) own a smartphone, and (6) speak English. The participants will be enrolled before 28 weeks of gestation. Participants must own a smartphone to be able to answer the daily surveys and collect data. Participants must speak and read English, given that the daily survey questions are currently provided in English only. Participants will be excluded if they (1) are unable to provide consent, (2) have a pre-existing diagnosis of anxiety or depression, (3) are unable to wear a smartwatch, or (4) have a medical contraindication to breastfeeding. Participants who are unable to provide consent will be excluded. We will exclude participants with a formal diagnosis of anxiety or depression to reduce the effect of confounding variables, as pre-existing anxiety or depression can impact pregnancy outcomes [17]. Participants must also be able to breastfeed, as we will track breastfeeding rates and attitudes during the postpartum period as one of our main outcomes. Finally, someone who is unable to wear a smartwatch for the entire period is excluded, as they would not be able to collect physiological data such as heart rate, sleep, and activity.

Recruitment

Participants will be recruited in 4 ways to allow for maximum reach. This population has increased contact with physicians, allowing for increased opportunities for recruitment. First, informational posters will be affixed to walls in the waiting

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room at the Tufts Medical Center's obstetric clinical areas. Second, the Tufts Medical Center's obstetrics and gynecology prenatal practice patients will be messaged with a notification regarding the study at around 20 weeks of gestation through a health care provider-patient online portal. Third, participants can be recruited through phone calls from 20 to 24 weeks of gestation. Finally, participants can be approached at a midtrimester (14-28 weeks of gestation) appointment in person. Eligible participants will be identified by the Tufts Medical Center research team using information from their medical charts. This screening log will be stored in a password-protected folder and deleted after the trial completion. To reduce the time spent in the obstetrics and gynecology office and for patient convenience, participants will be able to walk through the informed consent process over the phone if they elect and sign consent forms electronically. Once individuals choose to participate, they will be guided by a research coordinator regarding the enrollment process, which starts with scanning a QR code that brings the users to a brief enrollment survey. This will be conducted at an in-person prenatal care appointment (at approximately 24-28 weeks of gestation). This enrollment survey provides the participants' email and due dates to the Northeastern University research team, allowing the instant transfer of information from people who are only interacting in person at the Tufts Medical Center with the Tufts staff to the Northeastern University research team. Participants will install all the necessary applications and set up their smartwatch with guidance from the research coordinator and a study-specific installation physically provided to them.

Data Collection

Overview

Data will be collected in the wild over approximately 18 weeks using five methods: (1) surveys (1-time baseline assessments at key perinatal milestones), (2) passive data collection from smartphones, (3) passive data collection from Garmin smartwatches, (4) EMAs, and (5) postpartum logging via the smartphone app.

Surveys

Overview

Three questionnaire surveys will be completed by participants throughout the study. These surveys are used to obtain information at each milestone (start of the third trimester, delivery, and 6 weeks post partum) about the mother's experiences and well-being.

Survey Technology

The surveys will be delivered as an email link using the Qualtrics platform and can be completed online via a smartphone or computer.

Survey Metrics

The surveys consist of questions from the following validated questionnaires: National Institute of Health demographics form [18], Mother Infant Lactation Questionnaire [19-21], Pregnancy Risk Assessment Monitoring Systems [22,23], Hunger Vital Sign [24-27], Housing Instability Index [28,29], General Health Questionnaire [30,31], Big 5 Inventory-10 [32,33], Body Understanding Measure for Pregnancy Scale [34], Maternal Health Literacy Inventory in Pregnancy [35,36], Eating Attitudes Test [37-39], Infant Feeding Intention Scale [40,41], Abuse Assessment Screen [42,43], Childbirth Experience Questionnaire [44-46], Iowa Infant Feeding Attitudes Scale [47,48], Edinburgh Postnatal Depression Scale [49-54], Perinatal Posttraumatic Stress Disorder Questionnaire II [55,56], Neonatal Eating Assessment Tool [57], Breastfeeding Self-Efficacy Scale [58,59], and the Self-Acceptance Scales for Pregnant Women [60,61]. The final survey will also include questions regarding their overall experience within the study.

Survey Scheduling

The first of the 3 surveys will be sent to the participants at 32 weeks of gestation. The second survey will be sent to each participant when they self-report the date of delivery to the research team. The third and final survey will be sent to the participants at 6 weeks post partum.

For all 3 surveys, participants will receive follow-up emails containing reminders about the surveys every 3 days until the survey is completed. If the participants do not self-report delivery to the research team, and it is 1 week or more past their due date, the research team will message the participant. The Tufts research team will also have access to patients' records to confirm the pregnancy status.

Passive Smartphone Data

Passive smartphone data are collected to obtain real-time objective data about participants' behavior and activity.

Passive Smartphone Technology

Passive data will be collected by a smartphone. Participants will use their own smartphones, and data will be collected through the Beiwe app, which has been used in other studies to collect data on the pregnant population [2,14].

Passive Smartphone Data Metrics

The data collected by the Beiwe app are shown in Table 1.

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Table 1. Smartphone data variables.

Sensor	Description	Frequency	Compatible device
GPS	Location (latitude and longitude)	Every 10 min	iOS and Android
Accelerometer	Physical activity (this can be sitting, standing, walking, in a vehicle, running, or on a bicycle)	Continuous	iOS and Android
Gyroscope	Orientation or angular velocity (rotation or positioning of the phone)	Continuous	iOS and Android
Magnetometer	Magnetic fields (compass)	Continuous	iOS
Time	Date and time	Continuous	iOS and Android
Wi-Fi	Wi-Fi connection status	Every 15 min	Android
Bluetooth	Bluetooth scan (search for name and devices nearby)	Every 15 min	Android
Reachability	Network status	In response to when the network status changes occur	iOS
Battery status	Battery percentage level and charging status	Continuous	iOS and Android
Call and SMS text message logs	Dump of daily call log and SMS text message log	Once daily	Android

Passive Smartphone Data Scheduling

Smartphone data are recorded continuously for the entirety of the study. Data collection is only paused when the phone is shut down.

Passive Smartwatch Data

Smartwatch data are collected passively to obtain real-time objective data about the participants' behavior and activity whenever the participant is wearing the watch.

Passive Smartwatch Technology

Participants will be provided with a Garmin Vivosmart smartwatch that synchronizes with the Labfront Companion application to collect passive data. The Garmin Vivosmart was selected due to its ability to track interbeat intervals and previous history of safe use in this population [62,63], along with being recommended by Labfront. In addition, Garmin Vivosmart watches have been widely used in research and have been shown to collect accurate data [64-66].

Passive Smartwatch Data Metrics

The data collected by Garmin Vivosmart are shown in Table 2. The sampling rates can be adjusted and will fall within the ranges provided.

Table 2. Smartwatch data variables.

Variable	Description	Sampling rate
Daily summary	Summary of the data collected from each day	Daily
Activity summary	Summary of activity types (eg, walking, running, and cycling) from each day and their intensities	15 min
Actigraphy	Monitors rest and activity cycles using an accelerometer	10 s to 1 min
Sleep	Sleep duration and stages are calculated using heart rate and actigraphy data	Auto-detect
Heart rate	Beats per min measured using photoplethysmogram sensors	1 s to 60 min
Stress	Numerical output depicting stress level calculated based on heart rate and activity	10 s to 60 min
Steps	Number of steps calculated using an accelerometer	1 min to 15 min
Respiration	Breathing rate measured in breaths per min	10 s to 60 min
Interbeat interval	Time interval between different beats of the heart	Each heartbeat

Passive Smartwatch Data Scheduling

Smartwatch data are recorded continuously for the entirety of the study. Data collection is paused only when the watch is shut down, dies, or is removed.

EMA Data

Overview

EMAs are used to provide additional insights into passive data by collecting real-time insights into the factors that influence breastfeeding outcomes. EMAs have been widely used in psychological and health research to assess momentary states and situational factors that influence outcomes over time [67]. Using EMAs alongside traditional longitudinal methods, this

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protocol offers a novel approach in capturing breastfeeding behaviors and maternal health with real-time accuracy.

EMA Technology

EMAs will be delivered via a smartphone through the Beiwe app [14].

EMA Metrics

The daily EMA survey includes questions adapted from the Perceived Stress Scale [68-70] to map responses to the circumplex model of affect [71]. These questions pertain to mood, confidence, and personal autonomy. Weekly EMA surveys include EMA-adapted questions from the Perceived Stress Scale [68-70], Self-Acceptance Scale for Pregnant Women [60,61], Maternal Antenatal Attachment Scale [72,73], and Breastfeeding Effectiveness Scale [74-76]. These questions have been adapted to follow a 5-point Likert Scale. After delivery, the EMA survey will include additional daily questions focused on breastfeeding attitudes and complications during the postpartum period [4,77].

EMA Scheduling

The EMA questions are delivered daily. Once a week, additional weekly questions are added to the daily survey. The EMAs are delivered each day at 6 PM, as this is the time of day when participants are most likely to answer [78,79]. At the end of the day, the participants are likely to have completed their daily activities and can reflect on their experiences more thoroughly. This timing has also been used in previous EMA studies to promote thoughtful responses and improve participant engagement [3,49,80].

To enhance participant retention and commitment throughout this longitudinal study, we designed each EMA to be brief and minimally intrusive, with completion times of approximately 2 minutes. This is shorter than most previous EMA studies, such as the study by Burke et al [81], in which participants completed 3 EMAs per day, each lasting 3 to 5 minutes. Given the extended nature of this protocol study, this optimized approach is expected to reduce participant burden and enhance the reliability of longitudinal data collection.

The additional weekly EMA questions are delivered on Mondays at 6 PM to increase compliance, as EMA surveys typically receive higher compliance earlier in the week, on weekdays, and in the evening [78,79] (Figure 2).

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Figure 2. Ecological momentary assessment (EMA) schedule showing the number of questions asked daily during pregnancy and the postpartum period, with the number in each circle depicting the number of questions asked.

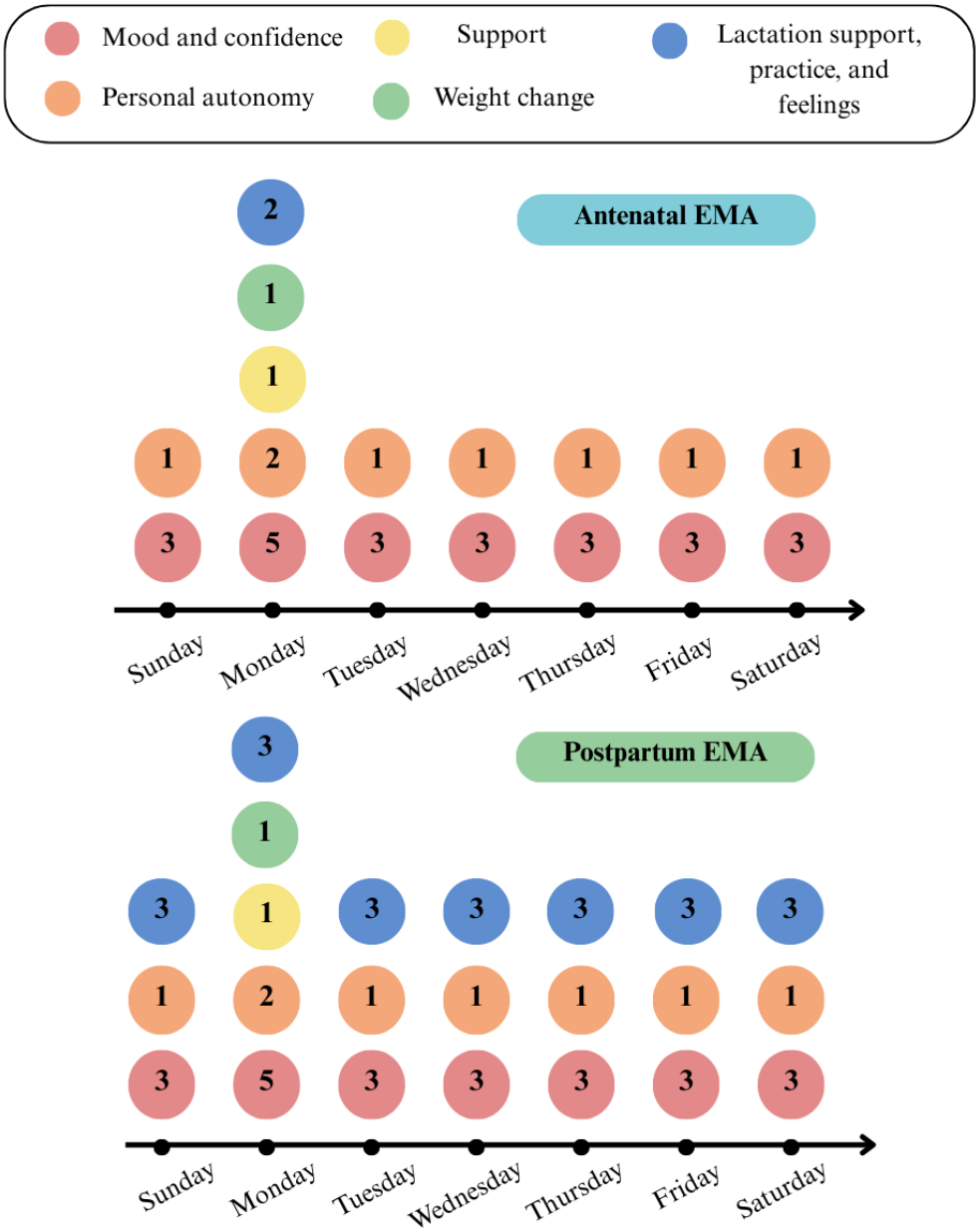

Postpartum Logging Data

The data logged postpartum is about the infant but is logged manually by the mothers.

Postpartum Logging Technology

Participants will log data about their babies using the smartphone app Huckleberry [16].

Postpartum Logging Metrics

The metrics collected for this study through the Huckleberry app are feeding data, tummy time, and sleep data [16]. For feeding, mothers will log when the babies were fed, how long they were fed, what they were fed, and the amount they were fed. For tummy time, mothers will record when the babies did the tummy time and its duration. For sleep, participants will log when their babies sleep and for how long.

Postpartum Logging Scheduling

Participants will log the information regarding their newborn's sleep, feeding, and tummy time. They will also be able to do this after the event has occurred. They will record the information from delivery to 6 weeks post partum. At the conclusion of the study, participants will download the data from the Huckleberry app and share it with the research team. The participants will be able to upload the link provided by the Huckleberry app into a Qualtrics survey, which eliminates the need for users to go through the process of downloading large files and uploading them again, and keeps the data secure, as Qualtrics is a Health Insurance Portability and Accountability Act–compliant platform. This will enable the easy transfer of data from the participants to the research team.

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Data Synchronization and Storage

To ensure consistency across the Beiwe and Huckleberry apps and the Labfront application, all data will be aligned using standardized timestamps. Before study initiation, each participant's smartwatch will be synchronized to the designated study time zone. During data processing, all streams will be harmonized based on these timestamps, allowing for the precise alignment of physiological, behavioral, and EMA data. A unique study ID, whose key is stored separately from the data, will link participant data across platforms, ensuring the proper integration of multiple data sources. This approach not only enables reliable data merging but also enhances robustness by allowing the research team to account for missing information in 1 platform with corresponding data from another. All data are stored in password-protected folders on the Northeastern University server. Only approved members of the research team will have access to these data. Data will be deidentified as much as possible.

Data Checks and Collaboration

Data quality checks will be performed every morning between 8 AM and 10 AM by the research team to assess completion rates and wear time and to ensure that data values are within the expected range. Low wear time, missing data, and missing surveys will result in an email being sent from the research team to the participants to remind them of how to properly wear the watch, open the Garmin application to synchronize their daily watch data, and answer the surveys. If missing data are due to a technical difficulty, the research team will find a solution or give the participant a new device. If participants no longer meet the requirements, for example, can no longer wear the watch or are leaving the country, they will be removed from the study. If participants withdraw or are removed from the study, their data will be deleted and not included in the analysis. The Northeastern University and Tufts Medical research teams will have regular meetings to ensure proper trial conduct and to communicate any changes that need to be made. The research team will also, nonsystemically, keep track of any reported harm that occurs to participants; however, we predict that harm will be unlikely to occur. Potential risks for participants include discomfort or rash from the smartwatch, emotional discomfort when answering EMA questions or survey questions, and a potential loss of confidentiality and data security.

Ethical Considerations

This protocol has been approved by the Tufts Health Sciences Institutional Review Board (STUDY00005835 protocol version 5.14.2025). This study is being conducted in collaboration with the Tufts Medical Center, which is Health Insurance Portability and Accountability Act–compliant. All members of the research team have undergone training on research involving human participants. We will obtain informed consent from all participants. The privacy and confidentiality of participants will be protected. Participants are compensated for their participation in this study.

Results

The pilot study following this protocol is expected to begin in October 2025. The primary goal of this pilot study is to evaluate the feasibility of our protocol for implementation in future larger-scale studies. The quality of the watch and smartphone data will be assessed daily, evaluating the scalability and adaptability of the methods for use with another cohort. This daily check includes running a script to analyze the wear time and completion rates and verifying that the data values are within the normal range. Participant engagement and retention rates will be assessed through metrics, including survey and EMA completion rates, self-logging data frequency, timeline of survey completion, perceived participant burden, usability of smartphone apps and smartwatch applications, and overall participant experience. We will also measure the data volume logged by participants in the Huckleberry app to understand the expected amount of data to be logged by future participants. We will also determine the amount of data that the smartwatch adds to the study and how much the data impact digital phenotyping. This will help to determine the advantage of including the watch in addition to the smartphone. Finally, digital phenotyping, starting with mood, activity, stress, and sleep, will be conducted to determine whether we can use the data collected during the third trimester to determine delivery outcomes, baby behavior, breastfeeding outcomes, and postpartum depression. These results will provide evidence on the viability of digital phenotyping using longitudinal pregnancy data, supporting a comprehensive investigation into third-trimester predictors of pregnancy outcomes.

Discussion

Anticipated Findings

Overview

Pregnancy is a period of continuous and significant physiological, psychological, and social change, creating an opportunity for digital phenotyping to passively capture this period. The variability in due date causes a nonfixed study duration and unpredictable delivery-triggered phase transition. Pregnant participants also have a heightened interest in their health, creating an opportunity to leverage their increased engagement to collect more data, but requiring consideration of the participant burden. Finally, pregnant women are increasingly vulnerable due to physiological changes. We have addressed these challenges in the subsequent sections.

Adapting to Nonfixed Study Duration

The variability in pregnancy duration introduces a fundamental challenge for study design, as the length of participation cannot be standardized across all individuals. This unpredictability affects compensation plans, technical planning, and survey logic within the research app. To address this, our protocol was designed to be flexible, allowing for individualized adaptation to both shorter and longer durations of data collection. Most apps require a set period for the study duration. We did not use an in-house application; therefore, we had to negotiate a contract such that the timeline is not fixed. Future apps in the research

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space should plan for this, as pregnancy studies will always have variation in duration. In addition, at the start of the study, data storage should be planned for the full duration of the pregnancy. As the study proceeds, it may be possible to predict preterm or postmature births to better optimize data storage. For compensation, we set a limit and communicated this to the participants. Other forms of motivation for participation should also be considered to supplement the financial component. One potential alternative form of compensation is to share weekly updates of the participants' trajectories.

Implementing Delivery-Triggered Phase Transition

Another key challenge in developing this protocol is the unpredictable timing of the transition from prenatal to postpartum data collection. Because delivery dates may not be immediately known to the research team, it is difficult to ensure timely updates to survey content. This requires a flexible protocol capable of managing delayed notifications and uneven data collection across the study phases. This was a significant challenge that required additional consideration. We used an application that is optimized for protocols with an intervention at a fixed date. The system is not set up for variation in the period before the intervention, which in our case is childbirth. To mitigate this challenge, we ask participants to self-report their delivery directly to the research team; however, this may cause a delay in notifying the research team. Once reported, the research team can manually trigger a change from antenatal to postpartum EMAs. This process is streamlined so that within 24 hours of the participant notifying their delivery team, the research team can trigger the phase transition. We have designed a failsafe method to reduce potential large delays—the research coordinator at the clinical site will review due dates and verify if a participant has delivered on a weekly basis. In addition, if a participant misses this report by a few days, we will still have their passively recorded data and any EMA questions that are asked in both periods.

Minimizing Participant Burden

This protocol seeks to strategically optimize a larger amount of data collection by leveraging high engagement during pregnancy and minimizing the participant burden. While pregnancy presents a unique opportunity for increased data collection, studies must remain unobtrusive and align with existing tools and routines to maintain sustained participation. To leverage the increased engagement of the pregnant population, we use multiple apps to collect data from various streams, including allowing users to input data about their babies' behavior in addition to their own data. We use the Huckleberry app for the manual input of data, as Huckleberry reports that the app is already used by more than 4 million parents worldwide [82]. Furthermore, we use both smartphones and smartwatches to collect continuous data. We also streamlined the EMA delivery by minimizing the number of questions asked and asking the questions only once a day. By delivering the EMAs at 6 PM, we reach participants during the time they are most likely to answer while considering typical bedtimes during pregnancy. We also ask a series of questions, requiring only a few minutes each night to reduce the time required of each participant.

Protecting Participant Vulnerability

Pregnancy is a vulnerable time with complex physiological, psychological, and social changes, requiring sensitive and tailored data collection approaches. This protocol is streamlined according to the actual clinical care that participants receive during pregnancy and the postpartum period. Participants are recruited remotely and in person at already-scheduled appointments throughout the second trimester. Enrollment, including providing devices and meeting with the research coordinator, also occurs at an already-scheduled appointment. After the study, the devices are returned to the clinic when participants come in for their next postpartum appointment. In addition, we optimized the phrasing of the questions to be sensitive to the vulnerability of the pregnant population and used questionnaires developed specifically for pregnancy. For example, instead of using generic depression questionnaires, such as the Patient Health Questionnaire-9, we use the Edinburgh Postnatal Depression Scale, which is tailored to postpartum participants.

Limitations

Certain aspects of this protocol require manual and timely tasks to be done. An example of this is that available data collection apps supporting digital phenotyping are not set up to account for a nonfixed study length. The exact data of childbirth is unpredictable, and a delay from self-reporting and implementing the change in the EMAs should be anticipated. Handling this transition phase manually is increasingly tedious as the study becomes larger, implying that scalability is constrained by the time of the research coordinator. Another example of a manual task is transferring the data collected in the Huckleberry app to the research team. In the future, an app that provides the participant with their health information should also provide research protocols for a more seamless experience. An additional limitation of the protocol is that it requires participants to wear the wearable device provided by the study team. It would be better for participants if the data collection tools were device-agnostic, allowing them to use their own devices. Finally, this protocol may have a higher than usual dropout rate because of not meeting the criteria of a viable pregnancy, due to the many complications that can occur during pregnancy. We mitigate this partially by starting data collection as late as the third trimester, which reduces the opportunity for complications compared to data collection starting earlier in the pregnancy.

Future Work

We intend to use participant feedback and completion rates from this study to refine the protocol for a future large-scale study of pregnancy with varying conditions. We will also use the results of longitudinal data analysis from this study to determine the effect size of factors, such as activity, feelings of support, mental health, mood, and breastfeeding intentions during the third trimester, on pregnancy, breastfeeding, and mental health outcomes. These estimated effect sizes will inform power analyses in future research endeavors.

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Acknowledgments

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Data Availability

The datasets generated during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

AG wrote the original draft of the manuscript. AG, TM, AP, and AS led the development of the protocol. SR, ASC, and DL assisted in the development of the protocol. AS is the primary investigator and AP is the coprimary investigator. AS and AP led the conceptualization of the project and were responsible for overseeing all aspects of the project. All authors contributed to and approved the final submission of this manuscript.

Conflicts of Interest

None declared.

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Abbreviations

EDD: estimated due date
EMA: ecological momentary assessment

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Protocol

Implementation of a Digital Health Intervention (CHAMP) for Self-Monitoring of Hypertension: Protocol for 3 Interlinked Implementation Studies

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Abstract

Background: Hypertension affects 31% of the global adult population. Artificial intelligence–based chatbots may support self-management of hypertension and other chronic disorders. Chronic Disease Management Program (CHAMP) is a digital health intervention designed to support chronic disease self-management, comprising a patient-facing chatbot and an artificial intelligence–augmented clinical decision support system linked to electronic medical records.

Objective: This project aims to optimize the deployment of CHAMP across primary care centers by developing implementation strategies and pilot-testing their appropriateness and effectiveness.

Methods: We report 3 interlinked studies. Study 1 is a *rapid evidence review* to evaluate the factors influencing the implementation of mobile health and chatbot interventions in health care settings and the strategies and processes involved. We will follow the Cochrane Rapid Reviews Methods Group methodology and use the Consolidated Framework for Implementation Research and the unified theory of acceptance and use of technology frameworks to analyze the data. Study 2 is *a formative, mixed methods study* to inform the state of CHAMP deployment to date, the organizational structure of primary care centers, and the barriers and facilitators influencing the implementation and scale-up of CHAMP in primary care centers. We will interview members of the CHAMP development and initial implementation team, health care providers (HCPs), primary care centers' leadership, and patient users and nonusers of CHAMP; conduct 1-day on-site visits to primary care centers; and assess the readiness to change among HCPs using validated questionnaires. Study 3 involves the *development of implementation strategies for the implementation of CHAMP in primary care centers.* We will develop a process map informed by the findings of studies 1 and 2 to outline the patient journey; map the barriers and facilitators influencing the implementation of CHAMP; and develop a set of implementation strategies to effectively implement CHAMP using the Expert Recommendations for Implementing Change taxonomy to define the implementation strategies and the action, actor, context, target, and time framework to define the strategy implementation processes. In parallel, we will use evidence-based behavioral science to test variations of the chatbot's messages to increase patient engagement.

Results: To date, the evidence review protocol (study 1) has been registered on PROSPERO. We have completed title and abstract screening and are in the full-text screening phase. For study 2, we obtained ethics approval and conducted the semistructured interviews with HCPs, primary care centers' leadership, and members of the CHAMP development and initial implementation team. We are awaiting institutional review board approval to start the interviews with patients.

Conclusions: The study results will inform the further implementation and scale-up of CHAMP across primary care centers in Singapore. Successful implementation of digital health interventions to support self-management of chronic disorders may improve health care delivery without further straining health care systems.

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Trial Registration: PROSPERO CRD42024613653; https://www.crd.york.ac.uk/PROSPERO/view/CRD42024613653
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KEYWORDS

chatbots; artificial intelligence; AI; digital health; hypertension; chronic disease management; implementation science; barriers; facilitators; implementation strategies

Introduction

Background

Hypertension is a leading risk factor for cardiovascular disease worldwide [1]. It is estimated that hypertension affects approximately 31% of the global adult population [2] and a similar proportion of people in Singapore, an island state in Southeast Asia [3]. Despite this high prevalence, approximately half of those affected are unaware of their condition [3,4]. Furthermore, approximately 25% of the people with a known diagnosis of hypertension are not treated, and two-thirds of people receiving treatment are not well controlled [3-5]. Home blood pressure monitoring (HBPM) is an important component of effective hypertension treatment [6-11]. It is associated with improved blood pressure (BP) control [7,10,11] and is cost-effective [12]. However, only 50% of individuals with hypertension adhere to HBPM programs [12,13] due to a variety of reasons, such as the lack of knowledge about the benefits of HBPM; associated costs of acquiring a BP monitor; and low engagement with long-term, rigid HBPM protocols [12-14]. Furthermore, health care providers (HCPs) often report concerns about the accuracy of measurements and devices and also about patient anxiety associated with BP readings that may increase the practice and staff burden [12,14,15].

The effectiveness of HBPM appears to increase if cointerventions are implemented. A systematic review conducted in 2017 reported a pooled decrease in systolic BP from –1.0 mm Hg (95% CI –3.3 mm Hg to 1.2 mm Hg) with no cointervention support to –6.1 mm Hg (95% CI –9.0 mm Hg to –3.2 mm Hg) when personalized support was provided either face-to-face or via teleconsultations [11]. The use of digital interventions in health care settings is increasing, and it has the potential to enhance health care delivery while decreasing costs. Digital health interventions, delivered using mobile devices (apps and other mobile health [mHealth] interventions) or virtual consultations with HCPs, are effective in decreasing systolic and diastolic BP in patients with hypertension [16,17]. Particularly, multimodal interventions, including medication and BP monitoring reminders, health education, and healthy lifestyle advice, appear effective in lowering BP in patients with hypertension [18,19]. Artificial intelligence (AI)–based chatbots have recently emerged as an alternative tool to deliver reminders and other behavioral prompts to support the self-management of chronic disorders by encouraging real-time monitoring, providing patient education and clinical decision support, and offering more personalized services to patients and HCPs [20,21]. Recent systematic reviews offer preliminary evidence that AI-based chatbots promote healthy lifestyle change [22-25]; smoking cessation [26,27]; and self-management of chronic disorders [6,21,28], such as hypertension [29]. In addition, HCPs [30] and patients [31-33] seem to find chatbots acceptable and would be willing to use them, particularly if they complement clinical care [29,33] and are not used for severe conditions [33,34]. However, users have also expressed concerns regarding data privacy and confidentiality and the accuracy of advice provided by the chatbots [30,32].

Chronic Disease Management Program (CHAMP) is a recently developed digital health intervention that aims to provide chronic disease management support to patients and HCPs. The intervention consists of a patient-facing chatbot deployed in WhatsApp (Meta Platforms, Inc), a popular messaging platform, and an AI-augmented clinical decision support system that is linked to electronic medical records (Figure 1). The current version of the chatbot sends regular reminders to patients to measure their BP and share their readings and provides advice on follow-up actions if the BP is outside the reference range for the patient. Future versions of CHAMP aim to include self-monitoring support for diabetes, hyperlipidemia, and other chronic disorders. These reminders will incorporate insights from behavioral science to deliver messages (eg, lifestyle advice) that are meaningful, personalized, and timely to encourage self-monitoring. CHAMP was developed within a large academic health system serving the population of western Singapore, comprising 4 general hospitals and 7 government-funded primary care centers serving a population of approximately 1 million inhabitants. CHAMP is currently being implemented in all primary care centers within the academic health system. However, the implementation and scale-up of CHAMP across several primary care centers requires a systematic, evidence-based approach to ensure that the system is effectively integrated into existing workflows and that patients are able and willing to use CHAMP. There remains a knowledge gap about how best to introduce digital technologies, such as CHAMP, within primary health care services. Earlier studies highlight several potential challenges, such as a lack of initial interest from HCPs, poor integration into current workflows, complex digital interventions, a lack of training, and a lack of leadership support [35-37].

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Figure 1. Diagrammatic overview of the Chronic Disease Management Program (CHAMP) chatbot interface and functionalities. Patients enrolled in CHAMP (left) receive regular messages through a WhatsApp chatbot reminding them to monitor their blood pressure (BP) and send the results in a systolic or diastolic BP and heart rate format. The chatbot also advises patients' next actions according to the submitted BP readings (eg, to repeat the BP reading and to consult with a health care provider). Patient data are received by Endeavor AI (center), the academic health system's proprietary artificial intelligence (AI) platform. The data collected will feed proprietary models that inform the frequency of patients' reminders and advice and a customized patient information dashboard for health care providers (right). NUHS: National University Health System.

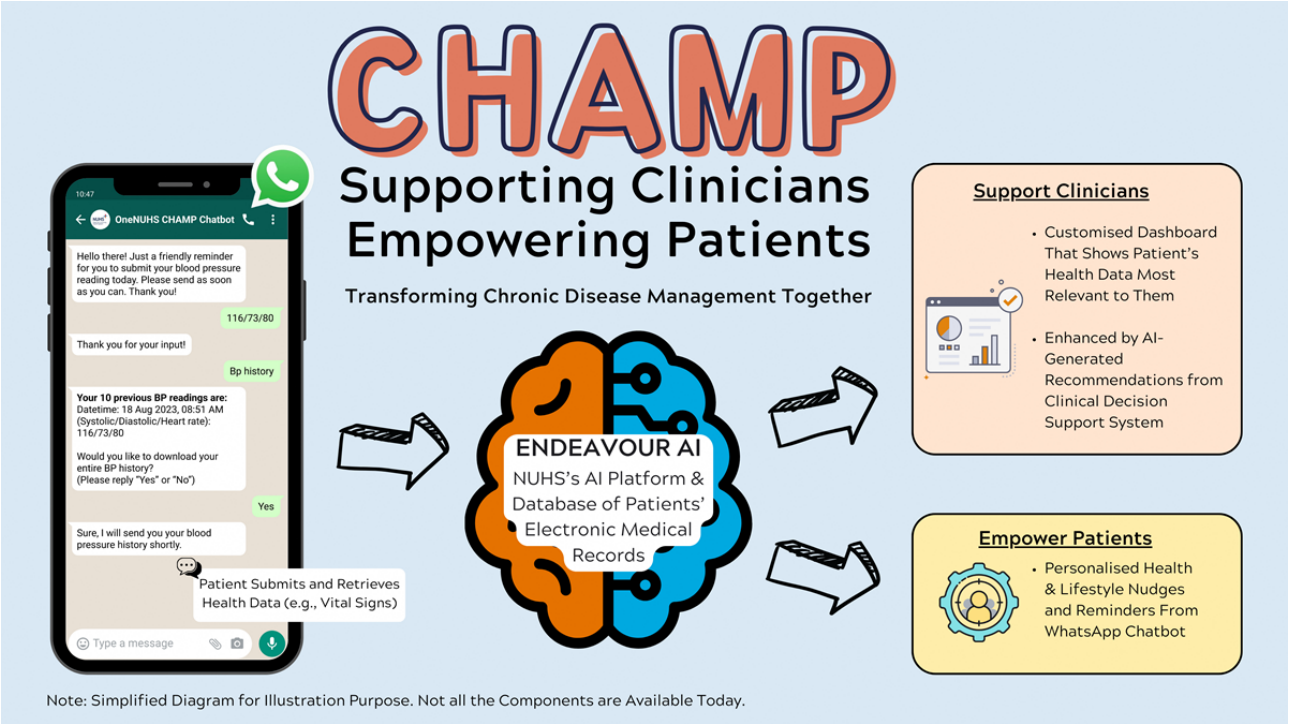

This Study

This protocol outlines 3 interlinked research studies on the implementation of CHAMP for hypertension self-monitoring in western Singapore to test the overall hypothesis that CHAMP's deployment is feasible and can be optimized at scale, such that it will benefit primary care center operations by streamlining the management of patients with high BP. This research aims to optimize the deployment of CHAMP across primary care centers in western Singapore by developing effective implementation strategies, informed by the findings of studies 1 and 2. At the same time, this study will use a methodology that is commonly used in implementation studies in Western, high-income country settings but has been used more sparingly in Asian settings. Therefore, this study also intends to test whether a similar methodology is feasible for implementation studies in Asian settings.

Methods

Overview

This project consists of 3 interlinked implementation studies. Study 1 consists of a rapid umbrella review to describe the global evidence on the factors influencing the implementation of chatbots and other mHealth interventions for chronic disease management and the implementation strategies used to implement these interventions in health care settings. Study 2 will evaluate the barriers and facilitators influencing the implementation of CHAMP in primary care centers in western Singapore by conducting semistructured interviews with relevant stakeholders, assessing the state of CHAMP implementation to date through site visits to all primary care centers and assessing the organizational readiness to implement CHAMP. Finally, study 3 will develop a process map and will generate a set of implementation strategies informed by the results of studies 1 and 2 to enhance the implementation of CHAMP, along with generating a suite of personalized messages to deploy in CHAMP based on evidence-based behavioral science. Figure 2 presents the links between the 3 studies.

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Figure 2. Diagram of the links between the 3 studies presented in this protocol.

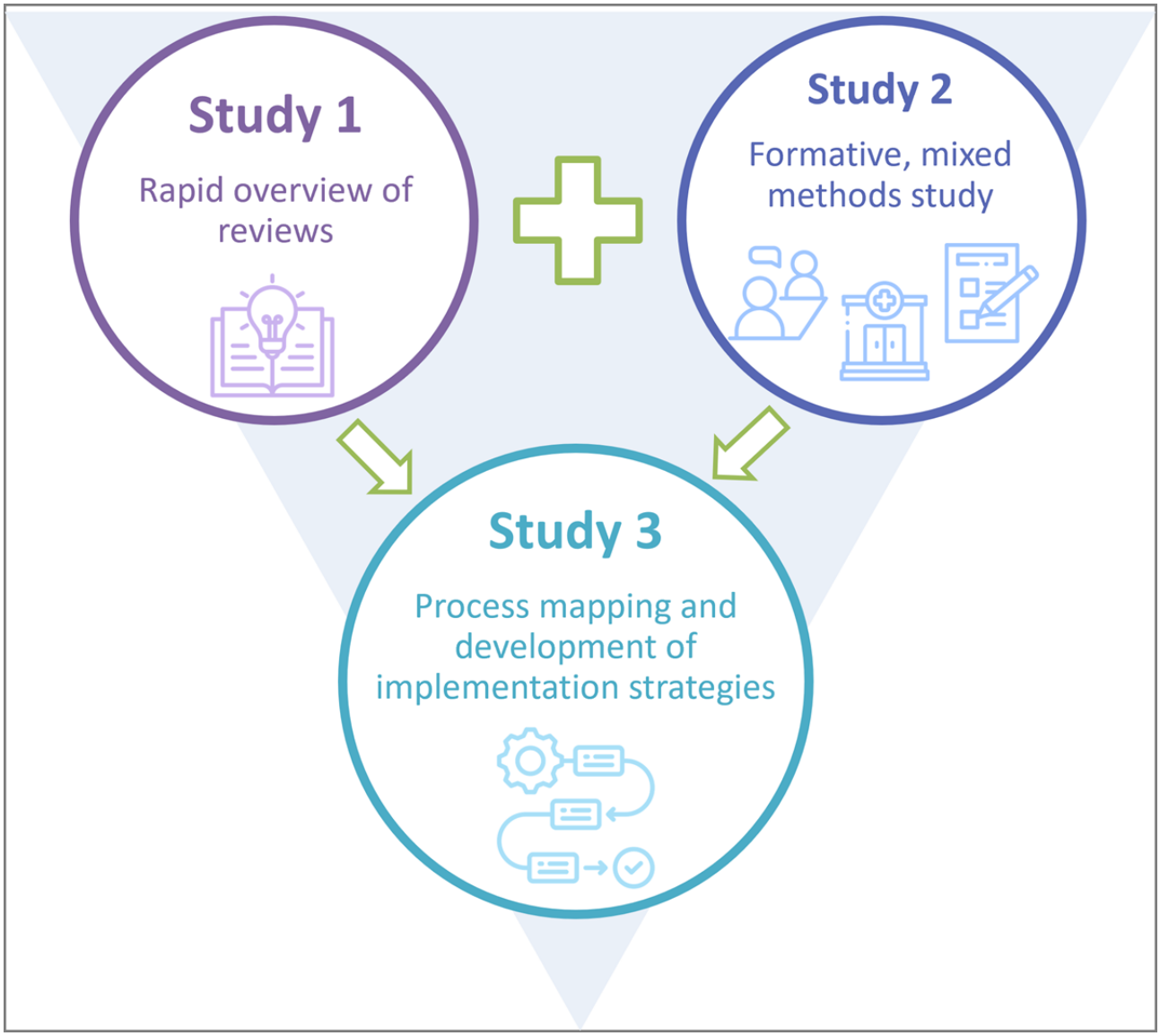

Study 1: Rapid Evidence Review

Study Aims

The rapid review aims to assess the factors that influence the implementation of mHealth interventions in health care settings and the implementation strategies and processes used to implement them. Specifically, we will focus on the factors, strategies, and processes influencing the implementation of conversational agents (or chatbots) for chronic disease self-management. The research questions guiding the review are as follows:

1. What are the barriers and facilitators influencing the adoption and implementation of conversational agents (or chatbots) for chronic disease management in health care settings?
2. What implementation strategies are currently used to facilitate the adoption and implementation of the conversational agents (or chatbots) in health care settings?
3. What are the processes used to implement and evaluate these interventions?

Methods

The review will follow the Cochrane Rapid Reviews Methods Group [38] methodology. We have registered our review protocol on PROSPERO (CRD42024613653), and we will report our findings according to the PRIOR (Preferred Reporting Items for Overviews of Reviews) statement [39].

Search Strategy

We will develop a comprehensive yet focused search strategy combining terms from 3 concepts: conversational agents, implementation strategies, and chronic diseases. The chronic diseases concept will be refined according to the number of retrieved articles to focus only on cardiovascular disease. The search will be restricted to evidence synthesis studies using a validated search filter [40]. Multimedia Appendix 1 provides the MEDLINE search strategy. The searches will be conducted in MEDLINE, Embase, and Web of Science.

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Eligibility Criteria

Overview

This rapid overview or review will include evidence synthesis studies, such as systematic reviews, scoping reviews, and mapping reviews and nonsystematic literature reviews. Articles reporting on primary studies, protocols, editorials, conference abstracts, or letters to the editor will be excluded. We will limit our search to articles in English, published since 2014.

The eligibility criteria will be defined according to the population, intervention, comparison, outcome, and setting (PICOS) framework.

Population

We will include reviews reporting on adults (aged ≥21 years) with cardiovascular diseases, such as hypertension, diabetes, and hypercholesterolemia. Reviews reporting on other chronic diseases, such as cancer, mental health disorders, and rheumatological and autoimmune disorders, will be excluded from the overview.

Intervention

We will include studies involving mHealth interventions, such as conversational agents (or chatbots) or applications delivered using a mobile digital device such as a smartphone, tablet computer, or wearable device. Nondigital interventions and other digital interventions, such as teleconsultations, passive collection of sensor data, or interventions targeting health care providers or the automation of health care processes, will be excluded from the review.

Outcomes

The included studies will report any of the following outcomes: (1) barriers and facilitators influencing the implementation of conversational agents, (2) implementation strategies used in the implementation of conversational agents, and (3) processes and process adaptations leading to the implementation of conversational agents.

Setting

We will include studies describing interventions delivered in any health care setting, including community or primary health care facilities, the outpatient clinics of general or specialist hospitals, and secondary and tertiary health care institutions.

Data Collection and Analysis

The results of the database searches will be uploaded to EndNote (version 21; Clarivate), and duplicate citations will be removed. The resulting library will be uploaded to Rayyan (Rayyan Systems, Inc), a web-based tool developed to facilitate screening of articles for systematic reviews [41]. The screening process will include 2 phases: title and abstract screening and full-text screening. Following a rapid review methodology, the screening will be initially conducted by 2 reviewers working in parallel (10%-20% of the library) to standardize the screening process and agree upon eligibility criteria. Subsequent screening will be conducted by 1 reviewer. Disagreements that arise during screening will be resolved through discussion between the reviewers or by engaging a third reviewer. The study selection process will be summarized in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram [42].

Data from the included studies will be extracted in a Microsoft Excel form developed by the research team. Two reviewers, working independently and in parallel, will extract data for about 10% of the included studies to pilot the data extraction form and standardize data extraction. Subsequently, data extraction will be performed by 1 reviewer. The data extraction form will be informed by the Consolidated Framework for Implementation Research (CFIR) [43,44] and the unified theory of acceptance and use of technology (UTAUT) [45] frameworks. CFIR [44] is a widely used framework in implementation science to determine the contextual factors influencing implementation. UTAUT [45] is an encompassing framework widely used in digital health to evaluate the factors influencing the adoption of digital health interventions. As CFIR is a generic implementation framework, we will use the UTAUT framework to complement the “innovation” and “individuals” sections of CFIR, with a framework focusing specifically on the acceptance of digital health interventions. Figure 3 [45] presents the components of each framework.

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Figure 3. Components of the Consolidated Framework for Implementation Research (CFIR) and the unified theory of acceptance and use of technology (UTAUT) frameworks to be used to code retrieved evidence in study 1.

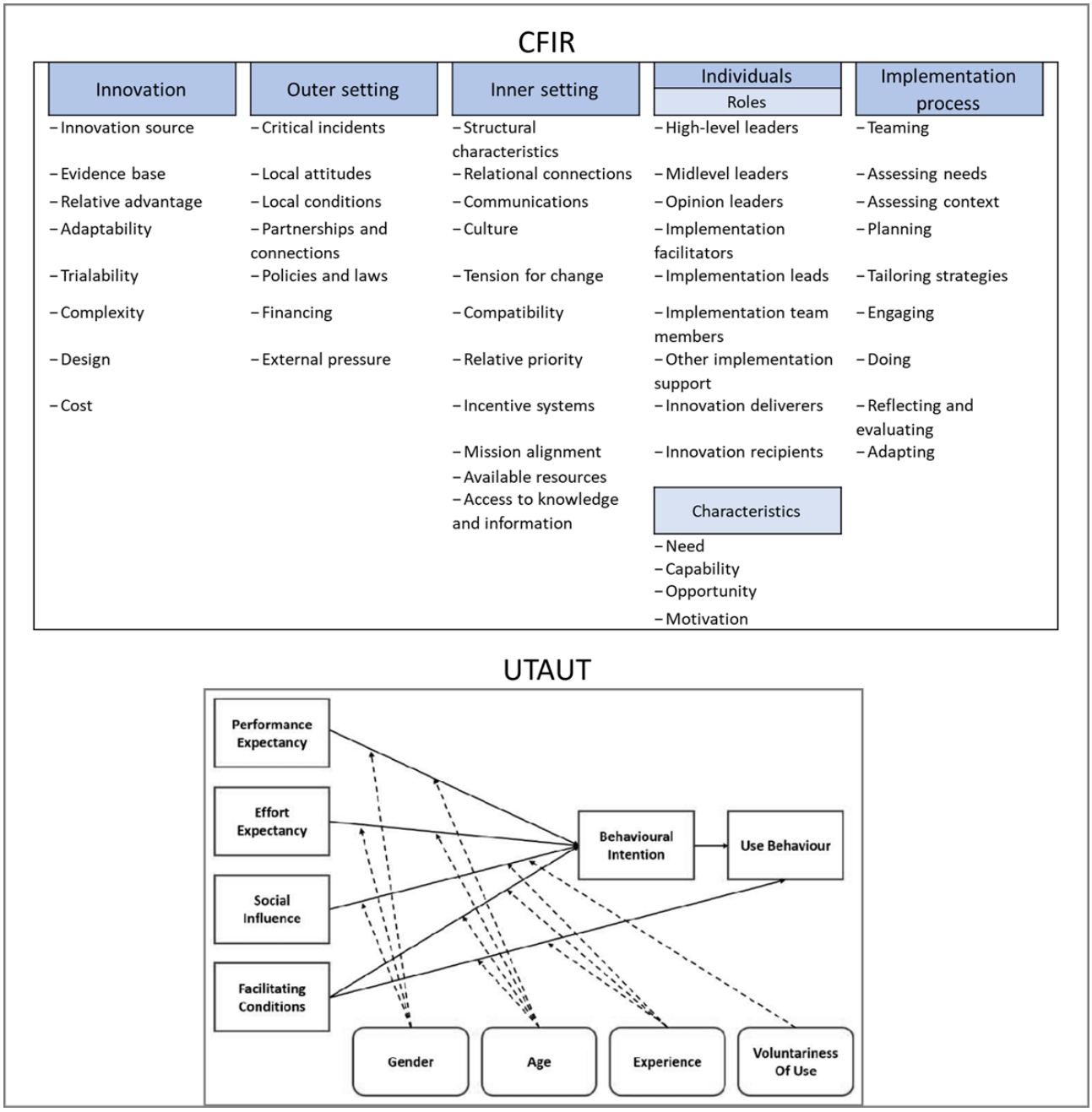

Data analysis will follow the framework analysis methodology [46]. We will use CFIR and UTAUT to develop a framework that will guide data coding. We will follow a deductive coding approach for data analysis. Two reviewers (LM and NHLH) will perform the data analysis independently and in parallel. Reviewers will meet regularly to review their findings and discuss any disagreements. If the reviewers are unable to reach a consensus, a third reviewer (last author) will act as an arbiter.

Expected Outcomes

The overview will provide global evidence on the barriers and facilitators influencing the implementation of mHealth interventions (including chatbots) and the implementation strategies and processes used when implementing these interventions. The research data from the review will be made available through a peer-reviewed publication.

Study 2: Formative Mixed Methods Study

Study Aims

Study 2 aims to assess the state of CHAMP deployment to date, the organizational structure of the primary care centers implementing CHAMP, and the perceived barriers and facilitators of the implementation and scale-up of CHAMP. We will address the following research questions:

1. What are the barriers and facilitators influencing the adoption and implementation of CHAMP in the primary care centers where the chatbot has been implemented at the time of the study?
2. What is the readiness to change among HCPs and leadership teams at the primary care centers?

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3. What are the processes and implementation strategies used in the primary care centers to implement CHAMP to date?
4. What are the most effective and locally appropriate strategies used to implement CHAMP in the primary care centers?

Methods

Overview

Study 2 will include a mixed methods study comprising 2 qualitative, complementary methods: semistructured interviews with relevant stakeholders and 1-day site visits to carry out on-site observation and a quantitative survey to assess readiness to change. This study requires ethics approval from 2 boards. It is currently under review by Singapore's Ethics and Compliance Online System and has been reviewed (and approved) by the National University of Singapore Institutional Review Board (NUS-IRB-2024-669). The findings from study 2, taken together with the results from study 1, will be used to develop an implementation process map and design relevant implementation strategies in study 3.

Semistructured Interviews

Study Population

We aim to interview the following stakeholders:

- Members of the CHAMP development and initial implementation team who were involved in the initial deployment of CHAMP in primary care centers
- Primary care centers' leadership
- HCPs, including family physicians and care managers (nurses trained to provide follow-up care and health education to patients with chronic conditions), who are participating and those who are not participating in CHAMP's rollout
- Adult patients (aged ≥21 years) with a clinical diagnosis of hypertension or who require frequent BP monitoring for other conditions, who are enrolled or not enrolled in CHAMP

Sample Size

We aim to recruit between 40 and 60 participants for the interviews. We will use purposive sampling, recruiting 15 to 30 HCPs and 15 to 30 patients from the 7 primary care centers, 3 to 5 members of the primary care centers' leadership, and the members of the CHAMP development and initial implementation team. The total number of interviewees will be determined by the eligible population (number of HCPs, leaders, and members of the CHAMP team eligible and willing to participate in the study) and, particularly for patients, by reaching thematic saturation [47-49], defined as the number of interviews when no new codes emerge from the data. This was estimated to be approximately 12 interviews by Guest et al [49].

Participant Recruitment

We will use different recruitment modalities according to the participants' group.

First, the members of the CHAMP development and initial implementation team, HCPs, and primary care centers' leadership will be invited to participate in the interview via email. The place, time, and modality (face-to-face or virtual) of the interview will be agreed with the participant before the interview. We will aim to interview HCPs involved and not involved in patient recruitment for CHAMP.

Second, the patients currently enrolled in CHAMP will receive a message via CHAMP's WhatsApp channel, enquiring their willingness to participate in research associated with CHAMP.

Third, the patients who are not enrolled in CHAMP will be recruited face-to-face during their regular check-up visits at the primary care center.

Procedure

We will conduct one-to-one semistructured interviews following an interview guide. Interviews are estimated to last 30 to 45 minutes and will be digitally recorded for subsequent analysis. The interviews will have a retrospective focus to understand CHAMP's implementation process to date, lessons learnt, and the factors that influenced its implementation.

The interviews will be developed by the research team and will be based on the CFIR [44] and the UTAUT [45] frameworks (Multimedia Appendix 2). The interview guides will be piloted with 1 or 2 participants to ensure content and context relevance, feasibility, and a suitable flow of questions. We will use the pilot participants' feedback to edit the interview guides before starting data collection.

Data Analysis

Recordings of the interviews will be transcribed verbatim. The interview data will be analyzed using the framework analysis approach as outlined by Gale et al [46]. The analysis will be guided by the CFIR [44] and UTAUT [45] domains. Two researchers working independently and in parallel will deductively code the data using codes developed in advance by the research team. If the interviews include relevant information that would not fit the codebook, the researchers will inductively develop new codes. The research team will code the first 3 transcripts in parallel, following which they will meet to discuss the coding and reach consensus on the final codes and themes. Subsequently, the researchers will code the rest of the transcripts independently. During the whole process, the research team will meet, discuss, and reach consensus on the final codes and themes. We will use NVivo (version 14.0; Lumivero) to code the data.

One-Day Site Visit

Overview

We will conduct a series of observations in the primary care centers to assess their structure, staff-to-patient ratio, demographic of the patient population, patient journey, the number of research or implementation projects the primary care institution is currently involved with, and other relevant information. Concurrently, we will aim to understand CHAMP's current implementation workflow. This includes the number of HCPs involved in CHAMP's implementation, steps to enroll patients, type of HCP (physician and care manager) enrolling and educating patients on the use of CHAMP, duration of enrollment or education procedure, and the provision of written materials to reinforce learning. If possible, the site visit will

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include the observation of "live" patient enrollment into CHAMP.

Procedure

One-day visits to all primary care centers in western Singapore will be conducted by 2 to 3 members of the research team. The date and time of the visit will be arranged with the primary care center leadership. During the visit, the researchers will passively observe the primary care center's operations and, if required, engage in informal interviews with the leadership team, administrators, and HCPs to complement the observations. We will attempt to observe clinical consultations by physicians and care managers, if possible. Findings from the observations and informal interviews will be recorded in a structured form developed by the research team. Verbal consent will be taken before the stakeholder informal interviews.

Readiness to Change Assessment

Study Population

We will include the following stakeholders: leadership teams and HCPs, including physicians and care managers working in chronic disease management teams in primary care centers. We will invite all eligible HCPs to participate in the study and aim to collect responses from at least 50% of the eligible population.

Study Design

Readiness to change will be assessed using 2 brief self-reported questionnaires.

First, the Organizational Readiness for Implementing Change (ORIC) [50] is a reliable and validated questionnaire that evaluates readiness to change at an organizational level by assessing the concepts of change commitment (eg, "people who work here are determined to implement CHAMP") and change efficacy. This measure is based on the theory of the determinants and outcomes of organizational readiness for change by Weiner [51] and consists of 12 statements rated using 5-point Likert scales.

Second, the Readiness Thinking Tool (or Readiness Monitoring Tool) [52,53] assesses readiness at an organizational level. This validated tool contains 19 elements grouped in 3 constructs: motivation (6 elements), innovation-specific capacity (5 elements), and general capacity (8 elements)—all rated on 4-point Likert scales. Multimedia Appendix 3 presents the ORIC [50] and Readiness Thinking Tool [52,53] surveys.

Participant Recruitment and Study Procedure

Participants will be invited to participate in the study via email. The invitation email will contain a link to the surveys for the participants to access if they agree to be part of the study.

Data Analysis

We will use descriptive statistics to analyze the data. We will perform subgroup analyses to determine the readiness to change among specific HCP groups (eg, physicians, care managers, and nurses) and primary care center leadership teams and HCPs working in each of the primary care centers included in the study. The results of these assessments will offer a perspective on the implementation context for CHAMP across sites and will be used to design site-specific targeted implementation strategies to optimize the implementation and scale-up of CHAMP.

Expected Outcomes

Study 2 will produce a comprehensive, contextually relevant list of barriers and facilitators of the implementation of CHAMP in primary care centers in western Singapore, including the HCPs' readiness to implement CHAMP.

Study 3: Development of Implementation Strategies for the Implementation of CHAMP in Primary Care Centers

Study Aims

In study 3, we aim to develop a set of implementation strategies to effectively implement CHAMP and evaluate the outcomes of implementation in the primary care centers. We will also use behavioral science frameworks to enhance patients' engagement with CHAMP. The research questions guiding this study are as follows:

1. What are the most appropriate and effective strategies to implement CHAMP in the primary care centers of western Singapore?
2. How and what aspects of CHAMP can be improved to increase patients' engagement with the platform and, ultimately, more positive health outcomes?

Methods

Process Mapping

The information obtained in study 1 (rapid evidence review) and study 2 (on-site visits, semistructured interviews, and readiness to change surveys) will be used to develop a process map to outline the patient journey and map the barriers and facilitators influencing the current deployment of CHAMP. We will use the implementation research logic model [54] as a template to outline the process map. Once completed, the process map will be shared with relevant stakeholders (analogous to the groups from which study 2 interview participants are drawn) for input and further refinement.

The iterative development of the process map will assist the research team in outlining the implementation strategies, mapping these strategies to the relevant influencing factors, and the proposed theories of change and mechanisms of implementation. The process map will be revisited at regular intervals during study 3 (see the Development of Implementation Strategies section) to evaluate the progress and success of CHAMP implementation. To evaluate the implementation success, we will attempt (in future studies) to compare the intended outcomes of implementation, as outlined in the process map, with the actual results of implementation and how stakeholders evaluate the outcomes and success of this exercise.

Development of Implementation Strategies

The findings from studies 1 and 2, coupled with the readiness assessments mentioned earlier, will inform the development of implementation strategies to enhance CHAMP's implementation and scale-up. We will develop a set of evidence-informed, pragmatic, context-driven implementation strategies to address

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the barriers to and enhance the facilitators of implementation. We will use the Expert Recommendations for Implementing Change taxonomy [55] to define the implementation strategies, and the action, actor, context, target, and time framework [56] to define the strategy implementation processes. The implementation strategies will be developed by the research team in collaboration with the CHAMP development and implementation team and the HCPs in the primary care centers. Examples of implementation strategies and how they could address specific barriers are shown in Table 1. The implementation strategies will be presented in the form of a pragmatic research logic model booklet and will be used to guide subsequent implementation and scale-up of CHAMP.

Table 1. Examples of barriers that are associated with implementation strategies based on the Expert Recommendations for Implementing Change (ERIC) and action, actor, context, target, and time (AACTT) frameworks.

Targeted barrier	ERIC strategy	Actor	Action	Context	Target	Time
Lack of a clear directive from the top management	Mandate use	Head of the department	Mandates the use of CHAMP[a]	Primary care center	HCPs[b] who will prescribe CHAMP	At the department meeting
The clinical team not familiar with CHAMP	Conduct ongoing training	CHAMP team	Conducts workshop on CHAMP functionalities	Primary care center	HCPs who will prescribe CHAMP	Before launching the implementation study
Patients unsure about enrollment	Involve patients	HCPs who will prescribe CHAMP	Empower and activate patients to use CHAMP	Primary care center	Patients	During clinical consultation
Patients who miss submitting blood pressure readings	Intervene with patients to enhance adherence	HCPs who will prescribe CHAMP	Embed and test behavioral levers	Reminder messages	Patients	During the stipulated self-monitoring period

[a]CHAMP: Chronic Disease Management Program.

[b]HCP: health care provider.

Leveraging Behavioral Science

Overview

Effective implementation of evidence-based practice depends on behavior change. In relation to CHAMP, a key indicator of success rests on patients' interactions with the chatbot and compliance with the messages (eg, reminders to submit BP readings and lifestyle advice) it conveys. To enable this, researchers have developed numerous frameworks for guiding the development, design, and implementation of behavior change interventions, one of which features prominently in the digital health literature—MINDSPACE (messenger, incentives, norms, defaults, salience, priming, affect, commitments, and ego) [57]. The MINDSPACE framework represents 9 different evidence-based strategies for promoting behavior change in people. These strategies have been used in a variety of health situations, ranging from the promotion of vaccination uptake, regular exercise, and healthy eating habits to smoking and alcohol cessation [57]. Unlike traditional cognitive models that assume people consciously analyze their options and act in ways that are consistent with their own best interests, contextual models, such as MINDSPACE, tend to focus on people's reliance on automatic processes of judgment to make decisions [58]. Hence, while cognitive strategies emphasize reflection, training, persuasion, and education, MINDSPACE leverages aspects of the choice or contextual environment to bring about behavior change in people. A recent meta-analysis of 14 digital intervention studies relying on different MINDSPACE strategies showed that digital interventions improved cancer screening uptake and adherence among at-risk individuals [59]. Digital interventions relying on MINDSPACE hold considerable promise in promoting behavior change in a relatively cheap, quick, and efficient manner. Drawing on the findings of studies 1 and 2, we will use MINDSPACE to systematically test variations of the chatbot's messages in effectively engaging patients. A meta-analysis of 40 web-delivered health behavior change programs has shown that tailored interventions (eg, personalization, interactivity, frequency, and convenience) resulted in significantly better health outcomes compared with control conditions at posttest and follow-up time points [60]. In CHAMP, one approach could be the use of behavior-informed messages to increase physical exercise in patients.

Study Design

Study 3 uses a randomized controlled trial design to evaluate the effectiveness of behavior-informed messages (administered via CHAMP) in promoting physical exercise among patients. The intervention compares the current practice of sending standard education messages about the benefits of exercise (ie, control) with behavioral-informed messages that encourage physical activity in patients through goal setting (ie, intervention group) as well as goal setting and feedback (ie, intervention plus group).

Procedure

Patients will be randomly allocated to 1 of the 3 study arms using a computer-generated randomization sequence created via Python's (Python Software Foundation) random module. The allocation sequence will be concealed from the study team before assignment to minimize selection bias. Randomization will occur at the individual patient level. Participants will be assigned to 1 of the 3 groups mentioned subsequently.

The first group is the control group. This group represents the current status quo in which patients receive regular information about the benefits of exercise.

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The second group is the intervention group. In addition to regular information about the benefits of exercise, patients in this group will receive regular prompts to log their exercise activity in the past week and their commitment in the following week. *Commitment* is one of several strategies in MINDSPACE.

The third group is the intervention plus group. In addition to regular information about the benefits of exercise, patients in this group will receive regular prompts to log their exercise activity in the past week and their commitment in the following week. They will also receive regular feedback on how often or well they are doing this (eg, frequency and adherence) relative to their peers to demonstrate social norms of physical activity. *Commitment* and *norms* are 2 of several strategies in MINDSPACE.

All messages will be delivered through the official CHAMP WhatsApp chatbot. Messaging timing and frequency are consistent across all groups.

Participants and Recruitment

Participants will be recruited from a pool of patients who are currently enrolled in the CHAMP system, an active platform using WhatsApp to send health-related prompts for BP monitoring. At the end of the initial 6-month data collection period, a data analyst will extract and anonymize the relevant data from the CHAMP system. The study team will only receive anonymized data to assess the outcomes.

Outcomes

Objective indicators: pre-and post-intervention's weight and BP levels will be extracted from health records data obtained during routine clinic visits.

Physical activity in the past 6 months: we will use a single self-reported question assessing patients' level of physical activity in the past 6 months. The questionnaire will be administered as part of routine care in the polyclinics, pre- and postintervention.

Data Analysis

We will perform a series of regressions to analyze our outcomes of interest. We will treat the intervention groups as treatment variables and use the current education-only group as the reference group. Hence, 1 of the aims of study 3 is to improve the chatbot's ability to engage with patients and, through this, improve patients' health outcomes. This not only supports evidence-based practice but also highlights the value of CHAMP to clinicians, patients, and the community at large.

Expected Outcomes

Study 3 will use data triangulation from the rapid overview of reviews (study 1), on-site visits, semistructured interviews, and readiness to change surveys (study 2) to inform the development of a process map summarizing the patient journey and factors influencing CHAMP implementation. The process map will inform the development of implementation strategies to enhance the current implementation of CHAMP in primary care centers. Finally, we will work with the CHAMP development team to enhance and personalize the chatbot's messages to patients, leveraging behavioral science and relevant findings from studies 1 and 2.

Ethical Considerations

Study 1 is a review of published literature and does not require ethics approval. For study 2, interviews with the CHAMP development and initial implementation team, HCPs, and primary care centers' leadership have been approved by the National University of Singapore Institutional Review Board (NUS-IRB-2024-669). For patients' interviews and on-site visits, we are awaiting approval by Singapore's Ethics and Compliance Online System. All participants will sign an informed consent form before the start of the studies (semistructured interviews and readiness to change surveys) and will be compensated for their participation in the studies. Any personal identifiable data will be stored in secure university servers. Only deidentified participant data will be used in papers or other dissemination materials.

Dissemination of the Study Results

Findings from these studies will be shared with the funders and stakeholders involved in CHAMP's development, including patients using the platform. Research findings will be presented at conferences and published in relevant peer-reviewed journals.

Results

To date, the following aspects of the studies have been initiated. For study 1, we registered the protocol on PROSPERO (CRD42024613653), developed the search strategy, and conducted the search on October 4, 2024, in MEDLINE, Embase, and Web of Science, retrieving 2835 citations. After deduplicating the library, we completed title and abstract screening and are currently conducting the full-text screening. For study 2, we obtained ethics approval for the interviews to HCPs, primary care centers' leadership, and CHAMP development and initial implementation teams. We completed 31 semistructured interviews. We obtained ethics approval for patient interviews and on-site visits, and they are currently ongoing. We started administering the readiness to change survey on February 3, 2025, and data collection is ongoing.

Discussion

Anticipated Findings

This paper presents a protocol for a multimethod, multistage study, aiming to implement a digital health intervention to support chronic disease self-management, such as hypertension, in government-funded primary care centers in western Singapore. Hypertension remains an important risk factor for cardiovascular disease and incurs the highest societal cost of modifiable risk factors, including metabolic, lifestyle, environmental, and substance use risk factors [61]. This study is among the first in Asia to assess and enhance the implementation of an AI-based digital intervention in primary care. The results from this research will inform the further implementation and scale-up of CHAMP across primary care centers in Singapore. Furthermore, this study will provide relevant contextual information to better design targeted

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implementation strategies to enhance the facilitators and overcome the current barriers to the implementation of CHAMP. The successful implementation of digital health interventions to support the self-management of chronic disorders, such as hypertension, may improve health care delivery without further straining health care systems.

Strengths and Limitations

An important strength of this protocol is presenting a multimethod, multistage study that will apply widely used, evidence-based implementation science frameworks and methodologies to design contextualized implementation strategies. The research presented in this protocol integrates frameworks specifically developed for use with digital interventions alongside well-established implementation frameworks. Applying them concurrently and evaluating their relevance and usefulness in driving the research and its reporting will offer a case study for how implementation science studies with a similar focus and research questions might be conducted. The rapid expansion of digitally delivered and AI-driven interventions and technologies in the last few years suggests that studies with such a focus will proliferate in the future. Limitations of this project include the implementation in primary care centers whose structure is unique to the Singapore context and the multicultural mix of the Singaporean population from which study participants will be drawn. Consequently, the findings of this study may not be fully transferable to other health care systems and populations.

Dissemination Plan

The findings from this study will be published in at least 1 peer-reviewed journal article. We also aim to present the studies' results in relevant scientific meetings or conferences. Beyond scientific dissemination, we will also undertake knowledge mobilization activities within the study context. These will include targeted events with study stakeholders and their peers, including those from other health care clusters and geographies in Singapore. We envisage preparing evidence briefs and hosting facilitated sessions (eg, workshops and webinars), such that policy and clinical stakeholders can identify relevant knowledge and data from this research that are suitable to inform their implementation planning within the domain of hypertension management and other chronic diseases.

Acknowledgments

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Authors' Contributions

LM is the guarantor for the study and is responsible for the study management. NHLH, ET, SCT, and NS were involved in the conceptualization of the study and are the study's coapplicants. All the authors were involved in writing and revising the manuscript.

Conflicts of Interest

NS is the director of London Safety and Training Solutions Ltd, which offers training, improvement, and implementation solutions to health care organizations and the pharmaceutical industry. All other authors declare no conflicts of interest.

Multimedia Appendix 1
Search strategy—MEDLINE (October 4, 2024).
[DOCX File , 13 KB - resprot_v14i1e72942_app1.docx]

Multimedia Appendix 2
Semistructured interview guides.
[DOCX File , 29 KB - resprot_v14i1e72942_app2.docx]

Multimedia Appendix 3
Organizational Readiness for Implementing Change and Readiness Thinking Tool surveys.
[DOC File , 66 KB - resprot_v14i1e72942_app3.doc]

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Abbreviations

AI: artificial intelligence
BP: blood pressure
CFIR: Consolidated Framework for Implementation Research
CHAMP: Chronic Disease Management Program
HBPM: home blood pressure monitoring
HCP: health care provider

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mHealth: mobile health
MINDSPACE: messenger, incentives, norms, defaults, salience, priming, affect, commitments, and ego
ORIC: Organizational Readiness for Implementing Change
PICOS: population, intervention, comparison, outcome, and setting
PRIOR: Preferred Reporting Items for Overviews of Reviews
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
UTAUT: unified theory of acceptance and use of technology

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Protocol

Changes in Gut Microbiome Following Acupuncture and Moxibustion in Patients With Parkinson Disease: Protocol for a Single-Group, Prospective, Observational Study

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Abstract

Background: Parkinson disease (PD), a prevalent neurodegenerative disorder characterized by motor and nonmotor symptoms, is becoming increasingly prevalent worldwide. Conventional treatment for PD involves dopamine therapy, including levodopa; however, this treatment is ineffective for nonmotor symptoms and may cause adverse effects. The gut-brain axis has been hypothesized to promote PD, and regulation of gut microbiome, which modulates the gut-brain axis, is emerging as a treatment target. Acupuncture and moxibustion exert therapeutic effects on PD and modulate the gut microbial composition.

Objective: We present a protocol for analyzing the effects of acupuncture and moxibustion on gut microbiome and exploring its association with symptoms in patients with PD.

Methods: This single-group, prospective, observational study will recruit 60 patients with idiopathic PD and 20 healthy participants. Baseline gut microbiome patterns and motor and nonmotor symptoms of both groups will be compared. Patients with PD will be treated with acupuncture, moxibustion, and intradermal acupuncture twice a week for 12 weeks (24 sessions total). Motor and nonmotor symptoms and gut microbiome changes in patients with PD will be compared before starting treatment (day 0), during treatment (6 weeks), at the end of treatment (12 weeks), and 2 months after the end of treatment (20 weeks). The correlation between motor and nonmotor symptoms of PD changed by acupuncture and moxibustion treatment and changes in gut microbiome will be analyzed. Healthy participants will be assessed for motor and nonmotor symptoms of PD and gut microbiome after screening.

Results: This study was supported by the National Research Foundation of Korea, funded by the Ministry of Science and ICT (Information and Communication Technology), Republic of Korea, and recruitment for the study started on October 21, 2021. As of February 19, 2025, recruitment and observation ended, and data analysis is being conducted.

Conclusions: This is the first clinical study to assess the effects of acupuncture and moxibustion on gut microbiome and explore its association with symptoms in patients with PD. The results will provide clinical evidence to explain the microbiome-gut-brain axis mechanism of acupuncture and moxibustion for PD and suggest the possibility of acupuncture as an alternative therapy for PD.

Trial Registration: Clinical Research Information Service KCT0006669; https://tinyurl.com/42jsxs5a

International Registered Report Identifier (IRRID): DERR1-10.2196/76551

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(JMIR Res Protoc 2025;14:e76551) doi:10.2196/76551

KEYWORDS

neurodegenerative disorders; gut-brain axis; microbial dysbiosis; motor and nonmotor symptoms; complementary medicine

Introduction

Parkinson disease (PD) is the second most common neurodegenerative disorder [1], and its incidence has increased drastically worldwide over the past few decades, placing it as one of the most rapidly expanding neurological disorders worldwide [2,3]. The rapid growth of PD is influenced by global aging, as the prevalence of PD increases with age [4]. Therefore, the development of treatment strategies for patients with PD is expected to become increasingly important.

PD is characterized by motor symptoms such as tremor, rigidity, bradykinesia, and postural instability due to altered aggregation of α-synuclein in the brain structures termed Lewy bodies, as well as by early prominent death of dopaminergic neurons in the substantia nigra [5]. However, PD is not only characterized by motor symptoms but also by nonmotor symptoms such as constipation, depression, anxiety, anosmia, pain, and sleep behavior disorder, which have been found to occur in the prodromal phase before the onset of motor symptoms, contributing to the decreased quality of life in affected patients [6]. Based on this knowledge, a study has recently suggested that PD should be approached as a systemic disease, rather than simply as a movement disorder caused by brain dysfunction [7].

Levodopa symptomatic therapy based on conventional brain pathology is the current mainstay of PD treatment [8]. However, nonmotor symptoms are known to be unresponsive to levodopa [9], and excessive and prolonged therapy is associated with a risk of adverse events, such as dopamine dysregulation syndrome [10] and levodopa-induced dyskinesia [11]. Therefore, current treatments that target the brain alone are unlikely to be effective in treating PD, indicating the need for alternative treatments.

The gut-brain axis theory posits that the gut and brain communicate bidirectionally with each other via the blood and vagus/sympathetic nerves to regulate various human physiological and pathological functions, and the gut microbiome is gaining attention as a potential modulator of the gut-brain axis [12]. As the highly complex relationship between the gut and brain in PD has been recognized, the role of gut microbiome as a modulator of PD has also been highlighted [13].

In Traditional East Asian Medicine (TEAM), both acupuncture and moxibustion have a long history of clinical use in the treatment of PD. Recently, there has been a growing demand for complementary and alternative medicine (CAM) for PD worldwide, to compensate for the limitations of conventional PD treatments, with acupuncture playing a large role [14]. In a previous review, acupuncture and moxibustion were reported to be superior to dopamine monotherapy in improving motor and nonmotor symptoms and managing long-term symptoms in PD [15]. In another study [16], the addition of acupuncture to dopamine replacement therapy was associated with significantly superior Unified Parkinson's Disease Rating Scale (UPDRS) I-IV score improvements compared with those noted with dopamine replacement therapy alone.

Recent experimental studies have shown that acupuncture modulates the gut microbial composition [17,18]. Based on this evidence, a study using an in vivo PD model reported that GB34 and ST36 acupuncture enhanced motor symptoms and dopamine neuron protection by modulating gut microbial dysbiosis and inhibiting neuroinflammation [19]. This suggests that the effects of acupuncture may also be mediated by modulating the gut-brain axis through gut microbiome regulation. However, all studies conducted in this field to date have been experimental, highlighting the need to explore the effects of acupuncture and moxibustion on gut microbiome and explore its association with clinical symptom improvement in patients with PD.

Herein, we present a protocol for a study analyzing the effects of acupuncture and moxibustion on the gut microbiome and exploring its association with symptoms in patients with PD. This study will provide new clinical evidence on the mechanisms of PD treatment with acupuncture and moxibustion, thereby increasing the level of evidence for acupuncture and moxibustion as alternative treatment methods for PD.

Methods

Study Design

This protocol describes a single-group, prospective, observational study aiming to analyze differences in gut microbiome between patients with idiopathic PD and healthy participants, to observe changes in gut microbiome after 12 weeks of acupuncture and moxibustion in patients with PD, and to correlate these changes with changes in motor and nonmotor symptoms of PD that were altered by acupuncture and moxibustion treatment. The gut microbiome patterns at baseline in healthy participants and screened patients with PD will be analyzed to determine whether the gut microbiome of patients with PD is different from that of healthy participants. Patients with PD will be treated with acupuncture, moxibustion, and intradermal acupuncture twice a week for 12 weeks, yielding a total of 24 sessions. The motor and nonmotor symptoms of PD and gut microbiome changes in response to acupuncture and moxibustion will be compared before starting treatment (day 0), during treatment (6 weeks), at the end of treatment (12 weeks), and 2 months after the end of treatment (20 weeks). The correlation between motor and nonmotor symptoms of PD changed by acupuncture and moxibustion treatment and changes in gut microbiome will be analyzed. The enrollment, interventions, and assessments of patients with PD are summarized in Table S1 in Multimedia Appendix 1. A schematic of the study process is shown in Figure 1. Healthy participants will be assessed for motor and nonmotor symptoms of PD and gut microbiome after screening. The enrollment and assessment

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of healthy participants are summarized in Table 1. Kyung Hee University Korean Medicine Hospital, Seoul, Republic of Korea, will serve as the study site. The study protocol was registered with the Clinical Research Information Service (KCT0006669) on October 15, 2021. This protocol was reported in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (Multimedia Appendix 2).

Figure 1. Flowchart of the study process. BBS: Berg Balance Scale; BSS: Bristol Stool Scale; GSRS: Gastrointestinal Symptom Rating Scale; MDS-UPDRS: Movement Disorder Society–Sponsored Revision of the Unified Parkinson's Disease Rating Scale; MYMOP: Measure Yourself Medical Outcome Profile; PD: Parkinson disease; PDQ-39: 39-Item Parkinson's Disease Questionnaire; S&E: Schwab and England Activities of Daily Living Scale; TDS: Total Dyspepsia Symptom Scale; TUG: Timed Up and Go Test.

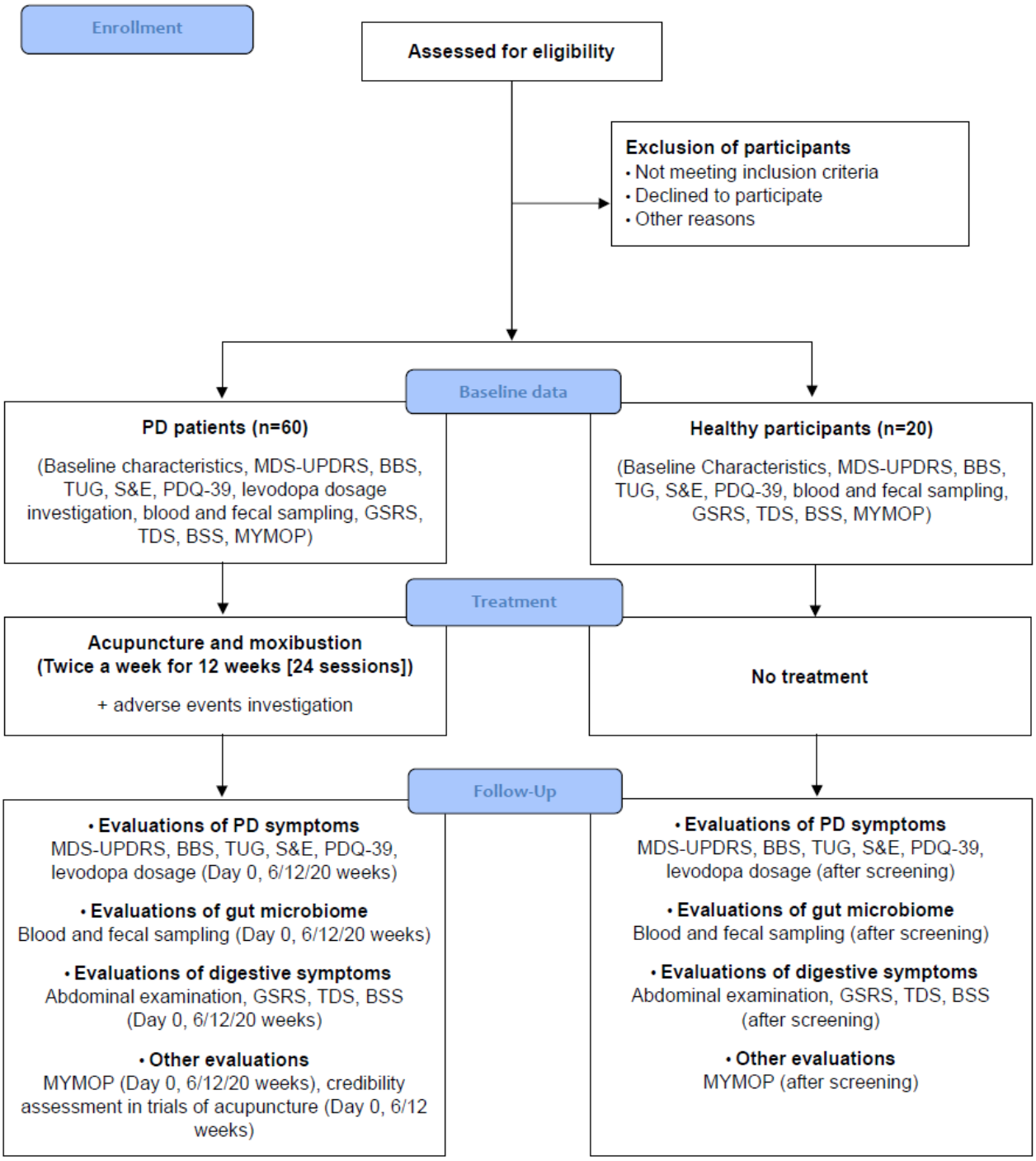

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Table 1. Schedule for the enrollment, interventions, and assessments of healthy participants.

Visit	0	1
Day	–14 to 0	0
Week	0	1
Visit window	—	±7
Informed consent	✓	
Demographic information	✓	
Medical history	✓	
Medications investigation	✓	
Vital sign	✓	
Hoehn and Yahr stage	✓	
Evaluating inclusion and exclusion criteria	✓	
MDS-UPDRS[a]		✓
BBS[b]		✓
TUG[c]		✓
S&E[d]		✓
PDQ-39[e]		✓
Blood sampling[f]		✓
Fecal sampling[g]		✓
Abdominal examination		✓
GSRS[h]		✓
TDS[i]		✓
BSS[j]		✓
MYMOP[k]		✓
Korean medicine doctor interview		✓

[a]MDS-UPDRS: Movement Disorder Society–Sponsored Revision of the Unified Parkinson's Disease Rating Scale.
[b]BBS: Berg Balance Scale.
[c]TUG: Timed Up and Go Test.
[d]S&E: Schwab and England Activities of Daily Living Scale.
[e]PDQ-39: 39-Item Parkinson's Disease Questionnaire.
[f]Analyzing gut microbiome–related metabolites.
[g]Analyzing gut microbiome.
[h]GSRS: Gastrointestinal Symptom Rating Scale.
[i]TDS: Total Dyspepsia Symptom Scale.
[j]BSS: Bristol Stool Scale.
[k]MYMOP: Measure Yourself Medical Outcome Profile.

Eligibility

Inclusion and exclusion criteria for patients with PD are summarized in Textbox 1.

Since patients with early-stage PD typically show a good response to anti-Parkinson agents such as levodopa [20], it is challenging to isolate and evaluate the additional effects of acupuncture and moxibustion in this population. Therefore, this study included patients who have been taking anti-Parkinson agents for more than 5 years or who were at Hoehn and Yahr stage 2-3, representing the midstage or beyond. Inclusion and exclusion criteria for healthy participants are summarized in Textbox 2.

Dropout criteria are summarized in Textbox 3.

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Textbox 1. Inclusion and exclusion criteria for patients with Parkinson disease (PD).

Inclusion criteria

- Men and women aged 50-85 years
- Patients with idiopathic PD who have been taking anti-Parkinson agents (excluding anticholinergic drugs) for >5 years
- Hoehn and Yahr stage 2-3
- Patients who have no cause of cognitive or motor impairment other than PD
- Patients who have voluntarily agreed to participate
- Patients who have not participated in other clinical trials within the last 1 month

Exclusion criteria

- Patients diagnosed with secondary Parkinsonism or atypical Parkinsonian syndrome
- Consumption of oral antibiotics that may affect results within the past month
- Loss of consciousness for more than an hour due to head trauma
- Patients with severe vision or hearing problem
- Consumption of probiotics that may affect results within the past month
- Consumption of medication (such as analgesics, anti-inflammatory drugs, or antibiotics) that may affect the gastrointestinal system within a week from the time of fecal sampling
- History of severe heart disease (eg, myocardial infarction or heart failure)
- Patients with a medical history of neurosurgical procedure (eg, deep brain stimulation)
- Patients who have been diagnosed with cancer or treated for cancer
- Patients with glaucoma
- Chronic alcohol consumption or drug abuse
- Women who are pregnant or breastfeeding
- Patients with diseases such as coagulation disorders that cannot be treated with acupuncture
- Patients with clinically significant psychiatric symptoms or medical diseases
- Participants who are judged by the investigator to have nonconformity for participation in the trial for any reason

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Textbox 2. Inclusion and exclusion criteria for healthy participants.

Inclusion criteria

- Men and women aged 50-85 years
- Participants who have no problems with cognitive function and who have voluntarily agreed to participate in the study through written consent
- Participants who selected to match the "Patients with PD" group with age, sex, and other health conditions, excluding the diagnosis of Parkinson disease (PD)

Exclusion criteria

- Participants diagnosed with PD
- Participants who have taken oral antibiotics within the past 1 month, as it was assumed that this medication could affect the results of this study
- Participants with a history of loss of consciousness for more than 1 hour due to brain trauma
- Participants with vision or hearing problems to the extent that the examination cannot proceed smoothly
- Participants who have consumed health functional food such as Lactobacillus within the last 1 month, as it is assumed that this health functional food could affect the results of this study
- Participants who took medications that could affect the gastrointestinal tract, such as pain relievers, anti-inflammatory drugs, and antibiotics, within 1 week of stool collection
- Participants with a history of serious heart disease such as myocardial infarction or heart failure
- Participants with a history of malignant tumor
- Participants with a history of glaucoma
- Participants with a history of chronic alcohol or substance abuse
- Participants with clinically significant psychiatric symptoms or medical conditions
- Any participant that the investigator judged to be physically or mentally inappropriate to participate in the clinical trial based on other laboratory findings

Textbox 3. Dropout criteria.

Dropout criteria

- Participants who do not comply with the study physician's instructions
- Participants who have taken other medications that may affect the results of the study without the consent of the study physician
- Patients who have developed other secondary infections and disease conditions that may affect Parkinson disease symptoms
- Participants who have withdrawn consent or requested discontinuation of treatment

Recruitment

For the study, 20 healthy participants and 60 patients with PD will be recruited through walk-ins or hospital and school bulletin boards, public transportation billboards, newsletters, and other online advertisements. Participants who wish to participate will receive an explanation of the consent form, provide written consent of their own free will, and participate in the study if the researcher determines that they are suitable through a screening process. The screening items are as follows: demographic information, medical history, PD diagnosis, treatment history, medications, vital signs, Hoehn and Yahr stage assessment, and inclusion and exclusion criteria evaluation (Table S1 in Multimedia Appendix 1 and Table 1 on code rather than the participant's name.

Interventions

All patients with PD will receive acupuncture, moxibustion, and intradermal acupuncture treatments twice a week for 12 weeks, for a total of 24 sessions.

Acupuncture Treatment

Acupuncture treatment for patients with PD will be performed by a Korean medicine doctor specializing in internal medicine of Korean medicine or by a Korean medicine doctor with at least 2 years of clinical experience in the field under the supervision of a specialist, using disposable sterile acupuncture (Dongbang Acupuncture, Co, Ltd) with a thickness of 0.25 mm and a length of 30 or 40 mm. The acupuncture points will be 12 basic acupuncture points and 36 additional acupuncture points selected according to the relevant nonmotor symptoms (Table 2). A total of 25 points or more on both sides will be chosen. After inserting the needle vertically approximately 5-30 mm deep into each point and inducing qi with twirling for 10-15 seconds, the needle will be retained for 15 minutes and removed. All acupuncture treatments will be performed in compliance with the STRICTA (Standards for Reporting Interventions in Clinical Trials of Acupuncture) guidelines [21].

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Table 2. Acupuncture points planned for use in patients with Parkinson disease.

Type	Acupuncture points
Basic acupuncture points	• Bai hui (GV20), bilateral Fengchi (GB20) • Upper limb: Hegu (LI4), Zhongzhu (TE3), Quchi (LI11), Shousanli (LI10), Waiguan (TE5) • Lower limb: Yanglingquan (GB34), Zusanli (ST36), Xuanzhong (GB39), Taichong (LR3), Zulinqi (GB41) • Auricular acupuncture: Shenmen
Additional acupuncture points selected according to nonmotor symptoms	• Constipation: Bilateral Tianshu (ST25), Yanggu (SI5), Yangxi (LI5) • Frequent urination, dysuria, sexual dysfunction: Jingqu (LU8), Taibai (SP3), Taixi (KI3), Fuliu (KI7) • Sialorrhea: Shaofu (HT8), Dadu (SP2), Dadun (LR1), Yinbai (SP1) • Dysgeusia, dysosmia: Shangxing (GV23), bilateral Yingxiang (LI20) • Pain: Ouch point • Sleep disorder: Neiguan (PC6), Shenmen (HT7), Zhaohai (KI6), Shenmai (BL62) • Anxiety, depression: Jingqu (LU8), Zhongfeng (LR4), Yingu (KI10), Ququan (LR8) • Fatigue: Qihai (CV6), Guanyuan (CV4), Zhongji (CV3) (moxibustion) • Cognitive impairment: Shishencong • Dysphagia: Chengjiang (CV24), Lianquan (CV23), Danzhong (CV17) • Dyspepsia: Zhongwan (CV12), Gongsun (SP4) • Dizziness: Neiguan (PC6), Shenmun (HT7), Lieque (LU7) Fenglong (ST40), Taibai (SP3)

Electric Moxibustion Treatment

Using electric moxibustion (Onttum, TechnoScience Co, Ltd), heating stimulation will be applied to the bilateral Tianshu (ST25), Zhongwan (CV12), Qihai (CV6), Guanyuan (CV4) at 40 °C mode for the duration of the acupuncture treatment (15 minutes).

Intradermal Acupuncture Treatment

After acupuncture and moxibustion treatments are completed, intradermal acupuncture (Press Needle, Dongbang Medical Co, Ltd) will be attached to the bilateral Yanglingquan (GB34), Zusanli (ST36), and auricular Shenmen. Patients will be instructed to frequently apply acupressure to the attachment area.

Outcome Measurements

Evaluation Overview

The efficacy of acupuncture and moxibustion in managing the motor and nonmotor symptoms of PD will be evaluated using the Movement Disorder Society–Sponsored Revision of the Unified Parkinson's Disease Rating Scale (MDS-UPDRS), Berg Balance Scale (BBS), Timed Up and Go Test (TUG), Schwab and England Activities of Daily Living Scale (S&E), 39-Item Parkinson's Disease Questionnaire (PDQ-39), and levodopa dosage investigation. To assess the association between acupuncture treatment-induced changes in symptoms and gut microbiome changes in PD, we will investigate changes in gut microbiome–related metabolites through blood sampling and changes in gut microbiome through fecal sampling. Participants' digestive symptoms will be assessed by abdominal examination, Gastrointestinal Symptom Rating Scale (GSRS), Total Dyspepsia Symptom Scale (TDS), and Bristol Stool Scale (BSS). Subjective perception of health will be assessed using the Measure Yourself Medical Outcome Profile (MYMOP). Credibility assessment in trials of acupuncture will be conducted to evaluate the impact of psychological factors on patients with PD.

Evaluation of Motor and Nonmotor Symptoms of PD

The MDS-UPDRS, the primary outcome of this study, was developed to complement the UPDRS as a tool to assess motor and nonmotor symptoms in patients with PD [22], and the Korean version has been validated [23]. The MDS-UPDRS comprises the following four parts with a total of 65 items: (1) nonmotor experiences of daily living, (2) motor experiences of daily living, (3) motor examination, and (4) motor complications. Of these, 48 items are scored from 0 to 4, with 0 (robust), 1 (slight), 2 (mild), 3 (moderate), and 4 (severe), and the 17 remaining items are scored as yes or no. Scores are calculated by summing the scores for each item, with higher scores indicating more severe symptoms of PD. The BBS is used to assess balance [24] and is also useful in evaluating equilibrium in patients with PD [25], and the Korean version of this tool has been validated [26]. This tool comprises 14 items that are scored from 0 (worst) to 4 (best), and the total score is evaluated. The TUG is used for assessing gait in older adults [27] and is used to evaluate walking ability in patients with PD [28]. This test measures the time taken to get up from a chair, walk around a 3-meter return point, and return to the chair in the initial position. The S&E is a component of the UPDRS that evaluates functional independence and is widely used as a standard Parkinson assessment tool [29]. The patient's function is evaluated using an 11-point scale with 10% increments, from 100% (completely independent) to 0% (vegetative functions are not functioning or bedridden). The PDQ-39 is used for assessing health-related quality of life (HrQoL) in patients with PD [30], and the Korean version has been validated [31]. The PDQ-39 comprises 8 dimensions with 39 items. Each item is scored from 0 (never) to 4 (always), with a higher total score

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indicating poorer HrQoL due to PD. Levodopa dosage investigation includes assessment of the daily dose and number of levodopa doses administered to patients with PD. Changes in type and dose of levodopa from pretreatment will be investigated first as “yes or no” and then dichotomized into “decrease or increase” for participants with no change for comparison between groups. Evaluation will be conducted at day 0, 6 weeks, 12 weeks, and 20 weeks in participants with PD and after screening in healthy participants.

Evaluation of Gut Microbiome–Related Metabolites and Gut Microbiome Change

Blood samples will be used to assess changes in gut microbiome–related metabolites. Blood will be collected from participants after an 8-hour fast before blood collection, and changes in metabolites will be determined using liquid chromatography-mass spectrometry and gas chromatography-mass spectrometry analyses. Western blotting will be applied to confirm changes in strain-derived factors in the blood of patients with PD. Participants’ fecal samples will be used to analyze the composition of the gut microbiome using 16S rRNA sequencing and fecal microbiome transplantation to assess the correlation between gut microbiome and response to acupuncture treatment. A small amount of feces will be collected using 4N6 FLOQSwabs (Copan Diagnostics Inc). For participants with PD, 2-3 g of feces will be collected using a Stool Collection Tubes With DNA Stabilizer (Invitek Diagnostics) for fecal microbiome transplantation. A FastDNA SPIN Kit for Feces (MP Biomedicals) will be used to isolate DNA from feces for DNA extraction and sequencing. DNA will be subjected to polymerase chain reaction targeting the V3-V4 variable region of bacterial 16S rRNA as a template, followed by sequencing library construction and sequencing reactions on the MiSeq Platform (Illumina, Inc). Sampling will be conducted at day 0, 6 weeks, 12 weeks, and 20 weeks in participants with PD and after screening in healthy participants.

Evaluation of Digestive Symptoms

Abdominal examination is a Korean medicine diagnostic method based on the Korean medicine theory that when a disease is inside the body, its response manifests on the body surface [32]. Participants will undergo manual palpation of Zhongwan (CV12) and Tianshu (ST25) for tenderness, while the presence or absence of gastric stuffiness and rigidity below the heart will be checked. The GSRS is a globally used self-reported gastrointestinal symptom scale that covers upper and lower gastrointestinal symptoms [33]. It comprises 15 questions in 5 domains (abdominal pain, reflux syndrome, indigestion syndrome, diarrhea syndrome, and constipation syndrome) scored on a 7-point scale from 1 (no symptoms) to 7 (very severe symptoms). The TDS has been used in previous studies to assess functional dyspepsia [34,35] and comprises 8 items (postprandial fullness and bloating, early satiety, epigastric pain, epigastric burning, nausea, vomiting, belching, and other symptoms) rated on a scale of 0 (absent) to 3 (severe). The BSS is the most widely used measure of stool formation, ranging from the hardest (type 1) to the softest (type 7) [36]. Evaluation will be conducted at day 0, 6 weeks, 12 weeks, and 20 weeks in participants with PD and after screening in healthy participants.

Other Evaluations

The MYMOP is a 4-item self-reported health assessment tool that measures subjective symptom change in response to treatment [37]. Using a scale of 0 (as good as it could be) to 6 (as bad as it could be), participants rate the 1 or 2 symptoms that have worried them the most, important activities, and general well-being in the past week. It will be conducted at day 0, 6 weeks, 12 weeks, and 20 weeks in participants with PD and after screening in healthy participants. The credibility assessment in acupuncture trials assesses the patient's credibility of acupuncture treatment, rating 4 items on a scale of 1 (absolutely not) to 6 (absolutely yes) [38]. This tool will be used to evaluate the impact of psychological factors on the outcomes of patients' credibility of acupuncture and moxibustion treatment in this study. This assessment will be conducted at day 0, 6 weeks, and 12 weeks in participants with PD and after screening in healthy participants.

Safety Assessments and Monitoring

At each visit, the participants’ subjective and objective adverse events will be investigated and classified into mild, moderate, and severe as follows: mild, participant feels little to no discomfort and symptoms interfere little with usual activities of daily living (ADL), most likely not requiring treatment; moderate, participant may experience discomfort that interferes with usual ADL, which may allow the participant to continue the study but may require treatment; severe, participant feels very uncomfortable, interfering with usual ADL, unable to continue participating in the study, and may require treatment or hospitalization. The causal relationship between reported adverse events, acupuncture treatments, and blood collection will be categorized by the Korean medicine doctor in charge as follows: more than 90%, definitely; 70%-90%, probably; 50%-70%, possibly; 30%-50%, probably not; and less than 10%, definitely not.

Sample Size

This study is not intended to statistically validate the intervention effect of acupuncture and moxibustion on PD but was rather conducted as an exploratory study comparing gut microbiome markers in patients with PD and healthy participants and the effects of acupuncture and moxibustion on the gut microbiome in patients with PD. Therefore, the sample size required for the study will be 60 patients with PD and 20 healthy individuals, depending on the financial resources and study environment, and in consultation with experts in gut microbiology.

Statistical Analysis

Overview of Statistical Analysis

SPSS (ver 21.0, IBM SPSS Statistics for Windows) will be used for analysis. All measures will be presented as mean (SD) for continuous variables and as n (%) for dichotomous variables. For efficacy endpoints, the amount of change or rate of change from baseline to end of treatment and follow-up will be calculated.

All data obtained from participants will be analyzed in 2 forms: intention-to-treat (ITT) analysis and per-protocol (PP) analysis. The ITT analysis will be performed on all participants who

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undergo acupuncture and moxibustion at least once. For missing data on the evaluation variables, the last observation carried forward (LOCF) method will be applied. PP analysis will further be performed on participants who completed the entire study. The evaluation will be based on the results of the ITT analysis and is presented with reference to the PP analysis.

Demographic Information Analysis

For both patients with PD and healthy participants, continuous data will be presented as mean (SD) or as median, minimum, maximum, and 95% CIs, whereas categorical data will be shown as frequencies and percentages.

Analysis for Changes in Clinical Outcomes

For the following clinical outcomes with continuous variables, the mean (SD), median, minimum, maximum, and maximum of each outcome will be presented for change in score from day 0 to 6 weeks, 12 weeks, and 20 weeks, and a 1-way repeated measures ANOVA will be performed to test for statistically significant changes in any of the following factors: total MDS-UPDRS score, total MDS-UPDRS score part I score, total MDS-UPDRS part II score, total MDS-UPDRS part III score, total MDS-UPDRS part IV score, BBS, TUG, S&E, PDQ-39, levodopa dosage investigation, abdominal examination, GSRS, TDS, BSS, and MYMOP.

Changes in Gut Microbiome–Related Metabolites and Gut Microbiome

Differences in microbiome at each time point will be measured using weighted-unweighted UniFrac distance metrics and subsequently tested using analysis of similarity (ANOSIM). Correlations of clinical outcomes and treatment effects with key microbiomes will be analyzed using Spearman rank correlation analysis, with $P<.05$ considered significant. Principal component analysis will be applied to analyze metabolite distribution in the sample. Partial least squares-discriminant analysis will be applied to identify differences between patients with PD and healthy participants when analyzing metabolite distributions. Selected gut microbiome and metabolite changes will be analyzed by 1-way repeated measures ANOVA, with significant differences between time points determined at $P<.05$. The pathway analysis or enrichment analysis will be performed to analyze the metabolic pathways of the selected metabolites. The Kyoto Encyclopedia of Genes and Genomes database [39] will be used to identify interactions between metabolites. Receiver operating characteristic analysis will be conducted to confirm whether the selected metabolites reflect the representativeness of the disease or treatment.

Comparative Analysis of the Gut Microbiome Between Healthy Participants and Patients With PD

Differences in gut microbiome between healthy participants and patients with PD will be determined by testing the acquired data for normality and performing a parametric test with an independent *t* test if the population is normal or a nonparametric test with the Mann-Whitney *U* test if the population is not normal.

Safety Analysis

For all adverse events that occurred during treatment, the frequency of adverse events will be analyzed according to whether they were associated with treatment or not. The number and proportion of participants with at least one adverse event, 95% CI, and the number of occurrences will be presented.

Ethical Considerations

The study protocol was approved by the institutional review board of Kyung Hee University Korean Medicine Hospital (KOMCIRB 2021-07-002-001; approved on September 14, 2021). This study is conducted in accordance with the principles of the Declaration of Helsinki. Participants who wish to participate receive an explanation of the consent form from the study researcher and give written consent of their own free will. All data from participants will be simultaneously recorded in an eCRF with an identification code rather than the participant's name to protect personal information.

Results

The study was supported by the National Research Foundation of Korea, funded by the Ministry of Science and ICT (no. 2022M3A9B6017813). Recruitment for the registry commenced on October 15, 2021, and was scheduled to end on September 13, 2023. Recruitment began on October 22, 2021, and as of February 19, 2025, participant recruitment and observation ended, and data analysis is being conducted.

Discussion

The clinical efficacy of acupuncture for PD has been consistently reported. Pereira et al [40] analyzed 17 randomized controlled trials (RCTs) on acupuncture for PD published in English between January 2011 and July 2021 and found that the combination of acupuncture and conventional treatment was superior to conventional treatment alone for motor and nonmotor symptoms of PD. Similarly, Lee et al [15] analyzed 16 RCTs, investigating 15 acupuncture treatments and 1 moxibustion treatment, published between 2008 and 2013, and comparing acupuncture or moxibustion with conventional therapies such as dopamine, found that all but one showed significant improvement in the acupuncture or moxibustion treatment group. In particular, for nonmotor symptoms of PD, for which effective treatments remain lacking, Li et al [41] reported through an analysis of 27 RCTs that acupuncture treatment could improve depression, quality of life, cognition, total mentation, behavior and mood, and ADL in patients with PD. Based on these clinical study data, the Clinical Practice Guideline of Korean Medicine for Parkinson's Disease recommended combination treatment of acupuncture and anti-Parkinsonian drugs for patients with PD, while moxibustion treatment may also be considered [42].

Attempts to identify the mechanisms of action of acupuncture in PD to support clinical data are still ongoing. Previous experimental studies using PD models have shown that acupuncture exerts neuroprotective effects through activation of neuroprotective agents such as brain-derived neurotrophic factor, glial cell line-derived neurotrophic factor, and cyclophilin

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A [43], effective in PD symptoms by inducing neuromodulation, thus controlling inflammation and brain functional connectivity [44,45], and p53 signaling-mediated neuroprotective effect [46]. However, these opinions are insufficient to reflect the systemic nature of PD and do not fully explain the improvement in nonmotor symptoms associated with acupuncture.

The gut-brain axis mechanism of PD stemmed from the perspective that PD should be managed and treated as a systemic disease [7]. Braak et al [47] observed that unknown pathogens invade the body through the intestines, while Lewy bodies selectively move from the intestines along the central nervous system and metastasize to the brain; based on the hypothesis that the motor and nonmotor symptoms of PD appear according to this metastasis, they proposed the Braak stage, which divides this process into 6 stages. This finding has drawn attention to the role of the gut in the pathology of PD. Recently, it has also been hypothesized that PD is divided into brain-first and gut-first, based on the division of positive and negative rapid eye movement sleep behavior disorder in the prodromal phase [48]. The fact that gastrointestinal symptoms, such as constipation, appear very early in the prodromal phase [49] and that 60%-80% of patients experience gastrointestinal symptoms [50] may also support the gut-first PD hypothesis.

Imbalances in the gut-brain axis caused by gut microbial dysbiosis can lead to increased inflammatory signaling and epithelial permeability, both of which are known to play an important role in neurodegenerative diseases such as PD [19]. The neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine increases α-synuclein and influences compositional changes in gut microbiome, including the phylum Proteobacteria [51]. Gut microbiome dysbiosis also induces microglial activation and neuroinflammation, which may promote α-synuclein overexpression, resulting in motor dysfunction [52,53]. Taken together, these results suggest that regulation of gut microbiome may have significant potential as a key treatment for PD, functioning through modulation of the gut-brain axis.

In the TEAM theory, the functional connection and communication between acupoints, the brain (ancient heart), and the gut is clinically important [54]. Based on the traditional theory, a previous review study [55] has reported that acupuncture has an effect on various diseases, including metabolic diseases, gastrointestinal diseases, mental disorders, and nervous system diseases, by regulating gut microbiome. Further, a large number of experimental studies on the relationship between PD and gut microbiome have been published recently, and the number is rapidly increasing [55]. In a previous experimental study including a PD model [19], we found that acupuncture treatment with GB34, which has been shown to exert neuroprotective effects on the brain, and ST36, which has been shown to enhance digestive function, improved motor function and anxiety, and increased the levels of dopaminergic fibers and neurons in the striatum and substantia nigra, increased the diversity of gut microbiome (alpha-diversity) and restored a gut microbiome to a composition more similar to that of robust controls (beta-diversity) compared with that noted in the PD group, in addition to restoring the increased levels of proteobacteria at the phylum level, suggesting that acupuncture exerts effects on improving gut microbiome imbalances. In another previous study [56], we conducted a clinical study to investigate whether acupuncture treatment for 2 weeks could effectively improve motor symptoms of PD using the UPDRS II+III in 73 patients with PD. This study showed that both the acupuncture treatment group and the control group showed improvement in motor function, with no significant intergroup difference; however, at the follow-up of 2 months after the end of treatment, the acupuncture treatment group continued to maintain these improvements in symptoms, while the control group reported a regression. Considering the results of these previous experimental studies, we hypothesized that acupuncture in this clinical study affected changes in gut microbiome to improve PD symptoms in a sustainable manner. To verify this hypothesis, we present the protocol of this study to explore changes in gut microbiome caused by acupuncture and moxibustion in patients with PD and explore its association with improvement in clinical symptoms of PD.

This protocol has limitations. First, as this study was designed as a single-group, prospective observational study with a primary focus on analyzing pre-post changes of patients with PD, a control group of healthy participants was included for baseline comparison rather than incorporating a control group within the PD cohort. This limits the internal validity of the intervention findings, as changes may be influenced by natural disease progression or placebo effects rather than the treatment itself. Second, although the sample size was determined based on feasibility rather than statistical power calculations, 60 patients with PD and 20 healthy participants may limit the reliability and generalizability of both within-group and between-group comparisons and increase the risk of type II error. Third, as no blinding was applied, the use of subjective, patient- and clinician-reported outcomes such as MDS-UPDRS, PDQ-39, and MYMOP increases the risk of detection and expectation bias, potentially compromising causal inference in this single-arm design. Fourth, adverse events are assessed by the treating Korean medicine doctors without independent adjudication or standardized grading criteria, which may limit the objectivity and consistency of safety reporting in this study. To address these limitations, future studies should adopt an RCT design with an adequately powered sample size, blinding procedures, and standardized outcome and safety assessments to enhance the internal validity, causal inference, and generalizability.

This study has limitations that must be weighed when interpreting the findings. Nutritional management is recommended for patients with PD, including dietary distribution to optimize levodopa absorption, dietary interventions for the improvement of nonmotor symptoms, and regular monitoring of food intake [57]. This leads to differences in dietary habits between PD patients and robust people, with PD patients showing higher protein and higher fiber dietary habits than robust people [58]. Fibers activate various beneficial microbiomes and suppress harmful species, and protein also has a significant impact on the gut microbiome [59]. Since this study does not investigate the nutritional intake of PD patients and healthy individuals, the influence of dietary differences should be considered when comparing the gut microbiome results between the two groups. Furthermore, levodopa dosage

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may affect gut microbiome composition [60]. Although this study investigates levodopa dosage in PD patients as part of clinical outcomes, it does not exclude the potential confounding effect of dosage adjustment on the gut microbiome. Therefore, any significant changes in levodopa dosage should be taken into consideration in the results.

The study will generate data on the effects of acupuncture and moxibustion on gut microbiome of patients with PD and explore its association with improvement in clinical symptoms. If the study results demonstrate that acupuncture and moxibustion change the gut microbiome in patients with PD, it will be the first clinical evidence to support a microbiome-gut-brain axis mechanism for acupuncture and moxibustion treatment of PD, ultimately contributing to the potential of acupuncture and moxibustion as an alternative treatment for PD.

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Data Availability

Data sharing does not apply to this protocol, as no datasets have been collected or analyzed.

Authors' Contributions

HGL contributed to the investigation, methodology, writing – original draft, and writing – review and editing. SK contributed to the conceptualization, project administration, supervision, methodology, and funding acquisition. MY and SYB contributed to the investigation and writing – review and editing. HJP contributed to the conceptualization, project administration, supervision, methodology, and writing – review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Planned schedule for the enrollment, interventions, and assessments of patients with Parkinson disease.
[DOCX File , 25 KB - resprot_v14i1e76551_app1.docx]

Multimedia Appendix 2
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 78 KB - resprot_v14i1e76551_app2.pdf]

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Abbreviations

ADL: activities of daily living
ANOSIM: analysis of similarity
BBS: Berg Balance Scale
BSS: Bristol Stool Scale
CAM: complementary and alternative medicine
CRF: case report form
GSRS: Gastrointestinal Symptom Rating Scale
HrQoL: health-related quality of life
ITT: intention to treat
LOCF: last observation carried forward
MDS-UPDRS: Movement Disorder Society–Sponsored Revision of the Unified Parkinson's Disease Rating Scale
MYMOP: Measure Yourself Medical Outcome Profile
PD: Parkinson disease
PDQ-39: 39-Item Parkinson's Disease Questionnaire
PP: per-protocol
RCT: randomized controlled trial
S&E: Schwab and England Activities of Daily Living Scale
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
STRICTA: Standards for Reporting Interventions in Clinical Trials of Acupuncture
TDS: Total Dyspepsia Symptom Scale
TEAM: Traditional East Asian Medicine
TUG: Timed Up and Go Test
UPDRS: Unified Parkinson's Disease Rating Scale

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Protocol

Health and Physical Education Preservice Teachers' Health Literacy Levels and Teaching Practices: Protocol for a Design-Based Research Approach

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Abstract

Background: Research examining the design and impact of health literacy (HL) programs and interventions on preservice teachers' HL and health and physical education (HPE) teaching practices to enhance students' HL is nonexistent. However, research indicates that many teachers and preservice teachers report low levels of HL, and recent research has highlighted preservice teachers' challenges in teaching HPE to enhance their students' HL capabilities. This is concerning, as HL is a focus in curricula and schooling both in Australia and internationally. Therefore, teachers are engaging in professional development aimed at enhancing their HL teaching practices, which raises questions about how further development of initial teacher education can enhance preservice teachers' HL capabilities and teaching practices in schools.

Objective: This protocol aims to provide details of a study to be conducted in the University of Sydney, involving final-year HPE preservice teachers, aimed at developing their HL capabilities and teaching practices.

Methods: The proposed methodology underpinning the research program follows a 7-stage design-based research approach, with the 7 stages outlined in 4 sequential studies. These 4 studies include a systematic review, a qualitative focus group study, a pilot study, and a controlled trial study. This paper details the plan for conducting the 4 studies in a comprehensive and transparent manner, thus contributing to the methodological evidence base in this field.

Results: The pilot study was conducted between July 2024 and December 2024, and data analysis was conducted between January 2025 and June 2025. The controlled trial will be conducted between July 2025 and December 2025. Final data analysis will occur between January 2026 and June 2026.

Conclusions: This project will assist in determining what key stakeholders see as important to include in an initial teacher education program designed to enhance HPE preservice teachers' HL capabilities and teaching practices. The design principles generated from this project will contribute to the inclusion and development of initial teacher education programs and practices and strengthen preservice teachers' HL and their teaching of HPE, thereby enhancing HL teaching practices. This is significant considering that HL is included in the curriculum internationally, and the development of HL for school-age students has been identified as a World Health Organization goal.

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KEYWORDS

health literacy; education; teacher education; preservice teachers; initial teacher education

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Introduction

Background

Health literacy (HL) is a relatively new phenomenon in the field of education [1,2], despite being a concept used in the health and medical field for at least 3 decades. HL was first mentioned in 1974 [3] and was further conceptualized in the health and medical field, as it has been recognized as a cognitive skill leading to positive health outcomes, particularly a reduction in lifestyle diseases and an increased ability to navigate the health care system [4-6]. Over the last 3 decades, HL research has found that higher HL levels are associated with decreased government spending, less frequent hospital visits, and increased patient knowledge and understanding [7,8].

More recently, greater focus has been placed on electronic HL (eHL). eHL can be defined as "the ability to seek, find, understand, and appraise health information from electronic sources and apply the knowledge gained to addressing or solving a health problem" [9]. This rise in eHL research has been in response to young people spending a greater amount of time online and on social media [10], which was seen to be particularly relevant in the COVID-19 pandemic [11]. This, alongside growing digitalization, has seen an infodemic of health information and misinformation, making it difficult for people to navigate and understand health resources online [12].

The social determinants of health are the conditions in which people are born, grow, live, work, and age and include a range of factors that influence health [13]—many of which youth have limited control over (eg, food security). In recent years, much of the research in the field of HL has focused on investigating whether HL is an independent determinant of health [14-16]. Large-scale research studies that used the European HL Survey across 8 European countries [14,15] supported that HL is a "relevant, independent, direct determinant of self-assessed health" [17]. HL is now being recognized as a social determinant [18]; this highlights the importance of creating systems for youth that develop and enhance HL knowledge and capabilities.

In recent years, HL has been reconceptualized to indicate the complex relationships among the individual, school education, community, and the health services they seek to access. Therefore, HL is not considered to be learned through only 1 system, setting, structure, or relationship [16,18]. The understanding of HL has evolved to include HL of two interrelated components: (1) individual HL and (2) the HL environment [19]. Individual HL "is the skills, knowledge, motivation and capacity of a person to access, understand, appraise and apply information to make effective decisions about health and health care and take appropriate action" [19], while the HL environment "is the infrastructure, policies, processes, materials, people and relationships that make up the system and have an impact on the way that people access, understand, appraise and apply health-related information and services" [19]. Both dimensions are important to consider in current HL research, particularly for this study, as preservice teachers are likely to have developed and will continue to develop their own HL through a combination of personal and professional experiences, including formal university education.

HL plays a critical role in empowering an individual [20], which leads to several countries including HL in their national documents and goals. The World Health Organization published an HL report in 2013, making explicit recommendations to strengthen HL levels of school-age children [21]. In response to this, HL was then included in the school curricula both in Australia [22] and internationally as well as in the education policies [23-25]. The current Australian health and physical education (HPE) curriculum [26] and the New South Wales (NSW) Personal Development, Health and Physical Education syllabus [27] (which will be referred to as HPE throughout this paper) have both adopted HL through HL being named as one of the 5 underpinning propositions, using 3-level hierarchal model proposed by Nutbeam [28]. The definition formulated by Nutbeam [28] is commonly used across international curricula and identifies HL in a hierarchical model, with 3 dimensions (functional, interactive, and critical HL), with each level being more advanced in terms of health decisions and impact on health outcomes. Functional HL is the first of the 3 dimensions and is recognized as the ability to use basic reading and writing skills to understand health information as well as apply instructions given by a physician, such as submitting a prescription or taking medication. Slightly more advanced is the interactive dimension, where individuals can apply health information in different contexts. The third dimension is critical, defined as "the cognitive skill and development outcomes which are oriented towards supporting effective social and political action, as well as individual action" [28]. When applied to classroom settings, the focus is on moving students toward being able to engage in community action, advocacy, critical thinking, analysis of policies, and engagement with leaders (ie, critical HL).

The ability of schools, school principals, other school-based leaders, and teachers to advance HL through curriculum, teaching, and learning across the whole school environment is central to the implementation of HL in schools and the promotion of HL for children and adolescents [29-32]. Therefore, the teacher plays a key role in developing students' HL levels [33-35]. Despite the importance of the teacher's role, research shows that Australian teachers (1) have insufficient understanding of how to best develop HL [30] and (2) only have access to limited professional development programs that focus on the promotion of HL [29,30,32]. These findings from Australian settings are in line with the findings from international studies. A cross-sectional study of 520 schoolteachers in an education zone in Colombo, Sri Lanka, found that 33% of the teachers fell into the "limited" HL category, as determined by the European Union HL survey [4]. The study by Denuwara and Gunawardena [4] also found that teachers who were aged 45 years or younger were associated with lower HL levels compared to their older colleagues. Furthermore, another study [36] found that 74% of the Turkish primary teachers have low or limited levels of HL. In response to this need to increase teachers' HL levels, many schools have engaged in teachers' professional development [29,30,32,35] and adopted structural changes such as a whole-school approach to developing HL [35]. Although the evidence suggests that these approaches are effective, they require significant systemic changes and are costly in terms of time and finances [37].

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Therefore, this poses questions about the roles of universities in developing preservice teachers' HL and their ability to teach HL through initial teacher education programs.

One study conducted in Indonesia [38] found that of the 704 biology preservice teachers, 53% were identified as having low levels of HL. The study, which focused on HL levels in relation to COVID-19 information, concluded with revealing important findings that suggested that preservice teachers had limited capabilities when it comes to analyzing and evaluating health-related information [38]. The 2 main limitations of the study were its focus on COVID-19 HL and not exploring preservice teachers' teaching of HL. Two recent studies conducted in Australia used a set of data to compare the HL levels of final-year primary generalist and secondary specialist HPE preservice teachers with one another and with the general population [39,40]. The studies examined HL levels using the reliable and valid HL Questionnaire (HLQ) [41] and found that HL levels were lower among primary generalist preservice teachers than among HPE specialist preservice teachers across all 9 sections of the HLQ. Interestingly, when compared to the general Australian population, the results showed that primary generalist preservice teachers had lower HL levels across domains 8 to 9 of the HLQ, indicating lower HL representative of functional and interactive HL [39]. This finding is significant, considering both primary and HPE teachers have a responsibility to teach HL within HPE as per the Australian curriculum [26] and NSW syllabus [27]. The first study then discussed possible reasons for these differences, using interview data and a document analysis of the university's scope and sequences for both programs, highlighting that the HPE cohort spent considerably more time in health-related units than the primary cohort. From this, it can be gathered that the more time spent in initial teacher education units as well as more explicit teaching of HL, including its key concepts, could possibly be connected to higher HL levels and perceptions of teaching HL. Data obtained from interviews with the primary preservice teachers' cohort revealed that they wanted more time spent on HL development and more explicit mention of HL in their only initial teacher education unit. Interviews also highlighted concerns in teaching HL in an increasingly digital world, acknowledging the importance of eHL development. Interestingly, although the HPE cohort consisted of individuals who were specialists in teaching HPE, participants still expressed concern about teaching HPE to enhance students' critical HL, indicating the need for redesigning and restructuring initial teacher education units in initial teacher education programs to consider these suggestions [39,40].

Despite recent research highlighting a need for preservice teachers' HL development, there has been no known HL intervention for promoting preservice teachers' HL and HL teaching. Much of the research on HL intervention programs exists in the clinical setting [42,43]. Although these studies generally focus on enhancing a practitioner's HL, the principles may be applied and adapted to suit broader university settings. The commonality between studies indicates the significance of realistic and explicit scenario-based learning [42,44,45], which can be achieved through internet access to develop digital HL skills [45,46]. Kripalani and Weiss [43] highlighted the significance of modeling within programs, including modeling clear communication and teach-back techniques, which may be useful to replicate in a classroom setting. The research conducted by Mogford et al [45] suggested interactive pedagogy and critical consciousness strategies to create an HL intervention for university programs but not specific to initial teacher education. The research recommended structuring a university's initial teacher education unit to best develop critical HL by dividing the program into 4 parts: *knowledge*, *compass*, *skills*, and *action*. However, the researchers have yet to conduct pretesting and posttesting to determine whether these parts have an impact on university students' HL. Nonetheless, these suggestions could be used to inform the co-design and refinement of an HL intervention for preservice teachers.

Objectives

To the best of our knowledge, no study has reported on the design, implementation, and impact of an intervention program on developing preservice teachers' HL levels and enhancing HL teaching practices. This study aims to fill this research gap. The aim of this study is to co-design an HL intervention program in a unit of study in 1 initial teacher education program at the University of Sydney. Using a design-based research (DBR) approach, embedding a pilot study and controlled trial (CT), a series of design principles will be created that will be evidence informed and can be used to underpin the design of future initial teacher education units and programs.

This project will investigate how HL curriculum goals can be implemented in initial teacher education programs to enhance HPE preservice teachers' HL and eHL teaching practices. To address this overarching research question, this study will examine the extent to which a unit of study in an initial teacher education program may impact preservice teachers' HL and eHL levels and the extent to which it influences preservice teachers' teaching of HPE to enhance HL and eHL teaching practices.

Theoretical Framework

The socioecological model [47] underpins this study as it examines the interrelationship between individuals and groups and assesses the way that these relationships exist within a broader social network or ecology [48]. The framework adopts a social constructivist approach [49,50], which is the idea that knowledge is formed in collaboration with others [49]. Wharf Higgins et al [50] argued that although health behaviors are perceived as outcomes of cognitive decisions, this view is limited because intrapersonal, interpersonal, and community levels all influence an individual's health knowledge, behaviors, and capabilities. In the same way, HL is socially constructed, with influences of the micro, meso, and macro contexts, determining a person's HL level. Using the socioecological model proposed by Bronfenbrenner [48], this study will consider the interaction between the micro, meso, and macro contexts, which is important because it recognizes that universities play a significant role in developing an individual's HL and the teaching of HL through HPE in schools to enhance students' HL. This framework will be used in this study by ensuring that quantitative data on HL and eHL levels are triangulated with qualitative data to determine how the experiences of engaging

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with the health education unit may have influenced the development of preservice teachers' HL and eHL capabilities and teaching practices.

Methods

Research Design and Procedure

Overview

To investigate the developmental nature of the research questions, a robust methodological framework is required. Reeves' [51] original design-based research model will be used to underpin the research methodology [52] for this study (Figure 1). The justification for selecting a DBR model is that, at its core, DBR assumes real-world practice is contextual; hence, for effectiveness, an applied practice must be flexible to the needs of the group [52,53]. The study will focus on the premises of the model, which is needed to move beyond the limited measures of learning to address the nature of learning in the real world [54]. This is important considering university initial teacher education programs exist predominantly in the mesocycle of the socioecological model [49]. The DBR model, in recent years, has been applied to complex education intervention studies [55,56], divided into 4 key stages. For this study, a 7-stage process has been developed to reflect the changing nature of the design, which underpins this study.

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Figure 1. A diagrammatic overview showing how the proposed research aligns with the design-based research model proposed by Reeves [51] (adapted from Sultoni et al [52], which is published under Creative Commons Attribution 4.0 International License [57]).

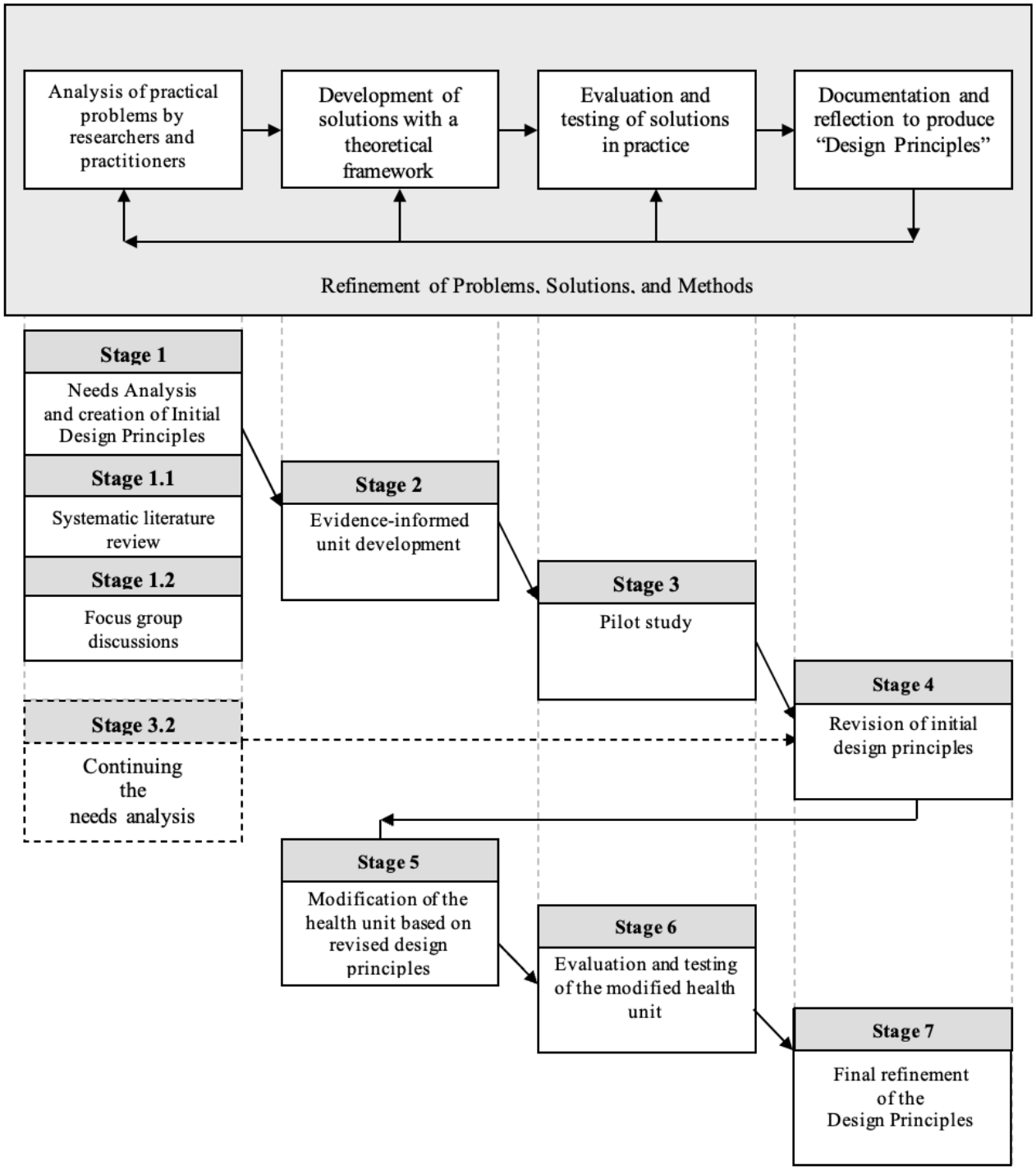

Stage 1: Needs Analysis and Creation of Initial Design Principles

Overview

The aim of stage 1 is to conduct a detailed needs analysis of the problem to inform the creation of an initial series of design principles. These initial design principles will be used in stage 2 to inform the co-design of an existing initial teacher education unit in a Bachelor of Education (HPE) program. The needs analysis will involve two steps: (1) a systematic literature review will be conducted to explore current research on an analysis of features and characteristics of university HL and eHL interventions and (2) a series of semistructured interviews will be conducted to further develop the findings of the systematic literature review and situate them in an Australian and NSW initial teacher education contexts. These steps are described in detail subsequently.

Stage 1.1: Systematic Literature Review

The aim of the systematic literature review is to determine the need for an HL and eHL intervention and the features and

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characteristics to be included within the initial teacher education unit. The research will examine, appraise, and provide recommendations from the available literature to support what could form an impactful initial teacher education unit (ie, one that has the potential to enhance HL among preservice teachers). This systematic review will follow the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [58], and the protocol of the study will be registered with PROSPERO. The review will be informed by the Cochrane Handbook for Effective Systematic Literature Reviews [42]. This will include identifying studies relevant to this research, collating the data, considering the statistical analysis, and interpreting the results. The population, intervention, comparison, and outcome method will be used for determining the search terms for the systematic literature review, as this has been identified as an effective way to align with research questions for health-based interventions [59]. The population will consist of university students or higher or further education students enrolled in teacher education courses or health courses. Intervention will include programs aimed at developing HL and eHL levels using key strategies. Comparison will be between a study that includes a CT and a study involving usual control methods. The primary outcomes will be HL and eHL as well as HL teaching practices embedded within HPE.

More specifically, database fields will be searched using the terms provided in Textbox 1.

Textbox 1. Database field search strategy.

- Population: Universit* OR college OR TAFE

AND

- Intervention: health literac*

AND

- Comparison: “control trial”* OR “control group”* OR RCT* OR quasi* OR “CT” OR experimental* OR pre* OR post* OR evaluat*

AND

- Outcomes: “Health literac”* OR teach* OR school* OR students* OR peers* OR universit* OR “health education” OR HLQ OR hosp* OR patient*

The databases that will be searched include MEDLINE, Embase, The Cochrane Library, PubMed, PsycINFO, and EBSCOhost. These databases have been selected based on existing systematic literature reviews and literature reviews in the field of HL and health education [14,46,60]. Reference lists from included articles will also be searched to identify and examine other relevant studies for the systematic literature review. Data from 1974 until mid-2023 will be reviewed, as 1974 was the year the term HL was first published in education literature [3]. Results will be limited to peer-reviewed articles written in English. Stage 1.1 will inform the first publication.

Stage 1.2: Semistructured Interviews With Key Stakeholders

The aim of the semistructured interviews is to further develop an analysis of the practical problems by including practitioners to inform and validate the initial design principles revealed in stage 1.1. The interviews will be conducted via Zoom (Zoom Communications, Inc) [61]. The participants for stage 1.2 will include the unit coordinator and lecturers or tutors of the final-year initial teacher education unit at the university, 9 other lecturers or tutors of HPE preservice teachers at other Australian universities, and 2 early-career HPE teachers (n=11). The semistructured interviews will situate the findings from the systematic literature review in an NSW educational context. The discussions will also help to develop a better understanding of what is needed for effective HL and eHL development, how this knowledge will transfer into schools, and what preservice teachers need to feel most confident in teaching HPE to enhance students’ HL and eHL from the perspective of key stakeholders. The face-to-face interview recordings will be transcribed by the lead researcher, and the online interviews will be transcribed from Zoom interview recordings. To analyze the interview data, we will follow an inductive approach in the qualitative research to ensure that it is exploratory rather than guided by particular themes [62]. The reflexive thematic data analysis model by Braun and Clarke [63] will be adopted. A reflexive approach to thematic analysis has been considered as it acknowledges the researchers’ subjectivity as a resource that can analyze the data [63]. This is because the researcher, as a student, has completed the unit that is going to be co-designed and refined. Therefore, coding of these interviews will be conducted in parallel with another researcher not involved in the unit, to reduce bias, as well as following the reflexive approach of the researcher. The process consists of familiarizing oneself by writing notes on the transcripts. Codes will then be used to summarize portions of the data. Once coded, themes will be compared by examining the similarities between the codes from the previous step to find thematic concerns. Then, the boundaries of the themes will be considered to determine whether there are enough data to support them. Once themes are defined and named, they will be analyzed deductively using the socioecological framework. The findings from this stage will further establish or add to the initial design principles established through the systematic literature review. An initial outline of the semistructured interview questions (for a head of the HPE department in an NSW secondary school) can be found in Multimedia Appendix 1. This stage will inform the second publication. Ultimately, the results of the systematic literature review and the semistructured interviews will form the initial

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design principles to be used to co-design the existing initial teacher education unit.

Stage 2: Evidence-Informed Initial Teacher Education Unit Development

The aim of stage 2 is to develop solutions, based on stage 1, within the socioecological framework. To do this, the initial design principles and data from stage 1 will be used in conjunction with the initial teacher education unit of study coordinator and lecturer to co-design the unit of study.

The initial teacher education unit is currently scheduled for the final year of an HPE course at the university and focuses on health promotion in community health issues. It is a 6-credit point unit (equates to one-eighth of a full-time student load) that runs for 8 weeks and is compulsory for all final-year HPE preservice teachers. The unit runs parallel with the final-year professional experience unit, which requires preservice teachers to complete their final school placement and consequently complete their teaching performance assessment (TPA), which is completed at this university as the Assessment for Graduate Teaching (AfGT) [64].

Intervention programs in initial teacher education co-designed with stakeholders have proven to be more efficient than informing an intervention based solely on the dissemination of information [65]. In this study, a co-design approach has been selected, using a participatory approach that relies on the knowledge of stakeholders, which is common in the health education field [66]. Co-design that includes the ideas of stakeholders is more likely to be accepted, adopted, and sustained [67]. Both the systematic literature review and the semistructured interview data, through the initial design principles, will be used to co-design the final-year initial teacher education unit with the unit coordinator. This process will be based on the same rationale, outcomes, structure, and assessment type. The process will include content development, which aims to produce modules for the initial teacher education unit, tutorial and assessment activities, provocation questions, scenario-based learning, and tutorial tasks.

Stage 3: Testing of the Developed Initial Teacher Education Unit

Overview

The aim of stage 3 is to evaluate and test the solutions in practice, that is, the impact of the co-designed unit of study on HL levels and the teaching of HL. Specifically, this stage will determine the feasibility, acceptability, and potential efficacy of a CT in a real-world setting to assess the 3 primary outcomes (preservice teachers' HL levels, preservice teachers' teaching practices in HPE and HL in coursework, and HL teaching practices) as outlined subsequently. Testing the feasibility of an intervention program focuses on increasing the validity of the intervention by deciding whether key factors, including timelines, recruitment, and delivery, are feasible before conducting a CT [68]. To test acceptability, qualitative interview data will be collected to determine the extent to which the intervention program is acceptable to the target population and suitable for their needs [69]. To ensure bias is removed, the questions for these interviews have been created by the lead researcher, who is also the lecturer and tutor, alongside researchers who are not engaged with the cohort and are therefore possible participants.

The testing of the co-designed unit of study will therefore be conducted. To do this, the participants of the pilot study will include the final-year HPE cohort at the university in their initial teacher education unit [70]. There will be approximately 30 preservice teachers in the class. In addition to the primary outcomes mentioned subsequently, the feasibility and acceptability of the co-designed unit of study will be determined by interviewing the lecturer through a semistructured interview (n=1) and obtaining consent from preservice teachers (n=5) in a focus group discussion to identify whether the unit achieved the unit outcomes, the feasibility of the content and learning experiences, and how the unit was conducted in a realistic setting. An overview of the semistructured interview questions is provided in Multimedia Appendix 2. An overview of the focus group discussion questions is provided in Multimedia Appendix 3.

To triangulate the data, patterns of convergence or divergence between quantitative results (eg, questionnaire data) and qualitative findings (eg, interviews) will be identified. This process will assist in enhancing the coherence of the study and assist in coming to practical conclusions for the initial design principles. The primary outcomes for this stage are mentioned subsequently.

Stage 3.1: Preservice Teachers' HL and eHL Levels

HL will be measured objectively using the HLQ [41]. The HLQ will be administered in week 1 and again at the conclusion of the unit in week 8. Data will be analyzed using protocols developed in previous studies [40,41,70]. This will include using SPSS (version 28; IBM Corp) for analysis of HLQ scores, applying robust ANOVA with the Welch method. The selected HLQ assesses HL as a multidimensional concept categorized in 9 sections rather than producing a single score, hence offering a broad and valid understanding of a person's HL capabilities. The 9 sections have been deemed valid for young adults [41] and reliable, with the composite reliability ranging from 0.8 to 0.9 [41,70]. To measure eHL levels, the University of Copenhagen's eHealth Literacy Questionnaire [71] will be used. This multidimensional tool assesses eHL across 7 scales and does not generate a single score but rather provides a broader understanding of eHL levels across different areas and scales. For this, the same analysis process as the HLQ will be used, as mentioned earlier. This will address the research question "To what extent can a unit of study impact preservice teachers' HL and eHL levels?" These findings will assist in answering the key question of the study and achieving the main aim of the co-designed unit, which is to enhance preservice teachers' HL and eHL levels, making this the most prioritized outcome of the study.

Stage 3.2: Preservice Teachers' Teaching Practices in HPE and HL in Coursework

Teaching practices will be assessed through work samples created in the initial teacher education unit. Data will be collected at the end of each tutorial and through the assessment tasks. These will be annotated by both the lead researcher and

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an additional researcher not involved with the cohort to identify how HL concepts have been applied in different contexts, which is important because research indicates that HL must be adjusted to suit different settings and educational goals [33]. In line with the Australian HPE curriculum and the HL proposition in the NSW Personal Development, Health and Physical Education syllabus [26-28], the 3-level hierarchical model proposed by Nutbeam [28] (functional, interactive, and critical) will be used to analyze the application of HL to health-related coursework tasks. The work will be deductively analyzed to determine where it is situated in relation to the hierarchical model [28]. This process is commonly used in other research projects in the field that examine evidence of HL content and teaching [32,72]. By analyzing the data deductively, this study aims to assess how preservice teachers plan for HPE teaching and learning that will enhance their students' HL levels. This outcome will address both subsidiary research questions.

Stage 3.3: HL Teaching Practices

This outcome will be measured using data from preservice teachers' final-year professional experience placement, a supervised working placement, administered in a parallel unit of study. This is an important outcome as it will assist in determining if the preservice teachers can transfer their HL and eHL learning experiences into their health education classes and whether students can, as a result, develop their own HL and eHL. The sample size will be the number of consenting students who choose health lessons (n=20). The data collected will be the participating students' completed AfGT. The AfGT has been approved by the Australian Institute for Teaching and School Leadership [72] expert advisory group and deemed valid as a TPA, having been developed to assess practice and competency, aligning with the national program standard at the graduate level. Data will be analyzed using the same process in stage 3.2, with deductive analysis to determine if and how the teaching and learning strategies have applied HL according to Nutbeam's hierarchy [28].

Follow-up interviews with preservice teachers (n=5) will also be conducted to reflect and triangulate the evidence from the TPA. The AfGT will be used as a discussion point for the interviews, and participants will be encouraged to bring additional artifacts (eg, additional lesson plans, lesson resources, or work samples) from their internship for further evidence. Sample semistructured interview questions are provided in Multimedia Appendix 4. Interview questions were selected to assist in measuring quality and improvements in teaching, as professional reasoning is closely linked to teaching professionalism [73]. The same interview analysis process will be conducted, as explained in stage 1.2. Both primary outcomes 2 and 3 will be used to answer the following research question: "To what extent can a unit of study influence preservice teacher's teaching of HPE to enhance HL?" Stage 3 will inform the third publication.

Stage 4: Revision of Initial Design Principles

The aim of stage 4 is to focus on documentation and reflection to produce a revised set of design principles. To revise the design principles, the proposed strategy is to collate the data from stage 3 and refine accordingly using the data from stage 3.2. These revised principles, with evidence-based modifications, are necessary to modify the initial teacher education unit in stage 5.

Stage 5: Modification of the Initial Teacher Education Unit Based on Revised Design Principles

The aim of stage 5 is to continue with the development of solutions. This will be the modification of the initial teacher education unit of study based on the revised design principles. To do this, the initial teacher education unit of study will be further co-designed with the unit coordinator. This will follow the same rationale, outcomes, structure, and assessment type. The process will include making changes based on the pilot study and revision of design principles.

Stage 6: Evaluation and Testing of the Modified Initial Teacher Education Unit

The aim of stage 6 is to re-evaluate and test the revised solution in practice. The location of this stage will be at The University of Sydney and/or The Australian Catholic University and The University of Tasmania. The modified health unit will be tested through a CT, including the final-year HPE cohort (n=30) from the university and another Australian university (n=30). Although not often used in education, a CT has the advantage of providing a more precise estimate of effect when comparing 2 educational groups, one of which receives an intervention program [74]. The lecturer (n=1) in the intervention group will conduct the modified unit while the other university final-year cohort will deliver their usual unit (with no changes implemented). To enhance validity, baseline information will be collected from both cohorts using a demographic data questionnaire and a pretest score for their HLQ. To reduce the risk of contamination, both universities will conduct their courses independently without communicating about content or sharing resources. Data will be gathered using the valid and reliable instruments administered in stage 3 to complete preintervention and postintervention research on both groups. A series of 2-tailed *t* tests will also be conducted for the HLQ. Coding of the artifacts will be compared as well. Data will be analyzed following the same procedure used in stage 3. A power analysis will be conducted to determine whether the sample size is sufficient to detect statistically significant changes. If it is detected to be underpowered, this will be identified in the publication as a limitation of stage 6. Stage 6 will inform the fourth publication.

Stage 7: Final Refinement of the Design Section Principles

The aim of the final stage (stage 7) of the study is to use the data collected between stages 1 to 6 to create a concluding series of design principles to assist future initial teacher education program leaders, unit of study designers, initial teacher education lecturers, and tutors in initial teacher education who coordinate and teach within HPE.

Ethical Considerations

Ethics approval and consent to participate were sought and accepted from the University of Sydney human research integrity and ethics committee for this study (2024/081).

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Participants who consented to the study will be made aware that their data will remain anonymous and any interview data will be de-identified. However, the consent form did indicate that if participants wished to withdraw from the HLQ and eHLQ, their data would not be removed as it was anonymous and therefore the researchers cannot distinguish their data from other participants.

Results

Stages 1.1 and 1.2 were conducted between January 2024 and May 2024, and the results have been submitted for publication. Stage 2 was conducted between June 2024 and July 2024, and stage 3, being the pilot study, was conducted between July 2024 and December 2024. Data analysis was performed between January 2025 and June 2025. The CT will be conducted between July 2025 and December 2025. Final data analysis will be conducted between January 2026 and June 2026.

Discussion

Anticipated Findings

The anticipated findings are an increase in HL and eHL levels of the preservice teachers who participated in the refined health education unit. The interview data are expected to contribute to the understanding of the preservice teachers' perceptions of the unit and their confidence in planning and teaching HL learning experiences. By collecting these pretest and posttest data as well as the data from the interviews with key stakeholders, this study will assist in the development of the initial design principles. The purpose of this study is to evaluate the impact of a final-year HPE HL and eHL intervention and the extent to which it is transferred into learning and curriculum goals in the classroom. The intervention uses a DBR approach to determine the current HL and eHL intervention programs used in the university setting as well as recommendations for the co-design process from the perspective of key stakeholders. Determining these design principles will help support the co-design of the initial teacher education unit aimed at enhancing HL levels and HL teaching practices. This paper describes the systematic creation of a series of design principles using literature, semistructured interviews with key stakeholders, and the final principles modified through the pilot testing process. Findings from this study are expected to contribute to initial teacher education programs internationally and inform the design process of the initial teacher education units.

Comparison to Prior Work

Studies have identified preservice teachers' low levels of HL and eHL and recognized a need for development of these capabilities [39,40]. However, there is no published intervention that focuses on the development of preservice teachers' HL and eHL levels. Therefore, this research will extend previous research by applying a DBR approach to co-design a health education unit and implement and evaluate the potential impact of this unit on HL and eHL levels and teaching practices.

Strengths and Limitations

The key strength of this study is its novel contribution to the field. Other strengths include the DBR within a mixed methods approach, the use of validated instruments, and artifact (AfGT) coding, along with qualitative interviews, to triangulate the data. However, there are also some limitations to be acknowledged, including the small sample size (n=30), which may impact the statistical power of this study. In addition, because this study was initially conducted in a single Australian university, the CT will be necessary to provide stronger evidence of impact. As the CT will include an additional university, the groups will not share data or resources; however, some contextual and demographic differences between the 2 universities may remain.

Future Directions

Findings from this study, particularly the initial design principles informed by literature and key stakeholder input, will inform the development of other health education programs aimed at developing HL and eHL levels and teaching practices. Although this study will determine whether HL and eHL practices can be transferred into teaching, future research may broaden the context of the health education units' delivery, refining some elements to test the suitability of the design principles in other contexts, such as in the medical field or allied health.

Dissemination Plan

Results from this study will be disseminated through peer-reviewed journal publications and conference presentations. The final design principles will be shared with key stakeholders involved in the co-design process, allowing them to potentially include these design principles in their health education programs, which would enhance the broader impact of the study.

Authors' Contributions

Conceptualization: CKA, LRP, WGC
Data curation: CKA
Formal analysis: CKA
Investigation: CKA, LRP, WGC
Methodology: CKA, LRP, WGC
Project administration: CKA
Resources: CKA
Supervision: LRP, WGC
Validation: LRP, WGC
Visualization: CKA
Writing – original draft: CKA

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Writing – review & editing: CKA, LRP, WGC

Conflicts of Interest

None declared.

Multimedia Appendix 1
Example of semistructured interview questions for stage 1.1—semistructured interviews with key stakeholders.
[DOCX File , 16 KB - resprot_v14i1e69900_app1.docx]

Multimedia Appendix 2
Example of semistructured interview questions for stage 3—lecturers.
[DOCX File , 15 KB - resprot_v14i1e69900_app2.docx]

Multimedia Appendix 3
Example of focus group interview questions for stage 3—preservice teachers.
[DOCX File , 15 KB - resprot_v14i1e69900_app3.docx]

Multimedia Appendix 4
Example of semistructured interview questions for stage 3—preservice teachers.
[DOCX File , 15 KB - resprot_v14i1e69900_app4.docx]

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Abbreviations

AfGT: Assessment for Graduate Teaching
CT: controlled trial
DBR: design-based research
eHL: electronic health literacy
HL: health literacy
HLQ: Health Literacy Questionnaire
HPE: health and physical education
NSW: New South Wales
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
TPA: teaching performance assessment

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Protocol

Platelet Indices as Unequivocal Markers of Active Disease in Patients With Nonradiographic Axial Spondyloarthritis: Protocol for a Cross-Sectional Study

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Abstract

Background: Spondyloarthritis is divided into axial and peripheral subtypes. The axial subtype is further divided into ankylosing spondylitis (AS) or radiographic axial spondyloarthritis and nonradiographic axial spondyloarthritis (nr-axSpA). Although AS and nr-axSpA share some common features, nr-axSpA lacks X-ray–based sacroiliitis as defined by the modified New York criteria, that is, the presence of either bilateral grade 2 sacroiliitis or unilateral grade 3 sacroiliitis, which is present in AS. Disease activity in either of them is measured via C-reactive protein (CRP) levels or magnetic resonance imaging (MRI) of the pelvis showing sacroiliitis due to the presence of bone marrow edema. A person with active disease can have normal CRP and MRI findings, especially in nr-axSpA. Immune system activation during inflammation has been shown to alter platelet maturation and morphology, as reflected by platelet indices. These platelet indices have been studied in the past in various autoimmune diseases, such as psoriatic arthritis, AS, and rheumatoid arthritis, and have been correlated with disease activity. Particularly, in spondyloarthritis, platelet indices are more central to the pathology of sacroiliitis, and CRP, which is currently used, is a generalized marker of inflammation. Therefore, platelet indices can provide a better understanding of inflammation, particularly in patients with sacroiliitis.

Objective: This study aims to investigate whether platelet indices can be better markers of inflammation in patients with nr-axSpA. We will determine whether platelet indices are reliable biomarkers for measuring disease activity in patients with nr-axSpA.

Methods: All patients who are classified as having axial spondyloarthritis as per the Assessment of Spondylarthritis International Society criteria will be included in this study. Patients will be divided into 2 case groups: group A (patients without radiographic sacroiliitis [nr-axSpA]) and group B (patients with radiographic sacroiliitis [AS]). Healthy individuals will be enrolled as controls to compare and correlate platelet indices such as platelet count, plateletcrit, mean platelet volume, and platelet distribution width with CRP, erythrocyte sedimentation rate, and MRI findings in patients with AS and nr-axSpA.

Results: This is a nonfunded study. The data collection started on February 1, 2025, and we expect to complete the study by December 2027. As of July 2025, 7 individuals had been enrolled in groups A and B, respectively, and 5 individuals had been included in the control group. At the end of the study, we will be able to correlate whether platelet indices are trustworthy biomarkers of active disease in patients with nr-axSpA.

Conclusions: If platelet indices prove to be better markers of active disease in patients with nr-AxSpA, then these markers should be included in the routine evaluation of these patients.

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KEYWORDS

nonradiographic axial spondyloarthritis; ankylosing spondylitis; platelet indices; sacroiliitis; CRP-negative spondyloarthritis; C-reactive protein

Introduction

Background

Spondyloarthritis is divided into axial and peripheral subtypes. The axial subtype is further subdivided into ankylosing spondylitis (AS) or radiographic axial spondyloarthritis (r-axSpA) and nonradiographic axial spondyloarthritis (nr-axSpA). Both represent conditions with inflammatory back pain that start in individuals aged 45 years or younger and are present for at least 3 months, as per the Assessment of Spondyloarthritis International Society (ASAS) criteria. Although both AS and nr-axSpA share some common features, nr-axSpA lacks X-ray–based sacroiliitis as defined by the modified New York criteria [1,2].

Patients with AS were diagnosed on the basis of the modified New York criteria, which had a sensitivity of 95% and specificity of 85% [3]. However, this criterion led to delayed diagnosis of patients in the early stages of inflammation as no magnetic resonance imaging (MRI) findings were included to identify the active inflammation of sacroiliac joints that were not visible on conventional X-rays, and neither did it include a separate criterion for nonradiological spondyloarthritis, a subgroup of patients who may lack any radiological findings of inflammation of the sacroiliac region. With the advent of newer imaging modalities, such as computed tomography scans and MRIs, newer criteria, such as the Amor criteria [4] and the European criteria [5], were developed for early diagnosis of inflammation of the axial skeleton. Subsequently, the ASAS criteria [6] provided a new classification criterion that included both AS and nr-axSpA. This is currently applied as a classification criterion and has a sensitivity and specificity of 66.2% and 97.5%, respectively, for the imaging arm and 80% for the clinical arm. Although this is a classification criterion and should not be used for diagnostic purposes, it is the only criterion encompassing both early and late phenotypes of spondyloarthritis [6].

Labeling of the disease as active often requires either raised C-reactive protein (CRP) levels or an MRI showing active lesions in the sacroiliac joint, along with a clinical score showing disease activity [7]. A high CRP level or active lesions on MRI facilitates the use of anti–tumor necrosis factor (TNF) therapy for patients. CRP levels also predict the response to treatment with biologicals (anti-TNF). Higher CRP levels during the initial evaluation indicate a better response to anti-TNF agents [7]. Similar to patients with AS, patients with nr-axSpA also need to fulfill these criteria for the use of anti-TNF agents [8]. Apart from anti-TNF agents, other drugs that are used are interleukin 17 inhibitors and Janus kinase inhibitors such as tofacitinib, sulfasalazine, and etoricoxib [9].

The literature shows that patients with clinically active disease can have normal CRP levels and MRI findings. Unfortunately, patients with active disease without evidence of inflammation are not eligible for anti-TNF therapy and are considered CRP-negative. As there is no objective evidence of inflammation, such patients present a dilemma for rheumatologists when deciding whether to escalate therapy [7]. MRI, too, may not show active inflammation in patients with active disease if bone marrow edema is below a certain threshold, and such lesions can be detected only via bone biopsy, which is invasive [8].

Such patients need alternative and reliable markers of active inflammation, as early escalation of therapy can control their symptoms and prevent or slow down radiographic progression.

The 2 entities, r-axSpA and nr-axSpA, were devised to include the entire spectrum of axial spondyloarthritis and its staging for research purposes. There is some controversy regarding whether to consider them as the same disease. Nr-axSpA is distinct in other aspects, such as a shorter duration of disease, self-limiting nature, and lower CRP levels; however, the actual clinical burden may remain at par with r-axSpA [10].

Hence, it is imperative that patients with nr-axSpA, who are more likely to be CRP-negative or normal and may not show sacroiliac joint lesions on MRI, should be assessed for alternate markers of active disease [11]. This emphasizes the need for more biomarkers in patients with nr-axSpA, as they are more prone to false-negative CRP or MRI results.

Various studies have shown that platelet indices used in numerous rheumatological diseases, such as psoriasis, rheumatoid arthritis, AS, and scleroderma, correlate well with inflammatory markers and clinical scores of disease activity [12-15]. However, no study, in particular, has been conducted in patients with nr-axSpA, where the probability of having a normal CRP or MRI is much higher.

Activation of the immune system causes the release of inflammatory cytokines, autoantibodies, and immune complexes. When chronic, inflammation may influence thrombopoiesis and erythropoiesis, thereby altering the properties of different blood indices such as red cell distribution width (RDW), platelet distribution width (PDW), and mean platelet volume (MPV). There may be changes in platelet maturation and morphology. Parameters such as MPV have shown an inverse correlation with acute-phase reactants and joint involvement in spondyloarthropathies [16].

Byun et al [17] showed PDW correlated well with disease activity measures such as the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score (ASDAS)-CRP in patients with AS, even in patients whose traditional inflammatory markers were within the normal range. Platelet count (PC) also correlated with CRP levels [14]. However, this study did not include platelet indices such as plateletcrit and MPV. Moreover, no comparison was made with a control group. The study did not include any other biomarkers apart from platelet indices. The study also had no separate analysis for the nr-axSpA, which has

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a greater propensity of not showing any objective signs of inflammation or disease activity.

A retrospective study showed that plateletcrit was a positive marker of active inflammation, whereas MPV and PDW were negative markers in patients with rheumatoid arthritis [13]. Again, this study did not include PC among the indices.

Targońska-Stępniak et al [18] showed that in rheumatoid arthritis, PC and plateletcrit proved to be reliable positive markers of inflammation, and PDW was a negative marker. The study showed that these were inexpensive and reliable markers that correlated well with traditional inflammatory markers such as erythrocyte sedimentation rate (ESR) and CRP, clinical scores such as disease activity score and ultrasound findings and scoring (power Doppler ultrasonography) [18]. The study omitted MPV in its analysis. In patients with spondyloarthritis, platelets play a more central role in pathogenesis and are more likely to show an intimate relationship with disease activity than in patients with rheumatoid arthritis.

Kang et al [11] studied the correlation of platelet indices with inflammation markers and MRI findings in patients with axial spondyloarthritis. They found that platelet indices such as PDW and MPV may reflect the imaging changes on MRI. There was an inverse relationship between these indices and the disease activity. Inflammation suppressed the megakaryopoiesis, leading to decreased platelet size. Moreover, platelet consumption could have caused this observation. This relationship was even stronger in individuals with a shorter disease duration. As CRP levels and MRI findings are moderately correlated, biomarkers with better predictability are required. However, there were some drawbacks in the study as they included smokers, which could have altered the platelet indices, and they did not provide information on whether these findings were the same for both patients with AS and nr-axSpA.

Although there is ample literature focusing on platelet indices and their usability, reliability, availability, and low cost in the field of inflammatory rheumatological disorders, to date, no study has focused on their use in patients with nr-axSpA.

In this study, we will evaluate the viability of platelet indices in patients with nr-axSpA and determine whether they correlate with other objective evidence of inflammation, such as CRP levels and MRI sacroiliac joint findings, as well as clinical disease activity scores, such as BASDAI and ASDAS-CRP. Patients with nr-axSpA are expected to have a higher probability of having normal CRP levels and MRI findings. Therefore, this study is vital because this subgroup of patients has not been specifically studied previously, and there is a much greater need for alternative markers of disease activity in this subgroup.

Axial Spondyloarthritis Spectrum, Pathophysiology, and Differences

According to the literature, at least 10% of patients with nr-axSpA progress to r-axSpA or AS, as observed during a follow-up of 2 years [19,20]. There is evidence suggesting r-axSpA as a continuation of nr-axSpA, as MRI changes, such as bone marrow edema, transform into structural changes such as erosions and sclerosis, which are detected on X-rays. Reports suggest that some of these patients with nr-axSpA have a self-limiting phenotype that never progresses and, therefore, should not be considered the same as AS [10]. The term AS was coined in 1904 by Eugene Frankel and was perceived as a disease causing inflammation in the sacroiliac joint, further progressing to the spine, and causing fusion of the axial skeleton [21].

According to studies in China, Europe, and the United States, a variable number of patients (1%-60%) may progress over the course of 2 to 15 years. Approximately 30% of patients with nr-axSpA may never progress to AS despite high disease activity, raised ESR, or CRP levels [21]. The CORRONA (Consortium of Rheumatology Researchers of North America) study showed a higher prevalence of nr-axSpA among women. The French and German studies showed the same pattern. The female patients had less structural damage and more peripheral symptoms [21]. Although patients with nr-axSpA had less structural damage, they showed an equivalent burden of the disease in terms of disease activity indices, such as the BASDAI, and functional indices, such as the Bath Ankylosing Spondylitis Functional Index, pain, quality of life index, and fatigue. Some studies showed that patients with nr-axSpA have higher disease activity and lower quality of life than patients with AS. Hip arthritis was more prevalent in patients with nr-axSpA, and these patients had future complications related to joint replacement surgeries. The CORRONA study also showed that impairment of activity was much greater in patients with nr-axSpA [21].

Measuring Disease Activity

The main variables used are MRI findings and CRP levels. MRI can detect early inflammation in the sacroiliac joint compared to radiographic changes, which appear at later stages. Inflammatory lesions such as bone marrow edema are seen along the sacroiliac joint and vertebrae.

Pitfalls in CRP and MRI

There is some disagreement regarding the use of CRP level as a marker of inflammation. Some studies have shown that CRP levels do not correlate well with disease activity. Some patients may have elevated CRP levels despite having low disease activity, and vice versa. Lower CRP levels are found in Asians and in patients with nr-axSpA. Nr-axSpA predominantly affects female individuals with lower CRP levels. CRP levels may be normal in about 40% to 60% of patients with axial spondyloarthritis, and they may be easily affected by BMI, treatment, and obesity. Studies have shown that a single CRP level may be insufficient to label a person as CRP-negative, and repeat CRP levels may be required in such cases, adding to the cost of managing the disease. Finally, inflammatory markers have shown poor predictability for early sacroiliitis [7,21-23].

Limitations of MRI findings include the variability in time between the onset of structural damage and clinical features. Moreover, bone marrow edema may be observed in otherwise healthy individuals, athletes, and pregnant women. Furthermore, a lack of training of both radiologists and rheumatologists in interpreting the MRI findings and determining a clinic-radiological correlation also contributes to the

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underdiagnosis or overdiagnosis of spondyloarthritis [22]. In a unique way, patients with nr-axSpA may show erosions without bone marrow edema, suggesting that early intervention might affect how the disease evolves [10].

MRI findings should also be interpreted in a clinical context. The lesions are not specific for axial spondyloarthritis, and they can be seen in various other conditions that are mechanical in nature or may be just findings in an otherwise normal individual. A total of 30% of patients with axial spondyloarthritis who are HLA B27 positive may not show bone marrow edema. Studies have shown that positive MRI may be visualized in only up to 15% of men who are HLA positive. Higher erosion is observed in patients with nr-axSpA than in those with AS, whereas this is reversed in fat metaplasia, suggesting that the latter might be the cause of bony structural changes [10].

Both MRI and CRP levels are insufficient to evaluate the disease activity status in patients with axial spondyloarthritis, especially in patients with nr-axSpA. Therefore, there is a need to search for alternative biomarkers that are reliable, inexpensive, and correlate well with clinical disease activity.

Platelet Indices: Use as Inflammatory Markers

Platelet indices include various parameters related to platelets in the automated Coulter report of complete blood count. These different indices reveal various aspects of platelet morphology and kinetics. Different machines may provide different indices, with the key indices being PC, MPV, PDW, and plateletcrit. All these are readily accessible and require no extra cost from the patient. Many of these indices have been shown to be associated with inflammation in various inflammatory and infectious conditions [24].

Robinson et al [25] assessed RDW and MPV in patients with psoriatic arthritis and AS. The study showed significantly higher RDW and MPV in patients with active disease. A cutoff value of more than 12.4 for RDW had a sensitivity of 83% and specificity of 69%. In the case of MPV, a cutoff value greater than 8.4 had a sensitivity of 67% and specificity of 70%.

Byun et al [17] showed that PDW can be used as an alternate biomarker of active disease in cases of AS where conventional acute-phase reactants such as ESR and CRP are within normal range.

Kang et al [11] conducted a study on 161 patients with axial spondyloarthritis to correlate platelet indices with disease activity and MRI scores. They found that PC was positively correlated with sacroiliac bone marrow edema and disease activity. The platelet indices correlated well with the erosion score of sacroiliac joint MRI. However, the study also included smokers, which could be a confounding factor when measuring platelet indices.

All these previous studies had shortcomings in one way or another, as some did not include all platelet indices, some had confounding factors such as the inclusion of smokers, which themselves can alter the platelet indices, and some did not mention findings specifically for patients with nr-axSpA.

Biomarkers

According to the World Health Organization, a biomarker provides information on diagnosis, prognosis, or disease activity and may be biological, chemical, or physical. Currently, CRP level is the sole biomarker used in spondyloarthritis. Although the treatment escalation is based on CRP elevation, it is a marker of generalized inflammation rather than being specific for spondyloarthritis. Various biomarkers have been studied for similar purposes in patients with spondyloarthritis. They can be categorized into different subtypes, such as markers for inflammation, bone homeostasis, antibody-associated, microbiome-associated, genetic markers, and miscellaneous. Along with the CRP level, the CRP to albumin ratio has also been proven to correlate with the disease activity score in axial spondyloarthritis. Other inflammatory markers studied were serum amyloid A; pentraxin 3; ratio of fibrinogen to albumin; adipokines such as leptin and omentin 1; cytokines such as TNF-α, IL-6, IL-17, IL-22, IL-31, and IL-33; and markers of bone homeostasis such as sclerostin, bone morphogenic proteins, matrix metalloproteases, osteoprotegerin, vimentin, and osteocalcin. Among the miscellaneous markers, complement 3 has been shown to correlate with disease activity and cardiometabolic risk. Despite all the biomarkers that have been studied and shown to correlate with disease activity, few are used in day-to-day practice. Accessibility, cost, and efficacy in predicting outcomes are major barriers to using these biomarkers in clinical practice [26]. A study showed that serum fetuin A levels were lower in patients with radiographic sacroiliitis and can serve as a marker for more severe disease. However, they showed no such correlation with spinal involvement [27]. Other markers of endothelial dysfunction, such as interleukin 18, endothelin 1, and soluble intercellular adhesion molecule 1, showed positive correlation with CRP and ESR in patients with AS and psoriatic arthritis [28]. Certain immunological biomarkers have also been studied to determine the phenotypes of axial spondyloarthritis and its activity levels, such as interferon gamma, interleukin 10, interleukin 17A, interleukin 22, interleukin 17f, 23 anti-CD74, zonulin, and monocyte chemoattractant protein 1 [29].

Research Gap Analysis

Both AS and nr-axSpA show similar impact in terms of disease activity and functional deterioration [20]. Responsiveness to therapy depends on disease activity measured solely by CRP or MRI [7]. Research has been conducted to identify new markers of disease activity across various inflammatory diseases such as rheumatoid arthritis, scleroderma, AS, and systemic lupus erythematosus [13-18]. The research has shown that platelet indices are reliable and inexpensive markers of active disease. They are cheaper and as reliable as CRP for evaluating disease activity. Despite extensive literature showing that platelet indices can be used for measuring disease activity in numerous rheumatic conditions, no such literature is available for patients with nr-axSpA. The previous studies that tried to address this issue did not include all platelet indices in their analysis, and the final statistics did not show a separate analysis of the nr-axSpA group either. This group of patients invariably has lower levels of CRP; therefore, they may be more readily labeled as CRP-negative. Hence, it is imperative to establish

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new objective markers of inflammation that can be used on a day-to-day basis for quantifying the level of inflammation, especially in patients with nr-axSpA. This can lead to better management and prognosis, even in patients with clinical-serological desynchrony. This study would bridge the abovementioned gaps by evaluating patients with nr-axSpA and comparing them to patients with AS as well as controls, thereby showing stronger evidence of how platelet indices can differentiate between active and inactive disease. A comparison with other biomarkers and clinical disease activity indices can prove their application to be even better as stand-alone or composite markers of inflammation.

Aim

This study aimed to evaluate whether platelet indices are reliable biomarkers for measuring disease activity in patients with nr-axSpA.

Objectives

This study has the following aims:

1. To evaluate whether platelet indices can differentiate between active and inactive disease in patients with nr-axSpA.
2. To compare platelet indices with other proven measures of disease activity in axial spondyloarthritis, such as CRP levels and MRI findings.
3. To compare the systemic immune inflammation index (SII) with other clinical disease activity scores in patients with nr-axSpA.
4. To determine whether biomarkers such as the CRP to albumin ratio, complement 3, neutrophil to lymphocyte ratio, and platelet to lymphocyte ratio correlate with disease activity in patients with nr-axSpA.

Methods

Study Design and Duration

This cross-sectional, case-control study will be conducted from June 2024 to December 2027.

Ethical Considerations

This study received ethical clearance from the institutional ethics committee (Datta Meghe Institute of Higher Education and Research) on January 6, 2024 (DMIHER[DU]/IEC/2023/59). The study participants will be provided with a consent form in their native language and English explaining the study in detail. Participants' identification data will be kept confidential. The participants will have full autonomy to opt out of the study at any point.

Inclusion Criteria

All patients diagnosed with axial spondyloarthritis as per the ASAS criteria and who provide consent will be included in this study. The cases will be divided into 2 groups. The first group will consist of patients with nr-axSpA (patients not presenting with radiographic sacroiliitis as per the modified New York Criteria), and the second group will consist of patients with radiographic sacroiliitis (either bilateral grade 2 sacroiliitis or unilateral grade 3 sacroiliitis). Normal healthy individuals will be included as controls.

Exclusion Criteria

Patients with metabolic disorders; recent pregnancy; known cases of tuberculosis, brucellosis, or active infections; malignancy; trauma; crystal arthropathy; a history of vasculitis or hemoglobinopathies; smokers; patients on antiplatelet drugs; and those who do not consent to participate will be excluded.

Controls

Age and sex matched, relatively healthy individuals with no known diseases, and no factors affecting the platelet indices and other acute-phase reactants will be included as a control group.

A detailed history will be obtained from all patients. Convenience sampling will be performed, and participants will be recruited consecutively from outpatient clinics. Subsequently, all included patients (as per ASAS classification criteria) will be sequentially divided into group A (nr-axSpA) and group B (AS or r-axSpA) based on radiographic sacroiliitis as per modified New York criteria. The control group will consist of healthy individuals. Patients will be clinically evaluated for disease activity status as per BASDAI, ASDAS-CRP, and SII scores. For BASDAI, a score of 4 or more will be considered as active disease. For ASDAS-CRP, a score of 1.3 or less will be considered as inactive disease, 1.3 to less than 2.1 as low activity, 2.1 to 3.5 as high disease activity, and a score of more than 3.5 as very high disease activity. For SII score, calculation will be done by formula (PC × neutrophil count or lymphocyte count) and will be correlated with other established clinical disease indices, as SII does not have a defined cutoff value for spondyloarthritis [30,31]. Patients' blood samples will be collected for complete blood count (for platelet indices such as PC, plateletcrit, PDW, and MPV via Coulter reports), CRP via immunoturbidimetry, ESR (by Westergren's method), HLA B27 by polymerase chain reaction, and complement 3 via turbidimetry. Neutrophil to lymphocyte ratio (cutoff value of 1.95 for high or very high disease activity) and platelet to lymphocyte ratio (cutoff value of 115.6 for active inflammation) will be calculated from the CBC Coulter report. CRP to albumin ratio (cutoff value of 0.75 for active inflammation) will also be included. None of the blood samples are fasting samples. Subsequently, patients will undergo pelvic MRI that will be read by 2 radiologists with a minimum of 10 years of experience in inflammatory pathologies. Both radiologists will independently look for radiological evidence of active inflammation. Spondyloarthritis Research Consortium of Canada (SPARCC) scoring will be used to grade the inflammation of the sacroiliac joint via MRI. This scoring will take active lesions from the sacroiliac joint using T2- sequences from MRI. Coronal sections will be used to identify these lesions. Each sacroiliac joint will be divided into 4 areas. A score of 0 will be assigned to areas with a normal signal intensity, and a score of 1 will be assigned to areas with an increased signal. The joints having an increased signal will receive an additional score of 1, and if the depth of the lesion is >1 cm, then another additional score of 1 per slice will be assigned. This scoring will be performed for 12 slides, and the maximum score could be 72 [32]. Both the

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pathologists and radiologists will be completely blinded to the included participants' group. The MRI scoring will be done individually by 2 different radiologists. In the groups, the platelet indices (PC, plateletcrit, PDW, and MPV) will be compared with the levels of CRP, ESR, C3, neutrophil to lymphocyte ratio, platelet to lymphocyte ratio, CRP to albumin ratio, clinical disease activity scores (BASDAI, ASDAS-CRP, and SII), and with MRI-based SPARCC score.

Sample Size

Sample Size With Justification

Sample size has been calculated with the help of Epi Info (version 7.2.2.2; EPI INFO), which is a trademarked tool from the Centers for Disease Control and Prevention.

Robinson et al [25] reported that the sensitivity of MPV values greater than 8.4 femtoliters in AS was 67%. Thus, in this study, P=0.67. The number of participants required for this study will be 196.53 ~ 197, with a power of 90%.

The formula used for the sample size calculation is as follows:

Where

n = required sample size; P=0.67, as per the study by Robinson et al [25]; q = 1 - p; and L = precision = 10%/

Calculation

Here, P=0.67, q = 1 – P=0.33, and loss% = 10%.

Statistical Analysis

Statistical analysis will be performed with the help of Epi Info (version 7.2.2.2; EPI INFO), which is a trademark tool from the Centers for Disease Control and Prevention.

Descriptive statistical analysis will be performed to calculate the means with corresponding SDs. The test of proportion will be used to find the standard normal deviate (Z) to compare the difference in proportions. Chi-square test will be performed to determine the associations. The receiver operating characteristic curve will be used to find the area under the curve, followed by the Youden Method, which will use the cutoff value of different parameters for outcomes. These cutoff values will be used in multivariable logistic regression models to identify radiographic sacroiliitis and active disease. Sensitivity, specificity, positive predictive value, and negative predictive value will be calculated to determine the efficacy of the diagnostic tools. A P value of less than .05 will be considered to indicate statistical significance.

Categorical variables will be presented as numbers and percentages, and continuous variables will be presented as median and mean (SD). For assessing the correlation of platelet indices (PC, MPV, plateletcrit, and PDW), C3, CRP to albumin ratio, neutrophil to lymphocyte ratio, and platelet to lymphocyte ratio with other measures of disease activity, such as BASDAI, ASDAS-CRP, SII, and MRI sacroiliac joint SPARCC score, linear regression will be used (univariate and multivariate). Cohen κ statistic will be used to assess interobserver difference, or interrater agreement, by measuring the agreement between 2 radiologists.

Results

After approval from the ethics and scientific committees, data collection was started on February 1, 2025. As of July 25, 2025, 7 participants have been included in groups A and B each and 5 individuals in the control group. We expect to complete the study by December 2027 and publish the results thereafter by January or February 2028. This is a nonfunded study.

Discussion

Anticipated Findings

Nr-axSpA is often difficult to evaluate in terms of confident assessment of disease activity. Most of these patients have clinical symptoms without any objective signs in our daily markers of inflammation. Such cases pose a challenge for clinicians in determining whether to increase or change medications. Therefore, there is an urgent need to establish new and credible markers that are easily available and have a more central relationship with sacroiliac joint inflammation. Platelet indices available in the literature fulfill these parameters but are not yet included in the standard of care. This study seeks to probe this issue and provide a better understanding of whether platelet indices are valuable in real clinical scenarios.

Tian et al [33] conducted a literature review to see if CRP levels and MRI findings correlated with patients with axial spondyloarthritis. Eighteen studies involving more than 1300 patients were included in this analysis. Although CRP levels showed a good correlation with spinal inflammation on MRI, no such correlation was observed between CRP levels and sacroiliac joint inflammation.

Landewe et al [7] evaluated the possibility of patients with axial spondyloarthritis with an initial normal CRP being deemed CRP-negative, and subsequently presenting with a raised CRP the second time. A total of 106 patients were enrolled, and 25% of them had normal baseline CRP levels; 50% of these patients later showed elevated CRP levels (up to 16 weeks). The study emphasized the reevaluation of CRP levels after at least 4 weeks to confirm that the patient had normal CRP levels.

Rusman et al [34] evaluated the presence of MRI-based inflammation in patients with nr-axSpA who had high disease activity. SPARCC scoring was used to grade the inflammation on MRI of the sacroiliac joints and spine. A total of 69 patients were included in this study, and only 39% of them showed signs of active inflammation on MRI despite having high disease activity. Among patients who did not have any MRI lesions at baseline, 93% showed no signs even after 6 months, even though they had disease activity.

Magrey et al [21] elucidated that nr-axSpA represents a clear-cut phenotype with a disease burden similar to AS, and there is a lack of understanding of the severity of this phenotype even among rheumatologists. The deferral in initiating adequate

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treatment in such patients often leads to a decreased quality of life and an unwarranted delay in proper care. This study highlights the need to identify biomarkers to detect this phenotype early and to predict clinical responses to overcome these obstacles.

Byun et al [17] showed that CRP and ESR, although widely used as markers of inflammation in patients with AS, were not completely reliable due to false-negative and false-positive values. Platelet indices, such as PDW and PC, showed a good correlation with objective clinical disease activity scores such as BASDAI and ASDAS, and CRP. The study concluded that PDW is a suitable adjunctive marker of inflammation in patients with normal CRP levels.

Qian et al [35] evaluated patients of AS who were followed up for 6 months on anti-TNF therapy. These patients had higher PCs at the start of therapy than the controls, and they showed lower PCs on follow-up starting from the first month. Patients who did not respond to therapy had more PCs than those who did. PCs also correlated well with ESR and clinical disease activity scores.

Conclusions

This study is expected to provide a decisive answer to whether platelet indices can be used as reliable markers of active disease in patients with nr-axSpA, especially in those with conventional inflammatory markers within the normal range and normal MRI findings of the sacroiliac joints.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

SA contributed to conceptualization, formal analysis, project administration, and supervision. AKA contributed to conceptualization, investigation, formal analysis, and visualization. JB contributed to resources, software use, writing, and validation. SK contributed to project administration and conceptualization. NR contributed to investigation and formal analysis.

Conflicts of Interest

None declared.

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Abbreviations

AS: ankylosing spondylitis
ASAS: Assessment of Spondyloarthritis International Society
ASDAS: Ankylosing Spondylitis Disease Activity Score
BASDAI: Bath Ankylosing Spondylitis Disease Activity Index
CORRONA: Consortium of Rheumatology Researchers of North America
CRP: C-reactive protein
ESR: erythrocyte sedimentation rate
MPV: mean platelet volume
MRI: magnetic resonance imaging
nr-axSpA: nonradiographic axial spondyloarthritis
PC: platelet count
PDW: platelet distribution width
r-axSpA: radiographic axial spondyloarthritis
RDW: red cell distribution width
SII: systemic immune inflammation index
SPARCC: Spondyloarthritis Research Consortium of Canada
TNF: tumor necrosis factor

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Protocol

Determining the Feasibility and Usability of a Co-Designed Culturally Appropriate Conversational Agent (DESI-Heart) to Support Self-Care in People With Cardiovascular Diseases: Protocol for a Single-Arm Pilot Trial

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Abstract

Background: Cardiovascular diseases (CVDs) are a leading cause of death and disability worldwide. For people living with CVD, clinical guidelines recommend ongoing self-care such as symptom monitoring, medication adherence, and lifestyle modifications. However, many people struggle to engage in this due to the complexity of disease management, limited understanding, and a lack of cultural support. Conversational agents (CAs) offer a solution by providing artificial intelligence–driven, voice-based support that enables human-like communication. While many CAs and digital interventions are good for people with CVDs, they are for mainstream populations and overlook culturally and linguistically diverse communities.

Objective: This study outlines the protocol for pilot testing the feasibility and usability of Diaspora Engaged Self-Care Intervention and Heart (DESI-Heart) program, to support self-care management among Indian diaspora populations with CVDs in Australia over an 8-week intervention period. The formative development of DESI-Heart is also described.

Methods: We integrated the Double Diamond Model and the ecological validity model to develop our DESI-Heart program. First, we co-designed the program with end users, who identified 4 key goals for engagement with self-care through culturally and linguistically appropriate approaches. Based on these priorities and ideas, we developed specific goals, including (1) medication reminders, (2) daily exercise guidance, (3) diet buddy, and (4) guided meditation. Participants will access the DESI-Heart program through a web-based CA, available on smartphones, laptops, or PCs. Based on their preferred timing, individuals will receive links to access specific components of the program corresponding to each goal. These links will be sent to participants via SMS or email, depending on their preference. A single-arm prepost pilot trial (N=28) will be conducted to evaluate the feasibility and usability of the DESI-Heart program among Indian adults living in Australia with CVDs. The primary outcome will assess feasibility indicators, including recruitment, engagement, and usability, while secondary outcomes will examine changes in self-care behaviors and quality of life.

Results: The DESI-Heart program received ethics approval in July 2024. Recruitment for the pilot trial is scheduled to begin in June 2025 and conclude by September 2025, with participant follow-up expected to be completed by the end of December 2025. All 28 participants have been recruited, and data analysis will be conducted once follow-up is finalized.

Conclusions: We have co-designed and developed the DESI-Heart program, a culturally and linguistically appropriate self-care intervention aimed at supporting Indian adults with CVD living in Australia. The next step is to conduct a pilot study to assess the feasibility and usability of DESI-Heart, which will inform the design of a larger evaluation trial. DESI-Heart has the potential to complement existing health services by helping individuals with CVD manage their condition within the community, while acknowledging their cultural backgrounds and language preferences.

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KEYWORDS

conversational agent; self-care; cardiovascular diseases; culturally and linguistically diverse communities; digital health, technology; behavior change; methodological consideration; mobile phone

Introduction

Cardiovascular disease (CVD) is the leading cause of death and disability worldwide, contributing to approximately 32% of the worldwide mortality rate [1]. In Australia, CVD contributes 19% to the total disease burden and accounts for approximately 27% of deaths [2]. Clinical guidelines recommend continuous self-care, including symptom monitoring, medication adherence, and lifestyle modification for effective management of these conditions [3]. Self-care is associated with reduced cardiac mortality, hospitalization and readmissions, and increased quality of life [4,5]. However, many individuals often struggle to incorporate and maintain consistent self-care due to complex regimens, limited health literacy, and lack of access to health care support [6,7].

The widespread availability and integration of digital technologies has enabled the development of innovative interventions to support self-care for people living with CVD in the community [8]. A systematic review and meta-analysis (n=9893) found that digital health services, such as mobile health interventions, played a key role in supporting self-care. These interventions were associated with a significant reduction in pain (Hedges g=−1.09; 95% CI −1.68 to −0.45) and disability (Hedges g=−0.77; 95% CI −1.59 to 0.05) [9]. Despite their potential, maintaining long-term engagement with digital interventions is challenging [10] due to users' lack of health and digital literacy, privacy and security concerns, and the complexity of user interfaces [10-14].

Conversational agents (CA) have emerged as a promising solution to overcome some of these user and engagement barriers by leveraging artificial intelligence (AI)–based systems that use natural language processing, enabling human-like interactions with users [15,16]. CAs offer multiple advantages: (1) the ability to interpret human speech and respond to it in a personalized manner similar to human health care providers [17]; (2) the ability to integrate and connect with technologies (eg, sensors or wearable devices) to provide data driven self-care via a CA [18]; (4) reduce barriers around digital literacy for the user [19]; and (5) capacity to communicate in multiple languages and dialects [20]. However, most CA-delivered self-care interventions have not been developed or adapted to meet the unique needs of culturally and linguistically diverse (CALD) communities [21]. This limits their effectiveness, as cultural factors significantly influence health beliefs and self-management behaviors [22].

Within Australia, the Indian community represents the second-largest immigrant community group, comprising over 721,000 people [23], and this population is at higher risk for poor CVD outcomes, including cardiovascular events, all-cause mortality, and hospitalizations [24]. Additionally, research indicates that more than half of the Indian immigrant population remains closely connected to their cultural values and belief systems, which shape their lifestyle choices and self-care decisions [25,26]. These cultural influences highlight the importance of involving individuals with lived experience of CVDs in the product design process to ensure the development of culturally relevant materials for their use [27].

To address this gap in culturally appropriate CA interventions, we have co-designed a culturally tailored CA intervention (Diaspora Engaged Self-Care Intervention and Heart [DESI-Heart]) to support self-care among individuals with CVD from the Indian diaspora in Australia. DESI-Heart integrates cultural elements specific to Indian communities—including language preferences, traditional health practices, and culturally congruent communication styles. In this protocol paper, we present a comprehensive overview of the co-designed DESI-Heart program, detailing its design and development process guided by established cultural adaptation frameworks. We also outline the planned pilot study to evaluate its feasibility and usability, and potential impact on self-care outcomes.

The primary aim was to evaluate the feasibility and usability of a co-designed culturally tailored CA (DESI-Heart) in supporting self-care management among Indian diaspora populations with CVDs in Australia over an 8-week intervention period.

The primary objectives were (1) to determine participant recruitment rates, retention rates, and adherence to the DESI-Heart program; and (2) to assess the usability of the DESI-Heart program using validated measures of the Bot Usability Scale.

The secondary objective was to evaluate preliminary effects of the DESI-Heart program on changes from baseline to 8 weeks in CVD self-care behaviors and quality of life.

Methods

Overview

The reporting and structure of the protocol were guided by the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2025 statement and checklist [28] (Multimedia Appendix 1).

Study Design

Theoretical Framework

To inform the development of the DESI-Heart program, we used a combination of 2 theoretical frameworks: the Double Diamond Model (DDM) and the ecological validity model (EVM) [29]. The DDM focuses on providing a well-defined

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and comprehensive representation of design progress in developing novel interventions [30]. The DDM comprises 2 adjacent diamonds, and each diamond represents the process of exploring a problem broadly (divergent thinking) and the process of taking action to resolve the identified problem (convergent thinking) [31]. The DDM model has 4 processes distributed across these 2 adjacent diamonds. The first diamond is termed the problem phase, which consists of two major processes: (1) discover and (2) define. The second diamond is the solution phase, consisting of the other two processes, which are (3) develop and (4) deliver [32]. While the DDM provided the structured design approach, we integrated the EVM specifically to enhance cultural appropriateness and relevance. The EVM model has been used as an effective framework to guide culturally adapted interventions by increasing the ecological and external validity of the intervention [29]. To operationalize this framework, EVM encompasses eight cultural dimensions, which include (1) language used, (2) attributes of persons involved, (3) incorporation of metaphors, (4) identifying content, (5) understanding concepts, (6) achieving culturally adaptive intervention goals, (7) methods involved in intervention, and (8) context of the intervention [29,33]. To address the discover, define, and develop phases, we conducted a co-design study with end users—individuals from the Indian diaspora living with CVDs—using steps 1 to 6 of the EVM process. The deliver phase will involve developing a protocol to test the feasibility, usability, and acceptability of the DESI-Heart program, using steps 7 and 8 of the EVM process (Figure 1).

Figure 1. Logic flow of this study's framework. CA: conversational agent; CALD: culturally and linguistically diverse; CVD: cardiovascular disease; DESI-Heart: Diaspora Engaged Self-Care Intervention and Heart; EVM: ecological validity model.

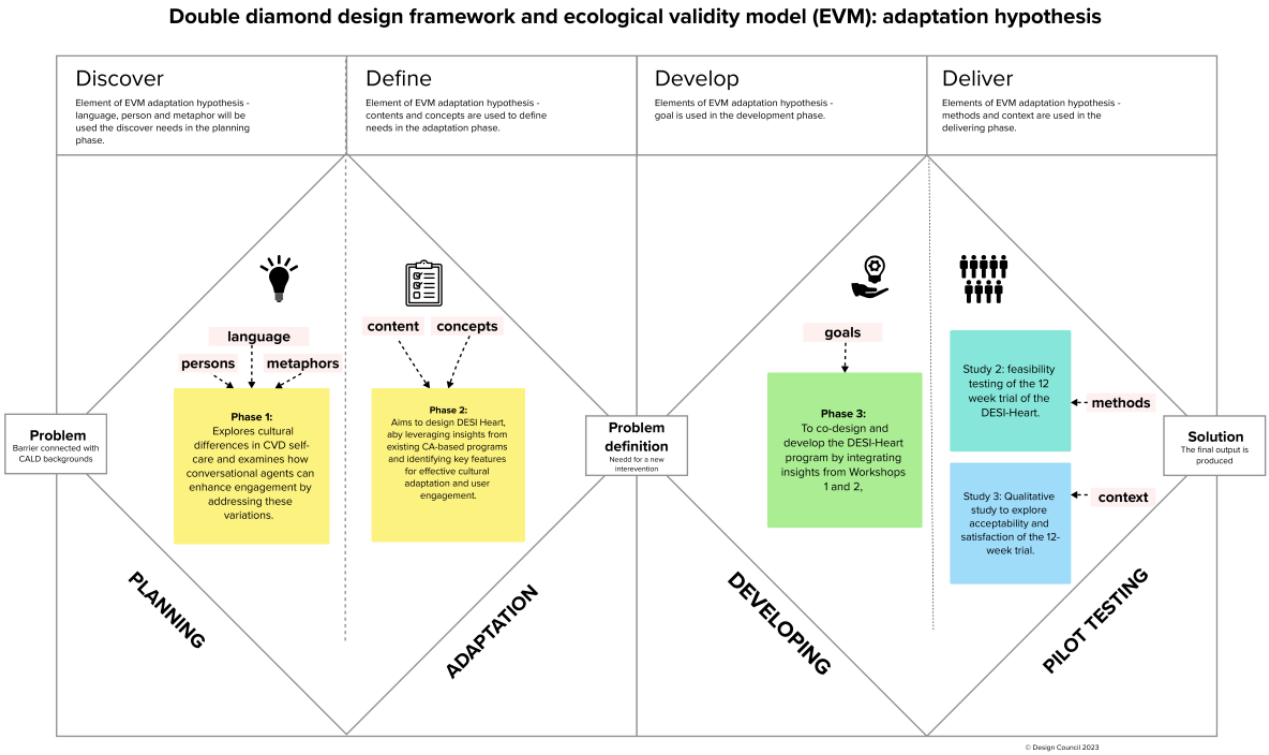

About CA

The intervention will be delivered using BuddyLink (Great Australian Pty Ltd), a research-grade, AI-enabled CA designed for developing and delivering interventions across various health care contexts [34]. BuddyLink is a validated platform for developing CAs, hosted in secure Australian data centers. The program relies on hard-coded, text- and logic-based conversations, with no AI or large language model principles underpinning its design. However, the current BuddyLink version uses AI in two assistive ways: (1) optional audio transcription or translation with transparent accuracy display, and (2) matching participant free-text inputs to predefined response options. BuddyLink has a proven record of secure, ethics-approved use across government, education, and health care projects, including health research at Deakin University [17,35].

Co-Design Results

In DESI-Heart, 4 major goals or modules were identified through co-design workshops with end users: medication reminders, daily exercise activities, diet buddy support, and guided meditations. Each component was specifically developed to address key self-care challenges identified by the Indian diaspora living with CVD (Figure 2).

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Figure 2. Screenshots of the DESI-Heart conversational agent. DESI-Heart: Diaspora Engaged Self-Care Intervention and Heart.

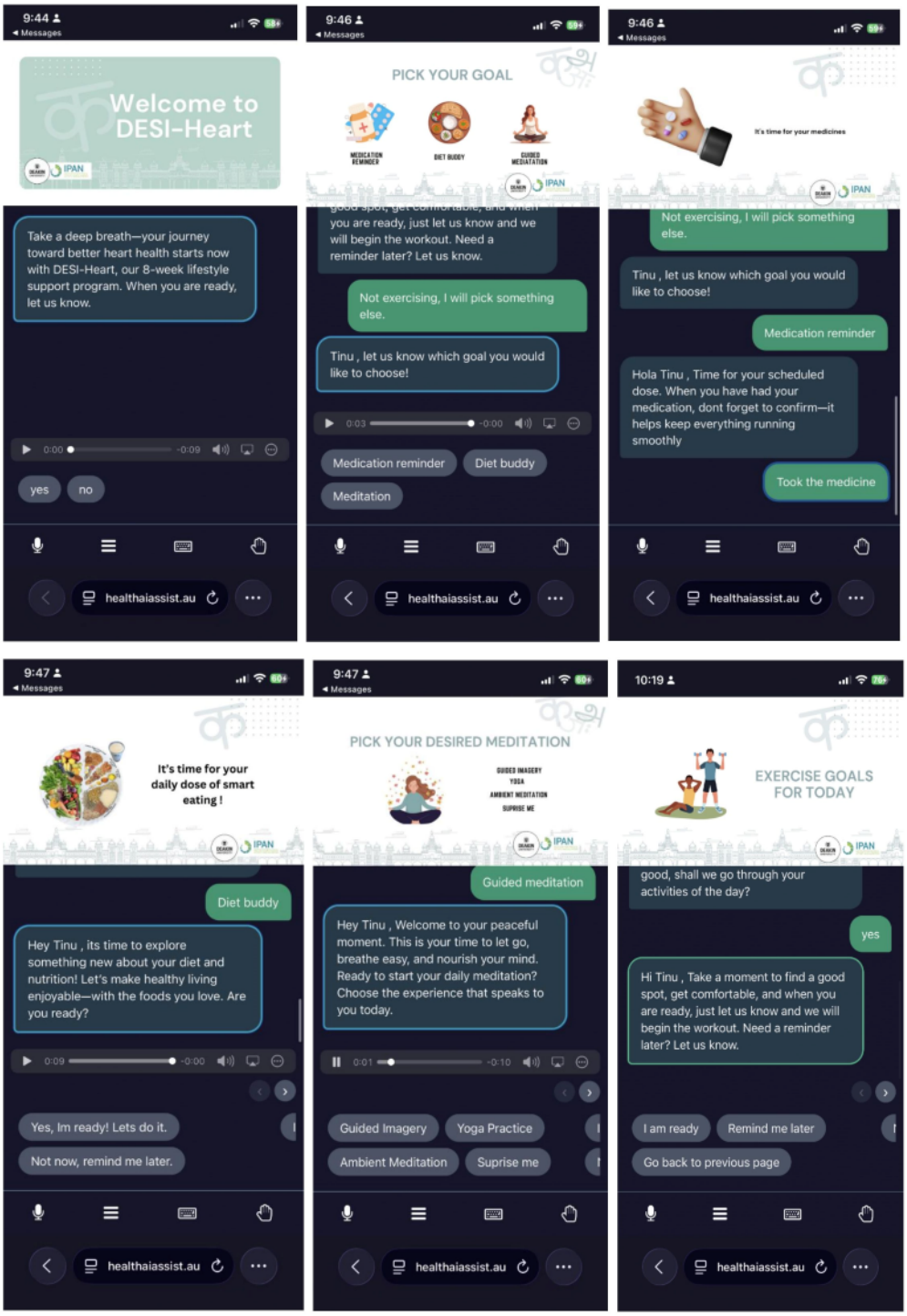

The medication reminders will support participants by providing timely alerts to take their medications. Additional features will include the ability to reschedule medication times, snooze reminders, and set alerts for medical appointments and diagnostic tests. Reminders will be scheduled according to the participant's preferred times. If there are any changes in medication timing or if new medications are added during the program, participants can request updates in their program by informing the research team. The system does not prescribe medications, but only provides reminders, which will also be integrated with the participant's Google Calendar, allowing them to track their medication schedule alongside other daily activities. However, participants will not have control over modifying this calendar, as it will function as a subscription calendar managed and updated by the research team.

The daily exercise component of the program is designed to support participants in meeting the Australian Physical Activity Guidelines, which recommend at least 150 minutes of moderate

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to vigorous physical activity per week, spread over 5 days or sessions [36]. To help achieve this, the DESI-Heart exercise program offers short, tailored workout sessions that include clear instructions and demonstrations, prerecorded by trained professionals. Participants will receive tailored exercise videos (≈2 minutes each) based on their preferred time of day. Each exercise will be delivered in 3 sets, scheduled across 5 days per week. Additionally, individuals with specific physical conditions will have access to condition-specific exercises to ensure the content remains safe, relevant, and appropriate for their needs. These exercise sessions are designed to resonate with the Indian community by incorporating culturally relevant content, speech, and delivery style. The demonstrations are led by trained professionals who reflect the participants' cultural background. This approach was recommended by participants during the co-design workshops, as they expressed a desire for a sense of belongingness with a supportive, familiar presence during their engagement with the program.

Diet buddy is a nutrition education component designed to align with CVD-related dietary recommendations. This feature draws on resources from the recently updated Australian Dietary Guidelines and Australian Guide to Healthy Eating [37]. The content has been culturally adapted to reflect the diverse dietary habits commonly observed among Indian Australian communities. It incorporates both northern and southern Indian food practices alongside typical Australian food practices, ensuring that the program is relevant, inclusive, and accessible to participants from different regional and cultural backgrounds. Delivered gradually over 8 weeks, the program offers culturally tailored content on each food group based on the Australian Guide to Healthy Eating series, including hydration-related guidance and education on healthy sources of protein, fiber, and fats. It also includes convenient and budget-friendly meal and snack plans, meal plating strategies, structured meal plans, a recipe matrix, and practical guidance on incorporating phenolic compounds, polyphenols, and plant sterols to support healthier eating habits. Each week will focus on one of these components over the 8 weeks to ensure thorough education and help inform participants' dietary practices.

Guided meditation is a key wellness component of the DESI-Heart program. Psychosocial stress is a commonly identified risk factor for CVD, and previous studies have shown that various forms of meditation and yoga can be effective in managing stress and improving CVD outcomes [38]. This component includes several modules, such as guided meditation, mindfulness breathing, and yoga, all of which are prerecorded with clear instructions and guidance from trained professionals. During the intervention period, participants will receive 1 meditation-based (≈10 minutes per meditation) session per day delivered via CA, over 8 weeks. The specific content, duration, and delivery times will be tailored to each participant's requirements. As with other components of the program, these materials are designed to resonate with the Indian community by incorporating culturally relevant content, language, and delivery styles to foster more engagement and appropriateness of the content.

Study Overview

An 8-week single-arm prepost pilot trial will be conducted. Participants will receive a personalized DESI-Heart program, which includes the 4 core modules described above, delivered via the CA at their preferred time of day. All assessments will be administered through web-based questionnaires at baseline and at the end of the 8-week program.

Sample Size

Preliminary calculations using G-power indicated that a total of 28 participants will be sufficient to allow an (estimated) proportion of 80% for recruitment to be estimated with a 95% CI of ±15%.

Participant and Recruitment

Participants will be adults (18 years and older) living with CVDs, including hypertension, heart failure, atrial fibrillation, coronary heart disease, or peripheral artery disease, and currently residing in Australia. Participants will also have to natively speak any Indian language apart from English; have access to the internet and a smartphone, tablet, or PC.

Participants will be excluded if they (1) have severe symptoms classified as New York Heart Association Class IV, a recent myocardial infarction or unstable angina, were referred to a cardiac transplant unit, or were in palliative care; (2) have severe chronic pulmonary disease; (3) live in a long-term care facility; (4) are unable to participate fully in this study for other reasons, including dementia, life-threatening comorbidities, or psychiatric disorders; and (5) did not identify themselves as part of any Indian community living in Australia. Participants will be recruited via social media (eg, Facebook [Meta]) and through Indian cultural associations, religious organizations, and community networks. To increase accessibility for less digitally literate or socially isolated individuals, we are also promoting this study via faith-based and community organizations, appealing to primary caregivers, and advertising at community gathering places.

Procedure

After participants have provided informed consent, researchers will schedule a Zoom (Zoom Communications, Inc) or phone call based on participants' preferences to complete the baseline data assessment. The baseline data assessment will include validated measures of self-care behaviors and quality of life, specifically: Medication Adherence Report Scale-10 [39], Godin Leisure-Time Exercise Questionnaire [40], Cardio-Med Food Frequency Survey Tool [41], and Self-Care Inventory [42]. During this session, participants will provide their sociodemographic details and medication history (Textbox 1).

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Textbox 1. Feasibility and usability criteria and metrics.

Green

- If one or more of the green criteria are met, this study will be considered feasible in its current form:
  - At least ≥80% of the target sample size is recruited and enrolled in the Diaspora Engaged Self-Care Intervention and Heart (DESI-Heart) program within 3 months [35]
  - At least ≥80% of participants remain in the DESI-Heart program [43]
  - At least ≥66% of participants completed the set goals delivered via the DESI-Heart program [44]
  - Attrition ≤20% [45]
- Conversational agent (CA) will be considered usable if the Bot Usability Scale score is >70 [46].

Amber

- If one or more of the amber criteria are met, this study will be considered likely feasible:
  - 50%-79% of the target sample recruited within 3 months
  - 60%-79% of participants remain in the DESI-Heart program
  - 50%-65% of participants completed the set goals delivered via the DESI-Heart program
  - Attrition: 20.1%-35%
- CA will be considered moderately usable if the Bot Usability Scale score is between 51-69.

Red

- If one or more of the red criteria are met, this study will be considered not feasible in its current form:
  - <50% of the target sample recruited within 3 months
  - <60% of participants remain in this study at 8 weeks
  - <50% of participants completed the set goals delivered via the DESI-Heart program
  - Attrition >35%
- CA will be considered not usable if the Bot Usability Scale score is 50 or below.

Participants will complete a comprehensive online orientation conducted by the researcher, covering this study and its features as part of the DESI-Heart program. For medication reminders, participants will be asked to specify the times and durations for which they would like to receive notifications. In addition, they can opt to receive reminders for medication refills, upcoming general practitioner consultations, or scheduled diagnostic tests, if they choose to include these in their medication reminder goals. For physical activity and guided meditation, participants can select their preferred duration, schedule a time for meditation, and choose the intensity of exercise. For diet buddy, participants can select the time they prefer to receive the prompts and share relevant health information (age and conditions) to receive customized nutritional guidance tailored to their specific needs.

After completing the baseline questionnaires, the platform's analytics system tracks user engagement metrics, including session frequency, duration, and completion patterns, to identify engagement barriers and inform future intervention refinements. By clicking the link, they will be directed to a web page where they can interact with the CA and access the program content. These links allow participants to access the intervention at any time. Upon accessing the platform, participants can select and complete goals of their choice, including revisiting missed goals or engaging with additional goals at the designated time. Participants will also have the option to choose their preferred language—English or one of several Indian languages (Hindi, Punjabi, Gujarati, Kashmiri, Bengali, Kannada, Tamil, Malayalam, and Telugu). Researchers will assist with the initial setup and help resolve any technical issues. Content will be delivered 4-5 times per day, 5 days a week, through prompts sent to participants' mobile phones or emails at their preferred times. Each prompt will include a link to a specific goal-based dialogue with the CA on the BuddyLink platform.

For each self-care component, the system will deliver culturally tailored instructions and demonstrations followed by questions to determine whether participants completed the activity, their experience, and if they had any concerns. Participants' responses to these questions will be recorded and saved to the BuddyLink database, enabling the research team to review weekly and modify content as required. During this period, researchers will check in via telephone weekly with participants to address any technical support needs.

After participants complete the 8-week DESI-Heart program, researchers will assist them in completing the follow-up post-study questionnaires online via Zoom. These will include all the questionnaires administered at baseline, minus the demographic questions. Additionally, participants will complete

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the Bot Usability Scale to report their perceived usability of the DESI-Heart program [46]. During pretesting, we observed that participants will be able to complete the full set of pre- and post-study questionnaires, including instructions, response time, and short breaks, within approximately 50 minutes. This supports the feasibility of administering the selected outcome measures without placing excessive burden on participants. Upon completion of the pilot study, participants will be remunerated for their time and involvement in the study (Figure 3). Subsequently, participants will also participate in an exit interview to better understand their perceptions of the DESI-Heart program, their level of satisfaction, and acceptability.

Figure 3. Overview of DESI-Heart study protocol. CVD: cardiovascular disease; DESI-Heart: Diaspora Engaged Self-Care Intervention and Heart.

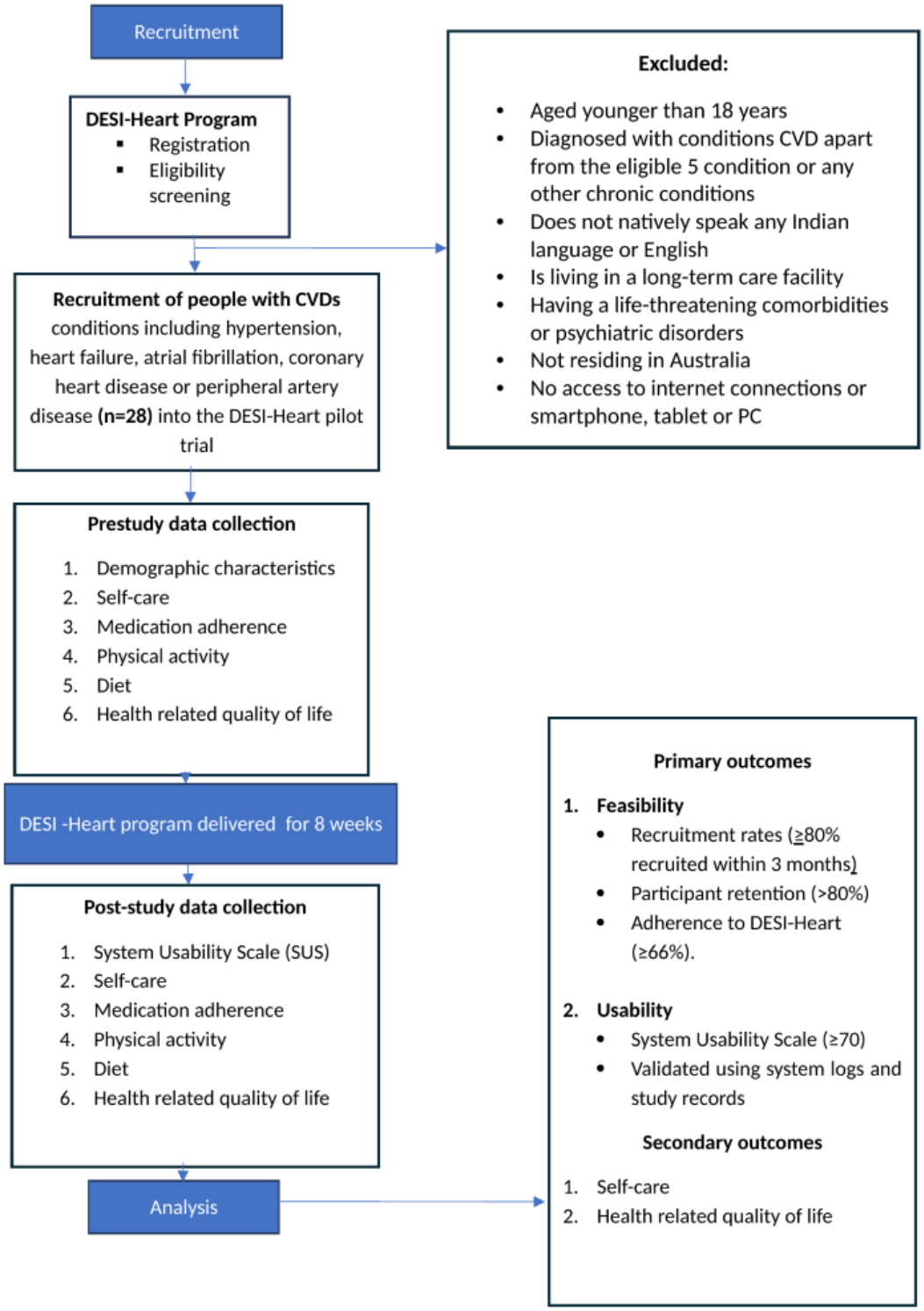

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User Testing

Before the commencement of this study, the platform was user-tested by research team members and volunteers over 2 weeks on both iOS (Apple Inc) and Android (Google LLC) operating systems. Feedback from this testing informed revisions to notification texts (via text messages and emails), improvements to navigation, adjustments to the user interface, and resolution of technical issues.

Outcome Measures

The feasibility of this study will be measured using recruitment rates, participant retention, completion of the prescribed self-care program, and attrition. Feasibility will be assessed using criteria outlined in Textbox 1, informed by previous studies [35,43-45] and a "traffic light" system [47], to ensure transparent and standardized progression to a definitive trial. Usability will be assessed by the Bot Usability Scale [46]. Participant scores will be cross-validated with system logs and study records capturing interaction history, which will be accessible through BuddyLink. The usability of the DESI-Heart program is defined as a score of 70 and above, which corresponds to a percentile of 70%, indicating high perceived usability [46].

The secondary outcomes include changes (from baseline to 8 weeks) in participants' self-care behaviors and quality of life as reported above (Table 1).

Table 1. Baseline and follow-up measures.

Assessment or procedure	Screening	Stage 1 (1 week)	Stage 2 (8 weeks)
Procedures			
Informed consent	✓	✓	✓
Demographic information	✓	✓	✓
Medication Adherence Report Scale-10 [39]		✓	✓
Godin Leisure-Time Exercise Questionnaire [40]		✓	✓
Cardio-Med Food Frequency Survey Tool [41]		✓	✓
Self-Care Inventory (SCI) [42]		✓	✓
Assessments			
World Health Organization Quality of Life (WHOQOL) [48]		✓	✓
Chatbot Usability Scale [46]			✓

Data Analysis

For the primary outcomes (recruitment, retention, program completion, attrition, and usability), the analysis will focus on reporting the observed frequencies and rates. For secondary outcomes, changes in quantitative measures between baseline and 8-week follow-up will be analyzed using paired-sample *t* tests (2-tailed). Analyses will be based on the normality of the data, and if parametric assumptions are not met, data transformation will be considered to better satisfy these assumptions. All analyses will be conducted using Stata (Version SE V.17.0; StataCorp). Data will be stored in the Qualtrics secure firewall-protected server hosted by Deakin University. Subsequently, the data will be transferred to a Deakin-managed Syncplicity server, and the data will be permanently deleted from Qualtrics.

Ethical Considerations

This study received ethics approval from the Royal Melbourne Hospital Human Research Ethics Committee (HREC/76317/MH-2021) for all procedures involving people living with CVDs. For this project, the platform operates as a dedicated instance with encrypted data storage, strict role-based access, and no local software requirements beyond a modern web browser. Personal identifiers or sensitive health data will not be collected; researchers can link participants only through nonidentifiable IDs, ensuring anonymity. Voice recordings are not stored, and transcriptions or logs can be deleted at any time upon request. End users retain full rights to access, correct, or delete their data via the platform's privacy portal. Messages and email links sent to participants are delivered via the BuddyLink platform solely to provide access to the intervention. Upon completion of this study, participants' mobile numbers and email addresses will be permanently deleted from the BuddyLink platform. The shared subscription calendar is independently hosted via Google Calendar. It will be sent to participants for download into their own calendars, and no information will be transferred to or shared via BuddyLink.

Before enrollment, all participants will be provided with a plain language statement outlining this study's purpose, procedures, potential risks and benefits, the use of CAs and optional AI-enabled features, and how their data will be managed. Participants will be able to ask questions and receive clarification from the research team before deciding to participate. Informed consent will be obtained through an online consent form. Each participant will be provided with a AUD $100 (US $66.50) Woolworths Essentials gift card as compensation upon completion of the study. The datasets generated and analyzed during this study will be securely stored on the Deakin-managed Syncplicity server. These data will not be publicly available but may be made accessible by the primary investigator upon reasonable request and with approval from the Royal Melbourne Hospital Human Research Ethics Committee. To disseminate the findings, a summary of the results will be emailed to participants and presented to research teams. Findings will also be shared with the scientific

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community through peer-reviewed publications and conference presentations.

Results

Recruitment for the pilot trial was scheduled to begin in June 2025 and concluded by September 2025. Participant follow-up will be completed by the end of December 2025. All 28 participants have now been recruited, and data analysis will be conducted once follow-up is finalized. Upon completion of data analysis, the findings from the pilot study will be submitted for publication.

Discussion

Principal Findings

This article outlines the protocol for pilot testing for the feasibility and usability of the DESI-Heart program, a systematically co-designed, culturally tailored CA designed specifically to support self-care management among Indian diaspora populations with CVDs in Australia. This innovative digital health solution addresses a critical gap in culturally appropriate self-care support for people living with CVDs belonging to different CALD backgrounds.

Through the advancement of natural language processing, AI, voice recognition, and large language models, CAs have become increasingly integrated into health care and health management [49]. These technologies offer scalable and cost-effective solutions that can provide medical support anytime through smartphones, mobile apps, or web-based platforms [50]. Evidence suggests that CA-based interventions can significantly support both patients and clinicians by assisting with specific tasks and processes [44]. Multiple CA-based interventions have demonstrated improvements in enhancing self-care behaviors, such as increased physical activity, healthier dietary habits, and better medication adherence [51]. However, much of the existing research and development has focused on the general population, with limited attention given to CA systems tailored for CALD communities [52]. Cultural beliefs and practices are deeply incorporated into everyday lives and affect how individuals approach self-care [22]. Due to these cultural differences, individuals from CALD communities often face additional challenges in navigating self-care. Their native cultural beliefs and practices may differ significantly from those of the host culture, leading to confusion, strain, or reduced engagement with mainstream health services [53,54]. This cultural disconnect can ultimately contribute to health disparities and poorer CVD outcomes among immigrant populations.

To address this gap, we applied DDM and EVM as cultural adaptation frameworks to guide the development and design of a culturally appropriate, CA-based CVD self-care management program. This methodologically rigorous approach ensured that cultural considerations were central rather than peripheral to the intervention design process. Through co-design workshops with end users, we identified key features to enhance the program's cultural relevance, gathered ideas to improve cultural appropriateness, and received suggestions to increase participant engagement with the culturally appropriate self-care intervention.

DESI-Heart program—includes 4 carefully designed core modules (medication reminders, physical activity support, dietary guidance, and stress management through meditation). The content has been specifically developed to resonate with the Indian community by incorporating culturally relevant examples, familiar language patterns, and delivery styles that align with cultural norms, in order to foster engagement and enhance content appropriateness. This program also provides access to DESI-Heart in multiple Indian languages, increasing the accessibility of support to those who speak languages other than English.

By providing culturally and linguistically appropriate self-care information and support, the DESI-Heart program aims to increase engagement in self-care behaviors that are culturally meaningful and sustainable. The CA used in this study has been designed to be user-friendly across varying levels of digital literacy, addressing a known barrier to digital health adoption among older adults and immigrant populations. It incorporates advanced voice recognition technology capable of understanding diverse accents, dialects, and several Indian languages, ensuring accessibility for a broader range of participants. Participants can interact with the CA either through voice commands or touch, allowing flexible access to care based on their preference. This makes DESI-Heart a more inclusive and accessible CA-delivered CVD self-care management tool, particularly when compared to existing CA interventions that often lack cultural tailoring [15,52]. Moreover, DESI-Heart supports participants in integrating their own cultural beliefs with key aspects of the host country's health care norms. This dual approach not only enhances the effectiveness of the intervention for CALD communities but also positions DESI-Heart as a model for culturally responsive digital health support.

Despite its innovative features, several important limitations of the DESI-Heart program warrant acknowledgment. While the program was designed based on general Indian cultural values, it did not fully account for the regional and linguistic diversity that exists within the Indian community, particularly the differences between northern and southern cultural practices. These regional variations can significantly influence health-related behaviors, beliefs, and preferences [55], which may affect the program's relevance and effectiveness for some participants. Additionally, as a pilot feasibility study with a relatively small sample size and single-arm design, this investigation cannot definitively evaluate efficacy outcomes. The current inclusion criteria limit the program's inclusivity, as participants with severe conditions or those residing in care facilities were not included, which may affect the interpretation and applicability of the findings.

Findings from this pilot study will offer critical insights to guide the design of a future, fully powered efficacy trial. These will include broader eligibility criteria, refined recruitment strategies, enhancements to CA-related features and functions to improve engagement, and tailored delivery preferences for specific participant subgroups, thereby strengthening the generalizability of the results. Future studies could also focus on specific ethnic

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groups with similar cultural and linguistic backgrounds to provide more targeted and appropriate support. Additionally, trial findings may guide the implementation and adaptation of this approach for CVD management services within other CALD communities, supporting their specific cultural needs and requirements while making health care more accessible, appropriate, and equitable. The knowledge generated may also contribute to a broader understanding of how to effectively incorporate cultural elements into digital health interventions.

Conclusions

The DESI-Heart program is a culturally and linguistically tailored self-care intervention designed to support Indian adults living with CVD in Australia. Through co-design workshops, end users identified 4 key goals to enhance self-care engagement by incorporating culturally relevant activities, knowledge, and content aligned with their cultural identity and linguistic preferences. This protocol outlines a pilot study to assess the feasibility and usability of the program, which will inform the design of a larger evaluation trial. Based on insights gained from this pilot study, future studies will incorporate comparator groups to rigorously assess the program's efficacy. This approach has the potential to strengthen existing health care services by providing more inclusive and accessible support for CALD populations.

Acknowledgments

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Authors' Contributions

ATS, PJ, and RM provided significant contributions to this study's design. ATS, ELN, and SD were involved in developing, recording, and finalizing the content for the intervention. ATS drafted this paper. All authors reviewed multiple revisions, provided feedback and edits, and approved the final version for submission.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT 2025 checklist: recommended items to address in a clinical trial protocol and related documents.
[PDF File (Adobe PDF File), 181 KB - resprot_v14i1e78923_app1.pdf]

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Abbreviations

AI: artificial intelligence
CA: conversational agent
CALD: culturally and linguistically diverse
CVD: cardiovascular disease
DDM: Double Diamond Model
DESI-Heart: Diaspora Engaged Self-Care Intervention and Heart
EVM: ecological validity model
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Validation and Testing of a Suicide Prevention Program in Preventing Suicidal Ideation and Improving the Mental Well-Being of School-Going Adolescents: Protocol for a Pre-Post Intervention Study

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Abstract

Background: Globally, around 800,000 people die by suicide annually, with 77% of these deaths occurring in low- and middle-income countries. Suicidal ideation, frequently observed among adolescents, is directly linked to suicide attempts. Pakistan has witnessed a marked escalation in suicide rates in recent years, with Gilgit-Baltistan (GB) reporting the highest incidence. Extensive research indicates that tailored suicide prevention strategies can mitigate suicidal ideation, attempts, and related fatalities.

Objective: This study aims to validate and evaluate the efficacy of suicide prevention programs, RAAHI (the guide) and safeTALK, tailored to the cultural and social context of GB, Pakistan, in preventing suicidal ideation and improving the mental well-being of school-going adolescents.

Methods: The investigation will assess the efficacy of the RAAHI intervention among 267 adolescents across 4 private schools in GB using an interrupted time-series design with a pre-post test framework. The first intervention, RAAHI, a suicide literacy module, is designed to empower participants with the knowledge and skills to recognize signs of suicidal ideation, engage them empathetically, and connect individuals in crisis with appropriate support. The second intervention, safeTALK, a 4-hour educational workshop, incorporates presentations, videos, discussions, and interactive sessions to teach participants the tell, ask, listen, and keep safe steps. Outcome measures include changes in knowledge, confidence, willingness to intervene, and help-seeking behaviors, analyzed using descriptive statistics, 2-tailed paired *t* tests, and ANOVA. Ethics approval was granted by the Aga Khan University Ethics Review Committee (2023-8509-24844).

Results: As of April 2025, 267 participants have been recruited from 2 of the 4 schools; data collection commenced in March 2025 and is projected to conclude in August 2025. Final results are expected to be published by February 2026.

Conclusions: This study will offer critical insights into the adaptation and effectiveness of the RAAHI suicide prevention intervention in a low-resource, culturally specific setting. The findings are anticipated to inform scalable suicide prevention initiatives in school settings across Pakistan and similar low- and middle-income contexts, ultimately contributing to reduced suicidal ideation and attempts among adolescents.

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KEYWORDS

prevention program; strategies; intervention; measures; mental well-being; mental health; psychological health; adolescent; teenage

Introduction

Background

Suicide is a notable global public health concern, resulting in a staggering number of fatalities annually [1]. It ranks among the 5 leading causes of death, representing more than one-third of all fatalities [2]. The rising global suicide rate, surpassing 800,000 deaths annually, underscores the urgency of addressing this critical public health concern [3]. In Australia, suicide is the leading cause of death among individuals aged between 15 and 24 years, with an annual rate of 11.6 deaths per 100,000 population [4]. Moreover, each suicide case potentially corresponds with more than 20 attempted suicides, emphasizing the urgent need for suicide prevention interventions. The World Health Organization [3] suggests an alarmingly high prevalence of suicidal ideation, encompassing nonfatal suicide attempts and self-harm. This tragic occurrence is widespread across the globe, with 77% of suicides taking place in low- and middle-income countries (LMICs) [2].

In addition, on a global scale, suicide ranks as the fourth leading cause of death for adolescents and young adults aged between 15 and 29 years [5]. Over the past 5 years, the United Arab Emirates has recorded the highest rate of suicides globally (11.4%), followed by the United Kingdom (10.80%), Nepal (10.33%), the United States (8.9%), and Pakistan (7%) [6]. Within the spectrum of mental health disorders, suicide emerges as the foremost cause of violent death, even among the economically active age group of people aged between 15 and 44 years [6]. According to a meta-analysis, 22.3% of college students at some point in their lives had suicidal thoughts, plans or made attempts [7]. In addition, a survey of 8113 high school students in Hawaii found that 16.4% of the adolescents reported having suicidal thoughts, and nearly 10% acknowledged having attempted suicide at least once in their lives [8].

Adolescents are highly susceptible to mental health problems due to academic stress, interpersonal issues, and the transition to adulthood; all of these factors exert substantial influence on their physical, emotional, social, and mental well-being [9]. In Pakistan, these challenges are exacerbated by social and cultural pressures, mental health being considered a stigma, and limited access to treatment, which impacts social functioning and academic success, with long-term consequences [10]. Evidence indicates that adolescents susceptible to self-harm often refrain from seeking support from parents or professionals; instead, they turn to their peers for assistance [11], who, due to their limited experience and knowledge, are usually not able to provide the required assistance.

Mental well-being signifies flourishing across emotional, psychological, and social domains, characterized by satisfaction, resilience against adversity, a sense of purpose, positive feelings, and the capacity for meaningful connections and activities [12]. Given the significance of mental well-being for adolescents and the concerning prevalence of mental disorders within this demographic, prioritizing mental health interventions tailored to address the unique needs and concerns of this demographic is essential due to the high burden of mental disorders prevailing in this age group [13]. Numerous suicide prevention programs aim at enhancing skills in identifying and supporting individuals at risk while also improving their self-efficacy, mental health literacy, and attitudes [14]. The enhancement of self-efficacy and mental health knowledge is linked to increased resilience in youth, fostering a sense of control, thereby significantly reducing the likelihood of engaging in suicidal ideation [15].

Increasing evidence suggests that school-based suicide prevention interventions are effective in their approach [11]. Such interventions span various levels of prevention, encompassing primary efforts, such as public awareness campaigns; secondary approaches, such as gatekeeper training programs; and tertiary interventions, such as psychotherapy and postvention strategies, including survivor support groups. Similarly, expanding the conventional classification of mental health interventions, suicide prevention strategies can be categorized into universal (targeting the public) or selective (aimed at specific high-risk groups with elevated lifetime risk, such as adolescent and psychiatric inpatients) [16].

A systematic review of 13 randomized controlled trials (RCTs) reported that the risk of suicide-related behavior among youth exposed to an educational intervention was 0.31 times lower compared to those in the unexposed group [17]. Similarly, another review of 14 studies assessing the impact of school-based gatekeeper training revealed enhancements in gatekeepers' knowledge, attitudes, self-efficacy, and inclination to intervene [18]. An RCT of the Signs of Suicide program showed a decrease in suicide attempts over a 3-month period [19]. Moreover, a large-scale RCT of a Youth Aware of Mental health program, involving more than 11,110 secondary school students across 10 European countries, revealed a 55% reduction in incidents of suicide attempts and a 50% decrease in severe suicidal ideation compared to control groups at 12 months after intervention [20].

In Australia, a crucial component of the integrated, regionally based approach to suicide prevention was gatekeeper training, which was widely implemented as a universal approach in secondary schools. Such training programs aim to equip students with skills to serve as peer gatekeepers, capable of identifying suicide warning signs, addressing concerns, and facilitating appropriate referrals for assistance and care [18,21].

safeTALK, a gatekeeper training initiative, seeks to elevate awareness regarding suicide prevention by framing it as a collective community responsibility, envisioning a helping role for every individual [22]. In addition, it empowers individuals without professional mental health backgrounds to confidently and effectively support someone showing signs of emotional distress. Studies have shown that this training enhances the effectiveness of informal mental health support for those experiencing emotional imbalance [2].

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Pakistan, located in Southeast Asia, grapples with numerous health and social challenges due to persistent waves of violence, political instability, and recurrent changes in the social infrastructure, which have significantly increased the burden of physical and mental ailments impacting individuals of all ages [23]. Unfortunately, Pakistan lacks accurate statistics on suicide deaths and suicidal attempts [24] due to underreporting of such cases, which happens because of social factors, particularly the stigma attached to such cases. However, recently published studies provide some insights into suicide deaths in Pakistan, where adolescents exhibited suicidal ideation and attempted suicide at the rates of 40% and 7%, respectively [25]. Moreover, in 2019, suicide mortality rates in Pakistan were estimated to be 8.9 per 100,000 population [26,27]. Gilgit-Baltistan (GB), comprising valleys located among the snow-clad mountains of northern Pakistan, has shown an alarming increase in adolescent mental health issues, including suicidal ideation and suicide rates, which has been particularly exacerbated during and following the COVID-19 pandemic [28].

To address the rising trend of suicidal ideations and attempts, prevention initiatives, such as the safeTALK program, hold significance, as they can help in disseminating awareness and education among adolescents through suicide literacy. Programs such as these aim to cultivate courage and confidence among adolescents to openly discuss suicidal thoughts and ideations and encourage help-seeking behaviors to approach professionals, such as psychologists or counselors. Extensive evidence supports the efficacy of the safeTALK program, which has been successfully implemented in various countries [29]. However, Pakistan, with its unique cultural and social setup, has yet to conduct a comprehensive analysis of the effectiveness of such programs.

The RAAHI suicide prevention program for school-going adolescents in GB was based on the theoretical frameworks of mental health literacy and resilience theory. Mental health literacy refers to the information and views about mental disorders that help with their detection, care, and prevention [30]. Improving mental health literacy enables people to recognize indicators of mental distress, cultivates good attitudes about getting help, and raises awareness of available support resources. By including mental health literacy in our program, we hope to provide teenagers with the tools to recognize and treat mental health concerns proactively. Self-determination theory states that when students feel autonomous and competent in their learning environment, they create a strong sense of academic productivity. According to the social cognitive theory [31], developing self-efficacy through supportive teaching improves learning ability, mediating the beneficial relationship between perceived teaching style and academic resilience [32]. Emotional dysregulation, defined as difficulties in understanding and managing emotions, is a substantial risk factor for adolescents' mental health concerns [33]. Cyberbullying involves repetitive harassment that can occur anytime, spreading swiftly to a huge audience, with anonymity magnifying its negative effects. Forms include defamation, harassment, and threatening communications, which have psychological and social effects for survivors, such as increased feelings of isolation, anxiety, sadness, and even suicide [34]. Adolescence is a phase marked by turmoil and upheaval, rendering individuals more prone to psychological disorders. These episodes often begin as fleeting but can become enduring, leading to psychiatric conditions, diminished performance, escalated medical expenses, and an elevated risk of subsequent self-harm. Global data indicate that the incidence of online harassment varies between 14.6% and 52%, while rates of being targeted by harmful digital acts range from 6.3% to 32%. The anonymity and widespread nature of cyberbullying can intensify emotional distress, potentially initiating or exacerbating suicides in susceptible youth [35]. Mindfulness significantly mediates the relationship between cyberbullying and cognitive emotion regulation among adolescents.

Resilience theory investigates how people respond positively to adversity, focusing on variables that facilitate recovery from difficult situations. In the context of suicide prevention, resilience refers to protective characteristics that assist individuals in navigating suicidal situations [36]. It includes a positive attributional style and a sense of purpose in life that protect people from suicidality during stressful circumstances [37]. Building resilience includes learning life skills, including problem resolution, emotional regulation, and effective coping mechanisms [38]. By incorporating resilience-building components into this intervention, we want to improve adolescents' ability to handle stress and minimize their vulnerability to suicidal thoughts and behaviors.

National and international suicide prevention strategies emphasize the significance of schools for targeted efforts [39], as they are conducive and accessible settings for implementing such programs. Leveraging the educational environment effectively enables reach and engagement with adolescents, thereby enabling the provision of relevant support and resources to mitigate the risk of suicidal ideation and behavior. Hence, this study intends to validate and assess the effectiveness of RAAHI (the guide) and a translated and contextualized version, named safeTALK, of the suicide prevention program in GB. Programs such as safeTALK can help lower teenager suicides by teaching them about suicide, giving them the confidence to talk about suicidal feelings, and encouraging them to seek help from professionals such as psychologists or counselors.

There is sufficient evidence that the safeTALK program is efficient and has been implemented in many other countries [29]. This study is the first of its kind in Pakistan to rigorously evaluate the impact of a suicide prevention program. Given the country's increasing suicide rates and the unique cultural and socioeconomic factors that influence mental health, such as stigma and limited access to services, this research is crucial for addressing a critical public health concern [40]. There is a notable scarcity of culturally adapted, evidence-based suicide prevention programs in Pakistan. Existing interventions often do not consider the unique sociocultural dynamics of Pakistani society, leading to less effective outcomes. Hence, this study aims to evaluate the effectiveness and contextual relevance of suicide prevention programs (RAAHI and safeTALK) in reducing suicidal ideation and enhancing mental well-being among school-going adolescents in GB. In addition, it examines how these programs influence suicide literacy, confidence in discussing suicide, willingness to seek help, mental health

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outcomes, adaptive coping strategies, and self-efficacy, ensuring their applicability within the local sociocultural context.

Research Questions

The primary research question about suicidal ideation is as follows: What is the effect of suicide prevention programs (RAAHI and safeTALK) in reducing suicidal ideation among school-going adolescents in GB?

The secondary research question is as follows: What is the effect of suicide prevention programs (RAAHI and safeTALK) among school-going adolescents in GB on (1) perceived suicidal awareness; (2) perceived Social Support Questionnaire; (3) suicide literacy; (4) attitude toward seeking help related to suicidal ideation; (5) life attitude schedule; (6) depression, anxiety, and stress level; (7) adaptive coping strategies; and (8) self-efficacy.

Null Hypotheses

The hypotheses are as follows:

- Hypothesis 1—suicidal ideation risk among school-going adolescents in GB is similar at baseline and 8 weeks following the implementation of the suicide prevention program.
- Hypothesis 2—Compared to baseline, there is no mean difference in suicide awareness, suicide literacy, and attitude to seek help after 8 weeks of participation in a suicide prevention program (RAAHI and safeTALK) among school-going adolescents.
- Hypothesis 3—Compared to baseline, there is no difference in the mean score of depression, adaptive coping strategies, and self-efficacy after 8-week suicide prevention programs (RAAHI and safeTALK) among school-going adolescents.

Methods

The protocol was prepared in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [41]. The trial has been registered in ClinicalTrials.gov (NCT06721364).

Study Design

This research will use a single-group quasi-experimental pre-post interrupted time-series design to allow for examining any change in the levels of the dependent variables before and after the administration of the intervention [42]. Moreover, there will be no control group, as it would be unethical to withhold intervention from potentially distressed adolescents [42]. The study design allows for assessing intervention effects over multiple time points; it is particularly suitable in settings where randomization is not feasible [43]. To control confounding variables, statistical adjustments and sensitivity analyses will be used to account for potential biases, such as maturation effects and historical events. In addition, the inclusion of multiple assessment points (time point 1, time point 2, and time point 3) strengthens internal validity by capturing trends over time rather than relying on a single before or after measure. By addressing these methodological considerations, we enhance the study's rigor and reliability.

Study Phases

This study will be carried out in 2 phases, from January 30, 2024, to October 30, 2025 (Figure 1). Phase 1 will comprise developing the RAAHI intervention by the researcher, followed by translation of the safeTALK intervention module, ensuring its contextualization and validating it through expert review. The effectiveness of the intervention will be evaluated in phase 2 using a quasi-experimental pre-post interrupted time-series design. RAAHI focuses on comprehensive suicide literacy and fostering open discussions to combat stigma about suicide, incorporating wellness education, while safeTALK is a shorter, more targeted workshop teaching specific intervention skills and immediate crisis responses using the tell, ask, listen, and keep safe (TALK) steps to emphasize immediate practical skills for identifying and addressing suicidal behavior by reducing depression and anxiety and improving adaptive coping strategies and the self-efficacy level.

Figure 1. Phases of the study.

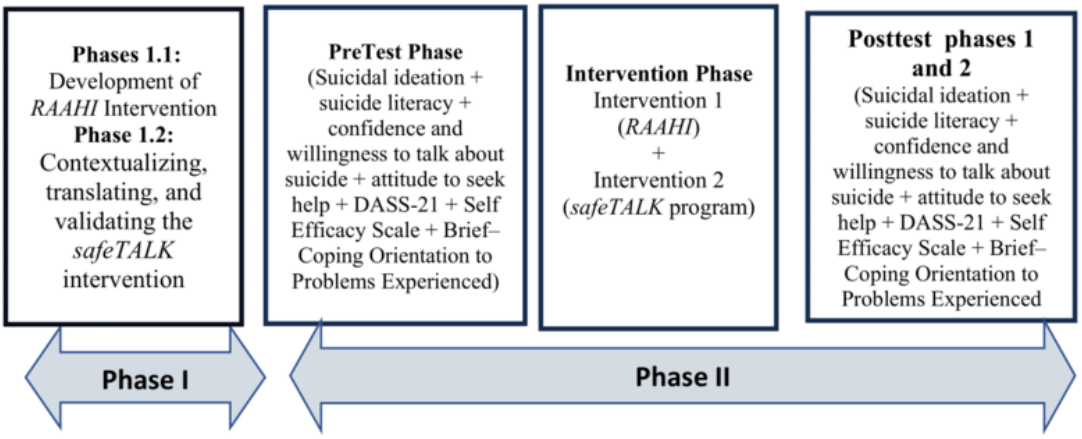

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Phase 1

Phase 1.1: Development of the RAAHI Module

During phase 1A, an interdisciplinary team comprising mental health nurses, psychologists, and educationists will create the RAAHI module for implementation. The objectives, content, timing, and activities for each module will be designed (Table 1). Experts in the field of mental health will then examine the material for clarity and appropriateness.

Table 1. Intervention module objectives and duration.

Session or week and suicide prevention intervention modules	Objectives	Duration (h)
RAAHI intervention		3
Module 1: circle of connection	Establish a warm and inclusive environment through an engaging ice-breaking activity, promoting a sense of connection among participants	
Module 2: common misconceptions and facts	Establish a warm and inclusive environment through an engaging ice-breaking activity, promoting a sense of connection among participants	
Module 3: warning signs for suicide	Provide a comprehensive overview of suicide warning signs, empowering participants to recognize and understand these indicators for prompt intervention	
Module 4: protective factors	Provide a holistic overview of protective factors against suicide, fostering understanding and encouraging the creation of a supportive and nurturing environment	
Module 5: coping strategies	Offer practical coping strategies, empowering participants with tools to manage negative thoughts, navigate challenges, and build resilience for improved emotional well-being	
safeTALK intervention		4
Module 1: introduction of safeTALK	Establish core beliefs about suicide and its prevention	
Module 2: importance of safeTALK	• Recognize individuals experiencing suicidal thoughts • Link individuals with suicidal thoughts to appropriate suicide first aid resources	
Module 3: Introduce steps of TALK[a]	Present standard procedures for safeTALK, including community and personal reasons, introducing TALK steps, which seek to increase people's self-awareness and help-seeking behavior while reducing suicidal ideation	

[a]TALK: tell, ask, listen, and keep safe.

Phase 1.2: Translation of the safeTALK Intervention Module and Contextual Validation

Translation of the RAAHI and safeTALK intervention material into Urdu, using the backward translation approach, and validation by experts will be carried out to make it culturally and contextually relevant. A team of mental health nurses, clinical psychologists, psychiatrists, and members of the Brain and Mind Institute at the Aga Khan University in Karachi, Pakistan, will validate the intervention module (Table 1).

Research Setting

GB, located in northern Pakistan, boasts spectacular mountain scenery, as it is spread over a region that has 2 mountain ranges: the Karakoram and the Himalayan. Although the region has great natural beauty, it grapples with poverty, limited mental health services, and harsh living conditions. Efforts to improve well-being in GB require addressing these challenges through initiatives. This study will be conducted in 4 private schools located in northern Pakistan. The rationale for selecting these schools is chiefly the readiness of the school management to implement, adopt, and sustain the intervention. Because this intervention will be used in the Pakistani context for the first time, the willingness of the school principals and their flexibility in mobilizing resources will play a major role. Although the setting will limit external validity, these study sites will be purposively selected, as they will facilitate assessing the feasibility of the intervention in a Pakistani context [44].

Study Population

Inclusion Criteria

Both male and female adolescents enrolled in grades 9 and 10 who can comprehend English and Urdu will be included. In addition, adolescents and their parents must provide consent to participate in the study.

Exclusion Criterion

Adolescents who will be absent or sick on the day of data collection and intervention will not be included in the study.

Sampling Strategy

A multicenter experimental study using consecutive sampling will be conducted to examine the effectiveness of school-based

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preventive interventions for suicidal behavior. Four schools in the GB regions will be recruited. Eligible schools will be randomly selected. Within the selected schools (clusters), all students in grades 9 and 10 will be invited to participate. This approach of inviting all eligible students within the selected clusters aims to enhance representativeness and minimize potential selection bias that could arise if only specific students were chosen from within each school. This is the best technique to explore the phenomena and to gain rich data from the participants [42]. The chosen design enables the detection of trends and changes over time. This method aids in distinguishing intervention effects from other temporal variables to observe whether changes correlate with the intervention time, which strengthens causal inferences. Multiple assessments establish a baseline trend, differentiating natural development from intervention-induced changes [45]. Regular data collection allows for adjustment of external events influencing outcomes. Despite lacking a control group, this approach enables each participant to serve as their own control, enhancing causal inference [46].

Sample Size

The sample size for this study was calculated using G*Power (version 3.1.9.2; Heinrich Heine University Düsseldorf) and Microsoft Excel, applying the paired sample formula. Data from the study by Bailey et al [47,48] reported pre- and postintervention knowledge scores with mean values of 16.88 (95% CI 16.17-17.19) and 20.88 (95% CI 20.36-21.41), respectively. To convert the CI into SD, statistical calculations were performed using the standard normal distribution and t-distribution, yielding SD values of approximately 2.2 for preintervention and 1.2 for postintervention scores. With a significance level (α) of .05, power ($1-\beta$) of 80%, an estimated effect size of 1.2, and a correlation coefficient of 0.5, the required sample size was determined to be 223 participants. Accounting for a 20% dropout rate [49], the final sample size was adjusted to 267 school-going adolescents to ensure sufficient statistical power for detecting meaningful differences in knowledge scores.

Recruitment of Participants

Step 1

Participants will be recruited from 4 private schools under the Aga Khan Education Service network using consecutive sampling. Approval will be obtained from the school principals, followed by coordination with the administration to arrange a designated space for study activities.

Step 2

A recruitment flyer will be distributed to students in grades 9 and 10. Interested students will be instructed to contact their parents to obtain initial verbal consent before participation.

Step 3

Parents will be provided with study details in a private setting. The researcher will explain the study's purpose, procedures, and expectations, addressing any questions. Written informed consent will be obtained for eligibility screening, intervention participation, and pre- and posttest assessments. To ensure transparency, parents will also receive a copy of the consent form for further review.

Step 4

Eligible students will be identified based on predefined criteria. Those who meet all eligibility requirements will be enrolled in the study.

To mitigate low participation rates, multiple outreach efforts, including follow-up meetings, will be conducted. In cases where logistical constraints arise, such as scheduling conflicts or space limitations, alternative arrangements (eg, rescheduling sessions or using available classrooms) will be made to facilitate smooth study implementation.

Procedure

Intervention 1: RAAHI

RAAHI is a suicide literacy module that is specially designed to provide individuals with essential knowledge and skills by equipping them with tools to navigate the complexities of mental health and suicide prevention. This module aims to empower people to recognize signs of suicidal ideation, engage in empathetic communication through open discussion, combat stigma, and connect individuals in crisis with appropriate support and resources. The duration of the module will be 3 hours. Hence, RAAHI seeks to create a world where suicide literacy is widespread, compassion is the key to preventing tragedy, and no one feels isolated in their struggle, thereby contributing to a more empathetic and supportive future (Table 1).

Intervention 2: safeTALK

The safeTALK program is an educational initiative designed for suicide prevention among adolescents, consisting of a 4-hour workshop that incorporates presentations, videos, discussions, and questions. The workshop is designed according to the standard practices of safeTALK to assist participants in (1) identifying warning signs of suicide; (2) avoiding frequent impulses to overlook, dismiss, or avoid discussions about suicide; (3) recognizing and responding to situations where suicidal thoughts may be present by applying fundamental TALK steps; and (4) connecting individuals contemplating suicide with first aid assistance and additional community resources [2]. The skill training program concentrates on bolstering adolescents' understanding of activities that promote mental well-being, fostering resilience, honing distress management abilities, and enhancing their capacity to identify early signs of suicidal ideation or behavior both within themselves and among others. The program also equips participants with strategies for suicide crisis intervention.

The intervention involves the components mentioned subsequently.

Phase 2: Testing the Effectiveness of the Suicide Prevention Program

Pretest Phase

Students willing to participate will be asked to provide their consent by signing a form or paper before starting the pen-and-paper pretraining survey. Students will be explicitly

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informed that participation is entirely voluntary, and their decision to participate or not to participate will not affect their training in any way. First, the psychologist and the researcher will conduct a risk assessment of the students for any previous history or current complaints of suicidal ideation and behavior. A 40- to 60-minute window will be allocated before the training commences to enable participants to complete the pretest survey. In addition, the level of suicide literacy will also be evaluated through validated and self-report questionnaires. Along with this, students' level of confidence and willingness to discuss suicidal ideation and attitudes toward seeking help from others, adopting coping abilities, and self-efficacy level will also be assessed. Following the pretest phase, the students will enter the intervention phase.

Intervention

The intervention phase consists of 2 workshops in which the students will be required to participate. The first workshop consists of 2 hours of RAAHI intervention which will provide them with general knowledge about suicide, risk factors, consequences, and preventive strategies; this will help participants improve their suicide literacy. Moreover, a booklet comprising different activities will also be provided to participants during the training. In addition, the second session will introduce the 4-hour safeTALK program, which seeks to increase people's self-awareness and help-seeking behavior while reducing suicidal ideation. This is a culturally relevant program as it applies basic TALK steps and connects the person with suicidal thoughts with suicide first aid help and further community resources. Moreover, a pocket card containing the "suicide alert steps" will also be provided to the participants at the end of the training. In this study, the safeTALK workshops will be delivered to adolescents, approximately 30 students at a time. The researcher, along with a psychologist, will administer this training with the help of translated videos and material in Urdu, which is culturally appropriate and has been modified and adapted from LivingWorks.

Posttest Phase

The data will be recollected on all outcome measures during posttest phase 1, which is right after the intervention, and posttest phase 2, which will be after 8 weeks of the intervention (Figure 2).

Figure 2. CONSORT (Consolidated Standards of Reporting Trials) diagram for participant flow.

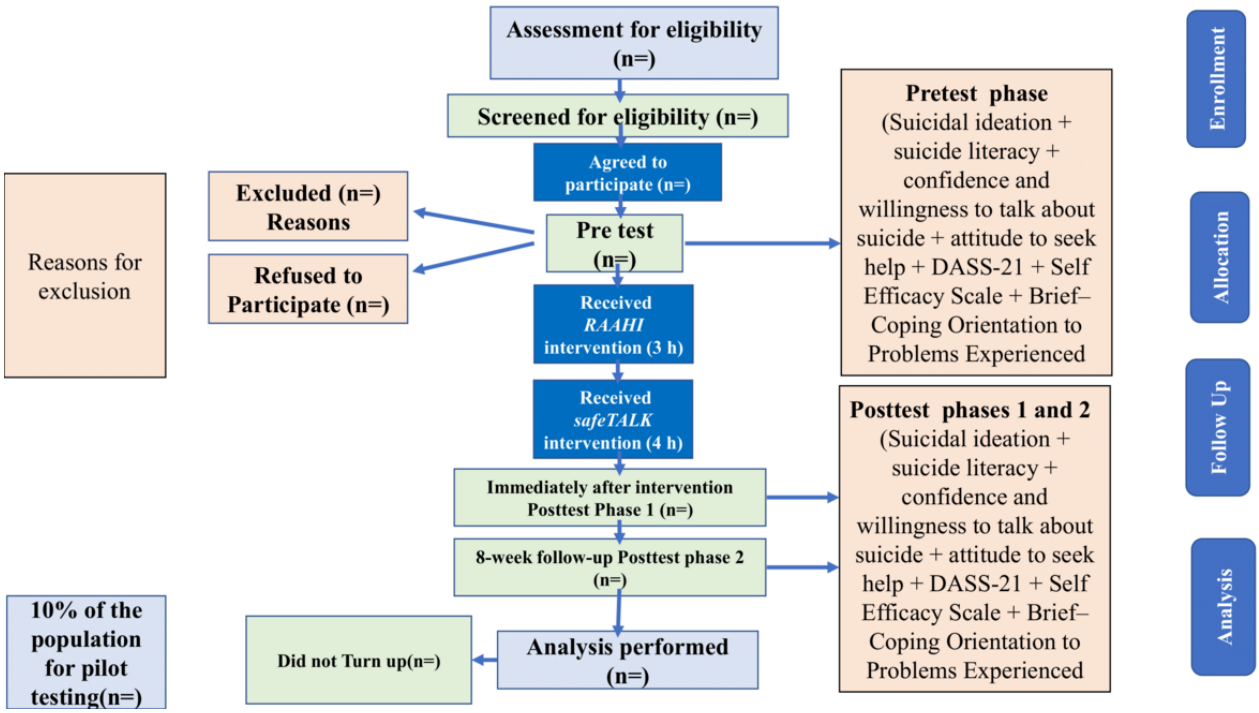

Data Collection Tools

A predesigned survey will be administered to individuals who express interest in participating in this study and willingly agree to provide the relevant information. The questionnaire consists of 3 sections. The first section will gather detailed demographic information and include eligibility questions, followed by the Modified Scale for Suicidal Ideation (MSSI) by Miller et al [43]. Its translated version is available as it was used in a study of suicide in Pakistan [50]. The second section includes questions about suicide literacy, confidence, and willingness to talk about suicide, followed by an attitude to seek help. In the last section, depression will be assessed using the Depression, Anxiety, and Stress Scale–21 Items (DASS-21), along with questions about the ability to adopt coping skills and self-efficacy.

Study Outcomes

Suicidal Ideation

The level of suicide literacy among the participants will be measured through the MSSI by Miller et al [43], comprising 21 items. It was translated and used in Urdu by Bakht et al [51]. The MSSI has shown strong internal consistency, with a Cronbach α coefficient ranging from 0.87 to 0.94 [52]. The

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severity of suicidal ideation, as assessed by the MSSI total score, is categorized into 3 levels. A total score ranging from 0 to 8 indicates a low level of suicidal ideation. In contrast, a total score between 9 and 20 suggests a moderate level of suicidal ideation. These adolescents may experience more frequent or persistent thoughts of suicide, potentially accompanied by feelings of hopelessness or despair. Finally, a total score of 21 or higher reflects a severe level of suicidal ideation, indicating a significant risk of self-harm or suicide. Adolescents in this category may have intense and intrusive thoughts of ending their life, and immediate intervention and support are often necessary to ensure their safety. Severe suicidal ideation is indicated by a total MSSI score exceeding 20, coupled with an intense suicidal intention, represented by a score of more than 1 on item 7. In addition, an active desire to make an attempt is signaled by a score exceeding 1 on item 3, while a serious plan for suicide is indicated by a score of more than 1 on item 15.

Perceived Suicide Awareness

In total, 14 items of the Perceived Suicidal Awareness Scale from a previous suicide prevention study were used to evaluate perceived suicide awareness [2,48]. The original Perceived Suicidal Awareness Scale consists of 5 items assessing perceived knowledge about suicide and help-seeking resources, 3 items measuring willingness to discuss suicide and seek assistance, 5 items evaluating confidence in discussing suicide and obtaining help, and 1 item examining the intention to seek help. Responses were recorded on a 5-point scale, ranging from 0 (strongly disagree) to 4 (strongly agree). The scale was translated into Urdu and subsequently back translated into English. Any inconsistencies were identified, deliberated upon, and resolved. The finalized version was piloted with the target population. This scale has shown strong internal consistency, with a Cronbach α coefficient ranging from 0.87 to 0.94. Questions will be asked to determine the participant's level of confidence while discussing issues regarding suicide. The questionnaire will use a Likert scale that will range from 1 to 3, where 1 will indicate "disagree," whereas 3 will be read as "agree." The scale was adopted from the studies by Kinchin et al [2] and Baggio et al [53]. The suicide skills confidence subscale (Cronbach α=0.84) assesses respondents' confidence in working with clients with suicidal thoughts in regard to training, skills, comfort, and supervision. Possible scores range from 4 to 20, with higher scores indicating greater confidence. The questionnaire will also focus on determining the participants' willingness to talk about suicide and suicidal ideation with others. To analyze the willingness, the statements will be assessed on a Likert scale ranging from 1 to 3.

Perceived Social Support Questionnaire

The Social Support Questionnaire was adapted from the Perceived Social Support (Fragebogen zur Sozialen Unterstützung) 6-item scale developed by Kliem et al [54] and Lin et al [55]. This German tool evaluates adolescents' capacity to recognize the availability of assistance from friends, family, and peers in times of need. For this study, minor adjustments were made to the questionnaire with the authors' permission while preserving its core purpose. The scale demonstrated high reliability, with an internal consistency (Cronbach α) of 0.90.

Suicide Literacy

Suicide literacy, a vital component of mental health literacy, encompasses knowledge of suicide's warning signs, causes, risk factors, and preventive measures [56]. The Literacy of Suicide Scale, developed and evaluated by McGillivray et al [20], includes 26 items assessing suicide literacy across 4 dimensions: signs and symptoms (5 items), causes and triggers (10 items), risk factors (7 items), and treatment and prevention (4 items) [56]. Each question has a correct answer, scored as 1 point, while incorrect or "I don't know" responses score 0. In this study, 1 question was removed, resulting in a 25-item scale with scores ranging from 0 to 25, where higher scores reflect better suicide literacy.

Attitude Toward Help-Seeking Behavior

The Attitude Toward Seeking Professional Psychological Help Scale by Fischer and Farina [57] will be used to assess participants' attitudes toward seeking help regarding mental health problems. This tool consists of 10 items rated on a Likert scale ranging from 1 (disagree) to 4 (agree). The total score, obtained by summing individual item scores, reflects a positive attitude toward seeking psychological help. With reliable psychometric properties, the instrument has a reliability index ranging from 0.80 to 0.86 [58].

Life Attitudes Schedule

The Life Attitudes Schedule–Short Form by Rohde et al [59] is a 24-item binary measure assessing thoughts and behaviors associated with an increased risk of future suicide ideation, attempts, and completions. Participants respond with either true (1) or false (0), and the scores are summed up from a scale score ranging from 0 to 24 to create a total scale score. Higher scores reflect greater engagement in life-enhancing behaviors, while lower scores indicate increased participation in life-threatening behaviors. The scale has exhibited commendable internal consistency, with a Cronbach α of 0.78 [60], and demonstrated excellent construct validity with regard to history of suicide attempts, depressive symptoms, and impulsivity [61].

Depression, Anxiety, and Stress Level

The depression, anxiety, and stress levels will be assessed by the DASS-21 questionnaire, which was translated into Urdu, the national language of Pakistan, by Gillani et al [62], to assess the perceived stress levels and psychological well-being of the Pakistani population in Islamabad. Its internal consistency was assessed, revealing a Cronbach α of 0.94. DASS-21 will serve as a screening tool, evaluating stress, depression, and anxiety over the past week through 21 items, each consisting of a set of 7 questions. Responses on the Likert scale range from 0 to 3, where "never" corresponds to 0, "sometimes" to 1, "frequently" to 2, and "always" to 3. [63]. Depression, anxiety, and stress levels of participants will be assessed using predefined cutoff values as follows: depression score of less than 6, anxiety score of less than 5, and stress score of less than 9, in accordance with the DASS-21 guidelines [64].

Adaptive Coping Strategies

The Brief–Coping Orientation to Problems Experienced questionnaire, a validated 28-item self-report tool developed

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by Carver [65], assesses both effective and ineffective coping strategies in response to stressful life events. Participants rate their engagement in each strategy on a scale from 1 (not doing at all) to 4 (doing a lot). The questionnaire encompasses 14 coping strategies, including self-distraction, active coping, denial, substance use, emotional support, instrumental support, behavioral disengagement, venting, positive reframing, planning, humor, acceptance, religion, and self-blame. Scores for each coping style range from 2 to 8, with higher scores indicating a greater inclination toward using that specific coping mechanism [66]. The tool has demonstrated an internal reliability of 0.86 [67].

Self-Efficacy

Self-efficacy will be measured using a 10-item Generalized Self-Efficacy Scale, which gauges individuals' optimistic beliefs about their competence, encompassing determination, problem-solving, and coping skills [68]. Responses range from 1 (not at all true) to 4 (exactly true). The Urdu translation was already done by Mansoor and Ahmad [69].

Feedback and Evaluation

At the conclusion of the workshop, the participants will be provided with a feedback questionnaire to freely share their thoughts about this session as well as comments on suicidal ideation. This feedback questionnaire has been adapted and modified from a previous study conducted in Pakistan [70]. All participants will be asked to complete a feedback questionnaire assessing several aspects on a Likert scale. These include the comprehensibility of the language used, relevance of the content, enjoyment of the session, effectiveness of strategies used, usefulness of the session, clarity and simplicity of activities, excellence of the overall training, practicality of the session, appropriateness of its duration, and inviting comments and suggestions for improvement [71].

Reliability and Validity of Tools

The appropriateness and relevance of the tool in the Pakistani context will be checked by experts. Psychologists will assess the validity through the validation of the content for clarity and relevance. The tools will be translated into Urdu by a linguistic expert. The Urdu versions of the questionnaires, alongside the English version, will be distributed to 4 mental health experts for assessment of language clarity, word choice and order, and representativeness of the construct. Feedback provided by the experts will be integrated into the questionnaires. In addition, back translation into English will be conducted by 4 experts. The content validity will be measured by following a standard protocol of content validity index (CVI) scores.

As mentioned by Yusoff [72], the researcher will seek definitive evaluation evidence for the tool. A rubric will be used, with a Likert scale, to assess relevance (1=not relevant, 2=somewhat relevant, 3=pretty relevant, and 4=very relevant) and clarity (1=not clear, 2=somewhat clear, 3=quite clear, and 4=very clear). Ratings of 1 and 2 will prompt consideration for potential adjustments, while evaluations of 3 and 4 will be considered acceptable. The evaluation panel will make recommendations for alterations, resulting in a clarity score of 0.95 and a relevance score of 0.86, according to the CVI analysis. Moreover, for determining the tool's reliability, Cronbach α will be used. Pilot testing, involving 10% (4/40) of the sample size, will be conducted to ensure reliability. The resulting CVI and Cronbach α coefficient will provide statistical confirmation regarding the reliability, validity, and clarity of the study questionnaire.

Data Collection

The principal investigator has received safeTALK training from LivingWorks and will train data collectors for the data collection process. The training includes presentations, videos, discussions, questions, and role-play. All participants will receive identical training at no expense, with no alterations in the delivery or content. Demographic information will be solely collected from participants who provide consent and agree to complete both pre- and posttraining surveys; however, the analysis will be restricted to data furnished by those who complete the surveys based on per-protocol analysis [73]. To promote data quality, study personnel will be trained in the administration of these instruments, and procedures for double data entry, verification, and management will be implemented to ensure accuracy and completeness. Data collection forms will be securely stored, with access limited to authorized personnel to maintain confidentiality [74]. Strategies to promote participant retention and complete follow-up will include clear communication about the study's importance and duration during the consent process, maintaining regular contact with participants and ensuring the study procedures are convenient and acceptable. For participants who discontinue or deviate from intervention protocols, efforts will be made to collect available outcome data to allow for intention-to-treat analysis, where feasible.

Time Frame for Data Collection

Each participant will receive a short questionnaire at 3 points in time: pretest baseline data (T1), immediately after the intervention (T2), and 8 weeks after the intervention (T3). This self-filled questionnaire will collect data on suicidal ideation, level of suicide literacy, level of confidence, and openness to disclose suicidal ideas to others. The researcher will be responsible for checking for and verifying any missing data with participants, which will help to identify and correct errors in the datasets.

Data Analysis

Statistical analysis will be conducted using SPSS (version 26; IBM Corp). The normality of data distribution will be assessed, and continuous variables will be summarized using means and SDs (for symmetrical distributions) or medians and IQRs (for skewed distributions), while categorical variables will be presented as frequencies and proportions. Changes in continuous variables (suicidal awareness, suicide literacy, and help seeking) over time will be analyzed using a linear mixed-effects model, and the binary outcome of current suicidal ideation will be analyzed using a population-averaged generalized estimating equation. Linear regression will be used to estimate β coefficients and 95% CIs for predictor variable effects. To compare pre- and postintervention scores on the Literacy of Suicide Scale, a paired samples 2-tailed *t* test will be used, and repeated measures ANOVA with a Bonferroni post hoc test will also be calculated. All primary and exploratory findings will

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include effect sizes, CIs, and significance levels. While exploratory subgroup analyses may be conducted, they will be clearly identified and interpreted cautiously due to their post hoc nature. Any deviations from the original analysis plan will be justified, and results will be presented with transparency in well-organized tables and figures, including appropriate titles, legends, and footnotes. Data distribution will be further assessed using histograms and the Shapiro-Wilk test to confirm normality assumptions, and the homogeneity of variances will be verified using the Levene test. Any anomalies in the data will be discussed in relation to potential methodological or contextual factors.

Data Monitoring and Management

Data monitoring and management for this study, coordinated by the School of Nursing and Midwifery at the Aga Khan University, with strategic guidance from a steering committee, involves several key roles and processes. Trained psychologists will collect data, while the primary author will oversee data management (entry validation, cleaning, and secure storage) and monitor participant safety during data collection using safeTALK training, with protocols for immediate counselor referrals if distress occurs. A dedicated, separate data analyst will conduct statistical analyses. An independent data monitoring committee, composed of external experts, including clinicians and a biostatistician operating under a charter, will periodically review trial data for safety, efficacy, and overall conduct, managing interim analyses with predefined stopping guidelines and restricted access to results. Comprehensive procedures are in place for managing and reporting adverse events, with investigators responsible for the timely reporting of serious events. Finally, independent personnel will conduct periodic audits, detailed in a separate plan, to ensure trial quality and compliance.

Ethical Considerations

Overview

This research is fundamentally guided by a commitment to ethical principles, ensuring participant protection. This study has received formal approval from the Aga Khan University Ethics Review Committee (AKU-ERC; 2023-8509-24844) and is transparently registered on ClinicalTrials.gov (NCT06721364). Should any significant adjustments to the study protocol arise (such as changes to eligibility, outcomes, or analysis), these will be communicated efficiently to the investigators, AKU-ERC, the trial registry, and other relevant parties (such as participants or journals) using an online portal.

Ethics Approval and Consent to Participate

The interventions in this study strictly adhere to the principles and procedures specified in the Declaration of Helsinki. All experimental protocols have been thoroughly reviewed and approved by the AKU-ERC (Multimedia Appendix 1). Informed consent will be obtained from all study participants, ensuring ethical standards are followed throughout the research process. Transportation incentives will be provided for participation.

Consent for Publication

Participants will be asked for their consent during the data collection process, explaining that the collected data may be used for the dissemination of scientific knowledge. However, no personal names or specific identifying information will be revealed in the published material to ensure confidentiality and privacy (Multimedia Appendix 2). Participants will also be requested to give permission to publish any relevant data or materials without disclosing their identity.

Participation in this study is entirely voluntary. The research team, composed of psychologists and the principal investigator, will secure informed consent from parents or guardians after clearly explaining the study's objectives during sessions at the school, allowing ample time for inquiries and ensuring a pressure-free decision environment. Students will provide their own informed assent (Multimedia Appendix 3). It is crucial that participants know they can withdraw from the study at any stage without facing any disadvantage; should they choose to withdraw, their collected information will be removed from the study analysis. Currently, no ancillary studies requiring separate consent for data use are planned.

Maintaining participant confidentiality is a priority throughout the research process—before, during, and after data collection. Personal information will be gathered securely, and anonymity will be protected by using unique identification codes and pseudonyms, effectively separating personal identities from research data. All electronic data files are password protected, and any reports generated will exclude identifying details such as names. While the study presents minimal potential risks, if a participant's results suggest potential susceptibility, this information will be confidentially discussed with their parents (only after obtaining explicit parental consent) to facilitate a referral for further assessment. This sensitive information will not be disclosed to school authorities. The psychologists assisting with data collection are prepared to identify and offer support for any immediate distress participants might experience.

Access to the final, anonymized dataset is carefully controlled, limited to the primary author, data analyst, principal investigator, and supervising committee members directly involved in data analysis and reporting. Importantly, there are no contractual limitations restricting the investigators' access to the data. The findings from this research will be shared through various channels, including publications in peer-reviewed journals, presentations at academic conferences, and mandatory reporting on the ClinicalTrials.gov database. In addition, summaries might be shared with participants and other relevant stakeholders when appropriate. Authorship for publications will align with the established International Committee of Medical Journal Editors guidelines. Following the main dissemination of results, the research team will address reasonable requests for access to the complete study protocol, the anonymized participant dataset, and the statistical code used for analysis.

Potential Risk to Participants

This study has minimal potential risks for the participants. While obtaining informed consent from the parents and assent from

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the participants, it will be made clear that information regarding those considered susceptible, based on their scores, will be shared with their parents, and they will be referred for further assessment after the parents' consent. However, the status of the participants will be kept confidential from the school authorities. The study will involve psychologists who will conduct the interview along with the principal investigator; hence, they will be able to screen the potential participants.

Ancillary and Posttrial Care and Referral Mechanism

The data will be collected by trained psychologists, and all the identified cases will be referred to a counselor who will also be hired for the study, so they can refer the extreme cases for further treatment. The employed counselors will be on hand at the study sites for data collection and intervention. The cases presenting extreme suicidal ideation thoughts will be referred for follow-up. The screening and referral expenses of the participants will be borne by the study [71]. The attendees will also be informed about the resources that are accessible, such as the hotlines of the suicide prevention organizations operating in Pakistan.

For this trial, the criteria for discontinuing or modifying allocated interventions for a participant will include a participant's explicit request to withdraw, the emergence of any unforeseen serious adverse events related to the intervention, or if the participant's mental state significantly deteriorates, requiring a different level of care. Strategies to improve adherence to the intervention protocol will involve clear communication of the program's duration and expectations during the informed consent process; regular engagement with participants, which may include follow-ups; and ensuring the intervention is delivered in a manner that is acceptable and feasible for the participants. Participants will be informed about any permitted or prohibited concomitant care or interventions during the trial period to avoid any potential confounding factors.

Results

Study Progress to Date

As of July 30, 2025, significant progress has been made in the initial phases of the project. This includes the successful acquisition of permissions from the AKU-ERC and relevant district education offices in GB and intervention development and validation. Furthermore, the pilot testing of the intervention materials was completed in October 2024, providing valuable insights for the main study. Currently, the recruitment of participants is underway and is scheduled to commence fully in August 2025. Importantly, funding for this project has already been confirmed through a grant from the Fogarty International Center at the National Institutes of Health.

Projected Timeline

This project is proceeding according to the subsequently mentioned timeline, which outlines the key milestones and their anticipated completion dates. Participant recruitment is expected to be completed by July 2025, followed immediately by baseline assessments, also in July 2025. The intervention delivery period is scheduled to run from July 2025 to August 2025. Postintervention assessments will take place in September 2025. Data cleaning and analysis will commence immediately following the postintervention assessments. Subsequently, manuscript preparation will begin, and the final phase will involve dissemination activities to share the study findings.

Discussion

Anticipated Findings

This study aims to evaluate the effectiveness of the RAAHI and safeTALK suicide prevention programs in improving the mental well-being of school-going adolescents in GB, Pakistan. This study's predicted findings indicate that the suicide prevention program will considerably improve the mental health of school-going teenagers in GB. Following the intervention, it is anticipated that suicidal ideation and actions will decrease substantially, with fewer adolescents reporting self-harm inclinations and suicide attempts. Furthermore, mental health indicators, such as depression, anxiety, and stress levels, are expected to fall sharply, while resilience, coping skills, and emotional regulation among adolescents are likely to increase. The program is also projected to raise suicide prevention awareness by educating students about risk factors and existing support systems, resulting in increased help-seeking behavior.

A positive transformation in the school atmosphere is expected, with less stigma around mental health talks and increased peer-to-peer assistance. Furthermore, teachers and school personnel are expected to take part in detecting and managing mental health issues more actively, resulting in a more conducive learning environment. In the long run, the program has the potential to develop long-term mental health initiatives within schools, ensuring that suicide prevention measures are integrated into student support services. Overall, the intervention is expected to make the school community safer and more resilient, helping to reduce the risk of suicide among adolescents in the region.

The effectiveness of school-based suicide prevention programs has been well-documented in high-income countries, where structured interventions have demonstrated significant improvements in mental health literacy, help-seeking behaviors, and suicide risk reduction [75]. However, there is a significant gap in the implementation and evaluation of such interventions in LMICs, particularly in South Asia. Previous research highlights that culturally tailored and community-based interventions are more effective in addressing the unique sociocultural determinants of adolescent suicide [76]. This study builds upon this evidence by evaluating safeTALK, a globally recognized suicide prevention program that was adopted, and RAAHI, a locally developed intervention, within the unique context of GB. Unlike previous studies, which primarily focus on universal school-based interventions, this research also considers the role of peer-to-peer support and capacity-building among educators in creating a sustainable suicide prevention model [77].

Given the alarming rise in suicide rates in Pakistan and the absence of structured prevention initiatives, these findings will provide valuable insights into the potential impact of these

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interventions on suicidal ideation, suicidal awareness, suicide literacy, attitudes toward help-seeking, and mental health outcomes (depression, anxiety, and stress) among participants following the intervention. These findings align with previous research indicating that structured suicide prevention programs can enhance awareness, reduce stigma, and foster positive coping mechanisms among adolescents [78]. However, while previous studies have predominantly focused on Western contexts, this study highlights the effectiveness of such interventions in a culturally unique and resource-limited setting [79]. Notably, the increase in self-efficacy and adaptive coping strategies suggests that these programs may play a role in promoting long-term resilience among at-risk adolescents [80]. Interestingly, our results may reveal gender-specific response patterns that deviated from those observed in high income countries [79]. This divergence likely stems from the distinct cultural and social landscape of GB, Pakistan, where mental health stigma and traditional gender roles significantly impact how individuals seek assistance [81]. Furthermore, this research offers novel data, demonstrating the efficacy of suicide prevention strategies within resource-constrained, rural areas.

Public Health Implications

As per the researcher's knowledge, this research study will be the first to establish the effectiveness of a suicide prevention program in improving the mental well-being of school-going adolescents in Pakistan. The results of this research will assist in upscaling suicide prevention interventions tailored to the cultural and social context of GB. RAAHI and safeTALK are expected to bring a positive change in this cohort of adolescents. The success of the intervention will be that people of Pakistan, especially adolescents, start normalizing talking about this taboo topic. This will help in recognizing and identifying those in need of help in any community. Moreover, awareness regarding suicide may improve resilience and increase help-seeking behavior among adolescents. Ultimately, this preventive intervention program will contribute to reducing the burden of suicide in Pakistan.

Future Directions

Future research in school-based suicide prevention, particularly in LMICs, should prioritize longitudinal studies to assess long-term impacts and expand to diverse populations, including out-of-school adolescents. Integrating digital mental health tools and developing gender-specific interventions will enhance scalability and effectiveness. Qualitative studies are vital to understanding cultural barriers and student experiences, guiding program refinement. Policy makers must implement national strategies combining school programs, peer support, and community engagement. Structured training programs, complemented by accessible professional care and community support, are essential for reducing stigma and promoting early intervention. Comparative studies of various prevention models will identify optimal approaches for LMICs.

Dissemination

Peer-reviewed publications and conference presentations will be prioritized to engage academic and mental health professionals. In addition, collaboration with the Ministry of National Health Services Regulations and Coordination, government of Pakistan; education departments; and nongovernmental organizations will facilitate the translation of research findings into school-based mental health policies. A key component of the dissemination strategy will involve community outreach programs, including workshops for educators, parents, and students, to enhance suicide literacy and mental health awareness [82]. Finally, digital platforms, such as webinars and social media campaigns, will be used to increase public engagement and encourage discussions on youth suicide prevention in Pakistan.

Strengths and Limitations

Because there is no standard intervention available for suicide prevention for adolescents in the Pakistani context, this research will assist in upscaling suicide prevention interventions tailored to the cultural and social context of GB among school-going adolescents in Pakistan. This study aims to bridge this gap by evaluating the effectiveness of suicide prevention programs specifically designed for Pakistani adolescents, thereby providing crucial data to inform national mental health strategies and policies. This study's strong pre- and postintervention design enabled a clear evaluation of the program's immediate effect on participants' mental health. The use of established measurement instruments bolsters the dependability of our results.

However, due to time, budget, and logistical constraints, this feasibility study will only be conducted in 4 schools in GB, Pakistan, limiting potentially diverse implementation experiences and outcomes in rural or public-school settings. This may restrict the generalizability of the study findings. Moreover, using a quasi-experimental design without an appropriate control group can potentially undermine the internal validity of the study. Third, this study's sample was limited to school-going adolescents, potentially restricting the generalizability of findings to out-of-school adolescents or other high-risk groups. In addition, the absence of a long-term follow-up limits our ability to determine the sustained impact of these interventions. However, reliance on self-reported data raises the possibility of response biases, particularly social desirability, which is significant given the prevailing mental health stigma in this area. Furthermore, while we acknowledge the potential influence of factors such as socioeconomic status, family support, and preexisting mental health issues, these were not fully controlled in our analysis. Future research should strive to include a broader range of variables to strengthen the study's conclusions. Finally, it is important to note that the results of this investigation are specific to the studied context and may not be readily applicable to different cultural or geographic populations.

Conclusions

This study aims to evaluate the impact of RAAHI and safeTALK, culturally adapted suicide prevention programs, on adolescents in GB across 8 weeks. By measuring changes in suicidal thoughts, knowledge, and confidence, the research will inform evidence-based strategies for researchers, clinicians, and policymakers. These programs present a viable approach to combat the rising suicide rates, improve mental health, and

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promote positive attitudes within the community. However, long-term success requires addressing systemic challenges to ensure these interventions are integrated into wider public health systems.

Acknowledgments

The authors gratefully acknowledge the invaluable contributions of the research team, psychologists, and statisticians, who played a crucial role in the study design and intervention module development. They also extend their sincere appreciation to the participating schools for their cooperation. Finally, they would like to thank LivingWorks Education for its generous provision of safeTALK intervention kits. Research reported in this paper was supported by the Fogarty International Center of the National Institutes of Health (award D43TW007292)—the Aga Khan University Trauma and Injury Research Training Program. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institute of Health. The funder had no role in the study design; collection, management, analysis, and interpretation of data; writing of this paper; or the decision to submit it for publication.

Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request

Authors' Contributions

YNP contributed to conception and design of the manuscript and protocol; conceived and designed the research project, which includes formulating the initial idea, setting the research objectives, and designing the methodology; and wrote the original draft. YNP was also responsible for the work's accuracy and integrity and ensured the accuracy and integrity of the entire research process, from data collection to interpretation, addressing any concerns that arose to maintain the scholarly rigor of the work. RN was responsible for drafting the work; writing the initial drafts of the manuscript, which involves structuring the paper and writing the Introduction, Methods, Results, and Discussion sections; critically reviewing important intellectual content; critically reviewing the manuscript to ensure it presented significant intellectual content, which included evaluating the validity of findings, coherence of arguments, and alignment with existing literature; and supervision. TSA approved the final version of the work; provided final approval of the manuscript before submission for publication, which signifies her endorsement of the work's quality and readiness for dissemination; and supervision. NM was responsible for critically reviewing the protocol and providing feedback; reviewing the research protocol periodically and providing feedback, which ensured that the methodology and procedures were sound and aligned with the research objectives; and visualization and supervision. UK was responsible for critically reviewing the manuscript; evaluating the content for accuracy, relevance, and coherence within the context of the research; developing the module (RAAHI) and ensuring that the safeTALK approach was relevant and effective within the specific context of the study; supervision; funding acquisition; and validation. SS was responsible for providing expertise in the development of the intervention module, integrating theoretical frameworks and practical knowledge to design effective interventions, data curation, formal analysis, investigation, methodology, and project administration. MK contributed to approving the manuscript before submission; formalizing it; ensuring clarity, coherence, and adherence to academic writing standards; conceptualization; and reviewing and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
The Aga Khan University Ethics Review Committee approval.
[PDF File (Adobe PDF File), 809 KB - resprot_v14i1e67193_app1.pdf]

Multimedia Appendix 2
Consent form.
[PDF File (Adobe PDF File), 130 KB - resprot_v14i1e67193_app2.pdf]

Multimedia Appendix 3
Assent form.
[PDF File (Adobe PDF File), 107 KB - resprot_v14i1e67193_app3.pdf]

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Abbreviations

AKU-ERC: Aga Khan University Ethics Review Committee
CVI: content validity index
DASS-21: Depression, Anxiety, and Stress Scale–21 Items
GB: Gilgit-Baltistan
LMIC: low- and middle-income country
MSSI: Modified Scale for Suicidal Ideation
RCT: randomized controlled trial
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TALK: tell, ask, listen, and keep safe

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Protocol

Collection of Ambulatory Electrocardiogram and Behavioral Data for the Identification of Digital Biomarkers for Heart Failure (CATCH-ECG): Protocol for a Prospective Cohort Study

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Abstract

Background: Heart failure (HF) is a complex clinical syndrome with a high morbidity and mortality rate. Despite advancements in treatment, the recurrence of HF remains a significant challenge, often leading to deteriorating health conditions and increased pressure on the health care system. Early detection of recurrence is pivotal in mitigating and managing the adverse outcomes associated with HF.

Objective: The primary objective of this study is to collect data to facilitate the identification of digital biomarkers that may indicate deterioration of the heart and, ultimately, develop algorithms that can predict HF.

Methods: This prospective cohort study is conducted in Copenhagen, Denmark, and will recruit individuals diagnosed with decompensated HF. Participants will be followed for a period of 1 year, during which they will undergo a quarterly assessment period every 3 months. Each quarterly assessment period spans 7 days and involves continuous monitoring using an ambulatory electrocardiogram sensor. Throughout each quarterly assessment period, participants will also complete daily assessments and questionnaires. All data will be collected using a dedicated mobile app installed on the participants' personal smartphones and securely stored in a cloud-based system.

Results: This study is part of the Cardio-Share Model for Cross-Sectoral Ambulatory Treatment of Congestive Heart Disease Based on Personal Health Technology project. Technical and regulatory preparation started in 2023. Recruitment for this study started in January 2025 and is expected to be completed by the end of 2026. The dataset will be anonymized and published for further research.

Conclusions: This study aims to provide a comprehensive longitudinal open-source dataset of HF recorded in real-world ambulatory conditions that enhances our understanding of HF signs and symptoms. This dataset will provide an important source for detailed analysis and understanding of HF based on ambulatory and contextual physiological data. Such insight has the potential to enhance the clinical management of individuals with HF and enable them to handle their condition at home.

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KEYWORDS

heart failure; digital phenotyping; ambulatory electrocardiogram monitoring; electrocardiogram; ECG; mobile health; mHealth; wearables; cohort study

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Introduction

Heart failure (HF) remains an increasing global health threat despite improvements in diagnostic and therapeutic methods. Due to an aging population and improved care and life expectancy of patients, the burden of HF on the health care system is increasing in Denmark and elsewhere, wherein HF alone accounted for 2% of Danish total health expenditure. Approximately 8% of patients with HF succumb within 1 year of diagnosis in Denmark [1], whereas 50% of patients diagnosed with HF still pass away within 5 years [2,3]. By 2030, it is estimated that, within the age group of 65 to 70 years, the incidence of HF will increase to 8.5% from 4.3% in 2012 [4,5] (ie, an unprecedented 50% increase in a little less than 2 decades). The high morbidity and mortality associated with HF may, in part, stem from discrepancies between the treatment prescribed by the physician and the regimen actually followed by the patient [6]. Additionally, delays in reporting noticeable HF symptoms to a general practitioner may result in missed opportunities for timely and effective intervention [7].

It has been suggested to address the growing prevalence of HF incidence and the lack of efficient treatment using mobile health (mHealth) technology [8]. Access to mHealth technologies such as ambulatory electrocardiogram (ECG) sensors and HF-specific smartphone apps seems to reduce mortality and HF-related hospitalizations and, thus, may reduce the burden of HF on the health care system. Studies have shown that the use of telemedicine and remote monitoring of patients with HF is associated with a reduced risk of cardiovascular-related mortality [9,10] and a reduction in rehospitalization [11-14]. Thus, according to the European Society of Cardiology guidelines, telemonitoring of patients with HF may be considered a class IIb indication [15].

However, most studies investigate the outcome of the intervention and do not investigate whether the collected data can be used for real-time monitoring of disease worsening or prediction of HF. In contrast to CHA_2DS_2-VASc [16] and other scores for assessing risk of stroke, there are currently no scores that allow for prediction of worsening of HF. Moreover, telemonitoring typically only collects very coarse-grained data such as symptoms, weight, heart rate (HR), and blood pressure, and whether wearable technologies for detailed monitoring of heart rhythm offer additional benefits is uncertain [15].

The purpose of this study is to collect a “rich” ambulatory dataset on HF. The aim is to collect data over a long period (1 year) in the free-living and daily environment of the patient in a very detailed manner. This would enable the detection of HF worsening before clinical symptoms are present.

The collected data include both physiological (ECG) and movement sensor data from a heart monitor, contextual and behavioral data from the sensor in the smartphone, and a series of patient-reported data based on experience sampling and surveys on a daily and weekly basis.

The data collected in this study will then be used for the identification of digital biomarkers, which can be used for continuous monitoring of the cardiovascular condition of the patient in real time and provide the input for algorithmic models for predicting disease deterioration. This study is part of the Cardio-Share Model for Cross-Sectoral Ambulatory Treatment of Congestive Heart Disease Based on Personal Health Technology (CATCH) project and, thus, is named the CATCH-ECG study.

Methods

Study Design and Participants

This study is a prospective observational cohort investigation involving the enrollment of 40 individuals with a clinical diagnosis of HF residing either in their own homes or in nursing facilities. Participants are recruited from the outpatient population receiving treatment for HF decompensation at the Department of Cardiology, Bispebjerg-Frederiksberg Hospital (BFH), within the Capital Region of Denmark (RegionH). Eligibility for inclusion is determined according to the criteria outlined in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Participant age of >50 years
- Diagnosis of heart failure (HF) with any of the following International Classification of Diseases (ICD) codes: I50.40—unspecified combined systolic and diastolic (congestive) HF, I50.20—unspecified systolic (congestive) HF, I50.30—unspecified diastolic (congestive) HF, I50.42—chronic combined systolic and diastolic (congestive) HF, and I50.9—HF (unspecified)
- Presence of at least one of the following: hypertension, diabetes, coronary disease, prior clinical ischemic cerebral attack (stroke or transient ischemic attack), or silent infarcts observed in brain imaging
- Willingness to use a smartphone app and chest-worn electrocardiogram (ECG) monitor for 1 year
- Participants displaying symptoms suggestive of HF, such as dyspnea, orthopnea, paroxysmal nocturnal dyspnea, or edema

Exclusion criteria

- Participants receiving palliative care with severe or end-stage HF (ICD code I50.84)
- Participants with a pacemaker or implantable cardioverter-defibrillator
- Life expectancy under 1 year
- Other significant cardiac conditions that could confound ECG recordings, such as arrhythmias requiring intervention
- Participants who may not be able to consistently provide data or adhere to study protocols due to cognitive, logistical, or other reasons and unable to read and understand Danish or English

Participants are enrolled on a rolling basis. The target age range is 50 to 80 years, with a normal distribution and an equal number of men and women, and recruitment is limited to a European population due to the low sample size requirement. Recruitment started in the first quarter of 2025, with plans to complete data collection by the end of 2026.

Sample Size

The primary objective of this study is data collection for algorithm development rather than hypothesis testing. Therefore, the sample size is not obtained from a power calculation but rather to ensure a diverse range of data points; capture variations; and ensure sufficient representation for subgroups based on age, gender, and other demographic factors. The target sample size is 40 participants. Hence, we aim to contact approximately 70 participants given an approximate conversion rate of 60%.

End Points

The following end points are needed to develop algorithms that can predict worsening HF. The primary end point is information on death and rehospitalizations.

The secondary end point is worsening of HF, determined based on patient readmission with decompensated HF and quality of life (QoL), which are assessed using the following repeated questionnaires throughout the study: Fatigue Assessment Scale (FAS) [17] and EQ-5D-5L [18].

Study Timeline

The timeline of the study is shown in Figure 1. The study visits are conducted at baseline (week 1) and at the end of the study (week 52) in the clinic at BFH.

Figure 1. The main timeline of the study, showing the clinical phases (blue), the ambulatory monitoring phase (green), and the clinical data collection phase (purple). The study runs for 1 year (52 weeks) for each participant and includes 2 clinical visits (onboarding and offboarding) and 5 quarterly assessment periods (QAPs), each lasting 1 week. ECG: electrocardiogram; EMA: ecological momentary assessment.

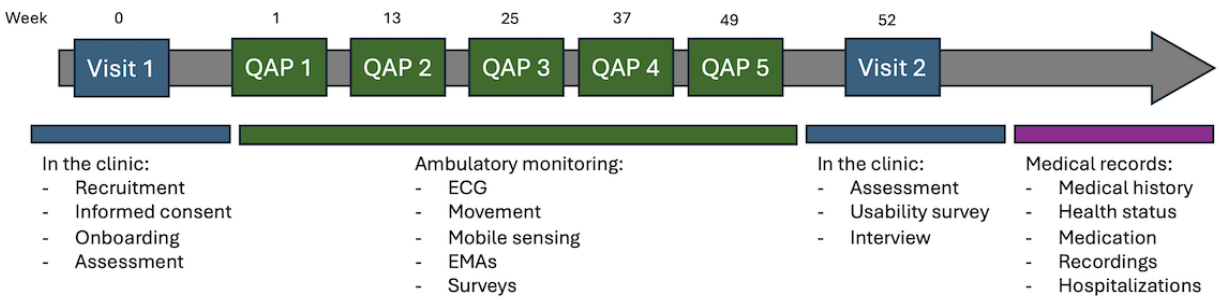

During visit 1 (onboarding), participants receive detailed information about the study and provide written informed consent. The study app is then installed on the participants' personal smartphones, and they are issued an ambulatory ECG sensor. Participants are guided through the setup process, including logging into the app, enrolling in the study, accessing study-related information, completing assigned tasks, pairing the ECG device with their smartphone, and replacing the sensor battery if necessary.

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As part of the onboarding visit, participants use the study app to fill in an onboarding survey collecting information about demographics, current cardiovascular diseases or problems, and smoking and drinking habits, as well as the FAS [17] and the EQ-5D-5L (QoL) [18] questionnaires. The participants are also helped to mount the device on their chest, connect it to the smartphone, and see the data being recorded. All of these activities also work as training in using the app and the sensor.

During the ambulatory monitoring phase, participants engage in 5 quarterly assessment periods, each lasting up to 1 week (7 days). Each quarterly assessment period is initiated through a phone call from the researchers.

During each quarterly assessment period, data are collected from the ECG sensor and the smartphone, as outlined in Table 1. This includes passive sensing data from the smartphone (top part of Table 1); electrophysiological and movement data from the ECG sensor; ecological momentary assessments (EMAs) on symptoms, sleep, stress, weight, and general health; and the FAS and EQ-5D-5L questionnaires. At the end of each quarterly assessment period, participants no longer need to wear the ECG sensor and can store it safely for the next quarterly assessment period. They can optionally continue to record their symptoms on the app. There are no clinical in-person visits during the ambulatory monitoring phase; all communication between the researchers and participants is done via the app or phone.

Table 1. Data features collected on the CARP (Copenhagen Research Platform) Studies app with source and sampling rate.

Source and parameter	Type of data collection	Sampling rate
Phone		
Device information	Sensed	Once
Battery	Sensed	EB[a]
Screen	Sensed	EB
Location	Sensed	EB
Steps	Sensed	EB
Activity	Sensed	EB
Weather	Sensed	30 min
Air quality	Sensed	30 min
ECG[b] sensor		
Device information	Sensed	On connection
HR[c]	Sensed	EB
ECG	Sensed	EB
IMU[d]	Sensed	EB
Device tap	PR[e]	EB
Participant		
Symptoms	PR	EB
Sleep	PR	Daily
Stress	PR	Daily
Weight	PR	Weekly
General health	PR	Weekly
Onboarding	PR	Once
Fatigue Assessment Scale	PR	Weekly
EQ-5D-5L	PR	Weekly

[a]EB: event-based.
[b]ECG: electrocardiogram.
[c]HR: heart rate.
[d]IMU: inertial movement unit.
[e]PR: participant-reported.

On completion of the study, participants attend a second clinical visit (offboarding), during which they fill in the FAS and EQ-5D-5L questionnaires one last time. They also complete the Copenhagen Center for Health Technology Unified Methodology for Assessment of Clinical Feasibility (CUMACF) [19] questionnaire in an online survey platform (Google Forms)

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plus an interview. The semistructured interview is designed to complement the questions asked in the CUMACF questionnaire and covers motivation for participation, usability, user-friendliness, acceptance, trust perceptions, and suggestions for improvements. A researcher interviews the participant either in the clinic or over the phone. This interview lasts no more than 30 minutes and is audio recorded. The CUMACF questionnaire and the interview play no role in data collection strategies or algorithm deployments.

Immediately after the offboarding meeting, clinical data on the participant are extracted from the medical record at BFH. The medical data collected are listed in Table 2.

Table 2. Data extracted from the medical record.

Category	Variables
Demographic information	Age, gender, race and ethnicity, height, and weight
Medical history	Hypertension, diabetes, atrial fibrillation, chronic lung disease, and cardiovascular disease
Health status	Diagnosis, NYHA[a] status, and HF[b] observations
Medications	Current medications from the following list: ACEi[c], ARB[d], β-blockers, mineralocorticoids, neprilysin inhibitors, HCN[e] channel blockers, nitrates, vasodilators, biguanides, loop diuretics, and thiazide diuretics
Cardiovascular measurements	Blood pressure, heart rate, ECG[f], and LVEF[g] measurements and recordings
Hospitalization and clinical visits	Hospital admissions and discharges, reason for hospitalizations, duration of stays, and cardiac procedures and surgeries

[a]NYHA: New York Heart Association.
[b]HF: heart failure.
[c]ACEi: angiotensin-converting enzyme inhibitor.
[d]ARB: angiotensin receptor blocker.
[e]HCN: hyperpolarization-activated cyclic nucleotide gated.
[f]ECG: electrocardiogram.
[g]LVEF: left ventricular ejection fraction.

Ambulatory Data Collection System

Data are collected using the Copenhagen Research Platform (CARP) [20]. CARP is a full-stack platform for digital phenotyping consisting of a back-end cloud-based infrastructure for the management of studies, participants, and data combined with a smartphone-based study app called CARP Studies [21] designed for running digital phenotyping studies. The study app is available for both iPhones and Android phones from the Apple App Store and Google Play Store, respectively. When a study is initiated in CARP, it is defined by a study protocol, which details what data are to be collected. This study protocol is downloaded to the app when the participant signs in and accepts the study invitation. The main user interface of the CARP Studies app is shown in Figure 2, showing details from the CATCH-ECG study protocol.

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Figure 2. The main user interface of the CARP (Copenhagen Research Platform) Studies app: (A) the task list shows the tasks that the user needs to attend to, (B) the study page shows a description of the study plus a set of messages to the user from the researcher, (C) the data visualization page shows the data collected, and (D) the device page shows the devices (such as the Movesense electrocardiogram sensor) and online services being used.

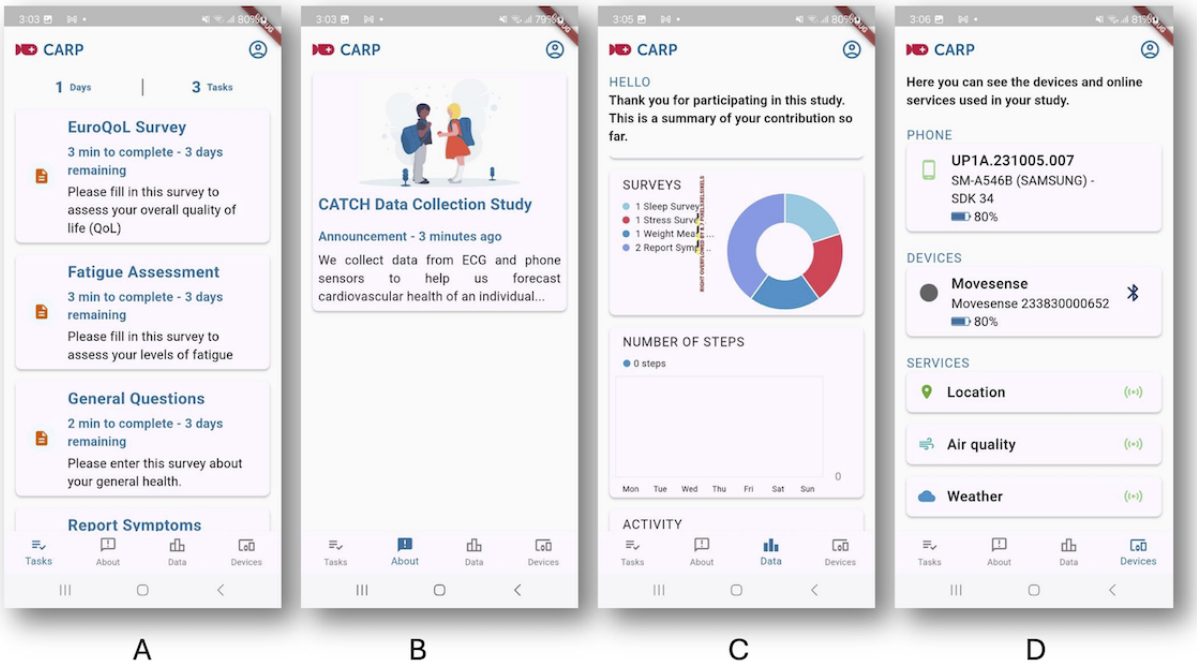

The app contains a description of the study and what data are being collected (Figure 2B). The app prompts users to perform scheduled tasks (Figure 2A) during their participation in the study, as described in Table 1. Tasks include providing details on experienced symptoms when felt; answering daily EMAs on, for example, stress and sleep; and filling in weekly surveys on fatigue and QoL. Participants receive notifications from the app when a task needs attention. The app continuously collects sensor data in the background, such as battery consumption, geolocation information, step count, and physical activity (Table 1).

In addition to the app, a chest-worn ECG sensor is used to collect continuous ECG, HR, and inertial movement data in free-living conditions. The CARP Studies app has an extensible software architecture [22] that allows users to use different brands of ECG devices. This study uses Movesense HR2 sensors (Movesense Oy) [23] and Cortrium C3+ (Cortrium ApS) [24]. The ECG sensor is connected directly to the study app using Bluetooth (Figure 2D). Movesense HR2 is a sports sensor for measuring 1-lead ECG, HR, and movement using a 3D accelerometer and gyroscope on board. The sensor is light in comparison to alternatives (9.4 g) and has options for being mounted using a band around the torso or, alternatively, using an adhesive electrode. Cortrium C3+ is an approved medical sensor for measuring 3-lead ECG and movement via the onboard 3D accelerometer. The sensor is heavier and is mounted using 3 adhesive electrodes.

The data collected is visualized in the app as shown in Figure 2C. This includes all types of data, such as participant-reported data, sensor data collected from the phone, and physiological data collected from the ECG sensor.

Data Collection

Table 1 summarizes the data types collected from the phone's sensors, from the ECG sensor, and as participant-reported data (both EMAs and surveys). The data collected are intended to reveal information about the participant's behavior (eg, screen activity and steps or inertial movement unit data), the environmental context (eg, location or weather), heart function (eg, ECG or symptoms), and general health and well-being (eg, sleep, stress, and fatigue assessments). It should be noted that this information originates from both sensor-based ("passive") and participant-reported ("active") data.

At the end of the study, as part of the offboarding visit, a usability assessment will be conducted using the CUMACF [19] method.

Table 2 summarizes the clinical data collected from the medical record. Clinical data are collected from a 5-year medical history when the study ends for each participant. These data provide a comprehensive view of the participants' health status before and during the data collection phase.

Data Management

Data during the study will be collected using the participants' personal smartphones and uploaded to a secure cloud infrastructure located at the Technical University of Denmark. Data collection on the participants' smartphones uses a randomly generated study-specific patient identifier. Clinical data on diagnosis, medical history, and medications, among other variables, will be collected at BFH and stored in a secure data storage platform (REDCap; Research Electronic Data Capture; Vanderbilt University [25]) in RegionH. Generation, transmission, storage, and analysis of health-related personal

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data during this study follow the European General Data Protection Regulation.

The Technical University of Denmark and RegionH are data controllers of their own data, and a shared data management agreement has been developed for sharing data in this study. The collected data will be kept as long as relevant for the research purpose of the study from which they were collected. This study does not share personal data with anyone outside the study, and personal data will not be published. It is the aim to publish the CATCH-ECG dataset in a public repository. All data will only be published anonymously and will have no personal identifiers.

Quality Assurance

Data are reviewed after each quarterly assessment period to monitor data quality, ensure compliance with tasks and proper data capture, and identify any usability or bugs in the system's setup. Noncompliant participants are contacted by the research team to explore reasons and propose solutions. Participants receive onboarding guidance for proper ECG sensor placement and are able to check that their HR is being detected correctly via the study app before starting the quarterly assessment period. While live signal quality monitoring is not performed during recording, all ECG data undergo detailed post hoc quality assessment using signal quality indexes and artifact detection during analysis.

A comprehensive report will be published summarizing the percentage of usable ECG and contextual data per participant and quarterly assessment period. Because ECG and smartphone sensors produce large, high-frequency datasets, moderate data loss is not expected to materially affect downstream analyses.

Outcome Assessment

The primary objective of this study is to predict rehospitalization or death due to cardiovascular symptoms, as specified in the End Points section. Secondary target data include the outcomes (increase or decrease) from the FAS [17] and EQ-5D-5L [18] questionnaires.

Data Analysis Plan

Digital Biomarker Discovery

This analysis focuses on leveraging ambulatory ECG data contextualized via actimetry sensor readings, smartphone-based activity detection, and participant-reported symptoms to identify anomalous cardiovascular patterns through statistical and machine learning methods. Known ECG-based risk indicators, particularly low HR variability [26,27], will be assessed across different contextual settings—rest, sleep, and intensive physical activities—to refine their prognostic capabilities regarding cardiac deterioration.

Further complex analyses will use machine learning techniques to detect both interpretable and black-box anomalies. For interpretable anomalies, multiple ECG-derived features such as P wave amplitude, QRS energy, and others will be computed. These features will be clustered together with contextual activity data to establish correlations with the primary and secondary study targets. Black-box anomaly detection will be conducted using advanced deep learning approaches, notably multi-instance learning, following methodologies similar to those proposed by Kamranfar et al [28].

Adaptive Risk Score Formulation

Another dimension of analysis will involve correlating established cardiovascular risk metrics—such as HR turbulence, HR recovery, and atrial fibrillation burden—with clinical end points and blood biomarkers, particularly kidney function and hemoglobin levels. The principal outcome of this analysis and of the broader dataset is the development of improved predictive risk scores for HF rehospitalization. These novel predictive scores will be benchmarked against traditional risk assessment tools, including the Framingham Risk Score and the pooled cohort equations, paving the way for a more personalized risk assessment.

Another important aspect of the collected data is the multiple recordings at quarterly assessment periods. Both the primary and secondary analyses will be conducted considering these repeated measures to observe the temporal evolution of digital biomarkers and risk scores as they approach the study end points. This approach aims to reveal whether a patient's health is improving or declining, thus enabling medical practitioners to make timely decisions to prevent further health deterioration.

Model Development and Evaluation

Feature selection will be guided by both clinical interpretability and statistical relevance. Candidate features include ECG-derived measures (eg, HR variability, QRS duration and amplitude, and P wave morphology) and contextual smartphone or actimetry signals (eg, sleep, activity intensity, and HR recovery). Data-driven importance ranking will be performed using mutual information, recursive feature elimination, and Shapley Additive Explanations values derived from preliminary models. Model training will follow a nested cross-validation strategy with patient-level outer folds to avoid temporal or patient-level data leakage. Inner loops will be used for hyperparameter tuning and feature subset optimization.

Model performance will be reported using the area under the receiver operating characteristic curve, the area under the precision-recall curve, the F_1-score, the Brier score, and calibration curves, with additional metrics (sensitivity and specificity) for binary classification tasks. Comparative analyses between interpretable and black-box models will be conducted to assess robustness and clinical utility.

Compliance, Usability, and Acceptance

Participants' compliance is measured using logs from the study app, which reveal what tasks have been completed and which EMAs and surveys have been answered. Compliance with ECG monitoring during the quarterly assessment period is extracted from the collected data.

Usability and long-term acceptance of the app will be assessed based on the CUMACF surveys and by performing a thematic analysis of the interviews. Compliance thresholds are defined a priori: ≥72 hours of usable ECG signals per 7-day quarterly assessment period and a ≥60% EMA response rate are considered adherent. Nonetheless, any participant contributing

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data temporally linked to clinical end points will be retained in an *intention-to-include* analysis, recognizing that even partial data may reveal meaningful pre-event signal patterns.

Ethical Considerations

The study will be conducted based on the principles expressed in the Declaration of Helsinki. The study, including the study protocol and all participant information materials, has been approved by the Scientific Ethics Committee for the Capital Region of Denmark (H-24052433).

Participants will receive both written and verbal information about the study. They will be given 24 hours to consider their participation and are encouraged to consult with a close relative such as a spouse or friend, if desired. Informed consent will be obtained through a signed consent form before enrollment in the study. Participants can withdraw from the study at any time during the study process, and they are informed that this has no consequence on their ongoing treatment at BFH.

The primary risk in this study is that participants may gain a false sense of reassurance, believing that they are being closely monitored. This is mitigated by informing the participants that they are not in any way monitored by health care staff during the study. This information is given at the onboarding visit and throughout the study. Participants are informed to always contact their physician if they have questions or concerns about their health. Participants may be exposed to discomfort when they wear the ECG monitor for a week. This discomfort has been mitigated by providing an ECG monitor that is small (37 × 37 × 8 mm) and lightweight (9.4 g) and can be attached to the participants' chest using either a strap or a self-adhesive electrode. Participants may spend more time on their smartphones due to this study, yet use of the app is voluntary, and participants can choose how much time they spend on the app without any consequence.

There will be no remuneration to the participants for taking part in the study, but they will be reimbursed for direct expenses related to the study, such as travel costs.

Data management is subject to the privacy policy of the Technical University of Denmark. This study will not share personal data with anyone outside the study. Personal data will not be published. However, as part of this research, the data will be subject to processing and analysis, and the results of such analyses will be disseminated through scientific publications in academic journals, conferences, and public datasets. Moreover, any such results will be published only in anonymized formats with no person-identifiable data.

Results

Study recruitment started in January 2025. This study is in the data collection phase. Data analysis is scheduled to start after all the data are collected. As of December 2025, we have recruited 9 participants. The Python scripts for data extraction and analysis are now available in an initial version. Results are expected to be published in 2027.

Discussion

Principal Findings

Several research studies have investigated the use of digital health technology for home monitoring of patients with HF, and promising results have been reported [9-14]. Telemonitoring of patients with HF is a class IIb indication according to the European Society of Cardiology guidelines [15]. Telemedicine seems to be a favorable way of patient management due to the possibility of detecting health deterioration in the early stages, especially in patients with chronic disease, where a regular follow-up is beneficial. In terms of chronic HF, the worsening of HF symptoms or, ultimately, HF decompensation could be prevented through regular telemedical follow-up visits, with the possibility of making early adjustments to the therapy and, through that, potentially preventing hospital admissions.

This study advances the field of cardiovascular disease management and digital health monitoring by facilitating the discovery of digital biomarkers based on longitudinal, ambulatory, contextual, and detailed monitoring of HF in the patients' free-living environment. By integrating passive collection of physiological, contextual, and behavioral data with active collection of patient-reported EMAs and surveys, this study offers a nuanced understanding of heart behavior during daily activities and sleep. This dataset will provide an unprecedented insight into the everyday details of patients living with HF. In turn, this will allow us and other researchers to design and evaluate advanced data science machine learning models for the identification, classification, clustering, and prediction of HF-related problems.

This foundational data science research will promote further research into mHealth apps for monitoring based on mobile and wearable sensing, replacing traditional norms that require a patient to travel to their health care provider. Through future development and validation of predictive models for HF deterioration, this study contributes to the creation of early intervention tools that can alert health care providers and patients about potential exacerbations. This proactive approach could prevent severe episodes and hospitalizations, reducing the burden on the health care system.

Limitations

Although the data acquired are novel and a valuable resource in learning more about contextual ECG rhythms in patients with HF, there are several limitations to this study.

First, the sample size of 40 participants, although sufficient for initial explorations of digital biomarkers, is relatively small and may not provide enough power to detect subtle associations or generalize the findings to the broader HF population. Second, participants are recruited from a single hospital in Copenhagen, which may limit the diversity of the study population and introduce selection bias. The homogeneity of the sample population may introduce difficulties when extrapolating the model to heterogeneous cohorts. Third, the reliance on technology in real-world settings introduces several challenges, including communication errors, which may lead to incomplete data capture. As participants are responsible for fitting their

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own ECG sensors, there is a potential for incorrect placement, which could introduce noise and artifacts in the ECG signals. Fourth, noncompliance or inconsistent use of the wearable devices or smartphone app could lead to data loss or incomplete datasets, affecting the study outcomes. Fifth, although the study design attempts to account for known confounders, there may be unmeasured variables that could influence the outcomes, such as socioeconomic factors, dietary habits, or other medical conditions. Sixth, the study relies on participant-reported measures on the app, which are subject to bias. Participants' reports might be influenced by their current health status, their mood, or misunderstandings of the questions.

Comparison With Prior Work

While there are other open-source datasets such as the Sleep Heart Health Study [29], they are not focused on cardiology-related outcomes and contain only polysomnographic data. The Copenhagen Center for Health Technology Contextualized Arrhythmia Database [30] is a good source of ambulatory ECG recordings, but it only has atrial fibrillation as a clinical outcome. The Telehealth Network of Minas Gerais [31] dataset contains all-cause mortality outcomes, including HF, and is used in deep learning–based data science analysis [32]. However, it only records 10-second ECG data at baseline in the clinic and not in an ambulatory manner. The Medical Information Mart for Intensive Care [33] dataset contains detailed physiological signals recorded from intensive care unit patients and includes HF events and patients but is not recorded in an ambulatory manner. The Sudden Cardiac Death in Chronic Heart Failure [34] is a dataset that contains ambulatory ECG recordings over an entire day but does not contain actimetry data or other valuable contextual information. This dataset also focuses on sudden cardiac death in end-stage HF (New York Heart Association class 3-4). There are multiple ambulatory ECG databases, such as the Beth Israel Deaconess Medical Center Congestive Heart Failure Database [35], China Physiological Signal Challenge 2021 database [36], and the Icentia11K dataset [37], but none of them contain follow-up outcomes that are needed for evaluation of HF risk. The proposed dataset from the CATCH-ECG study is, to the best of our knowledge, not available in the open-source clinical data repositories.

Conclusions

The CATCH-ECG study aims to collect data that help design a set of digital biomarkers for recognition, classification, and prediction of HF decompensation in an ambulatory setting. The data are collected and managed by the CARP infrastructure, including the CARP Studies app used by the participants. Data collection runs for a year (52 weeks) and includes five 1-week sampling periods (quarterly assessment periods). The data collected include ambulatory monitoring of physiological (eg, ECG), contextual (eg, geolocation), and behavioral (eg, physical activity) data combined with active collection of patient-reported EMAs (eg, on sleep) and surveys (on fatigue and QoL). Data collection also includes clinical data from the participants' medical records as well as qualitative usability data on the use of the sensor technology. The aim is to identify and publish the digital biomarkers along with an anonymized and publicly available dataset.

The potential scientific benefits of this study are substantial. By continuously monitoring heart activity using noninvasive ECG sensors and a mobile app, this study has the potential to provide a basis for developing predictive algorithms for the early detection of HF deterioration. Early detection can lead to timely interventions, reducing the need for hospital readmissions and improving patient outcomes. This proactive approach has the potential to benefit future patients by providing a model for effective HF management. Moreover, the collected data will contribute to the broader understanding of HF, aiding in the development of better treatment protocols and digital health solutions. This study is expected to significantly advance HF management by enabling early intervention and reducing health care system burden.

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Authors' Contributions

Conceptualization: JEB (lead), HD, SP, GM, CC
Formal analysis: GM (lead), SP, JEB (supporting)
Funding acquisition: HD (lead), JEB, SP
Methodology: CC (lead), GM, HD, JEB (supporting)
Project administration: JEB, HD
Resources: JEB
Software: JEB (lead), GM
Supervision: JEB (lead), HD, SP
Visualization: JEB (lead), CC (supporting)
Writing – original draft: JEB, GM, CC (lead), HD (supporting)
Writing – review & editing: JEB (lead), GM, CC (supporting)

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Conflicts of Interest

None declared.

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Abbreviations

BFH: Bispebjerg-Frederiksberg Hospital
CARP: Copenhagen Research Platform
CATCH: Cardio-Share Model for Cross-Sectoral Ambulatory Treatment of Congestive Heart Disease Based on Personal Health Technology
CUMACF: Copenhagen Center for Health Technology Unified Methodology for Assessment of Clinical Feasibility
ECG: electrocardiogram
EMA: ecological momentary assessment
FAS: Fatigue Assessment Scale
HF: heart failure
HR: heart rate
mHealth: mobile health
QoL: quality of life
REDCap: Research Electronic Data Capture

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Protocol

Transdiagnostic App–Based Cognitive Bias Modification Intervention for Paranoia (Successful Treatment of Paranoia; STOP): Protocol for a Mixed Methods Process Evaluation Embedded in a Randomized Controlled Trial

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Abstract

Background: Paranoia (unfounded concerns that other people are deliberately trying to harm you) can be a distressing experience that impacts day-to-day functioning for many people. Digitally delivered interventions are a promising mode of treatment that can increase access to support and reach populations underserved by current provision. One such intervention is the Successful Treatment of Paranoia (STOP) intervention, which is a transdiagnostic self-administered smartphone app for paranoia that was evaluated in England for efficacy in a large, multisite randomized controlled trial. Although there is growing evidence regarding how STOP may work, little is known about the factors that influence its implementation during or after a trial. Understanding these factors is critical for supporting the future adoption of STOP and may inform the implementation of other digital mental health interventions.

Objective: This paper aims to describe the protocol for a process evaluation that will explore intervention implementation to understand how much, by whom, and under what circumstances STOP was used in a trial context and what factors might influence future implementation in routine practice.

Methods: We will conduct a mixed methods process evaluation informed by guidance published by the Medical Research Council in the United Kingdom and embedded in the main STOP efficacy randomized controlled trial, with the aim of understanding who agreed to try STOP, how they used STOP, and users' and health care professionals' views on factors that will affect future implementation, including barriers and facilitators. Process evaluation participants will include three samples: (1) STOP trial participants (randomized participants and nonrandomized referrals who agreed to try STOP), (2) individuals experiencing paranoia who participated in the Adult Psychiatric Morbidity Survey in England, and (3) health care professionals in England. We will use mixed methods data collected in the STOP trial (demographics, app use, recruitment data, and qualitative data exploring intervention acceptability from the perspectives of users and health care professionals) and demographic data from another paranoia population collected in the Adult Psychiatric Morbidity Survey.

Results: The STOP trial was completed in December 2024, having recruited 274 participants. The process evaluation received funding in winter 2023. As of December 2025, data analysis for process evaluation studies 2 and 3 is ongoing following preregistration in July 2025. Results are expected to be completed and submitted for publication by February 2027.

Conclusions: Findings from this process evaluation will help develop an evidence-based understanding of implementing STOP, including identifying suitable implementation strategies for posttrial delivery both inside and outside mental health services. Our

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findings will inform future iterations and the upscaling of STOP and may inform implementation of other self-administered digital mental health interventions.

Trial Registration: International Standard Registered Clinical/Social Study Number ISRCTN17754650; https://www.isrctn.com/ISRCTN17754650

International Registered Report Identifier (IRRID): DERR1-10.2196/81167

(JMIR Res Protoc 2025;14:e81167) doi:10.2196/81167

KEYWORDS

paranoia; digital mental health; smartphone intervention; implementation; randomized controlled trial; process evaluation; implementation science

Introduction

Background

Paranoia refers to concerns that others may intend to harm you [1,2]. Freeman's [1] theoretical model of paranoia suggests a hierarchy, whereby more severe forms of paranoid worries in clinical populations (eg, believing others are trying to kill you) build on milder, everyday forms of social evaluative concerns (eg, believing others are talking about you behind your back), which are commonly experienced in the general population. Paranoia is often a distressing experience that can negatively interfere with many aspects of life, including people's everyday activities [3] and interpersonal relationships [4]. Many people can experience paranoia, including those with psychosis spectrum disorders, but it is also a transdiagnostic symptom and can be present in other mental health conditions as well, including depression and anxiety disorders [5]. Paranoia can also be experienced by nonclinical populations across the lifespan [3,6].

To improve the lives of those experiencing paranoia, developing support (eg, to reduce paranoia or sustain recovery) for this population has been identified as a research priority by patients, carers, researchers, and health care professionals in an international priority setting partnership [7]. One promising treatment mode for those experiencing paranoia is digital mental health interventions (DMHIs), or treatment that incorporates technology to improve users' mental health [8]. An early value assessment conducted by the National Institute for Health and Care Excellence identified specific DMHIs as suitable for full recommendation, subject to further data collection [9]. Early recommendation of this sort can improve the provision of care by increasing treatment options and access to support using fewer resources than in-person treatments [9]. Preliminary evidence suggests that DMHIs may be an acceptable and feasible treatment for paranoia [10].

What Is Successful Treatment of Paranoia?

While other DMHIs for paranoia have been developed, most are delivered via virtual reality, require clinical support, or focus on other psychotic experiences (eg, voices) and pay limited attention to more common, social evaluative concerns within paranoia (eg, that others are talking about you negatively) [10]. Successful Treatment of Paranoia (STOP) was developed to address these limitations by providing a self-delivered, smartphone-based transdiagnostic intervention specifically targeting interpretation biases underpinning paranoia. The intervention and its development have been described in detail elsewhere [11,12]. A brief description is included to contextualize our work.

STOP is a self-administered psychological intervention using the principles of cognitive bias modification for paranoia (CBM-pa). CBM-pa aims to address the cognitive interpretation bias that is thought to cause and maintain the symptoms of paranoia [13]. Individuals displaying this interpretation bias often interpret neutral or ambiguous social scenarios as personally threatening [13]. There is preliminary evidence from a feasibility randomized controlled trial (RCT) that interpretation biases can be modified by CBM-pa that was delivered via a desktop computer in a research laboratory setting (N=63) [14].

STOP in the RCT included a weekly session administered through a smartphone app either on users' personal smartphones or, if needed to avoid digital exclusion, on a study phone with a data plan provided free of charge to participants. Two versions of the intervention of varying lengths were evaluated to investigate "dose" effects (6 vs 12 weeks). Users scheduled weekly sessions at convenient times, during which they read 40 everyday social scenarios. In the sessions, users were encouraged to interpret ambiguous social scenarios in a nonthreatening way by completing a word puzzle and then answering a question about the meaning of the scenario (Figure 1 includes an intervention example). Session content was designed by clinicians, academics, and the McPin Foundation research charity's STOP lived experience advisory panel (LEAP) of 7 people who give voice to intended end users of the app to increase its clinical relevance and acceptability to users [11]. Automated phone and email reminders were sent at midnight 1 day before the scheduled session and again if a session was not completed on the scheduled day.

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Figure 1. Successful Treatment of Paranoia (STOP) intervention example.

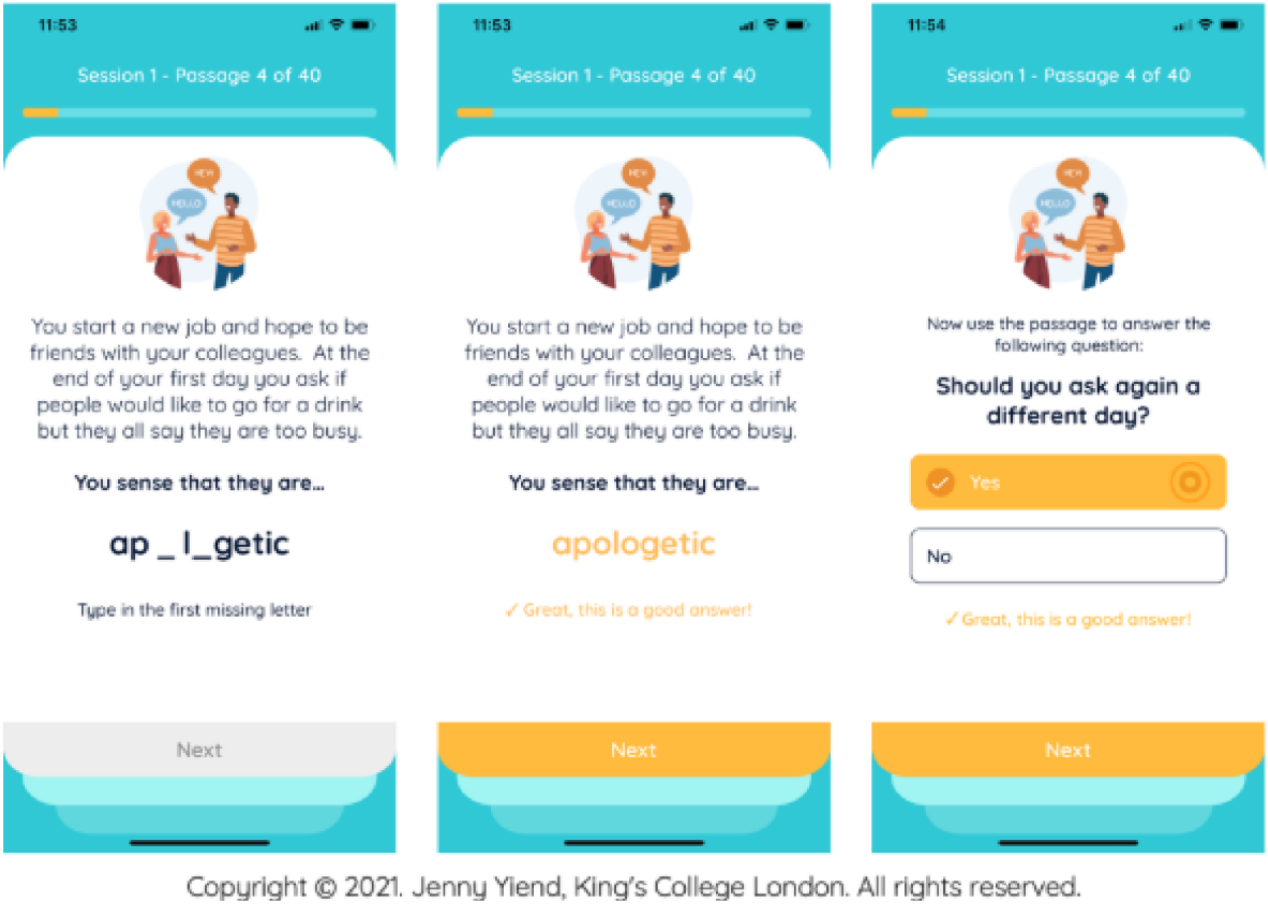

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How Do We Think STOP Will Work?

Program theories underpin interventions and explain how, why, for whom, and in which circumstances interventions are assumed to work and can be represented visually in a logic model [15]. A logic model for the STOP intervention was created after conducting a document analysis of the trial protocol and publications associated with the intervention (Figure 2) [11,12]. An initial program theory was developed from the logic model (Textbox 1).

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Figure 2. Logic model for the Successful Treatment of Paranoia (STOP) intervention.

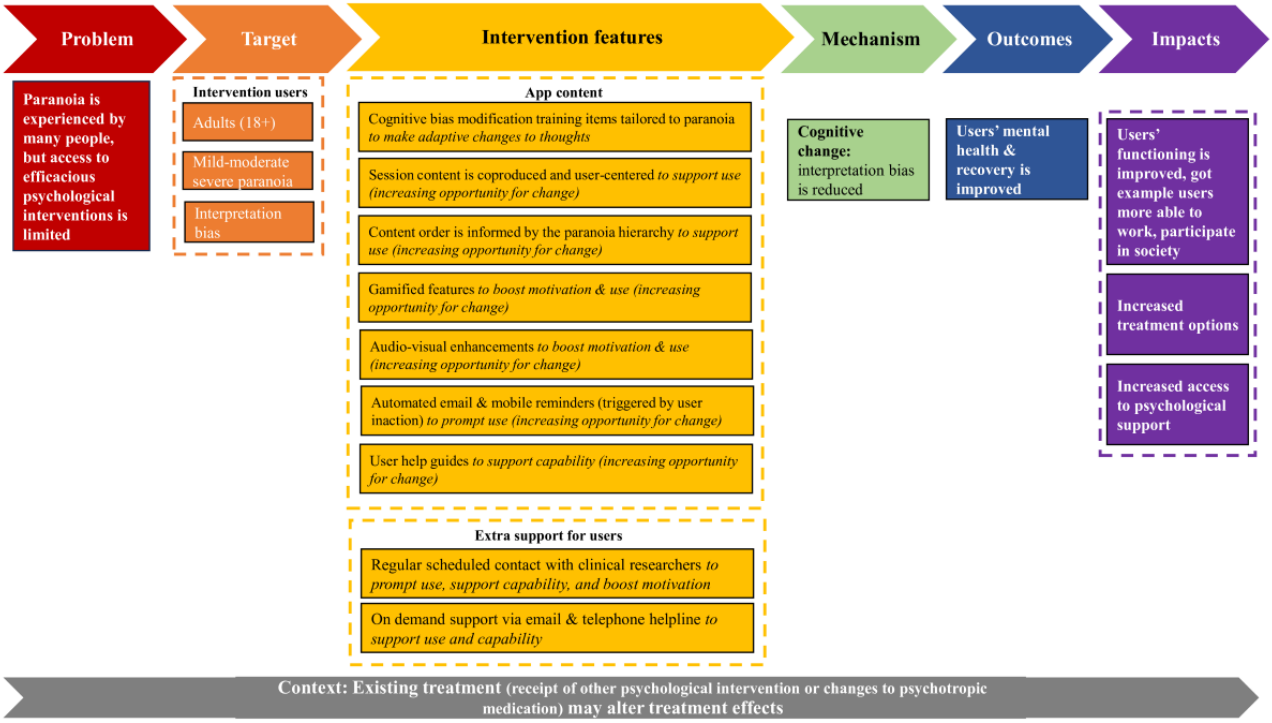

Textbox 1. Program theory for the Successful Treatment of Paranoia (STOP) intervention.

- Users complete cognitive bias modification for paranoia (CBM-pa) training items delivered via a smartphone app, which creates a cognitive change that enables the user to consider a more neutral interpretation of ambiguous situations.
- The cognitive change has a positive impact on users' mental health and recovery, including reducing symptoms of paranoia.

Why Conduct a Process Evaluation?

We will conduct a process evaluation to better understand the factors influencing DMHI implementation both during and after the trial. Exploring factors that may influence implementation is an important research focus as the implementation of DMHIs is a persistent challenge [16,17], and it is also acknowledged that interventions may be used differently across settings and populations [18,19]. There is some empirical evidence for this as reviews have demonstrated DMHI use can vary due to several factors, including patient characteristics (eg, age) and intervention features (eg, including human support) [20]. However, implementation remains a key area of uncertainty in the STOP trial as it is currently unknown what, or if any, factors influence the implementation of STOP (Figure 2, context box). A limited understanding of implementing STOP contrasts with a comparatively better understanding of how STOP is assumed to work, for which there is a growing evidence base [13,14] and plans to evaluate mechanisms of action in other trial work [12]. Intervention implementation is an important uncertainty to address given that STOP has the potential to be implemented in a variety of settings (as users choose where and when sessions are accessed) and by a variety of potential end users (as users may not need to be under the care of a health service or have a formal mental health diagnosis to use STOP) [12].

Evaluation Objectives

Our work aims to address these knowledge gaps by exploring the factors that influence the implementation of a self-administered digital intervention for paranoia in and after an RCT. The overarching objective of this evaluation is to develop an evidence-based understanding of implementing STOP by investigating how much, by whom, and under what circumstances STOP is and may be implemented in and after a trial. A secondary objective is to use this knowledge to identify the barriers and facilitators to implementing STOP in and after a trial.

Methods

Overview

We will conduct a mixed methods process evaluation of STOP. The protocol is reported using an amended version of the process evaluation recommendations from the Medical Research Council (MRC) process evaluation framework (Table S1 in Multimedia Appendix 1) [18]. We amended the reporting standards to fit the reporting of a protocol paper by removing sections that are not applicable (ie, those relating to reporting evaluation findings). Details of the core research team (CH, CD, JY, and PJ) are provided in Multimedia Appendix 2.

Ethical Considerations

The STOP trial was preregistered at ISRCTN (ISRCTN17754650) and approved by the London-Stanmore

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Research Ethics Committee (21/LO/0896, January 14, 2022) and the Medicines and Healthcare products Regulatory Agency (CI/2022/0033/GB, July 19, 2022), including approval for collecting additional qualitative data with STOP users and health care professionals. An additional qualitative study involving STOP trial participants was conducted and approved separately by the University of Bath Social Sciences Research Ethics Committee (0179-353). Written informed consent was obtained from all participants prior to data collection, with the option to withdraw at any time without specifying a reason. Participants were compensated for their time: trial participants received up to £115 (US $153; £20 [US $26.6] per follow-up assessment, an additional £20 [US $26.6] at the trial end, and £15 [US $19.95] after completing an additional interview), health care professionals received a £20 (US $26.6) voucher, and nonrandomized STOP users received £40 (US $53.2). All participants were assigned unique study identifiers, and only fully anonymized and deidentified data will be accessed for analyses. The process evaluation was approved by the University of Bath Social Sciences Research Ethics Committee as a requirement of the doctorate (5841-6196). Further ethics approval was not required because the process evaluation did not introduce additional trial procedures or data collection and will only use existing data from participants who consented to data archiving.

Process Evaluation Design

We will use the 2015 MRC process evaluation guidance as a methodological framework, which assumes that an efficacy evaluation in isolation provides a limited understanding of an intervention [18]. Instead of evaluating intervention efficacy, process evaluation in the MRC framework explores 3 proximal outcomes which can complement efficacy evaluations (Textbox 2) [18].

Textbox 2. Medical Research Council (MRC) process evaluation components.

- Context: external factors that influence intervention functioning or delivery.
- Implementation: intervention delivery in the evaluation.
- Mechanisms of impact: how interventions produce change.

How is STOP Being Evaluated?

Efficacy RCT

The process evaluation is embedded within the host RCT evaluating the efficacy and safety of STOP compared with an active control condition (a 12-week text reading control delivered through the STOP app, where users read and responded to items, including facts or unambiguous everyday experiences without a social component, such as making a cup of coffee) [12]. The RCT was preregistered (ISRCTN17754650), and a detailed protocol has been published [12]. The RCT was run by 2 main recruitment coordinating hubs at King's College London and the University of Bath in England [12]. Recruitment in the RCT ran from September 2022 to June 2024, closing after 274 participants were randomized, and data collection was completed in December 2024. Participants were recruited from 3 main sources, including 20 National Health Service (NHS) trusts, third sector organizations coordinated by the McPin Foundation, and via self-referral routes using recruitment posters or the study website [12]. Individuals aged 18 years or older who were experiencing mild to moderate-severe paranoia (operationalized as a score between 3 and 6 out of 7 on item 6 on the Positive and Negative Syndrome Scale [21] during screening) and displaying an interpretation bias toward paranoid meanings (operationalized as a score between −2 to +3 on a scale ranging from −3 to +3 the Similarity Rating Task during screening) were eligible for the RCT [12]. Individuals who were at high risk of suicide, lacked the capacity to consent, or could not communicate in written or spoken English were excluded from the RCT [12].

Planned Process Evaluation Studies

We will conduct 3 studies that will explore the implementation of STOP. The data sources and research questions per study are summarized in Figure 3. Study methods and progress are reported for each of the planned studies in further detail below. The process evaluation is preregistered on the Open Science Framework [22].

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Figure 3. Overview of Successful Treatment of Paranoia (STOP) process evaluation questions and methods. RCT: randomized controlled trial.

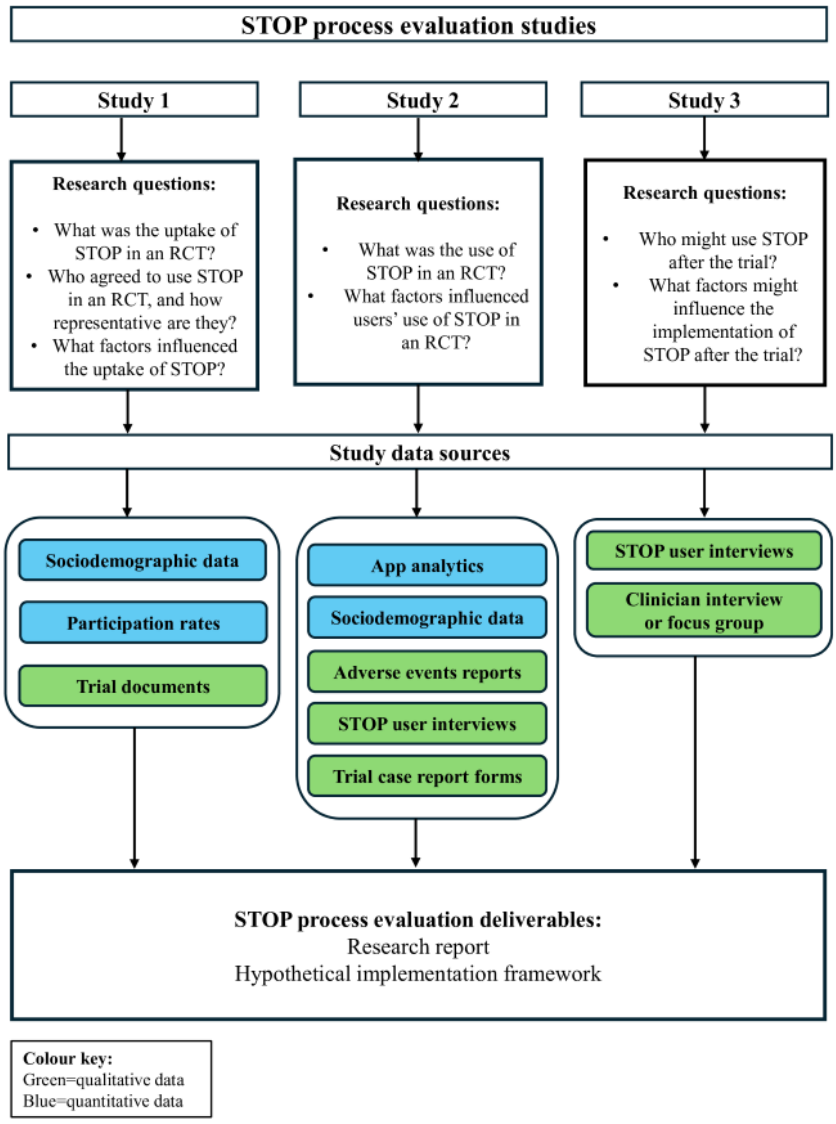

Study 1: Exploring the Uptake of STOP in an RCT

Overview

This mixed methods study will conduct analyses on STOP trial routine data and secondary analyses on sociodemographic data from another paranoia population in England.

Aim

To summarize who agreed to take part and try STOP in a trial (STOP uptake), to describe factors that influenced uptake, and to characterize and assess the representativeness of those agreeing to try STOP compared with another paranoia population in England.

Participants and Recruitment

STOP RCT participants and recruitment procedures are described earlier (in the Efficacy RCT section) and in full in the protocol paper [12].

Measures

Measures will include intervention uptake, factors influencing uptake, and the characteristics of individuals who agreed to try STOP compared with a paranoia population in England. Intervention uptake will be summarized using trial records to report the number and percentage of those agreeing to try STOP out of those who were approached to take part in the trial at different time points in the RCT (eg, consent, screening, and randomization) to summarize the uptake of STOP in a trial.

Factors influencing uptake will be identified from qualitative reasons reported by those agreeing to and declining to try STOP at different time points in the RCT (eg, consent, screening, and randomization), using STOP trial documents (eg, CONSORT diagrams, STOP case report forms, and recruitment trackers) to describe factors that facilitated or hindered the uptake of STOP in a trial.

Characteristics of those agreeing to try STOP compared with a paranoia population in England will be assessed using sociodemographic data obtained from STOP trial baseline data and from the Adult Psychiatric Morbidity Survey (AMPS) conducted in 2023 to 2024 by Public Health England, which provides data about treated and untreated psychiatric disorders among adults in England [23], to characterize and assess the representativeness of those agreeing to try STOP. We will

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compare those who agreed to try STOP with the subsample of responders endorsing items indicating paranoid thinking, which is a method that has been adopted in other analyses of AMPS [24,25]. We are unable to prespecify the variables or which items and measures will be used to indicate paranoia because data from the AMPS are not available at the time of publication [23]. However, based on the most recently available AMPS dataset published in 2016 [26], probable variables include age, sex, ethnicity, living arrangement, region, employment status, and current treatment.

Analysis

Rates of uptake will be summarized descriptively. Qualitative data from STOP trial documents will be analyzed in the latest version of NVivo (Lumivero) to provide an audit trail using a framework analysis approach [27,28], and findings from all trial documents will be triangulated. We will use the Consolidated Framework for Implementation Research (CFIR) [29] as a deductive framework to identify factors influencing uptake. Data that cannot be coded using a priori codes from the framework will be inductively coded in an "other" category. Qualitative analysis will be led by CH, but codes and themes will be developed and reviewed by the core research team (CD, JY, and PJ). STOP trial participants will be characterized using descriptive statistics from the trial's main outcome paper, supplemented as necessary by further information. Exploratory quantitative analyses will be conducted using relevant packages in the most recent version of R software (R Foundation for Statistical Computing) to test for between-group differences using chi-square tests and 2-tailed *t* tests where appropriate. If necessary, a *P* value correction will be used to account for multiple testing.

Status

Data collection is complete, but analysis has not yet started.

Study 2: Exploring How Much STOP Was Used in an RCT, and by Whom

Overview

This mixed methods study will use STOP trial routine data and will conduct secondary analyses of qualitative data generated from interviews with STOP users who consented to data archiving. The interviews were originally conducted as part of a qualitative evaluation of the host STOP trial or other research work, and not as part of the planned process evaluation, and have been previously disseminated as peer-reviewed publications [30,31].

Aims

To summarize how much STOP was used in an RCT, to characterize users of STOP, and to describe factors that predicted or influenced its use.

Participants

Participants include 182 trial participants who were randomized to the intervention arms, and 10 STOP intervention users consenting to participate in interviews for data archiving. The eligibility criteria for trial participants are described earlier (in the Efficacy RCT section). No exclusion criteria were added to participate in the interview studies, although STOP users needed an email account and access to a phone or computer to take part [30,31]. Interviewees were predominantly female (15/25, 60%) and White (16/25, 64%) [30].

Recruitment

The recruitment procedure for the host STOP trial is described earlier (in the Efficacy RCT section). In the qualitative studies, 2 samples participated in a one-off interview. The first sample comprises 8 participants who had completed the host STOP trial, were randomized to an intervention arm, provided informed consent for an optional qualitative interview, and consented to data archiving [30]. The second sample included 12 participants who were ineligible for the host trial but had tested a 6-week version of the STOP intervention on a dedicated study phone and consented to a one-off interview; the 2 participants who consented to data archiving will be included in our analyses [31].

Measures

Measures will include intervention use, predictors of use, and factors that hindered or facilitated use. Intervention use in the trial is the primary outcome of study 2 and will be quantified and treated as a count variable based on the number of sessions completed (0-6 or 0-12) for 6 or 12 weeks, which was electronically monitored by a digital health platform (HealthMachine; Avegen Health). Acceptable and target session completion was defined in the study protocol as the user entering a response on 20 (50%) or 30 (75%) training items per session, and both completion rates will be considered.

Predictors of use will be selected from 10 quantitative variables in STOP trial routine baseline data. Our selection was informed by available trial data and an existing digital engagement model [32]. The digital complexity model proposes a person-centered approach to treatment and is informed by established models of engagement [32], such as the cumulative complexity model [33] and has been adopted in other evaluations [34]. Predictors include user variables (life demands, resources, and clinical characteristics) and STOP intervention variables (delivery device and therapy burden). User life demands include self-reported employment and marital status. User clinical characteristics include self-reported number of years living with paranoia, self-reported paranoia severity measured using a validated clinical measure (the Paranoia Worries Questionnaire) [35], and interpretation bias severity measured using the Similarity Rating Task. We selected the most sensitive measures of paranoia and interpretation bias severity as predictors after observing data in the host trial. User resources include self-reported dyslexia and premorbid IQ measured using the Wechsler Test of Adult Reading [36]. Intervention components include the STOP delivery device (users' own smartphone or a study-provided phone) and intervention length (6 or 12 weeks, based on the allocated trial arm), both recorded in electronic databases used for the trial (MACRO; Ennov and HealthMachine).

Barriers to intervention use will be identified from qualitative self-reported reasons for lack of use from 3 sources. First, users reported reasons for missed sessions during check-in calls with a trained researcher. Second, reasons for withdrawal from the

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host trial are recorded in an electronic database (MACRO). Third, pooled interviews with STOP users will be used to identify whether any factors that hindered use were reported outside of routine trial data.

Facilitators to intervention use will also be identified from pooled interviews with STOP to determine whether any factors that facilitated intervention use were reported outside of routine trial data.

Procedure: Qualitative Interviews

A semistructured topic guide was created for each qualitative study (Supplementary Materials S1 and S2 in Multimedia Appendix 3). The topic guides were developed to explore users' experiences of a digital therapeutic relationship [30] and the perceived acceptability of STOP [37]. Trained researchers (TT and LE) conducted all one-off interviews online, which were recorded and transcribed. Anonymized transcripts will be accessed from secure institutional servers.

Analysis

Quantitative analyses will be conducted using relevant packages in the most recent version of R. To contextualize the substudy findings, STOP users will be characterized using descriptive statistics, including clinical and sociodemographic variables, taken from the trial's main outcome paper and supplemented as necessary by further information, and reported per intervention arm. Chi-square tests or pairwise comparisons will be used to test for differences between groups. To report intervention use, descriptive statistics will summarize the total number and proportion of intervention users in the host trial completing 0 to 6 or 0 to 12 sessions using acceptable and target rates. To test predictors of engagement, we will first assess the nature of the distribution and then run a linear regression analysis for normally distributed data or Poisson or negative binomial regression if data are not normally distributed (depending on overdispersion in the data). We will qualitatively analyze self-reported barriers and facilitators to intervention use using the same approach in study 1 (in the Analysis section) as analysis will be led by CH, supported by NVivo, and will deductively use the CFIR framework [29] in framework analysis [27,28], while inductively coding other data not captured in the initial framework.

Status

Data collection is complete, but analyses have not yet started.

Study 3: Qualitatively Exploring the Hypothetical Posttrial Implementation of STOP

Overview

This qualitative study conducted interviews and focus groups with health care professionals and will conduct secondary analyses on interviews with STOP users (described under study 2).

Aim

To identify the hypothetical barriers and facilitators to implementing STOP after the trial using the perspectives of STOP users and health care professionals.

Participants

Participants include STOP users and health care professionals. The STOP user participants are described previously (in the Participants section for study 2). Twenty health care professionals from 6 NHS trusts in England participated in an interview (n=11) or focus group (n=2). These participants were aged 26 to 61 (mean 38, SD 11.736) years and were predominantly clinical psychologists (15/20, 75%), female (15/20, 75%) and White (16/20, 80%).

Recruitment

The recruitment processes for STOP users are described earlier (in the Recruitment section for study 2). Health care professionals were recruited from NHS trusts in England. Participants were those who provided informed consent to take part in a one-off interview or focus group after trialing a tester version of the STOP intervention or had viewed a video demonstrating the app.

Procedure

The procedure for the STOP user interviews has been described previously (in the Procedure section for study 2). The health care professional topic guide was developed to explore the perceived acceptability of STOP (Supplementary Material S3 and S4 in Multimedia Appendix 3). Trained researchers (CH, AK, and HS) conducted the interviews and focus groups using Microsoft Teams, which were recorded and transcribed.

Analysis

Descriptive statistics for anonymized basic demographic data will be tabulated. To date, interviews and focus groups have been transcribed verbatim. Next, we will qualitatively analyze data using the same approach in study 1 (in the Analysis section) with analysis led by CH, supported by NVivo, and deductively using the CFIR framework [29] in framework analysis [27,28], while inductively coding other data not captured in the initial framework.

Status

Data collection and transcription are complete, and preliminary analyses have started.

Integrating Qualitative and Quantitative Data

Integration of quantitative and qualitative findings will be undertaken using a triangulation approach guided by the CFIR framework [29]. Integration will occur at the interpretation and reporting stages through a joint comparison of quantitative indicators (eg, predictors) and qualitative themes on barriers and facilitators. Quantitative and qualitative data will be synthesized within the CFIR framework [29] to identify key barriers and facilitators to implementing STOP in and after a trial (process evaluation aim 2). Therefore, our process will identify convergent and divergent findings and provide an evidence-based understanding of factors influencing implementation using mixed methods data.

Patient and Public Involvement

Patient and public involvement in the STOP trial is contributed via the LEAP, coordinated by the McPin Foundation, and is described in more detail in the protocol paper [12]. Within the

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process evaluation, the LEAP contributed to developing the health care professional topic guide, provided input on the process evaluation design, and a lived experience peer researcher collected and transcribed data in study 3.

Process Evaluation Deliverables and Dissemination Plan

We expect 2 deliverables from the process evaluation: (1) a research report and (2) a hypothetical implementation framework. First, we will report the process evaluation in an implementation paper. Second, our findings will generate a hypothetical implementation framework for the delivery of STOP after the trial, which will include implementation strategies that are tailored to delivering STOP both inside and outside mental health services. Both deliverables will be reviewed by the STOP LEAP, and disseminated as peer-reviewed, open-access journal articles and conference presentations. Our work will also be disseminated to potential end users through existing connections via the McPin Foundation's networks, the STOP LEAP, and other relevant end user networks.

Results

The STOP trial is now complete, including recruitment, data collection, and primary outcome analyses. Data collection concluded in December 2024, with 274 participants recruited. The primary outcome paper for the STOP trial is expected to be submitted for publication in winter 2025. Data collection for data used in the process evaluation was also completed in January 2025, and all data have been cleaned. Process evaluation analyses began on study 3 in August 2025 following preregistration in July 2025 and are expected to be finalized in winter 2025. Analyses for process evaluation studies 2 and 1 will commence in winter 2025 and spring 2026, respectively. Results from all 3 studies are expected to be finalized and submitted for publication in 2026. The overall process evaluation, including the development of a posttrial implementation framework, will be completed by February 2027.

Discussion

Expected Findings

Our process evaluation is expected to provide a detailed understanding of factors that influence implementation within a trial context. An evidence-based understanding of implementing STOP in an RCT will address a key uncertainty in the STOP logic model (Figure 2) and provide a more accurate understanding of actual implementation processes, which may differ from hypothesized ones [38]. Our process evaluation therefore offers unique insights beyond other STOP trial projects and can complement and contextualize efficacy findings. Insights into intervention-related implementation barriers and facilitators will inform future iterations of STOP. We will also develop an implementation framework for posttrial delivery of STOP, which will inform the upscaling of the intervention outside of an RCT setting; a persistent challenge [16,17] that must be addressed to avoid underuse of research efforts and to ensure the provision of optimal care to those experiencing mental health difficulties. Our framework may also be useful for other researchers or clinicians seeking to integrate self-administered DMHIs into routine care.

Comparison to Prior Work

Our findings can address important gaps in research and knowledge in this field. The process evaluation is conducted in a context where there is interest in developing treatments for paranoia [7], including those that are digitally delivered [2]. While an oft-cited advantage of digital treatments is the potential to implement this mode in a variety of settings [39], the literature has focused on service settings [38,40,41], which often have limited access to the resources needed to implement DMHIs [42]. Therefore, we will address this limited opportunity to learn about DMHI implementation in other settings, including settings without clinical support or guidelines, which may be of interest to other evaluators in this field. Furthermore, the process evaluation methodology is often underutilized [43,44]. Our work therefore addresses a methodological gap and aligns with wider priorities to strengthen implementation research in digital mental health [16,45] and may add to the growing evidence base that a concurrent investigation of efficacy and implementation using process evaluation can improve intervention evaluation and development in trials [18,46]. Finally, an evidence-based understanding about implementing STOP has implications for the provision of care to those experiencing paranoia. Our work could be applied to a care context where health care professionals can assume that those with paranoia are unsuitable for this treatment mode due to patients' illness factors, such as preexisting concerns about technology [47,48]. Evidence suggests that such staff views can be overgeneralizing, as paranoia does not preclude engagement with DMHIs [10] or can coexist with their use [49].

Strengths and Limitations

This process evaluation has several strengths. First, to our knowledge, we are the first to explicitly apply process evaluation methodology to evaluate a DMHI used by a transdiagnostic sample of individuals with paranoia. Furthermore, we undertake a rigorous approach to process evaluation by adopting an established framework for this evaluation method [18]. An additional strength is that most process evaluation data were collected as part of a large-scale clinical trial and thus were subject to quality control checks and may be less subject to responder bias, meaning that more reliable data will be used. Furthermore, we will use mixed methods data and a range of data sources, which may identify different factors affecting implementation. Triangulation of mixed methods data in analyses will enable an integrated interpretation of process evaluation findings, which will support the development of an evidence-based understanding of implementation that may be used in future work. Finally, we transparently report on the planned process evaluation approach, scope, and methods to contribute to good practice and share our work with other stakeholders.

However, the process evaluation should be considered in line with several limitations. Uptake rates may be limited by incomplete recording of individuals who declined participation at the initial approach, as data were only available for contacts

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made directly by STOP research assistants or shared with the trial team. Our use of secondary interview data with STOP users has several limitations. These studies did not explicitly address our evaluation aims, which may have limited the depth or relevance of feedback from STOP users to our process evaluation. Furthermore, the use of secondary data meant that we were unable to analyze data during data collection, limiting our ability to explore emergent themes. Qualitative data were also collected using opportunity sampling, which may introduce bias toward responders who may be more interested in intervention evaluation or had more positive experiences of STOP. Future evaluation work in the field could mitigate this limitation by prospectively embedding a process evaluation within trials. Additionally, we could not prespecify which variables we will use to assess sample representativeness in study 1 as the AMPS protocol or data are not available at the time of publication. Finally, the protocol will be published after data collection was completed for the process evaluation studies. To mitigate these limitations and enhance transparency, we will prespecify our analysis plans on Open Science Framework before starting analyses [22].

Conclusions

Overall, our work will develop an evidence-based understanding of the implementation of STOP in and after a trial, including identifying barriers to and facilitators of its implementation. Our process evaluation is also expected to develop a hypothetical implementation framework for posttrial delivery inside and outside of mental health services, which will inform upscaling and future iterations of the STOP intervention. Expected findings are anticipated to also have implications beyond the STOP trial and intervention. Our findings may also highlight the importance of process evaluation when trialing interventions by generating evidence that can inform the development or upscaling of other self-administered DMHIs.

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Authors' Contributions

Conceptualization: CH
Data curation: LE (supporting), CF (supporting), CH (supporting), HS (supporting), RT (supporting), TT (supporting), JY (lead)
Formal analysis: CD (supporting), CH (lead), PJ (supporting), JY (supporting)
Funding acquisition (STOP trial): PJ (supporting), JY (lead)
Funding acquisition (STOP process evaluation): CH (lead), PJ (supporting)
Investigation: LE (equal), CF (equal), CH (equal) AK (equal), HS (equal), RT (equal), TT (equal)
Methodology: CD (supporting), CH (lead), PJ (supporting), JY (supporting)
Project administration: CD (supporting), CH (lead), PJ (supporting), JY (supporting)
Resources: LE (equal), HS (equal), TT (equal), JY (lead)
Supervision: CD (supporting), PJ (lead), JY (supporting)
Writing—original draft: CD (supporting), CH (lead), PJ (supporting), JY (supporting)
Writing—review and editing: CD (supporting), LE (supporting), CF (supporting), CH (lead), PJ (supporting), AK (supporting), HS (supporting), RT (supporting), TT (supporting), JY (supporting).

Conflicts of Interest

None declared.

Multimedia Appendix 1
Process evaluation reporting standards completed checklists.
[DOCX File , 29 KB - resprot_v14i1e81167_app1.docx]

Multimedia Appendix 2
Process evaluation team expertise.
[DOCX File , 24 KB - resprot_v14i1e81167_app2.docx]

Multimedia Appendix 3
Interview and focus group topic guides.
[DOCX File , 42 KB - resprot_v14i1e81167_app3.docx]

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Abbreviations

AMPS: Adult Psychiatric Morbidity Survey
CBM-pa: cognitive bias modification for paranoia
CFIR: Consolidated Framework for Implementation Research
DMHI: digital mental health intervention
LEAP: lived experience advisory panel
MRC: Medical Research Council
NHS: National Health Service
RCT: randomized controlled trial
STOP: Successful Treatment of Paranoia

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Protocol

Benchmarking Environmental Health Influences on Food Security in Very Remote Indigenous Communities in Australia: Protocol for a Mixed Methods Study

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Abstract

Background: Many factors including the impact of colonization and subsequent intergenerational trauma contribute to health inequalities for Aboriginal and Torres Strait Islander people, respectfully referred to as Indigenous Australians. The unacceptable health gap is higher for the Indigenous Australians living in very remote communities. Food insecurity—a lack of regular access to safe, nutritious, and affordable food—is influenced by both housing and retail environments. Ensuring that houses have functional and adequately maintained kitchens and access to affordable, healthy food are significant policy challenges for Australian governments; yet, little is known about these environmental health drivers in very remote areas.

Objective: This study aims to benchmark environmental health food security risk factors impacting 19 very remote Indigenous communities in Western Australia. Specific objectives include using digital apps (1) to assess the appropriateness and suitability of kitchens in houses (internal environment), (2) to assess the affordability of food and sanitary goods (external environment) compared with the nearest town and capital city, and (3) to identify residents' perceptions of appropriate kitchens.

Methods: The mixed methods eHealth study includes 3 approaches. The internal environment is assessed via an in-house audit of facilities used to prepare, store, and cook food to maintain Healthy Living Principle 4 using a customized digital app and a 5-minute face-to-face yarn with tenants (n=130). This provides lived experience perspectives to inform housing and store pricing policy recommendations. The external environment assesses retail practices and food item (n=97) and sanitation product (n=28) prices in remote community stores, extending Healthy Diets ASAP (Australian Standardized Affordability and Price) to compare the mean price per product, the whole diet, and sanitation goods with the nearest town and capital city. Descriptive statistics and frequencies will be reported for the audits, and thematic analysis of the interviews will be undertaken.

Results: Tenant interviews and data collection for the in-house and retail audits across the 19 communities will be undertaken by mid-2026, and the analysis will be completed by the end of 2026. Findings will be collated and triangulated to provide benchmark data for environmental health determinants of food security in very remote Western Australian communities. Preliminary findings will be shared with each community to support their advocacy, policy, and practices for timely maintenance of homes, suitable kitchen design, and store retail practices.

Conclusions: This is the first study in Australia to explore the environmental health drivers of food insecurity in very remote Indigenous communities using digital technology from the perspectives of the tenant, in-house facilities, and in-store retail practices. The food security environmental health benchmarking will provide evidence for advocacy to promote culturally appropriate and practical solutions to improve living conditions and health of families in these areas.

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KEYWORDS

food security; remoteness; housing; environmental health; diet; Indigenous peoples; Aboriginal and Torres Strait Islander; nutrition; price; sanitation

Introduction

Context

This study is contextualized in very remote Australia and recognizes and respects Aboriginal and Torres Strait Islander people as custodians. This is acknowledged as a human right under the United Nations Declaration on the Rights of Indigenous Peoples [1]. Hereafter, the term "Indigenous" is used to refer respectfully to Australia's First Peoples, also known as Aboriginal and Torres Strait Islander Peoples and First Nations Peoples [2].

Background

The impact of colonization and the subsequent intergenerational trauma have resulted in an unacceptable health gap between the Indigenous and non-Indigenous Australian population [3], particularly for those people living in very remote communities. Health issues are also underpinned by geographical isolation, poor housing, socioeconomic disadvantage, and poor health literacy [4]. A specific health issue affecting many people residing in remote Indigenous Australian communities is food insecurity, driven by food stress resulting from low household income [5], coupled with a lack of access to affordable, nutritious, fresh food [6,7] and functional kitchens within homes to safely store, prepare, and cook food.

The research emerged from priorities identified by the Aboriginal or Torres Strait Islander sector. In 2022, the national Aboriginal health peak body (National Aboriginal Community Controlled Health Organisation) recommended that any policies or programs addressing food security be implemented in accordance with the 4 Priority Reform Areas of the National Agreement on Closing the Gap. This research aligns with these reform areas [8].

Western Australia was selected for this study, as it is the largest Australian state and has over 12,000 people living in over 200 remote Aboriginal communities [9]. With 89,000 people who identify as Aboriginal and Torres Strait Islander, 3.3% of Western Australia's population, the state comprises higher than the national average (3.2%) [10]. Only remote communities were included in this research, as housing conditions for Aboriginal families living in urban areas are not equivalent or comparable due to access to services. In general, life expectancy is lower in remote areas, with Aboriginal people living in cities expected to live around 5 years longer than those living in remote and very remote areas [11].

Cultural Determinants of Health

The cultural determinants of health and social and emotional well-being in Australian Indigenous peoples are protective factors that enhance resilience and strengthen, identify, and support health and well-being. These include a connection to country, family, kinship and community, language, cultural expression and continuity, self-determination, and leadership [12]. Almost a third of Indigenous Australians resided in remote or very remote areas in 2024 [13]. Over 89,000 people identify as Aboriginal or Torres Strait Islander in Western Australia, representing 3.3% of the population [10]. Geographically, Western Australia is the largest Australian state (the Aboriginal Lands Trust estate covers over 23 million hectares, 8.7% of the state), with 12,000 people residing in 200 remote Aboriginal communities [10,14,15]. There is a dearth of information available about the environmental influences of household food security in very remote communities in Western Australia.

Food Security

Food security is a priority for public health and critical for good health. United Nations Sustainable Development Goal 2—ending hunger in all its forms to achieve food security and improve nutrition and sustainable agriculture, recognizes challenges for people living in geographically isolated communities [15].

Defined at the individual and household level, food security exists when "all people, at all times, have physical and economic access to sufficient, safe, and nutritious food to meet their dietary needs and food preferences for an active and healthy life" [16]. The converse food insecurity exists when "the availability of nutritionally adequate and safe foods, or the ability to acquire acceptable food in socially acceptable ways is limited or uncertain" [17].

In Australia, the prevalence of food insecurity is higher among Indigenous people residing in remote areas than those living in urban areas [18]. The National Aboriginal and Torres Strait Islander Health Survey conducted in 2022-2023 found that 41% of households had experienced food insecurity in the last 12 months, and just over half (51%) of the households were in remote areas. Almost a quarter (24%) of these households had experienced severe food insecurity compared to 17% in nonremote areas [12]. For many people residing in remote Aboriginal communities, the ability to buy, store, and cook healthy and nutritious food is limited, sometimes impossible. When combined with poor housing conditions, inadequate maintenance or failure to repair houses, and essential health hardware needed to store, cook, and prepare food such as stoves and refrigerators, the community's efforts to achieve food security are undermined. Remote homes struggle to have access to affordable, continuous electricity and affordable, reliable access to safe-to-drink potable and palatable water [19].

Theoretical frameworks regarding the determinants of food insecurity have continued to evolve over time. The High-Level Panel of Experts on Food Security and Nutrition identifies 6 dimensions of food security including availability, access, utilization, stability, agency, and sustainability as essential. External resources are required to ensure food security, including clean water and sanitation, as "food must be available; households must have access to it; they must utilize it appropriately; and the whole system must be stable" [20]. The dimensions of agency and sustainability are particularly important in remote Indigenous communities and need to be

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aligned with Indigenous peoples' right to self-determination and leadership. Agency refers to "the capacity of individuals and groups to exercise a degree of control over their own circumstances and to provide meaningful input into governance processes" [21]. Information regarding inequities in the food system is essential to support agencies at the individual and community level to address imbalances of power and to influence policy to address food insecurity. Sustainability refers to "food system practices that contribute to long-term regeneration of natural, social, and economic systems, ensuring the food needs of the present generations are met without compromising food needs of future generations" [22]. Many remote community stores have failed to operate as viable businesses, in part due to small market share and the cost and complexity of transport logistics [23]; yet, no regular real-time price monitoring occurs. Sustainable food systems need to be supported by strong government policy informed by timely, relevant research.

The causes and consequences of food insecurity are numerous, interconnected, and far-reaching. They include economic, social, and environmental circumstances influencing the ability to purchase, prepare, and use food; food availability and production; geographic isolation; transport logistics; climate events; the availability of food preparation, storage, and cooking facilities; and food literacy skills [24-26].

Environmental Determinants of Food Insecurity—Food Access and Affordability

In 2024, over 200 food stores service remote Indigenous communities across Australia, providing 90% to 95% of the food consumed, and traditional foods contribute only a small, but important, supplement to people's dietary intake [19]. Community stores are either managed by store management companies, where external agencies maintain control, or are community-owned and managed. Often, community-owned stores serve smaller populations and have less purchasing power or ability to buy in bulk. Residents in communities with no store are required to travel many hours on unsealed or seasonally inaccessible roads to a retail provider in a regional town to purchase their food.

Restricted access to and the limited choice for a variety of healthy foods in remote stores have negatively impacted the dietary habits and health of Indigenous people living in remote communities [27]. The National Indigenous Australians Agency (2025), following consultation across these areas, reported that people in these communities often relied on "cheaper convenience foods, which are often nutrient-poor and higher in calories," as they were more affordable in these community stores [19]. Regular consumption of this food-insecure dietary pattern increases the risk of diet-related disease among Aboriginal and Torres Strait Islander Australians including diabetes, oral health issues, kidney disease, cardiovascular disease, and some cancers [19].

The prevalence of food insecurity in remote Indigenous communities and the role of community stores have been acknowledged for 30 years, with considerable policy inertia described in submissions to the numerous Parliamentary Inquiries over that time. In 2003, Food North, a government-commissioned report, identified the barriers and enablers to policy recommendations to address food insecurity in remote Indigenous communities across Australia [28]. Challenges identified related to transport logistics and supply change efficiencies, such as climate and weather events reducing the supply, quality, and affordability of food [28]. The lack of retail store viability in geographically isolated locations was described by remote community store managers [6,29]. Unregulated pricing of essential food items in these communities has been reported [28,30]. The 2009 House of Representatives Aboriginal and Torres Strait Islander Affairs' Committee Inquiry into remote Aboriginal and Torres Strait Islander community stores recommendation number 29 was that store policy should require the display of pricing and cross-subsidies to promote healthier foods [28].

In 2020, a Parliamentary Inquiry into food price gauging identified that although food costs are very high in many remote communities, there was no evidence of systemic price gouging taking place in remote community stores [31]. In addition, the inquiry recommended measures to improve governance and oversight of community stores. In 2022, the Western Australia Committee on the Commissioner for Children and Young People initiated an inquiry into the most effective ways for Western Australia to address food insecurity for children and young people affected by poverty, resulting in 24 recommendations [32]. The government response was to recommend the Health and Education Department support school lunches and breakfasts, the creation of a Food Stress Index map to guide interventions, and for the Premier to take responsibility for food relief [33]. Despite some submissions highlighting environmental barriers to food security in remote communities, there was little regard for these or the cultural determinants of health. However, the Australian government's National Strategy for Food Security in Remote Aboriginal and Torres Strait Islander Communities 2025-2035 highlights both these areas [19].

Environmental Determinants of Food Insecurity—Housing and Health Hardware

Housing conditions for the Indigenous Australian population often differ greatly from those of the non-Indigenous Australian population. The households are larger in size, more likely to include a lone parent, and frequently comprise multigenerational members of extended family and kinship networks [20]. The scarcity of housing in remote Indigenous communities is a challenge. Crowded housing has been widely documented over several decades and is seen as a major contributor to, and symptom of, Indigenous disadvantage [34,35].

In remote Indigenous communities, food insecurity [36] and poor hygienic conditions of bedding and sleeping areas have been associated with increased disease transmission [37], and overuse of showering, washing, and kitchen facilities (health hardware) due to the higher number of tenants leads to breakages [38]. These are examples of health-related disadvantages in crowded remote houses. Policies implemented to construct and maintain remote housing have been found to be suboptimal for many years [39,40].

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In addition to an insufficient housing stock in remote areas, the houses themselves deteriorate quickly [41] due to harsh climatic conditions, overcrowding, poor maintenance, and, in some cases, antisocial behavior [34,42,43]. Overcrowding also results in significant "wear and tear" on homes, driving up home maintenance costs. A lack of functional health hardware and the challenging internal living conditions of many houses resulting from unreliable access to maintenance are major concerns. An environmental health response to internal house living conditions aligns with the 9 Healthy Living Principles (HLPs) considered essential in a home to support personal health [44]. HLP 4 considers nutrition and reinforces the importance of functioning health hardware. Health hardware refers to the equipment or facilities in the house necessary to carry out healthy living practices, such as washing people, washing clothes, removal of human waste, and preparing food [44,45]. In 2018-2019, a small study found that 9% of First Nations households had no access to working facilities for food preparation, 4% had no access to working facilities to wash clothes and bedding, and 3% had no access to working facilities to wash household residents [46]. Nonfunctional health hardware has been associated with food insecurity and poor health in remote communities. Ali et al [47] found that poor remote housing maintenance and functionality were associated with gastrointestinal infections and skin, ear, eye, respiratory, and gastrointestinal illnesses. Quilty et al [48] found that homes lacking structural integrity, appropriate design, and insulation were more expensive to keep warm or cool or to operate essential health hardware (eg, refrigerators and stoves), leading to food scarcity and food insecurity. The last major survey of Indigenous housing quality in remote Western Australia was over 2 decades ago, a gap this research aims to fill [49].

The harsh climatic condition in many Australian remote Indigenous communities means that families spend time outside of their homes to escape overheated houses. Outdoor living spaces with suitable shading can reduce heat exposure and protect residents from the elements while meeting Indigenous people's kinship [50] and lifestyle needs [34]. O'Rourke and Nash [51] explored the uses and functions of yards in Indigenous housing in semiarid Queensland and the Northern Territory and found that 73% of Indigenous families expressed a preference for outdoor shaded areas over internal rooms. Specifically, for food security, it has been demonstrated that design around a central open or covered cooking area that enables the preparation of traditional food and cooking methods is preferred in remote Indigenous communities [52,53]. Open cooking areas also reduce odors and food waste problems within the house, allow for the variable size of the eating group, and reduce smoke, grease, and vermin damage to cupboards in the kitchen area [53].

Recent assessments of the health consequences of poor housing and yard use in remote Indigenous communities have largely focused on infectious diseases and comfort [47,54,55]. However, since it has been over 20 years since the last major survey of Indigenous housing quality in remote Western Australia, this study is urgently called for. Low participation rate in food security research in remote areas of Western Australia is another challenge [36] and a gap, which this study intends to fill.

This study aims to use innovative digital methodology to explore and benchmark the environmental health determinants of food insecurity in remote Indigenous communities, providing important information to the community for policy and advocacy purposes. Specific objectives include using digital methods (1) to assess the appropriateness and suitability of kitchens in houses (internal environment), (2) to assess the affordability of food and sanitary goods and retail practices (external environment) compared with the nearest town and capital city, and (3) to identify residents' concerns and perceptions of appropriate kitchens (internal environment).

Methods

Ethical Considerations

The Western Australian Aboriginal Health Ethics Committee granted ethics approval (HREC1370), and the Curtin University Health Research Ethics Committee granted reciprocal ethics approval (HRE2024-0727). As this research works alongside Indigenous practitioners and communities, the CONSIDER (Consolidated Criteria for Strengthening the Reporting of Health Research Involving Indigenous Peoples) was used to strengthen research practices and reporting to enhance research conduct and dissemination to support Indigenous health equity [56]. In addition, the research is consistent with the National Statement on Ethical Conduct in Human Research 2023, National Health and Medical Research Council's *Ethical Conduct in Research With Aboriginal and Torres Strait Islander Peoples and Communities: Guidelines for Researchers and Stakeholders* [57]. The research partnership agreement includes protection of Indigenous intellectual property and knowledge arising from the research, including financial and intellectual benefits generated in line with the Our Culture: Our Future report. The project also follows Indigenous Data Sovereignty protocols that ensure that data on or about Indigenous peoples reflect their priorities, values, cultures, worldviews, and diversity. After outlining the research, participants give informed consent. There is no compensation for participation.

Study Design

This mixed methods study aims to benchmark environmental health food security risk factors impacting 19 very remote Indigenous communities in Western Australia by auditing the appropriateness and suitability of kitchens in houses (internal environment), assessing food affordability and retail practices (external environment), and identifying residents' concerns and perceptions of appropriate kitchens. A key objective of this unique, practice-informed study is to establish a baseline for environmental health factors influencing household food security in remote Indigenous communities in Western Australia. Measuring and reporting on the 3 aspects of household food security together—household kitchen functionality, community kitchen preferences, and external retail practices—have not been previously undertaken.

Setting and Recruitment

This mixed methods study will be undertaken in 19 very remote Indigenous communities across 4 regions of Western Australia: the Pilbara, Goldfields, Midwest, and Central Desert regions.

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Very remote areas, as classified by the Australian Statistical Geography Standard-Remoteness Area classification, rely on the Accessibility/Remoteness Index of Australia, measuring the relative geographic access to services. Very remote areas [58] represent high levels of disadvantage based on the Australian Bureau of Statistics' Index of Relative Socio-Economic Disadvantage for Areas [59]. People living in very remote areas are 58% more likely to speak an Australian Indigenous language at home [60]. The research will be undertaken alongside Curtin University's #endingtrachoma project, which has established relationships with these communities. The #endingtrachoma project has been servicing Western Australia's remote communities since 2019 and is delivered in partnership with Indigenous environmental health practitioners (EHPs) in each community. The project facilitates an approach led by the community including in-home bathroom and laundry assessments and emergency maintenance [61]. The purposeful sample has been identified as "trachoma at risk" communities based on annual trachoma screening that identifies active trachoma prevalence of 5% or greater among Aboriginal and Torres Strait Islander children aged 5-9 years in the last 5 years [62]. #endingtrachoma has been building the capacity of local Indigenous EHPs to enter homes, identify and audit trachoma risk factors (eg, ability to wash), fix minor plumbing issues, yarn with tenants about hygiene, and provide hygiene resources. The #endingtrachoma project revisits each house every 4 months. An important component of the project is to transfer the auditing skills to the EHPs who service these communities. These EHPs are contracted to visit these communities every 4 months and collect data using the mobile app. This research will build on this to include environmental health and food security risks.

Indigenous Governance

A Research Governance Group to support and guide the research comprises Indigenous environmental health experts, a Department of Communities (Housing) representative, an Indigenous policy expert, and an Indigenous community advocate. These representatives live in the Midwest, Kimberley, Goldfields, and Perth or Peel regions of Western Australia. Reciprocity is reflected in this Research Governance Group, whose membership has been determined and agreed in consultation with different communities involved in the research. Roles of the group are to identify potential benefits and implications related to the values and aspirations of the community; avert any unintended consequences; provide advice on cultural security issues, barriers and enablers, data sovereignty and dissemination, and food security issues relevant to remote communities; and contribute to knowledge transfer strategies.

Community Engagement

The established relationships developed with each community through the #endingtrachoma project inform and support this research methodology. All data collection is informed by community aspirations to ensure food security. Permission to enter each community will be obtained prior to, and with an invitation from, the community chairperson of each community. Posters describing the study will be displayed in the community store, at the health clinic and art center, to advise community members of the date and purpose of the visit. Visits will coincide with the #endingtrachoma project visits.

Mixed Methods Approach

Overview

This mixed method study involves (1) an in-home digital healthy home kitchen functionality audit and food security check incorporating digital images where appropriate (n=197), (2) yarns (short interviews) with tenants (n=100) exploring their perspectives on food security issues and preferred kitchen design, and (3) store pricing survey using the digital Healthy Diets ASAP (Australian Standardized Affordability and Price) app [63].

Internal Environment—Community Housing and Kitchen Audits

Overview

Over 12 months, 197 households across 19 communities will be visited. No private or state-owned houses will be audited. Some tenants will be away, and not all houses will permit entry, and based on our previous experience, a 70% participation rate is achievable. The long-term engagement with the community and the support of EHP facilitate this. Nonparticipation is predominantly due to cultural reasons such as death in the family and lore. Where entry is allowed, the food security researchers will conduct the kitchen audit and a face-to-face yarn with an adult tenant (n=100). Researchers on this food security project have been working on the #endingtrachoma project for the past 5 years and have extensive knowledge of the remote communities involved and have built robust and genuine relationships with the community leaders, local service providers, and many of the community members.

In each community, an Indigenous EHP team member will lead the conversation to gain permission to enter each community-managed house. The EHPs are local people who live and work in remote communities. They hold a very strong understanding of the communities. With permission, they will introduce the food security researchers to the tenant, who will invite the householder to participate in the research. A project information sheet will be provided or read out if required, and signed consent obtained with the option to opt out.

Kitchen Audit

The food security researchers will conduct a digital healthy home kitchen functionality audit. This audit is based on the SafetyCulture Healthy Home app used in the #endingtrachoma project and is consistent with the HLP 4 criteria [44,64]. It will be a new tool developed for this research. Knowledge and experience from 5 years of completing the healthy home audits via the SafetyCulture app will guide the design of the kitchen app. The audit will assess cleanliness and functionality for food storage, preparation, and cooking in household kitchens. The audit captures issues associated with kitchen functionality, availability and state of cooking appliances, presence of cleaning and hygiene products, and kitchen requirements to prevent pests and vermin entering the house. The taps in the kitchen are turned on to ensure that both hot and cold water are available to the

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house. These details of the audit have been included as examples of auditing practices. The 64-item audit assesses evidence of pests, mold, waste disposal, basic utilities, kitchen, plumbing and electrical appliances (eg, oven, stove, refrigerator, freezer, ventilation, and other white goods), kitchen benches, cupboards and pantry, cooking utensils, cleaning and hygiene products, windows, and doors. A question is asked within the app to identify the number of people who slept in the house on the previous night. This provides an indication of crowding issues. Digital photographs are included in the audit data collection. The #endingtrachoma team will provide emergency plumbing fixes throughout the house, including the kitchen, as required. If the repair is unable to be carried out, the fault will be reported to the housing provider. A kitchen kit comprising household kitchen hygiene products and a small plunger will be offered to each house where a complete audit has occurred to thank tenants for their participation.

Yarning

Yarning is a conversational process that involves the sharing of stories and the development of knowledge and reflects Indigenous people's emphasis on oral traditions [65,66]. Yarning can involve a range of fluid narrative strategies such as anecdotes, stories, and personal experiences [67]. Burke et al [68] suggest that this fluid style of questioning is more likely to reflect Indigenous peoples' perspectives, as it is less confrontational. It is considered to be one of the most appropriate research methodologies to determine Australian Indigenous community members' perceptions of their health needs and is considered culturally safe if conducted in a way that is respectful, cooperative, and supports cultural practice [68,69]. Yarning has been shown to foster connection, establish trust, and enable researchers to explore topics in greater detail [70]. Tenants will be invited to have a one-to-one yarn, or if preferred, a group yarn, about what their kitchen might look like if they had the opportunity to design it and how they like to prepare the food they eat. The yarns will occur inside the homes while the kitchen audit and healthy home audits are being conducted. In some cases, the Indigenous EHP will instigate the yarn, and in other cases, where the EHP is busy fixing a plumbing issue, the yarn will be led by the research team (non-Indigenous). Either way, an Indigenous person will always be in the house when the yarns occur. The yarning question will encourage flexibility and disclosure. The participant will be asked to choose where they would like to have the yarn, and a Voice Memos mobile telephone audio recording app will be used to record the yarn.

External Environment—Community Store Pricing Audits

As food insecurity is driven by a complex range of factors, such as inadequate income to support meal planning and food purchases, food prices, poor access to safe storage and cooking facilities, limited transport options to access stores, and poor access to fresh and nutritious foods, focusing on the community store environment and pricing policies is a critical component of this study. A recommendation from the 2009 Parliamentary Inquiry into remote Aboriginal and Torres Strait Islander community stores [28] was a requirement to display pricing. However, under Australian Consumer Law, there is no specific legal requirement for stores with less than 1000 m^2 of floor space to display prices [71].

The Healthy Diets ASAP app [63] will be used to audit prices of food products (n=76) in each of the 15 independent stores located within the 19 remote Indigenous communities, along with audits in the 6 nearest regional towns and the capital city, Perth, for comparison. The digital survey tool has been tailored to assess the food affordability component of food security in remote Indigenous communities [72]. This Healthy Diets ASAP method allows the "assessment of price, price differential and affordability of healthy (recommended) and current (unhealthy) diets of Aboriginal and Torres Strait Islander people living in different locations with other population groups in Australia" [72]. Observation of evidence of pricing policies will also be undertaken, including the presence or absence of prices on shelves for all products. Photographs of food and hygiene items will be taken where appropriate and will confirm the presence of shelf pricing. Hygiene products (n=28) that are required to keep kitchens and work areas clean and support handwashing (eg, soap and detergent) will also be priced. Data will be collected in-store using an iPad and uploaded via a web-based portal. Permission will be sought from each community store manager to undertake the pricing audit, and entry to communities must be granted by the community chief executive officer (CEO) prior to each visit.

Reflexivity Statements and Addressing Potential Power Dynamics

Each researcher will include their reflexivity statement and procedures to support independent data verification to ensure the privileging of Indigenous peoples in the research process, which are outlined below. A number of activities are incorporated into the research to limit the potential for power dynamics and cultural differences to influence participant responses or researcher interpretations. Cultural mentors, elder and community members, and local Indigenous environmental health workers from each community assist with the process of continuous self-reflection. This reflection occurs during many stages of the project and ensures appropriate interpretation and communication between practitioners and community members. Indigenous researchers and advisors guide the research process and inform the timing and suitability of each visit to ensure that respect, reciprocity, and preservation of self-determination are central. Examples include:

- Data collection: Local Indigenous workers make approaches to houses and explain the research purpose. Non-Indigenous researchers are only invited to conduct interviews following tenants' consent and work alongside Indigenous workers and community members. Research team members have long-term relationships with community workers who help create safe interview conditions [73]. The yarns occur while the team members are working in the house. These connections and relationships provide a culturally safe and sensitive data collection, and yarning is used to facilitate 2-way knowledge sharing [74].
- Data interpretation: Two-way knowledge sharing is facilitated through yarning and feedback on the

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interpretation of data during analysis with the Research Governance Group and stakeholders in each community. Feedback is sought on culturally appropriate reporting, with language and interpretation a key part. Reports are modified based on feedback, and this process is iterative.

- Dissemination: To facilitate advocacy, the data are shared directly with stores and community leaders and relevant decision-makers (eg, the CEO, the Environmental Health Contracted service, and the store manager), who can then use it directly for advocacy purposes and to guide how the research project can use it to support their advocacy priorities.

This study will produce benchmarks based on measures and perceptions of environmental dimensions [75] influencing food security, in this case, food prices, kitchens, and tenants' perspectives.

Analysis

Kitchen Audit

Descriptive statistics of the 64 items in the kitchen audit using the SafetyCulture Healthy Homes app will be reported. Where appropriate, photographic images will be analyzed to assess the number of food security attributes recorded related to the 6 dimensions of food insecurity [21].

Store Pricing

Descriptive statistics of the price and availability of the 97-item hygiene data will be reported and relatively adjusted to the nearest regional town and capital city. The data from the remote store food and sanitation products will be entered digitally into an iPad using a web-based portal. Store pricing data will be directly uploaded to the Healthy Diets ASAP web-based portal, and analysis will be undertaken in accordance with the Healthy Diets ASAP protocol that compares the price, availability, and affordability of unhealthy and healthy food based on average income and family composition in the community (see protocol for more details [63]). The mean estimated family household income against the cost of unhealthy and healthy diets will be calculated and compared between the nearest urban and regional stores.

Yarns

Digital transcriptions from each interview will be deidentified, and a thematic analysis will be undertaken, guided by the theory of Braun and Clarke [76]. Two researchers (MS and CMP) will review the data to create initial themes and codes, and a coding frame will be created to ensure consistency and support idea generation. Themes will be reviewed for the need to combine or consolidate through consensus. The themes and codes will be shared with the other researchers and the governance committee to ensure that cultural protocols are followed.

Two-Way Sharing of Information

The results will be shared with each community in a timely and culturally appropriate manner, with processes guided by the research governance committee. To support transparency, accountability, and advocacy, results will be provided in plain language, and graphical pricing survey reports will be provided directly to store managers, community leaders (to disseminate among community members and household owners), and the governance group via easy-to-read fact sheets. Information will include the comparison of the average price and percentage of income needed to purchase a healthy and unhealthy diet at the community store, regional town store, and capital city; a summary of the kitchen audits; and key messages from the yarns. Security and access controls around the Indigenous data collected will be applied in accordance with Indigenous cultural protocols [77,78]. Only data that have the potential to directly benefit the community will be collected, and the process recognizes that Indigenous people are the decision-makers for the access, control, and use of the data.

Results

The project was funded in November 2024, and data collection commenced in February 2025. Accessing remote communities is challenging due to distance, a lack of transport options, weather restrictions, and costs. At the time of publishing, 10 remote communities had been accessed, with 47 yarns being recorded, 61 healthy kitchen audits being completed, and 8 remote store prices being analyzed. The final data collection is due to be completed by June 2026, and results will be analyzed by November 2026.

There are several expected outcomes associated with this research. The internal environmental health data collection will provide baseline information on the functionality of kitchens in the very remote communities that participate in this research. Broadly, the expected outcomes reported are shown in Textbox 1.

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Textbox 1. Expected outcomes of the benchmarking environmental health influences on food security in very remote Indigenous communities in Western Australia.

Overall project

- Number of remote communities providing permission for visits
- Number of kitchen audits attempted and completed
- Number of community-based advocacy campaigns associated with food security
- Advocacy to improve housing maintenance policy and timing for remote communities

Internal audits

- Number of completed kitchen audits by community
- Number of maintenance fixes to improve food security
- Number of nonfunctioning kitchen facilities
- Number of food security risks identified (per 64 items)
- Number of food security risks identified by food security dimensions
- Number of kitchen health hardware referrals or house by community
- Number of kitchen hygiene kits distributed or community
- Number of referrals to other agencies that focus on hygiene in the home project

Yarns

- Number of interviews
- Themes identified
- Number of ideas for future kitchen design

External audits

- The mean (SD) cost of the sanitation items
- The mean (SD) cost of the current diet
- The affordability of a healthy diet and the current diets
- Cost comparison of diet and sanitation items with the nearest town and the capital city

Dissemination

- Number of brief research or fact sheets by community
- Number of advocacy plans by community

The data generated as a result of this research will be prepared for dissemination and used to prepare targeted and community-led advocacy approaches to increase affordability, quality, and availability of food in remote communities; appropriate retail practices in remote community stores; improved remote house maintenance routines and priorities; the functionality of remote kitchens through plumbing fixes; and community-generated evidence on culturally appropriate kitchen design for remote community houses.

Discussion

Principal Findings

A key objective of this unique mixed methods, practice-informed study is to establish a benchmark for environmental health factors influencing household food security in remote Indigenous communities in Western Australia. Measuring and reporting on the 3 aspects of household food security together—household kitchen functionality, community kitchen preferences, and external retail practices—have not been previously undertaken.

Some previous research has addressed elements of this project. For example, Yashadhana et al [79] used participatory action research to explore eye health inequity in 4 remote Indigenous communities in the Northern Territory and north-western New South Wales. Their results identified that food insecurity was associated with economic disadvantage and its associated determinants including limited access to fresh, affordable food or a refrigerator to store food and medicine [79]. The findings also highlighted the importance of cultural sovereignty [79].

This study's approach of quantifying environmental health food security drivers in 19 remote communities, guided by the Research Governance Group, will provide unique data to understand food access issues, kitchen functionality, community preferences for food preparation facilities, and preferred kitchen design. The house maintenance referral processes already in

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place through the #endingtrachoma program will ensure that issues related to the functionality of remote kitchens are either solved on site (eg, plumbing fixes and broken taps) or elevated to a higher priority to the appropriate service provider (eg, broken stoves and ovens and unsafe electrical points). These issues critically affect food security. The approach and the baseline data generated will be used by communities to advocate for improved housing design and maintenance schedules to ensure the timeliness of maintenance issues within the home that affect health.

Community preferences for kitchens and food access will be used to advocate for culturally appropriate co-designed kitchens and houses. The findings support the philosophy that a house is a social determinant of health rather than simply an asset. The findings will be shared with relevant government agencies and decision-makers including, for example, those responsible for remote housing, retail, community services, and remote health. The format for presenting the findings will be tailored to suit the audience and may include reports to government agencies, face-to-face advocacy meetings, conference presentations, meeting agenda items for discussion, and fact sheets. Support will be offered to community members to become involved in dissemination strategies as interest grows.

Environmental health–enabling factors in community stores influence individuals' food choices. Bryce et al [80] have shown that the retail food environment influences the availability, cost, affordability, quality, safety, advertising, and promotion of food and can also influence consumer food choice and food security. This study builds on previous research to benchmark community store retail practices and food pricing surveys in remote Indigenous communities [6,7,72,81,82] and environmental health referral schemes to assist households to improve the environmental health determinants of trachoma [83]. This research works alongside the #endingtrachoma program, which was co-designed by Indigenous environmental health professionals, community health, local and state government staff, and academics. The research design incorporates the dissemination and proposed use of data by community members to advocate for more effective interventions and extends the #endingtrachoma service delivery model, which has been operated for the past 5 years [14].

Changes in the environmental health determinants of food insecurity are expected to reduce food insecurity, improve diet quality, and increase the likelihood of diet-related health benefits. This benchmarking study is likely to highlight suboptimal retail practices, such as the absence of prices on food items, and environmental health determinants of food insecurity, resulting in the need for additional advocacy efforts. This is the first time that sanitation items have been audited in remote locations, providing evidence to advocate for affordable products to protect families against diseases associated with poor hygiene.

This study uses digital tools to build on previous research linking health conditions to housing [47] and will add a contemporary benchmark of kitchen health hardware in very remote Australian communities [13,38,45]. Previous research stressed the importance of Indigenous families having adequately designed kitchens, both internal and external, to enable improved food security and maintain kinship [34]. Through both the kitchen audits and the yarns, this study will build knowledge about the environmental health determinants of food security in remote communities and support the development of strategies to address the issues identified [4,84]. A final strength of the methodology is that it prioritizes the voice of Indigenous people residing in very remote communities in Australia.

Strengths and Limitations

Several factors may influence this research, including geographic isolation and distance to travel to each community, climatic conditions and weather events (eg, floods and fires), and cultural practices (eg, Lore and Sorry Time), which dictate periods when communities are not accessible. Knowledge formed through involvement with the #endingtrachoma project will inform the most appropriate seasons and times to visit communities. Communities will not be entered without explicit approval from the community CEO. Different geographic locations and cultural practices mean that the results of the kitchen audit and yarns are not generalizable to other communities or populations.

There are limitations related to the choice of food price measure, as the purpose of the Healthy Diets ASAP is to compare the price of a healthy diet versus an unhealthy dietary pattern and does not measure a wider selection of food products available, for example, where dietary preferences differ between communities. Time limitations in the current methodology would not permit the auditing of more food items or the quality of food, which is an issue impacting food security in remote communities.

The strength of this study is the research that is to be conducted in 4 remote regions in Western Australia and 19 of the 46 very remote stores in Western Australia. The benchmarking and methodology established may be used to further research in other communities. A further strength is that the store price benchmarking results will be compared within regions and to the nearest town and urban center to highlight food insecurity and high prices as potentially significant issues in remote communities. Being able to work alongside a well-known and experienced existing project that has strong connections into the communities to be visited and working with local Indigenous people in their communities are also strengths of this study.

Conclusions

Household food security in remote communities in Australia is influenced by food affordability and the functionality of health hardware in remote housing, which impacts safe food preparation and storage. These conditions increase the risk of environmental health-related diseases among residents. Safe and suitable household kitchen infrastructure is essential to food security. Using digital technology and mixed methods, this research will provide local Indigenous communities, environmental health services, and stores with critical information to challenge decades of inaction on food insecurity in remote Australian communities. Benchmarking kitchen functionality and store pricing will provide transparent information to support targeted advocacy to improve access to

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safe, affordable, and nutritious food and the appropriate kitchen facilities to store and prepare it.

Acknowledgments

The researchers acknowledge the critical work being done by the environmental health practitioners in conducting Healthy Homes Assessments in remote Indigenous communities. The Healthy Homes Assessments collect data related to trachoma risk factors, specifically, those reducing the ability to wash people and clothes inside homes and identify functional issues impacting environmental health. The project either fixes these issues or reports them to the housing provider. The Western Australia Department of Health supports and has funded this research.

Data Availability

The datasets generated or analyzed during this study are not publicly available due to data sovereignty requirements.

Conflicts of Interest

CMP is the director of the Public Health Advocacy Institute located at Curtin University, and MS is the former director and current senior research fellow.

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Abbreviations

CEO: chief executive officer
CONSIDER: Consolidated Criteria for Strengthening the Reporting of Health Research Involving Indigenous Peoples
EHP: environmental health practitioner
Healthy Diets ASAP: Australian Standardized Affordability and Price
HLP: Healthy Living Principle

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Protocol

Impact of Psychosocial and Palliative Care Training on Nurses' Competences and Care of Patients With Cancer in Cameroon: Protocol for Quasi-Experimental Study

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Abstract

Background: Cancer is a leading cause of global mortality, accounting for nearly 10 million deaths in 2020. This is projected to increase by more than 60% by 2040, particularly in low- and middle-income countries. Yet, palliative and psychosocial oncology care is very limited in these countries.

Objective: This study describes a protocol for the development, implementation, and evaluation of a psychosocial oncology and palliative care course on Cameroonian practicing nurses' knowledge, self-perceived competence, and confidence in palliative and psychosocial oncology care provision for patients with cancer.

Methods: A single group pre-posttest design, incorporating both quantitative and qualitative methods will be used. First, a psychosocial oncology and palliative care course for practicing nurses in Cameroon will be developed. This course will then be implemented with 50 practicing nurses purposefully selected from 2 oncology units in the Littoral region and 4 hospitals in the Southwest region of Cameroon. Finally, to assess the impact of the training program we will undertake a pre and posttest survey of nurses' palliative and psychosocial oncology competences, a pre and post training audit of patients' nursing records to examine nurses' practice of palliative and psychosocial oncology care and undertake a critical-incident interview of nurses' transfer of learning to practice. Descriptive and inferential statistics will be used to analysis quantitative data, while qualitative data will be analyzed using the framework approach.

Results: This study was funded in September 2023. The training program development was initiated in March 2024 and completed in June 2024. Baseline data collection commenced in May 2024 and as of September 2024, we had collected data from 300 patient record. Training implementation is planned for October-December 2024, and post intervention data will be started in October 2024 and continue till April 2025. Data analysis will commence in October 2024 and we aim to publish study findings in peer review journals by November 2025.

Conclusions: This study will improve our understanding of Cameroonian nurses' palliative and psychosocial oncology competency gaps. It will result in the development of a palliative care and psychosocial oncology course and in the training of 50 nurses in psychosocial oncology and palliative care in Cameroon. This study will inform strategies for future psychosocial oncology and palliative care training initiatives in Cameroon and other low- and middle-income countries.

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KEYWORDS

palliative care; psychosocial nursing; oncology nursing; nurses; quality improvement; training; competencies

Introduction

The global need for palliative and psychosocial oncology care continues to grow with the increasing prevalence of life-limiting conditions such as cancer [1,2]. In 2020, there were 19.3 million new cancer diagnoses and close to 10 million cancer-related deaths worldwide. As high as 1.9 million of these deaths occurred in low- and middle-income countries (LMICs) [3]. The number of people requiring palliative care globally has increased significantly in the last 2 decades, from 20 million in 2014 [4] to 56.8 million in 2020 [5]. Unfortunately, LMICs, especially those in sub-Saharan Africa, who have little or no psychosocial oncology and palliative care services harbor up to 80% of this global need [1,6-8]. The limited palliative and psychosocial oncology services in these countries has been associated with barriers such as the lack of competent health care providers with palliative and psychosocial oncology skills, the nonintegration of palliative and psychosocial care in the existing health care system [7,8], the lack of policies to support effective palliative and psychosocial care provision [7,9], and the presence of legislation that limits opioid prescription resulting in poor pain relief, among others [10]. There is therefore a need for strategies to overcome these barriers and facilitate the integration of palliative and psychosocial oncology care into the national health care systems in LMICs [7,11]. Providing educational opportunities to enhance the skills of health care providers in palliative and psychosocial oncology care is one important strategy to ensure that patients have early access to these essential health care services [5,6,12].

Patients and their families who receive a cancer diagnosis experience a high prevalence of pain, emotional, spiritual, and psychosocial distress [9]. The provision of palliative and psychosocial oncology care to these patients and their families will help prevent and relieve these problems [1,6,9] and is cost effective [13]. This is therefore priceless in LMICs where there are limited health care resources, and the cost of care is mostly borne by patients and their families who lack the needed financial resources [13].

With the increasing incidence of cancer in Africa, oncology capacity building opportunities are needed to enhance health care provider's competences and possibly ensure adequate management of patients and their families [14]. Palliative and psychosocial care are important components of quality cancer care that reduces distress, anxiety, and depression and improves patients' quality of life and survival [6]. However, it requires close monitoring and presence, which may not be feasible for an already overloaded oncologists [15]. Thus, nurses are in an ideal position to provide palliative and psychosocial care to patients with cancer, particularly in Africa, with huge shortage of oncologists and physicians [16]. Nurse-led palliative and psychosocial have been shown to improve access to palliative and psychosocial care for patients with cancer in resource limited settings [15,17].

The Need for Palliative and Psychosocial Oncology Care in Cameroon

In Cameroon, there is an upsurge of noncommunicable chronic disease morbidity and mortality [18]. Although cancer is likely underreported, there were approximately 19,564 new cancer diagnoses and 12,798 cancer deaths in Cameroon in 2022 [19]. Similar to most sub-Saharan African countries access to cancer care in Cameroon is limited, although cancer is a leading cause of premature death in the country [20]. There are 3 main cancer centers situated in 2 regions of the country, serving patients from all 10 regions of the national territory [21-23]. The majority of patients visiting these centers present with advanced cancer diagnoses due to delays in access to screening, diagnosis, and treatment [23]. With the limited number of oncology centers and specialists in the country, patients with cancer are often admitted in secondary level hospitals found in each of the 10 regions. Thus, patients with cancer are often cared for by nononcology professionals, particularly nurses. The Cameroon ministry of Public Health has developed a national cancer control plan to increase the number of cancer cases detected and treated early [23]. Thus, the need for strategies to promote early and timely access to psychosocial and palliative care. A study in Cameroon on psychosocial distress and quality of life of patients with cancer [22] found that majority of patients (n=83, 69.2%) presented with clinically significant distress. Financial difficulties, fatigue, transportation issues, and difficulties with work or school were the most reported problems. Up to half of the participants had moderate to severe anxiety and depression symptoms. The quality of life was fair, and there was a statistically significant negative relationship between psychosocial distress and quality of life of patients. These patients however lack access to much needed palliative and psychosocial care.

Palliative care was started in Cameroon in 2003 by the Cameroon Baptist Convention Health Services [24]. The literature reports the lack of a palliative care policy framework in the national cancer control plan [8,23], and limited accessibility to palliative care drugs, especially morphine [25]. These represent a huge gap in access to cancer care and is therefore a significant burden on the population. Training nurses to provide palliative and psychosocial oncology care to patients with cancer in Cameroon can improve access to care, patient experiences and quality of life. A few studies in Cameroon suggested that nurses lack knowledge about palliative care and have negative attitudes toward care of the dying [26,27]. However, there has not been any palliative and psychosocial oncology care training targeting practicing nurses in Cameroon.

Study Aim

The overall aim of this proposed study is to develop, implement, and evaluate the impact of a psychosocial oncology and palliative care course on Cameroonian practicing nurses' knowledge, and self-perceived competence and confidence in palliative and psychosocial oncology care provision for patients with cancer, using Kirkpatrick's framework [28] for training

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program evaluation. Our specific aims are to develop a psychosocial oncology and palliative care training program for nurses in Cameroon, to implement the training program with 50 nurses who provide care to patients with cancer in selected health care facilities in the Littoral and South-West regions of Cameroon, to assess the impact of the training program on nurses' psychosocial oncology and palliative care knowledge and self-perceived competence and confidence in psychosocial and palliative care provision for patients with cancer after program completion, to assess the strengths and weaknesses of this training program and identify possible implementation challenges to inform future psychosocial oncology and palliative care curriculum initiatives in Cameroon, and to assess nurses' transfer of their learning from this training program in the care of patients with cancer and perceived impact on patient outcome.

Methods

Design and Methods

A single group pre-posttest intervention design will be used in this study and will incorporate both quantitative and qualitative methods of data collection and analysis. The study will be conducted in 3 phases: course development; course implementation, and course evaluation (Table 1). The Kirkpatrick's framework for training program evaluation will be used to evaluate the psychosocial oncology and palliative care training program. The Kirkpatrick's framework is selected for its unique focus on evaluating the outcomes of interventions beyond learners' satisfaction. It consists of four hierarchical evaluation levels including reaction, learning, behavior, and results. Patients and the public will not be involved in the design, or conduct, or reporting, or dissemination plans of the research.

Table 1. Summary of the phases of the study.

Study phase and objective	Activities
Phase 1: Develop a psychosocial oncology and palliative care course for nurses	• Engage nurse educators, palliative care experts and oncologist as course development team • Develop course through Delphi method • Inform course development with content from the psychosocial care competencies framework for nurses in Africa [6], the international psycho-oncology society's core curriculum [29] and a palliative care course for preregistration nurse training in Cameroon [26]
Phase 2: Course implementation	• Recruit nurses who care for patients with cancer in 6 hospitals from 2 Cameroonian regions • Deliver the course to 50 nurses over a 4 days duration through theoretical lessons and a practical session
Phase 3: Course evaluation	• Undertake a pre- and post-training assessment of nurses' palliative care knowledge, self-perceived competence and confidence in palliative care provision, and nurses' psychosocial oncology care competencies • Conduct a pretraining audit of nursing records of 300 hospitalized patients with cancer to assess nurses' baseline practice of palliative and psychosocial oncology care • Administer an end of course survey to evaluate the strengths and weaknesses of the course • After 6 months of training, undertake a posttraining audit of nursing records of 300 hospitalized patients with cancer nursing records to assess change in nurses' practice • After 6 months of training, conduct critical incident interviews with 18 nurses to assess transfer of their learning to practice

Settings and Sample

The study will be conducted in 6 health care facilities in the South-West and Littoral regions. This will include 2 oncology units in Douala in the Littoral region and 4 health care facilities in Fako in the South-West region. Patients in the Southwest region of Cameroon who receive a suspected diagnosis of cancer are referred to an oncology center in Douala, the neighboring town in the Littoral region. Thus, they travel long distances to access oncology care. Secondary level hospitals located in the Southwest region provide some consultation by a visiting oncologist. There are few health care providers in the Southwest region with palliative care training [30] and we do not know of any training in psychosocial oncology for nurses in Cameroon. A purposive sample of 50 nurses who work in hospital units that provide care to patients with cancer in the study hospitals from the oncology, medical, surgical, and intensive care units will be recruited, 9 nurses from each study site in the Southwest region and 7 nurses each from the oncology units in the 2 sites in the Littoral region. In a similar study in this setting [31], a power calculation showed that using a P value of .05 to determine a statistically significant result, 50 participants were required to give 98% power to find a significant difference in palliative care knowledge. In Cameroon, we have an estimate of 1 nurse per 1000 population [32]. In most secondary and tertiary level hospitals, there are about 10 nurses working in each of the targeted units. Thus, 50 nurses will be selected from an approximate population of about 220 nurses. Nurses who have worked in either the oncology, medical, surgical, or intensive care unit for at least 6 months will included in the study. We consider that 6 months of work in any of these units will allow the nurse to have encountered several patients with cancer and gathered relevant knowledge of their needs from which we can learn during the course and to which they can compare their post training competencies. The nurses have to provide consent and agree to participate during the entire training duration.

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Participant Recruitment Strategy

Permission to conduct the study has been obtained from the directors and supervisors of nursing services of the study hospitals. We are requesting assistance from the general supervisors of nursing services in each study site to identify nurses who meet the inclusion criteria of the study. Interested nurses will register for the training by completing an application form. Selected participants will be contacted to complete the course registration process and consent. All participants will provide consent to participate. Personal identifiers, will only be collected to match pretest and post questionnaires. The questionnaires will be anonymized by coding and removal of any personal identifiers.

Data Collection

All data collection activities will be undertaken by trained research assistants (RAs), under the supervision of the principal investigators. We will train the RAs on how to use the survey instruments and how to conduct the individual critical incident interviews. We will undertake a mock data collection and role play of interviews with the RAs during the training, to ascertain they can undertake the exercise. The principal investigators will undertake validation checks of the data to ensure that data is precise, accurate and complete.

Study Activities and Data Collection Methods by Aim

Study Aim 1: Develop a Psychosocial Oncology and Palliative Care Training Program

We will develop a psychosocial oncology and palliative care training program for Cameroonian practicing nurses using the psychosocial care competencies framework for nurses in Africa [6], the International Psycho-Oncology Society's (IPOS) core curriculum [29] and the palliative care course developed for preregistration nurse training in Cameroon [26,27]. At the outset of the study, we will establish a curriculum development committee consisting of 3 members including an oncologists, a palliative care nurse, and psycho-oncologist. The research team will work with the curriculum committee to contextualize the competency framework and IPOS core curriculum for use in the training of nurses in Cameroon. This will be done in collaboration with the psychosocial oncology society of Ghana [7]. We will work virtually via email exchanges, using the Delphi strategy [33] and will organize 2 Zoom (Zoom Video Communications) meetings to finalize and validate the training program.

Study Aim 2: Implement the Training With Nurses

The training will be organized at the conference room of participating hospitals to facilitate nurses' participation. Thus, 6 training sessions will be implemented with participants in the 6 study sites. Each training session will last 4 days. Day 1 and 2 will entail classroom training sessions; day 3 will be clinical case studies and scenarios through role playing under the supervision of a palliative care nurse, oncologist, and clinical psychologist and day 4 will be experience sharing, action plan development, and training evaluation. The classroom sessions will include interactive lectures assisted by PowerPoint (Microsoft) presentations, pictures and videos, presentation of case studies, sharing of personal experiences and group discussions of concepts and experiences. An international facilitator will be invited to take part in the training and give an opportunity for others to present virtually during the training. For the clinical case studies and scenarios, participants will be shared in groups of 5 to work on different clinical case studies and scenarios followed by sharing feedback with the entire team. A similar approach has been used and shown to be an effective strategy in the training of nurses in psychosocial oncology [34]. Participants will be provided with printed copies of the palliative care toolkit by Lavy and Woodridge [35]. In addition, they will be provided with links to online resources including the free online resources by IPOS.

Aim 3: Assess the Impact of the Training Program on Nurses' Psychosocial Oncology and Palliative Care Competences

A pretest and posttest survey will be used to assess the impact of the course on nurses' psychosocial oncology and palliative care knowledge and self-perceived competence and confidence in psychosocial and palliative care provision. An advantage of a pretest and posttest assessment is that it can be used to enhance understanding of what change, particularly in factual knowledge or skill sets that could be credited to a training program. All 50 study participants will receive a paper-based pretest evaluation to determine their baseline psychosocial oncology and palliative care knowledge, and self-perceived competence and confidence in psychosocial and palliative care provision. The paper-based assessment will take place at the hospital on the first day of training. Posttest data will be collected on the last day of the training. A questionnaire has been collated and comprises of 3 subscales to collect the pretest and posttest data. These subscales include a researcher developed demographic information subscale, the Palliative Care Quiz for Nursing [36], Perceived Palliative Care Self-efficacy Questionnaire [37], and the psychosocial oncology knowledge subscales [34]. The demographic questionnaire will collect information on participants' characteristics including nurses' qualification, hospital and unit of work, gender, religious affiliation, and previous education about palliative care and psychosocial oncology. The validated Palliative Care Quiz for Nursing will be used to assess change in nurses' palliative care knowledge, the Perceived Palliative Care Self-efficacy Questionnaire will be used to assess self-perceived competence and confidence in palliative care provision. These instruments have adequate psychometric property and have been used to assess student nurses' palliative care competencies in the study setting. For the assessment of psychosocial oncology competences, we have adapted the instruments used in the study by Mahendran et al [34] in Singapore.

Aim 4: Assess the Strengths and Weaknesses of This Training Program

A course evaluation survey will be administered to participants to explore their experiences of the course, their perspective of its strengths and weaknesses, and their plans for transfer of their knowledge and skills from this course to practice, in the care of patients with cancer. This will include both close-ended and open-ended questions to give nurses the opportunity to expand

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on their responses and provide all relevant information as they deem necessary. This survey instrument is under development by the team and will be administered by research assistants on the last day of each training session.

Aim 5: Assess Nurses' Transfer of Their Learning From This Training in the Care of Patients With Cancer

Individual critical incident in-depth interviews will be conducted with nurses to explore the transfer of their learning to practice, its perceived benefits to patients and implementation challenges. A random sampling technique will be used to invite 3 nurses from each study site for this interview. Thus, a total of 18 nurses will be interviewed. These interviews will be organized at month 6 following completion of the training for each hospital. An interview guide will be used and it is envisaged that the interviews will last for 1 hour and will be tape recorded. In addition, a pre- and posttraining audit of patient files will be carried out to assess the number of patients with cancer that nurses assessed for psychosocial distress and coping, depression, anxiety, and palliative care, the number they plan psychosocial nursing and palliative care interventions (cognitive behavioral therapy) for and the number that nurses referred or suggest referral to specialist mental health and palliative care services or psycho-oncologists. The pretraining audit will be conducted at baseline, using a checklist. We will select files of the 50 most recently discharged patients with cancer or patients who died during hospitalization from each study site. Thus, a total of 300 hospital files will be studied from the 6 sites. Six months after training implementation in each site, we will undertake the posttraining audit. We will randomly select 50 files of patients with cancer currently receiving or who received nursing care from trained nurses. In total we will study 600 files, 300 from baseline and 300 post training.

Data Analysis

We will evaluate changes in mean scores from pretest to posttest to assess the impact of the course on nurses' psychosocial oncology and palliative care knowledge, and self-perceived competence and confidence in psychosocial oncology and palliative care provision. A paired *t* test, will be used to calculate the change in nurses' psychosocial oncology and palliative care knowledge from pretest scores to posttest scores, and to examine the significance of this change. The between and within group variations of the pretest and the posttest scores in psychosocial oncology and palliative care knowledge before and after the training program will be assessed using ANOVA. The McNemars test will be used to assess changes from the pretest to the posttest in nurses' self-perceived competence and confidence in psychosocial and palliative care provision. Descriptive statistics (close ended responses) and content analysis strategy (open-ended responses) will be used to analyze data on nurses' evaluation of the benefits of the course on their psychosocial oncology and palliative care competencies, their experiences of the course and its strengths and weaknesses, and how they were able to use them in practice.

A framework analysis [38] will be used to analyze critical incidents where nurses implemented their learning in practice and their perspective of how that benefited the patients with cancer in their care. Themes will be used to describe these experiences. Finally, a content analysis of the change in nurses' practice in terms of the number and content of patients' assessment for psychosocial distress, depression, anxiety, and palliative care, the number of patients with psychosocial and palliative care nursing care plans and the number that were referred to specialist mental health or palliative care services by nurses before and after the training. All project team members, RAs, and program coordinator will be involved in data collection and analysis.

Ethical Considerations

Ethical approval for this study has been obtained through the University of Buea institutional review board (Ref-2023/2165-10/UB/SG/IRB/FHS). Participants will receive an information sheet regarding the study and will provide written consent for the study. Participation in the study will be voluntary and participants will also have the freedom to leave the study at any time without giving a reason to the study team. Data will be anonymized to ensure and no identifiable information will be stored. No compensation will be provided to research participants.

Results

This study was funded in September 2023. The training program development was initiated in March 2024 and completed in June 2024. We engaged 12 cancer care, psychosocial oncology and palliative care experts, and nurse educators in Cameroon (n=7), the United Kingdom (n=2), Ghana (n=1), Indonesia (n=1), and the United States (n=1) in a 3-round Delphi process for the development of a bespoke palliative care and psychosocial oncology training program. As of August 30, 2024, we had obtained administrative authorization from all participating hospitals. The collection of baseline data on nurses' practice of psychosocial oncology and palliative care as documented in the nursing records of patients with cancer was commenced in May 2024. As of September 19, 2024, we had completed an audit of the records of 300 hospitalized patients with cancer from all study sites. The implementation of the training program is planned for October-December 2024. Following course implementation, posttest data will be started in October 2024 and continue till April 2025. Data analysis will commence in October 2024 and will continue until June 2025. We aim to present study findings at national and international palliative care and psychosocial oncology conferences and publish papers in peer review journals by November 2025.

Discussion

Expected Project Outcomes

This protocol provides details of the steps for the development, implementation and assessment of the impact of a psychosocial oncology, and palliative care training program on Cameroonian nurses' palliative care and psychosocial oncology knowledge, self-perceived competencies, and practice. In this study, we are developing a palliative and psychosocial oncology course for nurses in Cameroon. We will pilot it with 50 nurses working in 6 hospitals in the southwest and littoral regions of Cameroon. We envisage that this training program will improve

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participating nurses' palliative care knowledge and self-perceived competence and confidence in psychosocial and palliative care provision for patients with cancer. The implementation of this training program will enhance our understanding of the components and strategies for an effective palliative care and psychosocial oncology training program for nurses in Cameroon. We also hope that study findings will support future psychosocial oncology and palliative care training initiatives in Cameroon and similar contexts.

The field of psychosocial oncology is still developing in Africa [39] and therefore, initiatives to enhance health care providers' competences in this practice area are crucial especially in sub-Saharan Africa. Given the limited numbers of oncologist, psycho-oncologist, mental health experts and palliative care physicians and nurses in Cameroon, it is important to train registered nurses, who make the most of the health care workforce in Cameroon to provide palliative and psychosocial oncology care to patients with cancer and their families. This project builds on previously successful educational initiatives in palliative care for nursing students in Cameroon to enhance care of patients with life-limiting illnesses including patients with cancer [26,27]. Training nurses in palliative care and psychosocial oncology in other contexts have yielded positive impacts in terms of improvements in their knowledge and skills in palliative and psychosocial oncology care provision, with positive patient outcomes [15,34,40,41]. Similar outcomes are anticipated for this training in Cameroon.

Similar to this study, most studies have used both validated instruments such as the Palliative Care Quiz for nurses, and nonvalidated self-reported tools to evaluate the effective of training programs [15,40,41]. However, the use of self-reported tools is limited, with the possibility of recall bias, and social desirability bias [42]. Participating nurses may not recall past practices and may also tend to please the researcher and answer questions in ways they consider right rather than giving a true self-assessment of their competencies. Furthermore, nurses could overrate or underrate their competencies, resulting in a response shift bias [43].

The Kirkpatrick's model of training program evaluation used in this study provides us with a logical structure and process to measure participants' learning, satisfaction and transfer of learning to practice. It will provide us with an understanding of the specific areas for improvement within this training program, based on its strengths and weakness, thus informing program enhancement [44]. We aim to disseminate our study's findings in a peer reviewed journal and local and international conferences. In addition, during program implementation we will engagement with general supervisors of nursing services, nurse educators, and other health care professions education stakeholders in Cameroon. This has the potential to inform nursing education reforms and drive the long-term goal of curriculum revision to include palliative care and psychosocial oncology in the training programs of health professionals in Cameroon.

Acknowledgments

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Data Availability

The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

All authors contributed to the conceptualization, writing-review and editing, and approval of the submitted manuscript and will be accountable for its contents. NB and TN performed supervision. NB, TN, and BA performed data curation. NB, TN, BA, EVA, EME, NE, and ASA performed investigation and methodology. NB, TN, and BA handled project administration, managed resource and software and conducted validation. NB wrote the original draft.

Conflicts of Interest

None declared.

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Abbreviations

IPOS: International Psycho-Oncology Society
LMIC: low- and middle-income country
RA: research assistant

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Protocol

Mixed Comparative Evaluation of a Training Program Dedicated to Cystic Fibrosis Reference Centers: Protocol for the Pilot Implementation of Shared Decision-Making in the Treatment of Diabetes in Adult Patients With Cystic Fibrosis

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Abstract

Background: Diabetes affects half of the patients with cystic fibrosis who are aged 30 years and older. Diabetes progresses asymptomatically over a long period of time. Two treatment options are possible: start insulin as soon as cystic fibrosis diagnosis is made with the additional constraints of cystic fibrosis or wait while monitoring the patient's clinical condition and start insulin when diabetes symptoms develop and therefore later. This situation is particularly well suited to shared decision-making (SDM) between the physician (health care team) and patient/relatives.

Objective: The aim of this study was to perform qualitative and quantitative analyses for evaluating the outcomes and experience of SDM implementation between the physician/health care team trained for SDM and patients/their relatives for cystic fibrosis–related diabetes.

Methods: A quasi-experimental with a comparison study will be developed. Three cystic fibrosis reference centers (CFRCs) will be trained in SDM by using a web-based training, including a validated decision aid and coaching for physicians and the medical team. Two control CFRCs will maintain their usual practices. A qualitative analysis through observation of consultations, individual semistructured interviews with patients, and focus groups in CFRCs will be conducted based on a thematic content analysis. Questionnaires related to decision-making and experience of decision-making with and without SDM implementation will be administered to patients and physicians.

Results: Forty patients will be included (8 patients in each center), that is, 60 consultation observations (2 consultations per patient in the intervention groups given the modalities of the SDM process) will be conducted in 2025. Eight focus groups will be conducted in the 5 centers (2 groups in each intervention CFRC and 1 group in each control CFRC). This qualitative corpus plus responses to the patient and physician questionnaires will make it possible to know whether the practice of SDM in CFRCs is increased by an implementation strategy and to analyze the experience of patients and their relatives regarding decision-making modalities. Analysis of the outcomes and experience of the implementation of SDM are of importance to identify the facilitators and barriers to SDM from patients' and CFRCs' point of views.

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Conclusions: Our study will give us keys to adapt, improve, and disseminate SDM more widely in the context of cystic fibrosis therapy. SDM could thus be used in routine clinical practice in CFRCs at the national level.

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KEYWORDS

shared decision-making; implementation; training; decision aid; cystic fibrosis

Introduction

Background

Many patients want to play an active role in their own care [1], and many health care professionals want the same for their patients [2]. Shared decision-making (SDM) in the physician-patient encounter is one way of meeting this wish. In SDM, "the information exchange is 2 ways […]. The defining characteristic of deliberation […] is its interactional nature (ie, between the physician and the patient or potential others), and both parties work toward reaching an agreement and both parties have an investment in the ultimate decision made" [3].

SDM often relies on information and decision support tools (decision aids), which provide written support for exchanges. Decision aids are increasingly digitalized and adapted to patients' health literacy levels [4]. They present management options with their benefits and risks, informing patients and enabling them to participate in the decision-making process if they wish so. They can be used both during and outside the consultation. For several years now, national and international health care policies have been encouraging the implementation of SDM for reasons ranging from ethical imperatives [5] to the reduction of unjustified variations in clinical practice [6]. However, despite the legal framework encouraging SDM in several countries (France [7], Germany [8], United Kingdom [9], United States [10]), the implementation of SDM in clinical practice is not yet widespread [11]. SDM research has focused on physician- or patient-mediated interventions to promote SDM [12]. Légaré et al [13] in their Cochrane review showed that a combination of both physician- and patient-mediated interventions is more likely to be successful. With regard to physician-mediated interventions, SDM training can teach health care professionals to involve patients in the decision-making process. A number of studies have shown the positive effects of training programs, such as improving physicians' SDM skills and increasing patient participation and satisfaction [14,15]. Joseph-Williams et al [16] in their systematic review also showed that patients want to be informed so that they can play an active role in decision-making. Patient-initiated interventions can also enhance the patient's ability to participate in the decision-making process. Patients who have learned to use tools that encourage them to ask questions to health care professionals participate more actively [17,18]. Finally, decision aids are a means of increasing SDM. The Cochrane systematic review by Stacey et al [4] based on 105 randomized controlled trials showed the beneficial effects of decision aids in improving doctor-patient communication (without increasing patient anxiety), improving patient knowledge, respecting patient rights, increasing physician and patient satisfaction, improving the quality of care, as well as reducing the decision-making conflict.

In 2017, we developed a decision aid based on the Ottawa Personal Decision Aid Guide [19] and the International Patient Decision Aid Standards Collaboration criteria [20] on the theme of cystic fibrosis–related diabetes treatment. Psychometric tests performed at the cystic fibrosis reference center (CFRC) in Lyon showed that the tool was valid and reliable [21]. In recent years, initiatives have been developing to implement SDM in routine clinical practice. Elwyn et al [22] in their systematic review of studies of decision support interventions concluded that the majority of studies do not base their design on an implementation theory or model. Although their review focused on the routine implementation of decision support interventions to promote SDM, there are other strategies for implementing SDM. For example, a large-scale, multicomponent SDM implementation program involving training of health care professionals in SDM and decision aids has been performed within the National Health Service in the United Kingdom (Making Good Decisions in Collaboration [MAGIC] Program). It showed that successful implementation of SDM in routine clinical practice (primary care, urology, obstetrics, oncology) was based on considering stakeholder attitudes, involving all stakeholders at an early stage and analyzing barriers and facilitators [23]. Such an approach is in line with the recommendations for implementation research developed by Grol and Grimshaw [24].

According to us, SDM seems to be particularly relevant in cystic fibrosis, where there are complex treatment options with variable short, medium, and long-term side effects, and where the disease and its treatments have a high impact on the patient's quality of life. This genetic disease affects almost 7000 people in France [25] and requires lifelong multidisciplinary care. From the moment of diagnosis, patients are regularly monitored in CFRCs. As a result, the doctor, the multidisciplinary team, and the patient/relatives have often known each other for a long time, forging a strong relationship based on mutual understanding and confidence.

A patient's quality of life is severely impaired by pulmonary exacerbations and regular digestive disorders. The patient's care load is considerable, combining daily respiratory physiotherapy, daily aerosol therapy, and multi-daily drug treatments. The social constraints (follow-up appointments every 3 months, daily medication intake, diet) associated with the disease and its treatment are considerable [26]. In addition, complications arise during the course of the disease such as diabetes. After the age of 30 years, half of all patients develop diabetes [27,28].

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Diabetes adds significant morbidity [28,29]. Cystic fibrosis–related diabetes is quite specific, differing from type 1 diabetes and type 2 diabetes. It has the particularity of being asymptomatic for a long time, with normal fasting blood glucose levels. For this reason, international recommendations suggest annual screening for diabetes from the age of 10 years, with an oral glucose tolerance test [30]. If diabetes is confirmed by the results of the oral glucose tolerance test, the question arises of how to treat it with insulin. If the patient's clinical condition is stable and the fasting blood glucose level is normal, there are 2 possible treatment options: start insulin as soon as the diagnosis is made or defer initiation of insulin therapy and reserve it for cases where the patient is experiencing impaired respiratory function, increased frequency of exacerbations, or weight loss. Each of these options is complemented by the appropriate dietary and exercise measures generally recommended for all patients with cystic fibrosis. To our knowledge, very little work has been done on SDM in cystic fibrosis [31] and none on SDM for the treatment of cystic fibrosis–related diabetes.

Research Assumption

We hypothesize that the practice of SDM by CFRC health care teams for the decision to treat cystic fibrosis–related diabetes will be favored by the implementation of an SDM intervention based on e-learning training integrating an information and decision support tool and coaching for physicians and the medical team.

Aims

Primary Objective

The primary objective is to evaluate the pilot implementation of an SDM intervention, that is, the adoption of SDM between the health care professional and the patient with cystic fibrosis–related diabetes among patients managed in centers receiving the intervention compared with patients managed according to the usual decision-making practice in control centers. SDM is a decision-making process in which the health care professional (plus medical team) and the patient (plus his/her relatives) exchange information on treatment options and then reach a common agreement on the decision to take. It is based on an information and decision support tool used during the consultation. The SDM intervention evaluated comprises 5 components.

1. Web-based SDM training (e-learning) for the entire CFRC medical team
2. Individual coaching for physicians and medical team
3. SDM implementation: (1) consultation 1, including patient activation and delivery of the information and decision support tool to the patient; (2) consultation 2 on discussion and decision-making; and (3) between the 2 consultations, the patient has a cooling-off period of 8-15 days, wherein the physician discusses the content of the consultation with the CFRC team
4. Link with institutional patient engagement initiatives
5. Integration of SDM into CFRC multidisciplinary concertation meetings

Secondary Objectives

The secondary objectives were to evaluate the effects of SDM on patients' level of knowledge of management options with benefits and risks, anxiety, and decisional conflict compared with patients managed in centers without intervention and to evaluate the effects of SDM on the physician-patient relationship in terms of information and decision-making.

In Intervention Centers

The objectives were as follows.

1. To evaluate the implementation of the SDM approach.
2. To evaluate the experience of the implementation of SDM regarding the treatment of diabetes in patients with cystic fibrosis. For patients: observations of SDM consultations, individual semistructured interviews based on an interview guide containing key items relating to information and participation in decision-making (barriers, helps) based on our previous work in the field, and questionnaires (9-item Shared Decision-Making Questionnaire [SDM-Q-9], CollaboRATE, knowledge, State-Trait Anxiety Inventory, SURE [Sure of myself, Understand information, Risk-benefit ratio, Encouragement] questionnaire). For health care professionals: focus groups with CFRC teams held at the start of the intervention and afterwards in each CFRC in the intervention group.
3. To identify the individual and organizational factors that influence the implementation of SDM in the treatment of diabetes in patients with cystic fibrosis by health care professionals: focus groups with CFRC teams, semistructured interviews with patients, and exchanges with institutional decision makers such as quality services.

In Control Centers

The objective is to describe the process and experience of making decisions about diabetes treatment. For patients with cystic fibrosis, in usual practice, the objective is to conduct observations of consultations dedicated to the discussion of insulin therapy, individual semistructured interviews, and questionnaires. For CFRC health care professionals, the objective is to conduct focus groups with teams from each CFRC (focus groups held once in each CFRC during the course of the study).

Methods

Ethics Approval

This study has been approved by the Scientific and Ethical Committee of the Hospices Civils de Lyon University Hospital on the data study (outside the Jardé law; MR004-ID 21_356).

Design and Setting of the Study

Based on our previous work on SDM in cystic fibrosis [21] and the Consolidated Framework for Implementation Research of Damschroder et al [32], this quasi-experimental here-elsewhere study compares the populations of 3 centers receiving the intervention with those of 2 centers not receiving it (controls). The 5 centers will be studied simultaneously to reduce the risk of contamination of the control group. The evaluation will

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follow a mixed methods approach, combining qualitative methods (consultations observations, individual semistructured interviews with patients, and focus groups with health care professionals) with quantitative methods (self-administered questionnaires). A convergent mixed methods approach will be used, with concomitant data collection, separate analysis, and subsequent linking of results. This study conforms to the StaRi (Standards for Reporting Implementation Studies) checklist (Multimedia Appendix 1).

Characteristics of the Participants

Patient Inclusion Criteria

The patient inclusion criteria were as follows: (1) older than 18 years, with cystic fibrosis, followed up in one of the 5 CFRCs; (2) be able to understand French; (3) have an oral glucose tolerance test at the stage of diabetes or with a blood glucose Holter considered by the clinician to be pathological, justifying possible insulin initiation; (4) have normal fasting blood sugar levels; (5) stable clinical pulmonary and nutritional status, enabling the 2 treatment options to be considered; and (6) having received the information and not exercised their right to object.

Patient Exclusion Criteria

Patients who had undergone a transplant and those receiving insulin therapy were excluded.

Inclusion Criteria for Health Care Professionals

Medical and paramedical professionals working in the adult CFRC (physicians, nurses, dietitians, psychologists, physiotherapists, etc) who have not exercised their right to object were included.

Description of Intervention and Comparisons

SDM Implementation Program

This program was divided into several parts and as already mentioned, theoretically based on the Consolidated Framework for Implementation Research [21] and on existing literature on the implementation of SDM [13], structured into 5 components (A to E) focusing on health care professionals and patients.

Component A: Health Care Professionals' SDM Training in the 3 CFRCs

A 2-hour e-learning course will be the common core of the training. It comprises 7 modules: (1) training objectives; (2) review of national and international literature on SDM; (3) understanding SDM; (4) cystic fibrosis–related diabetes; (5) developing an information and decision support tool; (6) communicate benefits and risks to the patient; and (7) encourage active patient participation by means of a video of 2 simulated consultations with a doctor from the CFRC in Lyon and a patient who volunteered to take part in the project since its inception: one consultation leading to a shared decision to start insulin now and the other to start later. The e-learning will be supplemented by a presentation by one of the researchers specialized in SDM at the 3 CFRCs to answer questions/comments from the teams.

Component B: Individual Coaching for Physicians and Medical Team After e-Learning

This will be performed by the SDM methodologist to improve physicians' adoption of SDM practice. In line with research on this method [33], coaching will be provided verbally. The SDM methodologist will observe 1 or 2 consultations in each of the CFRCs, providing both oral and written feedback. Her feedback will be standardized across the 3 CFRCs on the 3 essential components of SDM (bilateral information/deliberation/common agreement on the decision taken).

Component C: Implementing SDM in 6 Steps

The 6 steps are as follows.

1. Initial consultation with the patient to discuss diabetes treatment options, detailing the benefits and risks of each option. The physician and patient inform each other, discuss throughout the consultation with the help of the information and decision support tool, elicit their preferences, and work toward reaching an agreement on the decision to take.
2. Patient activation strategy: this patient-mediated method is based on the "Ask 3 questions" tool used in international SDM implementation studies [20]. It consists of short questions that patients can ask their doctor to enable them to participate more fully in decision-making if they so wish (ask 3 questions: what are my options? what are the possible benefits and harms of those options? how likely are the benefits and harms of each option to occur?) [20]. This tool is displayed in the waiting room before the consultation.
3. The physician gives the patient a paper version of the information and decision support tool [21].
4. The physician presents the exchanges with the patient to the CFRC team trained in SDM to obtain their feedbacks.
5. A cooling-off period of 8-15 days is required before the second consultation. During this period, the patient can discuss with his or her family, general practitioner, or any other health care professional outside the CFRC as well as with the CFRC team, and can call, based on the information and decision support tool, if he or she so wishes.
6. A second consultation takes place after this period of reflection to make the decision (in this case, to take insulin now or later). Several attitudes are possible: clear patient preference for one option, patient decides alone, refusal by the patient to choose an option, or the physician decides on the basis of the therapeutic thesaurus. It should be noted, however, that this is not the paternalistic model, as far as it is the patient who, after being informed, asks the doctor to decide; thereafter, they come to a common agreement on the decision taken (decision taken together), resulting in SDM.

Component D: Link With Institutional Initiatives to Promote Patient Involvement

This will be performed by means of a short questionnaire describing the current situation on the topic. At the start of the study, this questionnaire will be supplemented by a phone interview with the hospital quality manager or referent. As CFRC teams are integrated into university hospitals that implement patient engagement initiatives, it will be important

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to collaborate with their management teams to work together on integrating the SDM approach into these hospitals.

Component E: Integrating SDM Into CFRC Multidisciplinary Concertation Meetings

In order to best integrate SDM into the 3 CFRCs in the intervention group, we will organize in 2025 and in 2026 a meeting in each of the CFRCs to see how to integrate SDM into the recommendations for practice in multidisciplinary concertation meetings, and we will consider the organizational and practice specificities of each of these 3 CFRCs.

Standard Care

Insulin therapy decisions are made according to the usual practice defined in each CFRC, with decision-making procedures specific to each center and each CFRC physician/dietitian/nutritionist/team. The decision-making process generally involves 2 consultations (Figure 1).

Figure 1. FORAIDMUCO study protocol. SDM: shared decision-making; SDM-Q-9: 9-item Shared Decision-Making Questionnaire; STAI: State-Trait Anxiety Inventory; SURE: Sure of myself, Understand information, Risk-benefit ratio, Encouragement; OPTION: Observing Patient Involvement in Shared Decision Making.

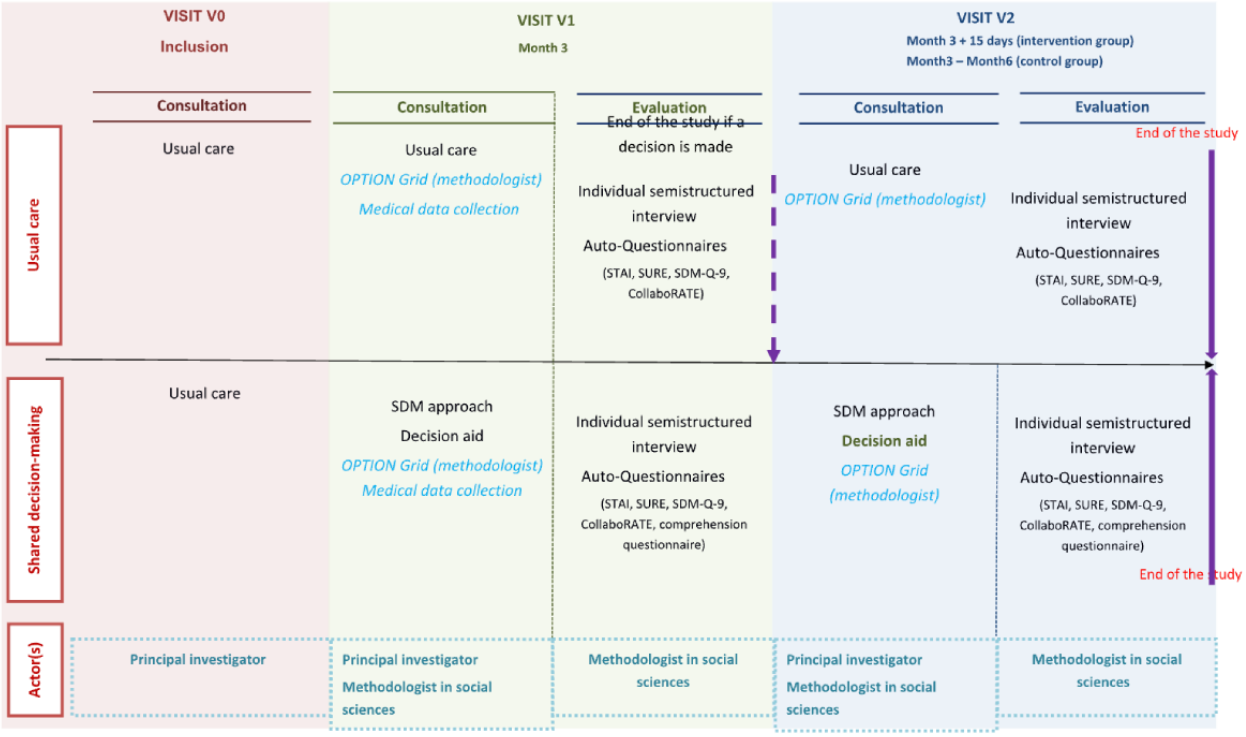

Outcomes and Measures

The outcomes are measured using the following measures.

1. Adoption or nonadoption of SDM: SDM-Q-9 [34,35], CollaboRATE questionnaire [36], OPTION (Observing Patient Involvement in Shared Decision Making) questionnaire [37,38]
2. Level of patient knowledge: knowledge questionnaire developed by the authors on the basis of their previous work [39] and the literature since no validated knowledge questionnaire exists
3. Patient anxiety level: Spielberger State-Trait Anxiety Inventory [40]
4. Patients' level of decisional conflict: SURE questionnaire [41]
5. Patients' experience of information and decision-making procedures and more specifically of SDM implementation
6. Individual and organizational factors influencing SDM implementation

Inclusion Visit (V0)

When the patient comes to the CFRC following orally induced hyperglycemia, the physician will check the patient's eligibility criteria. During this visit, the physician will present the study and give the patient the information note. The physician will record the patient's nonopposition in the consultation report. The methodologist in social sciences must be informed of the patient's inclusion by sending an email containing the patient's first and last initials and the date of the V1 visit so that she can contact the investigating center to schedule her visit.

Visit V1

In the CFRCs of the control group, the physician will present the patient with information on diabetes management according to his or her usual practice. In the CFRCs in the intervention group, the physician will present the patient with information on diabetes management according to SDM (options, benefits, and risks) by using the information and decision support tool. The patient will be "activated" prior to the consultation, inviting him/her to ask questions using the "Ask 3 questions" tool. During the V1 visit for the control and intervention groups, the

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investigator will fill in the patient's clinical data and SDM-Q-9 adapted to the physician immediately after the consultation. The patient fills in the questionnaires immediately after the consultation (the questionnaires are handed over by the methodologist or a member of the CFRC). The methodologist in social sciences will observe the physician-patient interaction during the consultation and complete the OPTION questionnaire; conduct an individual semistructured interview with the patient immediately after the consultation; ensure that the patient completes the SURE, CollaboRATE, SDM-Q-9, and Spielberger State-Trait Anxiety Inventory questionnaires (if the patient does not read French, the methodologist will read the questionnaires to the patient and fill them in with his/her agreement); and collect the patient's sociodemographic characteristics.

Decision-Making Visit (V2)

In the CFRC control group, insulin therapy decision-making will be performed according to the physician's usual practice. In the CFRCs of the intervention group, the decision-making visit will take place after a cooling-off period of 8 to 15 days following the V1 consultation. A discussion based on feedbacks from this period will take place between the physician and the patient, and either there is a common agreement on the decision taken (SDM) or the decision is taken by the patient or the decision is taken by the physician at the patient's demand. During this visit, the investigator will complete the SDM-Q-9 adapted to the physician immediately after the consultation. The patient fills in the questionnaires immediately after the consultation (the questionnaires are handed over by the methodologist in social sciences or a member of CFRC). The methodologist in social sciences will observe the physician-patient interaction during the consultation and complete the OPTION questionnaire, conduct an individual semistructured interview with the patient immediately after the consultation, and ensure that the patient completes SURE, CollaboRATE, SDM-Q-9, and the Spielberger State-Trait Anxiety Inventory. If the patient does not read French, the methodologist will read the questionnaires to the patient and fill them in with his/her agreement.

In the control and intervention groups, the methodologist in social sciences will attend the face-to-face consultation (possibly by videoconference if conditions require and allow) and will conduct the individual interview with the patient immediately after the consultation. If the patient is not available, the interview can take place up to V1+48 hours. The end of the research for patients in both groups is defined by the end of the individual interview at V2 or V1 for the control group if a decision is made following the consultation.

Health Care Professional Focus Groups

Two focus groups will be conducted in the intervention CFRCs (one at the start of the study and one at the end) and one in each of the 2 control centers by the methodologist in social sciences on the basis of a moderation guide containing the key items on which participants will be invited to discuss (barriers, facilitators of information and decision-making, dedicated time with and without SDM, information and decision support tool, etc). The discussion group will be made up of 4-8 health care professionals (physicians, nurses, physiotherapists, dietitians, psychologists, etc) depending on the center and will be as representative as possible of the CFRC's health care professional categories. In the intervention centers, the participating health care professionals will not necessarily have taken the e-learning training course. However, the group should be identical for both discussion groups unless a member is absent or leaves.

Data Collection and Analysis

Sample Size

As this is a pilot study, 40 patients will be included and interviewed over a 12-month period. The number of patients included corresponds to the active patient file of the 5 CFRCs over the 12-month inclusion period. Five physicians (1 in each center) will be involved in this study.

Analysis

All patients and health care professionals included in this study are in accordance with the inclusion and noninclusion criteria. The primary end point is the adoption or nonadoption of SDM from the patient's and health care professional's point of view. The secondary end points are patient knowledge; patient anxiety levels; patients' level of decisional conflict; patients' experience of information and decision-making procedures, and more specifically of SDM implementation; effect of SDM on the physician; and individual and organizational factors influencing SDM implementation.

Statistical Methods

Descriptive Analysis

A descriptive analysis of the characteristics of the patient population included (age, sex, history and severity of disease) and of the health care professionals on the CFRC teams (physicians, nurses, dietitians, psychologists, physiotherapists, etc, age, sex, profession, previous training in SDM) will be performed in the 2 study groups. Quantitative characteristics will be described by mean and standard deviation or by quartiles and minimum and maximum values depending on the shape of the distribution. Qualitative characteristics will be described by the numbers and percentages in each category. The comparability of the characteristics will be checked using the chi-square test for qualitative variables and the Wilcoxon test for quantitative variables. Data on the implementation of SDM in the intervention group will also be the subject of a descriptive analysis on the proportion of patients with at least one SDM consultation and the proportion of patients with 2 SDM consultations.

Analysis: Primary End Point

Adoption of SDM as perceived by the patient and measured using SDM-Q-9 will be analyzed in patients with no missing data on this criterion, although an approach to managing missing data may be considered. The frequency distribution of the 6 modalities of SDM-Q-9 will be described for each group in the patient unit. A total score will be obtained by summing the scores for each of the 9 questions. A transformation will be applied to obtain a total score between 0 and 100, with 0 indicating nonadoption of SDM as perceived by the patient and conversely 100 indicating adoption of SDM as perceived by

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the patient. The total score will be described in each group by mean, standard deviation, median, quartiles, and range, and will be compared between the 2 groups with a nonparametric Wilcoxon test. For patients in the intervention group, the variation in the responses to each of the SDM-Q-9 questions between the 2 consultations will be tested using the McNemar test (test adapted to paired data). Total SDM-Q-9 scores between the 2 consultations will be compared using the Wilcoxon signed-rank test. The same analysis will be performed on the health care professional unit to compare the adoption of SDM as perceived by the health care professional. Discordances between patient and health care professional responses to each of the 9 questions on SDM-Q-9 will be described and tested using the McNemar test. The total SDM-Q-9 score obtained on the patient unit and the professional unit will be compared using the Wilcoxon signed-rank test.

Analysis: Secondary End Points

In accordance with the scoring rules of the OPTION grid, an OPTION score will be calculated for each patient-health care professional dyad if 100% of the 5 OPTION grid items have been completed. A total score between 0 and 20 will then be obtained by summing the answers to the 5 OPTION grid items between 0 and 4. The total score will be converted between 0 and 100, with high values indicating exemplary behavior by the dyad in adopting SDM. The OPTION score will be expressed as the mean and standard deviation for each group and will be compared using the Wilcoxon test.

In accordance with the scoring rules of the SURE questionnaire, a SURE score will be calculated for each patient if 100% of the 4 questionnaire items have been completed. A total score between 0 and 4 (a high value indicates a decisional conflict) will then be obtained by summing the binary responses of the 4 questionnaire items. The SURE score will be expressed as the mean and standard deviation for each group and will be compared using the Wilcoxon test. The percentage of patients whose SURE score is less than or equal to 3 (indicating a decisional conflict) will also be calculated in each group and compared using the chi-square test.

In accordance with the scoring rules of the CollaboRATE questionnaire, a CollaboRATE score will be calculated for each patient if 100% of the 3 questionnaire items have been completed. A total score between 0 and 9 (high values indicating a high level of SDM) will then be obtained by averaging the answers to the 3 questions between 0 and 9 on the questionnaire. The CollaboRATE score will be expressed as the mean and standard deviation for each group and will be compared using the Wilcoxon test.

A Spielberger State-Trait Anxiety Inventory score will be calculated for each patient if 100% of the 20 questionnaire items have been completed. A total score between 20 and 80 (high values indicating a high level of anxiety) will then be obtained by summing the scores associated with the 20 items. For questions 3, 4, 6, 7, 9, 12, 13, 14, 17, and 18, 1 point is awarded for not at all, 2 points for somewhat, 3 points for moderately, and 4 points for very much. For questions 1, 2, 5, 8, 10, 11, 15, 16, 19, and 20, the scoring will be reversed, that is, 4 points for not at all, 3 points for a little, 2 points for moderately, and 1 point for a lot. The Spielberger State-Trait Anxiety Inventory score will be expressed as the mean and standard deviation for each group and will be compared using the Wilcoxon test.

Semistructured individual interviews designed to assess the experience of information and decision-making procedures in the control and intervention groups and the effects of SDM on patients' and health care professionals' experience of care in the intervention groups only will be analyzed by means of a thematic content analysis conducted using NVivo 10 (QSR International) and 2 researchers participating in the study based on the interview guide developed and previously tested with patients at the CFRC in Lyon. The focus groups conducted in the control and intervention groups designed to analyze the individual and organizational factors influencing the implementation or nonimplementation of SDM will be transcribed on the basis of notes taken during the focus groups and will be analyzed on the basis of the interview guide developed.

Results

Forty patients will be included (8 patients in each center), that is, 60 consultation observations (2 consultations per patient in the intervention groups given the modalities of the SDM process) will be conducted in 2025. Eight focus groups will be conducted in the 5 centers (2 groups in each intervention CFRC and 1 group in each control CFRC) in 2025. This qualitative corpus plus responses to the patient and physician questionnaires will make it possible to know whether the practice of SDM in CFRCs is increased by an implementation strategy and to analyze the experience of patients and their relatives regarding decision-making modalities. Analysis of the outcomes and experience of the implementation of SDM are of importance to identify the facilitators and barriers to SDM from patients' and CFRCs' point of view.

Discussion

This is the first study protocol on cystic fibrosis treatment in France, which is designed to train health care professionals on SDM and implement and evaluate the outcomes of the SDM approach. Training materials and health care professionals trained in SDM could boost SDM implementation in cystic fibrosis therapy in French-speaking countries, where the so-called clinical champions in SDM are needed. Moreover, patients experiencing SDM could support and participate in the SDM acculturation process.

The aim of our study is also to propose an original study based on mixed methods combining quantitative and qualitative analyses by using validated evaluation tools (particularly in French) and to conduct the study with patients and health care professionals for whom the potential benefits are multiple: to support in decision-making concerning diabetes treatment; to improve communication between physicians, health care team, and patients; to improve the quality of experience of the decision-making steps; and to acculturate health care professionals to SDM and formalize their practice, thanks to SDM training.

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The protocol and information and the decision support tool developed could serve as a basis for other situations in the field of cystic fibrosis, as in the case of lung transplantation, subject to the adaptations to be made. There are many opportunities for SDM in cystic fibrosis, but little is known about patients' experience of SDM [42]. The training materials and the teams already trained could prove to be the key to future success, with those trained becoming trainers for other centers. International comparisons could also be developed, notably within the framework of the La Collaboration Francophone sur la Prise de Décision Partagée FREeDOM (French collaboration on SDM), which brings together health care professionals, patients, researchers, and public decision makers, notably from Quebec, Switzerland, Belgium, and France, interested in adapting the approach developed to their countries/context.

Although this is the first French study to train health care professionals and implement and evaluate SDM in cystic fibrosis treatment, compared to the usual clinical practice, the number of CFRCs involved is limited, which will potentially limit the generalizability of the results obtained. This study will nonetheless be conducted at the national level. In addition, only a small number of patients with cystic fibrosis are concerned about the development of diabetes, which could impact the duration of our project in order to obtain the desired number of patients.

Acknowledgments

We would like to thank the patient partners and health care professionals of the 5 cystic fibrosis reference centers who participated in the development of this study and the Vaincre la Mucoviscidose Association for funding this study.

Data Availability

Datasets that will be generated and analyzed during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

NM, SH, SP, CG, JH, ID, and QR developed the methodology. NM wrote the first draft of this paper. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
StaRi (Standards for Reporting Implementation Studies) checklist.
[PDF File (Adobe PDF File), 235 KB - resprot_v14i1e62931_app1.pdf]

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Abbreviations

CFRC: cystic fibrosis reference center
FREeDOM: French collaboration on shared decision-making
MAGIC: Making Good Decisions in Collaboration
OPTION: Observing Patient Involvement in Shared Decision Making
SDM: shared decision-making
SDM-Q-9: 9-item Shared Decision-Making Questionnaire
StaRi: Standards for Reporting Implementation Studies
SURE: Sure of myself, Understand information, Risk-benefit ratio, Encouragement

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Protocol

Assessment of Heterosexual-Identified Men Who Have Sex With Men and Men of Diverse Sexual Identities: Protocol for an International, Multilingual, Online, Comparative Sexuality Study

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Abstract

Background: Sexuality is multidimensional and complex, and involves identity development, attraction, and behavior. Heterosexual-identified men who have sex with men (H-MSM) experience sexual identity and behavior discordance, yet it is unknown how H-MSM compare to concordant heterosexual men and gay, bisexual, and queer (GBQ+) men in terms of sexuality constructs.

Objective: This study aims to survey adult cisgender men in Canada, the United States, and the United Kingdom to gain greater insights into how demographics, identity development, attraction, behavior, technology use, relationship negotiation and communication skills, and pre-exposure prophylaxis and life satisfaction relate to each other, and then to interview H-MSM for an in-depth follow-up on survey concepts.

Methods: Purposive sampling will be used to recruit men via online and offline venues. Data collection will be multifaceted and include an online questionnaire for adult cisgender men and a subsequent interview for H-MSM. The survey will be available in English, French, and Spanish. Structural equation modeling, underpinned by hegemonic masculinity and sexual script theories, will be performed to test the relationships among survey variables. Interpretive phenomenology will be employed on the qualitative data to consider how unique sociocultural factors influence the sexuality and experiences of H-MSM, allowing for similarities and differences across participants to be identified and explored.

Results: Data collection began on November 26, 2024, and as of February 2025, data collection remains ongoing. We expect to conclude data collection and data cleaning by mid-summer 2025. Data analysis will begin in fall 2025. Our findings will provide

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a more nuanced understanding of the identity development, attraction, behavior, relationship negotiation, and technology use of H-MSM in comparison with GBQ+ men and concordant heterosexual men.

Conclusions: This research aims to broaden the scope of existing literature and support advancements in interventions and knowledge to support the overall health and well-being of H-MSM. An examination of potential differences among H-MSM, concordant heterosexual men, and GBQ+ men aims to improve the understanding of H-MSM as a distinct population, without dismissing them as closeted GBQ+ men. This study aims to provide key insights into avenues for research and practice with men whose sexuality and sexual behaviors may be outside of commonly accepted norms.

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KEYWORDS

heterosexual-identified men who have sex with men; sexuality; survey; interviews; structural equation modeling; interpretive phenomenology

Introduction

Background

Sexuality is neither fixed nor uniform, rather it is a multidimensional construct shaped by the following key components: identity, attraction, and behavior [1,2]. Sexual identity refers to both the label one uses to define their sexuality (eg, straight, gay, bi, pan, and fluid) and the social group status [3]. While sexual identity can change over time and develops in relation to contextual factors, including prescribed social norms and environment, it is often influenced by sexual attraction [3,4]. Sexual attraction, defined as the desire for sexual intimacy toward an individual or a group of people [5], serves as the primary foundation upon which one forms their sexual identity [4]. Together, sexual identity and sexual attraction work to motivate individuals' sexual behaviors, referring to the sexual practices someone engages in both individually and with others [6].

Sexual identity, attraction, and behavior are often perceived as aligning with one another (ie, concordance), and for many individuals, they indeed do (eg, a cisgender man identifies as gay, is attracted to other men, and has sex with other men). Importantly, some individuals experience discordance among their identities, attractions, and behaviors (eg, a cisgender man identifies as straight, is attracted to men and women, and has sex with men). Specifically, studies have shown that some heterosexual men (ie, men who identify as being straight) are attracted to and engage in sex with other men [7,8].

Heterosexual-identified men who have sex with men (H-MSM) experience sexual identity and behavior discordance, and they are a concealed population group. A recent knowledge synthesis found that H-MSM may comprise 0.5%-3.5% of heterosexual men and 1.26%-5.4% of men who have sex with men (MSM) [8]. Unlike gay, bisexual, and queer (GBQ+) men and concordant heterosexual men, H-MSM exhibit incongruence between their identified sexual orientation and sexual activity. Health outcomes among H-MSM remain an underexamined area, although preliminary research suggests that they may experience unique disparities compared to both heterosexual men and openly gay or bisexual MSM [9]. Extant research conducted in the United States and Europe has found that H-MSM may feel greater guilt and shame, have less ability to cope, and have poorer sexual communication in their relationships than their gay and bisexual counterparts [9]. These factors introduce adverse physical and mental health outcomes for H-MSM, particularly with regard to shaping their views of self [9]. Previous research has demonstrated that H-MSM often view themselves as less happy compared to the average person and report receiving less social support than heterosexual men [9]. As such, H-MSM may benefit from specific interventions to support mental health–related outcomes, including stress reduction, increased support and resources, improved communication, and facilitated identity development, which would likely be most effectively mediated by internet-enabled and mobile (eg, smartphone) technologies [8,9]. Indeed, research shows that H-MSM frequently use internet-enabled and mobile technologies, partially because these platforms provide greater privacy compared to in-person venues [8]. Thus, there are possibilities that H-MSM will feel more comfortable with accessing support services via technology as such interventions may be more likely to protect their anonymity.

Theoretical Foundations

Hegemonic masculinity and sexual script theories can be intertwined to help develop a stronger understanding of sexual identity congruence and incongruence among cisgender men. Both theories provide possible explanations for various sexual attitudes, self-expressions, and behaviors. More specifically, the theory of hegemonic masculinity states that maintaining masculine traits is culturally appealing and synonymous to what it means to be both heterosexual and a man [10]. According to this theory, adopting a sexual minority identity (eg, gay, bisexual, and queer) leads individuals to be perceived as less masculine and less worthy [10,11]. Similarly, the sexual script theory argues that sexual behaviors are socially constructed and are influenced by cultural, interpersonal, and intrapersonal pressures on how men should act [12,13]. That is, individuals navigate around attitudes toward sex, sexuality, and gender to determine how they will interact with others in different sexual situations. For example, men are expected to hold sexual agency and be sexually dominant and sexually motivated [14]. Some recent research suggests that heterosexual men do not always approve of these gendered sex scripts, yet they may still comply with them [15,16].

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However, H-MSM tend to embrace hegemonic masculinity and traditional sex scripts to avoid being labeled as GBQ+, to maintain their heterosexuality, and to be perceived as respectable [9]. Men who identify as GBQ+ often find themselves challenging hegemonic masculinity and gendered sex scripts [17]. Thus, H-MSM may be more likely than both concordant heterosexual men and GBQ+ men to uphold higher levels of conformity to masculine norms, sexual identity confusion and exploration, and internalized homophobia. They may also have greater attraction to narcissism, a trait that has been associated with hypermasculinity [18]. Relatedly, there is emerging evidence that H-MSM enjoy discreet encounters and rough and aggressive sex with other men but emphasize relationships with women [9]. Perhaps heterosexual men feel pressured to treat women delicately, while MSM are more willing to be sexually adventurous. If so, there are possibilities that H-MSM have higher degrees of sexual sensation seeking, sexual compulsivity, and rough sex than concordant heterosexual men. However, only minimal research has examined these phenomena among all sexually active men to compare men of different identities and concordance statuses.

Moreover, scholars argue that traditional sex scripts instruct men to be hypermasculine and maintain sexual agency over their partners [14]. As such, regardless of sexual identity, embracing hegemonic masculinity and traditional sex scripts, characterized by upholding hypermasculine traits, may prevent sexually active men from openly communicating about sex with their partners, which may have further ramifications for sexual satisfaction. Indeed, sexual communication has been linked to greater sexual satisfaction [19].

Technology use may also influence sexual and relationship communication and other sexual behaviors. Technology, for example, has been used to facilitate sexual interactions, especially among MSM [8,20,21]. Research has also shown that H-MSM enjoy meeting male sexual partners online as opposed to meeting them in-person at GBQ+ venues as the internet gives them greater privacy, allowing them to remain discreet [8]. Therefore, H-MSM may exhibit greater technology use related to sex-seeking than other sexually active men. However, questions remain on how technology use influences sexual communication and satisfaction. Research on the role of technology in sexual communication and satisfaction among sexually active men is necessary to identify possible pathways for improving sexual relationships.

Furthermore, hypermasculinity can be damaging toward help-seeking and well-being, contributing to adverse health outcomes [22]. For instance, previous research has found that endorsing more heterosexual self-presentation and experiencing greater sexual identity uncertainty can be barriers to pre-exposure prophylaxis (PrEP) adherence [23]. Indeed, scholars have concluded that men often perceive help-seeking, even related to sexually transmitted infection treatment and prevention, as a sign of weakness and as being incompatible with what it means to be a masculine man [22,24,25]. Help-seeking, though, can mitigate stress and improve life satisfaction [26]. Thus, areas of identity, attraction, and behavior associated with hypermasculinity could be connected to lower PrEP uptake, worsened attitudes toward PrEP, and lower life satisfaction. More research is needed to understand these relationships and to promote HIV prevention efforts among H-MSM and other sexually active men.

Focus of This Study

This study extensively explores the identity development, attraction, behavior, relationships, and technology use of H-MSM compared to GBQ+ men and concordant heterosexual men. H-MSM are an understudied population, and little is known about their specific experiences regarding identity development, attraction, behavior, relationships, and technology use. Currently available health services, supports, and interventions might overlook H-MSM, potentially limiting their access to care, tailored sexual health resources, mental health support, and community-based programs that address their specific needs. As such, the objectives of this study are to (1) survey men (H-MSM, GBQ+ men, and concordant heterosexual men) in Canada, the United States, and the United Kingdom to gain greater insights into how demographics, identity development, attraction, behavior, technology use, relationship negotiation and communication skills, and PrEP and life satisfaction relate to each other and (2) interview H-MSM about the constructs measured in the survey. These data will help researchers identify potential priority areas affecting H-MSM and will be used to develop pilot psychosocial interventions focused on helping H-MSM. Including GBQ+ men and concordant heterosexual men in the study will be useful in drawing comparisons and further investigating the experiences of H-MSM.

Research Questions

The research questions are as follows:

1. How do the demographics, identity development, attraction, behavior, technology use, relationship negotiation and communication, health, and well-being of H-MSM influence each other, and how do these variables differ between H-MSM and GBQ+ men as well as concordant heterosexual men?
2. How do identity development, attraction, and behavior predict the relationship negotiation and communication of H-MSM?
3. How does technology use moderate the relationship negotiation and communication of H-MSM, if at all?
4. How do identity development, attraction, behavior, relationship negotiation and communication, and technology use differ according to participant demographics?
5. How do H-MSM narratively conceptualize their identity development, attraction, behavior, relationship negotiation and communication, and technology use?

Methods

Study Design

This study uses a mixed-methods design employing both quantitative and qualitative research methods. The study is conducted virtually, and recruitment efforts span Canada, the United States, and the United Kingdom. Data are collected through an online survey as well as semistructured interviews.

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Study Team

The research team consists of 1 principal investigator, 6 co-investigators, 1 research coordinator, 3 graduate research assistants, and 2 community advisors. Members of the study team are also practicing psychotherapists.

Ethical Considerations

This study has been approved by the University of Regina's Research Ethics Board (approval number: #610). Informed consent will be obtained from each participant before their involvement in both surveys and interviews. More specifically, prior to participating in the survey, individuals will provide informed consent online. In addition, verbal consent will be obtained prior to beginning the interviews. Participants can skip any questions they do not wish to answer. Participants will be informed of their right to withdraw during the consent process and in the consent form. Participants are welcome to leave the interview at any time and to withdraw their interview data within 7 days of completing the interview. This is outlined in the consent form and will be explained in the consent process. Participants can also contact the principal investigator with any questions or concerns.

Recruitment

Recruitment will be purposive and multipronged as H-MSM are hidden and difficult to reach [8]. We will advertise recruitment on MSM mobile apps (eg, Grindr, Scruff, and Squirt) and other social media apps (eg, Facebook, Instagram, and Snapchat) that are known to be successful for recruiting MSM. These advertisements will also be displayed in various venues that sexually active men may frequent, including sexually transmitted infection and public health clinics. GBQ+ men are more likely to participate in research when advertisements display affirming images, while H-MSM are more likely to avoid research when stereotypical caricatures of GBQ+ are displayed [8]. Thus, using multiple advertisements with diverse representation will help us in recruiting diverse participants and will ensure that we obtain a representative sample. The advertisements will contain the survey link, which includes the online consent form, and a weblink to Eaton Lab [27] for further details on the study.

People will be eligible to participate in the survey if they self-identify as a man and reside in Canada, the United States, or the United Kingdom. They also must be 18 years or older to participate and must be able to read fluently in English, Spanish, or French. Participants will be excluded if they do not identify as a man or do not reside in Canada, the United States, or the United Kingdom. They will be excluded if they are under 18 years of age or cannot read fluently in English, Spanish, or French.

To participate in the interview, individuals must indicate at the end of the survey that they are interested in participating in an interview. Additionally, participants must meet the above inclusion criteria and self-identify as a heterosexual, cisgender man who has had sex with at least one other man in their lifetime. Additionally, participants can only participate in an interview if they speak fluent English.

Multiple strategies will be used to identify and remove false responses or software robots, both representing common problems in internet-based research [28-30]. For example, a rapid succession of responses from the same IP address is one of the most common indicators that those responses are fraudulent [28]. Software robots also sometimes provide irrelevant answers to open-ended responses. Therefore, such cases will be removed prior to data analysis. Further, attention checks (eg, "Please select 4") will be used throughout the survey to ensure that participants are real humans who are reading the questions and not blindly providing responses to enter the raffle for an incentive.

Data Collection

Data collection will be multifaceted and include an online questionnaire and subsequent interview, dependent on participant eligibility.

Surveys

Upon agreeing to participate, participants will be directed to the online survey, which will be administered through Qualtrics. The survey is estimated to take approximately 30-45 minutes. The survey will be offered in English, French, and Spanish, depending on the participants' preferences. The survey is divided into 12 sections: (1) screening, (2) demographics, (3) identity development, (4) attraction, (5) behavior, (6) coping with same-sex attraction, (7) relationship negotiation and communication, (8) technology use, (9) PrEP, (10) life satisfaction, (11) additional demographics, and (12) contact or follow-up information. The English survey questionnaire is provided in Multimedia Appendix 1. The study's questionnaire is programmed through Qualtrics XM Software, Version 2019.

Interviews

Interviews will focus on developing a stronger understanding of the identity development, attraction, behavior, relationship negotiation and communication, and technology use of H-MSM and will be held via Zoom (Zoom Communications), which is an online video and audio meeting program. Participants will be given the option of phoning into the Zoom meeting or joining via a Zoom link. These Zoom meetings require either a phone-in and code to be entered or an account number and an individual login password. Therefore, individuals will be able to participate in the interviews from wherever they wish, although they are encouraged to be alone in a safe and quiet environment throughout the duration of the interview. Interview questions will relate to topics surrounding sex and sexuality, particularly participants' sexual orientation, attraction, behavior, and relationships. The interview questionnaire is provided in Multimedia Appendix 2.

Measures

A matrix of survey measures is provided in Multimedia Appendix 3.

Demographics

Participants will be asked to complete a demographics questionnaire created for this study. Questions pertain to age, gender identity, sex assigned at birth, sexual identity, sexual orientation, race, religion, marital status, and past sexual activity.

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Identity Development

This study's questionnaire uses 7 validated scales to assess constructs related to identity development, including sexual identity, sexual orientation beliefs, identity confusion, and internalized homophobia.

Sexual identity will be measured using 4 validated scales: Kinsey Scale [31], Heterosexual Self-Presentation Subscale of the Conformity to Masculine Norms Inventory-46 (CMNI-46; α=.90) [32], Measure of Sexual Identity Exploration and Commitment (α=.75-.93) [33], and Sexual Orientation Identity Development Scale (α=.61-.81) [13].

The Kinsey Scale will be used to examine differences in identity questions, as it captures the continuum of sexual experiences, demonstrating that sexuality cannot be easily categorized [31].

The Heterosexual Self-Presentation Subscale of the CMNI-46 [32] measures conformity to traditional masculine norms, a common ideal among H-MSM, and has shown good internal consistency. This subscale is relevant to this study as many H-MSM report not wanting to be perceived as gay. The CMNI-46 has been used to measure specific masculine norms within a sample of H-MSM [34,35] and can be used to measure conformity to specific masculine norms [36]. This particular subscale of the CMNI-46 relates to an individual's sentiments regarding being perceived as gay and is pertinent to this study's sample as many H-MSM report not wanting to be perceived as gay [9].

The Measure of Sexual Identity Exploration and Commitment is a self-report questionnaire designed to assess the complexities of sexual identity development and has been used to examine the processes of sexual identity formation across diverse populations, encompassing various sexual orientations, genders, and cultural backgrounds [31,37]. It consists of 22 items across 4 subscales: commitment, exploration, sexual orientation identity uncertainty, and synthesis or integration. These subscales provide greater data related to sexual identity development. Worthington et al [33] demonstrated construct validity, and Dillon et al [37] found that the exploration and commitment subscales were valid. Rosenberg [38] demonstrated criterion validity for H-MSM and others. Furthermore, both Dillon et al [37] and Worthington et al [33] demonstrated high internal consistency of subscales, with the latter also finding good test-retest reliability across 2-week intervals.

The Sexual Orientation Identity Development Scale [32], though not yet validated with H-MSM, has been used with plurisex Latinx youth [39]. The measure is adapted from the Brief Ethnic Identity Scale [40] and measures identity exploration, resolution, and affirmation. Higher scores suggest higher levels of sexual orientation identity exploration, resolution, and affirmation. Toomey et al [41] found strong convergent validity when relating constructs to internalized homonegativity and self-esteem among Latino/a LGBQ adolescents (age 14-24 years), as well as factorial validity in confirmatory factor analysis. Further, Toomey et al [41] found good internal consistency between items.

Sexual orientation beliefs will be measured by the Sexual Orientation Beliefs Scale (α=.75-.84) [42]. This instrument measures beliefs about sexual orientation and includes 4 subsets: naturalness (items 1-6), discreetness (items 7-12), homogeneity (items 13-23), and informativeness (items 24-31). Although not yet validated with H-MSM, Arseneau et al [42] found strong factorial validity, good test-retest reliability, and good internal consistency with heterosexual undergraduate students.

The final facets of identity development and confusion, and internalized homophobia will be measured using the Sexual Identity Confusion Scale (α=.89) [43,44] and the Shidlo-Revised Nungesser Homosexual Attitudes Inventory (α=.94) [45,46], respectively. The Sexual Identity Confusion Scale is a self-report measure designed to assess the degree of confusion individuals experience regarding their sexual identity. It captures the uncertainties and conflicts that may arise during the process of sexual identity development. Sandfort et al [44] reported good internal consistency. The Shidlo-Revised Nungesser Homosexual Attitudes Inventory is a self-report measure designed to capture attitudes toward homosexuality, particularly focusing on internalized homophobia among gay men. Shidlo [46] identified construct validity, and Nungesser [45] demonstrated good internal consistency with each factor. Factors include attitudes toward one's own homosexuality, attitudes toward other homosexuals, and attitudes toward the disclosure of one's own homosexual identity to others. The Sexual Identity Confusion Scale and the Shidlo-Revised Nungesser Homosexual Attitudes Inventory have not been validated in H-MSM.

Attraction

Four components of attraction, including current levels of sexual desire or interest, sexual preference, attraction, and intimacy, will be captured by the study's questionnaire using items drawn from existing literature as well as validated scales.

Current levels of sexual desire or interest will be measured using 2 moderately correlated items ("How would you rate the degree of your current sexual interest?" and "How would you rate your current desire for sexual activity?"), which were previously used by Štulhofer et al [47] in a sample of men who had reported having exclusively or mostly male sexual partners in the past 5 years (r_s=0.63; P<.01). Both items use a 5-point scale, ranging from 1 (very high) to 5 (very low). Scores are summed and reversed so that higher scores denote more sexual desire.

Sexual preference will be measured using the Sexual Preference Scale (=0.67; P<.01) [48], which measures attraction until age 15 years, current attraction, fantasies, and physical contact. It aims to capture the spectrum of sexual orientation, ranging from identified exclusive heterosexuality to identified exclusive homosexuality. The scale uses a numerical spectrum ranging from 0 (exclusively attracted to the same sex) to 100 (exclusively attracted to the opposite sex), increasing in increments of 10, to quantify an individual's sexual orientation. McConaghy and Blaszczynki [48] reported physiological validation of the questionnaire by measuring penile volume.

The Attraction/Intimacy Inventory (α=.91-.99) [49] will be used to measure attraction or intimacy. The Attraction/Intimacy Assessment Inventory is a 20-item self-report measure designed to evaluate various aspects of interpersonal attraction and intimacy between individuals. The inventory has been used in

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various studies to explore relationships and has demonstrated good internal consistency, as indicated by Cronbach α coefficients reported in the literature [49]. Furthermore, the inventory's test-retest reliability has been supported, making it a reliable tool for measuring attraction and intimacy over time.

Given the relationship between narcissism and hypermasculinity [18] and the valuation of hypermasculinity within hegemonic masculinity and traditional sex scripts [15,16], especially among H-MSM [9], examining attraction toward narcissism may be helpful for understanding differences across groups of men and understanding how certain forms of attraction influence relationships, community, and health. Specifically, narcissistic trait attraction will be measured using an unnamed scale previously used by Haslam and Montrose [50] in a study assessing narcissistic trait attraction among a sample of young adult heterosexual females. Haslam and Montrose [50] asked participants to consider 20 statements relating to the extent that they found narcissistic personality traits attractive in a potential mate. These 20 statements have been derived from the 40-item Narcissistic Personality Inventory and have been formatted to a Likert-type style. Accordingly, the scale is adapted from the Narcissistic Personality Inventory, which is a scale that is validated for use among nonclinical populations. To the best of our knowledge, this scale has not been used with H-MSM.

Behavior

Five facets of sexual behavior will be captured in the study's questionnaire, including sexual satisfaction, coping with same-sex attraction, sexual sensation seeking, sexual compulsivity, and engagement in rough sex.

Sexual satisfaction will be assessed using 3 items previously used by Gonzaga et al [51] (α=.76) to measure this construct in a sample of romantic couples. Gonzaga et al [51] standardized and averaged the items to create a scale of sexual satisfaction. The items demonstrated good internal consistency and assessed: (1) how much participants agreed about sexual relations with their partner, (2) how enjoyable they found their sexual relations with their partner, and (3) how satisfactory they found the sexual relations with their partner. Similarly, coping with same-sex attraction will be measured using 46 items previously adopted in a study by Dehlin et al [52]. Specifically, in their study investigating sexual orientation change efforts in a sample of current or former members of the Church of Jesus Christ of Ladder-day Saints (LDS), Dehlin et al [52] asked participants which of several activities they had engaged in to "understand, cope with, or change" their sexual orientation. The first question generally asked if participants have or have not attempted a specific coping mechanism. For each coping strategy endorsed, 4 subsequent questions were asked: one related to the age they started the effort, another related to how long the effort lasted (in years), another related to the perceived effectiveness of each method, and another asking if they aimed to accept or change their sexual orientation. The authors reversed the scores for all the effectiveness items. These options were developed by the research team based on several sources, including direct clinical practice with LDS LGBTQ individuals and familiarity with LDS culture or practice and doctrine [53,54].

Sexual sensation seeking and sexual compulsivity will be measured using the Sexual Sensation Seeking Scale and the Sexual Compulsivity Scale (α=.75-.89) developed by Kalichman et al [55]. The former measures the degree to which one might seek new and exciting forms of sexual arousal [56], and the latter measures the extent of how compulsive one's sexual thoughts and behaviors are [55]. The authors demonstrated convergent, divergent, and discriminant validity of the Sexual Sensation Seeking Scale in MSM, and showed that the scale had good internal consistency and test-retest reliability. Likewise, the authors demonstrated convergent, divergent, and discriminant validity of the Sexual Compulsivity Scale in MSM. This scale has been used in H-MSM; however, it has not been validated in this group specifically (eg, [57,58]).

Finally, attraction to rough sex will be measured in this study through items adapted from measures previously used by Hebernick et al [59]. Four items were used in the original study by Hebernick et al [59] to assess participants' attraction to rough sex in a sample of undergraduate students. The measures involved single items and not a scale, indicating that a scale for attraction to rough sex should be created. These items have only been assessed as individual items. These 4 items have been adapted to fit this study, resulting in 28 additional items. The research team will consider conducting an exploratory factor analysis and confirmatory factor analysis to examine the structure of these items when combined to measure overall attraction to rough sex.

Relationship Negotiation and Communication

Relationship negotiation and communication will be assessed by measuring heterosexual scripting and sexual communication. The Heterosexual Script Scale (α=.88) [60] will be used to measure heterosexual scripting, and the Sexual Communication Scale (α=.83-.96) [61] will be used to measure sexual communication.

The Heterosexual Script Scale measures the endorsement of sexual double standards, courtship strategies, and commitment strategies. It includes 4 subscales: courtship and commitment subscale, men as powerful initiators subscale, men value women's appearance subscale, and sex defines masculinity and women set sexual limits subscale. Seabrook et al [60] reported discriminant validity of the scale's distinct subscales, and construct validity was demonstrated by showing that the scale is correlated with (but distinct from) traditional gender role attitudes, traditional sexual scripts, sexism, self-objectification, and self-sexualization among undergraduate students.

The Sexual Communication Scale [62] measures the frequency of bidirectional communication, ease of own communication, and ease of partner's communication. Moazami et al [61] found that the scale had good factorial validity and internal consistency among undergraduate students. For our purposes, the scale has been adapted, and 2 versions have been created: one for communication with men (12 items) and one for communication with women (12 items). A total partner sexual communication score can be computed by adding the scores of all 12 items.

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Technology Use

Seven categories of technology use will be measured in this study, including incidental information acquisition frequency, internet use levels, social media use, intent to use dating apps, attitude toward looking for romantic partners via dating apps, privacy settings, and Grindr use. We could not find measures on technology use validated for the study population. Therefore, we have selected items from extant research on closely related topics.

Incidental information acquisition frequency will be measured with 3 items that have been used to measure nonpurposeful information acquisition related to HIV/AIDS (α=.798) [63]. Venoit et al [63] found good reliability of these items in their original study with a sample of young MSM. In addition, internet use levels will be measured using 6 items used by Venoit et al [63] in the same study. A total of 13 items developed by the last author (LBM) via a survey of how sexual and gender diverse youth experience online negativity will measure how often individuals are online and use different apps on a regular basis.

Intent to use dating apps and attitude toward looking for romantic partners via dating apps will be measured using items that have previously been developed and used in a study to capture these behaviors and attitudes among participants (α=.79-.80) [63]. Chan [64] used 8 items to measure intent to use dating apps to look for romantic relationships and casual sexual relationships, and 6 items to measure attitudes toward using dating apps to look for romantic partners and attitudes toward looking for casual sexual partners via dating apps. All of the items were developed for the original study by Chan [64] and demonstrated strong internal consistency.

Grindr use will be measured using items previously used by Rice et al [65]. In a sample of young MSM, Rice et al [65] developed and administered a series of 10 items aimed to assess participants' Grindr use patterns. Items included questions, such as how frequently they logged on to the app, the length of time they had been a Grindr user, the content of their profile photo, the time and day of typical use, concurrent substance and Grindr use, and motivations for using Grindr.

Lastly, participants will be asked to answer 5 single items to measure their personal privacy settings and the presence of different privacy settings across their technological use. All items are binary and have been developed specifically for this study.

PrEP Assessment

This study will measure participants' uptake, knowledge, attitudes, and stigma regarding HIV PrEP. One item assesses whether participants currently take PrEP. To assess participants' knowledge, attitudes, and stigma surrounding PrEP, this study uses items previously developed and used by Walsh [66]. A total of 13 items used by Walsh [66] to measure knowledge of PrEP in a sample of MSM will be used in this study. Walsh [66] reported good confirmatory factor analysis model fit and internal reliability (α=.90). Participants' attitudes toward PrEP will be assessed using 5 items previously employed by Walsh [66] for this purpose. Walsh [66] reported good confirmatory factor analysis model fit and internal validity (α=.79), and Mueses-Marín et al [67] found good construct validity among Columbian MSM.

Life Satisfaction

Because hypermasculinity can be damaging to well-being [23] and because sexual communication and health are associated with improved life satisfaction [62,68-71], this study will include a measure of life satisfaction. Specifically, this study will measure participants' life satisfaction using the Satisfaction with Life Scale [71], which has been used extensively in MSM. The scale consists of 5 items and has demonstrated high internal consistency and strong test-retest reliability (α=.87) [71].

Analytical Plan

Data analysis will leverage a multimethod approach, integrating both quantitative and qualitative techniques.

Proposed Quantitative Analysis

Using Mplus version 8.9 [72], structural equation modeling (SEM) will be performed to test the relationships among the study variables. Models will be underpinned by hegemonic masculinity and sexual script theories and will be used to assess if and how measures of sexual identity, attraction, and behavior predict relationship negotiation and communication, and if and how these relationships are moderated by technology use. SEM will also be used to predict PrEP uptake and life satisfaction. The means and variance-adjusted weighted least squares estimator will be used to accommodate ordinal data for mediation [73]. In accordance with the best practices within SEM, both the measurement and structural models will be evaluated. First, the measurement model will be evaluated with confirmatory factor analysis to ensure the items adequately load onto their respective latent variables. Subsequently, control variables and paths between latent variables will be added to test the structural model. Then, the identification of the structural model will be confirmed before evaluating its model fit.

Model fit of both the measurement and structural models will be compared to prespecified criteria. For example, good model fit will be indicated by a nonsignificant χ^2 result, a comparative fit index and Tucker-Lewis index of ≥0.95, a root mean square error of approximation of ≤0.06, and a standardized root mean square residual of ≤0.08 [74-77]. Modifications to each model will be considered one at a time and will be based on theory and extant research. Alternative models will be compared. The parameters will be evaluated once model fit is achieved.

Proposed Qualitative Analysis

Audio files will be uploaded to NVivo (Lumivero), a qualitative research software, which will be used to transcribe the interviews verbatim. Members of the research team will then check the quality of the transcription and provide edits as appropriate. Data from the interviews will be analyzed using interpretive phenomenological analysis (IPA), which is encouraged for use with marginalized communities, such as H-MSM, as it emphasizes contextual understanding [77]. IPA focuses on the participants and considers how unique sociocultural factors influence their experiences, allowing for similarities and differences across participants to be identified

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and explored [78]. To maintain the focus on participants and critically examine the similarities and differences across their stories, findings will focus on sharing and not generalizing their experiences [79].

To identify themes from the data, guidelines for IPA coding will be followed [78]. First, the researchers will immerse themselves in the data by reading and rereading the transcripts multiple times. After becoming familiar with the data, coders will record initial comments or codes related to content, context, symbols, metaphors, and other important aspects of language. During this stage, coders will also record their initial interpretations of participants' stories. Throughout this process, the coding team will meet to reflect on initial thoughts, address any questions and concerns, acknowledge biases, and share feedback on effective coding strategies. Then, each coder will independently organize all codes into preliminary themes and subthemes. All members of the coding team will then meet to reflect on the similarities and differences between each coder's organization of the codes. In this meeting, the coding team will finalize the themes and subthemes by reaching a consensus. Descriptions of each theme and subtheme will then be prepared and reported with exemplar quotes from the participants.

Several strategies will be employed to strengthen the trustworthiness of the study. For example, the inclusion of H-MSM as well as clinicians with relevant expertise throughout each stage of the study will help ensure that the study is meaningful and the findings are redistributed to relevant audiences. In addition, multiple coders, memo writing, an audit trail, peer feedback, and member checking will be used to strengthen the study.

Results

Data collection began on November 26, 2024, and as of February 2025, data collection remains ongoing. As of February 2025, we have enrolled 231 participants, including 25 H-MSM, 158 GBQ+ MSM, and 48 concordant heterosexual men. We expect to conclude data collection by mid-summer 2025. Subsequently, we will begin analyses. We expect that the findings will provide a more nuanced understanding of the identity development, attraction, behavior, relationship negotiation, and technology use of H-MSM in comparison to GBQ+ MSM and concordant heterosexual men.

Discussion

Principal Results

Findings from this study will contribute to a more comprehensive understanding of how identity, attraction, and behavior interact within different subgroups of men. By exploring these outcomes, we hope to generate knowledge that might inform future interventions aimed at supporting the health and well-being of H-MSM.

Comparison With Prior Work

This is the first comparative study of men's sexuality that will intentionally sample and focus on H-MSM to ensure that they are well represented in the study while also including concordant heterosexual men and GBQ+ men. Many previous studies have not accounted for sexual identity-behavior discordance [80], and other studies recruited MSM and only happened to include H-MSM [80]. Meanwhile, other studies intentionally examined sexual identity-behavior discordance but did not oversample H-MSM [81]. Moreover, most studies of H-MSM used qualitative designs [7]. Thus, this study will build upon the existing research by recruiting large samples of H-MSM, concordant heterosexual men, and GBQ+ MSM to investigate the similarities and differences among men having different sexualities, behaviors, and attractions.

An examination of potential differences among H-MSM, concordant heterosexual men, and GBQ+ MSM aims to improve the understanding of H-MSM and encourage the need to include them in further research and practice without dismissing them as closeted GBQ+ men [8,9]. Indeed, knowledge of differences among H-MSM, concordant heterosexual men, and GBQ+ MSM may strengthen arguments for specifically targeting H-MSM in future research and public health interventions. To this end, affirming sexual identities, regardless of concordance or discordance with sexual behaviors and attractions, may play a role in encouraging help-seeking related to health services. As such, this study seeks to support the normalization and validation of H-MSM, an understudied population in need of greater attention.

This study also provides opportunities to examine how identity development, attraction, behavior, and technology use influence relationship negotiation and communication, an area of sex research in need of greater attention. In fact, research with H-MSM has not previously considered sexual communication. Nonetheless, healthy sexual communication is critical for greater sexual satisfaction [19], which is linked to greater life satisfaction [62,68-71]. Thus, this study will explore factors that may affect sexual communication among H-MSM, offering potential insights to consider when designing interventions targeted toward promoting healthy sexual behaviors in H-MSM.

Further, this study will examine possible predictors of PrEP uptake among H-MSM. Previous research on PrEP uptake centered on the voices and experiences of GBQ+ MSM and only included H-MSM who were labeled as sex workers [82,83]. Therefore, this study seeks to extend the knowledge base of PrEP and HIV prevention to H-MSM with the hope of informing the means of facilitating health-seeking behaviors and improving health outcomes. Such evidence could highlight directions for future research and practice related to encouraging PrEP use to prevent the spread of HIV.

Strengths and Limitations

This study has several methodological strengths. First, this study provides a large-scale, comprehensive examination of identity development, attraction, behavior, relationships, and technology use among H-MSM compared to GBQ+ men and concordant heterosexual men. Second, the study leverages both quantitative and qualitative methodologies. Third, the study employs multiple recruitment strategies to reach a diverse sample of participants across Canada, the United States, and the United Kingdom. This research will broaden the scope of existing literature and

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contribute to advancements in interventions and knowledge to support the overall health and well-being of H-MSM.

This study design has several limitations. As a cross-sectional study, causality will not be established. The lack of repeated measures and probability sampling will limit the consistency and generalizability of the findings. Nonetheless, this study will be able to draw theoretically-driven comparisons to support the design of future interventions and investigations.

Future Directions

Findings from this study are positioned to support future research and intervention development for H-MSM, a historically underserved and hard-to-reach population. Future studies may wish to address the limitations of this study, particularly by using longitudinal designs to assess changes over time and employing probability sampling to improve generalizability.

We hope to disseminate our findings through multiple channels, particularly given the relevance for both academic and community-based settings. These include conference presentations, knowledge mobilizations targeting community-based sexual health services, and peer-reviewed publications.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study will be available on Borealis once data collection and cleaning are complete.

Authors' Contributions

ADE contributed to conceptualization, methodology, formal analysis, investigation, writing – original draft, writing – review and editing, visualization, supervision, and funding acquisition. TRS contributed to conceptualization, methodology, formal analysis, investigation, data curation, writing – original draft, writing – review and editing, visualization, supervision, and project administration. MR contributed to data curation, writing – original draft, writing – review and editing, and supervision. SR contributed to methodology, data curation, writing – original draft, and writing – review and editing. SK contributed to writing – original draft and writing – review and editing. OWJB contributed to software, investigation, data curation, writing – review and editing, and supervision. PAS contributed to conceptualization, methodology, and writing – review and editing. TJC contributed to writing – review and editing. AB contributed to conceptualization and writing – review and editing. DV contributed to conceptualization and writing – review and editing. LBM contributed to conceptualization and writing – review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
English survey questionnaire.
[DOCX File , 118 KB - resprot_v14i1e66897_app1.docx]

Multimedia Appendix 2
Interview questionnaire.
[DOCX File , 17 KB - resprot_v14i1e66897_app2.docx]

Multimedia Appendix 3
Survey matrix.
[XLSX File (Microsoft Excel File), 54 KB - resprot_v14i1e66897_app3.xlsx]

Multimedia Appendix 4
Peer-review reports by the Education and social work (12B) Committee, Insight Grants, Social Sciences and Humanities Research Council of Canada (SSHRC).
[PDF File (Adobe PDF File), 711 KB - resprot_v14i1e66897_app4.pdf]

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Abbreviations

CMNI-46: Conformity to Masculine Norms Inventory-46
GBQ+: gay, bisexual, and queer
H-MSM: heterosexual-identified men who have sex with men
IPA: interpretive phenomenological analysis
LDS: Church of Jesus Christ of Ladder-day Saints
MSM: men who have sex with men
PrEP: pre-exposure prophylaxis
SEM: structural equation modeling

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Protocol

Health Education Campaign to Improve Malaria Knowledge, Prevention, and Treatment Behaviors in Rural East Nusa Tenggara Province, Indonesia: Protocol for a Cluster-Assigned Quasi-Experimental Study

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Abstract

Background: Malaria is a major health issue that is distributed across 85 countries globally including Indonesia. Indonesia is in the process of achieving malaria elimination. Currently, a high burden of malaria exists in the rural eastern part of the nation, including East Nusa Tenggara Province where the number of malaria cases increased significantly during COVID-19. To achieve malaria elimination, malaria awareness must be measurable and integrated into malaria policy. Currently, malaria awareness among rural communities in the region is low, and interventional studies aiming at improving malaria awareness in rural areas in Indonesia are poorly documented.

Objective: This study aims to investigate the impact of a local wisdom-based health education campaign combining local music, the voice of subdistrict leaders, and loudspeaker announcements on malaria-related behaviors in rural communities. Specifically, we aim to assess the effect of this intervention on (1) improvement in the malaria awareness index among rural communities and their associated factors, (2) changes in appropriate malaria treatment-seeking behavior (AMTSB) and its associated factors, (3) enhancements in knowledge and practice of malaria prevention measures and their associated factors, and (4) increased use of long-lasting insecticide-treated nets and their associated factors.

Methods: This study used a cluster-assigned quasi-experimental design with pretest and posttest assessments in control and intervention groups. The control group, consisting of 12 villages, received malaria education integrated into routine health services provided by local health centers. The intervention group, comprising 13 villages, received the same education as the control group, in addition to a malaria campaign conducted once a week for 20 weeks. Before and after the campaign, a household survey was conducted to assess behavioral aspects of malaria, including general knowledge of malaria, AMTSB, and malaria prevention measures knowledge and practice. Improvement in the malaria awareness index, AMTSB, good level of malaria prevention measure knowledge, and good level of malaria prevention measure practice will be determined based on the difference scores for each index before and after the intervention in both groups. The chi-square test will be used to assess score differences. Binary logistic regression analysis will be conducted to identify key risk factors associated with changes in each index.

Results: The intervention was conducted from the last week of August 2024 to the second week of January 2025. A total of 894 respondents participated before and after the intervention. The project is currently in progress, with multiple papers being drafted for publication in peer-reviewed journals.

Conclusions: This study is expected to provide significant findings to comprehensively investigate the change in behavioral aspects of malaria due to a local wisdom-based malaria education campaign. The findings could assist stakeholders in Indonesia

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with developing malaria health policies that are contextually relevant, thereby supporting global efforts to achieve malaria-free status by 2030.

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KEYWORDS

malaria awareness; local wisdom-based malaria education campaign; rural community; malaria elimination; malaria health policy; COVID-19; malaria knowledge; malaria prevention measure knowledge and practice; malaria treatment-seeking behavior

Introduction

Malaria is a major health problem spreading across 85 countries globally, with an estimated 249 million people with malaria in 2022, of which 2% were from the Southeast Asia (SEA) region [1]. The action plan in this region indicates that the entire SEA region is targeted to achieve malaria elimination by 2030 [2]. Two countries in the region, Maldives and Sri Lanka, obtained a malaria elimination certificate from the World Health Organization (WHO) in 2015 and 2016, respectively, while other countries have a high burden of malaria, with India and Indonesia in particular contributing to 88.1% to the total number of malaria cases in the region [1]. One important indicator for a region to be categorized as having eliminated malaria is the absence of local malaria transmission cases for 3 consecutive years [3].

Following the global commitment, Indonesia has also set a national goal to eliminate malaria by 2030 [4]. Much progress has been obtained toward this commitment. Of the total 514 districts, 75.7% have received malaria elimination certificates since 2023 [5], and malaria is currently concentrated in rural areas [4]. However, there is a huge disparity between the western and eastern parts of the country in this achievement. Most of the districts in the western part have been classified as malaria elimination zones, while a limited number of districts have received malaria elimination certificates in eastern Indonesia, including some in East Nusa Tenggara (ENT) Province [5]. ENT Province has 22 districts and is the third largest contributor to malaria cases at the national level [6]. The number of malaria cases increased during the COVID-19 pandemic, from 12,909 in 2019 to 15,830 in 2022 [7]. Of the total number of districts in this province, 9 districts (41%) have received malaria elimination certificates, while the rest are still categorized as high, medium, or low endemic malaria areas [8]. East Sumba District is one of the high malaria-endemic settings in ENT Province, with the total number of malaria cases reaching 5537 in 2022 [9] and the majority of cases due to *Plasmodium falciparum* [10].

Malaria is a complex health issue influenced by multiple factors including *Plasmodium* types [11-13], sociodemographic factors [14-16], environmental factors [17-19], and behavioral aspects of malaria [20]. The distribution of malaria cases shows the different patterns within and between regions, due to variations in the environment, vectors, and social conditions of the local community [21]. Various studies have been conducted in ENT Province as an effort to reduce the incidence of malaria in this area [22-27]. Studies of the aspects of malaria parasites show that the prevalence of *P. vivax* malaria is greater than *P. falciparum* malaria [22-24], and this presents a major challenge for efforts to achieve malaria elimination considering that *P. vivax* malaria treatment requires high public awareness to complete the treatment for 14 days for the optimal results [28]. Studies on malaria vectors in this region show that the prevalence of mosquito biting in this area peaks at midnight both indoors and outdoors [25,26]. Studies of environmental aspects show that increasing the distance of residence from mosquito larval habitats is followed by a decrease of the risk of malaria in all age groups [27]. However, studies on the behavioral aspects of local communities are very poorly documented in ENT Province, though malaria knowledge significantly contributes to achieving malaria elimination [29,30]. Community behavior and their perspectives are very important in the efforts to achieve malaria elimination in certain areas [31-33].

In the context of Indonesia, several studies of community behavior regarding the knowledge and practice of malaria prevention have been conducted in various provinces [34-36]. The results of these studies indicate that community members have the awareness to practice several malaria prevention methods. However, all these observational studies were conducted in the western part of Indonesia where most of the districts have been categorized as malaria elimination zones [6].

Some studies on community behavior regarding the knowledge and practice of malaria prevention have been conducted in ENT Province [37-43]. A study conducted by the National Health Research Agency in 2018 in eastern Indonesia including ENT Province reported significant variations between provinces in terms of malaria prevention practices in rural communities [37]. Other studies on malaria prevention measures knowledge (MPMK) and malaria prevention measures practice (MPMP) in the region indicated that the Tetun ethnic group used traditional plants to prevent malaria [38], the use of mosquito nets was only common in rural communities of low endemic settings [43], and communities in high endemic areas have a low level of MPMK compared with community groups in low endemic areas [44]. Another study of malaria prevention measures revealed that knowledge on long-lasting insecticide-treated nets (LLINs), which are the most effective prevention measures to prevent malaria [33,45], was only common in the high endemic settings in this province [42]. Regarding malaria treatment-seeking behaviors of the local community, the current literature reveals that the prevalence of appropriate malaria treatment-seeking behavior (AMTSB) among rural communities in the province is very low [41]. Research on malaria awareness in this rural community

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demonstrated that the level of malaria awareness of rural communities in ENT Province was very low [39] and significant variation in malaria awareness was present among ethnic groups, with the Sumba ethnic group having the lowest level [40]. However, they were all observational studies that only observed the behaviors of rural communities at a certain time. The results of experimental studies on the behavioral aspects related to malaria in rural communities in ENT Province are less documented. This indicates that there have been no efforts by various parties to increase malaria awareness in rural communities in this region. Therefore, innovation is needed to increase malaria awareness among rural-dwelling adults who are an important community group to achieve malaria elimination [46]. Increasing malaria awareness in rural communities allows them to seek the right treatment if they are sick [33,47], reduces the prevalence of malaria [48], and accelerates the elimination of malaria [49].

In the global context, the literature indicates that interventional studies have significantly improved malaria knowledge [50,51], encouraged communities to adopt various malaria prevention measures [51-55], and promoted early malaria treatment-seeking behaviors [56]. In Indonesia, experimental studies using video media have substantially increased malaria knowledge among the elderly in Mimika District, Central Papua Province [57], and Kulon Progo District, Special Region of Yogyakarta [58]. However, these studies were conducted with small sample sizes. A current systematic review on interventional studies for malaria and dengue control indicates that the use of various media in interventions has enhanced disease knowledge among both the general population [59] and school communities [60]. However, there is a lack of studies in the Indonesia context focusing on this approach [59].

The use of loudspeaker media [61], use of local-based songs [62], and local government involvement [63] have been identified as highly effective for increasing health awareness among rural communities [61,62]. However, the impact of these three culturally relevant approaches on malaria-related behavioral changes in rural communities in Indonesia remains unexplored, despite rural populations contributing significantly to the country's malaria burden [4]. Therefore, these interventional studies will fill these gaps with the following objectives: (1) determine the impact of locally based interventions on improving the malaria awareness index among rural communities and their associated factors including sociodemographic factors and environmental variables, (2) investigate the effectiveness of locally based interventions on improving AMTSB among rural communities and their associated factors, (3) assess the influence of a locally based intervention on enhancing knowledge and practice of malaria prevention measures among rural communities and their associated factors, and (4) estimate the effect of a locally based intervention on increasing the use of LLINs in rural settings and their associated factors.

This study is expected to provide significant findings to comprehensively clarify the change in the behavioral aspects of malaria in the rural ENT Province because of the application of a locally based intervention. Improvement in the malaria awareness index, variation in MPMK and MPMP, and a change in malaria treatment-seeking behaviors among rural communities will be recognized. The findings of this study could assist public health policy makers in Indonesia to design malaria policy to boost malaria elimination progress in the country. The findings might also be beneficial for other countries with similar sociodemographic characteristics to support global actions to achieve a malaria-free area by 2030.

Methods

Study Population

East Sumba District was selected as the study area because it is classified as a high malaria-endemic region [64]. The district consists of 22 subdistricts and 156 villages [65]. The total population in the district is 248,776, with an almost equal distribution of male (51.4%) and female (48.6%) residents. Approximately one-half of the population is engaged in the agricultural sector. The district has 4 hospitals, 22 public health centers, and 78 subsidiary public health centers across the region [65]. This study was conducted in 4 selected subdistricts where there is 1 public health center in each subdistrict, as indicated in Figure 1.

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Figure 1. Map of study sites.

Study Design and Sampling Technique

This study used a cluster-assigned quasi-experimental design with pretest and posttest assessments in both control and intervention groups. The cluster unit for this study was the village, which was not randomized because the research team aimed to implement the intervention across all villages within a selected subdistrict, where the subdistrict leader would serve as a role model to encourage the community to improve malaria awareness. To obtain a representative sample, the research team randomly selected 4 of the 22 subdistricts, of which 2 were assigned as the intervention groups and 2 served as the control groups. The first 3 subdistricts each had 6 villages, and the fourth subdistrict had 7 villages; therefore, a total of 25 villages participated in the study, representing about 16% of all the villages in the district. Of these, 13 villages were assigned to the intervention group, while 12 villages formed the control group. The number of sampled households selected from each village was proportional to the number of households in that village. Within each selected village, households were randomly sampled to serve as an experimental unit as indicated in Figure 2.

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Figure 2. Flowchart of the selection of malaria-endemic settings and the village populations. KAP: knowledge, attitude, practice; SD: subdistrict; V: village.

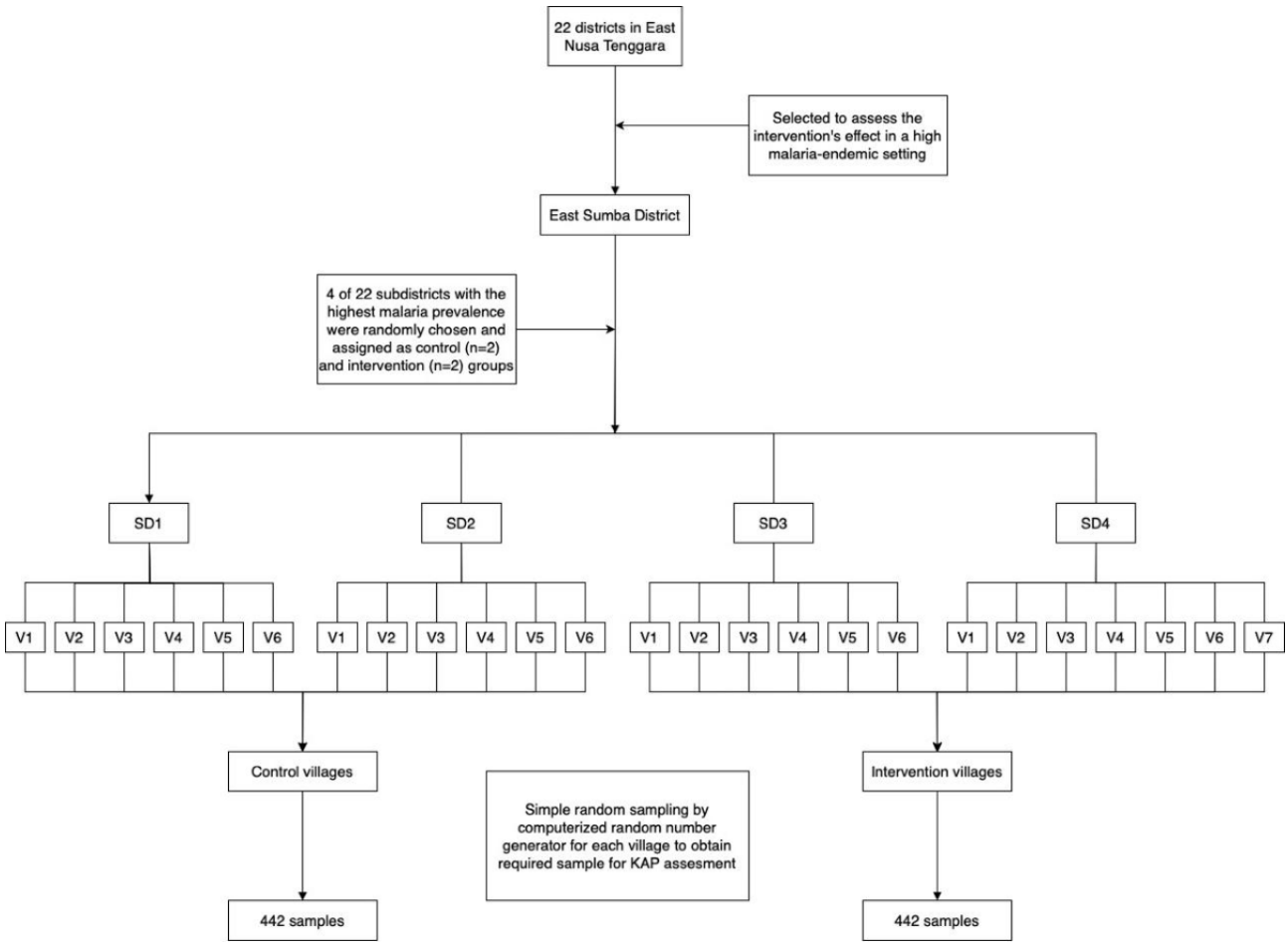

Sample Size Calculation

To determine the required sample size for the baseline prevalence of study outcomes, the research team applied the Leslie-Kish formula for calculating the sample size in cross-sectional studies [66]:

where n_0 is the initial sample size; p is the prevalence of malaria awareness in ENT Province (48.8%) [39], Z is the confidence level at 95% (standard value of 1.96), and d is the relative precision (0.05); therefore, the initial sample size was 384 participants. For the population survey, a community correction factor of 2 was applied, doubling the required sample size to 768 participants. Additionally, a 15% buffer was added to account for potential incomplete data, primarily due to nonresponse or failure to complete interviews. Thus, the final sample size was determined to be 884 participants with 442 individuals in the control group and 442 individuals in the intervention group. This number served as a guideline for recruiting participants for the household survey, which was conducted both before and after the intervention.

Eligibility Criteria

Individuals were eligible for recruitment if they had resided in the selected villages for at least 12 months and did not intend to migrate or relocate within the next 6 months after initial contact. Furthermore, participants were required to be at least 18 years old. All participants were required to provide written informed consent. For those who were unable to read or write, the consent form was read aloud by trained research assistants (RAs), and participants provided consent using a thumbprint on an ink pad. The RAs graduated from public health degrees and were local nurses with prior experience in data collection and employment at local public health centers. These professionals were recruited to ensure the study's data collection process was conducted effectively.

Study Procedure for Malaria Awareness Campaign

This study followed a 4-stage process to achieve its primary outcomes, as described in the following sections.

Phase I (Preparation Stage)

During this phase, the research team submitted an application to the Health Research Ethics Commission of Nusa Cendana University Kupang ENT Province, Indonesia, to obtain research ethics approval. Following approval, the research team coordinated with local authorities at various administrative levels, from the provincial level to the village level, in East Sumba District to obtain permission letters for conducting the study in the selected areas.

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Phase II (Baseline Phase)

After securing the necessary approvals and obtaining the recommendation letter from the relevant authorities, the research team conducted a household survey with both the intervention and control groups. Before data collection, respondents were provided with a general overview of the study, and informed consent forms were obtained before their participation. The survey aimed to assess behavioral aspects of malaria and was conducted using a questionnaire that had been modified from a previous study conducted in rural ENT Province [67]. The questionnaire consisted of 40 questions designed to collect data on key malaria-related behaviors, including general knowledge of malaria, treatment-seeking behavior, and the use of malaria prevention methods. The questionnaire was completed by either the head of the household or another household member aged 18 years or older.

Phase III (Intervention Stage)

In the control group, malaria education for the local community was integrated into routine services at the local health center. These educational sessions were provided during the first prenatal visit by pregnant women to the health center, food supplement distribution activities, and immunization programs conducted during integrated service post activities at the village level. These activities were conducted once per month, and malaria-related information was disseminated once per village on average. The primary audience for these sessions included pregnant women, mothers with children younger than 5 years, and young children. Occasionally, malaria education was provided to all individuals attending the health centers. In the intervention group, malaria education followed the same structure as in the control group but was supplemented with a health education campaign targeting the entire village community.

The intervention followed the steps outlined in the following paragraphs.

First, the research team met with the subdistrict head and village leaders in the 2 selected subdistricts designated as the experimental areas. After obtaining their approval, the research team recorded a campaign message delivered by each subdistrict leader. The campaign content, developed by experts in malaria-related behavior, mathematical modeling, and rural development, included the main symptoms of malaria, prevention strategies, and the appropriate treatment-seeking behavior for suspected malaria cases. During the campaign, the subdistrict head occasionally emphasized key points in the local language to improve comprehension. The recorded message was then combined with a locally popular song to enhance engagement. The final recording was 15 minutes long. Second, 6 health promotion staff members from Baing and Mahu Public Health Centers were selected as RAs to play the recording. The recording was broadcast using loudspeakers to ensure wide community outreach. Third, the RAs played the recorded message once per week for 20 weeks in the 13 intervention villages. The intervention started in the fourth week of August 2024 and concluded in the second week of January 2025. In each selected village, the intervention was conducted in 4 different locations per week to ensure that all community members were reached. The principal investigator maintained weekly communication with the RAs to ensure that the intervention was being conducted properly. Over the 20-week intervention period, the research team monitored implementation by visiting the experimental villages once a month for 5 months.

Phase IV (Evaluation Stage)

At this stage, the research team conducted a household survey in both the intervention and control groups using the same questionnaire that was administered during the baseline phase of the study. The final data collection was done from the third week of January 2025 to the second week of February 2025. Since the research aims to assess the impact of the intervention on all rural adults, participants surveyed before and after the intervention may differ, depending on respondent availability during the data collection period.

Data Collection Methods

Data were collected in face-to-face interviews, guided by a questionnaire adapted from a previously published study [67]. The questionnaire consists of 5 sections covering demographic characteristics, general knowledge of malaria, treatment-seeking behavior, practice of malaria prevention measures, and practice of malaria treatment-seeking behaviors. Each section contained questions to capture key behavioral aspects of malaria. A detailed list of the questions for each section is provided in Multimedia Appendix 1. Furthermore, this data collection was conducted by local nurses and health promotion workers from the selected health centers. These enumerators participated in a 1-day intensive training to improve their understanding of the study background and objectives. Moreover, enumerators were trained how to approach the potential participants in this study and how to conduct the interview following the guidance of this study and local culture. The same enumerators were responsible for recruiting participants during both baseline data collection and the postintervention phase. For secondary data collection, malaria register books from each public health center were reviewed to obtain data on the number of malaria cases and malaria-related deaths over a 10- year period from 2013 to 2023. Data on the number of malaria cases in each public health center throughout the district were collected from the Health Department of East Sumba District for the same period.

Independent Variables of the Study

This study considers demographic and environmental factors as independent variables. Demographic variables include gender, age, education level, occupation, and socioeconomic status (SES). Respondents' SES will be measured based on ownership of durable assets such as a television, refrigerator, car, electricity, telephone, and radio; the number of bedrooms; and home infrastructure conditions such as access to drinking water sources and the presence of water channels around the house [68]. Using principal component analysis, respondents' SES will be categorized into 5 quantiles ranging from the lowest (quantile 1) to the highest (quantile 5) [69]. Environmental variables in the study include the location of the residence, categorized as rice fields, coastal areas, or hilly areas, and accessibility to villages, classified as easy, moderate, or difficult to access. Additionally, the study considered proximity to health

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facilities, including the type and distance of the nearest health facilities. For secondary data from the health center, patient records from 2013 to 2023 were reviewed for all patients with suspected malaria, and positive or negative cases were confirmed based on laboratory examination results. The number of malaria cases based on gender, age group, type of *Plasmodium*, time (year and month), location of residence, and type of treatment and the number of deaths since the period under review were collected from the 4 selected health centers.

Outcome Variables

The study considers 10 potential outcomes variables, with the first 7 serving as the primary outcomes of the intervention, while the remaining 3 represent secondary findings. The first primary outcome of the study is improvement in the malaria awareness index among rural communities. If the malaria awareness index after the intervention is higher than that before the intervention, it indicates that the health education campaign effectively enhanced malaria awareness. This index will be assessed based on 12 questions covering general knowledge of malaria, treatment-seeking behavior, and knowledge of malaria prevention measures, following the methodology of a previous study [39]. Each correct response will be assigned a score of 1, while incorrect answers will receive a score of 0, with a total possible score of 12. Participants' knowledge level will be categorized based on their accuracy rate: 0% (zero awareness), 1% to 59% (poor awareness), 60% to 79% (good awareness), and at least 80% (excellent awareness). Those classified as having excellent or good awareness will be considered aware of malaria, while participants in the other categories will be classified as unaware of malaria [39,70]. The malaria awareness index will be calculated before and after the intervention in both the intervention and control groups to evaluate the effectiveness of the health education campaign.

The second outcome variable in this study is improvement in AMTSB. This improvement will be demonstrated if the proportion of rural adults exhibiting AMTSB after the intervention is higher than before the intervention. AMTSB is defined as seeking malaria treatment at professional health facilities within 24 hours of experiencing malaria symptoms [41]. The proportion of rural adults engaging in AMTSB will be calculated both before and after the intervention in both the intervention and control groups. This assessment will be based on the 3 key questions from the malaria treatment-seeking behavior section of the questionnaire.

The third outcome variable in this study is improvement in good MPMK. This improvement will be demonstrated if the percentage of the rural population with good MPMK after the intervention is higher than before the intervention. A good level of MPMK is defined as the ability to correctly answer at least one-half of the total questions in the MPMK section, as indicated in previous studies [41,59]. The level of MPMK will be assessed before and after the intervention in both the intervention and control groups.

The fourth outcome variable is the use of bed nets during the dry season in high malaria-endemic settings. Community behaviors regarding bed net use may exhibit seasonal variations, as individuals may adjust their practices depending on weather conditions [71]. This outcome will be assessed based on the participants' self-reported responses to a survey question asking whether they slept under a bed net the night before the survey.

The fifth outcome variable in this study is the variation in the use of a bed net in the dry and wet seasons. The literature indicates that bed net use might fluctuate based on seasonal weather conditions, as individuals adapt their malaria prevention behaviors accordingly [71,72]. This malaria awareness campaign began at the end of August 2024, during the dry season, and concluded in the second week of January 2025, which corresponds to the wet season in the study area. The study will examine seasonal differences in bed net use by analyzing responses to 4 key questions from the malaria prevention practice section of the questionnaire. The disparity in bed net use between dry and wet seasons will be assessed for both the intervention and control groups.

The sixth outcome variable in this study is improvement in good MPMP. Improvement will be demonstrated if the percentage of the rural population practicing good MPMP after the intervention is higher than before the intervention. A good level of MPMP is defined as the ability to correctly answer at least one-half of the total questions in the MPMP section, as indicated in a previous study [73,74].

The seventh outcome variable in this study is variation in access to basic drinking water and its associated factors among rural communities in ENT Province, Indonesia. Household access to basic drinking water is defined based on the WHO Joint Monitoring Program guidelines, which classify water sources into 4 categories: no service, unimproved, limited, and basic [75]. To analyze this variable, a dichotomous classification will be used, where households will be categorized as either having access to an improved drinking water source (Yes=1) or lacking access to an improved drinking water source (No=0). This classification will help determine disparities in access to safe drinking water and identify key factors influencing these differences.

The secondary outcomes of this study are derived from the analysis of patient medical records from 4 selected health centers, along with additional data from the Department of Health, East Sumba District. The eighth outcome variable focuses on the monthly number of malaria cases recorded over the past 10 years, from 2013 to 2023. By integrating data from both health centers and the Meteorological Agency of East Sumba, this study aims to explore the impact of climatic variables on malaria case fluctuations in this region, following the methodology of a previous study [76]. This analysis will provide valuable insights into seasonal and long-term trends in malaria transmission, which could help inform future malaria prevention and control strategies.

The ninth outcome variable in this study examines the demographic variations in malaria prevalence among communities residing in hilly and coastal areas over the past 10 years (2013-2023). Among the 4 selected health centers, Baing and Nggongi Public Health centers are located in coastal areas, whereas Mahu and Kananggar Public Health Centers are situated in hilly regions. Given that vector distribution and species composition may vary between different geographic settings

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[77], previous studies in Indonesia have reported significant differences in malaria prevalence between coastal and hilly areas [78]. By analyzing malaria case records from these health centers, this study aims to assess regional disparities in malaria burden and determine how demographic and environmental factors contribute to these differences. This information may help tailor malaria prevention and control efforts to the specific needs of different geographic regions.

The tenth outcome variable in this study investigates malaria prevalence and malaria-related mortality rates in East Sumba district over the past 10 years (2013-2023). Data on the number of malaria cases and malaria-related deaths were obtained from malaria register books at the health centers and malaria reports from the Health Department of East Sumba District. Therefore, the trends in malaria prevalence and mortality rates over the 10-year period in the study area will be revealed, following the methods of previous studies [79,80].

Statistical Analysis

All statistical analyses will be conducted using SPSS version 27 (IBM Corp), and *P* values <.05 will be considered statistically significant.

For the first outcome variable, descriptive statistics will be used to summarize participants' sociodemographic characteristics and environmental variables including gender, age group, SES, education level, family size, distance to the nearest health facilities, village accessibility, and household location. A chi-square test will be applied within each study group (intervention and control) to evaluate the association of basic malaria understanding, basic malaria knowledge, the level of malaria knowledge, and the level of malaria awareness before and after the intervention. Unpaired sample *t* tests will be used to investigate the statistical differences. Comparisons will be performed within groups (pre- and postintervention) and between groups to determine the impact of the intervention [61]. Furthermore, a binary logistic regression model will be used to identify the potential factors associated with malaria awareness in both the intervention and control groups [39].

For the second outcome variables, descriptive statistics will be used to summarize participants' sociodemographic and environmental characteristics including gender, age group, SES, education level, family size, distance to the nearest health facilities, access to village, and household location for both study groups. A chi-square test will be used to evaluate the association between AMTSB and the sociodemographic and environmental characteristics of participants. Unpaired samples *t* tests will be used to assess the statistical differences. Comparisons will be conducted within and between groups for both pre- and postintervention periods. Moreover, binary logistic regression analysis will be used to identify predictors associated with AMTSB among participants in both study groups [41]. Only predictors that demonstrate statistically significant differences ($P<.05$) will be retained in the final model.

For the third variable response, participants' sociodemographic characteristics and environmental variables in each group will be reported using descriptive statistics. The association between a good level of MPMK with predictors will be investigated using a chi-square test. Unpaired samples *t* tests will be used to investigate the statistical differences. Comparisons will be conducted within and between groups for both pre- and post-intervention periods. Furthermore, binary logistic regression analysis will be performed to identify key risk factors influencing MPMK [44,81] among rural communities in both study groups.

For the fourth outcome variable, descriptive statistics will be used to summarize participants' sociodemographic characteristics and environmental variables based on the awareness that malaria can be prevented. Associations between bed net use and its predictors will be examined using a chi-square test. Binary logistic regression analysis will then be conducted to identify the primary risk factors associated with bed net use during the dry season among rural communities [71].

For the fifth outcome variable, participants' sociodemographic characteristics, environmental variables, and malaria-related behavioral aspects in both the intervention and control groups will be analyzed. Data will be presented as proportions for each season (dry and wet seasons) to examine the seasonal variations in malaria prevention behaviors. The associations between bed net use and its predictors will be evaluated using a chi-square test for each season. The main risk factors for bed net use during the dry and wet seasons will be investigated using binary logistic regression analysis. The adjusted odds ratio will be used to quantify the strength of the associations between bed net use and its predictors in each season [71,72].

For the sixth outcome variable, participants' sociodemographic characteristics, environmental variables, and behavioral aspects of malaria in each group will be reported using descriptive statistics. The association between a good level of MPMP and its predictors will be investigated using chi-square tests. Unpaired samples *t* tests will be used to investigate the statistical differences. Comparations will be performed within and between groups for both pre- and postintervention periods. Moreover, binary logistic regression analysis will be performed to identify the primary risk factors influencing MPMP [73,74] among rural communities in both study groups.

For the seventh outcome variables, descriptive statistics will be used to summarize participants' sociodemographic characteristics, environmental variables, and malaria-related behaviors based on their source of drinking water. The associations between access to improved drinking water and its predictors will be assessed using chi-square tests. Furthermore, a binary logistic regression model will be used to determine predictors influencing access to improved drinking water [75].

For the eighth outcome variable, descriptive analyses of climatic factors across different subdistricts will be performed. Data will be aggregated at the subdistrict level, and statistical estimates will be generated for each variable. Specifically, the total number of malaria cases and the average malaria incidence will be computed. Climatic variables, including maximum, minimum, and mean temperature values, will be calculated. Moreover, data from all 22 subdistricts will be analyzed, focusing on malaria cases and climatic parameters, including maximum, minimum, and average temperature values. To depict

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the seasonal dynamics, seasonal variations in climatic parameters and malaria cases will be plotted, covering the 2 main seasons. A time series for both predictor and outcome variables will be plotted to deliver an overall perspective. A map of malaria cases will be generated. Scatterplots will be developed to illustrate relationships between malaria cases and predictor variables, following the methods of a previous study [76].

For the ninth outcome variable, malaria cases records from 2013 to 2023 will be analyzed across different geographic areas. Data from Baing and Nggongi Public Health Centers, representing coastal regions, will be combined, while records from Mahu and Kananggar Public Health Centers, representing hilly areas, will be aggregated separately. Malaria prevalence will be calculated on a monthly, yearly, and cumulative basis over the study period. To visualize the demographic trends, malaria prevalence will be plotted against key demographic variables. The disparity of malaria prevalence in demographic variables will be investigated using a chi-square test [10,82].

For the tenth outcome variable, descriptive statistics will be used to calculate frequencies and percentages of overall malaria prevalence and trends in malaria transmission considering variations by season, month, year, sex, age, and species of malaria parasite. Epidemiological characteristics, including age group, sex, and *Plasmodium* species–adjusted malaria-related mortality rates in East Sumba District will be presented as percentages followed by their 95% confidence intervals. Chi-square tests will be used to compare the associations of malaria burden by age groups and sex. The malaria prevalence and mortality rate will be illustrated in a map to assess the distributions of the cases geographically [79,80].

Ethical Considerations

We adhered to the Declaration of Helsinki to ensure that the rights, integrity, and confidentiality of the respondents are strictly protected. All respondents signed consent forms before being interviewed. For this interventional study, we received human ethics approval from the Human Ethics Committee of Nusa Cendana University Kupang ENT Province Indonesia (ethics ID: 42/UN15.21/KEPK/2024) as shown in Multimedia Appendix 2. All respondents who participated in this study were involved voluntarily without compensation in the form of material; however, they received additional knowledge about malaria. Data obtained from this study will be strictly kept by the principal investigator, and no personal respondent information will be shared during the dissemination of the study results. The research team secured official permission letters from relevant authorities at the provincial, district, subdistrict, and village levels to conduct the study within the designated areas. Written consent forms were collected from all participants participating in this study.

Dissemination

The findings of this interventional study will be disseminated through national and international conferences and published in peer-reviewed journals.

Results

The time frame of the project is presented in Table 1.

Table 1. Timeline of research phases.

Research phases	January-May 2024	June-July 2024	August 2024-January 2025	February 2025	March 2025-December 2026
Questionnaire and question guide development	✓	—[a]	—	—	—
Ethics approval	—	✓	—	—	—
Training of field workers	—	✓	—	—	—
Household surveys for pretest data	—	—	✓	—	—
Data entry	—	—	✓	—	—
Data analysis	—	—	✓	—	—
Manuscript preparation and submission	—	—	✓	—	—
Intervention in 13 villages	—	—	✓	—	—
Household surveys for posttest data	—	—	—	✓	—
Data entry	—	—	—	—	✓
Data analysis for the final outcome	—	—	—	—	✓
Manuscript preparation and submission	—	—	—	—	✓

[a]Not applicable.

Primary data collection for the baseline survey was conducted between August 2024 and September 2024. A total of 894 rural adults participated in face-to-face interviews in both the intervention and control groups. These participants were drawn from 25 villages across East Sumba District. The intervention commenced in the last week of August 2024 and concluded in the second week of January 2025. The project is currently in the process of drafting multiple research papers, which will be submitted for publication in peer-reviewed journals to disseminate the findings. This study was funded by the Directorate General of Higher Education, Ministry of Education and Culture of the Republic of Indonesia (main contract number:

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073/E5/PG.02.00.PL/2024) on June 11, 2024, and an extension contract number from the Research Center of Nusa Cendana University Kupang ENT Province (contract number: 448/UN15.22/SP2H/PL/2024) on June 12, 2024.

Discussion

Principal Findings

This research endeavors to examine the impact of integrating multiple media into an interventional study designed to influence malaria-related behavioral changes among rural communities. The intervention incorporated local governmental leaders, traditional music, and loudspeaker announcements, recognizing their potential to enhance community engagement and facilitate effective malaria awareness campaigns. Local authorities play a pivotal role in public health initiatives as they serve as trusted figures within their communities and possess extensive experience in mobilizing the local population [63,83]. Furthermore, music has been shown to be a powerful tool for fostering social connection and disseminating health information, particularly in efforts to promote preventive behaviors for infectious diseases [62]. The use of loudspeakers as a communication medium has also been identified as an effective approach for delivering malaria health messages and ensuring continuous information dissemination in rural settings [61]. Moreover, integrating music-based education enhances learning outcomes among populations with low literacy rates [84], making it a particularly effective strategy for engaging rural communities. This is particularly relevant in ENT Province, where high school dropout rates remain a challenge [85,86]. By leveraging these culturally relevant and widely accessible communication methods, this quasi-experimental study has the potential to generate a significant impact on improving the malaria awareness index, AMTSB, knowledge of malaria prevention measures, and practice of malaria prevention measures among rural adults in ENT Province, Indonesia.

Interventional studies have demonstrated a positive impact on improving malaria-related behaviors at the community level across various settings [50,51,55,60,87-89]. In SEA, several interventional studies have shown significant contributions to behavioral change in malaria prevention and treatment [52,61,90,91]. For instance, a study conducted in Northern Myanmar found that loudspeaker announcements delivering malaria prevention and treatment messages over 6 months significantly increased malaria awareness among villagers [61]. Similarly, a school-based educational intervention in India demonstrated a substantial improvement in malaria prevention and control knowledge among students in grades 9 to 12 [90]. In Pakistan, an interventional study targeting pregnant women indicated that the use of LLINs increased significantly following a 12-week health education program [52]. In Bhutan, a community-directed educational intervention on malaria prevention, implemented over 6 months, led to improvements in malaria-related knowledge, attitudes, and prevention practices among rural communities in Sarpang district [91]. In Indonesia, there is a notable gap in interventional studies focused on malaria education. Most existing research has been conducted in school settings [60] and is primarily concentrated in the western region of the country [59]. To the best of our knowledge, this is the first study in SEA to investigate the combined impact of local leadership, traditional music, and loudspeaker announcements as intervention media to enhance malaria knowledge, improve prevention practices, and encourage early treatment-seeking behaviors among rural communities affected by malaria.

The data collection instruments used in this study were adapted from a validated questionnaire, with modifications made to ensure ease of administration. The measurement of key variables, including the malaria awareness index, AMTSB, MPMK, and MPMP, was based on standardized indicators from reputable international journals. This methodological approach allows for comparability with national and international studies, enhancing the credibility and applicability of the findings. Consequently, the study's results will serve as an important reference for guiding malaria health policy in rural Indonesia and supporting the national commitment to achieving malaria elimination by 2030.

Despite its strengths, this study has several limitations. First, village selection was not randomized for the control and intervention groups, which may introduce potential selection bias. However, the allocation strategy ensured that the distribution of villages between study groups was comparable in terms of malaria endemicity, and the intervention was designed to maximize its impact by including all villages within a selected subdistrict. Second, most of the data collected in this interventional study relied on self-reported responses from participants, covering aspects such as general malaria knowledge, symptoms, diagnosis, and prevention measure knowledge. This reliance on self-reported data introduces the potential for recall bias. However, to mitigate this limitation, all MPMP were directly observed by RAs during data collection, improving the reliability of reported behavioral measures.

Conclusions

This study is expected to provide significant findings to comprehensively investigate the change in behavioral aspects of malaria among rural communities following the implementation of a local wisdom-based malaria intervention. Changes in the malaria awareness index, MPMK, MPMP, disparity in using core prevention measures such as LLINs in 2 different seasons, and malaria treatment–seeking behaviors among rural communities due to the implementation of a local wisdom-based health education campaign will be recognized. These findings will provide evidence-based insights into the effectiveness of locally driven health education strategies in malaria-endemic regions. Therefore, this research will contribute to the development of contextually relevant malaria policies in Indonesia. Furthermore, it aligns with global malaria elimination efforts, supporting Indonesia's commitment to achieving a malaria-free status by 2030.

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Acknowledgments

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Authors' Contributions

Conceptualization: RDG
Data curation: RDG
Formal analysis: RDG
Funding acquisition: RDG (lead), ML (supporting), DMS (supporting), YPB (supporting)
Investigation: RDG (lead), DK (supporting)
Methodology: RDG
Project administration: RDG (lead), ML (supporting), DMS (supporting), YPB (supporting), DK (supporting)
Supervision: RDG
Validation: RDG
Visualization: RDG (lead), YPB (supporting)
Writing - original draft: RDG
Writing - review & editing: RDG (lead), ML (supporting), DMS (supporting), YPB (supporting), DK (supporting)

Conflicts of Interest

None declared.

Multimedia Appendix 1
The questionnaire for primary data collection in pre and post-test.
[PDF File (Adobe PDF File), 169 KB - resprot_v14i1e66982_app1.pdf]

Multimedia Appendix 2
Ethics approval of nusa cendana university kupang east nusa tenggara indonesia.
[PDF File (Adobe PDF File), 432 KB - resprot_v14i1e66982_app2.pdf]

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Abbreviations

AMTSB: appropriate malaria treatment-seeking behavior
ENT: East Nusa Tenggara
LLIN: long-lasting insecticide-treated bed net
MPMK: malaria prevention measures knowledge
MPMP: malaria prevention measures practice
RA: research assistant
SEA: Southeast Asia
SES: socioeconomic status
WHO: World Health Organization

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Protocol

Intradialytic Changes and Prognostic Value of Ventriculo-Arterial Coupling in Patients With End-Stage Renal Disease: Protocol for an Observational Prospective Trial

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Abstract

Background: The acute effect of hemodialysis (HD) on left ventricular mechanics has been evaluated in several studies; however, their results are not consistent. Eventually, the heart and the arterial system behave as an interconnected system and not as isolated structures; thus, the evaluation of the interaction of cardiac contractility with the arterial system would provide a more comprehensive understanding of cardiovascular function and cardiac energetics. However, there have not been any studies demonstrating changes in terms of volumes, contractility, intraventricular pressure gradient distribution, and vascular properties in response to changes in loading conditions and their impact on the outcome in patients undergoing HD. Recently, a noninvasive method for assessing left ventricular pressure-volume loop and ventriculo-arterial coupling (VAC) from feature-tracking cardiac magnetic resonance or echocardiography has been proposed. We believe that this method allows a comprehensive evaluation of the hemodynamic status of the patients undergoing HD, including the relationships between cardiac function and arterial elastance, and might provide prognostic information.

Objective: The primary objective of this study is to evaluate changes in VAC before and after a HD session. The secondary objective is to assess the prognostic value of VAC parameters in predicting adverse outcomes.

Methods: A 2D transthoracic echocardiogram will be performed before and after a HD session in patients with end-stage renal disease. We target to enroll 323 patients. Images will be analyzed with advanced software based on speckle-tracking, able to reconstruct the pressure-volume loop. From the pressure-volume loop, arterial (Ea) and ventricular (Ees) elastance will be derived. VAC will be calculated as the Ea/Ees ratio. Patients will be followed up for 18 months. Primary endpoints will be a composite of all causes of death, nonfatal myocardial infarction, and hospitalization due to worsening heart failure.

Results: The study received funding in August 2024, with patients' enrollment scheduled to take place from January 1 to June 30, 2025. Data analysis will start in April 2025 and is expected to continue until June 2026. The findings of the study are tentatively planned for publication in the winter of 2027.

Conclusions: This study will provide data on the changes in VAC induced by HD and their potential prognostic value. This assessment could be useful for tailoring volume depletion during HD and to improve patients' outcomes.

Trial Registration: ClinicalTrials.gov NCT06622928; https://clinicaltrials.gov/study/NCT06622928

International Registered Report Identifier (IRRID): PRR1-10.2196/71948

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(JMIR Res Protoc 2025;14:e71948) doi:10.2196/71948

KEYWORDS

ventriculo-arterial coupling; pressure-volume loop; end-stage renal disease; hemodialysis; echocardiography

Introduction

Background

One of the main goals of HD therapy is to remove from the patient the excess fluid that accumulates in the body due to kidney failure. Optimal fluid volume management is an essential component of HD adequacy, but the amplitude of volume fluctuation is still a quite challenging clinical condition. In fact, HD in patients with end-stage renal disease (ESRD) removes a large amount of fluid from the body in a few hours. Therefore, patients with ESRD on HD are characterized by central volume fluctuations related to volume expansion in the interdialytic period and fluid loss during HD. They also tend to have changes in cardiac structure and function, which have been recognized as key prognostic factors [1]. A myriad of mechanisms, such as chronic volume and pressure overload, anemia, uremia, high-flow arteriovenous shunts, fluid retention, abnormal calcium and phosphate metabolism, and hyperparathyroidism, can lead to cardiac abnormalities [2]. Furthermore, HD-induced acute hemodynamic changes in electrolytes, arterial pressure, blood volume, and sympathovagal balance can negatively impact cardiac function [3]. In fact, patients with chronic kidney disease exhibit a pronounced risk for cardiovascular events: 50% of all patients with chronic kidney disease stages 4 to 5 have cardiovascular diseases, and cardiovascular mortality accounts for approximately 40% to 50% of all deaths in patients with advanced chronic kidney disease (stage 4) as well as ESRD (stage 5), compared with 26% in controls with normal kidney function [4].

Changes in left ventricular (LV) volume during HD will alter LV contraction and strain. The acute effect of HD on echocardiographic indices of cardiac structure and function has been evaluated in several studies; however, their results are not uniform. Eventually, the heart and the arterial system behave as an interconnected system and not as isolated structures; thus, the evaluation of the interaction of cardiac contractility with the arterial system would provide a more comprehensive understanding of cardiovascular function and cardiac energetics. However, there is still scanty data on changes in volumes, contractility, intraventricular pressure gradient distribution, and vascular properties in response to changes in loading conditions and their impact on the outcome.

Ventriculo-Arterial Coupling

The concept that the cardiovascular system works better when the heart and the arterial system are coupled has been well demonstrated [5-7]. When the heart pumps blood into the vascular tree at a rate and volume that matches the capability of the arterial system to receive it, both cardiovascular performance and its associated cardiac energetics are optimal [8]. A contractility or arterial tone that is too high or too low decouples these processes and can lead to cardiac failure independent of myocardial ischemia or the toxic effects of sepsis and related systemic disease processes. This optimization means that the LV workload and the arterial system optimally match when the LV ejects the blood into the arterial system and is quantified by ventriculo-arterial coupling (VAC) parameters. This process is optimized without excessive changes in LV pressure, and the mechanical energy of LV ejection is completely transferred from the ventricle to the arterial system [9].

VAC can be defined as the ratio of the arterial elastance (Ea) to the ventricular elastance (Ees). This ratio was first proposed by Suga and Sagawa [10] as a method to evaluate the mechanical efficiency of the cardiovascular system and the interaction between cardiac performance and vascular function. The Ea/Ees ratio has been consistently demonstrated to be a reliable and effective measure of cardiovascular performance [11]. The balance between myocardial oxygen consumption and the mechanical energy required to perform this work appears to be optimal when the heart and the peripheral vascular system are coupled (ie, the Ea/Es is near unity). In this case, the LV provides an adequate stroke volume with the lowest possible energetic consumption [12]. Thus, VAC is an effective index of the mechanical performance of the LV and the dynamic modulation of the cardiovascular system.

Hypothesis and Study Aims

The relevance of VAC as a parameter of hemodynamic optimization could be related to the fact that VAC is a parameter of cardiovascular efficiency whereas the classical hemodynamic parameters are exclusively parameters of cardiovascular efficacy.

With these concepts in mind, the main scientific questions and hypotheses of this project are:

1. What is the impact of HD on ventricular function?
2. What is the impact of HD on ventricular and arterial elastance?
3. What is the prognostic value of intradialytic VAC changes?

Accordingly, we sought to study patients with ESRD to assess (1) VAC parameters before and after the HD session, and (2) the value of VAC parameters in predicting adverse outcomes.

Methods

Trial Design

This research is designed as an observational cohort study with a prospective approach. Participants will be enrolled and monitored over a period of time to assess how hemodynamic changes induced by HD influence future outcomes. As an observational study, the researchers will not intervene but will simply collect and analyze data as events occur naturally during the study period.

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Study Settings

The following study centers were used:

1. BBNura Center of Efferent Therapy and HD: the HD service has been operating in Astana since 1988. Four HD centers are working around the clock to provide emergency care to patients requiring renal replacement therapy.
2. Nazarbayev University is ranked in the top 30% of international research universities in the Times Higher Education World University Rankings 2024. The Doctor of Medicine program received full international accreditation from the Eurasian Centre for Accreditation and Quality Assurance in Higher Education and Health Care, recognized by the World Federation for Medical Education.
3. Heart Center-University Medical Center opened its doors on October 12, 2011. Today, it is the leading heart surgery clinic in Central Asia, offering tertiary medical and quality services.

Recruitment

Patients with ESRD undergoing permanent HD in a specialized center in Astana, Kazakhstan, will be recruited (Textbox 1).

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Adults aged 18 years or older.
- Standard renal replacement schedule with 3 dialysis sessions per week.
- Dialysis vintage of at least 3 months.
- Dialysis adequacy with single-pool Kt/V >1.2 as recommended by international guidelines for thrice weekly HD.

Exclusion criteria

- Previous kidney transplantation.
- Myocardial infarction, unstable angina, or stroke during the previous 6 months.
- Severe stage III to IV congestive heart failure according to the New York Heart Association classification.
- Chronic atrial fibrillation or other known arrhythmia.
- History of nonadherence to the prescribed weekly dialysis schedule in the previous month.
- BMI >40 kg/m^2.
- History of malignancy or other clinical conditions associated with very poor prognosis.
- The main reasons for these criteria were to avoid confounding factors that may affect the hemodynamic parameters and to exclude patients with unstable conditions.

Expected Outcomes

Patients will be followed up for 18 months. Clinical variables and intradialytic changes in VAC parameters will be related to outcome events. The primary endpoint will be a composite of all causes of death, nonfatal myocardial infarction, and hospitalization due to worsening heart failure. Based on previous studies, we expect a mortality rate of around 10% per year [13], an incidence of acute myocardial infarction of 3.9 per 1000 patients per year [14], and an incidence of hospitalization due to worsening heart failure of 5.8 per 100 persons per year [15].

Participant Timeline

The schedule of the study project including enrolment and assessment is outlined in Table 1.

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Table 1. Schedule of the study project from 2024 to 2026.

Events	January	February	March	April	May	June	July	August	September	October	November	December
2024												
IREC[a] approval							✔					
Hiring research assistants								✔				
Logistic set-up (workstation, software, training with Medis imaging bioengineering)									✔	✔	✔	✔
Checklist (VAC[b])									✔	✔	✔	✔
Manuscript preparation (review)								✔	✔	✔	✔	✔
2025												
Patient recruitment, informed consent, and data collection from eligible participants	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Data analysis (VAC)				✔	✔	✔	✔	✔	✔	✔	✔	✔
1-year follow-up			✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Manuscript preparation: (VAC)							✔	✔	✔	✔	✔	✔
2026												
Final data collection	✔	✔	✔									
Data analysis (outcomes)	✔	✔	✔	✔	✔	✔						
Manuscript preparation: (outcomes)							✔	✔	✔	✔	✔	✔

[a]IREC: Institutional Research Ethics Committee.

[b]VAC: ventriculo-arterial coupling.

Sample Size

The sample size was calculated based on 95% CI, margin of error 5%, and estimated incidence of cardiovascular events 30%, as follows:

where N is the sample size, is a critical value from the standard normal distribution corresponding to the desired 95% CI (1.96), *P* is the proportion of estimated incidence (0.3), and E is the desired margin of error (0.05) [16].

Feasibility of Recruitment of the Sample Size

Patients on HD are often fragile and may not accept to undergo an additional investigation, although noninvasive. We will try to limit the number of noncompliant patients with several actions (Textbox 2).

Textbox 2. Action plan to reduce the number of uncompliant patients.

- Involvement of the referring nephrologist in the explanation of the study.
- Clear explanation to the patient on the nature of a transthoracic echocardiogram (Multimedia Appendix 1).
- Patients are coming 3 times per week; thus, we will give them the freedom to choose any appropriate day for the study.
- We will provide a summary of the echocardiographic study to the dialysis center to be shared with the patients.

Data Collection Methods

Demographic characteristics, full medical history, and dialysis-related parameters of study participants will be recorded on purpose-built data-collecting sheets (Multimedia Appendix 2). The study design diagram of the chronological sequence of the echocardiographic evaluations is presented in Figure 1. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trial) reporting guidelines [17] have been used (Multimedia Appendix 3). Concomitant care and interventions during the HD session will be left to the attending nephrologist.

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Figure 1. Time sequence of the echocardiography evaluation. HD: hemodialysis.

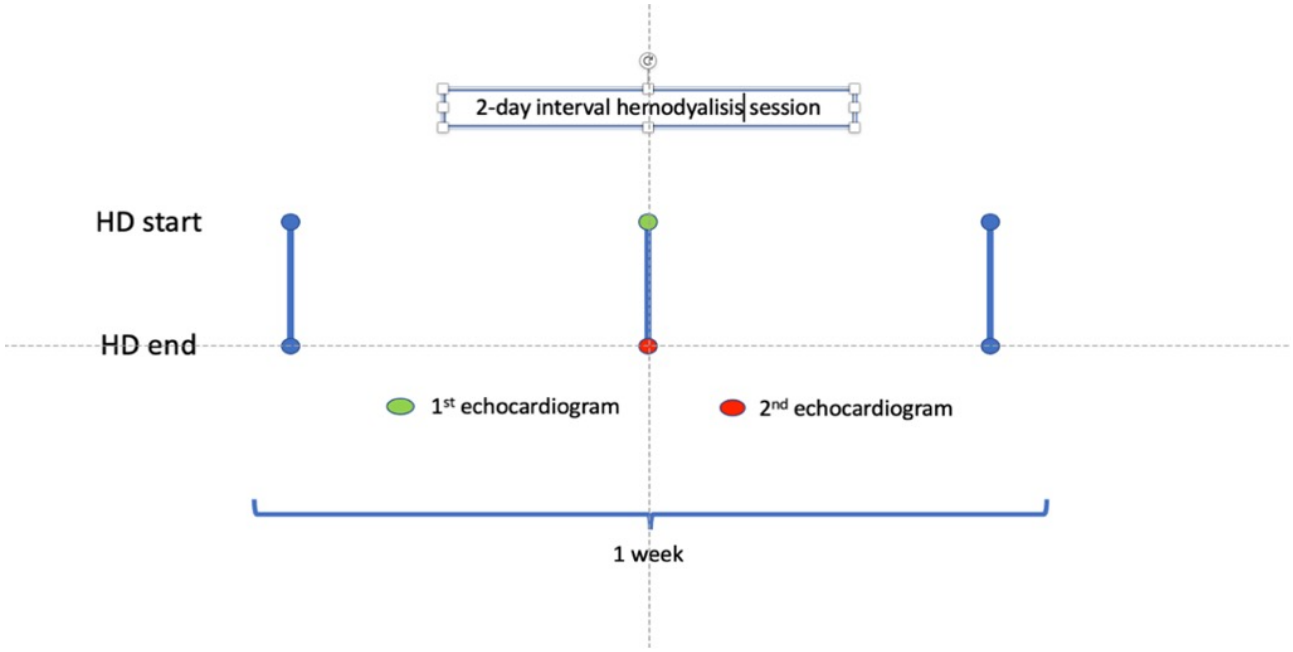

Echocardiography

2D and Doppler echocardiogram will be acquired by a skilled sonographer before and immediately after the HD session. Care will be taken in acquiring 2D apical views (4-chamber, 2-chamber, and long-axis views) aiming for the best visualization of the LV endocardial border. Images will be saved on digital media storage devices and analyzed offline at the echocardiographic core laboratory of our institution.

Echocardiographic images will be analyzed offline using dedicated software based on a mathematical model [18] (QStrain, Medis BV). The LV end-diastolic and end-systolic volumes and ejection fraction will be determined from the modified biplane Simpson method. Left atrial volume will be calculated using the biplane area-length method. LV volume and mass and left atrial volume will be subsequently indexed by body surface area. The peak early filling (E wave), the late diastolic (A wave) velocities, and the deceleration time will be assessed from the transmitral flow. The peak systolic (s'), early diastolic (e'), and late diastolic (a') mitral annular velocities will be measured at the septal annulus using spectral Doppler.

LV volumes, estimated end-diastolic pressure, and brachial systolic and diastolic pressures will be used as input. The software reconstructs the pressure-volume (P-V) loop by determining the end-systolic pressure-volume relationship (ESPVR) and end-diastolic pressure-volume relationship (EDPVR) using the single-beat algorithms previously described in the literature [19]. Once the EDPVR and ESPVR are identified, the end-diastolic and end-systolic LV volumes and systolic and diastolic brachial pressures will be used to close the P-V loop. Finally, the P-V relation will be depicted for the entire cardiac cycle where each point of the curve is described as (Vt, Pt). In the P-V loop, the classic phases of the cardiac cycle are displayed: isovolumetric contraction, ejection, isovolumetric relaxation, and diastolic filling (Figure 2).

Based on this integrated P-V loop, the hemodynamic parameters to be calculated, both before and after the HD session, are listed in Textbox 3.

The pre- and posthemodialysis changes will be calculated and considered as potential prognostic indicators.

Figure 2. (A) Schematic representation of a pressure-volume loop. (B) Example of pressure-volume loop loop derived from echocardiographic images in one representative subject. Ea: arterial elastance; EDPVR: end-diastolic pressure-volume relation; EDV: end-diastolic volume; Ees: left ventricular systolic elastance; ESPVR: end-systolic pressure-volume relation; ESV: end-systolic volume; PE: potential energy; PVA: pressure-volume area; SW: stroke work.

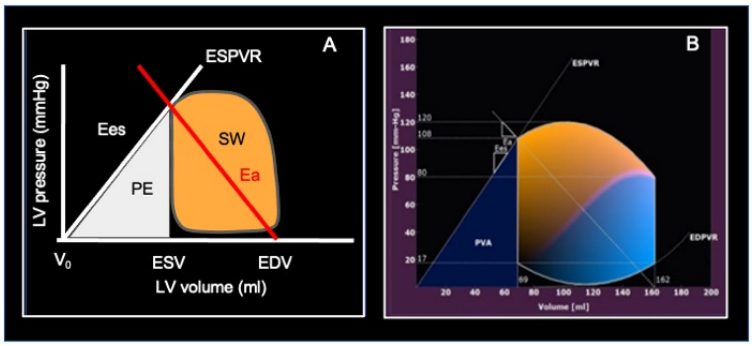

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Textbox 3. Parameters derived from the pressure-volume loop and collected for analysis.

- Left ventricular systolic elastance: reflecting ventricular contractility and represented by the slope of the end-systolic pressure/volume (P-V) relation.
- Arterial elastance: reflecting the effective arterial afterload and represented by the slope of the line connecting the end-diastolic volume on the volume axis to the end-systolic P-V point on the P-V loop.
- Ventricular-arterial coupling: calculated as the ratio between arterial elastance and left ventricular systolic elastance.
- Stroke work (SW): the external work performed by the myocardium to eject blood, computed as the area enclosed by the P-V loop.
- Potential energy: ventricular energy dissipated during isovolumetric contraction.
- Pressure-volume area: the total mechanical energy generated by the contraction of the left ventricle, equal to the sum of potential energy and SW.
- Work efficiency: the efficiency of the mechanical energy transfer from the ventricle to the arterial tree, expressed as the ratio between SW and pressure-volume area.

Data Management

This research involves a medical record review, image acquisition and analysis, and data analysis. Each participant will be assigned an ID number and all hard copy data collected or used during this study will be stored in a cabinet in the locked office of the study personnel. All electronic data will be stored on password-protected computers of the study personnel in their locked offices and the locked personnel building. Only essential research personnel will have access to any of these patient files.

Statistical Analyses

Statistical analysis will be performed with Statistical Package Stata (StataCorp) and R-studio (Posit). All continuous variables will be presented as mean (SD) or median (IQR) based on their distribution. Paired comparisons of continuous variables will be performed with a 2-tailed paired Student *t* test or Wilcoxon test, when appropriate. Paired comparisons of categorical variables will be conducted with the McNemar test. Event-free survival for each of the echocardiographic and VAC parameters will be assessed using Kaplan-Meier analysis and compared with a log-rank test, where each index will be dichotomized according to the median of its distribution. The prognostic value will be determined using the Cox proportional hazards model. Differences will be considered statistically significant when $P<.05$. Interclass correlation coefficients (ICC) will be calculated to assess the inter- and intraobserver agreement of P-V loop measurements.

Ethical Considerations

The study was approved by the Nazarbayev University Institutional Research Ethics Committee in July 2024 (Multimedia Appendix 4), and secured funding in August 2024, after a peer-reviewed process (Multimedia Appendix 5).

One of the physicians at the dialysis center will explain the aim of the study and the echocardiographic procedure. Written informed consent will be obtained from all participants before the procedure (Multimedia Appendix 6).

Participation in the study is on a voluntary basis, thus no compensation will be offered to patients.

Important protocol modifications during the study will be submitted to the Institutional Research Ethics Committee of Nazarbayev University for approval.

Results

Overview

At least 323 patients are required to estimate the incidence of cardiovascular events with 95% CI and a 5% margin of error. Data collection is scheduled to occur between January 1, 2025, and June 30, 2025. As of March 18, 2025, a total of 32 participants have been recruited, who underwent echocardiogram before and after the HD session. Data analysis is planned to start in April 2025 and continue through June 2026, with certain data being collected concurrently during the analysis phase. The publication of study outcomes is tentatively projected in Winter 2027.

Our Experience

Our group has an established experience in advanced echocardiography and image postprocessing. We have applied strain and hemodynamic forces analysis in athletes and patients with hypertension [20]. Our group has already applied this method, including VAC analysis, in a preliminary group of patients with ESRD on maintenance HD. Two illustrative cases are represented in Figure 3.

Patient #1 had 3.5 liters of fluid subtraction during the HD session with VAC improvement due to an increase in Ees (from 1.8 to 2.9 mm Hg/mL). The contractile reserve was not recruitable due to reduced preload (reduced stroke volume) and the patient had sinus tachycardia at the end of the HD session due to adrenergic activation. Patient #2 had 1.8 L of fluid subtraction, with poor tolerance and symptoms at the end of the HD session. The analysis of echocardiographic images revealed VAC worsening due to Ees decrease (from 2.6 to 1.2 mm Hg/mL). In this case, contractility is strongly dependent on preload, thus the LV did not tolerate the effective circulating volume reduction.

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Figure 3. Illustrative cases of 2 patients (Pt #1 at the top, Pt #2 at the bottom) with VAC analysis before and post dialysis.

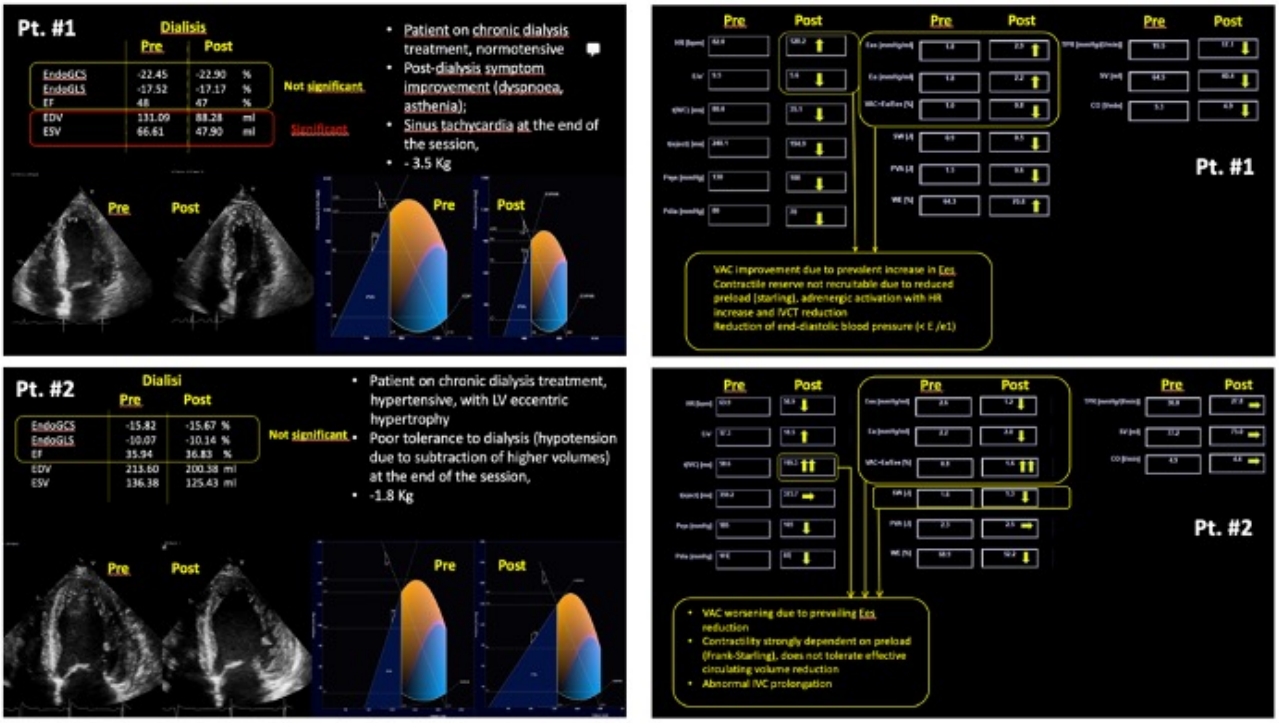

Discussion

Principal Findings

Data on the value of VAC in patients on HD are scanty and controversial. Moreover, no research on this topic has been conducted in the Republic of Kazakhstan. The results of this study will provide insights into the hemodynamic changes induced by HD in patients with ESRD and will improve the understanding of the pathophysiological events induced by acute volume depletion. The prognostic value of HD-induced VAC changes will be also assessed at follow-up.

Comparison to Previous Work

The association between myocardial and arterial function markers has been used to describe and quantify VAC in hypertension [21-23], diabetes [24], and inflammatory diseases [25]. More specifically, combined ventricular and arterial stiffening has been demonstrated in patients with heart failure with preserved ejection fraction (HFpEF) [26]. In patients with heart failure, abnormal VAC is implicated in the pathophysiology of left and right heart clinical deterioration [27]. In addition, different patterns of abnormal VAC are recognized in heart failure with reduced ejection fraction versus HFpEF. The results of these studies suggest that in hypertension and diabetes, there is a close link between arterial stiffness and myocardial deformation, which appears to be a harbinger of HFpEF if left untreated. In addition, there is evidence that treatment options may improve both myocardial dysfunction and vascular stiffness and thus improve VAC. Systemic inflammatory processes and oxidative stress may cause an increase in arterial stiffness (leading to an increase in Ea) in parallel to myocardial stiffening (causing an increase in Ees), while anti-inflammatory treatment improves arterial stiffness in parallel with myocardial stiffness contributing to the reversal of ventricular-arterial decoupling.

VAC assessment has prognostic value in several clinical scenarios. Valvulo-arterial impedance can specifically describe the hemodynamic consequences of aortic stenosis and provide prognostic information in patients with aortic stenosis even when asymptomatic [28]. There is also evidence that VAC is associated with outcomes in patients with sepsis or after myocardial infarction [29,30].

In patients with renal dysfunction, increased arterial stiffness coupled with a matched increase in ventricular stiffness has been reported [31,32]. These findings have important hemodynamic consequences as a stiff heart-arterial system generates more systolic pressure changes for a given stroke volume.

Sasso et al [33] evaluated 15 patients on HD. They concluded that HD influences both Ees and Ea/Ees ratio acutely, although this effect seems due only to the acute reduction in preload and blood pressure, without any clinically significant effect on intrinsic LV contractility and VAC. In a study on 234 HD patients, Obokata et al [34] found that Ea/Ees ratio was independently associated with adverse outcomes, providing an incremental prognostic value over the clinical score and left ventricular ejection fraction. Recently, Zuo et al [35] used an approach similar to ours (pre- and posthemodialysis assessment of VAC). They concluded that VAC is a reliable index for stratifying the risk of cardiovascular diseases in HD patients.

Strengths and Limitations

The approach we are planning to use in this study allows a noninvasive assessment of the cardiovascular efficiency and the changes induced by volume changes during HD in patients with ESRD. The endocardial borders, evaluated by

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echocardiographic speckle tracking, can be used directly as input to the present model to provide a noninvasive assessment of VAC. Using standard echocardiographic images and advanced image analysis, we will be able to evaluate the heart-arterial system interaction from the VAC. We believe that, using this approach, a comprehensive analysis of the hemodynamic effects of volume changes induced by HD will be feasible. This will allow a better understanding of the pathophysiological changes induced by HD, with the potential of tailoring the optimal dialysis modalities and identifying those patients who are at higher risk of LV remodeling and future cardiovascular events.

Some challenges of this approach can be anticipated. First, echocardiographic image quality may affect proper visualization and tracking of the LV endocardial border. Second, a low frame rate can hamper the temporal resolution of the method. Finally, inter- and intraobserver reliability should be high to exclude changes due to variability.

Future Directions

Further research should investigate whether modifying VAC through targeted interventions could improve clinical outcomes in HD patients. Expanding the study to larger, multicenter cohorts would enhance the generalizability of our findings. In addition, incorporating advanced imaging techniques to assess VAC dynamically over time may provide deeper insights into its prognostic role in patients undergoing chronic HD.

Dissemination Plan

The final results will be presented at the main international nephrology and cardiology meetings and conferences. The development and findings of the project will be reported in relevant international journals.

Conclusions

In conclusion, this research protocol outlines the process of noninvasive assessment of VAC before and after a HD session in patients with ESRD. The methodology we are applying does not require complex and sophisticated tools apart from the analysis software. We believe this approach will provide additional information to the relevant stakeholders and assist other researchers in developing similar studies in different clinical settings.

Acknowledgments

We acknowledge the contribution of Aidana Mustafa, MD, and Aigerim Yermekbay, MD, during the start-up of this research project. The technical expertise of Gulzhanat Aitkulova, MD, in acquiring the echocardiographic images is highly appreciated.

This work is supported by the Ministry of Sciences and Higher Education of the Republic of Kazakhstan (grant number AP23490021). This funding source had no role in the design of this study and will not have any role during its execution, analyses, interpretation of the data, or decision to submit results.

Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization: AS and AG
Data curation: BT and MM
Formal analysis: ZK, DJ, MM, GP, and GT
Funding acquisition: AS
Investigation: ZK, AG, and AK
Methodology: AZ, MK, and MB
Project administration: AS and MB
Resources: AS, AG, and MB
Supervision: AS and GT
Visualization: AZ, DJ, and GP
Writing—original draft: AK, AZ, ZK, and DG
Writing—review and editing: AS, BT, DG and GT

Conflicts of Interest

GP is a scientific advisor for Medis BV.

Multimedia Appendix 1
Explanation of the echocardiographic exam in three languages (Kazakh, Russian and English). This will help patients to understand the nature of the procedure.
[PDF File (Adobe PDF File), 172 KB - resprot_v14i1e71948_app1.pdf]

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Multimedia Appendix 2
Case report form used in the study.
[DOCX File , 560 KB - resprot_v14i1e71948_app2.docx]

Multimedia Appendix 3
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trial) checklist.
[DOCX File , 228 KB - resprot_v14i1e71948_app3.docx]

Multimedia Appendix 4
Approval of the study from the Nazarbayev University Institutional Research Ethics Committee (IREC).
[PDF File (Adobe PDF File), 183 KB - resprot_v14i1e71948_app4.pdf]

Multimedia Appendix 5
Peer review report from the Ministry of Sciences and Higher Education of the Republic of Kazakhstan.
[PDF File (Adobe PDF File), 506 KB - resprot_v14i1e71948_app5.pdf]

Multimedia Appendix 6
Informed consent.
[DOCX File , 33 KB - resprot_v14i1e71948_app6.docx]

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Abbreviations

Ea: arterial elastance
EDPVR: end-diastolic pressure-volume relationship
Ees: ventricular elastance
ESPVR: end-systolic pressure-volume relationship
ESRD: end-stage renal disease
HD: hemodialysis
HFpEF: heart failure with preserved ejection fraction
ICC: Interclass correlation coefficients
LV: left ventricle
P-V: pressure-volume
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trial
VAC: ventriculo-arterial coupling

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Protocol

Validation and Comparison of Pediatric Appendicitis Scores and Management Strategies (Project SPASMS): Protocol for a Prospective Multicenter Observational Study

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Abstract

Background: Abdominal pain is a common reason for children to attend the Emergency Department (ED) with acute appendicitis being the most common surgical cause. Various clinical prediction scores (CPSs) have been developed to assist in determining

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the risk of appendicitis; however, CPSs have been inadequately validated in children and haphazardly adopted in Australia and New Zealand (ANZ) EDs.

Objective: This study aims to compare and validate various CPSs for diagnosing pediatric appendicitis in children presenting to ANZ EDs.

Methods: This prospective multicenter observational study across 10 ANZ EDs is recruiting children 5-17 years presenting to participating EDs with acute right-sided or generalized abdominal pain lasting ≤7 days and clinician suspicion of appendicitis. CPSs will be calculated by the study team from clinician-recorded data and clinician gestalt recorded on a visual analog scale. Accuracy of CPSs will be assessed by the area under the receiver operating characteristic curve and proportions correctly identified as either low-risk or high-risk based on the CPSs published cutoffs. The final diagnosis of appendicitis will be confirmed on histopathology, and the absence of appendicitis confirmed by telephone, email, or a combination of both to follow up for those discharged directly from ED.

Results: This study received funding in July 2023 and started enrolment in August 2023. As of October 2024, we have enrolled and completed follow-up on 1227 participants with an expected end date in mid-2025.

Conclusions: This study aims to determine the best-performing CPS for diagnosing pediatric appendicitis in ANZ EDs. Implementation of this CPS in ANZ EDs has the potential to reduce health care costs, rationalize the use of health care resources, and improve the management and outcomes of childhood appendicitis.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12622001293752; https://tinyurl.com/242wwenx

International Registered Report Identifier (IRRID): DERR1-10.2196/67941

(JMIR Res Protoc 2025;14:e67941) doi:10.2196/67941

KEYWORDS

pediatric; emergency medicine; clinical prediction scores; appendicitis; abdominal pain

Introduction

Background

Abdominal pain is a common reason for children to attend the emergency department (ED), with acute appendicitis being the most frequent cause requiring surgical intervention [1]. Many clinical prediction scores (CPSs) [2-31] have been developed and ED clinicians are encouraged to use CPSs to assist with determining the risk of appendicitis [32]. Most CPSs involve calculating a score based on combinations of clinical features and laboratory findings to classify patients into low-, intermediate-, or high-risk. The most frequently used CPSs in children are the Alvarado score [2], the Pediatric Appendicitis Score (PAS) [3], and the pediatric appendicitis risk calculator (pARC) [4], with each based on different sets of collected variables.

The Alvarado score is one of the most widely studied CPSs for the diagnosis of acute appendicitis in adult populations based on 8 variables with a total score of 10 [2], and it has since been studied in pediatric populations with varying results [33-44]. The PAS was developed specifically with slightly different variables for diagnosing appendicitis in children [3] and has been validated in multiple studies in various settings [42-54]. However, both the Alvarado score and PAS have been found to have limited clinical utility due to a large proportion of the scores falling into the intermediate risk group and failing to consider variability in clinical presentation based on factors such as age, sex, and duration of pain. This led to the development of the pARC score, which uses a multivariable prediction model that includes variables such as age, sex, and duration of pain to quantify the risk of appendicitis on a continuous scale [4], with promising results noted on various validation studies since its development [36,43,44,55-57]. However, few have compared multiple CPSs for pediatric appendicitis, and most existing studies are limited by the number of CPSs included [36,40,58], validated only in retrospective cohorts [59], did not include more recent CPSs such as the pARC score [40,59,60], and did not compare CPSs to clinician gestalt. Moreover, most of these studies were performed overseas with limited validation in children in Australia and New Zealand (ANZ) EDs [61]. This can result in inconsistent practice and an increasing number of children exposed to potentially unnecessary imaging and laboratory investigations.

Objectives

The primary aim of the study is to externally validate various published CPSs for the risk of appendicitis in children aged 5 to <18 years presenting to ANZ EDs with acute abdominal pain and suspicion of appendicitis.

The secondary aims of the study are as follows:

1. To evaluate and compare the performance of various published CPSs:

(A) against clinician gestalt in ANZ for the likelihood of appendicitis at the time of ED assessment;

(B) in identifying, prospectively, the likelihood of complex appendicitis (defined as the presence of perforation, extraluminal fecalith, diffuse intraperitoneal pus, or a well-formed abscess) [62];

2. To describe the epidemiology and management of pediatric appendicitis, illustrating:

(A) The burden of disease in patients presenting with acute abdominal pain with the suspicion of appendicitis;

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(B) The incidence and type of surgical procedures undertaken in the management of appendicitis in ANZ (laparoscopic appendectomy, open appendectomy, nonsurgical management with intravenous antibiotics, and delayed appendectomy);

(C) The imaging procedures undertaken in patients assessed for possible appendicitis, and their accuracy in the detection of histologically confirmed appendicitis or surgically confirmed appendicitis in cases where histopathological findings are unavailable.

This will improve the accuracy of diagnosis, reduce health care costs, rationalize the use of health care resources, and improve the management of childhood appendicitis. It will also provide a description of the current diagnostic and management approaches in ANZ for pediatric abdominal pain and appendicitis.

Methods

Overview

The study is an endorsed Paediatric Research in Emergency Departments International Collaborative (PREDICT) network [63] study with Perth Children's Hospital (PCH) as the lead site. The study is a quantitative multicenter observational study that measures the performance accuracy of CPSs in identifying surgically or histologically confirmed appendicitis. Eligible CPSs (Multimedia Appendix 1) were identified in a rapid review by the study authors before study commencement [43]. Any CPS developed in either pediatric or adult populations was eligible except for: CPSs aiming only to differentiate simple from complex appendicitis or performed only for a subset of children (eg, preschool children and children with chronic illnesses); CPSs requiring variables unlikely to be routinely collected in a pediatric population identified a priori through consensus agreement by study authors (eg, rectal examination, biomarkers other than full blood picture, or C-reactive protein); and CPSs that included radiological parameters.

Study Setting and Population

Overview

The study population will be all children presenting to participating ANZ EDs with abdominal pain. Study sites all have EDs that manage pediatric patients and have a pediatric on-site general surgical service with the capacity to provide input, admission, and surgical intervention if needed.

1. Perth Children's Hospital (Western Australia, Australia)
2. Children's Hospital Westmead (New South Wales, Australia)
3. Gold Coast University Hospital (Queensland, Australia)
4. Monash Health (Victoria, Australia)
5. Queensland Children's Hospital (Queensland, Australia)
6. Royal Children's Hospital (Victoria, Australia)
7. Royal Hobart Hospital (Tasmania, Australia)
8. Sunshine Coast University Hospital (Queensland, Australia)
9. Sunshine Hospital (Victoria, Australia)
10. Starship Hospital (Auckland, New Zealand)

Participant Inclusion Criteria

To be eligible to participate in the study, a participant must meet the following criteria:

1. Age 5 to <18 years,
2. Presentation with generalized or right-sided abdominal pain,
3. Duration of pain for ≤7 days (ie, ≤168 h),
4. Clinician's concern for the possible diagnosis of appendicitis as defined by any one of the following:
5. Investigations performed (blood sample, imaging, or both, including external investigations before ED attendance),
6. Surgical consultation to assess the patient for possible appendicitis,
7. Senior ED clinician consultation to assess the patient for possible appendicitis,
8. Period of observation in ED to reassess patient for possible appendicitis.

For those hospitals with mixed ED and limited pediatric surgical capacity to operate on children under a certain age, the site-specific "pediatric" age range will be applied (eg, >10 years and <16 years). The age range of 5 to < 18 years was chosen due to the rarity and the atypical presentation of appendicitis in younger children [64], and many CPSs required variables on history or examination that might be difficult to determine accurately in younger children. Acute abdominal pain was defined as the duration of pain for ≤7 days in keeping with a previous study looking at abdominal pain and appendicitis [65], and a previous feasibility study found several patients with pain lasting for more than 5 days diagnosed with appendicitis [43].

Participant Exclusion Criteria

The following conditions exclude participation in the study:

1. Abdominal trauma that required medical review within the preceding 7 days,
2. Previous significant abdominal surgery (eg, appendectomy, short gut, ileostomy, and Hirschsprung disease),
3. Chronic illnesses that may affect the abdomen (including inflammatory bowel disease, chronic pancreatitis, cystic fibrosis, and sickle cell anemia),
4. Pregnancy,
5. Inability to obtain accurate history (eg, parent or guardian unavailable, language other than English and where no interpreter was available, or patients who are nonverbal due to pre-existing medical condition).

Outcome Measures

Overview

The primary outcome is the presence of appendicitis; this will be confirmed through the histopathology report when available, or the operation report if not available. Patients diagnosed with appendicitis but managed nonoperatively will be followed up to confirm the presence of appendicitis in cases where interval appendectomy was performed or excluded from analysis in cases treated conservatively with antibiotics only. A nonappendicitis diagnosis will be confirmed on follow-up via either recording of the primary diagnosis on hospital discharge if admitted to hospital, or contact at 30-60 days to ensure no progression in symptoms or representation to hospital for those

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discharged directly from the ED. The area under the receiver operating characteristic (ROC) curve (AUC) will be calculated for the various published CPS for the primary outcome of appendicitis.

Secondary outcomes include rates of uncomplicated and complicated appendicitis (defined as the presence of perforation, extraluminal fecalith, diffuse intraperitoneal pus, or a well-formed abscess) [62], negative appendectomy cases (based on histopathological findings), and missed appendicitis cases. These will be confirmed through the histopathology report when available, and the operation report if not available. To identify missed appendicitis cases, families of children who did not undergo appendectomy and were discharged directly from the ED will be contacted within 30-60 days of hospital discharge to assess for postdischarge status and whether their child had an appendectomy in the interim. For families unable to be contacted, medical records will be reviewed at 60 days to assess for representation. Other secondary outcome measures include length of hospitalization, rates of investigations, and rates of interventions.

Patient Recruitment and Data Collection

All suitable patients with abdominal pain will be identified on ED presentation and approached by a research nurse (if available) or the treating clinician for consent for (1) study participation, data access, and collection and (2) follow-up contact. Patients who are not captured on the index visit (ie, “missed” recruitment) will be identified by the research team through a review of the daily ED attendance record using the terms “abdominal pain,” “appendix” or “appendicitis” on triage text or discharge diagnosis text “appendicitis” or “abdominal pain.”

Basic demographic data of missed patients (including any interventions performed and management) will be recorded on a separate datasheet and collected at the earliest possible time. Missed cases, if assessed by the research team to be eligible, will have a retrospective case report form completed by the treating clinician, if possible, and the family will be contacted via phone or text message to obtain informed verbal consent for inclusion retrospectively for (1) study participation and data access and collection and (2) follow-up contact. Follow-up will not be conducted for patients who are admitted to the hospital under an inpatient medical or surgical team or those who experience severe morbidity, such as a new diagnosis of chronic illness or permanent disability, or are deceased. Participants who decline consent for data access and collection will be excluded from the study.

The treating clinician will complete, at the time of the ED visit, or retrospectively if missed initially, a case report form recording:

- demographic data (sex and age),
- eligibility (inclusion and exclusion criteria),
- caregiver verbal consent,
- the clinician's seniority and their perceived likelihood of appendicitis on a Visual Analog Scale from 0 being “Extremely unlikely” to 10 being “Extremely likely” and whether this perceived likelihood was formed before or after investigations (bloods, imaging, or both),
- history of the presenting complaint (location of initial pain, duration of pain, highest pain score, highest reported temperature during this illness, right lower quadrant (RLQ) or right iliac fossa (RIF) pain on arrival to ED, pain migration to RLQ or RIF, progression of pain, gradual onset of pain, pain pattern, history of pain with walking, anorexia, nausea, vomiting, difficulty with micturition, pothole tenderness, family history of appendicitis, respiratory tract infection in last 2 weeks, and bowel habit), and
- examination findings (RLQ tenderness, RIF tenderness, tenderness worst in RLQ, tenderness outside RLQ, presence of hop, cough, or percussion tenderness, degree of rebound tenderness, abdominal guarding, Rovsing sign, nature of bowel sounds, palpable abdominal mass, and abdominal rigidity).

Clinician management will proceed independently of study participation.

All data collected at sites will be transcribed to a REDCap (Research Electronic Data Capture; Vanderbilt University) database [66]. The following additional data will be collected from the patient's medical records: blood test results (white cell count, absolute neutrophil count, neutrophilia, and C-reactive protein), urinalysis (presence of leukocytes or nitrites), which will then allow the various CPSs to be automatically calculated in REDCap.

Between 30-60 days after the ED visit, the site research team will collect the following parameters in all eligible patients through a medical record review:

- detailed demographics (postcode, Medicare status, race or nationality, and referral source),
- prehospital management,
- management and imaging were undertaken both pre-ED in the community and the study hospital,
- time-related data (times of triage, clinician evaluation, ED, and hospital discharge),
- duration of ED and hospital stay,
- admission status and specialty unit consultations, including intensive care admission,
- medication use in ED, including antibiotics and analgesia,
- related surgical and nonsurgical interventions,
- other significant pathology or adverse events, including mortality, and
- disposition.

Follow-Up

All eligible patients will be contacted for a follow-up survey except when (1) the parent or guardian declined follow-up on the initial presentation, (2) the participants were admitted under an inpatient medical or surgical team with no further representations to ED within the follow-up period of 30 days, or (3) participant identified by the site research team to have experienced clinically significant adverse events. Any approved parental contact will occur via a telephone call, email, or text, with scripts for each contact method provided to participating sites. Follow-up emails will be automatically generated and sent

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out twice during the follow-up period with identifiable data accessible only to the local study site and the central coordinating study team, and will be removed from the REDCap database at 61 days postenrollment date by the local study research team. A maximum of 3 contact attempts will be made. If more than 60 days have elapsed from the time of presentation, or if there have been three failed contact attempts, the patient follow-up will be regarded as unsuccessful. The medical record for patients unable to be contacted will be reviewed and if sufficient information is documented in the medical record, this information may be used to substitute for the failed contact.

The follow-up survey will determine the following:

- if the child had any problems with abdominal pain since being discharged from the ED,
- if the child missed any childcare or school because of abdominal pain,
- if the carers took any time off work because of the child's ongoing pain, and
- if the child has been seen by another doctor, health professional, or hospital since the visit to the ED.

It will also collect the following details: details of ongoing problems; the number of missed days of school or childcare; the number of days off work; types and numbers of medical reviews; additional medical diagnoses; need for and duration of ED stay and hospital admissions including investigations (with a review of the relevant medical record); and related surgical interventions. Any eligible participants whose parent or guardian consented for data access and collection but declined follow-up will have their data collected and analyzed, but will not be contacted for follow-up. If participants withdraw consent and discontinue participation in the study at any time, there will be no effect on their medical care or access to treatment. If a participant withdraws before completing the study follow-up period, any known reason for withdrawal will be documented in the database. All information already collected as part of the study will be retained for analysis, but no further efforts will be made to follow up or obtain additional information regarding the participant. As an observational study, there are no anticipated adverse events related to the research. During the follow-up contacts, if any medical issues are identified by research staff, they will be referred to the managing clinicians (for patients in hospital), or the site investigator (for questions during follow-up), who will refer, if required, the patient to their general practitioner or ED for review.

To minimize information bias, the calculation of the CPSs will be performed by the research team and not by the treating clinician. If the study participant is transferred from a nonstudy site to a study site, the data collection form will be completed by the initial treating physician at the study site; if the study participant is transferred from a study site to a second study site, this will ideally be completed by the initial treating physician at the first study site.

Sample Size and Power Calculation

Based on a feasibility study performed at PCH ED before the multicenter study [43], we estimate a true appendicitis rate of 30% in the multicenter study, and that all the CPSs will be calculable in at least half of the patient cohort. We aim to have a sample size of 2400 children with undifferentiated abdominal pain enrolled, which will result in all CPSs being calculable in a minimum of 360 enrolled cases of true appendicitis. This will provide a level of precision such that a 95% CI around the AUC will range from 0.016 for an AUC estimate of 0.95-0.032 for an AUC point estimate of 0.75 [67]. It will also provide more than 85% power for a 2-sided test, with α=.05, to find a difference of .05 between 2 AUCs if both values are ≥0.80, assuming the correlation of risk scores amongst appendicitis cases and that amongst noncases have an average of at least 0.5 [68]. Under this same assumption, if both AUC values are ≥0.9, the planned sample numbers would provide more than 90% power to detect a difference of 0.04.

Statistics and Interim Analysis

We will follow Standards for the Reporting of Diagnostic accuracy studies (STARD) 2015 guidelines for statistics [69] and the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [70], and validation of CPSs will be performed and reported in according to the 2014 updated methodologic standards for interpreting clinical decision rules in emergency medicine [71]. The AUC will be calculated for the various published CPSs and the clinician's gestalt for the outcome of appendicitis. The sensitivity, specificity, negative predictive value, positive predictive value, negative likelihood ratio, positive likelihood ratio, and missed appendicitis rate will be calculated based on the published cutoffs for each score [2-31]. For the pARC, subanalysis will be performed for the following pARC categories based on previous validation studies [4,56]: ≤5%, 6%-15%, 16%-25%, 26%-50%, 51%-75%, 76%-90%, and >90% for pediatric EDs and <5%, 5%-14%,15%-24%, 25%-49%, 50%-74%, 75%-84%, and ≥85% for mixed ED. For clinician's gestalt, subanalysis will be performed for each point on the Visual Analog Scale. The AUC will also be calculated for complex appendicitis to assess the optimal cutoffs for each CPS to detect complex appendicitis.

The best-performing CPS will be identified by the highest AUC. Sensitivity and positive predictive value will be calculated to establish the CPS's ability to identify high-risk patients, and the misclassification rate (proportion of patients identified as low-risk who had acute appendicitis) and negative likelihood ratio will be calculated to establish the CPS's ability to identify low-risk patients. Accuracy will be reported as the proportion of patients not misclassified as either low-risk or high-risk as defined by published cutoffs. Baseline analyses of patient characteristics based on the risk groups as calculated by the best-performing CPS will be conducted by presenting simple counts and percentages with interquartile ranges.

Ethical Considerations

The study received ethics approval from the Child and Adolescent Health Service Human Research Ethics Committee (RGS5295) for Australian sites and from the Northern A Health and Disability Ethics Committee for the New Zealand site (2024 FULL 19738). It was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12622001293752) on October 6, 2022. Each participating site obtained site governance approval as per their

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ethics and governance committees. Informed consent will be obtained for all patients, with a waiver of consent for patients after 3 unsuccessful attempts to contact the parent or guardian for retrospective consent. Files containing private or confidential data will be stored only in secured locations accessible only by appropriate designated members of the research team, with all data de-identified before data entry onto the REDCap database. There is no compensation provided to participants.

Results

The study recruitment process and timeline are shown in Figure 1.

This study received funding in July 2023 and started enrolment in August 2023. At the time of protocol manuscript submission in October 2024, we have enrolled and completed follow-up on 1227 participants with recruitment and data collection expected to be completed by mid-2025. Data analysis is expected to be completed by late 2025, and the expected results to be published in early 2026.

Figure 1. Study process and timeline. CRF: case report form. *Dependent on consent and need for follow up. **Contact for retrospective consent can be performed concurrently with follow up in 30-60 days.

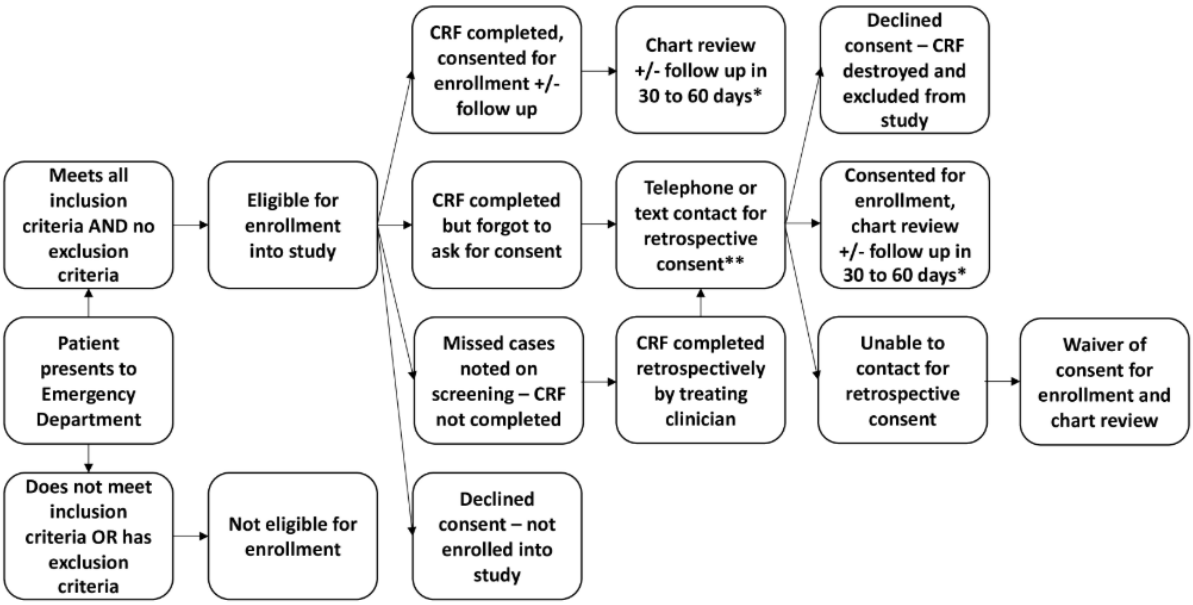

Discussion

Principal Findings

The pARC score was the best-performing CPS in the feasibility study through more accurate risk identification and stratification [43], and we hypothesize the pARC score will likewise have higher diagnostic accuracy in our multicenter study compared to other published CPSs.

Comparison With Previous Work

The inclusion of 30 CPSs and the prospective nature of the study, with a planned study size of 2400 patients would make it one of the largest prospective validation studies in children, comparing the largest number of CPSs compared with previous studies [36,39,40,43,44,59,60]. A total of 10 EDs across ANZ will contribute data, including a mix of community and tertiary pediatric centers, which will allow the study's findings to be broadly generalizable across ANZ EDs compared to previous ANZ studies in single centers [6,43,44].

Strengths and Limitations

Our study will allow the simultaneous comparative application and validation of 30 CPSs for diagnosing pediatric appendicitis outside their derivation settings. In addition to a high recruitment rate, the study will depend on high follow-up rates to ensure that our results accurately represent the whole population of children presenting to the ED with suspected appendicitis, as all patients lost to follow-up will be excluded from data analysis for CPS calculation. Ideally, all patients with abdominal pain would undergo investigations or appendectomy to determine the presence or absence of appendicitis; however, this would increase the rate of unnecessary investigations and potentially the rate of negative appendectomies should investigations be inconclusive. Therefore, a similar methodology to a previous PREDICT study looking at clinical decision rules for head injuries [72] was adapted using follow-up telephone or email contact to establish the presence or absence of appendicitis after discharge from the ED. It is also possible some patients with appendicitis would be treated conservatively with antibiotics and excluded from the study; however, this would represent a small number of patients as this is an uncommon practice in ANZ with only one patient in the feasibility study treated conservatively after a radiological diagnosis of appendicitis due to parental preference [43].

The predictor variables for the 30 CPSs were derived solely from original publications [2-31] and amalgamated into a single case report form developed by the study authors, which may introduce an element of interpretation in terms of the exact

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clinical terminology used in ANZ ED settings. The difficulty and variability of prospective clinician data collection in busy EDs in completing the case report form may result in a significant proportion of patients with multiple missing variables to calculate all CPSs; however, the feasibility study demonstrated the viability of the case report form used with all study CPSs being calculable in the majority of the patient cohort (ranging from 52% to 93.3%) based on constituent variables available [43]. Implementation of an appropriate method, such as multiple imputation, will be considered to minimize potential biases that may arise from missing data in the multicenter study [73].

Rates of computerized tomography imaging in ANZ EDs are lower than in the United States [74] due to concerns about radiation exposure and associated lifetime risk of malignancy and the more prevalent use of ultrasound in pediatric abdominal pain in Australian EDs [1]. The validation of CPSs in a different setting from those in which most of the CPSs are derived may be a potential key strength of the study and allow study findings to be generalizable across ANZ EDs and similar settings. Finally, one key strength of our study is its assessment of the accuracy of clinician gestalt in diagnosing pediatric appendicitis and comparison with to the best performing CPS, which may provide more compelling evidence to support and encourage the use of CPSs among clinicians for guiding clinical management of suspected appendicitis as part of an ED clinical pathway [75].

Conclusion

The study findings and subsequent implementation of CPSs in ANZ EDs have the potential to reduce health care costs, rationalize the use of health care resources, and improve management and outcomes of childhood appendicitis. Implementation of the pARC score in the clinical management pathway for suspected appendicitis at PCH ED has recently been established following the results of the feasibility study, and a postimplementation study is planned to be performed in the future to assess for improvement in patient outcomes through impact analysis testing.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

WHL, SO, EJM, SSC, SRD, NP, and MLB performed conceptualization and methodology. WHL, NP, and MLB acquired funding. WHL wrote the original draft. WHL, SO, EJM, SSC, SRD, NP, FEB, SD, SG, SJ, DT, VT, and MLB performed writing – review and editing. WHL, SO, EJM, SSC, SRD, NP, FEB, SD, SG, SJ, DT, VT, and MLB gave final approval of the version to be published.

Conflicts of Interest

None declared

Multimedia Appendix 1
Clinical prediction scores and variables were collected.
[DOCX File , 28 KB - resprot_v14i1e67941_app1.docx]

Multimedia Appendix 2
Peer review report by the Emergency Medicine Foundation (EMF) Queensland Research Program (Australia).

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[PDF File (Adobe PDF File), 103 KB - resprot_v14i1e67941_app2.pdf]

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Abbreviations

ANZ: Australia and New Zealand
AUC: area under the receiver operating characteristic curve
CPS: clinical prediction scores
ED: emergency department
pARC: pediatric appendicitis risk calculator
PAS: Pediatric Appendicitis Score
PCH: Perth Children's Hospital
PREDICT: Paediatric Research in Emergency Departments International Collaborative
REDCap: Research Electronic Data Capture database
RIF: right iliac fossa
RLQ: right lower quadrant
ROC: receiver operating characteristic
STARD: Standards for the Reporting of Diagnostic accuracy studies
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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Protocol

Pilot Implementation of HIV Self-Testing Delivery in Private Pharmacies Combined With a Respondent-Driven Sampling Method to Improve HIV Testing for Men Who Have Sex With Men and Transgender Women in Phnom Penh (ANRS 0100s): Protocol for a Prospective Mixed Method Feasibility Study

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Abstract

Background: Regular testing is recognized as a key strategy for HIV control. The 2023 Integrated Biological and Behavioral Survey (IBBS) in Cambodia revealed that nearly one-third of men who have sex with men (MSM) and one-fourth of transgender women (TGW) were never tested for HIV or not for more than 12 months. The majority of MSM and TGW were tested at community-based organizations (CBOs) facilities and by CBO outreach workers, while private facilities are poorly used for HIV testing (6% for MSM and 9% for TGW). Private pharmacies could be able to deliver HIV self-testing kits giving the advantage of confidentiality, anonymity, and time savings, in particular for those reluctant to visit CBOs. The recruitment of participants using a respondent-driven sampling method could provide the opportunity to reach MSM and TGW outside the network of CBOs.

Objective: This pilot study aims to evaluate the feasibility of free HIV self-testing delivery by a private pharmacy combined with a respondent-driven sampling method to improve HIV testing among MSM and TGW in Phnom Penh, Cambodia.

Methods: Both qualitative and quantitative approaches are used in this prospective feasibility study. The protocol was approved by the National Ethics Committee for Health Research in Cambodia (N0 351 NECHR). MSM and TGW aged more than 18 years old will be recruited via a respondent-driven sampling method with seeds recruited at hot spots and on social networks. The seeds will then distribute electronic and paper coupons to their networks physically and via social media, messaging, and calling applications. Each recruited peer will bring the coupon to receive direct and free access to one HIV self-testing kit at partner pharmacies as well as 10 additional coupons to recruit members of their networks. As for quantitative analysis, data from the study website will be imported, appended into a single matrix using Stata version 18SE (StataCorp), and analyzed using descriptive statistics, with a statistical significance level of .05. After 6 months, a qualitative assessment will be conducted among users, providers, and policymakers or key stakeholders to evaluate the acceptability and appropriateness of the strategy and to identify

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the barriers, facilitators, and recommendations. All transcripts will be analyzed according to the 6-phase reflexive thematic approach by Braun and Clarke. The results will be reported by participant-based and provider-based issues. QSR NVivo V.14 for Windows will be used to manage the data.

Results: The study was funded by Agence nationale de recherches sur le sida, les hépatites, et les maladies infectieuses émergentes (ANRS) in September 2023. Approval of the study protocol was successfully obtained from the NECHR in Cambodia and the Commission Nationale de l'Informatique et des Libertés (CNIL) in France (Autorisation Tacite) in February 2025. Data collection will be conducted between September 2024 and December 2025. The initial results are expected to be published in February 2026.

Conclusions: This public-private partnership intervention could allow the hidden population of MSM and TGW in Phnom Penh to be reached and tested.

Trial Registration: ClinicalTrials.gov NCT05745168; https://clinicaltrials.gov/study/NCT05745168

International Registered Report Identifier (IRRID): PRR1-10.2196/65351

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KEYWORDS

feasibility study; HIV self-test; MSM; TGW; respondent-driven sampling; private pharmacies; Cambodia; transgender women

Introduction

Background

Regular testing is acknowledged as a critical approach in HIV management. Knowing one's HIV-positive status leads to a decrease in high-risk sexual behaviors, prompt connection to health care services, early commencement of antiretroviral therapy (ART), and a significant decrease in the likelihood of transmitting HIV to sexual partners. Over the last 10 years, HIV testing services have considerably expanded [1].

The sharp rise in the number of new HIV infections among men who have sex with men (MSM) has continued in Asia, and sexual activity between men remains stigmatized and frequently hidden. HIV prevalence among MSM was 5% or higher in 10 of the 24 countries that reported these statistics to the Joint United Nations Programme on HIV/AIDS in 2019 [2]. Approximately 30% of all new infections in Asia are in MSM, and HIV incidence is high among young (15-24 years old) MSM [2]. In Southeast Asia, HIV prevalence and incidence continue to be elevated, especially among younger MSM [3]. For instance, a recent publication reported an HIV incidence of 7.4 per 100 person-years in Bangkok in this population [4]. Consensus was that reduction in HIV prevalence and incidence has not been observed among transgender women (TGW) in the region [3,5]. The implementation of preventive ART and HIV preexposure prophylaxis (PrEP) should have led to a reduction. Nonetheless, HIV prevalence and incidence remain high, with no indications of a downturn among young MSM and TGW in Southeast Asia [6]. Given the current rate of new HIV infections among MSM and TGW, the region is unlikely to achieve the target of eradicating AIDS by 2030.

A number of studies have been reported regarding HIV surveillance, HIV and sexually transmitted infection prevalences, population size estimations, and behavior patterns for either TGW or transgender men in the Asia Pacific region. The data show disturbing HIV infection rates throughout the region: Delhi: 49%; Mumbai: 42%; Phnom Penh: 37%; Jakarta: 34%; Surabaya: 25%; Bandung: 14%; Chiang Mai: 18%; Phuket: 12%; Bangkok: 11%; and Lahore: 0.5% [7].

Late diagnosis is a serious barrier to tackling HIV. Approximately 69% of people living with HIV in the Asia and Pacific region were aware of their status in 2018, up from 58% in 2015. However, this means approximately 1.9 million people did not know they were HIV positive. Progress on testing varies greatly between countries. In Thailand, 94% of people living with HIV were aware of their status in 2018, as were 86% of people living with HIV in Malaysia and 82% of people living with HIV in Cambodia. Stigma, discrimination, and punitive legal environments prevent many people from key populations from accessing testing services [8]. Indeed, in Malaysia and Sri Lanka, the rates of HIV testing and awareness among MSM are 43.3% and 40.3%, respectively, while the rates of HIV testing and awareness for TGW people are 43% and 36.9%, respectively [9].

Although Cambodia admirably achieved the 90-90-90 targets by 2020, there is still cause for concern regarding the HIV epidemic among key populations and unidentified priority populations. Compared with data from the 2019 Integrated Biological and Behavioral Survey (IBBS) survey, the 2023 IBBS key population data show an increase in HIV prevalence, from 4% to 5.5% among MSM and from 9.6% to 13.5% among TGW [10,11]. Despite these high prevalence rates, the uptake of HIV testing among MSM (<50%) and TGW (39%) remains low. Moreover, consistent condom use for anal sex with noncommercial sexual partners is suboptimal, at 69% for MSM and 38% for TGW [12]. Although PrEP has been found to protect against HIV infection in high-risk populations, the country struggled to reach the target PrEP enrollment rate (10,000 users by 2023) among MSM and TGW [13]. The 2023 IBBS report highlighted that nearly one-half of MSM and one-fourth of TGW did not report any HIV testing or not for more than 12 months. This suggests that undiagnosed HIV infections may persist in hard-to-reach MSM and TGW and new modalities of HIV testing approaches are hence needed to improve the uptake of HIV testing among these key populations. In addition, of those who reported HIV testing, the majority of MSM and TGW were tested at community-based organization (CBO) facilities (70.1% for MSM and 74.1% for TGW) and by

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CBO outreach workers (9% for MSM and 6% for TGW), while private facilities are poorly used for HIV [14].

From the perspective of the general population as well as some users from "hidden" or "marginalized" groups such as MSM and TGW, HIV self-test results should be interpreted in a private setting to ensure complete anonymity. HIV self-testing is a process in which a person performs an HIV rapid diagnostic test and interprets the result in private. Lay users can perform HIV self-testing reliably and accurately, achieving a performance comparable with that of trained medical professionals [15]. HIV self-testing has the potential to increase the number of people living with HIV who have access to testing, know their status, are diagnosed, and initiate treatment. HIV self-testing shares many characteristics with current HIV testing and counseling approaches, including products, accuracy issues, linkage to care, potential benefits and risks, and regulatory policies and frameworks [16]. Of some key populations, HIV self-testing increased testing frequency among high-risk MSM and could increase HIV diagnoses in the trans community [17,18]. In 2016, the World Health Organization (WHO) recommended HIV self-testing as a safe, accurate, and effective way to reach people who may not test otherwise, including people from key populations, men, and young people [15]. Representatives from 13 countries across Asia and the Pacific gathered to develop road maps to implement HIV self-testing in the region [19].

In 2017, Cambodia developed national consolidated guidelines on HIV testing services in which many approaches including HIV self-testing are recommended to increase HIV testing uptake, especially among hard-to-reach and key populations [20]. Recent evaluation of the Boosted-Integrated Active Case Management in Cambodia revealed that 66.5% who received assisted HIV self-testing wanted to confirm their HIV status [21]. Even though MSM and TGW had not heard about HIV self-testing, all of them expressed a willingness to try it [22].

Although HIV self-test kits are distributed primarily from public health facilities, HIV self-tests are also available through private ways and channels. Some studies, including the one conducted in Cambodia by Pal et al [22], suggest that MSM and TGW wish or prefer HIV self-tests to be available over the counter at pharmacies and other locations or through the internet [23]. HIV self-testing is already formally and informally available, and it will likely become increasingly available. Indeed, HIV self-test kits are authorized to be dispensed from pharmacies in some countries such as the United States and France [24,25]. In addition, HIV self-tests were reported informally on sale through the internet and in pharmacies in many countries—with specific reports on this from Australia, China, Namibia, Peru, South Africa, Philippines, and Malaysia [26].

Recent studies have also shown that the take-up rate for HIV testing was high, with most participants preferring oral fluid testing to finger prick testing. Many people (72%) who had never accessed HIV testing services took part in the test, with high reactivity rates [27].

Respondent-driven sampling, a form of peer referral–based sampling, has become a popular strategy to recruit "hidden" or "marginalized" populations such as MSM and TGW [28]. In Cambodia, this type of method is widely used and highly effective at reaching these populations [29,30]. To mitigate some of the challenges of implementing the methodology, such as notably slow recruitment rates, innovation around conventional respondent-driven sampling can be helpful [31]. Indeed, since there has been an increase in the use of the internet and online communities by gay and bisexual men in the last few decades to facilitate new connections for the purpose of information seeking, socializing, and seeking sex, several studies have reported innovative internet- and application-based respondent-driven sampling strategies in different aspects of HIV/AIDS research such as improving uptake of HIV self-testing among MSM; providing technical support, counseling, and referrals for further HIV testing services; and HIV prevention, care and treatment, and other services [32-37].

The main hypothesis of this study is that private pharmacies could deliver HIV self-testing kits, given the advantage of confidentiality, anonymity, and time savings, and this could be an effective intervention to improve HIV testing coverage for MSM and TGW. The second hypothesis is that a respondent-driven sampling method with a diversity of seeds recruited at hot spots and on social networks could help to identify a new network of a hidden key population.

Given the persistence of high HIV prevalence and incidence rates among MSM and TGW in southeast Asia, despite advancements in preventive treatments and PrEP, there is an urgent need to re-evaluate and innovate our strategies toward HIV testing and awareness. The complexities inherent in the sociocultural fabric of this region, alongside logistical challenges, underscore the necessity for localized, community-driven interventions that are sensitive to the unique needs and challenges faced by these key populations.

Primary Objective

The primary objective is to evaluate the feasibility of HIV self-test delivery by a private pharmacy network among MSM and TGW recruited through classic and digital respondent-driven sampling methods to improve HIV testing in Phnom Penh, Cambodia.

Secondary Objectives

The secondary objectives are to evaluate the acceptability and appropriateness of the strategy, identify barriers and facilitators, estimate the linkage to confirmatory testing for those with a reactive test and linkage to HIV care and ART for those with a positive confirmatory HIV test, estimate linkage to PrEP services for negative participants, identify the characteristics of participants and compare with those reported in IBBS 2023 for MSM and TGW in Cambodia, and evaluate the adherence of participants to 6-monthly repeated HIV testing.

Methods

Ethical Considerations

The National Ethics Committee for Health Research (NECHR) in Cambodia provided ethical approval for this ANRS-0100s study (number 351 NECHR).

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This study emphasizes voluntary patient participation, with comprehensive information provided by the research team about the study's objectives, procedures, timeline, potential risks and benefits, and any associated discomfort. Information is conveyed both orally and in written form in the Khmer language. Consent covers several key aspects, including overall participation, compensation, potential phone recontact, and participation in focus group discussions, necessitating prior informed consent before any study-related assessments. Participants also have the option to retain a copy of the consent form after signing. Additionally, the study integrates community-based workers to ensure nonstigmatizing, high-quality, and participant-tailored reception. To guarantee privacy and confidentiality, each participant is assigned a pseudonym or unique code (eg, NBZ0081@) that does not constitute personally identifiable information. Participants will receive incentives of US $2 for successfully returning their results and US $1 per recruited peer. For those participating in focus group discussions for the qualitative assessment, the study will cover transportation expenses for their time and contribution.

Study Design

A pilot study using a mixed qualitative and quantitative approach will be carried out to assess the uptake of HIV self-test delivery by a private pharmacy network among MSM and TGW recruited through a respondent-driven sampling method to improve HIV testing in Phnom Penh, Cambodia.

The participant recruitment method will use respondent-driven sampling by recruiting diverse seeds both at hot spots and on social networks.

After 6 months, a qualitative assessment of focus group discussions will be conducted among MSM, TGW, and pharmacists to evaluate the feasibility, acceptability, and appropriateness of the intervention and to identify barriers and facilitators.

Study Site

The study sites are located in Phnom Penh, specifically at 3 to 5 private pharmacies selected based on factors such as working hours, availability of dedicated space, and geographical balance. Furthermore, ART; voluntary, confidential counseling and testing; and PrEP sites in Phnom Penh will serve as the study participants' follow-up contacts after they have self-tested for HIV (Figure 1).

Figure 1. The 3 to 5 private pharmacies with their respective antiretroviral therapy (ART), voluntary HIV counseling and testing (VCCT), and preexposure prophylaxis (PrEP) sites in Phnom Penh that support the follow-up among study participants who report HIV self-test results.

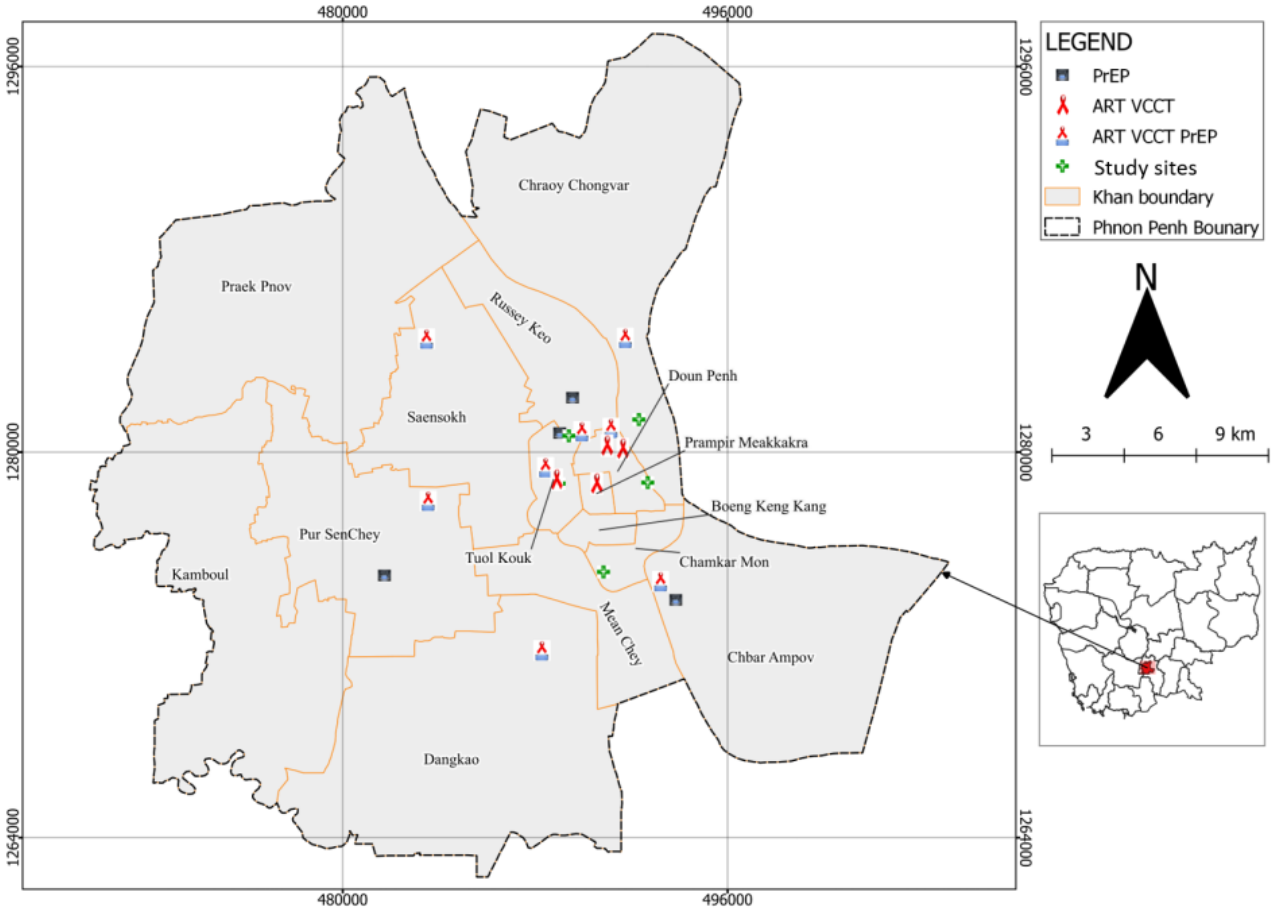

Study Population and Sample Size

MSM and TGW who are residing in Phnom Penh at the time of enrollment and meet the eligible criteria constitute the study population. The inclusion criteria are being at least18 years old (legal age in Cambodia); for MSM, to have at least one oral or anal intercourse with another man in the past 12 months; and for TGW, to be biologically male at birth, self-identify as a

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woman or third gender, and have at least one oral, anal, or vaginal intercourse with another man in the past 12 months.

We will use a pragmatic approach with the objective of recruiting the maximum numbers of MSM and TGW. According to IBBS 2019, the estimated number of MSM in Phnom Penh is 6300, and the estimated number of TGW is 1400. With 1500 participants (1000 MSM and 500 TGW), we will be able to estimate an HIV self-test uptake of 70% to within a 95% CI of +/- 2% to 2.5% (width of the confidence interval [in %]=1.96 x √(p x (1-p) / n)).

Procedures

Respondent-Driven Sampling Implementation

Implementation of respondent-driven sampling resembles snowball sampling with several critical caveats. Initial participants are purposefully recruited to be "seeds" as long as they fit the study's eligibility criteria. After completing the study procedures, seeds are offered a limited number of vouchers to recruit their peers to participate. In this study, two categories of vouchers will be used: paper and electronic vouchers. The latter was adopted for the main advantage that they could be passed electronically to the social networks of respondents regardless of geographical coverage [38]. When vouchers are redeemed, eligible participants also complete the same study procedures and are asked to recruit their peers, and this continues until recruitment goals are met. Using specially formulated statistical programs, sampling weights are developed and applied to estimate population parameters. For the purpose of respondent-driven sampling, effective seeds generate large recruitment chains and samples, which has been associated with motivation and a commitment to the research goals [27].

The study sites include 3 to 5 private pharmacy outlets in Phnom Penh with a proper dedicated room or space that secures privacy and secrecy. Pharmacists will be trained by the research teams about the study objectives, study procedures, communication with MSM and TGW, and counseling. We will recruit 15 diverse seeds both at hot spots and on social networks based on optimized criteria obtained from meeting with stakeholders and CBOs. Once consented to the study, the pharmacy provides the seed with a free HIV self-testing kit and two types of coupons (5 electronic coupons [e-coupons] and 5 paper coupons) to distribute to their networks either physically or via social media messaging, and calling applications such as Twitter, WhatsApp, and Telegram (e-coupons). Each recruited participant, so-called peers, will bring the coupon to be scanned at partner pharmacies to receive direct and free access to one HIV self-test kit. There, the pharmacist will notify a trained community worker or the research team of the participant visit; the community worker or research team member will conduct the study visit, including the informed consent process, explaining how to complete the questionnaire on the tablet (Multimedia Appendix 1), and providing the link to an external website to submit the HIV test results and obtain necessary support like tutorials and follow-up after receiving their HIV results. These recruited individuals will be considered wave 1 of recruitment and will each receive 10 additional coupons to recruit members of their networks. The next round of individuals recruited and enrolled will be considered wave 2 and so on. To return the HIV self-test results, participants, who will be provided a unique username and password, will upload a picture of the results labeled with their corresponding username to the external website that they received from the community worker or research team during their pharmacy visit. A token or incentive is granted to those who return the HIV self-test results. Each nonreactive participant will be provided another new coupon (paper or electronic format upon their preference) with a reminder to perform 6-monthly HIV tests for a period of 18 months. The study flow is represented in Figure 2.

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Figure 2. Study flow depicting participant recruitment by respondent-driven sampling, follow-up for HIV self-test results, willingness to repeat the test every 6 months, and qualitative study. ART: antiretroviral therapy; CBW: community-based workers; HIVST: HIV self-test; MSM: men who have sex with men; PrEP: preexposure prophylaxis; TGW: transgender women.

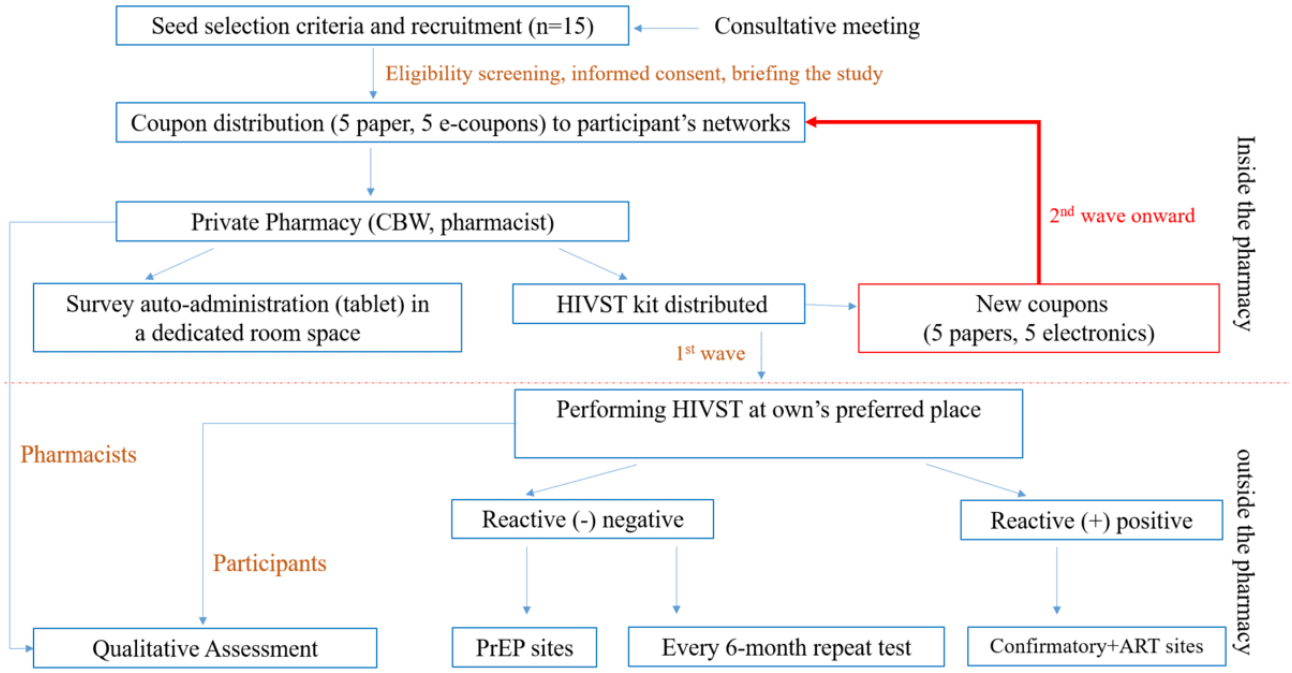

Qualitative Assessment

After 6 months, a qualitative assessment via focus group discussion (6-8 participants) among users (MSM and TGW) and providers (pharmacists) will be conducted to evaluate the feasibility, acceptability, and appropriateness of the intervention and to identify barriers and facilitators of this pilot intervention.

Participation in the focus group discussion and key informant interviews will be anonymous and voluntary. The interviews will be conducted in Khmer by trained researchers. Semistructured interview guides for focus group discussions among MSM and TGW emphasize their perception, the acceptability, and the appropriateness of their HIV self-test experience including facilitators and barriers and intention to promote and retake the HIV self-test (Multimedia Appendix 2). Focus groups will be conducted between participants and the trained research team in a dedicated room. Each focus group will be composed of 9 to 10 members for a 60-minute to 90-minute discussion that will be recorded anonymously to facilitate retranscription and translation. Records will be deleted at the end of the study.

As for the focus group with pharmacists, the guide covers the following topics: perception, acceptability and appropriateness, improvement, and willingness to sustain the strategy of HIV self-test distribution in private pharmacies (Multimedia Appendix 3). Regarding the in-depth interview with policymakers or key stakeholders involved in HIV programs, the interview guide aims to explore perceptions of the strategy, proposed improvements, and willingness to sustain and scale it (Multimedia Appendix 4).

Health Care Pathway and Support From CBOs

At every stage of study, The National Centre for HIV/AIDS Dermatology and STDs and CBOs who are closely working with MSM and TGWs will help define selected criteria, identify the seeds, localize their hot spots, and promote the study. The National Centre for HIV/AIDS Dermatology and STDs will also help review the tutorials for the HIV self-test device and the promotional messages and will organize consultative meetings with stakeholders. The CBOs, through community health workers, will coordinate the work between pharmacists and participants and counsel the participants regarding the necessary follow-up after returning the HIV self-test results.

According to the results, they will provide the participants with proposals for support for confirmatory tests, to ART clinics in case of a positive reaction, or to PrEP services in the case of a negative reaction.

Sample Collection and Tests

The HIV self-test used in the study is OraQuick, which is a private and rapid HIV test using oral fluid with safe, accurate, and quick results.

The OraQuick HIV self-test uses oral fluid to check for HIV-1 and HIV-2 antibodies. It provides results in about 20 minutes and can detect the virus in more than 99% of people who are infected with HIV. Because the test is a "screening" test, a second test to confirm the results is always advised, and participants will be referred for that purpose in case of a reactive HIV self-test.

Loss to Follow-Up

When a participant who has not explicitly withdrawn consent does not return the HIV self-test result after 1 week, the research team will reach them by phone. In addition, 1 week after

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returning positive HIV self-test results, if there is no information confirming the linkage to one of the partner ART sites or participants do not show up after receiving the reminder for a 6-month HIV self-test, the research team will reach them by phone.

A participant who does not show up for a given scheduled visit and for whom the study team fails to reach by phone will be considered lost to follow-up.

Analysis

Primary Outcome

The percentage (95% CI) of HIV self-tests delivered among the total number of coupons distributed will be determined and stratified by gender (MSM or TGW) and type of coupon (paper or electronic version).

Secondary Outcomes

In addition, the data collected from the study will enable estimation of the percentage (95% CI) of HIV self-test results recorded among the total number of HIV self-tests delivered and stratified by gender (MSM or TGW); for those contacted by phone, the percentage (95% CI) of HIV self-tests realized among the number of nonrecorded HIV test results; the percentage (95% CI) of participants with positive HIV self-tests linked to an ART site and stratified by gender (MSM or TGW); the percentage (95% CI) of participants with negative HIV self-tests linked to PrEP services and stratified by gender (MSM or TGW); the percentage (95% CI) of participants with 6-monthly repeated HIV testing during the 18 months; and the probability (95% CI) of HIV testing discontinuation as well as the median time to the occurrence of HIV testing discontinuation. The latter will be determined using Kaplan Meier analysis, to take into account censored data due to loss of follow-up.

Data from the questionnaires and HIV results will be obtained from a data server in a Microsoft Excel file and imported and appended into a single matrix using Stata version 18SE (StataCorp). We will describe the characteristics of key populations with summary statistics (proportions, 95% CIs, measures of central tendency), which will be analyzed using descriptive statistics with a significance level of .05.

The proportions of the key populations who receive the HIV self-test kit from the pharmacy and those who complete the test are key elements for informing the scaling of the intervention.

Qualitative Study

For the qualitative assessment, bilingual research staff will transcribe all interviews verbatim and translate them into English. All transcripts will be analyzed according to the 6-phase reflexive thematic approach by Braun and Clarke [39]. Two independent coders will thoroughly review the transcripts and apply open coding to generate initial codes. Subthemes will be directly identified based on transcripts rather than relying on pre-existing concepts. In axial coding, the codes will then be compared and organized into potential themes, which will then be assessed against the extracted codes and further refined until no more emergent themes are found. Any discrepancies in coding will be resolved through iterative discussions with a third research member. QSR NVivo V.14 for Windows will be used for data management.

Results

In this research project, we anticipate that the implementation of HIV self-testing through private pharmacy networks combined with a respondent-driven sampling strategy will significantly enhance HIV testing uptake among MSM and TGW in Phnom Penh, Cambodia. By providing a confidential, anonymous, and convenient testing option, we expect an increase in the number of individuals who know their HIV status, thereby facilitating early diagnosis and linkage to care. Additionally, we aim to estimate the uptake of HIV self-testing among MSM and TGW. Thanks to respondent-driven sampling and selection criteria that diversify the seeds, the study may lead us to identify new profiles or characteristics of MSM and TGW at risk of HIV acquisition compared with those described in the latest IBBS report. Furthermore, self-stigma among MSM and TGW and their willingness to repeat the HIV self-test every 6 months will be evaluated. Through focus group discussions, we will obtain insights into the perception of the appropriateness, acceptability, barriers, and facilitators of free HIV self-test distribution at private pharmacies via the respondent-driven sampling technique from both pharmacists (providers) and MSM and TGW (users). The innovative use of respondent-driven sampling is predicted to reach previously unidentified networks within key populations, potentially uncovering new cases and further broadening the impact of the intervention. Collectively, these results will constitute key elements to inform the scaling of the intervention policy in the country. Last but not least, the expected outcomes of this project are in line with the broader goals of reducing HIV transmission rates and improving health outcomes for MSM and TGW in southeast Asia, contributing to the global effort to curb the HIV/AIDS epidemic.

To date, significant progress has been made in preparation for the study's implementation. The study was funded by Agence nationale de recherches sur le sida, les hépatites, et les maladies infectieuses émergentes (ANRS; grant number: ECTZ176682) in September 2023. Approval of the study protocol was successfully obtained from the NECHR in Cambodia and the Commission Nationale de l'Informatique et des Libertés (CNIL) in France (Autorisation Tacite) in February 2025. An operation manual and respondent-driven sampling monitoring system have been designed to facilitate the implementation of the respondent-driven sampling methodology, and comprehensive preparations are underway to ensure project launch. The schedule of key activities is shown in Table 1. Data collection will be conducted between September 2024 and December 2025. The initial results are expected to be published in February 2026.

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Table 1. Timeline of key activities of the study and expected completion duration.

Activities	Estimated duration
Project launch	Month 1
Tool development	Months 1-5
Consultative meeting	Month 1
Data collection and follow-up	Months 4-21
Qualitative study	Months 9-11
Transcription and translation	Months 9-12
Data analysis and reporting	Months 13-15 (qualitative analysis) and months 16-23 (quantitative analysis)
Dissemination	Month 24

Discussion

Overview

Routine HIV testing is one of the cornerstones of efficient HIV management. This is particularly relevant in light of the persistently high HIV incidence among TGW and MSM in Asian countries, where stigma and discrimination can be significant barriers to accessing HIV services. Despite the expansion of testing coverage and the introduction of innovative strategies like PrEP, the ongoing stigmatization of sexual activity among men and the concealed nature of such interactions exacerbate the challenge of curbing new infections [6]. To reduce new infections (11,000 people living with HIV/AIDS were unaware of their status in Cambodia in 2022), screening programs must achieve the broadest possible coverage. Screening coverage remains insufficient for MSM and TGW. For example, in the Global Fund Funding Cycle 2024-2026, the target of 93,985 MSM is fair for the program's reach of 50,000 [40]. Furthermore, HIV/AIDS awareness among those aged 15 years to 24 years is critically low, at only 23% to 27%. This highlights the urgent need for expanded education and screening about HIV among young people. Therefore, maximizing testing coverage to achieve the first 95 targets as quickly as possible is the top priority. This situation underscores the necessity for new privacy-centric and stigma-reducing approaches.

This study's investigation into the deployment of HIV self-testing via private pharmacies combined with the respondent-driven sampling strategy presents a viable path to enhance testing uptake within hard-to-reach cohorts. Using private pharmacies aims to offer a discreet and accessible option for HIV testing, potentially navigating around the stigma and discrimination barriers. Furthermore, using respondent-driven sampling aims to leverage the social networks of MSM and TGW, reaching individuals less likely to use conventional health services, including those who do not self-identify as gay, thereby extending the reach to bridge populations [41,42].

This approach's success hinges on various factors, including pharmacy participation, HIV self-testing's acceptability within target groups, and respondent-driven sampling's capacity to yield representative samples. Should this model prove efficacious, its scalability could facilitate broader implementation within Cambodia and regions with similar epidemiological contexts.

In the MSM and TGW communities, community-based testing is promoted and well-accepted. Indeed, screening conducted by CBOs has proven to be the most effective method for identifying new infections within these communities [5,43]. A critical aspect of this project is assessing the acceptability of pharmacy-based testing among key populations and to understand how these communities embrace and potentially promote this testing approach.

Moreover, the study seeks to shed light on contemporary risk factors like chemsex, which is becoming increasingly relevant in discussions of HIV transmission among MSM [5]. By exploring these new dimensions, the research could contribute valuable insights into the complex interplay of social behaviors and HIV risk, further enhancing our understanding of the dynamics of the epidemic.

It will also address the potential challenges of late diagnosis and testing service underutilization by key demographics, highlighted by the disparities in HIV awareness and testing uptake across the country. The strategy aims to bridge these gaps, providing a pathway to bolster the initial stage of the HIV care continuum.

It is important to acknowledge the study's limitations, including the potential biases inherent in self-reported data and concerns regarding the findings' generalizability. Nevertheless, the outcomes of this research hold the promise of informing future public health initiatives, proposing a framework for incorporating HIV self-testing into a broader HIV prevention and care strategy focused on privacy, accessibility, and community engagement. This could notably contribute to the identification and engagement of bridge populations and the study of emerging risk factors within the context of HIV transmission.

Limitations

Our study faces specific limitations as well. The use of a respondent-driven sampling method based on paper and electronic vouchers, although innovative, might not capture the full diversity of the MSM and TGW populations, possibly resulting in skewed data. The stigma surrounding HIV and marginalized groups may also impact participation rates and individuals' willingness to disclose sensitive information.

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Excluding data from individuals who decline to participate in this study introduces a potential selection bias particularly in terms of understanding barriers to free HIV self-test distribution at private pharmacies. Moreover, distributing HIV self-test kits through private pharmacies, despite the convenience and guaranteed privacy and anonymity, might not reach individuals who are geographically, economically, or socially distanced from these facilities. Furthermore, recruitment will focus on hot spots and social networks in Phnom Penh, excluding, unfortunately, for legal reasons, younger MSM and TGW younger than 18 years. Preferences for these platforms may shift over time. Consultative meetings with CBOs and stakeholders, who are working closely with these communities, will aid in refining our outreach strategies.

These challenges call for a careful interpretation of our findings and highlight the need for additional investigation to achieve a more comprehensive understanding of HIV testing behaviors within these key populations.

Conclusion

This research project aims to address the high HIV rates among MSM and TGW in southeast Asia by introducing HIV self-testing through private pharmacies and using respondent-driven sampling to reach these marginalized groups. The feasibility of this approach would increase HIV testing uptake, detect new infections, and enhance the initial step of the HIV care cascade. Positive findings could serve as a basis for considering the expansion of this model to more pharmacies across the country, setting a precedent for future interventions and research in similar contexts.

The project also emphasizes a collaborative effort with community organizations and community workers, representing a public-private partnership to ensure a respectful, high-quality, and customized testing experience, thereby overcoming traditional barriers to HIV testing such as stigma and discrimination. The insights gained from this study are expected to contribute to the broader public health strategy against HIV/AIDS, offering evidence-based recommendations for policy and practice not only in Cambodia but potentially in other regions with analogous epidemiological and social landscapes.

Acknowledgments

This study is sponsored by Agence nationale de recherches sur le sida, les hépatites, et les maladies infectieuses émergentes (ANRS; grant number: ECTZ176682).

Data Availability

Data sharing is not applicable to this manuscript since no data sets were generated nor analyzed during the development of the study protocol described herein. Once the data collection begins, all investigators will have access to anonymized patient-level data.

Authors' Contributions

CD conceived and coordinated the study with the supervision of BS and VS. OS contributed to protocol development. EM participated in reviewing the interview guides for the qualitative assessment and coordinating their implementation. JLwas involved in sample size estimation and refining the respondent-driven sampling method. All authors participated in the writing and reading of the manuscript and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Questionnaire for pilot implementation of Hiv self-testing delivery in private pharmacies combined to a respondent driven sampling method to improve Hiv testing for men who have sex with men (MSM) and transgender women (TGW) in Phnom Penh.
[PDF File (Adobe PDF File), 346 KB - resprot_v14i1e65351_app1.pdf]

Multimedia Appendix 2
Topic guide for focus group among men who have sex with men and transgender women.
[PDF File (Adobe PDF File), 225 KB - resprot_v14i1e65351_app2.pdf]

Multimedia Appendix 3
Topic guide for group discussion with pharmacists.
[PDF File (Adobe PDF File), 206 KB - resprot_v14i1e65351_app3.pdf]

Multimedia Appendix 4

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Interview guide for key informants.
[PDF File (Adobe PDF File), 210 KB - resprot_v14i1e65351_app4.pdf]

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Abbreviations

ANRS: Agence nationale de recherches sur le sida, les hépatites, et les maladies infectieuses émergentes
ART: antiretroviral therapy
CBO: community-based organization
CNIL: Commission Nationale de l'Informatique et des Libertés
IBBS: Integrated Biological and Behavioral Survey
MSM: men who have sex with men
NECHR: National Ethics Committee for Health Research
PrEP: preexposure prophylaxis
TGW: transgender women
WHO: World Health Organization

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Protocol

Maintaining Resilience and Well-Being in the Era of Climate Change: Protocol of an Acceptability and Feasibility Pilot of the Bee Well Program for Treating Eco-Anxiety in Rural Children Exposed to Natural Hazards

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Abstract

Background: The effects of climate change on mental health are becoming widely recognized. Mental health can be impacted through direct and indirect exposure to natural hazards, as well as through the overarching awareness of climate change and the resultant environmental decline—the latter is termed eco-anxiety. Exposure to natural hazards also increases eco-anxiety, further compounding mental health impacts. Young people are especially vulnerable to the mental health impacts of climate change and have higher rates of eco-anxiety than other age groups. Those in rural areas are also more likely to be impacted by natural hazards, further underscoring the need to support this population. To date, there remains scant evidence regarding how to support young people with eco-anxiety, and few interventions, especially for children, have been evaluated. There is a need for further research to inform treatment for young people for climate change–related distress.

Objective: This study pilots a novel group-based mental health and resilience intervention in relation to eco-anxiety. Specifically, this project aims to explore the acceptability, feasibility, and clinical utility of a group-based eco-anxiety intervention.

Methods: The project is an exploratory pilot assessing the acceptability, feasibility, and clinical utility of a group-based intervention using a pre-post design with a single group. A minimum sample of 12 children aged 10-14 years located in a rural area and with exposure to at least one natural hazard will be enrolled in this study. In order to assess clinical utility, changes from preintervention to postintervention in distress, resilience, and climate emotions will be assessed. To do so, children will complete measures of psychological distress (subjective units of distress, Depression Anxiety Stress Scale-21–youth version), climate emotions, and resilience (Resilience Scale for Children-10) before and after the intervention. Acceptability will be assessed post intervention through a series of Likert scale and open-ended questions. Feasibility will be assessed through enrollment and the proportion of participants completing the full intervention. Eligible children will take part in a novel 5-module group-based intervention designed to build resilience, promote nature connectedness, build social support, and foster meaning-focused coping.

Results: This study has received ethics board approval by the University of New England's Human Research Ethics Committee (HE23-080). This study will be conducted from late 2024 to 2025. As of March 2025, 28 children have been enrolled in the study.

Conclusions: Rural children and young people are an especially vulnerable population for the mental health impacts of climate change. To date, the evidence base for interventions for treating eco-anxiety remains sparse, especially for young people and children who typically have higher rates of eco-anxiety than older age groups. This study will provide preliminary evidence of a group-based treatment for children and adolescents experiencing eco-anxiety that can inform practitioners.

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Trial Registration: Australia and New Zealand Clinical Trials Registry ACTRN12624001287527; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=388545

International Registered Report Identifier (IRRID): PRR1-10.2196/69005

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KEYWORDS

climate change anxiety; coping; climate emotions; eco-distress; eco-grief; treatment; youth; adolescents; young people; rural mental health

Introduction

Climate Change and Mental Health

Climate change is an ecological crisis that poses a significant threat to human health [1]. It has been widely reported that climate change can negatively impact mental health [2,3], both through direct and indirect exposure to natural hazards, as well as through the overarching awareness of climate change and the associated environmental decline, known as eco-anxiety [4]. The detrimental impacts of exposure to natural hazards such as bushfires and drought on mental health and well-being have been widely reported and can be enduring [5-7]. An emerging body of research has also routinely highlighted the deleterious impact of eco-anxiety on a range of mental health outcomes [8,9]. As climate change continues to accelerate the intensity, frequency, and severity of climate-related natural hazards [10], there is an increased likelihood of exposure and repeated exposures to these events. Direct exposure to natural hazards also increases climate change distress and concern [11], compounding exposure-related distress and leaving exposed individuals especially vulnerable to poor mental health outcomes.

Climate Change and Young People

Although much of the existing literature has explored the mental health outcomes of adults, children and young people are considered to be a priority at-risk group in relation to climate change [12,13]. Children are likely to be the most affected by climate change [14,15] and from early and developmentally significant life stages [16] while having contributed minimally to the climate crisis. Young people around the world report high levels of climate change concern [17], with higher levels of eco-anxiety observed in young people than in older age groups [18-21]. These high rates of eco-anxiety are also related to distress and poor mental health in children [22,23].

Young people are also especially vulnerable to direct and indirect exposure to natural hazards [24], in part due to exposure to parental stress [25,26] and erosion of normal support systems [27] at an age where coping skills are still emerging [28]. Recent evidence highlights high levels of depression, stress, anxiety, substance misuse, adjustment disorder symptoms, and low resilience in young people following the Black Summer 2019-2020 bushfires in Australia, especially for those who were directly exposed [11]. Children and young people residing in rural areas are further at increased susceptibility to poor mental health in relation to climate change due to (1) already higher rates of psychological distress compared with their metropolitan counterparts [29], (2) more likely exposure to adverse climate change–related hazard events, and (3) limited mental health service access in rural areas [30]. Despite the body of evidence pointing to the impacts of climate change on mental health, evidence to guide practice remains scant, with few interventions for eco-anxiety currently evaluated [3,31].

Climate Change and Resilience

Psychological resilience is a key protective factor for mental health and is understood as a process of adaptation to a stressor [32]. It has been argued that building resilience may be a key way to protect against impacts of climate change on mental health [33-35]. Climate change resilience—the ability to prepare for, adapt, and respond to climate-related hazards such as extreme weather events [36]—has most commonly focused on physical resilience, with less emphasis to date on how to build or foster psychological climate-resilience (ie, the ability to psychologically adapt to climate-related stressors).

Although psychological resilience has been widely studied, how to best build resilience and how resilience intersects with broader social factors and challenges such as climate change remains less well established [32]. Concomitantly, research examining how to build psychological climate-resilience remains in the nascent stages. This study thus crucially builds the literature base around developing psychological climate resilience in children in order to protect mental health.

Interventions

To date, evidence for interventions to support climate change–related distress remain scant, and interventions proposed to date lack empirical assessment. Suggestions from the limited literature point to fostering hope and optimism [37] and empowering young people to feel a sense of efficacy to support coping—such as through taking climate action—as potentially beneficial [22,24]. Meaning-focused coping in relation to climate change has been shown to predict better mental health outcomes in young Swedes [38], suggesting the potential value of fostering this specific coping style. However, allowing children to explore and express negative emotional states is also critical [39]. Additionally, the use of ecotherapy, enhancing connection with nature [31,40], and mindfulness, alongside psychoeducation [33] have also been proposed. Group-based approaches may also be well placed to treat eco-anxiety, allowing for social support [31]. Given that the mental health care sector will struggle to cope with the impacts of climate change [33,41,42], group-based approaches may also be more feasible as a treatment modality. However, little is known regarding the effectiveness of any eco-anxiety–informed interventions, with minimal evaluation of any interventions currently undertaken [31].

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Goal of This Study

This study pilots a novel group-based mental health and resilience intervention in relation to eco-anxiety for rurally located children who have been impacted by natural hazards. Specifically, the objective of this project is to explore the acceptability, feasibility, and clinical utility of a group-based eco-anxiety intervention.

Methods

Design

This project is an exploratory trial to assess the acceptability, feasibility, and clinical utility of a group-based intervention using a pre-post design with a single group (trial registration ACTRN12624001287527). This protocol is presented in line with SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) reporting guidelines [43].

Participants

Sample Size

Being an intervention pilot precludes definitive sample size calculation [44]. However, it has been argued that, for clinical intervention pilots, a minimum of 10 samples in the intervention group is required [45]. In order to allow for up to 20% attrition and ensure sufficient data for preliminary efficacy testing, a minimum sample of 12 is anticipated, which is sufficient to provide acceptability and feasibility data and preliminary data regarding clinical utility [44].

Setting

This pilot study is conducted in a rural region of northern New South Wales, Australia, with a population of approximately 80,000 people. This area is largely agricultural-dependent. The study is conducted in a community setting.

Eligibility

Inclusion Criteria

Persons aged 10-14 years, of any gender, living in a rural area (defined as areas with a Modified Monash Model 3 or higher, representing large rural towns through to remote communities) with self-reported exposure to one or more natural hazards (eg, fire, flood, tornado, drought) are included in this study. Given that the impacts of hazard exposure can be sustained well past the initial exposure [5,6], there are no time limits on exposure to the hazards. There are no restrictions on participants currently or previously having accessed other mental health interventions.

Exclusion Criteria

Persons outside of the age range, not residing in a rural area, or without exposure to a natural hazard are excluded from this study. Individuals who fail comprehension checks as ascertained by clinicians during provision of child assent or who have acute suicidal risk or a cognitive impairment/disability as reported by parents are also excluded.

Recruitment

Recruitment will occur through rural mental health and health care services, as well as through community groups and organizations and school-based well-being officers and psychologists. In particular, recruitment includes placing flyers and sharing project information with local Headspace and health centers, the University psychology clinic (which receives referrals for young people), and local youth organizations. Additionally, the project was presented to school psychologists and well-being officers to refer children to the project. Recruitment commenced in late 2024, with 28 children currently enrolled in the study.

Intervention

Development

Taking the best available evidence for treating eco-anxiety in young people and extensive consumer consultation and co-design, a group-based eco-anxiety intervention was developed. An expert and consumer advisory group consisting of a range of professionals, including teachers, psychologists, school well-being officers, environmental psychology researchers, and young end users provided co-design input into the development and refinement of the intervention manuals [46,47] and workbooks [48,49]. The Bee Well intervention has been developed both for teenagers (15-18 years) and children/adolescents (10-14 years); this protocol relates only to the child/adolescent version of the intervention.

Intervention Overview

The Bee Well intervention is informed by the resilience-building empirical evidence, alongside emerging evidence surrounding coping with climate change [37,38], which also points to the value of ecotherapy, nature connectedness, and nature immersion [40]. The intervention is designed to be run in a group setting in order to normalize climate change–related emotions and foster social support [31]. The intervention takes place predominantly outdoors to enable nature exposure and connection and consists of guided discussion and activities that focus on providing psychoeducation on emotional awareness and climate emotions, developing adaptive coping strategies for coping with climate change distress and hazards, and building resilience (see Table 1). The intervention also includes a nature restoration–based activity, occurring alongside discussions around meaning-making and coping, in order to foster efficacy and engage in shared action. Group members have their own individual workbooks and complete a range of individual and group activities, in addition to the nature restoration task. The intervention consists of 5 modules, with each module lasting approximately 60 minutes and will be co-delivered by a team of provisional and clinical psychologists with an interest in child and adolescent mental health, rural health, and/or eco-anxiety.

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Table 1. Intervention modules.

Module	Description	Purpose
Module 1: Finding Common Ground	In this module, individuals explore and share their own eco-emotions, including grief, worry, and hope, through 2 interactive group activities (exploring eco-emotions and exploring mixed feelings).	Psychoeducation regarding emotions; build emotional awareness, recognition of shared experiences, and enable group processing
Module 2: Taking Action Together	In this module, the group commences a shared nature restoration activity—flora-based or fauna-based—such as building bee hives. While engaging in the activity, the group also undertakes guided discussions regarding "taking action" and exploring their own relationships with nature.	Taking action together through engaging in nature restoration as a form of coping and building group-efficacy and a means to support meaning making and fostering peer connection
Module 3: Coping	In this module, the group is introduced to coping skills through activities and group discussions. Group members undertake a mindfulness nature meditation/journaling task as a means of connecting with nature and rewilding.	Build adaptive coping skills, including promoting nature connectedness as a means of coping, and fostering resilience
Module 4: Cultivating Resilience	In this module, the group completes the nature restoration activity. Further discussions focus on fostering resilience and developing individual coping and resilience plans.	Build sense of community, group-efficacy, and self-efficacy; build resilience
Module 5: Bringing It Together	In this module, the group reflects on the nature restoration activity and discusses how this project will restore nature into the future. This module also includes a final reflection on the learnings and outlines avenues for ongoing or future support.	Reflection on the intervention and learnings

The Bee Well intervention resources can be found in the publicly available manual and workbook [47,49]. The intervention delivery is provided by trained psychologists who are able to manage referral or escalation, as needed, should any distress arise from or during participation. Information on referral sources is also provided to parents as part of the information sheet.

Outcomes

Data will be collected before and after the intervention. The primary assessed outcomes will include changes in the psychological symptoms, resilience, and subjective ratings of distress, with secondary outcomes examining change in climate emotions, from preintervention to postintervention. Acceptability will also be assessed post intervention. Data will be collected by trained independent data collectors.

Psychological Distress

Psychological distress will be assessed using the Depression Anxiety Stress Scale (DASS)-youth version [50], which is a child and adolescent adaptation of the well-validated and widely used DASS-21 [51]. The measure consists of 21 items, with 7 items assessing each of the 3 conditions: depression, anxiety, and stress. Participants are asked to specify the frequency on a 4-point Likert scale (never to almost always), with which they have experienced symptoms. The DASS-youth version has replicated the original factor structure of the DASS-21 and has been validated for use in children aged 7-18 years [50].

Resilience

Resilience will be assessed using the Resilience Scale for Children [52]. This 10-item measure assesses individual resilience capacity in relation to 5 domains: sense of purpose and meaning, authenticity, equanimity, self-reliance, and perseverance. Respondents are asked to respond to a series of statements (eg, I think I'm okay just the way I am right now; when I get upset, I know how to calm down), indicating how well each statement described them. Items are scored on a 4-point Likert scale (1-4) from "not at all like me" to "a lot like me," with higher scores suggesting greater resilience. The Resilience Scale for Children is validated for use in children as young as 7 years [52].

Climate Change Emotions

Two items will be used to assess distress in relation to climate change. The first asks participants to respond to the question "are you worried about climate change?" on a 5-point Likert scale ranging from "not worried" to "extremely worried." The second item provides respondents with a list of 9 emotions (sad, helpless, worried, scared, hopeful, mad, hurt, powerless, and not bothered) and asks them to indicate if they feel each of these in relation to climate change (yes/no/prefer not to say). These items are adapted from Hickman et al [17]. The original items were designed for adolescents aged 16 years and older. Therefore, the wording of these items has been slightly modified to better suit the younger age range by psychologists with experience working with children and adolescents.

Subjective Units of Distress

This is a widely used short tool that asks respondent to rate how they are currently feeling. Children are presented with a feelings thermometer and asked to indicate how they are feeling from 0 to 10 (with 0 representing feeling happy/fulfilled/relaxed and 10 representing highest anxiety/distress ever felt).

Acceptability

Acceptability will be assessed through a series of 5-point Likert scale questions that are specifically designed for this intervention and based on our previous work [53]. Items such as "The workshop helped me feel better" are rated from strongly agree to strongly disagree. A series of open-ended questions regarding preferred and dispreferred components of the intervention, such as "what do you like about the workshop?" and "what did you not like?" are also asked to assess acceptability. Open-ended questions are also able to provide information on any unintended outcomes.

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Data Management

Hard copy data are collected and reviewed for any missing or inaccurate data. Data are then entered by a trained researcher. Data entry will be verified by a second researcher and all values inspected to ensure data quality. Hard copy data are securely stored in a locked filing cabinet. Unique identifier codes are stored separately to the data and accessible only to the project leads. Electronic data are securely stored on password-protected University cloud system. All data management and analyses are undertaken by the research team and are independent of the funding body. Adverse events will be identified by the research team through review of pre-post data upon collection. The research team will have access to the final deidentified dataset. Due to the small and short-term pilot nature of the study, no independent auditing systems are in place.

Planned Data Analysis

Acceptability will be determined based on the acceptability Likert scale results as well as the open-ended survey feedback. Open-ended questions will be analyzed via content analysis, and Likert scale acceptability items will be descriptively reported. Feasibility will be assessed based on the completion of the program by individual participants, that is, the ability to recruit into the study and the proportion of participants completing the full program, with feasibility determined by recruiting the minimal sample size and an 80% completion/retention rate [54,55]. Utility will be demonstrated through improvements in subjective distress, mental health symptoms, or resilience between preintervention and postintervention. A paired-sample 2-sided *t* test will be performed for the outcome measures to identify any changes in the outcomes before and after the intervention. Baseline missing data will be removed pairwise, and analyses will be performed using the last observation carried forward.

Ethical Considerations

This study has been approved by the University of New England's Human Research Ethics Committee (HE23-080). Parental consent will be provided prior to children taking part in the study. The confidentiality and the nature of the study will be explained to the participants, and their assent will also be obtained prior to the commencement of the intervention. Study data will be deidentified, with participants assigned a unique code for linking their preintervention and postintervention data. Any potentially identifiable information provided in the open-ended responses will also be removed from any published materials to ensure privacy. Parents and children will be made aware that they are able to withdraw at any time without providing a reason and without consequence, and adherence will be recorded as the number of modules completed. Protocol amendments will be reported to the ethics committee and the trial registry. Catering during the intervention modules is provided, but no other compensation is provided to the participants.

Results

Ethics approval was received in May 2023 (approval HE23-080). This study is being conducted over a 1-year period. As of March 2025, 28 children have been enrolled in the study. We expect results from this study to be published in late 2025. Results will be disseminated through conference presentations and workshops with practitioners, as well as through scientific publications.

Discussion

Overview

Intensifying climate change will exacerbate mental health symptoms and increase disorder prevalence, which will pose a significant strain for the mental health system [4]. Crucially, with escalating climate change, more individuals will be exposed to natural hazards and be more likely to face repeated exposures [10], with repeated exposure shown to further increase a range of mental health symptoms beyond single exposure alone [56]. Exposure to natural hazards also exacerbates climate change distress [11], further compounding the mental health sequalae of climate change. Accordingly, building resilience and adaptive capacity for future exposures is critical for protecting mental health. Interventions specifically addressing the mental health impacts of climate change and natural hazards are typically ad hoc and are not routinely or consistently delivered [57]. The evidence base also remains limited [31]. By building an evidence base for children, especially rural-dwelling children who are the most vulnerable to natural hazards, this study will contribute to informing mental health care by providing an evidence-informed intervention. Clinicians largely report feeling ill-equipped for treating eco-anxiety or climate-related distress in therapy [58], with practitioners in rural areas especially needing guidance on how to support mental health in relation to climate change [59]. Thus, this study will provide valuable guidance for clinicians. This brief group-based intervention to improve coping and resilience can be used to protect mental health in the future, which is critically needed to promote well-being as climate change escalates [60].

Comparison With Prior Work

This study builds off the limited research evidence to date regarding supporting children and young people experiencing eco-anxiety, especially following exposure to a natural hazard. This study extends prior work by drawing on the preliminary and available evidence to date for promoting mental health and managing climate change–related distress. For example, this study brings together previously identified or suggested components to support young people, such as fostering meaning-making coping [38] and empowering children [22] such as through encouraging them to take action [31], balanced with also providing a safe and supportive space to explore and express negative emotional states [39]. Further, this study integrates aspects of ecotherapy and fostering a relationship with nature [31,40]. Although these components have previously been suggested as means through which individuals might be supported, the evaluation of any eco-anxiety intervention or treatment component has been minimal [3,31].

Current evidence for the treatment of eco-anxiety includes a qualitative evaluation of a dream-discussion–based group-processing program conducted with 7 adult climate activists [61]. Another evaluation study surveyed past

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participants of Carbon Conversations—a climate change education program of small, facilitated groups who meet 6 times to discuss topics related to climate change and allows for the discussion of emotional responses to climate change [62]. The results of this evaluation showed that 50% of those who responded to the survey rated the program as helpful for facing their worries about climate change; however, no preassessment/postassessment was undertaken, limiting the understanding of the effectiveness of the group in reducing any distress or mental health outcomes. Participants were also adults and predominantly older than 30 years. To date, the examination of eco-anxiety following exposure to natural hazards also remains minimal, and there are no treatments evaluated for this. Therefore, this study expands upon existing work by taking the proposed treatment components from prior work and testing an intervention specifically designed for children and adolescents.

Limitations

Due to the nature of this pilot study, the sample size is small. This study is also not a randomized controlled trial, and random assignment to groups was not possible. Replication of results in randomized controlled trials with larger samples would be warranted after refinement of the intervention from the pilot. Although the current design is appropriate to gain insight into the effects of the intervention, the research would be strengthened by having longer follow-up times to better assess if the intervention effects are sustained. Outcome measures are child self-report only, and diagnostic interviews or parent reports may also be useful to incorporate into future research designs.

Conclusions

This study tests a novel group-based intervention for supporting rural children who have experienced a natural hazard in relation to eco-anxiety. The impacts of climate change on mental health are rapidly gaining attention [63], and eco-anxiety has been widely shown to be detrimental for mental health [64]. Exposure to natural hazards also amplifies climate distress [11]. Children and young people are among the most vulnerable for eco-anxiety [65,66], with those in rural areas also more prone to experiencing repeated exposures to natural hazards, making rural children and young people an especially vulnerable population. Yet, empirical studies on eco-anxiety in children remain relatively minimal, with most studies being descriptive only [22]. Although the deleterious impacts of climate change on mental health are widely recognized, mental health clinicians report feeling underprepared for dealing with climate change [58], and service delivery remains fragmented after natural hazards [57]. To date, the evidence base for interventions for treating eco-anxiety remains sparse [3,31] and even more so for young people and children. This study will provide preliminary evidence of a group-based treatment for children and adolescents experiencing eco-anxiety that can inform practitioners.

Acknowledgments

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Data Availability

Deidentified data are available from the authors upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the Peregrine Centre, Australia.
[PDF File (Adobe PDF File), 141 KB - resprot_v14i1e69005_app1.pdf]

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Abbreviations

DASS-21: Depression Anxiety Stress Scale-21 items
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Reduction of Salt and Sugar Contents in Canteen Foods and Intakes By Students and Staff at a Malaysian Higher Education Institution: Protocol for a Mixed Methods Study

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Abstract

Background: University students and staff members, especially those who frequently eat out and spend considerable time on campus, form a crucial demographic facing challenges related to high salt and sugar intake in out-of-home food. Recognizing the high prevalence of eating out among these populations, it is imperative to understand the salt and sugar consumption levels of campus communities.

Objective: This protocol describes the rationale and design of a 3-part cross-sectional and longitudinal interventional study to reduce salt and sugar contents in canteen foods and intakes among students and staff at Sunway University and Sunway College in Malaysia.

Methods: First, the knowledge, attitudes, and practices (KAPs) and perception, barriers, and enablers (PBEs) of salt and sugar intake and reduction were assessed among students and staff (part 1 of the study). Second, the KAPs and PBEs of salt, oil, and sugar reduction were assessed among canteen staff (part 2 of the study). Third, a longitudinal interventional study was conducted by implementing a campus-wide executive order to reduce salt and sugar in all foods sold on campus (part 3 of the study). The salt and sugar contents of selected foods were measured at baseline and at 3 months and 6 months postreduction. Participants who eat frequently on campus were selected as the intervention group, while those who do not comprised the control group. All participants had their urine electrolytes and body compositions measured and recorded 24-hour dietary intakes for 2 weekdays and 1 weekend at baseline, 3 months, and 6 months after salt and sugar reduction.

Results: The study protocols were approved by the institutional review board of Sunway University (SUREC 2024/029 and SUREC 2024/040). Recruitment for the cross-sectional studies began in May 2024, while that for the longitudinal intervention study began in June 2024. The 6-month intervention began in September 2024 immediately after the official launch of the campus-wide executive order to reduce salt and sugar. We targeted recruitment of 1000, 50, and 300 participants for parts 1, 2, and 3, respectively. We anticipate reduced dietary salt and sugar intakes by 30% and 50%, respectively (World Health Organization targets), and beneficial health effects on the participants.

Conclusions: The insights gained from this study will help to create a healthier food environment, benefitting individuals who regularly eat out, especially at the workplace.

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Trial Registration: ClinicalTrials.gov NCT06473038; https://clinicaltrials.gov/study/NCT06473038
International Registered Report Identifier (IRRID): DERR1-10.2196/69610

(JMIR Res Protoc 2025;14:e69610) doi:10.2196/69610

KEYWORDS
Nutritional intervention; workplace intervention; salt reduction; sugar reduction; study design

Introduction

Background

Cardiovascular disease stands as a significant global health challenge, ranking among the primary causes of premature death and disability, especially in low-income countries. The burden of cardiovascular disease persists as the primary cause of death globally, including in Malaysia [1]. In Malaysia, hypertension has consistently emerged as a leading contributor to premature mortality. The 2023 National Health and Morbidity Survey (NHMS) revealed a 29.2% prevalence of hypertension among Malaysian adults aged 18 years and older [1]. Alarmingly, although the prevalence of hypertension is associated with older age, 80% of hypertensive adults aged between 18-29 years were unaware they had the condition [1].

A direct and positive association between salt intake and blood pressure (BP) regulation has long been well-established. From the initial International Study of Salt, Potassium, and Blood Pressure involving over 10,000 participants [2] to the largest United Kingdom Biobank study involving more than 450,000 adult participants [3], a significant association between 24-hour urinary sodium excretion (as a gold standard for estimating salt intake) and BP at the individual level has been established. A systolic BP increase of 2 to 3 mmHg for each 1 g/day increment in estimated salt excretion was generally reported [3].

According to the Malaysian Community Salt Survey study, the mean intake of salt in Malaysia is 7.9 g/day [4], much higher than the recommendation by the World Health Organization (WHO) of less than 5 g/day [5]. In fact, the WHO has is targeting a reduction in population salt intake of 30% by 2025 [6]. According to the same Malaysian survey, 64.4% of participants consumed at least 1 meal out-of-home, while 20.8% of participants reported consuming all 3 meals (breakfast, lunch, and dinner) out-of-home [7]. Pertaining to the occasion of a meal consumed out-of-home, slightly more than half (55% of respondents) consumed breakfast out-of-home, followed by lunch (35.6%) and dinner (27.1%) [8]. In 2019, household spending on out-of-home foods increased to 11.2% from 8.7% in 2004 and 2005 [9].

Besides hypertension, the prevalence of other noncommunicable diseases in Malaysia is also on the rise. According to the 2023 NHMS, 15.6% of the population has diabetes, and 54.4% are either overweight or obese [1]. The 2019 NHMS revealed that over one third of Malaysian adults consume commercial, ready-to-drink beverages at least once a week [10]. This unhealthy habit is even more prevalent among adolescents and young adults. On average, these groups consume 56.9 g of sugar daily, equivalent to about 12 teaspoons, primarily from various sugar-sweetened beverages (SSBs) [10]. Almost half of this sugar intake comes from commercially packaged, ready-to-drink beverages like carbonated soft drinks (“sodas”) and sweetened Asian drinks [10]. The WHO advises that adults and children should limit their daily intake of free sugars to less than 10% of their total energy intake [11]. For an average adult, this equates to no more than 50 g, or 12 teaspoons, of free sugar per day. Further reducing free sugar intake to below 5%, or around 25 grams (6 teaspoons), per day can offer additional health benefits [11]. When considering free sugars from other sources, such as processed and homemade foods and beverages, the total free sugar intake of Malaysians who regularly consume SSBs likely exceeds WHO recommendations. Malaysia has implemented the sugar tax of 40 sen (US $0.09) per liter in July 2019, which applies to two main categories of SSBs: beverages containing more than 5 g of sugar per 100 mL and fruit- or vegetable-based drinks with over 12 g of sugar per 100 mL [12]. In 2024, the sugar tax increased by 25% or 10 sen (US $0.02) to 50 sen (US $0.11) per liter [13].

From a study conducted among Malaysian consumers and food operators, the high salt in foods consumed out-of-home was acknowledged and a comprehensive salt reduction policy involving all stakeholders is needed [14]. Consumers face limited awareness and knowledge, counterproductive practices among food operators, and challenges in accessing affordable low-salt products, while food operators encounter a lack of standardized guidelines, ineffective enforcement, and uncooperative consumer practices [14].

University students and staff members, especially those who frequently eat out and spend considerable time on campus, form a crucial demographic facing challenges related to high salt and sugar intake in out-of-home food. Recognizing the high prevalence of eating out among these populations, it is imperative to understand the salt and sugar consumption of campus communities. Furthermore, serving low-salt foods at workplaces has been shown to reduce salt intake by 1.4 g/day [15].

Therefore, this study aims to assess the effects of salt and sugar reduction in foods sold on campus at Sunway University and Sunway College, higher education institutions located near Kuala Lumpur, the capital of Malaysia. These workplaces and academic campuses serve as an out-of-home food environment where the campus community heavily depends on vendors for their meals. The insights gained will not only benefit the individuals who regularly eat out-of-home, but will also contribute to creating a healthier food landscape on university campuses, reducing BP and impacting the overall well-being of the individuals.

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Specific Objectives of the Study

The study is divided into 3 parts, each with its own specific objectives.

Part 1

Part 1 of the study will explore the knowledge, attitudes, and practices (KAPs) and perception, barriers and enablers (PBEs) of dietary salt and sugar intake among Sunway University and Sunway College community (students and staff). This part of the study has four objectives, which are as follows:

1. To assess participants' KAPs regarding salt consumption.
2. To assess participants' KAPs regarding sugar-sweetened beverage consumption and attitudes toward sugar taxation in Malaysia.
3. To assess participants' KAPs regarding diabetes mellitus.
4. To identify common PBEs in implementing salt and sugar reduction on campus.

Part 2

Part 2 of the study will explore the KAPs and PBEs of salt, oil, and sugar (SOS) reduction among campus canteen staff. This part of the study has two objectives, which are as follows:

1. To investigate campus canteen staff's KAPs regarding SOS usage and intake.
2. To identify PBEs in implementing SOS reduction in the foods sold by campus canteen staff.

Part 3

Part 3 is an interventional study on the reduction of salt and sugar in foods sold on campus. This part of the study will be divided into studies A and B, as described below.

Study A

Study A will investigate the salt and sugar contents of selected food sold on campus. This part of the study has three objectives, which are as follows:

1. To survey and compile a comprehensive list of existing foods sold at Sunway University and Sunway College.
2. To analyze the salt and sugar contents of the selected foods at baseline, 3 months, and 6 months after the campus-wide executive order to reduce salt and sugar is implemented.
3. To propose further recommendations for reducing salt and sugar content in foods sold on campus.

Study B

Study B will investigate the effects of salt and sugar reduction on the participants. This part of the study has three objectives, which are as follows:

1. To investigate dietary salt intake using dietary records and spot urine tests in a subset of participants at baseline and after a campus-wide executive order to reduce salt and sugar in all foods sold on campus is implemented.
2. To investigate the perceived intensity and pleasantness of saltiness of the participants in the intervention and control groups at baseline and after the campus-wide executive order is implemented.
3. To investigate the effect on the participants' anthropometric measurements and body composition at baseline and after the campus-wide executive order is implemented.

Methods

Study Protocol

The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist is found in Multimedia Appendix 1.The study protocol described herein was approved by the institutional review board of Sunway University, with the approval codes SUREC 2024/029 and SUREC 2024/040. The approved protocols are found in Multimedia Appendices 2 and 3, respectively. The study is funded by the Malaysia Society of Hypertension (MSH 2024/01), who has peer-reviewed the proposal and granted approval on the amended proposal (Multimedia Appendix 4). The study has been registered at ClinicalTrials.gov, with the identifier number NCT06473038. This 3-part nutritional intervention study titled "An Interventional Study of Salt and Sugar Reduction in Foods Sold on Campus at Sunway University and Sunway College" was carried out from May 2024 to April 2025. First, a cross-sectional study on the KAPs and PBEs of salt and sugar intake among Sunway University and Sunway College students and staff was assessed. Second, a cross-sectional study on the KAPs and PBEs of salt, oil, and sugar (SOS) reduction among campus canteen staff was conducted. Third, a prospective, longitudinal study involving an interventional reduction of salt and sugar in all foods sold on campus was conducted by assessing the salt and sugar contents of selected foods sold on campus before and after imposing a campus-wide executive order (the intervention) to reduce the salt and sugar in all foods. Those who eat frequently on campus (intervention group) and those who do not (control group) were recruited to participate in the interventional study. A flow chart of the study design is shown in Figure 1. This study only involved students and staff at Sunway University and Sunway College, Sunway City, Selangor, Malaysia.

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Figure 1. Flow chart of the study design. KAP: knowledge, attitudes, and practices; PBE: perception, barriers, and enablers.

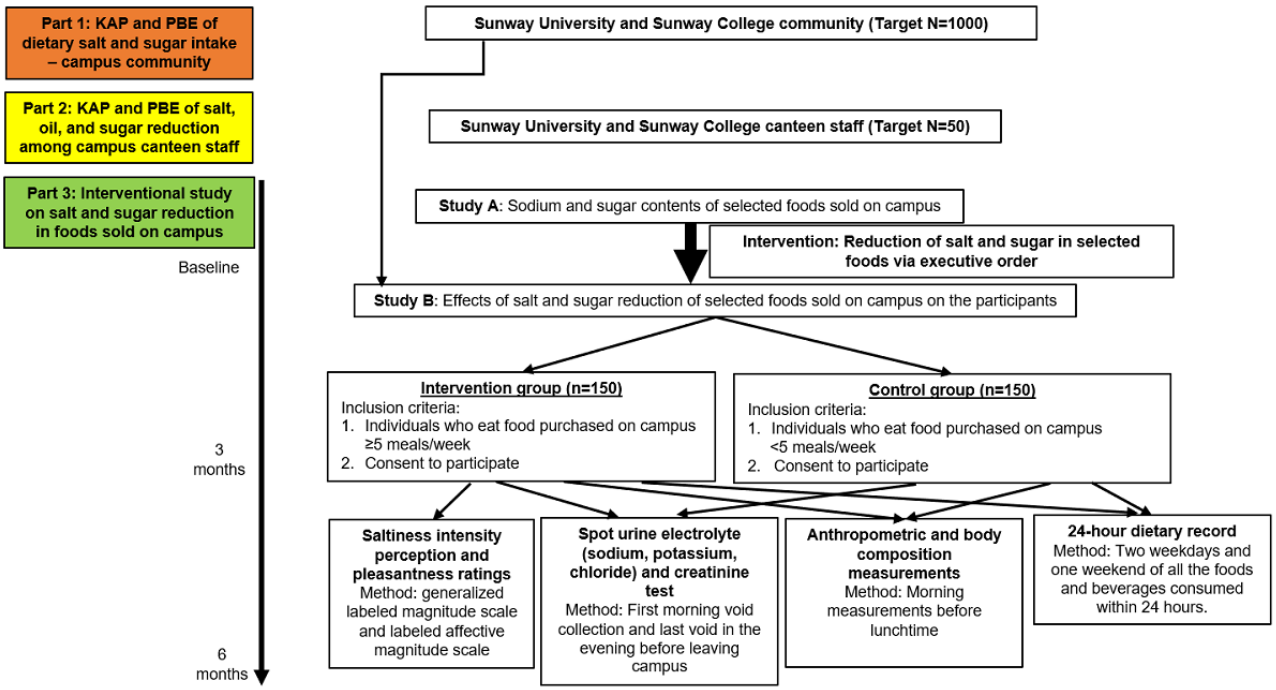

Ethical Considerations

Informed consent with identifying information omitted (except for email addresses for follow-up purposes) was obtained from all participants. The study was conducted according to the Declaration of Helsinki; participants' data were handled securely, and confidentiality was maintained. The study protocols were approved by the institutional review board of Sunway University (SUREC 2024/029 and SUREC 2024/040).

Compensation was provided as follows: for part 1 of the study, each participant was given a voucher worth MYR 10 (US $2.20) and the choice to enter a lucky draw to win 3 lucky draw food hampers worth MYR 200 (US $43.00) each; for part 2, each participant was given a voucher worth MYR 10 (US $2.20) upon successful completion of the questionnaire; for part 3, each participant was given MYR 10 (US $2.20) per time point (ie, at the start of the study, after 3 months, and after 6 months) for successful completion of the questionnaire, dietary records, anthropometric and body composition measurements, saltiness intensity perception and pleasantness ratings, and for providing urine samples (totaling MYR 30 or US $6.40 per participant).

Study Procedures

Part 1: KAPs of Dietary Salt and Sugar Intake

Sample Size Calculation

Using the Raosoft sample size web-based calculator [16], we determined that a minimum sample size of 370 was needed in order to achieve a 5% margin of error and 95% CI given a Sunway University and Sunway College population size of around 10,000 and a 50% response rate. Therefore, a target sample size of 1000 participants was set to account for midstudy dropouts. Recruitment took place from May to June 2024.

Instrument

Participants were invited to complete a web-based Google Form questionnaire (Multimedia Appendix 5) to assess the following:

1. Sociodemographic and lifestyle factors such as age, gender, ethnicity, education level, medical history, and smoking and alcohol-drinking practices
2. The frequency of eating meals on campus and general perceptions of the saltiness and sweetness levels of foods sold on campus
3. KAPs toward dietary salt (adopted from [17])
4. KAPs toward SSBs (adopted from [18]) and sugar tax attitudes (adopted from [19])
5. PBEs for implementing salt reduction (adapted from [14])
6. Knowledge of diabetes mellitus using a patient diabetes knowledge questionnaire (adopted from [20])
7. Diabetes Risk Score, a simple, fast, inexpensive, noninvasive, and reliable tool to identify individuals at high risk for type 2 diabetes (adopted from [21]).

A booth was set up in the campus lobby with high foot traffic. A promotional banner with a QR code that linked to the Google Form was set up, and promotional flyers were distributed to passersby. Promotion was also conducted through web-based course announcement boards and word-of-mouth, especially among academic staff.

Inclusion Criteria

Part 1 of the study included students and staff of Sunway University and Sunway College aged 18 years and older who understand English and were able to provide written informed consent via a Google Form.

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Exclusion Criteria

Individuals with an acute illness or psychological or psychiatric condition that may affect their ability to answer the survey questions objectively were excluded.

Part 2: KAPs and PBEs of SOS Reduction by Campus Canteen Staff

Sample Size Calculation

The estimated number of campus canteen staff that are involved in food preparation was around 65 people, and given an estimated response rate of 80%, the targeted number of participants was approximately 50 people. A townhall meeting with all the food vendors was held at a lecture hall, where the principal investigators explained the purpose of the study and conducted the pen-and-paper questionnaire on the spot. Recruitment took place from May to June 2024.

Instrument

A questionnaire on KAPs on SOS usage in food preparation (including on campus) and in habitual dietary intake by campus canteen staff was adopted from [22], while a questionnaire on PBEs to salt and sugar reduction by campus canteen staff was adopted from [14] (Multimedia Appendix 6).

Inclusion Criteria

Part 2 of the study included canteen staff aged 18 years and older who were involved in food preparation and able to provide written informed consent via a Google Form.

Exclusion Criteria

Individuals with an acute illness or psychological or psychiatric condition that may affect their ability to answer the survey questions objectively were excluded.

Part 3: Interventional Study on Salt and Sugar Reduction in Foods Sold on Campus.

Study A

Selected samples of food sold on campus were analyzed for their salt and sugar contents at baseline and at 3 months and 6 months after the campus-wide executive order to reduce salt and sugar in foods was implemented. Baseline collection took place from May to June 2024. The executive order was implemented in September 2024, and sample collection took place in December 2024 (3 months after the executive order) and March 2025 (6 months after the executive order). Compliance with the executive order was monitored solely based on the salt and sugar contents of the foods 3 months and 6 months after implementation of the executive order.

Food Sample Collection and Measurement Procedures

A targeted number of 4-5 food samples with the most popular sales numbers (verbally confirmed with vendors) per vendor for a total of 17 vendors on the campus were collected in resealable Ziplock storage bags. Salt levels in foods were measured by inductively coupled plasma-optical emission spectroscopy using the service of an outsourced International Organization for Standardization (ISO)/International Electrotechnical Commission (IEC) 1702-certified commercial laboratory (ALS Technichem, Malaysia). A complementary method of salt measurement in foods will be performed using the PAL-SALT pocket salt meter (Atago, Japan). The sugar profile of foods included the amounts of simple sugars (ie, fructose, galactose, glucose, sucrose, maltose, and lactose). The sugars were extracted and purified and the appropriate dilution was quantitated using high-performance liquid chromatography using the service of an outsourced ISO/IEC 1702-certified commercial laboratory (Permulab, Malaysia).

Study B

Before the actual lowering of salt and sugar in foods sold on campus, all the food vendors were briefed on the amount of salt and sugar to be reduced for all the foods sold.

Sample Size Calculation

According to the WHO/Pan American Health Organization Regional Expert Group for Cardiovascular Disease Prevention through Population-wide Dietary Salt Reduction Subgroup for Research and Surveillance [17], to meet the 0.5 g difference in sodium (salt), a sample size of 150 participants per arm was required. Therefore, a total of 150 participants who often ate foods sold on campus, defined as those who ate at least 5 meals of campus foods per week, were selected for part 1 of the study in a consecutive manner; they formed the intervention group who ate foods sold on campus that had reduced salt and sugar. Another 150 participants who did not often eat foods sold on campus, defined as those who ate less than 5 meals of campus foods per week, made up the control group.

Participants had to provide urine samples for the measurement of urinary salt, potassium, chloride, and creatinine; have body composition and anthropometric measurements taken, keep 24-hour dietary records, and complete saltiness intensity perception and pleasantness ratings of the foods on campus at the start of the study (baseline) and at 3 months and 6 months after the executive order (Multimedia Appendix 7). Recruitment and baseline measurements took place from June to August 2024, while measurements at 3 months and 6 months after the executive order were collected in December 2024 and March 2025, respectively. Data monitoring, harm monitoring, and trial auditing were required as this study did not involve any administration of a drug or therapy in a clinical setting.

Inclusion Criteria for the Intervention Group

Individuals who provided informed consent and ate at least 5 meals of campus food per week were included in the intervention group. This frequency was based on the average number of meals (including breakfast, lunch, dinner, and snacks) per day eaten on campus, which was determined in a pilot study of 100 people. The majority of the participants who ate on campus only did so on weekdays and did not have their dinners there.

Inclusion Criteria for the Control Group

Individuals who provided informed consent and did not eat campus food or ate campus food for <5 meals per week were included in the control group.

Exclusion Criteria

Individuals with an acute illness or psychological or psychiatric conditions were excluded.

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24-Hour Dietary Records

Participants were instructed to keep 24-hour dietary records for 2 weekdays and 1 weekend of the same week by writing down all foods and beverages consumed during a 24-hour period (each day starting at 12:00 AM and ending at 11:59 PM). Participants were asked to list the approximate time the meal was consumed, the place where it was consumed (eg, at home, on campus, or at a specific restaurant), and the type of eating occasion or meal (breakfast, lunch, dinner, snack, or other). The list of each food or beverage consumed included foods eaten between meals and all drinks, even noncaloric items like water. Specific details, ingredients, preparation methods, and brand names of each food or beverage consumed were also listed. Participants were instructed to pay attention to any sauce or gravy in the food, as these are usually high in salt and sugar. The portion size of each food or beverage item consumed was recorded using an appended "Food Portion Size" guide.

Urine Analysis

The intervention and control participants provided 2 spot urine samples—the first morning void and the last void in the late afternoon or early evening prior to the evening meal—at each of the 3 time points (baseline, after 3 months, and after 6 months). Urine electrolytes (salt, potassium, and chloride) and creatinine were measured using the potentiometry method (Alinity ci-series, Abbott) at the Laboratory Department of Sunway Medical Centre, Bandar Sunway. The average of the morning and afternoon readings was used to estimate 24-hour urine salt levels, using a previously published formula validated for the Malaysian population [23].

Assessment of Saltiness Intensity Perception and Pleasantness Ratings

Participants received verbal and written English instructions and then completed 2 rating scales assessing their perceived intensity of saltiness of the selected foods sold on campus (hereafter referred to as "intensity perception") and the extent to which they liked or disliked this level of saltiness (hereafter referred to as the "pleasantness rating"). The perceived saltiness intensity was measured by using the generalized labeled magnitude scale [24]; participants were asked to make a horizontal marking on a paper version of the scale. A 100-mm scale was constructed with 6 descriptors ranging from "barely detectable" to "strongest imaginable sensation of any kind." For pleasantness, the labeled affective magnitude scale [25] was used. It is a 100-mm scale that is constructed with 11 different levels ranging from "greatest imaginable disliking" to "greatest imaginable liking."

Anthropometric and Body Composition Measurements

Clinical measurements indicative of vascular health, namely, systolic blood pressure, diastolic blood pressure, and pulse rate, were taken using an automated blood pressure monitor (HEM-7121, Omron, Japan) after the participants had rested for 5 minutes. The height, waist circumference, and hip circumference of each participant were measured using a measuring tape, and the waist-hip ratio was calculated by dividing waist circumference by hip circumference. A bioimpedance body composition scale (HBF-375 Karada Scan, Omron, Japan) was used to determine weight, body mass index (BMI), total body fat, visceral fat, subcutaneous fat, skeletal muscle percentage, and resting metabolism rate. Based on previously published data for the Asian population, participants ≥23 kg/m^2 will be considered to be overweight and those ≥25 kg/m^2 will be considered to be obese [26]. The following previously published cutoff points relevant to the Asian population will also be used to summarize the results: for overall adiposity (total body fat) the cutoffs will be 20% for male participants or 30% for female participants [27] and for central adiposity (waist-hip ratio) the cutoffs will be 0.90 for male participants or 0.85 for female participants [28].

Data Analysis

The data collected from the Google Forms will be captured on Google Sheets and analyzed using SPSS (version 27; IBM Corporation) and R (version 4.5.1; R Foundation for Statistical Computing) statistical software. The data will be cleaned, coded, and checked for missing values before analysis.

Continuous variables will be tested for normality using Shapiro-Wilk tests. Normally distributed continuous data will be summarized as means and SDs, while skewed data will be presented as medians and IQRs. Categorical variables will be reported as frequencies (percentages) and compared using chi-square tests or Fisher exact tests where appropriate.

To account for individual dietary variability, including meals consumed outside campus, several adjustments will be made. Linear mixed-effects models (LMMs) or generalized linear mixed models will be used to analyze changes in dietary salt and sugar intake, incorporating random effects for participants to account for repeated measures (ie, baseline, 3 months, and 6 months). The models will adjust for potential confounders, such as age, gender, BMI, baseline dietary intake, and frequency of eating on campus.

For primary outcomes of the intervention effect analysis, including changes in 24-hour dietary salt and sugar intake (from food diaries), changes in spot urine salt excretion (using validated estimation equations for the Malaysian population), and anthropometric measure and /body composition changes (eg, weight, BMI, and body fat percentage), the statistical tests that will be performed are LMMs to assess time-dependent changes in intake while adjusting for individual heterogeneity and generalized estimating equations for binary outcomes like "met recommended daily intake" (yes or no). For secondary outcomes, including saltiness intensity perception and pleasantness ratings and changes in blood pressure, we will use repeated measures ANOVA or LMMs to track sensory adaptation and paired *t* tests (if normal) or Wilcoxon signed-rank tests (if skewed). Subgroup analyses based on eating frequency, gender, and BMI categories will also be performed to minimize interaction effects.

All statistical tests will be 2-tailed, with significance set at $P<.05$. Adjustments for multiple comparisons will be made using Bonferroni correction where necessary.

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Results

Recruitment for the cross-sectional studies (parts 1 and 2) began in May 2024. For the longitudinal intervention study (part 3), recruitment and baseline measurements took place from June to August 2024, and the 6-month intervention began in September 2024 immediately after the official launch of the campus-wide executive order. The timeline of the study is shown in Figure 2. There have been no deviations of the protocols since being registered in the ClinicalTrials.gov registry (NCT06473038) and published herein. There were variations on the actual sample sizes in all stages during the recruitment process, and these will be reported in our future publications on the findings of this study.

Figure 2. The schedule of enrolment, interventions, and assessments for the salt and sugar reduction study in foods sold on campus at Sunway University and Sunway College. KAP: knowledge, attitudes, and practices; PBE: perception, barriers, and enablers.

	Study period								
	Enrolment	Allocation	Postallocation						Closeout
Timepoint	$-t_1$ May-June 2024	0 Sep 2024	t_1 Oct 2024	t_2 Nov 2024	t_3 Dec 2024	t_4 Jan 2025	t_5 Feb 2025	t_6 Mar 2025	t_x Apr 2025
Enrolment									
Eligibility screen	×								
Informed c Comments	×								
KAP and PBE questionnaires for students, staff, and canteen staff	×								
Allocation		×							
Interventions									
Executive order to reduce salt and sugar in all foods sold on campus			♦—	—	—	—	—	—♦	
Assessments									
Study A: measurement of salt and sugar contents in selected foods	×				×			×	
Study B: effects of salt and sugar reduction on the participants (body composition, urine electrolytes, dietary records, saltiness ratings)		×			×			×	
Exit interview with selected participants									×

Discussion

The food environment, which encompasses factors such as the presence, ease of access, price, quality, and advertising of specific food options, significantly influences what people consume [29]. An unhealthy food environment contributes to unhealthy eating patterns; therefore, altering the food environment holds promise for fostering and supporting healthy behaviors, serving as a foundation for workplace and academic campus health initiatives [30]. Workplaces and academic campuses are sedentary settings where energy-dense foods and beverages are commonly available [31]. Viewed from an economic perspective, there is increasing concern regarding the financial impact of cardiometabolic diseases within workplaces, stemming from expenses linked to absenteeism, sick leave, disability, injuries, and health care claims [32]. However, looking on the bright side, the workplace and academic campus offer strategic environments for implementing initiatives aimed at fostering healthy eating habits, considering that employees and students dedicate up to 60% of their waking hours there [30]. Therefore, the workplace and academic campus have the potential to reach a significant portion of adults, including those who may not typically participate in preventive health programs [33].

In a review of 55 interventional studies aimed to promote healthy eating at workplace cafeterias, it was found that these interventions resulted in a higher intake of fruits and vegetables, improved dietary intake, improved health outcomes, and improved healthy food sales [34]. Specifically, similar salt or salt reduction intervention studies that have been conducted

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among workplace employees or academic campus communities have yielded mainly positive results. For example, a study in Portugal found that there was no significant decrease in consumer satisfaction and in food waste generated [35]. Another study in Ireland found that lower percentages of participants exceeded the recommended salt intake (4-6 g/day) at the intervention hospital cafeteria than at the nonintervention hospital [36]. A study in Japan found that there was a reduction of 1.4 g in salt intake at the intervention workplace [15], whereas another study in Germany found a reduction of 1.2 g in salt intake among men (but not women) at the intervention workplace [37].

One of the strengths of this study is that, to the best of our knowledge, it will be the first study to administer salt and sugar interventions at an academic campus in Malaysia with a sizeable sample of apparently healthy and mostly young adults. Similar dietary intervention studies on salt reduction in Malaysia have so far been limited to middle-aged and older adults with elevated blood pressure [38] or conducted at a pilot scale among the staff of the Ministry of Health, Malaysia (My STARS study) [39]. Our research is innovative because Malaysia has not yet established an effective and comprehensive strategy to reduce salt intake in food consumed outside the home. Our methodology will facilitate data collection essential for formulating such a policy.

However, we do recognize a potential major limitation of the study. Spot urine collections will be adopted instead of a standard approach of 24-hour urine collection. We recognize that any single urine collection may not be representative of usual individual intake. However, this method is considered an acceptable proxy for intake at the group level as we are using it as a way to monitor change rather than to determine absolute levels [40]. Obtaining complete 24-hour urine collections every 3 months during a 6-month intervention is rare and remains challenging [41].

Overall, this project aims to foster a culture of health and well-being within the Sunway University and Sunway College community while contributing to broader public health objectives and corporate social responsibility. Through collaboration between students, staff, and the institution, the project seeks to drive positive change in dietary habits, ultimately promoting a healthier lifestyle. This will contribute toward WHO goals to reduce the intake of salt by 30% by 2025 and further the reduction of free sugar intake to below 5% of total energy intake (25 g or 6 teaspoons) per day and toward the United Nation's third sustainable development goal focusing on good health and well-being.

Acknowledgments

The authors would like to thank all participants for participating in this study. This work is supported by the Sunway University Research Accelerator Grant Scheme (grant GRTIN-RAG-DMS-16-2024) and the Malaysian Society of Hypertension Research (grant MSH 2024/01). The funding bodies played no role in the design of the study; collection, analysis, or interpretation of the data; or in writing the manuscript.

Data Availability

All relevant data from this study will be made available upon study completion.

Authors' Contributions

YCC and YHS conceived and designed the study. YHS, MHC, FFLC, TPL, and PBO collated the questionnaires and collected the data. YHS wrote the first draft of the manuscript. All authors contributed to the manuscript revision and read and approved the submitted version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOC File , 121 KB - resprot_v14i1e69610_app1.doc]

Multimedia Appendix 2
Institutional review board of Sunway University ethical approval and approved protocol (SUREC 2024/029).
[PDF File (Adobe PDF File), 801 KB - resprot_v14i1e69610_app2.pdf]

Multimedia Appendix 3
Institutional review board of Sunway University ethical approval and approved protocol (SUREC 2024/040).
[PDF File (Adobe PDF File), 788 KB - resprot_v14i1e69610_app3.pdf]

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Multimedia Appendix 4
Malaysia Society of Hypertension peer-reviewed report, grant approval, and proposal.
[PDF File (Adobe PDF File), 1375 KB - resprot_v14i1e69610_app4.pdf]

Multimedia Appendix 5
Knowledge, attitudes, and practices and perception, barriers, and enablers questionnaire for students and staff.
[DOCX File , 140 KB - resprot_v14i1e69610_app5.docx]

Multimedia Appendix 6
Knowledge, attitudes, and practices and perception, barriers, and enablers questionnaire for campus canteen staff.
[DOCX File , 149 KB - resprot_v14i1e69610_app6.docx]

Multimedia Appendix 7
Longitudinal intervention study form.
[DOCX File , 939 KB - resprot_v14i1e69610_app7.docx]

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Abbreviations

BP: blood pressure
BMI: body mass index
KAP: knowledge, attitudes, and practices
LMM: linear mixed-effects model
NHMS: National Health and Morbidity Survey
PBE: perception, barriers, and enablers
SOS: salt, oil, and sugar
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SSB: sugar-sweetened beverages
WHO: World Health Organization

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Protocol

Repeated Pressure and Shear Stress at the Posterior Heel Following Localized Skin Cooling: Protocol for a Repeated Measures Cohort Study

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Abstract

Background: Pressure in combination with shear forces can deform soft tissues and lead to development of pressure ulcers. The prevalence rate of pressure ulcers in the United Kingdom remains unacceptably high and can occur across the human lifespan. The posterior heel represents a common anatomical site for pressure ulcers due to soft tissues lying adjacent to bony prominences and being exposed to pressure and shear during lying postures. Localized cooling and interface materials that reduce shear may offer potentially therapeutic benefits in the development of pressure ulcers. Yet the physiological mechanisms underpinning the potential benefits of localized cooling are not fully understood.

Objective: This study protocol aims to investigate how localized cooling influences the skin's microvascular, inflammatory, structural, and perceptual tolerance to repeated shear loading at the heel.

Methods: The protocol will be tested on individuals of different age, sex, skin tone, and comorbidities, using a repeated measures design. Three cohorts will be recruited: (1) young and healthy (n=35), (2) older and healthy (n=35), and (3) with spinal cord injury (n=35). Participants will complete 3 testing sessions using a custom-built shearing rig with integrated thermal plate, during which the posterior aspect of the heel will be exposed to a standardized mechanical stimulus to elicit repeated pressure and shear loading. The experimental condition of each session will be determined by the temperature of the thermal plate, which will be set to either 36 °C (no cooling), 24 °C (mild cooling), or 16 °C (strong cooling). Continuous measurements will include kinetic coefficient of friction (CoF) and skin blood flow (via laser Doppler flowmetry; 40 Hz). Pro- and anti-inflammatory biomarkers in skin sebum (via Sebutape), structural skin properties (via optical coherence tomography), skin conductance (in microsiemens) and ratings of thermal sensation, comfort, and acceptance (via Likert scales) will also be assessed before and after the shear stress protocol.

Results: Recruitment began in January 2024. As of February 2025, 43 participants had been enrolled in the study. Data collection and analysis are ongoing, and published findings are expected to be available in early 2026.

Conclusions: This analysis will help identify mechanisms of skin damage following repeated shear stress at the heel, furthering our understanding of superficial pressure ulcers. It will also establish physiological and perceptual thresholds for the protective effects of cooling from shearing-induced damage at the heel.

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KEYWORDS

pressure ulcer; wounds; temperature; local cooling; shear stress

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Introduction

Pressure ulcers constitute a type of localized damage to the skin and/or underlying soft tissue resulting from prolonged periods of pressure or pressure in combination with shear forces [1]. In the United Kingdom alone, the annual cost of treating chronic wounds, including pressure ulcers, has been estimated to be approximately £8.3 billion (US $12.7 billion) [2]. Accordingly, an improved understanding of the fundamental mechanisms underlying the physiological tolerance of human skin to mechanical loading and shearing could lead to the development of cost-effective, personalized solutions to prevent these wounds and improve patient care and quality of life [3].

Sustained localized mechanical loading and shearing of the skin can arise from lying and sitting postures, particularly in individuals with mobility impairment such as spinal cord injury (SCI) [4]. Internal tissue deformations occur as a result of sustained pressure and shear forces that can lead to changes in the physiology of skin and subdermal tissue, including ischemia in the blood vasculature, lymphatic impairment, and direct deformation damage [5,6]. It has been reported that nearly 30% of pressure ulcers occur at the heel, with this region being the second most likely area for pressure damage after the sacrum [7,8]. As opposed to the thick skin of the plantar heel, the posterior heel has thin, striated skin [9], which is very susceptible to pressure- and shear-induced damage [10]. Yet the mechanisms underlying the elevated risk of shear-induced damage at the heel remain under-studied.

Microclimate conditions within and around skin tissues strongly influence the tolerance of the skin to mechanical loading and shear [11]. For example, elevated temperature and humidity at the skin interface reduce the mechanical stiffness and strength of the skin [12] while also increasing its coefficient of friction [13]. These mechanisms can lead to a greater risk of tissue damage for the same mechanical stress [14,15]. In contrast, cooling reduces skin tissue's metabolic demands and could increase the skin's physiological tolerance to mechanical loads [12,16]. Early animal studies revealed that reduced skin temperature minimizes the risk of pressure ulcer formation [17,18]. This may occur through altered microvascular responses [18], as well as via downregulation of the expression of pro-inflammatory cytokines such as tumor necrosis factor α (TNFα), which is mediated by the stimulation of cold-sensitive transient receptor potential melastatin 8 (TRPM8)–expressing neurons in dorsal root ganglia [19,20]. Furthermore, our preliminary proof-of-concept experimental and modeling data on a representative skin site (the finger) indicated that skin cooling to 16 ºC can reduce friction by up to 35% for the same mechanical load [13]. This effect is likely due to changes in the viscoelastic properties of cooled skin tissues, which could in turn translate to reductions in shear stress. While this evidence highlights the potential therapeutic role of skin cooling for protecting tissue health, the mechanisms by which cooling enhances skin tolerance to pressure, shear, and friction remain poorly understood in humans [17-19,21-24].

In addition to its physiological effects, localized cooling of the skin can induce cold discomfort, which can limit acceptability and adherence to therapeutic interventions that promote skin integrity, particularly for vulnerable individuals at risk of pressure ulcers [25]. However, evidence on how the absolute temperature of a surface shearing against the skin contributes to thermomechanical discomfort is limited [26]. While the evidence above highlights the field's limited mechanistic understanding of the effects of skin cooling on skin tissue viability, commercially available microclimate management systems, which deliver local and full-body cooling, continue to be developed and applied to support pressure ulcer prevention [27-29].

It is also important to note that physiological and perceptual tolerance to pressure and shear at the skin interface may also vary as a function of age and comorbidities [30], which could in turn diminish the therapeutic efficacy of cooling. For example, aging-induced changes in skin biophysics and morphology [31], as well as decreases in both reflex cutaneous vasoconstriction and density of thermoreceptors [32], are likely to modulate the thermoregulatory and perceptual sensitivity of the skin to localized cooling. Similarly, autonomic and sensory dysfunctions resulting from SCI manifest in impaired control of skin blood flow and lack of sensation below the injury level [33,34].

Based on the evidence above, this study protocol aims to investigate (1) how different levels of localized cooling influence the skin's microvascular, inflammatory, structural, and perceptual responses to repeated pressure and shear loading at the heel; and (2) how metabolic, immunological, biophysical, and perceptual pathways underlying the effects of localized cooling on skin tolerance to shear are modulated by aging and SCI. The research that will be delivered via this protocol will be both important in improving scientific knowledge and timely to societal demands, as it will support the development of user-centered approaches to maintaining skin tissue viability via evidence-based therapeutic cooling.

Methods

Overview

Participants will attend 3 experimental sessions separated by a minimum of 24 hours in the Clinical Academic Facility located at Southampton General Hospital (Southampton, United Kingdom). During the sessions, participants will place the center of their posterior heel on a custom-built friction rig with an integrated thermal plate to undergo a standardized protocol eliciting repeated pressure and shear force. The study will use a randomized crossover design involving 3 plate temperatures: 36 ºC (no cooling), 24 ºC (mild cooling), or 16 ºC (strong cooling). Microclimate conditions at the interface between a loaded skin site at risk of pressure ulcer (eg, the sacrum) and a support surface (eg, a mattress) are commonly associated with skin temperatures of approximately 38 ºC. Following pilot testing, some participants (n=2) found a 38 ºC plate temperature to be borderline uncomfortable, so we decided to reduce the plate temperature to 36 ºC to improve thermal tolerability in the no cooling condition. The rationale for using 2 levels of cooling was 2-fold: first, prior research investigating localized cooling on tissue viability in animal models [17,18] used cooling

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interventions at 25 ºC, demonstrating the benefit of reduced skin temperature in preserving tissue viability. Second, one of the main aims of the study is to examine how different levels of cooling may influence the biophysical properties of the skin and perceptual thermal tolerances of both mild (24 ºC) and strong (16 ºC) cooling.

Participants

Three participant cohorts will be recruited: (1) young and healthy (n =35); (2) older and healthy (n =35); and (3) with SCI (n =35). This study protocol is being supported by a Medical Research Council grant (MR/X019144/1). As part of this grant, 2 distinct experimental protocols have been designed: (1) this study protocol, which aims to investigate temperature modulation of shearing forces at the heel; and (2) our companion study protocol (Gordon et al [35]), which aims to investigate temperature modulation of sustained mechanical loading at the sacrum [35]. The separation of the protocols is motivated by their intrinsic conceptual differences (ie, the pathophysiology of shearing-induced vs loading-induced mechanical damage) as well as by different experimental challenges associated with their delivery (ie, the development of a large, shearing-inducing, and thermally controlled friction rig for the heel vs a small thermomechanical indenter for the sacrum). By design, the same participant cohort will be recruited to evaluate regional differences in responses (sacrum vs heel) and assess how the addition of shear force may impact local tissue physiology and the efficacy of cooling.

The sample size justification for this protocol is based on the power calculations from Gordon et al [35], using changes in the peak hyperemic response, which is a robust, repeatable response. Specifically, we will recruit a minimum of 18 participants per group, with target recruitment of 35 individuals, to allow for sufficient statistical power and to account for up to 50% dropout. Participants will be screened for study participation using a set of inclusion and exclusion criteria. The young and healthy participants will be aged 18 to 35 years and the older and healthy participants will be aged 55 to 70 years. The participants presenting with SCI will have an injury level within T1 to S1. The younger and older healthy groups will undertake regular physical activity (1-3 times per week), be nonsmokers and nonvapers, and be free from comorbidities that would preclude them from taking part, such as hypertension or Raynaud's disease. Both male and female participants will be recruited for a subanalysis on the influence of sex; we will also recruit individuals with different skin tones, ranging from light to dark, as assessed by the Fitzpatrick scale [36]. Stratified skin sampling will be used to determine whether there is an influence of skin tone on pressure and shear tolerance at the skin of the heel.

Ethical Considerations

This project will recruit and test healthy individuals aged 18 to 70 years as well as individuals with SCI. The project will be conducted in line with the Southampton University Code of Practice for Research, complying with the Declaration of Helsinki. Written informed consent will be obtained from participants, as will relevant personal information (eg, perceptual skin sensitivity to cooling). Participants will have the unconditional right to withdraw from the study at any point.

Data management will adhere to the University of Southampton' policy on data quality, which forms part of the University's Information Governance Framework, complying with the requirements of the Data Protection Act 2018 and the University of Southampton's Ethics Committee (Ethics and Research Governance Online; ERGO) policies. This project involves human participants and will be conducted in line with the university's policy on the ethical conduct of research and studies involving human participants and the Medical Research Council's policies on ethics and data sharing. Data will be fully anonymized at the earliest opportunity and before being made available with open access in the university's data repository. All data that supports publication will be deposited and will be citable using a persistent identifier (DOI). Research findings will be published in high-quality, peer reviewed academic journals.

Participants will be eligible for compensation for their time upon successful completion of an experimental trial in the form of retail vouchers (maximum compensation value: £576 [US $785]). All experimental methods and measurements will be noninvasive, posing low risks to participants. However, mitigation measures are in place to manage any risks that may develop, including on-going skin temperature monitoring, checks of subjective well-being, and active skin rewarming following the cooling stimuli. The skin will also be checked for blanching erythema at regular intervals. Ethical approval for the stated measurements and procedures has been granted by the University of Southampton's Ethics Committee (ERGO 88984).

Experimental Procedures

The study uses a repeated measures cohort design. Once participants have been screened and recruited, they will be invited to their randomly allocated experimental sessions [37]. They will come to the laboratory wearing comfortable, loose-fitting attire. Upon arrival, participants will be seated while they acclimatize to the ambient conditions of the laboratory (21-24 °C; 50% relative humidity) before recording height and body mass (Seca 874; Seca GmbH).

Following the pre-experimental checks, participants will be seated on a hospital bed in a semireclined position supported by pillows and a back rest. An elevated ankle cushion (20 × 11 × 10 cm) will then be positioned under the right leg and placed under the gastrocnemius muscle belly. To standardize the position of the foot and ankle and minimize movement during the repeated shear movements, an adjustable orthotic ankle foot brace will be strapped on to the right foot and the ankle angle set to a neutral plantar grade position (90°). This will ensure the skin over the calcaneus is consistently in contact with the surface of the thermal plate when the heel is placed on the friction rig and provide a constant relative tension in the local skin site (Figure 1). The axial load will then be standardized to exert 15 N of normal force on the thermal plate.

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Figure 1. Experimental set up. The foot and ankle are supported by an orthotic brace and ankle support to standardize positioning while minimizing movement during the shearing protocol.

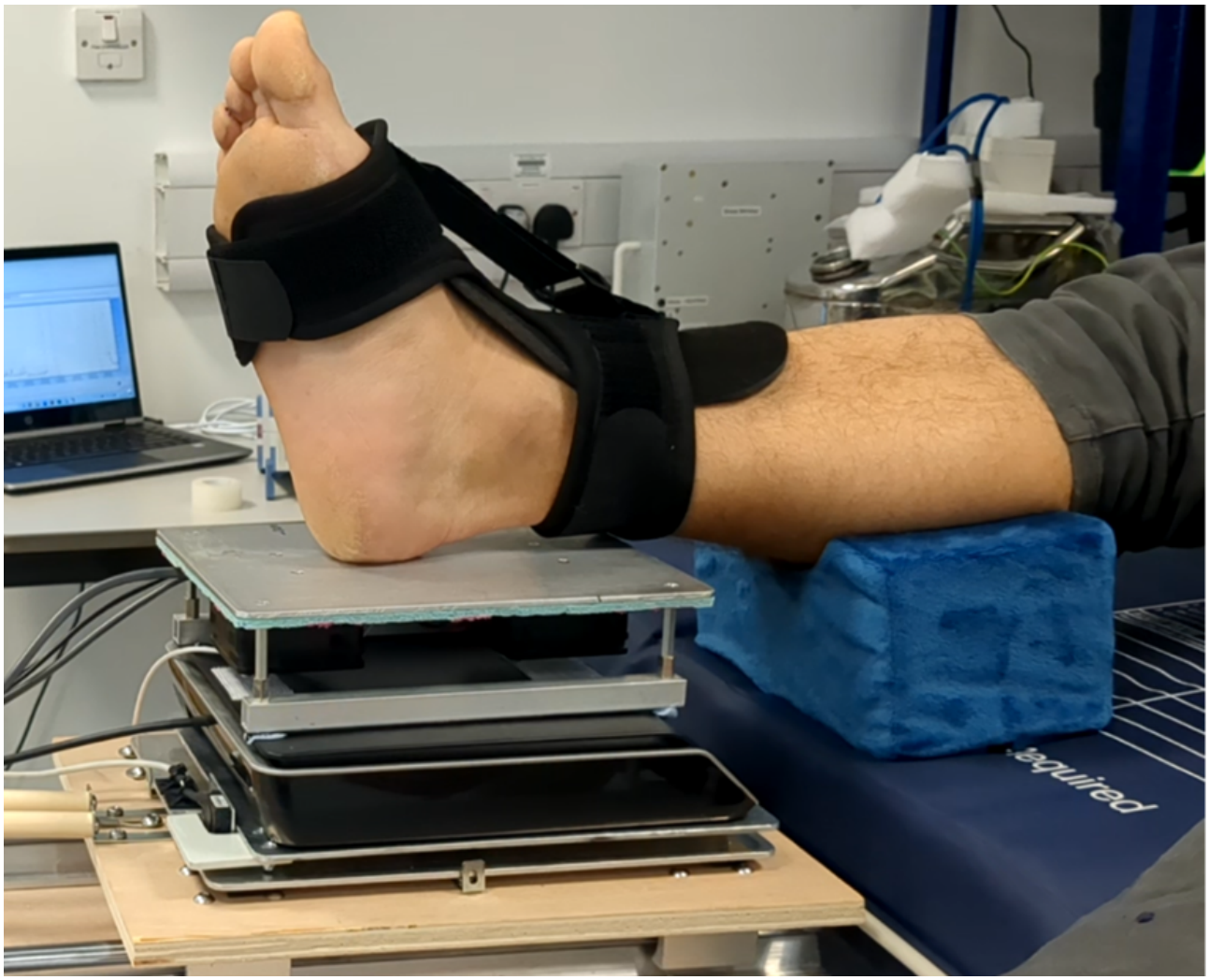

A series of measurements that run continuously or during discrete time points will be taken (Figure 2). First, baseline assessments, including structural and functional imaging of the posterior heel skin, will be captured using optical coherence tomography (OCT). This will be followed by sampling of skin sebum at the heel for subsequent biomarker analysis, using an established methodology involving a 2-minute application time and tweezer extraction to avoid cross contamination [38]. To provide an index of baseline local skin hydration, a capacitance meter will then be placed on the heel to measure skin conductance (in microsiemens). After the baseline measurements are completed, participants will place the heel on the thermal plate of the shearing rig [13]. The temperature of the aluminum thermal plate (22 × 16.7 cm) is controlled by a set of Peltier elements, and when applied to the skin, allows for the manipulation of local skin temperature (range 0 °C to >50 °C; variable temperature rates under PID control [Daisylab; MC Computing]). An optical fiber is integrated in the center of the plate through a 1-mm hole flush to its surface, allowing for the monitoring of skin blood flow via laser Doppler flowmetry (LDF) when the heel is static. An integrated force plate and low resistance trackway allow the recording of both normal and tangential forces (in newtons), respectively. The friction rig is interfaced with an analogue-to-digital data acquisition unit (MC Computing), sampling plate surface temperature (°C), normal forces, and tangential forces at 33 Hz. The kinetic coefficient of friction (CoF) according to Amonton's law [39] can be estimated as the ratio of tangential to normal force and defined as the resistance generated from 2 surfaces rubbing against each other [40].

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Figure 2. Standardized repeated shear protocol delivered at the heel. The friction rig will be used to deliver a standardized protocol to induce repeated shear stress under 3 thermal conditions: a control skin temperature with no cooling (36 °C) and 2 cooling temperatures of 24°C and 16°C. During the protocol, a series of noninvasive measurements will be conducted (estimation of skin friction from the ratio of tangential and normal fore and skin blood flow via laser Doppler flowmetry (LDF); inflammatory biomarker sampling from skin sebum; structural and functional imaging via optical coherence tomography (OCT); perceptual assessment of subjective thermal sensation, comfort, and acceptance; and measurement of skin conductance, to be used as an index of local skin hydration) at different time points (identified in the figure by the arrows).

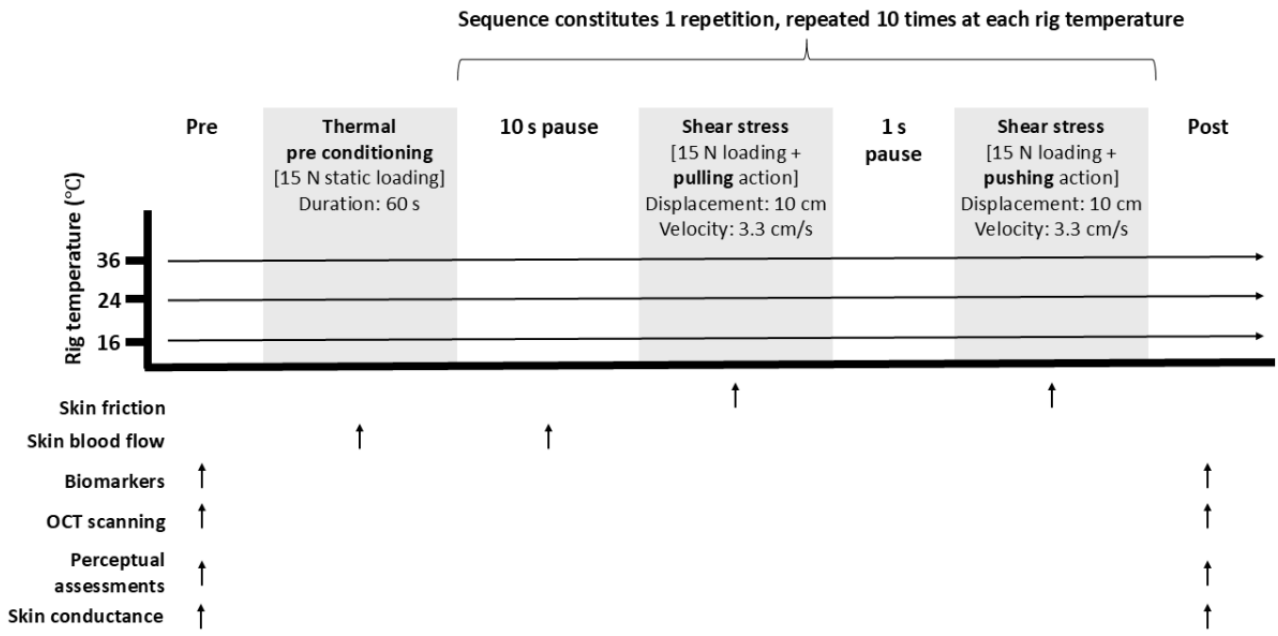

The friction rig has been modified to be situated on a linear rail system that allows bidirectional linear travel. The travel is achieved by a servomotor (Drylin SAW-0630 linear module with motor; Igus), which is fixed to the rig and causes 10 cm of displacement at the heel at a velocity of approximately 3.3 cm/s. The servomotor is equipped with a linear strain gauge (Loadstar RAS1 S-Beam Load Cell; LoadStar) providing measurements on the tangential pull (in newtons) of the shearing rig during the prescribed displacements. Participants will be asked to provide subjective ratings of thermal sensation, comfort, and acceptability using Likert scales (detailed below). At this point, the standardized protocol to cause repeated shearing stress will commence (Figure 2).

The protocol starts by participants placing the heel in the center of the thermal plate over the hole, where the LDF optical probe is located flush to the surface. Positioning of the bed and lower limb will be modified to provide a standardized 15-N axial load on the plate. Skin blood flow will be measured intermittently (accounting for displacement of the heel following the static loading phases) throughout the protocol via LDF (moorVMS-LDF laser Doppler monitor; Moor Instruments). The heel will remain in place for a 60-second thermal preconditioning period to allow for temperature adaptation at the skin interface (at 36 °C, 24 °C, or 16 °C). The repeated shearing sequence will then commence (Figure 2), initially with a 10-second pause, before the servomotor travels in one direction pulling the rig and displacing it by 10 cm, pausing for 1 second, then traveling in the opposite direction, pushing the rig back to the original starting point. This sequence completes one repetition, which is repeated 10 times. After completing the 10 shearing repetitions, participants' thermal perceptions will be recorded, followed by posttest OCT, skin sebum, and skin conductance measurements.

The sections below provide a description of the measurements to be used during the protocol.

Measurements

Skin Blood Flow

Skin blood flow will be monitored via LDF using a noninvasive optical probe, sampling at a 1-mm tissue thickness [41]. LDF has been validated [42] and widely used to assess changes in blood flow velocity (as an index of changes in flow) over bony prominences, such as the sacrum [21,22,24,43]. The optical probe is integrated within the custom-built friction rig, allowing concurrent manipulation of skin temperature while monitoring changes in skin blood flow prior to the repeated shearing protocol (ie, the thermal preconditioning phase). LDF values during the thermal preconditioning phase will be used to calculate the baseline skin blood flow (taken as the mean average during the 60-second period) and subsequently compared across test shearing repetitions.

Biomarkers

Pro-inflammatory biomarkers (interleukin [IL]-1α, IL-1β, TNFα, IL-6, IL-8, and interferon γ [IFNγ]) and anti-inflammatory biomarkers (IL-1 receptor agonist [RA]) will be extracted from skin sebum via the application of Sebutape (Cuderm). This approach has been optimized [44] to ensure both low- and high-abundance proteins can be quantified. In summary, Sebutape is applied to the heel for 2 minutes before

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the samples are extracted using tweezers and a gloved hand to avoid cross contamination. Stored samples will be coded and stored at –80 °C prior to analysis using standard ELISA (enzyme-linked immunosorbent assay) plates for targeted proteins. The extraction of skin inflammatory biomarkers will use chemical and mechanical stimuli for maximal extraction efficiency. Chemical extraction will involve 0.85 mL of extraction buffer, which consists of phosphate-buffered saline + 0.1% surfactant (dodecyl maltoside). The tapes will then be shaken with the buffer for 1 hour followed by 5 minutes of sonication. A 0.35-mL aliquot will then be used for total protein analysis. The remaining 0.5 mL will be centrifuged for 10 minutes at a speed of 15,000*g* at 4 °C. The supernatants will be discarded and the remaining solution with the pellet briefly vortexed and used for the immunoassay analysis, as prescribed by the manufacturer, using MSD U-Plex kits (MesoScale Diagnostics).

Skin Imaging

Skin imaging will be conducted using an OCT system (VivoSight; Michelson Diagnostics Ltd) that uses a laser source of near-infrared wavelength (1305 nm; class 1M [EN 60825-1]). The system includes a dynamic mode whereby the principles of speckle variance OCT are used to visualize the microvasculature in the superficial dermis. A total of 120 images with 50-µm spacing will be acquired as a 6 × 6 × 2 mm^3 (width × length × depth) stack. This technique will allow noninvasive characterization of the skin's epidermal and blood perfusion properties prior to and following the thermomechanical manipulations [45]. Using OCT is noninferior to punch biopsy for skin characterization [46]. The OCT probe will be placed gently on the skin, maintaining a static position during acquisition. Spacers at the probe interface will be used to optimize the focal point of the epidermis during scanning.

Perceptual Assessments

Participants' local thermal and comfort sensations will be assessed via Likert scales to establish time-dependent changes in subjective perceptions of cooling [47]. The Likert scales for thermal sensation, thermal comfort, and thermal acceptance were created based on the recommendations of Schweiker et al [48], using a ruler to draw a 100-mm horizonal line with evenly spaced anchors. Thermal sensation is measured on a 7-point scale from 1 (cold) to 7 (hot), with 4 as neutral. Thermal comfort used a 5-point scale ranging from 1 (comfortable) to 5 (extremely uncomfortable), and thermal acceptance used a 4-point scale ranging from 1 (clearly acceptable) to 4 (clearly unacceptable). Perceptual sampling will occur before and after the shear protocol (Figure 2).

Statistical Analyses

Data will be assessed for normality of distribution with the Kolmogorov-Smirnov test. Within- and between-subject mean differences (n=35 with 95% CIs) as a function of mechanical stimulus temperature (ie, 36 ºC, 24 ºC, and 16 ºC), time (ie, varying levels depending on the variables' sampling rate), and participant group (ie, young, older, SCI) will be analyzed. These independent and interactive effects will be assessed by means of 3-way mixed model ANOVAs (or Friedman tests) for biomarker expression, skin structural properties, biophysical properties (ie, imaging parameters), subjective thermal perceptions, and kinetic CoF. Post hoc analyses will be performed between shear stimulus temperatures, time, and participant groups based on the presence of main effects and using the Tukey test. Group-related covariables associated with sex, skin tone, and clinical status (applicable to SCI participants only) will be considered in all analyses to interpret the proportion of variance unexplained by the main effects (ie, temperature, time, and group) and their interactions.

Results

Recruitment began in January 2024. As of February 2025, 43 participants have been enrolled in the study. Data collection and analysis are ongoing, and published findings are expected to be available in early 2026.

Discussion

Prolonged mechanical loading from pressure, or pressure in combination with shear, over a bony prominence such as the heel can lead to skin damage and the formation of pressure ulcers [1]. Research that addresses the physiological tolerance of human skin to repeated mechanical shear is important for improving scientific knowledge and meeting societal demands. As such, this study protocol aims to investigate how cooling may influence the skin's pathophysiological responses to repeated shear loading at the heel and how these responses may be modulated by aging and the presence of SCI. This study will provide a comprehensive understanding of the physiological processes and the potential benefits of cooling strategies to minimize the pressure ulcer risk at the posterior heel, while generating novel insights on temperature-modulated skin tolerance in vivo. This information will be relevant to skin physiologists, bioengineers, medical device manufacturers, and clinicians.

The study benefits from using a repeated measures design to purposefully sample clinically relevant groups of individuals and targeting relevant physiological and perceptual mechanisms. The heel is an anatomical location that contains minimal subcutaneous tissue, making it a vulnerable site for the development of pressure ulcers by impacting the integrity of the superficial layers of the skin [49]. The heel is particularly susceptible to injury in patients who are required to maintain semirecumbent positions, for example in bed, where individuals may repeatedly engage in repositioning (eg, from sliding down in bed) or transferring between support surfaces. Movement is often initiated by loading through the heels, creating both pressure and shear forces at the skin interface. Recent studies have shown how repeated pressure exposure, and pressure in combination with shear, elicits a biophysical and biomarker response from the skin [11,44,50,51] indicative of early signs of damage.

Previous animal data have shown that reducing skin temperature during applied mechanical loading could lower the metabolic demands of the underlying tissues, protecting metabolic and myogenic components of skin blood flow [23]. There is further

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evidence to indicate that lowering skin surface temperature can reduce the kinetic CoF [13]. In addition, the effects of both heat and moisture in decreasing the resilience of the epidermis in load-bearing regions of the body are well documented [52,53]. However, whether these findings from other anatomical sites translate to the skin of the heel, and how these mechanical interactions may lead to the risk of tissue damage, are unknown [10].

The study has been robustly designed but is not without limitations. Shear forces will be delivered via a dry aluminum interface, which may limit generalizability to clinical scenarios where the heel interacts with bedding with varying moisture saturation. The authors recognize the importance of evaluating the effect of temperature modulation of friction using patient-centered materials (eg, textiles used in the fabrication of chairs and beds), and the subsequent translation of clinically relevant findings. This research is currently being undertaken in our laboratory. Given the lack of data on localized cooling at the heel, identifying how the effects of skin cooling vary both physiologically and perceptually will therefore be important for developing bespoke patient-centered solutions to maintain skin integrity under shear stress that are both effective and comfortable.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization: DF, PW
Data curation: DF, PW, RG
Formal analysis: DF, PW, RG, CS
Funding acquisition: DF, PW
Investigation: RG, CS
Methodology: DF, PW, RG, CS
Project administration: DF, PW, RG, CS
Writing – original draft: RG
Writing – review and editing: DF, PW, RG, CS

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report by the UK Research and Innovation (UKRI) Medical Research Council.
[PDF File (Adobe PDF File), 65 KB - resprot_v14i1e73250_app1.pdf]

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Abbreviations

CoF: coefficient of friction

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ELISA: enzyme-linked immunosorbent assay
ERGO: Ethics and Research Governance Online
IFNγ: interferon γ
IL: interleukin
LDF: laser Doppler flowmetry
OCT: optical coherence tomography
RA: receptor agonist
SCI: spinal cord injury
TNFα: tumor necrosis factor α
TRPM8: transient receptor potential melastatin 8

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Protocol

Promoting Intergenerational Health in Rural Kentuckians With Diabetes (PIHRK'D): Protocol for a Longitudinal Cohort Study

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Abstract

Background: The prevalence of type 2 diabetes mellitus (T2DM) is steadily increasing and has exceeded 20% in some rural Kentucky counties. In Kentucky, chronic diet-sensitive conditions and unhealthy behaviors are among the highest in the nation, with approximately 36.5% of adults with obesity and 13.3% diagnosed with T2DM, while only 15.3% meet physical activity recommendations, and 4.7% meet fruit and vegetable consumption recommendations. Family-based interventions can be used to promote health in rural communities that often comprise intergenerational households.

Objective: The purpose of the study is to determine whether leveraging family units as sources of social support promotes nutritional and physical activity changes among those who are overweight or have obesity and are diagnosed with T2DM.

Methods: This study consists of 3 phases (baseline, intervention, and postintervention). An overview of the study will be provided to interested participants, after which their consent will be sought. At baseline, demographic data, social support, physical activity, diabetes knowledge, diabetes self-management, dietary recall, obstructive sleep apnea, and sleep health, as well as social network data, will be collected using validated questionnaires. Anthropometric (weight, height, lean mass, and body fat) and T2DM-related (blood pressure, glycated hemoglobin A_{1c} [HbA_{1c}], total cholesterol, low-density lipoproteins, high-density lipoproteins, and triglycerides) clinical measures will also be obtained. During the intervention phase, participants will complete 6 months of medical nutrition therapy (MNT) alongside 1 member of their social network (eg, household member). In addition, participants will have the option to attend Dining with Diabetes program sessions that are offered at the county level through Cooperative Extension Service (Extension) agents. Follow-up data collection will include clinical measures, a dietary recall, and the assessment of participants' stage of behavior change at 3, 6, 9, and 12 months postintervention.

Results: This study was funded in November 2022 by the American Diabetes Association (ADA). Data collection started on September 1, 2023, and is projected to end in November 2025. We have enrolled a total of 48 participants in the study.

Conclusions: T2DM is a growing problem, particularly among vulnerable populations in rural Kentucky. This study plans to leverage family units as sources of social support with MNT and nutrition education through the Dining with Diabetes program. If effective, this approach will inform future family-based interventions in rural communities.

Trial Registration: ClinicalTrials.gov NCT06080425; https://clinicaltrials.gov/study/NCT06080425

International Registered Report Identifier (IRRID): DERR1-10.2196/69301

(JMIR Res Protoc 2025;14:e69301) doi:10.2196/69301

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KEYWORDS

type 2 diabetes mellitus; type 2 diabetes; intervention; family-based; physical activity; nutrition; rural; social support; self-care

Introduction

Background

Type 2 diabetes mellitus (T2DM) and obesity have a compounding effect on health disparities in rural communities in Kentucky. T2DM is a persistent public health condition affecting 34.1 million US adults [1]. Moreover, geographic disparities exist with some population segments, such as rural-dwelling Americans who experience greater vulnerability to this condition. The prevalence of T2DM in Kentucky's rural counties has reached 23%, compared to the overall state prevalence of 13.8% [2]. Moreover, in Kentucky, obesity and related conditions are among the highest in the nation, with approximately 40% of adults classified as obese, 40% with hypertension, and 38% with high cholesterol, while 30% meet physical activity recommendations, and 8.9% meet fruit and vegetable consumption recommendations [2,3].

The prevalence of T2DM increases with age, and an estimated 25% of older adults (≥65 years old) have T2DM [3,4]. The increased prevalence of T2DM among older adults is consistent with the increased prevalence of T2DM where an estimated two-fifths of older adults have obesity [5]. Even though residents in rural Kentucky communities are disproportionally affected by obesity and T2DM, they have poor social determinants of health, which contributes to and sustains poor health outcomes.

Environmental and behavioral factors are possible contributors to intergenerational obesity and T2DM in rural Kentucky communities. The literature indicates that patterns of obesity can be seen within families [6,7]. These patterns are thought to be due to the environments where people live, work, and play [8]. These environmental factors influence individuals' relationships with food within the family unit. Individuals raised in homes where unhealthy relationships with food have been developed are more likely to repeat these behaviors, thus increasing the potential for weight gain and obesity throughout the lifespan. Many of those with T2DM have at least 1 family member also with the condition, exhibiting a pattern of inheritance [9,10]. In addition, the likelihood of developing T2DM is 40% if one parent has T2DM and 70% if both parents have been diagnosed [11]. Familial links to diabetes via certain genetic factors and epigenetic changes have been noted [11]. However, those changes are mostly attributed to the environment and individuals' behaviors, demonstrating the complex relationship between gene expression and the environment. Specifically, T2DM has been linked to risk factors, such as unhealthy eating, a sedentary lifestyle, and stress [11]. Though gene expression modifications occur via epigenetics, those changes can be reversible through environment and behavior modifications [11].

Family-based interventions can be used to promote healthy and beneficial lifestyle behaviors [12]. With an estimated 59.7 million US residents living in multigenerational households [13], it is imperative we understand how this family structure impacts the health of its members. This type of family unit is particularly of interest in rural Appalachia since families share cultural health beliefs and health behaviors. In addition to intergenerational households, many families in rural eastern Kentucky live on the same piece of land passed through generations. Family-centered behaviors [14,15] have consistently influenced nutrition and overall health outcomes positively [16]. As disease management predominately occurs within the home, use of family-based interventions related to adult chronic diet-sensitive diseases have been associated with positive health-related outcomes [17-19]. Secure, supportive relationships with family or close friends improve personal management of these conditions. Thus, developing an intervention that enhances social support and mitigates environmental factors that hinder nutrition and physical activity is imperative for sustained behavior change.

The burden of T2DM and obesity can be alleviated with common self-care activities, specifically healthy eating and physical activity. This combination of self-care practices has been shown to be more effective than either alone. Both nutritional changes and increased physical activity are factors contributing to weight loss, which is an important aspect of obesity and T2DM management that improves health outcomes and reduces long-term health complications [20]. However, residents of rural Appalachian communities report inadequate diet and physical activity behaviors, a lack of access to nutritious foods and opportunities for physical activity, geographical isolation from health-promoting resources, and poorer health outcomes than the rest of the nation [21].

This project is informed by the National Framework for Health Equity and Well Being [22], which was recently developed by the Cooperative Extension Service (Extension), a trusted community entity identified as a critical resource to address health inequities in rural communities with limited infrastructure to support public health [23]. This framework explicitly acknowledges the multiple levels of influence on health outcomes and the role of the Extension as a mitigator of community-level health disparities and draws attention to health inequities at various societal levels, including root causes of structural inequity; norms, policies, and practices; and social determinants of health. As individuals flow through multiple sectors of environments that they live in, each has a direct influence individually and collectively. This research specifically focuses on how county-level Extension agents (federally mandated program) can be used to mitigate health disparities that contribute to intergenerational obesity and T2DM management in rural Kentucky. Community-level factors also impact health outcomes, such as a lack of access to nutritious, affordable food, as well as availability of health-related resources. In this study, community assets will be gathered using subjective and objective community audits and assessed at the participant level using social network analysis. Societal-level factors include social norms and cultural health beliefs that impact health decision-making within the community, particularly at the interpersonal level of families and households.

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Extension has a wealth of research- and practice-based programs that assist individuals throughout the lifespan to facilitate lifestyle changes that reduce chronic diet-sensitive conditions. As the largest providers of nutrition education in the country, Extension focuses on healthy eating, food security, physical activity, and obesity prevention [24]. This project intends to use the 4-session Dining with Diabetes education program offered in more than 25 states, including Kentucky. This program is nationally recognized, aligns with the Association of Diabetes Care and Education Specialists (ADCES) 7 Self-Care Behaviors, and increases self-efficacy for T2DM self-management [25-27]. This paper describes the protocol of Promoting Intergenerational Health in Rural Kentuckians With Diabetes (PIHRK'D), an intervention to determine whether leveraging family units as sources of social support promotes nutritional and physical activity changes among individuals with both overweight/obesity and T2DM and also to assess whether members of the household who engage in the intervention will show changes in anthropometric measures for an at-risk weight/body composition or maintain a healthy body composition.

Study Aims

The following are the aims of this study:

- Aim 1: Use social network analysis to describe (1) community assets (eg, access to healthy eating and ways to participate in physical activity) and (2) intergenerational links to obesity and diabetes (eg, parent, sibling, child).
- Aim 2: Deliver a tailored, household-specific nutrition therapy and physical activity plan.
- Aim 3: Determine the preliminary efficacy of tailored nutrition therapy and physical activity for those living within the household. The hypotheses for the third aim are that (1) participants (individuals with overweight/obesity and diabetes) will have a clinically meaningful change in HbA_{1c} (≥0.5%) and weight (≥–6%) and (2) members of the households will show improved anthropometric indicators of overweight/obesity or maintain a healthy weight.

Methods

Study Design

This longitudinal cohort study has been registered at ClinicalTrials.gov (NCT06080425; October 3, 2023). The study will test the feasibility, acceptability, and preliminary effectiveness of the proposed intervention. Analysis will be conducted at the individual level for the enrolled participants with T2DM and at the household level via cluster analysis. Study activities will occur in participants' homes and local Extension offices.

Ethical Considerations

The study was approved by the Institutional Review Board (IRB) of the University of Kentucky (approval number 83972; approval date August 1, 2023). Research staff members will obtain written informed consent from all participants meeting the inclusion criteria prior to study enrollment.

The principal investigator (PI) will ensure that all research personnel undergo Collaborative Institutional Training Initiative (CITI) training for conducting human subject research and gaining access to study data. The PI will monitor the study to ensure that all potential risks to participants remain minimal. In addition, all research personnel will be provided with a standard operating procedure manual that outlines recruitment strategies; the informed consent process, including study procedures, contact information for the University of Kentucky Office of Research Integrity, and the PI, study timeline, and an appendix of required data collection documents; and a copy of the most recent consent forms and IRB study approval letter.

Measures will be put in place to protect the confidentiality of participants and the data to be collected in this study. All data, including health information, will be deidentified to ensure the anonymity of the study participants and will be stored on password-protected servers at the University of Kentucky. To track participation over time, an enrollment log that includes participants' study IDs will be created, and only the study IDs (eg, deidentify) will be used when entering data into REDCap. Access to the study data will be restricted to authorized personnel directly involved in the research who will adhere to strict confidentiality protocols . Data and electronic records will be retained in accordance with regulatory and ethical standards for a minimum of 6 years post–study closure and then will be disposed of securely. All precautions will be taken to keep participants safe. Participants' personal information will be safeguarded, and explicit consent will be obtained before disclosing any potentially identifying information. To guard against a potential breach of confidentiality, all study files will be deidentified and kept on a password-protected secure server at the University of Kentucky. Study-related findings will be presented at scientific meetings and published in peer-reviewed journals. The research will also commit to full compliance with data protection laws, including the Health Insurance Portability and Accountability Act (HIPAA), reflecting an unwavering dedication to upholding the highest ethical and legal standards, while preserving the privacy and security of all participants.

The PI will invite the Office of Research Integrity to conduct mock audits on data collection and deidentification, encryption of audio files, and informed consent documentation to ensure research participants are properly protected. We will inform participants if we learn new information that could change their mind about continuing with the study. We may ask participants to sign a new consent form if the information is provided after they have enrolled in the study.

For each data collection time point that the participants complete, they will receive US $30 (baseline, 3 and 6 months, and 3 and 6 months postintervention). In addition, those participants who attend at least 3 of 4 sessions of Dining with Diabetes with a family member will receive a US $50 gift card. Family members who consent to participate and accompany participants will not receive any payment.

Eligibility Criteria

Community members interested in participating will be screened for eligibility to include adults (≥18 years old), diagnosed with T2DM, with more than 1 person in the household, and having

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their primary residence in the selected rural counties for at least 1 year. Adolescents (10-17 years old) will be permitted to participate in the study activities as family members but not as the main study participants. A trained research coordinator and research dietitian will obtain informed consent.

Intervention

The intervention phase of this feasiblity study consists of a 6-month nutrition therapy and physical activity intervention. The main component of this study is MNT, which will be used to tailor healthy eating and physical activity. Specifically, MNT has been shown to be an effective strategy to manage T2DM [28]. A research dietitian will conduct monthly in-home MNT sessions for members of the household, but the MNT will be tailored for participants who have overweight/obesity and T2DM. The research dietitian will meet with the household or at least the enrolled participant with T2DM monthly for 6 months. Dietary counseling will use motivational interviewing approaches and will focus on living with T2DM, appropriate and feasible food choices, glycemic control, the importance of weight management, and goal setting. In addition, the household will be provided with American Diabetes Association (ADA)-endorsed physical activity recommendations tailored to the participants' physical ability and their availability and access to opportunities for physical activity. The research dietitian's notes will be maintained for each session during the intervention. Notes will be maintained in the standardized framework of the Nutrition Care Process and the modified assessment, diagnosis, intervention, monitoring, and evaluation (ADIME) format.

As a supplement to MNT counseling and activity recommendations, participants will enroll in the group-facilitated Dining with Diabetes program at their local Extension offices. Participants will be encouraged to have a member of their household attend the Dining with Diabetes sessions with them in an effort to promote and reinforce healthy lifestyle choices. This program will be offered free of charge at the county Extension offices. Dining with Diabetes is an interactive 4-session program that includes direct education on healthy eating, food preparation strategies, physical activity, emotional health, identifying complications of diabetes, and problem-solving skills in a group setting. Each session provides participants with an opportunity to learn how to prepare and taste diabetes-appropriate recipes. Like MNT, each session of Dining with Diabetes encourages participants to set and discuss diabetes management-related specific, measurable, achievable, relevant, and time-bound (SMART) goals to improve overall health outcomes and address challenges faced with diabetes management. Existing evaluation tools for the Dining with Diabetes program will provide secondary data for this study. The pre- and postevaluation tools for this program measure knowledge gained related to food choices and physical activity, as well as motivation and confidence in managing diabetes. A 3-month follow-up evaluation is also provided with the program that measures sustainable behavior change related to food choices, preparing meals at home, and physical activity patterns. This program will be administered by Extension agents bimonthly, for 8 weeks, starting in month 2 of participant enrollment.

Extension agents are trained to offer Dining with Diabetes, with many choosing to regularly offer this program in their communities. This program was developed to be implemented by Extension, and previous studies have documented the effectiveness of the program in improving overall health metrics (eg, glycated hemoglobin A_{1c} [HbA_{1c}], hypertension) and increasing self-efficacy for diabetes self-management using Extension as a delivery mechanism [25,26]. See Table 1 for the schedule of enrollment, interventions, and assessments.

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Table 1. Schedule of enrollment, interventions, and assessments.

Time points	Enrollment study period		Intervention study period								Postintervention study period	
	$-t_1$	Baseline	t_1	t_{2a}	t_{2b}	t_{3a}	t_{3b}	t_4	t_5	t_6	t_9	t_{12}
Enrollment												
Eligibility screen	X[a]	—[b]	—	—	—	—	—	—	—	—	—	—
Informed consent	—	X	—	—	—	—	—	—	—	—	—	—
Intervention												
MNT[c]	—	—	X	X	—	X	—	X	X	X	—	—
Dining with Diabetes	—	—	—	X	X	X	X	—	—	—	—	—
Assessments												
HbA_{1c}[d] and blood lipids	—	—	X	—	—	X	—	—	—	X	X	X
Height	—	—	X	—	—	X	—	—	—	X	X	X
Body weight	—	—	X	—	—	X	—	—	—	X	X	X
Body fat	—	—	X	—	—	X	—	—	—	X	X	X
Lean mass	—	—	X	—	—	X	—	—	—	X	X	X
BMI	—	—	X	—	—	X	—	—	—	X	X	X
Blood pressure	—	—	X	—	—	X	—	—	—	X	X	X
24-hour dietary recall	—	—	X	X	—	X	—	X	X	X	X	X
Social network data	—	X	—	—	—	—	—	—	—	—	—	—
Demographics	—	X	—	—	—	—	—	—	—	—	—	—
IPAQ[e]	—	X	X	—	—	X	—	—	—	X	X	X
MOS[f] Social Support Survey	—	X	X	—	—	X	—	—	—	X	X	X
The Friends & Family Involvement in Adults' Diabetes	—	X	X	—	—	X	—	—	—	X	X	X
DDS[g]	—	X	X	—	—	X	—	—	—	X	X	X
Diabetes Empowerment Scale	—	X	X	—	—	X	—	—	—	X	X	X
DKQ[h]	—	X	X	—	—	X	—	—	—	X	X	X
DSMQ[i]	—	X	X	—	—	X	—	—	—	X	X	X

[a]Applicable.
[b]Not applicable.
[c]MNT: medical nutrition therapy.
[d]HbA_{1c}: glycated hemoglobin A_{1c}.
[e]IPAQ: International Physical Activity Questionnaire.
[f]MOS: Medical Outcomes Study.
[g]DDS: Diabetes Distress Scale.
[h]DKQ: Diabetes Knowledge Questionnaire.
[i]DSMQ: Diabetes Self-Management Questionnaire.

Outcomes

Anthropometry and point-of-care measures will be collected from participants at each data collection time point. Both the research dietitian and the research coordinator will be trained and will complete interrater reliability testing to complete data collection. Participants' height will be assessed through a portable Seca stadiometer. Their body weight, body fat, lean mass, and BMI will be collected via the Tanita DC-240 Total Body Composition Analyzer. Their blood pressure will be measured with the ADC e-sphyg Digital Aneroid Sphygmomanometer. Cholestech LDX (Cholestech Corp., Hayward, CA) and HbA_{1c} Now+ Analyzers will be used to measure blood lipids and HbA_{1c}, respectively.

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Sample Size

Power analysis for aim 3 was based on a total of 75 recruited participants, with an 80% retention rate, resulting in an analytic sample of 60 participants. The detectable effect size for a change in the primary outcome over time was Cohen f=0.14 at 80% power with 2-sided α=.05. This model assumes that a completely within-subject design with 5 testing occasions a first-order autocorrelation where r=0.5. Thus, with a total sample size of 60 participants, we would be powered to detect a small-to-medium effect.

Recruitment

Recruitment started on September 1, 2023, and will be conducted via Extension offices, local media (eg, newspaper, radio public service announcement [PSAs]), word-of-mouth, social media, University of Kentucky Healthcare outpatient clinics (eg, internal medicine, family medicine, endocrinology), and the United Kingdom's Barnstable Brown Diabetes and Obesity Center. Participants will be screened by the research dietitian to confirm obesity/overweight and T2DM diagnosis and identify each participant's placement within the Transtheoretical Model (Stages of Change): precontemplation, contemplation, preparation, action, maintenance, or relapse [29]. The Enrollment Stage of Change will be used to develop appropriate goals for each participant. The research coordinator will enroll the participants in the study. Beyond the primary enrolled participants, members of the participants' households will be invited to attend meetings with the dietitian and Dining with Diabetes program sessions. Household members will be screened for eligibility to include adults (≥18 years old), a diagnosis of T2DM, and the primary residence in the selected rural counties for at least 1 year. Adolescents aged 10- 17 years will be permitted to participate in the study activities as household members and not as the main study participants. To enhance participants' buy-in and sustainability, the research dietitian will use motivational interviewing principles [30] to work with them to improve self-efficacy of behavior change and set SMART goals each month [31].

Data Collection and Management

Data Collection Overview for Primary Participants

Demographics collected will include age, sex, race/ethnicity, marital status, and insurance status. In addition, 24-hour dietary recalls will be used to assess dietary intakes throughout the intervention by the research dietitian. The recalls will include 2 weekdays and 1 weekend day. Dietary recalls will be entered into the Automated Self-Administered Dietary Assessment (ASA-24) tool managed by the National Cancer Institute. ASA-24 uses a multipass method for capturing dietary recall data. From the collected data, Healthy Eating Index-2015 (HEI-2015) scores will be calculated. The HEI-2015 scores (0%-100%) will depict the quality of the diet in comparison to the Dietary Guidelines for Americans (DGA), with a higher percentage indicating higher alignment with DGA recommendations.

Validated surveys will be used to assess self-care activities and psychosocial factors pre- and postintervention. The International Physical Activity Questionnaire (IPAQ) short form will be used to collect physical activity data. [32] The IPAQ is a validated, self-reported, 6-item tool that collects weekly activity, resulting in a total activity score per week in Metabolic Equivalent Task (MET) minutes, with further categorization of high, moderate, or low activity levels. The following diabetes-related psychosocial factors and behaviors will also be collected through validated tools:

- Social support: The Medical Outcomes Study (MOS) Social Support Survey uses a 5-point Likert scale to score items related to perceived social support [33], and the Friends and Family Involvement in Adults' Diabetes is a 16-item measure that assesses how helpful and harmful family members'/friends' involvement in adults' T2DM self-care is [34].
- Diabetes distress: The Diabetes Distress Scale (DDS) is a 17-item scale that measures patient concerns about disease management, support, emotional burden, and access to care. The response scale for each question ranges from 1 ("not a problem") to 6 ("a very serious problem"). An average score of ≥3 indicates moderate distress and discriminates between high- and low-distress groups [35].
- Empowerment/self-efficacy: The Diabetes Empowerment Scale is a 23-item scale that measures diabetes-related psychosocial self-efficacy and uses 3 subscales: Managing the Psychosocial Aspects of Diabetes, Assessing Dissatisfaction and Readiness to Change, and Setting and Achieving Diabetes Goals [36].
- Diabetes knowledge: The Diabetes Knowledge Questionnaire (DKQ) is a 24-item survey that has a reliability coefficient of 0.78 and shows sensitivity to a diabetes knowledge intervention. In addition, it targets knowledge deficits that can be related to measurable outcomes, false statements, or common or serious misconceptions [37].
- Diabetes self-care activities: The Diabetes Self-Management Questionnaire (DSMQ) is a 16-item questionnaire to assess self-care activities associated with glycemic control and has an internal consistency of 0.84 [38].

Participants will not be removed from the study for nonadherence to the study protocol. In addition, if any participant chooses to leave the study early, data collected until that point will remain in the study database and will not be removed, but the participant will be discontinued from the study activities, such as medical nutrition therapy (MNT) sessions, and the participant will not be compensated for any sessions after removal from the study. Finally, if a participant indicates that their participation in the study is causing them distress, the PI will telephone the participant within 24 hours to see how they are managing and may suggest they contact their primary care provider. In the event the participant does not have a primary care provider, the PI will offer them a list of appropriate referral sources if they wish. In addition, to avoid future incidents, each case of possible distress will be reviewed with the PI and appropriate members of the investigative team, including a review of study materials and responses to distressed participants. This review will evaluate whether any aspect of the study requires modification.

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Data Collection Overview for Family Members

Demographics data for family members will include age, sex, race/ethnicity, marital status, and insurance status. Diabetes status (diagnosed diabetes, prediabetes, no diabetes) will be confirmed via point-of-care HbA_{1c} tests at baseline, and overweight/obesity will also be evaluated during baseline data collection. Family members will have the option to participate in MNT sessions, as well as attend the 4-week Dining with Diabetes program with the primary participants. Consistent with data collection of the primary participants, medications and anthropometric and point-of-care data will be collected at baseline, 3 and 6 months during the intervention phase, and 3 and 6 months postintervention. Data will be collected by the research coordinator and research dietitian, as outlined before.

Statistical Analysis

Community Assets Social Setwork Analysis

We will use an egocentric approach of social network analysis to understand the availability of resources within a 10-mile radius of each participant's home. Frequencies, proportions, and means will be determined, where appropriate, for each network for the following components: network size, closeness, and density. For each participant, 2 social networks will be mapped, perceived (participant) and objective (research coordinator).

Intergenerational/Familial Diabetes and Obesity Social Network Analysis

Frequencies, proportions, and means will be determined, where appropriate, for each network for the following components: network size, age, number of female alters in a network, number of males in a network, closeness, and proportion of the participant's network who are overweight/obese and have been diagnosed with prediabetes or diabetes.

Analysis of Clinical Outcomes

HbA_{1c} and weight will be assessed for the primary study participants using a longitudinal linear mixed model. Linear mixed models, an extension of the general linear model, are suitable when the independence of observations assumption is violated, which occurs when individuals are measured repeatedly over time. The primary outcomes will be HbA_{1c} values and weight measured at the 4 postbaseline follow-up points, each separated by 3 months, with a specific focus on the first postintervention follow-up point. In this hypothesis, "clinically meaningful" is defined as a ≥0.5% reduction in HbA_{1c} or a ≥6% reduction in weight. The main fixed effect of interest will be the categorical predictor of time, centered at the baseline testing occasion. To better understand how HbA_{1c} and weight change across the duration of the study, a significant overall effect of time will be followed up by comparing the adjusted means at adjacent time points (eg, baseline vs 3 months, 3 months vs 6 months, and so on). Additionally, the nature of change over time will be further characterized through the inclusion of polynomial trends (eg, quadratic functions). These tests will be adjusted for multiple comparisons using the Benjamini-Hochberg adjustment [39]. The model will incorporate random effects to account for repeated measures of individuals using an autoregressive covariance matrix to model the random effects. Since this is an observational, nonrandomized study, a set of baseline covariates (eg, age, weight, sex, race/ethnicity) will be used to control for demographic and other background trait characteristics.

Anthropometric indicators of family members presenting with overweight/obesity or a sustained healthy body composition will also be tested using a longitudinal linear mixed model. The primary outcome will be weight, measured at the follow-up testing occasions, with a specific focus on the first postintervention follow-up point. The main fixed effect of interest will be the categorical predictor of time. This analysis will include an additional set of random effects in addition to existing ones to account for repeated measures of participants, since family members are nested within the household, modeled using an unstructured covariance matrix. This analysis will include covariates at both the household (eg, family structure characteristics) and the individual (eg, age, gender) level to control for participant and household trait factors.

Results

This study was funded in November 2022 by a Nutrition & Diabetes Innovative Clinical or Translational Science (ICTSN) Research Award through the ADA, who played no role in the study design; collection, management, analysis, or interpretation of data; writing of this report; or the decision to submit for publication. Data collection started on September 1, 2023, and is projected to end in November 2025. A total of 48 participants have been enrolled, and recruitment has ended; in addition, 14 (29%) of those participants have completed the intervention.

Discussion

Summary of Anticipated Findings

It is expected that participants will have a clinically meaningful change in HbA_{1c} (≥0.5%) and weight (≥–6%), as they will have participated in MNT and Dining with Diabetes, both of which have been shown to improve diabetes-related clinical outcomes [25,26,28]. It is also hypothesized that members of the participants' households will have improved anthropometric indicators of overweight/obesity or maintain a healthy weight, as they are participating in the intervention and as the use of family-based interventions related to adult chronic diet-sensitive diseases have been associated with positive health-related outcomes [17-19].

Strengths and Limitations

One strength of this study is the use of a family-based intervention to assist participants diagnosed with T2DM, as these interventions can facilitate health eating and physical activity in both participants and family members. Another strength of this study is that study activities are conducted in the home environment or at Extension offices, providing a more accurate representation of the family system. Lastly, combining MNT, a clinical approach, with Extension, a community-based approach, to offer chronic disease management education is a strength as it allows for an opportunity to translate research into practice and provide positive behavior change.

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The limitations of this study include the pre-post design, which leads to difficulty in establishing causality, and other confounding variables could be contributing to the outcomes. Another limitation is that these results are from rural Kentucky participants and may not be generalizable to other rural areas within the United States or nationally.

Conclusion

This is a feasibility study, so there is no need to randomize participants to the intervention. Data collected on the feasibility and acceptability of leveraging family units as sources of social support with MNT and nutrition education through the Dining with Diabetes program, along with the intervention workflow and efficacy, will help refine the research for a large-scale study that would be randomized to show the intervention's effectiveness. The study-related findings will be presented at scientific meetings and published in peer-reviewed journals.

Acknowledgments

This study is supported by the American Diabetes Association (grant number 11-22-ICTSN-24).

Data Availability

BLS will have access to the final trial dataset and study-related materials. All data resulting from the American Diabetes Association–funded research that can be shared without compromising human subject protections will be shared to an approved open data repository within 6 months of publication or within 18 months of the conclusion of the funding period, if the study remains unpublished. The datasets generated or analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

BLS obtained funding and designed the study. BLS, MBP, HNB, CM, and BH contributed to the design of the study. BLS and CLO assisted with drafting the manuscript. BLS, MBP, HNB, CM, BH, AT, and OL critically revised the manuscript for intellectual content. All authors have approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report by the American Diabetes Association.
[PDF File (Adobe PDF File), 154 KB - resprot_v14i1e69301_app1.pdf]

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Abbreviations

ADA: American Diabetes Association
ASA-24: Automated Self-Administered Dietary Assessment
DDS: Diabetes Distress Scale
DGA: Dietary Guidelines for Americans
DKQ: Diabetes Knowledge Questionnaire
DSMQ: Diabetes Self-Management Questionnaire
Extension: Cooperative Extension Service
HbA_{1c}: glycated hemoglobin A_{1c}
HEI-2015: Healthy Eating Index-2015
IPAQ: International Physical Activity Questionnaire
IRB: Institutional Review Board
MNT: medical nutrition therapy
MOS: Medical Outcomes Study
PI: principal investigator
SMART: specific, measurable, achievable, relevant, and time-bound
T2DM: type 2 diabetes mellitus

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Protocol

Using Linked Health Service Data in Multimodal Modeling of Kidney Transplant Waitlist Outcomes: Protocol for the Maximizing Organ Donor Utility Systemwide (MODUS) Study

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Abstract

Background: Increasing deceased organ donation is a worldwide priority constrained by concerns of inadvertent transmission of cancer or infectious diseases from deceased organ donors. Up to 60% of potential donors referred for consideration for deceased organ donation in Australia do not proceed due to biovigilance concerns.

Objective: We aim to describe the impact of accepting or declining potential donors foregone for biovigilance concerns on patient and transplant outcomes.

Methods: The MODUS (Maximizing Organ Donor Utility Systemwide) study will use data for patients ever waitlisted for kidney transplantation and all potential donors referred for consideration for deceased organ donation. First, we will use binational data from the Australian and New Zealand Dialysis and Transplant Registry 2010-2020 to describe and evaluate factors impacting the current patient journey on the kidney transplant waitlist, including episodes of suspension and reactivation, time waiting, and whether transplanted. Second, we will quantify the time from offer decline to deceased donor transplantation and the impact of the intersectional disadvantage on the waiting time after decline for patients on the waitlist using flexible parametric survival models. Third, the MODUS study will use an established dataset of outcome data for all candidates for deceased organ donors referred to the New South Wales (NSW) Organ and Tissue Donation Service (OTDS) in 2010-2020 to describe donor referral risk profiles and determine any potential donor gains that could be made through better access to donor information at the time of decision-making, more accurate estimation of the absolute biovigilance risk, and varying of the acceptable biovigilance risk thresholds for accepting donors. Lastly, we will use the estimates derived from the first 3 aims as inputs for health economic models, where, using cohort- and individual patient-level simulations, we will quantify the impact of varying donor referral decisions on health care costs, quality-adjusted survival, the time on the waitlist, and the time to a kidney transplant.

Results: Linked health data were received in 2023. Data analysis is ongoing, and results will be disseminated at scientific conferences, published in the scientific media, and published via collaborator networks in 2025.

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Conclusions: The MODUS study will provide evidence of the individual-level and health service effects of increasing acceptance of deceased donor kidneys that would otherwise be declined due to biovigilance concerns. Specifically, we expect to report our findings on improvements in overall patient survival and quality of life by increasing the number of waitlisted people transplanted from donors with an acceptable biovigilance risk who are currently foregone. We will also report on the cost-effectiveness of a potential "informed biovigilance strategy" versus current practice. In doing so, we will develop evidence to support policy and complex clinical decisions in Australia's organ donor referral process with potential worldwide application.

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KEYWORDS

kidney failure; transplant waitlist; organ allocation; biovigilance; population study; health economic evaluation

Introduction

Kidney failure is a leading cause of morbidity and mortality. Worldwide, the number of people on dialysis or with a kidney transplant has more than doubled since 1990 [1]. In 2010, over 4.9 million people worldwide had kidney failure, of which 2.6 million were on dialysis or had a kidney transplant [2]. Kidney transplantation is the preferred treatment for kidney failure as it increases patient survival, improves the quality of life, and is more cost-effective than dialysis, making it a compelling option for those who are suitable [3]. In Australia, kidney transplantation rates have steadily increased; despite this, demand continues to outweigh donor supply [4]. Increasing opportunities for kidney transplantation through deceased organ donation is, therefore, a worldwide and national priority [5].

To access a deceased donor kidney transplant in Australia, people on dialysis must be assessed as eligible for transplantation to enter the deceased donor waitlist [6]. Potential transplant recipients must understand and accept inherent risks from the procedure and ongoing treatment and have a high likelihood of significant benefits from transplantation to be eligible. Risk-benefit assessments are conducted by a multidisciplinary team that reviews clinical and surgical factors, mental health, social circumstances, and impacts. Any significant risk of death from comorbidity (eg, heart disease, cancer, infection) is a contraindication for transplant, and patients will not be eligible for the deceased donor waitlist. When a donor kidney becomes available, all waitlisted patients are considered by the national organ allocation algorithm, designed to find an immunologically compatible match, while also prioritizing those who have waited the longest or who are under 18 years. The algorithm stratifies matches by blood group and balances the time spent waiting with the degree of donor-recipient matching nationally and by state of donor origin to generate a list of potential donor-recipient pairs in ranked order. In Australia, the time spent waiting is measured from initiation of dialysis to account for delays in reaching the active waiting list due to medical issues or delayed transplant suitability assessment and to ensure the sense of fairness prioritized by consumers [7,8]. At the end of 2019, there were 1100 Australians on the deceased donor kidney transplant waitlist, with a median wait time of 1-4 years and a transplant rate of 7 per 100 years on dialysis [4].

Prior research has focused on factors impacting access to the waiting list or transplantation and subsequent posttransplant health outcomes [9-11]. However, the time spent waiting is underexplored. Kidney transplant waitlists are dynamic and change daily as new people are added and existing people are transplanted or become unwell and so are temporarily or permanently removed from the kidney transplant waitlist or die while waiting [12]. Patients can enter a variety of clinical states after being initiated onto the waitlist, impacting their experiences. Intercurrent illness, surgery, or investigations may necessitate temporary suspension or permanent removal from the waiting list. It has not been described how events occurring after waitlisting impact equitable access to transplantation.

In 2009, the Australian government established a national program to increase capability and capacity within the health system to maximize organ donation rates [5]. Since 2009, the number of deceased organ donors has more than doubled in Australia [5]. Deceased organ donation is coordinated by the Organ and Tissue Authority, which has devolved to a national network of state-based donation specialist agencies called Organ and Tissue Donation Services (OTDSs). In Australia, New South Wales (NSW) has the greatest number of people waiting for a kidney transplant than other states and territories, as well as a more complex service delivery compared to other jurisdictions. Where some states have 1 kidney transplanting center, NSW has 8. Potential donors are identified by NSW hospitals and referred to the NSW OTDS for consideration for deceased organ donation (Figure 1) [13]. A donation specialist coordinates a thorough investigation, including medical history and assessment of the donors' medical suitability for donation, while also seeking consent for a donation from their next of kin. Potential donors who meet the medical suitability criteria and have consenting next of kin (intended donors) enter the national allocation algorithm to be matched with kidney transplant candidates. Those who do not meet the medical suitability criteria or who were not accepted by transplant centers are considered potential donors foregone. Those who undergo surgery for organ retrieval are considered actual donors, even if their organs are not eventually transplanted.

Improvements in donation rates in Australia have occurred unevenly. NSW has the greatest number of donors each year nationally. However, donation rates have not improved as much as in other states when standardized for population size (Figure 2) [13]. Furthermore, despite significant increases in potential donors referred to the NSW OTDS, our prior work has shown that the proportion of actual donors has increased at a much slower rate (Figure 3) [13]. Nationally, less than 42% of

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potential donors proceeded to actual donations in 2020 [5]. In NSW, only 22% of potential donors proceed to actual donation [14]. Improving donation in NSW, Australia's most populous state, would greatly impact national donation levels and outcomes for people on the kidney transplant waitlist.

Preventing the transmission of donor-derived infectious diseases or cancer (biovigilance) is a central concern in transplant programs. Donor medical suitability assessment is based on the perception of the biovigilance risk a donor poses. Evidence of an infectious disease, current or historic malignancy, and behaviors that increase the risk of blood-borne viruses is often obtained indirectly from hospital records, primary care records, family members, or friends. There is varied access to past medical records and limited possibilities to confirm risk within the donor assessment time frame for deceased donors. In this context, the actual risk of disease transmission may be unconfirmed, and transplant clinicians make recommendations and decisions under conditions of uncertainty. Donation decisions for deceased donor organs are time sensitive and may vary among clinicians. We have demonstrated previously that even when clinicians correctly interpret clinical information related to biovigilance, their recommendations of donor suitability may be inconsistent [15]. Furthermore, many of the surveyed clinicians were found to be risk averse when making donor decisions for their patients, even when the blood-borne virus risk of transmission from donor to potential recipient was <1:10,000 [15]. Further opportunities exist to increase the deceased donor pool among those currently excluded due to biovigilance concerns.

Our prior work has identified several potential missed opportunities for deceased organ donation in NSW. Of over 3000 potential donors referred between 2010 and 2015, approximately 10% had increased risk behaviors for blood-borne viruses (hepatitis B, hepatitis C, and HIV), but the majority were deemed not medically suitable for organ donation without specific testing to confirm or refute virus exposure [16]. Those potential donors who were tested showed a <1 in 100,000 risk of having the disease. Similarly, 29% of potential donors who were deemed not medically suitable due to their perceived risk of cancer transmission had a tumor with a low risk of transmission when verified by cancer registry records, and the use of their organs for transplantation would have been within clinical transplantation guidelines [17]. The inclusion of potential deceased organ donors with a low risk of disease transmission but currently foregone as donors may increase the donor pool and opportunities for transplantation. However, the potential impact of such practice changes and the downstream impact on the kidney transplant waitlist, patient outcomes, and health care costs are unknown.

Figure 1. Schema of the NSW deceased organ donor referral process. NSW: New South Wales.

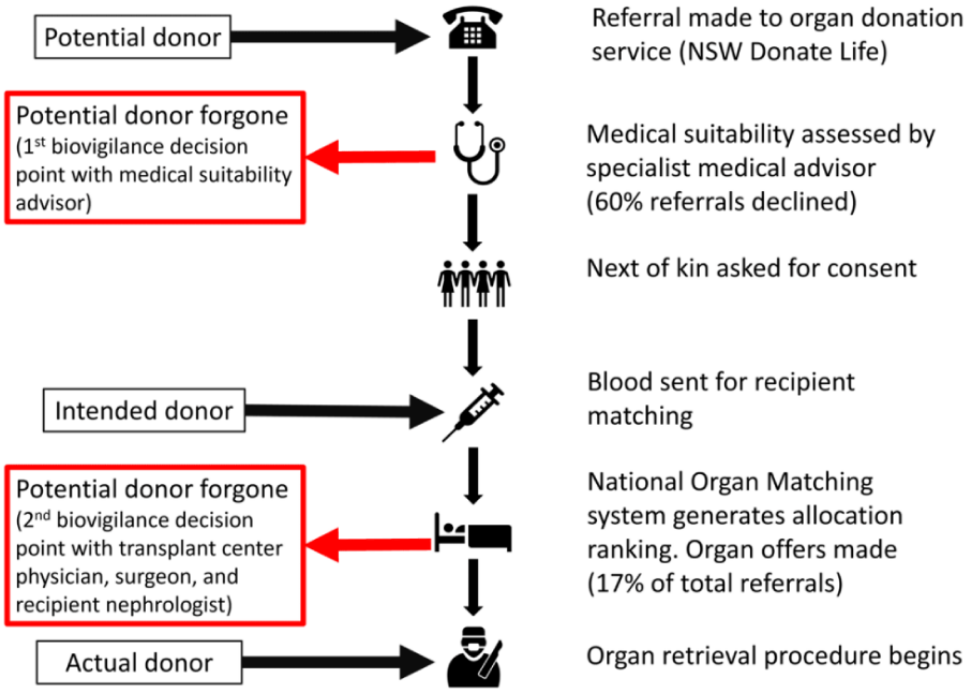

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Figure 2. Deceased kidney donor activity by Australian state over time, per million population, 2012-2023. ACT: Australian Capital Territory; NSW: New South Wales; NT: Northern Territory; QLD: Queensland; SA: South Australia; TAS: Tasmania; VIC: Victoria; WA: Western Australia.

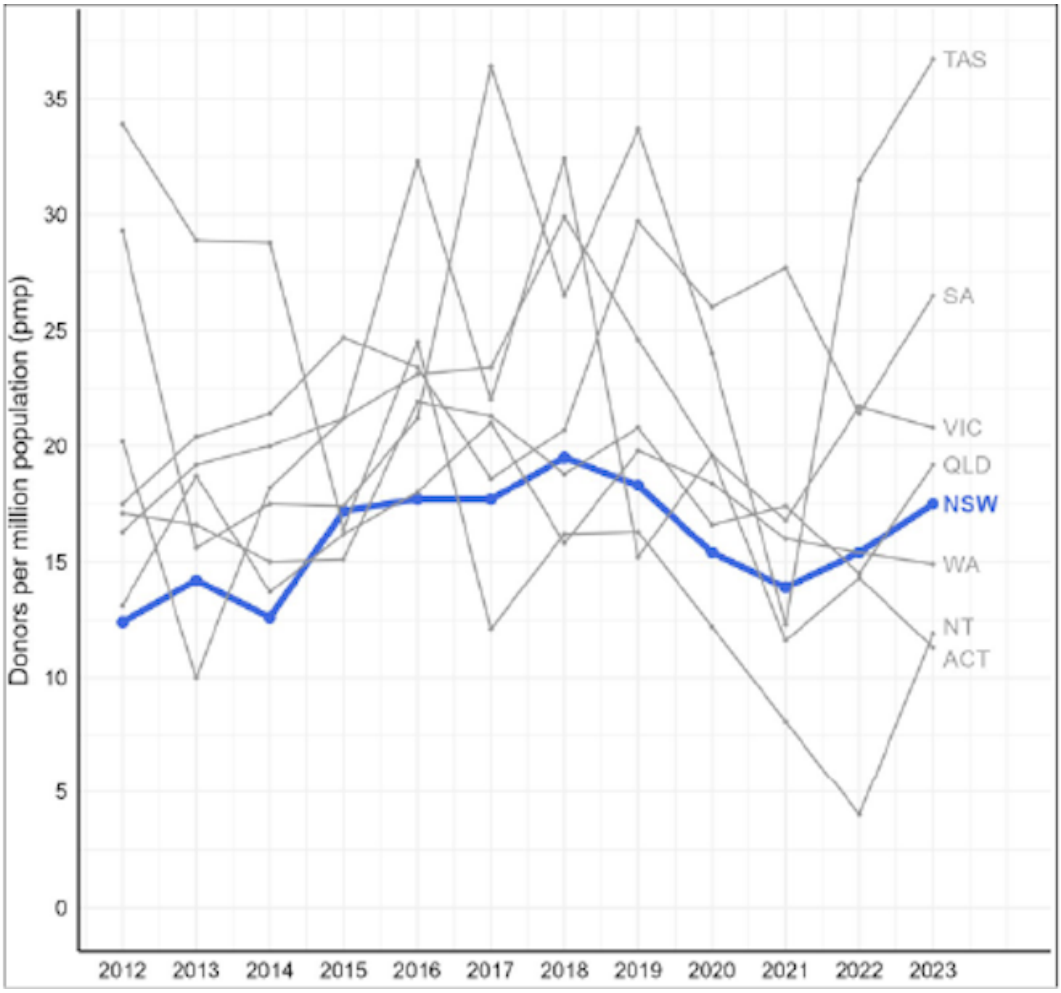

Figure 3. Number of deceased organ donor referrals who proceeded (actual donors) versus the number referred to the NSW OTDS for consideration for donation (potential donors) in NSW, 2010-2024. NSW: New South Wales; OTDS: Organ and Tissue Donation Service.

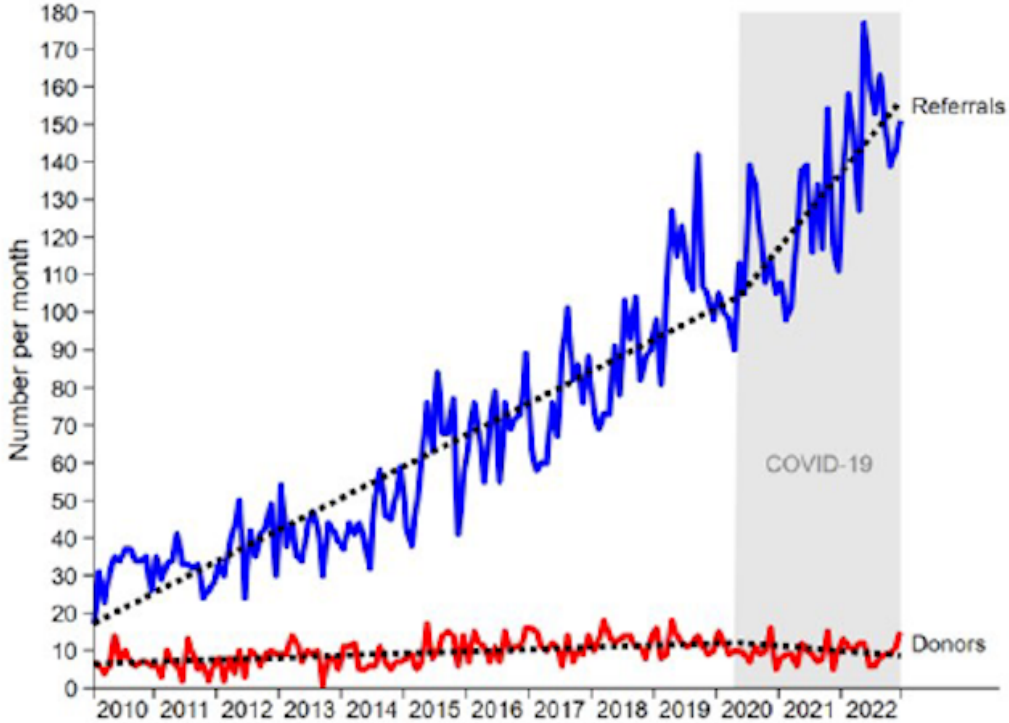

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In this study, we aim to investigate whether increasing kidney donor acceptance can improve access to kidney transplants for people with kidney failure in 4 related projects:

- Kidney transplant waitlist dynamics: Using binational individual-level data, we will describe and evaluate factors impacting the current patient journey on the kidney transplant waitlist, including all clinical transitions: suspension and reactivation, death before transplant, and transplantation.
- Impact of donor decline for patients on the kidney transplant waitlist: Using our linked data as the cohort study platform, we will use flexible parametric survival models to quantify the time from offer decline to deceased donor transplantation and the impact of the intersectional disadvantage on the waiting time after decline for patients on the kidney transplant waitlist.
- Deceased donor profiling: Using our linked data as the cohort study platform, we will describe donor referral risk profiles and determine any potential donor gains that could be made through better access to donor information at the time of decision-making, more accurate estimation of the absolute biovigilance risk, and varying of the acceptable biovigilance risk thresholds for accepting donors.
- Economic modeling of increased donor acceptance: Using health economic models (cohort- and individual patient-level simulations), we will quantify the impact of varying donor referral decisions on health care costs, health benefits (quality-adjusted survival), and efficiency measures (time on the waitlist and time to a kidney transplant).

Methods

Study Design

The MODUS (Maximizing Organ Donor Utility Systemwide) study will use a variety of existing data sources and methods to investigate (1) kidney transplant waitlist dynamics, (2) the impact of declining a first donor offer on patients on the kidney transplant waitlist, (3) deceased organ donor biovigilance risk profiles, and (4) the health care costs and benefits of increased deceased organ donor acceptance. All analyses will be performed using STATA, R and TreeAGE software.

Kidney Transplant Waitlist Dynamics

We will include all people who entered the kidney transplant waitlist for their first transplant between July 1, 2010, and December 31, 2019, in NSW from the Australian and New Zealand Dialysis and Transplantation Registry (ANZDATA) and OrganMatch. ANZDATA is a collaborative disease registry collecting clinical and treatment information about people undergoing dialysis or transplants for kidney failure from all treatment centers in Australia and New Zealand, updated annually since 1977. OrganMatch is a clinical transplant system that facilitates compatibility matching of recipients and donors for organ transplantation and maintains the kidney transplant waiting list. We will exclude those who had multiorgan transplants (eg, kidney + pancreas). Our study follow-up will be from waitlist entry until death, or December 31, 2019.

We will build a multistate model of the kidney transplant waitlist and use this to describe waitlist dynamics and evaluate all clinical transitions after entering the waitlist. Clinical states will include active on the kidney transplant waitlist, temporary or permanent suspension, kidney transplant (deceased donor, living donor, and paired kidney exchange donor), and death before transplant. We will exclude people who were already active on the waitlist (ie, prevalent cases). Posttransplant clinical states will include graft failure, return to dialysis, and re-entry into the waitlist for subsequent transplant. We will evaluate patient factors associated with health state transitions after waitlist entry. Patient factors selected a priori include sex, age at waitlist entry, ethnicity, comorbidity burden, and cause of kidney failure. Specifically, we will estimate transition intensity hazard ratios to indicate whether a transition is more or less likely to occur based on patient factors. Transitions of interest include waitlist entry to suspension, suspension to return to waitlist, suspension to death before transplant, and waitlist entry to transplant.

Impact of Donor Decline for Patients on the Kidney Transplant Waitlist

Using the ANZDATA and OrganMatch linked data detailed before, we will investigate patients who entered the kidney transplant waiting list in NSW from 2010 to 2020. We will use records of ranked offers for every actual donor against potential recipients. Using records of which donor-recipient pairs were accepted, we will determine which donor-recipient pairs were offered but declined by transplant teams. We will use logistic regression to estimate the odds ratios of decline of the first donor-recipient paired offer by prespecified clinically relevant recipient characteristics, including blood group, sex, age, ethnicity, immunological sensitization by panel reactive antibody (PRA), and comorbidities. Subsequent outcomes after the decline of the first offer will be examined, including the time to the next offer, the time to the next better offer (measured as the next donor offer with improved an kidney donor profile index [KDPI]), the number of offers to transplant if transplanted, the rate and duration of the time spent suspended from the list, receiving a transplant (deceased or living donor), and death. The time from decline to transplantation will be examined, by patient characteristics, using Kaplan-Meier curves and the restricted mean survival time. We will use flexible parametric survival models to examine the time from decline to deceased donor transplantation for patients with different characteristics and to make adjusted predictions on the time from decline to transplantation, evaluating the impact of the intersectional disadvantage for patients with different sociodemographic and clinical characteristics. Finally, we will assess whether the decline of the offer leads to the subsequent transplant of a better-quality kidney; KDPIs of declined kidneys will be compared to those of accepted kidneys using the sign test for matched pairs.

Deceased Donor Profiling

To profile donors, we will use an established dataset that contains outcome data for all candidates for deceased organ donors referred to the NSW OTDS from January 1, 2010, to December 31, 2020, including those who proceeded to donation (actual donors), were deemed suitable for donation but never

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proceeded (intended donors), and were foregone for medical unsuitability (potential donors foregone) [14].

We will investigate potential donors foregone who were deemed not medically suitable in NSW. Specifically, we will summarize prespecified demographic and clinical characteristics, including age, sex, blood group, comorbidities, and the calculated Australian KDPI, of all consented potential donors and compare those declared medically unsuitable for donation with those who did proceed to donation. We will summarize the given reasons these potential donors did not proceed to donate. Lastly, we will determine the proportion of potential donors foregone due to concerns around medical suitability but who were also of better or the same quality as those who proceeded to donate, overall and by calendar year.

Economic Evaluation of Increased Donor Acceptance

To quantify the impact of varying donor acceptance on health care costs, benefits, and efficiency, we will use individual-level simulation-based Markov models to compare the cost-effectiveness of the shift in clinical practice that encourages increased use of potential donors with specific biovigilance concerns but who are within current guidelines (eg, history of cancer or increased risk of infectious diseases, including blood-borne viruses) in the Australian health care setting. We will adopt a payer (Australian government) perspective. Biovigilance risk thresholds for acceptance of deceased organ donors will follow prevailing clinical guidelines [6]. Health states included in our analysis include being active on the kidney transplant waitlist, being suspended from the waitlist, having a functioning kidney transplant, transplant failure and return to dialysis, death from kidney failure, and death from other causes, as well as health states specific to cancer or blood-borne viruses.

The transition of kidney patients through different health states over a lifetime time horizon will be simulated based on transition probabilities over 3-month time periods (Markov cycles) derived from the published literature. Health outcomes will be measured in terms of life-years gained and quality-adjusted life years (QALYs) gained, which incorporates both the length and the quality of life (scale 0-1, where 0=death and 1=full health), based on the published literature. Costs will be measured in Australian dollars using data obtained from the Medicare Benefits Schedule, the Pharmaceutical Benefits Scheme, and relevant unit pricing based on Australian-Refined Diagnosis Related Group codes and the Independent Hospital Pricing Authority Net Efficient Price. A discount factor of 5% per year will be applied to costs and health outcomes, as per Australian government recommendations [18] of 2016 and Medical Services Advisory Committee recommendations of 2021 [19].

The cost-effectiveness of the shift in clinical practice to accept deceased donor organs with varying biovigilance risks, the risk of cancer, and the risk of blood-borne virus transmission aligned with current guidelines will be compared with the current practice, where these donors are typically declined. Cost-effectiveness will be measured as a ratio of incremental costs to incremental QALYs expressed as an incremental cost-effectiveness ratio (ICER) [20] or net monetary benefit. A willingness-to-pay threshold will be determined based on estimates from the literature per QALY gained and used to interpret the ICER. A strategy will be interpreted as cost-effective if the ICER is less than the willingness-to-pay threshold per QALY gained. Sensitivity analyses will be conducted using varying willingness-to-pay thresholds.

We will use individual-level simulation models to overcome some of the limitations of cohort-based Markov models, as well as to incorporate prespecified individual recipient and donor characteristics [21,22]. Recipient-level characteristics, such as age, sex, blood group, number of previous kidney transplants, dialysis vintage, and comorbidities, and donor characteristics, such as age, sex, donor type (donation by brain or circulatory death), and Australian KDPIs, will be used. We plan to undertake distributional cost-effectiveness analysis, a framework to incorporate health inequality impacts into the cost-effectiveness analysis comparing shifts in the clinical practice to accept deceased organ donors with an increased risk of cancer and blood-borne virus transmission with the current practice where these donors are typically declined [23]. The model structure and analyses will follow best-practice modeling guidelines from the International Society for Pharmacoeconomics and Outcomes Research [24]. Comprehensive deterministic and probabilistic sensitivity analyses will be conducted to account for all parameter uncertainties in the models.

Consumer Engagement

The MODUS study has been designed with input from peak consumer organizations and key stakeholders in the delivery of Australia's organ donation and transplantation service. Our research partners have been integral to the development of this study protocol; the NSW Ministry of Health has underwritten the Biovigilance Public Health Register and will contribute to outcome development, and the NSW OTDS will contribute expertise and help fidelity through close relationships with medical suitability advisors and transplanting hospitals; Kidney Health Australia has provided an ongoing vital consumer liaison. Increasing opportunities for transplantation are a priority for people with kidney disease. Our consumer liaisons will advise on project development, interpretation of results, and dissemination strategies for research findings.

Ethical Considerations

This study was approved by the University of Sydney Human Research Ethics Committee (project number 2020/828). ANZDATA obtained approval for the collection and secondary analysis of data of all patients included in the study by the Royal Adelaide Hospital Research Ethics Committee (approval number HREC/17/RAH/408R20170927). A waiver of consent was provided for data obtained from the NSW OTDS, as all participants were deceased. All data provided to research staff were deidentified to maintain patient privacy and confidentiality.

Results

The MODUS study was funded by the National Health and Medical Research Council (APP1171364) in December 2018. We received the linked health data from the Centre for Health Records Data Linkage in May 2023. We received data for 20,818 individuals, 3812 patients ever entered on the kidney

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transplant waitlist, and 8707 potential donors referred for consideration for deceased organ donation. Since October 2024, data analysis is ongoing for the 4 MODUS study aims. Study findings will be disseminated between 2025 and 2026 as the analysis for each project is completed.

Discussion

Summary

The MODUS study hypothesizes that increasing the acceptance of deceased kidney donors who are currently declined due to biovigilance concerns will lead to significant improvements in health outcomes for people with kidney failure. Specifically, the study anticipates that increased donor acceptance will increase the number of kidney transplants, reduce kidney transplant waiting times, and improve overall patient survival and quality of life. In addition, we hypothesize that increasing donor acceptance will also prove to both benefit patients with kidney failure and be cost-effective.

Our work is expected to generate critical evidence to support policy and practice changes: detailed insights into the factors influencing patient transitions on the kidney transplant waitlist, including suspension, reactivation, and transplantation; quantification of the time from donor offer decline to transplantation and the impact of the intersectional disadvantage on waiting times; identification of potential donor gains through improved access to donor information and more accurate biovigilance risk assessments; and evidence of the cost-effectiveness of increasing donor acceptance, measured in terms of health care costs, QALYs, and efficiency metrics.

Comparison With Prior Work

Previous research has primarily focused on factors affecting access to the kidney transplant waitlist and posttransplant outcomes. However, the MODUS study will extend beyond this scope of work to uniquely address the underexplored area of waitlist dynamics and the impact of deceased donor offer declines. By integrating binational data and advanced statistical models, this study will provide a comprehensive analysis that extends beyond the scope of prior work. Additionally, the economic modeling component will offer a novel perspective on the cost-effectiveness of policy changes in organ donation.

Organ donation systems vary significantly across countries, impacting donation rates and transplant outcomes. For instance, Spain's opt-out system has led to one of the highest organ donation rates worldwide, with 46 deceased donors per million population [25]. In contrast, countries such as the United States and Australia, which primarily use opt-in systems, have lower donation rates. The MODUS study's findings could inform the potential benefits of adopting more inclusive donor acceptance criteria, similar to Spain's approach, to increase donor pools and improve transplant outcomes.

Strengths and Limitations

Our study will use linked and registry-based health service data from multiple sources to provide robust estimates of patient and health service outcomes to inform our health economic assessment of interventions that could increase deceased organ donor acceptance. Yet, most of these data were not collected for research purposes and so may not contain granular patient information that could provide further insights, such as reason for kidney transplant waitlist suspension. There may also have been changes in clinical practices and donor referral processes during our look-back period that could impact our analyses. However, deceased organ donor trends and transplant outcomes have remained relatively stable over time. In addition, there may be missing data where we would use a complete case approach or multiple imputation. Our study's findings are highly relevant to the Australian context, but their applicability to other health care systems may be limited. The likelihood of physicians using the tools developed in the MODUS study will depend on several factors, including usability, feasibility, and user preferences. The study includes plans to assess these aspects during development to ensure successful implementation. Engaging with health care professionals through surveys and focus groups will help refine the tools and ensure they meet clinical needs. Training programs and integration with existing clinical workflows will also be essential to promote adoption.

Dissemination Plan

The findings of the MODUS study will be disseminated through multiple channels to ensure a broad reach and impact. We will present results at national and international scientific conferences to engage with both academic and clinical communities. We will submit research manuscripts to peer-reviewed journals to contribute to the scientific literature, prioritizing open access journals. We will also share our findings with our listed partner organizations (the NSW OTDS) and external stakeholders (the Australian Organ Transplant Authority and Kidney Health Australia) to facilitate knowledge transfer and plan appropriate interventions for implementation.

Conclusion

The MODUS study aims to provide compelling evidence that increasing the acceptance of deceased donor kidneys, currently declined due to biovigilance concerns, can significantly improve patient outcomes and be cost-effective. By addressing critical gaps in the understanding of kidney transplant waitlist dynamics and donor profiling, this study has the potential to inform policy and practice changes that enhance organ donation and transplantation processes, ultimately benefiting patients with kidney failure.

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the responsibility of the authors and in no way should be seen as an official policy or interpretation of ANZDATA or the NSW OTDS.

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Data Availability

The data that support the findings of this study are not publicly available due to their containing information that could compromise the privacy of research participants, but summary-level data may be available from the Collaborative Centre for Organ Donation Evidence (CODE), University of Sydney, upon reasonable request. The data collated for this study are under the management of the New South Wales Ministry of Health as a Public Health Register.

Authors' Contributions

BMR and KS contributed equally as the first authors of this manuscript. ACW and RLM were responsible for the conception and design of the MODUS (Maximizing Organ Donor Utility Systemwide) modeling study and the initiation of stakeholder collaborations. NDM, JB, and JH provided expertise in developing the described statistical analysis plans and data requirements. AR is a consumer coauthor and has provided their perspective on idea generation and study conception. AR, PC, MW, KW, and PK provided expertise on the manuscript, study design, and critical intellectual content. This work has been published on behalf of the MODUS Study Group: Prof Kirsten McCaffery, Dr Danielle Muscat, Prof Claire Vajdic, Dr Elena Cavazzoni, Prof Henry Pleass, Prof Nicholas Cross, Ms Rhonda Holdsworth, Prof Shilpanjali Jesudason, and Prof William Rawlinson.

Conflicts of Interest

None declared.

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Abbreviations

ANZDATA: Australian and New Zealand Dialysis and Transplantation Registry
ICER: incremental cost-effectiveness ratio
KDPI: kidney donor profile index
MODUS: Maximizing Organ Donor Utility Systemwide
NSW: New South Wales
OTDS: Organ and Tissue Donation Service
QALY: quality-adjusted life year

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Protocol

Examining Potential Implicit Bias in Oncologist-Patient Communication (CONNECT): Protocol for an Observational 2-Site Study

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Abstract

Background: Compared with White patients, minoritized patients (Black and Hispanic patients) have a higher incidence of advanced solid cancers and have a higher mortality. These patients also report poor patient-centered communication and worse pain assessment and management. Although many factors contribute to these disparities, physician implicit bias may be a contributing factor.

Objective: The primary goal of this study is to evaluate the role of implicit bias among oncologists and examine the impact on racial or ethnic differences in objective assessments of communication with minority patients with advanced cancer.

Methods: To accomplish this goal, we plan to recruit 65 oncologists and 325 patients (5 patients per oncologist) with advanced solid cancer from ambulatory cancer clinics within the diverse settings of the Mount Sinai Health System in New York City and the Duke University Health System in Durham, NC. We audio record patient-oncologist encounters during a postimaging visit, with 3 encounters for each of the patients. We will analyze the recorded visits and compare the patient-centered communication content of these conversations. Immediately after the recorded visit (no more than 2 weeks later, in order to minimize recall bias), patients are required to complete a follow-up survey to evaluate patient-centered outcomes. A 3-month follow-up survey is used to assess pain levels and control, use of analgesics, and psychological distress. A 6-month follow-up survey is used to assess psychological distress. We administer the Implicit Association Test to oncologists to assess their level of implicit bias toward patients who identify as Black or Hispanic after we finish recording patient encounters.

Results: Funding from the National Cancer Institute was received in March 2021. Patient and oncologist recruitment began in March 2022. We have recruited all 65 oncologists in the study, and patient recruitment is ongoing. The study team plans to continue to enroll patients until March 2025. As of December 2024, we have enrolled 245 patients. We expect to publish the findings in October 2026.

Conclusions: In this paper, we outline the study methods, describe the development of a codebook to assess pain conversations being used to evaluate primary and secondary outcomes, and discuss challenges and lessons learned throughout the study.

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KEYWORDS

oncology; communication; oncologist-patient communication; audio-recorded encounters

Introduction

Compared with White patients, minoritized patients (Black and Hispanic patients) have a higher incidence of advanced solid cancer and have a higher mortality rate [1,2]. Although many factors contribute to such disparities, physician implicit bias may be a contributing factor [3]. Moreover, disparities have been reported in the outcomes of minoritized patients with advanced solid cancer [4,5]. Rather than improving over time, these inequities have been widening [6]. Multiple studies have shown that minority patients with advanced cancer have inadequate discussions about treatment, prognosis, and goals of care [7,8] and are more likely to have suboptimal pain assessment and management [9]. These disparities translate into substandard cancer treatment, worse quality of life, and poorer survival among these patients than among White patients [4,5,9-12]. Thus, there is a critical need to address these gaps for patients with advanced cancer. Although patient- and system-level factors contribute to cancer disparities, physician-related factors, such as limited cultural competence and bias, also likely play relevant roles. Unlike the rare case of explicit bias, implicit bias occurs at an unconscious, unintentional level, where people make judgments about others based on their groups, rather than considering them as individuals. Although many researchers have discovered race disparities in communication [13], few have examined the role of implicit bias, a potentially modifiable factor. As such, 2 Institute of Medicine reports, *Unequal Treatment* and *Relieving Pain in America*, strongly recommend evaluation of the role of implicit bias in disparities [3,14]. However, almost no researchers have examined bias in oncology encounters.

The impact of implicit bias on the outcomes of ethnic minority patients with advanced cancer may be associated with different mechanisms. Minority patients have reported poor patient-centered communication (eg, respecting and responding to patients' wants, needs, and preferences), which can influence assessments, recommendations, and outcomes [15]. Implicit bias could be an underlying barrier to patient-centered communication, thus increasing the chance that ethnic minority patients receive care that is not standard or discordant with preferences and values, which can lead to less satisfaction with care [16-18] and increased psychological distress [19]. Additionally, there are disparities in pain assessment and management, which may also be related to the implicit bias of physicians [3]. Most previous studies specifically examined bias toward Black people as compared to White people [20], and only 4 studies included Hispanic people [20]. Further, most studies had a small number of participants and were focused on trainees (ie, medical students or residents) and not physicians in practice [21,22]. Prior research has focused on Black, noncancer populations and primarily used hypothetical patient vignettes [17,18]. However, significant knowledge gaps exist regarding the role of implicit bias in actual communication. Building on our prior research [23], we propose to confirm the extent of implicit bias among oncologists and examine how it affects objective and subjective outcomes, such as discussions of pain, pain control, and pain management, along with patient satisfaction with communication and psychological distress among ethnic minority patients with advanced cancer. This study will collect one of the largest datasets of conversations between oncologists and Black and Hispanic patients to date and will serve as the foundation for an intervention for oncologists and cancer patients. The specific aims of this study are to (1) evaluate the association of oncologists' implicit bias with racial or ethnic differences in objective assessments of patient-centered communication in oncologist-patient encounters; (2) examine the association of oncologists' implicit bias in explaining racial or ethnic differences in the subjective outcomes of psychological distress and satisfaction with communication among patients with advanced solid cancer; and (3) assess if implicit bias explains racial or ethnic disparities in oncologists' assessment of pain, use of guideline-concordant pain management, and pain control among patients with advanced solid cancer.

Methods

Ethics Approval

This study has been reviewed by the Icahn School of Medicine Protection of Human Subjects/Institutional Review Board (PPHS/IRB) and the Duke University Health System (DUHS) IRB, and it has been determined that the study procedures are in accordance with ethical standards for experiments on human subjects (Study-21-00396/IRB Pro00108633). We obtain informed written consent using an IRB-approved informed consent document. Subjects are free to withdraw from participation in the study at any time upon request. To preserve subject confidentiality, subjects are assigned coded study ID numbers. Using these study ID numbers, none of the collection forms will contain the names or medical record numbers of the subjects or other personal identifiers. We pay participants for their time and effort (enrollment [visit 1]: US $30, visit 2: US $15, and visit 3: US $15).

Overview

This study is a prospective 2-site observational trial that examines postscan encounters between oncologists and their patients with advanced solid cancer who have a prognosis of less than 2 years. We plan to enroll 65 oncologists and approximately 325 patients (4-7 patients per oncologist; with relatively equal proportions of those who identify as White, Black, and Hispanic) seen at outpatient cancer clinics at the Mount Sinai Health System (MSHS) and DUHS. We collect up to 21 audio recordings of encounters per oncologist, with 3 encounters for each of the 4-7 patients, and code the audio-recorded encounters.

Oncologist Recruitment

Study recruitment has occurred in waves over the past 3 years. We have introduced oncologists to the study and approached them during clinician meetings or individually. Oncologists are

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eligible if they provide care to patients with advanced solid cancer at MSHS or DUHS for at least a half-day per week and will continue practicing at either facility for at least 1 year.

Patient Recruitment

Before patient recruitment, the study staff had visited clinics to introduce the study to the clinic staff. This study includes patients with advanced solid cancer who are 21 years or older; are on active treatment (ie, chemotherapy, targeted therapy, and immunotherapy); identify as Black/African American, White, or Hispanic; are English-speaking; and are scheduled for a postscan visit. Patients are excluded if they are diagnosed with more than one malignancy (except for nonmelanoma skin cancer) in the last 5 years. Patients are identified via the electronic health record (EHR; both sites use Epic) from the schedules of consented oncologists and are sent a letter from their oncologist describing the study, with an opt-out number for declining to participate in the study. We attempt to recruit equal numbers of White, Black, and Hispanic patients.

Data Collection

Oncologists

We obtain oncologists' consent either through paper consent in the clinic by the study staff or via email through REDCap. We collect oncologist baseline surveys (see Multimedia Appendix 1) prior to the enrollment of the first patient via REDCap. We also collect a postencounter survey (see Multimedia Appendix 2) from oncologists after 1 of the 3 audio-recorded encounters. These surveys assess demographics, practice characteristics and patterns, and opioid prescription practices. After recording all encounters for the oncologists, we assess implicit bias using the Implicit Association Test (IAT) [19], which evaluates the level of implicit bias toward those who identify as Black or Hispanic. The IAT measures the strength of the association between concepts and stereotypes or evaluations [19]. We send oncologists a REDCap link with their IAT test. In a recent meta-analysis, 14 of 15 studies identified the existence of implicit bias against minorities among health professionals [24].

Patients

After sending recruitment letters, we call, email, or text potentially eligible patients to screen them. After the staff determine that patients are eligible (see Multimedia Appendix 3), we obtain consent either electronically via email through REDCap or in person during their encounter. We ask them to complete a baseline survey (see Multimedia Appendix 4) before their appointment and audio record their encounter. We use an innovative process of collecting all data on an iPad and implement a temporary lock on the iPad to prevent stopping or editing of the recording. Patients are required to complete a postaudio survey (see Multimedia Appendix 5) immediately after their appointment to assess pain levels and control, use of analgesics, ease of access to opioids, use of navigation or care coordination services, psychological distress, and satisfaction with communication. We store all consent forms, surveys, and audio recordings in REDCap. We clean and transcribe the audio recordings.

Outcomes

Our primary outcome is patient-centered communication, which we assess from coding audio-recorded encounters, open questions, reflective statements, empathic responses to empathic opportunities, and eliciting questions. Our secondary outcome involves discussions of pain, use of guideline-concordant pain management, and pain control, as well as satisfaction and psychological distress among patients with advanced solid cancer. We assess this through coding discussions of pain and goals of care conversations in audio-recorded encounters and postencounter surveys completed by patients after their postscan visit.

Data Analysis

To assess if implicit bias causes, in part, racial disparities in patient-centered communication, we use multilevel structural equation modeling, which allows for simultaneously examining several regression-type relationships while accounting for latent variables. Specifically, we assess models of complete versus partial mediation by comparing constrained models (direct effects constrained to zero) with unconstrained models that allow for partial mediation [25].

We use 3 established codebooks and 1 newly developed codebook with definitions and examples for each code. These codes include measures of patient-centered communication, goals of care, and pain. Four teams of 2 coders each code all transcripts for our primary and secondary outcomes. Coders listen to the audio-recorded encounters between the oncologists and their consented patients to record instances of goals of care conversations, discussions of patient-perceived pain, discriminatory behaviors, patient participatory behaviors, and effective communication skills (eg, open questions and empathic statements). All 8 coders are trained by the investigator through reviewing audio recordings until interrater reliability is achieved. Interrater reliability is achieved by ensuring that each coder is coding with at least 80% similarity to the other coder on their team. All teams are monitored regularly by the investigators.

The first codebook includes aspects related to our primary outcome (open questions, reflective statements, empathic responses to empathic opportunities, and eliciting questions) [26] and the REMAP (reframe, empathic opportunity, map out patient values, align with values, and propose a plan) framework for the goals of care conversations (eg, aligning with patient values and prognosis) [27]. The second codebook includes 6 global ratings for oncologist communication (ie, flow, attentiveness, warmth, respect, concerns, and rushed) and 1 global rating for patient communication (eg, guarded open). The third codebook includes codes for patient-perceived discriminatory behaviors (eg, stereotyping) [28] and patient participatory behaviors (eg, question asking and assertive responses) [29]. The fourth codebook includes codes assessing discussions of pain between the patient and oncologist (eg, initiates pain discussions, perceived impact of pain, and associated symptoms). Prior to the creation of the fourth codebook, the team used 2 frameworks (the SHARE [seek, help, assess, reach, and evaluate] approach [30] and the SOCRATES tool for clinical pain assessment [31]) to conduct a qualitative data analysis by coding 30 transcripts for discussions of pain,

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which allowed them to establish codes for the codebook based on common elements.

Statistical Power and Sample Size

To detect the effect size (relative risk of 0.80; proposed 20% difference) and assume an equal size of both groups, we need approximately 323 patients to find differences in our primary outcome, effective communication, which involves open-ended questions, reflective statements, empathic responses to empathic opportunities, and eliciting questions. We assume that enrolled patients of the same physician will be correlated, and the level of intraphysician or intracluster correlation will be low to moderate. We assume a 20% difference for the primary outcome of the 4 communication behaviors (aim 1) between minorities (Black and Hispanic people) and nonminorities based on our pilot and the literature demonstrating similar differences in patient-centered communication for Black and Hispanic people [17]. Assumptions regarding psychological distress and satisfaction with communication (aim 2) and the distribution of pain outcomes (aim 3) have been drawn from our prior studies or the literature [20,32]. We assume that all patients should have their pain assessed. As stated in the literature, pain management (requiring opioids) and pain control will be applicable to 80% of enrolled patients. Assuming a range of intraphysician or intracluster correlations from 0.001 to 0.010, power ranges from 0.81 to 0.99 indicate sufficient power to detect the effect of implicit bias for Black versus White people and Hispanic versus Black people regarding patient-centered communication, pain outcomes, psychological distress, and satisfaction with communication.

Results

This study received funding from the National Cancer Institute in March 2021. Patient and oncologist enrollment began in March 2022. We have recruited all 65 oncologists in the study, and patient recruitment is ongoing. Due to a lack of diversity among oncologists at both MSHS and DUHS, almost all enrolled oncologists identify as non-Hispanic White. There are 8 clinics located at DUHS and 8 at MSHS: gastrointestinal, sarcoma, melanoma, neuro-oncology, thoracic, breast, genitourinary, gynecologic, and head and neck. The study team plans to continue to enroll patients until March 2025. As of December 2024, we have enrolled 245 patients. We expect to publish the findings in October 2026.

Discussion

Principal Considerations

We anticipate that we will find that implicit bias among oncologists causes racial and ethnic differences in patient-centered communication and is associated with higher levels of psychological distress and lower levels of satisfaction with communication. We also anticipate that we will find that implicit bias among oncologists causes racial and ethnic gaps in pain assessment, which can lead to poor perception of pain control among minority patients with advanced solid cancer. Our findings will deepen our understanding of relationships among implicit bias, communication processes, management, and patient outcomes. This study is innovative because we assess implicit bias among oncologists who treat Hispanic patients and examine the goals of care over time using multiple postscan visits and audio recordings. No other team has assessed how the goals of care conversations evolve over multiple encounters. We outline the limitations and solutions below.

Limitations

Limitation #1: Incomplete Number of Recordings Being Collected From Each Patient

We planned to obtain 3 audio recordings per patient to assess how the goals of care conversations change over time as the disease potentially progresses. However, we encountered difficulties in recording 3 encounters as some patients entered hospice or died.

Solution #1: Modifying Expectations for Analysis

We assessed the goals of care conversations at the first audio-recorded visit for all participants and realized that we would only be able to examine changes over time in a subset of patients. Given the prevalence of patients becoming too sick to continue participating, we are not replacing recordings.

Limitation #2: Difficulty Identifying Scans and Cancer Stage

Staff at the MSHS experienced challenges identifying eligible participants, specifically those with advanced cancer coming for a postscan visit, as the data were not readily available in the patient's EHR. Unlike the DUHS, where the EHR includes stage information, at the MSHS, the EHR does not include this information, and thus, a labor-intensive manual review of all scheduled patients is needed. The manual review not only introduces a considerable workload for the staff but also poses a risk of oversight or delays in identifying eligible participants. The complexity of this task is compounded by the inherent variability in how medical information is recorded and cataloged within the EHR, making the identification of specific criteria, such as cancer stage, a labor-intensive and error-prone process.

Solution #2: Implementing Machine Learning–Based Approaches

To address this challenge, we are implementing a machine learning–based solution leveraging large language modeling. This approach offers several advantages over manual review. First, it eliminates the need for labor-intensive manual chart reviews, reducing the workload for staff and mitigating the risk of oversight or delays in identifying eligible participants. Additionally, by leveraging natural language processing techniques, the model can account for the inherent variability in how medical information is recorded and cataloged within the EHR, enhancing accuracy and efficiency in identifying specific criteria such as cancer stage. Furthermore, by integrating this solution into existing workflow systems, such as appointment scheduling software, we can automate the identification process, providing real-time eligibility screening for scheduled patients. This not only streamlines the recruitment process but also enables proactive identification of eligible participants, allowing for timely intervention and enrollment in the research protocol.

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Limitation #3: Advanced Practice Providers and Fellows Have Postscan Conversations With Patients Instead of Oncologists

Oncologists at both sites had postscan conversations with advanced practice providers (nurse practitioners and physician assistants) and oncology fellows in practice. During instances where advanced practice providers and fellows see patients along with the consented oncologists, the oncologists might not say much in the encounter. Having multiple health care professionals in these encounters impedes the study's objective of specifically recording conversations between patients and their oncologists who are enrolled in the study.

Solution #3: Making Requests to Oncologists, Fellows, and Advanced Practice Providers in Advance

When possible, the study coordinator emails oncologists in advance of the scheduled encounter. Often, oncologists agree to see the patients for the postscan conversation instead of their advanced practice providers or fellows. Third-party consents are obtained from advanced practice providers and fellows who may be a part of the recorded conversation.

Limitation #4: Differences in Racial or Ethnic Characteristics in the Patient Panels of Consented Oncologists

Our goal is to recruit 5-6 patients per oncologist. The DUHS currently has an equal number of Black and White patient participants recruited for the study owing to a low number of Hispanic patients who meet the eligibility criteria. Some oncologists see more Black patients than White patients, while others see more White patients than Black patients. At the MSHS, there is a higher number of patients who identify as Hispanic.

Solution #4: Meeting the Goals for Racial and Ethnic Diversity Across Sites

Due to the low number of eligible Hispanic patients at the DUHS, we are oversampling Hispanic patients at the MSHS. At the DUHS, the study team has been recruiting 3 Black patients and 3 White patients per oncologist, where possible. There have been some oncologists who see more Black patients and those who see fewer. We compensate for this by overrecruiting Black patients for some oncologists.

Conclusion

This is one of the first studies to examine the goals of care over time in a diverse sample of patients with advanced solid tumors. A more in-depth understanding of the reasons underlying the disparities in care will be an important step toward improving the outcomes of over 65,000 minority patients diagnosed with advanced cancer each year. The knowledge generated by our project could inform both oncologist-level and patient-specific interventions.

This study aims to evaluate the role of oncologists' implicit bias in racial and ethnic disparities in patient-centered communication, psychological distress, satisfaction with communication, pain assessment, and pain management among patients with advanced solid cancer. By collecting one of the largest datasets of conversations between oncologists and Black and Hispanic patients to date, this study lays the groundwork for developing interventions aimed at improving communication and care delivery. The significance of this study lies in its potential to deepen our understanding of the complex relationships among implicit bias, communication processes, management strategies, and patient outcomes. The findings generated by this project have the potential to inform both physician-level educational programs and patient-specific activation interventions, ultimately contributing to the reduction of disparities in cancer care.

In summary, this study has far-reaching implications for advancing equitable cancer care and underscores the importance of addressing implicit bias in health care delivery. By identifying and addressing barriers to effective communication and care, we can strive toward achieving better outcomes for all patients, regardless of race or ethnicity.

Acknowledgments

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Data Availability

This study is being conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH-funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive PubMed Central upon acceptance for publication.

Authors' Contributions

Writing – reviewing & editing: VCKD, KIP, CBS, BNR, ANA, RMT, MLA
Conceptualization: CBS, KIP
Writing – original draft: VCKD
Supervision: CBS, KIP, JAM, VCKD

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Funding acquisition: CBS
Project administration: CBS, KIP

Conflicts of Interest

CBS has received speaker fees from GSK and AstraZeneca and honoraria from Elevance Health. All other authors have no conflicts of interest to disclose.

Multimedia Appendix 1
Clinician baseline survey.
[DOCX File , 200 KB - resprot_v14i1e66086_app1.docx]

Multimedia Appendix 2
Clinician postencounter survey.
[DOCX File , 934 KB - resprot_v14i1e66086_app2.docx]

Multimedia Appendix 3
Patient prescreener survey.
[DOCX File , 362 KB - resprot_v14i1e66086_app3.docx]

Multimedia Appendix 4
Patient baseline survey.
[DOCX File , 1509 KB - resprot_v14i1e66086_app4.docx]

Multimedia Appendix 5
Patient postaudio survey.
[DOCX File , 617 KB - resprot_v14i1e66086_app5.docx]

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Abbreviations

DUHS: Duke University Health System
EHR: electronic health record
IAT: Implicit Association Test
IRB: institutional review board
MSHS: Mount Sinai Health System

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Protocol

Association Between Hair Trace Element Content and Children's Growth and Development: Protocol for a Cross-Sectional Surveillance Study

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Abstract

Background: Western Kazakhstan, a major industrial region, faces environmental challenges from the release of toxic elements due to intensive industrial activities. The combined impact of anthropogenic factors, trace element deficiencies, and harsh climatic conditions contributes to the deterioration of child health and growth.

Objective: This study aimed to investigate the elemental profile of the child population in the western region of Kazakhstan.

Methods: A total of 2279 school-aged children (aged 5 to 18 years) who are permanent residents of the Aktobe, Mangystau, Atyrau, and West Kazakhstan regions will be included in the study using a cluster sampling method. The elemental composition of their hair will be analyzed using inductively coupled plasma mass spectrometry on an Agilent 8900 inductively coupled plasma mass spectrometer (Agilent Technologies). Children's physical growth will be assessed according to the World Health Organization (2007) growth standards and characterized using the following *z* score values: body weight for age for children aged younger than 10 years, height for age, and BMI for age. The cutoff points of *z* score values make it possible to diagnose thinness, stunting, overweight, or obesity. Multiple linear regression analysis will be applied to assess the association between chemical element content in hair and *z* score measures of children's physical growth, as well as associations with gender, age, sociodemographic factors, and residential status. Reference values for chemical element content in biological substrates of the western Kazakhstan population will be established using 95% coverage intervals with 95% CIs following International Union of Pure and Applied Chemistry recommendations. The chemical element content will be reflected in a web-based atlas.

Results: After recruitment of participants, data will be collected between September 2023 and March 2025. Data processing and analysis will be completed in September 2025. Publication of the results is expected in December 2025. An analysis will be conducted to determine the differences in the levels of elements in groups of boys and girls, urban and rural children, and groups of children of different ages. According to the results of multiple regression analysis, chemical elements influencing the indicators of the physical development of children will be identified.

Conclusions: The identified associations between trace and macroelement content and children's growth indicators will allow for the development of region-specific public health measures, such as nutritional supplements, environmental remediation, and policies aimed at reducing exposure to toxic elements. In addition, identifying differences between rural and urban populations could inform the development of targeted prevention strategies. The developed web-based atlas of trace and macroelement content will be necessary for further research on the prevalence, etiology, risk factors, and possible mechanisms of development of environmentally dependent, endemic diseases in the region. Reference values of trace and macroelement content will also be established.

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KEYWORDS

trace elements; child health; child development and growth; children; Kazakhstan

Introduction

Background

The physical growth of children is defined as the irreversible and permanent increase in size, whereas development refers to the enhancement of psychomotor abilities. Both processes are largely influenced by genetic, nutritional, and environmental factors. Physical development is also shaped by socioeconomic conditions, family characteristics, malnutrition, and micronutrient deficiencies [1].

For optimal physical growth and development in children, adequate intake of trace and macroelements is essential. Insufficient intake of essential and conditionally essential elements can disrupt normal physical growth and mental development in children [2]. For instance, selenium plays a critical role in protecting cells from oxidative stress, maintaining resistance to infectious agents, and regulating tissue growth and differentiation processes [3].

Zinc is involved in key biological processes, including cell growth and differentiation, gene expression, and protein synthesis. Zinc deficiency can lead to growth retardation, impaired innate and adaptive immunity, and disrupted regeneration processes [4]. Moreover, zinc is closely associated with indicators of physical development and growth in children [5].

Iodine is an essential microelement required for the production of thyroid hormones. Iodine deficiency can result in goiter, hypothyroidism, miscarriage in pregnant women, stillbirth, congenital anomalies, infant and neonatal mortality, and growth failure. Adequate thyroid hormone levels are crucial for normal growth and the development of the nervous system during fetal development, infancy, and childhood [6].

In contrast, toxic metals, as environmental factors, negatively affect the physical development of children. Research indicates that arsenic, cadmium, and lead adversely influence growth and development at various ages. While lead has been shown to negatively impact cognitive development in children, the effects of mercury on physical development remain less understood [7].

Western Kazakhstan is the largest industrial region in the country. The operation of metallurgical, chemical, and oil industry enterprises, as well as the extraction of oil shale, potassium-magnesium salts, limestone, cement raw materials, chalk, expanded clay, and construction sand, results in the release of toxic chemical elements into the environment. This region is classified as a boron and chromium biogeochemical province, and iodine deficiency is endemic.

The combined effects of anthropogenic factors, deficiencies in vital trace elements, and the unfavorable climatic and geographical conditions in which much of the population of Western Kazakhstan resides contribute to a decline in health at both the individual and population levels [8-10].

The tense ecological situation on the territory of western Kazakhstan contributes to shifts in the trace element balance of the biosphere. The bioelement background of the living environment is reflected in the bioelement status of the human organism, leading to the deterioration of public health. Children are highly vulnerable to environmental pollutants, including toxic trace elements, which is why they are a key focus of environmental and public health research [11,12]. They are more negatively affected by toxic elements due to their behavioral patterns: they live and play closer to the ground, and they put their hands and objects in their mouths [13,14]. They consume more food, water, and air per unit of body weight than adults and have a higher absorption rate from the gastrointestinal tract [15,16]. Toxic and potentially toxic elements negatively impact children's development and health [17]. In addition, given the antagonistic and synergistic interactions between elements, excessive intake of essential trace and macroelements can also have negative consequences [17,18].

Recently, the number of studies assessing the elemental profile of the pediatric population has increased in various regions of the world, including Europe [11,12,18-26], Asia [27-34], North America [35-37], South America [38-40], Africa [17,41,42], and Australia and Oceania [43,44]. Many of these studies have found a link between the characteristics of the elemental profile and various factors, including the geochemical characteristics of the area of residence (eg, natural and anthropogenic contamination of areas with certain chemical elements) [22,45-47], diet [22,45,48-51], drinking water consumption [11,17,49], lifestyle [30,42,52,53], gender [17,21-25,38,54,55], age [22,54], and social differences [42,52]. Some studies focus on the relationship between the chemical element content in biological samples and children's health indicators [45,48,56,57].

Our study is the first large-scale study of the elemental profile of the child population in Kazakhstan. Data on the chemical element content of the adult population are presented in our previous work [58,59]. However, reference intervals have not been calculated for the child population. Studying the relationship between element content and growth indicators will enable the identification of the impact of the environment and nutrition on children's health in the region, which is necessary for effective risk assessment, early detection of micronutrient imbalances, and the development of measures to improve children's health in western Kazakhstan. Creating a digital atlas accessible to all that reflects the trace element content will enable early prenosological diagnostics of diseases and the adoption of preventive measures to eliminate elemental imbalances in western Kazakhstan.

Our scientific hypothesis is that elemental profile is associated with indicators of physical growth in the child population of

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the western region of Kazakhstan. The chemical element content in the biosubstrates of the child population differs between rural and urban residents.

Objectives

Our aim is to investigate the elemental profile of the school-aged children population living in the industrial western region of Kazakhstan.

The objectives of this study are as follows: (1) to assess the elemental profile of children in rural and urban areas, identify regional characteristics, and establish reference values for the chemical element content in the hair of children considering age and gender; (2) to evaluate the relationship between the chemical element content in hair and the physical growth and development of children in western Kazakhstan; (3) to develop maps illustrating the elemental profile of the child population in the western region of Kazakhstan; (4) to compare the elemental profile of children with that of the adult population to analyze ontogenetic changes in the concentration of chemical elements in the hair of western region residents; and (5) to compare the results of chemical element analysis in the hair of children from the western region with previously published data on other populations.

Methods

Research Design

This is a 1-stage, cross-sectional descriptive study (Figure 1). It will be conducted in populated areas of the western region of Kazakhstan: the Aktobe, Mangystau, West Kazakhstan, and Atyrau regions.

Figure 1. Flowchart of the study. BAZ: body mass index for age *z* score; HAZ: height for age *z* score; WAZ: weight for age *z* score.

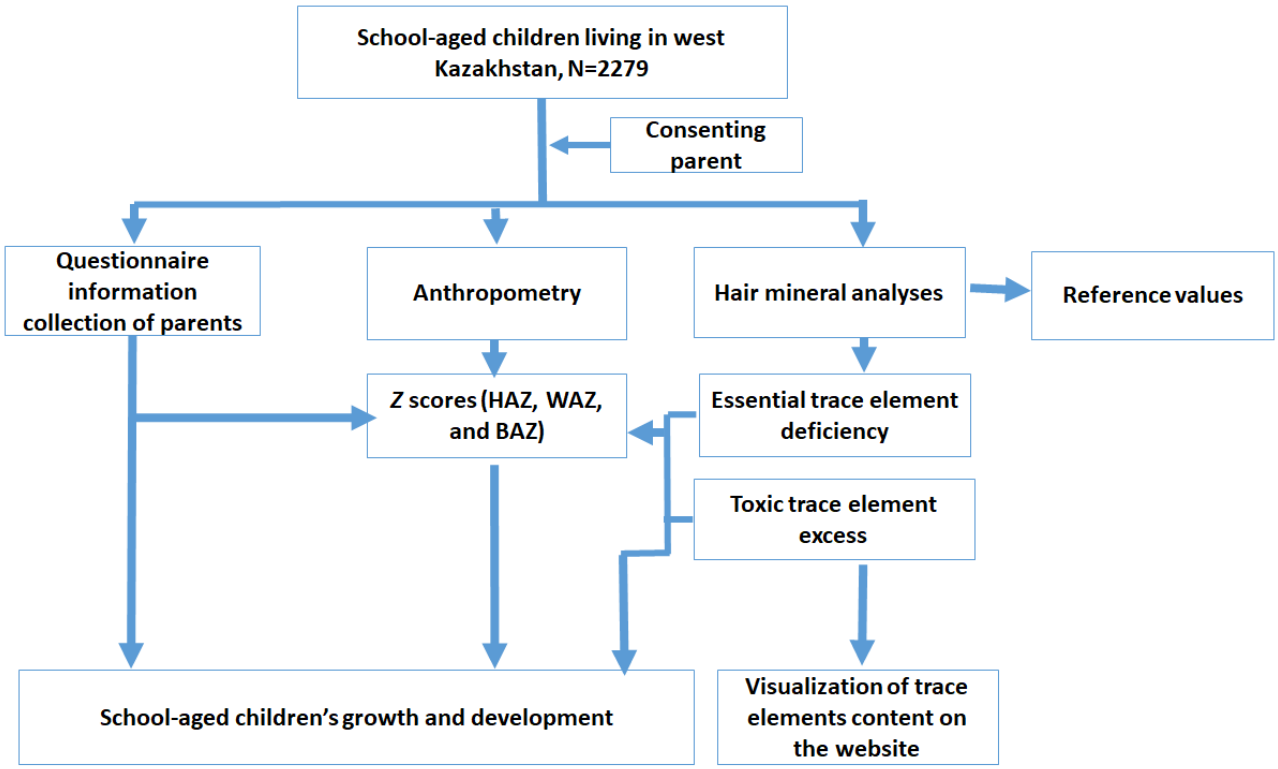

Inclusion criteria are as follows: (1) school-aged children (aged 5 to 18 years) who are permanent residents of the western region of Kazakhstan and (2) for whom written informed consent from parents or legal guardians is obtained before participation in the study.

Exclusion criteria are as follows: (1) comorbid somatic diseases, (2) endocrine or neurological disorders, (3) hereditary diseases and congenital developmental anomalies, and (4) use of vitamin or mineral supplements.

A total of 2279 school-aged children (aged 5 to 18 years) who are permanent residents of the Aktobe, Mangystau, Atyrau, and West Kazakhstan regions will be included in the study using a cluster sampling method. Schools will be randomly selected within each cluster, and within these schools, classes will be randomly chosen to form the study groups.

The sample size was calculated using official demographic data on the population aged 5 to 18 years across the 4 regions of western Kazakhstan [60]. The following formula was used to calculate the sample size:

Where the average intragroup variance is:

N_i is the number of objects in each class of the general population (N_1=204,124 in the Aktobe region; N_2=195,572 in the Mangystau region; N_3=168,154 in the Atyrau region; N_4=136,255 in the West Kazakhstan region; N=704,105). Data from previous studies conducted in western Kazakhstan [9]

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were used for the calculation. With a Δ (sampling error) value of 0.04 and an α of .05 (Z=1.96), the total sample size was 1847. To account for possible data loss, 2279 children will be recruited for the study. The sample will be divided into 4 age groups: preschoolers aged 5 to 6 years, schoolgirls and schoolboys aged 7 to 10 years and 11 to 15 years, and adolescents aged 16 to 18 years [61].

Study of the Elemental Profile of Children

Hair samples will be obtained using clean, stainless steel scissors from 3 to 5 areas of the occipital part of the head in quantities of at least 0.1 g. For elemental analysis of hair, proximal parts of strands of 3 to 4 cm in length will be used. Samples will be placed in envelopes with identification records.

The hair samples will be analyzed for the following 25 chemical elements: aluminum, arsenic, boron, beryllium, calcium, cadmium, cobalt, chromium, copper, iron, iodine, potassium, lithium, manganese, magnesium, sodium, nickel, phosphorus, lead, selenium, silicon, tin, vanadium, mercury, and zinc. The elemental composition of the hair will be analyzed using inductively coupled plasma mass spectrometry (ICP-MS) on an Agilent 8900 mass spectrometer (Agilent Technologies) using an SPS 4 automatic dispenser (Agilent Technologies; Table 1).

Hair samples will be subjected to sample preparation through washing and microwave decomposition. The hair strands will be washed using acetone and then rinsed 3 times with deionized water and air dried at 60 °C. The sample (sample weight=0.05 g) will be decomposed using nitric acid (Fluka 02650; Sigma-Aldrich) in a Berghof SW-4 DAP-40 microwave system (Berghof Products + Instruments GmbH) and diluted using distilled deionized water to a concentration of 0.5% to 1% of nitric acid before direct injection into the ICP-MS system.

The ICP-MS system is prepared for operation according to factory specifications and calibrated via external calibration against multielement standards. A tuning solution of cerium, cobalt, lithium, thallium, and yttrium of 10 µg/L in 2% acid (Agilent Technologies) is used for daily evaluation of the sensitivity of the mass spectrometer. The content of oxides and doubly charged ions does not exceed 1.5%.

Standards containing all elements to be assessed at concentrations of 0.5, 1, 5, 10, and 5000 µg/L are prepared before starting work using the Universal Data Acquisition Standards Kit reference solutions (PerkinElmer) through dilution in distilled deionized water acidified with 1% of nitric acid. To account for incomplete matching of sample matrices and calibration solutions for acidity and viscosity, the assay uses online internal standardization for rhodium isotope 103. An internal standard containing 10 µg/L of rhodium is prepared from a rhodium reference standard (PerkinElmer) on a matrix containing 8% 1-butanol (Merck KGaA), 0.8% Triton X-100 (Sigma-Aldrich), 0.02% tetramethylammonium hydroxide (Alfa Aesar), and 0.02% ethylenediaminetetraacetic acid (Sigma-Aldrich).

Sample collection is conducted using an SPS 4 autosampler (Agilent Technologies), and sample introduction is conducted using an Integrated Sample Introduction System 3 (Agilent Technologies). To eliminate polyatomic overlays, an ammonia-helium mixture is used as the reaction cell gas.

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Table 1. Conditions of analysis.

Condition	Parameters
RF[a] power	• 1550 W
Cooling gas flow	• 15 L/min
Auxiliary gas flow	• 0.9 L/min
Nebulizer gas flow	• 1.05 L/min
Sample introduction system	• ISIS[b] 3 for the Agilent 8900 mass spectrometer (Agilent Technologies) • MicroMist nebulizer (standard for base model 100), and sample uptake rate of 0.4 mL/min (Agilent Technologies) • Quartz double-pass Scott spray chamber (quartz spray chamber for the ICP-MS[c] mass spectrometer part number G8400-67150; Agilent Technologies)
Reaction or collision cell gas	• Ammonia and helium mixture
Reaction or collision cell gas flow	• 1 L/min
Cone material	• Platinum
Injector	• Fassel heater, single-piece quartz torch with a 2.5-mm internal diameter injector (standard for the Agilent 8900 ICP-MS mass spectrometer part number G3280-80053; Agilent Technologies)
Sample flow	• 400 µL/min
Internal standard flow	• 40 µL/min
Modes	• No gas mode: analytes include lithium, beryllium, boron, aluminum, silicon, phosphorus, sulfur, nickel, copper, zinc, gallium, germanium, arsenic, bromine, rubidium, strontium, zirconium, niobium, molybdenum, palladium, silver, cadmium, indium, tin, antimony, tellurium, iodine, cesium, barium, lanthanum, tungsten, platinum, gold, mercury, thallium, lead, bismuth, and uranium • Reaction or collision cell mode: analytes include sodium, magnesium, potassium, calcium, titanium, vanadium, chromium, manganese, iron, cobalt, selenium, and krypton
Dwell time per mass and scanning mode	• Single quadrupole mode: 50-100 ms • MS/MS[d] mode: 100-200 ms
Wait time	• Single quadrupole mode: 0 ms • MS/MS mode: 7 ms
Peak profile mode	• 1 scanning point for the first quadrupole and 3 scanning points for the second quadrupole
Readings per replicate	• 3
Replicate number	• 3

[a]RF: radio frequency

[b]ISIS: Integrated Sample Introduction System.

[c]ICP-MS: inductively coupled plasma mass spectrometry.

[d]MS/MS: tandem mass spectrometry.

Establishment of Reference Values of the Chemical Element Content

Establishment of reference values of the chemical element content in biological substrates of the population of the western region of Kazakhstan will be carried out by determining 95% coverage intervals with 95% CIs. The analysis will be carried out in accordance with the recommendations of the International Union of Pure and Applied Chemistry [62].

Assessment of Physical Growth

Anthropometric parameters (body weight and height) of children will be assessed once. Measurement of children's body weight will be carried out in electronic medical scales with an accuracy of 50 g. Height will be measured using a medical height gauge with a folding stool in the standing position. According to the manufacturer of the height gauge, the accuracy of the measurement is 0.1 cm.

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Children's physical growth will be assessed according to the World Health Organization (WHO; 2007) growth standards using the *z* score: the number of SDs (SD score; SDS) by which the anthropometric value differs from the median value of the standard population. A specialized program developed by the WHO, AnthroPlus, will be used to assess the growth of children [63].

When calculating *z* scores for children of the study sample, it is suggested to assume that they are equal to 0 for the standard population. Thus, the amount of deviation of sample *z* score values from 0 indicates the deviation of the growth indicators of children in this group from those of the standard population. To assess the physical growth of children and the influence of bioelements on it, we will use the method of anthropometric data assessment via *z* score, which consists of calculating the number of SDs or sigmas by which the studied indicator differs from the median of the standard population. If the anthropometric data of a particular child are lower than the median of the standard for a given age, the *z* score will be negative. Conversely, if the body mass or body length of a given child is above the median of the standard population, then the *z* score will have a positive value. Children's anthropometric data are characterized using *z* score values: body weight for age for children aged younger than 10 years (weight for age *z* score; WAZ), height for age (height for age *z* score; HAZ), and BMI for age *z* score (BAZ). The cutoff points of *z* score values make it possible to diagnose thinness, stunting, overweight, or obesity. The use of *z* score calculation methodology to estimate the anthropometric parameters of children in epidemiological studies has certain advantages over other anthropometric indexes, in particular over the analysis of percentile distribution due to the possibility of statistical analysis and comparison of groups [64,65].

To study the relationship between element content and physical growth, we considered it appropriate to use this method.

The following indicators will be calculated: WAZ for children aged younger than 10 years, HAZ, and BAZ. According to WHO recommendations, the interpretation of the obtained *z* score values is as follows:

- WAZ: SDS of <−2 for thinness, SDS of –2 to +2 for normal values, and SDS of >+2 for overweight or obesity.
- HAZ: SDS of <−2 for stunting, SDS of –2 to +2 for normal values, and SDS of >+2 for tall stature.
- BAZ: SDS of <−2 for thinness, SDS of –2 to +1 for normal values, SDS of +1 to +2 for overweight, and SDS of >+2 for obesity.

Blood pressure (BP) measurements in children will be taken by a certified physician using an appropriately sized cuff and an aneroid manometer. Three BP measurements will be obtained after the participant has rested for 5 minutes in a seated position with their feet on the floor. The mean systolic and diastolic BP for each participant is calculated from the recorded readings. Heart rate is determined through palpation of the radial artery.

Parents will be interviewed to identify medico-social factors (eg, age, parental education, and income).

The variables assessed in this study are presented in Tables 2 and 3.

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Table 2. Anthropometric and sociodemographic characteristics of the children and their parents.

Variable	Description
Age (y)	• Quantitative
Sex	• Female • Male • Intersex
Ethnicity	• Kazakh • Other Asian • Russian • Other European • Refuse to answer
Region of residence	• Aktobe • Mangystau • Atyrau • West Kazakhstan
Place of residence	• Urban • Rural
Body length (cm)	• Quantitative
Body weight (kg)	• Quantitative
BMI (kg/m^2)	• Quantitative
Head circumference (cm)	• Quantitative
Chest circumference (cm) at rest (normal calm breathing), at maximum inhalation, and at full exhalation	• Quantitative
WAZ[a]	• Quantitative
HAZ[b]	• Quantitative
BAZ[c]	• Quantitative
Mother's age at the time of childbirth (y)	• Quantitative
Father's age at the time of the child's birth (y)	• Quantitative
Pregnancy sequence number	• Ordinal
Baby's birth weight (kg)	• Quantitative
Child's height at birth (cm)	• Quantitative
Breastfeeding period (mo)	• Quantitative
Physical activity	• Low • Medium • High
Physical education and sports outside of school	• Dormant • Irregularly • Regularly
Duration of child's sleep (h)	• Quantitative
Systolic blood pressure (mm Hg)	• Quantitative
Diastolic blood pressure (mm Hg)	• Quantitative

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Variable	Description
Resting heart rate (beats per minute)	• Quantitative
Mother's height (cm)	• Quantitative
Mother's weight (kg)	• Quantitative
Father's height (cm)	• Quantitative
Father's weight (kg)	• Quantitative
Educational level of the mother	• Higher • Secondary specialized • Secondary
Educational level of the father	• Higher • Secondary specialized • Secondary
Family	• Complete • Incomplete
Number of children in the family	• Quantitative
Living space per family member (m^2)	• Quantitative
Harmful and hazardous working conditions of parents	• Yes • No • Refuse to answer
Parents working in the oil and gas industry	• Yes • No
Presence of pathology in the mother during pregnancy (if "yes," specify which pathology)	• Yes • No
Smoking by the mother or father	• Yes • No • Refuse to answer
Alcohol use by the mother or father	• Yes • No • Refuse to answer
Income	• Up to KZT 50,000 (US $92.35) • KZT 50,000-100,000 (US $92.35-$184.70) • KZT 100,000-150,000 (US $184.70-$277.06) • KZT 150,000-200,000 (US $277.06-$369.41) • KZT ≥200,000 (US $369.41)
Water consumption	• Tap • Bottled • Borehole or well • Filtered • Tap+bottled water
Parents' assessment of their child's health	• Excellent • Good • Satisfactory • Bad • Refuse to answer

[a]WAZ: weight for age *z* score.

[b]HAZ: height for age *z* score.

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[C]BAZ: BMI for age *z* score.

Table 3. Chemical element content in the hair of school-aged children.

Element type	Elements	Category
Macroelements	Calcium, potassium, sodium, magnesium, and phosphorus	Quantitative
Essential trace elements	Chromium, cobalt, copper, iron, iodine, manganese, selenium, and zinc	Quantitative
Toxic trace elements	Aluminum, arsenic, beryllium, cadmium, mercury, and lead	Quantitative
Potentially toxic trace elements	Boron, lithium, nickel, silicon, tin, and vanadium	Quantitative

Statistical Methods

Statistical processing of the results will be carried out using the SPSS (version 25; IBM Corp) and STATISTICA 10 (StatSoft) programs. The Kolmogorov-Smirnov criterion will be used to determine the normality of the distribution of quantitative variables. Variables with normal distribution will be presented as means and SDs, and variables with non-Gaussian distribution will be presented as medians and IQRs. Qualitative variables will be presented as absolute values and percentages. To assess statistically significant differences between quantitative variables, we will use the Student criterion, the nonparametric Mann-Whitney *U* test for 2 samples, and the Kruskal-Wallis *H* criterion for 3 or more samples. The Pearson chi-square criterion will be applied to identify intergroup differences for categorical variables. Multiple linear regression analysis will be applied to assess the association between chemical element content in hair and *z* score measures of children's physical growth, as well as the association with gender, age, and residential status. Logarithmic transformation will be conducted for variables with non-Gaussian distribution. The critical level of significance for testing statistical hypotheses is assumed to be.05.

Ethical Considerations

This research was approved by the institutional review board of the West Kazakhstan Marat Ospanov Medical University (meeting number 7.02, dated September 29, 2022). Written informed consent was obtained from the legal guardians of the participants. Participation was voluntary, and the participants had the right to withdraw from the study at any time. The original informed consent form or institutional review board approval cover secondary analyses using existing data with primary consent without the need for additional consent. The data are anonymized. The participants are identified by a numerical code. No compensation is provided to participants for this research.

Data Reporting and Visualization

From the data obtained, a web-based mapping will be carried out by color according to the concentration of chemical elements in children's hair. The data will be presented as a web-based atlas. The mapping is conducted using the cross-platform geographic information system software QGIS (version 3.18; QGIS Development Team). Vector data are taken from public sources. The color in the map represents the median chemical element content in hair

The atlas is being developed as a web application using modern adaptive design, where the site layout will change automatically depending on the user's screen. Data entry will be limited to authorized users, and access will be granted by the web application administrator.

Results

Recruitment of participants and data collection will occur between September 2023 and March 2025. Data processing and analysis will be completed in September 2025. Publication of the results is expected in December 2025. Table 4 shows an outline of the study plan.

Data on the trace element content in children's hair will be obtained (Figure 2). The chemical element content will be reflected in the web-based atlas, entitled "Elemental status of the child population of the Western region of the Republic of Kazakhstan." The electronic atlas containing 25 maps (aluminum, arsenic, boron, beryllium, calcium, cadmium, cobalt, chromium, copper, iron, iodine, potassium, lithium, manganese, magnesium, sodium, nickel, phosphorus, lead, selenium, silicon, tin, vanadium, mercury, and zinc) of the elemental profile of the child population of the western region of Kazakhstan will be available on the website [66]. Reference values for the 25 chemical elements in hair will be obtained. An analysis will be conducted to determine the differences in the levels of elements in groups of boys and girls, urban and rural children, and groups of children of different ages. According to the results of multiple regression analysis, chemical elements influencing the indicators of physical development of children will be identified.

The prevalence of physical development and growth disorders according to the WHO 2007 criteria will be determined. The incidence of normal and abnormal physical growth of children and adolescents by gender and residence status will be presented.

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Table 4. Quarterly scheduling of research work.

Item	2023				2024				2025			
	Quarter 1	Quarter 2	Quarter 3	Quarter 4	Quarter 5	Quarter 6	Quarter 7	Quarter 8	Quarter 9	Quarter 10	Quarter 11	Quarter 12
Outline of study design and preparation	✓											
Reference collection and review of the literature	✓	✓										
Data collection			✓	✓	✓	✓	✓	✓	✓			
Data compilation and tabulation							✓	✓	✓	✓		
Data analysis									✓	✓	✓	
Thesis writing									✓	✓	✓	
Final thesis preparation										✓	✓	
Submission												✓

Figure 2. Sample table of the comparative analysis of the chemical element content in children's hair.

Element (μg/g)	Gender			Residence status			Age range (y)				
	Boys, median (IQR)	Girls, median (IQR)	*P* value	Urban, median (IQR)	Rural, median (IQR)	*P* value	5-6, median (IQR)	7-10, median (IQR)	11-15, median (IQR)	16-18, median (IQR)	*P* value
Aluminum											
Arsenic											
Boron											
Beryllium											
Calcium											
Cadmium											
Cobalt											
Chromium											
Copper											
Iron											
Iodine											
Potassium											
Lithium											
Manganese											
Magnesium											
Sodium											
Nickel											
Phosphorus											
Lead											
Selenium											
Silicon											
Tin											
Vanadium											
Mercury											
Zinc											

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Discussion

Expected Findings

To assess the elemental profile of children, we will apply polyelemental analysis of hair. In biomonitoring studies, hair is a reliable biomarker for assessing the elemental profile of children and adolescents, as well as for analyzing the impact of environmental pollutants [67]. Elemental analysis of hair allows not only for the assessment of the current status of the human body but also for the reconstruction of past episodes of exposure and nutrition even if the action has already ceased. The growth rate of human hair is approximately 10 mm per month, and the level of elements in hair reflects their levels in the body over time, whereas the concentration of metals and metalloids in blood and urine changes rapidly after exposure (within a few days for blood and a few weeks for urine). Hair analysis has several advantages [46]. Hair is easy to take, collect, store, and transport, and the collection procedure is noninvasive. Chemical elements accumulate in hair at higher concentrations and persist longer than in blood, urine, and saliva [68].

Although the applicability of hair analysis is debated, the standardization of sample collection, reporting procedures, and analytical methods, as well as quality management, allow hair to be used as an effective marker in epidemiological studies. A clear methodology for such studies is ICP-MS, which can detect nanograms of several components of scalp hair and which we will use in this study [67,68].

There are many studies in scientific literature using elemental analysis of hair from children and adolescents to assess the impact of polluting factors in different countries, including Russia [69], Bolivia [38], Italy [23,24], Ethiopia [17], Japan [31], and Colombia [39]. It has been found that children living in polluted areas near industrial enterprises have significantly higher heavy metal and lower essential trace element content in bioassays. It is assumed that the adverse health effects on children and adolescents living near factories and industrial plants may be related not only to the excess of toxic metals but also to changes in mineral homeostasis. However, it should be recognized that the number of studies determining the concentration of chemical elements in hair in populations of children living in polluted areas is lower than that of similar studies conducted in adult populations. In addition, a significant part of contaminated territories and exposed populations, including children, has not been covered by such studies at all.

It should be noted that environmental pollution is not the only source of toxic metals in children's bodies. When conducting biomonitoring studies of children, the intake of trace elements (including toxic ones) from food and water should be considered [12,17,31]. Other important considerations include harmful habits such as smoking among family members [30,52,53], social status and income, the level of education of the parents [31,41,52,70], and ethnicity. Furthermore, the child population comprises different age groups, which differ not only in anthropometric data but also in the level and intensity of physiological processes associated with various stages of growth and development. There are also differences in social activity and the formation of behavioral patterns. This makes younger children more vulnerable to toxic trace elements than older children [13-16]. The relationship between chemical elements in hair and children's health is most often assessed in case-control studies involving groups of healthy children and children with diseases such as anemia [56]; night blindness [57]; myopia [71]; amblyopia [72]; inflammatory bowel disease [73]; autism spectrum disorder [74-78]; behavioral disorders [79]; Down syndrome, obesity, and growth delay [80]; attention-deficit/hyperactivity disorder [81-83]; cerebral palsy [84]; and developmental language disorder [85]. Some studies consider anthropometric [17,70,86], biochemical [86], and physiological [86] indicators as characteristics of children's health.

Hair is a useful tool in assessing the supply of zinc [87,88], selenium [89], copper [90], calcium, and magnesium to the child population [61].

Our project is a continuation of our previous cross-sectional study on the assessment of elemental profile conducted in adults aged 18 to 60 years. On the basis of the analysis of microelement status, medical and biological monitoring of population health at the population level was carried out [91,92]. The obtained data indicated that, among residents of western Kazakhstan, living near oil and gas fields affected the copper, iodine, aluminum, mercury, and lead content in hair. The increasing aluminum and mercury content was associated with decreasing distance to oil and gas fields, and the increasing copper, iodine, and lead content was associated with increasing distance to these fields. Our results demonstrate the need for regular biomonitoring of chemical elements to determine long-term temporal trends in the impact of chemicals on the health of the population of western Kazakhstan [58,59]. In the absence of state programs for biomonitoring the element content in the bodies of the population, which involve studying the population over a long period of time , the temporal trends of exposure to chemical elements can also be assessed taking into account the ontogenetic approach (ie, including different groups of the child population in a cross-sectional study).

The reference values of trace and macroelements obtained as a result of our study are recommended to be used for biomonitoring and environmental risk assessment in Kazakhstan. Our team includes researchers with experience in assessing and presenting the elemental profile of residents of the western region of Kazakhstan [58,59,93].

This study is conducted within the framework of the implementation of a scientific project with grant funding from the Committee of Science of the Ministry of Science and Higher Education of the Republic of Kazakhstan ("Elemental status of the child population of the Western region of the Republic of Kazakhstan"; grant AP19677517) (Multimedia Appendix 1).

We assume that the presentation of the results of our study in the form of an atlas of elemental profile will facilitate the perception of our findings.

We welcome collaboration with other researchers; our data can be made available upon request. We provide an opportunity for researchers to post data on the elemental profile of the

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populations they study on our website, with the possibility of visualizing them in the form of maps.

The results and conclusions of our study can be compared with data from other studies investigating the elemental profile of populations.

Limitations of This Study

The study design is limited to a single-stage cross-sectional study, with no opportunity to observe changes in elemental profile over time. We did not consider dietary intake of trace and macroelements. In addition, when interviewing mothers, their responses may be influenced by memory distortions.

Conclusions

A child's growth trajectory not only indicates their current health but also predicts long-term outcomes such as cognitive development, susceptibility to disease, and productivity in adulthood. Given the vulnerability of children and the region's unique geochemical and industrial characteristics, assessing physical growth alongside elemental profile provides a comprehensive picture of children's health and potential environmental exposure. Understanding the relationship between elemental profile and growth indicators can reveal the impact of environmental exposure on children's health in the region. Such findings could inform the development of region-specific public health measures such as nutritional supplements, environmental remediation, and policies aimed at reducing exposure to toxic elements. In addition, identifying differences between rural and urban populations could inform the development of targeted prevention strategies. The developed web-based atlas of trace and macroelement content will be necessary for further research on the prevalence, etiology, risk factors, and possible mechanisms of development of environmentally dependent, endemic diseases in the region.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report by the Committee of Science of the Ministry of Higher Education and Science of the Republic of Kazakhstan, National Centre for Scientific Technical Expertise.
[PDF File (Adobe PDF File), 197 KB - resprot_v14i1e72207_app1.pdf]

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Abbreviations

BAZ: body mass index for age *z* score
BP: blood pressure
HAZ: height for age *z* score
ICP-MS: inductively coupled plasma mass spectrometry
SDS: standard deviation score
WAZ: weight for age *z* score
WHO: World Health Organization

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Protocol

Identifying Factors Associated With HIV Viral Suppression and Health Care Outcomes in the Florida Cohort Study Wave 3: Protocol for a Prospective Cohort Study

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Abstract

Background: Ending the HIV epidemic remains a high public health priority, and the state of Florida continues to have high HIV prevalence and incidence.

Objective: This protocol aims to identify factors associated with the HIV care continuum and HIV-related comorbidities, with a focus on the impacts of alcohol use.

Methods: The Florida Cohort study wave 3 enrolled people with HIV aged 18 years or older from 9 clinical, case management, and community settings across Florida from 2020 to 2023. All participants completed a baseline questionnaire, and most (769/836, 92%) completed additional questionnaires at baseline and/or approximately 1 year after baseline. Data on HIV care and treatment, mental health, substance use, stigma, and technology were collected in the baseline questionnaire. Additional questionnaires covered alcohol use, gender identity, pet ownership, stigma and discrimination, antiretroviral therapy preferences, and the impacts of the COVID-19 pandemic. Questionnaire data were securely linked to HIV care continuum variables from Florida's state HIV monitoring system.

Results: Overall, the study enrolled 836 people with HIV. Among them, 397 (47.5%) were non-Hispanic Black, 131 (15.7%) were Hispanic, 505 (60.4%) were assigned male sex at birth, and 487 (58.3%) were aged above 50 years. Most (n=769, 92%) participants were linked to the state HIV reporting system and will be followed for up to 5 years to monitor HIV outcomes. A total of 31 (94% of 33 eligible) participants completed the gender identity questionnaire, 230 (91.3% of 252 eligible) completed

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the alcohol questionnaire, 287 (91.7% of 313 eligible) completed the COVID-19 questionnaire, 221 (85% of 260 eligible) completed the pet questionnaire, 461 (87.6% of 526 eligible) completed the stigma and discrimination questionnaire, and 210 (85.7% of 245 eligible) completed the antiretroviral therapy preference questionnaire.

Conclusions: This study provides opportunities to monitor changes in HIV-related outcomes as well as relevant attitudes, behaviors, and health care preferences; however, it has some limitations in terms of representativeness and tracking longitudinal outcomes.

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KEYWORDS

HIV; sustained virologic response; cohort studies; alcohol consumption, epidemiologic research design

Introduction

Background

In 2019, there were 13.2 HIV diagnoses per 100,000 people in the United States. The Ending the HIV Epidemic (EHE) initiative was announced with the goal of reducing new HIV infections by 90% by 2030 [1]. A key pillar of the EHE is helping more people with HIV achieve and sustain viral suppression to decrease transmission of HIV [2]. Florida, an epicenter of the HIV epidemic in the United States, has high rates of HIV incidence (19.9 per 100,000 people) and prevalence (578.7 per 100,000 people) in both urban and rural settings and in people with a diversity of racial and cultural backgrounds [3-5]. When the Florida Cohort study wave 3 began in 2019, only 70% of the 123,087 people with HIV in Florida had achieved viral suppression [5]. Identifying barriers that prevent people with HIV from sustaining viral suppression and achieving other care continuum steps, as well as facilitators associated with successful HIV outcomes, within Florida is needed to achieve the ambitious targets set by the EHE.

Numerous factors at the individual, interpersonal, community, and policy levels influence HIV viral suppression [6-8], including alcohol use, other drug use, housing status, mental health conditions, HIV stigma, having low income, and the lack of insurance coverage, among others [9-13]. Trends in alcohol use are changing as alcohol use among women has increased, and the COVID-19 pandemic has increased alcohol use in the general population [14,15]. At the same time, the influence of alcohol use on viral suppression may be lessening as antiretroviral therapy (ART) regimens become simpler and more forgiving [10,16,17]. However, alcohol use and ART can both negatively impact liver function. Therefore, monitoring alcohol use and interest in alcohol-related interventions remains important for improving the health of people with HIV [18].

Many of these factors that directly or indirectly impact viral suppression are infrequently recorded in medical records or surveillance data and can only be assessed by directly administering questionnaires to people with HIV. While there are many ongoing cohort studies of HIV, the Florida Cohort study is the only one focused on monitoring HIV-related factors across an entire state. In the previous iteration of the Florida Cohort study (wave 2), we collected data from more than 900 people with HIV between 2014 and 2018, linking data from individual questionnaires, medical records, and statewide HIV surveillance [19]. From these data, our team identified several factors associated with poor HIV viral suppression, including heavy alcohol consumption, other substance use, depression and anxiety symptoms, and suboptimal ART adherence [20-25]. We also examined several dimensions of HIV stigma and found that only health care–associated experiences of stigma and discrimination were significantly associated with poor viral suppression in this sample [26]. Many of these factors, attitudes, and behaviors are not well captured in medical records and may change over time. Moreover, changes in health care policies, HIV medications, alcohol and other substance use, and temporal events (such as pandemics) may correlate with changes in individual behaviors, health conditions, or attitudes and beliefs over time. Therefore, ongoing monitoring is needed to assess their continued impact on HIV care outcomes.

This Study

The Florida Cohort study wave 3 focused on factors that are not readily assessed via medical records, including alcohol and other substance use, experiences of stigma and discrimination, and mental health symptoms [27,28]. We sought to capture additional measures related to alcohol consumption and potential interventions that address alcohol use disorder. On the basis of feedback from community members and interests of research investigators, we also included new questions related to HIV stigma and discrimination, barriers to substance use and mental health services, interest in emerging options for health care such as telehealth, and challenges related to ART adherence. We also received supplements to study the impacts of the COVID-19 pandemic and HIV care among gender-diverse people with HIV; therefore, additional questionnaire items were added to capture these issues. Items were also added to support topics related to graduate student research. Thus, the overall goals of the Florida Cohort study wave 3 were to identify barriers to and facilitators of HIV viral suppression and other steps of the HIV care continuum, focusing on alcohol use, and monitor changing attitudes and beliefs that influence HIV care outcomes. This paper describes recruitment, study measures, and baseline characteristics of the study population in accordance with the CHERRIES (Checklist for Reporting Results of Internet E-Surveys) and STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) checklists (see Multimedia Appendices 1 and 2).

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Methods

Study Design and Study Population

The Florida Cohort study is a prospective cohort study that obtained baseline questionnaire data from study participants and linked questionnaire data to statewide HIV surveillance data, including HIV viral load, which will be tracked for at least 5 years after enrollment. The baseline questionnaire included several core measures. Participants had the option to complete additional questionnaires at baseline and follow-up questionnaires at 12 months based on the timing of enrollment and staff resources available at the different recruitment sites. Participants were eligible if they were aged 18 years or above, were living with HIV, and received most of their HIV-related care in Florida. All recruitment settings provided the study in English, whereas some sites offered the study in Spanish, and 1 location offered the study in Haitian Creole. We sought to enroll a sample of people with HIV who are similar to the overall population of people with HIV in Florida in terms of age, gender, race, and ethnicity, including Haitian Creole and Spanish-speaking individuals [5]. The enrollment target was 1000 people with HIV, which included at least 200 (20%) people who met the criteria for at-risk drinking (assessed via the Alcohol Use Disorders Identification Test–Consumption), 50 (5%) people who spoke Haitian Creole, and 150 (15%) people living and receiving care in rural areas [29]. These populations were underrepresented in the previous versions of the Florida Cohort study but are key populations for addressing the HIV epidemic in Florida.

Recruitment Settings

Recruitment began in October 2020 and continued through December 2023 and used a convenience sampling method. The study recruited participants from 9 counties in Florida (major cities noted in parentheses): Alachua (Gainesville), Columbia, Marion (Ocala), Duval (Jacksonville), Hillsborough (Tampa), Brevard (Melbourne), Palm Beach, Polk, and Miami-Dade (Miami; Figure 1).

Figure 1. (A) Locations and (B) timeline of recruitment for the Florida Cohort Wave 3 Study.

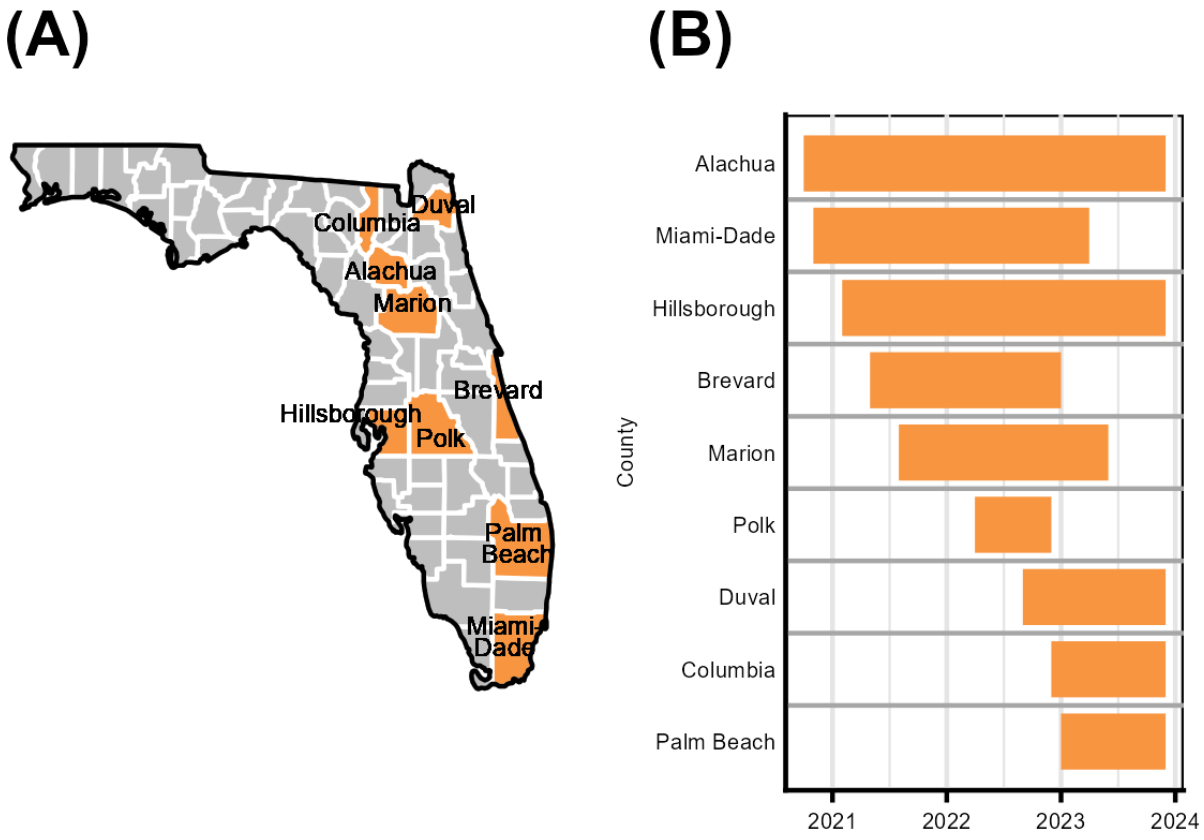

Most (828/836, 99%) participants were recruited from clinical care or community settings, including public health, academic, and community-based HIV clinics, and case management agencies. In Alachua, Columbia, Marion, Hillsborough, and Polk counties (Figure 1), recruitment occurred primarily within the Florida Department of Health (FDOH) clinics, where potential participants either provided a phone number to be contacted by a research team member or met with a study staff member who was present at the clinic. Recruitment sites in north-central Florida also included an academic infectious disease clinic in Alachua County and mailing flyers to Ryan White HIV/AIDS Program clients in area 3/13. In Duval County, recruitment focused on an HIV case management agency. In Miami-Dade, Brevard, and Palm Beach counties, recruitment focused on community-based Ryan White HIV/AIDS Program–funded clinics. Recruitment strategies in Miami-Dade also included displaying advertisements on buses. Spanish versions of the study were available in Polk and Miami-Dade counties, and the Creole version was offered in Palm Beach County. Initial enrollment procedures were modified to support

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remote enrollment after the start of the COVID-19 pandemic in 2020, including procedures to confirm eligibility, obtain consent, and enroll people via telephone or videoconferencing. By the end of 2020, most recruitment sites were able to enroll participants in person.

Additional study funding was obtained to provide a more representative sample of gender-diverse participants. To increase enrollment of gender-diverse participants, we provided recruitment information to medical and support agencies supporting transgender and gender nonconforming individuals in Alachua and Miami-Dade counties and worked with a private recruitment resource (TrialFacts) to publish recruitment advertisements on social media in the fall of 2023. Individuals who visited Facebook and Instagram within Florida were shown an advertisement for the study and could voluntarily click on the advertisement to be redirected to a prescreening form managed by TrialFacts. Those who indicated that they were living with HIV shared their contact information with the research team for routine screening and consent procedures, if eligible. Ancillary study protocols enrolled gender-diverse people without HIV, and details of these procedures will be described elsewhere.

Screening

All participants completed a brief screening form to confirm that they met the age and HIV status criteria and estimate the number of surveys available to them as a part of the study. These screenings could be performed in person or over the phone. Once eligibility was confirmed, they were scheduled for an appointment to obtain consent. The consent form was accessible through a unique link that was emailed to them, or they could review and sign a paper copy of the consent form. Paper consent forms could be mailed and reviewed over the phone or could be provided in person if the potential participant and recruiter were meeting face-to-face. Those who were emailed the consent form could proceed to the questionnaires through that same link after providing consent.

Questionnaire Development

The study team reviewed the questionnaires developed for the Florida Cohort study wave 2 and identified areas that were underexplored or not explored in previous iterations of the study [19]. Members of the research team then reviewed the relevant literature on the areas identified for further exploration in wave 3 to determine measures to assess these domains. An updated version of the questionnaire was then circulated to the wider research team to identify other areas of exploration, and researchers could suggest measures for inclusion. The initial version of the questionnaire was then reviewed by community consultants and revised accordingly. The surveys were then built in Qualtrics (Qualtrics International Inc) and tested by the research team to verify that the wording and skip logic were correct. Subsequently, the questionnaire was piloted among people with HIV enrolled in another Southern HIV and Alcohol Research Consortium (SHARC) study and revised based on participant feedback. Data from the pilot study were not included in the final dataset. Subsequent questionnaires were reviewed by the research team and community consultants before being added to the study.

Data Collection

Participants were encouraged to complete the study questionnaires online using a Qualtrics-based survey that could be completed either at the recruitment location or at home. The Qualtrics survey showed 1 or 2 questions per page, and the number of pages varied based on participants' responses. They were allowed to skip questions after dismissing a prompt to go back and answer any blank questions on the page. Participants could also return to the survey and change previous responses. Cookies were enabled so that participants could return to the same page that they were last on if they used the same device and browser.

Participants also had the option to complete questionnaires on paper or have the research assistant read the questions and enter the answers in Qualtrics. The Haitian Creole version of the survey was administered orally by a research assistant who was fluent in Haitian Creole. The order of questions was the same regardless of the administration method.

Questionnaires

Core Measures

All participants at all study sites completed a baseline questionnaire that included items on sociodemographic characteristics, alcohol and drug use, mental health symptoms, HIV care and treatment, and potential use of technology for health (Textbox 1). In March 2022, the baseline questionnaire was updated to include additional questions about interest in and barriers to mental health interventions, psychosocial distress, long-acting injectable ART, characteristics of sexual partners, reproductive history and health, and the use of mobile apps. These same items were included in the 12-month questionnaire for people who enrolled before this change. The baseline questionnaire at sites that only offered a single baseline questionnaire included some additional items related to alcohol consumption and HIV care that were included in separate questionnaires at most settings.

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Textbox 1. Summary of measures included in the Florida Cohort study questionnaires. The original source of questionnaire items is included unless they are items created specifically for this study.

Baseline questionnaire

- Demographics
- Socioeconomic status
- Symptoms of depression and anxiety [30,31]
- Receipt of and interest in mental health care
- Distress [32]
- Antiretroviral therapy (ART) and HIV care
- Interest in long-acting ART
- Recent alcohol use [29]
- Heaviest alcohol use [33]
- Other substance use
- Medical marijuana
- Sexual activity
- Women's Health (pregnancy, contraception, and screening)
- Use of computers and mobile devices (telehealth use, internet access, and app use)
- COVID-19 (testing and vaccination history) [34,35]

Alcohol questionnaire

- Recent alcohol use [36] (this topic was also included in the baseline questionnaire for participants at study sites where only a single baseline questionnaire was offered)
- Motivations for drinking [37]
- Negative consequences of alcohol use [38]
- Attempts to quit
- Drinking for pain management
- Withdrawal symptoms [39]
- Interest in alcohol treatment and intervention options

Gender identity questionnaire

- Gender identity and expression [40]
- Discrimination as a barrier to HIV care
- Gender-based discrimination [41]
- Access to gender-affirming care [41]
- Receipt of gender-affirming care [41]

Extended questionnaire

- Employment
- Safety net program use
- Evictions
- Other mental health conditions [42]
- Negative urgency [43]
- Gambling
- Care satisfaction
- ART access
- Other medical care and hospitalizations

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- Disclosure of HIV status
- Lifetime alcohol use [33]
- History of alcohol treatment and barriers to care (this topic was also included in the baseline questionnaire for participants at study sites where only a single baseline questionnaire was offered)
- Sexually transmitted infection diagnosis (this topic was also included in the baseline questionnaire for participants at study sites where only a single baseline questionnaire was offered)
- New sex partners
- Adverse life events [44]
- Interest in alternative therapies
- Past incarceration and HIV diagnosis while incarcerated

COVID-19 questionnaire

- Impacts of the COVID-19 pandemic
- COVID-19 testing
- Infection history
- Vaccination history and beliefs [34,35]
- Loneliness [45]

Pet questionnaire

- Pet ownership
- Pet services
- Impacts on health and health care [46]
- Social support [47]

Stigma questionnaire

- HIV-related stigma [48]
- Enacted stigma
- Disclosure of HIV status (this topic was also included in the baseline questionnaire for participants at study sites where only a single baseline questionnaire was offered)
- Discrimination in health care
- Experiences with disease investigation specialists

ART preference questionnaire

- Preference for long-acting HIV treatment options

12-month follow-up questionnaire

- Socioeconomic status
- Symptoms of depression and anxiety [30,31]
- Receipt of and interest in mental health care
- ART and HIV care
- Other medical care and hospitalizations
- Recent alcohol use [29]
- Other substance use
- Sexually transmitted infection diagnoses
- New partners
- Women's health (pregnancy, contraception, and screening)
- Telehealth use and access
- Payment app use

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- COVID-19 positivity and vaccination history

Additional Questionnaires

After completing the baseline questionnaire, participants were invited to complete 1 or more additional questionnaires at baseline (Textbox 1 and Figure 2). The availability of additional questionnaires depended on the study site and the time at which participants enrolled in the study (Figure 2).

An overview of each additional questionnaire is provided in Textbox 2, and Textbox 1 provides more information on questionnaire content.

All questionnaires were available in English or Spanish, except for the ART preference questionnaire, which was only available in English. The core and 12-month follow-up surveys were also available in Haitian Creole.

Figure 2. Questionnaire availability by (A) geographic location and (B) time period for the Florida Cohort Wave 3 Study.

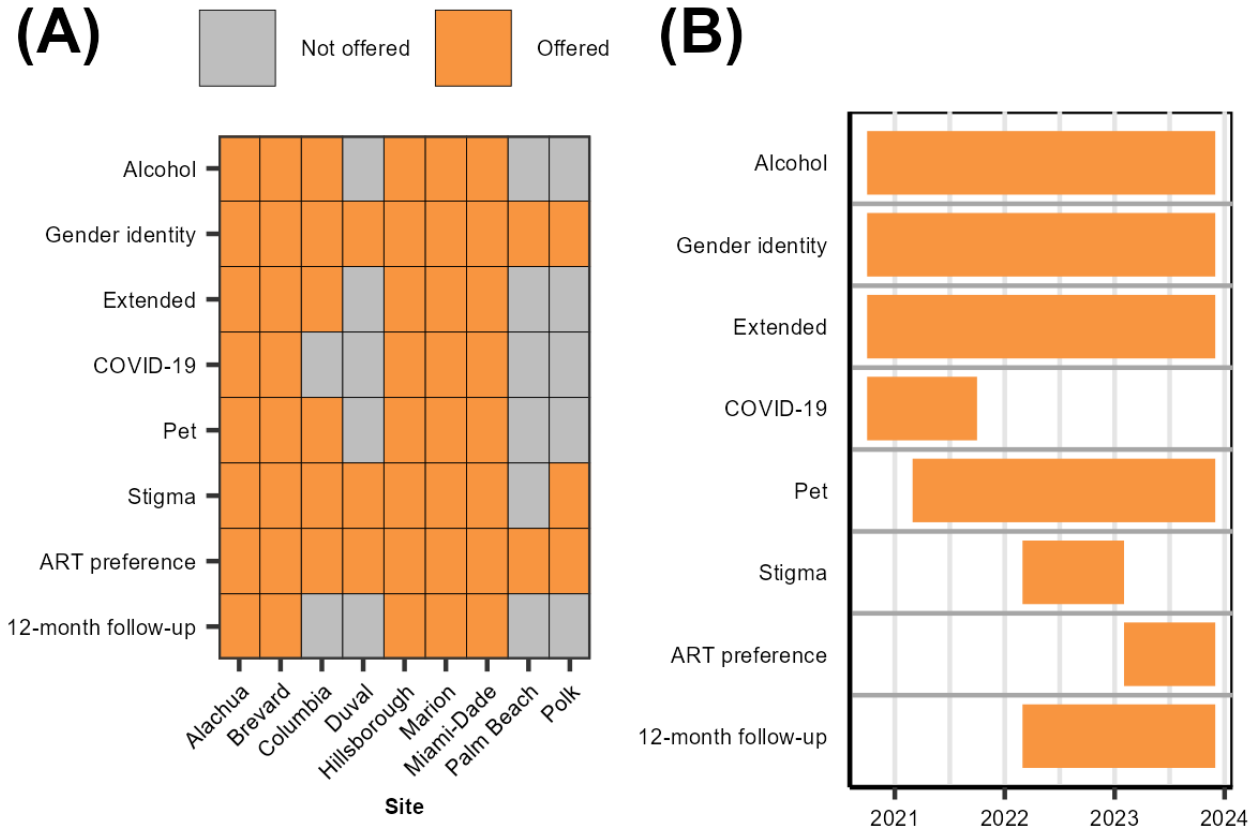

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Textbox 2. Overview of the additional questionnaires.

- The alcohol questionnaire focused on recent alcohol use and treatment interest. Measures included the 10-item Alcohol Use Disorder Identification Test (assesses drinking quantity and frequency and symptoms of alcohol dependence in the preceding 12 months), the revised short form of the Drinking Motives Questionnaire, a shortened version of the Sexual Motivations for Drinking Questionnaire, the Short Inventory of Problems–Revised, and the revised Clinical Institute Withdrawal Assessment of Alcohol Scale [36-39]. This questionnaire was available to participants completing the baseline visit who reported drinking alcohol at least twice a month in the preceding 12 months.
- The gender identity questionnaire focused on gender identity and related care. This questionnaire was available to participants completing the baseline visit who identified as a gender different from the one that aligned with their sex assigned at birth.
- The extended questionnaire included additional questions from researchers collecting preliminary data for other grants and questions from trainees to support dissertation research. This questionnaire was available to participants completing the baseline visit.
- The COVID-19 questionnaire focused on the impacts of the COVID-19 pandemic and practices. This questionnaire was available to participants completing the baseline visit.
- The pet questionnaire focused on pet ownership and its impacts on quality of life and medical care. This questionnaire was available to participants completing the baseline visit who reported having at least 1 pet.
- The stigma questionnaire focused on HIV-related stigma and discrimination in health care. This questionnaire was available to participants completing the baseline or 12-month follow-up visit.
- The antiretroviral therapy preference questionnaire focused on identifying antiretroviral therapy characteristics of greatest importance to people with HIV using a discrete choice experiment. This questionnaire was available to participants completing the baseline or 12-month follow-up visit.
- The 12-month follow-up questionnaire repeated measures of key variables from the baseline questionnaire. This questionnaire was available to participants who completed a baseline visit before February 2023.

Key Variables

Alcohol use in the preceding 12 months was assessed using the Alcohol Use Disorders Identification Test–Consumption, a 3-item measure that includes drinking quantity and frequency and heavy drinking episodes. At-risk drinking was defined as a score of 3 or greater for women and 4 or greater for men. Low-risk drinking was defined as any alcohol use below these cutoff scores [29].

Rurality was determined by linking rural-urban commuting area codes to participants' zip code data [49]. We grouped the codes into 2 categories, so that all rural-related codes were grouped together [50].

Training and Quality Assurance

All study recruiters received training before the enrollment of participants. In addition to training required by the institutional review boards (IRBs), training included sessions on the enrollment process; a review of the questionnaires; an overview of the use of REDCap (Research Electronic Data Capture; Vanderbilt University) for data collection and storage; secure communication using Microsoft Teams; and a discussion of ethical issues relevant to the study, including the informed consent process. Before actual enrollment, each recruiter was observed conducting a mock enrollment, and additional training was provided to certain staff who might conduct interviewer-administered versions of the questionnaire involving reading the questions out loud to participants.

State Surveillance Data and Medical Records

After obtaining participant consent, we securely linked survey participants to statewide FDOH HIV surveillance data under a formal data use agreement with FDOH. The linkage procedures have been previously described in detail [19]. The surveillance data include dates and results from laboratory tests for CD4 and HIV viral load tests from the Enhanced HIV/AIDS Reporting System (eHARS) managed by FDOH. Data are also linked to the National Death Index, which allows the team to examine survival over time. These results can be used to calculate aspects of the HIV care continuum, including engagement in care and HIV viral suppression. For the subset of participants who were recruited from FDOH clinics, the team also received data from electronic medical records managed by the FDOH, including information on medication prescriptions and medical condition diagnoses.

Follow-Up

The survey follow-up ended with administration of the 12-month follow-up questionnaire for participants at the sites where survey follow-ups were offered. Study staff attempted to contact participants who were enrolled at a site where the 12-month follow-up questionnaire was offered at 6 months to update their contact information as needed. For the 12-month follow-up questionnaire, up to 6 contact attempts were made using at least 2 forms of contact given at baseline before the participant was considered lost to follow-up.

All Florida Cohort study wave 3 participants will be followed in eHARS and through FDOH medical records through 2028, allowing for longitudinal data collection for these HIV-related outcomes. FDOH and eHARS records will be updated yearly.

Data Management and Data Sharing

All study data are maintained on secure servers at the University of Florida (UF). All enrollment, consent, and visit log data were entered into REDCap. Consent forms completed on paper were scanned into REDCap. Deidentified paper questionnaires were entered into Qualtrics by research study staff using a double data entry procedure to minimize data entry errors. Participant data were excluded from the final dataset if participants had previously completed the same study questionnaire, when

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questionnaires had substantial missing information, or when data entry seemed highly infeasible (eg, completing an entire questionnaire in less than 5 minutes when most other participants took 20 or more minutes to complete it; 8 participants). Data managers also reviewed the data to identify likely duplicate records. This included participants who gave different names but the same phone number or who had the same first and last name but with varying middle names or initials. IP addresses were not collected and could not be used to identify duplicates.

Deidentified datasets that do not contain FDOH information are available to investigators who submit a research plan through the SHARC Concepts System [51]. This requires researchers to submit the study rationale, aims and hypotheses, and a detailed research plan, which are reviewed by a team of researchers involved with SHARC and the Florida Cohort study wave 3. The reviewers provide feedback and can request changes and clarifications before approving the research plan and sharing the data. Data that include information from FDOH surveillance data or medical records will require separate data use agreements and approvals from FDOH.

Planned Analyses

The Florida Cohort study wave 3 allows for both longitudinal and cross-sectional analyses. Cross-sectional analyses include estimating the prevalence of at-risk alcohol use, identifying common motivations for alcohol use and negative outcomes related to alcohol use, and assessing interest in different alcohol-related interventions and treatments. We will also estimate the prevalence of other substance use, unstable housing, symptoms of anxiety and depression, and interactions between these conditions and alcohol use. For the longitudinal analyses, we will assess how alcohol use influences engagement in HIV care and viral suppression over time and how the COVID-19 pandemic impacted alcohol use among people with HIV. Additional analyses will be carried out to meet the goals of the junior faculty and student projects. Examples of these analyses include assessing the impact of psychosocial distress on ART adherence, assessing interest in mobile phone–based mental health interventions, and assessing the impacts of interpersonal violence on HIV care engagement.

Ethical Considerations

The IRB at the UF served as the IRB of record for this multisite study and approved all study activities before implementation (201801680). The IRBs at the FDOH, Florida International University, and the University of South Florida ceded to the UF. All participants provided written informed consent before participation, and individuals had the opportunity to opt out of the study. Identifiable participant data were maintained separately from research data on secure servers at the UF, and limited datasets were prepared by the data management team to ensure participant privacy and confidentiality. Data from the FDOH, including eHARS data, were only accessible through ResVault. Participants received incentive payments via gift cards or cash, depending on the study setting. The amount of compensation varied based on the number of questionnaires completed and the length of those questionnaires (ranging from US $10 to US $25 per questionnaire). Total compensation ranged between US $25 and US $120.

Results

Between October of 2020 and December of 2023, a total of 1291 people were screened. Of these, 172 (13.3%) were found to be ineligible, 34 (2.6%) were not interested, 179 (13.9%) provided consent but never completed the baseline questionnaire, 26 (2%) were withdrawn by the research team for various reasons (eg, duplicates or suspicious timing), and 44 (3.4%) were enrolled in a parallel study. In total, 836 (64.8%) people with HIV enrolled in the Florida Cohort study wave 3 and completed a baseline questionnaire. Most participants with HIV identified as non-Hispanic Black (n=397, 47.5%) and male (n=505, 60.4%) and were aged 50 years or older (n=487, 58.3%), and 131 (15.7%) identified as Hispanic. Most people with HIV reported some alcohol use, with 238 (28.5%) participants reporting at-risk use and 308 (36.8%) reporting low-risk use (Table 1).

Of the 836 participants with HIV, most (n=759, 90.8%) completed the modules in English, 27 (3.2%) participants completed the modules in Spanish, and 50 (6%) completed the modules in Haitian Creole.

Completion rates for additional questionnaires ranged from 94 to 85% (see Table 2). The follow-up rate for those eligible for the 12-month follow-up questionnaire was 54.7% (320/585). In addition, 97.5% 815/836) of the sample was linked to eHARS, and 63.3% (529/836) were linked to FDOH's electronic health record system.

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Table 1. Characteristics of people with HIV enrolled in the Florida Cohort study wave 3 (2020-2023) and of all people with HIV in Florida in 2022 [5].

Characteristic	People with HIV enrolled in this study (N=836), n (%)	People with HIV in Florida in 2022, %
Year of enrollment		
2020	38 (4.5)	__[a]
2021	324 (38.8)	—
2022	296 (35.4)	—
2023	178 (21.3)	—
Age (y)		
13-19	0 (0)	0.3
20-24	20 (2.4)	1.8
25-29	51 (6.1)	5
30-34	72 (8.6)	8.6
35-39	66 (7.9)	8.9
40-44	80 (9.6)	9.2
45-49	60 (7.2)	9.4
50-54	119 (14.2)	12
55-59	146 (17.5)	15
>60	222 (26.6)	29
Sex assigned at birth		
Male	505 (60.4)	74
Female	331 (39.6)	26
Gender (self-identified)		
Cisgender man	473 (56.6)	74
Cisgender woman	328 (39.2)	26
Transgender man	2 (0.2)	0
Transgender woman	20 (2.4)	0.5
Nonbinary	12 (1.4)	0
Race and ethnicity		
American Indian or Alaska Native	6 (0.7)	0.1
Asian	2 (0.2)	0.7
Hispanic	131 (15.7)	27.1
Native Hawaiian or Pacific Islander	0 (0)	0.1
Non-Hispanic Black	397 (47.5)	43.2
Non-Hispanic White	255 (30.5)	27.5
Multiracial or other	40 (4.8)	1.3
Rurality		
Rural, small town, or large rural town	52 (6.2)	—
Urban	779 (93.2)	—
Language of survey completion		
English	759 (90.8)	—
Spanish	27 (3.2)	—
Haitian Creole	50 (6)	—
Education		

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Characteristic	People with HIV enrolled in this study (N=836), n (%)	People with HIV in Florida in 2022, %
Less than high school	204 (24.4)	—
High school or general educational development	245 (29.3)	—
At least some college	386 (46.2)	—
Alcohol use		
At risk[b]	238 (28.5)	—
Not at risk	308 (36.8)	—
None	284 (34)	—
Site		
Alachua, Columbia, and Marion	251 (30)	—
Hillsborough	155 (18.5)	—
Miami-Dade	80 (9.6)	—
Polk	74 (8.9)	—
Palm Beach	83 (9.9)	—
Brevard	128 (15.3)	—
Duval	57 (6.8)	—
Online	8 (1.1)	—

[a]Not available.

[b]At-risk drinking was defined as scoring 3 or greater on the Alcohol Use Disorder Identification Test–Consumption measure for people with HIV assigned female at birth and 4 or greater for people with HIV assigned male at birth.

Table 2. Completion of the additional Florida Cohort study questionnaires.

Questionnaire	Eligible participants, n	Completed questionnaires, n (%)
Extended	590	545 (92.4)
Gender identity	33	31 (94)
Alcohol	252	230 (91.3)
COVID-19	313	287 (91.7)
Pet	260	221 (85)
Stigma	526	461 (87.6)
Antiretroviral therapy preference	245	210 (85.7)
12-month follow-up	585	320 (54.7)

Discussion

Anticipated Findings

The overall goals of the Florida Cohort study wave 3 were to identify barriers to and facilitators of HIV viral suppression and other steps of the HIV care continuum and monitor changing attitudes and beliefs that influence HIV care outcomes and beliefs among a diverse group of people with HIV in Florida. We also sought to learn more about alcohol consumption patterns and potential treatment interventions, understand the experiences of people with HIV related to the COVID-19 pandemic, and improve our understanding of the experiences of gender diverse individuals regarding HIV care and prevention. The Florida Cohort study also offered opportunities for ancillary data collection for other projects and will provide access to deidentified data for additional analyses.

The sample enrolled in wave 3 was similar to the overall population of people with HIV living in Florida [5]. There were a few exceptions to this. First, cisgender women and transgender people were overrepresented in the Florida Cohort study sample compared to their distribution statewide. Second, Hispanic people with HIV were underrepresented in wave 3. Although almost all questionnaires were available in Spanish, enrollment and data collection in Spanish were limited to 2 recruitment sites (Polk and Miami-Dade counties) that had a Spanish-speaking research assistant. Third, enrollment was higher in north and central Florida, which have lower overall prevalence of Hispanic people, than in south Florida, which has higher rates and total numbers of people with HIV [52]. Finally, the Florida Cohort study did not enroll people with HIV aged below 18 years. We did not enroll people with dementia or living in nursing homes. Therefore, adolescents and persons aged 70 or older were underrepresented.

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The Florida Cohort study wave 3 includes participants recruited from a network of clinics and organizations across the state. Unlike the previous wave, which focused largely on recruitment from FDOH clinics, wave 3 included a wider range of community clinics, case management agencies, and recruitment from the public. The Florida Cohort study wave 3 also included several counties that are listed as priority jurisdictions in the EHE initiative [3]. This wave also made a concerted effort to recruit key populations and surpassed the previous wave in recruitment of those who met the criteria for at-risk drinking, individuals who identified as transgender or gender nonconforming, and participants from rural areas, although the target of 150 was not met. Furthermore, we successfully enrolled a subset of participants who spoke Haitian Creole who had not been included in previous waves of the Florida Cohort study but will be helpful in understanding and addressing HIV disparities. People with HIV of Haitian descent are more likely to be diagnosed at a later stage and not achieve key steps in the HIV care continuum [53-55].

A major challenge to enrollment, especially during the first year of the study, was the COVID-19 pandemic and changing mitigation strategies implemented across the state at different times. This study was originally slated to start in March 2020, but the pandemic delayed the initiation of the study until October 2020. This study relied heavily on recruitment through clinics, which shifted to telehealth during the pandemic. Moreover, the management and staff at clinics that maintained in-person visits were understandably hesitant to allow recruiters into clinical spaces. In response, the team shifted to remote recruitment, which was generally less successful than in-person recruitment. Relying on remote recruitment methods where clinical staff served as intermediaries led to lower-than-expected enrollment in the first year of the study for all active sites, and this pattern continued in Miami-Dade County, where the COVID-19 restrictions lasted the longest.

Many lessons were learned during the implementation of this study. To reach a wider range of people with HIV and help the study better integrate into the clinic flow in a variety of settings, this study offered participants many ways to enroll, complete the surveys, and receive compensation. Although this worked well for many participants and sites, it also greatly complicated research staff training and the administration of the study. In addition, some of these methodologies worked better than others. For example, sites that offered consent forms, questionnaires, and payments via US mail frequently encountered problems with items being lost or participants returning either the consent forms or the questionnaires but not both. Once clinics began seeing patients in person again and allowed recruiters back into the clinic, the study team found that obtaining consent from participants in person and following up with a link to the questionnaires worked the best for most participants.

Follow-up rates for the 12-month questionnaire were lower than desired, although follow-up questionnaire data were not needed to answer the key study research questions. To improve follow-up rates, we would benefit from more consistent staffing and strategies to try to keep people more engaged in the study. We had limited face-to-face connections with people, and that could have also impacted follow-up rates. We successfully integrated new questionnaire items and collected information that individual researchers and graduate students could use for their research. At least 3 faculty members are using the Florida Cohort study data to support their research funded by National Institutes of Health individual career development awards, and at least 5 graduate students in epidemiology and nursing are using the data as part of their doctoral dissertations. This study offered opportunities for the research team to engage with clinic staff and HIV service team members across the state. By working with multiple clinic settings and locations, the investigators could learn about issues that were emerging in the community and that could be added to our questionnaires. Community members also helped us update our stigma questionnaire.

In the future, coded data without direct identifiers from this study may be linked to other datasets using a hash ID number, created by a formula that uses direct identifiers but cannot readily identify an individual. Subsequently, all ID numbers, dates, and codes can be removed to prepare a completely deidentified dataset. With IRB review and approval, this procedure has been tested linking data from the Florida Cohort study questionnaires to clinical, dispensing and claims data from the OneFlorida+ Data Trust, which includes medical information for more than 20 million patients on both public and private insurance [56], and the Substance Abuse Mental Health Information System, which includes information on substance use and mental health treatment.

Limitations

Our team used different recruitment strategies across different recruitment sites; therefore, it is not appropriate to compare any health behaviors or outcomes specifically by recruitment setting. Because we used a convenience sampling method, and non-English questionnaires were not available at all sites, any comparisons across race and ethnicity will need to be done with caution. In addition, several items, including ART preferences and COVID-19 vaccinations, were updated over time, limiting the ability to assess these constructs longitudinally. However, key measures such as symptoms of depression and anxiety and alcohol use remained the same.

Conclusions

In summary, the Florida Cohort study wave 3 enrolled a diverse group of people with HIV from several sites around the state, including both EHE and non-EHE counties. The data can be used to help address key barriers to steps in the HIV care continuum and achieve the goals of the EHE initiative within the state. The Florida Cohort study wave 4 began enrollment in 2024 and will include many of the core measures from wave 3 with additional items collecting formative data to inform alcohol and mental health interventions and enrolling people with HIV from new recruitment locations.

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Acknowledgments

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Data Availability

The questionnaire datasets generated and analyzed during this study are available from the Southern HIV and Alcohol Research Consortium Concepts System on reasonable request. Requests should be submitted via the Southern HIV and Alcohol Research Consortium Concepts System [57]. Data from the Enhanced HIV/AIDS Reporting System is not publicly available due to Florida Department of Health policy but can be requested from the Florida Department of Health. Access to the Enhanced HIV/AIDS Reporting System data requires a separate data use agreement.

Conflicts of Interest

JK has participated in the Speaker Bureau for Gilead Sciences and ViiV Healthcare. All other authors have no conflicts of interest to declare.

Multimedia Appendix 1
CHERRIES checklist.
[DOCX File , 20 KB - resprot_v14i1e69702_app1.docx]

Multimedia Appendix 2
STROBE checklist.
[DOCX File , 34 KB - resprot_v14i1e69702_app2.docx]

Multimedia Appendix 3
Peer review report from ZAA1 DD (10) - National Institute on Alcohol Abuse and Alcoholism Special Emphasis Panel CHAART Consortium RFA (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 145 KB - resprot_v14i1e69702_app3.pdf]

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Abbreviations

ART: antiretroviral therapy
CHERRIES: Checklist for Reporting Results of Internet E-Surveys
eHARS: Enhanced HIV/AIDS Reporting System
EHE: Ending the HIV Epidemic
FDOH: Florida Department of Health
IRB: institutional review board
REDCap: Research Electronic Data Capture
SHARC: Southern HIV and Alcohol Research Consortium
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
UF: University of Florida

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Protocol

Investigating the Role of Coenzyme A Restriction in the Pathophysiology of Preeclampsia: Protocol for a Combined Patient Screening and Laboratory Study

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Abstract

Background: Preeclampsia is 1 of the 3 leading causes of maternal mortality worldwide. Unfortunately, its exact pathogenesis is still unclear. Published metabolomic and gene expression analyses point to coenzyme A (CoA) restriction in the placenta as a factor underpinning the observed complications of preeclampsia, but this hypothesis has never been tested.

Objective: This pilot study aims to discover evidence supporting the CoA-restriction hypothesis through 2 avenues. The first of these involves developing a procedure for the quantitative determination of metabolites to discover if harmful metabolites are elevated in patients with preeclampsia, while the second seeks to emulate the onset of CoA restriction in cultured cells.

Methods: This manuscript provides a rationale and a protocol for a clinical study and laboratory experiments to test the hypothesis. The methods have 3 key aspects. Phase 1 comprises optimization of assays of 5 key metabolites arising from CoA restriction, namely L-leucine, ketoisovalerate, ketodeoxycholate, oleic acid, and sphingosine-1-phosphate. Phase 2 comprises recruitment of patients to obtain serum samples to measure the metabolites, and phase 3 comprises culturing and treating trophoblast cells to induce CoA restriction and test the effects of the metabolites on the cells. Patients with preeclampsia and healthy controls will be recruited based on World Health Organization criteria for preeclampsia. Exclusion criteria include multiple pregnancies, premature rupture of membranes, and various medical complications. Blood samples will be collected and analyzed using high-performance liquid chromatography/mass spectrometry (HPLC/MS) to quantify key metabolites associated with CoA restriction. For trophoblast cell studies, BeWo cells will be cultured under conditions likely to induce CoA restriction, including hypoxia and human chorionic gonadotropin supplementation, and will also be treated with the key metabolites to determine what effect they might have. Cell viability, apoptosis, energy metabolism, and gene expression (focusing on genes involved in CoA synthesis and metabolism) will be assessed. Statistical analysis will involve 2-tailed *t* tests or Mann-Whitney *U* tests to compare metabolite concentrations between patients with preeclampsia and controls. A correlation matrix will be used to explore associations between metabolite levels and patient characteristics.

Results: Institutional review board ethics approval has been obtained for this study. Patient recruitment started April 1, 2025. The 5 metabolites have been purchased in synthetic form and used to optimize the HPLC/MS assays in preparation for receiving blood samples. The trophoblast cell-line culture is being optimized.

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Conclusions: The findings of this study will demonstrate that key metabolite concentrations can be quantified using HPLC/MS and indicate if CoA restriction is associated with preeclampsia. If so, this provides a significant, novel avenue for research into the treatment and prevention of the disease.

International Registered Report Identifier (IRRID): PRR1-10.2196/66202

(JMIR Res Protoc 2025;14:e66202) doi:10.2196/66202

KEYWORDS

preeclampsia; coenzyme A restriction; patient samples; cell culture study; high-performance liquid chromatography-mass spectrometry

Introduction

Background

Preeclampsia is a major pregnancy-related disorder that affects approximately 3% to 10% of pregnancies worldwide [1], and it is also 1 of the 3 leading causes of maternal morbidity and mortality [2]. Women affected by preeclampsia usually present with new-onset hypertension and proteinuria developing during the second half of pregnancy, though presentation can vary. In severe cases, organ damage to the kidney and liver occurs, with hematological involvement and, if left to progress, women will experience neurological complications including seizures or eclamptic fits [3,4]. The babies of women with preeclampsia are at increased risk of intrauterine growth retardation, placental abruption, preterm rupture of membranes, premature delivery, and death [5]. It is therefore important to further investigate the pathophysiology of preeclampsia and potential drug targets, with the aim of reducing maternal mortality and morbidity worldwide.

Unfortunately, the exact pathogenesis of preeclampsia is still unclear, although it is generally thought that dysfunction of the maternal endothelium caused by systemic inflammation and oxidative stress plays a critical role in the development and progression of the disease [6]. A multiomics analysis of 7 untargeted studies has shown that a reduced level of placental coenzyme A (CoA) explains the change in concentration of at least half (26/51) of perturbed plasma metabolites in the first trimester of women who go on to be affected by preeclampsia [3]. Also, gene-expression changes indicate a reduced ability to synthesize CoA from vitamin B5, reduced expression of genes for enzymes consuming free cytosolic CoA, and elevated expression of enzymes releasing CoA from thioesters [3]. CoA is a fundamental carrier of acyl groups in many metabolic pathways that are critical for the cellular reactions involved in energy metabolism and branched-chain amino acid degradation [3]. Therefore, any disruption in the synthesis of this essential cofactor can lead to a disruption in energy metabolism and have significant physiological consequences, including preeclampsia.

Perturbed Metabolites

In this context, CoA restriction leads to elevated levels of potentially harmful metabolites, even in the first trimester. These include dietary unsaturated fatty acids, sphingosine-1-phosphate, branched-chain amino acids and their keto acids, and ketodeoxycholates (Figure 1) [7]. Unsaturated fatty acids, including oleic acid, bind to peroxisome proliferator activator receptor α (PPARα), promoting peroxisome formation. Transcriptomic data reveals elevated expression of genes for peroxisomal proteins. Particularly under CoA restriction, this can explain the known oxidative stress observed in preeclampsia. Depending on the receptors to which it binds, sphingosine-1-phosphate exerts various physiological effects, including cell survival, angiogenesis, vasoconstriction (inducing hypertension), macrophage recruitment, inflammation, and programmed cell death [8].

Figure 1. Clinical consequences of placental coenzyme A (CoA) restriction. Text in blue, red, black, and purple respectively denotes reduced concentrations, elevated concentrations, physiological conditions, and pathological states. Red and blue arrows respectively represent increased and decreased molecular concentrations. Black arrows depict the chains of consequence leading to disease states. The dashed lines separate different areas of metabolism. Pantothenate kinase 1 (PANK1) is the initial and regulatory enzyme in CoA synthesis from vitamin B5. This leads to elevated levels of unsaturated fatty acids, sphingosine-1-phosphate, and interruption of branched-chain aliphatic amino acid degradation. PPARα: peroxisome proliferator activator receptor α.

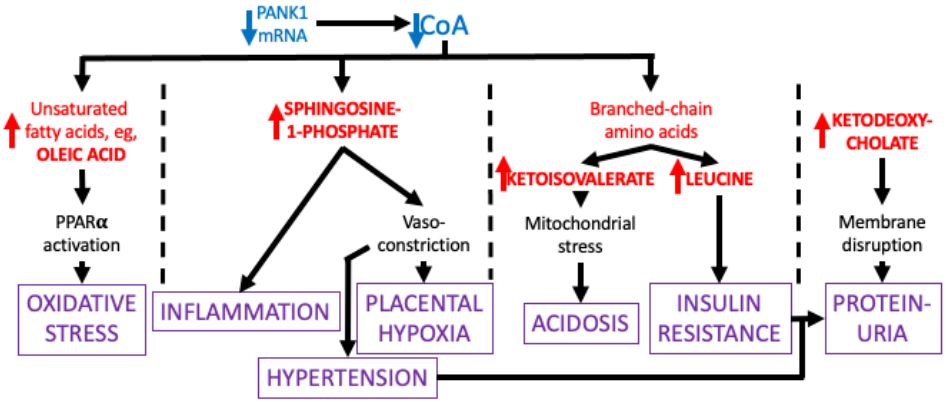

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The plasma levels of 6 amino acids are significantly elevated, including the branched chain amino acids valine, isoleucine, and leucine [3]. The latter can cause insulin resistance by blocking signaling via the mammalian target of rapamycin complex 1 (mTORC1), providing an explanation for the sometimes-observed elevated glucose level and possibly contributing to the proteinuria typical of preeclampsia. The equivalent ketoacids of these amino acids, as well as some of their intermediate degradation products, are elevated (indicative of CoA restriction) and are known to cause mitochondrial stress, acidosis, and neurotoxicity, especially 2-oxomethyl butanoic acid (also known as ketoisovaleric acid), 3-hydroxyisovaleric acid, and 3-hydroxybutanoic acid. Ketodeoxycholates are secreted from and recycled by the liver to disrupt ingested membranes. At high enough levels in plasma, they can disrupt the cell membranes of many organs, including the kidney (leading to proteinuria), blood cells, and the liver (contributing to hemolysis, elevated liver enzymes, and low platelets syndrome [HELLP]). The past multiomics study mentioned above also identified adverse positive-regulatory feedback loops [3]. In placental cells, they can cause a progressive increase in the concentration of the harmful metabolites that ultimately causes preeclampsia. Finally, it should also be noted that oleic acid, sphingosine-1-phosphate, and ketoisovaleric acid are also members of a predictive biomarker set for preeclampsia [7].

Placental Gene Expression Changes in Preeclampsia

A meta-analysis [9] revealed that the expression of over 7600 genes in the placenta is altered in preeclampsia. To test the hypothesis of CoA deficiency, the present study will focus on genes influencing the synthesis pathway of CoA and the above metabolites, as well as on insulin resistance. The pantothenate kinase 1 (PANK1) gene, whose transcription levels are low, and even lower in preeclampsia, encodes the crucial first step in CoA synthesis. Programmed cell death is thought to repress PANK1, which at this early stage is probably due to hypoxia. However, expression of the gene for the final step of CoA synthesis, dephospho-CoA kinase (DCAKD), is elevated. In preeclampsia, lipoprotein lipase (LPL) gene expression is elevated, which increases the release of fatty acids from chylomicrons, including oleic acid. The initial step in the pathway to sphingosine-1-phosphate is catalyzed by serine palmitoyl transferase, whose activity is increased by the elevated expression of its activator (serine palmitoyltransferase small subunit A [SPTSSA]).

Branched-chain amino acids are usually degraded within mitochondria. However, in preeclampsia, the placenta also overexpresses the gene for cytosolic branched-chain amino-transferase 1 (BCAT1), allowing ketoisovalerate to be produced even in the cytosol. In mitochondria, the next step of branched-chain amino-acid degradation is impeded by the elevated expression of an inactivating protein kinase (branched-chain ketoacid dehydrogenase kinase; BCKDK), whose expression should otherwise be repressed by the activated PPARα. Finally, the expression of phosphatidyl choline transfer protein (PCTP) is elevated to enable free fatty acids to enter mitochondria, but this protein also blocks insulin signaling via mTORC1, and it is of interest for this reason.

Trophoblast Biology

Preeclampsia can occur in the absence of a fetus but in the presence of trophoblast tissue with hydatidiform moles [10], indicating a crucial role for trophoblasts. Indeed, trophoblasts play a principal role in placental development [11]. Their cell lineage begins with cytotrophoblasts, which are the initial stem cells that proliferate in the first and second trimesters and go on to form daughter cells with defined roles. Those in the cell column first specialize into extravillous trophoblasts, from which 2 further cell types arise. Interstitial extravillous trophoblasts anchor the growing placenta to the uterus, while endovascular extravillous trophoblasts invade the maternal spiral arteries, replacing the endothelial lining to allow low-pressure perfusion of maternal blood through a lumen to the maternal veins.

This lumen is filled with chorionic villi, providing a very large surface area permitting exchange of gases and biochemicals between the maternal and fetal vascular systems. These villi have two cell layers. Cytotrophoblasts line the layer next to the fetal blood, while multinucleated syncytiotrophoblasts coat the surface next to the maternal blood. The latter are formed by trophoblast-cell fusion, which is promoted by human chorionic gonadotrophin (hCG) and insulin-like growth factors [12,13].

Trophoblasts have been grown in cell culture for 60 years. Apart from primary cell cultures and immortalized cell lines, there are also several gestational choriocarcinoma cell lines [14]. Of the latter, BeWo cells are derived from a cytotrophoblast and widely used as a model because they can also fuse to form a syncytium [15]. A recent transcriptomic comparison of cell lines indicated that none were very similar to various trophoblasts extracted by cell sorting, though BeWo cells were the closest [14]. However, a study focusing on a subset of preeclampsia markers showed that a BeWo-hypoxia model mimics a key pathogenic mechanism of preeclampsia [16]. Programmed cell death plays a critical role in embryonic implantation and placental development, but hypoxia and/or oxidative stress are thought to cause early aberrant trophoblastic cell death [17] that eventually results in preeclampsia.

Aims of This Study

Prior work indicates that CoA levels are reduced in the first trimester of pregnancies, triggering the rise of harmful metabolites that later cause preeclampsia. It is extremely difficult to test this hypothesis by direct measurement of CoA concentration, because it is bound to many different metabolites and proteins, and obtaining a biopsy from the diseased part of a placenta would be difficult and highly invasive. However, the metabolites generated as a consequence of CoA restriction are readily detected using mass spectroscopy, even though they are a mixture of hydrophilic and hydrophobic molecules. Hence, this pilot study aims to uncover evidence supporting the CoA restriction hypothesis through 2 avenues. The first of these is to provide the proof of concept of a methodology to quantify the metabolites (specified in Figure 1) and then compare the levels in patients with preeclampsia versus matched controls. The second seeks to emulate the onset of CoA restriction in cultured cells.

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Hence, this article outlines a 3-phase protocol (protocol version 1.1, May 23, 2024) for clinical samples and cell culture studies to screen for the indirect effects of CoA restriction (Figure 2). Initially, laboratory methods will be developed to quantify levels of the harmful metabolites in serum. Then, blood samples from patients with preeclampsia and matched controls will be taken to determine if the predicted harmful metabolites are elevated in patients with the disease. In parallel, trophoblast cells will be stressed to induce CoA restriction, and then investigated in 3 ways. The first will determine if the harmful metabolites appear in the cell culture medium, while the second will study the effect of these metabolites on otherwise healthy cells and the third will determine the expression level of genes known to be affected by the disease (ie, those described in the Placental Gene Expression Changes in Preeclampsia section) to determine if they have significantly changed.

Figure 2. Flow of materials and data through the CoA restriction study. The in vivo and in vitro components are demarcated by the dashed line. The top row of boxes indicates the control and disease or stressed material that is fed into the middle blocks, denoting laboratory techniques. The output data from these assays are then subject to statistical analysis to identify significant changes. Cell status refers to assays of cytotoxicity, apoptosis, and energy metabolism. HPLC/MS: high performance liquid chromatography/mass spectrometry; PE: preeclampsia; qPCR: quantitative polymerase chain reaction.

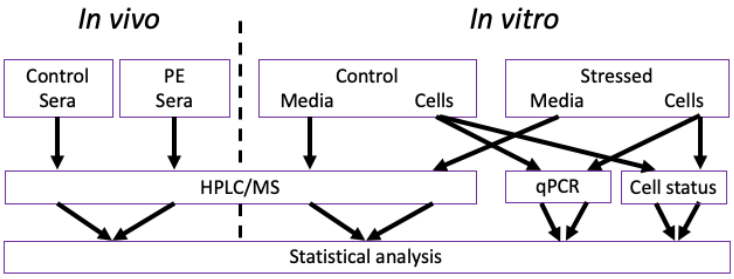

Methods

Objectives

This study has 3 objectives: first, develop a set of targeted high performance liquid chromatography/mass spectrometry (HPLC/MS) assays to accurately quantify the concentration of key harmful metabolites in patient blood samples and cell culture media; second, use this set of targeted assays to measure harmful metabolite concentrations in patients with preeclampsia and compare them with healthy controls to determine if they are elevated in preeclampsia; and third, subject the cultured trophoblasts to hypoxia and the harmful metabolites to determine what conditions initiate CoA restriction.

After completion of objective 1, the flow of materials, laboratory investigation, and data analyses will follow the paths outlined in Figure 2.

Development of Targeted Metabolomic Assays

Oleic acid (Sigma 05508), sphingosine-1-phosphate (Sigma 860492P), L-leucine (Sigma L8000), 3-methyl-2-oxobutyrate (Sigma 198994), and 12-ketodeoxycholic acid (Sigma SMB00913) have been purchased from Sigma Chemical Co. Pure compounds are solubilized and analyzed by direct infusion into an Orbitrap Exploris 480 mass spectrometer (Thermo Fisher Scientific Inc), the abundant intact precursor mass adducts are identified, and the collision energy is optimized for tandem mass spectrometry profiling. The compounds are then diluted in 0.1% formic acid and injected across a 15-cm C18 column to determine their retention time. The resulting precursor-fragment transitions and retention time boundaries thus constitute the specific assays for each metabolite.

The metabolite extraction procedure and absolute quantification limits are then optimized by spiking the metabolite standards into and then extracting them from the commercially available National Institute of Standards and Technology standard plasma matrix.

Recruitment

Women with preeclampsia will be identified by the obstetricians collaborating with the study from the antenatal clinics and wards at Latifa Hospital in Dubai. Women with preeclampsia who meet the inclusion criteria outlined below will be approached verbally, asking if they would like to participate in this study. A patient information sheet will be provided, and after they provide written informed consent, they will be recruited into the study.

Baseline clinical and laboratory characteristics will be collected from the patients' medical notes, including obstetric history, booking weight, height, renal and liver function, comorbidities, and smoking history. A data collection form has been designed for this purpose (Multimedia Appendix 1). The collected data will be anonymized and linked to samples by study ID only. Concurrent control participants will be identified following a review of the antenatal clinic lists to seek women with uncomplicated pregnancies who are undergoing routine antenatal care in the same antenatal clinic at Latifa Hospital in Dubai. Controls will be matched for approximate weight, age (5-year age group) and week of gestation. Control participants who meet the inclusion criteria outlined below will also be approached verbally, asking if they would like to participate in this study.

Patient blood samples will be taken at the time of routine phlebotomy for blood tests required as part of clinical care. As such, no adverse events specifically related to the study procedure are anticipated.

Blood samples will be collected in a heparinized EDTA (ethylenediaminetetraacetic acid) 10-ml container and transported immediately on ice to the laboratory for processing, as described in Blood Metabolite Analysis section below. One

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member of the research team has the responsibility for sample processing to ensure consistency. Metabolite measurements will be conducted by 2 members of the research team.

Preeclampsia will be defined as per the WHO Recommendations for Prevention and Treatment of Pre-eclampsia and Eclampsia [18]; specifically, the onset of a new episode of hypertension during pregnancy, characterized by persistent hypertension (diastolic blood pressure ≥90 mm Hg), and substantial proteinuria (>0.3 g/24 hours or more or a protein level of +2 or above in the urine dipstick test). The gestational week in which the sample is collected will be recorded for all women.

The exclusion criteria will include multiple pregnancy (eg, twins or higher-order gestations), premature rupture of the membranes; chorioamnionitis; oligohydramnios; fetal growth restriction; polyhydramnios; fetal anomalies; local or systemic diseases; tobacco use; and medical complications, including autoimmune disorders (antiphospholipid syndrome, systemic lupus erythematosus, hemolytic uremic syndrome, acute fatty liver of pregnancy, thrombotic thrombocytopenic purpura, and pheochromocytoma); hematologic disease; neurologic disorders; gestational hypertension; hereditary or acquired antithrombin III deficiency; connective tissue disease; diabetes mellitus; chronic hypertension; inflammation; and chronic renal diseases, as well as regular treatment within the last 3 months with aspirin, antihypertensive drugs, nonsteroidal anti-inflammatory drugs, or antibiotics [19].

Blood Metabolite Analysis

Briefly, 10 ml of blood will be collected in Becton Dickinson (BD) Vacutainer glass plasma tubes with either sodium heparin (366480, green closure) or sodium citrate (366415, blue closure) as an anticoagulant. Blood will be centrifuged at 2400 relative centrifugation force for 20 minutes at 4 °C to separate the plasma. Both the separated plasma and cell-culture medium will be stored at –80 °C. Before the analysis, precipitation of the plasma protein will be done by adding 200 µl of acetonitrile to 100 µl of a thawed plasma sample followed by vortexing. The solution will be then centrifuged at 18,000 relative centrifugation force at 4 °C for 10 minutes and the supernatant dried and reconstituted using 100 µL of water/methanol solution (95:5) containing 0.1% formic acid prior to 2 µL being injected and analyzed with HPLC/MS.

For HPLC/MS, the gradient is held for 1 minute at 5% mobile phase B, and it then progresses from 5% to 10% B over a period of 1 minute, 10% to 25% B over 2 minutes, 25% to 60% B over 2 minutes, and 60% to 95% B over 6 minutes, after which it is held at 95% B for 2 minutes, followed by washing and column equilibration steps. Mobile phase A uses water acidified with 0.1% formic acid, and mobile phase B uses 80% acetonitrile-water acidified with 0.1% formic acid. The mass spectrometry analyses will be performed using the targeted assay settings described above. Samples will then additionally be analyzed with untargeted methods developed for untargeted metabolomics [20-25].

Trophoblast Growth and Treatments

First, human placental–derived choriocarcinoma trophoblastic (BeWo) cells will be obtained from the American Type Culture Collection. In the unlikely event that this cell line is ineffective, others are available for investigation. The cells are cultured in Dulbecco's modified Eagle's medium/12 Ham's media (Sigma; catalog number D8437; 500 ml) supplemented with 10% fetal bovine serum (Sigma; catalog number F9665; 500 ml) and 1% penicillin streptomycin (Sigma; catalog number P4333; 100 ml). A total of 1×10^6 cells are dispensed into a culture flask, and the cells are incubated at 37 °C in a 5% CO_2 incubator for cellular attachment.

The first set of treatments will involve a solvent control and cells subjected to hypoxia, hCG supplementation (obtained from ProspecBio; catalog number HOR-250; 5 mg), or both to stimulate syncytialization. Cytotoxicity assays will be carried out as described below. The second set of treatments will involve addition of the abovementioned harmful metabolites at a range of concentrations and screened for cytotoxicity. Cells showing evidence of stress in microscopy will be tested for cytotoxicity, apoptosis, and energy metabolism, as described below. In such cases, the culture medium will be used for metabolite screening, as outlined above. The cells will be harvested to determine the expression level of 7 key genes, as described below, and stored frozen for transcriptomic analysis in a future project.

Trophoblast Cell Studies

Cell viability will be determined using a standard MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay kit (Abcam, catalog number ab197010; 250 tests) [26] according to the manufacturer's protocol. Energy metabolism will be studied by measuring glucose uptake and the adenosine diphosphate (ADP) to adenosine triphosphate (ATP) ratio, as described previously in the literature [27]. Given the known elevated expression of a membrane scramblase in the placenta of patients with preeclampsia [9], apoptosis and necrosis will be assessed using the Annexin V-FITC kit (Beckman Coulter), according to the manufacturer's instructions. Analysis will be performed using a BD FACsAria flow cytometer, collecting a total of 100,000 events. For cultures that appear stressed, metabolite concentrations will be determined by extracting metabolites from the culture medium and analyzing them with HPLC/MS in the same way as described above for the plasma samples.

Gene Expression Profiling

Primers for the BCAT1, BCKDK, DCAKD, LPL, PANK1, SPTSSA, and PCTP genes will be determined using the web tool provided by Thermo Fisher Scientific. After treatment, the BeWo cells will be gently washed with precooled phosphate-buffered saline. Total RNA will be extracted using the RNeasy mini kit (Qiagen). Quantitative polymerase chain reaction (qPCR) will be performed with a real-time PCR detection system and software (Applied Biosystems).

Data and Statistical Analysis

The patient metabolite-concentration data will be examined to determine differences between the preeclampsia and healthy patient samples and to determine if they follow normal distributions. If they do, paired and unpaired 2-tailed *t* tests will be carried out to determine if the concentrations are significantly different. If they are not, then the Mann-Whitney *U* test will be

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used. These same tests will be used for metabolite concentrations in the in vitro cell cultures. A correlation matrix will be calculated between the metabolite concentrations and patient characteristics, including weight, age, and week of gestation, to determine if there are any associations. In addition to the planned targeted analysis to test our hypothesis, the plasma metabolomes will also be measured with untargeted HPLC/MS, and the data will be analyzed using multiple-testing correction-adjusted *t* tests and partial least-squares discriminant analysis to identify which metabolites are altered by preeclampsia status. Pathway enrichment will be used to identify dysregulated pathways, which will then be compared with previously published data.

Power

This prospective, cross-sectional, case-control study will include 40 pregnant women, with 20 women diagnosed with, followed up on, and treated for preeclampsia at Latifa Hospital in Dubai, and 20 women (matched for approximate weight, age [5-year age group], type of pregnancy [single or multiple], and week of gestation) with normal pregnancies. This is about half the numbers in previous metabolomic studies of preeclampsia but should be sufficient to produce the variability required given that matched controls are involved. If not, this pilot study will provide the data to carry out a sample-size calculation for a future larger clinical study. The analysis of data from this study will be primarily focused on descriptive statistics and estimates of precision to inform a planned larger validation study. The proposed sample size in our study is also consistent with the findings from a study on the target sample sizes set for pilot and feasibility randomized controlled trials in the United Kingdom [28].

For the HPLC/MS metabolite measurement, assuming a coefficient of variance of 30%, which corresponds to several multiples of observed technical variation, power calculations indicate this study will be 80% powered to detect changes of 27%. The minimum detectable effect size was calculated using G*Power [29,30].

Ethical Considerations

The study has been granted approval by the institutional research board (IRB) of the Mohammed Bin Rashid University of Medicine and Health Sciences and the Dubai Scientific Research Ethics Committee (reference DSREC-05/2024_06). The approval includes consent forms, patient information leaflets in English and Arabic, and the data collection sheet. In addition, the consent form includes a statement informing patients of the option to opt out from the use of their samples for future secondary studies. The information leaflet and consent process clearly indicate to patients that they may also opt out of the study at any point in the process. All patient data will be anonymized. Patients will be given a study number, which will be used for any analysis. The code for the study ID linking it to the patient will only be available to 2 members of the research team, who will be collecting the clinical data. The clinical data will be deidentified when shared with the remainder of the study team for analysis. Patients' privacy and confidentiality is included in the IRB approval process and given high importance within the study team. Additional statistical analysis may be sought from statisticians with expertise in scientific methods. The final dataset will remain property of the university sponsoring the research and the study investigators while they carry out the roles identified in the IRB ethics approval. The study is funded by an internal university grant without commercial sponsors or competing interests. No financial compensation will be offered to patients other than any associated travel expenses.

Results

We have developed a targeted, standards-based HPLC/MS metabolomic assay calibration method. The targeted assays for L-leucine, 3-methyl-2-oxobutyrate, and 12-ketodeoxycholate (using parallel reaction monitoring) have been successfully developed and optimized. Work is presently ongoing to develop optimized chromatography and metabolite extraction and targeted parallel reaction monitoring HPLC/MS methods for oleic acid and sphingosine-1-phosphate. Evaluation of quantitative metrics, such as limits of detection and limits of quantification, are also ongoing. Data analysis has not yet commenced, but we anticipate that initial results for analysis and publication will be available by June 2026. Multimedia Appendix 2 shows a Gantt chart of the project timeline.

Discussion

Comparison With Prior Work

Prior metabolomic studies have sought to identify first-trimester biomarkers to predict preeclampsia occurring later in the pregnancy. These biomarkers were investigated by Hodgman et al [3], who took an approach combining their data with that of published gene expression and genome-wide association studies to uncover regulatory mechanisms that can explain the pathophysiology of preeclampsia. Given our prior observations, we hypothesize that the metabolites chosen for quantitative screening should be highly elevated in patients with preeclampsia, to a level that can explain the symptoms observed in the disease. The cell culture experiments aim to uncover what conditions cause elevated levels of the placenta-derived metabolites, with the gene expression profiling showing key transcriptional changes involved in generating these metabolite changes.

Limitations

This pilot study depends on being able to quantify metabolite levels using our equipment, which can be considered a limitation. If our objectives are achieved, the next potential limitation is the number of patients with preeclampsia and matched controls. At the very least, we expect to identify trends in the data. If the sample size is too small, then the data from this work will form the basis for a power calculation in a future study. Based on the current literature, the trophoblast culture experiments should succeed in revealing elevated levels of the harmful metabolites investigated in this study. If not, the work at least rules out certain possibilities, providing ideas for future studies.

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Conclusions

This pilot study describes a protocol for an ongoing study to develop a technique for quantifying the concentrations of key metabolites using HPLC/MS and then using it to screen cultured trophoblast cells and blood from healthy patients and patients with preeclampsia. This is a step toward testing the hypothesis that CoA restriction early in pregnancy leads to the elevation of metabolites that induce the symptoms of preeclampsia. Although we currently do not have any results to report, the publication of our protocol should aid research collaboration and early feedback. It could also reduce duplication of effort by other research groups. The output from this study has broader implications for the study of preeclampsia, with potential further applications to other significant antenatal diseases, such as hypertension, proteinuria, fetal growth restriction, HELLP, and gestational diabetes.

Data Availability

All metabolomics data generated as part of this study will be publicly available at the Metabolomics Workbench [31], a website of the NIH Common Fund's National Metabolomics Data Repository, where it will be assigned a unique project ID and accessed directly via its project DOI.

Authors' Contributions

Conceptualization: CH and WA
Methodology: RA-J, RKJ, ADG, AP, RR, WA, CH
Writing—original draft preparation: RA-J, RKJ, WA, CH
Writing—review and editing: RA-J, RKJ, ADG, AGS, FGM, RR, WA, CH
Supervision: RA-J, RKJ, RR, WA, CH
Project administration: RA-J, WA
Funding acquisition: RA-J, RKJ, AGS, FGM, RR, WA, CH

Conflicts of Interest

None declared.

Multimedia Appendix 1
Approved clinical data collection form.
[DOCX File , 47 KB - resprot_v14i1e66202_app1.docx]

Multimedia Appendix 2
Gantt chart project and dissemination plan.
[PPTX File , 47 KB - resprot_v14i1e66202_app2.pptx]

Multimedia Appendix 3
Peer review report from MBRU (Mohammed Bin Rashid University) College of Medicine Internal Grant Award 2023-2025.
[PDF File (Adobe PDF File), 215 KB - resprot_v14i1e66202_app3.pdf]

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Abbreviations

ADP: adenosine diphosphate
ATP: adenosine triphosphate
BCAT1: branched-chain amino-transferase 1
BCKDK: branched-chain ketoacid dehydrogenase kinase
BD: Becton Dickinson
CoA: coenzyme A
DCAKD: dephospho-CoA kinase
EDTA: ethylenediaminetetraacetic
hCG: human chorionic gonadotrophin
HELLP: hemolysis, elevated liver enzymes, and low platelets syndrome
HPLC/MS: high performance liquid chromatography/mass spectrometry
IRB: institutional research board
LPL: lipoprotein lipase
mTORC1: target of rapamycin complex 1
PANK1: pantothenate kinase 1
PCTP: phosphatidyl choline transfer protein
PPARα: peroxisome proliferator activator receptor α
qPCR: quantitative polymerase chain reaction
SPTSSA: serine palmitoyltransferase small subunit A

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Protocol

Assessing Day-to-Day Emotion Dynamics Within the Whole Family: Protocol for a Family-Wide Ecological Momentary Assessment Study (The Family and Child Emotion Study)

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Abstract

Background: Families play a pivotal role in shaping children's emotional development through emotion socialization. However, most research has focused on individual or dyadic relationships, such as those between parents and children, overlooking the more complex dynamics that emerge when multiple family members interact simultaneously. This limited perspective fails to capture the full scope of the interconnected emotional processes within family units. A contributing factor to this gap is the limited availability of models suited for capturing and analyzing complex, family-level data.

Objective: The Family and Child Emotion Study aims to address this gap by examining family-wide emotion dynamics across all family members—including parents and children—as they naturally unfold in daily life.

Methods: This protocol uses a pre-post design and a 7-day ecological momentary assessment period combined with ambulatory monitoring of heart rate and electrodermal activity within whole family units to examine interactions among mothers, fathers, and siblings, providing a comprehensive understanding of family-wide emotion processes. Data will be analyzed using a network analytical approach, specifically multilevel vector autoregressive modeling, to investigate dynamic emotional processes within and between family members.

Results: Funding was received in April 2020. Data collection began in September 2022 and will continue until March 2026. As of May 2025, the Family and Child Emotion Study has collected data from 48 eligible families. Data analyses will begin after March 2026, with results expected to be published in Fall 2027.

Conclusions: This study introduces an innovative approach for examining emotion dynamics within whole-family systems in naturalistic settings, offering practical guidance for collecting and analyzing complex, multilevel, and nested data. The primary aim is to investigate how family emotion networks contribute to children's emotional functioning and development. A secondary aim is to explore key factors, such as parental psychological functioning and child emotion regulation abilities, that may shape these networks. This protocol serves as a valuable framework for future researchers exploring family-wide emotion dynamics.

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KEYWORDS

ecological momentary assessment; family; child; emotion; physiology; regulation

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Introduction

Background

Emotions are central to our behaviors, social interactions, and daily functioning. Key emotional skills, such as recognizing, labeling, and regulating emotions, are crucial for optimal functioning within society. Children who struggle with emotion regulation are at a higher risk for a range of negative outcomes, including academic and social difficulties, impaired executive functioning, and psychopathology [1-5]. Therefore, understanding the processes that foster healthy emotion development in children is essential for promoting positive health and well-being. A robust body of literature identifies the family, and particularly parents and caregivers (hereafter "parents"), as a primary influence in shaping children's emotional development through emotion socialization [6-8]. Emotion socialization is the process through which children learn how to understand, express, and regulate emotions, primarily through interactions with caregivers, family members, and broader social contexts [6]. Most research on emotion socialization to date has focused on mother-child interactions. In recent years, research on emotion socialization has expanded to include fathers and siblings, yet still to a much lesser degree than research with mothers. Scarce research has captured more complex dynamics such as triadic family interactions involving multiple family members simultaneously [9-12]. As emotion socialization frequently occurs through subtle and indirect processes within the whole family (eg, via modeling and indirect teaching), research designs must account for these nuanced processes and consider how multiple family members influence one another in dynamic and interconnected ways [6,13].

Family Systems Theory revolutionized our understanding of families, moving beyond the individual and mother-child dyads that dominated the focus of research at the time [14,15]. Family Systems Theory posits that the family unit is more than a sum of its parts, but rather a complex system comprised of multiple subsystems—ranging from individuals to dyads and triads—that are interdependent and dynamically interact [14,15]. These subsystems engage in ongoing transactional and bidirectional exchanges, suggesting that isolating any single dyadic relationship provides an incomplete view of the family unit's functioning. The emphasis on individual or dyadic relationships in earlier emotion socialization research likely arose, in part, from methodological and statistical constraints, including challenges associated with collecting, managing, and analyzing complex family-level data. Technological advancements in data collection methods, such as physiological monitoring, ecological momentary assessment (EMA), and advanced statistical modeling techniques, including multilevel modeling and network analyses, now enable more sophisticated approaches to capturing the interconnected nature of family relationships in everyday life, providing greater ecological validity and adding nuance to family-based research. Despite these developments, no existing studies have examined emotion socialization at the whole-family level, limiting the dissemination of research protocols that can be used widely. In this paper, we present a protocol for the Family and Child Emotion Study (FACES), which examines real-world emotion dynamics within entire family units, including interactions among mothers, fathers, children, and their siblings. The study uses a pre-post design and a 7-day EMA period paired with ambulatory monitoring of heart rate (HR) and electrodermal activity (EDA) across all family members within a household. This research aims to deepen our understanding of how emotions are experienced, expressed, and regulated within family systems in daily life. Furthermore, this protocol provides a prototype for how such research can be designed.

Dynamic Emotion Exchanges Within the Family System

Family emotion dynamics encompass the patterns and trajectories through which aspects of emotional experiences—such as experiential, physiological, and behavioral components—fluctuate and interact among family members over time [16,17]. From a Family Systems perspective, these dynamics function primarily to maintain or restore homeostasis within the family unit [14,15]. As such, emotion exchanges are a key mechanism for emotion socialization within the family. Emotion socialization can occur in direct ways, such as when parents teach children about emotions and emotion expression, as well as indirect ways, such as when parents model emotion-related behaviors and react to children's expression of emotion [6]. Indirect emotion socialization may also occur through spillover effects from one dyad to another (ie, Spillover Hypothesis), where the emotional interactions between one dyad influence another [18]. For instance, emotions displayed during coparent interactions can affect their child. Similarly, emotional contagion occurs when emotions are indirectly transferred from one individual to another or to the entire group [19,20]. Taken together, family-emotion dynamics are complex and encapsulate many indirect modes of socialization that are thought to contribute to children's emotional development. However, studying these family-wide emotion dynamics requires accounting for several methodological and analytical factors during study design, implementation, and analysis.

Research Design and Methodological Considerations in Studying the Whole-Family Unit

Overview

Studying family-emotion dynamics requires a research design that balances ecological validity, multilevel emotion measurement, and advanced analytical methods. Each of these components is essential for capturing the complex and interconnected emotional interactions that occur within whole-family systems.

Ecological Validity

Ecological validity refers to the extent to which research findings can be generalized to real-world settings [21]. Ecological validity is essential for understanding family-emotion dynamics because emotional interactions within families are influenced by complex and context-specific factors that may not manifest in artificial or controlled environments such as a research laboratory. Knowing that emotional processes are shaped not only by the members themselves but also by the surrounding environmental context, studying families in their real everyday environments yields meaningful information. EMA strengthens

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ecological validity by facilitating real-time data collection of participants' experiences in their natural environments, such as at home or during daily routines [21,22]. The real-time assessment of emotions reduces retrospective bias and enhances the accuracy of reported emotions [23,24]. Furthermore, EMA can offer an additional layer of context by incorporating questions about participants' current activities, social interactions, and environmental factors, offering deeper insight into emotional experiences.

Emotion Measurement

Emotions are complex responses to specific events or stimuli, encompassing subjective experiences, physiological reactions, and behavioral responses [25]. Thus, to fully understand family-wide emotion dynamics, it is essential to examine emotional experiences across multiple levels. Many studies focus on the experiential aspects of emotion through self-report measures, which provide valuable insights into individuals' subjective emotional states. However, self-reports alone cannot capture other critical components of the emotional experience, such as physiological responses. Physiological aspects of emotion reflect internal processes regulated by the autonomic nervous system, including changes in HR and EDA (ie, bodily perspiration), both of which are strongly linked to emotional arousal, making them essential metrics for assessing emotional responses [26-29]. Measuring physiology in response to emotional experience necessitates the use of equipment capable of capturing the subtle, dynamic changes regulated by the autonomic nervous system. In-laboratory studies permit a wide range of tools used to collect physiological signals through sensors or electrodes placed on the body. However, capturing physiological responses in everyday life requires wearable ambulatory equipment that is both portable and nonintrusive. These devices must allow participants to carry out their daily activities while continuously recording physiological data. Examples of these types of technologies include wearable wristbands that either measure HR and EDA or just HR, as well as chest straps that measure HR. When studying emotion across families, it is crucial that assessment tools and equipment are suitable for individuals at different developmental stages, with equipment needing to be validated for use across age groups and appropriately sized for children [30]. A key advantage of ambulatory physiological monitoring is that it can be combined with EMA surveys, enabling the concurrent measurement of subjective emotional experiences and physiological arousal. In a family-wide context, fully understanding emotional processes requires the simultaneous collection of data from all family members to capture dynamic, real-time interactions. This approach allows researchers to investigate how emotions influence or align across family members. To achieve this, active participation from each family member is crucial, including completing emotional self-reports and having their physiological responses monitored.

Analytical Approach

The approaches described above yield numerous data points (eg, repeated surveys each day for several days), at multiple levels of measurement (eg, emotion self-report and physiology), for several family members, resulting in multiple levels of nested data captured repeatedly over an extended time frame. Thus, the analytic approach used for this type of data must account for the nested and interdependent nature of the data, as well as the longitudinal, repeated measurement design. Further, as with any intensive data collection design, approaches to missing data should be considered carefully. Other factors to consider include the synchrony between different family members' reports, synchrony in emotion reports (self-reported) and physiology obtained passively through a wearable device, and the directionality of effects. Finally, a whole-family analysis needs an approach that can generate family-level and person-specific values to allow for further testing of individual differences in families (eg, how emotionally cohesive a family is) and family members (eg, the extent to which fathers influence the family unit). Taking all of these factors into account, we recommend a network analytic approach, specifically multilevel vector autoregressive modeling [31-33]. As will be described further in the analytic section, resulting family-emotion networks will provide a measure of density, or how connected the family emotion network is, and a measure of centrality for each family member, measuring how influential the member is within the whole family unit. By capturing the dynamic interplay of emotional and physiological processes within family systems, these networks provide a deeper understanding of how emotions are expressed and regulated during everyday family interactions. This approach offers unique insight into the emotional climate of the family and the roles individual family members play in shaping shared emotional dynamics. Given that emotion regulation is a key predictor of mental health and well-being [4], understanding how families influence each other's regulation and emotion expression may offer insights into how family dynamics relate to psychological health and well-being.

FACES

The FACES project offers a novel approach to studying real-world emotion dynamics within whole-family units by combining an EMA research design with ambulatory physiological monitoring. Unlike the majority of existing research focusing on specific dyadic relationships, FACES tracks experiences of emotion within whole-family units, with the capacity to assess multiple dyadic, triadic, and whole-family interactions in families' daily interactions. The combination of EMA paired with ambulatory physiological monitoring is innovative and addresses calls for emotion measurement at multiple levels [17]. The primary objective of this protocol is to understand how family-emotion networks contribute to children's functioning and psychological health. Moreover, the networks will disentangle the contributions of specific family members to child outcomes. A secondary objective of the research is to understand which family, parent, and child factors may influence family-emotion networks (eg, parental psychology and child emotion regulation abilities). Finally, the project focuses on children in middle childhood and early adolescence, as these are important periods of meaningful emotional development [34]. During this period, children experience substantial advancements in their ability to identify, express, and regulate emotions, as well as in their understanding of others' emotions [34]. These skills form the foundation for effective social interactions and long-term emotional well-being.

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Research has shown that children as young as 7 years old can also participate independently in EMA research, providing reliable and valuable insights into their subjective emotional experiences [35]. By leveraging these methodological and analytic advances, FACES provides a comprehensive framework for capturing how family emotional dynamics unfold in daily life and how they shape children's emotional development in meaningful and lasting ways. Thus, the aim of this paper is to describe the FACES study protocol, including its design, recruitment procedures, measures, and planned analyses to support implementation, enhance reproducibility, and serve as a guide for researchers examining emotion dynamics within family systems. This protocol was reported in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines. The completed SPIRIT checklist is provided in Multimedia Appendix 1.

Methods

Study Design and Setting

The FACES protocol uses a repeated-measures design consisting of a 7-day EMA period, combined with a pre- and poststudy framework. Conducted entirely remotely from families' homes, this study integrates web-based surveys, daily self-reports of emotional experiences, and ambulatory monitoring of HR and EDA. Families are recruited from the local community and surrounding areas.

Recruitment

Families who express an interest in participating are invited to complete a screening phone call to determine their eligibility. Recruitment relies on community self-referral through advertisements via social media and flyers around the community, as well as through in-person outreach (eg, booths at community centers and local family-focused community events).

Eligibility Criteria

Families are considered eligible to participate if they meet all inclusion criteria and none of the exclusion criteria. To align with the study's focus on whole-family emotion dynamics, a minimum of two parents and two children is required for participation. A parent is defined as an adult who has cohabited with their children for at least 2 years and serves in a caregiving role. This inclusion criterion allows for the examination of emotion processes not only at the individual level but also within dyadic (eg, parent-child and siblings), triadic, and full-family interactions. Including multiple family members is essential to capture the complex, interconnected nature of emotional experiences within families. Participating children should have no more than a 4-year age gap, and both children must be between the ages of 7 and 14 years. All family members must be proficient in reading, speaking, and comprehending the English language. Families are ineligible if the participating children have any developmental delays, such as delays in speech, hearing, or sensory integration. Based on well-known influences on vagal activities, any history of cardiovascular health problems and any medications that any participating family member uses other than over-the-counter analgesics or oral contraceptives are taken note of [36].

Data Collection Procedures and Methods

Overview

Families begin by completing web-based questionnaires on Qualtrics (Qualtrics International Inc) sent via email, with a separate survey link provided for each family member. Once all participating family members have submitted the initial questionnaires, a research assistant drops off the study equipment (ie, phones, wristbands, chargers, and a laptop if needed) at the families' home. To ensure proper use and care of the study equipment, families attend a training session with a research assistant via Teams (Microsoft Corp). During this session, children also complete additional tasks on the Teams call. The day following the training session, families begin the 7-day EMA and ambulatory monitoring period using the Time2Feel app (Troon Technologies) and Empatica E4 wristbands [37]. At the end of the study period, a research assistant picks up the equipment from the families' homes, and family members complete final web-based questionnaires. In each family, one child aged 8 to 12 years is randomly selected to be the "focus child." Figure 1 gives an overview of the participant timeline.

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Figure 1. Consort diagram of participant flow. EMA: ecological momentary assessment.

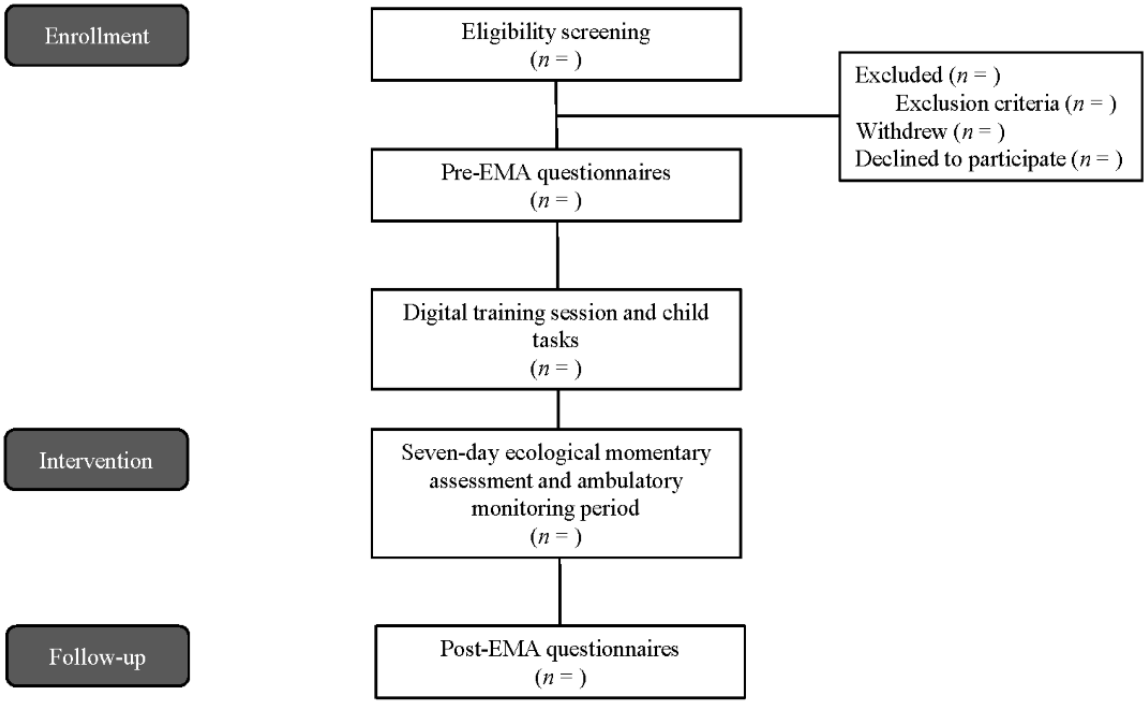

Pre-EMA Questionnaires

Each family member completes their own survey based on their role in the family (eg, one survey for each parent, one for the focus child, and one for the sibling). Separate links to these surveys are sent to each family member by email so they can complete their surveys independently. One of the parents provides demographic information about themselves, the other parent, and their children, including details such as age, gender, ethnicity, education level, occupation, medical diagnoses (physical and psychological), and household income. Both parents complete questionnaires that evaluate parenting practices, as well as their own and the focus child's emotion regulation. Children complete questionnaires that assess emotional functioning, including emotion-regulation abilities. All survey items are presented in a fixed order, with no randomization or adaptive questioning. Page breaks are inserted after each measure, and the number of questions per page varies depending on the length of the measure. If a participant leaves a question blank, a prompt appears notifying them that some questions have not been answered, giving them the option to return and complete them or continue regardless. Once a participant advances to the next page, they cannot return to previous pages to change their responses. Completing parent questionnaires takes approximately 40 minutes, while the child questionnaires take about 20 minutes. A member of the research team reviews each survey for completeness before scheduling the training session. If entire scales are missing from a survey, the research team follows up by emailing the family to confirm whether the missing responses were intentional or due to an error. Duplicate survey entries are identified and manually reviewed using the participant ID. If a duplicate survey contains missing sections that are completed in another entry, the responses are combined. Otherwise, the first complete entry is used for analysis. Both completed and partially completed questionnaires are included in analyses, depending on the extent and pattern of missing data. If participants complete only part of the survey but provide responses to key measures relevant to specific research questions, their data are retained for those analyses. Completion time is monitored through Qualtrics, but no strict cut-off is used to exclude responses based on duration alone. Instead, potentially invalid submissions (eg, extremely short completion times coupled with missing data) are reviewed on a case-by-case basis to determine inclusion.

Training Session and Child Tasks

Parents and children participate in a training session via Teams, led by a graduate or senior undergraduate research assistant. During this session, the research assistant explains the EMA period, including how to use the Time2Feel phone app, and provides step-by-step instructions for setting up and pairing the Empatica E4 wristbands with the app. Participants also calibrate their wristbands with the app to establish baseline measurements for HR rate and EDA. The focus child then completes a computer-based cognitive reappraisal task (CRT) [38].

EMA Period

Overview

For 7 days, parents and children complete between 4 and 8 brief Time2Feel surveys and wear their assigned Empatica E4 wristband each day from 4 PM to 8 PM on weekdays and 10 AM to 6 PM on weekends. The duration of the EMA period was chosen to strike a balance between collecting a sufficient number of observations for network analyses while also minimizing participant burden, as some studies have found that compliance with EMA protocols tends to decline over the course of longer study periods [39]. Additionally, EMA prompts were scheduled to occur outside of school and typical work hours to better align with parents' and children's daily routines, as recommended by Sosa-Hernandez et al [30].

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Time2Feel

Each survey contains four questions for children and five questions for parents. The first question asks, “How are you feeling right now?” where users are prompted to select their current emotional state from a list of 13 emotions: happy, nervous, sad, excited, relaxed, frustrated, scared, angry, surprised, proud, ashamed, guilty, and disgusted. The second question asks users to rate the intensity of their selected emotion on a slider from 0=very slightly or not at all to 100=extremely. The third question asks, “What are you doing right now?” with 12 activity options, including homework, cooking, chores, shopping, eating, playing games, work, exercising, watching television, relaxing, social media, and sports or outdoor activities. Users then indicate who they are with, selecting from 8 to 9 options (children: alone, mom, dad, brother, sister, whole family, friend, and group of friends; parents: alone, significant other, younger son, older son, younger daughter, older daughter, whole family, friend, and group of friends). Parents receive one additional question asking, “How stressed are you feeling right now about parenting?” where they rate their parenting stress on a sliding scale ranging from 0=very slightly or not at all to 100=extremely. Surveys are distributed four times daily using a stratified random-interval schedule, with one survey sent randomly in each of four time blocks. Participants may also receive up to four additional surveys triggered by a 15%-20% increase in baseline HR or EDA [40].

Empatica E4 Wristbands

The E4 wristbands are a certified medical wrist-worn device that collects real-time continuous physiological signals, including HR and EDA [41]. Each family member wears an E4 wristband for the allotted study hours of the 7-day EMA and ambulatory monitoring period. The Empatica E4 wristband is a validated tool for collecting HR and EDA data in both adult and youth samples [41]. Each wristband contains four sensors: photoplethysmography (PPG), EDA, infrared thermophile, and a 3-axis accelerometer [42]. HR is measured through the PPG sensor that detects changes in blood volume pulse, which is then translated into HR and interbeat intervals [42]. Although PPG is not considered the “gold standard” compared to electrocardiography (ECG), research indicates that HR recordings from the Empatica E4 are comparable to ECG measurements when movement is minimal [41].

EDA is measured using two electrodes that sit against the inside of the wrist that pass a current between the two electrodes to capture fluctuating changes in the electrical properties of the skin as measured in microsiemens (μS) at a sampling frequency of 4 Hz [42]. Though the wrist is not considered a “gold-standard” location to measure EDA, as there is a lower density of sweat glands compared to other sites (ie, palmar surface), it is much more practical and comfortable for the user and arguably provides an ideal signal-to-noise ratio when considering how often people use their hands in everyday activities [43]. The wristband is worn on the participants’ nondominant hands, snugly, to minimize motion artifacts. Each wristband was connected to the participants’ Time2Feel app via Bluetooth.

Post-EMA Questionnaires

Following the 7-day EMA and ambulatory monitoring period, parents and children complete a final web-based survey in the same format as the initial questionnaires. Post-EMA questionnaires ask about their experiences using the Time2Feel app and their own emotion-regulation practices. Additionally, parents are asked to report on the focus child’s emotion-regulation practices.

Strategies to Improve Adherence and Retention

Based on recommendations from Sosa-Hernandez et al [30], a training session is conducted to promote adherence and compliance with the study protocol. The orientation provides information about study procedures, demonstrates how to use study equipment, and offers families an opportunity to ask questions. During the EMA period, a research assistant is available via email or phone to provide technical support and answer any additional questions as needed. Families receive a check-in message on the third day of their EMA period via email or text, providing an update on their progress toward the bonus and addressing any challenges that have been noted by the research team. As an additional retention strategy, birthday and thank you cards are mailed to families’ home addresses [44].

Ethical Considerations

The FACES study was reviewed and approved by the University of Guelph’s Research Ethics Board (REB#19-07-018), in accordance with guidelines for research involving human participants. Informed consent is collected from each member of the family. Families complete a web-based consent form via Qualtrics prior to completing the initial questionnaires. The consent forms outline what each family member will take part in over the study period, the purpose of the study, the activities each family member will participate in, how long each activity will take, privacy and confidentiality, contact details for the primary investigator, and details about compensation. By consenting, family members agree to take part in study activities and data collection. However, consent can be withdrawn at any time or at any stage of the study without penalty, and any family member has the right to initiate withdrawal from the study. If any family member wishes to discontinue participation, the whole family is removed from the study. Participants are free to skip any questionnaire items they prefer not to answer and may opt out of specific study components that make them uncomfortable. For example, a child with sensory challenges may choose not to wear the Empatica E4 device for physiological data acquisition. In the demographic questionnaire, questions include nonresponse options (eg, “Prefer not to answer”), as well as an “Other” option with space to further specify. The initial web-based questionnaires use a closed survey format, meaning participants can only access the survey via a link sent by the research team. To begin the survey, participants are required to enter an ID provided by the researcher. Data collected through Qualtrics—including any personal information (eg, names and email addresses)—are securely downloaded and stored on a password-protected server within an encrypted network. Access to this data is restricted to authorized research team members, each using individual login credentials. Once

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downloaded, all data are deidentified, retaining only the family ID and participant role (eg, mother and father). Survey data and raw physiological data collected via the Time2Feel platform are stored on the protected server with family IDs and participant roles. Each family's survey responses and Time2Feel reports are stored separately and are not accessible to other family members. Any video recordings from Teams are immediately transferred to a secure server, and all files are promptly deleted from Teams after transfer. The University's secure server performs automatic, system-wide backups every night to ensure data integrity. Limits to confidentiality include potential disclosures involving potential child abuse or significant risks of harm to oneself or others. In such cases, the research team is legally required to take appropriate actions to ensure safety. This may involve reporting the information to the principal investigator, relevant authorities, or individuals who may be at risk. Families receive financial incentives after various stages of the study: the pre-EMA questionnaires, the EMA and ambulatory monitoring period, and the post-EMA questionnaires. Parents are compensated with CAD $20 (US $14.42) in gift cards for completing the pre-EMA questionnaires, CAD $50 (US $36.06) for participating in the EMA and ambulatory monitoring period, and CAD $5 (US $3.61) for completing the post-EMA questionnaires. Children receive CAD $5 (US $3.61) for completing the pre-EMA questionnaires, CAD $15 (US $10.81) for the EMA and ambulatory monitoring period, and CAD $5 (US $10.82) for the post-EMA questionnaires. Participants can also earn a CAD $5 (US $3.61) bonus for completing 80% or more of the EMA surveys.

Outcomes

A comprehensive list of all measures and outcomes is presented in Table 1.

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Table 1. List of study measures.

Outcome and measure	Type of report	Timepoints
Family-wide outcomes		
User experience and emotion reports		
Time2Feel emotion surveys	Self-report	EMA[a]
Empatica E4 wristband	Physiology	EMA
Usefulness, Satisfaction, and Ease-of-Use Questionnaire	Self-report	Post
Family functioning		
Family Functioning Styles Scale	Parent-report	Pre
Parent outcomes		
Emotion socialization		
Coping with Children's Negative Emotions Scale	Self-report	Pre
Gendered emotion beliefs		
Parents' Gendered Emotion Beliefs Scale	Self-report	Pre
Emotion regulation		
RESS[b]	Self-report	Pre
Negative emotionality		
CADS[c] (Adapted)	Self-report	Pre
Psychopathology		
Kessler 10	Self-report	Pre
Perceived parental stress		
Parental Stress Scale	Self-report	Pre
Child outcomes		
Emotion regulation		
RESS	Parent and child report	Pre, post[d]
Emotion Regulation Checklist	Parent report	Pre, post
Cognitive reappraisal task	Child task	EMA
Negative emotionality		
CADS	Parent and child report	Pre, post
Psychopathology		
Brief Problems Monitor	Parent and child report	Pre, post

[a]EMA: ecological momentary assessment.

[b]RESS: Regulation of Emotion Systems Survey.

[c]CADS: Child and Adolescent Disposition Scale.

[d]Parent-report on the RESS is completed only during the pre-EMA questionnaire, while the child report is completed at both pre- and post.

Primary Outcomes: Engagement and Family Outcomes

Time2Feel Engagement and Usability

To assess the feasibility and usability of the EMA protocol, engagement and compliance with Time2Feel for each family member is calculated as the percentage of completed surveys out of the total survey prompts received during the 7-day EMA and ambulatory monitoring period. A survey is considered complete if all questions are answered, while incomplete responses have at least one missing answer. Separate response rates are calculated for both random and deviation surveys.

After the 7-day EMA and ambulatory monitoring period, each family member completes the satisfaction and ease-of-use and subscales from the Usefulness, Satisfaction, and Ease of Use questionnaire to assess their experiences using the Time2Feel app [45]. The satisfaction subscale includes 4 items (eg, "I would recommend it to a friend"), while the ease-of-use scale consists of 9 items. Originally, the ease-of-use subscale contained 11 items (eg, "Using it is effortless"); however, items 7 and 8 were excluded due to low factor loadings (≤0.20) [45]. Gao et al [46] reported that the satisfaction and ease-of-use subscales had high internal consistency (αs from 0.88 to 0.95).

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Participants are also asked one open-ended question, inviting them to share any additional thoughts or experiences with the Time2Feel app.

Subjective Emotion Experiences

During the 7 days of the EMA and ambulatory monitoring period, families report on their emotion experiences using the Time2Feel app. Resulting variables include the specific emotion experience, the intensity with which the emotion is experienced, the activity the family member is engaged in at the time, and any individuals the family member was with at the time of the survey. Over the 7-day period, each family member's reported emotions are categorized as positive or negative, and their intensity ratings are used to calculate overall positive and negative affect scores. These scores are used to estimate family-wide emotion dynamics.

Physiological Arousal

HR and EDA are continuously recorded during study hours throughout the 7-day EMA period using the Empatica E4 wristband. Changes in blood volume pulse are used to estimate HR, while skin conductance levels are derived from EDA. Data are imported into AcqKnowledge version 5.0, and guidelines for quantifying HR and EDA are followed [36,47]. Physiological data are synchronized with EMA survey responses to examine physiological states during self-reported emotional experiences. For both HR and EDA, time-series data are segmented into 10-second increments using AcqKnowledge 5.0. Intervals within ±5 minutes of survey responses are averaged. This procedure results in 28-56 HR and EDA data points per family member, which are used to estimate family-wide emotion dynamics. These physiological indicators contribute to our understanding of how emotional states are experienced and coregulated across family members in daily life, addressing the study's primary aim of capturing the emotional processes that influence children's psychological functioning.

Family-Wide Emotion Dynamics

Family-wide emotion dynamics are indexed through two primary variables derived from the family emotion networks (see analytic plan): density and centrality [31].

Density is a measure of the overall connectivity of the network, reflecting how closely family members are linked through emotional and physiological states. It is calculated by averaging the strengths of all connections between family members. Each connection, or "edge," represents the strength of the shared emotional and physiological state between two members. Each family will receive a positive and negative emotion density score, representing the intensity of these emotions and their physiological states. Research highlights the significance of density, showing that denser networks are more ingrained and may therefore be more resistant to change [48]. Higher density scores indicate stronger and more consistent connections between family members' emotions.

Centrality is a measure of how central, or important, each family member is within the broader family network. It is calculated by summing the in-strength (ie, the influence from other family members toward the individual) and the out-strength edges (ie, the influence exerted by the individual toward other family members). Each family member will have a centrality score, which will indicate how impactful this family member is within the whole family. A higher centrality score suggests greater importance.

Secondary Outcomes: Family, Parent, and Child Variables

Family Functioning

Parents' beliefs about their families' strengths, abilities, and competencies in managing challenges and maintaining healthy functioning are assessed using the Family Functioning Styles Scale (FFSS) as part of the pre-EMA questionnaires [49]. The FFSS asks parents to indicate to what extent their family is characterized by 26 different qualities on a 5-point scale ranging from not at all like my family to almost always like my family (eg, "we generally agree about how family members are expected to behave"). The FFSS has been reported to have high internal consistency [49]. This measure is included to assess patterns of family functioning that may shape family-emotion networks, directly supporting our secondary objective of identifying family-level characteristics that influence the emotional dynamics observed during the EMA period.

Parent Emotion Socialization

Parents complete the Coping with Children's Negative Emotions Scale (CCNES) during the pre-EMA questionnaires [50]. This is a self-report measure that evaluates how parents respond to their children's negative emotions. The CCNES presents 12 vignettes describing hypothetical situations in which their child expresses negative emotions (eg, "if my child falls off his/her bike and breaks it, and then gets upset and cries, I would..."). Parents rate the likelihood of each response on a 7-point scale (1=very unlikely to 7=very likely) across six response types. These responses are categorized into six subscales: Minimizing Reactions, Punitive Reactions, Distress Reactions, Expressive Encouragement, Problem-Focused Reactions, and Emotion-Focused Reactions. Consistent with previous research, we use a version with the six response types combined into two overall scores: Supportive practices (Expressive Encouragement, Problem-Focused, and Emotion-Focused reactions) and Unsupportive practices (Punitive, Minimizing, and Distress reactions) [51]. This measure demonstrates good internal consistency and test-retest reliability, along with sufficient construct validity [50]. The CCNES is used to assess whether parent responses to children's negative emotions contribute to family emotion dynamics and influence child outcomes.

Parent Gendered Emotion Beliefs

Parents complete the Parents' Gendered Emotion Beliefs Scale (PGEB) during the pre-EMA questionnaires [52]. The PGEB is a 15-item questionnaire that assesses parents' gendered beliefs about emotion expression, gender-neutral beliefs, and gendered emotion socialization (eg, "I don't think boys should cry because it shows weakness"). Responses are rated on a 4-point scale, from strongly disagree to strongly agree. The PGEB has shown good internal consistency for both the overall scale and each of the three subscales [52]. The PGEB is used to examine how

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parents' gendered emotion beliefs may shape family emotion patterns.

Parent Emotion Regulation

Parents self-report on how often they engage in six emotion regulation strategies to manage negative emotions on the Regulation of Emotion Systems Survey (RESS) during the pre-EMA questionnaire [53]. This measure consists of 48 items using a 5-point scale ranging from never to always. Each of the six strategies—distraction, rumination, cognitive reappraisal, suppression, engagement, and relaxation—is assessed by 8 items each. Each subscale demonstrates high internal reliability [53]. Understanding parents' regulatory practices supports the objective of identifying individual and family-level factors that contribute to family emotion dynamics and child psychological outcomes.

Parent Negative Emotionality

In the pre-EMA questionnaire, parents report on their tendency to react frequently and intensely to negative emotions, adapted from the 7-item Child and Adolescent Disposition Scale (CADS) [54]. The measure is altered to have parents reflect on their own emotional behavior over the past 12 months and indicate how often negative emotionality occurred (eg, "moods change unpredictably"), using a scale from 4-point scale (not at all to very much/very often). The CADS questionnaire shows high internal consistency [54]. This measure is used to identify how parent emotionality influences child outcomes (eg, child emotionality and psychopathology).

Parent Psychopathology

In the demographics section of the pre-EMA questionnaire, parents are asked if they currently have a diagnosis for a psychological condition, and if so, what they have been diagnosed with, and at what age they were diagnosed. They are then asked to rate the severity of their condition from not severe—I rarely or do not experience any symptoms to extremely severe—I always experience symptoms. Additionally, parents fill out the Kessler 10 (K-10) during the pre-EMA questionnaire, which assesses 10 symptoms of anxiety and depression (eg, "how often did you feel tired out for no good reason?") on a 5-point Likert scale (none of the time to all of the time) [55]. The K-10 had been found to be a reliable measure in assessing symptomology in adults [56]. Parent psychopathology is assessed to support the study's goal of identifying parent-level factors that shape family emotion networks and child outcomes.

Perceived Parental Stress

Parents respond to the 17-item Parental Stress Scale (PSS) during the pre-EMA questionnaires [57]. The PSS measures perceived stress related to parenting (eg, "In the last month, how often have you been upset because of something that happened unexpectedly?") on a 5-point scale (strongly disagree to strongly agree). Adequate internal consistency of the PSS was found across a range of samples [57]. Assessing parental stress supports the study's aim of identifying parent-level factors that may shape family-emotion networks and influence children's emotional functioning.

Child Emotion Regulation

Child emotion regulation is measured through parent-report, child self-report, and a computerized CRT. These measures are described below.

Parents complete the RESS questionnaire for the focus child during the pre-EMA questionnaire [53]. Focus children also self-report their own strategy use during the pre- and post-EMA questionnaires.

Parents report on the focus child's self-regulation and ability to manage their emotions using the Emotion Regulation Checklist (ERC) at pre- and post-EMA. The ERC is a 24-item parent-report measure consisting of two subscales: emotion regulation and emotional lability and negativity [58]. Items are rated on a 4-point scale (rarely or never to almost always). The ERC has been validated for children aged 6 to 12 years and demonstrates acceptable internal consistency for both subscales [58].

The focus children's effectiveness in using cognitive reappraisal, an emotion regulation strategy known to reduce negative affect, is measured by their scores on the CRT [38]. This task is completed on Inquisit Web (Millisecond Software), a web-based platform, during the training session. In this task, children are trained to look and think about negative and neutral images of people and objects in different ways. When shown the "look" cue, children are instructed to observe the images naturally, without attempting to reappraise their emotions. When shown the "far" cue, children are trained to reappraise their emotions by either imagining the image as being far away from them or by imagining the image as being unreal. Following the cue and the image, children rate their negative emotion intensity on a feelings thermometer ranging from 0=felt no negative emotion to 3=felt a big amount of negative emotion. This task is comprised of a practice phase followed by a test phase consisting of 45 negative or neutral images, divided into three blocks with breaks in between. Image and cue types are counterbalanced and randomized across trials, resulting in three trial conditions: far negative (reappraisal), look negative (nonregulation), and look neutral (nonemotional). Cognitive reappraisal effectiveness is calculated as the percentage of negative affect reduced by reappraisal on far-negative trials compared to look-negative trials ([Look Negative Rating–Far Negative Rating]/Look Negative Rating)×100).

Child emotion regulation measures, including the RESS, ERC, and CRT, are used to examine how aspects of family functioning and parent characteristics (eg, psychopathology, emotionality, and perceived stress) relate to children's emotion regulation, a key component of psychological functioning and well-being.

Child Negative Emotionality

During the pre- and post-EMA questionnaires, both parents and the focus child report on the focus child's propensity to react frequently and intensely to negative emotions on the 7-item CADS [54]. They are asked to reflect on the child's emotional behavior and indicate how often these behaviors occurred in the past 12 months (eg, "moods change unpredictably") using a scale from 1=not at all to 4=very much/very often. The CADS presents acceptable internal consistency for both parent-report

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and child self-report [54]. Additionally, the CADS is used as an outcome measure to examine whether family emotion dynamics are associated with changes in children's emotion reactivity over time, supporting the study's aim of understanding how family-level processes relate to children's emotional functioning.

Child Psychopathology

In the demographic section of the pre-EMA questionnaire, parents are asked if either of their children that are participating in the study currently have a diagnosis for a psychological condition and if so, what have they been diagnosed with, at what age were they diagnosed and then asked to rate the severity of their condition from 0=not severe—he/she rarely or does not experience any symptoms to 3=extremely severe—he/she always experiences symptoms.

Parents report on the focus child's behavior and the focus child self-reports on their own behavior using the Brief Problems Monitor (BPM) as part of the pre- and post-EMA questionnaires [58]. The BPM includes 19 items rated on a scale from 0=not true to 3=very true, which measures internalizing problems (eg, "feels worthless or inferior"), attention problems (eg, "acts too young for his/her age"), and externalizing problems (eg, "argues a lot"). The internalizing and attention subscales each consist of six items, while the externalizing subscale contains seven items. Subscale scores are calculated by summing item ratings within each domain. A total problems score is computed by summing all 19 items. Both subscale and total scores are converted to standard T scores based on age- and gender-specific norms. T scores below 65 are considered within the normal range, while scores above 65 indicate clinically elevated concerns. Each subscale has been shown to display acceptable test-retest reliability correlations and internal consistencies [59]. Measures of psychopathology are included as outcome variables to examine how family emotion dynamics relate to children's emotional functioning, directly addressing the study's primary objective.

Statistical Methods

Sample Size

Simulations in triadic family network models with as many as 12 nodes demonstrate reliable network estimation with at least 59 families and as few as 56 time points [33]. Nodes are observed variables in the network, such as mother positive emotion, father positive emotion, child positive emotion, sibling positive emotion, mother HR, and father HR. Fewer nodes would require fewer families and timepoints. Published benchmarks indicate that temporal networks require more than 75 time points to achieve reliable precision and sensitivity and can accommodate up to 25% missing data [60]. The FACES study design provides between 28 and 56 time points per primary outcome for each family member with an estimated sample size of 70 families, or 280 individual family members. This design considers both data requirements and the need to minimize participant burden for children as young as 7 years [60].

Analytic Plan for Primary and Secondary Outcomes

To address study aims, the analytic plan involves a network analytic approach, specifically multilevel vector autoregressive modeling using the mlVAR package in R. The analytic plan includes three stages: (1) preparing the data, (2) estimating networks and calculating the primary outcomes (ie, network density and centrality outcomes), and (3) examining their relation with secondary outcomes (eg, individual emotion-regulation outcomes). This plan aligns with analytical approaches recommended by the developers of these methods and prior applications of network analysis to dyads and triads [33,61-63].

Data Preparation and Assumptions Testing

Descriptive statistics for all variables, compliance with EMA surveys and ambulatory physiology wear times, and mean satisfaction with the Time2Feel app (assessed via the Usefulness, Satisfaction, and Ease of Use questionnaire) are to be reported.

In terms of family emotion networks, mlVAR assumptions include equal time spans between timepoints (eg, EMA surveys), multivariate normality, and stationarity. To accommodate our pediatric sample, the FACES protocol features equal spacing within designated periods (eg, hourly from 4 PM to 8 PM on weekdays and 10 AM to 6 PM on weekends) but a longer overnight interval between the last survey of one day (eg, 8 PM) and the first survey of the next (eg, 4 PM). To address this, the network model excludes estimates of relationships between evening and morning surveys. Normality is assessed using the Kolmogorov-Smirnov test. Data are detrended to ensure stable means, variances, and autocorrelations over time. Then the Kwiatkowski-Phillips-Schmidt-Shin unit root test is used to examine stationarity [31]. In instances that stationarity assumptions are not met, a semiparametric time-varying vector-autoregressive model is used instead [64].

Secondary outcomes (ie, RESS and CADS) are analyzed using multiple regression. Their distribution and normality are assessed by examining skewness and kurtosis, and outliers are identified as data points that deviate more than 3 SDs from the sample mean. Identified outliers are winsorized [65].

Network Estimation and Family-Wide Emotion Dynamics

Temporal nomothetic (group-level) and idiographic (family-specific) networks are estimated using the mlVAR package and visualized with the graphicalVAR package in R [66,67]. These analyses produce Family-Wide Emotion Networks as shown in Figures 2 and 3. Figure 2 represents positive emotion-physiology dynamics within families, and Figure 3 represents negative emotion-physiology dynamics. Each node (circle) represents one of three indicators—emotion experience (positive or negative), HR, or EDA—for each of the four family members, resulting in 12 nodes per family (3 measures×4 individuals). The edges, or lines connecting the nodes, represent the effect of one family member's state on another while accounting for the influence of other family members in the network [31]. Thicker edges indicate stronger effects, which can be excitatory (green) or inhibitory (red). Nomothetic networks show average temporal associations across

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all families and are used to describe group-level patterns [35]. Idiographic networks, which represent how emotions and physiological states interact within individual families over time, are used to calculate metrics of density and centrality.

Two family emotion density scores are calculated: one for positive emotion and one for negative emotion. The model also calculates in-strength and out-strength edges for each node. In-strength shows how much a node is influenced by others, while out-strength indicates how much it influences other nodes. Using these measures, eight centrality scores are calculated—one for each family member in both the positive and negative emotion networks. The reliability and significance of edges and centrality measures are assessed using CIs and bootstrap methods [66].

Figure 2. Family-wide positive emotion network. This network represents positive emotion-physiology dynamics within families. Each node reflects a family member's positive emotion, HR, or EDA, resulting in 12 nodes per network. Edges show the effect of one node on another, controlling for all other nodes. Thicker edges indicate stronger effects. Green edges represent excitatory (positive) effects and red edges represent inhibitory (negative) effects. EDA: electrodermal activity; ER: emotion regulation; HR: heart rate.

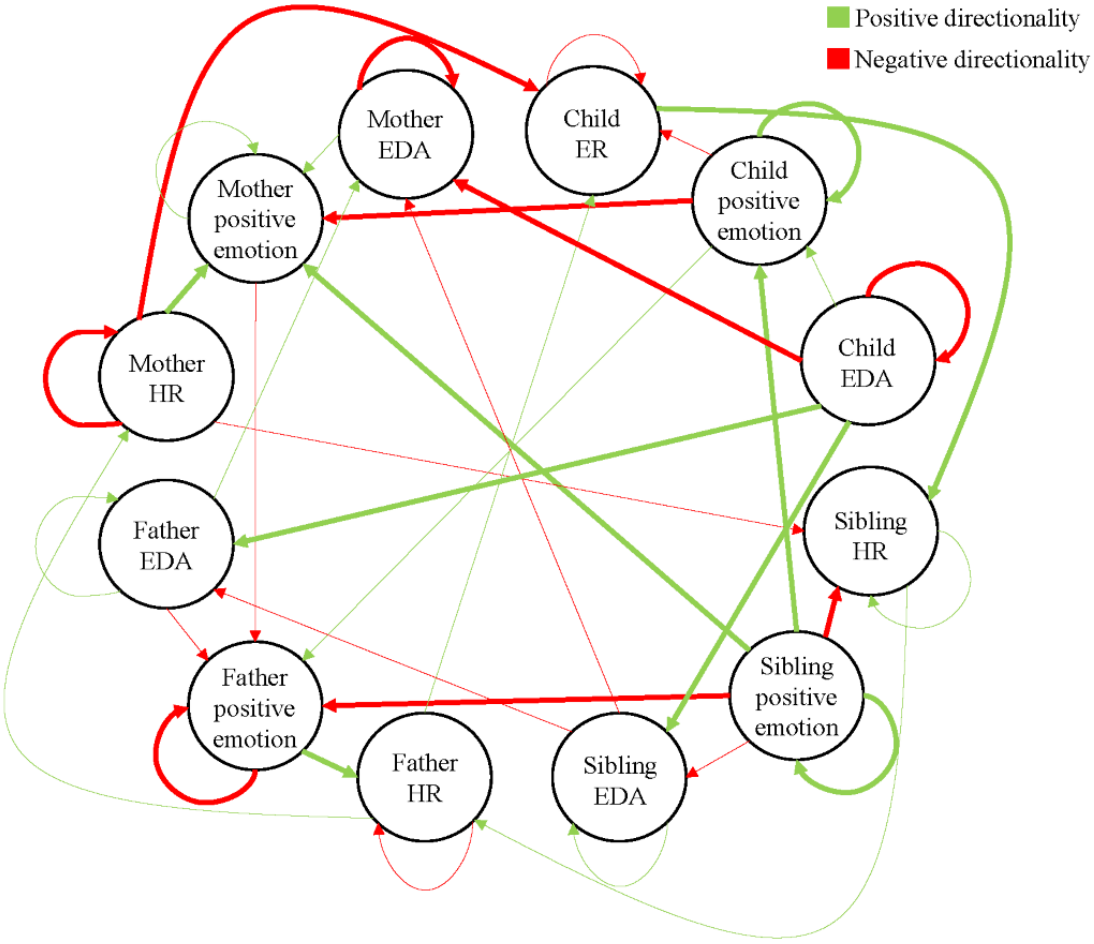

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Figure 3. Family-wide negative emotion network. This network represents negative emotion-physiology dynamics within families. Each node reflects a family member's negative emotion, HR, or EDA, resulting in 12 nodes per network. Edges show the effect of one node on another, controlling for all other nodes. Thicker edges indicate stronger effects. Green edges represent excitatory (positive) effects and red edges represent inhibitory (negative) effects. EDA: electrodermal activity; ER: emotion regulation; HR: heart rate.

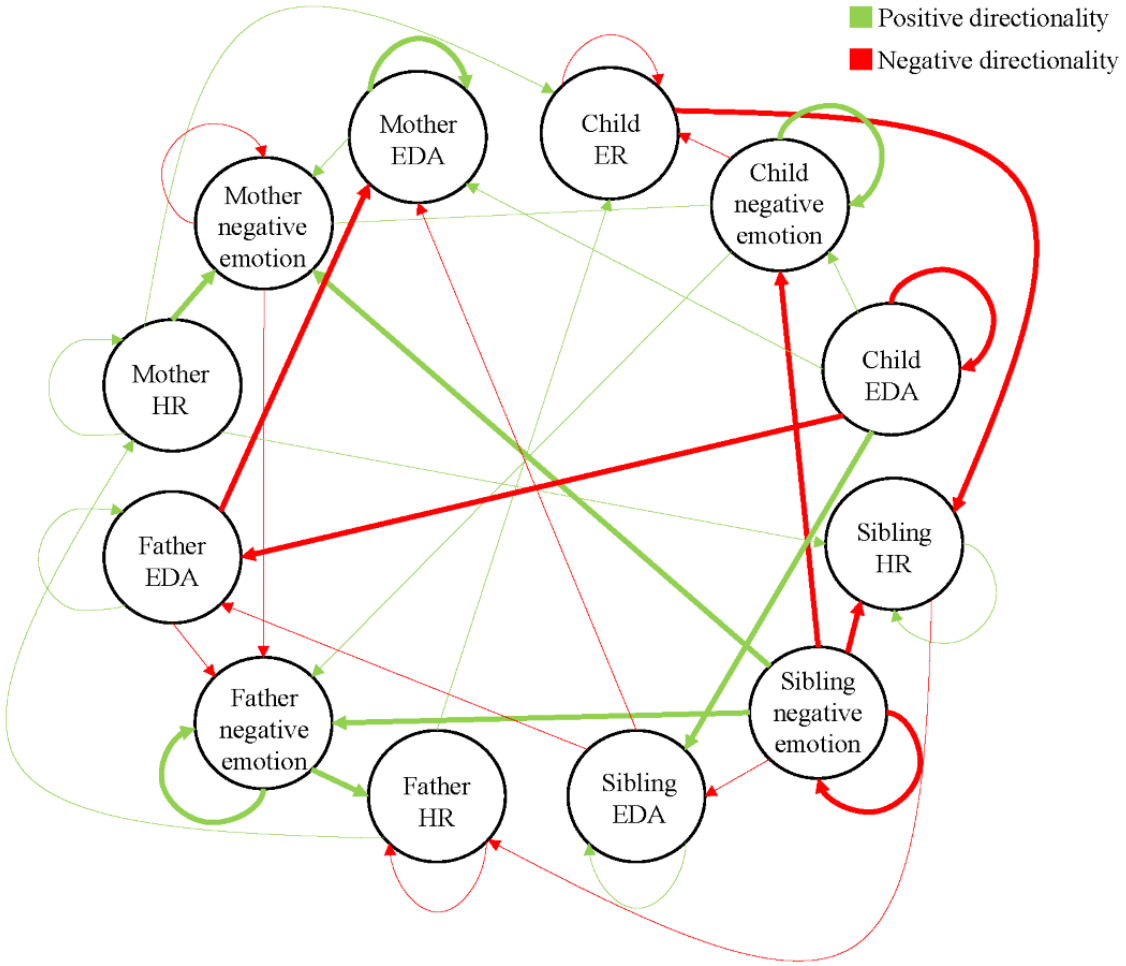

Family-Wide Emotion Dynamics and Secondary Outcomes

To test the primary objective of this protocol—how family emotion networks contribute to children's functioning—multiple regression analyses are conducted in which child emotion regulation (ie, RESS, ERC, and CRT) and child psychopathology (ie, BPM) are regressed on family-wide density scores. To examine the secondary aim—identifying which family, parent, and child factors may influence family emotion networks—additional regression analyses are conducted in which family-wide density scores are regressed on family (ie, FFSS), parent (ie, CCNES, PGEB, RESS, CADS, K-10, and PSS), and child (eg, CADS) factors. To disentangle the contributions of specific family members to child outcomes, regression analyses are conducted in which child emotion regulation (ie, RESS, ERC, and CRT) and child psychopathology (ie, BPM) are regressed on each family member's centrality score. This approach will clarify the specific contributions of individual family members to these child outcomes, accounting for their relative prominence and connectivity within the family emotion network.

Methods for Additional Analyses

Based on prior research demonstrating that real-time self-reporting of emotional experiences may support improvements in children's functioning, additional analyses include applying repeated-measures ANOVAs to test for changes in child emotion regulation (ie, RESS and ERC), child emotion reactivity (ie, CADS), and child psychopathology symptoms (ie, BPM) from pre- to post-EMA. If changes are detected, mediation analyses are then applied to test whether family-wide emotion dynamics variables account for the observed differences.

Missing Data Analyses

Based on prior research using EMA designs, an average of 25% missing data is expected [39]. Patterns and reasons for missingness will be examined using descriptive statistics and Little's Missing Completely at Random test. If the missing-at-random assumption is met and the amount of missing data is within the expected range, appropriate imputation methods are applied. For missing primary outcomes, including EMA survey responses and ambulatory physiology data, the Kalman filter is applied, as it accounts for the nested and time-series nature of the data [68,69]. For missing secondary

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outcomes, such as parent and child questionnaire data, multiple imputation is used to prevent biased parameter estimates associated with pairwise or listwise deletion [68,69]. Rates of missing data are to be reported.

Interim Analysis

There are no plans for interim data analysis.

Data Monitoring, Management, and Dissemination

Monitoring of data is completed by the research team on an ongoing basis.

Protocol Amendments

All protocol amendments are submitted to the University's Research Ethics Board for review and approval prior to implementation.

Harms

Any adverse events are to be reported to the University's Research Ethics Board as per ethical guidelines.

Auditing

Audits are conducted as required by the sponsoring institution's Research Ethics Board.

Authorship Eligibility Guidelines

Authorship eligibility will be determined based on substantial contributions to study conceptualization, design, analysis, and writing, based on the International Committee of Medical Journal Editors. Contributors who do not meet authorship criteria will be acknowledged. No professional medical writers will be used in the preparation of study-related publications.

Dissemination Policy

The findings from this study will be disseminated through multiple channels to maximize visibility and impact within the scientific and broader public communities. Key dissemination methods will be through peer-reviewed publications, presentations are national and international conferences, and media outlets (eg, the lab's official website, news interviews, and magazines).

Results

The FACES study was funded by the Social Sciences and Humanities Research Council of Canada via an Insight Grant (SSHRC #435-2020-0908) and the Natural Sciences and Engineering Council of Canada via a Discovery Grant (NSERC # RGPIN-2020-05855) as of April 2020. Data collection began in September 2022. As of May 2025, the FACES study has recruited and collected data from 48 eligible families. Data collection will continue until March 2026. Data analysis will begin after March 2026, with results expected to be published in Fall 2027.

Discussion

Overview

FACES presents an innovative protocol for examining day-to-day emotion dynamics within entire family systems. By combining questionnaires, real-time emotion tracking, ambulatory physiology monitoring, and advanced analytical methods, this approach captures the interconnected nature of family-wide emotional processes. Exploring emotion dynamics across the entire family unit addresses a major gap in the emotion and family literature, which up until now has heavily focused on individual experiences of emotion or emotion interactions between dyads (primarily mother-child relationships) [8,70]. Considering the whole-family system is essential for understanding children's emotional development and how emotions are influenced by the broader family context, this protocol was developed with two key objectives in mind: (1) to explore how family emotion networks influence children's emotional functioning and development, and (2) to identify family, parent, and child factors (eg, parental psychology and child emotion regulation abilities) that influence these emotion networks. This protocol serves as a valuable framework for future researchers exploring family-wide emotion dynamics.

Methodological Innovations

To our knowledge, combining EMA and ambulatory physiological monitoring across entire family units has never been explored, likely due to past limitations in technology and analytical methods. Recent advancements in technology and analytic approaches have made such research feasible. This protocol not only balances ecological validity by capturing emotional experiences in individuals' everyday contexts but also allows for a comprehensive assessment of emotion across experiential and physiological levels, within whole-family units. By pairing EMA emotion reports and ambulatory physiological monitoring, this protocol allows for a better understanding of how family members can influence each other's emotional states across multiple levels of measurement. This approach enables researchers to assess emotion synchrony, spill-over, and contagion across the whole family unit, recognizing that interactions extend beyond dyadic relationships to encompass more complex family dynamics. Furthermore, the short-term longitudinal design allows for data collection across diverse contexts while minimizing participant burden. Conducting the study in participants' natural environments, outside of regular business hours, and over the course of a week enables repeated and nested data collection without being too overwhelming for parents and children. Following recommendations from Sosa-Hernandez et al [30], this protocol implements participant training on study equipment, regular check-ins, and bonus remuneration to enhance compliance and participant satisfaction. Collectively, these features ensure a robust, ecologically valid assessment of emotional dynamics within family systems.

Analytical Contributions

Datasets generated from this protocol involve numerous data points collected at multiple levels of measurement across several family members. This structure results in nested data, where measurements are interdependent due to shared family contexts and repeated measurements. Our study advances the literature by looking at critical relationships within the family (influence of parents and siblings), as well as through multimethods (eg, subjective emotion reports and corresponding physiology). To appropriately model these complex emotion exchanges, we

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propose a network analytic approach, specifically multilevel vector autoregressive modeling [33]. The mlVAR approach accounts for the temporal and nested nature of family emotion data by capturing how emotions expressed by one family member influence and are influenced by others over time. This method provides key metrics for understanding family-emotion dynamics, such as density and centrality. Overall, these advanced statistical methods allow researchers to explore complex family-emotion dynamics, capturing how emotions change and stabilize within the family unit.

Limitations and Future Directions

Though this protocol serves as a guiding framework for researchers conducting family-wide emotion research, certain limitations must be acknowledged. The FACES protocol is the first of its kind to study family dynamics through a multilevel approach that examines both experiential and physiological aspects of emotion across family units of four. However, this protocol currently focuses solely on typical family structures consisting of two parents and two children and does not currently account for more complex family systems (eg, families with additional children or extended family members). Future research could be expanded to include these more complex and interdependent family configurations to better reflect the diversity and interconnected nature of families beyond the immediate household.

Although this protocol goes beyond subjective reports by incorporating physiological data, it does not account for behavioral or vocal indicators of emotion experiences**.** Expanding the protocol to include behavioral measures would enrich the understanding of emotional exchanges. Additionally, the Time2Feel app used in this study captures only singular emotions, limiting the ability to reflect complex emotional experiences that involve co-occurring emotions. Future adaptations could include options for reporting multiple simultaneous emotions to provide a more realistic depiction of emotional experiences.

This protocol includes four data collection points per day and restricts measurements to specific hours of the day (eg, after school or work hours). This limited-time sampling may not fully capture the breadth of daily emotional dynamics and could omit key moments of emotional variability. However, additional sampling must be balanced with participant compliance, especially when involving children, as research suggests they generally have lower compliance rates than adults [30]. Additionally, many children are not allowed to have phones during school, which is a limiting factor. Future protocols could consider increasing the number of daily measurement points and diversifying sampling times to provide a more comprehensive assessment of emotion throughout the day while also implementing strategies to improve compliance.

Compared to laboratory studies, managing technology in a home-based setting can be particularly challenging, as researchers cannot be physically present to troubleshoot issues. To address this, researchers are encouraged to provide adequate training on equipment and remain available to connect with participants digitally to troubleshoot. [30]. One significant challenge with ambulatory physiological monitoring is the increased risk of data loss due to motion artifacts [71]. Unlike studies measuring stationary physiology, ambulatory measurements of HR and EDA are susceptible to motion artifacts, which can render the data unusable or require extensive cleaning. To address this challenge, several studies provide guidelines for managing and cleaning datasets affected by motion artifacts [30,71]. Current wearable devices for ambulatory monitoring remain limited in their ability to manage motion artifacts. While the Empatica E4 wristband performs comparably to the “gold-standard” ECG when measurements are taken in a stationary setting, its data quality declines during ambulatory monitoring due to increased susceptibility to motion-related interference [40]. As wearable technology continues to evolve, future research protocols should prioritize devices better equipped to handle ambulatory assessment, ensuring more accurate and reliable physiological data collection in real-world settings.

Despite these limitations, the FACES protocol has many strengths and offers a unique and comprehensive method for evaluating family-wide emotion dynamics. This protocol holds promise for enhancing family emotion science.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

Conceptualization: NV, LS-H, KT

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Methodology: NV, LS-H
Analysis: LS-H, KT
Writing—original draft: NV, LS-H, CF, EB
Writing—review and editing: NV, LS-H, KT
Visualization: NV, CF
Supervision: KT
Project administration: NV, KT
Funding acquisition: KT

Conflicts of Interest

None declared.

Multimedia Appendix 1
Completed SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist for the FACES study protocol. [PDF File (Adobe PDF File), 1137 KB - resprot_v14i1e77364_app1.pdf]

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Abbreviations

BPM: Brief Problems Monitor
CADS: Child and Adolescent Disposition Scale
CCNES: Coping with Children's Negative Emotions Scale
CRT: cognitive reappraisal task
ECG: electrocardiogram
EDA: electrodermal activity
EMA: ecological momentary assessment
ERC: emotion regulation checklist
FACES: Family and Child Emotion Study
FFSS: Family Functioning Styles Scale
HR: heart rate
K-10: Kessler 10
PGEB: Parents' Gendered Emotion Beliefs Scale
PPG: photoplethysmography
PSS: Parental Stress Scale
RESS: Regulation of Emotion Systems Survey
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Nurse-Patient Communication During Postpartum Discharge Teaching: Protocol for a Mixed Methods Study

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Abstract

Background: Communication failures in inpatient maternity care are one of the leading causes of preventable maternal mortality. Most maternal mortality occurs during the postpartum period after hospital discharge. Nurses provide most direct inpatient maternity care and are responsible for postpartum discharge teaching, which is a critical moment for communicating about the care plan, concerns, warning signs, and follow-up plans to the patient, who will likely not be seen by a health care practitioner for 6 weeks, if at all.

Objective: The purpose of this study is to develop a deeper understanding of communication practices between nurses and first-time mothers during postpartum discharge teaching, including what supports or hinders the transfer of critical information and recommendations for improvement from the nurses and patients themselves. A secondary objective is to assess the acceptability, feasibility, and appropriateness of video-reflexive ethnography (VRE) as an intervention to improve care quality and processes.

Methods: We are using a health equity–informed mixed methods study design to develop a deeper understanding of communication practices between nurses and patients during postpartum discharge teaching for first-time mothers, including determinants for optimal communication and recommendations for improvement. Qualitative data will come from VRE, which will take place in 3 rounds: round 1 comprises video recording of actual postpartum discharge teaching, round 2 comprises independent review of the recording by both nurses and mothers, and round 3 comprises group reflexivity sessions with nurse participants. The planned analyses include a qualitative descriptive analysis of the video recordings and qualitative content analyses of the transcripts of the independent review and group reflexivity sessions. Quantitative data will come from a survey of nurse respondents regarding the feasibility, acceptability, and appropriateness of using VRE to reflect on and improve their practice. Survey results and reflections on VRE from round 3 will be integrated into a joint display.

Results: This project was funded in 2023 and approved by the Institutional Review Board of the University of Pennsylvania on December 6, 2023. Data collection will take place from 2024 to 2025. Results are expected to be published in 2026.

Conclusions: Our work aims to engage with nurses and first-time mothers to identify opportunities to improve postpartum discharge teaching and communication. Secondarily, we plan to find out whether study participants find VRE feasible, acceptable, and appropriate for improving the quality of care and health care communication.

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KEYWORDS

nurses; postpartum period; communication; discharge planning; ethnography

Introduction

Background

The United States has the worst rates of preventable maternal morbidity and mortality of any high-income nation despite national efforts to reverse increasing trends in these rates [1]. Most maternal mortality (53%) occurs in the 7th to 365th day post partum, in the period during which a woman is typically home from the hospital [2]. Communication failures in inpatient maternity care are one of the leading causes of preventable maternal mortality in the hospital [3-14]. Postpartum discharge teaching is a critical communication moment with mothers immediately before they leave the hospital after giving birth and is often the last contact that a woman will have with a health care practitioner for 6 weeks, if not more.

Nurses provide most direct inpatient maternity care. Critically, nurses provide most, if not all, postpartum discharge teaching. This education typically includes information about warning signs, what to do and who to contact if problems arise, self-care, and the need for follow-up. Communication at this moment has massive potential—to help women and families know when to return for care to prevent morbidity and mortality and know what is normal to avoid unnecessary trips to seek care. Nurses and patients are the experts when it comes to the provision of and experience with postpartum discharge teaching.

Video-reflexive ethnography (VRE) is a method developed from health service research and quality improvement in health care settings to help frontline practitioners improve care processes and quality, including communication [15-18]. Theoretically, VRE is informed by complexity theory and exnovation, wherein the strengths of existing clinical practices are revealed to further improve care [19]. This method is unique in its capacity to be both an intervention to improve communication and a facilitator to advance equity. Regarding the former, watching oneself communicate is an evidence-based method for improving communication skills. Regarding the latter, watching a video of the implementation of an evidence-based intervention allows the viewers to build an understanding of what it is about the intervention or its implementation that supports or detracts from equity efforts [20]. VRE has similarities to the postgame video watching that sports teams engage in to determine strengths and learnings before their next game. For example, VRE has been used to improve nurse-physician communication in hospital settings [15], as well as communication with patients and families [18]. The limitations of VRE include wariness of being recorded on the part of clinicians and the amount of effort required to conduct it well. Wariness of being recorded seems to be most easily overcome by having clinicians champion the experience of VRE to their colleagues [21]. While the amount of effort required for VRE to be conducted well is unlikely to change, experience and expert mentoring can facilitate the process. VRE has been minimally used in the inpatient maternity setting [21,22]. Studies in this area have indicated that using VRE in inpatient maternity settings is generally feasible and acceptable [21]. This method is a means of facilitating care improvement, revealing where communication falls short of shared understanding, and helping participants become aware of patterns or aspects of their communication that they want to change [15].

Objectives

The purpose of this study is to develop a deeper understanding of communication practices between nurses and first-time mothers during postpartum discharge teaching, including what supports or hinders the transfer of critical information and recommendations for improvement from the nurses and patients themselves. A secondary objective of this study is to understand the feasibility, acceptability, and appropriateness of VRE regarding improving nursing professional practice. The aims of this study are to (1) describe nurse-patient communication practices during postpartum discharge teaching; (2) determine barriers to and facilitators of effective communication during postpartum discharge teaching according to nurses and patients; and (3) determine the feasibility, acceptability, and appropriateness of VRE to improve nurse-patient communication during postpartum discharge teaching.

Methods

Overview

The overall strategy and methodology of this study is to use a health equity–informed [20] exploratory mixed methods design to develop a deeper understanding of communication practices between nurses and patients during postpartum discharge teaching for first-time mothers, including barriers to and facilitators (determinants) of optimal communication and recommendations for improvement from the nurses and patients themselves.

Study Setting

This study will be conducted on the postpartum unit at Pennsylvania Hospital, an urban academic hospital that is part of a larger academic health system. The hospital, in addition to being the nation's first, has the highest birth volume (approximately 5000 births per year) in Philadelphia, the city where it is located. The postpartum unit consists of roughly the same area on 3 hospital floors, one right over the other and connected via locked stairs (elevators allow visitors to access the different floors of the postpartum unit). The charge nurse typically assigns patients to each nurse on 1 of the 3 floors (there is 1 charge nurse per shift for all 3 floors). As part of an academic health system, the nursing staff engage in a wide array of quality improvement, evidence-based practice, and research projects. The city is highly diverse; approximately 30% of births annually are to Black women, and roughly 17% of births are to

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Asian and Latina women, with most of the rest being to White women.

Design

This is a health equity–informed exploratory sequential mixed methods study designed to develop a deeper understanding of communication practices between nurses and first-time mothers during postpartum discharge teaching and, secondarily, to evaluate the use of VRE for optimization of postpartum discharge planning. This work is informed by the health equity implementation framework by Woodward et al [20], which centers the clinical encounter (or patient-health care provider interaction) as 1 of 3 critical moments affecting health disparities. This framework [20] also includes facilitation, which is how the evidence-based intervention is implemented for equity. The authors note that they do not focus on facilitation as the science in this area as the adaptation of the implementation process to promote equity is nascent. We believe that VRE has the potential to be not only an evidence-based intervention in and of itself but also a means of facilitation to promote improved care processes, outcomes, and equity.

This exploratory mixed methods study involves VRE (qualitative data) followed by a survey (quantitative data) on VRE acceptability, feasibility, and appropriateness (Figure 1) [23]. VRE involves three rounds: (1) postpartum discharge teaching recording, (2) independent review of the round 1 recording by nurses and patients, and (3) reflexive review of round 2 findings by nurses in group sessions. Upon completion of the round 3 group reflexivity sessions, nurses will complete the survey. Both patients and nurses will complete a short sociodemographic questionnaire after their final session to collect information about race and ethnicity and years of nursing experience (for the nurses). For VRE, the planned analyses include a qualitative content analysis of the transcripts from the independent review and group reflexivity sessions with nurses. Coding for the qualitative content analysis will be both inductive and deductive (see the Analysis section for further details). For the survey, we will use descriptive statistics to report nurse responses regarding the feasibility, acceptability, and appropriateness of using VRE to reflect on their practice [23]. We will integrate the quantitative survey findings with the qualitative findings on the use of VRE from round 3 in a joint display. Table 1 provides further details.

Figure 1. Overview of the study phases. Solid boxes include nurse and patient participants. Hatched boxes include nurses only. Overlap of boxes indicates that there can be overlap in the phases of the study (eg, not all round 1 recordings will be complete before round 2 interviews begin).

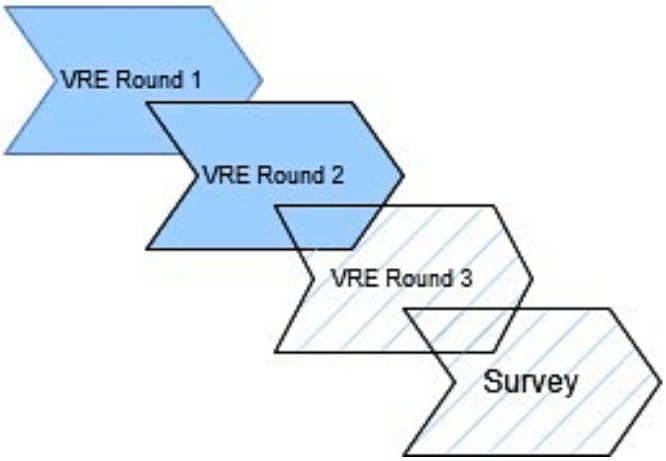

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Table 1. Data collection and analysis processes.

VRE[a] round	Analysis process
Before data collection	
Test whether the Owl cameras will sufficiently capture video and audio in postpartum hospital rooms.	—[b]
Pilot video review checklist: face validity with postpartum nurse educator and observation of postpartum discharge teaching sessions to test the checklist and iterate as needed.	The postpartum nurse educator's feedback was incorporated into the checklist. Two team members observed a postpartum discharge teaching session and spoke with the nurse about her process before incorporating her feedback.
Conduct a technical "dry run" before proposed recording dates to understand logistical issues and plan accordingly.	—
Round 1: video recording	
Nurses and patients will be consented before recording; we plan to oversample women from racial and ethnic minority groups.	—
Video record postpartum discharge teaching between nurses and patients.	—
The team views the video with the video review checklist (Multimedia Appendix 1).	Video-recorded postpartum discharge teaching will be evaluated and described according to the checklist (ie, presence or absence of clinical content, evidence-based teaching interventions, and effective communication techniques). Video clips will be chosen based on the presence or absence of something on the checklist through team consensus. The length and number of clips created may vary.
Round 2: independent review	
Participants will be sent a link to a separate subfolder within Box with their selected video clips for confidentiality and may independently review these clips of their postpartum discharge teaching interaction during a recorded video call.	—
Independent review will be conducted with a member of the study team (Multimedia Appendix 2). Participants will be encouraged to stop the video at any point and comment on their thoughts and feelings, including what they were thinking at the time (see the interview guide).	We will conduct qualitative content analyses of the transcripts of round 2 review sessions using both an inductive and deductive approach.
Specific recommendations to improve the interaction and communication in general will be solicited at the end of the session.	—
Patient comments will be edited into the video at the exact time stamp when they were made.	—
Round 3: reflexivity sessions	
Nurses will be invited to participate in group reflexivity sessions that will be held virtually.	—
We will ask participants to reflect on round 2 clips that have embedded patient comments (see the interview guide).	Transcripts of the reflexivity sessions will be analyzed using the qualitative content analysis described in round 2.

[a]VRE: video-reflexive ethnography.

[b]The left-hand column includes a step in the data collection process for which analysis was not applicable.

Eligibility Criteria

Nurses are eligible for recruitment if they are postpartum nurses at the study hospital and conduct discharge teaching. Patients are eligible for recruitment if they are first-time mothers being discharged with their infant, are aged older than 18 years, and speak English. We chose to limit eligibility to those aged older than 18 years because emancipation is not automatically granted to minors who become pregnant in the state where the study is being conducted. We also chose to limit eligibility to patients who spoke English due to the additional complexity that translation adds to a clinical interaction.

Ethical Considerations

This study received approval from the University of Pennsylvania Institutional Review Board (IRB) before initiation of data collection (December 6, 2023; protocol 854936). Informed consent was obtained from all participants (nurses and patients). Data in all research products, including findings shared with the nursing staff and leadership, will be deidentified. Participants received monetary compensation via a Greenphire ClinCard for taking part (US $60 for completion of round 1 and US $50 each for completion of rounds 2 and 3).

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Researcher Characteristics and Reflexivity

The principal investigator of this study is the nurse scientist at Pennsylvania Hospital, and before her work as an assistant professor, she practiced clinically as a nurse and then as a midwife. Her clinical practice informs her research questions and assumptions, as does her work as a maternal health service researcher focused on excellence and equity in quality and outcomes. Her background is part of what made VRE as a method so attractive because she recognizes the importance of patient and frontline providers' perspectives and expertise for improving care and outcomes. The research team, which has a history of successful collaboration, involves people with a wide array of lived experiences and sociodemographic diversity. Having so many people on the team coming from different points of view helps balance assumptions and presuppositions. Finally, one of our team members is a nurse from the postpartum unit where the work is being conducted. As a nurse champion, her presence and expertise on the team has had a positive impact on recruitment and will inform data analysis.

Sample Size and Recruitment Plan

The sample will consist of postpartum nurses who work in a large urban hospital and the new mothers who receive education from them before discharge. There are 86 nurses in the unit, and approximately 5000 women give birth in the hospital annually. We are looking to record 20 dyads (1 nurse and 1 patient; 40 total participants) for VRE round 1. Previous VRE research conducted elsewhere has reported recruitment rates of 75% of nurses [15]. To recruit nurses, we will (1) present the study at unit council meetings to get the word out and establish buy-in before speaking with individual nurses, (2) post recruitment flyers in nurse locker rooms and send reminder emails about the study, and (3) seek the collaboration of nurses who are informal leaders and unit champions to support recruitment efforts. At the unit council meetings, we will share information about the work, gather input, address concerns, and answer questions. We are also seeking to understand the following: the best times of day for video recording, optimal placement of recording equipment in different room configurations, and how nurses will know when a mother is about to be discharged (how much lead time the nurse will have). We hired one of the postpartum nurses to be a research team member. This nurse will be either a formal or informal leader in the unit and, in addition to sharing their clinical and contextual expertise with the research team, will receive training to consent participants and record postpartum discharge teaching. They will also participate in data analysis, interpretation, and dissemination. After attending unit council meetings, we will spend time in the unit talking with individual nurses and inviting them to participate.

Patient participants will be recruited on the day of discharge based on the assignments of nurse participants who are working on any given day. We will also place study flyers in shared lounge spaces on the postpartum unit.

Data Collection and Management

To collect data, we will use Owl cameras (a smart webcam designed with a 360° camera and microphone that becomes smarter over time; Owl Labs) set up on tray tables that will be wheeled into patient rooms before the beginning of the postpartum discharge teaching session. The Owl cameras interface with a videoconference platform (we will use Zoom [Zoom Video Communications]) to create a video and transcript. Audio and video of the meeting will be recorded to a secure research drive (the HIPAA [Health Insurance Portability and Accountability Act]-compliant Box). We are specifically recording to Box versus saving to Zoom and then transferring data to enhance data security. Table 1 presents both the data collection and management and analytic processes. Before collecting data, we will pilot a video review checklist at postpartum discharge teaching sessions. The video review checklist was initially developed based on existing recommendations for postpartum discharge teaching [22,24-26] and clinical expertise from the team. We then established face validity for the checklist by having the postpartum nurse educator review the checklist and pilot-test it during a postpartum discharge teaching session that was not part of the research. We will also have "dry run" days on the unit in which the research team will observe the postpartum nurses' workflow over the course of the day to understand how best to run the logistics of the study and test the equipment. We will also examine the postpartum discharge rooms to determine the best placement for the Owl cameras.

Postpartum discharge instructions are typically delivered in the late morning or early afternoon on the day of discharge. We will check in with the charge nurse shortly after shift change to ask whether any of the nurse participants working that day have a first-time mother being discharged. If they do, the study team member will approach the patient to invite them to participate in the study. If the patient agrees, the study team member will speak with the nurse about when they plan to conduct discharge teaching and proceed with setting up the recording session using the Owl camera.

The study team member will place an Owl camera in the room in a predetermined optimal position, make sure that it is on and recording to the Box folder, and that the setup is acceptable for the nurse and patient before leaving the room. After postpartum discharge teaching is complete, the study team member will collect the Owl camera and check to ensure that the team has the preferred contact method for each participant to schedule the round 2 interview.

VRE round 2 interviews will be conducted virtually via Zoom. In these sessions, nurses and patients will independently review the postpartum discharge teaching recording that they participated in and reflect on what went well and what might be done differently. Participants will be encouraged to reflect on what they were thinking during particular moments of the interaction, as well as on the experience as a whole. The interviews will be transcribed using the autotranscribe feature on Zoom and will again be saved to a secure research drive. Transcripts will be checked for quality by a trained research assistant. At the end of the round 2 interviews, patient participants will be asked to complete a short sociodemographic survey in REDCap (Research Electronic Data Capture; Vanderbilt University). Round 2 interviews will be processed for round 3. Patient comments from round 2 interviews will be

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inserted into the appropriate point in the round 1 video (eg, the patient comments on a particular interaction or thing said in the round 1 video). Patient comments from round 2 that are not tied to a specific moment in the round 1 video will be kept separate. The team will select topics to present to the nurses during round 3. To do this, the team will watch the round 1 and round 2 videos to identify themes that arise from the data, as well as for places where data adhere to or deviate from the codebook. The selection of themes will be iterative and evolving as round 3 will begin before round 2 ends and feedback from early round 3 sessions may inform future round 3 sessions (eg, probing deeper on a particular topic).

VRE round 3 (reflexivity sessions) will be conducted virtually with nurses only by the same team members who conducted the round 2 interviews. Nurse participants (2-5 per session) will watch clips from round 2 that are organized by theme. The themes will be selected deductively (eg, based on the framework by Woodward et al [20] or the video review checklist from round 1) and inductively by the research team, with consensus on themes to include being reached through discussion. The process of reviewing the videos and determining themes will be ongoing during round 2 but finalized before round 3 begins. The nurses will be encouraged to reflect on their postpartum discharge teaching practices as a group and offer recommendations to improve this teaching and nurse-patient communication to their colleagues. These sessions will be recorded as mentioned previously. Recordings and transcripts will be managed as described previously as well. At the end of round 3, nurses will be administered 2 surveys (via REDCap) to share sociodemographic data and rate the feasibility, acceptability, and appropriateness of VRE as an intervention to improve nurse-patient communication using 3 validated short scales (Multimedia Appendix 3) [27]. We provided the funding organization's review comments (Multimedia Appendix 4) and followed the Standards for Reporting Qualitative Research Guidelines in developing the manuscript (Multimedia Appendix 5).

Analysis

Table 1 provides details on study procedures and analysis. As described in Table 1, round 1 videos will be analyzed by comparing them to the video review checklist (Multimedia Appendix 1). For rounds 2 and 3 (Multimedia Appendix 2), we will conduct qualitative content analysis using a deductive and inductive approach [28-30]. The deductive codebook will be based on the health equity framework by Woodward et al [20] and the video review checklist. Initially, the entire team will review the round 2 interviews of 2 dyads (4 interviews total) to develop initial inductive codes and discuss the application of the deductive codes. A process of abstraction [30] will be used to condense similar codes into descriptive categories and subsequent themes. Themes will be developed iteratively, and the team will collectively define final themes and subthemes until thematic sufficiency is reached [31]. We will aim to reach for 100% agreement across the analytic sample. After that, the interviews will be divided between 2 groups comprising 2 team members each, who will proceed with coding. Questions or disagreements will be brought back to the full group during weekly meetings. The team members will practice data immersion by watching available videos from rounds 1, 2, and 3 and by reading the interview texts to gain familiarity with the scope and depth of responses. This process will be completed for the round 2 interviews first, followed by the round 3 sessions. Descriptive statistics will be used to report the survey data and sociodemographic information. We will present findings from the acceptability, feasibility, and appropriateness surveys in a joint display with qualitative findings related to the nurses' perspectives on the use of VRE. We plan to use ATLAS.ti (Scientific Software Development GmbH) and Stata (StataCorp) [32] to conduct the analyses. This study received IRB approval.

The research team will keep an audit document to track their analytic decisions and will debrief to discuss interpretive biases. We will incorporate the following techniques to increase the trustworthiness and rigor of our qualitative research: (1) development of standard operating procedures for recruitment, recording, and analysis; (2) prolonged engagement with the data; (3) audit trail maintenance to record the team's analytic decisions; (4) extensive memos and field notes to track theoretical and reflective thoughts; (5) engagement in researcher triangulation and peer debriefing; and (6) full of context [33].

Results

This study was funded in July 2023, although final approval for fund disbursement was received in February 2024. We received IRB approval in December 2023. Data collection will take place from July 2024 to December 2025. Results are expected to be published in 2026. To date, we have recruited 16 nurses and 10 patients. A total of 10 round 1 recordings been completed, and the follow-up round 2 independent reviews are in process as of this writing.

Discussion

Expected Findings

We expect that the main finding of this study will be nurse- and patient-generated opportunities to improve postpartum discharge teaching for first-time mothers. Furthermore, we expect to find some content and communication style variation in the postpartum discharge teaching that nurses provide to first-time mothers (round 1). We further expect that both nurses and patients will have observations as to what went well and what might be improved (round 2) and that the nurses—upon reflection as a group (round 3)—will have recommendations to improve these critical communication moments. This work is the foundational step in not only understanding how to improve postpartum discharge teaching but also building capacity to use VRE as a critical means of improving communication in maternity care (as communication failure is a leading root cause of preventable maternal morbidity, mortality, and racial disparities therein). Prior VRE work in general has been predominantly conducted outside of the United States. The VRE work conducted in the United States, while highly formative, has not been conducted in a maternity setting [15,17,18]. This is the first instance of VRE being conducted in a maternity setting in the United States of which we are aware. Other VRE work in maternity spaces has been conducted worldwide and proven highly informative (eg, suggesting that VRE was feasible

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and acceptable in a maternity setting in the United Kingdom [21,22]).

There are strengths and limitations to this work. Video recording clinical interactions is a sensitive subject. To address this, we have met with clinical nursing leadership at the hospital, who have confirmed with the research team that the videos will not be used to penalize nurses. We will ask for nurses' recommendations about how to address perceptions of risk of being penalized for future participants (eg, what circumstances might make participation feel like less of a risk and their suggestions to address risk). As a result, findings will only be shared with the leadership team as a deidentified aggregate. We will hire at least one postpartum nurse to be a study team member who will become a familiar presence during the study. This idea was endorsed by the clinical director and unit leadership. The nurse on the research team will not be a study participant. Other interested nurses will be encouraged to champion the work to their peers.

The Hawthorne effect is frequently mentioned as a concern. However, previous research indicates that many participants eventually stop paying attention to the recording device in the room [34-36]. To address this challenge, we will use an Owl camera, which has a small and less obtrusive footprint. We will also ask participants about their awareness of being video recorded as part of the postvideo survey. Prior work has found that it is important to minimize the time gap between initial video recording and independent review [15]. To address this, we will schedule independent reviews (round 2) with patients and nurses when their interaction is recorded with the goal of having that round 2 meeting within 3 weeks for nurses and 4 months for patients. The longer time frame allows for flexibility in scheduling for first-time mothers.

To assess the feasibility of this work, we engaged clinical leadership both as team members and as advocates for the project. With regard to ongoing feasibility, we will ask nurse participants to complete a feasibility survey as part of the postrecording data collection.

Even with these limitations, the planned study has numerous strengths. First, we are submitting a protocol as a point of rigor for the work. Second, VRE is a powerful (and underused in the United States) methodology for studying and improving clinical practice. Third, we have a stellar team representing contextual, clinical, and research experience and expertise, including VRE.

Future directions for this work include the development of evidence-based interventions to improve aspects of postpartum discharge teaching identified in this work. Other directions include the use of VRE to improve other aspects of health care communication in the inpatient maternity setting, perhaps as identified in other work based on incident reports [37].

Dissemination

Upon completion of this work, we plan to share the results back to the postpartum unit at the participating hospital during a unit council meeting and any further meetings recommended by the clinical and operational leadership. We will also offer to share the paper with the nurse and patient participants if they are interested. We will consider sharing this work at system-wide meetings as well. We will also disseminate our findings via conference abstracts and papers, with a plan to include the postpartum nurse hired to be part of the research team as a copresenter at one conference at minimum and as a coauthor on any papers. We plan to use the Systematic Development of Standards for Mixed Methods Reporting in Rehabilitation Health Sciences Research guide for reporting [38].

Conclusions

Communication failure is a leading root cause of preventable maternal mortality. We are beginning to focus on the postpartum period, especially after hospital discharge, as a critical period that is underserved, underresourced, and understudied. Nurses provide essential education for patients and their families before discharge after giving birth. This study will serve to advance our understanding of communication practices between nurses and first-time mothers during postpartum discharge teaching, including what supports or hinders the transfer of critical information and what improvements to the discharge education process nurses and patients recommend. This work has the potential to inform an array of future work, including an implementation science study of (1) incorporating evidence-based information and communication techniques into postpartum discharge teaching and (2) VRE as a method to improve critical communication (and equity therein) in inpatient maternity care (eg, handoff from labor and delivery to the postpartum unit).

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Video review checklist.
[DOCX File , 2726 KB - resprot_v14i1e72139_app1.docx]

Multimedia Appendix 2
Round 2 independent video review guide.
[DOCX File , 14 KB - resprot_v14i1e72139_app2.docx]

Multimedia Appendix 3
Survey instrument.
[DOCX File , 27 KB - resprot_v14i1e72139_app3.docx]

Multimedia Appendix 4
Response to funder's comments.
[PDF File (Adobe PDF File), 81 KB - resprot_v14i1e72139_app4.pdf]

Multimedia Appendix 5
SRQR checklist.
[DOCX File , 22 KB - resprot_v14i1e72139_app5.docx]

Multimedia Appendix 6
Peer review report by Betty Irene Moore Nurse Scholars and Leaders Fellowship Review Committee, UC Davis Health.
[PDF File (Adobe PDF File), 473 KB - resprot_v14i1e72139_app6.pdf]

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Abbreviations

HIPAA: Health Insurance Portability and Accountability Act
IRB: Institutional Review Board
REDCap: Research Electronic Data Capture
SRQR: Standards for Reporting Qualitative Research
VRE: video-reflexive ethnography

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Protocol

Neurofeedback Training for Managing Neuropathic Pain–Like Features in Chronic Musculoskeletal Pain: Protocol for an Open-Label Pilot Feasibility Clinical Trial

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Abstract

Background: Neuropathic pain (NP) is characterized as pain arising from lesions of the somatosensory nervous system. However, NP-like features have been found in several chronic secondary musculoskeletal (MSK) pain conditions in the absence of detectable lesion or damage to the somatosensory pathways. Emerging evidence has demonstrated associations between NP-like symptoms and altered neural activity within brain regions implicated in sensory perception and affective-emotional processing of pain with consistent findings of abnormal activity in the right insula (RIns) cortex and dorsal anterior cingulate cortex (dACC). Electroencephalography neurofeedback (EEG-NF) is a brain-computer interface biofeedback technique that allows individuals to self-regulate the real-time cortical brain activities of the regions of interest.

Objective: The primary objective of this study is to investigate the feasibility and safety of a novel EEG-NF intervention designed to simultaneously downtrain activity in the RIns and dACC in individuals with a chronic secondary MSK pain condition exhibiting NP-like features. In addition, this study will conduct secondary exploratory analyses to investigate EEG-derived neuronal changes and their associations with clinical and experimental pain outcomes following the EEG-NF training.

Methods: We will design a single-arm, open-label, pilot-feasibility trial. We will recruit adults aged 35-75 years with a score of ≥19 using the PainDETECT questionnaire and an average pain score of ≥4 on the 11-point Numeric Pain Rating Scale over the last 3 months, with a minimum pain duration of 3 months, to receive active EEG-NF training. Participants will receive auditory feedback as a reward for achieving a predetermined activity threshold of the RIns and dACC. Primary outcomes will evaluate feasibility, acceptability, and safety using both self-reported questionnaires and monitoring data. Collected data will be summarized descriptively, with mean (SD) reported where appropriate. Secondary outcomes will include EEG parameters, self-reported measures, heart rate variability, and quantitative sensory testing. An exploratory within-group pre-post statistical comparison will be conducted for all secondary outcome measures, and correlation analysis will be performed to explore relationships between EEG measures, self-reported outcomes, heart rate variability, and quantitative sensory testing measures.

Results: This study has received approval from the Health and Disability Ethics Committee and is registered with the Australian New Zealand Clinical Trials Registry. Participant recruitment began in April 2025 and is ongoing. As of October 2025, data collection has been completed, with a total of 5 participants enrolled, all of whom have completed the study to date. We expect to complete the study in March 2026. This study will generate data on feasibility, safety, acceptability, and preliminary data to inform a fully powered effectiveness clinical trial.

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Conclusions: The results and data generated will inform the design and sample size calculation for a fully powered randomized controlled trial aimed at evaluating the effectiveness of EEG-NF in targeting NP-like features in individuals with chronic MSK pain.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12625000706471; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?id=389568&isReview=true

International Registered Report Identifier (IRRID): DERR1-10.2196/78806

(JMIR Res Protoc 2025;14:e78806) doi:10.2196/78806

KEYWORDS

brain-computer interface; brain oscillations; chronic pain; electroencephalography; musculoskeletal; neuromodulation

Introduction

Chronic musculoskeletal (MSK) pain is the leading cause of disability, affecting over 1.7 billion people globally [1]. In New Zealand, one-quarter of the population is affected by some form of MSK disorder, and one-fifth of the population lives with chronic pain [2,3]. A subgroup of chronic MSK pain exhibits neuropathic pain (NP)-like qualities, which include symptoms such as burning, shocking, shooting, numbness, and “pins and needles” [4-8]. According to the International Association for the Study of Pain, NP is caused by a lesion or disease affecting the somatosensory system and may involve either the central or peripheral nervous system [9,10]. However, chronic secondary MSK conditions, such as knee osteoarthritis, low back pain, shoulder pain, neck pain, and osteoporosis, have been reported to exhibit NP-like qualities with widespread pain localization in 5.4%-33% cases in the absence of a verifiable lesion affecting the somatosensory system [4,8,11-14]. Similar findings have been observed in chronic widespread pain conditions, like fibromyalgia, which exhibit NP-like symptoms despite the absence of direct somatosensory lesions [15,16]. Moreover, patients with chronic MSK pain experience higher degrees of pain unpleasantness and bothersomeness, leading to emotional distress, which are part of the affective dimensions of pain [17,18]. Concurrently, the severity of symptoms or pain intensity may not always correlate to the extent of the MSK injury in these individuals [19,20].

Persistent pain associated with chronic MSK conditions and ongoing nociceptive input may lead to sensitization and widespread pain distribution, accompanied by altered sensory perception and changes in central processing within supraspinal structures [8,21]. Neuroimaging studies show that chronic MSK pain is associated with significant functional aberrations in brain regions involved in sensory processing, emotion and motivation, and pain inhibition [22,23]. Clinical aspects of pain correlate with these distinct anatomical brain regions and networks, as supported by functional neuroimaging data [24]. In particular, the insular cortex, specifically right insula (RIns) cortex and dorsal anterior cingulate cortex (dACC), plays a profound role in the sensory perception and emotional processing of pain and has been shown to exhibit alterations in chronic MSK pain conditions [25,26].

The insular cortex acts as a hub for cortical processing, including sensory, emotional, social, and cognitive information [27]. In particular, the insula serves as a hub linking multiple networks, including regions involved in pain mediation, such as the salience and ventral frontoparietal attention networks [28,29]. It has been shown that pain experience is associated with salience network, with the insular cortex serving as a key hub. The insular cortex is lateralized in function, with the RIns being predominantly involved in pain perception compared with the left insula [25]. Increased activation of the RIns has been reported in individuals with chronic MSK pain in both functional magnetic resonance imaging studies and electroencephalogram (EEG) studies in the gamma frequency band [30-32]. The insular cortex is also involved in modulating pain intensity, as it has been linked to pain catastrophizing [27,33]. Studies suggest that both the insula and the dACC are involved in the emotional processing of pain [34-37]. The dACC is the main proxy for the medial suffering pain pathway and is associated with motivational-affective component of pain [38]. Alterations in the activity of the dACC, such as increased activity in the alpha and beta frequencies and decreased functional connectivity to other regions, including the pregenual anterior cingulate cortex and somatosensory cortex, have been shown in people with chronic NP [38-40]. Previous studies have demonstrated that NP-like symptoms in individuals with painful knee osteoarthritis are associated with altered infraslow frequency (ISF) activity in the RIns and dACC, with significant correlations observed between ISF fluctuations and pain measures [30,41-44]. Therefore, targeting the ISF activity of both the RIns and dACC, which are associated with sensory and affective dimensions of pain, may modulate NP-like symptoms and produce clinical improvements in individuals with chronic MSK pain [26,27,38].

Currently, pharmacological treatments for NP conditions produce modest efficacy, potentially due to the variation in underlying mechanisms [45]. Furthermore, many available nonpharmacological treatments for NP conditions have demonstrated either low certainty of evidence or inconclusive results, highlighting the need for novel, innovative interventions [45,46]. Electroencephalography neurofeedback (EEG-NF) is a brain-computer interface biofeedback technique that allows individuals to self-regulate the real-time cortical brain activities of the regions of interest and reinforces learning using operant conditioning [47,48]. EEG-NF has been used successfully in several conditions, including chronic MSK pain, demonstrating clinical and EEG modulation [49-52]. EEG-NF training, which targets the ISF band in the brain, has been shown to provide clinical benefits [41,52]. Moreover, the ISF band has been shown to modulate higher-frequency brain oscillations through phase-locking mechanisms [53]. Previous studies have

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demonstrated that ISF EEG-NF training can influence resting-state brain networks and oscillations in various conditions, including targeting the dACC for chronic MSK pain [43,49,50,52,54,55]. However, to date, no studies have investigated the potential of ISF EEG-NF training for NP-like qualities in chronic MSK conditions. Furthermore, no research has explored the use of neurofeedback to simultaneously downtrain 2 distinct brain regions (dACC and RIns) as a targeted intervention for chronic MSK pain. This dual-target approach and ISF modulation for NP management highlight a novel strategy with the potential to achieve more comprehensive modulation of pain-related neural networks and clinical pain improvements.

Therefore, this study aims, for the first time, to explore the potential of downregulating the ISF activity of both the RIns and dACC using a novel ISF EEG-NF protocol in individuals with NP-like symptoms associated with chronic MSK pain conditions. Given the novelty of the proposed ISF EEG-NF training protocol, pilot testing of the protocol and assessment of feasibility and safety are necessary. The primary objectives of this study are (1) to pilot test and investigate the feasibility of the EEG-NF program, and (2) to investigate the safety of the ISF EEG-NF training. The secondary objectives are (1) to estimate the variability of the outcome measures for informing the sample size of a fully powered clinical trial, (2) to explore the immediate and short-term trends of the effects of the targeted ISF EEG-NF training on pain measures, and (3) to explore the changes in EEG current density activity at the targeted cortical regions (dACC and RIns) and the functional connectivity between these regions following ISF EEG-NF training.

Methods

Ethical Considerations

We obtained Ethical approval from the Health & Disability Ethics Committee, New Zealand (Reference 2023 EXP 19190). Research consultation with Māori was obtained from the Ngāi Tahu Research Consultation Committee (Reference 24402). The trial has been prospectively registered in the Australian New Zealand Clinical Trials Registry (ACTRN12625000706471).

All eligible participants will receive an information sheet with consent form outlining the study design and purpose. Participants who are enrolled will complete a digital consent form on the day before their baseline assessment and provide a signed paper copy upon attending in person. Participants may opt-out at any point during the study. All data for primary and secondary outcomes will be deidentified before analysis. In recognition of their time and contribution to the research, participants will receive NZ $200 (US $115) supermarket vouchers upon completion of all study sessions.

Study Design

A single-arm, open-label, pilot-feasibility clinical trial was designed according to the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT; Multimedia Appendix 1) and the Consolidated Standards of Reporting Trials (CONSORT; Multimedia Appendix 2) extension for pilot and feasibility trials. The trial will be conducted in Dunedin, New Zealand, and the study phases are summarized in Figure 1 [56,57]. This study was designed as an open-label trial to assess the feasibility, acceptability, safety, and preliminary data of the developed EEG-NF training. Given the pilot-feasibility design and exploratory nature of the study, inclusion of a control group was not necessary at this stage. The primary focus is to gather preliminary data on EEG-NF training implementation and variability in clinical outcomes, which will inform a future fully powered clinical trial [58-60]. A structured description of the intervention is summarized in Multimedia Appendix 3, following the Template for Intervention Description and Replication (TiDiR) guide (Multimedia Appendix 3) [61].

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Figure 1. Diagram of participant flow for the study. NF: neurofeedback.

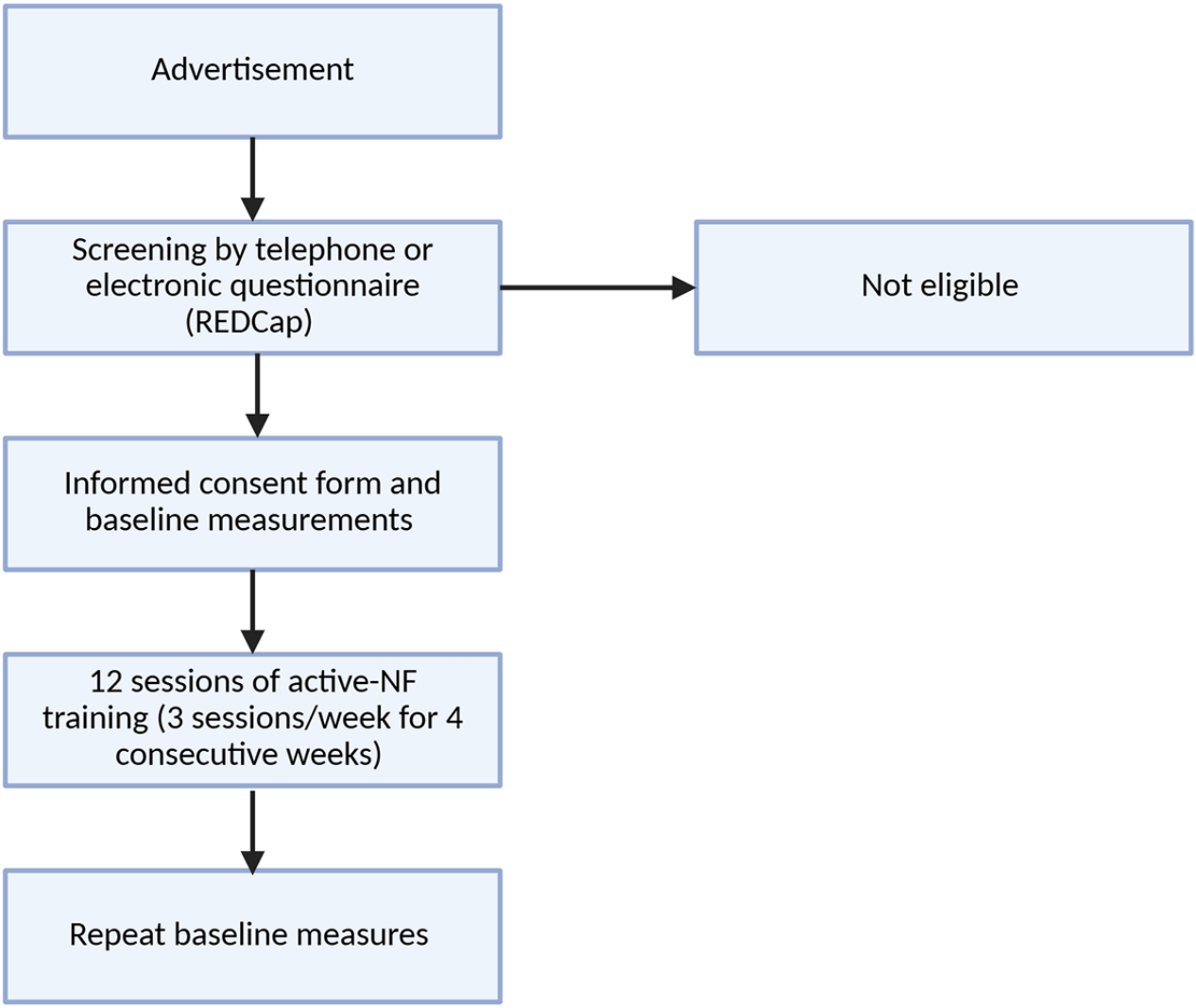

Recruitment

Convenience sampling will be used to recruit participants from the wider Dunedin community. Periodic advertising in community newspapers and social media will be carried out. Posters will be placed throughout the local community to advertise the study for participant recruitment.

Interested participants will undergo eligibility screening by telephone or through a secure online survey using Research Electronic Data Capture (REDCap; Vanderbilt University) web application [62]. As this is a pilot-feasibility study, a formal power-based sample size calculation was not undertaken. Instead, the sample size was determined as 6-12 participants over a 4-month recruitment period, in accordance with recommendations for feasibility studies and previous literature, ensuring adequacy to evaluate safety and feasibility outcomes while also permitting exploratory analyses [63].

Eligibility Criteria

Participants aged 35-75 years with MSK pain, averaging a score of ≥4 on the 11-point Numeric Pain Rating Scale over the past 3 months, with a minimum pain duration of 3 months, and a score of at least 19 on the PainDETECT questionnaire will be eligible to participate in this study [6,14,64-67].

Participants will be excluded if they have one of the following conditions or situations**:** systemic rheumatic conditions, neurological conditions, major psychiatric illness, cervical or lumbar radiculopathy, peripheral entrapment neuropathies, cognitive impairment, have undergone any surgery or intra-articular steroid injections in the 3 months before the study, have undergone any intra-articular hyaluronic acid injections in the 6 months before the study, are scheduled to undergo any surgery within 6 months of enrollment in the study, have undergone previous neurological procedures of the brain, are pregnant or up to 6 months postpartum, cardiovascular disease, peripheral arterial disease of limbs, uncontrolled hypertension (≥150/95 mm Hg), or uncontrolled diabetes.

Screening and Enrollment

Interested participants will undergo a brief preliminary screening for initial eligibility by telephone or through an online questionnaire using the REDCap online survey platform [68]. If the initial eligibility criteria are satisfied, participants will undergo a detailed screening based on their health information

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through a secure online survey. Participants will then be given an appointment for the final confirmatory screening.

A paper-based Montreal Cognitive Assessment will be carried out to screen for cognitive impairments [69]. The maximum Montreal Cognitive Assessment score is 30 points, and only those who score 21 or above will be eligible to participate in this study, based on normative data for the population included in the study [69,70]. If the participant meets this threshold and is found to be eligible, baseline assessment will continue.

Eligible participants will undergo 12 sessions (30 minutes each; 3 sessions per week) of ISF EEG-NF training and two 90-minute baseline and postintervention assessments at the Department of Anatomy–Research Clinic facility at the University of Otago, New Zealand. The intervention will be provided by a researcher experienced in the delivery of neurofeedback. Participants will be required to abstain from alcohol and caffeinated beverages for 24 hours and from food and drinks for at least 1 hour before any assessment sessions [71].

Intervention: ISF EEG-NF Training

At the start of each session, participants will be seated in a chair with back support and asked to remain relaxed for 10 minutes while the trainer prepares them for neurofeedback training. The ISF EEG-NF training will be administered using a 21-channel DC-coupled amplifier (BrainMaster Technologies Inc) with a Comby EEG lead cap containing Ag/AgCl sensors of an appropriate size, secured to the participant's head. Reference electrodes will be placed at the mastoids [72]. The impedance of the active electrodes will be continuously monitored to remain below 5 kΩ [49,52,72]. Participants will be advised to minimize eyeball, head, and neck movements, swallowing, and clenching of teeth to reduce motion artifacts in the EEG data [73]. Treatment adherence will be ensured by directly observing participants throughout the training sessions.

Participants will be instructed to relax, keep their eyes closed, and listen to the audio feedback. For this study, an ISF EEG-NF program to downtrain the RIns and dACC was developed using the BrainAvatar Live standardized low-resolution electromagnetic brain tomography projector software [52,74]. Standardized low-resolution electromagnetic brain tomography allows the selection of brain regions (region of interest [ROI]) for EEG-NF training based on the current density of the ROI and 3D brain mapping functionality [74-76]. A visual representation of the ROIs, direction of training, and an overview of outcome measures are provided in Figure 2. The figure was generated using BrainNet Viewer [77] and BioRender [78].

Figure 2. Regions of interest and outcome measures. dACC: dorsal anterior cingulate cortex; ECG: electrocardiogram; EEG-NF: electroencephalography neurofeedback; ISF: infraslow frequency; QST: quantitative sensory testing; RIns: right insula; ROI: region of interest.

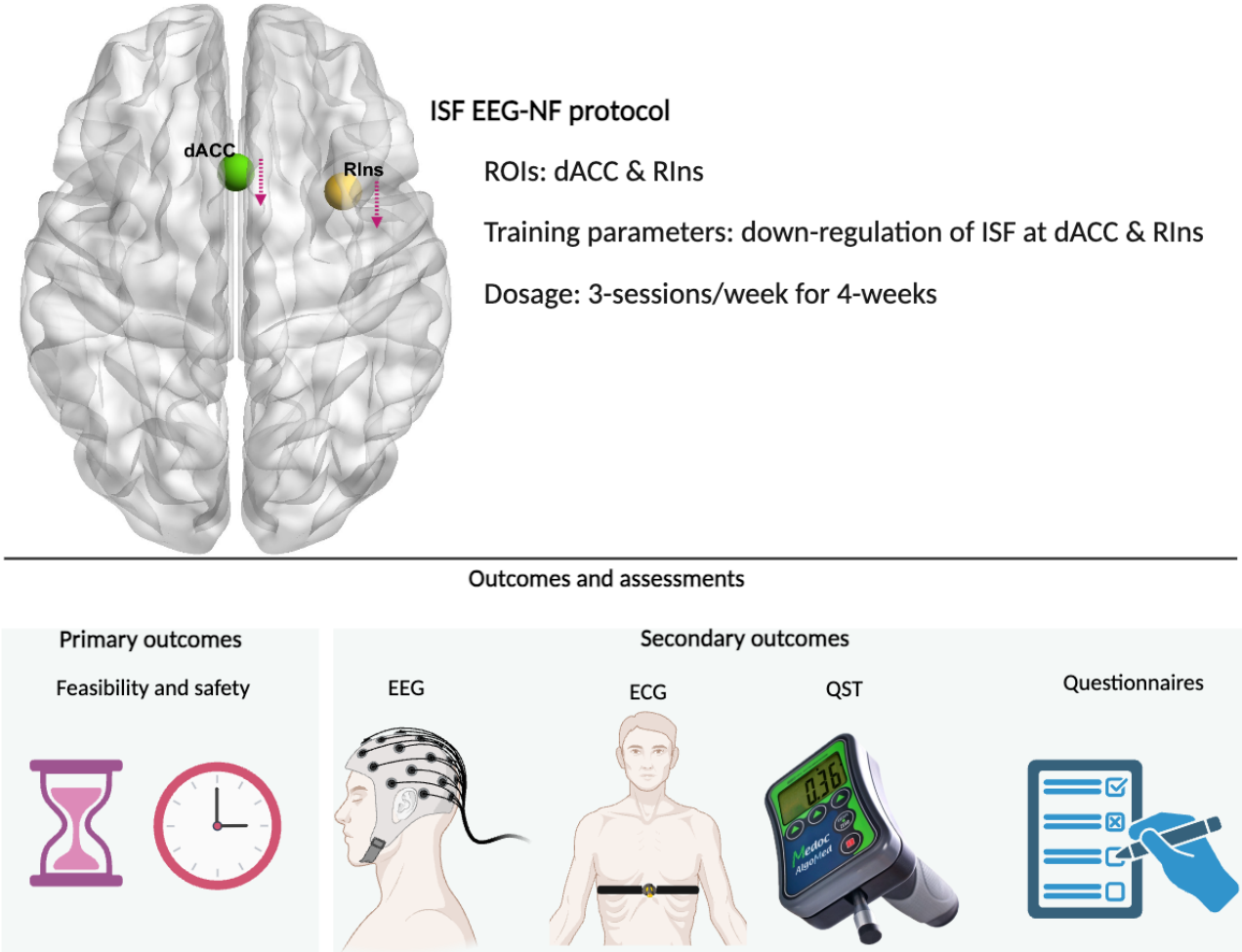

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The BrainMaster Technologies software (BrainAvatar) will deliver real-time auditory feedback when participants' brain activity is simultaneously downregulated within the ROIs—the dACC and RIns—in the ISF (0.0-0.1 Hz) band. The BrainAvatar auditory feedback is generated using Musical Instrument Digital Interface–based tones and sound effects. The auditory feedback serves as a primary reinforcement modality, providing immediate and intuitive cues that reflect real-time brain activity. The system incorporates a range of sounds, including simple tones, chimes, and naturalistic effects such as chirps or gongs, which vary in pitch, clarity, or occurrence depending on whether the individual's brainwave activity meets the targeted thresholds. For example, reward tones or sound effects are triggered only when the desired neural patterns are achieved, whereas the absence, distortion, or reduction of sound indicates deviation from the training goals. This dynamic modulation allows the brain to receive continuous, nonverbal information about its own functioning, supporting operant conditioning and the self-regulation processes central to effective neurofeedback training [47,48].

The auditory feedback (reward) will be captured using Audacity, a free and open-source audio recording and editing software [79]. Audacity can use the computer's microphone and sound card as its own audio-to-digital converter, eliminating the need for additional equipment. The auditory feedback will then be used to calculate the duration of successful neurofeedback training, defined as the cumulative time that the participant received the auditory reward feedback during the 30-minute neurofeedback session [80]. The duration of successful neurofeedback training from each participant across the 12 sessions will be included in the analysis.

The target ROIs were chosen based on previous literature related to EEG-NF and MSK pain conditions [30,31,50,52]. The reward threshold will be continuously monitored by the trainer and adjusted manually if cortical activity falls outside the desired threshold [49,52,72]. The duration and number of neurofeedback sessions were informed by recent studies using ISF EEG-NF for chronic pain management, which demonstrated changes in clinical pain outcomes, and were selected to ensure methodological rigor in this study [72,81].

Baseline Assessment

Once written informed consent is obtained, participants will complete questionnaires that include demographics and general health information, such as age, sex, and ethnicity. Assessment of resting-state EEG and clinical and experimental pain outcomes will be conducted by a researcher who is adequately trained in all procedures.

Primary Outcomes

The primary outcomes of this study will be the feasibility and safety measures [82]. These will be collected by the investigator throughout the study period, from recruitment until the last postintervention assessment session. Feasibility outcomes include the recruitment rate, defined as the number of participants attending a screening assessment each month; the enrollment rate, defined as the proportion of participants recruited from the total screened; the compliance rate, defined as the number of sessions attended by each participant out of the total sessions; and the dropout rate, defined as the number of participants who dropped out over course of the study [83,84]. All measures will be monitored through monthly audits of recruitment records during the first 4 months of the recruitment and intervention period.

An adverse event is defined as any harmful event or symptom from the trial that could reasonably be linked to the procedure or EEG-NF training. EEG-NF is a safe technique; however, all participants will be asked about any adverse events experienced from the previous session at each visit, and any worsened side effects compared with previous training will be recorded. All participants will be instructed to complete the Discontinuation Emergent Sign and Symptom scale [85], a 43-item checklist consisting of emotional, behavioral, cognitive, and physical symptoms. These symptoms can be considered possible side effects from neurofeedback training and have been used in previous literature as a measure of safety monitoring for similar studies [52,72].

Secondary Outcomes

Secondary outcomes of the study include self-reported questionnaires, resting-state EEG, electrocardiogram (ECG), and quantitative sensory testing (QST), assessed at baseline (T1) and postintervention (T2). Table 1 briefly describes each of the measurement tools used and the time points throughout the study. All tools are reliable and validated for use in individuals with persistent pain and are consistent with previous literature and the Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials (IMMPACT) recommendations for clinical trials in chronic pain [86-90].

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Table 1. Summary of secondary outcome measures, including descriptions and timeline used.

Outcome domain and constructs	Brief description of measurement tools	Measurement time points
Pain		
Pain severity and interference [91,92]	• The Brief Pain Inventory (BPI)–Short Form will be used to measure pain severity (0=no pain, 10=worst pain possible) and interference (0=does not interfere, 10=completely interfere) over the past 24 hours, past week, and past 4 weeks at T1 and T2. At each training session, a single-item BPI will measure pain severity and interference over the past 24 hours.	Full BPI: T1 and T2; Single-item BPI: every training session
Pain unpleasantness [93]	• Measured using an 11-point numeric rating scale from 0 (not at all unpleasant) to 10 (most unpleasant imaginable) for the past 24 hours and past week at T1 and T2. At each training session, unpleasantness over the past 24 hours will be measured.	Before every session
Pain bothersomeness [41,94]	• Measured using a 5-point scale ranging from “not at all” to “extremely” over the past 24 hours and past week at T1 and T2. Before every training session, bothersomeness over the past 24 hours will also be measured.	Before every session
Pain quality [6,8,66,95-100]	• PainDETECT questionnaire: 12 items, each symptom rated on a 5-point scale. Scores <12 indicate nociceptive pain, 13-18 indicate possible neuropathic pain, and ≥19 indicate likely neuropathic pain. • Short-form McGill Pain Questionnaire: 22 items, each rated on a 10-point numeric scale to assess pain quality. • Leeds Assessment of Neuropathic Symptoms: 5 items with weighted scores ranging from 0 to 24, assessing signs of neuropathic pain. • Dolour Neuropathique 4 interview: assess the presence of neuropathic pain symptoms; a cut-off score of 4 or more positive items indicates neuropathic pain.	T_1 and T_2
Fatigue [101]	• Measured using a 10-point numeric rating scale ranging from 0 (no fatigue) to 10 (fatigue as bad as it can be).	T_1 and T_2
General health and well-being		
Depression, anxiety, and stress [102,103]	• The Depression, Anxiety, and Stress Scale, containing 21 items. Each item is rated on a scale from 0 (never) to 3 (almost always) to quantitatively measure psychological distress.	T_1 and T_2
Pain personification [104]	• Pain personification questionnaire, containing 11 items scored on a 5-point Likert scale (1=strongly disagree, 5=strongly agree) to measure the participant’s experience of pain as an internal object.	T_1
Intolerance of uncertainty [105,106]	• Intolerance of Uncertainty Scale, containing 12 items. Each item is rated on a 5-point Likert scale ranging from 1 (strongly disagree) to 5 (strongly agree).	T_1
Sleep quality and disturbances [107,108]	• Pittsburgh Sleep Quality Index, containing 19 items measuring sleep quality and disturbances over a 1-month interval. Total scores range from 0 to 21, with higher scores indicating poorer sleep quality.	T_1 and T_2
Participant perceptions about intervention and its impact on health and pain		
Credibility/expectancy of the intervention [109]	• Credibility/Expectancy Questionnaire, containing 6 items to quantify how credible the participant perceived the intervention to be.	T_2
Acceptability of interventions [110]	• Numeric rating scale (0-7) assessing acceptability across 7 components of the theoretical framework of acceptability: affective attitude, burden, perceived effectiveness, ethicality, intervention coherence, opportunity costs, and self-efficacy.	T_2
Perceived treatment satisfaction [111]	• Single item numeric scale ranging from 0 (not satisfied at all) to 10 (highly satisfied).	T_2

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Outcome domain and constructs	Brief description of measurement tools	Measurement time points
Patient Global impression of change [112,113]	• The Patient Global Impression of Change score represents the participant's perceived change in pain compared with baseline. It is rated on a 7-point scale, from 1 (very much improved) to 7 (very much worse).	T_2
Mental fatigue [114]	• Mental fatigue will be assessed using a single-item numeric scale from 0 (I do not feel fatigued at all) to 10 (I feel extremely fatigued).	T_2
Mental strategies [72]	• Patients will be asked whether they used any mental strategies during training sessions and if yes, to report which strategies they used.	T_2
Level of motivation [52]	• The Current Motivation–Brain Computer Interface will be used at T1. It uses a 7-point Likert scale across 4 components: mastery confidence, fear of incompetence, interest, and challenge related to electroencephalography neurofeedback training. • A single-item 11-point numeric scale will be used for motivation before each training session, ranging from 0 (not motivated at all) to 10 (extremely motivated).	T_1 and before every training session
Mood [52,115]	• Mood will be measured before every neurofeedback session using a single item from the Brief Mood Introspection Scale, ranging from 0 (very unpleasant) to 10 (very pleasant).	Before every training session
Level of engagement with the training [52]	• A 10-point numeric scale will be used, ranging from 1 (least engaged) to 10 (highly engaged).	After every training session

Electroencephalographic Measures

Resting-state EEG will be recorded (sampled at 256 Hz) using a 21-channel system (Fp1, Fp2, F7, F3, Fz, F4, F8, T7, C3, Cz, C4, T8, P7, P3, Pz, P4, P8, O1, O2, A1, A2; BrainMaster Technologies, Inc) [43]. Raw EEG recordings will be collected for 10 minutes with participants' eyes closed. To minimize potential artifacts, participants will be instructed to avoid facial movements, head and neck movements, and swallowing. Alertness will be monitored by observing the presence of spindles and slowing of the alpha rhythm in the EEG stream to prevent drowsiness-related increases in theta power during the recording [116].

Each EEG file will be resampled to 128 Hz and bandpass filtered for 0.01-44 Hz in EEGLAB (MATLAB R2020a) [117]. Artifacts such as eye blinks, muscle artifacts, perspiration, and body movements will be filtered out using ICoN software [52,118].

Exact low-resolution brain electromagnetic tomography (eLORETA) software will be used to extract the following EEG variables. First, ROI current density, for which frequency-specific data will be collected by performing a voxel-by-voxel analysis containing 6239 voxels for each of the following frequency bands at the dACC and RIns: infraslow (0.01-0.10 Hz), slow (0.2-1.5 Hz), delta (2-3.5 Hz), theta (4-7.5 Hz), alpha (8-12 Hz), beta (12.5-30 Hz), and gamma (30.5-44 Hz). Comparisons will be made between participants' pretreatment and posttreatment measures using eLORETA statistical contrast maps. Multiple voxel-by-voxel comparisons in the logarithm of t-ratio with a threshold of $P \leq .05$ will be used to compute the cortical 3D distribution of current density [49].

Second, functional connectivity will be assessed using lagged linear connectivity, which is a statistical measure of coherence representing the phase synchronization between ROIs within the brain, as it combines the relationship between the phase and amplitude of the signals [23,24]. This measure reflects the level of communication between the ROIs [90]. Log-transformed lagged linear connectivity will be derived for all possible connections across the 7 frequency bands between the dACC and RIns.

eLORETA is an EEG source localization software that computes current density across the full brain volume [119] to localize cortical brain structures with fewer localization errors for EEG data extraction and analysis [120]. eLORETA has been widely used in previous literature for EEG analysis [121-123].

Cardiovascular Measures

Heart rate variability (HRV) metrics will be obtained using a Polar V800 heart rate monitor and a Polar H10 Chest Pro Strap [124]. The ECG monitor will be placed below the sternum and secured to ensure a fixed position for the participant. Raw heart rate and R-R (peak-to-peak R wave) interval time series data will be downloaded from the Polar Flow software for further processing and analysis. Kubios HRV Premium (v3.2.0) software will be used to analyze HRV from the R-R interval record exported from the Polar Flow software [125]. The root-mean-square of successive differences between normal heartbeats and stress index (SI) will be extracted for HRV analysis. Root-mean-square of successive differences quantifies the variability between adjacent respiratory rate intervals, demonstrating a lesser susceptibility to influence by the respiratory system and, due to this, is regarded as the most dependable HRV for monitoring vagal response [125,126]. The SI will be calculated using the square root of the Baevsky SI model [127]. Given that the insular cortex and dACC are key regions involved in interoception—integrating internal bodily signals to regulate physiological and emotional states—any

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changes in sympathetic and parasympathetic activity can be effectively captured through HRV analysis [80,128,129].

Quantitative Sensory Testing Measures

The following QST measurements will be performed at T1 and T2. All QST measures were included based on previous literature demonstrating variability in these clinical measures among individuals with chronic MSK pain and NP [130-132].

Pressure Pain Threshold

A computerized algometer (AlgoMed, Medoc) will be used to measure pressure pain threshold on the dorsal aspect of the nondominant wrist of the participant for 3 trials [133,134]. Two familiarization trials will be performed at the mid-forearm before the formal trials. Pressure will be applied to the test site gradually at a rate of 30 kPa/s for each participant by placing a 1-cm^2 probe perpendicular to the site until the participant reports that the pressure has become a pain sensation. Participants will be instructed to verbally inform the investigator immediately when they perceive pressure as pain. The average of the 3 tests will be used for analysis [135].

Punctate Pain Intensity

Punctate pain intensity will be assessed using a nylon filament (Semmens monofilament 6.65, 300 g) on the nondominant wrist of the participant for 3 trials [134,136]. The nylon monofilament will be applied perpendicular to the site on the nondominant wrist with enough force to bend the filament. Immediately after each trial, participants will report their pain intensity on a 101-point numeric pain rating scale (0 indicating no pain at all and 100 indicating the most intense pain they have ever experienced) [137]. The average across the 3 trials will be calculated.

Mechanical Temporal Summation

Mechanical temporal summation (MTS) will be assessed using a nylon filament (Semmens monofilament 6.65, 300 g) on the dorsal aspect of the nondominant wrist of the participant for 3 trials [134]. Participants will be instructed to provide a pain rating on a 101-point numeric pain rating scale. Immediately after this, 10 consecutive contacts with an interstimulus interval of 1 second will be performed, and participants will be asked to provide a pain rating on the 101-point numeric pain rating scale again. MTS will be calculated as the difference between the initial value after the first contact and the highest pain rating after the tenth contact. The average of these 3 trials will then be used in analysis.

Vibration Detection Threshold

A tuning fork (64 Hz, 8/8 scale) will be used to test a participant's ability to detect vibration and will be placed on the dorsal aspect of the nondominant wrist with suprathreshold vibration intensity. It will be held in place until the participant can no longer feel the vibration [134,138,139]. This will be graded on an 8/8 scale, with 8 indicating the highest level of sensitivity to vibration [140]. The vibration detection threshold will be determined using the mean of 3 consecutive tests for each location [141].

Medication and Other Treatment Monitoring

Any concurrent treatments will be monitored, including regular general practitioner visits, use of physiotherapists, osteopaths, chiropractors, and self-management as well as current medications. Any medications that participants are taking regularly will be recorded at the baseline assessment. Changes in dosage, as well as the frequency of use of pain-relief medications during the study period, will be noted at each session.

Analysis

Primary Outcomes

Participant demographics, feasibility, acceptability, credibility, and safety data over the course of the study will be summarized descriptively [142]. Mean (SD) or median (IQR) when distributional assumptions are not met and CI (75% and 95%) of the clinical and quantitative outcome measures for the participants will be derived using GraphPad Prism software [143]. Feasibility will be assessed against prespecified progression criteria: ≥50% of eligible participants consenting, recruitment meeting target within the planned window (~6 participants in 4 months), retention ≥80% at postintervention, adherence ≥75% of scheduled sessions, data completeness ≥85%, and mean acceptability ≥70%. Each metric will be reported as a point estimate with 95% CIs, and progression will be discussed in light of these thresholds [60,144,145].

Secondary Outcomes

A within-group pre-post statistical comparison (to be determined based on the normality of the data) will be conducted for all the secondary outcome measures using GraphPad Prism software (version 10.4.1; GraphPad Software) [143]. Similarly, correlation analysis will be performed to explore the relationship between EEG measures, self-reported outcomes, and HRV and QST measures. All analyses for this pilot-feasibility study will be unpowered due to sample size and are thus exploratory in nature.

Secondary outcomes will be interpreted descriptively and exploratorily, focusing on patterns, effect size estimates, and CIs rather than formal hypothesis testing, to generate preliminary trends and inform the design of a future powered clinical trial [146]. Changes in clinical ratings before and after the intervention will be analyzed to inform the design of future efficacy trials, using effect sizes, paired *t* tests, and Wilcoxon signed-rank tests.

Results

This study was funded in January 2025. As of October 2025, data collection has been completed, with a total of 5 participants enrolled. The target sample size for the study was 12 participants. Data analysis will commence in November 2025 and will continue for 3 months following the completion of data collection. The results of the study are expected to be published once data collection and analysis are complete in late 2026 or early 2027. Any deviations from the protocol, regardless of the reason, will be documented in the Australian New Zealand Clinical Trials Registry and reported in the final publication.

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Discussion

Principal Results

The primary aim of this study is to pilot test and assess the feasibility of the novel ISF EEG-NF training protocol targeting the dACC and RIns for individuals with NP-like qualities. This study, for the first time, aims to simultaneously downregulate the ISF activity of the RIns and dACC in a chronic pain population. Therefore, a preliminary study assessing the feasibility, acceptability, and safety of the intervention is imperative before advancing to a fully powered clinical trial to evaluate its efficacy.

Comparison With Previous Work

Previous studies, using comparable protocols have conducted dual region source-localized ISF EEG-NF training in individuals with chronic low back pain and major depressive disorders [50,147]. These studies successfully targeted the dACC, showing clinical improvements and variability following the training. In addition, a recent study using a similar methodology successfully targeted the insular cortex, specifically training the left posterior insula in healthy volunteers. This study explored the relationship between the duration of successful neurofeedback training and clinical outcomes, aiming to understand the impact of EEG-NF training on gastric slow-wave activity [80]. Thus, this study adopts a similar methodological framework to develop the ISF EEG-NF program [75,120], using established and reliable methods that have been successfully implemented in previous research [43,52,72,80,89]. The ROIs (RIns and dACC) are created with all the nearby voxels with a localization of 5 mm [41,52,120]. Moreover, no studies have attempted ISF EEG-NF to manage NP-like qualities in individuals with chronic MSK pain, highlighting the novelty of this project and its potential for future clinical translation.

This study will also introduce a novel approach to measuring EEG learning effects by assessing the duration of successful neurofeedback within each session, a method previously used in only one study [80]. The secondary aims will allow for exploratory analysis to better understand data variability and trends in EEG measures and clinical pain outcomes in individuals with NP-like qualities in chronic MSK conditions.

Limitations

During this study, several challenges may be encountered while assessing feasibility. One of the primary issues may be due to recruitment of participants. This could be attributed to the challenges faced by patients coming to the study location to receive treatment, as their pain may be debilitating, as highlighted in previous literature emphasizing activity limitations [148]. This study is also targeting a demographic that may be spread throughout the wider local community and thus may not encounter the flyers placed throughout the community. We plan to mitigate this by also including the study advertisement in newspapers, which may be more accessible for recruiting patients who are further away from the surrounding area. Since PainDETECT is being used as a screening tool, we are excluding patients with scores below 19, including those falling within the range of 14-18 that indicates a possible neuropathic component. This produces a challenge as it reduces recruitment and potentially excludes patients who may have a neuropathic component to their pain. However, only recruiting patients who score 19 or above strengthens the validity of the patients having a neuropathic component, as painDETECT has a high sensitivity and specificity [149]. That said, we acknowledge that this can impact patient recruitment and enrollment rates.

Conclusions

The data and findings of this study will aid in designing future fully powered clinical trials to further evaluate the efficacy of this novel ISF EEG-NF training for NP management. Additionally, the foundational data from this pilot open-label feasibility trial will provide the necessary information to enable future studies to perform power calculations for designing upcoming trials.

Acknowledgments

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Data Availability

The data generated during this study will be available on reasonable request from the corresponding author.

Authors' Contributions

JM is responsible for the conceptualization of this study. LSB, DRM, and JM were involved in data curation. JM handled funding acquisition. LSB and DRM conducted the investigation. JM, DBA, YOC, MLS, RM, and DDR contributed to the methodology. JM, DBA, YOC, RM, and DDR provided resources. JM, MLS, and YOC were responsible for software. JM, DBA, YOC, RM, and DDR supervised the study. LSB wrote the original draft. LSB, JM, DBA, DRM, MLS, YOC, RM, and DDR contributed to writing, review, and editing.

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Conflicts of Interest

MLS is the owner of Neurofeedback Therapy Services of New York, New York. The remaining authors have no conflicts of interest to declare.

Multimedia Appendix 1
SPIRIT checklist.
[PDF File (Adobe PDF File), 180 KB - resprot_v14i1e78806_app1.pdf]

Multimedia Appendix 2
CONSORT extension for pilot and feasibility trials.
[PDF File (Adobe PDF File), 183 KB - resprot_v14i1e78806_app2.pdf]

Multimedia Appendix 3
TiDiR checklist.
[PDF File (Adobe PDF File), 242 KB - resprot_v14i1e78806_app3.pdf]

Multimedia Appendix 4
Peer review report from the International Association for the Study of Pain (IASP) Early Career Researcher Grant Review Committee.
[PDF File (Adobe PDF File), 27 KB - resprot_v14i1e78806_app4.pdf]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
dACC: dorsal anterior cingulate cortex
ECG: electrocardiogram
EEG: electroencephalogram
EEG-NF: electroencephalography neurofeedback
eLORETA: exact low-resolution brain electromagnetic tomography
HRV: heart rate variability
IMMPACT: Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials
ISF: infraslow frequency
MSK: musculoskeletal
MTS: mechanical temporal summation
NP: neuropathic pain
QST: quantitative sensory testing
REDCap: Research Electronic Data Capture
RIns: right insula
ROI: region of interest
R-R: peak-to-peak R wave
SI: stress index
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TiDiR: Template for Intervention Description and Replication

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Protocol

Cocreation of Integrated Interventions Addressing Noncommunicable Diseases and Environmental Degradation: Protocol for a Participatory Qualitative Study

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Abstract

Background: Addressing the adverse impacts of climate change on human health requires a global effort across multiple sectors. People living in low- and middle-income countries are particularly vulnerable to the health crises induced by climate change. Therefore, context specific solutions to tackle such challenges are essential to ensure preventive measures are in place for mitigating such risks.

Objective: This protocol aims to outline an integrated, participatory approach to cocreate multisectoral interventions tailored to specific environmental and health challenges in Bangladesh, India, and Indonesia. This work is done as part of the Global Health Research Centre for Non-Communicable Diseases and Environmental Change, funded by the National Institute for Health and Care Research. The overall aim is to collaboratively design and assess interventions that deliver dual benefits for planetary and human health.

Methods: To address the multisectoral nature of the challenges, this study will adopt a cocreation methodology that blends co-design and coproduction approaches. While the problem areas are specific to each context—tackling air pollution due to plastic burning in Indonesia, improving dietary diversity of public food procurement systems and managing extreme heat in India, and mitigating drinking water salinity in Bangladesh—the underlying cocreation framework is consistent and can be adapted to the needs of each study setting. The workflow consists of 4 key stages guided by an existing cocreation framework: planning, developing, evaluation, and reporting, with the 6 core elements of the Medical Research Council's complex intervention development framework embedded throughout the process. Drawing on the Double Diamond design process, the cocreation stage

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involves the following phases: codevelopment of a theory of change to explore potential context-specific interventions, short-listing of intervention components through gap analysis and prioritization, co-designing and coproducing selected intervention components, and assessing appropriateness and feasibility of intervention implementation. The cocreation process will be evaluated using the Research Quality Plus for Co-Production framework to ensure methodological rigor and quality.

Results: Cocreation will take place over 6 months. Sampling and recruitment of cocreators (key stakeholders across sectors) have been completed in all 3 countries, with each cocreator group consisting of 20-30 members. We have developed the tools for the cocreation phase, informed by the findings from formative research, and received the necessary ethics approval to conduct these activities. We will generate a series of academic and nonacademic outputs on the cocreation process to disseminate the findings, as well as training materials for implementers to facilitate future adoption in similar settings.

Conclusions: The cocreation of multisectoral interventions to tackle both environmental change and health is a comparatively new domain of implementation research. This protocol addresses the complex, multidimensional, and unique nature of such interventions by developing a structured and scientifically sound approach to be implemented in real-life settings.

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KEYWORDS

multisectoral intervention; planetary health; cocreation; noncommunicable diseases; implementation research

Introduction

Environmental change and its impacts on human lives and livelihoods are a major global concern [1]. The adverse effects of rising global temperatures and extreme weather events are evident in increasing physical and economic losses as well as a surge in noncommunicable diseases (NCDs) [2,3]. Those living in low- and middle-income countries (LMICs) are often among the most vulnerable and disproportionately affected due to their high exposure and sensitivity to the impacts on ecosystems, human habitat, and infrastructure [4,5]. Health systems in many of these countries also have the lowest climate readiness scores, meaning that they are poorly prepared to adapt their available resources to climate vulnerabilities [6]. Given the complexity and scale of such climate change–induced health issues, there is a critical need to develop and implement context-specific solutions through collaboration across different sectors and disciplines, also known as multisectoral interventions [7]. Suited to local needs, these multisectoral interventions can help with early mitigation of risks and reduce the extent of human activities that lead to adverse environmental and health outcomes.

The National Institute for Health and Care Research (NIHR) Global Health Research Centre (GHRC) for NCDs and Environmental Change is a collaborative effort among researchers from 4 countries that aims to achieve dual benefits for health and the environment by developing such multisectoral interventions [8]. NIHR GHRC focuses on a context-specific environmental issue in each geographic region that is important both locally and globally. The first problem area is tackling air pollution from plastic burning in Indonesia, where increasing plastic pollution is a major threat because of both the production and import of large quantities of plastics [9]. The second problem area is managing extreme weather events such as heat waves and improving dietary diversity within public food procurement systems in rural India. Heat waves have been associated with increased risks of dehydration, heat stroke, cardiovascular complications, and mortality, especially among vulnerable populations such as older adults and those with preexisting NCDs [10]. Climate change can negatively impact agriculture and dietary diversity of rural and indigenous populations in such settings, which can worsen malnutrition in all its forms and diet-related NCDs [1,11]. The third problem area is mitigating drinking water salinity in coastal areas in Bangladesh, where surface water and groundwater bodies are becoming increasingly salinized because of rising sea levels and tropical storm surges. Regular intake of such saline water can result in a range of health issues, including hypertension and cardiovascular disease [12,13].

Multisectoral interventions designed to address these interconnected challenges must be grounded in local needs and priorities to be effective across diverse contexts. Guided by the Medical Research Council (MRC) framework [14] for developing and evaluating complex interventions, NIHR GHRC adopted cocreation as a collaborative participatory approach for developing and implementing complex multisectoral solutions [15]. Cocreation is an overarching term that includes both coproduction and co-design [16]. This involves engaging diverse stakeholders across multiple disciplines throughout the process of understanding the issue at hand as well as designing and evaluating contextually relevant solutions [15,16]. While a range of frameworks have been developed to assist with co-design [17-20], including policy co-design [21,22], coproduction [23], and cocreation of interventions [24], there is a lack of evidence that demonstrates how these could be integrated in the MRC guidance to develop a complex multisectoral intervention. Furthermore, given the dual focus on the environment and health in this study, it is important to incorporate planetary health perspectives in the design and evaluation of interventions in a structured way [25,26], following recently published guidance [27]. In addition, engagement and involvement with a range of stakeholders across multiple sectors and settings requires a culturally sensitive and setting-specific cocreation process. Therefore, this protocol outlines a practical, context-sensitive framework for cocreating solutions with the communities and partners involved in NIHR GHRC to guide the development of dual-benefit multisectoral interventions that address NCDs and environmental change.

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Methods

Study Setting

This study is being implemented in designated intervention and control areas within each participating country. Cocreation activities are limited to the intervention areas, where stakeholders are actively engaged in developing multisectoral interventions. Table 1 presents an overview of the country-specific projects.

Table 1. Study setting and problem areas of the National Institute for Health and Care Research Global Health Research Center for Non-Communicable Diseases (NCDs) and Environmental Change.

Country	Study locations	Problem	NCD risk	Potential solutions
Indonesia	Malang district	Air pollution due to plastic burning	Cardiovascular and chronic obstructive pulmonary diseases	Improved waste management to reduce plastic burning
India	Sarguja district, Chhattisgarh	Lack of dietary diversity in public food procurement systems (Integrated Child Development Services program [28] and Pradhan Mantri Poshan Shakti Nirman [29])	Nutrition and dietary health issues	Adaptation of school food menus and procurement processes to enhance dietary diversity
India	Srikakulam district, Andhra Pradesh	Extreme weather events due to heat	Cardiometabolic diseases	Strengthening health systems and community preparedness for heat-related health impacts
Bangladesh	Khulna district	Increased drinking water salinity	Chronic kidney diseases and cardiovascular diseases	Providing access to safe, nonsaline drinking water

Study Design

Overview

We will use a participatory qualitative study design to cocreate the interventions. Throughout the intervention cocreation process, we will follow the MRC framework for developing and evaluating complex interventions. The intervention identification, development, and feasibility assessment will be guided by the six core elements of the MRC framework: (1) consider context; (2) develop, refine, and retest program theory; (3) engage stakeholders; (4) identify key uncertainties; (5) refine intervention; and (6) economic considerations [14].

Stakeholder recruitment for the cocreator groups will be conducted through a nonrandomized purposive sampling to ensure diverse representation across characteristics of interest such as gender, role, socioeconomic status, and stakeholder influence, which are commonly adopted by cocreation studies [24]. The cocreator groups will be involved throughout all stages of the iterative process outlined subsequently. At the end of this process, the key outputs will include a set of contextually appropriate intervention components and corresponding implementation strategies to support effective and efficient delivery.

In addition, the cocreation workflow is informed by the framework and principles developed by Leask et al [24], which emphasize participatory engagement across 4 key stages: planning, developing, evaluation, and reporting. Figure 1 illustrates the iterative cocreation workflow adapted for this study.

Table 2 presents the frameworks used in guiding different phases of the cocreation process. While many implementation frameworks exist, these frameworks have been chosen based on their use in existing literature and appropriateness for our desired intervention output.

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Figure 1. The iterative cocreation workflow for multisectoral intervention development. NGO: nongovernmental organization; ToC: theory of change.

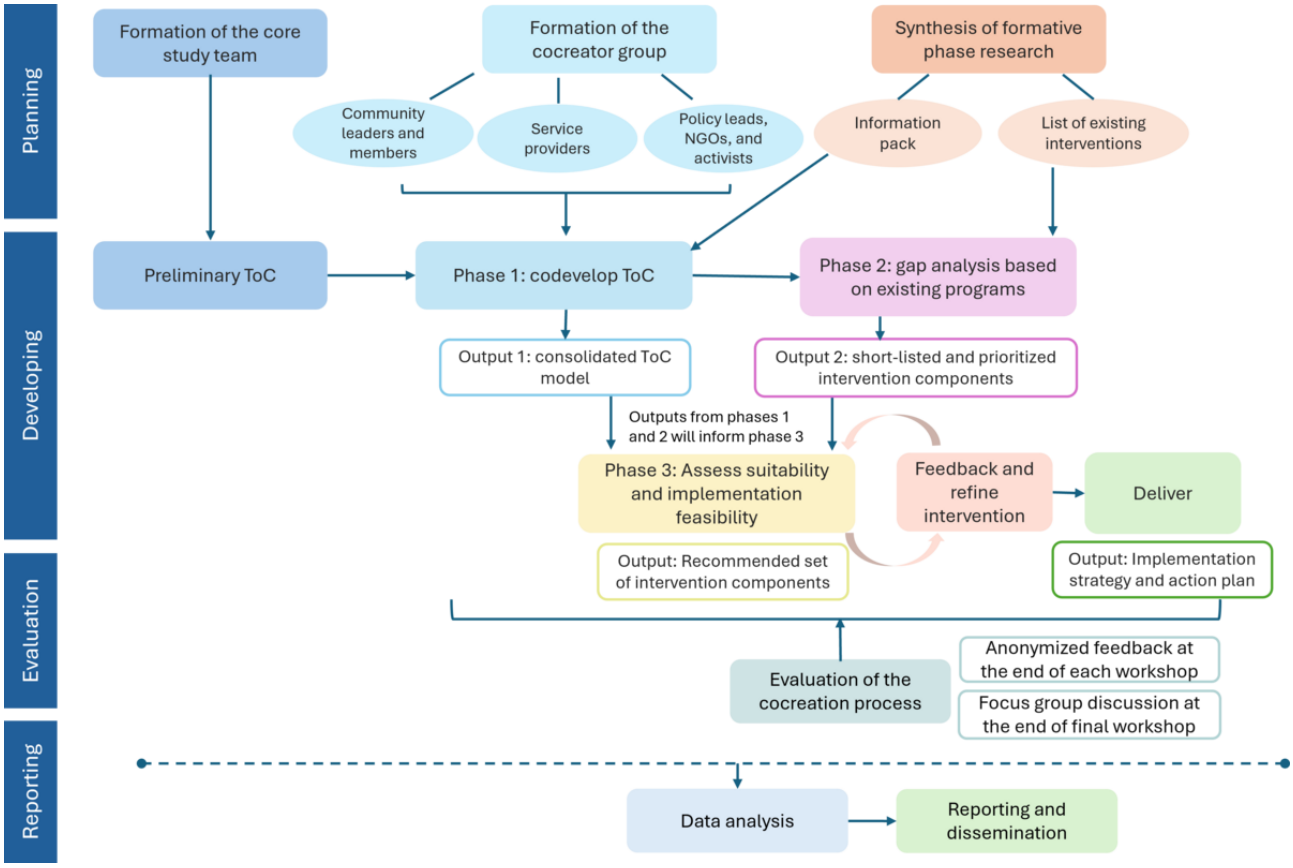

Table 2. Frameworks used throughout different cocreation phases and their purposes.

Cocreation phase	Purpose	Framework used
Overall cocreation process	• Guide the overall cocreation process	• Medical Research Council intervention development framework [14] and cocreation workflow by Leask et al [24]
Planning	• Contextual analysis	• Context and implementation of complex interventions framework [30]
Development of the intervention	• Guide the intervention design process • Pre-evaluate the cocreated intervention through a planetary health lens before implementation	• Double Diamond design model [31] • Planetary health framework [26]
Evaluation	• Evaluate the cocreation process	• Research Quality Plus for Co-Production framework [32]
Reporting	• Report cocreation outcomes using a structured checklist	• Leask et al [24]

Planning

The planning stage incorporates preparatory activities to inform the intervention development. The key objectives of this stage are to (1) develop a comprehensive understanding of the context based on the findings from previous formative research, (2) establish a core study team composed of researchers and community engagement members, and (3) recruit cocreators from relevant stakeholder communities to form a cocreation group. The core study team will define the cocreation process, provide necessary training and guidance, and support the recruitment of cocreator group members. The cocreator group will provide active input in the intervention development process and help with the development of implementation strategies.

As emphasized by the MRC framework, the success and outcome of an intervention are strongly influenced by the context in which it is implemented. Contextual understanding can enable, modify, constrain, or facilitate the intervention design and delivery [14,30]. Therefore, an in-depth understanding of the context is crucial for developing an intervention suited to that specific setting. To inform this context, we conducted formative research, including literature and policy reviews, as well as qualitative and quantitative research in each setting. These findings will be synthesized to

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describe the existing landscape of the issue, local community practices, availability of resources, and stakeholders' perceptions. We will use the context and implementation of the complex interventions framework to map these findings against relevant contextual domains: geographical, epidemiological, sociocultural, socioeconomic, ethical, legal, and political [30]. We will also consider other independent interventions implemented in the same setting and targeting the same population group, as these may influence the outcomes of the proposed intervention.

To ensure meaningful engagement with relevant stakeholders, core study teams composed of researchers and community engagement members will be formed in each country. These groups will support the preparation of information packages based on synthesized contextual information and training materials, aid in the recruitment of cocreator group members, and advise on specific stakeholder engagement methods.

Guided by these core study teams, stakeholders from the cocreator groups will be purposefully selected, with members across different groups equally represented, including those from vulnerable groups. This will be guided by the stakeholder mapping conducted as part of formative research and community engagement activities. The core study teams will collaborate with the cocreator group members to coproduce rules of participation and facilitate necessary training and knowledge-sharing opportunities.

Developing

Overview

The development stage includes a series of iterative phases, guided by the Double Diamond design process [31]. The key objectives of this stage are (1) codevelopment of a theory of change to identify potential interventions [33,34] (discover), (2) prioritization and short-listing of existing solutions (define), (3) assessment of suitability and implementation feasibility of proposed solutions through a planetary health lens (develop), and (4) development of implementation strategies to deliver the final intervention (deliver). A series of iterative workshops and interviews will be conducted with the cocreator groups to achieve these objectives. There may be several iterations of intervention refinement and implementation strategies based on stakeholder feedback before piloting and delivering the intervention.

Codevelop a Theory of Change Model

A theory of change describes why and how an intervention or program works. Depicted as a causal diagram, the theory of change can be an effective tool to design and evaluate interventions by outlining pathways to achieve intended outcomes, underlying assumptions, and indicators to measure change [34]. We will codevelop our theory of change in 2 stages by involving the core study teams and cocreator groups to ensure it is context specific and culturally responsive [35]. As the first step, the core study team will participate in an exploratory workshop to discuss the problem we are addressing and the scale and ambition of the solutions to aim for. On this basis, they will develop a preliminary theory of change, setting the overarching aim of intervention, identifying its intermediate goals, and outlining potential activities (intervention components) linked to these goals.

In the second workshop, the cocreator group will review and modify the proposed long- and short-term goals outlined in the theory of change to reflect community realities and needs. Similar to the first round, they will then identify a list of possible activities that align with these goals, taking into consideration context, scale, and feasibility. Any additional outcomes proposed will be integrated into the preliminary theory of change model to develop an updated theory of change. This will remain a living document and may be revised as necessary throughout the course of cocreation.

Short-Listing of Potential Interventions

Following the development of the theory of change, all identified interventions (activities), both those codeveloped and those identified through literature and evidence mapping, will be compiled. A gap analysis and prioritization exercise will be conducted with cocreator groups in smaller breakout sessions. These sessions will assess the strengths, limitations, and relevance of each option. The key discussion points will then be shared with the whole group to coproduce a short list of interventions, using a relevant prioritization technique. For example, these can include the impact-effort matrix, which prioritizes solutions based on their relative value to end users versus the resources needed to deliver the solution [36], or the must have, should have, could have, will not have (MoSCoW) method, which emphasizes end user requirements to classify solutions into respective groups [36,37].

Assessing the Suitability and Feasibility of Short-Listed Interventions

Short-listed interventions will be packaged based on alignment with the theory of change and assessed for suitability and feasibility in 2 steps—first, with community members and health care professionals and second, with policy-level stakeholders and planetary health experts.

In the first step, a workshop will be held to explore the cultural acceptability, perceived effectiveness, and implementation feasibility of each intervention. A decision matrix will be used to guide discussions around each of the following criteria [38]: social validity (cultural relevance, satisfaction, and equity), intervention coherence, and dual health-environmental impact [39,40]. The cocreator group will judge whether each intervention meets the outlined criteria or requires modification. Ideas for alternative solutions will also be sought in case the intervention does not meet the criteria. At the end of this workshop, the working group will incorporate the feedback and refine the proposed intervention package.

In the second step, we will evaluate the co-designed multisectoral intervention through a planetary health lens, informed by the planetary health framework for preimplementation assessment, which we tailored for the purposes of our codevelopment process based on previous theories [25,26] and guidance for assessing acceptability and feasibility [39-41]. This will involve in-depth discussions around health and environmental cobenefits and feasibility of intervention implementation, considering practicality, perceived

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fit with the infrastructure, cost to organizations and policy bodies, as well as aspects of governance. The final intervention package will be refined based on these assessments.

Development of an Implementation Plan

The final step in this stage is to develop a detailed implementation plan. Building on the theory of change, an implementation theory will be articulated, outlining how the desired changes should take effect in the setting for the implementation effort to be successful and how the implementation process will be operationalized. We will map the implementation strategies, that is, a set of methods and activities designed for the specific context, as well as identify the implementation agents, that is, the individuals and organizations engaged in the process [42].

Evaluation

The cocreation process will be evaluated continuously to ensure the outcomes generated through the process are representative of cocreators' opinions as well as suitable, tailored, and valid for end users [23,40]. Short anonymous feedback will be used after each workshop to incorporate participant needs and views while not overburdening them. A structured questionnaire for collecting participant feedback at the end of the final cocreation workshop will be developed using the Research Quality Plus for Co-Production framework [32]. The format will include focus group discussions, individual interviews, and surveys. These tools will be adapted to the needs of each setting, depending on the context, nature of the intervention, and how different groups of stakeholders will be involved in different stages of the cocreation process.

Reporting

The outputs from the cocreation process will be reported using a structured checklist such as the one proposed by Leask et al [24], to ensure transparency and consistency. Outputs will include artifacts directly derived from the workshops, such as the theory of change model and prioritized list of interventions, as well as qualitative data from the discussions during cocreation workshops and evaluation. Other outputs include a logic model and implementation strategies that will be developed for the final multisectoral intervention based on the cocreation workshop outputs.

Qualitative data collected during the workshops and evaluation process will be analyzed using hybrid thematic analysis [43] in NVivo (Lumivero) software. Inductive analysis will be used for coding the exploratory discussions from the theory of change building workshop, whereas deductive analysis will be used for the later stages, as those workshops should follow a more structured discussion supported by specific tools and frameworks. Any emerging themes will be captured using iterative inductive coding [44]. All findings will be triangulated with observations and field notes recorded by team members during cocreation activities. These combined data sources will inform the final reporting of the cocreation process and outcomes, providing a rich, contextualized account of the intervention development journey.

Ethical Considerations

Ethics approvals have been obtained from the research and ethics committee at Imperial College London and ethics committees of the George Institute of Global Health, India; the International Centre for Diarrhoeal Disease Research, Bangladesh; and Brawijaya University, Indonesia (Imperial College Research Ethics Committee reference: 6565249 [India], 6694705 [Indonesia], and 6700946 [Bangladesh]). Informed consent will be collected for all participants before their involvement in the cocreation workshops, and all identifiable data will be removed before dissemination. Where appropriate, participants will be compensated according to local guidelines in the study countries.

Results

Formative phase research activities started after NIHR GHRC was funded in October 2022. Cocreation workshops as part of this formative research phase will take place over a 6-month period, and the multisectoral interventions are expected to be implemented in each country by the end of December 2025. As part of the planning phase described earlier, core study teams have been established in each country to oversee and coordinate the overall intervention development process. Sampling and recruitment of cocreation group members, informed by research partnerships established with relevant organizations during the formative phase, have been completed in all geographic regions. Each cocreation group consists of 20-30 members depending on the project needs and study location. Due to the iterative nature of the process, findings from each stage may necessitate the involvement of new stakeholders. For example, community members and health care professionals are being recruited first for the cocreation workshops, and the selection of policy and planetary health experts will be based on the initial workshop outcomes. Community engagement activities have helped build trust with the community members and foster a deeper understanding of the local context. On the basis of emerging findings from formative phase research, we prepared tools for each stage of the cocreation process and obtained ethics approvals to conduct these activities.

We plan to produce a series of outputs on the cocreation process to ensure knowledge mobilization. First, we will publish scientific papers for academic audiences as well as present our findings at relevant conferences. The publications will describe the outputs of the cocreation process, outcomes of cocreation evaluation, and how planetary health perspectives were incorporated in the intervention design. Other outputs such as blog posts and videos will be developed for public and policy-level stakeholders and disseminated via NIHR GHRC's website, social media channels, and other relevant platforms. These outputs are intended to have a broader societal impact by reaching nonacademic audiences. Second, as part of our implementation plan, we will develop training materials for implementers of the codeveloped interventions to facilitate future adoption of these cocreation methods in similar settings. Finally, a formative evaluation report outlining key insights into the cocreation process will be produced for NIHR. This will include an assessment of how effectively the cocreation

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process supported the development of multisectoral interventions that are reflective of locally articulated priorities.

Discussion

Cocreation of Planetary Health Interventions

This protocol outlines the cocreation process for developing complex multisectoral interventions for addressing NCD burden due to environmental change in Bangladesh, India, and Indonesia. While participatory approaches are being increasingly adopted for developing and adapting a range of public health interventions [45,46], very few of these studies have been conducted in LMICs [47] or have incorporated a planetary health lens. The cocreation process described here builds on existing theories and frameworks and brings together a robust set of tools that can be adapted to a range of settings for developing complex multisectoral interventions with dual health and environmental objectives.

While the MRC framework provides general guidance for developing complex interventions and highlights the importance of theory-driven approaches [14], there is limited evidence and guidance on how to translate and transfer such approaches for cocreating complex interventions in low-resource settings [21,34]. Our protocol describes how such interventions can be cocreated in collaboration with the community and other relevant stakeholders, grounded in locally defined priorities and context-specific needs. In addition, most examples of complex intervention development processes tend to have a narrow focus, such as specific health care settings [48], focusing on a certain health care service or model [20,49] or aimed at developing tailored systems or programs [17,50-53]. This protocol provides an overview of developing multisectoral interventions that target both environmental and health domains and thus necessitate the integration of multiple components and sectors.

To accommodate this complexity, the cocreation workflow uniquely combines a range of tools and frameworks. We integrated the Double Diamond model into an adapted cocreation framework, guided by the core components of the MRC framework. By codeveloping a theory of change that helps identify shared solutions together and applying a structured prioritization process, the cocreation approach empowers communities to voice and address their needs and priorities. A key strength of this process is the systematic integration of environmental and health cobenefits while maintaining a balance between top-down and bottom-up approaches in assessing appropriateness and feasibility of implementation. By aligning the interventions with community needs and incorporating feedback from policy and system-level stakeholders, we seek to enhance both feasibility and system integration.

Limitations

While the cocreation process described in this study is adaptable to different contexts, challenges and limitations remain. The structure of participatory activities and modes of collaboration among stakeholders may depend on local dynamics and culture as well as the climate change issue at hand. For example, frequent flooding in study areas in Bangladesh may limit accessibility and frequency of cocreation activities during the rainy season; therefore, the plans will need to accommodate such factors beyond our control. In case of weak buy-in from local partners, adaptations will need to be made to the intervention development and delivery plans. Geographic distance of intervention areas and travel time may also affect participation, necessitating careful selection of workshop locations to ensure equitable access. Therefore, the suggested process may need to be further adapted to facilitate the maximum level of participation and uphold equity and power balance among all stakeholders throughout the process. The cocreation process described in this study does not include details of the co-design process of any educational and training materials. Given the diverse nature of these multisectoral interventions, we will develop targeted guidance for each setting, depending on available resources and identified needs for additional content.

Conclusions

This cocreation protocol describes a structured process to guide the development of multisectoral interventions that incorporate dual benefits to health and the environment in LMICs. Given the unavoidable effect of climate change on human health, it is increasingly important to consider planetary health aspects when codeveloping new or adapting existing multisectoral interventions that are integrated within the health system. By cocreating context-specific, community-driven solutions, we recognize and build upon the strengths of local actors, working collaboratively to support their leadership in sustaining these efforts. The cocreation process developed as part of NIHR GHRC can act as a blueprint for developing complex multisectoral interventions and be adapted to diverse settings beyond the work of NIHR GHRC.

Acknowledgments

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Data Availability

Data sharing is not applicable to this paper as no datasets were generated or analyzed during this study.

Authors' Contributions

NK conceptualized the study methodology under the supervision of PS, with contributions from all coauthors. CM, VJ, DP, LD, AN, VV, and SS contributed to funding acquisition for the National Institute for Health and Care Research and Global Health Research Centre. NK drafted the original manuscript, and PS and DP provided critical review and editorial inputs. All authors reviewed and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the NIHR Global Health Research Centre on NCDs and Environmental Change, National Institute for Health Research (NIHR), UK.
[PDF File (Adobe PDF File), 92 KB - resprot_v14i1e80368_app1.pdf]

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Abbreviations

GHRC: Global Health Research Centre
LMIC: low- and middle-income country
MoSCoW: must have, should have, could have, will not have
MRC: Medical Research Council
NCD: noncommunicable disease
NIHR: National Institute for Health and Care Research

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Protocol

COVID-19 Pandemic Experiences Among Adults, Youth, and Childcare Providers: Protocol for a Mixed Methods Study

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Abstract

Background: The COVID-19 pandemic challenged families, youth, and frontline workers, including childcare providers. Studying lived experiences before, during, and near the pandemic's end from multiple perspectives provides a more holistic and deeper understanding of its effects and impacts.

Objective: This study investigated how parental, childcare provider, and youth stress, mental health, and role overload relate to individual coping and family functioning, as well as vaccine attitudes and uptake patterns among youth, parents, and childcare providers. Information learned from this investigation will inform policy and messaging for future public health crises.

Methods: This study is an explanatory sequential mixed methods study designed to capture the voices of parents of children younger than 18 years of age, childcare providers, and youth aged 12-17 years through surveys and interviews. This retrospective cross-sectional study began with a web-based survey that included demographic questions and validated scales to assess personal well-being, household and family dynamics, behavioral problems, and vaccination-related perceptions, attitudes, and behaviors. Open-ended responses about pandemic experiences for themselves and their families were included. A subsample of parents, youth, and childcare providers was selected for in-depth interviews about their pandemic-related experiences. Descriptive statistics were used to summarize demographic characteristics, and internal consistency was assessed for all survey measures using Cronbach α. Future studies will use inferential statistical techniques to analyze survey measures, thematic analysis for open-ended survey responses and interview data, and mixed methods data integration to synthesize quantitative and qualitative findings.

Results: Data collection for the study began in August 2022 and finished in August 2023. Data analysis is currently in progress to address research questions, and study preparation and dissemination efforts are underway. A total of 506 adults and 93 youths answered a study survey, and 45 adults and 21 youths completed in-depth interviews. Among the 506 adults, 166 were childcare providers. The adult sample had a mean age of 42.8 (SD 9.15) years and was predominantly female (467/506, 92.3%), with 9.7% (49/506) identifying as Black, 4.7% (24/506) as Hispanic, and 81.2% (411/506) being parents of children aged 17 years or younger. The youth sample had a mean age of 14.5 (SD 1.63) years, and 55.9% (52/93) were female, 6.4% (6/93) were Black, and 17.2% (16/93) were Hispanic. Several dyads and triads participated. The sample included 42 parent-child dyads, 3 parent-parent dyads, 2 parent-parent-child triads, and 21 parent-child-child triads.

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Conclusions: These data will be used to understand the diverse experiences of families, youth, and childcare providers during and after the COVID-19 pandemic. This includes successful and unsuccessful adaptations, responses to policies and mandates, and the unmet needs for health messaging, programs, policies, and services. This research aims to guide the development of effective policies and public health communication, fostering scalable and sustainable messaging resources.

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KEYWORDS

COVID-19; pandemic; public health; vaccine hesitancy; mixed methods; family; coping; youth

Introduction

Background

The COVID-19 pandemic significantly impacted families, youth, and frontline workers, including childcare providers. Much of the impact resulted from isolation, social distancing mandates, school closures, loss of loved ones, and economic hardships. For some families, these factors resulted in role reversal for youth who assumed adult-like responsibilities. Public health adherence also dwindled as mixed messaging increased vaccine hesitancy in adults, including parents of youth [1]. Despite the many challenges, silver linings and elements of resilience emerged. To prepare and respond to future public health crises effectively, adopting a systems perspective is essential for illuminating the complex, interwoven lived experiences of families, youth, and childcare providers.

The pandemic affected children's mental health and well-being, with dyadic studies highlighting the importance of family relationships on mental health. A longitudinal study of mothers and their adolescent children (prepandemic in September 2019 and follow-up in May-June 2020) reported increased depression and decreased anxiety, with depressive symptoms being most significant in adolescents [2]. The authors suggest findings reflect resiliency (eg, more family time) and risk factors (eg, financial and interpersonal hardships) early in the pandemic. Other dyadic studies discovered that increased family activities helped mitigate the effects of reduced peer interactions during the pandemic [3]. Actor-partner models revealed that adolescents' perceived social support was linked to lower parental anxiety, though the reverse was insignificant [4]. Additionally, the relationship between perceived social support and anxiety in parents and their adolescents was mediated by perceived family resilience. These findings highlight the need to further explore other aspects of family dynamics that foster resiliency.

Households with children were more likely to experience job loss and reduced income [5]. Moreover, parents serving as frontline and essential workers worked longer hours under greater stress than prepandemic, leaving children to care for their own and siblings' instrumental and emotional needs and parents' needs [6]. These circumstances disproportionately impacted youth, especially children forced to shoulder adult responsibilities to adapt to pandemic demands. Role reversal during COVID-19 has focused on adult youth, suggesting that the role shifts may negatively affect their relationship with parents and contribute to poorer mental health outcomes, including stress, anxiety, and depression [7,8]. Given the changes in family dynamics and impact on youth, it is important to understand how these added stressors at home impacted them during the pandemic.

Another group overwhelmingly impacted by the pandemic was childcare providers. As essential workers, childcare providers returned to work while other parents worked from home or stayed at home. Extensive research has investigated how the pandemic exacerbated childcare providers' pre-existing financial and job-related stress [9,10]. Given their circumstances, the youth of childcare providers were more vulnerable to pandemic-related economic hardships and increased pressures for family adaptations. To our knowledge, no research has been conducted to determine the impact of the pandemic on the youth and families of childcare providers. Exploring this in this study will enable policymakers to address the unique impacts of the pandemic on childcare providers who are critical to child development and the labor force.

Families were also impacted by mixed messaging on how to protect oneself and others from COVID-19 [11]. Although vaccination is one of the most effective strategies to promote public health safety, vaccination rates have been declining [12]. A case study of three participants with differing vaccination views revealed shared and contrasting attitudes shaped by family health priorities, past trauma, and distrust in media and politicians [13]. Recommendations emphasized respecting autonomy and offering clear information to support informed decisions [13]. Exploring the characteristics and rationale of those who do and do not adhere to public health recommendations will enable us to better understand factors underlying decision-making and potential areas for improved public health messaging to reach everyone.

The pandemic had both positive (silver linings) and negative (thorns) influences on mental health, daily functioning, behavioral health choices, and long-term outcomes [14,15]. Silver linings encompassed personal growth, increased time with family and friends, and greater appreciation and gratitude [16]. Thorns included the death of loved ones, reduced medical services, chaos replacing routines, unemployment, food insecurity, isolation and lost social support, and educational interruptions [17]. Our qualitative study of parents and youth between the ages of 12-17 years found similar thorns and silver linings [18], as well as parents expressing concerns about developmental delays due to mandates such as masking and social isolation. Despite this, signs of resiliency emerged related to maturation and cultivating adaptive coping strategies such

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as finding ways to socialize safely, prioritizing health, and finding new leisure activities. Further understanding successful adaptations made during the COVID-19 pandemic will elucidate factors promoting resiliency during public health crises. These effective adaptations may inform policies designed to enhance the resiliency of families.

Aims and Objectives

Taking a systems approach, this study innovatively collected survey and interview data about multiple children in families and from multiple family members (dyads and triads) and childcare providers. By using an explanatory sequential mixed methods design [19], this study provides an evidence base for how families, youth, and childcare providers have and continue to cope with and adjust to the COVID-19 pandemic. The two primary objectives of this study are: (1) to investigate how parental, childcare provider, and youth stress, mental health, and role overload relate to individual coping and family functioning. Parent-youth dyads and parent-youth-youth triad data will uncover patterns in shared and nonshared experiences and differential needs to inform prevention and intervention strategies (eg, policies, programs, and practices); and (2) to predict patterns of vaccine attitudes and uptake in youth, parents, and childcare providers. We can explore parent and childcare provider vaccine attitudes and uptake preferences for youth.

Methods

Setting

This study was conducted in the United States, with most participants recruited from the Midwest region.

Study Population and Recruitment

Participant inclusion criteria included parents or caregivers aged 18 years or older caring for youth. Youth participants between the ages of 12 and 17 years old at the time of the survey could participate with parent consent. Childcare providers aged 18 years or older could participate regardless of whether they had minor children. All participants had to be proficient in written and spoken English and located in the United States.

Recruitment and enrollment efforts occurred between August 2022 and August 2023 (with one final youth participant enrolled in March 2024). Participants were recruited via an existing study at the university, local schools, community venues serving low-income families, listservs, newsletters, and community events (eg, disability expo). Recruitment occurred via flyers and emails with a study overview and study team email. Participants were encouraged to email the study team to receive a web-based link to the study eligibility screener. Efforts to diversify the sample included attending in-person community events tailored to select populations (eg, resource expo for families of children with developmental disabilities); community organizations serving families and youth; social media postings for local school districts and public health departments; and advertisements on family listservs, childcare resources, and statewide childcare provider listservs, and university faculty and staff newsletters.

Interviewees were selected among survey participants using purposive sampling based on characteristics essential to the study. A phased selection process was used to maximize sample diversity regarding demographics, vaccination status, and views. The eligibility and screening criteria for each phase are shown in Table 1. Selected participants included those who fully or partially completed the survey. Phase 1 recruitment focused on family dyads (parent-youth) and triads (parent-youth siblings) and childcare providers to meet study objectives. During weekly meetings throughout interview data collection, the study team discussed emergent themes from interviews and whether we were reaching saturation [20] or recruitment needed to be modified to obtain a more diverse sample. Phase 2 recruitment prioritized participants who were self-identified as Black or Hispanic, childcare providers, of lower socioeconomic status, unvaccinated, or had less favorable attitudes toward vaccines. Phase 3 recruitment centered on participants with a score of 1.5 SD above the mean on survey ratings of measures demonstrating hardship associated with the pandemic (eg, household chaos and stress) or nonmainstream beliefs (eg, vaccine hesitancy). Phase 4 recruitment focused on increasing youth representation. Recruitment occurred via email, followed by phone calls to parents.

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Table 1. Eligibility criteria and priority characteristics for interviewee recruitment.

Phase	Eligibility criteria	Priority characteristics
1	• Families with children younger than 18 years of age • Childcare providers	• Dyads (parent-youth and triads (parent-youth siblings)

2	• Adults, youth, and childcare providers meeting any of the following criteria:
	  • Racially diverse
	  • Lower socioeconomic status relative to the sample
	  • Vaccination status and intentions
		• Self-identified as Black or Hispanic
		• Annual household income less than US $49,000
		• Unvaccinated
		• No intention to vaccinate the child

3	• Adults meeting any of the following criteria:
	  • Outliers in survey responses related to the impacts of the pandemic and attitudes about vaccines
	  • Nonmainstream beliefs about vaccines
		• 1.5 SD above the mean on household chaos, perceived stress, and perceived economic hardship
		• 1.5 SD below the mean for trust in health care providers' recommendations on vaccines for children, and trust in public health agencies
		• Open-ended responses suggesting nonmainstream beliefs about vaccines or the pandemic (eg, negative vaccine attitudes and conspiracy theories)

4	• Youth-targeted recruitment	• All youth who partially or fully completed the survey

Study Design and Procedures

This study was an explanatory sequential mixed methods study [21] designed to capture the voices of parents of children younger than 18 years of age, youth aged 12-17 years, and childcare providers through surveys and interviews. This study began with a web-based survey that included demographic questions, standardized and validated scales to assess constructs of interest, and open-ended responses about pandemic experiences. Based on survey responses and their willingness to participate in a follow-up data collection, a subsample of youth and adult participants was invited to be interviewed about their experiences during the pandemic. The procedural design is shown in Figure 1; analysis of qualitative data and integration of data sources are not addressed in this paper.

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Figure 1. Procedural diagram.

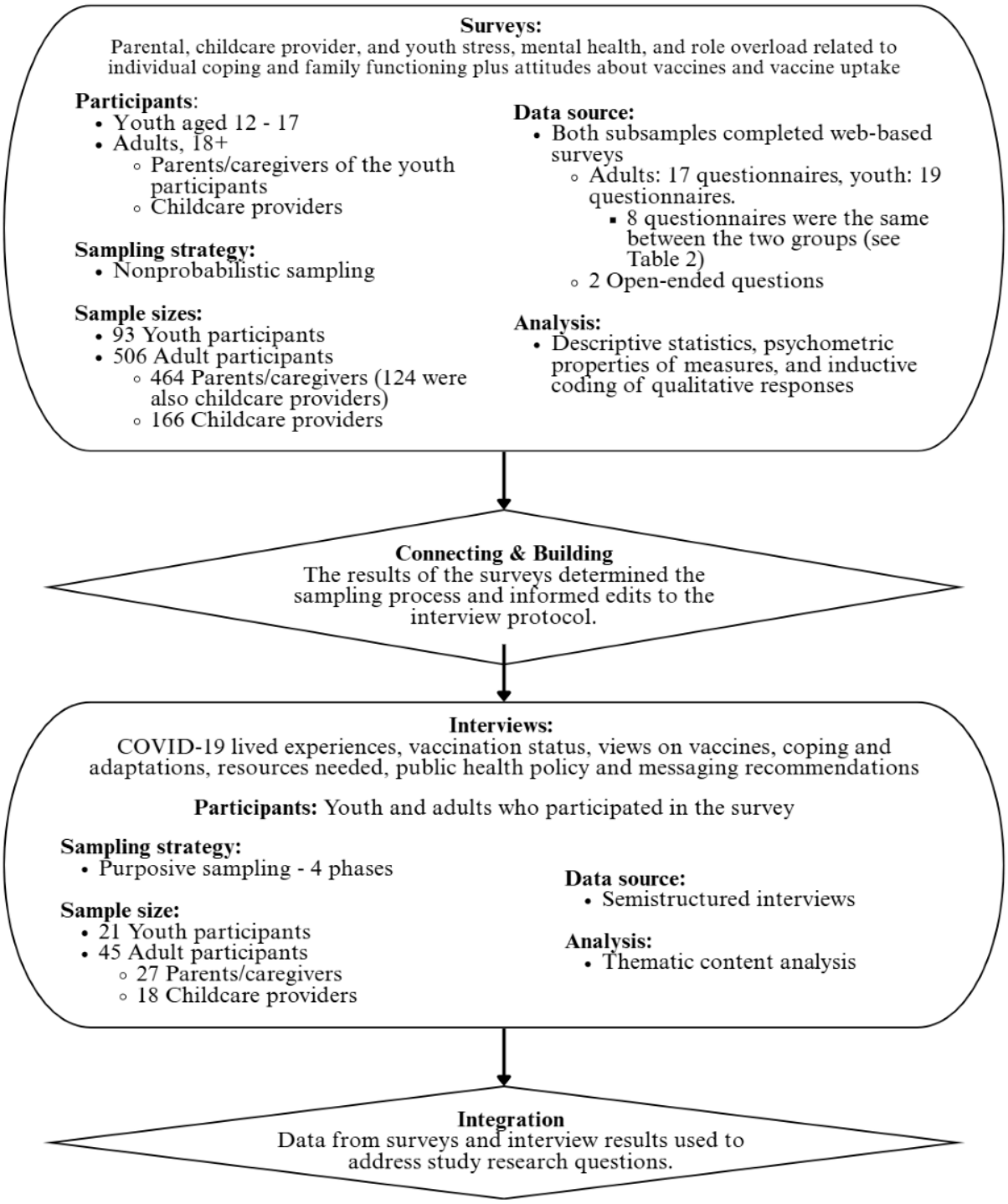

Adult and youth surveys were administered using the web-based survey platform Qualtrics (Qualtrics, Provo, UT). Adults who met the eligibility criteria via the survey screener received a personalized link to the main survey. Parents of children between the ages of 12 and 17 years had the opportunity to provide consent for their children to participate in the study. Consented youth aged 12-17 years received a link to the main survey, where they provided assent prior to the initiation of their web-based survey. The survey was designed to take approximately 40 minutes for adults and 20 minutes for youth. To maximize survey completion, reminders were programmed into Qualtrics to automatically send an email reminder to complete the survey every 3 days.

Initially, a screener survey with anonymous links was shared through university listservs and a university-based preschool, and these links could be shared with others. For the other listservs, individuals interested in participating were required to email the study team to learn more about the research study and receive a personalized link to the screener survey through Qualtrics. To ensure participants were valid respondents and to

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guard against bots, we incorporated a validation protocol consisting of numerous automated and manual checks that are presented in Textbox 1. Due to the rollout of the surveys through different listservs, data validation checks were progressively added in three phases. During each phase, the study team discussed cases not meeting these criteria to determine if they should be excluded from analyses. Figure 2 shows the number of participants identified as invalid respondents.

Textbox 1. Data validation protocol.

Phase 1: Participants accessed the screener via an anonymous link or emailed the study for a personalized link

- Step 1 (automated within Qualtrics)
  - Common to both the screener and the main survey
  - Completely automated public turning (CAPTCHA)
  - Logic that rejected multiple respondents entering the same email addresses
  - Prevention of indexing to stop search engines from showing the link to the survey in search results
  - Screener survey Viewing an embedded video with a question, “Please type the word that this video is about.”
  - Specific to main survey
  - Viewing an embedded picture with a multiple-choice question, “Where does this character live?”
  - 2 midsurvey checks: Check 1: solve this equation 1+2=3; check 2: “how seriously have you taken the survey?”
- Step 2 (manual inspection)
  - Screener and main survey
  - Reviewed respondents’ answers to embedded questions
  - Inspected duplicate IP addresses to ensure they originated from families only
  - Reviewed open-ended duplicate or nonsensical open-ended responses
  - Checked for unusual email addresses (example123456@gmail.com)
  - Cross-reference discrepancies in screener versus main survey (date of birth)
  - Removed participants who completed the survey too quickly (<15 min for adults and <7 min for youth)
  - Removed participants with duplicate start dates by the minute
  - Reviewed duplicate or nonsensical open-ended question responses
  - Called respondents who did not meet these criteria to determine validity
  - Discuss suspicious cases during study meetings to exclude from analyses

Phase 2: Participants were required to email the study for a personalized link to the screener and answer screening questions

- Steps 1-2 repeated from Phase 1
- Step 3 (manual inspection)
  - Email review for odd grammar, repeated text, and emails received in quick succession
  - Checked to make sure screener information matched what was provided in the email

Phase 3: Programmed additional checks into Qualtrics and called participants to ensure valid respondents

- Steps 1-3 repeated from phases 1 and 2
  - Validation check
    - Added questions about city, state, and zip code to confirm with the IP address

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Figure 2. Study flow diagram.

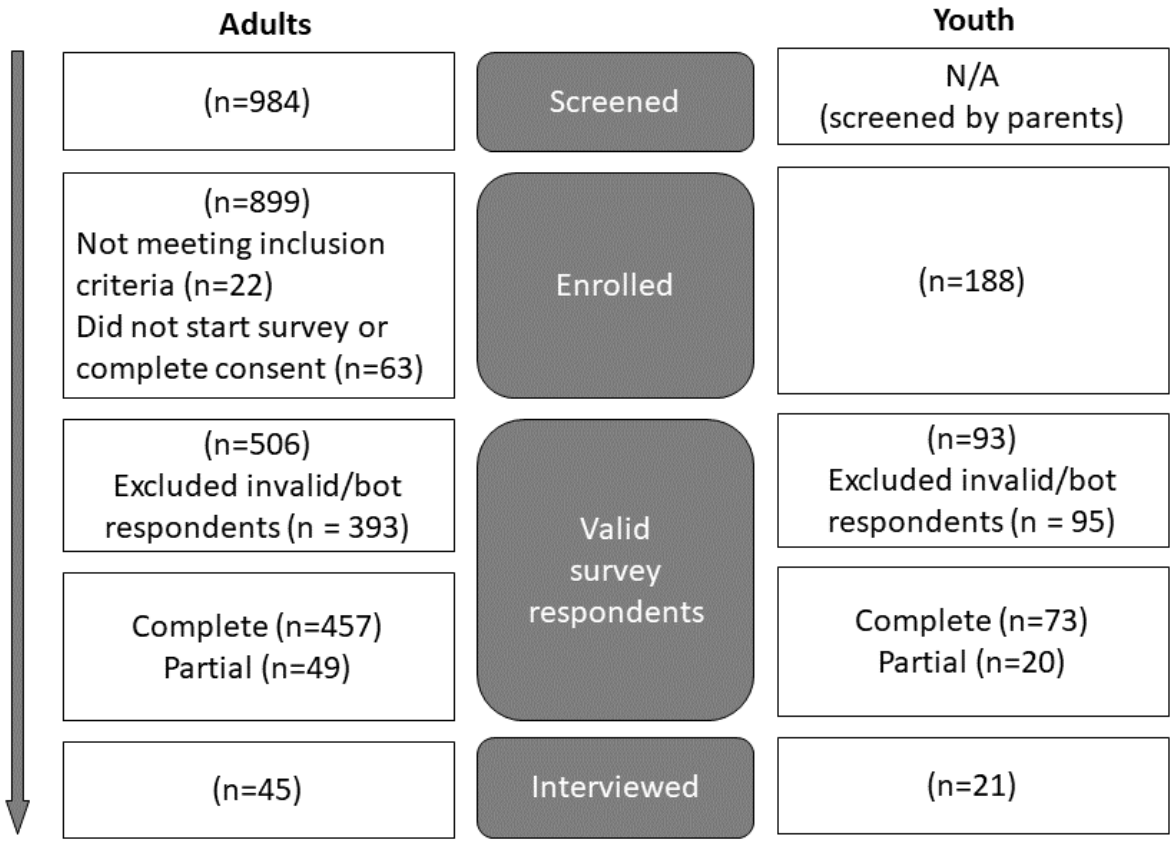

A subset of survey participants was invited to complete interviews based on criteria described previously. These participants were emailed or called to determine their interest in being interviewed and their schedule to set up a time. Parents of children aged 12-17 years were asked if their children would be willing to be interviewed, and if so, when would be the best time to speak with them. Some parents helped with scheduling their children's interviews. Interviews were conducted via Zoom (Zoom Video Communications Inc), telephone, or in-person based on participant preference and distance.

Measures

Overview

Standardized and validated questionnaires were programmed in Qualtrics. The web-based survey was pilot tested by the study team and Center staff to ensure usability, readability of questions, and technical functionality. Data were also reviewed to ensure proper data collection (ie, branching logic, forced choice questions, values within ranges, and completion time). Modifications were programmed into Qualtrics based on feedback and data quality until the survey was ready to publish on the web for public use.

Two surveys were administered: one for adults and one for youth aged 12-17 years. Survey measures, including respondent type and timepoint, are presented in Table 1. The adult web-based survey contained 17 standardized questionnaires, demographic questions, and two open-ended questions. Parents also answered demographic questions about all their children (eg, age, gender, and school openness status) and then a series of questions about their two oldest children, aged 17 years and younger. This series included questions about parentification, behavioral strengths and difficulties, confidence about having the child vaccinated, and open-ended questions related to the impact of the pandemic on each child. All participants completed questionnaires in a fixed order. To maximize readability, only one questionnaire was presented on each page. Matrix-style survey questionnaires with Likert scale radio buttons had repeating headers for clarity. Questionnaires requiring participants to compare various timepoints were presented side by side with drop-down Likert scale options. All survey items were forced responses, except for income-related household demographics. Other questionnaires that were not forced responses are indicated in Table 2. If participants did not feel comfortable providing these responses, we did not want that to prohibit them from completing the survey. Participants could not go back to previous surveys to modify their responses.

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Table 2. Survey measures by respondents and timepoints.

	Adults	Youth	Timepoint
General characteristics			
Demographics, employment, earnings[a], household	✓	✓	Post
School-related		✓	Post, mid
Information about their children	✓		post
Childcare provider information[b]			Post, mid
Personal well-being and beliefs			
Strengths and Difficulties Questionnaire[c]	✓	✓	Post, pre
Confusion, Hubbub, and Order Scale	✓	✓	Post, mid, pre
Perceived Economic Hardship[d,e]	✓	✓	Post, mid, pre
Perceived Stress Scale	✓	✓	Post
Personal Values	✓	✓	Post
Parentification Inventory[c]	✓	✓	Post, pre
Media Attention	✓	✓	Post
Depression Anxiety Stress Scale	✓		Post
Hong Psychological Reactance Scale	✓		Post
Conspiracy Mentality	✓		Post
Cultural Attitudes	✓		Post
Religiosity and Ideology	✓		Post
PROMIS[f]—Emotional-Behavioral Dyscontrol		✓	Post
PROMIS—Cognitive Functioning		✓	Post
PROMIS—Sleep-Related Disturbance		✓	Post
PROMIS—Emotional Distress Anxiety Pediatric Item		✓	Post
PROMIS—Depression		✓	Post
PROMIS—Positive Affect and Well-being		✓	Post
Child Adolescent Mindfulness Measure		✓	Post
Emotional Regulation Questionnaire		✓	Post
Brief COPE[g]		✓	Post
Adverse Childhood Experiences Checklist[a]		✓	Ever
Social Competence Scale		✓	Post
Vaccine perceptions, attitudes, and behaviors			
Parent Attitudes about Childhood Vaccines	✓		Post, pre
Vaccine Risk Analysis	✓		Post
Vaccine Confidence Index[c]	✓		Post, pre
Vaccine Hesitancy Scale	✓		Post, pre
Extended Parallel Process Model	✓	✓	Post

[a]Not forced response.
[b]Information only asked about childcare providers.
[c]Parents answered about the two oldest children, aged 17 years and younger.
[d]Youth only reported one timepoint.
[e]Partial forced response.
[f]PROMIS: Patient-Reported Outcomes Measurement Information System.

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[g]COPE: Coping Orientation to Problems Experienced.

Childcare providers also answered questions related to their roles as providers and an open-ended question related to the impact of COVID-19 on them as childcare providers. The youth web-based survey contained 19 questionnaires, some overlapping with adults and others unique to youth (eg, mental health), including two open-ended questions. Survey measure descriptions are organized by those common to both adult and youth surveys, followed by measures unique to adults and then unique to youth. Published scoring guidelines were used for all standard scales and questionnaires. Time points are assigned as pre (prior to March 2020), mid (during the pandemic—March 2021), and post (at the time of data collection, near the end of the pandemic—2022-2023).

Measures Common to Adult and Youth Surveys

The Strengths and Difficulties Questionnaire [22] was used to assess the youth's behavioral problems and prosocial behaviors from both parent and youth perspectives. This 25-item measure includes five subscales: Hyperactivity, Emotional Symptoms, Conduct Problems, Peer Problems, and Prosocial Behavior. Ratings were provided using a 3-point Likert scale (0=not true, 1=somewhat true, and 2=certainly true). Five items were reverse-coded so that higher scores denote more of that characteristic. Subscale scores are calculated by summing their respective items, and the Total Difficulties score is calculated by summing the scores of all four problem scales.

Household environmental and family chaos were evaluated using the Confusion, Hubbub, and Order Scale [23], a 15-item measure rated on a 4-point Likert scale from 1=very much to 4=not at all. Eight items are reverse-coded. Scores are calculated by summing all items. Higher scores indicate greater levels of disorganization, confusion, and noise within the home environment.

The Perceived Economic Hardship Questionnaire [24] was used to assess economic hardship. This 17-item measure comprises four subscales: (1) Not Enough Money for Necessities (6 items, rated from 1=strongly agree to 5=strongly disagree); (2) Inability to Make Ends Meet (2 items, with one item rated from 1=no difficulty at all to 5=a great deal of difficulty, and another reverse-coded item rated from 1=very short of money to 5=more than enough money left); (3) Financial Strain (2 items rated from 1=almost never to 5=almost always); and (4) Economic Adjustments (7 items rated from 1=not at all to 5=extremely). Scores are calculated by averaging all the items in each subscale. Higher mean scores indicate greater perceived economic hardship. Adults provided ratings for the Not Enough Money for Necessities and Inability to Make Ends Meet subscales at all three time points, and Financial Strain and Economic Adjustments were assessed only at the postpandemic time point. Youth provided ratings for the Financial Strain subscale only. Financial Strain and Economic Adjustment scales were not forced responses.

Perceived stress was assessed using the Perceived Stress Scale [25], a 10-item measure evaluating how stressful individuals found the specific situations over the past month. Both adults and youth rated items on a 5-point Likert scale from 0=never to 4=very often. Four items are reverse-coded, and the total score is calculated by summing all 10 items.

Personal values were evaluated with the Personal Values Scale [26], an 8-item measure. This scale assesses the significance individuals attribute to various aspects of their lives, including physical health, mental well-being, and interpersonal relationships. Adults and youth rate items on a 10-point Likert scale from 1=least important to 10=most important. Total scores are calculated by summing all eight items, with higher scores reflecting stronger personal values.

Parentification was assessed using the Parentification Inventory [27], which evaluates the extent to which youth engaged in adult-like roles and responsibilities typically reserved for parents. This 22-item measure includes three subscales: Parent-Focused Parentification, Sibling-Focused Parentification, and Perceived Benefits of Parentification. Responses are recorded using a 5-point Likert scale ranging from 1=never true to 5=always true. Subscale scores are computed by averaging corresponding items.

Attention to media was assessed using the Media Attention Survey [28], which measures individuals' level of attention to news stories across health-related topics, including health and nutrition, COVID-19, and other issues. Participants were asked how much attention they pay to these topics when reading newspapers, watching television news, or going on the internet. The survey includes three items, each rated on a 5-point Likert scale ranging from 1=none at all to 5=a great deal. Scores are computed by averaging the three items, with higher scores representing greater attention to media.

The Extended Parallel Process Model [29] was included to assess perception of COVID-19 vaccine efficacy using the framework for effective communication of health-related information. This 15-item scale is rated on a 5-point Likert scale ranging from 1=strongly disagree to 5=strongly agree. Mean scores were calculated for items within the Severity Subdomain, Susceptibility Subdomain, and mean for all items. Higher scores represented greater fear of susceptibility and severity from COVID-19. For the Response Efficacy Subdomain, which measures beliefs about the effectiveness of the COVID-19 and flu vaccines, mean scores were calculated, with higher scores indicating greater perceived efficacy.

Measures Unique to the Adult Survey on Well-Being and Beliefs

General psychological distress, including symptoms of depression and anxiety, was assessed using the Depression Anxiety Stress Scale [30]. This 21-item measure includes three subscales: Depression, Anxiety, and Stress. Adults rate items on a 4-point Likert scale ranging from 0=not at all to 3=very much or most of the time. Subscale scores are computed by summing the corresponding items and multiplying the total by 2 to match the 42-item version [30]. Higher scores indicate greater depression, anxiety, and stress.

Psychological reactance was measured using the Hong Psychological Reactance Scale [31], an 18-item measure with

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four subscales: Freedom, Conformity Reactance, Behavioral Freedom, and Reactance to Advice and Recommendations. Adults report about their own beliefs on a 5-point Likert scale from 1=strongly disagree to 5=strongly agree, with higher scores indicating greater psychological reactance. Scores are calculated by averaging all the items in each subscale.

Conspiracy mentality was assessed using the 5-item Conspiracy Mentality Questionnaire [32], which assesses individuals' general tendency to endorse conspiratorial beliefs. Adults rated their agreement with each item (eg, "Government agencies closely monitor all citizens") on a 5-point Likert scale from 1=certainly untrue to 5=certainly true, with higher scores indicating greater conspiracy thinking. A total score was calculated by averaging all items.

Cultural attitudes were measured using a 12-item scale Cultural Attitudes Questionnaire [33], which assesses individuals' cultural value orientations across four domains: hierarchy, egalitarianism, fatalism, and individualism. Adults rated how strongly they agreed with each statement (eg, "Society works best if power is shared equally") on a 7-point Likert scale ranging from 1=strongly disagree to 7=strongly agree, with higher scores indicating stronger endorsement of that cultural orientation. Each subscale score was calculated by averaging three corresponding items.

Religiosity and political ideology, and affiliation were measured using the 4-item Religiosity and Ideology questionnaire [34]. Religiosity was evaluated using one item on a 5-point Likert scale ranging from 1=very little to 5=a great deal. Higher scores for religiosity represent a greater role of religion in everyday life. Political ideology was measured using two items on a 5-point Likert scale, representing 1=very liberal to 5=very conservative. These items were averaged with higher scores representing more conservative views. Political affiliation is identified as Democrat, Republican, Independent, No preference, and Other party.

Measures Unique to the Youth Survey

Specific mental, physical, and social health outcomes were assessed using several Patient-Reported Outcomes Measurement Information System surveys: Emotional-Behavioral Dyscontrol [35] is an 8-item measure that evaluates emotional regulation and behavioral control. Responses are recorded using a 5-point Likert scale from 1=never to 5=always. The Emotional-Behavioral Dyscontrol total score is calculated by summing all items, with a higher score indicating greater emotional and behavioral dyscontrol.

Cognitive Functioning [36] is an 8-item measure used to assess cognitive performance. The first four items assess the frequency with which participants encounter specific cognitive challenges, using a 5-point Likert scale ranging from 1=never to 5=very often. The remaining four items evaluate participants' current levels of difficulty performing cognitive tasks, also rated on a 5-point Likert scale ranging from 1=none to 5=cannot do. All items are reverse-coded, and the total score is calculated by summing the responses to all items. Higher scores indicate better perceived cognitive functioning.

Sleep-Related Disturbance [37] is a 6-item measure evaluating sleep quality and disturbances. The first item assessed general sleep quality, ranging from 1=very poor to 5=very good. The remaining five items rated sleep disturbance behaviors on a different 5-point Likert scale from 1=not at all to 5=very much. One of these five behavior items is reverse-scored, and the total score is calculated by summing across the five items. Higher scores indicate greater severity of sleep disturbance.

Emotional Distress-Anxiety [38] is an 8-item scale measuring anxiety and emotional distress in youth. Youth are asked to rate how frequently they experienced the described feelings or situations during the past 7 days. Responses are recorded on a 5-point Likert scale ranging from 1=never to 5=almost always. The total score is calculated by summing scores for all items, with a higher score indicating a greater level of pediatric emotional distress and anxiety.

Depressive Symptoms [38] were measured using 8 items rated on a 5-point Likert scale ranging from 1=never to 5=almost always. The total weighted score was calculated by summing the raw scores of all items, multiplying the result by the number of items, and then dividing it by the number of items completed. A higher score indicates greater severity of depressive symptoms.

The Positive Affect and Well-Being [35] was used to measure positive affect and well-being. This is a 9-item measure rated on a 5-point Likert scale ranging from 1=never to 5=almost always. The total score is calculated by summing all items. A higher score indicates a greater sense of positive affect and well-being.

Mindfulness was measured using the Child and Adolescent Mindfulness Measure [39], a 10-item scale rated on a 5-point Likert scale from 0=never to 4=always true. All items are reverse-scored, and the total score is computed by summing all items. Higher scores reflect greater mindfulness.

Emotional regulation skills were assessed using the Emotion Regulation Questionnaire [40], a 10-item measure comprising two subscales: Cognitive Reappraisal (6 items) and Emotion Suppression (4 items). Subscale scores are calculated as the mean of their corresponding items. Items are rated on a 7-point Likert scale ranging from 1=strongly disagree to 7=strongly agree. Higher scores on the cognitive reappraisal subscale indicate greater effectiveness in reducing the experiential and behavioral components of negative emotions, whereas higher scores on the emotion suppression reflect a less effective strategy for reducing negative emotions.

Coping strategies for stressful events were measured using the Brief Coping Orientation to Problems Experienced [41]. This 28-item instrument assesses 14 coping strategies with 2 items in each: Self-Distraction, Instrumental Support, Active Coping, Behavioral Disengagement, Denial, Venting, Substance Use, Humor, Emotional Support, Positive Reframing, Planning, Acceptance, Religion, and Self-Blame. Responses were recorded using a 4-point Likert scale ranging from 1=do not do this at all to 4=usually do this a lot. All items were reverse-coded, and subscale scores were computed by summing the responses to the corresponding items. Higher scores indicate better coping.

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The Adverse Childhood Experiences Questionnaire [42] is a 10-item measure used to identify traumatic events experienced during childhood, specifically involving abuse, neglect, and household dysfunction. Each item prompts respondents to indicate whether specific events occurred in their child's life, with answers scored as 1=yes and 0=no. A total Adverse Childhood Experiences Questionnaire score is generated by summing the responses across all items. For this study, only eight nonreportable items were used. Scores range from 0 to 8, with a higher score indicating a greater exposure to adverse childhood experiences.

The National Survey of Children's Health Social Competence Scale is a 9-item survey used to measure social competence in adolescents, defined as the positive skills needed to interact respectfully, work well in groups, follow social norms, and resolve conflicts effectively [43]. Three items are rated on a 5-point Likert scale ranging from 0=not at all like me to 4=exactly like me, and 6 items rated on a 5-point Likert scale (0=none of the time to 4=all of the time). The sum is calculated with higher scores denoting greater social competence.

Measures Unique to the Adult Survey on Vaccination

Parent Attitudes about Childhood Vaccines [44] was used to measure parents' beliefs about childhood vaccinations based on their behavior, views on safety and efficacy, general attitudes, and hesitancy. Nine of the 12 items from the original scale were used in this study. Two items were dichotomous (yes or no), and one item was trichotomous (yes or no or don't know). The other items were rated on the Likert scales as follows: two items ranging from 0=do not trust at all to 10=completely trust; two items ranging from 1=not at all concerned to 4=very concerned; one item ranging from 1=not at all hesitant to 4=very hesitant. Mean scores of three items were calculated for the Self-efficacy subscale and two items for the General Attitudes subscale. Hesitancy was represented by the response to "Overall, how hesitant about childhood shorts would you consider yourself to be?" Items in the Behavioral subscale were summed and then categorized into tertiles, representing varying levels of hesitancy from low to high. Higher scores on all subscales indicate more negative attitudes about childhood vaccines.

Vaccine Risk Analysis [44] is a 5-item measure used to measure thoughts on benefits and risks regarding vaccinating themselves and their children. Ratings are on a 10-point Likert scale for two items, where 0=not at all beneficial to 10=extremely beneficial, two items rated 0=no risk to 10=extreme risk, and one item rated 1=risks far outweigh benefits to 7=benefits far outweigh risks. The composite vaccine benefit-risk index is computed by taking the mean of the 5 items, with 3 items reverse-coded, and item 5 rescaled to match the other 4 items. The mean of all 5 items is computed, with higher scores representing greater perceived risks from vaccines.

Vaccine Confidence Inventory [45] is a 4-item scale used to assess how confident participants are about the COVID-19 and flu vaccine. Items were rated on a 7-point Likert scale ranging from 1=strongly disagree to 7=strongly agree. This study omitted the question "vaccines are compatible with my religious beliefs." Mean scores were calculated for the items related to COVID-19 vaccines and flu vaccines. Higher scores represent greater confidence in these vaccines.

A modified version of the Vaccine Hesitancy Scale [46] was used to assess overall vaccine hesitancy using 15 items. Items are rated on a 4-point Likert scale ranging from 1=strongly agree to 4=strongly disagree. We abbreviated this survey to six items as follows: (1) "Vaccines are important for children to have, in general"; (2) "All childhood vaccines offered by my child's health care provider are beneficial"; (3) "I do what my child's health care provider recommends about vaccines"; (4) "Getting vaccines is a good way to protect my child from disease"; (5) "The information I receive about childhood vaccines from my child's health care provider is reliable and trustworthy"; and (6) "Having my child vaccinated is important for the health of others in the community." A principal components analysis was conducted to ensure these items were measuring a single domain, which yielded one factor that explained 78.2% of the overall variance. Higher scores on this measure indicate greater vaccine hesitancy.

Interviews

Open-ended, semistructured interviews were conducted by a lead interviewer and a notetaker who also ensured that all questions were asked and probed responses for more detail as necessary. Interviews were conducted via Zoom, telephone, or in-person based on participant preference and distance. The average duration for adult interviews was 91 minutes (range: 40-150 min), and youth interviews were 54 minutes (range: 36-77 min). Interview questions inquired about COVID-19 lived experiences at home, work, and school; vaccination status; views on current and future vaccines; coping and adaptations; resources needed; and public health policy and messaging recommendations. All interviewers received training on leading interviews. Training involved (1) practicing and debriefing to discuss modifications to improve the interview quality; (2) observing expert interviewers lead interviews with participants; and (3) leading interviews while expert interviewers took notes and provided feedback after each interview. Interviewers-in-training began leading interviews without expert interviewers present after both agreed they were ready. Interviews were transcribed verbatim, including nonverbal utterances.

Data Analysis

For this protocol paper, data analyses are limited to descriptive statistics and psychometric properties of measures. These analyses were conducted using R (version 4.3.3; R Core Team) and SPSS Statistics (version 29.0; IBM Corp). Initially, we aimed to collect data from 900 participants within 1 year, as this would allow for more sophisticated modeling and subgroup analyses after accounting for missing data. After 1 year of data collection, we chose to stop data collection because the recall time period would be too long. The sample size of 599 was deemed sufficiently large for most of our analyses. For example, a sample size of 500 is widely accepted as standard practice for SEM models [47,48]. Further, post hoc power analyses were conducted using G*Power (version 3.1.9.7; Heinrich-Heine-Universit t Düsseldorf [49,50]) to evaluate the statistical power of regression models. For the adult sample

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(n=506), with 6 predictors, an α level of 0.05, and assuming a large effect size of f^2=0.35, the achieved power (1-β) was >0.99. For the youth sample (n=93), using the same parameters, the achieved power was also >0.99.

Proposed studies will use quantitative analyses, including multiple regression and K-means or mixture modeling (latent profile analysis) to address the study aims. Group differences will be examined using ANOVA, followed by post hoc pairwise comparisons as appropriate. Qualitative data from open-ended survey responses and interviews will be analyzed using thematic analysis [51-53]. A consensus coding approach with independent coders will be used, using a multistage process: initial open coding, refinement into focused codes, axial coding, and final theme development via thematic analysis. Qualitative and mixed methods integration analyses will be conducted using MAXQDA (Version 2022; VERBI Software).

Ethical Considerations

All procedures performed in studies involving human participants were in accordance with the ethical standards of the Institutional and National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. The study was approved by the University of Illinois Urbana-Champaign Institutional Review Board (#24-0812). All data have been deidentified with unique numeric study IDs created for each participant. Digital copies of data are stored on university-maintained secure servers and password-protected computers. Hard copies of data are stored in locked file cabinets in a secure office. Pseudonyms will be used for qualitative data reporting. Audio and video files will be destroyed at the end of the study. Interested participants accessed a web-based eligibility screener with inclusion criteria questions. Participants meeting the criteria received a link to the web-based survey where they were asked to provide electronic consent via an information sheet prior to the start of the survey. The information sheet indicated that moving forward with the interview and answering questions represented their consent to the study and dissemination of findings via publications and presentations. Parents of children between the ages of 12 and 17 years could consent their children to participate in the study, and these children received a link to the main survey where they provided assent prior to the initiation of their web-based survey. Participants received an e-gift card compensation (US $20 for adults and US $15 for youth) after survey completion. Participants invited for the interviews received an additional US $25 e-gift card compensation.

Results

Overview

This study was funded in June 2022. Data collection concluded in August 2023 (except for one participant in March 2024), and data analysis, manuscript preparation, and dissemination are underway. To date, there are two published manuscripts using qualitative data from this study [13,18]. Regarding missing data, some instances arose from the diverse demographic characteristics of families and the survey's branching logic, which rendered certain items inapplicable to specific participants. For example, measures of sibling-focused parentification were not applicable to adults without multiple children. In future papers, we plan to address missing data using multiple imputation or full information maximum likelihood, depending on the research questions.

Participant Characteristics

Data were gathered from 506 adults, comprising 92.3% (467/506) female, 9.7% (49/506) Black, 4.7% (24/506) Hispanic, with 74.7% (378/506) reporting an annual household income of US $50,000 or more, and 16.8% (85/506) with incomes of US $49,000 or less. Additionally, 81.2% (411/506) were parents with children aged 17 years or younger, and 45.7% (231/506) held a graduate degree. The average age of adult participants was 42.8 (SD 9.15) years. The youth sample included 93 participants, 55.9% (52/93) of whom were female, 6.4% (6/93) Black, and 17.2% (16/93) Hispanic, with an average age of 14.4 (SD 1.63) years. Among the 506 adults, 166 were childcare providers, consisting of 98.2% (163/166) female, 16.9% (28/166) Black, and 3.6% (6/166) Hispanic. In this sample, there were 42 parent-child dyads, 3 parent-parent dyads, 2 parent-parent-child triads, and 21 parent-child-child triads. Demographic information for the adult and youth participants is summarized in Tables 3 and 4, respectively. The study flow from screening through study completion is presented in Figure 2.

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Table 3. Demographic characteristics of adults (n=506).

Characteristic	Adults (n=506)	Interviewed adults (n=45)
Age (years), mean (SD)	42.8 (9.15)	43.8 (6.27)
Number of children, mean (SD)	2.1 (1.18)	2.2 (1.25)
Number of children, n (%)		
Aged 17 years or younger	411 (81.2)	39 (86.7)
Aged 18 years or older	111 (21.9)	15 (33.3)
None	37 (7.3)	__[a]
1 child	108 (21.3)	8 (17.8)
2 children	214 (42.3)	19 (42.2)
3 children	93 (18.4)	5 (11.1)
4 or more children	49 (9.7)	9 (20)
Missing	5 (1)	0 (0)
Biological sex, n (%)		
Male	39 (7.7)	5 (11.1)
Female	467 (92.3)	40 (88.9)
Education, n (%)		
High school degree or GED[b]	23 (4.5)	—
Some college but no degree	60 (11.9)	—
Associate’s degree	42 (8.3)	—
Bachelor's degree	150 (29.6)	19 (42.2)
Graduate degree	231 (45.7)	21 (46.7)
Employment, n (%)		
Unemployed	46 (9.1)	—
Full-time	397 (78.5)	33 (73.34)
Part-time	62 (12.2)	9 (20)
Missing	1 (0.2)	0 (0)
Income, n (%)		
US $50,000 or more	378 (74.7)	33 (73.3)
US $49,000 or less	85 (16.8)	12 (26.7)
Missing or prefer not to answer	43 (8.5)	0 (0)
Marital status, n (%)		
Single or widowed	77 (15.2)	8 (17.8)
Married or civil union	395 (78.1)	34 (75.6)
Separated or divorced	34 (6.7)	—
Ethnicity or Hispanic, n (%)		
Hispanic	24 (4.7)	—
Non-Hispanic	482 (95.3)	41 (91.1)
Race, n (%)		
American Indian or Alaska Native [a]	—	—
Asian or Native Hawaiian or Other PI [a]	27 (5.3)	—
Black	49 (9.7)	—
White	402 (79.4)	36 (80)

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Characteristic	Adults (n=506)	Interviewed adults (n=45)
Multiracial	25 (4.9)	—
Something else	—	—

[a]Indicate sample sizes of less than 5 participants.
[b]GED: General Education Development.

Table 4. Demographic characteristics of youth (n=93).

Characteristic	Youth (n=93)	Interviewed youth (n=21)
Age (years), mean (SD)	14.5 (1.63)	13.8 (1.31)
Missing, n	2	2
Biological sex, n (%)		
Male	41 (44.1)	11 (52.4)
Female	52 (55.9)	10 (47.6)
Education, n (%)		
Sixth grade	7 (7.5)	—[a]
Seventh grade	18 (19.4)	5 (23.8)
Eighth grade	23 (24.7)	6 (28.6)
Nineth grade	16 (17.2)	—
10th grade	13 (14)	—
11th grade	11 (11.8)	—
12th grade	—	—
Ethnicity or Hispanic, n (%)		
Hispanic	16 (17.2)	5 (23.8)
Non-Hispanic	75 (80.6)	14 (66.7)
Missing	2 (2.2)	2 (9.5)
Race, n (%)		
Asian or Native Hawaiian or other PI[b]	—	—
Black	6 (6.4)	—
White	71 (76.3)	17 (81)
Multiracial	10 (10.8)	—
Something else	0 (0)	—
Missing	2 (2.2)	2 (9.5)

[a]Indicate sample sizes of less than 5 participants.
[b]PI: Pacific Islander.

Scale and Subscale Psychometric Properties

Internal consistency—an indicator of measurement reliability—was calculated for each scale and subscale (Cronbach α values are presented in Multimedia Appendix 1). A cutoff of 0.60 is considered an acceptable level of reliability for conducting analyses [53]. In this study, most scales and subscales met this threshold. For subscales with α values below 0.60, we explored item deletion to improve reliability values and found this approach increased values above 0.60 for the Parentification Inventory. The psychometric properties for each scale are presented in Multimedia Appendix 1.

Discussion

Principal Findings and Scientific Contribution

Using a mixed methods and multiple-informant approach, this study sheds light on the variety of lived experiences of parents, youth, families, and childcare providers during the COVID-19 pandemic. It will identify positive (silver linings) and negative (thorns) effects of the pandemic, successful and unsuccessful coping adaptations, and public health–relevant insights into how to prepare for future pandemics. These data will also enhance our understanding of behavioral and contextual factors influencing vaccine decision-making among families, youth,

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and childcare providers. At a general level, this knowledge will translate into how to tailor public health communication and health intervention campaign messaging to meet the differential needs of adults, youth, families, and childcare providers. At more specific levels, analysis of family functioning and dynamic, mental health, and attitudinal constructs will inform prevention and intervention recommendations (1) for families, youth, and childcare providers navigate the aftermath of the pandemic, as well as (2) for service providers and policy makers as they make decisions about resources (eg, infrastructure and programs) to prepare for future pandemics. Potential applications are detailed below.

This study will build upon current literature in several key ways. Our first aim—investigating how parental, childcare provider, and youth stress, mental health, and overload relate to individual coping and family functioning—allows us to examine shared and nonshared experiences over the course of the pandemic. Actor-partner models have examined dyadic reciprocity of social support on mental health outcomes at a single time point during the pandemic [4]. In this study, we ask questions across the course of the pandemic, which allows us to explore the dynamic temporal effects of the pandemic on outcomes such as household functioning, role reversal due to pandemic demands, including how other factors impacted this relationship, such as perceived economic hardships. These findings will inform how to adapt intervention and prevention programs to support the varied needs of family members rather than treating them as one-size-fits-all.

For childcare providers, we will explore how their experiences evolved over the course of the pandemic and how it impacted their home lives. Understanding these different needs will better inform prevention strategies and policies promoting resiliency and thriving during future public health crises.

COVID-19 detrimentally impacted people's views on vaccines, partly because of misinformation, distrust in government agencies, conspiracies, fear of side effects, and inconsistent messaging [54]. Few studies have assessed the impact of COVID-19 on adolescents' vaccine attitudes and beliefs to determine what factors contribute to vaccine behaviors. Rather, much of the literature focuses on parents' attitudes about vaccinating their children. Additionally, this has not been investigated in family dyads and triads or in childcare providers. Our second aim—predicting vaccine attitudes and uptake patterns in youth, parents, and childcare providers—expands upon this literature to inform more tailored public health messaging.

There are two published qualitative studies using these data [13,18]. One of these studies highlights the importance of understanding how risk and reward are assessed by people to inform their decision-making [13]. For example, Dariotis et al [13] describe three case studies that had varied experiences with vaccines before and during the pandemic and had different vaccination behaviors (eg, early adopter, never adopter, and adopted but felt coerced). A major take-home message of the study was that all three participants valued protecting their loved ones and family, even though their choices differed from each other. This is very informative because the same public health messaging will not work for other people who have similar attitudes and beliefs as each of these cases. The other study highlights that the pandemic had both positive and negative outcomes for youth and families. For some youth, the pandemic facilitated accelerated maturity. For other youth, especially during early childhood, the pandemic had detrimental effects on speech and social skills. These are just a few examples of how these data contribute to the literature on pandemic-related experiences for multiple family members, across early life developmental stages through adolescence, and childcare settings.

Strengths and Limitations

This study has numerous methodological strengths that address gaps in the literature. First, this study includes a large sample of parents who report on up to two children aged younger than 18 years, allowing for understanding parental perspectives on differential attitudes, behaviors, and impacts for multiple youth within families. Second, a subset of youth participants completed surveys and interviews, providing insights into shared and nonshared attitudes and experiences with parents and siblings. Taken together, having parents and youth in the same study allows for answering family systems research questions about the COVID-19 pandemic. Third, childcare providers are often invisible frontline workers, and hearing their perspectives is important for understanding pandemic impact and recommendations for future pandemics. In addition, studies of childcare providers typically examine the pandemic's impact on their work and not their own families, a gap this study addresses. Fourth, the mixed methods nature of this study provides both larger-scale quantitative estimates for constructs of interest and rich, in-depth qualitative data that, when triangulated, will give a more holistic understanding of the pandemic, including thorns, silver linings, and lessons learned.

This study has limitations. First, some measures vary from the originally developed scales. This was primarily done to adapt to the pandemic and its context. Second, participants retrospectively report pre- and midpandemic attitudes and perceptions. The pandemic occurred so quickly that a prospective study was not possible. We acknowledge the potential for recall effects of retrospective accounts. We contend that these data have merit because beliefs about the pandemic—even if changed by memory—impact current and future behaviors and beliefs. Third, surveying and interviewing people with nonmainstream beliefs is a challenge given social desirability and stigmatizing pressures. We engaged in best practices to diversify our sample.

Conclusions

In conclusion, with increasing distrust in government and health care communications and the potential for future public health crises, it is essential to comprehend the varied experiences of families, youth, and childcare providers during the COVID-19 pandemic. This encompasses both successful and unsuccessful adaptations, responses to policies and mandates, and unmet needs for health messaging, programs, policies, and services.

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Data Availability

These datasets generated or analyzed during this study are not publicly available due to privacy or ethical restrictions. The interview guides may be requested from the corresponding author.

Authors' Contributions

JKD conceptualized the study and led the investigation. JKD and DAE collected data and supervised project administration. JKD, DAE, IN, and CX formally analyzed data. JKD acquired resources and funding. JKD and DAE led original draft preparation. IN, CX, and RLS wrote, reviewed, and edited later drafts. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Psychometric properties of measures.
[DOCX File , 38 KB - resprot_v14i1e77521_app1.docx]

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Protocol

Chronic Pain and Posttraumatic Stress Among Patients in Substance Use Treatment: Protocol for NOR-APT, a Longitudinal Cohort Study

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Abstract

Background: Chronic pain conditions and posttraumatic stress disorder (PTSD) are highly prevalent among patients with substance use disorders (SUDs). Both can impact outcomes of SUD treatment and quality of life. There is a need for a large-scale study on the overlap of and interactions between SUD, chronic pain, and PTSD.

Objective: The Norwegian Addiction, Pain and Trauma study (NOR-APT) is the first longitudinal study to describe how substance use and outcomes of SUD treatment are impacted by (1) chronic pain and pain characteristics and (2) interactions between comorbid chronic pain and PTSD.

Methods: Self-reported questionnaire data were collected from patients in all types of SUD treatment at four hospital sites in Norway. The questionnaire data on substance use, pain, and posttraumatic stress symptoms will be combined with retrospective and prospective longitudinal data from high-quality demographic and health registries. The registry data cover, for example, treatment episodes, diagnoses, and prescribed medications and socioeconomic variables, with a follow-up period of altogether 20 years (approximately 2008-2029).

Results: Questionnaire data were collected during March 2021-June 2024. Altogether 1890 patients were approached, and 1645 (87%) questionnaires were completed. The estimated final sample size pending data cleaning (eg, removal of duplicates and validation of consent forms) is 1400-1500. Linkage of registry data for approximately 1000 with valid ID numbers and consent is planned for 2026 (retrospective) and 2029/2030 (prospective). At least 10 publications are planned in the period 2025-2028, based on funding received from the Foundation Dam, the Norwegian Research Council, Akershus University Hospital, and Oslo University Hospital. We plan to apply for further funding related to the use of the prospective registry data.

Conclusions: Results from the NOR-APT study will contribute to a better understanding of SUD, chronic pain and PTSD comorbidities, their interactions, trajectories and impact on SUD treatment outcomes, and subjective quality of life. Results can

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also contribute knowledge toward the development and assessment of treatment interventions that can improve SUD treatment outcomes.

Trial Registration: ClinicalTrials.gov NCT04908410; https://clinicaltrials.gov/study/NCT04908410

International Registered Report Identifier (IRRID): DERR1-10.2196/67663

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KEYWORDS

addiction; dependence; substance use; drug use; chronic pain; posttraumatic stress disorder; trauma; violence; injury; somatic

Introduction

Background

Substance dependence, chronic pain, and posttraumatic stress disorder (PTSD) are global burdens, and all three have been labeled as important public health concerns [1,2]. Recent reports show that the level of substance use [2], the level of chronic pain [1], and the level of trauma that can lead to PTSD [3-5] are stable or on the rise, both in Norway and internationally. Additionally, substance use, chronic pain, and PTSD often interact or overlap. Recent evidence points toward chronic pain, also called persistent pain, as a central comorbidity for patients with substance use disorders (SUDs) [6-16]. Chronic pain is a condition with serious detrimental effects on function, quality of life, family and social life, as well as mental health [17-19]. Comorbid SUD and chronic pain complicate the patients' condition [20] and may contribute to both the development and maintenance of a substance dependence [21-25].

There are few high-quality studies that describe chronic pain among patients in SUD treatment, and none describe how comorbid pain affects SUD treatment outcomes, function, and quality of life. Previous studies have had limitations, such as focus on a small subgroup of patients (eg, patients who have developed a dependence on their pain medication or patients receiving a specific medication), a small sample size, or limited data on pain characteristics. Although limited, existing literature supports a high prevalence of chronic pain among populations with opioid dependence (37%-57%) [6-8,11-15] and alcohol dependence (54%) [9]. Studies of pain in cannabis- and stimulant-dependent populations are almost nonexistent, despite the documented pain-relieving effects of the two substances [26,27] and evidence of a relationship between cannabis and chronic pain in other populations [28,29]. Stimulant use has been identified as a potential risk factor for chronic pain [30], and a link between pain and benzodiazepine use has also been demonstrated [31]. The conclusions of existing studies demonstrate a need for longitudinal studies with pain as a primary focus, and with sufficient sample size to examine sex differences [16,29,32].

In general populations, there is evidence that chronic pain co-occurs and interacts with PTSD [33-35]. Despite the high rates of chronic pain, trauma, and PTSD among patients with SUDs [36-40], the overlap and interactions between chronic pain and PTSD have not been much investigated among patients in SUD treatment, who are often excluded from studies on PTSD [41]. There are only two small studies (n=133 and n=170) on the overlap between chronic pain and PTSD in populations with SUDs; only patients with opioid dependence were included, and they could not draw firm conclusions due to low statistical power. The studies support more trauma and higher PTSD symptom levels among patients with comorbid chronic pain [42,43] and conclude that there is a need to better understand the trajectory of development of comorbid SUD, chronic pain, and PTSD and better understand how comorbid chronic pain and PTSD affect SUD treatment outcomes [42,44].

Increased knowledge of interactions between these three conditions may be of great importance to improve and tailor SUD treatment, as comorbid SUD, chronic pain, and PTSD can hinder positive outcomes of SUD treatment [45,46].

The Norwegian Addiction, Pain and Trauma (NOR-APT) study is the first to fill the need for a large, longitudinal study with a primary focus on pain and PTSD among patients in SUD treatment. By combining self-reported questionnaire data with retrospective and prospective data from health registries, the study has a follow-up period of patients of up to 15 years retrospectively and 5 years prospectively. The study will provide knowledge of how chronic pain and PTSD impact SUD treatment outcomes and patients' quality of life. The planned sample size allows perspectives on sex and different types of substance use.

Primary Aims and Research Questions

The overarching aim of the NOR-APT study is to generate new knowledge on the relationships between substance use and SUDs, chronic pain, and mental health (with a focus on PTSD), which in turn can contribute toward updated guidelines, individualized treatment, and development and evaluation of new treatments. Aims and research questions are further detailed in Table 1.

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Table 1. Aims, research questions (RQs), and data sources.

Aims and RQs	Data sources
Chronic pain in patients with different types of substance use	
Aim 1: estimate and describe the need for pain treatment among people in SUD[a] treatment, and how comorbid pain impacts SUD treatment outcomes	
RQ1: What is the chronic pain prevalence, pain intensity, and interference for patients ...	Dataset 1[b]
a. ... with opioid use?	
b. ... with alcohol use?	
c. ... with stimulant-, cannabis-, and other substance use?	
RQ2: What is the cause and location of the reported pain?	Dataset 1
RQ3: Is there a relationship between substance use or pain characteristics and chronic pain severity?	Dataset 1
RQ4: Is there a relationship between chronic pain characteristics and factors related to opioid agonist treatment (eg, medication type, dose, and time in agonist treatment)?	Dataset 1
RQ5: To what degree have patients with self-reported chronic pain been diagnosed and received treatment in the primary or specialist health care services?	Dataset 2[c]
RQ6: Are there differences between those who have received pain treatment and not when it comes to ...	Dataset 2
a. ... substance use characteristics?	
b. ... outcomes related to substance use, pain, or quality of life?	
The overlap between chronic pain and PTSD[d] symptoms	
Aim 2: explore the overlap between chronic pain and PTSD and received treatment for PTSD	
RQ7: What is the prevalence of overlapping chronic pain and PTSD?	Dataset 1
RQ8: Does pain characteristics (pain intensity, cause, location, and interference from pain on functioning) differ for patients with and without PTSD?	Dataset 1
RQ9: Are there differences in pain characteristics according to the type of traumatizing event and level of posttraumatic symptoms?	Dataset 1
RQ10: To what degree have patients with self-reported high levels of PTSD symptoms been diagnosed with and received treatment for PTSD?	Dataset 2
RQ11: Are there differences in substance use and pain outcomes for patients who have received PTSD treatment compared to those who have not?	Dataset 2
Aim 3: explore the trajectory for the development of comorbid SUD, chronic pain, and PTSD	
RQ12: How is the onset of substance use related to the onset of chronic pain and PTSD?	Dataset 1
RQ13: Can distinct trajectories for the development of the three comorbidities be identified and described in relation to SUD treatment outcomes?	Dataset 1
The impact of chronic pain on quality of life	
Aim 4: explore the relationship between chronic pain characteristics and quality of life	
RQ14: Does quality of life differ between patients with and without chronic pain?	Dataset 1
RQ15: Are there any associations between quality of life and ...	Dataset 1
a. ... pain characteristics, including pain intensity, duration, location, or cause?	
b. ... substance use (type of substances, frequency of use, age first used, and intravenous use)?	
c. ... type of medication received (methadone, buprenorphine, or buprenorphine-naloxone), dosage, and duration of opioid agonist treatment? (Patients in opioid agonist treatment only)	
Mental health comorbidities among patients with chronic pain	
Aim 5: explore the prevalence of mental health comorbidities and associations with chronic pain	
RQ16: What is the prevalence of psychiatric diagnoses other than PTSD (eg, depression, anxiety, personality disorders, attention-deficit/hyperactivity disorder) among patients with and without chronic pain?	Dataset 2
RQ17: What was the trajectory for first experiencing chronic pain and being diagnosed with any psychiatric diagnosis?	Dataset 2
Predictors of future outcomes	

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Aims and RQs	Data sources
Aim 6: explore whether self-reported factors at baseline impact outcomes in the 5-year follow-up period	
RQ18: Is self-reported chronic pain and pain characteristics associated with ...	Dataset 3[e]
a. ... health-related outcomes in the 5-year follow-up period (eg, use of health services and prescribed medications, diagnoses received, employment status and income, and mortality)?	
b. ... inclusion and retention in opioid agonist treatment or choice of medication type in opioid agonist treatment?	
RQ19: Is self-reported PTSD, type of traumatizing event, or level of PTSD symptoms associated with health-related outcomes in the 5-year follow-up period (eg, use of health services and prescribed medications, diagnoses received, employment status and income, and mortality)?	Dataset 3
Sex differences across all RQs	
Aim 7: explore sex differences in characteristics and outcomes	
RQ20: Are there sex differences in ...	Dataset 1-3
a. ... pain characteristics and the impact of pain on function?	
b. ... the proportion who have received pain treatment?	
c. ... interactions between chronic pain and posttraumatic stress symptoms?	
d. ... the proportion who has received a PTSD diagnosis and treatment?	
e. ... the proportion who has received any psychiatric diagnosis?	
f. ... impact of pain on quality of life?	

[a]SUD: substance use disorder.

[b]Dataset 1: cross-sectional questionnaire data.

[c]Dataset 2: retrospective registry data linked with cross-sectional data.

[d]PTSD: posttraumatic stress disorder.

[e]Dataset 3: prospective 5-year follow-up registry data linked with cross-sectional and retrospective registry data.

Methods

Design

The NOR-APT study is a longitudinal cohort study. Cross-sectional questionnaire data will be combined with both retrospective and prospective health care and demographic registry data. We will publish from three datasets: self-reported baseline data (dataset 1: cross-sectional), retrospective registry data linked with the cross-sectional data (dataset 2: retrospective cohort), and prospective registry data linked with the cross-sectional and retrospective data (dataset 3: prospective cohort).

The combination of self-reported questionnaire data with health and demographic registries is an underused study design [47], which provides longitudinal data with minimal strain on the participating clinics and patients. The retrospective health and treatment data will go back to the patient's first registration in each registry since the registries were established in 2008/2010, giving retrospective data for at least a 14-year period. The prospective data will have a follow-up period of 5 years from the time of completing the questionnaire. Altogether, the data will cover approximately a 20-year period from 2008 to 2029 (Figure 1).

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Figure 1. Visualization of study design, datasets, funding, and time frames. SSB: Statistisk Sentralbyrå.

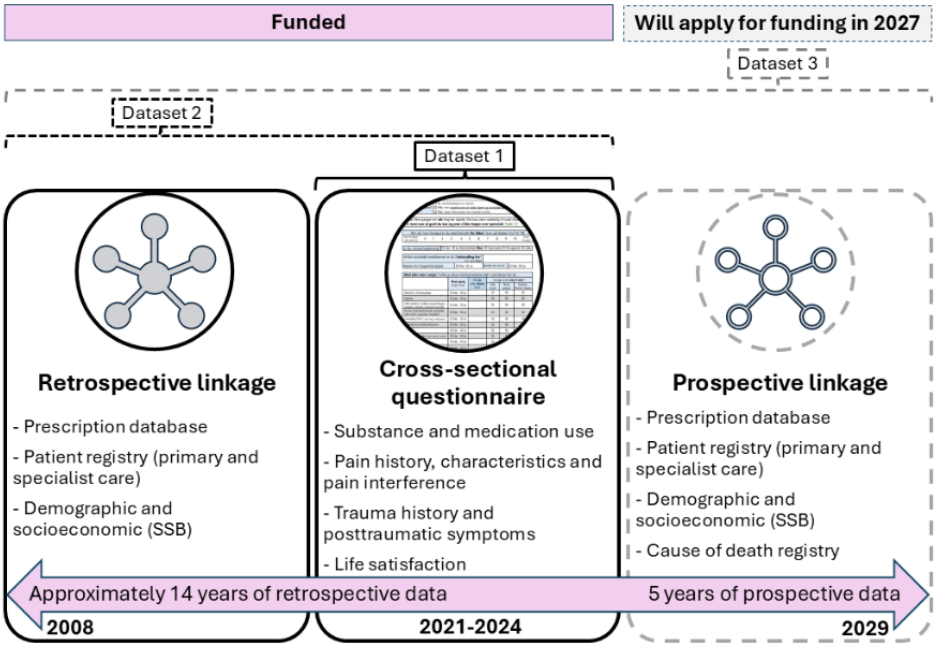

Setting

In Norway, SUD treatment is available free of charge or with a maximum deductible of up to about US $350 per year. This means data on patients in treatment will be less prone to selection bias related to the private economy compared to countries with different health care systems. Data were collected from inpatient, outpatient, and detoxification clinics at four participating hospitals covering catchment areas with urban, suburban, and rural areas with a total population of over 1,500,000: Akershus University Hospital (AUH), Oslo University Hospital (OUH), Vestfold Hospital Trust, and Telemark Hospital Trust. These four hospital sites together serve about one-fourth of patients receiving SUD treatment in specialist health care in Norway [48].

Participants and Sample Size Calculations

Participation was open to all patients (age ≥18 years) receiving any SUD treatment from detoxification, inpatient, and outpatient units at the four participating hospitals. Exclusion criteria were a lack of capacity to give informed consent or that physical or mental health concerns made participation too strenuous. Staff recruiting patients for the study were asked to take acute withdrawal, acute intoxication, and serious mental or physical health concerns into account when assessing capacity to give informed consent and to participate.

Based on previous studies, the expected prevalence of chronic pain was 30%-50% [8,9,18]. To achieve a sufficient sample size for detecting a chronic pain prevalence of 30% (α=.05; power=0.80), we needed 384 patients in each substance use subgroup (primarily in treatment for opioids, alcohol, stimulants, cannabis, or benzodiazepines). To detect a prevalence of 50%, 323 patients were necessary. We aimed to include a minimum of 350 patients in each substance use subgroup to provide sufficient power for comparisons between groups (eg, independent samples 2-tailed *t* tests require n=105 in each group) and adjusted regression analyses. Throughout data collection, we adopted recruitment strategies to reach 350 participants within each of the substance use subgroups, focusing recruitment on specific subgroups when necessary. Reaching 350 patients for the opioid and alcohol groups was feasible without targeted measures. Reaching 350 patients who were primarily in treatment for cannabis, stimulants, and benzodiazepines proved challenging, even though we implemented targeted recruitment for these groups to increase the number of patients. However, many patients were in treatment for polysubstance use, and we will be able to take this into account in analyses and can use this to increase sample statistical power (eg, by comparing patients with daily benzodiazepine use to those without while controlling for other substance use, regardless of whether benzodiazepine was named as the primary target in the treatment).

Procedure and Data Security

Data collection was rolled out in a stepwise manner (AUH: March 23, 2021, to June 27, 2024; OUH: March 14, 2022, to May 21, 2024; Vestfold Hospital Trust: September 13, 2022, to May 22, 2024; and Telemark Hospital Trust: June 2, 2023, to May 2, 2024). The first start of data collection at AUH coincided with societal lockdowns due to the COVID-19 pandemic, which resulted in a slow beginning and contributed to the delayed start-up at the three other hospitals.

The clinics received close follow-up and training from the project group in the start-up phases at each hospital and throughout the data collection period. The training consisted of information on the background for and aims of the study, how to present the study to patients, and how to guide patients in filling out the consent form and questionnaire, with a focus on avoiding recruiter selection bias and missing data. Clinicians were specifically asked to recruit from all patients, not only patients with known pain, or “easy” or better-functioning patients who would not need help completing the questionnaire. Training was provided through in-person or digital staff meetings and discussions. In addition, clinics were provided

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with two short informational videos and a short manual with tips for how to present the study, common pitfalls in data collection, and additional information about the purpose of the individual questionnaire items. The videos and manual allowed new hires to receive training in recruiting patients for the study, and those who had received training could revisit the information in the available videos and guide.

Clinicians informed the patients about the study and asked if they would participate. The patients completed the written consent form and could choose to provide their unique personal identification number for linkage to health registry databases. Patients who did not want to participate were asked to anonymously provide age, sex, and which substance they consider to be their main problem (these data will be used to assess self-selection bias and generalizability of the findings). Patients who declined providing this information were counted so we can calculate a participation rate.

Clinicians were instructed to help the patients with the questionnaire when needed and to do a quality control of responses to clear up misunderstanding and reduce rates of missing data. Consent forms and questionnaires were prenumbered with matching ID numbers. After completion by the patient, the consent form and questionnaire were kept separately under lock at the participating sites until they were sent securely to the study administration at AUH. Questionnaire data were entered into a database using REDCap (Research Electronic Data Capture) tools hosted at Yale University [49,50] and stored on the AUH secure disc. Unique identifiers linking the patient identities to their data are stored on a server for sensitive research material at AUH. The retrospective and prospective linkage of questionnaire data to registry data will be done by Statistics Norway or Helsedataservice, according to all relevant laws and regulations, and stored on secure servers.

Measures

Cross-Sectional Questionnaire Data

The questionnaire was developed based on literature and input from clinicians in the Pain Resource Group at OUH and the Research Committee at AUH. In total, 10 AUH patients piloted the questionnaire and gave feedback, after which the questionnaire was revised. We used validated questions when available and prioritized short and efficient questions and scales to reduce patient strain.

We collected information on age; sex (male or female); whether employed, a student, on sick leave, on benefits, or retired; and whether they smoked tobacco or used snuff or chewing tobacco (yes or no).

Substance use history and pattern were assessed using adapted questions from section E of the much-used and validated European Addiction Severity Index (EuropASI) interview [51,52]. Patients indicated which substances or medications they have ever used in their lifetime (yes or no), age of first use, and frequency of use in the last 4 weeks (categories collapsed to no use, sometimes, or daily or almost daily). The list of substance categories was revised somewhat to reflect current substance use in the population and the interests of this study. The categories “inhalants” and “more than one substance/medication per day” were removed. The category “other designer drugs, steroids” was removed and replaced with separate categories for “anabolic steroids,” “GHB/GBL” (ie, γ-hydroxybutyrate or γ-butyrolactone), and “khat.” “Alcohol, all use” was dropped, while “alcohol to intoxication” was kept. As the EuropASI is typically conducted as an interview, minor alterations and specifications were added to make it suitable for self-report. The final substance use categories presented in the questionnaire were alcohol to intoxication, heroin, opioid agonist medication (prescribed and illicit, eg, methadone, subutex [ie, proprietary name for buprenorphine], suboxone [ie, proprietary name for buprenorphine-naloxone], and buvidal [ie, proprietary name for long-acting buprenorphine, injected twice weekly]), other opioid-based painkillers (eg, morphine, oxycodone, and tramadol), cannabis or THC (ie, tetrahydrocannabinol, eg, hashish and marijuana), amphetamine or methamphetamine, cocaine, benzodiazepines (eg, valium [ie, proprietary name for diazepam] and sobril [ie, proprietary name for oxazepam]), GHB/GBL, hallucinogens (eg, LSD [ie, lysergic acid diethylamide], mushrooms, mescaline, and MDMA [ie, methylenedioxymethamphetamine]), anabolic steroids, and khat. Patients reported which substance they considered most problematic for them (EuropASI) and also which substance use they were currently receiving treatment for (question devised for this study). Further, patients indicate intravenous substance use in their lifetime and in the last 4 weeks (yes or no). Opioid agonist treatment (OAT) history and relation to pain were assessed by asking whether the first opioid use was to relieve pain (not used opioids, yes, no, or do not know), whether they had ever been enrolled in OAT, the type of medication they were prescribed (both current or previously), medication dose, age when the prescription started, and whether pain had ever influenced choice of medication type in OAT (no, yes, or do not know). If they responded yes, they were asked to elaborate which medication, report their age at the time, and provide a comment to explain.

Pain and pain characteristics included pain in the last 4 weeks (excluding pain from abstinence only; only patients who responded yes were asked to complete the remaining questions about pain), pain duration (<3 months, 3-12 months, 1-3 years, 4-6 years, 7-10 years, and >10 years), and cause of pain (disease, accident or injury, violence, surgery, other, and unknown). Pain location was assessed with a body map from the Norwegian Pain Association [53], where participants could mark up to 25 areas where they feel pain. Based on comments from patients in a previous pain questionnaire [8], we added the option to indicate any general pain in the skin, muscles, joints, or skeleton. We asked whether they had seen a doctor for their pain and what their age was at the time. Further, they were asked whether they received treatment for pain and the type of treatment (this is self-reported data on received treatment available in dataset 1. Additional data on received treatment will be available from the health registries in datasets 2-3). Pain intensity was assessed with four questions from the Brief Pain Inventory Short Form (BPI-SF) [54], a widely used measure validated in Norwegian [55], with responses on a numeric rating scale from 0=no pain to 10=worst imaginable. Pain interference of physical and emotional function was assessed through 7 questions from the BPI-SF [54], asking to what degree pain had influenced daily

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activity, ability to walk, ability to work or do chores around the house, mood, relationship to others, sleep, and joy of life. Responses were given on a numeric rating scale from 0=not affected to 10=completely interfered.

Exposure to potentially traumatizing events was assessed with a short version of the Stressful Life Events Screening Questionnaire (SLESQ), which lists 15 potentially traumatizing events [56]. Patients indicated which of the 15 events they had been exposed to; however, they were not asked the follow-up questions related to each item in the original questionnaire. Instead, patients were asked what their age was when the first event occurred and their age at the time of the event that caused the most distress. To shorten the questionnaire further, the layout was revised, and text that did not contain information necessary for understanding the questions was removed. This revision was shared with one of the developers of SLESQ to ensure that important concepts were not omitted.

To cover the *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) criteria for PTSD (re-experiencing, avoidance, negative thoughts or emotions, and overactivation), posttraumatic stress symptoms were measured through a 4-item version of the PTSD Checklist for DSM-5 (PCL-5) [57]. Only patients who had indicated at least one potentially traumatizing event were asked to complete the questions on posttraumatic stress symptoms.

Subjective quality of life, specifically life satisfaction, was measured by asking “All in all, how satisfied are you with your life nowadays?” with responses on a scale from 0=not satisfied at all to 10=very satisfied. This 1-item question was developed for UK national questionnaires [58] and has also been used in over 30 countries in the Organisation for Economic Co-operation and Development (OECD) Better Life Index and in Statistics Norway questionnaires on quality of life in the general Norwegian population [59]. Using one general quality of life question has the advantage of measuring subjective quality of life without predefining what should affect an individual’s quality of life. The question was placed at the beginning of the questionnaire to avoid other themes in the questionnaire influencing patients’ mood and response. We added a question in the same format as the BPI-SF [54], asking to what degree pain had influenced how satisfied they were with their lives, with a response scale from 0=not affected to 10=completely interfered.

Demographic and Health Registries

The Norwegian registries consist of high-quality data with a complete history of treatment episodes, diagnoses, and prescribed medications [47], as well as socioeconomic variables. Registry data will be linked to self-reported data through personal identification numbers retained by all residents in Norway.

Retrospective registry data (datasets 2-3) will cover information from each patient’s first registration in each registry and will be right-censored at the date on the consent form for completion of the questionnaire. The start date for the existence of the different registries varies from 1953 to 2016 (Table 2). Further, the start dates of different variables within the registries may also vary; for instance, a registry may have been started in 1967, but a specific data point or variable was not included until 2005. Thus, the time periods and left censoring points for analyses on the retrospective data may vary with different research questions and the use of variables. For instance, sociodemographic data are typically available far enough back in time to provide information on childhood conditions for most patients, while the somatic and mental health registries only have data available from 2009.

Prospective registry data (dataset 3) will be available from the date of the participant’s consent, until 5 years following the end of the data collection for the study. As data collection was conducted over several years, some patients will have a follow-up period of 5 years, while others may be closer to 8 years. Depending on the research question, all patients may have prospective data censored at the 5-year point following their completion of the questionnaire (or date of death, or date of emigration from Norway), or all follow-up data will be included in analyses adjusting for patient variation in time-at-risk (with right censoring occurring 5 years after inclusion of the last patient, or date of death, or date of emigration from Norway, if no event of interest has occurred). Registry names and variables for this study are detailed in Table 2.

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Table 2. List of registries, types of data to be extracted from the registries, and the year each registry was established.

Registry name	Variables or data	Data from
Primary registry sources		
Norwegian Patient Register	• Contacts with specialist health care services (somatic, mental health, and substance treatment services) • Time of treatments • ICD-10[a] codes for the treatments	2009
The municipal user and patient register (KPR[b])	• Contacts with the primary health care services (primary physicians, dentists, municipal mental health services, and emergency rooms) • Time of services • Reimbursement codes linked to ICD-10 codes	2016
Prescription Database (NorPD[c])	• All prescriptions dispensed from pharmacies or institutions • Date • Medication type and dosage • Profession of the prescriber	2004
Statistics Norway (SSB[d])	• Sociodemographic variables at the individual and household level • Level of education • Living conditions • Family situation (household, spouse or partner, and children) • Birth country • Employment status • Income • Benefits • Sick leave	1967
Cause of Death registry	• Date of death • ICD-10 codes related to the cause of death	5-year follow-up data
Secondary registry sources[e]		
National Quality Registry for Pain Management (SmerteReg)	• Contains information on treatment, pain intensity, and function for those participants who have been referred to teams for acute pain treatment at Norwegian hospitals	2014
Cancer registry	• Type of cancer • Time of diagnosis and treatment • Types of treatment	1953
National Trauma Registry	• Treatment for serious physical injuries by trauma teams at hospitals • Time of injury • Severity and type of injury • Type of accident (eg, traffic, violence, work, and self-harm) • Level of treatment	2014

aICD-10: International Statistical Classification of Diseases, Tenth Revision.

[b]KPD: Kommunalt Pasientregister.

[c]NorPD: Norwegian Prescription Database.

[d]SSB: Statistisk Sentralbyrå.

[e]We have consent from participants to retrieve data from these registries; however, as entry into the registries is dependent on specific conditions or events, we do not know whether there will be a sufficient number of participants present in these secondary registries to warrant analyses of data.

Datasets, Outcomes, and Analyses

Overview

Research questions and a preliminary analysis strategy are part of the preregistration on ClinicalTrials.gov (NCT04908410). This is an exploratory study; thus, there are no preregistered hypotheses.

The study involves two types of data (self-reported baseline cross-sectional data and longitudinal registry data), which will be combined into three different datasets with three different research designs (datasets 1-3).

Dataset 1: Cross-Sectional (Self-Reported Baseline Data)

The primary outcomes will be (1) self-reported mild, moderate, or severe chronic pain (duration of at least 3 months; *ICD-10*

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[*International Statistical Classification of Diseases, Tenth Revision*]) and (2) self-reported PTSD symptoms. Additionally, secondary outcomes will be related to pain (pain etiology and characteristics; pain treatment; impact of pain on substance use, opioid use, and choice of type of opioid agonist in OAT; and substances or medications that improve or worsen pain), trauma (types of potentially traumatizing events and age of the first event and the event that causes the most distress), and quality of life (current life satisfaction and impact of pain on life satisfaction).

The primary statistical models will be regression analyses with chronic pain and PTSD symptoms as outcomes, adjusting for relevant background, substance use, and pain characteristics. Secondary or explorative analyses include regression models with quality of life as outcome and chronic pain or PTSD comorbidity as primary predictors. Further, we will explore these models and the primary models within different subgroups of substance use (eg, alcohol only, alcohol combined with opiates, and stimulant use). We will use appropriate comparison tests (eg, 2-tailed *t* tests and chi-square tests) to compare patients with and without chronic pain, both in the total sample and substance use subgroups separately, and to compare patients with chronic pain and PTSD overlap to those who have neither or only one of the conditions.

Dataset 2: Retrospective Cohort (Retrospective Registry Data Linked With Cross-Sectional Data)

The primary outcomes will be (1) the proportion of patients who have received pain treatment (treatment for a pain-related *ICD-10* diagnosis) and (2) self-reported substance use at baseline.

Secondary outcomes include outcomes related to pain (pain intensity, pain interference, and impact of pain on substance use), the proportion of patients who are registered with a diagnosis or treatment for PTSD or other psychiatric disorders, as well as self-reported PTSD symptoms, quality of life, and dosage of OAT medication (when relevant).

The primary model will be a regression analysis with substance use as the outcome, with received pain treatment as the primary predictor (exposure), adjusting for other relevant sociodemographic and pain variables. Further, secondary or explorative analysis will include regression models with pain intensity and pain interference as outcomes, with received pain treatment as the primary predictor (exposure), and regression models with received PTSD treatment as the primary predictor (exposure), and PTSD symptoms, substance use, and pain intensity as outcomes. We will also use appropriate comparison tests (eg, 2-tailed *t* tests and ANOVA) between patients who have received pain treatment and PTSD treatment and those who have not.

Dataset 3: Prospective Cohort (Prospective Registry Data Linked With Cross-Sectional and Retrospective Data)

The primary outcomes will be time to first treatment for substance use and the number of treatment episodes following the index treatment (during which the questionnaire was completed). Secondary outcomes will be general health service use, prescribed medications, diagnoses and treatment related to pain and mental health, employment and income, housing, retention in OAT (when relevant), and mortality.

The primary model will be time-to-event analyses that take differing time-at-risk into consideration (eg, Cox proportional hazards model) to assess associations between chronic pain as an exposure and risk of new treatment episodes for substance use, controlling for other baseline variables. Secondary or explorative analyses will include regression analyses (such as logistic or linear regression) to investigate associations between chronic pain or PTSD and secondary outcomes, adjusting for relevant sociodemographic variables.

All Datasets

We will use network analyses (mixed graphical models) to explore which variables (demographics, substance use, pain, and mental health) are most strongly related to positive SUD treatment outcomes [60] and how the variables relate to each other, as well as explore the centrality and bridge centrality of different variables [61,62].

When sample size allows, comparisons between male and female populations will be made using appropriate statistical tests, and sex will at the very least be adjusted for in statistical models.

Ethical Considerations

The study was approved by the regional ethics committee south-east (REK/173249) and by the privacy office of the hospital sites. The study is registered on ClinicalTrials.gov (NCT04908410). Several measures were taken to ensure that participation was not a burden for the patients: (1) participation was voluntary, and provision of treatment was not contingent upon it. Written and informed consent was obtained. Patients could choose to only fill out the questionnaire or to also provide their personal identification number for linkage to health registries. (2) Ability to give informed consent was assessed, and patients were able to withdraw at a later stage by contacting the local or national principal investigator. (3) If the content of the questionnaire were to trigger negative feelings, clinicians were available to support the patients. (4) We focused on making the questionnaire short and simple to reduce the burden and time spent by the patients. (5) If the patient wanted to, they could discuss their responses to the questions in the questionnaire with their treatment provider, and potentially, new information disclosed in the questionnaire could directly benefit the patient. Patients were not compensated for their participation.

Training of Clinicians Who Recruited Patients

Clinicians were informed about the purpose of the study and trained in how to present participation and how to help patients complete the questionnaire to ensure high-quality data. Potential negative reactions patients might have to the themes in the questionnaire were also discussed with the clinicians, as well as the potential benefits for the patients if they wished information from the questionnaire to be used in their treatment.

Risk for the Patients and the Project

We considered that there was a very limited risk or strain for patients as a result of participating in the research project. There were no disadvantages for patients if they chose not to

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participate. Events that could have serious consequences but were considered unlikely to occur given our study procedures (Figure 2) include identifiable sensitive patient data coming into the hands of someone outside the research group or clinicians prioritizing study participation over treatment. Moderately serious events that we assumed could happen in a few cases were patients having emotional reactions to some of the questions in the questionnaire or becoming fatigued. In these cases, the clinicians were instructed to follow the procedures of the clinics and take care of the patients. The project group has received reports of a few instances where patients reacted with great emotional upset to questions related to traumatic experiences; the clinics followed up with the patients and ensured their safety.

Figure 2. Risk analysis of adverse events in the project.

		Likelihood				
Consequence	**Event**	**Rare**	**Unlikely**	**Possible**	**Likely**	**Almost certain**
5=Catastrophic	Unauthorized access to or disclosure of sensitive patient information	✓				
4=Major	Clinicians prioritize research over patient care.	✓				
3=Moderate	Patients have emotional reactions to sensitive topics in the questionnaire.		✓			
	Employees at the clinic experience an increased workload which affects their health.		✓			
2=Minor	Patients experience fatigue from completing the questionnaire.		✓			
	Delays in data collection leads to increased workload and time spent on the project.				✓	
1=Negligible	None identified.					

Results

Data Collection and Funding

The questionnaire data were collected between March 23, 2021, and June 27, 2024. Altogether 1890 patients were asked to participate, of which, 1645 (87%) completed the questionnaire. As of June 2025, responses have been entered into a database and are undergoing data cleaning (eg, removal of duplicates and validation of consent forms). Final sample size with unique participations and valid consent has not been determined, but it is estimated to be between 1400 and 1500.

Of the 1648 patients who completed the questionnaire, 1382 were also asked if they would provide their personal ID for linkage with registry data. The number of unique participants with valid consent and ID numbers for linkage to the registries is estimated to be approximately 1000-1100, which is about 76% of the 1382 who were asked for their personal ID, with the exact number pending validation of consent forms. Linkage with retrospective and prospective registry data is planned for 2025/2026 and 2029/2030, respectively.

The NOR-APT study is funded by the Foundation Dam (2024-2026), the Norwegian Research Council (2024-2027), AUH (2025), and OUH (2023). We plan to apply for further funding of the prospective registry data (dataset 3). The current funding covers the principal investigator, a 3-year postdoctoral position, a 3-year PhD position, and project costs. In total, 10 publications are planned in the period 2025-2028, based on the existing funding.

Study Progress

Data collection was completed in June 2024. We have entered all data into a database using REDCap [49,50]. Per June 2025 (the time of submitting this protocol), we are working on cleaning and finalizing the dataset, including removing duplicate participations and participations with unclear or nonvalid written consent.

Discussion

Expected Impact

Findings from the NOR-APT study will challenge current practice and knowledge in several ways. NOR-APT results will contribute to a foundation for the development and assessment of treatment interventions that can improve SUD treatment outcomes. Further, increased knowledge of the trajectories of developing comorbid substance use, chronic pain, and PTSD can also contribute to the development of early or preventive interventions to reduce the likelihood of developing comorbidities when one of the conditions is present. The study results can improve current knowledge and practice, both in the short term, through implementation of standardized screening

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to uncover treatment needs related to pain and trauma or recruitment of staff with pain and trauma competence, and in the long term, by stimulating interest in and studies on interventions for comorbid SUD, chronic pain, and PTSD.

Results are generalizable to SUD treatment in international contexts and may also be relevant for some related fields; for instance, findings among patients who are opioid-dependent can contribute to the ongoing discussion of opioid treatment of pain in pain clinics.

As a clinic-driven initiative, with a public hospital as the project owner, we are close to patients, clinicians, and clinic leaders. The NOR-APT study addresses major knowledge gaps related to comorbid chronic pain and PTSD among patients in SUD treatment. Currently, chronic pain and PTSD are typically not routinely screened for during SUD treatment; we assume the results from the study will show the importance of identifying these comorbidities and the importance of having guidelines for how these comorbidities can be included as targets in SUD treatment.

Further, awareness of the high prevalence and impact of comorbid chronic pain and PTSD can cause treatment clinics to recruit employees with expertise within chronic pain and trauma or provide broader training to clinicians to increase their confidence and skills in treating patients with these comorbidities. This can improve outcomes for patients and reduce costs for the clinics in the long-term, through more efficient treatment. Clinicians report that the assessments included in the study have already uncovered pain conditions and posttraumatic stress symptoms in patients that were previously not known to the clinics, and this is shedding new light on their substance use and treatment needs.

Finally, we are convinced that the results will contribute to the willingness to continue work toward evidence-based practices, through intervention studies for chronic pain management and PTSD among patients in SUD treatment.

Strengths

The NOR-APT study is to our knowledge the largest longitudinal study to investigate comorbid chronic pain and PTSD among patients in SUD treatment. Participation being open to patients with all types of substance use allows comparisons between patients with different substance use patterns, in the same catchment areas, using the same measures. The primary goal was to assess pain and PTSD; thus, the questionnaire includes a broad assessment of pain and trauma-related factors. The linkage of complete records from demographic and health registries with questionnaire data allows demographics and treatment history from registries to be seen in relation to the patients' self-reported pain characteristics, substance use patterns, and quality of life. It further allows the questionnaire data to be used in relation to other mental health disorders than PTSD, as information on all diagnoses the patients have received will be available.

Limitations

The questionnaire provides self-reported data, where there is a risk of self-report bias (such as memory bias and social desirability bias). It is also possible that there could be some self-selection bias where patients who found the themes most relevant (eg, patients with pain) may have agreed to participate, while patients who did not have pain saw participation as less relevant and declined. This could inflate pain prevalence estimates.

Although clinicians were asked to inform all patients about the study, regardless of any known pain or trauma, it is possible that clinicians may have had a bias toward presenting study participation to patients they believed would be more likely to say yes (eg, better functioning patients). Clinicians who had missed trainings and not seen the training materials could have believed the study was only relevant for patients with pain and thus selectively recruited patients with known pain. We explained and reminded clinicians of these potential biases throughout data collection and repeated that all patients, regardless of functioning and pain, should be included. Therefore, we assume that most cases of patients not being asked to participate would be related to the clinic's capacity and not factors related to the patient. At the same time, we are not naïve to the likely presence of some bias in our sample, for example, related to a preference for recruiting "easier patients" (which could reduce representativity for all patients in treatment or reduce pain estimates if these patients have more pain) or where some clinicians through misunderstanding recruited only patients with known pain (which would inflate our estimates of pain). We will compare our results to other studies and discuss these potential biases in our publications.

As the questionnaire was only available in Norwegian, patients who did not speak Norwegian could participate if clinicians helped them by translating the questions for them; thus, there is likely a selection bias where patients who did not speak Norwegian participated to a lesser degree. However, though no official statistics have been published, the proportion of patients in substance use treatment in Norway who do not speak Norwegian is fairly low, and language barriers were not reported as a challenge by the recruiting clinics. To assess the representability of our sample compared to the entire population of patients in treatment for substance use at the participating hospitals, and Norway overall, we will attempt to get the whole population data on immigration status from Statistics Norway. If the participation of patients with an immigration background is skewed, we will conduct weighted analyses.

Further, we can explore potential biases in participation related to age, sex, and which substance patients considered the most problematic for them, as we collected information on this from patients who declined participation. With self-reported data, missing or unclear responses can also be an issue, although clinicians were instructed to check the questionnaires and ask patients about any unclear responses.

All patients were receiving assessment or treatment from clinics for substance use and dependence treatment in the specialist health services. However, in the cross-sectional questionnaire, we did not ask patients to specify their SUD-related diagnoses, and we asked only about the use of substances, including medications, which substance they were receiving treatment related to, and which substance they perceived as most

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problematic. Thus, the questionnaire data only contain proxies for SUD. In the registry data, however, all *ICD-10* codes for SUD, mental health disorders, and somatic diseases will be available.

Concerning registry data, there is little risk of bias, as these data are not self-reported, and records for all patients will be complete or nearly complete, with little missing data. The limitation of registry data is that it only has information from official records; thus, undiagnosed conditions or other relevant events that are not part of the registers will not be available. Although the patients included in this study are in contact with service providers, it is possible that patients in SUD treatment are less likely to seek, be assessed for, and receive health care services related to other conditions, leading to underreporting of health problems from registries. The likely prevalence of PTSD and chronic pain can be estimated from the self-reported questionnaire data; however, this will not be possible for other mental health disorders or somatic conditions.

Acknowledgments

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Data Availability

The datasets analyzed during this study are not publicly available, as there is no ethics approval or consent from participants to make the data public. Questions regarding the dataset can be directed to the corresponding author.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
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Abbreviations

AUH: Akershus University Hospital
BPI-SF: Brief Pain Inventory Short Form
DSM-5: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition
EuropASI: European Addiction Severity Index
GBL: γ-butyrolactone
GHB: γ-hydroxybutyrate
ICD-10: International Classification of Diseases, Tenth Revision
LSD: lysergic acid diethylamide
MDMA: methylenedioxymethamphetamine
NOR-APT: Norwegian Addiction, Pain and Trauma
OAT: opioid agonist treatment
OECD: Organisation for Economic Co-operation and Development
OUH: Oslo University Hospital
PCL-5: PTSD Checklist for DSM-5
PTSD: posttraumatic stress disorder
REDCap: Research Electronic Data Capture
SLESQ: Stressful Life Events Screening Questionnaire

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SUD: substance use disorder
THC: tetrahydrocannabinol

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Challenges in Developing a Patient-Reported Symptom-Based Risk Stratification System for Suspected Head and Neck Cancer: Protocol for a Qualitative Case Study

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Abstract

Background: The Symptom Input Clinical (SYNC) system is being developed to enhance the timely reporting of head and neck cancer symptoms and ensure that high-risk patients receive faster diagnoses. A key feature of the system is a digital questionnaire co-designed with patient representatives to accommodate varying levels of digital literacy. The system integrates a validated algorithm that assigns risk scores to categorize cases as low or high risk and a dashboard that supports clinicians by providing them with patient reports. However, the development process has encountered challenges that necessitate a systematic evaluation of the process, roles, and experiences of team members.

Objective: This study aims to identify challenges faced during development, how these challenges were addressed, and the implications for future digital health innovations.

Methods: A qualitative single–case study approach will be used following the Standards for Reporting Qualitative Research guidelines focusing on individuals involved in the SYNC system's development. Participants will be selected using a combination of purposive and snowball sampling to ensure diverse perspectives, using meeting minutes and recommendations from key stakeholders. A total of 8 to 12 participants will be interviewed, representing clinical, research, and IT roles. Data collection will involve semistructured interviews, which will be conducted through Microsoft Teams. The interviews are expected to last between 40 and 60 minutes each. These interviews will be audio recorded, transcribed, and analyzed using framework analysis in Dedoose. The actor-network theory will guide the analysis by mapping interactions between human and nonhuman actors, such as developers, clinicians, and technological tools, to understand how they influenced the project's outcomes. Participant confidentiality will be maintained through data encryption, deidentification, and secure storage.

Results: We anticipate identifying key barriers and facilitators in the SYNC system's development, including technical, organizational, and collaboration-related challenges. The findings are expected to provide a detailed account of the challenges encountered, such as delays, security concerns, and coordination issues; an insight into how these challenges were mitigated; and lessons learned and recommendations for improving digital health technology development, including best practices for co-design, technical integration, and stakeholder engagement.

Conclusions: This case study will provide valuable insights into the complexities of developing digital health technologies, particularly in collaborative, multistakeholder environments. Documenting the challenges encountered in the SYNC system's development will contribute to best practices in digital health innovation.

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KEYWORDS

challenges; head and neck cancer; patient-reported symptoms; risk stratification; symptom-based

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Introduction

The Symptom Input Clinical (SYNC) system was developed to enhance the timely reporting of head and neck cancer (HNC) symptoms and ensure that high-risk patients receive faster diagnoses. It was developed in response to delays in the United Kingdom's "two-week wait" cancer referral pathway, which mandates that patients suspected of cancer be seen by a specialist within 2 weeks of general practitioner referral [1]. This process of referral does not stratify patients by actual risk level, meaning that high-risk individuals may wait alongside those with low clinical urgency, potentially delaying diagnosis and treatment [2].

The SYNC system is a clinician-led initiative designed in collaboration with patients and other stakeholders to improve risk-based triage. A Microsoft Excel–based version innovation, with clinicians entering information based on patient responses to obtain a risk score, was piloted in National Health Service settings across secondary care. The SYNC system is intended to improve upon this. Patients complete a digital symptom questionnaire upon referral; their responses are assessed via a validated algorithm to classify cases as low or high risk [3]. The system enables clinicians to access symptom and risk information prior to consultation, supporting earlier intervention for high-risk cases. The SYNC system includes a dashboard designed to support clinicians and cancer care service management teams by enabling them to monitor where the patient is in the pathway, including patients who have received, completed, and returned the questionnaire.

To optimize the design of the digital questionnaire, it was co-designed with relevant stakeholders, specifically patient representatives, to capture symptoms reported by patients in an accessible format to accommodate a range of health and digital literacy levels [3-8]. Patient representatives were recruited to participate in co-design and usability testing activities as part of the development of the SYNC digital questionnaire. Some of these individuals had prior experience with the urgent suspected cancer referral pathway for HNC and were engaged to provide lived experience perspectives. As co-design collaborators, patient representatives contributed to workshop discussions, validated early prototypes, and participated in think-aloud and task-based usability evaluations. Their insights were critical in shaping the content, structure, and interface of the tool, ensuring that it was understandable, user-friendly, and appropriate for patients at various levels of health and digital literacy.

The process of developing the SYNC system encountered numerous delays and challenges. These challenges emphasized the need to systematically study and document the processes, roles, and perspectives of team members to inform future developments in digital health technology. The first step in tackling the challenges is to identify them. This study will capture the key experiences of those involved in the process and planning during the development of the SYNC system. The information gathered in this study will help those planning similar projects in the future.

The aim of this study is to examine the development challenges encountered during the design of the SYNC system and how these influenced the project's scope, timeline, and implementation dynamics. The objectives are to (1) explore the experiences and roles of key stakeholders, including clinicians, researchers, and SYNC system developers, throughout the design process; (2) identify and analyze the strategies used to address technical, organizational, and communication-related barriers that emerged during development; (3) grounded in actor-network theory (ANT), assess how interactions between human and nonhuman actors (eg, individuals, algorithms, technologies, and institutional workflows) shaped the trajectory and evolution of the SYNC system; and (4) generate transferable insights to inform the design and implementation of future digital health technologies in comparable clinical and organizational settings. These objectives are exploratory in nature and grounded in the hypothesis that inclusive, context-sensitive design processes mediated by sociotechnical interactions play a critical role in shaping the design, usability, and long-term sustainability of digital health care innovations.

Methods

Overview

This research will adopt a qualitative single–case study design and adhere to the Standards for Reporting Qualitative Research guidelines by O'Brien et al [9] to ensure transparency and methodological rigor in reporting. Given the case study design and the aim to explore development challenges from a system-wide perspective, the Standards for Reporting Qualitative Research provide the most appropriate framework for guiding the design, conduct, and reporting of this study. A case study is an empirical inquiry that involves the study of an individual unit, such as a person, community, or project, with a focus on developmental factors in relation to their environment [10,11] and involving the collection of multiple forms of data [12]. This study will focus on individuals involved in the development of the SYNC system and will examine cross-team experiences and challenges, exploring how these factors influence the development processes. This method was chosen to enable an in-depth analysis of real-world challenges and the complex interactions among individuals, teams, and the technology.

Recruitment and Sampling Strategy

Participants will be selected using a combination of purposive and snowball sampling, which is particularly effective for engaging individuals with specific insights into a project's processes and challenges [13]. This method leverages existing social networks and relationships, enabling us to identify and recruit participants who are knowledgeable about the SYNC system conception and development. We will review minutes of previous meetings, and if someone is repeatedly mentioned or appears to have had a key influence on an element of study progress, we will highlight that individual as key in participant selection. Initial recruitment will involve purposive selection of key individuals involved in the SYNC system's development, ensuring representation across the various teams involved in the development process (and including individuals with clinical, research, and IT roles). They will be asked to recommend

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colleagues they believe could provide valuable input. In this way, stakeholders with smaller roles in the project will also be considered to ensure a broader range of perspectives and enhance the credibility of the findings. We plan to recruit between 8 and 12 participants from different roles, especially those whose roles in the project were delayed due to challenges encountered. There is no consensus on the number of interviews required to provide an adequate understanding of experiences within a particular setting. However, this range allows for sufficient depth in identifying themes while keeping data collection manageable. This sample size is considered sufficient to reach thematic saturation when exploring experiential dimensions within well-defined stakeholder groups, such as clinicians, researchers, and developers engaged in a co-design project [14]. Saturation will be assessed iteratively during data collection and analysis using the constant comparative method. We will evaluate for saturation when no new codes or themes emerge across at least 2 consecutive interviews or focus groups. A saturation grid will be maintained to document the emergence of themes and monitor redundancy in incoming data. If thematic saturation is not reached within the initial sample, additional participants will be recruited until saturation is achieved.

In case of challenges in recruitment due to potential participants' work commitments or other concerns, we will extend the recruitment period and be flexible in scheduling interviews (eg, offering them outside of normal working hours).

Data Collection

This study will use multiple data collection methods that will involve both qualitative interviews and document analysis. Data will be collected through semistructured interviews conducted via Microsoft Teams. This will allow participants the flexibility to take part from their preferred location and avoid the logistical challenges of travel. Interviews will last between 40 and 60 minutes and will be audio recorded with participants' consent. This approach will ensure a consistent format while enabling researchers to capture rich, detailed narratives. The interviews will focus on participants' roles, challenges experienced during the SYNC system development, and recommendations for improving similar projects (Multimedia Appendix 1). In addition to conducting interviews, the researchers will undertake review of relevant documents such as meeting minutes and other pertinent records to gather insights into any documented challenges. Participants will also be asked to provide any available documents that could help uncover developmental challenges. This will offer a more comprehensive understanding of the issues.

Data Analysis

Framework analysis, a qualitative method that uses a structured matrix to organize and analyze data (interview transcripts and collected documents) by case and code [15], will be used in this study. This method will ensure a clear audit trail for credibility and support input from the wider project team, including those with limited qualitative analysis experience. Framework analysis will be conducted using Dedoose (SocioCultural Research Consultants), with codes derived inductively and deductively from ANT [16]. The aim is to understand how people, ideas, technologies, and nature form networks. To ensure dependability, a second researcher will review a sample of the interview transcripts and documents to identify any additional codes. The first researcher will then use the agreed-upon codes to index the data. Coded data will be summarized in a matrix, enabling collaborative discussion regarding patterns in the data to further strengthen the reliability of the findings. Following these consensus meetings, the first researcher will use the matrix to produce narrative summaries of each theme, returning to the original data where necessary. The documentary analysis will be systematically integrated with interview data to cross-validate emerging themes and interpretations.

Guidance for qualitative studies in health informatics will be followed, ensuring that the findings are robust and credible [17]. This guidance adheres to established criteria for transparency and rigor in qualitative research.

Ethical Considerations

The study protocol for the co-design of the SYNC system was reviewed and approved by the Committee for Clinical Research at the Royal Marsden (CCR5686) and the UK Health Research Authority (Integrated Research Application System 315419). An amendment will be submitted to undertake this additional research. All participants will receive an information sheet and consent form via email outlining the study's objectives, procedures, and ethical considerations. Participants will be given 48 hours where possible to review the documents and confirm their willingness to take part by responding to the researcher.

To safeguard participant confidentiality, this study will implement encryption for interview recordings during transmission and storage. In publications, the researcher will avoid reporting specific details that could single out a participant. Interview recordings will initially be stored on the University of Bradford secure servers and transcribed using Microsoft Teams. Following an interview, the transcript will be checked against the recording for accuracy, and once complete, the recording will be deleted. Interview transcripts will be uploaded to Dedoose, a secure and collaborative research and evaluation data analysis application, and access will be restricted to the researchers involved through role-based access control and multifactor authentication. All data will be deidentified before analysis to protect participant identities. Data will be stored securely and retained only until the completion of the Evolution of a Patient-Reported Symptom-Based Risk Stratification System to Redesign the Suspected Head and Neck Cancer Referral Pathway (EVEREST-HN) study, with a clear policy for deletion based on the University of Bradford storage and retention policy. The informed consent form will outline how data will be handled, and participants will be informed of their rights regarding data withdrawal.

Theoretical Framework: ANT

The design and conduct of this study will be guided by ANT [16]. ANT challenged the traditional dichotomies, dissolving artificial boundaries among technology, organization, nature, and society, focusing on the interconnected networks of human and nonhuman actors that shape and are shaped by each other. ANT provides a framework for understanding how both human

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(eg, developers, clinicians, and patients) and nonhuman (eg, the SYNC system, organizational tools, and processes) actors interact within a network to influence the outcome of the project development. In the context of the SYNC system, ANT will help uncover how these interactions shaped the project, such as how collaboration between diverse teams impacted decision-making and how technical challenges influenced workflow. By mapping these relationships, ANT will highlight critical factors contributing to the system's successes and challenges, offering insights for improving future digital health projects. These ANT concepts have informed the interview questions and will inform the codes used to index the transcripts and project documents.

ANT will be particularly useful in identifying how roles and responsibilities were distributed among team members and how these roles evolved over time. It will also help uncover the influence of technical and organizational factors on the project's trajectory, offering valuable insights for refining processes in future digital health technology development.

Results

Overview

This study is expected to provide a comprehensive analysis of the challenges encountered during the development of the SYNC system, as well as the lessons derived from addressing these challenges. Data collection is scheduled to commence in August 2025. At the time of this manuscript submission, participant recruitment has not yet started. The data analysis and the anticipated findings will be formally reported in the first quarter of 2026.

Potential Limitations of the Proposed Methods

A limitation of the study design is the use of purposive and snowball sampling, which may present several challenges. Purposive and snowball sampling were selected to ensure inclusion of information-rich participants with direct involvement in the system's development and implementation, aligning with the study's aim to explore design- and process-level dynamics. There is no comprehensive list of individuals involved in the system's development, and so snowball sampling is essential to identify other participants. However, reliance on participants to recommend others could introduce selection bias, potentially limiting the diversity of perspectives captured and affecting the generalizability of the findings as insights might reflect only a subset of those involved in the project. For instance, participants may predominantly refer colleagues within their immediate teams or with similar views, which could overlook critical voices or unique experiences. Snowball sampling might not adequately capture perspectives from less connected stakeholders or peripheral team members, thus limiting understanding of complex interactions between technical and organizational factors. The use of minutes as a secondary route to sampling might help mitigate this risk. If critical or dissenting perspectives are underrepresented, this limitation will be noted and reflected in the interpretation of the findings.

Another challenge in small team projects is maintaining participant anonymity, especially when using single-case designs. It may be hard to disguise identities, at least from other people within the case, if not externally. Consequently, participants might worry about being identifiable, which could impact their willingness to share honest feedback. To minimize this, findings will be reported in a more generalized form by combining responses where possible. Additionally, the researchers acknowledge that their backgrounds and experiences may influence the research. Researchers' positionalities and potential biases will be actively considered throughout the study to enhance transparency and reflexivity. The lead author (CO) brings experience as a qualitative researcher and holds affiliation with the broader EVEREST-HN program, although they were not directly involved in the technical development of the SYNC system. This positioning offers both contextual familiarity and a degree of critical distance. Other members of the research team include system developers, clinical collaborators, and methodological advisors whose varying levels of involvement in the project may influence their interpretations. To mitigate potential biases, reflexive journals [18] will be maintained to document assumptions, role-related insights, and decision-making processes throughout the research. Coding will be conducted collaboratively, with at least one researcher not directly involved in the development of the SYNC system to provide an external perspective. Peer debriefing sessions will be held to challenge assumptions and ensure a balanced interpretation of the findings. Memo writing during analysis will also be used to capture reflections on how individual experiences may shape emerging themes. These strategies will support the credibility and rigor of the analysis while ensuring that findings are grounded in the participants' perspectives rather than the researchers' preconceptions.

Discussion

This protocol describes the methods that will be used for capturing the experiences and challenges of developing the SYNC system, which will offer actionable insights for designing and implementing similar technologies in health informatics. On the basis of a qualitative case study approach, purposive and snowball sampling, and ANT, the findings will address collaboration challenges, promote inclusive co-design, and optimize technical integration. This study is expected to generate important insights into the development of the SYNC system, a digital health innovation designed to support timely symptom reporting and risk stratification for patients referred with suspected HNC. The findings are anticipated to provide a detailed account of the challenges encountered during system development, including technical constraints, interprofessional coordination difficulties, governance processes, and changes in scope or delivery timelines. This study also aims to identify facilitators and adaptive strategies used by the development team to overcome these challenges. These findings will inform future efforts to design, implement, and scale similar digital health systems, particularly in the context of multistakeholder pathways.

While prior research [4,5,19], including the protocol by Albutt et al [3], has focused on the co-design and usability testing of

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the SYNC patient-facing questionnaire, limited attention has been paid to the underlying developmental processes and system-level barriers. This study addresses that gap by using a qualitative case study approach guided by ANT to examine how human and nonhuman actors, including clinicians, developers, and digital platforms, interacted during system development. In contrast to studies that primarily explore patient engagement or tool efficacy, this work contributes to the growing but underdeveloped literature on digital health implementation processes, organizational complexity, and collaborative design in real-world health care settings. A strength of this study will be its use of multiple data sources and perspectives to capture the layered complexity of system development. The application of ANT as a theoretical framework supports a more nuanced understanding of how actors influence and are influenced by their sociotechnical networks. By engaging participants from clinical, IT, and research backgrounds, this study will provide a richer, more holistic view of development challenges. The use of reflexive practices and team-based analysis will further enhance the trustworthiness of the findings.

This study will provide practical recommendations for future digital health innovations, particularly those implemented in time-sensitive pathways such as cancer referral. The findings may be used to guide best practices in co-design, risk algorithm integration, technical development, and stakeholder engagement. Future research should consider evaluating the impact of the SYNC system and similar digital triage tools after implementation, including effects on diagnostic timelines, patient outcomes, and system-level efficiency. Comparative studies across different disease areas or health care systems could further refine understanding of transferable practices and context-specific adaptations.

To maximize the reach and utility of the study findings, we will pursue a comprehensive dissemination strategy. This includes publication in peer-reviewed journals, presentations at relevant academic and professional conferences (eg, the American Medical Informatics Association, MedInfo, and Health Services Research UK), and targeted knowledge exchange workshops with stakeholders. In addition, we will develop a practical implementation resource summarizing key lessons learned, which will be shared with health care providers, innovation hubs, and digital health funders to inform future technology development and deployment efforts.

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Authors' Contributions

Conceptualization: JP, NR, VP, RR
Investigation: CO
Methodology: CO
Supervision: RR
Writing—original draft: CO
Writing—review and editing: CO, JP, NR, VP, RR

Conflicts of Interest

None declared.

Multimedia Appendix 1
Topic guide: case study interviews.
[DOCX File, 15 KB - resprot_v14i1e74262_app1.docx]

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Abbreviations

ANT: actor-network theory
EVEREST-HN: Evolution of a Patient-Reported Symptom-Based Risk Stratification System to Redesign the Suspected Head and Neck Cancer Referral Pathway
HNC: head and neck cancer
SYNC: Symptom Input Clinical

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Protocol

Cultural Adaptation of an Aboriginal and Torres Strait Islanders Maternal and Child mHealth Intervention: Protocol for a Co-Design and Adaptation Research Study

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Abstract

Background: There is limited evidence of high-quality, accessible, culturally safe, and effective digital health interventions for Indigenous mothers and babies. Like any other intervention, the feasibility and efficacy of digital health interventions depend on how well they are co-designed with Indigenous communities and their adaptability to intracultural diversity.

Objective: This study aims to adapt an existing co-designed mobile health (mHealth) intervention app with health professionals and Aboriginal and/or Torres Strait Islander mothers living in South Australia.

Methods: Potential participants include Aboriginal and/or Torres Strait Islander pregnant women and mothers of children aged 0-5 years, non-Aboriginal and/or Torres Strait Islander women who are mothers of Aboriginal and/or Torres Strait Islander babies, and health professionals who predominantly care for Aboriginal and/or Torres Strait Islander mothers and babies. Participants will be recruited from multiple Aboriginal and/or Torres Strait Islander–specific health services under the local health networks around metropolitan South Australia. In this study, data collection will be carried out via culturally safe, and family-friendly yarning circles, facilitated by Aboriginal research staff to collect feedback on the existing mHealth app from approximately 20 women and 10 health professionals, with the aim to achieve data saturation. This will inform the changes required to the mHealth app. All focus groups and interviews will be audio recorded and transcribed verbatim. Data will be inductively analyzed using realist epistemology via NVivo software (Lumivero). Themes about the mHealth app's cultural acceptability, usability, and appropriateness will be used to inform the changes applied to the app.

Results: With the feedback received from participating women and health professionals, changes in the smartphone app will be made to ensure the intervention is supportive and meets the needs of Aboriginal and/or Torres Strait Islander mothers and families in South Australia. Participation of community members will promote ownership, community engagement, and implementation.

Conclusions: A co-designed, culturally sensitive, and effective digital health intervention is likely to support Indigenous mothers and their children facing health disparities due to the disruption of Indigenous culture by colaying a foundation for a potential clinical trial and wider implementation.

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KEYWORDS

Aboriginal; co-design; mHealth; maternal; child health; digital health; children; women; female; cultural adaptation; Torres Strait; research study; Indigenous; digital health intervention; diversity; South Australia; pregnant; health professional; adaption; focus group; pretesting; usability; app; health disparities; information; technology; mobile phone

Introduction

The impact of colonization on Indigenous populations' health across the globe is well recognized [1]. The ongoing disadvantages of intergenerational trauma and structural violence have resulted in disparities in health outcomes between the Australian general population and Aboriginal and/or Torres Strait Islander communities [1]. Decolonization of interventions, health care organizations, health service provision, and policies are recommended as solutions.

Mothers and babies getting optimal care and support for a good start to life is a priority of the Australian National Aboriginal and/or Torres Strait Islander Health Plan 2013-2023 [2]. However, despite policies, strategies, and funding to mitigate the disparities in pregnancy and birthing outcomes, closing the gap is yet to be achieved [3]. The importance of traditional family and kinship ties and knowledge of birthing and parenting practices remain largely unrecognized in the mainstream health services accessed by Aboriginal and/or Torres Strait Islander communities [4,5]. This contributes to poorer health outcomes experienced by Aboriginal and/or Torres Strait Islander pregnant women, babies, and young children compared with Caucasian Australians [2,4,6]. Aboriginal and/or Torres Strait Islander women of childbearing age (15 years and older) are overrepresented in behavioral risk factors impacting health outcomes. In a recent Australian National Health Survey, a large majority of First Nations women failed to meet guidelines for physical activity, and vegetable or fruit intake [7]. Furthermore, 36% reported daily tobacco smoking, and 35% reported experiencing high or very high levels of psychological distress [7]. The cumulative effects of disadvantage and poorer health outcomes of women subsequently impact infant mortality for Aboriginal and/or Torres Strait Islander babies, which is 2.1 times the rate of non-Indigenous infants [8]. This highlights the urgency of more effective, ground-up, community-led resource and service development [9].

Mobile health (mHealth) apps are being used increasingly for health promotion because of their potential for greater reach [10,11]. Despite their growing popularity, very few evidence-based mHealth interventions for Aboriginal and/or Torres Strait Islander Australians exist [12]. A recent Aboriginal and/or Torres Strait Islanders survey of 398 women aged 16-49 years found that most respondents owned a smartphone, had internet access, and used social media daily [13]. This suggests that a smartphone app may be an effective health promotion tool for Aboriginal and/or Torres Strait Islander women or carers with children.

Evidence-based literature offers many perspectives on co-design. The term "co-design" is often used in research to describe a methodology that involves stakeholders in the "design of services, strategies, environments, policies or processes that impact them" [14]. Digital health solutions designed and developed in the context of mainstream health systems predominantly neglect socioeconomic determinants that are fundamental in understanding and addressing the distinct health challenges that Indigenous communities face [15]. Such an oversight might be rectified by integrating culturally safe co-design practices during the design and development phases [15]. Consequently, this project proposes that the culturally sensitive adaptation of a co-designed mHealth intervention has the potential to significantly benefit the health of many Aboriginal and/or Torres Strait Islander families within South Australia and nationally.

The mHealth program, Jarjums, co-designed with Aboriginal and/or Torres Strait Islander people was developed in New South Wales in collaboration with Aboriginal communities and found to be highly acceptable by women and health services [12]. The co-design of the app ensured culture was weaved throughout the project and the mHealth app [12]. The purpose of this mHealth app is to provide information and health behavior change strategies in the domains identified or selected by the co-design participants. The app explores women's and babies' health and well-being topics through 6 individual modules. These include (1) smoke-free families, (2) safe drinking, (3) feeling good, (4) women's business, (5) eating, and (6) exercising. The modules exploring children's health and well-being include (1) breathing well; (2) sleeping; (3) milestones; (4) feeding and eating; (5) vaccinations and medicines; and (6) ears, eyes, and teeth. Each module includes key messages around the benefit of changing behavior related to illness progression, tips addressing barriers to behavior change, cues for action, and links to further information.

As there are over 250 language or national groups with differing laws and customs across Australia, the current project will develop an adaptation of the intervention for South Australian–based Aboriginal and/or Torres Strait Islander women. The aim of this study is to consult with health professionals, mothers, and carers to culturally adapt a mHealth program called "Growin' Up Healthy Jarjums" for use by Aboriginal and/or Torres Strait Islander mothers and carers living in South Australia. This research will directly address gaps in the health evidence base and build on existing knowledge by ensuring that programs developed and effective in 1 location, are adapted and tested before they are implemented in the intended population in another location.

Methods

Study Design

This is a multisite project and will be conducted at 3 different Aboriginal health care services.

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There are 3 levels of involvement of Aboriginal and/or Torres Strait Islander people in this project. These are (1) Aboriginal and/or Torres Strait Islander chief investigators, (2) project governance by a separate Aboriginal and/or Torres Strait Islander Governance Group, and (3) Aboriginal research assistants (ARA).

The Governance Group will oversee the conduct of the project and guide the interpretation of data, dissemination, and translation of study findings. All members have extensive experience working in Aboriginal and/or Torres Strait Islander health care. Specifically, the group comprises research experts, organizational and departmental leaders from various affiliations including universities, government health strategy and research departments, local health networks, maternal and child service providers, and community representatives. The ARAs are local community members and involvement in Aboriginal health services is a crucial component of the research to build trust, safety, and engagement. The ARA involvement also supports capacity building for Aboriginal and/or Torres Strait Islander research.

The framework for the cultural adaptation process will be based on the stages of cultural adaptation stepwise model of Barrera et al [16-19]. Barerra et al [16] describe 5 stages to culturally adapt evidence-based interventions for the purposes of reducing health disparities among culturally diverse populations and include considerations for intercultural diversity. These stages of adaptation include (1) information gathering, (2) preliminary adaptation design (including modifications), (3) preliminary adaptation tests, (4) adaptation refinement, and (5) cultural adaptation trial [16].

In this qualitative study, the existing co-designed mHealth app, Growin' Up Healthy Jarjums, will be adapted by using focus groups and interviews to collect data on participants' perceptions, experiences, and ideas about the app. We will conduct sessions using traditional yarning style methodology, to ensure culturally responsive practices are respected. Yarning is an established culturally appropriate process to conduct research with Aboriginal and/or Torres Strait Islander people to both establish rapport and collect information [20]. The sessions will be predominantly conducted by ARAs.

The eligibility criteria include Aboriginal and/or Torres Strait Islander women aged 16 years and older living in South Australia, who are currently pregnant, or mothers of children aged 0 to 5 years. Non-Indigenous women, of similar age are also eligible if they are pregnant with or are mothers of Aboriginal and/or Torres Strait Islander children aged 0 to 5 years. All documents prepared to convey the study information and consent are in English. However, there is a possibility that eligible, interested women may not be able to communicate in English. Such instances will be managed on a case-by-case basis with the support of language interpreters.

Focus groups will be conducted with an estimated 4 to 6 women in each group, up to 20 women in total. It is expected that data saturation will be achieved with 2 to 3 focus groups with approximately 4 to 6 women each. The actual number may vary depending on achieving data saturation.

Recruitment of participants will involve ARAs directly approaching women in the waiting area or room of the participating sites. Information sheets, leaflets, and consent forms will be available to use for recruitment support. Eligible women may directly approach the research team after reading the study information poster at any of the participating sites or the information leaflet provided to them by clinic staff of the participating sites. Furthermore, participating clinics will have project handouts to offer to eligible women.

In addition, participants will be asked if they would like to pass the study information on to a friend or family member who can then choose to connect with the research team to obtain further information and potentially participate. Individuals will be screened for eligibility when they contact the research team by phone. Women who consent to participation will be invited to join a focus group or interview with an estimated duration of 1.5 hours. At the start of the focus group or interview, participants will be asked to complete a face-to-face survey with demographic, cultural, and socioeconomic items. The survey has been adapted from a previously piloted study and deemed to be appropriate by Aboriginal and/or Torres Strait Islander mothers [21,22]. The ARAs will also spread the information to their circle of friends or family and co-workers and recruit via word of mouth.

Health professionals who predominantly care for young Aboriginal and/or Torres Strait Islander mothers or children will also be recruited for interviews. They will be recruited to the study using a separate information sheet and consent form by either the ARAs or the non-Aboriginal and/or Torres Strait Islander Research Fellow involved in the project. This process will involve explaining the participant information sheet and consent form to the health professional. All participation is voluntary, and health professionals will be informed that their decision to participate, or not, will not impact their role or position.

The purpose of including health professionals is to ensure that the messages provided in the app are aligned with the evidence-based messages used within their practice. To garner their views on the use of the app as a tool to connect with Aboriginal and/or Torres Strait Islander families (one of the aims of the app), the appropriateness of the app will also be explored. Health professionals will be interviewed for input into the content and features of the mHealth app until data saturation is achieved.

Once the adaptation process is complete and all the suggested feasible changes are made in the app. Further work regarding the feasibility of the app will be undertaken by asking representative women or carer population to use the app for 4 weeks.

The snowball methodology is predicted to facilitate the recruitment phase of the project. Participating health service managers who agree to support the project will be sent an invitation email to circulate to their staff with the staff study information sheet.

A focus group or interview guide will be used to guide the discussion, although focus groups or interviews will be

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conducted using an iterative process, with the information gathered from initial focus groups used to guide the dialogue and resources used in sequential groups. Phone interviews may be conducted with participants if this is preferred. If required, an interpreter service will be used to provide support to potential participants who require language interpretation.

The focus group or interview discussion will primarily focus on how an mHealth intervention designed for this community would differ from the "Growin' Up Health Jarjums" program. Participants will be prompted to discuss images and artwork, language, videos, content, and delivery features of the original app.

All focus groups and interviews will be audio-recorded, with participant consent, and transcribed verbatim by a professional transcription service that will sign a confidential agreement before providing their service.

Participating women and health professionals can withdraw at any time, without giving a reason, throughout the study. Consent to participate can be retracted by contacting the research team; in-person, by phone, or via email. The contact information for the study team is provided on the study information sheets.

If the participant requests a specific response to be removed from the transcriptions, then the researchers will make reasonable attempts to achieve this. However, it may not be possible to remove every detail of a participant's contributions as it can be difficult to identify individual contributions within the focus group transcriptions.

If participants become distressed during the focus group or interviews when health content for the app is discussed such as child health, smoking or alcohol, and other drugs, a study-specific distress protocol will be adhered to. All events will be recorded and follow-up will be performed.

A generalized data-driven, inductive, thematic analysis will be completed with the transcribed, deidentified data [23]. Inductive analysis is a process in which data coding is undertaken without fitting it into any preexisting coding framework. An ARA and investigator will independently code themes using NVivo software (Lumivero) and complete analysis and write-up with the project team and project Investigators. The data will be interpreted sensitively with the input of ARAs. All personal, identifiable information will remain anonymous in reporting. Deidentified data analysis will be used in manuscripts for publication in peer-reviewed journals and for poster and oral presentations at national and international conferences or symposiums.

The feedback received from women and health professionals will be used to change the app by the technical team. The edited app will be screened by women for acceptability in a follow-up study.

Ethical Considerations

This project has been granted ethical approval by the Department of Health and Wellbeing Human Research Ethics Committee (2022/HRE00262) and Aboriginal Health Research Ethics Committee (#04-22-1018). A cross-institutional approval has also been obtained from Flinders University. Participation in this study is voluntary. Potential participants will be informed, both in writing on the consent form and verbally during the consent process that they can choose to not participate. Their decision not to participate will not jeopardize their relationship with their organization, health care providers, and research team and will not affect the delivery of care to them. Data will be anonymized during the transcription process and all identifiable, personal details of participants will be removed. Participating women will be reimbursed with a Aus $50 (US $33.64) shopping voucher for their time and provided with refreshments.

Results

The short-term outcomes of this research will include the start of the development of a culturally appropriate mHealth app to support Aboriginal and/or Torres Strait Islander maternal and child health. It is anticipated that the app will be a tool for women to connect with each other, connect with health professionals, and access evidence-based, culturally responsive health information in a way that is meaningful to them. The design, content, and features of the app will be a collaboration of ideas, stories, and evidence from women, the research team, and health services. Participants will have the opportunity to suggest additional areas of health or additional modules to include in the app. Potential benefits for participating women include opportunities to learn new information, and to engage with and comment on the use of new technologies. Participation of women will also promote ownership and community engagement of the project.

The anticipated long-term outcomes of the research include the contribution of the data to the knowledge on the preferences and potential use of a mHealth app for improving health outcomes of Aboriginal and/or Torres Strait Islander women and children. The resulting data will be used to source further funding opportunities for testing the feasibility, acceptance, and effectiveness of the app in a clinical trial. Ultimately, this app aims to promote health and reduce the rates of noncommunicable and communicable diseases among Aboriginal and/or Torres Strait Islander women and children. Findings may inform local and regional policies and provide advice on how to incorporate these new technologies as part of existing programs and practices.

As of July 2024, the project is ongoing in South Australia. The first phase of data collection will finish in September 2024 and the results will be shared with stakeholders in the form of reports, peer-reviewed publications, and conference presentations.

Discussion

The data might identify additional needs by participating women and health professionals. That will determine the scope of future research and implementation of mHealth technology related to Aboriginal and/or Torres Strait Islander women and children.

We anticipate that this new digital health intervention will help to reduce health disparities among Aboriginal and/or Torres Strait Islander mothers and their children, laying a foundation for a potential clinical trial and wider implementation.

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A strength of this study includes its sensitivity to culturally responsive research methodology. This is woven throughout the study design from the governance model and the inclusion of ARAs to the way in which members of the community will be recruited and the flexibility of the consultation process.

Some anticipated limitations include challenges with recruitment due to the nature of engaging with a specific cultural group. The study does rely on the shared understanding of ARAs with the community and it is anticipated this will foster the development of trusting relationships with participants and support recruitment.

Finally, while the app is currently designed for the South Australian–based Aboriginal and/or Torres Strait Islander community, there is diversity within the community and therefore, this could limit engagement. Questions about how to improve the cultural responsiveness of the app will be asked while gathering feedback.

Concurrently, a recent review on barriers and facilitators of engagement of Indigenous peoples with mHealth interventions revealed themes that echo the need for effective and timely co-design practices in this field [24]. Co-design has been identified as one of the most important factors determining the uptake of web-based therapeutic interventions for Indigenous communities or populations [25]. The review findings support the inclusion of culturally sensitive methodology as well as Indigenous governance and community consultation.

Project outcomes will be provided to organizations and participants while ensuring participants' confidentiality. Ethical reports and funding body reports will be completed and provided to the relevant figures. We anticipate that there will be numerous opportunities to share and use the data gathered from this research, including dissemination to research institutes, health organizations, and community groups.

Furthermore, this research can inform policy makers and peak organizations of the needs of mothers and families with young children.

Acknowledgments

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Data Availability

The data that will come out from the study will belong to the Aboriginal and/or Torres Strait Islander Community. Due to the sensitivity required in sharing and spread of that data, it will only be available upon reasonable request made to the corresponding author after approval from the project governance. The corresponding author will review any requests received with guidance from the Aboriginal and/or Torres Strait Islander Governance Group of the project.

Authors' Contributions

SI developed and designed methodology, provided resources, supervision and oversight, validation, and contributed to writing, reviewing, and editing. AD contributed to project administration and data curation. OE contributed to data curation, writing, and project administration. AB and CR contributed through review and editing. KC and KH contributed through review and editing as well as governance and design. NB contributed through review, editing, and software/application advice. CTR contributed through review, editing, and resource acquisition. SP contributed through review, editing, and study conceptualization. BB contributed through research supervision, design of methodology, resource and funding acquisition, review and editing, and conceptualization.

Conflicts of Interest

None declared.

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Abbreviations

ARA: Aboriginal research assistant
mHealth: mobile health

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Protocol

Home-Based Intervention Tool for Cardiac Telerehabilitation: Protocol for a Controlled Trial

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Abstract

Background: Among cardiovascular diseases, adult patients with congenital heart disease represent a population that has been continuously increasing, which is mainly due to improvement of the pathophysiological framing, including the development of surgical and reanimation techniques. However, approximately 20% of these patients will require surgery in adulthood and 40% of these cases will necessitate reintervention for residual defects or sequelae of childhood surgery. In this field, cardiac rehabilitation (CR) in the postsurgical phase has an important impact on the patient by improving psychophysical and clinical recovery in reducing fatigue and dyspnea to ultimately increase survival. In this context, compliance with the rehabilitation program is a key element for the therapeutic benefits of the program. The increase of mobile health care devices and software has greatly extended self-care capabilities across the spectrum of health care activities. Moreover, the possibility of telemonitoring the progress of this self-care provides elements of empowerment and awareness of one's state of health. As a branch of telehealth, CR can be optimized and facilitated using remote telemedicine devices.

Objective: The principal goal of the Innovation in Postoperative Rehabilitation Training and Monitoring (IPOTERI) study is to design, realize, and test a composite and integrated system for postsurgical rehabilitation therapies at home specialized for cardiac surgery. The secondary aims are to implement the system in a "real-life" context of postcardiac surgical rehabilitation, and to create a data set and a data collection methodology to prototype data analytics algorithms and artificial intelligence techniques for customizing the rehabilitation pathway.

Methods: The IPOTERI method consists of a telemonitoring platform that guarantees continuity of postoperative care, an intelligent home station based on an Android app for the patient with a user-friendly interface to record vital signals (electrocardiogram, blood pressure, oxygen saturation, and body weight) and access the planning of rehabilitation activities, and a decision support system that communicates with hospital medical records to transmit alerts and specific support information for the formulation and updating of the treatment and care plan.

Results: The pilot test started in June 2023 (protocol number 20406/2021) including 50 patients who will be monitored for 12-14 weeks using the developed platform, as described in the Procedures subsection of the Methods section.

Conclusions: The IPOTERI approach, based on the processing of data recorded during the monitoring of telemedicine devices used at home during the postsurgical rehabilitation of a cardiac patient, together with clinical data from the perioperative and postoperative periods could have positive effects on adherence to the rehabilitation program and clinical improvement as well as result in overall improvement of quality of life.

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KEYWORDS

cardiac rehabilitation; exercise; patient education; patient-centered approach; eHealth; artificial intelligence

Introduction

General Background

Cardiovascular diseases (CVDs) represent the leading cause of death worldwide, which are responsible for 17 million deaths annually according to the World Health Organization [1]. This figure is expected to increase, as it is estimated that 23 million people will die from CVDs worldwide in 2030, accounting for 31% of all deaths globally [2]. People with CVDs typically require steady assistance and management by both the patient and their caregivers, mainly due to comorbidity with other pathologies, including high blood pressure, diabetes, and hyperlipidemia.

Among CVDs, adult patients with congenital heart disease represent a population that has been continually increasing, mainly owing to the improvement of the pathophysiological framing, including the development of surgical and reanimation techniques that have contributed to enhanced survival of these patients into adulthood [3]. Recent studies indicate that approximately 20% of patients with congenital heart diseases will require surgery in adulthood and 40% of these cases will necessitate reintervention for residual defects or sequelae of childhood surgery [4]. In these patients, the benefits of cardiac rehabilitation (CR) techniques are particularly important and clinically impactful during the postoperative period.

Clinical Background of the CR Field

CR is an evidence-based program that is considered part of secondary prevention, which is focused on three main aspects: patient education, health behavior modification, and exercise training [5]. CR programs primarily target patients with ischemic heart disease, heart failure, or following cardiac surgery to reduce mortality and morbidity. A complete rehabilitation plan should include both a physical and psychological agenda, encompassing clinical evaluation, pharmacotherapy, psychological support, training, assessment and reduction of risk factors (both physical and psychological factors), and patient education for lifestyle modification. Thus, the gold standard of CR is an approach integrating health behaviors such as increased physical activity, improved dietary habits, and smoking cessation, along with promotion of medical adherence and psychosocial well-being strategies. There are multiple reported benefits of CR in patients following cardiac surgery. Several studies have documented that in addition to speeding up psychophysical recovery, CR improves clinical parameters, namely by reducing fatigue and dyspnea, ultimately resulting in increased survival with a drop in mortality at 10 years after surgery reaching up to 14% [6]. Interestingly, the benefit in terms of major event-free survival correlates with the number of rehabilitation training sessions to improve quality of life and reduce cardiovascular risk factors [7-9].

Although the clinical importance of CR is officially recognized, the proportion of patients admitted to a rehabilitation program remains small and there is overall low patient compliance [10]. Several factors may contribute to this low enrollment rate in CR programs, including physicians' and patients' approaches toward CR. In general, the percentage of patients who adhere to CR is variable, depending mainly on age, gender, and the presence of preexisting neurological complications [11]. Moreover, in addition to poor adherence, the capacity of services for CR in primary care is hindered due to limitations of human resources and adequate space in hospitals to support rehabilitative programs.

To overcome these problems, an alternative method to the traditional center-based CR (CBCR) model is home-based CR (HBCR), which is a new method that can be carried out in different settings, ranging from the home to a park, owing to the support of telemedicine.

Evidence from published studies comparing CBCR and HBCR has revealed that in some cases, the results are overlapping with improvements in 3- to 12-month clinical outcomes and no differences in hospitalization rates [12]. In particular, benefits have been documented regarding functional improvement, managing risk factors, and well-being perception. With respect to compliance, HBCR is associated with a lower dropout rate and higher degree of responsiveness and perseverance compared to CBCR [13]. For these reasons, an important aim will be to extend the applicability of HBCR to different patient subgroups, including older adults, women (who tend to have relatively poor compliance [14]), and high-risk patients. Based on current evidence, it is reasonable to believe that HBCR can be targeted to patients in a stable state with low to moderate risk. Furthermore, despite international guidelines recommending CR, there are no unique programs tailored according to pathology or country of origin. For example, in Italy, CR is part of the rehabilitation plan in the hospital; however, according to the Italian Survey on Cardiac Rehabilitation (ISYDE), the Italian cardiology rehabilitation network is only able to offer the intervention to approximately 60,000 patients per year against an estimated demand of more than 300,000 patients per year [15]. To reduce the imbalance between supply and demand, the ISYDE project was developed with the goal of obtaining a detailed snapshot of the number, distribution, facilities, staffing levels, organization, and program details of CR units in Italy.

Considering the increasing burden of CVD, from an economic perspective and taking into account the increasing pressures facing health systems, cost-effectiveness is an essential consideration for CR program development. Previous data on economic evaluations of HBCR have found positive effects compared to traditional care, although the heterogeneity in methodologies may limit the validity of these findings [16,17].

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Mobile Health for CR

Advances in mobile networks and the proliferation of smartphones and tablet devices constitute a global service delivery platform for many industries, including health care, and could offer the potential to broadly diffuse more intensive self-monitoring, feedback, and self-management tools at reduced cost. The increase of mobile health care devices and software has greatly extended self-care capabilities across the spectrum of health care activities. Current smartphones allow users to easily access a wide range of health educational materials and services anywhere at any time. Health apps running on smartphones or other portable devices enable the remote monitoring of vital parameters to diagnose health problems, track responses to treatments of chronic illnesses, detect drifts from the control condition, and provide early warning signals of potentially dangerous changes in a patient's health status. In this context, mobile phone interventions have become increasingly popular in the global health and development sectors as a potentially inexpensive and effective way to communicate with and deliver services to people. In particular, telemedicine offers the possibility of the prolonged longitudinal monitoring of patients, which would help to highlight early and subclinical signs of diseases or complications that could manifest at a later date, and thus allow therapeutic intervention at a stage of higher reversibility. In this field, where CR is needed but insufficiently implemented, alternative rehabilitation models using new resources of communication technologies (eg, mobile- and web-based platforms, wearable sensor devices) is a new challenge to deliver supervision, education, and counseling. With these technologies, it will also be possible to consent and improve continuity of care in vulnerable populations.

HBCR, as a branch of telehealth, can be optimized and facilitated with the use of remote telemedicine devices [18]. However, some studies demonstrated that there are no substantial differences in rehabilitation programs practiced using telemedicine or according to conventional protocols in terms of functional improvement, control of risk factors, well-being, and rehospitalization and survival rates [19-21]. In contrast to CBCR, HBCR associated with telemedicine appears to be able to improve some of the shortcomings of traditional rehabilitation programs [22]. These traditional services are often associated with high costs, both to the health care system and to the patient who must make multiple trips to the rehabilitation center during the treatment process or needs to be admitted directly to intermediate care facilities dedicated to rehabilitation only.

The Box 2.0 Study Protocol is an ongoing trial with the objective of achieving the early diagnosis of complications after cardiac surgery (for atrial fibrillation, heart failure, and surgical wound infections) through the application of telemedicine and mobile devices (ie, smart technology) [23]. In particular, the Box 2.0 study is focused on the use of smartphone apps for the remote assessment of certain vital signs, including oxygen saturation, electrocardiographic tracing, arterial blood pressure, body temperature, body weight, and actigraphy. In general, the availability of remote monitoring of the patient makes it possible to customize CR programs according to the limits and functional capacity of each patient, thereby increasing adherence to the suggested rehabilitation program. In practice, telemedicine allows the realization of a patient-centered rehabilitation approach, which is an essential element of precision medicine [24]. This practice aims to encourage the independence of patients, including older adults, which would allow them to stay in their familiar environment while maintaining an acceptable quality of life.

Although HBCR based on a patient-centered perspective is capable of improving the participation rate, the effectiveness and achievement of the program depend on the patient's attitude toward technology. In recent years, technology use in health management has involved populations of all age groups; however, the age group of 65-74 years represents the principal consumers of health digital tools, with higher adoption than found among those aged 18-34 years. Specifically, in the cardiology field, cardiac telerehabilitation is a mobile health tool that uses telecommunication technologies such as smartphone apps, wearable devices, and video consultations to propose remote CR services to increase convenience for patients while reducing health care costs. In addition, HBCR may bypass several barriers at the patient level, including transport difficulties; at the health care professional level, such as low endorsement; and at the health care system level, mainly due to limited facilities available providing this method. Furthermore, administering rehabilitation pathways outside the hospital environment by using remote monitoring and communication devices with patients would enable the acquisition of data (eg, heart rate during exercise and daily physical activity) in the context of the patient's daily routine; thus, the data collected will be more realistic, enabling designing a more personalized treatment program.

Study Aim and Objectives

The Innovation in Postoperative Rehabilitation Training and Monitoring (IPOTERI) study aims to create a tailored CR intervention using a mobile platform to support treatment during the postsurgery period with the goal of achieving the improvement of clinical and functional parameters and quality of life. The overall objective of the project is the analysis, design, implementation, and testing of a composite and integrated system for postsurgical rehabilitation therapies, specializing in cardiac surgery.

The project envisages the development and industrialization of a monitoring system that applies telemedicine techniques, combines microservices with innovative devices (ie, wearable and minimally invasive devices), and enables the continuous monitoring of the patient's main vital parameters to provide real-time feedback during the execution of the rehabilitation exercises assigned to the patient in the individual phases of the rehabilitation therapy. This will be achieved through the implementation of software systems capable of not only supporting the rehabilitation pathway but also of enriching the program with innovative devices and eHealth services. This system can help to support additional and alternative pathways to traditional hospital pathways and will be further capable of integrating artificial intelligence (AI) techniques that support physicians in telemonitoring.

The hypothesis of the clinical study is that processing of data, both qualitative and quantitative, collected at home during the

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postsurgery period using eHealth devices, together with clinical data related to the perioperative time window using AI algorithms will be an effective approach for personalizing and then optimizing a postsurgery CR path. We here describe the protocol for the design, realization, and clinical testing of a composite and integrated system for postsurgical rehabilitation therapies at home focused on cardiac surgery.

Methods

Ethical Considerations

The research and ethics described in this study have been reviewed and approved by the institutional review board of the Ethics Committee of the Vast Area Northwest of Tuscany for Clinical Trials (protocol 20406). All procedures performed in the pilot study will be in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All participants will provide written informed consent after a thorough review of procedures and questions and will be informed of their opportunity to opt out of the study at any time. All study data will be deidentified. No participation fee will be given to the patients, and all patients will enroll in the study voluntarily.

Setting

The IPOTERI project is a public-private partnership comprising a multidisciplinary team, including research centers, health care facilities, technological enterprises, and cybersecurity experts.

General Aspects of the IPOTERI Rehabilitation Platform

Platform Design Process and Overview

To define the best configuration of mobile support services for patients, we used the following methodology:

1. Formative research to determine the best way to implement HBCR, including a literature review, retrospective analysis of clinic data, and evaluation of eHealth devices potentially included in HBCR.
2. Development of the HBCR intervention: we implemented a software system that can support the rehabilitation pathway, but also enriched it with innovative devices and eHealth services that support the doctor in telemonitoring.
3. Pilot feasibility study: we will conduct a pilot study with patients who will receive the intervention to provide a context for testing the developed systems on a larger population sample.

The components of HBCR consist of a telemonitoring platform, an intelligent home station, and a decision support system (DSS) (Figure 1).

Figure 1. General architecture of the IPOTERI system. DSS: decision support system; C7: medical records; ECG: electrocardiogram.

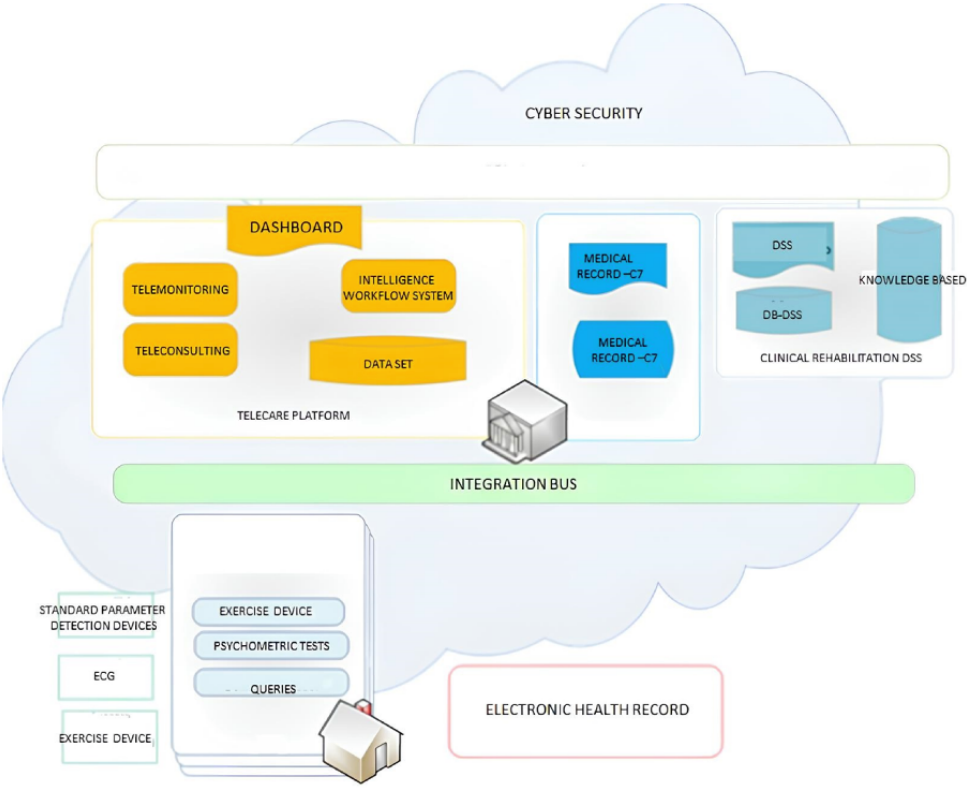

Telemonitoring Platform

The IPOTERI platform guarantees continuity of postoperative care and includes the following main functions: (1) activation of the telemonitoring process with detection of vital parameters, also in continuous mode, according to a protocol set by the doctor; (2) monitoring of rehabilitation activity, with feedback on the quality of exercise; (3) management of alerts for home events; and (4) verification of the adequacy of the patient's vital

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parameters and adherence to the proposed rehabilitation program through AI techniques.

The IPOTERI platform is divided into different levels: (1) the at-home level with the Intelligent Home Data Acquisition System; (2) the territorial level with the "Telecare Platform" system, a centralized system for collecting and analyzing data from patients' homes and hospital records; (3) the central level with the intelligent BUS system for connecting the components of the overall system; and (4) the hospital level with an integrated electronic medical record system that operates autonomously in the hospital and manages the clinical data of patients enrolled in the study.

Smart Home Station

The smart home station (SHS) is based on an Android app with a user-friendly interface for the self-recording of patients' vital signs. The interactive part is supported by a dashboard, as shown in Figure 2. From this dashboard, the patient can access the planning of rehabilitation activities and their illustrations by means of videos and also can request a video consultation or participate in activities planned by the doctor. The SHS is also able to integrate data and information from wearable and noninvasive devices to enable the continuous monitoring of vital parameters and support the performance of assigned physical rehabilitation activities. The devices consist of a wearable, noninvasive sensor capable of continuously recording vital parameters such as electrocardiogram (ECG), heart rate, blood pressure, and oxygen saturation, and a weight balance to detect weight variations. The SHS consists of medical devices integrated with two apps: eVoDroid that is integrated with the weight balance and Umana that is integrated with the Umana T1 sensor for ECG monitoring. The eVoDroid system is an app used to receive data via Bluetooth synchronization with integrated devices; the app detects the sensor and the acquired data are displayed in the appropriate fields. It is possible to repeat the measurement, confirm it, and cancel it. There is also a manual data screen, allowing the user to add the data directly. After specifying the type of measurement, the obtained values can be input in the editable fields provided. The Umana app allows data to be received via Bluetooth synchronization with the T1 heart monitor. Once the connection is established, continuous real-time monitoring of the ECG signal and the display of other parameters, including heart rate variability, oxygen saturation, and blood pressure, are possible. The saved data are sent to a server for further analysis of the detected signal.

At the territorial level, a dedicated "patient portal" has been defined in the Telecare Platform to carry out different activities (eg, view the agenda, carry out televisits, request a consultation) related to the rehabilitation plans along with associated video tutorials (Figure 3).

Figure 2. Smart home station. BPM: beats per minute; SpO2: peripheral capillary oxygen saturation.

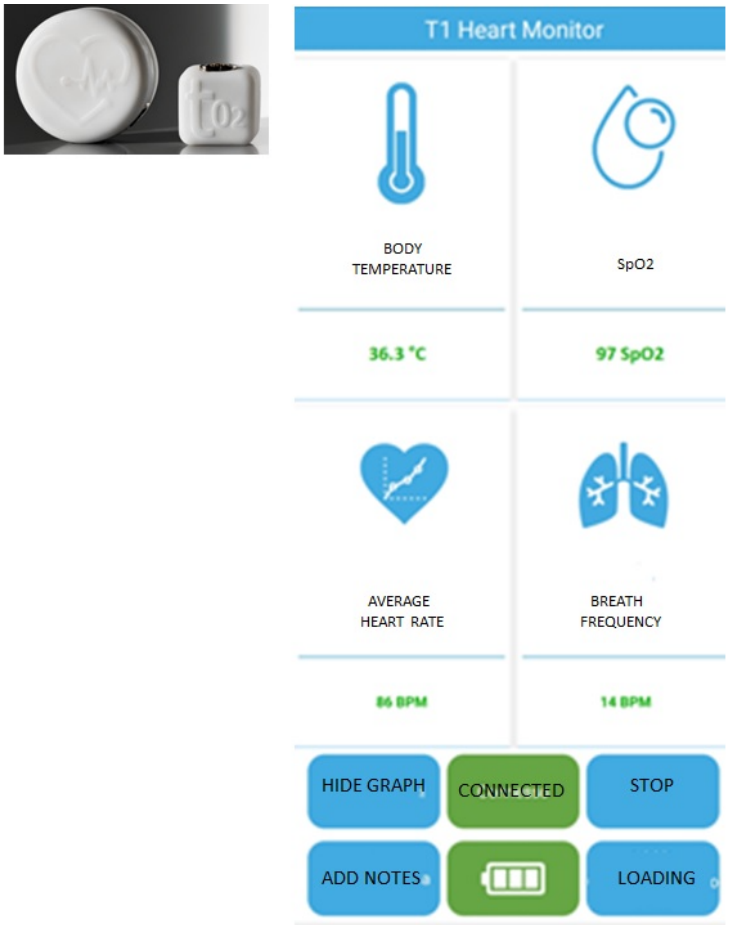

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Figure 3. Telecare Platform for access to rehabilitation plans and related video tutorials.

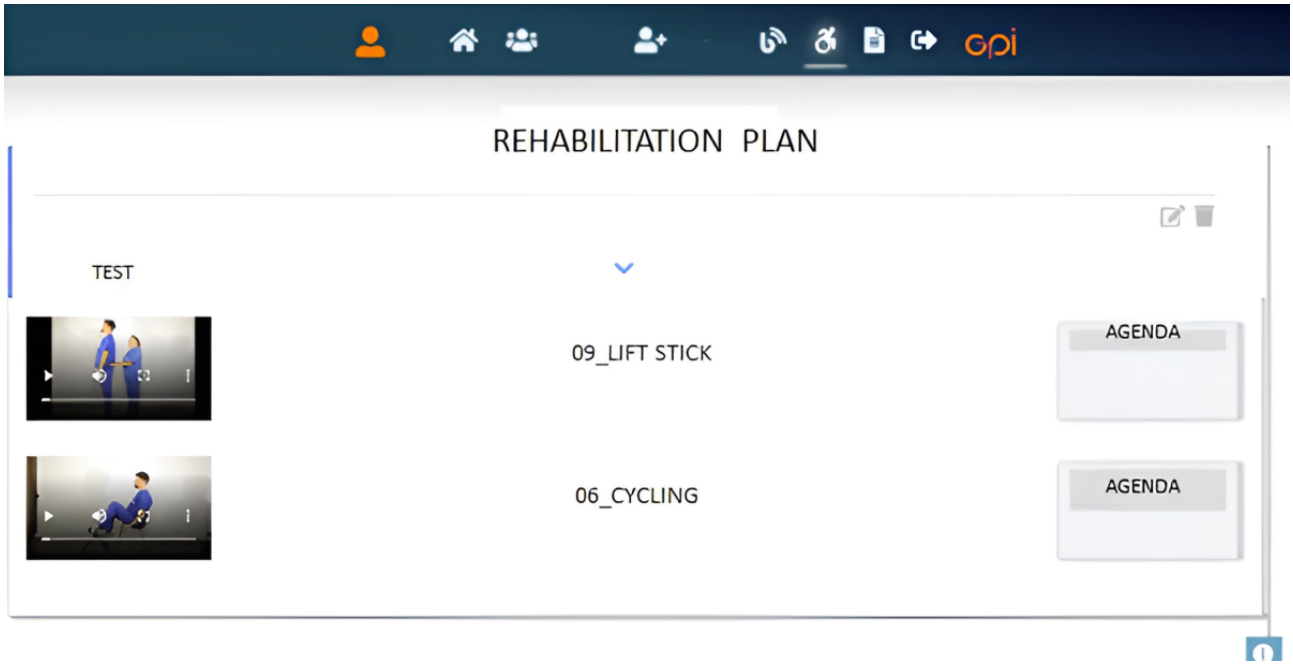

Clinical Rehabilitation DSS

The DSS facilitates the analysis of data collected during the telemonitoring process with hospital clinical data. The DSS communicates with hospital medical records (Figure 1) to transmit alerts and specific support information for the formulation and updating of the treatment and care plan (Figure 4).

Figure 4. Clinical rehabilitation decision support system.

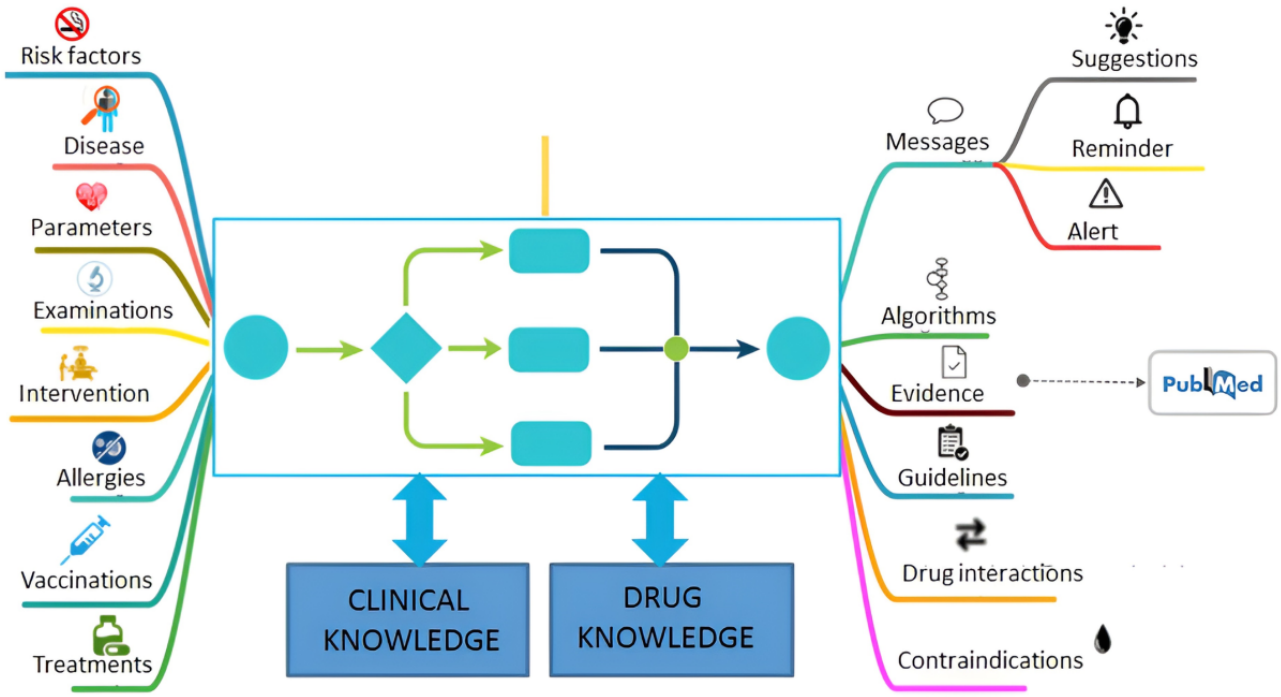

Pilot Test

Study Design and Aims

In the pilot test, patients will be enrolled among those receiving coronary-artery bypass grafting without complications in the postoperative period. During this pilot study, we will receive reports of several technical issues that could affect the functionality of the system. Thus, the data obtained in the pilot study will serve as a guide in the development of a telemonitoring system, including a software and hardware platform based on telemedicine monitoring microservices, to be applied within the project to a wider population.

Pilot Population to Test the IPOTERI Platform

The study participants will be divided into two groups: (1) an HBCR group and (2) a control group with the same clinical profile. The HBCR group will include all patients who will

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undergo cardiac surgery procedures and will be submitted to telemonitoring. The control group will be established to have the same clinical profile as the HBCR group but without telemonitoring to serve as a comparison group. The inclusion criteria are as follows: 18 years and older, no major complications after surgery, and good internet connectivity at home. The main exclusion criteria are stage 4 renal failure or undergoing dialysis treatment, overt chronic respiratory insufficiency, previous cerebral ischemic or hemorrhagic event, and cognitive impairment. Allocation to the HBCR group will be based on the patient's preference.

Procedure

After obtaining informed consent, preintervention clinical data will be collected, including anamnestic and instrumental data as well as predischarge data (Figure 4). At 7 to 21 days after discharge, patients will return to the hospital and will be submitted to a functional assessment by performing an aerobic exercise test, the 6-minute walking test (6MWT), according to a standard protocol. The patient will walk along a flat, hard, and measured corridor, with cones marking the turning points set by a physiotherapist [25]. The heart rate, distance traveled, arterial saturation, symptoms, and blood pressure will be monitored at the beginning and end of the exercise according to the normal clinical practice of the 6MWT. The step rate, expressed as the number of steps per minute, and the total number of steps will also be recorded. Heart rate and step rate will be recorded at the onset of symptoms and in the early stages of the exercise. The pace will be measured at the onset of symptoms and in the first 3 minutes of exercise according to the exercise table prescription.

Quality of life will be assessed based on the Psychological General Well-Being Index questionnaire [26]. During the entire monitoring period (12-14 weeks), a patient, doctor, or rehabilitator will be able to activate the teleconsultation services via a home kit. At the end of the study period, patients will undergo hematochemical examinations, echocardiogram, and functional assessment with the 6MWT. Patients who will be recruited and included in the personalized rehabilitation plan will be instructed on how to perform the functional test at home, which is aimed at assessing their rehabilitation progress and to help customize the rehabilitation program. The patient will be able to choose an exercise modality involving free walking outdoors or indoors, using an exercise bike, or a walker. If the patient performs the aerobic exercise by walking, they will be required to maintain a specific cadence or heart rate throughout the exercise. The rehabilitation program will be set based on these measurements at 60% of the walking cadence or maximum frequency reached for the first week, 70% for the second week, 80% for the third week, and 90% for the fourth week. The patient should exercise for at least 20 minutes in the first week and for at least 30 minutes per day in the following weeks. If the patient has difficulty maintaining the prescribed training goals, they will have the opportunity to interact with the doctor who can either maintain the current step increase in activity or go back one step. The rehabilitation exercises will be monitored and customized during the rehabilitation pathway through feedback with the rehabilitation therapist who will have the possibility to connect with the patient and review the execution of the exercises through the devices in the kit.

During this period, vital parameters such as ECG, respiratory rate, blood pressure, body temperature, and oxygen saturation will be recorded. All data from the rehabilitation phase will be collected and stored on the information and communications technology (ICT) platform and made available to the patient via a tablet gateway connected to the data collection center. The medical and rehabilitation staff may consult the acquired data to modify the rehabilitation program based on cardiac parameters, exercise perception, and general well-being.

At the end of the rehabilitation period, patients will undergo routine hematochemical examinations, echocardiogram, and functional assessment by the 6MWT, and they will complete the quality of life questionnaires again. In the 4th week, the patient will be tested at home by performing a walk at the maximum possible speed on a flat surface, either outdoors or indoors, for 6 minutes. During this exercise, the system will measure the continuous heart rate, respiratory rate, step rate, and oxygen saturation, and the data obtained will be used by the doctor and therapist to assess any changes in the exercises compared to the baseline examination. Based on this assessment, the doctor could decide to increase the intensity of the aerobic exercise to be performed by the patient, as described above. All data from the rehabilitation phase will be collected and stored on the ICT platform and made available to the patient via a tablet gateway connected to the data collection center. These acquired data will be available for consultation by medical and rehabilitation staff to modify the physical rehabilitation program on the basis of cardiac data, perception of effort, and general well-being.

At the end of the trial, a questionnaire will be filled out to assess the ease of acquisition of the proposed system, the ease of data transmission, and the level of comfort in managing rehabilitation with the help of the devices for the monitored patients. In addition, intervention satisfaction will be assessed with the following two items: "Overall, how satisfied are you with the IPOTERI tool?" and "How satisfied are you with the possibility of jointly participating in the IPOTERI therapy?" Fatigue severity will be assessed using the Borg rating of perceived exertion scale [27]. The scale is a very simple numerical list. Participants are asked to rate their exertion on the scale during the activity, taking into consideration feelings of physical stress and fatigue, disregarding any factor such as leg pain or breathlessness but focusing on the whole feeling of exertion.

AI Tools

The application of data-driven, machine learning (ML)–powered AI tools to the data collected will help to determine patterns, assess patient stratification, or compute meaningful indices for the clinicians to interpret. In the case of an insufficient population size, data *verticality* (ie, the amount of data *per patient*), or data heterogeneity, specific ML techniques will be used to enable the subsequent definition and testing of clinically relevant tasks once the data become sufficient. More precisely, an important step will be to provide appropriate *patient embedding*, which is paramount to unlock the ability to quickly and easily define and test prediction tasks over the patient

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population at a later date. *Embedding* a patient's data involves converting all of the data available for a patient into a fixed-sized vector (ideally of smaller size), which can be used to train ML models (ie, classifiers and clusters) once a sufficient number of patients are available for formal analysis.

Embedding is often performed by *encoders*, which are neural networks that are trained to perform a relatively straightforward task (eg, perform the identity function in the case of *autoencoders*), featuring an architecture with a relatively small internal layer of nodes. These nodes are therefore forced by the training process to "encode" the information presented at the input stage in a fashion that is appropriate to perform the task at hand. Encoders are used in lossy compression such as for feature extraction and several other tasks. In this study, we can use encoders to obtain a compact and actionable patient representation among all heterogeneous data types available for each patient.

Results

The pilot test started in June 2023 (protocol number 20406/2021) including 50 patients who will be monitored for 12-14 weeks using the developed platform, as described in the Procedures subsection of the Methods section.

Discussion

Projected Significance

This pilot study is designed to assess the acceptability, potential efficacy, and potential working mechanisms of the IPOTERI platform, a web-based tool for a postsurgery CR intervention.

To our knowledge, IPOTERI represents the first pilot experiment of the Italian experience of an HBCR program associated with telemedicine monitoring in a patient group who underwent cardiac surgery. The aim of the IPOTERI project is to develop a home-based patient telemonitoring system with the final goals of reducing the number of hospitalizations and outpatient visits, improving the communication between patients and hospital staff, and improving the psychological and emotional dimensions of CR. In the pilot study, we will provide a comprehensive description of the different components of the IPOTERI platform and the first release of the platform from patient enrollment to the rehabilitative program. The availability of remote patient monitoring will make it possible to customize CR programs according to the individual patient's functional limitations and capabilities. In turn, this would have the advantage of increasing adherence to rehabilitation programs.

In practice, telemedicine enables the realization of a "patient-centered rehabilitation approach," which is an essential element of precision medicine [28]. Moreover, prolonged monitoring of multiple physiological parameters of the patient can facilitate establishment of a large data bank, both in qualitative terms (number of variables) and quantitative terms with the same variable monitored over time. The accumulation of big data will necessitate the application of ML algorithms to integrate and analyze the data with a complex and dynamic approach. In this field, AI represents a potential new avenue for the integrated analysis of clinical, instrumental biohumoral data acquired longitudinally that are currently in the DSS along with data collected at single time points.

The requirement for AI in this context is becoming increasingly relevant in the age of telemedicine, which will facilitate the collection of a considerable amount of data, especially in the case of cardiovascular medicine given the complex and multifactorial physiopathological mechanisms underlying CVDs [29,30]. Scientific evidence already exists on the potential applications of AI in cardiology, using both structured and unstructured data, including data obtained from cardiac imaging methods and from eHealth devices [31-34]. For example, a recent position paper of the European Preventive Cardiology Association emphasized the usefulness of AI for the development of algorithms to improve an individual's response to exercise so as to optimize CR in the prevention and treatment of CVDs [35].

Furthermore, the introduction of AI techniques has made it possible to develop predictive variables for outcomes of interest such as adherence to a rehabilitation program and quality of life, which would otherwise likely be neglected because these have not been considered conventional clinical parameters [36].

Limitations

Although IPOTERI is a noninvasive technique offering a highly novel and potentially beneficial rehabilitation program, some patients may not be open to adopting this different approach and may prefer other traditional treatments. Moreover, although IPOTERI might improve patients' perceived well-being as the patient feels monitored, the scalability of this approach to clinical parameters is still unclear. There is a potential limitation related to the approach that could affect the adherence to the rehabilitation protocol. The results, rather than being related to methodological correctness, may be related to the usability of the different devices by the patients, who are often disinclined with technology. One way to reduce this problem will be to have the protocol managed by highly qualified operators, training patients appropriately, and enrolling them voluntarily according to a certain predisposition to using such devices.

Conclusions

The CR tool presented here could be feasible, safe, and comparable to the traditional in-hospital rehabilitation approach, indicating that rehabilitation after cardiac surgery can be carried out at home if planned with an integrated and user-friendly telemedicine service. The IPOTERI approach based on the processing of data, both qualitative and quantitative, recorded during the use of telemedicine monitoring devices at home by a patient during rehabilitation following cardiac surgery, together with clinical data referring to the perioperative and postoperative periods could have potentially positive effects on adherence to the rehabilitation program and clinical improvement, as well as in terms of quality of life. This project aims to evaluate the impact of telemedicine platforms on patients during postoperative rehabilitation. The possibility of adopting the same program in different contexts warrants future studies on a larger population to explore the actual effectiveness of telemedicine-based CR programs. The IPOTERI platform will be tested in only patients with a stable status; thus, future

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developments could consider the application of this platform in the management of patients with postoperative complications. Studies are also needed to assess the possibility of adopting the same program in different clinical settings, considering the possible implementation of hybrid CR models including components of both CBCR and HBCR.

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Conflicts of Interest

None declared.

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Abbreviations

6MWT: 6-minute walking test
AI: artificial intelligence
CBCR: center-based cardiac rehabilitation
CR: cardiac rehabilitation
CVD: cardiovascular disease
DSS: decision support system
ECG: electrocardiogram
HBCR: home-based cardiac rehabilitation
ICT: information and communications technology
IPOTERI: Innovation in Postoperative Rehabilitation Training and Monitoring
ISYDE: Italian Survey on Cardiac Rehabilitation
ML: machine learning
SHS: smart home system

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Protocol

Constructing TheKeep.Ca With Thrivers of Cancer in Manitoba, Canada, in Support of Enhancing Patient Engagement: Protocol for a Pragmatic Multimethods Study

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Abstract

Background: TheKeep.Ca was built to facilitate engagement with those experiencing cancer in Manitoba, Canada. Constructed between 2020 and 2024 with a group of patient advisors, the website includes information on engagement activities including research participation, the patient advisor role, and how those experiencing cancer can access these Manitoba activities. A link allows visitors to register to be contacted about activities that match their demographics, cancer history, and activity preferences. After TheKeep.Ca was constructed, this protocol was developed to establish TheKeep.Ca as a platform for scientific research focused on optimally engaging those experiencing cancer.

Objective: We asked the following questions: (1) What was the patient advisors' experience who participated in developing TheKeep.Ca? (2) What are the baseline characteristics of website traffic and registrants at TheKeep.Ca? (3) How does registering with TheKeep.Ca impact the cancer experience?

Methods: The planned launch date for the website and initiation of research activities is January 2025. For objective 1, the active patient advisors (N=6) participating in the website project will be invited to participate in project activities including with responses to a question prompt sheet, semistructured audio-recorded interviews, or both. Responses and interviews will be analyzed using reflexive thematic analysis to understand and inform practices for patient engagement on projects. At the website launch, TheKeep.Ca will become publicly accessible and indexable on internet search engines, but no additional promotional interventions will take place in the initial 6 months resulting in visitors primarily from web search traffic. For objective 2, Google Analytics and website registrant data collected during the first six months will be analyzed to obtain baseline characteristics of website visitors. For objective 3, an online survey will be emailed to registrants six months after the website launch characterizing their website experience, the activities they participated in, and collecting feedback on the website. For objectives 2 and 3, quantitative data will be analyzed using both descriptive and inferential statistics, and qualitative data from open-ended questions will be analyzed using thematic analysis guided by an inductive descriptive semantic approach.

Results: This study was approved by the University of Manitoba Health Research Ethics Board on December 12, 2024 (HS26614-H2024L263). Institutional approval from CancerCare Manitoba is pending as of December 23, 2024. Findings from objective 1 are expected to be finalized within the first six months after the website launch. Those from objectives 2 and 3 are expected by the 12-month mark. Reporting will include peer-reviewed journals, conferences, and a lay-language summary on TheKeep.Ca.

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Conclusions: The research outlined in this protocol will facilitate understanding patient advisors' experience in developing TheKeep.Ca. It will also characterize the website' effectiveness and its impact on the cancer experience, providing a baseline and direction for future research and development.

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KEYWORDS

patient engagement; patient empowerment; translational research; patient recruitment; development and research; protocol; Manitoba; Canada; cancer; patient advisor; website; research platform; thematic analysis; semi-structured interview; online infrastructure

Introduction

Background

The experience of living with cancer is not uniform, and not limited to patients currently receiving treatment. Comprehensive definitions of survivors of cancer include not only those receiving active treatment, those diagnosed and treated in the past but also the friends and family that support them [1]. Similarly, as a leading cause of morbidity and mortality for the global community, cancer does not selectively impact a specific population defined by race, lifestyle, or geographic location.

Because cancer can, and does, impact every human community, engaging with those impacted by cancer, in a way that seeks to understand how cancer services can be improved to provide optimal biomedical care in a way that is respectful, equitable, and supportive of the diverse lifestyles and identities of those living with cancer is essential for the promotion of ethical human care. Nonclinical trial research and work designed to obtain feedback from those with lived experience (eg, such as patient advisors) on service delivery initiatives are two ways that health care professionals can learn how cancer services can be developed to support better the diverse community of those impacted by cancer. However, identifying survivors of cancer to participate in such work can be challenging.

This project started with the goal of creating a website for connecting those experiencing cancer in Manitoba, Canada, with opportunities to improve the cancer journey for others. The website would allow interested survivors of cancer (1) the opportunity to join a database that would facilitate their voluntary participation by notifying them about emerging patient engagement opportunities in Manitoba such as nonclinical trials research or to function as patient advisors. Such a website would facilitate engagement with the Manitoba population with cancer without impacting other existing programs, including clinical service delivery, in the province. The website would be a platform used to study how to better recruit individuals for cancer research; (2) and a tool for rigorously exploring how online approaches can be used to overcome challenges to achieving representative engagement with Manitoba's diverse population with cancer that includes, but are not limited to, Indigenous peoples, recent immigrants, and those living in urban, rural, and remote communities.

Understanding Barriers to Recruitment for Nonclinical Trials Research

Language barriers, lack of infrastructure, costs related to advertising and supporting accessibility, and the functional capacity of participants living with illness are just some of the barriers that can impact the recruitment of representative samples for all types of research work [2,3]. In contrast to clinical trial research, which is generally integrated into the participants' health care, conducted by well-established teams with dedicated infrastructure to support participant recruitment, and comes with the incentive of possibly receiving an experimental intervention that may be superior to the standard of care [2], nonclinical trials researchers face unique challenges. Nonclinical research, such as qualitative and quantitative survey research, as well as longitudinal observational studies, often function with less infrastructure support, clear benefit to the participant, and require commitments on behalf of the participant outside of their responsibilities as recipients of clinical care [4].

Additionally, nonclinical trial studies are often "one-offs" undertaken by trainees, such as graduate and postgraduate researchers, as part of the completion of educational programs. Those responsible for the success of such projects (ie, the trainee) may have less access to gatekept patient populations and other supportive infrastructure, such as research nurses [2]. Unfortunately, these barriers likely result in fewer high-quality research projects, ultimately involving smaller, nonrepresentative samples, and delays in project completion—negatively impacting the quality and diversity of the scientific literature, accessibility to potential participants who may find benefit in participating in such research projects, and the professional trajectory of talented researchers.

Exploring Barriers to Patient Engagement

Outside of the research recruitment setting, for health care teams, including clinicians, researchers, and administrators, being able to connect with a diverse group of individuals with lived illness experience is becoming increasingly recognized as valuable for program development and improvement [5]. Engagement with individuals functioning as patient advisors to inform project planning, research design [6,7], and infrastructure development is increasingly recognized as an essential process for evolving patient-centered care [5,8,9]. However, as an area of research, understanding how to effectively identify, recruit, and engage with individuals is still evolving [5,10,11]. For instance, it has been suggested that patient advisors may be more likely to be individuals that are passionate about engaging with the health

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care system than the average patient, resulting in the population of individuals that is engaged with patient advisory work being less likely to be representative of the general patient population [8].

Important work is being carried out to explore how to create better and more meaningful patient engagement opportunities. For instance, aspects of patient engagement such as the timing of activities concerning project lifecycle [6], mitigating power imbalances [11,12], and evaluating outcomes of patient engagement [9] have an evolving body of literature in the spirit of moving from passive to authentic patient engagement [5,9,10,12]. However, questions related to recruitment for engagement appear to be less robustly addressed. A recent systematic review including 142 studies explored patient engagement as a part of research [9]. While the review did identify several different ways that participants were identified, including internet postings, paper advertisements, and invitations from clinicians, studies involving a specific analysis of the impact of different approaches on recruitment effectiveness were not found [9]. As identification of individuals for patient advisory work is often not embedded in the clinical practices of frontline care providers, it is likely that many of the same challenges to recruitment that face nonclinical trial research exist for patient engagement. Work exploring which recruitment approaches for patient engagement are most effective, and how these approaches enable engagement with different populations is important.

Using Online Infrastructure to Optimize Engagement

Using physical spaces primarily intended for clinical service delivery presents challenges for meaningfully engaging with patients and their friends and family about topics not directly related to patient care. In these clinical areas, such as in ambulatory oncology clinics, patients and their accompanying friends and family members may be already overwhelmed with information regarding their disease and its management [13]. On the other hand, online web spaces can be more easily purpose-built around the needs and interests of those experiencing specific aspects of an illness journey and can be accessed after clinical visits have concluded, during times convenient to the individual [13]. Importantly, the population with cancer is well documented to rely heavily on online information as part of the cancer journey, with some studies demonstrating daily rates of internet use related to cancer exceeding 80% [14]. If carefully developed to meet the needs of those living with cancer, online spaces may be effective at supporting engagement between those living with cancer and health care professionals working to evolve the cancer journey.

Research Objectives

This protocol outlines how a website intended to support and provide meaningful patient engagement will be studied to advance the science of effective engagement with those living with cancer. As outlined below, TheKeep.Ca website was developed through collaboration with a team of dedicated patient advisors with the aim of creating a webspace to facilitate connecting researchers and health care teams with those who have lived cancer experience as well as providing meaningful resources for those living with cancer in Manitoba and beyond. In addition to helping TheKeep.Ca evolve to better serve the needs of the cancer community in Manitoba, the outcomes from exploring the research objectives outlined in this protocol are intended to provide useful guidance for those intending to embark on pragmatic longitudinal patient engagement projects, such as the development of patient-centric websites, and contribute meaningful findings to the scientific literature regarding how to best engage, online, with those experiencing cancer.

Research Questions

1. What was the experience of the patient advisors who participated in the development of TheKeep.Ca?
2. How effective is TheKeep.Ca at engaging with the population with cancer in Manitoba in the six months after going live?
   - What are the characteristics of website visitors?
   - What is the conversion rate from unique website visitors to website registrants?
   - What are the characteristics of registrants on the website database?
3. How do the patient engagement activities that TheKeep.Ca facilitate impact the cancer experience for website registrants?
   - How does participating in engagement activities promoted by TheKeep.Ca impact the cancer experience?

Methods

Building TheKeep.Ca

Before initiating research activities, TheKeep.Ca website was developed over 4 years through several steps (Figure 1A). After funding had been obtained for the project, patient advisors, including past and present patients with cancer at CancerCare Manitoba (CCMB), were invited to join a patient steering committee to guide the project that was facilitated by the lead author (MT). The patient advisors were recruited both through the CCMB patient advisor program and by psychosocial staff at CCMB.

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Figure 1. Development of TheKeep.Ca and proposed research activities. (A) TheKeep.Ca was developed over 5 years with a group of patient partners beginning in 2020. Patient partners informed goals for the website, content development, research priorities, and methods. (B) In the six months following the website launch, the patient advisors' experience of being involved in TheKeep.Ca project will be explored using a qualitative approach. Six months following the launch, data from the registration surveys and Google Analytics will be used to characterize the website's effectiveness in engaging with the survivors of cancer population in Manitoba. A survey exploring the impact of registration on the TheKeep.Ca website will also be deployed at the 6-month mark with the results used to address the impact of the website on the cancer experience.

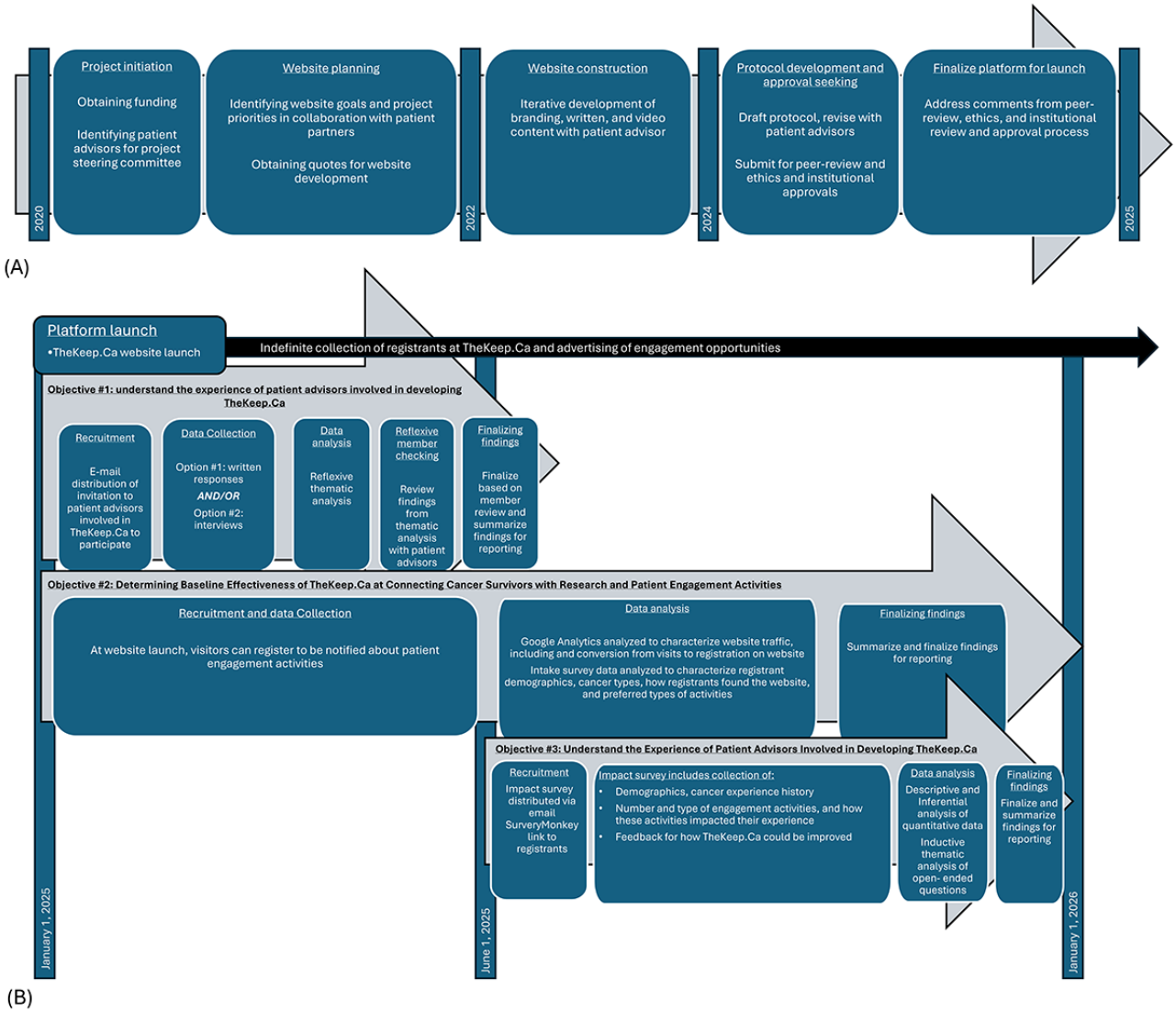

Through videoconferences, emails, and an online discussion board, the priorities for the website were identified by the steering committee. These included items to satisfy the requirements of the secured funding (ie, a website to inform website visitors about the role of being a patient advisor, a research participant in nonclinical trials research, and a method to populate a database of individuals interested in participating in these roles). Additionally, while the patient advisors identified several important components that could be added, developing a resource directory of supportive care for cancer resources to be hosted on the website curated by patients was selected as the initial patient advisor-championed project to be included on the website.

After the steering committee was formed and the key components were identified, the website was developed in coordination with a professional media design firm (Argyle Media Inc). Facilitated by the lead author (MT), the patient advisors on the steering committee participated in all aspects of developing the website branding, including providing both initial ideas and iterative feedback to the media firm for the logo and site design. Additionally, the patient advisors also participated in content creation for the website, including working alongside a freelance videographer and 2 science communication writers.

In total, 10 current or former patients were involved in the project, however, 4 left the project during its course for reasons including, but not limited to, competing priorities and changes in health status.

Studying TheKeep.Ca

Once the website was completed, this protocol was developed. Feedback was obtained from the patient advisor steering committee regarding what research objectives they considered important to include regarding the value of a patient engagement website. The protocol was developed by the lead author (MT) and last author (DEM), and then reviewed by the patient

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advisors, with revisions to this study's tools and methods made in response to their feedback before submission for peer review.

A schematic outlining the timeline for the activities described in this protocol is presented in Figure 1, including the development of TheKeep.Ca (Figure 1A) and the research activities proposed in this protocol (Figure 1B).

Research Objective 1: What Was the Experience of Participating in Developing TheKeep.Ca?

The patient advisors who continue to participate in the development of TheKeep.ca (N=6) through membership in the patient engagement steering committee will be invited to share their experience of partnering in the development of TheKeep.Ca. This will be completed within the context of a research study as a voluntary activity. Those who are interested in participating will be invited to contact the last author (DEM) of this protocol, who will obtain informed consent (Multimedia Appendix 1 for the consent form). They will then receive a short intake questionnaire to collect demographic information and details about their cancer experience (Multimedia Appendix 2).

Those who express interest in providing a voluntary written sample following the informed consent process will be provided with a question prompt to provide open-ended written responses (Multimedia Appendix 3). For those who consent to participate in a voluntary semistructured interview, an audio-recorded semistructured interview (estimated duration 60 to 90 minutes) will be conducted following the collection of all written responses. The semistructured interviews will be guided by an interview guide (Multimedia Appendix 4). The question prompts (ie, Multimedia Appendices 1 and 2) were developed by authors MT and DEM, based on feedback MT had received from the patient advisors on the steering committee involved in the project, and reviewed and revised by the steering committee before finalizing this protocol. Transcripts of the audio recordings will be prepared using a professional transcription service (ie, Scribie), and both the written survey responses and interview transcripts will be deidentified before analysis.

Reflexive thematic analysis (RTA) [15] will be used to analyze the data collected. RTA is a nuanced iteration of the thematic analysis approach initially described by Braun and Clarke [16]. Specifically, RTA explicitly addresses several methodological questions that have been identified since the initial publication describing thematic analysis by Braun and Clarke [16]. Specifically, RTA is not considered a positivistic, descriptive, rigid methodology. Instead, it embraces constructivism, an inductive flexible approach to data analysis, consideration of latent meaning, and an emphasis on the interpretation of the data by the researcher [15,17]. Compared to other iterations of thematic analysis, RTA was chosen because the experience of the patient advisors involved in the development of TheKeep.Ca was thought to be complex, with many aspects likely to be unknown a priori to the researchers, requiring more than a descriptive summary of the data collected to provide a meaningful exploration and contribution to the literature.

The steps for data analysis will be in keeping with those described for RTA [15-17], progressing in a relatively linear manner through six phases including (1) familiarization with the data once data collection is completed, (2) generating initial codes using line by line coding, (3) generating themes, (4) reviewing potential themes, (5) defining and naming themes, and (6) producing the report. In keeping with a nonpositivistic stance, the volunteers from the steering committee will be invited to provide member reflections in a group setting as part of phase 6 once a preliminary version of the report is ready. The purpose of this activity will be to "explore gaps in understanding … and consider how to acknowledge and present these in the written report" [15], as opposed to validating findings. The final report will be revised to reflect the findings from this final group activity.

Rigor and Trustworthiness

The trustworthiness of the research findings will be facilitated by ensuring practices that enhance credibility, transferability, dependability, and confirmability [18,19]. Prolonged engagement with this study's participants and data, as well as a review of study findings with participants before finalizing study results, are techniques that will be used to address the credibility of the findings. By providing a rich description of the data, the contexts in which it was collected, and the resulting findings, as well as by considering both latent and semantic themes, the transferability of this study's findings to other contexts related to patient engagement will be supported. Dependability will be supported by recording written field notes in addition to the audio recording of semistructured interviews, the keeping of a reflexive journal to document the processes and decisions related to the generation of codes during data analysis, and the use of NVivo (Lumivero LLC, version 13, released 2020) software which provides an auditable record of the steps by which the data was coded. Conformability, or whether the research findings follow from the data collected, will be supported through the techniques described in support of credibility, transferability, and dependability [18]. Additionally, conformability will be further supported by recording additional aspects of the research process in the reflexivity journal, beyond the specific decisions and processes related to the development of the codes. For instance, it is anticipated the DEM will record information about the daily experience of completing the data collection and analysis, as well as reflections on their personal experience with the research [18,19], in support of connecting personal experience with conducting research with the data and generated findings.

Reporting of the findings will conform with COREQ (Consolidated Criteria for Reporting Qualitative Research) guidelines to facilitate rigorous reporting [20]. In keeping with this, in addition to thorough reporting of study methods and findings reflecting the checklist items, a reflexivity statement will be included in the final report which will include, but not be limited to, a characterization of DEM's professional identity, and personal biases, assumptions, and reasons and interests in the research topic.

Research Objective 2: What Is the Baseline Effectiveness of TheKeep.Ca at Connecting Survivors

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of Cancer With Research and Patient Advisor Activities?

Data from website visitor metrics and registrant data collected over the first 6 months after the website goes live will be used to establish a baseline of the effectiveness of TheKeep.Ca at recruiting members of the Manitoba population with cancer for engagement activities. Google Analytics will be used to provide metrics related to user activity on the website. The methodology for using Google Analytics to understand website traffic is informed by that used by previous authors [21]. Specific metrics to be used will include, but not be limited to, total users, type of devices used, geographic locations of users, session length, websites' pages viewed, number of page views per page, bounce rate (ie, number of users leaving the site without viewing additional pages), site entrances, and page interactions.

Data from registrants on the TheKeep.Ca engagement database will be used to further characterize the effectiveness of the website, as well as the population that it effectively engages within the first six months after going live. Specifically, respondent demographics, information about their cancer experience, preferred types of activities, and how they found the website are tracked as part of the registration survey (Multimedia Appendix 5).

Data analysis will include the generation of descriptive statistics of the website metrics and registrant characteristics. Descriptive statistics will be generated from both the Google Analytics data as well as the registrant data. Inferential statistics, including chi-square and *t* test (2-tailed), will be used to describe differences in Google Analytics metrics between website visitors from Manitoba and outside of Manitoba, as well as by device. Additionally, inferential statistics will be used to describe differences in disease characteristics and engagement preferences by registrant demographics, including age, gender, and location. Open-ended question data will be summarized using a descriptive semantic inductive approach to thematic analysis [15,16], with the aim of providing a simple summary of open-ended question data.

Research Objective 3: How Does Registration on TheKeep.Ca Impact the Cancer Experience?

After the initial 6 months after TheKeep.Ca has gone live, an online SurveyMonkey survey (Multimedia Appendix 6 for the survey) will be distributed to the website registrants who consented to be contacted with a follow-up survey as part of the initial registration questionnaire. Demographic data and information about the registrant's cancer experience (ie, date of diagnosis, type of diagnosis, patient vs informal caregiver, and treatment intent) will be captured, as well as the number and type of engagement activities they have participated in that were advertised on TheKeep.Ca. Using a combination of Likert-style responses and open-ended questions the survey will evaluate the experience of being a registrant on TheKeep.Ca, the effectiveness of TheKeep.Ca in connecting individuals with engagement opportunities, the impact of engagement activities on the experience of registrants, and identify ways that TheKeep.Ca can provide a better experience to website registrants. Descriptive statistics will be generated to describe the respondent population and the overall experience of the group. Inferential statistics will be used to identify differences between populations, based on demographics and cancer experience, and the impact TheKeep.Ca had on respondents' cancer experience. Open-ended question data will be summarized using a descriptive semantic inductive approach to thematic analysis [15,16], with the aim of providing a simple summary of open-ended question data.

Development of the research protocol related to objectives 2 and 3 was informed by the CHERRIES (Checklist for Reporting Results of Internet E-Surveys) checklist to facilitate rigorous reporting [22]. For qualitative data, NVivo will be used to assist with qualitative data management and analysis. Quantitative data analysis will be conducted using SPSS (IBM Corp, version 27, released 2020).

Ethical Considerations

This study was approved by the University of Manitoba Health Research Ethics Board on December 12, 2024 (HS26614-H2024L263). Institutional approval from CCMB is pending as of December 23, 2024. Participants, including both registrants on TheKeep.Ca website as well as the patient advisors involved in the development of this project, did not receive compensation of any kind. Enrollment on TheKeep.Ca website is strictly voluntary, with informed consent being implied as part of the registration process.

All data will be deidentified before analysis. Data related to objective 1 will be linked to a master list, which will be destroyed following the completion of research activities outlined in this protocol. Data related to objective 2 (ie, registrant responses) will be deidentified before analysis for research purposes; however, names and contact information will be required to be retained on this data to facilitate screening and informing registrants of relevant patient engagement activities. However, this data will not be shared with any other party and be available only to the research team (ie, MT and DEM). Data from objective 2 is being collected in an anonymized fashion, with an absence of information that would support the identification of individuals. Notably, while the email addresses provided by registrants on the website will be used to collect data for objective 3, the responses will not be linked to the email addresses or the initial responses provided by the individuals at the time of website registration.

Patient advisor involvement, including participation on the steering committee, being listed as an author on this paper, and participation in the research activities related to objective 1, was strictly voluntary, and would not impact their ability to participate in any aspect of the activities related to this project. The patient advisors listed as authors on this protocol provided expressed written consent to be listed as such and fulfilled the criteria to be listed as authors in peer-reviewed journal publications, including active involvement in all aspects of the project and protocol development. Documentation of this consent was provided to the editor for review as part of this peer-reviewed process.

All images, names, and videos of individual thrivers of cancer presented on TheKeep.Ca website are used with expressed consent. The website does include stock images obtained from

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a third party (ie, Adobe Stock Images) which are used per the images' respective licensing agreements.

Results

TheKeep.ca will go "live" after this study receives institutional approval from CCMB, becoming searchable on major search engines (eg, Google) and accessible to the public. The results related to research objective 1 are expected to be submitted for peer-reviewed publication within 6 months after the website becomes accessible to the public with results related to research objectives 2 and 3 being submitted for peer review by the 12-month mark. In addition to being presented in peer-reviewed manuscripts, the results will also be shared at national and international conferences as well as presented on TheKeep.Ca website in written and video format using layperson language.

Discussion

Principal Findings

Addressing the three research objectives outlined in the protocol is important for informing future work in several ways. Regarding research objective 1, better understanding the experience of the patient advisors who were, and continue to be, involved in TheKeep.Ca project is important for evolving how TheKeep.Ca project is conducted in the future, as well as informing how other projects where authentic longitudinal patient engagement is desired. While high-quality reviews [5,9] and frameworks to guide patient engagement activity planning exist [23], such as those available through the Patient-Centered Outcomes Research Institute [24], the findings from this work will provide real-world examples of the experiences, challenges, and lessons learned from a complex project where authentic longitudinal engagement with thrivers of cancer was foundational. Specifically, identifying what parts of this project have been frustrating, stressful, or otherwise not rewarding, for the patient advisors as well as which aspects were viewed as providing a positive and meaningful experience is expected to make a meaningful addition to the literature [10].

Regarding objectives 2 and 3, obtaining baseline data regarding how effective the website is at engaging those living with cancer both inside and outside of Manitoba, as well as the characteristics of the registrants, is important for guiding future work to better engage with the diverse population of individuals living with cancer both inside and outside of Manitoba. It is anticipated that the baseline Google Analytics data will provide meaningful insights per who engages with TheKeep.Ca website. Similarly, the initial registrant experience survey (ie, objective 3) will provide important data about how to enhance the experience of those that register on TheKeep.Ca. This data will reflect the experience of engaging with TheKeep.Ca in the absence of planned social media campaigns and advertising at the cancer center. As the website develops, and campaigns to promote the website are developed, the baseline data will provide a real-world comparison to gauge the effectiveness of promotional interventions such as social media advertising campaigns, paid Google Adwords campaigns, and posters placed in cancer care facilities, or private businesses. This data will be helpful not only for helping TheKeep.Ca evolve into a tool for engaging meaningfully with Manitoba's population with cancer but also for other groups endeavoring to engage with either specific populations or a representative sample of those impacted by cancer [8].

Limitations

This protocol has two main limitations. First, to address research objective 1, not all patient advisors who participated in the development of TheKeep.Ca will be able to be invited for interviews. At the time of protocol submission, three of the initial patient advisors involved left the project, for several reasons—not all of which were disclosed. While, from both a scientific and quality improvement perspective, it would be ideal to explore the reasons for dropping out from the project to provide a better experience for those in the future, however, out of respect for the privacy of the individuals that withdrew, this is not possible. Ideally, experience data related to participation in the project would have been captured longitudinally, throughout the project. However, the decision to establish TheKeep.Ca as a research platform was made relatively late in the project history, as such the need to formally collect rigorous experience data was not considered previously.

Second, there is a risk that initial recruitment to the TheKeep.Ca registrant database will be limited, resulting in limited data to address objectives 2 and 3. TheKeep.Ca, as a research platform, represents a novel endeavor, making predicting the initial recruitment rate and the resulting sample size for the first six-month sample size impossible. Additionally, as the goal is to obtain baseline data for traffic and engagement with the site, before additional advertising interventions as outlined above, traffic may be very low. As a result, it is recognized that the generation of meaningful inferential statistics may not be possible. Regardless, the initial data from the first six-month period will serve as an important baseline, essential for understanding the impact of future campaigns to promote the website and recruitment to the website registry.

Conclusion

The webspace that became TheKeep.Ca was initially proposed as a simple tool to connect those who have experienced cancer firsthand with opportunities to engage with researchers and other teams working to improve the cancer journey in Manitoba, Canada. However, through endeavoring to seek authentic [9] collaboration with a group of patient advisors over several years, the simple proposal evolved into something with the potential to become much more than that. In keeping with the original proposal, TheKeep.Ca is a catalyst, enhancing the capacity for connection between those willing to share their hard-won firsthand knowledge with health care professionals. However, it is also a place where patient advisors can contribute directly to improving the cancer journey, as it provides online infrastructure for patient advisor-led initiatives—such as the curated resource directory. Lastly, through a rigorous research program, beginning with the work outlined in this protocol, TheKeep.Ca project aims to achieve these goals while, at the same time, advancing what is known about patient engagement for the benefit of those living with cancer in Manitoba and beyond.

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Acknowledgments

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Data Availability

To protect the confidentiality of the research participants, deidentified data, including qualitative data related to objective 1, and survey response data from objectives 2 and 3 will not be made publicly available. However, it may be obtained upon reasonable request to the authors, and subsequent approval of the request after review by the University of Manitoba Health Research Ethics Board.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Consent form for objective 1.
[DOCX File , 46 KB - resprot_v14i1e63597_app1.docx]

Multimedia Appendix 2
Intake questionnaire for objective 1.
[DOCX File , 28 KB - resprot_v14i1e63597_app2.docx]

Multimedia Appendix 3
Written prompt sheet for objective 1.
[DOCX File , 30 KB - resprot_v14i1e63597_app3.docx]

Multimedia Appendix 4
Semistructured interview guide for objective 1.
[DOCX File , 16 KB - resprot_v14i1e63597_app4.docx]

Multimedia Appendix 5
Registration survey for objective 2.
[PDF File (Adobe PDF File), 42 KB - resprot_v14i1e63597_app5.pdf]

Multimedia Appendix 6
Six-month follow-up survey for objective 3.
[PDF File (Adobe PDF File), 47 KB - resprot_v14i1e63597_app6.pdf]

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Abbreviations

CCMB: CancerCare Manitoba
CHERRIES: Checklist for Reporting Results of Internet E-Surveys
COREQ: Consolidated Criteria for Reporting Qualitative Research
RTA: reflexive thematic analysis

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Protocol

The Measurement of Vital Signs in Pediatric Patients by Lifelight Software in Comparison to the Standard of Care: Protocol for the VISION-Junior Observational Study

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Abstract

Background: Measuring vital signs (VS) is important in potentially unwell children, as a change in VS may indicate a more serious infection than is clinically apparent or herald clinical deterioration. However, currently available methods are not suitable for regular measurement of VS in the home or community setting, and adherence can be poor. The COVID-19 pandemic highlighted a need for the contactless measurement of VS by nonclinical personnel, reinforced by the growing use of telemedicine. The Lifelight app is being developed as a medical device for the contactless measurement of VS using remote photoplethysmography via the camera on smart devices. The VISION-D (Measurement of Vital Signs by Lifelight Software in Comparison to the Standard of Care—Development) and -V (Validation) studies demonstrated the accuracy of the app compared with standard of care (SOC) measurement of blood pressure, pulse rate (PR), and respiratory rate (RR) in adults, supporting certification of Lifelight as a class I Conformité Européenne medical device.

Objective: To support the development of the Lifelight app for pediatric patients, the VISION-Junior study is collecting high-quality data that will be used to develop algorithms for the measurement of VS (PR, RR, and oxygen saturation) in pediatric patients. The accuracy of the app will be assessed against SOC measurements made simultaneously with app measurements.

Methods: The study is recruiting pediatric patients (younger than 18 years of age) attending the Sunderland Royal Hospital pediatric emergency department of the South Tyneside and Sunderland National Health Service Foundation Trust. High-resolution videos of the face (and torso in children younger than 5 years of age) and audio recordings (to explore the value of crying, wheezing, coughing, and other sounds in predicting illness) are made using the Lifelight Data Collect app. VS are measured simultaneously using SOC methods (finger clip sensor for PR and oxygen saturation; manual counting of RR). Feedback from patients, parents, carers, and nurses who use Lifelight is collected via questionnaires. Anticipated recruitment is 500 participants, with subtargets for age, sex, and skin tone distribution (Fitzpatrick 6-point scale). Early data will be used to refine the algorithms. A separate dataset will be retained to test the performance of the app against predefined targets.

Results: The study started on June 12, 2023, and reached its recruitment target (n=532) in April 2024 after extending the deadline. Algorithm refinement is in progress, after which the performance of Lifelight will be compared with the SOC measurement of VS. The analyses are expected to be completed by mid-August 2024.

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Conclusions: Data collected in this study will be used to develop and assess the accuracy of the app for the measurement of VS in pediatric patients of all ages.

Trial Registration: ClinicalTrials.gov NCT05850013; https://clinicaltrials.gov/study/NCT05850013

International Registered Report Identifier (IRRID): DERR1-10.2196/58334

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KEYWORDS

vital signs; remote photoplethysmography; pediatric health assessment; pediatric health monitoring; pediatric; infant; infants; infancy; child; children; Lifelight; software; app; observational study; study protocol; clinical deterioration; COVID-19; SARS-CoV-2; pandemic; telemedicine; medical device; photoplethysmography; eHealth; mobile health; mHealth

Introduction

Measurement of vital signs (VS) is an essential part of clinical evaluation, providing important information about a patient's health; importantly, a change in VS may herald a deterioration in clinical condition [1] and may precede the emergence of physical symptoms during the early stages of an infection [2]. High pulse rate (PR) and respiratory rate (RR) have been shown to predict hospital admission in children [3]. Infections such as influenza, scarlet fever, and chickenpox are common causes of morbidity and mortality in immunocompromised children [4,5]. Three-quarters of children who develop severe sepsis from infection have a comorbid condition such as asthma, diabetes, cystic fibrosis, or cancer. Sepsis carries a mortality rate of almost 50% in the most vulnerable children [6]. Treatment of infection in children can be expensive, especially if intensive care is required.

Given that monitoring of VS is important in clinically vulnerable children to aid early detection of infection [7], a robust method that parents can use at home to measure VS is likely to be beneficial and would support remote initial assessment [8]. The measurement of VS is time-consuming and requires trained staff and multiple pieces of equipment, some of which need regular calibration. Accurate measurement of blood pressure (BP) using a sphygmomanometer requires the use of the correct size cuff for the patient. The physical contact of equipment can be uncomfortable and distressing for patients, particularly those with learning disabilities. Stress can affect BP, PR, and RR, such that the measurements may not accurately reflect the patient's state of health [7]. Standard of care (SOC) medical equipment is not suitable for regular measurement of VS in the home or community setting. Adherence to frequent VS monitoring using traditional technologies is low because of the inconvenience and stigmatizing nature of specialist hardware equipment (eg, thermometers, BP cuffs, and finger-clip oximeters) [7]. The COVID-19 pandemic has also highlighted the need for methods suitable for the remote or contactless measurement of VS that can be operated by people without specific medical training. The growing use of telemedicine since the pandemic also points to the need for easy but accurate measurement of VS.

Photoplethysmography (PPG) is an optical measurement technique that records changes in the light reflected from the skin surface due to volumetric changes in the facial blood vessels; small variations in perfusion provide valuable information about the cardiovascular system [9]. PPG has been used to measure PR [10,11], oxygen saturation [12], BP [13,14], and RR [10,15] and to detect atrial fibrillation [16].

Lifelight is an app being developed for the contactless measurement of VS using remote PPG via the camera on smart devices such as phones and tablets. The app captures the average color of regions of interest on the face 30 times every second for 60 seconds and sends these as red, green, and blue color values to a central server for processing, yielding VS values. The VISION-D (Measurement of Vital Signs by Lifelight Software in Comparison to the Standard of Care—Development) study in 2018-2019 measured VS in 8585 patients and healthy volunteers simultaneously using the app and SOC methods. The data were used for machine learning to develop the algorithms used to calculate VS. The subsequent VISION-V (Validation) study demonstrated the accuracy of the app compared with SOC methods for measuring PR, RR, and diastolic BP [17], providing the basis for the current Class I Conformité Européenne (CE) mark [18]. The app also received ISO 13485:2016 certification in August 2023 [19], and the accuracy of the app for measuring PR and BP against ISO standards in adults with stage 1 hypertension has recently been reported [20]. The VISION-MD (multisite development) study evaluates the app versus SOC in patients with a wide range of clinically relevant VS values, including critically ill patients, and across the full range of skin tones [21]. In VISION-MD, high-resolution full-face videos of participants' faces have been recorded, which has proved instrumental in improving the accuracy of VS measurement compared with the VISION-D and -V studies.

The VISION-Junior study explores the measurement of VS using a Lifelight app developed for pediatric patients (aged 18 years or younger) attending the pediatric emergency department. As in VISION-MD in adults, high-resolution full-face videos will be recorded. In younger children (younger than 5 years of age), the video will also include the torso to increase the surface area from which the signal is recorded, and because the torso is likely to move less than the face. Audio data will also be recorded, as crying, wheezing, coughing, and other sounds can also predict illness in children [22,23].

The aim of the VISION-Junior study is to assess whether the app can be used to accurately measure VS in pediatric patients. This protocol describes the collection of data that will initially be used to develop the algorithms for the measurement of VS in children. Later data will be used to assess the accuracy of the

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app across the range of VS values encountered in children of different ages. The objectives are as follows.

The primary objective is to collect data to support the development of the app for the accurate measurement of PR, RR, and oxygen saturation in pediatric patients and to assess the accuracy of measurements against SOC methods. Secondary objectives are: (1) to assess—using the collected PPG data—whether other (direct or indirect) measurements can be made using the app, including temperature, BP, PR variability, and audio analysis; (2) to evaluate the impact of subject-specific variables on the PPG VS measurements (eg, medication, cosmetics, facial or body hair, and skin tone); (3) to obtain data to understand patient and parent or guardian or carer habits and preferences for VS measurement using questionnaires (Multimedia Appendices 1 and 2); and (4) to assess the usability of Lifelight Junior for measuring VS in pediatric patients through questionnaires completed by participating health care professionals (Multimedia Appendix 3).

Most of the data collected in the study will be used to train the app algorithms to measure VS in pediatric patients. The remaining data will be kept separate and used to assess the accuracy of the algorithms at regular intervals during the data collection period. The study delivery process will be responsive to this learning curve to increase the likelihood that the predetermined accuracy target for each VS estimation is achieved by the study end.

Methods

The design and protocol for this study have been informed by the VISION-MD study [21] and earlier VISION studies [17].

Participants and Recruitment

Approximately 500 pediatric patients are being recruited at the Sunderland Royal Hospital pediatric emergency department of the South Tyneside and Sunderland National Health Service (NHS) Foundation Trust. All pediatric patients (younger than 18 years of age) attending the pediatric emergency department are potentially eligible for the study. The exclusion criteria are critical illness (as judged by the treating physician), including unconscious patients, patients who were noncompliant in terms of excessive movement during the VS measurements, and patients whose parents, guardians, or carers do not speak English (required to give informed consent). The study aims to recruit according to age, sex, Fitzpatrick skin tone, and medical history criteria, as subsequently described.

The research nurse approaches the parents, guardians, or carers of potential participants identified by the clinical team about taking part in the study. Potential participants aged 17 or 18 years or the parents, guardians, or carers of younger children are provided with an ethics-approved information sheet explaining the study aims, what is involved, and the requirements for participation. Younger children also watch ethics-approved age-appropriate videos (for ages 5-10 and 11-16 years) explaining the study on a tablet device (Multimedia Appendices 4 and 5).

The information sheet and videos were developed in collaboration with the Young People Advisory Group North England and the South Tyneside and Sunderland NHS Foundation Trust Young Persons Group. These groups also provided feedback on the design of the study, consent/assent forms, and other study documents at 2 in-person meetings.

Study Procedures

Demographic data (age, sex, ethnicity, skin tone [Fitzpatrick 6-point scale [24] ranging from type 1 for skin that always burns to type 6 for skin that never burns]) are recorded on an electronic case report form using the Castor electronic platform. Medical history questions are limited to the presence or absence of conditions that might affect skin perfusion and pigmentation, cardiovascular processes, and any prescription medicines for these conditions.

The study staff records a set of premeasurement observations and the presence or absence of sweat on the participant's face; any facial hair on the cheeks; tattoos, jewelry, birthmarks, scars, or other features on the face; the use of foundation or concealer; and the position of the participant (seated, prone, supine or lying on one side).

Patients may also be recruited into 1 of 3 subprotocols depending on premeasurement observations (Table 1).

The study staff ensures that participants have been at rest for at least 10 minutes before VS measurement starts (which can include the period of data collection described previously).

Table 1. Subprotocols.

	Subprotocol	Description
1	Blood pressure measurement	Blood pressure will be measured at the same time as other vital signs using standard of care equipment (sphygmomanometer) in participants who are able to cooperate and stay relatively still
2	Electrocardiogram	A 3-lead electrocardiogram will be recorded to assess heart rate variability in a representative subset of participants (based on age, skin tone, and illness; see Table 3)
3	Questionnaire	Guardians, parents, or carers and children will be asked to complete a questionnaire about their preferences for Lifelight-type technologies versus standard of care methods for measuring vital signs

In each study session, VS is measured as per the subprotocol using the SOC equipment, while simultaneously capturing a video of the participant's face using the Lifelight Data Collect app running on a tablet (standard iPad). This app is a research tool that captures and uploads video data to secure cloud storage for research purposes only and is distinct from the CE-marked Lifelight medical device developed from data collected from previous studies. The Data Collect app does not display any VS estimates and is not used for clinical interpretation or analysis.

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In each study session, at least 2 VS (PR, oxygen saturation, RR) and temperature are measured twice over a 60-second period using SOC equipment and methods.

A standard clinical finger clip sensor for the measurement of oxygen saturation and PR is placed on a finger. Oxygen saturation and PR are measured at 0, 30, and 60 seconds of the recording period and averaged.

RR is determined by counting chest rises throughout the 60-second period. The nurse may place their hand on the participant's chest to improve the accuracy of counting while being mindful not to obscure the camera's line of sight.

At the same time, a video of the participant's face (and torso in children younger than 5 years of age) and audio is captured for up to 3 minutes using the Data Collect app running on a tablet positioned approximately 1 meter away and angled toward the participant's face. Background luminosity is measured automatically. Recording is started and stopped by the research nurse via the iPad.

A maximum of 3 attempts at recording measurements is made. Once measurements have been completed, the study staff fill in postmeasurement questions relating to how much the participant moved, their position, whether they were wearing glasses, any hairstyle or other item (eg, face covering) that obscured any part of their face during the recording, and whether the app reported "face not found" at any point during the recording.

A questionnaire is also available to garner feedback on the technology from the clinical user's point of view (ie, the nurses who take the VS measurements). Questionnaire data are fully anonymized and recorded without any identifiable information.

Each study session, including approaching the participant, obtaining consent, and performing the study procedure takes about 30 minutes. Participants were not followed up after the VS measurements but continued to receive clinical care as appropriate for their condition.

Subprotocols

Participants are recruited into 3 subprotocols as appropriate (Table 1). Subprotocols 1 and 2 may be run concurrently with the main protocol if the research nurse considers it practical to also record BP and an electrocardiogram (Figure 1).

Figure 1. Study flow and data collection. BP: blood pressure; ECG: electrocardiogram.

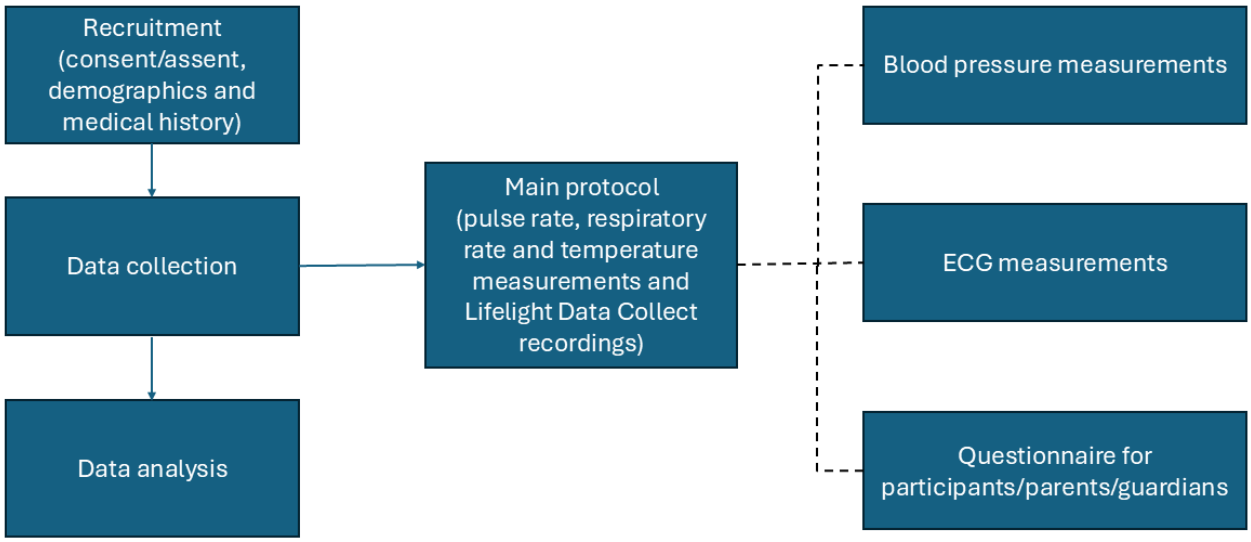

Ethical Considerations

The study is being performed in accordance with the spirit and the letter of the Declaration of Helsinki, the Good Clinical Practice Guidelines, and the protocol and applicable local regulatory requirements and laws. The VISION-Junior protocol was approved by the Health Research Authority and Health and Care Research Wales (IRAS reference 321956) and the Newcastle North Tyneside Research Ethics Committee on March 30, 2023. Informed consent is obtained electronically using Castor eConsent, a secure NHS-compliant platform. Informed consent is provided by participants aged 16 years and older and by the parent, guardian, or carer of younger children. Children younger than 16 years of age are also given the opportunity to sign an assent form. As the study is noninterventional, participants will not receive financial compensation for participation but may be offered small incentives such as stickers or certificates. Participation in the study is entirely voluntary, and participants may withdraw from the study at any time. Specific, explicit written consent was obtained from all individuals featured in the videos provided in Multimedia appendices 4 and 5, permitting use for publication purposes.

Privacy and Data Collection

Each study participant is assigned a unique sequential patient identifier; no identifiable data are stored. All documents are stored securely and can only be accessed by study staff and authorized personnel. The code linking the patient identifier to their personal information is kept within the hospital study site and can only be accessed by the research team within that site.

For each reading, a high-quality video of the face (and torso in young children) and an audio file are saved to the internal storage of the iPad in encrypted form and transmitted directly

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to the sponsor's NHS-compliant cloud server. Files were automatically deleted following upload to the server.

All data collected about participants during the study will be kept strictly confidential and handled according to the General Data Protection Regulations. Videos and audio recordings collected during the study constitute personal data as it may be possible to identify participants. Full-resolution, full-face, or torso video data are required to develop Lifelight Junior into a clinically useful device; the analysis cannot be performed using blurred videos. The data collected for research purposes only (not clinical care) are processed within the legitimate interests of Xim Ltd.

Data Handling

Analysis of the videos uses the encrypted files, which, in most cases, are processed automatically within a secure cloud infrastructure (ie, without any person viewing the videos); in rare cases, it may be necessary to analyze a video manually if the recording is not as expected. The analysis results in anonymized aggregate datasets. No decrypted files are stored at any point in the processing. The electronic case report forms are stored and managed using the Castor electronic cloud.

Performance Targets

While Lifelight is certified as a class I CE medical device [18], the performance of Lifelight Junior needs to be appropriate for routine clinical practice in pediatric patients. Table 2 lists the performance targets for Lifelight Junior for measuring VS in pediatric patients; training data collected during VISION-Junior will support progress toward these targets.

Table 2. Performance targets in VISION-Junior.

Vital sign	Performance target	Reference
Pulse rate	Root mean square error ≤5 beats per minute	[25]
Respiratory rate	Maximum error of 5 breaths per minute for 100% of measurements	Minimum standard met by all approved respiratory monitors
Oxygen saturation	Maximum error tolerance 4%	[26]

Sample Size

An estimated 500 pediatric patients (18 years old or younger) will be recruited into the study. This sample size is informed by the previous VISION-D, VISION-MD, and VISION-Acute studies [17,21]. However, the sample size cannot be formally calculated because it depends on the incremental improvement in the performance of the app achieved through machine learning using the training data generated early in the study. The split between training and testing data will be determined during the study according to the quality of the data collected. The study management team monitors the progress of data collection and accuracy and updates the study teams weekly. The study will continue until the accuracy of the app for measuring VS in pediatric patients is sufficient for various clinical use cases.

In addition, recruitment targets according to age, sex, Fitzpatrick skin tone, and medical history have been defined, as shown in Table 3, to ensure accuracy in a broad range of clinically relevant patients.

Table 3. Demographic and medical history recruitment targets.

	Targets
Age	≥12% aged 0-1, 1-2, 2-5, 5-11, 11-14, 14-18 years
Sex	≥40% male; ≥40% female
Skin tone	15% of participants will have Fitzpatrick skin tones 4, 5, or 6 (this is not a hard target as achieving this figure depends on the demographic diversity of the study region)
Medical history	≥40% in each of the following categories: • Febrile (≥38 °C) • Afebrile • Ill (as judged by the clinical staff); to ensure a spread of conditions, no more than 50% of recruited patients will have an acute respiratory illness (eg, bronchiolitis, asthma, virus-induced wheeze, pneumonia, and croup) • Well, including pediatric patients with a minor injury

Data Analysis

All statistical analyses will be performed using Python (Python Software Foundation). Training data will be used for machine learning to improve the performance of Lifelight Junior for measuring VS in pediatric patients. Appropriate machine learning models will be developed according to the data collected. This is likely to include signal processing and measurement algorithms for PR and RR, and multilayer neural network-based approaches for BP, similar to those used in the adult version of the app.

The separate set of test data will subsequently be used to determine the performance of the app for measuring VS in pediatric patients. Correspondence between VS measurements predicted by the app and the measurements taken manually using SOC methods will be compared using regression coefficients, mean error, and SD, and compared against the

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performance targets set out in Table 2. An accuracy target will be considered met if the mean error and SD for the app measurements are at least equal to the target (Table 2). Heat maps or scatter plots will also be developed.

Linear regression will be used to assess the impact of skin tone on the accuracy of the app for measuring each VS, using the Fitzpatrick skin tones as the explanatory variable.

Quantitative data from the questionnaires will be summarized. Thematic analysis will be used to analyze free-text responses to identify perceptions of the app and variations in the way patients, their parents or carers, and health care professionals interact with it and any challenges they encounter.

All analyses will be completed per protocol since there is no intention to treat. There will be no imputation of missing or implausible data, and any missing, implausible, or problematic readings will be excluded from analysis.

Results

The study started on June 12, 2023, and as of December 20, 2023, had recruited 303 participants. The study was extended until the end of March 2024 to enable the target recruitment (500) to be met; 532 participants had been recruited as of April 5, 2024.

Data are currently being used for machine learning to refine the algorithms to improve clinical accuracy. We anticipate that final analyses to determine the performance of the app against the targets set out in Table 2 will be complete by mid-August 2024. The performance of the app will be determined across the range of VS values encountered in children in clinical practice by comparing the VS values recorded using PPG versus standard methods.

Discussion

Principal Findings

This paper reports the protocol for obtaining data to develop algorithms for the measurement of VS in children using the app, and to evaluate the performance of the app against SOC measurement of VS in pediatric patients of all ages.

Monitoring of VS in children is challenging because existing methods (eg, BP measurement via an arterial line or cuff; PR and RR via electrodes, adhesive pulse oximeters, and adhesive temperature probes and thermometers) are either invasive or contact-based and can cause discomfort, pain or distress, may disturb sleep, and may damage paper-thin skin, potentially increasing the risk of infection. Frequent VS measurement using different techniques is also resource-intensive. The app being developed will provide contactless noninvasive measurement of VS.

Data collected in this and other studies will be used to train algorithms to develop the app for the measurement of VS in pediatric patients. The app aims to provide a risk-measured way for nonexperts to measure VS quickly and nonintrusively, and therefore, detect any early signs of deteriorating health or infection. This will make it easier for clinically vulnerable or immunocompromised children to attend school and interact with their peer groups, meeting their mental, physical, social, and educational needs, whilst providing reassurance to parents, guardians, or carers. Early detection of infection before any significant clinical deterioration occurs means that treatment can start sooner, improving the likelihood of a full recovery [27] whilst also potentially avoiding hospital admission and intensive care, which are expensive for the child's family (lost income, expenses) and health care providers. Lifelight can also be an effective tool for at-home monitoring and triage, reducing the burden on carers, emergency services, and hospitals. It may also be useful in nonspecialist health care settings such as primary care and prehospital care where specialist pediatric equipment is not available. Several other devices for the measurement of VS are currently being developed but all require physical contact, whether through a finger, the wrist, or the chest, and only one (Biospectral) is able to measure BP.

Limitations

This research may have some limitations. BP is inherently more complex to measure than PR and RR, in terms of the data form and machine learning and because reference measurements are less accurate. As with any recording device, signal quality may be compromised if the participant moves excessively or if light levels are insufficient. However, we expect the use of high-resolution video recording to overcome such issues. In addition, measurements can be easily repeated if a recording is of poor quality.

Skin type is a potential source of error with PPG devices, as melanin absorbs green light, potentially increasing errors in measurements in dark-compared with light-skinned individuals [24]. However, we have already shown that skin type does not affect the accuracy of Lifelight [17]. Although the Fitzpatrick Skin Type Scale is the current gold standard [24], its use has been criticized because of racial bias, weak correlation with skin color, and broad within-group variations in skin tone. Spectrocolorimetry, which uses multiple variables to categorize skin tone objectively, has been proposed as an alternative [24], which may be incorporated into later studies to confirm our findings.

Conclusions

The results of this study will be disseminated via submissions to relevant journals and conferences. The study team will explore different avenues and formats for the dissemination of the study findings with the Young People Advisory Groups and other groups to ensure a wide public audience, for example, through coproduced public talks, studies in community communications, and social media.

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Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are not publicly available due to their commercially sensitive nature, as mandated by Xim Limited's grant funders and investors, but are available from the corresponding author upon reasonable request.

Authors' Contributions

The VISION-Junior protocol and patient-facing documents were developed by NM, LF, GS, MK, GM, JF, JH, and IM and informed by the Young Persons advisory group North East (YPAGne) and the South Tyneside and Sunderland National Health Service Foundation Trust Patient and Public Involvement group. Statistical methods were developed by MK.

Conflicts of Interest

MK and GM are employees of Mind over Matter Medtech, which provides contracted services to Xim Limited, including grant bid writing, clinical trial design and management, health economic analysis, and regulatory submission support. However, the company has never contributed directly to the technical design or development of Lifelight and has not received benefits from Xim Limited other than financial payment for contracted work. SW and JF are employed by Xim Limited, the manufacturer of the technology. IM and JH have received compensation from the manufacturer for advisory services and have no conflicts of interest. NM, LF, and GS were responsible for facilitating the study and have no conflicts of interest.

Multimedia Appendix 1
Questionnaire to collect data from participants in the VISION-Junior observational pediatric study in order to improve the usability of the Lifelight app.
[DOCX File , 31 KB - resprot_v14i1e58334_app1.docx]

Multimedia Appendix 2
Questionnaire to collect data from parents/guardians/carers of participants in the VISION-Junior observational pediatric study in order to improve the usability of the Lifelight app.
[DOCX File , 32 KB - resprot_v14i1e58334_app2.docx]

Multimedia Appendix 3
Questionnaire to collect data from health care practitioners conducting the VISION-Junior observational pediatric study in order to improve the usability of the Lifelight app.
[DOCX File , 20 KB - resprot_v14i1e58334_app3.docx]

Multimedia Appendix 4
Participant information video (ages 5-11) explaining the VISION-Junior observational pediatric study process to prospective participants before consent.
[MP4 File (MP4 Video), 103294 KB - resprot_v14i1e58334_app4.mp4]

Multimedia Appendix 5
Participant information video (≥11 years old) explaining the VISION-Junior observational pediatric study process to prospective participants before consent.
[MP4 File (MP4 Video), 73685 KB - resprot_v14i1e58334_app5.mp4]

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Abbreviations

BP: blood pressure
CE: Conformité Européenne
NHS: National Health Service
PPG: photoplethysmography
PR: pulse rate
RR: respiratory rate
SOC: standard of care
VISION-D: Measurement of Vital Signs by Lifelight Software in Comparison to the Standard of Care—Development
VISION-V: Measurement of Vital Signs by Lifelight Software in Comparison to the Standard of Care—Validation
VISION-MD: Measurement of Vital Signs by Lifelight Software in Comparison to the Standard of Care—multisite development
VS: vital signs

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Protocol

Establishing a Digital Health Care Ecosystem in a Health Sciences University in South Africa: Protocol for a Mixed Methods Study

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Abstract

Background: Comprehensive and formalized digital health care ecosystems in health sciences tertiary education in South Africa do not currently exist, but they have the potential to influence teaching and learning, research, and community engagement.

Objective: A total of 3 key objectives underpin the study, that is, determining the health care curriculum needs and required content for the development of a formalized digital health ecosystem, determining the level of readiness of staff and students to participate in a digital health care ecosystem, and determining whether community engagement and strategic partnerships can contribute to the sustainability of a digital health care ecosystem.

Methods: A multipronged approach will be used to address the objectives, with a mixed methods design being undertaken. The qualitative phases will be phenomenological in nature, and triangulation of information along with thematic analysis will be conducted on the collected data. Quantitative data will be collected prospectively and cross-sectionally and analyzed using descriptive analysis. Sampling will include subject experts for the Delphi technique, staff and students at the University, clinical training and education partners, and community leaders. This study has received ethical approval from the Sefako Makgatho Health Sciences University Research and Ethics Committee (SMUREC/H/260/2023:PG).

Results: Data collection for the first phase will begin in January 2024 and conclude in December 2024. Phase 2 and 3 of the study will be conducted concurrently, with data collection starting in January 2025 and concluding in December 2026.

Conclusions: The establishment of a digital health care ecosystem has the potential to benefit staff, students, and communities through stakeholder collaboration, educational opportunities, research projects, and improved service delivery.

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KEYWORDS

health sciences; digital ecosystem; curriculum; community engagement; tertiary education institutions

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Introduction

Digital health care ecosystems are described as patient-centric models of health care delivery with the aim of encouraging collaborative, cross-organizational health care processes through technology-driven platforms [1]. The use of telecommunications and digital technologies to provide health care, monitor public health, and develop new and improved methods of delivering awareness programs is referred to as digital health care [2]. According to the World Health Organization (WHO) [2], "digital health" is a global term that encompasses concepts such as electronic health, telehealth, wearable devices, mobile health, and new developments in the field of artificial intelligence to support public health systems. The definition also includes the use of electronic patient and medical record keeping.

The benefits of digital health care are extensive, including serving populations in rural and remote areas with interventional and preventative care [3], the collation and pooling of medical data, and the organized and confidential management of patient records [2]. However, despite these benefits, there is evidence to suggest that health care professionals (HCPs) are inadequately trained to effectively use technology within the health care space [4-6]. This issue is especially true in the African context [7]. Despite Africa accounting for 23% of the global burden of disease, the continent has not optimized digital health care technologies to address challenges in health care service delivery [7]. South Africa has been passive in its efforts to ensure that HCPs are adequately trained. The COVID-19 pandemic highlighted the lack of preparedness in digital health care, which has been attributed to insufficient exposure to digital health care training during the tertiary education training of HCPs [8,9]. This is important because the lack of digital health care competencies and skills could pose significant challenges to the health care industry. Potential challenges that may arise from a lack of digital health care skills include reduced efficiency [10], ineffective use of digital health care tools [11], reduced patient satisfaction due to low HCP confidence [12], increased risk of errors [13], and lack of globally relevant skills [7].

Challenges faced by the health care system and universities during the pandemic were threefold [8,14,15]. First, staff and students were not well trained or competent in providing digital health care to patients. Second, some universities were not well invested in digital health care infrastructure. Third, the acceptance of communities to receive care via digital technologies was uncertain, considering the lack of consultation and stakeholder engagement [8,14,15]. It becomes apparent that countries, through their health care systems and tertiary training institutions, need to do the following three things: First, create, construct, and integrate curricula that align with the needs of a new era of HCPs. Second, provide the necessary infrastructure to allow student learning and clinical training opportunities within the digital health care space. Finally, to actively engage with communities to ensure their integration, involvement, and acceptance of digital health care services. The combination of these 3 elements creates what is referred to as a digital health care ecosystem [16]. Therefore, the objectives of the study were threefold: first, determining the health care curriculum needs and required content for the development of a formalized digital health ecosystem; second, determining the level of readiness of staff and students to participate in a digital health care ecosystem; and third, determining whether community engagement and strategic partnerships can contribute to the sustainability of a digital health care ecosystem. Figure 1 illustrates the envisaged digital health care ecosystem (Figure 1).

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Figure 1. Digital health care ecosystem.

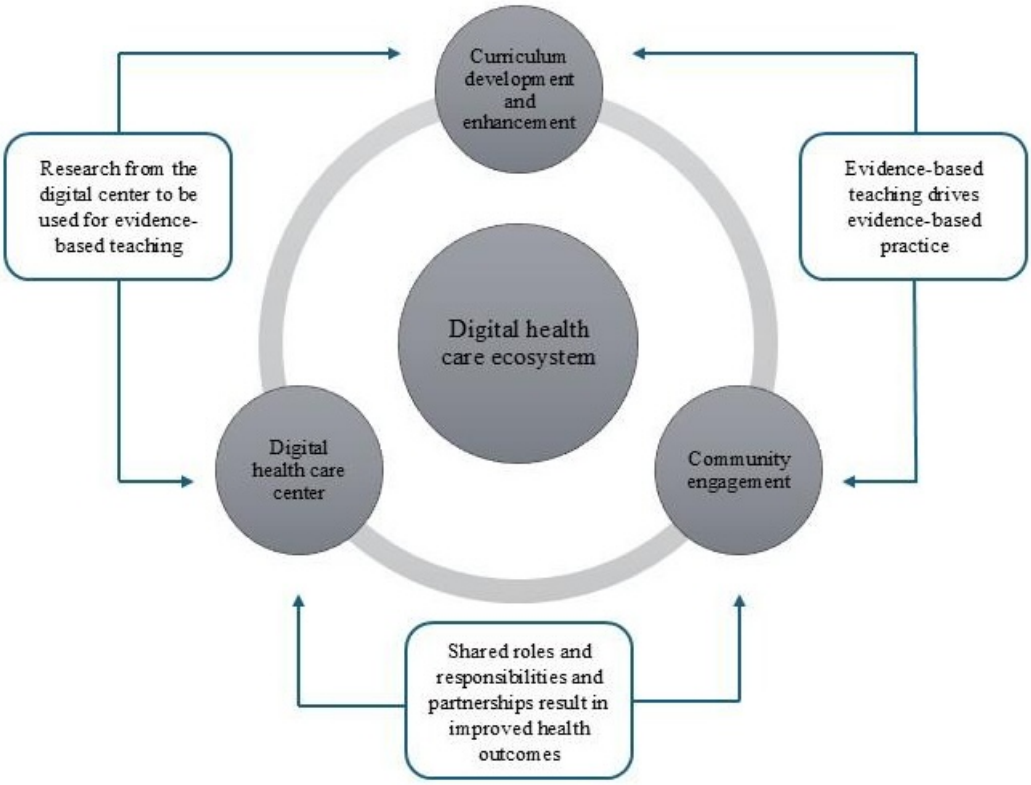

Methods

Study Design

A multiphase study, consisting of a mixed methods approach (ie, qualitative and quantitative designs) will be undertaken. The quantitative phases of the study will follow a prospective, cross-sectional design [17], while the qualitative phases will be phenomenological in nature, aiming to explore the experiences of participants [18]. The methodology for each of the 3 phases will be presented separately.

Phase 1: Developing and Obtaining Accreditation for a Digital Health Care Curriculum

During phase 1 of the study, the researchers aim to address 3 subobjectives to meet the main objective of this phase. The 3 subobjectives will be discussed separately, as their design and data collection procedures differ (Textbox 1).

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Textbox 1. Curriculum development.

Subobjective 1

Determining digital health care content and gaps in the current curriculum using gap identification frameworks when reviewing and analyzing curricula within a Health Care Sciences School.

- **Study design:** A quantitative, retrospective document review will be undertaken.
- **Sample:** A total of 6 published curricula from the Departments of Physiotherapy, Occupational Therapy, Human Nutrition and Dietetics, Nursing Sciences, and Speech-Language Pathology and Audiology will be included for review. Curricula from other departments or those that have not been published will be excluded from the review.
- **Data collection:** Each curriculum will be reviewed by the research team using the READ approach. The competencies, skills, and attitudes questionnaire [19] will be used to capture the data. Descriptive statistics will be applied to analyze the data.

Subobjective 2

Investigating the knowledge, skills, attitudes, and graduate attributes to be included in a digital health curriculum for students in a Health Care Sciences School.

- **Study design:** A prospective Delphi technique [19] will be undertaken.
- **Sample:** Potential participants for the Delphi expert panel will be identified through author and reference lists that will be compiled from a literature review, as well as referrals from academic directors and members of the academic community. To ensure diversity and representativeness in the participant group, a purposive sampling method will be used. Expert panel members will be considered for inclusion if they have published at least 2 or more papers or book chapters on digital health care, and if they are health care professionals. Experts with competing interests (such as digital health care company owners) will be excluded from participation.
- **Data collection:** Experts in digital health care (both national and international) who meet the eligibility criteria will be invited to participate in the study. Email invitations will be sent to all identified experts to participate in the Delphi study. Once consent is obtained, the first round of the survey will be sent via a Google link. Participants will have the option to add additional topics not included in the first-round survey, which will be added in the second round. After the first round, participants will be provided with the average ratings for each topic from the previous round. The second and third rounds will involve rating, scoring, and reaching a consensus on the survey items. An 80% agreement will be considered as consensus.

Subobjective 3

Developing a digital health care curriculum for a Health Care Sciences School in terms of module outcomes, content, teaching strategies, assessment outcomes, and submitting for evaluation and accreditation.

- **Study design:** An action-based approach to curriculum development will be undertaken [20].
- **Sample:** Task-team members, consisting of the researchers participating in the study will be included.
- **Data collection:** Information collected from the document review and the Delphi technique will be combined to establish the syllabus. A curriculum matrix will be developed based on the syllabus and will be populated with learning outcomes, assessment criteria, and assessment methods. The curriculum will be developed in accordance with the guidelines of the Health Professions Council of South Africa and the Council of Higher Education (South Africa). Once the curriculum is approved, it will be implemented. After six months of implementation, it will be assessed and changes will be made as needed.

Phase 2: Developing a Teaching, Learning, Clinical, and Research Center Situated Within a Health Care Sciences School

The second phase of the study aims to address 2 subobjectives in order to achieve the main objective for the phase (Textbox 2).

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Textbox 2. Establishing a digital health care center.

Subobjective 1

Conducting a readiness and needs analysis among staff and health care professionals regarding digital health care training needs.

- **Study design:** A quantitative, prospective survey design will be undertaken.
- **Sample:** All staff members associated with a Health Care Sciences School at a selected university will be included. Staff members will be selected for participation if they are part-time or full-time academic staff in the following departments: Physiotherapy, Occupational Therapy, Human Nutrition and Dietetics, Nursing Sciences, and Speech-Language Pathology and Audiology. To ensure a 50% distribution with a 5% margin of error and a 95% CI, 184 participants are required. All staff members in the School of Health Care Sciences will be targeted for inclusion to account for noncompletion of surveys and attrition during the study.
- **Data collection:** After obtaining permission from the Dean, an email with information and consent forms will be sent to all relevant staff members in the school. The questionnaire will be adapted from Bingham et al [21]. The link to the questionnaire will be emailed to all academic staff members. Once a questionnaire has been completed, access to the questionnaire will be terminated to prevent multiple submissions from the same participant. Descriptive analysis will be conducted on the collected data.

Subobjective 2

Developing a care services plan for the digital health care center and reviewing and consulting on existing technology and business plans to develop and validate the proof of concept for the establishment of a digital health care ecosystem.

- **Study design:** A qualitative explorative design will be undertaken.
- **Sample:** Snowball sampling will be conducted with at least 6 academic staff members from each department (refer to subobjective 1 for the list of departments), and data collection will cease once saturation is reached. Academic staff members with experience in clinical planning and involvement in health services programs will be included.
- **Data collection:** Staff members will be invited to participate in focus group interviews after obtaining permission from the Dean. A focus group interview schedule with open-ended questions will be used. The interviews will be voice-recorded and transcribed verbatim. Thematic analysis will be conducted using Tesch's eight-step model [22].

Phase 3: Evaluation of the Impact of Community Engagement in the Design, Establishment, Content, and Delivery of Digital Health Promotion Projects Offered Through the Digital Health Care Ecosystem

The third and final phase of the study is divided into 2 subobjectives (Textbox 3).

Textbox 3. Community engagement.

Subobjective 1

Evaluating the health needs of the local community.

- **Study design:** A cross-sectional, descriptive survey design will be undertaken.
- **Sample:** All relevant community stakeholders, including medical doctors, traditional healers, community leaders, and community health workers, will be considered for inclusion in the study. Purposive and network sampling will be used to identify as many relevant parties as possible for inclusion in the study. All community stakeholders, who have resided in the community surrounding the institution where the study will be conducted for at least 2 years, will be included. Community stakeholders with a conflict of interest (such as financial interests in the project) will be excluded from participation.
- **Data collection:** Known community stakeholders will be recruited for participation, and network sampling will be used to identify as many stakeholders as possible. Questionnaires will be circulated electronically to all participants. The questionnaires will be an adapted version of the Cooper University Health Care Health Assessment Survey [23]. Once a questionnaire is completed, access will be terminated to prevent multiple submissions. Descriptive analysis will be conducted on the collected data.

Subobjective 2

Exploring digital health care attitudes and service suggestions of shared roles and responsibilities of community members that can be implemented through digital health care in the specific community.

- **Study design:** A qualitative explorative design will be undertaken.
- **Sample:** All relevant community stakeholders (as given in subobjective 1) will be considered for participation. Purposive and network sampling will be used to identify as many relevant parties as possible for inclusion in the study. Data collection will cease once saturation is reached.
- **Data collection:** Community stakeholders will be invited to participate in focus group interviews, using a schedule with open-ended questions. The interviews will be recorded and transcribed verbatim. Thematic analysis will be conducted following Tesch's eight-step model [22].

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Recruitment

The population from the institution and its surrounding areas will be recruited for the study. Staff and students from the health sciences institution will be recruited from the following departments: Departments of Physiotherapy, Occupational Therapy, Dietetics and Human Nutrition, Public Health, Nursing Sciences, and Speech and Language Pathology and Audiology. The student population will consist of undergraduate students who are enrolled at the Health Sciences institution. All part-time and full-time staff members employed at the institution, who do not have a financial interest in participating, will be included in the study. Community stakeholders recruited for the study will be restricted to a 30-kilometer radius from the institution. Recruitment will be conducted through email communication, flyer distribution within the institution and surrounding community, and word of mouth.

Statistical Analysis

Due to the vast nature of the study, statistical analysis will vary for each subobjective. Quantitative data will be analyzed using SPSS (version 27; IBM Corp) software, while qualitative data will be analyzed using NVivo (Lumivero). To ensure optimal analysis of the qualitative data, Tesch's eight-step method of data analysis will be conducted before uploading the data into NVivo. Data will be prepared by transcribing all interviews verbatim. Coding will be conducted on data segments that share similar themes. Thereafter, categories and coding schemes will be developed based on the identified themes from a sample of the text. The coding scheme will first be tested on a relatively small sample to ensure that the scheme is applicable before being applied to the entire dataset. A researcher, who will not be involved in the initial development of the coding scheme, will assess coding consistency, after which conclusions will be drawn from the coded data [22].

Data Exclusion

For all quantitative phases of the study, data will be excluded from analysis if the dataset is incomplete (ie, if questionnaires are not fully completed). Data from all phases of the study will also be excluded if participants withdraw voluntary informed consent.

Validity and Reliability

The questionnaires that will be used in this study are adapted from previously developed and tested questionnaires, with additional questions drawn from the literature [19,21,23]. The content validity of the questionnaires will be conducted to ensure that the questionnaires have a fair representation of the constructs to be measured. Construct validity will be ensured by providing evidence that the theoretical structure of the questionnaire is relevant. Face validity will ensure that the questionnaire is transparent and relevant, as it appears to elicit information from the participants. A pilot study will be conducted with the aim of ensuring that the data collection tools are reliable. Construct and face validity will be determined by asking 10 health care professionals from different institutions across the country to provide feedback to the researchers. Health care professionals will be identified through purposive sampling to ensure that they have the necessary expertise regarding digital health care. Reliability will be determined by assessing whether the questionnaires answer the stated research questions, whether the questions are clear and unambiguous, and whether the language and terminology used are easy to understand. Following the pilot study, the questionnaires will be revised if needed.

Trustworthiness

Credibility will be ensured by building rapport and trust with the participants. The participants will be engaged in interviews to gain insights and understand their views. The researchers will ensure that honesty is maintained by giving information regarding the study to the participants. Dependability will be ensured by making the voice recorder and transcripts available to an external auditor for verification. Conformability and credibility will be ensured by conducting interviews until saturation is reached. Transferability is the ability to transfer research findings from one context to another [24]. The researchers will provide a thorough description of the research methods and setting in the research publications or any form of dissemination so that the applicability of the data to another context can be evaluated.

Ethical Considerations

As human participants will be used during the course of the study, ethical approval for the conduction of the study was obtained from the Sefako Makgatho Health Sciences University Research and Ethics Committee (SMUREC/H/260/2023:PG). Participants in all phases of the study will be provided with information pertaining to the phase that they are participating in, before being asked to sign a voluntary informed consent. Participants hold the right to withdraw from the study without providing reasons, and without prejudice. All data collected will be anonymized to ensure participants' privacy, and data will be stored in an encrypted electronic folder accessible only to the researchers. During the dissemination of results, the researchers will ensure that no identifying information is published. Participants in the study, regardless of the phase, will not receive remuneration for their participation. The research will be conducted in line with the regulations set forth by the Declaration of Helsinki.

Results

Phase 1 of the study will be conducted from January to December 2024. The second and third phases will be conducted concurrently, from January 2025 to December 2026. A detailed schedule of the study is provided in Table 1 below.

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Table 1. Projected time frames of the study.

Phase	Subobjective	Timeline
1	To determine digital health care content and gaps in the current curriculum by applying the gap identification framework when reviewing and analyzing curricula within a Health Care Sciences School.	January-June 2024 (completed)
1	To investigate which knowledge, skills, attitudes, and graduate attributes should be included in a digital health curriculum for students in a Health Care Sciences School.	April-October 2024 (completed)
1	To develop a digital health care curriculum for a Health Care Sciences School, in terms of module outcomes, content, teaching strategies and assessment outcomes, and submit it for evaluation and accreditation.	October-December 2024 (completed
2	To conduct a readiness and needs analysis among staff and health care professionals regarding digital health care training needs.	January-April 2025
2	To develop a care services plan for the digital health care center and to review and consult on existing technology and business plans to develop and validate proof of concept for the establishment of a digital health care center within a Health Sciences School.	May-December 2025
3	To evaluate the health needs of the local community.	January-June 2025
3	To explore digital health care attitudes and service suggestions, as well as shared roles and responsibilities of community members that can be implemented through digital health care in the specific community.	July-October 2026
4	Final write-up of all information collected in the study	October-December 2026

Discussion

Principal Findings

The establishment of digital health care ecosystems in tertiary institutions has the potential to have a significant positive influence on health care delivery in a country [2-6]. To successfully establish a digital health care ecosystem, it is essential to develop relevant curricula. Curricula represent an institution's vision and mission and are expected to be contextually relevant and globally responsive to the diverse needs of communities [25]. A digital health care curriculum will ensure the long-term viability of such ecosystems, and studies have shown that both academics and students agree that the integration of digital health ecosystems is long overdue [26,27]. The proposed changes to the curricula will inevitably alter clinical training opportunities for students to ensure the development of digital health care competence.

The introduction of clinical digital health care training into formal education allows students to participate in areas such as interprofessional education, offering care to rural and remote areas (including exposure to international contexts), as well as improving their digital literacy and awareness of trends within the Fourth Industrial Revolution [8,28,29]. Literature indicates that the theoretical and practical components are connected and their combination ensures that students acquire not only the knowledge but also the clinical skills, competencies, attitudes, and important graduate attributes to provide excellent patient care [30,31].

In the development of digital health care curricula and clinical training, partnerships with community stakeholders are important to ensure that the integration of technology will empower community members [32]. Communities must be involved in the conceptualization, technology innovation, development, implementation, and monitoring of the health care system to ensure health care democracy and sustainability [32,33]. Well-structured community engagement has the potential to minimize the gap between research and policy by ensuring support from key stakeholders [34]. In addition, community involvement is an essential aspect of good health governance [35].

Due to the geographical limitations of the study (ie, recruitment of participants from a 30 km radius of the institution where the study will be conducted), the results that are obtained from the study may not translate to other health care institutions. However, the principles followed in the design and establishment of the digital health care ecosystem may be universally applicable.

Conclusions

The establishment of a comprehensive digital health care ecosystem will be used for providing digital health care knowledge, conducting clinical training with students using a variety of digital health care approaches and technology, and conducting research into digital health care. The center aims to encourage stakeholder collaboration, provide educational opportunities, stimulate research, and provide service delivery using digital health care services. Important activities, such as interprofessional collaboration and community engagement, will be facilitated through the establishment of a digital health care ecosystem. The center would offer multidisciplinary and transdisciplinary health care services to multiple rural and remote contexts, including schools, old age homes, hospitals, and homes.

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Data Availability

Datasets generated or analyzed during the study are available from the corresponding author on reasonable request.

Authors' Contributions

SG contributed to conceptualization, funding acquisition, methodology, writing—original draft. MEC handled conceptualization, methodology, writing—original draft. MM assisted with formal analysis, methodology, visualization, writing—review and editing. RG contributed to investigation, methodology, writing—review and editing. TT handled project administration, visualization, writing—review and editing.

Conflicts of Interest

None declared.

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Abbreviations

HCP: health care professional
WHO: World Health Organization

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Protocol

The Utility of a Smartphone-Based Retinal Imaging Device as a Screening Tool in an Outpatient Clinic Setting: Protocol for an Observational Study

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Abstract

Background: Glaucoma, a disease leading to the degeneration of retinal ganglion cells, results in changes to the optic nerve head that are often diagnosed late when visual problems arise. With the prevalence of glaucoma surpassing 76 million adults worldwide and with glaucoma being the leading cause of irreversible blindness in the world, the early detection and management of glaucoma is imperative. Digital ophthalmoscopes, such as the D-EYE (D-EYE, Srl), have emerged as a technology that uses smartphone cameras with an attachment on the lens to visualize the retina and optic nerve head without the need for dilation. The purpose of this pilot study is to examine the acceptability and feasibility of a D-EYE digital ophthalmoscope to screen for ocular pathology involving the optic nerve, particularly glaucoma.

Objective: This study aimed to demonstrate the effect of a smartphone-based ophthalmoscope as a potential vision screening tool for optic nerve head pathology in participants enrolled in this study. The first specific aim was to determine the ability of the D-EYE smartphone ophthalmoscope to gather high-quality imaging to be used for grading the fundus into low- and high-risk categories for eye pathology. The second specific aim was to determine the difference in the quality of data capture between still retinal images and 30-second retinal video recordings produced by D-EYE smartphone ophthalmoscopes.

Methods: This observational pilot study enrolled 110 patients receiving routine eye care at the University of Florida Health from February 2019 to February 2022 to assess the use of the D-EYE device in capturing still images and 30-second videos of the bilateral retina and optic nerves of each participant. Study participants completed a survey to gather demographics and past medical history data with a particular focus on previous eye health history. Images were reviewed by 5 ophthalmology residents with interrater reliability analysis performed to assess findings.

Results: Ophthalmology resident review indicated greater visualizability and clarity of the bilateral retina and optic nerves with 30-second videos of retinal imaging compared with still-image ophthalmic capture. Furthermore, an increase in visualizability and clarity allowed for a more accurate measurement of the cup-to-disc ratio, a diagnostic marker for glaucoma. In addition, the likelihood of referral of the glaucomatous and healthy sample groups to ophthalmologists indicated a greater sensitivity of digital ophthalmoscopes in being able to detect retinal abnormalities requiring early intervention and management, supporting the technology's use as a screening tool.

Conclusions: This investigation suggests that the use of smartphone-based digital ophthalmoscopes can be more effectively applied as a screening tool by capturing 30-second videos compared with still images alone. This novel assessment of an emerging technology in the field of ophthalmology may better equip further research as smartphone camera technology advances.

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KEYWORDS

digital health; digital ophthalmoscope; ophthalmology; smartphone-based; mobile health; applications; screening tool; retinal imaging device; glaucoma; eye disease; visual problems; ophthalmoscope; ocular disease; cost-effective; mobile phone

Introduction

Vision Screening and Digital Ophthalmoscopes

Vision screening is a valuable component of health maintenance as loss of vision may lead to severe impairment in everyday tasks, such as driving, ambulating, reading, and social participation [1,2]. Glaucoma, the second leading cause of permanent blindness in the United States, is the acquired loss of retinal ganglion cells within the optic nerve, resulting in the progressive loss of peripheral vision [3,4]. The 2 most common types of glaucoma in the United States are primary open-angle glaucoma and primary angle-closure glaucoma, with most patients presenting asymptomatically until the optic nerve damage is severe enough [5]. It was estimated that by the year 2020, over 3 million adults would have glaucoma in the United States with nearly half not knowing that they have the disease [6].

Existing methods of screening for glaucoma involve comprehensive eye examinations performed by ophthalmologists. Often, patients who are at a higher risk for eye pathologies, such as glaucoma, do not participate in such screening efforts, and even when diagnosed, do not attend follow-up visits for complete eye examinations to monitor the progression of the disease. This is especially true for patients in low-income socioeconomic demographics. A study examining poor longitudinal glaucoma follow-up in India found that, adjusting for age and sex, independent predictors of poor follow-up included lack of formal education, lack of escort, and belief that follow-up is less important if one has no noticeable visual changes [7]. In addition, studies at a tertiary hospital eye department found various social and demographic factors contributing to poor adherence to follow-up, as patients who are African American or Latino, or who live far from their eye care provider are at a greater risk of nonadherence to follow-up appointments [8]. Studies performed in 3 major hospital departments found that patients presenting with advanced glaucoma are more likely to come from an underprivileged area and be of lower occupational class, to have no access to transportation, and to have a lower education level [9]. Factors such as income, education, ethnicity, and lack of transportation suggest an association between low socioeconomic status and prevalence of eye disease as well as lack of follow-up for eye health appointments.

With vision loss from glaucoma being irreversible and there existing a multitude of barriers to follow-up, early detection and management of the disease is imperative and solidifies a need for easily accessible, highly sensitive diagnostic technology. In a study assessing the comparison of smartphone ophthalmoscopy with slit-lamp biomicroscopy for grading vertical cup-to-disc (CtD) ratio (VCDR) on 110 patients, smartphone ophthalmoscopy showed substantial agreement with slit-lamp examination for the estimation of the VCDR [10]. This success in the estimation of VCDR can be used for glaucoma screening in low-resource environments. When compared with the use of a traditional direct ophthalmoscope, a 2018 Nature publication found that smartphone ophthalmoscopy produced more accurate clinical descriptions of findings in a fundal examination than direct ophthalmoscopy [11]. In addition, the study suggested that the use of a smartphone-based alternative to the direct ophthalmoscope may improve the accuracy and quality of fundal examinations by nonophthalmologists [11]. Implementation of smartphone ophthalmoscope technology may potentially be an effective way to screen patients for diseases of the eye within primary care clinics. Such an intervention would address the loss of follow-up to specialty ophthalmology clinics for complete ophthalmologic examinations in low socioeconomic status patients with eye disease. Early intervention may allow for the timely, evidence-based management of eye disease and prevent late-stage morbidities such as progressive loss of vision and permanent blindness.

Specific Aims

This study aimed to demonstrate the effect of a smartphone-based ophthalmoscope as a potential vision screening tool for optic nerve head pathology, particularly glaucoma, in participants enrolled in this study.

- Specific aim 1: to determine the ability of the D-EYE (D-EYE, Srl) smartphone ophthalmoscope to gather high-quality imaging to be used for grading the fundus into low- and high-risk categories for eye pathology
- Specific aim 2: to determine the difference in quality of data capture between still retinal images and 30-second retinal video recordings produced by D-EYE smartphone ophthalmoscopes.

Methods

Participants

This pilot study will use an observational research design to assess the ability of the D-EYE to capture high-quality imaging that can be interpreted by ophthalmologists. Furthermore, the study will investigate the difference in quality of imaging between still images and 30-second videos of the retina for clinical use based on ophthalmology resident feedback. Trained research assistants who are familiar with the protocol for recruitment and eligibility to participate in this study will recruit patients in coordination with medical staff at their respective clinical sites.

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The sample population will consist of 110 adults between the ages of 18 and 99 years (N=110). University of Florida (UF) Health Eye Center is the designated site where this study will be conducted.

Criteria to participate in this study include being a patient currently seen at the UF Health Eye Clinic and being between the ages of 18 and 99 years. The study will exclude patients matching the criteria such as loss of vision, blind patients, patients who require urgent procedures or are otherwise deemed unstable by medical staff, and patients with photosensitivity that prevents prolonged exposure to bright lights.

Participant data will be blinded from resident graders for review, and their existing medical records will provide a reference to determine the accuracy of interpretation from the ophthalmologist's review and offer insight as to the quality of imaging and preferred modality based on the reported interpretability and accuracy of the 5 resident reviewers.

Recruitment

Participants will be recruited in the study under the title, "The Utility of a Smartphone-Based Retinal Imaging Device as a Screening Tool in an Outpatient Clinic Settings." After identifying eligible participants for this study, trained research assistants will approach and recruit them. If these eligible participants are interested, a trained study member will review and obtain consent directly from the participant. A standardized informed consent script will be adhered to ensure consistency in the consenting process. Participants will receive a copy of the informed consent document.

Procedure

Research assistants, working in coordination with medical staff, will identify and determine the eligibility of patients entering the UF Health Eye Center for medical care. Consent will be obtained directly from the participants.

Before collecting the retinal imaging data, participants will complete a survey that provides pertinent demographic data, past medical history, and ophthalmology-specific questions regarding whether or not they have a diagnosed eye condition. After completion by the study participants, the paper files will be stored in a secured holding unit in accordance with the UF Institutional Review Board's guidelines.

Next, participants will have their retinal imaging collected by trained research assistants using the D-EYE. The D-EYE is a US Food and Drug Administration (FDA)–approved smartphone ophthalmoscope that was used over the course of this study. It is capable of gathering high-quality images and videos of the retina. The eye exam will occur in a low-lit room. Bilateral eyes will be examined by the D-EYE for 25-35 seconds. This footage will then be temporarily stored in the D-EYE encrypted app, along with the patient's medical record number and the patient's known eye pathologies (if any). The smartphone camera attachment is compatible with the D-EYE app, a Health Insurance Portability and Accountability Act (HIPAA)–compliant smartphone app. From the D-EYE app, the images collected (both still images and 30-second videos) can be uploaded to a UF-affiliated, secured Dropbox (Dropbox Inc.) that has been approved for data storage. The D-EYE smartphone app requires either a 4-digit password login, fingerprint scan, or face ID to access. Video and image recordings will not be stored on the device capturing the images but will be housed on the HIPAA-compliant UF Dropbox account.

The UF Dropbox cloud-hosting service will only be accessible to study personnel and resident ophthalmologists who are required to view the retinal imaging. Access to the UF Dropbox requires logging into the UF Health VPN and accessing the site through a password combination containing uppercase letters, lowercase letters, numbers, and punctuation marks.

The footage taken by the D-EYE will be reported to UF Ophthalmology residents through Dropbox. Five residents will then grade each fundus image based on (1) the clarity of the footage on a scale of 1-10 (still image vs 30-second videos), (2) whether the residents would refer the participant to an ophthalmologist for eye care, (3) whether to categorize the sample into the "healthy" or "unhealthy or needs care" category, and (4) if there are any optic neuropathies (glaucoma) present, stratifying the findings as either low, moderate, or high risk. Their responses will be cross-referenced with the patient's known eye history and the responses will be categorized as either hits, type I misses (resident lists as unhealthy but history suggests the eye is healthy), or type II misses (resident lists healthy but history suggests the eye is unhealthy).

Outcomes Measures

Certain listed measures will be collected for all participants. All data will be stored through a secured, university-affiliated Dropbox account approved by the Institutional Review Board, a HIPAA-compliant and university-supported app used for data capture and storage.

Primary Outcomes

Image Quality

The clarity of both the still images and 30-second videos will be rated on a scale of 1-10. Accuracy in determining CtD measurement will be assessed between the still imaging and 30-second videos with a determination of any differences in quality and measurements of data between the still images and 30-second videos.

Categorization

Based on the imaging results, the ability of residents to categorize participants' retinal imaging into either broad "healthy" or "unhealthy or needs care" groups.

Likelihood for Referral

Based on the imaging results, the residents will assess whether or not they would refer participants to an ophthalmologist for further specialized eye care.

Stratification

If there are any detectable optic neuropathies present, they will be stratified into either low-, moderate-, or high-risk groups based on the extent of the disease.

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Secondary Outcomes

Interpretability

Assessment of eye health will be grouped into either hits, type I misses (resident lists findings as unhealthy but history suggests the eye is healthy), or type II misses (resident lists findings as healthy but history suggests the eye is unhealthy).

Interrater Agreeability

Assessment of the level of agreement between independent resident ophthalmology graders regarding the image quality, categorization, likelihood for referral, and stratification of retinal images (still images and 30-second videos) captured from the D-EYE camera attachment.

Statistical Analysis

The information collected from the study consists of categorical data, distinguishing between accuracy and inaccuracy. The authors will be performing an interrater reliability test using the Cohen coefficient for each of the ophthalmology residents making a diagnosis. This will provide the authors with a level of agreement. All tests will be 2-sided and P values <.05 will be considered statistically significant.

To test the first aim, the authors will have 5 ophthalmology residents grade D-EYE images on a scale of 1-10 for clarity for the use of low-risk and high-risk stratification. Low-risk and high-risk stratification will be judged based on the likelihood that the resident will refer the patient to a specialist. Their grades will then be averaged, the SD will be calculated, and interrater reliability will be determined. Furthermore, the authors will test the extent to which clarity can be used for making a diagnosis. They will ask the residents to make a diagnosis and compare their judgments to existing patient history. These results will be stratified into hits, type 1, or type 2 misses. These will be used to calculate proportional variability (PV; PV+ and PV) values. Interrater reliability will also be calculated.

Ethical Considerations

This study, which includes human participant research, was approved by the Institutional Review Board of the Florida Department of Health (UFIRB201801242). The informed consent forms used in this study provide participants with a description of the study, its qualitative and quantitative measures, potential risks and discomforts, and explicitly ask the participants for a voluntary agreement to participate and allow their data to be collected. To maintain privacy and confidentiality protection, study data are de-identified as all participants are assigned a numerical code. This code follows the format of OC001. Anonymity of all study participants is ensured. No compensation of any sort is offered to the human participants. This is stated in the informed consent form. No identification of individual participants is present in any images of this paper or any supplemental material.

Results

A total of 110 participants underwent retinal screening assessments using the D-EYE attachment to iPhone 7 (Apple Inc). Both still images and 30-second videos of the participants' bilateral fundi were captured and were then compared in order to assess the clarity and quality of the imaging.

The D-EYE video footage showed the ability to achieve optic nerve head visualization with an overall proportion of 0.827 being visualized by graders. This was a notable improvement compared with still images, where graders were only able to visualize the optic nerve head with an overall proportion of 0.752. As such, video footage captured by the D-EYE suggests efficacy compared with previously established tools, and when combined with portability and cost, it may prove to be a useful clinical tool for physicians who want to assess optic nerve head health. One previous study that assessed the D-EYE showed that still imaging was possible in 74% of undilated cases [11]. This research corroborates this finding and also suggests that more consistent and better visualization could be achieved through the use of video rather than still imaging.

The intraclass correlation coefficient found when comparing grader CtD assessments was 0.576, thus suggesting statistically significant consistency in analysis across graders. Literature on interobserver agreement of VCDR has found moderate agreement between 6 glaucoma experts (median weighted of 0.67) while using stereoscopic conditions [11]. Compared with standard-of-care technology, D-EYE video footage suggests comparable efficacy in making CtD measurements.

Discussion

Based on the review of 110 participants' fundal imaging by ophthalmology residents, the pilot study indicated greater visualizability and clarity of 30-second videos of retinal imaging through the D-EYE as compared with still-image ophthalmic capture. Furthermore, the CtD measurement was more reliably measured in the 30-second video group. In addition, the likelihood of referral between the glaucomatous and healthy sample groups indicated a greater sensitivity of digital ophthalmoscopes in being able to detect retinal abnormalities, supporting the technology's use as a screening tool. Participants noticed no change in compliance or pain associated with either of the methods used in the study.

By comparing grader assessments of the overall health of the eye (measured as a likelihood of referral) with self-reported glaucoma status by participants, the authors aimed to ascertain whether D-EYE video footage could be used to provide valuable judgments on the need for additional ophthalmic care. The use of this technology, based on the results, shows that this tool has similar value as specialized ophthalmology examinations in assessment for glaucoma. With vision loss from glaucoma being irreversible and the prevalence of glaucoma rising worldwide, implementation of this easily accessible, highly sensitive diagnostic technology could provide a multitude of health benefits while addressing any barriers to health care.

One primary limitation in the study design is the subjectivity that is associated with grading fundus images by ophthalmologists. This study attempts to limit that by operating with the input of 5 ophthalmologists grading each image acquired in an effort to reach a fair conclusion for each fundus image.

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Integration of D-EYE technology into clinical settings confers advantages such as portability and steadily decreasing costs. This study has found that still images taken by the D-EYE are not yet clear enough to provide consistent optic nerve head visibility. Video footage, however, shows not only the ability to provide optic nerve head visualization, but also to assess important health metrics that can be useful both within ophthalmology clinics and in primary care settings. Future research should be aimed at assessing D-EYE efficacy in a larger population.

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Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

CtD: cup-to-disc
FDA: US Food and Drug Administration
HIPAA: Health Insurance Portability and Accountability Act
PV: proportional variability
UF: University of Florida
VCDR: vertical cup-to-disc ratio

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Protocol

Conversion of Sensitive Data to the Observational Medical Outcomes Partnership Common Data Model: Protocol for the Development and Use of Carrot

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Abstract

Background: The use of data standards is low across the health care system, and converting data to a common data model (CDM) is usually required to undertake international research. One such model is the Observational Medical Outcomes Partnership (OMOP) CDM. It has gained substantial traction across researchers and those who have developed data platforms. The Observational Health Care Data Sciences and Informatics (OHDSI) partnership manages OMOP and provides many open-source tools to assist in converting data to the OMOP CDM. The challenge, however, is in the skills, knowledge, know-how, and capacity within teams to convert their data to OMOP. The European Health Care Data Evidence Network provided funds to allow data owners to bring in external resources to do the required conversions. The Carrot software (University of Nottingham) is a new set of open-source tools designed to help address these challenges while not requiring data access by external resources.

Objective: The use of data protection rules is increasing, and privacy by design is a core principle under the European and UK legislations related to data protection. Our aims for the Carrot software were to have a standardized mechanism for managing the data curation process, capturing the rules used to convert the data, and creating a platform that can reuse rules across projects to drive standardization of process and improve the speed without compromising on quality. Most importantly, we aimed to deliver this design-by-privacy approach without requiring data access to those creating the rules.

Methods: The software was developed using Agile approaches by both software engineers and data engineers, who would ultimately use the system. Experts in OMOP were used to ensure the approaches were correct. An incremental release program was initiated to ensure we delivered continuous progress.

Results: Carrot has been delivered and used on a project called COVID-Curated and Open Analysis and Research Platform (CO-CONNECT) to assist in the process of allowing datasets to be discovered via a federated platform. It has been used to create over 45,000 rules, and over 5 million patient records have been converted. This has been achieved while maintaining our principle of not allowing access to the underlying data by the team creating the rules. It has also facilitated the reuse of existing rules, with most rules being reused rather than manually curated.

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Conclusions: Carrot has demonstrated how it can be used alongside existing OHDSI tools with a focus on the mapping stage. The COVID-Curated and Open Analysis and Research Platform project successfully managed to reuse rules across datasets. The approach is valid and brings the benefits expected, with future work continuing to optimize the generation of rules.

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KEYWORDS

data standardization; OMOP; Observational Medical Outcomes Partnership; ETL; extract, transform, and load; data discovery; transparency; Carrot tool; common data model; data standard; health care; data model; data protection; data privacy; open-source

Introduction

In health research, there are dozens of standards that can be used to represent data, and a recurring challenge surrounding the adoption of existing standards versus the creation of yet more. The retrospective adoption of standards is conceptually simple but is much harder to implement in datasets that are still actively collecting new data. Clearly, if everyone adopted a single standard from the start of all data capture, then such a problem would not exist; the reality of course is very different and data handling practices still vary considerably between research projects and health care organizations. The Observational Medical Outcomes Partnership (OMOP) Common Data Model (CDM) [1,2] is an international open community standard to standardize the schema and contents of the data by using a standardized vocabulary and medical terminology into clinical domains of OMOP CDM. As a concept, the ability to map between a research ontology, such as the International Classification of Disease (ICD) and Systematized Nomenclature of Medicine Clinical Terms (SNOMED-CT), with a single representation within the vocabulary is of immense value [3]. For an organization with data that are not in OMOP, there will always be an effect required to convert the data from the source standard to the OMOP CDM.

The Observational Health Care Data Sciences and Informatics (OHDSI) [4] program collates a suite of open-source tools [5,6] that can assist in the process of the extract, transform, and load (ETL) stages to convert data from the original format to OMOP. There are also tools that can assist in finding the most appropriate concept to use from the vocabulary using a similarity search [7]. Therefore, tools and options do exist that can assist in the conversion of data to the OMOP common standard. However, if the organization either does not have the knowledge or the capacity to undertake the conversion, the “final mile challenge” can be significant. White Rabbit [6] can profile the data and produce a metadata extract. Rabbit-in-a-Hat [5] can allow a data engineer to capture the required transformations in note form. What is missing, though, is an end-to-end process and the conversion of the outputs into actionable code. At present, an individual would most likely generate an SQL command or software script to convert the data based on the interpretations of the Rabbit-in-a-Hat output. This would require local expertise to create. Organizations may have a desire to adopt or curate data to a single standard, but the local capabilities do not always exist.

The European Health Care Data and Evidence Network (EHDEN) [8] is a Horizon IMI program established to help with this gap that funds approved organizations to work with data owners to convert their datasets to OMOP. This is a competitive process that will support datasets that can bring the most value to the wider OHDSI [4] consortium for data sharing. Not all datasets will qualify for support from EHDEN given its finite resources (it clearly cannot support every project seeking to transform to OMOP), and as so, it has eligibility criteria on the periodic calls it makes for support [9].

Most ETL processes work based on having access to the data at the time of designing the conversion, and indeed, the OHDSI tools run on the source data; allow notes to be curated for how data should be converted; and typically require manual development of scripts to convert data from source to OMOP. This approach relies on a team having access to the data, which may not for privacy reasons be desirable in relation to health care and sensitive research datasets. Some organizations may be cautious in allowing external organizations with OMOP knowledge access to core systems and data to undertake the ETL process. In many cases, this will involve setting up legal agreements such as data sharing or confidentiality agreements or generating pseudonymized versions of the data, which are often lengthy and complex tasks.

While, OMOP offers significant power and opportunity as a unifying standard, allowing differences in terminology to be mapped to a single standard, it does suffer from the challenge that curating data to OMOP can still be quite an art form with different curators taking different approaches. The vocabulary used within the OMOP CDM can be downloaded from the website Athena [10]. There is not a single vocabulary set to use, and therefore, the curators may have preferred vocabularies to represent the data. The vocabulary is also periodically updated resulting in a concept changing domains between releases, such as from being in the Observation domain to the Clinical Occurrence domain. The consequence is that someone curating the data today may make a different decision in the future because the vocabulary has changed. The vocabularies in Athena are in English, and therefore, a base assumption of Carrot is that English is the language in use.

The FAIR (Findable, Accessible, Interoperable, and Reusable) principles [11] are a globally accepted set of standards to promote best practices in datasets. CDMs can aid datasets to become interoperable, as they standardize all data to a single model. However, in the quest for interoperability, it is important that the provenance of the data is not lost when it is converted, as there is a risk of an illusion being created because data from multiple organizations are the same. Therefore, while converting

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data to OMOP can assist in making data FAIR, as it simplifies many of those challenges, it cannot be at the expense of understanding how data have been converted to OMOP.

There are many existing mechanisms to map and covert data [12-14] to the OMOP CDM, and those processes are well established. This paper does not seek to suggest the work presented here is better than any existing processes and protocols. The processes described here were in response to a specific set of constraints, such as limited availability of technical staff members, a desire to create a FAIR resource as a consequence, and most importantly that access to data was not available in most circumstances.

In this paper, we introduce Carrot, a software tool that aims to address these difficulties—namely the governance requirements around bringing OMOP expertise to the datasets, variations between individual curators within the OMOP framework, and the gap between current OHDSI tooling—while also automating as much of the process as possible. Carrot enables curators to map data to OMOP without needing access to the underlying data. This allows a central team of OMOP experts to undertake data curation of many datasets to enhance quality control and standardization while fulfilling a desire to ensure this central team never has access to data that would be in the scope of General Data Protection Regulation (GDPR). Separating the specialized OMOP knowledge from the application of the ETL process allows reduced and shortened governance work, saving data owners time and money in converting their datasets.

Similarly, Carrot provides tooling to guide curators toward standardization of their used OMOP terms wherever possible and automates much of the ETL process. In solving these challenges, Carrot brings reproducibility and transparency to the OMOP data curation process to assist datasets in meeting the increasing FAIR requirements.

Methods

Development Principles

The Carrot tools were developed using the Scrum Agile methodology [15] to deliver minimum viable products of each component followed by iterative development to expand the functionality over time. The team consisted of data engineers, OMOP experts, research software engineers, clinical academics, and patient and public representatives. All tools were made available via an MIT license [16] and hosted in GitHub repositories [17,18].

Privacy-by-Design Principles

The data held by an organization, referred to as a data partner, are identifiable personal data and within the scope of the Data Protection Act 2018 [19]. As such, we wanted to ensure the team undertaking the data mapping never had access to the underlying data and only operated on metadata that were outside of the scope of data governance regulations. Throughout the process, the only people to have access to or process personal data were the data partners. Such an approach was low risk and ensured privacy-by-design and data minimization principles were strictly followed.

Two software packages were created to separate the data conversion from the creation of transformation rules. The first software package was to handle the creation of mapping rules based solely on the metadata. This tool is called Carrot-Mapper [17,20]. The second software package was designed to reside within the data partner's network and use the rules to convert the data. This tool was called Carrot-CDM [18]. This approach defines two separate processes: one process to create the rules for mapping and a separate process that takes those rules and applies them to the data.

Reuse and Reproducibility

FAIR principles seek to ensure the required metadata are captured across the 4 categories of FAIR. Our desire is to embed these same principles into the design of Carrot such that the mappings generated were also FAIR. A key requirement of the software is that mappings from one dataset can assist in the mapping of another, reducing wasted effort. For example, significant work was undertaken in the United Kingdom to standardize questionnaires in response to COVID-19 that were used across many national cohorts [21], that way many different research cohorts agreed to use the same questionnaire rather than each creating their own to gather data from their participants related to COVID-19. Therefore, we wanted to ensure that once the questionnaire had been mapped for one data partner, it can be instantly applied to other datasets. Over time the efficiency can be increased as the mapping rules from previous work can be used in new work.

Data curation to a new standard could be considered an art form, as each individual undertaking such an activity may do so in a different way. As an artist may have a signature brush stroke, it is also true that data engineers will have their preference for how to convert data to OMOP. Therefore, to promote reproducibility our key principle was to minimize individual decision-making and the development of a standardized pipeline that produces the same results after each execution. That process was supported by features designed to provide feedback to the user regarding any curation issues compared with previously mapped datasets (see Mapping Standardization Tools section below).

Process Architecture

Overview

The mapping rule generation web application Carrot-Mapper is built using the Django Python web framework (Django Software Foundation), with the React JavaScript library for user interfaces, and PostgreSQL database. These are supported by serverless Azure Functions written in Python for asynchronous processing of the large amounts of data ingested with each new file upload. The Carrot-Mapper web application automatically deploys via GitHub Actions to Microsoft Azure infrastructure with each new release.

The minimal Carrot pipeline consists of 6 steps that are illustrated in Figure 1: (1) preprocess data to remove identifiable data and apply the standards in [22], (2) generate metadata report via White Rabbit [6], (3) transfer metadata file to Carrot infrastructure, (4) generate rules using Carrot-Mapper, (5) transfer rules to system housing data, and (6) use Carrot-CDM

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to apply generated rules to transform pseudonymized data to OMOP standard.

Note that Carrot-Mapper and Carrot-CDM handle steps 4 and 6, respectively, of the above pipeline. The formats of the metadata report and mapping rules file are open, ensuring that data partners have the option to implement their own drop-in solutions instead of one or the other software tools to fit their own infrastructure if desired. The Carrot team runs a central deployment of Carrot-Mapper, which can be used by multiple projects. A private instance of Carrot-Mapper can also be run within the data partner's infrastructure, although this reduces the utility of the system as it cannot draw on existing mapping rules generated for previous datasets and nullifies some of the benefits of reduced governance requirements. We ask all data partners to check the metadata and the contents of the scan reports to validate that no identifiable or personal data leaves the data partner's network at any time.

Figure 1. Carrot pipeline overview. (A) The raw, identifiable dataset. (B) Deidentified data. (C) The OMOP standardized deidentified dataset. OMOP: Observational Medical Outcomes Partnership.

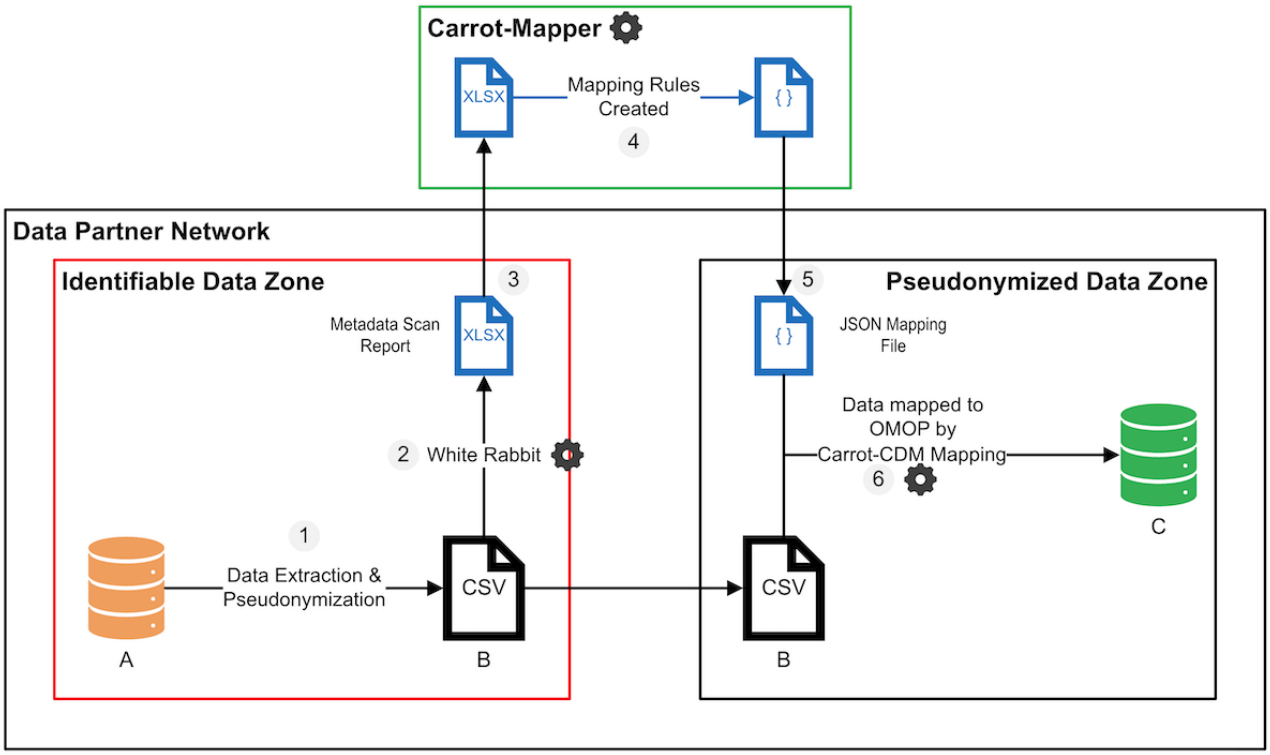

Minimizing Input From Data Partners (Step 1)

Each data partner remains responsible for the management of their data, including generating a pseudonymized and deidentified extract. There are some preprocessing steps that they must perform to use the tool, but we have minimized the workload on each data partner. In order to simplify the later steps of conversion to OMOP, we also ask the data partner to follow the steps at [22] under "Data Preparation," namely, presenting the data in a series of CSV files, with one CSV containing demographic data, all measurements in the metric system, dates and date times in the ISO-8601 format, digit grouping symbols removed, decimal numbers rounded to a maximum of 2 decimal places, CSV files encoded with UTF-8 and Unix and Linux line endings; and CSV file names limited to 30 characters.

The data partners do have a vital role in ensuring their data is represented correctly and all local insight is maintained during the process. What we have sought to minimize at this stage is the involvement of technical teams and to remove that burden.

Generating Metadata (Step 2)

The pseudonymized dataset held within the data partner's infrastructure (as generated by step 1 of the above 6-step process) is profiled by the open-source White Rabbit [6] data profiling tool, resulting in a metadata file known as a scan report. Alternatively, the scan report can be generated by hand or by other tools, so long as the resulting scan report file (an Excel file containing multiple sheets) has the correct structure.

The scan report details the tables and fields of the dataset, along with values present in each field. The Carrot data standards [22] instruct the data partner in the correct setup of the White Rabbit tool to ensure identifying data is not inadvertently present in the scan report. This includes setting the "Minimum Cell Count" to at least 5 to reduce the probability of possibly reidentifying conditions being included. The scan report should then be checked to remove any remaining data values that could be deemed confidential or sensitive.

A data dictionary may be optionally supplied. This can provide (1) vocabularies associated with certain fields and (2) descriptions of values when the field names and values are not self-explanatory. As an example, it would be possible to specify that a column contains SNOMED values. As the system is using

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the contents of the Athena system for OMOP, 18 existing vocabularies (eg, SNOMED-CT [23], ICD v9 [24], and Healthcare Common Procedure Coding System [25]; Multimedia Appendix 1) can be specified. The structure of the data dictionary is defined on the Carrot standards page [22].

Importantly these scan reports can also be used by the data partner to register the datasets within publicly available metadata repositories, such as the Health Data Research Gateway [26]. In doing so, we continue our theme of reducing the burden and ensuring one process can result in many benefits.

Uploading Scan Report and Data Dictionary Files (Step 3)

Both the scan report and optional data dictionary files are then transferred to the OMOP experts. The OMOP experts upload the scan report file and optional data dictionary file to Carrot-Mapper via a web form. This creates a new scan report instance within the system, with the user able to specify accompanying settings such as the project and dataset to which the scan report belongs, and the visibility and access to the scan report for other users. See the Users and Projects section below.

Upon upload of the scan report file (which can take a few minutes to process large and complex datasets), the Carrot-Mapper tool records all tables, fields, and values within the scan report file. This enables users to visually navigate the structure of the dataset within the mapping tool for the purposes of manual mapping (below) via the browser.

Each scan report has a status field that can be used to track the progress of the scan report upload and the manual mapping process, using the statuses “Upload in Progress,” “Upload Complete,” “Upload Failed,” “Mapping 0%,” “Mapping 25%,” “Mapping 75%,” “Mapping Complete,” and “Blocked.” This status field is automatically updated and can also be set manually from the main scan reports list page, for example, to progress through the stages from “Mapping 0%” to “Mapping Complete.”

The centralized system allows previous mapping rules to be reused. For example, assume a field “Sex” is provided with the value “M,” and this has previously been manually mapped to the OMOP concept 8507 “Male” in one scan R=report. In the case where a later scan report is uploaded with another field “Gender” and the value “M,” the system automatically applies the previous mapping rule to this value in this field in the new scan report. In this way, the utility of the system increases over time, as mapping rules are saved, and the manual effort required to generate mapping rules is reduced. This is particularly the case where a new scan report is supplied that describes a dataset that has been previously partially mapped, or where multiple datasets adhere to a shared standard. Only mappings from scan reports marked with the status “Mapping Complete” are eligible to be considered for reuse. This mechanism allows trusted and verified rules to be replicated, while works in progress are not mined for rules to apply to new scan reports. This mapping reuse algorithm runs at the time when a scan report file is first uploaded. The limitation is that it can only reuse rules when the column name is an exact match and the value is also an exact match. It has no intelligent processes to either translate from languages (such as Spanish to English) or to auto-correct for potential spelling mistakes (“Gendar” to “Gender”).

Additionally during this initial upload process, there is the automated mapping from recognized vocabularies. In the case where an entry in the data dictionary indicates that a field is encoded in a recognized vocabulary, the system will automatically create mappings to the (possibly multiple) standard and valid OMOP concept codes associated with each source code. Some scan reports can contain thousands of unique values in such fields, and as such, this feature can save days of repetitive and error-prone work for OMOP experts.

Throughout this stage, it is always clear how a rule was generated, whether it was manual, a reuse of an existing rule, or using the OMOP in-built relationships (such as mapping ICD to SNOMED). The interfaces of Carrot indicate this as M for manual, R for reuse, and V for vocabulary-based rule generation.

Generating Rules (Step 4)

Carrot-Mapper has been created as a web-based tool to assist in the generation of rules. A core reason for establishing a central tool for creating rules is that they can then be reused across projects and datasets. However, the requirement that Carrot-Mapper support rule reuse, and thus mappings related to multiple datasets be stored in a single location, also necessitates user authentication and granular permissions to control access to uploaded data (see Users and Projects section below for more details).

Once a scan report file has been uploaded and processed, manual mapping can proceed. The OMOP expert can navigate the contents of the scan report, organized in a hierarchical manner. The system allows the user to select a field or value and mark it with the desired target OMOP concept codes, as well as remove any incorrect codes (including reviewing those generated through vocabulary lookup or mapping rule reuse in step 3 above). At any stage in the mapping process, the user can see a summary view of the mapping rules currently extant and review, discuss, and remove any mapping rules. Once a user is satisfied that they have mapped all of the required fields and values, they can set the scan report status as “Mapping Complete,” which also makes the mapping rules defined in that scan report available for reuse by other scan reports. Mapping rules can be exported in CSV format (for human readability and review) or in JSON format for ingestion into the Carrot-CDM ETL tool at the next stage of the pipeline.

Mapping Rule Generation

Rules are generated using internal logic to minimize the work required from a user who wishes to add a new rule. Each table must have one field identified by the user as a “Person ID” field and one field as “Date Event,” which can be defined via the web application. For every field and value, the user can input the target OMOP concept ID. The web application handles this by looking up the OMOP ID in the OMOP database to access the OMOP term. This term is then mapped to a valid term and the related domain. These data points (valid term, domain, person ID, and date event) are sufficient to define a mapping rule. This feature removes some of the technicalities of OMOP

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from view, allowing the user to focus purely on the most accurate OMOP representation of the data.

Transfer Mapping Rules to Data Partner Network (Step 5)

The mapping rules JSON file, as exported in the previous step, is transferred into the data partner's network. These are the only data that enter the data partner's network.

Data Transformation (Step 6)

Within the data partner's infrastructure, the data partner sets up a machine with the Carrot-CDM tool installed. The Carrot-CDM package is an ETL tool to convert a dataset to OMOP using supplied rules. Built with Python, the package can be readily installed in the environment hosting the dataset. The task of Carrot-CDM is to convert the CSV files containing the dataset into an OMOP dataset, based upon the mapping rules generated by Carrot-Mapper.

Carrot-CDM operates by constructing a CDM object, containing a number of tables representing the tables or domains used in the OMOP schema. At present, these tables are a subset of all of those defined by OMOP, due to the priorities of the datasets and pipelines that have used Carrot until now. Once the CDM has been appropriately constructed, then conversion of the contents of the dataset can proceed. The OMOP mapping experts send the mapping rules in JSON format to the data partner, and the data partner loads the mapping rules file into the machine. The data partner also copies their pseudonymized dataset into the machine. Carrot-CDM is used to transform the dataset to the OMOP standard using the mapping rules provided. Carrot-CDM is platform independent and can be used via either command-line interface or graphical interface, depending on the user's preference.

Carrot-CDM handles both one-time data transformation and incremental transformation of an expanding dataset as new data is made available, using the same mapping rules as in the one-time case. Carrot-CDM can either monitor for the addition of new data and perform the transformation immediately or run on a schedule to run a transformation of new data added in each period, such as via a server-based scheduler. This means that longitudinal datasets, or those otherwise growing over time, can be efficiently mapped to OMOP. Carrot-CDM supports streaming, enabling essentially infinite datasets to be processed, as working memory is not a limiting factor.

Data Partner Validation

The data partners clearly hold the vital contextual information to provide assurance that the data mapping is appropriate and correct. Therefore, through steps 1, 2, and 6 (Figure 1) of the process, the data partner is consulted and many questions and clarifications are sought between both parties. The metadata extraction and initial upload can often highlight some discrepancies in data format and can highlight where the data dictionary does not exactly match all of the data picked up in the scan report. Therefore, the recommended process is for a highly collaborative and iterative process whereby the Carrot team has the insight in the process of curating data to OMOP, while the data partner has the insight and understanding of their data.

Users and Projects

Carrot-Mapper assigns user accounts to individuals and has an internal data model to organize dataset mappings and administrate access to them. These structures are projects, datasets, and scan reports. The basic unit is the scan report, formed from a single uploaded scan report file generated by the White Rabbit tool. Each scan report is a member of a single dataset. Multiple scan reports can be organized into a single dataset to represent successive iterations of a single dataset, such as with the addition of new tables, fields, or values. The usage pattern of datasets and scan reports is left to the user's choice.

At the highest level, projects represent the abstract notion of a view of a collection of datasets that are of interest to a particular group of users. A user must be a member of a project to access the datasets associated with that project. A many-to-many relationship means that datasets can be present in multiple projects, and it is sufficient that a user is a member of any related project to access a given dataset.

Assuming that a user has access to a given project, user access can then be further controlled on the level of datasets and individual scan reports. Permission to view datasets and scan reports is controlled first by setting their visibility as either "Public" or "Restricted," and then more granular viewing, editing, and administration operations can be controlled at the per-user level.

Mapping Standardization Tools

An additional internal tool within Carrot-Mapper highlights related OMOP concepts that are the target of mappings in the dataset corpus. This is provided as feedback to the mapping team to highlight misaligned target concepts (ie, those which are descendants or ancestors of other target concepts in the hierarchical OMOP structure) and encourage iterative convergence on a standardized OMOP vocabulary. Users are free to ignore this guidance if they choose, but the presentation of the potential inconsistencies places this information in the user's hands without extra effort.

Management

Carrot-Mapper presents users with a dashboard to show relevant statistics such as the total number of scan reports processed and mapping rules generated, grouped by data partner, and to track the progress of scan reports from the upload stage through to the completion of the mapping process.

User access to datasets and scan reports is configurable via dedicated administration pages for each, placing the user control into the hands of the dataset administrators to reduce reliance on the central Carrot-Mapper team.

Ethical Considerations

Research ethics approval was not required for this project as each data partner maintains their own governance and ethics for the original research studies. Anyone requiring access to the platform to perform research needs to apply for their own ethics

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approval. The data partners who use the Carrot system and methods in this paper will need to have the required ethics in place for the collection, storage, and use of data in place.

Results

As of July 2024, the installation of Carrot-Mapper has been used to generate mappings for 39 scan reports to the OMOP standard. There are 129 dataset objects across 13 projects. A total of 60,269 mappings have been generated, through manual means (n=6159), automatic (n=45,316), and reuse between scan reports (n=8794). These numbers are only for those scan reports marked as "Mapping Complete," indicating that they have been accepted as correct by the users, and their associated mappings are now available for reuse by new datasets. More (n=92,071) mappings are currently in progress without having been marked as archived or as completed.

This use of Carrot tools has been adopted by a number of projects, including COVID-Curated and Open Analysis and Research Platform (CO-CONNECT; see below), Alleviate [27], Defining Mechanisms Shared Across Multi-organ Fibrotic Disease to Prevent the Development of Long Term Multimorbidity (DEMISTIFI),

Mother and Infant Research Electronic Data Analysis (MIREDA), the National Institute for Health and Care Research Nottingham Biomedical Research Center, and most recently the East Midlands Secure Data Environment. Carrot is therefore an integral part of ongoing efforts by several organizations to standardize health data to the OMOP standard. Since Carrot-Mapper can be deployed by any user, with a separate database, it is not possible for the authors to accurately gauge the use of Carrot-Mapper beyond the centrally installed system deployed by the Carrot team.

Most mappings (over 75%) were automatically generated from vocabularies, indicating the importance and time-saving nature of the automated mappings feature. Existing mappings that have been verified are automatically reused on newly uploaded scan reports where they match, reducing wasteful replicated effort. While the proportion of mapping that is from reuse is currently low (less than 15%), we anticipate (and have seen even thus far) that as the number of mapped values increases, and iterations of the same dataset are progressively remapped over time, the number of reused mappings will rise compared with the number of manually added mappings. Even at this early stage, nearly 60% of the mappings that are not automatically generated from known vocabularies are from reuse.

Discussion

Principal Findings

Accessing and combining multiple datasets can be handled in a variety of ways. Principally, the choice of whether to standardize vocabularies then drives the choices available in further steps in any processing pipeline. Leaving datasets in their original formats requires later processing steps to understand and handle the heterogeneity in the underlying data sources. While this can be handled on a case-by-case basis for small numbers of datasets, at scale, this requires the creation and maintenance of a large number of connectors and middleware given the plethora of possible data sources. This is the approach taken by systems with a limited number of data sources such as OpenSAFELY [28] but is not an approach that is sustainable for many smaller datasets and data partners.

Converting datasets to a standardized vocabulary reduces the heterogeneity of the datasets at an earlier step in the pipeline, simplifying later processing steps and reducing the dataset-specific knowledge required by users of the data. However, it places the onus on formulating a consistent and correct mapping to the standard vocabulary. It is also not possible to cover every use case with a single standardized vocabulary, so some pipelines may be best served by using the raw data, while other use cases may lend themselves to a specific standardized vocabulary that is inappropriate for other uses.

In choosing a common standard vocabulary, a number of competing factors must be considered, including the suitability of the vocabulary to represent the original datasets, ease of conversion, availability of required expertise and tooling, and adoption by others. A wealth of standard vocabulary candidates exist, including OpenEHR, OMOP, and PCORnet [29].

Converting a dataset to a common standard can sometimes be partially automated—in the case of OMOP, many research ontologies such as SNOMED can be mapped directly—but in almost all cases this conversion requires a human element to decide the most appropriate mapping. This brings with it privacy and data protection implications if the process of manual mapping relies upon providing access to the dataset. The EHDEN program funds the conversion of datasets to the OMOP standard by using approved organizations to perform the conversion. This relies on governance assurances to ensure that only trusted and approved individuals are granted access to the dataset under conversion. This can be a relatively quick method for converting high-priority datasets to the OMOP standard but will not enable the conversion of lower-priority datasets given the competitive nature of the process.

The Carrot tools take a different approach, by only extracting to a central system the metadata required from the dataset to formulate a mapping. In this way, experts in OMOP conversion with access to the central Carrot system can create a mapping from the original dataset to the OMOP standard without ever having access to either identifiable or pseudonymized and anonymized data. This removes some of the governance requirements. In addition, it allows the creation of a corpus of mapping rules that can be shared and reused between datasets, and compared and aligned over time. Finally, Carrot can automate much of the mappings required from recognized standard vocabularies, reducing costs and opportunities for error.

The generation of rules by automated processes does have the ability to create more harm than good, as a human has to check and correct any potential errors. The use of automation in Carrot is limited to two scenarios. The first is where a concept has already been formally mapped by the OHDSI vocabulary from a nonstandard to standard concept. The second is where a previously human-approved mapping can be reused because the column and values exactly match. The user is presented

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with these and can see which rules were mapped from the vocabulary (marked with a V) and from reusing existing rules (marked with an R). We are currently gathering more evidence on the utility of these automated approaches and whether other automation is useful, such as the adoption of large language models.

The novel nature of the metadata access required by Carrot tools has created some additional governance issues, since many organizations did not have existing data access processes that were used to process lower risk metadata. In the use-case of CO-CONNECT, this required an extensive collaborative effort between our team and data partner organizations to satisfy them with the nature of the requests and to create new processes to enable them. This delayed some of the mapping work but is also an important output from the wider CO-CONNECT project.

Phenotype Generation

Bringing together the metadata from multiple datasets and their mappings to the OMOP standard enables leveraging the combined data to build phenotypes. For example, all fields and values across all datasets that are mapped to the OMOP concept code 317009 for asthma can be queried. In future work, we plan to provide a publicly available tool to present this information, allowing interested parties to interrogate the source values that map to a given OMOP concept code. This is valuable for understanding the varying ways in which this data is captured across datasets and allows external validation of the mappings generated by the central team.

Pipeline Integration

The Carrot tools have been built in such a way to be integrated into wider pipelines, as demonstrated in the CO-CONNECT project. The separation of the tasks into separate tools based on their requirements for human intervention provides a natural fit for integration into semiautomated pipelines. Work in this area continues, such as future extensions to support the postprocessing of OMOP data to encode relationships, work to further develop the JSON mapping rules file specification to fit common standards, and support of data-profiling tools in addition to White Rabbit.

Limitations

The Carrot tools remain under active development to extend and improve their functionality. In particular, work remains to monitor and handle the continual changes made to the OMOP vocabulary to provide reproducibility and transparency to the processes. The priorities of the initial use cases shaped the development process, in particular regarding support for OMOP tables. Further work is ongoing to widen the target OMOP tables the Carrot tools can support. The work presented has not run different methods in parallel; therefore, we make no claim over whether this approach is better, faster, or more efficient or uses less computing resources than others. Where data governance and protocols would allow such a comparison could be useful to evidence the benefits of the system. What we have sought to lay out is a protocol, supported by software, that was driven by the underlying constraints and challenges experienced.

The matching algorithm for reusing mappings across datasets is relatively simple, and ripe for further refinement as well as further user customizability. That is because even a small spelling mistake would prevent a match from being found. Additionally, Carrot cannot undertake any natural language processing, nor can it translate between languages.

Finally, further development remains to provide greater user ease, particularly around the self-administration of user accounts and streamlining the user journey to eliminate known areas that could be further automated.

While reducing some aspects of technical knowledge that are required by users (eg, removing the need for SQL knowledge typically required in most other workflows and automating the details of which OMOP concept codes relate to which target OMOP table), Carrot does still rely on an expert understanding of OMOP to be used to greatest effect. In this regard, it is to enhance rather than replace the capabilities of human curators and makes no claim to be able to process full datasets from end to end without human oversight and intervention. There is still a need for clinical specialties (eg, chronic pain) to agree on correct and consistent usage of terms to improve the interoperability of disparate datasets.

Conclusions

We have presented the Carrot tools, namely the Carrot-Mapper and Carrot-CDM software tools. These enable expert or novice curators to transform health datasets to the OMOP standard with access only to metadata, rather than the potentially sensitive data. This has the potential to radically reduce the governance work and cost required to perform this transformation, without sacrificing the expertise that can be brought by external curators.

Carrot-Mapper contains functionality to specifically reduce the repeated work required to map multiple datasets by reusing mappings between datasets. It further contains tools that can guide curators toward standardized mappings over time, reducing the dependence upon individual curators' different approaches to the preferred terminologies to represent data. All of this is achieved without ever exposing the sensitive data to the external team with OMOP knowledge.

Carrot-CDM is a robust and scalable ETL tool that can run within the data partner's infrastructure, completing the journey to an OMOP dataset without data movement beyond the data partner's boundaries, nor requiring external users to be granted access. In combination, the Carrot tools provide a means for OMOP experts to convert health care datasets to OMOP in a standardized manner, with reduced governance requirements compared with the existing tools available.

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Data Availability

There is no data to make available, but all the Carrot software is available on an open-source license.

Conflicts of Interest

AS, PRQ, and EJ were a part of the CO-CONNECT project. CC is director of the Alleviate pain data hub.

Multimedia Appendix 1
Details of the vocabularies that are used in Carrot-Mapper as default.
[DOCX File , 15 KB - resprot_v14i1e60917_app1.docx]

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Abbreviations

CDM: common data model
CO-CONNECT: COVID-Curated and Open Analysis and Research Platform
DEMISTIFI: Defining Mechanisms Shared Across Multi-Organ Fibrotic Disease to Prevent the Development of Long Term Multimorbidity
EHDEN: European Health Care Data and Evidence Network
ETL: extract, transform, and load
FAIR: Findable, Accessible, Interoperable, and Reusable
GDPR: General Data Protection Regulation
ICD: International Classification of Diseases
OHDSI: Observational Health Data Sciences and Informatics
OMOP: Observational Medical Outcomes Partnership
SNOMED: Systematized Nomenclature of Medicine
SNOMED-CT: Systematized Nomenclature of Medicine Clinical Terms

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Protocol

Mindfulness-Based Cognitive Therapy for Life (MBCT-L) Versus Stress Reduction Psychoeducation (SRP) for the Improvement of Mental Well-Being in Health Care and Other Public Sector Staff: Protocol for the Well at Work Randomized Controlled Trial

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Abstract

Background: Mindfulness-based and stress reduction interventions have been recommended by the National Institute for Health and Care Excellence guidelines in England and Wales as effective preventive mental well-being interventions for health care and other public sector staff at risk of poor mental health.

Objective: This trial aims to assess the effectiveness of the increasingly implemented Mindfulness-Based Cognitive Therapy for Life (MBCT-L) intervention versus a routinely available Stress Reduction Psychoeducation (SRP) intervention in reducing perceived stress and improving other mental health and work-related outcomes in national health care and other public sector service employees.

Methods: The trial is a multisite, single-blind, parallel-group, 2-arm superiority randomized controlled trial. Recruitment, interventions, and assessments will be conducted remotely via online platforms. We will recruit 260 health care and other public sector staff into 26 intervention groups across the United Kingdom, with the intervention delivered through human resource staff well-being provision channels affiliated with participating National Health Service trusts. Participants will be randomly allocated in a 1:1 ratio to either MBCT-L or SRP. Primary and secondary outcomes will be collected at 6, 12, and 20 weeks after randomization. The primary outcome will be the change in scores on the Perceived Stress Scale-14 from baseline to 20 weeks after randomization. Demographic, intervention-related, and health economic data will also be collected. Secondary outcomes will involve assessments of well-being, mental health state, and work-related engagement and performance. Adverse events will be recorded. Data analysis will involve multilevel modeling, and it will be conducted on an intention-to-treat basis. A substudy will involve online semistructured interviews after 20 weeks of randomization with a subsample of participants (n=30, 12%). Transcribed data will be subjected to thematic analysis to elicit qualitative outcomes on perceived well-being and work-related changes after intervention as well as drivers and barriers to intervention uptake and acceptability.

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Results: Recruitment of participants commenced on August 29, 2023. The target recruitment of 260 participants was reached on April 30, 2024. Follow-up outcome data collection was completed on September 30, 2024, and data analysis is underway. A total of 30 qualitative interviews have been conducted.

Conclusions: Findings will inform future recommendations on intervention suitability and implementation for public care staff well-being.

Trial Registration: International Standard Randomised Controlled Trial Number (ISRCTN) ISRCTN18049845; https://www.isrctn.com/ISRCTN18049845

International Registered Report Identifier (IRRID): DERR1-10.2196/67695

(JMIR Res Protoc 2025;14:e67695) doi:10.2196/67695

KEYWORDS

health care; National Health Service; NHS; staff; digital intervention; staff well-being; Mindfulness-Based Cognitive Therapy; therapy; Stress Reduction Psychoeducation; randomized controlled trial

Introduction

Background

Public sector employees present with higher levels of stress compared to those in other job sectors, with health care and public care staff, in particular, experiencing disproportionately high stress levels [1]. Stress levels in public sector employees have been further exacerbated by the COVID-19 pandemic, which has reportedly imposed additional stressors in the workplace, especially on health care staff [2-4]. In 2020-2021, stress, depression, or anxiety accounted for 50% of all work-related ill health, with the total number of cases of work-related stress, depression, or anxiety being 822,000, and a prevalence rate of 2480 per 100,000 employees in human health, social care, and education sectors in the United Kingdom [1]. Excessive stress and mental health problems, such as anxiety and depression, in public sector staff have also been broadly associated with further negative individual-level outcomes, such as burnout, compassion fatigue, and reduced quality of life and negative organizational outcomes, such as poor job satisfaction; presenteeism; and absenteeism and leaving work, including poor care provision [5-7]. Mindfulness-based training and stress management training are two approaches that have been recently recommended by the National Institute for Health and Care Excellence (NICE) [8] as effective psychotherapeutic interventions to be delivered in the United Kingdom in either online or face-to-face group modality to health care or other public care employees at risk of poor mental health.

While a broad range of organizational- and individual-level well-being interventions are currently being offered in National Health Service (NHS) trusts and other public sector workplaces, Stress Reduction Psychoeducation (SRP) is a standard usual care group program offered widely and in various formats across all geographic regions in England (United Kingdom) to health care staff as well as other public sector staff accessing psychotherapeutic interventions through their organizational well-being services affiliated with NHS trusts. Mindfulness-Based Cognitive Therapy for Life (MBCT-L) [9] is a newer, third-wave intervention, which is increasingly being implemented in the NHS and other public sector services. MBCT-L borrows its premises from the standard Mindfulness-Based Cognitive Therapy (MBCT) variant [10,11], which is a NICE-recommended treatment option for recurrent and mild to moderate acute depression [12], and is also included in clinical guidelines as a relapse prevention option in other countries [13-15]. Importantly, MBCT-L is an adaptation tailored to nonclinical populations and has been shown to be effective in improving well-being and mental health outcomes in various populations, including health care workers, as evidenced in previous work [16-20], including a recent randomized controlled trial (RCT) that showed moderate to large effects on health care staff well-being derived from MBCT-L compared to a waitlist control [21].

SRP and MBCT-L approaches are increasingly being implemented across the NHS trusts in the United Kingdom in online formats, particularly after the COVID-19 pandemic, in acknowledgment that digital modalities can overcome main barriers to intervention uptake and adherence [22]. However, MBCT-L is currently being offered as a workplace psychological program through the NHS trust's well-being services in a limited number of trusts across the United Kingdom. Notably, MBCT-L is a longer-duration program, commonly lasting 8 or 9 weeks if a practice (retreat) day is included, as opposed to SRP, the duration of which can vary between 4 and 6 weeks. Furthermore, MBCT-L requires more skilled staff for its delivery, that is, specifically MBCT-trained staff, whereas SRP programs can be delivered by classically trained cognitive behavioral therapy practitioners, psychological well-being practitioners, or other health care staff trained in supporting people with common mental health problems in managing their conditions.

SRP and MBCT-L approaches differ in their conceptual and practical premises; while SRP relies on behavioral stress reduction techniques coupled with well-being and goal setting [23], MBCT-L is an enhanced approach that combines both stress reduction and cognitive therapy elements in one program, embedding mindfulness practices as well [9]. Thus, a presumed advantage of MBCT-L over SRP approaches is that the former teaches foundational coping skills that not only alleviate transient stress but also cultivate a long-term change in one's attitude toward stress and promote a more positive outlook on stressful experiences and life more generally.

However, the 2 approaches have not yet been compared to one another in terms of their effectiveness as workplace interventions

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in improving stress and other well-being aspects and job-related outcomes. The findings of the review conducted by NICE in their recent guidance [8] indicated larger effects of face-to-face mindfulness-based approaches on stress and other mental health and job-related outcomes than stress reduction interventions in at-risk public sector populations. Moderate-quality evidence suggested that mindfulness-based approaches are effective in improving mental well-being; managing mental health symptoms; and decreasing absenteeism in public sector populations, including health care staff. Very-low-quality evidence suggested that such mindfulness interventions may improve job stress in such at-risk public sector populations. Furthermore, the reviewed mindfulness-based studies seemed to rely on mindfulness-based stress reduction approaches, largely without cognitive elements embedded, while some of the reviewed SRP studies included cognitive elements in their content and exercises. As for stress reduction approaches, moderate-quality evidence indicated that SRP was effective in improving job satisfaction; quality of life; and mental health literacy in targeted high-risk populations, including health care staff. Low-quality and very-low-quality evidence hinted that a stress management approach might be effective in improving stress and mental health symptoms in these populations.

Study Rationale

The NICE review did not include any online mindfulness-based studies, while the included stress management interventions were delivered either face-to-face or online. All 5 mindfulness-based studies and all 5 stress management studies included in the NICE review had a waitlist or usual care as a comparator or no well-being comparator intervention. Only 1 of the stress management studies was based in the United Kingdom, while there were no other mindfulness-based studies that were conducted in the United Kingdom. Finally, while the NICE review consolidated some qualitative data assessing barriers and facilitators to intervention uptake, it only included 1 qualitative study, which involved another type of intervention, that is, digital cognitive behavioral therapy [8]. The findings of the study indicated that there are a number of positive aspects of the digital modality of such a well-being intervention, including convenience and discreteness or anonymity, while specific barriers (eg, time pressures) and drivers (eg, managerial support) were reported to impact engagement with the given intervention.

Therefore, in light of the lack of online mindfulness-based studies in the NICE review and a lack of studies directly comparing mindfulness-based and SRP approaches, the proposed superiority trial will assess the effectiveness and cost-effectiveness of the 2 approaches. Furthermore, in light of the lack of qualitative studies exploring the acceptability or effectiveness of either approach, this study aims to gather in-depth qualitative data from a subsample of participants to explore the perceived impact of the intervention, including postintervention changes in well-being and work performance, barriers and facilitators to the uptake and acceptability of such interventions, and their engagement throughout the program. The overarching research question is as follows: Does MBCT-L demonstrate superior efficacy to SRP in reducing perceived stress and improving mental health and work-related outcomes among public sector employees? The findings of this study are expected to fill in the aforementioned gaps in the existing research and are intended to inform the NHS and other public sector organizations on how to best invest in their future resource provision to retain and support their staff at risk of poor well-being.

Methods

Aim, Design, and Setting of the Study

Overview

The proposed Well at Work study is a single-blind, multisite, parallel-group, 2-arm superiority RCT that aims to assess the clinical effectiveness and cost-effectiveness of MBCT-L versus SRP in health care and other public sector staff who are seeking to access well-being support through human resource channels affiliated with the participating NHS trusts. The primary objective of this trial will be to determine whether there is a difference in change in the primary outcome on the Perceived Stress Scale-14 (PSS-14 [24]) between the 2 intervention groups from baseline to 20 weeks after randomization. The secondary objectives will be to assess the differences in change in any of the secondary mental well-being and work-related outcome measures between the 2 arms from baseline to each follow-up time point, that is, at 6, 12, and 20 weeks after randomization. Recruitment, interventions, and assessments will be conducted remotely via online platforms using videoconferencing and electronic technologies.

Qualitative Study

A substudy will involve online semistructured interviews to be conducted 20 weeks after randomization, with a subsample of participants from each arm gathering qualitative data for in-depth insights into participants' perceived changes after intervention and their experiences and views in relation to intervention uptake and acceptability.

The Well at Work study is hosted by the University of Nottingham in the United Kingdom, which is the sponsor of the study, and will be mainly based across 4 public care (NHS) sites over 3 geographic regions in the United Kingdom, that is, Nottingham University Hospitals NHS Trust and Nottinghamshire Healthcare NHS Foundation Trust (the East of England); Sussex Partnership NHS Foundation Trust (South of England); and Tees, Esk and Wear Valleys NHS Foundation Trust (North of England). The online MBCT-L intervention will be offered across all 4 NHS trust sites, while 9 additional NHS trust sites will also be participating in the trial, namely Lincolnshire Partnership NHS Foundation Trust; Lincolnshire Community Health Services NHS Trust; Derbyshire Community Health Services NHS Foundation Trust; York and Scarborough Teaching Hospitals NHS Foundation Trust; South Tyneside and Sunderland NHS Foundation Trust; Leicestershire Partnership NHS Trust; Wrightington, Wigan and Leigh Teaching Hospitals NHS Foundation Trust; South West London and St George's Mental Health NHS Trust; and Northern Care Alliance NHS Foundation Trust. These additional sites will be channeling interested staff to 1 of the 4 main NHS trust sites delivering the interventions. Given the online intervention

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delivery format, the trial aims, with this approach, to achieve wide geographic coverage and outreach across health care and other public sector staff in the United Kingdom seeking well-being support through their organizations, which is offered via the participating NHS trust sites.

Patient and Public Involvement and Engagement

A patient and public involvement and engagement (PPIE) group consisting of members of staff working in the public sector has been formed and consulted on the design of the study. The PPIE group is intended to provide input into all key aspects of the trial throughout its duration, from conceptualization to implementation, evaluation, and dissemination.

Reporting of the protocol is according to SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (Multimedia Appendix 1).

Sample Selection

Potential participants will be directed to the study through existing integrated care services; well-being hubs; and other human resource channels, which are accessed by staff working in health care and other public sectors, for example, social care and teaching, through the NHS trust sites participating in the trial. The communication of study information will be facilitated through a study flyer that will be circulated widely across the participating sites via email and other communication channels, including staff communication hubs; staff well-being websites; staff networks, newsletters, and social media (eg, Facebook [Meta Platforms, Inc] and X [X Corp]); and staff induction or other events.

Staff expressing an interest in the study will be directed to an online link facilitated via REDCap (Research Electronic Data Capture; Vanderbilt University) [25,26] tools hosted at the University of Nottingham, which will include a participant information sheet (PIS) with information about the study, followed by an eligibility screening form. The contact details of the study researchers will be provided in the PIS should any interested participants wish to ask any questions. Upon completion of the eligibility form, eligible participants will be emailed a link to a participant consent form on the REDCap platform. In the consent form, participants will also be asked to indicate whether they would be willing to receive information at a later stage about the qualitative substudy. Following the provision of informed consent on REDCap, participants will be directed on the platform to the survey containing the baseline assessment questionnaires. The inclusion and exclusion criteria are listed in Textbox 1.

Textbox 1. Inclusion and exclusion criteria for the trial.

Inclusion criteria

- Aged ≥18 years
- Part-time, full-time, honorary, or voluntary employment, seeking access to well-being support through one of the participating sites
- Currently working (ie, not on a sick leave)
- Having a competent command of the verbal and written English language
- Having access to a stable internet connection on a PC, laptop, or tablet

Exclusion criteria

- Current diagnosis of a mental health condition from a general practitioner or mental health care professional
- Experience of significant life events currently causing significant distress
- Concurrently attending or planning to attend a psychological or well-being intervention within the subsequent 3 months

Screening

Exclusion criteria will be flagged up in the screening form, and interested participants deemed as ineligible will be contacted by the trial practitioner or facilitator team to verify their eligibility; if exclusion criteria are confirmed, interested participants will be signposted to alternative available support as appropriate, for example, to an MBCT for depression program run routinely at each involved site if participants experience high levels of depression. As this is the mechanism already in routine place for staff recruitment for these interventions through NHS trust well-being services, we will keep our exclusion criteria to the minimum.

Sample Size

With reference to the trial's primary outcome, 5 points on the PSS-14 will be considered as the minimum clinically important difference. Assuming a 2-tailed .05 significance level with 90% power (using analysis of covariance) and SD 7.7, a baseline and follow-up correlation of 0.2, and the correlation among follow-up measures of 0.7, a total of 76 participants will be needed to estimate the treatment effect from baseline at 20 weeks after randomization. Assuming the average group size is 8, the intraclass correlation coefficient is 15%, and the attrition rate is 25% (considering potential loss to follow-up), the final sample size was inflated to 208 participants to be randomly recruited in 26 groups (1:1 ratio) across all the recruitment sites. However, upon monitoring follow-up rates after approximately one-third of the participants were randomized, it was highlighted by a blinded independent statistician that the follow-up rate was approximately 62% and the group size was approximately 10. Therefore, the trial management group decided to update the sample size with 85% power to mitigate the loss to follow-up. A substantial amendment was submitted, and ethics approval was received for the sample size to be increased to 260 participants, divided across 26 groups.

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Ethical Considerations

The trial has been granted ethics approval by the research ethics committee (East Midlands-Nottingham 1), the Health Research Authority, and the Health and Care Research Wales Committee (reference number 23/EM/0109) and has received favorable approvals from the research and development governance bodies of the participating NHS trust sites. The study has also been reviewed by the National Institute of Health and Care Research Applied Research Collaboration East Midlands (ARC-EM) Scientific Committee as part of the funding application.

The trial will be overseen by an independent ARC-EM Scientific Committee. The members of the committee will be drawn from outside the institutions where the research team currently works to ensure the committee's independence from the research team. It will serve the function of a trial steering committee and a data monitoring committee. The trial will be reviewed every 6 months through reports to the ARC-EM Scientific Committee and presentations of progress to the committee by the study team. The data monitoring committee will review safety data and periodically review the conduct of the study. The steering committee will take responsibility for the scientific validity of the study protocol, assessment of study quality and conduct, and the scientific quality of the final study report. The sponsor and the investigators participating in the trial bear the final responsibility for the conduct of the trial. The trial will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, the principles of Good Clinical Practice, and the UK Department of Health Policy Framework for Health and Social Care.

All participants will sign the participant consent form. Participants will be informed in the PIS that entry into the trial is entirely voluntary and that their health care, work, and legal rights will not be affected by their decision. Furthermore, it will be explained that they can withdraw at any time during the trial (including at follow-up) but that in the event of their withdrawal, data collected up to that point cannot be erased and may still be used in the final analysis. It will also be clearly stated in the PIS that potential participants who decide not to take part in the trial can proceed with enrolling in the respective or other well-being interventions delivered routinely at a given site (but are not part of the trial). Moreover, for intention-to-treat (ITT) purposes, as stated in the PIS, participants will have the right to decide not to withdraw from the trial entirely but withdraw from the program (intervention) while they may still contribute to the trial by completing the web-based survey at the 3 follow-up time points, or they can carry on with their participation in the program but withdraw their partaking in the completion of the web-based survey at the follow-up time points. Insurance and indemnity for trial participants and trial staff are covered within the NHS Indemnity Arrangements for clinical negligence claims in the NHS, issued under the cover of Health Systems Global 96/48. There are no special compensation arrangements, but trial participants may have recourse through the NHS complaint procedures. The University of Nottingham, as the research sponsor, indemnifies its staff with both public liability insurance and clinical trials insurance for claims made by research participants.

Randomization and Blinding

Once consent is obtained on the REDCap platform, they will be randomly allocated in a 1:1 ratio to either the MBCT-L or SRP intervention. The online format and delivery of the interventions allow the allocation of participants to take place across the participating sites; this is expected to facilitate timely and sufficient recruitment within and across the intervention groups running at any site until the 2 intervention groups are full in each recruitment wave throughout the trial. Randomization will be conducted via a web-based randomization system set up by a clinical decision support system supported by the University of Nottingham. The randomization system will ensure that all the researchers involved in the outcome assessments (SP, PP, and JR) remain blinded to intervention allocation. Participant allocation to either intervention arm will be solely facilitated by a project administrator who will manage the randomization system independently of the research team following specified standard operating procedures. The study statistician will also be blinded to treatment allocation. In the event of inadvertent unblinding, the details of the unblinding incident will be recorded in the study log, relevant sponsor and monitoring committees will be informed (eg, the university sponsor, the research ethics committee, and the ARC-EM Scientific Committee), and the extent and impact of the unblinding will be assessed. All participants will complete the same outcome measures in the survey, so that researchers or outcome assessors will not be able to determine the participant's group based on the response. In view of the nature of the interventions, participants cannot be blinded; they will be informed of which treatment arm they have been randomized to and will be notified through a letter or via email sent to them by the project administrator, which will also include information on the intervention delivery (eg, dates and times, requirements for attendance, and joining instructions).

Interventions

Overview

The 2 interventions that participants will be randomized, MBCT-L or SRP, will be delivered online via a videoconferencing platform, that is, Microsoft Teams, taking place in a group format once a week at different times and days, allowing participants to indicate (at the time of consent) which group times they would opt for if they were to be randomized to either intervention. The sessions on either intervention will not be recorded. There will be 3 recruitment waves in total, with the interventions starting at various time points during a given recruitment wave and both intervention arms starting in the same week in each recruitment wave to allow synchronized data collection. The CONSORT (Consolidated Standards of Reporting Trials) flowchart (Figure 1) depicts an outline of recruitment, consent, randomization, and assessment processes.

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Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flowchart—revised. CF: consent form; MBCT-L: Mindfulness-Based Cognitive Therapy for Life; NHFT: Nottinghamshire Healthcare National Health Service Foundation Trust; NUH: Nottingham University Hospitals; PIS: participant information sheet; SPFT: Sussex Partnership National Health Service Foundation Trust; SRP: Stress Reduction Psychoeducation; TEWV: Tees, Esk and Wear Valleys National Health Service Foundation Trust.

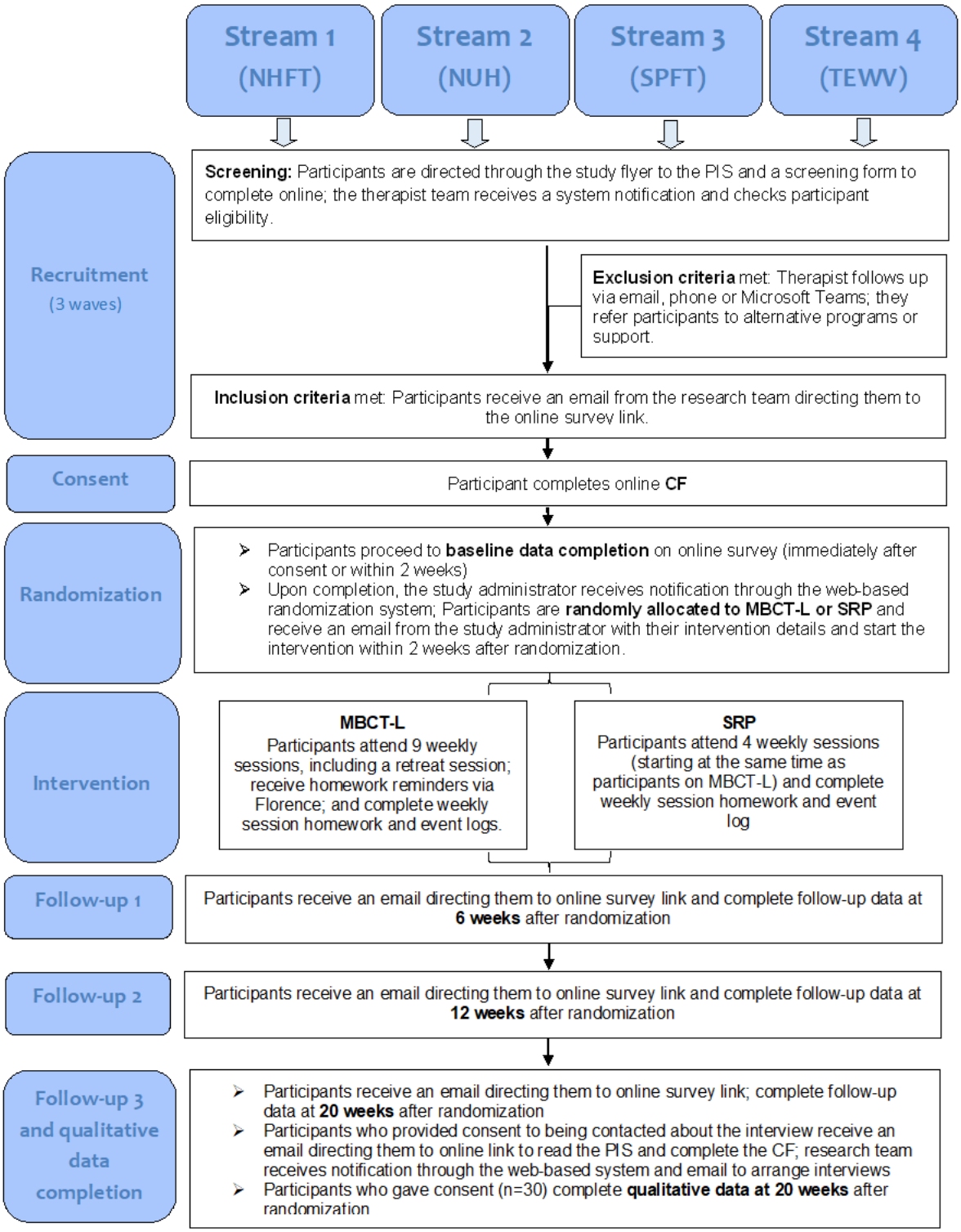

The MBCT-L Intervention

MBCT-L integrates conventional cognitive therapy techniques with stress reduction techniques and mindfulness practice, as in the original MBCT version, but has been adapted to apply to the general population as per established protocol [9]. The program includes 8 online weekly sessions lasting approximately 2 hours and an online practice day lasting approximately 6 hours. MBCT-L will run for 9 consecutive weeks or 10 weeks if a 1-week break is included (eg, due to school break or holidays) in a group-based format with an average of 8 participants recruited per group. The content includes themed teaching every week and guided meditation practices (eg, breathing practice and body scan), as well as everyday homework practices lasting

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30 to 45 minutes. Participants will receive frequent automated text reminders about their upcoming sessions and homework or home practices via an automated text messaging service provided by a Generated Health system, Florence [27]. The program will be delivered by approximately 8 trained MBCT practitioners or facilitators across the main NHS trust sites, who are part of the teaching team involved in the MBCT-L interventions already being offered to public sector staff through the NHS trust services and have been trained under, and follow, the same MBCT training protocol [9].

The MBCT-L program broadly follows an overarching structure of developing mindfulness skills intended to enhance attentional control and awareness, cultivating a deeper understanding of how distress is created and maintained and how mindfulness training can address factors that contribute to its maintenance, learning skillful ways of relating to experience developed through awareness and practice, and learning to recognize unhelpful reactive patterns in everyday life and cultivate the capacity to respond to these with mindfulness and compassion. In the second part of the program, participants practice the application of this learning to everyday life, including work, to respond more effectively to stress and enjoy the positive aspects of life.

The SRP Intervention

The SRP intervention will be delivered in 4 online weekly sessions lasting approximately 2 hours and running for 4 consecutive weeks or 5 weeks if there is a 1-week break (eg, school break or other holidays). The program will run as it is currently being offered as standard care across Nottinghamshire and all the other regions in England, through NHS Talking Therapies (formerly known as Improving Access to Psychological Therapies) or NHS trust or other health care services. Its content is focused on psychoeducation around well-being and stress management, combined with relaxation strategies [23]. Specifically, the program consists of sessions focused on areas of stress, well-being, and goal setting; sleep hygiene; anxiety and depression; behavioral activation; problem-solving; thinking errors; and a final recap, review of goals and thoughts for future well-being. Participants will be encouraged to work between sessions by engaging in a stress reduction technique of their preference daily for approximately 30 minutes and through a diary activity (eg, behavioral activation diary). They will receive email reminders to complete these and attend the upcoming sessions.

Recognizing that SRP programs can vary in their content and format or structure in how they are being offered across NHS trusts and other organizations in the United Kingdom, the standard 4-session structure will be adopted as the optimized form of its delivery. The SRP will also explicitly avoid embedding any mindfulness-based techniques, as these are not core or essential elements of a stress reduction approach, while it is important for the RCT to adhere to NICE-recommended standards, which indicate that 4 sessions are optimal when group sessions are delivered by experienced facilitators. The program will be delivered by 3 experienced facilitators (2 psychological well-being practitioners and 1 psychiatrist) across the SRP groups recruited across all sites, ensuring consistent delivery of the intervention across all participating NHS sites.

Intervention Compliance

Intervention adherence, compliance rates (ie, session attendance), and any other data specific to the intervention, where applicable, will be collected electronically via a password-protected Microsoft Online Form, as per routine therapy protocol during the MBCT-L and SRP interventions. Retention rates and turnover by randomized group will be determined after the first recruitment wave. We will consider participants as compliant if they have attended 50% of the sessions on either intervention. Participants will not be allowed to continue with the intervention if they miss the first couple of sessions in either intervention arm. Participant attendance will be recorded by the facilitators for each intervention, as per routine practice, and reported to the project administrator, who will monitor attendance and contact participants if they miss the first or second session. Home practice adherence will not be monitored or recorded; as per routine practice, participants will be strongly encouraged to engage in home practice outside the formal weekly sessions; however, a potential lack of daily commitment to practice should not affect participants' session attendance. Practitioners or facilitators will prompt participants to complete their daily home practice between intervention sessions and remind them of the upcoming intervention sessions.

Outcome Assessments

Overview

Participants who provide consent will be required to complete the outcome assessments via web-based surveys through REDCap, which will contain the primary and secondary measures at baseline (before the intervention); up to 2 weeks before randomization; and at follow-up time points at weeks 6, 12, and 20 after randomization. Participants in both arms will receive the same outcome measures. Participants will be able to save their responses and return to the survey to complete their assessments at a later point. For both incomplete baseline and follow-up surveys, participants will receive 3 automated email reminders through REDCap asking them to complete the survey. If the survey is still incomplete, the research team may then send out 1 further personalized email reminder from the study email address.

Primary Outcome

The primary outcome will be the change in the PSS-14 [24] score from baseline to 20 weeks after randomization. The PSS-14 was selected as the primary outcome measure as it is a well-validated and internationally used self-report scale of perceived stress and has been widely used in previous trials assessing changes in stress levels in diverse populations, including public sector workers.

Secondary Outcomes

All secondary outcome measures used in the trial are widely recognized as valid and effective scales in assessing well-being, mental health state, and work-related engagement and performance in various populations, including health care workers. Although these measures are relatively brief to

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administer, they present limitations due to their reliance on self-report, which can entail biases, such as recall bias, and may not index the full complexity of an individual's experience of stress or poor well-being. Secondary outcomes will all be collected at 6, 12, and 20 weeks after randomization. These standardized measures have been commonly used in intervention studies to assess changes in well-being, mental health state, work-related satisfaction, engagement, and performance (Textbox 2 [24,28-33]).

Textbox 2. Secondary measures used in the trial.

- Perceived Stress Scale-14 [24]: This is a self-report scale that assesses the degree to which the respondent has perceived situations in their life as stressful within the past month. Responses are obtained through 14 items requiring ratings of statements from 0 (never) to 4 (very often). The assessment at 6 and 12 weeks will be treated as secondary outcomes.
- Generalized Anxiety Disorder-7 [28]: This is a 7-item instrument used to measure or assess the severity of generalized anxiety disorder. Each item asks the individual to rate the severity of their symptoms over the past 2 weeks. Response options range from 0 (not at all) to 3 (nearly every day).
- Patient Health Questionnaire-9 [29]: This is a 9-item scale used to measure the severity of depression. Each item asks the individual to rate how often they have been bothered by the listed symptoms over the past 2 weeks, with responses ranging from 0 (not at all) to 3 (nearly every day).
- The International Trauma Questionnaire [30]: This is a brief measure of posttraumatic stress disorder and complex posttraumatic stress disorder. Respondents are asked to think of an experience that troubles them the most and indicate how much they have been bothered by that experience in the past month by responding to 18 questions on a scale from 0 (not at all) to 4 (extremely). Questions refer to ways people typically feel, think about themselves, and relate to others.
- Five Facet Mindfulness Questionnaire [31]: The questionnaire items assess 5 aspects of mindfulness and their impact on well-being. Participants are required to rate statements on a 5-point scale from 1 (never or very rarely true) to 5 (very often or always true) on facets of mindfulness relating to describing, observing, nonreacting, acting with awareness, and nonjudging.
- Copenhagen Burnout Inventory [32]: This measures personal and occupational burnout in 19 items, including overall physical and psychological fatigue (6 items), physical and psychological fatigue related to work (7 items), and client-related burnout (6 items). Answers include "always, often, sometimes, rarely, and never or almost never" or "to a very high degree, to a high degree, somewhat, to a low degree, and to a very low degree." The possible score range for the burnout scales is 0 to 100 (response options are coded in scores of 100, 75, 50, 25, and 0). Higher scores indicate a higher degree of exhaustion.
- Utrecht Work Engagement Scale-9 Item [33]: This measures 3 dimensions of work engagement, including vigor (3 items), dedication (3 items), and absorption (3 items). Items are presented as statements to which persons respond on a 7-point scale, with anchors 0 (never) and 6 (always or every day).

Economic Evaluation

We also plan to conduct an economic evaluation from the perspective of the NHS and personal social services.

Measures of Cost-Effectiveness

The primary measure of cost-effectiveness includes the incremental cost-effectiveness ratio (ICER) per quality-adjusted life year (QALY) gained for the MBCT-L versus SRP interventions.

Secondary measures include ICER per reduction in PSS-14 scores for MBCT-L versus SRP.

The following outcome data will be collected:

- Health-related quality of life outcomes will be collected at baseline and 6, 12, and 20 weeks after randomization. These will be measured via the widely used EQ-5D-5L [34].
- A health economics assessment adapted from the Client Service Receipt Inventory [35], which has been successfully used in a wide variety of studies of mental health, community-based health, and social care services, will be conducted. A mental health customized version will be administered to collect self-reported resource use for 6 months preceding data collection at baseline, 6 weeks preceding data collection at 6-week follow-up, 6 weeks preceding data collection at 12-week follow-up, and 8 weeks preceding data collection at 20-week follow-up. It is intended that the data gathered from these measures will be used for a cost-effectiveness analysis, subject to trial outcomes, should MBCT be superior to SRP.

Other Data Acquisition

We will aim to collect demographic data, including information about protected characteristics (eg, age, gender, ethnicity, pregnancy, marital status, highest qualification, religion, sexual orientation, disability, first language, caring responsibilities, and refugee and asylum seeker status). We will also gather job-related information on the job sector, job title, duration in the post, monthly salary, presenteeism, absenteeism, turnover intention, and service use (including well-being programs, primary care, outpatient appointments, inpatient appointments, private therapy, and medication), and, where available, practitioner or facilitator feedback data. Furthermore, data will be collected on recruitment uptake or rate; session attendance; compliance with treatment; any adverse events (AEs); attrition or dropout rates (in between intervention and loss to follow-up); and reasons for attrition or noncompliance, including diversion and inclusion barriers to intervention uptake and implementation.

Qualitative Study

A subsample of 30 participants (n=15, 50% in each intervention arm) will be recruited for the qualitative study after 20-week randomization (within an 8-week data collection window). The semistructured interviews will inquire into participants' perceived changes after intervention and their experience and

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views in relation to intervention uptake and acceptability. They will be conducted online via Microsoft Teams and will be video or audio recorded for transcription purposes, depending on the participant's preference for keeping the camera on or using the audio only.

Qualitative Study Outcomes

Semistructured interview data will elicit the following qualitative outcomes from participants:

- Perceived changes in their well-being and quality of life (ie, beneficial impacts and adverse effects)
- Perceived changes in their levels of work satisfaction, engagement, and performance (ie, beneficial impacts and adverse effects)
- Nature of well-being support sought and whether the given intervention has met their expectations
- Barriers and drivers to intervention route to uptake, attendance, engagement, and adherence (including aspects related to the intervention delivery and content or structure, personal or work circumstances, and managerial support)
- Recommendations for future improvement of intervention design and implementation

Dissemination

We will report the trial findings and recommendations on the digital intervention product refinements to our PPIE group and other stakeholders, scientific audiences, the NHS confederation, NICE, networks of nursing and medical directors of NHS organizations, social care directors, Academic Health Science Network-East Midlands, NHS England (previously known as Health Education England), and professional well-being practitioner groups who will be required to staff and deliver these interventions.

AEs in the Study

The structured context of MBCT-L and SRP includes psychoeducational materials or resources on how to manage distressing experiences arising during meditation or at other times in practice. The trained practitioners or facilitators delivering these interventions have a mechanism in place as routine practice for providing tailored advice and support at any stage. Once participants have commenced the intervention, they are prompted to report any AEs, emotional or physical, to the practitioner or facilitator. This will trigger a consultation meeting between the participant and the therapist team, who will provide advice and refer the participant to further support as appropriate (within the mental health well-being team, general practice, or mental health services). Participants are prompted to make adjustments during the meditation exercises to reduce any bodily discomfort and exert physical effort at a level that is comfortable for them during any body-moving exercises. Participants are also signposted in the PIS to available well-being support resources that they can access outside the trial.

AEs may occur and may or may not be linked to the intervention. These can include exacerbated emotional reactions, an increase in frequency or intensity of a preexisting (mental or physical) episodic event or illness, and worsening of symptoms present at baseline following the start of the study. Any AEs will be assessed for seriousness, expectedness, and causality. The causal relationship of an AE to the study intervention is assessed by the chief investigator in consultation with medical experts of the research team as "possible," "probable," or "definite" and will be reported as an AE in the study log and the ARC-EM Scientific Committee. Participants will be asked to contact the practitioner leading their intervention group or the study site immediately in the event of an AE. Any AEs will be recorded and closely monitored until resolution, stabilization, or it has been shown that the study treatment or intervention is not the cause. The chief investigator shall be informed immediately of any AEs and shall determine the seriousness and causality in conjunction with the therapists and the medical practitioners who are part of the research team. These will be recorded in the study log and instigate further investigation and follow-up if or as appropriate. The chief investigator shall be responsible for all AEs reported to the ARC-EM Scientific Committee and Ethics Committee Board.

Data Management Plan

Source data will include participant demographic data, consent, assessment data logged by participants and the research or study team on the REDCap system, as well as any other supplementary data logged by the research or study team. Source data will also include participant interview transcripts. Access to the research data will be limited to assigned trial staff and researchers to allow trial-related monitoring and audits and ensure compliance with data management regulations. All data will be stored on secure University of Nottingham platforms, that is, in access-restricted, password-protected online research folders on the University of Nottingham OneDrive (Microsoft Corporation). Access will be restricted by user identifiers and passwords (encrypted using a 1-way encryption method). Research data will be anonymized by allocating a unique trial-specific number or code in the database. It will be ensured that identifiable data will be stored separately from research data and that the researchers do not have access to the identifiable or randomization data to retain blinding.

Interview Data and the Use of Videoconferencing

Only platforms approved by the University of Nottingham (ie, Microsoft Teams) will be used for conducting interviews, as these platforms are encrypted. To retain privacy and confidentiality, researchers will ensure that they are working in an area where conversations cannot be overheard and the computer screen cannot be observed. Researchers will not use personal accounts or devices to contact participants. Interviews will be recorded on Microsoft Teams to facilitate transcription; interview recordings will be deleted from Microsoft Teams as soon as they are transcribed. The interview recordings will be pseudonymized, and any identifying information will be redacted in transcripts. Interview recordings and transcripts will be saved on access-restricted, password-protected online research folders on the University of Nottingham OneDrive.

The trial will follow the electronic data management policy and procedures of the University of Nottingham (sponsor) in accordance with the Data Protection Act 2018.

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Analyses

Statistical Method

All analyses will be conducted on an ITT basis; a description of the planned ITT and sensitivity analyses for both primary and secondary outcomes conforming to the estimand framework [36] has been provided in Multimedia Appendix 2. After exploratory analysis, multilevel modeling will be implemented to quantify the treatment effect estimate and its precision over the follow-up time points, with the treatment implementation group and each participant as a higher-level analytic unit and baseline measure, allocation status, follow-up time point, and interaction of follow-up×allocation as covariates with fixed effects. A similar analytic approach will be used to quantify the treatment effects on all secondary outcomes. Missing values will be explored and imputed using a multiple imputation approach under the missing at random assumption for the missingness mechanism [37]. Sensitivity analyses will be performed to explore the robustness of the treatment effect estimate, sensitive to the influence of data missingness, various limitations of the data, assumptions, and analytic approaches to data analysis. The latest available version of Stata (StataCorp) will be used for data analysis. A detailed trial statistical analysis plan setting out the proposed analyses has been published [38].

Economic Analysis

The initial estimates of cost-effectiveness will require a base case analysis before exploring the impact of uncertainty. To perform the base case analysis, first, each individual participant within the trial will have an estimated intervention cost, a health care cost, a QALY score based upon their EQ-5D-5L responses, and a PSS-14 score. Second, using ordinary least squares regression, incremental costs, QALYs, and PSS-14 scores will be estimated for MBCT-L versus SRP groups. These incremental values will then be used to estimate the ICER per QALY gained and the ICER per PSS-14 reduced. The base case analysis will use data from all participants who report complete data; however, a secondary analysis using all participants' data will be conducted, with missing data controlled for using multiple imputation [37].

The base case analysis will not include any productivity costs (ie, due to absence from work), as per NICE guidelines [39]. A secondary analysis will be conducted, whereby productivity costs will also be included, using a similar approach as the base case analysis. All analyses will be conducted using the latest version of Stata. Multimedia Appendix 3 provides a detailed economic analysis plan.

Qualitative Data Analysis

On the basis of the expected nature of the data as per previous studies, thematic analysis is intended to be applied to the transcribed data from the semistructured interviews. The analytic approach is anticipated to be reflexive, guided by key principles of the grounded theory framework and the guidelines by Braun and Clarke [40,41] following their 6-step thematic analysis methodological approach. The latest version of NVivo (Lumivero) software will be used for coding. The process of codebook development will be adopted until a code agreement has been reached, and a reflexive log will be kept to document coders' personal reflections and observations emerging during the coding and thematic analysis process [41], which will be used as a tool for minimizing potential bias in interpretation. A codebook example will be provided following the guidelines of Boyatzis [42], illustrating how codes were generated from participant quotes and how codes, in turn, led to the derivation of themes and subthemes. Interrater reliability between 2 raters will likely be determined based on the formula suggested by Miles and Huberman [43], which is suitable for small-scale participant samples and is defined as the number of agreements or the number of agreements and disagreements, with 75% being the minimum percentage to indicate adequate levels of agreement [44].

Results

Recruitment of participants commenced on August 29, 2023. The target recruitment of 260 participants was reached on April 30, 2024. Follow-up outcome data collection was completed on September 30, 2024. We anticipate data analysis to be complete by July 2025.

Discussion

Anticipated Findings

There has been increasing recognition of the importance of well-being in the public sector workplace and its association with individual and work-related outcomes [5-7]. In light of the disproportionately high rates of psychological distress in health care, public care, and other employees in the public sector [1], well-being support provision offered within organizational settings is conducive to maintaining a healthy and effectively productive workforce. The overall aim of this trial is to determine whether an online mindfulness-based variant, MBCT-L, is superior to an online stress reduction approach, SRP, in reducing perceived stress and improving other mental health and job-related outcomes in health care and other public sector employees. Both interventions are recommended by NICE as effective psychotherapies for improving psychological well-being in public sector employees at risk of poor mental health in the context of individual-level therapies that can reduce stress levels and improve general psychological well-being. While the two approaches differ in their nature, structure, and program duration, this study is the first to directly compare these two types of interventions for their effectiveness and cost-effectiveness, being delivered in online modalities. Beyond the primary outcome of perceived stress, the trial will secondarily assess intervention change on other aspects of mental well-being (eg, anxiety, depression, posttraumatic stress, and burnout), which have been found to be affected in these cohorts, as well as work-related outcomes, such as work engagement, satisfaction, and performance, which are factors linked to presenteeism, absenteeism, and turnover in the workplace [5-7].

Furthermore, the trial will collect additional data through the web-based survey, which will include, among other data, information on work engagement and turnover intention, absenteeism, and previous uptake of well-being support within or outside the work settings, to allow us to describe the mental

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health state and needs of the given cohort. The NICE committee also stressed the potential resource impact of rolling out such interventions in the workplace sectors. Moreover, we will aim to conduct a budget impact analysis to inform on intervention cost in practice, although this will depend on the outcomes of the trial in terms of the intervention's clinical effectiveness and cost-effectiveness.

While NICE recognizes that organizational-level and managerial-level policies and practices are important to address work-related issues, particularly in ensuring equality and work satisfaction, the committee has highlighted that local commissioners and health care providers have a responsibility toward enabling staff at risk of poor well-being to take up such well-being interventions in the workplace, within a supportive organizational culture and climate [8]. This is of particular importance, given the long-term impact of the COVID-19 pandemic on public care staff and considering its particular impact on individuals from Black, Asian, and minority ethnic communities and deprived socioeconomic backgrounds [45]. Preliminary reports from the NHS CHECK study, one of the largest ongoing cohort studies in the United Kingdom launched during the pandemic to longitudinally investigate the psychosocial impacts of COVID-19 on NHS staff, indicated that women, younger staff, and nurses faced poorer mental health outcomes than other health care staff and that NHS staff from ethnic minority communities faced significant workplace inequalities leading to negative health outcomes [46]. This trial will collect information on protected characteristics and recruitment uptake, session attendance and treatment compliance, attrition and dropout rates, and reasons for attrition and noncompliance. This includes barriers to intervention access, uptake, and engagement that may reflect issues related to equality, diversion, and inclusion, which will be explored in more depth via semistructured interviews in the qualitative substudy.

Considering that interventions that are perceived to tackle mental health can be heavily stigmatized in some cultures [47], a limitation of this study might be the potential lack of engagement by individuals of certain sociocultural backgrounds. We will emphasize in the trial that both interventions are intended to help people cope more effectively with stress in the workplace and busy personal lives in an attempt to address such stigma. Advertising will be wide and will be aimed at reaching all staff groups within the target cohort. We will keep engaging in discussions with PPIE representatives; equality, diversion, and inclusion representatives at NHS Trust; or well-being champions about any particular approaches within the set study design that may help in engaging staff from different ethnic groups. Our lead therapist team has also examined the content of the trial interventions to ensure that they are culturally sensitive to equality and diversity issues; however, the anticipated qualitative input by participants on their experience with and acceptability of the interventions, gathered via the semistructured interviews, will contribute to refining the interventions toward improved future practice. Along similar lines, the inclusion of selected NHS sites across the United Kingdom in this study represents a limitation of the study design and the representativeness of the data. Moreover, the measures used in the trial may pose a challenge to the interpretation of results, given their self-report nature and potential biases in recall or response bias.

A further shortcoming integral to the end point of assessing the superiority of MBCT-L is the lack of its wide availability across the NHS trusts in the United Kingdom compared to the readily available SRP programs. To overcome this limitation and use the digital intervention modality, we have adopted a study design that allows NHS trusts in the United Kingdom, where MBCT-L is not available, to partake in the trial as "channeling" sites, allowing the recruitment of eligible staff on either of the 2 interventions delivered through the 4 main NHS trust sites in the trial. It is hoped that this approach will also help mitigate potential low recruitment rates or loss to follow-up.

Possible unintended outcomes might include adverse effects following engagement with the interventions. Currently, relatively little has been reported on the potential adverse effects of MBCT in nonclinical populations. However, in a recent systematic review of AEs in meditation practices and meditation-based therapies, including relaxation and MBCT exercises [48], it was found that adverse effects during or after meditation practices occurred in nonclinical populations too and were associated with meditation practices, particularly anxiety and depression. The overall prevalence of meditation AEs was 8.3% in 55 studies, reporting at least 1 adverse effect, and this percentage is similar to those reported for psychotherapy practice in general. The structured context of MBCT and SRP includes psychoeducational materials and resources on how to manage distressing experiences arising during meditation or at other times, while there is a mechanism in place in the trial for the participant to consult the therapist in the event of excessive discomfort or distress or to be directed to other well-being support. This trial will log any adverse effects reported during the intervention period and at follow-up, with plans in place to review these events and the conduct of the trial with the National Institute of Health and Care Research ARC-EM Scientific Committee and the external steering committee as well as to terminate a participant's engagement in the trial or the trial itself, should the criteria for doing so be fulfilled.

Conclusions

The outcomes of this trial are expected to inform the NHS and other public care services as to which intervention might be more effective to be commissioned for provision to their staff who access such well-being interventions through the integrated care pathways of the NHS trust or other organizational well-being resource channels. Furthermore, we aim to inform NICE in light of its review findings that did not include any evidence of online MBCT or any studies comparing the effectiveness of MBCT versus SRP approaches. In terms of impact, we hope that there may be some immediate benefits not only to the staff receiving the interventions but also to those NHS services and other public care areas that already provide these interventions in the United Kingdom and internationally, so that they can refine their practices.

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Data Availability

The deidentified quantitative datasets generated or analyzed during this study will be made available in the University of Nottingham Data Repository [49]. Deidentified minimal qualitative data, including quotes from across the participant sample and the corresponding codes, will also be shared on this repository in the form of a codebook. The generated participant interview transcripts will not be made publicly available due to potential breaches of participant confidentiality, as the transcripts are expected to contain personal and sensitive material.

Authors' Contributions

EN and RM were involved in funding acquisition. EN, RM, NN, TS, CS, PB, SP, and BG contributed to conceptualization. SP, PP, and JR curated the data, and BG and MPC were involved in formal analysis. EN, RM, SP, CS, PB, BG, TS, NN, RG, and MPC were involved in the study methodology. LAW, RG, and SM contributed to resources. EN was involved in writing the original draft, and all authors reviewed and edited the manuscript.

Conflicts of Interest

RM is the lead of the National Institute of Health and Care Research (NIHR) Applied Research Collaboration East Midlands (ARC-EM) Mental Health and Well-Being Theme, supported by the Nottingham NIHR Biomedical Research Centre, the NIHR HealthTech Research Centre Mental Health (MindTech), and an NIHR Senior Investigator Award. LAW is supported by the Wellcome Trust; PB is a coauthor of the Mindfulness-Based Cognitive Therapy for Life program. CS has received research funding as Chief Investigator and co-applicant to evaluate mindfulness-based interventions for NHS staff. She co-leads Sussex Mindfulness Centre (SMC). SMC leads the England-wide NHS England-funded MBCT therapist training programme in NHS Talking Therapies services and SMC receives funding to offer MBCT courses to NHS staff. All other authors declare no conflicts of interest.

Multimedia Appendix 1
SPIRIT checklist.
[DOCX File , 110 KB - resprot_v14i1e67695_app1.docx]

Multimedia Appendix 2
Estimand framework.
[DOCX File , 37 KB - resprot_v14i1e67695_app2.docx]

Multimedia Appendix 3
Economic analysis plan.
[DOCX File , 40 KB - resprot_v14i1e67695_app3.docx]

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Abbreviations

AE: adverse event
ARC-EM: Applied Research Collaboration East Midlands
CONSORT: Consolidated Standards of Reporting Trials
ICER: incremental cost-effectiveness ratio
ITT: intention-to-treat
MBCT: Mindfulness-Based Cognitive Therapy
MBCT-L: Mindfulness-Based Cognitive Therapy for Life
NHS: National Health Service
NICE: National Institute for Health and Care Excellence
PIS: participant information sheet
PPIE: patient and public involvement and engagement
PSS-14: Perceived Stress Scale-14
QALY: quality-adjusted life year
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SRP: Stress Reduction Psychoeducation

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Protocol

World Health Organization Evidence-Based Self-Help Plus Intervention for Stress Management via Chatbot: Protocol for Adaptation to a Tech-Enabled Model

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Abstract

Background: This paper describes the adaptation of an evidence-based intervention for mental health, Self-Help Plus (SH+), to a digital platform, aiming to expand mental health support through innovative technological solutions. The SH+ intervention, designed by the World Health Organization (WHO), is a low-intensity, self-guided program aimed at improving mental well-being. The intervention has been integrated into a chatbot-driven mobile app called “ALBA” (Automated Well-Being Assistant).

Objective: This protocol describes the stages of transition (porting) from a traditional face-to-face, group-based approach to a tech-enabled model, tailored specifically for women with breast cancer and pregnant women. The adaptation of this approach is described, focusing on 2 key aspects: (1) the shift from in-person delivery to a tech-enabled intervention and (2) the customization of the intervention to address the unique needs of the selected target groups.

Methods: The development of the ALBA app involved a collaborative, multidisciplinary approach combining expertise in psychology, eHealth IT, interaction design, and specific domain knowledge related to pregnancy and oncology. The development process followed 2 primary methodologies: user-centered design and service design. These approaches emphasize understanding user needs, promoting iterative improvements, and continuously incorporating user feedback. The development followed the Obesity-Related Behavioral Intervention Trials (ORBIT) model, which involves a cycle of literature review, stakeholder consultation, content development, software development, and evaluation. At the same time, specific attention was dedicated to (1) adapting the SH+ protocol to suit the chatbot-driven ALBA platform, (2) tailoring content to the target population, and (3) incorporating interactive features to improve engagement and potential efficacy.

Results: The manuscript outlines the key steps and processes involved in adapting the SH+ intervention into the ALBA digital platform. This includes an overview of the challenges and opportunities of translating a face-to-face, group-based intervention into a tech-enabled model and provides insight into how customization for specific populations, such as women with breast cancer and pregnant women, was integrated into the design of the platform. This is in view of informing future studies on the development and adaptation of already validated protocols into mobile health (mHealth) interventions in the field of mental health and mental well-being.

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Conclusions: The digital adaptation of the SH+ intervention into the ALBA platform could represent a significant step forward in expanding the accessibility and personalization of mental health interventions in potentially different settings and target groups. The use of virtual coaching applications can play a central role in improving the availability and ease of access of psychological support, even in different and mHealth formats. Future developments could include further testing in real-world settings to expand (1) adaptations for various target groups and (2) the purpose of use to range from primary prevention to more clinically focused interventions.

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KEYWORDS

digital health; virtual coach; mobile application; breast cancer; pregnancy; stress management

Introduction

Theoretical Framework

The current scientific literature shows an increasing demand for psychological support within the general population, with even higher levels when considering vulnerable populations exposed to stressful situations [1]. The World Health Organization (WHO) strategy for global mental health is based on principles of inclusivity and scalability, covering the entire arch of mental health promotion and prevention for citizens exposed to the risk of mental distress. The gap between the prevalence of mental health problems and the services available to those in need of specific interventions represents a current public health challenge, and WHO has further underlined this issue through the “mental health Global Action Program” [2], where particular attention is also paid to the potential role of digital technologies in facilitating both availability of services and optimized delivery of the intervention [3]. Digital health is considered a pivotal strategy to promote equitable, affordable, and universal access, reducing the gap between services and those who can benefit from receiving mental health interventions [4]. Indeed, an increasing body of literature confirms the potential of new technologies—including telemedicine, mobile health (mHealth) initiatives, and digital therapeutics (DTx)—for promoting a continuum of care from clinic to home and a stepped-care approach. In particular, low-intensity mental health interventions could be considered appropriate for implementation within digital health solutions [5]. They usually refer to specific programs where the active involvement of health care staff and specialists is not necessarily required. They are based on solid principles from evidence-based psychological interventions embedded into a self-help approach. Among them, WHO is promoting Self-Help Plus (SH+), a low-intensity intervention for stress management initially developed for hard-to-reach vulnerable population groups [6]. These types of interventions are usually designed to be transdiagnostic and easily adaptable in different contexts. Because of their general structure and purpose, low-intensity approaches can be easily used to increase access to viable and evidence-based psychological interventions to a broader target audience, reporting either limited or mild symptoms linked with mental distress or illness within a stepped-care approach [7]. The potential combination of evidence-based, low-intensity interventions and mHealth approaches could lead to an effective, sustainable, and inclusive strategy for improving the scalability of mental health interventions both in terms of prevention and treatment [8].

Intervention Characteristics

Self-Help Plus (SH+)

SH+ is a transdiagnostic intervention based on acceptance and commitment therapy, a third-wave cognitive behavior therapy (CBT) [9]. SH+ is structured into 5 sessions comprising audio recordings featuring mindfulness practices and exercises and aiding participants with recognizing barriers and facilitators related to stress management. Several studies report positive effects of SH+, considering long-term efficacy in a target population of refugees and asylum seekers [10-15]. Other studies show a still-debatable effect of SH+ when used with health care professionals [16].

SH+ is particularly suitable for a digital version, considering that (1) it is largely based on third-wave CBT techniques, which are usually more suitable than other psychotherapeutic approaches for transferring into interventions delivered by mobile apps [9], and (2) it includes self-help materials, like the illustrated Doing What Matters in times of stress (DWM) booklet [17] encompassing exercises designed to reduce stress and increase social support networks, adaptive coping mechanisms, and resilience. The latter has recently been converted into a web app for populations in war (RESPOND PROJECT) [18].

Target Populations: Public Health Issues and Sustainability

The adaptation model is designed to target two specific groups usually exposed to stress and potentially stigmatized when accessing mental health services: women with breast cancer and pregnant women.

Physical illnesses like breast cancer often coexist with psychological distress, including stress, anxiety, and depression [19]. Furthermore, chronic fatigue, sleep problems, body image disturbance, and diminished social interactions emerge as characteristic comorbidities. Additionally, women diagnosed with primary breast cancer continue to exhibit susceptibility to psychological ailments over an extended duration, underscoring the profound influence of this medical condition on patients’ quality of life [19]. It has been observed that a positive psychological attitude improves disease management and recovery, underscoring the significance of addressing mental health issues in addition to physical ones [20]. Numerous studies

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have highlighted the efficacy of CBT interventions for improving mental health and overall quality of life for women with breast cancer [21,22].

A second target group for this exercise is pregnant women. The transition to motherhood is an event that entails a significant change in a woman's life. Pregnancy is characterized by major transformations in the woman, with an impact on her physical, mental, and social well-being. The literature shows that pregnant women experience various psychological symptoms, the most frequent being anxiety, stress, and depression [23]. Thus, women in the perinatal period may experience worries and the fear of being unable to manage the changes associated with the period and the baby or children yet to be born [24]. To date, psychoeducational interventions that promote women's psychological well-being during pregnancy are scarce and tend to focus mainly on samples of women with psychiatric symptoms (eg, perinatal depression disorder) [25].

Despite the demonstrated effectiveness of psychological support interventions at alleviating stress in these target populations, only a negligible proportion of women belonging to these groups have access to psychological support. Indeed, the need for public resources and mental health care services is increasing due to the aging population and the rising prevalence of cancer and diseases that accompany mental illness. However, there are several challenges to accessing mental care services. For example, only 17% and 28%, respectively, of Italian and German women with breast cancer benefit from psycho-oncological support [26,27]. On the other hand, in a Portuguese study, only 13.6% to 20.2% of women screened positive for possible depressive disorders sought help during pregnancy [28].

Many women face geographical barriers, with specialized centers often located far away and limited availability of qualified personnel. Stigma and self-stigma can also prevent patients from seeking psychological support [29].

Opportunities From New Technologies

The use of digital tools has been explored as a means of providing psychological support in the midst of mental health care accessibility and sustainability challenges. DTx has surfaced as a convenient and readily accessible alternative for individuals pursuing psychological support [30]. They offer evidence-based and clinically evaluated digital mental health interventions delivered through software, addressing various diseases and disorders by providing treatment, management, and preventive measures [31]. mHealth services could improve accessibility and standardization of service delivery, as well as reduce costs and potential stigma associated with access to service through a stepped-care approach enabled by technologies [32]. mHealth and DTx might support a patient-centric approach, empowerment, and self-care despite the potential lack of human contact [33]. Using digital tools to promote psychological well-being can be an optimal solution specifically for pregnant women and those with breast cancer, considering the flexibility and adaptability to patients' needs characterizing these tools, as well as reduced social stigma [34]. The literature reports promising results concerning the effectiveness of DTx based on CBT targeting psychological well-being for both our target groups [35-38].

Objectives

The primary aims of this paper are as follows:

1. To map a solid pathway to design and adapt an SH+ protocol into a technology-enabled intervention, for implementation through a novel technological tool, the chatbot ALBA (Automated Well-Being Assistant).
2. To emphasize the specific adaptations of a digitally delivered, low-intensity intervention when used with subpopulations particularly exposed to social-psychological stressors, such as women with breast cancer and pregnant women.

Methods

This section reports the development of a virtual coaching solution named ALBA. Subsequently, the section clarifies the adaptation process of the SH+ protocol into a mobile app.

Process Overview

The development of the intervention leveraged the integration of different expertise, including psychology, eHealth IT, interaction design, and domain knowledge on pregnancy and oncology. A multidisciplinary team was created to account for the users' different needs and to accommodate for psychological consistency of the intervention and the proper adoption of IT requirements and user-design principles in the process, to ensure high quality in terms of adaptability of the proposed tools in the digital context.

The entire development of the intervention is based on two main methodologies: user-centered [39] and service design [40]. These approaches emphasize understanding and meeting user needs, promoting iteration and continuous improvement based on user feedback. SH+ will be developed iteratively, following the Obesity-Related Behavioral Intervention Trials (ORBIT) model [41], as illustrated in Figure 1. The development process included a literature review; exploration, incorporating input from user representatives, health care providers, and eHealth experts, including designers and developers; intervention content development, which was identified and adjusted from the SH+ intervention manual; iterative software development and formative evaluation; and finally, considerations regarding privacy, security, and organizational anchoring.

After the preliminary phase of literature review and integration of the WHO protocol, we systematically carried out the subsequent steps to develop the ALBA chatbot prototype. Following the ORBIT development process ensures a scientifically step-by-step approach to recognize standardized creation of digital behavior change interventions. We then progressed to the initial stage of the ORBIT model, specifically Phase 1a (Define). This phase is designed to establish a solid foundation for the intervention by clearly defining the clinical problem to be addressed as well as the targets and ensuring that the intervention is conceptually sound and grounded in relevant theory and empirical evidence. In line with this, our goal was to adapt and refine the core components of SH+ prior to

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feasibility testing. Accordingly, this paper focuses on the initial adaptation methodology, and the process is described in detail in the following sections and summarized in Table S1 (see Multimedia Appendix 1). In contrast, real-world usage metrics, such as dropout rates, session completion, and participant feedback, will be addressed in later phases, including preliminary testing (Proof of Concept and Pilots) first and subsequent efficacy and effectiveness trials. These results will be presented in future publications.

Figure 1. The Obesity-Related Behavioral Intervention Trials (ORBIT) model [41].

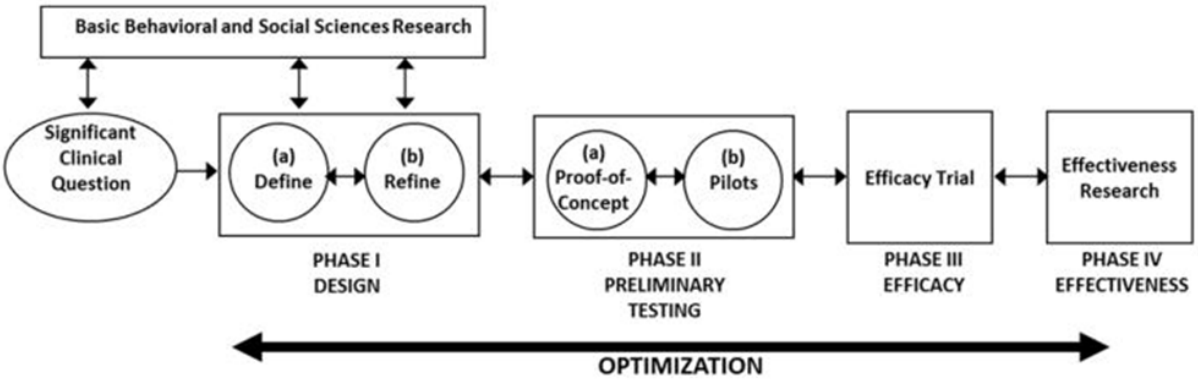

Adaptation from SH+

Content

The SH+ package has the following 3 main components: a prerecorded audio course, a facilitator manual, and the DWM booklet. All materials have been downloaded and translated (if necessary) from the WHO website [42]. The audio material imparts key information about stress management and guides participants through individual exercises and small group discussions. The innovation is that main intervention components are delivered as intended through the use of prerecorded audio, without the burden of extensive training and supervision to target hard - to - reach populations. SH+ is structured into 5 sessions based on acceptance and commitment therapy for stress management, namely (1) grounding, (2) unhooking, (3) acting on your values, (4) being kind, and (5) making room. The initial phase involved carefully examining the guide manual and audio. A judicious assimilation of selected components from the DWM booklet complemented this endeavor. Emphasis was placed on augmenting the visual and illustrative facets, notably by incorporating cartoon- and comic book–like elements.

The working group then ventured into adapting the group and in-person intervention to an individually delivered approach through a chatbot on an app. This transposition required various human and logistical factors to be changed or reconsidered to accommodate the new mode of psychological support delivery. ALBA is responsible for disseminating diverse content forms such as textual materials, auditory cues, video presentations, and graphical depictions (Figure 2A). The auditory components about SH+ exercises, alongside visual elements, are slated for comprehensive modification, tailored to suit an intervention delivered through mobile devices. Furthermore, the integration of psychoeducational elucidations of complex concepts is realized through videos or graphical representations. This strategic approach was conceived in response to the challenges posed by the transfer of substantial didactic information within the confines of a chatbot-mediated interaction.

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Figure 2. Automated Well-Being Assistant (ALBA) chatbot and its functionalities as a virtual coach (VC). AI: artificial intelligence.

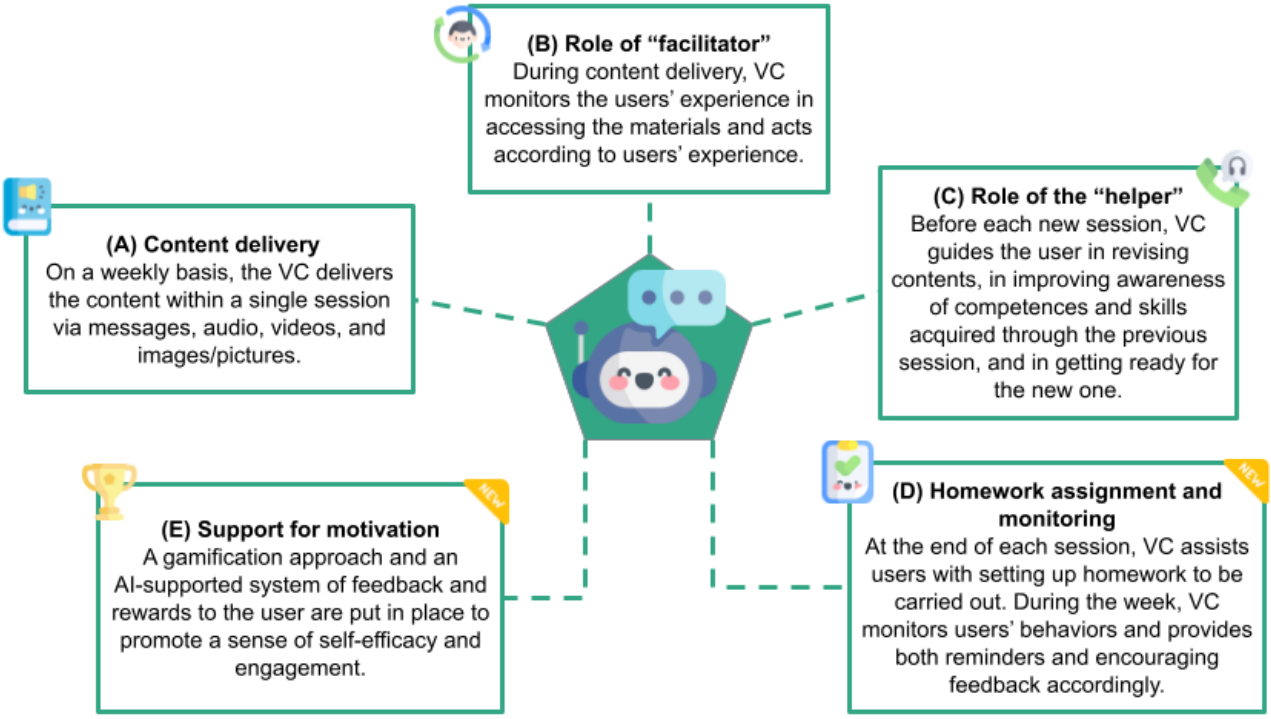

Guide

The facilitator guide manual of SH+ helps trained nonspecialist facilitators conduct the course using prerecorded audio materials. The facilitators run the group, run discussions, and answer any questions. They also make sure the group runs safely. They have a limited role in explaining content as this mostly comes from the audio. In the RESPOND interventions [18], the user also receives weekly support through a 15-minute telephone call from a "helper." The helper, as a trained individual, adheres to a predefined script and is responsible for initiating weekly telephonic interactions with the participant. These interactions serve multiple purposes of supporting, encouraging, problem-solving, and vigilantly tracking the participants' advancements along the trajectory of stress management.

The conventional role assumed by facilitators in the physical realm is supplanted within this context by ALBA. This automated agent guides participants throughout the sessions (Figure 2B). ALBA uses prewritten scripts with the option to provide personalized responses based on user button choices and free text answers. Although this approach may not offer the same level of customization as generative methods, it ensures SH+ protocol transposition standardization and safeguards against potential issues such as hallucinations and biases commonly associated with generative artificial intelligence models [43]. The intervention was constructed in such a way that ALBA is always the first to interact with the user. It is currently not possible for the user to ask specific questions. Additionally, the chatbot functions in an interactive capacity, prompting moments of introspection and contemplation. It engages participants through a series of inquiries, encompassing both directed and open-ended questions, thereby soliciting feedback pertaining to the comprehensibility and lucidity of the disseminated subject matter. ALBA will also assume a role similar to that of the helper within the RESPOND protocol framework (Figure 2C). Its operational function encompasses the supervision and oversight of exercise implementation, primarily bolstering participant engagement and fostering intervention adherence. Notably, integrating these roles constitutes an innovative and resource-efficient approach to orchestrating the participant's progression through the sessions. Moreover, this amalgamation inspires the participant with a consistent and reassuring sense of guidance.

Adaptation for the Target Populations

Participants

Participant recruitment will be conducted through word of mouth and direct acquaintances and by advertising the study within public health care settings. Only volunteers aged ≥18 years will be included. All data will be collected confidentially with participants' informed consent. For more details about co-design participant recruitment, see our previous study [44].

A thorough evaluation of the psychological states of prospective female participants is undertaken before they engage in the intervention. This evaluative process encompasses an appraisal of key indicators of mental well-being, thereby facilitating the discernment of suitability for study inclusion. This procedural component serves as a crucial gatekeeping mechanism and furnishes a foundational benchmark against which the eventual intervention's effectiveness can be gauged. Implementing baseline and subsequent temporal administration of questionnaires yields a comprehensive and scientifically based view, thereby illuminating the trajectory and impact of the final intervention over time. Regarding materials, they have been translated into Italian and culturally adapted for the target populations. Exemplary content designed for humanitarian emergencies is redrafted to suit the context of stressful events

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experienced by Italian women (eg, typical familiar environment, medical conditions). The chatbot's functionality is attuned to the distinctive requirements of the designated populations. To elucidate, all pertinent materials are tailored to encompass a prototype generic Italian female user, incorporating requisite specific adaptations (eg, Italian feminine adjectives and word desinences). Throughout the whole design process, a careful assessment is directed toward the potential transmutation of exercises into a stress-inducing factor (eg, focusing on body exercises for women diagnosed with breast cancer).

Session

The original SH+ intervention is organized in 2 - hour sessions and groups of 20 to 30 people on an established weekly schedule. ALBA releases dialogue sessions in this digital translation, but the intervention is literally in the end user's hands, offering a self-help intervention wherever she wants. Moreover, the user can personalize the session's day. The dialogue duration is fixed at 40 minutes. To support adherence, the session can be divided into 2 mini sessions on 2 subsequent days, preventing user fatigue and improving the usability of both the chatbot and the app. After completing a session, participants receive supportive and motivational reminders and feedback (Figure 3). This facilitates the establishment of a routine, increasing exercise completion in populations with different personal and time management needs, like pregnant women and women with breast cancer.

Figure 3. Representation of the intervention's structure in an exemplary week (Week 2: Session Unhooking). DWM: Doing What Matters in times of stress; SH+: Self-Help Plus; VC: virtual coach.

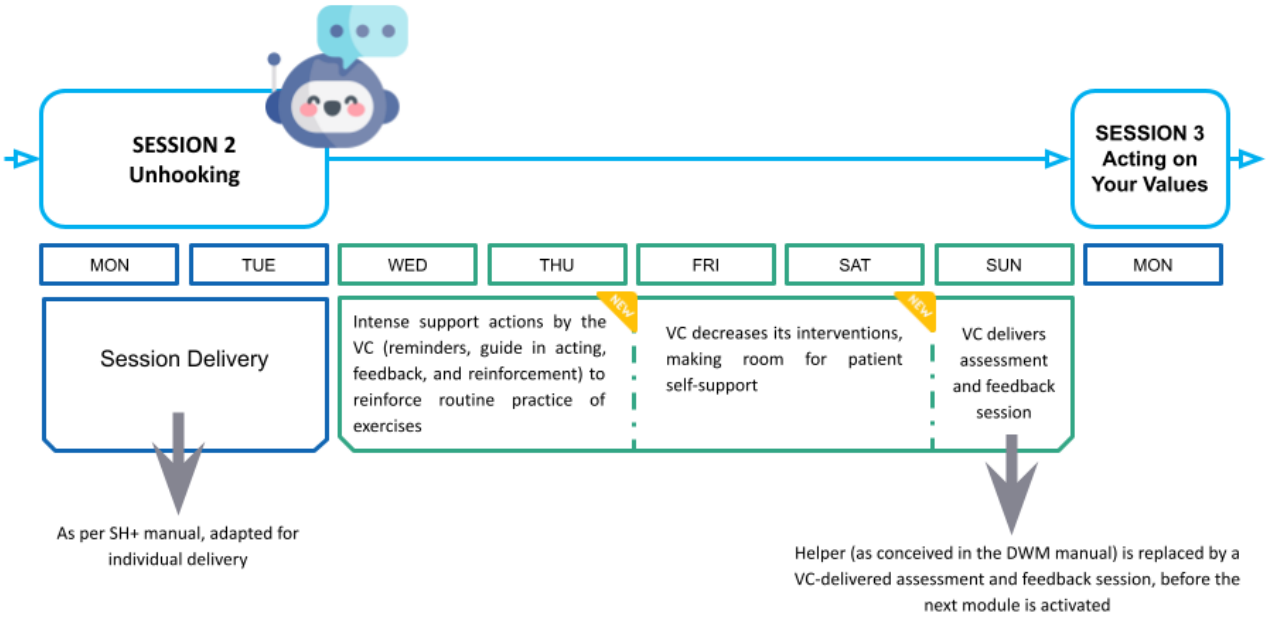

Key Points From Chatbot and mHealth Literature

Homework

User interface design and feedback are essential for personalized behavior change support systems. Incentives and reminders are useful strategies that facilitate adherence, learning, and safety during self-guided interventions [45,46].

ALBA will assign homework during the session delivery. This homework consists of exercises that should be carried out by the users before the following session, as per the facilitator's instructions. The diary section will support self-monitoring of exercise progress and completeness of sessions (Figure 2D). It is within this section that all reminder and feedback controls are created. Indeed, the novelty of this app is that the completion of exercises is monitored in the evenings before the next session, reinforcing engagement, which is different from standard SH+ in-person delivery. This will be achieved through the strategic incorporation of gamification elements (like badges) and timely feedback prompts interposed between sessions. This paper will not discuss all these sets of sophisticated IT rules and components.

Engagement

The design and deployment of conversational agents, such as chatbots, as virtual coaching solutions allow for maintaining the intuitiveness and naturalness of dialogue-based interaction while exploiting the benefits of full automation [47,48]. Moreover, gamification in health care is a promising way to improve patient adherence. It can make interventions more fun and engaging, increase patient awareness, and give patients ownership over their treatment [49].

Our app has a main page where users can dialogue with ALBA by selecting the toolbar button. It also includes other sections, as follows: the "Gallery," featuring educational videos and intervention introductions; the "Diary," strictly connected with the "Exercises" page with all available self-help exercises; and the "Progress" section providing users with an overview of their "journey" toward increased well-being. Here, users can see the sticker badges earned by practicing exercises between sessions appearing on their suitcase illustration, serving as long-term positive rewards. Badges also have symbolic meanings for psychological instruments and techniques acquired during the intervention. Instead of human helpers, the avatar-like chatbot

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serves as the primary support system, giving feedback and rewards, promoting a sense of accomplishment, and facilitating user motivation (Figure 2E).

Ethical Considerations

All future studies' data and our previous preliminary data [44] are confidentially collected in Italian and deidentified with participants' informed consent. Eventually, confidential audio recordings of semistructured interviews are used for data analysis, and participants are identified only by numeric codes. At the studies' conclusion, participants can request the research outcomes from the research manager. Participants did not receive any compensation. A local ethics committee will approve all future studies, as with our previous co-designed study [44]. Privacy issues require strict adherence to informed consent protocols and secure data retention compliant with the General Data Protection Regulations. Finally, the participants will be informed of the study's results through the dissemination of articles.

Results

The preliminary outcomes derived from the initial adaptation phase show a promising development trajectory. Our previous co-design study validated the chatbot's dialogues for effective content delivery [44]. Positive feedback highlighted the app's structure, user-friendly design, and perceived credibility. Key innovations included interactive elements, gamification, and personalized feedback. Methodical selections for facilitating the transition from manual modality to the application domain are shown in prototypical mock-up representations in Figure 4.

The app is poised to feature a subdued color palette, coupled with cartoonish character renditions, strategically created to alleviate the emotional burden of embarking on such a path to manage stress [50]. Moreover, this stylish choice also aligns with the cartoonish characters of the DWM booklet.

The app is poised to be compartmentalized into discrete segments, the utility of which will undergo rigorous evaluative scrutiny in a methodologically standardized manner, as delineated in the co-design investigations pertaining to Phase Ib of the ORBIT model. Subsequently, a comprehensive evaluation of usability and acceptability will be undertaken during Phase II. These future phases will consist of a plan encompassing the scrutiny of the app's prototypes through successive stages of deployment. This sequential study will initially involve a limited cohort of stakeholders, followed by an equivalently small sample of volunteer women contending with breast cancer and gestational conditions.

The complete array of dialogues and transcripts constituting the ALBA virtual coach, originating from the SH+ manual and DWM booklet, has been fashioned using the methodologies expounded in the preceding sections. These textual compositions are presently undergoing the technical instantiation process. A selected mockup extracted from these dialogues is visually depicted in Figure 5, offering a glimpse into their compositional structure and stylistic attributes. Noteworthy features encompass a spectrum of question types, comprising both structured dialogue and open dialogue exchanges concurring to foster a heightened degree of interactivity and engagement within the communication exchange.

Figure 4. Automated Well-Being Assistant (ALBA) app mock-ups of different sections (Exercises, Diary, Principal Menu, Galley, and Progress). DWM: Doing What Matters in times of stress; SH+: Self-Help Plus; VC: virtual coach.

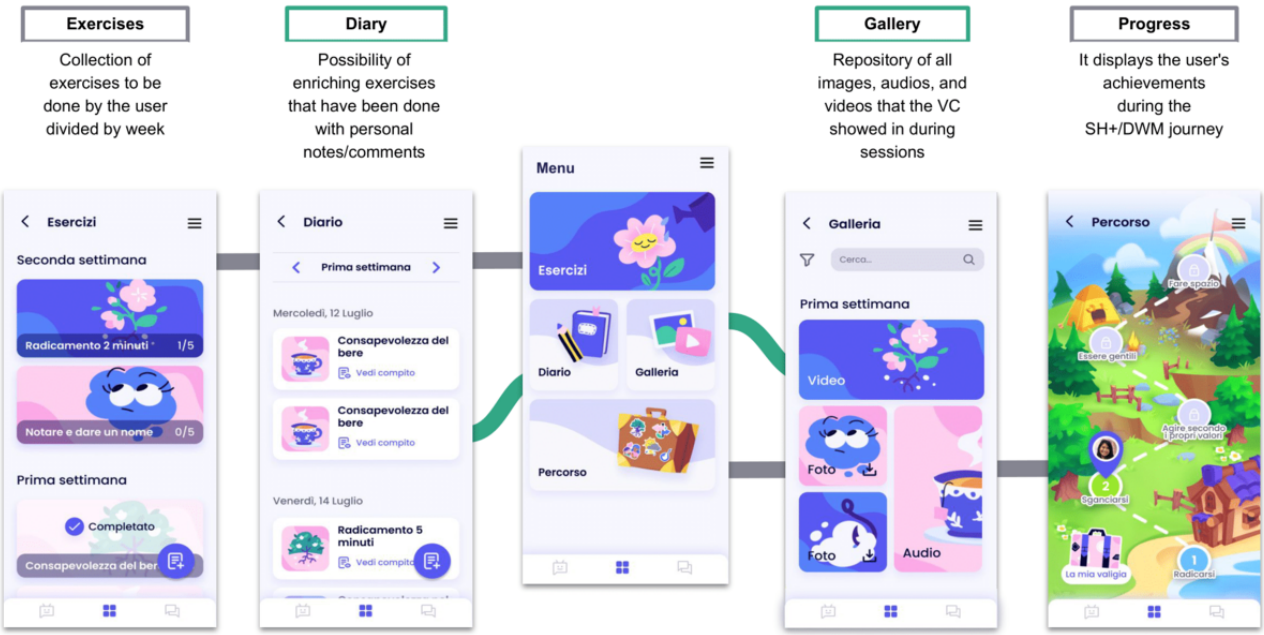

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Figure 5. Automated Well-Being Assistant (ALBA)'s dialogue section with open-ended questions and button-based responses (guided answers).

Discussion

Principal Findings

New technologies can improve the sustainability of the health care system by providing round-the-clock support to patients and optimizing the interventions provided by health care professionals [5]. Nevertheless, the innovations associated with developing and utilizing new technologies for mental health remain a subject of ongoing discussion. Empirical studies on evidence-based digital interventions for mental health, including internet-based CBT, have shown that these interventions are effective, feasible, and acceptable to users [51-53]. However, some limitations have been found, mainly regarding users' low engagement and completion rates [51,54]. Integrating human coaching and support in digital mental health interventions can help improve adherence and behavior change outcomes [55,56], although this may reduce the scalability of such solutions. In this optic, the use of chatbots for digital mental health interventions has attracted interest in the design community. A growing number of studies are reporting their acceptability and feasibility for users [57,58], as well as their effectiveness in reducing perceived stress [54], thereby improving symptoms of anxiety [59-61], depression [60,61], and insomnia [62]. A recent meta-analysis suggested that internet-delivered CBT is likely as effective as conventional face-to-face CBT. However, there are still unanswered questions about treatment moderators and implementation strategies [63]. Another study highlights the importance of understanding and accommodating diverse patient preferences when implementing self-management applications in cancer care. It underscores the significance of patient engagement in self-help and suggests that digital interventions can empower individuals to control their well-being. However, participant experiences varied, with differing perceptions of added value. Recommendations include refinements for improved user-friendliness and tailoring content to individual preferences through continuous evaluation and collaboration with end users to enhance intervention effectiveness and user experience [64].

In line with these new emerging technological tools to face sociopsychological demands, this paper seeks to provide insights beyond the end user interfaces, delving into the complexities of an mHealth app for stress management development, ALBA. This ongoing research adapts the transdiagnostic SH+ package to a chatbot intervention for women with breast cancer and pregnant women in Italy. ALBA replaces human facilitators, delivering text, audio, video, and graphics content; guiding

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participants; initiating interactions; and ensuring exercise implementation. The adaptation process involved careful consideration of cultural nuances and the psychological states of the target populations. The adaptation process required evaluating psychological states, tailoring materials, and customizing content for the users' specific needs. Moreover, the intervention was adapted to individual support: The chatbot-mediated approach aims to provide a resource-efficient and innovative way to help through digital translation, allowing flexible session delivery with personalized sessions and reminders to enhance adherence to the stress management path. The chatbot incorporates gamification elements, assigning homework, monitoring progress, and providing feedback through a diary section with badges as favorable reinforcement. Gamification principles enhance engagement and motivation, making the intervention more effective and enjoyable for end users.

This research underscores the inherent value of consistent daily engagement with virtual coaches, surpassing sporadic interactions with human specialists and thus mitigating constraints stemming from their limited availability [2,3]. Moreover, considering the link between costs and human interaction, the shift from group-based interventions to individualized approaches is explored. Although this shift may increase accessibility and affordability, it simultaneously triggers reflections on the communal synergy and interpersonal involvement integral to group interventions. Nevertheless, the chatbot offers a prospect to decipher the precise impact of virtual coaching interventions not burdened by an array of confounding variables [16]. This study also contributes to understanding their potential within the mental health landscape by delineating the nuanced advantages and considerations surrounding virtual coaching applications.

Another aim is to draw clinical attention to new target populations' stress triggers and management through the delicate and underestimated design phases. In all the adaptation steps, the end user viewpoint was considered. The research emphasizes the importance of considering end users and their perspectives in enhancing the accessibility of the intervention through a user-friendly, chatbot-guided system. The commitment to tailoring the intervention for Italian women is a comprehensive approach aimed at meeting the specific needs of the target demographic. Indeed, the need for support from these two populations is increasingly evident. The transposition of CBT techniques into digital tools is the most functional according to the literature both for pregnant women [65] and women with a breast cancer diagnosis [35], decreasing anxiety and depression symptoms. The application of digital CBT therapies is still open to experimentation, and this digital intervention will be included in this panorama.

Challenges and Limitations

The adaptation work for a digital stress management app has highlighted several practical challenges. One significant challenge is the need for intermediaries to guide during or between sessions, necessitating the anticipation and embedding of potential user queries or uncertainties within the application framework. To address difficulties such as comprehension issues, the app will offer feedback based on a manual and provide avenues for further assistance, including technical support or access to a psychologist.

Engagement maintenance during the transition from group to individual digital sessions is another key challenge addressed through gamification elements and interactive exercises with feedback and reminders. Subsequent empirical investigations are needed to validate these strategies and assumptions.

Future research questions and challenges include participant recruitment and privacy concerns. Although stress management's universal relevance aids recruitment prospects, obstacles may arise from stigma and health care access barriers. Alternative recruitment channels such as voluntary participation and partnerships are being explored.

Further Developments

ALBA will adhere to the successive stages of the ORBIT model. The initial emphasis will be on Phase Ib, followed by the comprehensive redefinition of components through standardized co-design investigations. Subsequent efforts will encompass the methodical assessment of prototype usability, in terms of app architecture, design iterations, and technical performance, and the evaluation of app efficacy after its revision in randomized control trials. These steps are needed to understand the user experience and acceptability of the app, proving its clinical efficacy and facilitating its possible successful implementation in real-world settings with these specific target populations. Every specification inherent to possible end user app utilization will be deeply considered and empirically validated.

An additional advancement involves examining the practical implications of utilizing this app within real-world settings. This would encompass a comprehensive evaluation of the intervention's efficacy and efficiency in rendering support and facilitating progressive care for the designated populations. It could shed light on sustainability in terms of the resource allocation and human capital expenditures stemming from implementing this preventative and low-intensity support framework. From a broader perspective, the potential exists for the creation of analogous applications, exhibiting tailored cultural and linguistic adaptations to address the needs of diverse target demographics, encompassing women who have breast cancer as well as pregnant women from varying cultural backgrounds.

Conclusions

Introducing ALBA, a new mobile tool designed for some vulnerable female populations, enriches the mHealth scientific literature. This innovation involves implementing an SH+ validated intervention using a new delivery tool, incorporating the previously outlined and targeted modifications. Using the SH+ protocol will shed light on the exploration in assessing the efficacy of the chatbot as an innovative intervention strategy, along with evaluating the impact of the evidence-based intervention on these specific groups. The commitment extends to comprehensive implementation research, delving into clinical outcomes and examining app implementation-related factors such as feasibility, fidelity, and accessibility.

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Acknowledgments

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Data Availability

The data generated and analyzed during the study are available from the corresponding author upon reasonable request. Before disclosure, data are aggregated and anonymized.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Description of the adaptation from SH+ to ALBA.
[DOCX File , 20 KB - resprot_v14i1e69644_app1.docx]

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Abbreviations

ALBA: Automated Well-Being Assistant
CBT: cognitive behavior therapy
DTx: digital therapeutic
DWM: Doing What Matters in times of stress
mHealth: mobile health
ORBIT: Obesity-Related Behavioral Intervention Trials
SH+: Self-Help Plus
WHO: World Health Organization

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Protocol

A Multipronged, Community-Partnered Intervention (The TALK) to Improve Parent-Adolescent Communication About Sexual Health and Racial Discrimination Among Black Male Adolescents and Young Adults and Their Caregivers: Protocol for a Feasibility and Acceptability Study

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Abstract

Background: Unsafe sexual behaviors among Black male adolescents and young adults increase their susceptibility to negative health outcomes that widen persistent health disparities. Parent-adolescent relationships and communication can impact Black male adolescents and young adults' sexual health behaviors, but parents and adolescents often lack knowledge and effective tools to improve health outcomes. Culturally tailored sexual health interventions that integrate the intersectionality of race, gender, family, and social influences on sexual health are limited yet needed to reverse these trends.

Objective: This project aims to develop a nurse-led multipronged intervention, The TALK, which is a parent-centered, adolescent-involved health promotion intervention for Black male adolescents and young adults.

Methods: This mixed methods study uses a community-engagement approach to develop and pilot a parent-centered eHealth intervention. There are 3 research phases: development, usability for community of interest, and testing for real world usability. First, The TALK development is tested with parents and caregivers by using the dscout platform, a digital platform for virtual ethnographic research used to explore early-stage user experience. Second, we will recruit parent-adolescent dyads for a pretest-posttest survey data collection to examine the usability, acceptability, and preliminary intervention outcomes. This phase focuses on the frequency and quality of parent-adolescent sexual health and racial discrimination communication, improvements in knowledge of HIV testing, improvements in parent-adolescent conversations around racial discrimination, and its impacts on sexual health and improved perceived racial identity among Black adolescents. Third, we will examine the usability of the intervention's web-based modules through promotion in real-world settings of barbershops and beauty salons across North Carolina through signage (with a QR code to scan and access the website). We will measure the usability through website metrics, including page views, average time on page, average session duration, pages per session, bounce rate, and traffic sources.

Results: This project was funded by the Gordon and Betty Moore Foundation and approved by the Duke University School of Nursing institutional review board in September 2022 (Pro00105116) for development with the community. Intervention components were developed in partnership with community partners in the first year. Data collection for phase 1 began in October 2022. Data collection for phase 2 began in July 2023 and ended in January 2024. Data analysis is scheduled for completion by July 2025. The primary and secondary results are expected to be published by January 2026.

Conclusions: Culturally tailored interventions that include content on the intersectionality of race, gender, and family and social relationships combined with strategies to improve parent-adolescent communication have promise for promoting sexual health and racial identity among Black male adolescents and young adults. Our findings have the potential to influence intervention design and research for other populations and contribute to broader efforts to reduce health disparities.

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KEYWORDS

parent-adolescent communication; sexual health; STI and HIV prevention; eHealth; mixed methods; community engagement

Introduction

Background

Black male adolescents and young adults aged 13-24 years are 13 times more likely to acquire HIV infections compared to White male adolescents and young adults, accounting for over half of all the HIV infections in this age group in the United States, with additional disparities in the Southern United States [1-3]. Racism, sociopolitical drivers of health, homophobia, and other longstanding barriers are the key drivers to disparities in HIV prevention, care access, and treatment among Black male adolescents and young adults. Without culturally relevant, effective prevention and care interventions, new adolescent infections among Black males are projected to rise by 13% annually, leading to 3.5 million new infections by 2030 [4]. Combating the HIV epidemic among Black male adolescents and young adults requires strategies that emphasize culturally tailored messaging that prioritize their needs and concerns and integrate important adult social influences such as parents and trusted community members (ie, barbers and stylists) [2].

Among the many contributors to HIV disparities, racialized discrimination affects Black male adolescents, leaving them increasingly vulnerable to HIV [5]. Studies have shown that racial discrimination and perceived racial identity are linked to sexual behaviors that increase HIV vulnerability, including inconsistent and/or condomless sex, multiple sexual partners, inconsistent condom use, and substance abuse before sex [6-9]. Black families play a crucial role in influencing how adolescents understand the meaning of race. Self-affirmation activities, parental messaging, and parent-adolescent conversations about racism and perceived racial identity early in adolescence have the potential to have a current and long-lasting impact on sexual health decision-making [10-15].

Parental engagement of Black parents in behavioral HIV prevention interventions has been found to be effective in delaying sexual debut and promoting condom use among male adolescents [16,17]. However, only a few interventions have kept up with the ever-evolving structure of the family; these interventions have mainly engaged fathers and sons or mothers and sons, and limited interventions have engaged Black fathers [16,17]. What is missing from adolescent sexual health interventions for Black male adolescents and young adults is an inclusive approach that engages both the mother and father, regardless of their marital or residential status (ie, living in or outside of the home) and interventions that are culturally and socially aligned with the lived experiences of community members. Furthermore, current interventions for adolescents are delivered primarily through face-to-face delivery or provider and facilitator-led programs, and although these interventions have shown some level of effectiveness, the need for multipronged, community-partnered interventions are warranted to improve sustainability over time.

Given the multiple social, structural, and political determinants of health affecting Black youth, it is imperative that interventions use a multipronged approach to address interconnected issues and maximize impact [18]. Multipronged strategies can provide a more comprehensive solution through interventions that are responsive to the needs and experiences of Black youth and engage community partners [19]. Barbershops and salons have a long history of being a unique, trusted, and effective space for health promotion, specifically for Black communities [20,21]. By regularly engaging with fathers, mothers, and their sons, barbers can facilitate and normalize conversations around sexual health norms and serve as a distribution point for sexual health materials such as digital and print educational media.

Overall, the availability of effective behavioral interventions for adolescents that address the unique circumstances and relationships they face as well as those utilizing technology are limited. Technology-integrated interventions are needed to keep up with the social changes of engagement [16]. Technology-delivered family interventions that include father and/or mother have the potential for widespread community reach and are urgently needed [22]. To our knowledge, there are no technology-delivered adolescent sexual health intervention strategies that address racial discrimination and perceived racial identity. In response, our intervention, The TALK, was co-developed with researchers, clinicians, barbers, and community members to improve parent-adolescent communication of sexual health and experiences of discrimination and racism.

Theoretical Framework

The TALK is grounded in the syndemic theory [23,24] and uses a social ecological framework to address the health needs and inequities of Black communities through a holistic approach that accounts for multiple nested levels of factors that contextualize health outcomes—from the individual to the structural [25,26]. In other words, the framework attempts to capture the complex interconnection and influence of multilevel determinants that help health researchers understand and explain Black health inequities, including the ways in which challenges such as stress function simultaneously with positive resistance, like resilience and other assets, improve the health of Black communities, especially around chronic illnesses such as HIV infections [27]. By combining the syndemic theory with a social ecological model, this study not only identifies the co-occurring and interacting conditions (eg, HIV risk, racial discrimination) but also situates them within a multilevel context that includes individual behaviors, family dynamics, community norms, and structural inequities. This integration allows us to design an

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intervention that is both theoretically grounded and practically responsive to the lived realities of Black male adolescents and young adults. The social ecological framework broadens the research lens with an intersectional and intersectoral approach for studying the experience of sexual health and HIV in Black communities [24,27,28]. To understand HIV infections among Black male adolescents and young adults, we must account for how structural, social, behavioral, and biological factors operate to create a context in which Black male adolescents are particularly vulnerable to acquire HIV. A syndemic approach describes how the co-occurrence and interactions between 2 or more conditions can disproportionately affect the health and well-being of marginalized communities [23,24]. The syndemic model [27] conceptualizes HIV transmission risk and racial discrimination as tightly interwoven and interacting public health issues contributing to HIV disparities among Black male adolescents and young adults. At each corner of the model are risk or protective factors associated with syndemic conditions. Adapted from ecological models [25,26], these factors are categorized into individual, interpersonal, cultural, and socioenvironmental levels of influence. Unlike traditional ecological models, culture is identified as a separate level of influence to underscore its importance in shaping health behaviors and outcomes.

The Talk intervention operationalizes the social ecological model by embedding targeted strategies at each level of influence. At the individual level, it enhances adolescents' knowledge of HIV prevention and fosters a stronger sense of racial identity. At the interpersonal level, the intervention strengthens parent-adolescent communication about sexual health and racial discrimination, aiming to improve both frequency and quality of these critical conversations. The cultural level is addressed by promoting positive racial identity and incorporating culturally affirming messages that resonate with the lived experiences of Black families. At the community level, the intervention engages trusted spaces of barbershops and beauty salons to disseminate health information and shift social norms. Finally, at the structural level, The TALK addresses systemic barriers to HIV prevention by offering culturally tailored, accessible eHealth tools.

Through this multilevel approach, The TALK aims to strengthen resilience and support within Black male adolescents and young adults' relationships and connection to the community to improve sexual health behavior and outcomes. By engaging parents, barbershops, and salons, the intervention empowers participants with shared language, nuanced communication skills, and tools to reduce discomfort associated with discussing sexual health.

Aims and Objectives

Our objective is to develop the first nurse-led multipronged intervention, The TALK, which is a parent-centered, adolescent-involved health promotion intervention for Black male adolescents and young adults by using the following specific aims.

Aim 1: develop The TALK for use with fathers, mothers, and adolescent males in partnership with beauty industry partners and an established community advisory council.

Aim 2a: determine the usability, acceptability, and preliminary intervention outcomes of The TALK (frequency and quality of parent-adolescent sexual health communication, improvements in knowledge of HIV testing, improvements in parent-adolescent conversations around racial discrimination, improved perceived racial identity among Black adolescents, and decrease risky sexual behaviors).

Aim 2b: explore the use of signage in the beauty industry to promote and market the use of The TALK app (number of downloads, amount of usage and time in the app, etc).

This approach is innovative in that it uses a community engagement approach to address the intersectionality of racial discrimination and HIV risk transmission factors and has potential for wide-scale dissemination by using various real-world approaches.

Methods

The TALK pilot is a nonrandomized study using convenience sampling.

Ethical Considerations

This study was reviewed and approved by the Duke University School of Nursing institutional review board in September 2022 (Pro00105116). The informed consent documents will include detailed information on all study procedures as well as the consent process. Participating parents and sons will provide electronic consent prior to the start of the baseline survey and gaining access to the 6-week eHealth intervention. Each week, participants will receive electronic access to a new module with accompanying survey, assessment, and/or activity with postintervention surveys after completing the final module, which are all opt-in opportunities and conducted on a digital device with whatever privacy settings are chosen by those participants. All surveys will be collected and housed in the secure Research Electronic Data Capture (REDCap) platform to safeguard participant information [29,30]. Data are deidentified and then analyzed. Each parent participant will be compensated with a US $250 gift card.

Participants

A representative group of fathers and mothers (n=60) along with their sons (n=60) will be recruited and engaged in The TALK intervention. The inclusion criteria for the study includes being a father (defined as biological father, stepfather, father figure, or father of an adopted son) or mother (defined as biological mother, stepmother, mother figure, or mother of an adopted son) of an adolescent son who identifies as Black/African American descent between the ages of 10 and 17 years. Parent and son dyads are included if both consent and agree to participate in The TALK over the 6-week period, including completing surveys, receiving research team communications, viewing resources and tools on The TALK on a weekly basis, and engaging in conversations and activities as instructed between parents and adolescents.

Recruitment

We will use an inclusive approach for recruitment, meaning father and son, mother and son or father, or mother and son will

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be recruited for participation over the 6 weeks (n=60 fathers and mothers, n=60 sons). Barbershops and salons serving primarily Black customers will be identified throughout North Carolina through a telephone directory and registries of the State Board of Cosmetology and Board of Barber Examiners. Program managers will contact barbershops and salons via email, phone, face-to-face, or through social media to inform about the web-based application and provide signage to post in their shops.

Intervention

The TALK intervention, a technology-based eHealth intervention delivered over 6 weeks, has 3 major components: (1) educational microlearning videos on various sexual health topics (eg, healthy relationships, sexually transmitted infections and HIV prevention, and pre-exposure prophylaxis), (2) 6 community-led podcasts that discuss sex, racial identity, and behaviors, and (3) an interactive parent-child activity using a deck of conversation cards to prompt dialogue (See Multimedia Appendix 1). Six electronic modules will offer content specific for parents, sons, as well as content for parents and sons to engage together. To allow individual and collective completion, modules will be released 2 at a time every 2 weeks. Communication is an essential component of healthy sexual development among Black male adolescents and young adults [31,32] and is a cornerstone of The TALK. To facilitate open communication between parents and Black male adolescents and young adults, each parental unit will receive a set of 30 conversation cards that spark conversation about relationships, consent, and perceived racial identity.

These health education tools are effective in promoting health, providing engaging health information and flexible delivery options [33-38]. Microlearning is an alternative method of educating that breaks down larger content to digestible short videos, infographics, or audio clips to increase engagement and has been shown to increase participant knowledge, self-efficacy, and self-care [39]. Various educational mediums offer several potential advantages such as providing consistency in the presentation and information delivered, reaching a broad audience, and video interventions can be a less resource-intensive means of delivering educational content [34,40,41]. Text messaging will also be used during the 6 weeks to alert users about certain contents and to access the app. Evidence suggests that inclusion of text messaging in health promotion interventions may lead to improved adolescent sexual health [42,43]. These technologies and a variety of engagement tools are combined to promote intervention adherence throughout the intervention.

Strategy

There are 3 phases for this project: development, usability for community of interest, and testing for real world usability. In phase 1/aim 1, the development of The TALK, a parent-centered, community-engaged approach is utilized by examining idea validation of the intervention through the engagement of 13 representatives of fathers and mothers by using the dscout platform. Dscout is a digital platform for virtual ethnographic research used to explore any early-stage user experience issues and deliver glitches and validate the user view and need for the solution prior to launch and preliminary testing. This approach to product development reduces the risk of launching new products by testing and iterating the concepts in a rapid cycle way with potential users before investing larger amounts of time and money into a full product launch. A representative group of fathers and mothers (n=13) will be recruited and engaged in The TALK intervention through the dscout platform under the leadership and management of consultants hired on the project. This process in conjunction with meetings with members of the community advisory council will inform intervention development, including design layout and content.

In phase 2, we will recruit 60 dyads, consisting of a parent/child, for pretest-posttest survey data collection with a total of 120 participants to examine the usability, acceptability, and preliminary intervention outcomes of The TALK. This phase focuses on the frequency and quality of parent-adolescent sexual health communication, improvements in knowledge of HIV, improvements in parent-adolescent conversations around racial discrimination, and its impacts on sexual health and improved perceived racial identity among Black adolescents. Participants will engage in The TALK intervention over a 6-week period. A mixed methods design will assess the pretest-posttest changes along with single-time point measures that will assess intervention and module-specific outcomes.

In phase 3, we will examine the usability of the web-based modules of The TALK intervention in real-world experiences, while signage will be used to market The TALK in 10 barbershops throughout North Carolina after a 6-week concept pilot in aim 2. We will conveniently identify 10 barbershops and salons primarily serving Black customers throughout North Carolina. To do this, our program manager and beauty industry partners will contact shops via email, phone, face-to-face, using telephone directory or registries of the State Board of Cosmetology and Board of Barber Examiners, or through social media to inform them about The TALK and provide signage (with QR code to scan and access the website) to post in their shops if they agree. Limiting to 10 shops allows for control in comparing the characteristics of the shops (size, location, zip code, clientele, etc) and for considering barbershop characteristics as potential factors related to the real-world use of The TALK. Our previous studies and others have found that salon-based and barbershop-based interventions must consider shop characteristics for implementation, as there is no one size that fits all [44]. We will measure the following website metrics: page views, average time on page, average session duration, pages per session, bounce rate, and traffic sources.

Data Collection

The measures table (Multimedia Appendix 2) summarizes each of the measures for phase 2 for analyzing the usability of the intervention. The TALK's usability will be examined using the System Usability Scale (α=.90), which is a 10-item survey rating participant responses as strongly disagree to strongly agree [45]. Sample questions include "I think that I would like to use this frequently. I thought The TALK was easy to use." Acceptability will be measured using the Acceptability of Intervention Measure (α=.85) [46,47]. This 4-item survey rates responses

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from completely disagree to completely agree. Sample questions include (1) The TALK meets my approval and (2) The TALK is appealing to me. A pre-post design will be used to examine the preliminary intervention outcomes of The TALK. Measures include improve frequency (Parent-Adolescent Communication Scale, α=.88) [48,49] and quality (Parent/Adolescent Communication-Jaccard, α=.93) [50-52] of sexual health communication, conversations about racism (Likert scale survey, principal investigator and consultant developed with validation assessed within this study), everyday experience of racial mistreatment (ecological momentary assessment, α=.80) [53], racial socialization (Racial Bias Preparation Scale's subscales Reactive Messages, α=.86, and Proactive Messages, α=.83) [54], and perceived racial identity (Multidimensional Inventory of Black Identity Teen Scale Survey, 7 subscales, α=.75-.88) [55-57]. We will also obtain HIV and testing knowledge from both adolescents and parents. Baseline data will be collected in week 1 and poststudy data will be collected in week 6. We will also examine the perspectives of the participants on the use of video messaging (short clips) for the web-based application. Example questions will include: did the video clips provide you with tools to help you communicate more effectively with your son? What did you like most about the video clips?

Single-time point measures will be collected at the end of modules 2-5 to provide module-specific data with module 2 including a knowledge-based questionnaire (5-items) created by the researchers (validation within this study), module 3 including an engagement survey with usage and effectiveness questions (8 items) created by the researchers, module 4 including the Multidimensional Inventory of Black Identity Teen Scale [57], and module 5 including the Racial Bias Preparation Scale [54]. Open-ended qualitative questions were also asked after modules 4 and 5 to receive feedback from the participants about intervention content experience and use. Demographic data will be obtained from fathers, mothers, and adolescents and will include age, marital status, education, socioeconomic level, and does the child live in the home with one or both parents. We will use our Health Insurance Portability and Accountability Act–compliant research electronic data capture in REDCap to send out text messages with reminders to participants to complete surveys and engage in modules.

Statistical Analysis

Demographic information will be summarized as the mean and standard deviation for continuous variables and frequency and percentage for categorical variables. Descriptive statistics for the intervention outcomes measures at each assessment point (week 1 and 6) and changes in these outcomes will be provided. Summary statistics will include n (%) for categorical measures and median (25th and 75th percentiles) along minimum and maximum values for continuous measures due to small sample sizes and expected skewness. For the continuous intervention outcomes, nonparametric Wilcoxon signed-rank tests for repeated measures will be used to test for change from week 1 to week 6 within each of the 3 participant groups (88 adolescents, 88 fathers and mothers). Nondirectional tests will be performed with the significance level set at .05 to increase statistical power based on the assumption that small-to-moderate change effect sizes within each group will be observed.

Results

This project was funded by the Gordon and Betty Moore Foundation and approved by the Duke University School of Nursing institutional review board in September 2022 (approval Pro00105116) for development with the community. Starting October 2022, intervention components were developed in partnership with community partners. User feedback on initial website design, videos, and comment cards were provided by parents of Black male adolescents and young adults (n=13) by using the dscout platform. Then, the intervention content was finalized using a community-engaged iterative process involving community members, stakeholders, and businesses. This collaborative approach was overseen by the research team and our community advisory board. Data collection for phase 2 began in July 2023 and ended in January 2024. Data analysis is scheduled for completion by July 2025. A manuscript on the intervention design process and findings is under review. The publication of the primary and secondary results is expected by January 2026.

Discussion

Anticipated Findings

This paper presents a protocol to deliver a culturally responsive and influenced sexual health promotion intervention specifically designed for Black parents and their adolescent sons. We anticipate that The TALK intervention will be feasible and acceptable, improve parent-adolescent communication, and improve knowledge of HIV and sexually transmitted infections among Black adolescent males. Additionally, this study will provide evidence that builds on growing literature contributing to digital interventions to improve sexual health and HIV education and communication among Black adolescents. Implementation of The TALK protocol will allow the authors to link their findings from a sample of Black parents and sons with the evidence of prior studies among Black mothers and daughters to better understand family relationship dynamics in regard to racial and sexual conversations. The TALK's structure, content, and utilization of technology was developed with feedback from beauty industry partners and community members with the goal of improving feasibility and acceptability of the intervention. These community-engaged steps are expected to improve the overall impact and outcome of the intervention. As a result, the goal is to influence future research in family communication about sexual health and HIV.

Strengths and Limitations

The design of this study has several strengths, including its focus on Black adolescent males and their parents/guardians, which has the potential to improve the shared knowledge and communication within the parent-adolescent relationship and influences Black adolescent males' behavior and health outcomes. The research team is experienced in nurse-led, community-engaged research and health promotion interventions using various technology-based methods, which improves intervention and research design and implementation. The sample size and analysis by different demographic characteristics can provide insights into the influence of

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similarities and differences on the changes experienced after the intervention by participants. The use of the dscout platform to develop and beta test the intervention can increase the cultural relevancy and appeal of an intervention throughout the stages of development. Previous community-based collaborations and research by the study team with Black communities have informed that the intervention's content and method design can impact participant recruitment and intervention relevance for the target population, which is promising for future research and broader impact on Black male adolescent health behavior and outcomes as well as the design of culturally relevant interventions. The anticipated limitations of this intervention include the self-report of improvements in communication and health behaviors (eg, sexually transmitted diseases, HIV testing). The intervention includes multiple electronically delivered modules that are prone to participant attrition, which will demand counter recruitment and retention efforts to maintain sufficient parent-adolescent pairs of complete data.

Future Directions

The findings of this study will be disseminated to the study's participants in a brief newsletter authored by the research team, social media posts (eg, video blogs, short posts), as well as in a lay community journal. Additionally, presentations will be given to the local Black community at local and regional community events. The findings will be disseminated to the scientific community by using multiple strategies such as presentations at national and international HIV conferences, publications in nursing and interprofessional peer-reviewed clinical and research-based journals, and media press releases. The intention to disseminate to scientists, clinicians, and the community will contribute to the science of behavior change.

To prepare for scalability, The TALK will expand its real-world use and application by becoming an available resource accessible in barbershops and salons across the southern region. There is a future need to examine the long-term impact of TALK on parents' communication engagement and sexual health outcomes of adolescents over time. Opportunities also exist for future engagement of The TALK as a resource for health care providers in clinical encounters. Linking culturally sensitive and relevant messaging in health care settings for parents and adolescents contributes to more effective communication. This can help bridge cultural gaps and make it easier for providers to discuss sensitive topics such as sexual health or the impact of lived experiences on health and well-being.

Conclusion

Disparities in HIV infections for Black adolescents and young adults persist despite an overall decrease in HIV incidence. Addressing Black male adolescents and young adults' perceived racial identity and primary social influences is integral to creating Black male adolescents and young adults' social norms around sexual behavior. The TALK offers a culturally responsive, community-informed approach to engaging parents and Black male adolescents and young adults in sexual health promotion strategies that normalize communication, increase individual sexually transmitted infection/HIV prevention behaviors, and could be used to influence pre-exposure prophylaxis use.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
The TALK intervention components.
[DOC File , 41 KB - resprot_v14i1e67403_app1.doc]

Multimedia Appendix 2
Study measures.
[DOC File , 55 KB - resprot_v14i1e67403_app2.doc]

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Abbreviations

REDCap: Research Electronic Data Capture

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Protocol

Collection and Analysis of Repeated Speech Samples: Methodological Framework and Example Protocol

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Abstract

Background: Speech and language biomarkers have the potential to provide regular, objective assessments of symptom severity in several neurological and mental health conditions, both in the clinic and remotely. However, speech and language characteristics within an individual are influenced by multiple variables that can make findings highly dependent on the chosen methodology and study cohort. These characteristics are often not reported adequately in studies investigating speech-based health assessment, which (1) hinders the progress of methodological speech research, (2) prevents replication, and (3) makes the definitive identification of robust biomarkers problematic.

Objective: This study aims (1) to facilitate replicable speech research by presenting a transparent speech collection and feature extraction protocol and design checklist for other researchers to adapt and design for their own experiments and (2) to demonstrate in a pilot study the feasibility of implementing our example in-laboratory protocol that reduces multiple potential confounding factors in repeated recordings of healthy speech.

Methods: We developed a collection and feature extraction protocol based on a thematic literature review to enable a controlled investigation of within-individual speech variability in healthy individuals. Our protocol comprises the elicitation of read speech, held vowels, and a picture description and extraction of 14 example features relevant to health. We collected speech using a freestanding condenser microphone, 3 smartphones, and a headset to enable a sensitivity analysis across different recording devices.

Results: We collected healthy speech data from 28 individuals 3 times in 1 day (the "day" cohort), with the same schedule repeated 8 to 11 weeks later, and from 25 individuals on 3 days within 1 week at fixed times (the "week" cohort). Participant characteristics collected included sex, age, native language, and voice use habits. Before each recording, we collected information on recent voice use, food and drink intake, and emotional state. Recording times were also documented. Analysis relating to exploring within-individual variability within the day and week cohorts, as well as the device-type sensitivity analysis, is ongoing, with findings expected later in 2025.

Conclusions: The wide variability in speech data collection, processing, analysis, and reporting in research on speech's use in clinical trials and practice is the motivation for this paper and the development of the speech curation protocol design checklist.

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Increased, more consistent reporting and justification of study protocols is urgently required to facilitate speech research replication and translation into clinical practice.

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KEYWORDS

speech; voice; replication; longitudinal; repeat recordings; within-speaker variability; health assessment

Introduction

Speech as a Digital Marker of Health

The linguistic and paralinguistic content of our speech contains rich information about our cognitive, neuromuscular, and respiratory functioning. There is a growing body of literature highlighting the potential of speech as an objective marker for disease diagnosis, monitoring, and prediction in a variety of clinical cohorts, including amyotrophic lateral sclerosis (ALS) [1], Parkinson disease [2-4], psychosis [5,6], and major depressive disorder [7,8] as has been summarized in several reviews [9-11]. Key advantages of recording speech for clinical applications include its noninvasive nature and the ability to conduct recordings both in the clinic and remotely using off-the-shelf consumer-grade audio equipment.

Challenges and Confounders in Speech Biomarker Research

Though speech has great potential as a signal, accurately detecting changes in speech driven by changes in health is challenging, and speech markers are yet to be used as an outcome measure in clinical trials or translated for clinical use. This is partly because speech is a multifaceted, complex, dynamic signal. Many speech changes associated with different health states can be subtle, forming one part of a measured signal that is also dictated by other speaker-specific factors and recording and analysis choices. There is a pressing need to understand, quantify, and adjust for the effect of such variables, as they can mask or even mimic the effect of health changes.

Potential confounding factors related to the speaker include hormonal variations within the menstrual cycle [12,13], fatigue [14], voice use habits [15-17], emotion [18], and hydration [19]. Systematic changes with age, menopause, and medication use have also been reported [20-23]. A growing body of literature highlights the impact of methodological choices, including recording environment, hardware choices, digitization formats, and choice of extraction tools, on speech characteristics and subsequent health state analysis [24-29].

Speech elicitation strategies are another important factor in speech-based health assessment. Common strategies include (1) structured tasks, such as reading passages and vocal function exercises such as sustained phonation [30,31]; (2) semistructured tasks, such as image description exercises [32,33]; and (3) minimally structured tasks and conversational speech that, for clinical cohorts, include clinical interviews [10,11]. Choosing the right tasks is vital for ensuring the clinical validity and sensitivity of the extracted speech measures [34]; each task can produce distinct acoustic, linguistic, and emotional content and be used for the targeted capture of different aspects of speech production [34,35].

Less-structured tasks pose technical challenges, such as the need for accurate speech-to-text conversion and diarization to determine who was speaking what and when [30]. Practice effects represent another potential confounder, where recorded speech changes due to repeated exposure to a task or activities [36,37]. Although expected in speech research, practice effects are rarely documented [9,38].

Despite an awareness of such effects, methodological details and important speaker characteristics in speech-based health assessment research are underreported in the literature. These factors can be unaccounted sources of variation that become particularly pertinent when effect sizes are small or context dependent [39], which is often the case in health analyses of speech. This is of particular concern for remote data collection outside of laboratory settings where there are more degrees of freedom, for example, recording devices and geometry and the acoustic environment. This weakens replicability and hinders the development of robust methodology and tools; the discovery and verification of biomarkers; and, ultimately, clinical translation.

Enhancing Speech Biomarker Research Through Methodology and Reporting

The lack of established methods for data collection and reporting exacerbates these issues highlighted above [40]. The Consensus Auditory-Perceptual Evaluation of Voice (Cape-V) protocol [41] and recommendations made by the American Speech-Language-Hearing Association Panel [42] are helpful starting points. However, they have limited applicability in detecting subtle changes and the broader range of speech characteristics associated with, for example, mental health and neurological disorders recorded remotely and longitudinally. These recommendations were also developed specifically for in-laboratory speech pathology assessments.

The Voiceome Study represents an attempt at standardization of longitudinal data collection for speech and language biomarker research [43]. A key feature is its recommendation of 12 speech elicitation tasks, and the study highlights that these tasks produce distinct feature clusters. However, the authors do not describe the clinical relevance of these prompts or provide any evidence base justifying their inclusion. The implications for participant burden and associated protocol acceptance and adherence by participants are also not discussed, which is an important issue in data collection [44]. The effects of the recording environment, recording time, hardware choices, and

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speech processing methods on the quality of extracted data are also not considered.

In conclusion, the effect of speaker-related factors and methodological choices necessitates increased reporting and justification of methods used in speech and language biomarker research, including more well-considered protocol design. To begin addressing this, we report on our detailed study protocol for collecting in-laboratory repeated speech samples from healthy individuals. Our aim in publishing this protocol is to promote transparency and reproducibility as a key step toward increased research replication and more reliable identification and validation of speech biomarkers in this domain [40,45,46]. This protocol is also a resource to replicate and adapt, including by researchers with less experience and specialist knowledge of speech processing.

Methods

Overview

Our pilot study builds on the literature to present an example protocol for speech corpora curation that reports and justifies methodological aspects for adaptation for other studies. We conducted this study with a specific research focus of assessing natural variability in individual voices and understanding the sensitivity of different recording devices to these variations. We collected and analyzed speech samples from healthy participants to avoid variability driven by pathology. Datasets of healthy individuals are also beneficial as baselines for comparison with clinical populations [34,47].

The consideration of participant burden and the acceptability of the protocol to participants was a part of the research process, as these factors have important implications for recruitment and protocol adherence and therefore data quality and completeness. While our protocol was designed with a specific scientific goal in mind, the core methodological aspects are relevant for researchers collecting longitudinal data to investigate other questions in speech and language biomarker research. Such research will benefit from the minimization of variations in speech between recordings due to methodological factors and clear reporting of methodology. By presenting our methodological choices in this study, we would like to enable other researchers to adapt our protocol in their own work in healthy and clinical cohorts, thereby facilitating replicable speech research.

Protocols for Investigating Within-Individual Speech Variability

Most protocols in the literature have been a part of studies assessing localized vocal tract pathology and dysphonia, analyzing a small number of speech characteristics relevant to localized speech pathology, typically with modest-sized cohorts. Many of these studies were also conducted before remote recording and mobile devices were a consideration [48,49].

Most recently, motivated toward speech pathology vocal tract assessment, Pierce et al [50] assessed variability in repeated speech samples from healthy female participants in a remote recording study. Participants completed 1 supervised baseline recording and then recorded themselves 3 times each day for a week within prescribed intervals in a well-described protocol. The 45 participants read aloud 2 passages of text and produced sustained vowel phonations each time using a cardioid head-mounted microphone. Participants were advised to record in a quiet room with no tiling; however, adherence to this was not reported. The authors [50] analyzed 32 speech features, observing significant voice production changes over a day but no significant changes across the week. They speculate that the "worse" voice they observed in the morning could be due to (1) voice production systems affected by physiological changes due to prolonged reclining while asleep and (2) low voice use before the participants completed their first recording. Other studies have demonstrated variations in voice based on the level of hydration in participants [19,50].

Several studies motivated by mental and neurological disorder assessment have quantified within-speaker change, framed as test-retest reliability assessment. Feng et al [51] recorded 40 healthy young adults twice, 2 to 3 days apart, in the same test room, completing 7 elicitation tasks in Mandarin. They observed that only half of the 56 speech features tested had moderate test-retest reliability, as estimated using intraclass correlation (ICC). Barnett et al [52] retrospectively analyzed speech features of 46 healthy individuals recorded twice, months apart, reading aloud a "Bamboo" passage. They also observed only moderate test-retest reliability in half of the analyzed features. Stegmann et al [53] reported an analysis of 22 healthy individuals recorded daily for 7 days and clinical cohorts with ALS (72 participants) and frontotemporal dementia (24 participants) recorded approximately a week apart. They reported that the test-retest reliability, also estimated using an ICC of commonly used speech features, was well below acceptable limits for clinical use.

Each of these analyses highlights that we should expect some degree of variation in voice between repeated recordings of an individual. However, in each of these analyses, various potentially confounding methodological details such as consistency in recording time and acoustic conditions—and adherence to instructions in the unsupervised ("in-the-wild") recordings—are not reported [12-29]. Therefore, at least in principle, measurement factors may be responsible for a proportion of the observed differences between repeated recordings of a given participant. An additional potential limitation of these works is the use of the same elicitation scripts in each recording. Increased speaker familiarity with the readings can result in practice effects [36,37], which could confound the assessment of within-individual speech variability [9,38]. Finally, to the best of the authors' knowledge, none of the aforementioned studies have provided data (either raw audio or extracted features).

To address our chosen research question of within-individual speech variability, our protocol improves on these previous works in that we collected data at set documented times in a controlled, supervised environment and used multiple microphone types (Table 1). We also combined several structured and semistructured tasks to elicit both naive and practiced speech, with both spontaneous speech and scripted, fixed content to control for various factors. As a step toward

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our methodological goal of improving the reporting of methods in speech corpora curation, we present our protocol in detail in the following section.

Table 1. Comparison of key methodological choices in protocols of studies observing within- and between-speaker variability.

Study	Sample, n	Cohort type	Schedule	Laboratory versus remote	Microphone	Speech type
This study	28	Healthy	• 3/d, twice in 8-11 wk • Fixed times	Laboratory	• Condenser • 3 phones • 1 headset	R[a], SV[b], and PD[c]
This study	26	Healthy	• 3 in 1 wk • Fixed days fixed time	Laboratory	• Condenser • 3 phones • 1 headset	R, SV, and PD
Garrett and Healey [48], 1987	20	Healthy	• 3 in 1 d	Laboratory	• Miniature condenser	R
Leong et al [49], 2013	18	Healthy	• 10 in 30 d, fixed time interval	Laboratory	• Moving coil	R and SV
Pierce et al [50], 2021	45	Healthy	• 3/d in 1 wk	Remote	• Headset condenser	R and SV
Barnett et al [52], 2020	46	Healthy	• 2 in 3-6 mo	NES[d]	• NES	R
Stegmann et al [53], 2020	72	ALS[e]	• Daily • 1 wk	Remote	• NES	R and SV
Stegmann et al [53], 2020	22	Healthy	• Daily • 1 wk	Remote	• NES	R and SV
Stegmann et al [53], 2020	24	ALS and dementia	• 2 in approximately 1 wk	NES	• NES	R, SV, and PD
Feng et al [51], 2024	40	Healthy	• 2 in 2-3 d	Laboratory	• Condenser	R, SV, CS[f], RS[g], and DDK[h]

[a]R: read, scripted speech.
[b]SV: sustained vowels.
[c]PD: picture description.
[d]NES: not explicitly stated by authors.
[e]ALS: amyotrophic lateral sclerosis.
[f]CS: connected speech.
[g]RS: repetition of heard speech.
[h]DDK: diadokinetic rate test.

Protocol

Overview

Herein, we describe our protocol, the methodological goal of which was to capture repeated speech samples with minimized measurement variability. We describe multiple methodological details relevant to wider speech and language biomarker research. To facilitate adaptation to new protocols addressing other research questions, we provide a checklist of key considerations (Multimedia Appendix 1).

This protocol's primary scientific focus was to assess within-speaker nonpathological variation in speech over time. In the "day" cohort, we aimed to record healthy volunteers speaking (1) in the morning, afternoon, and early evening of a single day (day 1) and (2) repeatedly at the same times on a second day 8 to 11 weeks later (day 2). In the "week" cohort, our aim was to record healthy volunteers on 3 days in 1 week at the same time each day.

Recruitment

As a pilot study in which we sought to develop methodology, we chose to investigate variability in healthy individuals to avoid the additional variability introduced by pathology. Healthy cohorts are also valuable to establish baselines with which to compare pathological speech [34,47]. We recruited adult staff and students at the study institute, and local residents were recruited via advertisements in a research recruitment circular, institute email lists, social media, and physical flyers and posters. Potential participants were asked to read a web-based information sheet and complete a pre-enrollment screening form that repeated the eligibility criteria and collected contact details and sociodemographic data to facilitate the recruitment of a balanced cohort.

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We excluded individuals aged <16 or >65 years; those aged >65 years were excluded to minimize speech effects associated with aging [23]. We also excluded smokers; those with dyslexia; and individuals currently receiving treatment for any speech, auditory, mental, neurological, respiratory, or other health disorder that could impact their speech. In addition, we excluded nonnative English speakers unless they had a sufficient level of English proficiency to read an intermediate or advanced text aloud, selecting level B2 of the Common European Framework of Reference for Languages as a threshold [54]. This was a compromise to ensure recruitment feasibility in a population with a considerable proportion of nonnative speakers in a strict timeline set by funder requirements, while minimizing confounders due to lack of reading and speaking proficiency for the specific speech elicitation tasks we were implementing.

Inclusion and exclusion criteria were provided on the web to all individuals who considered participation.

We regularly checked the cohort balance throughout recruitment to enable timely, targeted recruitment as needed. Sociodemographic groups that were underrepresented at pre-enrollment—male participants and participants aged >30 years—were prioritized for follow-up and recruitment. After an initial round of advertising, in subsequent advertising, we advertised for male participants exclusively.

Researchers emailed individuals to allocate them to 3 recording sessions in 1 day (day cohort) or week (week cohort) according to their availability and preference. Emails at each stage of participation used text templates individually adapted for more personable communication to encourage engagement. Each provisional participant's recording sessions were scheduled, and they were emailed links to an electronic enrollment and consent form hosted on Qualtrics (Qualtrics International Inc) within 72 hours of the first session. This was to minimize the unnecessary collection of data from individuals who agreed to attend but subsequently decided not to participate.

Data Collection Schedule

Participants in the week cohort were scheduled for recording on a Monday, Wednesday, and Friday, fixed days that avoided the weekend to minimize confounders associated with different days of the week. Each participant in the week cohort was recorded at the same time on each day, to also minimize within-day variability between recordings [50]. Participants in the week cohort were given the option to have their session start between 10 AM and 12 PM or 3 PM and 5 PM. Participants in the day cohort were scheduled for recording starting between 8 AM and 10 AM, 1 PM and 3 PM, and 5 PM and 7 PM). A minimum time between sessions of 3.5 hours was maintained to maximize the likelihood of measuring differences in speech with time of day. The same participants were scheduled to return for a second day of recording at least 8 weeks later. Day 2 of recording was scheduled for the same day of the week as day 1 and scheduled at the same times.

Recording Session Procedure

At each participant's first session, researchers explained the recording procedure, and those who had not already done so before the session completed their enrollment and consent. The forms collected basic sociodemographic data, height (as a proxy of larynx length), information on the participants' voice use habits in the previous 3 months, and their level of English, for nonnative speakers.

Before beginning the study, the project team discussed the clearest and most consistent way to instruct participants. Our aim was to make participants feel as comfortable as possible and encourage natural speech and reproducible positioning during recording. The team had regular discussions as data collection progressed on any difficulties in this regard and ways to improve participant instruction.

At the start of every recording session, participants were also asked to complete a prerecording questionnaire on Qualtrics that collected information on factors that might introduce between-recording variation in their speech. These included the times at which participants woke up and got out of bed, when they last ate and drank any liquid, the extent of their voice use that day before recording, how much sleep they had the previous night, and if they were experiencing any minor health issues that could affect their voice (Multimedia Appendix 2). The prerecording questionnaire also included the Pick-A-Mood tool [55]. Participants were also offered a drink of water at the start of each session; we recorded if they took this.

Participants were seated as comfortably as possible on an office chair at a desk. Their speech was recorded with an Audio Technica 2020USB+ condenser microphone on a shock mount fitted to a Rylock foam pop filter on a tabletop stand (Figure 1). The microphone was operated using Audacity open-source software running on a Dell Latitude 7440 laptop (i5 core, 16 GB RAM) running Windows 11 (Microsoft Corporation). The microphone gain was set to a fixed value at the start of every session to maximize the signal-to-noise ratio while avoiding clipping. Participants were positioned 30 cm from the condenser microphone, the distance at which the device's frequency response is specified. The chair's height and left-right position were adjusted so the participant's mouth was level with the pop filter and centered on the microphone. Participants were reminded not to move their chairs during the session. The participant and setup were surrounded by acoustic-absorbing foam and textiles.

We positioned 3 smartphones (Apple iPhone 11 [released 2019], Samsung Galaxy S20 FE 5G [released 2020], and Motorola G5 [released 2017]) directly adjacent to and in the plane of the pop filter with their microphones positioned on the estimated vertical midline of the condenser microphone. These positions were fixed through all recordings and were comparable to if the participant held their phone in front of them as if in a video call [7]. Smartphone positioning was checked before each session.

Participants also wore a budget consumer office headset (Plantronics Blackwire 3220). The American Speech-Language-Hearing Association Panel recommends the use of headset microphones as the microphone-mouth distance can be fixed for the duration of a recording [42]. Our headset was operated using Audacity run on a MacBook Air (Intel Core i5, 16-GB RAM; Apple, Inc), using a gain level fixed over all participants and sessions. Participants were instructed to position the headset microphone 2 finger widths from their cheek and

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to one side of their mouth, using a mirror as needed. The supervising researcher checked headset microphone positioning before recording.

Before commencing the elicitation tasks, the participants were instructed to complete them at their own pace and to speak at a natural volume and pace. They were also instructed to switch their phones off or into flight mode or leave the phones outside the recording room to prevent interference with the recordings.

At the beginning and end of each recording session, as well as between each exercise, the researcher running the session played an audio tone (an alarm tone on their mobile) to prompt the participant to proceed with the next speech task and to aid the manual separation of the tasks into individual audio files following the session.

Following the completion of the speech tasks, the researcher assisted the participant in removing the headset and stopped each recording device. Participants were thanked for their time and reminded of their next recording session appointment, where applicable. At the end of each participant's final recording session, researchers asked participants to consider completing a postparticipation questionnaire. Following their departure, the project team promptly emailed participants a link to the questionnaire and codes for shopping e-vouchers, compensating them for their time.

Figure 1. Recording setup from the side (left) and the front (right).

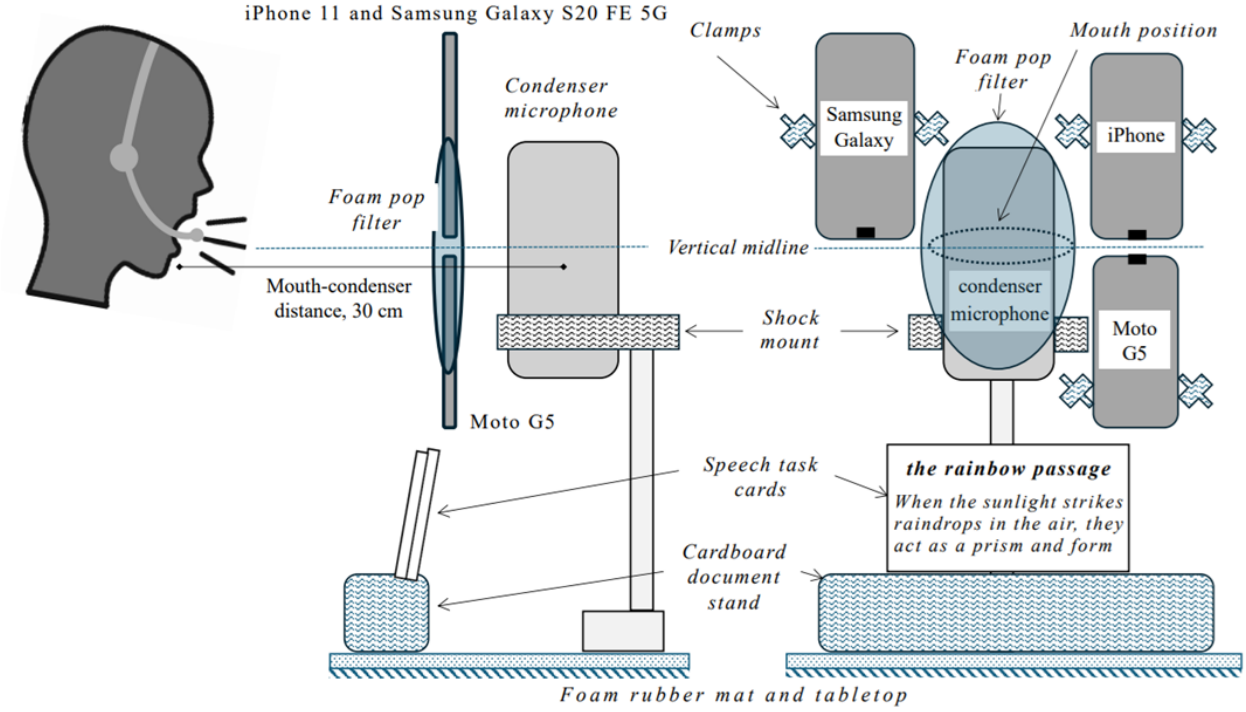

Speech Elicitation Tasks

Researchers provided participants with a varying combination of speech elicitation tasks in each session (Figure 2). Our choices balanced collecting several types of speech that, when combined, provide a variety of health-related indicators and sufficient amounts of each with participant burden and acceptance. A protocol with too many tasks, long recording sessions, or the elicitation of speech with personal content could deter potential participants and result in failures to complete all scheduled sessions.

Session 1 began with a short, simple reading, the "North Wind and the Sun" [56], as a form of warm-up exercise to help participants feel comfortable and settled before beginning the other tasks that would be the focus of our analyses. This was followed by a longer reading, "The Rainbow Passage" (long version) [57]; a timed picture description (up to 2 minutes) and 3 repetitions each of 3 held vowels, /a/, /o/, and /i/. In sessions 2 and 3, participants completed the 2 readings from the first session and the held vowels and an additional long reading in each, one of "Your Rate of Oral Reading" [58] and "Comma Gets a Cure" [59]. They also completed a new picture description in each of sessions 2 and 3. The elicitation task order was varied between sessions of each participant and between participants to avoid introducing systematic biases with specific tasks.

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Figure 2. Speech elicitation overview. Our protocol elicited nonpracticed long-scripted speech in each session, plus practiced short and long readings, except in session 1. Participants described a different picture and produced held vowels in each session. The task order was varied between participants and between sessions.

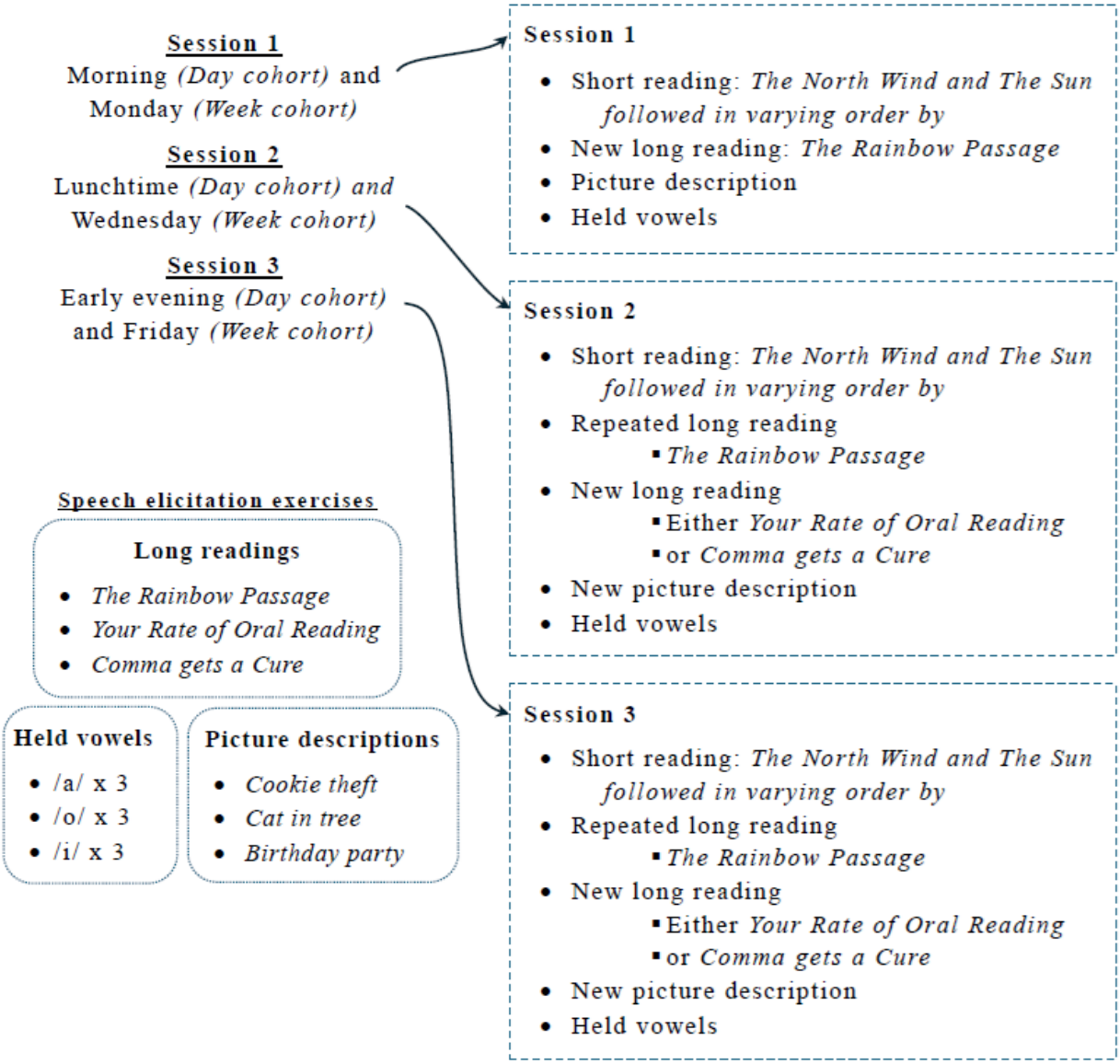

The scripted tasks provided standardized linguistic content. Repetitions of the "North Wind and the Sun" and "The Rainbow Passage" enable direct comparison of paralinguistic features for the same speech between sessions, although these repeated recordings will also be affected by practice effects. Recordings of "Your Rate of Oral Reading" and "Comma Gets a Cure" provided set linguistic content that was not subject to practice effects in the week study and in day 1 of the day study, as they were new to the participant.

We selected "Your Rate of Oral Reading" and "Comma Gets a Cure" as, along with "The Rainbow Passage," the 3 readings have a similar lexical and linguistic complexity and length, combined with a similar phonetic balance in the literature [30,31]. Therefore, we deemed them suitable for quantifying speech variability between sessions while avoiding practice effects.

"The Rainbow Passage" and "Your Rate of Oral Reading" were selected as factual texts rather than stories to minimize the likelihood of participants using a "storytelling" voice and therefore maximize the likelihood of them speaking in their natural voices. This choice was informed by our observations in the mobile health study, Remote Assessment of Disease and Relapse—Major Depressive Disorder (RADAR-MDD) [60], where participants tended to use emphasis and be expressive in reading a story. Our choice of "Comma Gets a Cure" was a compromise; it is a story but has desirable lexical and phonetic characteristics that have been well documented in the literature [30,31].

Picture description tasks provided spontaneous speech. We used 3 images: the Cookie Theft (original version), the Cat in the Tree, and the Birthday Cake [33]. All pictures are black and white designs, depicting a simple story situation with a central focus and interacting elements. Typically used in speech

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assessment in neurodegenerative disorders, for example, Alzheimer disease, to investigate cognitive characteristics via the linguistic content of an individual's speech [32], picture descriptions also have value in paralinguistic analysis [61].

Held vowel sounds provided standardized acoustic signals without any lexical, structural, or linguistic effects to account for, suitable for measurement of perturbation and quality measures [62,63]. The choice of elicitation tasks was advantageous from a data privacy perspective, as they did not elicit the disclosure of personal information.

Data Quality Control Checks, Storage, and Preparation

After each recording session, all audio files were named in the following format: ParticipantID_Device_Day_Session. They were then uploaded to a secure Microsoft SharePoint site maintained by King's College London, accessible only by project staff.

The researcher running the session also completed a data quality control log that detailed (1) the start time of each session, using the timestamp on the audio files; (2) if the participant drank any water during the session; (3) any interruptions or participant behavior that could affect the recording content or quality, for example, the participant moving their chair and subsequent chair repositioning; (4) any extraneous noise during the session; (5) any issues completing the vowel task; (6) any participant difficulties completing the tasks; and (7) any other event or observation not covered by the other fields that could affect the recording.

The researcher then checked that (1) all audio files were uploaded into the correct participant and session folders, (2) each file contained recordings of the correct speaker, and (3) all tasks were completed in the stated order. The researcher also noted any additional audible issues in the data not previously captured in the quality control log.

Recordings of individual elicitation tasks were then separated into individual files using Audacity. File names were appended to include which task they contained with the following naming convention: ParticipantID_Device_Day_Session_Task.

Preliminary Feature Extraction

We extracted 14 example features from condenser microphone recordings of "The Rainbow Passage." The purpose of extracting these features as part of our protocol development is to demonstrate the feasibility of our methodology pipeline. We present features captured with the condenser microphone only as our benchmark device, as example values that are not subject to any preprocessing that could erroneously affect the values extracted. These features were chosen as they are commonly used in speech-health research, representing timing and fluency characteristics and the speech production subsystems of respiration, phonation, and articulation (Table 2).

Table 2. Speech features extracted from the recordings to generate normative.

Features	Description
Timing and fluency	
Duration, second	Length of recording
Speaking rate, syllables second^{-1}	Total syllables divided by duration
Articulation rate, syllables second^{-1}	Total syllables divided by total speaking time
Pause rate, second^{-1}	Total pauses divided by duration
Respiration	
Intensity (mean), dB	Loudness of speech signal
Phonation	
Pitch (mean), Hz	Auditory perceived tone
Pitch (SD), semitones	SD of pitch
Harmonic:noise ratio (mean), dB	Extent to which harmonic structures are affected by noise
Spectral slope (mean)	Gradient of the voiced spectrum
Cepstral peak prominence (mean), dB	Amplitude of cepstral peak, relative to a regression line through the cepstrum
Articulatory	
First formant frequency (mean), Hz	First resonant frequency of the vocal tract
Second formant frequency (mean), Hz	Second resonant frequency of the vocal tract
Gravity (mean), Hz	Center frequency of the narrow band spectrum
Deviation (mean), Hz	Spread of frequencies around the spectral gravity

Timing and fluency features have previously been demonstrated to contain important clinical information for conditions including depression [7,64], ALS [65], and Parkinson disease [66]. Respiration and phonation features are widely used in speech-based mental health analysis [7,9,10]. Articulation features have been included as they indicate changes in speech

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intelligibility and speech-motor control and have been proposed as markers for a variety of health conditions [9-11,67].

To extract these features, we first used Parselmouth [68] to convert all audio files to single-channel 16-kHz waveform audio file format files with 16-bit resolution. Our acoustic features were extracted at two levels: (1) suprasegmentally—calculated over the entire reading—and (2) for individual occurrences of open /a/vowels of at least 50 ms duration from "The Rainbow Passage." For the /a/ vowels, we extracted the features per identified instance of the vowel and calculated the mean per recording over all instances. We provide suprasegmental acoustic features, as this is a common approach in paralinguistic analyses [69]. Extraction purely from /a/ vowels, in contrast, provides more granular, controlled acoustic measures of speech. The use of the open /a/ vowel has been recommended for more reliable extraction of voice quality measures [70]. We report results in terms of the median (IQR) for the day and week studies separately, providing a resource of normative values for use in future analysis.

As a more realistic and affordable approach toward clinical research, we implemented an automated approach to identify instances of /a/ in our files. First, we transcribed our files offline using the Open AI whisper-base.en model [71], an open-source automatic speech recognition (ASR) tool, which has been demonstrated, in independent testing, to have an average word error rate of 12.8% calculated over 9 different ASR test sets [72]. We then performed a forced alignment of the resulting transcripts using the Montreal Forced Aligner (MFA) [73] and English MFA acoustic model (version 2.0.0a). After identifying the vowels in the phonetic alignment, we extracted the features per identified vowel then took the per-participant, per-session mean of these features to form our final representation. We performed spot-checks of the accuracy of these alignments, dictated by timing and budgetary constraints. Forced alignment software is generally considered reliable, giving near human-level alignments [74,75]. We conducted cursory spot-checks to assess the reliability of alignments rather than performing a more formal analysis. Due to time and budget constraints, these checks were conducted "by ear" in Praat using the MFA-generated TextGrids to isolate the identified vowels. No specific alignment scores are provided as we lacked annotated ground truth data.

Features were extracted using Parselmouth [68], an open-source Python library that enables the use of Praat, a software package for speech analysis [76]. Speech timing features are extracted using intensity thresholds [77]. All prosodic, phonation, and articulatory measures were extracted using default Praat settings, except for the extraction of F0, which followed the 2-step approach recommended in the study by Vogel et al [64], and cepstral peak prominence, which followed settings recommended in the study by Murton et al [78].

Summary

Our protocol is unique (Table 1): it collects data using multiple microphone types in a controlled environment to control for and minimize variability attributable to hardware, setup, and acoustic conditions. The speech elicitation prompts enable the collection of acoustically rich and varied content while (1) containing a core amount of fixed phonetic content to enable comparable analyses and (2) introducing new readings in each session to minimize potentially confounding practice effects. We collated a list of factors we considered in designing our protocol that may be used as a framework by other researchers designing speech collection protocols (Multimedia Appendix 1).

Ethical Considerations

The pilot study received approval from the Research Ethics Committee of King's College London (reference LRS/DP-22/23-36194). As part of our pre-enrollment screening and again in our consent process, participants were asked to confirm their understanding of these criteria and reminded that they should not take part if they did not meet any of them. We did not collect any information in relation to these criteria for ethical reasons and as Article 5(1)(c) of the General Data Protection Regulation stipulates the collection of minimal necessary data [79]. Detailed health information was superfluous to our study aims and of a sensitive personal nature.

Upon completion of the recordings, participants were compensated for their time with e-vouchers redeemable in several shops. For the day cohort participants, these comprised £20 (US $25) for 3 sessions (day 1) and £60 (US $75) for 3 sessions (day 2) to encourage completion of both days. The participants of the week study received £40 (US $50) for 3 sessions.

Results

Data collection and preliminary analysis was funded from April 1, 2023, to March 31, 2024. Recruitment began on June 5, 2023. Pre-enrollment screening to exclude any hearing, speaking, neurological, or mental health disorders that might affect their speech was completed by 141 participants (Figure 3). In total, 28 and 26 participants enrolled in the day and week studies, respectively (Table 3). One participant in the week study completed 2 of the 3 recording sessions due to illness (Figure 3). Day 1 recordings began on June 14, 2023, and were completed on August 10, 2023. Day 2 recording began on August 9, 2023, and was completed on October 5, 2023. Week recordings commenced on June 19, 2023, and were completed on October 6, 2023. At the time of submission of this manuscript, analysis was in progress. We plan to submit of our core analysis later in 2025.

In the day study, the median recording start times for the morning sessions were 9:12 and 9:11 for days 1 and 2, respectively (Multimedia Appendices 3 and 4). The median afternoon and evening recording start times for both days were 14:05 and 18:04, respectively. In the week study, the most common recording slots were 10 AM to 11 AM and 12 PM to 1 PM, with 5 participants each (Multimedia Appendix 5). Recording times for each participant were consistent across the Monday, Wednesday, and Friday sessions, with differences in start times all <30 (median 13, range 3-22) minutes.

In total, the study comprised 245 recording sessions and produced 1225 audio files from 5 recording devices, totaling 169 GB of data. Using Audacity, we separated the readings of

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"The Rainbow Passage" from the condenser microphone and extracted our 14 example speech features using the methodology previously outlined. These values are provided for the day and week study participant groups (Table 4).

The focus of this paper is methodology development. Therefore, an analysis of within-individual speech variation and the ability of different devices to capture this variation is beyond the scope of this paper; it will be reported in future publications.

Figure 3. Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) flowchart describing participant recruitment, enrollment, and completion. *Preenrollment was completed via Qualtrics, email, and face-to-face communication.

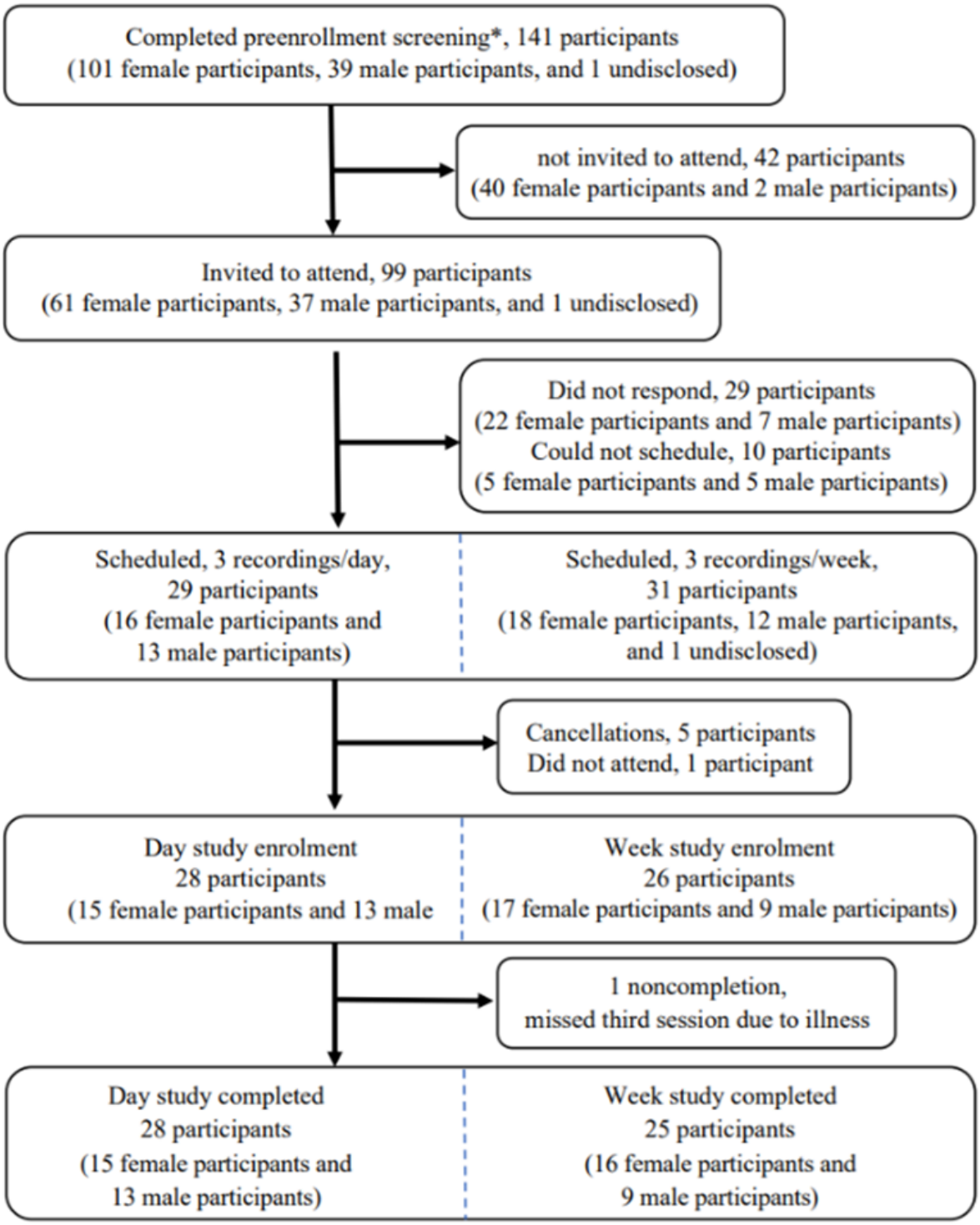

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Table 3. Participant characteristics.

Characteristics	Day (n=28)	Week (n=26)
Sex, n (%)		
Female	15 (54)	17 (65)
Male	13 (46)	9 (35)
Age (y), median (IQR)	26 (23-34)	29 (24-34)
Height (m), median (IQR)	1.70 (1.63-1.79)	1.71 (1.63-1.78)
Ethnicity, n (%)		
Asian or Asian British (Indian, Bangladeshi, and Chinese)	5 (18)	7 (27)
Arab	0 (0)	1 (4)
Black, African, Caribbean, and Black British (Caribbean)	1 (4)	1 (4)
White (United Kingdom and Ireland)	14 (50)	9 (35)
White, other	3 (11)	5 (19)
Mixed or multiple ethnic groups	4 (14)	1 (4)
Other ethnic groups	1 (4)	2 (8)
Language status, n (%)		
Native English speaker	24 (86)	17 (65)
Non–native English speaker[a]	4 (14)	9 (35)
Voice use in the 3 mo before recording, n (%)		
Low	1 (4)	2 (8)
Intermittent	7 (25)	6 (23)
Regular	19 (68)	15 (58)
High	1 (4)	3 (12)
Minor health issues, n (%)		
Allergies	2 (7)	4 (15)
Sinusitis	1 (4)	0 (0)
Acid reflux	1 (4)	1 (4)

[a]All B2 levels or above per the Common European Framework of Reference for Languages [54].

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Table 4. Normative median (IQR) feature values for a set of 14 example features extracted from condenser microphone recordings of "The Rainbow Passage."[a]

Feature extraction level[b]	Week (n=26), median (IQR)	Day 1 (n=28), median (IQR)	Day 2 (n=28), median (IQR)
Duration (s)			
Suprasegmentally	122 (110 to 136)	114 (104 to 126)	113 (103 to 123)
Speaking rate, (syllables s^{-1})			
Suprasegmentally	3.69 (3.40 to 3.99)	3.72 (3.53 to 4.06)	3.72 (3.49 to 4.00)
Articulation rate, (syllables s^{-1})			
Suprasegmentally	4.63 (4.32 to 4.91)	4.65 (4.47 to 4.87)	4.65 (4.48 to 4.91)
Pause rate (s^{-1})			
Suprasegmentally	0.233 (0.205 to 0.264)	0.215 (0.191 to 0.255)	0.214 (0.187 to 0.251)
Pitch mean (Hz)			
Suprasegmentally	187 (120 to 202)	146 (111 to 194)	154 (112 to 192)
Automatically identified /a/ vowels	183 (124 to 203)	150 (114 to 189)	157 (115 to 196)
Pitch SD (Hz)			
Suprasegmentally	2.91 (2.54 to 3.57)	2.78 (2.35 to 3.79)	2.89 (2.41 to 3.69)
Automatically identified /a/ vowels	0.37 (0.26 to 0.59)	0.38 (0.22 to 0.56)	0.35 (0.21 to 0.58)
Intensity (dB)			
Suprasegmentally	68.7 (67.1 to 70.1)	68.2 (66.7 to 69.8)	68.5 (66.8 to 69.9)
Automatically identified /a/ vowels	72.7 (70.8 to 74.5)	72.6 (70.2 to 74.6)	73.0 (70.7 to 74.7)
Harmonic:noise ratio (dB)			
Suprasegmentally	10.43 (7.28 to 12.02)	8.33 (6.39 to 9.85)	8.34 (6.69 to 9.97)
Automatically identified /a/ vowels	8.57 (4.62 to 10.61)	6.44 (4.38 to 7.97)	5.58 (3.72 to 8.33)
Spectral slope			
Suprasegmentally	–17.0 (–18.6 to –15.6)	–16.4 (–17.7 to –15.4)	–16.4 (–18.0 to –15.1)
Automatically identified /a/ vowels	–20.5 (–22.0 to –19.1)	–19.8 (–21.6 to –18.7)	–19.7 (–22.1 to –18.7)
Cepstral peak prominence (dB)			
Suprasegmentally	10.14 (9.56 to 10.74)	9.96 (9.43 to 10.69)	10.17 (9.36 to 10.77)
Automatically identified /a/ vowels	13.91 (12.84 to 15.03)	13.26 (11.76 to 15.03)	13.50 (11.91 to 14.82)
First formant (Hz)			
Suprasegmentally	477 (449 to 504)	482 (454 to 507)	475 (450 to 505)
Automatically identified /a/ vowels	648 (577 to 698)	639 (580 to 674)	628 (571 to 678)
Second formant (Hz×10^3)			
Suprasegmentally	1.65 (1.56 to 1.72)	1.57 (1.49 to 1.64)	1.57 (1.48 to 1.63)
Automatically identified /a/ vowels	1.33 (1.25 to 1.43)	1.26 (1.17 to 1.36)	1.25 (1.17 to 1.37)
Spectral gravity (Hz)			
Suprasegmentally	417 (362 to 465)	453 (388 to 487)	433 (367 to 497)
Automatically identified /a/ vowels	613 (511 to 687)	651 (564 to 706)	621 (544 to 696)
Spectral deviation (Hz)			
Suprasegmentally	330 (286 to 389)	363 (324 to 398)	357 (320 to 393)
Automatically identified /a/ vowels	361 (310 to 426)	370 (342 to 414)	362 (331 to 407)

[a]Feature definitions are provided in Table 2.

[b]Features are extracted suprasegmentally or from automatically identified /a/ vowels in readings of "The Rainbow Passage" recorded with a condenser

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microphone that did not apply any preprocessing.

Discussion

Principal Findings

We developed a protocol and checklist for study design, implementation, and reporting of repeated speech sample recording in the same individuals over time (Multimedia Appendix 1). The metadata reporting, scheduling, device choices, elicitation tasks, data storage and preparation, and feature extraction provide an adaptable template for other researchers collecting repeated speech samples.

Our specific research focus was to gain insights into speech variation over the course of a single day and week while controlling for practice effects. The protocol is unique among studies exploring within- and between-speaker variability in a nonpathological population in the variety of speech captured and the number and type of recording devices. This allows us to observe how within-individual variability is captured by mobile devices. Analysis of these aspects will be presented in future work.

The protocol also enabled us to generate a small but well-described dataset of normative values, which are underreported in the speech biomarker literature [34,47], of 14 example features commonly used in speech-health research. The insights resulting from this work provide us with a foundation for the design of future data collection and interpretation in clinical cohorts.

Limitations and Lessons Learned

The design and implementation of this protocol provided insights that will inform the methodology of future studies.

Protocol Development

The design of this protocol was made challenging by the absence of suitable established collection and reporting protocols [40]. Discipline silos are a core challenge in speech-based health assessment literature that hinders protocol development and reporting. There is a lack of teams integrating clinical-facing researchers who collect data and researchers who process and analyze the data, who are typically from engineering or computer science backgrounds. This can lead to gaps in the collection and reporting of speaker factors and methodological choices that can influence the measurement of recording speech. Consistent reporting of the effects of speaker-related, recording, and processing factors is urgently required to aid the development of robust speech collection protocols and processing pipelines [10,80] and to inform the statistical design of speech studies in clinical cohorts [47].

Speech Elicitation Strategies

The choice of speech elicitation strategies in any protocol is a trade-off between competing factors that include the need to capture indicators of different aspects of speech production, driven by the research question [34,35]; participant burden and adherence; and strategy-dependent technical challenges in extracting features from recordings. We prioritized a combination of strategies to elicit indicators of several aspects of speech production relevant to mental, neurological, and respiratory health that were quick and easy for participants and did not require them to disclose personal information. These may not be suitable for every biomarker study and application.

Resource Requirement

Although participant numbers were small (n=54), the resources required to implement all steps of the protocol—recruitment, data collection, preprocessing of audio files, and feature extraction—were substantial. Data collection and audio preprocessing were particularly labor intensive. Our 245 recording sessions extended from 8 AM to 7:30 PM. We preferred to run these sessions with 2 researchers present to help minimize the likelihood of errors, although this was often not logistically feasible. Regarding preprocessing, we estimate that splitting the 1225 audio files into their individual tasks required close to 720 hours of researcher time. This highlights the need for more efficient recording and annotation techniques to recruit large, well-powered studies.

One way to increase dataset size and minimize researcher burden when implementing a similar protocol in the future could be to collect data remotely using PCs or smart devices using collection platforms such as RADAR-base [81]. Such a solution does not require researcher time to run the recording sessions, and apps can be easily designed to record different speech elicitation activities individually, saving manual segmentation time. However, remote studies are more likely to result in missing data, incorrectly completed tasks, and more variable data quality [60,82].

Participant noncompliance, particularly in clinical cohorts, is a further concern in remote studies. Pierce et al [50] reported high adherence of 92% of their healthy participants to the prescribed recording times over 7 days. Over collection intervals of up to 18 months, we observed clinical cohort completion rates of 50% (IQR 21%-74%) and 41% (IQR 13%-67%) for the scripted and free-speaking speech tasks, respectively, in RADAR-MDD, where speech was one of >10 data streams. Within the sparse longitudinal literature, the Voiceome Study is a further example, where only 21% of participants completed ≥2 recordings [43]. Therefore, there is a need to understand participant motivation and functionality concerns in mobile data collection.

Recruitment Balance

Before beginning recording, we aimed to recruit a 50/50 balance of sex at birth. However, we quickly learned that this required a concerted effort to achieve in the fixed time that we had to complete our work, dictated by funder requirements. In total, 101 women completed pre-enrollment forms versus 39 men, which was only achieved following specific appeals for male participants. Our final overall cohort comprised 22 men and 32 women. While not 50/50, this is more balanced than the 75/25 female/male balance of the clinical speech cohort recruited in RADAR-MDD, which was attributed to the greater reported incidence of depression in women [7,60]. We did achieve good attendance once participants enrolled, with only 1 participant of 54 missing 1 session due to illness. This highlights that

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participants were engaged and willing to complete the speech tasks.

Recruitment Feasibility in Clinical Cohorts

The recording of healthy volunteers in this study was a deliberate design choice; a better understanding of healthy speech is needed to understand changes that accompany pathology. Our choice minimizes variability due to pathology and piloted data collection procedures for future larger studies. Adaptations may be needed to accommodate data collection in clinical populations.

When implementing our protocol, we benefited from the large pool of potential "healthy" volunteers in our institution. Clinical inclusion criteria could shrink the recruitment pool, and staff and students may be more reluctant to volunteer if it requires disclosure of a diagnosed mental health disorder. Therefore, it remains to be seen if a clinical cohort, such as participants with major depressive disorder, could be recruited for the same protocol recording in a controlled environment, given the need for set recording times and days for 3 to 6 sessions.

In separate research in a clinical cohort, we have observed that the choice of speech elicitation activity is also important for participant and patient engagement in the context of future mobile speech monitoring apps [44]. Fixed, repeated tasks increase the risk of disengagement; for example, we received participant feedback in RADAR-MDD that repeating the same reading every 2 weeks for up to 2 years became tedious. Recruitment in the Voiceome Study was high, but data contribution rates were low, and the lack of engagement was not discussed [43].

Metadata Collection

A range of speaker-specific factors dictate changes in speech; therefore, the collection of personal data is essential in speech-health studies, as such factors may relate to selection, information, or confounding biases. The collection of such information is a balancing act of analytical goals versus (1) ethical and regulatory considerations that dictate any personal information collected should only relate to what is needed for obtaining meaningful results; (2) participant acceptance and recruitment feasibility, as studies collecting more personal and sensitive information, which may also increase the participation time, may be more challenging to recruit; and (3) logistical considerations, depending on the time and resources available to complete data collection.

We had ethical, participant acceptability, and logistical factors in mind when deciding what information to collect in our protocol (Multimedia Appendix 2). Information that we did not collect but would recommend others consider includes (1) caffeine and alcohol intake before recording [83,84], (2) medications taken [85,86], (3) menstrual cycle phase at the time of recording and whether female speakers are menopausal [12,13], and (4) participant mood using a clinically validated tool.

As this protocol was for a pilot study, we did not consider getting feedback on metadata collection through patient public involvement work. However, this should be a core consideration when using the underlying methodology in future studies.

Equipment Setup

Our setup had 2 limitations with implications for speech measurement precision. First, it was possible for participants to move the position of the office chair on which they were seated during recording as it had wheels and was rotatable. This was a trade-off, as with the chair's height adjustment feature, participants could be easily centered on the microphone setup per our protocol. We mitigated this risk by observing participants during recording and making gentle reminders no to move the chair and, in rare cases, repositioning the participants. However, participant movement could not be completely excluded.

Second, there was a limit on how close participants could position their mouths from the microphone, depending on their BMI, as the condenser microphone was set back from the table edge in a fixed position for the study to minimize adjustment of the setup and fully surround it by the acoustic foam enclosure. This had the potential to result in deviations from mouth-microphone distance in our protocol. This issue could be mitigated by positioning the microphone closer to the desk edge, combined with an extension of the acoustic foam to surround the participant and microphone more fully.

In addition, early in the study, we occasionally observed small amounts of audible interference on recordings from mobile phones and, on rare occasions, phone alert tones and incoming calls. We subsequently requested that participants switch their mobile devices off, place them in flight mode, or leave them outside the recording room during sessions. We later began to set our study phones in flight mode, after occasional, new observations of interference in sessions where interference from the participants' phones could be excluded.

Feature Extraction

Our choice and specification of features to report represented a considerable challenge when developing the protocol. To the best of the authors' knowledge, there is no agreed minimal benchmark feature set in the literature for such a purpose. In addition, the perturbation and quality measures typically reported in the voice disorder literature [62,63] are limited; they do not adequately capture all the vocal effects associated with neurological and mental health conditions.

Meanwhile, predefined multivariate feature sets, such as the extended Geneva Minimalistic Acoustic Parameter Set (eGeMAPs) or the Computational Paralinguistics Challenge Set (ComParE), available in the openSMILE toolkit [87,88] were not designed for health assessments. For example, these feature sets do not contain specific timing and fluency measures, such as pause rate, a widely used feature in the ALS and depression literature [7,8,65]. A similar feature set to ours is published in the study by Larsen et al [89], but it contains jitter and shimmer measurements, which have limited utility when extracted from connected speech [70].

An additional challenge is that many commonly reported features are not uniformly defined or extracted by different

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extraction tools. For example, Lenain et al [90] compared vocal jitter across 3 toolboxes and only obtained weak correlations between the different implementations.

We used Praat as it is arguably more widely used in speech pathology and phonetics research. However, a weakness of Praat we observed relates to the number of settings associated with extracting each feature; finding guidance on preferred values for these settings is difficult. We also observed that default values were not ideal in certain circumstances. For example, when testing the pitch feature extraction code, we observed that the default pitch ceiling value of 500 Hz could result in false pitch readings of >300 Hz, well outside of expected ranges for this feature.

A challenge relating to extracting features over specific vowels is reliance on third-party ASR and forced alignment tools. Our choice of Whisper and the MFA was to allow us to extract normative feature values from a processing pipeline comprising standard, open-source, well-established tools. We used these tools offline to maintain data privacy and security. A limitation of our protocol is that, due to resource constraints, we were limited to spot-checks of alignments. However, in subsequent work using this dataset, we have observed differences in timing features extracted using word boundaries estimated from transcripts generated using different ASRs [27]. Further work, including manual verbatim and phonetic transcriptions, is required to explore the effects of different ASR tools on the quality and reliability of transcripts and to assess alignment accuracy and isolated vowels [91].

Analysis Plan

Overview

We will use data collected using this protocol to assess within-participant variability in speech features within 1 day and 1 week and between recording devices and elicitation tasks. The analysis will include the features we have already extracted (Table 2) as well as suitable linguistic features (see examples in the study by Botelho et al [92]) extracted from the picture description tasks.

Our analyses will be in 3 stages. First, we will use test-retest scatter plots to visualize systematic versus random differences between pairs of recording sessions. Second, we will use linear mixed effect models [93,94] to estimate the within- and between-person variance. Each feature will be tested in a separate model. The models will include a participant random intercept and 2 dummy variables indicating whether the recording was made in the middle of the collection period (lunchtime for recordings over 1 day; Wednesday for recordings over 1 week) or later (evening or Friday). Third, from these models, we will calculate the ICC, the proportion of variance attributable to between-person differences (0=all variation is within-person and 1=all variation is between-person).

We will use linear mixed effect models to estimate differences in speech features over the day or week, using separate models for each feature. The models will include a participant random intercept and 2 dummy variables indicating whether the recording was made in the middle of the period (lunchtime for recordings over 1 day; Wednesday for recordings over 1 week) or later (evening or Friday).

We will additionally conduct a device-type sensitivity analysis, also using linear mixed effects models, to compare recordings from our benchmark condenser microphone with other devices we used, as in the study by Botelho et al [25]. This will reveal how within-speaker variability is captured in recordings by different mobile devices, which commonly use preprocessing and whose microphone specifications may vary. This analysis is needed to increase our understanding of the ability of mobile health tools to reliably capture changes in speech in research and clinical practice. We expect to complete this analysis and submit the follow-up paper later in 2025.

Data Utility

The core research question we set out to investigate with the data collected with this protocol in developing our protocol was within-individual speech variation within 1 day and 1 week, toward longitudinal assessments of health. However, the resulting data have broader utility in speech research and therefore represent value for funding. This is important to consider in study design, given the large resources needed to generate speech corpora.

We have begun using the data to benchmark different speech technologies (eg, ASR) and quantify associated variability in the feature extraction pipeline [27]. We have also demonstrated practice effects in repeated readings [95]. Further utility is gained from recording over multiple devices and using different elicitation methods, allowing us to assess variability in speech features according to these key methodological choices. It is vital to characterize such variation in speech over repeated speech samples to identify and develop reliable speech marker pipelines for clinical research and practice. Finally, we are also preparing to make the datasets accessible to other nonprofit researchers, enabling other investigations.

Conclusions

In the speech-based health assessment literature, core methodological details and speaker characteristics are often underreported or the rationale for choices not explained. Underlying this, there is a need for more considered design of speech data curation. With this in mind, we have described a protocol for collecting nonpathological repeated speech samples. The core methodological aspects of this protocol cover design and reporting decisions that are relevant for researchers collecting longitudinal data for speech and language biomarker research. We encourage other researchers to adopt similar practices and consider the aspects we highlight in their own projects, thereby adding replicability and, ultimately, the translation of speech and language biomarkers into clinical research and practice.

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Acknowledgments

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Data Availability

All code is available upon request from the corresponding author. Datasets will also be made available subject to participant consent and completion of a data use agreement.

Authors' Contributions

NC and J Dineley were responsible for conception, design, acquisition, analysis, data interpretation, and manuscript drafting and editing. LLW was responsible for design, acquisition, analysis, and manuscript drafting and editing. EC was responsible for conception, analysis, and manuscript editing. CL, ZR, and TP were responsible for acquisition and analysis. FM was responsible for conception, design, and manuscript editing. J Downs and RD were responsible for conception and manuscript editing. TFQ was responsible for conception, data interpretation, and manuscript editing.

Conflicts of Interest

NC is a consultant to thymia Ltd. RD is a director of CogStack Ltd and Onsentia Ltd. All other authors have no other conflicts to declare.

Multimedia Appendix 1
Checklist of methodological aspects for consideration in protocol design and reporting.
[DOCX File , 385 KB - resprot_v14i1e69431_app1.docx]

Multimedia Appendix 2
Prerecording questionnaire completed by participants at the start of each recording session.
[DOCX File , 31 KB - resprot_v14i1e69431_app2.docx]

Multimedia Appendix 3
The day cohort reported recording times, median (IQR). Day 1 and day 2 were 8 to 11 weeks apart, on the same weekday.
[DOCX File , 24 KB - resprot_v14i1e69431_app3.docx]

Multimedia Appendix 4
Intervals between sessions, median (IQR) in minutes for day 1 and day 2 in the day study.
[DOCX File , 25 KB - resprot_v14i1e69431_app4.docx]

Multimedia Appendix 5
Distribution of recording times in the week study.
[DOCX File , 25 KB - resprot_v14i1e69431_app5.docx]

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Abbreviations

ALS: amyotrophic lateral sclerosis

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ASR: automatic speech recognition
Cape-V: Consensus Auditory-Perceptual Evaluation of Voice
ComParE: Computational Paralinguistics Challenge Set
eGeMAPs: extended Geneva Minimalistic Acoustic Parameter Set
ICC: intraclass correlation
MFA: Montreal Forced Aligner
RADAR-MDD: Remote Assessment of Disease and Relapse—Major Depressive Disorder

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Protocol

An Integrated Virtual Reality–Based Telerehabilitation Platform to Support Recovery and Maintenance of Functional Abilities Among Older Adults: Protocol for a Usability and Acceptability Study

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Abstract

Background: Population aging leads to increased disability, implying a significant effect on health care systems and the lives of caregivers. As an example, stroke is a major cause of common diseases and is one of the leading causes of disability in older adults. Rehabilitation is the most effective intervention to counteract patient disability and simultaneously reduce the burden on caregivers. In particular, repetitive and task-specific training seems to be the most effective intervention for poststroke rehabilitation. Virtual reality (VR) is a very useful tool to provide this type of intervention, making it fun through gamification.

Objective: This paper aims to present a protocol to evaluate the acceptability and usability of an upper limb rehabilitation solution based on VR. The RecoveryFun telerehabilitation system consists of a VR headset, wearable sensor, caregiver app, and clinical platform.

Methods: A total of 15 older adult patients with neurological conditions (eg, stroke or brain injury) fulfilling the inclusion and exclusion criteria were recruited in 3 recruitment centers, 5 from each site. The system was given to patients, and they were free to use it when they preferred at their home, with or without caregiver help, following the clinical session set by the physiotherapist. At least 20 minutes of use per week was requested. The physical therapist was able to remotely monitor the progress of the therapy and increase the difficulty and repetitions of the exergames, also considering the patient's fatigue and stress levels. The system was kept by the patients for 4 weeks, and there were several meetings and supervision via phone calls by the therapist. The main dimensions investigated were system usability, using the System Usability Scale (SUS) and User Experience Questionnaire, and acceptability, using the Quebec User Evaluation of Satisfaction with Assistive Technology (QUEST) 2.0. Upper limb function and patient's quality of life, as well as caregiver's perceived stress, were also assessed as secondary outcomes.

Results: The study started in May 2024 and ended in June 2024. We recruited 16 patients with their caregivers and 6 health care professionals in Italy, Belgium, and Switzerland. Results are expected to be published by winter 2025.

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Conclusions: The aim of the study is to propose and evaluate a new telemedicine system that would allow greater adherence to therapy without moving from home, reducing the burden on the caregiver. The system could also be used in rehabilitation centers as a complement to traditional rehabilitation. Finally, with the calibration system enabling the therapist to create customized clinical sessions for the patient, the system could be versatile and fun for a wide range of patients.

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International Registered Report Identifier (IRRID): RR1-10.2196/68358

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KEYWORDS

rehabilitation; upper limb; stroke; traumatic brain injury; immersive virtual reality; virtual reality; home care; asynchronous telerehabilitation

Introduction

Aging is characterized by a progressive decline in physiological integrity, leading to impaired functional ability and ultimately increased mortality [1]. This decline is partially linked to an increased risk of chronic diseases, including cardiovascular diseases, diabetes, neurological disorders, and cancer. Furthermore, individuals with chronic diseases, like multiple sclerosis, are also exposed to the decline in physiological integrity associated with aging. Additionally, age-related musculoskeletal disorders like arthritis, osteoporosis, and frailty are associated with pain, mobility disorders, an increased risk of falls and fractures, and impaired ability or even disability to perform activities of daily living [2].

Age-related diseases not only cause poorer health and disability in individuals but also significantly impact the lives of caregivers, increasing their stress due to the heightened caregiving burden [3]. Moreover, age-related diseases represent a burden on health care systems and economies through loss of productivity and high health care costs [4-6]. Thus, the aging population is challenging health care systems to ensure long-term rehabilitation for patients [7].

Given the increasing burden of age-related and neurological diseases, developing accessible, cost-effective rehabilitation methods is critical for improving health care outcomes globally.

In particular, the global prevalence of neurological diseases has risen sharply with the significant aging of the global population in recent years [8]. Notably, stroke is the third leading cause of long-term disability in most countries and can result in paralysis, speech impairment, loss of memory and reasoning ability, coma, or even death [9]. Additionally, acquired brain injuries, such as traumatic brain injury, can lead to similar long-term disabilities, including balance and motor impairments, cognitive complaints related to memory and concentration, and chronic headache [10].

The most commonly reported impairment after a stroke or acquired brain injury is the complete or partial loss of motor function in the upper extremities, which can hinder activities of daily living and significantly undermine the quality of life of patients [9].

However, recent studies indicate that highly repetitive, task-specific, and sufficiently challenging training may promote neuroplastic changes to restore motor function [11]. Hence, virtual reality (VR) exergaming has gained attention in rehabilitation, as it incorporates key elements of neuroplasticity (ie, feedback, repetition, intensity, and task specificity, leading to potential recovery in the upper extremities) [12].

VR-based interventions further support cortical reorganization by engaging patients in meaningful, goal-directed activities that stimulate neuroplasticity [13]. Combining physical and cognitive tasks, VR exergaming activates sensorimotor and cognitive networks, which may strengthen neural pathways and enhance functional recovery after stroke or brain injury [14].

Moreover, growing evidence suggests that VR exergaming can be effectively used in the context of telerehabilitation, as VR exergaming offers the possibility to generate individualized, safe, and multimodal simulations that have the potential to create a location-independent, effective rehabilitation environment [15]. This approach allows patients to transfer a part of their rehabilitation services from the clinical setting to their home environment [16]. Such a shift provides several advantages, including making rehabilitation programs more adaptable to patients' schedules, partially alleviating the time constraints experienced by therapists, reaching geographically isolated areas without clinical facilities, and reducing costs (eg, by decreasing travel to rehabilitation clinics or enabling home visits) [17,18].

In light of this, research regarding the usability and effectiveness of VR in rehabilitation has grown recently. However, the main application of VR to date is aimed at increasing balance [19]. The use of VR in upper limb rehabilitation can be a viable telerehabilitation solution that encourages patients to perform therapy when they want at home. To date, telerehabilitation systems for upper limb rehabilitation are limited to the use of semi-immersive rather than fully immersive reality, like is provided by RecoveryFun [20].

To address this gap, we developed RecoveryFun—an innovative motor and cognitive telerehabilitation system based on immersive VR and Internet of Things (IoT) targeted at patients with neurological conditions (eg, stroke or brain injury) with upper limb impairments. The RecoveryFun solution assists health care professionals with creating personalized rehabilitation plans, allowing them to customize exercises by type and difficulty level. Patients can perform these exercises comfortably at home or in the clinic using the provided VR headset. Through a clinical portal, health care personnel can

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monitor adherence to the rehabilitation plan, track progress, and make timely adjustments as needed.

Despite the growing interest in such systems, the market still lacks comprehensive, integrated VR telerehabilitation platforms. For this reason, this study will assess the usability and acceptance of the RecoveryFun prototype through practical functional testing of the system, games, and caregiver app.

Methods

Overview

The study was conducted using a pre-post approach, with a group of patients receiving the system and undergoing data collection before and after the installation and use of the technical solution. Three centers of recruitment were involved: Italian National Institute of Health and Science on Aging (IRCCS INRCA; Italy), Trainm (Belgium), and ZURZACH Care (Switzerland). Each center had to recruit 5 patients with their caregivers. A total of 30 participants had to take part in the trial, excluding the physiotherapists. The study lasted 4 weeks, during which time each participant followed an individualized rehabilitation plan of at least two rehabilitation sessions ranging from a minimum of 10 minutes to a maximum of 30 minutes per week. Each rehabilitation session was planned and scheduled by the therapist remotely via the dedicated clinical platform. The physiotherapist, by monitoring performance and adherence data regarding previous sessions, was able to create sessions customized to the patient by choosing the most useful level and exergames according to the rehabilitation goals. The patient could still perform more sessions if desired.

The RecoveryFun System

Overview

The RecoveryFun system is represented by a series of integrated components, which will be presented in detail in this section.

The patient is provided with a VR headset with the exergame VR application to perform his or her training session, a wearable sensor that connects to the network through a gateway to monitor physical parameters during training sessions, a tablet for remote support from the clinical staff, and a router to provide an internet connection.

The informal carer is able to monitor, support, and motivate the patient's activity using the mobile carer app. He or she also has the possibility to use the tablet to visualize the VR environment in which the patient is playing.

The professionals (carer, therapist, and management staff) rely on the clinical platform to manage the clinical session settings and monitor the patient's data, with a dedicated decision support system.

The RecoveryFun system architecture is represented in Figure 1.

Figure 1. RecoveryFun system architecture: (A) virtual reality (VR) headset, (B) wearable sensor, (C) clinical platform, (D) caregiver app, (E) smart services.

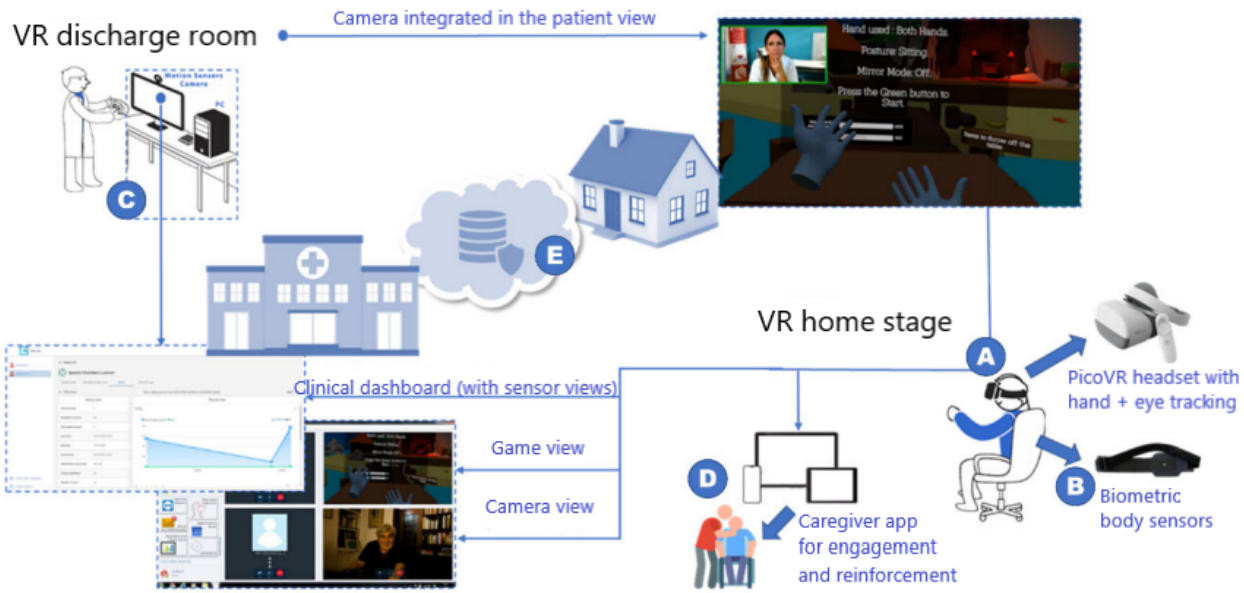

VR Headset

The RecoveryFun exergame app developed for rehabilitation purposes is implemented on the PICO 4 VR headset (Figure 2). The device represents the latest version available on the market from PICO at the time of system development. In addition to eye tracking, this VR headset is equipped with hand tracking functionality, which makes it easily usable by patients wearing biosensors during the training session.

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Figure 2. Virtual reality headset.

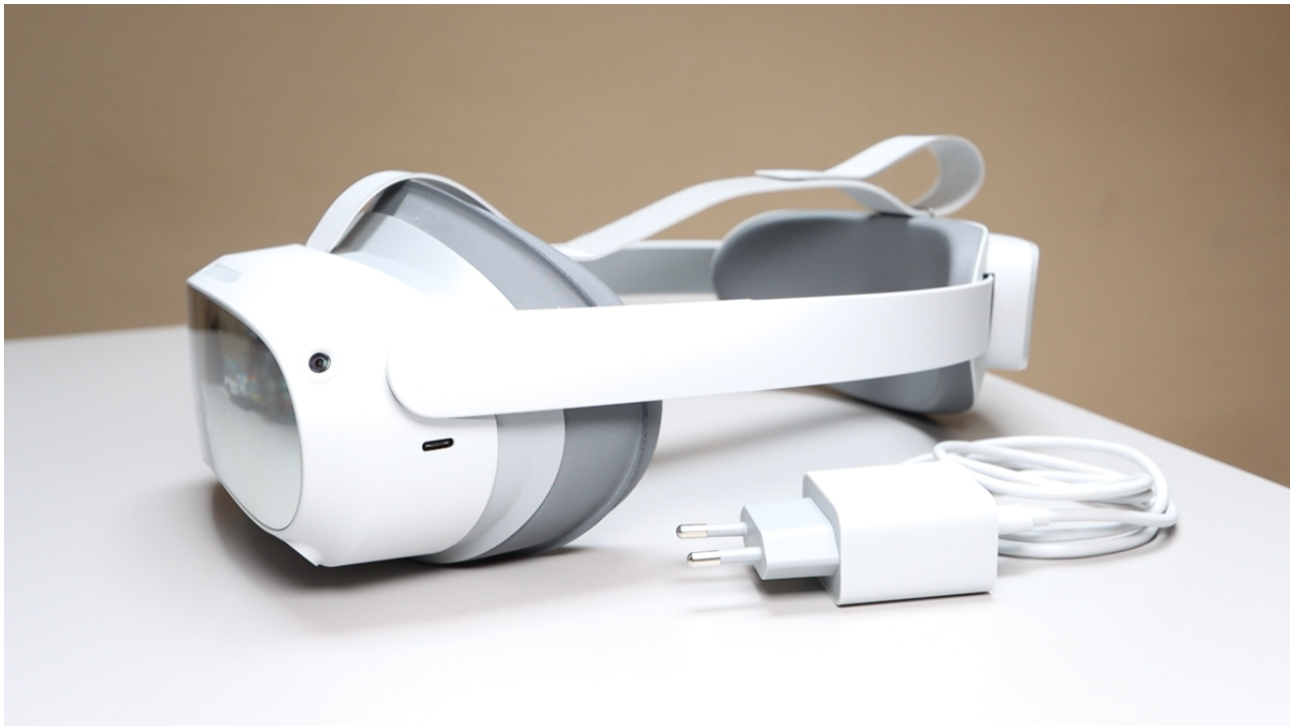

Exergames

A set of exergames is implemented in the RecoveryFun app for rehabilitation purposes. In particular, they are designed to improve and maintain upper limb functionality and to stimulate cognitive exercises. They are developed with special attention to the spatial anchoring of patients, as a measure to increase acceptance and reduce the risk of dizziness. For each exergame, the motion parameters are based on the measurements evaluated in the calibration phase performed during the first session with the physiotherapist. The calibration consists of a series of activities performed by the patient in the VR environment that serve to assess hand motricity, the space that can be explored by the upper limb, and reaction time, in order to adapt the exergames to the patient's specific needs and abilities. Activities performed by the patient to investigate these motor dimensions include opening and closing the hand, moving the arm in the frontal space, and hitting objects that appear in the explored space.

The system includes 7 different exergames, as described in the following paragraphs.

In e*scape from Alpatraz* (Figure 3), the patient has to grab an alpaca and drag it to the final line of the maze. The game stimulates eye motor coordination skills and offers a cognitive exercise in which the patient performs forced movements to reach the target. Motor control and proprioception of the upper limb are trained. This exercise improves muscle endurance, by requiring the patient to keep the arm elevated throughout the length of the line. In addition, in the most difficult level of the game, the patient must be able to recognize the correct line.

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Figure 3. Escape from Alpatraz exergame.

In *clapping hands* (Figure 4), the person has to imitate the gesture he or she sees then push his or her hand toward the image. The game stimulates the ability to reproduce observed gestures. All joints of the upper limb are trained. This exercise can also be useful if the patient has ideomotor apraxia.

Figure 4. Clapping hands exergame.

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Memory (Figure 5) requires the person to find pairs of similar images. It stimulates the user's memory and involves moving all the upper limbs. Since this exercise requires precise movements, patients with dysmetria may benefit from it.

Figure 5. Memory exergame.

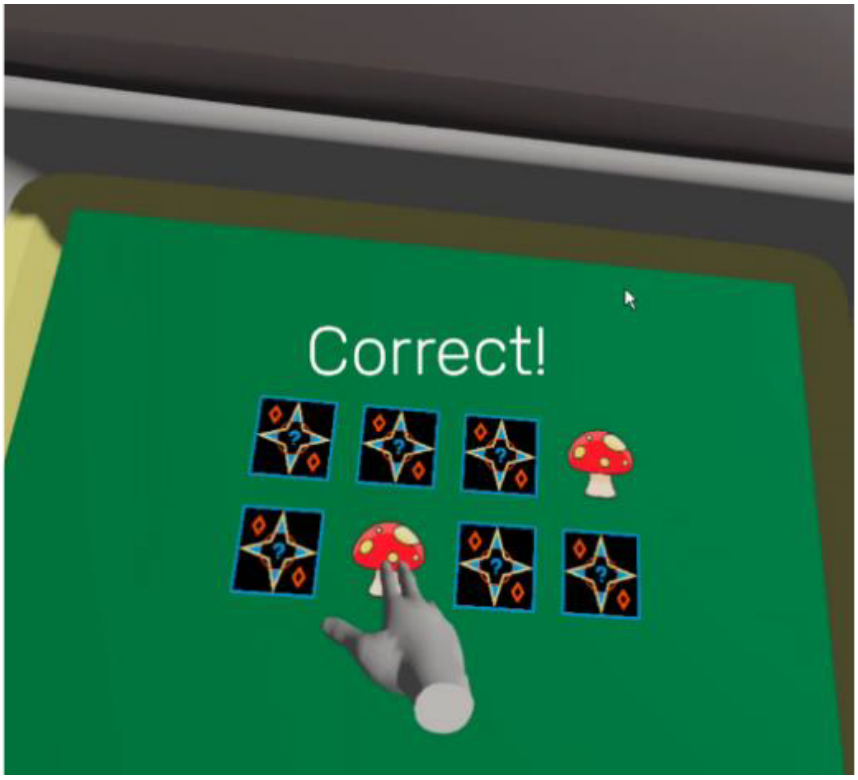

In *whack a mole* (Figure 6), the person has to hit moles with their hand and avoid the penguins. The game stimulates the patient's reaction time and requires flexing the shoulder and extending the elbow to reach the target. The patient has to quickly differentiate between the penguins and moles.

Figure 6. Whack a mole exergame.

Groceries (Figure 7) involves the person putting only the listed products into the shopping cart. At the start of the game, a shopping list is shown, and the person has to memorize it. The game trains skills such as spatial exploration (the patient has to move their head to find all the items) and memory. This exercise is repetitive and task-oriented, providing an effective approach for stroke recovery [10].

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Figure 7. Groceries exergame.

In *basket* (Figure 8), the person has to close his or her hand in a fist to charge the power of the shot (loading bar). When the patient fully loads the bar, he or she has to open the hand to score. The game trains finger flexion and coordination

Figure 8. Basket exergame.

Table trouble (Figure 9) requires the person to throw specific objects into the water. The patient has to move their arm across the entire field of view and in all spatial planes. This exercise can be particularly useful for patients with associative agnosia.

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Figure 9. Table trouble exergame.

Wearable Sensor

A biosensing wireless sensor (wristband), shown in Figure 10, is integrated in the IoT connected ecosystem to measure physiological parameters (photoplethysmography and galvanic skin response data) of end users during the rehabilitation session. The collected data are then processed by an appropriate algorithm to derive measures of stress and fatigue for clinicians to review.

Figure 10. Wearable sensor.

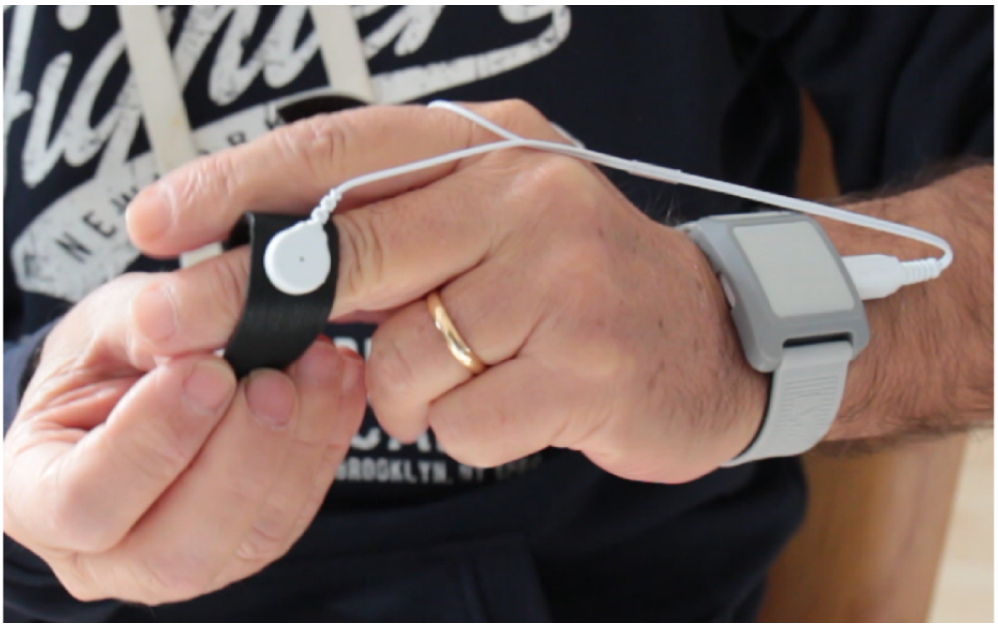

Caregiver App

The informal carer has access (only) to the secure mobile caregiver app installed on his or her smartphone (Figure 11). Its main goal is to enable the caregiver to motivate and support the end user with therapy adherence. No medical data are presented in the caregiver app. Moreover, motivational messages sent by the caregiver from this app are visible to the patient on the RecoveryFun VR app's home screen.

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Figure 11. Example caregiver app screens.

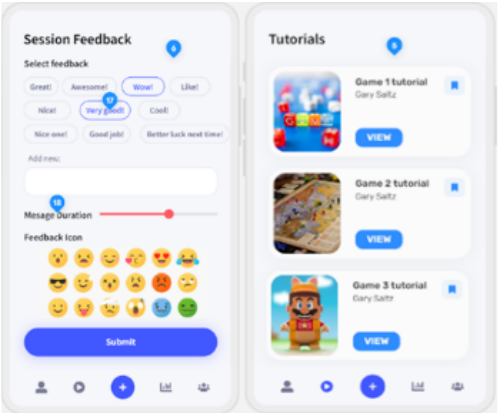

Using the app, the caregiver can monitor the patient's training adherence; send motivational messages to the patient, who will see them on the RecoveryFun VR app's home screen; and consult support material on the use of the system (explanatory videos and a frequently asked questions [FAQ] section) to help the patient use the devices, acting as first-level assistance.

Clinical Platform

Clinical personnel have access to the clinical platform provided as a secure web application (Figure 12). The system administrator can control access rights for each clinical user group (eg, doctors, physiotherapists, nurses).

Figure 12. Clinical platform screen.

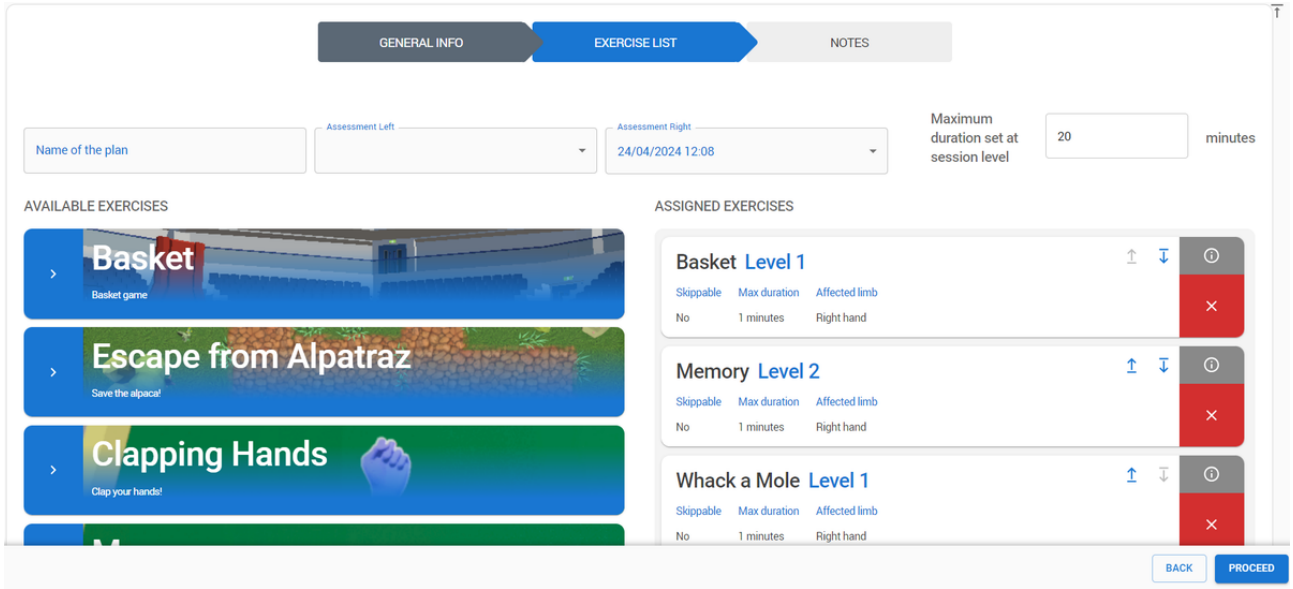

In the clinical platform, an authorized clinician can edit the clinical and administrative data for the assigned patients, manage the VR devices and assign them to a specific patient, associate the caregiver with the corresponding patient, create rehabilitation plans for specific patients, monitor the activity of patients (ie, observe the progress of the rehabilitation sessions executed, see the number and the duration of training sessions executed, evaluate compliance to the rehabilitation plan), and connect to a secure video channel to see the patients' activities in the VR environment.

Smart Services

The platform in the future will also include the presence of smart services, which are under development. This component of the system aims at improving clinicians' activities, allowing for further customization of the rehabilitation experience for the patient and providing a decision support system for the clinical staff.

The Field Trial

The field trial procedure was divided into different phases. Table 1 describes each of them.

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Table 1. Field trial phases.

Phase number	Phase name	Description
1	Recruitment, baseline evaluation, education sessions, and calibration	This phase first involved the recruitment assessment to ensure the patient met the inclusion and exclusion criteria and the baseline assessment with the patient and caregiver to collect their data. The first education session showed the patient and caregiver how to operate and properly use the system. The number of possible further education sessions was then planned based on the patient's and caregiver's confidence using the system independently at home. Finally, the calibration phase was executed if the patient agreed to participate in the study.
2	System installation and use	After the conclusion of the education sessions, the system was installed at home, and the patient began rehabilitation sessions, with the support of the informal caregiver. The physiotherapist constantly monitored the treatment progress through the clinical platform available to him or her.
3	Monitoring (at the end of each week)	The clinician called the patient weekly to ask how he or she was doing, how the sessions were going, and whether there were any difficulties or technical problems. If the problem could not be solved remotely, a meeting was scheduled at home or in the hospital.
4	Final evaluation (after 4 weeks of use)	The aim of this phase was to assess the usability and acceptability of the system and document any critical issues detected by the patient, to evaluate the perceived stress and usability of the system by the informal caregiver, and, finally, to collect information on the impact and usability of the system according to health professionals.

Recruitment

The population selected for the trial in the RecoveryFun project consisted of patients who had overcome an acute event and completed intensive inpatient rehabilitation. The patient we were referred to had already returned home and needed to maintain goals already achieved or increase functionality.

For the patient to be able to use the system properly (to date), specific physical and cognitive requirements are needed: The patient has to have good trunk control and be able to maintain a sitting position for at least 30 minutes without feeling fatigue, and he or she must have good upper limb function (gross and fine hand motor skills). Even when the game workspace is defined according to patient characteristics during the calibration phase, the shoulder range of movement must be wide enough to be able to reach the boundary of the minimum definable workspace. Moreover, the patient has to be able to transfer load onto the pelvis.

In addition, the patient should have a caregiver who, if necessary, can assist him or her during the game session (wearing the headset and the wearable sensor, initiating the games, and stimulating him or her).

The following activities were carried out during recruitment: patient and caregiver information and informed consent, verification of inclusion and exclusion criteria, collection of medical history, objective examination, administration of rating scales, and collection of patient and caregiver sociodemographic data.

Patients

Once the informed consent was obtained in duplicate, compliance with the study's inclusion and exclusion criteria was verified, and the baseline evaluation was carried out with the questionnaires and clinical trials provided by the study design.

Patient inclusion criteria were age ≥60 years; no more than 12 months from an acute event (eg, stroke or brain injury); Trunk Impairment Scale score ≥20; presence of an available caregiver during the study, and the following for the Fugl-Meyer Assessment (FMA) Upper Extremities scale: score ≥33 for motor function of the upper extremities (sections A-D) as well as (Section A.II. Volitional movement) values of 1 or 2 for shoulder elevation, shoulder abduction (90°), external shoulder rotation, elbow flexion and extension, and forearm pronation; (Section B. Wrist) values of 1 or 2 for items rating stability at 15° dorsiflexion (elbow at 90° and at 0°); (Section C. Hand) values of 1 or 2 for pincer grasp, pincer opposition, and cylinder grasp; and (Section D. Coordination/speed) a value of 1 or 2 for tremor. Sections H (Sensation) and J (Passive joint motion and Joint pain) were not considered, as these parameters do not influence the participants' capacity to participate in the intervention.

Patient exclusion criteria were an inability to give his or her informed written consent; presence of cognitive impairment (Montreal Cognitive Assessment score <24 [21]); not meeting the technical requirements based on the safety manual of the PICO headset (eg, having ocular pathologies such as cataracts, glaucoma, and diabetic retinopathy; binocular vision abnormalities; a high degree of myopia, astigmatism, or far-sightedness; corrective glasses that do not fit underneath the VR headset; allergy to plastic, polyurethane, or fabric; a pacemaker; an implanted defibrillator; or cochlear implants and other hearing aids; inability to independently put the VR goggles on); and the presence of a pathology that could impact the ability to use the VR system or be worsened by using the VR system (ie, epilepsy; migraine especially with aura and tension headache; vertigo or cybersickness; trigeminal neuralgia; pressure sensitivity and hyperalgesia in the face; psychotic disorders; severe cardiac or pulmonary conditions; open wounds, injuries to the head, skin infections, and dermatological issues

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that would prohibit wearing the headset; tremor or severe fatigue and exhaustion so that the participant is unable to concentrate or stay awake and attentive long enough to participate in the intervention for 20 minutes; various phobias [eg, claustrophobia]; and visual neglect).

Outcomes

The field trials aimed to assess the usability and acceptance of the RecoveryFun system and adherence to therapy. The primary outcomes of the study included usability perceived by the patient, assessed using the SUS [22] and UEQ [23]; usability perceived by the informal caregiver, assessed using the SUS [22]; and acceptance perceived by the patient, assessed using the Quebec User Evaluation of Satisfaction with Assistive Technology (QUEST) 2.0 [24].

The field trials also focused on the impact of the RecoveryFun system, as measured in the secondary outcomes. These included the impact of the system on the patient's quality of life, measured with the World Health Organization Quality of Life (WHOQOL-BREF) [21]; patient's functional ability, measured with the FMA [25]; stress perceived by the caregiver, assessed using the Perceived Stress Scale [26] and an ad hoc questionnaire; patient interest in using and attitude toward playing, assessed using an ad hoc questionnaire; and the impact of the system on the caregiver's ability to understand whether it is a helpful and supportive tool or causes additional difficulty, as assessed using an ad hoc questionnaire.

For these reasons, the protocol includes study-specific questions on demographics and attitudes toward technology from both the patient and the informal caregiver. In addition, questions related to subjective health and social support are also explored with the patient.

Tables 2 and 3 summarize the different tools adopted with each end user group in all the phases of the study.

Table 2. Tools and dimensions of the patient protocol.

Dimension	Tool	Recruitment	Baseline (T0)	Final evaluation (T1)
Functional ability	FMA[a] [25]	✓	—[b]	✓
Trunk stability	TIS[c] [27]	✓	—	—
Cognitive status	MoCA[d] [28]	✓	—	—
Sociodemographic characteristics; subjective health assessment; social support	Ad hoc questionnaire	—	✓	—
Attitude to technology	MPT-SOTU-C[e] [29]	—	✓	—
Quality of life	WHOQOL-BREF[f] [21]	—	✓	✓
Acceptance	QUEST[g] 2.0 [24]	—	—	✓
Usability	SUS[h] [22]	—	—	✓
Usability	UEQ[i] [23]	—	—	✓
Intention to pay	Ad hoc questionnaire	—	—	✓

[a]FMA: Fugl-Meyer Assessment.
[b]Not applicable.
[c]TIS: Trunk Impairment Scale.
[d]MoCA: Montreal Cognitive Assessment.
[e]MPT-SOTU-C: Matching Person and Technology Survey of Technology Use-Consumer.
[f]WHOQOL-BREF: World Health Organization Quality of Life Brief
[g]QUEST: Quebec User Evaluation of Satisfaction with Assistive Technology.
[h]SUS: System Usability Scale.
[i]UEQ: User Experience Questionnaire.

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Table 3. Tools and dimensions of the informal caregiver protocol.

Dimension	Tool	Recruitment	Baseline (T0)	Final evaluation (T1)
Sociodemographic characteristic	Ad hoc questionnaire	__[a]	✓	—
Attitude to technology	MPT-SOTU-C[b] [29]	—	✓	—
Perceived stress	PSS[c] [26]	—	✓	✓
Perceived stress	Ad hoc questionnaire	—	—	✓
Usability	SUS[d] [22]	—	—	✓
Impact of the system	Ad hoc questionnaire	—	—	✓

[a]Not applicable.

[b]MPT-SOTU-C: Matching Person and Technology Survey of Technology Use-Consumer.

[c]PSS: Perceived Stress Scale.

[d]SUS: System Usability Scale.

In addition, during the course of the month, weekly phone calls or messages were conducted, in which patients could report any critical issues, such as difficulties with playing the game, technical problems, or any feelings of discomfort related to possible motion sickness. The researcher, if necessary, visited the patient's home to solve the critical issues and make suggestions to improve the user experience.

Statistical Analysis

The first step of the data analysis involved the description of the sample. Continuous variables were reported as either mean and SD or median and IQR based on their distribution (assessed using the Kolmogorov-Smirnov test). Categorical variables were expressed as absolute numbers and percentages. The comparisons between pre- and postintervention conditions were conducted using paired *t* tests (for normal distributions), Mann-Whitney *U* tests (for non-normal distributions), or chi-square tests (for categorical variables). Moreover, a linear regression model on the outcome variation between baseline and follow-up was estimated in order to evaluate measure variation.

A limitation of this analysis is the absence of formal adjustments for multiplicity due to multiple outcomes and repeated measures, which may increase the type I error rate. This choice was driven by the limited sample size, as this is a pilot study primarily aimed at assessing feasibility and generating preliminary data. Although basic statistical tests were appropriately applied, no correction methods (eg, Bonferroni adjustment, false discovery rate control, or hierarchical testing procedures) were implemented, as such adjustments would substantially reduce statistical power in this context. Future larger-scale studies should incorporate appropriate multiplicity control strategies to ensure more rigorous error rate control and improve the robustness of the statistical inferences.

Dropouts and Replacement

When the physiotherapist noticed anomalies in the clinical platform that could be related to patient difficulties (eg, lack of use, numerous errors, or abandoned sessions), it was his or her responsibility, during the weekly monitoring, to investigate these aspects in order to keep the patient in the study.

If the patient expressed a wish to abandon the program, he or she was, of course, free to do so, provided that the physiotherapist had ensured that the decision was not based on any solvable problem. Taking into account that the usability and acceptability of the system were evaluated and that an objective was to assess the impact of the system on patient quality of life, a 20% dropout rate was considered acceptable. Therefore, our strategy consisted of replacing the patient if the dropout occurred in the middle of the study (at 2 weeks).

On the contrary, if the patient abandoned the study more than 2 weeks after the start, the researchers were required to note the reasons for leaving and to collect the data gathered up to that point (by the system, researchers, and physiotherapist), unless the patient specifically asked to cancel the data collection.

Providing for the replacement of participants who dropped out was desirable but not mandatory in this case.

To ensure the total number of patients in the project, at least 6 participants had to be recruited at each site.

Ethical Considerations

The study was approved in Italy by the Territorial Ethics Committee of Marche Region (Prot. CET-M 2023 353). Based on Swiss (Federal Act on Research involving Human Beings [Human Research Act]) [30] and Belgian [31] law, there was no ethics approval required.

The respect of ethical principles was one of the guidelines of the project and in this study in particular, because it involved a particularly vulnerable group.

All procedures involving human participants were in accordance with the ethical standards of the Helsinki declaration 1964 and its later amendments or comparable ethical standards.

All potentially eligible participants received comprehensive information about the study. All participants and caregivers were asked to provide signed informed consent prior to participating and were informed that data will be retained for up to 10 years after the end of the study. Each signature was personally dated by each signatory, and the informed consent and any additional patient information were retained by the

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investigator. A signed copy of the informed consent and information sheet were given to each patient.

Participants had to consent to the processing of their personal data in anonymous and aggregate form, in accordance with EU Regulation 2016/679 [32] on the protection of individuals with regard to the processing of personal data and Legislative Decree No. 101/2018 - Provisions for the adaptation of national legislation to the provisions of the European Regulation 2016/679 [33].

Participants were informed their data may be examined by authorized personnel or by members of the relevant ethics committee and officials of the competent regulatory authorities.

Participants could leave the project at any time if they considered participation too burdensome or felt uncomfortable for any reason.

No compensation was provided for participating in the study.

Results

The study was conducted from May 2024 through June 2024 in Italy, Switzerland, and Belgium. A total of 16 patients, 16 caregivers, and 2 health care professionals took part in the field trial. The data collected have been analyzed and are expected to be published by winter 2025. The study findings will be used for publication in peer-reviewed scientific journals and presentations in scientific meetings.

Discussion

In the face of an aging population, we will inevitably see an increase in acute cerebrovascular events, which are among the leading causes of disability in Europe, in the coming years [26]. Moreover, we will see an increase in the population's demand for health care services [27]. As a result, we can expect to observe an increased care burden on the part of families. Taking these facts into account, interventions are needed to relieve families of these burdens and try to ensure the highest possible level of care even in the long term.

In this regard, the main treatment following cerebrovascular events is physiotherapy, which allows the pursuit of hospitals' primary goal: regaining balance and standing in order to reduce the workload and ensure basic activities of daily living for the patient [34]. In particular, rehabilitation of the upper limb needs more time, as the required movements are finer and more complex [35].

Within this framework, the RecoveryFun project aims to offer an answer to these growing needs. RecoveryFun makes use of VR, as it is now recognized to be effective and helpful during upper limb rehabilitation for stroke patients [36]. In fact, the system is designed to provide personalized and fun upper limb telerehabilitation for patients. The professional, through his or her dedicated portal, can constantly remotely monitor the patient and motivate him or her to perform the exercises, resulting in more efficient work. In addition, the caregiver can significantly contribute to the patient's activity by using the caregiver app. He or she can monitor the patient's adherence to the therapy schedule, which is visible on the calendar screen, and easily send motivational messages. The caregiver can also provide first-level assistance if the patient has difficulty using the system autonomously, with the support of informative content such as video tutorials and the FAQ section uploaded to the caregiver app, and even contact technical support through the dedicated section.

All phases of the project were focused on the needs of the user and his or her caregiver in order for the system to be usable at home without the presence of a professional. Prior to the start of the experimentation, several tests were performed during the co-creation phase that helped optimize the system to be as responsive as possible to the needs of the end user. These tests were performed with both potential patients and professionals in the field.

In fact, although some of the devices used were already on the market, such as the Pico 4 Enterprise visor, the sensor was a prototype model that was not yet marketable. The games, platform, and dedicated caregiver app were developed for the project and optimized for the project's goal. The calibration of the viewer, which then conditions the professional's choice of games, required special work by the technical partners as it was not initially planned but was requested by the clinical partners because they wanted to avoid potential patient frustration during use as much as possible. Pilot tests were also carried out prior to the start of the trial to test the system with patients and collect any critical issues that the user might encounter.

The design of the study, described in this paper, allowed the solution to be tested for a period of only 1 month, which was a sufficient period to evaluate the usability and acceptability of the system. In fact, the study included a final evaluation in which both quantitative and qualitative instruments were administered. In addition, during the month, weekly feedback was collected via phone calls or messages. The main challenges of this study were to investigate whether the patient, even with low familiarity with technology, used the system consistently throughout the month-long trial and whether motivation was created.

To make sure to provide the system to patients who are able to use it, the choice of inclusion criteria took much time and thought within the consortium. In fact, the use of immersive VR for telerehabilitation is completely innovative and, according to the state of the art, has never been used before. The main concern of the researchers was not to generate frustration in patients, so specific criteria were identified to select patients with good upper limb function, excellent trunk control, and physiological or mild cognitive impairment.

Although the study focused on usability, the consortium decided to redo the FMA and WHOQOL-BREF also at the end of the test to collect more data and determine whether there was a change in upper limb function and quality of life for patients. The choice was also made due to existing evidence suggesting improvements in upper limb function in gross motor skills examined with the FMA [37]. Similarly, caregivers were given the Perceived Stress Scale again to assess any changes in perceived stress. This would be useful data for a potential future study on the effectiveness of the system.

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In fact, the system has great potential for future development and could be of great help to rehabilitation centers, even during hospitalization, to supplement traditional rehabilitation. This use in a "protected" environment could make patients feel more confident when using the system, thus motivating them to use the system to receive motor and cognitive stimulation even once they return home. Moreover, telerehabilitation technologies could have great cost benefits, even if cost is complex to calculate and varies from country to country. A meta-analysis and systematic review [38] has highlighted how telerehabilitation is an effective way to not only reduce costs but also provide an extra service to patients living in rural or isolated areas. The RecoveryFun system is intended to allow neuromotor stimulation to continue at home and enable a personalized program.

A limitation of the system is that patients who can use it must have very specific requirements that significantly reduce the eligible population. However, the system, being extremely versatile, could also be developed for other areas and for the treatment of other diseases while maintaining the telerehabilitation mode.

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The project website is available on the internet [40].

Authors' Contributions

Conceptualization: MB (equal), CF (equal), RAM (equal), SF (equal), PSS (supporting), VT (supporting), VB (supporting), LR (lead)
Funding acquisition: LR
Methodology: MB (equal), CF (equal), RAM (equal), SF (equal), PSS (supporting), VT (equal), VB (supporting), LR (lead)
Project administration: SF (supporting), PSS (supporting), VT (supporting), VB (supporting), LR (lead)
Supervision: LR
Writing – original draft: MB (lead), CF (equal), RAM (equal), SF (equal)
Writing – review & editing: MB (lead), CF (equal), RAM (equal), SF (equal), PSS (supporting)

Conflicts of Interest

None declared.

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Abbreviations

FAQ: frequently asked questions
FMA: Fugl-Meyer Assessment
IoT: Internet of Things
IRCCS INRCA: Italian National Institute of Health and Science on Aging
SUS: System Usability Scale
UEQ: User Experience Questionnaire
VR: virtual reality
WHOQOL-BREF: World Health Organization Quality Of Life Brief

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Protocol

Needs for Technology-Enhanced Health Professions Education in Eastern and Southern Africa: Protocol for a Descriptive, Cross-Sectional Survey

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Abstract

Background: The use of technology in its various forms has long been a feature of the education and training of health professionals in the industrialized world. As a result of the COVID-19 pandemic, health professions education institutions suddenly adopted “emergency remote teaching,” and this experience exposed the vulnerabilities of countries in Eastern and Southern Africa regarding modes of teaching and learning. In this region, the needs to migrate to effective technology-enhanced learning are not explicit.

Objective: The main objective of this study is to assess the needs for technology-enhanced health professions education in Eastern and Southern Africa. This will lead to the development of a tool reflecting different technologies used in health professions education. The tool will be used by educators to identify and bridge gaps in their use of technology in health professions education.

Methods: This will be a descriptive, cross-sectional survey, and data will be collected from medical and nursing programs at the bachelor’s degree level recognized by national professional bodies or government structures offered at tertiary institutions in countries in Eastern and Southern Africa. The substitution, augmentation, modification, redefinition (SAMR) model underpins our study and serves as an organizing framework for the different types of technology in current use in the institutions under study. The SAMR model is a tool that provides guidance in describing and categorizing uses of educational technology in the classroom. The model is intended to guide educators to enhance their teaching and learning through the adoption, adaptation, or transformation of educational approaches using technology. To obtain the purposive sample, a person from each program who is well-acquainted with the program will identify staff members and students who represent the totality of those populations fairly. Quantitative data were analyzed descriptively for each program. Data were then organized according to the SAMR framework to portray the types of technology in use and challenges encountered.

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Results: This research was funded in October 2023, and the first institutional review board approval was obtained in April 2024. Data collection began in September 2024 and ended in November 2024. Since this was a multi-institution study, we envisaged multiphase data analysis, which was completed in mid-December 2024. As of August 2025, the manuscript is under peer review for publication of the results.

Conclusions: The study will reveal gaps in the use of technology, and this will lead to the identification of needs for enhancing technology in health professions education.

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KEYWORDS

education 5.0; substitution, augmentation, modification, redefinition; SAMR model; technology-enhanced health professions education; cross-sectional survey

Introduction

Education is an integral pillar of any country's sustainable growth and development [1]. Higher education institutions are essential to a sustainable society's growth and development and should function as transforming forces [2,3]. Regarding Sustainable Development Goals, Kasinathan et al [4] observed that technology has significant potential to drive humanity into sustainable development. The world also now finds itself in the fourth industrial revolution, also called Industry 4.0 [5]. As has been the case with the previous industrial revolutions, education is changing to accommodate the needs of the new revolution. This new system or set of educational processes has been termed Education 4.0. It aims to develop the competencies and skills that workers in the fourth industrial revolution require through applying active learning, technology-based learning, and student-centered learning [6,7].

More recently, Education 5.0 has arisen as a new concept [8]. It also involves the use of new technologies to transform education, but additionally emphasizes the need for a constructivist, humanistic, and andragogical orientation poised for deep learning [4,9,10].

Some higher education institutions have been influenced by the Education 5.0 movement, which is highly rated in terms of its association with current business needs and integration with industrial and technological developments [11,12]. Education 5.0 functions within Society 5.0, which is regarded as a super-intelligent society that promotes the convergence of cyberspace and physical space and focuses on human-oriented solutions and social innovation [3,13,14]. The expectation of such a combination is to develop an environment where humans and robots with artificial intelligence coexist and work to improve the quality of human life. A further development in the field of technology for education is the advent of disruptive technology like artificial intelligence software and social media, which are already being used by teachers and students worldwide [15]. Rowan and Casey [16] suggest a triple helix "academia-industry-authority" approach to creating and sharing disruptive tools for addressing emerging needs for development. Advances in industrialization require technology to enable adaptation to complex systems in the health sciences.

Against this background, the use of technology in its various forms has long been a feature of the education and training of health professionals [1,17]. Worldwide, a plethora of opportunities for using technology in such training have been developed and used, including augmented and virtual reality platforms that are available for use in modern education [18]. In clinical education, the process of acquiring knowledge and skills needs to be more experiential, self-directed, and hands-on than in many other disciplines. However, virtual or mixed reality interventions are becoming more accessible and can be used in an integrated way with current, more traditional learning systems [19]. Rath et al [20] point out that augmented reality and virtual reality technologies are already having a major influence on medicine and health care, the implication being that students need to be exposed to important skills in these areas.

Even before the COVID-19 pandemic struck, those institutions that had not taken serious measures to migrate to a higher level of use of technology would have been aware that they were lagging behind the requirements of modern educational approaches. In the situation created by the pandemic, students were unable to attend their usual learning events and yet had to move forward in their training. There is good evidence that the advent of large-scale national lockdown policies resulting from the COVID-19 pandemic stimulated the development of technology-enhanced health professions education (TEHPE) [21,22]. However, a study by Jeffries et al [23] found that while COVID-19 resulted in a transition to more web-based health professions education (HPE), the change was subsequently unstable since the change to technology was not always widely accepted, was marred by inequities (socioeconomic, gender, and geographical), and was not subject to ongoing evaluation to indicate where improvements were needed. Besides the lack of opportunities for essential learning in practical settings, the large-scale use of web-based learning during the pandemic also had ethical consequences—education with basic humanity was neglected and professionalism, interpersonal relationships, mentoring, and communication skills suffered. This trend may be continuing [24].

Challenges to expanding the use of technology in educating health professionals have also been discussed. Challenges such as unavailability, a lack of skills leading to resistance, and a lack of support that curtails the adoption and use of technology have been identified and some solutions have been outlined [17,25]. While acknowledging the empowering possibility of technology use in education in Africa, Cole [26] stresses the reality of the digital divide between and within countries and

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relating to gender. There is often a lack of connectivity, computers and other devices (let alone the more sophisticated technologies listed in the previous paragraph), and digital literacy. Even electricity supply has been and may still be a challenge [27]. An in-depth investigation of e-learning in sub-Saharan Africa and low-resource settings by Barteit et al [28] makes for sobering reading. They conclude that e-learning for medical education was not doing justice to medical students in these settings; that short, one-off projects were common (so-called "cul-de-sac pilots"); and that "technological development has overwhelmed rather than revolutionized medical education." Both Cole [26] and Barteit et al [28] stress the need for sustained investment in integrating technology into existing platforms. There are also legitimate doubts about the effectiveness of the use of technology in training health professionals. In a large-scale Indian study by Hirkani and Supe [29], the evidence was mixed even though students had a positive attitude towards it. The authors concluded that more evidence needs to be generated regarding its effectiveness so that future decisions can be based on evidence. In Pakistan, Sadiq et al [30] report a broadly successful project to empower educators in incorporating greater use of technology in their teaching, but also noted educators' limited e-learning skills and failure to engage with the new technologies, as well as technical hurdles encountered. Granger et al [31] have also found that the grand vision of Education 4.0 is in danger of being watered down by technology mostly being used for lower-level pedagogical changes (substitution and augmentation) in the substitution, augmentation, modification, redefinition (SAMR) model [32]. In this regard a study from Uganda revealed low uptake of TEHPE activities after 10 years of effort, again with lower-level pedagogical changes. The empirical evidence gathered in the study led to recommendations to create an e-learning unit, to improve skills and knowledge in educational technologies, to expand infrastructure for TEHPE, and to design and implement an educational technology policy [33].

From the available evidence reviewed, there is clear evidence that TEHPE is thoroughly in place in the world, and that this trend is likely to have intensified during the COVID-19 pandemic. Interestingly, however, there is little information available about the extent to which TEHPE is currently being used in the training of health professionals specifically in Eastern and Southern Africa. It is also not known whether the sudden spurt in TEHPE during the COVID-19 pandemic has been maintained, nor is it known whether what has been retained is of a quality that deserves its retention. The obstacles impeding its use and the factors facilitating its use in this geographically specific setting are similarly not known.

The SAMR model underpins our study and serves as an organizing framework for the different types of technology in current use in the institutions under study [34]. The SAMR model is a tool that provides guidance in describing and categorizing uses of educational technology in the classroom. The model is intended to guide educators to enhance their teaching and learning through the adoption, adaptation, or transformation of educational approaches using technology (Figure 1).

Figure 1. The substitution, augmentation, modification, redefinition (SAMR) model.

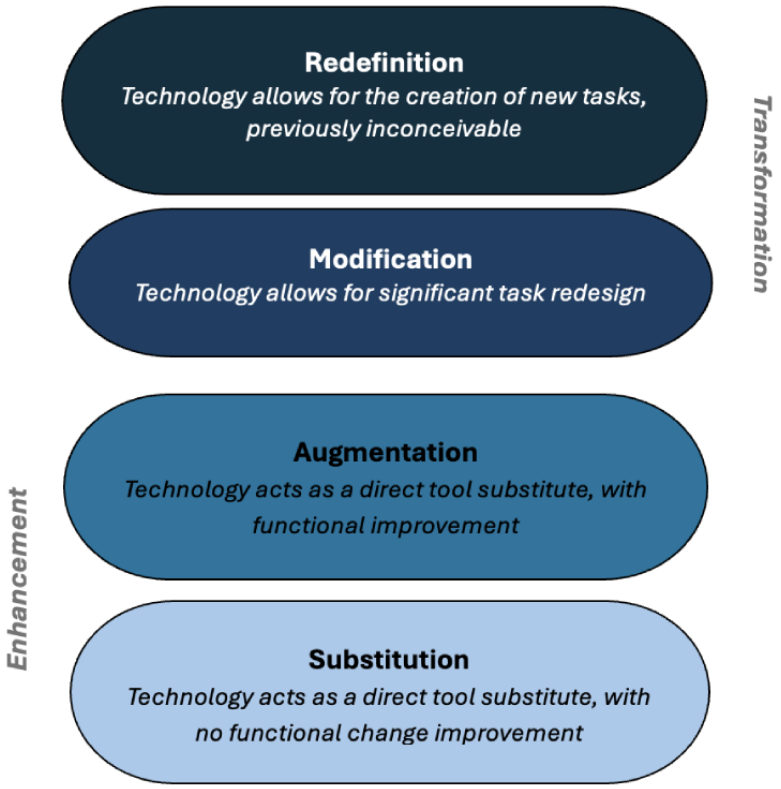

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To demonstrate our conceptual understanding and application of the SAMR model, we describe each level briefly and include hypothetical examples of each [32,34]. There are 2 dimensions in the model, enhancement and transformation, and 2 levels in each dimension.

1. Enhancement – substitution and augmentation: At the substitution level, digital technology is substituted for analog technology, but the substitution generates no functional change [34,35]. For example, an educator may substitute hard copy handouts with electronic versions. At the augmentation level, technology is exchanged, and the function of the task or tool positively changes in some way. An example is when an educator adds links to electronic versions of learning material. Larger volumes of electronic material, like books and videos, are examples.
2. Transformation – modification and redefinition: At the level of modification, technology enables significant task redesign. Examples of this include the recording of lectures and podcasts, which are textual, visual, or audio tools for the construction of knowledge that can be shared across groups of students. At the redefinition level, technology enables the creation of new tasks that were previously inconceivable, like tools for visualization of narrative and structural aspects of text. Examples of this include artificial intelligence and the use of software for data analysis.

Methods

Study Design

This is a descriptive, cross-sectional survey to yield quantitative and qualitative data that address our study aim and objectives outlined below. We aim to assess the needs for TEHPE in higher-education institutions for health professionals in Eastern and Southern Africa.

Relating to the education of health professions in higher education institutions offering health sciences programs, the objectives of the proposed study are as follows:

1. To determine the types of educational technology being used.
2. To identify the frequency with which different technologies are being used.
3. To reveal the reasons why these technologies are being used.
4. To determine teacher and student opinions about the usefulness of the technologies.
5. To identify obstacles to the use of these technologies.
6. To verify factors facilitating the use of these technologies.

Study Participants

The study population will be health care professionals who are also educators in HPE programs in selected Eastern and Southern African higher institutions of learning. Given the short implementation timeframe for this study, it will be feasible to focus only on educators and students in undergraduate medical and nursing programs in Pan-African Consortium for Technology-Enhanced Health Professions Education (PACoTEH) member countries as the study population. These are higher education institutions offering HPE programs for doctors and nurses at the University of Botswana, National University of Science and Technology (Zimbabwe), University of Zambia, and University of Zimbabwe.

Inclusion Criteria

Programs in Eastern and Southern African countries that train doctors and nurses, offer bachelor's degree–level qualifications in medical and nursing programs, are recognized by national professional bodies or government structures, and are offered at accredited tertiary institutions are eligible for inclusion in the study.

Exclusion Criteria

Undergraduate medical and nursing programs in countries outside of Eastern and Southern Africa and programs whose students are not available during the short period for the study will be excluded.

Sampling

Due to the nature of the inquiry in our study, nonprobability, purposive sampling will be used to apply our judgment when choosing members of the population expected to possess information on the technology that has been used in HPE [36]. Given the short implementation timeframe due to delays in securing ethics approvals at some institutions, the sample will be drawn from educators and students in undergraduate medical and nursing programs in PACoTEH member countries. Given that these 2 programs are the largest in health professions, the data would be representative of the entire population. Specifically, a program director or educator will be selected by researchers from that institution, drawing on the local knowledge they have of available staff. This person should be fully familiar with the program under consideration. From each program, a minimum of 20 students will be purposively sampled, spread equally over their number of years of study. Educators will also be sampled purposively to obtain a spread of candidates by seniority, gender, and academic discipline.

Data Collection Procedures

Newly developed questionnaires for staff, students, and educators will be administered using web-based programs (eg, Microsoft Forms) with closed- and open-ended questions to obtain quantitative and qualitative data, respectively. In addition to demographic data, the questions are designed to collect data that answer the study objectives, and some of the questions identify the different types of technology according to the SAMR Model. The questionnaires will be availed to the program director who will identify eligible staff members. The staff members, in turn, will identify students that meet the sample described above. All data will be entered into an electronic database and password-protected. The database will be maintained at one of the consortium institutions. The questionnaires are provided in Multimedia Appendix 1.

Data Analysis and Presentation

We will build an analytic element to compare data according to the nature of the variables obtained. This will enable us to determine differences in the technology used between programs and countries and the needs for enhancement of the technology. Quantitative data will be summarized using frequency

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distributions and averages in tables and graphs. Associations and correlations between the data collected for objectives 1-6 (dependent variables) and biographical and institutional data (independent variables) will be determined using relevant statistical techniques. For example, Pearson *r* will be used to measure the correlation between the types of educational technology being used and the frequency across the institutions, and *t* tests and chi-square tests will establish if there is a significant difference, which may lead to the recommendation of some types of technology over others. Qualitative data will be analyzed thematically, and the coding framework will include data familiarization by all authors, display, reduction, concluding and verifying using the study objectives and the SAMR model as a guide to identifying themes [37,38]. The coding will be inductive (generating codes from the data), and while there will be no fixed number of coders, efforts will be made to capture the nuances of the data according to the study objectives. For validation, the authors will check the themes for accuracy and comprehensiveness against the raw data and reach consensus.

Qualitative methodological rigor will be respected to address the transferability, replication, and credibility of our work. Thematic analysis may not lend itself to replicability because it is a form of pattern recognition where themes are identified from the content, requiring inter-rater cross-referencing for reliability and converging meanings from different researchers [39]. The use of the SAMR framework strengthens the trustworthiness of our study because it requires the collection of data that demonstrate the relationship between knowledge and practice. The framework also enables replication through the formatting of data collection methods and analysis. Findings from quantitative and qualitative data analysis will be organized and presented according to the SAMR framework to portray the types of technology in use and challenges encountered. Finally, from the challenges outlined, needs for enhancing technology in HPE will be identified.

Ethical Considerations

We adhere to relevant safeguards required during research involving human research participants as outlined in the Belmont report of 1979 and the International Conference on Harmonization of 2002 [40,41]. Each institution obtained ethics approval (National University of Science and Technology, NUST/IRB/2024/071, approved April 19, 2024; University of Botswana, UBR/RES/IRB/B10/428, approved September 23, 2024; University of Zambia, 5662-2024, approved August 31, 2024; and University of Zimbabwe, JREC/446/2024, approved October 9, 2024).

To promote confidentiality, identifiable details in the questionnaire will be kept to a minimum. The custodian of the responses will not share this information with other members of the team and will code it before analysis starts. The informed consent procedure will be written in understandable language explaining the aims of the study and the participant's role in it and list potential risks and benefits, making clear that the participant is free to refuse or withdraw without penalty. The consent form and participant information sheet are given in Multimedia Appendix 2.

Pilot Study

The instrument (whether validated or not) will be pretested using 2 program directors, 4 students, and 3 educators who will not then be included in the sample. Corrections will be made as indicated. This pilot test will be used to check the clarity of questions and the usability of the web-based format, but no measures of validity are planned.

Results

This research was funded in October 2023, and approval from the first institutional review board was obtained in April 2024. Data collection commenced in September 2024 and ended in November 2024. Data analysis was accomplished by mid-December 2024. As of August 2025, the manuscript is under peer review for publication of the results.

Discussion

Expected Findings

This study aims to assess the needs for enhancing the use of technology in HPE in Eastern and Southern Africa. There has been a movement to promote the use of technology in the education of health professionals worldwide. However, institutions in this region lag behind in the use of technology, and it is not clear where improvements are needed [17,21,23]. The magnitude of the impact of COVID-19 on teaching and learning was more severe in institutions that could not respond to the requirements for remote teaching and learning, and this further exposed the vulnerabilities of the region. To keep up with the pace of industrialization and remain a part of the global village, it is imperative to identify the attributes that enable the use of the variety of technologies that are abundant elsewhere [5].

Data from educators and students is expected to yield quantifiable information on the types of technology available and in use, while qualitative data will reveal experiences of its use. This combination of data, organized along the SAMR framework, informs us on how technology has been substituted and augmented and the modifications and redefinitions that have been applied [32,33,35]. This enables the identification of a variety of practical needs for the improvement of resources and capacity deficiencies that impede the use of technology. We expect this study to glean deeper insights into how to enhance the use of technology in Eastern and Southern Africa.

Study Limitations

The main study limitation is the small size of the sample, which may not be fully representative of the population. This can be rectified in a subsequent study using stronger probability sampling methods with larger samples or by conducting case studies to give qualitative depth to the main findings. The study is also limited by selection and sampling bias. We choose only to use nursing programs offering a bachelor's degree in a university. The great majority of nursing programs are at the diploma level, and we will fail to gather information about these relatively under-resourced programs. Additionally, as a multi-institution study, the processes for ethics approval for

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each institution are beyond the control of the researchers, which may cause delays to the projected timelines.

Conclusions

The importance of technology in HPE is unquestionable. In this global village, it is imperative to promote uniformity across the education of health professions worldwide. The SAMR framework offers a model to identify gaps, which subsequently enable the institution of measures to bridge them.

Acknowledgments

We acknowledge input and guidance from the rest of the PACoTEH members. This proposal was supported by the US National Institutes of Health/Fogarty International Center (grant 1R25TW011217), which also includes cofunds from the US Department of State's Office of the US Global AIDS Coordinator and Health Diplomacy and the President's Emergency Plan for AIDS Relief to the African Forum for Research and Education in Health. The content in this proposal is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health and the African Forum for Research and Education in Health.

Data Availability

The datasets generated or analyzed during the current study will be available from the corresponding author upon reasonable request.

Findings will be made available to the funder of the study, to all PACoTEH members, and to all participating programs and institutions. Findings may also be presented at academic conferences and published in peer-reviewed journals.

Authors' Contributions

SRC, the team leader, conceived of the idea and took the lead in protocol writing, revision, and approval of the final manuscript. DRP identified the conceptual framework and participated in protocol writing, revision, and approval of the final manuscript. EK, PK-M, KSD, LJvdM, and MK participated in protocol writing, revision, and approval of the final manuscript. RG was instrumental in shaping the study design, including sampling and data collection, and participated in protocol writing, revision, and approval of the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Data collection tools.
[DOCX File , 21 KB - resprot_v14i1e67331_app1.docx]

Multimedia Appendix 2
Consent form and participant information sheet.
[DOC File , 151 KB - resprot_v14i1e67331_app2.doc]

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Abbreviations

HPE: health professions education
PACoTEH: Pan-African Consortium for Technology-Enhanced Health Professions Education
SAMR: substitution, augmentation, modification, redefinition
TEHPE: technology-enhanced health professions education

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Protocol

Using mHealth to Predict Asthma Exacerbations in Children and Adolescents (Mobile Health for Kids With Asthma): Protocol for an Observational Study

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Abstract

Background: Asthma exacerbation is a major cause of emergency department visits in children and adolescents. Most of the existing asthma prediction scores and biomarkers are designed to predict severe exacerbations in the medium to long term. Mobile health (mHealth) is a promising approach for integrating real-time, multimodal data to improve the prediction of asthma exacerbation. Using mHealth can enable the identification of at-risk children and the implementation of timely interventions.

Objective: The primary objective of the Mobile Health for Kids With Asthma (MoKA) study is to develop a validated predictive model for imminent asthma exacerbation in children using multimodal data, including participant-reported questionnaires through

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the RespiSentinel mobile app, augmented with publicly sourced environmental and epidemiological data. Furthermore, we will evaluate the association between the frequency of nocturnal cough measured in real time and asthma control and severe asthma exacerbation, and the acceptability of the RespiSentinel app in asthma self-management.

Methods: This is a prospective cohort study with in-person and remote recruitment at 7 tertiary pediatric centers in Canada. Parents of children aged between 1 and 17 years, as well as children who have experienced at least one wheezing episode or asthma exacerbation during the 12 months before recruitment, will be eligible to participate (estimated number of children: n=2000). The planned duration of study participation is 6 months following the date of enrollment (cohort entry), regardless of the number of asthma exacerbations during the follow-up period. The primary outcome will be asthma exacerbation defined by asthma symptoms requiring systemic corticosteroid use and an urgent care or emergency department visit or hospitalization. The predictive model will be created using questionnaire data on asthma control via the RespiSentinel app as well as by integrating publicly available local daily data on air pollutant levels (National Air Pollution Surveillance Program) and weekly prevalence of respiratory viruses (National Canadian Respiratory Virus Detection Surveillance Program). Nocturnal cough frequency will be determined by using nighttime audio recordings, and their contribution to predict imminent asthma exacerbation will be evaluated. Acceptability of the RespiSentinel app will be assessed through an app-based questionnaire.

Results: We will train and validate an asthma exacerbation prediction model using multimodal data sources. This approach may help patients, their families, and health professionals anticipate upcoming loss of asthma control and take the necessary steps to prevent a severe asthma exacerbation.

Conclusions: The MoKA study will harness real-time mHealth data to identify children at imminent risk of asthma exacerbation with the ultimate goal of designing timely interventions to prevent morbidity in this group of patients.

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KEYWORDS

children; asthma; prediction; exacerbation; multimodal data

Introduction

Background

Asthma is the most common chronic inflammatory respiratory disease in children and young adults, manifesting with cough, wheezing, and respiratory distress [1]. Globally, asthma affects more than 300 million people [2-4], including approximately 81 million children [5], with the prevalence expected to reach 400 million people by 2025 [2]. Severe asthma exacerbations, defined as a loss of baseline control requiring systemic corticosteroids, an emergency department (ED) visit, or a hospitalization [6], cause a significant burden to patients, their families, and the health system [4,7]. Exacerbations lead to school and parental work absenteeism, lower quality of life among children and their caregivers, and are a significant contributor to health care use and individual and societal costs [8,9]. Severe exacerbations are common, with approximately 10% of Canadian children with asthma having had 1 or more asthma-related ED visits in the previous 2 years [10,11]. Asthma morbidity and mortality are higher in children and adolescents compared with adults [12], and morbidity is particularly high in preschool-aged children [13,14] who represent >50% of all asthma-related ED visits [10].

Risk Factors for Asthma Exacerbations

There are several known risk factors for severe asthma exacerbations. These can be grouped into clinical factors such as poor asthma control [15,16], previous exacerbations [17], and obesity [18] and patient-related factors such as poor medication adherence [19,20], socioeconomic status [21,22], comorbid allergic diseases [23,24], and genetic predispositions [25]. Furthermore, some environmental factors, including exposure to tobacco smoke [26,27] and indoor or outdoor allergens and pollutants [28,29], contribute to asthma exacerbations. Being able to predict severe asthma exacerbations in the short term could lead to timely interventions including improved adherence to controller medications, avoidance of certain exposures, and timely access to medical care. While various models have been developed to predict asthma exacerbations based on the risk factors and patient clinical profiles [30], existing pediatric predictive scores are limited by the integration of only a subset of these risk factors [15,17] and the lack of real-time data. Therefore, most studies aim to predict exacerbations over the following months or years. Other predictive models include objective measures such as oscillometry [31,32], spirometry and the fraction of exhaled nitric oxide [33-35], blood biomarker levels [36], and exhaled breath condensate analysis [37,38]. However, these measures are not easily accessible outside of pediatric centers or have only been used in a research setting. Oxygen saturation can be reliably and readily measured through mobile apps [39]; however, its use has been studied during acute asthma exacerbations and using hospital-grade devices [40,41]. Oxygen saturation, including its use in composite scores such as the Pediatric Respiratory Assessment Measure [42] and the Modified Pulmonary Index Score [43], is predictive of exacerbation severity and the risk of hospitalization. However, baseline oxygen saturation has not been studied as a predictor of asthma exacerbation. Thus, there is a need for simple and accessible predictive tools that can be applied to a representative sample of children with asthma in a timely fashion to create a significant impact on their care.

Mobile Health and Asthma

Mobile health (mHealth), a subset of telehealth defined as the use of mobile devices for medical practice, is a promising approach that promotes the self-management of chronic

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conditions, including respiratory diseases [44,45]. mHealth can provide patients with unlimited access to health data and knowledge and provide physicians with remote monitoring of patients. Studies have shown that patients who use mHealth for various chronic respiratory conditions report greater self-awareness and self-confidence in disease monitoring [46] and reduced health care use, with improved health outcomes [47]. Parental perspectives on mHealth are positive [48,49], though few mobile tools are available to parents of children with chronic respiratory conditions. Physicians report better patient engagement and care outcomes with the use of mHealth compared with standard care [50,51]. As a research tool, mHealth can collect real-time and real-world patient-reported data, which can be used for disease phenotyping, to assess treatment response, and to predict adverse outcomes [52,53]. These data can be harnessed to identify children at high risk of impending asthma exacerbations.

While patient-reported data are valuable predictors of exacerbations, the addition of an objective measure can improve predictive models. Although lung function is a commonly assessed objective measure in children, it is challenging to measure in younger children, it has limited accessibility outside of clinic visits, and its utility in predicting future exacerbations in young children has not been shown [16,30,54]. Conversely, nocturnal cough is an easily measured and common parent-reported symptom in the prodrome period before asthma exacerbation, as cough frequency and intensity usually increase in the days leading to the exacerbation [55,56]. Studies have shown that the patterns of nocturnal cough are associated with asthma control and the detection of possible asthma exacerbation [56,57], with an increased occurrence of cough at the beginning of night sleep, particularly in the first 30 minutes to 1 hour [56,58]. With the accessibility of sound acquisition through mobile phone microphones and techniques in artificial intelligence allowing scalable and automated cough detection [59], home recordings of cough frequency [60-62] could be an additional objective tool that can be integrated into an mHealth app to predict asthma exacerbations, although more studies in children are required to validate its use.

To address these knowledge gaps, we will conduct the Mobile Health for Kids With Asthma (MoKA) study, an app-based prospective study to predict severe asthma exacerbations in children using multimodal data. This study will use the RespiSentinel mobile app, which our team created specifically for the MoKA study. RespiSentinel is an Android- and iOS-compatible mHealth app that allows the collection of patient-reported research data through the completion of questionnaires. While it contains useful and curated information on asthma, the RespiSentinel app allows automatic cough recordings and comprises several features including reminders on medication refill and intake, as well as the assessment of asthma control.

The MoKA study has three objectives: (1) to train and validate a model to accurately predict the risk of an imminent severe asthma exacerbation by integrating multimodal data (ie, self-reported asthma symptoms, comorbidities, medications and adherence, environmental data, and respiratory virus prevalence data); (2) to explore the association between nocturnal cough frequency evaluated through automated detection and asthma exacerbation within the following week in children and to integrate the cough patterns into the predictive model; and (3) to assess the acceptability of the RespiSentinel app among participants.

Methods

Study Design and Participants

The MoKA study is a multicentric, app-based prospective cohort study funded by the Canadian Institutes of Health Research (application 469005) with remote and in-person recruitment. We will use social media publicity campaigns to target eligible participants across Canada and will conduct in-person recruitment in respiratory and asthma clinics, EDs, or hospitalization units at 7 tertiary care pediatric centers in Canada: the Centre Hospitalier Universitaire Sainte-Justine (CHUSJ), Montreal; Montreal Children's Hospital, Montreal; Centre Hospitalier Universitaire de Québec-Université Laval, Quebec; Centre Hospitalier Universitaire de Sherbrooke, Sherbrooke; the Children's Hospital of Eastern Ontario, Ottawa; the Hospital for Sick Children, Toronto; and the Stollery Children's Hospital, Edmonton. Inclusion criteria include (1) parents whose children are aged between 1 and 13 years and adolescents aged between 14 and 17 years; (2) children or adolescents with one or more wheezing episode or asthma-related ED visit or hospitalization in the past 12 months for which systemic or inhaled corticosteroids or a bronchodilator was prescribed; (3) living in Canada; and (4) understanding English or French. While the recruitment strategies may differ by site, in general, research assistants will identify potential participants based on eligibility criteria through electronic medical records. Then, they will contact the eligible participants, explain the purpose and procedure of the study, and invite them to participate in the study. These eligible participants may ask as many questions as they wish for further clarification before signing the voluntary e-consent form to enroll in the study. After downloading the RespiSentinel app, they will create an account linked to their phone number, as a validation code is sent to the participant's phone at each log-in, for security purposes. The participant will be able to personalize the app by selecting optional notifications (eg, medication administration reminders) and choosing the day of the week they would like to receive the questionnaires. This personalization does not interfere with data collection for the MoKA study but offers the participants a choice in the use of nonstudy features.

Recruitment began in October 2023 with a pilot recruitment phase at CHUSJ and developed to full recruitment by January 2024 at CHUSJ. The integration of the other sites is ongoing. We anticipate recruitment to end in December 2026.

For objective 2 on the automated cough detection, children sharing a room with another person will be excluded because of the complexity of sound analysis in that setting. Informed consent (and assent from adolescents, when appropriate) will be obtained from parents. In some participating institutions, this study is judged to be minimal risk and allows consent to be given by adolescents (usually aged ≥14 years) with asthma. In such cases, a copy of the consent form can be sent to the parents.

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Cohort entry (ie, start of follow-up) will be defined as the date on which children meet all inclusion criteria and informed consent is obtained. The participants are expected to remain in the study for 6 months after cohort entry and will have follow-ups throughout this period, regardless of whether they experience asthma exacerbations during the follow-up period (Figure 1). Furthermore, the participants will have the option to continue the study for an additional 6 months if they wish.

Figure 1. Mobile Health for Kids with Asthma (MoKA) study procedure.

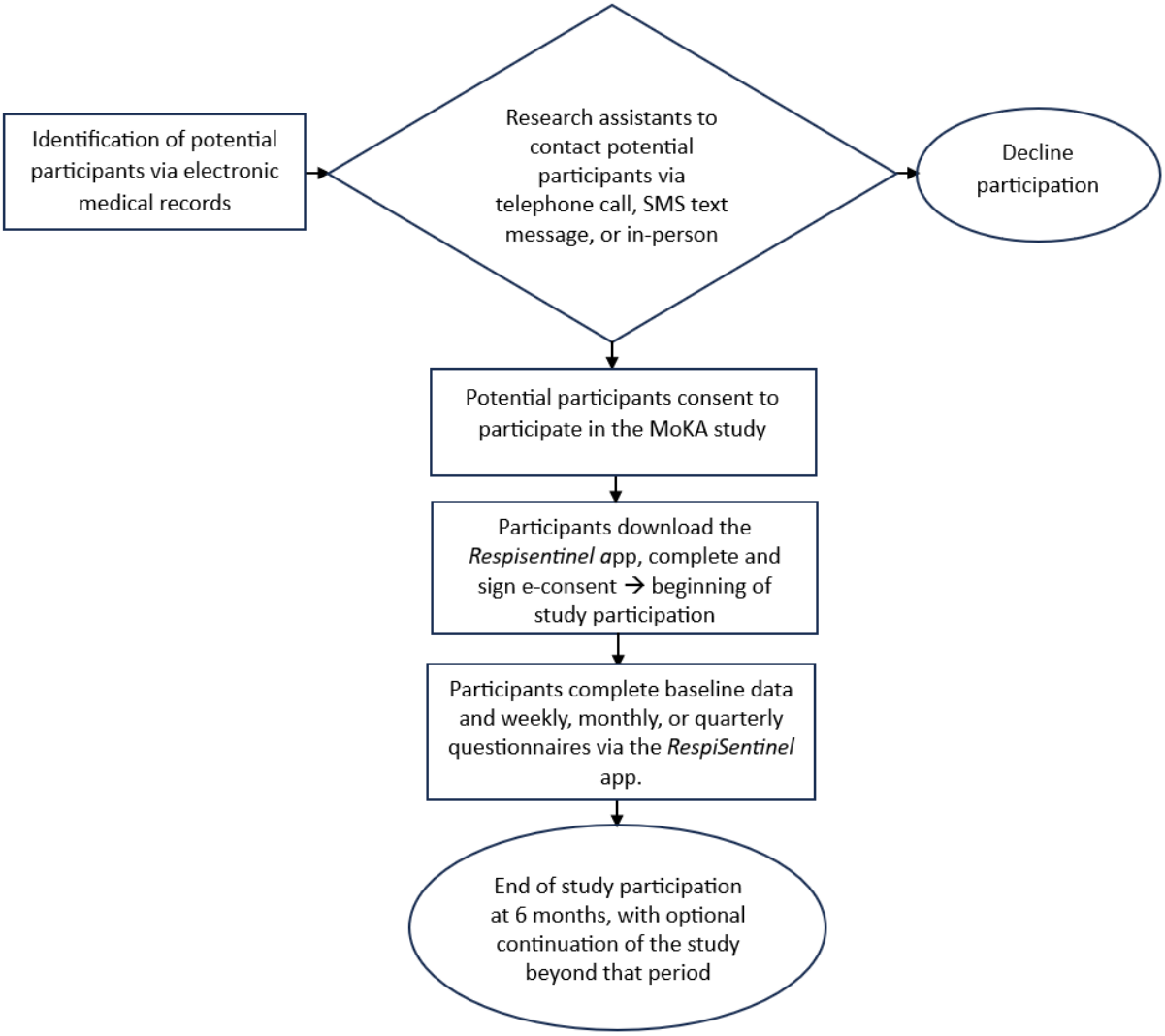

The RespiSentinel App

Built specifically for the MoKA study and published by CHUSJ, RespiSentinel is a free, accessible Android- and iOS-compatible app that allows for the collection of patient-reported research data through the completion of questionnaires by parents of children with asthma or adolescents with asthma themselves. The overall architecture of RespiSentinel is provided in Figure 2. Following a short questionnaire screening for eligibility to participate in the MoKA study, an e-consent form approved by the research ethical board (REB) of CHUSJ is made available directly within the app. After consenting, a PDF version of the consent form is accessible through the app at any time (or can be sent to the participant's email upon request). Once consented, the participants complete 2 baseline questionnaires, one on their general health and demographics and another on their asthma clinical history, current therapy, and environmental exposure. Subsequently, through in-app notifications sent to the participants at predetermined frequencies, they are prompted to complete weekly questionnaires on their general asthma symptoms and control, and monthly questionnaires on their use of asthma-related health resources, lung function, and overall health. The participants are prompted to answer a questionnaire every 3 months, asking for their feedback and comments on the RespiSentinel app. For the automated cough detection module, a licensed software development kit was provided by Resmonics [63], which was integrated into the RespiSentinel app by the app developers. Resmonics has developed a validated cough detection algorithm for adults [56,64], which is being used in ongoing studies for children [65].

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Figure 2. Simplified architectural presentation of the RespiSentinel app. Researchers and administrators of the RespiSentinel app manage participant data through an administrator page. Access is restricted using 2-factor authentication. Resmonics' ResGuard software development kit is integrated into the RespiSentinel app, which is available on the Apple App Store and Google Play Store. The data entered by participants are stored on the Amazon Web Services (AWS) cloud. A Django backend server provides the framework for data management, including push notifications that are sent to participants as reminders to complete questionnaires.

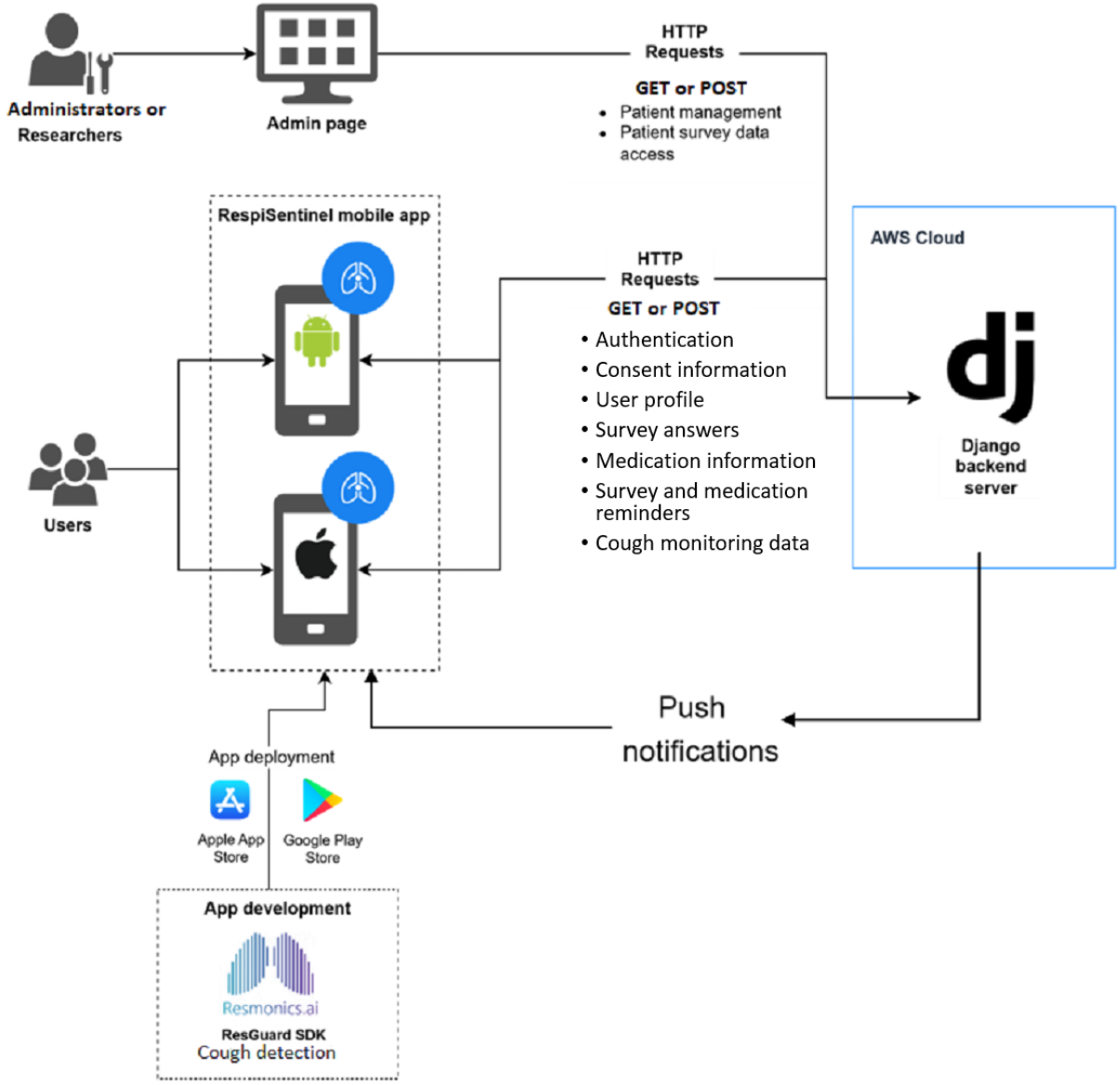

In addition, several patient-oriented and desired features are available within the app, which were identified through a previous survey of 200 parents of children with asthma [66,67]. These features include curated educational videos on symptom recognition and inhaler use techniques. The RespiSentinel app includes the ability to track asthma symptoms and control, monitor medication intake, receive personalized alerts on medication renewals, and record significant events such as exacerbations and medical visits. The data on asthma control will be presented in a user-friendly graphical form that can be downloaded (eg, to share with their physician at a medical visit). Missing or erroneous data will be minimized through push notifications reminding participants to complete questionnaires via the app.

Study Outcome Measures

The primary outcome for objectives 1 and 2 will be an imminent severe asthma exacerbation, defined as an increase in asthma symptoms leading to the use of systemic corticosteroids and an urgent care visit, ED visit, or hospitalization in the following week [68]. The occurrence of a severe exacerbation (ie, a dichotomous variable) will be assessed through a monthly parent- or self-reported questionnaire in the RespiSentinel app during the follow-up period. Specifically, this will be assessed through 3 separate questions: "In the past month, did your child go to an urgent care or walk in clinic for asthma?", "In the past month, did your child go to the emergency department for asthma?" and "In the past month, was your child hospitalized for asthma?" If the participant answers "yes" to any of these 3 questions, the self-reported exact date of the medical consultation for the exacerbation and whether the child received oral or systemic corticosteroids for the asthma exacerbation will

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be collected. Given that participants are not necessarily followed for their asthma at the recruiting sites and can seek care at any point of care, self-reported exacerbations will be used, which have been shown to correlate well with administrative data [69], even over longer recall periods. A participant will be considered to have had the primary outcome of severe exacerbation if they had an asthma-related urgent care visit, ED visit, or hospitalization requiring corticosteroids. If a participant has an exacerbation during the follow-up period, we will instate a 2-week lag period following the date of the exacerbation during which the participant will not contribute to the prediction model. This will avoid counting an ongoing severe exacerbation as a new event, thereby preserving the model's purpose of identifying and potentially intervening with children at high risk of an imminent exacerbation.

For objective 3, the outcome is the acceptability of the RespiSentinel app. The assessment of the acceptability of the RespiSentinel app by users will focus on the usability of the current version of the app (a posteriori acceptability) by assessing the depth, amount, breadth, and duration of user engagement through the frequency and number of measures recorded, the number of log-ins, the time spent on the app, and the number of pages accessed. We will also assess the a priori acceptability of the future version of the app, which will integrate an exacerbation risk score and automatic cough detection, after presenting the participants with a vignette describing these features. We will use a 5-point Likert scale and free-text comments to assess the a priori and a posteriori acceptability of the RespiSentinel app. The assessment will focus on various areas, including but not limited to the usefulness of the RespiSentinel app in tracking asthma symptoms and medications intake, the feedback on asthma control, the ability to share asthma control trends with clinicians, the ability to communicate the risk of asthma exacerbations, and the visual or graphic depiction of asthma control. A systematic review found an overall acceptability of mHealth apps in asthma of 3.32 (SD 0.64) using a 5-point scale [70]. A score of ≥3.5 (≥70%) will be considered acceptable.

Independent Variables

For the prediction of severe asthma exacerbations, asthma control will be defined using an age-appropriate (age <6 or ≥6 years) 4-item Global Initiative for Asthma criteria for parent- or self-reported asthma control [1] and adapted for weekly assessments. The participants will respond "yes" or "no" to the 4 items focusing on whether the child had daytime symptoms, nighttime asthma symptoms, used asthma rescue medicines, or had a limitation of activities because of asthma during the previous week. The number of positive criteria will be used as a discrete variable and to categorize asthma as uncontrolled (3 or 4 positive answers), partly controlled (1 or 2 positive answers), or well controlled (no positive answers) [1]. In addition to asthma control, we will collect the following participant-reported variables: sociodemographic characteristics, comorbidities (eg, eczema and allergies), prematurity, the time from the last asthma exacerbation, tobacco and vaping exposures, asthma control (as defined earlier), and asthma therapy (ie, type and dose) and adherence to controller therapy through the number of weekly self-reported missed doses.

Furthermore, we will integrate local temperature, humidity, and aeroallergen levels when available, air quality indexes and air pollutants based on residential postal code, and weekly provincial prevalence of 7 common respiratory viruses. Specifically, the daily levels of nitrogen dioxide, ozone, sulfur dioxide, and fine particulate matter (PM2.5) from the monitoring station closest to the residential home will be considered. The provincial surveillance data on respiratory viruses include influenza viruses (A and B), respiratory syncytial virus, human rhinovirus or enterovirus, human parainfluenza virus, human metapneumovirus, human coronavirus, adenovirus, and SARS-CoV-2 [71]. This publicly available data will be obtained retrospectively through external sources such as Environment Canada [28], the National Air Pollution Surveillance Program [26], and the National Canadian Respiratory Virus Detections Surveillance Program [72], and retrospectively integrated into the database during the analyses.

Spirometry (ie, the forced expiratory volume in 1 second [FEV_1], forced expiratory flow at 25%-75% [FEF_{25-75}], and forced vital capacity [FVC]) and oscillometry (ie, resistance at 5 Hz) results from clinic visits will be integrated when available. To do so, participants will be asked to upload a picture of their test results in the app, if available. Research personnel will manually enter these data into the database. We acknowledge that many children will not have access to regular pulmonary function testing. This variable will be treated as optional, and a subgroup analysis will be performed among participants for whom these data are available.

Automated detection of nocturnal cough (ie, times per hour) through Resmonic's software development kit for cough detection will be integrated into the RespiSentinel app [73]. This cough detection algorithm has been previously validated in adults but not yet in children. Parents will be invited to audio record the first 2 hours of sleep, in line with previous studies [56,58], weekly at a minimum for baseline reference and daily when the child is symptomatic (eg, at the start of a respiratory infection or symptoms caused by other triggers). The recording will be done through any mobile device equipped with a microphone that can be left at the bedside and on which the RespiSentinel app is loaded (eg, tablet or smartphone). While the participants must start the recording, no further interventions are required as the recording will automatically shut off after 2 hours and detect the cough episodes during that period. Parents or adolescents will fill out a questionnaire on the sleeping environment (ie, sleeping alone or with another individual) and the use of asthma control and reliever medication on the day of the recording.

Study Procedure

Several recruitment strategies will be considered, based on the feasibility at each site. Figure 1 depicts the study procedure. First, we will advertise the study in pediatric respirology and asthma clinics and conduct a social media campaign. Second, we will approach patients presenting with asthma in the respiratory clinics, EDs, and hospitalization units at the participating centers. Third, eligible patients identified through their medical chart (eg, ED databases) will be contacted via SMS text messages inviting them to participate in the MoKA

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study. The participants will download the RespiSentinel app on a mobile device. e-Consent, based on best practices [74], will be provided to the participants through the app, with a copy sent to the participant. For adolescent participants, a copy of the consent form may also be sent to a parent. Once logged in using their mobile number and a unique code sent to the participant by SMS text message, the user can personalize their child's profile (or their own, if an adolescent is answering for themselves) by providing information on asthma triggers, comorbidities, and current asthma therapy. Questionnaires will be pushed to the users via the app at a predetermined frequency. We will ask the parents to record their child's cough through the app as previously described. The recording is programmed to shut off after 2 hours automatically. External data will be integrated into the database retrospectively.

Data Analysis

The results will be reported using the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) [75] and CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) guidelines [76]. We will describe the baseline characteristics, retention, and analytic indicators of user engagement, including the number of measures recorded by users, frequency of interactions, number of features accessed by users, number of log-ins, and time spent using the app. Multiple imputation will be applied to manage missing data using random forest imputation for epidemiological data [77,78].

For objective 1, we will train and validate a predictive model for an imminent severe asthma exacerbation using an 80:20 approach (ie, 80% of the data for training and cross-validation and 20% for testing). We will standardize time-varying and fixed variables including self-reported asthma control, baseline comorbidities, exposures, asthma therapy, medication adherence, pulmonary function results, and external data, such as temperature, humidity, air quality indexes, and provincial virus prevalence data for inclusion in the prediction model. For time-varying variables, data from the week before asthma exacerbation will be considered. An extreme gradient boosting ensemble decision tree learning algorithm using binomial logistic regression will be trained and hyperparameters (ie, the number of trees, maximum tree depth, and the number of features considered at each split) optimized using grid search and 10-fold cross-validation within the 80% training split [79,80]. We will assess the overall model performance and the generalizability using the area under the receiver operating characteristic curve (primary measure), F_1-score, precision, and recall from the 20% test dataset. The covariate importance will be assessed using a feature or covariate importance plot and Shapley additive explanations values [81,82]. In secondary analyses, we will also assess and compare the performance of other machine learning algorithms, such as support vector machines, random forests, naïve Bayes, and neural networks.

For objective 2, the integrated software will automatically classify events into cough and noncough events from raw audio data and automatically calculate cough frequency per hour [56,58]. We will estimate the association between cough frequency and asthma exacerbation in the forthcoming week using a generalized estimating equations approach to binomial logistic regression, adjusting a priori for other studied potential predictors of asthma exacerbations included in the predictive model. In secondary analyses, we will estimate the association between cough frequency and asthma control using a generalized estimating equations approach to negative binomial regression.

For objective 3, we will perform descriptive analyses of acceptability measures, including percentages for each category on the Likert scale and the participant-desired features. Using term frequency–inverse document frequency from the Python (Python Software Foundation) scikit-learn library [83], we will also extract key points from user comments to guide the development of the future app.

Study Sample Size

On the basis of the previously published data from the CHUSJ [84] and data from the latest months of recruitment at CHUSJ, we estimate a general recruitment pool of approximately 5000 children with asthma-related ED visits per year and an 8% consent rate for the MoKA study. While recruitment methods and consequently general recruitment pools vary from one recruiting site to another, based on this consent rate and assuming a general recruitment pool of 10,000 patients per year across all sites, we expect to recruit a sample of 2000 participants (an average of 667 participants per year over a 3-year recruitment period). Extreme gradient boosting can detect an area under the receiver operating characteristic curve >90% with sample sizes that are smaller than this, including models with 20 to 110 predictors [79,85]. Therefore, we plan to recruit a sample of 2000 children with asthma over 3 years. On the basis of previous studies, severe exacerbations occur in up to 50% of preschool-aged children [13] and 25% of school-aged children [72] who had an exacerbation in the previous year. To enhance the generalizability of our findings, we aim to recruit approximately 70% (1400/2000) preschool-aged children and 30% (600/2000) school-aged children, with an estimated average of 30% (600/2000) of children developing an asthma exacerbation. Because the required sample size depends on the complexity of the algorithm for data analysis, we will also construct a learning curve a priori [86] (describing the classifier performance relative to training sample size) using the first 250 and 500 patients. This will help determine the required sample size and avoid additional recruitment and resource use once the classifier algorithm has reached its efficiency threshold. For objective 2, in adults, nocturnal cough frequency has a sensitivity of 75% and specificity of 70% for predicting asthma exacerbations 4 days later [56]. Assuming 30% of participants will experience an asthma exacerbation, we aim to recruit a minimum of 270 children with cough data.

Ethical Considerations

The study has been approved by the CHUSJ REB (MP-21-2023-4333) and approval was sought from the REBs at participating centers before the start of recruitment at these sites. Although interested and eligible parents of children with asthma and adolescents can self-consent through the REB-approved e-consent form in the app, the research team will contact participants by telephone to ensure their understanding of the study and answer any questions that they

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may have. This approach will ensure informed consent and assent. Participants will have the option to withdraw from the study at any time if they wish. As part of the MoKA study, participants will consent to have their data kept in the RespiSentinel databank for potential future use and access by the same or other researchers, in compliance with national, provincial, and institutional confidentiality and data protection policies and principles. A data access committee has been created for requests to access data in the RespiSentinel databank.

Coded data from the app, including questionnaire answers and cough recordings, will be uploaded to the RespiSentinel databank on a secure server hosted by Amazon Web Services in availability zone 3, specifically located in the Central Canada region with Amazon CloudFront edge locations in Toronto, Ontario, and Montreal, Quebec. Data are stored via Amazon Simple Storage Service. Participants' identifying information and the key linking this information to the coded data can only be accessed by members of the research team at the center that recruited them. To further ensure data confidentiality, different levels of data access will be restricted within the local team. The developers of the RespiSentinel app (third-party vendor bld.ai) do not have access to identifying information. The coordinating center (ie, CHUSJ) can only download coded data from all participating centers. To ensure data security, we have implemented additional protective strategies, such as data encryption during transfer and at rest, restricted access to the database via a Secure Shell key, and tracking of all activities in the database through CloudWatch. The data downloaded for analysis will be stored in password-protected files on a password-protected computer within a secure institutional server. There will not be any compensation to participate in this study, although monthly US $18 (equivalent to 25 Canadian dollars) gift certificates will be drawn among participants.

Results

From October 1, 2023, to April 25, 2024, a total of 127 participants consented to the MoKA study, with a predominance of children aged <5 years (94/127, 76.4%), boys (82/127, 64.6%), and White participants (68/127, 53.5%). The mean age was 4 (SD 2.8) years. The baseline assessment revealed that 64% (35/55) of children had eczema, 7% (4/55) had rhinitis, and 20% (11/55) had food allergies. Atopic conditions were common among family members of participating children, with 68% (52/76), 38% (29/76), 35% (27/76), and 38% (29/76) of caregivers reporting asthma, eczema, allergic rhinitis, and environmental allergies, respectively. Among siblings, asthma and eczema were also common in 61% (19/31) and 48% (15/31), respectively. Regarding environmental exposures, 55% (29/53) of families had cats and 47% (25/53) had dogs. In addition, 14% (5/36) and 11% (4/36) of respondents reported cigarette or e-cigarette use, respectively.

In the 4 weeks before enrollment in the MoKA study, 70% (62/88) of participants perceived their child's asthma as well controlled. However, based on specific questions on asthma control over the same period, 59% (52/88) and 36% (32/88) of participating children had daytime and nighttime asthma symptoms, respectively. Nearly half of the children (42/85, 49%) used salbutamol, and 34% (30/88) experienced limitations in activities because of asthma. In the 12 months before enrollment, 35% (31/88) of children had 1 asthma-related ED visit, 28% (25/88) had 2 asthma-related ED visits, and 18% (16/88) had ≥4 asthma-related ED visits. Asthma-related hospitalizations during the same period occurred in 35% (31/88) of children. Adherence to asthma control medications was 73% (64/88; defined as reporting daily or frequent use of their controller medication, or 5 to 6 days per week), with the most commonly used medications being fluticasone propionate and ciclesonide.

Discussion

Anticipated Findings

The MoKA study was designed to address two main knowledge gaps: (1) whether the use of nearly real-time data can improve the prediction of severe asthma exacerbations in children and (2) whether mHealth can be used to facilitate asthma management through the prediction of severe asthma exacerbations.

Predicting Asthma Exacerbation

Several studies have reported predictive scores for asthma exacerbations in children, which integrated risk factors [15] and various objective measures [30,33,36]. However, the published models mostly evaluated longer-term predictions (eg, over the next year) using selected retrospective data, while our study aims to predict asthma exacerbations within the next week, thus allowing caregivers to act upon symptoms rapidly. Nonetheless, these prior studies provide insight into important risk factors, which we will collect and integrate into our model. A previous asthma exacerbation has consistently been identified as the most important predictor of future asthma exacerbations [87,88]. A systematic review of 26 studies found that previous asthma-related ED visits and hospitalizations were predictive of future asthma exacerbations [88]. Although the included studies were heterogeneous in defining exacerbation and the duration of follow-up, children with a history of exacerbation had up to 9.9 times the risk for a future exacerbation compared with those without a prior exacerbation [88]. Other studies have combined multiple risk factors in a single model to predict exacerbations. In a retrospective study using electronic medical record data collected from 3000 participants, Niu et al [15] built a risk score model to predict severe asthma exacerbations in the next 12 months in children and young adults. Allergic sensitization and exposure to smoke were major risk factors for preschool children, while obesity and abnormal spirometry were found to be predictive factors for asthma exacerbations in teenagers and young adults [15]. In another study using insurance claims data, Hatoun et al [89] derived an asthma exacerbation risk score to predict an asthma exacerbation in the next year. Their predictive model included age, presence of persistent asthma, prescription fill patterns of asthma medications and oral steroids, the number of outpatient visits, an exacerbation in the last 6 months, and whether spirometry was performed.

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Environmental Data in Prediction of Asthma Exacerbation

Environmental factors play an important role in triggering asthma exacerbations [90]. Thus, we have decided to include location-specific environmental data in our model. Most children with asthma present with allergic conditions, mainly to pollen and pets, and are sensitive to indoor and outdoor pollutants [91-93]. Several indoor exposures have been associated with the risk of asthma exacerbations in children [28,29], including tobacco smoke exposure, cockroaches, carpets, dust, and indicators of dampness. Various studies have demonstrated an association between outdoor air pollution levels, particularly PM2.5, ozone, and nitrogen dioxide and asthma exacerbations in children [94,95]. Interestingly, a study using a mobile app with connected devices conducted in 40 children found that exposure to higher levels of same-day PM2.5 and previous day ozone was associated with decreased lung function [96]. While the MoKA study will include these data retrospectively, the goal is to eventually include these variables in real time. Previous studies have identified important risk factors for asthma exacerbations, although they often evaluated a subset of these risk factors. In the MoKA study, we will integrate the aforementioned clinical, participant-reported, and environmental risk factors into our predictive model, which may optimize the prediction of upcoming asthma exacerbations and allow for timely interventions.

Lung Function in Predicting Asthma Exacerbation

Other studies included objective measures such as lung function testing to predict asthma exacerbations in the medium to long term (ie, 3-12 months). Lung function, specifically low values of FEV_1 and FEV_1/FVC, and high airway resistance as measured by oscillometry, can predict future asthma exacerbations [31,33,97,98], although this association remains debated [99,100]. In addition, the fractional exhaled nitric oxide and bronchodilator response have predictive value for asthma exacerbations [33] and for loss of asthma control [34]. Other objective measures such as eosinophil counts as a marker of inflammation may also be useful in the prediction of exacerbations in children [36,101]. While lung function and biomarkers of inflammation may be useful in identifying children at risk for exacerbations, these measures are not easily accessible in children and are usually assessed at clinic visits, which does not allow the prediction of exacerbations in the short term.

Innovations in Predicting Asthma Exacerbation

One novel aspect of the MoKA study is the exploration of automatic nocturnal cough detection as an objective measure in the prediction of poor asthma control and asthma exacerbations. Hirai et al [102] demonstrated that in children, exacerbations are characterized by increased cough frequency in the first 2 hours after falling asleep and at waking, with a median of 119 coughs per night. The cough count is also significantly higher in children with severe exacerbations compared with moderate exacerbations and compared with nonasthma controls [55]. However, these cross-sectional studies only examined cough during exacerbations without comparing it to intraindividual baselines. Sample sizes were limited as manual cough counting was labor intensive. The MoKA study will provide further insight into the usefulness of real-time automatic nocturnal cough detection through mHealth in predicting asthma exacerbations in children.

One strength of the RespiSentinel app used in the MoKA study is the availability of participant-centered and participant-desired resources, including curated educational materials and videos, and optional reminders to take and fill medications. These features were implemented following a survey of parents of children with asthma [66,67]. In addition to increasing participant engagement in the MoKA study, the initial feedback from participants was positive, with these resources helping them manage their child's asthma. The acceptability of the RespiSentinel app as an mHealth tool will be formally assessed in the MoKA study.

Limitations

Our study may incur a selection bias based on internet access. However, if a parent or patient declines participation solely because of their inability to access the internet, we will provide these participants with a refurbished phone and a pay-as-you-go internet access card. Thus far, in the MoKA pilot study and based on 2 previous mobile platform–based studies, we have not had any participants refuse participation based on this criterion. Self-selection bias or volunteer bias may also occur as participating families may be more inclined to engage with asthma management measures. As the possibility of selection bias is inevitable in any cohort study, even with traditional recruitment methods, this limitation will be acknowledged in our publications. Although the recall period is relatively short (1 week for asthma control and 1 month for asthma exacerbations), recall bias may nonetheless occur. To mitigate this risk, participants are encouraged to complete these questionnaires in a timely fashion through regular notifications. As with any self-reported data, social desirability bias may be an issue. To address this, participant anonymity and information confidentiality are ensured, the questionnaires were designed to be neutral, and participants are aware that data entered will not be shared with their treating physician. Self-report bias is possible as the participants will fill in information through the RespiSentinel app, particularly for perceived asthma control. This is mitigated by the evaluation of asthma control through a standardized symptoms-based questionnaire in addition to participant-perceived asthma control. We anticipate that there will be missing data and variable lengths of follow-up among the participants. To mitigate this, in addition to the reminders generated by the RespiSentinel app, we have set up a protocol to call or send email reminders to participants if they miss up to 3 consecutive questionnaires.

Conclusions

The MoKA study harnesses mHealth to construct a model to predict asthma exacerbations in children and adolescents in a timely manner. Specifically, we built the RespiSentinel app to collect asthma-focused and patient-reported outcomes in real time. To facilitate participant engagement, the RespiSentinel app provides patient-oriented tools for asthma management that were developed with parents of children with asthma. Combined with externally sourced data and a novel automated cough

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detection tool, the predictive model derived by the MoKA study will offer the opportunity to inform users of their exacerbation risk in near real time using more comprehensive multimodal data. In addition, as an mHealth tool, the RespiSentinel app is a scalable infrastructure that integrates an e-consent form, push notifications to participants to answer questionnaires, data synthesis to provide summaries for the participants, and a data management platform. This infrastructure can easily be reused and adapted for other studies.

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Conflicts of Interest

None declared.

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Abbreviations

CHUSJ: Centre Hospitalier Universitaire Sainte-Justine
CONSORT-EHEALTH: Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth
ED: emergency department
FEV_1 : forced expiratory volume in 1 second
FVC: forced vital capacity
mHealth: mobile health
MoKA: Mobile Health for Kids with Asthma
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
REB: research ethical board

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Protocol

Evaluation of the Accuracy, Usability, and User Perspectives of the Ecological Momentary Dietary Assessment App Traqq Among Dutch Adolescents: Protocol for a Mixed Methods Study

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Abstract

Background: Self-reported dietary intake data are crucial in nutrition and health research; however, their accuracy is compromised by challenges such as portion size estimations, food identification, memory-related bias, social desirability bias, and reactivity bias. Dietary assessment in adolescents is particularly challenging due to irregular eating habits, meal skipping, and parent or peer influences, potentially resulting in misreporting. Leveraging adolescents' receptiveness to technology, we investigated the use of an innovative smartphone app (Traqq) that facilitates dietary assessment using repeated short recalls instead of traditional 24-hour recalls. Evaluation studies of the Traqq app in Dutch adults have shown successful results, but its suitability for other target populations, such as adolescents, requires further investigation.

Objective: We designed a comprehensive, 3-phase study to evaluate the Traqq app's accuracy using repeated short recalls, usability, and user perspectives among Dutch adolescents aged 12 to 18 years. This manuscript details the study setup, research methods, and basic characteristics in phases 1 and 2.

Methods: In phase 1, adolescents (aged 12-18 years) downloaded the Traqq app and completed a demographic questionnaire. It was used on 4 random school days over 4 weeks, using 2-hour recalls on 2 days and 4-hour recalls on 2 days. A food frequency questionnaire and 2 interviewer-administered 24-hour recalls served as dietary reference methods to assess the Traqq app's accuracy. In addition, usability was evaluated using the System Usability Scale and an experience questionnaire. In phase 2, user experiences were further explored through semistructured interviews within a subsample of 24 adolescents. These first 2 phases of this mixed methods study are now finalized for data collection. Phase 3 will focus on collecting user insights to inform app customization through cocreation sessions.

Results: Recruitment concluded in September 2022 with 102 adolescents; 98 (96%) provided dietary data via the Traqq app, and 79 (78%) completed the evaluation questionnaire. Adolescents had a mean age of 15 (SD 2) years. The mean BMI was 19.9 (SD 3) kg/m^2. A total of 64 (63%) participants were girls, 81 (84%) attended high school, and 88 (92%) were born in the Netherlands. Interviews were held with 6 (25%) boys and 18 (75%) girls. Cocreation sessions will be planned after all data have been analyzed.

Conclusions: In this holistic study, we combine quantitative and qualitative methods to evaluate the dietary assessment performance among adolescents of the Traqq app, which was initially designed for adults. Specifically, next to quantitative comparisons of the Traqq app's dietary assessment methods, we conducted semistructured interviews, and we will carry out

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cocreation sessions. With this user-centered, synergistic approach, we aim to establish a list of requirements for a dietary assessment app for adolescents, resulting in more efficient assessments, improved compliance, and enhanced overall accuracy in this population.

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International Registered Report Identifier (IRRID): DERR1-10.2196/70194

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KEYWORDS

dietary assessment; app; recall; accuracy; usability; evaluation; mixed methods study; technology; adolescents

Introduction

Accurate dietary assessment is crucial for understanding the relationship between the intake of food, energy, and nutrients and nutrition-related health issues [1-4]; however, this is inherently challenging. Currently, many studies exploring diet-disease associations mainly rely on self-report methods, such as food frequency questionnaires (FFQs), 24-hour recalls (24hRs), and food records, which are prone to bias, for example, memory-related bias, social desirability bias, and measurement errors related to difficulties in estimating portion sizes. Assessing adolescents' dietary intake is particularly challenging [5,6] due to their irregular eating habits, meal skipping, dining out [7,8], and susceptibility to peer or caregiver influence, which can potentially result in misreporting [9,10]. In addition, adolescents perceive current dietary assessment methods, especially for reporting complex meals [6,10], as challenging, leading to low compliance rates [11]. Adolescents' receptiveness to technology [5,12], particularly mobile assessment technologies [13], could significantly advance dietary assessment in this challenging population.

Few digital tools are specifically designed for adolescents, and those available often replicate traditional dietary assessment methods such as 24hRs or food records in web or app-based formats [8,14-18]. Adolescents generally prefer apps over web-based technologies, resulting in more complete registration [13]. However, these tools still face common method-related limitations such as estimation errors, errors related to food identification, social desirability bias, and memory-related bias [11,18]. Developers of the EaT app, a food record app for young adults (aged 18-30 years), addressed issues related to food identification by tailoring the food database to adolescents' dietary habits. They recorded purchase locations, tagged food items to identify outlets, included foods from the 30 largest ready-to-eat food chains in Australia, removed less-common items, simplified food names, and merged nutritionally similar foods. These improvements enhanced the app's usability, highlighting the need to tailor tools specifically for adolescents to improve compliance [19].

The web-based 24hR tool, myfood24, has also been tailored for use among adolescents [20,21] by including features such as autofill, spell check, and tooltips. While it showed promising reliability compared to interviewer-administered 24hRs, concerns remained about adolescents' memory during dietary recall [8]. Nevertheless, research shows that adolescents can accurately recall foods consumed within 24 hours [6], with shorter recall windows potentially providing even more accurate data. Therefore, a promising alternative to traditional dietary assessment methods is near real-time recording, based on the ecological momentary assessment principles [22], via repeated short recalls on a single day, such as repeated 2-hour recalls (2hRs) and 4-hour recalls (4hRs). These short time intervals reduce memory reliance, require minimal time commitment, and reminders help users to report their intake throughout the day [23,24]. We previously developed such an ecological momentary dietary assessment app for adults (Traqq), as described elsewhere [25], with validated repeated 2hRs on 1 day, offering more accurate assessments than traditional 24hRs [26]. While the use of short recalls via the Traqq app has shown promise in adults, its application for adolescents still needs to be investigated.

In addition to evaluating the use of short recalls via the Traqq app, the app itself also needs to be evaluated among adolescents. The app's simple and clear design, effective for adults, may not appeal as much to adolescents. Research emphasizes the importance of engaging features such as game elements, social features, rewards, and motivational messages to encourage adolescents in using a dietary assessment app [11]. Such features are not included in the Traqq app's adult version. Therefore, it is imperative to assess and adapt the current design of the Traqq app to meet the needs and preferences of adolescents [27] using a combination of both quantitative and qualitative methods.

The objectives of this observational mixed method study are (1) to *quantitatively* evaluate the accuracy of the smartphone-based 2hR and 4hR methods for assessing energy, nutrient, and food group intake in adolescents compared to traditional methods and usability questionnaire, (2) to gather further user perspectives through *qualitative* semistructured interviews, and (3) to obtain a list of requirements facilitating the redesign of Traqq to better meet adolescents' needs and preferences through cocreation sessions. In this paper, we detail the study setup and research approaches used to address the objectives outlined earlier.

Methods

Study Design

In the first phase of this mixed methods study, a quantitative evaluation of the accuracy, usability, and user perspectives of the Traqq app was performed among 102 adolescents. Phase 2 included a qualitative approach to evaluate user experiences. The third and final phase will involve cocreation sessions with 10 to 12 adolescents (Figure 1). Data collection for phases 1

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and 2 has been completed, with data analysis currently ongoing. Phase 3, the cocreation sessions, will take place after all data from phases 1 and 2 have been analyzed.

In week 1 of phase 1 (ie, the quantitative evaluation), adolescents downloaded the Traqq app and completed a demographic questionnaire. Over the following 4 weeks, dietary intake was assessed via the Traqq app on 4 random nonconsecutive days, via two 2hR days and two 4hR days. Two interviewer-administered 24hRs and an extensive FFQ at the end of the period served as reference methods. Adolescents also completed an online evaluation questionnaire. In phase 2, semistructured interviews were conducted with a subsample. Phase 3, the cocreation sessions, will be scheduled after analyses of data from phases 1 and 2 have been completed.

Figure 1. Flowchart of the Traqq-Z study design. 2hR: 2-hour recall; 4hR: 4-hour recall; FFQ: food frequency questionnaire.

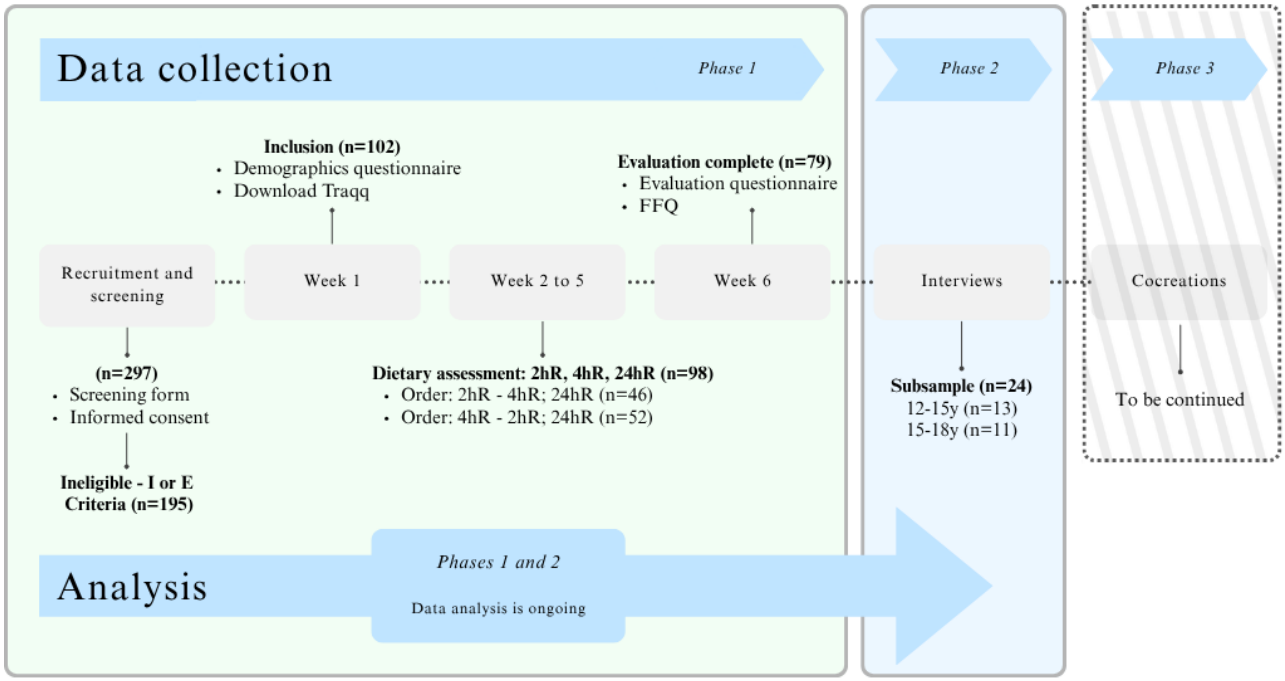

Ethical Considerations

On January 19, 2022, the Medical Ethics Committee (METC Oost-Nederland) concluded that this study did not fall under the Dutch Medical Research Involving Human Subjects Act (2022-13477). Subsequently, on February 23, 2022, this study received approval from the Social Sciences Ethics Committee at Wageningen University & Research. Prior to participation, all participants and their parents or caregivers provided written informed consent. All data were anonymized in accordance with ethical standards, ensuring no personal identifiers were present. Participants received a small gift voucher and a personalized dietary report as a token of appreciation.

Study Population

Recruitment for phase 1 took place between February 2022 and September 2022 and aimed to include 100 adolescents (ie, 50 adolescents aged 12-15 years and 50 adolescents aged 16-18 years). Adolescents were recruited through the volunteer database of the division of Human Nutrition and Health of Wageningen University & Research and other channels, such as social media and schools in Wageningen and neighboring municipalities (the Netherlands). The volunteer database consists of volunteers aged more than 18 years. Adults born between 1960 and 1985 were notified about the study and asked if their child in the age range of 12 to 18 years would be willing to participate. Adolescents willing to participate were invited to an online information meeting (n=297), with parents or caregivers joining for those aged below 16 years. Before the information meeting, an information letter including an informed consent form was sent. During the meeting, the study was explained and questions were answered. Adolescents aged 16 years and older signed their own consent, while those aged 12 to 15 years provided coconsent with a parent or caregiver. Adolescents were eligible if they spoke and read Dutch, were not visually impaired, had a smartphone with internet and email, were willing to maintain current dietary habits for the duration of the study, and were not participating in a dietary intervention study. A total of 102 adolescents were included. Among them, 53 (52%) adolescents were aged 12 to 15 years and 49 (48%) adolescents were aged 16 to 18 years. After phase 1, 24 adolescents joined the qualitative evaluation in phase 2. Among them, 13 (54%) adolescents were aged 12 to 15 years and 11 (46%) adolescents were aged 16 to 18 years. Phase 3 aims to include 10 to 12 adolescents.

Phase 1

Dietary Assessment

Overview

Dietary intake was assessed with the Traqq app on 4 random nonconsecutive days within a 4-week study period, using two 2hR days and two 4hR days. Adolescents were randomly assigned to start with either 2hR days (n=46, 47%) or 4hR days (n=52, 53%). Recalls were scheduled on weekdays for consistency with typical school routines.

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Interviewer-administered 24hRs and an FFQ served as reference methods, with 24hRs unannounced on nonrecall weekdays. Adolescents completed an FFQ at the end of the study.

App-Based 2hR and 4hR Days

On 2 random days, adolescents received invitations via the Traqq app to report their food intake every 2 hours (ie, 2hR days), and on 2 other days, every 4 hours (ie, 4hR days). This resulted in 8 reminders on 2hR days and 4 on 4hR days with a reporting window of 90 minutes; for example, for a single 2hR between 6 AM and 8 AM, the notification was sent at 8 AM with a reporting deadline of 9:30 AM. The morning following a Traqq recall day, an invitation was sent to assess nighttime food intake (Figure 2). The 2hR-day and 4hR-day sampling schemes were tailored to each adolescent's sleeping patterns to avoid disturbances. To illustrate, if an adolescent indicated waking up at 9 AM, the first invitation was sent at 10 AM instead of 8 AM. No invitations were sent after 10 PM. If an adolescent missed more than 1 recall (except nighttime), that day was considered invalid and a new recall day was scheduled.

Adolescents reported their food intake directly in the app by clicking on notifications or opening the Traqq app. The Traqq app uses an extensive food list based on the Dutch Food Composition Database [28]. After selecting a food item, adolescents reported the quantity in household measures (eg, cups or spoons), standard portion sizes (eg, small or large), or grams, along with the eating occasion (ie, breakfast, lunch, dinner, or snack). Adolescents could also use the *My Dishes* option to record ingredients for specific recipes or create quick entries for frequently consumed combinations (eg, daily breakfast). If adolescents did not consume anything during a specified time window, they could select the "I did not eat or drink anything" option [25]. While adolescents were instructed to complete recordings independently, they were advised to ask parental assistance for home-cooked meals, particularly for specific recipes or ingredients, and the app prompted them if help was needed.

Figure 2. Example of a 2-hour recall day (Monday) and a 4-hour recall day (Thursday).

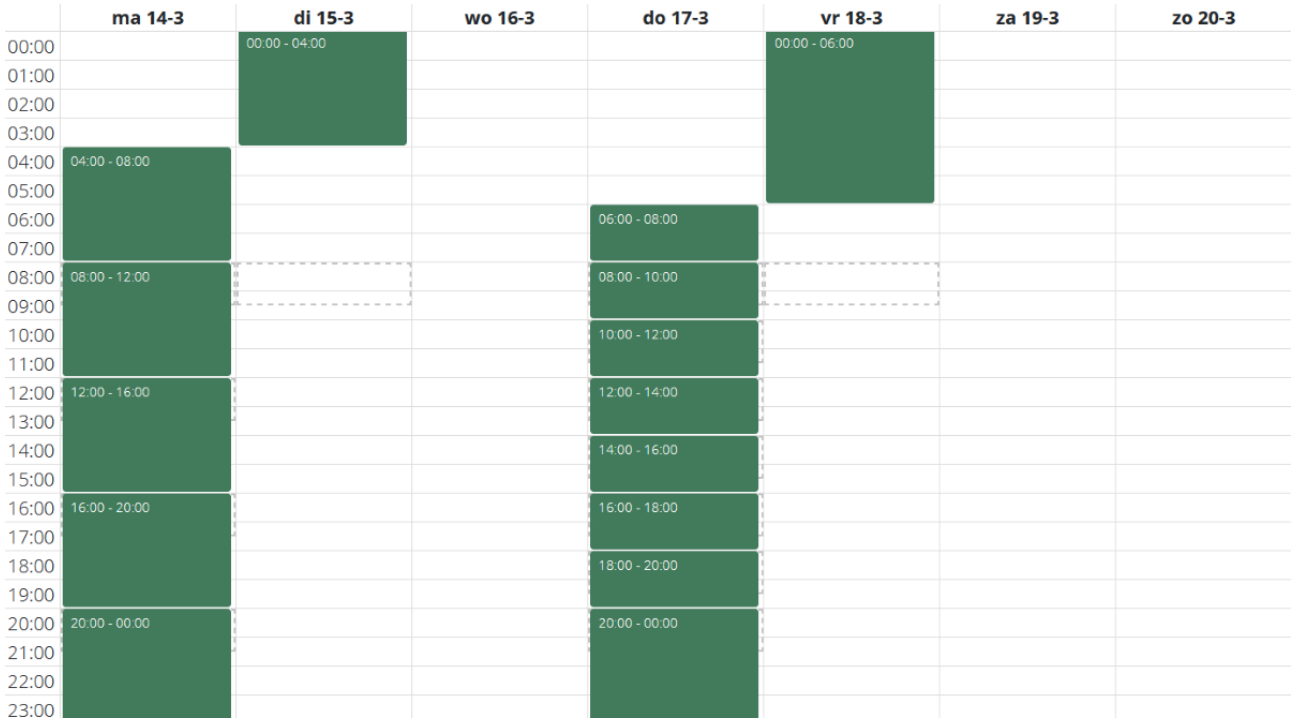

Interviewer-Administered 24hRs

In addition to the 2hR and 4hR days, 2 unannounced 24hRs were administered via telephone by trained dietitians using the multiple-pass approach [29]. Similar to the Traqq app, portion size estimation methods included household measures, standard portions, or grams. To minimize disruption to school hours, adolescents were contacted in the afternoon or evening, with multiple attempts made to reach them on recall days. In case of nonresponse, a new 24hR was randomly scheduled. Dietitians transcribed 24hRs into food codes using the Dutch Food Composition Database [28]. Regular meetings were held with all dietitians to ensure quality and consistency in food coding.

Computation of Dietary Recall Data

Data from the 2hR days, 4hR days, and the 24hRs were entered in the computation module of Compl-eat [30]. Total intakes of energy, macronutrients, micronutrients, and food groups were calculated using the Dutch Food Composition Database [28]. Dietary intake data were thoroughly checked by trained dietitians, according to a standardized protocol. Dietitians checked the data for completeness and unusual amounts. Reporting errors were corrected according to a standardized approach, using standard portion sizes and recipes, for example, 250 glasses of cola was corrected to 1 glass of 250 g. Adolescents were not contacted in case of discrepancies.

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Web-Based FFQ

At the end of the 4-week study period, adolescents were asked to complete a validated semiquantitative FFQ, with a reference period of 4 weeks [31]. This extensive FFQ was administered online with the self-administered Dutch FFQ tool [32]. Adolescents indicated the frequency of consumed food items by selecting answers ranging from "not consumed" to "7 days per week." In addition, portion sizes were estimated using natural portions and common household measures. Energy and nutrient contents of foods were based on the Dutch Food Composition Database [33] and multiplied by the portion size and frequency of consumption to calculate the mean daily intake of energy, macronutrients, and micronutrients. In addition, the average daily intake (in grams) of food items was calculated by multiplying the frequency of consumption by portion size. Trained dietitians conducted multiple quality checks to safeguard the quality of the data.

Demographics

At the start of the study, adolescents completed a demographic and personal characteristics questionnaire, including questions about the date of administration, sex ("boy" or "girl"), and country of birth ("the Netherlands" or "other"). Age was categorized into 12- to 15-year and 16- to 18-year age groups. Adolescents were asked, "Who do you live with most days of the week?" with 7 options: "both parents or caregivers," "2 cohabiting parents," "mother and partner," "father and partner," "mother," "father," "living independently," or "other." For analyses, coparenting, living with the mother or father and partner, and living with the mother or father separately were grouped as living separately. The education level was categorized according to the Dutch system into 3 options: "primary school" (including "grade 8 [±12 years]" and "other"), "secondary school" (including "year 1" to "year 6" and "other"), and "other" (including "Vmbo," "Vmbo-t [theoretical, mavo]," "Vmbo-(g)t," "Havo," "Vwo," and "other"). For analyses, "Vmbo," "Vmbo-t," and "Vmbo-(g)t" were grouped as intermediate vocational education and "Havo" and "Vwo" as higher vocational and academic education. Height and weight were collected to calculate BMI (kg/m²) and categorized into normal weight, underweight, and overweight based on age- and sex-specific BMI cutoffs according to the Schofield 10 to 18 years equation:

- For girls: basal metabolic rate = (200.0 + [8.4 × weight]) + (465.4 × [length / 100]).
- For boys: basal metabolic rate = (515.3 + [16.2 × weight]) + (137.1 × [length / 100]) [34].

Adolescents self-reported their weekly physical activity by indicating how many days (<1 d up to >7 d) they exercised for at least an hour, including all forms of sports or exercise and commuting to school. Other questions about physical activity included sports ("yes" or "no"), such as fitness, swimming, tennis, etc; average number of times exercise was performed per week (<1 time per wk up to >7 times per wk); and average duration of exercise (<1 h up to >2 h). The last 2 questions were converted into 1 variable, "average exercise time." Questions about whether adolescents follow a diet to gain weight ("yes" or "no"), a diet to lose weight ("yes" or "no"), and their sleeping patterns were also included.

User Evaluation

During the final study week, adolescents completed an evaluation questionnaire about their experiences with the dietary assessment methods (ie, 2hR days, 4hR days, 24hRs, and FFQ) and the Traqq app in general [35]. The questionnaire, adapted from previous studies, assessed ease-of-use, convenience, reporting burden, perceived accuracy, likelihood of future use, and overall experience [36,37]. It included a question about parental assistance in home-cooked meals and app use, with responses recorded on a 5-point Likert scale from 1 (strongly disagree) to 5 (strongly agree). Adolescents also completed the System Usability Scale (SUS) for the Traqq app [38], a 10-item questionnaire with a similar 5-point Likert scale from 1 (strongly disagree) to 5 (strongly agree) [35,39,40]. Adaptations were made for clarity within this specific population. The SUS score was calculated by subtracting 1 from the scale position for positive questions and subtracting the scale position from 5 for negative questions. The average was then multiplied by 2.5 to obtain the final overall value (range 0-100) [38]. Out of 100, an SUS score >68 indicates above-average usability, while a score >80 indicates excellent usability [38].

Quantitative Analysis

In this paper, demographic characteristics are presented as means with SDs for continuous variables and as frequencies (n and %) for categorical variables in adolescents for phases 1 and 2. Future analysis will evaluate the accuracy of the 2hR and 4hR days methods against 24hRs and the FFQ using correlation coefficients, mean and percent differences, Wilcoxon signed rank, and ANOVA tests [26]. Criteria as specified by Lombard et al [41] will be used as the reference to interpret the results. Usability will be evaluated using descriptive statistics per answer category (number and percentage). Statistical analyses were and will be performed with SPSS software (version 28.0.1.1; IBM) and R Statistical open-source software (version 4.3.3; Hornik and R Core Team).

Phase 2

Semistructured Interviews

Qualitative semistructured interviews were conducted online via Microsoft Teams by a single researcher (LLEK) in September 2022. This approach was chosen for its effectiveness, which is comparable to in-person interviews [42], and aimed to explore adolescents' experiences and preferences regarding the use of the Traqq app. The interview script (Multimedia Appendix 1) included questions about user-friendliness (ie, "What makes it enjoyable or interesting to use the app?"), intuitiveness (ie, "How did you experience using the app?"), perceived burden (ie, "Were there specific time periods when tracking was more difficult?"), notification timing (ie, "What did you think of the response time for notifications?"), interface usability (ie, "How can the app's clarity be improved?"), food entry clarity (ie, "How did you experience logging your foods and drinks?"), portion size estimation (ie, "How was your experience estimating portion sizes?"), motivation for long-term use (ie, "How many consecutive days would you like to use the

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app?”), and preferences for future app use (ie, “What makes it enjoyable or interesting to use the app?”). During each session, adolescents also performed a think-aloud exercise [43,44], verbally expressing their thoughts while reporting their dietary intake for the past 4 hours.

Qualitative Analysis

Semistructured interviews (length between 22 and 49 min) were audio-recorded and transcribed verbatim. The capability, opportunity, motivation-behavior (COM-B) model was used to inform the subsequent content analysis [45]. This model suggests that for individuals to perform a specific behavior (eg, using an app), they must possess the necessary capabilities (ie, physical and psychological ability to use of the Traqq app), have adequate opportunities (ie, physical and social environment that facilitate the use of the Traqq app), and be sufficiently motivated (ie, automatic and reflective mechanisms that activate or inhibit the use of the Traqq app) [45,46]. Comprehensive analysis was achieved by using a combination of deductive and inductive coding methods. The deductive coding was guided by the COM-B model, which provided a theoretical framework to categorize behavioral determinants. Inductive coding allowed for the identification of additional themes emerging from the data that may not be captured within the COM-B structure [45,46]. Both researchers independently coded all transcripts, and any differences in code lists were discussed and adjusted to reach consensus, resulting in a final list. To ensure accessibility, all codes were translated into English, and the coding and analysis of the interviews were conducted using QDA Miner Lite (version 2.0.9; Provalis Research). Further analysis of the semistructured interviews is ongoing.

Phase 3

Cocreation

During the third phase of the study, a cocreation approach will be used to redesign the Traqq app’s interface, actively involving end users to better align with adolescents’ needs and preferences. At least 2 cocreation sessions will take place, each with approximately 5 adolescents per session, divided by each age group (ie, 12-15 years and 16-18 years age groups). Insights from the semistructured interviews will inform these sessions.

Each session starts with an icebreaker exercise, followed by discussions on user personas and experience journey maps derived from the interview analyses [47,48]. First, adolescents will review identified touchpoints—interaction moments with the Traqq app—and reflect on the emotions associated with them, particularly those eliciting negative emotions. In the second part of the cocreation session, adolescents will collaborate in groups to redesign interactions with the Traqq app that mitigate these negative emotions, using paper prototyping tools. Both groups will test each other’s prototypes, enhancing the codesign process quality, engagement, and educational value. In this case, each group could use the other group to “user test” their paper prototypes.

Qualitative Analysis

The researchers will collect, process, and analyze all data. Because this project follows a cocreation and coanalysis approach, not all procedures need transcription, as adolescents will document many aspects. However, key parts of the recordings from the sessions will be transcribed. Data analysis will involve coding by 2 researchers using Atlas.ti/QDA Miner Lite, using a combination of general inductive and deductive thematic analysis [49]. Data collection and analysis will be conducted in a forthcoming phase of the study.

Results

Participant Characteristics (Phase 1)

In total, 102 participants were included in phase 1 of the Traqq-Z study (Table 1). The mean age was 15 (SD 2) years. Most (n=64, 63%) of the participants were girls. A total of 88 (92%) participants were born in the Netherlands. Most (n=81, 85%) of them attended high school and 36 (37%) engaged in exercise for an average of more than 6 hours per week. A total of 40 (42%) participants were physically active for an average of 3 to 5 days per week. Moreover, 84 (88%) participants had a healthy BMI, and 75 (78%) lived with both parents. The mean SUS score was 72 (SD 15).

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Table 1. General characteristics of the adolescents included in phase 1 of this study (N=102).

	Total[a]	12- to 15-year age group	16- to 18-year age group
Sample, n (%)	102 (100)	53 (52)	49 (48)
Girls, n (%)	64 (63)	29 (55)	35 (71)
Age (y), mean (SD)	15 (2)	14 (1)	17 (1)
BMI (kg/m^2), mean (SD)	19.9 (3)	18.5 (3)	21.5 (3)
BMI category[b], n (%)			
Underweight	2 (2)	2 (4)	0 (0)
Normal weight	84 (88)	45 (90)	39 (85)
Overweight	10 (10)	3 (6)	7 (15)
Basal metabolic rate (kcal/day), mean (SD)	1545 (205)	1484 (186)	1610 (207)
Born in the Netherlands, n (%)	88 (92)	46 (92)	42 (91)
Living situation, n (%)			
Living with both parents or caregivers	75 (78)	41 (82)	34 (74)
Living separately[c]	18 (19)	9 (18)	9 (20)
Living independently	3 (3)	0 (0)	3 (6)
Educational level, n (%)			
Primary school	5 (5)	5 (10)	0 (0)
Secondary school	81 (85)	44 (88)	37 (80)
Intermediate vocational education	4 (4)	0 (0)	4 (9)
Higher vocational and academic education	5 (5)	0 (0)	5 (11)
Other	1 (1)	1 (2)	0 (0)
Average exercise time (h/wk), n (%)			
<1	6 (6)	4 (8)	2 (4)
1-2	16 (17)	9 (18)	7 (15)
2-4	19 (20)	10 (20)	9 (20)
4-6	19 (20)	10 (20)	9 (20)
>6	36 (37)	17 (34)	19 (41)
Physical activity[d] (d/wk), n (%)			
<1	3 (3)	2 (4)	1 (2)
1-2	11 (11)	3 (6)	8 (17)
3-5	40 (42)	23 (46)	17 (37)
6-7	17 (18)	8 (16)	9 (20)
7	25 (26)	14 (28)	11 (24)
System Usability Scale, mean (SD)	72 (15)	68 (13)	67 (12)
Number of complete dietary data collections, n (%)			
Two 2-hour recall days[e]	49 (48)	26 (49)	23 (47)
Two 4-hour recall days[e]	77 (75)	39 (74)	38 (78)
Two 24-hour recall days	91 (89)	48 (91)	43 (88)
FFQ[f]	81 (79)	43 (81)	38 (78)

[a]Missing: 6 for BMI, BMR, born in the Netherlands, living situation, educational level, exercise time, and physical activity, and 14 for SUS.

[b]On the basis of the Schofield 10- to 18-year equation, for girls: BMR = (200.0 + [8.4 × weight]) + (465.4 × [length / 100]), and for boys: BMR = (515.3 + [16.2 × weight]) + (137.1 × [length / 100]) [34].

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[c] Living separated includes coparenting, living with the mother or father and partner, and living with the mother or father separately.

[d]Physical activity for at least an hour per week (ie, all the forms of sports or exercise in a day, including travel time to and from school).

[e]No more than one 2-hour recall or 4-hour recall missed per day.

[f]FFQ: food frequency questionnaire.

Participant Characteristics (Phase 2)

In phase 2, interviews were held with a subsample of 24 adolescents divided between the age groups of 12 to 15 years (n=13, 54%) and 16 to 18 years (n=11, 46%), with a mean age of 15 (SD 2) years. This subsample included 18 (75%) girls, 20 (83%) participants had a healthy BMI, and 18 (75%) lived with both parents. Most (n=21, 88%) of them attended high school and 10 (42%) engaged in exercise for an average of 1 to 2 hours per week. A total of 7 (29%) participants were physically active for an average of 6 to 7 days and 7 (29%) participants for 7 days per week as shown in Table 2.

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Table 2. General characteristics of the adolescents included in phase 2 of this study (N=24).

	Interview subsample[a]	12- to 15-year age group	16- to 18-year age group
Sample, n (%)	24 (100)	13 (54)	11 (46)
Girls, n (%)	18 (75)	9 (69)	9 (82)
Age (y), mean (SD)	15 (2)	14 (1)	17 (1)
BMI (kg/m^2), mean (SD)	19.9 (3)	18.1 (3)	22.1 (3)
BMI category[b], n (%)			
Underweight	1 (4)	1 (8)	0 (0)
Normal weight	20 (83)	12 (92)	8 (73)
Overweight	3 (13)	0 (0)	3 (27)
Basal metabolic rate (kcal/day), mean (SD)	1478 (156)	1417 (145)	1550 (141)
Born in the Netherlands, n (%)	21 (88)	11 (85)	10 (91)
Living situation, n (%)			
Living with both parents or caregivers	18 (75)	11 (85)	7 (64)
Living separately[c]	4 (17)	2 (15)	2 (18)
Living independently	2 (8)	0 (0)	2 (18)
Educational level, n (%)			
Primary school	1 (4)	1 (8)	0 (0)
Secondary school	21 (88)	12 (92)	9 (82)
Intermediate vocational education	0 (0)	0 (0)	0 (0)
Higher vocational and academic education	2 (8)	0 (0)	2 (18)
Other	0 (0)	0 (0)	0 (0)
Average exercise time (h/wk), n (%)			
<1	0 (0)	0 (0)	0 (0)
1-2	10 (42)	5 (38)	5 (46)
2-4	8 (33)	5 (38)	3 (27)
4-6	6 (25)	3 (24)	3 (27)
>6	0 (0)	0 (0)	0 (0)
Physical activity[d] (d/wk), n (%)			
<1	0 (0)	0 (0)	0 (0)
1-2	4 (17)	2 (15)	2 (19)
3-5	6 (25)	3 (23)	3 (27)
6-7	7 (29)	4 (31)	3 (27)
7	7 (29)	4 (31)	3 (27)
System Usability Scale, mean (SD)	66 (25)	64 (28)	69 (69)

[a]Missing: 2 for SUS.

[b]On the basis of the Schofield 10- to 18-year equation, for girls: BMR = (200.0 + [8.4 × weight]) + (465.4 × [length / 100]), and for boys: BMR = (515.3 + [16.2 × weight]) + (137.1 × [length / 100]) [34].

[c]Living separated includes coparenting, living with the mother or father and partner, and living with the mother or father separately.

[d]Physical activity for at least an hour per week (ie, all the forms of sports or exercise in a day, including travel time to and from school).

Discussion

This paper describes the design of the Traqq-Z study, which aims to evaluate the accuracy, usability, and user perspectives of the Traqq ecological momentary dietary assessment app in adolescents. We included 102 adolescents, with half (n=53, 52%) aged 12 to 15 years and the other half (n=49, 48%) aged 16 to 18 years, who were primarily girls and in high school.

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Response rates were consistently high, except for the two 2hR days. The adolescents rated the adult version of Traqq as above-average in terms of usability. A subgroup of 24 adolescents, equally divided between the age groups of 12 to 15 and 16 to 18 years, participated in semistructured interviews to further explore user preferences. Quantitative evaluation of the repeated short recall approach will reveal its potential in adolescents. Moreover, the evaluation questionnaire and semistructured interviews will yield valuable insights into adolescents' needs and preferences for dietary assessment tools. In the final phase of the study, cocreation sessions will involve adolescents in redesigning an app tailored to their requirements.

The Traqq-Z study's strength lies in its mixed methods approach, which comprehensively evaluates the accuracy of a novel dietary assessment approach (ie, repeated short recalls), usability of the Traqq app, and user preferences, offering insights into factors influencing accuracy, usability, and compliance [50]. An important aspect is the evaluation of the novel short recall approach, namely 2hR days and 4hR days. While repeated 2hRs effectively assess dietary intake in Dutch adults [26], they might be less suitable for adolescents due to restrictions on smartphone use during school hours. Evaluating different time intervals will help identify the optimal approach. Compliance rates suggest that 4-hour time windows are more effective in adolescents than 2-hour windows. Further analyses will show if these higher compliance rates lead to more accurate intake data.

Adolescents rated the current version of the Traqq app with above-average usability, scoring 72 out of 100 on the SUS. This score exceeds expectations for a version not yet tailored to adolescents. Comparable usability scores were found for other adolescent dietary assessment tools, such as the EaT app (69 out of 100) and the web-based myfood24 (74 out of 100) [19,21]. These findings indicate that the current version of the Traqq app serves as a solid starting point. Analyses of the evaluation questionnaire and semistructured interviews will pinpoint areas for improvement and customization opportunities for the app.

This research also facilitates tailoring of the app to adolescents through a user-centered design approach. Involving target users in the redesign process ensures that the adapted app meets their needs and preferences. Cocreation sessions allow adolescents to refine the tool, which is crucial for identifying and addressing potential issues such as difficulties in estimating food intake. Integrating insights from both quantitative and qualitative evaluations into the redesigned Traqq app aims to improve usability, compliance, and accuracy [51]. Validation studies comparing the current and adapted versions with reference methods will follow to confirm these adaptations.

Moreover, while more than 3 recall days per method would likely yield more accurate dietary intake estimates [52], 2 recall days were selected due to their acceptable agreement with the FFQ for regularly consumed foods and nutrients [53], as well as to minimize participant burden. Altogether, this approach offers valuable insights into the feasibility and optimal recall period of the repeated short recall approach for assessing dietary intake among adolescents.

To conclude, the most important asset of the Traqq-Z study lies in its comprehensive study design. The results include both quantitative data, including dietary intake data acquired through two 2hR days, two 4hR days, 2 interviewer-administered 24hRs, and one FFQ and an evaluation questionnaire. In addition, qualitative data from semistructured interviews will provide further insight into the needs and preferences of adolescents on dietary assessment tools. Cocreation sessions involve adolescents in the redesign process of a tailored version of the Traqq app. An extensive evaluation of the redesigned dietary assessment app is crucial to ensure usability and accuracy of the method, not just against traditional methods, but against objective measures as well.

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Authors' Contributions

DAL, AMMV, AW, IK, EJMF, and EMB-B contributed to the conceptualization and design of the study. Data were collected by AMMV and LLEK. LLEK analyzed the data and completed writing the final paper with DAL and EMB-B. All authors reviewed and commented on draft versions and approved the final paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guide—user perspectives.
[DOCX File , 17 KB - resprot_v14i1e70194_app1.docx]

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Abbreviations

2hR: 2-hour recall
4hR: 4-hour recall
24hR: 24-hour recall
COM-B: capability, opportunity, motivation-behavior
FFQ: food frequency questionnaire
SUS: System Usability Scale

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Gut Microbiota, Antipsychotics, and Metabolic Alterations in Children and Adolescents: Protocol for a Longitudinal Observational Study

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Abstract

Background: Over the past decade, numerous studies have emphasized the important role of gut microbiota (GM) in maintaining the body's homeostasis. Imbalances in GM have been linked to many dysfunctions, such as metabolic and neurodevelopmental disorders. GM can be influenced by many factors, among them the use of certain medications, such as second-generation antipsychotics (SGAs), and, in turn, act upon the endocrine, immune, and nervous systems. Despite the growing interest in the microbiota-gut-brain axis, significant gaps remain in our understanding of how SGAs affect GM and the host metabolic profile.

Objective: This study aims to build on the current knowledge on the impact of SGAs on clinical parameters, microbial and metabolic profiles, and behavior of children and adolescents undergoing treatment with SGAs.

Methods: This is a prospective longitudinal study, in which the effects of SGAs will be assessed before and 3 to 6 months after their introduction. An integrated approach will be used, encompassing clinical data (such as weight, lipid profile, and glucose levels); microbiome and metabolome analyses; emotional, behavioral, and sleep patterns (assessed through psychiatric scales); and dietary habits.

Results: This project was funded in November 2023 and will start data collection in January 2026. It is expected to be completed in 2027.

Conclusions: This study is expected to provide insights into the multidimensional effects of SGAs on children and adolescents, including clinical data, GM microbial profile, metabolism, and behavior. The findings may contribute to a better understanding of treatment impacts and provide information on more personalized therapeutic strategies.

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KEYWORDS

psychiatric disorders; gut microbiota-brain axis; microbiome; metabolome; second-generation antipsychotics

Introduction

Communities of microbes, collectively known as microbiota, have evolved in close association with their hosts and colonize various regions of the human body, with the highest concentrations in the gastrointestinal tract [1]. Growing evidence supports the relevance of GM to the host's health. It is involved in a wide range of physiological processes, such as nutrient metabolism, gastrointestinal motility, immune regulation, and even neurological functioning [1,2]. On the other hand, GM composition is influenced by numerous host-related factors, including age, lifestyle, and pharmacological intervention, such as antipsychotic medications [3], which are the focus of this study.

In early life, GM is particularly susceptible to environmental factors, with long-lasting effects on immune, metabolic, and neuroendocrine pathways [4]. Perturbations during key developmental stages could predispose children to different conditions through immune dysregulation and altered neurodevelopmental signaling. These connections are yet to be understood, and they highlight the importance of studies focused on pediatric populations.

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The use of antipsychotics, especially second-generation antipsychotics (SGAs), has extended far beyond their primary indications and is increasing among children aged as early as 3 years [5]. SGAs are prescribed for off-label conditions including anxiety, autism, and attention-deficit/hyperactivity disorders [5,6]. Despite its therapeutic potential, the use of SGAs in youth is associated with important side effects, which include weight gain, metabolic disturbances, heart disease, and sedation, among others [7-9].

Children and adolescents appear to be particularly susceptible to antipsychotic-induced impacts [10]. These side effects can emerge rapidly and be widespread, with studies reporting a notable increase in weight within the first 15 weeks of treatment [11] and clinically relevant weight gain (≥7%) associated with almost all antipsychotic medications investigated [12]. Notably, agents considered neutral in adults may lead to weight gain in younger populations, as discussed elsewhere [10,13].

Given the complex nature of the effects of SGAs, comprehensive monitoring, which addresses the interaction between SGAs and clinical, microbial, metabolic, and behavioral data, is important for developing safer and more personalized treatment strategies. In accordance, the primary purposes of this study are to evaluate changes in key clinical parameters, GM composition, and metabolic profile in children and adolescents before and after treatment (3 to 6 months) with SGAs. The secondary goals are to assess behavioral, emotional, sleep, and dietary parameters and to explore their potential associations with microbial, metabolic, and clinical changes. For that, the following specific objectives were defined:

- Evaluate changes in weight, BMI, abdominal circumference, glucose levels, and lipid profiles at the 2 time points
- Compare GM and metabolic profiles before and after SGA therapy
- Evaluate behavior, emotional regulation, and sleep quality using validated psychometric tools (Emotional Regulation Checklist, Adolescent Behavior Inventory, and Pittsburgh Sleep Quality Index), previously adapted to the population under study
- Investigate changes in dietary patterns before and after treatment and their associations with the evaluated parameters
- Explore, through statistical modeling techniques, potential connections between the studied factors and the introduction of SGAs and other variables that might influence the results, such as drug and age.

In this way, this study aims to address a current gap in the literature, as no previous research, to the best of our knowledge, has yet integrated clinical parameters with metabolome and microbiome data in the context of SGA therapy. The results could help identify associations that may, in the future, contribute to elucidating the mechanisms through which GM could be associated with the side effects of these medications.

Methods

Study Design

This prospective observational study will evaluate the effects of SGAs in children and adolescents at 2 time points: before (baseline) and 3 to 6 months after treatment initiation. No intervention will be applied, and all data will be collected as part of participants' routine clinical care, thereby allowing the monitoring of temporal changes in metabolic, microbial, behavioral, and clinical parameters associated with the use of SGAs. This study adheres to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines [14], which provide a structured framework for transparent and comprehensive reporting of observational research.

Study Population

Participants will be recruited from the General Child Psychiatry, Autistic Spectrum Disorder, and Attention-Deficit/Hyperactivity Disorder outpatient clinics of the Hospital das Clínicas of the Universidade Federal de Minas Gerais. Eligible participants will include children and adolescents, aged 6 to 17 years, who have a clinical indication for antipsychotic treatment but have not yet started it.

Sample Size

In this observational study, participant recruitment will occur progressively, depending on the availability of eligible individuals initiating SGA therapy in the clinical setting. This design aligns with routine clinical practice; however, it may influence the number of participants recruited over time. The sample size estimation was calculated with 1-sample *t* test [15,16], using differences in body weight before and after treatment as the primary outcome, given its robust and early response to SGAs.

Statistical power and significance level were set at 0.80 and 0.05, respectively, which are commonly accepted values [15,16]. An effect size of 0.58 was estimated based on unpublished data from a previous study conducted by our research group. Given the limited sample size of the previous dataset and the proximity of this estimate to the conventional threshold for a medium effect size, a more conservative Cohen d_z [16] of 0.5 was adopted for the calculation. Based on this assumption, a minimum of 34 participants is required.

The previous data also indicated a dropout rate of approximately 23% (7 of the 30 recruited participants did not bring any samples, did not return for the second sampling at the due time, or interrupted SGA treatment). Thus, considering this information, the final number of participants required for the study is 45 [15]. As GM and metabolome data become available, this estimate may be refined.

Data Collection

Recruitment will take place during patients' routine medical visits. If SGA treatment is indicated, the research will be explained to parents and patients, and upon both parental consent and child's assent, blood and feces samples will be collected before and approximately 3 to 6 months after the therapy starts. During the initial visit, after recruitment, patients' height,

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weight, and abdominal and hip circumferences will be measured. Dietary patterns questionnaires, kindly provided by the South American Youth/Child Cardiovascular and Environmental Study group [17], will be completed by the parents or the child and returned to the researcher.

To minimize discomfort, blood samples will be collected alongside routine laboratory tests (fasting glucose, glycated hemoglobin, total cholesterol and fractions, and triglycerides), scheduled for the follow-up appointment, with no need for additional venous access. For metabolomic analysis, plasma will be extracted from blood samples conditioned in 4-ethylenediaminetetraacetic acid tubes by centrifugation at 3000 g for 15 minutes at 4°C and divided into as many as possible 300 µL aliquots. Metabolomics will be conducted through an academic partnership using liquid chromatography coupled with mass spectrometry [18].

Regarding fecal samples, a collection kit (Coloff) will be provided during the same visit in which the laboratory tests will be requested, along with detailed instructions for use and storage. Fecal collection may be carried out at home, preferably on the same day or the day before the blood tests. Participants will be instructed to maintain the material under refrigeration (2°C to 8°C) until delivery to the research staff, which will then be aliquoted into 0.25 µg and maintained at −80°C until further processing. For microbiome analysis, total DNA will be extracted from fecal samples using the QIAamp PowerFecal Pro DNA Kit (Qiagen), according to the manufacturer's instructions. The concentration and quality of the extracted DNA will be assessed with the NanoDrop 2000 spectrophotometer (Thermo Fisher Scientific). Shotgun metagenomics will be performed on the Illumina platform by a sequencing service provider to be defined (paired-end 150 bp), with at least 6 GB of data per sample.

Given the limited evidence supporting behavioral improvements solely attributable to antipsychotics in youth and the significant risk of adverse effects, behavioral changes will also be investigated. This approach will be carried out using validated and standardized instruments that assess the emotional and behavioral status and sleep patterns of each participant, as reported by caregivers and patients. Key assessment tools include the following:

- Child and Adolescent Behavior Inventory: a broad-spectrum tool for evaluating behavioral and emotional symptoms in children and adolescents aged 6 to 18 years, which has been validated for the Brazilian population [19,20]. It covers multiple domains, including anxiety, depression, attention problems, and conduct disorders.
- Emotion Regulation Checklist: this tool assesses emotional functioning, focusing on regulation and lability or negativity; it has also been validated for the Brazilian context in children aged 3 to 12 years [21,22].
- Pittsburgh Sleep Quality Index: This questionnaire assesses various dimensions of sleep quality over a 1-month period [23]. It has been validated for use in Brazilian children and adolescents [24] and is particularly useful for identifying sleep disturbances.

Data Analysis

Microbiome and Metabolome

Metagenomic data analysis involves several steps using different bioinformatic tools. Initially, quality control will be performed to remove low-quality sequences and adapter contamination. FastQC [25] will be used for quality assessment and Trimmomatic [26] for trimming. Host DNA will be removed by alignment to the host genome using Bowtie2 [27]. Filtered reads will then be assembled into contigs with metaSPAdes [28], followed by gene prediction using Prodigal [29]. Taxonomic profiling will be conducted using Kraken2 [30]. Functional profiling will be assessed with DIAMOND [31] in combination with UniProtKB [32], followed by mapping to the KEGG (Kyoto Encyclopedia of Genes and Genomes) Orthology system [33,34].

Statistical analysis and data visualization will be conducted to explore community structure, diversity, and differential features across samples, using *R* packages including Phyloseq [35], Vegan [36], and DESeq2 [37]. Differentially abundant and clinically relevant microorganisms identified before and after the beginning of antipsychotic therapy will be quantified using quantitative PCR to determine their absolute concentrations and improve experimental reproducibility. Specific primers will be selected from the literature, and standard curves will be constructed for each target.

Metabolomic data will be processed using the R package XCMS [38] for peak detection, alignment, and normalization. Subsequent univariate and multivariate statistical analyses will be conducted in MetaboAnalyst [39], and significant metabolites will be annotated against curated databases, including KEGG [33], Lipid Maps [40], and the Human Metabolome Database [41]. This approach will enable comparisons between time points and the identification of metabolic patterns associated with the treatment.

Psychiatric Scales and Nutritional Data

The psychiatric scales were selected based on their specific indications, with each scale's scoring system used to assess the presence and severity of symptoms. The results will be analyzed together with other variables, such as clinical, microbiological, and metabolic data, to provide a comprehensive understanding of the impact of SGAs on patients' behavior, sleep pattern, and emotional conditions.

The Dietary Determinants Questionnaire (DDQ) and the Food Frequency Questionnaire (FFQ) [17] will be used to investigate dietary habits, and the resultant information will be included in the analysis if participants present alterations in any of the other variables assessed by the study (clinical, microbiological, metabolic, or psychiatric). The DDQ will be analyzed qualitatively by thematic sections (the use of dedicated software is not planned at this stage). Items directly relevant to the study aims will be identified and dichotomously coded, for example, "consumes a given food" versus "does not consume," and "perceives being overweight" versus "perceives being underweight," to characterize parental practices, child/adolescent eating autonomy, and overall dietary behavior.

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The FFQ will be analyzed qualitatively and categorically, based on the frequency of consumption of each food item (eg, never or up to once a week, 2 to 4 times a week, or up to once a day). This categorization will allow the identification of dietary patterns associated with the participants' nutritional profiles, with an emphasis on relevant food groups (including ultraprocessed foods and sugar-sweetened beverages, among others). In addition, an integrated individual-level analysis will be conducted by combining FFQ and DDQ data with the clinical outcomes observed during the study.

Statistics

Clinical outcomes (body weight, BMI, waist and hip circumference, glucose, and lipid profiles) will be analyzed using regression-based approaches appropriate to the data distribution, with change in body weight as the primary outcome. Models will be adjusted for age, diagnosis, sampling interval, SGA type, and dose (chlorpromazine equivalents).

To integrate datasets, correlation analysis will be used to assess associations between changes in GM (diversity measures and differential abundance of clinically relevant bacterial taxa), metabolic profile, and clinical outcomes. When sample size allows, analyses will be stratified by SGA and age group. A significance level of .05 will be used, and CIs for the outcomes of interest will be provided.

Ethical Considerations

The study protocol has been submitted and approved by the National Research Ethics Commission, Brazil (CAAE 79026224.4.0000.5149). The ethical aspects of this study have been carefully considered to ensure the protection and well-being of all participants. Potential benefits include improved understanding of the metabolic and behavioral effects of the use of SGAs, which may contribute to more personalized treatment strategies. Minimal physical risks are associated with blood collection, and potential psychological or social discomfort may arise from fecal sampling. There is no planned compensation, since this is an observational study without any intervention; however, a dedicated team will be available to provide assistance whenever necessary.

All participants and their legal guardians will receive comprehensive information about the study, including its objectives, procedures, potential risks, compensation, and benefits. Informed consent will be obtained from parents or legal guardians, along with assent from the children, before engaging in any activity related to the project. The informed consent form clearly states the voluntary nature of participation, the right to withdraw from the study at any time without penalty, and the measures to ensure confidentiality. In this regard, personal and clinical data will be anonymized and securely stored, with access restricted to authorized research personnel only, in compliance with data protection regulations.

Results

The project was funded in November 2023 and will be conducted in accordance with the approved protocol. Data collection is projected to begin in January 2026 and run until June 2027. Results are expected to be available for publication in 2027.

Preliminary, unpublished data from a previous study conducted by our research group enabled the evaluation of participant adherence and identification of key logistical and procedural challenges. In that cohort, 30 participants were recruited; 11 provided fecal samples; 7 discontinued their participation. An approximate 23% dropout rate was observed among initially consenting, eligible individuals, mainly associated with fecal samples requirements.

In the previous study, participants were homogeneous in age (mean 8.7, SD 4.1) and gender (all male). Clinical profiles included 20 children with autism spectrum disorder, 8 with oppositional defiant disorder, and 2 with comorbid attention-deficit/hyperactivity disorder and oppositional defiant disorder. Similar proportions in diagnostic categories and gender distribution are expected in the present project.

Discussion

SGAs are an important therapeutic option in child and adolescent psychiatry, helping to stabilize disorders such as schizophrenia, bipolar disorder, and psychotic depression. They are also used to manage other conditions, including autism, tics, and aggressive behavior in children [13]. However, antipsychotic-induced weight gain and related metabolic disturbances are frequent and clinically relevant adverse effects, which result from multiple interacting mechanisms and contribute to reduced life expectancy [10,13,42].

As discussed previously [10,13], SGAs can interfere with appetite and metabolic regulation, resulting in energy imbalances. These effects occur through different mechanisms, such as alterations in hormone levels (eg, leptin, ghrelin, adiponectin, and insulin) and neurotransmitter pathways, including dopamine D2 receptor antagonism, a common feature of antipsychotics that is associated with eating behavior [10]. Alterations in GM have also been implicated in SGAs adverse effects, as these medications can modify gut microbial composition [3], and promote, for example, inflammatory cytokine release, which could contribute to metabolic dysregulation through bidirectional gut-brain interactions [10]. Metagenomics and metabolomics, addressed by this study, may provide valuable insights into the potential associations between alterations in GM and plasma metabolites, contributing to the understanding of the biological pathways involved in SGA-related metabolic impacts.

Different strategies can be used to mitigate the undesirable effects of antipsychotics, including the use of adjunctive medications such as metformin, which may help prevent or reduce metabolic complications, including weight gain [43]. The use of metformin, though widespread, also presents challenges. Gastrointestinal side effects such as nausea, diarrhea, and abdominal discomfort are common, particularly at the beginning of treatment. Therefore, adherence can be compromised, especially among pediatric or psychiatric populations. In this context, studies on the interaction between SGAs, GM, and dietary patterns are important to inform

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evidence-based nutritional approaches and reduce excessive pharmacological intervention.

These considerations have led to growing interest in understanding how antipsychotic medications influence GM. For example, a study similar to the present one identified taxonomic and functional alterations on GM of overweight children in treatment with SGAs [44]. However, since dietary patterns and microbiota profiles vary substantially across populations, achieving clinically meaningful understanding of the impacts of SGAs in GM and successful microbiota-based interventions require longitudinal investigations in diverse treatment contexts.

This study presents relevant strengths, particularly its comprehensive approach, which addresses various domains of participants' functioning that could be impacted by SGA treatment. The use of validated psychometric tools and standardized protocols for sample collection increases methodological rigor. Additionally, within-participant comparisons reduce the risk of bias related to interindividual variability. However, the study also presents considerable limitations, particularly related to sample size, constrained by the availability of eligible patients, variations in the interval between samplings, and expected dropout rates, which highlights the need for strategies that increase engagement.

An additional and important limitation is the predominance of male participants, reflecting the clinical population most frequently referred for antipsychotic treatment in the study setting. This gender imbalance restricts the generalizability of the findings, although efforts will be made to include female participants whenever possible. The assessment at only 2 time points can also be considered a limitation, as it restricts the evaluation of long-term trajectories of microbiome, metabolome, and clinical outcomes. Although a third follow-up visit would strengthen the study, feasibility constraints prevented its inclusion in this protocol. Furthermore, the observational design does not allow causal inferences, and potential confounders such as comorbidities, concurrent medications, and environmental factors may influence the outcomes despite attempts at standardization.

Therefore, although this study may bring relevant information by integrating different aspects that might be affected by SGA medications on a pediatric population, there are considerable feasibility challenges that must be acknowledged. Variations in follow-up intervals and difficulties related to participant adherence and sample collection may affect data completeness and introduce heterogeneity. The predicted sample size also limits statistical power, restricting the scope of multilevel analyses. However, this limitation is expected to lessen as a larger number of participants will allow for more precise effect size estimation. As a final point, the findings should be regarded as exploratory and hypothesis-generating, primarily aimed at identifying trends and contributing to future studies with larger cohorts.

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Data Availability

Data sharing is not applicable to this paper as no datasets were generated or analyzed during this study.

Conflicts of Interest

None declared.

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Abbreviations

DDQ: Dietary Determinants Questionnaire
FFQ: Food Frequency Questionnaire
GM: gut microbiota
KEGG: Kyoto Encyclopedia of Genes and Genomes
SGA: second-generation antipsychotic
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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Establishing Barriers to and Enablers of Nurse-Enabled Subcutaneous Therapy Self-Administration Programs for Patients With Myeloma: Protocol for a Qualitative Descriptive Study

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Abstract

Background: Multiple myeloma (MM) is associated with the greatest symptom burden of all hematological cancers and, despite substantial improvements in treatment options with high response and survival rates, is still considered incurable, with patients undergoing multiple lines of therapy over many years. Subcutaneous (SC) injections are a common mode of delivery for current and future MM therapy, with evidence suggesting that programs that give patients or carers responsibility for administration can bring benefits to the patient and health care system by reducing the number of required visits to hospital.

Objective: This study will explore and describe barriers to and enablers of implementing nurse-enabled SC therapy self-administration programs for patients with MM to develop a road map for national scalability.

Methods: This qualitative descriptive study is informed by the Consolidated Framework for Implementation Research. Participants included key stakeholders from across Australia, including patients, carers, health professionals, and policymakers with experience of implementation, facilitation, and participation in nurse-enabled SC therapy self-administration programs. Data were collected via virtual focus groups or semistructured interviews and analyzed using the framework method to identify barriers and enablers. The Expert Recommendations for Implementing Change matching tool will be used to develop strategies to target barriers and enhance enablers, informing the development of a national road map.

Results: This study was funded in March 2024 and approved by Peter MacCallum Cancer Centre Human Research Ethics Committee in May 2024. Data collection was conducted between June 2024 and November 2024. A total of 32 participants were recruited. Data analysis is underway, with results expected to be published in February 2026.

Conclusions: To our knowledge, this study will be the first of its kind to identify and compare barriers to and enablers of implementing nurse-enabled SC self-administration programs for patients with MM. Applying the Consolidated Framework for Implementation Research to guide study processes provides an evidence-informed approach to understanding how discrete and intersecting factors influence program implementation and sustainability, informing the development of a comprehensive implementation road map. As the availability of SC therapies grows for other cancers and chronic diseases, this model of care could serve as a blueprint for broader applications, impacting patient quality of life and optimization of health care use.

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KEYWORDS

multiple myeloma; self-administration; nurse-enabled therapy; subcutaneous therapy; implementation science

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Introduction

Background

Multiple myeloma (MM) is the second most prevalent hematological cancer worldwide. It is largely a disease of older adults, with a mean age at diagnosis of 70 years [1]. The 5-year relative survival rate for MM has increased from 26% in the period between 1988 and 1992 to 56% in the period between 2014 and 2018 [2]. Despite these advances, MM remains an incurable disease characterized by prolonged, continuous periods of treatment targeting its relapsing, remitting nature. However, improved disease control has brought new challenges, including extended periods of specialist hospital surveillance and increased burden of travel, inconvenience, and cost for patients and carers, especially for those from regional, rural, and remote areas [3].

The emotional, physical, and financial impact of living with MM is considerable for both the patient and those caring for them. Patients report a complex combination of disease- and treatment-related side effects that impact health outcomes, including decreased physical functioning (98.9%), cognitive impairment (80.2%), and financial difficulties (78.4%) [4]. The consequences of MM also place a considerable burden on carers, who fear for the future and experience disruption to routine, decreased ability to work due to time spent in hospital, and worries about end of life [5,6].

Having the ability “to care for myself” is recognized as one of the most prevalent patient-reported unmet needs among people with incurable cancer [7,8]. Information and knowledge to help manage the impact of cancer and its treatment has been proven to ameliorate anxiety and improve quality of life and motivation to self-care. This may be especially beneficial for people living with MM and their caregivers [9,10].

The evidence summarized above points to a need to develop contemporary models of care responsive to the long-term challenges faced by people affected by MM. One opportunity to address the impact of MM on the lives of patients and carers is to reduce the burden of frequent travel to specialist centers for treatment. The option for self-administration of subcutaneous (SC) injectable therapy offers an opportunity to decrease the impact of treatment burden and its time toxicity [11], with additional favorable impacts on health care resource use.

Bortezomib Self-Administration Program

Bortezomib is a proteasome inhibitor used in the treatment of newly diagnosed and relapsed MM. It is delivered via SC injection over approximately 20 seconds [12]. Our team implemented and sustained a nurse-enabled subcutaneous therapy self-administration program (NEST-SP) for patients receiving bortezomib, wherein patients or a nominated carer are offered the opportunity to learn how to administer their SC bortezomib injection at home. This program has resulted in avoidance of 3 out of 4 weekly hospital visits for patients and carers per treatment cycle. Initial evaluation data from the first 20 patients showed that attending the hospital for their injection resulted in an average time commitment of 4.5 hours per treatment day compared with 6 minutes when self-administering the injection at home [13]. These findings also demonstrated an opportunity for considerable savings for patients regarding costs of transport, parking, and food incurred when visiting the hospital [13]. Further evaluation of 70 patients in the program revealed that self-administration saved approximately 1400 hours of hospital day therapy unit chair time, creating greater capacity in the health care system for patients unable to self-administer their medication at home and a saving of approximately Aus $71,000 (US $47,229.20) for the hospital [13].

However, while interventions can work well in one context, scaling to other settings can be problematic. This may be due to various factors that can influence the uptake of an intervention, such as complex health systems, funding constraints, personal preferences or motivations, and workforce challenges [14]. Other MM teams across Australia have been unable to initiate or sustain an NEST-SP. Anecdotal reasons reported for this include inflexible systems, short expiry times on in-house compounded bortezomib, risk management considerations, beliefs about patient capability, and resourcing.

With multiple SC immunotherapies, including anti-CD38 monoclonal antibody and T cell–redirecting antibodies, including bi- and trispecific antibodies, in development for MM [15], there is considerable opportunity to expand NEST-SPs to benefit patients across Australia and worldwide. Studies to expand understanding of the barriers to and enablers of implementing complex health interventions such as new models of care that potentially offer patient- and system-level benefits are urgently needed.

Using Implementation Science to Capture Broad-Ranging Complexities

Implementation science (IS) provides a systematic approach to understanding factors that influence the uptake of evidence-based interventions in practice [14]. Evidence-based IS frameworks offer a theory-informed approach to understanding and addressing factors that hamper effective implementation by exploring the barriers to and enablers of intervention uptake. By making barriers and enablers known, it is possible to develop new or apply evidence-informed interventions or strategies tailored to strengthening enablers and overcoming barriers [16].

This study will use the Consolidated Framework for Implementation Research (CFIR; described below) [17,18] to allow for the systematic exploration and description of barriers to and enablers of implementing NEST-SPs for patients with MM. Identified barriers will be mapped to the CFIR Expert Recommendations for Implementing Change (ERIC) matching tool [19]. The data generated will be used to inform future development of a national implementation road map to facilitate nationwide scaling of NEST-SPs.

The study objectives are as follows:

1. To develop an understanding of barriers to and enablers of implementing nurse-enabled SC immunotherapy self-administration programs for patients with MM.
2. To identify potential strategies to address these barriers and enhance enablers of program implementation in other contexts.

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3. To generate data to inform future development of a national road map for implementation of an NEST-SP.

Methods

Qualitative Approach

We will undertake a qualitative descriptive study informed by a pragmatic research approach [20]. Pragmatism as a research paradigm is based on the assumption that researchers choose the method or design that best addresses the needs of the problem being researched and that knowledge is based on experience [21]. As the intent of this study is to learn from the experiences of those who have attempted to implement or have received care through NEST-SPs, a pragmatic paradigm aligns well [22]. A qualitative approach was chosen to enable in-depth exploration of a topic about which little is known [23] and enable purposeful exploration of participant experiences through consideration of CFIR constructs to generate a novel and comprehensive understanding of barriers to and enablers of the implementation and sustainability of NEST-SPs.

In keeping with best practice principles of undertaking qualitative research [24], reflexivity will be a key consideration throughout the study to address transparency and rigor [25]. We acknowledge that the study team comprises clinicians and researchers with extensive experience in myeloma and nurse-enabled interventions and a shared belief in the potential benefits of NEST-SPs, which may influence data collection and interpretation. Strategies to mitigate this include self-interview and structured team reflexive discussion [25]. The manuscript complies with the Standards for Reporting Qualitative Research checklist [26] relevant at the study protocol stage.

Study Population

Patients with MM, carers (to include family members or friends), multidisciplinary health care professionals (HCPs) who are experts in the management of MM, policymakers, and industry partners from across Australia were recruited. This breadth of perspectives is required to reflect the complexity of factors that need to be considered across all domains of the CFIR to establish the barriers to and enablers of the program.

Patients had a diagnosis of MM and experience receiving SC therapy either through an NEST-SP or as administered by a health professional. Carers will have experience supporting a patient through a diagnosis of MM and SC therapy.

HCPs had experience caring for patients with MM and the process of administering SC therapies through either an NEST-SP or a hospital chemotherapy day unit.

The policymakers were representatives from government and regulatory agencies, senior hospital administration, and the pharmaceutical industry to reflect the perspective of NEST-SP development that relates to factors beyond the chemotherapy day unit.

Sample Selection and Recruitment

A purposive sampling [27] approach was used to ensure the recruitment of individuals with relevant experience in and knowledgeable about SC therapy delivery in MM. Stakeholder mapping was used to create a list of potential HCP and policymaker participants from HB's network and checked for completeness by the study team to ensure inclusion of all required stakeholders. Recruitment of patients and carers was advertised through Myeloma Australia, a national nongovernmental organization.

Informed by the work of Hennink et al [28], and aligned with the choice of applying a deductive framework analysis approach to the data to be generated [29,30], we aimed to undertake 6 distinct focus groups, each one exploring the perspectives of diverse stakeholder participants (Textbox 1). Evidence from rigorous assessment of the number of focus groups required to generate credible deductive codes indicates that 1 focus group yields over 60% of deductive, high-prevalence codes per stakeholder group, with considerable decline in the number of codes generated in each focus group conducted after this [28]. For our study, 1 focus group per stakeholder grouping (stratum) to a maximum of 6 focus groups was determined to be adequate to achieve code saturation (capturing most and the most prevalent codes relevant to the CFIR domains being explored) [[31]]. We aimed to recruit a prespecified minimum and maximum number of participants to each of the 6 focus groups—detailed in Textbox 1. These numbers are informed by consideration of the study purpose (to identify barriers and enablers), generation of concrete codes (via a framework analysis informed by the CFIR), and stratification by stratum or group characteristics (Textbox 1) [28]. Although we recognize that interviews and focus groups generate different types of data and may impact how saturation is achieved [29], we offered the opportunity to take part in an interview for anyone who wishes to contribute but, because of work commitments or health concerns, is unable to attend a scheduled focus group.

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Textbox 1. Allocation of study participants into focus groups.

Focus group 1

- Patients and carers with experience of a nurse-enabled subcutaneous therapy self-administration program (NEST-SP)
- Number of participants: minimum of 4 and maximum of 6
- Patients and carers (stratum: consumers)

Focus group 2

- Patients and carers without experience of an NEST-SP
- Number of participants: minimum of 4 and maximum of 6
- Patients and carers (stratum: consumers)

Focus group 3

- Health care professionals (HCPs) with experience facilitating an NEST-SP
- Number of participants: minimum of 5 and maximum of 8
- Hematologists, oncologists, nurses, pharmacists, and general practitioners (GPs; stratum: health professionals)

Focus group 4

- HCPs without experience facilitating an NEST-SP
- Number of participants: minimum of 5 and maximum of 8
- Hematologists, oncologists, nurses, pharmacists, and GPs (stratum: health professionals)

Focus group 5

- HCPs from a private health service
- Number of participants: minimum of 5 and maximum of 8
- Hematologists, oncologists, nurses, pharmacists, and GPs (stratum: health professionals)

Focus group 6

- Policymakers
- Number of participants: minimum of 4 and maximum of 6
- Senior hospital administrators and representatives of Cancer Australia, the Department of Health, Disability, and Aging, and the pharmaceutical industry (stratum: industry, administrators, and policy)

Email invitations to participate were sent with a participant information letter. The invitation included an overview of the study and an outline of participation requirements. There was one participant information letter for patients and carers and another for HCPs, industry partners, and government officials. The participant information letter included contact details should a potential participant wish to ask any questions before deciding to take part. The email also included a link to a secure online form for collecting informed consent and demographic data and offered the option to receive a copy of the results at the end of the study.

Data Collection

To gather comprehensive perspectives, we conducted focus groups and, if necessary to achieve minimum numbers for each stakeholder group, semistructured interviews to address the study objectives.

Following ethics approval and consent, participants were allocated to a focus group according to expertise and experience facilitating or participating in an NEST-SP. Participants who were unable to attend a focus group were offered a semistructured interview. An explanation of how participants were allocated to focus groups can be found in Textbox 1.

Focus groups (or interviews) were conducted using study-specific schedules informed by the CFIR and developed by the project team. A series of schedules appropriate to each stakeholder group was developed and checked for clarity and completeness of issues to be explored by the project team ahead of data collection. An example of a focus group schedule can be found in Table 1.

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Table . Example of a focus group schedule based on the Consolidated Framework for Implementation Research domains and constructs (focus group 1: patients and carers with experience of a nurse-enabled subcutaneous therapy self-administration program).

Domain and construct	Focus group questions
Innovation domain	
Innovation adaptability construct	"How does the program work at your hospital?"
Innovation design construct	"Is there anything you can think of that would make the experience better?"
Innovation evidence construct	"What kind of information or evidence did you use or would have liked to have when deciding whether to take part in the program?"
Outer setting domain	
Critical incidents construct	"For those receiving bortezomib during the COVID-19 pandemic, was the self-administration program impacted at all? If yes, in what way?"
Inner setting domain	
Structural characteristics construct	"Have you experienced any difficulties in participating in the program?"
Physical infrastructure construct	"Can you think of anything that would make the program easier for you to access or adhere to?"
Individuals domain	
Implementation facilitators construct	"Which health professionals from the hospital do you have contact with as a participant in the program?"
Innovation recipient construct	"How confident were you that would be able to self-administer your bortezomib injections? Why/why not?"
Implementation process domain	
Sustainability construct	"Is there anything about the program that you think would make people not want to take part?"

IS Framework

The CFIR [17] was chosen to inform key aspects of the study design, including selection of study participants and data collection, analysis, and reporting [17].

The CFIR comprises 5 domains: innovation, outer setting, inner setting, individuals, and the implementation process. Within each domain sit several constructs that describe different aspects of the implementation process as they relate to each domain [17].

Table 2 outlines the ways in which the CFIR domains relate to and guide the study design.

Table . Consolidated Framework for Implementation Research (CFIR) domains as they relate to the study design.

CFIR domain	Study-specific description
Innovation	All elements related to the innovation being implemented (the NEST-SP[a]; eg, source, evidence base, trialability, adaptability, complexity, design, and cost)
Outer setting	All factors influencing facilitation of the program that sit outside the inner setting (eg, local attitudes and conditions, policies, financing, and external pressures to implement an NEST-SP)
Inner setting	All factors related to the direct implementation and facilitation of the NEST-SP (eg, drug prescribing, drug dispensing, drug delivery, patient and carer education, and patient monitoring)
Individuals	All key stakeholders—including patients, carers, physicians, nurses, pharmacists, senior hospital administrators, pharmaceutical industry representatives, and government officials
Implementation process	All factors related to the process of implementation of the NEST-SP (eg, needs assessment, planning, engagement, adaptation, and evaluation)

[a]NEST-SP: nurse-enabled subcutaneous therapy self-administration program.

Focus groups and interviews were conducted virtually using Zoom (Zoom Video Communications) and were audio and video recorded to allow for transcribing. Transcriptions will be checked for accuracy by a research assistant (RA), and in each transcript, participants will be deidentified and assigned a unique identifier.

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Each focus group or interview ran for approximately 60 to 90 minutes and was facilitated by 2 members of the study team (HB and an RA). Consent was reconfirmed with participants verbally before focus group or interview commencement, and each focus group participant was asked to maintain confidentiality regarding any information shared during the discussion.

Data Analysis

All data will be transcribed verbatim, deidentified, and entered into NVivo (version 14; Lumivero; an online qualitative data management software platform) [30] to organize and support analysis and visualization.

The framework method approach will be used to organize and analyze the data. This 7-step approach includes transcription, familiarization, coding, development and application of a working analytical framework, and charting and interpreting the data [32]. Framework analysis is a qualitative technique initially developed for policy and health research in the United Kingdom [33]. It is more prescriptive than other research methodologies, providing a 7-step approach to systematically analyze data by participants and themes using a data matrix. In the matrix, rows represent stakeholder groups, and columns represent themes, enabling researchers to compare data across participants and themes as data analysis progresses. A deductive approach will be used to code transcripts, organize data, and assign data according to CFIR domains and constructs as part of the data matrix [32].

Study-specific definitions for CFIR constructs developed by the project team members will be used to guide application of the framework method for analysis of the focus group and interview data [32]. An example of how this technique will be applied in this study is provided in Multimedia Appendix 1.

Data will be analyzed within and across each of the participant stakeholder groups to explore similarities and differences regarding barriers and enablers. Two members of the project team (HB and an RA) will analyze and code the first 2 transcripts to assess intercoder reliability. Any differences in opinion will be resolved by inviting another member of the project team to independently code the data extract. The remaining transcripts will be coded by one member of the project team (HB).

Interview transcripts will be coded according to the domains of the CFIR. This analysis will take place in 2 stages: a deductive approach to sort participant data against the CFIR domains and an inductive approach to populate the domains with content themes as evident in the qualitative data. Barriers and enablers will be compared within and across groups and stakeholders to identify similarities and differences. All barriers will be mapped to the CFIR ERIC matching tool at this stage. Consideration of prioritization of ERIC strategy selection will take place in the next phase of this work (to be detailed in a future protocol) [19]. While we recognize that a dominant deductive approach to analysis may limit emergent themes relevant to the CFIR domains, the next stage of this work will provide the opportunity for a different group of key stakeholders to add to and further expand the understanding of barriers and enablers obtained from participants in this study, further strengthening the credibility of the data generated.

At the completion of this analysis, the data will be used to populate and develop the implementation road map. An evidence-informed framework such as the National Health and Medical Research Council's guide to the development, implementation, and evaluation of clinical practice guidelines [34] will be used to inform this phase of the work.

Ethical Considerations

Ethics approval was granted by the Peter MacCallum Cancer Centre Human Research Ethics Committee (approval HREC/107517/PMCC). Informed consent is mandatory for all participants via an online form. Focus group and interview transcripts will be deidentified to maintain participant anonymity and kept in password-protected folders only accessible to study staff.

As outlined in the participant information letter, patient and carer participants were informed that, if they find any questions upsetting or they do not wish to answer a question during the focus group or interview, they can wait for the next question or choose to leave the focus group or interview. If a participant decided to leave a focus group, a member of the study team made contact at the conclusion of the focus group to offer support as needed. Contact details for the consumer liaison officer (patient and carer participants) and local ethics committee representative (health professional, administration, policy, and industry participants) are included in the participant information letter. If a patient or carer became distressed because of disease-related issues, they were referred, with their permission, to Myeloma Australia's telephone support line service. If the withdrawal of a participant resulted in a focus group falling below the minimum group composition requirements (Textbox 1), we saw to recruit an appropriate replacement.

At the beginning of each focus group, participants were reminded that any personal information shared during the discussion must be kept confidential. They were assured that there is no right or wrong answer or perspective and that all responses are valuable. If any sensitive data were disclosed intentionally or unintentionally, the group was reminded of the confidential nature of the discussion. If any concerns arose as a result of disclosure (eg, patient safety or issues relevant to practice), these were discussed among the study team, and a documented plan to respond was developed and enacted.

Data will be stored in accordance with National Health and Medical Research Council guidelines for conduct of research for the duration of the project and 5 years after completion of the final publication in accordance with best practice research guidelines.

Participants were not incentivized to take part in this study.

Results

This study was funded in March 2024 and approved by the institution ethics committee in May 2024. Data collection was conducted between June 2024 and November 2024. A total of 76.2% (32/42) of the approached participants were recruited.

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There were 6 focus groups and 10 semistructured interviews carried out. Participant numbers per focus group ranged between 3 and 7. Data analysis is nearing completion, with results expected to be published in February 2026.

Discussion

Insights from the development, implementation, and facilitation of our NEST-SP demonstrate that NEST-SPs require multidisciplinary collaboration and key stakeholder engagement that vary across health care settings and teams.

To our knowledge, this study will be the first of its kind to identify and compare barriers to and enablers of implementing NEST-SPs for patients with MM. Applying the CFIR to guide the study provides an evidence-informed structure to understand how discrete and intersecting factors influence program implementation [35].

Evidence generated from this study will be used to inform early development of an implementation road map to support national implementation of NEST-SPs for people affected by MM. The road map will undergo further development by stakeholders from diverse settings in subsequent studies building on this research.

The implementation of an NEST-SP has the potential to improve patient experience and quality of life by allowing people to spend less time in hospital, reducing the time [36] and financial toxicity [11] of unnecessary travel and addressing a commonly reported unmet need among people with cancer—“to be able to take care of myself” [7,8]. Furthermore, evidence indicates that nurse-enabled care may enhance patient self-management capacity [37] for patients with cancer and other chronic conditions [38]. Importantly, approaches to care that enable self-management may address inequities in care experienced by patients living in regional, rural, and remote locations where time and cost toxicity impact access to and acceptability of care, potentially impacting treatment decision-making [39] and disease-specific outcomes.

As the availability of SC therapies for other cancers and chronic diseases grows, the implications of this work have the potential to extend beyond MM. Importantly, in the next study building on this work, participants from regional cancer centers in Australia will be recruited to consider, add to, and further strengthen the findings of this research. Their perspectives will help inform equitable application and opportunity for implementation of this initiative across diverse health settings and resources, ensuring its applicability and utility for cohorts of patients with cancer in rural and remote areas known to experience poorer cancer outcomes than those of their metropolitan counterparts [40,41].

This study will improve our understanding of the barriers and enablers experienced across Australian health services seeking to implement NEST-SPs. The data generated will help inform future approaches to effective implementation of NEST-SPs. The application of the CFIR framework is novel for this work, providing a structured, evidence-based approach to exploring barriers to and enablers of innovations in health care delivery.

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Data Availability

The data generated by this study will be available from the corresponding author on reasonable request.

Authors' Contributions

HB, MK, LG, AK, and SH all contributed to funding acquisition, conceptualization, methodology, writing of the original draft, and review and editing.

Conflicts of Interest

AK is on the advisory board for Janssen, Bristol-Myers Squibb, and Glaxo Smith Kline and has received speaker fees from Janssen and Amgen. All other authors declare no other conflicts of interest.

Multimedia Appendix 1
Example of a data coding matrix.
[DOCX File, 14 KB - resprot_v14i1e85053_app1.docx]

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Abbreviations

CFIR: Consolidated Framework for Implementation Research
ERIC: Expert Recommendations for Implementing Change
HCP: health care professional
IS: implementation science
MM: multiple myeloma
NEST-SP: nurse-enabled subcutaneous therapy self-administration program
RA: research assistant
SC: subcutaneous

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Perceptions, Barriers, and Facilitators of Provider-Initiated and Voluntary HIV Testing and Counseling Among Health Care Workers: Protocol for a Multicenter Cross-Sectional Study

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Abstract

Background: HIV testing and counseling interventions have been pivotal in efforts to curb the HIV epidemic, with diverse delivery models implemented globally. However, existing studies primarily focus on individual perspectives, with limited attention given to the essential role of health care workers in the effective implementation of voluntary counseling and testing (VCT) and provider-initiated testing and counseling (PITC) services in China.

Objective: This protocol describes the design of the Provider-initiated Views on PITC and VCT Study (PIVOT Study), which aims to assess health care workers' perceptions, barriers, and facilitators related to the implementation of PITC and VCT in Guangdong Province, China.

Methods: The PIVOT Study is a multicenter, cross-sectional observational study. Eligible participants are health care workers employed at various health care service institutions, including hospitals, VCT clinics, the Centers for Disease Control and Prevention, and community health centers. We will use a convenience sampling method. Data will be collected via a structured digital questionnaire covering 5 domains: sociodemographic information, general health status, psychosocial characteristics, knowledge related to PITC and VCT, and experiential insights regarding service provision. Descriptive statistics will be used to characterize variable distributions, and multivariable logistic regression models will assess associations between independent and outcome variables. Secondary analyses will explore subgroup differences based on age, years of experience, sex, institution type, and geographical location. A total of approximately 400 health care workers will be recruited.

Results: The PIVOT Study proposal was submitted in December 2024 and received funding approval in May 2025, with official project initiation planned for July 2025. Study design and survey instrument revisions were completed between December 2024 and March 2025. A pilot survey was completed from April to May 2025, followed by questionnaire testing and refinement from June to August 2025. Formal data collection was conducted from September to November 2025, with data cleaning and preliminary analyses scheduled from December 2025 to January 2026. Final data analysis and manuscript preparation are planned from February to June 2026.

Conclusions: The PIVOT Study will generate important insights into health care workers' perspectives on PITC and VCT service delivery in China. The findings are expected to inform the development of targeted strategies to strengthen HIV testing efforts, particularly among underrepresented populations such as older adults. Study results will be disseminated through peer-reviewed journals and national and international conferences.

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KEYWORDS

HIV testing and counseling; HIV prevention strategy; health services accessibility; health care workers; China

Introduction

Background

The Joint United Nations Programme on HIV/AIDS estimated that, as of 2023, approximately 39.9 million individuals worldwide were living with HIV [1]. In China, this number has risen from 0.65 million in 2005 to an estimated 1.1 million in 2021 [2,3]. The ongoing HIV/AIDS epidemic remains a pressing public health challenge, presenting significant obstacles for prevention and control efforts.

HIV testing and counseling interventions have been pivotal in efforts to curb the HIV epidemic, with diverse delivery models—such as voluntary counseling and testing (VCT) and provider-initiated testing and counseling (PITC)—targeted at reducing undiagnosed infections and addressing the needs of key populations affected by the epidemic [4-6]. VCT is conducted in clinical settings, with an emphasis on pre- and posttest counseling and upon obtaining informed consent from the individual [7]. In contrast, PITC, as a streamlined model, simplifies information gathering and counseling on high-risk behaviors, uses an opt-out system, and is integrated into routine health care services [8].

While some systematic evidence examines the effects of VCT and PITC on individuals' behaviors, psychological well-being, and care, much of this research primarily focuses on individual outcomes [9-11]. Consequently, there is a notable lack of evidence regarding the essential role of health care workers in ensuring the effective implementation of VCT and PITC. Moreover, the successful implementation of HIV testing and counseling—an inherently complex process—depends on well-defined procedures, an in-depth understanding of protocols, and proficient communication skills among health care professionals [4]. However, how these factors influence the ability of health care workers to carry out VCT and PITC remains unanswered. If these factors are inadequately addressed, patients may experience decreased uptake of testing services, suboptimal counseling quality, increased psychological distress, and delayed linkage to appropriate care [12]. Previous studies have highlighted that failures in VCT and PITC delivery can reinforce HIV-related stigma and compromise health outcomes [13].

Research Questions

To address these identified gaps, the Provider-initiated Views on PITC and VCT Study (PIVOT Study) was established to generate foundational evidence. This multicenter observational study aims to elucidate the current perceptions, barriers, and facilitators related to PITC and VCT among health care workers in China, along with their correlates. The primary and secondary research questions of the PIVOT Study are as follows.

- Primary research questions: What are the perceptions of PITC and VCT among health care workers? What are correlates of these perceptions? What barriers do health care workers encounter in the implementation of VCT and PITC?
- Secondary research questions: How can the effectiveness of PITC and VCT be enhanced from the perspective of health care workers? Based on health care workers' perceptions and barriers, how can the effectiveness of PITC and VCT be enhanced? What specific support do health care workers need to improve the quality of PITC and VCT services?

This protocol outlines the study design, target populations, survey instruments, and procedural methodologies. It serves as a vital resource for researchers aiming to replicate the described cross-sectional approach and represents a valuable guide for those interested in facilitating a deeper understanding of the barriers and facilitators influencing PITC and VCT from the perspective of health care workers.

Methods

Ethical Considerations

During the planning phase, stakeholder meetings were convened, involving health care providers from various health care service institutions, social workers from the Guangdong Association of STD & AIDS Prevention and Control, and research team members to evaluate the feasibility of the PIVOT Study. All investigators and personnel received training in research ethics and the protection of human subjects (Multimedia Appendix 1). All procedures contributing to this work comply with the ethical standards of relevant national and institutional committees on human experimentation and with the Helsinki Declaration. The anonymity and confidentiality of the participants in this study will be ensured and maintained according to laws and regulations. Digital informed consent will be obtained from all participants before any procedure. The PIVOT Study has received preliminary ethics approval from the Human Research Ethics Committee of the Guangdong Provincial Center for Disease Control and Prevention (W96-027C-KS), which was granted to support the initial pilot study and funding application process. Following funding approval and confirmation that all data were fully anonymized and involved no individual-level identifiers in any datasets, transcripts, or publications, the study received a waiver of full ethical review, and the documentation of this waiver has been provided in Multimedia Appendix 1.

Dissemination

Findings from the PIVOT Study will be disseminated widely through peer-reviewed scientific journals and at national and international conferences.

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Study Design and Setting

The PIVOT Study is a multicenter, cross-sectional study focused on health care workers across various health care service institutions in Guangdong Province, including hospitals, VCT clinics, the Centers for Disease Control and Prevention, and community health centers. Using a convenience sampling method, the study aims to assess the current perceptions, barriers, and facilitators related to PITC and VCT from the perspective of these professionals. We did not predefine the number of participating institutions. Instead, we aimed to maximize diversity in health care service settings. The final number of participating institutions and geographical areas will be reported as part of the study results.

Patient and Public Involvement

Patients and the public were not involved in the design, conduct, reporting, or dissemination plans of this research.

Study Population

Eligibility Criteria

The eligibility criteria are presented in Textbox 1.

Textbox 1. Eligibility criteria.

Inclusion criteria

- Aged ≥18 years
- Worked in any health care service institution for at least 12 months
- Understands the survey instrument of the Provider-initiated Views on PITC and VCT Study (PIVOT Study)

Exclusion criteria

- Unable to provide informed consent
- Participated for less than 12 months in any health care institution
- Submitted incomplete or invalid survey responses

Sample Size

This study uses logistic regression, which informs the required sample size calculations. For logistic regression analysis, the final sample size is established as 10 to 15 times the number of covariates, guided by findings from previous research [14]. The study will assess 7 variables related to sociodemographic and general health conditions, 5 variables addressing psychosocial characteristics, 2 variables concerning perceptions of VCT or PITC implementation, and 3 variables focused on experiences with VCT or PITC implementation. This totals 17 variables, necessitating a minimum sample size of 255 participants, derived from the 15-fold multiplier. To enhance statistical power for subgroup analyses, we will recruit an additional 40% of participants. Consequently, the final sample size will be at least 360 participants. Accounting for potential missing data and ensuring validity, we will distribute a minimum of 400 questionnaires.

Data Collection

Data collection will be conducted via a digital questionnaire encompassing 5 key components: sociodemographic information, general health status, psychosocial characteristics, knowledge related to the implementation of VCT or PITC, and experiential insights regarding these services. A convenience sampling approach will target health care workers within various health care institutions in Guangdong Province, spanning the period from September 2025 to November 2025. The notification package containing survey instructions and questionnaire QR codes will be coordinated by 2 trained research assistants in collaboration with provincial health authorities. These assistants will receive prior training covering ethical communication practices, technical procedures for QR code distribution, and standardized responses to participant inquiries. Quality control measures will include real-time monitoring of submissions through the online dashboard with automated validation checks such as a minimum completion time threshold of 10 minutes, coupled with weekly progress updates to participating institutions. Before the commencement of the survey, the digital questionnaire will reiterate the study's objectives. Participants will be adequately informed about the focus of the PIVOT Study and will electronically sign an informed consent form via the online platform. We will ensure the confidentiality of all participants' private information and guarantee their right to withdraw from the study at any time.

Survey Instrument

The design of the questionnaire and selection of variables were informed by key constructs from the theory of planned behavior (eg, attitudes, subjective norms, and perceived behavioral control) and the capability, opportunity, and motivation (COM-B) framework, both of which are commonly applied in implementation research. Multidimensional variables will be collected, encompassing sociodemographic factors (eg, age, sex, years of experience in health care, type of health care institution, and geographic location), health conditions (eg, general health and specific health issues), psychosocial characteristics (eg, depressive symptoms, feelings of loneliness, resilience, perceived stress, and job satisfaction), experiences with VCT or PITC implementation, perceptions regarding the implementation of VCT or PITC, and experiences with referral services. Given the ongoing paradigmatic evolution in the demographic landscape of individuals living with HIV in China—driven by increased accessibility to effective antiretroviral therapy [15,16], better management of coinfections and comorbidities [17], and a rising number of new infections among older adults [18,19]—the PIVOT Study also seeks to

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explore health care workers' perspectives on this demographic, including their understanding of older adults' sexual behaviors, their attitudes toward aging populations, and their views on sexual education targeted at older adults.

Given that older adults represent a population at potential risk for HIV infection, the PIVOT Study also tries to explore health care workers' perspectives on this demographic, including their understanding of older adults' sexual behaviors, attitudes toward older adults, and views on sexual education targeting older populations. Additionally, insights from the promotion of HIV testing will inform the implementation of hepatitis C virus (HCV) testing. Thus, we have also incorporated perceptions related to HCV testing. Specific variables within each domain are detailed in Table 1. Prior to the formal launch of the survey, the instrument was adjusted through a preliminary presurvey (pilot study). A preliminary pilot survey was conducted to assess face validity and content validity. The questionnaire was subsequently revised based on participant feedback. Formal evaluation of the instrument's reliability and validity will be conducted upon completion of data collection.

Table . The survey instrument content of the Provider-initiated Views on PITC and VCT Study.

Domain	Variable
Sociodemographic	• Not specifically listed
Health conditions	• General health • Specific health
Psychosocial characteristics	• Depressive symptoms • Loneliness symptoms • Resilience • Perceived stress • Job satisfaction
Perceptions of VCT[b] or PITC[c] implementation	• Channels of awareness for VCT • Knowledge related to VCT implementation • Number of VCT clinics known • Channels of awareness for PITC • Knowledge related to PITC implementation
Experience with VCT or PITC implementation	• Experience with VCT implementation • Reasons for failure of VCT implementation • Experience with PITC implementation • Approach to PITC implementation • Reasons for failure of PITC implementation
Experience with referral services implementation for people living with HIV	• Experience with referral service implementation for people living with HIV • Number of referral services implementation for people living with HIV • Willingness to implement referral services for people living with HIV
Perceptions of HCV[a] testing implementation	• Knowledge related to HCV • Experience with HCV testing • Approach to HCV testing implementation
Perceptions related to older adults	• Attitudes toward older adults • Sexual knowledge of older adults • Attitudes toward sexual health education in older adults
Perceptions related to digital health in HIV/AIDS control and prevention	• Attitudes toward digital health in HIV/AIDS control and prevention • Perceived necessity of using digital health in HIV/AIDS control and prevention

[a]HCV: hepatitis C virus.

[b]VCT: voluntary counseling and testing.

[c]PITC: provider-initiated testing and counseling.

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Data Security and Data Management

Data Download

Data will be exported from the digital platform in CSV format upon the study's closure and updated weekly to a secure institutional storage platform. According to the data security protocols, access to these data will be restricted to 3 administrators (BW, HD, and XF) from the PIVOT Study.

Data Security Protocols

The primary principle guiding data security is that all access to data is strictly on a need-to-know basis, a policy that permeates all aspects of data management throughout the study. All project-related data, including survey results and laboratory testing outcomes, will be stored on a secure file storage platform. To ensure the integrity of data handling, stringent protocols must be followed when accessing, storing, and downloading data under institutional guidelines. Given the sensitive nature of the data, particularly regarding work experiences with PITC and VCT, maintaining a high level of anonymity is paramount. The survey will remain anonymous.

Statistical Analysis

Statistical analyses will be conducted using Python (version 3.8 with the following libraries: pandas [version 2.0.0], NumPy [version 1.24.2], and SciPy [version 1.10.1]; Python Software Foundation); SPSS (version 24.0; IBM Corp); and SAS (version 9.4; SAS Institute Inc). Descriptive statistics will characterize the distribution of variables, while multivariable logistic regression models will be used to assess the associations between independent variables and outcome variables. The assumptions for conducting logistic regressions will be checked and confirmed to be fulfilled, including multicollinearity, linearity, independence, and outliers [20]. Subgroup analyses will explore differences based on age, years of experience in health care, sex, type of health care institution (including hospitals, VCT clinics, Centers for Disease Control and Prevention, and community health centers), and geographic location (comparing the Pearl River Delta region to non-Delta areas). The statistical significance was set as $P<.05$.

Results

The PIVOT Study proposal was submitted in December 2024 and received funding approval in May 2025, with official project initiation planned for July 2025. Study design and survey instrument revision were conducted between December 2024 and March 2025. A pilot survey was conducted from April to May 2025, followed by questionnaire testing and refinement scheduled from June to August 2025. Formal data collection will be undertaken between September and November 2025, and data cleaning and preliminary analyses will be conducted from December 2025 to January 2026. Final data analysis and manuscript preparation are planned from February to June 2026. A visual representation of the anticipated study timeline is provided in Figure 1.

Figure 1. Anticipated study timeline for the Provider-initiated Views on PITC and VCT Study.

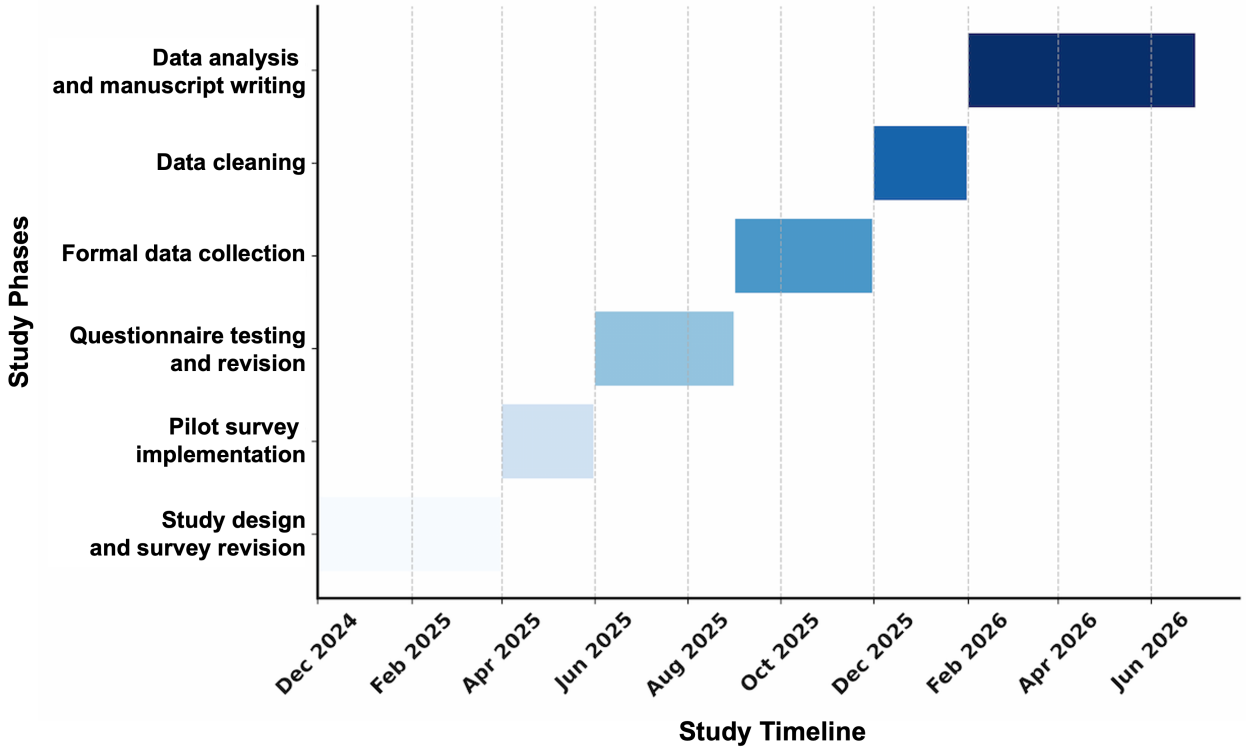

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Discussion

Summary

Despite the essential role of health care workers in expanding HIV testing services, little is known about their decision-making processes and contextual barriers regarding PITC and VCT in China. The PIVOT Study addresses this gap by systematically comparing perceptions, implementation challenges, and contextual facilitators for PITC and VCT among frontline health care workers in diverse clinical settings. Findings from this study will inform context-specific strategies to improve provider engagement and optimize the integration of HIV testing approaches into routine care.

Anticipated Findings

Recent epidemiological data in China have shown a notable increase in the incidence of HIV infections among older adults, highlighting an emerging public health challenge. However, existing prevention strategies have largely focused on younger populations, leaving a critical gap in addressing the unique needs of older individuals. By prioritizing older adults in the PIVOT Study, we aim to contribute to a more inclusive understanding of HIV prevention and emphasize the necessity of targeted interventions such as age-appropriate counseling, tailored risk communication, and community-based screening programs. The focus represents a timely response to shifting epidemiological trends and underscores the study's relevance to contemporary public health needs.

To eliminate the HIV epidemic by 2030, the Joint United Nations Program on HIV/AIDS has set forth an ambitious global target known as the 95 - 95 - 95 strategy, aiming for 95% of the individuals living with HIV to be diagnosed, 95% of those diagnosed to receive sustained antiretroviral therapy, and 95% of those on therapy to achieve viral suppression by 2025 [21]. By the end of 2020, China reported progress rates of 79%, 93%, and 96% toward these targets, respectively [22]. Over the past 4 decades, China has achieved significant advancements in the prevention and control of HIV/AIDS, in line with the nation's socioeconomic progress [3]. Nevertheless, there remains a notable gap in reaching the initial 95% target compared to other upper–middle-income countries [2]. Despite substantial annual investments in HIV/AIDS prevention and treatment, enhancing HIV testing efforts may require a focus on optimizing the allocation of these resources. Understanding health care workers' perceived barriers and facilitators has been shown to be critical for improving the success of HIV testing initiatives and optimizing resource use [23,24].

Both VCT and PITC implementations are predominantly driven by individual willingness rather than a coordinated collective effort [7,10]. A lower willingness to engage with testing often translates to increased effort and cost in connecting high-risk groups with HIV testing and care services [25]. The lack of coordination, stemming from limited accessibility for high-risk populations, can result in disparities in HIV testing rates, ultimately impeding progress toward timely diagnosis and treatment [2]. Yet, much of the current research on PITC and VCT focuses solely on service recipients. In this context, the PIVOT Study could offer an essential perspective, aiming to assess health care workers' perceptions of PITC and VCT and to identify barriers and facilitators impacting these initiatives from the viewpoint of these professionals. The findings of the PIVOT Study could provide a solid foundation for optimizing resource allocation in HIV testing and counseling interventions across various contexts. For instance, identifying barriers such as time limitations, stigma concerns, or lack of institutional support may guide the development of specific strategies, such as task-shifting models, stigma-reduction training, or decision-support tools embedded in routine clinical workflows.

Beyond its primary focus on HIV testing and counseling, the PIVOT Study also recognizes the broader implications for HCV elimination efforts. Given the high rates of HIV-HCV coinfection among key populations, strategies that enhance HIV testing uptake may simultaneously facilitate earlier HCV diagnosis and linkage to care. Strengthening PITC services could thus play a pivotal role in integrated infectious disease control programs, aligning with global health initiatives aimed at the elimination of viral hepatitis as a major public health threat.

This study offers several innovative contributions to the field. First, it highlights the critical importance of expanding HIV prevention efforts to older adults, a demographic increasingly affected by HIV but often underrepresented in public health interventions. Second, it underscores the potential for HIV testing strategies to contribute to broader infectious disease control initiatives, particularly in supporting HCV elimination efforts. Together, these aspects enhance the novelty, practical relevance, and public health significance of the PIVOT Study.

Limitations

Our study also had some limitations. First, causality among the study variables cannot be concluded due to the cross-sectional design. Future longitudinal research is essential to elucidate the causal relationships among these variables. Second, the use of nonprobability sampling methods may limit the representativeness of our sample and introduce potential selection bias, as participants were not randomly selected. Third, we required participants to have at least 12 months of experience in HIV-related service provision to ensure that their perceptions and reported barriers were grounded in substantive professional practice. However, we acknowledge that this criterion may have excluded newer health care workers who could provide valuable insights from a fresh or evolving perspective. Fourth, the PIVOT Study was conducted in a province in southern China, where participation bias cannot be avoided, although multicenter studies have broadened representativeness. Guangdong Province, being economically developed and relatively successful in AIDS prevention and control, may not reflect the unique geographic and demographic challenges faced by other regions. Thus, findings may not be generalizable to provinces with different contexts. More experimental research in more provinces is needed to test our findings. Additionally, our sample size was estimated using a rule-of-thumb approach based on the number of predictors, without formal power or sensitivity analysis, due to the exploratory nature of the study and lack of prior pilot data. This may limit the statistical power, particularly for subgroup comparisons. Finally, the data from our study rely on

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self-reported information, which led to inevitable recall bias among participants.

Acknowledgments

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BW, YLu, FY, YLi, XF, and HD share senior corresponding authorship.

BW, LF, KL, and CA share senior first authorship.

Funding

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Data Availability

The data collected in this study will not be publicly available. However, the corresponding author can be contacted for deidentified data.

Authors' Contributions

BW, Y Lu, FY, Y Li, XF, and HD conceived the study. BW, LF, KL, MD, and CA drafted the protocol. BW and LF contributed to formal analysis. SH, SX, LW, GW, and ZL revised the manuscript. All authors have read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Human Research Ethics Committee of Guangdong Center for Disease Control approval document.
[PDF File, 3218 KB - resprot_v14i1e69832_app1.pdf]

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Abbreviations

COM-B: capability, opportunity, and motivation
HCV: hepatitis C virus
PITC: provider-initiated HIV testing and counseling
PIVOT: Provider-initiated Views on PITC and VCT Study
VCT: HIV voluntary counseling and testing

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IL-6/GP130/JAK/STAT3 Pathway Activation in Pancreatic Ductal Adenocarcinoma and Its Association With Clinical Features: Protocol for a Retrospective Cross-Sectional Study

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Abstract

Background: The proinflammatory cytokine interleukin 6 (IL-6) contributes to pancreatic tumorigenesis by activating the Janus kinase (JAK)–signal transducer and activator of transcription 3 (STAT3) signaling cascade. Targeting the IL-6/glycoprotein 130 (GP130)/JAK/STAT3 axis may therefore represent a promising therapeutic approach for pancreatic adenocarcinoma.

Objective: This study investigates the activation of the IL-6/GP130/JAK/STAT3 pathway in archived biopsy samples from patients with pancreatic adenocarcinoma, quantifying its expression in both tumor and stromal compartments. In addition, potential associations between pathway activation and clinical outcomes are explored, including tumor stage, patient survival, and metabolic parameters such as diabetes, use of oral antidiabetic drugs, insulin therapy, and hemoglobin A_{1c} levels.

Methods: We will conduct a retrospective cross-sectional analysis of patients with pancreatic adenocarcinoma treated at the Cantonal Hospital of Fribourg, Switzerland, between 2010 and 2025. Eligible cases are identified through tumor board records. Archived pathology specimens will be immunostained using a phospho-STAT3 antibody to assess GP130 receptor activation. The percentage of positively stained cells will be quantified separately for tumor tissue, stroma, and adjacent normal tissue using QPath software. Sample size calculations are based on the assumption that patients with higher IL-6 pathway activation have poorer prognoses. Detecting a 5% difference in activation requires 84 patients per group for 90% power or 104 per group for 95% power. Diabetes will be analyzed as a dichotomous variable, while IL-6/GP130/JAK/STAT3 activation will be treated as a continuous variable. Descriptive statistics will summarize pathway activation and clinical variables. Mean differences between groups will be compared, and survival outcomes will be evaluated using Cox proportional hazards models. Hazard ratios will be calculated for all metabolic parameters to assess potential associations between pathway activation and diabetes. All analyses will include 95% CIs, with missing data reported transparently.

Results: This project is supported by a research grant from the Cantonal Hospital of Fribourg (HFR 2/2021 and 4/2022). It was approved by the Ethics Committee of Bern, Switzerland (project 2024 - 01215). As of October 12, 2025, clinical records from 150 patients have been identified. Screening of additional patient records from 2024 to 2025 is ongoing.

Conclusions: This study represents one of the first translational investigations of IL-6/GP130/JAK/STAT3 signaling in pancreatic adenocarcinoma. By correlating molecular pathway activation with clinical and metabolic features, it will provide new insights into disease heterogeneity and support the development of personalized, pathway-targeted therapeutic strategies.

Trial Registration: Registry of All Projects in Switzerland (RAPS) 2024-01215; https://raps.swissethics.ch/runningProjects_list.php?q=%28BASECID~contains~2024-01215%29

International Registered Report Identifier (IRRID): DERR1-10.2196/76811

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KEYWORDS

pancreatic cancer; IL-6; STAT3; survival; inflammation; interleukin 6; signal transducer and activator of transcription 3

Introduction

Clinical Perspective

Pancreatic ductal adenocarcinoma (PDAC) remains one of the solid cancers with the worst prognosis. It has become the third leading cause of cancer-related death, largely because of late discovery and unresectability but also because of the lack of highly efficient chemo-, immuno-, and radiotherapies [1]. The ESPAC (European Study Group for Pancreatic Cancer) trials [2-5] showed that chemotherapy improves survival in the adjuvant and neoadjuvant setting in borderline resectable patients. Still, survival remains worse than in most other cancers. While immunotherapy has been a game changer in many cancers, there has not been such a breakthrough for pancreatic cancer so far [6].

An overall survival of 10% at 5 years has not been exceeded in most countries [7]. In Switzerland, overall survival has recently increased to 13% for the period, whereas incidence also increased by more than 10% compared with the period of 2008 - 2012 [8].

Given that chemotherapy administration is frequently constrained by rapid patient deterioration, including weight loss and impaired glucose metabolism, we aim to investigate the association between these clinical features and the tumor stage/prognosis with the inflammatory interleukin 6 (IL-6)/glycoprotein 130 (GP130)/Janus kinase (JAK)/signal transducer and activator of transcription 3 (STAT3) signaling pathway.

Pathophysiology

The proinflammatory cytokine IL-6 plays a pivotal role in tumorigenesis by activating the JAK-STAT3 signaling cascade. Upon binding to its IL-6 receptor α (IL-6Rα) on the cell surface, IL-6 induces dimerization with the coreceptor GP130, leading to phosphorylation of JAKs and subsequent activation of STAT3. Phosphorylated STAT3 translocates to the nucleus, where it promotes the transcription of genes involved in cell survival and proliferation. Recent findings have identified integrin β3 as a gene product associated with prognosis [9]. Moreover, IL-6/STAT3 signaling has been implicated in the progression from pancreatic intraepithelial neoplasia to PDAC [10]. IL-6 also contributes to the activation of cancer-associated fibroblasts via pancreatic stellate cells, key components of the tumor stroma [11]. Additionally, PDAC cells appear to exploit IL-6 signaling to prime the liver microenvironment for metastatic colonization [10]. These insights suggest that targeting the IL-6/GP130/JAK/STAT3 axis may offer a promising therapeutic strategy for pancreatic cancer. A phase 1 clinical trial has been initiated [12], evaluating a combination therapy comprising trametinib (mitogen-activated extracellular signal-regulated kinase [MEK] inhibitor), ruxolitinib (JAK2/STAT3 inhibitor), and retifanlimab (programmed cell death protein 1 [PD-1] inhibitor) [13-15]. Figure 1 shows the relevance of the pathway.

Pancreatic cancer is increasingly recognized for its impact on glycemic metabolism, with inflammatory cross talk proposed as a key underlying mechanism. Tumor-derived cytokines, notably IL-6 and tumor necrosis factor α (TNF-α), contribute to adipose tissue inflammation, impairing insulin sensitivity. TNF-α interferes with insulin receptor signaling in adipocytes, potentially promoting lipolysis and elevating levels of nonesterified fatty acids [16], which are commonly observed in obesity and type 2 diabetes, and are known to exacerbate insulin resistance and induce β-cell toxicity [17]. A study by Fogar et al [18] demonstrated a correlation between portal vein IL-6 levels and fasting serum glucose concentrations. Furthermore, preclinical evidence indicates that IL-6/GP130/JAK/STAT3 pathway activation upregulates autotaxin expression in adipocytes, while genetic suppression of autotaxin enhances insulin sensitivity and reduces hepatic steatosis in knockout mice compared to wild-type controls [19].

Inflammatory signaling within the tumor stroma is also implicated in chemotherapy resistance and disease progression. Specifically, the IL-6/GP130/JAK/STAT3 axis has been associated with cancer cachexia [20] and neural invasion [21]. Several therapeutic agents targeting this pathway have been proposed for pancreatic cancer treatment [22]. Given the marked heterogeneity of pancreatic tumors, precision therapies are urgently needed. However, the prevalence and clinical relevance of IL-6/GP130/JAK/STAT3 pathway activation in patients with pancreatic cancer remain poorly defined. Moreover, it is unclear whether pathway activation correlates with metabolic dysregulation or the presence of cachexia [23].

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Figure 1. JAK-STAT3 pathways in pancreatic cancer. CAF: cancer-associated fibroblast; EMT: epithelial-mesenchymal transition; IL-6: interleukin 6; GP130: glycoprotein 130; JAK: Janus kinase; MMP: matrix metalloproteinase; PDAC: pancreatic ductal adenocarcinoma; STAT3: signal transducer and activator of transcription 3; TAM: tumor-activated macrophages; VEGF: vascular endothelial growth factor.

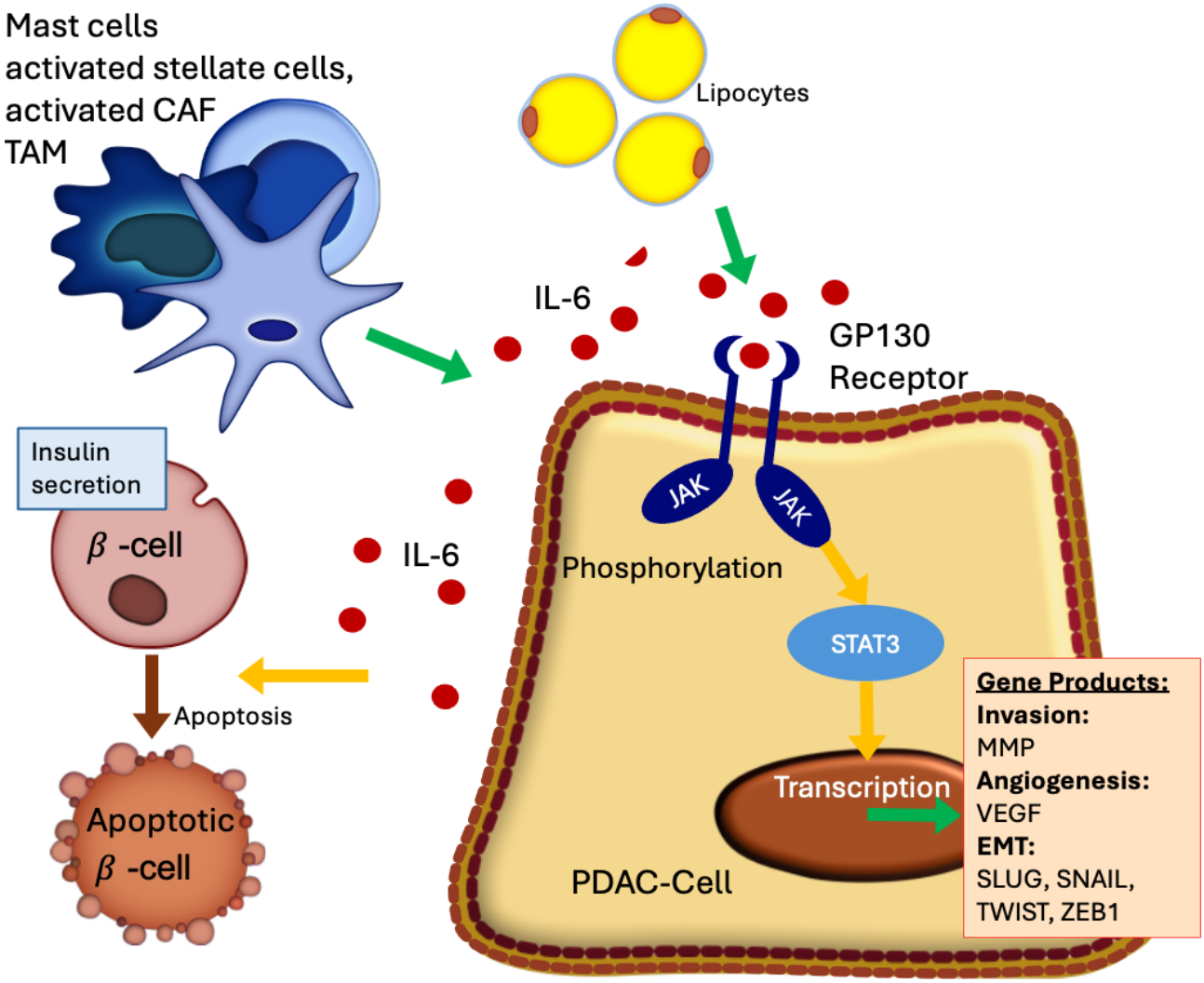

Aim of This Study

This study aims to evaluate the activation of the IL-6/GP130/JAK/STAT3 signaling pathway in previously collected tissue samples—including pancreatic biopsies, surgical specimens, and liver biopsies—from patients diagnosed with pancreatic adenocarcinoma. The study will quantify pathway activation and assess its association with tumor stage, overall survival, and metabolic parameters, including the requirement for oral antidiabetic agents, insulin therapy, and hemoglobin A_{1c} levels.

Methods

Recruitment

Overview

A retrospective cross-sectional study will be performed, including patients who were treated in our hospital between 2010 and 2024. We will use the existing clinical database of the Hospital Freiburg/Fribourg (HFR) to identify patients who received an operation for pancreatic adenocarcinoma and patients with advanced pancreatic cancers who could not undergo a resection and for which histological material is available. The data for patients with pancreatic adenocarcinoma will be obtained from the HFR database. The histological material (pancreas biopsies, surgical specimens, or liver biopsies) comes from the same patients and is currently stored in the HFR-affiliated laboratory Promed. Figure 2 shows the inclusion process.

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Figure 2. Inclusion process.

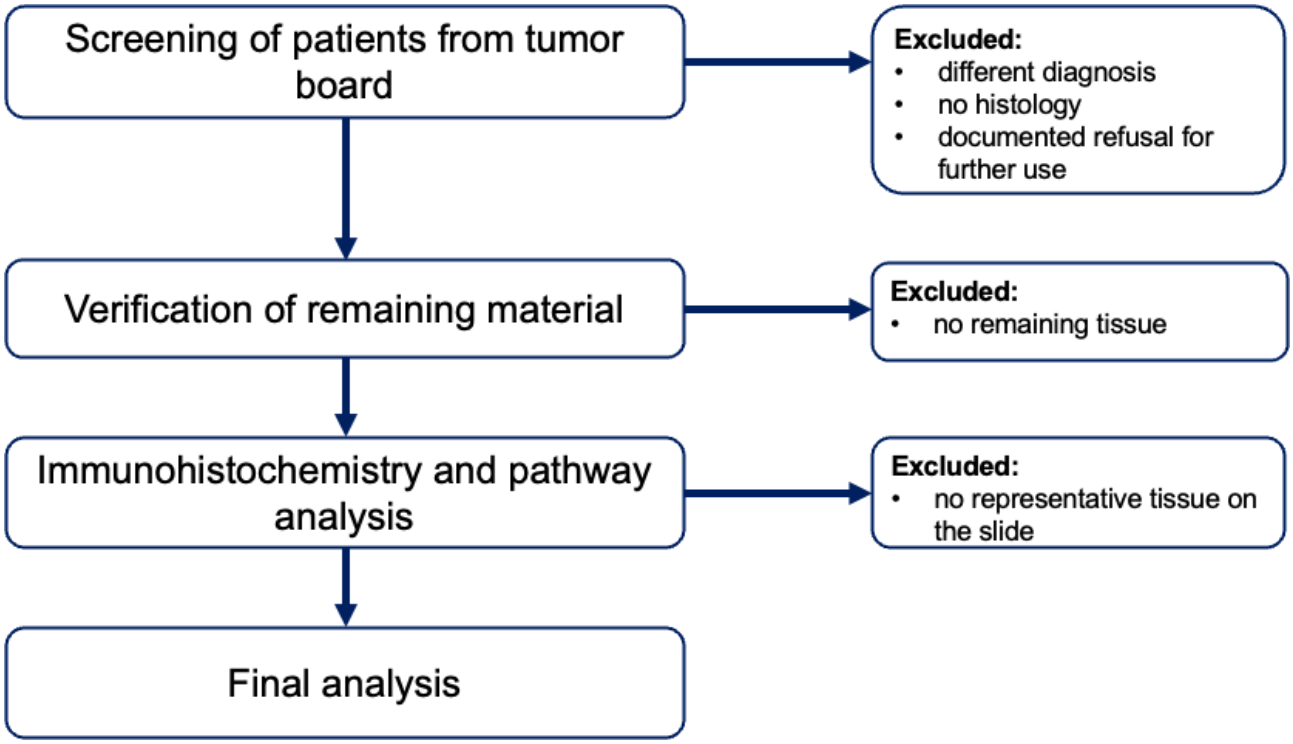

Inclusion Criteria

All patients with a histological diagnosis of pancreatic cancer (PDAC) where sufficient histological material for immunohistochemistry analysis is available will be included, and the required clinical data will be recorded.

Exclusion Criteria

Patients will be excluded if there is documented refusal of further use of clinical samples or data.

Materials

Samples

We will use previously taken histology samples (either after pancreatic resection, biopsies of liver metastasis, or endoscopic ultrasound–guided pancreas biopsies). The different origins of samples will be considered in the analysis. The samples were stored as tissue blocks in paraffin at Promed laboratory. They will be brought as slides to the core facility at École Polytechnique Fédérale de Lausanne (EPFL).

Immunohistochemistry

Immunohistochemistry will be performed using the Discovery Ventana ULTRA (Indianapolis, IN) system at the Histology Core Facility, EPFL, Lausanne, Switzerland (Phospho-STAT3 (Tyr705) (D3A7) XP rabbit monoclonal antibody [mAb]; Cell Signaling Technology, Leiden, The Netherlands). Stained slides will be scanned and images provided for activation analysis.

Examined Parameters

Primary End Point

The primary end point was IL-6/GP130/JAK/STAT3 pathway activation measured by immunohistochemistry (Phospho-STAT3 (Tyr705) (D3A7) XP rabbit mAb) in both tumor and stoma (where available) in percent. The activation will be measured using QuPath image software (version 0.5.1; Bankhead et al).

Secondary End Points

Clinical features—including tumor stage, surgical resection status, overall survival from the time of diagnostic biopsy, obesity, prior weight loss, presence of cachexia, and glucose metabolism disturbances—will be analyzed for their association with activation of the IL-6/GP130/JAK/STAT3 signaling pathway. Glucose metabolism will be assessed using a composite definition of prediabetes/diabetes based on hospital-recorded diagnoses, elevated hemoglobin A_{1c} or glucose values (including fasting glucose), and the use of antidiabetic medications. Additional comorbidities, such as rheumatic or autoimmune diseases, will also be considered in the analysis.

Statistical Analysis

Power

We hypothesize that patients exhibiting strong activation of the IL-6/GP130/JAK/STAT3 pathway have a poorer prognosis compared to those with lower activation levels. Assuming a difference in pathway activation of 5% versus 10% (SD 10%) between patients who underwent surgical resection (early-stage disease) and those who did not (advanced-stage disease), a sample size of 84 patients per group would yield 90% statistical power, while 104 patients per group would achieve 95% power.

For our second primary outcome—the association between IL-6 pathway activation and diabetes—we will treat diabetes as a dichotomous variable and pathway activation as a continuous variable. Based on an expected difference in activation of 8% versus 11% (SD 7%), with higher activation in patients with diabetes, a sample size of 98 patients per group would provide 85% power. Given that approximately 50% of patients with

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pancreatic cancer are reported to have diabetes, this sample distribution appears feasible, though not guaranteed.

Sample size calculations were performed using MedCalc [24]. As complete clinical data may not be available for all patients, each analysis will be conducted using both complete-case and imputed datasets.

Evaluation Outcomes

Percentages of IL-6 pathway activation and measured clinical features will be reported. Means of values (pathway activation, laboratory values) will be compared. Survival differences between patients with strong versus weak pathway activation will be compared in a Cox hazard analysis. To determine the optimal cutoff, we will perform a threshold analysis. Hazard ratios (between patients with weak and with strong pathway activation) will be calculated for all examined metabolic parameters to investigate a possible association between pathway activation and diabetes. A regression model incorporating demographic, clinical, and pathway-related parameters will be fitted, with 95% CIs. The number of cases with missing data for all analyses will be reported.

Ethical Considerations

This project was reviewed and approved by the Ethics Committee of Bern, Switzerland (project 2024 - 01215).

Informed Consent, Further Use Without Consent

Since 2020, patients at HFR have provided general consent for the secondary use of their clinical data and biological material. However, patients diagnosed before this date did not provide such consent. Given the high lethality of pancreatic cancer, the vast majority of eligible patients are now deceased, making it impossible to obtain informed consent retrospectively. An exemption from informed consent was therefore requested and granted in accordance with Article 34 of the Swiss Human Research Act [25]. This exemption was justified because the anticipated gain in scientific knowledge offers significant potential benefit to patients and society, and that such findings could not be obtained without access to data from individuals who are deceased. In this context, the societal interest in advancing research was deemed to outweigh the individual interests of the affected patients.

Data Protection

Uncoded Data, Coding, and Storage of the Key

Clinical data will be transcribed from the hospital database and pseudonymized by authors CM and FS. Each patient will be assigned a unique code, and a separate key document linking codes to patient identities will be created and securely stored under double lock by the principal investigator. All analyses will be conducted using coded data in accordance with this study protocol and in full compliance with applicable data protection regulations.

Information on the Storage of Data and Samples

Clinical data will be extracted from both paper and electronic medical records and entered into a secure, password-protected trial database (REDCap). All personally identifiable information—including names, addresses, exact dates of birth, and hospital patient numbers—will be stored separately from the study dataset. Digital documents will be password protected, and physical records will be securely stored in a restricted-access research office.

Histological samples will be identified and deidentified by the laboratory Promed, replacing patient names with unique numerical codes. These samples will be prepared and sent to EPFL for immunohistochemical staining. Upon completion, the stained slides will be returned to our laboratory for assessment of pathway activation levels. Any remaining material will be returned to Promed for secure storage.

Risk-Benefit Assessment

This project is expected to enhance our understanding of the role of IL-6/GP130/JAK/STAT3 pathway activation and its histological patterns in shaping the clinical phenotype of pancreatic adenocarcinoma, particularly its impact on glucose metabolism. These insights may contribute to the development of more targeted therapeutic strategies and help identify patient subgroups that could benefit from an IL-6 receptor blockade as part of their treatment regimen.

There is no risk to individual patients, as the study relies exclusively on previously collected routine clinical data and archived biopsy material. All data will be pseudonymized before analysis, and study results will not influence patient care.

The risk of inadvertent patient identification is minimal. Access to uncoded data is restricted to trained medical personnel—specifically, the three named investigators at HFR and the pathologist at Promed—who are bound by professional confidentiality through both their employment and the research framework. All digital files will be password protected, and physical documents will be stored securely in restricted-access facilities. This project is fully compliant with Swiss legal and ethical standards.

Risk of Bias

To minimize the risk of biased conclusions due to nonrepresentative sampling, we will include all patients diagnosed with pancreatic cancer at HFR, applying the least restrictive exclusion criteria possible. As HFR is the only hospital in the canton of Fribourg with an oncology department, the vast majority of patients with pancreatic cancer in the region receive care at this institution. Consequently, only a small number of patients who seek treatment outside the canton are expected to be excluded, supporting the representativeness of our sample.

Results

This project is supported by two research grants from the Hospital of Fribourg (HFR 2/2021 and 4/2022). As of October 12, 2025, clinical records from 150 patients have been included. Screening of additional patient records from 2024 to 2025 is ongoing.

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Discussion

Expected Findings

We hypothesize that IL-6/GP130/JAK/STAT3 pathway activation is comparable between tumor tissue and adjacent stromal tissue. Furthermore, we expect that patients with stronger pathway activation will exhibit poorer prognosis, more significant weight loss, and greater or more recent disturbances in glucose metabolism. We do not anticipate an association between pathway activation and long-standing diabetes. Potential confounding factors include pancreatitis and other concurrent inflammatory conditions, such as pneumonia, which may independently influence pathway activation and metabolic parameters.

Strengths and Weaknesses of This Study

A major strength of this study is that it represents only the second investigation of IL-6/GP130/JAK/STAT3 pathway activation in a substantial number of pancreatic cancer patient samples, following the recent work by Campos et al [9]. While the Campos study focused primarily on mechanistic insights, our study emphasizes the correlation between pathway activation and clinical symptoms and outcomes, offering novel perspectives on its relevance in patient care. We will also assess the presence of pancreatitis and antibiotic use, which may help exclude infectious diseases as sources of inflammation.

A potential limitation is the sample size, which may be insufficient to detect statistically robust associations across all variables. Additionally, the study design does not allow for longitudinal analysis, as only a single tissue sample per patient is available. Therefore, we cannot determine whether pathway activation varies over the course of disease progression.

Conclusion

This study contributes important new insights into the IL-6/GP130/JAK/STAT3 pathway activation in patients with PDAC. Preliminary findings suggest that patients with advanced-stage disease exhibit higher levels of pathway activation in both tumor and adjacent stromal tissue. These results support the hypothesis that stromal activation mirrors tumor activation and may play a role in disease progression. To further disentangle the influence of patient or tumor genetics from disease dynamics, longitudinal sampling would be necessary to assess changes in pathway activation over time.

Funding

This project is supported by two research grants from the Hospital of Fribourg (HFR 2/2021 and 4/2022).

Data Availability

The study results will be published in anonymized form, based solely on statistical analyses, ensuring that no individual can be identified from the published data. Findings will be disseminated to health care professionals and the broader public through publication in an international peer-reviewed medical journal, adhering to the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines. All assessed parameters will be reported, with supplementary materials provided as appropriate. Additionally, results will be presented in abstract form at relevant scientific conferences.

Data will be shared only in a fully anonymized form upon request to the corresponding author and subject to ethical approval, in accordance with the ethical research policies of the University of Fribourg and the standards of major medical journals.

Authors' Contributions

Conceptualization: LHB, CM, SP, LV
Funding: LHB, CM, SP, LV
Administrative tasks (ethics, coordination of workflow): LHB, CM, SP, LV, FS, CG-G, MA
Data collection: CM, FS
Pathology assessment: IE, RV
Interpretation and statistics: CM, FS, CS, MA
Article writing (first draft and follow up): CM, FS, MA
Article writing (critical appraisal): LHB, CG-G, CS, MA

Conflicts of Interest

None declared.

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Abbreviations

EPFL: École Polytechnique Fédérale de Lausanne
ESPAC: European Study Group for Pancreatic Cancer
GP130: glycoprotein 130
HFR: Hospital Freiburg/Fribourg
IL-6: interleukin 6
IL-6Rα: interleukin 6 receptor α
JAK: Janus kinase
mAb: monoclonal antibody
MEK: mitogen-activated extracellular signal-regulated kinase
PD-1: programmed cell death protein 1
PDAC: pancreatic ductal adenocarcinoma
STAT3: signal transducer and activator of transcription 3
TNF-α: tumor necrosis factor α

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The Effect of Semaglutide With Lifestyle Intervention on the Physical Health of Patients Treated With Antipsychotic Drugs in a Secure Mental Health Setting: Protocol for an Uncontrolled Pretest-Posttest Pilot Mixed Methods Study

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Abstract

Background: Antipsychotic-induced weight gain is a common side effect of antipsychotic drug treatment, particularly with second-generation medications such as clozapine and olanzapine. Weight gain in patients undergoing antipsychotic therapies is a significant concern, often compounded by factors related to their condition that can be particularly challenging in a secure care setting. While there is significant evidence to support the benefits of semaglutide, one of the available glucagon-like peptide-1 receptor agonists, in promoting weight loss for those who have a general weight-related health issue and meet the referral criteria for specialist services, it is unclear whether it will be as successful in people who have specifically gained weight due to medication-associated side effects and who reside in a secure care setting.

Objective: This study aims to assess the impact of semaglutide in combination with a lifestyle behavior change intervention on the physical health measures of patients in a secure setting who have atypical antipsychotic–induced weight gain and identify enhancements to the intervention, specifically geared toward improving adherence and acceptability from both staff and patient perspectives.

Methods: This 2-year uncontrolled pretest-posttest pilot study aims to recruit 20 inpatient participants. Adult patients of any diabetic status with a minimum BMI of 35.0 kg/m^2 (or a BMI of 32.5 kg/m^2 for people from South Asian, Chinese, other Asian, Middle Eastern, Black African, or African-Caribbean descent) who are receiving inpatient treatment and are treated with either olanzapine or clozapine will be eligible for inclusion in the study. Patients will receive semaglutide (Wegovy) at a maintenance dose of 2.4 mg once a week for 2 years. All participants will also receive a lifestyle behavior change intervention.

Results: The findings will reveal whether the format of the interventional approach is both sustainable and effective for adult patients diagnosed with severe mental illness and living with obesity who are currently residing in a secure mental health setting. Implementation changes that could improve the acceptability of and adherence to the intervention will be explored.

Conclusions: This research should be beneficial for patients with severe mental illness who are living with obesity and are residing in a secure setting as the findings may ultimately reduce the mortality risk in this patient group.

Trial Registration: ClinicalTrials.gov NCT06754163; https://clinicaltrials.gov/study/NCT06754163

International Registered Report Identifier (IRRID): DERR1-10.2196/76013

(JMIR Res Protoc 2025;14:e76013) doi:10.2196/76013

KEYWORDS

antipsychotics; semaglutide; obesity; glucagonlike peptide-1; GLP-1; body weight loss; diabetes; severe mental illness

Introduction

Background

Obesity represents a common clinical challenge among patients with severe mental illness (SMI) as it contributes to increased comorbidities [1] and reduces life expectancy by up to 25 years [2]. Many medications prescribed for SMIs, such as antipsychotics, are associated with weight gain, increased appetite, and metabolic changes that can complicate weight management [3,4]. Such side effects are especially prevalent

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with second-generation antipsychotics [5], also known as serotonin-dopamine antagonists, which are atypical for their lower risk of extrapyramidal side effects [6]. Notably, olanzapine and clozapine, both atypical antipsychotics, carry a particularly high risk of weight gain [7-12].

Behavioral lifestyle interventions incorporating modifications in diet and physical activity (PA) remain the foundation of treatment for overweight and obesity; however, they are often not associated with clinically meaningful and sustainable weight loss either in the general population [13] or in individuals with SMI [14]. There is evidence suggesting that, while people with SMI can engage in and benefit from lifestyle interventions, in general, greater support using a more tailored approach is needed [15,16]. In addition, lifestyle interventions still need to be translated into routine care [17] and improved for the management of antipsychotic-induced weight gain (AIWG) [18]. Furthermore, such interventions are not effective to prevent or treat adverse metabolic effects caused by antipsychotics [19]. Therefore, pharmacotherapy is recommended as an additional tool for long-term weight management in people with a BMI of at least 30 kg/m^2 or at least 27 kg/m^2 in those with weight-related comorbidities [20-22].

There is increasing evidence supporting pharmacological treatment for weight reduction with antiobesity drugs. While several antiobesity drugs are available [23], treatment with glucagon-like peptide-1 receptor agonists (GLP-1 RAs) for obesity management appears to be effective for and well tolerated by people with schizophrenia [24]. GLP-1 is an incretin hormone responsible for glucose regulation and satiety. It improves β-cell functioning and glucose tolerance and plays a crucial role in stimulating glucose-dependent insulin secretion [25,26]. As a result, GLP-1 RAs are being used increasingly to manage type 2 diabetes (T2D) by improving glycemic control [26,27]. Semaglutide is one of the GLP-1 RAs approved for treatment of T2D [28], and it has also been assessed for efficacy and safety in weight management among adults with overweight or obesity regardless of diabetic status [29-31] and evaluated in combination with behavioral interventions [32]. Treatment with semaglutide demonstrated superior, clinically meaningful, and sustained weight loss in patients with obesity (BMI of ≥30 kg/m^2) or overweight (BMI of ≥27 kg/m^2 to <30 kg/m^2) who had at least one weight-related comorbidity without T2D in various Semaglutide Treatment Effect in People With Obesity (STEP) trials [33]. In addition to reduced weight, treatment with semaglutide also significantly improved waist circumference, cardiovascular functioning, and physical functioning compared to placebo [34].

While semaglutide shows benefits for weight-related health issues in the general population living with obesity [35,36], its effectiveness for AIWG in a specific psychiatric setting remains unclear. Siskind et al [24] demonstrated the effectiveness of GLP-1 RAs for weight loss in individuals treated with clozapine and olanzapine, but out of 168 participants, only 17.9% reported a decrease in BMI. However, only 3 studies were included in their review, where the treatment with GLP-1 RAs ranged from 12 to 24 weeks. A more recent systematic review conducted by Bak et al [37] also explored the effectiveness of GLP-1 RAs in AIWG, but only limited data were available. Semaglutide was not used in any of the studies, and furthermore, lifestyle interventions were not included in the trials despite evidence in the general semaglutide trials suggesting that a multifactorial approach improves clinical outcomes [32].

Prasad et al [38] explored semaglutide for the treatment of AIWG, and initial results suggested the potential effectiveness of the drug; however, a more rigorous trial is required. Specifically, only 2 out of 12 patients involved in their study were receiving clozapine and olanzapine, and the dose of semaglutide did not reach the dose approved for the management of obesity. Furthermore, 2 short-term (26-36 weeks) clinical trials have been registered to assess the effects of semaglutide on people prescribed clozapine or olanzapine [39,40]. However, these do not include dietary or PA components, not all participants will be residing in a psychiatric setting, and individuals with T2D or treated with corticosteroids or other hormone therapy are excluded from the study. Both studies exclude individuals that either are treated with diabetes medication or have been diagnosed with diabetes despite GLP-1 RAs demonstrating their efficacy for reducing obesity-related adverse health effects in adults regardless of obesity status [41].

Study Objectives

The primary objective of this study is to evaluate the effectiveness of semaglutide (Wegovy) in combination with a lifestyle intervention. Specifically, this study explores whether body weight is reduced and, secondarily, whether other physical health outcomes, including change in waist circumference, BMI, blood pressure, resting heart rate, and blood cholesterol, are improved in patients with SMI who are treated with clozapine or olanzapine and are residing in a psychiatric setting. In addition, secondary outcomes will be assessed to understand the mechanism through which the intervention influences the patients' overall lifestyle and contributes to changes in specific aspects of their physical and mental health. Therefore, an evaluation will be conducted to understand the effectiveness of the intervention, which has been modified from a previous STEP protocol for implementation in a secure mental health setting (STEP@STAH). The feasibility of the intervention, participant engagement, and factors that could influence the outcomes of the study will be explored. This study also aims to inform a future lifestyle intervention by exploring potential barriers and facilitators from both patient and staff perspectives.

Methods

Design

A 2-year uncontrolled pretest-posttest intervention study will be conducted in a secure mental health hospital that provides specialist mental health care for patients with some of the most complex and challenging mental health needs in the United Kingdom from both forensic and nonforensic pathways. The efficacy of semaglutide in combination with a lifestyle intervention for AIWG in individuals with SMI residing in a psychiatric setting who have been treated with clozapine or olanzapine will be evaluated.

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This study has been designed for patients to receive semaglutide once a week. Participants will be offered a lifestyle behavior change intervention including dietary advice, PA advice, and psychological support according to their personalized care plan from the time of enrollment into the trial. The behavioral element of the intervention, which was designed by the hospital's dietetics team, will be introduced by KB and supported on the ward by members of the care team. The program covers 24 nutrition and exercise topics and includes the provision of fact sheets, a food diary, and a workbook. Participants will also have access to an extensive range of support resources.

A mixed methods design will be used in the study to conduct an effective evaluation of the intervention. Quantitative data will be collected on patient outcomes during the 2-year intervention, and participants' engagement with the 3 elements that will support the medication—psychological therapy, diet, and PA—will be explored. Qualitative data will be gathered to evaluate the intervention, specifically exploring its fidelity, effectiveness, acceptability, and implementation within a secure mental health setting. These data will be collected from both staff and patients to maximize feedback on the intervention.

Participants

Up to 20 inpatient participants with SMI—with a minimum requirement of 5 participants—who are currently treated with either clozapine or olanzapine will be recruited for the study. A minimum of 5 is necessary to ensure that preliminary data are obtained and the feasibility of the intervention is assessed [42]. A maximum of 20 patients ensures that the study remains manageable in terms of monitoring and data collection and analysis while still providing sufficient diversity so that meaningful patterns are observed. Using a mixed methods approach, and considering the data that will be collected, the minimum sample size will provide valuable insights, whereas the maximum sample size will ensure the practicality of the pilot study. Inclusion and exclusion criteria for patients are listed in Textbox 1.

Textbox 1. Eligibility criteria.

Inclusion criteria

- Age ≥18 years
- BMI ≥35.0 kg/m^2 (or ≥32.5 kg/m^2 for people from South Asian, Chinese, other Asian, Middle Eastern, Black African, or African-Caribbean descent)
- Ability to provide informed consent as assessed by their responsible clinician
- Current prescription for olanzapine or clozapine
- Current residence in an inpatient setting
- Sufficient level of English to read and understand the information sheet (may require verbal explanation or support from staff)

Exclusion criteria

- Age ≤17 years
- Meeting any of the contraindications for semaglutide, including hypersensitivity to the active substance or to any of the excipients
- Breastfeeding
- Pregnancy or likelihood of becoming pregnant
- Diagnosis of dementia or Huntington disease
- Admission to a psychiatric intensive care unit or acute ward
- Discharge anticipated within 6 months' time or less

The recruitment is clinician mediated, with random selection for prioritization in the event of a Wegovy shortage in the United Kingdom. Although a shortage is not anticipated, this step is included for completeness. In case prioritization is required, the random selection process will be conducted by the project manager, who will provide the selected participants' ID to the pharmacy. All other participants will remain on the waiting list until the medication becomes available, but they will be expected to start taking part in the lifestyle intervention.

Responsible clinicians (RCs) conduct an informed consent process with the potential participants before formal screening. If the number of eligible participants exceeds the available medication supply, a final priority list will be randomly generated. RCs may delegate the informed consent process to the researcher or other suitable delegate, such as a specialty physician.

Potential participants are provided with a participant information sheet and are given at least 24 hours to consider whether they would like to take part.

After a minimum of 24 hours, the potential participant is reapproached by the RC to determine whether they wish to continue with the study. At this point, patients are given the opportunity to ask any questions they may have. If the patient agrees to be involved in the project, the RC gives them the consent form to sign.

Once the patient has provided informed consent, the RCs oversee the referral and screening process. This may be done

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in liaison with the pharmacy team to identify and assess any potential contraindications or caution for use, including diabetic retinopathy and history of pancreatitis, ensuring that only eligible participants can be enrolled in line with safety guidelines and prescribing recommendations.

Semaglutide is not considered a critical care medication for those enrolled in the trial; therefore, the random selection method, which does not prioritize any particular group of patients, is appropriate to maintain the trial's scientific integrity. This approach ensures unbiased allocation, facilitating the cohort study design that will be used to evaluate the medication's effectiveness across different patient groups and enhancing the validity of the study's findings.

Patients on the medication waiting list will continue with the healthy lifestyle element of the intervention. This will allow for the assessment of the impact of the nonpharmaceutical element of the intervention on the patients' BMI and overall physical health outcomes.

Pharmacological Treatment

Semaglutide (Wegovy) injection is the medication that will be used in the trial. An induction dose of 0.25 mg, titrated up every 4 weeks to 0.5 mg, 1.0 mg, 1.7 mg, and 2.4 mg, will be administered, with a maintenance dose of 2.4 mg or up to the maximum tolerated dose. To reduce the likelihood of gastrointestinal symptoms, the dose should be escalated over a 16-week period to a maintenance dose of 2.4 mg once weekly. In case of significant gastrointestinal symptoms, delaying dose escalation or lowering to the previous dose until symptoms have improved will be considered. Weekly doses higher than 2.4 mg will not be administered as they are not approved for use.

If patients are unable to lose at least 5% of their initial body weight after 6 months of treatment, a clinical decision will be required on whether to continue treatment considering the benefit and risk profile of the individual patient. This decision will be made in consultation between the RC and the patient, with input from other members of the clinical team. It will also consider the patient's adherence to the other elements of the intervention, including diet and PA. This 6-month evaluation is in accordance with the UK National Institute for Health and Care Excellence guidelines.

The semaglutide injection will be administered once weekly on the same day of the week throughout the study period. Injections will be administered in the thigh, abdomen, or upper arm at any time of the day irrespective of meals, with the injection site selected according to the patient's preference. The medication will be administered by a member of the clinical care staff or by the participant with support if preferred and safe to do so. When administering the medication, the National Institute for Health and Care Excellence guideline TA875 [28] and standard hospital prescribing processes will be followed.

If a dose is missed, it should be administered as soon as possible and within 5 days after the missed dose. If more than 5 days pass, the missed dose should be skipped, and the next dose should be administered on the regularly scheduled day. In either case, patients can then resume their regular once-weekly dosing schedule. If more doses are missed, reducing the starting dose for reinitiation should be considered.

Behavioral Therapy: Integrated Care Approach

A care team information sheet will be provided to all staff involved in the care of patients participating in the study—this includes the clinical care team, health care assistants, sports and exercise therapists, dietitians, and occupational therapy technical instructors. This emphasizes the importance of the multidisciplinary approach in supporting patient participants over the 2-year study period and demonstrates the alignment with standard care practice. Such a coordinated effort aims to support patients effectively and ensures the success of the study through consistent and comprehensive personalized care.

Measurements

The primary outcome is change in body weight, and the physical secondary outcomes include changes in waist circumference, BMI, blood pressure, resting heart rate, and blood cholesterol. All physical health outcomes are routinely collected and will be extracted by the hospital's business intelligence team at the end of participation. All variables will be compared across a maximum period of 36 months for each participant as follows: up to 12 months prior to enrollment in the study, at baseline, and up to at least 24 months (104 weeks) of treatment.

Each patient's physical health outcome measures will be evaluated longitudinally, both before and after treatment, to assess the treatment's impact. Subgroup analyses will also be carried out to determine whether the nature of a patient's pretreatment physical health history impacted their likelihood of responding to semaglutide therapy. The delayed start nature of the trial will also allow for a comparison of the subgroup of patients who engaged in the nonpharmacological intervention (healthy eating and exercise) with those who were also administered the drug immediately upon enrollment to determine whether exercise and diet can have an impact on patients alone or whether they can only serve as an adjunct to the actions of semaglutide. The patients who are placed on the waiting list for the medication will be monitored for changes in physical health outcomes, as well as additional outcomes such as PA and exercise, appetite and diet, and quality of life. This will essentially have the format of a delayed start study.

All patients will also be monitored for physical health problems as per usual care, particularly T2D, for which semaglutide is prescribed. Blood samples will be taken by a member of the physical health team and sent for analysis every 6 months, and the levels of hemoglobin A_{1C} will be used as indicators of T2D risk. Any patient incidents that staff believe are related to the patients' participation in the trial will be referenced as such in the Datix risk management information system. This will then be consulted at the end of the study. Recording and reporting of adverse events, including incidents and reactions, will be conducted in accordance with the hospital's standard clinical practices. The clinical care team information sheet advises staff to reference the patients' participation in the STEP@STAH study in the Datix record when reporting any incidents they believe may be related to the study. The Datix record will then be consulted at the end of the study. Adverse events and

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reactions will also be reviewed by the principal investigator and the study steering group (SSG).

In addition to physical health measures, other secondary outcomes will be assessed to determine whether the level of PA and exercise, appetite, and quality of life are affected by the STEP@STAH intervention. For that reason, the following additional tools will be used to collect data that will be correlated with the physical outcomes.

Control of Eating Questionnaire

Changes in how the individual perceives self-control over their eating behavior (eg, across restraint and discipline, emotional eating, cognitive restraint, and uncontrolled eating) will be explored. While the Control of Eating Questionnaire, which includes 21 items to assess food cravings, is a valid measurement of the experience of cravings [43], the computer-based Leeds Food Preference Questionnaire will also be used to assess food preference to help contextualize the Control of Eating Questionnaire data and explore "liking and wanting component of food preference and food reward" in more detail [44].

Impact of Weight on Quality of Life–Lite–Clinical Trials Version Health Survey

Changes to health-related quality of life will be assessed using the Impact of Weight on Quality of Life–Lite–Clinical Trials Version. This questionnaire was specifically designed for clinical trials exploring the impact of weight and obesity on quality of life [45]. These will be correlated with the physical health outcomes to determine whether any physical benefit is associated with positive changes in quality of life, particularly in areas most affected by weight-related issues.

Food, Activity, and Sleep Diary Sheet

The food, activity, and sleep diary sheet will provide a descriptive overview of participants' lifestyle over the trial period and will be used to provide an indication of how well they adhered to the nonpharmacological aspect of the trial. Diary sheets will be used not only to capture individual experiences [46] but also in conjunction with the activity monitors and PA dashboard to provide an indication of how well the patient engaged with the program. This can then be correlated with the primary physical health outcome of BMI. Although this will be descriptive, it will provide an indication of the adherence of the patient to a quality lifestyle.

Activity Monitoring Tool and Wearable Tracking Devices

Patients will wear these for 7 days (24 hours per day) every 3 months to monitor their ongoing PA. The data will be downloaded and stored on the participant master log. This will then be correlated with changes in physical health to determine, for example, whether weight loss is associated with an overall increase in PA and exercise. These devices will also monitor sleep patterns and will correlate with patient self-reported sleep in the food, activity, and sleep diary sheet. While these devices will be used to monitor PA, they will also be used as an additional tool to improve BMI and PA as their effectiveness in promoting a healthy lifestyle has been demonstrated in previous lifestyle interventions [47].

Interviews

Barriers, facilitators, acceptability of the intervention, and potential benefits of the nonpharmacological element will be also explored qualitatively via semistructured interviews from both the patient and staff perspectives. Interviews will be conducted and analyzed by KB, a PhD student.

All additional secondary outcome measures are outlined in a Gantt chart (Table 1) together with a timeline of the interviews. In addition to these, PA data are also routinely collected within the hospital and will be extracted by the business intelligence team and aggregated into weekly figures retrospectively.

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Table . Schedule of additional secondary outcome measures and interviews.

Outcome measures and interviews	Year 1 (month)													Year 2											
	0	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12
COEQ[a]	✓		✓		✓			✓							✓					✓					✓
LFPQ[b]	✓						✓						✓						✓						✓
IWQOL-Lite-CT[c]	✓			✓			✓			✓			✓			✓			✓			✓			✓
Actigraph leap				✓			✓			✓			✓			✓			✓			✓			✓
FAS[d] diary sheet	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Patient interviews	✓							✓					✓												✓
Staff interviews													✓												✓

[a]COEQ: Control of Eating Questionnaire.

[b]LFPQ: Leeds Food Preference Questionnaire.

[c]IWQOL-Lite-CT: Impact of Weight on Quality of Life–Lite–Clinical Trials Version.

[d]FAS: food, activity, and sleep.

Statistical Analysis

All outcomes will be analyzed to evaluate the effectiveness and feasibility of the study. As the primary objective is to investigate changes in physical health metrics from baseline until the final follow-up, repeated-measure ANOVA will be used to carry out a multivariate analysis to determine the potential interrelationship between the different variables. Differences in weight change will be assessed using percentages. Changes in various metabolic syndrome components will be assessed using paired 2-tailed *t* tests and Wilcoxon signed-rank tests.

Subgroup analyses will also be carried out to determine whether the nature of a patient's pretreatment physical health history (diabetes status), their demographic data (biological sex, age, and ethnicity), and their clinical data (primary and secondary diagnosis) impacted their likelihood of responding to semaglutide therapy.

Correlation analysis will be used to identify patterns within the data and specifically to explore the relationship between the level of PA and exercise, appetite, and quality of life and physical health outcomes.

Thematic framework analysis, which is often used in applied research [48], will be used to analyze qualitative data. Through this method, data will be organized and interpreted systematically; therefore, meaningful insights will be identified. Initial codes will be generated from the transcripts to capture meaningful units of data related to barriers, facilitators, and acceptability. Codes will be organized into broader themes and subthemes through iterative review and comparison. Themes will represent patterns and recurring topics across the data. Themes will be interpreted in relation to the research questions, aiming to provide insights into factors influencing the intervention's implementation and acceptance among patients and staff. The analysis will be conducted by a PhD student, KB, but will be reviewed and discussed with the supervisory team.

Oversight of the Study

The SSG will meet on a regular basis to oversee the progress of the study and act as study monitor. Responsibilities include

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reviewing adverse events and protocol deviations and considering the implications and identifying changes that may be required.

The SSG is responsible for providing updates to the hospital medical advisory committee and the medicine management group.

Ethical Considerations

All data collected as part of this study will be stored securely in a password-protected SharePoint 365 folder accessible only to authorized members of the research team. No personal identifiers will be collected or stored alongside the research data; instead, each participant will be assigned a unique study ID to ensure confidentiality. Interviews will be fully anonymized during transcription. Transcription will be undertaken by the researcher, and audio recordings will be permanently deleted immediately after the transcript has been completed and verified for accuracy. Participant privacy will be protected throughout the research process, and no information that could directly or indirectly identify participants will be included in any publications or reports arising from the study. No compensation or financial incentives will be provided for participation in this study. This project has been approved by the National Health Service Research Ethics Committee (Integrated Research Application System 336454), St Andrew's Healthcare Service Evaluation and Research Approval Committee (2024/254), and the Loughborough University Ethics Committee (2024-19540-21442). It was registered on December 20, 2024, as a clinical trial on ClinicalTrials.gov (NCT06754163). Written consent will be obtained from participants by a team member before enrolling in the study.

Results

As of April 2025, a total of 15 participants have been enrolled of the target sample size of 20. The results of the study, which are projected to be obtained by mid-2027, will be shared internally within the hospital where the study is being conducted and will also form part of a PhD thesis. Key stakeholders will receive a short summary of the findings, and all participants are given the option to request the findings of the study in the consent form. Additionally, this study will be submitted to a peer-reviewed academic journal and will also be presented at relevant academic conferences and shared via social media where appropriate.

Discussion

People with complex mental health conditions being treated in hospitals include patients who are prescribed antipsychotic medications, which can lead to obesity. Many of these individuals have developed or are at risk of developing T2D, a condition that can reduce the life span. The aim of this study is to explore the effectiveness of semaglutide, one of the GLP-1 RAs, in combination with a lifestyle intervention in promoting weight loss and improving metabolic outcomes among individuals with obesity or overweight and SMI who are residing in a psychiatric setting. Specifically, this study seeks to explore whether clinically meaningful reduction in body weight and improvement in other physical health outcomes, such as waist circumference, BMI, blood pressure, resting heart rate, and blood cholesterol, can be achieved for inpatients treated with clozapine or olanzapine. It is anticipated that treatment with semaglutide in combination with a lifestyle intervention will be associated with weight loss and improve other physical outcomes.

It is expected that the findings of this study will be consistent with previous findings in the literature. Clinical studies have shown that semaglutide reduces energy intake; increases feelings of satiety, fullness, and control of eating; reduces feelings of hunger and frequency and intensity of cravings [49]; and reduces the preference for high-fat foods [35]. In addition, the drug has been shown to reduce fasting blood glucose by stimulating insulin secretion and lowering glucagon secretion when blood glucose is high [41,50], which is crucial for preventing complications associated with hyperglycemia [51]. The efficacy and safety of semaglutide for weight management in combination with a behavioral intervention focused on reducing calorie intake and increasing PA has already been evaluated in various STEP trials [32]. Compared with placebo, treatment with semaglutide demonstrated to be effective and clinically meaningful for those who had at least one weight-related comorbidity without T2D [33]. A weight-related comorbidity refers to another medical condition that developed because of excess adiposity in individuals with obesity, such as T2D, obstructive sleep apnea, increased vascular mortality, and cancer [52]. In the STEP trials that excluded participants with T2D, eligible participants had conditions such as dyslipidemia, obstructive sleep apnea, hypertension, or cardiovascular disease [13]. In addition to reduced weight, treatment with semaglutide also significantly improved waist circumference, cardiovascular functioning, and physical functioning compared to placebo [34]. The efficacy of semaglutide was demonstrated regardless of race and ethnicity, age, sex, baseline body weight, BMI, presence of T2D, and level of renal function [53]. All patients were on a reduced-calorie diet and an increased-PA program throughout the STEP trials in addition to having access to individual psychological counseling to help them adhere to the regimen.

While the results of the STEP trials demonstrated the effectiveness of treatment, this was limited to the general population. Given the limited evidence of its effectiveness also in individuals with SMI, there is a need to extend such evidence to a population within a psychiatric setting due to the life span inequity they experience.

It is anticipated that the findings of this study will inform clinical guidelines for health care professionals in managing obesity in people treated with antipsychotics in a secure care setting, ultimately improving their quality of life. Therefore, it is expected that semaglutide will prove its effectiveness as an adjunctive therapy to address obesity in such settings. Additionally, this study aims to contribute to the development of a multicomponent lifestyle intervention for weight management in a secure mental health setting, enhancing the effectiveness of therapeutic treatments while minimizing the side effects of antipsychotic drugs.

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While the use of a mixed methods design combining robust quantitative measures with qualitative insights and the length of the study duration are the real strengths of this study as they allow for a comprehensive evaluation, several limitations must also be acknowledged. The study sample is relatively small and was recruited from only 1 mental health hospital, which may limit generalizability. However, this study aims to assess the feasibility and efficacy of the treatment rather than provide conclusive claims. The use of a single-arm design is another limitation of the study as it is difficult to assess whether the results are due to the treatment with medication or the lifestyle intervention. However, this will be further explored qualitatively.

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Data Availability

As this is a study protocol, no data are currently available. Data sharing is therefore not applicable to this article as no data sets were generated or analyzed.

Authors' Contributions

KB contributed to study conception and study design and drafted the manuscript. FK, JK, LM, and KCB contributed to study conception and study design and substantively revised the manuscript. KCB is the chief investigator of the study. DA, EH, MH, AS-R, MO, NR, and PS contributed to study conception and study design. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AIWG: antipsychotic-induced weight gain
PA: physical activity
RA: glucagon-like peptide-1 receptor agonist
RC: responsible clinician
SMI: severe mental illness

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SSG: study steering group
STEP: Semaglutide Treatment Effect in People With Obesity
STEP@STAH: Semaglutide Treatment Effect in People With Obesity intervention protocol modified for a secure mental health setting
T2D: type 2 diabetes

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Enhancing Access to Family Planning Services in Uganda Through Community Health Extension Workers: Protocol for a Pilot Evaluation

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Abstract

Background: In Uganda, 22% of all women of reproductive age have an unmet need for family planning services. Access to contraceptive services, especially long-term reversible contraceptives such as implants, remains a challenge. The number of trained health providers is also not sufficient to address the needs for contraception. The Uganda Ministry of Health implemented a community-based implant provision pilot project where community health extension workers (CHEWs) were trained and accredited to insert implants at community level.

Objective: This study aims to evaluate the implementation and acceptability of stakeholders toward task shifting the provision of family planning implants to CHEWs in Uganda.

Methods: The evaluation will use a cross-sectional design using both quantitative and qualitative methods. The quantitative component will use a noninferiority design, whereas the qualitative component will use a descriptive approach. The noninferiority design involves a comparison of the competence of the currently authorized cadre to offer the service to the proposed cadre (CHEWs). Compared with a randomized controlled trial, the noninferiority design is more appropriate for this evaluation because the CHEWs and the authorized cadre are not comparable in terms of level of training and competencies. The authorized cadre has gone through formal training, which is not comparable with the training the CHEWs have received, and so the comparison is such that the competencies of the CHEWs are noninferior or at most equal to the competencies of the authorized cadre. Quantitative data will be collected among 92 CHEWs and 92 qualified health workers using performance assessment checklists and practice-based questionnaires that were developed based on the training manuals. Competency will be measured on a continuous scale and summarized as mean (SD) scores. Qualitative data will be collected through key informant interviews (n=23), in-depth interviews (n=24), and focus group discussions (n=18). Qualitative data will be analyzed using thematic analysis following the framework method for the analysis of qualitative data using ATLAS.ti (version 9).

Results: Preliminary findings indicate improved confidence and capacity of community health workers to provide implants despite challenges such as poor waste disposal, record keeping, and data management. By August 2025, training of research assistants had been concluded, and data collection had started. We anticipate that the data collection will be completed by the end of October 2025, the data analysis will be completed by November 2025, and the final results will be published by December 2026.

Conclusions: This pilot will generate contextual information that can be used to improve access to family planning services at the community level.

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KEYWORDS

community health workers; contraceptives; family planning; Uganda; evaluation; protocol; reproductive health

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Introduction

Background

The Sustainable Development Goals target 3.7 aimed to achieve 75% of the global demand for contraception by 2030 [1,2]. However, many women of reproductive age might never get access to quality contraceptive services and commodities for reasons such as insufficient information about available methods, stigma [3], shortage of family planning commodities, and few adequately trained health providers. A modeling study estimated that the global prevalence of modern contraceptive use among 1.9 billion women of reproductive age increased from approximately 55.0% in 2000 to 57.1% in 2019 [4]. However, the study also noted that approximately 164 million women of reproductive age still face unmet need for family planning and that Sub-Saharan Africa experiences a disproportionately higher proportion of women with an unmet need for family planning (23.1% [5]) compared with other regions such as Asia and Latin America, where the unmet need is approximately 10% [4].

In many low- and middle-income countries, the number of trained health providers is not sufficient to address the need for contraception [6,7]. In addition, less than half of the available trained health workers serve rural areas, where a significant proportion of the population resides [7,8]. To address this challenge, the World Health Organization acknowledges task shifting as an innovative approach to promote and accelerate equitable access to care, especially in low- and middle-income countries. It is defined as "the rational redistribution of tasks among health workforce teams," where tasks are moved, transferred, or delegated, as appropriate, from trained and qualified health workers to other health workers with shorter training and fewer qualifications [8], to make more efficient use of the available human resources for health and improve service access.

In 2010, Uganda developed ambitious goals and targets for the transformation of its people and the achievement of a modern and prosperous society as per Vision 2040. Between 2010 and 2040, the country aimed to reduce the maternal mortality rate from 336 to 15 deaths per 100,000 live births, increase modern contraceptive prevalence rates from 35% in 2016 to 50% in 2030, and reduce unmet need for family planning from 28% in 2016 to 10% by 2030 [9]. To achieve these targets, various strategies have been instituted, including scaling up self-care and task shifting through engaging community health extension workers (CHEWs) to support service access and increase family planning uptake at the community level.

Community-Based Implant Provision Project

The Uganda Ministry of Health developed a CHEWs strategy to support the achievement of the ambitious Vision 2040 and the 2030 Sustainable Development Goals targets. The objective of the strategy is to competently train and launch a cadre of health care providers, known as CHEWs, to deliver quality, preventive, promotive, and selected basic curative health services at the community level, including providing contraceptives.

The Uganda Ministry of Health implemented a pilot community-based implant project, which involved training CHEWs to provide long-acting reversible contraceptives. Specifically, CHEWs were trained to insert family planning implants and refer clients who needed services of removing the implants to health facilities. This approach has previously been tested in Ethiopia [10] and Nigeria [11]. However, there is a need to generate context-relevant evidence in Uganda to support the community-level provision of implants, even as global health stakeholders advance task shifting and sharing [12,13], community-based service delivery, and self-care for sexual and reproductive health.

The community-based implant provision project was piloted in Lira City, Kyotera, and Namutumba districts in Uganda. All CHEWs in the aforementioned districts underwent additional training specific to family planning focused on implant insertion. The additional training focused on implant provision and was designed to equip the CHEWs with knowledge, skills, and clinical competencies to provide Implanon NXT (Organon Pharma Limited) insertion as well as appropriate referral for implant removal. The training on implant insertion was provided for 8 days, with 4 days of classroom-based learning and 4 days of facility-based practicum. The training was delivered by national-level trainers using a training manual developed by the Uganda Ministry of Health. After successful training, the CHEWs were accredited and deployed at their immediately supervising health facility to conduct implant insertion services. By the end of the training, the CHEWs were expected to have acquired knowledge and demonstrate the following clinical competencies: (1) provide effective client counseling sessions addressing concerns and misconceptions, for informed choice and obtain consent from at least 3 to 5 women, (2) perform comprehensive client screening and medical eligibility for Implanon NXT, (3) prepare the insertion site, (4) perform Implanon NXT insertion in 5 clients using correct techniques, (5) provide clear postinsertion care instructions to 5 clients, (6) manage clients with family planning–related side effects and provide appropriate referral pathways (optional), (7) accurately and appropriately record the family planning services provided in family planning registers and client cards (5 records), and (8) maintain a safe and sterile environment during 5 procedures.

The project was facility-based, whereby CHEWs were stationed at their supervising facilities within their communities. During the duration of the intervention, the CHEWs worked alongside and were supervised by health workers to offer Implant NXT contraception to any woman who required it, was eligible, and consented. The CHEWs were then accredited to offer the services independently.

General Objective

The overall objective is to evaluate the implementation of a community-based implant intervention to inform efforts aimed at task shifting the provision of long-term reversible family planning methods in Uganda.

Specific Objectives

The specific objectives of the study are to (1) explore the perceptions of the stakeholders toward implant provision task

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shifting to the CHEWs (stakeholders including the CHEWs, clients, health workers or professionals, and policymakers), (2) assess the acceptability of the community-based implant insertion by CHEWs among the stakeholders (health workers at the facility and family planning clients in the community), and (3) determine the competence of the CHEWs regarding insertion of implants following training.

Methods

Study Site

The evaluation will be conducted in 3 pilot districts in the regions of East (Namutumba), North (Lira Municipality), and South (Kyotera) (Figure 1). These districts were selected because training and certification of the CHEWs have been completed and the electronic Community Health Information System has been rolled out.

Figure 1. A map of Uganda showing the districts included in the community-based implant project.

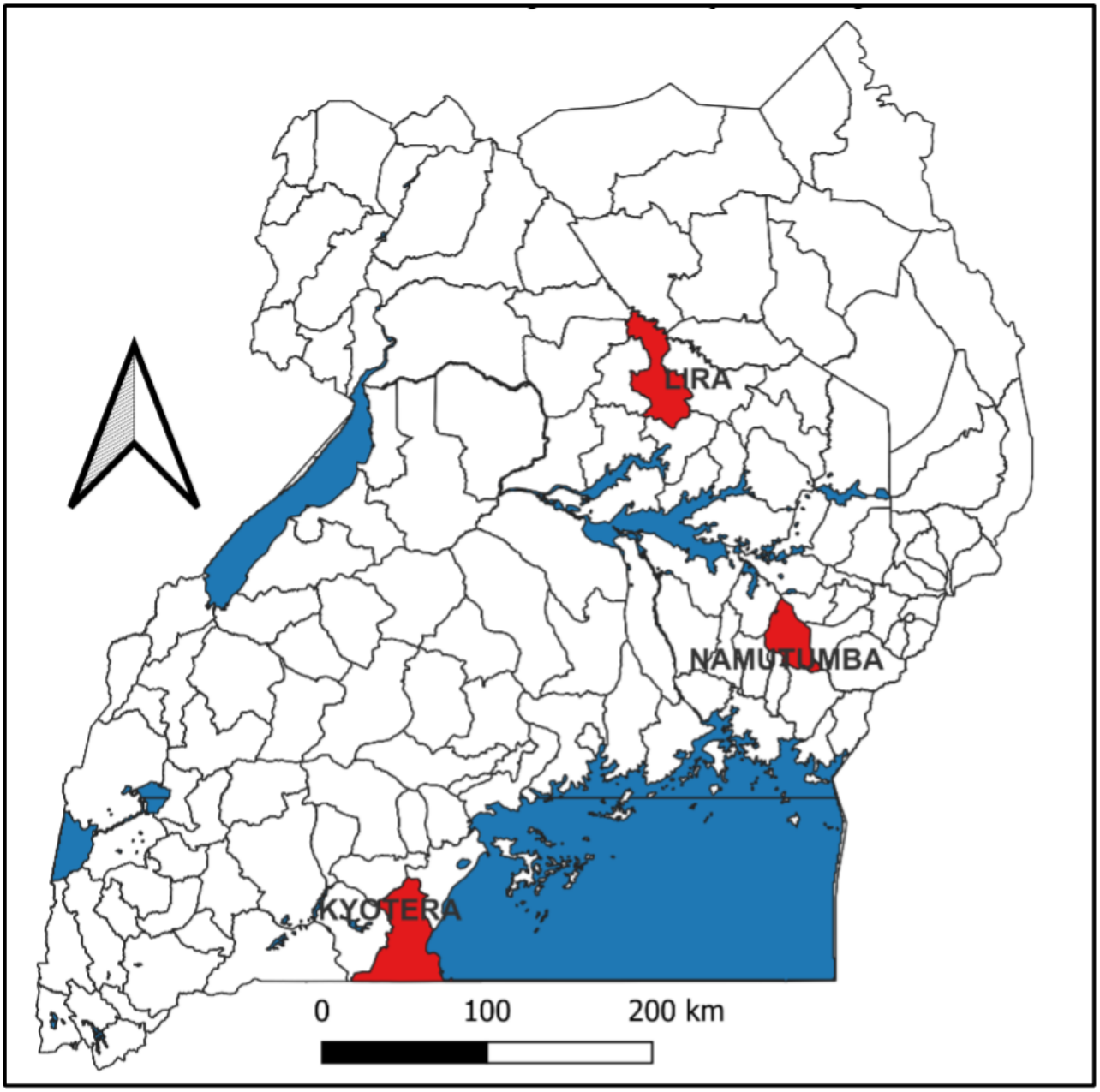

Study Design

The evaluation will use a convergent parallel mixed-method cross-sectional design using both quantitative and qualitative methods. The quantitative component will use a noninferiority design [14]. This involves a comparison of the competence of the currently authorized cadre to offer the service to the proposed cadre (CHEWs). The noninferior design is methodologically more rigorous than pre-post designs that have been used for assessments in previous studies [10,11].

The qualitative component will use the descriptive qualitative study approach. The descriptive qualitative study approach is an emerging approach that has been used in health care research to understand or identify participants' experiences and

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perceptions [15] of the intervention or why the intervention worked or did not work and how the intervention might be improved [16].

Study Population

The study population will include trained CHEWs, clients, health workers, program managers, and policymakers.

Inclusion Criteria

The evaluation will include CHEWs who were trained and engaged in implant insertion as well as health workers who were engaged in the intervention as either trainers or supervisors of the CHEWs. Health workers engaged in the provision of long-term reversible family planning or those at the policy level at the national and district levels will also be included. The evaluation will also include clients defined as women of reproductive age who have obtained family planning services provided by CHEWs. To obtain perspectives from spouses of family planning users, men who are aged ≥18 years and in a relationship or union with a woman will also be included in the evaluation.

Exclusion Criteria

Critically ill clients or those deemed unable to answer questions due to living with cognitive disabilities will be excluded. All potential respondents who refuse to respond or do not consent, or those who will not be available during the duration of the study, will be excluded.

Sample Size Estimation

Quantitative Data

Sample Size Estimation: Noninferiority Design

CHEWs will be assessed on their competency to insert implants, under some domains with corresponding items, following training in the selected districts. The assessment of the competency of the CHEWs will be compared to the competency of the qualified health facility providers in the cadre currently authorized to insert implants. Competency will be measured on a continuous scale and summarized as mean (SD) scores. The competency of CHEWs should not be *worse than* that of the authorized cadre, within a margin of acceptable difference ($-d_{NI}$), accounting for the mean (SD) score competency of authorized cadres (μ_B) and that of CHEWs (μ_A), and a 1-sided test.

We assumed an SD (σ^2) of the competency scores, and the noninferiority limit ($-d_{NI}$) was set at −10. At a power of 90% and 1-sided 95% CI, this resulted in a total of 138 participants (69, 50%, cadres authorized to provide implants and 69, 50%, CHEWs) needed to demonstrate that there is truly no difference between the competency of the cadres authorized and the trained CHEWs. We adjusted for a nonresponse rate of 10% and a design effect of 1.2 because multiple CHEWs selected from similar settings and cadres authorized selected from the same health facilities observations will be correlated. This adjustment will result in a minimum of (138×1.2)/0.9=184 (92 CHEWs and 92 authorized cadres).

Compared with a randomized trial, the noninferiority design is more appropriate for this evaluation because it would be a false assumption to randomize participants to receive the service by the CHEWs or the authorized cadre because the 2 groups are not comparable in terms of level of training and competencies. The authorized cadre has gone through formal training, which is not comparable with the training the CHEWs have received; therefore, the best approach for any comparison is such that the competencies of the CHEWs are noninferior or at most equal to the competencies of the authorized cadre.

Qualitative Sample

The qualitative approach will be used to obtain data on perceptions and acceptability of the intervention among stakeholders. Qualitative data will be collected using focus group discussions (FGDs), in-depth interviews (IDIs), and key informants. A minimum of 6 FGDs will be conducted among men in relationships and among women of reproductive age, giving a cumulative total of at least 18 FGDs across all districts. Each FGD will comprise 7 to 9 participants. In each district, we will also conduct a minimum of 5 IDIs among CHEWs and 4 among clients. This gives a cumulative minimum total of at least 24 IDIs. In addition to the IDIs, we will conduct 5 key informant interviews (KIIs) per district involving health managers such as the district health officer, assistant district health officer in charge of maternal and child health, as well as health facility managers and supervisors. This will give a cumulative minimum total of at least 15 KIIs. An additional 8 KIIs will be conducted at the national level to obtain views from program managers and policymakers. However, data will be collected based on the concept of saturation.

Sampling Procedure

CHEWs and Authorized Cadre: Noninferiority Design

Simple random sampling with replacement will be used to sample CHEWs to observe in each district. In each district, we will construct a sampling frame comprising all trained CHEWs. Simple random sampling (using a Microsoft Excel random number generator) with replacement will be used to identify individual CHEWs that will be observed. The authorized cadre will be selected using a similar approach. Where the number of authorized cadres is smaller than the estimated sample size, we will recruit from neighboring districts because the competence of the authorized cadre should not be dependent on the place where the health worker provides the services.

Qualitative Sample

Purposive sampling will be used to identify key stakeholders engaged in family planning activities within the selected districts and at the national level. The respondents will be selected based on their knowledge and experience in offering family planning services. In total, we plan to conduct approximately 65 interviews across the selected intervention districts.

Study Variables

Acceptability of the Community-Based Implant by CHEWs Among the Communities

Acceptability will be measured based on the constructs of the theoretical framework of acceptability [17]. These constructs include (1) affective attitude: how the stakeholders feel about

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the intervention; (2) burden: the perceived amount of effort that is required to participate in the intervention; (3) ethicality: the extent to which the intervention aligns with an individual's value system; (4) self-efficacy: the participant's confidence that they can perform the behaviors required to participate in the intervention; and (5) intervention coherence: the extent to which the participant understands the intervention and how the intervention works.

Perceived Effectiveness

Perceived effectiveness is the extent to which the intervention is perceived to be likely to achieve its purpose, and the opportunity costs refer to the extent to which benefits, profits, or values must be given up to engage in the intervention.

Perceptions of Community Members Toward the Use of CHEWs to Insert Implants

This is a qualitative variable. We will focus on both positive and negative opinions. We will analyze for convergence and divergence of perceptions.

Perceptions of Programmers and Policymakers Toward the Implant Provision Task Shifting to the CHEWs

This is a qualitative variable. We will generate both positive and negative opinions about how the stakeholders perceive the idea of task shifting implant provision to the CHEWs.

Competencies of the CHEWs to Insert Implants

We will measure the clinical competencies around implant insertion using an observation checklist. One observation will be made for each CHEW. For each CHEW, we will observe the process from counseling before the implant is inserted until the end, including postinsertion counseling. For each observable item, the CHEW will be marked as having performed the task as satisfactory, unsatisfactory, or not done. Satisfactory will mean that the step or task has been efficiently performed in its proper sequence or individually, unsatisfactory will mean that the task was not performed correctly or in sequence, and not done will mean the task was omitted or not performed, yet it was necessary. Satisfactory will fetch a mark, unsatisfactory will fetch 0.5, and not done=0. CHEWs will be considered competent if they score 80% and above.

Data Collection Methods

Quantitative Data Collection

The quantitative data will be collected through observations among CHEWs and authorized cadres inserting implants as part of the noninferiority assessment. The observation data will be collected using an observation checklist that was developed based on the implant insertion curriculum. The observation data will be used to quantitatively assess competence during the insertion of implants.

Qualitative Data Collection

Key Informant Interviews

KIIs will be conducted among health workers engaged in the intervention as either trainers or supervisors of the CHEWs, as well as representatives of organizations engaged in provision of long-term reversible family planning. Additionally, those at the policy level, such as district health officers and family planning experts at the Ministry of Health, will be included.

Focus Group Discussions

FGDs will be conducted among CHEWs to elicit opinions and perceptions about engaging CHEWs in implant insertion. Additional data about the acceptability of the intervention will also be collected using this approach. The FGDs will comprise 7 to 9 participants. Data will be collected using an FGD guide. Data will be collected in the predominantly spoken local languages, specifically Lango (Lira), Luganda (Kyotera), and Lusoga (Namutumba). All discussions will be audio recorded after obtaining consent.

In-Depth Interviews

IDIs will be conducted with CHEWs engaged in the intervention and clients who have had implants inserted by the CHEWs. These interviews will focus on getting individual insights, opinions, and perspectives about the acceptability, feasibility, and quality of services received. They will also generate insights into the experiences during the procedure. The IDIs will be conducted using in-depth guides that have been translated into Langi, Luganda, and Lusoga after obtaining informed consent.

Data Management

Quantitative Data

Quantitative data will be collected on smartphones using electronic questionnaires programmed with Open Data Kit software. Back-to-back encryption will be implemented to protect the respondents' data. A routine data quality assessment check will be carried out on a daily basis. The IT administrator will check the data received at the server for extreme values, incompleteness, and incorrectly entered fields. A report will be generated based on these findings and immediately communicated to the regional team leaders through the survey coordinator. The final datasets will be uploaded to MakSPH's secure and password-protected server after cleaning. The data manager and IT administrator will download data from the server and export it to R Software (R Development Core Team) for analysis after necessary cleaning.

Qualitative Data

All audio interviews will be transcribed verbatim from the local language to English. In cases where the participants turn down the request to audio record the discussions or interviews, notes will be taken and expanded immediately to enrich the transcripts.

Data Analysis

Quantitative Data Analysis

Quantitative data will be cleaned and analyzed using STATA (version 15), through univariate, bivariate, and multivariate analyses using appropriate statistical tests. For example, the chi-square test for independence will be used to assess whether CHEWs differ from the authorized cadre in the performance of specific tasks involved in the process of inserting implants. The chi-square test is computed based on the null hypothesis that the proportion of CHEWs who perform a specific task is equal to the proportion of the authorized cadre who perform that task. This hypothesis is rejected at a P value of .04. The chi-square

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test statistic is also computed with the assumption that all observations are independent, and therefore, the analysis will control for factors such as the observer, the health facility, and the district that might cause dependence or clustering of observations. Findings will also be presented as proportions, in tables and figures, odds ratios or prevalence ratios, and *P* values at a 95% confidence level.

Qualitative Data Analysis

Thematic content analysis techniques will be done using ATLAS.ti software (version 9). The transcripts will be analyzed using a thematic approach following the framework method for the analysis of qualitative data, where data will be compared and contrasted by themes. Thematic network analysis will allow for the generation of relevant themes. Transcripts will first be coded by a multidisciplinary team that includes members with expertise in public health, social sciences, and medicine. Initial codes will be discussed and refined into a working analytic framework during in-person meetings. Later, the initial codes will be applied to all transcripts while allowing new codes to emerge, leading to a final framework that will be agreed upon by the research team. The final framework will be used to develop categories and subsequently themes. The same codebook will be used at the different data analysis time points to allow the team to compare and draw conclusions at the different data collection points.

Ethical Considerations

Overview

Ethical approval was provided by the Makerere University School of Public Health Higher Degrees Research Ethics Committee (approval number SPH-2024‐291). The evaluation protocol was also registered with the Uganda National Council of Science and Technology prior (registration number HS5966ES). We also obtained administrative approval from the respective district local governments before conducting any study procedures.

Voluntary Participation

All participants will be informed of the purpose of the study, their right to refuse to participate in the study, and their possible decision not to participate will not be held against them or affect their status (eg, as employees, partners, or beneficiaries). Participants will be enlisted on the basis that they can understand the principles of their involvement in the study, give consent or assent, engage with the study team, and show a willingness to freely express their experiences and opinions.

Written Informed Consent

All prospective participants will provide written informed consent before engaging in any study activities. This consent process will involve provision of detailed information on risks, benefits, confidentiality, and the purpose of the research and the voluntary nature of the survey. Participants will be given an opportunity to ask any questions they may have before signing the form.

Confidentiality

To ensure privacy and confidentiality, all interviews will be held in private locations. No identifiable data, such as names, ages, addresses, and contact information, will be collected by the research team. All quantitative data will be collected via password-protected tablets that will be transferred to a password-protected server after data collection daily. All final data will be presented only in aggregate to protect confidentiality and safety.

Results

By August 2025, research assistants who will support the data collection had been trained. Preliminary findings indicated support from facility health workers, which improved confidence and capacity of community health workers to provide implants. Challenges included lack of facilities for waste disposal and lack of tools for record keeping and data management. We anticipate that the data collection will be completed by the end of October 2025, the data analysis will be completed by November 2025, and the final results will be published by December 2026.

Discussion

Anticipated Implications

We will discuss the findings and their implications for improving access to family planning services at the community level. We anticipate that in general, the competence of CHEWs in insertion of implants will not differ significantly from that of the authorized cadre. We will compare how task sharing has been used for other service delivery, such as community case finding during integrated management of childhood illnesses, to identify lessons to inform family planning provision. For example, policymakers in Kenya noted concerns about the policy framework within which community health workers can distribute drugs at the community level and how this might affect the delivery of vertically oriented programs [18]. Conversely, task shifting in maternal and child health service delivery has the potential to reduce the workload on authorized cadre to spend more time on tasks that require more advanced training [19].

We will also compare our findings with similar approaches in Burkina Faso [20], Kenya [21], Ethiopia [10], Ghana [22], and Nigeria [11]. In Burkina Faso, health providers, community representatives, government officials, and clients were generally agreeable with the idea of implants being provided by trained community health workers [20]. However, community health workers in Burkina Faso were trained to provide several family planning options in addition to the implants. In Kenya, 95% of 434 respondents agreed that task sharing can increase and expand access to family planning services. It was found to benefit both clients and health service providers, particularly where the community health workers were provided with training, support supervision, and conducted within the requisite policy environment [21]. Similarly, qualitative findings from Ghana revealed that community health nurses could provide safe intrauterine devices to clients if they were well trained and

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provided with the requisite resources and technical support supervision [22].

Findings will also be compared with other studies that used similar noninferiority designs that assessed for safety, quality, and acceptability of community health workers providing the implants in rural settings [23]. We will also discuss other factors to be considered before scale-up, such as the influence of the fact that the services are provided by CHEWs on cost, method choice, and uptake [24], and the broader impact on health system performance [25].

Methodological strengths and limitations will also be discussed to inform future research.

Strengths and Limitations

This study has several strengths and limitations. The study applies a noninferior design, which is methodologically more rigorous compared with pre-post designs that have been used for assessment in previous studies [10,11]. In addition, the study uses a convergent parallel mixed methods design, which allows for the collection of both quantitative and qualitative data to reinforce each other. The limitations are the risk of clustering of observations around factors such as the district, the health facility where observations are made, and the observers making the observations. However, we will adjust for clustering in the quantitative analysis.

Dissemination Plan

Findings will be disseminated to the districts where the study took place, the Ministry of Health, and other stakeholders to inform scale-up. Findings will also be disseminated to the scientific community through abstracts and scientific manuscripts.

Acknowledgments

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Disclaimer

No generative artificial intelligence tools were used in the preparation of this manuscript.

Data Availability

The datasets generated or analyzed during this study will be available from the corresponding author on reasonable request by writing an email to the corresponding author.

Authors' Contributions

Writing – review & editing, methodology, project administration: LK; Writing – original draft, methodology, supervision: SNK; Investigation, methodology, supervision: FK; Conceptualization, funding acquisition, investigation, supervision, writing – review & editing: RA; Methodology, project administration, supervision, writing – review & editing: AT; Methodology, supervision, writing – review & editing: SN; Methodology, investigation, funding acquisition, writing – review & editing: CKN.

Conflicts of Interest

None declared.

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Abbreviations

CHEWs: community health extension workers
FGD: focus group discussion
IDI: in-depth interview
KII: key informant interview

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Life Course Trajectories for Young Pasifika in Aotearoa: Protocol for the 25-Year Follow-Up of the Pacific Islands Families Study Cohort

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Abstract

Background: From birth, many young Pacific people in Aotearoa New Zealand experience a disproportionately high burden of psychological distress, metabolic disease, and socioeconomic disparities within education and employment which contribute to significant health inequalities. Further research is needed to understand the drivers influencing these outcomes.

Objective: This paper provides a comprehensive overview of the quantitative component of the Pacific Island Families Study: Ala mo Tupulaga Pasifika Aotearoa (PIF:ATP; Life Course Trajectories for Young Pasifika in Aotearoa), the latest follow-up of the longitudinal PIF birth cohort study, which uses a mixed-methods approach.

Methods: The PIF Study is a multidisciplinary longitudinal study that tracks the health and development of 1398 Pacific children born in 2000 at Middlemore Hospital, South Auckland, Aotearoa, New Zealand. Data collection has occurred at 10 time points from infancy through young adulthood, with this PIF:ATP assessment phase occurring at ages 25 - 26 years, which aims to reach at least 750 cohort members. The assessments will take place at participants' homes or at Auckland University of Technology for those residing in Auckland. Data collection will be conducted across multiple sites, including Auckland, Wellington, Hamilton, and Whangārei in Aotearoa New Zealand, as well as Brisbane, Sydney, and Melbourne in Australia. Physical measurements such as weight, height, waist and hip circumferences, grip strength, body fat mass and muscle mass, blood pressure and pulse, glucose and lipid screening, and skin carotenoid concentration will be undertaken. In addition, self-reported data will be collected on psychological well-being (eg, depression, anxiety, and family functioning), nutritional and metabolic well-being (eg, food intake and physical activity), and economic well-being (eg, educational attainment, employment status, and job occupation and industry).

Results: Data collection is scheduled to commence in June 2025 and conclude by December 2026. The first set of results and analysis is expected to be published from December 2027 onward. Reporting of all results will comply with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines.

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Conclusions: This paper presents the protocol for the 25-year follow-up of the first Pacific longitudinal cohort study, which will comprehensively examine psychological, nutritional, metabolic, and economic well-being of Pacific young adults. With 25 years of longitudinal data and extensive expertise in life course research, this protocol outlines the design, methodology, and scope of the quantitative component of the PIF:ATP research program. This phase is uniquely positioned to address key issues identified by Pacific communities and generate evidence to inform meaningful interventions and guide policy development while providing robust, contemporary, high-quality empirical evidence.

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KEYWORDS

pacific youth health; longitudinal research; life course epidemiology; determinants of health; psychological wellbeing; nutritional and metabolic wellbeing; economic wellbeing; protocol

Introduction

Background

Pacific peoples in Aotearoa, New Zealand represent a diverse mix of ethnicities and cultural groups, including migrants and their descendants from Samoa, Tonga, the Cook Islands, Fiji, Niue, Tokelau, Tuvalu, and other Pacific nations across Polynesia, Melanesia, and Micronesia. Census data reveal that 8.9% of New Zealand's population identify as being of Pacific ethnicity [1], with two-thirds of them born in New Zealand [2]. This underscores a demographic shift, with the majority of Pacific peoples now being a local rather than an immigrant population.

The New Zealand Pacific population is youthful, with more than half (58.7%) aged 29 years or younger, in contrast to the New Zealand European population, where a smaller proportion (35.9%) falls within this age range [1]. However, they experience a disproportionately high burden of psychological distress and increased risk of developing poor metabolic outcomes compared to the general population [3-8]. Additionally, they face significant disparities in tertiary education and employment, which often contribute to long-term health inequalities [9-11]. While existing evidence highlights a complex interplay of cultural, familial, and economic factors that influence health and well-being, there remains a critical gap in understanding the specific mechanisms underlying these influences and their relevance to Pacific young adults. Building on 25 years of research investment, the Pacific Island Families Study: Ala mo Tupulaga Pasifika Aotearoa (PIF:ATP) research program, which translates as "Life Course Trajectories for Young Pasifika in Aotearoa," is an epidemiologically robust study designed to explore these mechanisms as Pacific young adults navigate critical life course transitions.

The PIF Study is a multidisciplinary longitudinal investigation of the health and development of Pacific peoples in New Zealand. Beginning in 2000, the study follows a birth cohort of 1398 Pacific children born at Middlemore Hospital in South Auckland, representing one of the largest and longest-running longitudinal studies of Pacific health globally [12,13]. Data have been collected across 10 waves to date, with assessments at 6 weeks, 1 year, 2 years, 4 years, 6 years, 9 years, 11 years, 14 years, 17 years, and 22 years post partum (Table 1). The PIF Study embodies a Pacific-centered approach, initially advocated by Pacific communities, led by Pacific researchers, and dedicated to advancing Pacific health and development. This reflects a commitment to community-driven research while promoting Pacific leadership in academia.

Table . An overview of cohort follow-up and retention across measurement waves.

Informant type	6 weeks	1 year	2 years	4 years	6 years	9 years	11 years	14 years	17 years	22 years
Teacher questionnaire	—[a]	—	—	—	559	692	707	—	—	—
Child assessment	—	—	1064	909	897	891	952	931	632	471[b]
Paternal interview	—	825	757	—	591	790	646	—	—	—
Maternal interview	1376	1224	1144	1048	1001	996	1029	958	—	—

[a]Not available.

[b]The participant numbers were lower than anticipated due to significant disruptions during the data collection phase. This period coincided with Severe Tropical Cyclone Gabrielle and the Auckland Floods, which led to a national state of emergency being declared on February 14, 2023 [14].

The PIF:ATP extension now examines these participants at ages 25 - 26 years, focusing on their transition into adulthood. It uses mixed methods and multifaceted approaches, combining quantitative and qualitative data collection to capture the complexity of health and development within the Pacific context. This protocol paper only covers the quantitative element of the

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study. As in previous phases, qualitative themes will be guided by preliminary descriptive quantitative analyses which will identify potential areas of inquiry. These areas can then be explored in depth using qualitative methods, providing further insight into the underlying drivers of patterns revealed by the survey.

Following the quantitative and qualitative phases, findings will be translated into practice through collaboration with Pacific health providers, policymakers, and key stakeholders. This will ensure research outcomes inform service delivery, policy decisions, and health promotion activities for Pacific communities. While this article focuses on the quantitative aspects of the study, the overarching themes—psychological well-being, nutritional and metabolic well-being, and economic well-being—will be explored across the study's quantitative, qualitative, and knowledge translation and implementation phases.

Psychological Well-Being

Pacific peoples report high levels of life satisfaction, family well-being, and strong social connections and support from family and friends [3,15]. However, they also experience significant health and socioeconomic disparities compared to other New Zealanders. In particular, mental health inequalities are pronounced, with Pacific peoples experiencing higher rates of psychological distress, mental disorders, and suicidal behaviors [3-7,16]. These disparities represent a critical public health concern in New Zealand.

Young Pacific people face the greatest challenges, reporting the highest levels of mental distress, self-harm, and suicide mortality among all Pacific age groups [3,17-19]. Alarmingly, these disparities emerge early in life. Data from the New Zealand Health Survey show that Pacific children are more likely than their non-Pacific peers to experience emotional difficulties and behavioral problems, even after adjusting for age and sex [20]. Similarly, the Growing Up in New Zealand study—a longitudinal birth cohort study that began in 2009‑2010, involving approximately 6000 children and their families—found that, at the age of 8 years, Pacific children reported higher levels of depressive and anxiety symptoms compared to European and Asian children [21]. This disproportionate burden on young Pasifika is part of a broader "pandemic of psychological distress among youth" in New Zealand [22].

Cultural identity, sense of belonging, and engagement in cultural practices [23-26] are important drivers of psychological well-being among Pacific peoples. However, some inconsistent findings warrant further investigation. For instance, mothers who maintained strong connections to their Pacific culture but a relatively weak connection to mainstream New Zealand culture (Separators) or who engage with both Pacific and New Zealand culture (Integrators) exhibited elevated depressive symptoms relative to those who either adopted the mainstream New Zealand culture and relinquished their Pacific culture (Assimilators) or were culturally disengaged (Marginalists) [27]. Interestingly, another PIF Study analysis revealed contrasting patterns: in unadjusted analyses, Marginalists showed significantly greater odds of mental disorder symptoms than Integrators, while Separators demonstrated significantly lower odds. However, after statistical adjustment, these odds were nonsignificant, suggesting confounding [25]. Nonetheless, these discrepancies highlight the need for additional studies to better understand the complex relationships between cultural identity and mental health outcomes in Pacific populations.

Family functioning, such as parent-child relationships, parenthood, and intergenerational cultural differences, also plays a critical role in shaping mental health outcomes. Findings from the PIF Study reveal that Pacific children who report strong relationships with their parents, and whose parents demonstrate high levels of positive parenting, experience significantly lower rates of depressive symptoms [26,28]. However, findings from the New Zealand Mental Health Monitor and Health and Lifestyles Survey underscore that stigma surrounding mental health remains a significant issue within Pacific communities [3]. Qualitative research with Tongan youth revealed concerns that traditional interpretations of mental distress, commonly held by family and community members, often perpetuate shame and stigma [29]. Despite these insights, the interplay between individual, familial, societal, and structural determinants of Pacific mental health remains poorly understood. Further research is needed to disentangle these factors and better inform culturally responsive interventions [22].

Nutritional and Metabolic Well-Being

Nutrition-related noncommunicable diseases (NCDs), such as obesity, type 2 diabetes, and heart disease, are major health concerns for Pacific communities in New Zealand and across the Pacific region [30,31]. Findings from the PIF Study show that the cohort has experienced rapid weight gain, with more than 70% classified as overweight or obese by the age of 14 years [8]. Many also exhibit early signs of metabolic risk, increasing their likelihood of developing NCDs later in life [32]. As an example, there is increasing evidence suggesting that elevated serum uric acid in children and adolescents is a risk factor for type 2 diabetes, hyperuricemia, gout [33,34], cardiometabolic diseases [35], and metabolic syndrome [36] later in life. Results from a nested study of a subsample of PIF Study cohort members (n=204) at the age of 14‑15 years showed that these children have high serum uric acid levels with a positive association between appendicular skeletal muscle mass and serum uric acid in both sexes [37].

Childhood physical growth and weight gain are shaped by a complex interplay of factors, including parental perceptions, cultural influences, gender, acculturation, and environmental conditions [38,39]. For example, nutrition and metabolic health outcomes among Pacific youth can be moderated by family and cultural factors, such as the positive impact of parental education on children's BMI [40] and the negative impacts of food insecurity on body composition [41] and educational achievement [42]. However, how these childhood determinants translate into adult health outcomes remains unclear.

As the PIF Study cohort transitions into adulthood, they continue to face significant challenges related to food intake and metabolic health. Earlier findings from the PIF Study found food purchasing decisions of mothers are driven more by expiry dates, cost, and perceived palatability rather than by food

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labeling or nutritional knowledge [43]. At the age of 14 - 15 years, the majority consumed sugary drinks more than twice daily, and 75% reported consuming sugar-containing foods at least 4 times per day [37]. A better understanding of how Pacific youth navigate food literacy and food security, particularly amid rising living costs, is essential. These findings suggest that existing public health messaging may not be effective in influencing healthier food choices among Pacific youth.

While food intake and eating behaviors play a crucial role in shaping long-term health outcomes, physical activity and sedentary behaviors during childhood and adolescence also significantly influence health trajectories. A systematic review and meta-analysis of longitudinal studies showed a prospective negative association between muscular fitness in childhood and adolescence and levels of adiposity and cardiometabolic parameters in later life, alongside a positive association with bone health [44]. Pacific peoples are considered among the most muscular populations globally. Compared to other ethnic groups, Pacific adults [45] and children [46] tend to have greater muscle mass and less body fat relative to their height and weight. Traditionally, they also possess a larger body frame and a higher proportion of central fat compared to peripheral fat, traits that may reflect adaptations developed before and during their migration across the Pacific Ocean [47].

Building on this understanding, findings from the PIF Study further illustrate the role of body composition in physical performance. Among the nested subsample at the age 14 - 15 years, a 6-minute walk test was conducted, with heart rate measurements recorded at 0, 6, and 7 minutes. Results showed that after controlling for age, each kilogram increase in body weight was associated with a shorter walking distance for boys, but no change in walking distance for girls. Heart rate change during the walk test increased in both groups [48]. These results highlight how body composition differences can impact physical performance among Pacific youth.

Despite young adulthood being a critical period for shaping lifelong health trajectories [49], research on Pacific young adults' nutrition, metabolic health, and physical activity remains limited. Furthermore, recognizing young adults as a distinct subpopulation in health research and policy [50] could provide key insights into the long-term determinants of NCDs and inform more effective, culturally responsive strategies for prevention and intervention.

Economic Well-Being

In addition to the aforementioned psychological, nutritional, and metabolic challenges, economic well-being plays a crucial role in the overall well-being of Pacific populations in New Zealand. Despite enrolling in tertiary education at similar rates to the general population, Pacific peoples face significant barriers to academic success and career advancement [51]. This is evident in their underrepresentation in higher levels of education, such as bachelor's degrees, and lower tertiary course completion rates which were 12% points lower than the New Zealand average in 2022 [52-54]. In the workforce, Pacific peoples experience higher rates of unemployment and not in employment, education, or training than the general population [55]. Recent studies indicate that Pacific workers are disproportionately concentrated in the manufacturing, construction, and retail and hospitality sectors, predominantly employed as laborers, plant and machinery operators, and customer service representatives. This occupational clustering reinforces labor market segregation and systemic inequalities, with limited opportunities for upward career mobility [56,57]. In contrast, Pacific peoples hold only 5.1% of senior managerial and leadership positions, primarily within the public sector [58].

These educational and labor market disparities contribute to lower average income and wealth among Pacific peoples [59-61]. The "Pacific pay gap," where Pacific workers, particularly Pacific women, earn lower wages than other ethnic groups, has been attributed in part to systemic racism, unconscious bias, and discriminatory workplace practices [57]. This entrenched inequity reflects broader structural inequalities and limits the economic advancement and social mobility of Pacific communities in New Zealand. These disparities also have intergenerational consequences, as differences in parents' education and socioeconomic status account for gaps between European and Pacific peoples in tertiary enrollment and achievement [62]. Thus, educational and socioeconomic inequalities among the current generation of young Pacific peoples will have sequelae for the next generation.

The impact of these economic disparities extends beyond economic struggles, influencing health outcomes significantly. As noted in the Ministry of Health's Te Mana Ola: Pacific Health Strategy in New Zealand, "Pacific peoples experience longstanding and unacceptable health inequities…[which]…are strongly linked to the wider determinants of health such as education, employment, and housing" [63]. These inequities are evident in rates of psychological distress, which follow a socioeconomic gradient. Adults with the lowest material living standards experience distress rates 30 times higher than those with the highest living standards [9]. A similar gradient is also observed for Pacific self-harm and suicide rates across levels of neighborhood deprivation [6,18,19]. Additionally, BMI and waist circumference among the total population, and dietary behaviors of adolescents, are strongly associated with socioeconomic status in New Zealand [10,11]. Thus, addressing the socioeconomic disparities experienced by Pacific peoples is critical not only in their own right but also due to their spillover effects on health outcomes. While research on these issues remains limited, it is evident that the complex factors contributing to these disparities accumulate across the life course, beginning from gestation and continuing into adulthood. Longitudinal and cross-sectional data from PIF:ATP are essential for understanding why young Pacific peoples face educational and labor market disparities in New Zealand. These data can identify critical intervention points across the life course and inform the development of more effective services in education, employment, and social welfare to promote equitable outcomes for Pacific young adults.

The 3 themes of PIF:ATP—psychological, nutritional and metabolic, and economic well-being—are theoretically underpinned by the key features of the Fonofale model of Pacific health and well-being [64]. The Fonofale model reflects the interconnected nature of well-being from a Pacific perspective, emphasizing a holistic view where physical, mental, and social

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health are interdependent. Well-being is maintained when these dimensions are in balance and harmony. This holistic health is imbedded in family (the foundation of the fale or house) and culture (the roof of the fale), with well-being domains depicted as structural pillars of the fale. Within this framework, the concept of self is relational: an individual's sense of identity is deeply connected to family and culture, and any disconnection from these relationships can disrupt their overall well-being [64]. Such disconnections can arise from an inability to meet social obligations to family, village, and church (via fa'alavelave or gifting, remittances, and tithing). In short, connections to family and culture, and having the economic means to meet familial and cultural commitments, are central to Pacific views of well-being [65]. The 3 studies within the PIF:ATP program therefore capture the critical features of Pacific health and well-being as conceptualized in the Fonofale model.

Study Objectives

The quantitative component of the PIF:ATP program has three objectives: (1) quantitatively measure outcomes in psychological well-being, nutritional and metabolic well-being, and economic well-being among 25-year-old Pacific young adults; (2) consider the interrelations between these outcomes (eg, how mental distress is related to dietary patterns and employment status, how nutrition is related to occupation and mental health); and (3) identify risk and protective factors related to each set of well-being outcomes.

Specifically, we will examine sociocultural, environmental, and employment factors that influence the psychological well-being of Pacific young adults in either positive ways (eg, increased resilience to mental distress or protection of psychological well-being) or negative ways (eg, increased vulnerability to mental distress), and the mechanisms through which these factors operate. For nutritional and metabolic well-being, we will use comprehensive physiological measurements including anthropometrics (height, weight, BMI, waist, and hip circumference), body composition analysis (fat mass and muscle mass), blood pressure, metabolic screening (nonfasting glucose and lipid profiles), functional assessments (grip strength), and biomarker analysis (skin carotenoids). These measures will allow us to identify factors contributing to both favorable metabolic outcomes (such as healthy lipid profiles and normotensive status) and adverse outcomes (including obesity-related parameters and diabetes risk indicators). In addition, physical activity levels and sedentary behaviors will be assessed. The economic well-being component will examine educational and employment trajectories, with particular attention to factors that facilitate tertiary course completion, stable employment, and career progression, as well as those that lead to educational discontinuation, unemployment, or precarious employment. Throughout all analyses, we will pay particular attention to the underlying mechanisms connecting these various dimensions of well-being among Pacific young adults.

Methods

Study Design and Population

The PIF:ATP program will follow up the PIF Study birth cohort at the age of 25 years. Assessments and interviews with the PIF Study cohort have been conducted at multiple developmental stages, including at 6 weeks and 1 year, 2 years, 4 years, 6 years, 9 years, 11 years, 14 years, 17 years, and 22 years postpartum (see Table 1 for an overview of e-cohort follow-up numbers across measurement waves) [8,13]. The upcoming wave of data collection, scheduled for 2025 - 2026, will target participants aged 25-26 years and aims to engage at least 750 cohort members. Many cohort members have left New Zealand and moved overseas since birth, particularly to Australia, and there has been much internal migration within New Zealand as well. There are no exclusion criteria for participation in the PIF:ATP Study. However, of the original cohort, 138 participants have formally withdrawn, and 7 are deceased. The assessments will take place at participants' homes or at Auckland University of Technology (AUT) for those residing in Auckland. Data collection will be conducted across multiple sites, including Auckland, Wellington, Hamilton, and Whangārei in New Zealand, as well as Brisbane, Sydney, and Melbourne in Australia. While most participants currently reside in Auckland, 23% have relocated to Australia, and 10% live elsewhere in NZ, primarily in Wellington, Hamilton, and Whangārei. This phase will focus on collecting cross-sectional data on psychological, nutritional and metabolic health, and economic well-being, while also incorporating relevant longitudinal data from earlier waves into analyses where appropriate.

Study Recruitment and Procedures

A total of 6 field researchers will first attempt to contact participants via phone using the contact details held by the PIF Study. If a participant's phone number has changed or is no longer in use, researchers will follow up via email or a home visit. If these efforts are unsuccessful, they will reach out to the participant's nominated relatives (eg, mothers, fathers, and 2 additional contacts provided in previous study phases) to help re-establish contact. In addition, flyers will be distributed within Pacific communities in Auckland to increase outreach to original cohort members. In cases where direct contact methods are unsuccessful, participants' publicly available social media accounts will also be used to reach re-establish contact.

During the initial phone call, field researchers will provide potential participants with detailed information about the 25-year follow-up, including what their participation entails. Researchers will also address any questions the participant may have before scheduling an interview appointment. Participants will be advised to wear loose-fitting clothing to accommodate a blood pressure cuff. They will also be informed that a small blood sample will be collected via finger-prick test. Additionally, they will be asked to avoid food, alcohol, caffeine, cigarettes, and exercise for at least 30 minutes before the appointment, as these factors may temporarily impact some of the physical measurements such as elevating blood pressure.

At the in-person visit, conducted at the participant's home or at AUT campuses, the field researcher will provide a detailed

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explanation of all study procedures, including physical measurements. Participants will complete questionnaires related to psychological well-being while the researcher prepares equipment for the physical assessments. Once the survey is completed, physical measurements will be taken, followed by completion of additional questionnaires covering food intake, physical activity, and economic well-being. The entire assessment is expected to last approximately 2 to 2.5 hours.

Outcomes

Physical Measurements

Please see Table 2 for an overview of the physical measurements.

Table . Overview of physical measurements to be taken in Pacific Islands Families Study: Ala mo Tupulaga Pasifika quantitative study (25-year follow-up).

Variable	Instrument	Supplier	Unit precision	Precision of measurement	Final value	Type
Height	SECA stadiometer	Seca GmbH and Co KG, Hamburg	0.1 cm	0.5 cm	Average of 3 valid measurements	Continuous
Weight	Patient weight scale	Wedderburn scales Ltd	0.1kg	0.5 kg	Average of 3 valid measurements	Continuous
BMI	Derived (weight/height²)	—[a]	0.1 kg/m²	—	Calculated once	Continuous
Waist circumference	SECA anthropometric measuring tape	Seca GmbH and Co KG, Hamburg	0.1 cm	0.5 cm	Average of 3 valid measurements	Continuous
Hip circumference	SECA anthropometric measuring tape	Seca GmbH and Co KG, Hamburg	0.1 cm	0.5 cm	Average of 3 valid measurements	Continuous
Waist-to-hip ratio	Derived	—	0.1	—	Calculated once	Continuous
Waist-to-height ratio	Derived	—	0.1	—	Calculated once	Continuous
Body fat mass	Tanita BC-545N	Tanita Corporation, Tokyo	0.10%	—	Average of 3 valid measurements	Continuous
Muscle mass	Tanita BC-545N	Tanita Corporation, Tokyo	0.1kg	—	Average of 3 valid measurements	Continuous
Blood pressure	Omron HEM7121	Omron Healthcare, Kyoto	1 mm Hg	10 mm Hg	Average of the last 2 valid measurements	Continuous
Pulse rate	Omron HEM7121	Omron Healthcare, Kyoto	1 bpm	10 bpm	Average of the last 2 valid measurements	Continuous
Blood glucose	CardioChek PA Analyzer	PTS Diagnostics	0.1 mmol/L	—	Single measurement	Continuous
Total cholesterol	CardioChek PA Analyzer	PTS Diagnostics	0.1 mmol/L	—	Single measurement	Continuous
HDL[b] cholesterol	CardioChek PA Analyzer	PTS Diagnostics	0.1 mmol/L	—	Single measurement	Continuous
Grip strength	Camry-EH 101-Digital Hand Dynamometer	Camry	0.01 kg	—	Maximum of 3 measurements	Continuous
Skin carotenoids	Veggie Meter	Longevity Link, Utah	1 Carotenoid Score	—	Average of 3 valid measurements	Continuous

[a]Not applicable.

[b]HDL: high-density lipoprotein.

Height

Height (cm) will be measured using a portable SECA stadiometer (Seca GmbH and Co) without shoes. A total of 3 measurements will be taken, with a maximum allowable difference of 0.5 cm. If the difference exceeds this threshold, additional measures will be taken until consistency is achieved. The final recorded height will be the average of the 3 valid measurements.

Weight

Weight (kg) will be measured using patient weight scale (Wedderburn-WMMS6111) with participants barefoot and wearing light clothing. A total of 3 weight measurements will

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be recorded, with a maximum allowable difference of 0.5 kg. If the variation exceeds this threshold, additional measures will be taken until consistency is reached. The final weight will be the mean of the 3 valid measurements.

BMI

BMI will be calculated using the standard formula: BMI=weight (kg)\height^2 (m). This measure provides an indicator of body weight relative to height.

Waist Circumference

Waist circumference (cm) will be measured using a SECA anthropometric nonstretchable measuring tape at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest. Participants will stand in a relaxed posture, with arms at their sides and feet together. A total of 3 measurements will be taken, ensuring a maximum difference of 0.5 cm. If exceeded, additional readings will be taken. The final recorded value will be the average of the 3 valid measurements.

Hip Circumference

Hip circumference (cm) will be measured using a SECA anthropometric measuring tape at the level of the greatest buttock protrusion, ensuring that the tape remains parallel to the floor and snug but not compressing the skin. Participants will stand with their feet together and weight evenly distributed, and any bulky clothing will be removed to ensure accuracy. A total of 3 measurements will be taken, with a maximum allowable variance of 0.5 cm. If exceeded, measurements will be repeated. The final value will be the average of the 3 valid measurements.

Body Fat Mass and Muscle Mass

Body fat percentage (increments of 0.1%) and muscle mass (weight of muscle in the body) will be assessed using the Tanita InnerScan Body Composition Monitor (BC-545N, Tanita Corporation). The device uses Bioelectrical Impedance Analysis to determine body fat percentage and muscle mass. A total of 3 measurements will be recorded, and the average value will be recorded.

Blood Pressure and Pulse Rate

Blood pressure and heart rate will be measured using the Omron Auto Blood Pressure Monitor (HEM7121, Omron Healthcare). Participants will remain seated and relaxed, with 3 readings taken at least 3 minutes apart. The following parameters will be recorded: (1) systolic blood pressure, (2) diastolic blood pressure, and (3) heart rate (pulse, bpm). If the difference between the 3 systolic blood pressure or diastolic blood pressure readings exceeds 10 mm Hg or the heart rate varies by more than 10 bpm, additional measurements will be taken until 3 consecutive readings fall within these thresholds. The final recorded values will be the average of the last 2 valid measurements as the first readings of blood pressure and pulse rate are often less reliable due to initial participant adjustment.

Glucose and Lipids Screening Test

A nonfasting finger-prick blood test will be conducted using the CardioChek PA Analyzer, which provides the results within 2 minutes. The following biomarkers will be measured and recorded to the nearest mmol/L: (1) blood glucose, (2) total cholesterol, and (3) high-density lipoprotein. Each participant will undergo a single measurement.

Grip Strength

Grip strength (kg) will be assessed using a portable hand dynamometer, a validated measure of overall physical capability [66]. Participants will be instructed to grip the dynamometer as tightly as possible. A total of 3 trials will be conducted for each hand, and the maximum will be recorded for both the left and right hands [67].

Skin Carotenoid

Skin carotenoid concentration in the fingertip fat pad will be assessed using noninvasive reflectance spectroscopy with the Veggie Meter (Longevity Link). This method provides an objective and reliable biomarker for fruit and vegetable consumption, supported by previous studies [68-70]. The device functions by gently compressing the finger, temporarily displacing blood from the measurement area. It then emits light, analyzes the reflected light spectrum, and calculates a carotenoid score within a few minutes, which serves as a biomarker for dietary intake [70]. To ensure accuracy, measurements will be made using a multimeasurement mode, with 3 sequential readings within 10% of each other averaged over a 45-second period.

Self-Reported Questionnaires

Psychological Well-Being

Psychological well-being will be assessed using the following scales:

1. The Kessler Psychological Distress Scale: The Kessler Psychological Distress Scale is a widely used measure of nonspecific psychological distress [71]. It has been validated across multiple settings and diverse populations, including in New Zealand [9,72].
2. Generalized Anxiety Disorder 7-item Scale: Participants will be assessed for symptoms of anxiety using the Generalized Anxiety Disorder 7-item scale [73], a self-report screening tool that has been validated for use with both adults and adolescents in the general population across many different cultures, demonstrating sound psychometric properties [74].
3. Beck Depression Inventory-Revised: Depressive symptoms will be measured using the Beck Depression Inventory-revised [75], a widely used screening tool with strong psychometric properties for assessing depression severity in adults and adolescents [76].
4. Adult Self-Report Behavior Checklist: Externalizing problem behaviors will be assessed using the aggression, rule-breaking, and intrusive behavior subscales of this checklist [77]. It assesses behavioral and emotional problems in adults aged 18 - 59 over the past 6 months and has well-established psychometric validity [78].
5. World Health Organization-5 Well-Being Index: This 5-item questionnaire measures mental well-being and positive psychological functioning. Substantial empirical

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evidence supports its validity, reliability, and cross-cultural applicability [79,80].

6. World Health Organization Quality of Life-Brief Version: This 26-item instrument assesses quality of life across 4 domains: physical, psychological, social, and environmental. It has been extensively validated for reliability and cross-cultural relevance [81].
7. Pacific Identity and Wellbeing Scale-Revised: It is developed by a Cook Islands Māori researcher, this tool evaluates the influence of culture and identity on health outcomes [82]. The scale consists of 6 subscales: "Perceived Familial Wellbeing," "Perceived Societal Wellbeing," "Group Membership Evaluation," "Pacific Connectedness and Belonging," "Religious Centrality and Embeddedness," and "Cultural Efficacy." Cultural identity and engagement will be measured with the latter 5 subscales. Family functioning will be measured with the first subscale, "Perceived Familial Wellbeing.". The Pacific Identity and Wellbeing Scale-Revised has demonstrated strong internal reliability, construct validity, and applicability across the 4 major Pacific ethnic groups [82,83].
8. Systemic Clinical Outcome and Routine Evaluation: This 15-item questionnaire assesses family functioning across 3 dimensions: strengths, difficulties, and communication [84]. Systemic Clinical Outcome and Routine Evaluation has demonstrated good internal and test-retest reliability and criterion validity [85].
9. Cognitive Emotion Regulation Questionnaire-Short: The Cognitive Emotion Regulation Questionnaire-Short assesses cognitive strategies individuals use to regulate emotions in response to stressful or threatening life events [86]. It consists of 18 items across 9 subscales: self-blame, other-blame, rumination, catastrophizing, positive refocusing, planning, positive reappraisal, putting into perspective, and acceptance. Higher subscale scores indicate a greater tendency to use the corresponding cognitive emotion regulation strategy [86].
10. Nature Relatedness-6: This scale measures an individual's subjective connectedness to nature, with higher scores indicating stronger connection to the natural environment [87]. Prior research demonstrates that greater nature relatedness correlates with psychological well-being [88], reduced perceived stress [89], and lower anxiety levels [90], supporting its use in examining psychological well-being among Pacific young adults.
11. The Normalized Difference Vegetation Index: Vegetation density around participants' residential neighborhoods will be quantified using Normalized Difference Vegetation Index methodology [91]. Following geocoding of participants' home addresses, Normalized Difference Vegetation Index values will be derived through spectral analysis comparing near-infrared and visible light reflectance in order to examine the link between residential green space and psychological well-being. In addition to vegetation density, residential distance to nearest green spaces will also be analyzed. Studies have linked greener spaces to lower depression, anxiety, and stress levels [92,93].

Nutritional and Metabolic Well-Being

To assess nutritional and metabolic well-being, the following questionnaires will be used:

1. Food Frequency Questionnaire: Dietary patterns will be assessed using a validated 57-item short version of the Food Frequency Questionnaire [94]. This short version has been validated for use with New Zealand subpopulation groups. It captures data on food consumption (eg, bread, potatoes, and protein sources) to estimate nutrient intake [94].
2. Household Food Security: Household food security will be assessed using an 8-item questionnaire designed to measure access to nutritionally adequate and safe food. This tool has been widely used in various phases of the New Zealand Health Survey [95].
3. International Physical Activity Questionnaire-Short Form: This questionnaire measures physical activity levels, including types and intensity of activity and sedentary behavior, to estimate total physical activity in days per week and minutes and hours per day [96].
4. Sedentary Behavior Questionnaire: Sedentary behaviors will be evaluated using the Sedentary Behavior Questionnaire, a validated tool assessing habitual sedentariness across occupational, transportation, household, and leisure-time domains. Given the link between sedentary behavior and cardiovascular risks, the Sedentary Behavior Questionnaire provides a comprehensive measure with strong psychometric properties [97].

Economic Well-Being

The following items will be used to assess economic well-being:

1. Tertiary course completion: This will be measured by tracking all courses attempted at universities, institutes of technology and polytechnics, wānanga (publicly owned tertiary institutions or Māori universities that offer education rooted in Māori cultural values), industry training organizations, and private training establishments.
2. Employment status: Employment status will be categorized as unemployed, employed part-time, employed full-time, or not in the labor force, based on standard questions from Statistics New Zealand's Household Labour Force Survey [98].
3. Occupation: Occupation will be assessed using standard questions from the New Zealand Census and coded according to the Australian and New Zealand Standard Classification of Occupations, which ranks jobs based on skill level and specialization [99].
4. Industry of employment: This will be identified using standard questions from Statistics New Zealand's Household Labor Force Survey and coded according to the Australian and New Zealand Standard Industrial Classification [99].

In addition to these core measures, there will be supplementary questionnaires to examine key factors influencing economic outcomes. These questionnaires will explore (1) reasons for tertiary course incompletion, (2) reasons for unemployment or being out of the labor force, and (3) factors influencing occupational and industry choices. The development of these

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items will be informed by validated measures from the Household Labor Force Survey [98], as well as findings from the Graduate Longitudinal Study New Zealand, which identifies factors that facilitate or hinder qualification completion among tertiary students [100,101].

Sociodemographic Questions

Additional sociodemographic and contextual information will be collected, including gender, ethnicity, spoken languages, faith or religion, sexual orientation, household size, relationship status, and parental status.

Data Management

All digital data will be securely stored on REDCap (Research Electronic Data Capture; Vanderbilt University), a secure, web-based software platform [102,103], with backup copies maintained on the AUT-supported Microsoft Teams platform. For participants who complete paper forms, either by choice or due to internet connectivity issues, these forms will be securely stored in lockable filing cabinets at AUT South Campus. Access to this storage area is restricted by swipe card and limited to authorized researchers directly involved in the study.

Access to the database of participants' contact details is restricted to researchers and field interviewers employed on the PIF Study. Permissions to access this data are managed by the PIF Study Director. For external collaborators, such as named investigators from other institutions involved in PIF Study projects, access to research data is facilitated through a dedicated, project-specific Microsoft Teams site. Only researchers directly associated with the specific project are granted access to this site. All PIF:ATP data will be securely retained for 10 years following the conclusion of the PIF Study, after which it will be permanently destroyed.

Data Analysis: Statistical Considerations

Reporting of all findings for each study will comply with the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines [104]. A completed STROBE checklist is provided as Checklist 1 to document the reporting standards for each study within the PIF:ATP program. All analyses will be performed using contemporary specialist software, such as Stata SE version 18.0 (StataCorp). Results will be interpreted based on both statistical significance (2-sided α=.05) and effect sizes. Following a description of participant flow (recruitment and attrition) and characteristics, crude frequencies of primary exposure and outcome variables across measurement waves will be reported.

Important social determinants of health such as family size, household income, neighborhood socioeconomic deprivation measured contemporaneously with psychological, nutritional and metabolic, and economic outcomes will be included in the analyses. Where appropriate, analyses will also incorporate antecedent data collected over the cohort's life course including childhood family circumstances from birth to adolescence. All findings will be contextualized within the broader historical, social, political, and economic circumstances in which they occurred. This approach ensures that structural determinants, including migration, systemic inequities, housing, and policy changes, are considered.

Apposite longitudinal models will be developed for each study, taking into account various considerations such as the distribution of outcome variables (eg, binary when thresholds are used for Kessler Psychological Distress Scale and Generalized Anxiety Disorder 7-item scale). Distributional assumptions for continuous variables will be checked, and transformations will be applied where necessary (eg, logarithmic transformations for BMI). Measurement wave time will also be included in all longitudinal analysis. Patterns over time will be investigated using degree-2 fractional polynomial regression models [105], or indicator variables when the number of measurement waves is relatively small. Group-based multitrajectory modeling will also be used when multiple outcomes are simultaneously considered (eg, investigating dietary patterns) [106].

Multitrajectory modeling identifies latent clusters of individuals following similar trajectories over time across multiple outcome indicators. Although relatively recent, this technique has been rapidly adopted and applied to longitudinal research of psychological and psychiatric outcomes in adolescents and young adults [107]. All longitudinal analysis will accommodate within-person correlations, modeled using unstructured or exchangeable matrices, and Huber-White robust sandwich estimators of variance will be used to provide insurance against model specifications. Generalized estimating equations will be used for population-averaged panel-data models, while multilevel mixed effects models will be used for models containing both fixed effects and random effects and hierarchical structures. Both these statistical approaches have been successfully used in many previous PIF Study analyses and publications [25,40,108].

To assess model predictive ability, a key factor in establishing causality, Lasso methods will be used [109]. Unlike techniques that evaluate models in the hold-out sample, Lasso helps to avoid overfitting by minimizing an estimate of the out-of-sample prediction error. K-fold cross-validation will also be used as a check, and the 10-fold cross-validated area under the receiver operating characteristic curve (AUC) will be used for binary variables. In k-fold cross-validation, the dataset is randomly partitioned into k approximately equal subsamples (or folds). At each iteration, one fold is retained as the validation data for testing the model and estimating the AUC, while the remaining k-1 folds are used as training data for model estimation. This process is repeated k times, with each fold used once as validation data [110]. K-fold cross-validation and Lasso avoid the optimistic estimates of predictive performance that can occur when the same data are used for both model specification and predictive assessment. Patterns of attrition will be assessed using binary Generalized Estimating Equation models. Following complete case analyses, sensitivity analyses will be conducted, where data from participants who attrite or have missing values will be imputed. As in previous PIF Study analyses and publications [25,111,112], multiple imputation (MI) methods will be used, and the data will be reanalyzed.

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Pacific Data Governance

The development of Pacific data principles by the Pacific Data Sovereignty Network has provided culturally centered frameworks for use when making decisions about how to approach Pacific data. The Pacific Data Sovereignty Network supports the notion that Pacific data should be subject to Pacific governance, and Pacific organizations should be able to access Pacific data to support their development aspirations or work that benefits Pacific families and communities [113].

With these principles in mind, the PIF:ATP team has put in place 2 advisory groups, an expert science group and an expert community liaison group, to provide Pacific guidance, cultural support, and scientific feedback from a Pacific perspective. All members are of Pacific descent and have long-standing careers and relationships working and interacting with Pacific families and communities. Alongside the PIF:ATP research investigators (of whom most are of Pacific descent), this collaborative network ensures several layers of Pacific governance and oversight are used to deliver on the principles of Pacific data sovereignty. Moreover, several members of the research team are part of the Pacific Data Sovereignty Network Advisory group and can bring this expertise and network of support and collaboration to the study if necessary.

Information from the study is also regularly disseminated back to families and communities through various channels including community fono (meetings), summary booklets, Pacific language videos, social media platforms, and traditional academic outputs for those interested, such as journal articles and conference presentations. Many of these forums act as a means of "sharing" where data are presented and audiences are able to provide feedback and interact with researchers. This feedback process has proven beneficial in previous measurement waves and provided guidance on priority issues for Pacific families, which we have been able to explore and examine in subsequent data collection waves.

Ethical Considerations

This study received funding in October 2024 (reference number: Health Research Council of New Zealand 24/623) and was granted ethical approval in April 2025 by the Health and Disability Ethics Committee (reference number: 2025 EXP 22302) and in May 2025 by the Auckland University of Technology Ethics Committee (reference number: 25/165). Participants will receive an information sheet and consent form via email or post, depending on their preference. After reviewing the materials and confirming willingness to participate, participants will sign the consent form electronically via REDCap [102,103] before any data collection begins. Participation is entirely voluntary, and participants may withdraw at any time without consequence. As a token of appreciation, participants will receive a NZ $100 (~US $57.77) mea'alofa (gift) voucher for their valuable contribution. Those opting to complete their assessment at the AUT laboratory will also receive a NZ $30 (~US $17.33) petrol voucher to help cover travel expenses to and from campus.

Results

Data collection is scheduled to commence in June 2025 and is anticipated to conclude by December 2026. Based on the attrition rates observed in previous waves, we aim to recruit approximately 750 cohort members. Data analysis will begin in January 2027, with the first results expected to be published December 2027 onward.

Discussion

Principal Findings

The PIF:ATP is the 25-year phase of the only prospective study focusing specifically on Pacific peoples. It will provide valuable insights into the long-term interrelations among psychological, nutritional and metabolic, and economic well-being in Pacific young adults. The findings will illuminate how mental distress, dietary patterns, and economic situation interact over time. In addition, the study will identify both cross-sectional and longitudinal risk and protective factors associated with mental health, nutrition, and economic well-being. By identifying these factors, this research aims to inform future interventions and policies designed to improve the mental health, dietary behaviors, and economic outcomes of Pacific young adults.

Strengths and Limitations

The unique PIF:ATP program is well positioned to identify health and well-being trajectories from birth to early adulthood, determine relationships between early and later life events, and make causal inferences and identify potential interventions. Nevertheless, the major limitation of the study is the potential impact of sample attrition on the number and profile of participants. While we will check the patterns of attrition as in previous PIF publications [8,13,114], it remains a concern as differential attrition can introduce bias. If certain groups of participants (eg, those with poorer health or who have migrated to Australia) are more likely to not be measured, it may limit the generalizability of our findings. To account for this, we will evaluate the impact of attrition on our results and ensure that our conclusions remain robust.

Given that the previous wave experienced lower participation rates, which highlighted the challenges of locating and contacting participants, we will implement targeted strategies to enhance retention and re-engagement. These include prioritizing the recruitment of field researchers with strong connections to Pacific communities in Auckland. Their cultural understanding and established networks will be critical for encouraging participation. Additionally, we will use social media engagement strategies to increase visibility and encourage continued involvement. We will also extend the data collection period to 18 months, compared with the previous standard 12-month timeline, to reach more participants.

Conclusions

The PIF:ATP research program will measure outcomes in psychological well-being, nutritional and metabolic well-being, and economic well-being among 25-year-old Pacific young adults. By addressing a significant gap in knowledge, this study

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will build a strong evidence base to inform health and well-being strategies and make services and health promotion activities more accessible, acceptable, and effective for Pacific young adults. The PIF:ATP program is uniquely positioned to leverage its comprehensive dataset spanning 25 years of the cohort's life course, addressing key issues identified by Pacific communities and advancing knowledge on the well-being of Pacific young people.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Conflicts of Interest

None declared.

Checklist 1
STROBE checklist.
[PDF File, 142 KB - resprot_v14i1e77460_app1.pdf]

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Abbreviations

ATP: Ala mo Tupulaga Pasifika
AUT: Auckland University of Technology
GAD-7: Generalized Anxiety Disorder 7-item scale
NCD: noncommunicable diseases
PIF: Pacific Islands Families study
REDCap: Research Electronic Data Capture
STROBE: Strengthening the Reporting of Observational studies in Epidemiology

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Moringa oleifera Supplementation for Reducing Heavy Metal Toxicity and Oxidative Stress in Pregnant Women: Protocol for a Nonrandomized Trial Study

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Abstract

Background: Heavy metals present in the environment, including lead, cadmium, and mercury, pose significant health risks to pregnant women and fetal development through food, water, and air contamination. Exposure to these metals has been linked to miscarriage, low birth weight (LBW), preterm birth, and developmental issues in children. The mechanism of oxidative stress, characterized by increased 8-hydroxy-2'-deoxyguanosine (8-OHdG) and malondialdehyde (MDA) levels, contributes to DNA damage, genomic instability, and adverse pregnancy outcomes. Additionally, DNA methylation changes induced by metal exposure may further exacerbate these risks. Certain micronutrients play a crucial role in heavy metal detoxification, and *Moringa oleifera*, a locally available plant rich in antioxidants and chelating compounds**,** has demonstrated protective effects against mercury (Hg), lead (Pb), and cadmium (Cd) toxicity in experimental studies. However, intervention studies on pregnant women remain scarce.

Objective: The objective of this study was to evaluate the effect of *M. oleifera* supplementation in reducing heavy metal toxicity and oxidative stress biomarkers, 8-OHdG and MDA, in pregnant women exposed to high levels of heavy metals.

Methods: A quasi-experimental, nonrandomized pre-post test design is used. Pregnant women with elevated heavy metal levels, identified through initial screening, will be included in the intervention group, receiving *M. oleifera* supplementation for 2 months. The control group will consist of women from similar geographical regions who will not receive the intervention. Primary outcomes will include changes in heavy metal concentrations, measured using inductively coupled plasma mass spectrometry (ICP-MS). Secondary outcomes will focus on reductions in oxidative stress biomarkers, measured via enzyme-linked immunosorbent assay (ELISA). Statistical analyses, including analysis of covariance (ANCOVA), will be used to adjust for baseline differences between the groups.

Results: A total of 26 mothers for each group have participated. As of February 2025, the laboratory analyses have been ongoing, and the result is expected to be published at the end of 2025. The protocol anticipates that the intervention group will show a significant reduction in both heavy metal levels and oxidative stress biomarkers compared to the control group, suggesting the potential efficacy of *M. oleifera* in detoxifying heavy metals and reducing oxidative stress.

Conclusions: This study is expected to provide preliminary evidence on the potential effectiveness and safety of *M. oleifera* supplementation for reducing heavy metal toxicity and oxidative stress in pregnant women.

Trial Registration: Australian New Zealand Clinical Trials Registry; ACTRN12625000162415; https://www.anzctr.org.au/ACTRN12625000162415.aspx

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KEYWORDS

antioxidants; environmental exposure; micronutrients; maternal health; detoxification; DNA damage

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Introduction

Heavy metals such as cadmium (Cd), mercury (Hg), and lead (Pb) exist in water, air, and food, contributing to cumulative exposure in humans [1,2]. According to the World Health Organization (WHO), Pb exposure alone is responsible for nearly 1 million deaths annually and more than 21 million disability-adjusted life years (DALYs) lost, with more than 95% of this burden occurring in low- and middle-income countries (LMICs) [3]. Prenatal exposure to Pb and other heavy metals is particularly harmful as it has been linked to miscarriage, preterm birth, low birth weight (LBW), and developmental problems in children [4-6]. Studies have shown that no level of lead exposure is considered safe during pregnancy, and even low-dose exposures can disrupt fetal development. These risks highlight the urgent need for public health interventions targeting environmental metal exposures in vulnerable populations, especially among pregnant women in LMICs where monitoring and remediation remain limited.

In Makassar, Indonesia, 717, 347, and 816 LBW cases were reported in 2021, 2022, and 2023, respectively. Preliminary investigation also revealed significantly elevated levels of blood Pb (1.35–101.00 µg/L) and Cd (0.55–17.00 µg/L), exceeding reference values in various countries [7]. For context, the US Centers for Disease Control and Prevention (CDC) considers blood Pb levels above 5 µg/dL (50 µg/L) as elevated in adults [8-10], while the WHO identifies Cd concentrations exceeding 1 µg/L in blood as potentially toxic. These findings highlight a concerning level of environmental exposure during pregnancy. Although specific to Makassar, such elevated exposures reflect broader environmental health challenges in urban Indonesia and Southeast Asia, where industrial emissions, traffic pollution, and inadequate regulation contribute to rising heavy metal contamination.

One key mechanism underlying the heavy metal toxicity is oxidative stress, which causes damage to lipids, proteins, and DNA. Biomarkers such as malondialdehyde (MDA) and 8-hydroxy-2’-deoxyguanosine (8-OHdG) reflect oxidative damage and are commonly elevated in metal-exposed individuals [7-9]. Additionally, heavy metals can disrupt DNA methylation [10], an epigenetic process critical for normal fetal development, thereby contributing to adverse pregnancy outcomes [11-13]. Heavy metals such as Pb, Cd, and Hg exert toxic effects partly through the generation of reactive oxygen species (ROS), leading to oxidative stress [14]. This imbalance between ROS and antioxidant defenses causes damage to cellular lipids, proteins, and DNA, as reflected by increased levels of oxidative stress biomarkers such as 8-OHdG and MDA [15,16]. These molecular injuries are particularly harmful during pregnancy as they disrupt placental development and fetal growth processes [17,18]. Studies have shown that oxidative stress plays a central role in the pathogenesis of adverse pregnancy outcomes [19], including preeclampsia [20], miscarriage [21], LBW [22], and preterm birth [23]. A previous study by Zinia et al [24] indicated that high maternal blood Cd levels (0.62 µg/L in early pregnancy and 0.70 µg/L in late pregnancy), Pb levels (early pregnancy 0.74 vs late pregnancy 0.70 µg/dL), and Hg levels (early pregnancy 2.37 vs late pregnancy 1.95 µg/L) were inversely associated with birth weight.

Although certain micronutrients such as zinc and cysteine may assist in the detoxification of heavy metals [25], their use as targeted interventions remains inconsistent and often inaccessible to at-risk populations. Therefore, *Moringa oleifera* has emerged as a promising, locally available resource. Moringa contains flavonoids, phenolic acids, glucosinolates, and phytates and exhibits antioxidant and metal-chelating properties that can mitigate the toxic effects of heavy metals [26,27]. These compounds have been shown in in vitro and in vivo studies to counteract oxidative stress and inflammation induced by toxicants, including heavy metals.

Beyond laboratory studies, there is growing evidence of moringa’s nutritional and therapeutic effects in humans. Moringa leaf supplementation has shown improvements in hemoglobin levels in children with iron deficiency anemia and increased breast milk production in postpartum women [28]. In a clinical trial, moringa leaf powder (0.5 g/d) led to significant reductions in body weight, blood pressure, and lipid profiles in overweight individuals with hyperlipidemia [29]. In pregnant women, moringa has emerged as a beneficial supplement, particularly in enhancing maternal and neonatal health. A study in southern Ethiopia found that the consumption of moringa was associated with an increase in birth weight by approximately 115.77 g, suggesting its potential role in improving neonatal outcomes [30]. Moringa leaves are rich in iron, which is crucial for preventing anemia during pregnancy. A study in Karachi reported that pregnant women consuming moringa leaf powder showed hemoglobin levels of 9.09 g/dL in the third trimester, indicating a potential benefit in managing anemia [31]. No contraindications for moringa use during pregnancy were reported in the reviewed studies, suggesting it is generally safe for consumption [32].

Although moringa grows abundantly in many regions of Indonesia, particularly in Makassar, it is typically consumed sporadically as a vegetable, with unmeasured doses and limited awareness of its therapeutic potential. In other areas, such as Java, consumption is even more limited. These factors underscore the need for a standardized, supplement-based intervention to realize public health benefits of moringa. Despite the well-documented risks of heavy metal exposure during pregnancy, interventional studies remain scarce, particularly in Indonesia. To date, there has been no clinical trial examining the efficacy of moringa in the detoxification of heavy metals among pregnant women. In addition, most existing research is observational and lacks an evaluation of strategies to reduce maternal metal levels or oxidative damage. This study seeks to address this gap by investigating the effect of standardized *M. oleifera* supplementation on heavy metal level and oxidative stress reduction in pregnant women. We hypothesize that pregnant women receiving *M. oleifera* supplementation will have significantly lower blood heavy metal concentrations and oxidative stress biomarkers than before receiving.

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Methods

Study Design

This study is an ongoing quasi-experimental investigation that uses a nonrandomized pre-post test methodology. Expectant mothers were divided into 2 cohorts, one receiving an intervention and the other serving as a control. This study applied a nonrandomized pre-post test design due to practical considerations related to (1) practical management, (2) geographical differences, and (3) time constraints.

First, practical management considers that managing the study is easier when specific locations are designated for the intervention group and other locations for the control group. This approach ensures that the intervention (*M. oleifera* supplementation) can be efficiently delivered and monitored in each location without the complexity of randomizing participants across multiple sites. Furthermore, grouping participants by location helps streamline logistical operations such as monitoring compliance and ensuring consistent follow-up over the course of the intervention period.

Second, although the geographical settings of the intervention and control groups may differ, they were comparable in terms of demographic characteristics and environmental conditions. This allowed us to evaluate the effects of moringa supplementation in different geographical settings while maintaining comparability between groups. In addition, by focusing on distinct locations for intervention and control, we ensure better resource allocation and minimize the logistical challenges that would arise from attempting to randomize participants across a broader region.

Third, time was considered a constraint due to limitation in the laboratory. We could not receive heavy metal analysis results from the initial screening at the same time for all participants. Therefore, women with high levels of heavy metals at the first screening were included in the intervention group to avoid delays. This ensures that these participants can begin the 2-month intervention with *M. oleifera* as soon as possible after obtaining the result, considering the limited research timeframe. Furthermore, because we limited the overall time for the study, randomizing participants could cause delays in implementing the intervention and complicate the process of ensuring that those with high levels of heavy metals receive timely treatment.

A nonrandomized approach allows for a more timely intervention, while still enabling an effective comparison between the intervention and control groups. Statistical methods will be used to control for baseline disparities and account for potential differences between the groups.

Moringa Leaf Extract Supplementation

Collecting Moringa Leaves

The moringa leaves used in this study were collected from moringa trees growing in the Gowa and Takalar regencies. Fresh and healthy leaves were used for supplementation. The leaves chosen were mature, dark green leaves from the tenth stalk down from the tip of the branches. A previous study [33] has shown that mature moringa leaves exhibit a higher antioxidant activity than younger leaves.

Washing and Drying

The harvested moringa leaves were washed by dipping them in water and rinsing them several times with running water to remove any dirt or impurities. After washing, the leaves were air-dried for 2 h to remove the excess water. The leaves were separated from the stalks. The drying process was conducted out in an oven at a temperature of 30 - 40 °C for 3 - 4 hours or until the leaves reached a moisture content of less than 10%.

Extraction

The dried moringa leaves were ground into a fine powder using mesh 60. The powder was extracted using distilled water (Aquadest). The extraction process involved soaking moringa powder in distilled water, after which the mixture was squeezed and filtered through a muslin cloth to separate the extract from the residue. The obtained extract was further processed using a rotary evaporator and dried using a freeze dryer until a dry extract was produced.

Capsule Supplement Production

The dry extract was ground again using mesh 100 to obtain a fine extract powder. This powder was then mixed with corn starch as a filler in a 4:1 ratio (400 mg of moringa extract and 100 mg of corn starch per capsule). Each capsule contained 400 mg of moringa leaf extract. Participants in the intervention group received 2 capsules twice daily (totaling 2000 mg/d) for a period of 8 weeks, beginning immediately upon enrollment (between gestational weeks 20 - 32). In cases where participants gave birth before completing the 2-month supplementation period, they were instructed to continue consuming the remaining *M. oleifera* supplements until the full course was completed. This approach aimed to ensure consistency in the intervention dosage, regardless of the timing of delivery, and to maintain the study's internal validity.

Quality Control

After production, supplementation with moringa leaf extract capsules was tested to ensure weight uniformity and quality, including checks for moisture content, microbial presence, and organoleptic tests to ensure product safety and quality. The dosage of moringa leaf supplementation in this study was determined based on several previous safety studies [34-36], which indicated that the consumption of moringa leaves is safe at doses up to 2000 mg/day for humans and has the potential to be a safe source of antioxidants for pregnant women.

Participant Recruitment

This research has been conducted in Makassar City, specifically at 6 community health centers where expectant women receive prenatal services. The 6 selected community health centers are located in areas with varying environmental characteristics, including industrial zones, regions near landfill sites, and coastal areas. While the types of pollution sources differ, all sites share a common feature: exposure to potential environmental contaminants. Each represents an urban setting with a plausible risk of heavy metal exposure through air, water, and food pathways. Thus, despite differences in specific pollution types,

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the study sites are considered comparable in terms of overall environmental risk exposure. This selection strategy ensures that the intervention and control groups are drawn from communities facing similar environmental health challenges. Moreover, such variation may enhance the generalizability of findings across different urban pollution contexts. Three centers were assigned as intervention sites and 3 as control sites based on operational convenience and to avoid information spillover between groups.

The study will include 59 pregnant women in each group of intervention and control who underwent an examination at health centers in Makassar and fulfilled the following inclusion criteria: (1) pregnancy during the second or third trimester, (2) intention to deliver in Makassar, (3) living in Makassar for a period exceeding 1 year, and (4) blood levels of Hg, Pb, or Cd exceeding the reference value. Participants will be excluded based on self-report during interview if they (1) are having twin pregnancy, (2) had known chronic medical conditions, such as diabetes, cancer, kidney diseases, (3) are taking other antioxidant or mineral supplements beyond standard care, (4) are diagnosed with micronutrient deficiencies, (5) relocate during the intervention period, and (6) are unwilling to comply with follow-up procedures.

The required sample size was calculated using an estimated effect size (Cohen *d*) of 0.42, derived from a previous intervention study in South Sulawesi, which assessed the effects of *M. oleifera* supplementation on oxidative stress biomarkers in pregnant women exposed to passive smoking [37]. The study reported a mean difference in 8-OHdG levels between treatment groups of approximately 12.96 ng/mL with a pooled SD of ~30.68 ng/mL, yielding a moderate effect size. Using a 1-sided test with α=.05 and 80% power, the minimum required sample size is 37 participants per group. To account for an anticipated 20% dropout rate, the sample size was increased to 44 participants per group, yielding a total of 88 participants.

Approximately 200 pregnant women attending routine antenatal care (ANC) visits at the community health centers were sequentially approached and invited to participate in the study. They were first interviewed to determine eligibility based on inclusion and exclusion criteria. Those meeting the criteria were provided with detailed information about the study and asked to provide written informed consent. Following consent, a blood sample was collected to assess baseline levels of heavy metals.

Only participants with elevated levels above reference thresholds were considered eligible for inclusion in the intervention phase. For the intervention group, eligible participants were contacted and provided with *M. oleifera* supplements along with instructions for daily consumption over a 2-month period. They were informed that a follow-up blood collection would occur at the end of the supplementation period during a routine visit.

For comparison, the control group was recruited from a different health center in a separate subdistrict administrative unit that did not receive moringa supplementation. This approach minimized contamination between groups and allowed for feasible implementation of the intervention. Follow-up blood sampling was also conducted after 2 months, aligned with their next scheduled antenatal visit, but without providing moringa supplementation.

Ethical Considerations

This study was approved by the Ethics Committee of the Public Health Faculty (number: 1549/UN4.14.1/TP.01.02/2024). All participants were informed about the study's purpose, procedures, potential risks, and right to withdraw at any time before data collection. Written informed consent was obtained after that. Initial screening for heavy metal exposure was conducted after informed consent was obtained. All historically collected data will be deidentified before the analyses. The participants received the equivalent of around US $6.25 for compensation.

Research Procedure

Overview

The research step is presented in Figure 1.

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Figure 1. Research step. Fe: ferrum (iron supplement); Hg: mercury; Pb: plumbum (lead); Cd: cadmium; 8-OHdG: 8-hydroxy-2'-deoxyguanosine; MDA: malondialdehyde.

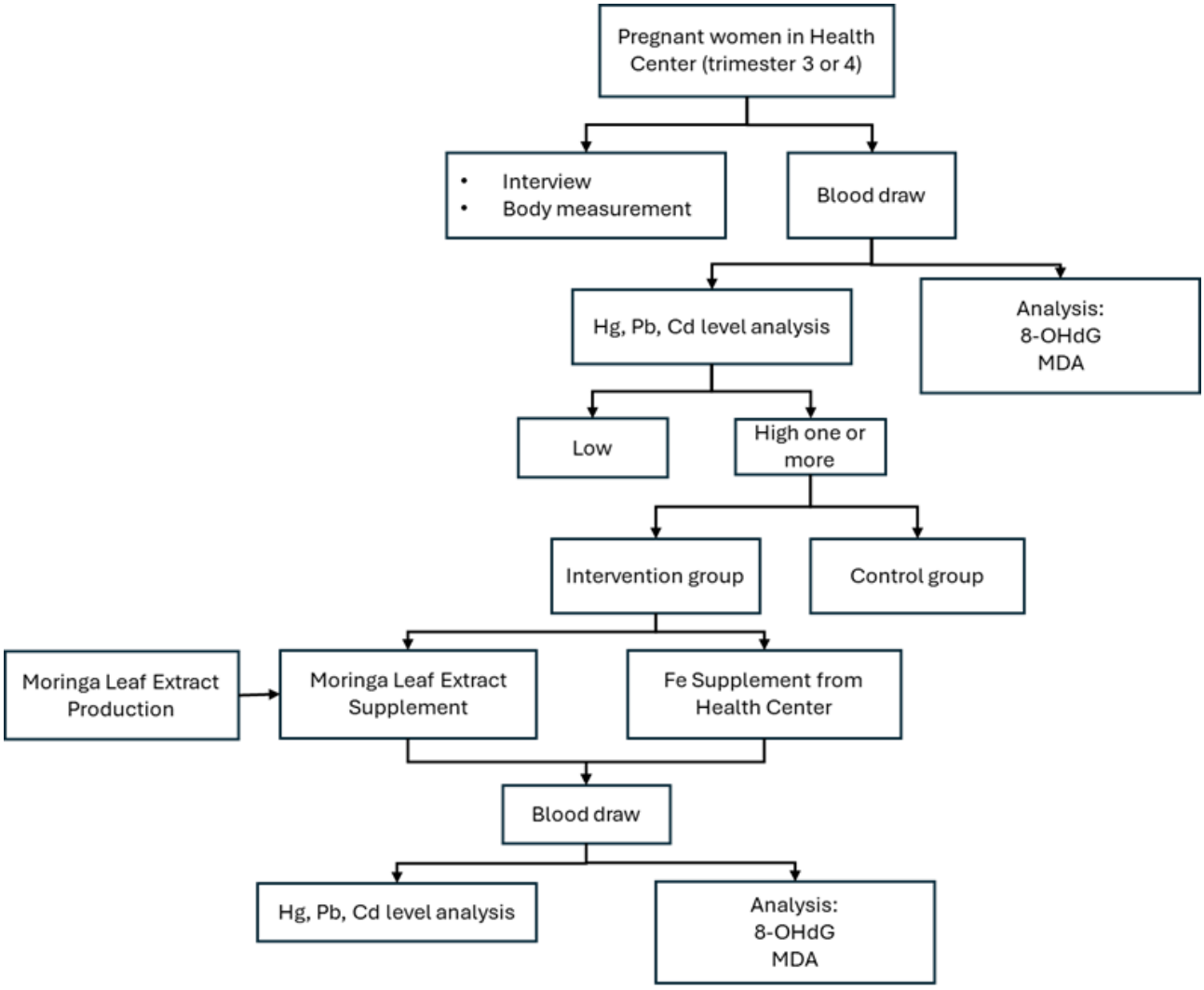

Data Collection

An interview has been conducted with pregnant women using a questionnaire that contained questions about their characteristics and potential exposure sources. Data on food/supplement intake will also be obtained using a 24-hour recall form and a Food Frequency Questionnaire (FFQ) to assess exposure to heavy metals through food. Each participant provided 10 mL of venous blood sample, acquired using a tube lined with ethylenediaminetetraacetic acid (EDTA) and kept at a temperature of 2 - 8 °C until analysis. For MDA and 8-OHdG analyses, blood samples were centrifuged to obtain plasma and stored at temperatures of −80 °C until analysis.

Heavy metals, 8-OHdG, and MDA concentrations as the outcomes will be measured at 2 time points: baseline (preintervention) and postintervention (after 8 weeks). The measurements at baseline will be performed at enrollment, before the administration of *M. oleifera* supplementation. The measurements at postintervention (after 8 weeks) will be performed at the end of the 2-month supplementation period, when the same biomarkers (blood heavy metals, 8-OHdG, MDA) will be reassessed to evaluate changes.

Intervention Group

In addition to receiving iron capsules, which are standard supplements provided by the health centers as part of the national prenatal care program, participants in the intervention group also received *M. oleifera* extract supplementation at a dose of 2000 mg/day, administered as 2 capsules taken twice daily (totaling 2000 mg/day) for a continuous period of 8 weeks. Supplementation began immediately upon enrollment, which occurred between gestational weeks 20 and 32. Therefore, the regimen lasted from the time of enrollment until 8 weeks later, typically ending between weeks 28 and 40 of gestation. For participants enrolled in the late third trimester who delivered before completing the full 8 weeks, they were instructed to continue consuming the remaining *M. oleifera* supplements until the full course was completed. This approach aimed to ensure consistency in the intervention dosage, regardless of the timing of delivery, and to maintain the study's internal validity.

To support adherence, we collaborated with health cadres at each participating health center. The cadres will be responsible for supervising, reminding, and ensuring that the mothers consistently take the moringa capsules. A WhatsApp group was established specifically for the cadres to facilitate regular communication, provide reminders, and monitor the supervision

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process throughout the 8-week supplementation period. We have also added a simple adherence log that will be maintained by the cadres, documenting capsule intake daily based on direct questioning or observation. These dual approaches—cadre monitoring and pill counts—will allow us to triangulate adherence data and better distinguish true intervention effects from variability due to compliance.

Participants will be actively monitored for adverse events throughout the 8-week intervention period. At the follow-up visit, participants will be asked about any symptoms or side effects experienced, using a structured checklist and open-ended questions. Specific adverse events of interest include gastrointestinal discomfort (nausea, vomiting, and diarrhea), allergic reactions (skin rash and swelling), and general intolerance to the supplement.

Any serious adverse events, including pregnancy complications such as preeclampsia, gestational diabetes, preterm labor, or hospitalizations, will be recorded and reviewed by the study physician. Although these are not primary outcomes, maternal and fetal complications will be documented to ensure a complete safety profile.

Prior evidence suggests that *M. oleifera* supplementation at a dose of 2000 mg/day is safe for human use, including during pregnancy. However, all safety data will be recorded in participant case report forms, monitored by the study team, and summarized in the final report.

Control Group

Mothers in the control group will receive only the standard iron supplement. Although iron itself may influence oxidative stress, this effect can be controlled by equalizing iron intake across groups. They will be counseled on dietary sources of antioxidants and offered *M. oleifera* supplementation after study completion if desired. This delayed intervention strategy has been approved by the local ethics committee and was explained during informed consent.

To minimize the risk of measurement and performance bias, participants in the control group were not informed about the specific intervention given to the other group.

Biomarker Analysis

Heavy Metal Analysis

The measurement was conducted to determine Hg, Pb, and Cd levels in the blood of pregnant women during the second or third trimester. Heavy metals were analyzed using inductively coupled plasma mass spectrometry (ICP-MS) (Thermo Fisher Scientific, Bremen, Germany) and performed in micrograms per liter. To ensure analytical accuracy and method validation, we used certified reference materials (CRM BCR®-636, lyophilized human blood, Joint Research Center-JRC, European Commission) as a quality control standard. For quality assurance and quality control (QA/QC), calibration curves were generated using multielement standard solutions of known concentrations. Blank samples were included in each analytical batch to monitor contamination.

Oxidative Stress Analysis

In this study, 8 OHdG and MDA are used as biomarkers of oxidative stress because they capture two complementary pathways: DNA oxidative damage and lipid peroxidation, respectively. Both markers have been validated in pregnant populations exposed to heavy metals such as Pb, Cd, and Hg. Alternative enzymatic antioxidants (eg, glutathione peroxidase, catalase) require immediate enzyme activity preservation, which cannot be guaranteed under our field conditions; 8 OHdG and MDA, by contrast, remain stable in frozen plasma and are therefore better suited to the study's logistics.

Plasma concentrations of MDA (nmol mL^{-1}) will be quantified in duplicate using a commercially available ELISA kit (Thermo Fisher Scientific, Bremen, Germany). 8 OHdG (ng mL^{-1}) will be measured in duplicate with a validated ELISA kit (Bioassay Technology Lab, Shanghai Korain Biotech Co. Ltd). For each assay run, an 8-point standard curve, reagent blanks, and low-/high-quality control samples will be included. Concentrations will be derived from the standard curves using a 4-parameter logistic model, and any sample with a coefficient of variation > 10 % on duplicate readings will be reassayed. Laboratory technicians will be blinded to group allocation to minimize measurement bias.

Data Analysis

All analyses will be conducted using the R statistical software (latest version). Data entry and cleaning will be conducted by trained staff using a double-entry verification. For 24-hour food recall data, participants will be asked to estimate portion sizes using visual aids, and data will be reviewed during collection for completeness and clarity. For the FFQ, if participants leave implausible answers (eg, extremely high frequency), the data will be reviewed and clarified during the interview or excluded from analysis after documentation. Implausible intake frequency will be cross-checked with interview notes and food recall summaries to determine plausibility. An intention-to-treat (ITT) analysis will be performed to preserve the benefits of initial group allocation. For missing or partial responses, multiple imputation will be considered for covariates in the adjusted models. For missing outcome data at follow-up, last observation carried forward (LOCF) will be used when feasible. Sensitivity analyses will be conducted to assess the robustness of findings under different missing data assumptions. Outliers will not be automatically excluded unless clear reporting errors are confirmed. Outliers in biomarker measurement will be identified using the interquartile range method and retained unless proven to result from analytic error or sample contamination. All statistical analyses will be conducted with and without outliers to assess the robustness of the results.

Descriptive statistics will summarize participant characteristics. All continuous variables, including heavy metal concentrations and biomarker levels, will be checked for normality before analysis. In the case of non-normal distributions, appropriate data transformations (eg, log transformation) will be applied. If normality cannot be achieved, nonparametric tests (eg, Mann–Whitney *U* or Wilcoxon signed-rank test) will be used as alternatives. Analysis of group differences (pre- and postintervention). For each group, analysis will be conducted

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using the paired *t* test or Wilcoxon signed-rank test, depending on data distribution, to assess changes in heavy metals, MDA, and 8-OHdG levels before and after intervention. The significance level (alpha) will be set at .05, and all tests will be one-tailed.

For comparison between the groups (intervention vs control), analysis will be conducted using the difference-in-differences (DiD) method to measure the difference in changes between the intervention and control groups. The results will provide an overview of the impact of moringa leaf supplementation on the reduction of heavy metal levels and prevention of DNA damage in pregnant women. To address potential selection bias and confounding due to the nonrandomized design, we will use analysis of covariance (ANCOVA) to adjust for baseline differences in key variables such as maternal age, gestational age, education level, and baseline levels of heavy metals, MDA, and 8-OHdG.

Assumptions for ANCOVA will be checked using diagnostic plots and tests. Normality of residuals will be checked using the Shapiro–Wilk test and Q-Q plots. The homogeneity of variance test will use the Levene test from the car package. Linearity and homoscedasticity will be checked using residual versus fitted plots.

The interaction effects between intervention status and baseline heavy metal levels will be examined by adding interaction terms to the ANCOVA models. Additionally, stratification will be considered a sensitivity analysis to minimize bias. Baseline heavy metal levels will be included as covariates in the statistical models to account for variation in environmental exposure across recruitment areas. In addition, we will conduct exploratory subgroup analyses to assess potential effect modifiers. Outcomes will be examined separately for each heavy metal to assess whether the reduction effect of *M. oleifera* differs by metal type. Additional exploratory subgroup analyses may include stratification by trimester of pregnancy, nutritional status (BMI), and geographic location/pollution source.

If substantial differences are observed, these findings will be interpreted cautiously due to limited statistical power. All subgroup analyses will be considered hypothesis generating and reported transparently. If no significant interaction is found, primary analyses will focus on aggregate outcomes across all participants. Reduction in each individual heavy metal will be reported separately, along with a composite index. No interim analyses or stopping rules are planned due to the short duration of the trial and the nature of the design.

Results

Overview

The study was funded in 2024 and data collection began in July 2024. A total of 26 mothers in each group have participated. As of February 2025, the laboratory analysis is ongoing for the second step. We expect the results to be published at the end of 2025.

Expected Outcomes

Reduction in Blood Heavy Metal Levels

The primary outcome of this study is the reduction in blood Pb/Cd/Hg level. The hypothesis is that supplementation with *M. oleifera* will result in a reduction in the blood levels of heavy metals in pregnant women compared to those in the control group. Hence, the expected results are as follows: (1) A measurable decrease in the blood Pb/Cd/Hg concentration will be observed in the group receiving *M. oleifera* supplementation for 2 months. (2) The intervention group is expected to show a greater reduction in blood heavy metal levels than the control group, based on pre- and post-test analyses.

Scientific implications expected are that the result would provide evidence that *M. oleifera* has the potential to detoxify, thereby demonstrating that it is a safe and effective approach to reducing heavy metal accumulation in expectant mothers, who are at a higher risk of exposure to environmental pollutants.

Reduction in 8-OHdG and MDA Concentrations

Hypothesis: *M. oleifera* will reduce 8-OHdG and MDA levels in pregnant women compared with the control group.

The expected results are as follows: (1) Significant reduction in 8-OHdG and MDA levels in the intervention group, indicating a protective effect against oxidative stress and DNA damage. (2) The intervention group will show lower levels of 8-OHdG and MDA after the intervention than the control group.

These findings will indicate that the antioxidant compounds of *M. oleifera* are effective in inhibiting DNA damage and protecting cells against oxidative stress. This is especially important for pregnant women to ensure fetal health and reduce complications.

Safety and Tolerability of M. oleifera

Hypothesis: *M. oleifera* supplementation will be safe for pregnant women, with no significant adverse effects reported during the intervention period. Hence, the expected results are as follows: (1) Minimal to no adverse effects in the group receiving *M. oleifera* supplementation. (2) This safety profile is consistent with previous studies indicating that 2000 mg/day is safe for pregnant women.

This will provide further evidence that *M. oleifera* is a safe supplement for pregnant women, supporting its use in future clinical applications and maternal health programs.

In the final analysis, changes in heavy metal levels (Pb, Cd, and Hg) will be reported individually, as well as in aggregate if appropriate. Similarly, biomarkers of oxidative stress (8-OHdG and MDA) will be analyzed and reported separately. While the study is not powered for definitive subgroup comparisons, exploratory reporting by relevant characteristics (eg, trimester, nutritional status, and baseline exposure level) will be presented to generate hypotheses for future studies.

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Discussion

Principal Anticipated Findings

This study is expected to demonstrate that *M. oleifera* supplementation during pregnancy reduces blood levels of heavy metals and decreases oxidative stress biomarkers (8-OHdG and MDA). It also aims to confirm the safety and tolerability of moringa in pregnant women, laying the groundwork for its use as a low-cost, locally available intervention for mitigating environmental pollutant-related health risks.

Several animal studies have shown that moringa leaf extracts can significantly reduce heavy metal accumulation in vital organs and mitigate oxidative stress caused by Pb, Cd, and Hg exposure. These effects are attributed to its high content of flavonoids, phenolic acids, glucosinolates, and carotenoids, which act as free radical scavengers and binders of toxic metals.

While direct clinical evidence in pregnant women remains limited, moringa has been used traditionally in many parts of Indonesia and other countries as a nutritional supplement and natural remedy, including during pregnancy. Small-scale human studies in nonpregnant populations have reported improvements in antioxidant status and reductions in lipid peroxidation following moringa supplementation. This study assumes that the biological mechanisms observed in preclinical research—namely, antioxidant protection and chelation of toxic metals—will translate to similar detoxifying effects in pregnant women.

Importantly, while this study does not evaluate direct clinical outcomes (eg, birth weight, gestational age), the primary focus is on biomarker-based improvements, which are commonly used as surrogate indicators of fetal and maternal risk. The findings are expected to strengthen the biological plausibility for moringa as a preventive intervention in polluted environments and inform the design of future clinical outcome studies.

While the study aims to demonstrate reductions in blood heavy metals and oxidative stress biomarkers following *M. oleifera* supplementation, such findings—if observed—should be interpreted with caution. Positive outcomes would indicate that moringa is a promising candidate for reducing biochemical risk factors associated with environmental exposures in pregnancy. However, this study does not assess long-term or clinical outcomes (eg, fetal growth and birth weight) and therefore cannot confirm improvements in maternal or fetal health. Additionally, the study does not evaluate cost-effectiveness or scalability of implementation.

Conversely, if no significant effects are observed, several factors could explain this, including insufficient dosage, short intervention duration, limited sample size, or individual variability in absorption or baseline exposure. These considerations will guide future study design and refinement of the intervention strategy. Ultimately, findings from this study should be viewed as hypothesis-generating, laying the groundwork for larger, randomized trials with extended follow-up and clinical endpoints.

Comparison to Prior Work

Previous studies have supported the antioxidant potential of *M. oleifera*, particularly its ability to reduce oxidative stress. For instance, in infertile women, moringa supplementation reduced oxidative stress markers and slightly increased antioxidant biomarkers, suggesting potential benefits for reproductive health [38]. Another study [39] demonstrated that supplementation with moringa leaf extract decreased levels of MDA in pregnant women, suggesting its role in reducing lipid peroxidation. This supports the hypothesis of the present study regarding moringa's capacity to attenuate oxidative stress.

However, while there is growing interest in the detoxifying potential of moringa, evidence of its effect on heavy metal levels in humans remains limited. Currently, most studies demonstrating metal-chelating and detoxification effects of moringa have been conducted in animal models [40-46], showing efficacy in reducing Hg, Pb, and Cd accumulation. These include experimental studies in rodents that found significant reductions in blood and tissue metal concentrations after moringa supplementation.

This study extends this line of research by being one of the first protocol studies designed to evaluate whether these benefits translate into pregnant human populations exposed to environmental heavy metals. By integrating biomarker-based outcomes (heavy metals, 8-OHdG, and MDA), this study aims to address a critical evidence gap in prenatal environmental health interventions.

Thus, if our hypothesis is confirmed, it will add to a growing body of evidence supporting the nutritional role of antioxidant-rich plants in maternal health and offer novel evidence of moringa's detoxifying role in reducing human heavy metal burden during pregnancy.

Strengths and Limitations

This study has several limitations that should be acknowledged. First, the nonrandomized design introduces a risk of selection bias and limits internal validity. While the selection of different locations for the intervention and control groups was based on logistical and feasibility considerations, this may lead to differences in participant characteristics and environmental exposures. To mitigate this, statistical adjustments such as ANCOVA will be used, and effort has been made to select sites with comparable demographic profiles.

Second, blinding was not feasible in this trial—neither participants nor investigators are blinded to the intervention. This raises the potential for performance and detection bias, although this risk is minimized by the use of objective laboratory-based biomarkers assessed by independent laboratory technicians.

Third, the sample size may limit statistical power, particularly for detecting small effects or conducting subgroup analyses. As a result, findings from this study should be interpreted as preliminary and exploratory, forming a basis for future hypothesis-driven studies.

Fourth, the short duration of intervention (2 mo) and the use of biomarkers instead of clinical outcomes (such as birth weight

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or gestational age) limit the ability to draw conclusions about long-term maternal or fetal health impacts. While changes in oxidative stress and metal levels are valuable surrogate outcomes, future studies should evaluate direct clinical endpoints.

Finally, although both study groups were drawn from similar urban settings, environmental variability (eg, differences in pollution sources or background exposure levels) may confound the results. These residual environmental factors could influence outcomes independently of the intervention and are difficult to fully control.

Despite these limitations, the study addresses an important gap by testing a locally available, low-cost, and traditionally accepted intervention in a vulnerable population. Its findings will help guide the development of larger, more rigorous trials in the future.

Conclusion

If our hypothesis is confirmed, moringa supplementation may offer a promising, locally available intervention for mitigating metal-induced oxidative stress during pregnancy. However, conclusions must remain preliminary until supported by completed trial data.

Future Directions

Future studies should consider RCTs with larger sample sizes and multicenter recruitment to confirm causality. Investigating the dose-response relationship of moringa and including additional biomarkers (eg, GPx and catalase) would offer deeper insights into its antioxidant mechanisms. Longitudinal studies can assess whether reductions in oxidative stress lead to better birth and developmental outcomes. Future research should explore whether reductions in heavy metals and oxidative stress markers translate to improved birth outcomes, such as birth weight, gestational age, or neurodevelopmental status.

Dissemination Plan

The findings of this study will be disseminated through peer-reviewed journal publications, conference presentations, and policy briefs to local and national health stakeholders. Collaboration with the Makassar City Health Office is planned to integrate results into maternal health programs. Community workshops will also be organized to share findings with participants and local health workers, promoting the evidence-based use of moringa.

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Data Availability

Data will be available upon request.

Authors' Contributions

Conceptualization: HA, AK. Data curation: HA, UN. Formal analysis: HA, MA. Funding acquisition: HA. Methodology: HA, AK. Project administration: HA, UN. Writing-original draft: HA, UN, AK. Writing-review & editing: MA, MM, ACN, SME.

Conflicts of Interest

None declared.

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Abbreviations

8-OHdG: 8-hydroxy-2'-deoxyguanosine
Cd: cadmium
Cu: copper
DNA: deoxyribonucleic acid
Fe: iron
Hg: mercury
ICP-MS: inductively coupled plasma mass spectrometry

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LBW: low birth weight
MDA: malondialdehyde
Pb: lead
SDG: sustainable development goals
Se: selenium
Zn: zinc

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Translation and Cultural Adaptation of the Measure Yourself Concerns and Wellbeing (MYCaW) Questionnaire Into German: Protocol for the iSWOP Study

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Abstract

Background: The growing population of cancer survivors faces persistent physical and emotional challenges that significantly impact health-related quality of life (HRQL). To address these multifaceted needs, robust and culturally adapted patient-reported outcome measures (PROMs), such as the Measure Yourself Concerns and Wellbeing (MYCaW) questionnaire, are essential for understanding and improving survivors' subjective experiences.

Objective: This protocol aimed to outline the systematic translation and cultural adaptation of the MYCaW questionnaire into German. The MYCaW questionnaire, a PROM, is designed to capture individualized concerns and assess overall well-being, particularly in cancer care settings. By adhering to common guidelines, this research will provide a tool for assessing individualized concerns and patient needs among German-speaking patients with cancer.

Methods: Following International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines, this study will use a structured methodology involving forward and backward translation, expert review, patient review process, and preliminary validation to ensure linguistic and cultural equivalence. This study is approved by the ethics committee of the Medical Association Berlin (reference Eth-27/10). Construct validity will be assessed through comparison with the European Organisation for Research and Treatment of Cancer—Quality of Life Questionnaire, Core 30 (EORTC QLQ-C30) and the MIDOS (Minimal Documentation System; in German: Minimales Dokumentationssystem) questionnaire, to evaluate both quality of life and symptom burden.

Results: Funding of the study was obtained in January 2023. Patient recruitment started in the first quarter of 2023, and the cognitive debriefing phase is ongoing. Validation with the larger patient sample (N=120) is scheduled to conclude in the fourth quarter of 2025, with publication of the study results anticipated in the first quarter of 2026. The adaptation process will include translation, expert review, and cognitive debriefing with patients and health care professionals to ensure linguistic clarity and cultural relevance.

Conclusions: The translation and adaptation of MYCaW into German will contribute to expanding the availability of validated PROMs for German-speaking populations. By following rigorous international guidelines, this study aims to produce a reliable, culturally appropriate, and linguistically adapted German version of the MYCaW questionnaire for assessing patient concerns and well-being in oncology and supportive care settings. Future validation studies will be necessary to assess the psychometric properties of the adapted questionnaire and its applicability in clinical and research contexts. Potential challenges, such as maintaining conceptual equivalence in translation and ensuring broad representativeness in the validation process, will be addressed through iterative refinement. Once validated, the German MYCaW will provide a valuable resource for patient-centered research and care, helping to capture individualized concerns that might be overlooked by standardized instruments.

Trial Registration: German Clinical Trials Register DRKS00013335; https://drks.de/search/de/trial/DRKS00013335

International Registered Report Identifier (IRRID): PRR1-10.2196/74288

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KEYWORDS

health-related quality of life; HRQL; patient-reported outcome measures; PROM; cross-cultural adaptation; oncological patients; psychometric validation

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Introduction

A growing number of people are living with cancer or have survived it, making the well-being of these individuals an important area for research [1]. In addition to the advances in early detection and the increasing efficacy of oncology therapies, understanding and improving the health-related quality of life (HRQL) of patients with cancer has gained increasing attention. Many patients with cancer face persistent physical and emotional challenges long after completing primary therapy. Long-term and late effects of cancer treatments—such as chronic pain, cognitive dysfunction, and severe fatigue—can significantly impact HRQL [2,3]. These impairments often necessitate comprehensive strategies to address the multifaceted needs of oncology patients.

The assessment of HRQL relies on validated patient-reported outcome measures (PROMs) [4]. These tools provide invaluable insights into patients' subjective experiences, aiding clinicians and researchers in identifying specific areas requiring intervention [5]. One such tool, the Measure Yourself Concerns and Wellbeing (MYCaW) questionnaire, is recognized for its ability to capture individualized concerns and overall well-being [6]. MYCaW uses a patient-centered approach, allowing participants to report their primary concerns and assess their well-being, making it particularly useful in integrative oncology settings. The MYCaW questionnaire was first introduced in 2006 by Paterson et al [6] at the University of Bristol with support from the Medical Research Council Health Services Research Collaboration. Earlier work on MYCaW at the Bristol Cancer Help Center was recognized for its impact, earning a place on the shortlist and winning the Healthcare and Medical Research category at the 2003 Charity Awards. In 2020, Polley et al [7] and Seers et al [8] took over responsibility for MYCaW and Measure Yourself Medical Outcome Profile (MYMOP) leading to the foundation of Meaningful Measures Ltd [7-9] to manage the licensing of the questionnaire [10], while providing tailored guidance on capturing person-centered outcomes.

Most PROMs focus on predefined domains such as symptom burden, functioning, or general quality of life [4,11,12]. While these instruments are essential, they often fail to capture the individualized concerns that many patients identify as most pressing. In integrative oncology, where care extends beyond symptom control to include psychosocial and existential dimensions, such patient-defined concerns are particularly relevant [13,14]. Studies have shown that individualized priorities—such as fear of recurrence, family-related worries, or coping with identity changes—are frequently underrepresented in standardized PROMs [15]. Internationally, the MYCaW questionnaire has proven effective in addressing this gap and has been successfully adapted into several languages [16-20]. However, no validated German version currently exists. This represents a significant unmet need, as German-speaking oncology patients and researchers lack access to a culturally adapted tool for systematically documenting patient priorities and for enabling comparability across international studies.

The cross-cultural adaptation and validation of PROMs are essential to ensure their relevance and applicability across different languages and cultural contexts [21]. Translation is a critical first step in this process, requiring not only linguistic precision but also cultural sensitivity to maintain the questionnaire's conceptual equivalence and reliability. To guide this process, the widely recognized framework by Beaton et al [21] outlines a systematic multistep methodology involving forward and backward translations, expert review, and patient review processes to ensure conceptual equivalence between the original and adapted versions. In addition, the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) principles for good practices in translation and cultural adaptation emphasize maintaining linguistic precision and cultural sensitivity [22], while the Consensus-based Standards for the selection of health status Measurement Instruments (COSMIN) guidelines provide recommendations for assessing the measurement properties of translated instruments [23], such as validity, reliability, and cross-cultural equivalence. Together, these frameworks ensure that adapted tools are both culturally relevant and psychometrically sound.

This study protocol outlines the process of translating the MYCaW questionnaire into German and aims to provide a detailed framework for its cultural adaptation. By achieving a validated German version, this research aims to facilitate its use among German-speaking patients with cancer, enabling a deeper understanding of their self-reported individualized concerns and needs.

The primary objective of this protocol is to describe the methodology used in the translation and adaptation of the MYCaW questionnaire into German. Ultimately, the study aims to contribute to the broader field of patient-centered oncology care by enabling more accurate and culturally appropriate assessments of HRQL in German-speaking settings.

Methods

Study Design

This study will follow the ISPOR guidelines for the translation and cultural adaptation of patient-reported outcome measures [22] and the COSMIN guidelines for assessing cross-cultural validity and measurement invariance [23]. The process includes preparation, translation, patient review, and validation. The study protocol was written using the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) reporting guidelines [24].

Study Setting

This study is conducted by the Research Institute Havelhöhe (Forschungsinstitut Havelhöhe) at the hospital Gemeinschaftskrankenhaus Havelhöhe in Berlin within the Network Oncology [25].

Ethical Considerations

This study adheres to the principles of the Declaration of Helsinki and has received approval from the Ethics Committee of the Berlin Medical Association (Ethik-Kommission der Ärztekammer Berlin) under reference Eth-27/10. This trial is

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registered in the German Clinical Trials Register (DRKS00013335; registered on November 27, 2017). Written informed consent will be obtained from all participants before enrollment. Any significant protocol deviations or modifications will be reported to the Ethics Committee and the German Clinical Trials Register. A completed SPIRIT 2013 checklist is provided (see Checklist 1). Patients and the public were not involved in the design, reporting, or dissemination plans of the study protocol of this research but will be involved in the conduct of the outlined study in the future during the debriefing and validation process. All participants receive written and verbal information about the study, including its purpose, procedures, risks, and benefits, and will give written informed consent before participation. They may withdraw at any time without consequences. Participant privacy and confidentiality will be strictly protected. Identifiable information will be stored separately from research data on secure, password-protected institutional servers accessible only to authorized study personnel. Data will be pseudonymized for analysis, publication, and possible sharing and retained only as long as legally and scientifically required. Participation involves minimal risk and no invasive procedures. No financial incentives are offered. This protocol complies with JMIR's ethical reporting guidance

Translation Process

Figure 1 shows the flowchart illustrating the systematic process of the questionnaire translation into German language following the ISPOR guidelines. The steps ensure linguistic and conceptual equivalence between the original and translated versions, maintaining validity and reliability. The translation process involves 2 independent bilingual translators (native German speakers fluent in English) who will produce 2 German versions of the MYCaW questionnaire. These versions will be, after discussion of discrepancies, combined into a single German draft (see Figure 1).

The translators will focus on maintaining conceptual equivalence rather than literal translation, considering cultural nuances and medical terminology.

This process is followed by 2 back-translations into English with the help of 2 native independent English speakers fluent in German. The backward translations will be compared with the original MYCaW questionnaire to identify discrepancies (see Figure 1). A reconciliation meeting including translators and a third bilingual expert will be held to resolve semantic, idiomatic, and conceptual discrepancies, ensuring conceptual equivalence. A panel of experts, including oncologists, psychologists, and patient representatives, will review all versions to ensure linguistic and cultural accuracy. The panel will finalize a pretest version of the German MYCaW questionnaire.

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Figure 1. Flow chart of the translation process according to International Society for Pharmacoeconomics and Outcomes Research (ISPOR) guidelines. MYCaW: Measure Yourself Concerns and Wellbeing.

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Participant Review

A total of 15 patients with cancer will be recruited for cognitive debriefing based on diversity in age, cancer type and stage, treatment history, and educational background. This purposive sampling approach is intended to enhance representativeness within the single-site setting and to capture a broad spectrum of patient perspectives. Inclusion criteria are providing written informed consent, being 18 years and/or older, having a confirmed (any) cancer diagnosis, and having sufficient German language proficiency. Exclusion criteria are no written informed consent and cognitive impairment of the patient. The pretest version will be evaluated by these patients for its clarity, cultural relevance, and ease of understanding. Semistructured interviews will be conducted to gather participants' feedback on specific items (see Figure 1).

Analysis of Cognitive Debriefing Interviews

Cognitive debriefing interviews will be audio-recorded, transcribed verbatim, and analyzed using qualitative content analysis according to Mayring [26]. In addition, 2 researchers will independently code the transcripts, combining deductive categories (eg, clarity, cultural relevance, and comprehensibility) with inductive categories emerging from the data. Discrepancies will be resolved by discussion or with a third reviewer. Findings will be summarized in matrices to identify key issues and inform refinement of the German MYCaW version.

Validation Phase and Psychometric Testing

The subsequent validation phase will include approximately 120 participants from the same site, but purposive sampling will again be applied to ensure heterogeneity in demographic and clinical characteristics. This sample aligns with COSMIN recommendations for studies assessing psychometric properties. Specifically, it meets thresholds considered "very good" for evaluating internal consistency and construct validity and provides sufficient power for exploratory analyses of structural validity and reliability. Content validity will be assessed through patient feedback, which helps ensure that the questionnaire items are relevant, comprehensive, and representative of the real experiences of the patients with cancer. This will involve qualitative methods such as interviews or surveys to compare MYCaW content with participant-reported concerns and well-being issues. Internal consistency will be evaluated using Cronbach α, with a commonly accepted threshold for good internal consistency of 0.7 or higher [27]. This will be calculated for each subscale of the MYCaW questionnaire to ensure that items within each dimension of HRQL are consistent and reliable in measuring the same underlying construct. To ensure consistency and reliability in the qualitative analysis of patient concerns, all coders will undergo structured training in the use of the adapted MYCaW coding framework. This training will include familiarization with category definitions, practice sessions using sample data, and calibration exercises to align interpretation. Coding discrepancies between raters will be addressed through a consensus process involving joint review and discussion. If no consensus can be reached, a third independent expert will be consulted to resolve the disagreement.

To assess construct validity, the MYCaW questionnaire that will be compared with the EORTC-QLQ C30 is the European Organisation for Research and Treatment of Cancer—Quality of Life Questionnaire, Core 30 (EORTC-QLQ C30) [11], and the MIDOS questionnaire [28] for HRQL measures will be used to examine whether the MYCaW questionnaire captures similar constructs and whether changes in MYCaW scores align with changes in other established measures. This approach helps to ensure that the MYCaW questionnaire is measuring HRQL in a manner consistent with these validated tools. While the EORTC-QLQ C30 evaluates HRQL across multiple domains (symptom scales and functioning scales), the MIDOS assesses symptom burden in palliative or supportive care contexts. This dual comparison allows analysis of both standardized and patient-prioritized concerns.

Contingency Planning

To mitigate potential recruitment delays, the study timeline allows for flexible enrollment extensions. Collaboration with clinical teams at the study site will be strengthened to ensure participant identification and recruitment. These steps are aimed at ensuring timely recruitment without compromising statistical validity.

Timeline and Milestone Plan of the Study

Table 1 presents the timeline of the MYCaW translation and validation process. Key milestones and projected completion dates are highlighted, with further details available in Figure 2 (Gantt chart). The finalized German version will undergo preliminary testing with a larger sample to assess reliability and validity (see Table 1). The psychometric properties to be evaluated include content validity, internal consistency, and construct validity. These psychometric evaluations are critical to ensuring that the translated MYCaW questionnaire is both reliable and valid for assessing HRQL among German-speaking oncology patients.

Figure 2 presents the Gantt chart outlining the timeline of the MYCaW translation process. Key milestones and projected completion dates are highlighted, with further details available in Table 1.

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Table . Timeline of the study.

Phase and timeline	Translation process
Year 2023: Translation process completion (Phase 1)	
Quarter 4, 2023 to Quarter 2, 2024	• Finalize the German MYCaW[a] version after translation, reconciliation, and expert review.
Year 2024: Patient review process and preliminary validation (Phase 2 - 3)	
Quarter 2, 2024 to Quarter 3, 2024	• Patient review process. • Test the prefinal version with 15 patients, conduct interviews, and refine based on feedback.
Quarter 3, 2024 to Quarter 4, 2024[b]	• Finalize the German version, begin validation with a larger sample (N=120) of participants, and assess psychometric properties (content validity, internal consistency, and construct validity).
Year 2025: Data analysis, final testing, and study conclusion (Phase 4 - 6)	
Quarter 4, 2024 to Quarter 3, 2025	• Continue validation and finalize data collection. • Complete recruitment, conduct final psychometric analysis, and review preliminary results.
Quarter 3, 2025 to Quarter 4, 2025	• Conclude study and finalize participant follow-up. • Publish findings, present results, and complete study.
December 2025: Study officially ends.	

[a]MYCaW: Measure Yourself Concerns and Wellbeing.

[b]Contingency planning allows for time extensions in quarter 3–quarter 4, 2024, to allow for potential recruitment delays.

Figure 2. Milestone plan of the iSWOP (Implementierung eines Fragebogens zur Erfassung von Sorgen und Wohlbefinden bei onkologisch-palliativen PatientInnen) study to ensure adequate enrollment, Q3–Q4 2024 allows for potential extensions in the event of recruitment challenges.

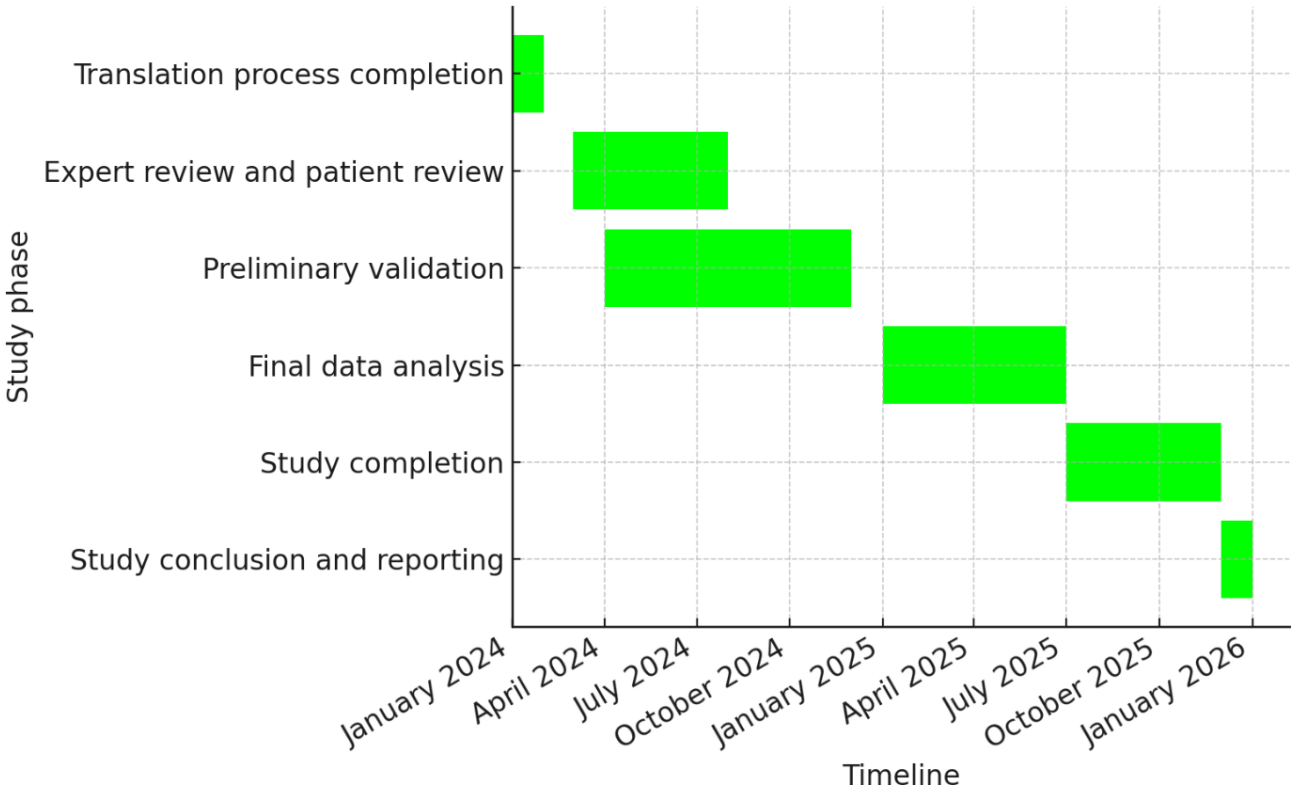

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Results

The study was funded in January 2023. Recruitment began in the first quarter of 2023, with cognitive debriefing currently being underway. Validation with a larger patient sample (N=120) is projected to be completed by the fourth quarter of 2025, with results expected for publication in the first quarter of 2026. A standardized coding framework will be developed for analyzing patient concerns, with interrater reliability assessed to ensure consistency. The final German MYCaW version is expected to maintain the conceptual integrity of the original while being accessible and meaningful for German-speaking oncology patients.

Discussion

Principal Findings

This study outlines a systematic approach to the translation and cultural adaptation of the MYCaW questionnaire into German, which is essential for capturing individualized patient concerns in integrative oncology. MYCaW has been widely used in various research settings to assess patient-reported concerns and overall well-being. Its flexible and patient-centered design allows individuals to express their most pressing issues, making it particularly suitable for integrative oncology and supportive care [6]. Across health care contexts, MYCaW has shown value in complementing standardized HRQL tools.

Several studies have used MYCaW to explore the impact of interventions, assess patient priorities, and track changes in well-being over time [6,20,29,30]. Previous research demonstrated that MYCaW captures nuanced, patient-specific concerns that standardized questionnaires may overlook, thereby facilitating tailored interventions that may improve overall quality of life [6,8]. For example, in a palliative care setting, MYCaW's open-ended design provided valuable qualitative insights into patient needs, and health care professionals reported it as easy to use and beneficial for patient-focused discussions [29]. A standardized coding framework with 5 super-categories and 36 specific categories was developed to analyze concerns, achieving high interrater reliability (κ=0.905) [29]. In addition, studies comparing MYCaW with established HRQL measures, such as the EORTC QLQ-C30, also found it complements existing tools by offering a more individualized assessment [30].

Like MYCaW, the precursor questionnaire MYMOP has also been used extensively to evaluate patient-centered outcomes. While MYMOP focuses on symptom-specific concerns and treatment effects, both instruments share a common philosophy of prioritizing patient voice and individualized health concerns [31]. MYCaW is particularly relevant in psycho-oncology due to its focus on well-being.

Regarding translation and cultural adaptation, MYCaW has already been successfully adapted into several languages, including Danish, Polish, Hebrew, Romanian, Somali, Spanish, and Turkish [16,17]—following rigorous methodologies. These efforts underscore the importance of careful linguistic validation to preserve validity and reliability [32]. The German translation and adaptation of MYCaW presented here follows internationally recognized frameworks (ISPOR and COSMIN) [22] and the Meaningful Measures protocol, ensuring conceptual equivalence and cultural relevance [21]. Expert review, reconciliation meetings, and cognitive debriefing interviews with patients are designed to secure both linguistic fidelity and relevance to the target population. Validation against 2 widely recognized PROMs, the EORTC QLQ-C30 and the MIDOS questionnaire, will allow for a nuanced analysis of MYCaW's psychometric performance and its alignment with both functional quality-of-life and symptom-specific metrics. This dual approach provides a robust framework for assessing construct validity in the German oncology context. The German MYCaW adaptation aligns with similar initiatives in other languages, which have emphasized the need for iterative refinement through patient and expert feedback [33]. These processes are essential for ensuring that the instrument effectively captures the lived experiences of diverse patient populations.

The study has several strengths, notably its systematic methodology and adherence to international guidelines. By incorporating cognitive debriefing and semistructured interviews, the protocol ensures that the German MYCaW will be linguistically accurate and culturally relevant to German-speaking patients with cancer. Once validated, it will provide health care professionals with a valuable tool for addressing individualized concerns and needs in oncological care. Nevertheless, some limitations remain. The cognitive debriefing phase includes 15 participants, sufficient to identify major issues but not necessarily capturing all nuances in a diverse population. Although purposive sampling will be applied to maximize heterogeneity, recruitment is restricted to a single site, which limits representativeness across the German-speaking cancer population. While the German version may also be linguistically appropriate for Austria and Switzerland, cultural relevance in these settings has not been tested and will require future studies. Patient and public involvement in this protocol has been limited, though their perspective will be integrated during debriefing and validation; in the future, earlier engagement in study design could enhance cultural sensitivity. Finally, inherent biases in forward-backward translation may influence conceptual equivalence, despite the safeguards of expert panel and reconciliation meetings. Future studies should focus on larger-scale validation and psychometric testing to further refine the German MYCaW and enhance its applicability in routine clinical practice [34].

Several risks to validity must also be acknowledged. A small debriefing sample may overlook issues of comprehension or cultural resonance; this will be mitigated through purposive sampling to ensure variation in age, diagnosis, and educational background. Single-site recruitment limits generalizability, but careful documentation of participant characteristics will support assessment of transferability. The qualitative analysis of interviews is inherently interpretative; to strengthen credibility, 2 independent coders will apply the Mayring qualitative content analysis, with discrepancies resolved through discussion or arbitration by a third reviewer. Conceptual equivalence in translation is another challenge; this will be minimized through

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systematic reconciliation, expert panel review, and iterative patient feedback.

Conclusion

In conclusion, MYCaW has been shown internationally to be a valuable tool for assessing individualized patient concerns and well-being. Its successful application in diverse settings highlights its relevance, and the ongoing translation and adaptation efforts aim to expand accessibility across different linguistic and cultural contexts. The German translation and adaptation will address an important gap by providing a culturally appropriate instrument for patient-centered oncology research and care, thereby contributing to a more comprehensive understanding of cancer survivors' needs. While the protocol is methodologically robust, larger multicenter studies will be needed to confirm generalizability across the wider German-speaking population. Future projects should also involve patients and the public more actively at earlier stages of study design. Finally, the methodology described here may serve as a blueprint for similar cross-cultural adaptation studies.

Trial Status and Protocol Amendments

The current protocol version is 1.0, dated from January 17, 2023. The trial is ongoing and currently enrolling. The first participant was enrolled on January 23, 2023, and recruitment is expected to be completed in the fourth quarter of 2025 with the follow-up completed by the end of 2025. Any amendments to the study protocol (eg, changes in recruitment procedures, sample size, or analysis plan) will be documented in a version-controlled protocol file, reported to the ethics committee, and prospectively updated in the trial registry (DRKS00013335). Major changes will also be transparently reported in subsequent publications.

Dissemination

The findings will be presented at international and national scientific conferences such as the European Society for Medical Oncology congress, the European Congress of Integrative Medicine, the German Cancer Congress of the Cancer Society (Deutscher Krebskongress) or the congress of the German Society of Oncology and Hematology. For scientific publication, the paper will be submitted to peer-reviewed journals with a focus on oncology, integrative oncology, or psycho-oncology, such as *BMC Cancer*, *Supportive Care in Cancer*, or *The Oncologist*. Targeted communication with stakeholders in the patient community involves presentations at patient-oriented congresses such as the Cancer Patients Europe Annual Conference [35] or the European Association for Cancer Research Congress Patient Involvement in Cancer Research [36]. Furthermore, results will be communicated through lay summaries published in newsletters of the hospital or of patient organizations, for example, Haus der Krebs-Selbsthilfe—Bundesverband eV, Leben nach Krebs eV [37], and Deutsche Stiftung für Junge Erwachsene mit Krebs [38], and disseminated digitally via the hospitals' social media channel as well as these organizations. These efforts will ensure that findings are accessible and understandable for patients, caregivers, and the wider community.

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during this study.

Authors' Contributions

Conceptualization: AT, LS, CJ, SLO, SJ, JR, FS
Methodology: AT, FS
Data curation: AT
Formal analysis: AT
Validation: AT, FS
Visualization: AT, FS
Project administration: FS
Funding acquisition: FS
Writing – original draft: AT, FS
Writing – review & editing: AT, LS, CJ, SLO, SJ, JR, FS
Translation (English to German, forward translation): AT, FS
Translation (German to English, backward translation): KA

Conflicts of Interest

FS reports grants from Helixor Heilmittel GmbH (travel costs and honoraria for speaking), grants from AstraZeneca (travel costs and honoraria for speaking), and grants from Abnoba GmbH, outside the submitted work. AT reports grants from the Medical

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Section of the Goetheanum (honoraria for speaking), outside the submitted work. None declared by the other authors. No payment was received for any other aspects of the submitted work. There are no patents, products in development, or marketed products to declare. There are no other relationships, conditions, or circumstances that present a potential conflict of interest.

Checklist 1
SPIRIT 2025 checklist.
[PDF File, 515 KB - resprot_v14i1e74288_app1.pdf]

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Abbreviations

COSMIN: Consensus-based Standards for the selection of health status Measurement Instruments
EORTC-QLQ C30: European Organisation for Research and Treatment of Cancer—Quality of Life Questionnaire, Core 30
HRQL: health-related quality of life
ISPOR: International Society for Pharmacoeconomics and Outcomes Research
MYCaW: Measure Yourself Concerns and Wellbeing
MYMOP: Measure Yourself Medical Outcome Profile
PROM: patient-reported outcome measure
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Effects of a Violence Prevention Intervention Therapeutic Meeting With Aggression in Forensic Psychiatric Inpatient Care: Protocol for an Observational Study

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Abstract

Background: Aggression and violence are prevalent in forensic psychiatric inpatient care. These behaviors significantly impact treatment outcomes, create challenging work environments for staff, and strain relationships between patients and caregivers. Managing such behaviors poses a formidable challenge that necessitates innovative approaches and evidence-based interventions. The Therapeutic Meeting with Aggression (TERMA) model is a staff training program designed to equip staff with strategies to de-escalate patient aggression, thus reducing violence and increasing patients' and staffs' perceived safety.

Objective: The aim of this project is to evaluate the violence prevention model TERMA regarding perceived safety by patients and staff and adverse events within forensic psychiatric inpatient care. In addition, the project will investigate whether the organizational culture affects the implementation of the TERMA model.

Methods: The project includes an observational study with a before and after design. Implementation of the TERMA model consists of an 8-seminar staff training program. Data sources include questionnaires, medical records, and registries. Quantitative data will be analyzed using descriptive and comparative statistics. To analyze changes between measurements, dependent sample 2-tailed *t* tests will be used for normally distributed data, and the Wilcoxon signed-rank test will be applied when normality is not met. The project will also include qualitative interview studies, which are planned to be analyzed using qualitative inductive content analysis.

Results: Participant enrollment began in July 2023 and was concluded by the end of 2024. Data collection and analysis of quantitative data are expected to be completed by early 2026, after which the study findings will be submitted for publication in peer-reviewed scientific journals. Collection of qualitative data is scheduled for the second half of 2025 and 2026.

Conclusions: This study can add valuable knowledge about the effects of the violence prevention model TERMA.

Trial Registration: ClinicalTrials.gov NCT05932108; https://clinicaltrials.gov/study/NCT05932108

International Registered Report Identifier (IRRID): DERR1-10.2196/74295

(JMIR Res Protoc 2025;14:e74295) doi:10.2196/74295

KEYWORDS

mental health; forensic psychiatry; de-escalation; aggression; staff training; inpatient violence

Introduction

Background

Aggression and violence are common within forensic psychiatric inpatient care, encompassing verbal and physical threats, as well as escalations that may result in physical injuries [1,2]. A meta-analysis found that 17% of patients in psychiatric inpatient care had been involved in at least one incident of interpersonal violence [3], and research indicates that the proportion is even higher, exceeding 20%, in forensic psychiatric inpatient care [4]. Studies from forensic psychiatric care report a higher

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prevalence of patients who are violent compared to acute care settings and general psychiatric hospitals [5]. Several factors could contribute to the escalation of aggressive incidences in forensic psychiatric inpatient care, including shortage of staff; insufficient knowledge or practice in aggression management; and changes in patient demographics, prevalence of mental health disorders, treatment approaches, and institutional policies [5].

In psychiatric (inpatient) care, aggression and violence have traditionally been seen as linked to mental illness and other individual patient characteristics. Therefore, response has centered on reactivity and control, and staff education has emphasized self-defense, control, and restraint techniques. However, over the last 2 decades, focus has shifted toward seeing aggressive patient behavior as a result of a complex interplay of diverse internal, external, and situational factors. Violent behavior may lead to injury but may also have other consequences, such as diminished therapeutic relationships [6], lower job satisfaction, and increased psychological stress [7,8]. Previous research on staff and patient experience of aggression and violence that resulted in coercive interventions (including seclusion, restraint, and medication) shows that incidents negatively affect treatment, work environment, job satisfaction, and therapeutic relationships between patients and staff [9]. Research also indicates that structured de-escalation models increase active listening between staff and patients that helped reduce seclusion and coercive methods within the ward [10]. In addition, the use of coercive measures as a response to violent behavior is problematic for both patients and staff and harmful for the therapeutic alliance. Moreover, patients experience these measures punitively [9].

To reduce the use of coercive measures, the recommended response to potential violence and aggression risk in forensic psychiatry is de-escalation of the situation [6]. It involves staff intervention before a situation reaches a point where more restrictive measures become necessary [6]. Several de-escalation models have been developed and are being used within psychiatric inpatient settings [11], including positive behavioral support [12,13], M4 ("managing the team, managing the environment, managing the patient, and managing aggression") [14], the Bergen model [15], and the subsequent Therapeutic Meeting With Aggression (TERMA) model. A common objective among these models is the reduction of coercive interventions, but there are some distinct differences between the models [16]. Positive behavioral support focuses on bolstering staff confidence and modifying perceptions of challenging patient behavior with the primary objective of establishing a safe and secure environment [12]. It includes comprehensive staff training with a particular emphasis on enhancing communication skills and using tools to manage challenging patient behavior [12]. M4 centers on theoretical elements, including the analysis of organizational patterns of aggression, and places emphasis on risk management [14]. The Bergen and TERMA models place a central focus on treatment, communication, and the delivery of patient-centered health care within the specific context of forensic psychiatric settings. The models are designed to address and mitigate aggression and violence using a system of low-intensity interventions organized according to the patient's aggression level, risk of violence, and history of previous violent acts [15]. At present, forensic psychiatric hospitals use a variety of de-escalation models, emphasizing both proactive and reactive measures to maintain a secure and therapeutic care environment. Communicative and cognitive de-escalation in the form of verbal discussion is one of the most common practices in de-escalation, emphasizing stimulus reduction and attempting to guide the patient away from unwanted behavior [17].

One obstacle to successful implementation of new work practices is that staff resist the change. A certain degree of resistance is common and expected when new practices are introduced [18,19]. Resistance to change refers to the reluctance or opposition displayed by staff when confronted with alterations in their work environment, practices, or procedures [20]. This resistance can manifest in various forms, such as skepticism, reluctance to adopt new practices, or active opposition to proposed changes [18,21]. Several factors contribute to resistance to change, including uncertainty and fear of the unknown, comfort with the status quo, lack of involvement in the change process, concerns about competence, previous negative experiences, workload and time constraints, and current cultural and organizational factors [22]. A number of factors are important to induce staff receptiveness to change, including work atmosphere, an effective framework of well-established procedures and methods, visible support for the change from leadership [18], transparent and open communication about the reasons for the change, the expected benefits, and how it aligns with broader organizational goals [22], and regular updates and opportunities for staff to ask questions or express concerns [18]. This significantly contributes to creating a sense of security and comfort, potentially resulting in a reluctance to embrace change or explore new techniques and work methodologies among experienced staff [21]. In addition, staff needs the necessary resources, tools, and technology to implement and sustain the changes effectively [18].

In Sweden, someone having been found guilty of a crime committed under the influence of a severe mental disorder can be sentenced to forensic psychiatric care instead of prison. Forensic psychiatric care is compulsory, and the sanction is not determined by time, as stipulated by the Swedish Courts' Forensic Mental Health Act. Recent measurements indicate that the median care duration is 7.5 years but can be even longer [23]. Patients within forensic psychiatric care in Sweden represent a highly heterogeneous group [24]. Most common diagnoses include different forms of psychotic disorders, substance use disorders, and personality disorders. Comorbidity is prevalent, and 2 or 3 concurrent diagnoses are very common [25]. A large proportion of patients in forensic psychiatry are offenders who have committed violent crimes, and consequently, they present a distinctive set of challenges related to aggression and violence [24,26].

Delivering health care services within the framework of mandatory care poses challenges, including amotivation, noncompliance, and impediments to trust between patients and staff [27]. The indefinite duration of care adds complexity to the task of establishing a secure health care environment [23]. Forensic psychiatric inpatient care confronts these challenges

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and requires adaptation to ensure the effective implementation of treatment and the resulting discharge [28]. Violence and aggression are prevalent in forensic psychiatric inpatient care [3], posing a complex challenge that requires innovative and evidence-based interventions [4,16]. Current recommendations advocate for a proactive rather than a reactive approach to dominate staff education [29].

Objectives

There is a lack of evidence regarding the effects of de-escalation models such as the TERMA model. Therefore, the aim of this project is to evaluate the violence prevention model TERMA regarding adverse events and perceived safety by patients and staff within forensic psychiatric inpatient care. In addition, the project will investigate whether the organizational culture influences the implementation of the TERMA model and the experiences of patients and staff in situations involving threats, violence, and the use of coercive measures. The project includes the following research questions:

- To what extent does the implementation of TERMA impact the perceived safety and perception of violence preventative culture in the wards of staff and patients in a forensic psychiatric inpatient setting?
- What is the effect of implementing TERMA on the frequency of incidents of aggression and violence, health care and occupational injuries, and the use of coercive measures in a forensic psychiatric inpatient setting?
- How does the organizational culture of a forensic psychiatric inpatient unit impact changes in perceived safety, incidents of aggression and violence, health care and occupational injuries, and the use of coercive measures?
- How do patients perceive threatening and violent situations, exposure to coercive measures, and the implementation of TERMA in a forensic psychiatric inpatient setting?
- What are the attitudes and perceptions of staff toward working with TERMA, how do they respond to threatening and violent situations, and what is the impact of these factors on the work environment in a forensic psychiatric inpatient setting?

Methods

Overview

This study uses an observational before and after design. The choice of TERMA was a pragmatic one, as it was being implemented in the clinic. However, the research design, including research questions, outcome measures, and methods of analysis, was not influenced by the clinic. The project was registered on ClinicalTrials.gov (NCT05932108) before starting the study. The protocol complies with the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [30,31], and the results will be reported according to established recommendations.

Participants and Setting

Participants meeting the study's inclusion criteria will be recruited from the Sahlgrenska University Hospital in Gothenburg. The forensic psychiatric clinic consists of 96 patient rooms, of which 12 are allocated to the high-security ward and 84 are dedicated to rehabilitation wards. The layout includes shared spaces such as a common room, a communal dining area, and a kitchen. Due to a shortage of health care rooms, some patients share rooms. In total, staff, comprising nurses, assistant nurses, psychiatrists, and other various professional occupations, amount to approximately 290 people. These various professional categories collaborate within health teams to formulate comprehensive health care plans and treatment strategies. The study encompasses both patients and staff within the forensic psychiatry setting. The inclusion and exclusion criteria for patients and staff are presented in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria (patients)

- Men and women aged ≥18 years committed to rehabilitation units
- Placed under the jurisdiction of the Mental Care Act (1991:1129) on Forensic Psychiatric Care
- Understand (speak and read) Swedish
- Assessed by the treating physician as mentally able to understand and consent to the study
- Willing to participate and sign a consent form

Exclusion criteria (patients)

- Minors (aged ≤17 y)
- Treated under legislation other than the jurisdiction of the Mental Care Act (1991:1129) on Forensic Psychiatric Care
- Cannot understand and speak Swedish and are thus unable to understand the study material
- Not assessed by the treating physician or assessed and deemed mentally unable to participate in research
- Unwilling to participate

Inclusion criteria (staff)

- Men and women aged ≥18 years working within forensic psychiatric inpatient care
- Understand (speak and read) Swedish
- Willing to participate and sign a consent form

Exclusion criteria (staff)

- Not directly involved in patient care within forensic psychiatric inpatient facilities
- Cannot understand and speak Swedish and are thus unable to understand the study material of the study
- Unwilling to participate

Enrollment

All patients in the included wards will be assessed for eligibility by a member of the research team together with the ward staff and the responsible physician. Eligible patients will be given information about the study and asked to participate. Patients will be informed, both orally and in writing, that participation in the study is voluntary. They will also be assured that they can withdraw their consent at any time, and their decision to participate or not will not affect their care. Patients who indicate their willingness to participate will be issued a consent form. When returning the completed consent form, patients will receive the E13 questionnaire, which will include a randomly assigned identification number to ensure confidentiality throughout the research process.

All staff will be assessed for eligibility by a member of the research team. Eligible staff will receive detailed information about the study and be invited to participate. Information will be provided both orally and in writing. Staff who express their willingness to participate will be provided with a consent form. Upon returning the completed consent form, staff will receive 2 questionnaires (the E13 and the Organization Values Questionnaire [OVQ]), each coded with a randomly assigned identification number to ensure confidentiality throughout the research process.

Design and Implementation of the TERMA Model

The TERMA model originates from Norway and has been used within both inpatient and outpatient psychiatric care. When it was first introduced in Sweden, it was given the name the Bergen model after the city it was developed in. At this time, it was adopted to align Swedish health care laws and adjusted to clarify a theoretical nursing approach. The Bergen model offers a specialized framework for managing aggression and violence within both inpatient and outpatient forensic psychiatric care [15]. After the evaluation of the Bergen model by Bergendahl et al [15], the model was adopted by another clinic in Sweden; further modifications were made; and the original name from Norway, TERMA, was reintroduced.

The core objective of the TERMA model is to proactively prevent aggression and violence by using a tiered system of low-intensity interventions, which are stratified based on the patient's aggression level, risk of violence, and history of violent acts.

The TERMA model is rooted in the principles of compassionate health care and emphasizes treatment, communication, and effective management.

The foundation of TERMA acknowledges the inherent capabilities of all individuals, each possessing a unique self-awareness; distinct life experiences; expectations; needs; preferences; and available resources such as talents, interests, and education. Within TERMA, a central element involves a

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collaborative partnership between health care professionals and patients. They work together to formulate a personalized treatment plan, drawing upon the patient's individual illness history and collectively identifying potential obstacles to effective care.

The TERMA model is structured in a "cascading" order, wherein the response to violence or aggression escalates if the interventions at one level do not prove enough.

These levels are designed to correspond with specific situational demands and environmental factors, optimizing their relevance and applicability. The *primary level* centers on the patient's daily behavior and overall health status. It involves proactive measures aimed at understanding the patient's emotional state, as well as managing stress and anxiety. Building trust and establishing balanced roles are key components at this stage. At the *secondary level*, the focus shifts to risk assessment and violence management. The aim is to cultivate mutual understanding between the patient and health care workers regarding the situation. The emphasis is on finding common ground and agreeing on acceptable solutions while preparing for further escalation if necessary.

When violence becomes inevitable, the *tertiary level* is activated. Here, the primary goal is to create a calm and secure environment for the patient, other patients, and staff. Clear leadership and low-intensity approaches are vital for diffusing tension, and physical restraint, if required, is executed with precision. Following the resolution of the situation, a situational analysis is offered to the patient to enhance understanding and prevent future incidents.

The implementation of TERMA is conducted through a staff training program consisting of 8 seminars. The seminars are divided into 4 theoretical sessions and 4 practical training sessions. The staff members first receive theoretical knowledge, followed by hands-on practice in restraint and self-defense techniques. This mixed format facilitates a holistic understanding of TERMA and equips staff with the skills necessary for implementation. The TERMA intervention will be uniformly implemented across all wards of forensic psychiatry at the Sahlgrenska University Hospital.

Quantitative Sources and Collection of Data

Data will be collected from questionnaires, medical records, and administrative registers. Questionnaire data will be obtained from both patients and staff at baseline and 6- and 12-month follow-up. To assess perceived safety, data will be gathered from both patients and staff members using the E13 [15]. The E13 assesses self-reported safety, feelings of security, and violence preventative culture within the hospital wards. Respondents will be presented with 13 statements, and their level of agreement will be rated on a 4-point Likert scale, ranging from (1) "completely disagree" to (4) "completely agree," with an additional "do not know" option available [15]. The questionnaire assigns a value of "1" to response options 3 and 4 for all items, except for the 3 negative items (items 4, 8, and 12), where a value of "1" is assigned to options 1 or 2 [15]. All other responses are scored as "0." Thus, the sum score range for each questionnaire was 0 - 13 [15].

The OVQ will be used to investigate the organizational culture in the wards. The survey will only be distributed to staff. The OVQ is based on the concepts of the competing value framework, which measures the 4 dimensions within each business: collaboration, creation, competition, and control [20]. These values compete in a very real sense for a business's limited resources (funding, time, and people). The questionnaire contains 52 items, each rated on a 10-point Likert scale from "disagree" to "strongly agree" [20]. Data regarding incidents of threats and violence, patient and occupational injuries, and the application of coercive measures will be extracted from medical records and the local clinical registry known as MedControl PRO. These data points will be collected in 3 distinct phases: before the introduction of TERMA, at the 6-month juncture following implementation, and upon the culmination of a 12-month period. For staff members, supplementary descriptive data will be collected through a dedicated questionnaire, while background information pertaining to patients will be retrieved from their medical records.

Outcomes

The primary outcome will be change in perceived safety reported by both patients and staff, as measured by the E13 scale total score (0 - 13), between baseline and 6- and 12-month follow-up assessments. Secondary outcomes include changes in organizational culture, as measured by the OVQ and its subscales between baseline and 6- and 12-month follow-up assessments. Correlation between E13 and OVQ scores at baseline, 6-month follow-up, and 12-month follow-up will be analyzed. The number and severity of aggression incidents from 1 year before baseline to 1 year after conclusion of the study will be analyzed.

Statistical Analysis

Descriptive statistics and comparative statistics will be used in the analysis. All data will be analyzed at a group level and reported using means and SDs. To analyze changes between the measurements, the plan is to use dependent sample 2-tailed *t* tests (if data are normally distributed) or the Wilcoxon signed-rank test (if data are not normally distributed). Regression models will be used to explore the relationship between organizational culture and the outcome of the implementation of TERMA. *P* values will be considered statistically significant if they are <.05.

Qualitative Data Collection and Analysis

This project will also include qualitative design using semistructured individual interviews with both patients and staff members. Approximately 15 to 25 interviews are estimated to be suitable for answering the research questions in each study. The plan is to analyze data collected from the interview with qualitative inductive content analysis, but the decision if the method is appropriate will be based on the depth of the collected data and research questions [32-35]. Incorporating a qualitative design will facilitate greater understanding of patients' perceptions of threatening and violent incidents, their experiences with coercive measures, and the use of TERMA within a forensic psychiatric inpatient environment. It will also

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offer valuable insight into staff perspectives regarding their approach to working with TERMA, their reactions to instances of threat and violence, and the resulting impact of these dynamics on the overall work environment within a forensic psychiatric inpatient setting.

Patient and Public Involvement

To our knowledge, there was no patient and public involvement in the development or design of the TERMA model. In this research project, we sought to address this by actively involving patient representatives in various stages of this study. They were consulted about data collection and gave input on the choice of outcome measures to ensure that they are relevant from a patient perspective. In addition, we plan to engage them in the interpretation of the data. For the qualitative studies, the patient representatives will be engaged in the design of the interview guides as well as the interpretation of data. Finally, the patient representatives will be involved in the dissemination of the findings for all the studies.

Ethical Considerations

The study has been approved by the Swedish Ethical Review Authority (2023-02451-01). All steps of the project have been designed to adhere to the principles outlined in the Declaration of Helsinki [36]. Written and verbal informed consent will be obtained from all participants, with clear information provided about their right to withdraw from the study at any time. The vulnerable nature of patients in forensic psychiatric care has been taken into consideration during the planning of the project, and special consideration will be taken when asking patients to participate in the project. They will also be reassured that participating in this research study will have no impact on their usual care. Permission obtained from the treating physician at each ward will be included in the project. Participants received no compensation to be part of the study. The methods used will be carefully considered to align with the study's purpose, and the principles of confidentiality and integrity will be strictly maintained throughout the process. The collected data will be stored in a secure database maintained by the department and the university. This database is anonymized, and all analyses will be conducted on deidentified data, minimizing the risk of breaching confidentiality. The collected data are treated confidentially and presented in a way that ensures participants cannot be identified.

Results

Recruitment of participants began in July 2023 and concluded by the end of 2024. Collection of data from patient and staff questionnaires will be completed 13 months thereafter. Data from administrative registries will be collected retrospectively for the entire period. Data collection and analysis of quantitative data are expected to be completed by early 2026. Collection of data for the qualitative studies is planned for the second half of 2025 and 2026, and analysis is planned for 2026 and 2027. Results from this project will be published in peer-reviewed scientific journals and presented at international conferences.

Discussion

This study protocol outlines an observational study aimed at evaluating the de-escalation method TERMA regarding adverse events and perceived safety by patients and staff within forensic psychiatry and if they are affected by organizational culture. Despite numerous de-escalation methodologies, there remains a significant gap in research regarding their use in forensic psychiatric care [11,16]. While the TERMA de-escalation model demonstrates promise, it currently lacks a robust body of research to support its application and assess its impact on perceived safety within forensic psychiatric inpatient wards. Previous evaluations of the Bergen model, which TERMA is closely related to, have shown positive influence on ward environment in psychiatric inpatient units [15]. The TERMA model prioritizes treatment, effective communication, and compassionate health care within forensic psychiatric settings, while also emphasizing improved communication and individualized action plans.

Various factors contribute to the current state of aggression within forensic psychiatry, with a prominent factor being the shortage of staff in forensic psychiatry [16,37]. In addition to assessing the intervention's effectiveness, this project aims to identify if organizational culture may be a factor affecting the success of the implementation. Conducting research to comprehend this phenomenon and address the existing knowledge gap is crucial for multiple reasons, including ensuring patient care and safety, fostering a secure work environment for staff, enhancing education and practice, and holding relevance for the community [38]. Complex interventions, as described in this protocol, often involve multiple interacting components, making standardized methods and procedures less applicable [39]. This study combines questionnaires, data from medical records, and registries in the forensic psychiatric inpatient care setting, supplemented by qualitative data sources. A strength of the study is the use of validated questionnaires when assessing the effect of the implementation [39]. Data from these sources provide comprehensive insights into the impact of TERMA on perceived safety and perception of violence preventative culture. The shortage in research regarding de-escalation methods and their implementation in forensic psychiatry underscores the significance of this study. In addition, it will offer valuable information regarding the challenges and potential solutions when implementing a new de-escalation method within forensic psychiatry.

Authors' Contributions

All authors were involved in the design of the project. SW is the principal investigator for the project. PD and SW drafted the manuscript, with substantial contribution and critical revisions from all other authors. All authors reviewed and approved the final manuscript.

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Conflicts of Interest

None declared.

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Abbreviations

M4 : managing the team, managing the environment, managing the patient, and managing aggression
OVQ: Organization Values Questionnaire
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TERMA: Therapeutic Meeting With Aggression

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Frailty Trajectories and Influencing Factors in Patients With Non-Hodgkin Lymphoma During Chemotherapy: Protocol for a Longitudinal Mixed Methods Study

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Abstract

Background: High-intensity chemotherapy for non-Hodgkin lymphoma (NHL) has been shown to improve survival outcomes. However, its substantial toxicity may induce or exacerbate patient frailty, which is strongly associated with treatment interruptions, increased adverse effects, and reduced survival rates. Despite this, the dynamic progression of frailty and its specific contributing factors among patients with NHL undergoing chemotherapy remain poorly understood.

Objective: This study aims to investigate the heterogeneity of frailty trajectories and explore their risk factors in patients with NHL. We seek to generate insights into the dynamic relationship between frailty and disease course. The findings may offer health care professionals dynamic insights into frailty progression and could help inform strategies for the early identification of high-risk populations through the systematic assessment of key factors. Ultimately, this work seeks to contribute to the evidence base for developing interventions that could mitigate or prevent frailty.

Methods: This longitudinal mixed methods study will recruit 250 patients newly diagnosed with NHL from multicenter hospitals in China. Quantitative data will be collected at 3 time points: before chemotherapy, during the third cycle of chemotherapy, and at the end of chemotherapy. We will use validated questionnaires (ie, the Tilburg Frailty Indicator) to gather information on sociodemographics, frailty, cognition, physical condition, health literacy, anxiety, and nutrition. Qualitative data will be collected via semistructured interviews and observations at the end of chemotherapy. The growth mixture model and logistic regression analysis will be used to analyze quantitative data, and the diachronic analysis method and the directed content analysis method will be used for the qualitative data. Both types of data will be analyzed in parallel and separately. Finally, we will integrate the datasets to identify areas of confirmation, complementation, or discordance.

Results: The research protocol and informed consent form were approved by the Medical Ethics Committee of the First Affiliated Hospital of Henan University of Science and Technology (2024-03-K171). Recruitment began in January 2025, with 168 participants enrolled as of September 2025. The data collection and analysis processes are expected to be finalized by March 2026. Data management is still ongoing; therefore, data analysis has not yet been conducted.

Conclusions: As a pilot trial, this research is primarily designed to assess the feasibility of our methods and generate preliminary data on frailty progression. The findings could offer initial insights and help inform the development of future strategies for the early identification of high-risk populations through systematic screening, with the ultimate goal of informing interventions that may prevent frailty.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2500097921; https://www.chictr.org.cn/searchproj.html proj=ChiCTR2500097921

International Registered Report Identifier (IRRID): DERR1-10.2196/76628

(JMIR Res Protoc 2025;14:e76628) doi:10.2196/76628

KEYWORDS

frailty; non-Hodgkin lymphoma; chemotherapy; longitudinal mixed methods study; protocol

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Introduction

The Frailty of Patients With Non-Hodgkin Lymphoma

According to global health statistics, approximately 544,352 new cases of non-Hodgkin lymphoma (NHL) were reported worldwide in 2020 [1]. Chemotherapy remains the frontline treatment for NHL, significantly improving cure and survival rates. However, factors including systemic chronic inflammation, recurrent fever, chemotherapy-induced adverse effects, and high disease relapse rates contribute substantially to the deterioration of physical and mental function in patients with NHL, thereby predisposing them to frailty [2]. Frailty is a clinical syndrome in which an individual's physiologic reserve capacity and resistance are reduced, resulting in increased vulnerability to stressors and, consequently, a high risk of adverse health outcomes [3]. Frailty can lead to an increased risk of falls, infections, myelosuppression, prolonged hospitalization, and mortality [4]. A previous study reported that, among patients with NHL aged over 65 years, the prevalence of prefrailty was 62.1%, whereas the prevalence of frailty was 39.9% [5]. It is important to research how to alleviate frailty in patients with NHL.

However, most frailty studies are cross-sectional in nature. Previous studies have revealed a high incidence rate and several influencing factors, such as the Charlson Comorbidity Index, malnutrition, and impaired mobility [5]. However, cross-sectional studies evaluate data at a certain time point and cannot observe dynamic changes in frailty. Previous longitudinal studies [6] have only assessed frailty status before and after chemotherapy and reported the proportion of people with changes in frailty status but could not carefully observe the change trajectory of frailty over the course of chemotherapy and the influencing factors of different trajectories. It is essential to understand the longitudinal changes in patients with NHL. First, Gobbens et al [7] defined frailty as a dynamic process characterized by the interplay and mutual influence of multiple factors. Second, the National Comprehensive Cancer Network recommends that health care providers promptly identify, assess, monitor, and document the frailty of patients with cancer across all age groups and disease stages during their initial visit, routine cancer treatments, and posttreatment follow-up [8]. To the best of our knowledge, there is a notable lack of comprehensive longitudinal studies examining the frailty of patients with lymphoma throughout their chemotherapy treatment. A longitudinal study can systematically observe the progression of frailty in patients across various disease stages and types of lymphoma. Early identification of frailty can facilitate more effective prevention and management strategies, thereby providing health care professionals with valuable insights for delivering precise and targeted care.

The Necessity of Longitudinal Mixed Research

Longitudinal mixed studies can help understand the experience and influencing factors of complex phenomena from multiple perspectives and reduce biases in research, and the results of dynamic trajectories are also generalizable. This is because frailty is a multidimensional concept involving physical, psychological, and social aspects [3]. Longitudinal quantitative studies tend to adopt predefined universal scales for objective measurement of various factors, failing to reflect the specific experiences and perceptions of patients. The incorporation of qualitative research can provide an in-depth understanding of the changing process of subjective experiences, such as personal histories, feelings, and needs of respondents, enhancing the depth and breadth of the research [9].

In summary, while the significance of the frailty trajectory and its influencing factors in patients with NHL has been highlighted, it remains unverified. Consequently, there is a pressing need for additional high-quality studies to address this gap. Such research may provide health care professionals with dynamic insights into frailty progression. Identifying key contributing factors could help inform strategies for the early identification of high-risk populations through systematic screening. Ultimately, this work could contribute to the evidence base for developing interventions aimed at frailty prevention. Furthermore, the findings might inform the development of relevant health policies.

Aims

The study's aims are as follows:

1. To explore and describe patterns of change in frailty scores over time in patients with NHL
2. To investigate potential predictors of frailty trajectories by integrating quantitative longitudinal data with qualitative insights

Methods

Theoretical Framework

The integral conceptual model of frailty (ICMF) and the health ecology model (HEM) will be used to guide this study. The ICMF was developed by Gobbens et al [7]. This model posits that frailty is influenced by a multitude of factors, including social demographics, chronic conditions, and lifestyle choices. This progression culminates in various forms of frailty—physical, psychological, and social—and results in adverse health outcomes such as illness, disability, and mortality. The previous research is reliable and reproducible [10]. Therefore, we use the ICMF to guide the identification and selection of factors influencing frailty in longitudinal quantitative research. Specifically, physical (ie, gender and age), psychological (anxiety), and social (marital status) factors contribute to the frailty of patients with NHL, and both these factors and patients' frailty status evolve dynamically throughout the chemotherapy cycles.

The HEM underscores the intricate interplay between environmental factors and human health. The HEM has been extensively applied in guiding mixed research on influencing factors [11], and the results of these studies are good. On the basis of each of the 5 dimensions of the HEM (personal traits, living and working conditions, psychological and behavioral characteristics, interpersonal network, and macro factors), we developed an interview framework to explore the risk factors of frailty and integrate the findings of qualitative and quantitative data.

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The interaction between the ICMF and HEM will be implemented during the mixed methods integration phase using iterative joint displays. These tables will serve as an analytical tool to directly facilitate dialogue between the 2 models. The process consists of 2 steps. In step 1 (quantitative data driven), a joint display will be developed to examine a key quantitative finding (ie, "unmarried patients [ICMF social domain] exhibit significantly worse frailty trajectories"). The left column of this display will present this quantitative result, whereas the right column will provide qualitative excerpts from participant interviews illustrating lived experiences of social support (HEM interpersonal network dimension) and its interaction with other ecological levels (ie, HEM organizational level: access to support groups; HEM community level: transportation barriers affecting socialization). Conversely, in step 2 (qualitative data driven), a prominent theme from qualitative analysis (ie, "the pervasive experience of financial toxicity influencing treatment decisions," an HEM community and policy construct) will be placed in the left column of the joint display. The right column will then display quantitative data (ie, income levels, comorbidity scores, or medication adherence rates from the ICMF biological domain) to demonstrate the prevalence of this experience and correlate it with measurable outcomes. The theoretical framework for this study is built by combining these 2 theories (Figure 1).

Figure 1. Theoretical framework of the study.

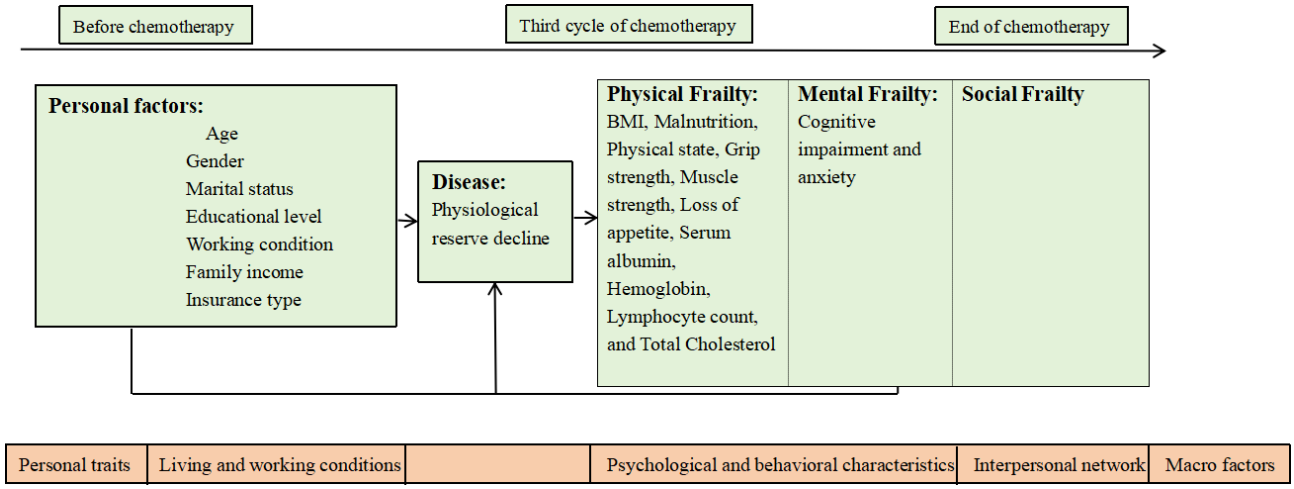

Study Design

A longitudinal mixed methods approach will be used in this study. This study intends to conduct separate quantitative and qualitative analyses. First, case information, somatic measurement data, and questionnaire responses will be collected from patients who meet the specified inclusion criteria at multicenter hospitals in China. The heterogeneity of trajectories and influencing factors will be identified through rigorous quantitative analysis. Second, in-depth qualitative interviews will be conducted with patients whose frailty trajectories exhibit significant changes and a tendency toward deterioration, yielding qualitative insights into factors contributing to frailty. Finally, the quantitative and qualitative data will be integrated in this study to conduct a more targeted mixed analysis. Figure 2 shows a diagram of the longitudinal mixed methods design. The survey began in January 2025 and is scheduled to end in March 2026 (Figure 3).

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Figure 2. Flowchart of the longitudinal mixed methods study design. GMM: growth mixture model; NHL: non-Hodgkin lymphoma.

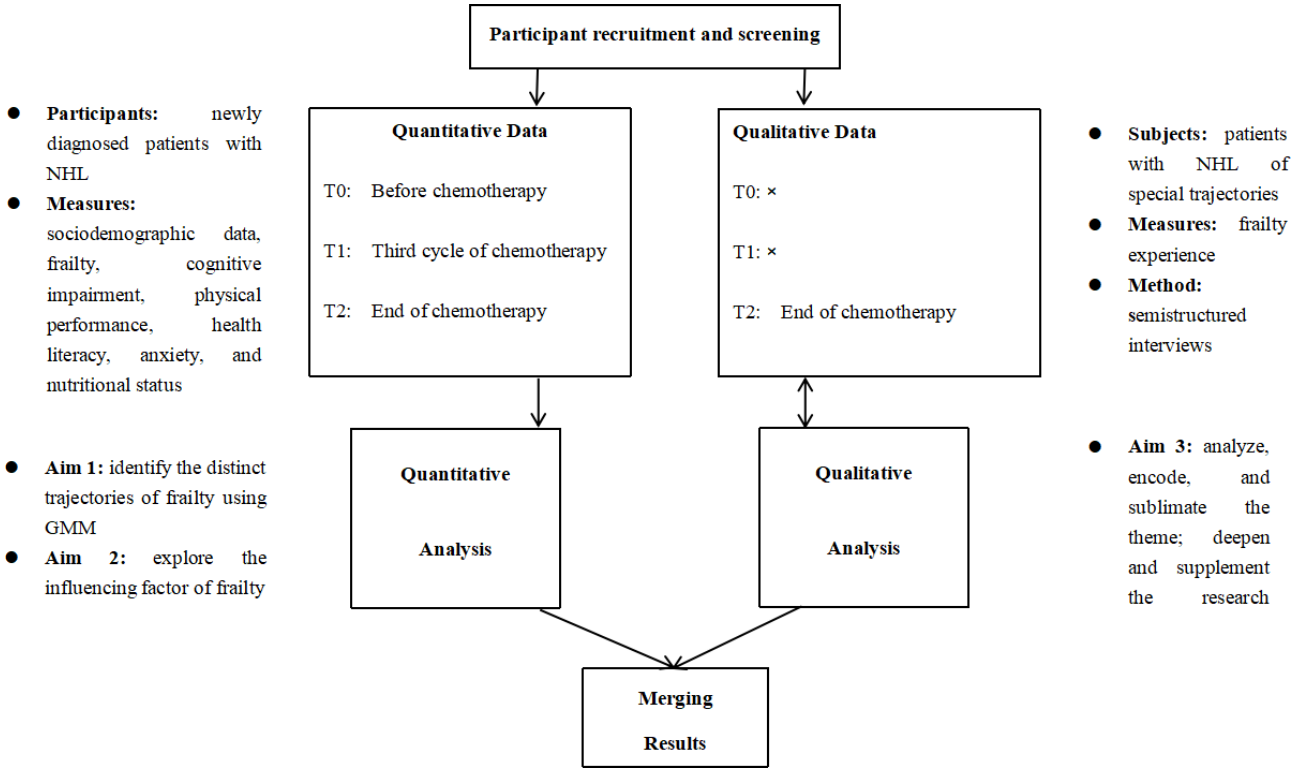

Figure 3. Project timeline.

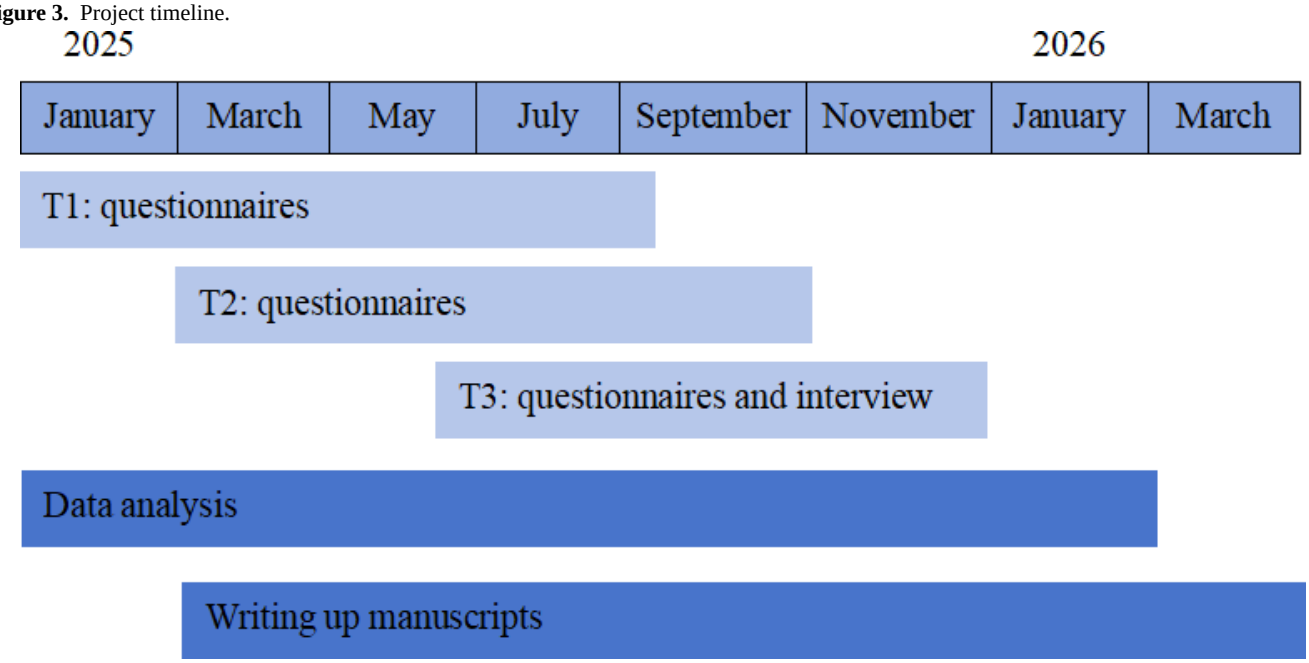

Quantitative Component

Data Collection

Patients who have been newly diagnosed with NHL will be recruited from the department of hematology of 5 large public hospitals in China via a multicenter, consecutive convenience sampling strategy. This method was selected for its feasibility, cost-effectiveness, and practicality in clinical settings. To reduce selection bias and enhance rigor, the following measures will be taken. All eligible patients at participating sites will be invited sequentially during the enrollment period to avoid preferentially recruiting more motivated or healthier individuals. Strict predefined inclusion and exclusion criteria will be applied to maintain a homogeneous study sample. Each site will keep a detailed log tracking the number of patients screened, those who decline, and their reasons. This will enable transparent assessment of recruitment and potential nonparticipation bias. Comprehensive baseline demographic and clinical data will be collected for all participants, allowing for comparison with the broader target population and establishing the generalizability of the findings.

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The National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Lymphoma (2024 edition) [12] indicate that, if a patient responds effectively to treatment, the efficacy evaluation may demonstrate either a complete or partial response within 2 to 4 cycles of chemotherapy. Following the completion of chemotherapy, the disease can remain stable for an extended period. Therefore, the time points of this longitudinal study are before chemotherapy (T1), the third cycle of chemotherapy (T2), and the end of chemotherapy (T3). Prechemotherapy measurement (baseline) captures frailty status before treatment, helping distinguish the disease's effect from treatment-related toxicity. Measuring after the third cycle of chemotherapy (T2) captures acute toxicity—such as fatigue or neuropathy—when side effects are most severe and frailty often increases. The T3 measurement (after treatment completion) helps identify recovery in responders or persistent frailty in nonresponders, revealing medium-term outcomes. All eligible patients will be identified via the hospital's case management system and invited to participate within 24 hours of admission. Researchers will administer standardized questionnaires in accordance with the same guidelines either in the ward meeting room or at the participants' preferred location. Data collection will be conducted by 2 researchers, who will subsequently collate and archive the data. To ensure quality control, the following methods will be used in this study. First, unified training will be conducted for the implementation members of the research group. The principal researcher will elaborate on the content and significance of each item of the questionnaire and inform them of the precautions in the process of questionnaire administration. Second, theoretically, the questionnaire should be filled out independently by the research participants. If the research participants fail to understand or are unable to fill the questionnaire out by themselves, the researchers should communicate fully with them and fill it out objectively and truthfully on their behalf. Third, after the completion of the questionnaire, the investigators should collect it immediately and check and verify it promptly to ensure completeness and quality. We will strictly follow the requirements of the CONSORT (Consolidated Standards of Reporting Trials) statement to record the flow of participants throughout the research process, and provide a complete CONSORT flowchart in the final research paper.

Population and Sampling

The interaction effect repeated-measure analysis in the G*Power software will be used to calculate the required sample size, with each study participant measured 3 times. Under the conditions of an average correlation coefficient ρ of 0.5, power ($1-\beta$) of 0.8, significance level α of .05, and effect size f of 0.14 (to align with reported effect sizes [f=0.10-0.25] from related cancer studies [13], the chosen value [f=0.14] is a conservative, small effect size to ensure that we can detect even modest clinical changes), the initial calculated sample size was 105 participants. In addition, this study aims to adopt the Bayesian information criterion (BIC) of the growth mixture model as the primary model evaluation index [14]. Considering a follow-up loss rate of 20%, and to meet the requirement of N≥200 for BIC applicability, the final sample size should be at least 250 participants.

The inclusion criteria are as follows: (1) age of ≥18 years; (2) confirmed histopathological diagnosis of NHL; (3) treatment with cyclophosphamide, hydroxydaunorubicin, oncobin, and prednisone or with rituximab, cyclophosphamide, hydroxydaunorubicin, oncobin, and prednisone chemotherapy regimens; and (4) absence of severe cognitive impairment or communication disorders.

The exclusion criteria are as follows: (1) previous history of chemotherapy in conjunction with comorbid conditions and (2) history of psychiatric illness or use of psychotropic medications.

The shedding criteria are as follows: (1) voluntary withdrawal from the study and (2) chemotherapy-related incidents resulting in termination of treatment or patient death.

Study Measures

Overview

The variables in this study were chosen based on the literature, theoretical research frameworks, and expert consultation. Through a systematic review and meta-analysis, the research team concluded that the incidence rates of lymphoma, leukemia, and hematologic malignancies were 31.8%, 18.45%, and 10.4%, respectively, and identified some influencing factors of frailty (ie, gender, age, physical capabilities, general health condition, severity of disease, neurological and mental status, and biomarkers). By integrating the 3 dimensions of physical, psychological, and social frailty, we established that (1) the study population would comprise individuals with NHL and (2) the predictors would include sociodemographic factors, disease characteristics, physical condition, hand grip strength, nutritional status, mild cognitive impairment (MCI), and anxiety. The instruments and measurement times used in this study are shown in Table 1. The specific scales used are outlined in the following sections.

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Table . Instruments and measurement times.

Instrument	Measurement time		
	Before chemotherapy	Third cycle of chemotherapy	End of chemotherapy
Sociodemographic questionnaire	✓		
Tilburg Frailty Indicator	✓	✓	✓
Montreal Cognitive Assessment–Basic	✓	✓	✓
Short Physical Performance Battery	✓	✓	✓
Chinese Version of the All Aspects of Health Literacy Scale	✓	✓	✓
Generalized Anxiety Disorder Scale	✓	✓	✓
Controlling Nutritional Status Score	✓	✓	✓

Sociodemographic Questionnaire

The comprehensive information questionnaire encompasses the following components. Personal factors include gender, age, marital status, and educational attainment. Disease-related factors include disease stage, comorbidities, grip strength, muscle strength, serum albumin levels, hemoglobin concentration, white blood cell count, C-reactive protein levels, and lymphocyte count. Among them, muscle strength was assessed by measuring the isometric strength of flexion in the dominant elbow joint. Grip strength was evaluated using a CAMRY electronic hand dynamometer (model EH101). The maximum grip strength value obtained from either hand was recorded as the representative measure. Low grip strength was defined according to sex-specific cutoffs: <30.2 kg for men and <17.2 kg for women.

Frailty

The Tilburg Frailty Indicator (TFI) will be used to evaluate frailty status [15]. The scale is a self-report questionnaire designed for patients, encompassing physical, psychological, and social dimensions. It consists of a total of 15 items. Each item uses a binary scoring method, resulting in a total score ranging from 0 to 15 points. A score of 5 or higher indicates frailty, with higher scores reflecting more severe levels of frailty. This scale has good reliability (Cronbach α>0.75) and validity.

Cognition

The cognition of patients will be measured via the Montreal Cognitive Assessment–Basic [16]. The assessment comprises 10 categories: executive function (1 point), immediate recall (0 points), fluency (2 points), orientation (6 points), computing ability (3 points), abstract thinking (3 points), delayed recall (5 points), visual perception (3 points), naming (4 points), and attention (3 points), totaling 30 points. For individuals with less than 6 years of education, a score between 13 and 19 indicates MCI. Those with 7 to 12 years of education are diagnosed with MCI if they score between 15 and 22 points. Individuals with more than 12 years of education require a score between 16 and 24 points for an MCI diagnosis. Previous studies have shown that the Montreal Cognitive Assessment–Basic has a sensitivity of 81% to 97% and a specificity of 60% to 86% for screening for MCI [17].

Physical Condition

The Short Physical Performance Battery will be used to measure physical condition [18]. The assessment comprises 3 components: a balance function test, a walking speed test, and a sit-to-stand test on a chair. Each component is evaluated on a scale from 0 to 4, yielding a total score ranging from 0 to 12. A total score of less than 10 indicates motor function abnormalities, with good reliability (Cronbach α>.85) and validity [19].

Health Literacy

The Chinese version of the All Aspects of Health Literacy Scale will be used to measure the health literacy of patients [20]. The assessment encompasses 3 dimensions and 11 items, including the ability to use written health information, the capacity to communicate effectively with health care providers, and the ability to evaluate and apply health information. The overall health literacy is categorized as high (>24 points), moderate (21-24 points), or low (<21 points), with good reliability (Cronbach α>0.79) and validity.

Anxiety

The Generalized Anxiety Disorder scale assesses the patients' anxiety levels over the previous 2 weeks [21]. It comprises 7 items, with scores categorized as follows: a score of 0 to 4 indicates no anxiety, a score of 5 to 9 indicates mild anxiety, a score of 10 to 14 indicates moderate anxiety, and a score of 15 to 21 indicates severe anxiety, with good reliability (Cronbach α>0.859) and validity. The sensitivity and specificity were 84.31% and 91.67%, respectively.

Nutrition

The Controlling Nutritional Status score will use 3 indicators to screen for early malnutrition: serum albumin, total cholesterol level, and total lymphocyte count [22]. The scoring system is as follows: normal (score 0-1), mild malnutrition (2-4), moderate malnutrition (5-8), and severe malnutrition (9-12). The score has been widely used in nutritional screening for common malignant tumors [23].

Strategies to Minimize Participant Burden and Reduce Attrition

This study involves collecting data for 66 items. Of these, 12 will be retrieved from the hospital's medical record system, 15

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will be measured by the research team, and only 33 will require direct input from patients. To reduce participant burden, the following measures will be implemented. First, all questionnaires will be administered during patients' regular follow-up visits to avoid extra hospital trips. Second, to ensure that the measurement time does not exceed 20 minutes, this study will adopt a modular and segmented design for the reorganized questionnaire order. For instance, physical measurements such as BMI, grip strength, balance, gait speed, and chair stands will be grouped together. Third, a low-intrusion communication plan (ie, short reminder calls between assessments) will be used to sustain engagement without causing inconvenience. Fourth, if a participant cannot finish all measures, priority will be given to key instruments (ie, the TFI) to preserve essential data. Finally, reasons for dropout will be carefully documented. Should dropout rates exceed expectations, the team will meet to develop further strategies.

Quantitative Data Analysis

The data will be imported into SPSS Statistics (version 26.0; IBM Corp) and R software (R Foundation for Statistical Computing) for comprehensive statistical analysis, and the test level will be treated according to a bilateral α of .05.

Different descriptive statistical methods will be used based on the types of data collected. For continuous variables that follow a normal distribution, the mean and SD will be used. Categorical variables will be summarized using frequency distributions and percentages. The frailty scores of patients with NHL at various time points will be treated as continuous variable data.

The participants who complete follow-up will be compared with those who are lost to follow-up. Continuous variables will be analyzed via independent-sample *t* tests (2-tailed), whereas categorical variables will be assessed via chi-square tests and the Fisher exact probability method. Repeated-measure ANOVA will be initially conducted to examine the frailty scores of patients with NHL across different time points, determining whether there are significant differences during various periods. This analysis will also provide a preliminary evaluation of the overall trend in frailty scores.

The growth mixture model will be used to analyze the potential categories of the trajectory. Initially, a single-class model will be constructed, followed by incrementally increasing the number of classes. The fit indexes of successive models will be compared to determine the optimal model considering both practical significance and statistical criteria. The goodness-of-fit indicators will include, first, the information criteria: the Akaike information criterion, BIC, and sample size–adjusted BIC. Lower values indicate better model fit. Second, likelihood ratio tests and bootstrap-based likelihood ratio tests will compare the K–1 and K-class models based on differences in likelihood ratios. A P value of <.05 suggests that the K-class model is statistically superior to the K–1 class model. The third indicator is entropy. This metric evaluates classification accuracy on a scale from 0 to 1, with higher values indicating greater precision. An entropy value of 0.80 indicates a classification accuracy exceeding 90%.

Chi-square tests and the Fisher exact probability method will be used for univariate analysis of categorical variables, whereas one-way ANOVA will be used for continuous variables to identify statistically significant indicators and conduct a preliminary analysis of differences among various trajectory categories within the datasets. Multivariate logistic regression analysis will be subsequently conducted, with the final determined frailty trajectory types of patients with NHL serving as the dependent variable. Indicators that were statistically significant in the univariate analysis will be included in the regression model for further analysis. The significance level α will be set at .05 to ultimately determine the influencing factors of frailty trajectories in patients with different types of NHL.

Qualitative Component

Data Collection

This study will use the descriptive phenomenological research method. A semistructured interview approach will be used. The interviews will be scheduled in advance with the participants and take place in a quiet conference room to ensure privacy and prevent interruptions. The interviewees will be encouraged to articulate their perspectives and experiences comprehensively. We will use appropriate probing questions, paraphrasing, and summarization. In addition, nonverbal behaviors such as facial expressions and the body language of the interviewees will be observed and documented. Each participant's interview will last approximately 30 to 40 minutes. The interview questions will be developed initially based on the HEM, existing research results, and experts' assistance. The interview guides will be constantly updated to adapt to the situations encountered during the research process. Within 24 hours following the conclusion of each interview, the recorded content will be transcribed into textual data. The transcription will include annotations of the interviewees' basic information, recording durations, and interview time stamps. To safeguard the privacy of the respondents, their names will be anonymized via numerical identifiers. In the process of conducting the interviews, the following points will be focused on: (1) the content of later repeated interviews will be largely driven by the results of the previous interviews, and (2) this study will focus on "change"; that is, participants will reflect on the evolution of their frailty experience throughout the course of chemotherapy, as well as the factors that influenced these changes. The interview outline is shown in Textbox 1.

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Textbox 1. Interview outline.

1. During the therapeutic process, did you have any sense of frailty and what was the severity level?
2. Has the sense of frailty changed from the start of the treatment until now?
3. During the therapeutic process, which aspects of your individual health status do you think could have influenced the aforementioned state and has the degree of influence changed?
4. During the therapeutic process, which behavioral traits or habits do you think could have influenced the aforementioned state and has the degree of influence changed?
5. During the therapeutic process, which aspects of interpersonal relations or interactions do you think could have influenced the aforementioned state and has the degree of influence changed?
6. During the therapeutic process, which aspects of living or working conditions do you think could have influenced the aforementioned state and has the degree of influence changed?
7. During the therapeutic process, which aspects of macro factors (such as economy, policy, and culture, etc.) do you think could have influenced the aforementioned state?

Population and Sampling

To alleviate the burden on participants and enhance the efficiency of this study, we will use a targeted sampling strategy. Specifically, interviews will be conducted with patients who exhibit significant variability in their frailty status and frailty duration based on quantitative research findings. The sample size will be determined when data saturation is achieved, meaning that no new themes emerge from the interviews.

Qualitative Data Analysis

The text materials will be imported into the NVivo software (version 12.0; Lumivero), and 2 individuals will independently conduct repeated reading, sorting, and coding of the imported materials. This study will be guided by the HEM and use the diachronic analysis method and the directed content analysis method. The specific steps are as follows: (1) determine the analysis unit, taking the sentences related to the time-varying influencing factors of frailty expressed by the patients with NHL as the minimum analysis unit; (2) thoroughly read the original materials multiple times and carefully study the text content; (3) develop a classification outline based on the HEM, taking personal traits, psychological and behavioral characteristics, interpersonal networks, work and living conditions, and macro factors as names for theme coding; (4) conduct content coding and classification, mark the significant connotations and concepts in the text content, classify the relevant content into the corresponding theme categories, and further analyze and classify the content to form subthemes; and (5) interpret and explain the results, establish the connection between the text content and the extracted themes and subthemes, and find the corresponding text examples from the original materials. Any discrepancies concerning data coding and subject classification will be systematically addressed through regular discussions. All study data will be meticulously retained to ensure their validity and integrity.

Integrating Quantitative and Qualitative Data

A convergent parallel mixed methods approach will be used, wherein quantitative and qualitative data will be collected and analyzed independently. The influencing factors will be synthesized during the result interpretation phase to comprehensively explore the determinants of frailty in patients with NHL. Specifically, the factors impacting the frailty trajectory of these patients will be examined separately. Multiclassification logistic regression will be used to understand the factors affecting the subgroup classification of frailty trajectories. In addition, an in-depth study will be conducted on the frailty experience of patients with NHL and the descriptive characteristics of the influencing factors. The results will be synthesized into a unified, side-by-side comparative display. The integration of quantitative and qualitative data will be achieved through the development of joint display tables. These tables will visually juxtapose the key quantitative findings and qualitative themes side by side for each research question. This will allow for a systematic comparison. First, we will analyze consistent or convergent findings. When quantitative and qualitative findings converge and are mutually corroborated, we will interpret this as strong evidence for a robust conclusion. The qualitative data will provide rich, contextualized examples to illustrate the statistical trends. Second, we will analyze complementary findings. When findings of one method elaborate, clarify, or provide new dimensions to the findings of the other method, we will use them to build a more nuanced and comprehensive understanding of the phenomenon. Third, we will analyze discordant or inconsistent findings. Crucially, any instances of discordance will be treated as valuable opportunities for deeper analysis. We will actively investigate potential explanations for these discrepancies by re-examining the data. Possible reasons may include, first, temporal differences. Quantitative measures capture a snapshot in time, whereas qualitative interviews may reflect experiences over the entire chemotherapy cycle. A second possible reason is the level of analysis. Quantitative data may reflect group-level trends, whereas qualitative data may reveal individual-level exceptions or unique experiences. A third possible reason is response bias (social desirability bias in surveys [quantitative] vs anonymity and depth in interviews [qualitative]). The fourth possible reason is measurement versus meaning. Numbers measure magnitude, whereas narratives capture meaning and context, which may not always align directly. We will report these discordances transparently and use them to generate new hypotheses or propose refined explanations that account for the complexity of the data.

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Feasibility Considerations

To ensure the feasibility of the mixed methods approach within the oncology setting, the following strategies will be implemented. Quantitative and qualitative data collection will be staggered to avoid burdening participants, with interviews conducted flexibly (in person or virtually). Our research team will receive specialized training for working with an oncology population. Finally, a pilot phase will test and refine the integrated protocol's flow and acceptability.

Patient and Public Involvement

Patients and the public were actively engaged in the design process for selecting the frailty scale, follow-up time points, result analysis, and dissemination. First, 5 patients with NHL of diverse ages, genders, and educational backgrounds were recruited to complete the TFI, the G8 questionnaire, and the Groningen Frailty Indicator. Among them, 4 patients found the TFI to be straightforward and comprehensive in capturing the multidimensional aspects of frailty, whereas 1 patient preferred the simplicity of the G8 questionnaire. On the basis of these patient insights, the TFI was ultimately selected as the primary tool for assessing frailty. Second, semistructured interviews were conducted with patients who had completed their chemotherapy regimens. These revealed that most patients experienced significant physical frailty and fatigue during the third cycle of chemotherapy and exhibited pronounced psychological frailty at the time of diagnosis. Consequently, we determined that follow-up assessments would take place before the initiation of chemotherapy, during the third cycle, and upon completion of the treatment. During the phase of result analysis, they will sense check our interpretations and help prioritize findings from a patient perspective. We will partner with patient and public involvement members in the dissemination phase through co-designing lay summaries, developing accessible materials, and offering opportunities for copresentation.

Ethical Considerations

The study, research protocol, and informed consent form were approved by the Medical Ethics Committee of the First Affiliated Hospital of Henan University of Science and Technology in December 2024 (2024-03-K171), and the study will be conducted in accordance with the Declaration of Helsinki.

To rigorously ensure comprehension and voluntariness among patients who may be experiencing frailty, cognitive impairment, or treatment-related distress, we will implement an enhanced consent process. This involves explaining the study using a simplified consent form followed by a structured verification of understanding. Using the teach-back method, we will ask participants to explain key aspects in their own words (ie, "Please tell me what you believe the main purpose of this study is"). We will also directly assess their understanding of the core elements of consent: the study's purpose, procedures, and risks and their right to withdraw without any impact on their clinical care. This dialogue will continue iteratively until clarity is achieved. Consent will be sought in a private setting to minimize pressure and will be reaffirmed as an ongoing process at subsequent visits. Participants will receive a $10 comfort package containing a soft blanket, a high-quality water bottle, and hypoallergenic lip balm as a token of appreciation for their participation.

During the study, the collection, use, and disclosure of research information will be conducted strictly in confidence and authorized in accordance with regulatory requirements. Patient information will not be disclosed outside the research center to ensure confidentiality. To safeguard the integrity of the study participants' information, data will be stored in a segregated database accessible only by authorized researchers. Qualitative study records will be transcribed anonymously to protect participant identity. There are no anticipated ethical, legal, or security concerns associated with the collection, storage, or dissemination of any data related to this research. The findings of this study will be shared with academic, clinical, and public audiences to broaden their impact. Regarding the academic audience, results will be published in an international peer-reviewed journal following CONSORT guidelines and presented at nursing conferences. Regarding the clinical audience and participants, plain-language summaries will be provided to participating hospitals and staff, with results offered for presentation at clinical meetings. Participants will also receive a summary if they consent. Regarding public and patient engagement, key results will be shared via social media. In line with SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines, anonymized data and study documents will be made public on Figshare within 12 months of publication (ie, accessible to researchers with an approved proposal and data sharing agreement).

Results

Participant recruitment began in January 2025. The number of recruited participants was 168 in September 2025. The data collection and analysis processes are expected to be finalized by March 2026. Data management is still ongoing; therefore, data analysis has not yet been conducted. The results are expected to be published in August 2026.

Discussion

Anticipated Findings

To the best of our knowledge, this is the first longitudinal study of frailty among patients with NHL. First, this study deepens the application of the frailty integration model to a longitudinal study. Previous research has established the efficacy of the ICMF in cross-sectional studies [24]. However, an outstanding feature of the ICMF is that the processes leading to frailty change dynamically over time [15]. Second, we investigate the application and validation of the longitudinal mixed methods approach in the context of frailty, thereby expanding the scope of research within this domain. Frailty is a multidimensional syndrome encompassing physical, psychological, and social dimensions and is influenced by a myriad of factors. The use of longitudinal mixed methods research can increase both the depth and breadth of our understanding of this complex condition. Finally, this study will explore and describe patterns of change in frailty among patients with NHL. This study will

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also identify the potential predictors of frailty in patients. This study will take a longitudinal mixed methods approach to collect and integrate quantitative and qualitative data. By combining the benefits of these 2 methods, this study uses statistical analysis and data mining techniques alongside in-depth interviews and observational methods to conduct a comprehensive and rigorous examination of frailty among patients undergoing chemotherapy. This approach seeks to thoroughly investigate influencing factors and explore the underlying mechanisms to facilitate the early identification of at-risk patients by health care professionals. The findings are expected to inform the development of targeted nursing interventions and provide a stronger evidence base for dynamic clinical decision-making.

However, we acknowledge several potential methodological threats and outline proactive strategies to mitigate them. Participant dropout may introduce bias. To minimize attrition, we will use flexible scheduling, maintain regular contact through check-in calls, and offer compensation. All dropout reasons will be meticulously recorded and analyzed. Inconsistency in data collection across sites is a risk. To ensure uniformity, all research staff will undergo centralized, standardized training using a detailed manual of procedures. Ongoing quality assurance checks will be conducted. Participants' recollections in qualitative interviews may be imperfect. To enhance accuracy, interviewers will use timeline anchoring techniques with visual aids and ask probing questions focused on specific events and experiences.

Strengths and Limitations of This Study

This research has the following strengths. The first strength is that a longitudinal mixed methods approach will be used to explore frailty in patients with NHL from both quantitative and qualitative perspectives. The second strength is that this is the first multicenter, mixed methods study conducted in China to investigate the heterogeneity and correlations of frailty in patients with NHL. The third strength is that our longitudinal study design will enable us to observe the trajectory and risk factors associated with changes in frailty among patients with NHL over time. This study will provide dynamic information for future frailty interventions and policy formulation. The limitations of this study are the potential loss of follow-up, inconsistency in data collection across sites, and recalling bias.

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Authors' Contributions

Conceptualization: RD, YZ, YD, JL, BZ, HY
Data curation: YZ, YD
Formal analysis: RD, YZ
Funding acquisition: HY
Investigation: YZ, YD
Methodology: YZ, YD
Writing – original draft: YZ, RD
Writing – review & editing: YZ, RD, HY

Conflicts of Interest

None declared.

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Abbreviations

BIC: Bayesian information criterion
CONSORT: Consolidated Standards of Reporting Trials
HEM: health ecology model
ICMF: integral conceptual model of frailty
MCI: mild cognitive impairment
NHL: non-Hodgkin lymphoma
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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TFI: Tilburg Frailty Indicator

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Protocol

Evaluation of a Global Initiative for Asthma Education and Implementation Program to Improve Asthma Care Quality (CARE4ALL): Protocol for a Multicenter, Single-Arm Study

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Abstract

Background: Poor symptom control and exacerbations of asthma diminish quality of life and pose a significant burden to patients and society. Implementing evidence-based management as recommended by the Global Initiative for Asthma (GINA), especially introducing inhaled corticosteroid–containing treatments, has the potential to vastly reduce exacerbations and the high burden of asthma in China. However, domestic implementation of the GINA recommendations has been unsatisfactory, especially in lower-level hospitals; thus, an enhancement to the awareness of and adherence to the GINA recommendations among Chinese physicians is needed to improve patient outcomes.

Objective: This study aims to bridge the gap between the GINA recommendations and the current clinical practice in China by demonstrating the benefits of an asthma quality improvement program (QIP).

Methods: A single-arm study will be conducted at around 30 hospitals across China to assess the impact of a specially designed asthma QIP. Approximately 1500 patients with asthma aged ≥14 years will be enrolled in participating hospitals and followed up for 48 weeks. The QIP—targeted at all pulmonologists and specialist nurses—will include an initial comprehensive training (including a pretraining questionnaire and posttraining quizzes) provided by a dedicated, qualified training team based on the GINA 2021 recommendations, followed by regular reinforcement learnings (integrated into the regular department lectures delivered by department directors), with multiple offline and online approaches (eg, an online patient management platform) provided as supportive tools. During this study, GINA implementation performance will be continuously monitored to inform necessary adjustments at the hospital level. The primary end point is change from baseline in the proportion of participants with an inhaled corticosteroid–based maintenance or reliever treatment at week 48. Secondary end points and exploratory end points include changes in clinical practice and patient outcomes such as treatment patterns, asthma control, and hospitalization rates due to exacerbations.

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Results: This study has been completed, with 1500 patients enrolled and 1271 patients completing the study. The last visit of the last patient was on September 3, 2024, and the database lock was on September 28, 2024. Final analysis of data has started in October 2024.

Conclusions: The Change Asthma Clinical Practice through GINA Education and Implementation for All Patients With Asthma (CARE4ALL) study will hopefully help improve asthma management and patient outcomes in China by bridging the gap between evidence-based GINA recommendations and the current clinical practice.

Trial Registration: ClinicalTrials.gov NCT05440097; https://clinicaltrials.gov/study/NCT05440097

International Registered Report Identifier (IRRID): DERR1-10.2196/65197

(JMIR Res Protoc 2025;14:e65197) doi:10.2196/65197

KEYWORDS

asthma; management; quality improvement program; Global Initiative for Asthma; GINA; guidelines; implementation; health care; delivery

Introduction

Asthma is a chronic inflammatory disease, characterized by repeated episodes of breathlessness, wheezing, chest tightness, and coughing, which affects more than 330 million people worldwide [1]. Within China, as reported by the China Pulmonary Health study, the prevalence of asthma is 4.2% among adults aged at least 20 years, representing 45.7 million patients, and it is anticipated to increase further due to changes in environment and lifestyle [2]. However, the current status of asthma management in China is far from satisfactory.

Asthma control is defined as the level to which the various manifestations of asthma have been reduced or eliminated by treatment [3]. As it is closely linked to patients' health status, the achievement of good asthma control has been set as the key element that drives patient management [3-6]. The rate of well-controlled asthma, as defined by the Global Initiative for Asthma (GINA), is only 28.5% in China's urban areas [7] and is expected to be even lower in remote areas [8]. Moreover, poor asthma control is associated with a much higher risk of exacerbations, which is a major cause of disease morbidity and medical resource use [9]. According to a multinational, cross-sectional survey, 17.8% of patients with asthma in China experienced at least one exacerbation within the past 12 months [10], much higher than 8.4% in the United Kingdom and 12.5% in the United States [11]. Previous studies revealed that the suboptimal asthma control and the high exacerbation burden in China might be largely attributed to underdiagnosis and undertreatment in asthma management [2,10,12]. Though the underlying reasons may be complicated, low awareness of and adherence to guideline recommendations among physicians, insufficient disease awareness, and poor treatment adherence (including incorrect technique of inhalers) among patients might all play a part [12,13].

The GINA strategy report (also known as GINA) has been updated annually since 2002 to provide physicians with up-to-date, evidence-based recommendations for asthma prevention and management [6]. Commencing asthma treatment with short-acting β_2-agonists (SABAs) alone has been a long-standing approach in the field [14], but concerns were raised as overuse of SABAs was shown to be associated with an increased risk of asthma-related death [15]. As more relevant evidence emerged, in 2019, GINA concluded that adults and adolescents with asthma should not be treated with SABAs alone for consideration of safety, regardless of asthma severity [14]. Since then, inhaled corticosteroid (ICS)–containing therapies have been recommended for all patients with asthma by both international and Chinese guidelines [6,8,14]. However, ICS-containing therapies are largely underused in China. For example, in a multinational cross-sectional survey conducted in 2020 on physicians (including general practitioners, family medicine physicians, or internal medicine physicians), the results from China showed that 31.9% of the respondents regarded inhaled SABAs only as the typical treatment of mild asthma, suggesting the suboptimal awareness of guideline recommendations among Chinese physicians [16]. Considering the critical role that physicians play in the delivery of asthma care, limited understanding and implementation of guideline recommendations would inevitably translate to compromised patient outcomes.

The unsatisfactory quality of medical care and the high disease burden call for national actions to increase physicians' awareness of and adherence to management recommendations to improve patient outcomes [17]. Studies from China have shown that interventions targeted by health care professionals at the hospital level can increase physicians' adherence to guideline recommendations and, in turn, improve patient asthma outcomes [18,19]. However, the existing studies either only conducted a short-term, one-off intervention program [18] or were limited to a single study center [19]. Such interventions can be better delivered in the form of a quality improvement program (QIP), which is a set of systematic and continuous activities designed to monitor, analyze, and improve the quality of health care processes [20]. QIPs for asthma care have been demonstrated to effectively change physician practices and improve clinical outcomes in other countries [21]. For example, the Enhancing Care for Patients With Asthma study, developed to augment the implementation of the Expert Panel Report 3 Guidelines in four American states [22], successfully improved the consistency of practices with the Expert Panel Report 3 Guidelines and subsequently decreased asthma-related emergency department visits and hospitalizations by 37.7% and 47.1%, respectively, based on a retrospective analysis [23]. QIPs have also been successfully conducted in China for other

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diseases [24,25], but the feasibility and benefits of such QIPs for asthma care have not been assessed in China.

The Change Asthma Clinical Practice through GINA Education and Implementation for All Patients With Asthma (CARE4ALL) study will conduct the first-ever multifaceted QIP for China asthma care, targeting physicians with a specialization in pulmonary or respiratory care. The QIP aims to bridge the gap between the recommendations from the GINA 2021 (the latest update at the time of study design) and the clinical practice among participating health care professionals, and to improve patient outcomes through enhanced quality of care. By evaluating the clinical impact of such a QIP in a nationwide cohort, the ultimate objective of the CARE4ALL study is to pilot and establish a widely applicable QIP model for improving domestic asthma management in China.

Methods

Study Design

This is a multicenter, single-arm study (NCT05440097) with primary data collection to assess the impact of an asthma QIP in improving the adherence of health care professionals specializing in pulmonary or respiratory care to recommendations from the GINA 2021 and quality of care. This study's methodology and procedures are shown in Figure 1.

Figure 1. Study design. GINA: Global Initiative for Asthma; QIP: quality improvement program.

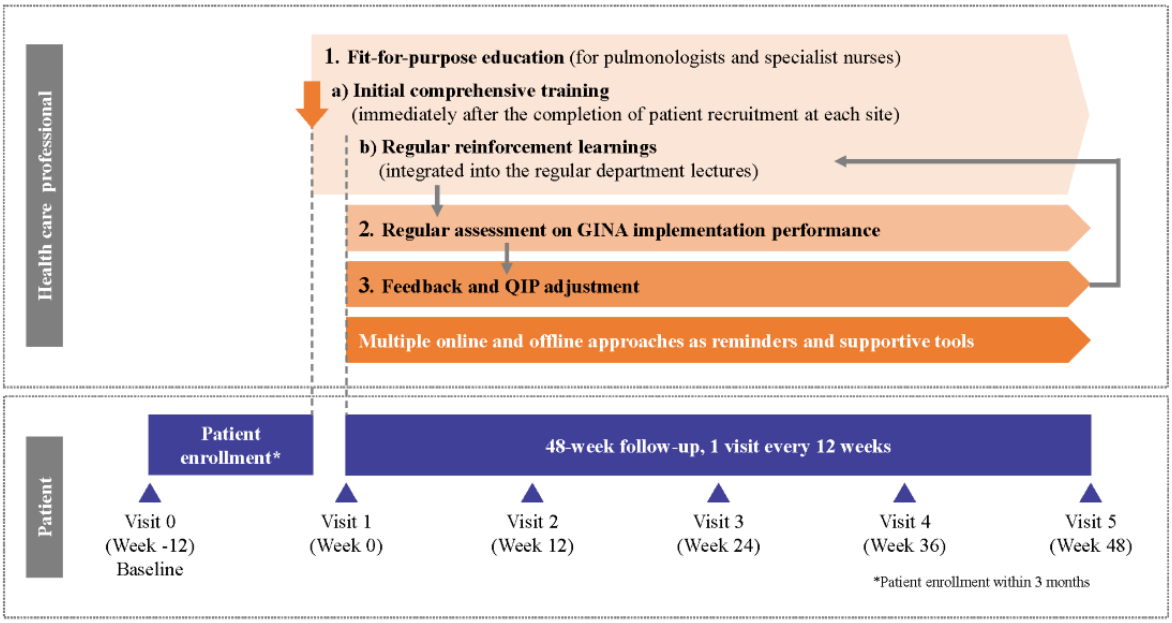

Study Sites and Participants

Site Selection

This study selected a total of around 30 tertiary and secondary hospitals that met all the following criteria: (1) classified as public general hospitals (excluding traditional Chinese medicine hospitals), (2) having an emergency unit and a respiratory department with wards and fundamental equipment (eg, spirometry), (3) having access to GINA-recommended treatment regimens, (4) visited by ≥500 patients with asthma in the past one year, and (5) willing to provide all pulmonologists with regular GINA education and comply with GINA 2021 recommendations. To represent the real-world asthma care situation in mainland China, hospitals were selected across as many provinces or municipalities as possible located below an altitude of 1500 meters, with a balance of hospital levels (preferably around 20 at the tertiary level and around 10 at the secondary level).

Patients

Outpatients with physician-confirmed asthma will be consecutively recruited at participating hospitals. Patients will be eligible for enrollment if they are ≥14 years old and provide written informed consent. Exclusion criteria include previous diagnosis of clinically relevant chronic respiratory disease other than asthma (eg, chronic obstructive pulmonary disease); any significant medical conditions that may put the patient at risk, influence this study's results, or hinder the participants from fully complying with this study's procedure; any medical conditions other than asthma that requires treatment with systemic or oral steroids; and participation in another clinical study with an investigational product administered in the last three months before visit 1 (Figure 1).

Study End Points

As the QIP aims to align physicians' clinical practice with GINA recommendations, study end points measured to what extent the physicians' practice complied with GINA-recommended best practice, which could be reflected in various aspects. First, patient medication patterns directly reflected whether physicians had prescribed asthma medications as recommended by GINA. Thus, the primary end point measured the change from baseline at week 48 in the proportion of patients receiving ICS-based maintenance or reliever medications (as the mainstay of the GINA-recommended asthma medication scheme), while several secondary end points were designed to characterize more fully the patients' asthma medication patterns (Textbox 1). Second, the physician's knowledge, skill, and action together reflected

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their understanding of and ability to implement GINA strategies. Thus, the exploratory end points included measurements on the proportions of patients whose pulmonologists develop or review an asthma action plan (a GINA-recommended management tool) for them and check to ascertain their inhaler technique, as well as scores measuring the physicians' own asthma knowledge and inhaler technique (Textbox 1). Moreover, the physicians' patient management skills and the quality of their communication and education for the patients were expected to improve through the QIP, which in turn would positively influence the patients' disease knowledge levels and self-management behavior. As such, the exploratory end points included assessments of the patients' asthma knowledge, inhaler skills, and compliance, to serve as indirect indicators of the physicians' patient management proficiency (Textbox 1).

By aligning current clinical practice with GINA recommendations, the ultimate goal of the QIP is to enhance patient outcomes, as improved quality of care is expected to bring about better asthma management results. Therefore, several key secondary end points sought to evaluate changes from baseline in patients' asthma control (assessed by the five-item Asthma Control Questionnaire), and patients' health-related quality of life and incidence of severe asthma exacerbation were also evaluated as exploratory end points (Textbox 1). Together, these end points on patient outcomes will help demonstrate the clinical benefits that can be actualized through the QIP.

Textbox 1. Study end points and outcome measures. Asthma treatment at each study visit refers to the treatment received within the prior 12 weeks according to medical records. For instance, in the primary end point, "a participant with an ICS-based maintenance or reliever therapy at week 48" is defined as a participant who has used inhaled corticosteroid (ICS)–based maintenance or reliever therapy between week 36 and week 48 based on medical records and in-hospital or out-of-hospital prescriptions.

Primary

- Change from baseline in the proportion of participants with an ICS-based maintenance or reliever therapy at week 48.

Secondary

- Change from baseline in the proportion of participants with well-controlled asthma (five-item Asthma Control Questionnaire [ACQ-5] ≤0.75) at week 48.
- Distribution of ACQ-5 scores [proportion of participants with well-controlled (ACQ-5 ≤0.75), partially controlled (0.75<ACQ-5≤1.5), and not well-controlled (ACQ-5 >1.5) asthma] at weeks 12, 24, 36, and 48.
- Change from baseline in the proportion of participants on the treatment of ICS-formoterol as a reliever at weeks 12, 24, 36, and 48.
- Change from baseline in mean ACQ-5 scores at weeks 12, 24, 36, and 48.
- Change from baseline in the proportion of participants achieving an improvement in ACQ-5 of ≥0.5 units at weeks 12, 24, 36, and 48.
- Change from baseline in the proportion of participants with an ICS-based maintenance or reliever treatment at weeks 12, 24, and 36.
- Distribution of asthma treatment (eg, ICS-containing medications, ICS-long-acting β_2-agonist, ICS-formoterol, oral corticosteroids, leukotriene receptor antagonists, theophylline, and traditional Chinese medicine) at baseline and weeks 12, 24, 36, and 48.

Exploratory

- The proportion of participants whose pulmonologists developed or reviewed the written asthma action plan at weeks 0, 12, 24, 36, and 48.
- The proportion of participants whose pulmonologists watched the patient using their inhaler to check their technique at weeks 0, 12, 24, 36, and 48.
- Annual hospitalization rate due to asthma exacerbations per patient.
- Number of severe asthma exacerbations at baseline, weeks 12, 24, 36, and 48.
- Change from baseline in health-related quality of life evaluated by mean Standardized Asthma Quality of Life Questionnaire for 12 years and older scores at weeks 0, 12, 24, 36, and 48.
- Change from baseline in the proportion of participants with an ICS-based maintenance or reliever actual treatment at week 48.
- Change from baseline in mean Medication Adherence Report Scale for Asthma scores at weeks 12, 24, and 48.
- Change from baseline in the inhaler skill scores of pulmonologists at weeks 12, 24, and 48.
- Change from baseline in the inhaler skill score of patients at weeks 12, 24, and 48.
- Change from baseline in the scores of the asthma knowledge questionnaire for patients at weeks 12, 24, and 48.
- Change from baseline in the scores of the patient expectation of asthma treatment questionnaire at weeks 12, 24, and 48.
- Change from baseline in the scores of the asthma knowledge questionnaire for pulmonologists at weeks 12, 24, and 48.
- Level of asthma control at baseline by self-assessment and by the Global Initiative for Asthma assessment.
- Level of asthma control at baseline, weeks 0, 12, 24, 36, and 48.
- Patient characteristics and related symptoms after COVID-19 infection.

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Interventions

The QIP delivered at the hospital level targeted all pulmonologists and specialist nurses at each participating hospital with the goal of encouraging asthma management per the GINA 2021 recommendations in their routine clinical practice. The program included initial comprehensive training, which was delivered by a dedicated qualified team (including asthma experts in the same province or region as the participating hospital) immediately after the completion of patient recruitment at each site. This timing of training commencement was designed to avoid biasing the baseline data of clinical characteristics by training-induced behavior changes. The education content was based on recommendations from the GINA 2021, including, but not limited to, asthma diagnosis and assessment, evidence-based asthma treatment and the scientific rationale, and patient education and management (eg, asthma action plan, the rationale for medication adherence, etc). A posttraining quiz was conducted to ensure the successful delivery of the training. Thereafter, pulmonologists and specialist nurses were required to attend regular reinforcement learnings to enhance their understanding of GINA-recommended asthma management and address practice gaps identified from the GINA implementation performance assessment. During this study's period, multiple online and offline approaches served as supportive tools to increase adherence to the GINA recommendations (Figure 2). In addition to pulmonologists- or nurses-targeted efforts, layperson-style patient pamphlets and an online patient management platform were developed to help enhance patients' adherence to asthma treatment (Figure 2). The platform housed patient education materials, incorporated a patient self-management tool, and provided a communication channel to facilitate physician-patient interactions.

A scientific steering committee consisting of external asthma experts, most of whom are committee members of the Asthma Group of the Chinese Thoracic Society, was established to control the overall quality of the QIP. The committee reviewed and approved the overall design of this study and ensured that the education plan and related materials were scientifically and clinically appropriate. The committee was also involved in the review and interpretation of this study's results.

Monthly assessments of GINA implementation performance were conducted to guide QIP adjustments (eg, targeted reinforcement learnings) at the hospital level. GINA implementation performance was assessed against 6 predefined key performance indicators (Textbox 2) for each participant's visit. The proportion of participants achieving each checkpoint was calculated at the hospital level, which can help identify gaps in GINA implementation and determine future targeted training needs. Assessment feedback was provided to the scientific steering committee and the directors of participating departments. If the GINA implementation performance was unsatisfactory at a participating department (defined as the average percentage at the department level lower than 80% for at least one performance checkpoint), the scientific steering committee discussed the root cause with the department director and provided instructions for an improved plan.

Figure 2. Multifaceted approaches designed to facilitate GINA implementation in the QIP. GINA: Global Initiative for Asthma; ICS: inhaled corticosteroid; QIP: quality improvement program.

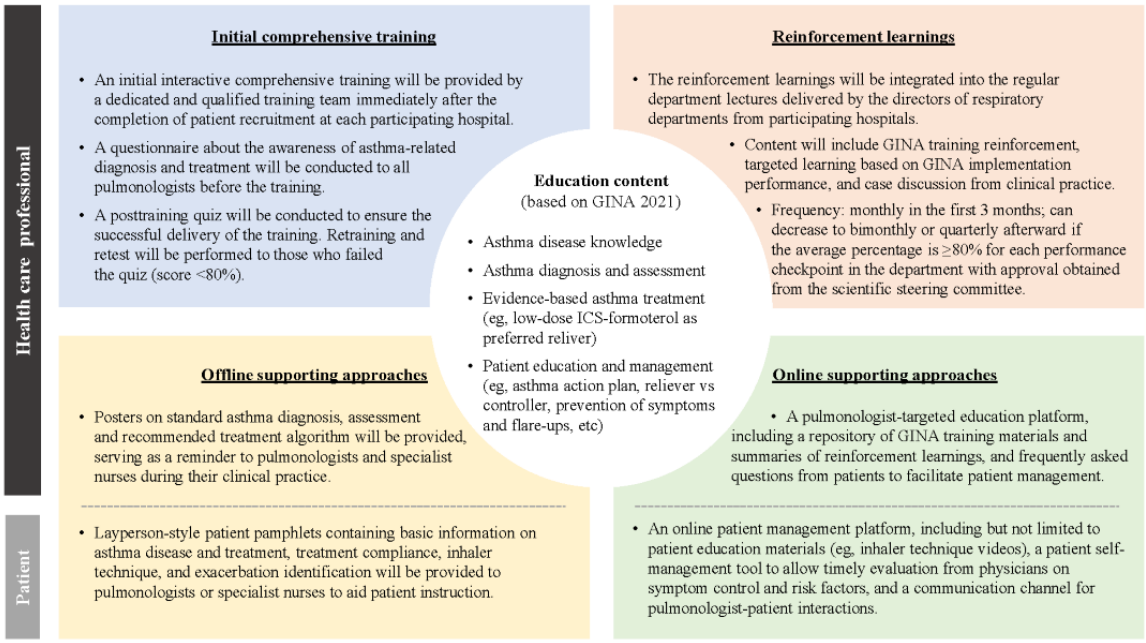

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Textbox 2. Key performance indicators for Global Initiative for Asthma implementation performance and data source.

Questionnaires collected from participating patients after each visit

- Whether or not the pulmonologist or the specialist nurse assessed the patient's symptom control over the past four weeks?
- Whether or not the pulmonologist or the specialist nurse watched the patient using their inhaler?
- Whether or not the pulmonologist discussed treatment adherence?
- Whether or not the pulmonologist developed or reviewed the written asthma action plan?
- Whether or not the pulmonologist reduced the dosage of asthma treatment? If yes, whether the patient had a pulmonary function test before dosage reduction?

Medical records

- Whether or not the pulmonologist has provided ICS-containing medication for maintenance or as a reliever?

Assessment and Data Collection

The electronic data capture system was used for data collection and query handling, and all data was recorded in the electronic case report form per prespecified instructions. All data were obtained from medical records generated during routine clinical practice except for the questionnaires to be completed by patients. During this study, usual care activities were performed as needed and no additional examinations were required.

At each study visit (including baseline and follow-up visits, Figure 1), medical records on asthma-related assessment and treatment during the past 12 weeks were collected, and two patient-reported outcome questionnaires—a five-item Asthma Control Questionnaire and Standardized Asthma Quality of Life Questionnaire—for patients aged 12 years and older was administered. The Medication Adherence Report Scale for Asthma, the asthma knowledge questionnaire for patients (study-defined, designed based on The Validity and Reliability of an Asthma Knowledge Questionnaire Used in the Evaluation of a Group Asthma Education Self-Management Program for Adults With Asthma), the patient inhaler skill assessment and the patient expectation of asthma treatment questionnaire (study-defined) will also be administered at baseline or follow-up visits (Multimedia Appendix 1). Additionally, patients' demographics, clinical characteristics within three months, and historical data (eg, asthma history, comorbidities, and comedication history) were collected at baseline, and hospitalization and outpatient visit records related to asthma were collected at follow-up visits (Multimedia Appendix 1). To better reflect real-world conditions, no free medications were provided in this study, and information on the sources from which patients purchase their medications was collected at baseline. Participants were encouraged to return to this study's hospital if they had asthma-related conditions or worsening symptoms. In case of emergency, they could choose to visit a hospital other than this study's hospital but were required to report it to study pulmonologists or study staff with supporting documents (eg, medical record of hospitalization summary). Data generated from other hospitals were collected as per protocol. A patient might withdraw from this study at any time at their own request; at the time of withdrawal from this study, an early study discontinuation visit was conducted for any data that needed to be collected.

Data Analysis

Sample Size Estimation

With a 30% dropout rate and a within-participants correlation of 0.25, approximately 1500 patients are required to provide an 80% power at a significant level of .05 to detect an increase from baseline of 5% at week 48 in the proportion of patients with an ICS-based maintenance or reliever therapy, which is assumed to be 40% at baseline [26].

Statistical Plans

The main analyses that assess the impact of QIP were performed using the full analysis set (FAS), which consisted of all enrolled participants with at least one nonmissing postintervention GINA treatment assessment. Baseline demographics and characteristics will be presented for all enrolled participants and FAS. Continuous variables will be summarized descriptively as appropriate. Categorical variables will be presented as frequency counts and percentages. When applicable, 95% CIs will be presented with estimates of proportions.

Analysis of the primary end point were conducted in the FAS with a mixed effect logistic regression model, considering the measurement time point (baseline or post baseline) as the fixed effect and hospital, pulmonologist, and patient as the random effects. In case of lack of convergency, the hospital and pulmonologist were removed from the model. A sensitivity analysis was conducted with a generalized estimating equations model including the same covariates as in the primary analysis. Secondary and exploratory end points were presented primarily with summary statistics. For the analysis of end points, by-visit end points were analyzed using observed data, and missing data were not imputed.

Subgroup analyses were performed as appropriate according to age (<18, 18–65, or >65 years), age of asthma onset (<20, <40, or ≥40 years), phenotype of asthma (allergic or nonallergic), hospital level (tertiary or secondary), occupation (asthma-related or not), baseline characteristic, questionnaire response status (with or without response), adherence, patient expectation of asthma treatment, asthma history, asthma severity class, type of the participating hospital department (pulmonary and critical care medicine or nonpulmonary and critical care medicine), geographic region (North or South), change from baseline in ICS-containing treatment (with-to-with, with-to-without,

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without-to-with, or without-to-without ICS-containing treatment), and change from baseline in ICS-formoterol as reliever (with-to-with, with-to-without, without-to-with, or without-to-without ICS-formoterol as reliever). Any participants with a missing value for a predefined subgroup were excluded from the analysis of that subgroup.

Ethical Considerations

This study's protocol had been approved by the Ethics Committee of Beijing Chao-Yang Hospital, Capital Medical University (2022-KE-22).

Informed consent was obtained from a participant or their legally authorized representative before conducting any procedure specifically for this study on the participant.

Participants were assigned a unique identifier by the sponsor. Any participant records or datasets that were transferred to the sponsor contained the identifier only; participant names or any information that would make the participant identifiable were not transferred.

Participant payment outlines were discussed in the informed consent process. Participants were paid a CN ¥ 200 (approximately US $27.50 as of December 12, 2024) transportation fee per on-site visit for reasonable expenses incurred due to their participation in this study.

Results

This study has been completed, with 1500 patients enrolled and 1271 patients completing the study. The last visit of the last patient was on September 3, 2024, and the database lock was on September 28, 2024. Final analysis of data has started in October 2024.

Discussion

Rationale and Study Design

Poor symptom control and exacerbations of asthma impair work and activities, diminish quality of life, and pose a significant burden to patients and society [9,27]. Implementing evidence-based management as recommended by GINA has the potential to improve the quality of domestic asthma care and vastly reduce the disease burden of asthma in China [17]. In line with GINA recommendations, the latest versions of the Chinese guidelines and an expert consensus for asthma management also advocate for ICS-based maintenance and relieving treatment [8,28]. Meanwhile, ICS-containing medications such as budesonide and budesonide-formoterol have been included in China's National Essential Drug List and National Reimbursement Drug List, ensuring patients' access to these asthma medications (including those with special needs such as school-aged patients who may require more than one canister with a single prescription to maintain medication availability both at school and at home). However, at present, domestic asthma control is still unsatisfactory with patients' treatment patterns deviating from the GINA recommendations, suggesting that Chinese physicians' suboptimal awareness of and adherence to the recommendations [2,12,16] may be an important underlying factor that warrants further improvement. Experience from other countries has demonstrated that clinical benefits can be achieved through QIPs for asthma care [21-23]. As such, the CARE4ALL study will conduct China's first-ever nationwide multifaceted QIP targeting physicians with a specialization in pulmonary or respiratory care, which aims to transform the suboptimal asthma control status in China by bridging the gap between GINA recommendations and current clinical practice among Chinese physicians.

Expected Results

We expect that the physicians' awareness of and adherence to the GINA recommendations will be enhanced through the QIP, which would be manifested as more widespread clinical practices that are per evidence-based asthma management, including the implementation of standard, GINA-recommended treatment. We further anticipate that the improved quality of care provided by the physicians would translate to better asthma control and health-related quality of life among the patients. If this study demonstrates these benefits of the QIP in standardizing asthma management in China, this QIP could be considered as a standard model that the whole country can apply to reduce the burden of asthma in China.

Strengths

As the first nationwide QIP for asthma care with a prospective evaluation of clinical impacts in China, the CARE4ALL study has several strengths in its design which differentiate it from previous simple, small-scale educational interventions. First, multifaceted intervention will be provided for physicians to aid understanding and encourage close adherence to the GINA recommendations. The initial comprehensive training intends to familiarize physicians with GINA, which will be reinforced by regular learning sessions typically unseen in routine educational events. Additionally, both online and offline supporting materials are readily available to physicians for easy reference and patient education. Second, different from routine physician-oriented educational events and toolbox, this QIP will also provide physicians with support to facilitate patient management in clinical practice. As effective asthma care requires patients to be actively engaged in multiple self-management behaviors, improving patients' adherence with GINA-recommended practices (eg, ICS-containing medications, appropriate device technique, use of an asthma action plan, etc) is of great importance to the ultimate success of the GINA implementation. Notably, apart from layperson-style patient education materials aiming to raise patients' awareness of disease management and treatment strategies, an online patient management platform will be developed to facilitate timely evaluations of symptoms and effective physician-patient communications. These interventions are expected to improve patients' treatment adherence and consequently asthma control as demonstrated by previous studies [29,30].

Third, the GINA implementation at the hospital level will be monitored based on the 6 performance indicators and dynamically improved based on feedback from the scientific steering committee, which consists of national asthma experts. Therefore, all the participating hospitals can benefit from constructive instructions from the committee. Finally, while primary health care facilities in remote rural areas will be

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excluded due to their inadequate administrative and data management capacity, this study will encompass both tertiary and secondary hospitals from as many provinces or municipalities as possible, aiming to provide unprecedented coverage to better represent the real-world situations in China [18,19]. In China's current medical system, most asthma patients are diagnosed and treated under specialist care rather than by general practitioners, thus this study, by specifically targeting pulmonologists, will exert a direct and substantial effect on shaping the clinical practice of asthma care in China's medical system. As such, experiences and lessons from the program will hopefully inform a valuable model for asthma care improvement in the whole of China as well as for similar programs for other chronic diseases.

This QIP is expected to exert a sustained impact on asthma care practices. First, unlike brief educational events [18], the intervention for our study will last for one year, providing a sustained framework for cultivating evidence-based clinical practice behaviors in physicians. Second, both online and offline supporting materials used during the QIP will continue to be accessible to physicians after the program finishes; coupled with continuous assessments of GINA implementation performance, these resources will aid in maintaining physicians' awareness and adherence to GINA-recommended asthma management. Lastly, by not providing free medications, this study will closely mirror any potential influence that medication accessibility or affordability may have on patients in real-world conditions, thereby enhancing the generalizability of the findings.

Limitations

This study has two key limitations. First, it lacks a concurrent control arm. Instead, it follows the before-and-after design and compares variables measured before and after the QIP, which is an approach often adopted in QIP-evaluating studies for the purposes of better reflecting real-world settings and maintaining simplicity. The effectiveness of this before-and-after design in reflecting the effects of QIP interventions has been widely demonstrated [23,31,32]. Second, multiple sources will be used for data collection, likely leading to missing and inconsistent data. Given that patients may be admitted to other hospitals due to exacerbations, data collection from multiple sources will be inevitable. Past and new hospitalizations out of the study hospital due to exacerbations will be recorded based on medical records rather than patients' personal accounts to reduce missing data and minimize recall bias.

Conclusions

In summary, the CARE4ALL study should help improve asthma management and patient outcomes in China by bridging the gap between evidence-based GINA recommendations and the current clinical practice. This multifaceted QIP is expected to provide valuable insights for further quality improvement in asthma care at the national level.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

All authors handled the conceptualization of this study. KH wrote the original draft. WW, YW, YL, XF, HS, and CW reviewed and edited the writing. All authors (except HS, who died on April 16, 2024) read and approved the final version of this paper. HS had read and approved a previous version.

Conflicts of Interest

AstraZeneca is involved in this study design, data collection, data analysis, and preparation of this paper. The authors declare no other conflicts of interest.

Multimedia Appendix 1
Protocol schedule of activities.
[DOCX File , 22 KB - resprot_v14i1e65197_app1.docx]

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Abbreviations

CARE4ALL: Change Asthma Clinical Practice through Global Initiative for Asthma Education and Implementation for All Patients With Asthma
FAS: full analysis set
GINA: Global Initiative for Asthma
ICS: inhaled corticosteroid
QIP: quality improvement program
SABA: short-acting β2-agonist

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Protocol

Standardized Outcomes for Randomized Controlled Trials Targeting Early Interventions in Patients With Moderate-to-Severe Traumatic Brain Injury: Protocol for the Development of a Core Outcome Set

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Abstract

Background: With more than 60 million new cases around the world each year, traumatic brain injury (TBI) causes substantial mortality and morbidity. Managing TBI is a major human, social, and economic concern. In the last 20 years, there has been an increase in clinical trials in neurocritical care, leading mostly to negative results. The evaluation of neurological outcomes, predominantly as primary outcomes, using clinical scales (Glasgow Outcome Scale) has limitations that could explain these results. Moreover, patient-centered outcomes are seldom reported despite their recognized clinical relevance.

Objective: The aim of this project is to establish a core outcome set (COS) for patients with moderate-to-severe TBI in randomized control trials in neurocritical care research.

Methods: This study will follow five distinct steps: (1) systematic review to identify outcomes that have been reported in trials; (2) semistructured interviews with patients and their families to identify their priorities after TBI and explore potential patient-centered outcomes; (3) health care stakeholder focus groups with clinicians, researchers, and policy makers to describe potential outcomes; (4) an eDelphi survey with stakeholder groups to make a list of previously identified core outcomes; and (5) a consensus workshop to establish a COS for moderate-to-severe TBI clinical trials.

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Results: The systematic review was published in August 2024. Regarding Step 2, 30 semistructured interviews of patients and relatives were performed from July 2021 to December 2023, and analyses were completed in October 2024. Step 3 is currently under development, and Step 4 is planned for the end of 2025. Step 5 is expected to occur during fall/winter 2026.

Conclusions: Establishing a COS, to be consistently measured and reported in TBI trials in neurocritical care will ensure rigorous reporting, avoid bias, and improve the integrity, transparency, and usability of clinical research. The French context of the study is the main limitation, but we are seeking international collaboration on the project. The results of each step of the project will be disseminated through abstracts, publications, and patient associations.

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(JMIR Res Protoc 2025;14:e54525) doi:10.2196/54525

KEYWORDS

core outcome set; outcomes research; patient-centered outcomes; traumatic brain injury; patient outcome; head trauma; patient-centered

Introduction

Despite advances in critical care medicine in the last decades, mortality in patients with traumatic brain injury (TBI) remains high at approximately 15% after trauma [1]. Survivors of TBI experience major consequences: mood disturbances [2], memory loss, neuropsychological impairment [3,4]. Caregivers also experience major burdens with strain, isolation, and disappointment [5,6].

Many work groups recommend that various outcome domains or outcome measurements [7,8] be collected to assess neurological recovery after TBI, mainly in the continuum of rehabilitation. Most often, this involves a combination of multiple measurement scales that collectively capture all dimensions affected by a TBI [9,10].

Nevertheless, in neurocritical care, the primary outcome in most randomized controlled trials (RCTs) is the Glasgow Outcome Scale [1,11]. Indeed, given the broad spectrum of sequelae after acute brain injury, Jennett and Bond [12] proposed the use of the Glasgow Outcome Scale in 1975 to assess neurological recovery after TBI. Since then, this 5-grade scale (death, vegetative state, severe recovery, moderate recovery, and good recovery) has been extensively reported in the neurocritical care literature to compare the efficacy of various treatments after trauma [13-15]. The Glasgow Outcome Scale was considered too simplistic, leading to the creation of an 8-grade extended version in 1981 [16]. The Extended Glasgow Outcome Scale is used extensively in neurocritical care literature to evaluate neurological recovery, often as a primary outcome in clinical trials [17].

Recently, major concerns have been raised regarding the relevance of these scales and their methodological limitations in neurocritical care clinical research. The Glasgow Outcome Scale has substantial interobserver variability, albeit possibly decreasing over time [18]. Nevertheless, this puts score reliability and accurate patient classification into question [19,20], which could lead to erroneous results despite rigorous analysis. Moreover, analysis of data from this scale is often inappropriate, since these data are generally considered continuous when they are ordinal [21]. In addition, assessment conditions can vary and affect patient evaluation. Evaluation can be performed via telephone [22] or face-to-face interviews, for only brain injury or all injuries (brain and peripheral body parts), or by trained or untrained assessors. These variables are frequently not described in other studies [3,11,18]. However, it is recommended that such assessments should be performed by a certified expert in the presence of the patient and caregiver [23]. Certain authors have recently questioned the consistency between these scales and patient quality of life [24,25]. This raises the question of a patient's understanding of their situation and handicap, which is never evaluated in randomized controlled trials, despite being recognized as an important factor [26]. The aforementioned methodological issues and limitations associated with these scales could explain the litany of negative results in neurocritical care research over the past 30 years [1,15,17,27,28].

Core outcome sets (COSs) can minimize reporting bias, promote consistency in clinical trials, enable direct comparisons of the effect of different interventions, and ensure that outcomes are relevant and important to patients, health care professionals, and caregivers [29]. Hence, the use of COSs for patients with TBI in neurocritical care could reduce the considerable inefficiencies in biomedical research. With more than 60 million new cases of TBI diagnosed globally each year [30,31], there is an urgent need to develop COSs in this area. Accordingly, this project aims to establish a COS for trials in patients with moderate-to-severe TBI included in interventional trials performed during the early phase of the pathology and other types of research including observational studies (eg, registries and other quality indicators for clinical care). This core outcomes set will improve the quality of trials, respond to patient needs, and help rectify decades of negative results.

Methods

Overview

The project will be developed in 5 steps according to the methodology of the Core Outcome Measures in Effectiveness Trials (COMET) initiative. The aim of the COMET initiative is to create a COS built by stakeholders, including patients [32,33]. First, we will perform a systematic review of the outcomes in TBI clinical research at the acute phase. Second, we will organize semistructured interviews with patients who survived moderate-to-severe acute TBI and their family caregivers. Third, we will organize semistructured interviews

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and focus groups of stakeholders involved in the health care pathway of patients with TBI. Fourth, we will perform an eDelphi survey. Finally, a consensus workshop will finalize the process.

Step 1: Systematic Review

Step 1 was completed in August 2024, and the original article was published [34]. We identified 29 domains related to the 557 different outcomes that will be used for interviews with health care professionals (Step 3) and the eDelphi survey (Step 4).

Step 2: Semistructured Interviews With Patients and Their Families

Explanation and Overview

We will organize semistructured interviews with patients in the late phase of TBI and their family caregivers. To the best of our knowledge, semistructured interviews involving both patients with TBI and their families have been poorly explored. Throughout the qualitative research, we will follow the Interpretative Phenomenological Analysis (IPA), a methodology described by Smith et al [35].

Participants and Recruitment

Patients with TBI aged 18 years and older and a family caregiver (the patient's choice) will be eligible to participate. A purposive sampling strategy will be used to organize a minimum of 15 semistructured interviews with the dyad (patient and their family caregiver). The aim is to perform individual semistructured interviews with patients alone and then perform another individual dedicated interview with relatives alone to avoid cross-contamination of interview responses between the 2 parties. However, given the potential challenges for patients (mood disorders, speech disorders, and difficulties in concentration), relatives may attend the patient's semistructured interview to assist them. The final interviews will depend on when data saturation is reached. We will define saturation as the point when new themes or variations of a given theme cannot be identified. Participants will be recruited from participating centers across France (Bordeaux, Nantes, Rennes, and Saint-Etienne, along with any other contacted centers). The patients and their caregivers will be asked by physical and rehabilitation specialists to participate in the study. Patients in the late phase of TBI will be recruited—defined as the moment when a patient has been discharged at least partially, meaning they no longer require full-time care in a health care facility. The consequences of TBI on their social and personal environments will be assessed.

The steering committee will carry out a sampling strategy to achieve maximum variation in demographics (age, sex, and socioeconomic status) and clinical characteristics (patients with good or poor recovery). We will follow the Consolidated Criteria for Reporting Qualitative Health Research (COREQ) guidelines [36].

Data Collection

Each semistructured interview, performed with an IPA approach according to participants' life experiences, will last a maximum of 90 minutes and take place remotely via videoconference. This is due to the uncertainties in the aftermath of the COVID-19 pandemic. In any case, these interviews will take place outside the hospital to encourage open discussion and limit the stories due to the feeling of disempowerment that could occur in a clinical setting. Each interview, performed by a nurse researcher (senior in qualitative research) and a PhD student, will cover the following for both patients and families: (1) an introduction (5 minutes), where the facilitator will explain the aims of the study and ask the participants to introduce themselves; and (2) the interview (60 minutes), where the participants and families will be asked to discuss their experiences of living with the consequences of TBI, including perceived benefits, harms, and complications related to the pathology and its treatments. The topic guide was tested with 3 dyads and adjusted accordingly (Multimedia Appendices 1-2).

Data Analysis

The interview transcripts will be imported into NVivo 12 software (v.1.8; QSR International) [37] to facilitate qualitative data analysis. We will follow the 7 IPA steps described by Smith et al [35]: (1) reading and rereading, (2) exploratory noting, (3) constructing experiential statements, (4) searching for connections in experiential statements, (5) naming the personal experiential themes and consolidating and organizing them, (6) moving to the next case, and (7) working with personal experiential themes to develop group experiential themes across cases. The IPA method reflects the experience, beliefs, values, attitudes, and reasons underlining participant choices, along with those of their relatives. The preliminary themes will be discussed with other investigators to ensure that the full range and depth of data are captured (investigator triangulation) and with patient associations for the full themes.

Step 3: Stakeholder Interviews

Explanation and Overview

Field investigations, in-depth and semistructured interviews, and focus groups will be performed to capture the expectations and practices regarding the management of TBI patients and to detail the range and depth of individual values, beliefs, and attitudes toward outcomes. These interviews or focus groups will not quantify the frequency of opinion. Reporting will adhere to the COREQ guidelines.

Participants and Recruitment

Interviews and focus group discussions will be conducted with the following stakeholder groups: (1) health care providers (anesthesiologists, intensivists, neurosurgeons, rehabilitation specialists, nurses, and psychologists); (2) representatives from research, funding, policy, and other stakeholder organizations; and (3) patients and their relatives. A minimum of 60 stakeholders is expected at this point and will be identified from the investigator networks and by snowball effect. At this stage, the steering committee will reach out to stakeholders in other countries to participate in specifically dedicated interviews. Participants will be identified to obtain a maximum variation of representation in professional experience and responsibilities (health care providers and representatives from stakeholder organizations). Recruitment will continue until saturation has

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been achieved. Informed consent will be obtained from all participants and specific institution review board (IRB) approval will be sought.

Data Collection

From a grounded theory perspective [38], field investigations will be conducted in intensive care and rehabilitation units. Interviews and focus groups will incorporate the results from the systematic review and semistructured interviews with patients and their families, allowing other stakeholders to discuss these elements as well. Stakeholders will be asked to reflect and talk about (1) caring for patients with TBI, (2) the benefits and harms of TBI-related outcomes, (3) outcomes believed to be relevant and important to include in future clinical research, and (4) the results obtained from the semistructured interviews with the patients and their families. Face-to-face interviews will be conducted; however, if this is not feasible, web or telephone conferences will be arranged. Each interview will last between 60 and 120 minutes. The interviews will be recorded and transcribed verbatim.

A field researcher has been hired for a 24-month postdoctoral position to complete Step 3. She is a former intensive care nurse with a PhD in sociology from the University of Nantes and has extensive experience in field investigations and conducting interviews. She has no conflicts of interest related to the topic.

Data Analysis

Data analysis is expected to begin in 2025. Verbatim transcripts from interviews and focus groups will be transcribed word for word and anonymized. Following the grounded theory methodology [38], each transcript will undergo a constant comparison across individuals and stakeholder groups. Analytical themes will be developed inductively to identify the concepts relevant to the participants, from which a list of outcomes will emerge.

Step 4: Delphi Consensus Survey

Explanation and Overview

At this stage, international contacts will be established to conduct an international eDelphi survey [29,39,40]. This survey will gather opinions and organize the outcomes into a prioritized list. The Delphi method is an iterative consensus technique involving sequential surveys completed anonymously by a panel of participants with relevant knowledge and expertise, ensuring equal influence among all participants [41]. We will aim to retain a minimum response rate of 70% for all rounds.

Participants and Recruitment

There is no standard sample size required for Delphi processes. At this point of the protocol, there is no goal regarding the minimum number of stakeholders that will be involved in the Delphi process (ie, patients, family caregivers, nurses, allied health professionals, policy makers, and clinicians in critical care, rehabilitation, and neurosurgery). To ensure maximum variation in sampling, participants will be recruited by using a similar strategy, and approximately one-third of each stakeholder group will be recruited from the participating regions. The participants will be recruited through participating hospitals or institutions and patient organizations. Informed consent will be obtained from all participants.

Data Collection

Overview

The list of outcomes will be obtained from Steps 1, 2, and 3. The outcomes will be listed individually and grouped under each relevant domain according to the COMET initiative definitions [32,42]. The survey will be reviewed by the steering committee. The surveys will be completed over the internet by using a unique identifier, which will enable us to identify participants completing all 3 rounds of the eDelphi survey. At least 3 reminders will be sent to participants during the Delphi rounds.

Round 1

Participants will be asked to rate each outcome using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) process [43]. The process recommends a 9-point Likert scale to rank importance. Rankings between 7 and 9 indicate outcomes of critical importance, those between 4 and 6 indicate outcomes that are important but not critical, and those between 1 and 3 indicate outcomes of limited importance. An option “unable to score” will also be available. All outcome domains will be randomized to minimize ordering bias. Participants can suggest additional outcomes and provide reasons for their rankings. The additional outcomes will be recorded (if not duplicated with a previous outcome), grouped in the relevant outcome domain by 2 members, and reviewed by the steering committee. We will review the distribution of scores for all outcomes for each stakeholder group (ie, patients/caregivers, clinicians, health professionals, etc). Any outcomes with a median or mean over 7 will be retained for round 2, along with additional outcomes retained by the steering committee.

Round 2

Participants will review the group scores and their own scores for each outcome. They will rerank the outcomes (including additional outcomes identified in round 1) using the 9-point scale and explain the reasons for any changes in their scoring. An outcome with a median or mean over 7, and with 70% or more participants in both stakeholder groups (ie, patient/family member and health professionals) rating the outcome to be of critical importance (7-9), will be included in round 3.

Round 3

Participants will be shown their own scores, along with the distribution of scores for each outcome across all stakeholder groups and within individual stakeholder groups. A summary of the results from Steps 2 and 3 will be provided. Participants will be asked to rerank all outcomes and indicate whether they should be included in the COS. To assess the relative importance of the outcomes, they will choose the most important and least important in each outcome domain.

At this point, the recruitment of stakeholders for Step 4 and the Delphi process will not be undertaken for at least 2 years. Data analysis of Step 4 (Delphi process) will be further elaborated and will not be more detailed at this stage.

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Step 5: Consensus Workshop

A face-to-face consensus conference will be held for stakeholders to review, comment on, and endorse the COS. This conference will be chaired by members of the steering committee. As of yet, the number and origins of participants at the workshop have not been established. This sample size is based on the Outcome Measures in Rheumatology (OMERACT) consensus workshop. Purposive sampling will be carried out to ensure maximum variation of demographic and clinical characteristics. Informed consent will be obtained from all participants. All discussions will be recorded and transcribed. The overall conference program is outlined in Textbox 1.

Given the timeline of the project, Step 5 will not be undertaken for another 3 years (around mid-2026). The articulation, organization of the workshop, and data analysis will be further elaborated but not detailed here. Figure 1 articulates the differences between the 5 steps.

Textbox 1. Conference program details.

1. Presentation of results: Detailed results from Steps 2, 3, and 4 will be distributed to the participants. The results will be presented during a plenary session of the consensus workshop, and the outcomes will also be shown according to the consensus classification.
2. Breakout group discussion: Participants will be divided into several groups. A trained facilitator will moderate a group discussion on the results from Steps 3 and 4, consensus classification of outcomes, similarities and differences in stakeholder groups, and the resolution of any disagreement, uncertainties, or issues identified.
3. Plenary discussion: Each breakout group will present a summary of their discussion. The conference chair will moderate the discussion.
4. Endorsement of core outcome set (COS): Participants will be asked to formally endorse the core outcomes set which will include the outcome classified as consensus.

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Figure 1. Summary of the project regarding the development of a core outcome set in neurocritical care for patients with traumatic brain injury (TBI). RCT: randomized controlled trial.

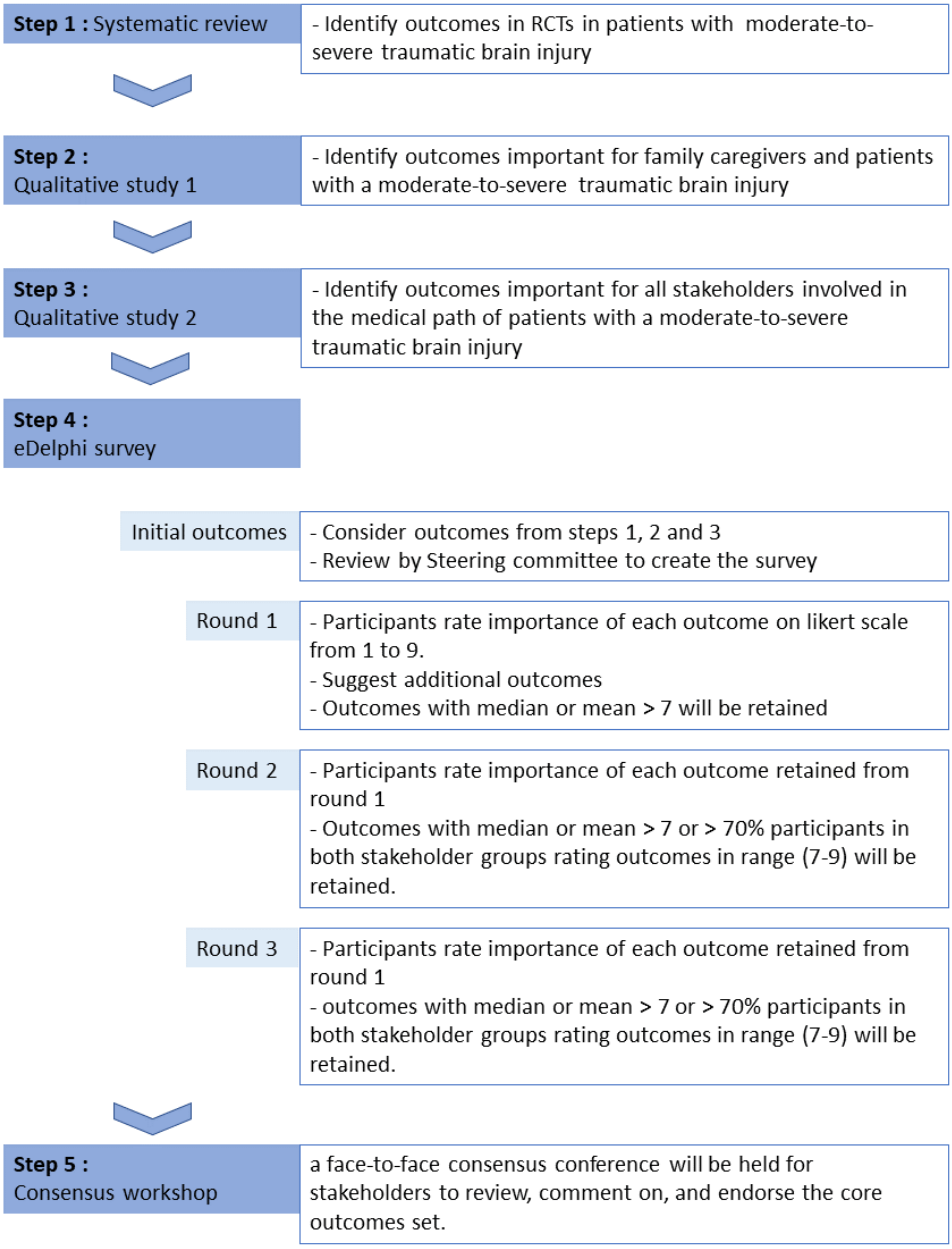

Ethical Considerations

All steps will be performed according to the appropriate guidelines and regulatory processes.

Step 1

Ethical approval is not required for this step.

Step 2

Patients and relatives provided informed consent to participate in the semistructured interviews (CERAR IRB 00010254 - 2022–093). The analysis of the interview transcripts will be anonymized to respect privacy and anonymity. Finally, patients and relatives will receive €50 (US $52.12) each for compensation for their time to perform these interviews.

For the elaboration and recruitment of patients for Step 2 (semistructured interviews), the group is currently working with the association of patients and families ("Union Nationale des Associations des Familles de Traumatisés Crâniens").

Step 3

Interviews and focus groups with health stakeholders will also comply with rules and regulations. Although no IRB is necessary in France regarding surveys [44], oral consent will be collected from participants. Verbatim analyses and data will be anonymized and deidentified.

Step 4

No health data are collected in Step 4. Moreover, IRB approval is not mandatory in France for this type of research. However, we will comply with all national authorities' guidelines in case

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of international collaboration. We will also comply with laws and regulations for the publication process.

Step 5

No health data are collected in Step 5. Moreover, IRB approval is not mandatory in France for this type of research, but we will comply with all national authorities' guidelines in case of international collaboration. We will also comply with laws and regulations for the publication process.

Results

Step 1 was completed, and the paper was published in August 2024 [34]. This systematic review was performed from January 2021 to October 2023.

Regarding Step 2, 30 semistructured interviews were carried out (15 patients and 15 caregivers) throughout France. The interviews were performed between July 2021 and December 2023. The results of the verbatim analysis (ie, group experiential themes through cases) were finalized in September 2024, and we expect to begin the publication process by the end of 2024. We aimed to understand the quality of life of both patients and family caregivers, focusing on what matters most to them in their daily lives. The elaboration of Step 3 began in May 2024. The aim of this part of the project is to understand different stakeholder points of view regarding the choice of end points in clinical research.

Although Steps 2 and 3 have not yet been achieved, we have already begun engaging with the scientific community, clinicians, health professionals, other health care stakeholders, and patient associations for the upcoming Delphi process, which is scheduled for the beginning of 2026. This proactive approach ensures that we will have the most comprehensive group of participants for the Delphi process. Step 5 will mark the finalization and dissemination of the COS. This step is preplanned to start in fall/winter 2026.

Discussion

Principal Findings

This project introduces a novel clinical research methodology for TBI through the development of a COS. This COS includes a rigorous multidimensional evaluation of the outcome of patients and encourages the integration of Patient-Reported Outcome Measures (PROMs) in this context. We believe this initiative will address decades of negative findings on this topic, emphasizing the urgent need to improve patient outcomes amid strained resources. The project involves various stakeholders, especially patients and family caregivers, in a rigorous methodological approach that has been successfully tested in other medical disciplines [32,45].

Many work groups have published common data elements [46,47] recommended for RCTs. However, these common data elements are unsuitable for RCTs targeting early interventions in neurocritical care. Notably, our systematic review [34] highlighted the low use of patient-reported outcomes in RCTs, despite increasing advocacy for their use by researchers [26,45].

The study's French context is its main limitation, but we are pursuing international collaboration to ensure its global relevance. Furthermore, given that health systems in high-income countries are often comparable, the findings should be globally applicable.

The results of each step will undergo scientific validation and publication. The dissemination plan includes communications in both national and international congresses involving key stakeholders in TBI research, such as anesthesiologists, intensivists, neurosurgeons, trauma leaders, neuropsychologists, and nurses. Targeted congresses include the French Society of Anesthesia and Intensive Care, European Society of Intensive Care Medicine, the European Society of Anesthesia and Intensive Care, and the International Brain Injury Association—among others. Publications will be submitted to peer-reviewed journals. Where resources allow, we intend to publish our findings in open access whenever possible. Finally, the final COS will be published in a major journal (eg, British Medical Journal, Lancet Neurology), given the initiative's importance and its potential to improve research quality.

We also intend to share our findings with patient associations and through social media. We will disseminate our findings through public engagement activities, based on existing initiatives in their respective countries/institutions, such as European Researchers' Night, alongside collaborations with private insurance companies (ie, AXA and MMA).

The COS will emerge from a consensus process designed to improve the quality and relevance of research evidence in neurocritical care RCTs involving patients with TBI. We expect that the COS will be used only in the RCTs but may also be valuable in other types of research, such as observational studies (eg, registries) and as quality indicators for clinical care.

Conclusion

This project aims to improve the integrity, transparency, usability, and impact of research related to patients with moderate-to-severe TBI. It will ensure that outcomes relevant to all stakeholders are consistently reported in trials, thereby minimizing outcome reporting bias. Ultimately, this will protect patients from potential harm, enable patients and clinicians to make informed treatment decisions, and allow researchers and policy makers to maximize the public value of research.

Acknowledgments

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Data Availability

Publications will be made accessible as much as possible (eg, the Step 1 systematic review), depending on available funding. Full data may be available provided upon adequate request to the corresponding author.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Topic guide for patients with traumatic brain injury (TBI) used in Step 2 of developing a core outcome set (COS) in neurocritical care.
[DOCX File , 17 KB - resprot_v14i1e54525_app1.docx]

Multimedia Appendix 2
Caregivers' topic guide used for Step 2 of developing a core outcome set (COS) in neurocritical care for patient with traumatic brain injury (TBI).
[DOCX File , 18 KB - resprot_v14i1e54525_app2.docx]

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Abbreviations

COMET: Core Outcome Measures in Effectiveness Trials
COREQ: Consolidated Criteria for Reporting Qualitative Health Research
COS: core outcome set
GRADE: Grading of Recommendations, Assessment, Development, and Evaluation
IPA: Interpretative Phenomenological Analysis
IRB: institutional review board
OMERACT: Outcome Measures in Rheumatology
PROM: Patient- Reported Outcome Measure
RCT: randomized controlled trial
TBI: traumatic brain injury

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Original Paper

Methodology for the Positive Voices 2022 Survey of People With HIV Accessing Care in England, Wales, and Scotland: Cross-Sectional Questionnaire Study

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Abstract

Background: Due to advances in treatment, HIV is now a chronic condition with near-normal life expectancy. However, people with HIV continue to have a higher burden of mental and physical health conditions and are impacted by wider socioeconomic issues. Positive Voices is a nationally representative series of surveys of people with HIV in the United Kingdom. It monitors the physical, mental, and social health, well-being, and needs of this population so that they can be addressed.

Objective: This paper aimed to describe the methodology, recruitment strategies, and key demographic features of participants recruited for the second national round of Positive Voices (PV2022).

Methods: PV2022 was a national, cross-sectional questionnaire study that included people attending HIV care at 101 of the 178 clinics in the United Kingdom between April 2022 and March 2023. Data from the HIV and AIDS reporting system (HARS), a national surveillance database of people with HIV and attending care that is held at the UK Health Security Agency (UKHSA), was used as a sampling frame. The information collected in PV2022 included demographic and socioeconomic factors, HIV diagnoses and treatment, mental and physical health, health service use and satisfaction, social care and support, met and unmet needs, stigma and discrimination, quality of life, lifestyle factors, and additional challenges experienced due to the COVID-19 pandemic. Data linkage to HARS enabled the extraction of clinical information on antiretroviral therapy (ART), HIV viral load, and CD4 lymphocyte counts. Probabilistic sampling was used to provide a randomly selected, representative sample of people attending HIV care who could be invited to complete a paper or online questionnaire. At the start of 2023, due to under-recruitment mainly due to the impact of the monkeypox (Mpox) outbreak, a separate sequential recruitment strategy was initiated in 14 of the largest clinics to increase participant numbers.

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Results: Of the 4622 participants who completed the questionnaire, 3692 were recruited through probabilistic recruitment and 930 through sequential recruitment. The overall response rate (measured as the number of people who completed a questionnaire of those who either accepted or declined) was 50%. Survey respondents represented approximately 1 in 20 people diagnosed with HIV in England, Wales, and Scotland. The median age of participants was 52 years, 3428 of participants were men, 2991 were White, and 1121 were Black.

Conclusions: PV2022 is currently the largest survey of people with HIV in the United Kingdom (as of September 2024). The PV2022 findings will be used to explore the health and well-being of the HIV population and examine associations with demographic, socioeconomic, lifestyle, and other HIV-related factors.

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KEYWORDS

HIV care; national survey; quality of life; Positive Voices; transgender population; gender-diverse population; health disparities; health services research; living with HIV; HIV stigma; social determinants of health; longitudinal cohort; access to care; welfare services; health policy; preventive care

Introduction

In the last 2 and a half decades, advances in HIV treatment have greatly reduced the mortality rate among people with HIV [1]. As a result, HIV is now viewed as a chronic condition with near-normal life expectancy [2]. As the population of people with HIV is ageing (half are now aged 50 years and older) [3] and health service delivery models are undergoing continuous change [4], it is essential to understand the types and levels of health needs of people with HIV and to assess long-term outcomes and quality of life [5].

In 2022, there were 94,397 people diagnosed with HIV and accessing care in England [6]. It was estimated that 95% of people with HIV were diagnosed; 98% of those diagnosed were on treatment; and 98% of those on treatment were virally suppressed and therefore unable to transmit HIV [7,8]. Research has indicated that despite substantial improvements in prognosis for people with HIV on treatment and the high coverage of specialist HIV care, there remains a significant level of psychosocial need among people with HIV [9]. They experience higher levels of mental health symptoms [9], with the prevalence of depression and anxiety around twice as much as the general population [10-12]. High levels of perceived and internalized stigma associated with HIV status are experienced by people with HIV, impacting their mental health [13]. Socioeconomic issues, such as poverty, unemployment, unstable housing, lack of social support, and intimate partner violence have also been shown to impact people with HIV, affecting both physical and mental health [14-16]. Understanding these needs is particularly crucial following a period of significant changes in health and social care service provision, due to policies of austerity and the COVID-19 pandemic [17]. Positive Voices (PV) collects and analyses these types of data, providing valuable insights that are used to inform national HIV policy and prevention programs and to evaluate and commission HIV specialist services.

PV is a cross-sectional questionnaire study of people with HIV who receive HIV specialist care in England, Wales, and Scotland, carried out every 3-5 years. In 2014, an extensive pilot phase that included formative research with the HIV community and health care staff facilitated the development of the survey methodology, which was subsequently used for the national roll-out in 2017 (Positive Voices 2017 [PV2017]) [9,18]. Our paper aims to describe the methodology and study design of the second round of the study: Positive Voices 2022 (PV2022).

Methods

Study Design

PV2022 was a national, cross-sectional questionnaire survey of people with HIV attending HIV outpatient care in England, Wales, and Scotland. The questionnaire data were linked to clinical data on antiretroviral therapy (ART), HIV viral load, and CD4 lymphocyte count from the HIV and AIDS reporting system (HARS), a national surveillance database of people with HIV attending care, held at the UK Health Security Agency (UKHSA).

Setting

In December 2020, all HIV clinics that routinely report to HARS were emailed by the PV team and asked whether they wished to express an interest in becoming a PV2022 study site. A total of 101 clinics, over half (57%) of the 178 HIV clinics in the country, returned an expression of interest, 98% of whom were in England (99/101), 1 was in Scotland (1/101), and 1 in Wales (1/101). Sixty-two (61%) clinics had previously participated in the previous round of the study (PV2017). Initially, the recruitment of participants was planned to begin in 2021, but was delayed as patient attendance at clinics was disrupted due to the COVID-19 pandemic restrictions. In April 2022, the recruitment of participants began, as services had started returning to face-to-face consultations. However, following the pandemic, many clinics had adopted a hybrid approach of giving remote telephone or video consultations as well as seeing patients in clinic. Refer to Multimedia Appendix 1 for a list of participating clinics.

In this paper, “clinic staff” has been defined as clinicians (nurses or doctors) and researchers who worked in the participating HIV clinics.

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Sample Size

HARS was used as a sampling frame to provide a representative, random sample of people with HIV within each participating clinic who could be approached to participate in the PV2022 survey. HARS is a surveillance database held at the UKHSA that consists of pseudonymized data on the demographic, clinical, and treatment characteristics of people with HIV that is reported each quarter year by all HIV service providers in England [19,20].

The population of patients attending the participating clinics was approximately 74,000. The sample was to include 1 in 5 patients attending each of these clinics. Data from the pilot study and PV2017 indicated a proportion of individuals would be nonrecruitable due to being deceased, no longer attending clinic, being lost-to-follow-up, having been imprisoned or having an incorrect hospital identification number. Therefore, considering this, a sample list of 17,121 patients was created with the assumption that approximately 14,400 would be recruitable. Based on the response rate in PV2017 and observed declines in response rates in other large population-based studies in recent years, the PV2022 response rate was expected to be between 30% and 50%, resulting in 4320 to 7200 participants being recruited. The precision of prevalence estimates of measures such as diagnosed depression, occurring at approximately 30% prevalence, would therefore be ±1.4% and ±1.1% (with 95% confidence) for the response rates of 30% and 50%, respectively. Within a key demographic subgroup comprising 10% of the population, the precision would be ±4.4% and ±3.3%, respectively.

Study Population and Selection

Clinic staff were asked to approach their patients who had been randomly sampled from HARS and included in a list provided by the PV team. Each selected patient was assigned a unique identifier that was displayed on their survey packs or could be used to access their online questionnaire.

The PV team had made efforts to oversample the transgender and gender-diverse HIV population by adding to each clinic's list all patients recorded on HARS who identified as trans or gender-diverse. This was carried out to ensure a sufficient number of participants from this population group were represented, as it had been reported that this cohort was experiencing larger health inequalities in comparison with the general population [8].

Inclusion Criteria

The inclusion criteria were people diagnosed with HIV, aged 18 years or older, residing in the United Kingdom, accessing care at a participating HIV clinic in England, Wales, or Scotland, and able to complete the questionnaire in English either online or on paper.

Exclusion Criteria

There were no set exclusion criteria, however the preselected patients were defined as nonrecruitable if they were unable to take part in the survey for any of the following reasons: moved abroad, transferred care to another clinic, lost contact with the clinic for more than 12 months, had died, had any mental or emotional issue affecting their ability to give implied consent, had a language barrier or literacy difficulties, or were imprisoned or deemed a vulnerable adult.

Study Management

PV2022 was a collaboration between the University College London (UCL) NICHE team, the UKHSA HIV national surveillance team, and a NICHE Patient and Public Involvement representative. "A Person-Centered Needs Informed Model of Care for People with HIV" (NICHE) is a National Institute for Health Research (NIHR) funded program of research to improve the health and well-being of people with HIV. The PV team oversaw all aspects of the research including the study design, the development of the questionnaire and study documents, the oversight of the ethics and governance processes, the monitoring of response rates and recruitment at the participating sites and considered strategies to support and boost recruitment.

Questionnaire Development

Half of the questions in PV2022 were identical to those in PV2017 and were considered core questions to the survey series. These included demographic and socioeconomic factors, HIV related factors, comorbidities, met and unmet health, social and welfare service needs, quality of life measured by EQ-5D-5L, height and weight, smoking and alcohol status by the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C), recreational drug use and general practice (GP), and HIV clinic satisfaction, enabling assessment of trends over time in these factors. New items included in the PV2022 questionnaire included self-reported HIV viral load (whether undetectable or not at last test); questions exploring how well participants understood and trusted the concept of Undetectable equals Untransmittable (U=U), if U=U knowledge and trust impacted on how they felt about their HIV status, a modified version of the Duke-UNC (University of North Carolina) Functional Social Support Questionnaire [21], the 14-item Resilience Scale (RS14) [22], the General Practice Physical Activity Questionnaire (GPPAQ) [23], and questions on the impact of COVID-19 and the uptake of COVID-19 vaccines. In addition, the measure for anxiety and depression in 2017 [24] was replaced with standardized separate measures for depression and anxiety symptoms: the Patient Health Questionnaire-9 (PHQ-9) [25], and the General Anxiety Disorder Questionnaire-7 (GAD-7) [26]. Questions on stigma and discrimination were expanded to take account of internalized and other stigma and included an adapted validated stigma scale [27]. In addition, participants who completed the study online in PV2022 were able to opt-in to complete "Positive Outcomes," an HIV Patient Reported Outcome Measure (PO-PROM), a tool designed for use in clinical settings to assess the needs and concerns of people with HIV [28]. Table 1 details the topics included in PV2017 and PV2022 questionnaires. The PV2022 questionnaire was evaluated online by two groups of people with HIV (up to 10 per group) during November and December 2021. Members of these groups had previously participated in PV2017 and had provided their consent to be contacted again to take part in further research. They provided helpful feedback on the length of the questionnaire, the readability and phrasing of questions,

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and the flow and overall order of questions. The questionnaire was modified accordingly.

Table 1. Questionnaire topics, questions, survey tools, and clinical data collected in Positive Voices 2017 and Positive Voices 2022.

Questionnaire topic	PV2017[a]	PV2022[b]
Demographics (age, gender, ethnicity, and sexual orientation)	✓	✓
Socioeconomics (education, employment, housing, financial status, and religion)	✓	✓
HIV diagnosis and treatment (year and country of diagnosis, year started on ART[c], adherence, and side effects)	✓	✓
Self-reported HIV viral load and when last test conducted	—[d]	✓
U=U[e] (understanding of and trust in U=U)	—	✓
Non-HIV diagnosed conditions and treatments (cardiovascular conditions, joint and bone, cancer, mental health, and other long-term conditions)	✓	✓
Mental health and well-being (mental health symptoms [General Health Questionnaire, GHQ-12])	✓	—
Mental health and well-being (depression symptoms [Patient Health Questionnaire, PHQ-9], anxiety symptoms [Generalized Anxiety Disorder questionnaire, GAD-7], modified DUKE-UNC Functional Social Support questionnaire [DUKE-FSSQ], and the Resilience Scale [RS14])	—	✓
Quality of life, life satisfaction and self-rated health (EQ-5D-5L,Office for National Statistics Life Satisfaction and self-rated health questions)	✓	✓
Disclosure and discrimination (disclosure, discrimination in health care settings)	✓	✓
Stigma (internalized stigma and anticipated stigma)	—	✓
Sex and relationships (partner status, sexual behavior, sexually transmitted infections diagnoses)	✓	✓
Women's sexual and reproductive health (pregnancy and contraception)	✓	—
Sexual satisfaction (physical and emotional sexual satisfaction)	—	✓
General health and lifestyle (height, weight, smoking, alcohol [Alcohol Use Disorders Identification Test-Consumption, AUDIT-C] and recreational drug use)	✓	✓
General health and lifestyle (exercise and physical activity [General Practice Physical Activity Questionnaire, GPPAQ])	—	✓
GP[f] and HIV service use and satisfaction (GP and HIV satisfaction, patient experience measures, and use of GP and HIV support services)	✓	✓
Health service use and satisfaction (expanded list of health and social care service use)	—	✓
Impact of COVID-19 pandemic (COVID-19 diagnosis, vaccination status, and access to technology for online appointments)	—	✓
Met and unmet needs (need for HIV related services, health services, social and welfare services)	✓	✓
HIV Positive Outcomes Patient Reported Outcome Measure (PO-PROM[g]) (online questionnaire only, opt-in option)	—	✓
Clinical information from HARS[h]		
Antiretroviral treatment regimen	✓	✓
Laboratory measures (viral load and CD4 lymphocyte count)	✓	✓

[a]PV2017: Positive Voices 2017.
[b]PV2022: Positive Voices 2022.
[c]ART: antiretroviral therapy.
[d]—: not applicable.
[e]U=U: Undetectable=Untransmittable.
[f]GP: general practitioner.
[g]PO-PROM: Positive Outcomes patient-reported outcome measure.
[h]HARS: HIV and AIDS reporting system.

Study Documents

Each participating clinic was provided with electronic copies of the study materials including the protocol, manual of operations, participant information leaflet, privacy notice, waiting room poster, and a password-protected study log that listed each clinic's sample list of randomly selected participants. Study documents such as the protocol were also available on

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the study website [29]. Questionnaire packs, 1 for each participant within the clinic's sample, were dispatched by courier to the site. The pack consisted of a sealed envelope labelled with the participant's clinic number, hospital name, and unique identifier displayed on the outside, as well as the patient information leaflet, questionnaire, a freepost envelope, and a signposting sheet detailing community support organizations such as the Terrence Higgins Trust, a British charity that campaigns and provides services relating to HIV and sexual health.

Site Initiation Meetings

Each participating site attended 1 of the site initiation meetings that took place remotely on Microsoft Teams between February and March 2022. A maximum of ten clinic sites attended each meeting. Information on how to identify, contact, and recruit participants was explained, and a demonstration was given on the procedure for completing the study log (refer to Recruitment and Data Collection section). Sites were asked to nominate a PV2022 champion within their clinic who would act as the main contact with the PV team. All the site initiation meetings were completed by March 18, 2022, just before the recruitment of participants commenced in April 2022.

Recruitment and Data Collection

The first participant was recruited on April 11, 2022, and recruitment closed on March 31, 2023. At each site, clinic staff were asked to complete a study log on their recruitment outcomes and return it to the PV team each month. The information they recorded in their study log included the mode (whether in-person, email, text, or post) and date of each participant's initial contact, the survey distribution method (in-person, email, text, or post), the survey distribution date, the recruitment status (whether nonrecruitable, accepted, or declined), and the reason if the status was nonrecruitable.

The PV team provided a brief script for email and text message approaches as a guide for clinic staff. Online questionnaires were sent by a link by email or text message, or patients received their survey pack containing the paper questionnaire at their next clinic attendance. Clinic staff decided on the method of approach used in accordance with each participant's preferred and usual method of communication with their clinics.

Change to the Sequential Recruitment Strategy at Specific London Sites

Reviewing the study logs monthly, it was established that several sites were underrecruiting. Consequently, the recruitment period was extended from 6 to 12 months to allow clinics additional time to reach their recruitment targets. Further email correspondence with clinics revealed that many had resource pressures, fewer face-to-face clinic appointments after the start of the COVID-19 pandemic, and the 2022 Mpox outbreak had been an unanticipated challenge impacting upon recruitment, particularly in London. In response, the PV team designed a sequential recruitment strategy whereby a site could approach any eligible participant attending the clinic sequentially, that is, approach patients as they entered the clinic instead of contacting participants from their preselected sample list. In total, 14 HIV clinics across 7 NHS trusts in London that had recruited less than 10% of their minimum target after 8 months were offered a switch to the sequential recruitment strategy, which they commenced at the beginning of December 2022, having been sent new recruitment packs, survey labels, and a simpler study log that reflected the new strategy.

Participants recruited through the new sequential recruitment strategy were only able to complete the paper questionnaire. Staff were asked to encourage participants to complete their questionnaires in the clinic when they came for their consultation rather than taking them home, as questionnaires sometimes got lost, forgotten, or were not returned to the PV team at UKHSA.

Secure Storage and Transfer of Data

Paper questionnaires and study logs were securely stored within each clinic. The sites were responsible for collecting, storing, and returning the paper questionnaires completed in their clinic to the PV team at the UKHSA by using the Freepost envelopes provided in the participant packs or by courier.

Data Management

When paper questionnaires were received by the PV team, data were double data-entered (entered by 2 separate data input personnel) into Snap Survey software (Snap Survey Ltd) and each questionnaire was scanned. Online responses were extracted from Snap Survey as an electronic csv file. The data from both sources was then imported into Stata (version 15.0, StataCorp) and merged to create a master questionnaire data file. Data discrepancies between the 1st and 2nd date entries of the paper questionnaires were checked and resolved by referring to scanned copies of questionnaires.

Linkage

Data on ART use, the most recent CD4 lymphocyte count, and HIV viral load measurement were linked from HARS to the survey data using the participant's clinic ID number and unique identifier.

Data Security

Paper questionnaires were stored securely in locked cabinets at UKHSA where they will remain for a maximum of 10 years and then be securely destroyed. The online version of the questionnaire was hosted on a secure HTTPS connection and data were encrypted at the point of transmission and stored on a secure, dedicated, virtual server hosted at UKHSA.

All data were securely held at UKHSA, encrypted, and restricted to the PV team. Data collection, storage, and use were consistent with the procedures described in the NHS Information Governance Toolkit. A data-sharing agreement was developed to ensure the secure transfer of pseudonymized data between UKHSA and UCL for data analysis.

All researchers were trained to handle data according to Caldicott guidelines, the General Data Protection Regulation, and Section 60 of the Health and Social Care Act.

Ethical Considerations

The Positive Voices study was granted ethical approval by the London Harrow Research Ethics Committee (13/LO/0279) on March 28, 2013. All the updated documents for PV2022 were

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submitted as a substantial amendment and subsequently approved on June 23, 2021. The patient information leaflet provided information on how the patients could participate, the potential risks and benefits of participation, and contact information for the PV team. Clinic staff were advised to tell each eligible participant that participation was voluntary and that their decision to participate would not affect their care. A privacy notice was available online with further information about data security [29]. Consent was implied on voluntary completion of the questionnaire. All participants received a digital gift voucher for 5 GBP (equivalent to US $6.50) as an acknowledgement for their time and consideration. This incentive was chosen based on findings from the formative work undertaken before the survey began, where participants expressed a requirement for an incentive. The PV team provided monthly feedback to sites showing the number of completed questionnaires received either by post or online from participants from their clinic. If a patient agreed to participate in the survey but no questionnaire had been returned, clinic staff were asked to send up to 3 reminders using the preferred method of contact initially used. Participants were not asked to provide identifiable information for the survey. However, at the end of the survey, participants were given the option of providing their personal contact details, either phone number or email address, if they were willing to be contacted for future research. If contact details were given, this personal information was unlinked from their survey data and stored securely on a separate password-protected database at UKHSA.

Results

Overview

The PV2022 survey was completed by 4622 people diagnosed with HIV, representing approximately one in 20 people living with HIV and accessing care in England, Wales, and Scotland in 2022 [19]. Overall, 4540 participants provided sufficient demographic information to enable linkage to HARS to acquire additional clinical data, which included treatment information, viral load, and CD4 lymphocyte count. The most popular completion method was by paper questionnaires with 2829 (61%) compared with 1793 (39%) online questionnaires. A third (930/2829, 33%) of the paper questionnaires were completed by participants recruited sequentially. Of the 4622 participants, 1737 provided their phone numbers or email addresses as contact details regarding further research, and 897 completed the optional PO PROM questionnaire online.

Response Rate

To calculate the response rate, the number of completed questionnaires (n=4622) was divided by the number of people who accepted (n=8096) or declined to participate (n=1088), which gave an overall response rate of 50%. In addition, 4994 people had been contacted by email or text but had not responded, which may have reflected further declines although may also have been due to messages not being received, read, or being discounted as an unsolicited message. By including these nonresponses in the calculations, it would have given a response rate of 33%. The true response rate likely lies somewhere between 33% and 50%.

A total of 930 (20%) participants were recruited through the sequential recruitment strategy, a higher response rate (55%) compared with the original preselected participant recruitment strategy (49%, Figure 1). Of the 930 sequentially recruited participants, 906 were able to be matched to HARS: 222 (25%) of these had initially been preselected to take part in the survey. Response rates differed by demographic characteristics (taken from HARS) as shown in Figure 1. Men had a higher response rate (60%) (3428 completed out of 5715 accepted or declined) compared with women (1124/2580, 44%) and White people had a higher response rate (2991/4724, 63%) compared with Black African people (983/2380, 41%) or those of other ethnicities (648/1158, 56%). Response rates were also higher in older age groups, with the highest response rate (592/851, 70%) in the people aged 65 years or older (Figure 1). Multimedia Appendix 2 provides the corresponding numbers for all groups shown in Figure 1.

Figure 1. Positive Voices 2022 response rates by recruitment mode, gender, ethnicity, and age among participants of Positive Voices 2022 (N=4622).

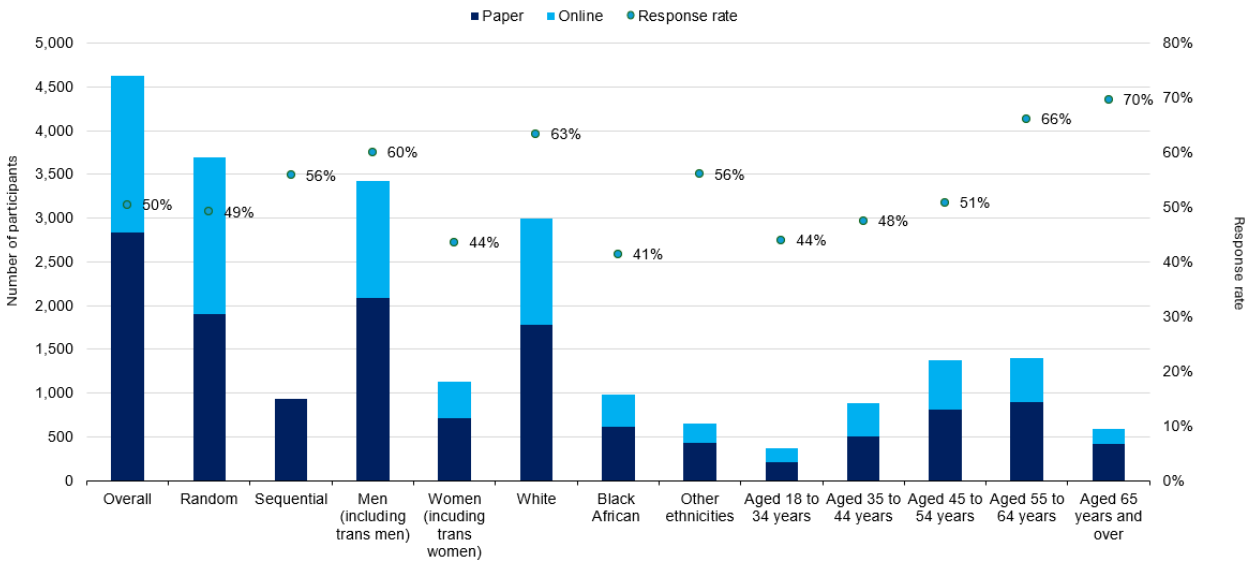

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Age, Gender, and Ethnic Distribution of PV2022 Participants

The median age of PV2022 participants (n=4620) was 52 (IQR 43-60) years, and about 3 quarters of participants had been diagnosed with HIV more than 10 years ago (Table 2). Nearly a quarter of participants were women (24%) and over a fifth (21%) of participants were Black African people (Table 2).

Gender identity of participants completing PV2022 broadly reflected the gender identity distribution of people accessing HIV care in the United Kingdom. However, there was some overrepresentation of men (6% higher), and underrepresentation of women (8% lower) compared with HARS data (Figure 2). A total of 67 PV2022 participants identified as transgender or gender diverse.

Compared with the national population of people accessing HIV care, Black African individuals were underrepresented in the PV2022 sample (10% lower), and White participants were overrepresented (13% higher; Figure 2).

Participants from the sequential recruitment route were younger compared to the preselected random recruitment strategy (median age 49 (IQR 39-57) years versus 53 (IQR 45-60) years, for sequential versus random recruitment respectively), overrepresented men (85% vs 72%) and White people (67% vs 64%) and underrepresented Black African people (14% vs 23%).

A higher proportion of participants who completed the online questionnaire were White compared to participants who completed the paper questionnaire (67% online vs 63% paper; Figure 1 and Multimedia Appendix 2.

Table 2. Demographics and year of HIV diagnosis among Positive Voices 2022 participants.

Characteristics	Participants (n=4622), n (%)
Age group (years)[a]	
18-34	369 (8)
35-44	885 (19.2)
45-54	1375 (29.8)
55-64	1397 (30.3)
65+	592 (12.8)
Gender	
Man (including trans men)	3428 (74.2)
Woman (including trans woman)	1124 (24.3)
Nonbinary	26 (0.6)
In another way	8 (0.2)
Prefer not to say and unknown	36 (0.8)
Ethnic group	
White	2991 (64.7)
Black African	983 (21.3)
Black other	138 (3)
Asian	189 (4.1)
Mixed	143 (3.1)
Other (including prefer not to say and unknown)	178 (3.9)
Year of diagnosis	
2019-2023	214 (4.6)
2014-2018	801 (17.3)
2009-2013	957 (20.7)
2004-2008	1063 (23)
2003 or earlier	1497 (32.4)
Unknown	90 (1.9)

[a]Age was missing for 2 participants.

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Figure 2. Representativeness of Positive Voices 2022 participants compared with the national population of people with HIV who attended HIV services in 2022.

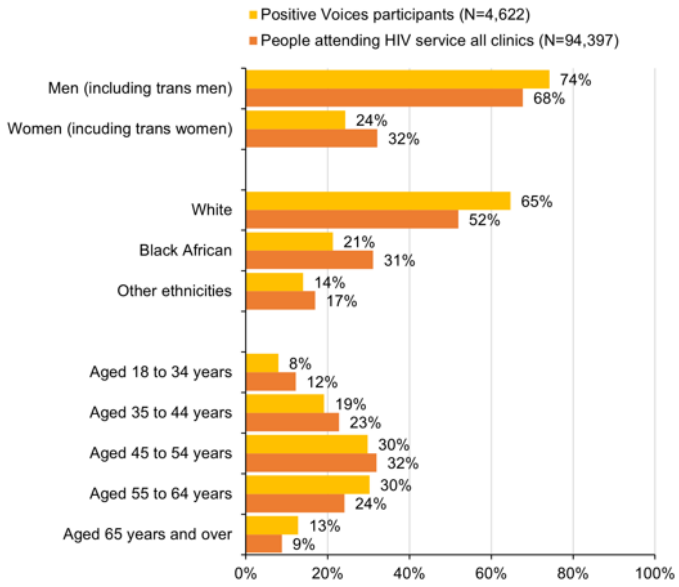

Survey Distribution Method

The survey approach method was available for 4375 of the 4622 responses received. Over half of these participants, 54% (2371/4375), were approached in person, 23% (1001/4375) were contacted by phone, 17% (727/4375) received a text message, 5% (214/4375) were contacted by email, and 1% (62/4375) received the questionnaire by post.

Discussion

Principal Findings

In this paper, we have described the methods, design and sample demographic characteristics of the Positive Voices 2022 study. PV2022 is the largest questionnaire study to date of people with HIV in England, Wales, and Scotland. The outputs from the study will provide a unique insight into the health and well-being of people with HIV, particularly regarding mental health, met and unmet needs, experiences of stigma, and the impact of COVID-19 pandemic [30]. The overall response rate for PV2022 was estimated to be between 33% and 50% compared with 52% for the previous iteration of the survey (PV2017) [9]. Several factors impacted on the response rate in PV2022. In particular, the first 6 months of the recruitment period (between April and September 2022) coincided with the Mpox *clade* IIb outbreak, primarily among gay and bisexual men in London and other large cities in England [31]. The impact of this outbreak on sexual health and HIV services resulted in a significant deployment of clinic staff and resources to manage the outbreak and to provide a vaccination program to contain the infection [31]. Feedback from some of the largest clinics that were open to recruitment for PV2022 over the duration of the Mpox outbreak suggested that recruitment had been challenging to prioritize during this period, particularly as the methodology required considerable clinic staff time commitment.

As a result of a challenging recruitment environment, the switch to sequential recruitment in December 2022 resulted in an improvement to study recruitment. This was mainly because the strategy of sequential recruitment did not require the administration time that had been required for the original strategy. Furthermore, as these participants were only able to complete the paper questionnaire and not the online version, clinic staff recommended questionnaires be completed within the clinic setting and discouraged participants from taking the questionnaires home, where they may have remained uncompleted or unreturned. Although this strategy was not always successful, the proportion that completed and submitted their questionnaire within the clinic was higher in comparison with the original recruitment strategy.

Other potential factors that may have impacted upon the response rate for PV2022 related to the COVID-19 pandemic. The widespread adoption of online health care appointments during the pandemic meant that fewer patients attended regular HIV appointments in person [32,33]. A recent systematic review identified interruption in attendance of in-person clinic consultations, reduced adherence to treatment, and a subsequent increase in mortality among people with HIV, as a consequence of the changes in service delivery due to the COVID-19 pandemic [34]. As the most effective mode of recruitment for PV2022 was in-person with clinic staff, the decreased frequency of participants attending clinic likely contributed to the lower response rate seen in PV2022 in comparison with PV2017. Less personal interaction between patients and clinic staff may also have impacted upon participants' enthusiasm for completing questionnaires when approached. When clinic staff were able to personally hand out the survey packs within the clinic, they were better able to explain the importance of the study and the impact the results would have on policy and service planning. Evidence suggests that initial approach and personal connection greatly impacts on survey completion rates in all populations [35,36] which has implications for future survey planning, particularly as some appointments remain online.

Recent evidence has suggested that survey fatigue and nonparticipation, had increased as a result of the proliferation of online surveys during and following the COVID-19 pandemic

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[37]. Whilst the pandemic clearly impacted upon research in terms of recruitment and data collection, evidence suggests that the effects reached far wider. The pandemic exacerbated inequalities in health and access to health care, particularly amongst those living in economic hardship [38] and for Black African individuals and those of other minority ethnic groups [39], and the HIV population consists of a high proportion of these groups.

Strengths of PV2022 include the large sample size, the inclusion of a broadly representative sample of 1 in 20 people with HIV in England, Scotland and Wales (as evidenced by comparison with the national HARS database) and the linkage of participant self-reported questionnaire data to HIV clinical data from HARS. With increasing interest in patient experience and outcome measures, other clinical conditions could use a similar survey method to survey their patient group. PV2022 also has some limitations: as the study was only available to people with HIV in care, it did not represent those people with HIV who were not receiving care in 2022, whose mental and physical health, and experiences of health care, may be different and valuable for informing and improving HIV specialist services. Similarly, nonresponders to participate in the study may differ from responders with respect to health, lifestyle, and other factors. Further efforts to reach these groups and identify their needs are crucial. In addition, the sampling frame for the initial recruitment method was based on those attending care in 2020, and therefore our data are unable to represent those who have been newly diagnosed in the interim. Future work by the PV team will examine the recruitment challenges to PV2022 and will involve participant and public involvement groups and clinic staff. This will inform future rounds of the Positive Voices survey and optimize response rates.

PV2022 formed part of the formative work of the NIHR funded NICHE program of research led by UCL. NICHE aims to improve the mental and physical well-being of people with HIV by designing and evaluating a targeted psychosocial intervention as part of routine HIV care [29]. Findings from PV2022 informed the development of the intervention for the "Psycho-Social Intervention for People With HIV – Evidence From a Randomised Evaluation" (SPHERE) trial, which commenced in United Kingdom HIV clinics in August 2024. Results from Positive Voices 2022 have been published in a government report [30] that has directly informed the HIV action plan for England which aims to end stigma and inform interventions to improve patient-centered care and the provision of HIV clinical and support services. Further analysis of the data will be presented at HIV conferences, published in peer-reviewed journals and disseminated through the extensive NICHE PPI network.

Acknowledgments

The authors would like to thank all the PV2022 study participants who generously participated in this research. The authors would also like to thank the clinic staff in all the 101 participating sites for their hard work and dedication. PV2022 was conducted by the UK Health Security Agency and University College London and represents independent research funded by the National Institute for Health Research (Program Grants for Applied Research, A person-centered Needs Informed model of Care for people with HIV, to improve well-being, mental health and reduce socioeconomic disadvantages and stigma, (NICHE; NIHR202038). The views expressed in this publication are those of the authors and not necessarily those of the NHS, the National Institute for Health Research, or the Department of Health and Social Care. Funding was also received from the UK Health Security Agency and Gilead Sciences Ltd.

Data Availability

The data sets generated during this study are not publicly available due to ongoing analysis and dissemination plans by the NICHE and UKHSA teams. However, data may be available from the corresponding author on reasonable request.

Authors' Contributions

CK, AA, VM, AB, MK, VD, FL, CS, and AR contributed to conceptualization. CK, AA, VM, AB, MK, VD, FL, and AR managed methodology. CK, AA, VM, AB, CH, HK, AF, APM, AR, FL, JS, AS, and APM handled investigation. JS, CK, MK, FL, and AR wrote the original draft. JS, CK, AA, HK, APM, VM, AF, CS, AB, AS, VD, AR, FL, and MK contributed to review and editing. AR, FL, CS, VD, and MK managed funding acquisition. AR, FL, and MK handled supervision.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Full list of participating clinics and clinic teams.
[DOCX File , 18 KB - resprot_v14i1e58531_app1.docx]

Multimedia Appendix 2

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Table of Positive Voices 2022 (PV2022) Response rates* by recruitment mode, gender, ethnicity, and age among participants of PV2022 linked to HARS* (N=4622).
[DOCX File , 17 KB - resprot_v14i1e58531_app2.docx]

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Abbreviations

ART: antiretroviral therapy
AUDIT-C: Alcohol Use Disorders Identification Test-Consumption
GAD-7: Generalized Anxiety Disorder questionnaire-7
GP: general practice
GPPAQ: General Practice Physical Activity Questionnaire
HARS: HIV and AIDS reporting system
NICHE: A Person-Centered Needs Informed Model of Care for People with HIV
NIHR: National Institute for Health Research

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PHQ-9: Patient Health Questionnaire-9
PV: Positive Voices
PV2017: Positive Voices 2017
PV2022: Positive Voices PV2022
PO-PROM: Positive Outcomes Patient Reported Outcome Measure
RS14: 14-item Resilience Scale
SPHERE: Psycho-Social Intervention for People With HIV–Evidence From a Randomised Evaluation
UKHSA: UK Health Security Agency
U=U: Undetectable equals Untransmittable
UCL: University College London
UNC: University of North Carolina

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Protocol

Assessment of Geriatric Problems and Risk Factors for Delirium in Surgical Medicine: Protocol for Multidisciplinary Prospective Clinical Study

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Abstract

Background: An aging population in combination with more gentle and less stressful surgical procedures leads to an increased number of operations on older patients. This collectively raises novel challenges due to higher age heavily impacting treatment. A major problem, emerging in up to 50% of cases, is perioperative delirium. It is thus vital to understand whether and which existing geriatric assessments are capable of reliably identifying risk factors, how high the incidence of delirium is, and whether the resulting management of these risk factors might lead to a reduced incidence of delirium.

Objective: This study aimed to determine the frequency and severity of geriatric medical problems in elective patients of the Clinics of Oral and Maxillofacial Surgery, Vascular Surgery, and Orthopedics, General Surgery, and Trauma Surgery, revealing associations with the incidence of perioperative delirium regarding potential risk factors, and recording the long-term effects of geriatric problems and any perioperative delirium that might have developed later the patient's life.

Methods: We performed both pre- and postoperative assessments in patients of 4 different surgical departments who are older than 70 years. Patient-validated screening instruments will be used to identify risk factors. A geriatric assessment with the content of basal and instrumental activities of daily living (basal activities of daily living [Katz index], instrumental activities of daily living [Lawton and Brody score], cognition [6-item screener and clock drawing test], mobility [de Morton Mobility Index and Sit-to-Stand test], sleep [Pittsburgh Sleep Quality Index and Insomnia Severity Index/STOP-BANG], drug therapy [polypharmacy and quality of medication, Fit For The Aged classification, and anticholinergic burden score], and pain assessment and delirium risk (Delirium Risk Assessment Tool) will be performed. Any medical problems detected will be treated according to current standards, and no intervention is planned as part of the study. In addition, a telephone follow-up will be performed 3, 6, and 12 months after discharge.

Results: Recruitment started in August 2022, with 421 patients already recruited at the time of submission. Initial analyses of the data are to be published at the end of 2024 or the beginning of 2025.

Conclusions: In the current study, we investigate whether the risk factors addressed in the assessment are associated with an increase in the delirium rate. The aim is then to reduce this comprehensive assessment to the central aspects to be able to conduct targeted and efficient risk screening.

Trial Registration: German Clinical Trials Registry DRKS00028614; https://www.drks.de/search/de/trial/DRKS00028614

International Registered Report Identifier (IRRID): DERR1-10.2196/59203

(JMIR Res Protoc 2025;14:e59203) doi:10.2196/59203

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KEYWORDS

delirium; older patients; perioperative assessment; age-related surgical risk factors; geriatric assessment; gerontology; aging; surgical medicine; surgical care; surgery; multidisciplinary; prospective study; perioperative; screening; palliative care; health informatics

Introduction

Background

From the advances in surgical medicine with the development of less stressful surgical and anesthetic procedures, more and more older people are receiving surgical care who would not have been treated surgically a decade ago [1]. However, older age is associated with numerous additional problems, such as frailty [2], cognitive impairment [3,4], sleep disorders [5,6], and polypharmacy [7,8]. These age-associated problems are not routinely recorded but make older patients vulnerable. Perioperative delirium of vulnerable older patients is a major problem. Delirium is distressing for the individual, increases the burden of care, and has long-term negative consequences in terms of cognition, self-care ability, and prognosis [9].

Thus, incidences of perioperative delirium in older people are reported to be as high as 50% [10,11]. Factors influencing the incidence of delirium include duration and depth of anesthesia, the size of the surgical procedure, the duration of the preoperative fasting period, preoperative blood pressure, and frailty, brain disorders, hearing impairment, or history of sleep disturbances [12].

Perioperative delirium is a relatively common and serious complication after surgery [13-15]. The *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) includes delirium into the broader category of neurocognitive disorders, which include acquired cognitive dysfunction [16,17]. Delirium is defined as an attention deficit disorder that develops over a short period of time, with additional cognitive impairment that cannot be explained by other preexisting neurocognitive impairments [18]. According to the *DSM-5*, the typical symptoms that characterize delirium are (1) “disturbance in attention,” (2) “disturbance develops over a short period of time,” (3) “additional disturbance in cognition,” (4) “disturbances in the first 2 criteria are not better explained by another preexisting disorder,” and (5) “disturbance is a direct physiological consequence of another medical condition, substance intoxication, or withdrawal” [19,20]. In general, the incidence of delirium in surgical procedures is 2%-3%, and in high-risk patients, it is even much higher at 50%-70% [11,21]. Nevertheless, precise causes as well as risk factors and incidences for the development of postoperative delirium are not yet known or deciphered [10].

In the literature, several potential risk factors for postoperative delirium are indicated. Among these are the duration and depth of anesthesia [22,23], the extent of the surgical procedure, the duration of the preoperative fasting period [10,24], the preoperative blood pressure, as well as frailty, brain disorders, hearing disorders, or sleep disorders in the history [2,25]. Delirium with its multifactorial genesis is a major challenge in risk stratification and diagnosis. Validated screening tools exist for many of the risk factors [26-32]. However, recording all risk factors is not effective in everyday clinical practice and is difficult to implement in terms of time. It is therefore necessary to compile a specialist assessment in order to identify patients at risk of delirium as effectively and reliably as possible.

Some of these risk factors are captured by validated screening instruments. Identifying risk factors allows better preoperative management [10]. Still, the regular recording of dementia, the need for assistance in daily life, or the accumulation of several diseases by geriatric screening to determine geriatric care needs is practically not established. Comorbid geriatric problems leading to functional limitations are therefore often overlooked, although they represent a major social and economic problem [33,34].

Aim of This Research

We aim to analyze which parameters of our comprehensive geriatric assessment are associated with the occurrence of delirium depending on the specialty, and what parameters are to be included in a time-effective, target-oriented, and implementable assessment.

Methods

Study Design and Setting

This prospective clinical observational study analyzes the frequency and risk factors for perioperative delirium in patients after surgical treatment in the Department of Orthopedics and Trauma Surgery, the Department of Vascular and Endovascular Surgery, General Surgery, and the Department of Oral and Maxillofacial Plastic Surgery of the University Hospital of Düsseldorf in the intensive care unit and normal ward. The University Hospital of Düsseldorf is the largest hospital in the state capital of North Rhine-Westphalia, Germany. It houses more than 50,000 in-patients per year [35].

Study Population

Inclusion criteria will be patients (aged 70 years and older) presenting for elective and emergency surgery at the Departments of Oral and Maxillofacial Surgery, Orthopedics and Trauma Surgery, General Surgery, and Vascular Surgery. In addition, we will also contact the included patients by telephone 3, 6, and 12 months after discharge to ask about their health status in a standardized way. No interventions are planned as part of this study, and any medical problems uncovered will be treated according to standard medical practice.

A case number calculation is hardly possible due to the sparse data. Therefore, one goal of this study is to collect robust data on the incidence of delirium and to be able to plan further studies on the basis of this solid data. Initially, we will offer participation in this study to all consecutive presenting patients who meet the inclusion criteria (Textbox 1). The initial recruitment period is planned to be 6 months. The goal is to enroll at least 100 patients per discipline, in total over 400

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patients. If this number is not reached within this period, the recruitment period will have to be extended accordingly. Solid incidence figures are to be determined within the framework of this pilot study, so further studies can then be planned with possible case number calculation.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Patients presenting for elective surgery at the Clinic for Oral and Maxillofacial Plastic Surgery, Orthopedics and Trauma Surgery, General Surgery, and Vascular Surgery.
- Age 70 years.
- Consent of the patient or caregiver.

Exclusion criteria

- No consent to participate.
- Unstable clinical situation.
- Patients requiring palliative care.
- Very advanced dementia (Reisberg VI-VII).

Recruitment

Patient recruitment starts in August 2022. We have been in negotiations with other surgical disciplines for almost a year, aiming to include as many different surgical specialties as possible. We are therefore submitting this study protocol during ongoing recruitment. After inpatient admission in the respective disciplines, the eligible patients are informed about the clinical examination by the study doctor. The patients are given sufficient time to think about their participation and to discuss it with their caregivers. They can also clarify any questions with the study doctor. After the patient has given and signed his or her consent, he or she takes part in the study (Figure 1).

Figure 1. Study procedure overview. Timeline including recruitment, pre- and postoperative assessment, surgery, discharge assessment, and the assessment by phone after 3,6, and 12 months.

Measures and Parameters

In the context of this study, in addition to routine preoperative preparation in elective and emergency older patients, a geriatric assessment (Textbox 2) with the content of basal and instrumental ADL (basal ADL: Katz index [26]; instrumental ADL: Lawton and Brody score [27]; emotion: World Health Organization-5 scale [28]; cognition: 6-item screener and clock drawing test; mobility: de Morton Mobility Index and Sit-to-Stand test [29]; sleep: Pittsburgh Sleep Quality Index, Insomnia Severity Index, and STOP-BANG [30-32]; drug therapy: polypharmacy and quality of medication, Fit For The Aged classification, and anticholinergic burden score), pain assessment, and delirium risk (Delirium Risk Assessment Tool) is to be performed. The Fit For The Aged list evaluates drugs in terms of their benefit-risk profile when used in older patients. The aim is to reduce the number of potentially inadequate medications in patients aged over 65 years old [36]. In an emergency setting, the tests to record the acute status were carried out directly preoperatively. Tests such as sleep quality and well-being, which cover a longer period before the operation, were carried out postoperatively if not otherwise possible. Through this, the study gains a broad spectrum of possible risk factors while using validated and clinically approved assessment tools.

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Textbox 2. Depiction of the pre- and postoperative parameters.

Preoperative parameters

- Age (years), gender, and BMI
- American Society of Anesthesiologists classification
- Comorbidities, risk factors, previous radio and chemotherapy
- Preoperative medication and calculation of anticholinergic load (anticholinergic burden score)
- Delirium Risk Assessment Tool
- Routine laboratory values

Geriatric assessment

- Katz index
- Instrumental activities of daily living score according to Lawton and Brody
- Mobility and strength
- de Morton Mobility Index
- Handgrip strength (Hydraulic hand dynamometer)
- Sit-to-stand test
- Emotion World Health Organization-5 scale
- Nutritional status
- Mini Nutritional Assessment Short-Form
- Skinfold thickness over the triceps muscle
- Brain performance
- 6-Item-Screener
- Clock-Drawing-Test
- Hearing ability
- Hearing Handicap Inventory for the Elderly-Short Form
- Sleep disorders or sleep quality
    - Pittsburgh Sleep Quality Index
    - Insomnia Severity Index
    - STOP-BANG–Risk score for obstructive sleep apneas
- Pain assessment

Postoperative parameters

- Nursing Delirium Screening Scale (routinely performed in the recovery room by anesthesia)
- Confusion Assessment Method
- Confusion Assessment Method-Intensive Care Unit
- Alertness, Abbreviated Mental Test 4, Attention, Acute Chance or Fluctuating Course
- postoperative pain assessment
- Mobility (de Morton Mobility Index, instrumental activities of daily living, and Katz index) before discharge

Follow-up

- Instrumental activities of daily living
- Katz index
- G8 screening test
- Pain assessment
- World Health Organization-5 scale

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Testing is done every 8 hours in the Intensive Care Unit Confusion Assessment Method-Intensive Care Unit and twice daily in the normal ward (Confusion Assessment Method and Alertness, Abbreviated Mental Test 4) until postoperative day 7 or discharge [37]. Further testing is done as needed or after revision, operation, and so on.

Patients are assessed perioperatively during the daily ward rounds with a focus on their general condition and the presence of delirium. The instruments NuDesc, Confusion Assessment Method, which are routinely recorded in-house, and the Alertness, Abbreviated Mental Test 4, which was introduced in 2020, are used for this purpose [38]. The simultaneous use of these instruments also allows their comparison regarding their quality criteria and may lead to a reduction in monitoring effort in the medium term if one of these instruments proves to be superior (Figure 2).

Figure 2. Overview of preoperative evaluation, pre- and postoperative assessment, and analysis. 4AT: Alertness, Abbreviated Mental Test 4, Attention, Acute Chance or Fluctuating Course; ACB: anticholinergic burden; ADL: activities of daily living; ASA: American Society of Anesthesiologists; CAM: Confusion Assessment Method; CAM-ICU: Confusion Assessment Method-Intensive Care Unit; DEMMI: de Morton Mobility Index; DRAT: Delirium Risk Assessment Tool; FORTA: Fit For The Aged; HHIE-SF: Hearing Handicap Inventory for the Elderly-Short Form; IADL: instrumental activities of daily living; ISI: Insomnia Severity Index; MNA-SF: Mini Nutritional Assessment Short-Form; Nu-Desc: Nursing Delirium Screening Scale; OSA: obstructive sleep apnea; PSQI: Pittsburgh Sleep Quality Index; WHO: World Health Organization.

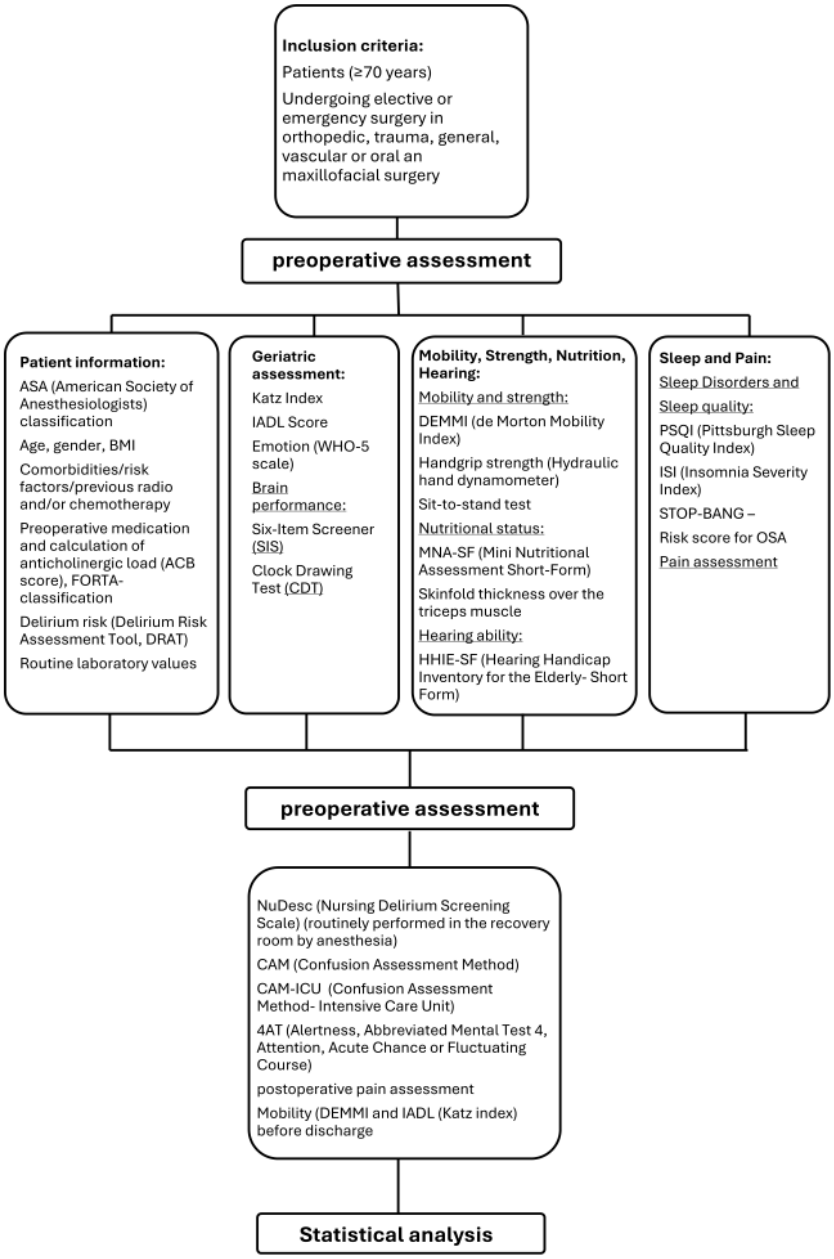

Follow-Up

We plan to contact patients by telephone 3, 6, and 12 months after discharge to inquire about their current health status. Here the patients are asked about changes in sleeping behavior, changes in medication, changes in mobility, and possible rehabilitation treatment. Furthermore, ADL and Katz, G8 Screening Test, a pain assessment, and the World Health

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Organization–5 scale are recorded. Bellera et al [39] created the G8 geriatric screening test, which evaluates drug use, general health, age, mobility, nutritional state, and cognitive status.

Evaluation Outcomes

We aim to determine the frequency of perioperative delirium in patients after surgical treatment in the Clinic for Orthopedics and Trauma Surgery, in the Clinic for Vascular and Endovascular Surgery, and in the Clinic for Oral and Maxillofacial Facial Plastic Surgery at the University Hospital Düsseldorf in the intensive and normal care unit. We want to use the comprehensive assessment to create a risk profile for patients with delirium. The individual risk factors are to be evaluated with regard to their use in the context of a specialized geriatric assessment.

Statistical Analysis

The evaluation is performed as descriptive statistics with the listing of the frequencies of geriatric problems and perioperative delirium. To investigate the correlation between perioperative delirium and clinical and geriatric parameters, the correlation is determined. The parameters that correlate significantly with the incidence of delirium are examined in a further step in the context of logistic regression analysis for their concrete and independent influence on delirium incidence. Calculations are performed using the statistical program SPSS (version 28.0; IBM Corp) and Jamovi [40]. A P value of <.05 is considered significant. If the normal distribution of the dependent variables was confirmed by the Shapiro-Wilk test, homoscedasticity was confirmed by the Levene test and significant outliers were eliminated by boxplots, the mean differences were analyzed using the independent t test. The Mann-Whitney U test is used to analyze the mean differences of the dependent variables that were not regularly distributed. Chi-square tests are used to analyze bivariate correlations between relevant variables and the occurrence of delirium (delirium vs no delirium). The odds ratios of the relationships are calculated with 95% CIs. Two-sided statistical tests are used, and the α level of .05 is used to determine significance. Significance is defined as a P value of less than .05, very significant as a value of less than .01, and highly significant as a value of less than .001. To reduce the possibility of a type I error in repeated testing, Bonferroni correction is used [41]. The factors that cause delirium and that are classified as statistically significant at a significance level of P=.05 are determined using binomial logistic regression analysis.

Ethical Considerations

The study was approved by the Ethics Committee of the Medical Faculty of the Heinrich Heine University Düsseldorf (2022-1810). This study is registered in a publicly accessible database according to DvH2013, § 35 (DRKS-ID; DRKS00028614 [42]). Meeting the requirements for data protection and confidentiality, the data are pseudonymized. It is not possible to identify individual participants or users in figures and illustrations of the manuscript or supplementary materials. No compensation is provided to participants for research.

This study was approved by the ethics review board of the University Hospital of Düsseldorf (2022-1810_2) and all the participants provided written informed consent.

Results

The comprehensive preoperative geriatric assessment was developed to capture as many potential risk factors for delirium as possible. The findings aim to assist in the development of a specialist and condensed preoperative assessment. Recruitment started in August 2022, with 421 patients already recruited at the time of submission. Initial analyses of the data are to be published at the end of 2024 or the beginning of 2025. Recruitment will continue until August 2025. A final analysis will be issued in a subsequent publication.

Discussion

We intend to determine the frequency of delirium in the aforementioned specialist disciplines. Furthermore, a specialist risk profile is to be created using a comprehensive geriatric assessment in order to specifically identify patients at risk in the future.

Relevance of This Study

Delirium occurs particularly in older patients where (1) patients aged 65 years account for up to 40% of all surgical procedures, (2) 50% undergo emergency surgeries, and (3) 75% are affected by surgical mortality [43]. Also, prevalence is particularly increased in those patients who are older, neurocognitively impaired, or emergency-associated patients [44,45]. The reason why delirium is gaining increasing importance in the age group of older patients becomes clear against the background of 2 facts: first, because the total population is getting older, and second, because this group of patients is being operated more and more frequently [46].

Despite the clinical relevance of delirium, there is still no established screening that considers the risk factors of the older patient group in particular so far. This deficiency was the decisive criterion for the establishment of a screening system in the current study, which focuses on the special needs of these older patients. Building on this, the current screening system is therefore intended to create further prevention options in order to meet the needs of the older patient group.

Further on, the need for a new screening system arises from the fact that the presence of delirium is not only a patient-specific problem: postoperative delirium places an additional burden on hospital care in that the average hospital stay is prolonged by an average of 48-72 hours due to postoperative delirium. It is also associated with a 30-day mortality rate of 7%-10% [9,10,47]. The prolonged hospital stays that result, combined with the need for more intensive therapy, lead to increasing costs for the hospital and ultimately for the entire population [48]. A sound assessment that can act preventively on emerging problems and thus prevent the development of delirium, if necessary, would be of both individual and economic benefit.

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Limitations

As described above, predisposing discipline-specific risk factors for the development of postoperative delirium have not yet been thoroughly investigated. The current screening system is intended to circumvent precisely this deficiency and to identify potential risk factors to prevent the development of such delirium in older patients.

Focus was placed on the extraction of clinically relevant examination procedures for the diagnosis of delirium and the elimination of irrelevant procedures, as there is often insufficient time in daily clinical practice to perform comprehensive examinations. General assessments that address the classification of postoperative delirium have already found their way into clinical practice [13,49,50]. However, these do not place a separate focus on the existing risk factors of the group of older patients, who should be given a separate status against the background of the problems described above. What has so far complicated the breakdown of such risk factors is the fact that it is insufficiently possible to distinguish between the normal aging process, the associated increasing physical degradation, and existing medical diseases that accelerate such a decay.

Method Criticism

The screening system presented here is intended to identify risk factors that can be used for regular screening of older patients. The findings of this study assist in preventing postoperative delirium in the future and reduce the frequency of perioperative problems and mortality in these patients [51,52].

The potential risk factors for the development of postoperative delirium already described above had an influence on the structuring of the screening system presented here. Therefore, the following examination parameters have also found their way into the present screening, which are (1) preoperative history, (2) geriatric assessment, (3) mobility and strength, (4) emotion, (5) nutritional status, (6) brain performance, (7) hearing ability, (8) sleep disorders and sleep quality, (9) pain symptomatology, and (10) postoperative evaluations. They are intended to help extract and further eliminate several different potentially delirium-inducing elements.

Further Questions

Recording systems have not yet been significantly established, that would be needed for determining dementia, the need for assistance in everyday life, or multimorbidity. These would also be important for determining geriatric care needs.

It has been shown that a geriatric assessment could make perioperative risks more understandable, also in the case of delirium [53]. Marcantonio et al [54] have already elaborated that such a geriatric assessment would reduce delirium by over 30% and severe delirium by over 50%. In this context, the question arises which parameters of such a geriatric screening system could be related to the reduction of delirium frequency.

Conclusions

We want to investigate whether the risk factors addressed in the assessment are associated with an increase in the delirium rate. The aim is then to reduce this comprehensive assessment to the central aspects to be able to conduct targeted and efficient risk screening.

Many of the known risk factors cannot be easily translated into risk prevention strategies comprehensively in everyday clinical practice. Since each discipline poses different challenges to patients, it is necessary to develop assessments that can be implemented in the individual disciplines.

Acknowledgments

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Data Availability

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

ADL: activities of daily living
DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)

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Protocol

Harnessing Big Heterogeneous Data to Evaluate the Potential Impact of HIV Responses Among Key Populations in Sub-Saharan Africa: Protocol for the Boloka Data Repository Initiative

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Abstract

Background: In South Africa, there is no centralized HIV surveillance system where key populations (KPs) data, including gay men and other men who have sex with men, female sex workers, transgender persons, people who use drugs, and incarcerated persons, are stored in South Africa despite being on higher risk of HIV acquisition and transmission than the general population. Data on KPs are being collected on a smaller scale by numerous stakeholders and managed in silos. There exists an opportunity to harness a variety of data, such as empirical, contextual, observational, and programmatic data, for evaluating the potential impact of HIV responses among KPs in South Africa.

Objective: This study aimed to leverage and harness big heterogeneous data on HIV among KPs and harmonize and analyze it to inform a targeted HIV response for greater impact in Sub-Saharan Africa.

Methods: The Boloka data repository initiative has 5 stages. There will be engagement of a wide range of stakeholders to facilitate the acquisition of data (stage 1). Through these engagements, different data types will be collated (stage 2). The data will be filtered and screened to enable high-quality analyses (stage 3). The collated data will be stored in the Boloka data repository (stage 4). The Boloka data repository will be made accessible to stakeholders and authorized users (stage 5).

Results: The protocol was funded by the South African Medical Research Council following external peer reviews (December 2022). The study received initial ethics approval (May 2022), renewal (June 2023), and amendment (July 2024) from the University

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of Johannesburg (UJ) Research Ethics Committee. The research team has been recruited, onboarded, and received non–web-based internet ethics training (January 2023). A list of current and potential data partners has been compiled (January 2023 to date). Data sharing or user agreements have been signed with several data partners (August 2023 to date). Survey and routine data have been and are being secured (January 5, 2023). In (September 2024) we received Ghana Men Study data. The data transfer agreement between the Pan African Centre for Epidemics Research and the Perinatal HIV Research Unit was finalized (October 2024), and we are anticipating receiving data by (December 2024). In total, 7 abstracts are underway, with 1 abstract completed the analysis and expected to submit the full article to the peer-reviewed journal in early January 2024. As of March 2025, we expect to submit the remaining 6 full articles.

Conclusions: A truly "complete" data infrastructure that systematically and rigorously integrates diverse data for KPs will not only improve our understanding of local epidemics but will also improve HIV interventions and policies. Furthermore, it will inform future research directions and become an incredible institutional mechanism for epidemiological and public health training in South Africa and Sub-Saharan Africa.

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KEYWORDS

HIV, key populations; Sub-Saharan Africa; big heterogeneous data; Boloka data repository

Introduction

In 2024, the world is at a critical juncture in the HIV response, counting down 6 years toward the global goal of ending AIDS as a public health threat by 2030 [1,2]. Despite the investment and focus on addressing HIV/AIDS, it remains a significant public health threat with persistent prevention and treatment challenges globally, regionally, in Sub-Saharan Africa, and in South Africa [1-3]. South Africa has the largest HIV epidemic in the world, with about 8 million people living with HIV, which represents approximately 1 in 5 of the estimated 38.4 million people living with HIV globally in 2022 [1,4]. While there has been a steady decline of 30.5% (n=198,311) in new infections in the last 5 years, the country still has an unacceptably high HIV incidence (South African National HIV, Prevalence, Incidence, Behaviour, and Communication Survey) [3-5]. South Africa has the largest HIV treatment program in the world to meet the treatment needs of the highest proportion of people living with HIV [1].

Key populations (KPs), including female sex workers and their clients, gay men and other men who have sex with men, transgender people, people who use and inject drugs, and incarcerated persons, face a disproportionate risk of HIV acquisition and onward transmission [6]. As a result of unmet prevention and treatment needs, 51% of new HIV infections are acquired by key populations and their sexual partners despite making up approximately 1.5% of the total adult population in Sub-Saharan Africa [1]. The estimated prevalence of HIV was 59.5% among female sex workers and 29.7% among men who have sex with men in South Africa in 2020 [3,4]. Given social network dynamics, the overall impact of the unmet needs of key populations on onward transmission may be even greater. Other modeling studies have a higher risk of onward transmission due to the unmet prevention and treatment needs among key populations using the transmission population attributable fraction over time ($tPAF_t$) [7]. This demonstrates the need for the specificity of the HIV response in characterizing and addressing heterogeneity in onward transmission for a more significant impact in the reduction of new infections. This disproportionate risk of HIV is driven by discrimination, stigma, and criminalization of behavior [8,9]. These same factors, alongside social network dynamics, make collecting data on HIV burden and specific HIV prevention and treatment needs challenging due to distrust of institutions and fear of poor treatment, arrest, or violence [10-12].

In South Africa, where there is robust HIV surveillance compared with other Sub-Saharan African countries, there is no specific mechanism or centralized system to gather and monitor key population data. The existing HIV surveillance systems include the district health information system (DHIS) and the integrated electronic registers, which both collect patient-level HIV data but have no identifiers for KPs, making it difficult to disaggregate data by these subpopulations [13]. The inability to disaggregate information among KPs can lead to misallocation of resources and services, perpetuating health inequities. This lack of adequate data can also lead to underestimation of the disproportionate risk of onward transmission and ultimately missed opportunities for targeted approaches that can lead to a significant reduction of new HIV cases [7,14,15]. Despite this lack of a centralized system, data on KPs are being collected on a smaller scale by numerous stakeholders, including program implementers, the government, academic partners, and others. There exists an opportunity to harness these different data sources for integration and in-depth analyses.

In generalized epidemic settings, there has been a tendency to focus the HIV response on the general population rather than KPs [16-18]. The scientific justification for the project presented here is that continued reliance on nonspecific population-based approaches to guide programs has limited the broader impact of the HIV response in a generalized epidemic setting like South Africa. At the same time, there is limited data to determine the extent to which a KP-tailored HIV response could reduce HIV incidence in South Africa [6,7,19-21]. A more specific HIV response will likely optimize the use of limited resources [7,20]. The proposed work can support program implementers, funders, and policy makers in making well-informed choices as to where, what, and whom to prioritize and how to deliver effective HIV

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control programs to maximize health benefits at a population level. An effective control of the HIV epidemic in South Africa requires a focus on KPs [22].

To address the identified gaps in the field, we are in the process of designing and developing a big data platform called "The Boloka data repository" and harmonization of disparate data from multiple data sources. The Boloka data repository seeks to store a diverse range of data, including empirical, observational, and programmatic data, to improve understanding of HIV acquisition and transmission among KPs. In addition, the Boloka data repository seeks to evaluate the potential impact of HIV responses in South Africa in the context of a generalized epidemic setting. Boloka is a South African Sepedi, Sesotho, and Setswana word that means to "store or keep." In this case, we will store or keep big heterogeneous data. These data, including HIV-related and relevant data for KPs from the year 2000 onward in South Africa, can be used to inform policy and programming. By harnessing big heterogeneous data, more data-driven and ultimately more effective HIV response strategies can be generated.

In this protocol paper, we describe the process for developing the Boloka data repository for South Africa. It is envisaged that once the Boloka data repository has been developed, it can be adapted to other countries throughout Sub-Saharan Africa. This study has 3 specific objectives: First, to build a Boloka data repository to handle data on KPs. Second, to collate available HIV-related data for KPs in South Africa from 2000 onwards. Third, to make the data user-friendly for use by stakeholders and authorized users.

Methods

Overview

To achieve the stated objectives, this study project will be developed in the following 5 key stages (Figure 1) [23].

Figure 1. The 5 stages of the Boloka data repository initiative [23], with permission from RNPM. UN: United Nations.

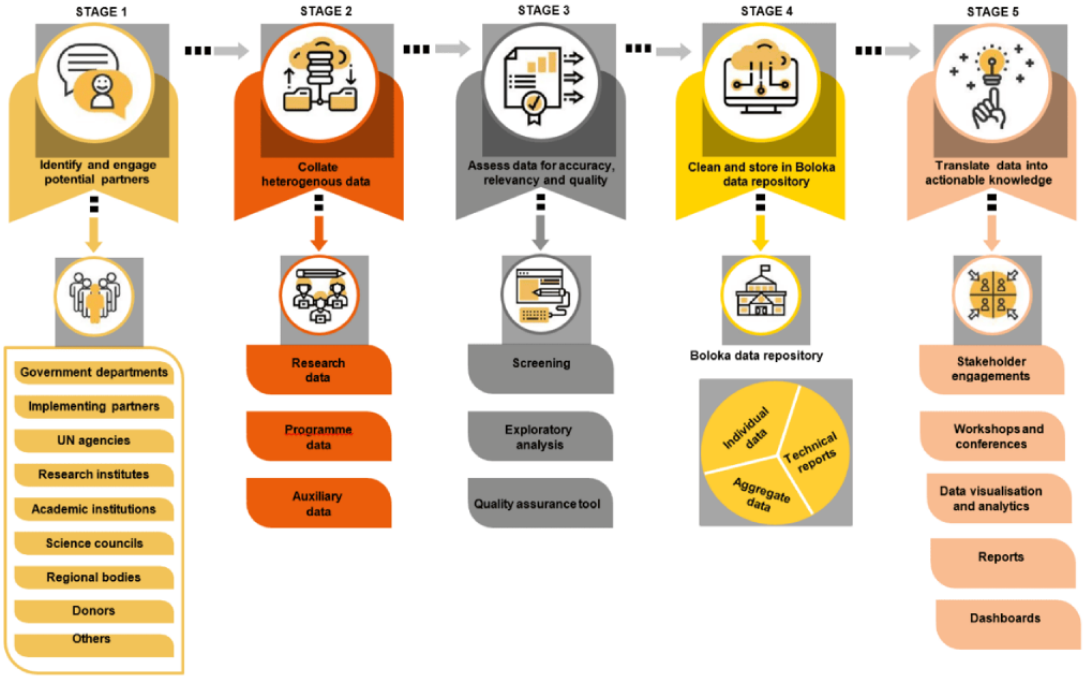

Stage 1: Engage Key Stakeholders to Develop Meaningful Data Partnerships

A range of stakeholders (potential data partners) will be engaged to explore data sharing partnerships and facilitate the collation as well as the organization of the diverse data sources (Table 1). A list of current and potential data sharing partners and the nature of data they are in possession of is being developed (Multimedia Appendix 1 shows the list of potential and current data partners as well nature of data).

A key stakeholder in this work is the South African National AIDS Council (SANAC), which will act as a partner in both the sharing of data and the facilitation of connections to additional potential data sharing partners. A transdisciplinary participatory approach will be adapted to develop meaningful partnerships ensuring collaboration between researchers and data partners, buy-in, project performance, co-ownership, and sustainability [24-26] guided by key principles of mutual trust, sharing, transparency, and responsibility [25,26]. Stakeholders will be given an opportunity to give input at all stages about various components of the Boloka data repository, including which data are collected, how they are stored, data confidentiality, data privacy, and data security, as well as how others may access them using the approved data management processes of the respective data partners. The Boloka research team will also engage with stakeholders regarding priority research questions that will be answered using the data (January 2024 to December 2026). This will ensure that the questions asked have use for those directly involved in the HIV response.

The data processing agreement (DPA) and data partnership or user and related agreements will be signed between the University of Johannesburg and the respective data partners

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[27]. These documents will govern the rights and duties of the parties in line "Protection of Personal Information (POPI) Act number 4 of 2014," henceforth referred to as the POPI Act, and any other applicable data protection, security, storage, regulation, and legal requirements [28]. Through these agreements, it will be ensured that the collection, storage, use, disclosure, transfer, disposal, and other processing of any personal information is in line with the prescribed data protection law. The signed agreements will be stored at the University of Johannesburg records management unit.

The Boloka data repository initiative will be executed in the South African Medical Research Council/ UJ (SAMRC/UJ) Pan African Centre for Epidemics Research (PACER) Extramural Unit, which is part of over 40 research centers and institutes, and 20 prestigious national research and industry-funded chairs that the University of Johannesburg is hosting. The South African Medical Research Council/ UJ (SAMRC/UJ) Pan African Centre for Epidemics Research Extramural Unit is one of the flagship initiatives that is supported under the Global Excellence and Stature strategic initiative [29].

Table 1. List of current and potential Boloka Project data partners.

Partner category	Examples of data partners
Country coordinating mechanism	SANAC (South African National AIDS Council)
International and Regional UN Agencies	Centers for Disease Control and Prevention (CDC), UNICEF, United Nations Development Programme, UNAIDS, WHO, United Nations Population Fund.
Government Departments	National Departments of Health, Social Development, Correctional Services, Basic Education.
Nongovernmental organizations (NGOs), nonprofit organizations (NPOs), and other	Beyond Zero (BZ), Networking HIV & AIDS Community of Southern Africa (NACOSA), Sex Workers Education and Advocacy Taskforce (SWEAT), Aurum, TB/HIV Care, Right to Care, Sisonke, U.S. President's Emergency Plan for AIDS Relief (PEPFAR) funded organizations.
Science Councils	Human Sciences Research Council (HSRC), South African Medical Research Council, Council for Scientific and Industrial Research.
Research Institutes in Universities	Desmond Tutu HIV Foundation, Centre for the AIDS Programme of Research in South Africa, Perinatal Health Research Unit.
Local and international donors	Global Fund, President's Emergency Plan for AIDS Relief (PEPFAR), UNAIDS, European Union (EU), Department for International Development (DFID), Canadian International Development Agency (CIDA), Directorate-General for International Cooperation (DGIS), Bill and Melinda Gates Foundation (BMG).
National Universities	All South African Universities.
Regional economic communities	Southern Africa Development Community.

Stage 2: Acquire and Collate Heterogeneous Data

Overview

The Boloka data repository will leverage and collate available and diverse data from various sources across places, times, and populations (Multimedia Appendix 1 shows the list of potential or current data partners and data types). The inclusion and exclusion criteria (Textbox 1), as well as the Boloka data indicator tool (Multimedia Appendix 2), will guide the eligibility of the data source. The inclusion of HIV-related data from the period 2000 and onwards will enable the capturing of the developments that took place over time in the HIV field. The use of reliable and granular data collected over time is essential for improving population health, setting targets as well as developing strategies for targeted HIV response.

The team reviewed the Joint United Nations Programme on HIV/AIDS global monitoring tool and the National Department of Health (NDoH) national indicator dataset form used for global, regional, and national HIV reporting to identify primary and secondary indicators in line with global, regional, and national priorities. The team also reviewed existing validated questionnaires or instruments from various data partners to further refine priority indicators; from this, broader categories of HIV-related interest areas were formed (Figure 2). Accordingly, each potential data partner is required to indicate the primary and secondary indicators that they have collected data on the Boloka data indicator tool (Multimedia Appendix 2).

Where possible, data will be disaggregated at individual, facility, district, or sub-district levels to enable advanced analyses that are not possible with higher-order aggregated data. This will help us develop an in-depth understanding of various subsets of the populations within the larger datasets. Where data are aggregated, we will seek data disaggregated by sex, gender, age groups, socioeconomic status, geo-location, facility type, and temporal factors to understand a range of HIV indicators, including heterogeneity of HIV risk and burden, engagement in HIV services (treatment cascade, pre-exposure prophylaxis uptake and continuation), and population size estimates, among others. The process for requesting and accessing data varies based on the data type and institution. As such, the process of acquiring and collating the data for the different data types is discussed below.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria:

- Study topic: HIV, key populations, HIV prevention and treatment.
- Study area: South Africa.
- Language: English.
- Time frame: Collected in the year 2000 or later.
- Data type: Research and program data.
- Data regulation: Secondary dataset or study with primary consent, specifying that the original consent or ethics approval covers secondary analysis without additional consent from participants.

Exclusion criteria:

- Study topic: Non-HIV.
- Study area: Non–South Africa.
- Language: Non-English.
- Time frame: Collected before the year 2000.
- Data type: Social media data.
- Data regulation: In circumstances where primary consent is needed from the participants, such datasets or studies will be excluded as it may not be feasible to go back to the participants for reconsent.

Figure 2. Boloka HIV-related indicator list.

Research Data

For open access data, which is typically aggregated or deidentified individual data, we will adhere to procedures set by the respective institutions to obtain access in line with the POPI Act. This may require the submission of designated data access request forms before gaining direct access to the dataset. For data that are only available upon request, we will contact the data partner to understand their specific procedures for accessing data. This typically requires the completion of a data access request form and the sharing of relevant information, such as the project proposal, ethics approval, and timelines for analysis. For institutions such as the NDoH, district health information data is made available for public use upon request and completion of their data user agreement (DUA) forms. The data or indicators requested should be aligned with the approved National indicator dataset, which outlines the data elements and indicators collected by the NDoH. In such cases, the request and DUA forms will be completed to access data. For institutions in possession of data that are not typically available for public access (eg, implementing partners), we will seek to develop formal partnership agreements and additionally use the University of Johannesburg DPA to ensure adherence to the Protection of Personal Information Act in terms of data privacy and security before any data sharing. Once agreed upon, a formalized partnership agreement will be approved by the legal team of both parties. These agreements will be reviewed in accordance with the policies of the respective organizations.

Program Data

For institutions in possession of data that is not typically available for public access, we will seek to develop formal partnership agreements and additionally use the University of Johannesburg DPA to ensure adherence to the POPI Act in terms of data privacy and security before any data sharing. Once agreed upon, a formalized partnership agreement approved by the legal team of both parties will be signed. These agreements will be reviewed in accordance with the policies of the respective organizations.

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Stage 3: Screen Data for Relevance and Quality

Overview

Once data are acquired and determined to be eligible according to the inclusion and exclusion criteria (Textbox 1), they will go through a process of screening and assessment for accuracy, relevance, quality, completeness, and consistency before inclusion in the Boloka data repository. Due to limited information and validated tools on how to specifically check for relevance and quality for some of the data types [30], we will adopt the Framework for Data Quality developed by the Federal Committee on Statistical Methodology (FCSM) [31] and the Information Quality Assessment Framework [32]. Below are further details on the data screening process by the different data types.

Research Data

For research data, a multistep quality assessment process will be carried out using the Global HIV Quality Assessment Tool (Multimedia Appendix 3) [33]. This tool will be used to review and verify the suitability and quality of research data sources in terms of study design and implementation, along with criteria for HIV indicators, specifically prevalence, incidence, engagement in the HIV care continuum, and population size estimates [33]. There will be close supervision and checks to minimize errors by using an honest data broker mechanism to manage and maintain datasets. In addition, 2 individuals (research assistants) will perform the initial quality assessment. Any discrepancies identified will be addressed by a third assessor (Project Manager and Principal Investigator [PI]). Exploratory analyses will be conducted to understand the nature of the data and identify outliers and missing data that will be cleaned for data quality and accuracy. This will be an iterative process to ensure that we leverage and assemble the best available data.

Program Data

It is important to highlight that program data present unique data quality challenges. Program data are typically aggregated to administrative units, and information on individuals is generally not available. Hence, it is not always feasible to link program exposure directly to an outcome [34]. In terms of screening the program data for inclusion into the Boloka data repository, the World Health Organization's "Data quality review: a toolkit for facility data quality assessment—Module 1: Framework and metrics" will be adapted for use [35]. This framework is made up of 4 dimensions. For this study, dimensions 1 and 2 will be used: completeness and timeliness of the data (dimension 1) and internal consistency of reported data (dimension 2). Dimension 1 focuses on the data elements and indicators collected. For example, the NDoH and implementing partners' data elements and indicators will be assessed and checked for completeness [35]. Dimension 2, that is, the internal consistency of the data, relates to the coherence of the evaluated data. In this regard, 4 metrics of internal consistency will be used [35]: (1) presence of outliers, (2) consistency over time, (3) consistency between indicators, and (4) consistency of reported data.

In this initial screening, articles, reports, and datasets will be excluded if their scope does not adhere to the inclusion criteria mentioned in Textbox 1. Data that focuses on the general population will be included in addition to data with a focus on KPs, as the general population provides important KP contextualization. Furthermore, data that have been empirically collected will be prioritized. Estimates and modeled data will be included but carefully reviewed to ensure they meet quality standards and are deduplicated within the datasets.

A report detailing the results of the quality assessment will be written. The report will include the recommendations for data quality improvement plans considering the context and existing constraints. A feedback loop will be used to engage with stakeholders on the potential data quality issues and anomalies, such as completeness of data, discrepancies, and inaccuracies. In addition, the data quality results will be available and stored alongside the data in the repository as part of the metadata.

Stage 4: Clean and Store Data In A Data Repository

Overview

Data will be extracted from data sources and put into a staging area before being transformed and loaded into the data repository (Figure 3). We will use the Data Intensive Research Initiative of South Africa (DIRISA) platform, which will enable the provision of much-needed timely information at a level and scale that will improve understanding of HIV heterogeneities. Structured data will be preprocessed and normalized into a standardized format using the Boloka Data Harmonization Tool (Multimedia Appendix 4). The repository will be flexible and updatable for structured data by design [36]. Unstructured data will be stored in the NoSQL data store. Preprocessing will entail data cleaning, transformation, and integration to make the data complete for analysis. Data management will involve assembling multiple big, existing HIV data sources and datasets, capturing, preprocessing, cleaning, integrating, and building them into the Boloka data repository.

For disaggregated data, personal identifiable information will be encrypted and hashed to ensure anonymity and protect privacy. This role is also performed by the appointed honest data broker. Ideally, the Boloka data repository will not store any identifiable personal information, but a procedure in accordance with the POPI Act will be put in place for handling this issue if such information comes with the data. The honest data broker mechanism will be set up to screen the data for compliance in terms of the latter before it passes to the Boloka data repository. The resulting data repository will be responsive to the size and scope of the collected data. It will be dynamic and flexible to accommodate diverse data that has a high number of dimensions.

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Figure 3. Envisaged Boloka data storage process flow. AI: Artificial Intelligence; AWS: Amazon Web Service; DHIS: District Health Information System; NDoH: Nation Department of Health; S3: Simple Storage Service; SANAC: South African AIDS Council; SFTP: Secure File Transfer Protocol; NoSQL: Not Only Structured Query Language.

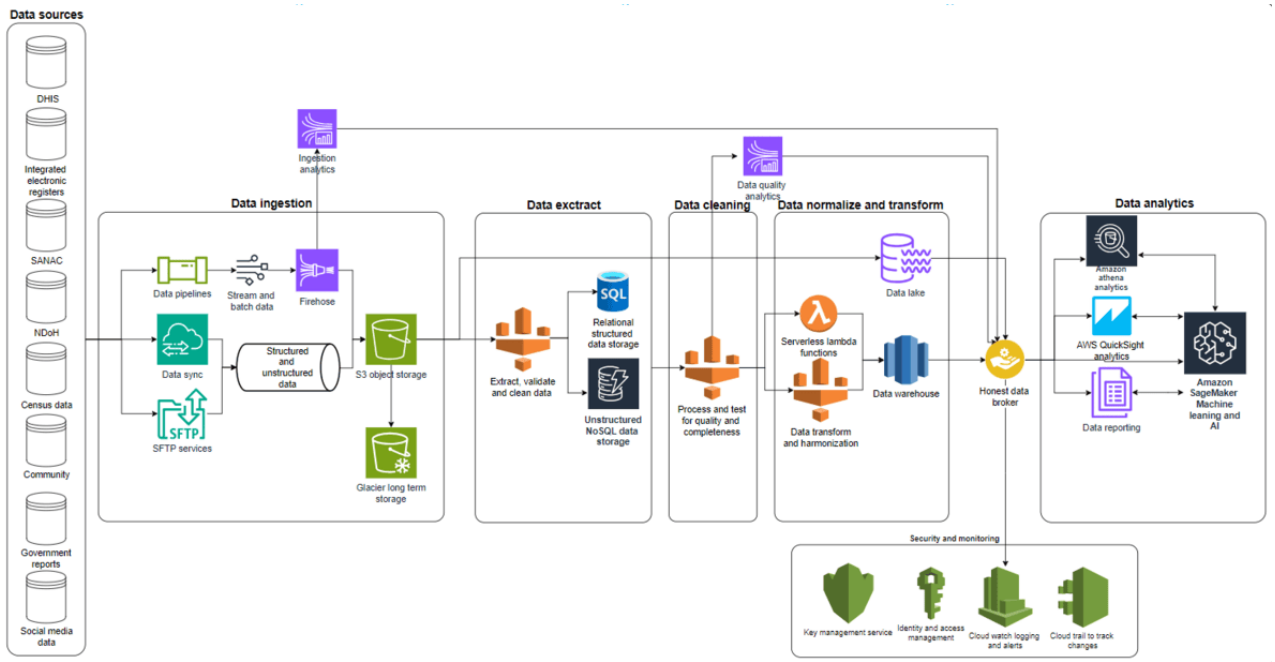

Data Security and Access

The access to the data repository will be secured with login credentials (username and password) in conjunction with multifactor authentication (MFA) to ensure compliance with the POPI Act and avoid any confidentiality breaches as well as contravention of human rights. Access to the repository will be made to the PI and Project Manager through a formal and written request. Login credentials (password) will be updated on a 3-month basis to enhance layers of security and reduce the risk of unauthorized access.

Stage 5: Translate Data Into Actionable Knowledge

Knowledge created from available data will be applied to address real-world challenges. To ensure that findings are incorporated into program and policy decisions promptly, the study will establish a feedback loop with stakeholders and authorized users throughout the project lifespan. Knowledge sharing will be done through dissemination workshops, consultative meetings, reports, dashboards, data visualization, and other methods deemed appropriate. This will support open communication and 2-way feedback between researchers and stakeholders (Multimedia Appendix 5). This participatory process will contribute towards improved use of available data and narrowing the gap between science and practice. Various forms of analysis will be planned in partnership with stakeholders to answer research questions that are relevant to their respective organizations and national priorities. Ultimately, the translation of research will seek to strengthen health systems and, therefore, improve health outcomes throughout South Africa, specifically for KPs and other vulnerable populations. Our goal is to make the Boloka data repository an accessible tool that can be used by local, regional, and international stakeholders for more effective and efficient health care management, prevention, and programming.

The University of Johannesburg Strategic Communication Department designated official will promote and market the initiative using the University of Johannesburg's communication technologies, media, and platforms. They will promote public understanding of the study and research outputs throughout. This will include articles in the daily press, magazines, and other popular media, public lectures, and interviews or programs on television or print media.

Ethical Considerations

Ethics approval (May 2022), renewal (June 2023), and amendment (July 2024) have been secured from the University of Johannesburg, Faculty of Health Sciences, Research Ethics Committee for conducting secondary analysis of data (REC-1504-2022) (Multimedia Appendix 6). Data partners will only share deidentified secondary datasets, and no personal information of the participants will be retrieved as per the POPI Act and the University of Johannesburg DPA, which governs the sharing, storage, and use of personal information. For example, in cases of NDoH, the routine data is aggregated and not at an individual level. The South Africa National HIV Prevalence, Incidence, Behavior and Communication Surveys (SABSSM) data is open access and unique identifiers were used. Data handling, processing, and analysis will be guided by the University of Johannesburg DPA, POPI Act, and data partnership agreement or request form. There is no monetary compensation for the data partners for being part of the Boloka project.

Results

As of December 2022, the protocol was funded by the South African Medical Research Council following external peer reviews. Subsequently, the study received ethics approval from the University of Johannesburg, Faculty of Health Sciences,

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Research Ethics Committee. The research assistants, students, and postdoctoral fellows who will partake in the creation of the data repository and subsequent analyses were recruited, onboarded, and received online training and resources in research ethics evaluation (TRREE), management and analysis of data in epidemiology (MADE), data types, and structures. The team will continue to tap into opportunities for professional development training, including sensitivity training for KPs and training on data privacy, specifically regarding the POPI Act and DIRISA functionalities for the duration of the study (January 2024-February 2027). The progress as of September 2024 is described below according to the 5 stages.

Stage 1: Identify and Engage Key Stakeholders to Develop Meaningful Data Partnerships

Overview

The stakeholder engagement is ongoing using the data partner tracking tool (Multimedia Appendix 7) listing potential and current stakeholders and their level of engagement with data (eg, district, provincial, and national) is in place.

Research Data

The research team secured open access data from 5 (2002, 2005, 2008, 2012, and 2017) South Africa National HIV Prevalence, Incidence, Behavior and Communication Surveys from the Human Sciences Research Council (HSRC) on January 5, 2023. Since the data is open access, no signing of DPA was required to access and secure the data. Engagement with stakeholders is expected to conclude in December 2026 in terms of finalizing data sharing agreements, and an example of the University of Johannesburg DPA has been shared for consideration by the potential data partners. An engagement with NDoH was done in 2022, and HIV-related routine data was secured (April 2024).

Program Data

The research team had a series of meetings with SANAC regarding the Boloka data repository. These meetings have established a strong partnership and system for the coordination of data-sharing partnerships. The partnership with SANAC is essential in ensuring that the Boloka data repository is used to guide national HIV strategy related to KPs. This strong relationship will ensure the complementarity of the Boloka data repository rather than duplication of SANAC's efforts to develop "The Situation Room," a central HIV data repository for program data in South Africa. The Situation Room, still in its infancy stages, seeks to enable data checks and balances, dynamic visualization, and sharing of the national, provincial, and district HIV data in the general population to monitor progress toward reaching set targets. The Boloka data repository will be a resource for KP data toward SANAC's efforts. SANAC introduced the research team to its implementation partners to acquire potential data partners, namely Beyond Zero [37], Networking HIV and AIDS Community of Southern Africa (NACOSA) [38], Sex Worker Education Advocacy Taskforce (SWEAT) [39], Sisonke [40], and AIDS Foundation South Africa (AFSA) [41] as well as Perinatal HIV Research Unit (PHRU) [42].

A series of engagements have been carried out with the respective organizations; the engagements are at different stages. Beyond Zero has been engaged since September 2022, and a final copy of the University of Johannesburg and Beyond Zero data-sharing agreement is under review by the Beyond Zero legal team before it is signed by both parties. A data partnership agreement with PHRU is expected to be finalized by the end of December 2024. For this partnership, the PHRU data-sharing agreement is being developed by their legal department. With AFSA, the agreement is in the early stages of communication. In addition to engagements with SANAC and its implementing partners, the research team has consulted with other community leaders who work or worked with community-based organizations, such as treatment action campaigns.

Stage 2: Acquire and Collate Heterogeneous Data

Overview

Significant progress has been made in securing program data, published research data, and technical reports. The security of the acquired data is prioritized during this interim period; thus, the data have been stored in a secure staging area and will later be moved to appropriate data storage software.

Research Data

Open access data from 5 cycles (2002, 2005, 2008, 2012, and 2017) of the population-based multistage cluster cross-sectional of up to 85,000 randomly selected households in South Africa has been secured from the HSRC (January 5, 2023). The South African HIV Behavioural, Sero-status and Media data is within the restricted access level. The data was accessed by completing a non–web-based internet data request form detailing the name of the project, a brief description of the intended use, and the expected date of project completion. The surveys provide data on HIV incidence, prevalence, antiretroviral therapy (ART), viral load suppression, drug resistance, risk behaviors, and HIV care, among others. The Key Population Implementation Science (KPIS) data on HIV testing and engagement in care was secured at Emory University (May 16, 2022) for the degree purpose of postgraduate students. Further, data on HIV testing proficiency was generated by a postgraduate student from the health care facilities in Eastern Cape Province (May 2023).

Data from the Demographic Health Surveys Program has been secured (August 2022). This required registration and submission of a data access request form along with the justification of the request. The demographic health survey collects indicators such as HIV prevalence, prevention and treatment, stigma, and discrimination, as well as sexual behavior. We also secured HIV-related data from the NDoH, and the data includes the following HIV indicators: HIV testing and HIV prevention; ART (ie, ART initiation, ART rate, viral load & CD4 T lymphocyte count testing, ART type, ART adherence); sexually transmitted infections; maternal and neonatal (antenatal HIV test, ART initiation, ART adherence, live birth, infant HIV test); management of inpatients and management of primary health care facility.

There are plans to use data from the 1173 NDoH High Transmission Area sites across South African provinces based in communities that function like clinics and provide services

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to KPs. The NDoH's High Transmission Area program reaches key and vulnerable populations with HIV, tuberculosis, and sexually transmitted infections prevention and management services in key hotspots across the country.

Program Data

This protocol will also leverage a partnership with the largest HIV service provider for key populations in South Africa, TB HIV Care, a nonprofit organization, building on a decade-long period of dynamic and exciting work; preliminary discussions have already taken place with the Chief Executive Officer. TB HIV Care focuses on preventing, finding, and treating HIV and TB across 7 provinces and 22 districts in South Africa [43]. Its KP program provides services to sex workers and people who use drugs. Furthermore, data-sharing agreements are being drafted and checked for Beyond Zero, NACOSA, and AFSA, as detailed above.

Stage 3: Assess Data for Accuracy, Relevance, And Quality

Overview

The data received in stage 2 went through screening and assessment for accuracy, completeness, and consistency before its placement in the staging area. The data received was screened and filtered for relevance and inclusion by a member of the research team using the FCSM and the Information Quality Assessment Framework [32] where applicable.

Research Data

South African HIV Behavioural, Sero-status and Media data has undergone a quality check to assess the completeness of the data received. Using the Needs Assessment Form, the DHIS data received has been checked to assess the relevance of the data to the project aims. The assessment checked that the data included the relevant indicators and if the data was complete. This process has been done by 2 researchers on the team.

Stage 4: Clean and Store Data in The Boloka Data Repository

The data have been placed in the staging area before being stored in the data repository. South African Medical Research Council/UJ (SAMRC/UJ) Pan African Centre for Epidemics Research Extramural Unit secured cloud-based storage on the DIRISA platform on June 14, 2024. DIRISA is a "component of the National Integrated Cyberinfrastructure System that coordinates and promotes sound research data management practices and supports data-intensive research" [44]. The access will grant the University of Johannesburg permission to use the DIRISA platform, along with access to the support tools and resources. The resources have been shared to provide access to DIRISA training materials. Through this platform, KP data will be harmonized into a centralized storage area that is managed and protected. All data is to be cleaned and converted into a standardized format to create a structured, flexible, and updatable data repository. The designing of the Boloka data repository will be completed by December 2026. Multimedia Appendix 8 shows the summary of planned and executed milestones for this project.

Stage 5: Translate Data Into Actionable Knowledge

Authorized users and stakeholders will have the capability to generate customized reports and export the data to applications such as Stata software (StataCorp) for further dissemination. Authorized users and stakeholders will submit a data request before receiving log-in credentials to access the data repository. Initial secondary data analyses using analytic methods attuned to the structure of available data, including cross-sectional and longitudinal analyses, are being conducted to improve our understanding of HIV among KPs for a targeted response. The proposed analyses will be a transdisciplinary collaborative effort to enable joint application of theories and methods to share conceptual frameworks, innovations, and best practices for solving public health problems. In this regard, the proposed analyses will be jointly finalized with program partners to identify priority research questions that will measure program progress, guide programmatic decision-making, and ultimately improve the response to HIV.

Data synthesis and initial analyses are being planned with a transdisciplinary team of infectious disease epidemiologists, public health scientists, statisticians, data scientists, data analysts, implementing partners, and data partners who will bring complementary expertise on global key populations insights, key population modeling, epidemiology, human rights, and the development of a sustainable data platform. We have already worked with some of the data partners to determine the research agenda that targets policy and practice outcomes, that is, determining common research questions, models, and methods to improve South Africa's HIV response. The doctoral students who will use the Boloka data repository for their dissertations have begun writing their research proposals and seeking ethical approval.

Some factors are critical for the success of this project in achieving the envisaged medium- and long-term impacts, as shown in Figure 4.

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Figure 4. Key success factors for Boloka data repository and envisaged impacts. SANAC: South African National AIDS Council.

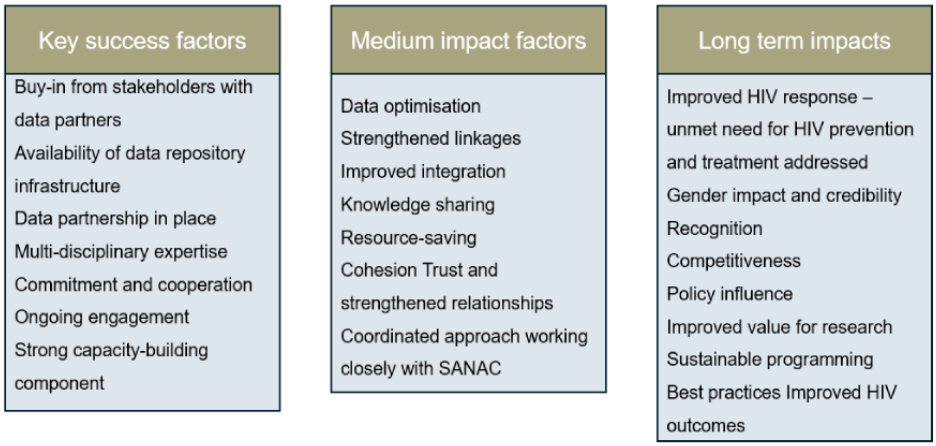

Discussion

Principal Findings

It is anticipated that there will be data challenges that are common across projects of this nature due to the POPI Act. The University of Johannesburg has already established a mechanism to address these. Potential POPI Act–related challenges have been highlighted in the University of Johannesburg DPA, which is standard for all data-driven projects.

The Boloka data repository will be a lasting resource for the country to guide regional policies and strategies to address HIV, particularly among KPs. Therefore, in addition to traditional research dissemination led by the research team and the proposed feedback loop (Multimedia Appendix 4), the data repository will be widely accessible to all data partners and stakeholders. This co-ownership with stakeholders will enable alternative possibilities for analyses and translation of data to real-world settings. The knowledge, historical context, and applied understanding that stakeholders possess provide opportunities for transformative change. The protocol will provide the opportunity to document lessons learned into a knowledge base, which may be applied to other countries in Sub-Saharan Africa.

The Boloka data repository will contribute to improved storage, retrieval, and access to KP data; linkages of surveillance data collection systems and other data collection efforts; integrated data reporting for monitoring national trends and patterns; recommendations for research, policy, and planning; as well as changes in current and future research. The Boloka data repository will provide a richer empirical basis for policy and program debates in a relatively neglected area of health research in the country. The data, along with its analyses and research outcomes, can form the basis of regularly reported statistics by stakeholders. The Boloka data repository will be maintained up to date to serve as a real-time sustainable resource to guide HIV planning, resource allocation, policy formulation, and programming.

Strengths and Limitations

The Boloka project seeks to build a complex data repository to house and analyze big heterogeneous data from KPs to guide the HIV response in South Africa and, ultimately, SSA. This initiative is crucial in developing policy recommendations for innovative methods towards ending the HIV epidemic in 2030. The Boloka initiative is a novel approach that has the potential to enhance knowledge translation. It will also provide opportunities for capacity-building among academic trainees and stakeholders. Furthermore, the Boloka repository will contribute to the optimization of the HIV data systems necessary for epidemic control. Various data types will be used through integrated analysis to uncover latent outcomes. However, the use of secondary data has limitations as no changes can be made toward improving internal validity. The data requested are from cross-sectional surveys that lack the ability to establish causality. Mitigation of data security, integrity, and confidentiality issues has been described in the relevant sections.

Conclusions

We posit that a truly “complete” data infrastructure that systematically and rigorously integrates empirical, contextual, observational, and programmatic data for KPs will not only improve our understanding of local epidemics but will also improve HIV interventions and policies. Furthermore, it will inform future research directions and become an incredible institutional mechanism for epidemiological and public health training. Achieving epidemic control in South Africa necessitates moving beyond HIV data silos, harnessing underused heterogeneous data, and conducting unconventional analyses. Creating a comprehensive and accessible data infrastructure inclusive of heterogeneous data will improve our understanding of HIV among KPs and accelerate the production of high-quality evidence. Empowered with this evidence, scientists, program leaders, community stakeholders, and policy makers will be able to tailor and optimize HIV service delivery to the most vulnerable populations, thus making the South African National Strategic Plan goal possible. The amassed evidence will provide opportunities for comprehensive and innovative analyses that seek to address priority research questions to improve our understanding of HIV among KPs, assist in setting program targets, guide programmatic decision-making, and ultimately improve the response to HIV in South Africa and other Sub-Saharan African countries. Efforts will be made to incorporate the findings from this study into the South African HIV response strategy.

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Acknowledgments

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Authors' Contributions

RNPM and SB conceptualized the protocol and initial draft of the manuscript and provided overall leadership for executing the review to completion. RNPM, EP, AR, KW, KR, KAV, AB, CS, BS, MS, MJ, LLO, KJ, HIS, XL, BO, NH, PD, FW, YAS, LM, MR, and SB contributed to the introduction, methodology, and progress updates of the study. RNPM, EP, KAV, AB, CS, BS, MS, MJ, LLO, KJ, and HS were responsible for engaging with key stakeholders and initiating the data-sharing process. RPNM and EP were responsible for engaging with the legal team and finalizing data-sharing agreements. LM and MR were responsible for the facilitation and linkage to key stakeholders. NH and PD provided insights into the Boloka Data Storage Process Flow. HS and KJ drafted the Boloka Indicator list; KAV and AB drafted the Boloka Harmonization Tool—and the rest of the team reviewed the tools for further input. RNPM was responsible for the management and coordination of review activities. All authors discussed the results and contributed to the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
List of potential and current data partners as well as nature of data.
[DOCX File , 15 KB - resprot_v14i1e63583_app1.docx]

Multimedia Appendix 2
Boloka Data Indicator Tool.
[DOCX File , 59 KB - resprot_v14i1e63583_app2.docx]

Multimedia Appendix 3
Global HIV Quality Assessment Tool.
[DOCX File , 129 KB - resprot_v14i1e63583_app3.docx]

Multimedia Appendix 4
Boloka Harmonization Tool.
[DOCX File , 223 KB - resprot_v14i1e63583_app4.docx]

Multimedia Appendix 5
Proposed feedback loop.
[DOCX File , 289 KB - resprot_v14i1e63583_app5.docx]

Multimedia Appendix 6
Ethics approval letter.
[DOCX File , 147 KB - resprot_v14i1e63583_app6.docx]

Multimedia Appendix 7
Data Partners Tracking Tool.
[DOCX File , 153 KB - resprot_v14i1e63583_app7.docx]

Multimedia Appendix 8
Summary of planned and executed milestones for this project.
[DOCX File , 14 KB - resprot_v14i1e63583_app8.docx]

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Abbreviations

AFSA: AIDS Foundation South Africa
ART: antiretroviral therapy
DHIS: District Health Information System

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DIRISA: Data Intensive Research Initiative of South Africa
DPA: Data Processing Agreement
DUA: Data User Agreement
FCSM: Federal Committee on Statistical Methodology
HSRC: Human Sciences Research Council
KP: key population
KPIS: Key Population Implementation Science
MADE: management and analysis of data in epidemiology
MFA: multifactor authentication
NACOSA: Networking HIV and AIDS Community of Southern Africa
NDoH: National Department of Health
PACER: Pan African Centre for Epidemics Research
PHRU: Perinatal HIV Research Unit
PI: Principal Investigator
POPI: Protection of Personal Information
SABSSM: South Africa National HIV Prevalence, Incidence, Behavior and Communication Surveys
SAMRC: South African Medical Research Council
SANAC: South African National AIDS Council
SWEAT: Sex Worker Education Advocacy Taskforce
tPAFt: transmission population attributable fraction over time
TRREE: training and resources in research ethics evaluation

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Protocol

Estimating the Effect of Adhering to the Recommendations of the 2019 Canada's Food Guide on Health Outcomes in Older Adults: Protocol for a Target Trial Emulation

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Abstract

Background: The 2019 Canada's Food Guide provides universal recommendations to individuals aged ≥2 years. However, the extent to which these recommendations are appropriate for older adults is unknown. Although ideal, conducting a large randomized controlled trial is unrealistic in the short term. An alternative is the target trial emulation framework for causal inference, a novel approach to improve the analysis of observational data.

Objective: This study aims to describe the protocol for a target trial emulation in older adults, with an emphasis on key aspects of a hypothetical sustained diet and physical activity intervention.

Methods: To emulate the target trial, nonexperimental data from the Quebec Longitudinal Study on Nutrition and Successful Aging (NuAge; N=1753 adults aged ≥67 years) will be used. NuAge includes 4 yearly measurements of dietary intakes, covariates, and outcomes. The per-protocol causal contrast will be the primary causal contrast of interest to account for nonadherence. The sustained intervention strategy will be modeled using the parametric g-formula. In the hypothetical trial, participants will be instructed to meet sex-specific minimal intakes for vegetables and fruits, whole grains, animal- and plant-based protein foods, milk and plant-based beverages, and unsaturated fats. The eligibility criteria, follow-up, intervention, outcomes, and causal contrast in the emulation will closely align with those of the target trial, with only minor modifications. We will attempt to emulate the randomization of treatment by adjusting for baseline covariates and prebaseline dietary habits.

Results: Data collection for NuAge was completed in June 2008. For this study, the main analysis was started in May 2024. Submission of the manuscript is expected by February 2025.

Conclusions: Emulating a target trial will provide the first evidence of the adequacy of the 2019 Canada's Food Guide recommendations for older adults in relation to health outcomes.

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KEYWORDS

aged; Canada's Food Guide; diet; dietary guidelines; target trial emulation; hypothetical trial; Healthy Eating Food Index-2019; HEFI-2019

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Introduction

Background

The latest edition of Canada's Food Guide (CFG) was published in 2019 [1]. Compared with the previous edition, key changes include the removal of the prespecified number of servings to consume each day, a shift toward qualitative (eg, "eat plenty of...") instead of quantitative recommendations, and the provision of universal recommendations instead of age- and sex-specific recommendations. In addition, CFG recommendations primarily aim to reduce chronic disease risk. The evidence supporting CFG recommendations focuses on reducing the risk of cardiovascular disease, cancer, and type 2 diabetes risk [2]. However, evidence from a nationally representative survey of adults aged ≥65 years from Canada suggested that greater adherence to recommendations was insufficient to meet calcium, vitamin D, and folate requirements [3]. In Canada, one-third of community-dwelling older adults are at high nutrition risk [4,5], highlighting the importance of maintaining adequate nutritional status in this stratum of the population. Similarly, in the absence of specific recommendations on the amount of protein foods to eat, older adults may be eating less protein than required to maintain muscle mass [6-8]. CFG also provides brief physical activity recommendations but without explicit acknowledgment of the importance of these recommendations for older adults [1]. Indeed, performing a minimal amount of physical activity is paramount to maintaining muscle mass [6,7]. Thus, the universal recommendations in CFG may not be appropriate for older adults because they face unique challenges in consuming a healthy diet [9] and may require specific nutritional strategies [10].

Ideally, a randomized controlled trial (RCT) should be conducted to investigate the adequacy of CFG recommendations in older adults. However, such an RCT is unlikely to be conducted in the short term. An alternative is the target trial emulation framework for causal effect estimation using observational data [11-14]. Informally, the target trial emulation framework aims to emphasize and resolve design challenges in observational data analysis by explicitly emulating a hypothetical trial to estimate a causal effect [11]. In nutritional epidemiology, common issues with design and analyses can yield results that are largely inconsistent with those of randomized trials [15]. For example, the lack of consideration of the compositional nature of diet can dramatically influence effect estimates, that is, increasing the intake of one food must be compensated by decreasing the intake of another food in substitution modeling [15-17]. Furthermore, diet is a lifelong sustained exposure. In an observational study, the effect of diet assessed at a given time may actually reflect the cumulative exposure to previous dietary habits. In turn, ignoring previous dietary habits may result in a misalignment of "time zero" [18], as dietary habits are not randomly assigned at the beginning of the observational study. In other words, ignoring previous dietary habits makes it impossible to distinguish the effect of prospective or hypothetical dietary modification from the effect of retrospective dietary habits. The target trial framework is a helpful tool to highlight and address common issues in nutritional epidemiology. Ultimately, a successful emulation of the target trial based on observational data could yield effect estimates that more closely align with those of a hypothetical future RCT. Example applications of the target trial framework include the emulation of interventions on diet [19-22], physical activity [23], or both [24].

Objectives

To the best of our knowledge, a target trial framework has not been used to assess the effect of adhering to CFG recommendations. Accordingly, this study aims, first, to describe the protocol for the emulation of a target trial using observational data from the Quebec Longitudinal Study on Nutrition and Successful Aging (NuAge [25]), which includes a cohort of 1753 adults aged 67 to 84 years at baseline, and, second, to address key aspects of the target trial emulation in the context of a sustained lifestyle intervention strategy involving diet and physical activity. Key aspects are the description of the sustained lifestyle intervention strategy, the attempt to emulate randomization, as well as assumptions and limitations specific to diet intervention. Notably, more general introductory texts to the target trial framework are available elsewhere [11,12,14].

Methods

Research Question and Hypothesis

Explicitly acknowledging the causal nature of a research question is a prerequisite to causal effect estimation using observational data [26-28]. This study aims to examine the adequacy of the universal dietary recommendations provided by CFG for older adults. Expressed as a counterfactual statement, we aim to answer the following question: What would be the difference in a given health outcome at the end of the follow-up if all eligible participants had increased their adherence to CFG recommendations on healthy food choices, compared to if they had maintained their habitual diet?

Specifically, among adults aged 67 to 84 years followed for 3 years, and compared with maintenance of habits, we aim to (1) estimate the causal effect of adhering to CFG dietary recommendations on markers of muscle health (eg, physical function and muscle strength), general health (eg, waist circumference, blood pressure, and glucose), and cognitive health (ie, Modified Mini-Mental State Examination) and (2) estimate the causal effect of adhering to a *reformulation* of CFG dietary recommendations, including more protein foods and a minimal physical activity recommendation, to amplify the positive health effects.

Accordingly, we hypothesize the following:

- *Hypothesis 1: adhering to recommendations positively influences general and cognitive health but does not influence muscle health.*
- *Hypothesis 2: increasing the consumption of protein-rich foods positively influences muscle health, and meeting minimal physical activity recommendations (≥30 min per day) further amplifies positive health effects.*

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Study Design and Sample

Data from the NuAge prospective cohort will be used to emulate the target trial [25]. The NuAge cohort comprised 1753 generally healthy community-dwelling adults aged 67 to 84 years at baseline and followed for 3 years. The baseline and each annual follow-up evaluation included a comprehensive assessment of sociodemographic data, diet, physical activity, functional status, as well as physical and mental health status [25].

The NuAge sample is relevant to our research question. The target population of CFG recommendations comprises all individuals aged ≥2 years, which is compatible with the NuAge target sample of generally healthy older adults from the greater Montreal, Sherbrooke, and Laval areas of the province of Quebec, Canada.

Target Trial

The target trial framework has been suggested as a potential solution to improve the analysis of nutritional epidemiology studies aiming at causal inference [13]. Informally, the target trial framework helps to align the observational data analysis with that of a hypothetical trial. This framework is appropriate for the research question in this study, as we aim to estimate the effect of adhering to a hypothetical diet and physical activity intervention using observational data. The first step of a target trial emulation is the description of the target trial, that is, the protocol for the hypothetical RCT we wish to conduct [11,14]. The second step is the emulation, that is, describing how the target trial is emulated and conducting the study described in this protocol.

Table 1 presents the target trial and its emulation using observational data from NuAge. Key differences between the target trial and its emulation are that participants will be required to provide complete dietary assessment and covariate data at baseline (ie, eligibility component) and that we will attempt to emulate the randomized assignment by adjusting for dietary intakes before baseline as well as baseline covariates (ie, assignment component). Each part of the target trial and its emulation are described in the subsequent sections.

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Table 1. Emulation of a dietary intervention target trial using observational data from the Quebec Longitudinal Study on Nutrition and Successful Aging (NuAge [25]).

Trial component	Target trial specification	Target trial emulation
Eligibility criteria	• NuAge inclusion criteria: individuals aged 67-84 years; living in Montreal, Laval, or Sherbrooke; not cognitively impaired; and free of disabilities in activities of daily living • Exclusion criteria: class II heart failure, chronic obstructive pulmonary disease requiring home oxygen therapy or oral steroids, inflammatory digestive diseases, and cancer treatment in the past 5 years	• The inclusion and exclusion criteria are the same as those specified in the target trial. • Furthermore, participants will be required to have complete baseline dietary assessment (at least one 24-hour recall with ≥500 kcal and FFQ[a]) and provide baseline covariate data.
Interventions[b]	• Each individual would be assigned to 1 of the 4 following strategies: • Control group (habitual diet, ie, typical North American diet) • Adherence to Canada's Food Guide recommendations on healthy food choices • Adherence to Canada's Food Guide recommendations on healthy food choices and including a high-protein reformulation • Adherence to Canada's Food Guide recommendations on healthy food choices, including a high-protein reformulation and a minimal physical activity component • Each strategy is followed until the end of follow-up. Participants assigned to a lifestyle strategy are expected to maintain their dietary intake or amount of physical activity at or above the prespecified threshold by the corresponding intervention strategy.	• The intervention component will be the same as that specified in the target trial. • Furthermore, we will assume that each dietary assessment period (ie, within 2 months beginning at each time point) accurately reflects the average diet in the interval between follow-ups.
Assignment	• Participants are randomly assigned to a dietary strategy but are not blinded to their assignment.	• We will attempt to emulate randomized assignment by adjusting for dietary intakes before baseline and baseline covariates.
Outcomes	• The outcomes are physical function and muscle strength, general health indicators, and cognitive health.	• The outcomes will be physical function and muscle strength, general health indicators, and cognitive health.
Time zero and follow-up	• The study starts at baseline and ends at incomplete follow-up or 3 years after baseline, whichever occurs first.	• The study will start at baseline and end at incomplete follow-up or 3 years after baseline, whichever occurs first. • An incomplete follow-up is defined as missing data for questionnaires (nonresponse or loss to follow-up) or missing outcome data at the end of follow-up.
Causal contrast[c]	• Intention-to-treat effect • Per-protocol effect	• Observational analog of both contrasts: • Secondary: intention-to-treat effect • Primary: per-protocol effect
Statistical analysis	• Intention-to-treat analysis: apply inverse probability weighting with adjustment for prebaseline and baseline factors associated with incomplete follow-up to account for study dropouts • Per-protocol analysis: apply the parametric g-formula algorithm to compare postintervention outcomes between groups receiving each treatment strategy, adjusting for pre- and postbaseline factors associated with adherence to intervention strategies and incomplete follow-up.	• Analysis will be the same as that specified in the target trial for both contrasts. • However, the observational analog will require additional adjustments for confounding at baseline and before baseline due to previous dietary pattern.

[a]FFQ: food-frequency questionnaire.

[b]Refer to the *Hypothetical Interventions* section for detailed intervention.

[c]The observational analog of the intention-to-treat contrast corresponds to the baseline values of the intervention, which are assigned and initiated at the same time.

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Eligibility Criteria

The inclusion criteria for the target trial are the same as those for NuAge [25]. In the emulation, participants will be required to have at least one 24-hour dietary recall completed at baseline with ≥500 calories, as well as complete covariate data at baseline, as identified in the *Assignment* section.

Hypothetical Interventions

Overview

The hypothetical intervention strategies evaluated will be as follows:

1. No change in dietary habits or physical activity (similar to a control intervention)
2. Adherence to CFG recommendations
3. Adherence to CFG recommendations, including reformulation (ie, higher intake of protein foods)
4. Adherence to CFG recommendations, including reformulation (ie, higher intake of protein foods) and performing at least 30 minutes of aerobic physical activity

Physical activity recommendations are not traditionally at the forefront of CFG recommendations. However, CFG does mention that "at least 150 minutes of moderate-to vigorous-intensity aerobic physical activity per week ... is recommended to achieve health benefits" [1]. Thus, recognizing the key role of exercise in maintaining health and muscle for older adults, the fourth hypothetical intervention includes a formal physical activity recommendation. In the target trial, the physical activity corresponds to performing aerobic exercise of light to vigorous intensity for at least 30 minutes per day [6].

The Challenge of a Well-Defined Nutritional Intervention

Emulating a well-defined dietary intervention for CFG recommendations is challenging. First, recommendations in the latest edition of CFG are qualitative and flexible (eg, "eat plenty of vegetables and fruits" [1,29]). Thus, various suitable yet distinct dietary patterns can align with the recommendations. Second, CFG recommendations target both food intakes (eg, vegetables and fruits) and nutrients (eg, saturated fats). The nutrient-based recommendations can be met by modifying the consumption of various foods. For example, to achieve the hypothetical intervention of "decreasing consumption of calories from saturated fats," one could decrease saturated fats from dairy, nuts, and low nutritive value foods altogether. Arguably, the relationship between these food categories and a given health outcome may vary greatly.

To estimate a causal effect using observational data, the hypothetical interventions must be clearly defined to the point where "no meaningful variation" in the intervention remains [30,31]. In other words, the hypothetical diet interventions should be elaborated until no additional dietary characteristics are deemed impactful regarding the outcome of interest. Another consideration is that the modeling of hypothetical interventions should ideally be conducted with dietary intakes expressed using the same units. For example, mixing food intakes expressed in servings and grams in a statistical model may cause poor estimation of causal effects [17]. Finally, the statistical approach used to account for total energy or total food intake also affects the causal effect of interest and should be consistent with the research question [17,31-33].

Diet Simulations

For this study, adherence to CFG recommendations was defined based on simulated diets generated by Health Canada [34] and summarized in Multimedia Appendix 1 [34]. The simulated diets were designed to meet CFG recommendations on healthy food choices and nutrient requirements (Dietary Reference Intake).

These diets achieve near-perfect Healthy Eating Food Index (HEFI)-2019 scores (>78/80) through relatively high intake of recommended foods (ie, vegetables and fruits, whole grain foods, protein foods, and unsweetened milk and plant-based beverages with protein) and null intakes of foods not recommended (ie, non–whole grain foods; other low nutritive value foods; juice, sugary drinks and alcohol; and fatty foods rich in saturated fats). The HEFI-2019 score indicates the extent to which dietary intakes are consistent with CFG recommendations on healthy food choices [29,35].

Notably, the HEFI-2019 could have been used as a main exposure to measure adherence to CFG. However, the use of a composite score metric would not completely satisfy the criterion of a well-defined intervention to estimate a causal effect. First, high HEFI-2019 scores and high adherence to CFG recommendations can be achieved through many different strategies or dietary patterns. In the context of observational data, the specific strategies through which individuals achieve a high HEFI-2019 score would be based on dietary habits and patterns self-selected by the participants. This approach is similar to asking hypothetical trial participants to modify their intakes without clearly specifying how, which would obscure the estimated causal effect. Second, the HEFI-2019 score includes recommendations on foods and nutrients. As described earlier, mixing servings and grams in statistical models may cause poor estimation of causal effects [17].

We stress that the diets simulated by Health Canada were not actually consumed by older adults. Therefore, the simulated values for vegetables and fruits, whole grain foods, and plant-based protein foods *exceed* the 99th percentile of the distribution of usual intakes of these food categories, as estimated in adults aged ≥65 years from the Canadian Community Health Survey 2015–Nutrition [3]. In Table 2, the target intakes for vegetables and fruits, whole grains, and plant-based protein foods in the adherence to the 2019 CFG recommendations intervention were revised to correspond, at most, to the 90th percentile of the distribution of usual intakes among Canadians aged ≥65 years in 2015 [3].

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Table 2. Emulation[a] of hypothetical diet and exercise interventions by sex in the Quebec Longitudinal Study on Nutrition and Successful Aging (NuAge) cohort [25].

Sex	Recommended foods (RA[b]/d)						Dietary supplement[c]	Foods and beverages not recommended (RA/d)[d]			Physical activity (min/d)[e]
	Vegetables and fruits	Whole grains	Plant-based protein foods	Animal-based protein foods	Milk and plant-based beverages with protein	Unsaturated oils and fats		Other foods	Sugary drinks and alcohol	Non–whole grains	
Control (no change)[f]											
Male individuals	—[g]	—	—	—	—	—	—	—	—	—	—
Female individuals	—	—	—	—	—	—	—	—	—	—	—
Adhering to the 2019 Canada's Food Guide recommendations on healthy food choices[h]											
Male individuals	6	1.5	1.0	2.0	1.0	1	No change	Minimum	Minimum	Minimum	No change
Female individuals	5	1.5	0.8	1.5	1.0	1	No change	Minimum	Minimum	Minimum	No change
Adhering to the 2019 Canada's Food Guide recommendations on healthy food choices, including extra protein[i]											
Male individuals	6	1.5	1.5	3.5	1.5	1	No change	Minimum	Minimum	Minimum	No change
Female individuals	5	1.5	1.3	3.0	1.5	1	No change	Minimum	Minimum	Minimum	No change
Adhering to the 2019 Canada's Food Guide recommendations on healthy food choices, including extra protein and physical activity											
Male individuals	6	1.5	1.5	3.5	1.5	1	No change	Minimum	Minimum	Minimum	30 or more
Female individuals	5	1.5	1.3	3.0	1.5	1	No change	Minimum	Minimum	Minimum	30 or more

[a]The emulation of all hypothetical interventions will be implemented using a substitution approach in statistical models. In all models, 1 variable for total food intake and 1 variable for total beverage intake will be included, and foods not recommended will be left out from the models (ie, non–whole grain foods; other low nutritive value foods; juice, sugary drinks and alcohol; and fatty foods rich in saturated fats).

[b]RA: reference amount.

[c]Dietary supplements were not intervened on but were, nonetheless, excluded from foods and beverages not recommended to avoid being considered in the substitution. In other words, participants would not be instructed to modify their dietary supplements in the hypothetical trial.

[d]Minimum indicates that consumption would be set at the smallest amount, permitting a concomitant increase in recommended foods to meet Canada's Food Guide targets. Portions for foods not recommended may vary on an individual basis.

[e]Physical activity corresponds to aerobic exercise of moderate or higher intensity [6].

[f]Values will be the averages observed at baseline in the NuAge cohort. In other words, values will be the observed intakes for the food categories or amount of physical activity when no change is applied.

[g]Not applicable.

[h]Values are derived from Health Canada's simulated composite diets of adults aged ≥71 years. Participants would be expected to meet these targets for each food category. The specific food choices within these categories would be at the participants' discretion. Values for vegetables and fruits, whole grain foods, and plant-based protein foods were truncated to correspond, at most, to the 90th percentile of the distribution of usual intakes among Canadians aged 65 years in 2015.

[i]Extra protein foods were added as follows: +0.5 RA of plant-based protein foods (eg, 25 g of nuts), +1.5 RA of animal-based protein foods (eg, 150 g of cooked unprocessed red meat, fish, or poultry or 3 small eggs), +0.5 RA of milk or plant-based beverage with protein (eg, 125 mL of milk or plant-based beverages with sufficient protein).

Because the 2019 CFG does not have a portion size system, reference amounts (RAs) were used as a proxy for servings. RAs are regulated quantities of foods that reflect the portion size typically consumed at 1 sitting in Canada. RAs were used by Health Canada to simulate a diet consistent with the 2019 CFG recommendations and dietary reference intake (Multimedia Appendix 1 [34]); therefore, RAs are adequate for this study.

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Implementation

In the target trial, the sustained intervention strategy could be implemented as follows:

- Step 1: the participants' usual dietary intake and physical activity would be assessed by research dietitians at each study visit.
- Step 2: if reported food intakes and duration of physical activity were equal to or above the prespecified thresholds (Table 2), no change would be suggested to the participants' diet or physical activity. If food intakes or duration of physical activity were below the prespecified thresholds, participants would be instructed to increase food consumption to exactly the prespecified portions or increase physical activity duration to 30 minutes per day (when applicable).
- Step 3: if changes are required, participants would be instructed to decrease consumption of foods not recommended by the same amount as the increase in step 2. For example, if a 2-serving increase in vegetables and fruits is required to meet the prespecified intervention thresholds, participants would be instructed to substitute 2 servings of vegetables and fruits for non–whole grain foods; other low nutritive value foods; juice, sugary drinks and alcohol; and fatty foods rich in saturated fats.

In the emulation, for all hypothetical interventions, substitution will be implemented by including total intakes as a covariate and excluding foods not recommended from the models. More precisely, a variable reflecting total food intake (in RA/d) and a variable reflecting total beverage intake (in RA/d) will be included in all models. Hence, total food and beverage intakes will be constant across hypothetical diet interventions. In this approach to account for total energy, all model coefficients reflect the action of increasing intakes of recommended foods and a concomitant decrease in *any* of the foods not recommended [32]. On one hand, this approach can be potentially confusing [17,33], as the default interpretation of model coefficients assumes increasing the intake of each *food included in the model* while simultaneously decreasing the intake of foods *excluded from the model* [32]. On the other hand, the standard model is generally consistent with the implementation of dietary intervention in feeding trials [16,36,37]. The standard model also reduces the number of variables to be considered as intervention variables. Otherwise, 4 additional dietary components would have to be modeled for foods not recommended (ie, non–whole grain foods; other low nutritive value foods; juice, sugary drinks and alcohol; and fatty foods rich in saturated fats). Finally, the explicit description of the intervention strategies in the target trial protocol clarifies the estimand of interest, as done in an earlier study [19,31].

Notably, nutrient-based recommendations in CFG (ie, saturated fats, free sugars, and sodium intake) are not explicitly modeled to avoid the problems associated with mixed-unit models [17]. In the target trial, we assume that nutrient-based targets would be met by reducing consumption of foods not recommended (ie, non–whole grain foods; other low nutritive value foods; juice, sugary drinks, and alcohol; and fatty foods rich in saturated fats). In that regard, food-level substitution analyses in Canadians support this assumption for saturated fats [38,39].

The extra protein intervention consists of increasing the intake of both animal-based and plant-based protein foods by 1.5 and 0.5 RA per day, respectively, as well as milk and plant-based beverages with sufficient protein by 0.5 RA per day. Regarding the amount of food, this corresponds to adding 150 g of cooked unprocessed red meat, fish, or poultry or 3 small eggs; 25 g of nuts and seeds; and 125 mL of milk or plant-based beverages with sufficient protein while proportionally decreasing the intake of foods not recommended. In a previous RCT [40], older women aged 60 to 90 years were able to consume an additional 160 g of cooked lean red meat without substitution, thereby supporting the feasibility of the protein intervention in this hypothetical study.

Assignment

We will attempt to emulate random allocation or randomization by adjusting for dietary intakes in the year before the intervention, as well as adjusting for covariates at the start of the study. Covariates were identified using the causal diagrams depicted in Figure 1, based on background knowledge of the relationship between the hypothetical lifestyle intervention and outcomes.

Dietary components that are the foundation for healthy eating in CFG include intakes of vegetables and fruits, whole grains, protein foods (plant- and animal-based protein foods, milk, and plant-based beverages with protein), and unsaturated oils and fats [1].

Covariates, including age at baseline, biological sex, region, education, living alone, smoking and drinking (alcohol) habits, major chronic diseases (ie, hypertension, diabetes, cancer, and heart disease), the number of medications, supplement use (eg, vitamins and minerals), and height and weight, are as follows:

1. *Z*, baseline covariates: age, sex, region, education, history of smoking, height, and former cancer history
2. *P*, previous exposure (ie, exposure of time-varying intervention before baseline): dietary habits before baseline
3. *L*, (time-varying) covariates: weight, number of medications, supplement use, living alone, major chronic diseases (eg, hypertension, diabetes, cancer, and heart disease), and smoking and alcohol habits
4. *X*, (time-varying) treatment: diet and physical activity habits
5. *Y*, end of follow-up outcome: muscle health, general health, and cognitive health

Contrary to dietary habits, data on physical activity habits before baseline were not collected in NuAge. In this case, the potential effect of previous physical activity habits will not be accounted for in the models that aim to emulate the sustained physical activity intervention strategy. For the models emulating the sustained diet intervention strategy only, physical activity habits during the study will be used as a covariate, hence mitigating the confounding of previous physical activity, at least to some extent.

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Figure 1. Causal directed acyclic graph (DAG) depicting (A) confounding and (B) successful emulation of randomization using g-methods at baseline between the intervention strategy (X) and outcome (Y). Baseline covariates (both time-invariant [Z] and time-varying [L]) and previous diet and physical activity habits (P) must be considered to emulate randomization. Time-varying treatment and covariates are not shown in this DAG to focus on randomization emulation. Subscripts indicate the time points, where 0 represents baseline.

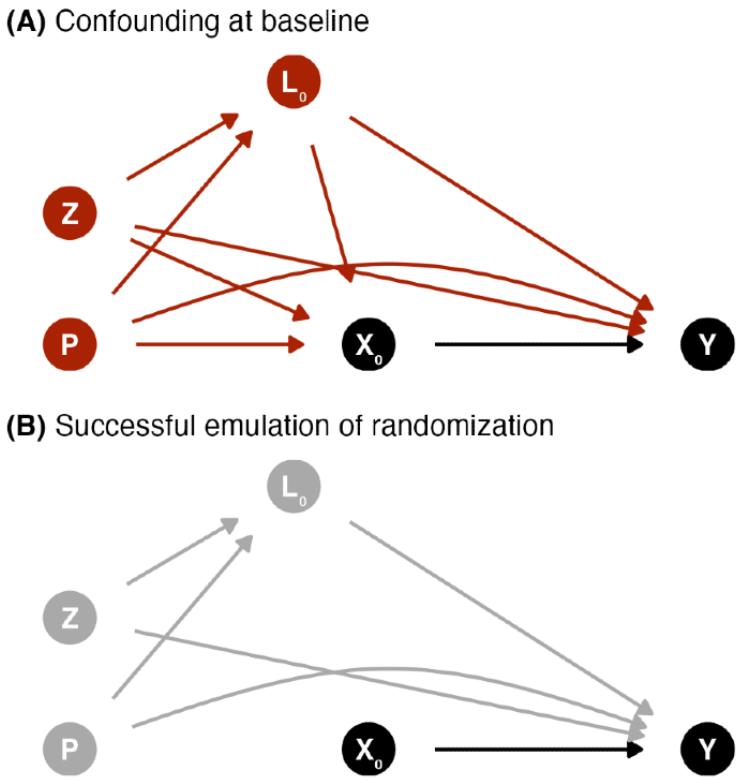

A successful emulation of randomization requires that there is no unmeasured confounding. However, this is never guaranteed with observational data. Thus, we emphasize our assumptions that (1) the causal graph accurately depicts the relationship under study and (2) the covariates included are a sufficient set of covariates to address confounding.

Outcomes

The primary outcomes will be the mean end of follow-up values for muscle strength (ie, handgrip using vigorimeter, elbow flexor, and knee extensor) and physical function (ie, normal and fast walking and "timed up-and-go"). Outcome values were measured according to a standardized protocol in NuAge [25].

For secondary outcomes, mean end of follow-up values for a set of relevant variables will be considered by domains:

- *General health:* waist circumference, blood pressure (systolic and diastolic), blood glucose, and estimated glomerular filtration rate
- *Cognition:* the modified Mini-Mental State Examination score

Time Zero and Follow-Up

In the target trial of a sustained lifestyle intervention, participants would be met at baseline and then regularly to ensure that diet and physical activity habits are consistent with the intervention assigned by the random allocation. The hypothetical diet and physical activity intervention would be assigned and initiated at baseline. In the emulation, annual follow-ups with comprehensive diet, physical activity, and covariate data collection are available to emulate the hypothetical intervention. Hence, participants would be followed from the study baseline (time point 0; ie, the time at which the intervention strategy would also be assigned and would begin), at each year (ie, time points 1 and 2), and until the end of the study (time point 3). We also assume that the diet and physical activity habits measured at each follow-up time adequately reflect the habits during the entire year.

The end of follow-up outcome measurements will be used to estimate the effect of the sustained lifestyle intervention strategy. Measures of dietary intake and physical activity throughout the study (ie, time point 0 to time point 3) will be used to emulate the sustained lifestyle intervention. Dietary intakes in the year preceding the intervention will be estimated using the frequency questionnaire completed at baseline (ie, time point 0). Missing covariate data at a given follow-up will be carried forward once, after which participants will be considered as having incomplete follow-up.

Causal Contrast

The estimand of interest in this study, the target causal effect of a sustained lifestyle intervention strategy, is

$$E(Y^{1,1,1,1}|C = 0) - E(Y^{0,0,0,0}|C = 0) \quad \textbf{(1)}$$

that is, the expected value of a given health outcome Y at the end of follow-up if all participants had increased their adherence to CFG recommendations on healthy food choices and physical activity, when applicable, at all 4 time points (X_k*=1, always intervene*) versus if all participants had maintained their habitual diet and physical activity (X_k*=0, never intervene*). The estimand

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(equation 1) also indicates that all participants completed the intervention (C=0), that is, in the absence of incomplete follow-up.

The causal contrasts of interest are the observational analogs of intention-to-treat and per-protocol analyses [11]. Given the observational design, participants are not expected to have followed a treatment strategy unknown to them at the time of data collection. Therefore, the primary analysis will be the per-protocol contrast of a sustained lifestyle intervention strategy. In the per-protocol analysis, nonadherence to the hypothetical interventions can be accounted for. In the target trial, participants with a condition after baseline that would have prevented or limited participation in a hypothetical lifestyle intervention would be allowed to discontinue the intervention (eg, lengthy hospitalization, prolonged bed rest, and incident cancer). In the emulation, if such conditions occur in a sufficiently large number of participants, these participants will be "excused" from following the hypothetical intervention [23]. In other words, participants who would have been unable to pursue the study due to major events will not be considered as having incomplete follow-up if they attended the annual assessment. Allowing participants to discontinue adhering to the hypothetical intervention strategy mitigates confounding by the disease burden [23].

The intention-to-treat analysis will be a secondary analysis of a hypothetical point intervention, for example, dietary counseling at baseline only. Notably, it will not be possible to conduct an intention-to-treat analysis identical to that of a controlled study where the interest is to estimate the effect of being *assigned* to an intervention [11]. However, it is possible to conduct an observational analog of the intention-to-treat analysis. In the observational analog, the intention-to-treat analysis aims to estimate the impact of a hypothetical intervention in which adherence is measured at baseline only.

Statistical Analysis

Modeling of Hypothetical interventions

Stratification and multivariable regression (ie, covariate adjustment) are conventional statistical approaches to address confounding in nutritional epidemiology. However, the conventional approaches are not adequate to estimate cumulative treatment effects (eg, diet over time) in the presence of time-varying confounding (eg, weight status over time) and treatment (eg, previous diet) [41,42]. In this study, nonadherence to the hypothetical interventions and incomplete follow-up will be considered using general g-methods for the per-protocol analysis [11,42]. Among g-methods, the parametric g-formula provides the most flexibility for analyses involving hypothetical dietary interventions, as used in previous studies [19,22,43]. Briefly, in the context of an observational study, the parametric g-formula and its implementation into an R package (R Foundation for Statistical Computing) [44] use parametric models to predict the joint history of previous diet and physical activity habits (ie, the hypothetical sustained intervention strategy) and confounding variables. For example, linear regression models are used to predict continuous covariates (eg, body weight), while logistic regressions are used to predict binary or categorical variables (eg, indicator variable for dietary supplement use). The per-protocol causal contrast of the hypothetical intervention presented in Table 2 is then emulated based on Monte Carlo simulated data generated using the g-formula algorithm [44]. The parametric g-formula correctly accounts for time-varying confounding in the presence of feedback between the intervention and the confounding variables, as confounding is addressed using standardization [41,42]. Furthermore, standardization allows for estimating an average causal effect (ie, marginal effect) consistent with the estimand of interest (equation 1) rather than a conditional effect. In summary, "threshold interventions" that depend on the reported dietary intakes or amount of physical activity [43,45] and the parametric g-formula [44,46] will be used to emulate the intervention of *consuming at least x servings of food* and *doing at least x minutes of light to vigorous physical activity.*

Figure 2 presents the causal directed acyclic graph (DAG) of the hypothesized relationship between a sustained lifestyle intervention strategy (X_0, X_1) and an end of follow-up outcome Y for 1 follow-up after baseline (year 1). The model is limited to year 1 for clarity, but the hypothesized causal structure extends to additional follow-ups. The exposure of interest X_k is the joint and cumulative effect of a sustained diet and physical activity intervention strategy measured at baseline and follow-ups.

In the context of this target trial emulation (Figure 2), P includes dietary habits before the baseline assessment. P can have an effect on baseline dietary habits (eg, previous healthy habits increase the likelihood of baseline healthy habits) and dietary habits throughout the target trial emulation (eg, previous healthy habits increase the likelihood of adhering to healthy habits). Furthermore, P influences baseline and time-varying confounding. Finally, given the long-term effect of chronic exposure, P potentially affects Y directly.

The intention-to-treat analysis is similar to the per-protocol analysis. However, only baseline diet and physical activity habits and covariates are considered, as well as prebaseline diet and physical activity. In both the per-protocol and intention-to-treat analyses, loss to follow-up (eg, nonresponse or missing follow-up and health outcomes not measured) will be accounted for using g-methods such as inverse probability weighting.

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Figure 2. Directed acyclic graph depicting the hypothesized relationship among previous dietary exposure, time-varying interventions (diet and physical activity), and covariates. Arrows from the Z node are not shown for clarity but would point toward all baseline and time-varying nodes, as well as the outcome. Only 1 follow-up is shown for visualization purposes, but the hypothesized causal structure extends to additional follow-ups. Subscripts indicate the time points, where 0 represents baseline and 1 represents time point 1.

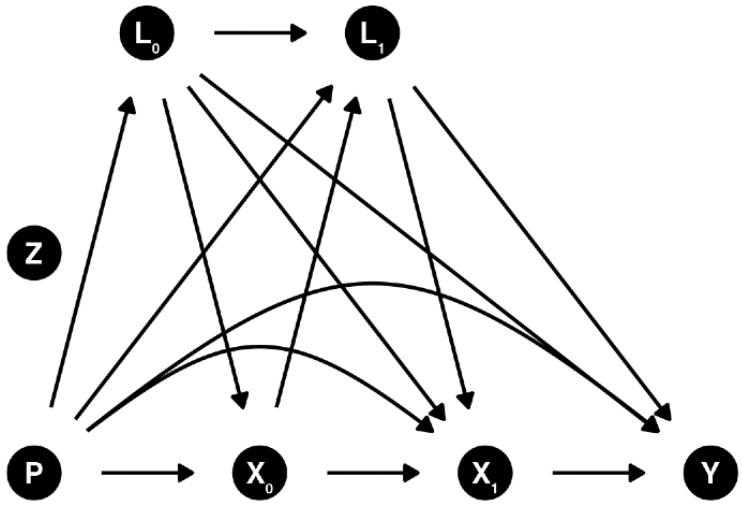

Dietary Assessment

In NuAge, diet during the year before baseline was assessed using 1 semiquantitative food-frequency questionnaire [47]. Dietary intakes at baseline (ie, time point 0) and each annual follow-up (ie, time points 1, 2, and 3) were assessed using 3 repeated face-to-face interviewer-administered 24-hour dietary recalls.

Dietary intakes measured using 24-hour dietary recall are more accurate (ie, have less systematic error or bias) than food-frequency questionnaire [48-50] but are particularly affected by random measurement error (ie, within-individual random error) [50]. When several variables measured with errors are considered simultaneously in a regression model, the regression coefficients may be biased in any direction [51]. To account for random measurement error, the National Cancer Institute Markov Chain Monte Carlo (NCI MCMC) multivariate method could be applied [52]. However, the combination of the parametric g-formula and multivariate measurement error correction using the NCI MCMC method is not feasible. The NCI MCMC method estimates time-invariant measurement error–corrected intakes, while the g-formula algorithm is designed for time-varying exposures.

Recognizing the importance of accounting for measurement error, the correction for measurement error will be reserved for the secondary intention-to-treat analysis. For the intention-to-treat contrast, the time-varying values of exposure and the time-varying values of confounding are not considered. Thus, the NCI MCMC method will be used to obtain measurement error–corrected estimates of the relationship between dietary intakes measured at baseline and outcome at the end of follow-up. Notably, the three 24-hour dietary recalls collected at each time point contribute to reducing random errors, at least to some extent, even in the absence of measurement error correction.

Sensitivity Analysis to Assess the Impact of Measurement Error

For the secondary intention-to-treat analysis, results based on the measurement error–corrected and –uncorrected dietary intakes will be compared. The difference between the estimated relationships will allow to extrapolate the impact of not accounting for random errors in the primary *per-protocol* analysis.

Physical Activity Assessment

Physical activity throughout the study will be assessed using the Physical Activity Scale for the Elderly questionnaire [53,54]. Rather than the total Physical Activity Scale for the Elderly score, specific questions estimating the total time of physical activities will be used to be consistent with the intervention strategy.

Covariates and Subgroups

To the extent permitted by the number of observations for each outcome, continuous covariates will be modeled using restricted cubic splines with 3 to 5 knots (at percentiles 10-50-90, 5-35-65-95, or 5-27.5-50-77.5-95) [55]. Categorical covariates will be modeled to ensure a sufficient sample size at each level.

The effect of dietary changes will be estimated for the entire sample. The sample will also be stratified by biological sex to reflect both potential biological differences and, to some extent, gender differences (although not reported).

Variance Estimation

The variance will be estimated using a minimum of 200 bootstrap sample replicates to consider uncertainty at each step of the estimation [56].

Software and Code

The main statistical analyses will be conducted using R software (version 4.3.1 or greater) and the *gfoRmula* package [44,57]. The manuscript results will be generated using Quarto markdown (Posit PBC). Codes for main analyses and generation

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of manuscript results will be shared in a publicly available code repository.

Ethical Considerations

The original NuAge protocol was approved by the research ethics boards of the *Institut universitaire de gériatrie de Montréal* and the *Institut universitaire de gériatrie de Sherbrooke* (Quebec, Canada). The NuAge Database and Biobank [58] has received approval by the *Centre intégré universitaire de santé et de services sociaux de l'Estrie—Centre hospitalier universitaire de Sherbrooke* Research Ethics Board. Secondary analyses of data from the NuAge Database and Biobank for the study described in this protocol are approved by the McGill University Research Ethics Board Office (#22-11-041).

All participants of NuAge provided informed consent. From the initial cohort of 1793 participants, 1753 (97.77%) agreed to the integration of their data and biological samples into the NuAge Database and Biobank for future studies.

Secondary analyses based on the NuAge Database and Biobank use deidentified data, which do not allow participants to be identified by the investigators.

NuAge participants voluntarily consented to participate and were not provided with monetary compensation.

Results

Data collection for NuAge was completed in June 2008. For this study, the main analysis based on the final curated data started in May 2024. The manuscript will be written according to the Strengthening the Reporting of Observational Studies in Epidemiology statement. We anticipate the submission of the manuscript to a peer-reviewed academic journal by February 2025.

Discussion

Principal Findings

In this study protocol, we have described a target trial to assess the effect of adhering to CFG recommendations on healthy food choices. The emulation will be performed using data from the NuAge Database and Biobank [58]. Benefiting from the flexibility of observational data, we also aim to compare adherence to multiple reformulations of CFG recommendations, including the effect of increasing the intake of protein-rich foods and the amount of aerobic physical activity on selected health outcomes. Furthermore, we have outlined the rationale for using simulated diets to emulate adherence to CFG recommendations, the process of selecting covariates to attempt to emulate randomization with causal diagrams, and the challenges of addressing random measurement error.

We emphasize that the purpose of emulating a target trial using observational data is to improve the quality of observational analysis [11,14]. In other words, the target trial framework aims to support the coherence between the causal research question and the observational data analysis [26]. However, estimating causal effects with nonexperimental observational data depends on strong assumptions. The key assumptions are that there are no unmeasured confounders, no measurement errors, and no model misspecifications (eg, functional form of covariates and model outcome distribution) [19]. We first recognize that the absence of residual or unmeasured confounding cannot be guaranteed. The extent to which this assumption is sufficiently satisfied depends on the appraisal of covariates considered. In that regard, we have used graphical tools, DAG, to explicitly describe our analytical assumptions and to identify confounding variables [59-61]. Second, the absence of measurement error assumption will not be satisfied considering the use of dietary intake data measured with 24-hour dietary recalls. On one hand, 24-hour dietary recalls have the least systematic error or bias compared with other common instruments, such as food-frequency questionnaires [48,49]. On the other hand, 24-hour dietary recalls are largely affected by within-individual random errors [50], which can cause bias in any direction in multivariable models [51], as in this study. This issue is mitigated, at least to some extent, by using average data from 3 repeated 24-hour dietary recalls at each follow-up. Sensitivity analyses comparing estimates based on measurement error–corrected and –uncorrected baseline dietary intakes will be used to assess the impact of random measurement errors. Third, the absence of model misspecification will be assessed by examining differences between the observed value of time-varying covariates and the predicted value of time-varying covariates as modeled with the g-formula.

Limitations

The strengths of this study and protocol include the explicit emulation of a hypothetical trial, the thorough description of the emulation of the sustained dietary intervention, and the use of background knowledge and DAG to derive a sufficient set of confounders. Limitations must be addressed. First, the NuAge sample size is relatively limited (N=1753), although comprehensive nutrition and covariate data were collected. Second, the target food intakes based on diet simulations from Health Canada *exceeded* the 99th percentile of the usual intake distribution of Canadians aged ≥65 years from Canada in 2015 [3]. A revision of the dietary intervention targets may be needed if observed dietary intakes in NuAge deviate significantly from targets (Table 2), as was done in a previous nutrition target trial emulation [22]. Third, the presence of random measurement error associated with 24-hour dietary recalls may bias estimates. Finally, the target trial emulation cannot replace an actual RCT. Evidence from an RCT will be required to confirm the value of either CFG recommendations or the enhanced CFG recommendations.

Conclusions

In conclusion, the target trial framework is useful for estimating the causal effect of adhering to CFG recommendations using nonexperimental data when an RCT is impractical [11,19]. Coupled with key assumptions, including the absence of unmeasured confounding, the absence of measurement error, and no model misspecification, we believe that the emulation will provide timely evidence regarding the effect of adhering to CFG recommendations in older adults and inform on the added value of a reformulation.

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Acknowledgments

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Data Availability

The datasets analyzed during this study are available in the GitHub repository [62].

Authors' Contributions

The study was conceptualized by all authors. DB and SC were involved in the methodology. DB was involved in data curation, formal analysis, visualization, and writing of the original draft, and SC supervised the study. All authors reviewed and edited the paper.

Conflicts of Interest

DB was a casual employee of Health Canada (2019 to 2020) and held a doctoral training award from the Fonds de recherche du Québec - Santé (2019 to 2021). DB has no conflicts of interest. SC receives research funding from the Canadian Institutes of Health Research, Fonds de recherche du Québec, Canadian Foundation for Dietetics Research, Canadian Foundation for Innovation, and Canadian Cancer Society. None of these agencies has funded or been involved in this study. NP is the NuAge database administrator; NP and SC serve as NuAge steering committee members. NuAge was supported by a research grant from the Canadian Institutes of Health Research (MOP-62842). The NuAge Database and Biobank is supported by the Fonds de recherche du Québec (2020-VICO-279753); the Quebec Network for Research on Aging, a thematic network funded by the Fonds de recherche du Québec - Santé; and the Merck-Frosst Chair funded by La Fondation de l'Université de Sherbrooke.

Multimedia Appendix 1
Healthy Eating Food Index-2019 dietary constituents and score among simulated diets by Health Canada, by age and sex group. [DOCX File , 20 KB - resprot_v14i1e65182_app1.docx]

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Abbreviations

CFG: Canada's Food Guide
DAG: directed acyclic graph
HEFI: Healthy Eating Food Index
NCI MCMC: National Cancer Institute Markov Chain Monte Carlo
NuAge: Quebec Longitudinal Study on Nutrition and Successful Aging
RA: reference amount
RCT: randomized controlled trial

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Protocol

Clozapine for Treatment-Resistant Disruptive Behaviors in Youths With Autism Spectrum Disorder Aged 10-17 Years: Protocol for an Open-Label Trial

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Abstract

Background: Autism Spectrum Disorder (ASD) is a complex neurodevelopmental condition emerging in early childhood, characterized by core features such as sociocommunicative deficits and repetitive, rigid behaviors, interests, and activities. In addition to these, disruptive behaviors (DB), including aggression, self-injury, and severe tantrums, are frequently observed in pediatric patients with ASD. The atypical antipsychotics risperidone and aripiprazole, currently the only Food and Drug Administration–approved treatments for severe DB in patients with ASD, often encounter therapeutic failure or intolerance. Given this, exploring pharmacological alternatives for more effective management of DB associated with ASD is essential. Clozapine, noted for its unique antiaggressive effects in schizophrenia and in various treatment-resistant neuropsychiatric disorders, independent from its antipsychotic efficacy, remains underexplored in youths with ASD facing severe and persistent DB.

Objective: This study aimed to evaluate the efficacy, tolerability, and safety of clozapine for treatment-resistant DB in youths with ASD.

Methods: This is a prospective, single-center, noncontrolled, open-label trial. After a cross-titration phase, 31 patients with ASD aged 10-17 years and with treatment-resistant DB received a flexible dosage regimen of clozapine (up to 600 mg/day) for 12 weeks. Standardized instruments were applied before, during, and after the treatment, and rigorous clinical monitoring was performed weekly. The primary outcome was assessed using the Irritability Subscale of the Aberrant Behavior Checklist. Other

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efficacy measures include the Clinical Global Impression Severity and Improvement, the Swanson, Nolan, and Pelham questionnaire-IV, the Childhood Autism Rating Scale, and the Vineland Adaptive Behavior Scale. Safety and tolerability measures comprised adverse events, vital signs, electrocardiography, laboratory tests, physical measurements, and extrapyramidal symptoms with the Simpsons-Angus Scale. Statistical analysis will include chi-square tests with Monte Carlo simulation for categorical variables, paired *t* tests or Wilcoxon tests for continuous variables, and multivariate linear mixed models to evaluate the primary outcome, adjusting for confounders.

Results: Recruitment commenced in February 2023. Data collection was concluded by April 2024, with analysis ongoing. This article presents the protocol of the initially planned study to provide a detailed methodological description. The results of this trial will be published in a future paper.

Conclusions: The urgent need for effective pharmacological therapies in mitigating treatment-resistant DB in pediatric patients with ASD underscores the importance of this research. Our study represents the first open-label trial to explore the anti-aggressive effects of clozapine in this specific demographic, marking a pioneering step in clinical investigation. Adopting a pragmatic approach, this trial protocol aims to mirror real-world clinical settings, thereby enhancing the applicability and relevance of our findings. The preliminary nature of future results from this research has the potential to pave the way for more robust studies and emphasize the need for continued innovation in ASD treatment.

Trial Registration: Brazilian Clinical Trials Registry RBR-54j3726; https://ensaiosclinicos.gov.br/rg/RBR-54j3726

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KEYWORDS

neurodevelopmental disorders; clozapine; psychopharmacology; antipsychotic medication; autism spectrum disorder; youth

Introduction

The autism spectrum disorder (ASD) comprises a continuum of neurodevelopmental disorders that manifest in early childhood [1], characterized by impaired communication and social interaction, restricted and repetitive behavioral patterns, and occasionally impaired cognition or verbal language [2]. In the United States, the prevalence of ASD in 8-year-old children is 27.6/1000 (1 in 36 children) and 3.8-fold higher in boys than girls [3]. The diagnosis of ASD is an integrative process that includes the collection of current and developmental histories, direct observation, and clinical evaluation. Various standardized instruments may also support and substantiate the diagnosis [1]. Patients with ASD frequently present comorbid psychiatric conditions including, but not limited to, obsessive-compulsive disorder, intellectual disability, oppositional defiant disorder, mood and anxiety disorders, sleep disturbances, eating disorders, and attention-deficit/hyperactivity disorder [4].

The management of ASD involves a multidisciplinary approach, using behavioral and educational strategies to improve the patient's quality of life and promote independence. First-line behavioral treatments comprise applied behavior analysis, cognitive behavioral therapy, and social skills training [5]. While pharmacological treatments do not directly address the core symptoms of ASD, they are used to manage psychiatric comorbidities and severe disruptive behaviors (DB) associated with autism (ie, irritability, hetero-aggression, self-injury, tantrums, and severe oppositional defiant symptoms) [6]. DB are common and can be observed in up to 1/4 of children with ASD [7]. Thus, pharmacotherapy can be pivotal in protecting the physical well-being of both autistic individuals and their caregivers, mitigating social exclusion, and enhancing overall quality of life [8]. The atypical antipsychotics risperidone and aripiprazole are the only drugs approved by the United States Food and Drug Administration for the treatment of irritability associated with ASD, and they are commonly used to treat DB in this population [9]. However, many patients do not respond adequately: approximately 30% of patients fail to respond to risperidone and 50% to aripiprazole [10].

It is essential to highlight that there are other psychosocial therapeutic resources (eg, behavioral therapies) and pharmacological treatments (eg, antidepressants and mood stabilizers) for managing DB. However, some patients, with a pronounced treatment resistance to these approaches, require the use of antipsychotics for the management of more severe symptoms. For those who do not respond adequately to the antipsychotics commonly used in clinical practice, clozapine emerges as a "last-resort" therapeutic alternative, as these patients still demand alternatives.

Clozapine, the first atypical antipsychotic developed, is the treatment of choice for treatment-resistant early-onset schizophrenia (EOS) and is noted for its anti-aggressive effects across several mental disorders [11]. Observational studies have also demonstrated its benefits in reducing treatment-resistant DB in ASD [12]. For instance, Beherec et al [13] analyzed medical records of 6 patients with ASD with refractory DB receiving clozapine, noting a reduction in the number of days with aggressive episodes and concomitant antipsychotic dosing. In addition, Rothärmel et al [14] reported maintained long-term benefits and favorable tolerability in their initial 6-patient cohorts. They corroborated these findings with a replication study involving an additional sample of 13 patients who exhibited a significant reduction in DB (65.2%, P=.003), leading to improved quality of life.

Clozapine therapy requires caution and rigorous monitoring during treatment due to its potential health risks, which include severe neutropenia [15], myocarditis [16], and seizures [17]. However, for some children and adolescents with ASD, the

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balance of risks and benefits is favorable, particularly when intense and treatment-resistant aggression leads to significant impairments [18]. Although preliminary and exploratory studies showed positive results, no prospective interventional studies with objective measures investigated the efficacy and tolerability of clozapine for treatment-resistant DB in pediatric patients with ASD, highlighting the need to explore it as a potential treatment for this subset of patients.

In this sense, this study aims to evaluate the efficacy, tolerability, and safety of clozapine in treating patients with ASD aged 10 to 17 years with DB resistance or intolerance to conventional antipsychotics. In addition, the study evaluates changes in adaptive functioning among patients and the impact of clozapine on caregivers' quality of life. Drawing on prior evidence regarding clozapine's specific anti-aggressive effects, this study explores its potential as a viable treatment for intractable cases. Accordingly, the hypothesis is that clozapine will prove efficacious and tolerable, with a safety profile acceptable for this clinical population. This article outlines the study protocol, which was initially drafted before the study's completion. Recruitment began in February 2023, and data collection concluded in April 2024. This protocol is now published to provide a comprehensive methodological description. Trial results will be reported in a future publication.

Methods

Study Design

This open-label, noncontrolled trial administers clozapine to all participants. The rationale for this study design, instead of a randomized controlled investigation, was based on the logistical and ethical challenges inherent in conducting a study within a pediatric ASD subpopulation characterized by refractoriness and severe DB. The study's framework facilitates direct observation of adverse events and potentially severe risks related to clozapine use in vulnerable patients. Independent evaluators carry out baseline and follow-up assessments.

Participants

The estimated sample consists of 30 patients aged 10 to 17 years who have been diagnosed with ASD and exhibit treatment-resistant DB.

Eligibility

Inclusion Criteria

This study includes patients of both sexes aged between 10 and 17 years with a confirmed diagnosis of ASD according to the *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) [19] criteria. Also, they must present DB (eg, psychomotor agitation, angry outbursts, oppositional defiant behavior, property destruction, self-injury behavior, or hetero-aggression) that are not caused by a coexisting medical or psychiatric condition, which could act as a trigger for the onset of these symptoms. Individuals must exhibit severe symptoms, impairing different function domains, reflected by a score of 5 or higher (markedly ill) on the Clinical Global Impression-Severity (CGI-S) scale, specifically anchored to DB. Treatment resistance, as defined by the research team, refers to the continued presence of severe DB despite adequate treatment (therapeutic failure) or intolerance to at least 2 antipsychotic agents, with at least 1 being atypical.

Exclusion Criteria

Patients who present the following conditions are excluded: unstable clinical illness or condition preventing the use of clozapine (eg, refractory epilepsy and heart or hematological diseases); insufficient psychosocial resources to follow the study protocol strictly (eg, correct drug administration and weekly attendance to the research center for clinical evaluations and blood testing); previous failure to clozapine treatment due to inadequate response after sufficient duration and dosing (a minimum of 400 mg/day for 6 weeks) or due to intolerable adverse events, such as leukopenia or cardiotoxicity; or pregnant, breastfeeding, or fertile patients not using an adequate contraceptive method.

Recruitment

Our protocol uses a convenience sampling strategy. The study is disclosed in services for university hospitals, integral health of childhood and adolescence, and specialized assistance services for patients with neurodevelopmental disorders through informative material prepared by our research team, inviting patients, who meet the criteria for our study, to participate. Furthermore, we contact child and adolescent psychiatry outpatient clinics, special education institutes and ASD support groups in the metropolitan region of Porto Alegre in the state of Rio Grande do Sul (Brazil), disseminating our research and asking them to refer patients who could benefit from the intervention. It is also disclosed using traditional media (television, newspaper, and radio) and the Hospital de Clínicas de Porto Alegre (HCPA) social media website and institutional email. Legal guardians who intend to participate in the study contact the research team by phone or email.

Screening

Caregivers interested in participating are invited to a screening assessment with a child and adolescent psychiatrist experienced in ASD to determine the patient's eligibility for the study. During the evaluation, the psychiatrists verify the ASD diagnosis according to *DSM-5* criteria [19] and with the support of the Childhood Autism Rating Scale, Brazilian version (CARS-BR) [20]. Clinical features on the presence of severe DB and psychopharmacological treatment history are assessed. The research team informs caregivers about the study's objectives, procedures, potential benefits, and risks associated with clozapine therapy, including side effects, and the mandatory requirement for weekly blood tests. Selected patients undergo a baseline evaluation, which includes data collection, laboratory tests, an electrocardiogram, and a physical examination. The psychiatrist confirms cardiometabolic and hematological stability as part of this initial assessment.

Measures of Evaluation

Trained evaluators apply the following questionnaires and instruments before, during, and after the intervention:

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Baseline Sociodemographic and Clinical Data

Data on age, sex, ethnicity, education level, socioeconomic status, clinical, and therapeutical history (eg, comorbidities, previous interventions, gestational and neonatal history, neurodevelopmental milestones, ASD diagnosis and support level, characteristics of DB, family psychiatric history, and response to previous and ongoing pharmacological treatments) are collected at the beginning of the study.

The CARS-BR

This scale comprises 14 items that help diagnose ASD in children and differentiate it from other developmental disorders [20]. It is fast to apply, suitable for all ages, and has objective and quantifiable scores through direct observation. The CARS-BR is used before and during the intervention to evaluate the central symptoms of ASD.

Schedule for Affective Disorders and Schizophrenia for School-Age Children–Present and Lifetime Version, DSM-5 Update

This semistructured interview evaluates the presence and severity of psychiatric disorders in children and adolescents in the present and throughout life [21]. In this study, it is used to assess psychiatric comorbidities.

CGI-S and Clinical Global Impression-Improvement

The Clinical Global Impression Severity (CGI-S) scale evaluates the global severity of the patient at baseline through an increasing score (1 to 7) considering the last 7 days [22]. The patient must score ≥ 5 (markedly ill) to meet the inclusion criteria. Also, the Clinical Global Impression–Improvement (CGI-I) compares the level of improvement or impairment of the patient every week after starting the pharmacological treatment through a score ranging from 1 (very much improved since the initiation of treatment) to 7 (very much worse since the initiation of treatment).

Aberrant Behavior Checklist, Irritability Subscale

Irritability is 1 of the 5 Aberrant Behavior Checklist (ABC) subscales with 15 items; it is easy to use and reliable [23]. This subscale is widely used in clinical trials to evaluate the efficacy of pharmacological treatments for irritability and DB in ASD, assessing several DB and changes over time. The ABC, Irritability (ABC-I) score change following clozapine treatment is the primary outcome of this open-label trial.

The Swanson, Nolan, and Pelham Questionnaire, Version IV

This questionnaire has 26 items to evaluate inattention, hyperactivity, impulsivity, and oppositional defiant behavior and is a complementary instrument to diagnose attention-deficit/hyperactivity disorder [24]. Our protocol uses this tool for additional assessment of DB.

Vineland Adaptive Behavior Scales, Third Edition

The Vineland Adaptive Behavior Scale, Third Edition (VABS-3) is a semistructured interview to evaluate adaptive behaviors divided into domains, such as communication (receptive, expressive, and written), daily living skills (personal, domestic, and community), socialization (interpersonal relationships, play and leisure, and coping skills), motor skills (gross, fine, and advanced motor coordination), and maladaptive behavior (internalizing, externalizing, and critical items) [25]. In our protocol, this tool evaluates how clozapine treatment impacts patients' adaptive behaviors.

Side Effects Questionnaire Based on the Ugvalg for Kliniske Undergelser Side Effect Rating Scale for Psychotropic Drugs

The Ugvalg for Kliniske Undergelser Side Effect Rating Scale for Psychotropic Drugs (UKU) scale is divided into 4 sections, with 48 items evaluating the physical, psychological, neurological, and autonomic side effects of psychotropic drugs [26]. Each item is scored from 0 to 3, reflecting the intensity of the side effects. The scale has been specifically adapted for this study to monitor clozapine's side effects comprehensively.

Simpsons-Angus Scale for Extrapyramidal Side Effects

This widely used scale consists of 10 items that evaluate the presence and severity of extrapyramidal side effects [27]. Each item is rated on a scale from 0 to 4, and the total score is obtained by summing the items and dividing them by 10, with scores up to 0.3 considered within the normal range. The Simpsons-Angus Scale for Extrapyramidal Side Effects (SAS) is a standard tool for evaluating drug-induced movement disorders.

Europe Health Interview Surveys Quality of Life, Abbreviated Instrument

The Europe Health Interview Surveys Quality of Life, Abbreviated Instrument (EUROHIS-QOL 8-item) assesses the quality of life across 4 domains, with 2 items per domain: physical, psychological, environmental, and social [28]. This study uses it to evaluate the caregivers' quality of life, thus monitoring the potential effects of clozapine treatment on this aspect.

Intervention

Throughout the study, a team of child and adolescent psychiatrists skilled in managing clozapine undertakes weekly evaluations of patients at the research facility. Out of 2 different evaluators assesses each patient. The first evaluator conducts the baseline assessment, and the second evaluator conducts all subsequent evaluations while following the same patient throughout the study protocol. This includes monitoring the therapeutic response of clozapine and managing any associated adverse effects. In addition, evaluators receive training to apply the evaluation measures accurately. Patients with significant medical comorbidities undergo specialist physician evaluation to confirm clinical suitability for the study. Eligible patients are prescribed clozapine therapy through a flexible titration regimen. Dose adjustments are made gradually over weeks to achieve a personalized dose. Implementing CGI scales during the titration phase facilitates the determination of an individualized fixed dose for each patient. Once the dosing has been stabilized, the clozapine intervention spans 12 weeks, during which the dose should remain constant. However, if necessary, minor changes may be made to ensure optimal patient outcomes. Blood tests

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follows the schedule outlined in Table 1. In addition, physical evaluations, including measurements of blood pressure, heart rate, abdominal and pelvic circumferences, weight, and BMI, are carried out weekly.

Table 1. Study timeline and measures of evaluation. From the beginning of the intervention to a stable clozapine dose, the titration duration varies to determine the most appropriate therapeutic dose for each individual patient.

	Baseline	DP[a]	V1[b]	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12
Physical evaluation[c]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CBC[d]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Monitoring of severe adverse events	N/A[e]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Adverse events[f]	N/A	✓	✓	N/A	N/A	✓	N/A	✓	N/A	N/A	✓	N/A	N/A	✓
CGI-S[g]	✓	✓	✓	N/A	N/A	N/A	N/A	✓	N/A	N/A	N/A	N/A	N/A	✓
CGI-I[h]	N/A	✓	✓	N/A	N/A	N/A	N/A	✓	N/A	N/A	N/A	N/A	N/A	✓
Metabolic panel[i]	✓	N/A	✓	N/A	N/A	N/A	N/A	✓	N/A	N/A	N/A	N/A	N/A	✓
ABC-I[j], CARS-BR[k], and SNAP-IV[l]	✓	N/A	✓	N/A	N/A	N/A	N/A	✓	N/A	N/A	N/A	N/A	N/A	✓
VABS-3[m]	✓	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	✓
EUROHIS-QOL 8-item[n]	✓	N/A	✓	N/A	N/A	N/A	N/A	✓	N/A	N/A	N/A	N/A	N/A	✓
ECG[o]	✓	N/A	✓	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
K-SADS-PL[p]	✓	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
AST[q], ALT[r]	✓	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A

[a]aDP: Dose progression with a flexible titration schedule to reach a stable clozapine dose for each patient.

[b]V: visit.

[c]Weight, height, BMI, blood pressure, heart rate, and abdominal and pelvic circumference.

[d]CBC: Complete blood count.

[e]N/A: not applicable.

[f]Application of the Simpson-Angus Scale for extrapyramidal side effects and side effects questionnaire based on the Ugvalg for Kliniske Undergelser side effect rating scale for psychotropic drugs.

[g]CGI-S: Clinical Global Impression-Severity.

[h]CGI-I: Clinical Global Impression--Improvement.

[i]Fasting blood glucose, total cholesterol, high- and low-density lipoprotein, and triglycerides.

[j]ABC-I: Aberrant Behavior Checklist, Irritability Subscale.

[k]CARS-BR: Childhood Autism Rating Scale–Brazilian version.

[l]SNAP-IV: Swanson, Nolan, and Pelham questionnaire, version IV.

[m]VABS-3: Vineland Adaptive Behavior Scales-third edition.

[n]EUROHIS-QOL8: Europe Health Interview Surveys Quality of Life Abbreviated Instrument.

[o]ECG: electrocardiogram.

[p]K-SADS-PL: Schedule for Affective Disorders and Schizophrenia for School-age Children, present and lifetime version.

[q]AST: aspartate aminotransferase.

[r]ALT: alanine aminotransferase.

The initial dose of clozapine is 12.5 mg or 25 mg, divided into once or twice-daily doses. The starting dose of clozapine will be determined using an initial dose reference of approximately 0.3 mg/kg, rounded to the nearest multiple of 6.25 mg, with a maximum initial dose not exceeding 25 mg daily. Dose titration is tailored to the patient's response and tolerability, up to 600 mg daily. Clinical management of clozapine considers individual conditions and comorbidities. The therapeutic range for most patients is expected to be between 200 and 400 mg/day. After the clozapine dosage reaches 100 to 200 mg per day, gradual discontinuation of other antipsychotics commences using plateau cross-titration. While the study does not mandate clozapine monotherapy, it aims the reduction of other psychotropics, particularly antipsychotics.

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Clinical Monitoring and Adverse Event Management

Patients and caregivers receive educational materials on clozapine treatment and psychoeducational guidance from psychiatrists. Also, they can contact the researchers via phone in case of emergency symptoms (eg, fever, flu-like symptoms, sore throat, dyspnea, chest pain, and seizures). Caregivers are instructed to search for emergency services in case of severe symptomatology. Moreover, the team of psychiatrists is available to other physicians as required.

The study follows guidelines for clozapine treatment in EOS [29]. During all visits, psychiatrists proactively manage side effects to alleviate patients' discomfort and optimize treatment adherence. If needed, side effects are treated symptomatically. Also, a consultant pediatrician and other specialists may be consulted whenever required. Advice on diet control and exercise is emphasized, and metformin may be used to mitigate weight gain and metabolic abnormalities from the beginning of treatment [30]. Prophylactic measures must be discussed with all caregivers to prevent constipation, and early prescription of stool softeners (ie, polyethylene glycol) might be used to avoid obstruction and ileus [31].

An electrocardiogram is performed before and after the clozapine treatment to assess the pharmacological impact on cardiac electric activity. Also, blood testing is performed before and during the treatment to monitor the risk of blood dyscrasias. To start clozapine therapy, patients must display the following hematological criteria: neutrophil >1500/µL and leukocyte >3000/µL [32]. Lithium carbonate may be prescribed to increase the neutrophil count in case of benign neutropenia [33], and the clozapine treatment must be suspended if neutrophil reduces under 1000/µL. Metabolic parameters (eg, fasting glucose, triglycerides, and cholesterol).

Data Collection and Management

Initial data is collected upon obtaining caregiver consent and confirming patient eligibility. Subsequently, qualified patients commence with clozapine therapy, marking the beginning of the treatment study and systematic clinical data acquisition. Measures of evaluation are applied as delineated in Table 1. Per the methodology of our study, we make provisions for remote consultations through video call using Google Meet, but only in exceptional circumstances in which patients cannot attend the research center personally. It is important to note that all participants must strictly adhere to the protocol of weekly blood sample collections, regardless of the consultation modality.

All evaluations are registered in HCPA's electronic medical record system, and data is collected and managed using the Research Electronic Data Capture (REDCap) hosted at the HCPA. REDCap [34,35] is a secure web-based software to support data capture for research studies. It provides an intuitive interface for validated data capture, audit trails for tracking manipulations and data export, automated export procedures for continuous data downloads in common statistical packages, and procedures for data integration and interoperability with external sources.

Outcome Measures

The study will assess the efficacy of clozapine in reducing DB, as measured by ABC-I scores. Secondary measures include the CGI-S and Clinical Global Impression Improvement scales, ASD symptoms (CARS-BR), adaptive behaviors (Vineland Adaptive Behavior Scale - third edition), hyperactivity, impulsivity, and oppositional defiant behaviors (the Swanson, Nolan, and Pelham questionnaire), and quality of life of caregivers (EUROHIS-QOL 8-item). The safety and tolerability of the treatment are evaluated using an adverse effects inventory, the SAS, physical evaluation parameters, and blood testing (Table 1).

Statistical Analysis

Overview

Qualitative variables will be presented as absolute and relative frequencies, and quantitative as mean and SD or median and IQR, as appropriate. The distribution of quantitative variables will be assessed using the histogram and quantile-quantile graph. Categorical variables will be compared using the chi-square test of independence with Monte Carlo simulation (when any cell in the contingency table presents an expected frequency < 5), and continuous variables before and after treatment will be compared using the paired *t* test or Wilcoxon signed rank test. The multivariate linear mixed model will assess the primary outcome to reduce possible confounding variables. The magnitude and direction of the association for quantitative secondary outcomes will be evaluated using the robust Poisson regression for binary variables and the generalized linear model for gamma-distributed variables. Multiple comparisons will be performed using the Bonferroni post hoc when needed. The significance level of 5% will be adopted for all analyses, which will be assessed using the PASW [Norman H. Nie] Statistics software (version 18.0 or higher) [36] and R [R Core Team] (version 4.3 or higher) [37].

Sample Size Calculation

The sample size was calculated to detect a reduction in the ABC-I score using the PSS Health tool (version 0.3.1) based on a relevant mean difference of 10 points [38]. Given a power of 99%, a significance level of 1%, and a SD of the expected difference of 9.7 [39], the calculation yielded a required sample size of 27 patients. Anticipating a 10% attrition due to losses and refusals, the sample size was adjusted to include 30 patients. Considering the vulnerable population and the demanding protocol, an over-enrollment strategy can be used to mitigate the impact of potential attrition further and ensure robustness.

Ethical Considerations

This study fully complies with the Regulatory Standards and Guidelines for Research with Human Beings (Resolution 466/12) and upholds the ethical principles of the Declaration of Helsinki. Informed consent is obtained from legal guardians, who may choose to withdraw the patient from the study at any time without consequences. Whenever possible, patient assent is sought. In cases where it is not feasible, the legal guardian decides on the patient's behalf. The study has received approval from the Research Ethics Committee of Hospital de Clínicas de Porto Alegre (CAAE 54677821.0.0000.5327), and its

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protocol is registered in the Brazilian Registry of Clinical Trials (RBR-54j3726). The research team continuously supports the patients and their caregivers throughout the study, especially regarding the emergence of alert signs associated with clozapine use. The Brazilian pharmaceutical company Cristália supplied the clozapine (Pinazan) for the participants. However, the company does not influence the study design, intervention, data analysis, or publication of the results. This ensures that the research team can make independent decisions.

Results

Recruitment for the study commenced on February 10, 2023. A total of 33 patients were initially enrolled in the study. However, before the commencement of the intervention, 2 patients were withdrawn from the study due to their guardians' decision not to participate further, and 3 patients discontinued treatment due to adverse events. Data collection was completed by April 2024. No primary or secondary outcomes are being reported in this manuscript, as it focuses solely on describing the study design and methods. The results of the study are expected to be published by June 2025.

Discussion

It is anticipated that clozapine will demonstrate efficacy in reducing DB resistant to conventional treatments in youths with ASD. In addition, we expect to observe an acceptable safety profile by using rigorous monitoring in a pragmatic outpatient setting. In our view, this is the first quasi-experimental study to investigate the use of clozapine for this specific purpose and population. We foresee that our findings will align with several observational studies that have also highlighted clozapine as a valuable tool in similar cases.

Clozapine is recognized as a potential therapeutic alternative for addressing refractory aggressive behaviors in various neuropsychiatric disorders [12]. This study will explore the possibility that clozapine use may also extend to alleviating severe DB in children and adolescents with ASD. Regarding clozapine use to reduce aggression in young patients, a prospective open-label study showed a significant reduction of aggressive behavior in children and adolescents with treatment-resistant EOS during clozapine treatment for 12 to 24 weeks, reducing the need for emergency drugs and isolation [40]. In addition, observational studies suggested the efficacy of clozapine in patients with ASD and severe DB not responsive to conventional treatments [11,13,14]. However, only a small-scale, prospective intervention study explored the potential of clozapine in 3 children with ASD. In this study, Zuddas et al [41] evaluated 2 boys (8 years old) and 1 girl (12 years old) with DB resistant to haloperidol before and after the clozapine treatment. All children improved over 3 months, with a reduction in the Children's Psychiatric Rating Scale scores from 99 to 60, 99 to 80, and 81 to 53. Although the boys demonstrated gradual improvement until 8-month follow-up (from 60 to 50 and 80 to 53), the girl had a complete relapse of symptoms after 5 months, with similar scores to baseline [41].

Considering that other studies examining the role of clozapine in ASD with treatment-resistant DB have maintained an observational design, prospective clinical studies with objective metrics and larger samples are needed to evaluate its efficacy. Thus, the present study aims to investigate the efficacy of clozapine in mitigating treatment-resistant DB in pediatric patients with ASD. The treatment of DB in ASD may improve adaptive behavior, which could favor the development of socialization, communication, cognition, daily activities, and the quality of life of patients and caregivers [8,42]. Also, behavioral improvement and clinical stabilization could allow patients to engage in other therapeutic modalities or actively participate in community activities or programs.

This study's assessment of clozapine safety and tolerability in the pediatric ASD population is essential, particularly as these factors have been understudied in this group, unlike in patients with EOS [43]. A recent naturalistic study on clozapine in youth with neurodevelopmental disorders (ASD and/or ID) and treatment-resistant aggression showed significant improvements in clinical severity, functioning, and aberrant behaviors. Of the 26 patients, 61.5% were responders. Common side effects included increased appetite, sialorrhea, and repetitive behaviors, with 2 cases of seizures. This study supports clozapine's potential in managing aggression in this population [44]. In contrast to the recently published study, our approach adopts a more interventional design. We also emphasize early detection and management of clozapine-induced side effects and serious adverse events. This includes intensive clinical monitoring through weekly evaluations by child and adolescent psychiatry specialists, pediatric support, regular laboratory tests, and close collaboration between doctors and caregivers. Furthermore, our study will evaluate the acceptability of clozapine outpatient treatment in this population, with a particular focus on adherence, considering the drug's complex side effect profile, the frequency of required medical visits and blood tests, and the level of caregiver involvement. This approach aims to assess a practical framework for real-world clinical practice.

Regarding the limitations, the study features a small sample size and an uncontrolled open-label design, which introduces the possibility of biases, such as expectancy bias from both families and investigators. Nevertheless, this study constitutes an important initial step in clinical investigation, laying the groundwork for future controlled clinical trials with larger sample sizes. Furthermore, follow-up studies are necessary to evaluate the long-term efficacy and safety of clozapine.

Our dissemination plan involves publishing the results of this open-label trial in a high-impact international scientific journal, with the aim of providing evidence for the potential efficacy and safety of clozapine in managing DB in youths with ASD. Following this open-label clinical trial, our research team will conduct a longitudinal follow-up study with the same cohort to assess the sustained efficacy and safety of clozapine. In addition, a qualitative study is proposed to examine the caregivers' experiences with clozapine therapy. Therefore, this trial is envisaged as a foundational step informing subsequent research endeavors.

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Data Availability

The dataset collected and examined in this study will be accessible through the lead author upon adequate request.

Authors' Contributions

ALST and MRBC collaborated on the conceptualization of the initial protocol, with GS, FM, LOC, EBB, LD, and ABF contributing to writing the original draft of the manuscript. RBB was responsible for formal analysis. The final writing with review and editing of the text was performed by ALST and OSB, with FM and GS handling the visualization of the manuscript. ASGM and LAR were responsible for supervision on all steps of the study design and manuscript editing.

Conflicts of Interest

LAR has received grant or research support and served as a consultant to the bureau of the speakers from Abbott, Adium, Apsen, Abdi-Ibrahim, Aché, Bial, Medice, Novartis/Sandoz, Upjohn/Viatris, and Shire/Takeda in the last 3 years. The ADHD and Juvenile Bipolar Disorder Outpatient Programs chaired by LAR have received unrestricted educational and research support from the following pharmaceutical companies in the last 3 years: Novartis/Sandoz and Shire/Takeda. LAR has received authorship royalties from the Oxford Press and ArtMed. Other authors declare no conflicts of interest.

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Abbreviations

ABC: Aberrant Behavior Checklist
ABC-I: Aberrant Behavior Checklist, Irritability Subscale
ASD: autism spectrum disorder
CARS-BR: CARS-BR: Childhood Autism Rating Scale, Brazilian version
CGI-I: Clinical Global Impression-Improvement
CGI-S: Clinical Global Impression-Severity
DB: disruptive behavior
DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)
EOS: early-onset schizophrenia
EUROHIS-QOL8: Europe Health Interview Surveys Quality of Life, Abbreviated Instrument
HCPA: Hospital de Clínicas de Porto Alegre
REDCap: Research Electronic Data Capture
SAS: Simpsons-Angus Scale
UKU: Ugvalg for Kliniske Undergelser Side Effect Rating Scale for Psychotropic Drugs
VABS-3: Vineland Adaptive Behavior Scale - third edition

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Protocol

Evaluating the Benefit of Home Support Provider Services for Positive Airway Pressure Therapy in Patients With Obstructive Sleep Apnea: Protocol for an Ambispective International Real-World Study

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Abstract

Background: Adherence and persistence to positive airway pressure (PAP) therapy are key factors for positive health outcomes. Home support providers participate in the home implementation and follow-up of PAP therapy for patients with obstructive sleep apnea (OSA). In Europe, home support provider service levels are country (or area) specific, resulting in differences in content and frequency of patient interactions. However, no robust evaluation of the impact of these differences on clinical and patient outcomes has been performed.

Objective: The AWAIR study aims to evaluate and compare the impact of different home support provider service levels on PAP adherence and persistence in 4 European countries.

Methods: This real-world, ambispective, cohort study—conducted in France, Belgium, Spain, and Portugal—will recruit adults with OSA who started PAP therapy between 2019 and 2023 and were followed by an Air Liquide Healthcare home support provider. Given the large number of eligible participants (around 150,000), the study will use a decentralized and digital approach. A patient video will present the study objectives and the participation process. A secure electronic solution will be used to manage patient information and consent, as well as to administer a web-based questionnaire. Retrospective data, collected during routine patient follow-up by home support providers, include the level of service and device data, notably PAP use. Prospective data collected using an electronic patient-reported outcome tool include health status, OSA-related factors, patient-reported outcomes including quality of life and symptoms, OSA and PAP literacy, patient-reported experience, and satisfaction with PAP therapy

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and service. Hierarchical models, adjusted for preidentified confounding factors, will be used to assess the net effect of home support provider services on PAP adherence and persistence while minimizing real-world study biases and considering the influence of country-level contextual factors. We hypothesize that higher levels of home support provider services will be positively associated with adherence and persistence to PAP therapy.

Results: As of December 2024, the study has received approval in France, Portugal, and 2 regions of Spain. The study began enrollment in France in October 2024. Results are expected in the second quarter of 2025.

Conclusions: The AWAIR study has a unique design, leveraging an unprecedented number of eligible participants, decentralized technologies, and a real-world comparative methodology across multiple countries. This approach will highlight intercountry differences in terms of patient characteristics, PAP adherence, and persistence, as well as patient-reported outcomes, patient-reported experiences, and satisfaction with the home service provider. By assessing the added value of home support provider services, the results will support best practices for patient management and for decision-making by payers and authorities.

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KEYWORDS

obstructive sleep apnea; positive airway pressure; real-world evidence; home support provider; adherence; electronic patient-reported outcome; comparative real-world study

Introduction

Obstructive sleep apnea (OSA) is the most prevalent form of sleep-disordered breathing, affecting nearly 1 billion adults aged 30-69 years worldwide [1]. OSA is characterized by repetitive collapse of the upper airway during sleep, resulting in complete (apnea) or partial (hypopnea) airway obstruction [2]. OSA can cause daytime symptoms that impair quality of life and has been linked with a variety of cardiometabolic diseases, neurocognitive impairment, depression, road traffic accidents, and all-cause mortality [3-12]. Identification and management of OSA are therefore important to reduce those risks.

Positive airway pressure (PAP) therapy remains the gold standard treatment for severe OSA because high-quality evidence and long-term assessment are lacking for noncontinuous PAP therapies [13,14]. PAP therapy has been shown to reduce road traffic accidents, blood pressure, cardiovascular risk, and health care use [15-19]. However, the effectiveness and cost-effectiveness of PAP therapy are linked to sufficient daily device use, with regular and continued long-term usage [16,19-24], which appears challenging in all geographies [25,26].

In most European countries, home support provider companies supply the PAP device and support its use by the patient. However, the type and level of services provided differ markedly between countries. Services can range from mainly logistical support (ie, device delivery in Belgium, Germany, and the Netherlands) to a personalized support plan for patients integrating motivational interviews to enhance adherence (as in some regions of Spain and Portugal) [27-29]. Also, the number of regulated home visits varies from none to several per year (like in France and Portugal). The use of PAP telemonitoring also varies widely, being routine for almost all patients in France throughout the PAP treatment period [30] but not used (or only used in the first months of therapy or in specific situations) in other countries. Criteria for the reimbursement of PAP therapy also differ markedly between European countries and are likely to influence adherence and persistence. For example, while the fees paid to the home support providers in France increase as the number of hours of PAP use increases [30,31], in Belgium and Germany, nonadherence can result in the cessation of patient reimbursement.

The large number of patients treated with PAP therapy and the heterogeneity of home support provider service levels across Europe provide a unique opportunity to evaluate the optimal management approach. This requires an assessment of the added value of the service and of its impact on PAP adherence and persistence; quality of life; patient-reported outcomes (PROs), including quality of life and symptoms, patient-reported experience (PREs), and satisfaction.

Air Liquide Healthcare (ALH) is composed of several home support provider companies operating in more than 40 countries worldwide and 10 European countries. Support to patients with sleep apnea requiring PAP treatment is provided in all these countries. ALH designed the AWAIR (Assessment of the Benefit of the Home Support Provider Service Level Associated With Positive Airway Pressure Treatment in Patients With OSA on Treatment Adherence and Persistence: an International Real-World) study to assess and compare PAP adherence and persistence across 4 different European countries and according to the level of service. The study will consider the main confounding factors for adherence and persistence to PAP therapy and will provide unique information about differences in patient profiles across countries, PROs, OSA and PAP literacy, and experience and satisfaction with PAP therapy and service (PREs).

Methods

Study Design

This international, ambispective, real-world, cohort study is being conducted in 4 European countries (France, Belgium, Spain, and Portugal). It includes a retrospective analysis with the reuse of home support provider data routinely collected for PAP-related services and a prospective evaluation with the

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collection of patient data using a web-based patient questionnaire.

Study Objectives

The main objective of the study is to compare PAP adherence and the PAP therapy persistence rate between countries and between different levels of home support provider service.

The study's other objectives are to (1) identify service components that influence PAP adherence and persistence; (2) identify factors associated with PAP adherence and persistence; (3) describe in each country sociodemographic and OSA-related clinical characteristics, home support provider PAP-related service, OSA and PAP literacy of participants (perceived and actionable competence), patient experience and satisfaction with PAP therapy and home support provider support, patient-reported OSA symptoms, and quality of life (determined using the EQ-5D-5L questionnaire [32]); and (4) describe patterns of PAP use.

Participants

Process for Selecting Patients

Eligible participants are adults (aged 18 years and older) who started PAP therapy between January 1, 2019, and December 31, 2023; for whom PAP services were delivered by an ALH affiliate in France, Belgium, Spain, or Portugal; and had a valid email address or smartphone number.

Potential participants were identified by applying these inclusion criteria to the data sourced from each home support provider database. In France and Portugal, all patients who met the above inclusion criteria were informed about the study. In Spain and Belgium, which have regional- or hospital-level regulatory processes, potential participants are only included from representative investigational sites. After providing the information about the study, patients who either consented to participate (Portugal, Spain, and Belgium) or did not "opt-out" (France) are enrolled in the study. These processes are described in more detail in the Ethical Considerations section.

The digital and decentralized nature of the study using e-consent and an electronic patient-reported outcome (ePRO) tool means that patients are not directly recruited by investigators. Instead, a secure electronic solution, Dr Data Consent, is used to provide direct and individual information about the study, obtain consent, and provide access to the web-based questionnaire. This solution is compliant with European and French legislation and regulations on the protection of personal data, as well as ethical guidance about patient's rights management. Its technology is powered by blockchain thus guaranteeing full traceability on e-consents.

Process for Contacting and Recruiting Patients

The list of eligible patients that was extracted from each home support provider database contains patient contact details (ie, email address or smartphone number). This list is uploaded into Dr Data Consent and an algorithm checks the validity of the contact details. Eligible patients with valid contact information receive an email or SMS invitation to connect to this platform for the consent process. The invitation does not include sensitive data.

An explanatory video is provided, within the Dr Data Consent account of each patient, to ensure that potential participants fully understand the study's aims, procedures, and their rights.

Those who provide consent are granted access to the ePRO tool and invited to complete the questionnaire, which should take them an estimated 10 minutes.

Ethical Considerations

The study protocol was developed in collaboration with a scientific committee composed of experts in OSA and methodologists from the 4 countries involved. The regulatory process and patient consent for a study with the reuse of data and a questionnaire were different for the 4 countries.

In France, the study followed the methodology MR-004 of the French Data Protection Authority (Commission Nationale Informatique et Liberté) concerning research that reuses data that have already been collected [33] and was approved by the local ethics committee of Angers University Hospital in November 2023 (2023-159). In Portugal, the study was considered observational and required approval by a central ethics committee; the approval was obtained from the ethics committee of Lisboa in May 2024 (24/24). In Spain, the study was considered observational and required approval by the ethics committee at each participating hospital; approval was obtained from the CEIm Hospital Universitario Ramón y Cajal of Madrid in July 2024 (095/24) and from the CEIm Hospital Universitario Doctor Peset of Valencia in December 2024 (127/24) and is pending for other regions. In Belgium, the study was considered interventional and required approval by a central ethics committee (Commissie voor Medische Ethiek Ziekenhuisnetwerk Antwerpen Institutional Review Board, Ziekenhuis aan de Stroom Middelheim) and by the local ethics committee at each participating hospital. Ethics approvals from the belgian central ethics committee are still pending.

In France, potential participants have the option to decline the reuse of their personal data through an "opt-out" process. Conversely, in Belgium, Portugal, and Spain, an "opt-in" process has been established, requiring explicit consent from participants to join the study.

No compensation is provided to participants.

Outcome Measures

Study outcomes, time points, and data sources are summarized in Table 1. An ePRO tool will be used to administer the patient questionnaire. The ePRO tool was designed to assess various aspects of a patient's status, condition, and experience at 2 time points: the time of ePRO completion and the beginning of PAP therapy. This included sociodemographic characteristics (age, relationship status, employment, education level, and social support), health status (BMI, smoking status, alcohol intake, comorbidities, sleep duration, and use medications to aid sleep), OSA-related factors (when PAP therapy was started, apnea-hypopnea index before starting PAP, and OSA symptoms), PAP therapy experience and satisfaction (tolerability of PAP, attitude to PAP, device noise, and level of motivation

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to use PAP), patient experience and satisfaction with home support providers, quality of life (including current health status), and OSA-PAP literacy. The full ePRO questionnaire is provided in Multimedia Appendix 1.

Home support provider service will be assessed using 4 components: frequency of interactions between the home support provider and a patient; content of support (logistical, educational, supportive, or behavioral); personalization of support according to patient profile or needs; and telemonitoring (telemetry, data visualization, and alerts triggering home support provider interventions).

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Table 1. Study outcomes.

Category and outcome	Time points	Source
Sociodemographic and OSA[a]-related clinical characteristics		
• Demographics (age and sex) • BMI	At the start of PAP[b] therapy	ALH[c] ERP[d]
• Occupational status and highest education level • Sleep characteristics: bed sharing, sleep duration, and sleep medication • Smoking status and alcohol consumption • BMI	At the time of ePRO[e] completion	ePRO tool
• Comorbidities: diabetes, stroke, myocardial infarction, coronary stenting or heart surgery, heart failure, cardiac arrhythmia, hypertension, GORD[f], COPD[g], asthma, chronic rhinitis, cancer, anxiety or depression, and insomnia	Before starting PAP therapy	ePRO tool
• Apnea-hypopnea index at the time of diagnosis	Before starting PAP therapy	ALH ERP and ePRO tool
PROs[h]		
• Symptoms: snoring, excessive daytime sleepiness, daytime fatigue, lack of energy, waking up feeling tired, poor sleep, falling asleep at the wheel, nocturia, abrupt awakening with choking and gasping, morning headache, irregular breathing during sleep, decreased libido, depression, anxiety, irritability, and memory or concentration difficulties	Before and after starting PAP therapy	ePRO tool
• Quality of life using the EQ-5D-5L [32]	At the time of ePRO completion	ePRO tool
OSA and PAP literacy		
• Perceived and actual competence related to disease literacy and PAP use assessed using 13 variables with binary responses	At the time of ePRO completion	ePRO tool
Experience and satisfaction with PAP therapy		

• Measured using a visual analogue scale for
  • Difficulty tolerating PAP (discomfort related to pressure, and mask)
  • Likelihood of continued use
  • Perceived health benefits
  • Global satisfaction
  • Noise acceptance/impact
  • Motivation to use
	At the time of ePRO completion	ePRO tool

Experience and satisfaction with home support provider		

• Measured using a 5-point Likert scale for
  • Home support provider availability for logistical support
  • Home support provider availability for educational support
  • Satisfaction with home support provider
  • Perceived value of home support provider
	At the time of ePRO completion	ePRO tool

Characteristics of PAP therapy		
• Type of PAP device and mask	At the start of PAP therapy	ALH ERP
• Elevated apnea-hypopnea index • Elevated unintentional leaks	1, 4, 6, and 12 months after starting PAP therapy and annually thereafter	Device data
Home support provider PAP-related service		
• Number and type of interactions (home visit, phone call, and digital interaction) • Number of mask changes • Implementation of telemonitoring	1, 4, 6, and 12 months after starting PAP therapy and annually thereafter	ALH ERP

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Category and outcome	Time points	Source
PAP adherence		
• Mean number of hours per day of PAP use • Mean PAP use categorized as: 0-2 hours/day, 2-4 hours/day, 4-6 hours/day, and ≥6 hours/day • Proportion of adherent patients defined as (1) mean PAP use ≥4 hours/day, (2) mean PAP use ≥4 hours/day on ≥70% of days, and (3) mean PAP use ≥4 hours/day on ≥80% of days	1, 4, 6, and 12 months after starting PAP therapy and annually thereafter	Device data
PAP persistence		
• Percentage of days with or without PAP use defined as the ratio between the number of days with PAP usage (starting from 1 minute of use) over the number of days in the follow-up period • Patients without PAP discontinuation (still in therapy), with temporary discontinuation, or with permanent discontinuation • Patients still in therapy and with mean PAP use ≥4 h/day	4, 6, and 12 months after starting PAP therapy and annually thereafter	Device data and ALH ERP

[a]OSA: obstructive sleep apnea.

[b]PAP: positive airway pressure.

[c]ALH: Air Liquide Healthcare.

[d]ERP: Enterprise Resource Planning.

[e]ePRO: electronic patient-reported outcome.

[f]GORD: gastro-esophageal reflux disease.

[g]COPD: chronic obstructive pulmonary disease.

[h]PRO: patient-reported outcome.

Data Sources, Flow, and Management

Potential participants will be identified by applying the inclusion criteria to the data sourced from the ALH Enterprise Resource Planning (ERP) systems. Initially, potential participants will receive an email or SMS invitation to connect to a secure platform for the consent process. Those who provide consent will be granted access to the ePRO tool and will be invited to complete the questionnaire, which takes about 10 minutes.

The study database will be created from 3 data sources: the ALH ERP systems that contain data routinely collected for PAP-related services; the database containing information about PAP device use (collected remotely through the Internet of Things or by download from device memory cards during home provider support visits); and the ePRO tool. Database structure and content will be standardized across countries.

Because the ALH ERP and PAP device use databases are primarily designed for administrative, logistical, and patient follow-up purposes, rather than research, all data will undergo thorough review for completeness, accuracy, and reliability before statistical analysis. These reviews will be conducted in accordance with a detailed data management plan, involving multiple experts with complementary areas of expertise. All decisions made during the review process will be fully documented.

All identifiable personal information will be protected and stored in the study database in pseudonymized form so that it cannot be viewed by the study sponsor or any external vendors that are processing the study data. A summary of data sources and data flow is provided in Figure 1.

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Figure 1. Diagram of data sources and data flow. AHI: apnea-hypopnea index; ALH: Air Liquide Healthcare; ePRO: electronic patient-reported outcome; ERP: Enterprise Resource Planning; HSP: home support provider; IoT: Internet of Things; PRE: patient-reported experience; QoL: quality of life.

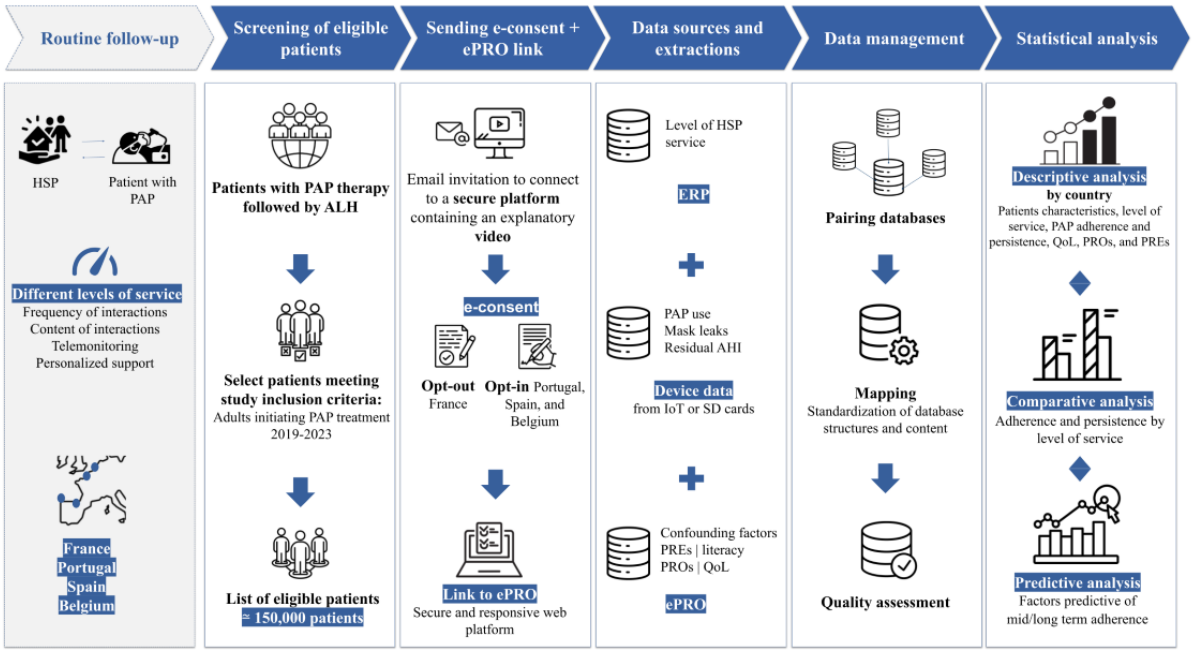

Statistical Methods

Sample Size

This study aims to include all adults starting PAP therapy managed by an ALH home support provider in the participating countries who met the selection criteria during the study time period. This approach minimizes selection bias and sampling errors, ensuring precise and reliable results. Inclusions will be possible at the national level (France) or only at some investigational sites in countries requiring regional or hospital-level regulatory processes. All potential participants will be informed whenever ethics committee approval is obtained from the respective regions or hospitals. It is expected that around 30% of the 150,000 eligible participants will not be enrolled due to the absence of (or incorrect) email, or refusal to participate. Therefore, the number of included patients is expected to be around 100,000. With a sample of this size, the probability of showing a statistically significant difference in adherence between different levels of service if one exists is >99%, even if there were important imbalances between groups.

Statistical Analysis

Statistical analyses will be performed according to a predefined statistical analysis plan (Table 2).

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Table 2. Statistical analysis plan details.

Objectives	Main outcomes	Key explanatory variables	Statistical methods
Compare PAP[a] adherence and the PAP therapy persistence rate between different levels of home support provider service	• PAP adherence: (1) mean number of hours/day of PAP use and (2) adherent patients defined as those with mean PAP use ≥4 hours/day • PAP persistence: (1) percentage of days with PAP use, (2) patients still in therapy, and (3) patients still in therapy and adherent	• Fixed effect: Level of service (standard of care, personalized care plan, or high service level) • Random effect: Country	Multilevel model adjusted for selected confounding factors
Identify service components that influence PAP adherence and persistence	• PAP adherence: (1) mean number of hours/day of PAP use and (2) adherent patients defined as those with mean PAP use ≥4 hours/day • PAP persistence: (1) percentage of days with PAP use, (2) patients still in therapy, and (3) patients still in therapy and adherent	• Fixed effect: Frequency of interactions, content of support, personalization of support, and telemonitoring • Random effect: Country	Multilevel model adjusted for selected confounding factors
Identify factors associated with PAP adherence and persistence	• PAP adherence: (1) mean number of hours/day of PAP use and (2) adherent patients defined as those with mean PAP use ≥4 hours/day • PAP persistence: (1) percentage of days with PAP use, (2) patients still in therapy, and (3) patients still in therapy and adherent	• Fixed effect: Frequency of interactions, content of support, personalization of support, telemonitoring, sociodemographic characteristics, OSA[b]-related clinical characteristics, and characteristics of PAP therapy • Random effect: Country	Multilevel model
Descriptive Analysis	• Sociodemographic characteristics • OSA-related clinical characteristics • OSA and PAP literacy • Experience with PAP therapy • Experience with home support provider support • Quality of life • Home support provider PAP-related service	N/A[c]	Usual descriptive statistics: Analysis by country
Describe patterns of PAP use	• Mean PAP use categories over time	N/A	Data visualization such as Sankey diagrams

[a]PAP: positive airway pressure.

[b]OSA: obstructive sleep apnea.

[c]N/A: not applicable.

Patient Datasets

Retrospective data will be available for all included patients (included population). Prospective data from the ePRO tool will be available for the subset of patients who complete the questionnaire (ePRO population).

Multilevel Models

Individuals living in the same country share a common health care system, lifestyle, and climate, and tend to be more similar than individuals from other countries. Therefore, individuals are considered nested within a country. This correlation of observations violates the assumption of independence for standard regression analysis leading to biased standard errors of parameter estimates. Therefore, we will fit multilevel linear or logistic mixed models using the country variable as a random effect to test the association between adherence or persistence and levels of service while accounting for this nested data structure.

Confounding Factors

Potential confounding factors were identified a priori based on a literature review and clinician expertise, and include age, sex, BMI, sleep duration, symptoms before starting PAP therapy, occupational status, highest education level, bed partner, comorbidities, smoking status, alcohol consumption, apnea-hypopnea index at the time of diagnosis, and prescriber specialty. Factors consistently described as being associated with PAP therapy adherence or persistence will be automatically included in statistical models comparing the effect of service on adherence or persistence. Other potential confounding factors will be selected based on their association with adherence or persistence in a univariate analysis. Full details of the confounding variables considered and the supporting sources are provided in Multimedia Appendix 2. Quantitative bias analysis will be performed to evaluate the impact of unmeasured confounders using a metric named the e-value [34]. The e-value can be defined as the strength of association that an unmeasured confounding factor would need to have in order to explain away the observed association.

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Data Visualization

Data visualization (eg, with the use of Sankey diagrams) will be used to represent the pattern of changes in mean PAP use categories over time.

Sensitivity Analyses

Sensitivity analyses will be performed after removal of data collected during the COVID-19 lockdown periods, and before and after June 2021 (the time of the Philips Respironics world product recall [35,36].

Ancillary Study

While the association between PAP adherence and costs has been demonstrated in the United States [21,23,37-42], data from Europe remain limited [43,44]. To further determine the benefits of home support providers, an ancillary study, named APAIR (Association Between Positive Airway Pressure Adherence, Morbi-Mortality and Costs Among Patients With Obstructive Sleep Apnea in France: Real World Study Using Claims and Telemonitoring Data), will be conducted in the subset of AWAIR study participants from France. APAIR will investigate the association between PAP adherence and persistence, and key outcomes (mortality, morbidity, and health-related costs). AWAIR study participants from France will be identified in the French Healthcare Claims Database (Système National des Données de Santé), which provides longitudinal patient-level data for approximately 99% of the French population [45]. Data on hospitalizations and sick leave related to the complications of OSA will be retrieved for these individuals. The aim of APAIR is to obtain data relating to new and more relevant thresholds for PAP adherence and the personalization of PAP therapy support (eg, for those with higher health risks or higher health care resource use).

Results

As of December 2024, the AWAIR study has received approval in France, Portugal, and 2 regions of Spain. Patient enrollment started in France in October 2024, with around 90,000 patients informed about the study. Results of the AWAIR study are expected in the second quarter of 2025.

Discussion

Study Rationale

The high and increasing number of patients with OSA treated with PAP therapy drives concerns among health systems regarding the associated health care resource consumption and costs. This has led some countries to implement significant changes in the patient pathway, notably toward more home-centered models [30,46]. Regardless of the care setting, PAP adherence and persistence are essential because they are associated with health benefits [19], whereas poor adherence and PAP therapy terminations have been associated with increased disability, health care resource consumption, and direct or indirect costs [47-49].

Despite a large body of evidence regarding the factors associated with PAP adherence [50] and persistence [25,51], and the reimbursement of PAP-related services in many European Union countries, there is currently a lack of evidence regarding the impact of home support provider services on these outcomes. In addition, although defined by country or local regulations, the level of home support provider service is poorly described. Differences exist in service frequency, content, and communication channels between home support providers and patients, the use of PAP telemonitoring, and the qualifications of home support provider personnel. Some of these components have been shown to impact PAP adherence [29,30,52,53].

Our working hypothesis is that a higher level of home support provider service would be associated with better PAP adherence and persistence. This study will also investigate between-country differences in terms of patient characteristics, OSA-related characteristics, and services, and identify which components of service are most effective at improving adherence and persistence.

We anticipate that this research will provide valuable evidence to inform decision-making by authorities and payers regarding the regular reassessment of services and associated tariffs. It could also support guidelines relating to the follow-up of individuals receiving PAP therapy.

Design Rationale

The comparative, real-world design with between-country comparisons was the most feasible approach for this study. A randomized controlled trial was not viable because home support provider services are implemented for all patients prescribed PAP. The need to include a control group without services in a randomized trial would have markedly reduced ethical approval and acceptance of the study and would have introduced important bias related to behavioral factors for those accepting home support provider management. Furthermore, the controlled conditions of clinical trials do not adequately capture the complexity of factors influencing adherence in real life. Furthermore, there was a need for evaluation of the real-world impact of home support providers on a representative, unselected population. Real-world studies provide information about outcomes with less rigid treatment patterns compared with a controlled trial [54] and bridge the gap between clinical research and everyday practice. We followed the Haute Autorité de Santé methodological recommendation for real-world studies, proposing a design consistent with identified questions, using preexisting high-quality data, integrating PROs and PRE, and ensuring transparency [55].

Strengths

One of the major strengths of this study is its large sample size, which enhances the representativeness of the population and the generalizability of the findings. The retrospective design allows for long-term evaluation of PAP adherence and persistence and ensures that there is no influence on participants' behavior because data were collected prior to their inclusion in the study. In addition, the AWAIR study will describe between-country differences in home provider services and patient characteristics for the first time, and report on patient satisfaction and experience with PAP therapy.

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In contrast with conventional clinical trials, the real-world setting ensures that the results will reflect the usual course of care [56]. This is particularly important for evaluating adherence because it minimizes the risk of bias that could arise from study participation. Furthermore, real-world evidence is particularly relevant for meeting health authority post-approval effectiveness requirements [57]. Well-conducted comparative effectiveness research can provide valid results similar to randomized trials for this measure of known confounding factors [56], and can use methods (such as stratification, matching, or regression analyses) to account for or adjust for such factors and yield valid results [58]. In the real-world comparative AWAIR study, adjustment for potential confounders identified through literature review and clinical expertise, combined with the use of hierarchical models accounting for contextual differences related to the international nature of the study, will help the data to provide an accurate assessment of the net effect of home provider services on PAP adherence and persistence while minimizing the potential biases inherent in real-world studies. Additionally, the use of an ePRO tool facilitates the collection of data on confounding factors that would not otherwise be available in the retrospective database analysis, along with PROs, PREs, and health literacy across a large and diverse patient population from various geographic regions [59].

Limitations

Selection bias cannot be entirely ruled out because participants were required to have a valid email address or smartphone number to be eligible for the study. This may lead to underrepresentation of certain subgroups of PAP users, such as older adults. Patients who answer the questionnaire might also differ from those who do not answer it. In addition, this study will only include individuals who use PAP supplied by a home support provider affiliated with ALH and it is possible that the level or content of additional services may differ slightly from other home support providers in the same country. To assess the potential impact of such biases, we will compare the characteristics of our study population with published data on OSA, focusing on age, sex, and disease severity.

Data from the ePRO tool may be subject to recall bias and inaccuracy because participants will complete the web-based questionnaire at variable periods of time since the start of PAP therapy (up to 5 years later for those who started PAP in 2019) and medical data will directly be provided by the patient. Confounding bias other than the key confounding factors considered is another limitation, particularly with respect to medical follow-up (data that will not be collected in this study).

Finally, the period over which this study was conducted included times before and during the COVID-19 pandemic (including lockdowns), and the worldwide recall of a PAP device made by Philips Respironics [36]. Sensitivity analyses will be performed to determine whether these factors had any influence on the overall study findings.

Challenges

The study faced several challenges, including the regulatory classification of an ambispective study and the heterogeneous regulatory processes between countries. In France, the reuse of data for clinical research is facilitated by a simplified procedure that does not exist in other countries. Although the decentralized approach used in this study (ie, e-consent + ePRO tool) has advantages, especially in terms of managing a large number of participants, proposing the study to potential participants remotely can decrease the rate of enrollment. This is why a video-based approach was chosen because using videos to explain the research aims and procedures to potential participants of a clinical trial was preferred by patients over paper-based systems and improved their understanding [60].

Another challenge is the quantity of data to be processed due to the large number of participants and the daily PAP data collected over up to 5 years, requiring robust data management and quality control systems. Moreover, data were collected for routine home support provider services, in different countries with different services and enterprise resource planning systems, with different data collection processes, which adds another layer of complexity to the study. Therefore, those involved in the study need to have a good understanding of the data collection processes, data structures, formats, contents, and constraints of each system to allow standardization of data to constitute a research-ready database.

Opportunities

Clinical trials are critical in the assessment of health products and services. However, managing and executing randomized controlled trials pose significant challenges in terms of inclusion, data collection, follow-up, comparator group, and costs [61]. Specifically in patients with OSA treated with PAP, it was shown that recruitment strategies in randomized trials could result in a lack of representativeness of the participants, because only up to 20% of typical patients with OSA meet the eligibility criteria, limiting the generalizability of the results [62]. The expanding availability of real-world data combined with advancements in operational tools and methodologies presents a significant opportunity to develop alternative study designs that leverage existing data. Furthermore, the European Health Data Space will create a common framework in Europe for the reuse of health data for research [63]. The design of the AWAIR study integrates multiple real-world data sources (including operational databases, device data, and an ePRO tool), the use of comparative real-world methods, and the implementation of e-consent. This innovative approach not only makes the study more robust but also sets a precedent for future research in similar fields, particularly regarding the number of participants who will consent and complete the ePRO tool. The design allows the study to be continuously enriched with data from new countries to measure the effect of other service levels and also to extend patient follow-up to assess longer-term persistence or include other patients in the countries of interest to assess the impact of changes in service levels.

Conclusions

The AWAIR study has a unique design, leveraging an unprecedented number of eligible participants, decentralized technologies, and a real-world comparative methodology across multiple countries. This approach will highlight intercountry differences in terms of patient characteristics, PAP adherence and persistence, PROs, PREs, and satisfaction with home

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support provider services. By assessing the added value of home support provider services, the results will support best practices for patient management and decision-making by health authorities and payers.

Acknowledgments

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Authors' Contributions

SA, MS, HT, CF, FB, and SB contributed to the study conception and design. HT and SO were involved in the regulatory process. JT, FG, PP, ICP, and LB provided the scientific validation of the outcomes and the content of the patient questionnaire. SA, HT, SB, HS, and BB designed the ePRO. MS, FB, SA, and CF provided the statistical methodology of the study. SA and MS outlined the first draft of the manuscript. All authors reviewed the manuscript and provided critical revisions of the manuscript. All authors approved the final version of the manuscript.

Conflicts of Interest

HS and BB have no conflicts of interest to declare. ICP, PP, LB, and FG have received consulting fees from Air Liquide Group. SA, JT, MS, HT, SB, and MHG are employees of Air Liquide Group. FB and CF are employees of Horiana, the contract research organization (CRO) of the study. SA, MS, and HT are shareholders at Air Liquide.

Multimedia Appendix 1
Full study questionnaire.
[DOCX File , 1425 KB - resprot_v14i1e65840_app1.docx]

Multimedia Appendix 2
Confounding factors.
[DOCX File , 30 KB - resprot_v14i1e65840_app2.docx]

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Abbreviations

ALH: Air Liquide Healthcare
APAIR: Association Between Positive Airway Pressure Adherence, Morbi-Mortality and Costs Among Patients With Obstructive Sleep Apnea in France: Real World Study Using Claims and Telemonitoring Data
AWAIR: Assessment of the Benefit of the Home Support Provider Service Level Associated With Positive Airway Pressure Treatment in Patients With Obstructive Sleep Apnea on Treatment Adherence and Persistence: an International Real-World Study
ePRO: electronic patient-reported outcome
ERP: Enterprise Resource Planning
HSP: homecare support provider
OSA: obstructive sleep apnea
PAP: positive airway pressure
PRE: patient-reported experience
PRO: patient-reported outcome

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Protocol

Core Outcome Set Development for Tension-Type Headache Treatment Using Traditional Chinese Medicine: Protocol for a Delphi Consensus Study

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Abstract

Background: Tension-type headache (TTH) is the most common type of headache and the second most common health-related complaint among children and adults. Traditional Chinese medicine (TCM) offers unique therapeutic benefits in treating TTH. However, the lack of standardized evidence—such as inconsistencies in outcome selection and reporting in clinical studies, a lack of consensus on outcomes and measures, high risks of selective reporting bias, and missing data—has limited the development of robust evidence supporting the efficacy of TCM in treating TTH. Therefore, establishing a core outcome set (COS) is crucial for standardizing TCM clinical studies for TTH, thereby enhancing the quality and comparability of research findings.

Objective: This study aims to develop a COS for future clinical studies on the treatment of TTH with TCM.

Methods: The COS will be developed through the following 3 stages. First, systematic reviews and semistructured interviews will be conducted to identify potential essential outcomes, which will be evaluated by the steering committee to finalize a preliminary list of outcomes. Data will be processed using thematic analysis to ensure comprehensive coverage of relevant outcomes. Second, a 2-round Delphi survey will be conducted, inviting stakeholders, including health care experts and patients with tension-type headaches, to determine the importance of each outcome. Statistical analysis will be used to assess the level of consensus and prioritize outcomes based on predefined criteria. Third, a face-to-face consensus meeting will be held to finalize the COS and recommend measurement times for each outcome. Key outcomes will be interpreted based on their clinical relevance and feasibility of measurement, ensuring the COS is comprehensive and applicable in clinical settings.

Results: The protocol has been registered in PROSPERO, with the review commencing on October 1, 2024, and anticipated results by November 15, 2024. The systematic reviews will be finalized, followed by the Delphi survey and consensus conference in late 2024 and early 2025. The COS findings will be reported per COS-STAR (Core Outcome Set–STAndards for Reporting) guidelines, published in an international journal, presented at conferences, and disseminated to participants for clinical application.

Conclusions: This study is necessary as developing a COS for future TCM clinical studies in the treatment of TTH can maximize the value of data from individual trials and provide high-quality research evidence.

Trial Registration: Core Outcome Measures in Effectiveness Trials Initiative 1473; https://tinyurl.com/3ts62s2p

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International Registered Report Identifier (IRRID): PRR1-10.2196/63481

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KEYWORDS

tension-type headache; core outcome set; traditional Chinese medicine; systematic review; Delphi; protocol

Introduction

Background

Tension-type headache (TTH) is a neurological disorder characterized by mild to moderate headaches [1]. It is the most common type of headache and second most common health-related complaint among children and adults [2,3], and negatively affects their ability to participate in various activities in school, sports, social, and home settings, especially when the headache becomes chronic and frequent [4]. Many studies have shown that TTH significantly impacts mood, sleep, and liveliness; anxiety or depression is more common in patients with headaches than in those without headaches [5-7].

Traditional Chinese medicine (TCM), which includes Chinese herbal medicine, acupuncture, and massage, plays an increasingly important role in the treatment of TTH [8-13]. In particular, acupuncture is frequently used to treat TTH [14] and has been approved as a supplementary therapy option for TTH by the European Federation of Neurological Societies [15]. Several randomized controlled trials (RCTs) of TCM for TTH have been conducted in China. Although an individual RCT is valuable, pooling data from numerous RCTs can give more substantial evidence to support therapeutic decision-making [16]. The normalization and homogeneity of research outcomes are crucial when pooling data from multiple studies. However, we found the following problems in the selection and reporting of outcomes in RCTs and systematic reviews on the effects of TCM on TTH.

Many studies only reported the effectiveness rate of composite indicators [17], and certain clinical studies failed to include critical or relevant outcomes, such as headache frequency, severity, duration, impact on quality of life, and analgesic use. As a result, these studies were not suitable for secondary analysis [18], which precludes the incorporation of many results into systematic reviews or meta-analyses. This limitation undermines the ability to provide higher-level evidence for clinical practice, thereby diminishing the research's value and contributing to unnecessary waste. In addition, selective reporting of results may exist in current clinical studies, as researchers are more likely to select statistically significant results, leading to overestimation of outcomes and exaggeration of efficacy [10,13,19]. Outcome measures were poorly defined, with total effectiveness rates inconsistently defined using a variety of concepts [17]. The outcome measures for different studies were heterogeneous, and systematic reviews have shown significant heterogeneity among studies, which is not conducive to intervention comparisons and meta-analysis [10,11,13]. Furthermore, outcomes were developed without considering the opinions of patients and other stakeholders. The International Headache Society Committee proposed an evaluation of outcomes in clinical trials [20]. However, there is still a lack of consensus on the collection and reporting of RCTs of TCM for the treatment of TTH, which limits the comparison and aggregation of data from individual trials and reduces their research value.

Therefore, to address the above problems, it is necessary to develop a core outcome set (COS) for TCM clinical studies (COS-TCM) for TTH. Developing, disseminating, and implementing a COS can address and overcome inconsistencies in outcome selection, measurement, and reporting [21]. Currently, there is no specific COS-TCM for TTH. After searching the Core Outcome Measures in Effectiveness Trials (COMET) database, we identified 1 COS associated with TTH. The International Headache Society Committee proposed an evaluation of TTH outcomes in clinical trials in 1995 (1st edition) [22] and 2010 (2nd edition) [15]. However, the standardized outcome set in COS may be biased toward Western patient populations and lack access to Chinese clinical experts and Chinese patients. There are no COSs available that include outcomes relevant to TCM syndromes. Therefore, developing a COS-TCM for TTH will enhance the quality of evidence from clinical studies of TCM for TTH, promote the translation of clinical research into clinical practice, and provide recommendations for health care decision-making [23,24].

This study was registered in the COMET Initiative (1473) and will be conducted according to the Core Outcome Set-STAndards for Development [25] and Construction of Core Outcome Set of TCM Clinical Trials guidelines [26]. This study protocol referred to the Core Outcome Set-Standardized Protocol Items [27], which are shown in Multimedia Appendix 1.

Scope and Aim

Aim

This study aims to develop a COS for future clinical studies on TCM for the treatment of TTH, in order to improve the use of evidence synthesis by standardizing outcome reporting and guaranteeing that all studies contribute valuable data.

Scope

The scope of the COS-TCM encompasses several key areas. It focuses on the health condition of TTH and targets a population of patients with TTH who are aged 18 years and older. The types of interventions included are various TCM therapies, such as herbal medicine decoction, Chinese patent medicine, acupuncture, moxibustion, cupping, massage, Tai Ji, Baduanjin, Qigong, and other nondrug treatments. This scope applies to any type of clinical study.

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Methods

Design

The study design is structured in 3 stages, providing a comprehensive framework for developing the COS-TCM. Initially, semistructured interviews and a systematic review will be conducted to identify potential essential outcomes. This will culminate in a preliminary list of outcomes, evaluated and finalized by the steering committee. The second stage involves selecting various stakeholders to participate in a 2-round Delphi survey, aiming to gather diverse opinions on the COS-TCM. Finally, a consensus meeting with key stakeholders will be convened to finalize the COS-TCM. Figure 1 illustrates the flowchart of the study process.

Figure 1. The flowchart of the study core outcome set (COS). TCM: traditional Chinese medicine; TTH: tension-type headache.

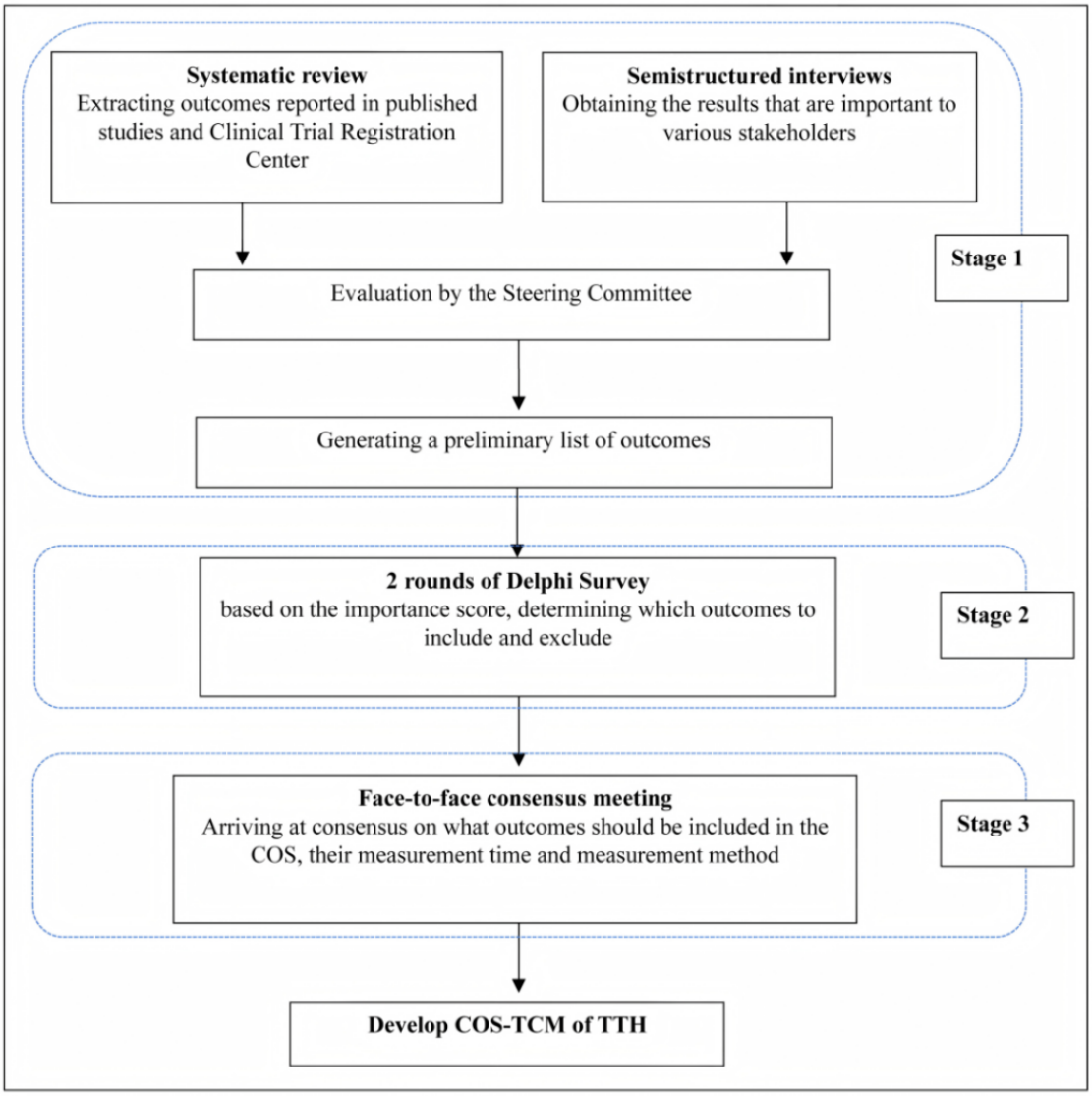

Steering Group

The steering group will consist of 5 individuals from various scientific fields, including 2 TCM clinical neurology experts, 2 Western medicine clinical neurology experts, and a methodologist. The group will examine and approve the study protocol, determine the preliminary checklist of the reporting outcome set, and take part in a consensus conference to advance the construction of the COS.

Working Group

The working group will consist of 20 members, including clinicians, methodologists, professors, and graduate students from Xiyuan Hospital, China Academy of Chinese Medical Sciences. The group will be responsible for conducting routine research tasks and related meetings, contacting experts, and seeking advice from the steering committee when disagreements need to be resolved.

Involvement of Stakeholders

Various stakeholders, including health professionals and patients, will be included in the COS development process. Health professionals will include TCM and Western medicine practitioners who specialize in cerebrovascular disease, methodologists who specialize in evidence-based medicine, and researchers. Core journal editors will select from journals focusing on neurological diseases, such as the *Chinese Journal of Neurology*, *Chinese Archives of Traditional Chinese*

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Medicine, *Journal of Neurology and Neurorehabilitation*, *Chinese Journal of Evidence-Based Medicine*, and *Global Traditional Chinese Medicine*. Other relevant experts include clinical trial personnel, industry representatives, and policy makers. The study will invite patients with TTH to participate.

Patient and Public Involvement

Considering that patients' opinions are significant for the formulation of the COS, this study will involve semistructured interviews, 2 rounds of Delphi survey, and consensus meetings.

Stage 1: Identification of Potentially Significant Outcomes

Step 1: Systematic Review

According to the guidelines of the COMET Initiative [21], a systematic evaluation will be performed to screen the spectrum of critical potential outcomes. Previous COS-TCM studies will be used for systematic review as the research starting point [28-30]. This study will include all clinical studies (regardless of research type) that report TTH outcomes.

Search Strategy

PubMed, the Cochrane Library, Embase, Web of Science, SinoMed, Chinese National Knowledge Infrastructure, Chinese Citation Database, China Science Periodical Database, Chinese Clinical Trial Registry, and Clinicaltrials.gov will be systematically searched from inception to January 31, 2024. The search strategy for English databases is shown in Multimedia Appendix 2. The languages will be restricted to English and Chinese.

Inclusion Criteria

The inclusion criteria for the study encompass several key aspects. First, the study must be a clinical investigation, which can include randomized controlled studies, case-control studies, cohort trials, or case series. Participants should be patients diagnosed with TTH who are 18 years or older. The diagnosis must be made using any internationally recognized classification, such as those outlined in the International Classification of Headache Disorders, including the first edition (1988), the second edition (2004), and the third edition (2013) by the Headache Classification Committee of the International Headache Society. The intervention under consideration should involve TCM therapies for those included in the treatment group. In addition, if a study primarily investigates secondary TTH as a consequence of conditions such as mental disorders, infections, or endocrine diseases, a thorough review of the full text will be conducted to determine the presence of headache-related outcome measures. Studies that report such outcomes will be eligible for inclusion.

Exclusion Criteria

The exclusion criteria encompass several specific aspects. Clinical trials that investigate the outcomes of comorbidities related to TTH, such as nausea caused by TTH, are excluded. In addition, studies primarily focused on assessing pharmacodynamics or pharmacokinetics are not considered. A study involving fewer than 10 cases is also excluded.

Data Extraction

A data extraction table was designed and will be used to extract basic study information, including author information, year of publication, country, Western medicine diagnostic standards, type of TTH, TCM syndrome names and diagnostic criteria, interventional measures, study type, conclusions, outcomes and their definitions, time points, and method of outcome measurement. A total of 2 trained reviewers will be responsible for independent study screening and data extraction. Disagreements will be resolved by consulting with a third researcher. If any data is missing, the reviewers will contact the authors of the research by email or telephone to obtain the missing data.

Step 2: Semistructured Interview

A systematic review has been conducted to summarize the outcomes of existing clinical studies. However, this mainly represents the researchers' perspectives. According to the current guideline recommendations of the Core Outcome Set-STAndards for Development [25] and the COMET handbook (version 1.0) ADDIN [31], the opinions of clinicians and patients on the treatment of TTH with TCM can be obtained through semistructured interviews.

Participants

In this study, we will use heterogeneous and purposive sampling methods to recruit participants. Purposive sampling is widely used in qualitative and mixed-methods research because it enables researchers to select samples based on specific study objectives and criteria. This approach allows for the selection of more representative samples within a limited timeframe, thus conserving significant time and effort and reducing costs. Specifically, we will recruit patients diagnosed with TTH from the Xiyuan Hospital of the China Academy of Chinese Medical Sciences, as well as clinical doctors from 15 tertiary hospitals nationwide, to ensure the diversity and representativeness of the sample. The criteria for patient selection include age, gender, type of disease, duration of illness, and type of treatment, aiming to capture a broad range of patient experiences and treatment outcomes. For clinical doctors, the selection will focus on geographical diversity and professional background to obtain a wide spectrum of clinical perspectives. We plan to recruit 30 clinical doctors and 30 patients. Although no standardized method exists for determining the sample size for semistructured interviews, previous studies suggest that data saturation typically occurs when the sample size reaches 30 [24,30,32]. By adhering to these criteria and methods, we ensure that the selected sample adequately reflects the diversity and complexity of the research topic, thereby enhancing the quality and reliability of the study findings. Detailed inclusion and exclusion criteria for clinical doctors and patients in the semistructured interviews are provided in Table 1.

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Table 1. Inclusion and exclusion criteria for clinicians and patients in semistructured interviews.

Category	Inclusion criteria	Exclusion criteria
Clinicians	• Senior titles in neurology or TCM[a], with more than 5 years of work experience. • At least a bachelor's degree. • Engage in headache treatment.	• None.
Patients	• Diagnosed with TTH[b], no limitations on status. • Aged 18 years and older. • Receiving TCM treatment. • Sign informed consent forms. • Capable of reading, understanding, and speaking Chinese or English.	• Severe diseases such as heart failure, cerebral infarction, cerebral hemorrhage, and tumors.

[a]TCM: traditional Chinese medicine.

[b]TTH: tension-type headache.

Data Collection

Considering previous studies and the characteristics of TTH, we designed a semistructured interview. The development of the interview questions involved a thorough review of existing literature and consultation with experts in the field to ensure content validity. The interview will be conducted by professional researchers in a specific consultation room or office, with face-to-face interactions with participants conducted as often as possible. All interviews will be recorded to facilitate comprehensive data analysis. Before the interview, participants will be informed of the study's purpose and content, and they will be required to sign an informed consent form.

For patients, the semistructured interview will explore several key areas. Participants will be asked about the duration of their headache experience or how long they have been diagnosed with TTH. They will describe their main symptoms and the treatment they are currently receiving. In addition, they will be queried about their satisfaction with the current treatment and any recommendations they have for its improvement. Further questions will address the areas they would most like to improve and the outcomes they hope to enhance after treatment.

For clinicians, the interview will focus on their professional experience and treatment approaches for TTHs. Clinicians will discuss how long they have worked in their field and their methods for treating tension-type headaches. They will be asked about the outcomes they believe the therapies will enhance for patients. Furthermore, they will identify which outcomes they prioritize in the treatment of TTHs, listing at least 5 indicators they are concerned with.

To evaluate the validity of the interview questions, we conducted a pilot test with a small group of participants and clinicians not involved in the main study. Feedback from this pilot test was used to refine the questions, ensuring clarity and relevance. In addition, an expert panel reviewed the questions to confirm that they accurately capture the dimensions of interest related to TTH.

Data Analysis

A total of 2 researchers will independently conduct the data analysis. Disagreements will be resolved through discussions or with the assistance of a third researcher. After sorting out the recorded text, the data will be analyzed using the frame analysis method, including familiarity, identifying thematic frames, indexing, charting, mapping, and interpretation to obtain essential outcomes for patients and clinicians [33].

Step 3: Merging and Collating Outcomes

After completing the systematic review and semistructured interviews, the results from these 2 components will be merged. Guided by the COS-TCM standard, 2 researchers will independently collect the outcomes, resolving any disagreements through consultation or with the input of a third researcher. The data collation process begins with importing the extracted indicators into a Microsoft Excel table for sorting. Outcomes are assigned and matched to the corresponding study numbers to facilitate tracing. Following this, the outcomes undergo preliminary sorting, during which duplicates are removed. All study numbers and amounts indicating the results and frequency of application for each outcome are recorded.

Subsequently, the original outcome measures are standardized. For example, the names of outcomes are standardized, and composite results are reduced to a single result without altering the original meaning of the index. Finally, the names and frequencies of all outcomes are counted. The outcome domains are then determined, with the collected outcomes further classified into 7 domains according to the COMET manual [31] and COS-TCM [26] standards: TCM syndromes, symptoms and signs, physical and chemical testing, quality of life, long-term prognosis, economic evaluation, and safety events.

Step 4: Generating a Preliminary List of Outcomes

A preliminary list of outcomes will be finalized after evaluation by the steering committee. If the number of results collected in the indicator pool is small (≤100), all the outcomes will be included in the outcome list. If the number exceeds 100, the steering committee will conduct an internal vote on the indicator pool. If 90% of the members do not agree to include an item in the original list, it will be removed. Outcomes added by the steering committee will also be included to form the initial outcome list.

Stage 2: Delphi Survey

Involvement of Stakeholders

Stakeholders, including health care experts and patients with TTH, will be invited to participate. Health care experts include

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TCM and integrated Chinese and Western medicine practitioners who are engaged in the field of cerebrovascular disease, Western medicine clinicians in the field of cerebrovascular disease, methodologists in the field of evidence-based medicine, researchers, core journal editors, and other relevant experts.

As the project team's leading unit, the China Academy of Chinese Medical Sciences formed the Encephalopathy Project Team of the TCM Evidence-based Medicine Center with 15 hospitals from 15 provinces. Qualified health care experts from these 15 hospitals will be recruited to participate in the Delphi survey. Patients will be recruited from the Encephalopathy Department of Xiyuan Hospital. The inclusion and exclusion criteria for the health care experts and patients are listed in Table 2.

Table 2. Inclusion and exclusion criteria for health professionals and patients in the Delphi survey.

Category	Inclusion criteria	Exclusion criteria
Health professionals	• More than 1 year of work experience. • Bachelor's degree or above. • Experience working in tertiary hospitals. • Published at least one clinical trial on cerebrovascular disease.	• None.
Patients	• Diagnosed with TTH[a], no limitations on status. • Aged 18 years and older. • Receiving TCM[b] treatment. • Sign an informed consent form. • Capable of reading, understanding, and speaking Chinese or English.	• Patients with severe diseases such as heart failure, cerebral infarction, cerebral hemorrhage, and tumors will be excluded based on medical history, physical examinations, and auxiliary tests.

[a]TTH: tension-type headache.

[b]TCM: traditional Chinese medicine.

Sampling Strategy

Since there is no reliable method for estimating the required sample size, the sample size will be determined according to the needs and conditions of the study [34]. Based on the sample size of previous studies and the implementation specification for the Delphi survey in the COS-TCM [26,35,36], we aim to involve 100 stakeholders, including 30 TCM and integrated Chinese and Western medicine clinicians, 15 Western medicine clinicians, 45 patients, 5 researchers, and 10 methodologists. In total, 2 rounds of the Delphi survey will be conducted.

Round 1 of the Delphi Survey

Developing a Questionnaire for Round 1 of the Delphi Survey

A questionnaire for round 1 of the Delphi survey will be formulated based on a preliminary list of outcomes obtained from systematic reviews, semistructured interviews, and evaluation by the steering committee. The questionnaire will consist of 4 parts, including the description of the purpose of the study, personal information of the respondent, evaluation of the importance of outcome indicators, and open questions. Participants will need to provide arguments for the inclusion or exclusion of each outcome in a COS. These arguments can then be summarized and used to develop proposals for voting on the inclusion or exclusion of each outcome in the second round. The open questions will be mainly supplementary to the questions considered necessary by the participants but not included in the questionnaire. To improve the intelligibility of the questionnaire, different terms will be designed for different stakeholder groups. For example, for Western medicine experts, the interpretation of TCM terms can be translated into the Western medicine language in which they are proficient. A general explanation will be added for patients. Stakeholders will be involved in the design of the questionnaire in advance. Delphi survey items commonly use a 9-point critical or relevant outcome to score the importance of outcomes [26,31]. Scores of 1-3 indicate that the outcome is nonessential," 4-6 indicate that the outcome is "important but not vital," whereas 7-9 indicate that the outcome is "necessary for inclusion." If participants are unable to assess the importance of some outcomes, they will be able to select "uncertain."

Process of Round 1 of the Delphi Survey

The first round of the Delphi survey is expected to be completed within 3 weeks. We will email the electronic version of the questionnaire to health care experts. They will be required to complete the questionnaire within 3 weeks and will be reminded by text messages 1 week and 48 hours before the end of the survey. The working group will assess the number of participants at the end of the second week. If the response rate to the Delphi survey (number of respondents/number of invited participants) is less than 70%, the survey will be extended for another 2 weeks. To increase the awareness rate, the questionnaire will be distributed on workdays. We will recruit eligible patients from the Department of Encephalopathy at Xiyuan Hospital. The consulting doctor will be responsible for introducing the content of the questionnaire to the patient and obtaining their consent and signature on the informed consent form. Team members will then hand out questionnaires to patients for immediate completion. We will try our best to answer the patients' questions.

Data Analysis for Delphi Round 1

The working group will gather all submitted questionnaires and calculate the response rate, average score, score distribution among health professionals and patients, and the number of participants from various stakeholder groups for each outcome item. To ensure that the outcomes of Delphi round 1 are fully shown and can be rescored, all outcomes will be retained in subsequent rounds [31,35,36]. Newly added items can be

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included in Delphi round 2 if the steering committee deems them to be different from the results of Delphi round 1.

Round 2 of the Delphi Survey

Process of Round 2 of the Delphi Survey

Participants who completed the first round of the Delphi survey will be invited to participate in the second round. Each participant will be shown their first-round results, the score distribution of other stakeholders, and a summary of arguments. Based on this feedback, participants will be requested to regrade and score the additional questions in the second round. If the score for an outcome changes significantly between rounds, for example, from "not important" (1-3 points) to "critical" (7-9 points), the rationale for the change will be asked to be mentioned. Participants will also be able to provide suggestions for each survey item.

The Delphi round 2 questionnaires will be distributed like that of round 1 and will be expected to be completed within 3 weeks. For health care professionals, we will provide an electronic version of the questionnaire. A week and 48 hours before the end of the survey, we will send text messages to participants who have not completed the questionnaire. We will recruit eligible patients from the Department of Encephalopathy of Xiyuan Hospital and send the questionnaires to them after obtaining their consent.

Data Analysis for Round 2 of the Delphi Survey

After completing the questionnaire, the working group will calculate the response rate, average score, and score distribution for each item. After analyzing all the data, the average scores for the 2 rounds will be compared, and the reasons for score changes will be analyzed to evaluate whether there was attrition. Considering the results of the second round, in combination with the consensus definition, the outcomes will be categorized as "consensus in," "consensus out," and "no consensus" (Table 3) [31].

Table 3. Definitions of a consensus.

Classification of consensus	Description	Exclusion criteria
Consensus in	Consensus that the outcome should be included in the COS[a].	≥70% of participants score the outcome as 7-9, and <15% score it as 1–3 in both stakeholder groups.
Consensus out	Consensus that the outcome should not be included in the COS.	≤50% of participants score the outcome as 7-9 in both stakeholder groups.
No consensus	Uncertainty about the importance of the outcome.	Anything else.

[a]COS: core outcome set.

Stage 3: Consensus Meeting

Stakeholder Selection

After the 2 rounds of the Delphi survey, we will conduct a consensus meeting. To ensure the quality of the meeting and enhance the credibility of the results, we will invite representatives of various interest groups who have completed all Delphi surveys, steering committee members, and other representative senior experts from various stakeholder groups, regardless of their participation in the previous research process. At the same time, senior clinical experts in the field of TCM, especially academicians, TCM masters, nationally famous TCM practitioners, and leaders of academic groups, will be invited. Patients who participated in both rounds of the Delphi survey will be invited to the consensus conference. The inclusion and exclusion criteria for health professionals who will participate in the consensus meetings are listed in Textbox 1.

The first and the second must be qualified, while the third and the fourth can be qualified by any one of them.

Textbox 1. The inclusion and exclusion criteria for health care professionals who will participate in the consensus meeting.

Inclusion criteria:

- Master's degree or above, with more than 10 years of work experience.
- Clinicians with experience working at tertiary hospitals and at least in the position of associate chief physician.
- Participated in or hosted clinical research projects related to headache.
- Familiarity with evidence-based medicine and methodological research.

Exclusion criteria:

- None.

Sampling Strategy

According to the current guideline recommendations of COS-TCM standards [26], we will invite 25 stakeholders from all over the country, including 9 TCM experts, 5 Western medicine experts, 3 researchers, 5 methodologists, and 3 patients, to participate in the consensus meeting.

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Consensus Meeting Process

The consensus meeting to determine the final COS will be face to face, preferably in Beijing. In exceptional cases, a network video conference will be held. The meeting will last for 2 days.

We will report on our previous work, including the preliminary list of outcomes generated using a systematic review and semistructured interviews and the results of the 2 rounds of Delphi. We will focus on reporting the outcomes of the second round, with outcomes categorized as "consensus in" from all stakeholder groups being prioritized for inclusion in the COS, and outcomes categorized as "consensus out" being excluded. The outcomes categorized as "no consensus" will be discussed at the meeting, and all participants will rate their importance using a 9-point Likert scale. The final COS will be developed according to the consensus definitions [5]. If some outcomes are still considered "no consensus" after 2 rounds of grading, the steering group will determine their inclusion in the final COS.

After formulating the final COS, the measurement method for the outcome index will be determined. The questionnaire will be designed based on the results of the system evaluation. Participants will discuss and vote on the measurement time and methods of the outcome indicators. For the measurement time and method of each outcome indicator, we will select the indicator with the highest percentage recommended in the consensus meeting.

Ethical Considerations

This study received approval from the Ethics Committee of Xiyuan Hospital, China Academy of Chinese Medical Sciences (approval number 2021XLA003-1). We followed the committee's ethical guidelines rigorously to ensure compliance and safeguard participant rights. All participants provided informed consent after receiving comprehensive information about the study, and they were assured that their involvement was voluntary, with the option to withdraw at any time without repercussions. We are dedicated to maintaining participant privacy and confidentiality; all data were anonymized and securely stored, accessible only to the research team. The findings will be presented in a way that does not reveal individual identities. There are no conflicts of interest in this study, and while participants did not receive financial compensation, we extend our heartfelt thanks for their contributions. Data for the systematic review were sourced from publicly available literature, in line with ethical standards for data sharing. The outcomes from the Delphi survey and consensus meeting will contribute to the development of the COS-TCM and will be reported without identifying individual participants.

Results

The protocol for this study has been registered in PROSPERO. The literature search has been completed, and the analysis of the systematic review results is currently under review. The findings will be published once the review process is finalized. A total of 19,033 articles were retrieved from 8 databases. After merging Chinese and English records and removing duplicates, 8074 duplicate articles were identified. Through title and abstract screening, 8844 articles were excluded for irrelevance, and 45 articles were excluded for being in languages other than Chinese or English. Further full-text review led to the exclusion of 672 articles for irrelevance, 67 articles due to inaccessible full texts, and 5 articles due to single-author, noncore publications. This process resulted in 1335 articles related to TCM.

Among these, there were 52 guidelines and clinical pathways, 102 systematic reviews and meta-analyses, 590 RCTs (including 177 on acupuncture, 293 on Chinese herbal medicine, and 120 on other therapies), 66 nonrandomized controlled trials, 1 cohort study, 4 case-control studies, 27 protocol registrations, 113 case series, 28 case reports, 21 cross-sectional studies, 226 review articles, 91 expert opinions, and 14 animal experiments. After the abstract screening, 650 articles were excluded, and 24 articles were excluded after a full-text review due to a lack of reported outcomes. Finally, 626 articles were included for further analysis. The PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist is provided in Multimedia Appendix 3 of the initial draft. The Delphi survey involving stakeholders is scheduled to begin on November 30, 2024, and will be followed by a face-to-face consensus conference on February 1, 2025.

Upon completion of the development of the COS, the study findings will be reported in adherence to the COS-STAR (Core Outcome Set–STAndards for Reporting) statement [37]. This study will be disseminated through publication in an international journal and presentation at national and international conferences focused on TTH to promote the adoption of the Clinical Outcome Scale. The COS findings will be distributed to all participants by email or courier to support its clinical use.

Discussion

Expected Findings

Given the differences among various headache types, it is essential to specify the headache type of study participants in the clinical research design to ensure study accuracy. TTH represents the most common primary headaches and are characterized by pressing or tightening (nonpulsating) sensations on both sides of the head, are of mild or moderate intensity, and are not exacerbated by activity [38]. The current research on COS for headaches mainly focuses on migraine, such as the guidance on the design of outcome indicators for clinical trials of medications, patient-valued indicators, and identification of meaningful migraine outcome measures [38-40]. Compared with migraine, TTH generally receives less attention but has a substantial impact on individuals and society, compromising the quality of life in terms of work, study, and sleep and causing a social burden that cannot be overlooked [2,41-43]. Currently, only 1 published COS is available for TTH, which was initially published in 1995 [22] and updated in 2010 [20]. The clinical research of TCM on TTH have been increasing over the past 10 years [17]. However, there is no COS for TCM clinical research on the treatment of TTH. TCM has a unique diagnosis and treatment mode, and there are significant differences between the evaluation outcomes of TCM and Western medicine

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[44]. Thus, developing a COS for clinical studies on TCM for the treatment of TTH is necessary.

This study was designed according to standard procedures and developed in 3 stages [25,26,31], with each stage conducted under the guidance of the steering group. In designing the COS, special attention is given to several key aspects. In the systematic review, we aim to include the intervention methods of TCM as comprehensively as possible to ensure the thoroughness of literature retrieval. Given the prevalence of nonstandard outcomes in clinical trials of TCM, we will standardize the outcomes obtained from systematic reviews and semistructured interviews. This includes standardizing the names of outcomes, dividing composite outcomes into single outcomes, and classifying outcomes into specific domains to ensure the standardization of COS [37].

Given the limited number of clinical RCTs for TCM treatment of TTHs, we have included observational studies to enrich the core outcome set, increase the diversity of outcomes, and enhance the robustness of our core outcome set. This approach ensures a more comprehensive evaluation of the effectiveness and safety of TCM treatments. To address the differences between these 2 types of studies, we plan to establish different core outcome sets for experimental (RCT) and observational studies. For example, in RCTs, we may focus on factors such as treatment duration and cost, whereas in observational studies, we may emphasize long-term outcomes and the impact on quality of life.

In this study, we included various TCM treatment methods to evaluate their comprehensive impact on tension-type headaches. This diversity helps capture the broad efficacy and patient responses to different treatment methods. However, it also introduces complexity in interpreting the results. We believe this approach is beneficial. First, the inclusion of treatment diversity allows us to assess the overall impact of TCM treatments on tension-type headaches. This method enables us to observe potential synergistic effects and individual differences among different treatment methods, providing more comprehensive guidance for clinical practice. Second, to address the variability of treatment methods, we used standardized outcome measurement tools in the study design. These tools ensure the comparability of results between different treatment methods. In addition, we used stratified analysis and subgroup analysis to handle data heterogeneity, ensuring the robustness of the results. It must be acknowledged that including various TCM treatment methods may introduce a certain degree of heterogeneity, which could affect the interpretation of results. Therefore, we used mixed-effects models in the analysis to adjust for potential differences between different treatment methods.

The study will also comprehensively cover different stakeholders in the Delphi survey and consensus meetings. This includes TCM and Western medicine practitioners, methodologists, researchers, core journal editors, and other relevant experts, as well as patients with TTH, to ensure the representativeness and authority of the COS. In designing the questionnaire for the Delphi survey, we will focus on improving its intelligibility. For instance, TCM terminology will be translated into the language of Western medicine for specialists, while patients will receive a general explanation. The questionnaire distribution will be tailored to the characteristics of stakeholders: healthcare experts will receive a combination of email and electronic questionnaires for efficiency and better data statistics, while patients will complete the questionnaire face to face with a doctor to enhance compliance and understanding. These measures are intended to ensure a higher response rate.

Conclusion

There is a lack of COS for TCM treatment of TTH; therefore, developing one is essential. This study will solve problems posed by nonstandard outcome indicators and limited measurement time, maximize the value of individual trial data, and provide high-quality research evidence for treating TTH with TCM.

Acknowledgments

We thank the patient advisers for contributing to the research. This research was supported by the project “Development and Research of Chaiqiong Qiwei Granules, a Class 1.1 Innovative Traditional Chinese Medicine for the Treatment of Tension-Type Headache” (XYZX0303-12), the Fundamental Research Funds for the Central public welfare research institutes (ZZ13-024-3), the Scientific and Technological Innovation Project of China Academy of Chinese Medical Sciences (CI2021B006), Capital’s Funds for Health Improvement and Research (No. 2020-2-4173), the National TCM Leading Personnel Support Program (NATCM Personnel and Education Department (2018; 12), the Innovation Team and Talents Cultivation Program of National Administration of Traditional Chinese Medicine (ZYYCXTD-C-202007), and the China Academy of Chinese Medical Sciences Innovation Fund (CI2021A01301 and CI2021A00911).

Authors' Contributions

GF, YC, Liang X, JW, and YZ conceived the study. CG, JW, and YZ provided insight into the tension-type headache patient experience. GF, YC, XF, XG, and WC contributed to the systematic review, and Teng J, Tang J, and Liao X provided supervision for all aspects of the manuscript. GF, YC, Liang X, JW, and YZ wrote the protocol and manuscript.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
The COS-STAP (Core Outcome Set-STAndardised Protocol Items) Statement.
[DOCX File , 20 KB - resprot_v14i1e63481_app1.docx]

Multimedia Appendix 2
The search strategy of English databases.
[DOCX File , 20 KB - resprot_v14i1e63481_app2.docx]

Multimedia Appendix 3
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist.
[DOCX File , 29 KB - resprot_v14i1e63481_app3.docx]

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Abbreviations

COMET: Core Outcome Measures in Effectiveness Trials
COS: core outcome set
COS-STAR: Core Outcome Set–STAndards for Reporting
COS-TCM: core outcome set for TCM clinical studies
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
RCT: randomized controlled trial
TCM: traditional Chinese medicine
TTH: tension-type headache

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Protocol

Histopathological Comparison and Expression Analysis of COL1A1, COL3A1, and ELN in the Proximal and Distal Ventral Dartos of Patients With Hypospadias: Protocol for Prospective Case-Control Study

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Abstract

Background: The exact cause of penile curvature in hypospadias remains unknown. Resection of the dartos fascia has been observed to straighten the penis, indicating the involvement of the dartos fascia in the superficial chordee. However, the characteristics of dartos tissue in the distal territory of the ventral penile shaft may differ from those in the proximal aspect of the penile shaft.

Objective: This study aims to investigate the distinct histopathological profiles and expression of COL1A1 (collagen type 1), COL3A1 (collagen type 3), and ELN (elastin) in proximal and distal ventral dartos of patients with hypospadias compared to those without hypospadias.

Methods: This prospective case-control study compares the ventral dartos tissue of patients with hypospadias at different locations with that of patients without hypospadias. Dartos samples will be taken during surgery, with age matching. Histopathology examination uses hematoxylin and eosin and Masson's trichrome stain. The mRNA expression of *COL1A1*, *COL3A1*, and *ELN* will be quantified using a 2-step reverse transcription–polymerase chain reaction analysis.

Results: Previous studies have documented different characteristics of dartos tissue between patients with hypospadias and those without hypospadias. Some studies even suggest resection of the dartos tissue during hypospadias repair. However, this is the first study to compare the characteristics of ventral dartos tissue in patients with hypospadias based on its location along the penile shaft, suggesting potential differences between the distal and proximal locations. We have obtained ethical approval to conduct a prospective case-control study aimed at elucidating these differences in dartos tissue characteristics. The findings of the study are anticipated to be available by 2025.

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Conclusions: Differences in the characteristics of dartos fascia based on its location may require tailored surgical strategies. If the properties of distal dartos tissue closely mirror those of typical dartos tissue, the possibility of avoiding its excision during hypospadias surgery could be considered.

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KEYWORDS

chordee; superficial chordee; COL1A1; COL3A1; dartos tissue; dartos fascia; ELN; elastin; histopathological

Introduction

Hypospadias is a common congenital malformation characterized by the displacement of the urethral meatus on the ventral side of the penis, incomplete ventral prepuce development, and penile curvature known as chordee [1-3]. Hypospadias represents the most prevalent form of penile deformity, with data indicating its occurrence in 1 out of every 125-300 male births [4-6]. The severity of this anomaly varies, with meatus locations ranging from the glans to the scrotum [3].

Hypospadias is typically categorized as either distal or proximal, depending on the location of the meatus [7]. Approximately 70% of cases are classified as distal hypospadias, typically considered as less severe [3,8]. However, certain variants of distal hypospadias may present with severe chordee, necessitating more intricate reconstruction procedures [9]. Chordee, one of the triads of hypospadias, can be further classified as either superficial or deep [6,10]. Superficial chordee involves the superficial fascia, whereas deep chordee affects deeper structures such as the deep fascia, urethral plate, corpus spongiosum, and tunica albuginea, and may involve a disproportion of corpora [10].

The exact cause of the chordee remains unknown. However, resection of the dartos fascia during hypospadias procedures has been observed to straighten the penis, indicating the involvement of the dartos fascia in the superficial chordee [11]. Changes in the structure of collagen (predominantly collagen type 1), reticulin (collagen type 3), and elastin components within the dartos fascia could influence its elasticity and mobility in cases of hypospadias [12]. Previous research has indicated that dartos fascia in hypospadias tends to be thicker and less elastic [13,14]. Dartos fascia also exhibited lower concentrations of collagen types 1, 2, and 3 compared to the normal control group [15].

Studies exploring the association between dartos fascia and chordee remain limited, primarily consisting of qualitative studies [16]. Some studies have suggested the resection of dartos fascia during hypospadias reconstruction surgery [15]. However, there is a lack of studies comparing the characteristics of ventral dartos in patients with hypospadias based on their location towards the meatus, classified as proximal and distal dartos. Variations in dartos fascia characteristics according to location may necessitate different surgical approaches. Therefore, this study aims to investigate the distinct histopathological profiles and expression of COL1A1 (collagen type 1), COL3A1 (collagen type 3), and ELN (elastin) in proximal and distal ventral dartos of patients with hypospadias compared to those with a normal penis.

Methods

Study Design

This study is a prospective case-control study comparing ventral dartos in cases of proximal and distal phenotypic variants of patients with hypospadias with dartos of patients without hypospadias. Dartos samples will be collected during hypospadias repair surgery (cases) and circumcision (controls), with the matching of ages between cases and controls and random allocation. The protocol has been developed in accordance with the 2013 SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist for reporting protocol studies [17].

Study Population and Recruitment

Patients will be recruited from our university-affiliated academic tertiary care hospitals in Jakarta, Indonesia. The inclusion criteria for the cases are as follows: (1) male patients with prepuberty from 6 months to 9 years; (2) a confirmed diagnosis of hypospadias, established through physical examination by a pediatric urologist; and (3) undergoing hypospadias repair at our hospitals during the recruitment period. Conversely, the exclusion criteria for cases are specified as follows: (1) a history of previous hypospadias repair, (2) inadequate tissue samples for analysis, and (3) undescended testis.

The inclusion criteria for the control group consist of (1) male patients with prepuberty from 6 months to 9 years, (2) confirmation of a normal penile condition through a physical examination conducted by a urologist, and (3) undergoing circumcision at our hospitals during the recruitment period. Conversely, the exclusion criteria for controls are outlined as follows: (1) a history of previous genital surgery, (2) insufficient tissue samples for analysis, and (3) undescended testis.

Participants meeting the inclusion criteria and not meeting any of the exclusion criteria will be invited to participate in the study as either cases or controls. According to the sample size formula (5% α and 20% β), each group requires approximately 50 patients (rounded up from 43.18). Considering our patient volume, we anticipate completing recruitment within a 9- to 12-month time frame.

Data Collection

The following data will be collected:

- Patient demographics: information such as age and socioeconomic status.

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- Clinical variables: detailed medical history, associated comorbidities, family history, and birth weight.
- Phenotypic data being captured: location of the urethral opening, plate objective screening tool, urethral defect ratio, penile curvature assessment, and glans-urethral meatus-shaft hypospadias score.

Location of Urethral Opening

The location of the urethral opening is given in Figure 1 [18].

Figure 1. Location of the urethral opening.

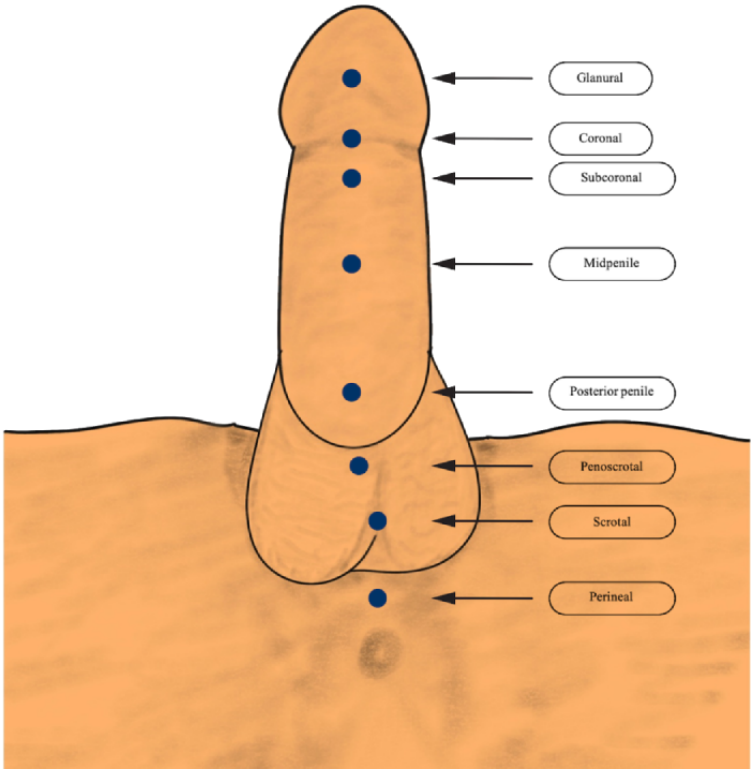

Plate Objective Scoring Tool

Plate objective scoring tool (POST) score is shown in Figure 2 [19,20]. The distal extent of the urethral plate at the midline is identified as point A. The glanular knob, where the mucosal edge of the plate changes direction, is marked as point B, while the glanular-coronal junction is designated as point C. The distance from point A to point B represents the neomeatal length, while the distance from point B to point C indicates the length of the prospective glanular fusion. The POST score has been used to quantify the urethral plate quality in distal hypospadias. This tool's correlation with postrepair complications underscores its relevance in optimizing surgical outcomes [20].

Figure 2. Plate objective scoring tool score calculation (AB/BC). POST: Plate objective scoring tool.

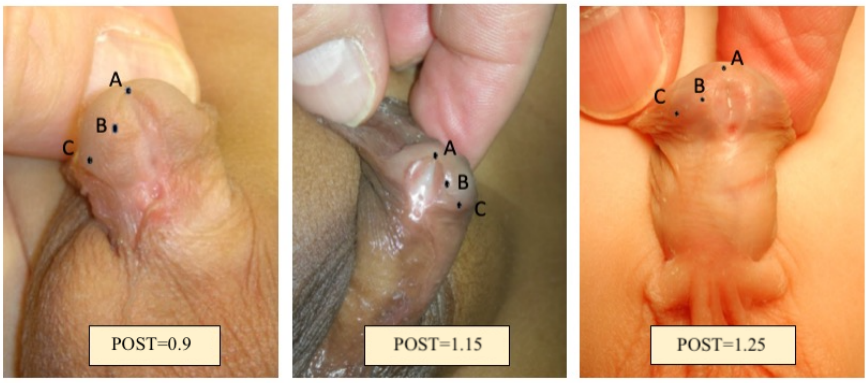

Urethral Defect Ratio

Urethral defect ratio (UDR), which is illustrated in Figure 3, is an objective hypospadias classification system [21]. The stretched penile length is measured along the lateral aspect of the penile shaft, extending from the tip of the glans to the superior border of the pubic bone. Stretching is facilitated using a stay suture in conjunction with a metal ruler. The bifurcation site of the corpus spongiosum penile curvature is evaluated following complete degloving of the penile skin. The distance between the glandular knobs (B–B imaginary line) and the bifurcation site of the corpus spongiosum penile curvature is

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defined as the urethral defect, and the UDR is calculated by dividing UD by stretched penile length [21].

Figure 3. Urethral defect ratio. B–B: the distance between the glandular knobs.

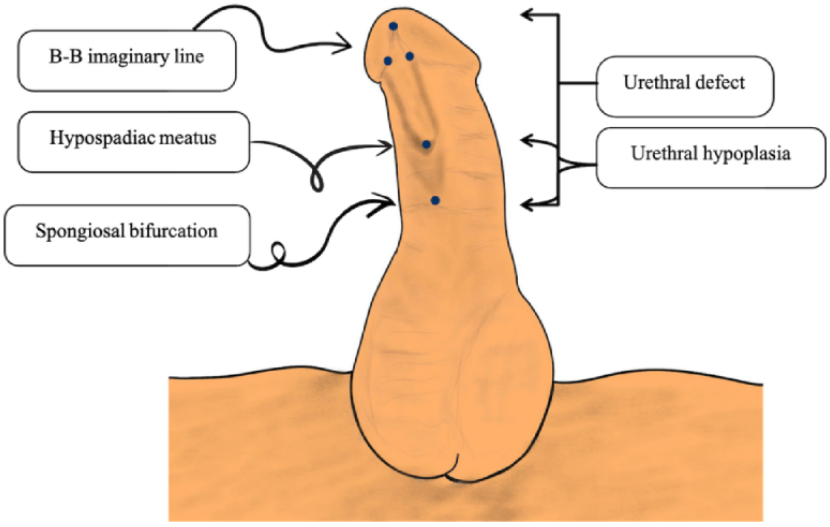

Penile Curvature Assessment

Penile curvature assessment is shown in Figure 4 [22]. To evaluate penile curvature intraoperatively, we have established a standardized protocol using mobile apps. This involves capturing a lateral photograph of the penis from a distance of 25-30 cm, ensuring alignment parallel to the penile shaft, and incorporating an upward oblique angle between 10° and 30° along the same vertical axis. The captured image is subsequently processed using specialized software, such as Angle Meter 360, where 3 critical anatomical landmarks are marked: the penile base, the point of angulation, and the distal midpoint.

In Figure 4, three key reference points are established for measurement: (1) corresponds to the intersection of the midline axis of the distal penile shaft with the Y-line, defined as a perpendicular line originating from the tip of the glans, (2) represents the intersection of the midline axes of the proximal and distal segments of the penile shaft, and (3) signifies the intersection of the midline axis of the proximal penile shaft with the X-line, a perpendicular line drawn at the level of the pubic bone. The degree of penile curvature is calculated by subtracting the measured angle from 180°.

Glans-Urethral Meatus-Shaft Hypospadias Score.

In the glans-urethral meatus-shaft (GMS) scoring system, each of its 3 components is assigned a numerical value ranging from 1 to 4 [23]. The total GMS score can range from a minimum of 3, indicative of very mild hypospadias, to a maximum of 12, representing severe hypospadias. Studies have demonstrated its predictive value for postoperative complications, highlighting its utility in guiding surgical decision-making [24].

Figure 4. Penile curvature assessment. The distal midpoint (A); the point of angulation (B); and the penile base (C).

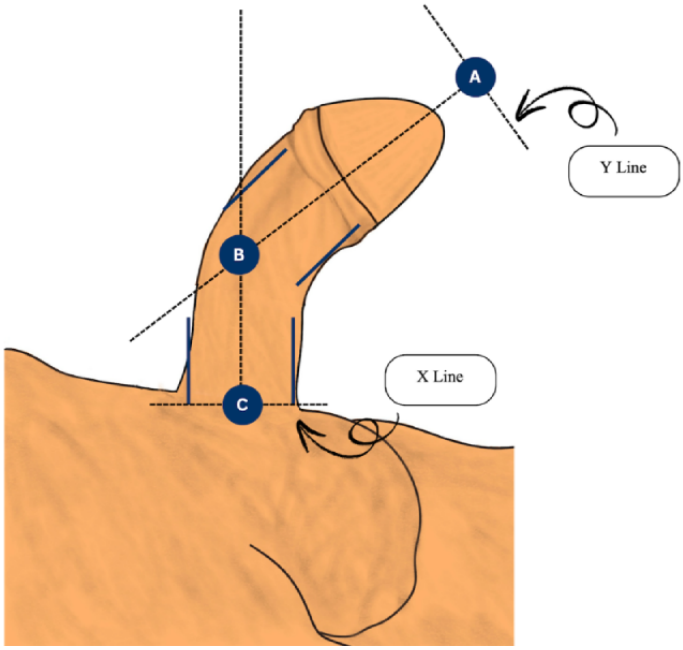

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Dartos Fascia Sampling

Dartos fascia samples are obtained following penile degloving in the hypospadias group. The dartos tissue is collected from the ventral side at two distinct locations: distal to the urethral meatus (distal to spongiosa bifurcation) and proximal to the urethral meatus (proximal to spongiosa bifurcation). Conversely, in the control group, dartos tissue is acquired from the ventral side coronal area. The illustration of the samples' location is shown in Figure 5. The size of dartos tissue collected at each location ranges from 25 to 100 mm^2. To mitigate collection bias, all samples are obtained by a single surgeon.

Figure 5. Dartos fascia sampling in the hypospadias group (solid line: distal dartos, dashed line: proximal dartos) and control group (circle).

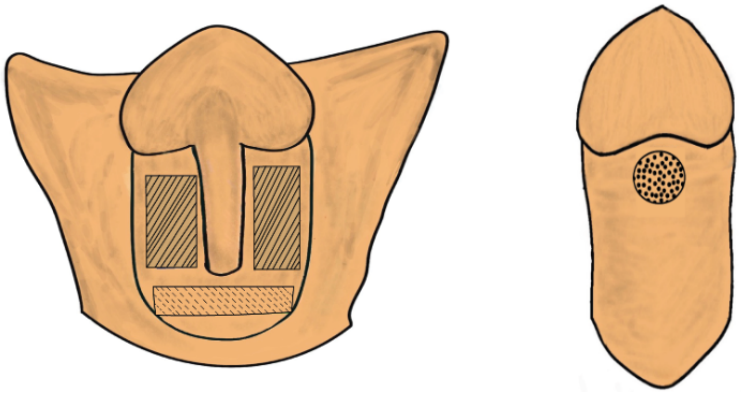

Histopathology Preparation

Dartos samples will be immersed in a 10% buffered formaldehyde solution for fixation. Subsequently, the fixed tissue will undergo dehydration, infiltration, and embedding in liquid paraffin to achieve solidification. The paraffin-embedded blocks will then be sectioned using a microtome at a thickness of 4-5 µm and mounted onto glass slides. Two distinct staining methods, namely hematoxylin and eosin and Masson's trichrome stain, will be used to assess the cross-sectional area and collagen percentage of the dartos tissue. All histopathological assessments and quantifications will be conducted in a blinded manner using the QuPath software.

Reverse Transcription–Polymerase Chain Reaction Analysis

Messenger ribonucleic acid expression levels of collagen genes (*COL1A1* and *COL3A1*) and elastin gene (*ELN*) will be quantified through a two-step reverse transcription–polymerase chain reaction analysis. Dartos tissue samples will be preserved with RNA later, followed by total RNA extraction using an RNA extraction kit. Subsequently, the extracted RNA will undergo reverse transcription to synthesize complementary deoxyribonucleic acid, which will then be amplified via PCR to detect the expression levels of the target genes.

Statistical Analysis

All data will undergo analysis using SPSS (version 24.0; IBM Corp) software. Descriptive statistics will be used, presenting frequency for categorical variables and mean or median for numerical variables. Comparative analysis of collagen percentage and expression of *COL1A1*, *COL3A1*, and *ELN* among proximal hypospadias dartos, distal hypospadias dartos, and normal dartos will be conducted using either 1-Way ANOVA or Kruskal-Wallis test, contingent upon the normality of data distribution. Post hoc analysis may use the Bonferroni test, Games-Howell test, or Mann-Whitney test as deemed appropriate. Subanalysis based on hypospadias classification (distal and proximal) and chordee severity (mild, moderate, or severe) will also be performed. Subanalysis based on the UDR and POST scores will also be performed [17].

Ethical Considerations

The Medical Research Ethics Committee at Universitas Indonesia approved our study protocol in March 2024 (KET-473/UN2.F1/ETIK/PPM.00.02/2024). Participants and/or their guardians will receive comprehensive information both verbally and in writing to ensure informed consent. Upon choosing to participate, they will be requested to sign the informed consent form.

Results

Previous studies have documented different characteristics of dartos tissue between hypospadias and patients without hypospadias [11,13-15]. Some studies even suggest resection of the dartos tissue during hypospadias repair [15]. However, no previous study has systematically compared the distinct characteristics of proximal and distal dartos tissue in patients with hypospadias. We have obtained ethical approval to conduct a prospective case-control study aimed at elucidating these differences in dartos tissue characteristics. The findings of the study are anticipated to be available by 2025.

Discussion

Anticipated Findings

The exact etiology of chordee in hypospadias remains unknown. Nonetheless, inadequate management of chordee during hypospadias repair may escalate the incidence of complications. Moreover, significant chordee can impede sexual function in later adulthood [10]. The aberrant curvature may result in ineffective insemination, painful erections, or hindered vaginal insertion. Therefore, meticulous management of chordee in hypospadias is imperative [18].

Numerous studies have indicated abnormalities in dartos tissue in hypospadias [11,13-15]. Surgical procedures involving penile

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degloving and dartos tissue excision have been proposed to alleviate superficial chordee [15,18]. However, our preliminary observations during hypospadias surgery have revealed distinct characteristics between the dartos tissue located proximally and distally to the meatus. Specifically, we have noted that the proximal dartos tissue tends to exhibit greater thickness and reduced elasticity, potentially contributing to superficial chordee. Consequently, we aim to conduct a comparative analysis of the extracellular matrix properties of distal and proximal dartos tissue in this study. Variations in dartos fascia characteristics according to location may necessitate different surgical approaches. Should the characteristics of the distal dartos resemble those of normal dartos tissue, sparing its resection during hypospadias surgery may be feasible. Using the distal dartos as a secondary layer for neourethral coverage could potentially enhance surgical outcomes.

Conclusion

Differences in the characteristics of dartos fascia based on its location may require tailored surgical strategies. If the properties of distal dartos tissue closely mirror those of typical dartos tissue, the possibility of avoiding its excision during hypospadias surgery could be considered.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

COL1A1: collagen type 1
COL3A1: collagen type 3
ELN: elastin
GMS: glans-urethral meatus-shaft
POST: plate objective scoring tool
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
UDR: urethral defect ratio

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Protocol

Effectiveness of Composite Ayurveda Regimen in a Black Box Design for the Management of Rheumatoid Arthritis: Protocol of a Single Arm, Community-Based Study

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Abstract

Background: Rheumatoid arthritis (RA) is an autoimmune disease that affects joints and can have extra-articular manifestations. RA usually tends to be progressive and leads to substantial health care burdens, both in terms of disability and economic costs. Despite the various treatment modalities available, there is still an urgent need for safe and effective medicine based on the pattern of disease presentation. The increasing interest in complementary and alternative medicine has created a demand for extensive research in this area.

Objective: This clinical study is designed to evaluate the effectiveness and tolerability of a composite Ayurveda regimen in RA.

Methods: The study is a single-arm (pre-post design), community-based interventional study with a black box design being conducted at 6 study centers. A total of 240 participants aged between 18 and 65 years, diagnosed with RA as per the 2010 American College of Rheumatology and the European League Against Rheumatism criteria are recruited as per the selection criteria. All the participants received Ayush-SG and *Rasnasaptak Kashaya* for 84 days along with customized treatment as per the disease presentation and associated complaints. The outcome measures include the change in disease activity score (DAS)-28 with erythrocyte sedimentation rate, disease-specific biochemical and inflammatory markers, Disability Index score, change in the participant's assessment of pain and frequency of use of conventional analgesics or nonsteroidal anti-inflammatory drugs from baseline. The tolerability of interventions is assessed through the occurrence of adverse events. Categorical variables will be analyzed with McNemar chi-square test, and continuous variables will be assessed using the paired *t* test or Wilcoxon test for pre-post assessment. The level of significance will be 5%.

Results: The recruitment of participants was initiated in December 2023. The participant recruitment was completed in March 2024 and out of 240 participants enrolled, 222 (92.5%) completed the study up to the last follow-up. Data verification, compilation, and analysis are under process. After data analysis, the study's findings will be published in a peer-reviewed journal.

Conclusions: This interventional study that incorporates the black box approach may provide a strong framework for managing RA. This design is a more reliable method for evaluating the effectiveness and tolerability of the composite Ayurveda regimen in RA.

Trial Registration: Clinical Trial Registry-India CTRI/2023/06/054203; https://tinyurl.com/4prvwr6z

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KEYWORDS

rheumatoid arthritis; Amavata; Ayush-SG (coded drug); Rasnasaptak Kashaya

Introduction

Background

Rheumatoid arthritis (RA) is a chronic inflammatory autoimmune disease that can damage joints and affect extra-articular organs. In 2019, 18 million people worldwide were living with RA. Women accounted for 70% of cases, and over half were older than 55 years [1]. The articular manifestation of RA includes symptoms such as musculoskeletal pain, swelling, and stiffness of joints. It is usually symmetric and initially manifests in small joints and progresses to larger joints. Over time, joint inflammation can lead to joint destruction, including loss of cartilage and bone erosion [2]. The symptoms of RA vary in patients; some patients have mild self-limited disease, while many experience joint destruction, severe physical disability, and multiple comorbidities. RA tends to be progressive in nature, involving a worsening of symptoms over time, and often begins for many people during the early or middle years of life, thus causing a heavy burden on society in terms of disability, health, and economic costs. The available evidence for pain management in RA involves the use of disease-modifying antirheumatic drugs and medications such as nonsteroidal anti-inflammatory drugs (NSAIDs) which play an important role in its management but may suppress the immune system and, lead to an increased risk of infections as well other side effects as gastrointestinal disturbances [3,4]. People from all over the world are also developing an interest in traditional herbal practices. It is reported that 60% to 90% of persons with arthritic conditions use complementary and alternative medicines [5-7]. In a study conducted in the United States, it was reported that around 60% of persons with arthritic conditions including RA use complementary and alternative medicines. Of these, 28% reported a history of herbal therapies, and 22% used diet supplements [8].

RA resembles the condition *"Amavata"* (rheumatism due to Ama) described in Ayurveda, where both the *Ama* (undigested or intermediate product of digestion or metabolism that act as a toxin in the body) and *Vata Dosha* (*Dosha* responsible for movement and cognition) become vitiated and located in the *Sandhi* (joints) leading to pain and inflammation in the joints. The causative factors of Amavata are described as *Viruddha Ahaara* (antagonistic food), *Viruddha Vihaara* (antagonistic lifestyle), *Mandagni* (subdued digestive power), a sedentary lifestyle, and exercising immediately after meals. Long-term adherence to these etiological factors causes vitiation of *Vata* along with impaired digestion and metabolism in the body leading to the formation of *Ama*. The gradual accumulation of *Ama* obstructs different *Srotas* (structural or functional channels) in the body and further vitiation of *Tridoshas* (3 regulatory functional factors of the body). The Ama and Vata along with other vitiated Doshas lead to the impairment of *Dhatus* (major structural components of the body) mainly joints causing the *Amavata* [9].

The Ayurvedic classics describe various treatment modalities and therapeutic formulations based on the condition and clinical presentation of the disease. The disease pattern of *Amavata* in a person depends on the extent of *Ama* association, *Dosha* vitiation, and the chronicity of the condition. In cases of *Amavata* with significant *Ama* association, there may be obstructions in the *Srotas*, leading to symptoms like severe pain, swelling, elevated temperature, and redness in the joints. The treatment for this scenario should prioritize digesting *Ama* and clearing the obstructions in the *Srotas* along with alleviation of vitiated *Dosha*. If there is only mild *Ama* association and less *Dosha* imbalance, symptoms may be limited to joint pain, stiffness, and minimal swelling, indicating medications that digest *Ama* and alleviate *Doshas* predominantly *Vata*. In chronic cases, patients may experience symptoms like mild aching stiffness, fatigue, or anemia. The choice of medicines varies according to each pattern of presentation and must be determined by the practitioner following a thorough assessment of the patient's condition. In a standard randomized controlled trial (RCT), it is not feasible to design a customized regimen that tailors medicine selection to specific conditions. In such instances, a specialized trial design should be considered to facilitate the prescription of medicines tailored to the clinical manifestations and disease stage of each individual. To address this issue, it is essential to consider modifying study designs, including exploring alternative approaches such as "black-box" designs [10].

The treatment plan for *Amavata* is focused on the digestion of *Ama* and the alleviation of *Vata*. For digesting the *Ama* and removing obstruction from the *Srotas*, drugs having *Katu* and *Tikta* Rasa (pungent and bitter tastes), *Pachana* (enhancing digestion), and *Dipana* (enhancing metabolic fire) properties have to be administered [11]. Ayush-SG, *Rasnasaptak Kashaya*, and *Guduci* (*Tinospora cordifolia*) have the above-said properties. Ayush-SG is a coded drug developed by the Central Council for Research in Ayurvedic Sciences (CCRAS) for the management of Amavata [12]. *Rasnasaptak Kashaya* is described in the context of *Amavata* treatment in Ayurveda classics [13]. *Brihat Saindhawadi Taila* and *Dashang Lepa* are used for local application to pacify pain and inflammation of the joints [14-16]. Considering the major patterns of disease presentations, a black box design has been planned for this study and the treatment has been tailored according to the accompanying symptoms.

Objectives

The primary objective of the study is to evaluate the effectiveness of a composite Ayurveda regimen on the disease activity score (DAS) in RA.

The secondary objective is to evaluate the effectiveness of the composite Ayurveda regimen on the disease-specific biochemical and inflammatory markers and assess the tolerability of Ayurveda regimen in RA.

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Methods

Study Design

This is a single-arm (pre-post design), community-based interventional study with a black-box research design.

Study Setting

The study is conducted through 6 research institutes under CCRAS at New Delhi, Patiala, Guwahati, Gwalior, Vijayawada, and Chennai in identified areas predominantly dwelled by the scheduled caste population near the institute.

Inclusion Criteria

Participants aged between 18 and 65 years, diagnosed with RA as per the 2010 American College of Rheumatology and the European League Against Rheumatism criteria [17], and willing to give written informed consent for participation are enrolled in the study.

Exclusion Criteria

Participants presenting with complications of RA, for example, deformity of joints/bones, pleura-pericardial disease, participants with extra-articular manifestations of RA and gastrointestinal symptoms, those with joint prosthesis or unable to walk without support or confined to a wheelchair, participants with Hemoglobin <8 g/dL, diagnosed with other arthritis like osteoarthritis, gouty arthritis, tuberculous arthritis, psoriatic arthritis, spondyloarthropathy, active fibromyalgia, juvenile chronic arthritis, ulcerative colitis, or other systemic inflammatory conditions and autoimmune diseases, having blood pressure ≥ 160/100 mm Hg, or hemoglobin A_{1c} (HbA_{1c})>8%, on medication with corticosteroids, antidepressants, anticholinergics, etc or Ayush interventions/folk medicine or any other drugs that may influence the outcome of the study are excluded from the study. Participants with diagnosed concurrent neurological, pulmonary, or endocrine disorder, or unstable cardiovascular disease, with concurrent serious hepatic disorder (defined as aspartate aminotransferase or alanine aminotransferase, total bilirubin, alkaline phosphatase > 2 times upper normal limit) or renal disorders (defined as S Creatinine > upper normal limit); participants with alcohol use disorder (CAGE score >2) or any other substance abuse; and pregnant or lactating woman are not enrolled in the study.

Study Procedure

The participants have been screened from the out-patient departments, camps, or door-to-door visits in the identified areas. Before the initiation of the study, the head of the village or local administrative authority and the residents of the area were informed about the study in detail, in their regional language. Participants diagnosed with RA have been enrolled based on the defined inclusion and exclusion criteria.

Laboratory investigations such as complete blood count with an erythrocyte sedimentation rate (ESR), liver function test, renal function test, and C-reactive protein, RA factor (quantitative), serum immunoglobulin G, and serum immunoglobulin M have been conducted at baseline and the end of the treatment (84th day). HbA_{1c} levels are determined at baseline only (Figure 1).

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Figure 1. Flow diagram depicting the study schedule for the assessment of the effectiveness of composite Ayurveda regimen for the management of rheumatoid arthritis. ADR: Adverse Drug Reaction; DAS: disease activity score; ESR: erythrocyte sedimentation rate; VAS: visual analog scale.

Intervention

The treatment regime was customized based on the major patterns of disease presentation in each participant. All of them have been given oral medication Ayush-SG one gram in tablet form twice a day with lukewarm water after meals and *Rasnasaptak Kashaya* 20 mL twice a day (80 mL water added in 10 g of course powder and boiled until remains 20 mL) before meals for 12 weeks. Along with this, *Brihat Saindhavadi Taila* has been given for local application in cases with only articular manifestations (joint pain, stiffness, and minimal swelling). Participants with severe pain and swelling (boggy swelling or affusion elicited by fluctuation test), elevated body or joint temperature, and redness of joint, have been administered *Guduchi Ghana vati* (*Sanshamani Vati*) orally in the dose of 500 mg twice a day with lukewarm water after meals and

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Dashanga Lepa for local application. *Punarnavadi Mandura* has been given orally in a dose of 500 mg twice a day with lukewarm water after meals in participants with mild aching, stiffness, fatigue, and anemia.

Incidental medication has been given to the participants in case of any associated complaints. For constipation, *Triphala Churna* has been given in a dose of 5 g orally with lukewarm water at night before sleep. For *Mandagni*, *Vaishwanar Churna* has been administered in a 2.5 g dose orally with lukewarm water twice a day just after food. For the participants having insomnia/anxiety, *Ashwagandha Churna*, 3 g has been given orally twice a day. The duration of incidental medication is decided by the investigator as per the requirement.

The medicines were purchased from Ayurveda manufacturing pharmacies that are certified with good manufacturing practices. Ayush-SG was procured from the Central Ayurveda Research Institute's Ayurveda Pharmacy, Jhansi, Uttar Pradesh, India. All other medicines administered in the study were procured from the Indian Medicines Pharmaceutical Corporation Limited (Mohan, Almora, Uttarakhand, India).

Withdrawal Criteria

The participant has been withdrawn from the study if they have not been willing to continue, if there has been a worsening of RA symptoms, or if they have developed any other illness mentioned in the exclusion criteria. The decision to withdraw a participant from the study has been made solely by the Investigator, who has then had to provide a detailed justification and indicate the line of further management if needed.

In the case of any adverse event, serious adverse event, or adverse drug reaction, the Institutional Ethics Committee (IEC) and Data Safety Monitoring Board are to be informed and participants are to be withdrawn from the study.

Compliance

During the intervention period, compliance has been evaluated based on the amount of study medication that is consumed. This has been assessed using a compliance assessment form issued to the participants to fill up.

Concomitant and Rescue Medication

Concomitant therapy has been continued for diabetes mellitus, hypertension, or any other disease, that has not been specifically mentioned in the exclusion criteria**.** The investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care during the intervention period**.** The name, indication, dose, unit, frequency, start date, and stop date (if applicable) for all interventions (medicine/procedure/therapy) have been recorded on each participant's case record form (CRF)**.** Administration of any rescue medicines in case of any medical emergency has been documented in the CRF.

Outcome Measures

The primary outcome of the study is the change in the DAS-28 score (with ESR) [18] and it is assessed at baseline and the end of the treatment (84th day). Secondary outcomes include the change in disease-specific biochemical and inflammatory markers (RA factor, C-reactive protein, and ESR) and serum immunoglobulin levels (Immunoglobulin G and Immunoglobulin M), participants' assessment of Pain, Global assessment of disease activity, change in Disability Index score and frequency of use of conventional analgesic/NSAIDs medicines and occurrence of adverse events if any. The change in disease-specific biochemical and inflammatory markers and serum immunoglobulin levels are assessed at baseline and on the 84th day. The participants' assessments for pain and global assessment of disease activity are assessed using the visual analog scale [19] ranging from 0 mm (no pain) to 100 mm (worst possible pain) at baseline, 28th day, 56th day, and 84th day. The change in Disability Index score is assessed using the Indian Health Assessment Questionnaire [20] at baseline, 28th day, 56th day, and 84th day. The frequency of use of conventional analgesic/NSAIDs medicines and occurrence of adverse events are also assessed in a time frame of baseline, 28th day, 56th day, and 84th day (Figure 1).

Sample Size

Due to the low prevalence of RA (around 0.7% to 1%) [21], it is not feasible to recruit the participants based on the scientific line of sample size theory. Therefore, based on feasibility and the availability of resources, a total of 240 participants have been recruited from 6 institutes (40 participants at each center), within the given time frame.

Recruitment

The eligible participants have been screened for inclusion and exclusion criteria from the outreach out-patient departments/camps/door-to-door visits conducted in the identified area/village under the selected study sites. The participants have been informed about the study in detail (in their regional language) through banners and IEC materials.

Allocation

Since the study is conducted in a black box study design and the intervention is classified based on major disease patterns, allocation does not apply to this study.

Data Collection Methods

Demographic data, clinical history, details of concomitant medications, the score of 2010 American College of Rheumatology and the European League Against Rheumatism criteria, DAS-28, and other assessment parameters of the participants have been recorded in the CRF. The participants were followed up on the 28th day, the 56th day, and the 84th day**.** During follow-ups, the occurrence of any symptom and the need for any rescue medication have been recorded. The contact number of the investigator along with the address of the CCRAS institute have been provided to the participants at the time of enrollment**.** Participants have been instructed to inform about any adverse event that happens during the study period**.**

Besides a hard copy of CRF, the data have been recorded in e-CRF also. All source documentation supporting entries into the CRFs are maintained and will be kept readily available. To ensure the quality, the data are checked for consistency, omissions, and any apparent discrepancies. The reason for

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withdrawal or dropping out of participation is recorded in the CRF.

Data Monitoring

A Data Safety Monitoring Board has been constituted to monitor the clinical study and to ensure the safety of the participants. The inspection of various records of the clinical study (CRFs and other pertinent data) will be done by the CCRAS representatives and regulatory authority to ensure strict adherence to the study protocol and correct documentation of the data. Any problems faced by the research staff at the participating site have been addressed timely. The Clinical Monitoring Committee is responsible for verifying the CRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research.

Deviation From the Protocol

Any deviation from the study protocol is implemented in the study only after approval from the IEC.

Ethical Considerations

The study is conducted according to the national ethical guidelines for biomedical and health research involving human participants (2017) by the Indian Council of Medical Research; and Good Clinical Practice guidelines for clinical trials in Ayurveda, Siddha, and Unani Medicine, 2013. Approval from the IEC of all the concerned institutes has been obtained, and the study has been registered with the Clinical Trial Registry-India (CTRI/2023/06/054203 dated June 20, 2023). The participants have been educated by the investigator verbally and using a written patient information sheet in their regional language and have been asked to provide consent in writing regarding their participation in the study. The participants have been made aware that they are free to leave the study if they wish to discontinue without giving a reason, and without my medical care or legal rights being affected. All the information and records of the study participants including their names and identities are kept confidential in password-protected Microsoft Excel sheets. All the study participants are covered by a clinical trial insurance policy which included coverage for any adverse events occurring during the study.

Statistical Analysis

After data collection, verification of its accuracy and limits will be done. The filtered data will be used for additional analysis and interpretation. The Categorical variables will be reported in number (percentage) and analysis of pre-post-trial outcomes will be done by the Mc-Nemar chi-square test. The continuous variables (like scores and lab parameters) will be analyzed by paired *t* test/Wilcoxon test as per the distribution of data in the pre-post trial situation. The assessment parameters assigned in more than 2 follow-ups will be analyzed using the r-ANOVA/Friedman test/ Cochran Q test. The continuous data having normal distribution will be represented as mean (SD) and the data not having normal distribution as median (IQR). The 5% level of significance will be used throughout the analysis. The SPSS (version 26.0; IBM Corp) software will be used to conduct the analysis.

Results

The enrolment of the participants in the study was initiated in December 2023 and the final follow-up was completed in March 2024. Out of 240 participants enrolled, 222 (92.5%) participants have completed the study. Data verification, compilation, and analysis are under process. The findings from the study will be published in peer-reviewed journals after the completion of data analysis.

Discussion

Expected Findings

The selected composite Ayurvedic regimen is anticipated to reduce DASs in study participants with RA. This study was designed using a black box approach, which allows for the selection of medicine according to the pattern of disease presentation and associated symptoms instead of evaluating a specific medicine for a particular diagnosis [10].

Ayurvedic approach to treating a disease depends on the breaking of pathogenesis and alleviation of symptoms. The selection of medicines depends on different stages of pathogenesis that are usually assessed by the presentation of the disease. The available studies for the evaluation of Ayurvedic interventions in rheumatoid mostly used study designs such as single-arm studies, non-RCTs, and RCTs using controls from either Ayurveda or modern conventional drugs [22-25]. In these studies, the intervention was the same for all participants diagnosed with RA and did not consider differences in clinical conditions or the relationships with *Dosha* or *Ama*. Furst et al [26] have used modified RCT as a double-blind, randomized, double-dummy design to evaluate the efficacy of Ayurvedic medicines, both alone and in combination with the standard drug, methotrexate. In this study, 148 distinct Ayurvedic formulations with various dosage forms were used, allowing physicians to prescribe the appropriate combination of drugs based on the specific needs of the patient [26]. In our study, we have designed a single-arm black box design that allows the management of RA in different clinical manifestations on the basis of pathogenesis in terms of the association of *Ama* and *Dosha* along with the chronicity of the disease. For this, a predefined composite Ayurvedic regimen was used that is anticipated to reduce DASs in study participants with RA along with a change in disease-specific biochemical markers. Ayush-SG and *Rasnasaptak Kashaya* were given to all participants, while other medications were customized as per the form of disease presentation.

Ayush-SG contains 3 main ingredients as follows: *Shunthi* (*Zingiber officinale* Roscoe), *Guggulu* (*Commiphora wightii* Bhan), and *Godanti Bhasma* (Incinerated calcium sulfate/ gypsum) [12]. *Shunthi* is known to have anti-inflammatory, analgesic, immunomodulatory, and antioxidant activities [27]. Studies show that guggulipid, the oleo-gum resin of the plant *Commiphora wightii*, demonstrates significant antiarthritic and anti-inflammatory effects by targeting key molecular pathways involved in inflammatory responses [28,29]. *Rasnasaptak Kashaya* contains *Shunthi* along with other herbal ingredients such as *Rasna* (*Pluchea lanceolata* Oliver and Hiem), *Gokshura*

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(*Tribulus terrestris* L), *Guduci* (*Tinospora cordifolia* [Willd] Miers), *Punarnava* (*Boerhaavia diffusa* Linn), *Eranda* (*Ricinus communis* Linn), *Devadaru* (*Cedrus deodara* [Roxb] Loud), and *Aragvadha* (*Cassia fistula* Linn). All these drugs possess anti-inflammatory activities and *Gokshura*, *Eranda*, and *Devadaru* have analgesic properties also. *Rasna* and *Guduci* have antiarthritic and *Aragvadha* has antirheumatic properties additionally [30-36]. A previous study on *Vatari Guggulu*, *Rasnasaptak Kashaya*, and *Brihat Saindhavadi Taila* has shown a significant change in DAS-28, disability index (Indian Health Assessment Questionnaire), and quality of life assessment (SF-36) scores when administered for 12 weeks [37].

Guduci Ghanavati contains an aqueous extract of *Tinospora cordifolia*, which possesses antiarthritic, anti-inflammatory, immunomodulatory, and antipyretic properties. The in vivo studies on aqueous extract of *T cordifolia* showed significant anti-inflammatory effects comparable with indomethacin and the mode of action is opined to be similar to that of a nonsteroidal anti-inflammatory agent [36].

Brihat Saindhavadi Taila is described as effective in pacifying pain in Amavata [37]. It is found effective in alleviating pain, swelling, and tenderness when administered locally in combination with other internal medications [14,38]. Most of the ingredients in this formulation possess anti-inflammatory properties [39-44]. *Eranda*, the base oil in the formulation, contains ricinoleic acid that has shown anti-inflammatory properties on peripheral application in an in vivo study in guinea pigs [45].

Dashanga lepa consists of 10 ingredients as follows: *Sirisha* (*Albizzia lebbeck* Benth), *Madhuyashti* (*Glycyrrhiza glabra* Linn), *Tagara* (*Valeriana wallichii* DC), *Raktachandanam* (*Pterocarpus santalinus* Linn), *Ela* (*Elettaria cardamomum* [Linn] Maton), *Jatamansi* (*Nardostachys jatamansi* DC), *Haridra* (*Curcuma longa* Linn), *Daruharidra* (*Berberis aristata* DC), *Kushta* (*Saussurea lappa* CB Clarke), and *Hrivera* (*Pavonia odorata* Willd). Most of the ingredients in this formulation have potent anti-inflammatory properties, and *Tagara* and *Jatamansi* have analgesic action too [46-54]. The anti-inflammatory and analgesic activities of *Dashanga Yoga/lepa* have been demonstrated in an in vivo study conducted on Wistar rats [55].

Anemia is one of the common comorbidities found in RA patients [56]. *Punarnavadi Mandura* contains ingredients such as *Amalaki* (*Phylanthus embelica* Linn), *Danti* (*Baliospermum montanum* Muell – Arg), *Pippali* (*Piper longum* Linn), *Punarnava*, *Kushtha* (*Saussurea lappa* C.B. Clarke) and *Daruharidra* (*Berberis aristata* DC) along with a mineral drug *Mandura bhasma* (incinerated iron oxide). An in vivo study conducted on *Punarnavadi Mandura* has shown significant hematinic activity against mercuric chloride-induced anemia in albino rats [57]. A previous clinical study on the drug also showed significant improvement in serum iron and serum ferritin levels with improvement in the symptoms of anemia such as fatigue, pallor, etc [58].

The pharmacological properties of the ingredients in the formulations and previous studies suggest that the selected composite Ayurveda regimen for the study will be effective in the management of RA. The findings from the study will be disseminated through reputed peer-reviewed journals after the completion of the data analysis. This research represents an initial effort using a black box design, which could lay the groundwork for customized interventions rooted in Ayurvedic concepts of pathogenesis and symptomatology.

Strength and Limitations

This study is planned using a black box design that will help in providing evidence-based data regarding the effect of personalized medications in Ayurveda for the management of RA. However, the study protocol has some limitations also. The study protocol does not include the assessment of inflammatory markers such as anticyclic citrullinated peptide. In this study, 3 distinct categories are considered for the composite Ayurvedic regimen. Future research could be designed to address a wider variety of disease presentations.

Future Scope

This study protocol could be extended to similar conditions that are presented with a wide range of symptoms that require a more individualized approach. Future RCTs may be planned to compare the Ayurveda treatment regimen with conventional standard treatment protocol.

Conclusions

This interventional study that incorporates the black box approach may provide a strong framework for managing RA. This design may be a more reliable method for evaluating the effectiveness and tolerability of the composite Ayurveda regimen in RA.

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Conflicts of Interest

None declared.

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Abbreviations

CCRAS: Central Council for Research in Ayurvedic Sciences
CRF: case record form
CTRI: Clinical Trial Registry-India
DAS: disease activity score
ESR: erythrocyte sedimentation rate
HbA1c: hemoglobin A1c
IEC: Institutional Ethics Committee
NSAID: nonsteroidal anti-inflammatory drug
RA: rheumatoid arthritis
RCT: randomized controlled trial

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Protocol

Antibiotic Use In Utero and Early Life and Risk of Chronic Childhood Conditions in New Zealand: Protocol for a Data Linkage Retrospective Cohort Study

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Abstract

Background: The incidence of many common chronic childhood conditions has increased globally in the past few decades, which has been suggested to be potentially attributed to antibiotic overuse leading to dysbiosis in the gut microbiome.

Objective: This linkage study will assess the role of antibiotic use in utero and in early life in the development of type 1 diabetes (T1D), attention-deficit/hyperactive disorder (ADHD), and inflammatory bowel disease.

Methods: The study design involves several retrospective cohort studies using linked administrative health and social data from Statistics New Zealand's Integrated Data Infrastructure. It uses data from all children who were born in New Zealand between October 2005 and December 2010 (N=334,204) and their mothers. Children's antibiotic use is identified for 4 time periods (at pregnancy, at ≤1 year, at ≤2 years, and at ≤5 years), and the development of T1D, ADHD, and inflammatory bowel disease is measured from the end of the antibiotic use periods until death, emigration, or the end of the follow-up period (2021), whichever came first. Children who emigrated or died before the end of the antibiotic use period are excluded. Cox proportional hazards regression models are used while adjusting for a range of potential confounders.

Results: As of September 2024, data linkage has been completed, involving the integration of antibiotic exposure and outcome variables for 315,789 children. Preliminary analyses show that both prenatal and early life antibiotic consumption is associated with T1D. Full analyses for all 3 outcomes will be completed by the end of 2025.

Conclusions: This series of linked cohort studies using detailed, complete, and systematically collected antibiotic prescription data will provide critical new knowledge regarding the role of antibiotics in the development of common chronic childhood conditions. Thus, this study has the potential to contribute to the development of primary prevention strategies through, for example, targeted changes in antibiotic use.

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KEYWORDS

early childhood; chronic childhood conditions; antibiotics; data linkage; study protocol; routine data

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Introduction

The incidence of many chronic childhood conditions such as type 1 diabetes (T1D), attention-deficit/hyperactive disorder (ADHD), and inflammatory bowel disease (IBD) has increased globally in the last 2 decades [1]. The total global incidence of childhood and adolescent T1D is larger than previously estimated, with nearly 1 in 2 children currently undiagnosed, with most underdiagnoses occurring in low-income countries [2]. Current global incidence estimates range from 128,900 to 149,500 per annum [3,4]. For ADHD, although recent geographical estimates are unavailable, the highest incidence rates are reported in countries with a higher sociodemographic index [5]. The global incidence of IBD is increasing steadily and varies greatly by geographical areas, with the highest annual pediatric incidence of IBD reported to be 23/100,000 person-years in Europe, 15.2/100,000 in North America, and 11.4/100,000 in Asia/the Middle East and Oceania [6].

In New Zealand, the annual incidence of T1D is reported to be 23/100,000, and this is increasing by 4.1% annually [7]. It is estimated that 2%-5% of school-age children in New Zealand are affected by ADHD [8], with a recent study showing that the total ADHD medication dispensing prevalence had almost doubled from 516/100,000 in 2007-2008 to 996/100,000 in 2016-2017, with the highest dispensing prevalence reported for those aged 7-17 years [9]. In the case of IBD, recent New Zealand estimates have shown age-specific incidence rates of 39.5/100,000, which is 1.6-fold greater than what was measured 10 years earlier—this is among the highest in the world [10]. Research indicates significant ethnic differences in T1D and IBD, with European children having higher rates than Māori and Pacific children [7,11]. Furthermore, ADHD prevalence and treatment access vary by socioeconomic status [12].

The etiology of these diseases is not well understood, but environmental factors, genetics, immune-regulatory pathways, and microbial exposures are considered important [13,14]. Early life gut microbiome development is a critical window for immune and neurodevelopment. In early childhood, establishing a healthy microbiome is vital for shaping the immune system and influencing neurodevelopmental outcomes [15]. Microbial colonization begins at birth and evolves with a diverse gut microbiome linked to better health outcomes. Antibiotic use during this period may also be a risk factor that can disrupt the microbiome development by depleting beneficial bacteria, leading to dysbiosis [15,16], which may impair immune training and increase susceptibility to these chronic conditions [17].

Several studies have assessed associations between antibiotic use and the development of these chronic conditions during the prenatal period and early life years [18-20], but results have been inconsistent, with some showing positive associations [20] and others showing no association [21-23]. These inconsistencies may, at least in part, be explained by limitations in study design. For example, antibiotic use is often assessed through recall, which is vulnerable to bias. Moreover, studies often rely on short-term prescription history prior to disease onset, which may result in issues of reverse causality (if antibiotics were prescribed to treat early symptoms of the disease itself) [24,25]. Further, studies have often focused on only one specific class of antibiotics without considering the full spectrum of antibiotics used [25]. Importantly, most research has been conducted in Europe (particularly Scandinavia) and the United States, and it remains unclear whether results can be extrapolated to other parts of the world, including New Zealand, which, compared to other Organisation for Economic Co-operation and Development countries, including Scandinavia [26], is known to have a very high use of antibiotics among children [27].

The series of linked cohort studies for which the methods are described in this protocol paper will assess associations between prenatal and early life antibiotic use and the development of childhood T1D, ADHD, and IBD. These studies using detailed, complete, and systematically collected antibiotic prescription data will provide critical new knowledge regarding the role of antibiotics in the development of these common chronic childhood conditions. Thus, this study has the potential to contribute to the development of primary prevention strategies through, for example, targeted changes in antibiotic use. The central hypothesis of this study is that early life antibiotic use is associated with the development of childhood T1D, ADHD, and IBD.

Methods

Study Design, Setting, and Population

The study design involves several retrospective cohort studies using linked administrative health and social data from Statistics New Zealand's Integrated Data Infrastructure (IDI) [28]. Antibiotic use and T1D, ADHD, and IBD are defined as described below. To date, data for all children born in New Zealand between October 2005 and December 2010 (N=334,204) and their mothers have been extracted from the Department of Internal Affairs birth data in the IDI. Children's antibiotic use has been defined for 4 time periods (at pregnancy, at ≤1 year, at ≤2 years, and at ≤5 years). The development of T1D, ADHD, and IBD (which consists of Crohn disease and ulcerative colitis) has been measured from the end of the antibiotic use periods until death, emigration, or the end of the study in 2021, whichever came first, accumulating approximately 3,000,000 person-years. Children who emigrated overseas or died before the end of the antibiotic use period have been excluded from the analysis, as they cannot be followed up for the occurrence of these chronic childhood conditions. At the end of follow-up, children had reached the age of 11-16 years.

Data Sources

The IDI is a database of deidentified administrative and survey data about people and households in New Zealand [28]. It includes data about health, education, income, social support payments, migration, and other life events, which can be linked at the individual level. The IDI provides a longitudinal record of events and is a growing resource. As of September 2018, the IDI holds over 166 billion pieces of information from more than 14 organizations [28,29]. Table 1 lists the datasets that are being used for this study with a brief description of the data and the variables extracted from these datasets.

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Table 1. Data collections available within the integrated data infrastructure for linking cohorts' demographic data with antibiotic use and selected health outcomes [30].

Data collections	Descriptions	Characteristics/variables extracted
Births (from 1840): This data collection was used to define the cohort and identify the mothers of the children.	This collection holds all births in New Zealand, including month and year of birth, sex, ethnicity, first and second parent as recorded on birth registration, and their sex, age, ethnicity, type of relationship, weight at birth, gestation, and their age.	Sex, date of birth, birth weight, ethnicity
Pharmaceutical data (from 2005): This data collection was used to analyze antibiotic prescription.	This collection holds claim and payment information from pharmacists for subsidized medicines, including Pharmaceutical Management Agency (PHARMAC[a]) identifier of primary active chemical ingredient, quantity, number of repeats, and date of dispensing.	Date of prescription dispensing, Anatomical Therapeutic Chemical codes for medicines, including antibiotics and treatments for T1D[b], ADHD[c], and IBD[d]
Maternity (from 2003): This data collection was used to calculate the gestational period and maternal age at birth and to identify the mode of delivery.	The National Maternity Collection provides statistical, demographic, and clinical information about selected publicly funded maternity services up to 9 months before and 3 months after a birth.	Mothers' date of birth, ethnicity, last date of menstruation, mode of delivery, maternal age at delivery
Mortality (from 1998): These data were used to identify the date of death.	This collection holds the underlying cause of death for all deaths registered in New Zealand using the International Classification of Diseases, Tenth Revision, Clinical Modification codes, including all registered fetal deaths and date of death.	Date of death
International travel and migration (from 1997): This data collection was used to identify children who emigrated from New Zealand.	This collection holds arrival and departure records and migration records.	Date of departure
Laboratory claims (from 2003): This data collection was used to obtain laboratory testing information.	This collection holds primary-care test subsidies.	Laboratory test(s) conducted (results of tests are not available), including testing for T1D, ADHD, and IBD
NNPAC[e] (from 2007): This data collection was used to identify any diagnosis procedure for nonadmitted patients.	NNPAC provides national consistent data on nonadmitted patient (outpatient and emergency department) activity.	Diagnosis for various health conditions, including T1D, ADHD, and IBD
Publicly funded hospital discharges (from 1998): This data collection was used to identify the principal and additional reasons for hospitalization and procedure performed during hospital stay.	This collection contains summarized information detailing publicly funded hospital discharges and procedures by New Zealand hospitals using the codes of the International Classification of Diseases, Tenth Revision, Clinical Modification.	Disease/procedure classification, diagnosis for various health conditions, including T1D, ADHD, and IBD.

[a]PHARMAC is a government agency in New Zealand responsible for managing the funding and procurement of pharmaceuticals and medical devices.

[b]T1D: type 1 diabetes.

[c]ADHD: attention-deficit/hyperactivity disorder.

[d]IBD: inflammatory bowel disease.

[e]NNPAC: National Non-Admitted Patient Collection.

Definition of Antibiotic Exposure

Antibiotic exposures in utero and for the first 5 years of life are identified for all cohort members born between October 2005 to December 2010 from pharmaceutical data. Dispensing dates and dose and number of purchases are identified, and each antibiotic prescription is categorized by (1) class, according to the Anatomical Therapeutic Chemical classification J01 "Antibiotics for systemic use" (eg, penicillins, cephalosporins, sulfonamides); (2) spectrum, that is, broad or narrow; and (3) whether antibiotics target Gram-positive or Gram-negative bacteria or both. These categorizations of individual antibiotics are provided in Table 2 [31].

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Table 2. Antibiotics by class and spectrum of activity [31].

Class of antibiotics, chemical name of antibiotic used among the cohort	Spectrum of activity (narrow/broad)	Antibiotics targets Gram-positive/Gram-negative bacteria
Cephalosporins and cephamycins		
Cefaclor monohydrate	Moderate	Both
Cefalexin	Moderate	Both
Cefamandole nafate	Broad	Both
Cefazolin	Moderate	Both
Cefoxitin sodium	Moderate	Both
Ceftazidime	Broad	Both
Ceftriaxone	Broad	Both
Cefuroxime axetil	Moderate	Both
Cefuroxime sodium	Moderate	Both
Cephalothin sodium	Broad	Both
Cephradine	Broad	Both
Macrolides		
Azithromycin	Broad	Positive
Clarithromycin	Broad	Positive
Erythromycin	Broad	Positive
Erythromycin (as lactobionate)	Broad	Positive
Erythromycin estolate	Broad	Positive
Erythromycin ethyl succinate	Narrow	Positive
Erythromycin stearate	Narrow	Positive
Roxithromycin	Broad	Positive
Other antibiotics		
Aztreonam	Broad	Negative
Chloramphenicol	Broad	Both
Chloramphenicol sodium succinate	Broad	Both
Ciprofloxacin	Broad	Both
Clindamycin	Broad	Both
Colistin sulfomethate	Broad	Positive
Fleroxacin	Broad	Both
Framycetin sulfate	Broad	Both
Gentamicin sulfate	Broad	Both
Imipenem	Broad	Both
Levofloxacin	Broad	Both
Lincomycin	Broad	Both
Lincomycin hydrochloride	Narrow	Positive
Moxifloxacin	Broad	Both
Neomycin sulfate	Broad	Both
Ofloxacin	Broad	Both
Paromomycin	Broad	Positive
Pyrimethamine	Broad	Both
Sodium fusidate (fusidic acid)	Narrow	Both

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Class of antibiotics, chemical name of antibiotic used among the cohort	Spectrum of activity (narrow/broad)	Antibiotics targets Gram-positive/Gram-negative bacteria
Spectinomycin hydrochloride	Moderate	Both
Spiramycin	Broad	Both
Sulfadiazine sodium	Broad	Both
Sulfadiazine	Broad	Both
Tobramycin	Broad	Both
Triacetyloleandomycin	Broad	Positive
Trimethoprim	Broad	Both
Trimethoprim with sulfamethoxazole (cotrimoxazole)	Broad	Both
Vancomycin	Narrow	Positive
Penicillins		
Amoxicillin	Broad	Both
Amoxicillin with clavulanic acid	Broad	Both
Amoxicillin clavulanate	Broad	Both
Benzathine benzylpenicillin	Narrow	Both
Benzylpenicillin sodium (Penicillin G)	Narrow	Both
Dicloxacillin	Narrow	Both
Flucloxacillin	Narrow	Both
Flucloxacillin magnesium	Narrow	Both
Penicillin G benzathine (Benzathine benzylpenicillin)	Narrow	Both
Phenoxymethylpenicillin (Penicillin V)	Narrow	Both
Piperacillin	Broad	Both
Pivampicillin	Broad	Both
Pivmecillinam hydrochloride	Narrow	Both
Procaine penicillin	Narrow	Both
Ticarcillin	Broad	Both
Tetracyclines		
Demeclocycline hydrochloride	Broad	Both
Doxycycline	Broad	Both
Lymecycline	Broad	Both
Minocycline hydrochloride	Broad	Both
Rolitetracycline	Broad	Both
Tetracycline	Broad	Both
Tetracycline hydrochloride	Broad	Both

Definition of Health Outcomes

The selected health outcomes of the study population are determined through linkage with the following data collections: (1) hospital discharges, (2) pharmaceutical data, (3) nonadmitted patient collection, and (4) laboratory claims, for the period starting from birth or end of antibiotic exposure period of each child to the end of 2021. The specific case definitions, including the International Classification of Diseases, Tenth Revision codes corresponding to the health outcomes under consideration, are provided in Table S1 of Multimedia Appendix 1 [32-35]. To ascertain the prevalence of T1D, we used 3 distinct algorithms to identify cases, facilitating a comprehensive comparison of results to ensure consistency. For IBD, the identification of cases, as outlined in Table S1 of Multimedia Appendix 1, will be subject to further validation against several cohorts of patients with IBD obtained from collaborating gastroenterologists. This validation will involve exploring various combinations of medications prescribed for IBD,

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including those listed in Table S1 of Multimedia Appendix 1. The analysis aims to provide insights into the diversity of medication regimens associated with IBD cases. Any refinements or enhancements to the algorithms as well as insights gained from the medication combination analysis will be documented and incorporated into the final analysis.

Other Variables

Fixed covariates/confounders that will be considered in the analyses include sex, ethnicity, deprivation index (based on mesh block) [36], birth weight, gestation, mode of delivery, rurality, and maternal age. Time-dependent covariates include hospitalization for infections and other chronic diseases and selected prescription medications (eg, paracetamol, antivirals, antifungals).

Follow-Up of Vital Status and New Zealand Residency

Linkage to border movements and mortality data are used to determine whether cohort members are still alive and are based in New Zealand. Those who have emigrated or died prior to their fifth birthday are excluded from the analyses; the follow-up time for those who died or emigrated after the fifth birthday is censored up to that point, which means that the event of interest or health outcome being investigated may not be observed for some individuals.

Statistical Analysis

To date, the primary focus has been on data preparation that consisted of (1) constructing the cohort through data linkage; (2) identifying the antibiotic exposure variables for all cohort members; (3) identifying other variables, including confounders for all cohort members; and (4) identifying T1D, ADHD, and IBD cases within the cohort using the definitions described in Table S1 of Multimedia Appendix 1. The next stage involves analyses that focus on assessing associations between antibiotic use and the health outcomes described above. For this, we will use Cox proportional hazards regression, with attained age as the analysis time scale. As noted before, children have been followed up until the estimated date of diagnosis, emigration from New Zealand, death, or the end of the study period (December 31, 2021), whichever comes first.

For each health outcome, analyses will be conducted to measure associations with antibiotic use during specific early life periods (pregnancy, ≤1 year, ≤2 years, and ≤5 years, as well as combinations of these periods). Antibiotic use will be based on the number of prescriptions, which will enable the assessment of dose-response associations. In addition to considering all antibiotic classes combined, we will also conduct analyses where antibiotics will be grouped into different classes/categories (Table 2); this will provide insights into which specific groups of antibiotics may be most strongly associated with the 3 outcomes of interest. Analyses will be stratified by mode of delivery to assess whether associations may be different in different subgroups (effect modification) as has been shown for cesarean section births, with larger effect sizes shown for associations between antibiotic use and T1D for caesarean section births [20,37]. In addition to stratified analyses, we will also assess the role of potential confounders such as sex, prioritized ethnicity, deprivation index, and rurality by using multivariable analyses.

Nested case-control analyses will be conducted as an additional way to address potential bias and confounding. Controls will be matched to cases on year and month of birth, sex, ethnicity, and other potential confounding factors such as residence and deprivation. In addition, to address potential medical surveillance bias, matched controls that occur in the same data collections as the cases will be selected. Nested case-control analyses will also enable the evaluation of possible reverse causation (ie, the health outcome of interest resulting in the prescription of antibiotics rather than the other way around) by disregarding antibiotic use in the 6 months before diagnosis of the cases and the equivalent time point of the matched controls. Moreover, control for confounding by maternal factors will be achieved through within-mother analysis of disease-discordant pairs of siblings. Factors remaining constant between pregnancies could, for example, be the mother's attitude toward antibiotic prescriptions as well as the general practitioner's antibiotic prescription practices, which will influence the child's exposure to antibiotics; other types of analyses can typically not adjust for this. Further, confounding by indication, where the reason for prescribing antibiotics may be linked to the development of chronic conditions, will only be addressed once primary care data become available, enhancing the rigor of the study.

Study Power

Based on national and international data, we have assumed that at least half of the children will have been prescribed antibiotics within the first year of life (52% in a Finnish study, 15% for specific antibiotic classes [38]). Based on age-specific statistics of the Virtual Diabetes Register, which is an annually updated national register of all patients with diabetes mellitus from 2010 to 2015, we estimate that 400 cases of T1D can be identified within the cohort [39]. Furthermore, based on hospitalization data, as per the age-specific data, we estimate that at least 200 IBD cases (170 cases of Crohn disease and 30 cases of ulcerative colitis) can be included in the study based on hospitalization data. Finally, for ADHD, and as noted earlier, medication dispensing has doubled from 516 per 100,000 in 2007-2008 to 996 per 100,000 in 2016-2017 in New Zealand [9]. Although a breakdown by age group is not available, we estimate that at least 1000 cases can be identified in the cohort. This is a conservative estimate based on our experience with other IDI projects [34], and it is likely that this number is substantially higher (up to 3% of the study population). Thus, we assume that case sets will have a minimum size of 1000 for ADHD, 400 for T1D, and 200 for IBD. Hazard ratio (HR) estimates that are detectable with 80% power ($P<.05$, 2-sided) under different population size and exposure prevalence scenarios are summarized in Table 3. Assuming an exposure prevalence of 33%, this study has 80% power to detect an HR of 1.2 for ADHD, 1.4 for T1D, and 1.5 for IBD. Analyses of specific strata of the study population (eg, based on sex or ethnicity) will have sufficient study power to detect similar effect sizes (Table 3). Considering a lower exposure frequency of 10% (eg, for specific antibiotic classes), the study has 80% power to detect an HR of 1.3 for ADHD, 1.5 for T1D, and 1.7 for IBD. Assuming a further

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reduction in exposure frequency of 5% (eg, for specific antibiotics), the study has 80% power to detect an HR of 1.5 for ADHD, 1.7 for T1D, and 2.0 for IBD (Table 3).

Table 3. Study power: hazard ratio detectable (power 80%, $P<.05$, 2-sided) under different population size and exposure prevalence scenarios.

Strata	Study population (N)	Scenarios for attention-deficit/hyperactivity disorder					Scenarios for type 1 diabetes					Scenarios for inflammatory bowel disease				
		Cases (n)	Exposure prevalence (hazard ratio)				Cases (n)	Exposure prevalence (hazard ratio)				Cases (n)	Exposure prevalence (hazard ratio)			
			50%	33%	10%	5%		50%	33%	10%	5%		50%	33%	10%	5%
All	300,000	1000	1.2	1.2	1.3	1.5	400	1.3	1.4	1.5	1.7	200	1.5	1.5	1.7	2.0
Sex	150,000	500	1.3	1.3	1.5	1.6	200	1.5	1.5	1.7	2.0	100	1.7	1.7	2.0	2.4
Ethnicity	60,000	200	1.5	1.5	1.7	2.0	80	1.8	1.8	2.2	2.5	40	2.2	2.2	2.7	3.2

Ethics Approval

This study was approved by Human Research Ethics Committee of the University of Otago (reference: HD21/053). Microdata access approval for the project was provided by Statistics New Zealand. To ensure confidentiality, all data are deidentified before access. Access to linked datasets is limited to authorized personnel, and data handling follows ethical guidelines. Sensitive data will be managed securely. Although the data within IDI are fully deidentified, there are several requirements that govern the use of IDI data that this study will adhere to. These are (1) statistical outputs can only be disseminated after outputs have been checked and approved by Statistics New Zealand, (2) the IDI confidentiality rules require the suppression of counts and associated results of analyses on samples smaller than 6, and (3) the random rounding of counts can be up or down to the next multiple of 3.

Results

As of September 2024, we have completed the data linkage, involving the integration of antibiotic exposure data with outcome variables and all relevant covariates for 315,789 individuals. Preliminary analyses show that both prenatal and early life antibiotic consumption is associated with T1D. Full analyses for all 3 outcomes, that is, analyses adjusted for potential confounders, stratified by ethnicity and sex, and further sensitivity analyses will be completed by the end of 2025.

Discussion

Antibiotics are widely used in human populations, particularly children. It is therefore important to assess and quantify potential adverse effects of this exposure at the population level so that they can be balanced against the many benefits of these therapies. We hypothesize that antibiotic use will result in a positive and significant hazard risk for the development of chronic childhood conditions. The unique data infrastructure established through Statistics New Zealand's IDI provides a robust way of assessing such relationships across a large cohort, consisting of the entire New Zealand population who can be followed up for many years. Findings will be of relevance both locally and internationally, particularly in regions with similarly low antimicrobial resistance rates, such as certain European countries [40]. Additionally, in areas with high pediatric antibiotic usage, such as parts of North America and Asia [41], these insights can inform public health strategies aimed at optimizing antibiotic stewardship.

The proposed series of studies, which are large by international standards and based on detailed, complete, and objectively collected antibiotic prescription data, will provide critical new knowledge regarding the role of antibiotics in the development of common chronic childhood conditions. As such, it will provide an important addition to the limited number of studies conducted in humans and has the potential to contribute to the development of feasible avenues for primary prevention, through, for example, targeted changes in antibiotic use in both quantity and type and targeted use of prebiotics or probiotics. Additionally, this study may be expanded to encompass other conditions such as asthma and allergies, which have also been associated with early life antibiotic exposure [42].

The focus of this study is on the effects of antibiotics on the host, but the results are also relevant to the broader issue of antibiotic overuse and its link with increased microbial resistance. New Zealand has comparatively low rates of antimicrobial resistance [43,44]. However, resistance has steadily increased, and experience gained from other countries suggests that this will become more common in New Zealand, raising patient risk and costs for the health system [45]. Antimicrobial resistance is considered one of the biggest man-made public health threats of modern times [43]. Clinicians and public health researchers have advocated that New Zealand needs to urgently institute a range of measures to significantly reduce antimicrobial consumption [46,47]. A systematic review of interventions aimed at reducing antibiotic prescribing for respiratory tract infections across several settings has led to substantial reductions [48], although efforts in New Zealand have not yet resulted in a decrease of antibiotic consumption [45]. This study may provide additional evidence for the need to reduce (unnecessary) antibiotic consumption both in New Zealand and internationally.

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Data Availability

The datasets generated and analyzed for this study are not publicly available. Statistics New Zealand's integrated data infrastructure microdata are available for research purposes, and access is granted based on meeting the conditions set by Stats New Zealand through a secure laboratory environment.

Disclaimer

These results are not official statistics. They have been created for research purposes from the integrated data infrastructure, which is carefully managed by Stats New Zealand.

Authors' Contributions

JD, AtM, and MB conceived the original idea for this data linkage study. All authors contributed to the development of the study methodology. SR wrote the first draft of the manuscript, with assistance from JD, AtM, MC, AK, AE and MB. All authors contributed to the writing of the paper and read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Health outcome classification, corresponding International Classification of Diseases Tenth Revision codes, and case definitions. [DOCX File , 20 KB - resprot_v14i1e66184_app1.docx]

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Abbreviations

ADHD: attention-deficit/hyperactive disorder
HR: hazard ratio
IBD: inflammatory bowel disease
IDI: integrated data infrastructure
T1D: type 1 diabetes

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Protocol

Using a Sober Curious Framework to Explore Barriers and Facilitators to Helping Sexual Minority Women Reduce Alcohol-Related Harms: Protocol for a Descriptive Study

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Abstract

Background: Globally, women consume less alcohol than men, but alcohol consumption among women has declined less in recent years than among men. Drinking rates and alcohol-related harms vary substantially across population groups of women, and sexual minority women (eg, lesbian, bisexual, and queer) are at notably high risk. An emerging body of literature suggests that in addition to minority stress (eg, stigma, discrimination), drinking norms and drinking cultures likely influence sexual minority women's drinking. Almost no research has explored these factors as possible targets of interventions. Sober curiosity is a rapidly growing wellness movement that may be particularly salient for sexual minority women. It encourages individuals to be "curious" about the reasons they choose to drink and alcohol's effects on their life and health.

Objective: The aims of this research are to (1) explore the perspectives of the drinking social worlds of sexual minority women, their awareness of the sober curious movement, perceptions of their own and their peers' drinking and desire to drink less, and perceived barriers and facilitations to changing their drinking behaviors and (2) identify key elements of an alcohol reduction intervention tailored for sexual minority women.

Methods: We conducted a comprehensive review of the literature on alcohol interventions with sexual minority women. The handful of studies we found paid scant attention to drinking cultures, normative beliefs, or other key elements of sober curiosity. To address the study aims, we are conducting 2 descriptive studies with adult (>18 years) sexual minority women using mixed methods. One includes focus group interviews (n=24-36) and a national survey (n=100-120) with sexual minority women in Scotland. The other includes in-depth interviews (n=18-20) with sexual minority women in the United States. Data from the 2 countries and 3 sources will be analyzed using qualitative and quantitative methods to identify patterns and relationships across data to validate or corroborate findings.

Results: Each of the studies received ethics approval in August 2023 and is currently open for recruitment. We anticipate completing data collection in spring 2025. The results of qualitative analyses will be summarized as themes, and results of survey

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data analyses will be summarized in tables. Findings will be presented to 2 panels of international experts who will assist in identifying critical elements of an alcohol reduction intervention tailored to the unique needs of sexual minority women.

Conclusions: With the assistance of the expert panels, we will use Acceptability, Practicability, Effectiveness, Affordability, Side-Effects, and Equity criteria to inform the development of a tailored intervention building on tenants of sober curiosity to assist sexual minority women in reducing harmful drinking.

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KEYWORDS

sexual minority women; drinking; sober curiosity; women; sober; minority; alcohol; protocol; barriers; facilitators; disparities

Introduction

Background

Overview

Hazardous alcohol consumption is a pattern of alcohol use that increases the risk of harmful consequences [1]. As a leading risk factor for poor health outcomes worldwide, hazardous drinking is a global public health concern. According to the World Health Organization (WHO) [2], heavy drinking is a causal factor in more than 200 disease and injury conditions; it is also among the top 4 risk factors highlighted in the WHO global strategy for prevention and control of noncommunicable diseases. Efforts to reduce hazardous drinking are a major challenge because in many parts of the developed world, consuming alcohol at risky levels is widely socially acceptable and oftentimes viewed as preferable to abstinence, particularly within social worlds structured around heavy drinking norms [3].

The 2018 WHO Global Status Report on Alcohol and Health [4] suggests that women's drinking has decreased in most countries. However, this is not the case in some Western high-income countries including the United States [5], the United Kingdom [6], and Australia [7]. An increase in women's drinking is among the most prominent trends in alcohol consumption in the United Kingdom in recent history [8]. Further, alcohol consumption patterns and alcohol-related harms are not evenly distributed across population groups of women [9-12]. As described by Bloomfield's [13] "alcohol harm paradox", although different groups of women may drink similar quantities of alcohol, they often experience differential harms based on their level of social disadvantage. It is important to understand the contemporary determinants of health that contribute to hazardous drinking and make it more (or less) difficult for socially marginalized women to reduce alcohol consumption, particularly when alcohol is readily accessible and is used to facilitate or form social connections. In this paper, we review the literature regarding existing alcohol interventions for sexual minority women (eg, lesbian, bisexual, and queer), discuss barriers and facilitators to interventions that support sexual minority women who wish to reduce their alcohol use, and describe 2 studies, one in Scotland and one in the United States, that aim to support the development of an intervention designed to reduce alcohol-related harms among sexual minority women.

Sexual Orientation–Related Disparities in Alcohol Use

Hazardous drinking is among the most prominent health-related disparities when comparisons of heterosexual and sexual minority women are undertaken globally [14-16]. For example, findings from a US national sample found that compared to heterosexual women, sexual minority women were nearly 4 times as likely to engage in heavy episodic drinking [17]. A population-based study conducted in England found that lesbian, gay, and bisexual (LGB) adults (32%) were more likely than heterosexual adults (24%) to drink at harmful levels [18]. This sexual orientation–related disparity is hypothesized to be due to several factors: (1) minority stress related to discrimination and marginalization that impacts mental health and contributes to using alcohol as a coping strategy [14,19-21]; (2) sexual minority women are more likely than heterosexual women to have experienced lifetime trauma, including childhood sexual abuse, childhood physical abuse, adult sexual assault, and intimate partner violence [22-27], that also contributes to alcohol use as a means of coping [28]; (3) the predominantly alcohol-driven nature of the commercial lesbian, gay, bisexual, transgender, queer, and other sexual and gender minority (lesbian, gay, bisexual, transgender, queer or questioning [LGBTQ+]) scene, which facilitates connections and provides a key social environment for many LGBTQ+ individuals and communities [29,30]; and (4) the important role that alcohol plays in identity formation for LGBTQ+ people [14,30,31].

An emerging body of literature suggests that heavy drinking norms also contribute to the heavier drinking patterns of sexual minority women [32]. Drinking is primarily a social activity, often a central part of social occasions in a "social world" where members come together around something they have in common, such as an occupation or an identity [3]. In addition, research suggests that sexual minority women perceive the expectation to drink to be higher in LGBTQ+ spaces than in other contexts [33]. Understanding the drinking norms and drinking behaviors of sexual minority women is essential to informing the development of effective interventions to reduce heavy drinking and alcohol-related harms.

Alcohol Treatment and Sexual Minority Women

In the general population, women are less likely than men to seek help related to their drinking [34-36]. Women who drink heavily report experiencing gendered stigma that negatively impacts their desire or ability to access mainstream alcohol treatment services and their experiences when help is sought. Such stigma may be particularly salient for sexual minority

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women who are already stigmatized based on their sexual identity [35,36]. For example, Dimova et al [37] found that sexual minority women (and sexual minority men) who accessed alcohol treatment were rarely asked about their sexual or gender identity, which precluded exploration of how these factors might impact their drinking or desire to reduce drinking. Both lesbian and bisexual women also reported experiencing heterosexist assumptions (eg, that they were partnered with a man) and feeling judged because of their drinking. Moreover, one recent study using data from the 2020 US National Survey of Substance Abuse Treatment Services found that only 2.4% of substance use treatment facilities offered LGBTQ+-tailored programming [38].

Compared to intervention studies aimed at reducing hazardous drinking among women in the general population, those that focus on the experiences of sexual minority women are more recent and more limited [14,39,40]. The small body of literature on interventions designed to reduce drinking among sexual and gender minority populations has focused predominately on sexual minority men [14,41]. A few studies have been conducted on sexual minority women's perceptions and experiences of alcohol treatment in the United States, but nearly all have focused on formal treatment or 12-step programs such as Alcoholics Anonymous (AA) [42-48]. Interventions that might be appropriate for heavy-drinking sexual minority women who are not accessing services or for whom alcohol use is not yet problematic enough to warrant formal treatment—but likely to worsen without early intervention—have not been explored.

Many alcohol treatment programs, especially 12-step programs such as AA, emphasize powerlessness, character defects, and making amends to those harmed by one's drinking—features that may be off-putting for sexual minority women who experience stigma, discrimination, and rejection based on their gender and sexual minority status. While AA is not affiliated with a religious organization, it uses a framework based on religious spirituality. Sexual minority women who do not identify with a particular religion or who have had negative experiences with religious institutions are less likely to access AA [43]. Access to nonreligious and affirming alternatives to AA is important, given research documenting low rates of endorsing religiosity and an absence of a protective effect of religiosity on heavy drinking among sexual minority women relative to heterosexual women [49,50]. Sexual minority women and sexual minority men are more likely than their heterosexual counterparts to express interest in accessible, nonstigmatizing alternatives to AA and traditional treatment approaches [51]. Sober curiosity, described in detail in "Potential Usefulness of an Intervention Based on Sober Curiosity" section, is an identity-affirming approach to alcohol reduction that offers such an alternative.

Existing Evidence Regarding Alcohol Interventions With Sexual Minority Women

In a large global scoping review of studies focused on alcohol and other drug use among sexual minority women, Hughes et al [14] describe the dearth of research related to substance use interventions as "a gaping hole." Although studies of alcohol treatment effectiveness sometimes report findings for sexual minority participants, they rarely report findings specific to sexual minority women. For example, Zajac et al [52] used data from 5 randomized clinical trials to compare the effectiveness of contingency management with financial incentives versus standard intensive outpatient care treatment among 920 LGB and heterosexual participants with a substance use disorder. Differences between LGB and heterosexual participants were compared across 3 substance use outcomes: treatment retention, the longest duration of abstinence, and percent negative substance use screens. Contingency management plus intensive outpatient treatment did not show statistically significant differences for any of the 3 outcomes. However, the LGB group means were higher than those of heterosexual participants for treatment retention and the longest duration of abstinence. Although not strong enough to reach statistical significance, these differences were considered potentially clinically significant. Unfortunately, analyses aggregated LGB participants, which prohibited specific examination of outcomes among sexual minority women.

In another study that combined sexual (and gender) minority participants, Gilmore et al [53] evaluated Positive Change (+*Change*) with 24 undergraduate students from a large university in the Southwestern United States. Of the 24 participants, most (n=17) identified as cisgender heterosexual; 7 identified as sexual minority, gender minority, or both sexual and gender minority. The intervention included content from an integrated alcohol and sexual assault risk reduction program developed for women and a web-based adaptation of a brief motivational interviewing personalized feedback protocol. +*Change* had high usability and acceptability ratings among both cisgender heterosexual and sexual and gender minority participants. Differences based on sexual and gender identity were not examined because of the small sample size.

In the only intervention study undertaken with sexual minority women prior to 2020, Fals-Stewart et al [54] evaluated the efficacy of behavioral couples therapy plus individual therapy compared to individual-based therapy only among lesbian and gay couples, in which at least 1 partner had an alcohol use disorder. Treatment intervention components included developing recovery contracts with partners, teaching partners communication strategies and strategies for reducing triggers and exposure to alcohol, and increasing shared activities. Results indicated that among lesbian couples, those who received the behavioral couples therapy condition reported fewer heavy drinking days at 12-month follow-up compared to those receiving individual therapy only.

Pachankis et al [55] conducted a small (N=60) sexual minority women–adapted cognitive behavioral therapy (CBT) intervention that focused primarily on mental health. This waitlist-controlled trial, Empowering Queer Identities in Psychotherapy, was designed to help sexual minority women understand emotion-driven behavior, reduce emotional avoidance, and learn behavioral skills and other resilience-building strategies. Pachankis et al [55] found that Empowering Queer Identities in Psychotherapy demonstrated preliminary efficacy in reducing sexual minority women's depression, anxiety, emotion dysregulation, and rumination in the intervention compared to the waitlist control group. The

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effects of alcohol use were marginally significant, with the immediate intervention group outperforming the waitlist control group. Minority stress responses were not significantly affected by the intervention. In line with previous research, findings suggested that greater attention to sexual minority women's elevated rates of trauma and hazardous drinking is needed to enhance CBT interventions for sexual minority women.

Boyle et al [56] examined the feasibility and efficacy of reducing alcohol-related risks using personalized normative feedback delivered within a digital competition designed to challenge negative stereotypes and norms about sexual minority women's drinking. This study was the first to find that activities aimed at correcting sexual minority women–specific drinking and coping norms via personalized normative feedback reduced alcohol consumption among participants receiving this condition compared to those in the control condition who received information about nonsexual minority–specific topics.

In a study conducted with Australian same-sex attracted women, Bush et al [57] used SMS text messaging to examine the feasibility, acceptability, and efficacy of an alcohol intervention called the Step One program. In total, 97 same-sex attracted women who met the criteria for hazardous drinking by scoring ≥8 on the Alcohol Use Disorders Identification Test were randomly assigned to the Step One condition (n=47; mean age 37 years old)—which included a variety of SMS text messages about the health benefits of reducing alcohol intake—or a control condition of messages containing a link to a website with health information and support services for LGBTQ+ people (n=50; mean age 34 years). Participants in both conditions showed significant reductions in alcohol consumption and improved well-being over 4 weeks. The frequency of help-seeking was low; only 4 intervention group participants and 3 control group participants sought help. In total, 10 participants in the intervention group were interviewed about acceptability. Overall findings indicated that the intervention needed to be revised prior to its implementation.

Except for the study by Bush et al [57], all the intervention studies described earlier were conducted in the United States. Although a variety of approaches were used (eg, personalized normative feedback, couples therapy, and CBT), they were all based on individual behavior change models, which have limited effectiveness for heavier drinkers [58]. Efforts that target individual drinkers typically ignore the fact that most drinking is social, occurring in the company of others, and that how much one drinks is influenced by others (eg, pressure to drink more or less).

In summary, sexual minority women have seldom been the focus of intervention studies. When included as part of LGBTQ+ samples, outcomes are rarely reported separately by gender and sexual identity. Consequently, given this population's social and structural marginalization, it is unknown whether existing treatment options are suitable for sexual minority women. Because the drinking patterns of sexual minority women appear to be in large part motivated by seeking social connection and a sense of belonging, any intervention developed for sexual minority women must address these social and affective needs [59-61]. An intervention that incorporates these elements within sober curiosity, a wellness movement that challenges the centrality of alcohol in social life and questions the notion that alcohol is required on all social occasions [62], offers a potentially scalable approach to alcohol interventions suitable for sexual minority women. Supported by popular and well-known periods of nondrinking such as "Dry January" or "Sober October," sober curiosity is geared toward developing longer-term, sustainable lower-risk drinking practices.

Potential Usefulness of an Intervention Based on Sober Curiosity

There is evidence of substantive social change regarding alcohol consumption, including the exponential rise in the marketing and availability of no or low alcohol (referred to as "NoLo") content wines, beers, and spirits [63,64] and a growing number of sober venues and events, as well as proliferation of web-based support forums that are based on sober curiosity tenets. For example, Grace [65], author of *This Naked Mind* and founder of The Alcohol Experiment, reported on February 22, 2023, that in less than 1 year, more than 80,000 people globally had subscribed to the This Naked Mind web-based alcohol reduction program; notably, most subscribers are women. Similarly, Club Soda in the United Kingdom reportedly has helped "tens of thousands" of people reduce their harmful drinking.

The sober curious movement encourages individuals to question the centrality of drinking alcohol in their daily lives, to make a conscious decision to "be curious" about their reasons for drinking, and to consider if drinking alcoholic beverages is necessary in situations where drinking would typically occur. The growing popularity of sober curiosity provides support for a more positive identity for light or nondrinkers than has been previously available. It offers opportunities for both personal and social change, recognizing that individual alcohol consumption behaviors cannot be separated from their contexts. However, no research has examined how sober curiosity or similar interventions to reduce alcohol consumption are perceived by sexual minority women. An established literature on the links between minority stress and poor health [66-68] provides strong evidence that the contexts in which sexual minority women live and experience life differ in important ways (eg, marginalized identities and shame) from heterosexual women's life experiences, making it critically important that such experiences be considered in any intervention effort to reduce sexual minority women's alcohol consumption.

Drawing on several decades of our own and others' research investigating and seeking to understand sexual minority women's drinking, we believe that a sober curious approach may increase the desire of sexual minority women to reduce alcohol consumption and increase their self-efficacy to resist drinking. Sexual minority women typically participate in alcohol-centric social contexts (social worlds) to connect with other sexual minority people, establish inclusive friendships with like-minded people, and gain social supports that are limited in other contexts [59,60]. These social worlds, although contoured by heavy drinking norms, can be especially helpful during periods of transition or stressful events (eg, coming out, experiencing violence, or relationship dissolution), contexts in

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which sexual minority women may be more likely to drink heavily [69].

Sober curious approaches could promote wider availability of alternatives that meet important personal and interpersonal needs but do not involve drinking alcohol. This alternative is promising, given research that has found social norms, particularly perceived peer-drinking norms, are strongly predictive of heavy drinking among sexual minority women [32,70,71]. Sober curiosity focuses on shifting cultural and subcultural heavy-drinking norms (not just individual behavior), and interventions that are shaped around the philosophy of sober curiosity may be an important way to address persistent sexual orientation–related disparities in hazardous drinking among women. Sober curiosity is nonjudgmental; it emphasizes alcohol and its addictive properties rather than the person as the "problem." Research across various domains of sexual minority women's health suggests that approaches that are nonpathologizing and nonstigmatizing, that focus on community norms and social connection, and that emphasize health, wellness, and mindfulness are likely to be most effective for sexual minority women [72]. Yet, no studies have been conducted that use these approaches in conjunction with sober curious principles to address sexual minority women's drinking.

Therefore, we are conducting 2 studies that combined to use a variety of methods to explore the feasibility, potential usefulness, and key elements of a tailored intervention based on sober curiosity for sexual minority women. One of the studies includes focus groups and a national survey with sexual minority women in Scotland; the other includes in-depth interviews with sexual minority women in the United States, followed by a review of findings by 2 international panels of experts. The aims of this research are (1) to explore the perspectives of the drinking social worlds of sexual minority women, their awareness of the sober curious movement, perceptions of their own and their peers' drinking and desire to drink less, and perceived barriers and facilitations to changing their drinking behaviors and (2) to identify key elements of an alcohol reduction intervention tailored for sexual minority women.

Conceptual Framework

The conceptual framework informing our work incorporates "social world" perspectives [58] and tenants of the health equity framework [73]. The social worlds of heavy-drinking sexual minority women are characterized by a connection point that can be thought of as a space where drinking alcohol is perceived to be an important aspect of shared activities or of a shared culture [3]. Research addressing heavy drinking social worlds is nascent; yet, this perspective can provide a unique lens for understanding and addressing harmful drinking in at-risk populations. The health equity framework builds on 3 foundational concepts: equity at the core of health outcomes; multiple, interacting spheres of influence; and historical and life-course perspectives. It illustrates how complex interactions between people and their environments affect health behaviors and outcomes. The importance of each of these concepts for LGBTQ+ people is highlighted in a 2011 landmark report on LGBT health [74].

Why Scotland and the United States?

Scotland

Most sexual and gender minority health research, especially research on alcohol use, has been conducted in North America [14,75-78]. We chose to collect data from sexual minority women in Scotland because the sober curiosity movement appears to be more prominent in the United Kingdom than in other European countries and in most other parts of the world [79,80]. Further, hazardous drinking in the UK general population is more prevalent than in other countries in continental Europe [81], and alcohol-related harm is disproportionately higher in Scotland than in the rest of the United Kingdom [82]. In 2018, as part of a raft of evidence-based strategies to tackle this "alcohol crisis," Scotland became one of the first countries in the world to implement minimum unit pricing with the aim of reducing alcohol-related deaths and decreasing health care use [83,84]. Although relatively little research on alcohol use among sexual and gender minority people has been conducted in Scotland, or in the United Kingdom, limited research has documented higher rates of hazardous alcohol use in sexual and gender minority people in the United Kingdom relative to their heterosexual counterparts [85]. Thus, although no studies have compared rates of sexual and gender minority drinking in Scotland and in the United States, there is reason to believe that sexual minority women in each country are at heightened risk of harmful alcohol use. Our research aims to understand similarities and differences in the cultural contexts of sexual minority women's drinking in the 2 countries and how such differences impact sexual minority women's drinking.

The United States

Because Scotland's population is predominately White (only 4% are Asian, African, Caribbean or Black, mixed, or members of other ethnic groups) [86] and because we wanted to include diverse sexual minority women's perspectives, we chose to also collect data in the United States. We created a sampling frame consisting of diverse sexual minority women in regard to age, sexual and gender identity, race or ethnicity, education, and geographic residence from participants enrolled in an ongoing longitudinal study of risk and protective factors for hazardous drinking among sexual minority women [87].

Methods

Study Design

We are currently conducting focus groups and a national web-based survey with sexual minority women in Scotland and in-depth individual interviews with sexual minority women in the United States. This mixed methods or triangulated approach, using both qualitative (focus group and individual interviews) and quantitative (web-based survey) methods conducted in 2 countries, was intentionally chosen to maximize understanding of similarities and differences in cultural contexts and influences on sexual minority women's drinking. Triangulation is commonly used in both qualitative and quantitative research and is especially helpful in understanding complex human behavior. Triangulating methods and data can enhance the

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validity and credibility of findings, mitigate potential biases, and give more confidence in the findings [88]. Figure 1 summarizes the qualitative and quantitative components of the studies and includes the planned number of participants in each component of the studies.

Figure 1. Overview of research components.

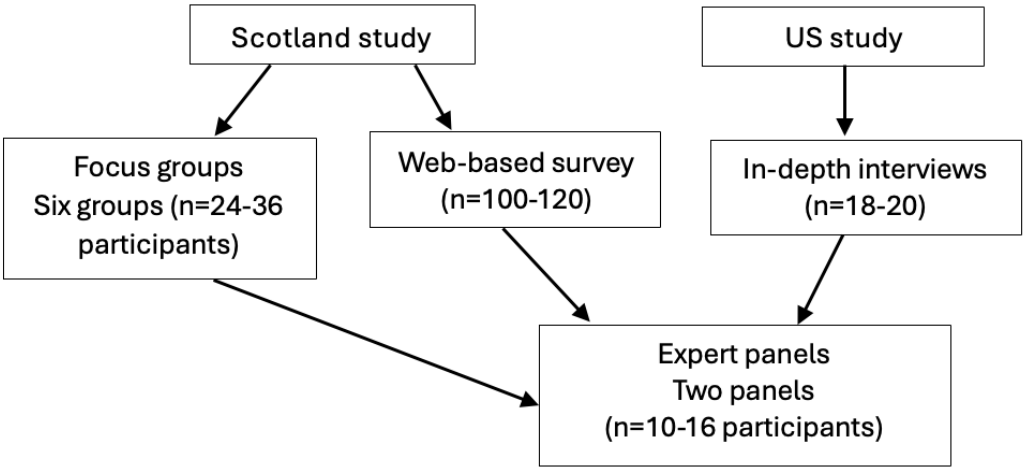

Focus Groups

The Scotland study will include 5 to 6 focus groups, each with a purposive volunteer sample of 4 to 6 adult sexual minority women. Focus group interviews are conducted in person or via Zoom (Zoom Video Communications) and are led by team members (primarily LB and BM) who are experienced qualitative researchers with expertise in alcohol use among sexual minority women; some team members identify as part of the sexual minority women's community. Focus group discussions are organized around specific topics and include broad areas of inquiry [89] developed by the research team. The focus group interview guide was adapted following the first and second focus group sessions to improve clarity and more effectively address the study aims. Areas of inquiry include (1) perceptions of alcohol use in sexual minority women's "communities" in Scotland; (2) openness to reducing alcohol consumption (are they sober curious?); (3) factors and barriers that impact sexual minority women's decisions and preparedness to reduce consumption (eg, drinking norms and drinking behaviors of peers); (4) attitudes toward, perceived availability of, and experiences with NoLo alcohol beverage alternatives; (5) conditions that would support reducing their own and other sexual minority women's alcohol consumption; (6) messaging and framing about reducing alcohol consumption that sexual minority women would find appealing (or off-putting); and (7) the potential benefits and barriers to a successful sober curious alcohol reduction intervention with sexual minority women. The focus group interview guide is available upon request.

Web-Based Survey

We will complement data collected in focus groups with data collected from a larger convenience sample of Scottish sexual minority women (N=100-120) recruited to participate in a web-based Qualtrics survey. Our team developed the survey using existing literature and a previous study on sober curiosity conducted by Lunnay et al [90] with midlife women in Australia. We pilot-tested the survey with 10 sexual minority women in Scotland and the United States prior to its official launch. The survey includes approximately 80 questions (3-5 questions per page) and takes an average of 15-20 minutes to complete. Like focus groups, the survey includes questions about demographic characteristics, patterns of alcohol use (eg, frequency and quantity), drinking contexts, drinking companions, drinking motivations and perceived drinking norms of peers, as well as help-seeking, familiarity with the sober curious movement, or aspects of it (eg, Dry January, Sober October, and NoLo alcohol beverages), and perceived barriers and facilitators to reducing alcohol consumption. We also include a few open-ended questions to collect qualitative data that will be used to triangulate data from the focus groups (eg, participants' descriptions of barriers and facilitators to reducing drinking).

Scotland Study Recruitment

We are recruiting adult (age 18 years or older) sexual minority women who reside in Scotland and who report moderate (between 7 and 14 units per week) or heavy (>14 units per week) alcohol consumption. Although there is no agreed international definition of low- or moderate-risk drinking [91,92], researchers in the United Kingdom [93] have used 7-14 units per week to indicate "moderate" drinking. Efforts to support effective behavior change must consider local sociocultural contexts and build on existing community assets. In each country, we are working to recruit diverse samples of sexual minority women in terms of age, education, geographic location (eg, rural and urban), and identity (eg, lesbian, bisexual, queer, and nonbinary gender). In addition, because sexual minority women's "communities" are not homogenous, and distinct groups within it are more or less marginalized and have different levels of capacity and resilience than others, we are using recruitment strategies that attract sexual minority women across different sociodemographic statuses. We are posting advertisements in local LGBTQ+ publications, advertising the study via social media and relevant mailing lists, and conducting outreach through partnerships with LGBTQ+ organizations in Scotland (eg, *LGBTQ+ Health & Wellbeing*, *LGBTQ+ Youth-Scotland*, and *The Equality Network*) and LGBTQ+ sports groups. Interested individuals are directed to a web-based screener where

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they answer several questions about their age, sexual identity, residence, and current drinking to determine eligibility. Prospective participants are informed that, in appreciation of their time and contributions, they will receive an Amazon gift card worth approximately US $38 for participation in a focus group or US $12.40 for completion of the web-based survey.

US Study

In-Depth Interviews

In a separate but complementary study, we are conducting in-depth interviews with a purposive, diverse sample of approximately 18-20 sexual minority women in the United States. Interviews lasting approximately 60 minutes are conducted via Zoom or phone by 2 researchers (LB and Ellen Riggle) with extensive qualitative training and research experience in sexual minority women's health. Questions explore the same areas of inquiry as the focus groups in Scotland. For example, sexual minority women are asked about their perceptions regarding alcohol use within sexual minority women's social worlds and about their personal experiences with drinking. During interviews, we ask if sexual minority women are aware of the sober curiosity movement, are interested in considering ways to reduce their alcohol consumption (are they sober curious?), factors and barriers that impact their decisions and preparedness to reduce consumption, alternatives to alcoholic beverages and alcohol-based events perceived to be available, attitudes toward and experiences with NoLo beverages, and perceptions of conditions that would support consideration of reducing their own and other sexual minority women's alcohol consumption. The US interview guide is available upon request.

Recruitment for US In-Depth Interviews

We are recruiting adult sexual minority women who participated in a longitudinal study of drinking among sexual minority women led by first author Hughes [14, 94]. This approach permits more efficient and accurate identification of sexual minority women who either drink at moderate or heavy levels (ie, at least 14 drinks per week on average) or reported that they were thinking of cutting down on their alcohol use. The sample will include sexual minority women with diverse demographic characteristics, such as age, race or ethnicity, sexual identity (eg, lesbian, bisexual, and queer), residence (urban or rural), educational level, and relationship status. Interviews last 60-90 minutes, and participants are given a US $50 Amazon gift card in appreciation of their time.

Ethical Considerations

The Scotland study received ethics approval from Glasgow Caledonian University (HSL NCH 22 040), and both the Scotland and the US studies received ethics approval from Columbia University (AAAU7672), the lead institution. The studies were reviewed and deemed to be exempt given that they were judged to pose little or no risk to the research participants. For the Scotland focus groups, informed consent is obtained by the researchers prior to commencing research procedures. An information sheet is provided to individuals who participate in the web-based survey with passive consent implied by virtue of survey completion. For the US study, verbal informed consent is obtained by the project manager prior to scheduling each participant's interview. Following a verbal review of the consent form, questions are asked of each participant to ascertain that they understand what is involved in their participation. Documentation of consent is maintained on a password-protected end-point device. Participants receive a copy of the consent form via email for their records. Scotland focus groups are conducted either in person or on Zoom (to accommodate the participation of sexual minority women who live in rural or other outlying areas). Participants are invited to provide a pseudonym to be used in focus group discussions, and any names or information that could potentially identify a participant are redacted from the transcripts. Each focus group participant is assigned a unique ID number linked to their demographic and contact details, which are saved separately on a password-protected system in a password-protected file. Audio files are destroyed after the transcripts are reviewed and verified. Deidentified transcripts will be available to members of the research team for analyses. Scotland survey participants are also each assigned a unique ID number and are asked to provide an email address in order to receive the link for the study incentive (Amazon gift card). The key that links ID numbers to email addresses is kept on a password-protected system in a password-protected file separate from the dataset with the survey responses. The ID numbers are used to keep track of who has been sent a gift card. Individual interviews in the United States are conducted by phone or Zoom. Audio files are coded with the participant's identification number but without any information that could be used to identify them. The list that links codes to names and addresses is kept on a password-protected end-point device in a password-protected file separate from the audio files. Once interviews are completed, the audio files of the interviews are saved on a secure electronic system (ie, Box). Once the interview transcripts are reviewed and verified, the audio files will be destroyed.

Data Analysis

Given the range of data sources used, it is essential to triangulate data to address the completeness, convergence, and dissonance of key themes. We will analyze data from each of the 3 sources separately.

Data from the focus groups (Scotland) will be analyzed using Krueger's framework analysis [95] for narrative focus group data that considers words, context, internal consistency, frequency of comments, extensiveness of comments, intensity of comments, specificity of responses, and big ideas. This process involves six interconnected steps: (1) data collection; (2) immersion in data; (3) memoing to identify ideas and concepts; (4) indexing descriptive statements; (5) formation of categories, drawing on within- and between-group comparisons; and (6) interpretation. In-depth interview data from the US study will be analyzed using inductive thematic analysis drawing on six phases described by Braun and Clarke [96]: (1) immersion through reading and rereading data and noting initial ideas, (2) generating initial codes, (3) searching for themes, (4) reviewing themes, (5) defining and naming themes, and (6) producing the report, including selection and use of extract examples. Thematic analysis is a method for identifying and organizing patterns of meaning, or themes, across a dataset to make sense of shared

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meaning and collective experiences [97]. Analyses of the Scotland and US qualitative data will be guided by a social worlds' perspective, which aligns with constructivist and symbolic interaction theory and "supports identification and investigation of groups below the level of society but above the level of friendship groups, where relatively coherent heavy drinking cultures may operate" [3].

Although data will be analyzed separately, we will be particularly interested in comparing themes from the focus groups and the in-depth interviews to identify similarities and differences in the findings and to identify patterns and relationships across data to validate or corroborate findings. We expect that these comparisons will provide a more comprehensive understanding of factors that serve as facilitators or barriers to sexual minority women who wish to reduce their alcohol intake.

Several strategies will be used to enhance the trustworthiness of the qualitative findings [98]. These include prolonged engagement with the narrative data, researcher triangulation, with multiple researchers each bringing their perspective to analyses, and regular peer debriefing and reflexive meetings via Zoom with research team members (authors of this paper). The team members are part of a research collaboration among Columbia University School of Nursing, Center for Sexual and Gender Minority Health Research and international partners at Glasgow Caledonian University, Research Centre for Health, and Torrens University Australia, Research Centre for Public Health, Equity and Human Flourishing. The research team includes individuals from multiple disciplines (eg, public health, sociology, psychology, nursing, and social work). More than half of the team members identify as being part of either sexual minority or gender minority communities. As a check to ensure findings accurately reflect the experiences and perspectives of the participants, member checking will involve validating the findings with stakeholders involved in the research (eg, members of the research team) and with at least 3 focus group participants and 3 participants from the in-depth interview portion of the study.

Survey data will be analyzed using SPSS (version 29; IBM Corp). Analyses will initially screen for and correct outliers, data entry errors, or other inconsistencies. We will decide whether to use cases with incomplete data (eg, surveys that were only partially completed) based on the number and relevance of key questions that have valid responses. All statistical tests, for example, comparing rural versus urban sexual minority women, will be 2-sided (α=.05). Given the exploratory or descriptive nature of the study, we believe that data from 100 to 120 survey participants will provide sufficient information to inform our research aims. We will explore how findings from closed- and open-ended survey questions map onto key themes from the qualitative studies.

Comparisons of the perceptions and experiences of sexual minority women in Scotland and in the United States will identify thematic commonalities and differences and to formulate hypotheses about how drinking alcohol among sexual minority women relates to social contexts, group identity, and cultural norms. Although we expect to find similarities in the cultural contexts of sexual minority women across these 2 high-income countries, understanding differences and how they shape drinking norms and behaviors will elucidate key elements of a future tailored intervention aimed at helping sexual minority women reduce the risk of harmful drinking.

Results

The study was funded in July 2023, and data collection began in September 2023 after the study received ethics approval from the 2 lead institutions (August 2023). The Scotland study received ethics approval from Glasgow Caledonian University (HSL NCH 22 040) and from Columbia University (AAAU7672). As of December 2024, we completed 4 of the 6 planned focus groups (Scotland) and 18 of the 20 planned in-depth interviews in the United States. Data collection for the web-based survey in Scotland was paused in October 2024 for several months after discovering that about two-thirds of the approximately 150 responses were invalid (exhibited evidence of bot automation, eg, duplicate IP addresses). To address this, we removed the Amazon gift card incentive from recruitment advertisements and submitted the revised protocol to the 2 human participant review committees for ethical approval. As of December 2024, we have 64 valid survey responses. We expect to complete data collection in both Scotland and the United States by June 2025.

Results of qualitative analyses (data from focus groups and individual interviews) will be organized and summarized as themes, and results of survey data analyses summarized in tables. Findings from the studies will be presented to 2 international panels of experts; each panel will include 4-6 experts. Panel participants will consist of researchers with expertise in sexual minority women's use of alcohol, the development of alcohol interventions for women, or sober curiosity approaches. This will serve 2 purposes: peer review (having other researchers or experts review the findings to ensure their validity and to identify potential biases) and identification of key factors to be included in a planned intervention that will incorporate tenants of sober curiosity. We will use Acceptability, Practicability, Effectiveness, Affordability, Side-Effects, and Equity [99] criteria to consider important socioecological and cultural factors that provide an overarching understanding of key elements of an intervention tailored to assist sexual minority women to reduce harmful drinking.

Discussion

Principal Findings

To our knowledge, this project is the first attempt to investigate sexual minority women's openness and readiness to reduce alcohol consumption within a sober curiosity framework and with the view to designing an intervention tailored for sexual minority women. Understanding how sexual minority women might justify or rationalize their alcohol consumption in different contexts and social worlds, their interest in changing their drinking behaviors to reduce their alcohol consumption, and their perceived barriers and facilitators to doing so will provide new insights. We anticipate that findings will provide essential

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preliminary data to develop (and subsequently evaluate) an intervention that incorporates tenets of the sober curious movement and is aimed at reducing harmful drinking among sexual minority women, with scalability to other high-income countries with similar drinking-related social norms. Such an intervention will respond to sexual minority women's reported need for social connection and will support alcohol reduction strategies while retaining social support.

Strengths and Limitations

First, the use of mixed methods to collect data, including both qualitative and quantitative methods, and the inclusion of 2 countries are strengths of this research. For example, while the perspectives of sexual minority women about alcohol use and sober curiosity in the web-based survey may be influenced by misunderstandings of the questions, focus group and individual interviews allow for such misunderstandings to be explored and corrected. However, relationships among drinking behaviors and patterns, sexuality, and gender are complex [5,30,60,100], and information to be gleaned from the current research may not capture these complexities. For example, qualitative research from Scotland and Australia highlights the ways in which drinking alcohol facilitates engagement with LGBTQ+ communities, aids in expressing sexuality and identity, and challenges heteronormative perspectives of women's drinking [30,100]. Our focus on sober curiosity and ways that sexual minority women might reduce their alcohol consumption does not consider the performative role that alcohol use, including heavier use, plays in "doing" gender and sexuality and in connecting with the LGBTQ+ community in pleasurable and meaningful ways. Future work should consider the complex meanings and social functions of alcohol in the lives of sexual minority women.

Second, because findings are from nonrepresentative samples of sexual minority women in Scotland and in the United States, they have limited transferability. Both countries are characterized by high income and relatively low levels of stigma (eg, compared to non-Western and low-income countries). There may be important cultural differences that shape alcohol use among sexual minority women who live in countries and cultural contexts where either same-sex sexuality or alcohol use among women is more stigmatized. Further, given limited time and resources, we may not be able to reach as diverse a sample as intended. For example, factors such as poverty and homelessness or disability influence sexual minority women's drinking. More research using mixed methods and larger samples across different cultural contexts is needed to further refine the understanding of factors that influence sexual minority women's drinking and perspectives about sober curiosity.

Third, although trauma is not a focus of the studies, it is well documented that experiences of lifetime trauma, particularly adverse childhood experiences, are more prevalent among sexual minority women [24] and are strongly linked with alcohol use among sexual minority women [14,101]. Thus, our failure to address trauma may limit important insights about key elements of an alcohol reduction intervention for sexual minority women.

Conclusions

The sober curious movement is gaining positive attention and momentum in mainstream society in many parts of the world. Now is an important time to leverage this momentum to address heavy drinking social norms and behaviors within sexual minority women's social worlds. An intervention developed and offered to sexual minority women within this growing movement may provide an acceptable and effective way to support sexual minority women to reduce alcohol-related harms. However, such interventions will likely need to recognize the positive aspects of drinking (eg, facilitating social connections) and the pervasive impact of trauma on sexual minority women's drinking as well as the linkages among connection, coping, and identity, if they are to be optimally effective.

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Data Availability

The datasets generated and analyzed as part of this project will be available from the corresponding author on reasonable request after the research team has completed analyses related to the study aims.

Conflicts of Interest

None declared.

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Abbreviations

AA: Alcoholics Anonymous
CBT: cognitive behavioral therapy
LGB: lesbian, gay, and bisexual
LGBTQ+: lesbian, gay, bisexual, transgender, queer or questioning
WHO: World Health Organization

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Protocol

Development and Impact of a Community-Delivered, Multisectoral Lifestyle Management Service for People Living With Type 2 Diabetes (Logan Healthy Living): Protocol for a Pragmatic, Single-Arm Intervention Study

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Abstract

Background: Type 2 diabetes is the fastest-growing chronic condition in Australia, with higher prevalence in disadvantaged groups. Logan Healthy Living by UQ Health Care is a proof-of-concept, interprofessional allied health clinic focused on supporting people with and at risk of type 2 diabetes in Logan, a region in South East Queensland, Australia, with high levels of health inequity. Logan Healthy Living is supported by the Queensland Government through Health and Wellbeing Queensland and a broader multisectoral alliance including primary health care; tertiary hospital and health services; and government, community, and university sectors.

Objective: This paper describes the establishment of Logan Healthy Living and outlines the evaluation protocol for the service's type 2 diabetes lifestyle management program.

Methods: The context and setting of Logan Healthy Living are presented, and the process for establishing the multisectoral partnerships, development and governance of the service, and the facility are described. The lifestyle management program is an 8-week, group-based program that includes 1 hour of education and 1 hour of supervised, individually tailored exercise each week. The theoretical underpinnings and the program are described in detail. The Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework will guide evaluation of the program and inform key questions regarding the number and characteristics of the clients (reach); diabetes-related distress, health behaviors (physical activity and diet), quality of life, self-management self-efficacy, loneliness, community involvement, anthropometric measures, hemoglobin A_{1c} levels, physical function, and health care use (effectiveness); referral pathways (adoption); fidelity, appropriateness, acceptability, and costs (implementation); and long-term effectiveness (maintenance). Data will be drawn from a purposefully embedded minimum dataset and data registry, with the process for designing and embedding data collection into practice (via surveys, in-person measures, and client management software) described in detail.

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Results: Ethics approval has been obtained for the data registry. Logan Healthy Living is a 4-year proof of concept that concludes on December 31, 2024, with findings expected to be reported starting in 2025.

Conclusions: While multisectoral responses are needed for complex community health challenges, the processes for achieving these are rarely documented, and the description of the development of Logan Healthy Living has the potential to inform future partnerships. The findings of the evaluation will provide important new knowledge on the impact of a community-delivered type 2 diabetes program on individuals, the community, and the health system in an area of high health inequity.

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KEYWORDS

type 2 diabetes; lifestyle management; allied health; evaluation; protocol

Introduction

Background

Type 2 diabetes is a chronic condition where the body becomes resistant to the normal effects of insulin and gradually loses the capacity to produce enough insulin in the pancreas [1]. The onset of type 2 diabetes is associated with both nonmodifiable (eg, genetic) and modifiable (eg, health and behavioral) risk factors [1]. Worldwide, in 2020, type 2 diabetes was the ninth leading cause of death, affecting 7% of the population, with prevalence rates only expected to increase [2]. In Australia, type 2 diabetes impacts an estimated 1.2 million people [1], with a further 2 million having prediabetes [2]. It is the fastest-growing chronic condition in Australia [1], with health system expenditure estimated at Aus $3.4 billion (US $2.1 billion) per year [3]. Type 2 diabetes has a significant impact on individuals. Along with the symptoms of the disease itself, many people experience diabetes-related complications (eg, retinopathy, peripheral vascular disease, and ischemic heart disease) and are at increased risk of multimorbidity (eg, cardiometabolic, vascular, and mental health conditions), which collectively impact their quality of life, impair functioning, and increase financial and economic burden [4]. Type 2 diabetes disproportionately affects disadvantaged groups. For example, people of a low socioeconomic status and with low levels of education [5], immigrants, and those from culturally and linguistically diverse backgrounds have increased risk of type 2 diabetes [6]. Furthermore, the intersection of disadvantage is likely to magnify risk and burden of disease [7].

Management of type 2 diabetes is primarily focused on achieving glycemic control through modification of health behaviors (typically physical activity and nutrition) and, where required, medication. Evidence-based management of type 2 diabetes emphasizes person-centered, team-based care with integrated long-term treatment approaches, as well as the involvement of social community support [8,9]. Self-management, where the person with type 2 diabetes works in partnership with their social supports and health professionals to understand, manage, and optimize their health, is the goal. Management of modifiable risk factors is a core component of self-management, with such strategies focused on building positive health behaviors, including physical activity and nutrition, and optimizing psychological well-being [9,10]. Multidisciplinary, group-based approaches to lifestyle modification have consistently been shown to positively impact a range of health and well-being outcomes for people living with type 2 diabetes [11]. To support this in practice, the Australian National Diabetes Strategy (2021-2030) has called for a multisectoral response by government and communities to provide the integrated care required [12].

UQ Health Care (a not-for-profit health care wholly owned enterprise of The University of Queensland) has established Logan Healthy Living as a specialist clinic designed to respond to this need [13]. Purposefully established in South East Queensland in the City of Logan, an area of Queensland with high burden of type 2 diabetes and intersectional disadvantage, Logan Healthy Living was designed with the aim of reducing the burden of disease on individuals, the community, and the health system [13]. The core service of Logan Healthy Living is a group-based lifestyle management program delivered by an interprofessional allied health team focusing on supporting people living with and at risk of type 2 diabetes in Logan. The program has 3 main foci: physical activity, healthy eating, and well-being [14]. Logan Healthy Living is a 4-year proof of concept delivered by a Queensland-first alliance among primary health care; tertiary hospital and health services; and government, community, and university sectors.

A key feature of the establishment of Logan Healthy Living was the integration of an outcome-based funding model—a model that prioritizes value-based care and patient-centered outcomes and leverages multisectoral partnerships. Critical to value-based care models is the collection and use of data to continually evaluate the impact of the service on the participants as well as the health system more broadly [15]. Moreover, leveraging this approach for practice-based evidence generated in “real-world” settings can add to the currently limited evidence on community-based, self-management programs for people living with or at risk of type 2 diabetes [16]. With dimensions at both the individual level and multiple ecological levels, the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework [17,18] offers a balanced and pragmatic approach to the evaluation of applied community-delivered programs considering factors such as the characteristics of the participants who take up the program (reach) and participant satisfaction (implementation). The RE-AIM framework has been applied across multiple evaluations, including diabetes health coaching [19], diabetes prevention programs [20], and telephone-delivered type 2 diabetes support [21]. To simultaneously support reporting for the outcome-based funding model and evaluate the real-world

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impact of a routinely delivered community program, a comprehensive continuous evaluation protocol informed by the RE-AIM framework was developed.

Objectives

The purpose of this paper is to describe the development of Logan Healthy Living and the protocol for program evaluation of this allied health care service. Specifically, we describe the context and setting of the service, the multisectoral partnership and co-design activities contributing to the service development, governance, and participants and recruitment channels. We then describe the protocol for the evaluation of the service according to the RE-AIM framework.

Methods

This protocol was prepared using the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist [22].

Context and Setting

Logan Healthy Living by UQ Health Care is located in the City of Logan in South East Queensland, Australia. With an estimated population size of 345,098 [23], the City of Logan is identified as one of the most culturally and linguistically diverse and socioeconomically disadvantaged areas in Australia. The proportions of the population speaking a language other than English at home; being born overseas; identifying as Aboriginal or Torres Strait Islander, Māori, or Samoan; being unemployed; and having one or more chronic health conditions are above South East Queensland averages [23]. The region has also experienced rapid population growth and has an aging population [24]. The City of Logan has a strong focus on community services and fostering connection, with a wide range of no- and low-cost community social programs, including Logan City Council Libraries; arts, culture, and heritage initiatives; sport and recreation facilities (including the Active and Healthy program offering >100 weekly free and low-cost health and well-being activities); and parks and community gardens. Logan also has a diverse range of cultural groups and grassroots networks supporting community connection [25].

In Logan, estimates of the prevalence of type 2 diabetes and associated indicators of burden of disease are consistently higher than state-based estimates for Queensland. Almost 20% (18.5%) of people aged ≥75 years living in Logan have type 2 diabetes (12.4% for those aged 55-74 years and 1.7% for those aged 18-54 years) [26], with the third highest rate of insulin-treated type 2 diabetes in Australia (an indicator of advanced or nonresponsive progression of the disease) [24]. Type 2 diabetes accounts for 31% of potentially preventable hospitalizations in Logan, making it the leading cause of potentially preventable hospitalizations [24]. Those living with type 2 diabetes in the area are also disproportionately likely to die from diabetes-related causes, with the average diabetes-specific mortality rate in Logan being 32% higher than that for Queensland in general [24].

Development of Logan Healthy Living

The concept of a multisectoral, allied health–delivered lifestyle management program for people living with type 2 diabetes in Logan emerged from an existing partnership between UQ Health Care and Metro South Health (the region's public health care provider) [27]. In 2014, Metro South Health and UQ Health Care established an innovative, integrated primary-specialist model of care for the medical management of people with complex diabetes, the "Beacon" model [28]. The Beacon model saw complex diabetes management provided within a community practice by a multidisciplinary team consisting of an endocrinologist from Logan Hospital, 2 to 3 general practitioners (GPs) with a special interest in diabetes from UQ Health Care, and a diabetes nurse educator from the Metro South Health community team who provided 1:1 consultation (at times before the GP with a special interest in diabetes to assist in triage). The aim of the Beacon model was to build capacity in primary care for managing complex diabetes through advanced management plans and subsequently diverting people with type 2 diabetes from tertiary care. While the Beacon model demonstrated favorable outcomes in changes in hemoglobin A_{1c} (HbA_{1c}) concentration and the percentage of patients meeting combined clinical targets of HbA_{1c} concentration, blood pressure, and low-density lipoprotein cholesterol [29], key stakeholders acknowledged that the Beacon model alone was not sufficient to address the rising community need. Moreover, it lacked a health behavior change program focused on self-management—a critical component for the management of type 2 diabetes [11].

To address these needs, in approximately 2019, what would eventually be known as "Logan Healthy Living" was envisioned, expanding on the existing partnership between Metro South Health and UQ Health Care and integrating learnings from the Beacon model and UQ Health Care's experience in delivering interprofessional, allied health services at other sites. The first phase of service development was establishing an alliance of partners underpinned by a commitment to prevent chronic disease and keep people well and out of hospital in Logan. UQ Health Care and Metro South Health led the establishment of the alliance, which in turn also included the Brisbane South Primary Health Network, The University of Queensland, and Griffith University. By early 2020, the alliance had established a proof-of-concept model for a comprehensive lifestyle management program delivered by an interprofessional team of allied health professionals and infused with a student allied health workforce.

Concurrently, in 2019, the Queensland Government established the state's first prevention agency, Health and Wellbeing Queensland [30]. The concept of Logan Healthy Living, a service delivering comprehensive lifestyle management programs to support behavior change and self-management, was put to the board of Health and Wellbeing Queensland by UQ Health Care and Metro South Health on behalf of the alliance. The proposal was strongly aligned with the vision and strategic plan of the newly formed Health and Wellbeing Queensland, which included developing and trialing new models of care for the prevention and management of chronic disease.

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Here, the intention was to reduce pressure on the tertiary health care system, address health inequities, and build multisectoral partnerships that drive system-level change for improved health and well-being outcomes. In 2021, Health and Wellbeing Queensland joined the alliance, with UQ Health Care and Health and Wellbeing Queensland entering into a 4-year agreement (2021-2024) to support the delivery of a tailored lifestyle management program. UQ Health Care secured additional revenue agreements and financial contributors to deliver on the commitment to reduce financial barriers for participants. The UQ Health Care and Health and Wellbeing Queensland service-level agreement outlined a comprehensive suite of deliverables and biannual key performance indicators. These key performance indicators were designed to evaluate the program according to the RE-AIM indicators across the 3 priorities identified previously (reduce the burden of disease on individuals, the community, and the health system). Examples of the agreed upon key performance indicators are summarized in Table 1.

Table 1. Examples of key performance indicators for Logan Healthy Living.

Evaluation domain	Key performance indicator
Reach	• Participant's type 2 diabetes status (at risk, newly diagnosed, complex, or chronic) • Participant's demographic characteristics • Participant retention • Participant attrition
Effectiveness	• Participant's knowledge, health literacy, and intention to change • Participant's healthy behavior action (health behavior change and anthropometric measures) • Health system impact
Adoption	• Referral pathways
Implementation	• Participant satisfaction • Staff satisfaction • Participant safety (adverse events) • Student training
Maintenance	• Participant sustained healthy behavior • Sustainable funding

The development and design of the service was community led and iteratively co-designed with key stakeholders, including consumers. Activities included participant journey mapping to inform program and resource development, consultation with student placement providers, and learning needs assessments for local GPs. A key event for consumer and stakeholder engagement was a half-day "design-jam" led by UQ Ventures and held on campus at Griffith University in Meadowbrook, where approximately 60 end users, delivery providers, academics, clinicians, community leaders, and representatives of other key stakeholders (eg, Metro South Health, Brisbane South Primary Health Network, and the Aboriginal and Torres Strait Islander Community Health Service) came together to progress their combined vision and implementation plan for the service. Subsequent planning days have also been hosted, which have similarly included Logan Healthy Living staff, key stakeholders, and consumers.

Simultaneously, the plan for routine collection of reporting and evaluation data was co-designed by key stakeholders, including researchers from The University of Queensland; the Logan Healthy Living Clinical and Operations Manager, administration team, and clinicians; and relevant content experts. Key to successfully collecting the range and breadth of data required was the intent to embed data collection into routine service delivery. Led by a researcher employed by the Health and Wellbeing Centre for Research Innovation (a research center jointly funded by The University of Queensland and Health and Wellbeing Queensland; SG), along with a senior academic experienced in evaluation (GH) and a data analyst (EW), a pragmatic data collection and consent process was co-designed and embedded into daily operations. Data are collected through both practice management software (Gensolve) and clinical trial software (REDCap [Research Electronic Data Capture]; Vanderbilt University) and facilitated day to day by the Logan Healthy Living clinical team, with technical and content support on an as-needed basis from The University of Queensland. Implementation of the data collection process was supported by on-site training sessions and a comprehensive manual developed by the data analyst. The Clinic and Operations Managers have been essential in establishing and building a culture for collaboration and prioritization of data collection.

Facilities

Logan Healthy Living went live for operations in July 2021. The service initially operated from Griffith University Logan Healthcare Centre, where it was intentionally colocated with the Beacon Clinic and Metro South Health Chronic Disease Diabetes Service (which included diabetes educators, nurse practitioners, and a podiatry service). In February 2023, Logan Healthy Living moved into its permanent, purpose-built location in a dedicated health and medical clinic, Meadowbrook Medical Centre, colocated with the UQ Health Care Meadowbrook GP clinic and the Logan Hospital endocrinology outpatient services (Logan Endocrine and Diabetes Service). The Meadowbrook Medical Centre is centrally located in the City of Logan and

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positioned within the community's transport and retail hub, Logan Hospital, and the Logan Healthy Kids Club and Good Start programs operated by Children's Health Queensland. The site is also set to become part of a larger health precinct, with a planned staged expansion of Logan Hospital and an additional 2 private hospitals.

Logan Healthy Living occupies 400 m^2 at Meadowbrook Medical Centre and includes a gym floor, 5 curtained consultation spaces, 2 individual consultation rooms, 2 large private rooms (used for staff or student rooms or for group education sessions), and an integrated open space dedicated to delivering group education. The open gym includes a range of exercise equipment, including cardiovascular training equipment (treadmill and stationary bicycle), parallel bars, steps and stairs, and resistance and balance training equipment. UQ Health Care invested in state-of-the-art resistance training machines by HUR Australia [31] that use air resistance and SmartTouch software for automatically programming and tracking load and equipment position (eg, seat heights), with participants tapping on and off the equipment with a personalized radio-frequency identification wristband. HUR Australia equipment was selected to reduce the barriers and improve safety with resistance training for older adults and new exercisers; the HUR Australia equipment is fully automated and applies smooth and consistent resistance across the range of motion.

The clinic is staffed by a range of allied health professionals, including physiotherapy, exercise physiology, dietetics, diabetes education, and health psychology professionals. With its student-infused model, the service also provides clinical education and placements for students from Griffith University and The University of Queensland. These include clinical placements for physiotherapy, exercise physiology, dietetics, and psychology students (ranging from 4 to 20 weeks in length) and project placements in a wide range of health disciplines such as nutrition and dietetics, pharmacy, social work, and health service management. Students from a range of disciplines work together to provide an interprofessional model of care. Beyond providing health care services, Logan Healthy Living is also further embedding itself into the community by contributing to the development and career selection of a locally based workforce, with the aim to promote workforce sustainability in the region. Examples of these activities include facility tours with question-and-answer sessions and opportunities for work experience with the Logan Healthy Living team for local high school students with interest in health careers.

Governance

Logan Healthy Living is governed by a multisectoral steering committee that is cochaired by UQ Health Care and Health and Wellbeing Queensland. Beyond UQ Health Care and Health and Wellbeing Queensland, the steering committee includes representatives from The University of Queensland, Griffith University, Metro South Health, Logan Hospital, Brisbane South Primary Health Network, and Logan Healthy Living participants. Members of the steering committee are responsible for providing program leadership and direction (eg, understand strategic implications and outcomes and accept responsibility for program strategy and overall benefit realization) and governance (eg, risk identification and mitigation, stakeholder management, and monitoring of progress) and maximizing program benefits (eg, monitor program outputs and monitor implementation and evaluation). Additional stakeholders are also consulted by the steering committee, such as broader consumer groups, the Aboriginal and Torres Strait Islander Community Health Service, Children's Health Queensland, and Diabetes Australia.

Logan Healthy Living is connected to the broader community governance of the Logan region through the Meadowbrook Partnership Group. Established in 2018, the group comprises representatives from key organizations who are positioned to influence integration and impact in Logan. Membership includes Brisbane South Primary Health Network; Logan City Council; Metro South Health; Economic Development Queensland; Loganlea State High School; The University of Queensland; Griffith University; and the Department of State Development, Infrastructure, Local Government, and Planning. Collectively, the membership represents state, federal, primary care, education, and local government stakeholders. All members have strong community relationships and understanding of local issues. Logan Healthy Living (clinical and operations manager) and UQ Health Care (chief executive officer) are members of the Meadowbrook Partnership Group. Figure 1 shows the network of key stakeholders involved in the development and delivery of Logan Healthy Living.

Figure 1. Logan Healthy Living key stakeholder network.

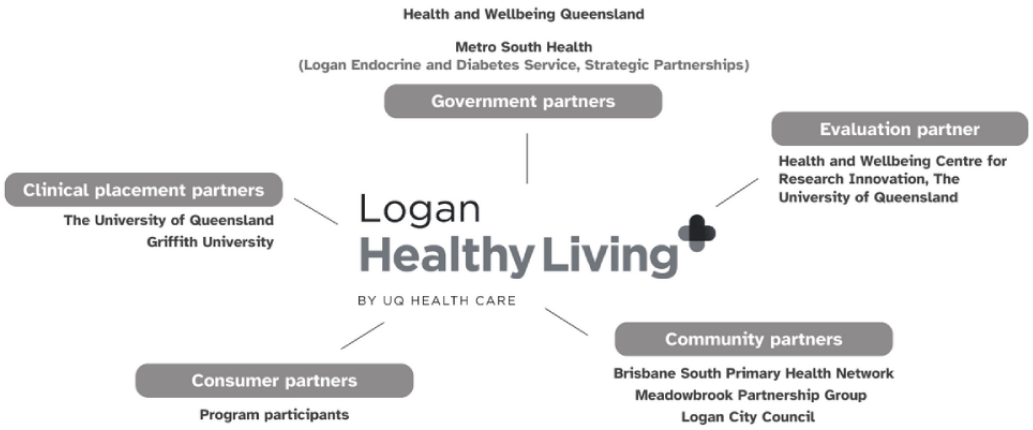

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Program Cost, Participants, Referral Pathways, and Intake Process

Logan Healthy Living delivers services at no cost to participants. Where possible, reimbursement for the lifestyle management program is sought through Medicare, Australia's universal health insurance scheme that provides free or subsidized health care (Medicare Benefits Schedule) and selected medication (Pharmaceutical Benefits Scheme, including diabetes medications) for Australian and New Zealand citizens, permanent residents, and some temporary residents. Specifically, Logan Healthy Living seeks reimbursement through the Medicare Benefits Schedule (group allied health service for type 2 diabetes), which funds 1 intake assessment (Aus $74.80 [US $46.99]) and 8 group sessions (Aus $18.65 [US $11.72] per session per person) per calendar year [32]. To claim Medicare benefits, the group sessions must include between 2 and 12 people; last at least 60 minutes; and be delivered by a credentialed diabetes educator, accredited exercise physiologists, or accredited practicing dietitian [32]. While the lifestyle management program is the primary service, participants are also able to access 1:1 consultations with health professionals on an as-needed basis.

To be eligible for the Logan Healthy Living lifestyle management program, participants must have a diagnosis of type 2 diabetes and be aged ≥16 years. While the program is intended for people living in the Logan region, no one is excluded from the service based on their geographical address. Participants may be excluded if it is identified by the clinical team that a group program may not be a feasible method of service delivery (ie, a participant requiring 1:1 education support). At Logan Healthy Living, services are currently delivered in English, and there is no access to free interpreter services (eg, through state or national government programs). However, clinical services have been delivered to participants who do not speak English when supported by a carer or support person.

Participants are primarily referred to the program by GPs using a referral form for group allied health services under Medicare for patients with type 2 diabetes. Participants are also able to self-refer through an expression of interest form on the service's website. Word of mouth and marketing activities support self-referrals, such as the service's website and newsletter, referrals from specialists (eg, the Logan Endocrine and Diabetes Service), and local advertising (eg, booths at local shopping centers, open days, and notice boards). Self-referrals may also be driven more broadly through the activities and promotion of the service by members of the alliance (eg, Metro South Health, Health and Wellbeing Queensland, Brisbane South Primary Health Network, UQ Health Care, Griffith University, and The University of Queensland). Where participants self-refer and do not have a GP referral, they are encouraged to obtain one so that the service can be reimbursed through Medicare; however, in cases in which there are barriers, this does not preclude admission into the lifestyle management program. For example, participants may experience financial barriers to primary care. While visits to GPs are subsidized by Medicare in Australia for some people, visits often attract a gap payment; services that provide no-gap primary care (bulk bill only) are limited; and some participants may not be eligible to enroll in Medicare and, therefore, ineligible for subsidized consultations. Participants can re-enroll in the program once per calendar year.

Upon presenting to Logan Healthy Living, participants are booked for an intake assessment, which is arranged over 2 appointments (appointments 1.1 and 1.2). The first appointment (1.1) is focused on medical history screening (using referral information where possible) and physical assessments. If it is identified at this first appointment that more information is required to safely prescribe exercise, the team may place the participant's referral on hold until medical authorization to exercise is provided by the referring GP or (if self-referred) the participant's usual GP. The second appointment (1.2) is focused on identifying barriers to participation in the lifestyle management program, goal setting, and an introduction to the exercise program. In between the 2 appointments, participants complete web-based, self-report surveys and are invited to indicate whether they agree or disagree to providing written informed consent for their data to be included in a research data registry (further details on ethics are described in the evaluation protocol in the Ethical Considerations section). Screening for completion of surveys and consent forms is conducted by the reception team, with face-to-face support for completion provided by the clinicians at the second appointment if required. After completion of the intake assessment, participants are allocated to the next available group according to their support needs and whether they are most suited for a "recently" diagnosed or "chronic" group allocation based on time since diagnosis.

Logan Healthy Living Lifestyle Management Program

Overview

The lifestyle management program is the primary service delivered by Logan Healthy Living. The program was developed and is delivered in line with the American Diabetes Association Standards of Care in Diabetes [33], which outline recommendations for a range of factors related to the management of people with type 2 diabetes. In particular, the Logan Healthy Living lifestyle management program follows the key recommendations for diabetes self-management education and support, medical nutrition therapy, routine physical activity, health behavior counseling, and psychosocial care. The program incorporates a range of behavior change strategies (as described in the Behavior Change Technique Taxonomy by Michie et al [34]), including goals and planning (eg, goal setting and action planning), feedback and monitoring (eg, biofeedback), social support (eg, unspecified, emotional, and practical), shaping knowledge (eg, instruction on how to perform the behavior), comparison of behavior (eg, demonstration of the behavior), repetition and substitution (eg, graded tasks), comparison and outcomes (eg, credible source), identity (eg, framing and reframing), and self-belief (eg, verbal persuasion about capability) [34].

Program Structure

The lifestyle management program is delivered face-to-face in groups over 8 weeks using an interprofessional model of care. Each week includes one 2-hour session that comprises a

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60-minute education workshop and a 60-minute supervised exercise ("movement") session. Each group has a maximum of 10 participants and is assigned an education workshop and an exercise lead (either health psychologist and exercise physiologist or diabetes educator and physiotherapist, respectively) who supports and provides services to the group throughout the 8 weeks. "Recharge" sessions are offered at 1, 3, 6, 9, and 12 months following completion of the 8-week program to provide an opportunity for participants to reconnect with their health care team, review their goals, and participate in a follow-up assessment before being discharged at 12 months. The 1-month recharge is conducted face-to-face, with the remaining sessions conducted via telephone. The education workshops and supervised movement sessions are conducted on-site at Logan Healthy Living, with movement sessions conducted in the fully equipped, on-site gym.

Program Content

A week-by-week overview of the topics, key concepts, and resources provided in the education workshops is detailed in Table 2. The education workshops were designed to be patient centered and focus on diabetes self-management education with the clinical support needed to facilitate the knowledge, decision-making, and skill mastery necessary for diabetes self-care. Education workshop topics are integrated with social prescribing, where opportunities for community engagement related to that week's content are signposted to support longer-term behavior change and address the broader social determinants of health. In addition to being signposted to local programs, participants are signposted to Health and Wellbeing Queensland's suite of prevention programs, including 10,000 Steps and Deadly Choices [30]. The supervised movement session comprises an individually prescribed exercise program targeting combinations of cardiovascular fitness, strength, or flexibility depending on participant presentations. All participants are provided with the opportunity to have an individually prescribed home exercise program or access to Physitrack [35], an app that supports home exercise prescription and monitoring.

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Table 2. Overview of the education workshop topics for the Logan Healthy Living lifestyle management program.

Week	Description	Key concepts	Handouts
1	Welcome and orientation	• Acknowledgment of Country[a] • Overview of the allied health team • Overview of program structure • Instructions and rationale for pre-exercise checks • Group introductions • Group activity: "What health behaviors impact my diabetes?"	• Pre-exercise checklist • Lifestyle management program journey plan • Opportunities for community engagement
2	Diabetes education	• What is type 2 diabetes • The role of insulin, insulin sensitivity, and insulin resistance • Key management strategies • Blood glucose testing, HbA_{1c}[b], understanding one's "normal," hypo- and hyperglycemia, and management strategies • Effects and complications of type 2 diabetes • Understanding the annual cycle of care • Identifying other support (family, friends, and community) • Introduction to self-management • Important services to connect with	• What is type 2 diabetes • Key management strategies • Instructions for blood glucose testing • Team of support and recommended review time frames • Services to find out more about type 2 diabetes—National Diabetes Services Scheme, DESMOND[c] Australia, Diabetes Connect by Diabetes Australia, and Logan Healthy Living Facebook page
3	Nutrition part 1	• Carbohydrates and how different types affect blood sugar • Healthy eating guidelines • Understanding what a diet looks like living with type 2 diabetes (5 main food groups) • Hydration • Healthy eating for diabetes • Meal timing and consistency	• A guide to a nourishing lifestyle—a breakdown of the 5 main food groups • How to build a healthy plate • Recommended meal timing • Tips for staying hydrated • Local services providing nutrition support
4	Nutrition part 2	• Understanding food labels • How food labels can help with diabetes management • Grocery shopping efficiently (saving money) • Modifying favorite meals to make them healthier	• Tips for reading food labels • Tips for enjoying home cooking and putting nutrition advice into practice • Local services providing food banks
5	Movement medicine	• The importance of enjoying movement • what is physical activity and exercise • What are the benefits of exercise • The importance of exercise for type 2 diabetes • Physical activity guidelines • Safely exercising with type 2 diabetes • Group activity: "Where can you find the motivation and inspiration to exercise?"	• Benefits of exercise • Pre-exercise checklist • Types of movement (aerobic, balance, flexibility, and resistance training) • Making exercise work for oneself • Exercise and blood glucose levels • Local services providing opportunities for movement
6	Stress management	• Understanding stress and what happens to the body when one is stressed • Understanding how stress impacts type 2 diabetes • The importance of social support • Group activity: managing stress—stress bucket analogy and brainstorming ways to manage stress	• What is stress • Identifying stressors • Sources of support • Local services providing well-being activities

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Week	Description	Key concepts	Handouts
7	Healthy habits	• Understanding how to set goals effectively • Review of goals and progress • Planning for life after the program • Creating and sustaining healthy habits • Planning for future success and overcoming barriers • Group activity: building healthy habits (understanding prompts, habits, and rewards) • Group activity: identifying barriers and "helpers"	• Tips for changing behavior and the habit cycle • Ideas for goal setting related to type 2 diabetes • "Planning for the future" activity—identifying what success looks like, what support systems are needed, and what has worked so far and planning for healthy habits • Information on local organizations offering a range of services (eg, community centers and libraries) • "Active and Healthy" booklet by the City of Logan (free and low-cost activities in the area)
8	Wrap up—review and future planning	• Review of educational workshops • Review of action plans (movement, community connection, nutrition, support networks, and rewards and motivations) • Group activity: bingo (revision of each topic)	• Summary of key takeaways from each topic • How to stay connected with Logan Healthy Living (recharge session schedule, gym memberships, meet-ups, Facebook group, blogs, and allied health consultations)

[a]An Acknowledgment of Country is delivered at the beginning of each week.

[b]HbA_{1c}: hemoglobin A_{1c}.

[c]DESMOND: Diabetes Education and Self-Management for Ongoing and Newly Diagnosed.

Evaluation Protocol for the Logan Healthy Living Lifestyle Management Program

Guided by the RE-AIM framework, the evaluation protocol was developed in partnership with the Health and Wellbeing Centre for Research Innovation at The University of Queensland and the other members of the steering committee and was designed to inform the service-level agreement and key questions regarding the uptake, effectiveness, costs, and sustainability of the program.

Study Design

The evaluation is a single-arm intervention design where participants are evaluated at intake to the service (before the program); at the end of the supervised program (8 weeks); and at approximately 1, 3, 6, 9, and 12 months after the end of the supervised program. For participants who do not re-enroll in the program, annual follow-ups are conducted at 2, 3, and 4 years.

Measures

Overview

A summary of measures that are being collected from participants to describe contextual information, program effectiveness, and acceptability is provided in Table 3, with further details and outcomes from other data sources described in the following sections. All self-report surveys are administered using REDCap, service-level data are extracted from practice management software, and physical measures are administered by clinicians on-site.

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Table 3. Outline of participant self-report measures and timing of assessments[a].

Measures	Structured program		Extended follow-ups				
	Intake	8 weeks	1 month	3 months	6 months	9 months	12 months
Contextual information							
Sociodemographic	✓						
Smoking and smoking changes[b]	✓	✓					✓
Digital health use	✓	✓					✓
Community involvement	✓	✓		✓	✓	✓	✓
Program effectiveness							
Diabetes-related distress	✓	✓		✓			✓
Health behaviors (physical activity, sitting, and nutrition)	✓	✓		✓	✓	✓	✓
Quality of life	✓	✓		✓	✓	✓	✓
Self-management self-efficacy	✓	✓		✓			✓
Loneliness	✓	✓		✓			✓
Anthropometry	✓	✓		✓	✓	✓	✓
Physical function	✓	✓					
HbA_{1c}[c] level	✓		✓				
Self-reported health care use	✓						✓
Acceptability							
Satisfaction		✓					

[a]All self-reported 12-month assessments (except smoking) are repeated annually at the 2-, 3-, and 4-year follow-ups.

[b]Smoking status is assessed at intake, and change in smoking status is assessed at 8 weeks and 12 months.

[c]HbA_{1c}: hemoglobin A_{1c}.

Reach Outcomes

Program Uptake

Program uptake will be described by reporting the number of participants who enroll in and commence the lifestyle management program compared to those considered ineligible. These outcomes will be tracked using appointment data from the practice management software, Gensolve. Withdrawals from the program and reasons for withdrawal will be tracked by clinicians using REDCap.

Sociodemographic and Other Contextual Characteristics

Demographic data are collected at intake on time since diagnosis of type 2 diabetes, age, sex assigned at birth, gender, postcode, First Nations status, country of birth, language spoken at home, highest level of education, occupation, and employment status. Other contextual information is collected at intake and tracked throughout the program. Smoking status is assessed at intake, and smoking changes are collected at the 8-week and 12-month follow-ups. Use of digital health technologies (eg, apps, wearables, and telehealth) is collected at intake, 8 weeks, 12 months, and then annually. Community involvement is collected at each of the assessments except for the 1-month follow-up by asking participants to report whether they take part in the following activities outside the home: social-based groups, exercise-based groups, combined social and exercise groups, and art and craft–based activities.

Effectiveness Outcomes

Diabetes-Related Distress

The primary effectiveness outcome for the evaluation is diabetes-related distress. Diabetes-related distress will be assessed using the Problem Areas in Diabetes scale [36]. The Problem Areas in Diabetes scale is a self-report, validated questionnaire that comprises 20 items assessing diabetes-related problems, with participants asked to indicate whether each item is “not a problem,” “a small problem,” “a moderate problem,” or “a somewhat serious problem.” Scores of ≥40 to 40 are considered “severe distress”; distress on specific items is considered when the total is not ≥40 but the score on one or more items is ≥3. Participants have “no evidence of distress” when both previous definitions are not met.

Health Behaviors

Physical activity will be assessed using the Active Australia Survey, a validated self-report measure [37]. The Active Australia Survey is designed to measure participation in leisure-time physical activity. It offers a short and reliable set of questions that can be easily administered via self-report or interview. Sitting time will be measured using an adapted version of the AusDiab multicontext sitting questionnaire, which

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asks participants to recall weekday and weekend day sitting time over the previous 7 days [38].

Nutrition-related behaviors will be assessed using 14 self-report items sourced from the 13-item Diet Quality Tool by O'Reilly and McCann [39] and 4 items from the evaluation of the Get Healthy Service [40], with redundant items removed. The Diet Quality Tool [39] has been validated in an Australian clinical population and reflects overall dietary quality relative to national recommendations. The New South Wales Get Healthy Service items, derived from population surveys—daily servings of fruit and vegetables as per the National Nutrition Survey [41], as well as daily servings of sweetened drinks per day and takeaway meals per week from the New South Wales Population Health Survey [42]—are useful stand-alone items for comparing results to those of other interventions such as the Get Healthy Service.

Alcohol consumption will be assessed using the brief 3-item version of the Alcohol Use Disorders Identification Test. The Alcohol Use Disorders Identification Test provides both a continuous score that correlates with alcohol consumption and adverse drinking consequences and a valid screening tool for detecting alcohol use disorders and risky drinking with validity in numerous populations, including primary care samples [43].

Quality of Life

Quality of life will be assessed via self-report using the EQ-5D-5L. The EQ-5D-5L is a widely used and validated tool to measure health-related quality of life [44]. The questionnaire comprises 5 dimensions—mobility, self-care, usual activities, pain or discomfort, and anxiety or depression—and participants are asked to report their level of difficulty with each dimension: *no problems*, *slight problems*, *moderate problems*, *severe problems*, and *extreme problems*. It also asks participants to self-rate their health on a numerical scale from 0 to 100.

Self-Management Self-Efficacy

Self-management self-efficacy will be measured via self-report using the Patient Motivation Questionnaire [45]. The Patient Motivation Questionnaire comprises 10 statements related to patients' understanding and confidence in the self-management of their condition. The score is calculated as a total out of 10, with 8 items required to be completed.

Loneliness

Loneliness will be assessed via self-report using a valid and reliable scale that asks 4 questions to capture different aspects of loneliness [46]. The first 3 questions are from the University of California, Los Angeles, 3-item loneliness scale. Scores from the 3 items are used to determine whether the participants are lonely (scores of 6-9) or not lonely (scores of 3-5). The final question is a direct question on how often the respondent feels lonely.

Anthropometric Measures

A combination of directly measured and self-report methods will be used to assess weight (kg) and waist circumference (cm). Directly measured weight will be assessed during the 1.1 intake appointment, the 8-week group appointment, and any subsequent face-to-face recharge appointments (not including the 1-month follow-up). Where participants do not attend face-to-face follow-up appointments for direct measures, they will be asked to self-report their weight and waist circumference. Instructional videos will be provided on how participants can best self-administer these measures. The combination of self-report and direct measures is standard practice at the clinic to allow for flexibility in collecting the data in a timely way with respect to the measurement time points while also allowing participants to have measures directly taken if they are at the clinic at the time of their follow-up.

HbA_{1c} Measures

HbA_{1c} level will be collected using a combination of approaches. For all participants, data will be collected by state pathology laboratories, with the tests conducted closest to intake and the 1-month follow-up after the supervised program (ie, approximately 3 months after baseline) being requested from relevant data custodians. A subsample of participants will have their HbA_{1c} levels collected via finger prick at intake and at the 1-month follow-up, with the point-of-care protocol introduced in January 2024 due to availability of resources.

Physical Function Measures

The 2-minute step test [47], time to complete 5 sit-to-stand exercises [48], and grip strength [49] will be assessed at intake and at 8 weeks to evaluate physical function.

Health Care Use

Health care use will be assessed using a self-report measure of use of GP, hospital, and emergency services at baseline and the 12-month follow-up based on questions adapted from those used in the Household, Income, and Labour Dynamics in Australia Survey [50,51]. In addition, Queensland Health records will be used to quantify emergency department presentations, hospital admissions, bed days, and potentially preventable hospital admissions related to type 2 diabetes (according to the Queensland Health key performance indicator attribute sheets for diabetes-related potentially preventable hospital admissions).

Adoption Outcomes

Adoption will be described by estimating the number of referrals and their referral sources.

Implementation Outcomes

Fidelity

Fidelity will be assessed using adherence to the program, where adherence is the number of sessions attended. These data will be drawn from the practice management software.

Appropriateness

Appropriateness of the program will be assessed by continuing to monitor program adaptations. These will be tracked using a log similar to that in Table 3.

Acceptability

Acceptability will be determined by assessing participant satisfaction. Participant satisfaction will be assessed using a 4-point Likert scale at the end of the supervised group component of the program (8 weeks), where 1=*not at all satisfied*, 2=*somewhat satisfied*, 3=*satisfied*, and 4=*highly satisfied*. Participants will be asked to rate their overall service

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satisfaction, satisfaction with the quality of the services, satisfaction with the first appointment being scheduled within a reasonable period, satisfaction with the staff providing the service, and satisfaction with the written information.

Costs

Cost of delivery will be assessed using appointment data collected using the practice management software and overall operating costs.

Maintenance Outcomes

Primarily, participant maintenance will be considered using their longer-term outcomes collected at approximately 12 months after the 8-week structured program. Additional perspective will be provided by the extent of re-enrollment after 12 months (or as early as 9 months if clinically indicated), as well as the long-term outcomes at the 2-, 3-, and 4-year follow-ups among those who do not re-enroll in the program.

Sample Size

The number of participants receiving treatment is not connected to an a priori sample size requirement as it would be in a traditional intervention study. Nonetheless, it is useful to consider how much evaluation data provide an adequate degree of power to detect changes in outcomes. These approximate requirements, based on simple bivariate tests and presented in Table 4, show that even a brief evaluation with few participants should be adequate for some outcomes (such as physical activity), whereas a long-running evaluation with many participants might be required to detect the expected changes in sitting time or potentially clinically meaningful changes in quality of life based on the EQ-5D-5L visual analog scale.

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Table 4. Approximate number of evaluated participants required to detect 0- to 8-week changes in effectiveness outcomes with 80% to 90% power and 5% 2-tailed significance.

Measure	Effect size	Assumed values, *r* (SD)	Required number of participants[a]	
			80% power	90% power
Diabetes-related distress				
PAID-20[b] score	MCID[c]=5	0.65 (15)	52	69
Health behaviors				
Active Australia MVPA[d] (minutes per week)	Moderate effect (0.5 SD)	0.4 1)	40	53
Sitting time (minutes per day)	Expected effect=30	0.4 (340)	1212	1622
Fruit consumption (servings per day)	Small effect (0.2 SD)	0.5 (1)	199	265
Vegetable consumption (servings per day)	Small effect (0.2 SD)	0.5 (1)	199	265
Sweet drink consumption (cups per day)	Small effect (0.2 SD)	0.5 (1)	199	265
Takeaway meals (times per week)	Small effect (0.2 SD)	0.5 (1)	199	265
Quality of life				
EQ-5D-5L visual analog scale (0-100)	MCID=6	0.6 (65)	739	989
EQ-5D-5L index score	MCID=0.262	0.75 (0.2)	5	6
EQ-5D-5L visual analog scale (0-100)	Small effect (0.2 SD)	0.6 (1)	159	213
EQ-5D-5L index score	Small effect (0.2 SD)	0.75 (1)	101	134
Self-management self-efficacy				
Patient Motivation Questionnaire score	Small effect (0.2 SD)	0.5 (1)	34	44
Loneliness				
UCLA[e] Loneliness Scale score	Small effect (0.2 SD)	0.75 (1)	101	134
Anthropometry				
Weight (kg)	Very small change=1	0.99 (26)	427	571
Waist circumference (cm)	Expected effect=2	0.97 (17)	36	48
Physical function				
2-minute step test (steps)	MCID=11	0.65 (25)	31	40
Sit-to-stand test (seconds)	MCID=2.3	0.65 (5.5)	34	45
Grip strength (left hand; kg)	Expected effect=1.5 kg	0.9 (11)	87	115
Grip strength (right hand; kg)	Expected effect=1.5 kg	0.9 (11)	87	115
HbA_{1c}[f]				
HbA_{1c} level (%)	MCID=0.5%	0.7 (1)	21	28
Health care use				
Number of general practitioner visits	Small effect (0.2 SD)	0.5 (1)	199	265
Number of emergency department presentations	Small effect (0.2 SD)	0.5 (1)	199	265
Number of hospital visits	Small effect (0.2 SD)	0.5 (1)	199	265

[a]Number of participants with pre- and postevaluation data collected.

[b]PAID-20: Problem Areas in Diabetes.

[c]MCID: minimum clinically important difference.

[d]MVPA: moderate to vigorous physical activity.

[e]UCLA: University of California, Los Angeles.

[f]HbA_{1c}: hemoglobin A_{1c}.

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Data Analysis

Reach, adoption, and implementation outcomes will be reported using descriptive statistics. The effectiveness of the lifestyle management program on effectiveness outcomes (all continuous) will be assessed by examining changes over time in linear mixed models accounting for repeated measures. Missing data in these mixed models will be handled through evaluable case analysis, with adjusted models including any characteristics that may differ between those providing data at different time points. The sensitivity of the conclusions to missing data handling will be evaluated using multiple imputation. All relevant time points will be reported, with the primary end point for effectiveness being 8 weeks (except for HbA_{1c} level and GP visits) and the primary end point for maintenance being approximately 12 months. The main evaluation will focus on all participants enrolled in the program, and a further per-protocol evaluation will consider outcomes for adherent participants only. Health care use in the 12 months before and the 12 months following enrolment in Logan Healthy Living will be compared using appropriate paired nonparametric tests (Wilcoxon signed ranks test and McNemar chi-square test). Costs will be estimated where possible. Sensitivity analyses will be conducted to explore whether health care use differs by a range of factors, including demographic and clinical characteristics.

Ethical Considerations

The data registry has ethics approval from the Metro South Health Human Research Ethics Committee (project ID 84062) and has received ratification from The University of Queensland Human Research Ethics Committee (2022/HE001421). At intake, participants are provided with the participant information and consent form for the data registry by the clinical team electronically and invited to opt in by providing written informed consent. Data for the data registry are collected in an identified manner, with data stored in REDCap and The University of Queensland Research Data Manager in password-protected folders. Participants are not provided with any compensation for taking part. Hospital use data will be drawn from centrally held medical records and obtained on request from relevant data custodians.

Iterative Adaptations to the Program

Since the opening of Logan Healthy Living in July 2021, several iterative adaptations have been made to the service delivery model to better meet the needs of the participants and the clinical team. Adaptations have been informed by stakeholder feedback (clinicians, students, and consumers) and biannual key performance indicator reports. Clinician and student reflections and feedback are discussed in regular team meetings, and participant feedback is openly encouraged through all interactions with Logan Healthy Living. Feedback from participants was sought more formally through qualitative focus groups conducted in the first years of operation that aimed to identify barriers to and facilitators of maintaining behavior change following the lifestyle management program [52]. In addition to identifying barriers that resulted in service changes (eg, ongoing access to resources such as Physitrack and the gym), participants reported that there was a sense of belonging and safety within the program, which facilitates an open dialogue for feedback on services. Key changes in response to consumer feedback are communicated to participants using a range of mechanisms, including “You said...we listened...” posters that outline feedback and corresponding changes to service delivery, which are displayed around the facility, and via clinic newsletters and social media posts. A summary of key service delivery model adaptations is provided in Table 5.

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Table 5. Summary of key service delivery model modifications.

Year	Feedback or challenge	Modification
2022	Initially conducted as 1 appointment, the intake assessment took approximately 3 hours, and participants reported fatigue.	The intake assessment was split into 2 appointments (1.1 and 1.2).
2023	Participants wanted the opportunity to continue to attend Logan Healthy Living to exercise.	"Open" gym time was scheduled, where participants could independently use exercise equipment once they had finished the lifestyle management program.
2023	Participants had access to Physitrack during the lifestyle management program and for 3 months after, and feedback indicated that they wanted access for longer.	Participants are provided with access to Physitrack for up to 12 months after the lifestyle management program.
2024	Demand for access to the gym was increasing, and access times were unsuitable for a large number of participants.	"Open" gym concept was expanded to a full, low-cost gym membership model with expanded opening times.
2024	Recharge sessions were scheduled as a group, and attendance was poor.	To improve attendance, recharge sessions are individually scheduled and delivered face-to-face at 1 month and via telehealth (telephone) at 3, 6, 9, and 12 months.
2024	Participants expressed a desire to have ways to continue to connect socially with their peers after completion of the lifestyle management program.	A community engagement social group was started. This included a bimonthly scheduled opportunity for participants to engage with each other socially and to inform them of local community engagement activities. This activity is jointly supported by the community development team of Logan City Council.
2024	The time taken to complete the intake assessment (eg, time from referral to commencing the lifestyle management program) was resulting in high attrition and low rates of uptake of the program.	The intake process was streamlined so that appointments were booked concurrently (1.1 and 1.2) to minimize time between referral and commencing the program.
Ongoing	Feedback is continually sought on the program materials and resources from all stakeholders (participants, students, and clinicians).	Program materials and resources are iteratively adapted to respond to feedback and ensure that they are up-to-date (eg, that local services are current and still operating).

Results

The 4-year proof of concept concludes on December 31, 2024, with reporting of the results anticipated in 2025. Results will be reported in conference abstracts and publications and with stakeholders informed through reports (with authorship determined according to scientific authorship guidelines). Findings will be shared with Logan Healthy Living participants using a range of channels, including clinic posters, newsletters, and social media.

Discussion

Overview

This paper describes the development and evaluation protocol for Logan Healthy Living, an interprofessional, community-delivered allied health service for people living with or at risk of type 2 diabetes in Logan, a region in South East Queensland, Australia. Delivered by a multisectoral alliance including primary and tertiary health care, government, and university partners, Logan Healthy Living is a proof-of-concept service that will be comprehensively evaluated using the RE-AIM framework and drawing from data at the level of the participants, service, and health system.

In this project, the evaluation outcomes are continuously monitored and collected in partnership between researchers and clinicians, with data collection embedded into usual practice. This is driven simultaneously by a value-based funding model and the opportunity for evidence-generating practice, with the establishment of agreed upon key service performance indicators being a pivotal influence in the buy-in required to embed this into practice. While the benefit for research is obvious, what has also emerged is the potential of continuous monitoring to inform iterative adaptations to the program, with the ability to respond in real time to optimize the health care service to suit participant and health system needs. Ongoing findings have also been used to inform collaborative strategic planning between partners to drive further development and expansion of the program and services. These "ripple effects," such as establishing new networks, partnerships, and services to meet the needs of these adaptations, will be monitored and reported in detail in an attempt to capture the nontraditional impacts of the program on the community.

While there is a call for multisectoral responses to complex health system challenges [12], including chronic diseases such as type 2 diabetes, responses to these calls are rarely documented in detail, and the learnings from these processes are potentially lost. The detailed description of the alliance, establishment of the service, and protocol for the evaluation have the potential to inform future multisectoral partnerships and the development of community-delivered models of care for type 2 diabetes prevention and management, as well as for chronic diseases more broadly. For example, there were challenges experienced in streamlining referrals and data sharing between government health care providers and Logan Healthy Living. While they were partners within the alliance, formal pathways for these activities were not established, which meant that referrals were

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limited to advertising and recommendations from health professionals and participants were required to replicate intake assessments that could have been avoided, thus reducing burden. Future programs can ensure that such details are determined as part of the establishment process. The limitations of the evaluation must also be acknowledged, including the lack of a comparison group; reliance on survey data due to practical considerations, which may introduce self-report bias; and the potential high rates of missing data given that the evaluation is within a service delivery rather than research context.

Conclusions

The implementation and evaluation of a community program within a culturally diverse region of a low socioeconomic status with rising rates of type 2 diabetes provides an opportunity to further understand the interplay of social determinants of health and chronic disease and the impact that a purposefully designed service can have on reducing the burden on the participants, the community, and the health care system. The outcomes of the evaluation will provide valuable insights into the impact of this model of care in practice, with the findings expected to inform potential scale-up through local, state, and national partnerships.

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Data Availability

Data sharing is not applicable to this paper as no datasets were generated or analyzed during this study.

Conflicts of Interest

DG and WW are employed by UQ Health Care Ltd, who deliver and operate Logan Healthy Living. JC, JM, and RL are employed by Health and Wellbeing Queensland, who provide a financial and governing contribution to Logan Healthy Living. All other authors declare that they have no competing interests.

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Abbreviations

GP: general practitioner
HbA1c: hemoglobin A1c
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Improving Pre-Exposure Prophylaxis Provision as Part of Routine Gynecologic Care Among Black Cisgender Women (Project PrEP4Her): Protocol for the Implementation of an Intervention

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Abstract

Background: Although HIV pre-exposure prophylaxis (PrEP) has been proven to be an effective prevention tool in decreasing HIV transmission, achieving adequate PrEP uptake has remained a challenge among Black cisgender women living in the Southern United States. Gynecology clinics, which provide primary health care services for many cisgender women, have the potential to be an ideal setting for the integration of PrEP services.

Objective: We designed an intervention, PrEP4Her, which aims to implement PrEP service delivery at gynecology clinics in Alabama, the United States, as part of routine reproductive and sexual health care visits to improve PrEP engagement rates among Black cisgender women.

Methods: Guided by the information gathered on (1) factors impacting PrEP implementation at gynecology clinics, including key barriers and facilitators to PrEP implementation and potential strategies to address the identified barriers (in-depth interviews with the gynecology care team), (2) structural barriers and provider-level barriers to PrEP implementation (cross-sectional study among gynecologists), and (3) implementation strategies on how to integrate PrEP services into routine gynecology care (in-depth interviews and focus groups with Black cisgender women), a multicomponent implementation strategy, tailored for Black cisgender women, was developed to integrate PrEP in routine women's health visits (ie, PrEP4Her). To determine the efficacy of the program, we will measure implementation outcomes, reach (increase in the absolute number of Black cisgender women receiving PrEP prescriptions), effectiveness (increase in the proportion of PrEP prescriptions over time), and adoption (proportion of team members willing to implement PrEP4Her) using the RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) framework. In addition, acceptability (the extent to which providers and Black cisgender women feel PrEP4Her to be acceptable—in-depth interviews); Feasibility (appropriateness of PrEP4Her for a larger, full-scale trial—the Feasibility of Intervention Measure scale); and fidelity (the degree to which PrEP4Her program was implemented as designed—electronic survey with patients) will also be assessed.

Results: The qualitative and quantitative data from the gynecology care team and the qualitative data from Black cisgender women were collected from August 9, 2022, to April 19, 2023, and were integrated through joint displays to identify major themes. The combined findings provided a comprehensive understanding of factors that were fundamental in the development and refinement of PrEP4Her implementation. The PrEP4Her was implemented from January 29, 2024, to August 16, 2024. The information gathered is being used to assess PrEP4Her efficacy (based on reach, effectiveness, adoption, acceptability, feasibility, and fidelity).

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Conclusions: Upon completion of our research, our interdisciplinary team, which includes experts in infectious diseases, implementation science, community-engaged research, and psychology, will be primed to lead a multisite type III implementation trial for PrEP service delivery at gynecology clinics across the Southern United States.

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KEYWORDS

Black; cis-Gender women; PrEP; pre-exposure prophylaxis; South; HIV; gynecology

Introduction

Black people only constitute 13% of the US population but account for more than half of the new HIV diagnoses [1]. These disparities are more pronounced in the South [2], where the highest acquisition and mortality rates are documented among Black people [3]. In response to these inequities, the US federal agencies are working in a coordinated manner to end the HIV Epidemic with a mandate to focus on populations facing HIV inequities and geographic hot spots, with prioritization to increase utilization of effective biomedical prevention tools like HIV pre-exposure prophylaxis (PrEP), that reduces HIV transmission with consistent use [4-7]. The US state of Alabama has been prioritized for End the HIV Epidemic efforts due to high HIV incidence and prevalence rates. In Alabama, where the rate of HIV diagnoses in 2020 was 14.1 per 100,000 people, most new diagnoses occurred among Black men and women [8]. In addition, in 2021, Alabama had a PrEP-to-Need ratio of 5.55, with the highest unmet need for PrEP occurring among the Black community (PrEP-to-need ratio among Black vs White individuals: 2.94:11.30) [9].

When focusing on cisgender women, who account for approximately one-fifth of new HIV diagnoses in the United States, only 8% of the 227,010 women with a PrEP indication are currently receiving PrEP prescriptions [10-13]. This low PrEP uptake is similar in Alabama, where only 7% of the PrEP clientele comprised of cisgender women in a university-affiliated infectious diseases-led PrEP Clinic [14]. Among cisgender women, Black cisgender women are even more disproportionally impacted by the HIV epidemic, currently accounting for 54% of all new HIV diagnoses among cisgender women, nationally [15]. These disparities are mirrored in Alabama's HIV incidence, where Black cisgender women are 9 times more likely to be diagnosed with HIV compared with White cisgender women [16]. With Black cisgender women in the Southern United States being disproportionately impacted by the HIV epidemic, approaches to increase PrEP uptake among this population present an opportunity to ameliorate these inequities.

Previous studies among Black cisgender women have found PrEP uptake barriers to occur at multiple levels (ie, individual, interpersonal, and Meso levels) [17]. Some individual-level barriers include a lack of awareness of PrEP and concerns around PrEP-related stigma, including fear of being labeled as HIV-positive with PrEP use, limiting PrEP uptake in this population. In addition, some provider-level barriers have also been discovered, such as a lack of knowledge on current PrEP clinical care guidelines, misconceptions related to insurance coverage, and provider bias preventing culturally appropriate PrEP-related discussions [18]. In addition, providers' stereotypic beliefs or prejudices (ie, having higher levels of color-blind racial attitudes) lead to a decreased willingness to counsel and prescribe Black cisgender women PrEP [19]. As such, overcoming current inequities requires innovative strategies to engage Black cisgender women in PrEP service delivery tailored to their preferences.

Of the total HIV diagnoses among Black cisgender women, the majority occur in those of reproductive age [20]. There is strong evidence to support that 70% of women in the United States are seeking routine annual care for reproductive health and nearly half access contraceptive services [21,22]. Safety-net programs created for cisgender women to receive reproductive health care, like family planning clinics, have been evaluated in Southern states as sites for PrEP implementation [23,24]. However, a major barrier to PrEP uptake is low provider knowledge on the delivery of PrEP services. Interventions focused on improving provider knowledge alone have fallen short on seeing huge gains in PrEP uptake among women [25-28]. In Addition, previous studies have shown that even with increased PrEP access in clinical care settings that specialize in women's health care, PrEP uptake has been low and providers have struggled in optimizing these spaces for PrEP service delivery [22-27,29]. Gynecologists have been shown to be ideal PrEP service delivery candidates, as national data supports higher willingness to prescribe PrEP among gynecologists compared with general practitioners [30]. Furthermore, 81% of patients seen by gynecologists are of reproductive age (18-44 years old), which also reflects the age range among cisgender women more likely to acquire HIV [31]. In line with this, our previous work among Black cisgender women in the state of Alabama also revealed they preferred PrEP services to be delivered by gynecologists in a clinical care setting [32].

Informed by compelling preliminary data, we designed an implementation study to determine the requisite steps and strategies for the implementation of PrEP services into routine gynecological care visits at a university-affiliated clinic in Birmingham, Alabama, which provides services to women with low income across the state [33]. Our gynecological pilot site is a large center that sees over 17,000 patients (40% Black cisgender women) annually, with the majority being of reproductive age, who reside in both urban and rural areas of Alabama. This paper outlines the protocol for this multicomponent implementation strategy, which evaluated key individual-level, inner-setting, and process-level determinants for the implementation of PrEP service delivery in gynecology clinic settings. The intervention aimed to develop and refine a

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multicomponent implementation strategy (PrEP4Her) that integrated PrEP in a gynecology clinic, which was then piloted to deliver PrEP for Black cisgender women attending routine gynecologic care visits. The PrEP4Her intervention is aimed at improving PrEP engagement among Black cisgender women in order to reduce the HIV disparity among this population.

Methods

Study Setting

The PrEP4Her was implemented at the University of Alabama at Birmingham gynecological Continuity clinic.

Development of the Protocol

To explore perceived barriers and facilitators for integrating PrEP into routine gynecological care, qualitative and quantitative data were collected. In-depth interviews were conducted with gynecologists, practice managers, medical assistants, nurses, and pharmacists at our gynecological clinical site via teleconference. The interviews covered topics, such as factors effecting PrEP implementation at gynecological clinics, key barriers or facilitators to PrEP implementation, potential strategies to address the identified barriers, and any emerging topic areas for subsequent exploration. In addition, existing PrEP coverage services and programs for uninsured Black cisgender women were discussed with medical service providers, case managers, and social workers. After each interview, interviewers documented field notes, including emerging topic areas for subsequent exploration. The qualitative data were analyzed by an expert qualitative researcher using the NVivo (Lumivero) qualitative data management software. First, a preliminary codebook was developed, which included inductive codes, that emerged from the data, and pattern codes, that connected concepts to one another. The lead qualitative analyst along with a team of 2 researchers applied these codes to a subset of interview transcripts and adjusted the code definitions until an adequate interrater reliability was achieved. The finalized codebook was then used to analyze the remaining transcripts, noting major themes. Finally, data matrices were created to visually represent associations between key concepts and patterns in the data.

In addition to interviews, a cross-sectional study was conducted in collaboration with the Alabama Section of the American College of Obstetricians and Gynecologists and the university's Center for Women's Reproductive Health in the Department of Obstetrics and Gynecology to understand barriers to future state-wide implementation that needed to be measured during this pilot study. Surveys were conducted with English-speaking, currently practicing gynecologists or advanced practitioners at gynecological clinics (n=39), to evaluate structural barriers to PrEP as well as any potential provider-level barriers. The surveys documented information on sociodemographic, HIV, and PrEP knowledge [34,35], HIV- and PrEP-related stigma [36,37], and questions ascertaining current routine testing and screening practices. The data from the surveys reported findings on willingness to prescribe PrEP by the independent variables (sociodemographics: race and ethnicity, clinic name, gender, years of practice, clinic resources, characteristics of populations served; knowledge: PrEP and HIV; stigma: PrEP and HIV; and practice: sexual history, sexual transmitted infections testing, and sexual transmitted infections treatment) as well as willingness to prescribe PrEP (primary outcome) and the capability of the clinical-setting for providing PrEP services (secondary outcome).

To explore the desired PrEP educational materials and communication strategies from gynecologic care teams, in-depth interviews, and focus groups were conducted with Black cisgender women. The inclusion criteria for the in-depth interviews and focus groups were the same and included (1) self-reported HIV-negative status, (2) being Black cisgender women, (3) ability to speak in English, and (4) age of 18 to <54 years (the choice of age range is based on the current HIV epidemiology reporting highest HIV incidence among cisgender women aged <54 years). An informed consent was signed by eligible Black cisgender women before the interview and focus group participation. The semistructured interviews covered topics such as sexual health, education needed to increase awareness and knowledge, stigma, and communication with the care team. The qualitative data were analyzed in a similar manner as described above by the expert qualitative data team.

To develop and refine a multicomponent implementation strategy (PrEP4Her) that aimed to integrate PrEP in gynecology clinics, an intervention mapping technique was used [38]. First, key barriers to PrEP implementation among Black cisgender women and providers were reviewed from the data collected with the PrEP4Her community advisory board (CABs, with the full description provided below). Next, using existing knowledge of components identified from studies that implemented PrEP at family planning clinics in the South, an initial list of components was created. Although family planning clinics may have differences from our gynecological setting in terms of the type of care providers and resources, they share a mission for providing reproductive and sexual health services, which may result in overlap with strategies needed for our research population. Using the knowledge gained through the reported findings, the team modified their list of components for PrEP4Her in a way that was more suited toward our gynecological clinics. Table 1 and Textbox 1 outline the preliminary name, definition, and operationalization of components based on current feedback from the PrEP4Her CAB, established by Proctor et al [39-41]. The team then mapped the implementation strategy and linked it to the desired implementation outcomes. This was followed by developing a content-specific implementation strategy. After implementation strategy materials were refined, appropriate operational steps needed to integrate PrEP into the clinical site were reviewed. JS, who has expertise in implementation science and has previously worked with family planning clinics in Southern settings to improve HIV prevention among Black cisgender women, also helped with PrEP4Her implementation.

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Table 1. Specification of components of the implementation strategy ("PrEP4Her").

Implementation strategy	Number 1	Number 2	Number 3	Number 4	Number 5	Number 6
Actor	Medical assistant or care provider	Study staff or PrEP[a] expert	PrEP expert	PrEP expert and information technician	PrEP expert and graphic designer	PrEP expert
Action	Charts evidence-based sexual history questionnaire in the medical record	Provides 1.5-hour training on HIV, risk, and PrEP indications and care	Creates easily accessible pocket cards with indications for PrEP	Creates templates in electronic medical records for PrEP visits and order sets	Develops informational content to include in educational materials tailored to Black cisgender women	Develops 30-minute training tutorial on how to communicate with patients about sexual health and PrEP, tailored to Black cisgender women
Target	Patient	Providers or staff	Provider	Provider	Patient	Patient
Temporality	Medical assistant (before every patient encounter with a provider) or provider (beginning of every visit)	1 month before PrEP4Her being implemented at our pilot site	Continuously carried by providers and displayed in shared workspaces	1 month prior to PrEP4Her being implemented with instructions on how to access placed in shared workspaces and sent through email communications	Placed in waiting areas and private examination rooms, accessible during every visit and replenished by study staff members	1 month before PrEP4Her being implemented and presentation accessible in the shared workspace as well as emailed to all providers
Dose	5-minute screener at every visit	1.5-hour training occurring once before 6-month pilot	As needed by providers during clinical care	As needed by providers during charting	Available during the entire 6-month pilot for every clinic	Once before 6-month pilot and then available as needed

[a]PrEP: pre-exposure prophylaxis.

Textbox 1. Pre-exposure prophylaxis 4Her components and outcomes.

- Named pre-exposure prophylaxis 4Her components
- Universal sexual health screening for gynecological patients
- Synchronous training of gynecological care team on HIV, pre-exposure prophylaxis indication, pre-exposure prophylaxis care (for both daily and long-acting injectable regimens), and stigma
- Pre-exposure prophylaxis indication job aids
- Electronic medical record documentation aids, including pre-templated notes and order sets
- Educational materials for Black cisgender women on HIV and pre-exposure prophylaxis
- Asynchronous training on effective communication strategies with patients about sexual health and pre-exposure prophylaxis
- Implementation outcomes affected
- Figure 1. for detailed description of how each implementation strategy maps to implementation outcomes. In short, we will be evaluating the following proximal implementation outcomes: reach, adoption, fidelity, acceptability, and preliminary effectiveness. Distal outcomes will not be evaluated in this study.
- Justification
- Implementation strategy components selected for this study have been selected based on observed, researched, or hypothesized barriers based on a review of the literature. These components may be subject to change based on findings in Aim 1 and feedback from our community advisory board.

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Figure 1. Pre-exposure prophylaxis implementation science research logic model. CAB: Community Advisory Board; GYN: gynecology; PrEP: pre-exposure prophylaxis.

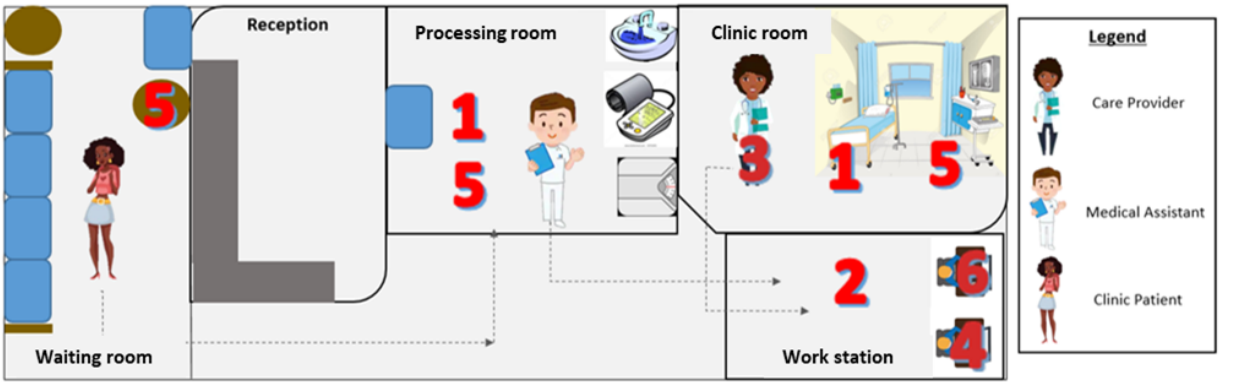

PrEP4Her Components		
1. Universal Sexual History – Brief, gender-neutral sexual history screening assessment [42].	**2. Job Aids** – 2-sided pocket cards for white coats/scrubs that will include CDC guidance summary criteria for PrEP among cis-gender women and 5Ps [43,44].	**3. Educational Materials** – Pamphlets, tailored for Black cis-gender women that contain information about HIV and PrEP [45].
4. Synchronous HIV and PrEP Training – ~ 1.5-hour PrEP informational training (adapted from Sales et al. in family planning clinics) made available on UAB CFAR website.	**5. EMR Documentation/Order Aids** – Premade order sets within UABs electronic medical record for initial and 3-month PrEP visits as well as a PrEP note template.	**6. Asynchronous Training on Communication Strategies** – ~ 15 minute training on communicating empowering, "gain-framing" messaging, made available on CFAR website [46].

Conceptual Framework

This multiphase study will be evaluated using the RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) conceptual framework and will link our multicomponent implementation strategy to proximal implementation outcomes. Figure 1 depicts the research logic model for the implementation of the PrEP4Her study. The PrEP4Her components box shows the implementation strategies (A to F): A: carrying out the universal sexual health screening for gynecological patients in the medical record; B: providing training on HIV, PrEP indication, PrEP care, and stigma for the gynecological providers; C: creating job aids such as pockets cards to easily identify those with a PrEP indication; D: creating aids for electronic medical record documentation such as creating templates for PrEP-related visits and order sets; E: developing educational material tailored toward Black cisgender women; and F: developing training tutorials on communication methods with patients about sexual health and PrEP, tailored toward Black cisgender women. Moreover, the change of mechanisms box shows how the strategies in the PrEP4Her components box are anticipated to impact the implementation outcomes (the superscripts indicate the implementation strategies that are expected to cause the change). Finally, the proximal implementation outcomes box outlines the expected outcomes that will be assessed as per the RE-AIM framework; the superscripts again indicate the PrEP4Her components that will impact each of the outcomes. The project is expected to improve the conditions deemed as potential barriers to PrEP usage among Black cisgender women, ultimately achieving the desired outcomes of increased PrEP uptake among Black cisgender women. Our study describes the planning and piloting stages of the implementation research logic model, evaluated by the RE-AIM framework, in which we will work with key informants and Black cisgender women to assess the reach, adoption, and preliminary effectiveness of integrating PrEP services within a gynecological clinic in Birmingham, Alabama, with the ultimate goal of increasing uptake of PrEP.

The Role of CABs

Two CABs, one for Black cisgender women (N=5) and one for gynecology practitioners (N=7), have worked and will continue to work with the study researchers. The CABs are led by a graduate-level researcher, who is also a part of this project. The CABs previously provided help with the interpretation of the qualitative findings and in selecting and refining components of the implementation strategy (PrEP4Her). Currently, the CABs meet monthly and advise on how to disseminate study results. At least 10 meetings were or will be held during the study, with a shared decision-making structure. Detailed notes will be documented to evaluate the meeting processes.

Piloting PrEP4Her to Deliver PrEP for Black Cisgender Women Attending Routine Gynecologic Care Visits

PrEP4Her is a multicomponent implementation strategy, which was evaluated through a 1-arm pilot at a university-affiliated gynecological clinic. We chose a 1-arm trial, as PrEP was not routinely offered at gynecological clinics in Alabama and there were only 3 Black cisgender women on PrEP at the university-affiliated PrEP clinic at the study start, which meant a comparison between other gynecological clinics or between our PrEP clinics would have had limited meaning. Upon completion of PrEP4Her development, gynecological staff members, practice managers, and clinicians received training as well as implementing job and documentation aids within the clinic. In addition, educational materials were placed in all areas where patients are seen within the clinic. Figure 2 outlines the

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workflow for PrEP4Her along with the detailed description of each component. Implementation outcomes for PrEP4Her were monitored over a 6-month time frame (Jan-Aug 2024). Of the RE-AIM components, only reach, effectiveness, and adoption will be evaluated as a part of this study. In addition to the 3 components of RE-AIM, we will also evaluate the acceptability, feasibility, and fidelity of the trial.

Figure 2. Pre-exposure prophylaxis 4Her components [42-46]. Image created by LE. CDC: Centers for Disease Control and Prevention; CFAR: Center for AIDS Research; PrEP: pre-exposure prophylaxis; UAB: University of Alabama at Birmingham.

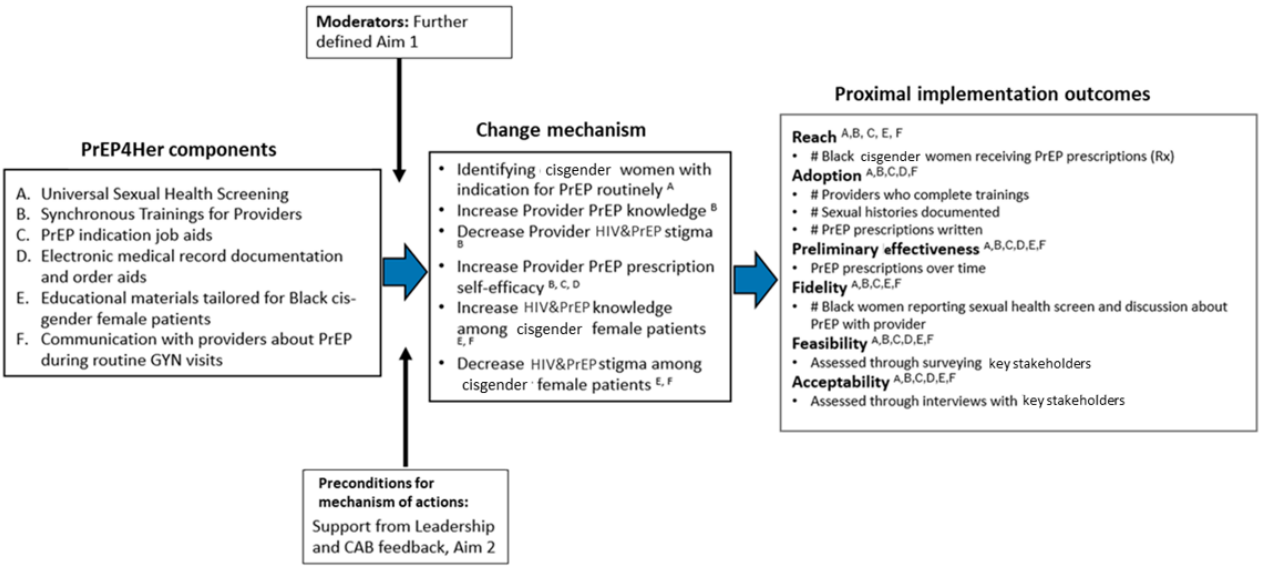

Reach Outcome

Reach in RE-AIM captures the ability to engage the target population in the intervention. In PrEP4Her, this will correspond to the absolute number of Black cisgender women who receive a PrEP prescription. In addition, the proportion of Black cisgender women prescribed PrEP among those who had a PrEP indication, will also be evaluated. PrEP indication will be based on the sexual risk screener (component 1 in Figure 2) documented in the chart during patient visits. For this study, PrEP indication will be defined based on the Centers for Disease Control's guidance summary criteria. According to this guidance, cisgender women not living with HIV meet at least one of the following criteria are considered to have a PrEP indication: (1) HIV-positive sex partner not virally suppressed, (2) bacterial STI in the past 6 months (ie, gonorrhea or syphilis), (3) more than one sex partner, (4) inconsistent condom use, (5) sex for exchange of goods, or (6) being in a high-prevalence network [44]. PrEP prescription data will be obtained from the university's electronic medical records visit data during the pilot period. Although measuring the number of PrEP discussions with Black cisgender women by electronic medical record audit was also considered an important aspect to examine reach, it was deemed to add little value due to the anticipated inconsistencies in documentation by providers in reporting PrEP discussion in their clinic notes. However, we have incorporated this element in our surveys with Black cisgender women, evaluating their experiences with providers in receiving PrEP health counseling.

Effectiveness Outcome

Effectiveness in RE-AIM evaluates the effect of the intervention on the primary outcome as well as effect modification. Effectiveness of PrEP4Her will be determined by the increase in PrEP prescriptions over time. In addition, patient factors associated with PrEP prescription will be evaluated [47]. PrEP prescription data from the electronic medical records will be extracted at baseline, at 3 months, and at 6 months of PrEP4Her implementation, to evaluate effectiveness. Moreover, information on patient demographics (ie, age, race, ethnicity, and insurance status) will also be obtained. Using this data, frequencies for PrEP prescription will be reported overall and for each independent variable at baseline, 3 months, and 6 months.

Adoption Outcome

Adoption in the RE-AIM determines the ability of the setting's staff members to adopt the intervention. This will be determined by measuring the proportion of key informants within the pilot site who were willing to initiate the PrEP4Her implementation strategy. This will be assessed by evaluating the training and sexual history documentation.

Training

A website will be created as a part of this study, to aid in easy access of training materials for providers and staff members. During initial training, the number of providers and staff members who attend the meetings will be documented. In addition, viewing training on the website will be captured through collecting para data (tracking clicks).

Acceptability Outcome

Acceptability is defined as the extent to which key informants felt PrEP4Her was acceptable (ie, providers delivering the intervention and Black cisgender women receiving the intervention). This will be measured by conducting key-informant interviews. The sample will include 15-20 participants, with at least 10 providers, and approximately 10-15

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Black cisgender women seen during the 6-month pilot period. Recruitment of providers will be carried out directly from the pilot study, whereas recruitment of Black cisgender women will be done through flyers and direct referrals from clinical staff members. Interview guide questions will be grounded in a theoretical framework of acceptability by Sekhon et al [48]. Interviews will be conducted virtually to allow for flexibility, using a secure system. Interviews will be digitally audio recorded, professionally transcribed, and deidentified. A preliminary codebook will be developed consisting of a priori deductive codes (based on the theoretical framework), inductive codes (emerging from the data), and pattern codes (connecting concepts to one another). The analysis of these data will be carried out in a similar manner as described above by our expert qualitative team.

Feasibility

Feasibility of the intervention will determine if PrEP4Her is appropriate for a larger, full-scale implementation trial. This information will be captured using the validated scale, Feasibility of Intervention Measure [49], through surveys conducted before interviews among key informants. The survey will include straightforward items such as "[PrEP4Her] was appealing to me," "[PrEP4Her] seemed suitable," and "[PrEP4Her] seemed easy to implement," which respondents will rate on a 5-point Likert scale. Descriptive statistics will be calculated to determine feasibility.

Fidelity

Fidelity to the intervention protocol will be assessed as the degree to which the PrEP4Her implementation strategy was implemented as designed [50]. To measure fidelity, all patients seen during the 6-month pilot period will be given a flyer by the staff upon clinic checkout with information to take a brief 5-minute electronic survey. Recruitment will end once 300 surveys have been completed. While this intervention is tailored to Black cisgender women in terms of developed educational materials and provider communication, implementation strategy components are universal to all patients and, therefore, targeted sampling of only Black cisgender women will not be conducted. The brief electronic survey will include the following questions: (1) Did your provider (or other clinical staff members) take a history asking about your sexual activities and health? (2) Did you see educational materials during your visit about HIV prevention and a prevention method called PrEP (3) Did you speak with a provider about PrEP? (4) For those who spoke with a provider about PrEP, would you please describe the conversation and how you felt about communicating with your provider about this prevention strategy? As the survey contains both close-ended and open-ended questions, data will be analyzed both, quantitatively (descriptive statistics) and qualitatively (inductive and pattern coding).

The findings from the pilot will provide the necessary information to refine PrEP4Her for broader dissemination and future multisite implementation studies.

Ethical Considerations

Human Subject Ethics Review Approvals

The following study was approved by the University of Alabama at Birmingham's institutional review board (IRB#300008345) on December 2, 2022.

Informed Consent

An informed consent was collected and documented from all gynecological interview participants. The quantitative data used for this study was covered under the study's institutional review board and was secondary in nature that data was abstracted from available deidentified electronic medical records.

Privacy and Confidentiality

All data were deidentified before being analyzed.

Compensation Details

All CAB members received a US $50 stipend per meeting. Each interviewee and focus group participant was compensated with US $50. Patients who will complete the electronic survey determining Fidelity will receive a compensation of US $20 after completion.

Results

Figure 3 outlines the PrEP4Her study timeline. The in-depth interviews with the gynecological care team were conducted between August 9, 2022, to April 19, 2023. A total of 10 in-depth interviews were conducted (40% were attending or training physicians). In addition, the cross-sectional study used data collected from surveys with gynecologists from July 15, 2022, to February 1, 2024 (n=39; 80% female). Moreover, the in-depth interviews and focus groups with black cisgender women (n=20) were conducted between Aug 9, 2022, to Apr 19, 2023. The qualitative findings from in-depth interviews with the gynecological care team (physicians, nurses, and medical assistants) and in-depth interviews and focus groups with women patients (64% black) highlighted a gap in care delivery for women (manuscript in the process of publication), suggesting additional training of providers may be beneficial. This was added as one of the strategies to improve PrEP uptake under the PrEP4Her implementation.

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Figure 3. PrEP4Her study timeline BCGW: Black cisgender women; IRB: institutional review board; GYNs: gynecologists; PrEP: pre-exposure prophylaxis.

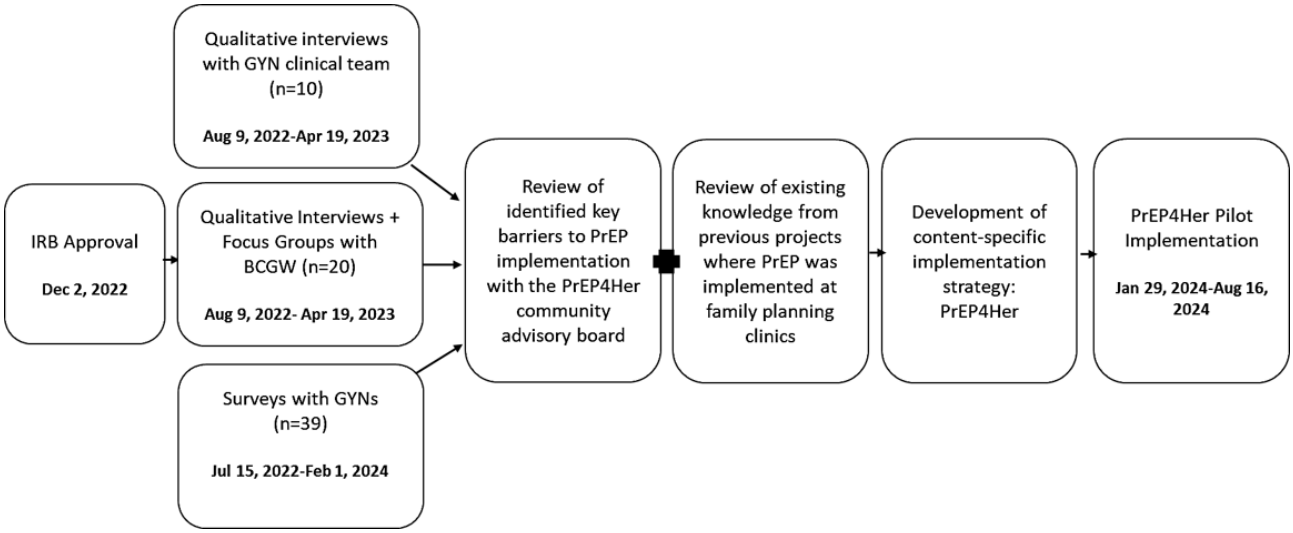

The qualitative and quantitative data were integrated through joint displays, bridging results using visual displays to connect major themes [51]. The combined findings provided an in-depth and granular understanding of key factors that were necessary to address in the development and refinement of PrEP4Her, as well as in the development of implementation strategies to support the integration of PrEP services into routine gynecological care. The PrEP4Her pilot was implemented from January 29, 2024, to August 16, 2024. The data gathered during the program are being used toward assessing the program's efficacy by measuring PrEP4Her's reach, effectiveness, adoption, acceptability, feasibility, and fidelity. The findings obtained would help guide the implementation of PrEP4Her at a larger scale.

Discussion

Anticipated Findings

The quantitative and qualitative data gathered to inform the development of PrEP4Her indicated a need to integrate PrEP services into an already existing and stretched gynecology clinic workflow by optimizing medical assistants and apps to aid in sexual history screening and provision of PrEP services. In addition, there was a gap in knowledge around PrEP as an HIV prevention option for cisgender women and the desire among Black cisgender women to have sexual health and PrEP services integrated into routine gynecology care. This information helped guide the PrEP4Her program implementation in the most effective manner.

PrEP is a highly effective method to decrease HIV acquisition among cisgender women. However, its impact to improve HIV outcomes among women has been hindered due to poor understanding of how to effectively identify strategies to improve uptake among cisgender women. Previous studies conducted at family planning clinics, aiming to improve PrEP uptake, found that although many cisgender women were willing to start PrEP, only a few obtained a prescription for PrEP, highlighting a gap between PrEP knowledge delivery and PrEP uptake. While cisgender women are disproportionately impacted by the HIV epidemic, Black cisgender women living in the Southern United States face heightened challenges such as decreased access to health care services and structural racism, which leads to medical mistrust and greater bias when engaging with providers [52]. Keeping these inequities in mind, the study aims to improve PrEP prescription in this population. We designed a novel intervention, PrEP4Her, which will be focused on increasing PrEP uptake as an effective HIV prevention tool among Black cisgender women by improving access and expanding provider options. Given the pilot site's Southern US location and the patient population served, preliminary results from this pilot will provide substantial guidance on the successful refinement and implementation of PrEP4Her in similar clinical-care settings across the South. In addition, sampling of gynecological providers across the Southeast United States allowed for greater generalizability of our implementation strategy to other Southern US states that have similar contexts (eg, access to medical resources, access to transportation, proximity to clinics, socioeconomic status, etc.).

PrEP4Her intervention is a novel approach hypothesized to significantly improve PrEP uptake among Black cisgender women. Completion of this study will result in the development of a culturally tailored strategy to improve uptake of PrEP among Black cisgender women. If PrEP4Her shows feasibility, acceptability, and preliminary efficacy in enhancing PrEP uptake for Black cisgender women, a subsequent R01 application will be prepared to conduct a fully powered implementation trial across multiple gynecology care sites across the South. Even in the absence of preliminary efficacy of the pilot, the knowledge gained around determinants and components to include in the PrEP4Her implementation strategy for integrating PrEP services into gynecological settings will provide novel insights to inform future HIV prevention research among this highly impacted group. The findings obtained from this study will be submitted to peer-reviewed journals for publication and presented at local and national conference meetings. Moreover, to disseminate these findings to the nonacademic community, we are currently in discussion with our patient CAB on the most appropriate method to do so. In addition, we are currently working with our institution's communication team to ensure that the patient

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community is made aware of PrEP being offered at the gynecology continuity clinic.

Despite our efforts, our study has a few limitations. It is often challenging to engage clinical care teams to conduct interventions due to workflow demands and time constraints. This may impact the overall efficacy of PrEP4Her due to low adoption and lack of fidelity to PrEP4Her components. To overcome this barrier, investigators will work with leadership in identifying "champions" within the clinic setting to encourage PrEP4Her implementation. Inclusion of a physician practicing in the gynecology continuity clinic as part of our investigative team embeds a committed champion within our pilot site. In addition, recruitment of Black cisgender women will be carried out from our clinical site, to take part in both interviews and quantitative surveys throughout this proposal and this may pose a challenge. To overcome this, we will use well-established research advertising through the university and will also leverage provider referral and referral from our research staff to meet recruitment goals. There is a potential for selection bias, as Black cisgender women who are interested in participating in the study may experience less HIV and PrEP stigma than the general population. To overcome this, efforts will be placed to recruit participants via pamphlets at our clinical site with nonstigmatizing, health-promoting messaging to engage a representative sample. Finally, due to time and budgetary constraints, quantitative evaluation of PrEP adherence with drug level testing via blood or hair for those prescribed, will not be conducted. While this is not currently a primary end point for this study, we will measure PrEP adherence more objectively in a subsequent efficacy trial.

Conclusion

PrEP4Her intervention, by integrating PrEP services into existing gynecology clinic workflow, is aimed at improving PrEP uptake among Black cisgender women, a population disproportionately impacted by the HIV epidemic. Completion of the intervention will be followed by a multisite type III implementation trial for PrEP service delivery at gynecology clinics across the Southern United States.

Acknowledgments

Jessica Sales provided consultation in the development of the intervention.

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We attest that generative artificial intelligence was not used for the generation of any portion of this manuscript.

Data Availability

The datasets generated during this study or those that will be generated or analyzed in the future will be available from the corresponding author on reasonable request.

Authors' Contributions

LE conceptualized the study and acquired funding for this project. LTM, AW, MCK, DP, HMG, and MJM advised on the project investigation and methodology. BJ performed activities associated with administration. MS wrote the manuscript. All authors provided feedback on the manuscript.

Conflicts of Interest

LE serves as an investigator on a Merck pharmaceuticals research grant.

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Abbreviations

CAB: Community Advisory Board
PrEP: pre-exposure prophylaxis
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance

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Protocol

Measuring Mental Health in 2 Brazilian University Centers: Protocol for a Cohort Survey

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Abstract

Background: Global concern for the mental well-being of university students is on the rise. Recent studies estimate that around 30% of students experience mental health disorders, and nearly 80% of these individuals do not receive adequate treatment. Brazil, home to around eight million university students, lacks sufficient research addressing their mental health. To address this gap, we aim to conduct a longitudinal mental health survey at 2 Brazilian universities.

Objective: This paper outlines the research protocol for a web-based mental health survey designed to assess the well-being of Brazilian university students.

Methods: The survey targets undergraduate students (N=8028) from 2 institutions: UniFAJ (Centro Universitário de Jaguariúna) and UniMAX (Centro Universitário Max Planck). Students will be invited to respond to self-reported questionnaires, including theSMILE-U (lifestyle and quality of life), the *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) self-rated level 1 cross-cutting symptom measure, and a brief version of the Adult Self-Report Scale for attention-deficit/hyperactivity disorder. Students who exceed thresholds for conditions such as depression, anxiety, and attention-deficit/hyperactivity disorder will receive additional diagnostic instruments. The survey will be conducted annually, tracking individual and group trajectories and enrolling new cohorts each year. Data will be analyzed using cross-sectional and longitudinal methods, focusing on descriptive, associative, and trajectory analyses.

Results: The first wave of data collection began in February 2024 and is expected to conclude in December 2024. As of October 2024, a total of 2034 of 7455 (27.2 in 100) eligible students had completed the questionnaire. Cross-sectional statistical analysis is planned to commence immediately after data collection and is expected to be completed by June 2025.

Conclusions: This survey uses a scalable, cost-effective design to evaluate mental health conditions among Brazilian university students. The longitudinal framework facilitates the monitoring of mental health trends, supports the development of targeted interventions, and informs policy initiatives in higher education.

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KEYWORDS
study design; university students; mental health screening; longitudinal survey; college students

Introduction

The mental health of university students is a widely recognized global concern. The transition to university life marks a crucial developmental phase characterized by individuation, the establishment of new social connections, and increased autonomy and responsibility [1]. This period aligns with continued, rapid brain development at a time when university students are exposed to multiple risk factors known to affect mental health, including psychosocial stressors, recreational drug use, alcohol binging, and disruptions in sleep patterns [2]. Mental health disorders typically present before or during young adulthood, often going unrecognized for years, resulting in significant delays in receiving treatment. Failing to adequately address mental health issues in a timely fashion can lead to the progression of more complex outcomes, such as school dropout, addiction, and self-harm. Indeed, the international prevalence estimates of mental health disorders reveal higher rates among college students compared to the general population. For example, a multicenter study involving 13,984 students from 8 countries, led by the World Health Organization (WHO), demonstrated that one-third met the clinical criteria for a psychiatric disorder in the previous year [3]. The most frequently reported were depressive disorders (18.5%) and anxiety disorders (16.7%-18.6%), followed by alcohol (6.8%) and other substance use disorders (3%). Moreover, approximately 22.6% of university students reported experiencing suicidal thoughts. Tragically, suicide stands as the second leading cause of death within this population [4].

The presence of psychiatric disorders is linked to numerous detrimental consequences both in the short and long term. In the short term, individuals may experience a decline in their quality of life, poorer academic performance, increased absenteeism, and a higher likelihood of course dropout [5-7]. In the long term, individuals endure lower quality of life, higher unemployment rates, and socioeconomic impairment [8,9].

Though the alarming data presented above were derived from studies conducted in countries with diverse income levels, to date, there is a disproportionately limited body of evidence addressing the mental health issues of young adults attending universities in low- and middle-income countries. The few studies that have been conducted in Brazil have tended to focus on medical students, also unveiling concerns about rates of mental distress in this population [10] with approximately 37% of them undergoing psychiatric treatment. In a study by Campos et al [11], the most prevalent diagnoses were depression (39.1%) and anxiety disorders or phobias (33.2%) and 4.5% declare previous suicide attempts. Severe mental health disorders such as psychotic disorders (3.7%) and bipolar disorder (1.9%) were less common [11].

In Brazil, there are approximately eight million students enrolled in 2714 higher education institutions [12]. Extrapolating from international prevalence estimates, over two million Brazilian university students may be struggling with mental health issues.

UniFAJ (Centro Universitário de Jaguariúna) and UniMAX (Centro Universitário Max Planck) are private university centers located in the medium-sized cities of Jaguariúna and Indaiatuba in the southeast of Brazil. Together, they serve approximately 8000 students enrolled in undergraduate programs spanning technical fields (eg, administration, accounting, architecture, law, or engineering) and health sciences (eg, medicine, nursing, psychology, biomedicine, or veterinary medicine). These institutions are representative of the broader Brazilian university population, as more than 75% of Brazilian students are enrolled in private universities.

To address the gaps in national and international literature, we propose to measure the mental health of all undergraduate students of UniFAJ and UniMAX. The survey will assess the prevalence of psychopathological symptoms and identify associated factors. The survey will also address another largely unexplored facet of mental health issues, namely the longitudinal course of mental health and quality of life. To achieve these goals, we designed a web-based mental health survey suitable for Brazilian students. This paper aims to describe the protocol and methods for conducting a web-based mental health cohort study in 2 private Brazilian universities. We hypothesize that, consistent with international studies, we will find high rates of common mental disorders, such as anxiety and depression. Furthermore, we expect to identify distinct patterns of mental health disorders unique to the low- and middle-income context of Brazil. By following students over time, we hypothesize that mental health disorders will correlate with poorer academic performance and quality of life, consistent with findings in the international literature.

Methods

Overall Design

This study will use validated self-report questionnaires delivered through an electronic web-based survey. The protocol will be repeated annually starting in 2024, allowing for the evaluation of mental health trajectories over time and the inclusion of new cohorts of incoming students to assess potential trends specific to these groups. This study of the university population is an arm of a large mental health project carried out by the National CISM (Center for Research and Innovation in Mental Health) [13]. CISM aims to study and expand, over the next 10 years, knowledge about mental health conditions in the State of São Paulo, the biggest one in Brazil.

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Participants and Recruitment

All undergraduate students enrolled at UniFAJ and UniMAX will be invited to participate annually. Invitations will be sent via email, providing a brief explanation of this study's objectives and encouraging participation through the electronic survey link.

We have devised several strategies aimed at maximizing participation. First, we will conduct wide media campaigns in the university to promote awareness concerning mental health and discuss the importance of this study. Second, professors of all disciplines will be encouraged to remind students to engage in the survey. Third, nonresponders and survey noncompleters will receive at least 3 invitation reminders via email, followed by 3 reminders via text message (WhatsApp; Meta Platforms). Importantly, students will be informed that the time spent on the survey will count as an equivalent complementary academic activity. All these steps will be executed anonymously to ensure students' privacy.

Upon receiving the invitation, students are required to read and sign an informed consent form (ICF). The consent form will clearly state that the participation is voluntary and that declining will not affect their academic standing or relationship with the university. Additionally, students who opt out will not receive further invitations.

The exclusion criteria are being younger than 18 years of age and limitations in accessing or responding to the survey (ie, no access to electronic devices or internet connection or being illiterate). These exclusions are expected to be negligible within this study population.

Instruments

We selected empirically validated psychometric self-report questionnaires, all of which have been translated and validated for Brazilian Portuguese and can be administered electronically. A key challenge in designing this survey was balancing the need for a comprehensive assessment of the targeted phenotypes with the potential impact of a lengthy survey on participant engagement. To address this, we adopted a 2-step strategy aimed at minimizing survey duration while maintaining comprehensiveness (Figure 1). In the first step, in addition to collecting sociodemographic and overall lifestyle or quality of life information in Short Inventory Lifestyle Evaluation [14], we will screen for an array of mental health conditions using the *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) cross-sectional adult symptoms scale level 1 [15] and a short version of the Adult Self Report Scale for attention-deficit/hyperactivity disorder [16] (Table 1). In the second step, participants scoring above predefined thresholds in any domain will be invited to complete domain-specific psychometric scales. These scales assess conditions such as depression, mania, generalized anxiety, sleeping disorders, borderline personality disorder, obsessive-compulsive disorder, attention-deficit/hyperactivity disorder, substance use (Multimedia Appendix 1). After completing the relevant scales, participants will have the option to answer a questionnaire on personality traits (the Big Five Inventory [17]). The total time required to complete the survey will vary depending on the domains assessed, ranging from approximately 20 to 40 minutes. This streamlined approach ensures a balance between thorough mental health assessment and participant engagement by limiting survey fatigue.

Figure 1. Initial data collection scheme: The figure illustrates the initial data collection scheme, and the scales applied according to the screening presented. ASSIST 2.0: Alcohol, Smoking and Substance Involvement Screening Test; ASRS-18: Adult Self Report Scale; BFI: Big Five Inventory; BPDS: Borderline Personality Disorder Scale; GAD-7: Generalized Anxiety Disorder Scale-7; HCL-32: Hypomania Checklist scale; OCI-R: Obsession and Compulsion Inventory; PHQ-9: Depression Patient Health Questionnaire-9; PSQI: Pittsburgh Sleep Questionnaire; QSD: Sociodemographic Questionnaire; SMILE-C: University Short Multidimensional Inventory Lifestyle Evaluation.

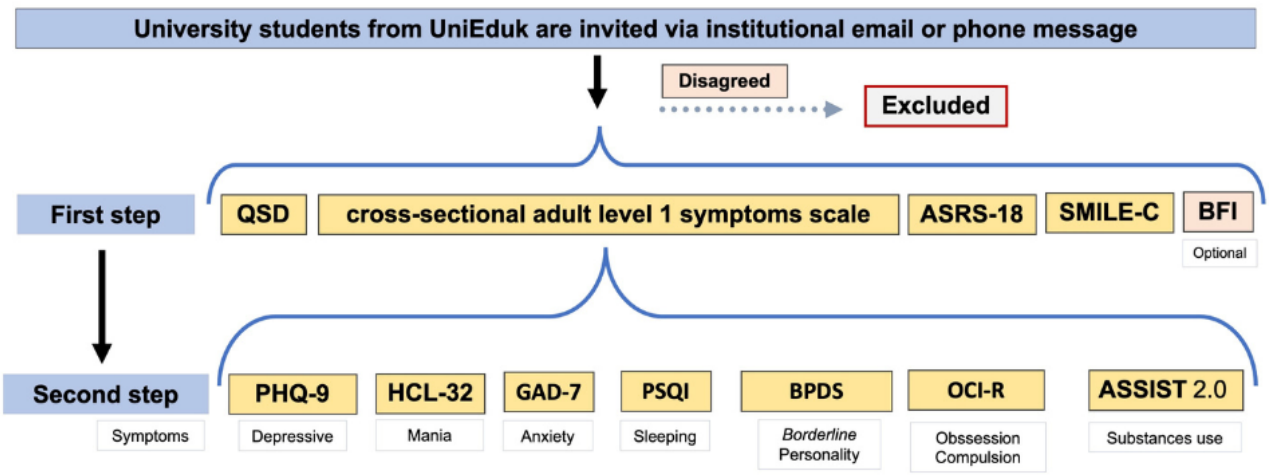

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Table 1. Instruments used in step 1.

Instruments	Description
Sociodemographic Questionnaire (QSD)	The questionnaire was developed specifically for this study, including age, sexual identity and orientation, income, academic course, professional and career expectations, religiosity, use of social networks, and medical, psychiatric, or psychotherapeutic history.
The University Short Multidimensional Inventory Lifestyle Evaluation (SMILE-C)	Multidimensional assessment of lifestyle in 7 domains (diet, substance use, physical activity, stress management, social relationship, sleep, and screen time), along with an overall lifestyle score. The instrument comprises 24 questions that evaluate the frequency of behaviors considered healthy, with a response scale ranging from 0 to 4, where a higher score corresponds to a healthier lifestyle.
Adult Self Report Scale (ASRS-18)	Assesses symptoms of attention-deficit/hyperactivity disorder (ADHD) in adults, over the past 6 months, via 18 items divided into 2 domains: A (inattention) and B (hyperactivity-impulsivity). Responses for domain A vary as follows: 0=never, 1=rarely, 2=sometimes, 3=often, and 4=very often. As a screening measure, all participants will complete only the short version of this scale, which consists of 4 items (4, 5, 6, and 9) from part A and 2 items (1 and 5) from part B (hyperactivity). Those who score above 4 points on the short version will receive the complete version. Individuals are considered to have a possible diagnosis if they present at least 6 symptoms in at least 1 of the domains, or in both.
Cross-sectional adult level 1 symptoms scale (CSA) level 1 symptoms scale	Comprises 23 screening items that assess the frequency and intensity of symptoms across 13 domains of relevant symptomatology to frequent or severe psychiatric diagnoses. These domains include: sadness, irritability, mania, anxiety, somatic symptoms, suicidal ideation, psychosis, sleep disturbance, memory, repetitive thoughts and behaviors, dissociation, personality functioning, and substance use. Each item is rated on a 5-point scale (0=not at all; 1=very mild or rarely; 2=mild or several days; 3=moderate or more than half the days, and 4=severe or nearly every day).
Big Five Inventory (BFI)	The “Big Five” is an established model that analyzes 5 dimensions of personality: extroversion (tendency toward assertiveness and sociability), agreeableness (tendency toward reliability and altruism), conscientiousness (tendency to be careful and diligent), neuroticism (tendency toward negative emotions and sadness), and openness (tendency toward creativity and imagination). Likert-type scale with 44 items, where responses range from 1 (totally disagree), 2 (disagree a little), 3 (neither agree nor disagree), 4 (agree a little), to 5 (totally agree).

Data Collection Instruments

Data collection will be performed using REDCap (Research Electronic Data Capture; Vanderbilt University), a secure digital platform designed for data management and research studies. REDCap facilitates the deployment of standardized digital instruments while ensuring participant anonymity [18]. The platform provides a convenient “survey queue” for participants to access the survey questionnaires and a “to-do list” so they can keep track of their progress. This allows for the tracking of initial participation, completeness status, and longitudinal data collection for all participants. The REDCap feature best suited to address automation of the communication process and is, furthermore, better at data collection is the automated invitations. The participants receive an individual link, and we can choose how many reminders will be sent as well as their periodization.

Survey Distribution Tools

We will upload student data straight from a file containing the emails of all enrolled students (provided by the university’s administration sector), in order to generate a unique individual ID link for each student. This will allow us to track the participants’ survey engagement or completion rate.

Reports and Alerts

The reports and alerts feature in REDCap will be used to monitor specific events and outcomes, particularly for suicide risk management (Figure 2). Suicide risk monitoring will rely on responses to the cross-sectional adult level 1 symptoms and PHQ-9 (Patient Health Questionnaire-9 depression) scales. The platform is programmed to generate immediate email alerts to this study’s team if participants affirmatively respond to either of 2 questions directly addressing suicidal ideation and suicide plans. This study’s team then immediately notifies a relevant health care team associated with our research group. Upon receiving this notification, the health care team will contact the participant to offer them appropriate psychiatric care. If the participant does not answer the first contact, the health care team will call again every day for 3 days. If the research participant accepts the offered care, they will be evaluated by psychiatry professionals and given necessary referrals. If they do not agree, this study’s team will register this nonagreement, and monitoring by the research team will end.

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Figure 2. Suicide risk monitoring: The figure illustrates the monitoring protocol for participants identified as high risk of suicide.

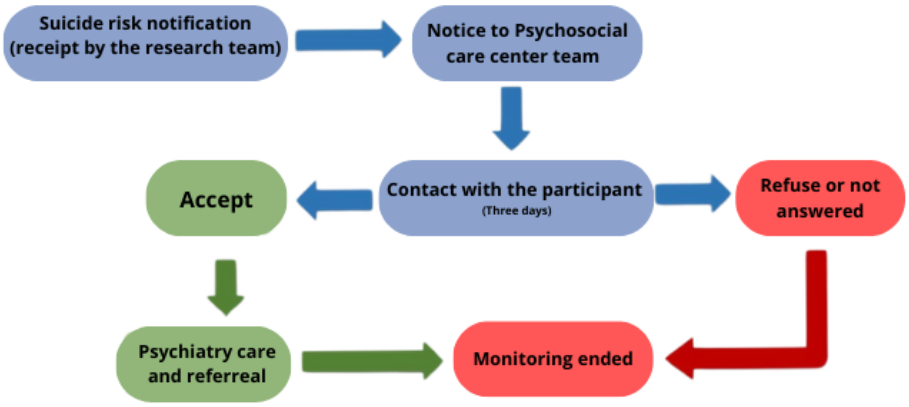

Statistical Analyses

Given the annual assessments and longitudinal tracking of students throughout their university journey, we will use statistical methods suitable for both cross-sectional and longitudinal analyses. To enhance the representativeness of the sample, poststratification weights will be applied based on demographic data (eg, sex or age major) of the entire target sample provided by the university. All tests will be performed with a significance level of P=.05.

Descriptive Analysis

We will perform descriptive analyses to characterize this study's population. Summary statistics such as means, SDs, and medians will be computed for continuous variables (eg, age and quality of life) and frequencies and proportions for categorical variables (eg, gender or sexual orientation). Psychometric scales will be categorized into binary outcomes (absence or presence) based on established cutoff values.

Simple Cross-Sectional Analyses

We will explore associations between sociodemographic characteristics, quality of life scores, personality traits, and the prevalence of psychopathological symptoms using parametric and nonparametric statistical tests (eg, chi-square tests for categorical variables, t tests [2-tailed], or Mann-Whitney U tests for continuous variables). For significant associations, odds ratios will be calculated to identify predictors of psychopathological symptoms. Linear or logistic regressions will be used to adjust for potential confounders, depending on the distribution of the outcome variable. Leveraging this study's design and large sample size, we will use data to infer potential changes in mental health indicators throughout the students' academic programs. This will involve comparing data from students at different stages of their academic journey (eg, first-year vs final-year students). To achieve this, generalized estimation equations will be used, with the independent variable year as a proxy for time. Models will control for confounding factors such as gender, age, and socioeconomic status.

Longitudinal Analyses or Cohort Analyses

By tracking students longitudinally throughout their university journey, we aim to identify variations in mental health outcomes and analyze the evolution of symptomatology over time. Generalized estimation equations will be used, including time as an independent variable to model these changes and examine patterns at both individual and group levels.

Ethical Considerations

This study adheres to the Code of Ethics of the World Medical Association (Declaration of Helsinki). This protocol was reviewed and approved by the Ethical Board Committee of the UniFAJ and UniMAX University Center (decision 6.153.870, 2023). This study follows the ethical principles outlined in Resolution 466/2012 of the National Health Council [19], which sets the guidelines and regulatory standards for research involving human beings in Brazil and complies with Law 14,874 which specifically governs human research ethics in the country. This study is registered in the Brazilian national system used to manage and oversee research involving human participants (Plataforma Brasil, under CAAE: 67251922.4.0000.0191), ensuring adherence to national regulations for research registration and monitoring.

Participation in this study is entirely voluntary. They will receive comprehensive information about the research objectives, methodology, and their rights. To ensure informed consent, this study uses a digital ICF via the REDCap e-consent platform. The ICF is presented in a clear and accessible format, explaining the purpose of the research and the voluntary nature of participation, and guarantees confidentiality and anonymity. Participants will be instructed to read the ICF and confirm their consent by responding to a specific question: "Have you understood the guidelines, and do you agree to participate freely, knowledgeably and spontaneously in this research?" If they agree, they are asked to enter their full name so that it can be attached to their acceptance to take part in this study. Additionally, the participant's electronic signature will be collected, and a copy of the ICF will be provided via email. The participant will then be directed to a link to the digital survey. If they do not agree, the participant will receive a thank you note and the contact will be closed.

Participation in this study will be voluntary, with participants' time and autonomy respected at all stages of the research. Participants may withdraw from this study at any time without any negative consequences or impact on their academic standing. This study involves completing a digital survey, ensuring a noninvasive and risk-free process. Study data will be deidentified to protect participants' privacy and for data

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protection risks. No monetary compensation will be provided to the participants.

Results

The first wave of data collection for this cohort began in February 2024 and is scheduled to conclude in December 2024. As of October 2024, a total of 2034 of 7455 (27.27%) eligible students had completed the questionnaire. Cross-sectional statistical analysis is planned to commence immediately after data collection and is expected to be completed by June 2025.

Discussion

Principal Findings

The psychological well-being of young adult college students is gaining significant attention, as it is one of the major determinants of their overall academic success, personal development, and prospects. A healthy lifestyle, access to mental health services, and the cultural relevance of mental health interventions are some of the themes that the university students consider relevant [20]. Meanwhile, the existing literature endures a dearth of evidence concerning the mental health of university students in low- and middle-income countries. We have presented the protocol of our cohort study, outlining the design of a web-based survey suited for Brazilian university students, aimed to improve our knowledge about the mental health of this population, mitigating an important literature gap.

In this way, we can address the hypotheses of this research. The prevalence of common mental disorders in the world is, as shown, high. A replication study for other universities in the country allows us to learn about the prevalence of these disorders and the risk factors in Brazil. The prior work of the WHO evaluated sociodemographic correlates of mental disorders among first-year university students. They also used web-based self-report questionnaires about *DSM-IV* (*Diagnostic and Statistical Manual of Mental Disorders* [Fourth Edition]) mental disorders: major depression, mania or hypomania, generalized anxiety disorder, panic disorder, alcohol use disorder, and substance use disorder. Their results show high rates, one-third of the students screened positive for 1 common mental disorder [3]. We had some similarities and differences with the study by Auerbach et al [3]. Our protocol is also a web-based self-report questionnaire that contains sociodemographic aspects and mental health scales. We access more sociodemographic aspects than the WHO study and, in the same way, we access more mental health disorders instead (Figure 1) of only common mental disorders. Finally, our research had been projected to follow these universities' students, identifying some risk factors and consequences of mental health disorders.

The studies conducted in Brazil are mostly cross-sectional and their focus is on medical students [10]. The study by Miguel et al [10] showed higher rates of common mental disorders when in comparison to the WHO study [3]. Our study protocol describes a proposal to systematically and longitudinally survey the mental health of a large population of university students in Brazil. Our plan was based on methodological decisions that balance quality, precision, scalability, cost, and the likelihood of participant engagement.

Among the challenges encountered during the design of this web-based mental health survey, we have highlighted the need to assess a large number of potential participants and assess most psychopathological symptoms while aiming to be concise to achieve a maximum response rate and increase generalizability. Although university students are the majority in the digital world, they usually do not seek support [21]; therefore, another challenge is to engage them in web-based mental health surveys, through the many incentives we have described, we have accomplished a response rate of 2034 of 7455 (27.27%), which is relatively high compared to other web-based surveys.

Ethical considerations addressed here are related to the importance of interaction with the local health care services to provide assistance if cases of psychiatric emergency (ie, risk of suicide) are detected, as well as ensuring data privacy. We have also strived for this longitudinal study proposal to be as cost-efficient as possible considering financial constraints.

Our proposed use of an internet portal improved participant engagement and data integration and reduced longitudinal data collection's time and expense [22,23]. Indeed, automated data capture minimizes the need for paid researchers to run participants and enter data, while also reducing data entry errors [24]; as our survey involves multiple questionnaires, the platform allows for easier and more engaging access for potential participants [25]. Our dissemination plan has internal importance for promoting and preventing mental disorders at UniFAJ and UniMAX universities. The results of the research can be shared with the students themselves and with the university coordinators, guaranteeing confidentiality. Another of our dissemination plans is to share this data and results with the media and with the governments.

Finally, we believe that this protocol could be useful for monitoring mental health cross-sectionally and longitudinally in thousands of universities across Brazil, either to assess their mental health in a cost-efficient manner or guiding interventions such as preventive mental health programs or even screening students with high risk of having mental disorder. This would allow a positive impact on the burden of mental health in university students and ultimately in our communities.

Limitations

There are disadvantages associated with digital research. For example, open-ended questions cannot be explored with immediate follow-up questions and participants are unable to seek clarification of ambiguous items [26]. To address this issue, in the present survey, participants can easily email the project team with any questions they may have.

Selection bias presents another challenge for digital research. Internet access is affected by myriad variables including income, geographical location, mental health status, and age [27,28]. We do not anticipate serious issues with internet accessibility. UniFAJ and UniMAX have free internet access for all students. In addition, there were 181.8 million internet users in Brazil at the beginning of 2023, which means it is 84.3% of the

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population [29]; and the southeast, where UniFAJ and UniMAX are, has an even greater user concentration. Our plan to remind participants via WhatsApp to finish their questions is sound, as WhatsApp is the most used social media by Brazilians, around 169 million [29]. Thus, though we cannot fully account for all these possibilities, the present strategy maximizes accessibility in a way that will mitigate these potential confounding issues and, consequently, increase the response rate.

After identifying participants, the present protocol contains strategies to maximize the probability that participants will continue to engage with and complete the survey. For example, one way to increase engagement is to provide participants with information about this study that (1) knows their interests, (2) helps them understand the importance of their participation in mental health research, and (3) increases their confidence about participating. To this end, the research team will hold meetings with UniFAJ and UniMAX course coordinators to transmit detailed study information so that it reaches the students. Furthermore, a 2-minute video will be sent to all participants. This video contains information about the research team, the reason for the research and its objectives, details about the questionnaires (application time, confidentiality, or freedom to decline), and the opportunity to ask questions via email. We intend to demonstrate the importance of participation in promoting mental health among the university population.

The security of collected data is ensured by the REDCap platform, a trusted and secure data collection and storage platform [30] used throughout the scientific community. The platform allows for the long-term reduction of research costs, the possibility of use on many devices, and rapid data entry, review, and analysis [31].

As noted in the Introduction section, there is a paucity of data that have been collected from low- and middle-income countries. Existing studies were carried out mainly with students from specific courses [32]. The data analysis will summarize the data collected and integrate information about the mental health of this population. It will allow us to better understand the mental health of the Brazilian university population This survey is a structured means for assessing this population's mental health given that it has been well established that preventive actions are feasible, cost-effective, and efficient in improving overall mental health [33] and this period of life represents a hub that critically impacts their responsibilities, mental health, values, and outcomes [34]. We believe that the results of this survey could in the future guide policy makers in the design and implementation of preventive programs destined specifically for this public group and ultimately have a positive impact on the mental health of our communities.

Conclusion

College and university students have high rates of mental health issues. We have developed and described a web-based mental health survey that will allow us to evaluate and detect these issues with low cost and reasonable response rate in a university in Brazil. These efforts will allow us, soon, to monitor and test the efficiency and impact of mental health preventive programs. The accurate and representative data about mental health disorders, their risk factors, and the quality of life of these universities' students can lead the path for new policies to ensure mental health and quality of life for these populations.

This model could be scaled up across other universities in Brazil to easily assess the mental health status of their students and have a significant impact on the mental health of our communities.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

All authors contributed to this paper. TDS contributed to the conceptualization, formal analysis, project administration, review and editing of the writing, and supervision. AGN carried out the formal analysis, writing of the original draft, and supervision. PF handled the conceptualization, investigation, data curation, review and editing of the writing, and supervision. VM worked on the writing of the original draft and supervision. GCAdA, CFPV, LCdO, LOdC, EMMK, and LAZG assisted in the writing of the original draft, software, and methodology. LDFC aided with the resources and visualization. VCCJ conducted the visualization, software, and methodology. EdCH was responsible for the validation and visualization. ECMF was involved in the funding acquisition, supervision, validation, and visualization. AC did the project administration, resources, funding acquisition, supervision, validation, and visualization.

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Conflicts of Interest

None declared. AC has served as a consultant for Knight Therapeutics and Libbs, but this work is not related to the topic of this manuscript.

Multimedia Appendix 1
Instruments to be used in step 2.
[DOCX File , 17 KB - resprot_v14i1e63636_app1.docx]

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Abbreviations

CISM: Center for Research and Innovation in Mental Health
DSM-5: Diagnostic and Statistical Manual of Mental Disorders [Fifth Edition]
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders [Fourth Edition]
ICF: informed consent form
PHQ-9: Patient Health Questionnaire-9
REDCap: Research Electronic Data Capture
UniFAJ: Centro Universitário de Jaguariúna
UniMAX: Centro Universitário Max Planck
WHO: World Health Organization

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Protocol

Estimating the Burden of Common Mental Disorders Attributable to Lifestyle Factors: Protocol for the Global Burden of Disease Lifestyle and Mental Disorder (GLAD) Project

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Abstract

Background: The Global Burden of Diseases, Injuries, and Risk Factors Study (GBD) collects and calculates risk-outcome data for modifiable lifestyle exposures (eg, dietary intake) and physical health outcomes (eg, cancers). These estimates form a critical digital resource tool, the GBD VizHub data visualization tool, for governments and policy makers to guide local, regional, and global health decisions. Despite evidence showing the contributions of lifestyle exposures to common mental disorders (CMDs), such as depression and anxiety, GBD does not currently generate these lifestyle exposure-mental disorder outcome pairings. This gap is due to a lack of uniformly collected and analyzed data about these exposures as they relate to CMDs. Such data are required to quantify whether, and to what degree, the global burden of CMDs could be reduced by targeting lifestyle

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factors at regional and global levels. We have established the Global burden of disease Lifestyle And mental Disorder (GLAD) Taskforce to address this gap.

Objective: This study aims to generate the necessary estimates to afford the inclusion of lifestyle exposures as risk factors for CMDs in the GBD study and the GBD digital visualization tools, initially focusing on the relationship between dietary intake and CMDs.

Methods: The GLAD project is a multicenter, collaborative effort to integrate lifestyle exposures as risk factors for CMDs in the GBD study. To achieve this aim, global epidemiological studies will be recruited to conduct harmonized data analyses estimating the risk, odds, or hazards of lifestyle exposures with CMD outcomes. Initially, these models will focus on the relationship between dietary intake, as defined by the GBD, and anxiety and depression.

Results: As of August 2024, 18 longitudinal cohort studies from 9 countries (Australia: n=4; Brazil: n=1; France: n=1; Italy: n=3; The Netherlands: n=3; New Zealand: n=1; South Africa: n=1; Spain: n=1; and United Kingdom: n=3) have agreed to participate in the GLAD project.

Conclusions: Our comprehensive, collaborative approach allows for the concurrent execution of a harmonized statistical analysis protocol across multiple, internationally renowned epidemiological cohorts. These results will be used to inform the GBD study and incorporate lifestyle risk factors for CMD in the GBD digital platform. Consequently, given the worldwide influence of the GBD study, findings from the GLAD project can offer valuable insights to policy makers worldwide around lifestyle-based mental health care.

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KEYWORDS

mental health; depression; anxiety; diet; lifestyle; mental disorders; epidemiology; burden of disease

Introduction

Mental disorders rank among the top 10 leading causes of disease and economic burden worldwide. They account for 4.9% of global disability-adjusted life years [1] and it has been projected that by 2030 mental disorders will account for more than half of the economic burden attributable to noncommunicable diseases [2]. Given the recognized burden on individuals, communities, and economies [1,3], identifying risk factors for common mental disorders (CMDs), namely depression and anxiety disorders, is critical for early prediction, prevention, and treatment. While known risk factors such as genetics, childhood adversity, and family conflict have a significant impact on CMD risk [4], preventative efforts should also address potentially more modifiable factors that may have broader reach.

Over the past decade, evidence has emerged highlighting lifestyle behaviors as modifiable risk factors for CMDs. A recent meta-review, drawing from top-tier data such as meta-analyses of prospective cohort studies, Mendelian randomization studies, and randomized controlled trials, emphasized the significant role of lifestyle behaviors pertaining to diet quality, physical activity, smoking, and sleep in CMD risk [5]. Furthermore, current evidence indicates that targeting these lifestyle behaviors can ameliorate the risk of CMDs. For example, data involving adult participants from France estimate that 14% of incident cases of depression are attributable to a combination of unhealthful diet, weight, and smoking [6]. Promisingly, data from Norwegian adults show that 12% of de novo depression could be averted if an individual engages in at least 1 hour of physical activity per week [7]. Collectively, this evidence highlights the importance of lifestyle factors in mental health outcomes, which has implications regarding prevention and treatment.

Despite ample evidence supporting the inclusion of lifestyle-based mental health care in clinical recommendations and population-level strategies [8], exemplified by clinical practice guidelines from organizations such as the Royal Australian and New Zealand College of Psychiatrists [9], the global implementation of these strategies for addressing CMDs remains limited. Global nutritional recommendations focus largely on individual food groups or constituents, and not on the dietary patterns, such as the Mediterranean diet, that are commonly used in research. As such, the evidence regarding whether dietary components would be useful to the target population's mental health is unclear. Furthermore, it is widely acknowledged that numerous structural barriers hinder the improvement of lifestyle behaviors, including social, financial, and environmental determinants [10,11]. These barriers also exist in mental health treatment and care [12]. Therefore, there is merit in attempting to reduce the incidence of CMDs by improving lifestyle behaviors, not just at the individual level, but also through population and policy-level strategies. To inform such strategies worldwide, rigorous global data are required to quantify the contribution of lifestyle behaviors to the risk of population CMDs.

The largest epidemiological study worldwide, the Global Burden of Diseases, Injuries, and Risk Factors Study (GBD), provides important global health estimates that inform public health priority setting and policies. A critical tool used by the GBD to communicate the current state of health and disease for different countries is the digital platform, the GBD VizHub Data visualization tool [13]. This digital platform allows policy makers to quickly ascertain where the greatest improvements in public health could be achieved by targeting specific risk

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factors. The GBD currently provides comprehensive estimates of lifestyle risks, such as diet, for a range of physical conditions, but has yet to incorporate estimates of these lifestyle risks for CMDs. This may be due to challenges in operationalizing and standardizing the measurement of lifestyle factors and CMD outcomes across studies, aligning them with GBD classifications and definitions, and establishing clear cause-and-effect relationships, particularly given the typical clustering of lifestyle risk factors [14-16]. In addition, studies investigating the associations between lifestyle risk factors and CMDs often face issues such as a lack of global representation, small sample sizes, inconsistent methodologies, residual confounding, and measurement error, particularly in regard to measuring dietary intake or ensuring adherence in intervention studies [17]. Consequently, while these factors are well-recognized risk factors for physical illnesses like heart disease and diabetes, the potential for lifestyle targets to be considered relevant to the population's mental health has historically been neglected [18].

To include lifestyle exposures as risk factors for CMDs on the GBD digital platform, the Global burden of disease Lifestyle And mental Disorder (GLAD) Taskforce (a large-scale, coordinated, international collaborative effort) has been formed. The Taskforce comprises global epidemiological experts who will work with GBD representatives to oversee the comprehensive evaluation of the association of lifestyle risk factors with CMDs, starting with dietary intake as the exposure of interest (the GLAD project). These experts have developed a harmonized approach for individual studies to conduct analyses (the GLAD project) to enable the integration of lifestyle factors as a risk for CMDs in the GBD. This paper outlines the processes by which the GLAD project and participant member studies will execute this harmonized data analysis protocol on their own datasets and disseminate their results through peer-reviewed publications. The overarching aim of the GLAD project is to generate robust, comparable evidence on the global risk of CMDs attributable to lifestyle factors, ultimately enabling their inclusion as risk factors for CMDs within the GBD framework. We hypothesize that more healthful lifestyle factors, such as higher intakes of healthful dietary components (eg, fruits, vegetables, whole grains, and fiber) will be associated with a lower risk of CMDs. Conversely, we hypothesize that less healthful lifestyle factors, such as higher intake of less healthful dietary components (eg, processed meat, sugar-sweetened beverages, and sodium) will be associated with a higher risk of CMDs.

Methods

Recruitment

The GLAD project is a collective, multistudy initiative led by Deakin University's, Food and Mood Center, which is situated within the Institute for Mental and Physical Health and Clinical Translation, School of Medicine, Barwon Health, Geelong, Australia. The GLAD project will be completed by the GLAD task force, comprising the project team, the advisory group, and the working group containing all member studies (Figure 1).

Figure 1. The GLAD taskforce composition and responsibilities within the GLAD project. GLAD: Global burden of disease Lifestyle And mental Disorders.

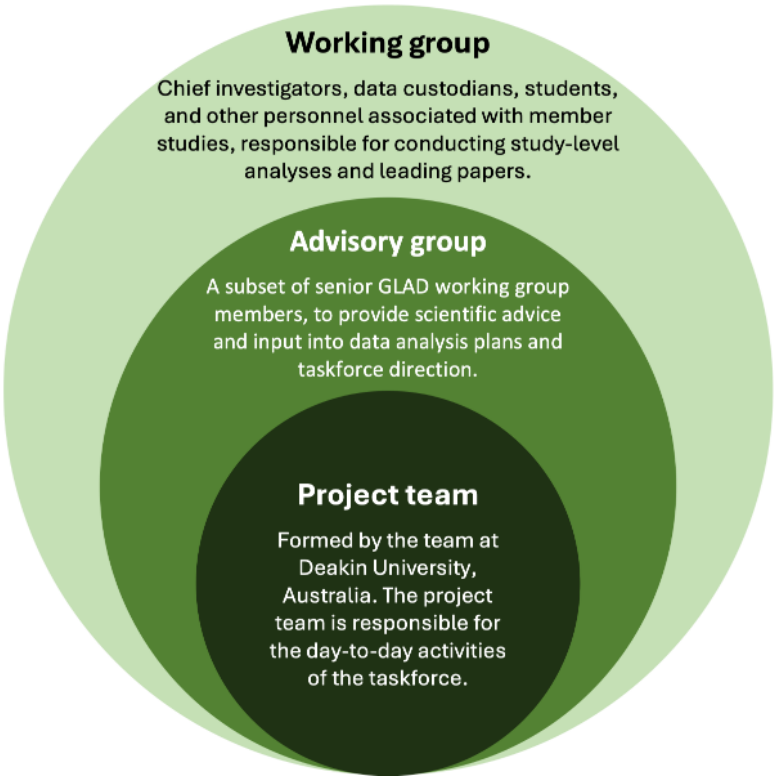

To identify potential member studies for participation in the GLAD project, which would apply the harmonized data analysis protocol to their own datasets and contribute their results to the broader initiative, we used a multistep process. The first step was to identify epidemiological studies that had the necessary variables by which the study lead or representative could execute

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our analysis plan (eg, food frequency questionnaires from which to derive GBD-defined dietary risks combined with mental health questionnaires to identify cases of depression or anxiety). This process involved a literature search to identify potentially eligible studies and key contacts to approach for invitation to participate in the GLAD project. To operationalize the dietary risk variables, we used previous GBD papers, which contained the definitions of each dietary exposure (Table 1) and depression and anxiety (Table 2) [1,19]. In addition to using the literature to identify potentially eligible datasets, we also drew on previous collaborations of the GLAD project team and researchers in the field of nutritional psychiatry (eg, via the International Society of Nutritional Psychiatric Research), as well as promoting the project on Food and Mood Center social media sites. Data custodians of identified studies were contacted, and those with relevant data and who had the capacity to participate in the GLAD project completed an expression of interest via the Food and Mood Center website.

To be eligible for inclusion, member studies must have dietary intake (Table 1) and depression and anxiety outcomes (Table 2) consistent with GBD definitions, or the ability to recode existing variables accordingly. Any deviations to these definitions must be reported and will be accounted for accordingly as reported below in "Future Directions: Meta-analyses." Any study design, in any location, with any sample size, is eligible to be a member study and can complete the required data analysis.

Table 1. Dietary exposure definitions and required coding for the GLAD project[a].

Dietary risk factor	GBD[b] exposure definition	Required coding[c]
Fruits	Average daily consumption of less than 310-340 g of fruit including fresh, frozen, cooked, canned, or dried fruit, excluding fruit juices and salted or pickled fruits.	grams/day
Vegetables	Average daily consumption of less than 280-320 g of vegetables, including fresh, frozen, cooked, canned, or dried vegetables and excluding legumes and salted or pickled vegetables, juices, nuts and seeds, and starchy vegetables such as potatoes or corn.	grams/day
Legumes	Average daily consumption of less than 90-100 g of legumes and pulses, including fresh, frozen, cooked, canned, or dried legumes.	grams/day
Whole grains	Average daily consumption of less than 140-160 g of whole grains from breakfast cereals, bread, rice, pasta, biscuits, muffins, tortillas, pancakes, and other sources.	grams/day
Nuts and seeds	Average daily consumption of less than 10-19 g of nuts and seeds.	grams/day
Milk	Average daily consumption of less than 360-500 g of milk including non-fat, low-fat, and full-fat milk, excluding plant derivatives.	grams/day
Red meat	Any intake of red meat including beef, pork, lamb, and goat but excluding poultry, fish, eggs, and all processed meats.	grams/day
Processed meat	Any intake of meat preserved by smoking, curing, salting, or addition of chemical preservatives.	grams/day
Sugar-sweetened beverages	Any intake of beverages with ≥50 kcal per 226.8-g serving, including carbonated beverages, sodas, energy drinks, and fruit drinks, but excluding 100% fruit and vegetable juices.	grams/day
Fiber	Average daily consumption of less than 21-22 g of fiber from all sources including fruits, vegetables, grains, legumes, and pulses.	grams/day
Calcium	Average daily consumption of less than 1.06-1.1 g of calcium from all sources, including milk, yogurt, and cheese.	grams/day
Seafood omega-3 fatty acids	Average daily consumption of less than 430-470 mg of eicosapentaenoic acid and docosahexaenoic acid.	milligrams/day
Polyunsaturated fatty acids	Average daily consumption of less than 7%-9% of total energy intake from polyunsaturated fatty acids.	total percentage of daily energy intake
Trans fatty acids	Any intake of trans fat from all sources, mainly partially hydrogenated vegetable oils and ruminant products.	total percentage of daily energy intake
Sodium	Average 24-hour urinary sodium excretion greater than 1-5 g.	grams/day
Ultra-processed foods (optional)	Any intake of ultraprocessed foods, as defined by the Nova system as any food item in Nova category 4 ("ultraprocessed food"), in grams [20].	grams/day

[a]Based on the GBD (Global Burden of Diseases, Injuries, and Risk Factors Study) risk exposure definitions (Pages 217-218 in Supplementary Appendix 1 in the study by the the GBD 2019 Risk Factors Collaborators [19]).

[b]GBD: Global Burden of Diseases, Injuries, and Risk Factors Study.

[c]Analyses using continuous exposures are required by the GLAD Taskforce. The units listed here are recommended, however, these may be rescaled to more meaningful units in papers (eg, per 10 g) provided the original units are available to the project team.

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Table 2. Mental health definitions and recommended coding for the GLAD[a] project[b].

Mental disorder	Outcome definition	Diagnostic reference	Recommended coding[c]
Major depressive disorder	Involves the presence of at least one major depressive episode, which is the experience of either depressed mood or loss of interest/pleasure, for most of every day, for at least two weeks.	DSM-IV-TR[d]: 296.21–24; 296.31–34. ICD-10[e]: F32.0-9; F33.0-9.	0=no MDD[f]; 1= MDD
Anxiety disorders (any subtype)	Involves experiences of intense fear and distress, typically in combination with other physiological symptoms. Anxiety disorders will be modeled as a single cause for "any" anxiety disorder to avoid the double-counting of individuals meeting criteria for more than one anxiety disorder. Epidemiological estimates reporting an outcome for "any" or "total" anxiety disorders will be included if they reported on at least three anxiety disorders.	DSM-IV-TR: 300.0-300.3; 208.3; 309.21; 309.81. ICD-10: F40-42; F43.0; F43.1; F93.0-93.2; F93.8.	0=no anxiety disorder; 1=anxiety disorder

[a]GLAD: Global burden of disease Lifestyle And mental Disorders.

[b]The definitions and diagnostic references presented in this table are the current definitions used by the GBD (Page 4 in the Supplementary Appendix in the study by the GBD 2019 Mental Disorders Collaborators [1]). Since GLAD members may use alternative methods to ascertain disorder status, definitions or diagnostic references may vary slightly. For example, somatic forms of depression may be captured more by symptom scales, or studies using prescriptions may use Anatomical Therapeutic Chemical codes to determine incident depression and anxiety.

[c]Outcomes must be binary (condition present vs condition absent). For studies that only use symptom scales, validated cutoffs can be used to determine condition present versus condition absent (refer to Multimedia Appendix 1).

[d]*DSM-IV-TR*: *Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition, Text Revision)*.

[e]*ICD-10*: *International Statistical Classification of Diseases, Tenth Revision*.

[f]MDD: major depressive disorder.

Statistical Analysis

Overview

The GLAD project and the following methods have been prospectively registered on the Open Science Framework [21]. The methods outlined herewith are based on the most up-to-date definitions used by the GBD, at the time of writing this protocol. Given that the GBD is subject to change, future iterations may vary in accordance with such amendments. The initial iteration of the GLAD project will focus on dietary exposures, and the methods described within this protocol refer specifically to this first iteration. Subsequent updates to the protocol may be made when additional lifestyle risk factors are considered in future iterations of the GLAD project.

Exposure and Outcome Definitions

Definitions of dietary intakes and CMDs are based on definitions used by the GBD [1,18]. In addition to the 15 dietary intakes used by the GBD, ultraprocessed food intake will be included where practicable given the increasing literature in the field linking this dietary exposure to a wide range of health outcomes [22-25]. In doing so, we will use the most widely adopted food classification system based on the purpose and extent of industrial food processing, Nova, to define ultraprocessed foods [20]. Furthermore, we will follow best practice guidelines when categorizing foods according to the Nova food classification system [26].

CMDs can be measured differently across epidemiological studies. They are most commonly assessed using self-reported symptom scales with cutoffs for diagnosis, from medical records, or using diagnostic interviews. Multimedia Appendix 1 outlines some commonly used tools and their recommended cutoffs for identifying symptoms of depression and anxiety. The sensitivity, specificity, and diagnostic accuracy of these tools largely depend on the population. When undertaking meta-analyses, we may conduct a sensitivity analysis to determine if the magnitudes of associations change based on exposure and outcome measurement or ascertainment type.

Covariates and Confounders

To address the anticipated heterogeneity of member studies' available data, a set of core confounders are provided for the purpose of generating a consistent minimally adjusted analysis. The conduct of additional analyses (eg, using additional variables, fitting sensitivity models, or exploratory analyses) is at the discretion of the study author or authors based on available data and reviewer requests when studies are submitted for publication.

To be included in the GLAD project, member studies must adhere to the iteratively adjusted models (Textbox 1).

Textbox 1. The iteratively adjusted statistical models required for the Global burden of disease Lifestyle And mental Disorders (GLAD) task force.

- Model 1: Unadjusted model, with the dietary variable (as listed in Table 2) as the exposure and depression or anxiety as the outcome.
- Model 2: Minimally adjusted model, with the dietary variable of interest, depression or anxiety, and with baseline mental disorder status (or lifetime history of mental disorders for cross-sectional studies), age, sex, and a measure of socioeconomic status, such as household income, employment status, or education.
- Sensitivity model: Same as model 2, but with adjustment for total energy intake.

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Of particular relevance in nutritional epidemiology are methods for adjusting for energy intake. Intake of specific nutrients are correlated with total energy intake, and so appropriate adjustment is required to disentangle the effect of the nutrient from the effect of energy. For example, an individual may alter intake of a specific nutrient by changing dietary composition, and not by changing total energy intake. As such, controlling energy intake can reduce confounding, and failure to appropriately control for total energy intake may nullify associations between nutrient intake and disease outcomes [27]. Given the correlation between nutrient intake and energy, the application of Willett's residual method is recommended to account for total energy intake [27]. This involves fitting a regression model with the dietary variable as the outcome and total energy intake as the exposure, predicting residuals from this model, and then using these predicted residuals in the analysis models [27].

Reporting Baseline and Demographic Characteristics

To describe participant characteristics, authors of member studies include a table containing descriptive statistics, given as n (%) for categorical variables, and mean (SD) or median (25th-75th percentile) for continuous variables. A column containing *P* values will not be included, as statistical tests do not meaningfully assess differences between samples or populations, nor should they be used as the basis for assessing confounders [28].

Estimating Risk Ratios, Odds Ratios, and Hazards Ratios

Each study is required to use risk ratios (estimated by Poisson regression with robust SE) as the primary means of assessing the association of dietary intake with CMDs. Risk ratios are based on incident cases, and so models will need to exclude participants with depression or anxiety at baseline. Furthermore, to determine incident risk, studies must have dietary exposures at baseline and depression, or anxiety measured at a subsequent time point. Where the estimation of a risk ratio is not possible (refer to Figure 2), for example, where the total number of people exposed at baseline is not available (such as for retrospective or case-control studies) [29], odds ratios are estimated using standard logistic regression techniques. Where only time-to-event data are available, hazard ratios are used, estimated by a Cox proportional hazards model. For rigor, all effect estimates will be accompanied by a 95% CI and exact *P* value [30].

Models can be fitted using any statistical analysis software, including R (R Core Team), SAS/STAT (SAS Institute Inc), Stata (StataCorp LLC), and SPSS (IBM Corp). Before fitting the relevant models, Member studies must assess model assumptions. Should any model assumptions be violated, an alternate approach to analysis may be selected. For example, the nonlinearity of continuous variables should be investigated, and transformations or nonlinear models fitted where necessary. Similarly, should any of the assumptions of Cox proportional hazards models be violated, alternative strategies will be deployed to account for these violations.

In addition to the models listed above, the following subgroups shall be fitted separately for each exposure-outcome pairing, where data allows: (1) sex, (2) age, (3) year (for longitudinal studies with multiple waves of follow-up), (4) country (for multicenter studies), and (5) all symptom scales and diagnostic measures (for studies with depression and anxiety measured via multiple measures. For age, studies should explore the relationship between the risk factors and mental disorders with age to see if a continuous measure is appropriate. Where a continuous measure is not appropriate, studies should generate appropriate age categories for their dataset by inspecting the frequency of outcomes by age groups. As a guide, the GBD currently uses 0-6 days (early neonatal), 7-27 days (late neonatal), 28-365 days, 1-4 years, 5-9 years, then 5-year intervals from 10-95 [31].

Figure 2. The types of ratio measures that can be obtained from binary outcome data. Odds ratios will be estimated using logistic regression, risk ratios will be estimated using Poisson regression with robust SE, and hazard ratios will be estimated using Cox regression.

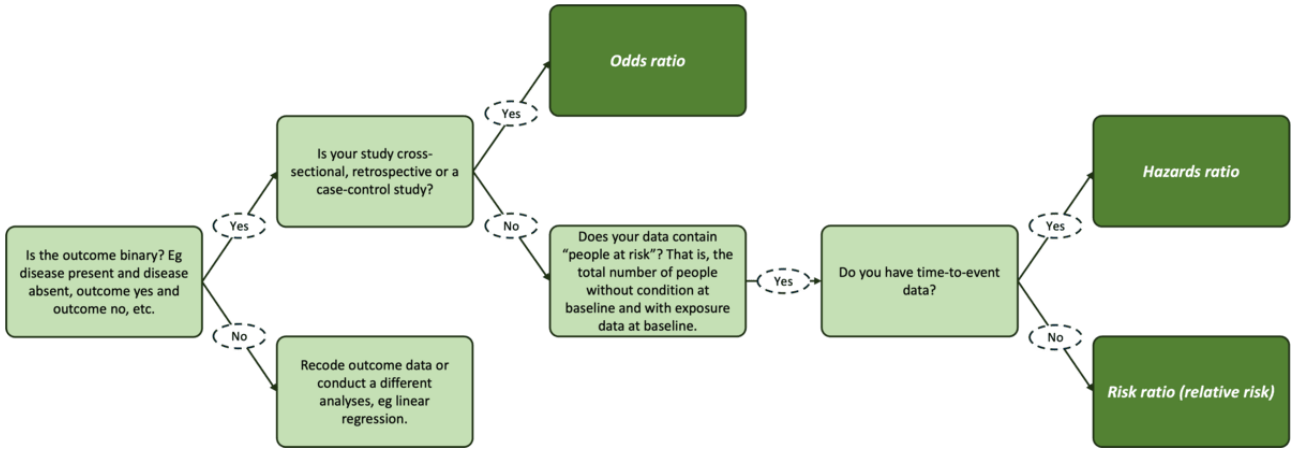

Sensitivity Models

Multiple Testing

Given the need for multiple models to be fitted within each study, the GLAD Taskforce recommends a *P* value adjustment procedure, such as the Simes method, to minimize the chance of a type 1 error and determine whether multiple testing may be influencing results [32]. This should be applied to all models in a study where multiple models are required.

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Outliers and Influential Data

Initial models include all available data points, with sensitivity analyses included for any influential or outlying observations. Influential observations are determined by predicting residuals, Cook's distance, or DFBETA after fitting the relevant model. Although several cutoff points have been proposed to identify influential observations, conventional cutoffs are applied: 3 for standardized residuals [33]; 4/(n-p) for Cook's Distance [34], where n=sample size and p=number of parameters in the model; and 2/√n for DFBETA [35].

Missing Data

Each study initially uses a complete-case model, whereby individuals with missing observations are excluded from the model. Member Studies with missing exposure, outcome, and covariate observations conduct a missing data analysis to determine the influence of missing data. While a multiple imputation approach is preferred, other methods such as k-nearest neighbor imputation or inverse probability weighting may be used where an imputation approach is not possible or appropriate [36-41].

Future Directions: Meta-Analyses

Upon completion of the analysis phase of the GLAD project (phase 2), the GLAD project team and advisory group will lead a meta-analysis (phase 3). A separate protocol will be created for this phase of the GLAD project. Briefly, the GLAD project team will conduct a systematic literature review to identify any relevant studies not already participating in GLAD. After screening abstracts and full text, data will be extracted from all identified studies and studies participating in GLAD. A random effects meta-analysis will be performed to pool results from all eligible studies. We will perform a meta-regression to quantify how the risk can vary by demographic factors, and methodological biases [42]. Where studies have used different assessment methods for mental health outcomes, different tools to ascertain dietary intake, any slight deviations to definitions, or where studies use different analysis strategies, we will perform cross-walking or sensitivity analyses to ensure comparability [43]. Papers using methods that deviate substantially from the methods described in this paper will be excluded from the meta-analysis. The resulting meta-analysis will be reported according to the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses).

Ethical Considerations

Each member study will have obtained informed consent from participants and had their study approved by institutional ethics review boards. Full details for ethics for each study can be found in previous studies [44-65] and a summary is provided below. This study is registered in the Open Science Framework (osf.io/zbg6x).

Results

As of August 2024, 18 longitudinal studies have agreed to participate in the GLAD project (Table 3). These studies have sample sizes ranging from 639 participants to 171,000 participants (Table 4).

The GLAD project comprises 3 essential phases, which will be repeated for other lifestyle exposures of interest: (1) conducting a systematic search to identify relevant studies and recruit study leads to contribute data, (2) generating estimates of study-level associations of dietary risk factors with CMDs using harmonized data analysis protocols developed by the GLAD Taskforce and approved by the GBD, and (3) pooling results from each study to provide the GBD with robust estimates to calculate the diet-CMD risk-outcome pairs in the first instance.

As of August 2024, phase 1 of the GLAD project has been completed, and phase 2 is due for completion in early 2025, at which time phase 3 of the GLAD project is due to begin (Figure 3).

Phase 1 includes searching for and recruiting studies with suitable data, harmonizing data definitions by ensuring member studies use the exposure definitions listed in Table 1 and the outcome definitions listed in Table 2, and harmonizing data analyses by ensuring member studies follow the statistical analysis plan presented in this paper.

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Table 3. Details of the ethics approval for currently listed member studies[a].

Study name	Ethics review board
The African-PREDICT[b] study [44]	North West Department of Health and Health Research Ethics Committee of the North-West University.
Child to Adult Transition Study [45]	Royal Children's Hospital Human Research Ethics Committee.
Dunedin Study [46]	Health and Disability Ethics Committee, Ministry of Health.
Environmental Risk (E-Risk) Longitudinal Twin Study [47,48]	Joint South London and Maudsley and the Institute of Psychiatry Research Ethics Committee.
Fragility in the Elderly Lombardy Study [49]	Ethics committee of the University of Pavia.
Geelong Osteoporosis Study [50]	Barwon Health Human Research Ethics Committee.
Health4Life [51,52]	University of Sydney, NSW[c] Department of Education, University of Queensland, Curtin University, and relevant Catholic school ethics committees.
Healthy Life in an Urban Setting [53]	Ethical Review Board of the Academic Medical Center Amsterdam.
Longitudinal Aging Study Amsterdam [54]	Medical ethics committee of the VU University Medical Center.
Lothian Birth Cohort 1936 [55,56]	Multi-Centre Research Ethics Committee for Scotland and Lothian Research Ethics Committee.
Melbourne Collaborative Cohort Study [57]	Cancer Council Victoria's Human Research Ethics Committee.
Moli-sani Study [58]	Ethical committee of the Catholic University in Rome.
Netherlands Study of Depression and Anxiety [59]	Medical Ethical Committee of the Vrije Universiteit (VU) Medical Centre and medical ethical committees of the participating universities.
Northern Ireland Cohort of Longitudinal Ageing [60]	School of Medicine, Dentistry and Biomedical Sciences of Queen's University Belfast.
NutriNet Brasil [61]	Ethics committee of the School of Public Health from São Paulo University
NutriNet-Santé [62]	Ethics committee of the French National Institute for Health and Medical Research and by the National Commission on Informatics and Liberty.
Piccolipiù/Piccoli+/Piccolipiù in Forma [63]	Ethics committees of the Local Health Unit Roma E (management center), of the Istituto Superiore di Sanità (National Institute of Public Health) and of each local center.
REgistre GIroní del COR [64,65]	Institut Municipal d'Assistencia Sanitaria Ethics Committee

[a]Additional studies may be participating in or providing data for the GLAD project and not be listed here.

[b]African-PREDICT: African Prospective study on the Early Detection and Identification of Cardiovascular disease and Hypertension.

[c]NSW: New South Wales.

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Table 4. Overview of the studies participating in the GLAD[a] project.

Study name	Study location	Maximum possible sample size[b], n	Age range
The African-PREDICT[c] Study [44]	South Africa	1202	20-30 years
Child to Adult Transition Study [45]	Australia	1239	Older than 8 years
Dunedin Study [46]	New Zealand	1037	0-45 years
Environmental Risk (E-Risk) Longitudinal Twin Study [47,48]	United Kingdom	2232	0-18 years
Fragility in the Elderly Lombardy Study [49]	Italy	639	Older than 65 years
Geelong Osteoporosis Study [50]	Australia	1518	Older than 30 years
Health4Life [51,52]	Australia	6639	11-13 years; 14-17 years
Healthy Life in an Urban Setting [53]	The Netherlands	24,789	18-70
Longitudinal Aging Study Amsterdam [54]	The Netherlands	3805	55-85 years
Lothian Birth Cohort 1936 [55,56]	United Kingdom	1091	Older than 60 years
Melbourne Collaborative Cohort Study [57]	Australia	41,500	Older than 40 years
Moli-sani Study [58]	Italy	24,325	Older than 35 years
Netherlands Study of Depression and Anxiety [59]	The Netherlands	3348	18-65 years
Northern Ireland Cohort of Longitudinal Ageing [60]	United Kingdom	8500	Older than 50 years
NutriNet Brasil [61]	Brazil	109,245	Older than 18 years
NutriNet-Santé [62]	France	171,000	Older than 18 years
Piccolipiù/Piccoli+/Piccolipiù in Forma [63]	Italy	3328	0-4 years
REgistre GIroní del COR [64,65]	Spain	11,158	Older than 26 years

[a]GLAD: Global burden of disease Lifestyle And mental Disorders.

[b]Maximum possible sample size refers to the largest reported sample size from study publications, study websites study protocol, or profile papers. The actual sample size to be included in the GLAD project may vary.

[c]African-PREDICT: African Prospective study on the Early Detection and Identification of Cardiovascular disease and Hypertension.

Figure 3. The tasks, responsible parties, phases, and expected timeline of the GLAD project. CMD: common mental disorder; GBD: Global Burden of Diseases, Injuries, and Risk Factors Study; GLAD: Global burden of disease Lifestyle And mental Disorders.

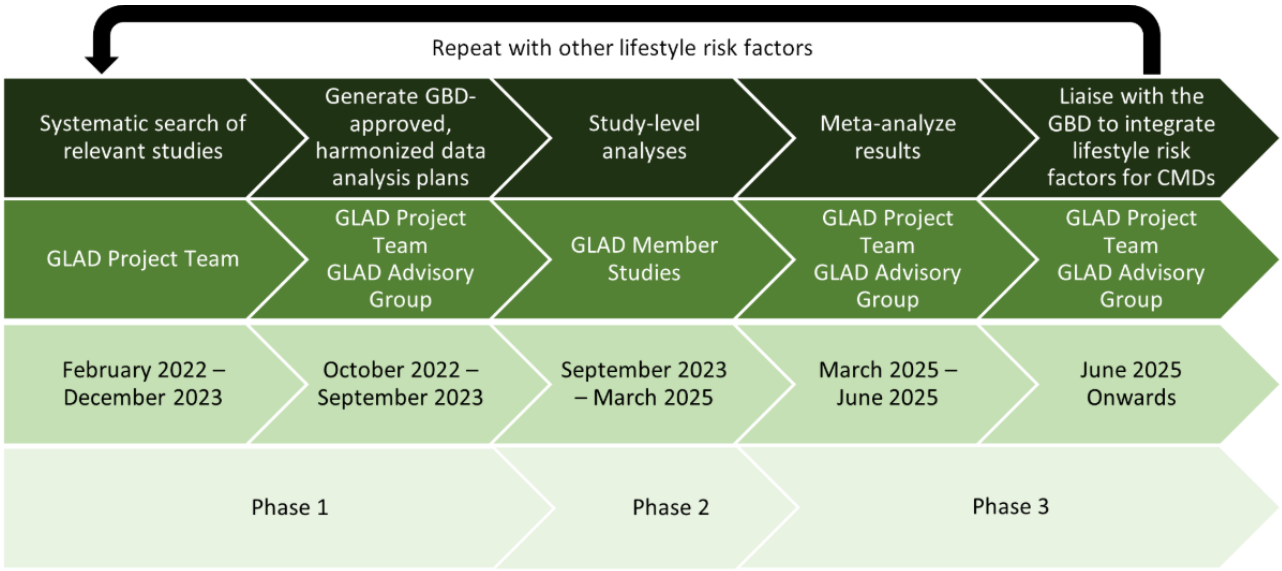

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Discussion

Anticipated Impact

The GLAD project is a global collaboration designed to estimate the risk of CMDs attributable to lifestyle risk factors, with this protocol focusing on dietary risk factors. The anticipated results will provide the GBD with the required threshold of evidence for lifestyle risks to be causally related to CMDs, thereby enabling lifestyle-CMDs risk-outcome pairs to be integrated into the GBD framework. Specifically, the GLAD project will demonstrate that GBD-defined lifestyle risks (eg, diets low in fruit) will be associated with increased risk of CMDs. The GBD study is the largest and most comprehensive global epidemiological health study, providing metrics for 369 diseases and injuries and 87 risk factors [19,66]. These health metrics, including estimates such as the burden of disease and disability-adjusted life years, are publicly available via the GBD digital platform [13] and provide critical information for clinicians, researchers, and policy makers worldwide. While lifestyle risk factors, including dietary intake defined as per GBD-specific definitions, have been considered in the context of chronic physical conditions in the GBD study, they have not yet been linked with mental health outcomes. As the first global collaborative study to link these lifestyle risks with CMDs, using the definitions and methods concordant with the GBD, the results of the GLAD project can be used to link these lifestyle factors as risks for CMDs in the GBD. This effort will allow us to quantify the potential reduction or elimination of the CMD burden by targeting these risk factors at regional and global levels, and to ensure these data are available freely online via the GBD VizHub Data visualization tool.

Risk factors for CMDs in the GBD are currently limited, and so, the inclusion of these additional lifestyle risk factors will represent a significant expansion in the scope of the GBD, which will have global policy implications. Our work builds upon the previous efforts of studies that have successfully integrated novel risk factors for CMDs in the GBD. For example, bullying victimization has been successfully incorporated into the GBD as a level 3 risk and is now routinely integrated into GBD papers [67,68]. By emulating the successful integration of these other risk factors into the GBD, our comprehensive, collaborative approach to harmonized statistical analyses across multiple, internationally renowned epidemiological cohorts has the potential to establish a basis for evidence-backed preventive strategies focused on lifestyle risk factors to reduce the burden of CMDs. Furthermore, by operationalizing the definitions to be in line with the GBD, which are used to inform global policy guidelines, and by capturing data from different regions, sexes, and ages, these results have the potential to bring benefits to individuals and communities on a global scale.

There is substantial observational [69-71], intervention [72-76], and meta-analytical [5,77-79] evidence linking these lifestyle factors to CMDs globally, which suggests that lifestyle factors are potentially suitable (and importantly, modifiable) preventive strategies. This has been recognized by the Royal Australian and New Zealand College of Psychiatrists, with lifestyle treatments integrated into the recent clinical practice guidelines for mood disorders, including depressive disorders [9]. A 2020 meta-review identified that targeting lifestyle variables like physical activity and smoking can be used effectively in the prevention and treatment of CMDs [5]. However, there was less evidence for the role of targeting diet in preventing CMDs, particularly as defined by international policy guidelines or as per the GBD framework. In order to incorporate additional lifestyle factors into guidelines globally, we need comprehensive epidemiological evidence, with a particular focus on dietary risks. The GLAD project will address previous methodological limitations through global collaborations and following a rigorous methodological framework informed by the GBD.

Although mechanistic evidence is currently limited, the causal role of lifestyle risks for CMDs has been supported by shared biological mechanisms between lifestyle factors and CMDs. These pathways include inflammation, oxidative stress, epigenetics, hypothalamic-pituitary-adrenal axis regulation, and the gut microbiome [80]. Inflammation has been linked to CMDs previously, and physical activity, diet, sleep, and smoking have all been shown to impact inflammation [5]. As such, improving dietary intake, increasing physical activity, improving sleep, and smoking cessation may improve mental health via anti-inflammatory properties. Another mechanistic pathway shared by CMDs and many lifestyle risk factors (including diet, physical activity, sleep, and smoking) is the microbiome [80,81]. Many of the dietary risks listed in the GBD, including fruit, vegetable, whole grain, and fiber intake, have pre- and probiotic potential which has been shown to beneficially influence the gut microbiome, and other GBD-defined dietary risks, such as processed meats and sugar-sweetened beverages (which are markers for a high-fat diet), Western-style diet (have been shown to increase anxiety and depression via gut microbiome alterations) [80]. Despite the evidence linking lifestyle risk factors with CMDs, including studies identifying potential mechanisms of action, studies assessing the relationship between lifestyle risks as defined by the GBD with CMD outcomes are lacking. Further, to integrate lifestyle risks for CMDs in the GBD, evidence needs to be generated globally, and not just from individual studies. As a global collaborative project, the results from the GLAD project will therefore provide the necessary evidence to incorporate lifestyle as a risk factor for CMDs in the GBD, which will enable policy makers around the world to make policy decisions regarding the potential public health benefit of population-level lifestyle improvements to mental health.

Strengths and Limitations

Currently, the GBD is unable to include lifestyle exposures such as dietary intake as a risk for CMDs due to the following: difficulties determining directionality and causality, inconsistency in dietary variables and methods, small sample sizes, and lack of global representation. A strength of the GLAD project is that it will address all these methodological considerations. We will (1) prioritize prospective studies using incident cases (ie, excluding those with baseline CMDs) to obtain risks of CMDs attributable to dietary intake, and not the other way around (to determine directionality or temporality), (2) include all study designs (including from experimental or randomized controlled trials to strengthen causal conclusions),

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(3) conduct harmonized data analyses approved by the GBD (to improve consistency between studies and specificity of the diet-CMD relationship), and (4) pool data from multiple studies from around the world (to address sample size and global representation).

Despite the clear strengths of the GLAD project, there are some limitations. First, the GBD study is an ongoing and dynamic study, and definitions and methods are constantly evolving. Every effort will be made to ensure the taskforce are following GBD-approved methods, however, some changes from the GBD may be unavoidable. Second, since the GBD does not currently include ultraprocessed food as a dietary risk factor, the definitions and methods used by the task force may not reflect those used in future iterations of the GBD. Finally, although food intakes provide a general overview of diet quality, people do not eat food items in isolation. The current methods used by the GBD do not currently consider dietary patterns. This may limit interpretations to specific food items and not to an overall dietary pattern.

Conclusion

This multicountry, 5-year project has the potential to highlight the role of modifiable lifestyle risk factors in the prevalence and incidence of CMDs. Given the global burden of depression and anxiety, new approaches and targets for their prevention and management are of unprecedented importance.

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Data Availability

The GLAD project is a multicountry collaborative effort for which individual collaborators apply a harmonized protocol developed by the task force to their own data. Data are not pooled in a shared repository or location, nor publicly available. The data custodians of each dataset may or may not make their data available upon request.

Disclaimer

The opinions, methods, and conclusions reported in this paper are those of the authors and are independent from the funding sources. This manuscript has been prepared in accordance with the requirements of the GLAD task force, as part of a global collaborative project to inform the GBD.

Authors' Contributions

AON and FNJ conceptualized the GLAD task force and project. AON acquired the funding for the project. DNA, RO, and MML contributed to the development of methodology, data curation, and project administration. DNA, RO, MML, FNJ, and AON contributed to the resources (provision of study materials), supervision of the project, and writing the original draft of the manuscript. All authors contributed to the validation of the methodology, and critically reviewing and editing the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Commonly used tools and scales for assessing common mental disorders, and their cut-offs for indicative diagnosis.
[DOCX File , 62 KB - resprot_v14i1e65576_app1.docx]

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Abbreviations

CMD: common mental disorder
GBD: Global Burden of Diseases, Injuries, and Risk Factors Study
GLAD: Global burden of disease Lifestyle And mental Disorders
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

Optimizing the Pharmacotherapy of Vascular Surgery Patients at Hospital Admission and Discharge (PHAROS): Protocol for a Quasi-Experimental Clinical Uncontrolled Trial

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Abstract

Background: Patient safety is essential in pharmacotherapy, especially in surgical contexts, due to the elevated risk of drug-related complications. Vascular surgery patients are particularly susceptible because of their complex medication needs and underlying health conditions. Improved safety monitoring and targeted pharmaceutical care in collaboration with physicians are crucial to minimize these risks and enhance patient outcomes.

Objective: This protocol evaluates whether structured pharmaceutical care interventions—including medication reconciliation, medication review, and patient education—can reduce the prevalence of drug-related problems at hospital admission and discharge in vascular surgery patients.

Methods: This prospective, uncontrolled study was conducted over 1 year in the Vascular Surgery Department at the National Institute of Cardiovascular Diseases in Bratislava, Slovakia. The study included adult patients with carotid artery disease or lower extremity artery disease who were on 3 or more medications, with an estimated sample size of approximately 100 patients. The primary intervention involved 3 key changes in practice: medication reconciliation at both admission and discharge, where hospital pharmacists review and verify medication lists; medication review to identify and address drug-related problems; and patient education at discharge. Pharmacist-proposed interventions were documented and communicated to the physician for treatment adjustments. The primary outcome is the change in drug-related problem prevalence from hospital admission to discharge. Secondary outcomes include the acceptance rate of pharmacist recommendations and patient understanding of pharmacotherapy. Data collection involved documenting the number, type, and frequency of drug-related problems; the anatomical therapeutic chemical classification of medications associated with drug-related problems; and patients' social, demographic, and clinical characteristics, with a focus on factors related to drug-related problems, comorbidities, and medication use. Data analysis will use the paired Wilcoxon signed-rank test to compare the prevalence of drug-related problems and medication counts between admission and discharge. Continuous variables will be presented as means (SDs), while categorical variables will be reported as counts and percentages. Patient understanding of pharmacotherapy will be evaluated using a 3-point scale, classifying understanding as good (2-3 points per medication), modest (1-2 points), or poor (0-1 point).

Results: Recruitment began in September 2021 and concluded in August 2022. Data collection occurred continuously during hospital stays, capturing demographics, comorbidities, pharmacotherapy, and drug-related problems at admission and discharge. Important milestones included the initial data review, which began in August 2023 to assess recruitment and data quality, including

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an early evaluation of drug-related problems. The primary analysis was completed in January 2024, focusing on the reduction in drug-related problems, intervention acceptance, and patient understanding. The final report was to be prepared by June 2024, disseminating the findings on pharmacist-led intervention impacts.

Conclusions: This study should demonstrate that pharmacist-led interventions in collaboration with physicians can reduce pharmacotherapy risks and optimize medicine management for patient safety.

Trial Registration: ClinicalTrials.gov NCT04930302; https://clinicaltrials.gov/study/NCT04930302

International Registered Report Identifier (IRRID): RR1-10.2196/60728

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KEYWORDS

pharmacotherapy; hospital pharmacy; vascular surgery; patient safety; risk reduction; pharmacist-proposed interventions

Introduction

Background

Pharmaceutical care was first defined in 1990 by Hepler and Strand [1] as "the responsible provision of drug therapy for the purpose of achieving definite outcomes that improve a patient's quality of life." Worldwide, pharmaceutical care is currently considered a patient-centered approach, replacing the previous product orientation (dispensing medications) [2,3]. The pharmacist actively cooperates not only with the patient but also with health care professionals in health promotion, disease prevention, evaluation, monitoring, and adjustment and initiation of drug use in order to ensure an effective and safe drug regimen, achieve positive clinical results, and reduce the economic costs of care [2,4].

Currently, patient safety in health care delivery is at the forefront of interest worldwide [5,6]. Patient safety is the absence of preventable harm to a patient during the process of providing health care and reduction of the risk of unnecessary harm associated with health care to an acceptable minimum. Hospital pharmacists [4,7] can make a significant contribution to the safe, effective, and rational use of medicines by hospitalized patients, especially high-risk medication and look-alike and sound-alike medications, through their close surveillance as well as advising on the most appropriate use of medicines [7]. Identification of drug-related problems (DRPs) and proposal of solutions for DRPs by hospital pharmacists is a tool to ensure safe and effective pharmacotherapy for patients [8,9].

The Pharmaceutical Care Network Europe Association (PCNE) defines a DRP as a problem, event, or circumstance related to pharmacotherapy that affects or has the potential to affect a desired therapeutic effect [10]. An example is the arbitrary withdrawal of metformin by patients due to persistent diarrhea [11]. The PCNE has developed a classification system as a tool to accurately identify DRPs. The current version is V9.00 as of 2019 [10]. This classification tool is used throughout our study to ensure consistency in identifying and categorizing DRPs.

DRPs are generally all problems related to the use of a drug [10]. DRPs include adverse drug reactions (ADRs), an unintended reaction after medication administration [11-14], medication errors, and any phenomenon that may lead to improper use of a drug under the control of a health care professional or patient [15-17].

Although it is not common practice in Slovakia to report all DRPs, this is not an issue unique to the country. Many nations face similar challenges, especially where comprehensive pharmacovigilance systems are still developing [18]. In 2019, only 1128 suspected ADRs were reported, of which only 8% were reported from pharmacists. Overall, up to 26% of reports were classified as severe (ie, required hospitalization of the patient or caused permanent harm to the patient). Although state authorities have seen an increase in the number of spontaneous reports, their number probably does not correspond to their actual occurrence. Currently, we do not have statistically evaluated health care costs due to medication errors in Slovakia [18].

We distinguish between intentional and unintentional DRPs [10,19,20]. There is no uniform classification of the severity of DRPs. It is necessary to focus on the identification and elimination of unintentional DRPs.

At the same time, according to current statistics, the average age of the population is increasing worldwide, which is directly related to the higher prevalence of polymorbidity and polypharmacy in the population [21-23].

There are certain indicators on the basis of which an increased incidence of unintentional DRPs can be expected. In a hospital environment, these are the high number of drugs, which is related to low adherence, potential interactions, accumulation of medication errors, more frequent hospitalizations, and increased treatment costs [24-27]; a low level of understanding of the therapy being used among patients [28-30]; older age of patients [21-23,28]; and absence of caregivers for older adult patients [29].

These indicators may be associated with the incidence of treatment errors related to primary care.

Prior Work

Pharmacists use several strategies to reduce DRPs, including medication reconciliation (MedRec), medication review (MedRev), and patient education [30-34]. Prescription errors during hospital admission are common, with studies showing that these errors occur in up to 67% of patients [35]. MedRec has been shown to identify at least one DRP in 60% of patients, with 18% being clinically significant [36]. The incidence of drug discrepancies during hospital transitions, especially at discharge, is high, with some studies showing significant discrepancies upon patient discharge [37,38]. According to a

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2020 Organization for Economic Co-operation and Development report, pharmacy-led MedRec before discharge reduces drug discrepancies and the associated risks to patient health [39]. A meta-analysis conducted by Mekonnen et al [40] in 2016 found that pharmacist-led MedRec reduces hospital readmissions by 67%, emergency admissions by 28%, and hospitalizations by 19%.

MedRec involves obtaining a best possible medication history (BPMH) from various sources, including medical records, community pharmacies, and patient interviews. This is compared with the patient's current medication list to identify discrepancies, which are then discussed with health care professionals and resolved [32-34,41,42]. MedRev further optimizes pharmacotherapy by eliminating unnecessary medications, adjusting dosages, or addressing drug interactions [43].

Studies on pharmaceutical interventions typically focus on specific patient groups, such as those with cardiovascular diseases, renal failure, or older adult patients. For example, Stemer et al [44] identified 487 DRPs in 138 visits, with a 54.7% acceptance rate for pharmacist recommendations. Hohn et al [45] found a rate of 0.41 unintentional medication errors per patient in vascular surgery patients. In patients with chronic renal insufficiency, pharmacist interventions improved renal function, particularly in more severe cases [46]. Older adult patients also showed positive outcomes, with pharmacist interventions reducing hospital readmissions by 16% and hospitalization rates due to DRPs by 80% [47].

Overall, pharmacist-led interventions are effective in reducing DRPs, improving pharmacotherapy, and enhancing patient outcomes. However, the types and numbers of DRPs detected vary across studies, indicating the need for standardized definitions in research on DRPs [19,33,48].

Trial Objectives

This study aims to assess the impact of pharmaceutical care in collaboration with physicians on the prevalence of DRPs at hospital admission and discharge in patients with carotid artery disease or lower extremity artery disease hospitalized in the Department of Vascular Surgery. These patients often experience polypharmacy, making them particularly suitable for pharmacotherapy optimization through pharmacist-led interventions. MedRec, MedRev, and patient education provided by pharmacists are new interventions at our hospital and were not part of the standard of care prior to the study.

The key focus area of this project is the identification of DRPs, their occurrence, and their type. As part of further research, we want to analyze the degree of acceptance of the proposed changes in pharmacotherapy by physicians, document the Anatomical Therapeutic Chemical Classification (ATC) groups of drugs with the highest incidence of DRPs, and identify patients at highest risk for DRPs taking into consideration their personal and health information.

Trial Hypotheses

The null hypothesis is that pharmaceutical care provided at hospital admission and hospital discharge does not reduce the prevalence of DRPs in patients with carotid artery disease or lower extremity artery disease hospitalized in the Department of Vascular Surgery.

The alternative hypothesis is that pharmaceutical care provided at hospital admission and hospital discharge reduces the prevalence of DRPs in patients with carotid artery disease or lower extremity artery disease hospitalized in the Department of Vascular Surgery.

Methods

Study Design

This study is a single-center, prospective, uncontrolled biomedical clinical trial conducted over 1 year. The study took place in a hospital setting, specifically in the Department of Vascular Surgery at the National Institute of Cardiovascular Diseases in Bratislava, Slovakia. The intervention included MedRec, MedRev, and patient education, all performed by a trained pharmacist following the High 5s Project Standard Operating Protocol for Medication Reconciliation [24] and PCNE guidelines [10]. All pharmacist recommendations and proposed changes to therapy were documented in writing, recorded in the patient's medical record, and communicated to the attending physician.

Our study followed the Standards for Quality Improvement Reporting Excellence (SQUIRE) guidelines [49].

Study Population

Adult (≥18 years of age) vascular surgery patients with carotid artery disease or lower extremity artery disease admitted for hospitalization at the study setting during the course of the study were recruited.

Inclusion Criteria

To participate, patients needed to be ≥18 years old at the date of admission for hospitalization, taking at least 3 medications administrated systematically, and have carotid artery disease or lower extremity artery disease.

Exclusion Criteria

Patients were excluded for any of the following reasons: admitted for an acute condition; transferred from other hospitals or wards; not willing to sign the informed consent form for the study; not understanding the Slovak language; had any mental disorder affecting memory and recall ability (such as Alzheimer disease); any other reason, at the investigator's discretion, why he or she deemed the participant not eligible for study participation (all such reasons were recorded); or participating in another clinical study.

Study Sample Size

To calculate the sample size, we aimed to accept a type I error rate with a P value ≤.05. The study seeks to achieve 80% power to detect a small effect size of 0.3 using the Wilcoxon signed-rank test. Based on these assumptions, the required sample size was calculated as 94 patients. To account for potential dropouts, the sample size was increased to 120 patients. The sample size calculation was performed using G*Power

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software version 3.1 [50]. Similar studies published in this field have comparable sample sizes [51].

Data Sources and Measurements

Data were drawn from the hospital information system (HIS), medical and nursing reports, patient interviews, and contacting outpatients.

Primary Outcomes

The primary outcome is a change in the prevalence of DRPs at hospital admission versus hospital discharge.

Secondary Outcomes

The secondary outcomes are the acceptance rate of the pharmaceutical intervention by physicians and patient understanding of their pharmacotherapy.

Variables

The variables collected include the number, type, and frequency of DRPs; ATC of drugs causing DRPs; medical, social, and demographic characteristics of patients; health condition of patients; comorbidities; and patient understanding of their pharmacotherapy assessed on a 3-point scale at hospital admission.

We assessed the patients' basic social, demographic, and clinical characteristics, with a particular emphasis on evaluating their pharmacotherapy and the incidence of DRPs. Additionally, we examined the degree of acceptance of pharmacists' recommendations by physicians and the outcomes of DRP resolutions. Our analysis will also identify the medications most frequently associated with the occurrence of DRPs. Patients' understanding of their pharmacotherapy was also be evaluated.

Time Points for Intervention

At Hospital Admission

Current Condition at Patient Admission

A vascular surgery patient with carotid artery disease or lower extremity artery disease comes for a planned hospitalization with a report from the attending physician, with or without an internal preoperative examination. The physician, in cooperation with the nurse, examines the patient on admission, draws information from the patient's medical records, and in the case of rehospitalization, from the HIS and internal preoperative examination. The physician will prepare an admission report, which will record the patient's previous illnesses, the current state of health, the reason for hospitalization, and all associated illnesses. Patients often bring a list of medications they are taking; the physician will consult with the patient on the completeness of this list. He or she detects then records possible allergies to drugs and food and other forms of intolerance or allergic manifestations. He or she is interested in the use of addictive substances, alcohol, and drugs of abuse and the frequency of their use. The patient signs informed consent that he or she consents to hospitalization and treatment. The admission report, which also includes the drug course (current drug record, which is updated once a day; if necessary, it is possible to insert notes, consultation examinations, orders for laboratory tests, and other information), will be prepared both in the HIS and in printed form. Each hospitalized patient has a printed medical record that is more comprehensive and contains more detailed information than the HIS records. It contains all the patient's health results, required examinations, daily drug courses, all daily updated nursing records, records of the patient's diet, and more. Based on the prescription of medications in the course, the nurse prepares and administers medications to the patient, and a sudden change in pharmacotherapy by the physician is reported to the nurse orally then recorded in the course. Some patients keep some of their medication with themselves and dose it themselves according to the physician's instructions.

MedRec by Pharmacists at Patient Admission

The patient is normally admitted to a planned hospitalization by the physician in cooperation with the nurse, as aforementioned. If the patient is older than 18 years, takes more than 3 medicines, speaks and understands the Slovak language, and has signed informed consent to participate in biomedical research, after being placed in a bed, a pharmacist comes to the patient's bedside and performs a MedRec. During the MedRec, the pharmacist creates a record of the patient's therapy, the original of which is placed in the patient's medical record, and a copy is placed in the pharmacist's records.

The steps in the MedRec involved the following. As part of the invitation for the hospitalization (by telephone or in writing), the patient was asked to bring all their medications and a complete medication list, which was used in consultation with the pharmacist regarding their proper use. The BPMH was completed.

The source of information can be a drug record, an admission report, hospital records, historical records from the HIS, or information from the patients or their family member. A BPMH is different and more complex than the routine history of primary treatment (which is often a rapid history of patient treatment). The BPMH includes the name of the medicine, dose, and frequency and administration route of the medicines that the patient is currently taking, although it may differ from what was actually written in the drug list.

The types of drugs that need to be recorded in the BPMH include prescription drugs, over-the-counter drugs, nutritional supplements, herbal medicines, medicinal teas, recreational drugs, and regular consumption of certain foods (eg, grapefruit). Special emphasis should be placed on specific forms of medicines, such as inhalers, eye drops, topical semisolid medicines, or medicines taken every few weeks (bisphosphonates).

One of the recorded parameters is patient understanding. This is evaluated in 3 steps and scored as 0 or 1: The patient knows (1) or does not know (0) the name of the drug, the patient knows (1) or does not know (0) the indication of the drug, and the patient knows (1) or does not know (0) the dosage of the drug. The 3-point scale was based on previously published studies by Cline et al [52], Boonstra et al [53], and Marfo et al [54], who evaluated patients' knowledge based on their understanding of the drug name, dosage, duration of treatment, indication, relationship of the drug to food, duration of therapy, or route

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of administration. If the patient was unable to attend the interview, other sources were used to obtain a medical history or to clarify conflicting information. Other resources should never be a substitute for a thorough conversation with the patient or family members.

Regarding verification and documentation of the BPMH, the BPMH list should be verified by more than one other source. Sources for the initial acquisition of an overview of pharmacotherapy are the admission report, the history of hospitalization, outpatient reports, HIS, and the course at admission.

According to the World Health Organization standard operating procedure, a retroactive MedRec model was used for our biomedical research. In a retroactive model, in accordance with the aforementioned method, the patient is admitted by a physician in cooperation with a nurse by default, and a drug course—a daily prescription of drugs for the patient – is created. In this case, the BPMH is determined after admission by a physician or nurse.

The result of the MedRec is a comparison of medicines prescribed to and actually used by patients (BMPH) with marked discrepancies.

During the process of obtaining the BPMH, the pharmacist informs patients to always share their doubts about the correct use of the medication with the medical staff.

MedRev With Pharmaceutical Intervention at Patient Admission

The basis for patient therapy optimization is the acquisition of the BPMH and patient factors, such as the reason for hospitalization, current health status, comorbidities, height, weight, heart rate, blood pressure, and the results of examinations of biochemical and hematological parameters.

The detected BPMH is written in the case report form. It is then analyzed in the context of the patient's overall health condition, and DRPs are identified. Each detected discrepancy is assigned an alphanumeric code according to the PCNE V9.00 classification. The patient's personal data are anonymized.

Discrepancies in therapy should be consulted with the treating physician within 24 hours of admission.

Evaluation of Therapy Based on DRPs and PCNE Classification

After receiving the BPMH and a detailed study of the reason for hospitalization, current medical condition, and any patient comorbidities, the pharmacist collects information about the patient's weight, height, heart rate, and blood pressure from the admission report. Subsequently, the results of biochemical and hematological examinations are studied. The pharmacist focuses on the results of examinations related to pharmacotherapy and the determination of the function of elimination organs. These are mainly the levels of serum potassium, serum creatinine, serum uric acid, liver transaminases, lipidogram, and C-reactive protein. Renal function is calculated based on the Cockcroft and Gault creatinine clearance estimate.

Duplicate Treatment

The pharmacist controls duplication in the drugs used, considering the use of the same substance in 2 drugs, use of the same substance in 2 dosage forms, use of 2 substances from the same pharmacological group, and double inhibition of the renin-angiotensin-aldosterone axis by angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers.

Duplicity is recorded in written form in the final evaluation of the patient's pharmacotherapy; duplication is discussed with the patient, who confirms or refutes the actual use of the duplicate drugs, and the most appropriate procedure is proposed in collaboration with the attending physician.

Indications of Used Drugs and Contraindications

The pharmacist checks the indications of the drugs used according to the patient's comorbidities. The pharmacist checks whether all comorbidities are treated according to evidence-based medicine and according to treatment procedures developed by local, national, or international authorities. The result of this step is the identification of missing drugs in the patient's pharmacotherapy.

Furthermore, drugs whose use has no clear indication are identified. In older adult patients (≥65 years), the pharmacist also considers the use of potentially inappropriate drugs. The pharmacist follows the EU (7)-PIM list [55], which was designed for patients aged 65 years and older. The result of this step is the identification of drugs that do not have a clear indication or are inappropriate due to the patient's age.

The pharmacist also checks whether the prescribed drug is appropriate for the specific patient.

Drugs that the patient should and should not take, drugs whose indications are not clearly known from the available data, and contraindicated drugs are recorded in the final evaluation of the patient's pharmacotherapy, in cooperation with the attending physician; subsequently, the most appropriate procedure is proposed.

Drug Management

The pharmacists verify compliance with maximum recommended doses, considering patient-specific factors, and records any excess in the pharmacotherapy evaluation. They assess the suitability of dosage forms, administration practices (including infusion components, timing, and food interactions), and screen for potential drug interactions using LexiComp and other resources, documenting any clinically significant findings. All observations and recommendations are reviewed with the attending physician to determine the appropriate course of action.

Adverse Drug Reactions

If a newly manifested ADR not documented in the patient's medical history is suspected, the pharmacist evaluates the degree of causality between the drugs used and the manifestations of the ADR, which is proven on the basis of laboratory parameters or the patient's subjective complaint. The pharmacist reports suspicions of ADR to the State Institute of Drug Control via an electronic form available from [56].

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ADRs are recorded in the final evaluation of the patient's pharmacotherapy.

The individual DRP findings shall be entered in the form as an appropriate code according to the PCNE classification [10].

The result of the pharmacist's intervention at patient admission is the completion of the MedRec form at admission and creation of an accurate list of medicines taken by the patient. All comments on pharmacotherapy with the proposed solutions are written in the form of a summary report and undergo consultation with the physician.

At Hospital Discharge

Current Condition at Patient Discharge

When discharging a patient, the attending physician evaluates the patient's state of health and prepares a discharge report with complete information about the procedures that the patient underwent during hospitalization. The discharge report also includes the current results of the patient's laboratory examinations, an overview of current pharmacotherapy, and recommendations to the patient's general practitioner. The nurse explains the regimen measures in relation to his or her state of health to the patient and gives the patient medication for the 3 days following discharge.

MedRec by Pharmacists at Patient Discharge

The pharmacist performs MedRec when discharging a patient from the hospital, similar to the process at admission. When evaluating a patient's pharmacotherapy on discharge from hospital, the BPMH obtained at the patient's admission will be used as a source of information. The BPMH is then compared with the list of medicines that are recorded in the release report. The pharmacist will compare 2 lists of medicines, focusing on the identification of DRPs with special regard to the re-introduction of the chronic therapy the patient was taking before hospitalization. As part of this research, the pharmacist met with the patient during his or her discharge from the hospital and discussed with him or her the management of further pharmacotherapy. Pharmacists provided an understandable summary list of a patient's medicines explaining the importance and the correct use of the medicine.

MedRev With Pharmaceutical Intervention at Patient Discharge

The pharmacist analyzes the pharmacotherapy in the context of the patient's state of health and the results of laboratory tests, similar to the patient's admission, as described in the previous sections. Detected DRPs are then consulted with the treating physician and recorded in the case report form.

The result of the pharmacist's intervention at discharge is the completion of the MedRec form for discharge and the documentation of all comments on pharmacotherapy in the form of a summary report. Discrepancies and comments are consulted with the physician.

The complete scheme of the procedure can be seen in Figure 1.

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Figure 1. Procedure scheme.

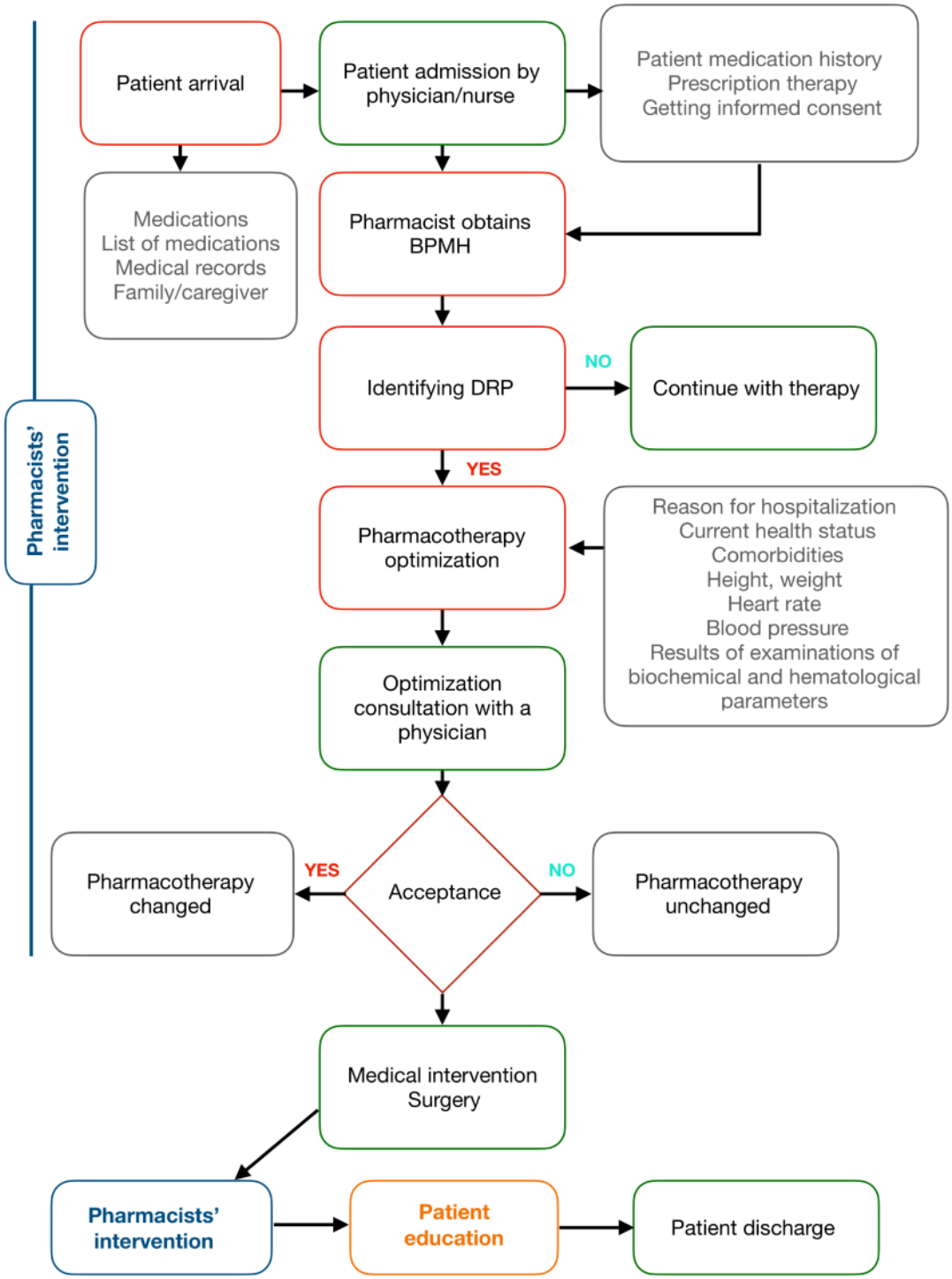

Ethical Considerations

Human Subject Ethics Review Approvals

The study was approved by the Ethics Committee of the National Institute of Cardiovascular Diseases (approval number 1625/21; May 26, 2021) and registered on ClinicalTrials.gov (trial registration number NCT04930302; June 16, 2021). All research procedures adhered to the ethical standards of the institutional and national research committees and were conducted in accordance with the 1964 Helsinki Declaration and its later amendments or comparable guidelines.

Informed Consent

Written informed consent was obtained from all participants before any research-related activities were initiated. The consent form, approved by the Ethics Committee, was provided in Slovak to ensure participants' understanding. By signing the consent form, participants consented to the publication and presentation of their pseudonymized data.

Privacy and Confidentiality

Patients' personal data were anonymized to ensure confidentiality. The Participant Identification Sheet was securely

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stored at the study center, alongside other documentation. Anonymized data were entered into the case report form in the MIA DMS online database, which operates within Europe.

Compensation Details

No compensation was provided to participants for their involvement in this study.

Results

This protocol outlines the planned study design and anticipated timeline for the PHAROS trial, aimed at evaluating the impact of pharmacist-led interventions on DRPs in patients undergoing vascular surgery. The key stages of the trial and their anticipated completion dates are described in the following sections.

Study Initiation and Recruitment

Patient recruitment began in September 2021 and was completed in August 2022. The target sample size of 100 patients was reached.

Data Collection

Data collection occurred continuously during each patient's hospital stay, including assessments at admission and discharge to document patient demographics, comorbidities, pharmacotherapy details, and DRPs. These data will help evaluate the prevalence and types of DRPs, intervention acceptance rates, and changes in patient understanding of pharmacotherapy.

Analysis and Reporting Milestones

For the initial data review, preliminary data analyses began in August 2023 to assess recruitment efficacy and data integrity. This phase includes an initial assessment of DRPs and intervention types recorded during patient admission.

The primary analysis, including full data analysis encompassing outcomes related to DRP reduction, intervention acceptance, and patient pharmacotherapy understanding, was completed in January 2024.

For the final report and dissemination, the study findings, including the impact of pharmacist interventions on patient outcomes, were compiled and prepared for dissemination by June 2024.

A timeline of the PHAROS trial (Figure 2) illustrates each phase of the study, from patient recruitment through final analysis and reporting.

These timeline indicators and progress markers will enable ongoing tracking of study completion and ensure that each stage of data collection and analysis aligns with the study's objectives.

Figure 2. Timeline of the PHAROS trial.

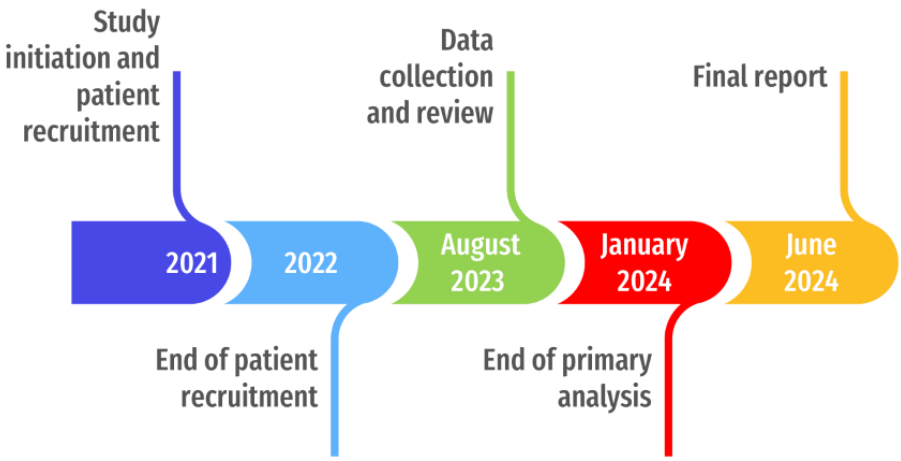

Statistical Methods

Continuous variables will be characterized as the mean with standard deviation. Categorical variables will be expressed as numbers and percentages.

To compare the number of drugs, active substances, and DRPs at hospital admission and discharge, the paired Wilcoxon signed-rank test will be used due to the non-normal distribution of differences between the 2 time points. Normality will be assessed with the Shapiro-Wilk test. To determine the effect size of the intervention, Cohen *d* will be calculated and categorized as small, medium, or large based on established intervals. Patients' understanding of their pharmacotherapy at hospital admission will be evaluated using a 3-point scale. The average score per medication will be calculated, categorizing patients into groups based on their understanding: good (2-3 points per medication), modest (1-2 points per medication), and poor (0-1 point per medication).

Discussion

Importance

The PHAROS study is the first prospective clinical trial in Slovakia to evaluate pharmacist-led interventions on DRPs in vascular surgery patients. Our findings add to the growing body of evidence that pharmacist involvement can reduce the prevalence of DRPs, improve patient understanding of medications, and enhance overall pharmacotherapy outcomes for hospitalized patients.

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Comparison With Prior Work

Several studies have examined the role of pharmacists in preventing and managing DRPs across various clinical settings [57], including vascular surgery. Hohn et al [45] and Martínez López et al [51] documented a decrease in DRPs due to pharmacist-led interventions, reporting an average of 1.3 and 1.7 DRPs per patient, respectively. These studies support the role of pharmacists in reducing DRPs and improving medication safety in hospitalized patients. Findings from Schmelzer et al [58] and other international studies also demonstrated a significant reduction in DRPs at discharge.

The impact of pharmacist-led interventions on vascular surgery patients specifically has not been extensively studied. However, studies in other settings, such as those by Hohn et al [45] and Rychlíčková et al [59], have shown positive outcomes from pharmacist interventions. Singh et al [60] highlighted the underprescription of statins in patients with peripheral artery disease, attributing this to clinician-related barriers such as concerns about adverse effects. The PHAROS study aims to contribute to this literature by demonstrating that pharmacist involvement in MedRec and MedRev supports DRP management and optimizes pharmacotherapy, underscoring the importance of pharmacist intervention in promoting guideline-adherent care.

An important aspect of the PHAROS study is its focus on patient education. Based on the prior literature, educating patients about their medications is strongly associated with better adherence and a reduction in DRPs [31,32,61,62]. Including patient education as part of the pharmacist's role is intended to support informed patient participation in their treatment.

Challenges and Barriers

Despite the promising outcomes of pharmacist-led interventions, challenges remain in their implementation. One significant barrier is resistance to change among health care professionals, especially in settings where the role of pharmacists in medication management is not well established. As noted by Hohn et al [45], physicians may be hesitant to accept pharmacist recommendations, particularly in complex cases involving polypharmacy and comorbidities. Successful pharmacist-led interventions require clear protocols, comprehensive training, and effective collaboration with other health care professionals. The lack of legislative requirements for MedRec and MedRev in Slovakia demonstrates the need for policy changes to integrate pharmacists systematically into patient care transitions. This is particularly important, as international guidelines, such as those from the European Association of Hospital Pharmacists [63], emphasize the role of MedRec in ensuring safe and effective care.

Future Directions

Building on the results of this pilot study, future research should seek to validate these findings through a larger, randomized controlled trial, which would allow for a more rigorous assessment of pharmacist-led interventions on DRPs. Such studies could incorporate a control group, a larger sample size, and postdischarge follow-up to evaluate long-term effects. Expanding research to diverse health care settings and patient demographics could provide insights into optimizing pharmacist interventions across various clinical contexts.

Limitations of the Study

Our study has several limitations. First, it was conducted as a single-center trial and performed in specific departments and with specific indications; therefore, the results may not be applicable under different conditions. Second, the study did not include a control group. Although all investigators were trained in all study processes, some degree of subjectivity is possible in the assessment of DRPs. Moreover, the number of patients was limited. However, trained hospital pharmacists strengthened the methodology used in our trial.

Conclusions

The study should determine that pharmaceutical care provided at hospital admission and at hospital discharge could reduce the prevalence rates of DRPs in our study setting. The pharmacist-led interventions upon hospital admission and discharge, followed by patient education, might be implemented in daily practice in health care in our hospital.

Acknowledgments

This study would not have been possible without the support of the Chief of the Vascular Surgery Department, Ján Tomka, MD, PhD, as well as the cooperation of the physicians from this department.

Data Availability

Only investigators from the National Institute of Cardiovascular Diseases have access to all patient data. They maintain an accurate and comprehensive list of biomedical research participants, along with the alphanumeric codes assigned to them, all documented in the "Participant Identification Sheet." Both the completed Participant Identification Sheet and all research data are securely stored. Anonymized personal data are entered into the case report form in the online MIA document management system (DMS) database and are accessible only to investigators. The data sets used and analyzed during the study are available from the corresponding author upon reasonable request.

Authors' Contributions

All authors contributed equally to the study conception and design. All authors read and approved the final manuscript. TT is responsible for the overall content as the guarantor.

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Conflicts of Interest

None declared.

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Abbreviations

ADR: adverse drug reaction
ATC: Anatomical Therapeutic Chemical Classification
BPMH: best possible medication history
DRP: drug-related problem
HIS: hospital information system
MedRec: medication reconciliation
MedRev: medication review
PCNE: Pharmaceutical Care Network Europe Association

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SQUIRE: Standards for Quality Improvement Reporting Excellence

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Protocol

Vaping, Acculturation, and Social Media Use Among Mexican American College Students: Protocol for a Mixed Methods Web-Based Cohort Study

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Abstract

Background: The tobacco industry has a history of targeting minority communities, including Hispanic individuals, by promoting vaping through social media. This marketing increases the risk of vaping among Hispanic young adults, including college students. In Texas, college enrollment among Mexican Americans has significantly increased over recent years. However, little research exists on the link between social media and vaping and the underlying mechanisms (ie, outcome expectations, attitudes, and beliefs) explaining how vaping-related social media impacts vaping among Mexican American college students. Moreover, there is limited knowledge about how acculturation moderates the association between social media and vaping. Hispanic individuals, particularly Mexican Americans, are the largest ethnic group in Texas colleges; thus, it is crucial to understand the impact of social media and acculturation on their vaping behaviors.

Objective: We outline the mixed methods used in Project Vaping, Acculturation, and Media Study (VAMoS). We present descriptive analyses of the participants enrolled in the study, highlight methodological strengths, and discuss lessons learned during the implementation of the study protocol related to recruitment and data collection and management.

Methods: Project VAMoS is being conducted with Mexican American students attending 1 of 6 Texas-based colleges: University of Texas (UT) Arlington, UT Dallas, UT El Paso, UT Rio Grande Valley, UT San Antonio, and the University of Houston System. This project has 2 phases. Phase 1 included an ecological momentary assessment (EMA) study and qualitative one-on-one interviews (years 1-2), and phase 2 includes cognitive interviews and a 4-wave web-based survey study (years 2-4) with objective assessments of vaping-related social media content to which participants are exposed. Descriptive statistics summarized participants' characteristics in the EMA and web-based survey.

Results: The EMA analytic sample comprised 51 participants who were primarily female (n=37, 73%), born in the United States (n=48, 94%), of middle socioeconomic status (n=38, 75%), and aged 21 years on average (SD 1.7 years). The web-based survey cohort comprised 1492 participants self-identifying as Mexican American; Tejano, Tejana, or Tejanx; or Chicano, Chicana, or Chicanx heritage who were primarily female (n=1042, 69.8%), born in the United States (n=1366, 91.6%), of middle socioeconomic status (n=1174, 78.7%), and aged 20.1 years on average at baseline (SD 2.2 years). Of the baseline cohort, the retention rate in wave 2 was 74.7% (1114/1492).

Conclusions: Project VAMoS is one of the first longitudinal mixed methods studies exploring the impact of social media and acculturation on vaping behaviors specifically targeting Mexican American college students. Its innovative approach to objectively measuring social media exposure and engagement related to vaping enhances the validity of self-reported data beyond what national surveys can achieve. The results can be used to develop evidence-based, culturally relevant interventions to prevent vaping among this rapidly growing minority population.

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KEYWORDS

vaping; social media; Mexican American; college students; marketing; acculturation; protocol; artificial intelligence

Introduction

Background

The tobacco industry has a history of targeting marketing campaigns toward specific minority groups [1,2]. In particular, Hispanic individuals, especially young adults and college students, are increasingly subjected to effective vaping promotions on social media, which raises their risk of e-cigarette use, commonly referred to as vaping [1,2]. Hispanic individuals are the largest and fastest-growing ethnic minority in the United States, comprising 19.1% of the total population, with 58.9% of this demographic being of Mexican heritage, primarily identifying as Mexican American [3]. In Texas, a majority-minority state with the second-largest Hispanic population in the United States, Hispanic individuals are the largest ethnic minority group, nearly 90% of whom are of Mexican heritage [4]. Moreover, the youthful profile of the Hispanic population, with approximately 50% aged <29 years, makes them a particularly appealing target for e-cigarette marketing [5,6]. One limitation of previous research is the study of Hispanic individuals as a homogeneous group. Despite variations in tobacco use behaviors by country of origin, there is a lack of ethnic-specific studies on Mexican Americans [7]. Moreover, little research has explored the link between social media and vaping among Hispanic college students even though national data show that they vape at rates comparable to those of their White peers and their use of social media is high [8].

Social media plays a crucial role in the acculturation process as it provides a platform for language practice, information seeking, and social interaction, all of which are integral to acculturation [9]. Social media facilitates cultural exchange by enabling users to connect, share content of cultural significance, and influence each other's perspectives, thereby playing a pivotal role in shaping evolving cultural norms, beliefs, and identities within communities [10]. Of concern, Mexican American college students who are less acculturated yet use English-language social media might be more prone than their more acculturated peers to adopt the intrapersonal outcome expectations (eg, "e-cigarettes help me look cool and stay slim"), social norms (eg, perceived peer and family use and e-cigarettes being socially acceptable), and attitudes and beliefs (eg, e-cigarettes are safer and more convenient than cigarettes) promoted on social media, which elevates their risk of vaping [10]. Therefore, it is crucial to understand how social media influences intrapersonal mechanisms and mediators and, in turn, vaping behavior among individuals with varying levels of acculturation. This knowledge is important to developing evidence-based, culturally relevant interventions aimed at preventing vaping among this rapidly growing, vulnerable minority population.

Objectives

The primary goals of Project Vaping, Acculturation, and Media Study (VAMoS) are to (1) identify mechanisms underlying vaping-related social media exposure and engagement and vape use among Mexican American young adults and (2) examine the role of acculturation as a moderator of these mechanisms. Project VAMoS has 3 aims, which will be implemented in 2 phases and addressed using multiple methods. Aim 1 seeks to characterize vaping-related social media and vape use from the perspective of Mexican American college students using ecological momentary assessments (EMAs) and one-on-one qualitative interviews and was completed in years 1 and 2 (phase 1). Aim 2 seeks to identify intrapersonal mediators of the relationship between exposure to vaping-related social media and subsequent vaping, and aim 3 seeks to determine the moderating role of acculturation on the direct and mediated paths of aim 2. Aims 2 and 3 are addressed using a 4-wave, biannual web-based survey in years 2 to 5 (phase 2).

Guided by social cognitive theory [11,12], we hypothesize that outcome expectations, social norms, and attitudes and beliefs will mediate the association between social media and vaping. Guided by acculturation theories [13,14], we further hypothesize that these mediated associations will be moderated by acculturation such that they will be stronger for those who use English-language media and for less acculturated students, including first-generation college students and female individuals [15,16]. Figure 1 presents the conceptual framework used to guide this study as well as the data collection timeline.

Figure 1. Data collection timeline and conceptual model.

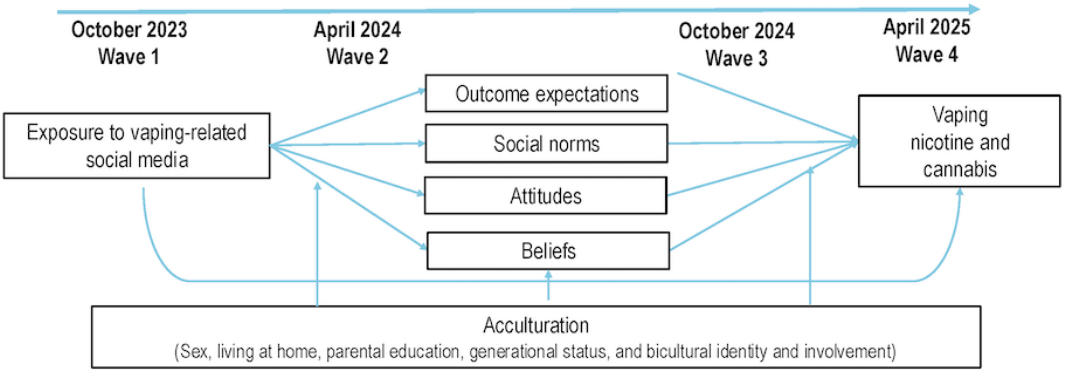

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Methods

Overview

Project VAMoS is a 5-year study examining the independent and combined influences of social media exposure and engagement and acculturation on the vaping behaviors of a longitudinal cohort of Mexican American college students aged 18 to 29 years in Texas. VAMoS is a study that is conducted entirely on the web, including participant recruitment, data collection, and incentive delivery to participants. In this paper, we describe the protocol and present the planned mixed methodologies to be used in Project VAMoS. We present descriptive analyses of the participants enrolled in the study, focus on methodological strengths, and discuss lessons learned during the implementation of the study protocol related to recruitment and data collection and management.

Sampling

Sampling frames were constructed by requesting names and email addresses of full- or part-time undergraduate students through Texas's Public Information Act from the public information officers at 6 universities (University of Texas [UT] Arlington, UT Dallas, UT El Paso, UT Rio Grande Valley, UT San Antonio, and the University of Houston System). These 6 universities were selected because they are designated as Hispanic-serving institutions and all have large proportions of Hispanic students [17].

We received 100% of the requested information from all 6 colleges. Simple random samples using probability-based sampling frames of student names were drawn from each of the 6 colleges to minimize self-selection bias and improve generalizability [18]. The EMA study, qualitative interviews, and web-based surveys were and will be conducted in English, consistent with the cross-sectional web-based survey we conduct annually at Texas colleges as part of the tobacco prevention program [19]. However, participating students had the option to submit vaping-related social media content in Spanish, and our team had expertise to analyze such data.

Study Procedure and Participants

Phase 1: EMA Study (Years 1-2; March 2023 to May 2023)

An introductory invitation email explaining the study's objectives was sent to random samples of 5000 students at 5 of the 6 universities in the study (UT Arlington, UT El Paso, UT Rio Grande Valley, UT San Antonio, and the University of Houston), totaling 25,000 students, between March 24, 2023, and May 3, 2023. Eligibility criteria for the EMA study included (1) self-identifying as Mexican Americans, (2) being a degree-seeking college student, (3) being aged between 18 and 25 years, (4) being an active user of at least 2 social media platforms in the previous 30 days, (5) vaping in the previous 30 days, and (6) owning a smartphone and being willing to download the LifeData RealLife Exp mobile app.

Those who met the eligibility criteria were guided to a web-based consent form, and those who consented completed a baseline survey administered using the Qualtrics platform (Qualtrics International Inc). After completing the baseline survey, participants were invited to download the EMA app onto their smartphones via a QR code granting them access to the EMA study. Participants were provided with detailed study instructions that explained data collection procedures and offered step-by-step tutorials on how to use the app's features to complete the daily EMAs.

In total, 2 types of EMA data were collected over the 14-day-period: daily diary and event-based assessments. Daily diaries were delivered at 10 AM each day on weekdays and at noon each day on weekends. In both cases, participants had 8 hours to complete the survey, with up to 3 reminders delivered every 2 hours. The mobile EMA system alerted participants to complete the surveys through an in-app push notification, which rang and made the phone vibrate. Event-sampling assessments were initiated by participants and were available via a button on the app home screen. Participants were instructed to initiate an event-based assessment when they (1) encountered a vaping-related post on social media or (2) vaped. For the vaping-related social media post assessments, participants had the option to upload a screenshot or photo of the post. All assessments were date and time stamped.

Qualitative Interviews (Years 1-2; May 2023 to November 2023)

A total of 37% (19/51) of the students who participated in the EMA also completed a 1-hour, one-on-one qualitative interview that occurred between May 2023 and November 2023. The purpose of the qualitative interviews was to more deeply understand how vaping-related social media to which participants were exposed and with which they engaged during the 14 days shaped their outcome expectations, social norms, and attitudes and beliefs (ie, mediators) and, in turn, their vaping behaviors. For example, we showed participants a set of three screenshots of vaping-related content, which was in both English and Spanish and included (1) an advertisement for various flavors of vapes, (2) a video outlining tips to quit vaping, and (3) a humorous skit about locating a friend based on the scent of their vape.

We probed their reactions to the intended message of the content; its appeal to both the interviewee and other e-cigarette users; and whether, how, and why the content enticed vaping. Findings from the qualitative interviews also provided the basis for the measures and items in the web-based survey, ensuring culturally relevant content and terminology. For example, we identified and verified the terminology used for social media concepts and vaping products and verified that the vaping products and social media platforms that we planned to assess (eg, Instagram, TikTok, and YouTube) were appropriate. If participants identified other platforms or newly emerging tobacco products, our plan was to also assess those.

The interviews were conducted in English by trained bilingual staff (to capture "Spanglish" terminology) who were either college students attending one of the participating colleges (ie, UT Rio Grande Valley) or recent graduates of the University of Texas Health Science Center (UTHealth) Houston School of Public Health. The interviews were digitally recorded and transcribed, and transcripts were analyzed using a thematic

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approach. Several members of our team audited the themes to ensure appropriate inferences. Each of the 19 participants was assigned a code number so that data from the EMA study and qualitative interviews could be deidentified. The code number was used to link data across the 14-day EMA study and the qualitative interviews.

Phase 2: Cognitive Interviews (Year 2; July 2023 to September 2023)

While designing the web-based survey, we conducted 1-and-a-half–hour cognitive interviews with 10 participants who had completed both the EMA and qualitative interviews. The purpose of the cognitive interview was to refine and finalize all measures and items for the web-based survey [20,21]. All cognitive interviews were conducted by trained staff through Microsoft Teams (Microsoft Corp) and were digitally recorded. We directed participants to complete the survey while on Microsoft Teams with both their own and project staff's cameras off and then let us know when they finished the survey; following completion, the staff walked through each question and the participants' answers, asking them to use the "think-aloud" method articulating their thought processes as each question was reviewed. Furthermore, the cognitive interviews incorporated specific, customized questions or "probes" regarding the survey questions. These probes yielded more detailed information than the think-aloud responses. This approach provided clarity on how participants formulated their answers as well as an estimate for approximate completion time.

4-Wave Web-Based Survey Study (Years 2-5; October 2023 Until 2025)

Following the incorporation of changes and recommendations from the cognitive interviews, we began to recruit for the web-based survey. An invitation email was sent to 165,966 undergraduate students across the 6 schools describing the study and providing a link with a brief eligibility screener survey between October 2023 and December 2023. Eligibility criteria for the survey included (1) self-identifying as Mexican American, (2) being a degree-seeking college student, and (3) being aged between 18 and 29 years. Those who met the eligibility criteria were guided to a web-based consent form that included the purpose and timeline of the study and described the incentive structure. Those who consented completed a baseline survey and established the cohort for Project VAMoS.

The survey was programmed in Qualtrics and was distributed using the built-in Qualtrics Mailer. Each participant received a unique link to the survey, which could only be completed once [22]. During data collection, participants' names, emails, and other information from the contact list were automatically saved to a secure server. Each participant was assigned a unique ID number, which allowed us to track student progress on each survey and match their data across waves without inclusion of personally identifying information in our survey database. Thus, we were able to track responses in progress and send reminders and thank-you messages to participants. In addition, this link automatically saved participants' data as they progressed through the survey. If they needed to leave the survey before finishing, a participant could return to it at any time before the survey closed. Participants who did not complete the baseline or wave-1 survey after receiving the initial email invite received up to 4 follow-up reminders to their school email addresses.

Measures

Phase 1: EMA Measures

Daily EMA measures captured data across 3 main constructs: acculturation, social media use, and vaping. For acculturation, participants provided information on their language preferences, engagement in cultural practices, and sense of ethnic identity. Regarding social media use, participants detailed how often they accessed social media per day, the time spent daily (in hours) on social media, the platforms they engaged with, the type of social media interactions they had (eg, comments, follows, likes, and shares), and their encounters with vaping-related content or advertisements. Participants also reported daily vaping behaviors, including frequency of use; device features; nicotine concentration; flavor preferences; use of other tobacco products, cannabis, and alcohol; and social contexts in which they vaped. All EMA questions were structured to capture participants' behaviors and experiences specifically for the previous day, allowing for a comprehensive understanding of their activities over a 24-hour period. Multimedia Appendix 1 shows the constructs assessed and example measures.

Qualitative Interview Guides

To provide a general outline for the qualitative interviews, we drafted a qualitative interview guide consisting of questions and follow-up probes to prime participant responses. The qualitative interview guide was informed by responses obtained from the EMA study. Participants were asked about vaping and use of social media. Probes sought to determine exposure to and engagement with vaping-related social media content over the previous 14 days and how this influenced their outcome expectations, social norms, and attitudes and beliefs (ie, mediators), subsequently affecting their vaping. After conducting 10 qualitative interviews, we observed that many participants disclosed vaping not only nicotine but also cannabis or tetrahydrocannabinol (THC), with some exclusively using cannabis or THC. Therefore, we revised the guide to explore the differences that participants perceived between vaping cannabis or THC and vaping nicotine. Specifically, these questions served to tease out distinctions in use patterns, contexts, and perceptions between the 2 substances. For example, we asked questions such as the following—"Are there places where and/or times when you use nicotine versus THC?"—to better understand the situational and behavioral differences in vaping these products.

Phase 2: 4-Wave Web-Based Survey Study

At wave 1 (baseline), participants completed a self-report survey consisting of 142 measures. Measurement selection was guided by the conceptual model in Figure 1, informed by the EMA and qualitative interviews, and refined through the cognitive interviews. Vaping measures were selected or adapted from national surveys, including the Population Assessment of Tobacco and Health Study, the Behavioral Risk Factor Surveillance System, the Youth Tobacco Survey, and the

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National Survey on Drug Use and Health [23-26] (Multimedia Appendix 1).

The constructs assessed included sociodemographic characteristics, susceptibility to vaping, patterns of nicotine and cannabis or THC use, symptoms of dependence, cessation, outcome expectations from vaping, prevailing social norms, attitudes and beliefs, exposure to and engagement with social media, social media use patterns, and potential problems with social media [27]. We also assessed acculturation using proxy measures such as country of birth [28] and scaled measures such as the American Identity Measure [29-31] and included correlates of quality of family interactions and relationships [32]. Covariates assessed confounders and included use of other tobacco products and alcohol, experiences of racial or ethnic discrimination [33], and symptoms of depression [34] and anxiety [35].

At wave 2, we made several revisions. First, we shortened the survey by removing all items that would not change over time, such as sex at birth. We also did not ask participants to respond to "ever use" items at wave 2 (eg, ever used e-cigarettes) if they responded affirmatively at wave 1. Second, we included a limited number of new items; for example, we collected participants' race as defined by the US Census Bureau and intrapersonal measures of impulsivity, sensation seeking, and social anxiety [36-39]. Third, we asked participants to provide their personal social media handles or usernames for YouTube, Instagram, X (formerly known as Twitter), and Reddit to objectively assess the vaping-related social media content to which participants were exposed. We also asked participants to share 3 subreddits to which they subscribed and with which they frequently engaged also for objective assessment of vaping-related social media content. Consistent with our previous research [40,41], these data will be collected via the YouTube application programming interface (API) and web scraping for Instagram and X [42]. We will search for publicly available posts, videos, and hashtags with which our participants engage. We will not have access to the posts that participants see in their feeds or "for you" pages as these are not publicly available data and, thus, are outside the scope of our institutional review board (IRB) protocol.

Before analysis, all personally identifying information will be replaced with a unique ID number that matches the participants' ID number for the web-based survey, allowing us to link all the data for analysis. Custom-developed Python scripts (Python Software Foundation) will be used for API data collection from YouTube, and the Selenium toolkit [43] or Zeeschuimer [44] will be used for all browser-based web scraping (Instagram, YouTube, and X). The Python Reddit API Wrapper [45] will be used to collect data from Reddit. Depending on the platform, the date range of available posts will vary. We will scrape as much publicly available data as possible. The collected social media data will be studied computationally (with manual content analysis used to check validity). In terms of the former, we will use topic modeling, a computational natural language processing technique that we have successfully used in previous work [46], to identify statistically significant themes from (1) the posts of each user, (2) the aggregated posts of all users, and (3) the posts from subreddits that users follow and that they provided to us. Particularly for the latter, the data will be voluminous. Previous work has established the utility of generative artificial intelligence as a topic modeling tool to discover latent themes in large volumes of unstructured textual data [47]. We will adapt prompts developed and tested by others for topic modeling using ChatGPT (OpenAI) [48] to provide up to 5 themes for each user, 15 themes for all aggregated users, and 15 themes for each subreddit. We will then conduct a manual content analysis of a random sample of 150 posts from the aggregated posts of all users and the posts from subreddits that users follow to evaluate the robustness of the ChatGPT-based results. Our use of generative artificial intelligence will provide objective assessments of vaping-related social media content, which will allow us to characterize content that appeals to and entices Mexican American college students to use vapes.

Ethical Considerations

Human Participant Ethics Review Approvals

The IRB at UTHealth Houston (HSC-SPH-19-0796) approved all aspects of the study protocol. UT Austin approved the reliance on the UTHealth Houston IRB.

Informed Consent

All eligible participants in this study provided electronic informed consent before their participation in the 2 phases. Participants were informed about the study's objectives, procedures, potential risks, and benefits. They were informed that their participation was voluntary and that they could withdraw from the study at any time.

Privacy and Confidentiality

All collected data were deidentified to protect participants' privacy at the baseline wave. Personal information is removed before analysis, and the data are securely stored, with access restricted to authorized personnel.

Compensation Details

Phase 1

Participants who completed the EMA study were compensated with e-gift cards (US $10-$50) based on the percentage of daily diary assessments completed over the study period, with a minimum requirement of 50% of assessments completed to receive an incentive. Those who completed at least 7 daily diaries over the 14-day period received US $10 in e-gift cards (5/51, 10% of the participants), those who completed at least 10 daily diaries received US $35 in e-gift cards (13/51, 25%), and those who completed ≥13 of their daily diary EMAs received US $50 in e-gift cards (28/51, 55%). Participants were not compensated for event-based EMAs so as not to encourage false reporting of vaping or encounters with vaping-related social media content. Participants who completed the qualitative interviews were compensated with a US $50 e-gift card. Individual incentives were distributed within 2 weeks of completing the EMA and qualitative interviews.

Phase 2

Participants who completed the cognitive interviews were compensated with a US $50 e-gift card, which was distributed within 2 weeks of completing the interview. Individual

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incentives were and will be offered at each of the 5 waves of the web-based survey. Students receive a US $25 e-gift card for completing each of the first 4 waves (totaling US $100) and a larger e-gift card of US $30 for completing the fifth and final wave. In addition, to maximize retention, we send an infographic with preliminary results between each survey (see Figure 2 for the infographic distributed between waves 1 and 2). Individual incentives are distributed within 2 weeks of survey completion.

Figure 2. Infographic distributed between baseline and wave 2 of the web-based survey.

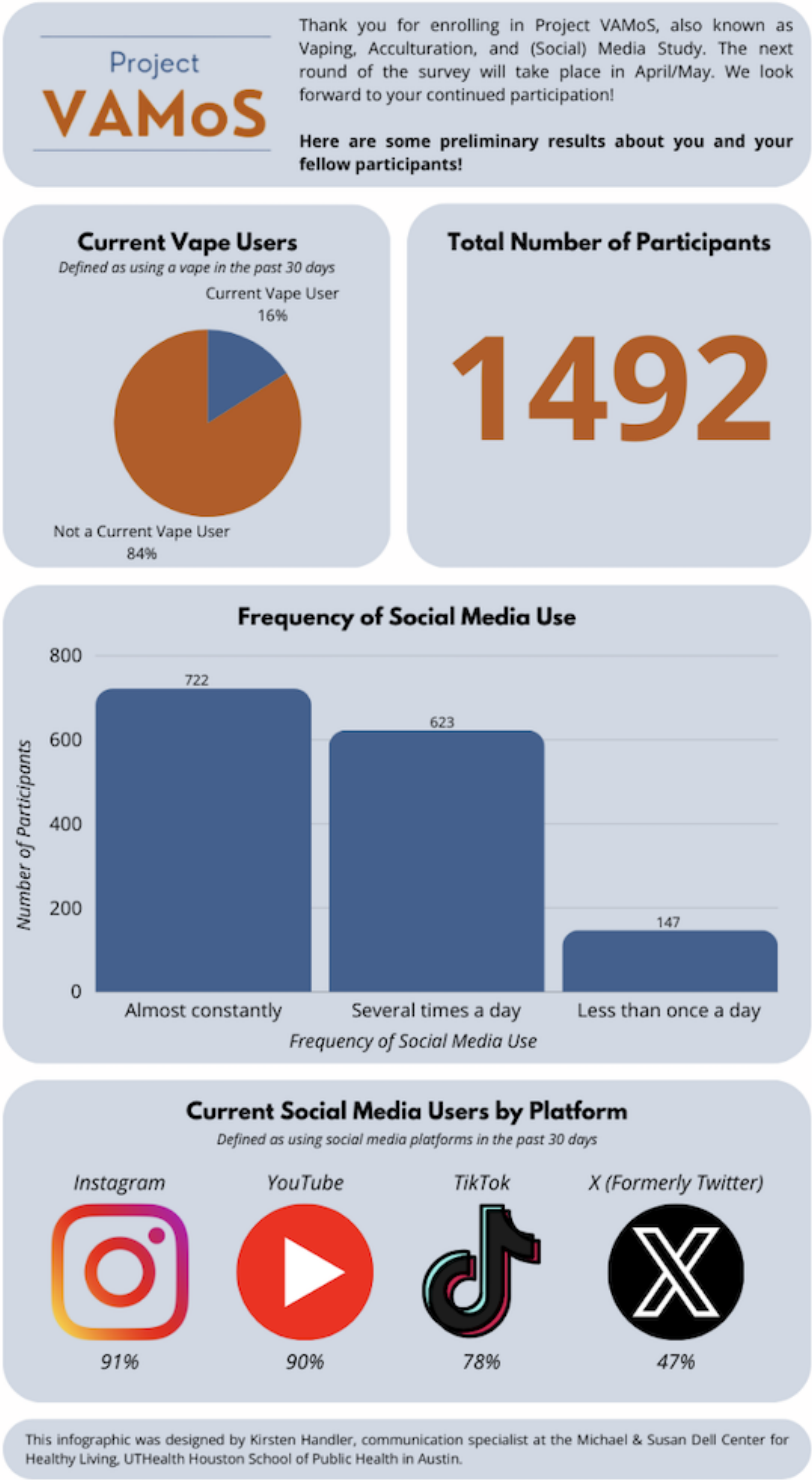

Data Integrity and Security

We used rigorous protocols and advanced security measures to protect the integrity of the web-based survey data against bots and fraudulent respondents. First, we created a contact list with email addresses provided by each college and then distributed the survey using a unique, 1-time-use link for each participant in Qualtrics [22]. This setting prevented multiple survey completion attempts from the same individual by placing a

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cookie on the participant's browser when they submitted a response. Participants are only able to complete the survey once; if the respondent clicks on the survey link after completing it, the presence of the cookie will prevent them from beginning a new survey. In addition, we incorporated a Completely Automated Public Turing Test to Tell Computers and Humans Apart (CAPTCHA) to ensure that surveys are completed by humans, not automated bots. Other strategies used to maximize the validity of the web-based survey data include the use of skip patterns within and across waves, which minimize participant fatigue and eliminate inconsistent responses; the use of "soft prompts" in most survey pages so that participants who skip questions are asked to verify their intent to leave the question blank; and the display of a limited number of items per screen or page [49,50]. In addition, participants are given the option to review and modify their responses using a Back button to enhance data accuracy. At wave 2, we added a human and attention check item to further ensure data validity and reliability [49].

Data security in Qualtrics is supported through advanced technological measures and robust policy enforcement. Qualtrics uses transport layer security encryption (also known as HTTPS) for all transmitted data. Qualtrics services are hosted by trusted data centers that are independently audited using the industry standard Statement on Standards for Attestation Engagements 18 method [49]. Access to datasets containing personal or identifying information is strictly limited to authorized members of the research team. These individuals undergo training in data privacy, confidentiality, and security protocols. Furthermore, they must use secure, complex passwords to access the Qualtrics data servers.

Final Data Quality Checks

Additional data quality checks were and will continue to be implemented to ensure the highest-quality survey data. Our team thoroughly reviews the survey responses for evidence of poor data quality. For example, we search for discrepancies in responses, such as participants providing contradictory answers to questions that should logically correlate or displaying a potentially problematic pattern of responses (eg, straight lining or selecting the same answer option several times in a row and a completion time of <10 minutes). Despite the exclusion of 0.2% (4/1824) of the participants at wave 1 due to these quality concerns, these participants received their incentive for taking part in this phase of the survey after we verified that a proper email address had been provided.

Maximizing Retention

To optimize retention across all waves of data collection, our team (1) fosters participant identification with the study by using our project name on all materials and correspondence [50-52]; (2) makes participation convenient by allowing participants to respond to the survey on a computer, smartphone, or other personal devices anywhere and at any time during the survey period [50]; (3) shares key study results via an infographic every 6 months; (4) sends multiple reminders (starting at wave 2, we sent reminders via email and SMS text message); and (5) keeps the survey open for up to 6 weeks to accommodate students' school and work schedules.

Results

Overview

Funding for Project VAMoS began in August 2022 and will conclude in March 2027. Data collection for phase 1 (EMA and qualitative interviews) was completed by June 2023. Phase 2, wave 1, was completed between November 2023 and December 2023; wave 2 was completed between April 2024 and May 2024. Wave 3 was completed between October 2024 and November 2024, and wave 4 will be completed between April 2025 and May 2025 (Table 1).

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Table 1. Vaping, Acculturation, and Media Study timeline. Timeline: August 1, 2022-March 31, 2027.

	Year 1 (2022-2023)		Year 2 (2023-2024)		Year 3 (2024-2025)		Year 4 (2025-2026)		Year 5 (2026-2027)	
	August-January	February-July	August-January (wave 1)	February-July (wave 2)	August-January (wave 3)	February-July (wave 4)	August-January	February-July	August-January	February-March
Phase 1: survey development and qualitative interviews										
Survey development	✓	✓								
Ecological momentary assessment		✓								
Qualitative interviews		✓	✓							
Phase 2: cognitive interviews and data collection										
Cognitive interviews		✓	✓							
Survey refinement		✓	✓							
Recruitment of participants			✓							
Survey data collection			✓	✓	✓	✓				
Data collection from social media				✓	✓	✓	✓			
GenAI[a] classification					✓	✓	✓	✓	✓	
Participant retention				✓	✓	✓				
Cleaning and analyzing data		✓	✓	✓	✓	✓	✓	✓	✓	✓

[a]GenAI: generative artificial intelligence.

EMA Eligibility and Completion Rates

In spring 2023, a total of 25,000 invitations were sent to potential participants, and 1116 (4.5%) students were screened to participate in the EMA study, of whom 113 (10.1%) were eligible and 79 (7.1%) completed a baseline survey that collected information on their demographics, social media use, and tobacco use behaviors. Of the 79 eligible participants, 24 (30%) did not proceed with the EMA study, and 4 (5%) were dropped due to inactivity (ie, did not complete the daily assessments). Thus, 45.1% (51/113) of the participants took part in the 14-day EMA study to address aim 1 (Figure 3). Completion rates were calculated to determine the feasibility of EMA as a means of obtaining daily data among Mexican American college students. Of a possible 714 prompts, a total of 608 (85.2%) were sent to participants over 14 days; this discrepancy is due to some participants disabling the LifeData app before the study concluded, meaning that they were not able to receive further prompts. Of the 608 prompts sent, we received 583 (95.9%) complete responses. Of the overall sample of 51 participants, 5 (10%) completed at least 10 daily diaries, 13 (25%) completed at least 11, and 28 (55%) completed ≥13 of the daily diary EMAs. The average completion rate was 83.2% (SD 24.9%; range 7%-100%).

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Figure 3. Flow diagram of ecological momentary assessment (EMA) participant recruitment.

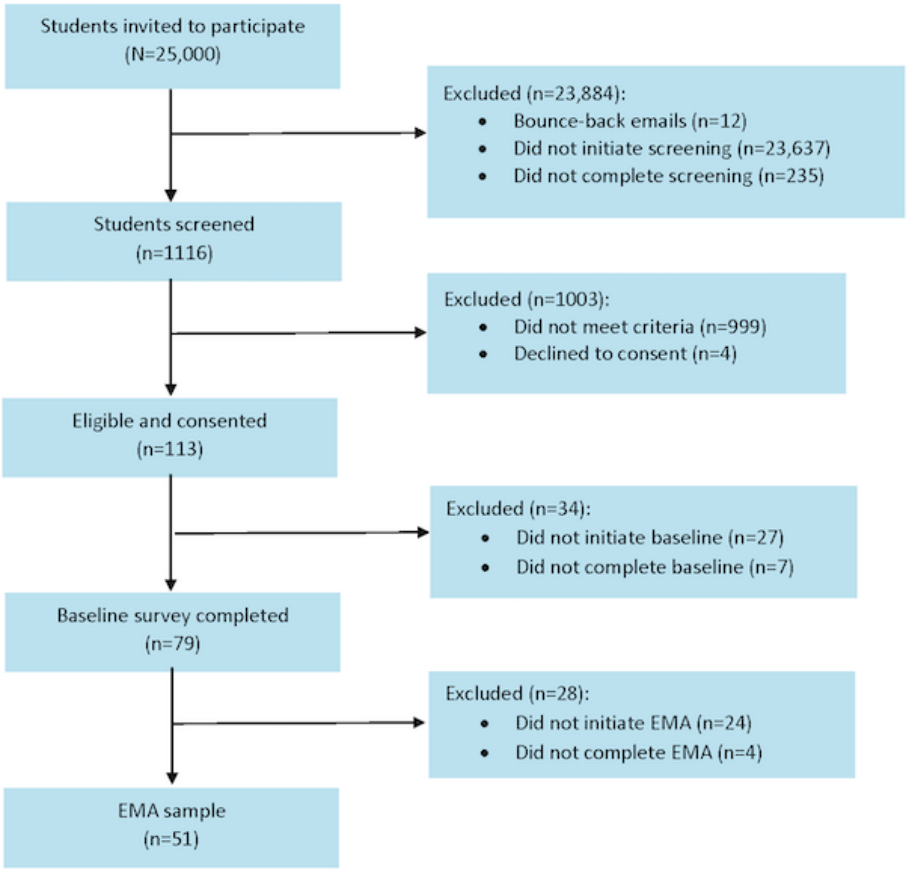

4-Wave Web-Based Survey Eligibility and Retention Rates

In fall 2023, a total of 165,966 invitations were sent to potential participants, and 7798 (4.7%) students were screened to participate, of whom 1824 (23.4%) were eligible (Figure 4). Of those 1824 eligible participants, 26 (1.4%) declined to consent, 4 (0.2%) were excluded due to poor-quality data, 22 (1.2%) did not meet the age criteria and were excluded, and 280 (15.4%) did not complete the survey. Thus, 81.8% (1492/1824) of Mexican American students were recruited from all 6 participating universities to establish our cohort and address aims 2 and 3 (Figure 4). Of the baseline cohort, the retention rate in wave 2 was 74.7% (1114/1492).

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Figure 4. Flow diagram of web-based survey participant recruitment.

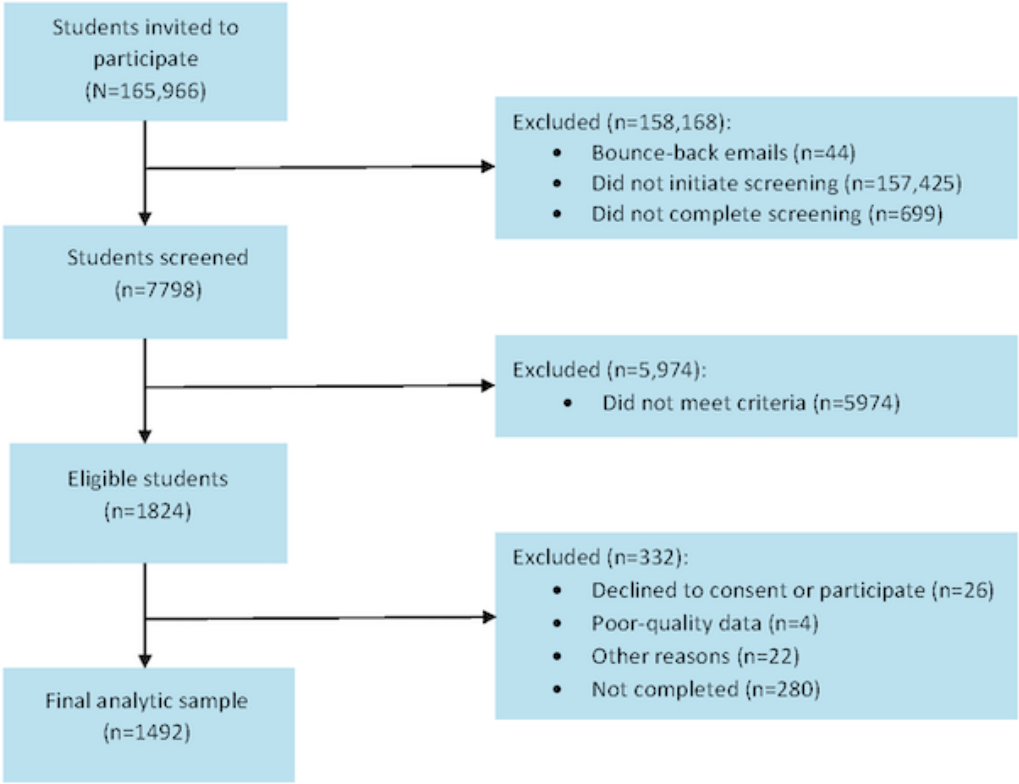

Sample Characteristics

For the purposes of this paper, descriptive statistics were used to summarize the characteristics of the EMA study participants (Table 2) and the baseline characteristics of the participants who form the cohort for the web-based survey (Table 3). The final EMA analytic sample comprised 51 current vaping and social media users who were of Mexican American heritage. Participants (Table 3) were primarily female (37/51, 73%), born in the United States (48/51, 94%), of a middle socioeconomic status (38/51, 75%), and aged 21 years on average (SD 1.7 years). The final sample for the web-based survey included 1492 participants who were of Mexican American; Tejano, Tejana, or Tejanx; or Chicano, Chicana, or Chicanx heritage. Participants (Table 3) were primarily female (1042/1492, 69.8%), born in the United States (1366/1492, 91.6%), of a middle socioeconomic status (1174/1492, 78.7%), and aged 20.1 years on average (SD 2.2 y).

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Table 2. Descriptive statistics for the ecological momentary assessment sample (N=51).

Characteristic	Values
Age (y), mean (SD)	21 (1.7)
Sex, n (%)	
Male	14 (27)
Female	37 (73)
Country of birth, n (%)	
United States	48 (94)
Mexico	3 (6)
Socioeconomicstatus, n (%)	
Low (1-3)	4 (8)
Middle (4-7)	38 (75)
High (8-10)	9 (18)
Socioeconomic status, mean (SD)	5.9 (1.7)
Federal Pell Grant, n (%)	
Yes	40 (78)
No	11 (22)
School attended, n (%)	
UT[a] Arlington	11 (22)
UT El Paso	12 (24)
UT San Antonio	10 (20)
UT Rio Grande Valley	10 (20)
University of Houston System	8 (16)

[a]UT: University of Texas.

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Table 3. Descriptive statistics for the survey sample at wave 1 (N=1492).

Characteristic	Values
Age (y), mean (SD)	20.1 (2.2)
Sex, n (%)	
Male	450 (30.2)
Female	1042 (69.8)
Country of birth, n (%)	
United States	1366 (91.6)
Mexico	114 (7.6)
Other	12 (0.8)
Socioeconomicstatus, n (%)	
Low (1-3)	260 (17.4)
Middle (4-7)	1174 (78.7)
High (8-10)	56 (3.8)
Socioeconomic status, mean (SD)	4.9 (1.5)
Federal Pell Grant, n (%)	
Yes	474 (31.8)
No	1018 (68.2)
School attended, n (%)	
UT[a] Arlington	264 (17.7)
UT El Paso	240 (16.1)
UT San Antonio	405 (27.1)
UT Rio Grande Valley	321 (21.5)
University of Houston System	195 (13.1)
Year in college, n (%)	
Freshman	522 (35)
Sophomore	368 (24.7)
Junior	295 (19.8)
Senior	307 (20.6)

[a]UT: University of Texas.

Discussion

Expected Findings

Project VAMoS is one of the first longitudinal mixed methods research projects to explore the influences of social media and acculturation on vaping behaviors focusing exclusively on Mexican American college students. The results of this project will provide evidence for the roles of intrapersonal mediators (eg, outcome expectations and social norms) in the associations between vaping-related social media content and subsequent vaping. The results will also determine the moderating role of acculturation in the association between vaping-related social media content and subsequent vaping, as well as in the mediated paths between vaping-related social media content and subsequent vaping. In turn, results can inform the tailoring of culturally relevant interventions and the development of countermarketing policies to prevent vaping among Mexican American college students [53].

Project VAMoS is innovative in 3 key areas. First, unlike many studies that consider Hispanic individuals as a homogeneous group, this project specifically focuses on Mexican Americans, acknowledging the diversity within this population, particularly in tobacco use patterns related to country of origin and acculturation levels [54]. Second, the project delves into the underlying mechanisms or mediators—such as outcome expectations, social norms, and attitudes and beliefs—that influence how exposure to vaping-related social media content affects vaping behavior. These mediators are identified through an EMA study and one-on-one qualitative interviews and are empirically examined in a comprehensive, 4-wave survey study. Finally, in addition to subjective assessments, the project conducts objective assessments of the social media content that participants actually view and engage with on popular platforms

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such as Instagram, TikTok, and YouTube. This approach minimizes the biases often associated with self-reported data [55].

Refining and Finalizing the Web-Based Survey

Some items were developed or refined based on findings from the EMA study and one-on-one interviews and then tested through cognitive interviewing to ensure their appropriateness for the study population [11,12]. For example, given the diverse range of substances that can be vaped, we incorporated options such as cannabis, THC, or delta-9; delta-8 THC; cannabidiol; caffeine; essential oils; vitamins; and more to include more potential vaping choices. In addition, we refined survey questions to ensure that they specifically addressed the substances that participants are vaping by including the terms "with nicotine" or "with cannabis/THC" without assuming exclusive consumption of either substance. As another example, we added response options such as "I do not know" or "neutral," along with time frames such as "When you were younger?" or "currently" to some acculturation measures. Moreover, we amended and will continue to amend items that are and are not included in subsequent waves in response to findings from the baseline survey wave. We will also add items in response to changes in the marketplace, such as the introduction of a new vaping device type, or in the policy landscape, such as a state or federal ruling regarding vapes or the marketing and promotion of these products.

Items were also added in response to the 2023 Surgeon General Report titled Social Media and Youth Mental Health [56], which concluded that there are gaps in current knowledge related to "the mental health impacts posed by social media" and that, currently, we cannot conclude that social media is sufficiently safe for young people. Accordingly, at wave 1, we assessed symptoms of depression, suicidal ideation, and anxiety [34,35]. At wave 2, we added measures to assess sensation seeking and impulsivity [38,39]. Symptoms of depression and anxiety increase risk of vaping both nicotine and cannabis or THC [57,58], whereas sensation seeking is associated with the uptake of vaping nicotine [59,60] and impulsivity increases risk of current vaping [61]. Therefore, the inclusion of these mental health and personality constructs complements existing measures assessed in Project VAMoS and will enable us to examine their role as potential mediators and moderators of the association between social media use and vaping.

Lessons Learned

Recruiting participants to join the EMA took more time than planned. Thus, we revised the eligibility criteria from vape use in the previous week to use in the previous 30 days. Similarly, recruiting participants to join the web-based survey took longer than planned; thus, we expanded the age range eligibility criteria from 18 to 25 years to 18 to 29 years and expanded recruitment from freshman students to all undergraduate levels, and we sent up to 4 email reminders rather than just 3. However, recruitment for the EMA study was completed in 6 weeks, and recruitment for the web-based survey was completed in 8 weeks. These adjustments broadened our participant pool, thereby creating a more representative cohort of college students. These challenges might be due to the specific nature of the inclusion criteria, such as being Mexican American [62]; potential hesitancy among young adults to participate in substance use research studies [62-65]; or the omission of incentive details from the invitation emails sent to participants to comply with IRB requirements.

This project provides an opportunity to better understand how Mexican American college students self-identify across racial categories. In wave 1, a total of 78.2% (1167/1492) of the participants identified solely as Hispanic when responding to a combined race and ethnicity question, whereas only 20.2% (301/1492) specified their race (data not shown). In response, at wave 2, we adopted a best practice approach aligning with the US Census Bureau's guidelines [66,67]. Specifically, we separated the race and ethnicity question into 2 items on the survey to allow participants to identify with a specific race while also recognizing their Hispanic ethnicity. Such an approach ensures that our data more accurately reflect the diverse racial backgrounds within the Mexican American population, enhancing our understanding of the associations among race, ethnicity, and social factors in the Mexican American community [66,67].

Strengths and Limitations

This project has many strengths. A major strength is the focus on Mexican American college students. Most studies have examined Hispanic populations as a single group, overlooking the differences in vape use patterns influenced by country of origin and acculturation levels. In addition, the Mexican American population in Texas is on the rise, with an increasing number of young individuals from this group enrolling in college annually [68]. Another major strength is the innovative approach in objectively measuring both exposure to and engagement with social media related to vaping. These objective assessments optimize the validity of self-reported social media exposure and engagement data and represent a distinct advantage that cannot be replicated by national surveys such as the Population Assessment of Tobacco and Health Study [23]. Furthermore, our EMA study and in-depth semistructured interviews enhance our research by enabling us to uncover culturally pertinent terms and concepts for evaluation in our web-based survey. Finally, the longitudinal design of our web-based survey allows for mediation tests to identify the intrapersonal factors that explain whether and how baseline levels of vaping-related social media content impact subsequent vape use at follow-up [69].

The project is not without limitations. First, we focused on college students, which limits generalizability. Nonetheless, this drawback is somewhat mitigated by the rapidly growing rate of college enrollment among Mexican American young adults. Second, we only recruited participants from Texas. However, Texas is a majorly minority state with the second-largest Hispanic population in the United States, predominantly consisting of Mexican Americans [4]. Moreover, Texas has the second-largest population of Hispanic college students in the United States [68]. This demographic profile enables us to concentrate on the largest Hispanic subgroup in the country.

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Implications

The results of this research will offer unique insights into the prevalence, patterns of use, and determinants contributing to vaping among Mexican American college students. This information will inform the development of evidence-based, culturally relevant prevention interventions and policies specifically for the growing population of Mexican American college students. Moreover, results from mediation analyses will pinpoint the most effective intervention targets (namely, significant mediators), and the outcomes of such analyses will highlight which subgroups (namely, significant moderators) are most at risk from the impacts of exposure to and engagement with vaping-related social media content.

The results gathered from the EMA study, in-depth semistructured interviews, and objective assessment of social media content will reveal the vaping messaging that attracts Mexican American college students to vaping and influences them to vape. These insights will then serve as a foundation for developing economical counteradvertising and health messaging strategies. These strategies can be effectively disseminated through social media platforms to reduce vape use among Mexican American college students, thereby lowering their risk of tobacco-related morbidity and mortality. Finally, research in this area contributes to the broader goal of health equity by ensuring that the health needs of ethnic minority groups are adequately addressed. By understanding and addressing the specific health behaviors and their determinants within minority communities, public health initiatives can move toward reducing health disparities.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are not publicly available as the study is ongoing but are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Examples of ecological momentary assessment and web-based survey measures.
[DOCX File , 23 KB - resprot_v14i1e63584_app1.docx]

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Abbreviations

API: application programming interface
EMA: ecological momentary assessment
IRB: institutional review board
THC: tetrahydrocannabinol
UT: University of Texas
UTHealth: University of Texas Health Science Center
VAMoS: Vaping, Acculturation, and Media Study

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Protocol

Exploring Climate Change's Impact on the Cardiopulmonary Health of Adults Living in the Canton of Valais, Switzerland: Protocol for a Development and Usability Pilot Study

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Abstract

Background: Climate change is affecting public health and well-being. In 2016, Swiss emergency departments (EDs) treated 1,722,000 cases, with 4718 daily admissions. In 2023, the ED of Sion Regional Hospital recorded 75,000 consultations. The links between climate change and health are complex, necessitating urgent research on its impact on cardiopulmonary health in Valais, Switzerland. Raising awareness among frontline professionals is crucial for developing health promotion and disease prevention strategies.

Objective: This study explores the preliminary effects of climate change on cardiopulmonary health in Valais and assesses adult patients' knowledge of its health consequences. Findings will inform adaptations in patient care, health promotion, and disease prevention at Sion Hospital's ED. The feasibility of patient selection and data collection will also be evaluated.

Methods: Using a convergent, parallel, mixed methods design, data will be collected from September 21, 2024, to September 20, 2025, with a target sample of 60 patients. The quantitative phase will examine patient recruitment feasibility, consultation reasons, and triage levels, correlating them with climate variables (temperature, nitrogen dioxide, particulate matter, sulfur dioxide, and ozone). It will also analyze sociodemographic profiles. The qualitative phase will explore patients' knowledge of climate change and its potential links to their ED visits. The feasibility and acceptability of the study process will be assessed. The protocol follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) Extension for Pilot and Feasibility Trials.

Results: Data collection started on September 21, 2024, following the approval by the ethical commission. Data collection will take place over 1 year, until September 20, 2025.

Conclusions: This study will test the feasibility of a larger investigation and examine potential associations between Valais' changing microclimate and population health. Findings will establish patient profiles and explore their perceptions and knowledge of climate change, informing future health interventions.

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KEYWORDS

climate change; global warming; emergency department; emergency nursing; sustainable care; ecological medicine; cardiopulmonary; cardio health; Valais; Switzerland; pilot study; study protocol; humanity; air pollution; impact; comorbidities; adults; mixed methods design; feasibility; health promotion; disease prevention; acceptability

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Introduction

The planet's climate crisis is directly damaging human health. Globally, 3.6 billion people live in areas highly sensitive to climate change. Rising temperatures, extreme weather events, air pollution, and the spread of infectious diseases are just some of the major health threats exacerbated by climate change [1]. Climate change has many other direct and indirect effects on human health, including physical and mental disorders. Projections for 2025 estimate that climate change will be responsible for 250,000 additional deaths per year between 2030 and 2050 [2,3]. Worldwide, 9 out of 10 people breathe poor-quality air, and more than 7 million people die every year because of this pollution [4]. Greenhouse gas emissions, particulate matter (PM), nitrogen dioxide (NO_2), tropospheric ozone (O_3), and sulfur dioxide (SO_2) are the pollutants with the most significant impact on human health. There has been a concurrent 57% increase in heatwave episodes since 2010. Heat-related deaths among people >65 years of age have risen by 70% in 2 decades [5].

In recent years, several studies have been conducted on the various components of the relationship between health and climate change in Switzerland, particularly via the Swiss Study on Air Pollution and Lung and Health Diseases in Adults cohort [6]. A review of 22 studies by Cicci et al [7] highlighted positive associations between high temperatures and ischemic heart disease, acute myocardial infarction, the risk of congestive heart failure, and the number of emergency department (ED) consultations. Indeed, increasing numbers of ED admissions [7,8] hospitalizations for respiratory and cardiovascular diseases have been linked to nonoptimal temperatures and exposure to pollutants and unconventional natural gas development, while more cases of decreased lung function or chronic obstructive pulmonary disease have been linked to exposure to SO_2, NO_2, and PM_{10} [9-11]. Finally, climate change is leading to global warming, that is, the phenomenon of increasing average air temperatures near the Earth's surface [12]. This prolongs plant growth and pollination seasons and often increases the overall amount of pollen produced. This phenomenon can lead to increased respiratory allergies, rhinitis, and asthma in sensitive patients with immunoglobulin E–mediated allergic reactions [13,14].

In addition to its impacts on health, climate change can compromise many social determinants of good health, exacerbating the inequalities in morbidity and mortality that particularly threaten vulnerable populations. Indeed, environmental risk factors, such as demographics, geography, biology, health, sociopolitical and socioeconomic status, health system capacity, and overall equity, are responsible for 80% of common illnesses and 25% to 33% of the total disease burden [15]. Vulnerability has 4 primary features: integrity (a person's sense of soundness), challenge (vulnerability is experienced when there is a perceived challenge to one's integrity and uncertainty about how to respond to it), capacity for action (the perceived ability to withstand, integrate or cope with the challenge), and multidimensionality (how vulnerability varies from one person to another and from one experience to another) [16,17]. Older adults, infants from the age of 0-1 year, people with chronic diseases, those living in urban environments with low socioeconomic status or experiencing social isolation [5,18], and people living at higher altitudes [7] are all considered to be population groups vulnerable to climate change. Finally, regarding biological sex, Bayentin et al [19] and Gebhard et al [20] found that hospitalizations for ischemic heart diseases and myocardial infarction were higher among younger women than among younger men. Women have a higher core temperature, skin temperature, heart rate, and blood pressure than men, which can lead to decreased heat tolerance. However, men have a 33% higher incidence of stroke and a 41% higher prevalence of stroke than women [7].

EDs are gateways to the health care system. Their mission is to provide immediate specialist care to patients with urgent or life-threatening needs. Despite their heterogeneous profiles, EDs must provide patients with efficient, high-quality care, which the Institute of Medicine defines as the ability of a health service to increase the likelihood of achieving desired health outcomes in line with current professional knowledge [21]. Quality of care is a multidimensional concept that implies safe, responsive, effective, efficient, equitable, and patient-centered care [21]. In Switzerland, the National Ordinance on Quality of Care and Patient Safety sets out how health care facilities, institutions, and health care professionals must be actively committed to ensuring the quality of care and promoting patient safety. Moreover, through their collaboration, patients contribute to achieving the defined objectives of high-quality care and safety.

Ever more attention is being paid to the relationship between the environment and health. Climate change is causing health problems that did not exist before, leading to new health care needs. It is, therefore, essential to explore preliminary associations between climate variables and sociodemographic and health variables. Specifically, the primary outcome of the quantitative phase is the systematic assessment and analysis of the feasibility of patient recruitment, the reasons for their consultation, and their triage level. This first outcome will be correlated with climate variables (maximum and minimum temperature and concentrations of NO_2, PM, SO_2, and O_3) to investigate whether climate variables influence hospital admissions. The secondary outcome is an exploration of the sociodemographic profiles of adult patients consulting at Sion Hospital's ED. For the qualitative stage, the primary outcome is evaluating the level of acceptability of an interview guide to explore patients' knowledge about climate change and its potential links with their ED visits, and the secondary outcome is an exploration of patients' knowledge about climate change. Given the nature of the study, we decided to focus solely on cardiorespiratory comorbidities. As part of a larger study, other comorbidities should be explored, such as metabolic comorbidities (metabolic syndrome; type 2 diabetes, often associated with cardiovascular disorders; hypercholesterolemia; and hyperuricemia or gout), psychiatric comorbidities (depression, anxiety disorder, schizophrenia, and bipolar disorder), musculoskeletal comorbidities (osteoarthritis, fibromyalgia, and osteoporosis), endocrine comorbidities

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(hypothyroidism and hyperthyroidism), or gastrointestinal comorbidities (celiac disease and inflammatory bowel disease).

Nurses are pivotal in recognizing and addressing the direct health impacts of climate change. They are uniquely positioned to promote overall health with their sensitivity to patients' vulnerabilities and emerging health needs. This includes identifying how climate change affects health in their daily practice, educating patients and communities about related risks, and fostering environmentally sustainable behaviors [22]. To achieve this, studies must be conducted on climate change and its health consequences. The first step is to assess the feasibility of the methods and procedures for a future large-scale study.

Methods

Design

Achieving this development and usability pilot study's objectives requires a convergent, parallel, mixed methods design. Pilot studies are commonly used in health-related research in disciplines such as nursing and medicine [23], frequently to generate data for sample size calculations. This seems especially relevant when there are no data from previous studies to inform the process [24-26].

Quantitative Phase

Overview

Data collection will occur from September 21, 2024, to September 20, 2025 (Figure 1).

Figure 1. Pilot project's quantitative and qualitative phases.

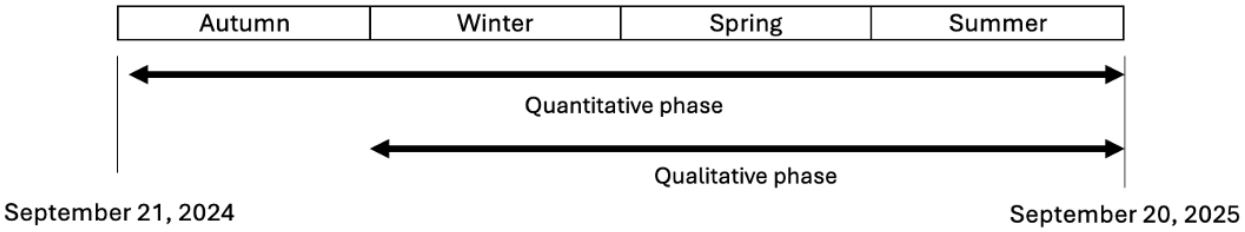

The quantitative phase's objectives are to assess and analyze patient recruitment's feasibility, the reasons for adult patients' consultations at Sion's ED, their triage level, and their sociodemographic profiles. These variables will be analyzed with climate variables (maximum and minimum temperatures and concentrations of NO_2, PM, SO_2, and O_3) to investigate potential associations between hospital admissions and various climate variables. The secondary outcome is an exploration of the sociodemographic profiles of the adult patients consulting at Sion's ED.

A sample size of 40 to 60 adult patients is planned, that is, 15 per season. Pilot studies are often conducted to generate data for sample size calculations. This seems especially sensible when there are no data from previous studies to inform this process. This is the case in the context of this study. It is the first time such a study has been carried out in the canton of Valais. A general rule of thumb is to take 30 patients or greater to estimate a parameter [24,26]. During the triage process, the triage nurse recruits patients for the quantitative phase. Then, the nurse in charge collects the variables of interest.

Inclusion Criteria and Data Collection

We will include all adult patients aged 18 years and older, who consulted at Sion's ED and have cardiopulmonary comorbidities (ischemic heart disease, hypertensive heart disease, heart arrhythmias, heart failure, chronic obstructive pulmonary disease, asthma, obstructive sleep apnea, pneumonia, pulmonary fibrosis, and pulmonary cancer) sorted into levels 3, 4, or 5 according to the Valais triage scale. According to the Valais Swiss sorting scale, level 3 is considered semiurgent with a maximum response time is 60 minutes. Levels 4 and 5 are nonurgent, with a waiting time of 120 and 180 minutes, respectively (nonurgent). The patient must be able to speak, understand, and read French and sign the informed consent form with full knowledge of the facts. Eligible participants who sign this form but die during or after their ED consultation will be included in the study. The exclusion criteria are patients classified at levels 1 or 2 on the triage scale or who do not possess the capacity for discernment (as diagnosed by an ED physician). A level-1 classification on the Valais triage and severity scale implies a life-threatening condition. The patient's pathological situation could lead to death or the loss of an organ or a limb if care is not provided immediately. The patient must be transferred to an emergency care unit immediately. A level-2 triage classification requires urgent treatment since the pathological situation is not life-threatening but is susceptible to rapid deterioration. The patient must be transferred to an emergency care unit and assessed by a physician as quickly as possible. We believe it is, therefore, inadvisable to involve patients triaged at levels 1 and 2 in the pilot study as their rapid care is vital. Finally, Sion's ED does not accept patients under 18 years of age, as they are referred directly to the pediatric ED.

The variables to be analyzed can be divided into two categories: (1) sociodemographic data such as sex, age, place of residence (commune and postal code) and marital status (single, married, divorced, widowed, separated, or in a couple); and (2) medical and clinical data collected during ED visits, such as triage level, reason for the consultation, diagnosis based on the *ICD-10(International Statistical Classification of Disease, Tenth Revision*) classification, medical or surgical history, smoking status, and ED readmissions in the last 6 months. All these questions, except for ED readmissions in the last 6 months, will be collected by the nurse in charge during history taking and other exchanges with the patient. In this way, the data collection

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process for the study's variables of interest will not prolong emergency care or diminish its quality.

Sociodemographic, medical, and clinical data will be analyzed in conjunction with climate data, for example, O_3 concentrations and air pollution data (Table 1). Data come from MétéoSuisse, Switzerland's official meteorological service, under the Federal Office of Meteorology and Climatology, and from RESIVAL, the Valais network collecting information on local climatic parameters.

Table 1. Databases and variables of interest for meteorological data.

Databases	Variables of interest								
	T_{max}	T_{min}	T_{mean}	NO_2[a]	PM_{25}[b]	PM_{10}	SO_2[c]	O_3[d]	Pollen
MétéoSuisse [27]	✓	✓	✓						✓
RESIVAL [28]			✓	✓	✓	✓		✓	

[a]NO_2: nitrogen dioxide.

[b]PM: particulate matter.

[c]SO_2: sulfur dioxide.

[d]O_3: tropospheric ozone.

Recruitment Procedure in Triage

The procedures for participant recruitment will be carried out by triage nurses—the first nursing staff patients meet when they arrive at the ED—and the nurse in charge. The principal investigator will explain the participant selection process to all the ED nurses at 2 team meetings (each 45 minutes long at the ED) and through an email containing a Microsoft PowerPoint presentation with a voiceover that will be sent out before those meetings. This will enable nurses to ask pertinent questions about their understanding of the recruitment algorithm. The triage nurses' role is to prioritize the patient's health status for their ED stay. They will be responsible for identifying whether patients meet all the inclusion criteria and, thus, for initiating the selection process. The nurse in charge or the triage nurse will then ask the patient whether they consent to participate in the study. If they agree, the nurses will collect the signed consent form. If the patient wishes, they can be given a 24-hour period to reflect. In this case, a stamped addressed envelope with the consent and information sheet will be given to them. As a reminder of the process and to ensure that it is carried out homogeneously, the participant selection algorithm (Figure 2) will be posted in every triage station and at the door of each cubicle. Indeed, nursing care in emergency contexts is often represented using an algorithm, so it is a visual tool that professionals in this field are familiar with. This will promote adhesion to and understanding of the algorithm.

The triage nurse or the nurse in charge will explain the study's purpose and the patient's contribution. They will then provide the patient with the study information document and the consent form. These additional explanations will not significantly lengthen triage time nor compromise the quality of care. The patient will have time to read the documents before entering the cubicle. When patients are given their discharge papers home (eg, a prescription, a follow-up appointment, a potential sick note for their employer, or other recommendations), the nurse in charge and the charge nurse, who oversees the operations of their specific nursing unit during a set period while working alongside the team, will ascertain the patient's decision to participate in the study. If the patient agrees, they will collect the signed consent and the document with the variables of interest. Their primary role is to ensure that all nursing functions within the department run smoothly and efficiently, verify whether they have decided to participate in the study, and collect their signed consent form if this is the case. They will answer any patient questions and remind them that their data will be coded and that they may receive a telephone call from the principal investigator.

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Figure 2. Patient selection algorithm.

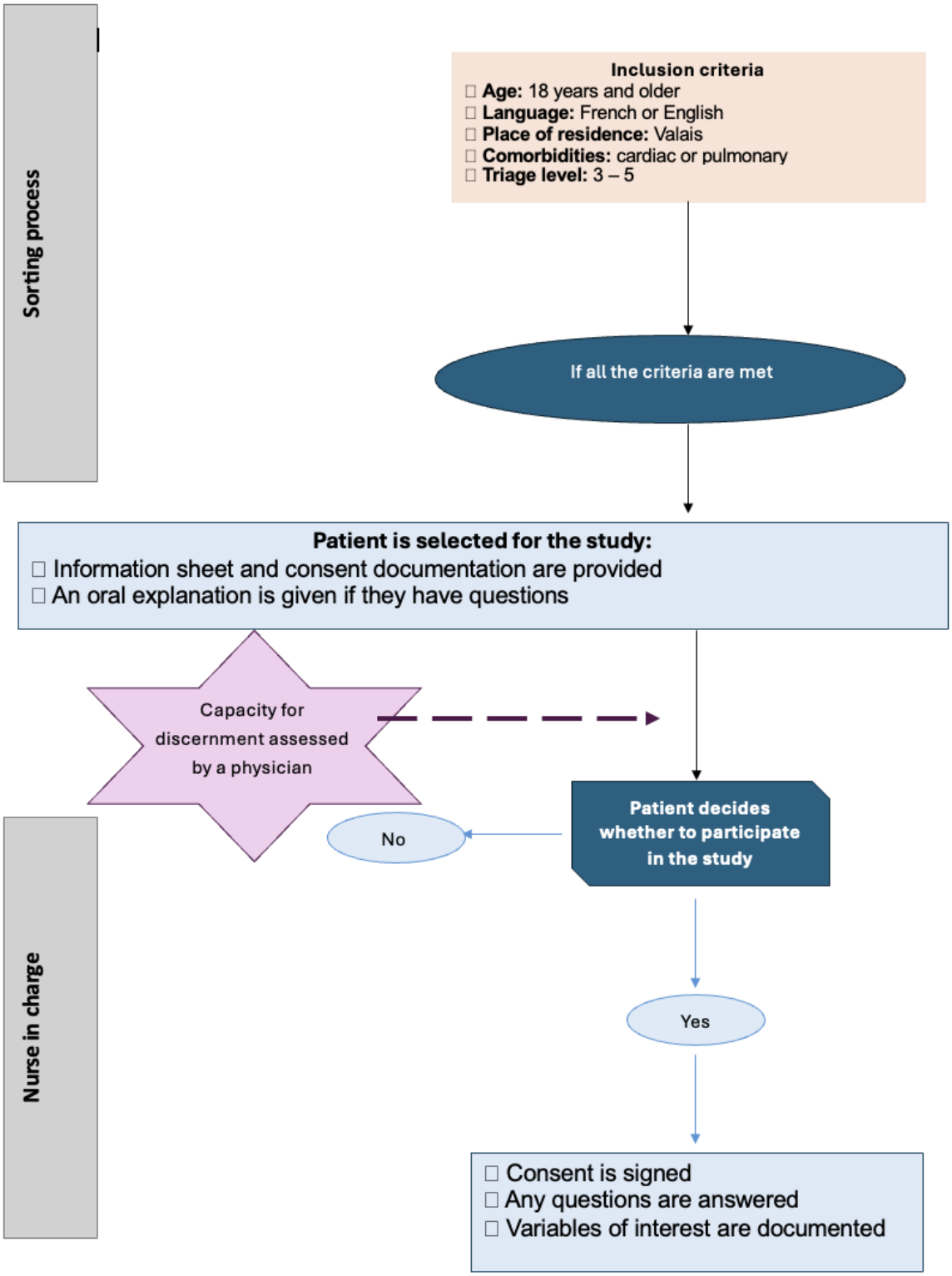

Measuring Temperatures and Pollution

In Valais, the RESIVAL measurement station network monitors and analyzes air pollution levels and calculates mean daily air quality parameters (24 hours from 0 Coordinated Universal Time to 0 Coordinated Universal Time) all across the canton [28]. Daily temperature variables (T_{min}, T_{max}, and T_{mean}) and pollen variables will be taken from MétéoSuisse, Switzerland's official federal national weather and climate service that operates under the Swiss Federal Department of Home Affairs. It is responsible for weather forecasting, climate monitoring, meteorological research, data collection, and public weather-related services [27].

Qualitative Phase

Overview

The qualitative phase's primary outcome is to explore patients' knowledge about climate change and its potential links with

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their ED visits. The secondary outcome is an exploration of patients' knowledge about climate change. Indeed, factors outside of medical care, such as health beliefs, knowledge, attitudes, and behaviors such as smoking, are categorized as social determinants of health [29].

The inductive approach will guide the qualitative phase. A thematic analysis will be carried out independently by 2 researchers (OPS and PJPA). The level of theme identification will be latent or interpretative. During the pooling, disagreements will be settled by the intervention of the third researcher (HV).

Criteria and Data Collection

A nonprobability sample of patients participating in the study's quantitative phase will be selected for inclusion in the qualitative phase. The exclusion criterion established is the patient's incapacity for discernment, according to the patient's family doctor or family, or having a severe psychiatric disorder. The qualitative phase will be documented through individual interviews of 30-45 minutes until data saturation is reached. Data saturation will be reached when the data collected no longer yields any new significant or thematic information relevant to answering the research question. The theoretical number of interviews required is approximately 10-15. At least 6 weeks after the ED consultation, the principal investigator will contact participants on an aleatory basis by telephone to ask them to participate in a 30-45-minute interview. Six weeks were chosen so as to be far enough removed from any potential hospitalization that followed the index ED consultation. More information will also be collected and explored regarding the social determinants of health, categorized into five domains: (1) neighborhood and environment (where patients live, work, and play), (2) health and quality of access to health care (patients' use of health services to achieve the best health outcomes), (3) the social and community context (people with whom patients communicate and connect), (4) patients' access to education, and (5) economic stability (patients' financial resources). These domains can affect wellness, illness, and disease conditions [30]. By recognizing how social determinants impact health outcomes, nurses can play a key role in addressing health disparities and promoting health equity. Indeed, health disparities—variations in health linked to social, economic, and environmental disadvantages within a society [31], are pressing issues that demand immediate attention. Each area will be explored through a question and a follow-up question. Thus, the semistructured interview guide (Multimedia Appendix 1) consists of 5 questions and 5 follow-up questions. The aim is for the patient to share information about their daily life in relation to these 5 areas.

Withdrawal and Discontinuation

In the event of the patient's withdrawal from the study's quantitative phase, their data will not be included in the analysis. However, if the patient withdraws from the qualitative phase, their data will still be incorporated into the analysis of the quantitative phase. Participants withdrawing from the qualitative phase will be replaced in order to maintain the estimated number of interviews required. Participants can withdraw from the qualitative phase at any time, which could be due to a change of mind or to any complication resulting in a loss in their capacity for discernment or ability to understand and speak French (eg, an altered state of consciousness, intubation, tracheostomy, and tracheotomy).

Statistical Analysis

Statistics calculated in a pilot study are used to assess the feasibility of the full-size study and refine its methodology. A variety of methods can be used to address the objectives established for a pilot study, and these need not be statistical [23,26]. Indeed, statistical uncertainty must be taken into consideration before any of the pilot study's findings are generalized. The goal of publishing results from pilot studies is not to focus on their statistically significant findings but rather to provide their estimated effects on all the measures of interest and to describe the lessons that have been learned and will be informative in planning subsequent studies [23,32].

Factors such as the population's sociodemographic characteristics, economic conditions, and access to outpatient and hospital care facilities may confound the relationship between climate variables and hospital admissions.

More specifically, numerical and qualitative data will be analyzed according to good clinical research practices. Statistics will be generated from the raw data collected from the ED's patient records and the appropriate meteorological and air pollution websites (MétéoSuisse and RESIVAL). A database gathering sociodemographic variables (sex, age, place of residence, and marital status), health variables (triage level, reason for the consultation, diagnosis based on the *ICD-10* classification, medical or surgical history, smoking status, and ED readmissions in the last 6 months), meteorological (maximum and minimum temperature), and air pollution data (NO_2, $PM_{2.5}$, PM_{10}, SO_2, O_3, and pollen concentrations) will be prepared on a Microsoft Excel spreadsheet. They will be imported into and analyzed using SPSS software (version 29.0; IBM Corp). Descriptive statistics such as mean and SD (for quantitative variables) and frequency and percentages (for qualitative variables) will be calculated. Parametric statistical tests will be applied to normally distributed variables. Nonparametric statistical tests will be used for variables with non-Gaussian distributions. This data analysis will enable us to better describe the study participants' profiles. To estimate the effects of meteorological, sociodemographic, and health data, we will calculate a conditional quasi-Poisson regression and distributed lag nonlinear models. The model will estimate the association between hospital admissions and predictor variables (sociodemographic, health, meteorological, and air pollution variables). One advantage of the Poisson pseudomaximum likelihood estimator is that the scale of the dependent variable does not affect the parameter estimates [10]. In this type of regression model, a pseudolikelihood is applied to properly scale the SD of the coefficients proportionally to the potential overdispersion. We will use overdispersed generalized additive models with random effect meta-analysis to investigate the associations between variables [8]. ANCOVA models will also be developed to compare the means of a continuous dependent variable (hospital admissions) across multiple factor variables (autumn, winter, spring, and summer) and to determine

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covariates' effects (sociodemographic, health, meteorological, and air pollution variables). This approach ensures a more nuanced understanding of how various factors and covariates collectively influence hospital admissions. Finally, the participant inclusion rate and study retention or drop-out rates will also be estimated, as will the total sample size required for the full-scale study.

The statistical significance threshold will be set according to the number of variables and the size of the database developed (2-sided *P* values<.01 will be considered statistically significant, with 95% CIs and Bonferroni adjustments for multiple comparisons).

Feasibility and Acceptability Phase

Feasibility refers to the practicality and appropriateness of the processes involved in patient selection and data collection within the pilot study. It evaluates the ability to recruit and retain participants, the functionality of inclusion and exclusion criteria, the adequacy of recruitment methods, and the efficiency, reliability, and acceptability of data collection tools and procedures [33,34]. Acceptability refers to the extent to which the study recruitment and data collection procedures, and interventions are considered appropriate, satisfactory, and appealing to participants, and other stakeholders. It evaluates the willingness of participants and involved personnel to engage with and adhere to the study's requirements [33,34]. The acceptability will be explored through an inductive approach. Three focus groups, each consisting of 4-6 ED nurses, will be conducted to explore variables such as time, objectives of the pilot study, implications, satisfaction, potential barriers, and facilitators to collect data, and ease of the process through open-ended questions. Finally, patients' level of acceptability of the interview guide will be explored through an open-ended question at the end of the individual interview "Do you feel that the guide enabled you to share meaningful insights?"

Feasibility will be assessed through 2 different approaches. The first approach will assess feasibility through the same focus groups used to assess acceptability. On a scale of 1="don't agree at all" to 5="completely agree," nurses will rate the process of the communication and training process to which they have been subjected (study protocol, mentoring, printed selection algorithm, principal investigator's feedback, and communication about the project). The second approach will consist of the proportion of expected data and data collected.

Ethical Considerations

The research protocol (2024-00900) for this pilot project was presented to its different partners. A request for authorization to proceed was presented to Swiss Ethics. The cantonal ethical commission for research on human beings, represented by Jean-Marie Annoni, gave its final approval on October 23, 2024. The support of the University of Applied Sciences and Arts Western Switzerland is assured. Participation in the study will be voluntary and pose no risk to the patients. In the context of this study, it is highly unlikely that participants will be exposed to any inconvenience or risk. Whether they participate in the study will in no way alter their care pathway or the quality of the care and follow-up they receive. Should the participant request them, the principal investigator will send them the pilot study's results by email or post. Participation in this study will be of no direct benefit to the patient. However, the results may help improve the overall delivery of care by providing emergency medicine that is better adapted to the patient's health status and needs. Finally, the preliminary results of the development and usability pilot study will enable the research team to propose a larger-scale study.

Given the nature of the variables to be collected, personal data will be coded to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of the people participating in the research. The coding process will be based on the best-practice recommendations found in Article 29 of the Working Group on Data Protection (the independent European advisory body on data protection and privacy). A collaboration agreement has been drawn up with Hôpital du Valais in the canton's French-speaking area. The principal investigator will be granted access to data obtained with patient consent for the duration of the study. The data collection process will be carried out in compliance with the appropriate data protection, human research, and ethical principles, thus ensuring respect for patients' rights and the confidentiality of their medical information. The coding key will be kept separate from the study data.

For the purposes of this development and usability pilot study, data will be stored on the Haute École de Santé Valais-Wallis' OneDrive server. The coding key between personal data and the numerical code, as well as the transcripts of each individual interview, will be kept by the principal investigator.

Results

Data collection started on September 21, 2024, following approval by the ethical commission. Data collection will take place over 1 year, until September 20, 2025. After 1 season of data collection, that is, between September 21, 2024, and December 21, 2024, a total of 60 patients were screened. The quantitative phase will begin in February 2025.

Discussion

Principal Results

The results of this development and usability pilot study will enable us to assess the feasibility of its methods and procedures with a view to carrying out a larger study. Indeed, it is important to adapt the patient selection algorithm to the clinical field's requirements and frontline carers' needs. By definition, the flow of patients coming to EDs cannot be predicted. The selection algorithm must be simple and not significantly delay a patient's treatment or slow its commencement. Our assumption is that we will have to make changes in 2 stages. These will still be communicated to managers and the entire care team. Concerning sociodemographic profiles, the hypothesis is that cardiovascular disease, active smoking, previous smoking, and diabetes are factors of vulnerability to climate change. In conjunction with the qualitative part, we hypothesize that vulnerable patients are aware of reduced quality of life during extreme temperatures or pollution peaks. However, little, if any, action is taken to

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anticipate and prevent this. Patients' levels of technical literacy are, therefore, potentially low. Finally, we hypothesize that the qualitative interview guide's acceptability level is high. The interview guide has been pretested, and the exchange lasts no more than 45 minutes [32].

The results of the present development and usability pilot study could constitute a first step toward developing sustainable, ecological care. Indeed, today's duality of a health care system that provides benefits to patients and the population but has deleterious environmental consequences is becoming less and less acceptable. Finally, this development and usability pilot study will establish guidelines for a future larger-sized study.

Limitations

Data will be collected over 1 year so that all 4 seasons and their particularities—especially regarding climatic variables—can be studied. This development and usability pilot study is a single-center study and will only represent results from the Hôpital du Valais' ED in Sion. Finally, its objective is to assess and analyze the potential for adult patient recruitment, the reasons for patients' consultations, and their level of triage. It will also test the acceptability of an interview guide to explore patients' knowledge of climate change and its links with their ED visits. These preliminary results will constitute the first milestone in the assessment of the practicality of recruiting and retaining participants and in the determination of the most appropriate participant selection process to ensure stakeholder adherence for a full-scale study.

Conclusions

Climate change is a central concern for the discipline of nursing. Nurses are strategically placed to respond to the impacts of climate change through their practice, research, and training in developing, implementing, and sustaining innovation for climate change mitigation and adaptation. To do so, they must be given the tools to come to grips with the global health emergency, that is climate change. Taking stock of the current situation, particularly in the alpine canton of Valais, in Switzerland, will require a thorough assessment. This development and usability pilot study's preliminary results will be used to inform a future large-scale study whose findings we may be able to generalize and identify climate change's impact on the environment and the health of Valais' population.

Acknowledgments

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Data Availability

All data generated or analyzed during this study are included in this published article.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guide.
[PDF File (Adobe PDF File), 23 KB - resprot_v14i1e67128_app1.pdf]

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Abbreviations

ED: emergency department
ICD-10: International Statistical Classification of Disease, Tenth Revision
PM: particulate matter
NO2: nitrogen dioxide
O3: tropospheric ozone
SO2: sulfur dioxide
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Supporting Physical and Mental Health in Rural Veterans Living With Heart Failure: Protocol for a Nurse-Led Telephone Intervention Study

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Abstract

Background: Heart failure (HF) remains a disease of notable disparity for rural veterans, despite recent advancements in clinical treatment. Managing HF in the home is stressful and complex for rural veterans who experience unique barriers to optimal physical and mental health, necessitating adequate support and problem-solving skills.

Objective: This study aims to (1) adapt, to the rural sociocultural context, a culturally sensitive, tailored, telephone support and problem-solving intervention (CARE-HF [Supporting Physical and Mental Health in Rural Veterans With Heart Failure]) using findings from preliminary qualitative research and (2) evaluate the effects of CARE-HF on problem-solving and physical and mental health outcomes among rural veterans with HF.

Methods: This study involves a repeated-measures, single-group design. The intervention content was adapted and tailored to the rural sociocultural context using preliminary qualitative data and guided by the Theories of Social Problem-Solving and Stress, Appraisal, and Coping. Veterans are recruited from Veterans Administration home-based cardiac rehabilitation clinics, cardiology clinics that serve veterans, veterans-based community resource centers, and social media campaigns. Veterans with HF (N=100) receive the CARE-HF intervention. This nurse-led intervention comprises 8 telephone sessions that use a five-step, problem-solving process to manage common HF problems in the home: (1) identifying the problem and viewing it in a positive manner, (2) goal setting, (3) generating potential strategies for problem management, (4) choosing and implementing strategies to manage the problem, and (5) evaluating strategy effectiveness. Veterans receive initial problem-solving training during the first session, with follow-up sessions focusing on problem-solving skill reinforcement and assisting veterans in applying these principles to manage self-identified, HF-related problems experienced in the home. Data are collected at baseline and 3, 6, 12, and 18 months from baseline on problem-solving and outcomes of interest (ie, HF self-care; HF symptoms; health care utilization; depressive symptoms; anxiety; HF-specific, health-related quality of life; stress; resilience; and coping). Demographic data will be analyzed using descriptive statistics and multilevel growth curve modeling with restricted maximum likelihood estimation to compare a series of models using Akaike information criteria and Bayesian information criteria fit indices while controlling for covariates.

Results: Recruitment started in April 2023. As of December 2024, we have enrolled 56 veterans. Recruitment is anticipated to end in June 2025, with data collection continuing until all enrolled veterans have completed the 18-month follow-up period.

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Conclusions: Adapting and testing a culturally sensitive, tailored, telephone intervention to aid support and problem-solving in the home has the potential to provide individualized care to rural veterans where they reside, thereby reducing travel burden while also increasing access to evidence-based care programs. If effective, telephone support and problem-solving interventions could be a low-cost, accessible method to improve physical and mental health in rural veterans with HF.

Trial Registration: ClinicalTrials.gov NCT05839067; https://clinicaltrials.gov/study/NCT05839067

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KEYWORDS

heart failure; veterans; problem-solving; self-care; heart failure symptoms; depression; anxiety; HRQOL; health-related quality of life; stress; resilience; coping; mental health; nurse-led intervention; social support; telehealth; chronic disease management

Introduction

Background

Heart failure (HF) is a chronic, progressive disease of notable disparity for rural veterans despite recent advancements in clinical treatments [1] and overall improvements in HF-related outcomes [2]. Incidence, hospitalization, and mortality rates continue to be highest in rural versus urban individuals with HF [2,3]. In rural veterans, specifically, HF is the second leading cause of cardiovascular-related hospitalization, accounting for about 30% of total hospitalizations [4]. Lower levels of health literacy, higher rates of food insecurity, the presence of food deserts, the lack of community support services, poverty, and limited health care access contribute to the disparities in HF-related outcomes in rural veterans [5-7] and influence physical and mental health [7].

Rurality impacts patients' ability to maintain optimal HF self-care and disease management in the home. Specifically, rural veterans with HF experience unique challenges, which are stressful, such as difficulties in obtaining fresh fruits and vegetables and low-sodium foods, which are a vital component of the HF dietary regimen [8]. The lack of local health care services and pharmacies, as well as public transportation, adds to the complexity of managing HF in a rural area [8] and increases the travel burden for veterans associated with receiving medical care [9]. In fact, only 9% of physicians practice in rural areas, which is significant given that 20% of the population in the United States lives in rural areas [6]. These rural-related social determinants of health play a crucial role in the ability to maintain optimal HF self-management and influence patient outcomes in rural veterans with HF [7].

Likewise, depression and anxiety are influenced by the progression of HF [10], with increased symptoms and decreased physical functioning contributing to poor mental health [11,12], and are associated with higher mortality and hospitalization rates [10,13]. Notably, depression and suicide rates are highest in rural patients compared to their urban counterparts, yet only 10% of mental health professionals practice in rural areas, leaving many rural veterans without access to mental health care [14] and placing them at even greater risk for poor HF outcomes [10,13]. Thus, rural veterans living with HF lack substantial support in aiding disease management and mitigating the negative emotions that often accompany living with HF, necessitating the development of novel interventions to support physical and mental health in the home.

Social support and problem-solving are essential coping resources that aid stress management, support resiliency, and enhance coping processes [15,16]. In rural veterans with HF, social support and problem-solving skills are critical to maintaining physical and mental health [8,17,18]. Patients with HF need to appraise and manage diverse symptomatology, adhere to dietary restrictions, cope with negative emotions, and negotiate daily activities [11,12]. Rural veterans with HF also need to successfully address rural-related challenges and barriers that undermine overall health [7]. Previous research suggests that the use of rational, systematic problem-solving strategies to manage HF-related problems is associated with better HF self-care [8,17] and may reduce HF symptom severity [18] and mental distress [17]. However, rural veterans often lack access to support and problem-solving interventions in their communities. Furthermore, when such services are available, they typically are not tailored to the rural sociocultural and educational context, nor are they able to address the specific emotional needs of veterans [19].

Culturally sensitive, tailored interventions that provide support and focus on enhancing problem-solving skills [16] hold considerable promise for increasing uptake in rural veterans with HF. Tailored support and problem-solving programs may be beneficial for veterans who need more assistance outside of a "standardized, one-size-fits-all" disease self-management program. Furthermore, the use of telephones allows for an easy-to-access, cost-effective, and successful modality for delivering such interventional programs to rural areas where access to broadband internet may still be problematic [20-22].

Our previous research assessed the preliminary efficacy of a 12-week, nurse-led, tailored, telephone-based, problem-solving and support intervention (Coping in Heart Failure [COPE-HF] Partnership) for patients with HF on changes in self-care, HF symptoms, depressive symptoms, and health care utilization in a three-arm randomized clinical trial [17,18]. Participants in the COPE-HF Partnership were all recently discharged from an acute care facility for issues related to HF and resided primarily in urban areas. A trained nurse interventionist partnered with the patient to manage HF-related self-care and disease management problems encountered in the home. Data were collected at baseline and 5, 9, and 13 weeks. The intervention was associated with improvements in self-care management;

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notably, patients had less health care utilization over the intervention period versus the other groups [17]. Patients who received the intervention also reported fewer HF symptoms, with a significant decrease in HF symptom severity over the intervention period [18]. Although not significant, improvements in depression were also found in the intervention group [17].

To prepare for the sociocultural adaptation of the CARE-HF (Supporting Physical and Mental Health in Rural Veterans With Heart Failure) intervention to the rural population, we conducted a qualitative study with rural patient–care partner dyads living with HF (n=11) to identify and describe the problems experienced in the home related to HF and associated management strategies [8]. The findings of this study showed that rural residents with HF experience significant problems related to self-care and disease management adherence due to the rural environment and lack of resources, as well as differences in cultural and personal values and beliefs related to health care. These problems resulted in a variety of physical and mental health sequelae and strained interpersonal relationships. However, most dyads developed effective workarounds and management strategies to overcome these challenges [8]. The problems and management strategies identified in this study provide the basis for the adaptation of intervention content for the rural population included in the CARE-HF intervention.

The CARE-HF also builds upon the COPE-HF Partnership intervention, in that it includes self-care and disease management components [17,18]. However, it differs in that the CARE-HF intervention is more holistically focused, also incorporating mental health, interpersonal, and social components. In addition, all components of the CARE-HF intervention are adapted to the rural sociocultural context and include specific problems and management strategies pertaining to physical and mental health drawn from the rural setting [8]. Because of the expanded focus of the CARE-HF intervention, additional study outcomes, not examined in the parent intervention, are included in the CARE-HF study.

Conceptual Framework

The Theories of Social Problem-Solving [16] and Stress, Appraisal, and Coping [15] provide the foundation for the CARE-HF intervention (Figure 1). Rural veterans with HF encounter a unique variety of problems that require cognitive appraisal and appropriate problem-solving to successfully cope with HF-related challenges. The two-fold cognitive appraisal process is influenced by individual characteristics and consists of primary appraisal (determination of the significance of the problem) and secondary appraisal (evaluation of available resources) [15]. Effective problem-solving requires a positive problem-orientation approach which elicits rational problem-solving versus avoidance, impulsivity, and carelessness. Problem-solving involves accurate problem identification, generation of appropriate strategies, active decision-making, and strategy implementation and evaluation [16]. The goal of the CARE-HF intervention is to move rural veterans with HF toward a positive problem orientation and use of rational problem-solving strategies, thereby supporting a more adaptive problem-solving style and enhancing physical and mental health [15,16].

Figure 1. Conceptual model based on the Theories of Social Problem-Solving and Stress, Appraisal, and Coping.

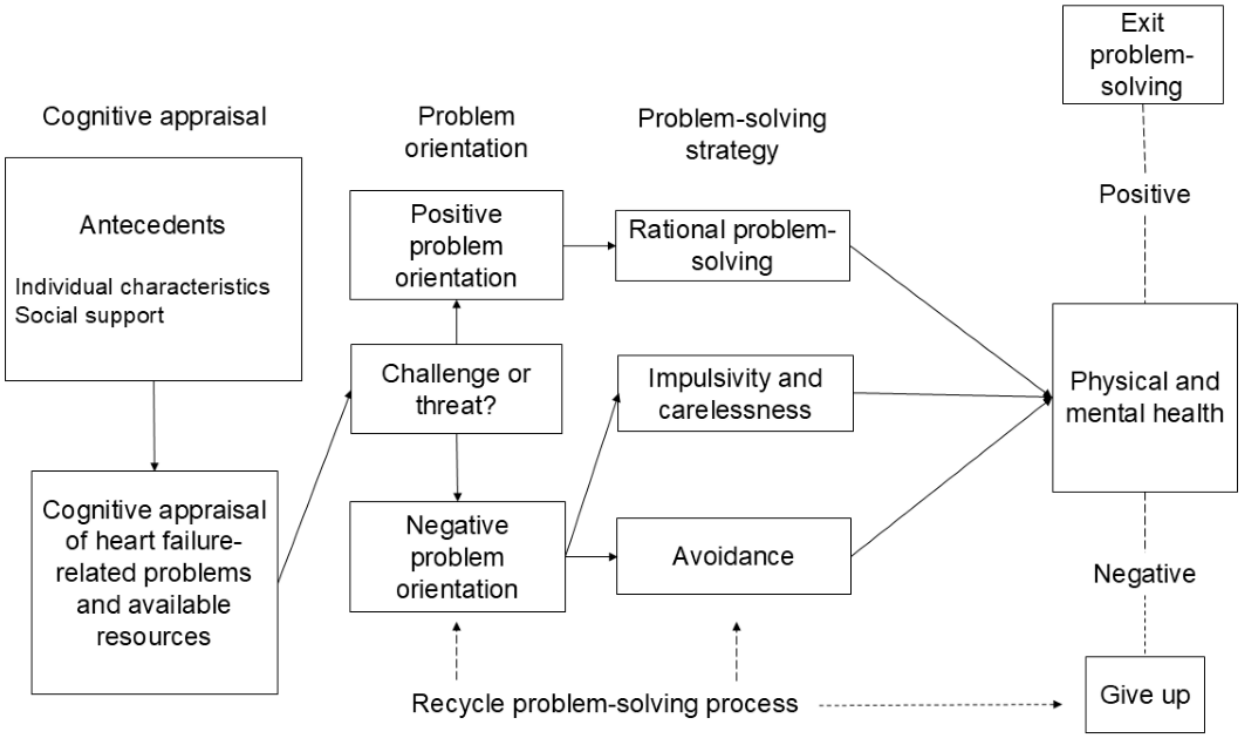

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Purpose, Aims, and Hypotheses

The overall purpose of this study is to adapt to the rural sociocultural context and test the efficacy of a tailored, telephone-based intervention (CARE-HF) to support the physical and mental health of rural veterans by enhancing disease self-management and coping processes. To accomplish this goal, our research aims are to:

1. Adapt the CARE-HF intervention content to the rural sociocultural context using findings from preliminary qualitative research.
2. Examine the effectiveness of the CARE-HF intervention on study outcomes (HF self-care, HF symptoms, health care utilization, depressive symptoms, anxiety, health-related quality of life, stress, resilience, and coping), process (problem-solving), and antecedent (social support) in a sample of rural veterans with HF (N=100) at baseline and 3, 6, 12, and 18 months from baseline.

Our hypotheses are as follows:

- Hypothesis 2a: Increases in HF self-care, health-related quality of life, resilience, coping, and problem-solving will be noted at 3 months from baseline and sustained throughout the 18-month follow-up period.
- Hypothesis 2b: Decreases in HF symptoms (frequency, severity, and interference with physical activity and enjoyment of life), health care utilization, depressive symptoms, anxiety, and stress will be seen at 3 months from baseline and sustained throughout the 18-month follow-up period.

Methods

Cultural Adaptation

To address aim 1, before recruitment and study initiation, steps were taken to adapt the CARE-HF intervention content to the rural sociocultural context using some aspects of the ADAPT-ITT (Assessment, Decision, Adaptation, Production, Topical Experts, Integration, Training, and Testing) model [23]. Specifically, qualitative findings from preliminary research in rural patients with HF [8,12] guided the context of problems and potential strategies included in the program materials and telephone intervention sessions. The problems presented during the card sorting task, a component of the sessions, are drawn directly from this preliminary rural research [8,12]. In addition, during the telehealth sessions, veterans' values and beliefs are assessed and inform the potential strategies identified in the problem-solving process to enhance adherence and tailor the program to the unique needs of each rural veteran.

Ethical Considerations

This study was approved by the Florida State University Institutional Review Board (protocol STUDY00003764) to collect verbal consent via the telephone according to the principles of the Declaration of Helsinki, with potential participants maintaining the opportunity to opt out of the study. Telephone sessions are recorded to monitor intervention fidelity. However, all participant data are deidentified and stored in accordance with the General Data Protection Regulation Rules to maintain privacy and confidentiality. Veterans enrolled in the study receive compensation in the form of US $20 gift cards to a superstore following each completed data collection point, for up to a total of US $100 in gift cards if the entire study is completed. No identifiable information or images of research participants will be included in research reports. The CARE-HF protocol is registered at ClinicalTrials.gov (NCT05839067).

Design and Sample

This study includes a repeated-measures, single-group design. Veterans are recruited from Veterans Administration home-based cardiac rehabilitation clinics, cardiology clinics that serve veterans, veterans-based community resource centers, and social media campaigns using study flyers. Veterans with HF (N=100) will be recruited over 3 years, with the anticipated enrollment of 5 or more veterans per month. The desired sample size was based on a power analysis for repeated-measures ANOVA with 5 time points, α=.05, a medium effect size (f=0.25), and 80% power, plus oversampling for potential attrition (20%) estimated from studies involving patients with HF [17,18]. Veterans are eligible for participation if they (1) have a diagnosis of HF; (2) are aged 18 years or older; (3) have New York Heart Association functional class II-IV HF; and (4) can read, write, and communicate verbally in English, and excluded if they have a history of cognitive impairment.

Data Collection

Telephone data collection is conducted by a trained research assistant who verbally asks each item and records participants' responses in an online HIPAA (Health Insurance Portability and Accountability Act)–compliant Qualtrics database. Data are collected at baseline and 3, 6, 12, and 18 months from baseline. In addition to a sociodemographic and clinical survey (age, gender, comorbidities, education, and HF class), a set of self-report surveys is used to measure the study variables (Table 1). We also collect data on standard Veterans Administration Office of Rural Health metrics.

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Table 1. Study variables.

Variables	Baseline	3 months	6 months	12 months	18 months
Covariates					
Social support	✓				
Process					
Problem-solving	✓	✓	✓	✓	✓
Outcomes					
HF[a] self-care	✓	✓	✓	✓	✓
HF symptoms	✓	✓	✓	✓	✓
Health care utilization		✓	✓	✓	✓
Depressive symptoms	✓	✓	✓	✓	✓
Anxiety	✓	✓	✓	✓	✓
HF-specific, health-related quality of life	✓	✓	✓	✓	✓
Stress	✓	✓	✓	✓	✓
Resilience	✓	✓	✓	✓	✓
Coping	✓	✓	✓	✓	✓

[a]HF: heart failure.

Study Measures

Social Support

The 12-item Interpersonal Support and Evaluation List measures perceived belonging, tangible, and appraisal support. The 3 subscales will be combined to obtain a single index of perceived support, in addition to the evaluation of the individual subscales. Scores range from 0-36, with higher scores suggesting a higher perception of available support [24]. Previous studies support its construct validity using the original 40-item version [24] and its internal consistency reliability (α=.90) [25].

Problem-Solving

The 25-item Social Problem-Solving Inventory Revised-Short measures problem orientation and problem-solving style using 5 subscales: positive and negative problem orientation, rational problem-solving, impulsivity and carelessness, and avoidance styles. The 5 subscales will be combined to provide a total score, with higher scores representing more of an adaptive problem-solving style and lower scores suggesting more of a maladaptive style. Higher scores on the individual subscales suggest more of the problem-solving characteristics [26]. Research supports its validity [16,26] and its reliability (α=.91) [25].

HF Self-Care

The 39-item Self-Care of Heart Failure Index v 7.2 measures HF self-care across 4 subscales: self-care maintenance, symptom perception, symptom management, and self-efficacy (α=.73-.88 across all subscales) [27,28]. Scores are standardized (0-100), with higher scores on each subscale suggesting better self-care principles. Scores ≥70 on each subscale are considered adequate; improvement of ≥8 is considered clinically significant [27].

HF Symptoms

HF symptoms are measured using the Heart Failure Symptom Survey. This survey contains 14 common symptoms of HF, which are rated on an 11-point scale (0–10) across 4 domains (frequency, severity, interference with activity, and interference with quality of life) based on the last 7 days. Higher scores indicate more of the respective domain in relation to the specific symptom [29]. Empirical evidence supports its content validity [29] and reliability (α=.96) [25].

Health Care Utilization

Health care utilization is determined by the frequency of emergency department visits and readmissions for HF and assessed via self-report. There are acceptable levels of agreement between self-report and medical record data [30].

Depressive Symptoms

Depressive symptoms are measured using the 20-item Center for Epidemiological Studies—Depression Scale. Overall scores range from 0 to 60, with higher scores indicating the presence of more depressive symptoms. A cutoff score of 16 indicates an individual is at risk for some degree of depression. Previous studies support its validity (Radloff [31]) and reliability (α=.90) [25].

Anxiety

The Generalized Anxiety Disorder-7 scale is a valid and reliable (α=.92) 7-item scale that assesses the presence of anxious symptoms over the past 14 days, using a Likert scale to rate the frequency of the symptoms (0=not at all, 1=several days, 2=more than half of the days, and 3=nearly every day). Total scores range from 0 to 21, with higher scores indicating more severe anxiety symptomatology [32]. In this study, the following recommended anxiety severity categories will be used: none or

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normal (0-4), mild (5-9), moderate (10-14), and severe (15-21) [32].

Health-Related Quality of Life

The multidimensional 21-item Minnesota Living with Heart Failure Questionnaire measures the physical, socioeconomic, and emotional dimensions of HF-specific, health-related quality of life. This self-report survey asks respondents to evaluate the way they have felt in relation to the specific dimension over the last 4 weeks. Scores for the individual dimensions, as well as a total score, are obtained by summing the individual items. Higher scores suggest worse health-related quality of life relative to the specific dimension or overall. A change of ≥5 points is considered clinically meaningful [33]. Previous studies support its validity [33] and reliability (α>or=.80 across dimensions) [34].

Stress

The valid and reliable 10-item Perceived Stress Scale measures stress and includes questions relative to feelings and thoughts experienced during the last month using a Likert scale with scores ranging from 0 (never) to 4 (very often). Higher scores indicate higher levels of acute stress [35].

Resilience

The 25-item Five-by-Five Resilience Scale has 5 subscales that measure adaptability, emotion regulation, optimism, self-efficacy, and social support on a 5-point Likert scale (1=very inaccurate to 5=very accurate). Higher scores represent higher levels of resilience relative to the specific facet. Previous research shows adequate validity and reliability (α=.81-.93 across subscales) [36].

Coping

The Brief Coping Orientation to Problems Experienced is a 28-item scale that measures 14 coping strategies over 3 subscales (active emotional coping, avoidant emotional coping, and problem-focused coping) on a 4-point scale ranging from 1 (I haven't been doing this at all) to 4 (I have been doing this a lot). Higher scores on the subscales suggest more use of the specific type of coping strategy [37]. Previous research has indicated the measure is valid [37] and reliable (α=.78) [38].

Procedure and Intervention

CARE-HF

Veterans are trained to use social problem-solving skills to manage common HF-related problems in the home during 8 telephone sessions led by a trained registered nurse interventionist (NI).

Initial Telephone Session

Before the first session, veterans are mailed program materials and a manual presented at a sixth-grade reading level. To start the first telephone session, participants receive an overview of the program manual, tailored to the rural context, which includes information about social problem-solving principles. The manual also includes detailed real-life examples drawn from the rural setting of how to use the five-step, problem-solving process to evaluate and manage HF-related problems based on previous research (Table 2) [8]. Each example includes a positive problem-orientation approach and rational problem-solving strategies to address these HF-related problems. The NI uses fatigue as an example when discussing how to apply the iterative five-step, problem-solving process to manage actual HF-related problems. The five-step, problem-solving process is based upon the "Theory of Social Problem-Solving" and rational problem-solving principles and includes (1) identifying the problem and viewing it in a positive manner, (2) setting a goal related to problem management, (3) generating potential strategies to address the problem, (4) choosing and implementing one to two strategies to manage the problem, and (5) evaluating the effectiveness of chosen strategies [16].

Veterans are then asked to participate in a card-sorting task. Veterans are given a set of cards portraying HF-related problems identified in previous research (Table 2) [8,12] and asked to prioritize the cards from the highest priority problem to the lowest. Then, the NI will guide veterans in applying the problem-solving process to the HF-related problem identified as the highest priority. Next, the NI describes the benefits of reframing the problem in a positive manner and facilitates the selection of preliminary strategies to manage them. In doing so, the NI explores through discussion with the participants how their values and beliefs can be incorporated into potential strategies. Participants then choose one to two strategies on which to focus, the results of which are reviewed at the next session. The five-step, problem-solving process is reinforced throughout the intervention period in the follow-up telephone sessions.

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Table 2. HF[a]-related problems and examples.

Problem categories	Examples
Monitoring and managing HF symptoms	• Fatigue (tiredness) • Forgetfulness • Edema (swelling) • Activity intolerance • Difficulty breathing (shortness of breath)
Staying on your special diet program	• Access to suitable foods • Shopping for and cooking correct foods • Limiting fluids (if recommended) • Barriers to eating foods with less salt • Personal food likes and dislikes • Not sure how to read and understand food labels
Staying on your HF treatment program	• Take daily weights • Exercise regularly (as recommended) • Keep regular health care visits • Get immunizations (flu, RSV[b], pneumonia, and COVID-19) • Use oxygen (as directed) • Stop smoking
Dealing with unhelpful emotions	• Sadness • Anxiety • Decreased quality of life • Depression • Anger • Negative life changes
Social isolation and loneliness	• Unable to do normal activities (community, church, family, and friends) • Fewer or no invitations to social events with friends and family • Feeling as if you have no one to turn to for support • Feeling alone
Medicine management	• Difficulty in obtaining medicine • Unable to pay for medicine • Problems in preparing medicine • Trouble in taking medicine on time • Taking several medicines for other health problems
Health beliefs	• How you view your health and wellness (accept, do not accept, positive, or negative) • How well you think you can do health activities for yourself (good, ok, or not well) • Your view of how well the heart medicine and treatment works (works well, no change, or does not help)
Caring for yourself (self-autonomy)	• You want to do everything for yourself and or make health care decisions whether you can or not • Family or friends want to do everything for you and or make health care decisions whether you can or not
Social support and community resources	• Family or friends who live close by • Church members and social group friends • Neighbors • Local senior center • Home health • Grocery store or grocery delivery programs nearby • Food pantry • Pharmacy nearby • Public transportation
Managing HF and other health issues	Managing HF and: • Diabetes • Neurological disorders

[a]HF: heart failure.

[b]RSV: respiratory syncytial virus.

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Follow-Up Telephone Sessions

Seven follow-up telephone sessions occur weekly for the first month (sessions 2-4) and then biweekly for the second and third months (sessions 5-8). Each session begins with an evaluation of the previous week's problem, including the veterans' perceptions of the effectiveness of the strategies used. If needed, problem-solving guidance is provided or reinforced via verbal feedback from the NI. If the problem improves and no further problem-solving is required, the NI works with the veterans to establish a maintenance plan using rational problem-solving strategies. Veterans then repeat the card sorting task to identify new problems and the iterative five-step, problem-solving process starts over. Both current and new problems are identified by the veterans and examined during each follow-up telephone session. Each follow-up session lasts approximately 30 minutes. Figure 2 provides an overview of the study and associated major activities.

Figure 2. Study overview.

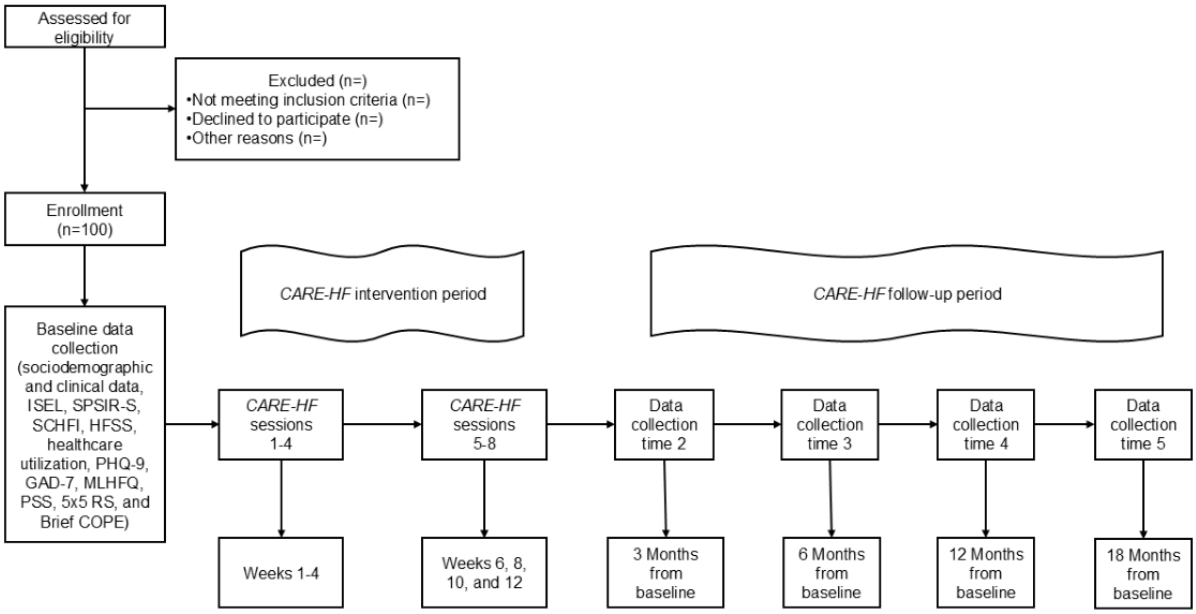

Intervention Fidelity

Strategies to enhance intervention fidelity are based upon the National Institutes of Health Behavior Change Consortium recommendations [39]. Standardized training for research staff who are conducting inclusion and exclusion screening, data collection, and intervention sessions occurred before study implementation to ensure adequate skill acquisition for the defined roles. The primary investigator trained staff initially until a minimum of 90% accuracy was achieved in covering the key elements of the defined role using role-playing, scenarios, and scripts. Fidelity checks of eligibility screening and informed consent, data collection contacts, and intervention sessions are also performed by the primary investigator every three months using a checklist of key elements for the specific activity to ensure that 90% of core elements are being consistently performed. Retraining of research staff occurs as needed to ensure that they meet the 90% criterion.

Data Analysis

Preliminary Analyses

Descriptive statistics will be computed on all time-invariant and time-varying study variables. Cronbach α values will be calculated for all measures containing multiple items to assess internal consistency. In the case that internal consistency is low ($\alpha<0.6$), an if-item-deleted analysis will be performed, and items that are not a good indicator for the underlying construct will be excluded.

Main Analyses

Multilevel growth curve modeling will be used for the testing of aim 2 or the evaluation of the effectiveness of CARE-HF. For each outcome variable, a series of models will be estimated and compared using incremental fit indices, including the Akaike information criteria and the Bayesian information criteria. The first model is an intercept-only model. Then, a growth curve model with a linear growth component will be estimated. Finally, a model with a quadratic growth component will be tested. The multilevel modeling and restricted maximum likelihood estimation method will be used in R (R Foundation for Statistical Computing) [40]. This method can deal with dropouts and missing data without excluding incomplete cases. In addition to fixed effects, random effects will be estimated.

Covariates

Several covariates will be considered for inclusion: age, biological sex, race and ethnicity, and educational attainment. Only covariates that are statistically significant predictors of at least one outcome will be included. That is, the same covariates will be used in all analyses for the primary aim.

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Expected Outcome

We anticipate that the CARE-HF intervention will improve problem-solving, HF self-care, health-related quality of life, resilience, and coping and decrease HF symptoms, health care utilization, depressive symptoms, anxiety, and stress across all time points from baseline.

Results

Funding for this study was received in October 2022, and recruitment started in April 2023. As of December 2024, a total of 56 veterans have been enrolled, 4 veterans have completed the study, and the remaining veterans are in varying phases of intervention or follow-up. Recruitment is anticipated to end in June 2025, with follow-up data collection continuing until all enrolled veterans have completed the 18-month follow-up data collection period. Data analysis is forthcoming and will be conducted after the study completion.

Discussion

Significance of This Study

In recognition of the extraordinary challenges that rural patients encounter in maintaining optimal health, the American Heart Association [22] recently recommended the use of telehealth to increase health equity and provide vital access to cardiovascular supportive care in this population. Although mobile apps and virtual platforms are popular telehealth modalities for intervention delivery, their use in rural populations is plagued by technological challenges [22]. However, the use of telephones to deliver support and problem-solving interventions to rural patients with HF eliminates these technological issues and has been effective in optimizing HF self-care [17,18] and reducing depressive symptoms [41].

With an increasing focus on innovative methods to support physical and mental health and enhance health equity among rural veterans with HF, this study will provide important evidence on the effectiveness of an innovative, telephone-based, support and problem-solving intervention on HF self-care, HF symptoms, health care utilization, depressive symptoms, anxiety, health-related quality of life, stress, resilience, and coping. The CARE-HF intervention has the potential to improve the clinical care of rural veterans with HF, as well as be expanded to other populations. If this novel intervention is found to be effective and sustainable, it can be further tested in a larger randomized clinical trial, with the long-term goal of translating this intervention into clinical care for veterans with HF to enhance HF disease self-management and mental health.

Limitations

This study has some limitations. First, enrollment is restricted to rural veterans with HF; therefore, generalization of findings may be limited. Second, this is a single-group study that lacks a comparison group, reducing our ability to make meaningful comparisons across outcomes. Third, a lengthy follow-up period is included to examine the sustainability of the intervention effect and assess the need for booster sessions, but this may also contribute to a higher-than-desired attrition rate. Despite these limitations, this study will provide valuable insights for program evaluation and improvement, as well as intervention adherence and sustainability of effect to inform future research.

Conclusions

This study adapts to the rural sociocultural context and tests a tailored, telephone-based, support and problem-solving intervention designed to help rural veterans manage HF-related problems experienced in the home. If the intervention is effective, it will provide support for a highly accessible, low-cost method to aid rural veterans in maintaining optimal physical and mental health. This study fills an important research gap but, more importantly, provides the basis for future work to evaluate potentially effective and accessible services for rural veterans living with HF.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

LJG performed conceptualization, funding acquisition, project administration, supervision, methodology, writing – original draft, and writing – review and editing. LA handled funding acquisition, supervision, writing – original draft, and writing – review and editing. JH conducted investigation, methodology, and writing – original draft. TL managed funding acquisition, formal analysis, methodology, writing – original draft, and writing – review and editing. MBH contributed to funding acquisition, project administration, investigation, methodology, writing – original draft, and writing – review and editing.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT Checklist.
[PDF File (Adobe PDF File), 122 KB - resprot_v14i1e63498_app1.pdf]

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Abbreviations

ADAPT-ITT: Assessment, Decision, Adaptation, Production, Topical Experts, Integration, Training, and Testing

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CARE-HF: Supporting Physical and Mental Health in Rural Veterans With Heart Failure
COPE-HF: Coping in Heart Failure
HF: heart failure
HIPAA: Health Insurance Portability and Accountability Act
NI: nurse interventionist

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Protocol

Centering Birthing Experiences of Women of Color: Protocol for a Qualitative Maternal Near Miss Study

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Abstract

Background: In the United States, Black women are 3-4 times more likely to experience maternal near miss (MNM) or severe maternal morbidity (SMM) than non-Hispanic White women. However, there is a limited narrative-based investigation into Black and other marginalized women's MNM experiences. Additionally, limited extant research on the impact of MNM and SMM on birthing women's families or support persons and health care providers precludes the development of multilevel, patient-centered methods to eliminate these racial or ethnic disparities.

Objective: This paper presents the protocol for a study that aims to draw insights from the experiences of racially and socioeconomically diverse mothers with MNM and SMM, their family or support persons (eg, partners), and health care providers to inform legislation, clinical practice, and infrastructure for optimal social support using PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) guidelines. Using a storytelling approach to assess participants' risk factors, document underlying causes, and research clinical causes of MNM, researchers hypothesize these data will inform policies to improve maternal conditions and provide safe and effective prevention and treatment options for birthing persons.

Methods: Morehouse School of Medicine (MSM) will partner with health services and community-based organizations to promote inclusive participant recruitment for this multiphase study. In phase 1, qualitative interviews were conducted with birthing women (n≤87) who have experienced MNM and SMM. In phase 2, we will conduct qualitative interviews with the following groups: birthing women's partners or support persons (n≤50), health care providers serving birthing women (n≤50), and adults who lost their mothers to pregnancy-related complications (n≤50). In each phase, the total number of participants interviewed will be based on theoretical saturation, that is, the point in iterative data collection and analysis when all important insights have been exhausted from the data already available.

Results: Recruitment for phase 1 started in July 2021. As of March 2024, we have recruited 87 racially and socioeconomically diverse birthing women. Of those, 74% (64/87) self-identified as Black or African American, 20% (17/87) as Hispanic or Latina, and 9% (8/87) as Native American or Alaska Native. Severe preeclampsia accounted for 46% (40/87) of participants' pregnancy-related adverse experiences. Qualitative interviews grounded in narrative-based medicine are ongoing. Recruitment for phase 2 will occur between July 2023 and December 2024. Study results will be published in peer-reviewed scientific journals.

Conclusions: The findings from this research will deepen the understanding of how severe obstetric complications (1) are experienced by birthing women; (2) are perceived by their partners, support persons, and health providers; and (3) impact the lives of bereaved family and community members.

(JMIR Res Protoc 2025;14:e58410) doi:10.2196/58410

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KEYWORDS

maternal health disparities; maternal near miss; minority health; mental health; narrative-based medicine; experiences; birthing experience; women; Black women; United States; maternal morbidity; patient-centered; racial; ethnic; disparities; socioeconomically; pregnancy; childbirth; postpartum; antenatal

Introduction

Maternal health encompasses the well-being of both mothers and their newborns during pregnancy, childbirth, and the postpartum period. Despite advancements in medical technology and health care systems, there remain persistent challenges with maternal mortality (MM) and morbidity. The Centers for Disease Control and Prevention reports that the MM rate for the United States in 2021 was 32.9 deaths per 100,000 live births, compared to a rate of 23.8 in 2020 and 20.1 in 2019—statistics that suggest MM is increasing [1]. Likewise, severe maternal morbidity (SMM) is also on the rise in the United States [2]. SMM involves unforeseen birth outcomes that cause short-term and long-term health effects for birthing persons, including hemorrhage, cardiac arrest, organ failure, major surgery, and other life-threatening complications that require interventions [3]. Sadly, disparities in adverse pregnancy-related outcomes are widening. Research shows women of color experience disproportionate rates of MM and SMM in comparison to their non-Hispanic White counterparts [4,5]. This issue is perpetuated by racism embedded within the maternal health care infrastructure to the extent of which social determinants, such as higher income and education, no longer serve as protective factors for health [5-9].

The World Health Organization (WHO) contends that maternal near miss (MNM), defined as “a woman who nearly died but survived a complication that occurred during pregnancy, childbirth or within 42 days of termination of pregnancy,” is a more useful indicator for studying the evaluation and improvement of obstetric health care than MM [10]. To date, little is understood about the contributors to MNM, especially for women and birthing people of color. Public health’s tendency to rely on medical records and statistics often renders those most affected by health disparities unseen, unheard, and unnoticed in the discourse [11]. As Silverio et al [12] wrote, “it is not uncommon for quantitative approaches to be unable to detect the nuances of the experiences we seek to understand.” Social context is needed to conceptualize the intricacies of health inequity as a means for developing effective and sustainable solutions [13]. Therefore, using a narrative-based medicine (NBM) model [14], this study centers on women of color’s lived experiences [15] with surviving life-threatening pregnancy complications. Additionally, we are collecting a multistakeholder perspective by interviewing health care providers and partners or support persons who have witnessed an MNM experience and gathering narratives from adults and caretakers of adults, who lost their birth mother due to maternal causes. Using this approach, we hope to obtain an understanding of these stakeholders’ perceptions and the impact of their experiences. Our goal is to uplift participants’ stories as data points for influencing maternal health legislation, clinical practice, and health care strategy.

Methods

Study Design and Conceptual Framework

This study explores the burden of MNM and SMM using a narrative or storytelling approach recognizing birthing persons’ experiences as legitimate sources of data. We used the Three Delays Model [16] to inform data collection and analysis. This model posits that MNM and SMM are largely the result of three critical delays, that are, first, delayed decision to seek care—barriers to making this critical decision include underestimation of the severity of the problem and its potential complications, poor understanding of danger signs and the potential scope of complications, cultural beliefs, customs, and attitudes (eg, distrust) regarding seeking care, and lack of social supports, among others. Second, delayed action or delay in reaching an appropriate site of care—getting to care, by definition, requires adequate transportation. A notorious problem in the developing world, transportation is also a challenge in many US states. Many states lack a sufficient number of perinatal providers; for example, half of Georgia’s 159 counties lack a maternity provider [17]. Barriers like health care insurance enrollment and coverage, provider network limitations, as well as financial constraints can also be difficult to navigate. Further, lack of social support and lack of personal agency may hinder a woman’s ability to act. Third, delayed diagnoses and appropriate treatment once a facility is reached—lack of facility resources (ie, equipment, blood, and drugs), a deficit of appropriately trained personnel, and systems that are poorly organized to manage obstetrical and medical emergencies are among the factors which can contribute to this delay.

Eligibility and Recruitment

In phase 1, to be eligible for the study, participants had to meet the criteria of (1) self-identity as Black or African American, Indigenous, or Latinx; (2) older than 18 years of age; (3) meet WHO near miss criteria, that is, experience with severe postpartum hemorrhage, severe preeclampsia, eclampsia, sepsis or severe systemic infection, and ruptured uterus during pregnancy; and (4) can speak and read English. Additionally, the screener survey was modified to include specific questions about medical interventions participants may have experienced to differentiate between MNM and SMM experiences. Recruitment occurred from July 2021 through April 2022. States originally chosen for recruitment included Georgia, Louisiana, New Jersey, and the DMV area (Washington, DC; Maryland; and Virginia) due to their high rates of MM. In September 2021, New York, Connecticut, South Carolina, and Mississippi were added to increase recruitment, followed by the addition of Alabama, Texas, and Oklahoma in December 2021. After numerous inquiries from birthing persons outside the previously included states, the study was expanded to include the entire United States in March 2022.

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In phase 2, health care providers must meet the criteria of (1) self-identify as a physician, nurse practitioner, physician assistant, midwife, pediatrician, psychologist, or doula; (2) over 50% of their patient population identifies as a racial or ethnic minority; and (3) had a patient that experienced an MNM or witnessed an MNM. Support persons or partners will be considered eligible if they meet the criteria of (1) self-identify as a support person for a birthing person who experienced an MNM; (2) self-identify as Black or African American, Indigenous, or Latinx; (3) older than 18 years of age; and (4) can read and speak English. For adults whose mothers died due to maternal causes and caretakers of adults whose mothers died due to maternal causes, participants are considered eligible if they meet the criteria of (1) the death of the mother must have occurred within 1 year of the adult's birth; (2) self-identify as Black or African American, Indigenous, or Latinx; (3) older than 18 years of age; and (4) can read and speak English. An eligibility screener survey was created via REDCap (Vanderbilt University) for both phases of the study to identify participants.

Data Collection

All internal and external team members were required to complete the basic Collaborative Institutional Training Initiative course. Team members were also trained in research interviewing techniques, including how to ask additional questions that may be relevant to each specific interview.

Before the interviews, each participant completed the screening survey to verify their eligibility. Participants also completed a voluntary survey collecting sociodemographic data in addition to data surrounding the structural determinants that may have contributed to their MNM experience. These factors include age, parity, marital status, place of residence, education level, income, neighborhood characteristics, food insecurity, and so forth. Scheduling for interviews took place over email or messages via the technology platforms provided by Optum. Interviews were conducted virtually over the Zoom platform (Zoom Video Communications), included both audio and video, and typically lasted between 1 and 2 hours.

Birthing persons were identified through contacts with Morehouse School of Medicine (MSM) partner organizations, including our national community partner Reaching Our Sisters Everywhere (ROSE). ROSE was founded to address breastfeeding disparities in Black communities and works to normalize breastfeeding by providing resources and networking opportunities for individuals and communities. As a national expert, and in partnership with communities, ROSE builds equity in maternal and child health and fatherhood initiatives through culturally appropriate training, education, advocacy, and support. This partnership served as an opportunity to combine our advocacy and support of the community. ROSE used its network to recruit participants and assisted in conducting interviews. MSM and ROSE team members closely supported one another in debriefing some of the challenging and emotionally charged conversations held with participants about their MNM experiences [12]. This study was supported by Optum, the health services business of United Health Group, through grant support and research participant recruitment. Screening criteria were the same across all tools, and participants were cross-referenced against past and scheduled participants to avoid duplication of data.

Consent for interview facilitation and recording and transcription of interviews in addition to the demographic information were all collected via REDCap. A detailed informed consent form was developed by the research team and approved by the MSM institutional review board (IRB). The consent form was completed during the Zoom session with a team member present to answer any questions prior to beginning the interview. After determining that mental health effects were a common theme during several interviews, the consent form was modified in the event that emergency professionals needed to be contacted. The adjusted language stated, "This certificate does not stop Morehouse School of Medicine from giving out information to prevent harm to you or others." Any participants who mentioned suicidal ideation were also sent a Patient Safety Plan Template. This template, completed by individuals in their own time, collects warning signs, coping strategies, crisis contacts, and other material for participants to reference as needed [18]. Acknowledging that reliving traumatic experiences may have an effect, all participants received a detailed list of mental health resources located in their indicated state of residence.

Folders containing information about interviews and data analysis, including recruitment tracking, team interviewer availability, interview scheduling, and progress, were securely stored in an encrypted drive. Access was restricted to certified team members via password. Regular biweekly meetings were set up for the internal team to discuss updates and recruitment strategies. Additionally, separate biweekly working sessions were held with the funder.

As aforementioned, this study uses the power of storytelling, particularly NBM, which applies the narratives of patients or participants to medical practice [14]. We sought to understand participants' interactions with health providers, perceptions of quality of care, the circumstances of their "near miss," social support received, and their lived experiences prior to becoming pregnant. The interview guide was developed using the Three Delays Model and the International Consortium for Health Outcomes Measurement Set of Patient-Centered Outcome Measures for Pregnancy and Childbirth. These measures, including survival, morbidity, patient-reported health and well-being, and patient satisfaction with care were developed for providers to assess to improve patients' health outcomes and well-being [19]. The interview guide was submitted to and approved by the MSM IRB. In total, the interview guide contained 12 main questions and 13 probing questions.

For example, 1 key question of the interview guide used the Three Delays Model:

> *How was the process when you arrived at the hospital and how was your complication resolved? Take me through this part. What was said to you? Did you know what was going on? What was communication like? How did you feel at that moment?*

- Who/what were obstacles or facilitators to timely care?
- What was the wait time for care?
- Reasons for any delays

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- Perceptions of quality of care

Furthermore, most of the interviews were spent answering the "near-miss" question:

> *Tell me about your birth experience. Tell me the story, all the way from beginning to end, describe the setting, who was involved, do you have any pictures you would like to share, please address important timelines...*

After the completion of the interviews, each participant received an email with a US $100 gift card as compensation. Also included in the email was the list of mental health resources and a link to the screener if any participants wanted to share the study with others.

Ethical Considerations

All Collaborative Institutional Training Initiative certificates were submitted and approved by the MSM IRB (ID number 1754465-15). Informed consent and the ability to opt out were provided to every participant. Participant data were deidentified. All participants who completed an interview were compensated with a US $100 gift card.

Data Analysis

After interviews were transcribed using a transcription service, transcripts were uploaded into Dedoose, a web-based qualitative data analysis program developed by SocioCultural Research Consultants, LLC [20]. A qualitative analysis training session was conducted and recorded for all Optum and MSM team members involved in the process. Our team used an open coding approach in which the codes identified emerged from the data itself, also known as inductive coding [21,22]. Once codes were found, they were classified under larger themes to establish a codebook. Research team members met periodically to refine and collate codes. Each coded transcript was reviewed by another team member to ensure the consistency of the code application. If there were any disagreements regarding codes, team members were informed to bring it to the attention of the principal investigator, and a final code would be decided via a team discussion. Additionally, any suggestions for new codes were brought to the attention of the principal investigator. Data analysis began in May 2022 and was completed in March 2023. Coding included about 12-15 team members per round.

Our research question is qualitatively focused, though we will collect and analyze quantitative data in a few ways. We will use demographic and quantitative data first to comprehensively describe the study population. Second, we will use these data to explore whether qualitative themes vary across participant characteristics such as race, age, income, education, and the presence or absence of social support. As we iteratively review the interview data throughout the analysis process, we will also examine thematic differences across other relevant factors that may emerge. Finally, given there are adequate data to support these analyses, we will assess whether factors including demographic (eg, race, age, income, and education); psychosocial; and clinical (eg, receipt and timing of prenatal care) factors are associated type of pregnancy-related complications experienced. We will perform qualitative analyses with SAS (version 9.4; SAS Institute) and SPSS Statistics (version 29; IBM Corp) [23,24].

Results

This study was funded in 2021 and recruitment for phase 1 started in July 2021. As of March 2024, we have recruited 87 racially and socioeconomically diverse birthing persons for phase 1. Of those, 74% (64/87) have self-identified as Black or African American, 20% (17/87) as Hispanic or Latina, and 9% (8/87) as Native American or Alaska Native (Table 1). Given the relatively low representation of some racial or ethnic groups, we will tailor ongoing recruitment efforts for phase 2 to improve inclusivity.

Table 1. Demographics of participants who completed an interview about the maternal near miss or severe maternal morbidity experience (N=87).

Variable	Values, n (%)
Race and ethnicity	
Black or African American	64 (74)
Hispanic or Latino or Latina	17 (20)
Native American, Alaska Native	8 (9)
Asian	4 (5)
Middle Eastern	1 (1)
Indian	1 (1)
Hawaiian or Other Pacific Islander	0 (0)
White	0 (0)
Other	4 (5)

Severe preeclampsia accounted for 46% (n=40) of participants' pregnancy-related adverse experiences (Table 2). Qualitative interviews grounded in NBM are ongoing.

Recruitment for phase 2 is scheduled to occur between July 2023 and December 2024. Findings from each phase will be published in peer-reviewed scientific journals.

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Table 2. Pregnancy-related complications that participants indicated experiencing (n=86).

Variable	Values, n (%)
Severe preeclampsia	40 (46)
Severe postpartum hemorrhage	22 (26)
Eclampsia	3 (4)
Ruptured uterus	2 (2)
Sepsis or severe systemic infection	1 (1)
Other	18 (21)

Discussion

Principal Findings

Collecting stories from our participants' unique birthing experiences, as they relate to severe pregnancy-related complications, has allowed us to investigate the contributors to MNM and SMM and seek opportunities for improvement. Additionally, the majority of this study's participants completed college or a graduate or professional degree and reported an annual household income of $50,000 or more. Therefore, gathering demographic data from participants provides insight into whether socioeconomic "protective" factors, including income and education, have a significant impact on a birthing person's likelihood of experiencing MNM and SMM.

Sharing narratives from women of color who have experienced an MNM and SMM not only provides an opportunity to amplify the voices of those who have been historically silenced; but also, the evidence needed to advance maternal health justice. These perspectives are imperative in guiding the development of health priorities, policies, and strategies that drive optimal experiences for all birthing people. Some of our recommendations include equitable and respectful health care training, workforce diversification promotion, and health system disparity dashboards. Gathering stories from additional stakeholders will allow us to use their perspectives to refine our recommendations.

Strengths and Limitations

Initially, the interviews conducted were determined to be experiences of SMM and MNM. Using the WHO near-miss approach, the screener survey was edited to include questions regarding critical interventions [10]. Participants were asked which critical interventions were performed to save their lives, including cesarean section, blood transfusion, and intensive care unit admission. After implementing these changes, the following interviews were determined to be the experiences of MNM. All SMM interviews were noted as such, and they were organized separately from the MNM interviews. Additionally, we noted many completed screener surveys were fraudulent. There was an influx of emails, in both the internal email account and our funder's email account, that were spam and fraudulent. Screeners and emails were determined to be fraudulent if there were multiple screeners completed with different answers under the same email, the email addresses provided were invalid, and the open-ended answers or email communication did not grammatically make sense. To combat this issue, we incorporated a reCAPTCHA (Google) into our survey. Campbell et al [25] explain that humans and advanced bots can successfully avoid these mechanisms; this was consistent with our findings, given that reCAPTCHA did not seem to reduce the number of fraudulent screeners completed.

Future Directions

At this time, the study has expanded to include partners and support persons of those who have experienced an MNM, health care providers who have witnessed an MNM, and adult children and their caretakers who lost their mothers due to maternal causes. Garnering a multistakeholder perspective about MNM, SMM, and maternal deaths will allow us to examine the impact that severe obstetric complications may have on family members, survivors, and health care providers.

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Data Availability

The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

NHG was the principal investigator and performed the conceptualization, project administration, supervision, and writing (review and editing). KHS coordinated the submission and performed writing (review and editing). OF contributed to the supervision and writing (review and editing). LC performed supervision and writing (review and editing). TL performed the writing (review and editing). AS contributed to writing (review and editing). KB contributed to writing (review and editing). KS contributed to writing (review and editing). AM performed writing (review and editing). SM contributed to writing (review and editing).

Conflicts of Interest

None declared.

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Abbreviations

IRB: institutional review board
MM: maternal mortality
MNM: maternal near miss
MSM: Morehouse School of Medicine
NBM: narrative-based medicine
PRISMA-P: Preferred Reporting Items for Systematic review and Meta-Analysis Protocols
ROSE: Reaching Our Sisters Everywhere
SMM: severe maternal morbidity
WHO: World Health Organization

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Protocol

Effects of a Monophasic Hormonal Contraceptive With Norgestimate+Ethinyl Estradiol on Menstrual Bleeding: Protocol and Design of a Multicenter, Prospective, Open-Label, Noncomparative Study in Italy

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Abstract

Background: Norgestimate (NGM) is a progestin with negligible androgenic activity that is available in combination with ethinyl estradiol (EE) as a monophasic combined oral contraceptive (COC). It has been more than 30 years since a clinical study evaluated the effects of monophasic NGM/EE on menstrual cycle characteristics in healthy women, and in the interim, there has been growing recognition that clinical trials of contraceptives should evaluate a wide range of potential positive and negative impacts for users.

Objective: The aim of this study is to investigate menstrual cycle control during the use of a monophasic COC formulation containing NGM 0.25 mg and EE 0.035 mg (Effimia; Italfarmaco SpA), using established methodologies as well as patient-reported outcomes.

Methods: This is a prospective observational study being undertaken in a target population of 228 healthy Italian women aged 18-35 years who are starting oral contraception for the first time or switching from another COC. The participants are asked to complete a diary for 6 cycles recording information about their menstrual cycles (frequency, duration, regularity, estimated flow volume, and breakthrough bleeding), any unscheduled bleeding, and an evaluation of dysmenorrhea, using a 100-mm visual analog scale from 0=no pain to 100=very severe pain, and any adverse events. Compliance is assessed after 3 and 6 months via returned medication. The primary end point is the change from baseline in the rate of intermenstrual bleeding during the sixth cycle. At baseline, 3 months, and 6 months, acne will also be assessed using the Global Acne Grading Scale, and participants will complete a Profile of Mood State to assess premenstrual syndrome and the Female Sexual Function Index to evaluate the quality of their sex life. A subgroup of 28 participants at 1 site (Genoa) is also providing a blood sample for the assessment of metabolic, endocrine, and coagulation parameters.

Results: Study enrollment began in July 2023 and is expected to be complete by December 2024. Data analysis is expected to be complete by October 2025.

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Conclusions: This study into the effects of monophasic NGM/EE 0.25/0.035 mg on menstrual characteristics in healthy Italian women will provide up-to-date data on these effects and includes assessments of a range of other parameters, such as acne severity and patient-reported outcomes, in line with recent international consensus recommendations.

Trial Registration: ClinicalTrials.gov NCT06067256; https://clinicaltrials.gov/study/NCT06067256 and EudraCT 2021-003027-15; https://www.clinicaltrialsregister.eu/ctr-search/trial/2021-003027-15/IT

International Registered Report Identifier (IRRID): DERR1-10.2196/63683

(JMIR Res Protoc 2025;14:e63683) doi:10.2196/63683

KEYWORDS

combined oral contraceptive; ethinyl estradiol; menstrual cycle; monophasic; norgestimate; hormonal contraceptive; menstrual health; Italy; women's health; patient-reported outcomes; methodology; observational study; reproductive health; data analysis; assessment

Introduction

Combined oral contraceptives (COCs) are the most commonly prescribed form of hormonal contraception in Italy and in other European countries [1]. These contraceptive pills contain a combination of estrogen and progestin to suppress ovulation (the primary contraceptive effect) and to change endometrial and cervical secretions, hindering the passage of sperm [2]. COCs may be monophasic or multiphasic. Monophasic COCs contain the same dose of estrogen and progestin in each pill, whereas the ratio of these hormones varies over the course of a cycle in multiphasic COCs.

Since the first development of COCs in the 1960s, formulations have been modified to reduce the risk of undesirable adverse events (AEs) and cardiovascular health risks [3]. The early progestins used in first- and second-generation COCs were chemically related to testosterone and caused androgenic AEs such as acne, hirsutism, and oily skin, which could undermine adherence as well as negative effects on high-density lipoprotein cholesterol [4]. Newer progestins have been structurally modified to be less androgenic or are structurally related to spironolactone [5,6]. In addition, estrogen doses have been progressively lowered, and most COCs in use today contain ≤0.035 mg of ethinyl estradiol (EE) [3]. COCs containing the first- and second-generation progestins were associated with a markedly higher risk of venous thromboembolism (VTE) compared with COCs containing the newer-generation progestins [7].

One such newer-generation progestin is norgestimate (NGM). NGM is a third-generation progestin derived from 19-nortestosterone [8]. It is rapidly hydrolyzed in vivo to norelgestromin, the primary active metabolite (75% to 80%), and levonorgestrel (20% to 25%) [9]. Both NGM and its metabolites have activity similar to endogenous progesterone but have a very poor affinity for androgen receptors and are therefore less androgenic than earlier progestins such as norgestrel, gestodene, or levonorgestrel [9,10]. In addition, unlike levonorgestrel, NGM increases levels of sex hormone–binding globulin in plasma, but does not bind to sex hormone–binding globulin, and is associated with reduced levels of free testosterone [11]. Data show that COCs containing NGM carry a lower risk of VTE than COCs containing cyproterone acetate, desogestrel, dienogest, drospirenone, or gestodene [12,13]. On the other hand, contraceptive patches containing norelgestromin are associated with a slightly higher incidence of VTE compared with levonorgestrel-containing COCs, presumably because of the high cumulative dose of EE that accompanies the transdermal route of administration [9].

Women want their contraceptives to be effective in preventing pregnancy, convenient, safe, and well tolerated, and with excellent cycle control [14]. Unscheduled bleeding has a number of negative impacts on a woman's life, in addition to the inconvenience, including the potential for a negative effect on their sexual life and confusion about the status of their cycle [14]. Some women may interpret unscheduled bleeding as an indication that the COC is not working or interrupt use because of it [14]. Monophasic COCs containing 0.030-0.035 mg of EE offer women the greatest likelihood of a regular bleeding pattern with a low risk of estrogen-associated risks as well as the option of fewer periods by reducing or eliminating the placebo period altogether [15]. As well as preventing pregnancy and potentially providing better cycle control (increased regularity and reduced intermenstrual bleeding), COCs may also offer improvements in acne and premenstrual or menstrual symptoms, such as mood changes, headaches, and pelvic pain [16]. However, effects on these parameters vary between COCs [16].

A large German study (N=59,701) demonstrated that the use of a monophasic COC containing 0.25 mg of NGM and 0.035 mg of EE reduced the rate of breakthrough bleeding in healthy women compared with the rate before they started taking NGM/EE [17]. Similar results were seen in an Italian study among 92 women receiving NGM/EE [18]. However, both of these trials were conducted more than 30 years ago, and there has been no recent research in Italy to confirm the effects of monophasic NGM/EE in healthy women. Moreover, since then, there has been growing recognition that clinical trials of contraceptives should evaluate a wide range of potential positive and negative impacts for users [19].

Thus, this study is being undertaken to investigate menstrual cycle control during the use of a monophasic COC formulation containing NGM/EE 0.25/0.035 mg (Effimia; Italfarmaco SpA), using established methodologies as well as patient-reported outcomes (PROs).

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Methods

Recruitment

This prospective, open-label study is being conducted at 6 centers in Italy in healthy women aged 18 to 35 years who are starting oral contraception for the first time or planning to switch to a new COC for the purpose of contraception and not for therapeutic reasons. No specific tests are performed before enrollment, consistent with Italian guidelines that such tests are not indicated in women without individual or family risk factors [20]. Patients who are switching need to undergo a 1-month washout phase prior to entry by discontinuing their previous COC 1 month prior to starting NGM/EE 0.25/0.035 mg. The participants must be residents of Italy and be sufficiently proficient in Italian to understand the informed consent form and the instructions for COC use. The key exclusion criteria are contraindications to the COC according to the current summary of product characteristics, concomitant conditions that place users at risk of AEs, or the use of COC for indications other than contraception, such as polycystic ovarian syndrome, endometriosis, or recurrent menometrorrhagia. Complete inclusion and exclusion criteria are shown in Textbox 1. Certain concomitant medications are not permitted for the duration of the study to minimize the potential for drug interactions or confounding of end-point assessment (Textbox 1).

Textbox 1. Complete inclusion and exclusion criteria.

Inclusion criteria (all must be met)

- Healthy women aged between 18 and 35 years (inclusive) in need of contraception.
- Residing in Italy and having a good knowledge of the Italian language, such as to correctly understand the informed consent form and the instructions for use and to ensure potential adherence to the study.
- Willing and able to understand and complete the written informed consent form.
- Willing to comply with the study protocol.

Exclusion criteria (any 1 of these disqualifies an individual from participating)

- Any contraindications to the use of combined oral contraceptives (COCs) according to the current summary of product characteristics of Effimia, that is, women presenting (or having ever presented) with myocardial infarction, transient ischemic attack, stroke, angina pectoris, deep vein thrombosis, pulmonary embolism (or presence of blood clots in organs other than legs and lungs), any blood clotting disorder (such as protein C deficiency, protein S deficiency, and antithrombin-III deficiency), or who need to undergo surgery or lie down for a long period of time (including the risk of previous deep vein thrombosis, arterial thromboembolism, hypertension in the course of treatment, and diabetes). If any of the listed conditions should appear during the use of the tested COC, the product must be stopped immediately, and the participant withdrawn from the study.
- Severe diabetes with blood vessel damage, heart valve disease with complications, severe hypertension, severe hypercholesterolemia or hypertriglyceridemia, hyperhomocysteinemia, migraine with aura, hepatitis C (and taking medications for this condition), endometrial hyperplasia, or unexplained vaginal bleeding.
- Women who are breastfeeding or pregnant or suspect they are pregnant.
- Current or history of any liver disease not yet recovered (liver function not yet normalized), any benign or malignant tumor of the liver, any breast or genital organs cancer (even suspected), or jaundice during pregnancy or while using hormonal contraceptives.
- Galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption syndrome.
- Hypersensitivity to the active substances or to any excipients of the tested COC (eg, norgestimate, ethinyl estradiol, or lactose).
- Use of any of the following during the study period (according to the summary of product characteristics of Effimia): treatments for tuberculosis (eg, rifampicin), epilepsy (eg, primidone, phenytoin, barbiturates, carbamazepine, or oxcarbazepine), HIV and hepatitis C virus infection (protease inhibitor drugs and nonnucleoside reverse transcriptase inhibitors such as ritonavir, nevirapine, efavirenz, and also ombitasvir, paritaprevir, or dasabuvir), fungal infections (eg, griseofulvin), arthritis, osteoarthritis (etoricoxib), or pulmonary arterial hypertension (bosentan), and St John's wort used as an antidepressant. Medicines containing cyclosporine, antiepileptic lamotrigine, tranexamic acid, theophylline (used to treat respiratory problems), and tizanidine (used to treat muscle pain or cramps) should not be taken as well.
- Use of hormonal contraceptives in the previous month.
- BMI ≥30 kg/m^2 (class I obesity).
- Smoking >15 cigarettes per day.
- Off-label use of COC (eg, for polycystic ovarian syndrome, endometriosis, or recurrent menometrorrhagia).
- Currently taking part or who took part in clinical studies with experimental products in the previous month.
- Incapacity or inability to comply with the study protocol (unreliability in the intake of the product or in the completion of the diary) according to the investigator's opinion.

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Ethics Approval

The study protocol and amendments were approved by the ethics committee at the coordinating center (Territorial Ethics Committee—Liguria; application 202100302715-003), with the latest version approved on June 17, 2024. The study is being conducted in accordance with the Declaration of Helsinki (seventh revision, 2013), the Convention of Oviedo in April 1997 and the additional protocol in January 1998, and the national laws, regulations, and applicable guidelines of Italy. In addition, the study is consistent with the International Conference on Harmonization Tripartite Guidelines for Good Clinical Practice requirements. Prior to any procedures, participants are given information about the study and asked to sign an informed consent form. Their personal data are deidentified before being stored and protected according to the current European General Data Protection Regulations. The women do not receive any financial compensation for participating in the study.

Procedures

During the baseline visit, participants have a physical examination, including an assessment of acne severity (using the Global Acne Grading Scale [GAGS] [21]), and provide a complete medical and menstrual history (Figure 1). They are asked about the characteristics of their menstrual cycle (frequency, duration, regularity, estimated flow volume, and breakthrough bleeding), any unscheduled bleeding, and an evaluation of dysmenorrhea, using a 100-mm visual analog scale (VAS) from 0=no pain to 100=very severe pain. Participants are also being asked to complete a Profile of Mood State (POMS) to assess premenstrual syndrome and the Female Sexual Function Index (FSFI) to evaluate the quality of their sex life, using the validated Italian language versions of these questionnaires [22-24]. At 1 site (Genoa), 28 participants are also providing a blood sample for the assessment of metabolic, endocrine, and coagulation parameters (Textbox 2).

At the baseline visit, participants are provided with NGM/EE 0.25/0.035 mg for the first 3 cycles and a diary, in which they are asked to record cycle evaluation parameters (Table 1), their medication-taking behavior, concomitant medications including over-the-counter medications (start and stop dates and dose), and any AEs.

Study participants are asked to return to the study site for 2 further visits, at day 84 and day 168 (Figure 1), and to bring their diaries and medication with them (whether used, partially used, or not used). At visit 2, researchers check the diaries to verify that participants are completing them correctly and provide them with new diaries and another 3 cycles of NGM/EE 0.25/0.035 mg. At both visits 2 and 3, the same assessments are conducted as at the baseline visit (physical examination, GAGS, POMS, FSFI, and dysmenorrhea VAS), and participants are asked about concomitant treatments, adherence, and AEs. At visit 3, the diaries are collected for final verification, and the subgroup of participants from Genoa provides another blood sample. In the case of an early withdrawal before the end of the sixth cycle, the investigator asks the participant to return for a final visit and records the reasons for the participant's decision to discontinue the study.

Figure 1. Study design. AE: adverse event; COC: combined oral contraceptive; FSFI: Female Sexual Function Index; GAGS: Global Acne Grading Scale; POMS: Profile of Mood State; VAS: visual analog scale.

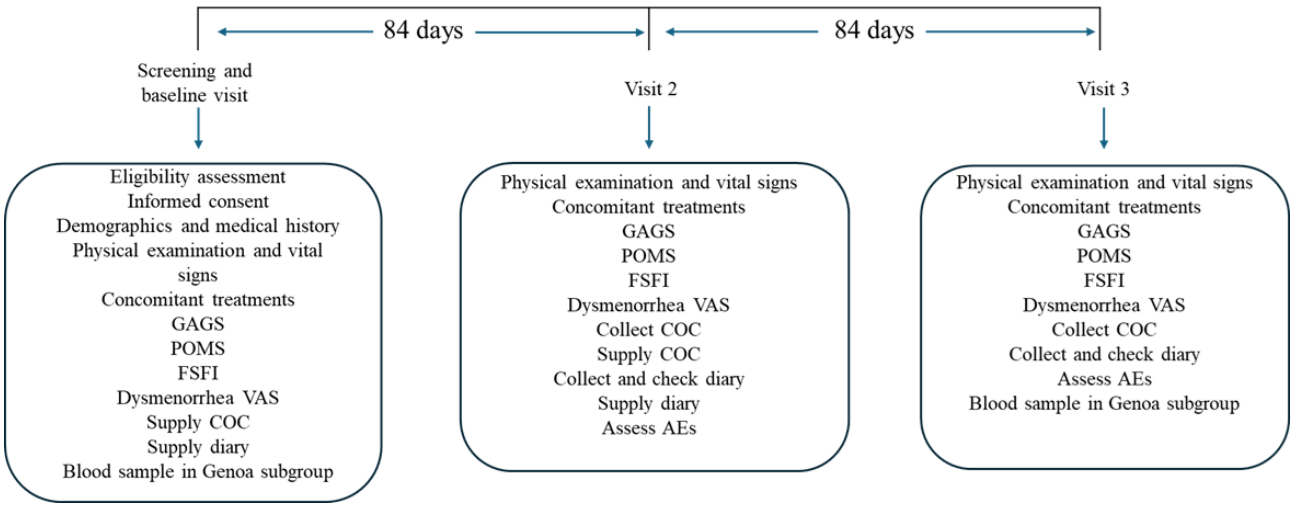

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Textbox 2. Parameters evaluated in blood samples in the subgroup of participants from Genoa.

Metabolic

- Glucose
- Insulin
- Total cholesterol
- High-density lipoprotein cholesterol
- Low-density lipoprotein cholesterol
- Triglycerides

Endocrine

- Total testosterone
- Dehydroepiandrosterone
- Androstenedione
- Sex hormone–binding globulin
- Free androgen index

Related to coagulation

- Fibrinogen
- Factor VII
- Antithrombin III
- Factor VIII
- Protein C
- Thrombin time
- Anticoagulant functional protein C
- Total protein S
- Activated protein C resistance

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Table 1. Cycle evaluation parameters.

Parameter	Normal	Abnormal
Frequency	• ≥24 and ≤38 days	• Absent (no bleeding): amenorrhea • Infrequent (>38 days)
Duration	• ≤8 days	• Prolonged (>8 days)
Regularity	• Regular (shortest to longest cycle variation: ≤7 to 9 days[a])	• Irregular (shortest to longest cycle variation: ≥10 days)
Flow volume (participant determined)	• Participant considers normal	• Participant considers light • Participant considers heavy

Breakthrough bleeding (bleeding or spotting between the cyclically regular onset of menses)	• None	• Random
		• Cyclical (predictable):
		  • Early cycle
		  • Mid cycle
		  • Late cycle

Unscheduled bleeding on progestin±estrogen gonadal steroids (contraceptive pills, rings, patches, intrauterine contraceptive devices, or injections)	• None (for a participant on gonadal steroid medication) • Not applicable for participants not on gonadal steroid medication	• Present

[a]Normal variation depends on age; these data are calculated excluding short and long outliers.

Data Management

Investigators collect the information in a validated electronic data system managed by a contract research organization (Advice Pharma Group Srl). The contract research organization is responsible for checking the completeness of the data, monitoring the quality of the data, identifying any extreme values (outliers), and storing the information securely according to legal requirements. Access to the data is strictly limited to authorized personnel only, and individual patient information is deidentified prior to analysis.

End Points

The primary objective of the study is to investigate menstrual cycle control by evaluating breakthrough bleeding (ie, bleeding or spotting between the cyclically regular onset of menses) during the use of the monophasic NGM/EE 0.25/0.035 mg COC. This is measured by calculating the intermenstrual bleeding or spotting occurrence rate at the sixth cycle and comparing this with the rate at baseline.

Secondary outcomes include the change from baseline at visits 2 and 3 in other parameters of cycle control (frequency, duration, regularity, participant-determined flow volume, and unscheduled bleeding), GAGS score, POMS, FSFI, and dysmenorrhea severity based on the VAS rating. Adherence and contraceptive failure rate over the 6-month study period are also secondary outcomes, as are changes from baseline in the metabolic, hormonal, or coagulation parameters in the subgroup of participants from Genoa. Adherence is being evaluated as a percentage of tablets taken, based on the medication returned by participants at each visit. Contraception failure is defined as the proportion of women who become pregnant during the 6-month study period. The reasons for any contraception failure will be identified and listed (eg, discontinuation or poor adherence).

Safety Outcomes

AEs, including any serious adverse events (SAEs), are the key safety outcome. An AE can be any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of NGM/EE 0.25/0.035 mg, whether considered related or not. This may include exacerbation of existing conditions, suspected drug-drug interactions, or clinically significant abnormal laboratory findings, although an abnormal laboratory finding may not be considered as an AE if there is no change compared to baseline values. Abnormal laboratory values or test results represent an AE only if they induce clinical signs or symptoms, are clinically significant, or require therapy. An SAE is any AE that results in death, is life-threatening, requires inpatient hospitalization or prolongation of an existing hospital stay, results in persistent or significant disability or incapacity, or results in a congenital anomaly or birth defect. Other medical events that may jeopardize the participant or may require a medical or surgical intervention to prevent an SAE are also considered to be serious.

Investigators will record any AEs or SAEs in a case report form, with a description of the event, date of occurrence, an assessment of its severity and potential relationship to NGM/EE 0.25/0.035 mg, and the outcome (including date of resolution). If there is at least a reasonable possibility that NGM/EE 0.25/0.035 mg is the cause of the AE (ie, that causality cannot be ruled out), the AE will be considered as an adverse drug reaction. The severity of the AE will be rated as mild (transient and generally not interfering with usual activities), moderate (sufficiently discomforting to interfere with usual activities), or severe (inability to perform usual activities). AEs of special interest in this study are hypertension, arterial thromboembolism,

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myocardial infarction, stroke, transient ischemic attacks, venous thrombosis and pulmonary embolism, liver and breast tumors, cancer of the cervix, and disturbances in liver function (such as increased hepatic enzyme levels).

Statistical Analysis

Based on the previous large-scale study with NGM/EE 0.25/0.035 mg, the rate of breakthrough bleeding is expected to decrease from 4.5% before use to 3% after 6 cycles, and the rate of intermenstrual spotting to decrease from 9% to 4% [17]. Therefore, a sample size of 175 participants would have 80% power to detect a treatment effect on breakthrough bleeding at a 1-sided α level of 5%. To account for a potential dropout rate of 30%, we plan to screen 240 women for eligibility and enroll 228 participants, an average of 38 participants at each of the 6 centers.

Two datasets have been defined for analysis: the per-protocol set, which includes all participants with full treatment adherence and no major protocol deviations, and the intention-to-treat set, which includes all enrolled participants who received at least 1 dose of NGM/EE 0.25/0.035 mg. The primary outcome will be evaluated only in the per-protocol population to avoid any effects of noncompliance on the interpretation of this outcome. However, secondary efficacy outcomes and safety will be assessed in the intention-to-treat population using robust statistical methods against missing data, like linear mixed models.

Continuous variables will be described using the mean and standard deviation if they are normally distributed or using the median and interquartile range if nonnormally distributed. The distribution of these variables will be assessed using the 2-tailed Student *t* test for paired data or the Wilcoxon signed rank test. Categorical variables will be described using frequencies and percentages and compared using the chi-square test or Fisher exact test [25]. There will be no imputation for missing data, and data from unscheduled visits will not be included in the analysis. No adjustment for multiplicity will be made to adjust for a type I error in secondary end points. A P value of .05 is considered to be statistically significant.

All statistical analyses will be performed using the R statistical software (version 3.5 or later; R Foundation for Statistical Computing). The final analysis will be completed after all participants have completed the study, any queries have been resolved, and the database has been locked.

Results

Study enrollment began in July 2023 and is expected to be complete by December 2025. The last participant's last visit is anticipated to be in June 2026, and data analysis will be complete by October 2026.

Discussion

Overview

We anticipate that our study will confirm previous research [17,18], showing that monophasic COC with NGM/EE 0.25/0.035 mg reduces breakthrough bleeding in healthy women. However, our study will also investigate other effects of this COC on menstrual characteristics (regularity, flow volume, and dysmenorrhea). Moreover, the study will assess the impact of NGM/EE 0.25/0.035 mg on the other factors women want from their oral contraceptives in terms of pregnancy prevention, safety, and tolerability [14].

The absolute risk of VTE is 6.29 per 10,000 woman-years in women taking COCs, which while being twice the rate in women not taking COCs is still low [26]. Although the risk is low, it is still present; therefore, physicians should be vigilant to the potential for this AE among their patients taking COCs. The risk of VTE appears to be lower with NGM than with many other types of progestin [12,13], so we do not anticipate the development of VTE among women participating in this study, which is probably too small and of too short a duration to estimate the incidence of VTE associated with NGM/EE 0.25/0.035 mg. Nevertheless, thromboembolism of any type is an AE of special interest in the study, and any occurrence will be thoroughly investigated and reported.

Our study includes an evaluation of the effects of NGM/EE 0.25/0.035 mg on acne using the GAGS. It is expected that acne will improve during the use of monophasic NGM/EE 0.25/0.035 mg since the exacerbation of acne is usually related to the androgenic potency of the COC [27].

Comparison to Prior Work

The previous large-scale study conducted in Germany among 59,701 women evaluated 342,348 menstrual cycles and showed a reduction in breakthrough bleeding from 4.5% at baseline to 3% during cycle 6 of the COC and in intermenstrual spotting from 9% to 4% during cycle 6 [16]. In the Italian study by Affinito et al [18], in which 92 women received monophasic NGM/EE, the incidence of breakthrough bleeding decreased from 3.3% to 0% at cycle 6, and the rate of spotting from 14.3% to 3.7%. Our study will include at least twice the number of women as in the earlier Italian study and therefore a more robust assessment of the effects of NGM/EE on these menstrual characteristics.

The large German study highlighted the extremely high contraceptive efficacy of NGM/EE, showing a use-efficacy Pearl index of 0.25 (95% CI 0.19-0.31) pregnancies per 100 woman-years [17], and no pregnancies were reported in the earlier Italian study [18]. There was a low incidence of AEs and a high rate of compliance in both these analyses [17,18]. Our study will provide updated information on the contraceptive efficacy, adherence rate, and safety or tolerability profile of NGM/EE 0.25/0.035 mg. The substudy is investigating the effect of NGM/EE 0.25/0.035 mg on lipid and metabolic parameters, expected to be negligible based on previous research [17,18].

Strengths and Limitations

A key difference between our study and the earlier ones is the incorporation of PROs to gather subjective information about the impact of monophasic NGM/EE on the women who take it, specifically the impact on sexuality, mood, and menstrual pain. The inclusion of PROs in our study predated, but is nevertheless consistent with, international consensus recommendations on

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research into contraceptive-induced menstrual changes, which recommend investigating the physical and psychosocial impact of these changes on the lives of the women who take them, including their sexual well-being and anxiety or stress [19].

Sexual side effects are a leading reason for women to discontinue or switch contraceptives [28], so it is important to ask women about the effect of COCs on their sexual function. The reported impact of COCs on sexual function is highly variable and encompasses negative, positive, and no effects [29,30]. Female sexuality is complex, and the association between hormone levels and sexuality is nonlinear and multidimensional since a number of different hormones regulate sexual response [29]. Data suggest that the androgenicity of the progestin and the dosage of EE in COCs have a negligible impact on sexual function [31]. Based on the available literature, we do not anticipate a significant effect of NGM/EE 0.25/0.035 mg on sexual function, but to our knowledge, this is one of the first studies to investigate the effects of this COC on sexuality using a validated instrument, the FSFI.

We are also investigating any changes in mood after 6 cycles of NGM/EE 0.25/0.035 mg using the POMS. This instrument has been used previously to investigate changes in mood during oral contraceptive use [32,33], but to our knowledge, this is the first study to use POMS to evaluate mood in women taking NGM-containing COCs.

Finally, our study includes an assessment of the severity of pain associated with menstruation in accordance with international consensus recommendations [19]. Previous studies have evaluated the incidence of pain in women taking monophasic NGM/EE but not the severity of pain [17,18]. This is an important distinction because pain is a continuum rather than a binary outcome. Data indicate that at least 90% of women experience some kind of discomfort during menstruation [34], although their experiences vary across time [35]. Dysmenorrhea is often underreported for many reasons, including that symptoms are considered normal or that women find the symptoms tolerable [36]. Therefore, pain was likely underreported in clinical trials because participants may only report pain that is new, worse, or acute [34]. Using a tool like VAS will provide nuanced information about both the incidence and severity of menstrual pain in women taking NGM/EE 0.25/0.035 mg. Limitations of our study are the absence of a control group and the relatively short duration of follow-up.

Conclusions

This study into the effects of monophasic NGM/EE 0.25/0.035 mg on menstrual characteristics in healthy Italian women will provide up-to-date data on these effects, since there has been no similar study for more than 30 years, and includes the assessment of NGM/EE 0.25/0.035 mg on PROs, in line with recent international consensus recommendations.

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Conflicts of Interest

GG received honoraria for sponsored lectures and participation in advisory boards from Bayer AG, Teva/Theramex, Exeltis, Italfarmaco, Opocrin, Organon, and Gedeon Richter outside of the scope of this manuscript. AC, GC, AMF, GM, and VB declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. EP and MM are employees of Italfarmaco SpA. EC is a medical consultant for Italfarmaco SpA.

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Abbreviations

AE: adverse event
COC: combined oral contraceptive
EE: ethinyl estradiol
FSFI: Female Sexual Function Index
GAGS: Global Acne Grading Scale
NGM: norgestimate
POMS: Profile of Mood State
PRO: patient-reported outcome
SAE: serious adverse event
VAS: visual analog scale
VTE: venous thromboembolism

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Protocol

Assessing Pulmonary Function in Children and Adolescents After Cancer Treatment: Protocol for a Multicenter Cohort Study (Swiss Childhood Cancer Survivor Study FollowUp–Pulmo)

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Abstract

Background: Childhood cancer survivors (CCS) are at risk of pulmonary dysfunction due to cancer treatments, but evidence on prevalence and risk factors remains limited. Most previous studies had small sample sizes or retrospective study designs, little information about treatments, or a lack of standardization of pulmonary function tests (PFTs) or limited their investigation to certain PFTs. Since spirometry mainly assesses the large airways but cancer therapy also affects peripheral airways, additional functional tests are needed. The nitrogen multiple breath washout test (N_2MBW) is sensitive to peripheral airway damage in other patient populations, but its benefit in CCS is unknown. Therefore, comprehensive and standardized evaluation of pulmonary function after cancer treatment in childhood, using different PFTs that include N_2MBW, is needed to address these knowledge gaps and provide insights into possible early stages of pulmonary dysfunction.

Objective: In the Swiss Childhood Cancer Survivor Study (SCCSS) FollowUp–Pulmo, we will comprehensively assess lung function in children and adolescents after treatment for cancer to identify risk factors for pulmonary dysfunction, assess the ability of N_2MBW to detect pulmonary dysfunction compared to other PFTs, and investigate the association of functional outcomes from PFTs with self-reported respiratory symptoms.

Methods: SCCSS FollowUp–Pulmo is a prospective multicenter longitudinal cohort study embedded in routine clinical care that enrolls CCS aged 6-20 years for whom at least 1 year has passed since a childhood cancer diagnosis, who have completed

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treatment, and who attend regular pediatric oncological follow-up care. Inclusion criteria comprise any of the following: systemic anticancer treatment (chemotherapy, immunotherapy, or targeted agents), thoracic surgery, thoracic radiotherapy, or hematopoietic stem cell transplantation (HSCT). CCS undergo a standardized pulmonary assessment, including spirometry, body plethysmography, diffusing capacity of the lung for carbon monoxide (DLCO), and N_2MBW, and complete a questionnaire on respiratory symptoms and lifestyle. Data from previous and subsequent routine care PFTs will be included in this study.

Results: Recruitment started in June 2022 at the University Children's Hospital Bern, Switzerland. Subsequently, patient recruitment expanded to the University Children's Hospitals in Basel and Geneva, Switzerland. By October 2024, we had invited 220 patients, of which 201 have already participated in this study, resulting in a response rate of 91%. Their median age at the time of the study was 14 years (IQR 10-17), and the median time since diagnosis was 7 years (IQR 4-10). The study will continuously enroll new CCS.

Conclusions: This study will contribute to a comprehensive understanding of pulmonary function in CCS and assess related risk factors, as well as the utility of N_2MBW compared to other PFTs. The results will assist in the development of more targeted screening and risk-stratified follow-up care.

Trial Registration: ClinicalTrials.gov NCT04732273; https://clinicaltrials.gov/study/NCT04732273

International Registered Report Identifier (IRRID): DERR1-10.2196/69743

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KEYWORDS

childhood cancer survivors; respiratory function tests; late effects; pulmonary toxicity; multiple breath washout test; cohort study

Introduction

Survival Rates and Long-Term Complications

Advances in childhood cancer treatment and supportive care have resulted in survival rates that now exceed 80% in high-income countries [1]. Yet, even as cancer treatments are curative in targeting cancer cells, they can harm healthy tissue and potentially cause late complications, such as second neoplasms and chronic diseases [2,3]. The cumulative incidence of such late effects among childhood cancer survivors (CCS) thus predisposes them to increased morbidity and premature mortality [4]. Among late effects, pulmonary complications are the third-leading cause of excess mortality after second neoplasms and cardiovascular diseases [5].

Pulmotoxic Treatments

Several cancer treatment modalities can be pulmotoxic. These include the chemotherapeutic agents busulfan, bleomycin, carmustine, and lomustine; thoracic radiotherapy; thoracic surgery; and hematopoietic stem cell transplantation (HSCT) [6,7]. The underlying mechanisms of pulmonary toxicity involve alveolar, vascular, and parenchymal damage resulting from chemotherapy and radiotherapy, which may progress to lung fibrosis [6-8]. HSCT-related lung damage can result from intensive conditioning regimens, infections, or graft-versus-host disease (GvHD), while surgery of the chest or lungs may reduce lung volumes and impair chest wall compliance [7,9]. However, recently published recommendations for surveillance of pulmonary function among CCS from the International Late Effects of Childhood Cancer Guideline Harmonization Group (IGHG) could not consistently confirm the pulmonary toxicity of all these treatments, particularly certain chemotherapeutics, due to limited and low-quality evidence [10]. Other chemotherapeutics, such as methotrexate and cyclophosphamide, have also been suspected of causing lung damage [8,11], but findings across studies remain inconsistent [12,13]. Considering that these treatments may harm developing lungs and potentially lead to progressive pulmonary damage [14], it is important to study their effects on lung function.

Prevalence and Detection of Pulmonary Dysfunction

Pulmonary dysfunction in CCS exposed to pulmotoxic treatments has been reported in varying proportions of CCS (44%-77%), depending on study populations and criteria used to define obstructive, restrictive, and diffusion impairments [12,13,15,16]. The lung has a large functional reserve, and early disease may often remain asymptomatic, particularly when it affects the lung periphery [17]. Most studies have used conventional pulmonary function tests (PFTs), such as spirometry, body plethysmography, and diffusing capacity of the lung for carbon monoxide (DLCO), to assess lung function in CCS. However, spirometry and body plethysmography lack the sensitivity to detect changes in small airways [18], which may be damaged first [6]. The nitrogen multiple breath washout test (N_2MBW), which measures ventilation inhomogeneity of the ventilated lung, detecting small airway disease, has been increasingly used in other patient populations, including those treated with allogeneic HSCT [19-21]. In a small prospective study of adult CCS, N_2MBW identified more cases of pulmonary dysfunction than spirometry, even among those who had not been exposed to previously defined pulmotoxic treatments [22]. Though larger prospective studies with standardized assessments are still needed, these findings suggest that N_2MBW could be a valuable complementary test in screening CCS for early pulmonary damage.

Current Knowledge Gaps

The recently published IGHG recommendations not only summarized existing evidence but also highlighted large knowledge gaps and methodological weaknesses in previous research [10]. These gaps emphasize the need for prospective, longitudinal studies with larger sample sizes and a broader range of treatment exposures to characterize the onset and progression

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of treatment-related pulmonary dysfunction. The long-term effects of newer chemotherapeutic and immunotherapeutic agents on lung function are understudied [23]. Evidence on how treatment-related complications, comorbidities, and genetic variants influence lung damage risk is limited as well. Similarly, standardization is lacking in PFTs and in the use of appropriate age- and sex-specific reference values. For example, results should be reported as z-scores rather than just proportions of patients with reduced lung function. Additionally, few studies have assessed diagnostic tests specific to the location and type of potential dysfunction, such as N_2MBW for peripheral inhomogeneity in ventilation. More data are also needed on the association between PFT outcomes and clinical symptoms. To address these gaps, we designed the Swiss Childhood Cancer Survivor Study (SCCSS) FollowUp–Pulmo.

Study Objectives

The primary objective of SCCSS FollowUp–Pulmo is to longitudinally investigate lung function in children and adolescents after cancer treatment using a comprehensive set of PFTs that also assess small-airway disease. Second, the study will investigate possible effects of treatment-related risk factors (systemic anticancer agents, thoracic radiotherapy, thoracic surgery, and HSCT), treatment-related complications (pulmonary infections, GvHD), and existing comorbidities (eg, pulmonary or cardiac disease) on lung function. Third, the study will examine the ability of N_2MBW to detect pulmonary dysfunction in comparison with other PFTs. Fourth, it will investigate the association between lung function and self-reported respiratory symptoms.

Methods

Study Design and Inclusion Criteria

SCCSS FollowUp–Pulmo is a multicenter prospective longitudinal cohort study integrated into the routine clinical care of several children's hospitals in Switzerland. The study is an interdisciplinary collaboration between the pediatric hematology/oncology and pediatric pulmonology departments of respective centers, the Institute of Social and Preventive Medicine (ISPM) at the University of Bern, and the Swiss Childhood Cancer Registry (ChCR). The ChCR is a nationwide, population-based cancer registry that includes Swiss residents diagnosed up to the age of 20 years with leukemia, lymphoma, central nervous system (CNS) tumors, malignant solid tumors, or Langerhans cell histiocytosis, classified according to the *International Classification of Childhood Cancer, Third Edition* (ICCC-3) [24]. Although the ChCR captures over 95% of children diagnosed in Switzerland [25], SCCSS FollowUp–Pulmo will also include a few patients treated and followed up in Swiss clinics who may not be registered in the ChCR due either to registration delays or residency outside of Switzerland.

All CCS aged 6-20 years for whom 1 year or more has elapsed since cancer diagnosis, who have completed treatment, and who are in regular pediatric hemato-oncological follow-up care are eligible for SCCSS FollowUp–Pulmo. The following treatment modalities possibly affecting lung function are included in SCCSS FollowUp–Pulmo: any systemic anticancer treatment (chemotherapy, immunotherapy, or targeted therapy) [26]; thoracic surgery involving the chest or lungs (excluding central line placement) [27]; radiation of the lungs, the chest (axilla, mantle, mediastinal), or scattered radiation from other radiation fields, including the whole abdomen or any upper abdominal field, spinal doses of 30 Gray or higher, and total body irradiation [27]; and HSCT [28]. Excluded are CCS who were treated only with surgery or radiation outside the thorax due to their low risk for pulmonary dysfunction [29] and patients with relapse or in palliative care at the time of recruitment.

Ethical Considerations

Ethical approval was granted by the Ethics Committee of the Canton of Bern, Switzerland (KEK-BE: 2019-00739), and the study is registered on ClinicalTrials.gov (NCT04732273). All participants provide a signed informed consent form. If any patient declines to participate, their data are not collected. Data are entered into the Research Electronic Data Capture (REDCap) database version 14.0.10 (Vanderbilt University), which complies with legal requirements for data security and data protection.

Study Procedures

The study is coordinated by the ISPM research team, which is responsible for overall study management, monitoring recruitment progress, and handling administrative and financial aspects. Clinical teams at each participating center include pediatric oncologists, pulmonologists, data managers, and study nurses.

Step 1: Selection of Eligible CCS

Eligible CCS are identified in 2 ways: (1) the ChCR provides an initial list of eligible patients to participating hospitals, and (2) a member of the clinical team regularly screens upcoming follow-up appointments, cross-referencing with the ChCR and identifying any additional eligible patients (Figure 1). This process ensures the inclusion of all eligible patients. The treating physician organizes pulmonary function assessments for the upcoming oncological follow-up appointment. Detailed recruitment procedures are developed at each center to consider clinical workflows.

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Figure 1. Flowchart of SCCSS FollowUp–Pulmo procedures. CCS: childhood cancer survivors; ChCR: Swiss Childhood Cancer Registry; ISPM: Institute of Social and Preventive Medicine; REDCap: Research Electronic Data Capture.

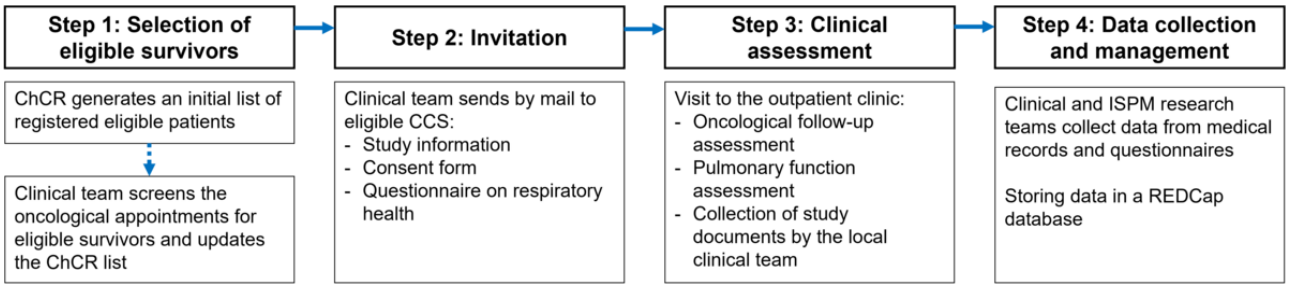

Step 2: Invitation

The clinical team sends the study information, consent form, and a questionnaire on respiratory health to eligible survivors prior to their next oncological follow-up appointment that will include PFTs. CCS who consent to participate send the documents back or bring them to the consultation.

Step 3: Clinical Assessment

At the oncological follow-up assessment, patients first meet their pediatric oncologist, who obtains a history, performs a physical examination, and refers them to pediatric pulmonology for PFTs. Since the PFTs are scheduled within the follow-up care, they are conducted irrespective of study consent. Patients with pathological results will undergo repeated PFTs, as clinically indicated (Figure 2). The clinical team collects the signed consent form and questionnaire. If patients do not complete the consent form and questionnaire prior to or during the clinical visit, they can still return the documents later. If a patient declines to participate, no data are collected for study purposes.

Figure 2. Timeline of pulmonary function assessments during SCCSS FollowUp–Pulmo. *The duration of cancer treatment varies based on the specific cancer diagnosis and the corresponding treatment protocol, while the age at which a patient transitions out of pediatric oncology follow-up may vary individually, depending on the cancer treatment protocol and the practices of the respective center. PFT: pulmonary function test; SCCSS: Swiss Childhood Cancer Survivor Study.

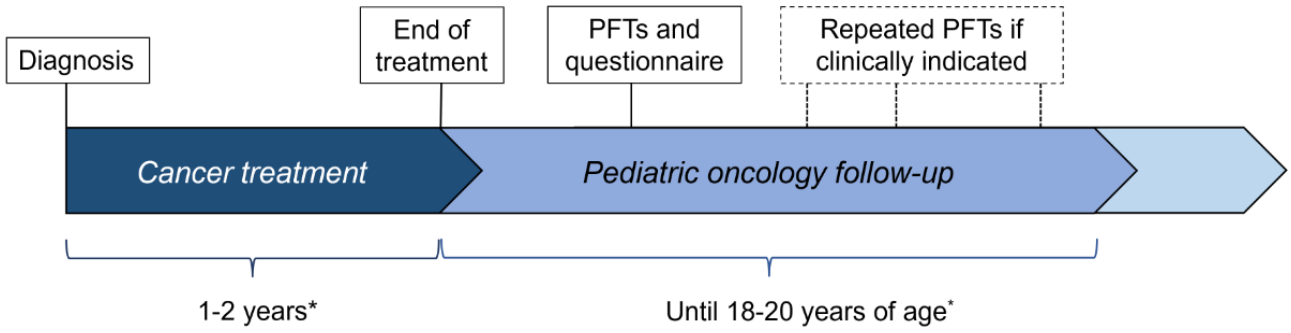

Step 4: Data Collection and Management

The clinical team at the respective study centers and the research team at the ISPM extract the data of each consenting participant from medical records, PFTs, and questionnaires. All data are stored in the REDCap database. In the database, each patient has a unique REDCap ID.

Exposures and Outcomes of Interest

Pulmonary Function Tests

CCS undergo a set of PFTs, including spirometry, body plethysmography, DLCO, and N_2MBW, according to the American Thoracic Society/European Respiratory Society (ATS/ERS) recommendations [30,31]. PFTs are conducted in pediatric lung function laboratories by trained technicians. Standard operating procedures for PFTs are harmonized among centers to ensure comparability, with quality control performed by lung function technicians. Because N_2MBW is not yet widely used in clinical settings, centralized quality control is additionally performed to ensure that only high-quality tests and the latest algorithms are included. Specialized software developed by experts at the University Hospital in Bern detects evidence of leaks, insufficient waiting time between tests, early termination of tests, synchronization issues, and abnormal breathing patterns or volumes in accordance with consensus guidelines [32,33]. Experienced pulmonologists interpret and review the results of PFTs.

Since asthma and allergic conditions are common differential diagnoses in young patients, including CCS, most clinics also measure fractional exhaled nitric oxide (FeNO) in those with obstructive patterns on spirometry or asthma-like symptoms [34]. High FeNO levels suggest an asthmatic or allergic etiology, while low levels may indicate noninflammatory causes related to cancer treatment effects.

Table 1 shows the main outcome measures from PFTs, their interpretation, anatomical correlates, and studies for reference values used for respective PFTs. SCCSS FollowUp–Pulmo also collects all prestudy PFT data from patients who previously underwent these assessments and subsequent PFTs conducted as part of ongoing clinical care.

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Table 1. PFTs[a] performed in CCS[b], their interpretation, and anatomical correlates.

Test	Main outcomes	Meaning of abnormal results	Anatomical correlates	Reference values
Spirometry	FVC[c], FEV_1[d], FEV_1/FVC, $FEF_{25\%-75\%}$[e]	Airway obstruction, reduced dynamic lung volume	Fibrotic destruction of lung tissue and large airways, reduced lung compliance	Quanjer et al [35]
Body plethysmography	FRC[f], SR_{eff}[g], SR_{tot}[h], RV[i], TLC[j], VC[k]	Reduced static lung volume, hyperinflation	Fibrotic destruction of lung tissue and large airways, reduced lung compliance	Hall et al [36]
DLCO[l]	DLCO	Reduced alveolar-capillary gas transfer, reflected by diffusion deficits	Alveolar-capillary membrane damage	Stanojevic et al [37,38]
N_2MBW[m]	LCI[n], S_{ACIN}[o], S_{COND}[p]	Increased ventilation inhomogeneity of airways with reduced global, alveolar, and conducting ventilation	Fibrotic damage of small airways	Ramsey et al [39]
FeNO[q]	FeNO	Eosinophilic airway inflammation as a key component of allergic asthma	Allergic inflammation as an alternative cause of pulmonary obstruction	Jacinto et al [34]

[a]PFT: pulmonary function test.

[b]CCS: childhood cancer survivors.

[c]FVC, forced vital capacity.

[d]FEV_1, forced expiratory volume in 1 second.

[e]$FEF_{25\%-75\%}$, forced expiratory flow at 25%-75% of the FVC.

[f]FRC, functional residual capacity.

[g]SR_{eff}: specific effective resistance.

[h]SR_{tot}: specific total resistance.

[i]RV: residual volume.

[j]TLC: total lung capacity.

[k]VC: vital capacity.

[l]DLCO: diffusion capacity of the lung for carbon monoxide.

[m]N_2MBW: nitrogen multiple breath washout test.

[n]LCI: lung clearance index.

[o]S_{COND}: conductive ventilation inhomogeneity index.

[p]S_{ACIN}: acinar ventilation inhomogeneity index.

[q]FeNO: fractional exhaled nitric oxide (measured in CCS with symptoms suggestive of asthma, eg, wheeze, dyspnea, cough, or signs of obstruction in spirometry).

Medical and Questionnaire Data

Information obtained from medical records includes anthropometric measures, respiratory disease history, physical evaluation, PFTs, cancer diagnosis and treatment, and additional data from the medical history, including comorbidities and significant treatment-related complications (GvHD, pulmonary infections) (Table 2). CCS complete a detailed questionnaire on respiratory health that includes sections on respiratory symptoms, infectious diseases, exercise-induced problems, allergic and pulmonary diseases, family history of respiratory conditions, lifestyle and environmental factors, and sociodemographic information.

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Table 2. Description of medical and questionnaire data collected as part of SCCSS[a] FollowUp–Pulmo.

Data source and data items	Description
Medical records	
Personal information and anthropometric measures	• Date of birth • Sex • Height • Weight • BMI
Respiratory history and physical evaluation	• Recent history of airway infections • Lung auscultation • Thoracic inspection • Signs of dyspnea • Oxygen saturation
PFTs[b,c]	• Spirometry • Body plethysmography • DLCO[d] • N_2MBW[e] • FeNO[f]
Cancer diagnosis	• Date of diagnosis • Type of cancer and location • Metastases • Relapse • Second malignant neoplasm
Cancer treatment	• Treatment protocol and arm • Start and end dates • Cumulative doses of all individual chemotherapy drugs, targeted agents, and immunotherapies • Radiotherapy (cumulative dose, location, duration) • Surgery (location, type) • HSCT[g] (autologous or allogeneic, donor type and source, conditioning regimens, complications)
Additional data from medical history	• GvHD[h] (acute or chronic, affected organs, grade, treatment) • Significant pulmonary infections during or after cancer treatment (diagnosis, causing pathogen, duration of hospitalization) • Comorbidities
Questionnaire	
Respiratory symptoms	• Cough (type, duration, with or without a cold) • Wheeze (frequency, duration, triggers) • Dyspnea(frequency, duration, triggers)
Infectious diseases[i]	• Otitis • Sinusitis • Pneumonia
Exercise-induced problems	• Frequency • Types • Triggering situations
Allergic diseases	• Allergic rhinitis • Hay fever • Atopic dermatitis
Pulmonary diseases[j]	• Asthma • Bronchitis • Lung fibrosis • Emphysema

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Data source and data items	Description
Lifestyle and environment	• Physical activity (compulsory school sport, recreational sport) • Active and passive smoking (amount and type of tobacco products)
Sociodemographic data and family history	• Citizenship • Parental education and profession • Family history of asthma, chronic bronchitis, hay fever, and atopic dermatitis

[a]SCCSS: Swiss Childhood Cancer Survivor Study.

[b]PFT: pulmonary function test.

[c]For each pulmonary function test, the date, test quality, and multiple outcomes (as listed in Table 1) are recorded.

[d]DLCO: diffusing capacity of the lungs for carbon monoxide.

[e]N_2MBW: nitrogen multiple breath washout test.

[f]FeNO: fractional exhaled nitric oxide.

[g]HSCT: hematopoietic stem cell transplantation.

[h]GvHD: graft-versus-host disease.

[i]Data includes the recurrence and treatment of each disease.

[j]Data includes the treatment of each disease.

Sample Size Calculation

To determine the sample size needed for our study, we based calculations on the study by Schindera et al [22], who assessed lung function in long-term CCS using spirometry and N_2MBW. This single-center study was conducted on Swiss CCS and applied the same inclusion criteria for treatment exposures, making it a suitable reference. The main outcome from N_2MBW was the lung clearance index (LCI). The mean LCI z-score was 1.37 (SD 2.69). We calculated the number of participants necessary to achieve a statistical significance level of 0.05 and a power of 0.80, while accounting for a 15% dropout rate. This calculation indicated that a minimum of 146 participants would be required to detect a similar deviation in LCI with sufficient statistical power. We plan to include a larger sample size to increase precision, improve our ability to detect smaller deviations, and ensure adequate power to analyze other lung function outcomes and investigate specific subgroups of patients defined by tumor type and treatments received.

Statistical Analysis

To compare PFT outcomes with normal values, we will calculate z-scores and percent-predicted values using external Global Lung Initiative (GLI) reference data [35-37,39]. We will define pulmonary dysfunction as z-scores below –1.64 or above +1.64 for respective PFT indices since these thresholds represent deviations from the reference population mean and indicate abnormalities in pulmonary function. To characterize pulmonary function among CCS, we will analyze z-scores for predefined outcomes and assess differences based on characteristics such as treatment exposure, age at treatment, and time since cancer diagnosis. We will assess group differences using appropriate statistical tests based on the type of variable, such as the *t*-test or the Mann-Whitney test for continuous variables and the χ^2 test or the Fisher exact test for categorical variables. For analyses of associations between outcomes and covariates, we will apply regression models adjusted for potential confounders. For longitudinal data, we will use mixed effects models to account for repeated measures over time. We will use Stata (Stata Corp LLC) and R (Foundation for Statistical Computing) for statistical analyses.

Results

Recruitment started in June 2022 at the University Children's Hospital in Bern, in March 2023 at the University Children's Hospital in Basel, and in March 2024 at the University Children's Hospital in Geneva. The number of new participants per month varies across the centers, depends on clinical capacity, and is steadily growing (Figure 3). As of October 2024, a total of 220 patients had been invited to participate in the study. Of those, 201 patients consented to and underwent PFTs, resulting in a response rate of 91%. Bern registered 125 (62%) participants, Basel 70 (35%), and Geneva 6 (3%). The time required to perform all PFTs and complete the questionnaire was 45-60 minutes per participant.

More than half of the 201 participants (n=119, 59%) were male, the median age at the time of the study was 14 years (IQR 10-17), and the median time since diagnosis was 7 years (IQR 4-10), as shown in Tables 3 and 4. The most common diagnoses were leukemia (n=105, 52%), lymphoma (n=22, 11%), and neuroblastoma (n=18, 9%). All but 2 (1%) participants had been treated with chemotherapy, 25 (13%) had received thoracic radiotherapy, and 15 (8%) had undergone thoracic surgery. In total, 20 (10%) participants had undergone HSCT, with 11 (6%) having been treated with autologous and 9 (4%) with allogeneic HSCT.

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Figure 3. Number of participants in SCCSS FollowUp–Pulmo since the start of the study. SCCSS: Swiss Childhood Cancer Survivor Study.

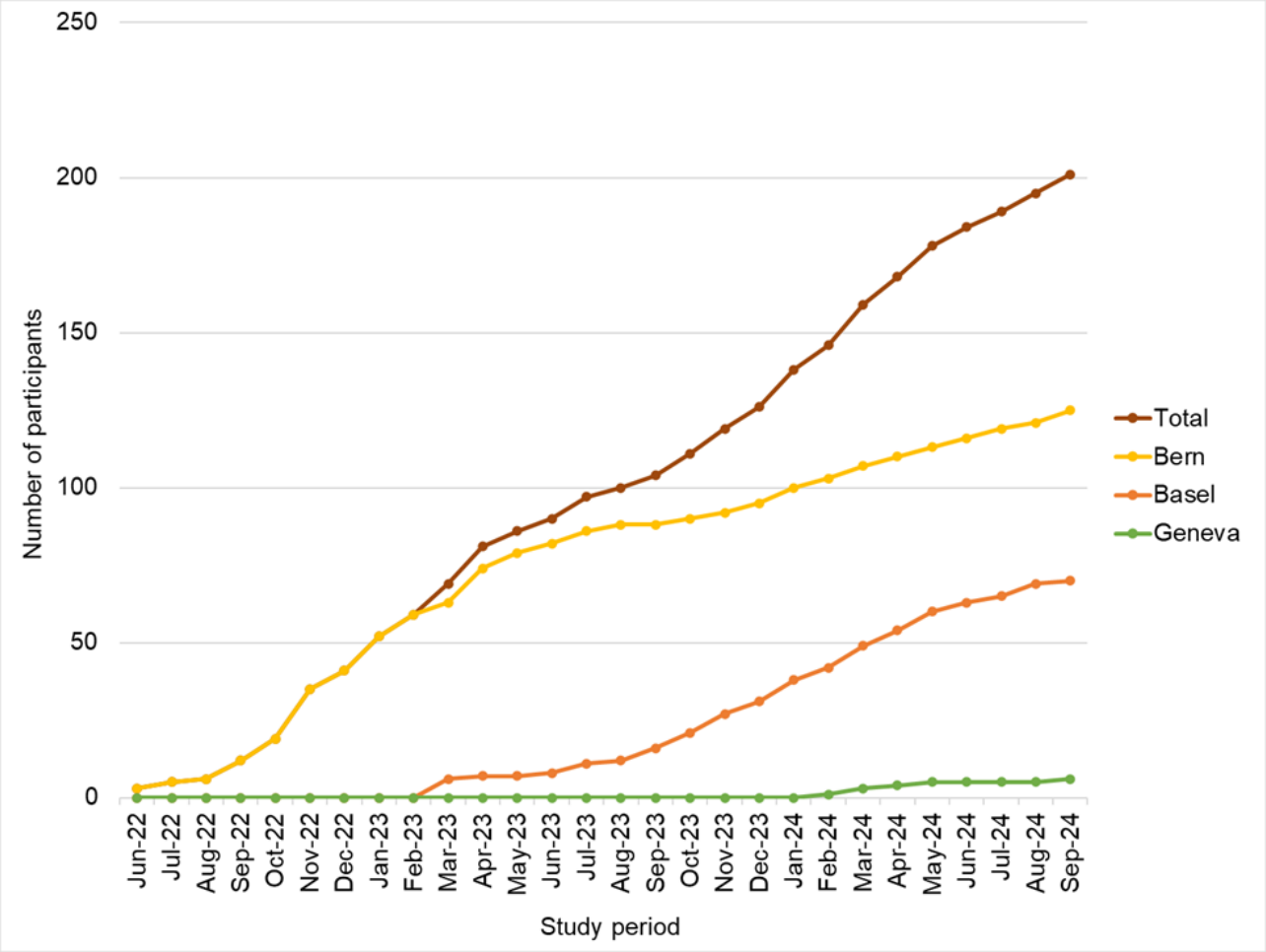

Table 3. Demographic characteristics of CCS[a] participating in SCCSS[b] FollowUp–Pulmo up to October 2024.

Characteristics	Participants (N=201)
Sex, n (%)	
Male	119 (59)
Female	82 (41)
Age at the time of study (years), median (IQR)	14 (10-17)
Age group (years), n (%)	
6-10	47 (23)
11-14	73 (36)
15-18	66 (33)
≥19	15 (8)

[a]CCS: childhood cancer survivors.

[b]SCCSS: Swiss Childhood Cancer Survivor Study.

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Table 4. Clinical characteristics of CCS[a] participating in SCCSS[b] FollowUp–Pulmo up to October 2024.

Characteristics	Participants (N=201)
Age at diagnosis (years), median (IQR); range	5 (3-9); 0.1-17
Time since diagnosis (years), median (IQR); range	7 (4-10); 1-17
Time since diagnosis (years), n (%)	
<5	68 (34)
5-10	83 (41)
11-15	41 (20)
>15	9 (5)
Diagnosis (ICCC-3[c]), n (%)	
Leukemia	105 (52)
Lymphoma	22 (11)
CNS[d] tumor	11 (6)
Neuroblastoma	18 (9)
Retinoblastoma	0
Renal tumor	15 (8)
Hepatic tumor	2 (1)
Bone tumor	6 (3)
Soft tissue sarcoma	14 (7)
Germ cell tumor	2 (1)
Other tumor[e]	2 (1)
Langerhans cell histiocytosis	4 (2)
Chemotherapy[f] (n=199, 99%), n (%)	
Pulmotoxic chemotherapy	16 (8)
Other treatments, n (%)	
Thoracic radiotherapy[g]	25 (13)
Thoracic surgery[h]	15 (8)
HSCT[i] (n=20, 10%), n (%)	
Autologous	11 (6)
Allogeneic	9 (5)
Relapse, n (%)	15 (8)

[a]CCS: childhood cancer survivors.
[b]SCCSS: Swiss Childhood Cancer Survivor Study.
[c]*ICCC-3*: *International Classification of Childhood Cancer, Third Edition*.
[d]CNS: central nervous system.
[e]Other malignant epithelial neoplasms, malignant melanomas, and other/unspecified malignant neoplasms.
[f]Any chemotherapy alone or combined with other treatments.
[g]Radiotherapy involving chest, abdomen, spine, or total body irradiation alone or combined with other treatments.
[h]Surgery involving the thorax or lungs alone or combined with other treatments.
[i]HSCT: hematopoietic stem cell transplantation alone or combined with other treatments.

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Discussion

Summary

This prospective, multicenter cohort study of lung function in children and adolescents after cancer treatment investigates risk factors, compares the detection of pulmonary dysfunction using N_2MBW and conventional PFTs, and examines the association of functional outcomes from PFTs with respiratory symptoms.

Comparison With Previous Research

Previous studies of pulmonary dysfunction after treatment for childhood cancer have mostly been retrospective, based on chart reviews [14,40-42]. This has entailed methodological weaknesses, particularly a risk of selection bias because CCS for whom PFT results were obtained might overrepresent symptomatic CCS or those treated more intensively. We identified several prospective studies on pediatric CCS, but like the retrospective ones, they mostly recruited specific groups of patients treated with previously defined pulmotoxic treatments, such as HSCT [42-44] or thoracic radiation [14,45], or specific tumor types like leukemia [46] or lymphoma [47,48]. Data on the pulmotoxic effects of individual agents, such as busulfan [49], melphalan [50], cyclophosphamide [46,50], and methotrexate [51], remain limited. By including CCS exposed to systemic therapies, including any chemotherapy, targeted agents, or immunotherapy, our study will provide a better understanding of treatment-related pulmonary dysfunction in a broadly representative population of CCS. Continuous recruitment will allow us to collect data on the pulmonary effects of newer treatments used in contemporary protocols, whose impacts remain largely unknown [52]. Detailed information from medical records will allow the investigation of effects of comorbidities and treatment-related complications on PFT outcomes.

Previous studies have rarely included sensitive tests, such as N_2MBW, that can detect early changes in the lung periphery. Most have used spirometry, body plethysmography, and DLCO [12,14,15,49]. A study investigating 57 pediatric CCS with a median follow-up time of 6.2 years from end of treatment did not find differences in ventilation inhomogeneity measured using N_2MBW compared to healthy controls [53]. In contrast, several studies on patients after allogeneic HSCT have reported the LCI to be a sensitive measure for early pulmonary complications [20,21,54]. This study will obtain N_2MBW data for CCS exposed to a wide range of treatment modalities and investigate whether N_2MBW is more sensitive than other PFTs in detecting early pulmonary dysfunction.

Another drawback of many existing studies is that they report PFT data using binary cut-offs and describe results as either normal or abnormal [12,15,49]. This reduces statistical power and introduces interpretations based on predefined threshold values. Reporting PFT results as raw data and z-scores based on internationally agreed-upon, age-adjusted reference values will allow better comparison and pooling across studies. Limited data exist on how lung function correlates with clinical symptoms [10]. Questionnaire data collected in this study will help investigate symptoms and other patient-reported outcomes, as well as their correlation with PFT results.

Collaboration With Other Ongoing Studies

The SWISS-Pearl Study (ClinicalTrials.gov ID: NCT05427136), currently conducted in multiple centers in Switzerland, investigates lung function in patients with pediatric cancer. The study includes spirometry, body plethysmography, N_2MBW, magnetic resonance imaging of the lungs, and questionnaires at different points during cancer treatment. We plan to combine that study with ours to create a comprehensive database, enabling us to analyze lung function trajectories in patients and survivors of pediatric cancer.

The GECCOS (Genetic Risks for Childhood Cancer Complications Switzerland) study is a nationwide cohort study collecting germline genetic data from patients and survivors of childhood cancer in Switzerland [55]. In consenting patients, we will link clinical and PFT data with the genetic data from GECCOS, allowing us to investigate the effects of genetic predisposition on pulmonary toxicity. This will assist the development of personalized treatment strategies and risk-adapted long-term care for survivors.

Study Limitations

A current limitation of this study is the limited number of participants and the heterogeneity of the study population, which can limit the statistical power for conducting subgroup analyses. For instance, exploring rare tumors or assessing specific effects of individual chemotherapeutic agents may at present be challenging. However, we plan to expand the study to more centers and pool data with international collaborations. Another limitation is the lack of systematic baseline PFT assessments before cancer treatment, making it difficult to distinguish treatment-related pulmonary dysfunction from preexisting conditions. Future studies should include pretreatment PFTs to better track changes in z-scores over time and improve the assessment of therapy-related effects. Finally, there is a small risk of selection bias because CCS with a longer time since the end of treatment, who do not experience respiratory symptoms or were not exposed to pulmotoxic treatments, may be less likely to participate in the study, potentially leading to underrepresentation of healthy CCS. Yet, because the study is embedded in regular follow-up care and supported by oncologists, with initial results showing a high participation rate, exceeding 90%, this bias should be minimal.

Conclusion

This multicenter cohort study prospectively investigates pulmonary dysfunction in young CCS. By assessing lung function as an intermediate outcome, rather than established disease or mortality, this study will provide a resource for evaluating pulmonary dysfunction at an earlier stage in the disease trajectory, particularly within the early years posttreatment. The initial response shows that integrating standardized pulmonary evaluations into routine follow-up care in Switzerland is feasible and widely accepted by both survivors and health care providers. The findings of this study will provide new insights to inform the development of guidelines and recommendations for pulmonary follow-up care.

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Acknowledgments

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Data Availability

Researchers interested in collaborative work can contact the corresponding author (CK) to discuss planned projects.

Authors' Contributions

All authors contributed to the study's conception and design. MŽ, CS, GS, and CK wrote the initial draft of the manuscript, and all authors provided feedback on earlier versions. All authors have read and approved the final manuscript.

Conflicts of Interest

PL reports relationships with Vertex, OM Pharma, Vifor, Polyphor, Santhera, Allecra, and Sanofi Aventis. These include grants, consulting fees, payments for lectures, advisory board memberships, and travel reimbursement. None of these relationships are associated with this study.

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Abbreviations

CCS: childhood cancer survivors
ChCR: Swiss Childhood Cancer Registry
CNS: central nervous system
DLCO: dffusing capacity of the lung for carbon monoxide
FeNO: fractional exhaled nitric oxide
GECCOS: Genetic Risks for Childhood Cancer Complications Switzerland
GvHD: graft-versus-host disease
HSCT: hematopoietic stem cell transplantation
ICCC-3: International Classification of Childhood Cancer, Third Edition
IGHG: International Late Effects of Childhood Cancer Guideline Harmonization Group
ISPM: Institute of Social and Preventive Medicine
LCI: lung clearance index
N_2MBW: nitrogen multiple breath washout test
PFT: pulmonary function test
REDCap: Research Electronic Data Capture
SCCSS: Swiss Childhood Cancer Survivor Study

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Protocol

Real-World Effectiveness of COVID-19 Vaccines (ChAdOx-1s, CoronaVac, BBIBP-CorV, mRNA-1273, and BNT162b2) in Jakarta: Protocol for Test-Negative Design of Health Care Data

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Abstract

Background: ChAdOx-1s, CoronaVac, BBIBP-CorV, mRNA-1273, and BNT162b2 are the five common COVID-19 vaccines used in Jakarta. Randomized controlled trials have provided robust evidence of the safety and efficacy profile of these vaccines, but their real-world vaccine effectiveness against symptomatic COVID-19 and deaths in communities with social inequalities and health care constraints remains unclear.

Objective: This study aims to evaluate the real-world effectiveness of these COVID-19 vaccines during the waves associated with the Delta and Omicron variants by analyzing existing electronic health care sources.

Methods: A population-based study with a test-negative case-control design will be used to evaluate COVID-19 vaccine effectiveness in Jakarta, focusing on the Delta and Omicron waves. It includes adults 18 years and older who underwent reverse transcription polymerase chain reaction testing for symptomatic COVID-19, classifying them as cases or controls based on their test results. The analysis will consider multiple COVID-19 vaccines introduced during these periods, with participants categorized by vaccination status. Several potential confounders will be assessed, including demographic factors and comorbidities. Data will be linked from various health datasets, and statistical analyses will be performed to determine vaccine effectiveness and potential waning immunity over time. After data linkage, patients' identities will be encrypted.

Results: The research, funded from 2022 to 2024, involved proposal preparation and ethical review in 2023 and enrollment from early 2024 to July 2024, resulting in about 4 million linked data points. Data analysis is ongoing, with initial results expected for publication in early 2025.

Conclusions: This study will be the first to evaluate the effectiveness of different types of COVID-19 vaccines (inactivated, viral-vector, and mRNA) used in Jakarta during the pandemic, providing valuable scientific evidence to inform future vaccination strategies in the country.

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KEYWORDS

COVID-19; protocol; vaccine; vaccine effectiveness; Delta; Omicron

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Introduction

Background

Since its emergence in December 2019, SARS-CoV-2, which is the virus that causes COVID-19, has been continuously spreading worldwide [1]. As of November 12, 2021, this pandemic has caused more than 250 million cases and more than 5 million deaths over the previous 2 years [2]. Vaccination programs are one of the most successful public health interventions that primarily aim to develop herd immunity and protection against pathogens. To date, the World Health Organization has approved 8 COVID-19 vaccines that are efficacious in preventing infection, reducing the level of severity and the number of deaths due to SARS-CoV-2 infection [3]. However, most data were generated from clinical trial studies that were different from a real-world setting due to their well-controlled nature [4]. Furthermore, real-world vaccine effectiveness (VE) studies were mostly conducted in high-income nations, and few studies came from low- and middle-income countries, even though these countries might have unique social and economic characteristics that not only affect vaccination acceptance but also disease outcomes [5]. A previous study has reported the association of living in an impoverished neighborhood with an increased risk for mortality even after COVID-19 vaccination [6]. Therefore, studies investigating how these COVID-19 vaccines might perform in real-world settings where social inequalities exist are still essential for informing policies and strategies to improve disease outcomes in future pandemics, especially in societies with health care system constraints [7]. This study aims to evaluate COVID-19 VE against symptomatic and fatal SARS-CoV-2 infection during the Delta and Omicron waves in Jakarta, where income inequality and socioeconomic segregation have become a common phenomenon [8].

Study Objectives

The primary objective is to study real-world VE against symptomatic COVID-19 (mild, moderate, and severe).

The following secondary objectives were also explored:

- Real-world VE against mortality 30 days after the first positive COVID-19 result
- Real-world VE based on vaccination status at the time of the reverse transcription polymerase chain reaction (RT-PCR) test
- Real-world VE based on the time since receipt of the last vaccine dosage

Methods

Study Design and Setting

This population-based study adopts a test-negative case-control design to analyze COVID-19 VE against symptomatic and fatal SARS-CoV-2 infection from available health care datasets in the Special Capital Region of Jakarta, one of the provinces with the highest population density (15,900 people per km^2 in 2020) and case rate per population relative to other regions in Indonesia [9]. Despite its robust development and economic growth, the contrast between rich and poor neighborhoods was highly prevalent in many parts of Jakarta's districts [8,10].

This study will estimate VE against COVID-19 during the period of interest, which were the COVID-19 waves associated with the Delta and Omicron variants, from June 1 to August 31, 2021, and January 1 to April 2, 2022, respectively. Within each of these periods, a cycle of sustained upward and downward trends of the test positivity rate was observed [11-15] (Figure 1). Furthermore, the Delta and Omicron variants were estimated to be responsible for around 90% of SARS-CoV-2 infections in Jakarta during these two periods [14,16].

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Figure 1. Trend of the national COVID-19 positivity rate in Indonesia from 2021 to 2022. This modified image is cited from Our World in Data.

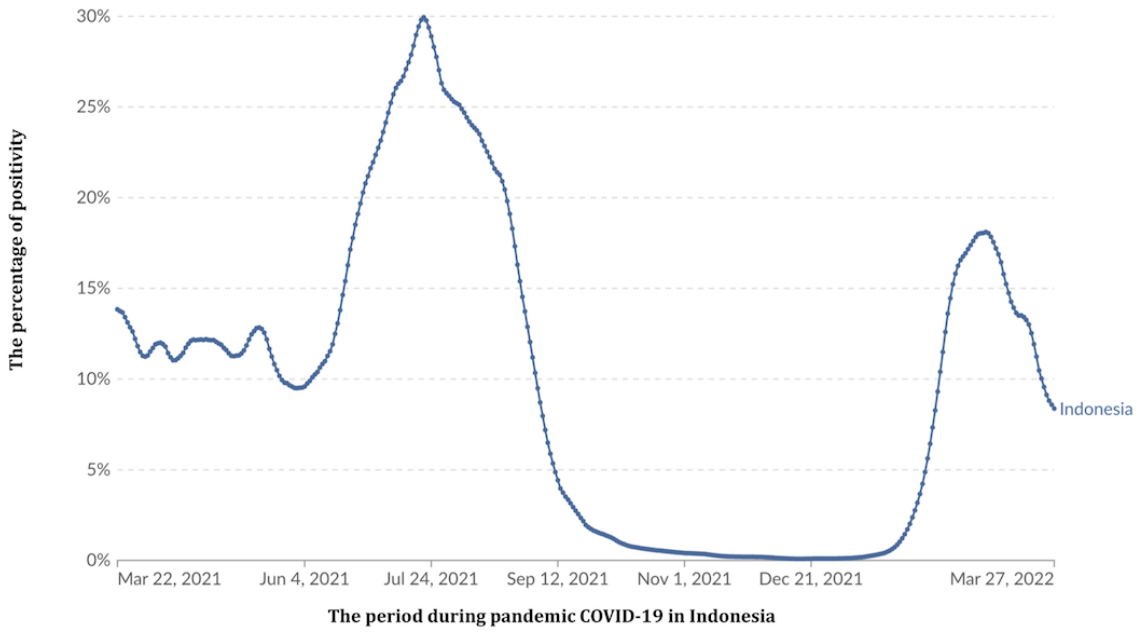

During the Delta and Omicron periods, several brands of COVID-19 vaccines were introduced in Jakarta for vaccine rollout, such as AstraZeneca, SinoVac-CoronaVac Biofarma, Covovax-Novovax, Indovax, Johnson & Johnson, Moderna, Sinopharm BBIBP, and Pfizer (Table S1 in Multimedia Appendix 1) [17]. Among these COVID-19 vaccines, Coronavac-Sinovac was the earliest COVID-19 vaccine to be introduced in January 2021 and used for mass vaccinations of doses 1 and 2, followed by AstraZeneca, Sinopharm, Pfizer, and Moderna in August 2021 [18,19]. Booster vaccinations 6 months after the 2-dose primary vaccination with Moderna and Pfizer vaccines were initially introduced to health care workers in July 2021, followed by the approval of the AstraZeneca vaccine as a booster in the national vaccination program in January 2022 [20,21]. To expedite the booster vaccination coverage, the timeline for booster administration was shortened to 3 months after the 2-dose primary vaccination, and additional inactivated COVID-19 vaccines, such as SinoVac and Sinopharm, were included in the national booster program [22]. Different from Pfizer, Moderna, and AstraZeneca, these inactivated COVID-19 vaccines were only approved as boosters for patients who received similar vaccine platform for their primary vaccination regimen [23]. Until the end of the Omicron period, all of the distributed COVID-19 vaccines in Jakarta were developed from the ancestral strain of SARS-CoV-2.

Study Participants

The study will include people 18 years or older who domiciled in Jakarta and underwent an RT-PCR test for SARS-CoV-2 infection due to symptoms of influenza-like illnesses within 10 days of the test date. Although people may have more than one RT-PCR result during the period of interest, this study will only account for the first positive or negative result per person as the index test date for each of the COVID-19 waves. People who had at least one sample with a positive SARS-CoV-2 RT-PCR result during the period of interest will be classified as cases, while people with a negative SARS-CoV-2 RT-PCR without any positive results over the period of interest will be classified as controls.

People with a positive RT-PCR test result within 90 days of the preceding index test date, with inconclusive RT-PCR results, who received different vaccines for dose 1 and dose 2 or a heterologous primary vaccine series, or who had a time interval between dose 1 and dose 2 that was less than the government recommendation (<21 days for Pfizer and Sinopharm, <28 days for CoronaVac and Moderna, and <12 weeks AstraZeneca) will be excluded from the analysis. We will also exclude people with incomplete vaccination records, such as people who declared receiving 2 vaccine doses without being able to verify the previous dose.

Study Variables

The primary outcome in this study is symptomatic SARS-CoV-2 infection, defined as a positive RT-PCR test within 10 days from the onset of influenza-like illness. The secondary outcome in this study is fatal SARS-CoV-2 infection, defined as death within 30 days after a positive RT-PCR test result [24]. Meanwhile, the primary exposure in this study was vaccination status, which can be classified as unvaccinated, dose 1 or partial vaccination, dose 2 or primary vaccination, and booster dose. People without any vaccination entries after data linkage with the PCARE Vaksin dataset at the end of each period of interest will be classified as unvaccinated persons. For vaccinated people, we will only consider the last vaccination data entry that happened before the patients' index RT-PCR test date.

Several covariates should be assessed as potential confounders in the study, such as age in years at the index test date, gender, calendar week of the RT-PCR collection during the period of interest, living in impoverished neighborhoods, presence of any

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comorbidities, occupation, and reinfection status. The calendar week of the RT-PCR collection during the period of interest will be presented as a whole number starting from week 1 as the start of the period of interest. Living in an impoverished neighborhood will be presented as a dichotomous variable. People will be classified as living in an impoverished neighborhood if their neighborhood number at the subdistrict level is listed as one of the impoverished neighborhoods in the 2018 Jakarta Governor's regulation concerning improving the quality of settlements in residential areas. Occupation will be presented as categorical variables that consist of health care worker, public or government official, and civilian. Reinfection or people with previous SARS-CoV-2 infections will be presented as a dichotomous variable. People with a previous positive RT-PCR SARS-CoV-2 result that occurred more than 90 days after the current case will be classified as people with a previous SARS-CoV-2 infection [25].

To control for unmeasured confounders [26], such as societal preventive measures or the changing dynamic of the viral transmission within the community, this study will match each case with a control using a ratio of 1:2 by matching for age within 10 years of the case's age, gender, and the calendar week of the RT-PCR collection during the period of interest. The matching procedure will be assessed with standardized mean differences, with values less than 0.1 indicating sufficient matching [27,28].

Data Sources

This study will analyze the final datasets derived from the integration of several datasets provided by the Jakarta Provincial Health Office, Ministry of Health, and Social Security Agency on Health after April 2022 (Table 1). Variables such as ID number and date of birth will be used for the dataset linkage (Figure 2). From the New All Records (NAR) and Suspect and Probable (SUSPROB) datasets, symptomatic people with a positive or negative first RT-PCR test result within each of the periods of interest will be identified as cases or controls. Furthermore, people identified as cases will be linked to the entries in the REV POS dataset to extract the outcome of their disease course (Figure 2). People with incomplete data for ID number, date of birth, gender, swab collection date, PCR test result, domicile address, outcome, and date of death (if the case ends in death) will be excluded from further data linkage.

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Table 1. List source for merged datasets.

Name	Developer	Description	Variable identified
NAR[a]	Ministry of Health Republic of Indonesia	Record of all RT-PCR[b] SARS-CoV-2 tests carried out by affiliated laboratories	• Name • ID number • Date of birth • Sex (male, female) • Comorbidity • Domicile address • Laboratory name • Reason for testing • Swab collection date • RT-PCR result confirmation date • RT-PCR testing result
SUSPROB[c]	Jakarta Provincial Health Office	Record and follow-ups of all people with influenza-like illness or probable COVID-19	• Name • ID number • Date of birth • Sex (male, female) • Comorbidity • Domicile address • Presence of influenza-like illness (fever, chill, cough, etc) • Date of symptom onset • Travel history • Plan swab testing date • Swab collection date • RT-PCR testing result
REV POS	Jakarta Provincial Health Office	Records and follow-ups on all positive cases in Jakarta	• Name • ID number • Date of birth • Sex (male, female) • Comorbidity • Domicile address • Date of swab collection • Case severity (asymptomatic, mild, moderate, severe) • Outcome (survived or death) • Date of death
PCARE[d] Vaksin	Social Security Agency on Health Indonesia (BPJS Kesehatan)	Record of all administered COVID-19 vaccines and their recipients	• Name • ID number • Date of birth • Sex (male, female) • Domicile address • Occupation or vaccination batch group (health workers, government officials, elderly, children, civilians) • Name of health care facility/vaccination center • Vaccination date • Vaccination ticket number • Vaccination dose • Vaccine name • Vaccine batch/lot number
Variant dataset	Jakarta Provincial Health Office	Sequencing and genotyping results of the randomly picked positive SARS-CoV-2 samples in the Jakarta area	• Sample registry number • Date of sample collection • Name of the sender laboratory • Date of the sample arrival at sequencing lab • Name of the sequencing lab • Date of the sequencing test • Date of result confirmation • Variant of SARS-CoV-2

[a]NAR: New All Records.

[b]RT-PCR: reverse transcription polymerase chain reaction.

[c]SUSPROB: Suspect and Probable.

[d]PCARE: Primary Care.

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Figure 2. Study workflow. PCare: Primary Care.

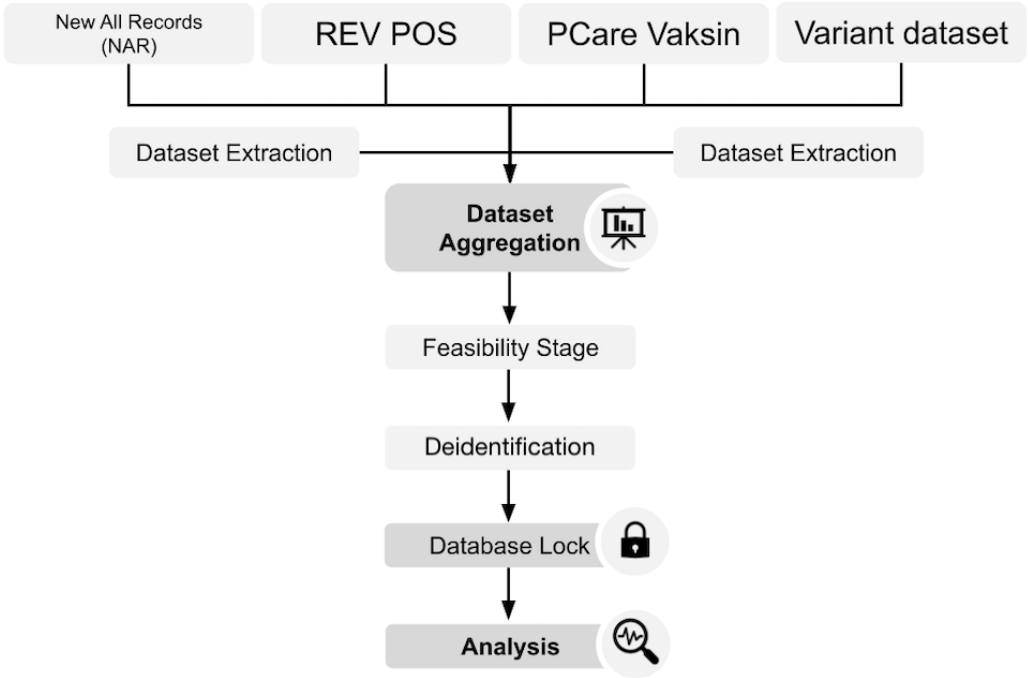

People with data linked to the entries within the Primary Care (PCARE) Vaksin dataset will be classified as vaccinated people (Figure 2). To avoid misclassification of foreigners as unvaccinated people, the study will only use entries with national identity card numbers as ID numbers from each of the study datasets. Vaccinated people with incomplete data on vaccination date and vaccine name will be excluded from the final dataset (Table S2 in Multimedia Appendix 1). From the final dataset, a subset of data containing the matched cases and controls will be created (Table S3 in Multimedia Appendix 1).

As genomic testing was not routinely performed in Indonesia, no data linkage will be performed on the variant dataset. In contrast, the variant dataset, which consisted of the genomic test result of the randomly sampled specimen from the population, will be used to confirm the dominant SARS-CoV-2 variant in Jakarta during each period of interest.

Sample Size

The calculation formula for the sample size used in this study will follow the methodology described by O'Neill [29]. Assuming vaccination coverage between 20%-90%, a precision of ±5%, a type 1 error rate of 0.05, and an anticipated VE of 50%-90%, the minimum sample size needed for each specific COVID-19 vaccine brand and dose VE analysis is roughly around 15,000, with 5000 cases and 10,000 controls [24,29] (Table S4 in Multimedia Appendix 1).

We expect to analyze 400,000-900,000 people after the aggregation of all datasets. Therefore, we should have enough data to conduct the VE analyses for each specific COVID-19 brand and regimen in our final dataset. We will compare the proportion of COVID-19 vaccines received by eligible people in our dataset during each period of interest to those reported by the Ministry of Health [17] (Table S1 in Multimedia Appendix 1). Furthermore, we will exclude people who received COVID-19 vaccine brands with vaccination coverage of less than 20%, as these vaccines are usually distributed briefly in the population or only available to specific subgroups within the community. Moreover, we might consider combining different COVID-19 vaccine brands with the same platform into one group to decrease the required sample size, especially for the subgroup VE analysis [24].

Statistical Analysis

We adopted our VE analysis from the Interim Guidance of Evaluation of COVID-19 Vaccine Effectiveness by the World Health Organization, where the final estimate of absolute VE (aVE) will be determined by calculating the adjusted odds ratio (aOR) for vaccination using the formula aVE = (1 – aOR) × 100% [24]. Unconditional multivariable logistic regression will be used to analyze the aOR of having symptomatic and fatal SARS-CoV-2 infection between the unvaccinated and vaccinated participants. We will perform separate analyses for the Delta- and Omicron-dominant periods. Furthermore, within each period, we will also analyze each vaccinated person separately by their vaccine brand or platform and vaccination doses, such as dose 1, dose 2, or booster. For the main aVE analyses, we will include only vaccinated people with the last dose 1 or dose 2 vaccination date within 14-90 days or with the last booster dose within 7-90 days before their index test date and compare them to the unvaccinated people.

One main logistic model will be assembled by forward inclusion, and only covariates with less than 20% missing data will be considered to be included in the model building. Assessment for confounders and effect modifiers will be performed with the Wald test and by observing the change in the primary exposure coefficient SE. Covariates that act as confounders will be included in the model. If effect modification is present, it is essential to report VE and CIs for each subgroup individually.

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The linearity between continuous variables and the log odds of having symptomatic SARS-CoV-2 infection will be assessed, and the continuous variables will be modified into categorical variables if necessary. The overall fit of the final multivariate logistic regression model will be assessed with Hosmer and Lemeshow goodness-of-fit test [30], as matching might incur matching-related bias from the cases and controls having similar exposure, thus underestimating the aVE. We will also perform conditional logistic regression as a sensitivity analysis for measuring the aVE estimation against symptomatic SARS-CoV-2 infection or our primary objectives [31,32]. Furthermore, for the analysis of the Omicron period, we will perform an additional analysis of relative VE (rVE) by comparing recipients of one booster dose to recipients of the 2 doses who were eligible to receive the booster dose. The rVE will be calculated using the formula rVE = [(aVE from booster dose – aVE from 2 doses and eligible for booster)/(1 – aVE from 2 doses and eligible for booster)] × 100%. For the rVE analyses, we will include only people whose last booster dose was within 7 to 90 days before their index test date and compare them to people whose last 2-dose vaccination date was ≥90 days before their index test date [24].

This study will also conduct subgroup analyses based on the time between the last vaccination date and test index date to assess for waning of immunity (Table 2). These subgroup analyses will be conducted separately for each wave and vaccine brands or regimens. Similar to the main analysis, each vaccinated subgroup will be compared to unvaccinated people.

Table 2. Subgroup analysis based on time since last vaccination.

Subgroup	Description
1	7-14 days between the last vaccination dose and index test date
2	14-28 days between the last vaccination dose and index test date
3	28-56 days between the last vaccination dose and index test date
4	56-90 days between the last vaccination dose and index test date
5	90-180 days between the last vaccination dose and index test date
6	>180 days between the last vaccination dose and index test date

A 2-sided *P* value derived from the multivariable logistic regression analysis will be used to assess VE. Data linkage and data cleaning will be performed in Google Collaboratory with the Python programming language. Furthermore, the Statsmodel library package will be used for statistical analysis [33].

Ethical Considerations

The research protocol received ethics approval from the Ethical Committee of Persahabatan Hospital Jakarta (40.A.1/KEPK-RSUPP/11/2022). The research conducted in accordance with this protocol will not collect consent from people as it involves the use of secondary data. A consent waiver statement has been issued by the Ethical Committee of Persahabatan Hospital Jakarta (DP.04.03/D.XX.10.4/0001/2024).

Results

This research received funding from 2022 to 2024. The proposal preparation, protocol development, and ethical review processes began in 2023, alongside efforts to gather access to datasets from various stakeholders. Enrollment commenced at the beginning of 2024 and was completed in July 2024 after the data-cleaning process. A total of approximately 4 million data points were available from the linked datasets. Data analysis is currently underway, with the first results expected to be submitted for publication at the start of 2025.

Discussion

The general objective of this research is to estimate the real-world effectiveness of COVID-19 vaccines during the Delta and Omicron waves. Since the study covers two different periods, the results may also reveal changes in VE across these two variant phases. The study follows World Health Organization guidelines for conducting real-world COVID-19 vaccine research and incorporates linkage across multiple research datasets to enhance its validity. The use of the Google Collaboratory online platform for data integration demonstrates adaptability to modern technologies. As of mid-2024, there are over 4 million combined records from RT-PCR test results and vaccination data.

Vaccine effectiveness refers to the average response to the vaccine under real-world conditions, assessed through observational studies, and is generally lower than the efficacy observed in controlled settings [34]. When a vaccine is administered to the general population, various factors such as individuals' medications and overall health status, and vaccine storage and administration conditions, among others, can diminish its effect and increase variability in responses among recipients. This phenomenon is anticipated for all vaccines, underscoring the importance of continuous monitoring for emerging data as vaccination programs progress. The collection, analysis, and communication of these experiences are crucial for gaining authoritative knowledge on effectiveness, including potential rare or delayed side effects. Assessments of COVID-19 VE also contribute to understanding the overall community immunity required to safeguard the population [35].

The study's inclusion of a wide variety of vaccine platform, including mRNA, adenovirus-based, and inactivated vaccines, is one of its main strengths. For low- and middle-income countries, which may depend on several types of vaccine due to availability constraints, this variety enables a more nuanced knowledge of vaccination performance across various methods.

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In contrast to many previous studies, this study additionally considers important factors that could affect the chance of vaccination and the risk of contracting or dying from COVID-19 in various communities. The study provides a more complete picture of VE in the real world by taking these factors into account, particularly in different urban environments like Jakarta.

Nevertheless, certain limitations still exist despite the test-negative design study design's attempts to lessen biases. If those who test negative for COVID-19 were exposed but did not exhibit symptoms, misclassification bias may occur, as indicated in Table 3 on potential biases related to test-negative design. Furthermore, since those who choose to get tested might not be representative of the whole community, health care–seeking behavior may introduce additional bias. Collider bias is still a worry and has not yet been completely mitigated, even though sampling has been used to reduce problems like selection bias. This is especially important because the study looks at communities with different socioeconomic and health characteristics, which could affect the results. Addressing collider bias in future research could significantly improve the reliability and validity of the findings, offering a clearer understanding of the true VE in different contexts.

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Table 3. Potential biases of COVID-19 vaccine effectiveness studies using test-negative design.

Potential bias	Explanation	Magnitude	Direction on VE[a] estimate	Outcome/subgroups affected	Method to control	Comments
Health care–seeking behavior bias (access to health care)	Individuals who are more likely to get vaccinated tend to seek medical care more frequently, which increases their chances of being identified as cases	Large	Underestimate VE	Nonsevere outcome	Using TND[b]	By using TND, we only include individuals who seek care for similar symptoms or indications thus reducing differences in health care–seeking behavior, but TND can create collider bias
Health care–seeking behavior bias (vaccine status)	Vaccinated individuals less likely to seek testing for COVID-19–like illness due to perception of protection	Small to moderate	Underestimate VE	Nonsevere outcome	Using TND	TND partially controls this bias
Collider bias	This arises when we restrict analysis on a collider variable (eg, testing). TND only analyzes individuals who were tested.	Unknown	Depends on how health care–seeking behavior and infection affects testing	Nonsevere outcome	Limit to severe individuals or older adults	We could not control this bias because the information on the collider variable (testing) is not available.
Misclassification of the exposure	During high levels of transmissibility, infection may occur soon after vaccination. Meanwhile, vaccines need time to confer an acceptable protective immune response.	High	Underestimate VE	All	Limit analysis only after vaccine performance has acceptable time to confer acceptable protection (eg, 14 days after the first or second dose, 7 days after third dose)	This study excludes infection that occurs <14 days after vaccination in the analysis of primary vaccine (first and second dose) and excludes events (eg, infection) that occur <7 days after vaccination in the analysis of booster vaccines. This measure will prevent underestimation of VE in the time when infection occurs during suboptimal immune response after vaccination.
Misclassification of the outcome	False positive and false negative	Small	Underestimate VE	All	Use only highly sensitive test (eg, RT-PCR[c])	This study only includes RT-PCR SARS-CoV-2 results (see eligibility criteria) to control this bias
Spurious waning bias	This refers to an apparent VE reduction over time that does not reflect the decay of immunity over time but rather results from biases or confounding factors in the study design or analysis (eg, different variants, differences in exposure risk).	Small to large	Underestimate VE	All	Perform analysis for specific variant/period. Control difference in viral dynamic transmissibility over time. Perform stratification analysis by time since vaccination.	To prevent bias due to variants, this study conducts two sets of analyses (Delta and Omicron). To prevent bias due to differences in exposure risk over the periods of interest, we conducted matching case and control by calendar week of sample collection. To show VE waning, we perform stratification analysis by time since vaccination.

[a]VE: vaccine effectiveness.

[b]TND: test-negative design.

[c]RT-PCR: reverse transcription polymerase chain reaction.

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The response to the COVID-19 pandemic has highlighted new challenges in Indonesia's healthcare system, particularly data fragmentation from numerous health applications and insufficient standardization [36]. Disparities in recording and storing health data in Indonesia also present challenges during the pandemic [37]. Both of these obstacles hinder large-scale health research in the country. To address this, dataset integration is necessary to obtain comprehensive and complete data. Upon completion of our study, it is hoped to demonstrate the capability of health researchers in Indonesia to conduct research using big data, serving as an initiation for the digital transformation of health care.

Acknowledgments

This study will receive an AstraZeneca research funding grant (ESR-21-21574 – D8111L00006.) as an external sponsor, and the sponsor will not be involved in conducting the study.

Data Availability

The data that supports the findings of this study will be available upon request from EB and FA. The data, which contain personal information, are not publicly available due to the strategic health policy of the province of Jakarta.

Authors' Contributions

Conceptualization: EB, FA, FM
Methodology: FA, FAGS, ATR, RAR, HA
Project administration: FM, MIDR, IA
Supervision: EB, FA
Validation: EB
Visualization: FA, FAGS, MIDR
Writing – original draft preparation: FA, FAGS, MIDR, IA
Writing – review and editing: EB, FA, FAGS, MIDR, IA
All authors mentioned critically reviewed the manuscript for significant intellectual content and approved the final version for publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1
List source datasets.
[DOCX File , 16 KB - resprot_v14i1e56519_app1.docx]

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Abbreviations

aOR: adjusted odds ratio
aVE: absolute vaccine effectiveness
NAR: New All Records
PCARE: Primary Care
RT-PCR: reverse transcription polymerase chain reaction
rVE: relative vaccine effectiveness
SUSPROB: Suspect and Probable
VE: vaccine effectiveness

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Protocol

Maternal Metabolic Health and Mother and Baby Health Outcomes (MAMBO): Protocol of a Prospective Observational Study

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Abstract

Background: Metabolic disease is increasingly impacting women of reproductive age. In pregnancy, uncontrolled metabolic disease can result in offspring with major congenital anomalies, preterm birth, and abnormal fetal growth. Pregnancy also accelerates the complications of metabolic diseases in mothers resulting in an increased risk of premature cardiovascular events. Despite the convincing evidence that preconception care can largely mitigate the risks of metabolic disease in pregnancy, there are few data about how to identify the highest-risk women so that they can be connected with appropriate preconception care services.

Objective: The aim of the study is to determine the maternal phenotype that represents the highest risk of having adverse neonatal and maternal pregnancy outcomes.

Methods: This will be a prospective cohort study of 500 women recruited in early pregnancy. The primary outcome is a composite of offspring born small for gestational age (SGA) or large for gestational age (LGA) (customized birthweight ≤10th and ≥90th centile for gestational age). Secondary outcomes are (1) composite of adverse neonatal birth outcomes (SGA, LGA, major congenital abnormalities, preterm birth [<37 weeks' gestation]) and (2) composite of new maternal metabolic outcomes (gestational diabetes, diabetes in pregnancy, type 2 diabetes [T2D] or prediabetes; gestational hypertension, preeclampsia, eclampsia or new essential hypertension after pregnancy; and gestational weight gain ≥20kg or new overweight/obesity at the 12-18 months postpartum visit). A multivariable logistic regression analysis will be conducted to identify candidate predictors of poor pregnancy outcomes due to metabolic disease. From this model, model coefficients and the associated 95% CIs will be extracted to derive the risk score for predicting the delivery of LGA/SGA offspring (primary outcome) and composites of adverse neonatal outcomes and maternal outcomes (secondary outcomes).

Results: Seed funding for the project was acquired in November 2022 and subsequent funding was acquired in May 2024. The first participant was recruited on March 23, 2023. At the time of manuscript submission, 402 participants have been recruited. Data analysis has not yet been performed. Results are expected to be published in the first half of 2027.

Conclusions: This is a prospective observational cohort study that intends to identify the metabolic disease risk factors, or combination of factors, that are most likely to cause adverse maternal and fetal health outcomes. These characteristics will be used to develop a risk calculator which will assist in identifying the highest risk women and in triaging them to appropriate services. The study has been approved by the institutional Human Research Ethics Committee (HREC/90080/MH-2022).

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12623000037606; https://tinyurl.com/yeytsxtp

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International Registered Report Identifier (IRRID): DERR1-10.2196/72542

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KEYWORDS

preconception; large for gestational age; small for gestational age; pregnancy outcomes; metabolic disease; diabetes; obesity; hypertension

Introduction

The offspring of mothers with pre-existing metabolic diseases—obesity, diabetes, and hypertension—have an increased risk of significant congenital anomalies and premature birth compared with the offspring of mothers without metabolic disease [1]. These offspring are also twice as likely to develop obesity, diabetes, and hypertension in childhood [2]. For the mothers, pregnancy accelerates the complications of metabolic diseases, resulting in an increased risk of premature cardiovascular events including ischemic heart disease, stroke, and death [3]. Although the consequences of uncontrolled metabolic disease in pregnancy are entirely preventable, our current clinical services are not effective. This is because the highest-risk women are often not identified prior to pregnancy and because high-risk women frequently have poor access to appropriate care.

The women who are most at risk of adverse consequences of metabolic disease in pregnancy are women of low socioeconomic status, women who have experienced trauma, and women living in rural and remote areas [4]. Major barriers for these women accessing and using preconception services include (1) failure to be identified as "high risk" by a health care provider prior to pregnancy; (2) accessing a suitable referral pathway; (3) attending clinic appointments especially if limited by remoteness or finances; and (4) accepting care for metabolic diseases which are often stigmatized diseases and may have implications for the women's place in her family or wider cultural group. Ironically, there are well-developed services for preconception care of women with severe metabolic disease. However, these services are generally based in tertiary maternity hospitals in metropolitan cities. Due to geographical factors and because referral pathways and clinic entry criteria are often unclear, these services are often used by high socioeconomic status women with a relatively low risk of adverse pregnancy outcomes.

We hypothesize that the mothers and offspring at the highest risk of the adverse consequences of metabolic disease are predictable based on the phenotype of the mother prior to pregnancy. Despite the high fetal morbidity that can be associated with metabolic syndrome, little has been done to identify and capture at-risk individuals at a preconception or early antenatal stage. The aim of this study is to develop risk calculators that best predict (1) a mother's risk of having a neonate with abnormal fetal growth (large for gestational age [LGA] or small for gestational age [SGA]); (2) a mother's risk of having a serious adverse neonatal outcome; and (3) a mother's risk of developing new metabolic disease after pregnancy (Figure 1). We will translate this to a user-friendly mobile app that will allow any health care worker to access and triage women to appropriate preconception care.

Figure 1. Schematic of the rationale for research study.

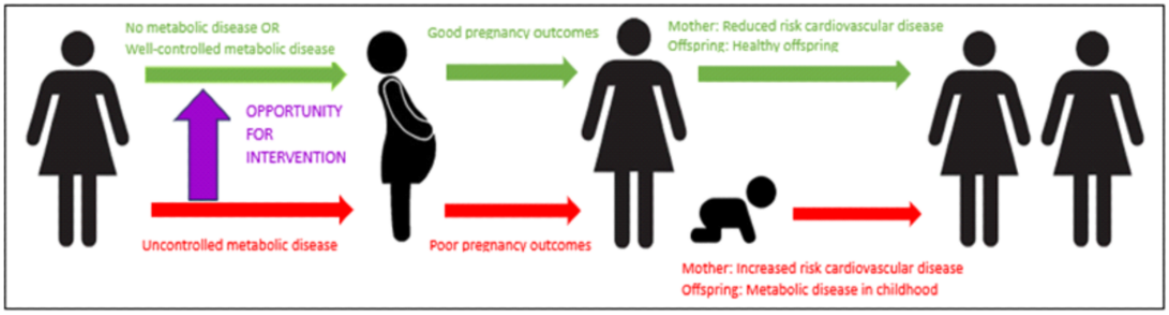

Methods

Study Design and Setting

Study phase I is a multicenter prospective observational cohort study. Study phase II involves the development of risk calculators from the observational cohort established in phase I. The study was prospectively registered with the Australian New Zealand Clinical Trials Registry (ACTRN12623000037606).

The observational cohort study will recruit 500 women who have been referred to either a public or a private tertiary maternity hospital (Figure 2). Both hospitals are tertiary referral centers based in metropolitan Melbourne Australia, and collectively manage >8000 births per year. The recruiting maternity hospitals accept referrals from the entire state of Victoria, such that the hospital populations comprise of metropolitan women and a smaller group of women living in regional and rural areas.

The first participant was recruited on March 23, 2023. The projected timeline for recruitment is that the last participant will be recruited in June 2025. It is anticipated that the last participant will have completed all study visits by June 2026.

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Figure 2. Flowchart of the anticipated study cohort.

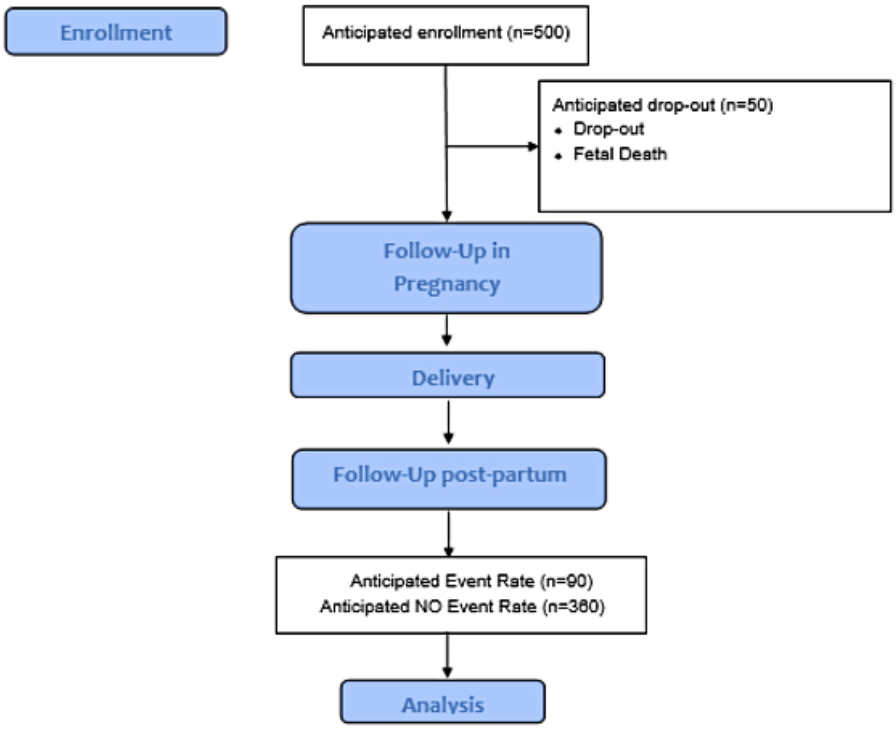

Eligibility and Recruitment

Inclusion Criteria

Eligibility for the study will be women aged 18 years and older with pregnancies of 20±4 completed weeks of gestation who provide written consent and are attending a prespecified study site for maternity care. The study will include those with multifetal pregnancies, chronic disease, and those using medications of any type. Women from non–English speaking backgrounds will be included and telephone interpreting services and cultural liaison officers will be used as required.

Exclusion Criteria

Women will be excluded from the study if they do not have maternity care at one of the prespecified study sites before 20±4 completed weeks of gestation. Women will also be excluded if they do not wish to provide informed consent or are unable to provide informed consent. This may be due to the inability to read and write, intellectual disability, or a severe active mental illness. It is anticipated that fewer than 1 out of 1000 women screened at maternity hospitals would fulfill this criterion.

Withdrawal Criteria

Participants are free to withdraw from the study at any time through revocation of consent (patient preference) or via ceased communication with the recruitment site (lost to follow-up). All data collected prior to the withdrawal of consent will be included in the analysis. Participants who start with maternity care at the recruiting hospitals and then move to seek maternity care elsewhere may continue to take part via telephone/telehealth study visits. Participants who have a pregnancy or neonatal loss will not continue in the study, but information collected until this point will be included in the analysis.

Recruitment Procedure

Women will be recruited when they attend maternity care visits between 16 and 24 weeks' gestation. Initial contact will be made by the maternity care provider. Subsequent contact will be made by a dedicated study nurse/doctor at the time of the standard maternity care visit. All participants will receive standard individualized antenatal care based on their clinical needs.

No study activities will be performed before eligibility has been assessed and informed consent has been formally documented. To encourage attendance at clinical visits, parking and meal vouchers will be provided. At the final visit, women will be provided with a comprehensive summary of their metabolic health and a plan for appropriate long-term follow-up.

Expected Outcomes

Primary Outcomes

Metabolically prone offspring defined as a composite of offspring with birthweight ≥90th centile (LGA) and offspring with birthweight ≤10th centile (SGA) based on population-based charts [5,6].

Secondary Outcomes

A composite of adverse neonatal outcomes includes the following:

- Offspring with birthweight ≥90th centile on population-based charts (LGA).
- Offspring with birthweight ≤10th centile on population-based charts (SGA).
- Offspring with major congenital abnormalities.
- Offspring born preterm (<37 completed weeks' gestation).

A composite of new maternal metabolic disease that develops during pregnancy or <18 months postpartum is defined below:

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- Gestational diabetes (GDM) as per the International Association of the Diabetes and Pregnancy Study Group (IADPSG)/World Health Organization (WHO) definition (reference); or diabetes in pregnancy as per WHO/IADPSG definition; or previously undiagnosed type 2 diabetes as per American Diabetes Association/WHO definition; or prediabetes as per American Diabetes Association definition (Table S1 in Multimedia Appendix 1).
- Gestational hypertension; or pre-eclampsia; or eclampsia; or new essential hypertension after pregnancy (Table S2 in Multimedia Appendix 1).
- Gestational weight gain ≥20 kg or new overweight/obesity after pregnancy (BMI ≥25 kg/m^2 and body weight increase of ≥5 kg compared with prepregnancy weight) at the 12-18 months postpartum visit.

Clinical Assessments

A schedule of assessments and measurements is presented in Table 1.

Table 1. Summary of study activities.

	Visit 1 (20, SD 4 weeks gestation)	Visit 2 (36, SD 4 weeks gestation)	Visit 3 (Peripartum)	Visit 4 (12-18 months postpartum)
Informed consent and eligibility	✓	✓		
Collect basic demographic details including postcode	✓			
Collect past medical, surgical, obstetric, and gynecological	✓			
Collect new medical, surgical, obstetric, and gynecological		✓	✓	✓
Adverse events		✓	✓	✓
Medication	✓	✓	✓	✓
Allergies	✓	✓	✓	✓
Smoking, drug, and alcohol use history	✓			
Maternal Anthropometry				
Height	✓			
Weight	✓	✓		✓
Waist circumference	✓	✓		✓
Bioimpedance	✓	✓		✓
Blood tests				
Glucose, insulin, and c-peptide	✓	✓		✓
HbA_{1c}[a]	✓	✓		✓
CRP[b]	✓	✓		✓
Leptin	✓	✓		✓
Provide maternal and neonatal mouth swabs to participants		✓		
Collect 75g OGTT[c] result		✓		✓
Collect obstetric ultrasound results		✓		
Collect maternal and neonatal mouth swabs for epigenetic analysis		✓	✓	
Collect obstetric medical records including the birth summary		✓	✓	
Collect height and weight data from the childhood development book (“Baby book”)		✓		✓

[a]HbA_{1c}: hemoglobin A_{1c}.

[b]CRP: C-reactive protein.

[c]OGTT: oral glucose tolerance test.

Medical History and Medications

At the first visit, a full medical history will be taken by a trained clinician including past medical history and surgical history. Outcomes of previous pregnancies will be recorded including outcome of the pregnancy, gestation, pregnancy complications, and (if relevant) birthweight and neonatal complications. Current medications including dose, and dosing schedule will be

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recorded. Smoking, alcohol, and recreational drug use will be recorded.

Blood Pressure

Blood pressure will be measured after 5 minutes of rest in a seated position using an appropriately sized cuff on the bared left upper arm supported at heart level. Auscultatory readings with an aneroid sphygmomanometer and stethoscope or automated oscillometric readings with a single read per activation device will be collected by trained operators.

Weight, Height, and Waist Circumference

Weight will be measured by a trained technician on calibrated digital scales with an accuracy of ±0.01 kg. Participants will be asked to wear light clothing but no shoes. Height will be measured by a trained technician using a standing stadiometer with an accuracy of ±0.5 cm. Waist circumference will be measured with an accuracy of ±0.5 cm using a standard tape measure according to the WHO guidelines (at the end of a normal expiration, at the midpoint between the lower margin of the last palpable rib and the top of the iliac crest, as the average of 2 measurements). BMI will be calculated by dividing weight in kg by height in meters squared.

Bioimpedance Analysis

Bioimpedance will be performed using the DC-430MAS Tanita Dual Frequency Body Composition Analyser. Data obtained from bioimpedance analysis will include fat mass (%), fat mass (kg), free fat mass (kg), muscle mass (kg), and bone mass (kg).

Laboratory Assays

Phlebotomy is a low-risk procedure. At each visit, the required blood samples will be taken for glucose, insulin, C-peptide, high-sensitivity C-reactive protein, and leptin using an aseptic technique. Samples will be mixed by inversion and centrifuged at 4 °C. Plasma from the tubes will be aliquoted into 5 microtubes with 2 spare microtube samples. Plasma samples will be batched for analysis to minimize interassay error. The sample will be stored at –80 °C before analysis. Spare tubes will only be used in the event of a processing error.

Samples will be tested by commercial laboratories accredited by the National Association of Testing Authorities (Australia) and The Royal College of Pathologists of Australia for compliance with National Pathology Accreditation Advisory Council (Australia) standards and ISO (International Organization for Standardization) 15189. Test results were interpreted in accordance with normative reference values. The study database allows the management of the samples.

Calculated Insulin Resistance

Homeostasis model assessment of insulin resistance (HOMA-IR) values will be calculated by the equation (fasting insulin [μU/mL] × fasting glucose [mM])/22.5. Insulin resistance is defined by a HOMA value >4 (reference).

Oral Glucose Tolerance Test Results and Other Forms of Testing for Gestational Diabetes

The 75-g oral glucose tolerance test (OGTT) is a standard of care to screen for GDM at 24-28 weeks' gestation in Australia. A 75-g OGTT may also be performed at 10-20 weeks of gestation if there are risk factors for GDM. A diagnosis of GDM may also be made using other methods such as HbA_{1c} (hemoglobin A_{1c}), glucose readings from a period of fingerstick monitoring, or by evaluating continuous glucose monitoring CGM) metrics. If the woman is considered to have GDM by the treating clinical team, she will also be given this diagnosis for the purpose of the study. All medications used to treat GDM will be recorded.

For all such women, a 75-g OGTT or some other form of testing for diabetes should be repeated >6 weeks' post partum and these results will also be collected.

Obstetric Ultrasound

Obstetric ultrasounds are routinely performed in Australia to assess fetal morphology at 20-22 weeks' gestation. The fetal morphology scan report will be collected from all participants. Fetal growth scans may be performed at 28, 32, or 36 weeks for obstetric indications. If growth scans are performed, the estimated fetal weight and abdominal circumference will be collected from ultrasounds that have been formally reported. The reported customized growth centiles are based on GROW customized charts which are customized for known constitutional variables (maternal height, weight, ethnic origin, and parity) but not pathological factors such as smoking and diabetes. This method of customization has been demonstrated to classify the greatest number of offspring at risk of perinatal mortality [7-9]. Any congenital anomalies reported on ultrasound will also be recorded.

Obstetric Discharge Summary

All neonates born at recruiting maternity hospitals have a standard obstetric discharge summary on discharge from the hospital. Neonatal information collected will include date of birth, gestation at delivery, birthweight, birthweight centile, sex, Apgar's score, neonatal complications (hypoglycemia, jaundice, congenital anomalies [major/minor], and others). Maternal information will include mode of delivery, and maternal pregnancy complications (GDM, gestational hypertension/preeclampsia, and others).

Cheek Swab (for Epigenetic Analysis)

Swabs will be taken from mother and baby using a sterile regular flocked dry swab using a kit supplied at 36 (SD 4) weeks of gestation. These samples will be self-collected by rubbing the swab against the inside of the cheek 10 times and reinserting the swab into the plastic applicator. Samples will be given to nursing staff before discharge. The swabs will be sent to pathology for long-term storage until all samples are collected.

Sample Size

We estimate recruitment of 500 participants over 24 months, with an estimated dropout of 5% inclusive of dropouts due to fetal/neonatal death. The primary outcome variable of interest is LGA/SGA offspring (yes/no) due to the known association with short- and long-term metabolic consequences and the fact that most babies with congenital anomalies and prematurity will have abnormal fetal growth. By definition, LGA (<90th centile for gestational age) and small for gestational age (>10th centile

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for gestational age) occurs in 20% of the population. With 475 participants (500 minus 25 dropouts), we would expect 95 offspring of interest compared with 380 normal-weight offspring.

Sample size calculation for the multivariable prediction modeling was conducted using the pmsampsize package in Stata (version 17.0; StataCorp) according to the 3 criteria (shrinkage, overfitting, and precision). From prior data, it is anticipated that the primary outcome of interest (presence of LGA/SGA offspring) will occur in 20% of the population. Åmark et al [10] reported an area under the receiver operating characteristics curve (AUC) of 0.8 from a logistic regression-based prediction model. Therefore, a minimum sample size of 440 is required with at least 88 events to ensure the expected shrinkage required is 10% or less (to minimize the potential overfitting), and a small absolute difference of 0.05 in the model's apparent and adjusted Nagelkerke R^2 value.

We anticipate that ≈20% of women will develop a maternal metabolic disease of interest including ≈15% who develop diabetes, ≈5% who gain excessive weight (>20 kg), and ≈15% who develop a hypertensive disease of pregnancy. Given the anticipated overlap of these conditions, ≈20% (n=90) of women will have at least one maternal metabolic disease of interest (secondary outcome).

Methodology

Data Collection

Study data are collected using paper case report forms. These paper documents will be kept in a locked cupboard accessible only to local research staff. Patient information is collected and stored by the investigators in a confidential REDCap (Research Electronic Data Capture system; Vanderbilt University), with password protection and restricted access. This will include patient information transcribed from the hospital's electronic medical record. REDCap is a secure, web-based app designed for research studies, providing a validated data entry interface, audit trails for data tracking, automated export procedures, and secure procedures for data import [11]. Internet access to the REDCap database will use a secure server located at the University of Melbourne, Australia (REDCap consortium host). Access will be limited to local research staff, approved data administrators, and project statisticians.

All biological samples will be labeled with a reidentifiable study number. The electronic study information will be stored in a dedicated, limited-access clinical database. Only study investigators and key study staff will have access to the database. Biological samples will be stored at –80 °C until all samples are collected. They will then be processed in batches by the local pathology network according to standard protocols.

Epigenetic samples (buccal swabs) will be stored at –80 °C until all samples are collected. DNA will then be extracted using standard processes for DNA extraction, and samples will be prepared for shipping. Methylation analysis will occur at an external genomics facility [12,13]. Once processed, data will be interpreted with the assistance of appropriate clinicians at Murdoch Research Institute. These samples are hypothesis-generating only and will not be included in the prediction modeling.

Data Management

Management of comprehensive and valid records will be the responsibility of each site. To ensure a systematic approach to data collection, the same team of study nurses will work between the sites using the same protocol and standard operating procedures. Data integrity will be maintained through a review of the collected data prior to, during, and after each study visit. Medication and adverse event data will be reviewed during each study visit. In addition, every 3 months the study coordinator will review the data collected to ensure completeness and consistency of data. Any data discrepancies will be queried with the participant by email or telephone within 4 weeks of being noted. All data, including the attendance of study visits, will be captured on a REDCap database. This will ensure that the study can meet regular deadlines required for process reporting as required by the Human Research Ethics Committee.

Data and Safety Monitoring

We anticipate very few study-related adverse events or serious adverse events. The only anticipated adverse events are phlebotomy-related side effects (ie, bruising, bleeding, vasovagal syncope) and a negative psychological response to clinical visits (ie, having weight measured). These events will be circumvented by having provided participants with a full and comprehensive review of study visits at the time of enrolment and prior to each study visit.

Reports of measurements taken at the time of clinical visits including weight and bioimpedance data, and the results of laboratory tests that are clinically relevant, will be made available to participants. Results that are not clinically relevant will not be disclosed to participants as they will not impact clinical care and may be difficult to interpret (ie, lack of reference ranges in pregnant women). Any concerning results will immediately be relayed to the treating maternity team. All other results will be reviewed within 1 week. The outcomes of participants will be discussed with the chief investigator each month. Any systematic problems with data management and adverse event monitoring or reporting will be rectified. REDCap queries will be addressed monthly by the study coordinator and reviewed quarterly by the study statistician.

Ethical Considerations

This is a prospective observational cohort study that intends to identify the metabolic disease risk factors, or combination of factors, that are most likely to cause adverse maternal and fetal health outcomes. No study-related adverse events are anticipated. The study has been granted ethics approval from the Royal Melbourne Hospital Human Research and Ethics Committee (HREC/90080/MH-2022) and recruitment is ongoing. Each participant will provide written informed consent before any study activities are undertaken and participants are free to withdraw consent at any time. Confidentiality will be maintained and only group data will be presented. Dissemination will be through peer-reviewed publications at national and international conferences, national and international obstetric medicine societies, and specialist colleges.

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Statistical Methods

This study will follow the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis reporting guidelines for prognostic studies [14]. Summary characteristics of the study cohort will be described using means (with SD) or medians (with IQRs) for continuous variables, depending on the shape of the distribution, and numbers and percentages for categorical variables.

A risk calculator will be developed to determine the risk of an abnormally grown fetus (ie, the primary outcome of the study). Participant data will be split randomly into either training (70%) or validation (30%) datasets according to standard prediction model methods. Multivariable logistic regression analysis will be conducted to identify candidate predictors of poor pregnancy outcomes due to metabolic disease. After starting with the most comprehensive model that includes all potential risk factors for an LGA or SGA offspring (ie, the primary outcome). These include categorical variables including maternal SES (based on postcode), maternal parity, maternal smoking status, maternal obesity class, maternal preexisting diabetes, maternal preexisting renal disease, essential hypertension, use of antihypertensive medication, use of metformin, gestational hypertension, preeclampsia/eclampsia, previous LGA/SGA offspring, major congenital anomaly, and continuous variables including maternal age, maternal gestational weight gain, maternal glycemic control (HbA_{1c}), total daily dose insulin, maternal systolic blood pressure, maternal diastolic blood pressure, birthweight of previous offspring, fasting glucose, plasma insulin, plasma C-peptide, plasma leptin, HOMA-IR.

A backward selection method will be performed to determine which combination of risk factors generates the most parsimonious predictive model. The number of candidate variables will be limited to data collected in the dataset. From this parsimonious model, model coefficients and the associated 95% CIs will be extracted to derive the risk score for predicting the delivery of LGA/SGA offspring. Internal validation of the model will be performed using 5-fold cross-validation and bootstrap validation. The performance of the model will be assessed using the AUC and calibration slope.

A similar approach will be taken for the secondary outcomes, and these models will be used to develop risk calculators for a composite of neonatal adverse outcomes and a composite of maternal adverse outcomes. Ongoing statistical input will be provided by the University of Melbourne.

Results

This project was funded by a National Health and Medical Research Council Investigator Grant awarded in November 2021 (CIA Price 2022-2026; 2007957), and by a Translational Challenge Grant from the Ramsay Hospital Research Foundation awarded in April 2024 (CIA Price 2024-2027; 2023/TCG/0038). The first participant was recruited on March 23, 2023. At the time of manuscript submission, 402 participants have been recruited. The projected timeline for recruitment is that the last participant will be recruited in June 2025. Therefore, it is anticipated that the last participant will have completed all study visits by June 2026. Data analysis has not yet been performed. Results are expected to be published in the first half of 2027.

Discussion

Why Predict Adverse Pregnancy Outcomes?

Uncontrolled maternal metabolic disease can profoundly impact both maternal and neonatal outcomes. Major congenital anomalies due to maternal metabolic disease are a common cause of neonatal death and long-term disability. For example, the risk of a major congenital anomaly such as congenital heart defect or spina bifida is 25% with suboptimally controlled diabetes (HbA_{1c} >10%) compared with 3% with well-controlled diabetes (HbA_{1c} <7%) [15,16]. Similarly, preterm birth can result in long-term neurodevelopmental issues and poor academic outcomes [17].

Even in children born at term, abnormal fetal growth can result in a long-term predisposition to metabolic disease. Around half of children born LGA (>90th centile for gestational age) or SGA (<10th centile for gestational age) [16] go on to develop metabolic syndrome (obesity, dysglycemia, and hypertension) by school age [2] with subsequent deterioration of metabolic disease in early adolescence [18]. This occurs due to a combination of factors including altered body composition at birth, altered appetite at birth, and atypical organ development including a lower endowment of cardiac myocytes, pancreatic beta cells, and nephrons [19].

For women, metabolic disease during pregnancy is an independent risk factor for later cardiovascular disease [20]. In the decade after preeclampsia, a meta-analysis including 200,000 women demonstrated a 4-fold increase in the relative risk of developing chronic hypertension and a 2-fold increase in the relative risk of ischemic heart disease and stroke [21]. For women who develop GDM, the lifetime risk of T2D is increased by 7-fold [22]. Lee et al [23] found that all-cause mortality was increased in women who were obese during pregnancy (BMI>30 kg/m^2) versus normal BMI after adjustment for confounding factors (hazard Ratio 1.35, 95% CI 1.02-1.77). Pregnancy loss due to late first-trimester miscarriage or stillbirth is also associated with increased cardiovascular disease in the mother, likely because pregnancy unmasks an underlying endothelial dysfunction [15].

Why Existing Prediction Models Are Inadequate

There are very few studies that have aimed to predict adverse pregnancy outcomes based on the maternal phenotype, and most of these have used maternal characteristics in combination with obstetric tests such as biomarkers in blood or ultrasound [24-27]. To the investigator's knowledge, there has only been one study that has used maternal prepregnancy characteristics to predict the risk of poor pregnancy outcomes [28].

The Generation R study group used easily obtainable maternal preconception characteristics including age, ethnicity, parity, BMI, and smoking status to model the risk of offspring born LGA/SGA. Basic models demonstrated an AUC of 0.63 (95% CI 0.61 to 0.65) and 0.64 (95% CI 0.62 to 0.66) for preterm birth/SGA and LGA, respectively. Interestingly, more complex

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models involving sociodemographic and dietary details only led to small improvements in the model [28].

However, the Generation R study was a population-based prospective cohort study that aimed to identify early and genetic causes and casual pathways leading to abnormal growth and development of the offspring [29]. Risk prediction modeling in this study focused on all potential causes of LGA and SGA in a whole population cohort. This study did not specifically focus on LGA/SGA in the context of metabolic disease, nor did it consider the metabolic outcomes of the mother. Women with metabolic disease are known to be at higher risk of adverse pregnancy outcomes than the general population [30]. This cohort requires information about the risk of poor pregnancy outcomes both for themselves and their offspring.

Within an established pregnancy, Frick et al [31] found that LGA offspring (>95th centile) could be predicted based on increasing maternal BMI, diabetes status, and the presence of chronic hypertension. However, this prediction was less accurate in non-Caucasian women, in smokers, and in nulliparous women. In parous women, LGA offspring were predicted based on the birth-weight Z-score of previous offspring, a prior history of GDM, and a decrease with interpregnancy interval. This study then refined the prediction model using early fetal ultrasonography [31].

A population-based study from Ontario Canada (n=634,290) found that it was possible to predict and prevent severe maternal morbidity with moderate discrimination. Those women who had poor short-term pregnancy outcomes were older, had more medical comorbidities, and conceived using assisted reproductive technologies [32]. Similarly, Akinci et al [33] reported that in a small cohort (n=164), prepregnancy obesity, greater gestational weight gain, and a fasting glucose level (>5.5 mmol/L) on the 75-g OGTT predicted the development of metabolic syndrome in postpartum women with moderate to high discrimination.

What the Metabolic Health and Mother and Baby Health Outcomes Study Will Contribute

There are very few studies that use maternal characteristics to predict both maternal and fetal/neonatal pregnancy outcomes, even though they are inextricably linked. There are also few studies that consider the impact of metabolic disease as a whole rather than focusing on individual components of metabolic disease- hypertension, obesity, or dysglycemia.

We anticipate the Metabolic Health and Mother and Baby Health Outcomes (MAMBO) project will be able to fill this gap by developing a risk prediction tool that (1) considers how multiple maternal metabolic risk factors interact to result in adverse pregnancy outcomes, and (2) considers both maternal and neonatal pregnancy outcomes.

A risk calculator that can be used as a mobile app would provide health care workers with a simple effective tool to objectively calculate pregnancy risk and to triage women to appropriate services based on a standard dataset. Health care providers would require very little background knowledge to use the risk calculator. However, the tool would produce personalized data about the risks of an adverse pregnancy outcome. This would assist health care workers in effectively communication with the woman, her family, and with other health care providers.

Limitations

Ideally, the MAMBO cohort would have been recruited prior to conception. However, this would have required a very large sample size to allow for women who did not conceive in a specified timeframe and for additional dropouts due to the lag time between recruitment and conception. Therefore, the pragmatic decision was made to recruit women at 20±4 weeks' gestation. Existing data demonstrates a strong correlation between maternal anthropometric data and biomarkers in early pregnancy and the prepregnancy period [34].

The MAMBO cohort consists entirely of women attending major metropolitan maternity hospitals. Although these hospitals accept referrals from primary care and smaller hospitals that provide maternity care for women living in rural and remote locations, nonmetropolitan women are likely to be underrepresented in this cohort. Women from minority culture groups and women from non–English speaking backgrounds may also be less likely to participate in a prospective cohort study. To address these issues, translators and cultural liaison officers will be made available. We will aim to pair study visits with usual maternity care appointments. The final clinical study visit can be performed by phone if necessary.

Outcomes and Significance

Growing numbers of women are impacted by metabolic disease when they pursue pregnancy. However, women of low socioeconomic status, non-English speaking backgrounds, and women living in rural and remote areas are less likely to access preconception care services. Therefore, these women are at a greater risk of short-term adverse pregnancy outcomes, and long-term due to metabolic programming in the infant and unmasking of endothelial dysfunction in mothers.

The development of a risk calculator that predicts the women most likely to have poor pregnancy outcomes may assist in preventing these adverse pregnancy outcomes. It would allow women to be triaged by any health care professional and would ensure that the highest risk women are identified and have the opportunity to be referred to high-quality preconception care services and to receive information on how to prevent adverse health outcomes for themselves and their offspring. The risk calculator also has the potential to act as a platform that assists health care professionals in providing lower-risk women with basic preconception care information.

Conclusions

Currently, the women at the highest risk of adverse pregnancy outcomes due to metabolic disease are the least likely to access preconception health interventions. The MAMBO project intends to bridge this gap by developing a risk prediction tool that allows any health care practitioner to accurately assess risk, and to triage women to appropriate preconception care services. In this way, we aim to prevent adverse maternal and fetal health outcomes.

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Acknowledgments

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Data Availability

The datasets generated during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Additional tables.
[DOCX File , 18 KB - resprot_v14i1e72542_app1.docx]

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Abbreviations

AUC: area under the receiver operating characteristics curve
GDM: gestational diabetes

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HbA_{1c}: hemoglobin A_{1c}
HOMA-IR: homeostasis model assessment of insulin resistance
IADPSG: International Association of the Diabetes and Pregnancy Study Group
LGA: large for gestational age
MAMBO: Metabolic Health and Mother and Baby Health Outcomes
OGTT: oral glucose tolerance test
REDCap: Research Electronic Data Capture
SGA: small for gestational age
T2D: type 2 diabetes
WHO: World Health Organization

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Protocol

Italian Medical Professionals' Practices, Attitudes, and Knowledge in Travel Medicine: Protocol for a National Survey

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Abstract

Background: The evolving global health landscape highlights the importance of travel medicine, making it necessary for health care professionals to understand the epidemiologic profiles among varied traveler populations and keep themselves updated in this rapidly changing field. However, in Italy, travel medicine clinics have significant gaps in resource allocation, staff training, and infrastructure.

Objective: This protocol of a cross-sectional study aims to create and validate a questionnaire to assess the knowledge, attitudes, and practices of health care professionals in travel medicine in Italy. The final goal is to provide a tool to evaluate the state of travel medicine, guide training initiatives, and be able to monitor trends over time.

Methods: The study population consists of health care professionals who practice travel medicine in Italy. The questionnaire will be developed by adapting an existing English survey and conducting a scoping review to align the questionnaire with contemporary scientific discourse. The validation process includes face validity, content validity, and expert evaluation. The sample size, determined through power analysis, ranges from 218 to 278 participants. The questionnaire will undergo a pilot test on a smaller sample size (10% of the total) to identify and address any issues. Statistical analysis will include central tendency and dispersion measures, categorical summaries, group comparisons, and regressions. This research received ethical approval, and informed consent will be obtained from all participants.

Results: As of July 2024, we completed the questionnaire validation involving 9 experts. The validated version of the questionnaire includes 86 items. Furthermore, we conducted a pilot test on 53 individuals during the SIMVIM (Italian Society of Travel Medicine and Migrations) course on travel medicine held in Lucca, Italy, on June 14, 2024.

Conclusions: This cross-sectional study will guide strategic planning and targeting training and awareness activities in areas deemed most critical or lacking. The study's structured approach and periodic assessments will facilitate the identification of educational gaps, the dissemination of best practices, and the overall improvement of health care services for travelers in Italy.

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KEYWORDS

travel medicine; Italy; cross-sectional; survey; KAP; medical professional; medical professionals; Italian; global health; epidemiology; scoping review; power analysis; dissemination; healthcare service; healthcare services; survey protocol; awareness; assessment

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Introduction

Background

The ever-changing landscape of global health threats has made travel medicine an essential field for health care professionals. In the backdrop of dynamic global health scenarios, travelers play a significant role in the epidemiology of infectious diseases, as evidenced by the COVID-19 pandemic [1,2], as well as the spread of Ebola [3], Zika [4], and antimicrobial-resistant pathogens in recent years [5]. Their mobility, potential exposure to diseases outside their native countries, and the possibility of disease transmission across borders make them a crucial cohort for epidemiologic surveillance. By integrating international travelers into epidemiologic disease surveillance, it is possible to obtain a more nuanced understanding of the presence, frequency, seasonality, and geographic distribution [6]. This understanding might pivot over time due to various factors, such as outbreaks, climate change, vector habitat alterations, emerging or reemerging diseases, or effective public health initiatives [7-9].

It is necessary for health care professionals to understand the epidemiological profiles of the different types of travelers, keep themselves up-to-date in this rapidly evolving field, effectively inform travelers before departure, and offer posttrip assessments and possible treatments [10].

The quality of pretravel counseling, an indispensable measure for optimal risk management of travelers, hinges on the experience and knowledge of the health care professional providing the consultation [11]. It is through this expertise that personalized strategies to mitigate health risks—from behavioral norms to prescription prophylaxis and often expedited vaccination protocols—are crafted.

Around the European region, travel medicine is structured in highly different ways [12].

In Italy, Local Health Units ASL (Azienda Sanitaria Locale, under the “Servizio sanitario nazionale,” SSN) have travel medicine specialized ambulatories that provide pre-travel medical consultations, vaccinations, and prophylaxis. These services are offered by the SSN in co-payment, resulting in cost savings for the travelers. In addition, the “Unità Sanitaria Marittima, Aerea e di Frontiera” (USMAF) at airports and ports offers travel medicine services. There are a total of 343 ambulatories; Table 1 and Figure 1 describe them in detail. Health care professionals working in these units can be doctors, nurses, and health assistants; they can provide information about health risks in different countries, mandatory or recommended vaccinations, and prophylaxis.

Table 1. Complete list of the authorized travel medicine ambulatories by the Italian Ministry of Health (decree 3 August 2022) by region. The population of that region in 2022 (Istituto Nazionale di Statistica [ISTAT]) and the density of ambulatories per 100,000 inhabitants are also listed.

Region	Travel medicine ambulatories, n	Population (2022 ISTAT), n	The density of ambulatories (n/100,000 ambulatories)
Abruzzo	9	1,269,860	0.71
Basilicata	4	536,659	0.75
Calabria	9	1,841,300	0.49
Campania	10	5,592,175	0.18
Emilia Romagna	49	4,426,929	1.11
Friuli Venezia Giulia	14	1,192,191	1.17
Lazio	27	5,707,112	0.47
Liguria	10	1,502,624	0.66
Lombardia	59	9,950,742	0.59
Marche	16	1,480,839	1.08
Molise	3	289,840	1.03
Piemonte	25	4,240,736	0.59
Puglia	20	3,900,852	0.51
Sardegna	9	1,575,028	0.57
Sicilia	9	4,802,016	0.19
Toscana	30	3,651,152	0.82
Umbria	5	854,137	0.58
Val d’Aosta	1	122,955	0.81
Veneto	28	4,838,253	0.58
Province Trento	2	542,050	0.37
Province Bolzano	4	533,267	0.75

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Figure 1. Number and density of travel medicine ambulatories in Italy.

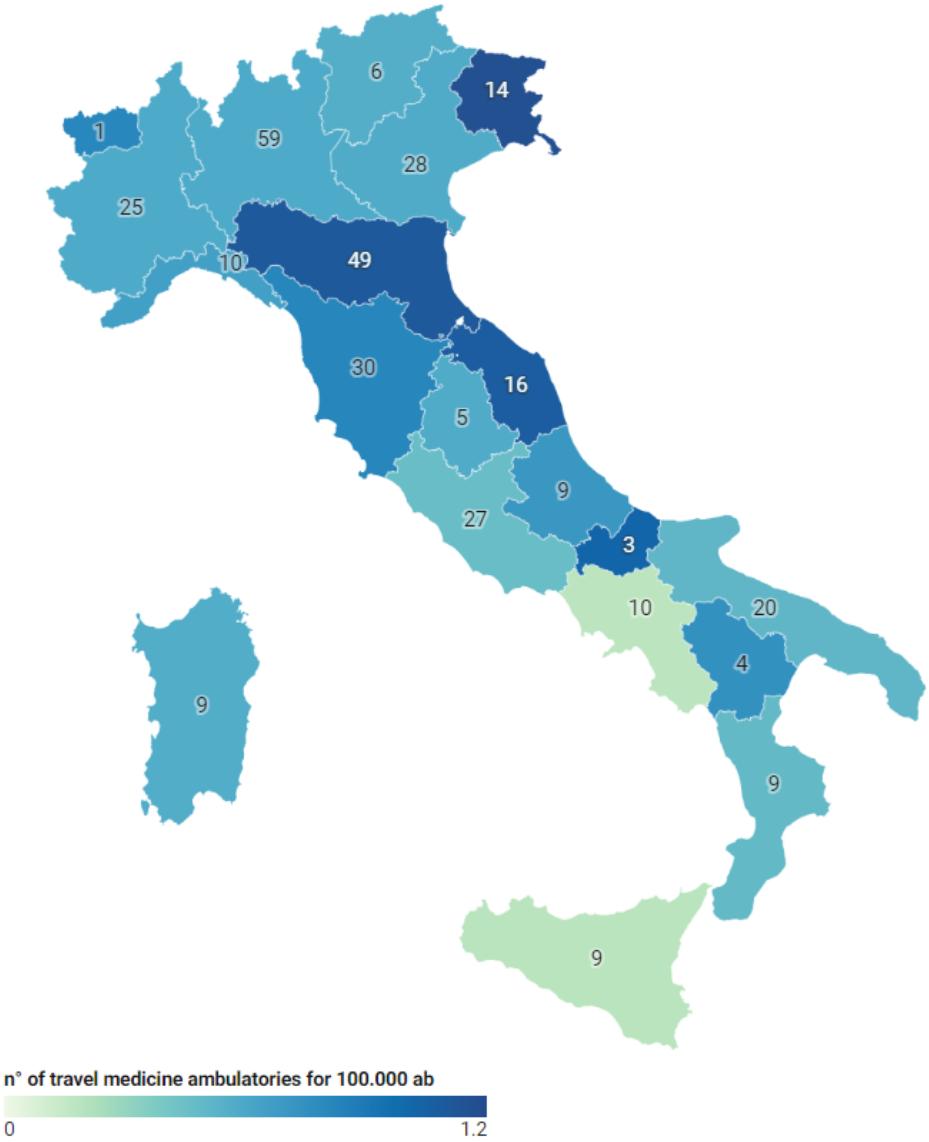

Typical training is not required for travel medicine doctors working in these health facilities, even if many of them are infectious disease or public health specialists.

The Italian National Vaccination Plan (PNPV) for 2023-2025 highlights the importance of travel medicine [13]. It emphasizes that professionals should be well-informed about the global epidemiology of both infectious and noninfectious risks travelers face, current regulations, and immunization requirements in destination countries.

A national survey conducted in 2018 by the Italian Society of Travel Medicine and Migrations (SIMVIM) underlined the operational dynamics, challenges, and potential avenues for the evolution of Italian Travel Medicine Ambulatories [14].

A total of 79 travel medicine ambulatories participated in the survey nationwide. These clinics, on average, allocate about 10 hours per week to their services, corresponding to approximately 18 users each week. Concerning training, 70.9% of the health care staff had their last significant training or update in the 2-year window of 2017-2018. The survey showed that while these clinics play a commendable role in ensuring traveler health, considerable gaps exist in resource allocation, staff training, infrastructure, and integration with the broader National Health System.

Given this intricate background, there is an evident need for validated tools to assess the knowledge, attitudes, and practices (KAP) of health care professionals in the domain of travel medicine in Italy. These tools can offer a snapshot of the national scenario and potentially unveil a new path for health care professional training. In this context, we developed the protocol of IMPAKT (Italian Medical Professionals Practices, Attitudes and Knowledge in Travel Medicine), a cross-sectional study aimed at creating and validating a questionnaire to assess the KAP of health care professionals (doctors, nurses, and health assistants) involved in travel medicine within Italy. The survey will be disseminated through all available channels of SIMVIM and would be sent by email to official email addresses associated with travel medicine clinics.

Objective of the Study

While the 2018 survey focused primarily on the operational aspects of travel medicine ambulatories, the aim of this study

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is to create and validate a questionnaire to assess the knowledge, attitudes, and practices of health care professionals in travel medicine in Italy, ultimately providing a tool to evaluate the state of travel medicine allowing a more detailed understanding of the educational and training needs at the individual and regional level in Italy.

Methods

Overview

KAP surveys are a widely used tool in cross-sectional studies to investigate health-related behaviors and health-seeking practices [15]. A KAP survey allows a target population to be studied in terms of knowledge, attitudes, and practices through the use of questionnaires (structured or semistructured) that are self-administered or administered by interviewers. Furthermore, the survey allows both qualitative and quantitative data to be collected [16]. Figure 2 shows a schematic representation of the proposed methodology.

The information for this study will be collected in a structured, self-administered questionnaire. For this study, "Knowledge in Travel Medicine" is defined as the understanding and awareness of health care professionals about travel-related health risks, prevention strategies, diagnostic measures, treatments, and appropriate interventions.

"Attitude toward Travel Medicine" among Italian health care professionals aims to analyze their perspectives, beliefs, feelings, and inclinations about the importance, relevance, and role of travel medicine in the patient's general care. This involves assessing their perception of the value of travel health advice, perceived barriers, and their motivation to stay updated in this evolving field. "Practices of Travel Medicine" are defined by the actual behaviors, interventions, and actions taken by health care professionals involved in travel medicine. This includes the frequency and accuracy of pre-travel consultations, the administration of travel vaccinations, the provision of malaria and other travel-associated diseases prophylaxis, post-travel assessments, patient education on travel health precautions, and documentation practices, among others.

Figure 2. Diagram representing the phases and objectives of the Italian Medical Professionals Practices, Attitudes and Knowledge in Travel Medicine (IMPAKT) study. KAP: knowledge, attitudes, and practices.

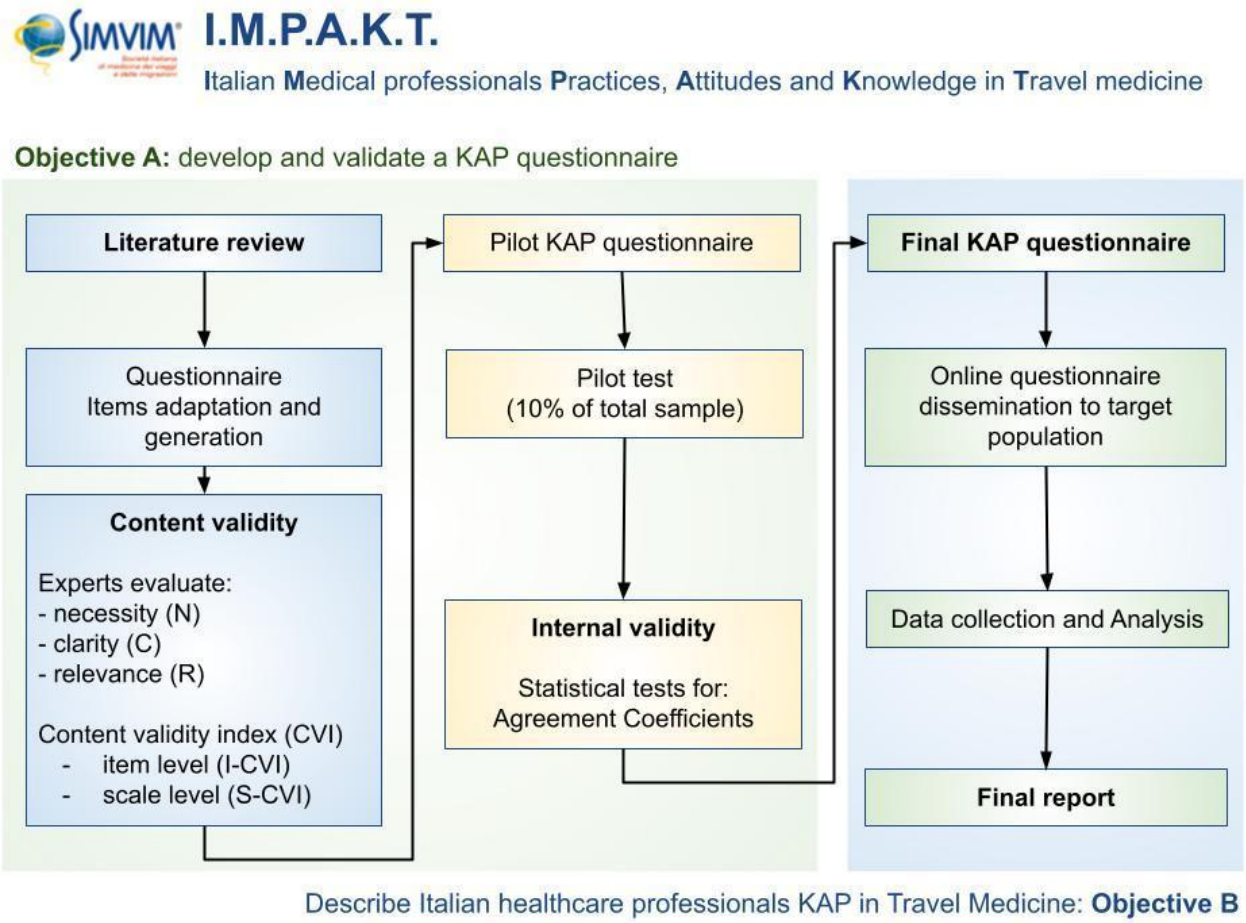

Ethical Considerations

This research received ethical approval from the ethics committee of the University of Pisa on October 11, 2023 (review 39/2023; protocol 0136227/2023). Every participant will be provided with a privacy notice that explains the purpose of data collection, storage, and processing in compliance with the General Data Protection Regulation and Italian regulations. Before proceeding with the questionnaire, explicit consent will be obtained from the participants.

To ensure confidentiality and data protection, each participant will be assigned a unique identification code. The association

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between identifiers and emails will be kept in a separate file protected by a password. Data will be deleted 5 years after the end of the study. This procedure ensures that the data collected will be anonymized, safeguarding the privacy of all participants.

Inclusion and Exclusion Criteria

The study population includes health care professionals (ie, doctors, nurses, or residents) who practice travel medicine in Italy. Textbox 1 shows the inclusion criteria for study participants.

Textbox 1. Inclusion and exclusion criteria.

The following are the inclusion criteria:

- Being a health care professional (HCPs are medical doctors, nursing professionals, midwifery professionals, dentists, pharmacists, and trainees in the above categories).
- Practicing in Italy.
- Age≥18 years.
- Giving informed consent.

In addition, at least one of the following:

- Being a member of SIMVIM (or other associations or societies interested in travel medicine).
- Working or having worked in the last 5 years as a travel medicine consultant.
- Have participated in the previous 5 years in a workshop, seminar, or congress on travel medicine.
- Working in a travel medicine ambulatory.

The following are the exclusion criteria:

- Not being a health care professional.
- Practices the profession outside of Italy.
- Consent not given.
- Withdrawal of consent.

Questionnaire Development

To structure the questionnaire for our study, we will adapt the one used by Kumar et al [17]. Kumar et al [17] developed a 106-item questionnaire in English to assess the existing expertise of Indian medicine and infectious diseases resident doctors with respect to travel medicine. We will adapt this English questionnaire to the Italian context, translating, modifying, and adding specific items to better capture the peculiarities of Italian travel medicine practice. Therefore, this already validated questionnaire will be a reference for the development of our questionnaire, as it has a similar aim and a similar target population.

Except for COVID-19–related papers, we will conduct a nonsystematic literature assessment of pertinent scientific publications over the last 5 years to guarantee a thorough representation of travel medicine issues in the questionnaire. This title-only review will cover a summary of the themes in travel medical literature with a title analysis. The aim is to align the questionnaire with the current scientific discourse on travel medicine. Multimedia Appendix 1 contains the PubMed query that will be used.

Regarding the translation of the Kumar et al [17] questionnaire, two separate translators among the investigators will translate each item (question) into Italian separately. The goal is to make sure there are no appreciable differences between the two translations and that they both express the same concept. A third translator will be sought in cases of disagreement. By evaluating the item and the two translations, this third translator will serve as an arbitrator, settling the conflict and producing a version that is agreed upon.

A back-translation will be carried out to confirm the accuracy of the translated items and to make sure the content has not been changed or misinterpreted during the translation process.

The English items and the back-translated English items will be compared to check for any discrepancies.

Items from the 2018 SIMVIM survey will be integrated into the questionnaire [14]. In addition, new items proposed by one investigator will undergo scrutiny by two other investigators before being added to the item pool to be examined by experts.

Questionnaire Validation

In the following sections, the steps of the validation process of the questionnaire are described, those steps include the evaluation of face and content validity.

Face validity refers to experts' initial agreement that a test is a legitimate representation of the domain in question [18]. After formulating the initial draft of our questionnaire, we will solicit feedback from experts in travel medicine. Their assessment is centered on readability, comprehensibility, feasibility, layout, and style, ensuring the questionnaire is valid in these aspects.

Content validity aims to minimize bias during the early stages of instrument operationalization [19].

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To validate the content of our travel medicine questionnaire, we identified 3 key components to assess overall content validity. Indeed, we disassembled the overall validity into specific components [20], focusing on three determinants:

1. Necessity: Is the question necessary to be asked to the health care professional to assess their knowledge/attitude/practices of travel medicine? Each item can be rated as 1 (neither useful nor necessary), 2 (useful but not necessary), and 3 (essential).
2. Clarity: Are the question phrasing, structure, or provided options comprehensible? Each item can be rated as 1 (not clear), 2 (slightly clear/needs major revision), 3 (clear/needs minor revision), and 4 (very clear).
3. Relevance: Is the question pertinent to the domain of travel medicine, particularly in gauging knowledge, attitude, or practice? Each item can be rated as 1 (not relevant), 2 (slightly relevant/needs major revision), 3 (relevant/needs minor revision), and 4 (very relevant).

Experts will evaluate each question based on these determinants using a Likert scale. This approach allows specificity in content validation and facilitates a rigorous critique from experts. It also enables us to identify any discrepancies in expert opinions concerning the questionnaire's necessity, clarity, and relevance.

Experts (at least 3) with proven knowledge in travel medicine are selected to evaluate the content validity of the questionnaire. Experts enrolled in the study will provide their advice free of charge and sign informed consent to the study as other subjects.

At least one of these requisites is necessary to be qualified as an expert:

- A minimum of 10 years of clinical practice focused on travel medicine or related fields.
- Holding a Certificate in Travel Health (CTH) or similar certifications.
- Experience in educating or training other health care professionals about travel medicine, either as a faculty member of an educational institution or as a speaker in seminars/workshops.
- Contribution to the development of travel medicine guidelines or protocols.
- Authorship of peer-reviewed articles, book chapters, or research papers specifically focused on travel medicine or closely related fields.

An electronic questionnaire version will be shared with these experts alongside specific instructions about the validation objectives.

The item-level content validity index (I-CVI) and the scale-level content validity index (S-CVI) are the two main indices for determining a tool's content validity; we will use both indexes, following other cross-sectional studies [20,21]. Our panel of experts will rate each item using the aforementioned criteria. Following this, scores will be dichotomized, converting them into "1" or "0" based on established rating criteria. Necessarily, the dichotomous variable will be categorized as "1" if the item is rated as "3" (essential) or "0" otherwise. Likewise, for clarity and relevance, the dichotomous variables will be categorized as "1" for experts, giving a rating of 3 or 4 and "0" otherwise.

Content validity indices will be computed (I-CVI and S-CVI/Ave [scale-level content validity index/average]) using these dichotomized scores, and the items with a score higher than the minimum required score (I-CVI≥0.82) will be included in the questionnaire. Polit and Beck have endorsed an S-CVI/Ave value of 0.90 or higher as excellent [22,23].

Sample Size

The sample size for this cross-sectional study was calculated to determine the minimum number of travel medicine professionals needed to ensure a representative sample of the broader population of travel medicine professionals in Italy. Knowing that there are about 500 members affiliated with SIMVIM in 2022 and 343 authorized travel medicine ambulatories, we ran an analysis from 500 to 1000 as a possible population range. We set the confidence level at 95% and the margin of error at 5%, 8%, and 10%.

Based on these parameters and using the formula:

We determined the total sample sizes of respondents necessary to achieve sufficient statistical power, available in Table 2. Therefore, to achieve adequate statistical power, it is necessary to administer the questionnaire to a population sample of subjects between 218 and 278.

Table 2. Sample simulation, power analysis results.

Population size, n	Margin of error, %	Sample size, n
1000	5	278
500	5	218
1000	8	131
500	8	116
1000	10	88
500	10	81

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Pilot Test

A pilot cross-sectional study will be conducted on a smaller sample size (around 10% of the total sample size) to identify any issues with the expert-validated version of the questionnaire or data collection methods. The results collected from the pilot study will allow any adjustments to be made before the full-scale data collection.

The pilot study will be used to assess internal validity through agreement coefficients, which represent statistical measures used to quantify the degree of consensus or concordance among various respondents to a questionnaire. These parameters evaluate the consistency and reliability of ratings, taking into account the chance agreement. A Cronbach α over 0.7 will be considered sufficient, with a 0.8 benign optimal [24-26].

After evaluation of the aforementioned settings, we will finalize the KAP questionnaire, which will incorporate only items that meet the predetermined criteria.

Dissemination and Data Collection

Upon validation and pilot testing, the questionnaire will be disseminated using an online form containing (1) an introduction to the questionnaire with the aim of the study, (2) a privacy disclaimer and informed consent, (3) a subject data section, and (4) a KAP questionnaire.

The form will be shared through all available channels of SIMVIM. As the primary association uniting professionals practicing travel medicine in Italy, SIMVIM provides an ideal platform for the widespread dissemination of the form. The study will be featured in SIMVIM's regular email newsletter, ensuring it reaches all members directly. It will also be published on the official SIMVIM website, making it accessible to a broader audience. Furthermore, the study will be presented during in-person training and update events organized by SIMVIM for professionals in the field. Finally, the questionnaire link will be sent by email to official email addresses associated with travel medicine clinics. For each distribution method, we will track the number of individuals the questionnaire is presented to, enabling the calculation of a response rate. However, a potential limitation of our study is the overlap in membership between different contact methods, which may prevent the calculation of an overall response rate. For each participant, after giving the informed consent, the personal data in Table 3 will be collected through the online form, and an ID number will be assigned, which will substitute the email to anonymize results.

Table 3. Participant personal data to be collected in section 1 of the questionnaire.

Item (question)	Variable	Valid input	Reason
Q1	ID	Automatic (2023.001, 2023.002)	Anonymization
Q2	Date	Date (DD/MM/YYYY)	Participant identifier
Q3	Email	String @ string	Participant identifier
Q4	Age	Numeric (18-100)	Stratification and inclusion criteria
Q5	Sex	Factor (0=prefer not to say, 1=male, 2=female, and 3=other)	Stratification
Q6	Profession	Factor (0=medical doctor, 1=nurse, 2=health care assistant, 3=pharmacist, and 4=other health care professional)	Stratification and inclusion criteria
Q7	Work type	Factor (0=not working, 1=public fixed term, 2=public indeterminate, 3=private, 4=other, and 5=not working)	Stratification
Q8	Work region	Factor (21 levels, 19 regions, and 2 autonomous provinces)	Stratification
Q9	Country of practice	Factor (0=others, 1=Italy)	Stratification and inclusion criteria
Q10	Years of experience	Numeric (0-100)	Stratification and inclusion criteria
Q11	Travel medicine ambulatory	Factor (0=no and 1=yes)	Stratification and inclusion criteria
Q12	Education	Factor (high school diploma=1, university degree=2, graduate master=3, and PhD=4)	Stratification
Q13	Medical residency	Only for MD, string (description of the medical residency)	Stratification
Q14	Travel history	Numeric (number of intercontinental travels in the past 10 years)	Stratification
Q15	Main travel reason	Factor (0=job, 1=volunteering, 2=tourism, and 3=visiting friends and relatives)	Stratification
Q16	Workshop participation	Factor (0=no and 1=yes)	Stratification and inclusion criteria
Q17	Membership	Factor, more than one possible (0=none, 1=SIMVIM, 2=SITI, and 3=other)	Stratification and inclusion criteria

Statistical Analysis

The data obtained from the final questionnaire will undergo statistical analysis to ensure a comprehensive interpretation. The measurements of the central trend (mean and median) and dispersion (SD and IQR), depending on the part of the questionnaire analyzed, will be calculated. Categorical responses will be summarized using percentages, frequencies, and

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graphical representations (bar charts, histograms, and pie charts) will be used for visual summaries. Differences among groups in KAP scores will be assessed using *t* tests (2 groups) or ANOVA (2+ groups). Mann-Whitney *U* test or Kruskal-Wallis test will be used if the data does not meet the assumptions of the parametric tests. Chi-square tests or Fisher exact tests will be applied to compare categorical data among groups.

When assessing predictors of a particular outcome (eg, certain knowledge scores predicting practices), either multiple linear regression (for continuous outcomes) or logistic regression (for binary outcomes) will be used. Relevant assumptions for each regression model will be verified before the analysis is performed.

A *P* value of less than <.05 will be considered statistically significant for all tests. When conducting multiple comparisons, correction methods such as Bonferroni correction will be applied to check the familywise error rate. All statistical analyses will be performed using the statistical software R (R Foundation for Statistical Computing).

To ensure geographical representation, considering that the Italian health care system is organized federally, the stratification of results by region will be conducted only if a significant proportion of respondents declare to operate in that region (Q8). If not all the 19 regions and 2 autonomous provinces are sufficiently represented, an additional stratification by macro area will be conducted.

Results

The PubMed query described in the Methods section yielded a total of 1067 articles published between 2018 and 2023. A screen of the article titles allowed us to identify 13 overarching topics into which knowledge items could be classified. The identification of these topics was primarily guided by the structure of the CDC Yellow Book [27], which provides a comprehensive framework for travel medicine. The literature retrieved through PubMed was subsequently used to corroborate the relevance and coverage of the selected topics. The following topics represent key domains in travel medicine: (1) general principles of travel medicine, (2) pretravel consultation, (3) posttravel consultation, (4) vaccination and immunoprophylaxis—general principles, (5) travelers' diarrhea, (6) travel-associated infections including malaria, (7) yellow fever, (8) bacterial diseases, (9) viral diseases, (10) travelers with additional considerations, (11) travel by air, land, and sea, (12) environmental hazards and risks, and (13) travel medicine ambulatory organization.

As of July 2024, we completed the questionnaire validation involving 9 experts. The validated version of the questionnaire includes 86 items. Furthermore, we conducted a pilot test on 53 individuals during the SIMVIM course on travel medicine held in Lucca, Italy, on June 14, 2024.

Discussion

This research project, jointly developed by the University of Pisa and the SIMVIM, aims to create a "diagnostic" tool for assessing the state of Travel Medicine in Italy. Given the inherent nature of travel medicine, as also highlighted in the PNPV 23-25 [13], it is crucial to ensure that health care professionals providing travel medicine services are well-trained and continuously updated to deliver high-level services to travelers.

This cross-sectional study, as outlined in the protocol, will serve as a guide to strategically plan and target training and awareness activities in areas deemed most critical or lacking. These activities are already being conducted by SIMVIM and other scientific societies focused on travel medicine in Italy, but without a structured approach due to the lack of a national standardized evaluation tool. In addition, by periodically repeating the questionnaire (annually or biennially), it will be possible to monitor the trends in knowledge, practices, and attitudes of health care professionals, thus ecologically assessing the impact of organized activities in Italy.

Specifically, it will be feasible to evaluate whether the level of knowledge on each topic has increased or decreased based on the themes covered in "update workshops" and conferences organized nationally. This approach will also consider the equity principle at the base of the Italian national health system [28], identifying any educational gaps in specific geographical areas of the country to make it possible to address them with specific interventions.

Furthermore, in the spirit of equity and equal access to care and prevention, systematic collection and analysis of practices used in travel medicine clinics will be conducted. This will help assess the national status and identify best practices to be disseminated nationally. If any shortcomings or structural deficiencies are highlighted, solutions could be formulated with the involvement of stakeholders, whether political or from the industry.

In conclusion, we believe that the effort to develop a tool refined by national experts can significantly contribute to the development and dissemination of good practices and better knowledge of travel medicine in Italy. Sharing this protocol could also lead other Beveridge health care systems to replicate a similar approach, thereby enhancing prevention and care to safeguard the health of travelers.

Acknowledgments

The study will be conducted using existing resources and facilities within the University of Pisa and SIMVIM, and no additional external funding will be sought or required. During the preparation of this work, the authors used ChatGPT and Grammarly for English grammar checks. After using this tool/service, the authors reviewed and edited the content as needed and took full responsibility for the content of the publication.

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Data Availability

The data sets generated during and/or analyzed during this study are not publicly available due to privacy restrictions.

Authors' Contributions

FB conceived the study. FB, FV, AA, Todaro A, ET, GAGL, and MF performed the literature search and drafted the manuscript. LDA, Tomasi A, and CR provided expert insights and contributed to the manuscript revision. All the authors approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Additional material.
[DOCX File , 6 KB - resprot_v14i1e59511_app1.docx]

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Abbreviations

ASL: Azienda Sanitaria Locale
CTH: Certificate in Travel Health
I-CVI: item-level content validity index
IMPAKT: Italian Medical Professionals Practices, Attitudes and Knowledge in Travel Medicine
KAP: knowledge, attitudes, and practices
PNPV: Italian National Vaccination Plan
S-CVI/Ave: scale-level content validity index/average
S-CVI: scale-level content validity index
SIMVIM: Italian Society of Travel Medicine and Migrations
USMAF: Unità Sanitaria Marittima, Aerea e di Frontiera

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Protocol

Genetic, Epidemiological, and Clinical Risk Factors for Perinatal Anxiety and Depression in Dubai: Protocol for a 2-Point Prospective Observational Study

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Abstract

Background: Perinatal anxiety and depression can significantly impact maternal well-being, infant development, and mother-child bonding. There is a relative lack of research on the overall burden of and risk factors for perinatal and postpartum depression and anxiety in the Middle Eastern region.

Objective: We aimed to investigate genetic, epidemiological, and clinical risk factors for anxiety and depression in antenatal and postnatal mothers.

Methods: This study is a 2-point, cross-sectional, observational study of pregnant women at a tertiary care hospital in Dubai, United Arab Emirates. We will evaluate the point prevalence of depression and anxiety with the Edinburgh Postnatal Depression Scale, the Generalized Anxiety Disorder 7 scale, and the Holmes-Rahe Stress Inventory and analyze the risk factors in affected and unaffected women. The women will be evaluated with structured interviews, initially in the antenatal period (between 20 to 26 weeks) and again in the postnatal period (between 6 weeks to 6 months after delivery). Whole-genome sequencing will be conducted to comprehensively map genomes and detect variants associated with depression and anxiety after the initial interview. Social factors such as family characteristics and partner support, as well as lifestyle factors such as exercise, vitamin D intake, and obstetric factors, along with intrapartum and neonatal events affecting maternal mental health, will also be assessed.

Results: We will assess the prevalence of depression, anxiety, stress, and risk factors in the antenatal and postnatal period between July 2025 and June 2026 at Dubai Hospital. The association of genetic, social, and demographic risk factors with depression and anxiety will be compared in women who screen positive for depression and anxiety and those who screen negative.

Conclusions: This research aims to identify genetic variants associated with perinatal anxiety and depression in Middle Eastern women and to develop a comprehensive risk assessment tool for identifying women at high risk for perinatal anxiety and depression.

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KEYWORDS

perinatal anxiety; perinatal depression; genetic risk factors; clinical risk factors; depression; anxiety; antenatal depression; postnatal depression; antenatal anxiety; postnatal anxiety

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Introduction

Background

The World Health Organization's guide for integrating perinatal mental health into maternal and child health services reflects the global recognition of this crucial health concern [1]. The impact of mental health disorders on the workforce is significant, with 15% of working-age adults worldwide experiencing such conditions. Anxiety and depression alone lead to the loss of 12 billion working days annually [2]. During pregnancy, untreated depression and anxiety in the perinatal and postpartum periods have far-reaching consequences, beyond the economic implications. These conditions are associated with obstetric complications [3], poor birth outcomes, and reduced health-seeking behavior [4] during and after pregnancy [5]. Furthermore, these conditions can impair mother-child bonding [6], with infants of mothers with such conditions at a higher risk for physical, emotional, and behavioral issues [4]. Addressing perinatal mental health is therefore crucial for the well-being of the mother, child, and the wider family unit in both the short and long term.

Previous publications [6-10] on perinatal mental illness in the United Arab Emirates reveal a wide range in reported prevalence, from 10% to 85.6%. Women of Middle Eastern ethnicity (ie, from the United Arab Emirates, Saudi Arabia, Oman, Kuwait, Yemen, Syria, Iraq, Iran, and Jordan) are highly prone to depression (50% prevalence) and anxiety (48.5% prevalence) compared to women from South and Southeast Asia (from India, Pakistan, and the Philippines: 29% prevalence of depression and 25.2% for anxiety), while North African women (from Egypt, Sudan, and Somalia) have a prevalence of 39.6% for depression and 43.4% for anxiety. Globally, rates of perinatal depression and anxiety are estimated at 1 in 10 in high-income countries and 1 in 5 in low- and middle-income countries [1]. Given these increased local rates, factors causing mental health issues in the obstetric population in this region must be addressed as a priority. There are very few systematic reviews or primary studies of good value from the Middle East and North African region to accurately assess the prevalence of these disorders [6]. Table 1 provides a summary of past results from these studies.

An unpublished pilot study conducted at Dubai Hospital in 2024 found that only 0.65% of pregnant patients treated in the Department of Obstetrics and Gynecology had anxiety, depression, or both documented in their diagnoses. This critical gap in identifying and treating perinatal mental health conditions underscores the urgent need for comprehensive research in this field.

Table 1. Prevalence of maternal mental health disorders in the Middle East and North African region in past studies.

Country	Study	Year	Sample size, n	EPDS[a] score	Antenatal depression, %	Postnatal depression, %	Antenatal anxiety, %	Postnatal anxiety, %	Both anxiety and depression, %
Egypt	Saleh et al [11]	2013	120	≥13	__[b]	18	—	—	—
Oman	Al Hinai and Al Hinai [12]	2014	282	≥13	—	12	—	—	—
Oman	Al-Azri et al [13]	2016	959	≥13	24		—	—	—
United Arab Emirates	Alhammadi et al [14]	2017	504	≥10	—	33	—	—	—
Saudi Arabia	Alqahtani et al [15]	2018	575	≥14	27	—	24	—	—
Turkey	Durankuş and Aksu [16]	2022	260	≥13	35	—	—	—	—
Egypt	Khamees et al [17]	2021	120	≥14	44	—	—	—	—
Turkey	Guvenc et al [18]	2021	212	≥13	—	34	—	—	—
United Arab Emirates	Tambawala et al [10]	2023	438	≥10	43	44	44	40	32

[a]EPDS: Edinburgh Postpartum Depression Scale.

[b]Not available.

Several risk factors are thought to increase the risk of poor perinatal mental health [8]. These factors encompass sociodemographic, genetic, lifestyle, clinical, and endocrine risk factors. Risk factors also include depression during the second and third trimesters of pregnancy, the number of children, religion, and the use of formula for feeding. Additionally, factors like educational level, lack of breastfeeding, stressful life events [1], gestational diabetes [19], and employment status after delivery have been found to be of borderline significance [8]. These risk factors are crucial for early identification, underscoring the importance of screening pregnant women during pregnancy and post partum. We therefore aim to evaluate the most relevant sociodemographic risk factors for perinatal anxiety and depression among pregnant women in Dubai. Studying the specific risk factors in our local population will help identify region-specific factors that could allow for more tailored interventions to improve outcomes for mothers and infants in Dubai.

Recent studies have identified multiple genes that contribute to both depression and anxiety, with many genes being common to both conditions [20]. Analysis of genome-wide association studies from the Psychiatric Genomics Consortium database found a very strong correlation between anxiety and depressive

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disorders and also revealed a complex interplay of multiple genetic variants that underlie these psychiatric disorders. Studies also indicate that variations in genes related to the hypothalamic-pituitary-adrenal axis, serotonin transporters, and other neurotransmitter systems probably increase the risk of anxiety and depression [21-23].

Understanding these genetic risks in greater depth is critical for determining the underlying molecular mechanisms of these disorders, which may lead to the development of more tailored therapeutic strategies. Furthermore, understanding the interplay of genetic and environmental risk factors during the perinatal period should inspire preventive treatments that improve both maternal health and newborn development.

To the best of our knowledge, no previous study has analyzed perinatal mental health by looking at genetic, clinical, and sociodemographic risk factors in the United Arab Emirates. These risk factors need to be identified to prevent, screen, diagnose, and treat anxiety and depression during this vulnerable period.

Objectives

This study aims to investigate the sociodemographic, genetic, lifestyle, and clinical risk factors associated with anxiety and depression in perinatal and postnatal women in Dubai. (Textbox 1).

The prevalence of anxiety and depression in perinatal and postnatal women in Dubai is higher than global averages and is associated with a unique cluster of sociodemographic, genetic, lifestyle, and clinical risk factors. Cultural factors, traditional family structures, and social expectations could be protective or may hinder access to mental health services in this region. There is a need to assess the prevalence rate of anxiety and depression and associated genetic factors in the Middle Eastern region. As in type 2 diabetes and obesity, genetic susceptibility to psychiatric disorders could be more prevalent in the Middle Eastern region compared to other populations. Understanding these genetic risks in greater detail is crucial for uncovering the underlying biological mechanisms of these disorders, potentially leading to the development of more targeted therapeutic interventions. Moreover, elucidating the interplay between genetic and environmental risk factors during the perinatal period could inform preventive strategies that benefit maternal health and infant development.

Textbox 1. Objectives.

Primary objective

- To investigate the point prevalence of anxiety and depression in antenatal and postnatal mothers using the Edinburgh Postnatal Depression Scale and Generalized Anxiety Disorder 7 scale in Dubai Hospital

Secondary objectives

- To identify genetic variants in severe cases of depression and anxiety
- To find correlations among the stress, demographic, social, clinical, and lifestyle factors associated with the mental health of antenatal and postnatal women

Methods

Recruitment

Figure 1 outlines the variables that will be obtained from the participants, with further details provided below.

This will be a cross-sectional observational study conducted at Dubai Hospital, a tertiary center that receives patients from all 7 emirates of the United Arab Emirates. Participants will be pregnant women who, after 20 weeks of gestation, attend antenatal clinics and inpatient admissions at Dubai Hospital. Dubai Hospital caters to Emirati nationals as well as expatriates from mainly South Asia, Southeast Asia, and North Africa, including countries such as India, the Philippines, Egypt, and Sudan. Emirati nationals comprise 65% of the patients and will be the main group in the study. The age range of our participants will be 15 to 50 years.

Participants will be recruited using convenience sampling of pregnant patients attending Dubai Hospital during the study period. Patients who provide detailed informed consent and agree to participate in the study will be interviewed while in the clinic for their antenatal care appointments. A similar study [10] conducted during the COVID-19 pandemic revealed that patients were very willing to discuss their mental health issues confidentially in a safe environment. Women with any preexisting diagnosed psychiatric condition will also be included in our prevalence study, as the association of genetic and other risk factors in these women will be helpful for our results. Exclusion criteria will be the inability to give informed consent, the inability to understand Arabic or English, a lack of willingness to be contacted for follow-up, and a lack of willingness to undergo genetic testing.

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Figure 1. Patient recruitment and study interventions. EPDS: Edinburgh Postnatal Depression Scale; GAD-7: Generalized Anxiety Disorder 7; HRSI: Holmes-Rahe Stress Inventory.

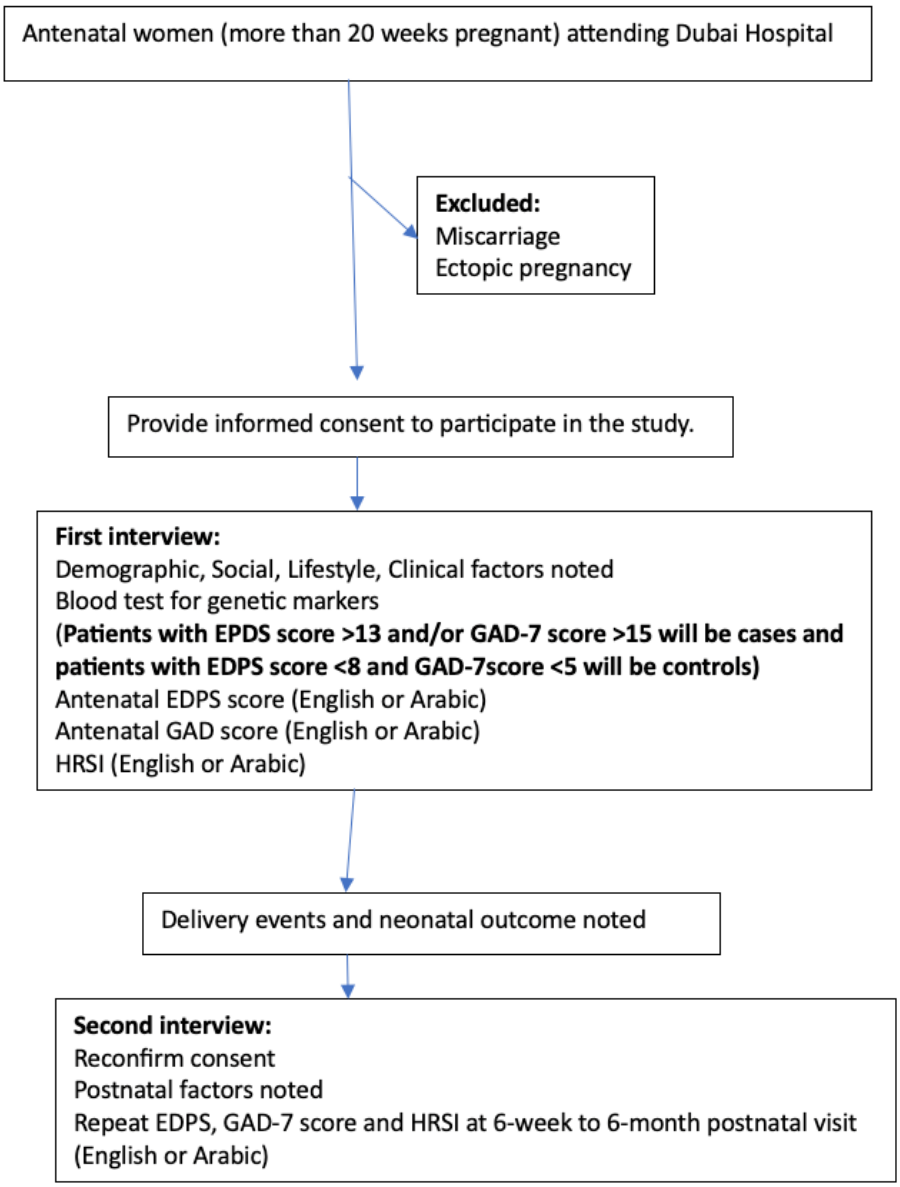

Testing

After an interview, the patient will be directed to give a blood sample for genetic testing. We aim to evaluate 100 patients for genetic risk factors. The first 50 patients with an Edinburgh Postpartum Depression Scale (EPDS) score ≥13 and/or Generalized Anxiety Disorder 7 (GAD-7) score ≥15 will be assigned as cases, and the first 50 patients with an EDPS score <8 and GAD-7 score <5 as controls. The timing of the blood sample collection will coincide with the 24-week glucose tolerance test. This scheduling will prevent any additional discomfort among the pregnant women.

To evaluate genetic factors, we will use a long-read genome sequencing platform. The sequencing data will be analyzed using a Flamingo server, a high-performance computing cluster. This computational infrastructure will enable the robust and efficient processing of the genomic data required for our analysis. The system requires 8 ml to 10 ml of blood and high-molecular-weight DNA. After a long read of whole genome sequencing, established pipelines for genome mapping and variant detection will be used. We will try to identify rare variants that might play a vital role in the etiology of the condition.

Data Collection

The prevalence of postnatal depression, anxiety, and stress at 6-week to 6-month postnatal visits will be assessed for the same patients whose antenatal EPDS, GAD-7 and Holmes-Rahe Stress Inventory (HRSI) scores were taken. Delivery and postnatal events will also be noted at these visits.

Demographic data, lifestyle factors, and social factors, along with the EPDS, GAD-7, and HRSI scores, will be noted by a trained researcher in a structured interview. Obstetric factors and delivery events will be obtained from the electronic medical records of the patients. Demographic information will include age, nationality of the women and their partners, emirate of residence, BMI, marital status, educational level, occupation, length of working hours, temporary or permanent nature of

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employment, being a health care worker, and total monthly income. The partners' education, occupation, consanguinity, military service, and age difference with the participant will also be recorded.

Social factors such as family size (nuclear or extended), loss of a parent in childhood, number of years of marriage, whether the marriage is polygamous, history of intimate partner violence, history of partner mental illness, whether the pregnancy is planned or unplanned, whether there is a support network including the extended family, financial difficulties, loneliness, body image, drug use, alcohol misuse, and chronic illness will be noted. A personal or family history of mental illness will be recorded.

Lifestyle factors will be evaluated, including diet, caffeine intake, sleep disturbance, and vitamin D deficiency, as well as whether the participant exercises at least 30 minutes a day or has sedentary habits. Clinical high-risk factors such as grand multiparity, poor obstetric history, assisted conception, gestational diabetes mellitus, gestational hypertension, cigarette or alcohol use during pregnancy, or any preexisting medical disorders will be mentioned.

Delivery events and postnatal factors such as birth by caesarean section; intrapartum complications; congenital malformations; neonatal intensive care unit admission, with duration of admission; crying, sleeping, or feeding problems of the neonate; gestational age at delivery; husband or family presence at delivery; gender of baby; and baby birth weight will be noted. History of postnatal emotional support from family, poor maternal sleep, and use of maternity leave will be obtained from the postnatal women at the second interview.

Mental Health Assessment Tools

Depression symptoms will be assessed by the EPDS (Figure 2), which is validated for both English and Arabic [7,24,25]. It is a self-reported 10-item questionnaire scored from 0 to 3, with the minimum and maximum total scores ranging from 0 to 30 points. A cutoff of ≥10 points is used for identifying depression and ≥13 for severe depression; a "yes" response to question 10 is used to identify suicidal ideation.

Figure 2. Edinburgh Postpartum Depression Scale (EPDS).

Please UNDERLINE the answer which comes closest to how you have felt IN THE PAST 7 DAYS, not just how you feel today.

In the past 7 days:

1. I have been able to laugh and see the funny side of things
   - As much as I always could
   - Not quite so much now
   - Definitely not so much now
   - Not at all

2. I have looked forward with enjoyment to things
   - As much as I ever did
   - Rather less than I used to
   - Definitely less than I used to
   - Hardly at all

*3 .I have blamed myself unnecessarily when things went wrong
   - Yes, most of the time
   - Yes, some of the time
   - Not very often
   - No, never

4. I have been anxious or worried for no good reason
   - No, not at all
   - Hardly ever
   - Yes, sometimes
   - Yes, very often

*5. I have felt scared or panicky for no very good reason
   - Yes, quite a lot
   - Yes, sometimes
   - No, not much
   - No, not at all

*6. Things have been getting on top of me
   - Yes, most of the time I haven't been able to cope at all
   - Yes, sometimes I haven't been coping as well as usual
   - No, most of the time I have coped quite well
   - No, have been coping as well as ever

*7. I have been so unhappy that I have had difficulty sleeping
   - Yes, most of the time
   - Yes, sometimes
   - Not very often
   - No, not at all

*8. I have felt sad or miserable
   - Yes, most of the time
   - Yes, quite often
   - Not very often
   - No, not at all

*9 I have been so unhappy that I have been crying
   - Yes, most of the time
   - Yes, quite often
   - Only occasionally
   - No, never

*10.The thought of harming myself has occurred to me
   - Yes, quite often
   - Sometimes
   - Hardly ever
   - Never

Anxiety symptoms will be assessed using validated English and Arabic-translated versions of the Generalized Anxiety Disorder 7 (GAD-7) questionnaire [26] (Figure 3). This 7-item questionnaire assesses tension, restlessness, and irritability and is scored from 0 to 3 and has an overall score range of 0 to 21. A score ≥5 will be considered to indicate a risk of anxiety and will be used as a cutoff in our study.

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The HRSI [27] (Figure 4) will be used to identify the level of stress with life change unit values. The cumulative impact of these life changes can significantly affect one's health, emphasizing the importance of managing and mitigating stress. A score of 150 points or less indicates a relatively low amount of life change and a low susceptibility to stress-induced health breakdown. A score of 150 to 300 points indicates a 50% chance of a health breakdown in the next 2 years, and 300 points or more implies an 80% chance of a health breakdown in the next 2 years.

Figure 3. Generalized Anxiety Disorder (GAD-7) questionnaire.

Over the last two weeks, how often have you been bothered by the following problems?	Not at all	Several days	More than half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it is hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid, as if something awful might happen	0	1	2	3

Column totals _____ + _____ + _____ + _____ =

Total score _____

If you checked any problems, how difficult have they made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

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Figure 4. Holmes-Rahe Stress Inventory (HRSI).

Mark down the point value of each of these life events that has happened to you during the previous year.

LIFE EVENT	MEAN VALUE
1. Death of spouse	100
2. Divorce	73
3. Marital Separation from mate	65
4. Detention in jail or other institution	63
5. Death of a close family member	63
6. Major personal injury or illness	53
7. Marriage	50
8. Being fired at work	47
9. Marital reconciliation with mate	45
10. Retirement from work	45
11. Major change in the health or behavior of a family member	44
12. Pregnancy	40
13. Sexual Difficulties	39
14. Gaining a new family member (i.e. ... birth, adoption, older adult moving in, etc.)	39
15. Major business readjustment	39
16. Major change in financial state (i.e. ... a lot worse or better off than usual)	38
17. Death of a close friend	37
18. Changing to a different line of work	36
19. Major change in the number of arguments w/spouse (i.e. ... either a lot more or a lot less than usual regarding child rearing, personal habits, etc.)	35
20. Taking on a mortgage (for home, business, etc. ...)	31
21. Foreclosure on a mortgage or loan	30
22. Major change in responsibilities at work (i.e. promotion, demotion, etc.)	29
23. Son or daughter leaving home (marriage, attending college, joined mil.)	29
24. In-law troubles	29
25. Outstanding personal achievement	28
26. Spouse beginning or ceasing work outside the home	26
27. Beginning or ceasing formal schooling	26
28. Major change in living condition (new home, remodeling, deterioration of neighborhood or home etc.)	25
29. Revision of personal habits (dress manners, associations, quitting smoking)	24
30. Troubles with the boss	23
31. Major changes in working hours or conditions	20
32. Changes in residence	20
33. Changing to a new school	20
34. Major change in usual type and/or amount of recreation	19
35. Major change in mosque activity (i.e. ... a lot more or less than usual)	19
36. Major change in social activities (clubs, movies, visiting, etc.)	18
37. Taking on a loan (car, tv, freezer, etc.)	17
38. Major change in sleeping habits (a lot more or a lot less than usual)	16
39. Major change in number of family get-togethers ("")	15
40. Major change in eating habits (a lot more or less food intake, or very different meal hours or surroundings)	15
41. Vacation	13
42. Major holidays	12
43. Minor violations of the law (traffic tickets, jaywalking, disturbing the peace, etc.)	11

Sample Size

The sample size for this prevalence study was calculated based on an expected prevalence of 33% (expressed as 0.33), as reported in a previous study [14] on postnatal depression in Dubai, a desired precision of 5% (expressed as 0.05), and a 95% confidence level. The required sample size is approximately 350 participants. We will, however, aim to recruit 420 women to allow for a 20% dropout rate. We are confident we will achieve this number given the number of pregnant women seen at Dubai Hospital in one year.

Statistical Analysis

Data analysis will be done using SPSS Statistics (version 25.0; IBM Corp). Univariate statistics and distribution will be assessed, and continuous variables will be presented as the mean and SD or median and IQR. Categorical variables will be expressed as the frequency and percentage. Initial associations between genetic variants of the serotonin gene (*5-HTTLPR*) and

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oxytocin gene (*OXTR*) with depression and anxiety will be tested using the χ^2 test. The Fisher exact test will be used to evaluate genotype-phenotype relationships.

The normality of continuous variables will be assessed using the Kolmogorov-Smirnov test. A significance level of $P<.05$ will be used to determine deviation from a normal distribution. Variables found to be nonnormally distributed will be analyzed using appropriate nonparametric statistical methods. To account for potential confounding factors, logistic regression will be used. Linear regression will be applied to continuous outcomes, such as severity scores. The correlations between demographic factors, clinical factors, lifestyle factors, stress, and antenatal EPDS and GAD-7 scores, as well as the correlations between postnatal factors and EPDS and GAD-7 scores of the postnatal patients, will be calculated using Pearson correlations, Kendall rank correlations, and Spearman correlation tests. The Mann-Whitney *U* test will be used for pairs of independent samples and the Kruskal-Wallis test for sets of more than 2 independent demographic variables.

Ethical Considerations

Informed consent will be obtained from all participants, and they will be provided clarification on the aim of the study and assurance about information confidentiality. Participants can withdraw consent at any point. Women identified as having severe depression or anxiety by the trained interviewer will be referred to our hospital psychologist immediately. Women identified as suicidal (based on their answer to question 10 of the EPDS) will be promptly referred to psychiatry services in accordance with the hospital referral system. Ethical approval will be obtained from the Hospital Ethics Committee and the Dubai Scientific and Research Ethics Committee. The data will be deidentified and no monetary compensation will be given.

Results

The point prevalence of prenatal and postnatal depression and anxiety will be determined at our institution. The genetic markers associated with depression and anxiety in participants of Middle Eastern ethnicity will be identified, and the relationship between other risk factors and their mental health impact will be investigated in the enrolled patients.

Discussion

Comparison With Prior Work

There are only a few past studies on perinatal anxiety and depression in the Middle Eastern region. One study [14] conducted before COVID-19 showed a 33% prevalence of postpartum depression. A comparable study [10] conducted at the same location during the pandemic found a 43.6% prevalence of depression and 42% prevalence of anxiety. However, the risk factors were not assessed in these studies. We discovered just one study [28] that examined the relationship between genetic markers and postnatal depression in Jordanian women. The overall prevalence of maternal mental health problems in Middle East is higher than other regions of the world, and the reasons behind this disparity need to be investigated.

Limitations

While this study design should provide useful information about perinatal mental health, some limitations must be addressed. The recruitment of participants from a single tertiary care hospital in Dubai may impact the generalizability of our findings. The calculated point prevalence may not accurately reflect the true burden of perinatal mental health problems in the population. The study population may not accurately reflect the larger community, particularly those who do not have access to tertiary health care services.

Measurement constraints include the use of self-reported screening measures like the EPDS and GAD-7. Although validated, these tools are susceptible to reporting bias and may be influenced by cultural variables influencing how women in this region perceive and report mental health symptoms. The targeted method for identifying genetic factors may overlook other relevant genetic variants. Furthermore, the cross-sectional design limits our capacity to assess how these genetic factors interact with environmental cues during the perinatal period.

Despite these limitations, this study is an essential step toward better understanding perinatal mental health in the Middle East, and the data will be useful for future longitudinal and more extensive studies in this field.

Conclusions

This study is designed to provide a deeper understanding of the multifaceted factors contributing to anxiety and depression in antenatal and postnatal women. By engaging in this research, the clinicians involved will gain expertise in using validated mental health assessment tools like the EPDS and GAD-7 scales and in understanding the implications of genetic causes for depression and anxiety. Furthermore, the study's comprehensive approach, which includes sociodemographic, lifestyle, and clinical factors, will enable obstetricians and gynecologists to adopt a more holistic and informed approach to patient care. This enriched understanding will enhance the ability to identify at-risk individuals, implement early interventions, and collaborate effectively with mental health professionals.

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Data Availability

The data supporting the findings of this study will be made available from the corresponding author upon reasonable request to any researcher wishing to use them for noncommercial purposes without breaching participant confidentiality. The data will not be publicly available due to privacy and confidentiality concerns.

Authors' Contributions

ZYT contributed to research design, conceptualization, methodology, and manuscript writing and editing. NK contributed to research design and manuscript writing. SS contributed to research design, data collection, and project administration. JL contributed to data analysis and interpretation. WA contributed to overall research design and project management.

Conflicts of Interest

None declared.

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Abbreviations

EPDS: Edinburgh Postnatal Depression Scale
GAD-7: Generalized Anxiety Disorder 7
HRSI: Holmes-Rahe Stress Inventory

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Protocol

Survey of Hand Hygiene, High-Touch Device Use, and Proper Habits of Health Care Workers for Infection Risk Prevention: Protocol for a Cross-Sectional Study

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Abstract

Background: Care-related infections are infectious diseases that occur in a care setting. The most important prevention methods are hand hygiene and the proper use of gloves and gowns. Recent literature points out that hand contact with mobile devices or potentially contaminated environments can promote an increased occurrence of health care–associated infections (HAIs).

Objective: This study aims to analyze the correlation between the microbial population present on the hands of health care professionals in the wards of the Tor Vergata Hospital in Rome and the microorganisms present on the surfaces of their smartphones and tablets by searching for the main agents responsible for HAIs.

Methods: Sterile swabs will be used to collect samples from hands and smartphones, which will then be plated on nutrient agar and other selective media for microbial count. Colonies showing growth and morphological characteristics suggestive of potential pathogens will be isolated and subjected to further analysis for identification at the species level and for antimicrobial resistance profiling (using a proprietary automated analytical profile index system). Sampling will be conducted quarterly (first 2 weeks of each quarter) to assess any changes in microbial flora. In parallel, an Italian version of the World Health Organization questionnaire on health care workers' knowledge of hand hygiene and a questionnaire on the use of high-touch devices will be administered to participants. Each quarter, 30 health workers will be selected, resulting in a total of 120 health workers and 240 samples collected by the end of the study. For each sample, the analysis will focus on quantifying the total bacterial load at 37 °C and 22 °C, along with detecting coliforms or *Escherichia coli*, *Enterococci*, *Staphylococci*, *Acinetobacter*, *Klebsiella*, *Pseudomonas*, and any associated antimicrobial resistance.

Results: The study aims to begin sample collection by June 2025. The protocol was properly evaluated and approved by the territorial ethics committee "Lazio Area 2" on March 21, 2024, with the code 76.24 CET2 utv_ptv.

Conclusions: The findings of this study will be crucial in highlighting the need for targeted education and training of health care practitioners involved in the study, with a focus on the prevention of HAIs.

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KEYWORDS

health care–associated infection; nosocomial infection; fomite; hand hygiene; universal precautions; infection prevention; infectious disease; handwashing; decontamination

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Introduction

Health care–associated infections (HAIs) are infectious diseases that occur in a health care setting, both in hospitals and all health care facilities [1]. They are among the major complications related to care processes, causing prolonged hospital stays, aggravation of underlying pathologies, and long-term disabilities with consequent clinical, social, and economic impacts [2]. Moreover, it is estimated that HAIs are responsible for 16 million additional inpatient days and 37,000 deaths with HAI as a primary cause each year [3]. The Italian law 81/08 (which primarily aims to ensure and guarantee an adequate level of safety in the workplace) emphasizes the importance of responsibly managing infectious risk, including in the proper provision and use of protective clothing (including hospital gowns) as well as remarking on the importance of avoiding exposure of uniforms to the external environment [4]. Studies have shown suboptimal adherence to infection prevention protocols among health care workers, with hand hygiene compliance ranging from 7.7% to 89.7% [5].

The "Regional Hand Hygiene Intervention Plan" from the Lazio Region highlights handwashing as the most effective intervention for the prevention of HAIs, although it notes suboptimal adherence in care facilities to this correct practice [6]. Another important prevention method concerns the correct use of gloves, which in no way replaces the need to wash hands; moreover, their incorrect use can increase the risk of pathogenic germ transmission from caregiver to patient or vice versa [7]. In addition, over the past 10 years, there has been widespread use of smartphones in the workplace among health care workers [8-10]. These high-touch devices have become integral to health care practice, serving as valuable tools for disease diagnosis, drug reference, medical calculators, and communication among health care teams [11, Figure 1]. However, the constant contact with hands and potentially contaminated environments, coupled with the presence of a touch screen, makes smartphones potential vectors for microbial transmission [12-15]. Studies have revealed the presence of various pathogens, including multidrug-resistant bacteria, on the surfaces of smartphones used by health care workers [16-18]. Notably, contamination is not limited to the touch screen; the posterior surface of smartphones has also been found to harbor significant bacterial contamination [19]. These findings underscore the potential role of smartphones in the spread of nosocomial infections, particularly in settings where appropriate preventive measures, such as proper hand hygiene and disinfection of the cell phone surface, are lacking [20-26]. As evidence of this, several studies have shown that 58% of staff reported cleaning their phones once a day, at best [27], and that a range of 44%-90% do not clean their devices at all [28]. There are also early studies referring to Italy that would support the need to investigate this dynamic further, although they were limited to analyzing the phenomenon in individual departments [29-31]. The purpose of our study is, therefore, to analyze the correlation between the microbial population present on the handprints of health care professionals in the wards of the Tor Vergata Hospital in Rome, which will serve as a pilot for this study, and the microorganisms present on the surfaces of workers' smartphones and tablets by searching for the main agents responsible for HAIs, promoting the use of modern surveillance platforms for nosocomial infections. This will allow for a more accurate evaluation of all possible prophylaxis interventions.

Figure 1. Steps of the study. HAIs: health care–associated infections; TBC: total bacterial count.

This study, conducted by the Department of Biomedicine and Prevention, Section of Hygiene and Preventive Medicine, University of Rome Tor Vergata, is part of the Digital Lifelong Prevention (DARE) project (code PNC_0000002 - CUP:

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B33C22001340002) and specifically will contribute to the collection of data needed to carry out the activities of pilot 1: "Data mining and AI approaches to predict/prevent risk of Healthcare Associated Infections (HAIs)," under work package 3, task 3.1 (Digital Tools in Children and Aged Frail Subjects).

Methods

Recruitment

Participants in the study will be selected voluntarily from a population of health care workers (nurses, doctors, and health care assistants) who use high-touch devices in the very high (eg, intensive care unit), high (eg, surgical wards), and medium (eg, general medicine) infectious risk departments. The division of the wards into very high risk, high risk, and medium risk will be based on the detailed analyses carried out at Tor Vergata Polyclinic in a recent study [32]. Participants who do not use a smartphone or tablet or who do not have them at the time of the study will be excluded from the sampling. Recruitment of participants will be voluntary from among health workers in the departments involved. Both sample collection and questionnaire administration will be carried out in a selected room of the health worker's department. The surveys will be conducted during the afternoon shift change (at 2 PM). This study will last 1 year, and sampling will be performed throughout. In the participating hospital, 30 health care workers per quarter will be selected, for a total of 120 health care workers and a total of 240 samples taken; alert microorganisms will be tested for on each sample.

Staff

Staff involved in the project will include nurses and prevention technicians who will be responsible for taking samples. Biologists and laboratory medicine residents will also be involved in the laboratory analyses in support of the teaching staff of the Department of Biomedicine and Prevention, Section of Hygiene and Preventive Medicine of Rome Tor Vergata. The physicians specializing in hygiene and preventive medicine will be in charge of collecting questionnaires and analyzing the collected data, supported by the teaching staff.

Privacy Policy

The following privacy policy will be given to each recruited health professional:

Dear Participant,

> *We wish to inform you that the GDPR (EU Regulation No. 2016/679) provides for the protection of individuals with regard to the processing of personal data.*
>
> *According to the indicated regulation, such processing will be based on the principles of lawfulness, fairness and transparency, adequacy, relevance and limitation, accuracy and updating, non-excessiveness, and accountability.*
>
> *Information on the processing of your data:*
>
> *We are conducting a research project called "Survey on hand hygiene, use of high touch devices and correct habits by health care workers for the prevention of infectious risk." The aim of this research is to better understand the handwashing and device usage habits of healthcare workers. To do this, we will be taking swabs of your hands and your device, and you will also be asked to fill out a questionnaire.*
>
> *Your participation in this research is completely voluntary, and there are no consequences if you choose not to provide your data. However, providing your data is essential for us to conduct this study, so if you decline, you won't be able to participate.*
>
> *We take data protection very seriously and will implement all necessary measures to safeguard your information and rights. Your data will not be shared with any third parties, and any results published will be anonymized and aggregated.*
>
> *You have the right to decide whether or not to give your consent for us to use your data after reading this information.*

Questionnaire

During the collection of samples, the validated World Health Organization questionnaire, translated into Italian and adapted for the Lazio Region, on hand hygiene will be administered to all participants to collect information on sociodemographic characteristics (age, gender, profession, and department). A short questionnaire will be administered with questions on the use of high-touch devices and personal protective equipment (PPE; eg, gloves, gowns) in the workplace. Personal and sensitive data of the participants in the study will not be collected. Questionnaires can be found in Multimedia Appendix 1. Both questionnaires will be completed in the presence of the researchers and consist of closed-ended questions on a 7-point Likert scale.

Sample Collection and Laboratory Testing

Samples, both from hands and smartphone touch screens, will be taken using sterile nylon-tipped flocked swabs (Copan SRK Elution Flocked Swabs, Biogenetics Diagnostics srl, Ponte San Nicolò PD, Italy), applying methods for environmental microbiology for small surfaces [33,34]. The swabs will be supplied with 2.5 mL of a sterile surface recovery kit transport solution (Letheen Broth Solution, a nutrient and neutralizing solution), in which the microorganisms taken/flocked with the swab are resuspended. This solution is useful for preserving the bacteria and neutralizing the activity of possible disinfectants on the surfaces.

Samples will be taken by properly trained, qualified staff capable of complying with all asepsis regulations. Hand sampling will be performed for each participant on all fingertips and palms, always with the same swab for both hands. A swab will be used for each smartphone that will be swiped on both the anterior (touch screen) and posterior parts.

After the sampling session and immediately after delivery of the completed questionnaire, the samples will be transferred to the Laboratory of Environmental Microbiology, Department of Biomedicine and Prevention, Tor Vergata University, for

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subsequent analysis, which will be performed according to current microbiological procedures.

Each questionnaire is assigned a sequential number, which is written on the corresponding swab tube.

The analysis includes a quantitative and qualitative assessment, searching the heterotrophic plate total bacterial count (HTBC) at 37 °C and 22 °C for coliforms or *Escherichia coli* (*E coli*), *Enterococci*, *Staphylococci*, Gram-negative bacteria, *Pseudomonas aeruginosa*, and *Mycetes*. In addition, the isolated strains will be typed through standardized miniaturized tunnels for biochemical analytical profile index tests. We decided to select the microorganisms that are most frequently associated with the occurrence of HAIs [35,36]. Sampling is carried out immediately after delivery of the completed questionnaire, using a swab and a tube containing 2.5 mL of transport solution. Each questionnaire is assigned a sequential number, which is written on the corresponding swab tube. The standard sampling procedure for environmental surface sampling will be used.

The swabs are transferred to the laboratory immediately after sampling and are then seeded as follows. For the determination of both HTBC at 37 °C and 22 °C, the bulk seeding technique is used with 500 µl per sample on plates of a tryptone soy agar medium, which are then placed in a thermostat at 37 °C and 22 °C for 48 hours and 72 hours, respectively. Per sample, 250 µl are distributed and spatulated on a plate with a Harlequin *E coli*/coliform chromogenic medium for the determination of *E coli* and total coliforms; 250 µl are distributed and spatulated on a sterile Slanetz and Bartley agar plate for the determination of *Enterococci*; 250 µl are distributed and spatulated on a plate containing a Baird Parker agar medium for the determination of *Staphylococci*; 250 µl are distributed and spatulated on a plate with MacConkey Agar medium for the determination of Gram-negative bacteria; 250 µl are distributed and spatulated on a plate with a cetrimide agar base medium for the determination of *Pseudomonas*; and 250 µl are distributed and spatulated on a plate with a Sabouraud medium for the determination of *Mycetes* (yeasts and microfungi). All plates are then transferred to a thermostat at 37 °C for 24-48 hours.

After the appropriate culture times, the plates are observed, and a count of the colonies grown is made. The results obtained, expressed as colony-forming units (CFUs)/dm^2, will be recorded on a table (Multimedia Appendix 2) that includes sample ID, date of sampling, and any observations. In addition to a quantitative evaluation, a qualitative evaluation will be carried out based on the observation of colony morphology, and after the selection of the different types, the identification of individual types will be preceded by a specific miniaturized biochemical test (analytical profile index test) following the procedure indicated by the manufacturer. Colonies in each treated plate will be screened for resistance by using broad-spectrum antibiotics: 10 µg ampicillin, 4 µg gentamicin, and 5 µg chloramphenicol, placed separately on Muller-Hinton agar plates and incubated in aerobiosis at 37 °C for 18 hours.

Minimum inhibitory concentration will be performed using the automatic ID/AST Vitek 2 Compact instrument (Biomerieux, France) and Gram-positive and Gram-negative susceptibility test cards (AST-P577 and AST-N117; Biomerieux, France).

The diffusion method according to Kirby-Bauer [15,18,27] will be used for the antibiotics aztreonam, minocycline, and levofloxacin. Breakpoints will be interpreted according to Clinical and Laboratory Standards Institute guidelines [37]. This type of investigation will have a quarterly periodicity that may allow us to assess any quantitative and qualitative changes in the microbial flora at different times of the year due to seasonal differences in temperature and humidity.

Data Recording

The questionnaire responses, quantitative data from plate reading, annotations made on the sampling form, and results of bacterial identifications will be recorded on an Excel Professional Plus 2016 (Italian language; Microsoft Corporation) worksheet.

Statistical Analysis

A descriptive statistical analysis will be conducted to outline the sociodemographic data of the healthcare worker sample and the responses to the questionnaires, aimed at determining the frequency of high-touch device and PPE use and awareness of contamination. Subsequently, inferential investigations will be carried out between the sociodemographic data of the sample and the results from the microbiological swabs. The results for the descriptive section of the questionnaire will be expressed in terms of numbers and percentages. As for the quantitative microbiological results, these will be expressed as means (SDs) and medians (IQRs), as it is expected that the distribution of some variables will not be Gaussian-like. The microbiological results will be presented by stratifying against the questionnaire variables. For the qualitative analysis, we will construct a heat map with R software (version 4.5.0; R Foundation for Statistical Computing) to determine which continuous variables will be transformed into dichotomous variables, using a threshold of 100 CFUs/dm^2 as indicated in recent literature [12], so that dichotomous and continuous variables can be compared on a single map. For the species under investigation, we will describe the frequency of occurrence. To graphically show the relationship between the questionnaire variables of interest and bacterial concentrations, scatter plots will be constructed expressing the bacterial concentrations on a logarithmic scale (lnCFU/dm^2), color differentiating and constructing different CIs in the graph according to the categorical variable (eg, different cleaning methods, frequency of training, gender). Box-and-whisker graphs will also be constructed to show the distributions of the HTBC at 37 °C and 22 °C, and for specific agents according to the above categorical variables. Quantitative analyses will be performed using SPSS version 22.0 (IBM Corp), verifying the normality of continuous variables using the Shapiro-Wilk test and performing parametric (*t* test) or nonparametric (Kruskal-Wallis) tests depending on the results of this analysis. Samples will be compared according to the following variables: gender, type of ward, cleaning frequency, cleaning method, type of telephone case, and gown use. Subsequently, variables with a significance of $P<.20$ will be selected for multiple linear regression models to describe the

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relationships between quantitative and categorical microbiological variables.

Steps of the Study

The following steps will be followed for this study:

1. A total of 30 health professionals from the University Polyclinic of Rome Tor Vergata will be selected voluntarily and will undergo both hand and high-touch device sampling for a total of 2 samples per professional.
2. The two questionnaires will be submitted at the same time.
3. Laboratory and statistical investigations of the samples and responses to the questionnaires will be carried out.
4. This procedure will be repeated on a seasonal basis for 1 year.

Ethics Approval

The protocol was properly evaluated and approved by the territorial ethics committee "Lazio Area 2" on March 21, 2024, with the code 76.24 CET2 utv_ptv. Participation in this survey is entirely voluntary. The administration of the questionnaire and the collection of any samples will only commence after participants have provided their informed consent. All data collected will be processed in strict accordance with current privacy regulations (further details can be found in the dedicated 'Privacy Policy' section). The information obtained from this study will be published in an anonymized and aggregated form, ensuring that individual responses cannot be identified, and it will not be shared with any third parties. It is important to note that there are no forms of compensation offered to participants or those submitting the questionnaire for their involvement.

Results

The study aims to start sample and questionnaire data collection in June 2025 and continue with the collection until the following year.

The results may be published in national and international journals, which will be led by the University of Rome Tor Vergata once the trial is over. The results, even if negative, will be shared with the scientific community.

Discussion

Our study aims to identify the main pathogens responsible for HAIs and to promote the use of modern surveillance platforms to monitor and prevent these infections.

The research is set in a context where HAIs represent a major public health challenge with significant clinical, social, and economic impact. Although the importance of hand hygiene and the proper use of PPE in the prevention of HAIs is widely recognized, adherence to these practices is often suboptimal in health care facilities.

This study aims to investigate the correlation between the microbial flora present on health care workers' hands and that present on their electronic devices. The expected results of the study could contribute to a better understanding of the role of electronic devices in the transmission of HAIs and promote the adoption of more effective preventive measures. The expected results of the study could contribute to a better understanding of the role of electronic devices in the transmission of HAIs and promote the adoption of more effective preventive measures.

It would be interesting to assess the impact of the health care environment on the contamination of electronic devices. To this end, it could be hypothesized that wards with a high prevalence of multidrug-resistant pathogens have higher device contamination than those with a lower prevalence.

It is also worth evaluating the effectiveness of various preventive measures, such as hand hygiene, disinfection of device surfaces, and the use of protective cases, in reducing the contamination of electronic devices.

Another important consideration is to analyze the influence of health care workers' behavior on the contamination of electronic devices. For example, it could be hypothesized that health care workers who use the devices during treatment procedures have a higher contamination rate than those who only use them during breaks. However, the study has some limitations. First, the sample size (120 health care workers) may not be large enough to guarantee the generalizability of the results. Second, the study focuses on a single hospital, which may limit the applicability of the results to other health care settings. In conclusion, this study represents an important contribution to research on HAIs and the role of electronic devices in their transmission. The expected results could provide useful information for the development of more effective prevention strategies and the promotion of a more conscious use of electronic devices by health care professionals.

The purpose of the study is to emphasize the importance of proper hand hygiene and proper use of high-touch devices and PPE during work for the prevention of HAIs. If the results highlight the presence of multiple alert organisms, it will be important in a follow-up study to promote educating staff on the prevention of HAIs. Following this, new methods of monitoring could be implemented to improve adherence to good practices for preventing HAIs.

Acknowledgments

This is a nonprofit study. The main cost of the study will be for laboratory expenses, the burden of which will be covered with funds from the National Complementary Plan Initiative, Digital Lifelong Prevention (DARE; code PNC_0000002 - CUP: B33C2200134000) and by the Department of Biomedicine and Prevention, Section of Hygiene and Preventive Medicine, University of Rome Tor Vergata, along with the cost of administering questionnaires and collecting samples.

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Data Availability

The datasets generated during or analyzed during this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

Conceptualization: LP
Methodology: PDF, MM
Software: MM
Validation: GM, AA, AM
Investigation: LG, MC
Resources: MC, CM
Data curation: AA, GM
Writing – original draft preparation: MM, GM, AA, CM, LG
Writing – review and editing: MC, CM, FP, MM, AM
Visualization: LP, PDF
Supervision: LP, GM, AA
Project administration: LP
Funding acquisition: LP
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Conflicts of Interest

None declared.

Multimedia Appendix 1
Hand hygiene questionnaire.
[PDF File (Adobe PDF File), 763 KB - resprot_v14i1e60450_app1.pdf]

Multimedia Appendix 2
Positivity of microorganisms in analyzed samples table.
[DOCX File , 14 KB - resprot_v14i1e60450_app2.docx]

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Abbreviations

CFU: colony-forming unit
DARE: Digital Lifelong Prevention
HAI: health care–associated infection
HTBC: heterotrophic plate total bacterial count
PPE: personal protective equipment

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Protocol

Improving Accessibility for Work Opportunities for Adults With Autism in an End-to-End Supported Workplace Program: Protocol for a Mixed Methods Cohort Study

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Abstract

Background: Adults with autism have a strong desire and need for employment that matches their strengths, skills, and interests. Yet, they are more likely to be un- or underemployed than their neurotypical peers. Facilitators to successful employment include positive attitudes toward and awareness of autism in the workplace, and provision of adequate support and accommodations, including mental health support. Despite previous workplace programs identifying the need for adapted recruitment and interviewing processes, awareness training, and ongoing employee support, there are no programs that specifically provide these supports and adaptations for employees with autism.

Objective: In this study protocol, we describe a framework for a new end-to-end supported workplace program for adults with autism that encompasses 8 key areas to promote inclusive workplaces and improve recruitment and retention of employees with autism.

Methods: Candidates with autism (n=15) will complete 2 workplace skills training sessions at the University of Sydney's Brain and Mind Centre, before attending a tailored interview, onboarding session, and paid 12-week placement at consulting firm Ernst and Young (EY). EY managers and colleagues (n=30) will complete a half-day awareness and inclusion training program before supporting the adults with autism through their 12-week placements. Tailored mental health support will also be provided. This mixed methods cohort study will assess the change in the daily functioning and well-being of employees with autism, as well as the change in the managers' and colleagues' knowledge, attitude, and confidence in working with adults with autism following the training programs. These changes will be analyzed using repeated measures of ANOVAs.

Results: Data collection for this study was completed in February 2022. As of November 2024, data analysis was in progress. This study is expected to be submitted for publication in June 2025.

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Conclusions: This study holds the potential to enhance the recruitment and retention of adults with autism, as well as their overall experience in the workplace.

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KEYWORDS

autism; neurodiversity; inclusive workplace; recruitment; job retention; accessibility; work opportunities

Introduction

Background

Adults with autism have a strong desire and need for employment that matches their strengths, skills, and interests [1-3]. Yet, adults with autism are far less likely to be employed than their neurotypical counterparts [4-6], with global estimates of unemployment rates for adults with autism ranging up to 80% [7]. In Australia, the estimated rate of workplace participation for adults with autism is 42%, compared to 53% for individuals with other disabilities and 83% for those without a disability [8]. For adults with autism who do manage to secure employment, they are all too often in posts that are deemed unsuitable: either inconsistent with their skillset and abilities (mal-employment) or for which they are overqualified (underemployment) [9,10]. They can also find it difficult to maintain such employment [4-6].

A variety of barriers to successful employment outcomes for adults with autism have been identified at each stage of the recruitment and employment experience, including conventional hiring processes that are unsuited to candidates with autism, limited promotion of and requests for workplace accommodations, and a lack of employment-related and mental health supports [5,11,12]. Traditional job application and interviewing processes typically rely on in-vivo problem-solving skills and the navigation of complex social situations, which can pose unique challenges to some candidates with autism during recruitment [13-16]. Moreover, once in the workplace, employees with autism often report multiple environmental challenges, including navigating social expectations, experiencing aversive sensory stimuli, and stigmatizing attitudes from managers and coworkers [2,3].

Many organizations acknowledge a lack of awareness and knowledge of autism in the workplace [17], which has been linked to increased prejudice and stigmatizing attitudes [18]. For example, some employers perceive the costs of supporting employees with autism as outweighing any potential benefits [19,20]. This is despite evidence suggesting that employing adults with autism can provide substantial benefits, such as increased work ethic and quality of work, without incurring additional costs [21-24]. These studies underscore the need for more research to explore ways to reduce stigma and improve understanding of autistic people in the workplace.

Conversely, studies have identified a range of personal and environmental factors that can lead to successful employment outcomes for adults with autism [1,25,26]. Personal factors include having the knowledge to navigate recruitment and employment processes, work-related experience or skills, and insight into one's strengths and challenges [25]. However, environmental factors have been identified as potentially having the greatest impact on successful employment for autistic people [26,27]. These factors include positive employer attitudes toward and awareness of autism, collaboration between the autistic employee and the workplace, and the provision of adequate support and accommodations, including mental health support [5,26,28,29].

While all autistic people experience autism in different ways and have different needs [30], there is some commonality in identified workplace supports. These include support in relation to executive skills, such as attention, planning, and problem solving [31]; navigating social environments within the workplace, which can be a source of both anxiety and confusion; and managing challenging sensory information [2]. There is also greater recognition that many autistic people experience co-occurring mental health concerns, such as depression and anxiety, associated with disability [32]. In fact, recent research found that mental ill health is a predictive factor in both vocational confidence and participation in adults with autism [18,33]. These findings suggest that mental health supports adapted to the needs of autistic people may be particularly important for workplace programs.

Research also points to the importance of the degree of "fit" between the job and the individual [25]. This job-matching process may need to take into account the task and social demands of the role, as well as individual skills, such as cognitive abilities, preferences, and sensory needs [2,3,17,25]. The better the job fit, the more likely the individual will succeed [25], highlighting the need for customized, tailored approaches that match individuals to specific roles.

The provision of appropriate support and accommodations can be dependent upon candidates disclosing their autism. However, many adults with autism are reluctant to disclose due to stigma and previous experiences of discrimination [34,35]. For adults with autism who do wish to disclose, the process is shrouded in tension, stress, and confusion as to how and when it should be done [35,36]. When adults with autism receive support to disclose, they are more likely to experience positive outcomes and receive the required accommodations [34,35,37]. Thus, any support program should support adults with autism in this nuanced process of disclosure during the selection phase.

A growing number of successful programs have been developed with the aim of recruiting and retaining neurodivergent employees [38-41]. Findings from these programs highlight the strengths and benefits that employees with autism can bring to an organization, such as diversity in thinking. In addition, they have identified the need for a range of accommodations,

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including building autism awareness in organizations seeking to employ autistic people, adapting recruitment and interviewing processes, and providing ongoing support to autistic job seekers and employees with autism once they are in their roles [38-41]. To date, however, programs have tended to focus on one aspect of these recommendations rather than providing comprehensive end-to-end support and adaptations for employees with autism and their employers.

End-to-End Supported Workplace Program: A Framework

To improve workplace outcomes for adults with autism, there is a clear need for a holistic end-to-end approach, focusing on enhancing employers' attitudes toward and understanding of autism, as well as providing adequate accommodations and services for candidates with autism throughout their recruitment and workplace experience [2,17,25,28]. Moreover, a tailored approach is required, matching work opportunities to an individual's skills and strengths and providing workplace support based on individual needs, preferences, and experiences [3,25,28].

Therefore, this study protocol proposes a framework that encompasses 8 key areas (Figure 1) to promote inclusive workplaces and enhance recruitment and retention of employees with autism before and during a 12-week placement at consulting firm Ernst and Young (EY). First, both the individual and the workplace are assessed to ascertain strengths and the supports needed to enable inclusive workplace practices. For the individual, this assessment includes their history of employment, strengths, skills, and interests, as well as expectations regarding job demands and practical requirements. For the workplace, it includes current workplace practices and safety within those practices, role and organizational demands, employer beliefs and attitudes, and existing presence and potential for inclusive support practices. Appropriate workplace adaptations can be recommended at this stage to enhance inclusive practices.

Figure 1. Supported workplace program framework.

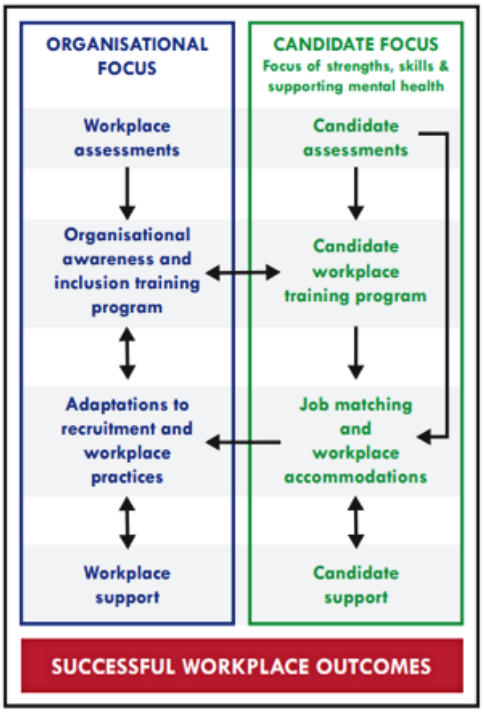

Next, training is provided, where required, to both workplace staff and candidates with autism. For the workplace, this training is designed to target knowledge and awareness, stigmatizing attitudes, and implementation of inclusive workplace practices. It also aims to influence adaptations to recruitment, onboarding, and employment processes across the organization. For candidates with autism, the training prepares and empowers them to navigate recruitment and workplace practices and roles, disclosure in the workplace, and the provision of workplace support and accommodations.

Candidates with autism are then matched with a role based on their preferences, strengths, and skills and provided with any necessary workplace accommodations during a 12-week placement.

Ongoing support is provided to both the organization and the candidates with autism throughout the program. The organization receives support during recruitment, onboarding, and the 12-week placement to continue disability and autism education and offer ongoing guidance on specific situations as they arise. Similarly, employees with autism receive support from mental health and autism workplace specialists throughout the placement, providing employment and mental health support, and tailored guidance addressing individual and contextual (workplace) challenges.

Drawing on the framework and available research, this study protocol describes a pilot program that encompasses an end-to-end 12-week supported work placement for adults with autism, based on individual needs, strengths, and preferences, as well as workplace training for candidates and workplace

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staff. Employers' attitudes, knowledge, and confidence in supporting autistic people in the workplace before and after taking part in the program will also be explored. The results will provide researchers and employers with greater insight into how to optimize job fit and direct resources that can improve employment outcomes for adults with autism.

Objectives

The study's primary aims will be divided into 2 separate streams.

Stream 1: Adults With Autism

The primary objective of Stream 1 is to determine the feasibility of a 12-week supported work placement for autistic individuals based on individual needs, strengths, and preferences, with adaptations to traditional recruitment, interviewing, onboarding, and workplace processes. It is hypothesized that participating in the supported workplace program will result in improved workplace outcomes for adults with autism, as measured by job satisfaction, mental well-being, and general well-being. The secondary objective is to explore the facilitators and barriers (for example, autistic characteristics, social skills, mental health, and previous work experience) associated with successful employment (for example, increased job satisfaction and ongoing employment) in adults with autism.

Stream 2: Managers and Colleagues

Stream 2 investigates the knowledge and attitudes of—and support required by—the managers and colleagues of the adults with autism as they navigated the same processes. The primary objective in this stream is to determine the effectiveness of a face-to-face training workshop and 12-week supported workplace program in enhancing colleagues' and managers' knowledge, attitudes, and confidence in working with adults with autism. It is hypothesized that the program will increase employers' knowledge and confidence in supporting people with autism in the workplace. A secondary objective explores the colleagues' and managers' current knowledge and attitudes toward hiring and managing autistic people and those living with disability more broadly.

Methods

Design Overview

The study uses an exploratory mixed methods cohort design with qualitative and quantitative data collected at multiple time points. Adult participants with autism will be screened for eligibility and invited to complete workplace skills training sessions at the University of Sydney's Brain and Mind Centre (BMC), before attending an interview, an onboarding session, and a paid 12-week placement at EY in Sydney, Australia. EY managers and colleagues will complete a 2.5- to 3-hour training session, either face-to-face or online, before supporting the adults with autism through their 12-week placements.

The screening data of participants with autism will be collected via online questionnaires and face-to-face psychometric assessments, while baseline, midpoint, and postprogram data from adults with autism and baseline and postprogram data from colleagues and managers will be collected via online questionnaires. Postprogram semistructured qualitative interviews will be conducted with all participants via Zoom (Zoom Communications).

Ethical Considerations

The protocol has received research ethics approval from Belberry Human Research Ethics Committee (HREC 2020-11-1229-A). Participants will be paid a standard wage for their internship hours but will not be paid for assessments conducted before or after the internship program for assessments or training. Participants will not be made aware whether their job is likely to be extended post internship. This is a discussion that will not be expected to happen and not until after the internship is complete.

Setting

Partnering With EY

The 12-week supported workplace program will take place in partnership with EY. The roles available to adults with autism as part of the program will be based at EY's head office in Sydney, Australia. Participants will also have the opportunity to work from home based on personal preference and to allow for ongoing COVID-19 restrictions, if applicable. Some roles are based on advertised positions. Others are new positions developed specifically to match the candidates' strengths and skills, as indicated by the preprogram assessments and workplace skills training sessions. Face-to-face training workshops for EY managers and colleagues will be held at the EY head office and online.

Brain and Mind Centre, University of Sydney

The study will be implemented by researchers from the Clinic for Autism and Neurodevelopment Research (CAN Research) at the University of Sydney's BMC. Candidates with autism will be predominantly recruited from previous participants of studies conducted by CAN Research. Preprogram screening assessments and workplace skills training sessions for adults with autism will take place at the BMC.

Participants

Adults With Autism

Eligible participants will include those who have a current diagnosis of an autism spectrum condition and meet the criteria for an autism spectrum condition, as assessed at visit one by the Autism Diagnostic Observation Schedule—2nd Edition Module 4 (ADOS-2; Lord et al [42]), are fluent English speakers, can give written informed consent, and can work part- or full-time in Sydney for a period of 12 weeks. Participants will be excluded if they are not available for the study duration, have a drug or alcohol dependence, are younger than 18 years, or do not meet the criteria for an autism spectrum condition on the ADOS-2.

Managers and Colleagues

Eligible participants will include those who are available to manage or supervise at least one autistic adult working in their team at EY, have access to the internet, and can provide informed consent. Participants will be excluded if they are younger than 18 years or do not have reliable access to the internet.

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Recruitment

Adults With Autism

Adults with autism will be recruited from several sources, including a database of participants with autism who had previously taken part in studies at CAN Research and through external advertising. A job ad will also be posted on the online recruitment website SEEK to attract potential participants who may not yet be connected with autism support services.

All potential participants will be emailed a link to the online participant information sheet and consent form. Potential participants who express interest in the program via previous or current programs at CAN Research may have already completed the ADOS-2 and other executive function measures as part of those studies. They will, therefore, be screened for remaining eligibility criteria via a phone call from a researcher and an online questionnaire. Participants who express interest in the program after receiving information via the Clinic for Autism and Neurodevelopmental Research, ASPECT, or SEEK, will first be invited to the BMC to complete the ADOS-2 and other executive function measures. They will be screened for other eligibility criteria via an initial conversation with researchers at the BMC and an online questionnaire. Once identified, it will be up to EY to follow their standard human resource recruitment procedures to decide if they will hire candidates. The decision about which job is offered and whether the candidates accept the position will be entirely up to EY and the candidate. The rate of pay and the role will be provided to the candidate at the level expected for any person hired in that position. The decision about whether the internship will lead to a more permanent position is left up to EY at the end of the placement. Candidates are, however, not made aware that their position could be extended until completion of the placement to reduce the expectation of this outcome.

Managers and Colleagues

EY managers and colleagues will be recruited internally by the EY Diversity, Equality, and Inclusion (DE&I) Team. Managers and colleagues will be recruited from three tiers: senior managers and partners who led the teams involved in the program; managers working directly with the adults with autism, known as “counselors”; and colleagues working alongside the adults with autism, known as “buddies” (the counselor and buddy system operates within EY for all new starters). EY will identify specific teams to take part in the program depending on whether there is a vacant role available or the possibility of a newly created role within the team. Managers and colleagues are advised that participation is voluntary and has no impact on their employment relationship with EY. An internal EY email is sent with a link to an online participant information letter, consent form, and an online survey.

Workplace Skills Sessions

Once consent is obtained, eligible participants in both streams will complete baseline questionnaires and attend tailored workplace skills sessions.

Stream 1: Adults With Autism

The current literature has highlighted the requirements for, and benefits of, both recruitment and workplace support [1,9,25,28,38]. In response, we have developed two 2.5-hour workplace skills sessions for autistic participants to attend, covering resumes and interview skills, workplace scenarios, disclosure, and requesting accommodations. These will be held either at the BMC or online via Zoom.

Before the first session, participants will be asked to bring in a current copy of their CV to work on during the session. Facilitators will also provide a CV template and a completed example for guidance. Each section of the CV and its importance will be explained to the participants before individual feedback and guidance are provided. During the latter half of the first session, facilitators will share information on how to prepare for and take part in an interview. Participants will be offered the opportunity to prepare for and role-play common interview questions, to help reduce some of the anxiety experienced before and during interviews. We will also explain the specific adaptations EY is making to its interview process to prepare participants for their own interviews.

During the second session, facilitators will first share information about various aspects of the workplace that can sometimes pose challenges to employees with autism, including unwritten rules, communication and feedback, and ambiguous social etiquette. Participants will be given the opportunity to share examples of their experiences in previous workplaces and brainstorm possible solutions that they can use in the future. Finally, facilitators and participants will discuss options for full and partial disclosure and the type of accommodations available in the workplace. There will be an opportunity for role play and participants will be encouraged to complete an accommodations request form, which will be provided to EY.

Stream 2: Managers and Colleagues

Research has also highlighted the importance of providing workplace staff with training and guidance before taking part in a neurodiversity program [28,38]. To inform the training within this stream and to embed it within the context of this specific workplace, a sample of EY managers, colleagues, and employees with autism were previously surveyed about their attitudes and beliefs about autism [18]. EY managers and colleagues taking part in the program will attend a mandatory 3-hour training session before taking part in the supported workplace program. This can be attended in person or online, based on preference, availability, location, and COVID-19 restrictions. The training includes modules on autism awareness; disability inclusion; adapting recruiting, hiring, and onboarding practices; and tailored employee support and advancements. It is designed to provide attendees with a greater awareness of the unique barriers that employees with autism can face in the workplace and the support and opportunities that will make a difference in their experience and overall outcomes. Importantly, it offers real-world examples of challenges and solutions and will give attendees the opportunity to ask questions about, and role-play, specific scenarios that may occur in their teams.

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Job Matching

Adults with autism taking part in previous workplace programs indicated that they want placements that match their skills and interests [38]. Data from the executive function screening measures and baseline questionnaires will therefore be used to develop a personalized profile of strengths, skills, and preferences for each autistic candidate. This profile will include areas of interest; preferred working, communication, and feedback styles; executive function strengths; and preferred ways to manage potential challenges.

The profiles will be provided to EY's DE&I Team, alongside CVs developed during the workplace skills sessions. The DE&I Team will use these documents to match the candidates' strengths, skills, and experience with available roles within the participating teams, or to work with teams to create tailored roles for the duration of the 12 weeks. It is hoped that the better the job fit, the more likely the individual will have a successful workplace experience [5,25].

Interviews

Once roles have been identified or created, the candidates with autism will be invited to interview. Interviews will be held in-person, with online options dependent on COVID-19 restrictions. Conventional interviewing practices can pose a number of challenges for candidates with autism [1,12]. To help overcome these barriers, standard interview processes may be adapted by, for example, reducing the interview duration; providing example questions in advance; allowing additional time and flexibility in how questions are answered; adapting the surroundings based on individual needs and preferences; and minimizing conventional interview requirements, such as eye contact and small talk. These changes will allow participants with autism a more supportive environment where they can focus on showcasing their strengths and skills rather than expending energy on interpreting ambiguous questions, dealing with sensory overload, or masking.

Onboarding

Adaptions to onboarding will be recommended to make processes more accessible to candidates with autism, including reducing the time required for in-person and online onboarding to two half-days, delivering shorter sessions, and creating new written and graphic process documentation to allow for different learning styles. A buddy system will also be implemented during onboarding and throughout the 12-week placement to give employees with autism additional support and a designated go-to person to provide consistent guidance and feedback [5].

Ongoing Support

Based on previous literature, showing that both employees with autism and their managers and colleagues benefit from ongoing support [5,38], the research team will provide weekly check-ins to all participants throughout the 12-week placement. The check-ins will be by email, phone, or Zoom calls depending on personal preferences. Both sets of participants will also be encouraged to call, text, or email researchers at other times should they need additional ongoing support or feedback. In addition, adults with autism will be offered mentoring sessions with an independent mental health-focused clinical psychologist and autism workplace specialist, who can provide more specialized workplace mentoring, mental health support, and career advice should it be required. Should this be required, support will be provided by a clinical psychologist working in the laboratory of the CAN Research but independently from this specific research study. This particular clinic has extensive experience working with the mental health needs of adults with autism and complex cases (eg, suicidality, acute mental health needs) will determine the level of support and whether withdrawal from the program is appropriate.

Accommodations

Accommodations lists will be created by participants during the workplace skills sessions so that the workplace can implement preferences in advance of autistic participants starting in their roles. This will ensure that participants will arrive in an environment already set up to support their individual differences and unique needs [28]. By reducing the anxiety associated with disclosure and requesting accommodations [34,36], including being unsure of what is available and how to ask for it, autistic participants will be able to more confidently and comfortably settle into their roles [1,5]. The accommodation lists will also provide a greater awareness of how simple and inexpensive most accommodations can be [20]. Options for accommodations may include noise-canceling headphones; natural lighting; clothing preferences; quiet desks; supportive software; preferences for instructions, meetings, and performance reviews; and support with prioritizing and managing workflow.

Primary and Secondary Outcome Measures

Measures, data sources, and time points are summarized in Tables 1 and 2. Measures have been selected that assess different aspects of the framework, which feed into the primary and secondary objectives for each stream.

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Table 1. Summary of measures for adults with autism in the supported workplace program.

Measure	Screening	Preprogram	Midprogram (6 weeks)	Postprogram (12 weeks)
Autism assessments				
Autism Diagnostic Observation Schedule, Second Edition (ADOS-2) [42]	✓			
Ritvo Autism Asperger's Diagnostic Scale 14-item screener (RAADS-14) [43]	✓			
Drug and alcohol use				
Alcohol Use Disorders Identification Test (AUDIT) [44]	✓			
Drug Use Disorders Identification Test (DUDIT) [45]	✓			
Demographic factors				
Online questionnaire developed by the research team	✓			
Social cognition				
Camouflaging Autistic Traits Questionnaire (CAT-Q) [46]	✓			
Sensory Responsiveness Scale, Second Edition (SRS-2) [47]	✓			
Behavioral factors				
Adult Repetitive Behaviour Questionnaire-2A (RBQ-2A) [48]	✓			
Adult Sensory Profile (ASP) [49]	✓			
Executive function				
Trail Making Test (TMT)	✓			
Controlled Oral Word Test (COWAT)	✓			
Wechsler Test of Adult Reading (WTAR) [50]	✓			
Executive skills				
Online questionnaire developed by the research team	✓			
Work preferences and experience				
Online questionnaire developed by the research team	✓			
Daily functioning				
World Health Organization Quality of Life Scale (WHO-QOL BREF) [51]		✓	✓	✓
World Health Organization Disability Assessment Schedule 2.0 (WHODAS) [52]		✓	✓	✓
General well-being				
Bergen Insomnia Scale (BIS) [53]		✓	✓	✓
Brief Resilience Scale (BRS) [54]		✓	✓	✓
Coping Strategies Questionnaire [55]		✓	✓	✓
Short online physical activities questionnaire developed by the research team		✓	✓	✓
Mental well-being				
Depression Anxiety Stress Scales (DASS-21) [56]		✓	✓	✓
World Health Organization–Five Well-Being Index (WHO-5) [57]		✓	✓	✓
Job satisfaction				
Job Satisfaction Survey [58]			✓	✓
Work-life balance				
Work-life Balance Survey [59]			✓	✓
Workplace factors				
Everyday Discrimination Scale [60]			✓	✓
An evidence-based question on bullying			✓	✓

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Measure	Screening	Preprogram	Midprogram (6 weeks)	Postprogram (12 weeks)
Job Content Questionnaire [61]			✓	✓
Physical Work Environment Satisfaction Questionnaire [62]			✓	✓
Inclusion and diversity				
Online questionnaire developed by the research team				✓
Qualitative interview				
Questions developed by the research team, held via Zoom				✓

Table 2. Summary of measures for managers and colleagues in the supported workplace program.

Measures	Preprogram	Posttraining or postprogram
Demographics and job factors		
Online questionnaire developed by the research team	✓	
Knowledge of and attitudes toward autism		
Online questionnaire developed by the research team	✓	✓
Social distance perceptions		
Adapted Bogardus Social Distance Scale [43]	✓	✓
Views on working with autistic people		
Online questionnaire developed by the research team	✓	✓
Self-efficacy		
Adapted Self-Efficacy Scale [63]	✓	✓
Stress		
Kessler-10 (K-10) [64]	✓	✓
Inclusion and diversity		
Online questionnaire developed by the research team	✓	✓

Adults With Autism

Screening Assessments

Autistic participants will be screened for eligibility and asked to provide demographic information. We will collect additional data on executive function; social cognition; behavioral traits; and work skills, preferences, and previous workplace experience to begin developing personalized job-matching profiles.

Preprogram

Following the screening, eligible autistic participants will complete an online survey to help finalize the personalized job-matching profiles and provide baseline data for pre-, mid-, and postprogram analysis. This will include questions on daily functioning, general, and mental well-being (see Table 1).

Midprogram

Autistic participants will complete an online survey six weeks into their 12-week placements. As well as daily functioning, general and mental well-being data will be collected on job satisfaction, work-life balance, and workplace factors, such as discrimination, bullying, job content, and physical environment (see Table 1).

Postprogram

At the end of the 12-week placement, participants will be reassessed on the measures given at baseline and mid-program, as well as completing a short online questionnaire designed by the research team to assess their perception and experience of inclusion and diversity in the workplace during their employment. Participants will then be invited to an individual semi-structured interview with a researcher via Zoom. This interview will explore their views and experiences of the program, including any potential barriers, and facilitators to a successful placement, as well as provide an opportunity to debrief and ask questions.

Managers and Colleagues

Managers and colleagues will be invited to take part in the program by the DE&I Team at EY and confirm they meet eligibility criteria during the informed consent process.

Preprogram

An online survey previously designed by the research team for another project sample in the same workplace [18] will be used to assess managers' and colleagues' attitudes toward and knowledge of autism, social distance perceptions, views on working with autistic people, self-efficacy, and stress. The

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survey also includes an assessment of attitudes toward diversity, inclusion, and corporate culture.

Postprogram

Managers and colleagues will complete the same online survey at the end of the 12-week placement. They will then be invited to an individual semi-structured interview with a researcher via Zoom. This interview will explore their experiences of supporting their autistic coworkers and any potential barriers and facilitators in doing so, as well as provide an opportunity to debrief and ask any questions.

Analysis and Results

As this is an exploratory pilot program, 10-15 adults with autism will be recruited, alongside their managers and coworkers. Outcomes for both streams will be determined by:

- Quantitative assessments include completion and drop-out rates, percentage of components completed, job and workplace satisfaction, and employer attitudes and beliefs.
- Qualitative assessments that include employer and employee experiences and satisfaction with each component of the program. A per-protocol analysis will be conducted, whereby only complete data will be included in the analysis, where appropriate, imputation techniques will be used. As this is an exploratory study set in a real-world workplace, it is not feasible to control for confounding variables. There is no anticipated source of bias.

Quantitative

Stream 1: Adults With Autism

The primary objective in this stream is to determine the feasibility of a 12-week supported work placement for autistic individuals. The secondary objective is to explore the facilitators and barriers associated with successful employment in adults with autism. Data will be visually checked for data entry accuracy, and descriptive statistics will be used to check whether scores are within the valid range for each measure. Repeated measures ANOVAs will be used to assess temporal changes in the primary outcome measures taken at pre-, mid-, and postprogram time points, including changes to daily functioning, general and mental well-being, job and workplace satisfaction, and work-life balance.

Multiple linear regression will be used to explore intrinsic facilitators and barriers associated with successful employment for adults with autism. Predictor variables will be assessed for collinearity and then each predictor assessed with a univariate model. Significant predictors ($P<.05$) will be used to fit a multiple regression model to determine predictors of successful employment outcomes.

Stream 2: Managers and Colleagues

The primary objective in this stream is to determine the effectiveness of the training workshop and pilot program in enhancing colleagues' and managers' knowledge, attitudes, and confidence in working with adults with autism. A secondary objective explores the colleagues' and managers' current knowledge and attitudes toward hiring and managing candidates with autism.

Data will be visually checked for data entry accuracy, and descriptive statistics will be used to check whether scores are within the valid range for each measure. Repeated measures ANOVAs will be used to determine temporal changes to managers' and colleagues' knowledge, attitudes, and confidence in working with adults with autism, with primary outcome measures taken at pre-, mid-, and postprogram time points. Descriptive statistics will be used to explore and describe current knowledge and attitudes.

Qualitative

Audio recordings will be collected from participants in both streams via Zoom and transcribed verbatim. A semistructured interview schedule will be used to identify aspects of the program, such as adaptations to recruitment and workplace processes, which were perceived to be beneficial to the adults with autism, as well as areas that may need further improvements. The transcriptions will be deidentified, and each participant will be given a participant identification number as a pseudonym to protect anonymity.

Data Analysis

A total of 2 independent researchers will code the interview transcriptions using NVivo 11 (QSR International), using the Framework Method by Ritchie and Spencer [65] to analyze the data. The Framework Method is a type of thematic analysis commonly used to analyze semi-structured interviews that involve systematically reducing data into a matrix that allows for comparison between and within individual cases. The Framework Method allows for the structured identification of commonalities and differences in datasets. The method includes 5 stages: (1) transcription; (2) familiarization, beginning with transcription of the data; (3) categorization, where a thematic framework will be identified by the two coders. The coding will involve an iterative process as the codes are refined, and discrepancies resolved by a third investigator; (4) indexing, where key themes of direct quotes will be provided to demonstrate the richness of the themes. Further, subthemes within these key themes will provide a more in-depth understanding; and (5) charting, when themes will be tabulated so that the key and subthemes are easily identified.

Results

The data collection for this study began in early 2021 and was completed in February 2022. As of November 2024, the analysis was in progress. This study is expected to be submitted for publication in June 2025.

Discussion

Principal Findings

This study seeks to explore the feasibility of a 12-week supported workplace program that includes adaptations and accommodations before and during the placement. It will also investigate employers' attitudes, knowledge, and confidence in supporting employees with autism. Crucially, it builds on previous research and workplace programs to include workplace and candidate training sessions and ongoing tailored specialist

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support for both adults with autism and their managers and colleagues. It is anticipated that participating in the supported workplace program will result in improved workplace outcomes for adults with autism, as measured by job satisfaction, mental well-being, and general well-being. It is expected that the program will increase employers' knowledge and confidence in supporting people with autism in the workplace.

Comparison With Previous Work

There have been a number of supported workplace programs developed to improve employment for neurodiverse employees [38-41]. However, these programs tend to focus on a specific accommodation or only one element of employment, for example, adapting typical hiring and interviewing practices. This study incorporates the accommodations and supports identified in previous studies to propose an end-to-end framework. This framework aims to enhance recruitment and retention of employees with autism by providing support to both the employees and their managers before, during, and after the 12-week program.

The benefits of employment are well recognized. Improving workplace outcomes for adults with autism can offer significant benefits for the autistic community and the employment sector [21,22]. As well as economic independence, employment can offer adults with autism a sense of identity and accomplishment, improve quality of life, provide structure and opportunities for social interaction, and facilitate a contribution to society with less reliance on government funding [22,29]. Conversely, unemployment has been associated with lower life satisfaction and ill health [66].

Many adults with autism display myriad strengths that can contribute to the workforce, including excellent attention to detail, an expansive memory, an affinity for rules and guidelines, and the ability to analyze complex patterns in social and physical environments [23,24]. Workplace-specific research suggests adults with autism have higher levels of reliability, trustworthiness, attention to detail, and accuracy in visual tasks; expedient levels of concentration and memory; and lower levels of absenteeism than their counterparts [1]. By exploring the barriers, facilitators, and individual characteristics associated with successful employment, this study will provide employers with greater insight into where and how to direct resources in order to attract and retain talented candidates with autism. In turn, this will enhance the well-being and life satisfaction of adults with autism who want to work but have been unable to find roles that suit their strengths and skills. The findings from this study will be disseminated through publication in peer-reviewed journals.

Strengths and Limitations

A growing number of programs with the aim of recruiting and retaining neurodivergent employees have been developed. However, these programs have tended to focus on providing a specific accommodation rather than end-to-end support. A strength of the current study is the implementation of an end-to-end framework to support employees with autism throughout the 12-week work placement. The mixed methods approach will allow for an in-depth analysis of the individual factors contributing to successful employment. We note, however, that the findings of this work may not be generalizable to all work contexts. EY primarily employs individuals with university-level education. They also have an established intention to increase neurodiverse employment throughout their workforce. Finally, we note that the individual assessments conducted on this sample size will provide limited opportunity to detect meaningful outcomes for predicting success. The completion of these measures is aimed at collecting pilot data for a much larger trial.

Conclusion

The findings from this study will provide a greater understanding of factors relating to successful employment for adults with autism as well as provide insight into current attitudes in the workplace. Greater insights into current attitudes and knowledge of autism in the workplace, and the impact of a structured training program, will also help inform the development and implementation of much-needed similar training programs at other organizations. Former UN Secretary-General Ki-Moon [7] has called for companies to understand autistic individuals' "unique and often exceptional skills, and to enable work environments where they can excel." This study seeks to take another important step toward realizing that reality.

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Data Availability

The datasets generated or analyzed during this study are not publicly available due to ethics considerations but are available from the corresponding author upon reasonable request.

Authors' Contributions

AJG, NG, EP, and VG were involved in the funding acquisition and conceptualization of the study and data curation. ES, LH, EP, AJG, and VG conducted the investigation and project administration. AJG, NG, EP, VG, and ES were involved in methodology. AJG provided overall supervision. LH and AJG wrote the first draft. All authors contributed to and reviewed drafts of the study protocol and approved the final submission.

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Conflicts of Interest

None declared.

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Abbreviations

ADOS-2: Autism Diagnostic Observation Schedule–2nd Edition
BMC: Brain and Mind Centre
CAN Research: Clinic for Autism and Neurodevelopmental Research
DE&I: Diversity, Equality, and Inclusion
EY: Ernst and Young

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Protocol

Nonadherence to Diabetes Complications Screening in a Multiethnic Asian Population: Protocol for a Mixed Methods Prospective Study

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Abstract

Background: Yearly screening for microvascular complications of diabetes mellitus (DM), namely diabetic retinopathy (DR), diabetic nephropathy (DN), and diabetic foot complications (DFC), is recommended to reduce their incidence, and delay or prevent their progression. Poor adherence to screening is common, but prospective data on the magnitude and predictors of nonadherence to DR, DN, and DFC screening in Singapore are unavailable.

Objective: The Understanding Non-Adherence to Diabetes Complications Screening study aims to determine the rates, predictors, and clinical and economic impact of nonadherence to diabetic complications screening in patients with type 2 diabetes in Singapore. The study describes the methodology and participants' baseline characteristics that may be associated with nonadherence to DM complications screening.

Methods: In this prospective, mixed methods, clinic-based study, patients who underwent DR, DN, or DFC screening and were offered an annual rescreening appointment, were recruited from 6 primary care centers. Patients' sociodemographic, medical, clinical, and patient-reported characteristics were recorded at baseline. Nonadherence to DR, DN, or DFC screening is defined as not attending the annual rescreening appointment within 4 months of the scheduled rescreening date. Adherence and clinical data will be recorded at 16 months post enrollment. Additionally, selected participants and health care professionals will undergo qualitative interviews to elicit barriers or facilitators of adherence to rescreening.

Results: Ethical approval was obtained in November 2016. Study enrollment commenced across the 6 sites between June 2018 and February 2019, and baseline data collection ended at all sites in January 2020. 974 eligible patients (2123 screenings; median age of 61.0, IQR 55.0-67.0 years; male: 515, 52.9%; Chinese: 624, 64.1%) consented and completed the baseline assessment. Of these, 734 (75.4%), 603 (61.9%), and 786 (80.7%) attended DR, DN, and DFC screening, respectively. Most (n=793, 81.4%) attended more than 1 complication screening on the same day; had received secondary or lower education (n=701, 71.9%); had hypertension (n=711, 73.4%) and dyslipidemia (n=828, 85.1%); and 43.1% (n=419) were obese (BMI>27.5 kg/m^2). Median DM duration and hemoglobin A_{1c} levels were 6.3 (IQR 3.0-12.0) years and 6.9% (6.4%-7.6%), respectively. Over half (n=532, 55.1%) had not received prior DM education. Furthermore, participants reported low levels of diabetes-related self-efficacy (median 1.4, IQR 1.0-3.9 out of 5).

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Conclusions: At baseline, we have successfully enrolled almost 1000 patients with type 2 diabetes scheduled for annual DR, DN, or DFC rescreening, and potential predictors of nonadherence to rescreening were systematically collected. Follow-up phases will focus on establishing the rates and associated modifiable predictors of nonadherence to DR, DN, or DFC rescreening, which may inform program initiatives.

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KEYWORDS

diabetes complications screening; diabetic retinopathy; diabetic nephropathy; diabetic foot complications; nonadherence; mixed methods; microvascular complications; quality of life

Introduction

Microvascular complications of diabetes mellitus (DM), namely diabetic retinopathy (DR), diabetic nephropathy (DN), and diabetic foot complications (DFC) are common, and impose a profound quality of life, health, and economic burden on the individual and society [1,2]. Regular screening for these complications can reduce their incidence and delay or prevent the progression of blindness, end-stage renal disease, and diabetic foot ulcers [3-7]. In Singapore, guidelines recommend that individuals with DM have a dilated fundus examination, assessment of urine albumin excretion and serum creatinine, and foot examination or education annually. However, screening programs are only cost- and clinically-effective if uptake is high, and studies conducted overseas have shown poor adherence to screening, ranging from 20% to 60% [8-10]. At a population-based level, the Singapore Epidemiology of Eye Disease study (2004-2011) showed that 80% of individuals with DM had undiagnosed DR, a proxy indicator of nonadherence to DR screening [11]. However, current data on nonadherence to DR, DN, and DFC screening in Singapore are lacking.

Several factors have been associated with nonadherence to DM complications screening including low educational attainment, issues with appointment access, and lack of social or family support [8,12-17]. However, most existing research is limited by a retrospective study design, or only using qualitative data collection, meaning that predictors of nonadherence to DM complications screening remain largely unknown. Additionally, nonadherence to screening has been associated with poor DM control [6,18], more severe disease [19,20], frequent treatment [21], and hospitalization needs [6]. Indeed, a systematic review exploring patients' nonattendance at eye screening programs revealed that repeated nonattendance was associated with an increased risk of sight-threatening DR [20]. However, the studies included were conducted mostly in Western populations and may not be applicable to Asian populations due to different screening guidelines, and regional, political, social, economic, cultural, and health care systems.

To date, there are no prospective and contemporary population data on the rates; predictors; and clinical and economic impact of nonadherence to DM complications screening in Singapore. Furthermore, our understanding of the barriers or facilitators to screening adherence faced by patients with DM is limited. Such information is crucial for health care professionals and policy makers to make decisions on resource allocation and for informing interventions to improve adherence to DM screening programs. Against this background, we are conducting a prospective, multicentered clinic-based study (Understanding Non-Adherence to Diabetes Complications Screening [UNADS]) to ascertain the rates (aim 1); associated predictors (aims 2a and 2b); and clinical (aim 3) and economic impact (aim 4) of nonadherence to DM complications screening in primary care "polyclinic" patients with type 2 DM (T2DM) in Singapore using a mixed methods approach. In this paper, we provide a detailed description of the study design, data collection tools and protocols, and associated analytical plans. Furthermore, we present the patients' baseline characteristics and suggest factors that may potentially be associated with nonadherence to DM complications screening.

Methods

Conceptual Framework

We used Green and Kreuter Predisposing, Reinforcing, and Enabling Constructs in Educational Diagnosis and Evaluation (PRECEDE) and Policy, Regulatory, and Organizational Constructs in Educational and Environmental Development (PROCEED) model [22] to inform our mixed methods study design. This model has two distinct components: (1) "PRECEDE" which constitutes five diagnostic and planning phases to facilitate the identification of priorities and setting of objectives, and (2) PROCEED which consists of four phases and focuses on the identification of criteria for policy implementation and subsequent evaluation. PRECEDE-PROCEED has been widely used to identify and conceptualize barriers to health care screening in other health fields [23-26]. Our study used the first 5 "PRECEDE" phases (Figure S1 in Multimedia Appendix 1). The first phase (social diagnosis) establishes the health problems which impact the quality of life of the target population and the second phase (epidemiological diagnosis) documents the importance of these problems through survey and epidemiological data. The third phase (behavioral and environmental diagnosis) focuses on the systematic identification of health practices and other factors linked to health problems. The fourth phase (educational and ecological diagnosis) identifies the factors that, when modified, will most likely result in the desired behavior change. These factors are then classified as predisposing, enabling, or reinforcing. The last phase (administrative or policy assessment) of PRECEDE analyses policies, resources, and circumstances prevailing organizational situations that could hinder or facilitate meeting the objectives of the fourth phase. Based on our consultations with senior health care professionals from the

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SingHealth Polyclinics (SHP) and 2 National Healthcare Group Polyclinics (NHGP), and data from the NHG DM registry and Singapore Epidemiology of Eye Disease study, nonadherence to DM complications screening was already identified as a major public health issue in Singapore [11,27]. Therefore, in this study, we focus on the implementation of phases 2-5 via a prospective, mixed methods study that combines a quantitative data collection phase followed by in-depth qualitative interviews.

Study Setting and Design

In Singapore, DM complications screening is performed mainly at 23 primary health care government polyclinics. Of these, 4 SHP and 2 NHGPs were involved in our study, based on high attendance by minority ethnic groups, that is, Malays (Geylang [NHGP]) and Indians (Hougang [NHGP]), and high patient volume to maximize recruitment potential (ie, Bedok, Bukit Merah, Outram, and Pasir Ris [SHP]).

Standardized and uniform research protocols were applied at all sites. Each participant completed a baseline assessment on the day of enrollment and will be followed up at 16 months post enrollment (Figure 1). Baseline assessments involved the collection of quantitative data including clinical and sociodemographic information, and patient-reported outcomes. At 16 months following the baseline assessment (ie, up to 4 months after the scheduled annual rescreen appointment), a trained clinical research coordinator will determine if the participant attended the annual rescreening appointment from polyclinic records. Participants who attended or did not attend rescreening will be deemed “adherent” or “nonadherent,” respectively. The clinical research coordinator will then arrange a follow-up visit for all participants (both adherent and nonadherent) at the study site to collect study-related clinical information that is not available in the electronic medical records (EMRs). Furthermore, purposively selected participants will be invited to participate in focus groups or semistructured interviews regarding barriers or facilitators to adherence with DM complications screening. In addition, semistructured interviews will also be conducted with health care professionals (eg, polyclinic doctors and allied health professionals) to elicit their perceptions on why some patients do not comply with their screening visits.

Figure 1. UNADS mixed methods study design. DFC: diabetic foot complication; DM: diabetes mellitus; DN: diabetic nephropathy; DR: diabetic retinopathy; T2DM: type-2 diabetes mellitus; UNADS: Understanding Non-Adherence to Diabetes Complications Screening.

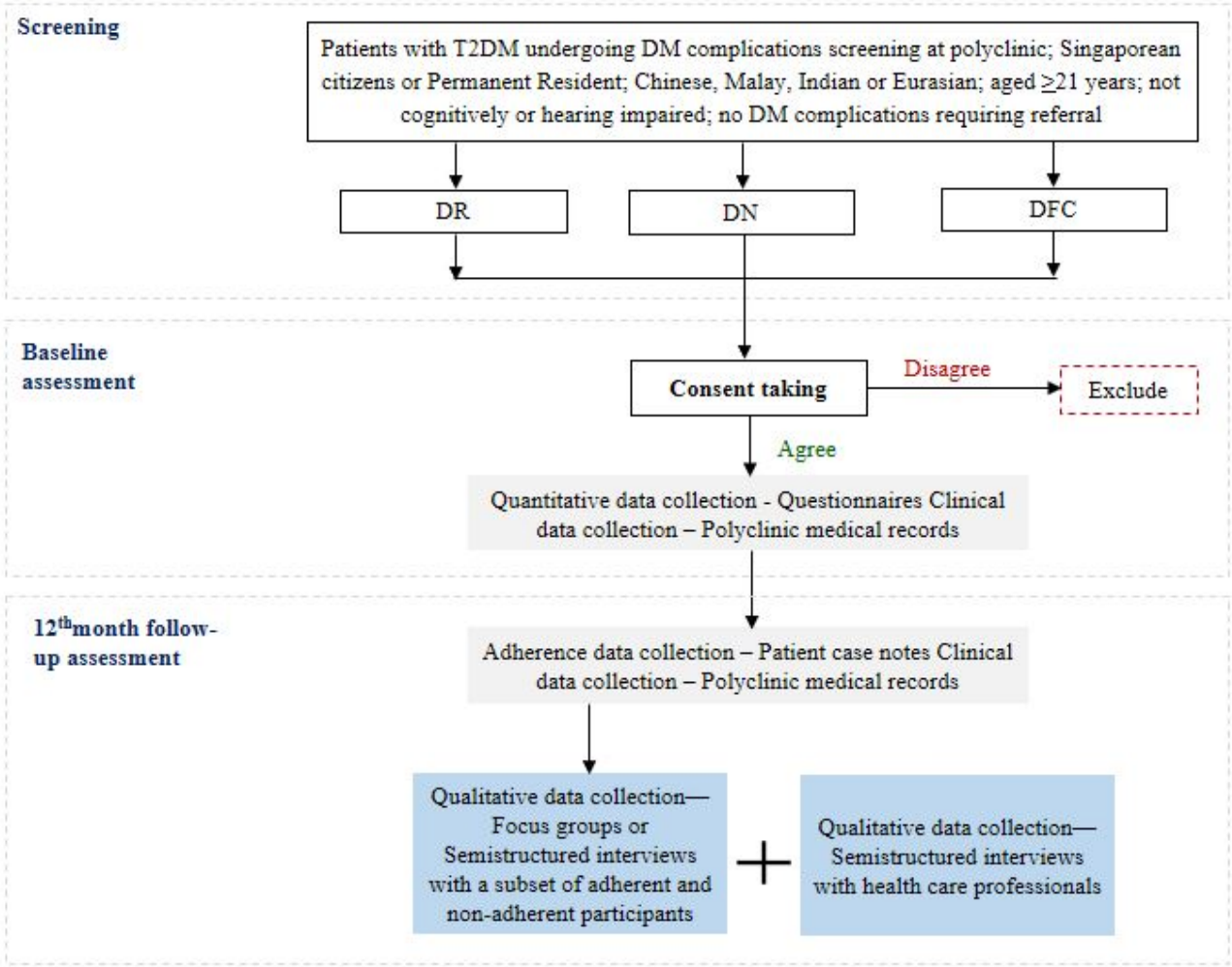

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Ethical Considerations

The study was approved by the SingHealth Centralized institutional review board (reference #2016/3041), and all patients enrolled in this study provided written informed consent prior to participation. All health care professionals who will be enrolled in qualitative interviews will be verbally consented prior to participation. The study was conducted in accordance with the Declaration of Helsinki.

To ensure confidentiality, each patient is assigned a unique identification number linked to the identifiable data (eg, name, contact details), which are saved separately on a password-protected system in a password-protected file, at each study site. Hard copies of the data were stored in secured cabinets at each study site. Audio files will be coded with the participant's identification number but without any information that could be used to identify them. Audio files and transcripts were stored in password-protected folders in shared drives of the Singapore Eye Research Institute. All data collected, including transcripts of the audio files, will be only accessible to approved research team members.

Each study participant will receive a reimbursement of S $20 (US $15.29) for each screening type for which they are recruited as part of the study. For example, a participant who completes baseline assessments for attending DR and DN screening will receive a total of S $40 (US $30.57) worth of vouchers. Similarly, the participant will receive a total of S $40 (US $30.57) worth of vouchers upon completing the respective follow-up assessments.

Study Population and Procedures

Quantitative Phase

Population

Patients with T2DM who underwent DM complications screening at one of the study sites and received a referral for an annual rescreen at the participating sites were eligible. All eligible participants were Singaporean citizens or permanent residents of Chinese, Malay, Indian, or Eurasian ethnicity; aged 21 years and older; free of significant hearing impairment that could affect the study protocol, and cognitive impairment assessed using the 6-item Cognitive Impairment Test [28]. Patients who had type 1 DM or with complications necessitating referral to tertiary care (eg, presence of moderate or worse DR, overt proteinuria, or neuropathy) were deemed ineligible to participate. Each patient was assigned a unique study identification number for each type of screening attended and enrolled in this study. For example, a patient attending DR and DN screening appointments on the same or different days (bundle screening) was assigned 2 unique study identification numbers.

Sample Size Determination

Assuming the nonadherence rate for DR, DN, and DFC is 50%, 30%, and 40%, a sample size of 1111 for DR, 933 for DN, and 1067 for DFC was needed to obtain a 95% CI of ±3% around the rates of nonadherence estimates with 80% power. Accounting for nonresponse and loss to follow-up of 20%, a sample size of 1444 for DR, 1213 for DN, and 1387 for DFC was needed. Furthermore, assuming a nonadherence rate of 50% and a probability of exposure (barriers or facilitators) of 15% among those who are adherent, these proposed sample sizes would be able to detect an odds ratio (OR) of 1.47, 1.6, and 1.5 of nonadherence to DR, DN, and DFC screening, respectively, for a barrier or facilitator. Additionally, assuming that the effect of bundle screening would be 30% on DN and DFC screening where DR screening (n=1444) was treated as a constant, we required 849 and 971 for DN and DFC, respectively. In total, we required a sample of 3264 patients.

Data Collection

All study assessments were undertaken by trained project members. A full description of all study procedures is provided in Table S1 in Multimedia Appendix 2.

- Sociodemographic, medical, and diabetes-related information and social history were collected via an in-house questionnaire and from EMR.
- Anthropometric parameters: height and weight were measured on the day of assessment if not available in the participant's EMR.
- Clinical parameters: blood pressure (BP) was assessed using a digital automatic BP monitor [29] Dinamap model Pro Series DP110X-RW, 100V2; GE Medical Systems Information Technologies, Inc) on site if not available in EMR. Participants' hemoglobin A1c (HbA1c), lipids (low- or high-density lipoprotein cholesterol, triglycerides, total cholesterol), serum creatinine, urine albumin creatinine ratio, and estimated glomerular filtration rate (eGFR) were collected from EMR if assessed 12 months or less. Otherwise, a venous blood sample drawn via venipuncture and a midstream urine sample were sent to Innoquest Laboratories Pte Ltd or National Healthcare Diagnostics, in Singapore for same-day analysis. The eGFR was calculated using the Chronic Kidney Disease Epidemiology Collaboration formula [30].
- Ocular parameters: retinal graded results of participants who attended the Singapore Integrated Diabetic Retinopathy Programme, a teleophthalmology-based screening program, were obtained from participants' EMR.
- Patient-reported outcomes hypothesized to be associated with screening adherence were assessed using the following validated questionnaires: Revised Diabetes Knowledge Test [31,32], Health Literacy Test for Singapore questionnaire [33], 3-item Health Literacy Questionnaire [34], Diabetes Empowerment Scale (Short form)–Self Efficacy [35], Problem Areas in Diabetes Questionnaire [36], and Questions on Social Support [37,38].
- Specially crafted items designed to elicit barriers from the patient's perspective based on known barriers from the literature and expert panel input were also included (eg, history of adherence or nonadherence to DM complications screening, time taken to reach screening appointments, DM-related education needs and experiences, and attitudes toward diabetes control).

All baseline quantitative data were collected in hard copy format and subsequently entered into the REDCap (Research Electronic Data Capture; Vanderbilt University) system.

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Analytical Plan

Basic proportions will be used to assess the rate of nonadherence to each DM complications screening, and 2-screening bundles (eg, either DR+DN, DR+DFC, or DN+DFC screenings) and 3-screening bundles (ie, same-day screenings for all 3 complications; aim 1). Baseline sociodemographic, medical, clinical, and patient-reported factors will be analyzed continuously or categorically where appropriate, and logistic regression models will determine the associations between the various factors with nonadherence to each of the 3 DM complications screening visits, as well as to the 2- and 3-screening bundles (aim 2a). Linear and logistic regression models will be used to examine the relationships between nonadherence to each individual DM complications screening with intermediate pre-post changes in clinical outcomes collected at the follow-up visit (aim 3). To model the economic burden of nonadherence to DM screening, we will estimate and compare the cost of patients who are adherent versus nonadherent (aim 4). We will focus on long-term costs of nonadherence (time horizon: 40 years) as there is unlikely to be any substantial cost-saving in the short term. To estimate long-term costs of nonadherence, a decision tree model will be used, which captures possible benefits of screening adherence in terms of lower risk of developing complications and timely detection and treatment if complications occur which, in turn, would lead to lower costs in the long term. All analyses will be performed using Stata/SE (version 15; StataCorp).

Qualitative Phase

Our qualitative methodology aligns with the Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist (Multimedia Appendix 3) [39].

Population

Focus groups or individual semistructured interviews will be conducted with both adherent and nonadherent participants for the 3 DM complications screenings. Participants will be purposively selected across the spectrum of age, sex, and language spoken (ie, English, Mandarin, Malay, and Tamil) to ensure the applicability of results. In addition, health care professionals, including advanced practice nurses, nurse care managers or educators, and family physicians, will be invited to participate in semistructured interviews.

Sample Size Estimation

Nonadherent participants will be oversampled to focus on barriers to screening adherence as these are amenable to intervention. Interviews will be offered in English, Mandarin, Malay, or Tamil to capture issues applicable to English or non-English speakers. We estimate that 8 focus groups (3 “adherent” and 5 “nonadherent”) with 5 to 7 participants per group, and 15-20 semistructured interviews will be required, resulting in a total of 55-76 participants. We estimate that 8-10 health care professionals will also be needed for the semistructured interviews. Sampling will continue until thematic saturation is reached (ie, no new themes emerge).

Data Collection

Patient focus groups and semistructured interviews will be conducted by trained interviewers and note takers face-to-face at the Singapore Eye Research Institute or over the phone, after the completion of the 16-month follow-up. Sessions will be conducted according to an interview guide developed from a thorough literature review and based on expert panel opinion. The interview guide will comprise open-ended questions targeting predisposing (eg, beliefs about illness and Western and Chinese medicine), reinforcing (eg, role of family members in DM care), and enabling (eg, importance of screening) factors guided by the PRECEDE component (see Multimedia Appendix 4 for the full patient interview guides). Different guides will be used for adherent and nonadherent participants.

We will use the Theoretical Domains Framework (TDF) to inform our interview guide for health care professionals and synthesize our qualitative data (see Multimedia Appendix 4 for full health care professional interview guides) [40]. The TDF covers 12 domains (eg, knowledge, skills, beliefs, and motivation) that cover potentially modifiable barriers that can inform intervention [41]. We will include open-ended questions like “What factors do you think patients consider when they are deciding whether or not to be screened?” as well as questions about knowledge of screening guidelines, referral practices, and information provided to patients regarding the referral during the consultation.

All qualitative interviews will be audio-recorded using a digital recorder. Audio files will be transcribed (and translated into English where necessary) by a professional transcription and translation company and will be checked by the research team for accuracy.

Analytical Plan

An inductive analytical approach will be adopted based on the constant comparative method whereby broad themes will be developed from the raw content of the transcripts [42]. New or improved themes that emerge from later transcripts will be incorporated into the coding hierarchy, and earlier transcripts will be updated to reflect these modifications. Themes will be categorized as predisposing, enabling, and reinforcing barriers or facilitators based on phase 4 of the PRECEDE component. From the health care professionals’ interviews, data relating to factors influencing behavior during complications referral will be coded using the 12 TDF domains. The computer program QSR NVivo 12 will be used to code the data. Transcripts will be analyzed by two different coders and disagreement in coding will be resolved by discussion or a third, independent coder (aim 2b).

Preliminary Analyses

In this preliminary report, we compared the characteristics of participants and those who refused to participate (nonparticipants) using 2-tailed *t* test or chi-square statistics, as appropriate. Furthermore, we present baseline characteristics that may be associated with nonadherence to DM complications rescreening using descriptive statistics (mean [SD], median [IQR], counts, and percentages). All preliminary analyses were performed using Stata/SE, version 15.

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Results

Recruitment and Retention

Recruitment commenced on June 6, 2018, at Hougang June 11, 2018, at Bedok; June 19, 2018 at Outram; September 25, 2018, at Geylang; November 21, 2018, at Pasir Ris; and February 8, 2019, at Bukit Merah. The baseline quantitative data collection ended at all 6 sites on January 31, 2020.

A total of 3546 patients were screened across the 6 polyclinics. Of these, 830 (23.4%; Figure S2 in Multimedia Appendix 1) were excluded because (1) they received a less than 12-month (approximately 3-6 months) review referral at the polyclinic (n=604, 72.8%); (2) had significant hearing impairment (n=63, 8%); (3) had complications requiring referral to tertiary care (n=39, 5%); (4) had cognitive impairment (n=38, 5%); or (5) were not Chinese, Malay, Indian, or Eurasian (n=35, 4%). Of the remaining 2716 (76.6%) eligible patients, nearly two-thirds refused (n=1742, 64.1%) participation. Reasons for refusal included not being interested (n=901, 51.7%), lack of time (n=512, 29.4%), more than 1 study-related visit required (n=287, 16.5%), and "other" reasons (eg, does not want to share confidential information, the caregiver does not approve, does not believe in research; n=42, 2%). The remaining 974 (35.9%) eligible patients agreed to participate.

The response rate ranged from 9.5% in Bedok and 33.9% in PR to 85.0% in Geylang (Table 1). There were no significant differences in age and sex between participants and nonparticipants. Compared to participants, nonparticipants were more likely to only attend DR screening (n=730, 51.9%), not attend "bundle" screening appointments (n=909, 64.6%) and be from the Bedok site (n=498, 28.6%; all $P<.001$).

Table 1. Response rates of eligible patients to the UNADS[a] study by polyclinic sites.

Polyclinic sites	Eligible patients, n	Participants, n	Response rate, %[b]
SHP[c]–Bedok	550	52	9.5
SHP–Outram	638	197	30.9
SHP–Pasir Ris	322	109	33.9
SHP–Bukit Merah	365	57	15.6
NHGP[d]–Hougang	494	264	53.4
NHGP–Geylang	347	295	85.0
Total	2716	974	35.9

[a]UNADS: Understanding Non-Adherence to Diabetes Complications Screening.

[b]Calculated as participants as a percentage of eligible patients.

[c]SHP: SingHealth Polyclinics.

[d]NHGP: National Healthcare Group Polyclinics.

Baseline Profile of Study Participants

Of the 974 enrolled patients at baseline, 75.4% (n=734), 61.9% (n=603), and 80.7% (n=786) attended DR, DN, and DFC screening, respectively. Over 4 in 5 (n=793, 81.4%) attended 1 or more complication screenings on the day of enrollment.

Patient characteristics potentially associated with nonadherence to DM complications screening are outlined in the following sections.

Sociodemographics

The baseline cohort had a median age of 61.0 (IQR 55.0-67.0) years, with over two-fifths less than 60 years (n=413, 42.4%); and were primarily male (n=515, 52.9%; Table 2). Most participants were Chinese (n=624, 64.1%), followed by Malay (n=208, 21.4%), Indian (n=136, 13.9%), and Eurasian (n=6, 1%). A majority had received secondary or lower education (n=701, 71.9%), were employed (n=589, 60.5%), had a monthly household income of more than S $2000 (n=518, 62.5%), and lived in public housing (n=843, 86.6%). Furthermore, most were married (n=737, 75.7%) and reported taking less than 30 minutes to access the polyclinic site (n=720, 74.3%).

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Table 2. Baseline sociodemographic and lifestyle characteristics of UNADS[a] study participants.

Characteristics	Values
Screening attended, n (%)	
Diabetic retinopathy	734 (75.4)
Diabetic nephropathy	603 (61.9)
Diabetic foot complication	786 (80.7)
Bundle screening on the same day, n (%)	793 (81.4)
Sociodemographic factors	
Age (years), median (IQR)	61.0 (55.0-67.0)
Age groups (years), n (%)	
≤49	118 (12.11)
50-59	295 (30.29)
60-69	420 (43.12)
>70	141 (14.48)
Sex, (male), n (%)	515 (52.9)
Ethnicity, n (%)	
Chinese	624 (64.1)
Malay	208 (21.4)
Indian	136 (13.9)
Eurasian	6 (0.6)
Educational attainment, n (%)	
Primary or lower	153 (15.7)
Secondary or A-level	548 (56.3)
Tertiary	273 (28)
Marital status, n (%)	
Single	117 (12)
Married	737 (75.7)
Divorced or separated	61 (6.3)
Widowed	59 (6.1)
Housing type	
Public	843 (86.6)
Private	131 (13.5)
Monthly household income	
≤S $2000 (US $1524.80)	311 (37.5)
>S $2000	518 (62.5)
Employment status (yes), n (%)	589 (60.5)
Accessibility to polyclinic	
Less than 30 minutes	720 (74.3)
30 minutes to 2 hours	249 (25.7)
Lifestyle or health behavior factors	
Smoking	
Never or past smoker	870 (89.3)
Current smoker	104 (10.7)
Alcohol status	

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Characteristics	Values
Never or past drinker	763 (78.3)
Current drinker	211 (21.7)

[a]UNADS: Understanding Non-Adherence to Diabetes Complications Screening.

Medical and Clinical

Comorbidities were common overall, with a high prevalence of hypertension (n=711, 73.4%), dyslipidemia (n=828, 85.1%), and obesity (n=419, 43.1%; Table 3). Most participants rated their health status as "good to excellent" (n=775, 79.7%). Participants reported a median DM duration of 6.3 (IQR 3.0-12.0) years, and most were on diet control (n=915, 94.2%). Participants had median HbA_{1c}, and systolic and diastolic blood pressure values of 6.9% (IQR 6.4%-7.6%), and 130.0 (IQR 120.0-138.0) mm Hg and 70.0 (IQR 65.0-78.0) mm Hg, respectively. The median low-density lipoprotein cholesterol and eGFR was 2.1 (IQR 1.7-2.6) mmol/L and 88.5 (IQR 73.8-98.3) mL/min/1.73m^2, respectively.

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Table 3. Baseline medical and clinical characteristics of UNADS[a] study participants.

Characteristics	Values
Diabetes Management	
Diabetes duration, median (IQR)	6.3 (3.0-12.0)
Diabetes treatment, n (%)	
Insulin	68 (7)
Oral antidiabetic medications	789 (81.3)
Diet	915 (94.2)
Exercise	780 (80.3)
Health status	
Comorbidities	
None, n (%)	54 (5.6)
1-2 conditions, n (%)	640 (66.5)
3 conditions or more, n (%)	268 (27.9)
Hypertension (yes), n (%)	711 (73.4)
Dyslipidemia (yes), n (%)	828 (85.1)
Asthma (yes), n (%)	51 (5.2)
BMI (kg/m2)[b], median (IQR)	26.9 (24.1-30.3)
Obesity (yes), n (%)	419 (43.1)
Arthritis (yes), n (%)	96 (9.9)
Self-rated health status, n (%)	
Excellent or very good	281 (28.9)
Good	494 (50.8)
Fair or poor	198 (20.4)
Clinical factors	
Blood pressure (mm Hg), median (IQR)	
Systolic	130.0 (120.0-138.0)
Diastolic	70.0 (65.0-78.0)
HbA_{1c}[c] (%), median (IQR)	6.9 (6.4-7.6)
Lipids (mmol/L), median (IQR)	
Total cholesterol	4.1 (3.6-4.7)
HDL[d]	1.3 (1.1-1.5)
LDL[e]	2.1 (1.7-2.6)
TGL[f]	1.4 (1.0-1.8)
eGFR[g] (ml/min/1.72m^2), median (IQR)	88.5 (73.8-98.3)

[a]UNADS: Understanding Non-Adherence to Diabetes Complications Screening.
[b]BMI was calculated as weight in kilograms divided by height in meters squared.
[c]HbA_{1c}: hemoglobin A_{1c}.
[d]HDL: high-density lipoprotein.
[e]LDL: low-density lipoprotein.
[f]TGL: triglyceride level.
[g]eGFR: estimated glomerular filtration rate.

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Patient-Reported

In general, most study participants (n=764, 95.0%) had adequate health literacy (Table 4). More than half (n=532, 55.1%) reported not having received DM education either at the time of diagnosis of DM or in the past year. Most reported receiving "quite a lot or a great deal" of DM support (n=678, 69.7%). The median baseline diabetes knowledge scores of those on insulin and not on insulin were 16.0 (IQR 13.0-18.0) out of 22 and 9.0 (IQR 8.0-11.0) out of 14, respectively. Over 10% and 20% of the participants on insulin and not on insulin answered less than 50% of the questionnaire correctly, respectively. Participants reported low levels of diabetes-related self-efficacy (median 1.4, IQR 1.0-3.9 out of 5), and more than half rated their diabetes control status as "okay" (n=547, 56.6%). Almost one-fifth reported diabetes related-distress (n=171, 17.6%).

Table 4. Baseline patient-reported characteristics of UNADS[a] study participants.

Characteristics	Values
Health literacy[b], n (%)	
Not adequate	41 (5.1)
Adequate	764 (95.0)
Health literacy (3-item)[c], median (IQR)	10.0 (7.0-12.0)
Diabetes knowledge[d], median (IQR)	9.0 (8.0-11.0)
Not on insulin treatment	9.0 (8.0-11.0)
On insulin treatment	16.0 (13.0-18.0)
Diabetes education[e] (no), n (%)	532 (55.1)
Diabetes support (yes), n (%)	
No or a little bit of support	295 (30.3)
Quite a lot or a great deal of support	678 (69.7)
Satisfaction with diabetes support, n (%)	
Not at all or a little satisfied	143 (14.7)
Somewhat satisfied	180 (18.5)
Very satisfied or extremely satisfied	648 (66.7)
Self-rated diabetes control, n (%)	
Very good	255 (26.4)
Okay	547 (56.6)
Not good	80 (8.3)
Variable	84 (8.7)
Attitude toward glycemic control, n (%)	
Very important	916 (94.2)
A little or not important	56 (5.8)
Self-efficacy[f], median (IQR)	1.4 (1.0-3.9)
Diabetes-related distress[g] (yes), n (%)	171 (17.6)

[a]UNADS: Understanding Non-Adherence to Diabetes Complications Screening.

[b]Adequate health literacy was defined as 75% correct response in both sections, that is, 3 numeracy items and 27 reading comprehension sections.

[c]Higher score indicates higher health literacy level.

[d]Higher score indicates higher level of diabetes knowledge.

[e]Have you ever attended any diabetes education programs focusing on diabetic retinopathy, diabetic nephropathy, or diabetic foot complications management?

[f]Higher score indicates higher self-efficacy level.

[g]A total score of 8 or more suggests "possible" diabetes distress.

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Discussion

We established the UNADS study to provide urgently needed data on the rates, predictors, and clinical and economic impact of nonadherence to DM complications screening in a multiethnic Asian primary care population with T2DM using a mixed methods approach. A total of 974 patients with T2DM who completed 2123 DM complications screening visits across 6 polyclinics in Singapore were enrolled and have completed the baseline assessment. Most (n=793, 81.4%) were recruited while attending more than 1 complication screening on the same day. A spectrum of sociodemographic (eg, age, ethnicity, education and income levels, housing, and accessibility to nearest polyclinic), medical (eg, presence of comorbidities, and HbA_{1c} and lipid levels), and patient-reported factors (eg, DM-specific self-efficacy and knowledge levels, and self-rated DM control) which may potentially predict nonadherence to DM complications screening, were systematically collected. Completion of longitudinal quantitative and cross-sectional qualitative data collection and analyses will provide insights into the rates and modifiable risk factors of nonadherence to DM complications screening in this population; and contribute to the design of evidence-based interventions addressing those factors at patient, provider, and system levels in the public sector.

We found that more than two-fifths of our study participants were aged less than 60 years, were mostly Chinese, had secondary or lower education, and received a monthly household income of more than S $2000 (US $1546.05). These characteristics have been reported to be linked to nonadherence to DM complications screening by previous studies exploring factors related to attendance to DM-related screening programs [8,43]. For example, a large cohort study (n=24,832) of individuals with DM by Alice et al [8] reported that those aged less than 60 years and receiving a higher income were associated with the greatest risk (–1.3-fold) of nonadherence to eye examination guidelines in New South Wales. Furthermore, a mixed methods study investigating the barriers or facilitators of uptake of DM health screening conducted in Singapore showed that those of Chinese ethnicity (vs Indians), and those with lower education had lower odds of attending regular DM health screenings [43].

Our baseline analysis also showed a high prevalence of comorbid conditions such as hypertension, dyslipidemia, and obesity, which may be associated with an increased likelihood of not attending screening appointments. Comorbidity is common among people with DM and can create a number of challenges that affect a patient's ability to participate in regular screening [44]. Indeed, Baumeister et al [45] studied trends of barriers to receiving recommended eye care among individuals with DM in Germany using population-based data collected between 1997-2001 and 2008-2012 and found that eye care use declined over the 10-year period in those diagnosed with DM for more than 5 years, and in those with obesity, dyslipidemia, and multiple comorbid conditions.

We found that more than half of our baseline study sample had not received any DM-related education prior to DM complication screening. This is important, as evidence suggests that a lack of information on DM may predict nonadherence to regular annual screening. For instance, in a nationwide survey of 1288 individuals with DM conducted in Korea, Byun et al [12] found that those who had not received education about DM care were more likely to be screened less often for DR and DN. At baseline, our participants reported low levels of DM-specific self-efficacy, which may be important in predicting nonadherence to DM complications screening. Indeed, studies exploring screening attendance in other health care fields (eg, cancer) have shown that low self-efficacy is an important determinant of nonadherence to screening programs [46]. Nevertheless, full analysis of the follow-up data using regression models is essential to identify and confirm the modifiable predictors of DM complications screening in this population and to inform appropriate intervention in this multiethnic primary care population.

A key strength of the UNADS study is the application of the PRECEDE-PROCEED model, which offers a systematic classification of factors at individual, provider, and system levels by their relative importance and capacity for modification. This facilitates consideration of the determinants for change at individual-, provider-, and system-levels and allows for the development of more efficient and effective programs. Other strengths are its large sample size involving six polyclinics across 2 different health care clusters and the collection of rich longitudinal quantitative and qualitative data covering a wide range of exposures and outcomes.

The UNADS study has some important limitations. First, the COVID-19 outbreak and related restrictions had serious implications on its implementation. Due to the restrictions on face-to-face research activities, study enrollment was severely impacted, and the estimated target sample size was not achieved. However, as far more of our study participants attended bundle screening (81.4%) than originally estimated in our sample size calculations (30%), our final sample size was deemed adequate to accomplish our study's objectives. Secondly, our overall baseline response rate was low (35%) and this could lead to selection bias affecting the validity of our results. There were several reasons for this: survey fatigue experienced by patients attending busy sites like Bedok and Bukit Merah with several ongoing research projects; the need for biological sample collection at baseline and follow-up (if unavailable in the EMR); and the impact of restrictions imposed during the COVID-19 outbreak as explained above [47,48]. Third, we are unable to compare the predictors of nonadherence between 2 different complication screenings (eg, DR vs DFC, DFC vs DN) due to the small number of patients attending both DR and DFC (n=223), and DFC and DN (n=123) screenings. Finally, the use of self-reported measures may be subject to social desirability and recall bias.

The UNADS study is the first longitudinal mixed methods study to investigate the rates, independent predictors, and the clinical and economic impact of nonadherence to DM complications screening in multiethnic polyclinic patients with T2DM in Singapore. Our baseline data are comprehensive including several sociodemographic, clinical, health, and patient-reported characteristics that may predict nonadherence to DM

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complications screening. Completion of the follow-up phase will provide empirical evidence on the rates, and modifiable barriers or enablers of nonadherence to DM complications screening. Furthermore, the study results may inform public health interventions to develop culturally appropriate intervention programs to improve screening adherence in multiethnic populations. Finally, this study may contribute to reducing unnecessary disease burden with timely screening, monitoring, and treatment; improving health outcomes for Singaporeans with T2DM at the primary care level; and demonstrating significant cost-savings to the patient and society over time.

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Data Availability

The datasets generated and analyzed as part of this project will be available from the corresponding author on reasonable request after the research team has completed analyses related to the study aims.

Authors' Contributions

AA was responsible for conducting the formal analysis and investigation, managing the project, supervising the research process, drafting the original manuscript, and contributing to its review and editing. EF contributed to the conceptualization of the study, carried out formal analysis and investigation, managed project administration, supervised the research, and was involved in drafting, reviewing, and editing the manuscript. AW participated in formal analysis. EL, RM, and CS contributed to the conceptualization, and review and editing of the manuscript. NC, WE, CJ, LP, WT, WF, and SW were involved in the writing process, specifically in reviewing and editing the manuscript. EL served as the senior study investigator and lead author. The final version of the paper has been seen and approved by all coauthors.

Conflicts of Interest

None declared. Abbreviations BP: blood pressure COREQ: Consolidated Criteria for Reporting Qualitative Research DFC: diabetic foot complication DM: diabetes mellitus DN: diabetic nephropathy DR: diabetic retinopathy eGFR: estimated glomerular filtration rate EMR: electronic medical record HbA1c: hemoglobin A1c NHGP: National Healthcare Group Polyclinics. OR: odds ratio PRECEDE: Predisposing, Reinforcing, and Enabling Constructs in Educational Diagnosis and Evaluation PROCEED: Policy, Regulatory, and Organizational Constructs in Educational and Environmental Development REDCap: Research Electronic Data Capture SHP: SingHealth Polyclinics T2DM: type 2 diabetes mellitus TDF: Theoretical Domains Framework UNADS: Understanding Non-Adherence to Diabetes Complications Screening.

Multimedia Appendix 1
Supplementary Figures.
[DOCX File , 57 KB - resprot_v14i1e63253_app1.docx]

Multimedia Appendix 2
Details of the UNADS study procedures, participants and timeline for administration.
[DOCX File , 35 KB - resprot_v14i1e63253_app2.docx]

Multimedia Appendix 3
Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist.
[PDF File (Adobe PDF File), 189 KB - resprot_v14i1e63253_app3.pdf]

Multimedia Appendix 4
Additional materials.
[PDF File (Adobe PDF File), 159 KB - resprot_v14i1e63253_app4.pdf]

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Protocol

Addressing the Stigma of Mental Illness in Black Families and Communities in Ontario, Canada: Protocol for a Mixed Methods Study

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Abstract

Background: Racism and discrimination are among the factors perpetuating the persistent disparities within the Canadian health sector and related social and community services. Addressing issues of racism in Canada is crucial to reducing the mounting mental health disparities that subsequently impact the psychological well-being of diverse groups of people, particularly racialized and Black individuals. While some research has been conducted on mental illness–related stigma, very few peer-reviewed studies have attempted antistigma interventions to address mental health disparities in Black families and communities in Canada.

Objective: This study aims to generate critical knowledge to reduce mental health disparities and mental illness stigma experienced by Black families and communities and engage them in cocreating a best-practice model to guide policy and programming. Our study intends to engage individuals living with or affected by mental illness, service providers, and community leaders in Black communities who are interested in stigma reduction activities and advocacy in Ontario, particularly in the Greater Toronto Area (GTA), including Durham and York Regions, London, Ontario, Brampton, and Ottawa.

Methods: Informed by population health promotion approaches, critical race theory, and an intersectionality framework underpinned by social justice principles, this mixed methods study will engage individuals of Caribbean and African descent in 5 cities in Ontario. We will use online self-reported surveys with Black individuals (335/431) to assess depression, anxiety, stress, mental health knowledge, racial discrimination, and mental health stigma. We will also engage Black individuals (40/431) and service providers and community leaders (16/431) in focus groups and individual interviews (10/431). Results from the survey and focus groups will inform concept mapping activities with cross-sector leaders, decision makers, and community advocates (30/431) to cocreate a best-practice model to improve mental health outcomes in Black families and communities. Quantitative data will be analyzed using descriptive and inferential analyses through SPSS (IBM Corp). Qualitative data will be transcribed verbatim, and NVivo software (Lumivero) will be used for data management. We will apply Braun and Clarke's framework of 6 phases in thematic analysis.

Results: As of September 2024, the study has received ethical approval in Canada. We have completed data collection for phase one of the study and plans are far advanced to start recruitment for phases 2 and 3. Results from the study are expected in the last quarter of 2025 and the first quarter of 2026.

Conclusions: This project will generate a novelty of knowledge to contribute to effective ways of addressing mental illness stigma and promoting mental health literacy in Black families and communities and other vulnerable populations. In addition, the knowledge gained from this study will be taken back to Black communities to empower affected individuals and their families.

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KEYWORDS

racial discrimination; anti-Black racism; mental illness and stigma; Black families and communities; mental health; Ontario; study protocol; Canadian health sector; psychological wellbeing; Greater Toronto Area; social justice; Caribbean descent; African descent; depression; anxiety; stress; self-reported survey; Black individuals; community leader; empowerment

Introduction

Despite recent efforts in society to address social injustice and inequity, racism continues to violate Black Canadians' human rights in every facet of society [1-4]. The mental health of Black families and communities continues to be negatively impacted by structural and systemic discrimination based on racism [2,3,5]. Racism and discrimination devalue and often discredit people of African descent [4,5], leading to trauma, frustration, and a sense of powerlessness, which adversely impact Black people's mental health and quality of life [2,6-8]. Addressing issues of racism in Canada is crucial to reducing the mounting health disparities that subsequently impact the psychological well-being of diverse groups of people, particularly racialized and Black individuals [9-11].

Historical collective experiences of enslavement, displacement, and ongoing anti-Black racism produce and perpetuate intergenerational trauma and mental health problems among Black families and communities. Anti-Black racism has been explained as the systemic discrimination and prejudice embedded in institutions, policies, and practices targeted at people of African descent [12-14]. Evidence shows that anti-Black racism and racial discrimination are the causes of the persistent disparities within the Canadian health sector and related social and community services [15-17]. These disparities often result in poor access to both physical and mental health support among Black Canadians [11,18]. Related studies in Canada have found that the combined effect of racism and anti-Black racism experienced by Black people exposes them to emotional and psychological problems [1,5]. Mental illness stigma, a social construct that places shame on affected people, is another global health problem that appears to traumatize persons with mental illnesses or mental health challenges. For instance, a recent study by the Lancet Commission on ending stigma and discrimination in mental health underscored that stigma connected with mental illnesses is worse than the condition or diagnosis itself [19] and therefore has the tendency to prevent affected persons from accessing medical care and social support services [19-23]. Stigma and discrimination have various presentations that put affected persons and their families through emotional distress, which Thornicroft et al [19] termed double jeopardy. While mental illness stigma is a universal health problem, the stigma connected to a Black person diagnosed with mental health disorders in the Western world could be a threefold or triple-edged sword, as they have racism to deal with besides stigma and discrimination associated with mental illnesses. There is, however, a paucity of research on mental health and the stigma of mental illness experienced by Black families and communities in Canada, making it difficult to estimate the prevalence of mental health conditions [17,24].

The availability of socioeconomic resources is a social determinant of health as it allows individuals to improve the quality of their lives. Black people's lack of equal access to these resources in Canada impacts their mental well-being and that of their families [16]. Barriers created by anti-Black racism in Canada are among the reasons behind the economic privileges enjoyed by White individuals to the disadvantage of Black people [12,14,25]. For instance, recent data from Canada showed that Black people of active working age have the highest unemployment rates (13.1% vs 7.7%) than nonracial minorities [12,26]. Likewise, it is documented in the 2016 Canadian Census that the unemployment rate of Black people of active working age was 10% when juxtaposed with the Canadian average of 6% for the same group with similar levels of education [27].

In addition, the unemployment rate among Black youth (15-24 years) was higher (24.3%) when contrasted with the Canadian youth average (15.5%) [28] and these gaps were more extensive during the COVID-19 pandemic [29,30]. Some ramifications of anti-Black racism are the high levels of poverty, homelessness, and substance use in Black communities [1,31], which in turn predisposes affected individuals to poor mental health. For example, the lack of formal employment due to structural and systemic racism can contribute to the rise in mental health problems in Black neighborhoods compared with other racialized and nonracialized communities [32,33]. Also, Black people in Canada are among the most uneducated due to their inability to break through the concealed systemic and structural barriers within various educational institutions [5,34]. The very few who have completed college and university are often greeted with frustrations and emotional distress given the hardship some endure throughout their education, and this can have a toll on their mental health. Furthermore, Black immigrants admitted into Canada through the economic immigration programs often find it difficult to secure employment that commensurate with their qualifications and occupational expertise. Underemployment over time exposes them to high levels of work-related stress as they are compelled to settle for mismatched jobs that deskill them [35-37].

Besides the socioeconomic issues faced by Black Canadians, the criminal justice system has been unjust to Black families and communities, which is connected to the remnants of slavery and colonialism [38]. Anti-Black racism has created systemic inequalities within the criminal justice system, where Black Canadians have experienced discrimination and prejudice more than any ethnic group when it comes to being survivors of crime and imprisonment [12,38]. For example, a recent review of the experiences of Black Canadians adds to existing evidence that the continued social discrimination confronting Black people is due to anti-Black racism and this has given rise to racial profiling and police brutality [5,39,40]. The overrepresentation of Black people within the criminal justice system resulting

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from unconscious bias and anti-Black racism eventually has ramifications for affected persons and their relatives' psychosocial well-being. Arresting Black people and jailing them without a fair hearing could also lead to intergenerational trauma within Black families and communities. For instance, it is reported that Black persons are 20 times more likely than White persons to be shot dead by police in Toronto and this has created a sense of mistrust among Blacks in their dealings with the police [12]. Therefore, people of African and Caribbean origin continue to face these challenges produced by anti-Black racism and structural discrimination juxtaposed with White supremacy to produce or reproduce intergenerational distress that negatively affects the mental health of multiple generations of Black Canadians [11,24,41]. These incidents have become more egregious for Black refugees who have experienced premigration natural disasters or war-related traumas that have already impacted their mental health [2,42,43]. These premigration traumatic experiences, alongside postmigration experiences of anti-Black racism, not only compromise Black families and communities' mental well-being but also impede their social integration and adaptation to achieve their life goals and aspirations [44].

The lack of sufficient data on Black families and communities mental health and mental illnesses is a barrier to inclusive mental health policies and strategic planning of accessible programs and services. In addition, early detection and treatment of mental illness result in good prognosis [45,46], and without inclusive research data, Black families and communities are further marginalized and unable to access mental health promotion resources and timely diagnosis and care. Given the documented evidence on the cycle of anti-Black racism and silence on mental illness stigma, mobilizing Black Canadians and communities to break the silence and promote critical dialogue on mental health literacy is essential to reduce the existing mental disparities and fill a scholarly gap.

Study Objective

The overall goal of this proposed study is to generate critical knowledge to reduce mental health disparities and mental illness stigma experienced by Black families and communities and engage them in cocreating a best-practice model to guide policy and programming.

Specific Objectives

- **Research objective (RO)1:** To identify and examine the sociocultural and structural factors that reproduce or produce and challenge community silence and stigma of mental illness in Black families and communities.
- **RO2:** To interrogate the role of racism and discrimination in perpetuating community silence and stigma of mental illness in Black families and communities.
- **RO3:** To assess the mental health literacy in Black families and communities and identify mental health facilitators at individual, family, and community levels.
- **RO4:** To engage Black families and communities in co-designing a best practices model to inform inclusive policy and culturally safe mental health programming.

Methodology

Theoretical Approach

The project will be driven by a population health promotion framework underpinned by social justice principles. Guided by concepts of community empowerment and capacity building, the project will focus on creating supportive environments for health, strengthening local community action for health, and developing personal and collective skills in Black families and communities to enable them to take control of their mental health and well-being [47,48]. In addition, we will apply critical race theory [49-51] and an intersectionality framework [52,53] to interrogate how anti-Black racism operates to produce and perpetuate mental illness problems and related stigma at the individual, familial, and community levels. Further, we will investigate the prevailing mental health disparities in Black families and communities in Canada using the intersectionality framework.

Research Approaches

Mental illness-related stigma is a social construct often perpetrated by some family members and endorsed within varied social contexts [20,54]. While stigma experiences are everyday occurrences at all levels of society, interventions necessary to reduce mental illness stigma should involve multiple actors within communities to build collective capacities to fight all forms of stigma [54-56]. Therefore, this project will adhere to the principles and processes of community-based action research (CBAR). Community-based research methodology seeks to empower communities through research, education, and action [57-59]. In CBAR, community partners are actively involved in the research process compared with other conventional methodologies where community members or study participants are treated as passive participants [58]. A team of researchers well-versed in CBAR will collaborate meaningfully with identified Black community leaders, affected communities, and their representatives within the Greater Toronto Area (GTA) and other selected communities to set up project advisory committees to advise on research processes, community engagement, and ethical issues.

Methods

Overview

Given the complexity of the issues and the need for an in-depth understanding of the relationship between participants' mental health literacy, psychosocial measures, and behavior change outcomes, a mixed-methods approach is considered appropriate for the proposed CBAR project. Specifically, an explanatory sequential design will be adopted for this project. In this design, we will collect and analyze quantitative data to inform our qualitative data collection to build on the initial results from the quantitative analysis. This approach is helpful to obtain additional information to explain critical quantitative results.

Sample and Setting

The study will engage two populations: (1) individuals who self-identify as belonging to African, Caribbean, or Black communities, aged 18 years or older, living with or affected by

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mental illnesses, having family members living with mental illness, or having an interest in reducing mental illness stigma, living in the GTA, including Durham and York Regions, London, Ontario, Brampton, and Ottawa and (2) service providers and community leaders, aged 18 years or older, working with individuals and families of African, Caribbean, or Black communities and interested in reducing mental illness stigma in Black families and communities in the GTA, including Durham and York Regions, London, Ontario, Brampton, and Ottawa. Prospective participants will be reached using flyers, postcards, advertisements on social media platforms (including Facebook, Twitter, and LinkedIn), community collaborators' e-newsletters, community service centers, family health practices, faith organizations, and educational institutions. Participants will also be recruited through word of mouth, personal contacts, and Black businesses (eg, barbershops, salons, restaurants, and grocery stores).

Data collection will start from October 2024 to August 2025. We will adhere to the approved study protocol to ensure that participants know their rights and confidentiality will be strictly ensured throughout all 3 phases of the study.

Phase One (RO#1-3)

An online survey will be used to assess participants' mental health status using the Depression, Anxiety, and Stress Scale-21 Items (DASS-21) [60], stigma of mental illness using the Community Attitudes toward the Mentally Ill (CAMI) scale [61], discrimination using the Everyday Discrimination Scale (EDS) [62], and mental health literacy using the Mental Health Literacy Questionnaire-Short Version for Adults (MHLq-SVa) [63]. As an exploratory study, we will use a nonprobabilistic convenience sampling technique to recruit community members (n=335).

Phase Two (RO#1-3)

We will engage community members (n=40) and service providers/community leaders (n=16) in separate focus group discussions and 10 follow-up in-depth interviews. We will draw on the results of phase 1 to inform the interview guide to explore participants' understanding of mental health and mental illness, the relationship between anti-Black racism and Black mental health, barriers, and facilitators in reducing mental illness stigma, contexts, and conditions to promote Black mental health. That is, survey results could play key roles in informing the interview guides for qualitative studies. Surveys provide diverse perspectives that allow the interviews to focus on areas critical to the study's objective. Survey results often underscore critical themes and variables requiring additional inquiry through interviews. For example, qualitative interviews can focus on individuals to explore their unique lived experiences more extensively. In this way, the qualitative interviews help to critically examine a range of intricate issues within the survey population.

Phase Three (RO#4)

In this phase, we will apply an integrative knowledge translation approach to exchange knowledge and cocreate a best practices framework to address mental illness stigma and promote mental health in Black families and communities. We will engage a group of Black community members, service providers, cross-sector leaders, decision makers, and community advocates (n=30) in three concept mapping sessions to (1) share and discuss the results of phases 1 and 2; (2) engage every participant in brainstorming, sorting, and ranking essential elements of a best practices model to promote mental health equity in Black families and communities, use a computer program (GroupWidsom, Concept Systems Incorporated) to collate and generate concept maps based on everyone's input; and (3) discuss different configuration of concept maps, decide on a model with priorities, and discuss follow-up action and strategies (Table 1).

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Table 1. Study population and phase description.

Study phase	Target group	Involvement
Phase one (RO[a]#1-3): as an exploratory study, we will use a nonprobabilistic convenience sampling technique to recruit community members (n=335).	Individuals who self-identify as belonging to African, Caribbean, or Black communities, aged 18 years or older, living with or affected with mental illnesses, having family members living with mental illness, or having an interest in reducing mental illness stigma.	An online survey will be used to assess participants' mental health status using the Depression, Anxiety and Stress Scale-21 Items (DASS-21) [60] (Lovibond and Lovibond, 1995), stigma of mental illness using the Community Attitudes toward the Mentally Ill (CAMI) scale [61], discrimination using the Everyday Discrimination Scale (EDS) [62], and Mental Health Literacy Questionnaire-Short Version for Adults (MHLq-SVa) [63].
Phase two (RO#1-3): engage community members (n=40) and service providers and community leaders (n=16) in separate FGDs[b] and 10 follow-up IDIs[c].	Service providers (psychiatrist, psychologist, social worker, and psychiatric nurse) and community leaders, aged 18 years or older, working with individuals and families of African, Caribbean, or Black communities, interested in reducing mental illness stigma in Black families and communities in the 5 communities.	Interview guides that explore participants' understanding of mental health and mental illness, the relationship between anti-Black racism and Black mental health, barriers and facilitators in reducing mental illness stigma, and contexts and conditions to promote Black mental health.
Phase three (RO#4): engage a group of Black community members, service providers, cross-sector leaders, decision makers, and community advocates (n=30) in three concept mapping sessions.	Service providers, community leaders, and decision makers in the 5 selected cities who are committed to reducing racial discrimination, anti-Black racism, and mental illness stigma.	We will (1) share and discuss the results of phases 1 and 2, (2) engage every participant in brainstorming, sorting, and ranking essential elements of a best practices model to promote mental health equity in Black families and communities, (3) discuss different configurations of concept maps, decide on a model with priorities, and (4) discuss follow-up action and strategies.

[a]RO: research objective.

[b]FGD: focus group discussion.

[c]IDI: in-depth interview.

Data Analyses Planning

Quantitative and qualitative data will be analyzed separately but interpreted together to deepen the understanding of the interaction between social factors and contexts of community silence on mental health and mental illness stigma. For the quantitative part, we will carry out varied data analyses using statistical software such as SPSS (IBM Corp) to achieve parts of objectives 1, 2, and 3. As preliminary steps, we will conduct univariate analysis to determine the distribution (frequencies and percentages) and measures of central tendencies (eg, mean, median, modes, etc) and dispersion (variance or SD) to capture distributions of sociodemographics (age, gender, relationship status, immigration status, places of birth, employment status, and educational attainment) and other scales (structural and mental health–related factors). As part of the preliminary data analysis process, we will conduct bivariate analysis to determine associations between sociodemographics and social and structural and mental health–related factors (eg, mental health, mental illness stigma, mental health literacy, and discrimination).

The preliminary data analysis process will provide insight into the variables' selection for the final data analyses to achieve objectives 1-3. For objectives 1 and 2, we will use hierarchical linear regression modeling to determine the sociocultural and structural factors (including racism and discrimination) that produce or reproduce and challenge community stigma of mental illness in Black families and communities. Mental illness stigma will be the outcome variable measured by the CAMI scale [61], while sociocultural and structural factors (including racism and discrimination) will be included in the model as predictors. We will control the effect of sociodemographic factors in the model. Similarly, we will use hierarchical linear regression modeling to achieve part of objective 3, that is, to determine the factors associated with mental health in Black families and communities. The outcome variable (mental health) will be measured using DASS-21 [60], and predictor variables will include sociocultural factors, structural factors (including discrimination), and mental health literacy. Discrimination will be measured on the EDS [62] and the MHLq-SVa [63].

For the qualitative data, the voices of study participants informed by critical race and intersectionality theories will be inductively and deductively analyzed and interpreted using NVivo software (Lumivero) after transcription. Inductive thematic analysis, according to Nowell et al [64], offers stronger rigor and a methodical approach to produce meaningful and thought-provoking themes linked to the data without any preexisting coding frame or the investigator's analytic presumptions. Other studies have also found that inductive analysis can be used in a versatile way within mixed-methods design to explore complex social issues [65,66]. The qualitative (focus group and in-depth interview data) analysis will follow Braun and Clarke's [67,68] 6-stage framework for thematic analysis—familiarizing with the data, generating initial codes, searching for themes, reviewing the themes, defining the themes into a model, and writing the research report. Results from phase 1 will be used to engage participants in phase 2 discussions, and the findings from both phases will be integrated at the interpretation phase to inform integrative knowledge translation and concept mapping in phase 3 to cocreate the best practices model. A sketch of this study is shown in Figure 1.

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Figure 1. A sketch of the mixed methods study.

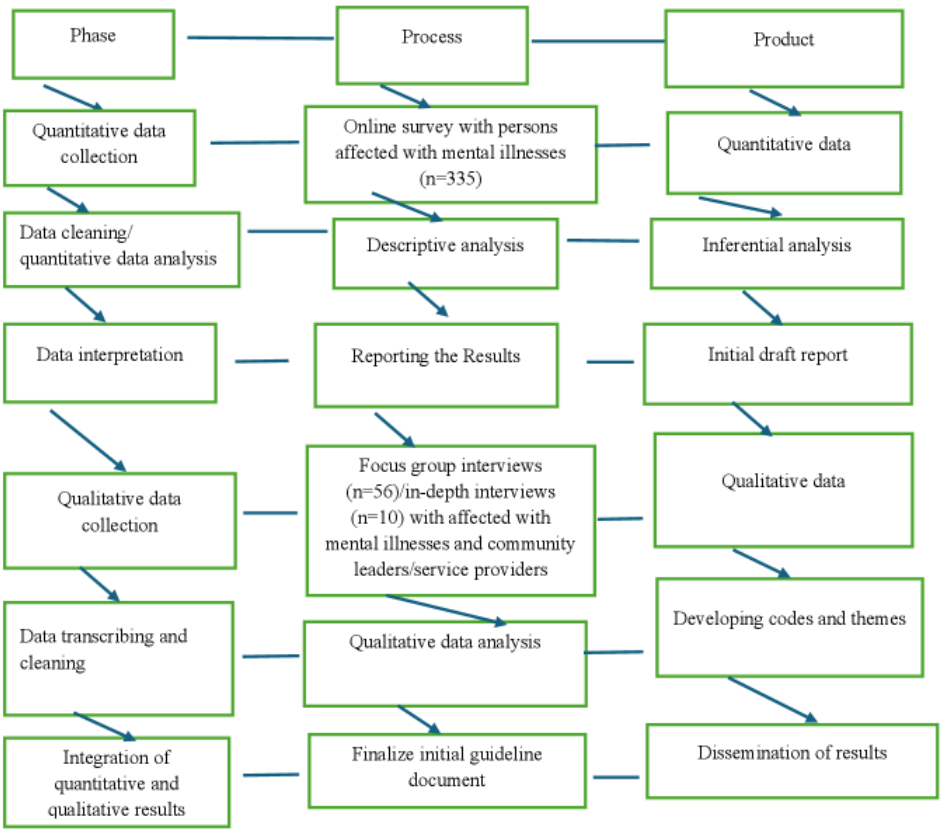

Ethics Approval

The study protocol has been approved by the Research Ethics Board of Toronto Metropolitan University (REB 2024-040).

Results

As of September 2024, the study has received approval in Canada. We have completed data collection for phases 1 and 2 of the study. That is, as of April 2025, the online survey with persons affected with mental illnesses and related stigma (n=335), four focus group discussions with persons affected with mental illnesses and related stigma (n=37), and two group interviews with community leaders and community service providers (n=19) have been completed. All audio recordings have been transcribed and preliminary data analysis is currently ongoing.

Plans are far advanced to start recruitment for phases 3 and 4. Our online survey started in October and ended in December 2024. Data collection for this study ends on July 08, 2025. Results of the study are expected in the last quarter of 2025 and the first quarter of 2026.

Discussion

Overview

This study with Black families and communities aims to generate critical knowledge to reduce mental health disparities, mental illness stigma, and anti-Black racism experienced by Black families and communities, while engaging Black families and communities in cocreating a best practices model to guide policy and programming. The results obtained from the three data sources (ie, quantitative, qualitative, and concept mapping) will form the basis for cocreating a best practices model to address mental illness–related stigma and promote mental health in Black families and communities. This project will be among the first few studies exploring the contextual needs of Black people to address mental health challenges in Black families and communities. While several studies have examined mental health and mental illness–related stigma among Black people in Canada [17,34,69], very few have attempted to co-design a contextual framework to deal with the growing mental health disparities in Black communities [70,71]. We will compare and contrast our findings with other related studies in different jurisdictions in our quest to cocreate a best-practices model that bridges the existing mental health disparity gap between Black and White communities in Canada. The involvement of community leaders and service providers in this study will inspire participants and community members to eagerly endorse and promote interventions and social support networks necessary to sustain the mental well-being of Black families and communities.

Dissemination of Findings

The findings from study will be shared with our community partners, who will disseminate the results through their local and national networks, as well as at Black community events and activities, after all results have been reviewed and approved by both academic and community research advisory committees. The findings will also be disseminated via academic conferences, peer-reviewed publications, and online open-access papers (eg, The Conversation). We will engage with the local

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media to raise awareness of the impact of anti-Black racism on the mental health of Black families and communities based on our findings. In addition, we will generate infographics and distribute them to our research team to share on their social media handles for a wider scope. The infographics will also be shared with policy makers, and further discussions on the study results will be arranged to inform policy decisions. Furthermore, we will share a summary of the results with all participants who requested copies during the project recruitment phase.

Strengths and Limitations

The study's strengths include the use of mixed methods, which could considerably enhance the depth and reliability of our study by combining both qualitative and quantitative strategies. The integrative analytic approach in mixed methods allowed us to address critical research questions more extensively than using a single method. The project team comprised both quantitative and qualitative experts, which paved the way for the exchange of knowledge through mentorship. However, there were some limitations to the project such as the lack of funds and other resources to enroll more people in the study and the inability to monitor the online survey participants. In addition, the use of two approaches for data collection and analysis proved to be time-consuming.

Conclusion

This project will generate a novelty of knowledge that will contribute to effective ways of addressing the stigma of mental illness and promoting mental health literacy in Black families and communities and other vulnerable populations. Also, the new knowledge gained from this study will be taken back to the Black communities to empower affected individuals and their families to promote the needed interventions. We anticipate that the best-practice model cocreated by the project will contribute to research innovation in Canada and beyond.

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Conflicts of Interest

None declared.

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Abbreviations

CAMI: Community Attitudes toward the Mentally Ill
CBAR: community-based action research
DASS-21: Depression, Anxiety and Stress Scale-21 Items
EDS: Everyday Discrimination Scale
GTA: Greater Toronto Area
MHLq-SVa: Mental Health Literacy Questionnaire-Short Version for Adults
RO: research objective

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Protocol

Providing Education and Training to Health Care Professionals to Address COVID-19 Health Disparities: Protocol for Implementation Project Using Reach, Effectiveness, Adoption, Implementation, and Maintenance Framework

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Abstract

Background: The COVID-19 pandemic has underscored the need for targeted interventions to address health care disparities among specific health care professionals and mitigate the impact of the virus. In response, we developed a comprehensive statewide educational program protocol focused on subject areas of health equity, cultural sensitivity, infection prevention and control (IPC), and quality improvement (QI).

Objective: The project aims to improve health care professionals' knowledge and practice skills in the 4 subject areas, increase their comfort level in implementing health disparities-related QI projects, and facilitate the successful completion of QI projects addressing COVID-19 health disparities within their practice settings.

Methods: The Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework was used in the planning and evaluation of this innovative educational program, which combines the Extension for Community Healthcare Outcomes (ECHO) learning model with one-on-one QI coaching. Participants engage in virtual interactive sessions led by experts and consultants, covering didactic presentations, case discussions, COVID-19 updates, and assessments. QI and health equity coaches provide guidance on developing QI projects targeting COVID-19 and other health disparities. Evaluation surveys are used for baseline, midpoint, and end-of-program assessment for self-reported comfort levels with knowledge and practice-based learning competencies in all 4 subject areas and health disparities-related QI project implementation. The Wilcoxon rank-sum test and Cochran-Armitage trend test will be used to compare pre- and postsurvey responses. Data from semistructured qualitative interviews, which capture insights into participants' application of ECHO training, will be analyzed using an inductive content analysis approach.

Results: A total of 50 ECHO sessions were held between November 2021 and May 2024. Overall, 510 participants attended at least one ECHO session, resulting in 3316 teaching encounters. The pre- and postsurvey data will be analyzed to study project impact and will be ready for publication in June 2026.

Conclusions: By using implementation science methods, an innovative and comprehensive educational protocol was developed that integrates the training curriculum, evaluation metrics, and coaching support, allowing for the translation of the training into actionable community projects focused on addressing health disparities. This model has shown initial promise in terms of feasibility and uptake. Further studies are needed to evaluate the long-term effectiveness of these QI projects in reducing COVID-19 disparities.

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KEYWORDS

health disparities; COVID-19; healthcare professional education; quality improvement; cultural sensitivity

Introduction

During the early stages of the COVID-19 pandemic, health care workers in the United States had to quickly familiarize themselves with new guidance related to prevention, diagnosis, treatment, testing, and minimizing the spread of the virus [1]. Preventive strategies included nonpharmaceutical interventions such as mask-wearing, social distancing, and social isolation [1,2]. Despite these concerted efforts to contain the virus, COVID-19 spread and disproportionately impacted marginalized communities. African Americans, Native Americans, and Latinos were overrepresented among cases and deaths from COVID-19 [3,4]. Existing disparities in underlying conditions, known to be associated with COVID-19 mortality, including hypertension, cardiovascular disease, kidney disease, and diabetes, augmented the disproportionate hospitalization and deaths experienced by historically marginalized groups, including communities of color [5]. A meta-analysis of 72 studies (75% of which were from the United States) found that prevalence ratios of COVID-19 were much higher in African American individuals, Hispanic individuals, and those of other races (1.79, 1.78, and 1.43, respectively) than in White individuals (0.70). Higher burdens were also found in hospitalization and mortality ratios for African American individuals, Hispanic individuals, and those of other races than in White individuals [5,6]. Another study examining SARS-CoV-2–associated deaths reported that Latinx American individuals, African American individuals, American Indian individuals, and Alaska Native individuals accounted for approximately 75% of COVID-19 deaths in persons aged less than 21 years [7].

Disparities extended to COVID-19 testing, vaccine implementation, and treatment across various groups and settings [6,8,9]. Racially minoritized and low-income community members were less likely to be tested due to the possibility of lost wages, stigma, and mistrust. A total of 9 rural counties had significantly lower vaccine access and coverage than urban counties [6]. Safety and efficacy concerns made women and African Americans more likely to refuse vaccination [10]. Implicit bias among health care workers resulted in substandard care for people of color and prevented them from proactively seeking testing or timely treatment [6]. The pandemic highlighted the need for health care systems and professionals to recognize, acknowledge, and address health disparities.

Health care professionals who serve marginalized communities face many difficulties, including personal isolation, professional stagnation, excessive workload, and lack of access to consultation and continuing medical education [11]. The University of New Mexico's Project Extension for Community Health Outcomes (ECHO) is an evidence-based telehealth intervention designed as a multidisciplinary virtual team-based educational program to overcome limitations in access to health care for vulnerable populations and individuals in rural areas [11,12]. Participation in Project ECHO improved provider knowledge, self-efficacy, and outcomes in patients with HIV [13], chronic pain [12], and substance use disorder [14].

Our "COVID-19 Disparities ECHO Project" seeks to reduce health disparities among high-risk and underserved populations in Nebraska through a multidisciplinary approach. As a longitudinal multilevel project, the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework is being used to assess the dimensions of the project's reach, efficacy, adoption, implementation, and maintenance. The 19-month program assists health care workers in identifying COVID-19 health disparities, developing targeted strategies to mitigate them by designing and implementing quality improvement (QI) projects, and promoting health equity and cultural sensitivity within their practice settings. There is a paucity of literature demonstrating effective interventions to reduce health disparities among underserved populations. This study protocol provides an in-depth description of the COVID-19 Disparities ECHO Project. It also highlights the rationale for an innovative educational approach that coalesces health equity and cultural sensitivity training with infection prevention and control (IPC) education and QI coaching in addressing COVID-19–related health disparities. Using the Standards for Quality Improvement Reporting Excellence (SQUIRE 2.0) [15] guidelines for QI publication, we describe the study overview, rationale for the study, specific aims, interventions, process and outcome measures, methods for qualitative and quantitative data analyses, ethical considerations, anticipated findings, potential impact, limitations, and future direction.

Methods

Overview of the COVID-19 Disparities ECHO Project

The COVID-19 Disparities ECHO Project is funded by the Nebraska Department of Health and Human Services through a Centers for Disease Control and Prevention (CDC) grant. The logic model assists with the planning, implementation, management, evaluation, and reporting of the COVID-19 Disparities ECHO Program (Textbox 1).

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Textbox 1. Logic model describing the use of the logic model to characterize the inputs leading to the main impact of the Extension for Community Healthcare Outcomes program.

Inputs

- Recruit subject matter experts and consultants.
- Faculty expertise and training resources in four subject areas:
- Quality improvement
- Health EquityA10357
- Cultural sensitivity
- Infection prevention and control
- QI tools to support participants' projects

Activities

- Develop content and curricula for each of the 4 subject areas.
- Build and deliver an integrative curriculum.
- Enroll health care workers.
- Conduct periodic assessments of participants' capability to inform the curriculum and coaching.
- Assist trainees with choosing, implementing, and completing quality improvement projects.

Outcomes

- Improve participants' reported confidence in their training in the 4 subject areas.
- Improve participants' perceived relevance of content from each of the 4 subject areas to their daily work.
- Improve participants' reported comfort with core aspects of infection prevention and control related to COVID-19.
- Improve participants' reported comfort with applying quality improvement principles and tools to their daily work in COVID-19.
- Improve participants' reported comfort with applying health equity frameworks and tools to understand why some populations have been traditionally underserved and are at a higher risk for COVID-19.
- Improve participants' reported comfort with using core principles of cultural sensitivity in their communications with populations that are traditionally underserved and at a higher risk for COVID-19.
- Improved state health department capacity and services to prevent and control COVID-19 infection (or transmission) among populations at high risk and underserved, setting the foundation to address future responses.

Impact

- To eliminate health disparities and improve the well-being of all Nebraskans.

The 19-month program consists of live virtual sessions held twice a month, each lasting 90 minutes. The 38 integrative sessions include 14 presentations on IPC and post–COVID-19 condition, 13 on cultural sensitivity principles, 20 on health equity, and 19 on QI. The presentation topics are adjusted based on the identified needs of the participants and the challenges they face with their QI projects. Participants who attend the sessions regularly and implement a QI project are eligible to receive a certificate of completion ("Health Equity and Quality Management Champion") at the end of the program.

The course materials for the sessions are designed by the project directors and subject matter experts (SMEs) in infectious diseases, QI, and health equity, in partnership with our institution's Center for Continuing Education. The sessions are delivered twice monthly for 90 minutes via videoconferencing. These sessions include short didactic presentations with participant engagement, facilitated by interdisciplinary experts and guest faculty on featured topics. Case studies are used to help participants integrate and apply content from multiple subject areas. COVID-19 updates are also provided to assist learners in implementing best practices related to their health care settings.

Continuing education credits are available for physicians, advanced practice providers, nurses, social workers, and case managers at no cost through our institution's Continuing Education offices. The available credits include the AMA (American Medical Association) PRA Category 1 Credit(s), American Nurses Credentialing Center (ANCC) contact hours, Association of Social Work Boards (ASWB) Approved Continuing Education (ACE) credits, and Pre-Approved Continuing Education (PACE) credits from the Commission for Case Manager Certification.

Project Aims and Objective

The project aims to reduce COVID-19–related health disparities in Nebraska by educating and coaching health care workers in the following four subject areas: IPC, QI, Health Equity, and Cultural Sensitivity. Individual session objectives are developed

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by SMEs on the topics being discussed and are consistent with the program's overall objectives, as outlined in Table 1. Coaching by QI and health equity experts are made available to the participants to assist them in implementing QI programs addressing COVID-19 disparities in their health care settings.

Table 1. The COVID-19 Disparities Extension for Community Healthcare Outcomes Project objectives.

Objectives	Description of objectives
Objective 1	Describe the principles of infection prevention and control and the skills required to implement these in their facilities, including challenges related to infrastructure, risk assessment, testing, contact tracing, vaccination, cleaning and disinfection, PPE[a] usage, hand hygiene, quarantine and isolation, outbreak response, and the long-term complications and management of COVID-19 infection.
Objective 2	Recognize the role of relevant data collection and analyses in better understanding where and how to intervene to improve challenges related to infection prevention and control (eg, vaccine hesitancy, the reluctance to test, etc) for patients who are at higher risk and historically underserved, including communities of color and people living in rural communities.
Objective 3	Design, implement, and learn from changes to infection prevention and control practices in their facilities using the knowledge and skills gained during training to address inequities in COVID-19 prevention, diagnosis, and treatment in their communities.

[a]PPE: personal protective equipment.

The primary outcome measures for the study include a change in self-reported knowledge and practice-based competencies in all 4 subject areas and comfort level in implementing QI projects focused on reducing health disparities. Successful completion of QI projects is also monitored, in addition to self-reported comfort with QI project implementation. The process measures to track the successful implementation of projects include session attendance, participant retention, and initiation of new QI projects.

Project Design and Implementation

Identifying an Implementation Strategy

The COVID-19 Disparity ECHO Project design was guided by the Consolidated Framework for Implementation Research (CFIR) and the Expert Recommendations for Implementing Change (ERIC, Detlev Offenbach) matching tool [16] to identify the implementation strategies necessary for creating a learning collaborative among program participants. One of these strategies is the creation of networks for communication to allow access to knowledge and information concerning COVID-19 disparities [16].

For COVID-19 Disparity ECHO Project to effectively educate health care professionals in COVID-19 prevention and disease management, it must translate into meaningful outcomes. As such, the RE-AIM framework was used in the planning and evaluation of the program [17]. RE-AIM evaluates interventions to optimize external and internal validity by addressing necessary measures for dissemination [18].

Reach

Reach is defined as the absolute number, proportion, and representativeness of individuals willing to participate in the ECHO program from the 93 counties and 19 local health departments in Nebraska.

Effectiveness

Effectiveness is the impact of an intervention on its outcomes. This measure will be evaluated using a mixed-mode approach. Surveys will be used to quantify the change in participants' confidence skills and their intent to apply knowledge gained from the ECHO project. Qualitative interviews will be used to gain in-depth perceptions of the relevance of the ECHO topic areas and their experiences of applying ECHO topics in professional settings using a QI approach.

Adoption

Adoption is the representativeness of settings and intervention agents willing to initiate a program. QI coaching is provided to support QI projects designed by participants.

Implementation

Implementation refers to the intervention agents' fidelity to the various elements of an intervention's protocol. The Center for Continuing Education monitors the credibility of each session.

Maintenance

Maintenance is the extent to which a program or policy becomes institutionalized or part of routine organizational practices and policies. At the individual level, it is defined as the long-term effects of a program on outcomes 6 or more months after the most recent intervention contact. The program cultivates health equity and QI champions who will be equipped at the county, institutional, and regional levels to serve as local resources on these topics.

Participant Recruitment

Nebraska is a largely rural state with many communities (66 of the 93 counties) defined as "medically underserved" [19,20]. To purposefully recruit participants across different health care organizations, the project team uses diversified recruitment techniques to reach organizations and individual health care workers. This includes announcing the training opportunity in various statewide health care facilities and local health department calls, sending emails to known distribution lists, and contacting health care personnel via telephone when the numbers are available. In addition, SMEs use word-of-mouth to recruit health care workers at affiliate organizations.

Participants from health care organizations whose representatives are enrolled in the project are eligible to receive the following benefits: (1) one-on-one coaching on QI and health equity, provided monthly or as requested, to develop and implement approved QI projects, (2) expense reimbursement of up to US $2000 per facility for costs related to their approved QI project, and (3) a certificate of completion from the COVID-19 Disparity ECHO Project recognizing their

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achievement as Health Equity and Quality Management Champion if they regularly participate in the training sessions and completed a QI project.

Curriculum Development

The University of Nebraska Medical Center (UNMC) COVID-19 Disparities ECHO Project team faculty consists of UNMC SMEs who are divided into three teams, each responsible for developing and presenting content in the following subject areas: (1) IPC, (2) QI, and (3) Health Equity and Cultural Sensitivity. Three project directors collaborated with two project consultants to develop a curriculum that balanced and integrated content from all subject areas, focusing on building participants' knowledge of how these subject areas inform and enrich one another. The project consultants served as experts and coaches in their respective areas of expertise and coordinated the contributions of other SMEs within their assigned faculty teams. The curriculum development is designed to be flexible, with a general outline prepared at the beginning of the project. Specific objectives of presentations and their sequence are adjusted based on periodic input from faculty and learners' needs. One of the project consultants serves as the health equity and cultural sensitivity coach, while the other serves as the QI coach for the learners. Both are available to provide one-on-one assistance to learners upon request, outside of regular sessions.

Structuring of ECHO Sessions

The sessions are conducted on Zoom (Zoom Video Communications Inc) [21]. Learners receive an email before each session containing the Zoom login information, a description of the activity, educational objectives, and requirements for successful completion to be eligible for continuing education credit for that particular session. Each session starts with a welcome message, disclosures, and an opening poll, followed by one or two short didactic sessions. A case study/discussion, COVID-19 updates, and a closing poll follow the didactic sessions. The details of these activities are outlined in Table 2. Each ECHO session is recorded, archived, and made available for viewing upon request after each session.

Table 2. General outlines of the COVID-19 Disparities ECHO[a] Project sessions.

Time allocated	Session activity	Description of activity	ECHO team leading the activity
10 minutes	Introduction and disclosures	The sessions begin with introducing the topic and disclosing the presenter's conflicts of interest.	Project manager
10 minutes	Opening poll	Participants are asked to choose one of following four responses regarding their experience in the previous session: (1) I learned something new that I have applied in my work setting, (2) I learned something new that I am planning to apply in my work setting, (3) I was reminded of how I can apply the information I already know in my work setting, and (4) I do not plan to apply this content to my work setting.	Quality improvement team
30 minutes	Didactics	Each session can feature up to two didactics covering one or two of the project's four subject areas. SMEs[b] and guest presenters deliver a short presentation for each didactic. SMEs develop interactive presentations that engage participants through discussion questions, polls, and interactive examples. Topics are selected and paired intentionally to highlight how subject areas contribute to and enrich one another.	SMEs on quality improvement, cultural sensitivity/health equity, and infection prevention or control
20 minutes	Case study or discussion	Each session includes a case study or discussion section which draws on subject matter from the didactics. The project consultants develop these collaborative exercises in collaboration with SMEs to reinforce the connections between subject matter areas.	SMEs on quality improvement, cultural sensitivity/health equity, or infection prevention and control
10 minutes	COVID-19 updates	Updates on COVID-19 in Nebraska are shared, including newly reported cases, hospital admissions, test positivity rates, mortality rates, and vaccination rates for COVID-19.	SME on infection prevention and control
10 minutes	Closing poll	At the conclusion of each session, participants respond to a poll regarding the session's content. Participants are asked to rate their confidence that they could apply that session's content in their work setting with one of the following four responses: Extremely, Moderately, Slightly, and Not at all.	Quality improvement team and project manager

[a]ECHO: Extension for Community Healthcare Outcomes.

[b]SME: subject matter expert.

Facilitating Quality Improvement Projects

The project team envisioned QI as both a subject matter area and a methodology to support participants' learning across all 4 subject matter areas. Year 1 of the project is focused on learning about the critical components of practical QI projects through didactic presentations, case studies, and interactive discussion exercises. During year 2, participants can receive coaching support for a QI project that addresses COVID-19 disparities in their facilities. QI content in year 2 sessions is designed to reinforce and support participation in these QI projects.

QI projects must address one or more areas of need relevant to COVID-19 and health equity (or cultural sensitivity) in their

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communities (Textbox 2). The learners submit QI Project proposals through the REDCap (Research Electronic Data Capture; Vanderbilt University) software [22]. The QI and health equity coaches review the proposals before acceptance. Accepted projects are assessed by the QI faculty team using the Quality Improvement Knowledge Application Tool Revised (QIKAT-R) [23]. The QIKAT-R assesses an individual's ability to decipher a quality problem within a complex system and propose an initiative for improvement.

Textbox 2. The COVID-19 Disparities Extension for Community Healthcare Outcomes (ECHO) project's suggestions of health equity and COVID-19 infectious disease prevention and control topic areas for quality improvement projects.

COVID-19 topic areas (participants' quality projects integrate one topic area from the suggestions of COVID-19 and health equity topics each)

- Vaccination and vaccine support
- Testing
- Contact tracing
- Case investigation
- Quarantine and isolation
- Preventive care and disease management
- The long-term impact of COVID-19
- Personal protective equipment (PPE)
- Non–health care services related to COVID-19 (ie, transportation and food assistance)
- Evidence-based policies or systems (ie, risk assessment, screening, and visitation)
- Environmental strategies (ie, cleaning or disinfection)
- Navigation and support services to address COVID-19 risk and prevention
- Communications about COVID-19 risk and prevention
- Plans for countermeasures and adaption services

Health equity topic areas (participants' quality projects integrate one topic area from the suggestions of COVID-19 and health equity topics each)

- Racial/ethnic identity
- Gender identity
- Sexual orientation
- Neighborhood/physical environment (eg, air/water quality, housing, and violence)
- Economic stability (eg, employment and poverty)
- Citizenship/immigration status
- Education access, quality, and literacy level
- Health care access, quality, and health literacy level
- Social and community context (eg, discrimination, family support, and community support)
- Cultural sensitivity (eg, religious sensitivity)

Data Collection

Monitoring and evaluating outcomes are fundamental to the ECHO model. The COVID-19 Disparities ECHO project used a mixed-mode approach to collect data for planning and assessing continuous learning guided by the RE-AIM Framework.

Quantitative Data

Session Attendance

Participant attendance and retention rates are collected using program registration, session registration, and continuing education claim data.

Session Polls

Participants are asked to respond to two polls—one at the conclusion of each session and another at the beginning of the following session—regarding their satisfaction with the didactic and case presentations, self-reported changes in knowledge, and

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the likelihood of implementing this knowledge (outlined in Table 2 for the session details).

Evaluation Surveys

Evaluation surveys are used for baseline, midpoint, and end-of-program assessment to gauge the program's impact on learning and comfort in implementing that learning in professional settings. While responses are submitted anonymously to protect participant privacy, information on participants' roles, workplaces, and demographic characteristics are collected to assess any differences in program outcomes across these factors. The evaluation surveys included questions on participants' confidence in training received to date in each subject area, perceived relevance of each subject area to their daily work, comfort with a set of knowledge and practice-based competencies in each subject area, and comfort with data collection/analysis and change implementation.

Quality Improvement Project Participation

The number of projects proposed, started, and completed will be counted and analyzed for COVID-19 and the health equity they addressed. The QIKAT-R tool is used to evaluate QI projects on submission, identify areas for improvement, and structure coaching support for participants to improve their ability to charter practical QI projects.

Qualitative Interviews

Qualitative interviews will be used to gather additional data on participants' experience implementing program learning in their workplaces. It consists of structured 30-minute interviews using a standardized protocol (Multimedia Appendix 1) with participants engaged in program sessions regardless of whether they chose to submit a formal QI project. Discussion during interviews focuses on participants' motivations for joining the program, previous experience with QI projects, experience in the program, and what changes they had been able to make or planned to make in their workplaces in each of the 4 subject areas.

Data Analyses

Quantitative Data Analyses

Descriptive statistics, including means, SD, medians, ranges, IQR, counts, and percentages, will be used to summarize pre- and postsurvey responses. Fisher exact test will be applied to compare the distribution of roles and workplaces between pre- and postsurvey participants. To compare pre and post responses, two methods will be used. First, the Wilcoxon rank-sum test will examine differences between the pre- and postsurvey groups across domains and subdomains. In addition, the Cochran-Armitage trend test will be used to compare pre and post responses, treating the data as ordinal categories. Comparisons of domain data stratified by role or workplace will also be performed using the Wilcoxon rank-sum test. All statistical analyses will be conducted using SAS Version 9.4 (SAS Institute), with a P value of <.05 considered statistically significant.

Qualitative Data Analysis

The qualitative data from the interviews will be analyzed using an inductive content analysis approach by 2 individuals. The analysts will first familiarize themselves with the interview transcripts, and then independently code the data by identifying key segments related to participants' motivations, previous experience with QI projects, program experiences, and workplace changes. These codes will be grouped into broader themes, such as barriers to change or motivational factors. These themes will be further compared and refined through discussion and input from a third individual not included in the analysis. The final themes will reflect the participants' experiences and will be interpreted in relation to the project's aims and objectives.

Ethical Considerations

The study was determined to be "Not a Human Subject Research" (due to being a program evaluation for a QI project) by the UNMC institutional review board (0561-23-EX). Formal "Informed Consent" is not required and does not apply to this study as it is a program evaluation for a QI project. All project data are maintained in secured online folders with access limited to the project team members. Only aggregated and/or deidentified data will be shared or reported, and participants will not be identified. No compensation is provided directly to the project participants. However, participants are eligible for claiming free educational credits for their participation in educational sessions. Furthermore, their organization is eligible for expense reimbursement for implementing approved QI projects as part of the training program.

Results

Between November 2021 and May 2023, a total of 38 ECHO sessions (2 sessions per month) were delivered. QI Coaching was provided to 23 participants (representing 15 organizations), who mentioned their interest in initiating a project to address health disparities. A total of 12 additional 60-minute ECHO sessions were organized on a monthly basis between June 2023 to May 2024 to provide ongoing guidance and support for participants already working on their QI projects and to encourage more participants to initiate their own QI projects. That resulted in 22 participants (including 6 new, who did not work on a QI project earlier) reaching out with interest and receiving coaching to work on their QI projects.

Overall, 510 participants attended at least one ECHO session between November 2021 and May 2024 resulting in 3316 teaching encounters. Data related to participants' self-reported comfort level with a core set of knowledge and practice-based competencies in all four subject areas, self-reported comfort with data collection, data analysis and change implementation, attendees' interviews, and QI project implementation will be analyzed to assess the impact of this project and expected to be ready for publication in June 2026.

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Discussion

Overview

This well-attended innovative educational project is expected to improve participants' self-reported knowledge and practice-based competencies in all four subject areas (IPC, QI, health equity, and cultural sensitivity). Participants are also expected to report an increase in their comfort level with implementing QI projects designed to reduce health disparities. Furthermore, QI project participation by the learners is anticipated to result in the completion of a wide range of health equity projects. Qualitative interviews of the participants are expected to provide insights into the factors associated with successful program implementation and the challenges linked to planning and implementing projects focused on reducing health disparities.

There is a critical need to address COVID-19 and other health disparities in rural states with primarily medically underserved and minoritized communities. Like other Midwest states, Nebraska has shown higher COVID-19 mortality rates among Blacks compared with Whites [24,25]. Midwestern states have a history of well-documented racial disparities in education, incarceration, employment, income, health, medical care, homeownership, voting access, wages, and numerous other socioeconomic factors [25,26]. Therefore, beyond understanding IPC principles, health care professionals, who are often the first point of contact for minoritized individuals, require an in-depth understanding of these complex drivers of COVID-19 inequities. Health education must be designed to improve how care is provided in health care settings to cultivate a more profound knowledge of the structural inequities that drive health disparities. The findings from this study are expected not only to highlight the knowledge gap of health care workers related to health equity and cultural sensitivity principles but also to provide evidence that a well-designed educational program can mitigate those gaps.

The ECHO model's use of case-based presentations, supplemented by short didactic presentations by SMEs, has been shown to improve the skills, knowledge, and ability to provide treatment by providers in underserved communities [27]. This model, by its design, addresses one of the most significant health care disparities in predominantly rural states (such as Nebraska), which relates to the lack of access to SMEs in rural communities. Choosing the ECHO model for our training allowed us to connect health care workers from across the state to SMEs in all four subject areas: IPC, health equity, cultural sensitivity, and QI. To address health disparities, health care workers need to have a basic understanding of existing health disparities in their practice areas and the underlying factors responsible for those disparities. SMEs in the area of health equity and cultural sensitivity prepared specific content throughout the training to explain these concepts. They also highlighted the need for health care professionals to gather, review, and analyze relevant data that is essential to gain deeper understanding of health disparities within their own practice settings and communities. QI SMEs provided one-on-one and group coaching, not only on how the participants can analyze the data for health disparities but also on how to set priorities, plan interventions, anticipate challenges, monitor progress, overcome barriers, and engage with relevant stakeholders to address the root causes of targeted health disparities.

Studies conducted before the COVID-19 pandemic highlighted the urgent need for interventions targeting factors that contribute to health care professionals' role in perpetuating health care disparities, such as racial and ethnic biases [28]. Attention to these subjects heightened following the disproportionate burden of the COVID-19 pandemic on minoritized populations. The case-based learning and discussion allow health care workers to understand how health equity and cultural sensitivity concepts directly apply to patient care. Therefore, the ECHO model is well-suited for training health care workers to reduce health disparities. Case-based learning during ECHO sessions has usually been used to discuss individual patient care during educational sessions. We took a modified approach and expanded case-based learning section to include discussions on nonclinical scenarios or focused questions that address broader problems in health care systems relevant to addressing COVID-19 and other health disparities [11,12].

More recently, The Joint Commission has revised the Leadership Standard for ambulatory care organizations, behavioral health care and human services organizations, critical access hospitals, and hospitals to address health care disparities as a quality and safety priority [29]. The COVID-19 Disparity ECHO Project curriculum provides an ideal outline for future educational projects focused on training health care leaders and frontline staff on taking a QI approach to identify and reduce various health care disparities.

The ECHO model has limitations. Traditional ECHO projects are best suited for providing educational tools for direct patient care rather than addressing the organizational and systemic changes needed to tackle COVID-19 disparities. Studies have shown that addressing health disparities requires the development of specific, measurable objectives and implementing strategies that will successfully address those inequities [30]. QI approaches are well-suited for addressing disparities because they offer strategies to target modifiable aspects of care delivery and a method for tailoring or changing an intervention. Integrating QI principles into our curriculum, including the novel approach of one-on-one coaching, assists health care workers in designing and implementing QI projects to reduce health care disparities in their communities. Adding QI and health equity coaches to the traditional ECHO model assists health care workers in applying the knowledge gained through training to their practice. We will gain more insights into this by monitoring the QI projects planned and completed by the participants enrolled in the training program.

While the new and innovative educational design combining the ECHO model with QI coaching and the participation of over 500 learners are strengths of our study, it also has some limitations. This is a single-center study limited to Nebraska and does not include a control group because the project was funded to offer this educational program to all health care professionals in the state. Furthermore, the actual impact of this project on the launch of new QI projects in the state for

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addressing COVID-19 and other health disparities is likely going to be underestimated, as many of the participants will continue to apply the lessons learned from this educational program for years to come. Another limitation is our inability to monitor participants' initiated QI projects for effectiveness in reducing COVID-19 health disparities because of the short follow-up timeframe. However, all QI projects proposed by the participants must be submitted to the project team for review and approval. Participants receive feedback for improvement and structured coaching support to ensure the successful completion of their QI projects, which is tracked as one of the outcome measures of this study. Although we are not able to follow up on the effectiveness of these QI projects in reducing health disparities, participants have received education, coaching, and tools to assist them in monitoring their own program effectiveness. Future studies will need to be conducted to evaluate the long-term effectiveness of these educational project-driven QI projects in reducing COVID-19 health disparities.

Findings from this project will be shared with participants, state and local stakeholders, and the general audience through our website and scientific publications. Future work should focus on evaluating the impact of ECHO training on patient-level outcomes including morbidity and mortality related to COVID-19 and other infectious diseases. In addition, this project model can be adapted in the future to train health care professionals in addressing health disparities related to various other infectious and noninfectious diseases, especially in resource-limited settings.

Conclusions

By using implementation science methods, an innovative and comprehensive educational protocol was developed for health care workers in Nebraska that integrates the training curriculum, evaluation metrics, and coaching support, allowing the translation of the training into actionable health care/community projects focused on addressing health disparities. This model has shown initial promise in terms of feasibility and uptake. Further studies to evaluate the long-term effectiveness of these QI projects in reducing COVID-19 disparities are needed.

Acknowledgments

The authors are grateful for the support and guidance of the University of Nebraska Medical Center-Infectious Diseases (UNMC-ID) subject matter experts in developing the program protocol.

Data Availability

The datasets generated during and/or analyzed during this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

MSA has received investigator-initiated study funding from Merck and Co Inc.

Multimedia Appendix 1
Qualitative interview of the UNMC (University of Nebraska Medical Center) ECHO (Extension for Community Healthcare Outcomes) program.
[PDF File (Adobe PDF File), 13 KB - resprot_v14i1e60901_app1.pdf]

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Abbreviations

ACE: Approved Continuing Education
AMA: American Medical Association
ANCC: American Nurses Credentialing Center
ASWB: Association of Social Work Boards
CDC: Centers for Disease Control and Prevention
CFIR: Consolidated Framework for Implementation Research
ECHO: Extension for Community Healthcare Outcomes
IPC: infection prevention and control
PACE: Pre-Approved Continuing Education
QI: quality improvement
QIKAT-R: Quality Improvement Knowledge Application Tool Revised
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
REDCap: Research Electronic Data Capture
SME: subject matter expert
SQUIRE: Standards for Quality Improvement Reporting Excellence
UNMC: University of Nebraska Medical Center

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Protocol

Examining the Longitudinal Impact of Within- and Between-Day Fluctuations in Food Parenting Practices on Child Dietary Intake: Protocol for a Longitudinal Cohort Study Within a Sample of Preschooler-Parent Dyads

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Abstract

Background: A healthful diet in early childhood is essential for healthy growth and disease prevention. Parents influence children's diets through supportive (eg, structure and autonomy support) and unsupportive (eg, coercive control and indulgence) food parenting practices. Historically, much of this work has focused on parents' "usual" feeding behaviors using survey methods. However, recent studies using ecological momentary assessment methods have allowed assessment of food parenting behaviors in "real time." This work has revealed that the practices used by parents to feed children vary across contexts and are influenced by factors such as stress or time constraints. Research is needed to understand the dynamic nature of food parenting and its impact on children's diets.

Objective: This study aimed to describe the methods and procedures used in the Preschool Plates cohort study, which aimed to (1) describe within- and between-day fluctuations in food parenting practices across time and context, (2) examine the longitudinal impact of within- and between-day fluctuations in food parenting practices on child dietary intake, and (3) identify momentary predictors of within- and between-day fluctuations in food parenting practices across time and context.

Methods: Preschool Plates is a longitudinal cohort study examining the impact of food parenting practices on the dietary intake of 3- to 5-year-old children. A total of 273 parent-preschooler dyads consented and enrolled, and 254 (93%) dyads completed baseline data collection. Dyads will be followed for 2 years using state-of-the-art measures, including an 8-day ecological momentary assessment protocol to assess food parenting, contemporary measures of food parenting, and 3 interview-led 24-hour dietary recalls, collected at baseline, 6 months, 12 months, and 24 months. Child height and weight will be measured at 3 time points.

Results: Recruitment for our baseline sample (N=254) occurred between October 2023 and September 2024. Participants will complete follow-up data collection after 6 months, 12 months, and 24 months. A racially and ethnically diverse cohort was enrolled, with 28.3% (72/254) of enrolled participants identifying as White and 71.7% (182/254) identifying as non-White.

Conclusions: Findings from the proposed study will inform the development of anticipatory guidance for feeding young children and randomized controlled trials designed to intervene on parents' responses to momentary factors to encourage interactions with children around feeding that promote optimal diet quality. For example, findings could inform the development of an ecological

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momentary (ie, real time) intervention that delivers content to participants' mobile devices in response to real-time assessments of context and circumstance.

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KEYWORDS

food parenting practices; dietary intake; preschoolers; nutrition; eating behaviors

Introduction

Background

A healthful diet during early childhood is important for healthy growth and development and helps protect against chronic diseases later in life [1]. Poor diet is a major contributor to chronic diseases, including diabetes, heart disease, stroke, and cancers, accounting for substantial morbidity and mortality [1]. In the last 2 decades, significant public health efforts have been made to improve children's dietary intake [2-4], resulting in only low to moderate improvements in youth diet quality. Currently, more than half of youth consume poor quality diets, failing to meet dietary intake recommendations of the American Heart Association [4-6]. Importantly, significant disparities in diet quality exist across population subgroups, with youth from families with lower household income and food insecurity reporting persistently worse diet quality [4]. Disparities in diet quality during childhood contribute directly to disparities in morbidity and mortality associated with chronic disease across the lifespan [1,4].

Parents are key agents of influence in the dietary intake of their young children. Children's eating behaviors and dietary intake are shaped significantly by their family and home food environment [7-13]. Parents influence their children's eating through their use of food parenting practices [7-9,13]. Food parenting practices include a broad range of goal-directed actions and behaviors that involve what foods are made available and accessible, as well as how parents interact with their children around food [7]. The leading conceptual framework of food parenting, developed by Vaughn et al [7], describes 3 higher-level domains of practices: *structure*, such as food availability, accessibility, and limit setting; *autonomy support*, such as praise and reasoning; and *coercive control*, such as pressure to eat and overt food restriction. *Indulgence* has been proposed to be either a subdomain of structure [7] or a fourth unique high-level domain of potential importance [14,15]; indulgent behaviors allow children greater freedom over what, when, and how much to eat. Current theory and research to date suggest that food parenting practices within the structure and autonomy support domains are "supportive" of healthy eating in children, while the practices within the coercive control and indulgent domains are "unsupportive" [7-9,13]. However, empirical evidence to support the impact of structure and autonomy support practices on child outcomes is much more limited than the evidence base examining the short- and long-term impacts of coercive control practices [7,9].

Understanding momentary impacts on the use of specific food parenting practices is crucial to the future development of interventions aimed at shifting parents' approach to feeding. Although experts generally agree that food parenting practices are goal-directed behaviors sensitive to circumstance, previous studies have typically assessed parents' "usual" use of food parenting via questionnaires. Consequently, scientific understanding of food parenting is based on relatively gross indicators of the dynamic interactions around child feeding that fail to account for potentially important variation across time and contexts [7,16-19]. For example, a parent might report via survey that their "usual" use of coercive feeding practices is low, but when their stress level is high or their child's behavior is challenging, they might pressure children to eat particular foods or place greater restrictions on children's eating.

More recently, researchers have begun using ecological momentary assessment (EMA) to capture food parenting practices, as they unfold in their natural environment across time and context [15,20,21]. Findings from studies by Loth et al [15,20] revealed that most parents used a variety of theoretically supportive and unsupportive food parenting practices on a given day. Furthermore, in qualitative individual interviews, parents of preschoolers described the following momentary factors that influenced their use of specific food parenting practices: parent mood or stress level, child mood, behavior or physical health, time constraints, lack of planning, and competing priorities [14]. Parents in this study described shifting their feeding strategies in response to momentary factors, highlighting the need for more nuanced approaches to investigating within- and between-day variation in food parenting practices [15]. Recent evidence on temporal relationships between such momentary variables (eg, stress and child behavior) and use of food parenting practices supports this perspective [21,22]. This preliminary work demonstrated that momentary influences can shift parents' engagement to food parenting practices that are unsupportive and associated with a higher risk of poor dietary intake over time. Developing an understanding of momentary factors that influence a parent's use of particular food parenting practices across multiple contexts will allow for the development of effective interventions that address the important contexts and momentary factors that influence how parents interact with young children at meals and snacks.

Food parenting practices that support healthy eating in young children have not been fully established. Several gaps exist in the literature on food parenting practices [7,13,19]. First, the bulk of research exploring the impact of food parenting practices on diet-related outcomes has focused on coercive parenting practices [7,8,17]. Research focused on a broad range of food parenting practices is needed, given the broad scope of practices regularly used by parents. For example, many structure and

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autonomy support food parenting practices have received little (eg, guided choices [7]) or no (eg, food preparation [7]) attention in prospective studies. Second, the use and impact of distinct food parenting practices are often explored in isolation, although parents are more likely to use combinations of food parenting practices (eg, rules or limits and food restriction) [14,15,23].

Exploring food parenting practices across all 4 higher-order domains (ie, structure, autonomy support, coercive control, and indulgence), as well as various combinations of practices used, is necessary to tease apart overlapping constructs and behaviors. This approach provides a more nuanced, yet comprehensive, understanding of the impact of food parenting practices on children's eating behaviors and dietary intake than is available in the current literature. Third, the bulk of studies on food parenting practices to date have been cross-sectional [7], making it difficult to draw conclusions about the temporal direction of the associations between food parenting practices and child outcomes, including dietary intake. Longitudinal studies with multiple data collection time points are required to ascertain the long-term impact of various food parenting practices on child dietary intake. Finally, until recently, most studies on food parenting practices have focused on samples that are predominantly White and higher income [7-9,16,17]. Preliminary research conducted within samples with more diversity suggests that families may differ, particularly with regard to race, ethnicity, parental education, or socioeconomic differences, in both the extent to which parents adopt a controlling approach to child feeding and the role that level of control within feeding strategies plays in child weight–related outcomes [22,24-26]. Enrollment of a cohort of parent-child dyads from racially, ethnically, and socioeconomically diverse backgrounds will allow for the exploration of associations of food parenting with child outcomes that are grounded in the cultural contexts of historically underrepresented groups.

Objectives

The objective of this protocol paper is to provide a detailed description of the Preschool Plates cohort study methods. Preschool Plates is a population-based, longitudinal cohort study that was designed to improve upon the rigor of prior studies to advance our understanding of the use and impact of food parenting practices in important ways. Specifically, the Preschool Plates cohort study aims to: (1) describe within- and between-day fluctuations in food parenting practices across time and context, (2) examine the longitudinal impact of within- and between-day fluctuations in food parenting practices on child dietary intake, and (3) identify momentary predictors of within- and between-day fluctuations in food parenting practices across time and context.

Findings from Preschool Plates will deepen our understanding of how clinicians and public health practitioners can best support parents in adopting and maintaining the use of supportive food parenting practices despite momentary day-to-day challenges.

Methods

Study Design and Participants

Preschool Plates is a longitudinal cohort study examining the impact of food parenting practices on the dietary intake of children aged 3 to 5 years. At baseline, a total of 273 parent-preschooler dyads were consented and enrolled, and 254 (93%) dyads completed baseline data collection.

Ethics Approval

Ethics approval was provided by the University of Minnesota Institutional Review Board (00018340). All caregivers provided informed consent, via an e-consent process, before the start of data collection. Due to the children's age (<7 years), assent was not obtained. Once collected, study data are stored in Box Secure Storage, which is a system that is authorized for the use of protected health information. Data included in this protocol paper has been deidentified. Participants were provided with a financial incentive as a way of thanking them for their time and engagement; details on the specific compensation are included below under the subheading Incentives.

Recruitment

Potentially eligible parent-child dyads were identified via MHealth Fairview primary care clinics. MHealth Fairview research services staff used electronic health records to identify current patients that were aged between 3 and 5 years and had been seen in a Fairview clinic within the previous 12 months. Only the parents of patients who had previously consented to being contacted for research studies were mailed a recruitment letter. This letter provided a brief description of the study and included a QR code where participants could provide their contact information and consent to being contacted by the Preschool Plates cohort study team.

A rolling recruitment approach was used, with letters sent to potentially eligible participants in batches until recruitment goals were met. Recruitment for our baseline sample occurred between October 2023 and September 2024. Initially, batches of potentially eligible participants were randomly selected from all potentially eligible participants. As recruitment progressed, targeted recruitment strategies were used with the goal of recruiting a racially and ethnically diverse sample. For a period of time, we intentionally mailed recruitment letters to patients from clinics located in more racially diverse neighborhoods, and at times, we limited mailings to individuals who identified as non-White. For detailed information on the demographics of the baseline sample enrolled, please refer to the Results section of this paper.

After potentially eligible participants indicated an interest in the study and provided consent to be contacted, a member of the Preschool Plates cohort study team reached out to them to complete a full eligibility screening. The inclusion criteria were as follows: (1) the target child aged is aged 3 to 5 years at baseline and lives in the same house as the reporting caregiver for ≥50% of the time, (2) the caregiver is primarily responsible for the child's feeding outside of childcare, (3) the caregiver is able to read and speak English or Spanish, and (4) the child has visited an MHealth Fairview clinic in the previous 12 months.

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The exclusion criteria were as follows: (1) caregiver is aged <18 years; (2) child has a history of major food allergies (eg, peanuts); (3) child uses medication (eg, insulin), has a developmental disability (eg, autism), or has a medical condition (eg, diabetes) that affects food intake and growth; and (4) child is in foster care.

Participants who were determined to be eligible and who remained interested in participating were engaged in the informed consent process over the telephone and scheduled for their baseline visit. Following this telephone conversation, an e-consent form was signed by participants. Figure 1 is a CONSORT (Consolidated Standards of Reporting Trials) diagram that outlines the recruitment, consent, and enrollment process for baseline data collection.

Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flowchart for the Preschool Plates cohort study.

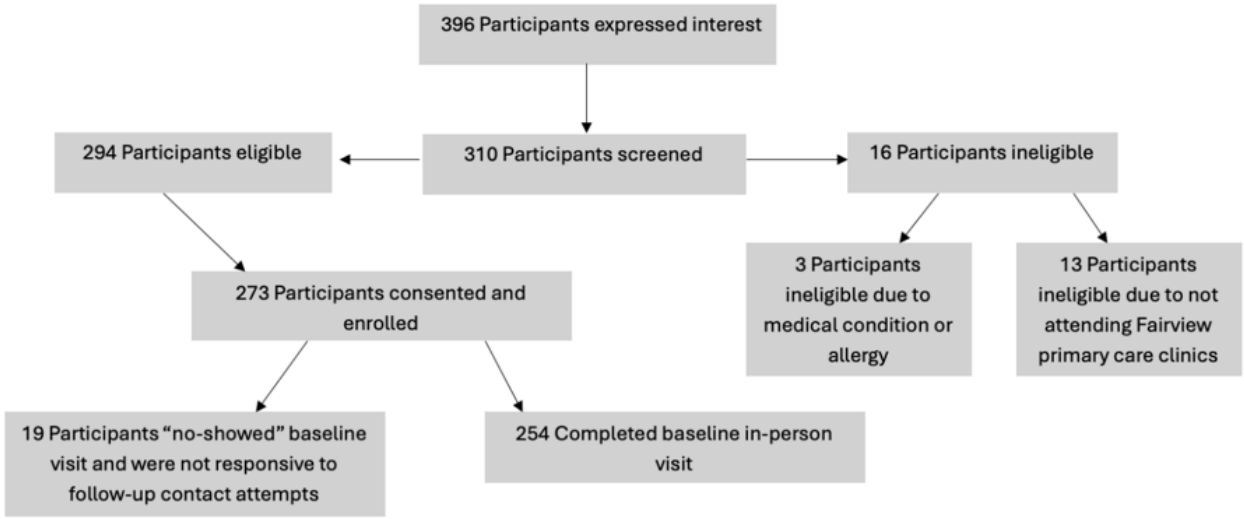

Data Collection Procedures

Overview

During their initial enrollment call, participants were briefed on data collection procedures, engaged in the informed consent process, and were scheduled for the in-person baseline visit.

At the baseline visit, participants received additional details on measurements and the data collection schedule and were trained on protocols for surveys, EMA, and 24-hour dietary recalls. Parents completed the baseline survey at this visit. Finally, height and weight measurements for the child participant were completed at this time. In total, Preschool Plates includes 4 data collection sessions over 2 years: baseline (T1), 6 months (T2), 12 months (T3), and 24 months (T4). T1, T3, and T4 include in-person data collection at the University of Minnesota; T2 includes only remote data collection activities.

At each time point, participants completed a survey to assess usual use of food parenting practices as well as additional parental, household, and environmental factors of interest. They also completed three 24-hour dietary recalls, reporting daily dietary intake on behalf of their child, to assess overall quality of diet and participated in 8 days of EMAs. Children's height and weight were measured by trained study staff at T1, T3, and T4.

All participant-facing study materials were available in English and Spanish. Materials were professionally translated and then further reviewed by bilingual study staff. Bilingual study staff were also employed to engage with participants who were Spanish speaking. Data collection methods and measures for study variables of interest are presented below and summarized in Table 1.

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Table 1. Constructs of interest, study measures, and methods.

Measurement methods and constructs	Description of measure
EMA[a]	
Signal prompts: salient momentary factors	EMA measures of salient momentary factors [14,20,21,27,28]
Event prompts: food parenting practices	Updated version of the Real-Time Parent Feeding Measurement Tool [15] and Child Dietary Intake [29,30]
24-hour dietary recalls: dietary intake	HEI[b] total, component scores: HEI-2015 [31,32] and HEI-2022 [32]
Surveys: food parenting practices	Comprehensive Feeding Practices Questionnaire [33], Food Parenting Inventory [34], Structure and Control in Parent Feeding [35], and Parenting around Snacking Questionnaire [36]
Covariates	
Child-level factors	
Child developmental stage	Ages and Stages Questionnaire [37]
Child temperament	Children's Behavior Questionnaire-Short Form [38]
Mood	Positive and Negative Affect Scale for Children [27,39]
Behavior	Strengths and Difficulties Questionnaire [40,41]
Time spent in day care	Days, hours, and a typical schedule
Parent-level factors	
Parenting style	Parenting Practices Questionnaire [42]
Global and mental health	NIH PROMIS[c] measures [43]
Family-level factors	
Household food security	USDA[d] Food Insecurity 18-item long form [44,45]
Acculturation	Acculturation Rating Scale for Mexican Americans [46]
Household structure	Survey measures to be developed
Demographics (for example, race or ethnicity, and income)	Survey measures to be developed
In-person measurements: height and weight	BMI and weight status

[a]EMA: ecological momentary assessment.

[b]HEI: Healthy Eating Index.

[c]NIH PROMIS: National Institutes of Health Patient-Reported Outcome Measurement Information System.

[d]USDA: United States Department of Agriculture.

Ecological Momentary Assessment

EMAs were used to assess specific food parenting practices used during shared eating occasions, as well as to identify momentary predictors of within- and between-day variability in use of specific food parenting practices.

The EMA protocol included 2 distinct types of assessments. the first was event-contingent assessments; for these, caregivers were asked to complete an EMA survey after every eating occasion during which they were present with the enrolled child. Event-contingent assessments were initiated by caregivers after each shared eating occasion (eg, meals or snacks); caregivers simply used their phone to click on a study-provided link. Event-contingent assessments included questions on food parenting practices and the child's food intake during that specific eating occasion. On average, participants took 4.41 (SD 6.35) minutes and a median of 2.77 minutes (IQR 1.90-4.32) to complete each event prompt. The second was signal-contingent assessments, for which caregivers were texted to complete a survey at random intervals situated within 4 time blocks throughout the day (eg, 7 AM-10 AM) to capture momentary variables of interest. Signal-contingent prompts were timed to expire after 1 hour of receipt of the text prompt. On average, participants took 1.74 (SD 2.71) minutes and a median of 1.22 (IQR 0.85-1.82) minutes to complete each signal prompt.

Caregivers were asked to complete 8 days of EMA data collection. A day was considered to be complete if they engaged in 2 event-contingent and 2 signal-contingent assessments; if a parent failed to complete adequate prompts on a specific day, they were given an additional day to complete the required prompts. At baseline, on average, it took parents 9.667 (SD 3.63 days; median 9.0, IQR 8-10) days to achieve 8 complete days. To minimize potential confounding effects of weekly rhythms (eg, weekday vs weekend variations in behavior, mood, or context), all participants began data collection on the same day of the week. This approach, which followed recommendations in the extant EMA literature [47-50], ensures that each

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participant's data collection period spanned identical calendar days.

Food parenting practices were assessed using an updated version of the EMA-based Real-Time Parent Feeding Practices survey tool [15]. This tool was developed by Loth et al [15] for the Kids EAT! study (described below in the Pilot Study section) to measure the real-time use of a broad range of food parenting practices within an EMA protocol and was updated with additional items for the Preschool Plates cohort study. The modified version of the Real-Time Parent Feeding Practices Assessment tool included 36 questions on food parenting practices situated within 4 higher-level theoretical domains, including structure (14 items), autonomy support (8 items), coercive control (6 items), and indulgent (8 items). Individual questions were designed to measure specific subconstructs, as outlined in the content map of fundamental constructs in food parenting practices by Vaughn et al [7], drawing from existing questionnaires where possible, such as the Child Feeding Questionnaire [18] and the Food Parenting Inventory [34]. These questions were adapted for use within an EMA protocol.

For example, an item on the Child Feeding Questionnaire was designed to measure parental pressure to eat and read, "I have to be especially careful to make sure my child eats enough." This question was adapted for this study to focus on a parent's specific behavior at the most recent meal or snack consumed by their child. The adapted question read, "At this meal or snack, did you have to encourage [your child] to eat more food than they wanted to?" (subconstruct: pressure to eat; higher-order domain: coercive control).

Additional example items within the Real-Time Parent Feeding Practices survey tool included the following:

- "At this meal or snack did you give [child] the choice of several specific options and let the child pick?" (subconstruct: guided choices; higher-order domain: structure)
- "Did you involve your child in helping to plan, purchase or prepare the foods that were served?" (subconstruct: child involvement; higher-order domain: autonomy support)
- "At this meal or snack did you try to avoid conflict by only preparing/serving foods that you knew your child likes/will eat?" (subconstruct: anticipatory catering; higher-order domain: indulgence).

Parents were asked to report on their use of all 36 food parenting practices following each shared eating occasion.

Eating occasion–level child dietary intake was assessed via a measure developed for and validated against the interview-led 24-hour diet recall for use within an EMA protocol [29,30,51]. Parents were asked which categories of foods were eaten by the target child at the eating occasion (yes or no): fruit; vegetables; whole grains (eg, whole grain breads or cereals, brown rice, oatmeal, and corn tortillas); refined grains (eg, white bread or cereals, flour tortillas, white rice, and crackers); dairy (eg, milk, cheese, yogurt, milk alternate such as soy milk, and ice cream); meat protein (eg, chicken, beef, and seafood or fish); beans, eggs, seeds, nuts, and tofu; sugary drinks (eg, pop, Kool-Aid, Capri Sun, Sunny Delight, and sports drinks); cake, cupcakes, cookies, or other baked goods; and candy (eg, sweets, chocolate, Gushers, and fruit snacks). When asked about food served at the meal, participants were also given the following guidance, "For a dish containing multiple foods (e.g. soups, sandwiches and casseroles), please select the main ingredients in the dish." For example, if you had beef and vegetable soup, mark both "meat protein" and "vegetables."

From these responses, 10 individual food categories were created, including fruit, vegetable, whole grain, refined grain, dairy, meat protein, plant protein, sugary drinks, baked goods, and candy. A modified version of the Healthfulness of the Meal Index [29], which was adapted from the Healthy Eating Index (HEI) categories [52], was also calculated. In alignment with prior research, the Healthfulness of the Meal Index was scored using an eaten or not eaten format. For example, an eating occasion received 1 point for the child consuming each of the following foods (fruit, vegetable, whole grain, dairy, meat protein, and plant protein) and 1 point for not eating each of the following foods (refined grains, sugary drinks, baked goods, and candy). Points were then summed with a range of 0 to 10 for each eating occasion. A similar Healthfulness of the Meal Index has been used within studies using EMA protocols to conduct research within similarly diverse populations of children [53]. This measure of eating occasion–level dietary quality provided direct correspondence between food parenting practices used at each eating occasion and types of foods eaten or overall healthfulness of the foods eaten, at the same, or subsequent eating occasions, allowing for an understanding of within-meal, and within-day associations between food parenting practices and dietary quality (refer to hypothesis 3 below in the Results Section).

Momentary predictors were assessed using a combination of items developed and pilot-tested as a part of the Kids EAT! study [15,20], as well as items developed or modified for use within an EMA protocol by others. Parents reported on their current mood [27] and stress level [22], as well as their child's current mood [28], using tools validated for use within a similar population and within an EMA protocol. Finally, additional momentary factors were assessed by asking parents to report on their experience of 12 specific factors identified within previous qualitative research as salient predictors of food parenting practices [14]. For example, parents responded to the following statement regarding how they had felt since the last assessment: "Busy with a number of work or household activities" (responses were evaluated on a 5-point Likert scale, ranging from 1=very slightly or not at all to 5=extremely).

Surveys

The baseline survey was designed to assess usual use of food parenting practices as well as additional parental, household, and environmental factors of interest. Participants completed the same survey at each time point (T1-T4). This survey was administered on the web via REDCap (Research Electronic Data Capture; Vanderbilt University), a secure, web-based data collection platform sponsored by the University of Minnesota and provided by the Clinical Translational Research Institute [39]. Participants took an average of 30 to 45 minutes to complete the survey. To enhance engagement, we incorporated

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visual elements within REDCap, including our Preschool Plates cohort study logo, motivational messages (eg, “Over Halfway Done! Keep it Up!”), and a progress bar to help participants track their completion status.

In the survey, food parenting practices were assessed using subscales from the following 4 questionnaires: Comprehensive Feeding Practices Questionnaire [33], Food Parenting Inventory [34], Structure and Control in Parent Feeding [35], and Parenting around Snacking Questionnaire [36]. In addition, covariates and effect modifiers of interest at the child level (eg, developmental stage [37], temperament [38], mood [39], and hours spent in day care), parent level (eg, parenting style [42] and mental health [43]), family level (eg, acculturation [54] and food insecurity [44,45]), child-level demographics (eg, age, race or ethnicity), parent-level demographics (eg, educational attainment and employment status), and family-level demographics (eg, public assistance, income, and socioeconomic status) were assessed via this survey.

24-Hour Dietary Recalls

Interviewer-led 24-hour dietary recalls were used to assess the quality and quantity of child dietary intake. Three 24-hour dietary recalls were collected for each child participant at baseline (T1) and each follow-up period (T2-T4). General availability to complete recalls was gathered for each participant individually by data collectors during their in-person visit. Participants had the ability to provide their availability for every day of the week, including weekends. Participants were given an 8-day window to complete their recalls, with a hard stop 14 days after their start date. The date and time for recalls were random but based on participants’ provided availability. Recalls were completed by a team of trained and certified staff based out of the Nutrition Coordinating Center using the Data System for Research [55].

A multiple-pass interview technique was used to prompt for a complete food and beverage recall and descriptions. Because preschool-aged children were not considered reliable reporters of dietary intake, recalls were conducted with the index child’s enrolled parent using protocols developed and validated by the Nutrition Coordinating Center for the collection of data on the dietary intake of young children [52]. Parents were provided with multiple resources to assist with dietary intake reporting, including the Food Amounts Booklet (designed for use with young children) to help estimate portion sizes. To reduce missing data and minimize bias from parental assumptions about foods consumed in their absence, we also provided the Foods Fed by Other Adults handout, which could be completed by individuals such as day care providers when the enrolled parent was not present.

Intake for the 3 recalls was averaged across days to create mean scores for intake of food categories of interest (eg, fruits, vegetables, sugary beverages, and salty and sweet snacks). Furthermore, HEI-2022 [32] total and component (eg, added sugars and sodium) scores will be calculated at each data collection time point (T1-T4) using methods designed for estimating overall dietary quality for an individual within an etiologic study, specifically the multivariate Markov chain Monte Carlo approach [56,57]. HEI is a scoring system that was developed to measure the degree to which a diet is consistent with the Dietary Guidelines for Americans and is a valid and reliable measure of diet quality [58]. The closer an HEI score is to 100 (range 0-100), the more aligned it is with the Dietary Guidelines for Americans [58,59]. The HEI-2022 total score is the sum of 13 subcomponent scores that measure adequacy (total fruits, whole fruits, total vegetables, greens and beans, whole grains, dairy, total protein foods, seafood and plant proteins, and fatty acids) and moderation (refined grains, sodium, added sugars, and saturated fats) [32]. This measure of overall dietary quality will help us to understand the longitudinal impact of specific patterns of food parenting on the child’s overall diet quality over time (at 6-month intervals for 2 years; refer to hypothesis 4 in the Results section).

Anthropometric Measurements

At the T1, T3, and T4 data collection visits, child participants’ height and weight were measured by trained study staff following a standardized protocol. For each visit, children were measured using a calibrated digital scale (to the nearest 0.1 kg) and a stadiometer (to the nearest 0.1 cm). Two measurements of height and weight were taken, and if the values differed by >0.5 units, a third measurement was collected. The final recorded values were determined by averaging the 2 closest measurements. All data collectors underwent training on proper measurement techniques, including instructions on positioning the child, ensuring minimal clothing, and verifying equipment calibration [53,54]. Data collectors underwent retraining every quarter. A measurement log was maintained within REDCap to record each measurement and any procedural notes.

In the event a family could not attend the on-campus visit for anthropometric measurements, parent consent was obtained to access the child’s medical records from the MHealth Fairview health system. Children whose data were extracted from electronic health records were required to have seen a health care practitioner within the preceding 6 months.

Retention Efforts

Retention strategies focused on consistent communication to ensure participant engagement and adherence. Participants received regular reminders to complete EMA, dietary recalls, and surveys. Study staff and data collectors were trained to follow up with participants promptly, typically within 1 business day, to address any questions, delays, or noncompliance.

Participants scheduled for in-person visits were contacted via text or phone calls to confirm the date, time, and location. Confirmation emails provided detailed logistical information, including GPS coordinates, parking instructions with photos, and other relevant details. Reminder texts were sent the day before visits to reinforce appointment schedules and logistical information.

Postcards were sent at multiple time points to maintain participant engagement and provide reminders for study activities. Mother’s Day and Father’s Day postcards were sent to all enrolled participants. Annual birthday postcards were mailed to parents and children during the study period. In addition, participants were sent a postcard reminder 2 weeks

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before remote data collection windows (T2) and 1 week before in-person visits (T3 and T4).

Participants returning for in-person visits at T3 received personalized coloring books created by study staff. This coloring book was tailored to the study's preschool-age population and was designed to encourage participant involvement in follow-up visits.

Incentives

Participants were compensated for their time and effort across the 5 data collection periods, with a maximum potential compensation of US $950 over the 2-year study period. At the baseline visit (T1), participants were provided with a Greenphire ClinCard, a reloadable payment card, which was used to distribute incentives throughout the study. Compensation was structured to reflect the time and effort required for specific study components. Surveys were completed at each time point (T1-T4) and were incentivized with US $50. For each set of three 24-hour dietary recalls, participants received US $25 per recall, totaling US $75 per data collection point. Completion of the 8-day EMA protocol was compensated with US $75 per time point. For anthropometric measurements collected in person at T1, T3, and T4, participants received US $50 per visit. If anthropometric data were collected from medical records rather than in person, no payment was provided for that time point's measurement. This incentive structure was designed to equitably compensate participants while encouraging engagement and retention throughout the study.

Pilot Study

Kids EAT! was a National Institutes of Health–funded K23 study (principal investigator: KAL), which used mixed methods (interviews, surveys, and EMA) to explore the real-time use of food parenting practices within a racially, ethnically, and socioeconomically diverse sample of parents of preschool-aged children (n=120) [15,20,60,61]. EMA protocols for Kids EAT! included asking parents to respond to a series of signal- and event-contingent prompts delivered to their smartphones. Results from Kids EAT! demonstrated feasibility in using EMA with parents from diverse backgrounds and collecting data from parents working shift work, during time periods when children were in school or day care, and from parents with differing levels of comfort with technology. The Preschool Plates cohort study protocol used the successful staff training models, data collection protocols, and participant incentive plans used in the Kids EAT! study. Kids EAT! parent participants were successfully engaged in several different data collection approaches similar to those proposed in this study, including web-based surveys and EMA.

Statistical Analysis Plan

Overview

R (R Foundation for Statistical Computing) will be used for data cleaning and main analyses. Distributions of key outcome variables will be assessed and transformed if necessary. Unless otherwise specified, hypothesis tests will be conducted using a 2-sided α level of .05.

EMA responses will be aggregated to derive scores for each of the 4 food parenting practice domains during each data collection period. Given the unequal number of questions related to each domain, 2 versions of domain scores will be created by computing (1) the number of items endorsed in each domain and (2) the proportion of items endorsed in each domain. Domain scores will be calculated for responses given at each event prompt (typically 2-8 per day over each 8-day data collection period).

Food parenting practice domain scores will be aggregated and compared visually and statistically at the event level (eg, breakfast, lunch, snack, and dinner) and by time period (eg, 9 AM to noon, 3 PM-5 PM, and 5 PM-9 PM). In addition, for each data collection period, we will fit linear mixed models for each domain of the form (M1) $D_{ij} = \beta_0 + \beta_1 Z_{ij} + \beta_2 X_i + b_i + \varepsilon_{ij}$, where D_{ij} is the domain score for person i at event prompt j, Z_{ij} is the event characteristic of interest (meal or time period indicator), X_i is a set of baseline characteristics for person i, b_i is a person-specific random effect, and ε_{ij} is the residual. Longitudinal response patterns in domain scores will be visualized and qualitatively compared. We will calculate each individual's SD, IQR, and entropy of domain scores across their longitudinal observations. How between-day fluctuations in food parenting differ across individuals will be quantified using longitudinal mixed models, similar to those described above, with the event characteristics Z_{ij} representing between-day factors such as day of the week. The SD, IQR, and entropy of residuals from these models will also be summarized to characterize between-day fluctuations.

The distribution of the summary measures (SD, IQR, and entropy) of the longitudinal models described above will be used to derive measures of the consistency and endurance of food parenting practices. A metric of within-day consistency across event characteristics (eg, meal type) will be derived by calculating the distribution of SDs of individual residuals from model (M1) and then calculating an individual's z score relative to this distribution. For example, an individual whose food parenting practices fluctuate substantially across meals will have a large SD of residuals relative to the population, so their z score will be relatively large. Consistency z scores will be used as predictors of child dietary intake in aim 2. Endurance will be measured by applying a similar z score approach but with models that incorporate data across multiple data collection periods. For example, model (M1) will be expanded to include data from times T2 to T4, and endurance z scores will be calculated from the distribution of spread summary measures (SD, IQR, and entropy) of the residuals from this expanded model.

Individual food parenting practice domain scores, as well as consistency and endurance metrics, will be used as inputs to a k-means algorithm (implemented using the *kmeans* package in R) to identify clusters of parents observed to use similar food parenting practices over the data collection period. For example, this technique might distinguish subsets of individuals who consistently and primarily use structure and autonomy support practices and those who use these practices less consistently or more commonly use coercive and indulgent practices. We will

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apply the k-means algorithm with a modest number of clusters (3-5) to ensure that the resulting groups are of sufficient size to accurately characterize them. Descriptive statistics will be used to summarize and compare the food parenting practices as well as demographic and family characteristics of each cluster. Cluster stability metrics and qualitative assessment of the scientific meaningfulness of the clusters will be used to choose a final number of clusters that will define subgroups for inclusion in the following analyses.

To examine the longitudinal impact of within- and between-day fluctuations in food parenting practices on child dietary intake, we will fit regression models for the outcome of child HEI measured from 24-hour dietary recall at time points T2 to T4. The main predictors of interest will be the individual-level summary measures of the 4 food parenting practice domains derived above. Our primary models will include the subgroup indicators classifying parents according to food parenting practice patterns, but we will also consider models that use average domain scores as well as consistency and endurance metrics. We will fit separate linear regressions for each data collection period, as well as longitudinal models that incorporate data across the time points T2 to T4. For period-specific models, we will include cluster indicators as well as consistency *z* scores that reflect the degree of within- and between-day fluctuations in food parenting practices during that period, along with relevant adjustment covariates. For longitudinal models, we will also include endurance *z* scores that reflect whether food parenting practices are maintained across data collection periods.

To identify momentary predictors of within- and- between-day fluctuations in the use of food parenting practices across time and context, we will combine the signal and event EMA survey data to understand how momentary factors (eg, mood, stress, and time constraints) affect food parenting practices. The main statistical approach will be to fit longitudinal linear mixed models of the form: (M2) $D_{ij} = \beta_0 + \beta_1 W_{ij} + \beta_2 X_i + b_i + \varepsilon_{ij}$. Here, W_{ij} represents a *vector* of momentary predictors, which will be derived by summarizing signal surveys within fixed time windows before the event *j*. Initially, we will define [illegible], with the superscript in parentheses indicating the number of hours before the event covered by that variable. For instance, [illegible] could reflect the average level of stress reported from signal surveys responded to in the 3 hours preceding the given event survey. We will fit separate models for each domain score during each data collection period; to increase power, we will also fit combined models that incorporate responses across multiple data collection periods. Single-predictor models (involving 1 type of momentary predictor, eg, stress) as well as multipredictor models will be considered. Time windows will be adjusted based on the observed response patterns of data, and if the momentary predictor data are overly sparse, multiple imputation will be used to fill in missing *W*values. In exploratory analyses, we will investigate whether momentary predictors interact with each other or with fixed and summarized individual characteristics (ie, consistency and endurance *z* scores) to impact food parenting practices. This will allow us to explore whether the strength of associations between momentary predictors and food parenting practices varies based on individuals' levels of volatility in these practices.

Some participants may respond sporadically to event prompts, resulting in gaps between event prompt responses, which make it difficult to assess longitudinal patterns. We will begin by characterizing missing data patterns by participant and temporal factors, including the end-of-day prompts asking participants to indicate why they did not respond to prompts on a given day. Then, we will define and analyze a subset of "regularly responding" individuals for which there is sufficient data to characterize between-day fluctuations in food parenting practices, for example, a subset of individuals who have at most 2 days of event prompt nonresponse during their data collection period. To explore overall patterns and associations with non-EMA outcomes, we will augment this regularly responding set with data from individuals with more sporadic response patterns but who, based on their responses to end-of-day prompts, more plausibly have responses missing at random (eg, reported "forgot" rather than "too stressed").

Food parenting practices and their associations with other measures may vary across subgroups defined by, for example, child developmental stage and parent cultural background. While our power to formally test for effect heterogeneity across these subgroups is limited, we will describe these differences by including interaction terms for these subgroups in the regression models described above.

Power Analysis

Given that the goal of this study is to describe patterns and associations and not evaluate a particular intervention, there is no formally defined primary end point. Hence, our power analysis focuses on describing the effect sizes that can plausibly be detected with the given analytic sample size of 200 families (accounting for approximately 20% attrition from our baseline sample).

Key outcomes are the mean levels of the 4 food parenting practice domains. With our sample size, 95% CIs for these means based on the total sample will have a margin of error of +0.17 or –0.17 SDs, corresponding to a small effect size per usual guidance [62]. For the clustering analyses, most participants will have at least 32 longitudinal observations spanning 8 days of data collection. Hence, we anticipate having an adequate sample size to accurately calculate individual summaries of the mean use, consistency, and endurance of food parenting practices, which will be used in the k-means clustering algorithm. To ensure that we can adequately characterize clusters based on demographic characteristics, we plan to restrict our clustering approaches so that they identify no more than 5 clusters, yielding an average cluster size of at least 30 participants; we will also restrict the minimum cluster size to 15 participants.

We calculate the detectable effect size of an analysis comparing mean child HEI between 2 groups of size n=100, for example, comparing families above and below the median of food parenting consistency or endurance. We have 80% power to detect a difference of 0.4 SDs, corresponding to the difference of approximately 4.7 units in total HEI given an HEI SD of 11.6

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units in children aged 2 to 4 years enrolled in the NET-Works study [63]. For comparing 2 groups of size n=50 (eg, quartiles), we will have 80% power to detect a difference of 0.57 SD, or 6.7 HEI units. Power for associations between continuous summary measures of food parenting practices and total HEI will be higher.

The study will yield at least 32 observations per person (4 event or signal responses per day ×8 days), resulting in a total of 6400 data points on each domain. We conducted a simulation to assess the power to detect an association between a binary covariate and a domain score using parameter values informed by data from Kids EAT! [15,20]. For covariates that vary only between individuals, we estimate 80% power to detect a difference of 0.55 items endorsed per signal survey for a given domain. Because the maximum number of possible items endorsed per signal survey ranges from 4 to 7 across domains, an effect of this magnitude seems plausible. For momentary predictors, we have 80% power to detect differences of 0.14 items endorsed per signal survey. In general, power calculations using binary covariates tend to be more conservative than those using continuous covariates; therefore, we anticipate the actual power to be higher than estimated in this simulation.

Results

Overview

Recruitment and data collection began in October 2023. At the time of this protocol paper's submission, data collection is still in progress and is expected to continue through November 2026. A racially and ethnically diverse cohort was successfully enrolled, with 28.3% (72/254) of enrolled participants identifying as White and 71.7% (182/254) identifying as Black, Indigenous, or people of color. Refer to Table 2 for detailed information on the characteristics of the Preschool Plates baseline sample.

Hypotheses

This study hypothesized the following:

1. Use of food parenting practices will vary within- and between-days; unique patterns will emerge across time (eg, time of day and day of week) and context (eg, location and type of eating occasion).
2. Distinct patterns in food parenting approaches will emerge; distinct pattern features will include mean levels of engagement in specific food parenting practices (by domain), as well as consistency in approach across day-, week-, and 6-month intervals, and endurance (or lack thereof) of patterns across time.
3. Healthful eating occasion–level dietary quality (ie, Healthfulness of Meal Index assessed via EMA) will be positively associated with supportive feeding practices (eg, structure and autonomy support) and inversely associated with unsupportive practices (eg, coercive control and indulgent).
4. Consistent and enduring use of supportive feeding practices will be associated with a more healthful overall diet quality (ie, HEI assessed via 24-hour dietary recalls) cross-sectionally and at 2-year follow-up, as compared to inconsistent or short-lived use of supportive practices and consistent and enduring use of unsupportive practices.
5. We expect to identify numerous momentary predictors of significance (eg, mood, stress, child behavior, and time constraints). Parents will shift within the day from supportive feeding practices toward unsupportive feeding practices in response to momentary predictors (eg, high stress, low mood, or limited time).

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Table 2. Characteristics of the Preschool Plates baseline sample (N=254).

Characteristics	Values
Child age (y), mean (SD)	3.48 (0.59)
Child's sex, n (%)	
Male	144 (56.7)
Female	108 (42.5)
Unknown	2 (0.8)
Child's race or ethnicity, n (%)	
Asian	44 (17.3)
Black	42 (16.5)
Hispanic	15 (5.9)
Mixed race	77 (30.3)
Native American	2 (0.8)
White	72 (28.3)
Unknown	2 (0.8)
Parent educational attainment, n (%)	
High school or less	26 (10.2)
Technical college graduate or some college	43 (16.9)
College graduate	78 (30.7)
Graduate degree	107 (42.1)
Parent employment status , n (%)	
Not currently employed	45 (17.7)
Part time (<40 h/wk)	66 (26)
Full time (>40 h/wk)	143 (56.3)
Income (US $), n (%)	
<50,000	51 (20.1)
50,000-74,999	42 (16.5)
75,000-99,999	34 (13.4)
>US $100,000	125 (49.2)
Unknown	2 (0.8)
Participation in ≥1 forms of government assistance, n (%): yes	110 (43.3)

Discussion

Principal Findings

The overarching goal of the Preschool Plates cohort study is to advance the evidence base of food parenting approaches for preventing poor dietary intake among children. We argue that parents' feeding practices vary across time and context and that a deeper understanding of variability and associated outcomes is necessary to inform the design of interventions to help parents consistently use supportive feeding practices despite challenging circumstances. Study findings will shed light on the developmental trajectory of the parent-child feeding relationship and reveal both the short- and long-term effects of food parenting practices on children's dietary intake. Long-term findings will be used to inform the future development of interventions designed to be responsive to momentary factors found to interrupt parents' use of supportive food parenting practices.

Conclusions

To the best of our knowledge, the Preschool Plates cohort study is the most comprehensive study to date to examine the real-time use and the short- and long-term impact of food parenting practices on child dietary intake. Findings will guide the future development of a randomized controlled trial using ecological momentary interventions or a real-time intervention that delivers intervention content to participants' mobile devices in response to real-time assessments of context, behavior, and circumstance, with the goal of improving children's dietary intake and consequently reducing the morbidity and mortality associated with chronic disease across the lifespan.

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Authors' Contributions

KAL contributed to conceptualization, funding acquisition, investigation, methodology, supervision, writing—original draft, and writing—review and editing. JW contributed to conceptualization, formal analysis, funding acquisition, investigation, methodology, supervision, writing—original draft, and writing—review and editing. MB contributed to formal analysis, writing—original draft, and writing—review and editing. NH contributed to project administration, supervision, visualization, writing—original draft, and writing—review and editing. TJB contributed to project administration, writing—original draft, and writing—review and editing. JAF contributed to conceptualization, formal analysis, funding acquisition, investigation, methodology, and writing—review and editing. JOF contributed to conceptualization, formal analysis, funding acquisition, investigation, methodology, and writing—review and editing.

Conflicts of Interest

None declared.

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
EMA: ecological momentary assessment
HEI: Healthy Eating Index
REDCap: Research Electronic Data Capture

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Protocol

A Health Service Research Study on a Low-Threshold Hearing Screening Program for Childhood Cancer Survivors in Switzerland: Protocol for the HEAR Study

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Abstract

Background: Hearing loss is a common late effect in childhood cancer survivors, caused by ototoxic cancer treatments, such as platinum chemotherapy, cranial radiation with doses of ≥30 Gray, and surgery involving the auditory system. Early recognition of hearing loss as part of follow-up care allows for therapeutic support to mitigate consequences. However, hearing tests are usually only repeated in childhood cancer survivors with abnormal hearing during or right after treatment ends, leaving hearing loss undetected in childhood cancer survivors with late onset or when missed during cancer treatment. Further, general follow-up care attendance may be low after childhood cancer survivors transition to adult care, contributing to missing hearing screening posttherapy. Low attendance may be attributed to childhood cancer survivors finding follow-up care burdensome and time-consuming, lacking awareness of their risk for certain late effects, or the absence of suitable interdisciplinary follow-up clinics. A low-threshold, easily accessible screening program requiring minimal participant effort may address these barriers and improve access to hearing loss screening for childhood cancer survivors.

Objective: The HEAR study aims to develop, conduct, and evaluate the feasibility of a low-threshold, community-based screening program for hearing loss in childhood cancer survivors, using the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework, a tool to plan and evaluate health interventions. Within the screening program, participating childhood cancer survivors completed a standardized hearing assessment at a local Swiss hearing aid provider's shop. This approach provides low-threshold access to detect hearing loss as it is easily and conveniently accessible for everyone.

Methods: Eligible childhood cancer survivors were identified through the Childhood Cancer Registry Switzerland and included those diagnosed with cancer between 1976 and 2019 before 21 years and who were ≥2 years post diagnosis. We invited eligible

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childhood cancer survivors by post. Participants scheduled a hearing test appointment at a hearing aid shop. They completed a baseline questionnaire before the hearing test, and 2 follow-up questionnaires afterward to assess program feasibility and participant experiences. Semistructured interviews with participants, hearing aid shop staff, and group discussions with health care professionals will provide qualitative insights. The RE-AIM framework will guide the program evaluation using the quantitative and qualitative data collected.

Results: As of February 2025, all participants have been recruited, and all steps of the study up to the group discussions and the RE-AIM evaluation have been completed.

Conclusions: The HEAR study introduces a novel, simple, and low-threshold approach to screening for hearing loss after cancer treatment through hearing aid shops located in the community and close to participants' homes. This approach has the potential to supplement existing follow-up care programs by reducing the burden of hearing screening for adult childhood cancer survivors and reaching those who might otherwise be lost to follow-up.

Trial Registration: ClinicalTrials.gov NCT06036407; https://clinicaltrials.gov/study/NCT06036407

International Registered Report Identifier (IRRID): DERR1-10.2196/63627

(JMIR Res Protoc 2025;14:e63627) doi:10.2196/63627

KEYWORDS

hearing screening; hearing problems; ototoxicity; platinum compounds; cranial radiotherapy; low-threshold screening; aftercare; childhood cancer survivors; participatory research; long-term follow-up; implementation science

Introduction

One in 10 survivors of childhood cancer experiences hearing loss [1]. Hearing loss is often caused by ototoxic treatments such as platinum chemotherapy, cranial radiation ≥30 Gray, and surgery involving the auditory system [1-3]. Aminoglycoside antibiotics and loop diuretics, commonly used during acute cancer treatment, are also known to have ototoxic effects [4,5]. Other chemotherapeutics, such as vinca alkaloids, have been associated with hearing loss more recently [6,7]. Undetected hearing loss can affect neurocognitive function, language development, school performance, and overall quality of life of childhood cancer survivors [8-11]. In a previous study, we showed that the incidence of self-reported hearing loss in childhood cancer survivors exposed to platinum chemotherapy and cranial radiation increased up to 63% 15 years after treatment [1]. Similarly, a US study found that the cumulative incidence of hearing loss continued to rise with age in medulloblastoma survivors, emphasizing the potential long-term consequences of ototoxic treatments [12]. Regular hearing tests are key for early detection, allowing timely interventions like hearing aids or speech therapy [13]. The International Guideline Harmonization Group for late effects of childhood cancer recommends hearing screening of childhood cancer survivors after treatment with cisplatin (with or without carboplatin) or cranial radiotherapy ≥30 Gray annually for children <6 years, every other year for children aged 6-12 years, and every 5 years from age 12 years onwards [2]. However, we found that in Switzerland, adherence to audiological monitoring in the clinics was insufficient, with one-third of at-risk childhood cancer survivors lacking posttreatment auditory follow-up screening [14].

In Switzerland, different models exist to monitor late effects once childhood cancer survivors leave pediatric care. Childhood cancer survivors may transition to a general practitioner, seek adult hematology/oncology services, or attend a specialized, interdisciplinary follow-up clinic established in some hospitals [15-17]. However, general follow-up care attendance in adult childhood cancer survivors is only around 40% [17-19]. Even when childhood cancer survivors received audiological monitoring after the end of treatment, there remains a risk that those who no longer attend follow-up care may develop late-onset hearing loss, resulting in undetected cases. Low attendance may be the result of childhood cancer survivors lacking awareness of the risk of late effects and long-term follow-up care options, or experiencing follow-up care as burdensome. Especially young adults may be hesitant to take time off work to revisit medical facilities associated with potentially traumatic memories [18,20,21]. Medical costs may pose an additional barrier.

Low-threshold screening programs could prove useful in addressing these challenges [18]. By "low-threshold screening programs" in this context, we mean programs that minimize barriers to participation as they are intended to be easily accessible, require little time and financial resources, and are integrated into familiar, community-based settings. Such programs aim to provide convenient access to simple, yet high-quality medical tests in nearby facilities. Examples of successful low-threshold programs for the general population include hearing tests in hearing aid shops, influenza vaccinations, blood pressure and blood sugar checks in pharmacies, and walk-in clinics for sexual health [22-24]. To our knowledge, there are no low-threshold programs tailored to screen for late effects in childhood cancer survivors. Offering a low-threshold screening program for adult childhood cancer survivors after transitioning from pediatric care may supplement existing follow-up care options, potentially enhancing overall attendance rates.

The HEAR study aimed to develop and assess the feasibility and effectiveness of a low-threshold screening program for detecting hearing loss in childhood cancer survivors. In this study protocol, we provide an overview of the study design, participant identification, data collection, and program evaluation procedures.

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The main objectives of the HEAR study were to (1) develop and pilot a low-threshold community-based screening program for hearing loss among adult childhood cancer survivors in Switzerland, which could supplement existing follow-up care; (2) evaluate the screening program using the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework [25,26]; and (3) assess the feasibility of maintaining or expanding the program.

Methods

Study Population

We identified eligible study participants through the Childhood Cancer Registry Switzerland (ChCR). The ChCR is a national, population-based registry in Switzerland. It includes all individuals diagnosed with leukemia; lymphoma; central nervous system tumor; malignant solid tumor according to the International Classification of Childhood Cancer, third edition; or Langerhans cell histiocytosis before age 21 years since 1976 [27]. Eligible for the HEAR study were childhood cancer survivors registered in the ChCR, who had been diagnosed with childhood cancer between 1976 and 2019, had survived ≥2 years since their diagnosis, were aged ≥18 years at the start of the study, and were at risk for hearing loss (Figure 1). We defined 2 risk groups for hearing loss: The high-risk group included childhood cancer survivors who had been exposed to established ototoxic treatments as defined by the International Guideline Harmonization Group guidelines, namely cisplatin, carboplatin, or cranial radiation ≥30 Gray [28]. The standard-risk group included childhood cancer survivors exposed to other treatments, including any non-platinum-based chemotherapy, radiation to the head with <30 Gray, or neck or spine with any radiation dose. Although these treatments are not explicitly defined as ototoxic, previous studies suggest that these treatments still carry a higher risk of developing hearing loss compared with siblings, likely due to the use of other suspected ototoxic agents such as aminoglycoside antibiotics, loop diuretics, or cerebral spinal fluid shunts [1,29].

Figure 1. Flowchart illustrating eligibility criteria and total invited cohort of childhood cancer survivors for the HEAR study (N=1604). ICCC-3: International Classification of Childhood Cancer, edition 3.

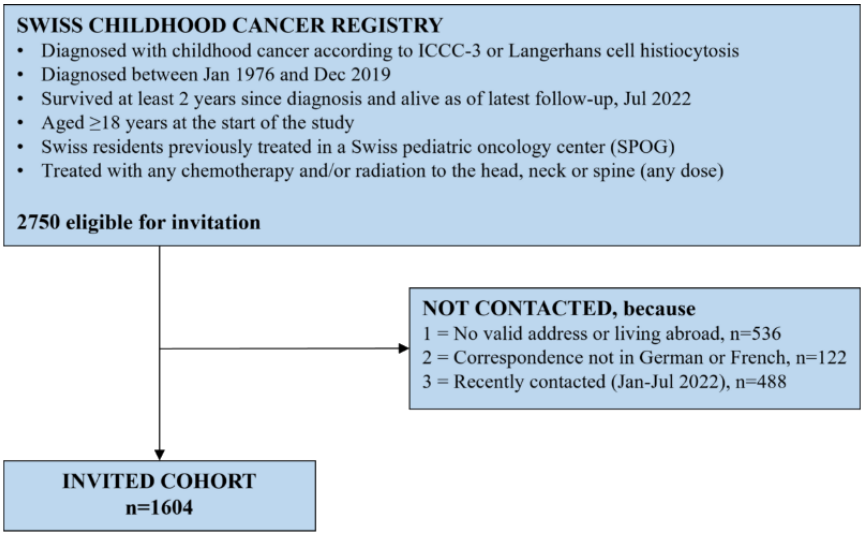

We excluded childhood cancer survivors who had only received radiotherapy to areas other than the head, neck, or spine due to a low risk of developing hearing loss; those who had been treated with surgery only since information regarding the exact surgery location was not readily available in the ChCR; those who did not speak German or French due to limited resources for study material translation; those who had been contacted in the last 6 months for another study (January-June 2022) to avoid overburdening, and those for whom we could not retrieve a valid address or who lived abroad.

Study Design and Study Procedures

Figure 2 illustrates the study procedures. We describe the process in detail in the following.

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Figure 2. Schematic chart of study design and study procedures of the HEAR study. CCS: childhood cancer survivors; ChCR: Childhood Cancer Registry; REDCap: Research Electronic Data Capture.

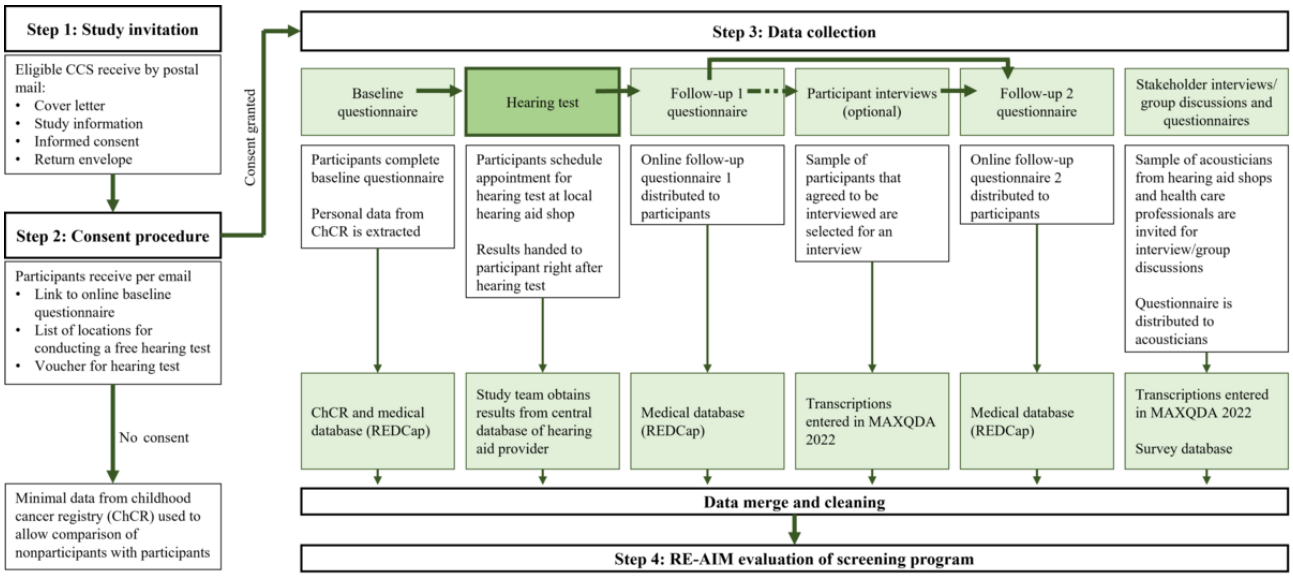

Step 1: Study Invitation

Eligible childhood cancer survivors identified from the ChCR received a cover letter, study information, informed consent, and a prepaid return envelope (Figure 2). We provided contact details (study phone hotline, and email) for questions or comments. Nonresponders received up to 2 written reminders after 3 to 9 weeks based on response patterns and seasonality (eg, avoiding holidays).

Step 2: Consent Procedure

After participants returned the consent form, we invited them by mail to attend a free hearing test at a local hearing aid shop, providing them with a voucher for the hearing test, a list of available shops across Switzerland together with contact information (email and telephone), and a link to complete a baseline questionnaire via a secure web-based platform.

Step 3: Data Collection

Baseline Questionnaire

In the baseline questionnaire, we asked for baseline information about participants' hearing. We sent up to 3 reminder emails, followed by a final reminder letter by regular mail if needed, addressing potential email errors. For details about the baseline questionnaire, see section "Data Collection: Quantitative."

Hearing Test

Participants themselves scheduled an appointment at a hearing aid shop of their choice. The hearing aid shops belong to a hearing aid provider with branches located throughout Switzerland. At the hearing aid shop, a certified acoustician first performed a video otoscopy to examine the condition of the external auditory canal and tympanic membrane. The acoustician then performed a bilateral pure tone audiometry from 125 Hz to 8000 Hz and, for participants with hearing loss >25 decibels, bone conduction from 250 Hz to 4000 Hz. The acoustician handed out and explained the hearing test results to the participants during the same visit. If results were outside the normal range, the acoustician advised participants to contact their family doctor; an ear, nose, and throat specialist; or an audiologist. We offered participants without a medical contact person to contact the study team for assistance in finding appropriate counseling. The hearing aid provider collected the coded audiogram data and digital otoscopy images from all hearing tests on their central database and sent them to us in an encrypted digital form after all participants had completed the hearing tests by the end of July 2023. Data from all locations were pooled for analysis.

Follow-Up 1 and 2 Questionnaires

After the hearing test, we sent participants 2 follow-up questionnaires by mail, a follow-up 1 questionnaire as soon as we got informed that a participant completed a hearing test, and a follow-up 2 questionnaire between 7 and 12 months after the hearing test. For follow-up questionnaires, we sent up to 2 reminder emails. For details about follow-up questionnaires, see section "Data Collection: Quantitative."

Participant Interviews

We also invited a subgroup of participants who expressed interest and completed the follow-up questionnaire 1 for personal interviews. We contacted potential interviewees by email, informing them in detail about the interview process and objectives. Interviewees could choose to participate either via video call or in person. Before the interview, interviewees signed an informed consent form. More details about the interviews can be found in the section "Data Collection: Qualitative."

Stakeholder Interviews/Group Discussions and Questionnaires

After the last participants had visited the hearing aid shops, we interviewed a sample of acousticians who had carried out the hearing tests, and the hearing aid providers' contact person. With the interview outputs, we developed a questionnaire for acousticians to gather insights from a larger sample. We emailed acousticians a link to an anonymous web-based questionnaire.

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We intend to organize group discussions with health care professionals to get input on the screening program from all stakeholders involved.

Step 4: RE-AIM Evaluation of Screening Program

The generated data will be used to evaluate the screening program using the RE-AIM framework [25,26]. We explain the RE-AIM evaluation in more detail in the section "RE-AIM Evaluation Framework."

Ethics Approval

The Ethics Committee of the Canton of Bern, Switzerland, provided ethical approval for this study (KEK-BE 2021-01624). The study was registered at ClinicalTrials.gov (identifier: NCT06036407). Participants provided informed written consent for study participation and permission to obtain the hearing test results from the hearing aid shops to use for research. If any patient declined to participate, their data were not collected, and they could decide to exit the study at any time point. All generated data excluded names or other identifying information. To protect the participants' privacy, the hearing aid shop employees were not informed about the medical history of the participants and were not allowed to ask participants about it during the test. Employees were only informed that participants had been exposed to some treatment in their childhood or adolescence, potentially leading to hearing loss. Further, hearing aid shop employees were not allowed to advertise any products to participants. Participants were not compensated for their efforts. This study protocol has been prepared in accordance with the Standards for Reporting Implementation Studies (StaRI) guidelines [30]. As this is a study protocol, items related to results and findings have not been addressed.

Patient and Public Involvement

For this participatory research project, we set up a stakeholder advisory group with 3 childhood cancer survivors, one of them working for a patient advocate organization, 5 health care professionals, and 2 representatives of the hearing aid provider. We consulted the group regarding the study design and communication with study participants, with a focus on ethical questions, information material for participants, and questionnaire/interview guide development. The advisory group members met repeatedly with the study team to discuss the ongoing study. All study participants had the opportunity to provide feedback in the follow-up questionnaires. The study team regularly reviewed feedback from questionnaires and incorporated it into the ongoing study whenever feasible.

RE-AIM Evaluation Framework

Overview

To assess the feasibility and effectiveness of the screening program, we plan to use the RE-AIM framework, a well-established tool for assessing the public health impact of health interventions [25]. The domains guiding the evaluation are Reach, Effectiveness, Adoption, Implementation, and Maintenance. We will integrate both qualitative and quantitative data sources to evaluate each domain. In the following section, we provide an overview of how we plan to apply the RE-AIM framework to evaluate the screening program.

Reach

Reach measures the extent to which the target population participates in the program. We aim to assess the number and proportion of the invited childhood cancer survivors who accepted the offer of a nearby hearing test and compare their characteristics with nonparticipants, including sex, age at survey and diagnosis, type of diagnosis, risk group, and language region. We intend to use data on clinical information from the ChCR and additional information from questionnaires to characterize participants. We plan to identify motives for participation using questionnaires and personal interviews with participants.

Effectiveness

Effectiveness focuses on evaluating the program's immediate and long-term impact (positive and negative) and whether the program achieves its objectives. Using audiogram results and self-reported information from questionnaires, we plan to analyze the number and proportion of participants with (newly) detected hearing loss, the proportion of those who contacted a physician for further evaluation, and the number of those acquiring a hearing aid after the screening program. Upon comparison to other populations, we will consider age-related differences in hearing loss prevalence. We plan to assess possible other effects of the program through questionnaires and interviews with participants.

Adoption

Adoption assesses the stakeholder's willingness to adopt and implement the program. Through questionnaires and interviews with stakeholders (hearing aid shop employees and health care professionals) and childhood cancer survivors, we plan to explore experiences and satisfaction with the screening program. We intend to assess the number and distribution of shops visited during the study using information from the hearing aid provider.

Implementation

Implementation evaluates the feasibility of implementing the program within real-world contexts, assessing the extent to which the program was delivered consistently and as intended. It also includes an estimation of required resources. We plan to study compliance with the program as well as facilitators and barriers to program implementation through interviews and questionnaires with stakeholders and childhood cancer survivors. We intend to estimate required resources based on information gathered through discussions with the hearing aid provider's contact person and health care providers.

Maintenance

Maintenance investigates the possibility of continuing the program beyond the research project for long-term sustainability. We plan to use data from questionnaires and interviews to get stakeholders' and childhood cancer survivors' insights and to identify necessary requirements and resources for the program's continuation.

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Data Collection: Quantitative

Clinical Data, Otoscopies, and Audiograms

The ChCR provided data on diagnosis; relapse; age at cancer diagnosis; year of cancer diagnosis; therapy type (chemotherapy, radiotherapy, surgery, or hematopoietic stem cell transplantation); cumulative doses of platinum-based chemotherapy (where available); and documented radiation dose (gray) of the field involving the head, neck, and spine. For eligible childhood cancer survivors who did not consent or respond to participate, the ChCR provided minimal data (sex, year of birth, year of diagnosis, cancer diagnosis, and therapy information). We will use this minimal data to compare participants to nonparticipants.

All hearing aid shops followed the same protocol and designated acousticians responsible for the study. The audiometries were carried out by standardized regulations (ISO [International Organization for Standardization] 9001) using audiometers and audiogram software from Natus Medical Incorporated [31]. The measurement equipment (audiogram and hearing test cabin) is subject to the Ordinance of the Federal Department of Justice and Police on Audiometric Measuring Equipment (Audiometry Ordinance) [32].

Study Participants and Acoustician Questionnaires

The information gathered in the interviews and questionnaires should help shape the program so that it can be used as an integral part of care for childhood cancer survivors. The questions within the questionnaires consisted of a combination of multiple-choice and open-ended questionnaire items, with the majority being multiple-choice items that can be statistically analyzed. The open-ended responses provide additional context but are not the primary source of qualitative analysis. For qualitative analysis, the primary sources are individual interviews and group discussions (see section “Data Collection: Qualitative”). Table 1 summarizes the study participants and the acoustician questionnaire’s content (baseline, follow-up 1, follow-up 2, and acoustician).

Table 1. Content summary of questionnaires sent to participants (baseline, follow-up 1, follow-up 2 questionnaires) and acousticians (acoustician questionnaires).

Questionnaire	Content summary
Baseline questionnaire	a. Personal, demographic, and socioeconomic data b. Reasons for participation and expectations c. Follow-up care attendance and perceived late effects of cancer and cancer treatments d. Previous hearing tests and hearing monitoring e. Hearing problems during childhood and at time of survey f. Risk factors for hearing problems g. Tinnitus
Follow-up 1 questionnaire	a. Hearing test experience i. Appointment scheduling, travel duration, transportation means, testing duration, and problems during shop visit ii. Feelings during/after the testing b. Understanding of results and information on how to proceed c. Choice of location of hearing aid shop d. Comparison to previous hearing tests e. Opinions on hearing test opportunity f. Interview participation
Follow-up 2 questionnaire	a. Actions taken after receiving the results b. Intentions to attend future hearing tests c. Facilitators and barriers for hearing tests d. Advantages/disadvantages of different hearing test opportunities (ENT[a] specialist, general practitioner, and hospital) e. Opinion on general follow-up care f. General study feedback
Acoustician questionnaire	a. General experiences with study participants b. Problems encountered during the hearing test c. Information provided to participants d. Differences between study participants and usual customers e. Opinions on the program and on the continuation of it f. Minimal personal demographics (age, gender, and training)

[a]ENT: ear, nose, and throat specialist.

We collected and managed questionnaire data using the REDCap (Research Electronic Data Capture; version 13.7.5; Vanderbilt University) tool hosted at the University of Bern, a secure, web-based software platform to support data capture for research studies [33,34].

Data Collection: Qualitative

Overview

Interviews with study participants and stakeholders facilitated in-depth insights into different perspectives, experiences, and

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opinions on the screening program, allowing a comprehensive program evaluation.

Interviews

We developed semistructured interview guides with input from the stakeholder advisory group and researchers with expertise in qualitative research. The initial guide version served as a fundamental question catalog that we iteratively refined based on feedback and insights from the first few interviews. Changes improved question clarity, sequence, and wording. An overview of the topics discussed in the respective interviewed groups is provided in Table 2.

Table 2. Interview guide content summary for participants and stakeholders (acousticians from the hearing aid shops and health care professionals).

Questionnaire	Content summary
Participant interview	a. Experiences at the hearing test b. Opinions on the screening program c. Advantages/disadvantages of conducting a hearing test in a hearing aid shop compared with more clinical settings (ENT[a], general practitioner, multidisciplinary follow-up clinic, and hospital) d. Preferences when conducting a hearing test e. Experiences with and opinions on general follow-up care f. Feedback on the study
Stakeholder interviews/group discussions	a. Experiences with and opinions on the program b. Challenges or difficulties encountered/anticipated c. For acousticians from hearing aid shops: i. Information provided to participants ii. Differences between usual customers and study participants d. For health care professionals: i. Opinion on this community-based screening program ii. Integration into existing follow-up care e. Opinions on feasibility for continuation beyond the research project f. Necessary requirements and resources for the program's continuation beyond research project

[a]ENT: ear, nose, and throat specialist.

We selected study participants using purposive sampling to ensure a balanced representation across sex, age, risk groups, education level, and language regions (German and French).

For interviews with acousticians, the hearing aid provider's contact person suggested 5 acousticians. Additionally, we invited the hearing aid provider's contact person for an interview.

Group Discussions

For the group discussions, we plan to invite health care professionals from the field of pediatric oncology, follow-up care, and audiology to gather their insights regarding the potential continuation of this screening program to supplement follow-up care for adult childhood cancer survivors in Switzerland. At this stage, we are planning smaller group discussions (n=2-3 participants per group) with pediatric oncologists; ear, nose, and throat specialist; and general practitioners to review the study findings, share experiences with the program, and explore its feasibility, as well as potential strategies for implementation. Depending on the outcomes of these group discussions, we will plan a larger focus group, with the number of people and composition of participants depending on the outcomes of the small group discussions.

Data Analysis: Quantitative

We will conduct quantitative data analysis using STATA (version 16; StataCorp) or RStudio (R Core Team). We plan to use descriptive statistics to assess baseline characteristics of the study population, together with chi-square tests, *t* tests, and analysis of variance for group comparisons.

Data Analysis: Qualitative

We recorded all interviews. A research assistant translated all French interviews into German. We transcribed the recordings verbatim into Microsoft Word before importing them into MAXQDA 2022 (VERBI Software) for detailed analysis. We verified all transcriptions against the audio recordings.

We will use thematic analysis as described by Braun and Clarke [35,36] as a guiding framework for data analysis of interviews and group discussions. Thematic analysis will allow us to systematically identify, analyze, and interpret themes emerging within the data.

As this protocol focuses on describing the study design and methodology, a detailed discussion of the data analysis processes (quantitative and qualitative) will be presented in future publications alongside the study results.

Dissemination

We intend to disseminate research findings via national and international conferences and publications in peer-reviewed journals. We plan to share the study results with the participants in the form of newsletters for a lay audience.

Results

We invited 1604 eligible childhood cancer survivors for study participation and recruited between July 2022 and January 2023. We invited participants to visit hearing aid shops for hearing tests and complete baseline questionnaires until July 2023 and follow-up questionnaires until July 2024. Interviews were

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scheduled between October 2022 and April 2023 for study participants, and between November 2023 and January 2024 for hearing aid shop employees. Group discussions with health care professionals are still in the planning stage; they are planned for early spring 2025. Analysis of quantitative and qualitative results for evaluation of the program using RE-AIM is ongoing.

Discussion

Summary

The HEAR study develops, conducts, and evaluates a new, low-threshold, community-based screening program for detecting hearing loss in adult childhood cancer survivors. Given the increased risk of hearing impairment from ototoxic treatments, the study aims to provide convenient access to high-quality hearing tests at local hearing aid shops, facilitating audiology follow-up care for adult childhood cancer survivors at risk [37,38]. The initiative could be used to supplement existing follow-up care and may serve as a model that could be extended to community-based screening programs for other late effects in adult childhood cancer survivors. The study protocol outlines the design, participant identification, data collection of the study, and program evaluation procedures.

Comparable Screening Programs for Childhood Cancer Survivors

Until now, no other comparable screening program for adult childhood cancer survivors exists to our knowledge. The presented screening program describes a decentralized option for follow-up care in the community outside the conventional medical facility setting. This novel initiative aimed to provide a more approachable option for adult childhood cancer survivors to undergo recommended screenings, broadening the range of follow-up options available to them. The approach taken in this study contributes to the empowerment of childhood cancer survivors, since the low-threshold and low-cost approach gives survivors the choice to have their hearing tested and to decide how they handle the results.

Scaling-Up Potential and Future Vision

Given the widespread presence of hearing aid shops in many parts of the Western world, this program could serve as a model for reaching childhood cancer survivors who may otherwise be lost to follow-up. The approach bears a large potential for scalability. Beyond audiological follow-up care, a similar approach could be extended to address other potential late effects of childhood cancer, such as screening for treatment-induced cataracts [39] in opticians' stores, or diabetes [40], high blood pressure, and hypercholesterinemia [41] in pharmacies.

Study Limitations

Although we aimed for a low-threshold screening approach, the study procedures requested by the ethics committee were the same as for conventional clinical studies, involving detailed information and legal consent forms. Being cognitively overwhelmed by trial information and confused by scientific and legal terminology in the consent form has been found to be a significant barrier to trial participation [42]. These procedures may have counteracted the intended low-threshold approach and may have mitigated the representativeness of the childhood cancer survivors taking part in the program.

The acousticians conducting the audiological evaluations lacked detailed knowledge about the medical history of the participants. This may have hindered their ability to perform a comprehensive audiological evaluation and client service. The results of the questionnaires and interviews with acousticians will allow us to evaluate the impact of this limitation.

There may have been a selection bias in study participation. Those who participated may have been interested in their hearing health, maybe due to existing problems. Childhood cancer survivors uninterested in the topic may have participated less. Further, despite aiming for a low-threshold approach, childhood cancer survivors with limited mobility may have been unable to participate in the screening program. Finally, the program cannot ensure that childhood cancer survivors with identified hearing problems are followed up appropriately in a medical setting, since it is the decision and responsibility of the childhood cancer survivors to organize a medical follow-up visit together with their physician.

Conclusions

The decentralized, low-threshold approach for follow-up care offers an alternative to centralized health care settings and allows adult childhood cancer survivors to access follow-up hearing assessments close to their homes. This approach saves time, reduces potential emotional stress associated with clinic visits, and minimizes health care costs by directing only those with abnormal screening outcomes toward further medical evaluation.

As such, this low-threshold hearing loss screening program for childhood cancer survivors may be a step toward enhancing reach and accessibility for hearing loss screening. If positively evaluated, this could be a valuable opportunity to supplement existing follow-up care, lowering the burden of hearing screening for adult childhood cancer survivors and maybe reaching those who would be otherwise lost to follow-up.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are not publicly available due to ethical restrictions, but are available from the corresponding author on reasonable request.

Authors' Contributions

CK and MA conceived the research idea. SS and LM set up the study and its design under the supervision of and input from CK, MA, MK, GM, NW, NXvdW, ZT, and the stakeholder advisory group. PJ ran the study and drafted the manuscript with the help of CN. All authors reviewed the manuscript, provided critical input, and approved the final version.

Conflicts of Interest

NW reports a relationship with Swedish Orphan Biovitrum AB that includes advisory board membership, consulting, and travel reimbursement. NW reports a relationship with Novartis that includes advisory board membership. None of these relationships are in association with this study.

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Abbreviations

ChCR: Childhood Cancer Registry
ISO: International Organization for Standardization
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
REDCap: Research Electronic Data Capture
StaRI: Standards for Reporting Implementation Studies

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Protocol

Improving Meal Acceptance of Individuals With Autism Spectrum Disorder (AUT-MENU Project): Protocol for a Bicentric Intervention Study

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Abstract

Background: Individuals with autism spectrum disorder (ASD) often exhibit low dietary diversity due to food selectivity, leading to various forms of malnutrition, such as obesity or micronutrient deficiencies.

Objective: The main objective of the AUT-MENU project is to improve meal acceptance among individuals with ASD. A secondary goal is to evaluate the effectiveness of a nutrition education course for parents of enrolled participants to reduce food selectivity.

Methods: The study is a bicentric intervention conducted in 3 care centers (Pavia and Milan) and 1 secondary school (Rome), involving approximately 200 participants with ASD aged 3 to 35 years. The study consists of an observational phase (T0) and an intervention phase (T1). At T0, biographical data, clinical characteristics, and dietary patterns of participants are collected. Based on T0 findings and existing nutritional recommendations for individuals with ASD, targeted menus are developed and tested. At T1, the same assessment tools used at T0 will be applied to evaluate intervention effects. Additionally, a nutrition education course for caregivers will be implemented between T0 and T1, with a pre- and postcourse knowledge questionnaire to assess its effectiveness.

Results: Due to different timelines depending on the centers and schools involved, participant enrollment and data collection will take place at different times between Pavia, Milan, and Rome. In September 2024, enrollment was held in the Pavia and Milan care centers for a total of 74 participants enrolled. In Rome, the enrollment phase has not yet started; activities are expected to be carried out similar to those in Pavia and Milan.

Conclusions: The AUT-MENU study is expected to yield significant insights and improvements in meal acceptance among individuals with ASD, particularly through the introduction of targeted menus in collective catering settings both in care centers and schools.

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KEYWORDS

autism spectrum disorder; collective catering; parent training; nutrition; food selectivity

Introduction

Background

In recent years, the scientific community has placed particular emphasis on investigating and elucidating the feeding-related behaviors of individuals diagnosed with autism spectrum disorder (ASD). Research has highlighted the rituals related to mealtime that are frequently observed among this population [1].

Individuals with ASD commonly present various feeding challenges, including food refusal, limited food intake, and behavioral difficulties during mealtime [2,3], which results in imbalanced food habits [4]. These challenges fall under the umbrella term of food selectivity (FS), a term also referred to in the literature as "picky eating" and "fussy eating" [4]. Specifically, FS is characterized by the rejection of specific types of food, whether familiar or unfamiliar, often refusing more foods than they accept [5]. This selectivity may involve entire food groups, such as fruits and vegetables, or foods that share specific sensory characteristics, including taste, texture, or odor. When FS persists over time, the individual can be classified as "picky eater," which may impact dietary variety and nutritional intake [5].

Valenzuela-Zamora et al [3] reported a prevalence of 23% to 69% for FS among a sample of 247 children with ASD aged 2-18 years compared with 267 children with neurotypical condition, where the prevalence ranges from 1% to 37%.

Specifically, individuals with ASD and FS tend to gravitate toward foods with soft or semiliquid textures, pale hues, mild flavors, homogeneity of hues within the same dish, and dishes containing ingredients of similar, noncontrasting color tones, while they show reluctance toward foods that are bitter, sour, or spicy. Additionally, they often avoid strong colors, strong odors, and high temperatures, leading to the exclusion of entire food groups [1,6] (eg, canned fish or vegetables such as broccoli and cauliflower). Moreover, individuals with ASD exhibit a notable preference for processed foods high in energy, simple sugars, saturated fats, and salt but deficient in essential minerals and vitamins [1]. Such preferences may contribute to an increased risk of becoming overweight or developing obesity and micronutrient deficiencies [2].

In certain instances, it is possible to pinpoint physiological factors that directly or indirectly contribute to these distinct feeding challenges, such as compromised sensory processing, issues in oral motor skills (chewing and swallowing), and gastrointestinal disorders [4]. Conversely, when identifiable organic factors are absent, FS may be interpreted as an expression of the restricted interests and behavioral inflexibility frequently linked with ASD [4].

The evolution of feeding challenges with age remains a subject of contention in the literature. In the systematic review by Page et al [7], 7 studies are included, exploring the relationship between age and feeding difficulties. Among these studies, only 3 indicate amelioration in eating challenges over time, regardless of interventions specifically addressing FS [7]. Specifically, these 3 studies followed a cross-sectional model. Beighley et al [8] found that FS, defined as "will eat only certain food," decreased with increasing age. Gray et al [9] compared eating behaviors among children with ASD from childhood to adolescence and found that parents reported that picky eating decreased and eating a variety of foods increased from early childhood to adolescence. Finally, Bandini et al [10] found that food refusal declined with age, but there was no significant change in food repertoire over the 6-year period.

Considering what has been described so far, the delicate nature of mealtime for individuals with ASD is clear, and it highlights the challenges of managing FS attitudes both in domestic and collective catering settings. Acting in the household environment may present a crucial window of opportunity since family mealtime is described by most parents as stressful and frustrating. Moreover, parents or caregivers may unintentionally exacerbate meal-related anxiety and stress through nonfunctional attitudes [2,11-13]. Therefore, it is essential to provide caregivers with valuable information to address the challenges that arise during these moments. The organization "Autism Speaks" has released the document "Parent's Guide to Feeding Behavior in Children With Autism" [14], suggesting simple strategies that can be easily implemented at the domestic level.

Collective catering is a critical setting too, as many adults with ASD consume their meals in the care centers where they reside, while children and adolescents have at least 1 meal a day at school. This setting opens a potential opportunity for intervention that, if properly exploited, can enable an improvement in the nutritional status of individuals with ASD through specifically formulated menus, leading to a cascade of beneficial effects on their health [1]. There are currently no specific guidelines about how to customize collective catering menus for participants with ASD in Italy. In fact, due to the specificity of the target population and the complexity of working with individuals affected by ASD, no multicenter studies aimed at improving food acceptance have so far been carried out on large groups across different age ranges.

The authors designed and conducted a pilot study, the FOOD-AUT project [6], in which canteen menus were adapted to meet the nutritional and sensory needs of adults with ASD, with the aim of reducing their FS and consequently improving their health. The study involved 22 participants and focused on adapting meals based on key sensory characteristics, such as texture, color, and shape, to enhance food acceptance. The results showed that personalized meal modifications could positively influence dietary variety and meal consumption in individuals with ASD. Since the pilot study was conducted in a single setting with a limited sample size, this study, the AUT-MENU project (improving the meal acceptance of participants with ASD), aims to extend the same model to multiple contexts, including care facilities and schools, to further evaluate its effectiveness. This broader implementation will

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strengthen the dataset and provide more robust evidence, ultimately supporting the development of specific dietary guidelines for collective catering services tailored to individuals with ASD.

Study Objectives

Primary Objectives

The primary objective of the AUT-MENU project is to assess meal consumption among individuals with ASD in collective catering settings both quantitatively (eg, portion intake) and qualitatively (eg, sensory characteristics influencing food acceptance, such as texture, color, smell, and shape). Based on these findings and existing dietary guidelines for individuals with ASD [1,6], the project aims to improve meal acceptance by adapting the proposed meals accordingly.

Secondary Objectives

The secondary objective is to evaluate the feasibility of a structured nutrition and behavioral education program for parents and caregivers of enrolled participants. This intervention aims to improve parents' knowledge on FS and meal experience at home, complementing the modifications implemented in the collective catering settings.

Methods

Study Overview

The AUT-MENU study is a single-arm pre- and postbicentric intervention study (without control). The study is conducted by a multidisciplinary team consisting of researchers from the Laboratory of Dietetics and Clinical Nutrition of the University of Pavia and the Research Centre for Food and Nutrition of Rome.

Setting

Overview

The study is being conducted in 2 different regions of Italy. In the northern region, 3 care centers have been involved: Tiglio Fondazione Onlus in Pavia, Dosso Verde in Milan, and Dosso Verde in Pavia. In the central region, the study is taking place in 1 high school in Rome: the "Giuseppe Garibaldi" Agricultural Technical Institute.

Tiglio Fondazione Onlus

Fondazione Tiglio is a nonprofit organization active since 2004. The center offers a range of residential and nonresidential services specifically designed for young adults or adults (≥18 years) with severe or profound intellectual, physical, and sensory disabilities as well as neurodevelopmental disorders (eg, autism). These services include educational, assistive, socio-health care support, work training, and recreational-cultural activities. The facility also provides an external catering service that offers a complete lunch for the users.

Dosso Verde Institute

The Dosso Verde Institute is a Neuropsychiatric Rehabilitation and Psychotherapy Center for Developmental Age. Founded in 1962, the institute provides residential, day, and outpatient services for minors (<18 years) with neurodevelopmental disorders, particularly ASD and intellectual disabilities as well as emotional and behavioral disorders, childhood and adolescent mental health issues, and learning disabilities. The Dosso Verde Institute has facilities in both Pavia and Milan. In the Pavia center, an external catering service is provided, while in Milan, meals are supplied by the internal kitchen of the primary school housed within the same building, "Regina Mundi."

"Giuseppe Garibaldi" Agricultural Technical Institute

The "Giuseppe Garibaldi" Agricultural Technical Institute is a secondary school in Rome, established in 1872. The institute is dedicated to training agricultural experts and technicians knowledgeable in the natural environment. The institute is also home to a boarding school, which accommodates students, including those from nearby schools, who come from distant areas and offers a semiboarding option with lunch services and afternoon study sessions. In the school, meals are prepared daily by a collective catering company.

Ethical Considerations

This study was approved by the Ethics Committee of the Department of the Nervous System and Behavioral Sciences in January 2024 (approval 155/23). The study adheres to all institutional guidelines and ethical principles outlined in the Declaration of Helsinki. Parents or legal guardians of all participants provided written informed consent before enrollment. They will receive detailed explanations regarding the study objectives, procedures, and potential risks and benefits. Participants will have the right to withdraw from the study at any time without consequences. All collected data will be anonymized and deidentified to protect participant privacy. Identifiable information will be securely stored and accessed only by authorized research personnel. Data will be reported in an aggregate format, ensuring that individual participants cannot be identified.

Selection Criteria

The target population for the study adheres to the inclusion and exclusion criteria listed in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Presence in medical records of a diagnosis of autism spectrum disorder (ASD; according to DSM-5 [Diagnostic and Statistical Manual of Mental Disorders {Fifth Edition}] diagnostic criteria) including all the 3 severity levels [15].
- Being a patient of Tiglio Fondazione Onlus in Pavia, Dosso Verde in Milan, and Dosso Verde in Pavia or a student of "Giuseppe Garibaldi" Agricultural Technical Institute in Rome.
- Children and adolescents aged 3 to 17 years from the Dosso Verde centers in Milan and Pavia, young adults aged 18 to 35 years from Tiglio Fondazione Onlus (Pavia), and high school students aged 14 to 19 years from the secondary school "Giuseppe Garibaldi" Agricultural Technical Institute.
- Signed informed consent from parents or legal guardians is required for each respondent.

Exclusion criteria

- Participants who are unable to feed themselves independently due to physical or cognitive impairments.
- Participants with allergies, intolerances, or conditions requiring a specialized diet.
- Participants with other neurological or medical conditions (eg, diabetes and epilepsy) that may affect food consumption or require specific medical attention, excluding ASD.

Recruitment

In Pavia and Milan, care centers with collective catering services were selected, while in Rome, schools offering afternoon activities—including lunch—were chosen. Researchers directly contacted care centers for individuals with ASD and schools offering lunch to present the project. Interested centers in Pavia and a high school in Rome participated in multilevel project presentation sessions. Initially, events targeted health care professionals (child neuropsychiatrists, therapists, and educators) and school staff, followed by meetings with parents. These sessions informed and trained professionals who would act as project supporters and addressed parents' questions. During parent meetings, informed and privacy consent were collected from parents or legal guardians.

Study Design

Overview

The study will last 36 months (November 2022-2025), including a 12-month experimental phase, from September 2024 until September 2025. Figure 1 shows the study timeline.

Figure 1. Study timeline. CREA: Research Centre for Food and Nutrition; CRF: case report form.

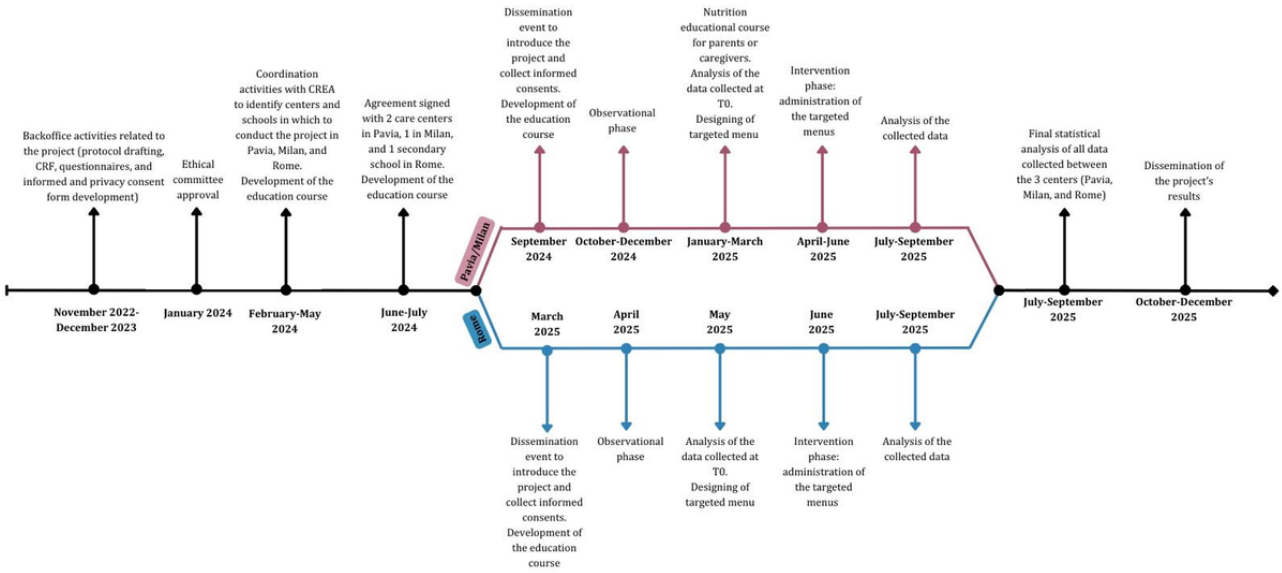

Meal Assessment and Menu Adaptation

The study was structured into 3 main phases: scouting, observation, and intervention. After enrolling the participating centers, researchers conducted a preliminary scouting phase by visiting care centers and schools to gain an in-depth understanding of lunchtime dynamics. This phase involved analyzing food service methods, types of cutlery used, staff interaction with participants, and portion sizes served. Based on these observations, portion sizes were standardized according to age groups to ensure consistency in meal assessment and prevent potential biases in data collection. The observation phase (T0) aimed to assess food consumption from standard menus during lunchtime, focusing on both quantity and quality aspects such as sensory characteristics such as shape, color, smell or taste, texture, and temperature. To systematically

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evaluate these aspects, the pictorial dietary assessment tool (PDAT) was used [16]. Each enrolled participant's meal was assessed over 3 nonconsecutive days within a 4-week period, with additional sessions scheduled for those absent to ensure complete data collection. A total of 12 PDATs were collected for each participant. To minimize observer influence and reduce bias, researchers passively observed the participants during lunch without direct interaction. They were responsible for completing the PDATs based on observed consumption patterns. To enhance the accuracy of qualitative data, researchers also tasted and photographed each dish to capture its sensory characteristics comprehensively. At the end of each survey day, the research team convened to align on the organoleptic properties of the meals, ensuring consistency in data interpretation. Data entry was performed daily by 3 researchers (CB, SB, and IZ), who decoded the PDATs using a predefined classification system and entered the information into a Microsoft Excel spreadsheet for further analysis. The collected data will serve to compare consumption patterns with sensory characteristics in order to identify key factors influencing meal acceptance. This information will then be used to collaborate with mass catering companies to create dishes aligned with the preferences of individuals with ASD. The authors expect that the sensory modifications will align with those implemented during the FOOD AUT pilot study [6], specifically short pasta shapes (eg, bucatini, penne, orecchiette, and farfalle); foods with low-intensity colors, such as white and beige; uniform hues within the same dish; dishes composed of ingredients with similar, noncontrasting color tones; vegetables that are more readily accepted than orange ones; soft or semisoft textures, avoiding foods that are difficult to chew; mild, nonpungent odors, avoiding strong-smelling foods like certain fish species (eg, mackerel); and delicate flavors, avoiding bitterness and sourness, with reduced use of strong spices, garlic, and onion.

However, the authors consider that having a larger sample than in the pilot study, the most accepted sensory characteristics might be slightly different. The intervention phase (T1) will involve introducing these modified menus and repeating the same assessment process used during T0. Each enrolled participant will undergo the same PDAT-based evaluation over 12 meals to determine whether the targeted menus are better received and lead to increased food consumption.

Nutrition Education Course for Parents and Caregivers

Between the T0 and T1 phases, a digital nutrition education course will be offered to subgroups of parents and caregivers of enrolled participants in the Milan and Pavia centers. The course aims to reduce meal-related behavioral difficulties, including FS in individuals with ASD. Participation will be voluntary, following an informational session on the project's objectives. Designed based on healthy eating guidelines and scientific literature on ASD and nutrition, the course is led by a multidisciplinary team, including a dietitian, nutrition biologists, speech therapists, and a psychologist. It consists of 7 modules delivered through weekly 1-hour sessions, integrating theoretical explanations with practical demonstrations using videos, images, and digital activities. The topics covered in the modules are as follows:

- Module 1: the role of nutrition on health and macro- and micronutrients.
- Module 2: FS: associated factors and consequences.
- Module 3: healthy plate tailored to the needs of individuals with ASD.
- Module 4: behavioral strategies for the consumption of nonpreferred foods.
- Module 5: sensory strategies for the consumption of nonpreferred foods.
- Module 6: environment and meal presentation.
- Module 7: mother-child relationship.

To assess the course's impact and feasibility, specific evaluation tools (detailed in the following section) will be used, along with the recording of attrition rates throughout the program.

Data Collection

Overview

Details of data collected from both participants and their families throughout the study period are presented in the following subsections and summarized in Table 1. Data regarding sociodemographic information, food habits, and feeding behaviors during mealtime were collected through 20- or 25-minute telephone interviews, conducted by a researcher. Data entry is carried out in parallel with data collection, through the daily entry of anonymized data into a preset database.

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Table 1. Summary of data collection tools.

Tool	Evaluated aspects	Addressed to	Filled out by	T0	T1
CRF[a]	General information of enrolled participants and their families	Parents or caregivers	Researcher (telephone interview)	✓	
KIDMED[b] [17] (3-24 years) and MEDQS[c] [18] (25-35 years)	Food habits and adherence to the Mediterranean diet	Parents or caregivers	Researcher (telephone interview)	✓	
BAMBI[d] [19] (3-11 years) and STEP[e] [20] (12-35 years)	Risk of food selectivity	Parents or caregivers	Researcher (telephone interview)	✓	
PDTA[f] [16]	Quantitative and qualitative food consumption	Enrolled participants	Researchers (in presence)	✓	✓
Nutrition knowledge questionnaire	Nutrition course knowledge	Parents or caregivers	Researcher (telephone interview)	Before and after the course	Before and after the course
Satisfaction questionnaire	Nutrition course satisfaction	Parents or caregivers	Researcher (telephone interview)	After the course	After the course

[a]CRF: case report form.

[b]KIDMED: Mediterranean Diet Quality Index for Children and Adolescents.

[c]MEDQS: New Validated Short Questionnaire for the Evaluation of the Adherence of Mediterranean Diet and Nutrition Sustainability in all adult population groups.

[d]BAMBI: Brief Autism Mealtime Behavior Inventory.

[e]STEP: Screening Tool of Feeding Problems.

[f]PDAT: pictorial dietary assessment tool.

Sociodemographic Information

Sociodemographic and socioeconomic information of the participants were collected at T0 in a case report form (Multimedia Appendix 1), which was divided into 2 parts. The first part collects data about the participants with ASD: gender, age, ethnicity, and clinical information (drug therapy, therapeutic paths, anthropometric measurements, and blood values), while the second part of the questionnaire aims to gather information about the primary parent, collecting marital status, age, ethnicity, educational level, and therapeutic approaches for managing FS.

Food Habits

Information regarding the food habits was assessed at T0. Specifically, the Mediterranean Diet Quality Index for Children and Adolescents questionnaire [17] and the New Validated Short Questionnaire for the Evaluation of the Adherence of Mediterranean Diet and Nutrition Sustainability in all adult population groups questionnaire [18] (Multimedia Appendices 2 and 3, respectively) were used to assess adherence to the Mediterranean diet and to get an overview of the consumption of the main food groups (fruits, vegetables, pasta and cereals, legumes, fish, meat, and dairy products).

Feeding Behaviors During Mealtime

Information regarding feeding behaviors during mealtime was assessed at T0. Specifically, Brief Autism Mealtime Behavior Inventory questionnaire [19,20], validated for a population of 3-11 years, and Screening Tool of Feeding Problems questionnaire [21], validated for a population of 12-99 years (Multimedia Appendices 4 and 5, respectively) were used to evaluate dysfunctional meal-related behaviors, including FS of participants with ASD.

Meal Assessment

The quantity and quality assessment of meals consumed during lunchtime are conducted using the PDAT [16] at both T0 and T1. Rather than relying on the gold standard weighing method, the PDAT offers a less invasive alternative, allowing for uninterrupted mealtime evaluation. Additionally, when compared to the gold standard, it has demonstrated high accuracy and strong correlations with macronutrient and micronutrient intake [16]. The PDAT consists of 2 sections (Multimedia Appendix 6): a quantitative and a qualitative component, with the latter developed by researchers based on findings from the FOOD-AUT project [6]. The quantitative section enables the monitoring of each meal component (first course, second course, side dish, accompaniment—bread, breadsticks, and crackers—dessert, fruit, yogurt, and beverages) by recording the amount consumed. To facilitate data collection, intake is recorded both numerically (empty plate, one-fourth, half, three-fourth, and fully consumed) and graphically. The graphic representation uses 4 circles (representing a plate divided into 4 sections), which range from white (not consumed) to blue (completely consumed). For beverages, a stylized glass is used, with a gradually increasing water fill indicating empty, one-quarter full, half full, three-quarters full, and full consumption. The qualitative section evaluates the sensory characteristics of each meal component, detailing its shape, color, smell or taste, texture, and temperature. The development of the qualitative part of the PDAT was finalized with the collaboration of a sensory expert, who helped define the possible alternatives for completing each of the main organoleptic characteristics.

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Nutrition Knowledge

Nutrition knowledge will be assessed in parents and caregivers participating in the nutrition education course. A questionnaire, designed based on the course topics, consists of 21 questions (3 per module; Multimedia Appendix 7). Researchers will administer the questionnaire via telephone interviews before and after the course to evaluate knowledge acquisition.

Satisfaction

Satisfaction will be evaluated in parents and caregivers attending the course through a 13-question questionnaire (Multimedia Appendix 8). Administered at the end of the program via telephone interviews, it aims to assess the course's usefulness, organization, and areas for improvement. Table 1 below summarizes which tools are administered, to whom, with what objective, and at what stage of the project.

Outcomes and Statistical Analysis

The main outcome of the study testing the improvement of the meal acceptance is an increased food consumption of the proposed targeted meals. Specifically, food acceptance of targeted menus will be calculated as the average intake of the 12 administered set meals, ranging from 0 to 1, comparing results collected at T0 and at T1. The improved food acceptance associated with targeted menus will be estimated assuming a threshold of acceptance of 0.6, calculated as the percentage of cases showing an average PDAT lower than that value. Since the results of the pilot study were encouraging [6], showing an average PDAT greater than or equal to 0.8 in 50% (n=22) of participants, a threshold of 0.6 is assumed as a precautionary measure due to the variability in standard meal composition.

Multiple correspondence analysis at T0 was used to study the association between specific sensory aspects and food consumption, categorized into 5 levels (1=no consumption to 5=total consumption). The analysis produced a map showing the distances between the categories of the qualitative variables and food consumption levels.

Concerning the subgroup of caregivers attending the nutrition education course, statistical analysis will focus on effectiveness evaluation of the course, measured by the comparison of nutrition knowledge score, the prevalence of FS score, and the adherence to the Mediterranean diet score before and after the education intervention and by the dropout rate at the end of the course.

Since no preliminary information is available on the average consumption and variability of the PDAT, the determination of sample size is made on the expectation of a possible decreased propensity of FS. FS is an attitude found in 80% of the population with ASD, starting as early as childhood [6]. Hence, setting a significant level of α=.05 and a test power of 90%, under the assumption that the rate of FS may decrease to 15 percentage points, namely from p(T0)=80% to p(T1)=65%, 150 participants could be sufficient [22].

Results

Due to different timelines depending on the centers and schools involved, participant enrollment and data collection will take place at different times between Pavia, Milan, and Rome. In September 2024, enrollment was held in the Pavia and Milan care centers for a total of 74 participants enrolled. The observation phase took place between October and December 2024 for a total of 4 weeks for each center, while the intervention phase is scheduled between April and June 2025. In Rome, the school in which to carry out the study has been selected, but the enrollment phase has not yet started; activities are expected to be carried out similar to those in Pavia and Milan.

Discussion

Principal Findings

The AUT-MENU study is expected to yield significant insights and improvements in meal acceptance among individuals with ASD, particularly through the introduction of targeted menus in collective catering settings. Specifically, the study anticipates that individuals with ASD will demonstrate an increased acceptance of and preference for the targeted menus compared to the standard ones, as evidenced by the FOOD-AUT pilot study [6]. By using PDAT to assess food consumption quantitatively and qualitatively, the study aims to identify and leverage the sensory characteristics of food that are most conducive to acceptance by individuals with ASD. These findings will provide valuable evidence for tailoring collective catering practices to better accommodate this population's specific dietary preferences and needs.

A notable outcome of the study is the expected reduction in FS and meal-related behavioral challenges, particularly in the subgroup of participants whose caregivers participate in the nutrition education course. The course is designed to equip caregivers with strategies to address FS effectively, promote healthier eating patterns, and improve the overall mealtime environment. It is anticipated that caregivers will demonstrate increased nutrition knowledge and confidence in implementing these strategies, leading to observable improvements in the dietary habits of their children or dependents with ASD.

On a broader scale, the study is expected to highlight the feasibility of implementing customized dietary interventions in collective catering environments. This includes the ability of catering services to target menus based on sensory preferences and the willingness of staff at care centers and schools to implement these changes. By working collaboratively with catering operators and using sensory-focused strategies, the study anticipates not only improved food consumption but also a better overall dining experience for individuals with ASD.

Improvements are expected also in caregivers' nutrition knowledge scores, FS prevalence scores, and adherence to the Mediterranean diet thanks to the educational course. These outcomes will highlight the importance of a multidisciplinary approach, involving dietitians, psychologists, speech therapists, and child neuropsychiatrists in addressing the complex dietary challenges faced by this population.

Finally, the AUT-MENU study is poised to contribute to the limited body of research on ASD and dietary interventions in collective catering settings. By disseminating findings through

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academic publications, conferences, and community outreach, the study aims to provide a replicable framework for similar interventions in other regions and contexts. While the study acknowledges limitations, such as the lack of representativeness of the sample and the absence of national prevalence data on ASD, the anticipated results will provide a critical foundation for future research and policy development, ultimately improving the nutritional health and quality of life for individuals with ASD.

Strengths and Limitations

The AUT-MENU study is unique in that it intervenes at the level of collective catering to improve the mealtime experience for individuals with ASD, an area that has not been explored previously. The intervention takes a holistic approach, addressing both collective catering and the domestic context to enhance participants' diets. To ensure that the mealtime experience of the enrolled participants remains undisturbed, the study uses validated and accurate noninvasive tools. However, a limitation of the study is the lack of a comprehensive national and subnational prevalence study on individuals with ASD in Italy, which affects the representativeness of the sample. The sample population is not representative of the ASD population in Italy, as the sample size could not be estimated based on the actual prevalence of ASD.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are not publicly available due to privacy reasons but are available from the corresponding author on reasonable request.

Authors' Contributions

MVC conceived the idea. CB and MVC identified research objectives. CB and SB took the lead on writing the manuscript. MVC, AS, MLS, SR, and HC revised the manuscript. MVC and CB contributed equally.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Case report form.
[DOCX File , 4527 KB - resprot_v14i1e57507_app1.docx]

Multimedia Appendix 2
Mediterranean Diet Quality Index in Children and Adolescents.
[DOCX File , 4527 KB - resprot_v14i1e57507_app2.docx]

Multimedia Appendix 3
New Validated Short Questionnaire for the Evaluation of the Adherence of Mediterranean Diet and Nutrition Sustainability in all adult population groups.
[DOCX File , 4527 KB - resprot_v14i1e57507_app3.docx]

Multimedia Appendix 4
Brief Autism Mealtime Behavior Inventory.
[DOCX File , 4529 KB - resprot_v14i1e57507_app4.docx]

Multimedia Appendix 5
The Screening Tool of Feeding Problems.
[DOCX File , 4527 KB - resprot_v14i1e57507_app5.docx]

Multimedia Appendix 6

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Pictorial dietary assessment tool.
[DOCX File , 676 KB - resprot_v14i1e57507_app6.docx]

Multimedia Appendix 7
Nutrition knowledge questionnaire.
[DOCX File , 22 KB - resprot_v14i1e57507_app7.docx]

Multimedia Appendix 8
Satisfaction questionnaire.
[DOCX File , 21 KB - resprot_v14i1e57507_app8.docx]

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Abbreviations

ASD: autism spectrum disorder
FS: food selectivity
PDAT: pictorial dietary assessment tool

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Protocol

Integrated Behavioral and Biological Surveillance Among People Living With HIV Visiting the Antiretroviral Therapy Centers in India: Protocol for a Cross-Sectional Surveillance

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Abstract

Background: The estimated number of people living with HIV (PLHIV) in India in 2023 is 2.54 million (range 2.16-3.03 million). With the initiation of antiretroviral therapy (ART) and the “Test and Treat” policy, the life expectancy of PLHIV on ART has substantially increased, consequently leading to a higher rate of comorbidities among PLHIV. The Joint United Nations Programme on HIV/AIDS (UNAIDS) 2025 targets aim for about 90% of PLHIV to have access to integrated and comprehensive health care services, with a concerted effort to reach the End of AIDS by 2030. Hence, the National Integrated Bio-Behavioral Surveillance (IBBS) among PLHIV (IBBS-PLHIV) has been implemented for the first time in India to establish a baseline understanding of the prevalence of sexually transmitted infections (STIs), noncommunicable diseases (NCDs), and related risk behaviors among PLHIV.

Objective: The primary aim of IBBS-PLHIV is to estimate the levels of HIV-related risk behaviors and the prevalence of other STIs and NCDs among PLHIV. The specific objectives are identifying the levels of HIV-related sexual and injecting risk behaviors; estimating the prevalence of STIs such as syphilis, hepatitis B virus, and hepatitis C virus; estimating the prevalence of NCDs such as diabetes and hypertension; understanding the lifestyle and behavioral risks associated with NCDs; and assessing the levels of violence, stigma, and discrimination experienced by PLHIV.

Methods: IBBS-PLHIV will be a cross-sectional, biennial surveillance among PLHIV aged 15 years or older. The first round will be implemented at 120 ART centers across 28 states, accounting for approximately 95% of the total estimated PLHIV. Consenting, eligible PLHIV will be recruited through consecutive sampling. The overall sample size at each ART center is approximately 225, and the surveillance period is 3 months. Behavioral data on demographics, reproductive and sexual health, lifestyle and sexual behaviors, stigma, and discrimination will be collected. Blood samples will also be collected to test for STIs and NCDs.

Results: IBBS-PLHIV was initiated on January 1, 2024, in a phased manner. Data collection was carried out over 3 months and completed by June 2024 across all 120 sites. A total of 25,257 PLHIV were recruited for the surveillance, including 11,921 males, 11,855 females, and 1481 hijra/transgender individuals. Data entry, followed by data matching and validation of all records, was completed in December 2024. The data are currently being analyzed, and the final findings are expected to be disseminated by December 2025.

Conclusions: Data collected through IBBS-PLHIV will help monitor the levels of HIV-related sexual and injecting risk behaviors among PLHIV. Additionally, it will provide estimates of the prevalence of NCD comorbidities and STI coinfections such as

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diabetes, hypertension, syphilis, and viral hepatitis. These findings will serve as a baseline and are expected to offer valuable insights for facilitating comprehensive HIV care and management through the effective integration of HIV and broader health service delivery.

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KEYWORDS

people living with HIV/AIDS; antiretroviral therapy; Integrated Bio-Behavioral Surveillance; India; protocol; biological surveillance; reproductive health; sexual health; communicable diseases; mental health; integrated care; stigma; discrimination

Introduction

Background

The HIV/AIDS epidemic is highly concentrated and confined to specific population groups and geographical locations. In India, the predominant mode of HIV transmission is through the heterosexual route (75%), followed by injecting drug use (12%), and the homosexual or bisexual route among men who have sex with men (5%) [1]. In India, as per the 2023 report, the estimated adult prevalence of HIV is 0.20% (95% CI 0.17%-0.25%), and the estimated number of people living with HIV (PLHIV) is 2.54 million (95% CI 2.17-3.04 million) [2]. Of these, about 2.48 million (97.5%) total infections were among adults aged 15 years and above. The estimated number of PLHIV per million population was 1841 [2].

The Joint United Nations Programme on HIV/AIDS (UNAIDS) is leading the global agenda to eliminate HIV/AIDS as a public health threat by 2030. The UNAIDS 2025 strategy emphasizes 3 targets for HIV services, focusing on the Sustainable Development Goals related to the HIV response [3]. The primary target is to achieve the 95-95-95 testing and treatment goals among all subpopulations and age groups of PLHIV by 2025. Accordingly, 95% of PLHIV should know their HIV status, 95% of those who know their status should be on antiretroviral therapy (ART), and 95% of those on ART should have suppressed viral loads by 2025. The strategy also emphasizes eliminating social and legal barriers to HIV services and integrating these services with other health services for PLHIV. By achieving the 2025 targets, it is expected that at least 90% of PLHIV and individuals at higher risk of HIV infection will be linked to integrated services that support their overall health and well-being [3,4].

As part of the National AIDS Control Programme (NACP) of the National AIDS Control Organisation (NACO), the free ART initiative was launched in 2004 in Delhi and 6 other high-prevalence states. Since then, ART services have been scaled up and decentralized to ensure access for all PLHIV. With the adoption of the Treat All policy in 2017, all PLHIV are initiated on ART regardless of CD4 count, clinical stage, or age. About 81 % of PLHIV in India know their HIV status, of whom 88% are on ART; among those, >= 95% have suppressed viral loads—translating to approximately 69% of all PLHIV having suppressed viral loads [1].

Noncommunicable diseases (NCDs) are emerging as a significant cause of morbidity and mortality among PLHIV. The increasing incidence of NCDs can be attributed to various factors, including chronic immune activation, medication side effects, coinfections, and the aging of the PLHIV population. Promoting awareness of NCDs through health education and early detection and diagnosis, followed by treatment and regular follow-up, is recommended to prevent and manage NCDs in this group. With the growing availability and accessibility of ART centers, many PLHIV are benefiting from integrated HIV care services [5].

HIV management and care services are provided to approximately 1.7 million PLHIV through 775 ART centers, 1307 link ART centers, and 320 partner-supported care and support centers [1]. However, stigma, lack of awareness, and missing linkages between testing and treatment services remain significant challenges to advancing the End of AIDS agenda. Additionally, the lack of data on key indicators, such as viral suppression rates among high-risk groups, makes it difficult to design effective health programs that address the specific needs of populations affected by the HIV epidemic in the country [6]. To overcome these challenges, improved surveillance of comorbidities among PLHIV within an integrated HIV care setting and the strengthening of existing data systems are highly recommended [7,8]. HIV Sentinel Surveillance (HSS), one of the earliest interventions under the NACP, has played a crucial role in characterizing the HIV epidemic and reinforcing HIV prevention and control efforts in India. HSS is an ongoing, cross-sectional surveillance activity conducted biennially to monitor the levels and trends of HIV prevalence across the country. It is implemented among 8 population groups: pregnant women, prisoners, migrants, truckers, female sex workers, men who have sex with men, hijra/transgender (H/TG) individuals, and injecting drug users. In alignment with the UNAIDS 2025 targets, the National AIDS and STD Control Programme has developed the Integrated and Enhanced Surveillance and Epidemiology (IESE) framework to study the epidemiology of HIV and other related sexually transmitted infections (STIs) among all high-risk populations. Under the IESE framework, a periodic cross-sectional Integrated Bio-Behavioral Surveillance among PLHIV (IBBS-PLHIV) was implemented in 2024 for the first time in India. This surveillance aims to collect epidemiological data using a scientifically rigorous methodology, guided by standard ethical considerations. This paper describes the objectives, detailed methodology, and data management plan of the IBBS-PLHIV surveillance, along with its expected outcomes.

Aims and Objectives of IBBS-PLHIV

The overall aim of the IBBS among PLHIV is to monitor the levels, trends, and determinants of HIV-related behaviors,

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service uptake, and comorbidities among PLHIV, to support improved planning of integrated care and treatment services.

Specific objectives are as follows:

- To generate evidence on HIV-related risk behaviors, such as condom use, number of partners among PLHIV, injecting drug use, and injecting practices.
- To estimate the prevalence of related STIs, namely, syphilis, hepatitis B, and hepatitis C, among PLHIV.
- To understand lifestyle behaviors and estimate the prevalence of associated NCDs, including diabetes, hypertension, heart disease, chronic respiratory illness, chronic liver disease, chronic kidney disease, and cancer.
- To assess the levels of violence, stigma, and discrimination experienced by PLHIV.

Methods

Surveillance Design and Setting

The IBBS-PLHIV is proposed as a biennial, cross-sectional surveillance survey among PLHIV aged 15 years and older. The survey is planned to be conducted over 3 months, from January to March, every 2 years until 2030.

For the first round, the surveillance will be conducted at 120 designated ART centers across 28 states, which account for approximately 95% of the total PLHIV burden in the country. The recruitment process will begin on January 1, 2024, and is expected to be completed by March 31, 2024, or earlier if the desired sample size is achieved.

Sample Size and Sampling Approaches

The sample size for each domain is calculated to measure consistent condom usage among adult PLHIV by gender. A domain refers to a geographical unit for which representative estimates will be generated.

In an experimental study conducted among HIV-positive women in 2 tertiary care hospitals in Mumbai [9], consistent condom use among spouses of HIV-positive women was 77%, which increased to approximately 96% in the intervention arm over 1 year. Based on this context, the sample size required to measure the trend has been calculated according to the considerations outlined below:

where D is the design effect; P_1 is the estimated proportion at the time of first surveillance (expected baseline value); P_2 is the estimated proportion at some future date, so that $(P_2 \sim P_1)$ is the magnitude of change needed to be detected (expected value after 2 years); $P=[(P_1+P_2)/2]$; $Z_{1-\alpha}$ is the z-score corresponding to the desired level of significance (1-sided); $Z_{1-\beta}$ is the z-score corresponding to the desired level of power; and $\Delta^2 = (P_2 \sim P_1)^2$.

Consistent condom use with a spouse is used as a key indicator to calculate the sample size for the surveillance population. The expected baseline value (P_1) and the expected magnitude of change (P_2) are 77% and 90%, respectively, based on the Mumbai Study [9]. P_2 is kept lower than the 96% observed in the Mumbai study, as that was conducted in a research setting. $Z_{1-\alpha}$ is 1.64 at a 95% CI, and $Z_{1-\beta}$ is 0.84 at 80% power, with a design effect of 2.

Based on the above equation and the parameters, the sample size was calculated to be 198, rounded up to 200. The IBBS-PLHIV surveillance aims to measure changes in the study variables separately for males and females. Therefore, the sample size is set at 200 males and 200 females for each surveillance domain. The surveillance will also include H/TG individuals as one of the surveillance groups. The number of H/TG individuals accessing ART centers is expected to be low due to migration and loss to follow-up. Therefore, a “take-all” approach will be implemented across selected ART centers for H/TG participants to ensure their participation.

The surveillance sites and subsites in the selected state or union territory will be chosen to spatially represent the established administrative or sociocultural regions, based on the laboratory facilities available at the selected sites. In the first round, 120 ART centers across 7 geographical regions (North, Central, West, East, Northeast, Southeast, and South) of India have been selected. During the IBBS-PLHIV, 1 premier public health research institute will be designated as the regional institute (RI) to provide technical assistance and supportive supervision at the sites within the states allocated to them (Table 1). All districts in each state will be grouped into 2-4 geographical domains, based on their geographical and sociocultural characteristics, to ensure that ART centers from each domain are included. Considering the wider spread and feasibility of implementation, 2 ART centers will be selected from each domain. For smaller states, such as Goa, the entire state will be considered a single geographical domain. As the calculated sample size is 200 for each domain and 2 ART centers are selected from each domain, the target sample size for each ART center will be 100 males, 100 females, and approximately 25 H/TG individuals. According to the 2023 HIV estimation, approximately 43% of PLHIV in India are females. Therefore, an equal gender distribution was set, also considering the feasibility of a multicentric surveillance that is planned to take place at regular intervals. Similarly, for the H/TG population, an estimate of H/TG individuals registered at each ART center was determined before the survey, which ranged up to 25. To include the largest possible H/TG population, an upper limit of 25 was set for each ART center, and a take-all approach will be followed. The findings for the H/TG population will be reported only as national aggregates. However, any findings reported will be based on weighted analysis to account for potential differences. Therefore, the overall sample size for PLHIV surveillance will be approximately 27,000 nationally, with around 4500 (2000 males, 2000 females, and 500 H/TG individuals) for each region in 1 round. This sample size will be sufficient to provide robust prevalence estimates of coinfections at the regional level, with an anticipated prevalence of 1% and an absolute precision of 0.5% for males and females separately. For the H/TG population, the sample size will be adequate at the national level to provide estimates of coinfections, provided that approximately 25 H/TG individuals are recruited at each ART center.

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Table 1. Representation of antiretroviral therapy sites to be included in the surveillance.

Region, regional institute, and states/union territory	Antiretroviral therapy centers (N=120)
North	
PGIMER[a], Chandigarh (4 states)	
Chandigarh	1
Haryana	2
Himachal Pradesh	2
Punjab	4
Central	
AIIMS[b], New Delhi (4 states)	
Delhi	4
Jharkhand	3
Uttar Pradesh	8
Uttarakhand	3
West	
ICMR[c]—NITVAR Pune (6 states)	
Goa	2
Gujarat	4
Madhya Pradesh	4
Maharashtra	8
Mumbai	2
Rajasthan	6
Northeast	
RIMS[d], Imphal (3 states)	
Manipur	3
Mizoram	4
Tripura	3
East	
ICMR—NIRBI[e] Kolkata (5 states)	
Assam	3
Meghalaya	3
Nagaland	3
Chhattisgarh	8
West Bengal	6
Southeast	
AIIMS, Bhubaneswar (2 states)	
Odisha	3
Andhra Pradesh	6
South	
ICMR—NIE[f] Chennai (4 states)	

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Region, regional institute, and states/union territory	Antiretroviral therapy centers (N=120)
Kerala	3
Karnataka	8
Tamil Nadu	8
Telangana	6

[a]PGIMER: Postgraduate Institute of Medical Education and Research.
[b]AIIMS: All India Institute Of Medical Sciences.
[c]ICMR: Indian Council of Medical Research.
[d]RIMS: Regional Institute of Medical Sciences.
[e]NIRBI: National Institute for Research in Bacterial Infections.
[f]NIE: National Institute of Epidemiology.

A consecutive sampling method will be used for all eligible and consenting PLHIV at selected ART centers to minimize selection bias. ART centers follow a standardized patient flow, and every PLHIV visiting the ART center is registered in the daily register. The sampling process begins at this point of daily registration, from where PLHIV will be directed to the medical officer in the order they visit the ART center on a given day. The medical officer will verify eligibility and direct eligible PLHIV to the counselor for recruitment into IBBS-PLHIV.

The sample size at each ART center is approximately 225, with a surveillance period of 3 months. Therefore, a maximum of 5 respondents will be recruited daily to ensure the quality of the collected data and samples. However, because a take-all approach is followed, if 1 or more H/TG PLHIV is present after the fifth recruitment, they will be included in the surveillance to ensure their participation. Samples will be collected until the end of the surveillance period or until the desired sample size is achieved. The key features of IBBS among PLHIV, based on the population groups, are shown in Table 2.

Table 2. Key features of the Integrated Bio-Behavioral Surveillance among people living with HIV by population groups.

Key population group	Description
Setting	A facility based at designated antiretroviral therapy centers
Sample size (per antiretroviral therapy center): female/male/hijra/transgender	100/100/25
Sampling methodology	Consecutive sampling
Behavioral data domain	Demographic characteristics, family planning practices (for males and females), child birth history (only for females), lifestyle behaviors, sexual health, stigma, discrimination, and violence
Clinical data	Height, weight, and systolic and diastolic blood pressures
Biological specimen	Venous blood
Biomarkers	Hepatitis B virus, hepatitis C virus, and syphilis

Characteristics of Participants

Inclusion Criteria

Males, females, or H/TG individuals with HIV/AIDS, aged 15 years or older, who are registered at the designated ART center, and visit the ART center during the surveillance period are eligible for recruitment in the surveillance. Only eligible PLHIV who provide written consent to participate will be included in the surveillance.

Exclusion Criteria

PLHIV under 15 years of age, those not registered at the designated ART center, or those who have already participated in the current round of surveillance will be excluded from the surveillance.

Data Collection

A written informed consent will be obtained from all eligible PLHIV who are willing to participate in the surveillance. Bio-behavioral data will be collected from all consenting respondents using a paper-based tool in the form of a structured questionnaire (Multimedia Appendices 1-3). Data on demographic characteristics, reproductive and sexual health behaviors, lifestyle behaviors, and experiences of stigma, discrimination, and violence will be collected, as outlined in Table 3. Additionally, clinical data such as height, weight, and systolic and diastolic blood pressures will be measured using standard instruments.

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Table 3. An overview of the surveillance variables to be collected.

Surveillance variables	Population group		
	Female	Male	Hijra/transgender
Background characteristics: age, literacy, marital status, and occupation	✓	✓	✓
Reproductive health: family planning practices	✓	✓	✗
Fertility: birth history, current pregnancy, and breastfeeding practices	✓	✗	✗
Sexual history: age at first sexual intercourse, recent sexual activity, number and type of sexual partners, and condom use	✓	✓	✓
Lifestyle behaviors, prevalence of comorbidities, and treatment	✓	✓	✓
Stigma and discrimination	✓	✓	✓

Sample Collection

Venous blood samples will be collected to test for CD4 count, viral load, random blood sugar, and biomarkers for other STIs, such as syphilis, hepatitis B virus, and hepatitis C virus. The CD4 count, viral load, and random blood sugar will be tested according to the routine guidelines followed at the ART center (Multimedia Appendix 4). To test for other STIs, blood samples will be processed according to the laboratory protocol to obtain serum. The serum will be stored at 2-8°C until transportation and sent weekly to designated laboratories for testing. The results of all reactive tests will be returned to the respondents through the ART centers for follow-up and treatment.

Testing Strategy

A linked anonymous testing strategy will be adopted for testing the blood specimens collected during IBBS-PLHIV. A 2-test protocol will be used for testing syphilis: rapid plasma reagin and *Treponema* pallidum hemagglutination assay. A 1-test protocol will be used for testing hepatitis B virus and hepatitis C virus, using rapid antigen testing kits (Multimedia Appendix 4). According to the Guidelines for Surveillance of Sexually Transmitted Diseases, diagnostic tests are most effective for assessing disease prevalence when they specifically detect active infections. Treponemal tests alone, which typically remain reactive for life, are insufficient for distinguishing between adequately treated and active syphilis infections. Therefore, a 2-test protocol is recommended for syphilis surveillance, incorporating a nontreponemal test with a titer cut-off (eg, 1:4 or 1:8) to monitor active infection trends [10].

By contrast, the surveillance of hepatitis B and C aims to estimate the disease burden of chronic infections. For this purpose, viral hepatitis screening is conducted using a qualitative 1-test protocol, as endorsed by the National Viral Hepatitis Program [11].

Implementation Plan and Structure

NACO will implement the surveillance activity at designated ART centers in selected states across the country. An implementation structure similar to the HSS among ANC attendees will be adopted. The State AIDS Control Society (SACS) and the respective District AIDS Prevention and Control Units/District Integrated Strategy for HIV/AIDS Units will coordinate and implement the activity at the state level. Three site personnel—a medical officer, a counselor or nurse, and a laboratory technician—will be involved in the surveillance activity at each site.

The ART medical officer will be responsible for the PLHIV surveillance at the ART center. The medical officer will verify the eligibility of the PLHIV based on the inclusion criteria and direct eligible individuals to the counselor. The counselor will confirm the eligibility of the PLHIV and, if found eligible, will administer the participant information sheet (PIS), informed consent form (ICF), and assent forms, as applicable. The counselor will collect behavioral data from all consented, eligible PLHIV using the data forms and maintain the forms until they are dispatched to the respective RIs. Additionally, the counselor will be responsible for filling out and maintaining the HSS register in a secure and confidential manner to ensure linked anonymous testing. The counselor will also oversee the dispatch of the data forms and registers according to the guidelines. The laboratory technicians will be responsible for measuring clinical data, such as height, weight, and blood pressure. The technician is primarily responsible for collecting and processing blood samples according to the protocol. The lab technician is also in charge of storing and transporting the samples to the linked surveillance laboratory. A completed data form, labeled with the state code, site code, sample number, and date of collection, along with 2 data form transportation sheets, will be sent to the respective RI every week. Similarly, the processed samples, properly labeled and packed, will be sent to the testing laboratories each week.

Overall, technical and monitoring support will be provided by national and regional institutes, SACS, and state surveillance teams. The activity will be implemented under the guidance of NACO's Technical Working Group for Surveillance & Epidemiology, in collaboration with bilateral and multilateral partners, as well as other relevant stakeholders. The respective SACS will be responsible for procuring and disseminating the surveillance materials to the ART centers. Procurement will be carried out according to the technical specifications set by the nodal agency to ensure quality and uniformity. The materials will be procured and disseminated before the initiation of the survey. Similarly, training for site personnel will be conducted by the SACS 1 week before the survey's start. An extension may be granted on a case-by-case basis to any sites that are unable to achieve the sample size within the surveillance period. In the event of termination of the surveillance at a particular site or domain due to unforeseen circumstances, data from that

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domain will not be included in the analysis if the sample collected up to the point of termination is insufficient. However, tests will be performed on the collected samples, and appropriate services will be linked for any positive results.

Ethical Considerations

Voluntary Participation

Participation in the surveillance is voluntary and free from coercion. Eligible respondents who refuse to participate will not be forced, and routine services will be provided. However, the reasons for refusal will be documented in the IBBS-PLHIV register.

Confidentiality

Any personal identifiers, such as name, contact number, address, and clinical diagnosis, will not be accessible to anyone except the site-level personnel involved in the surveillance. Confidentiality will be ensured by assigning a unique identification number to each participant. Any diagnostic results generated will be delinked from personal identifiers. A separate link register, containing only the respondent's ART number and surveillance sample number (with no other personal identifiers), will be maintained to facilitate follow-up service delivery. The delinked data will be accessible only to designated members of the surveillance team at the state, regional, and national levels. The anonymous data will be used for analysis, reporting, publication, and policy making. Only summarized, anonymized data will be used for publication. Additionally, any reporting required by government agencies, as per the law, will be conducted periodically. To ensure data privacy and confidentiality at each level, access to the data management portal is user specific. Each individual involved in the surveillance will be provided with unique log-in credentials, and their access will be restricted based on role-specific permissions. The database will be accessible only to authorized personnel at the state, regional, and national levels, and national guidelines for data management will be strictly followed.

Participant Information Sheet and Informed Consent

All eligible PLHIV will be provided with a PIS and written ICFs before data collection. The PIS will cover the objectives of this PLHIV surveillance, expectations from the respondents, information on biological test results, confidentiality, and voluntary participation. Written ICF will be obtained from sampled and eligible participants who are willing to participate in the surveillance. If the eligible participant is literate, the PIS and ICF will be provided for them to read. If the participant is illiterate, the PIS and ICF will be read aloud in the presence of a literate witness. The PIS and ICF will be translated into local languages. Any queries will be addressed promptly and adequately. Respondents will be shown all consumables and items used for biological sample collection and assured of confidentiality. For respondents aged 15-17 years, assent will be obtained along with the consent of a parent, guardian, or health care provider not associated with the survey.

Diagnosis and Treatment

All respondents who test reactive for any of the biomarkers will be contacted and informed of their diagnosis. They will be referred for appropriate treatment as per program guidelines.

The ethical considerations and informed consent process for the IBBS-PLHIV were reviewed and approved by the Institutional Ethics Committee of ICMR—National Institute of Epidemiology. The approval number is NIE/IHEC/202207-03, dated August 23, 2023.

Data Management

Data will be collected using prestructured, paper-based forms. These forms will be bilingual, with questions in both English and the regional language. The forms will be translated and pilot-tested before implementation. All collected data forms, samples, and related documents will be handled exclusively by designated surveillance team members at all levels.

Surveillance and data management will be conducted through a customized web-based portal. The portal is designed to facilitate the entry and updating of all surveillance activities, including site preparedness, daily data/sample collection status, transportation sheets, acknowledgment of data/sample receipts, sample checklists, laboratory results, supervisory visit forms, and surveillance data. Role-based access control is implemented to ensure data confidentiality and security. As a result, all entries can be made and managed only by designated users in a secure manner.

The designated RIs will manage data at the regional level. Upon receipt of the data forms, the data manager will ensure and acknowledge their safe arrival. Data entry operators will enter the data into the web-based portal. All data will be synced to a central server, allowing access from various sites/centers. Double data entry will be performed for all forms to minimize errors. Any personal identifiers (if present) will be delinked from the captured data to ensure confidentiality.

All personnel involved in data management and data entry will be appropriately trained to minimize errors. The data manager will also be responsible for cleaning and validating the entered data for further analysis. The data will be periodically monitored by the data manager to ensure consistency. Laboratory results will be directly entered into the portal by the linked surveillance laboratory. These results will be matched with the cleaned behavioral data using the IBBS number (12 digits) as a unique identifier. To ensure data integrity, data matching will be performed exclusively by the designated in-charge at the RI.

Data Analysis Plan

The matched data will be precoded for analysis, and missing data will be coded accordingly. The data will be analyzed to estimate the levels of sexual risk behaviors, the prevalence of STIs/NCDs, and associated behaviors among PLHIV. Results will be presented using descriptive statistics. Where required, means/medians, differences in means/medians, proportions, and their corresponding 95% CIs will be presented. Data from the first round of the PLHIV surveillance will be used to establish a baseline for the current HIV interventions, with subsequent rounds compared to assess the impact of integrated services.

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The sexual behavioral risks associated with HIV-related STIs and the lifestyle behavioral risks associated with NCDs among PLHIV will be analyzed using regression methods. All statistical analyses will be conducted using standard statistical software, and values with $P<.05$ will be considered significant. A weighted analysis will be performed to account for significant differences in PLHIV burden and sample size. A more detailed analysis plan for key indicators is provided in Multimedia Appendix 5.

Quality Assurance at the Surveillance Sites and Testing Laboratory

Overview

Training for surveillance activities, along with monitoring by the state, regional, and national teams, and interlaboratory comparison, will be conducted as part of quality assurance to minimize errors.

Training of the Site Personnel

As part of the IBBS-PLHIV, a 2-day in-facility training will preferably be conducted for the ART surveillance team at the site level to build their capacity on survey procedures. The training modules will cover data form collection and transportation, sample collection, processing, packaging, and transportation. Practical sessions on "Know Your Sentinel Site" and IBBS methodology will be included to ensure the proper implementation of the IBBS workflow.

Monitoring and Supervision

Trained surveillance team members at the state, regional, and national levels will monitor the survey. A supportive supervisory visit to all sites will be conducted within the first week of the surveillance to facilitate the identification and correction of any errors in advance. Adherence to the IBBS methodology, as well as the quality of data and sample collection, sample processing, and storage, will be ensured during supervisory visits. The first few forms will be thoroughly checked for data quality control to prevent further mistakes. In addition to on-site visits, the RIs and designated state surveillance team members will virtually monitor the sites for data and sample collection quality assurance. The data and sample collection status of each site will be monitored daily via virtual platforms. Similarly, periodic reviews of data forms, the PLHIV surveillance register, and the link register will be conducted virtually. The RI will provide refresher training in case any discrepancies are identified.

Quality Assurance at Testing and Reference Laboratories

The samples will be transported to designated testing laboratories weekly. Upon receipt of the samples, the laboratory in charge will perform a quality check on all received samples using the sample quality checklist. The status of accepted and rejected/invalid samples will be promptly communicated to the RI and the respective sites.

Interlaboratory comparisons will be conducted to ensure testing quality. All serum specimens that are positive for 1 or more biomarkers, along with 5% of negative specimens (those not positive for any of the biomarkers), will be sent to a national reference laboratory for quality assurance testing every fortnight. The negative specimens will be randomly selected.

Data Dissemination

The observations and surveillance results will be presented as top-line findings, technical briefs, national and state reports, and scientific publications. Publications based on these findings may be presented at scientific conferences and in peer-reviewed journals, in consultation with the Ministry of Health and Family Welfare, Government of India and with input from the technical resource group and technical working group of NACO. The findings from the surveillance survey will be presented to policy makers to inform program design, set benchmarks, and assess progress over time.

Results

The IBBS-PLHIV was initiated on January 1, 2024, in a phased manner. Data collection was conducted over 3 months and completed by June 2024 at all 120 sites. A total of 25,257 PLHIV were recruited for the surveillance, including 11,921 males, 11,855 females, and 1481 H/TG individuals. Data entry, followed by data matching and validation of all records, was completed in December 2024. The data are currently being analyzed, and the final findings are expected to be disseminated by December 2025. The state-wise gender distribution of PLHIV respondents is shown in Table 4.

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Table 4. State-wise gender distribution of people living with HIV respondents in the Integrated Bio-Behavioral Surveillance-People Living With HIV Program, 2024.

State	Female (n=11,855), n	Male (n=11,921), n	Hijra/transgender (n=1481), n	Overall, n
Andhra Pradesh	599	601	150	1350
Assam	301	303	18	622
Chandigarh	102	98	25	225
Chhattisgarh	807	794	81	1682
Delhi	410	430	104	944
Goa	200	200	3	403
Gujarat	401	400	64	865
Haryana	199	201	27	427
Himachal Pradesh	200	201	5	406
Jharkhand	301	298	29	628
Karnataka	797	805	88	1690
Kerala	301	299	22	622
Madhya Pradesh	398	416	7	821
Maharashtra	1009	1007	172	2188
Manipur	303	301	50	654
Meghalaya	202	203	0	405
Mizoram	468	459	0	927
Nagaland	298	302	0	600
Odisha	294	295	72	661
Punjab	404	397	77	878
Rajasthan	598	602	34	1234
Tamil Nadu	805	810	140	1755
Telangana	601	599	87	1287
Tripura	254	300	1	555
Uttar Pradesh	700	703	109	1512
Uttarakhand	300	300	16	616
West Bengal	603	597	100	1300

Discussion

Expected Findings

The IBBS-PLHIV will be a biennial cross-sectional survey aimed at monitoring the levels, trends, and determinants of HIV-related behaviors and comorbidities among PLHIV. Anticipated outcomes of IBBS-PLHIV include identifying HIV-related sexual behavioral risks, such as inconsistent condom use and partner types, as well as estimating the prevalence of HIV-related STIs, including syphilis, hepatitis B, and hepatitis C. The surveillance also aims to assess lifestyle behavioral risks such as smoking, alcohol consumption, and injecting drug use, as well as the self-reported prevalence of NCDs such as diabetes, hypertension, heart disease, chronic respiratory illness, chronic liver disease, chronic kidney disease, and cancer. Additionally, participants will be screened for diabetes through random blood sugar measurements and for hypertension through the measurement of systolic and diastolic blood pressure. Furthermore, the surveillance aims to assess the reproductive and sexual health needs of PLHIV, as well as the levels of violence, stigma, and discrimination they experience. To understand how the findings from the surveillance will improve HIV management among PLHIV, it is essential to examine the existing health care and HIV management cascade in India.

The health care system in India is diverse, with both public and private health care service providers. Rural areas are primarily served by the 3-tiered public health care system, which includes primary, secondary, and tertiary levels of care, while private providers predominantly cater to urban areas. The PHCs and subcenters are primary health care units that primarily focus on integrated preventive and curative care for the rural population. Secondary-level units, such as subdistrict hospitals and community health centers, serve as referral units. Tertiary-level care is provided by district hospitals and medical colleges. Both public and private providers contribute to secondary and tertiary

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health care services [12]. Similarly, a multitier model of HIV care is provided by the ART centers. Primary care is offered by ART centers and facility integrated ART centers located at government medical colleges, district hospitals, selected subdistrict hospitals, and private institutes. Secondary care is provided by ART Plus centers, while specialized care is offered at Centers of Excellence in selected medical colleges. Additionally, decentralized care is provided through link ART centers at subdistrict hospitals and community health centers, care and support centers, opioid substitution therapy centers, prisons, and targeted intervention sites [13]. In India, 775 ART centers, 1307 link ART centers, and 320 partner-supported care and support centers provide HIV management and care services to nearly 1.7 million PLHIV [1]. Additionally, a comprehensive care support and treatment service package includes free diagnostic and monitoring services, with an emphasis on long-term engagement in care, proactive management of opportunistic infections, and linkages to support services and social protection schemes. In summary, it ensures accessible and lifelong ART while addressing various aspects of care and social protection [5].

ART centers adhere to the Test and Treat policy, ensuring universal and unrestricted access to ART for PLHIV, regardless of their CD4 count or demographic factors. A comprehensive HIV cascade, including HIV testing, treatment, and care, has been globally adopted to achieve targeted viral suppression among PLHIV. Recent research highlights the benefits of early initiation of ART in improving the health of PLHIV and preventing HIV transmission to partners, thereby reducing HIV incidence. As a result, most HIV prevention programs have focused on evaluating and enhancing PLHIV engagement in the HIV cascade of testing, treatment, and care. Yet, only about 69% of the total PLHIV in India have their viral load suppressed, indicating substantial gaps despite the progressive estimates at the national level. Recent studies report an increase in high-risk sexual behavior among the general population, particularly among youth, urban populations, and females, who face disproportionately increased vulnerabilities to HIV infection in India [14-16]. While NACO has intensified treatment services, prevention remains the cornerstone of India's HIV response, emphasizing the need for monitoring risk behaviors among PLHIV to achieve zero transmission. Although some researchers have reported evidence of improved clinical and behavioral indicators based on retrospective analysis of PLHIV data, second-generation surveillance is globally recommended to identify the dynamics of HIV risk behaviors to improve prevention and treatment outcomes [17-19].

By contrast, despite declining HIV infections, the widespread use of ART has transformed HIV into a chronic condition, reducing AIDS-related deaths but increasing the prevalence of other comorbid conditions among PLHIV. India faces a dual burden of HIV and NCDs, driven by aging, the long-term effects of HIV, and ART [20]. Several studies in India have reported metabolic changes; insulin resistance; and increased risks of myocardial infarction, stroke, liver disease, kidney disease, and cancers, including non–AIDS-defining cancers, among PLHIV [21-27]. Similarly, a higher prevalence of STI coinfections is also being documented in significant proportions [28,29]. Further, evidence suggests that PLHIV frequently encounter stigma and discrimination due to their HIV status, both within their communities and health care settings, leading to the underutilization of HIV-related services [6,30,31]. In contrast to the decentralized, vertical HIV service delivery model, NCD and STI services are predominantly centralized through hospitals. While relevant national programs exist for each of the comorbidities, gaps in service delivery, human resources, and monitoring persist. India's HIV program focuses on continuous care and ART adherence; however, limitations remain in the structured integration with NCD/STI management [20]. Although a referral mechanism is in place at all ICTC and ART centers, where PLHIV are informed and referred to the nearest NCD/STI facility for linkage and treatment, resource limitations hinder follow-up and the provision of integrated care at ART centers [21]. Recent studies have underscored the need for enhanced data collection and surveillance of NCDs, STIs, associated behaviors, and the stigma and discrimination experienced by PLHIV to identify the limitations of existing programs [7,20]. Strengthening routine data collection and patient monitoring systems is essential for comprehensive HIV management, thereby addressing global health inequities.

In light of this, a robust IBBS among PLHIV has been pioneered in India under the IESE framework to oversee the management and advancement of public health response initiatives under NACP. Given the periodic nature of the surveillance, the data can be used to monitor the levels and trends of health conditions among PLHIV and evaluate the progress of program interventions. Data generated from the surveillance will ultimately lead to informed decisions for providing holistic HIV management services at ART centers, ensuring regular screenings for other infections and chronic conditions, facilitating more effective linkages and treatment, and addressing stigma.

Limitations

The surveillance will be implemented in 28 states across India, covering 95% of the country's HIV burden. It will be conducted at ART centers in government facilities and will include both PLHIV already registered and new registrants visiting the centers during the surveillance period. As mentioned, of the estimated 2.5 million adult PLHIV, only 1.7 million are on ART. As the surveillance is facility based, PLHIV who have never registered at ART centers will not be included in the sampling frame. This limits data collection from hidden populations of PLHIV who are unlinked to HIV/ART services, necessitating appropriate caution in interpreting the results. Likewise, the surveillance will not capture data from PLHIV accessing ART services through private facilities. The sample size is calculated to generate national- and state-level estimates; therefore, appropriate caution must be exercised when interpreting results at the district level.

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Data Availability

All individual-level data collected during the surveillance will be maintained by the National AIDS Control Organization (NACO), in accordance with its Data Management and Data Protection Guidelines. Data may be shared with requesting individuals or organizations upon approval by the competent authority, following the proper request process outlined in the guidelines available at [32].

Conflicts of Interest

None declared.

Multimedia Appendix 1
IBBS-PLHIV—female data form. IBBS: Integrated Bio-Behavioral Surveillance; PLHIV: people living with HIV.
[PDF File (Adobe PDF File), 1011 KB - resprot_v14i1e58252_app1.pdf]

Multimedia Appendix 2
IBBS-PLHIV—male data form. IBBS: Integrated Bio-Behavioral Surveillance; PLHIV: people living with HIV.
[PDF File (Adobe PDF File), 828 KB - resprot_v14i1e58252_app2.pdf]

Multimedia Appendix 3
IBBS-PLHIV—hijra/transgender data form. IBBS: Integrated Bio-Behavioral Surveillance; PLHIV: people living with HIV.
[PDF File (Adobe PDF File), 784 KB - resprot_v14i1e58252_app3.pdf]

Multimedia Appendix 4
Summary of the biospecimens, biomarkers, and testing strategy.
[DOCX File , 15 KB - resprot_v14i1e58252_app4.docx]

Multimedia Appendix 5
Key indicators: data analysis plan.
[PDF File (Adobe PDF File), 317 KB - resprot_v14i1e58252_app5.pdf]

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Abbreviations

ART: antiretroviral therapy
H/TG: hijra/transgender
HSS: HIV Sentinel Surveillance
IBBS: Integrated Bio-Behavioral Surveillance
ICF: informed consent form
IESE: Integrated and Enhanced Surveillance and Epidemiology
NACO: National AIDS Control Organisation
NACP: National AIDS Control Programme
NCD: noncommunicable disease
PIS: participant information sheet
PLHIV: people living with HIV
RI: regional institute
SACS: State AIDS Control Society
STI: sexually transmitted infection
UNAIDS: Joint United Nations Programme on HIV/AIDS

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Protocol

Immunogenicity of COVID-19 Vaccination in Immunocompromised Patients (Auto-COVID-VACC): Protocol for Multicenter Prospective Noninterventional Study

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Abstract

Background: Despite the availability of vaccines, immunocompromised patients are still at high risk for severe COVID-19. Vaccination has been proven to be an effective measure in preventing severe SARS-CoV-2 infections; however, data on B- and T-cell responses are lacking. While vaccination schedules for the general population have been defined, achieving immunogenicity in patients who are immunocompromised remains a challenge.

Objective: The primary objective is to analyze anti-spike–immunoglobulin G (IgG) titers after repeated messenger ribonucleic acid vaccinations in patients who are immunocompromised. Further objectives are to analyze data on humoral immune responses and to evaluate data on cellular immune responses.

Methods: This multicenter, prospective, noninterventional study aims to determine the immunogenicity and reactogenicity of an implemented standard-of-care COVID-19 vaccination strategy in patients who are immunocompromised. A total of 100 patients will be recruited at three study sites. Patients are eligible for study inclusion when they are 18 years or older, vaccinated according to the recent version of the COVID-19 vaccination standard, and if the patient is immunocompromised according to stage 3 of the classification "Stages of Immunosuppression." The study analyzes B- and T-cell responses generated within the standard-of-care COVID-19 vaccination strategy. Additional blood samples will be drawn at each scheduled outpatient visit. Study-related blood samples will be used to extract ethylenediaminetetraacetic acid plasma and peripheral blood mononuclear cells for evaluation of B- and T-cell responses to COVID-19 vaccinations. For this study, no additional visits or invasive procedures will be performed in addition to standard care.

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Results: As of August 2024, the study has enrolled 32 patients. The recruitment phase is still ongoing.

Conclusions: Results will be used to optimize vaccination and booster schedules for patients who are immunocompromised and to increase rates of protection against severe SARS-CoV-2 infections. Further, results may identify risk and treatment factors, which lead to low immune responses in patients vaccinated against COVID-19, as well as the impact of repeated vaccination on B- and T-cell responses.

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KEYWORDS

COVID-19; SARS-CoV-2; vaccination; vaccine; infectious diseases; immunocompromised; immunosuppression; communicable disease; observational study

Introduction

The novel SARS-CoV-2 was identified in December 2019 as a cause of severe pneumonia, acute respiratory distress syndrome, and potential multiorgan failure in humans [1,2]. The disease known as COVID-19 has turned into a worldwide pandemic, causing substantial morbidity and mortality, and is now (2024) considered an endemic disease. As of December 15, 2024, the World Health Organization reports a total of 7,079,587 COVID-19 deaths worldwide [3]. Patients who are immunocompromised, such as those with hematological malignancies, are highly affected by SARS-CoV-2 infections due to the high risk of severe courses of infection [4-8]. COVID-19 may not only result in a delay or discontinuation of the treatment for the underlying diseases but also result in high mortality rates of above 30% [4-6,9,10]. Prevention strategies are therefore focused on avoiding SARS-CoV-2 infection in these vulnerable patients and reducing the risk of critical disease following infection. This is addressed by nonpharmacological and pharmacological interventions. Nonpharmacological interventions such as wearing masks, physical distancing, and respiratory hygiene are effective for reducing SARS-CoV-2 transmission but were withdrawn for the general population by state authorities as of June 2022. For example, masking in public is no longer mandatory in many countries. Pharmacological interventions included several antiviral drugs as well as various therapeutic monoclonal antibodies that lost neutralizing capacity with the emergence of Omicron variants [11,12]. At the end of 2020 and the beginning of 2021, the first messenger RNA vaccines against COVID-19 were proven to be effective in the prevention of severe SARS-CoV-2 infection and licensed for use [13-15]. The German Standing Committee on Vaccination of the Robert Koch Institute (RKI) has been recommending 3 antigen contacts (infection or vaccination) to complete basic immunization, of which at least one should be by vaccination. Annual booster recommendations are advised for groups at high risk, such as people with an impaired immune response [16]. COVID-19 vaccination, therefore, represents the mainstay of COVID-19 prevention. Efficacy and safety have been demonstrated for several vaccines, leading to currently 15 vaccines listed by the Paul Ehrlich Institute in Germany and with marketing authorization in Europe (as of October 2024) [17]. Studies have shown that COVID-19 vaccination is efficient in patients who are immunocompromised. However, lower levels of antibodies have been reported in this patient group [18,19]. Patients who are immunocompromised had been excluded from the majority of registered studies. Further, studies focused mainly on B-cell immune responses, resulting in uncertainty regarding the extent of immune response and the role of T cell–generated immune response in these patients. The aim of this study is to determine the immunogenicity and reactogenicity of an implemented standard-of-care (SOC) COVID-19 vaccination strategy (Multimedia Appendix 1) in patients who are immunocompromised [20].

Methods

Overview

A new SOC vaccination strategy was implemented for patients who are immunocompromised at 3 university hospitals in Germany, the University Hospital of Aachen, Cologne, and Essen. This approach targets a vaccination strategy that is guided by individual immune responses to COVID-19 vaccines [20] (Multimedia Appendix 1).

Study Design

This is a multicenter, prospective, noninterventional study conducted at university hospitals in Germany that have implemented the SOC COVID-19 vaccination for patients who are immunocompromised [20]. This study aims to analyze the humoral and cellular immune response data generated within the procedures of the SOC COVID-19 vaccination [20]. Patients who are immunocompromised and will be vaccinated according to the vaccination standard [20] are eligible for study inclusion. To define immunocompromised, the classification “Stages of Immunosuppression” [21] was considered (Multimedia Appendix 2). Patients in stage 3 (eg, patients with a hemato-oncological underlying disease or patients receiving biologicals) are eligible for study inclusion. At each vaccination visit and follow-up visit, both defined in the vaccination standard, enrolled patients will undergo study-related assessment in addition to routinely performed assessments and interventions within their standard care. At the first visit, a SARS-CoV-2 antigen test will be performed. In case of a positive test result, the patient will be excluded from study enrollment. According to the vaccination standard [20], blood draws will be performed at each visit. For study purposes, additional blood samples will be drawn by using the same vein puncture at these visits (see

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visits and study-related assessments). These samples will be used for additional analysis of the immune response. The samples will be collected and stored until the analysis, which will be performed after the recruitment period. This guarantees that results obtained from study-related immune response assessments do not affect the standard vaccination strategy. Patients will also receive a patient diary before the first vaccination to document adverse drug reactions (ADRs) to the COVID-19 vaccine.

Study-Related Tests

Peripheral blood mononuclear cells will be isolated from whole blood ethylenediaminetetraacetic acid–containing tubes using density-based separation with Ficoll. Cells will be cryopreserved for immune phenotyping by flow cytometry at the end of the study. Immune phenotyping of lymphocytes allows specific analyses of lymphocytic subsets, which are defined by a higher number and composition of surface antigens. Using a customized panel of antibodies, we will be able to detect the major subsets of B- and T-cell lymphocyte lineages. All study-related immune response measurements will be performed in batches from stored samples after last-patient-last-visit at the University Hospital of Cologne. Sample remains are disposed of after study completion.

Objectives

Data for primary and secondary objectives are generated within the routine procedures of SOC COVID-19 vaccination [20]. Data for exploratory objectives will be generated from study-related assessments based on study-related blood sampling. Study-related blood sampling will be performed at the same timepoints and from the same vein puncture as for routine standard procedures (Textbox 1).

Textbox 1. Primary, secondary, and explorative objectives.

Primary objective

- To analyze the available data on anti-spike–immunoglobulin G titers after repeated messenger RNA (mRNA) vaccinations in immunocompromised patients

Secondary objectives

- To analyze the available data on neutralizing capacity against the Omicron-BA.1 variant after repeated mRNA vaccinations in immunocompromised patients
- To analyze the available data on neutralizing capacity against other Omicron sublineages after repeated mRNA vaccinations in immunocompromised patients
- To analyze the available data on binding antibody response against Omicron variants after repeated mRNA vaccinations in immunocompromised patients
- To analyze the available data on the waning of the humoral immune response against Omicron variants after the last mRNA vaccination in successfully vaccinated patients according to the standard of care
- To analyze reactogenicity data (see solicited adverse events) collected within this study

Explorative objectives

- To evaluate B- and T-cell immune response against Omicron variants after repeated mRNA vaccinations in immunocompromised patients
- To evaluate the waning of B- and T-cell immune response against SARS-CoV-2 (in particular Omicron variants) after the last mRNA vaccination in successfully vaccinated patients according to the standard of care
- To evaluate memory B-cell response against the Omicron variant after the last mRNA vaccine, in successfully vaccinated patients

End Points

The end points are listed in Textbox 2.

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Textbox 2. Primary, secondary, and exploratory endpoints.

Primary end point

- Time to reach an adequate immune response according to the recent version of the COVID-19 vaccination standard-of-care [20] after repeated messenger RNA (mRNA) vaccinations (Multimedia Appendices 1 and 3)

Secondary end points

- Time to Omicron BA.1-specific neutralizing antibody ID_{50} (50% inhibitory dilution) titers ≥30 after repeated mRNA vaccinations in immunocompromised patients
- Time to anti-spike-1/2 IgG (immunoglobulin G) increase ≥33.8 binding antibody units (BAU)/mL measured by SARS-CoV-2 TrimericS IgG (DiaSorin) after repeated mRNA vaccinations in immunocompromised patients
- Time to decrease of Omicron BA.1–specific neutralizing antibody ID_{50} titers <30 after last mRNA vaccination in successfully vaccinated patients according to the standard-of-care
- Time to anti-spike-1/2 IgG decrease <33.8 BAU/mL after the last mRNA vaccination in successfully vaccinated patients according to the standard-of-care measured by SARS-CoV-2 TrimericS IgG

Anti-spike-1/2 IgG titer ≥ 33.8 BAU/mL was interpreted as reactive, according to the manufacturer's instructions (DiaSorin). To determine Omicron BA.1-specific neutralizing serum titers, the lowest tested serum dilution was 1:30, which served as the lower limit of quantification.

Exploratory end points

- Time to detection of SARS-CoV-2–specific T-cell immunity
- Time to detection of SARS-CoV-2–specific antibody-secreting plasma cells
- Time to detection of SARS-CoV-2–specific memory B cells
- Time to waning of SARS-CoV-2–specific T cellular immunity
- Time to waning of SARS-CoV-2–specific antibody-secreting plasma cells
- Time to waning of SARS-CoV-2–specific memory B cells

Study Cohort

Eligibility criteria and other details have been listed in Textbox 3.

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Textbox 3. Eligibility criteria, premature study withdrawal, and enrollment failure

Inclusion criteria

- Patient is vaccinated according to the recent version of the COVID-19 vaccination standard for immunocompromised patients [20]
- Patient is 18 years of age or older at enrollment
- Written informed consent from patient has been obtained prior to any study-related procedures (see obtaining informed consent)
- Patient is immunocompromised according to stage 3 classification "Stages of Immunosuppression" [21] (Multimedia Appendix 2)

Exclusion criteria

- Patient is not vaccinated according to the recent version of the COVID-19 vaccination standard [20]
- Patient has a positive SARS-CoV-2 antigen test at the first visit

Premature withdrawal from the study

In case a patient fulfills one of the following criteria, the patient must be withdrawn from the study

- Patient has reached an adequate immune response as defined in the recent version of the COVID-19 vaccination standard [20] at the first visit

In case a patient has to withdraw prematurely from the study, all data that have been collected between enrollment and withdrawal will be used for the analysis.

Enrollment failure

Enrollment failures are not expected as patients, who are willing to participate and are vaccinated according to the recent version of the COVID-19 vaccination standard [20], are all included in the study.

A minimum set of enrollment failure information is required. Minimum information includes date of informed consent, demography, enrollment failure details, eligibility criteria, and information on any solicited adverse events or serious adverse events that may have occurred from the time informed consent was obtained to the time of withdrawal.

Visits and Study-Related Assessments

Visit details are listed in Textbox 4 and Table 1. The visit schedule is displayed in Table 1.

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Textbox 4. Visits and study-related assessments

Visit 1

Following assessments will be performed at this visit:

- Review of inclusion and exclusion criteria
- Written informed consent will be obtained
- Demographics including age and sex will be obtained
- Relevant medical history including all prior chemotherapy regimens and radiation therapy will be collected
- Collection and review of previous and concomitant medication
- SARS-CoV-2 antigen test obtained from nasal, pharyngeal, nasopharyngeal, or oropharyngeal swab
- Patient diary will be handed out and explained to the patient. Patient is instructed to record solicited adverse events that occur within 7 days after the time of vaccination in the patient diary (the day of vaccination plus the following 6 days)
- Prevaccination blood sampling for SARS-CoV-2–specific B- and T-cell immune response assessment will be performed (maximum 36 mL blood)

All following visits

- Review of any changes of concomitant medication since the last visit and documentation in the electronic case report form if applicable
- Review of patient diary and documentation of adverse events (see safety)
- Prevaccination blood sampling for SARS-CoV-2–specific B- and T-cell immune response assessment will be performed (maximal 18 mL blood)

Follow-up visits

Days in the follow-up period are counted from the day of the last vaccination onward. The visit schedule is displayed in Table 1.

Follow-up visit 1

The following assessments will be performed at this visit:

- Collection of patient diary and documentation of adverse events (see Safety section for details). The patient diary will remain at the study site together with the patients' medical records
- Blood sampling for SARS-CoV-2–specific B- and T-cell immune response assessment (maximal 18 mL blood)

All following follow-up visits

The following assessment will be performed at all subsequent follow-up visit:

- Blood sampling for SARS-CoV-2–specific B- and T-cell immune response assessment (maximal 18 mL blood)
- Previous and concomitant medication of interest

Information on previous and concomitant immunosuppressive medication within 90 days prior to providing informed consent will be recorded in the electronic case report form. In addition, all COVID-19 vaccinations and all therapeutic neutralizing antibodies against SARS-CoV-2 (tixagevimab-cilgavimab, sotrovimab, convalescent plasma, etc) a patient has ever received will be documented in the electronic case report form.

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Table 1. Visit schedule.

Procedures	Vaccination period		Follow-up period	
	Visit 1	All following visits[a]	FU[b] 1	All following FUs
Day[c]	0[c] (42[d])	28-day intervals[c,d]	28[e]	28-day intervals[e]
Visit window (days)	±5	±5	±5	±5
Informed consent	✓			
Demographics	✓			
Review of inclusion and exclusion criteria	✓			
Medical history	✓			
Concomitant medication	✓	✓	✓	✓
SARS-CoV-2 antigen test	✓			
SARS-CoV-2–specific B- and T-cell immune response[f]	✓	✓	✓	✓
Dispensing of the study diary	✓			
Collection of the study diary			✓	
Review of diary and documentation of solicited adverse events[g]		✓	✓	
Complete case report form	✓	✓	✓	✓
Standard cellular immunity[h,i]	✓	✓	✓	✓
SARS-CoV-2 Quantiferon[i]	✓	✓	✓	✓
Omicron-BA.1–specific nAB[i,j,k]	✓	✓	✓	✓
Anti-spike-1/2 IgG[l] antibodies[i,j]	✓	✓	✓	✓
Anti-nucleocapsid IgG[l] antibodies[i]	✓	✓	✓	✓
Anti-SARS-CoV-2 vaccination[i]	✓	✓		

[a]Visit only in case anti-spike-1/2-IgG titer was <847 BAU (binding antibody units)/mL at the previous visit according to standard-of-care COVID-19 vaccination.

[b]FU: follow-up.

[c]Day 0 is the day of the first visit and first vaccination. All days in the vaccination phase are counted in relation to the last vaccination, respectively.

[d]Applicable for patients posthematopoietic stem cell transplantation (HSCT) or chimeric antigen receptor (CAR)–T cell treatment. Day 0 is considered the day of HSCT or CAR-T cell treatment. All days in the vaccination phase are counted in relation to the day of HSCT or CAR-T cell treatment, respectively.

[e]Days in the follow-up phase are always counted in relation to the last vaccination.

[f]Maximum 36 mL blood is collected at visit 1. At all other visits, maximum 18 mL blood is collected.

[g]Solicited adverse events will be documented for 7 days after each vaccination.

[h]Contains blood cell count, T-lymphocytes (CD3, CD4, CD8), natural killer cells (CD16+56), B-lymphocytes (CD19), and activated T cells (CD38, HLA-DR).

[i]Performed as part of the COVID-19 vaccination standard [20] in the clinical routine. Data generated within the standard procedures will be used for analysis of the study objectives.

[j]Anti-spike-1/2 IgG titer ≥33.8 BAU/mL was interpreted as reactive, according to the manufacturer's instructions (DiaSorin). To determine Omicron BA.1-specific neutralizing serum titers, the lowest tested serum dilution was 1:30, which served as the lower limit of quantification.

[k]nAB: neutralizing antibody.

[l]IgG: immunoglobulin G.

Safety

Solicited Adverse Events

In order to evaluate the reactogenicity of COVID-19 vaccinations applied within the SOC [20], this study collects solicited adverse events (AEs) for 7 days (the day of vaccination plus the following 6 days) after each vaccination. As a noninterventional study, this study focuses on solicited AEs only, that is, on a subset of all AEs. Solicited AEs will be collected by the patient using a patient diary. Solicited AEs will be documented starting on the day of each vaccination within the SOC [20] and the following 6 days. The grading system of solicited AEs is based on the Toxicity Grading Scale for Healthy Adult and Adolescent Volunteers Enrolled in Preventive Vaccine

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Clinical Trials [22] and the Common Terminology Criteria for Adverse Events v5.0 (CTCAE) [23] grading systems (Multimedia Appendix 2).

Adverse Drug Reactions

An ADR is defined as a response to a drug that is noxious and unintended and which occurs at doses normally used in humans for prophylaxis, diagnosis, or therapy of disease or modification of physiological function. All ADRs related to one of the COVID-19 vaccines used within the COVID-19 vaccination standard [20] occurring during the study period will be documented in the electronic case report form (eCRF). A serious AE or serious ADR is any untoward medical occurrence that at any dose meets any of the following criteria: (1) results in death, (2) is life-threatening, (3) requires inpatient hospitalization or prolongation of existing hospitalization, (4) results in persistent or significant disability or incapacity, or (5) is a congenital anomaly or birth defect. Serious AEs occurring 7 days (the day of vaccination plus the following 6 days) after each vaccination will be collected in the eCRF.

Serious ADRs occurring during the study period (including the follow-up period) will also be collected in the eCRF.

Monitoring

The study sites will be monitored to ensure the quality of the data collected. The objectives of the monitoring procedures are to ensure that the subject's safety and rights as a study participant are respected; that accurate, valid, and complete data are collected; and that the study is conducted in accordance with the study protocol, the principles of Good Clinical Practice (GCP), and local legislation. The exact extent of the monitoring procedures is described in a separate monitoring plan. Monitoring will follow a risk-adapted on-site monitoring strategy. All principal investigators (PIs) agree that the monitor regularly visits the study site and assures that the monitor will receive appropriate support in their activities at the study site, as agreed in separate contracts with each study site. The declaration of informed consent includes a statement allowing the monitor to compare the CRFs with the study subject's medical records (doctor's notes, laboratory printouts, etc). The PI will secure access for the monitor to all necessary documentation for study-related monitoring. A monitoring visit report is prepared for each visit describing the progress of the study and any challenges. The PI will reasonably consider the corrective and preventive measures suggested by the monitor. All participant data relating to the study will be recorded on eCRFs. The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF. The investigator must permit study-related monitoring, audits, Research Ethics Committee or National Competent Authority review, and regulatory agency inspections, and provide direct access to source data documents.

Documentation

PIs will oversee and coordinate data collection, entry, and protection. Study-specific data will be collected by the study staff using designated source documents. Standard GCPs will be followed to ensure accurate, reliable, and consistent data collection. All study data must be verifiable to the source documentation. All source documents will be kept in a locked facility at the study site.

Data Management

Data management activities will be conducted by the Clinical Trials Centre Cologne (CTCC). The IT infrastructure and data management staff will be provided by the CTCC. The study database will be developed and validated before data entry based on standard operating procedures at the CTCC. The data management system is based on commercial trial software and stores the data in a database. All changes made to the data are documented in an audit trail. The trial software has a user and role concept that can be adjusted on a trial-specific basis. The database is integrated into a general IT infrastructure and safety concept with a firewall and backup system. The data are backed up daily. After completion and cleaning of data, the database is locked and the data are exported for statistical analysis. The data will be entered online at the study sites via the internet. Plausibility checks are run during data entry, thereby detecting many discrepancies immediately. The CTCC data management will conduct further checks for completeness and plausibility and will clarify any questions with the study sites electronically via the trial software. These electronic queries have to be answered by the study site without unreasonable delay. Further details will be specified in the data management manual. A guidance document for data entry in the eCRF will be provided. All participant data relating to the study will be recorded on eCRFs unless transmitted to the sponsor or designee electronically (eg, laboratory data) via secure platform transfer or encrypted email. The investigator is responsible for verifying that data entries are accurate and correct by electronically signing the CRF.

Archiving

All essential documents according to GCP of the International Council for Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH-GCP) chapter 8 will be archived for at least 10 years unless longer times are foreseen by local regulatory requirements. No records may be destroyed during the retention period without the written approval of the lead PI of the investigator-initiated trial. No records may be transferred to another location or party without written notification to the lead PI of the investigator-initiated trial. Digitization of paper-based documentation must meet regulatory requirements, especially concerning quality assurance, completeness, and correctness. Paper-based documentation must not be destroyed after digitization and must be archived according to applicable regulations.

Timelines for the Study Participant

Within a SOC vaccination [20], every patient will receive a varying number of COVID-19 vaccinations. Accordingly, patients will be documented within this study for varying durations depending on the number of vaccine doses needed according to the recent version of the COVID-19 vaccination standard [20] (Table 2).

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Table 2. Study timeline.

Milestone	Timepoint (quarter)
First patient first visit	Q2 2023
Last patient first visit	Q3 2024
Last patient last visit	Q3 2024
End of study	Q4 2024
Final study report	Q4 2024

Statistical Considerations

The primary analysis set comprises all enrolled patients who received at least one vaccination within the COVID-19 vaccination standard [20]. The statistical analysis is essentially descriptive and focuses on estimation of the time to event, that is, primary and secondary end points. The event-time distributions are described by the Kaplan-Meier method [24] with pointwise 95% confidence bounds [25] (18, "log-log"). Relevant percentiles (eg, quartiles) with 95% CIs are derived. Generally, quantitative variables are summarized by mean, SD, and percentiles (0, 25, 50, 75, 100), and qualitative variables by absolute (ie, count) and relative (ie, percentage) frequencies. Extreme values ("outliers") are flagged and listed.

Sample Size

The target sample size of 100 is sufficient to estimate event-free probabilities around the median "survival" with acceptable precision (half-width of a 95% CI) of about 10% for censoring rates less than 20% (Table 3).

Table 3. Sample size calculation.

Number of events	Half width[a] (%)
100	9.7
90	9.9
80	10.2
70	10.6
60	11.1
50	11.8
40	13.3
30	15.4
20	19.7
10	21.7
0	__[b]

[a]"Absolute" percentage points.

[b]Not applicable.

Ethical Considerations

Ethics

This study will be conducted in accordance with the protocol and with the following:

- Consensus on ethical principles derived from international guidelines, including the Declaration of Helsinki and the Council for International Organizations of Medical Sciences international ethical guidelines
- Applicable ICH-GCP guidelines dated July 1996 and its Addendum E6(R2) of June 2017

The study was approved by the lead Ethics Committee of the University of Cologne (Cologne, Germany; 22-1279-NIS), and approval by the responsible Ethics Committee for the study sites Aachen and Essen followed.

Obtaining Informed Consent

Patients will be informed verbally and in writing in a comprehensible language about the nature, scope, and possible consequences by the PI or subinvestigator. This includes consent to data access by representatives of the lead PI of the Investigator Initiated Trial (eg, monitors). The patient will be informed of potential benefits and possible risks associated with participation in the study. Of note, risks associated with study participation are considered minimal and are limited to data protection. No additional interventions (eg, vein puncture) or treatments are foreseen as part of study participation. Patients will be informed that withdrawal of consent is possible at any time without giving a reason and without jeopardizing the patients' further course of treatment. It is the PIs or subinvestigators responsibility to ensure that the patient fully understands the implications of participation in the study. Patients must not be enrolled in the study unless they have

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consented to take part in writing. The patients' medical records must contain a statement that written informed consent was obtained, including the date on which the consent was obtained. In addition, the authorized person at the study site (investigator or subinvestigator) who obtains the informed consent must also sign the informed consent form (ICF) according to the ICH-GCP guidelines. Patients must be reconsented to the most current version of the ICFs during their participation in the study if relevant. The signed consent form is archived at the study site as the original. Patients receive copies of the signed ICF. The ICF and all other documents handed out to the study participants will be submitted to the ethics committee before use. Monitors will check that the most recent ICF was used before the patient's inclusion and that it was dated and signed by the patient himself or herself.

Results

As of August 2024, the Auto-COVID-VACC study has enrolled 32 patients. The study is still in the recruitment phase.

Discussion

Overview

The COVID-19 vaccination standard, implemented at the University Hospital of Aachen, Cologne, and Essen, poses an individual vaccination approach for each patient depending on their individual immune response. The evaluation of the data on humoral and cellular immune responses generated within this COVID-19 vaccination standard will be used to optimize vaccination schedules for patients who are immunocompromised. Results may further help to identify the optimal timing of booster vaccinations within this patient population and their subsets and will lead to increased rates of protection against severe SARS-CoV-2 infections. As the patients included in this study have varying underlying diseases (eg, multiple myeloma, Hodgkin lymphoma) and follow different treatment concepts (eg, chemotherapy, immunotherapy, hematopoietic stem cell transplantation), study results may identify risk and treatment factors on the humoral and cellular immune response in patients receiving COVID-19 vaccination.

Limitations

This study design has several a priori limitations. The study focuses on COVID-19 vaccination only. Patients with SARS-CoV-2 infection are excluded when tested positive; however, studies have shown that SARS-CoV-2 infections also induce immune responses and therefore increase protection [26]. Future study results have to be interpreted cautiously due to the potential risk of bias as data are collected as part of an observational study and in the frame of a SOC COVID-19 vaccination schedule. Patients therefore are not randomized. Further, potential confounders are not included in the statistical analysis.

Conclusions

Patients who are immunocompromised are at high risk for severe SARS-CoV-2 infections. Data on the efficacy of COVID-19 vaccination in this group are still lacking. The study aims to determine the immunogenicity and reactogenicity of the COVID-19 vaccination standard in patients who are immunocompromised by evaluating the available data on humoral and cellular immune responses.

Acknowledgments

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Conflicts of Interest

LMC reports grants for a doctoral scholarship from the DZIF within the framework of this study. JS has received research grants from the BMBF, Noscendo, and Basilea Pharmaceuticals; has received speaker honoraria from AbbVie, Hikma, Pfizer, and Gilead; and has been a consultant to Gilead, Alvea Vax, and Micron Research outside the submitted work. CS reports honoraria and consultancy from Amgen, BMS, GSK, Janssen, MSD, Novartis, Pfizer, Roche, Sanofi, and Takeda; has received research support from Novartis, Takeda, and Janssen. RS reports grants from the German Center for Infection Research; lecture and speaker honoraria from Akademie für Infektionsmedizin e.V., Hikma, and Pfizer; and travel support from the European Confederation of Medical Mycology, Page Medical, and Pfizer, all outside of the submitted work. JP has received investigator-initiated grants from Pfizer; speaker fees from Pfizer, Gilead, Swedish Orphan Biovitrum, and Associates of Cape Code; and is a stockholder of AbbVie Inc. and Novo Nordisk—all outside of the submitted work. SCM reports grants from DZIF and has received speaker honoraria from Pfizer. OAC reports grants or contracts from BMBF, Cidara, DZIF, EU-DG RTD, F2G, Gilead, MedPace, MSD, Mundipharma, Octapharma, Pfizer, and Scynexis; consulting fees from Abbvie, AiCuris, Basilea, Biocon, Boston Strategic Partners, Cidara, Seqirus, Gilead, GSK, IQVIA, Janssen, Matinas, MedPace, Menarini, Molecular Partners, MSG-ERC, Mundipharma, Noxxon, Octapharma, Pardes, Partner Therapeutics, Pfizer, PSI, Scynexis, Seres, Shionogi, and The Prime Meridian Group; speaker and lecture honoraria from Abbott, Abbvie, Akademie für Infektionsmedizin, Al-Jazeera Pharmaceuticals/Hikma, amedes, AstraZeneca, Deutscher Ärzteverlag, Gilead, GSK, Grupo Biotoscana/United Medical/Knight, Ipsen Pharma, Medscape/WebMD, MedUpdate, MSD, Moderna, Mundipharma, Noscendo, Paul-Martini-Stiftung, Pfizer, Sandoz, Seqirus,

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Shionogi, streamedup!, Touch Independent, and Vitis; payment for expert testimony Cidara; and participation on a data review committee, data and safety monitoring board, and advisory board for Cidara, IQVIA, Janssen, MedPace, PSI, Pulmocide, and Vedanta Biosciences.

Multimedia Appendix 1
COVID-19 vaccination standard.
[PDF File (Adobe PDF File), 264 KB - resprot_v14i1e60675_app1.pdf]

Multimedia Appendix 2
Stages of immunosuppression (Table S1); Definition and grading of solicited adverse events (Table S2).
[DOCX File , 29 KB - resprot_v14i1e60675_app2.docx]

Multimedia Appendix 3
Primary end point definition for the Auto-COVID-VACC trial.
[PDF File (Adobe PDF File), 428 KB - resprot_v14i1e60675_app3.pdf]

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Abbreviations

ADR: adverse drug reaction
AE: adverse event
CAR: chimeric antigen receptor
CTCAE: Common Terminology Criteria for Adverse Events
CTCC: Clinical Trials Centre Cologne
eCRF: electronic case report form
ICF: informed consent form
ICH-GCP: Good Clinical Practice (of the International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use)
IgG: immunoglobulin G
PI: principal investigator
SOC: standard of care

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Protocol

Using Blood Group Genotyping to Predict Hemolysis in Patients With β-Thalassemia Major With Frequent Transfusions: Protocol for a Cross-Sectional Study

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Abstract

Background: Hemolytic transfusion reactions are a major complication in patients with β-thalassemia major receiving regular transfusions. These reactions can be influenced by blood group incompatibilities, particularly in settings with limited genotyping practices. In Indonesia, the role of blood group genotyping in predicting hemolysis has not been thoroughly studied.

Objective: This study aims to analyze the association between blood group genotyping and the incidence of hemolysis in people with thalassemia undergoing repeated transfusions.

Methods: This is a cross-sectional study involving people with β-thalassemia major younger than 18 years old who received regular transfusion with intervals of 2-4 weeks and have received more than 20 units of transfusion. Participants with leukemia, lymphoproliferative diseases, diabetes, solid tumors, and immunosuppression disorders were excluded from the study. Genotyping examination was conducted using Allele-Specific polymerase chain reaction (PCR ASP) while phenotyping was examined using immunoserology. Follow-up gene sequencing was conducted to observe the blood group variants. Hemolysis was assessed using several markers such as haptoglobin, free hemoglobin, lactate dehydrogenase, bilirubin, and hemoglobinuria, measured by Cobas C113, the enzyme-linked immunosorbent assay, and urinalysis.

Results: Clinical and laboratory data collection is completed. A total of 90 samples were collected, data analyses were undertaken, and the initial results were reported in September 2024.

Conclusions: The results of this study will provide information on the blood groups' systems that can predict hemolysis occurrence in patients with β-thalassemia undergoing repeated transfusion. These data will contribute to the best possible patient care management and blood transfusion therapy, thereby reducing the risk of hemolysis and improving the quality of life for patients with thalassemia in Indonesia.

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KEYWORDS

alloimmunization; phenotype; genotype; hemolysis; thalassemia; blood group; transfusions; study protocol; Indonesia; cross-sectional study; gene sequencing; hemoglobin; blood transfusion therapy

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Introduction

Background

β-Thalassemia is particularly prevalent in the Mediterranean, Middle East, and Southeast Asia. Annually, over 40,000 babies are born with β-thalassemia, with about 25,500 cases being transfusion-dependent thalassemia. Patients with transfusion-dependent thalassemia require lifelong packed red cell transfusions to maintain hemoglobin levels between 9 and 11.5 g/dL. In Southeast Asia alone, 20,420 newborns are affected each year, with the Mediterranean and Europe seeing 9914 and 1019 cases, respectively, and 341 cases occurring in America. According to the World Health Organization, Indonesia has a β-thalassemia carrier prevalence of 3%-10% per year [1], corroborated by the Ministry of Health of the Republic of Indonesia, which reports that 3.8% of the Indonesian population is carrier [2].

Patients with β-thalassemia who require repeated blood transfusions are at risk of transfusion-related complications, including excessive iron accumulation, alloimmunization, infections, and transfusion reactions [3]. We can divide transfusion reactions into two types: (1) acute transfusion reactions, which can occur from the time of transfusion to 24 hours after transfusion, and (2) delayed transfusion reactions, which can occur more than 24 hours to 1.5 months after transfusion. Delayed hemolytic transfusion reactions are particularly concerning in patients with thalassemia due to the chronic nature of their transfusion requirements. These reactions can lead to significant morbidity, including fever, decreased hemoglobin levels, and elevated markers of hemolysis, such as lactate dehydrogenase (LDH), bilirubin, and free hemoglobin [4]. Free hemoglobin can be measured in the decreased serum haptoglobin and hemoglobinuria due to intravascular hemolysis [5,6].

Lifelong blood transfusions can lead to the development of anti–red blood cell (RBC) antibodies, including alloantibodies and autoantibodies. The emergence of alloantibodies and autoantibodies to RBC antigens will impede the acquisition of compatible crosses, shorten transfused cells' in vivo survival, increase iron deposition in tissues, and delay the provision of safe transfusions [4]. The homogeneity of donor and recipient populations, RBC phenotype matching policies, and age at transfusion initiation can influence the frequency of alloimmunization, according to research and literature [4,7-9]. The incidence of alloimmunization in thalassemia is reported to range from 4% to 50%, with anti-E, anti-C, and anti-Kell being the most common alloantibodies identified [7,8]. These rates are influenced by factors such as donor-recipient population homogeneity, RBC phenotype matching policies, and age at the start of transfusion [4,7-9].

Current national guidelines in Indonesia for pretransfusion-packed red cell examination primarily focus on ABO and Rhesus D blood group systems. However, additional clinically significant blood group antigens, such as those within the Kell system, are often not routinely matched, which could increase the risk of alloimmunization and subsequent hemolytic reactions [4,10]. Moreover, many transfusions do not use leukoreduced products, which further increases the risk of transfusion reactions.

This study addresses the limited comprehensive assessment of blood group genotyping in Indonesia. The primary aim is to assess the association between blood group genotyping and hemolysis in patients with thalassemia in the Banyumas region of Indonesia, using molecular genotyping data to provide a more refined understanding of transfusion reactions within this specific population.

The development and application of molecular methods for blood group genotyping in patients with thalassemia could provide more precise cross-matching and monitoring of transfusion responses. Genotyping offers a detailed understanding of blood group antigen profiles beyond the standard serological methods, potentially reducing the risk of alloimmunization and improving transfusion safety and outcomes. Understanding the distribution of ABO, Rhesus, and Kell genotypes in the Indonesian Thalassemia population and their association with hemolysis could inform clinical practice and guide policy changes toward more personalized transfusion strategies [11,12].

In addition, genotype-phenotype discordance can occur in blood group antigens where the genetic data does not align with phenotypic expression due to factors like genetic mutations or epigenetic regulation. Understanding such discordance is crucial as it may affect transfusion outcomes and necessitate more sophisticated diagnostic approaches [13]. Moreover, other genetic factors, such as human leucocyte antigens or nonhuman leucocyte antigens genes, may influence the immune response to transfusions and impact the risk of hemolysis and alloimmunization. These aspects are essential for a comprehensive understanding of transfusion complications and are potential areas for future research [6].

Aim of the Study

The study aimed to analyze the association of blood group genotyping with the incidence of hemolysis in patients with thalassemia undergoing repeated transfusions at Banyumas Regional Hospital, a key referral center for thalassemia care in Indonesia. By identifying specific genotypes that predispose patients to hemolytic reactions, the study seeks to contribute to the development of tailored transfusion strategies that enhance patient care and reduce the risk of adverse outcomes.

Methods

Design

This study is a cross-sectional, observational analytic study designed to assess the association between blood group genotyping and the incidence of hemolysis in β-thalassemia major patients undergoing repeated transfusions. The study follows the STROBE (Strengthening the Reporting of Observational studies in Epidemiology). The completed STROBE checklist can be found in the Multimedia Appendix 1. STROBE guidelines are used for reporting observational studies cross-sectional design allows for a snapshot of data to identify potential associations between genotypes and hemolysis at a single point in time, it does not establish causality or capture

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changes over time [14]. This limitation highlights the need for future longitudinal studies to explore these relationships dynamically and over extended periods.

Setting

The study was conducted at Banyumas Regional Hospital in Central Java, Indonesia, from February 1, 2024, to the present. Banyumas Regional Hospital is a referral center for thalassemia care in southern Central Java and surrounding areas, providing an integrated thalassemia service since 2009.

Population and Research Participants

The participants of this study were patients with thalassemia who underwent repeated transfusions at Banyumas Hospital. Inclusion and exclusion criteria are summarized in Textbox 1.

Textbox 1. Inclusion and exclusion criteria for study participation.

Inclusion criteria:

- Age 0 to less than 18 years
- Participants were diagnosed with β-thalassemia major based on history taking, clinical examination, and hemoglobin electrophoresis results. Received red blood cell transfusions at a minimum interval of 2-4 weeks.
- Participants had received transfusions of at least 20 units [15].
- Received packed red cell blood transfusions (store 7 days).

Exclusion criteria:

- Participants with a diagnosis of leukemia.
- Participants with a diagnosis of lymphoproliferative disease.
- Participants with a diagnosis of diabetes.
- Participants with a diagnosis of solid tumors.
- Participants have immunosuppression disorders.

Calculation of sample size estimated proportion (prevalence) in finite population [15]. An assumed prevalence of 8%, based on the study conducted by Kasraian et al [11]. The minimum required sample size was determined to be 90 participants, assuming a 95% CI and a margin of error of 5%. The prevalence estimate was derived from previous studies reporting hemolysis rates in similar patient populations. The final sample size included 134 patients to account for potential dropouts and to ensure adequate power to detect significant associations between blood group genotypes and hemolysis. The sampling method is simple random sampling.

Data Collection and Measurement

Venous blood samples were taken as much as 6 cc in EDTA and without coagulant tubes, as well as urine samples. Genotyping examination using Allele-Specific polymerase chain reaction (PCR ASP) and phenotyping using immunoserology [12]. Follow-up gene sequencing to see blood group variants [13].

Genotyping and Phenotyping Identification

Genotyping

Blood group genotyping for ABO, Rhesus, and Kell alleles was performed using PCR ASP. Primers were designed and validated to ensure specificity and efficient amplification (Multimedia Appendices 2 and 3 for further details). Design criteria included appropriate length, GC content, and melting temperature, with in silico verification using NCBI (National Center for Biotechnology Information) BLAST. Experimental validation involved PCR (polymerase chain reaction) optimization, amplicon size confirmation by gel electrophoresis, and sequencing for allele confirmation. Quantitative PCR was used where necessary, with standard curve and melt curve analysis to ensure reliable quantification [16].

Phenotyping

Immunoserological phenotyping was conducted using the hemagglutination technique. The gel cards used were from Bio-Rad Laboratories, Dia Med GmbH, Switzerland for the detection of anti-A, anti-B, anti-D, anti-C, anti-E, and anti-K antibodies. Forward grouping was performed by reacting blood cells with antisera, while reverse grouping was performed by reacting serum samples with control blood cells. All reagents and techniques were standardized, and external quality controls were implemented to ensure the accuracy of the phenotyping results. Plasma samples that exhibited a positive result with the ID-Daicel antibody screen underwent antibody identification using an extended commercial 11-cell identification panel (ID-DiaPanel) using LISS/Coombs.

Identification of Hemolysis

Markers of hemolysis (haptoglobin, free hemoglobin, lactate dehydrogenase [LDH], bilirubin, and hemoglobinuria) were examined before and after transfusion [5,17]. Hemolysis was identified using the following cutoff values: plasma free hemoglobin>10 mg/dL, haptoglobin <25 mg/dL, LDH >300 U/L, indirect bilirubin>2 mg/dL, and urine hemoglobin >100 ng/mL. These cutoffs were used to assess the severity of hemolysis.

Alloimmunization, defined as the presence of alloantibodies against RBC antigens, will be identified using an indirect antiglobulin test. Positive indirect antiglobulin test results will prompt antibody identification (ID-DiaPanel) focusing on

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clinically significant antigens within the ABO, Rh, and Kell systems.

Data Analysis

The data analysis for this study will involve a comprehensive approach to evaluate the association between blood group genotyping and the incidence of hemolysis in β-thalassemia major patients undergoing repeated transfusions. A descriptive analysis will be conducted for all measured variables, with outliers assessed using boxplots and subsequently excluded from further analyses. The primary measure will be the incidence of hemolysis, evaluated through laboratory markers such as haptoglobin, free hemoglobin, LDH, bilirubin, and hemoglobinuria, measured both before transfusion and 1 hour post transfusion. Bivariate analyses using chi-square tests will be used to analyze the effects of various factors on hemolysis and alloimmunization. Following this, logistic regression models will identify independent predictors of hemolysis while adjusting for potential confounders identified in preliminary analyses. The regression models will include variables found significant in the bivariate analysis, with P values of <.05 considered statistically significant. Key independent variables include blood group genotypes (ABO, Rhesus, and Kell), age, frequency of transfusions, duration of thalassemia diagnosis, underlying medical conditions, and iron chelation therapy status. The selection of these variables was guided by previous literature identifying factors associated with hemolysis and their clinical relevance. Our primary hypothesis posits that specific blood group genotypes are significantly associated with an increased incidence of hemolysis in patients with thalassemia with repeated blood transfusion. In addition, we hypothesize that clinical factors such as age, transfusion frequency, and durations will also significantly influence hemolysis incidence. Missing data will be managed using multiple imputation methods to minimize bias, and sensitivity analyses will compare results from complete-case analyses with those including imputed data to ensure robustness.

Ethical Considerations

This study adheres to ethical standards for research involving human participants, as mandated by institutional guidelines and international regulations.

Human Subject Ethics Review Approvals

The study protocol has been approved by the Ethics Committee of the Faculty of Medicine, Public Health, and Nursing at Gadjah Mada University (approval number 1511/UN1/FK-KMK.3/S3KK.3/PJ/2023). This approval ensures that all research activities comply with ethical principles for conducting research involving human participants.

Informed Consent

Informed consent was obtained from all participants or their legal guardians before participation in the study. Participants were informed of their rights, including the ability to withdraw from the study at any time without any impact on their medical care. For secondary analyses using existing data, we confirm that the original consent covers secondary analysis without requiring additional consent.

Privacy and Confidentiality

All data collected during this study will be anonymized to protect participant identities. Personal identifiers will be removed from datasets, ensuring that individual participants cannot be identified from the data. Data will be stored securely and accessed only by authorized personnel involved in the study.

Compensation Details

Participants will not receive monetary compensation. Instead, they will be provided with the results of their blood group genotyping and phenotyping as part of their participation in the study. The compensation will be communicated clearly to participants during the consent process, ensuring transparency and fairness in the compensation process.

Identification of Participants in Images

No identifiable images of participants will be included in the article or Multimedia Appendices 1-3. If any images are deemed necessary for inclusion, a statement confirming that consent has been granted from identifiable individuals will be provided, along with relevant consent forms uploaded during resubmission.

Results

Data collection for this study was funded in June 2024, with recruitment and sample collection conducted from July 2024 to January 2025. A total of 90 samples were collected, and clinical and laboratory data compilation has been completed. Data analyses are currently underway, and the first results are expected to be reported in May 2025.

The flow diagram is outlined in Figure 1.

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Figure 1. Flowchart of β-thalassemia major participants, eligible participants will be enrolled, and peripheral blood and urine samples will be collected before and after transfusion. Required clinical data will be collected from patients' medical records. LDH: lactate dehydrogenase.

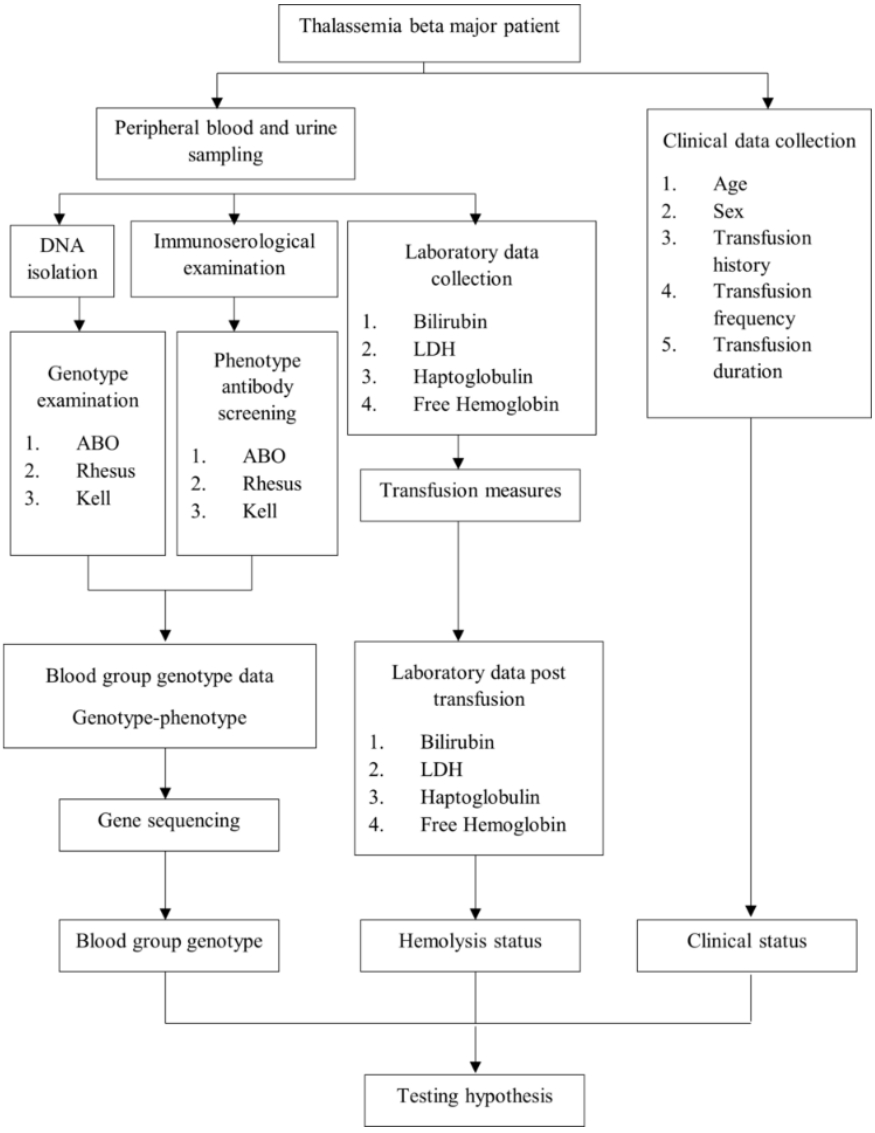

Discussion

Principal Findings

Our study generates baseline data for the Banyumas region in Indonesia, allowing for the development of targeted transfusion strategies tailored to the local population. These strategies contribute to the global understanding of thalassemia management by highlighting the importance of considering regional variations in blood group genetics. Thus, even with the limited sample size, the initial findings have the potential to inform clinical practice and policy changes within Indonesia, laying the groundwork for more personalized transfusion strategies and to global understanding of thalassemia in regions with limited data.

Preliminary findings suggest an association between certain blood group genotypes and higher hemolysis rates in patients with thalassemia receiving repeated transfusions. Though complete results are pending, initial data trends support our hypothesis that specific genotypes, especially within the ABO and Rh systems, correlate with increased hemolysis events, likely due to alloimmunization risks tied to blood group antigens [5].

Observed variations in markers such as LDH, bilirubin, and haptoglobin levels in particular genotypes strengthen the case for targeted monitoring. These trends suggest that some blood group genotypes may predispose individuals to hemolytic reactions, reinforcing the importance of considering genotype-matching in transfusion protocols for patients with thalassemia. While more data is needed for a conclusive analysis, these early insights indicate that genotype-specific risks should be addressed to enhance transfusion safety and efficacy [11].

Specifically, we anticipate that identifying specific blood group genotypes associated with hemolytic reactions will lead to more personalized transfusion strategies, ultimately improving patient care and outcomes [3]. This approach situates the study's purpose within the broader context of enhancing patient safety and expanding academic knowledge in this critical area of transfusion medicine.

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Limitations

This study has identified several limitations. First, the study's sample size of 90 patients may not adequately capture the full genetic and clinical diversity found in larger populations of β-thalassemia major patients in Indonesia or globally. Second, the single-center design of this study may introduce selection bias. This could limit the generalizability of the findings. Third, a cross-sectional study offers only a snapshot of data at a single point in time, failing to account for changes over time or establish causality between genotypes and the incidence of hemolysis. Furthermore, the absence of a cost-effectiveness analysis in this study limits our understanding of the economic implications of implementing genotype-based blood group testing in this population. Future research should address this limitation by conducting a formal cost-effectiveness analysis to evaluate the financial impact of routine genotyping in patients with thalassemia. Therefore, further investigation with larger populations, multicenter studies, and implementing a longitudinal design will be necessary to ensure generalizable findings and help establish causality and track changes over time.

Future research should investigate the long-term impacts and cost-effectiveness of blood group genotyping, and the genetic basis of alloimmunization in thalassemia. This information can inform policies to integrate genotyping into transfusion protocols, enhancing patient safety and quality of life.

Dissemination Plan

The dissemination plan for this study on the role of blood group genotyping in predicting hemolysis among people with β-thalassemia major undergoing repeated transfusions involves multiple strategies to ensure broad impact and application in clinical practice. We will submit the primary results for publication in high-impact, peer-reviewed medical journals and present them at national and international conferences to engage with experts and foster collaborations. In addition, workshops and seminars will be conducted at local hospitals and universities to educate health care professionals about the study's findings and their practical applications. Policy briefs and recommendations will be formulated for health care authorities and policy makers to promote the integration of blood group genotyping into standard transfusion protocols. Collaborating with patient advocacy groups will ensure that information is widely shared through newsletters, social media, and educational materials. Simplified educational materials will be distributed in hospitals, clinics, and support groups. The findings and resources will also be available on open-access platforms and internet-based forums to engage the global thalassemia and transfusion medicine community. This approach aims to inform clinical practice, guide policy development, and enhance patient education, ultimately advancing thalassemia care globally, with a focus on transitional countries.

Conclusions

Our study highlights the complex interaction between blood group genotypes and hemolysis risk in patients with thalassemia undergoing repeated transfusions. Early findings suggest that certain genotypes, particularly in the ABO, Rhesus, and Kell blood group systems, may be associated with a higher incidence of hemolysis due to alloimmunization. This underlines the importance of exploring molecular genotyping to ensure better transfusion compatibility. Observing variations in hemolysis markers such as LDH, bilirubin, and haptoglobin in relation to specific blood genotypes, our research emphasizes the potential benefits of genotype-matched transfusions. By identifying genotype-specific responses, we aim to reduce hemolysis and improve patient outcomes in long-term transfusion therapy. Further research with a larger cohort will be essential to confirm these preliminary associations and develop targeted transfusion strategies that prioritize genotype compatibility. Ultimately, this study serves as a foundation for implementing genotype-informed transfusion protocols, promising improved care quality and safety for patients with thalassemia.

Acknowledgments

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Authors' Contributions

VI, TT, and BM contributed to the conceptualization and methodology of the study. VI was responsible for investigation and writing the original draft. TT and BM provided supervision and contributed to writing-review and editing. All authors read and approved the final manuscript and take full accountability for its content.

Conflicts of Interest

None declared.

Multimedia Appendix 1
STROBE (Strengthening the Reporting of Observational studies in Epidemiology) statement—checklist of items that should be included in reports of observational studies.
[DOCX File , 36 KB - resprot_v14i1e64379_app1.docx]

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Multimedia Appendix 2
Protocol for identification hemolysis.
[PDF File (Adobe PDF File), 68 KB - resprot_v14i1e64379_app2.pdf]

Multimedia Appendix 3
Primers used in allele-specific polymerase chain reaction (PCR ASP) for ABO, Rh, and Kell blood group genotyping.
[DOCX File , 16 KB - resprot_v14i1e64379_app3.docx]

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Abbreviations

LDH: lactate dehydrogenase
NCBI: National Center for Biotechnology Information
PCR: polymerase chain reaction
PCR ASP: Allele-Specific polymerase chain reaction

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RBC: red blood cell
STROBE: Strengthening the Reporting of Observational studies in Epidemiology

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Protocol

Virtual Life Story Club Intervention to Improve Loneliness and Apathy in Community-Dwelling Older Adults: Protocol for a Mixed Methods Feasibility Study

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Abstract

Background: Reminiscence therapy is a noninvasive, nonpharmacological intervention that has been shown to improve cognition, mood, functional status, quality of life, and apathy in older adults. Group reminiscence therapy combines structured social engagement and recounting of personal stories that address both social connection (a risk factor for cognitive decline) and cognition. Life Story Club is an established, nonprofit organization that provides virtual group reminiscence therapy for older adults to reduce loneliness and promote a sense of belonging and has not been formally studied.

Objective: This study aims to explore the feasibility of a Life Story Club intervention to improve loneliness and apathy in community-dwelling older adults.

Methods: A prospective, single-arm, single-center, pilot study will be conducted to compare loneliness and apathy in 50 lonely individuals without dementia at baseline who receive a virtual group reminiscence therapy intervention. The intervention will be delivered weekly over 12 weeks. Loneliness will be assessed with the UCLA Loneliness Scale and apathy will be assessed with the Apathy Evaluation Scale before and after the intervention. Feasibility will be assessed using quantitative and qualitative measures including feasibility of screening and enrollment, acceptability, and program satisfaction. Qualitative interviews will be conducted with a subset of 30 individuals to explore acceptability, barriers, and facilitators of the intervention.

Results: The proposed study is funded by a pilot grant from the Institute for Clinical and Translational Research at Albert Einstein College of Medicine. Recruitment and data collection are planned for July 2025.

Conclusions: This study will provide evidence for the feasibility of virtual group reminiscence therapy for community-dwelling older adults to reduce loneliness and apathy. Our approach is both innovative and pragmatic because we will leverage an existing community-based service, with an established infrastructure and track record within the community to deliver the intervention. As such, the proposed research has the potential for broad implications for community-based research and aligns with multiple translational science principles.

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KEYWORDS

apathy; cognition; community-dwelling; loneliness; reminiscence therapy

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Introduction

Background

An estimated 6.9 million US older adults are living with Alzheimer disease and related dementias (ADRD) and the incidence increases with age [1]. ADRD is characterized by a progressive loss of cognition and function that eventually results in loss of independence and mortality. Currently, there are no curative treatments for ADRD. Thus, there is increased focus on nonpharmacological interventions that target modifiable risk factors for cognitive decline and dementia in older adults.

Apathy is a psychological syndrome characterized by a lack of motivation and interest, flattening of affect, and social withdrawal that predicts cognitive decline and increases the risk of ADRD by 20%-70% [2-10]. The prevalence of apathy ranges between 20% and 30% in community-dwelling older adults [11]. Apathy predicts the incidence of predementia syndromes mild cognitive impairment (MCI) and motoric cognitive risk syndrome, which is characterized by subjective cognitive complaints and slow gait [12,13]. Apathy is associated with social isolation related to a lack of interest in engagement [14]. Similarly, loneliness is highly prevalent in community-dwelling older adults (up to 43% [15]) and is associated with an increased risk of cognitive decline and ADRD [16,17]. Apathy and loneliness both represent potentially modifiable risk factors for cognitive decline and dementia and reminiscence therapy (RT) has been studied to target both these risk factors [18-20].

RT is a noninvasive, nonpharmacological intervention that has been shown to improve cognition, mood, functional status, quality of life, and apathy in older adults [18-24]. RT uses life story recollection in individual or group settings to improve psychological well-being. Prompts, photos, or music are all techniques used to trigger reminiscence, and the intervention can be delivered in person or virtually. Mechanisms for RT for apathy work through structured socialization with prompting from facilitators that stimulate motivation to engage. In addition, social stimuli lead to positive emotions through the sharing of personal stories. Sharing personal stories and a structured social environment that provides opportunities for meaningful engagement that may not happen in a casual social context address loneliness as well. A conceptual model of RT to address loneliness and apathy and how reminiscence may work as an intervention is visually depicted in Figure 1.

Figure 1. Conceptual model of a reminiscence therapy intervention for loneliness and apathy and mechanisms for how the intervention may work. The left side of the figure represents the current proposal where we propose to investigate the feasibility of reminiscence therapy for loneliness and apathy. This research will inform and support a future randomized controlled trial of a reminiscence therapy intervention to improve cognition.

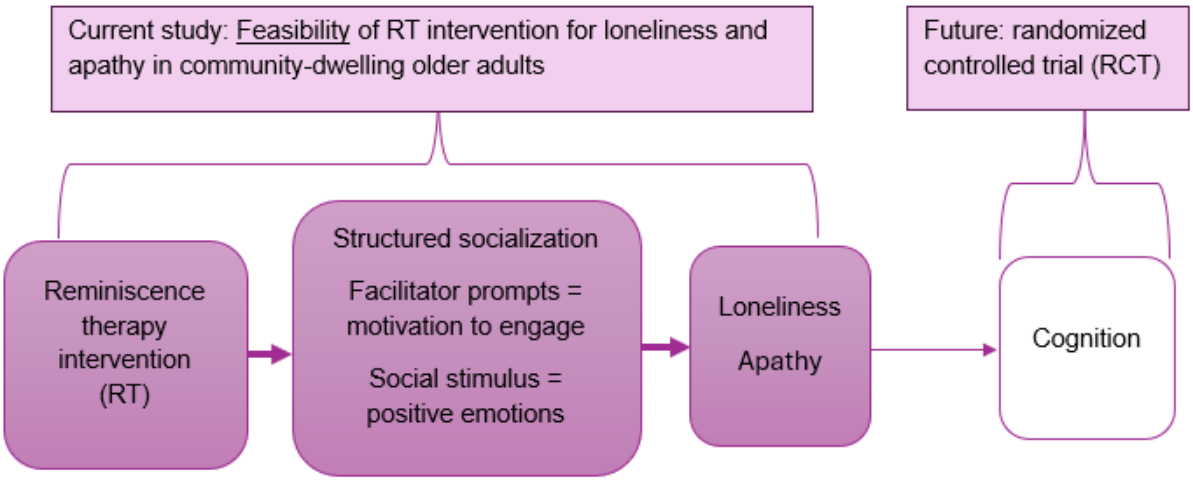

Cognitive decline in aging is multifactorial with multiple possible causes and there is significant variability in cognition based on the presence or absence of risk factors such as social factors (eg, loneliness) and apathy. In addition, the multiple aspects of social relationships (eg, meaning and purpose in life and social support) and psychological well-being (eg, depression) influence cognition via multiple possible paths. Meaning and purpose in life were associated with cognitive decline, and incident MCI and Alzheimer disease in prior studies [25]. In addition, studies investigating volunteering interventions to provide meaningful social, physical, and cognitive activities for older adults reduced brain aging [26]. RT is similarly organized to provide structured social engagement and stimulate cognitive activity through exercising autobiographical memory [27] and improvements in cognition may be mediated through improved life meaning and purpose. Depression is a well-known risk factor for cognitive decline [28] and loneliness and the relationship between loneliness and depression may be bidirectional [29]. In addition, apathy and depression are distinct neuropsychiatric conditions that often co-occur and symptoms may overlap [30]. Given the mechanisms of RT are not well understood, multiple aspects of social relationships and psychological well-being may be considered as mediators of the relationship between RT and health outcomes.

A growing body of research on RT for older adults targets individuals with ADRD and older adults in long-term care, as well as healthy older adults living in the community [18,20,21,31]. In addition, individual RT applied using virtual reality was shown to improve cognition and psychological well-being in institutionalized older adults, compared to traditional RT [32]. Studies on the effects of a virtually delivered group reminiscence therapy intervention that combines the benefits of a group intervention and is delivered virtually using

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communication technologies are scarce. The novelty of this proposal is that the intervention is designed, developed, and delivered via an established community-based organization by nonclinicians and has not been formally studied.

Life Story Club

Life Story Club (LSC) is an established, nonprofit organization founded in Brooklyn, New York, in 2019. The organization is dedicated to reducing loneliness in older adults through RT and has already successfully served more than 1500 older adults. LSCs are virtual, no-cost RT clubs that meet weekly. The clubs are led by trained facilitators who propose 2 story prompts per meeting to invite participants to share their stories (eg, "As a child, what did you say you wanted to be when you grew up?" Or, "Tell a story about a time you or your loved one didn't accept defeat."). Participants alternate responding to prompts and sharing their stories. Facilitators are nonclinicians with teaching, arts, or social science backgrounds. Facilitators undergo comprehensive training including shadowing, on-the-job learning, and certification in Mental Health First Aid and SAFECare LGBTQ+ (lesbian, gay, bisexual, transgender, queer/questioning, and others) Cultural Competency Training prior to leading a club. LSC serves roughly 400 older adults per year and clubs are offered in English, Spanish, Mandarin, or Cantonese. In addition, groups can be phone or video-based to provide for broader access. Clubs can also be tailored based on particular interests such as LGBTQ+ clubs or cooking clubs.

Weekly sessions follow a structured format to ensure consistency and engagement. Weekly prompts are sent to participants via email, text, or phone 1-2 days before the meeting. Sessions begin with greetings and icebreakers. The facilitator then introduces the prompt and shares an example story. Each participant shares a 5-minute story related to one of the prompts and participants are encouraged to engage with the storyteller's experience. Sessions conclude with final thoughts. LSC prompts are drawn from a library designed to evoke a range of autobiographical memories and reflections. Each week, prompts rotate across categories for broad depth and variety in storytelling experiences. LSC structure and prompt categories are detailed in Table 1.

Table 1. Life Story Club program structure.

Parameters	Descriptions
Weekly schedule	
Weeks 1-2	Introductory sessions with get-to-know-you prompts.
Weeks 3-7	Sessions tailored to participants' interests; participants take turns sharing stories based on weekly prompts.
Week 8	Dedicated recording session where stories are recorded for archival purposes.
Weeks 9-11	Regular storytelling sessions continue.
Week 12	Special event for unveiling of the group's Life Story Library.
Prompt categories and examples	
Cultural and historical memories	What is a historical "first" you've lived through?
Occasion-based memories	Can you tell us about a memorable celebration or gathering?
Location-based memories	Tell us about a meaningful or memorable hangout spot in your life.
Youth and childhood	Who was your childhood best friend?
Career-based memories	Can you tell us about an extraordinary day at work?
Current and future life	Can you share a story about a recent triumph?
Relationships	What was something passed down to you from a family member, friend, or mentor?
Identity and self-reflection	When was a time you changed your mindset or way of thinking?

Individuals are referred to LSC via primary care providers and through community outreach via naturally occurring retirement communities, public libraries, and older adult centers. Caregivers, family members, or individuals can also self-refer via the LSC website. RT as delivered by LSC can potentially improve accessibility and equity given its virtual delivery in multiple languages and can extend the reach of the intervention to homebound and rural older adults—the population who are at the highest risk for cognitive decline, tend to be hard to reach, and often not included in research for those reasons. LSC is a well-established community-based organization with a formalized infrastructure to serve community-based older adults.

Study Objectives

The purpose of this study will be to explore the feasibility of a virtual group reminiscence therapy (vGRT) intervention delivered by LSC to improve loneliness and apathy in community-dwelling older adults. Rather than developing a new intervention, we propose to capitalize on an existing community-based resource to deliver a novel, virtual RT intervention directly to individuals in the community. We hypothesize that a virtual, group RT intervention will be feasible and acceptable for community-dwelling older adults.

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Methods

Study Design

This study is a prospective, nonrandomized, mixed methods feasibility study testing the impact of the LSC intervention. The purpose of the proposed study design is to test the feasibility of the intervention and provide preliminary data for a larger randomized controlled trial (RCT).

Recruitment

Participants will be recruited via partnerships with local community-based organizations serving older adults, home care agencies, as well as referrals from health care teams within the health system (eg, post-acute care managers, primary care social workers, and providers). Retention will be maximized by using preintervention counseling, regular opportunities for questions and feedback from participants, and compensation for completing pretest assessments, posttest assessments, and qualitative interviews at costs consistent with Institutional Review Board guidelines. All participants who participated in the LSC intervention will be invited to participate in qualitative interviews and we will enroll up to 30 participants or until saturation is reached.

Inclusion and Exclusion Criteria

Inclusion criteria are (1) age 60 and older and (2) ability to speak sufficient English or Spanish to complete assessments. These criteria are established to ensure that participants can fully engage with the study materials and accurately report their experiences. Individuals with dementia based on the AD8 or previous diagnosis of dementia, severe auditory or visual loss, and lack of access to either an internet connection or telephone will be excluded. The AD8 is an 8-item cognitive screening test sensitive to detecting early cognitive changes associated with common dementias including Alzheimer disease; scores of 2 or more indicate cognitive impairment [33] and can be completed via telephone.

Intervention

LSC is a virtual, social storytelling space for older adults aged 60 and older where members can share life stories and connect with other members to promote a sense of belonging, purpose, and meaning. Clubs include up to 15 members that meet once a week for 1 hour. The number of participants per group is determined based on past levels of participation where 10-15 individuals are recruited per group and 6-8 attend each session due to the nature of the population (eg, multimorbidity and acute illness). The protocol for the study will not deviate from routine LSC protocols and will be offered similarly to the usual schedule and prompts as described in the introduction except for dedicated recording sessions which will be replaced by a usual session (Table 1). Clubs are led by a nonclinician facilitator who offers prompts to trigger discussion and reminiscence. Sessions begin with greetings after which 2 prompts are offered by the facilitator. The facilitator manages the group to encourage participation by all members. To promote technology equity (colloquially referred to as “techquity”), LSC has been delivered via live video or telephone according to participant preference to promote technology inclusiveness. Participants for this study will have the option to use video or telephone based on preference. The primary endpoint for this study will be 3 months based on durations of other RT interventions [31,34]. We will additionally collect assessment data at 6 months to preliminarily determine the feasibility and efficacy of a 6-month intervention in participants who continue to participate in the intervention over a longer period. Fidelity will be assessed via periods of observation by research staff to observe if components of the intervention are met (eg, 2 prompts per session and individual participation).

Data Collection

Assessments will be collected via telephone at baseline, 3 months, and 6 months post RT. Participants will receive a gift card for each completed assessment. Qualitative interviews will be conducted with a subset of 30 participants to assess satisfaction with the intervention, what aspects can be improved, and explore barriers and facilitators of participation, including digital literacy. A semistructured interview guide is included in Multimedia Appendix 1. Interviews will take place at an agreed-upon location over 60 minutes and will be conducted by the primary investigator or coinvestigator. We will collect data on the following outcome measures and covariates:

Primary Outcome

Our primary outcomes will be loneliness and apathy. This is based on our hypothesis that targeting these cognitive decline and dementia risk factors will result in improved cognition in the longer term. Given this is a feasibility study and 3- and 6-month intervals may be too short of a time frame to see a difference in cognition and that the study will not be powered to detect differences in cognition, we propose to examine differences in loneliness and apathy, risk factors for cognitive decline, which can plausibly change in this short interval.

UCLA Loneliness Scale

Loneliness will be assessed using the UCLA Loneliness Scale [35]. The UCLA Loneliness Scale is a well-validated and widely used tool designed to measure subjective feelings of loneliness and social isolation. It evaluates the overall sense of loneliness through 20 items that reflect social isolation and dissatisfaction with one’s social relationships [35]. Participants will be asked to rate each item on a 4-point Likert scale, ranging from 1 (never) and 2 (rarely) to 3 (sometimes) and 4 (often), with higher scores indicating greater loneliness. The total score will be derived by summing the responses across all items, with possible scores ranging from 20 to 80. In this study, loneliness will be treated as a continuous variable. The UCLA Loneliness Scale demonstrates high internal consistency and strong construct validity, correlating well with other measures of loneliness and social well-being [35].

Apathy Evaluation Scale

Apathy will be assessed using the Apathy Evaluation Scale (AES), a validated 18-item tool designed to measure the cognitive, behavioral, and emotional aspects of apathy [36]. Items are scored on a 4-point Likert scale, and higher scores indicate greater levels of apathy. The AES shows high internal consistency and good validity, with strong correlations to other

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measures of mood and motivation, distinguishing apathy from related conditions such as depression [36].

Secondary Outcomes

Secondary outcomes will be examined as potential mediators of effects between RT, loneliness, and apathy.

Cognition

Cognition will be measured by the telephone Montreal Cognitive Assessment (T-MoCA). The T-MoCA is a validated tool designed to screen for MCI across domains such as attention, memory, language, visuospatial skills, executive function, and orientation [37,38]. Adapted from the original Montreal Cognitive Assessment for remote administration, the T-MoCA is particularly useful for populations where in-person assessments may be challenging. The T-MoCA consists of 22 items and participants will be scored out of 22 points, with a score below 18 typically indicating cognitive impairment. The T-MoCA has shown good reliability and validity that is concurrent with the original in-person Montreal Cognitive Assessment [37].

PROMIS: Meaning and Purpose

Meaning and purpose in life will be assessed using the PROMIS (Patient-Reported Outcomes Measurement Information System) Meaning and Purpose Scale. The PROMIS Meaning and Purpose Scale is a validated tool that measures an individual's sense of purpose, significance, and meaning in life. This scale will assess the extent to which individuals feel their lives are filled with meaning, direction, and goals, contributing to overall well-being and mental health. Participants will respond to a series of items on a 5-point Likert scale, entailing 1 (never), 2 (rarely), 3 (sometimes), 4 (often), and 5 (always), with higher scores indicating a stronger sense of meaning and purpose. PROMIS provides a reliable and valid measure of meaning in life, demonstrating internal consistency across diverse populations [39]. It also shows strong correlations with other related constructs, such as life satisfaction and psychological well-being, reinforcing its construct validity [39].

Geriatric Depression Scale

Depressive symptoms will be assessed using the Geriatric Depression Scale–Short Form (GDS-SF) [40]. The GDS-SF is a widely validated screening tool for depressive symptoms in older adults. It is a shortened version of the original 30-item GDS and contains 15 dichotomous (yes or no) questions designed to assess mood and affect, with a focus on identifying symptoms of depression in the older adult population [40]. Scores range from 0 to 15, with higher scores indicating greater depressive symptoms. The GDS-SF is validated in multiple populations, with good internal consistency and strong concurrent validity when compared to other depression scales such as the Hamilton Depression Rating Scale (HDRS) [41].

MOS Social Support Scale

Social support will be assessed using the Medical Outcomes Study (MOS) Social Support Survey [42]. The MOS Social Support Scale is a widely used 19-item instrument designed to measure various dimensions of social support, including emotional, informational, tangible, affectionate, and positive social interaction. Items are rated on a 5-point Likert scale ranging from 1 (none of the time) to 5 (all of the time), with higher scores indicating greater perceived social support. The MOS Social Support Scale was validated across diverse populations, demonstrating high internal consistency and strong construct validity, with robust correlations to other measures of social functioning and mental health [42].

Covariates

Covariates were selected based on their reported associations with cognition, social connection, and overall health. Covariate data will be used to describe the population engaged in the study and will be informative in terms of feasibility and generalizability. Age will be recorded in years, calculated from the self-reported date of birth, as age influences cognitive decline [43]. Gender will be categorized as male or female based on self-report, considering that gender differences influence cognitive performance and vulnerability to cognitive decline [44]. Race will be self-reported and classified into categories to explore potential disparities in health outcomes, as prior studies highlight the role of race in health inequalities. Education, assessed in years of formal schooling completed, will be collected through self-report, as increased educational attainment is associated with better cognitive function and social engagement in older adults [45]. Participants will also self-report their occupation before retirement, recognizing that work-related activities can provide cognitive stimulation and social interaction, which impact mental health outcomes. Marital status will be evaluated at baseline, with responses categorized as never married, married, widowed, divorced, or separated, given that marital status is linked to social support and well-being, crucial for cognitive health [46]. Living arrangements will be documented to differentiate those living alone, with family, or in institutional settings, as prior studies suggest that living arrangements can affect loneliness and access to social networks [47]. Social determinants of health including transportation and housing will be assessed via self-report. The FRAIL Scale will be used to assess frailty through self-reported items related to fatigue, resistance, ambulation, illness, and weight loss, recognizing that frailty is associated with cognitive decline and increased risk for adverse health outcomes in older adults [48] and both loneliness and apathy are associated with frailty and functional decline [49,50]. Finally, overall health and comorbidities will be self-reported and supplemented by information from the electronic health record, encompassing chronic conditions such as diabetes, hypertension, and cardiovascular diseases, which have known associations with cognitive impairment and social functioning.

Feasibility Outcomes

Feasibility will be determined by screening, enrollment, and acceptability of the intervention. Acceptability of the intervention will also be assessed via program satisfaction surveys (eg, satisfaction, mood, belonging, connection with members) at 3 months and 6 months as well as qualitative interviews to explore program acceptability, barriers and facilitators of participation, and technology accessibility. Outcome measures including feasibility and health outcomes are detailed in Textbox 1 and Table 2. Benchmarks are

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determined by prior LSC metrics and expectations for recruitment, enrollment, and participation based on prior LSC participants. The metrics we propose are based on study-specific retention efforts (eg, preintervention counseling, relationship building with participants, and participant incentives).

Textbox 1. Feasibility outcomes.

Criteria

- Screening
- Enrollment
- Acceptability
- Program evaluation
- Barriers and facilitators
- Technology access

Benchmarks

- No. of individuals screened/total referred (≥70% good)
- No. of individuals who agree/total screened (≥70 good)
- No. of individuals who complete 9/12 visits/total enrolled (≥70 good)
- Survey
- Open-ended interview
- Open-ended interview

Table 2. Outcome measures.

Outcome measures	Assessment	Metrics
Primary outcomes		
Loneliness	UCLA Loneliness Scale	• Likert scale 1-4 (1=never, 4 often). • Total from a set of 20 items
Apathy	Apathy Evaluation Scale	• 18 items on 4-point Likert scale • Higher scores=increased apathy
Secondary outcomes		
Cognition	T-MoCA[a]	• Global cognition; ≤26=MCI
Meaning and purpose	PROMIS-meaning and purpose	• 4 items; higher scores=higher meaning or purpose
Depressive symptoms	Geriatric Depression Scale	• 15 items; Score of ≥5 suggests depression
Social support	MOS Social Support Scale	• 19 items; perceived social support; higher scores=greater support
Physical function	FRAIL Scale	• 5 items; self-reported fatigue, resistance, ambulation, illness, weight loss
Overall health	Global health status	• Self-reported physician diagnosis of 9 common conditions

[a]T-MoCA: telephone Montreal Cognitive Assessment; version 8.1 to be administered at baseline, version 8.2 at 3 months, and version 8.3 at 6 months to reduce practice effect.

Covariates/Demographics to be collected: age, gender, race/ethnicity, education, occupation before retirement, marital status, living arrangements, and social determinants of health (Montefiore version).

Data Analysis

The primary purpose of this exploratory project is to test the feasibility of an LSC intervention and to provide estimates of the efficacy of the LSC intervention to inform a future RCT. We will enroll a total sample size of 50 participants and expect an estimated 15% dropout rate. This sample size follows guidelines for pilot studies and is appropriate for exploring feasibility [51]. Descriptive statistics will be used to report sample characteristics, feasibility markers, and measures. Statistical analyses will be conducted using Stata (version 18.5; StataCorp LLC). Repeated-measures ANOVA will be applied

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to test for overall differences in loneliness and apathy at baseline, 3 months, and 6 months. Secondary outcomes will be analyzed for differences in trends before and after the intervention and associations with changes in loneliness and apathy. We will test whether these measures mediate changes in loneliness and apathy from baseline using linear regression models.

We will use field notes and memos throughout the qualitative interview process to explore qualitative data. Data will be deductively analyzed using NVivo 15 software.

Data Management and Monitoring

Data will be entered and stored in a secure, HIPAA (Health Insurance Portability and Accountability Act)-compliant REDCap (Research Electronic Data Capture; Vanderbilt University) database. Only study staff tasked with data entry and analysis will have access to the data. No identifying information will be written or transcribed for this study.

Ethical Considerations

This study is being conducted in accordance with the Declaration of Helsinki ethics code. The protocol will be reviewed by the Albert Einstein College of Medicine institution review board. Because the intervention poses no more than minimal risk, a waiver of written consent was requested. Oral informed consent will be sought via telephone prior to study enrollment and prior to qualitative interviews.

Results

The proposed research is funded by a pilot grant from the Institute for Clinical and Translational Research at Albert Einstein College of Medicine. Recruitment and data collection for the proposed research are planned for July 2025.

Discussion

This study will yield feasibility data on the use of a vGRT intervention to improve loneliness and apathy in community-dwelling older adults without dementia and a qualitative assessment of the intervention. Our protocol is unique in that the proposed study will provide preliminary data for a novel, vGRT to improve loneliness and apathy in community-dwelling older adults. The intervention has the potential to improve accessibility and equity given its virtual delivery in multiple languages and can potentially reach homebound and rural older adults—populations who are at the highest risk for cognitive decline, tend to be hard to reach and are often not included in research for those reasons. Our approach is both innovative and pragmatic because we will leverage an existing community-based service, with an established infrastructure and track record within the community to deliver the intervention, rather than developing a new intervention in a research setting. As such, the proposed research has the potential for broad implications for community-based research, and data can be informative for community-engaged aging research. Moreover, the intervention is scalable for older adults across cultures and geographic locations given the intervention is virtual and can be tailored based on the interests of participants.

The study has potential limitations. As a pilot study, the primary purpose of the proposed study is to test the feasibility of vGRT and provide preliminary efficacy data to improve loneliness and apathy. The pilot will include a single-arm and participants will not be randomized. The study will lay the groundwork for a future RCT of a LSC intervention to improve cognition in older adults. LSC engagement to date is consistent with prior work that has shown older adults can be exceptionally adherent to technological interventions with thoughtful planning and troubleshooting [52]. It is possible that technology access varies across populations and may affect the recruitment of diverse participants. We plan to collect quantitative and qualitative data regarding technology access which will inform future studies of LSC interventions. Future studies might also explore the provision of technology (eg, a tablet to allow access to videoconferencing software) to further promote access and participation. Currently, LSC is limited to 4 languages (English, Spanish, Cantonese, and Mandarin), which may exclude participants who speak other languages. In addition, the current study is restricted to individuals with and those without cognitive impairment and excludes individuals with dementia based on the AD8 assessment. The feasibility of LSC in its current format of virtual delivery, in a medium-sized group setting, with a nonclinical facilitator in individuals with advanced dementia remains an area of opportunity for future research.

In summary, this study will provide valuable data for a future RCT of a vGRT intervention to improve loneliness and apathy in community-dwelling older adults. If successful, the intervention can be widely scaled as a nonpharmacological intervention to prevent cognitive decline and promote social engagement in aging. The proposed methods to leverage community-based partnerships to establish and deliver effective interventions within communities can serve as a model for more community-engaged aging research.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study will be available from the corresponding author on reasonable request.

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Authors' Contributions

CP, HMB, and MEC were responsible for conceptualization, data curation, visualization, formal analysis, funding acquisition, and methodology. CP wrote the original draft. HMB and MEC were responsible for supervision. AB assisted with writing the first draft. All authors reviewed and edited the final draft.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Additional material including the interview guide and consent form.
[DOCX File , 26 KB - resprot_v14i1e70518_app1.docx]

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Abbreviations

ADRD: Alzheimer disease and related dementias
AES: Apathy Evaluation Scale
GDS-SF: Geriatric Depression Scale–Short Form
HDRS: Hamilton Depression Rating Scale
HIPAA: Health Insurance Portability and Accountability Act
LGBTQ+: lesbian, gay, bisexual, transgender, queer/questioning, and others
LSC: Life Story Club
MCI: mild cognitive impairment
MOS: Medical Outcomes Study
PROMIS: Patient-Reported Outcomes Measurement Information System
RCT: randomized controlled trial

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REDCap: Research Electronic Data Capture
RT: reminiscence therapy
T-MoCA: telephone Montreal Cognitive Assessment
vGRT: virtual group reminiscence therapy

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Protocol

Real-World Characteristics and Treatment Patterns of Patients With Transthyretin Amyloid Cardiomyopathy: Protocol for a Multicountry Disease Registry Study

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Abstract

Background: Transthyretin amyloid cardiomyopathy (ATTR-CM) is a systemic amyloidosis disorder with early clinical manifestations similar to other heart conditions, which complicates its diagnosis and management. The disease's insidious nature and its progression to heart failure emphasize the critical need for enhanced recognition and understanding of its clinical landscape.

Objective: This study aimed to understand the natural history and current treatment patterns for managing ATTR-CM in a diverse Asian cohort from Taiwan, Hong Kong, and Malaysia.

Methods: This study is a multicenter, noninterventional disease registry that plans to enroll patients diagnosed with ATTR-CM across approximately 17 sites in Taiwan, Hong Kong, and Malaysia. Almost 350 patients with a documented diagnosis of ATTR-CM after June 1, 2019, will be enrolled in the study. Deceased patients will be enrolled without the need for consent in accordance with applicable regulations. Their data will be gathered retrospectively through a 1-time review of their medical records, where permissible. Data related to clinical characteristics, treatment, and outcomes will be collected for each patient during the routine clinical practice while adhering to local standards of care. The end of data collection is planned for at least 12 months after the end of the enrollment period.

Results: As of March 16, 2025, ethical approvals for this study have been obtained or are under review at multiple sites across Taiwan, Hong Kong, and Malaysia. The study commenced on October 1, 2024, with the first participant's first visit and so far, 59 patients have been recruited: 35 from National Taiwan University Hospital (Taiwan), 13 from Taipei Veterans General Hospital (Taiwan), 2 from China Medical University Hospital (Taiwan), 2 from Sarawak Heart Center (Malaysia), and 7 from Queen Mary Hospital (Hong Kong). An interim report is scheduled for completion by December 31, 2025. The end of data collection, marked by the last participant's visit, is planned for October 1, 2027, and the final study report is expected to be finalized by June 1, 2028. Once established, the database will serve as a comprehensive resource for analyzing baseline characteristics, treatment patterns, and outcomes in patients with ATTR-CM from diverse health care systems.

Conclusions: This research will aid in understanding the demographic, clinical, and therapeutic patterns of ATTR-CM in Taiwan, Hong Kong, and Malaysia. This registry may influence advancements in early detection, diagnosis, and tailored treatment strategies in ATTR-CM.

Trial Registration: ClinicalTrials.gov NCT06651073; https://clinicaltrials.gov/study/NCT06651073

International Registered Report Identifier (IRRID): DERR1-10.2196/71314

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(JMIR Res Protoc 2025;14:e71314) doi:10.2196/71314

KEYWORDS

ATTR-CM; transthyretin amyloid cardiomyopathy; registry; real world data

Introduction

Background

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a systemic amyloidosis disorder caused by the accumulation of misfolded transthyretin proteins, leading to the formation of amyloid fibrils in the extracellular space [1]. These fibrils alter tissue structures and impair the function of various organs [1]. Due to nonspecific symptoms, ATTR-CM diagnosis is often delayed or missed [2]. If untreated, ATTR-CM is a fatal disorder, commonly progressing to congestive heart failure (HF), cardiac arrhythmia, conduction system disease, and complete HF [2,3]. Despite its severity, there is a scarcity of research, especially in Asia, on disease progression, treatment practice, clinical outcomes, and disease mortality in ATTR-CM [4].

ATTR-CM can be classified by the sequence of the *ATTR* gene, either wild-type, with no mutations (wt*ATTR*), or hereditary, with a mutation (h*ATTR*) [5]. Disease progression is generally slower in wt*ATTR*, whereas h*ATTR* often progresses more rapidly due to increased amyloid accumulation [5]. Many different mutations have been found in the *ATTR* gene, leading to variability in the initial signs and symptoms among patients with h*ATTR* depending on their specific genetic mutations [6,7]. In people of Chinese descent in Taiwan and Malaysia, Ala97Ser is found to be the most prevalent genotype, where it accounts for more than 90% of *ATTR* gene variations among affected individuals [8,9].

As ATTR-CM is an underrecognized disease, reported global prevalence rates vary, and the true prevalence remains uncertain [10,11]. A previous study suggested a prevalence rate of approximately 13% in patients with HF and myocardial wall thickening of more than 12 mm [12]. However, there are no large-scale studies, and the actual prevalence of ATTR-CM in Asia remains unclear [4].

Understanding the demographic and clinical characteristics of patients with ATTR-CM across a variety of health care systems is crucial for enhancing the recognition and early detection of the disease [13].

A panel of experts from Europe and the United States recommended three key approaches for monitoring the progression of ATTR-CM: (1) clinical and functional endpoints, (2) biomarkers and laboratory markers, and (3) imaging and electrocardiograph parameters (Figure 1) [2,4]. However, across Asian populations, the pathological presentation of ATTR differs, and expert consensus on monitoring the progression of ATTR-CM will vary across regions [14-16]. Due to limitations in health care accessibility across Asia and variations in clinical practice, there are alternative recommendations that take perspectives from Asian countries into consideration (Figure 1) [2,4].

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Figure 1. Criteria for assessing disease progression in patients with ATTR-CM. Consensus from experts recommends the three domains above for the long-term monitoring of patients with ATTR-CM. 6MWT: 6-minute walk test; ATTR-CM: transthyretin amyloid cardiomyopathy; ECG: electrocardiography; HF: heart failure; KCCQ: Kansas City Cardiomyopathy Questionnaire; LV: left ventricle; NAC: National Amyloidosis Centre (United Kingdom); NT-proBNP: N-terminal pro-B-type natriuretic peptide; NYHA: New York Heart Association.

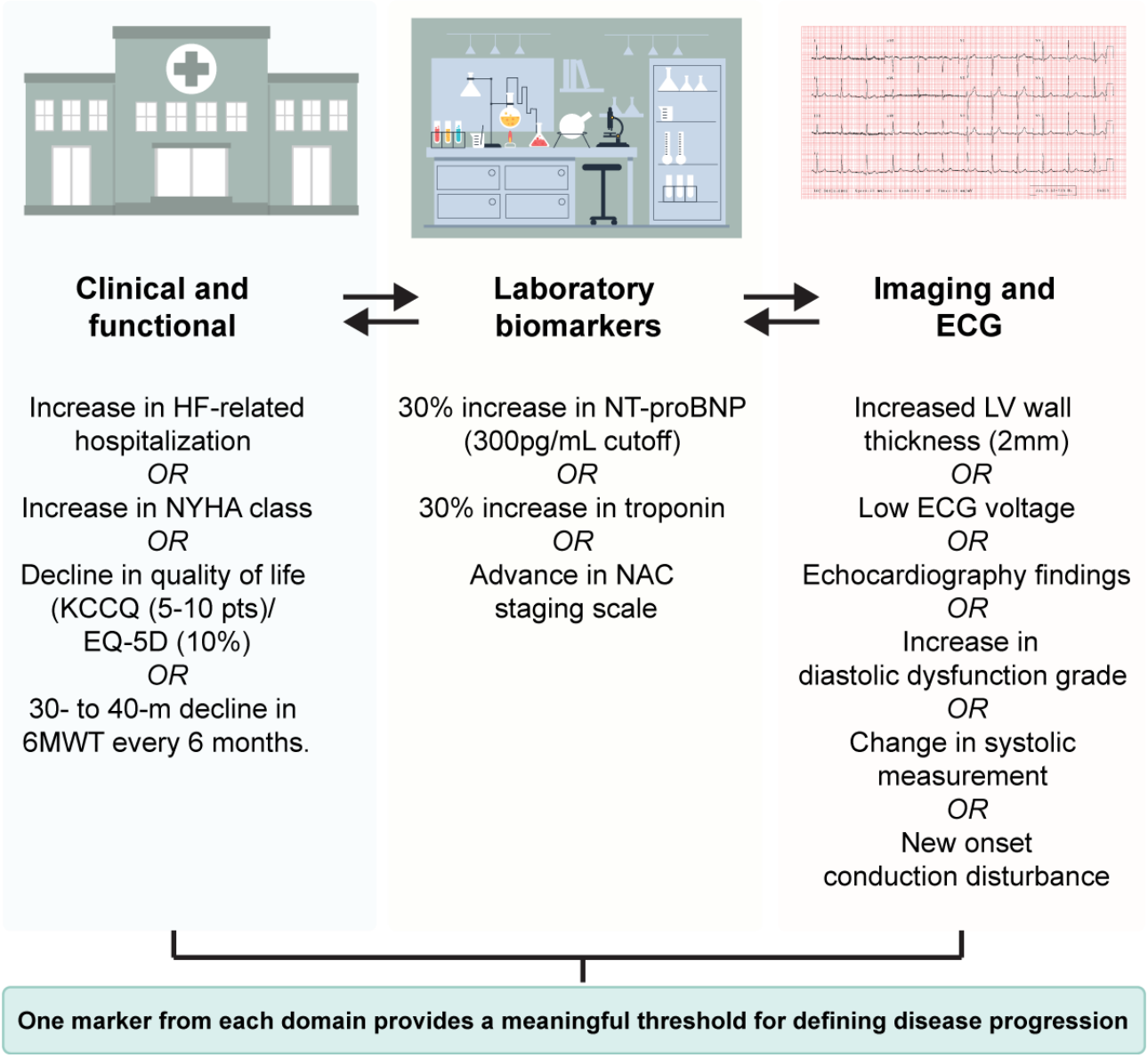

In assessing clinical and functional endpoints, the 6‐minute walk test remains a widely accessible and cost-effective tool in Asia [17]. In addition, measuring cardiac biomarkers, such as serum N‐terminal pro-brain natriuretic peptide and serum cardiac high‐sensitivity troponin, is useful for measuring disease progression [18,19]. However, in the event of poor accessibility, alternatives in imaging and electrocardiogram tools have not yet been established [4]. Clinical experience in Asia suggests, for example, that a “relative” low electrocardiogram voltage as an alternative to left ventricle wall thickness would be an important indicator of ATTR-CM progression in Asian patients [4]. Echocardiography is also suggested, as it is generally available across Asia. Clearly, there is a need for research that augments the methods and tools used to diagnose and monitor ATTR-CM progression. Monitoring these disease domains through a registry would aid in understanding the characteristics and progression of ATTR-CM in Taiwan, Hong Kong, and Malaysia, ultimately, this is needed to improve disease recognition, detection, and appropriate management across these regions [20].

Singapore and Thailand have established country-level patient registries for ATTR-CM; however, there is a pressing need for other Asian countries to develop similar registries as well as compare the data across countries in the Asian region [4,21]. In this article, we describe the protocol for a multicenter, noninterventional disease registry to characterize the natural history of ATTR-CM and treatment patterns in patients clinically diagnosed with ATTR-CM across Taiwan, Hong Kong, and Malaysia. This dataset, spanning 3 diverse nations, is essential for building a robust population base that captures variations in ethnicity, socioeconomic status, and medical insurance coverage, while also reflecting differences in clinical care practices across varied health care systems [13].

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Aims and Objectives

This study aims to understand the natural history and treatment patterns of patients with ATTR-CM in Taiwan, Hong Kong, and Malaysia. Primary, secondary, and exploratory objectives, respectively, are listed in Textbox 1.

Textbox 1. Study objectives.

- To characterize the natural history of patients with transthyretin amyloid cardiomyopathy (ATTR-CM), described by patient demographic and clinical characteristics at diagnosis of patients with ATTR-CM, and patient outcomes.
- To describe the treatment patterns in patients with ATTR-CM and to identify the prognostic factors for all-cause mortality and cardiovascular-related hospitalization in patients with ATTR-CM.
- To assess treatment effectiveness in patients with ATTR-CM and to evaluate the quality of life and health care resource usage in patients with ATTR-CM.

Methods

Study Design and Setting

This multicenter, noninterventional, disease registry enrolling approximately 350 patients diagnosed with ATTR-CM will be conducted across approximately 17 sites in Taiwan, Hong Kong, and Malaysia. All patients with a documented diagnosis of ATTR-CM after June 1, 2019 will be invited to participate in the study. The study size will be based on the number of eligible ATTR-CM cases identified in the medical records and meeting the inclusion criteria. However, the goal is to enroll approximately 350 patients diagnosed with ATTR-CM across the sites, with data collected throughout routine clinical practice. As it is a noninterventional study, no procedures or treatments will be mandated, and patients will receive their usual clinical care. The observation period for each patient will range from the index date (ie, the date of first documented ATTR-CM diagnosis) to whichever occurs first of death, patient withdrawal of consent, loss to follow-up, or end of data collection. The end of data collection is planned for a minimum of 12 months after the end of the enrolment period. This will allow all patients to have the opportunity to contribute at least 12 months of follow-up data (Figure 2).

Figure 2. Study design. ATTR-CM: transthyretin amyloid cardiomyopathy; ICF: informed consent form. The "index date" marks the point of first diagnosis, which may coincide with or precede study enrollment. Patients are then followed over time, capturing both retrospective data (before the index date) and prospective data (after the index date), at approximately 3-month intervals. The "observation period" extends from the index date until either the end of the study, patient death, withdrawal of consent, or loss to follow-up. Data are collected through a combination of retrospective review during a one-time medical record abstraction and routine clinical visits for prospective information.

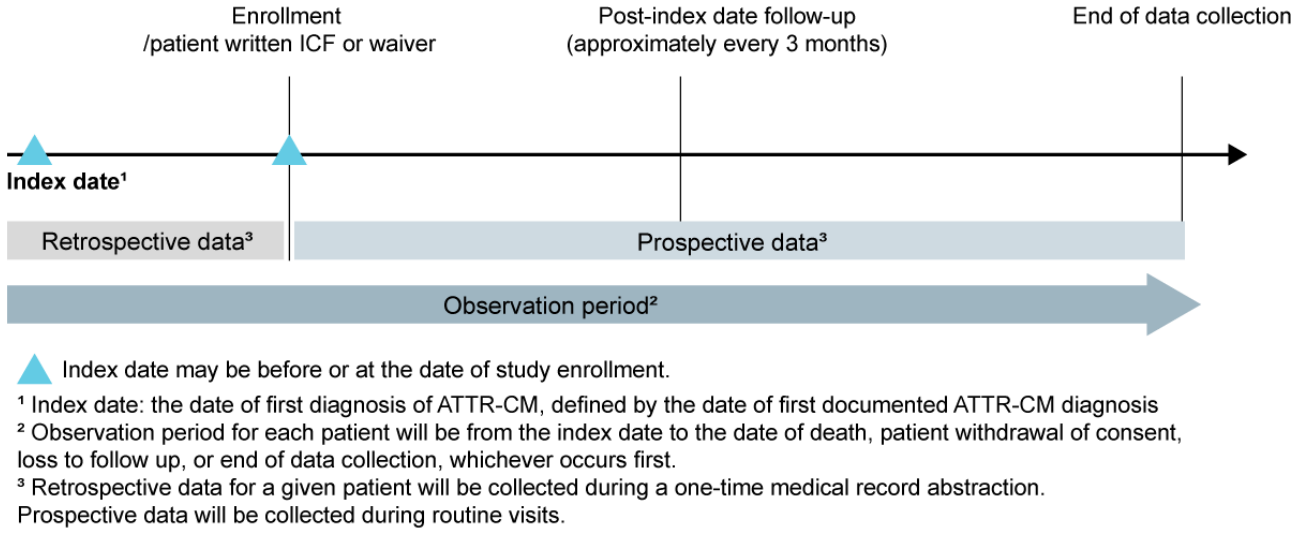

Study Participants

The inclusion criteria of this ATTR-CM registry are as follows: (1) adults (aged ≥18 years) at first ATTR-CM diagnosis; (2) confirmed diagnosis of ATTR-CM after June 1, 2019; and (3) able to provide informed consent. The eligibility criteria are broad enough to include all patients with ATTR-CM without any exclusion criteria.

Several strategies to address potential selection bias will be implemented. Each eligible patient will be consecutively assessed during the designated period using predefined criteria to ensure comprehensive inclusion and reduce bias. Recruitment will span a variety of clinical settings to capture a diverse and representative sample. The eligibility criteria are designed to be broad, promoting inclusivity and enhancing the generalizability of our findings. In addition, a screening log for individuals who do not participate will be maintained to gather minimal deidentified information to identify any systematic differences and further understand potential biases. Each enrolled participant or his or her legally acceptable representative will be provided with an informed consent form (ICF) that outlines the study objectives, procedures, risks, and benefits, and clearly states that participation is voluntary with

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the option to opt out at any time without affecting their clinical care.

Data Collection and Management

All variables described below will be collected as part of routine clinical practice or following standard practice guidelines in the countries where this study is being conducted. This study will not provide or recommend any treatment; all decisions regarding treatment will be made at the sole discretion of the treating physician, in accordance with their routine clinical practice administration of any specific assessment tools is not mandated and all clinical decisions will be made solely at the discretion of the treating physician in accordance with the local and international guidelines. The data to be collected retrospectively at enrollment and prospectively during follow-up is listed in Textbox 2.

Textbox 2. Data to be collected retrospectively at enrollment and prospectively during follow-up.

- Demographic data (age at enrolment, sex, and race or ethnicity).
- Diagnosis of transthyretin amyloid cardiomyopathy (ATTR-CM; date of first ATTR-CM diagnosis, age at first ATTR-CM diagnosis, method of diagnosis, etc).
- Physical measurements (height, weight, smoking status, blood pressure, and heart rate).
- Relevant medical history and comorbidities (first clinical cardiac symptom related to ATTR-CM, symptom onset date as the date of the first clinical symptom attributed to ATTR-CM, age at onset of symptom, treatment received for the first symptom if applicable with its start and stop dates).
- Emergency department visits.
- Type of ATTR-CM (wild-type ATTR or hereditary ATTR [hATTR] with genetic variants identified if applicable for patients with hATTR).
- Family history (known cardiomyopathy, polyneuropathy, and sudden cardiac death [among parents, siblings, and second- or third-degree family links]).
- Treatment for ATTR-CM (ATTR-specific pharmacologic treatment, including, treatment name, dosage, prescribed frequency, start date, end date, and any change in treatment).
- Prescription of heart and cardiovascular medication (including beta-blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor-neprilysin inhibitors, angiotensin II receptor blockers, digoxin, calcium channel blockers, diuretics, antiplatelets, lipid-lowering agents, and anticoagulants (within 6 months before the index date).
- Concomitant medications (including heart and cardiovascular medications and other concomitant medications from the index date).
- New York Heart Association functional class (closest available measurement to the index date).
- Kansas City Cardiomyopathy Questionnaire.
- Imaging and lab assessments (date of assessment and results).
- Survival status (date of death, reason for death: Cardiovascular-related, not cardiovascular-related, and indeterminate).
- Hospitalization (date of admission, date of discharge, reason for hospitalization categorized as cardiovascular-related, not cardiovascular-related, and indeterminate).
- Adverse events with explicit attribution to any of the study sponsor's drugs.

Multimedia Appendix 1 provides further details on each data collection element, including the timepoints at which the data will be recorded. The study case report form (CRF) includes an "ATTR-CM diagnosis" section detailing the methods used to diagnose ATTR-CM. The CRF captures a range of clinically validated approaches, including functional classification, imaging, biomarker screening, and genetic testing, consistent with established guidelines for ATTR-CM diagnosis.

The collected data will be from reliable sources of patient-level information available at the participating sites. This includes data available in the patients' electronic medical records as well as medical charts and any other documentation or communication by health care providers. All data listed above will be collected by trained site personnel and entered directly into the web-based electronic case report forms (eCRFs) at each participating study site. Sites will be responsible for entering extracted patient data into a secure Electronic Data Capture (EDC) database and all changes or corrections to eCRFs will be documented in an audit trail. The personal data will be stored at the study site in encrypted electronic or paper form and will be password-protected or secured in a locked room to ensure that only authorized study staff have access. Patient data will be deidentified before analysis. All identifiable information will be replaced with a unique patient-specific identifier, and data will be transmitted and managed using encryption.

Data Analysis

Detailed methodology for summary and statistical analyses of data collected in this study is documented in a statistical analysis plan. This study is descriptive and does not involve hypothesis testing, hence the actual sample size will be determined by the number of eligible ATTR-CM cases identified in the medical records that meet the inclusion criteria. Approximately 350 patients diagnosed with ATTR-CM are expected to be enrolled based on feasibility assessments, historical diagnosis rates, and the expected patient volume at the 17 participating sites across Taiwan, Hong Kong, and Malaysia. Continuous variables will be summarized using descriptive statistics, including the number

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of participants with nonmissing and missing values, mean, SD, median, 25th percentile (Q1), 75th percentile (Q3), minimum, maximum, and median (IQR). Means and medians will be presented with one more decimal place than the raw data, while SDs will be presented with 2 more decimal places. Categorical variables will be summarized using frequency counts (n) and percentages (%), with percentages calculated over nonmissing data.

Time-to-event analysis will be performed using the Kaplan-Meier methodology. Data will be presented as the number of patients at risk, with the event, and censored. The estimated median, Q1, Q3, and the 2-sided 95% CI, using Brookmeyer and Crowley method, will be provided for the main statistical estimators. CIs about a parameter estimate will be presented using the same number of decimal places as the parameter estimate.

Ethical Considerations

The study will be conducted while adhering to all of the legal and regulatory requirements to ensure the protection of patient personal data. Research practices described in Guidelines for Good Pharmacoepidemiology Practices issued by the International Society of Pharmacoepidemiology, Good Practices for Outcomes Research issued by the International Society for Pharmacoeconomics and Outcomes Research will be followed along with any other applicable national guidelines. There is prospective approval of the study protocol, protocol amendments, waiver of ICF for deceased patients, and other relevant documents (eg, ICFs) from the relevant institutional review boards or independent ethics committees.

Ethics approvals for this study have been obtained or are in progress at multiple sites across Taiwan, Hong Kong, and Malaysia. In Taiwan, approvals have been granted by the Research Ethics Committee for National Taiwan University Hospital (date of approval: August 22, 2024, National Taiwan University Hospital record number 202405071RSB), the Taipei Veterans General Hospital institutional review board (IRB; date of approval June 23, 2024; IRB Taipei Veterans General Hospital number 2024-06-026CC), and the Chang Gung Medical Foundation IRB for both the Linkou and Kaohsiung branches of Chang Gung Memorial Hospital (date of approval September 13, 2024, IRB number 202401282B0). Approvals have also been secured from the IRB of Taichung Veterans General Hospital (date of approval August 22, 2024, number SE24333B), and the Research Ethics Committee of China Medical University & Hospital in Taichung (date of approval September 19, 2024, number: CMUH113-REC3-124). In addition, the application has been approved by the Research Ethics Committee of Taipei Mackay Memorial Hospital (date of approval October 8, 2024, number 24CT039be). Applications are pending approval from the Far Eastern Memorial Hospital and the Chi-Mei Medical Center while an application is being prepared for IRB of Kaohsiung Municipal Siaogang Hospital, which is run by Kaohsiung Medical University.

In Hong Kong, ethics approvals have been obtained from the Hospital Authority's Central IRB for Queen Elizabeth Hospital and Princess Margaret Hospital (date of approval September 25, 2024, Central IRB reference number CIRB-2024-334-5), the Joint Chinese University of Hong Kong–New Territories East Cluster Clinical Research Ethics Committee (CREC) for Prince of Wales Hospital (date of approval: September 15, 2024, CREC reference number 2024.351) and by the IRB of the University of Hong Kong Hospital Authority Hong Kong West Cluster for Queen Mary Hospital (date of approval January 8, 2025, IRB reference number UW 24-623). An ethics application is being prepared for submission to the Hospital Authority Central IRB for Tuen Mun Hospital. In Malaysia, approvals have been obtained from the Medical Research Ethics Committee of Hospital Sultan Idris Shah in Serdang and the Sarawak Heart Centre (date of approval November 8, 2024, number 24-02846-UQ8). The application is currently under review by the IRB of the Medical Research Ethics Committee of Institut Jantung Negara Sdn Bhd.

Each enrolled participant or his or her legally acceptable representative will be provided with an ICF that outlines the study objectives, procedures, risks, and benefits, and clearly states that participation is voluntary with the option to opt out at any time without affecting their clinical care. No compensation will be provided to study participants.

Results

The study began on October 1, 2024, with the first participant's visit, and as of March 16, 2025, a total of 59 patients have been recruited. These include 35 patients enrolled from National Taiwan University Hospital, 13 patients recruited from Taipei Veterans General Hospital, and 2 patients enrolled from China Medical University Hospital in Taiwan. Two patients have been recruited from Sarawak Heart Center in Malaysia, and 7 patients enrolled from Queen Mary Hospital in Hong Kong. We anticipate that data collection will continue robustly, with an interim report scheduled for completion by December 31, 2025. The final phase of data collection, marked by the last participant's visit, is planned for October 1, 2027, and the final study report is expected to be finalized by June 1, 2028. Once established, the resulting database will serve as a valuable resource for analyzing baseline characteristics, treatment patterns, and outcomes in patients with ATTR-CM. This extensive dataset will not only provide insights into current clinical management but also guide future research efforts and inform evidence-based clinical practices in managing ATTR-CM.

Discussion

Anticipated Findings

The aim of this study is to understand the natural history and treatment patterns of patients with ATTR-CM in Taiwan, Hong Kong, and Malaysia. Therefore, a multicenter, noninterventional, disease registry study design was selected. The study aims to recruit patients diagnosed with ATTR-CM from approximately 17 sites in Taiwan, Hong Kong, and Malaysia. To be included in the study, patients will need to be adults (aged ≥18 years) at first ATTR-CM diagnosis or confirmed diagnosis of ATTR-CM after June 1, 2019. Reflected in the small number of global ATTR-CM studies, there is an absence of studies describing the populations of patients with ATTR-CM in Taiwan, Hong

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Kong, and Malaysia as such this study will ensure that the necessary data is available to improve the understanding of ATTR-CM [4]. The data collection was designed to align with routine clinical practice, following local standard practice guidelines.

ATTR is a variable disease, both phenotypically and geographically and TTR mutations appear to exist on an ethnic-specific spectrum [22-25]. In other studies, the most common TTR mutation is Thr60Ala in the UK and US patients, Val30Met in Japanese patients, Asp38Ala in South Korean patients, and Val30Met in Portuguese, Swedish, and Japanese patients while the Val122Ile mutation is endemic in the African-American population [26]. It is important not to rely solely on global data or data from other countries to inform the manifestation of ATTR-CM in Taiwan, Hong Kong, and Malaysia, particularly as Ala97aSer, the most common endemic mutation across these countries, which is less prevalent across the rest of the world, and as such has fewer reported cases and studies [27,28].

Across the global population as well as within individual nations, ATTR-CM has not received sufficient recognition, diagnosis, or treatment due to low public awareness and the absence of an effective therapeutic approach. However, even though there is a new understanding of the diagnosis, progression, and treatment of this disease worldwide [29], the prevalence and mortality rates based on real-world evidence (RWE) remain unknown in Asia [4]. This gap underscores the necessity for real-world data collection in Asia and this study is an initiative to fill in this knowledge void, starting with a clinical registry across Taiwan, Hong Kong, and Malaysia.

Establishing registries for rare diseases like ATTR-CM is fundamental to enhancing patient care pathways and ultimately improving disease outcomes [30,31]. Such registries are instrumental in generating RWE; they offer a systematic approach to monitor disease progression and assess the efficacy and safety of various treatment modalities [32]. The data compiled as per this protocol will enable a comprehensive understanding of ATTR-CM in the Asian context. An ATTR-CM registry for Asian countries is a critical step toward evaluating health care burden, clinical progression, health care strategies, and potential disparities. It will also facilitate a deeper analysis of treatment efficacy and safety, thereby improving the overall standard of care for patients with ATTR-CM [4].

As a multicenter, noninterventional, disease registry study aiming to collect real-world data on ATTR-CM, there are multiple strengths with this study design. Given the frequent undiagnosed instances of ATTR-CM in various clinical settings, this protocol is designed to ensure that the study sample accurately represents the target population through systematic patient assessment, nonrestrictive recruitment, and inclusive inclusion criteria. However, there are also some potential limitations inherent to the design of any multicountry and multicentric study. Center selection was based on each center's readiness to participate and the availability of patients diagnosed with ATTR-CM. Consequently, while the protocol uses systematic patient assessment with broad, inclusive criteria, the study sample may not fully capture the national or regional prevalence or diagnosis rates of ATTR-CM. This targeted recruitment approach may introduce selection bias, potentially limiting the generalizability of the findings. Furthermore, variations in routine clinical care and adherence to standard practice guidelines across these multiple sites in different countries may affect the consistency, completeness, and types of data collected.

Despite these limitations, this study aims to make substantial contributions to the limited existing literature on ATTR-CM by documenting the natural history and treatment patterns of patients in Taiwan, Hong Kong, and Malaysia. It holds the potential to improve the detection and management of ATTR-CM in Asia, ultimately improving patient outcomes and increasing survival rates.

Conclusions

Establishing an ATTR-CM registry across Asian countries is essential for generating real-world evidence on disease burden, clinical progression, health care strategies, and potential disparities, enhancing patient care pathways and informing tailored treatment approaches. By systematically documenting the demographic, clinical, and therapeutic patterns of patients in Taiwan, Hong Kong, and Malaysia, this study will fill critical gaps in the literature on natural history and treatment outcomes for ATTR-CM in the region.

Acknowledgments

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Authors' Contributions

All the authors were involved in the conception and design of the research protocol. They were all involved in the creation of the manuscript and gave final approval before submission for publication.

Conflicts of Interest

YHL has received speaker fees from Pfizer and AstraZeneca and institutional funding for clinical trials from Pfizer. HWC, ST, and RG are Pfizer employees.

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Multimedia Appendix 1
Overview of data collection categories and variables.
[DOCX File , 27 KB - resprot_v14i1e71314_app1.docx]

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Abbreviations

ATTR-CM: transthyretin amyloid cardiomyopathy
CREC: Clinical Research Ethical Committee
CRF: case report form
eCRF: electronic case report form
EDC: Electronic Data Capture
hATTR: hereditary ATTR
HF: heart failure
ICF: informed consent form
IRB: institutional review board
RWE: real-world evidence
wtATTR: wild-type ATTR

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Protocol

Implementation of Medication Disposal Programs and Availability of Same-Day Naloxone at Community Pharmacies: Protocol for a Secret Shopper Caller Approach

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Abstract

Background: Pharmacies can implement multiple strategies, including medication disposal programs (eg, disposal boxes, deactivation products, and mail-back envelopes) and offering over-the-counter naloxone, to prevent nonmedical opioid use and overdose. The quantity of opioid prescriptions dispensed in the United States is so high that every other adult could receive one opioid prescription per year. Many of these opioids go unused and are kept in homes rather than disposed of after ceasing use. The primary source of prescription opioids for nonmedical use is relatives or friends, which suggests that the diversion of excess and retained prescription opioids contributes significantly to nonmedical use. Naloxone is a life-saving medication that works as an opioid antagonist to reverse the effects of opioids and restore normal breathing to a person experiencing an overdose. All 50 US states have passed laws (eg, statewide standing orders) that allow pharmacists to distribute naloxone without an individual patient prescription, and the US Food and Drug Administration approved the first over-the-counter naloxone medication in March 2023. Individual and neighborhood characteristics are associated with nonmedical opioid use and overdose. It is essential to ensure that pharmacy-based overdose prevention practices are widely available to all individuals.

Objective: *:* This study aims to assess the extent to which disposal programs and same-day naloxone have been implemented in pharmacies across the United States and examine neighborhood characteristics in implementation. We hypothesize that as neighborhood disadvantage and the proportion of Black or African American residents in a neighborhood increase, the likelihood of a pharmacy having a disposal program or same-day naloxone decreases. We also hypothesize differences in medication disposal programs and same-day naloxone availability by retailer chain and type of pharmacy.

Methods: A secret shopper caller protocol will be used to identify pharmacies that have implemented a medication disposal program and have naloxone available on the same day without a prescription. We will conduct disproportionate stratified random sampling with the strata being pharmacy chains to maximize the likelihood of sampling corporations and independent pharmacies. The goal is to obtain a final sample of 1000 pharmacies. Neighborhood characteristics will be appended to the secret shopper data. To explore neighborhood and pharmacy characteristics associated with the availability of medication disposal programs

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and same-day naloxone, we will use logistic regression. This protocol represents the entire structure of the secret shopper caller approach.

Results: Data collection was completed in the spring of 2024. The expected results will be published in 2025.

Conclusions: This will be the first study to examine national estimates of medication disposal programs, same-day naloxone availability at pharmacies, and the geographic characteristics associated with their implementation.

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KEYWORDS

opioid; naloxone; disposal; mystery caller; pharmacy; protocol; naloxone availability; harm reduction; opioid disposal; medication disposal; secret shopper

Introduction

Overdose Prevention at Community Pharmacies

Community pharmacists are essential members of frontline patient care. Their role in the overdose epidemic is critical in the defense against substance use disorder and opioid overdose [1,2]. Pharmacists are trained about substance use disorder during their educational instruction and can enhance their knowledge through continuing education on overdose prevention and opioid use disorder interventions [3]. It has been reported that the majority of pharmacists feel comfortable consulting about overdose prevention methods [4]. To address the opioid crisis, pharmacies have participated in prescription drug monitoring programs, implemented medication disposal programs, and dispensed naloxone and other medications for opioid use disorder [1].

Medication Disposal Programs

Despite efforts in the United States to reduce the number of opioid prescriptions through prescribing guidelines [5,6] and drug monitoring programs [7,8], about 39.5 opioid prescriptions were dispensed per 100 persons in 2022 [9]. Many opioid medications go unused; a meta-analysis of postoperative opioid consumption for acute pain by US adults found that 61% [10] of medications remain after treatment. Among individuals who use prescription opioids inappropriately, most obtain them from family or friends, with or without their knowledge [11]. Thus, medication diversion is the primary source of prescription opioids for misuse. Facilitating the secure disposal of opioid medication during and after treatment is needed to prevent medication diversion.

The US Food and Drug Administration (FDA) endorses multiple methods to dispose of unused prescription opioids when they are no longer needed, including take-back days, disposal boxes, mail-back programs, and deactivation kits [12,13]. As of 2014, pharmacies have been able to offer these services to their customers [14]. Two studies examined the availability of medication disposal boxes in Kentucky and North Carolina [15,16]. In Kentucky, 144 medication disposal boxes had been implemented in community pharmacies as of 2020, with about 50% of counties having at least one box [16]. While rural counties in Kentucky had higher opioid dispensing rates than urban counties, they were less likely to have a medication disposal box [16]. In North Carolina, 350 (13.5%) pharmacies had implemented a medication disposal box as of 2021 [15]. The only study of national estimates of medication disposal box availability was conducted by the US Government Accountability Office in 2017. This assessment examined the list of authorized collectors from the US Drug Enforcement Administration (DEA) and found that 3% of pharmacies and other entities eligible to collect unused prescription drugs had registered with the DEA to implement a disposal box. A limitation of this study is that it relied on the DEA's list of authorized collectors, which is not a reliable indicator of active medication disposal boxes [15,17]. To our knowledge, no studies have examined pharmacy participation in the distribution of mail-back envelopes or deactivation kits.

Broad access to medication disposal programs has been linked to reductions in opioid-related overdose deaths. One study found that communities with drug take-back programs had a decline in opioid overdose deaths, highlighting the role of these programs in limiting the availability of prescription opioids for misuse [18]. Various state and local studies have found a positive relationship between the number of medication disposal locations and decreased prescription drug misuse [19-21]. For instance, a study conducted in New York State demonstrated that increased drug take-back locations were associated with a reduction in prescription opioid misuse [22]. These findings underscore the importance of increasing access to safe disposal options as part of broader strategies to combat opioid misuse. Further studies are needed to establish the full impact on population-level outcomes related to misuse and overdose.

Same-Day Access to Naloxone at Pharmacies

In 2023, the number of opioid-related drug overdoses in the United States decreased, rather than rose, for the first time since 2018 [23]. While there was a decrease in opioid-related deaths from 2022 to 2023, the number of deaths in 2023 (n=81,083) [24] was significantly higher than in 2018 (n=46,802) [25]. The provisional Centers for Disease Control and Prevention (CDC) data revealed that the decrease in opioid-related deaths was uneven across demographic groups, with Black individuals experiencing only a 6% reduction, Hispanic individuals having a 3% decrease, and American Indian or Alaska Native populations seeing a 2% increase. Naloxone is an opioid antagonist that is available as a nasal spray or injection [26]. Naloxone has been identified as a critical tool in combating the overdose epidemic in the United States [27,28]. During the last two decades, naloxone access has progressed from requiring a

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prescription to a standing order and recently to over-the-counter availability [29]. Studies that examined naloxone laws (layperson access) and opioid mortality have found that a decrease in opioid mortality occurs when naloxone is more accessible [30-32].

In 2023, the FDA approved the nasal spray naloxone for over-the-counter status [29]. This action theoretically should improve access to naloxone nationwide and will eliminate the need for a standing order or even a prescription. Previous studies that focused on naloxone availability with a standing order found that independent pharmacies, compared with chain pharmacies, were less likely to have same-day availability of naloxone [33-37]. Speculation has occurred that the status change of naloxone from prescription to over-the-counter may cause an increase in the price, thus adding a barrier to access [38,39]. Studies before the status change found that the out-of-pocket cost of naloxone varied greatly, with independent pharmacies charging more than community pharmacies [40,41].

Socioeconomic Disparities

There are existing individual and neighborhood differences associated with nonmedical opioid use and related harms [42]. A systematic review found that 34 out of 37 studies published between 2000 and 2018 identified at least one characteristic linked to opioid overdose. The studies indicated that individual and neighborhood disadvantages, such as neighborhood-level poverty rates, median household income, county-level unemployment rates, neighborhood-level educational attainment, neighborhood-level dilapidated housing structures, and population-level criminal justice system involvement, were associated with higher opioid overdose rates [42]. Researchers have also identified socioeconomic and racial or ethnic differences in both the distribution of pharmacies [43-45] and the dispensing of opioid analgesics [46-48]. When individuals are not able to manage their pain with prescribed opioids, they may resort to diverting medications or the use of alternative sources of opioids (fentanyl and heroin) [49]. These differences may hinder the adoption of diversion programs and overdose prevention efforts. Pharmacy-based overdose prevention practices must be widely available to all individuals to not exacerbate documented differences.

Objective

The overall objective is to assess the extent to which disposal programs and same-day naloxone have been implemented in pharmacies across the United States and examine place-based health disparities in implementation. Based on previous research [45,46,50-52], we hypothesize that as neighborhood disadvantage (hyp_1) and the proportion of Black or African American residents in a neighborhood (hyp_2) increase, the likelihood of a pharmacy having a disposal box or same-day naloxone decreases. We also hypothesize differences by retailer chain (hyp_3) and type of pharmacy (ie, large chain, midsize chain, or independent; hyp_4), following previous research indicating large differences in how pharmacy chains implement underage tobacco sales policies [53] and disposal programs in North Carolina [33].

Methods

Overview

This study uses a secret shopper caller protocol design and will be conducted at Wake Forest University School of Medicine and East Carolina University.

Participants

Eligibility

Pharmacies are eligible to be included in the study if they are listed on the 2023 list of active licensed pharmacies from Hayes Directories, Inc and have a physical location. Nonretail, compounding, and veterinarian pharmacies will be excluded.

Sample Size

The sample size is 1000 pharmacies from across the United States.

Sample

We have obtained the most recent list (October 2023) of active licensed pharmacies from Hayes Directories, Inc. The Hayes list provides the name, phone number, fax, street address, and if it is part of a chain (ie, 8 or more locations) of retail community pharmacies (N=56,451). We will conduct a disproportionate stratified random sampling with the strata being pharmacy chains to maximize the likelihood of sampling diverse corporations and independent pharmacies. We will classify pharmacies into corporate chains with over 1000 store locations in the Hayes Directories, Inc list, including subsidiaries and brands (eg, some Walgreens operate as Duane Reade). We will identify eight strata based on the number of pharmacies in our database: (1) CVS, (2) Walgreens, (3) Walmart, (4) Rite Aid, (5) Kroger, (6) Albertsons, (7) Publix, and (8) other retail pharmacies. With 8 strata, 125 pharmacies per stratum will allow us to reach our goal of 1000 pharmacies across the United States. We will oversample 25 stores per stratum in case there is a need for replacement, for a total of 1200 pharmacies.

Data Collection and Measures

Procedure

A total of 3 data collectors, “secret shoppers,” will be trained to call pharmacies posing as individuals who either need to dispose of medicine or obtain naloxone. The secret shoppers consist of one graduate student and two upper-level, 4th-year undergraduate students. Calls will be made rather than in-person store visits so that it is feasible to assess a sample of pharmacies across the nation. This also reflects the real-life scenario of community members calling pharmacies to determine available services before they visit the pharmacy. Secret shoppers will use a semistructured script when asking pharmacies about disposal programs and same-day naloxone. Training of the secret shoppers will consist of a 2-hour session in which data collectors will learn the script, make practice calls to pharmacies not within the sampling frame (up to 10 pharmacies per data collector), and agree on standard responses to potential questions. Separate calls will be made to query the availability of disposal programs and same-day naloxone. During and after each call, data collectors will fill out a secure REDCap

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(Research Electronic Data Capture; Vanderbilt University) [54,55] survey about their experience with the pharmacy staff they corresponded with on the call. The codebooks for the medication disposal program (Multimedia Appendix 1) and same-day naloxone without a prescription (Multimedia Appendix 2) have been included.

Primary Outcomes

There are two primary outcomes: (1) availability of a medication disposal box and (2) same-day naloxone. The two primary outcomes are distinct and do not occur within the same phone call. Each outcome represents a separate call type, addressing different aspects of the study. This will allow the secret shopper to capture the nuanced dynamics of the study's focus more accurately. The availability of a medication disposal box will be assessed with the following question posed by a secret shopper: "Hi, I have some Vicodin that I need to get rid of. I heard some pharmacies will take back medications or give you something to dispose of them at your home. Does your pharmacy do this?" The secret shopper will code if the pharmacist responds, "Yes, disposal box." Other potential options that can be recorded include "no"; "yes, give it directly to the pharmacist"; "yes, other option"; and "yes, but no additional information was provided." To assess same-day availability of naloxone without a prescription, the caller will ask, "Hi, I am calling to find out if I can get Narcan today?" and "Do I need a prescription?" If the pharmacist states that they have naloxone available that day and that a prescription was not needed, the pharmacy will be coded as having same-day naloxone without a prescription.

Other Measures

Using the secret shopper caller protocol, we will also collect data on where the medication disposal box and naloxone are located in the store, where they could dispose of their medication if the pharmacy would not take it back, where else they could get naloxone, and the cost of naloxone.

We will obtain neighborhood characteristics at the census block group and tract level for the sampled pharmacies from Social Explorer (a subscription service for census and other data) and the University of Wisconsin's Neighborhood Atlas (Table 1). We will use data from the 2022 (most recent) five-year estimates from the US Census Bureau's American Community Survey, a multiyear probability-based estimate suitable for use with small area units. The Neighborhood Atlas's Area Deprivation Index is publicly available and created at the block group level, providing a more localized measure of neighborhood disadvantage. Rurality will be defined based on the US Department of Agriculture's Rural-Urban Commuting Area Codes [56]. We will obtain county-level drug overdose rates for the most recent year available from the CDC's National Vital Statistics System.

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Table 1. Measures and data sources.

Variable (type or form)	Source	Level
Outcome		
Availability of a medication disposal box (yes vs no)	Secret Shopper	Store
Availability of same-day naloxone without a prescription (yes vs no)	Secret Shopper	Store
Predictors and covariates		
Pharmacy characteristics		
Corporate owner (top 7 pharmacy chains by number of stores exceeding 1000)	Hayes	Store
Type (chain, food, independent, and medical)	Hayes	Store
Neighborhood resources—Bernard framework's economic domain		
Area Deprivation Index	University of Wisconsin Neighborhood Atlas	Block group
Percentage of the population living under the federal poverty line (ratio scaled ×10, eg, 12%=1.2)	ACS[a]	Tract
Percentage of the population age ≥16 years that is unemployed (ratio scaled ×10, eg, 12%=1.2)	ACS	Tract
Neighborhood structure—Bernard framework's physical domain		
Area Deprivation Index	University of Wisconsin Neighborhood Atlas	Block group
Percentage of housing structures that are vacant (ratio, scaled ×10, eg, 12%=1.2)	ACS	Tract
Percentage of housing structures that are renter occupied (ratio scaled ×10, eg, 12%=1.2)	ACS	Tract
Rurality or urbanicity (rural-urban commuting area codes)	USDA[b]	Tract
Neighborhood composition—Bernard framework's institutional domain		
Percentage of the population identifying American Indian or Alaska Native as their race (ratio, scaled ×10, eg, 12%=1.2)	ACS	Tract
Percentage of the population identifying Black or African American as their race (ratio, scaled ×10, eg, 12%=1.2)	ACS	Tract
Percentage of the population identifying Latino or Hispanic as their ethnicity, of any race (ratio, scaled ×10, eg, 12%=1.2)	ACS	Tract
Percentage of the population identifying White as their sole race, of any ethnicity (ratio, scaled ×10, eg, 12%=1.2)	ACS	Tract
County overdose deaths		
County-level drug overdose deaths	CDC's[c] National Vital Statistics System	County

[a]ACS: American Community Survey.

[b]USDA: US Department of Agriculture.

[c]CDC: Centers for Disease Control and Prevention.

Data Management and Ethics

We will implement protections to limit any ability to link data with individuals. We will not collect information that identifies the pharmacists or pharmacy staff whom we speak to on the calls. The only identifiable information will be the pharmacies in our sample. To minimize the likelihood of a breach in confidentiality, data will be collected and stored in REDCap, a secure web application for building and managing surveys, and on a secure and encrypted storage system maintained by Wake Forest University School of Medicine IT Security. Public access to deidentified data will be made public after the study has concluded.

Data Analysis

Geocoding and Spatial Data

After address cleaning and standardization, we will use Environmental Systems Research Institute, Inc's geocoding service to geocode drop box locations and use the resulting latitude and longitude to "spatially join" pharmacy locations with a shapefile of census geographies to obtain a Federal Information Processing Standards code in ArcGIS Desktop

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10.6.1 (Esri). The Federal Information Processing Standards code will allow us to link data to standard area units such as block groups, tracts, and counties in a single dataset and provide a unique ID for each level of nested area units.

Statistical Analyses

Analysis for Availability Estimates

To provide weighted estimates based on the availability of a medication disposal box and same-day naloxone nationally and for each stratum, weighing will be based on the percentage of corporate pharmacies in our sample compared with the total population. Using procedures that account for the stratified survey design, we will estimate the proportion and 95% CI to describe availability nationally and in each stratum for each outcome. Analyses will be conducted using SAS 9.4 (SAS Institute).

Analysis for Logistic Regression Models

To explore neighborhood and pharmacy characteristics associated with availability, we will use logistic regression with robust SEs where the availability of medication disposal boxes and same-day naloxone without a prescription are the outcomes. The stratified survey design will be accounted for when fitting the logistic regression model. Robust SEs will be used to account for potential correlation due to pharmacies being in the same state. We will initially fit unadjusted models for each characteristic of interest and then will fit multivariable models that include characteristics of interest and any available potential confounders for the associations of interest. Analyses will be conducted using SAS 9.4. Estimates will be presented as odds ratios with 95% CIs.

Statistical Power

Power for Availability Estimates

With 8 strata in a stratified random sample, a sample of 1000 should provide a relative SE of 11.7% for the population estimate (ie, we would expect to be 95% certain that the national estimate was within ±3.1 percentage points of the estimate). Individual strata would have an average relative SE of 25% and <±10 percentage points for each stratum.

Power for Logistic Regression Models

The total sample size (N=1000) was determined by a logistic regression power analysis. Initial parameter estimates in the Monte Carlo simulations (using MPlus 8; Muthén and Muthén) were based on a previous study of medication disposal programs at pharmacies in North Carolina [15]. The unconditional and conditional models achieved power of over 0.80 with two-tailed α=.05. The minimum detectable effect size was estimated at level 1 to be 0.17 with a small, medium, or large intraclass correlation coefficient (ICC) value and was estimated at level 2 to be 0.48 for a small ICC value, 0.50 for a medium ICC value, and 0.43 for a large ICC value [57].

Ethical Considerations

Informed consent was waived for this study. The consent process would reveal the secret shopper caller protocol and potentially result in the collection of inaccurate data [58]. Data will not be collected or recorded in a manner that would identify human participants. This protocol has been approved by the Wake Forest University School of Medicine Institutional Review Board (00105728).

Results

Data for this study were collected from January to April 2024. As of April 2024, the sample consists of 1108 pharmacies. Expected publication of the results is the summer of 2025.

Discussion

Contributions to the Literature

The overall objective of this study is to assess the extent to which disposal programs and same-day naloxone have been implemented in pharmacies across the United States and examine neighborhood characteristics related to their implementation. Our central hypothesis is that same-day naloxone will be more readily available at chain pharmacies than at independent pharmacies. The availability of medication disposal programs and same-day naloxone will be assessed using a secret shopper approach. Furthermore, we hypothesize that as neighborhood disadvantage and the proportion of Black and African American residents in a neighborhood increase, the likelihood of a pharmacy having a disposal program or same-day naloxone will decrease.

Next Steps

As part of the larger study, following the completion of the secret shopper caller study, interviews will be conducted with a sample of 60 pharmacy managers whose pharmacies were assessed in the secret shopper study. The objective of these interviews is to develop preliminary approaches grounded in implementation science frameworks to improve the implementation of medication disposal programs and same-day naloxone at community pharmacies.

Use of a Secret Shopper Protocol to Assess Public Health Interventions at Pharmacies

The use of a secret shopper caller protocol allows for unbiased and direct observations of overdose prevention service quality and compliance within community pharmacies [58]. An evaluation of how well pharmacy staff adhere to protocols, policies, and laws regarding overdose prevention can be determined. Similar approaches have also been used to assess other public health interventions at community pharmacies [59]. This method allows for real-time feedback and identification of areas needing improvement, ensuring that interventions are delivered effectively and consistently.

Limitations

There are several limitations to the secret shopper study. One limitation is that callers only speak with one pharmacy staff member, who may not represent all pharmacy staff. For this study, we documented whether the staff member revealed their role in the pharmacy and, if so, what their role was. To limit uncertainty, a future study could add a specific question in the secret shopper script to confirm whether the interaction was with a pharmacist. Another potential limitation is that the secret

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shoppers will only speak English during interactions, which restricts the findings to English-speaking populations. Future research could address this limitation by incorporating multilingual secret shoppers. We expect that additional limitations may be identified during study completion, and these will be identified and described in the results-oriented paper upon completion of the study.

Conclusion

Upon successful completion of the study, we will have estimates of the availability of disposal programs and same-day naloxone at pharmacies across the United States and identify place-based health disparities associated with their implementation.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

KLE was responsible for the conceptualization, methodology, investigation, resource management, data curation, and writing of the original draft, as well as the review and editing. She also provided supervision, project administration, and funding acquisition. BL contributed to the investigation, writing the original draft, as well as the review and editing. KF conducted the investigation and contributed to writing the original draft, review, and editing. JM participated in the investigation, review, and editing. RLG handled formal analysis and contributed to the review and editing. DMK worked on formal analysis and both the original draft, review, and editing. LAE was responsible for conceptualization, methodology, investigation, writing the original draft, review, and editing, along with funding acquisition.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Mystery caller data collection form for medication disposal programs.
[PDF File (Adobe PDF File), 40 KB - resprot_v14i1e64344_app1.pdf]

Multimedia Appendix 2
Mystery caller data collection form for naloxone.
[PDF File (Adobe PDF File), 40 KB - resprot_v14i1e64344_app2.pdf]

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Abbreviations

CDC: Centers for Disease Control and Prevention
DEA: Drug Enforcement Administration
FDA: Food and Drug Administration
ICC: intraclass correlation coefficient
REDCap: Research Electronic Data Capture

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Protocol

Implementation and Evaluation of a Therapeutic Communication Educational Program for Nurses: Protocol for a Mixed Methods Study

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Abstract

Background: Admission to a hospital can be a very stressful and anxiety-provoking experience, as patients face many unknowns that can compromise their physical and psychological well-being. Patient-centered care necessitates that health care organizations and professionals actively comprehend patients' experiences and values, for which effective training in communication skills is essential.

Objective: This study will contribute to this field of research by evaluating a blended therapeutic communication training program.

Methods: The training consists of online e-learning that provides insights into important concepts of therapeutic communication, followed by a virtual reality patient-embodied experience shown to help nurses feel what it is like to be a patient themselves during a 1-day didactic training with experiential small groups. Theory on therapeutic communication is taught, focusing on how to use rapid rapport techniques and hypnotic and suggestive language to facilitate empathy. This is combined with practical exercises, ensuring an active learning process. By integrating these diverse blended learning training methods, the program aims to enhance nurses' communication skills, ultimately improving patient care. Applying the Kirkpatrick model for training evaluation, this prospective study will use a convergent mixed methods study design, integrating both qualitative and quantitative data. Qualitative data will include fieldwork, as well as individual and focus group interviews with the participating nurses. Quantitative data will include questionnaires that include the first two levels of the Kirkpatrick model and that are validated for this purpose. Inclusion started in April 2024, and the therapeutic communication training was scheduled for the first half of 2024.

Results: On February 8, 2024, we received permission from the authorizing body (Institutional Science Committee and NWMO Committee) to start our study. Data collection started in April 2024 and was completed by the end of 2024.

Conclusions: This study will systematically evaluate the effectiveness of therapeutic communication training in the acute admission ward for patients who require emergency treatment. The results will yield insights into the feasibility and acceptance of the implementation of therapeutic communication training among nurses in an acute admission ward in the Netherlands.

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KEYWORDS

therapeutic communication; rapport; periprocedural anxiety; pain; medical education; nursing program; educational program; nursing; implementation; analysis; study protocol; protocol; hospital admission; well-being; patient-centered care; training program; e-learning; therapeutic; mixed method; qualitative; quantitative; emergency treatment

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Introduction

Admission to a hospital can be a very stressful and anxiety-provoking experience, as patients face many unknowns that can compromise their physical and psychological well-being. Hospitalization exacerbates patients' emotional reactions and may impede their ability to cope with and adjust to this new environment [1]. Especially in the dynamic and acute setting of the acute admission ward, patients are susceptible to anxiety, stress, and pain [1,2]. In the acute admission ward, many medical procedures, such as invasive exams and surgery, are well known for causing preprocedural anxiety and stress, with a reported prevalence ranging from 11% to 80% among adult patients undergoing surgery [3,4]. Preoperative anxiety is associated with increased postoperative pain, chronic pain, and lower satisfaction scores, potentially by amplifying the body's stress response and sensitizing the nervous system [5-9].

Landmark studies on patients' experiences and values describe that anxiety and stress come from the fear of the unknown, the uncertainty of treatments and their side effects, and the loss of control [3,10]. Patient-centered care necessitates that health care organizations and their professionals actively comprehend patients' experiences and values [11-14]. To establish high-quality and effective communication within this framework, effective training in communication skills is essential. It may assist health care providers in managing anxious and painful patients.

Despite its recognized importance, communication skills are not consistently or systematically taught in medical and nursing education. There is no general agreement or regulation in the educational system on how to teach and learn communication skills. Communication skills seem to be acquired 'on the job', greatly depending on implicit contextual factors rather than conventional classes or training [15]. The question arises of how to best teach and learn therapeutic communication skills and how to sensitize its importance. We hypothesize that a real lived experience of a patient could be a powerful learning experience, allowing health care providers to develop a deeper, more empathetic understanding of the patient's perspective [16,17]. Furthermore, we hypothesize that this understanding fundamentally aids in learning therapeutic communication.

Therapeutic communication can be defined as a way of communicating with awareness of and positive influences on contextual factors [18-20]. Spoken words are potent and suggestive tools that can shape future experiences and perceptions. In addition, communication includes paraverbal elements such as voice pitch, pacing, tone, and volume. Nonverbal aspects such as eye contact and body language also play a significant role in shaping perceptions of the receiver. These elements are crucial for establishing rapport between individuals during interactions. Rapport, defined as a close and meaningful relationship with mutual understanding, involves both verbal and nonverbal communication [21,22]. Incorporating elements of therapeutic communication can improve patients' knowledge and understanding, foster trust, enhance self-care skills, increase treatment adherence, provide comfort, and aid in managing emotions, all of which are essential for health and well-being [23,24].

While various communication training programs exist, there is limited research on the effectiveness of short, blended-learning approaches that integrate virtual reality (VR)-based experiential learning to enhance therapeutic communication. This study aims to address this gap by evaluating the impact of a one-day blended-learning therapeutic communication training program. The training combines e-learning, VR patient-embodied experience, and didactic training with experiential small groups, providing an innovative approach to skill acquisition.

The main objective of this study is to evaluate the impact of our therapeutic communication training for nurses in the acute admissions ward of a tertiary hospital using the 4-level Kirkpatrick model for training evaluation [25,26], as shown in Figure 1. Our research questions are derived from the first two levels:

Level 1: How do participants *feel* about therapeutic communication training?

Level 2: Did participants *learn* about therapeutic communication?

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Figure 1. Kirkpatrick four-level training evaluation model.

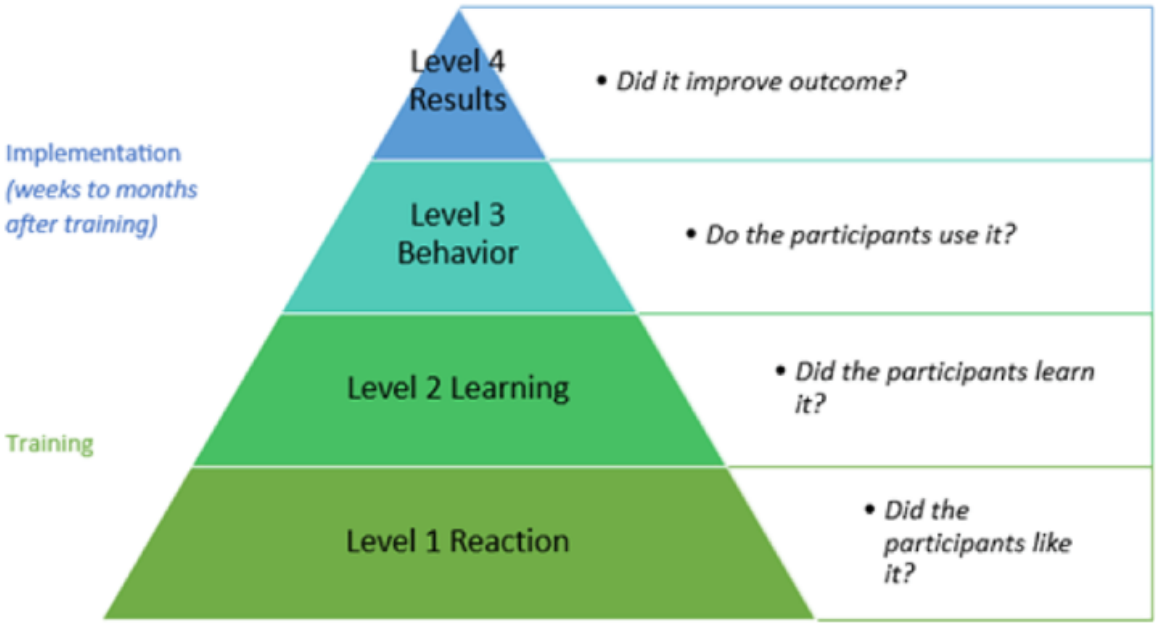

Methods

Setting and Participants

This prospective study will be conducted at the acute admission ward of the Leiden Universitair Medisch Centrum (LUMC) hospital, a tertiary teaching hospital in the Netherlands. In the acute admission ward, patients who need emergent care or treatment can be admitted for a short stay. The protocol was approved by the Institutional Science Committee as well as the non-WMO committee and will adhere to Good Clinical Practice (GCP) regulations.

To be eligible for the study, participants must daily communicate with patients or their relatives as part of their daily duties, speak proficient Dutch (local language) to be able to complete the surveys, and participate in an interview. Nurses leaving the ward within a year were excluded. For the quantitative analysis, nurses of a general ward will also be invited enhancing statistical power with a greater number of participants. In both wards, all eligible nurses were invited to participate in the therapeutic communication training during working hours, and they were invited through email to participate in the study. Participants will not receive any compensation and signed an informed consent form before the start of the study. Pragmatically, the interviews will take place during working hours, inviting nurses on call on the day of the interview. To include broad data, interviews are planned during day and evening shifts on different days of the whole week.

This study will not directly involve patients in the development of the therapeutic communication training, as it was designed based on established literature on patient stress and anxiety as well as previous research on the development and validation of VR-embodied experiences [16,17]. The primary objective of this study is to evaluate the effects of the training on nurses, focusing on their perceptions and learning outcomes. Direct patient involvement in this stage would require a substantial shift in study design and ethical considerations, particularly concerning data collection from patients.

Study Design

A convergent unblinded mixed method study design in which qualitative and quantitative data are used in multiple phases and merged and analyzed equally for an interactive approach [27]. Qualitative and quantitative investigations will take place before and after the implementation of the therapeutic communication training at the acute admission ward. Additional quantitative data is retrieved at a general ward.

Qualitative research, and in our case ethnography, has an important role in better understanding the social factors influencing medical and scientific routines [28]. A qualitative researcher (CK) will perform fieldwork and immerse themselves in the research population for an extended period, studying insiders' perspectives, behaviors, and culture. Qualitative outcome measures will include nonparticipatory observations, individual interviews, and focus group interviews with health care providers. During fieldwork, we aim to be naturalistic and nondirective, stepping back from action and minimalizing interference with regular care [29,30].

For quantitative data analysis, data saturation will be pursued [31]. For quantitative outcomes, our pragmatic feasible objective is to include at least 50% of all nurses, which amounts to 20 nurses of the total 40 nurses working in the acute admission ward, and 20 of the 40 nurses in the general ward.

Intervention

Therapeutic Communication Training

The training was developed based on landmark patient-centered studies and included important aspects of lived patient experiences [5-8,19,32-35]. The trainer is a hypnotherapist and anesthesiologist with extensive teaching experience currently working at the LUMC hospital.

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The blended therapeutic communication training program includes several components, including online and offline elements, and an overview can be found in Multimedia Appendix 1.

(1) Online e-learning: an online training module covering the basics of therapeutic communication.

(2) VR patient-embodied experience: this immersive experience enables nurses to feel firsthand what it is like to be a patient, enhancing empathy and insight. The VR experience shows the patient journey of a woman who will undergo knee surgery. She was brought into the preoperative holding area, given an IV drip, and driven to the OR. The video ended when the anesthesiologists induced general anesthesia. During the video, the health care providers do not apply therapeutic communication practices, show little empathy or personalized care, and give quite a few negative suggestions during the encounters. A more detailed description of the VR experience can be found in our recent work on patient-embodied VR experiences [16,17].

(3) 1-Day didactic training: this in-person session of a maximum of 10 participants features experiential small-group activities, reinforcing the concepts learned online and in VR. The theoretical foundation of the training focuses on therapeutic communication techniques such as rapid rapport building and strategic word choice using hypnotic language. Techniques such as reframing, mirroring, and positive suggestions are emphasized while avoiding the nocebo effects of negative language and expectations. Practical exercises ensure an active learning process, enabling nurses to apply these techniques effectively in their interactions with patients.

Quality Assurance

We hypothesized that the implementation of the therapeutic communication training program would require more than an initial training. To facilitate the full implementation process, nurses, researchers, quality advisors, and communication experts will work together to optimize the implementation process, as shown in Figure 2 and detailed below.

Figure 2. Implementation process.

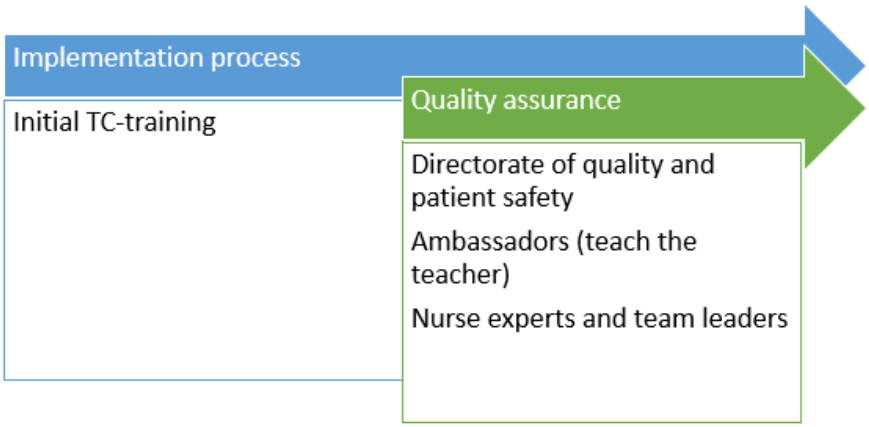

Directorate of Quality and Patient Safety

To ensure the quality of the learned knowledge of therapeutic communication, the Directorate of Quality and Patient Safety and the Communication Department of the Hospital will be involved throughout this research project. They will meet regularly with the nurse experts and team leaders of the ward to evaluate the implementation process.

Teaching the Teacher

We hypothesized that it would be necessary to have "therapeutic communication ambassadors" on the ward to be able to answer questions, plan clinical bedside lessons, and perform practical exercises. Recruitment of therapeutic communication ambassadors will start after all nurses in the acute admission ward follow the training. After an initial briefing, an invitation will be sent to participate in "Teach the Teacher" training to become a therapeutic communication ambassador. Team leaders will have the final choice of selection of these ambassadors. This training will be provided by the Radboud Academy, a partner institution of the Nijmegen Academic Medical Centre. During this course, participants will learn to obtain more in-depth knowledge on therapeutic communication, as well as the didactic competencies needed to become an ambassador of the therapeutic communication program.

Outcomes and Measures

Qualitative Outcomes and Measures

We have adhered to Consolidated Criteria for Reporting Qualitative Research (COREQ) criteria (Multimedia Appendix 2) for our qualitative outcomes including, among others, fieldwork, as well as individual and focus group interviews among the participating nurses before and after the training has taken place [36]. The interview guide can be found in Multimedia Appendix 3. Interviews will be audio-recorded, transcribed verbatim, anonymized, and then safely stored.

Focus group interviews are used to interview a small number of demographically similar people in social, psychological, and public health science [37]. During the interviews, nurses will be asked about their perceptions, attitudes, opinions, and views regarding therapeutic communication. Group members are free to talk and interact with each other. Instead of a researcher individually asking group members questions, focus groups will be used to observe group interactions to explore and clarify the beliefs, opinions, and views of participants. During these

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interviews, the interviewer will take notes and record the discussion for subsequent notetaking to learn from the group. The building of the a priori template and analysis was performed by the principal investigator (KH). For practical reasons, if it is not possible to conduct a focus group interview, individual interviews will be held to gather further data.

The interviews were conducted by research interns (NK and CK), and the researchers (MVV and KH), all with extensive experience in qualitative research. Interviews after the intervention will not be performed by KH, as she is the trainer of the therapeutic communication trainer, and this might induce biases. All interviewers introduced themselves initially and did not know the participants before the commencement of the study.

Quantitative Outcomes and Measures

Quantitative outcomes include questionnaires on current knowledge of therapeutic communication, as well as validated training analysis questionnaires following the Kirkpatrick analytical model [26]. Data collection will be conducted as shown in Figure 3.

Figure 3. Data collection of quantitative data.

Kirkpatrick Model Level 1 – Reaction: What are Participants' Reactions to Therapeutic Communication Training?

This questionnaire will be sent out after the training, including themes such as educational goals, trainees' preparation, the use of new teaching and learning methods, the use of learning tools, teaching environment, teacher assessment, and teacher characteristics on a 5-point Likert scale from very weak to excellent and can be found in Multimedia Appendix 4. [25].

Kirkpatrick Model Level 2 – Learning: Knowledge of Therapeutic Communication

For the purpose of this study, a standardized Nursing Education Program Implementation and Analysis (NEPIA) questionnaire was developed to evaluate knowledge of therapeutic communication. This questionnaire included five multiple-choice questions, with one or more correct answers, and can be found in Multimedia Appendix 5. This questionnaire was conducted and validated by a pilot of 10 nurses to evaluate the clarity of the questions. Their responses will not be taken into account in further analysis. This questionnaire aims to respond to the second level of the Kirkpatrick model: "Learning." What is the impact of therapeutic communication training on participants' self-efficacy regarding therapeutic communication?

Data Analysis

All data will be kept in password-protected files with limited user access on protected hospital network drives and collected in the electronic data capture system Castor EDC. For quantitative data analysis, SPSS 25 (IBM Corp) for Windows will be used. Chi-square tests, independent *t* tests, and Mann Whitney U tests will be used to test differences before and after training.

Qualitative analysis will be performed using template analysis [38] in ATLAS.ti (Lumivero). Initial themes for the interviews can be found in Multimedia Appendix 3. During the initial coding, a critical reflection will be performed (KH, MVV). If needed, themes are modified, or additional themes are added to ensure that the themes fit the data and that the data are not selectively analyzed to fit the themes. The initial analysis provided information for further participant selection and coding. Performing iterative data collection and analysis to guide decisions will improve the dependability of the results [39]. The template will be further developed by applying it to the full data set. The building of the a priori template and analysis of the interviews will be performed by the principal investigator (KH). We decontextualize the data to identify descriptions and cluster them into discrete categories. Overall, we aim to structure these experiences, and additional changes might be made to the template; more interviews might be needed. Qualitative data will be retrieved while pursuing data saturation; that is, until we are empirically confident, additional data will not lead to any new emergent input [31,40].

Ethical Considerations

The protocol was approved by the Institutional Science Committee and received a waiver from the institutional review board. The study will adhere to GCP regulations. Written informed consent was obtained from all participants. Participants received no financial compensation. Data will be anonymized.

Results

On February 8, 2024, we received permission from the authorizing authorities (Institutional Science Committee NWMO Commissie divisie 1) to start our study. Data collection started in April 2024 and concluded by the end of 2024. We expect to publish our results in 2025.

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Discussion

Overview

This study evaluates the effectiveness of a one-day blended-learning therapeutic communication training for nurses, integrating e-learning, VR patient-embodied experience, and didactic small-group training. Using the Kirkpatrick evaluation framework, we aim to assess whether this structured format enhances nurses' communication skills, specifically measuring their reaction (Level 1) and learning outcomes (Level 2). We anticipate that the training will be feasible, well-received, and effective in improving nurses' understanding and application of therapeutic communication techniques. If successful, this study could demonstrate the value of short, immersive training models in clinical education, particularly in fast-paced hospital environments.

Existing research underscores the importance of therapeutic communication in reducing patient anxiety and pain perception; however, most training programs are time and resource-intensive and often lack immersive experiential components. Our one-day format, enriched with VR-based patient embodiment, addresses these gaps by providing a scalable, high-impact intervention. Previous studies on therapeutic communication training have not consistently incorporated technology-driven experiential learning, making this approach unique in its accessibility and potential for broader hospital-wide adoption.

A key strength of this study is its mixed-methods design, ensuring a comprehensive evaluation of both subjective participant experiences and measurable learning gains. In addition, the blended-learning approach, including VR, offers a realistic, patient-centered perspective that may enhance the long-term retention of communication skills.

Another strength of this study is the opportunity to attend the training during working hours, enabling all nurses to participate. The team leaders of both wards will make an effort to accommodate this in the scheduling.

A limitation of this study is that only short-term learning outcomes are assessed, leaving a long-term impact on patient care remaining to be evaluated.

Dissemination

We intend to present our results within our hospital and advocate for its implementation in other wards, and if possible, throughout the hospital. To enhance the dissemination process, we will use social media platforms and in-house press releases. Furthermore, we aim to publish the results of this study in appropriate peer-reviewed, open-access journals to ensure they are accessible to clinicians, researchers, educators, and other relevant stakeholders within health care organizations, including patients. Furthermore, dissemination through social media and institutional press will support a wider engagement within health care communities.

Future Implications

In the case of proven effectiveness of therapeutic communication training and implementation, future research should be conducted using level 4 of the Kirkpatrick model for training evaluation: the improvement of patient outcomes. Finally, our results may be useful for other health care institutions and implementation researchers when planning or implementing therapeutic communication skills training.

Conclusion

This study systematically evaluates a short, immersive therapeutic communication training program by using blended-learning methods, including VR-based patient-embodied experiences, we aim to determine its feasibility and effectiveness in improving communication skills. If successful, this training model has the potential to enhance patient care, influence hospital-wide training initiatives, and serve as a blueprint for scalable communication education programs in health care settings.

Acknowledgments

We would like to acknowledge the health care professionals who will participate in this research; we thank them for their time and effort in contributing to this project. R Heemskerk, Y Huinen, N van Schagen, and J Schilstra have made significant contributions that have enabled the planning of our project. The medical work environment and implicit rationing of care will be respected during this study. We also thank research interns C Kwendé (Master of Anthropology) and N van der Kwaak (applied Psychologist), both with extensive experience in qualitative research, who will assist in conducting this study. This study was funded by Verpleegkundige Vernieuwing (Nursing Innovation), an initiative that supports nurses in building a future-oriented work and learning environment. A project group was established to submit the funding application, and the program selected this project following an internal review.

Data Availability

The datasets used and/or analyzed during this study are available from the corresponding author upon reasonable request. The original audio files were unavailable due to privacy restrictions.

Authors' Contributions

KH had the original idea for the study and contributed to the conceptualization, investigation, methodology, project administration, supervision, data collection, data curation, and formal analysis. LS contributed to conceptualization and recruitment project

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administration and management. MvV assisted with conceptualization, data curation, formal analysis, investigation, resources, software, supervision and participated in data validation and review and editing. EYS has evolved around education in medical training. She contributed to conceptualization, project administration, supervision, visualization, validation and writing – review and editing.

Conflicts of Interest

KH is the trainer and developer of the therapeutic communication training.

Multimedia Appendix 1
Therapeutic communication training.
[DOCX File , 14 KB - resprot_v14i1e65795_app1.docx]

Multimedia Appendix 2
COREQ checklist.
[DOCX File , 20 KB - resprot_v14i1e65795_app2.docx]

Multimedia Appendix 3
Interview guide.
[DOCX File , 14 KB - resprot_v14i1e65795_app3.docx]

Multimedia Appendix 4
NEPIA (Nursing Education on Patient Interaction Assessment) questionnaire – Kirkpatrick model, level 2.
[DOCX File , 15 KB - resprot_v14i1e65795_app4.docx]

Multimedia Appendix 5
Course evaluation using Kirkpatrick model, level 1.
[DOCX File , 16 KB - resprot_v14i1e65795_app5.docx]

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Abbreviations

COREQ: Consolidated Criteria for Reporting Qualitative Research
GCP: Good Clinical Practice
LUMC: Leiden Universitair Medisch Centrum
NEPIA: Nursing Education on Patient Interaction Assessment
VR: virtual reality

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Protocol

Assessing the Efficacy of Current Histopathological Tumor Reporting Systems for Evaluating the Response to Neoadjuvant Chemotherapy for Breast Carcinoma: Protocol for an Observational Study

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Abstract

Background: With a predicted 2 million new cases identified globally in 2018, breast carcinomas are the most common cancer in women and the primary cause of cancer-associated mortality. In the management of breast cancer, neoadjuvant chemotherapy treatment (NACT) has become a mainstay, particularly for patients with inflammatory and locally advanced breast cancer. It increases the possibility of breast-conserving surgery, facilitates tumor downstaging, and gives early indications of the effectiveness of treatment. Evaluating the histopathological response after NACT is crucial for prognosis and guiding subsequent treatment decisions. This study explores the various histopathological assessment systems used in breast carcinoma patients after NACT, focusing on the residual cancer burden (RCB) score, Miller-Payne system, Chevallier classification, Sataloff classification, National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B-18 system, and the American Joint Committee on Cancer residual tumor size (R) categories. We compare their methodologies, strengths, limitations, and clinical significance, providing a detailed analysis of their roles in improving patient outcomes.

Objective: The aim of this study is to confirm the diagnosis of breast carcinoma based on histopathology, to evaluate various scoring systems through assessments of histomorphological features affecting post-NACT patients with breast carcinoma, to compare the various systems regarding the response to therapy and forming prognoses, and to develop an ideal histomorphological assessment system for breast carcinoma in post-NACT patients. The study also focused on how breast tumors respond to NACT and how this response can guide treatment decisions and improve the formulation of prognoses.

Methods: This observational study will be retrospective and prospective; it will include 128 patients diagnosed with breast carcinomas who have undergone NACT and were referred to a tertiary care hospital between January 2019 and December 2024. Following chemotherapy, a thorough examination of the histopathological specimens will be conducted to assess any changes in histomorphology.

Results: Data collection started in September 2021 and will be completed by December 2025. Data analysis began in January 2025, and the results are expected to be published in December 2025. Institutional ethics committee clearance was obtained prior to commencement of the study. This is a nonfunded academic study.

Conclusions: This project aims to evaluate and compare histopathological assessment systems in patients with breast carcinoma after NACT. Various histopathological systems, such as the RCB score, the Miller-Payne grading system, and other systems, each provide valuable insights into how well tumors respond to chemotherapy. The aim is to reveal essential histopathological

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parameters, leading to the refinement and potential modification of grading systems to improve clinical decision-making, treatment outcomes, and personalized care; however, challenges persist in standardization and consensus.

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(JMIR Res Protoc 2025;14:e56825) doi:10.2196/56825

KEYWORDS

evaluation; comparison; histopathological assessment systems; breast carcinoma; neoadjuvant chemotherapy; prognosis; hormone receptor status; lymphnode status; residual cancer burden; Miller-Payne system; Chevallier classification; Sataloff classification; AJCC residual tumor size (R); clinical decision making; treatment outcome

Introduction

Background

With a predicted 2 million new cases identified globally in 2018, breast carcinomas are the most common cancer in women and the primary cause of cancer-associated mortality [1]. Breast cancer is not a single disease; each tumor has distinct features, such as size, kind, lymph node status, hormone receptor status, and human epidermal growth factor receptor 2 (HER2)/neu oncogene expression. Breast cancer takes diverse forms in different ethnic groups. The multitude of genetic mechanisms that ultimately determine the kind of breast cancer and its underlying biology most likely reflect this variability.

Neoadjuvant chemotherapy treatment (NACT) is used for inflammatory breast cancer and locally advanced breast cancer, as well as to reduce large tumors to allow for breast conservation therapy [2].

NACT has the ability to reduce or even completely reverse primary cancers and their metastases. Patients with clinically node-negative breast cancer who have unfavorable tumor characteristics and are expected to benefit from adjuvant systemic therapy can now also benefit from NACT [3]. NACT offers a number of advantages. With the full pathologic response serving as a proxy predictor of survival, it presents a rare chance to assess the response to therapy, evaluate new therapeutic agents more quickly, and stop ineffective treatments early.

Additionally, patients are spared the burden of toxicity and side effects when they switch to a different medication or adjust the dose if they become resistant to therapy. Moreover, NACT permits the collection of tumor samples prior to, during, and following treatment, and offers the chance for tailored therapy [4,5].

In the management of breast cancer, NACT has become a mainstay, particularly for patients with inflammatory and locally advanced breast cancer. It increases the possibility of breast-conserving surgery, facilitates tumor downstaging, and gives early indications of the effectiveness of treatment. Evaluating the histopathological response after NACT is crucial for prognosis and guiding subsequent treatment decisions. This study explores the various histopathological assessment systems used in patients with breast carcinoma after NACT, focusing on the residual cancer burden (RCB) score, Miller-Payne system, Chevallier classification, Sataloff classification, National Surgical Adjuvant Breast and Bowel Project (NSABP) Protocol B-18 system, and the American Joint Committee on Cancer (AJCC) residual tumor size (R) categories.

The RCB score is the system recommended in the European standards for assessing nodal and tumor regression. Three reactions are categorized under the NSABP B-18 system. The Miller-Payne system incorporates the change in cellularity between biopsy and resection specimens, while the Sataloff and RCB systems take into account the condition of the lymph nodes and residual tumor, and the Chevallier grade takes into account the possibility of some regression.

This research has four main aims: (1) individually assess various parameters used in different grading systems for breast carcinoma for making treatment prognoses after the chemotherapeutic intervention; (2) evaluate and juxtapose the grading systems; (3) determine the effectiveness of individual parameters for various grading systems so as to better understand treatment outcomes in patients and help clinicians assess ongoing treatment modalities and modulate them if required; (4) improve the reliability of prognosis prediction through better evaluation.

Review of Literature

Residual in situ carcinomas have imprecise prognostic significance, which was taken into account by Chevallier et al [6] in the pathological classification system they reported in 1993. In 1995, the breast and axillary nodes were examined pathologically for therapeutic effects by Sataloff et al [7], who developed a grading scale. The NSABP B-18 trial by Fisher et al [8] in 1997 and 1998 was one of the largest studies comparing neoadjuvant to adjuvant therapy. In 2003, a new histological grading system to assess the response of breast cancers to primary chemotherapy, the Miller-Payne system, was introduced that did not include the assessment of axillary lymph nodes; it assessed prognostic significance and survival [9].

The RCB score was developed by Symmans and coworkers [10] in 2007, and it is highly recommended that it be included in routine histopathological reports of breast cancers treated with NACT. While the majority of RCB features are commonly included in histopathological reports, certain elements, such as the proportion of ductal carcinoma in situ, cellularity, and the second greatest dimension of tumor size, need to be characterized by experience in the field. Standardized methods for reporting these markers are included in concise guidance at the RCB calculator website [11].

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Knowledge Gap Analysis

Many evaluation systems are presently in vogue for the assessment of histomorphological changes in post-NACT patients with breast carcinoma. Systems used to assess changes after therapy include the Chevallier grading system, Miller-Payne grading system, Sataloff grading system, and RCB score. These assessment systems have varying parameters to evaluate histomorphological changes. Because there are multiple assessment systems, assessments can vary indirectly, affecting post-NACT sequalae in patients. There is no international agreement on terminology, and how regression is defined varies from nation to nation. Hence, it is necessary to determine fixed criteria or a single system for the assessment of post-NACT patients. Despite the introduction of a number of national guidelines in Australia, Belgium, Germany, the United Kingdom, the Netherlands, the United States, and Hungary, among other countries, with the goal of standardizing specimen collection and reporting, there is no worldwide consensus on the interpretation of tumor regression, the definition of a pathologic complete response, or the measurement of tumor size in cases where fibrosis develops as a result of NACT or there is multifocality. Figure 1 shows the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) flow chart of the results, Textbox 1 shows the keywords used in the literature review, and Table 1 provides an overview of the various grading systems.

A comprehensive review of the literature was conducted, encompassing studies that used various grading systems for assessing histomorphological changes in patients with breast carcinoma undergoing NACT. The selected grading systems, including NSABP B-18, Chevallier, Sataloff, Miller-Payne, and RCB, were analyzed in terms of their parameters, methodologies, and reported prognostic implications.

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart. FNAC: fine needle aspiration cytology; NACT: neoadjuvant chemotherapy treatment.

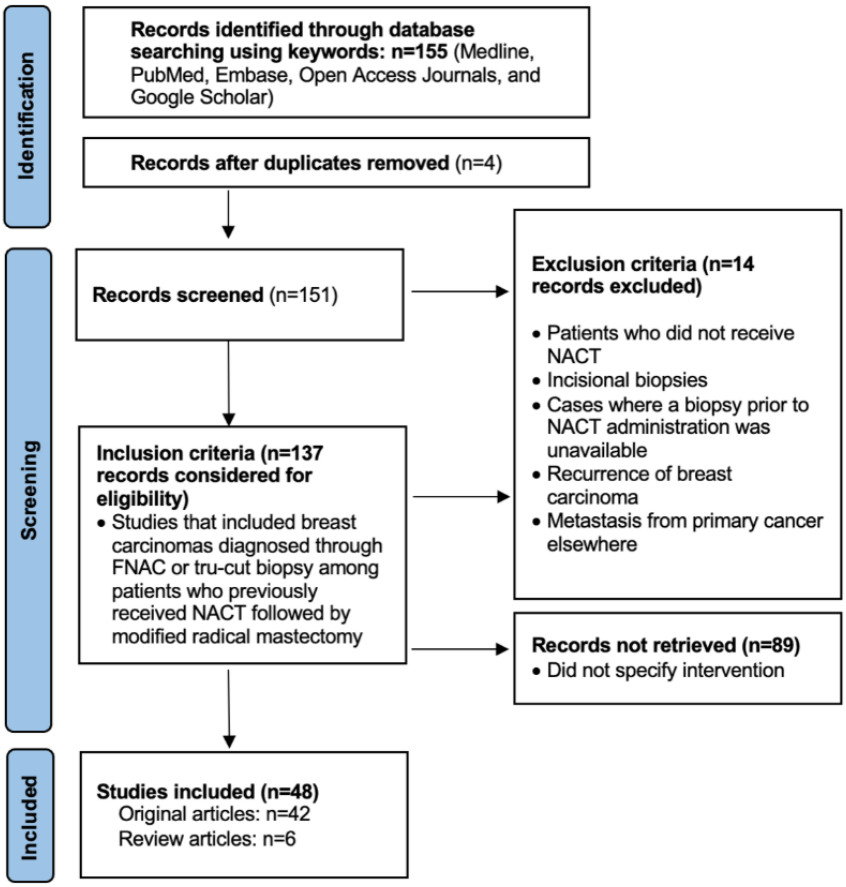

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Textbox 1. Keywords and translations used in the literature search.

Keywords

("histopathologic" [All Fields] OR "histopathological" [All Fields] OR "histopathologically" [All Fields]) AND ("assess" [All Fields] OR "assessed" [All Fields] OR "assessment" [All Fields] OR "assesses" [All Fields] OR "assessing" [All Fields] OR "assessment" [All Fields] OR "assessment s" [All Fields] OR "assessments" [All Fields]) AND ("system" [All Fields] OR "system s" [All Fields] OR "systems" [All Fields]) AND (("breast neoplasms" [MeSH Terms] OR ("breast" [All Fields] AND "neoplasms" [All Fields]) OR "breast neoplasms" [All Fields] OR ("breast" [All Fields] AND "carcinoma" [All Fields]) OR "breast carcinoma" [All Fields]) AND ("patient s" [All Fields] OR "patients" [MeSH Terms] OR "patients" [All Fields] OR "patient" [All Fields] OR "patients s" [All Fields])) AND ("neoadjuvant therapy" [MeSH Terms] OR ("neoadjuvant" [All Fields] AND "therapy" [All Fields]) OR "neoadjuvant therapy" [All Fields] OR ("neoadjuvant" [All Fields] AND "chemotherapy" [All Fields]) OR "neoadjuvant chemotherapy" [All Fields])

Translations

- Histopathological: "histopathologic" [All Fields] OR "histopathological" [All Fields] OR "histopathologically" [All Fields]
- Assessment: "assess" [All Fields] OR "assessed" [All Fields] OR "assessment" [All Fields] OR "assesses" [All Fields] OR "assessing" [All Fields] OR "assessment" [All Fields] OR "assessment's" [All Fields] OR "assessments" [All Fields]
- Systems: "system" [All Fields] OR "system's" [All Fields] OR "systems" [All Fields]
- Breast carcinoma: "breast neoplasms" [MeSH Terms] OR ("breast" [All Fields] AND "neoplasms" [All Fields]) OR "breast neoplasms" [All Fields] OR ("breast" [All Fields] AND "carcinoma" [All Fields]) OR "breast carcinoma" [All Fields]
- patients: "patient's" [All Fields] OR "patients" [MeSH Terms] OR "patients" [All Fields] OR "patient" [All Fields] OR "patients's" [All Fields]
- Neoadjuvant chemotherapy: "neoadjuvant therapy" [MeSH Terms] OR ("neoadjuvant" [All Fields] AND "therapy" [All Fields]) OR "neoadjuvant therapy" [All Fields] OR ("neoadjuvant" [All Fields] AND "chemotherapy" [All Fields]) OR "neoadjuvant chemotherapy" [All Fields]

Table 1. Various grading systems.

System	Report	Patients, n	Pathological complete response, %	Validated as prognostic for survival	Parameters included	Limitations
Chevallier method	Chevallier et al [6], 1993	45	26	OS[a], DFS[b]	Tumor cells, ductal carcinoma in situ, and lymph nodes	Does not assess tumor cellularity, LVI[c], or tumor heterogenicity
Sataloff method	Sataloff et al [7], 1995	36	16	DRFS[d]	Therapeutic effect on tumor cells and lymph nodes	This system does not include tumor cellularity, LVI, or tumor heterogenicity
NSABP B-18[e]	Fisher et al [8], 1998	1234	20	OS, DFS	Presence of invasive carcinoma	Metastases to lymph nodes were analyzed separately; does not include LVI or tumor heterogenicity
Miller-Payne system	Ogston et al [9], 2003	176	14	OS, DFS	Presence of invasive carcinoma tumor cellularity	Does not include the response in lymph nodes or LVI[c]
AJCC[f]	Carey et al, [12] 2005	132	17	OS, DFS	Tumor lymph node status (number and size)	This system does not include changes in cellularity or LVI
RCB[g] system	Symmans et al [10], 2007	432	24	DRFS	Size of tumor bed, tumor cellularity, lymph node status	This system does not include LVI

[a]OS: overall survival.

[b]DFS: disease-free survival.

[c]LVI: lymphovascular invasion.

[d]DRFS: distant recurrence–free survival

[e]NSABP B-18: National Surgical Adjuvant Breast and Bowel Project Protocol B-18.

[f]AJCC: American Joint Committee on Cancer.

[g]RCB: residual cancer burden.

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Methods

Study Design

This observational study will be retrospective and prospective and will include 128 patients who were diagnosed with breast carcinomas and underwent NACT after referral to a tertiary care hospital between January 2019 and December 2024.

Breast Specimens

Histopathological reporting will be performed according to the techniques shown in Figure 2. The pathological reports on breast specimens will include (1) the presence and size of the tumor bed, which is important for documentation, especially in cases with pathologic complete response; (2) the size and extent of residual tumor, including 2D measurements of the largest area of invasive cancer, the number of foci, or number of blocks with foci of invasion; (3) the average cancer cellularity of the residual tumor bed; (4) the appearance of the residual tumor and ita grade, if applicable, and a comparison to pretreatment carcinoma, if possible; (5) viability (necrosis and mitotic figures) and MIB-1 (Ki-67) proliferation index; (6) lymphovascular invasion; (7) presence and extent of ductal carcinoma in situ; (8) margins with respect to tumor bed, as well as invasive and in situ carcinoma. The report will also include a comment on the overall response to treatment and the lymph node status.

Figure 2. Macro- and microscopic reporting of breast carcinomas.

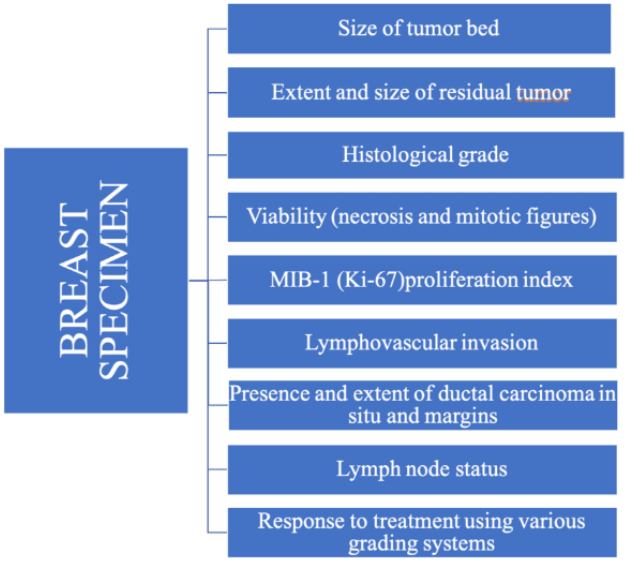

Assessment of Pathological Tumor Response

Histopathological evidence on the chemotherapeutic response will be graded based on hematoxylin and eosin (H&E)-stained sections on the basis of the parameters used by various histopathological assessment systems for patients with breast carcinoma after NACT.

General Methodology

A detailed history will be obtained for each patient, and a clinical examination will be performed. Radiological investigations and previous biopsies will be noted from the medical record of each patient. The resected specimens obtained after modified radical mastectomy (MRM) following NACT will be studied as per standard protocol. All specimens are fixed in 10% formalin and grossed; sections are taken from the lesion and the lymph nodes. The samples are processed and embedded in paraffin. The H&E-stained paraffin sections are then studied under the microscope. The histopathological specimens collected after chemotherapy were evaluated for histomorphological changes.

Statistical Considerations

Continuous variables will be summarized using tables of descriptive statistics: number of patients with recorded observations, mean, SD, median, minimum, and maximum. Categorical variables will be summarized using counts and percentages. Descriptive statistics will be presented by diagnosis. Diagnostic outcomes will be tabulated and compared for a unified post-NACT tumor reporting system.

Analytical Procedures

All results will be analyzed using Stata (version 15; StataCorp). We will calculate the sensitivity, specificity, positive predictive values, and negative predictive values for modification of the existing grading systems. Agreement analysis (primary and secondary end points) will be run to determine the percentage of agreement (overall, positive, and negative agreement) between both procedures, as well as κ coefficients, *P* values, and 95% CIs.

Continuous variables will be summarized using descriptive statistics, specifically the mean, SD, median, minimum, and maximum. Comparison of continuous parameters between pairs of groups will be performed using the *t* test or Wilcoxon Mann-Whitney *U* test; paired data will use the Wilcoxon signed rank test (nonparametric), as appropriate. Categorical variables will be summarized using frequencies and percentages, and they will be compared between pairs of groups using the χ^2 or Fisher exact test or, as appropriate, the McNemar χ^2 test for paired data.

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Sample Size

We will include 109 participants; this sample size was calculated using Epi Info (version 7.0; US Centers for Disease Control and Prevention) with a 5% precision level, 95% confidence level, and a design effect of 1%.

Inclusion and Exclusion Criteria

All patients with breast carcinomas diagnosed by fine needle aspiration cytology or tru-cut biopsy who had previously received NACT followed by MRM will be considered for the study. Patients who did not receive NACT, who underwent incisional biopsies, for whom a biopsy prior to NACT administration was unavailable, or who had recurrence of breast carcinoma and metastasis from a primary cancer elsewhere will not be included.

Ethics Approval

Institutional ethics committee clearance was obtained prior to commencement of the study (IEC DMIMS [DU]–DMIMS [DU]/IEC/2021/454, dated July 31, 2021). All the data captured were anonymized. A thorough history including clinical examinations, radiological tests, and prior biopsies will be documented from the patient's medical records in each case. An informed consent form will be provided to the participants enrolled in the study. This is an academic study and no compensation will be given to participants.

Study Plan

Table 2 shows an outline of the study plan.

Table 2. Quarterly scheduling of research work.

Item	Quarter											
	1	2	3	4	5	6	7	8	9	10	11	12
Outline of study design and preparation	✓	✓										
Reference collection and review of literature			✓	✓								
Data collection					✓	✓	✓					
Data compilation and tabulation								✓				
Data analysis									✓			
Thesis writing									✓	✓	✓	
Final thesis preparation										✓	✓	
Submission												✓

Results

Data collection started in September 2021 and will be completed by December 2025. As of December 2024, a total of 128 patients were recruited who had been diagnosed with breast carcinomas and had undergone NACT at a tertiary care hospital. Data analysis began in January 2025, and the results are expected to be published in December 2025.

Discussion

Overview

This study aims to evaluate various scoring systems through assessment of histomorphological features affecting post-NACT patients with breast carcinoma to compare various systems regarding the response to therapy and forming prognoses in order to develop an ideal histomorphological assessment system for breast carcinoma in post-NACT patients. We hypothesize that these assessments focus on how the response to therapy can guide treatment decisions and improve the formulation of prognoses.

Principal Findings and Comparison to Prior Work

After the literature search, we observed that there is no single reporting system for post-NACT mastectomy specimens that includes all parameters and predictors for management and prognosis of breast carcinoma in patients. The first objective is to confirm the diagnosis of breast carcinoma based on histopathology. The second objective is to evaluate various scoring systems through assessments of histomorphological features affecting post-NACT patients with breast carcinoma. The third objective aims, after comparing the various grading systems for reporting on post-NACT mastectomy specimens and mixed grading systems for breast carcinoma, to develop a more evolved and advanced grading system by modification of the existing systems and incorporation of their chief parameters. The fourth objective aims to help determine the most appropriate treatment protocol, predict treatment outcomes, and accurately speculate on the prognosis of the patient.

Strengths and Limitations

This study has several strengths. The first is that the study involves the evaluation and comparison of various histopathological assessment systems in post-NACT patients with breast carcinoma. This implies a comprehensive and multidimensional approach to understanding the impact of different evaluation methods on outcomes after chemotherapy.

Second, our focus on post-NACT patients with breast carcinoma indicates a patient-centric perspective, considering the specific challenges and responses in this subgroup. This approach acknowledges the unique nature of breast cancer and the significance of NACT. The study explicitly incorporates various grading systems, such as NSABP B-18, Chevallier, Sataloff, Miller-Payne, and RCB. This reflects a thorough exploration

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and integration of existing systems, aiming to provide a comprehensive understanding of their respective contributions. The inclusion of keywords like “treatment prognostication,” “tumor response,” and “clinical outcome” reflects a strong emphasis on assessing the practical implications of histopathological assessments. This aligns with the clinical relevance of these systems in guiding treatment decisions and predicting patient outcomes. Keywords like “hormone receptor status,” “HER2/neu,” and “molecular subtypes” indicate an awareness of the diverse molecular characteristics of breast cancer. This reflects an intention to explore how these factors may influence the effectiveness of NACT and subsequent histopathological assessments. The inclusion of “histomorphological changes” emphasizes the examination of structural and morphological alterations in breast carcinomas after NACT. This is crucial for understanding the impact of treatments at a microscopic level.

Overall, the study is geared toward unraveling the clinical implications of using various histopathological assessment systems in post-NACT patients with breast carcinoma. This aligns with the broader goal of improving treatment strategies and patient outcomes in this specific context.

Some limitations of our study include a relatively small sample size, which could affect the generalizability of the findings to a broader population. The study is conducted in a single-center setting, which may limit the diversity of the study population. Differences in interpretation can lead to variability in the assessment of the tumor response. The current tumor reporting system may not adequately predict long-term survival or recurrence in all cases, as it often focuses on the immediate pathologic response without integrating other biological markers. Developing and implementing a system that integrates multiple types of data requires significant adjustments in pathology workflows and clinical practices. Comprehensive reporting requires advanced technology, specialized training, and additional time for analysis, which may not be feasible for all institutions.

Conclusions

In summary, this project aims to evaluate and compare histopathological assessment systems in post-NACT patients with breast carcinoma because various histopathological systems, such as the RCB score, the Miller-Payne grading system, and other systems, each provide valuable insights into how well tumors respond to chemotherapy. The study aims to understand the essence of histopathological parameters, leading to the refinement and potential modification of grading systems to improve clinical decision-making, treatment outcomes, and personalized care, given that challenges persist in standardization and consensus.

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Authors' Contributions

AS coordinated the study. SV contributed to the design and conception of the study. AS and SV contributed to the design of the tables and figures. SV edited and approved the final manuscript and provided ongoing input.

Conflicts of Interest

None declared.

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Abbreviations

AJCC: American Joint Committee on Cancer
H&E: hematoxylin and eosin
HER2: human epidermal growth factor receptor 2
MRM: modified radical mastectomy
NACT: neoadjuvant chemotherapy treatment
NSABP: National Surgical Adjuvant Breast and Bowel Project
RCB: residual cancer burden

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Protocol

Co-Design for Developing and Integrating a Model of Care for Pain Management Centers: Protocol for a Biphase Qualitative Study

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Abstract

Background: Current gold standard chronic pain management applies a biopsychosocial lens to clinical care, integrating medication, psychosocial support, and physical reconditioning to promote sustained treatment success, increase quality of life, and control symptoms. However, only 40% of patients with chronic pain report adequate pain management. Unfortunately, evidence describing implemented treatment pathways or models of care (MoCs) that consistently use this holistic approach is lacking.

Objective: The aim of this study is to identify the barriers and facilitators to access and engagement in existing MoCs for chronic pain, explore aspects of the delivery of care that can be improved, and develop an improved MoC for pain clinics in New South Wales by directly liaising with people with chronic pain and their families.

Methods: A 2-phase qualitative study will be conducted using semistructured focus groups. Both phases will follow the same structure, so patients, carers, and clinicians will independently provide input into the proposed MoC, which will then be summarized and integrated by the research team. Participants will be encouraged to interact and speak freely across three core domains: (1) experience of chronic pain management, (2) barriers and facilitators to delivering/accessing a gold standard MoC, and (3) key improvement points to existing models. Each focus group will last 90 minutes and be audio-recorded and transcribed verbatim for qualitative analysis. The focus groups in phase one will generate initial recommendations for primary changes to the existing MoC, and these will then be integrated and presented for evaluation, feasibility, and acceptability by stakeholder groups during phase two.

Results: Data collection commenced in September 2023 and is expected to end by September 2025. As of February 2024, we have completed the focus group with clinicians (n=12) and patients (n=7) in phase one. Data have not been analyzed formally and will be reported in a future publication.

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Conclusions: Through the exploration of key stakeholders' perspectives of the barriers preventing access and the delivery of care in the current MoC for chronic pain, we aim to co-design an appropriate, feasible, and acceptable pathway to be implemented in pain services in the future.

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KEYWORDS

chronic pain management; model of care; co-design; clinical care; psychosocial support; quality of life; treatment; medication; Australia; qualitative study; focus group

Introduction

Worldwide, chronic pain affects 20%-50% of people and has become a leading cause of disability [1,2]. In 2018, chronic pain was estimated to affect 3.24 million people Australia-wide, and this is estimated to increase to 5.23 million by 2050 [3]. Clinical management of chronic pain applies a biopsychosocial lens [4]. This approach incorporates medication, psychosocial support, and physical reconditioning to promote treatment success [5]. Data from an extensive cross-sectional study reported that only 40% of patients with chronic pain consider their condition to be managed adequately [6]. This is possibly due to the lack of literature demonstrating the implementation of evidence-based treatment pathways or models of care (MoCs) consistently using this holistic approach [2,6].

Pain management centers (PMCs) aim to improve care delivery by promoting a multidisciplinary service for patients with chronic pain, in line with their various needs. This approach promotes collaboration among medical specialists following research-based biopsychological service delivery [7]. However, in Australia, long-standing systemic and site-specific difficulties have impacted the implementation of MoCs within PMCs. These issues include inconsistency (lack of fidelity) in the application of a biopsychosocial pain management approach, untimely (long wait times and poor responsiveness) access to services, minimal capacity to respond to increasing demands for chronic pain management, and insufficiency in identifying patients who require different therapies and facilitating their treatment [7].

In New South Wales (NSW), the MoCs in each local health district vary in accordance with the sociodemographic context and are influenced by the local history of the specific service development [7]. This is reflected in the inconsistency across services, referral pathways into the PMCs, and the provision of outpatient support. This leads to confusion for patients and referrers on how to access pain management services as well as what to expect from these services.

To standardize this approach, the NSW Agency for Clinical Innovation has recommended that pain clinics in all local health districts develop their MoC by adhering to evidence-based principles [7,8]. These include standardized guidelines and treatment/service protocols and pathways, comprehensive screening and assessment to identify the proper level of care, provision of appropriate interventions and therapies, clear definitions of triage and discharge criteria, exploration of technology-based care and interventions, better classification and coding of pain-related presentations, and adequate measurement of patient-reported outcomes (ie, at 3 months, 6 months, and 12 months) [7]. However, these guidelines are not operationalized by any PMC or not consistently applied, nor have patients been directly involved in guiding the development of a MoC that is accessible, appropriate, and feasible for them.

Co-design strategies have been widely used in clinical research, including in the field of chronic pain, to generate user-centric ideas and then successfully implement these ideas in practice [9]. The co-design process usually involves a structured discussion between relevant key stakeholders, including end users (patients and carers), researchers, funding representatives, and policy and decision makers [9]. Crucially, this involvement of multiple key stakeholders (eg, end users) aims to benefit the effectiveness of health-related interventions and services [9]. In addition, the co-designed approach aims to produce services that are more acceptable and applicable to these groups. Engaging stakeholders in service redesign enables longer-term refinement and sustainability of resources, and can inform the governance and policy required to optimize service structure and funding into the future [10].

This study explores the barriers and facilitators to implementing evidence-based, biopsychosocial MoCs from the perspectives of key stakeholders without aiming to measure individual adherence. Through focus groups with patients, carers, clinicians, and clinical leaders, we aim to identify challenges in current MoCs and codevelop practical recommendations. These stakeholder-informed insights will guide the future design and potential piloting of a more responsive, integrated MoC for PMCs.

Methods

Study Design

The project will be a 2-phase (sequential) study.

Phase One

Phase one will include semistructured focus groups of individual stakeholders (patients, clinicians/leaders, carers, and families). It will aim to identify the initial barriers and facilitators within the existing MoC at Royal Prince Alfred Hospital (RPAH).

Phase Two

Phase two will involve 2 half-day workshops (2 hours) and focus groups (1 hour) held on-site at RPAH. Each of the combined stakeholder groups (clinicians and clinical leaders, and patients and caregivers) will have one workshop, as shown in Figure 1. The workshop will explain the current MoC again

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and discuss more detailed study findings from phase one, with potential areas for improvement identified. The focus groups will examine the MoC and elaborate on any improvement across key elements (eg, design, service provision).

Figure 1. Visual representation of a biphase sequential focus group study, outlining each stakeholder group per phase.

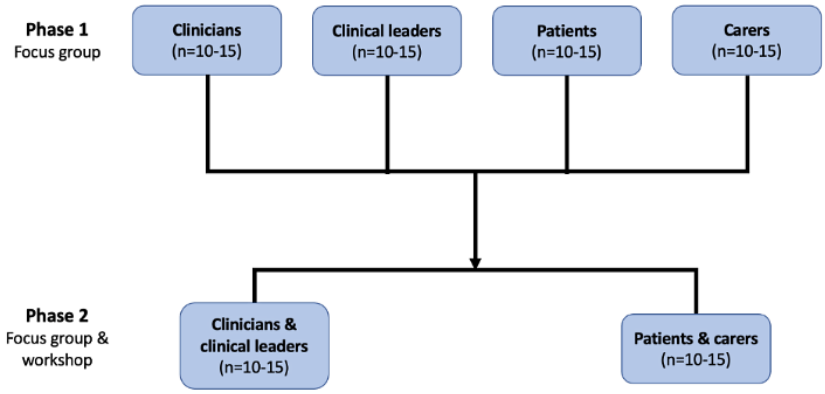

Study Setting

The focus groups will be run from the RPAH in the available board and meeting rooms or on Zoom (Zoom Communications) or Microsoft Teams.

Participants

Overall, we anticipate 4-6 focus groups with 5-10 participants in each group (see Figure 1). While we recognize the variability in pain types, treatment pathways, and professional roles, this heterogeneity reflects the real-world complexity of pain care and is essential for developing a flexible, contextually adaptable model. This is based on previous research [11] suggesting 3-6 focus groups are required to achieve thematic/code saturation with a semistructured interview guide, which is supported by evidence on meaning saturation for identifying diverse stakeholder perspectives [12].

We use a purposive (nonrandom) sampling strategy to recruit participants with relevant experience in pain care and education, aiming to obtain “information-rich” cases that can inform service improvements [13]. The credibility of this approach is boosted by including representatives from key stakeholder groups in our research [14].

Stakeholder groups consist of patients who have engaged in multidisciplinary care (eg, at least one psychology and one pain specialist consultation), carers who are directly involved in the care of these patients, clinicians actively involved in multidisciplinary pain care at RPAH or other sites, and external bodies (ie, government and nongovernment organizations engaged in policy or guidelines related to pain management on a district, state, or national scale).

Focus group composition will be structured in 2 phases. Phase one features homogeneous stakeholder-specific groups (eg, patients only, clinicians only) to encourage open discussion in a supportive environment, especially around sensitive topics [15]. This approach also shifts the power balance toward participants, which is ethically important when engaging groups whose voices are often underrepresented in research and policy [16].

Phase two introduces heterogeneity to promote cross-stakeholder dialogue and refine ideas. Specifically, we will group patients and carers (group 1) and clinicians with external stakeholders (group 2), as shown in Table 1. The first phase focuses on idea generation to reduce the influence of power dynamics between patients, carers, and clinicians. This structure reflects the need to balance homogeneity in phase one (to support openness) with diversity in phase two (to capture divergent perspectives) [17-19]. Group sizes of 5-10 per session are consistent with qualitative standards for achieving thematic and meaning saturation [11,12].

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Table 1. Summary of inclusion and exclusion criteria per stakeholder focus group.

Group	Inclusion criteria/definition	Exclusion
Patients (n=5-10)	Patients from RPAH's[a] Pain Management Centre who are currently receiving or have received treatment in the past for chronic pain (at least one initial session with a pain specialist and pain psychologist)	Patients who decline to participate or are ineligible given competing health priorities or general difficulties (eg, cognitive problems, self-reported poor English skills)
Carers (n=5-10)	Individuals providing care for patients currently or previously receiving treatment in the Pain Management Centre (eg, family members, friends, professional support workers)	Participants who decline to participate
Clinicians (n=5-10)	Directly involved in multidisciplinary clinical care for patients within their professional capacity at RPAH or other hospitals (eg, physiotherapists, psychiatrists, occupational therapists)	Participants who decline to participate or are ineligible because they have no professional experience or training related to chronic pain or model of care implementation
Clinical leaders (n=5-10)	Managers, service planners, patient navigators, and pain association leaders at professional bodies (eg, Agency for Clinical Innovation) who are responsible for decision-making at institutional or state/national levels	Same as for clinicians

[a]RPAH: Royal Prince Alfred Hospital.

Data Collection

Focus Group

The focus groups will be used for data collection in accordance with the predetermined open-ended focus group guide. The focus group questions are developed to discuss current chronic pain management, barriers and facilitators for the delivery of the current MoC, and future avenues of improvement.

Focus groups (phases one and two) will be conducted face-to-face or via Microsoft Teams. They will take 60 minutes and be facilitated by a research project staff member and one of our study investigators. Each focus group will be digitally recorded for video/audio (the anticipated duration is 60 minutes) and transcribed verbatim by the research team. In addition, a separate researcher from the team will observe each group and take notes on points of particular agreement or disagreement to ensure accuracy.

Facilitators will engage in ongoing critical reflection before and after interviews and focus groups to support reflexivity and reduce bias, including maintaining reflexive field notes. Where possible, interviews and groups will be conducted by researchers not directly involved in participants' clinical care. The research team will discuss and document positionality and potential power dynamics in team meetings throughout the study.

Survey

In phases one and two, all participants will be given questionnaires as part of the focus group. The questionnaires will collect the primary demographic data, including gender, age, pain history (patients/carers), and work experience (clinicians and clinical leaders).

Participant (patient) data from the electronic Persistent Pain Outcomes Collaboration (ePPOC) [20] questionnaires will also be extracted. The ePPOC is routinely administered before and after treatment for patients attending multidisciplinary pain clinics across Australia and New Zealand, including the RPAH PMC. Information extracted from the ePPOC will be deidentified and include information related to pain, physical disability, medications, cognition, mood, and health care use. ePPOC does not collect data from carers or clinicians; therefore, the custom tool complements, rather than overlaps with, ePPOC and allows us to characterize all stakeholder groups involved in the study.

Recruitment

Potential participants for phases one and two will be recruited separately. Participants from phase one may also consent to participate in phase two; however, consent will be collected for participation in each phase separately.

Clinicians and Clinical Leaders

For clinicians and clinical leaders, permission will be sought from clinical departments to send out invitations regarding the study, on behalf of the research team. Information will be distributed at departmental, multidisciplinary, and staff meetings to raise awareness and facilitate recruitment. Study staff will then contact those who reply positively to explain the study and what their participation would involve.

Patients and Carers

For patients and their carers, an invitation will be given to patients attending pain management outpatient clinics. Research staff will only approach patients or families after agreement is obtained from their treatment team. The research staff will explain the study, check eligibility criteria, and schedule a separate meeting to obtain consent and answer any further questions. This will be at a mutually convenient time and date. Potential participants will have at least 24 hours to consider participation.

Snowball Sampling

Those invited to participate (clinicians/patients) will be encouraged to refer their colleagues, patients, or carers to participate. They can either ask permission from their colleagues/patients/carers for the study staff to contact the potential participants and forward their contact details (email or phone) to the study staff (with their permission) or pass on contacts of the study staff to potential participants who might initiate contact with the research team. Once a member of the study team is in connection with the potential participant, they

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will explain the study, determine if the study is suitable for the potential participant, and forward a copy of the study information to consider before scheduling a meeting (either face-to-face or on Microsoft Teams) at a time and date that is mutually convenient. The purpose of this meeting is to ensure ample time is given to consider the study, to provide opportunities to answer questions, and to finalize consent.

Data Analysis Plan

Focus Group Data

Qualitative interviews and focus group notes will be transcribed verbatim and entered into NVivo version 14 (Lumivero), and two people will independently code the data. Inductive and deductive thematic analysis [21] will be used to identify themes within the data related to the research questions. Each transcript will be deidentified, read closely, and coded line by line inductively and descriptively before being coded deductively based on the agreed set of themes. These will then be integrated into the analysis of subsequent focus groups until meaning saturation is achieved.

Survey Data

Descriptive statistics from existing clinical data and a brief demographic questionnaire will be used to describe the demographic characteristics of all stakeholders to understand relevant contextual factors affecting their experience (eg, years experiencing chronic pain, interventions received, years of professional experience). Frequency and percentage will be used to describe these variables. Chi-square comparisons (ie, post hoc, with $P<.05$ considered as significant) will be conducted between groups to identify whether differences in sociodemographic and education characteristics can be captured. All statistical analyses will be performed using SPSS version 26 (IBM Corp) [22].

Withdrawal of Consent

If participants decide to withdraw from the study, the research team ceases to collect study information. Participants will be informed that withdrawal is possible at any time, with no consequences for their care or existing relationships with clinicians. If participants choose to withdraw before their initial focus group, their data will be erased from study records. However, their data will be retained and deidentified once they have participated in a focus group. Extracting an individual line of information from a communal focus group is difficult.

Ethical Considerations

Ethics

Ethics approval for phases one and two of this project has been provided by the Ethics Review Committee (RPAH Zone) of the Sydney Local Health District (SLHD; HREC/2023/X23-0224). Ethics approval was granted in early September 2023, and data collection began shortly after.

The study investigators will ensure all study procedures are in accordance with the National Health and Medical Research Council (NHMRC) Statement on Ethical Conduct in Human Research 2007 (updated 2018) [23] and NHMRC Australian Code for the Responsible Conduct of Research [24]. This work was conducted in accordance with the 1964 Declaration of Helsinki. Participants were not financially reimbursed, they were provided with refreshments during and after the focus groups.

Informed Consent

All participants provided informed consent and were able to opt out at any time without any repercussions for their care or engagement with the service. Their privacy and confidentiality are retained by appropriate data collection and storage in alignment with approved SLHD and The University of Sydney protocols.

Dissemination

It is anticipated that the findings and relevant outcomes of this project will be reported in international peer-reviewed journal articles and presented at relevant national and international conferences. A summary of research findings will be made available to participants.

Results

Data collection commenced in September 2023 and is expected to end by September 2025. As of February 2024, we have completed the focus group with clinicians (n=12) and patients (n=7) in phase one. Data have not been analyzed formally and will be reported in a future publication. Preliminary analysis from the clinician group suggested that the current MoC needs to be improved after further involvement from stakeholders, such as patients, carers, researchers, funding representatives, and policy and decision makers for future practice.

Discussion

Expected Findings

The primary aims of this study are to identify the barriers and facilitators to access and engagement in existing MoCs for chronic pain in PMCs in NSW, including pain education programs. This will include input from clinicians, patients, and carers from pain clinics across NSW; explore aspects of the delivery of care (including accessibility, quality, and feasibility) that can be improved for people with chronic pain; and uniquely co-design an improved MoC for pain clinics in NSW by directly liaising with people with chronic pain and their families.

Current MoCs vary significantly between individual clinics, including in adherence to existing guiding principles [8] and the specific needs required by the populations they serve. Some research about establishing MoCs exists, but most of it is focused explicitly on particular health conditions, such as lower back pain and opioid management [25-27]. Most of these services have evolved organically, and patients currently have minimal, if any, input into the care they receive [28]. This lack of awareness among users of PMCs minimizes their confidence and ability to engage with the services offered directly [7]. At the same time, pain clinicians have few opportunities to systematically evaluate and update the care plans they are providing to adapt to emerging evidence on biopsychosocial support for pain management [29].

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The findings of this proposed study could have significant implications for current pain management services, given the rapidly expanding population of people living with chronic pain in Australia and worldwide. An integrated model has been suggested to manage chronic disease, including chronic pain [30]. The core components of managing chronic disease include well-defined care guidelines, an existing health delivery system, and a continuous improvement process within the delivery system [30]. Therefore, within the current established MoC in the Australian health system, the study will explore across stakeholders to provide tight feedback loops and expedited implementation of evidence-based interventions that are tailored to the contextual features of the service, including scope, staff, and other resources. Additionally, a more self-sustaining and iterative MoC can be adapted across time and resources to match population needs and address traditional barriers by promoting tailored yet holistic care in a consistently biopsychosocial way.

Subsequently, it may reduce the cost and burden on existing strained resources and promote adherence to best practices. In current clinical practice, the evaluation of long-term effectiveness within the existing MoC is unclear. In contrast, short-term evidence may not be convincing enough for decision-making and operational management in pain management services [31]. This study will provide a concept of a stratified cost-effectiveness care model and promote a data analysis to evaluate the current pain service in the future.

Limitations

The primary limitation of this study is that the findings may be highly localized to health services in Australia. However, the process will be flexible enough to be generalized across other centers. Researcher presence (including dual roles across the clinician-researcher space) can potentially influence qualitative findings (across power hierarchies or comfort in content discussed). Another potential limitation is using a custom-developed demographic questionnaire alongside the ePPOC dataset. However, the alignment of the custom tool with validated sources and its role in complementing, rather than duplicating, ePPOC data support the reliability and interpretability of the combined dataset.

The study uses purposive and snowball sampling strategies, which may introduce selection bias by overrepresenting individuals who are more engaged, vocal, or closely connected to clinical services. This may limit the generalizability of findings to the broader population of patients, carers, or clinicians. However, this approach is appropriate for in-depth qualitative exploration and co-design, where capturing rich, experience-based insights from informed stakeholders is critical to developing a feasible and contextually relevant MoC.

A further limitation is the potential for bias introduced by researcher positionality, particularly where facilitators are known to participants or affiliated with the care team. To enhance trustworthiness, reflexive practices will be used throughout data collection and analysis, including reflexive journaling, debriefing sessions, and the involvement of multiple coders during thematic analysis.

Conclusion

In this protocol, we outline the development of MoCs for PMCs by co-designing with patients, carers, clinicians, and clinical leaders. This research project may help address current barriers to engaging with and delivering chronic pain care. Furthermore, the novelty of the co-designed MoC will provide a new approach to evaluating the care model of the health care system in the future.

Acknowledgments

Artificial intelligence was not used in the ideation or writing process.

Data Availability

The datasets generated and analyzed during this study will be available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

ePPOC: electronic Persistent Pain Outcomes Collaboration
MoC: model of care
NHMRC: National Health and Medical Research Council
NSW: New South Wales
PMC: pain management center
RPAH: Royal Prince Alfred Hospital

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Protocol

Optimization of Preemptive Therapy for Cytomegalovirus Infections With Valganciclovir Based on Therapeutic Drug Monitoring: Protocol for a Phase II, Single-Center, Single-Arm Trial

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Abstract

Background: Valganciclovir (VGCV) is the first-line drug for preemptive therapy of cytomegalovirus (CMV) infections. However, even when administered at the dose specified in the package insert, there is significant interindividual variability in the plasma concentrations of ganciclovir (GCV). In addition, correlations have been reported between the area under the concentration–time curve and therapeutic efficacy or adverse events. Therefore, therapeutic drug monitoring (TDM) can be used to improve the efficacy and safety of preemptive VGCV therapy.

Objective: This study aims to evaluate whether the dosage adjustment of VGCV based on TDM in patients undergoing preemptive therapy for CMV infections is associated with the successful completion rate of treatment without severe hematological adverse effects.

Methods: This phase II, single-center, single-arm trial aims to enroll 40 patients admitted at the Department of Rheumatology and Clinical Immunology, Kobe University Hospital, who will receive oral VGCV as preemptive therapy for CMV infections. Participants will begin treatment with VGCV at the dose recommended in the package insert, with subsequent dose adjustments based on weekly TDM results. The primary end point will be the proportion of patients who achieve CMV antigenemia negativity within 3 weeks without severe hematological adverse events. The secondary end points will include weekly changes in CMV antigen levels, total VGCV dose, and duration of preemptive therapy. For safety evaluation, the occurrence, type, and severity of VGCV-related adverse events will be analyzed. Additionally, this study will explore the correlations between the efficacy and safety of preemptive therapy and the pharmacokinetic parameters of GCV, CMV-polymerase chain reaction values, and nudix hydrolase 15 (*NUDT15*) genetic polymorphisms. The correlation between GCV plasma concentrations obtained from regular venous blood and blood concentrations will be examined using dried blood spots.

Results: This study began with patient recruitment in September 2024, with 5 participants enrolled as of June 16, 2025. The target enrollment is 40 participants, and the anticipated study completion is set for July 2027.

Conclusions: This is the first study to investigate the impact of TDM intervention in patients receiving VGCV as preemptive therapy. The findings are postulated to provide valuable evidence regarding the utility of TDM in patients receiving VGCV as preemptive therapy.

Trial Registration: Japan Registry of Clinical Trials jRCTs051240080; https://jrct.mhlw.go.jp/latest-detail/jRCTs051240080

International Registered Report Identifier (IRRID): DERR1-10.2196/72549

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(JMIR Res Protoc 2025;14:e72549) doi:10.2196/72549

KEYWORDS

valganciclovir; ganciclovir; cytomegalovirus; therapeutic drug monitoring; preemptive therapy; dried blood spots

Introduction

Background

Cytomegalovirus (CMV) establishes a latent infection after the resolution of acute infection. Its reactivation can occur in patients undergoing immunosuppressive therapy, leading to organ-specific infections such as febrile illness, pneumonia, and retinitis [1]. For patients at high risk of CMV infection, their viral load is regularly monitored. Preemptive therapy is initiated once the viral load becomes detectable, even in the absence of symptoms. Preemptive therapy is effective in preventing the onset of CMV infection and is recommended for patients undergoing hematopoietic stem cell transplant [2-4].

Valganciclovir (VGCV) is the first-line treatment not only for the prevention and treatment of CMV infections but also for preemptive therapy. It is rapidly metabolized to its active metabolite ganciclovir (GCV). Because GCV is primarily excreted by the kidneys, the dose of VGCV is adjusted based on renal function [5]. In patients who have undergone solid organ transplant, a correlation has been reported between the therapeutic effect of GCV on CMV viremia and the area under the concentration–time curve (AUC) [6]. Therefore, sufficient AUC exposure is necessary for adequate treatment. Additionally, the relationship between AUC and adverse effects has been reported [6-9]. These reports suggest that the effective range of GCV is between 40 and 60 µg·h/mL of AUC. However, a significant interindividual variability has been observed in the plasma concentrations of GCV, even when administering the dose specified in the package insert [6,10]. To this end, dosage adjustments based solely on the package insert are insufficient, and the usefulness of therapeutic drug monitoring (TDM) for GCV has been reported [7]. However, the utility of routine GCV concentration measurements and TDM remains controversial and is not currently being conducted [11].

Recently, dried blood spot (DBS) sampling, which involves collecting a small amount of blood from the fingertip onto a filter paper, has been increasingly performed in clinical practice as a less invasive method to facilitate TDM [12,13]. In addition, nudix hydrolase 15 *(NUDT15*) polymorphisms were reported to influence the antiviral efficacy and cytotoxicity of GCV [14]. However, the clinical utility of DBS and measuring *NUDT15* polymorphisms for VGCV treatment has not yet been established.

Study Objectives

The primary objective of this study is to evaluate whether the dosage adjustment of VGCV based on TDM in patients undergoing preemptive therapy for CMV is associated with the completion ratio of treatment without adverse hematological effects. Additionally, this study aims to investigate whether dosage adjustments based on TDM can reduce the time required for CMV pp65 negativity or the incidence rate of adverse effects. Factors related to the pharmacokinetics of GCV and the efficacy and safety of preemptive therapy with VGCV will also be investigated. Further, this study will explore the relationship between GCV plasma concentrations obtained from venous blood and DBS whole blood concentrations at each measurement point and the relationship between *NUDT15* genetic polymorphisms and adverse events. Moreover, an exploratory analysis will be conducted to determine the relationship between CMV antigen quantification using CMV pp65 and CMV viral load measured by quantitative CMV DNA polymerase chain reaction (PCR).

Methods

Study Design and Study Location

This is a phase II, single-center, single-arm interventional trial. A flowchart of the study design is shown in Figure 1. This study is being conducted at Kobe University Hospital.

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Figure 1. Flowchart of the study design. CMV: cytomegalovirus; VGCV: valganciclovir.

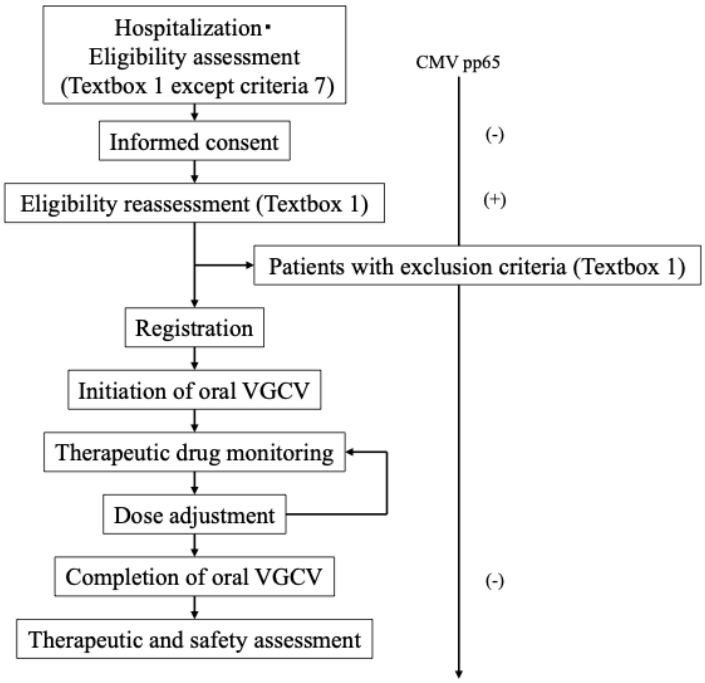

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria are presented in Textbox 1. Patients who meet inclusion criteria 1-6 will be asked by their attending physician to provide informed consent for trial participation. When the weekly measured CMV pp65 levels meet inclusion criterion 7, patients who provide written informed consent will be enrolled in this trial after confirming that they have not withdrawn their consent and still meet all the criteria.

Textbox 1. Study inclusion and exclusion criteria.

Inclusion criteria

1. Inpatients at the Department of Rheumatology and Clinical Immunology
2. Treated with prednisolone more than or equal to 0.5 mg/kg with/without immunosuppressive agents as initial therapy
3. Aged 18 years or older at the time of consent
4. Written informed consent has been obtained regarding their voluntary participation in this clinical study
5. No symptoms due to cytomegalovirus (CMV) infection (eg, fever, cough, dyspnea, abdominal pain, diarrhea, bloody stools, dysopsia)
6. Not received valganciclovir (VGCV) therapy for at least 2 weeks before starting this clinical study
7. Test positive for CMV pp65 antigen and meet one of the following conditions: (1) CMV pp65 antigen is more than or equal to 10 per 2 slides or (2) CMV pp65 antigen is more than or equal to 1 per 2 slides and less than or equal to 9 per 2 slides, and the retest result after 2 to 8 days is that CMV pp65 antigen is more than or equal to 5 per 2 slides and higher than the initial value.

Exclusion criteria

1. Patients undergoing dialysis
2. Significant bone marrow suppression such as neutrophil count less than 500/mm^3 or platelet count less than 25,000/mm^3
3. Pregnancy or possible pregnancy
4. Known allergies or drug sensitivities to VGCV, ganciclovir, acyclovir, or valacyclovir
5. Hemoglobin levels less than 8.0 g/dL
6. Taking probenecid
7. The investigator deems inappropriate

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Intervention

The study schedule is presented in Table 1. Patients will receive VGCV orally at the dosage specified in the package insert, based on creatinine clearance (Ccr) calculated using the Cockcroft-Gault equation [15]. On day 3 following the initiation of VGCV therapy, venous blood samples will be collected before and 2 hours after the morning dose of VGCV. The plasma concentrations will be measured using liquid chromatography-tandem mass spectrometry [16].

Table 1. Summary of the study schedule.

	Hospitalization	Preobservation period	Treatment period							Close-out	Postobservation period
			Week 1				Weeks 2-3				
			Day 1	Day 3	Day 4	Day 5	Day 1	Day 2	Day 3		
Enrollment											
Eligibility screening	✓	✓	✓								
Informed consent	✓										
Registration			✓								
Intervention											
Blood sampling for TDM[a]				✓			✓				
TDM					✓			✓			
Dose adjustment						✓			✓		
Blood sampling for *NUDT15*[b] genotyping										✓	
Assessments											
Patient's background[c]		✓									
CMV[d] pp65/CMV-PCR[e]		✓					✓			✓	✓
Laboratory data[f]		✓	✓	✓	✓		✓			✓	✓
Adverse events			✓	✓	✓	✓	✓	✓	✓	✓	✓
Concomitant medication		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

[a]TDM: therapeutic drug monitoring.

[b]*NUDT15*: nudix hydrolase 15.

[c]Including sex, age, height, weight, medical history, complications, and concomitant medications.

[d]CMV: cytomegalovirus.

[e]PCR: polymerase chain reaction.

[f]Including levels of white blood cell, neutrophil, hemoglobin, platelet, hematocrit, aspartate aminotransferase, alanine aminotransferase, albumin, blood urea nitrogen, serum creatinine, estimated glomerular filtration rate, sodium, potassium, and chloride.

Estimated Apparent Clearance

Individual estimated apparent clearance (CL/F) will be estimated using the post hoc Bayesian analysis based on a previously reported population pharmacokinetic model [17] as follows:

$$CL/F=7.09*(1+Ccr/68.3)\ (L/h)$$

$$Vc/F=10.8\ (L)$$

$$Q/F=3.96\ (L/h)$$

$$Vp/F=174\ (L)$$

$$Ka=0.23\ (/h)$$

$$T_{lag}=0.93\ (h)$$

where Vc/F, Q/F, Vp/F, Ka, and T_{lag} are the apparent volumes of distribution in the central compartment, apparent intercompartmental clearance, apparent volume of distribution in the peripheral compartment, absorption rate constant, and lag time, respectively. Additionally, interindividual variabilities of CL/F, Vc/F, Q/F, and Vp/F are 27.2, 153, 63.1, and 107%, respectively. Interindividual variabilities of Ka and T_{lag} are not included. The proportional residual variability is 42.9%. The individual AUC will be calculated using the following formula: AUC = daily dose of VGCV × (GCV molecular weight of 255.2/

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VGCV molecular weight of 354.4) / estimated individual CL/F. Subsequently, the dosage will be adjusted to achieve the target AUC (40-60 µg·h/mL) by using the dose adjustment shown in Table 2. Patients will be informed of the possibility of dosing higher or lower than the package insert recommendation during the consent process. Thereafter, weekly plasma concentration measurements and dosage adjustments will be performed using the same procedure as described above, with a treatment period of up to 3 weeks. Post hoc Bayesian estimation will be performed using NONMEM version 7.5.1 (ICON).

Table 2. Adjusted dosage of valganciclovir based on the estimated apparent clearance.

CL/F[a] (L/h)	Adjusted dose
2.7[b] < CL/F ≤ 4.1	450 mg once daily every other day
4.1 < CL/F ≤ 5.4	450 mg once daily for 2 days and 1 day off
5.4 < CL/F ≤ 8.1	450 mg once daily
8.1 < CL/F ≤ 12.2	450 mg twice daily and 450 mg once daily alternately
12.2 < CL/F ≤ 16.2	450 mg twice daily
16.2 < CL/F ≤ 24.3	900 mg in the morning and 450 mg in the evening
24.3 < CL/F ≤ 32.4	900 mg twice daily
32.4 < CL/F ≤ 40.5	1350 mg in the morning and 900 mg in the evening
40.5 < CL/F ≤ 48.6	1350 mg twice daily

[a]CL/F: estimated apparent clearance.

[b]For patients with CL/F less than or equal to 2.7 or greater than 48.6, consider dosage individually.

Protocol treatment will continue for at least 2 weeks up to a maximum of 3 weeks from the day of VGCV initiation until CMV pp65 is confirmed to be negative. If CMV pp65 is not confirmed to be negative at 3 weeks after the initiation of VGCV, posttreatment will be performed at the discretion of the physician. Additionally, DBS sampling will be conducted 2 hours after VGCV morning dose and before each meal on day 3 after VGCV initiation to investigate the correlation between DBS-derived whole blood concentrations and plasma concentrations. Finger-prick blood will be collected onto filter papers (Whatman 903 Protein saver card), and blood collection will be conducted to ensure a sampling diameter of at least 6 mm. Genetic polymorphisms of *NUDT15* will also be analyzed using blood samples collected in this study. DNA will be extracted from blood samples, and *NUDT15* polymorphisms in c.415C>T; rs116855232 (p.R139C) and c.416G>A; rs147390019 (p.R139H) will be genotyped using a TaqMan genotyping assay (ID: C_154823200_10 and C_162697298_10). The postobservation period will be 2 weeks after the completion of VGCV administration to assess adverse events and relapse of CMV infection.

Sample Size Calculation

A preliminary survey was conducted among 20 patients admitted to the Department of Rheumatology and Clinical Immunology at our hospital between January 2020 and August 2022. The proportion of patients who were unable to complete treatment with hematological toxicities was 65% (13/20). None of the patients failed to complete the treatment because of nonhematological adverse events. The proportion of patients who could not complete treatment for reasons other than adverse events was 5% (1/20). Except for the above cases, none of the other patients failed to become CMV pp65–negative within 3 weeks. Approximately 30% of the patients achieved CMV pp65 negativity within 3 weeks without severe hematologic adverse events. The incidence of hematologic toxicities when GCV AUC was maintained at 40-60 µg·h/mL by TDM was estimated to be 36.5%, based on a previous report [9]. Assuming that the rate of treatment incompletion due to reasons other than adverse events or the rate of failure to achieve CMV pp65 negativity within 3 weeks remained at 5%, the estimated rate of patients who would fail to complete treatment owing to adverse events or fail to achieve CMV pp65 negativity within 3 weeks of TDM would be 41.5%. Therefore, the proportion of patients expected to achieve CMV pp65 negativity within 3 weeks without adverse events under TDM was assumed to be 58.5%. Under conditions of a 2-sided significance level of 5% and a power of 80%, the required sample size to detect an increase in the proportion of patients completing treatment without adverse events was determined to be 31. Considering potential dropouts, the sample size was set at 40.

Ethical Considerations

This study was approved by the Clinical Research Ethics Committee of Kobe University (C230016) on June 28, 2024. This trial was registered in Japan Registry of Clinical Trials (jRCTs051240080) on June 28, 2024. All the participants will sign an informed consent form after receiving a detailed explanation of the study from the researchers. All participant data will be deidentified prior to analysis. Participants will not receive any financial compensation for their participation. This study will adhere to the protocols and principles outlined in the Declaration of Helsinki. Any modifications to the protocol will require approval from the ethics committee before implementation. To address potential claims resulting from health issues related to the study, the principal investigator has secured clinical research insurance covering compensation for death, serious disability, medical expenses, and medical benefits.

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Outcomes

Primary End Point

The primary end point of this study is to determine whether preemptive therapy with VGCV for CMV reactivation could achieve CMV antigenemia negativity within 3 weeks without severe adverse events. Severe adverse events are defined as leukopenia, neutropenia, anemia, and thrombocytopenia classified as grade 3 or higher according to the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0.

Secondary End Points

Secondary end points include the change in CMV antigen levels at weekly intervals after VGCV initiation, the total dose of VGCV administered, and the duration of preemptive therapy. Additionally, this study will examine the occurrence, type, and severity of adverse events caused by VGCV for a safety assessment. Furthermore, data that would be relevant to the efficacy or safety of preemptive therapy (estimated AUC at each time point of TDM measurement, Ccr at each time point of TDM measurement, CMV pp65 negativity within 3 weeks of VGCV administration, GCV plasma concentration at each measurement point, total GCV exposure, VGCV dose based on renal function at registration, and CMV antigen repositivity within 2 weeks of completion of treatment), pharmacokinetic parameters of GCV, blood concentration of GCV obtained from DBS, genetic polymorphisms of *NUDT15*, and CMV-PCR value will be collected.

Statistical Analysis

All analyses will be conducted using R software (version 4.5.1; R Foundation for Statistical Computing).

Primary Analysis

A binomial test will be performed for the primary end point. The null hypothesis will be defined as 30% of patients having completed preemptive therapy without severe adverse events. The *P* value will be used as the reference.

Secondary Analysis

The number of CMV pp65–positive cells will be examined before and weekly after the initiation of preemptive therapy, and the absolute and relative reductions in the number of these cells compared to baseline will be calculated. Correlation analyses between the absolute or relative reduction in the number of CMV pp65-positive cells and the estimated AUC will also be determined. Further, the median (or mean) total dose of VGCV and the duration of administration will be calculated. The types, severity, and incidence rate of adverse events during the study period will be summarized and stratified by renal function (Ccr≤30, 30<Ccr ≤60, 60<Ccr≤80, Ccr>80 mL/min) or estimated AUC (AUC<40, 40≤AUC≤60, AUC>60 µg·h/mL). Group comparisons will be conducted using Fisher exact test or other appropriate statistical methods.

Exploratory Analysis

The median (or mean) of the estimated AUC and dose-adjusted estimated AUC will be calculated for each renal function at the start of treatment (Ccr≤30, 30<Ccr≤60, 60<Ccr≤80, Ccr>80 mL/min). Kruskal-Wallis and Dunn multiple comparisons tests will be performed for each group. A correlation analysis will be conducted between Ccr and the recommended probable dose by using Bayesian estimation. Single and multiple regression analyses with the dose-adjusted estimated AUC as the objective variable and clinical information as the explanatory variables will be performed to explore the factors affecting the dose-adjusted estimated AUC. The proportion of CMV antigen-positive cells that disappear in less than 3 weeks of treatment will be calculated, and a binomial test will be performed against the proportions in the preliminary study. The patients will be grouped according to the presence or absence of disease or CMV infection recurrence, and the median (or mean) of the estimated trough blood concentration, estimated AUC, and total exposure will be calculated in each group. If necessary, the Mann-Whitney *U* test will be performed. The actual total dose of VGCV during the preemptive therapy and the total dose assuming that VGCV is administered at the dose stated in the package insert will be calculated, and a Wilcoxon signed-rank test will be performed. Patients will be grouped according to *NUDT15* genotype (wild-type, homozygous variant or heterozygous variant), and the number and proportion of adverse events in each group will be calculated. Fisher exact test will be performed. Additionally, the median (or mean) estimated trough plasma concentration, estimated AUC, and total exposure will be calculated for each group, and a Mann-Whitney *U* test will be conducted. If both CMV pp65 antigen and CMV-PCR are positive, the correlation will be analyzed using the Spearman rank correlation coefficient. *P* values calculated from the above analyses will be used as references.

Correlation analysis will be performed between plasma obtained by regular venous blood sampling and whole blood concentrations obtained via DBS. A preliminary analysis will be performed in 20 cases, which is half the sample size. If no clear correlation is determined, blood sampling using the DBS method will be discontinued in subsequent studies. Additionally, a simple regression analysis will be conducted with DBS whole blood concentration as the dependent variable and conventional plasma concentration measurements and clinical information as the independent variables.

Interim Analysis

After 20 cases, half of the sample size would have been enrolled, and the efficacy and occurrence of serious adverse events will be summarized. Regarding the efficacy, the probability of the effectiveness of TDM when the remaining cases are enrolled will be evaluated using a binomial distribution. Considering this probability and the incidence rate or grades of serious adverse events, we will decide whether the trial should be continued or discontinued based on a comprehensive assessment. To allow for flexibility, no specific statistical threshold is set in this decision-making process.

Data Collection and Management

After receiving consent from prospective patients, the investigators will assess their eligibility. To this end, the research secretariat will access the Research Electronic Data Capture (an electronic data system for clinical research; REDCap) system to confirm eligibility before inputting essential information for

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case registration and assigning a case number. The registration process will conclude upon the display of a confirmation of the case registration.

Data Monitoring

This study will undergo regular monitoring to safeguard human rights and welfare. It will be conducted with strict adherence to the protocol and all relevant regulatory requirements to ensure safety. The principal investigator has designated the individuals responsible for overseeing the procedures outlined for study monitoring. To ensure quality control, the monitor will assess adherence to the protocol and outline the procedures during the study.

Results

Recruitment for this study began in September 2024, and as of June 16, 2025, 5 participants have been enrolled. Study completion is anticipated by July 2027. The study protocol and statistical analysis plan will be made available to the Japan Registry of Clinical Trials. The findings of this study will be presented at medical conferences and published in scientific papers. After publication, the corresponding author will make the collected data accessible in a nonpersonally identifiable form upon reasonable request from other researchers within a prescribed period.

Discussion

To the best of our knowledge, this is the first study that will investigate the impact of TDM intervention on improving the completion rate of preemptive therapy in patients receiving VGCV. In this study, both patients and investigators are aware of dose adjustments. However, the efficacy and safety of the VGCV therapy will be evaluated objectively by clinical laboratory values and CTCAE version 5.0. Therefore, observer and confirmation bias will not occur.

The use of VGCV as preemptive therapy is not specified in its package insert. Still, it is common based on previous reports in patients who undergo hematopoietic stem cell transplant [2-4], suggesting its effectiveness in clinical practice in Japan. GCV is known to have large interindividual variability in plasma concentrations after oral administration of VGCV. A previous report indicated that patients with impaired renal function experience higher exposure to GCV, whereas those with better renal function experience lower exposure [7]. High plasma concentrations of GCV are associated with an increased frequency of adverse events, whereas low concentrations would lead to insufficient therapeutic efficacy. Therefore, achieving the target AUC through TDM would increase both safety and efficacy.

In solid organ transplant recipients, the association between GCV AUC and the reduction in the incidence of CMV viremia has been reported (AUC 46.3, SD 15.2 µg·h/mL: 2.9%; AUC 28.0, SD 10.9 µg·h/mL: 10.4%) [10]. Furthermore, higher steady-state AUC levels have been shown to result in lower incidence rates of CMV viremia during and up to 1 month after prophylactic treatment, indicating superior preventative efficacy [10]. In preemptive therapy as well, studies have reported a correlation between GCV AUC and treatment outcomes for CMV viremia, with optimal therapeutic effects observed at an AUC in the range of 40-50 µg·h/mL [7]. Thus, sufficient AUC exposure is necessary to ensure adequate therapeutic intensity. However, an association between GCV AUC and adverse event incidents have been documented. For example, the incidence of hemoglobin reduction was reported to be 51.9% at an AUC >50 µg·h/mL compared to 26.6% at an AUC ≤50 µg·h/mL [7]. Additionally, the incidence of leukopenia and neutropenia increased with increasing AUC levels. For leukopenia of grade 1 or higher, the incidence rate exceeded 50% at an AUC ≥60 µg·h/mL [10,11]. Therefore, from the perspective of efficacy and safety, a target AUC of 40-60 µg·h/mL is often recommended. Based on these findings, the target AUC in this study will be set at 40-60 µg·h/mL. The concomitant immunosuppressants may independently affect the incidence of CMV reactivation and/or hematological toxicity. Therefore, the concomitant medication data will be collected for the entire study period and consider them as adjustment factors in the analysis if necessary.

AUC is considered as an indicator of the efficacy and safety of GCV, and many blood collection points are required to accurately determine it, which results in significant burden for the patient. In this study, Bayesian estimation using a population pharmacokinetic model aimed at achieving target AUCs was considered useful for TDM with GCV. Several population pharmacokinetic models of GCV after VGCV administration have been reported [10,17-22], but none have been developed in Japan by using rich sampling data. Therefore, we decided to use a model developed for the Chinese population because of its racial proximity [17]. The selected report showed that the optimal sampling points were two (0 and 2 hours) or three (0, 2, and 4 hours) after VGCV administration [17]. In this study, the sampling points were set at the trough and 2 hours after VGCV administration to reduce patient burden.

To ensure high predictive accuracy for the AUC by Bayesian estimation, we required multiple blood samples. DBS sampling has the advantage that blood samples can be collected in a nonclinical setting such as at home, and only a small amount of blood is required for measurement. As multiple blood samples are required to calculate AUC, replacing venous blood sampling with DBS could reduce the physical burden on patients. However, the correlation between plasma concentrations measured by venous blood sampling and DBS whole blood concentrations remains unclear and investigating this relationship could contribute to less invasive TDM interventions.

Recently, pharmacogenomics, which investigates how genetic polymorphisms of metabolic enzymes or transporters influence the variability in drug responses, has attracted attention as a useful tool in personalized medicine. *NUDT15* polymorphisms are involved in the metabolism of thiopurine drugs. Genetic testing for codon 139 polymorphisms is useful for predicting acute severe adverse events for patients with refractory inflammatory bowel disease, acute lymphoblastic leukemia, or other conditions treated with thiopurine drugs [23]. Although recent reports suggest that *NUDT15* polymorphisms influence not only the antiviral efficacy but also the cytotoxic effects of GCV and acyclovir in vivo [14], no human studies have yet

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been conducted. The exploratory research in this study could provide useful information on the utility of *NUDT15* genotyping in the treatment of VGCV.

This study has a limitation. Because TDM of GCV is not commonly performed, this study is conducted at a single center to ensure the accuracy and speed of TDM measurements and to obtain an effect size without confounding. Therefore, the findings of this study may not be generalized. Once the usefulness of GCV TDM for preemptive therapy is confirmed, its application, including the impact of lag-time in GCV measurement and diverse patient characteristics at multiple institutions, needs to be clarified in the phase III trial. Overall, this study provides valuable evidence regarding the utility of TDM in patients receiving VGCV as preemptive therapy.

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Data Availability

The datasets generated or analyzed in this study are available from the corresponding author upon request after publication.

Authors' Contributions

Conceptualization: NT (lead)
Methodology: NT (lead), KI (supporting), YU (supporting)
Writing – original draft: NT (lead)
Writing – review & editing: YK (supporting), KY (supporting), TO (supporting), TS (supporting), JS (supporting), IY (lead)
Supervision: IY
Validation: IY
Approval of final manuscript: All authors

Conflicts of Interest

None declared.

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Abbreviations

AUC: area under the concentration–time curve
Ccr: creatinine clearance
CL/F: estimated apparent clearance
CMV: cytomegalovirus
CTCAE: Common Terminology Criteria for Adverse Events
DBS: dried blood spot
GCV: ganciclovir
PCR: polymerase chain reaction
REDCap: Research Electronic Data Capture
TDM: therapeutic drug monitoring
VGCV: valganciclovir

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Protocol

In Vitro Characterization of the Immune Response to an Epitope Ensemble Vaccine Against Rhinovirus in Pediatric Asthma and Adults With Chronic Obstructive Pulmonary Disease: Protocol for an Observational and Exploratory Study

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Abstract

Background: Human rhinoviruses (HRVs) are the leading cause of upper respiratory tract infections, responsible for over half of all such infections. Infection rates among young children can reach as high as 8-12 episodes per year. While HRV infections typically result in mild common colds, they can also lead to more severe respiratory conditions, often in conjunction with bacterial coinfections. In addition, HRVs are implicated in the exacerbation of obstructive respiratory diseases, including asthma and chronic obstructive pulmonary disease (COPD). T-cell responses play a crucial role in the immune defense against HRV. However, in patients with obstructive respiratory diseases, altered or dysregulated T-cell responses to HRV may not only fail to efficiently eliminate the virus but can also exacerbate inflammation and airway remodeling. Therefore, a deeper understanding of T-cell–mediated responses in the context of HRV infection, especially in vulnerable populations like those with COPD, is critical. It can provide new insights into mechanisms of both protection and disease exacerbation, potentially guiding the development of targeted therapies or vaccines that enhance protective immunity while minimizing harmful inflammation.

Objective: This study aims to (1) determine the population-wide coverage of HRV-specific T-cell responses, (2) characterize HRV-specific T-cell recall responses in disease cohorts compared to age-match healthy controls, and (3) identify biomarkers of protection and susceptibility within disease cohorts through a comparative analysis.

Methods: Participants with asthma and those with COPD, aged 5-15 and 40-70 years, respectively, will be recruited alongside healthy age-matched controls. Peripheral blood samples will be collected following informed consent from adult participants and from parents or guardians of minors, as applicable. Clinical, demographic, immunological, and genetic responses will be assessed both prior to and following in vitro stimulation with a pool of HRV-specific T-cell epitopes. Flow cytometry and functional assays will be used to analyze T-cell responses to HRV epitopes in the context of obstructive respiratory diseases.

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Results: This study was funded in January 2023 by the Ministry of Science and Innovation of Spain. The primary aim of the study was achieved within the same year. Recruitment for the secondary and tertiary aims is currently ongoing. Preliminary findings highlight the potential significance of HRV-specific T-cell responses in individuals with asthma and those with COPD. A detailed characterization of these immune responses will provide critical insights into host-pathogen interactions and may serve as a foundation for the development of effective T-cell–based vaccines or immunotherapies targeting HRV.

Conclusions: Here, we present an ethically approved study protocol for an observational and exploratory study investigating a novel epitope-based vaccine targeting HRV, with a focus on pediatric asthma and adult COPD cohort populations.

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KEYWORDS

asthma; COPD; chronic obstructive pulmonary disease rhinovirus; epitopes; vaccine; protocol; study design; exploratory; observational study.

Introduction

Rhinovirus and Its Context in Obstructive Respiratory Disorders

Human rhinoviruses (HRVs) are responsible for over half of all upper respiratory tract infections (URIs), with infection rates in young children reaching as high as 8-12 episodes per year [1]. HRV infections typically cause mild symptoms such as rhinorrhea, sore throat, coughing, sneezing, nasal congestion, and malaise [1]. They can also lead to more severe conditions, including acute otitis media and rhinosinusitis, often in association with bacterial coinfections [1,2]. In addition, HRVs are implicated in the development of lower respiratory tract diseases, such as pneumonia, bronchitis, and bronchiolitis [1], as well as in the exacerbation of asthma [3] and chronic obstructive pulmonary disease (COPD) [4].

The susceptibility to severe HRV infections and reinfections is influenced by a range of environmental and genetic factors, including impaired interferon responses and pre-existing conditions namely asthma and COPD [5]. Given the high frequency of HRV infections and their broad clinical implications, effective therapeutic and preventive strategies are urgently needed, as current treatments primarily focus on symptom relief, with no vaccine available to date. The development of such strategies would have significant public health benefits.

HRV Serotypes and Antigens

HRV is a small, nonenveloped virus belonging to the Picornaviridae family and the *Enterovirus* genus. It has a positive-strand RNA genome of approximately 7.2 kb [1,2]. The viral genome is translated into a single polyprotein, which undergoes proteolytic processing to generate 11 distinct viral proteins (Figure 1A). The HRV capsid is composed of 4 viral proteins (VPs): VP1, VP2, VP3, and VP4 (Figure 1B). With the exception of VPg, the remaining viral proteins are nonstructural and are involved in viral replication and assembly (Figure 1A). Notably, the capsid proteins exhibit considerable heterogeneity, leading to a broad range of antigenic diversity [6], particularly in VP1, which mediates viral entry by interacting with cell surface receptors (Figure 1B) [7].

HRV demonstrates exceptional diversity, with 3 recognized species: HRV-A, HRV-B, and HRV-C.

Each species includes numerous distinct serotypes, which can be differentiated through serological methods. At present, there are approximately 83 HRV-A, 32 HRV-B, and 55 HRV-C serotypes in circulation. Furthermore, high-resolution sequencing has identified multiple HRV serotypes within each serotype. HRV-A and HRV-C are primarily responsible for the majority of HRV-related respiratory infections and are more prevalent than HRV-B in individuals with asthma or COPD exacerbations [8-10]. Notably, HRV-C is associated with more severe infections compared to HRV-A and HRV-B species [11]. Given the significant impact of HRV on human disease, the development of an effective rhinovirus vaccine must target primarily HRV-A and HRV-C serotypes.

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Figure 1. Human rhinovirus proteome and structure. (A) Capsid and nonstructural proteins. (B) Rhinovirus capsid Viral Proteins (VP) related to the site of attachment to cell surface receptors (VP1-3) and internal capsid protein (VP4). Figure created with Biorender. RDRP: RNA-dependent RNA polymerase.

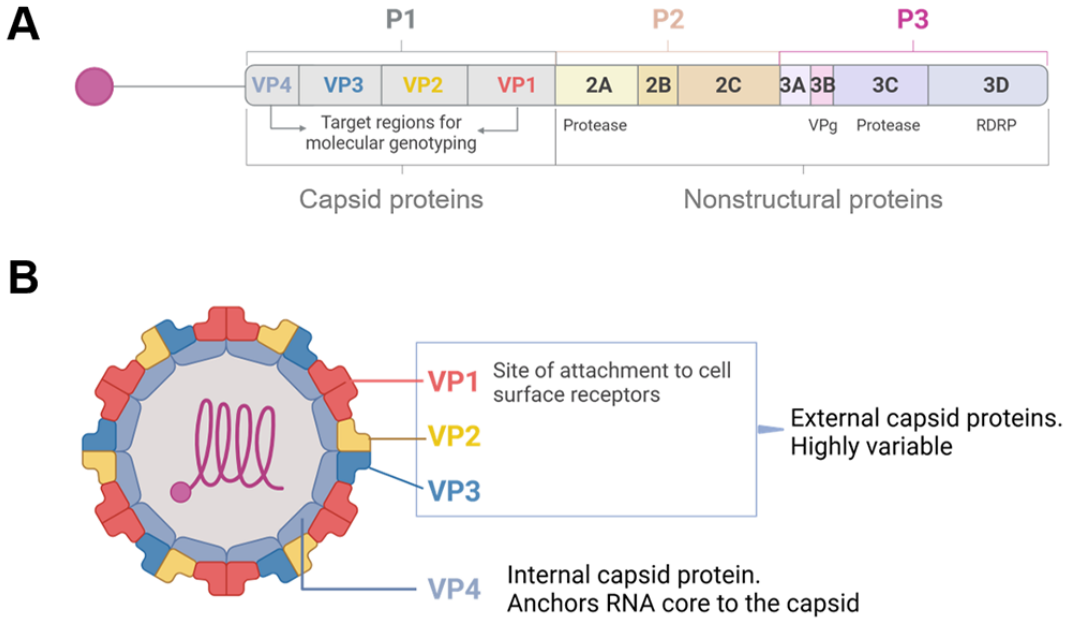

Rhinovirus Infection and Immune Response

HRV primarily infects epithelial cells of the lower respiratory tract, although it can also affect the upper respiratory tract (Figure 2). The viral entry process begins when the VP1 capsid protein attaches to various cell surface receptors. Most HRV-A and HRV-B serotypes enter airway epithelial cells via the ICAM-1 (intercellular adhesion molecule 1) receptor (also known as CD54), while a smaller fraction uses the low-density lipoprotein receptor [11]. In contrast, HRV-C serotypes predominantly use the cadherin-related family member 3 as their primary receptor for viral entry [12]. Once inside the host cell, the HRV genome is detected by endosomal toll-like receptors (TLRs) such as TLR7 and TLR8, triggering the production of type I interferons and proinflammatory cytokines such as RANTES, IP-10, interleukin (IL)-6, IL-8, and C-X-C motif chemokine ligand 5. The levels of these cytokines may influence the pathogenesis of symptomatic HRV infections, as they play a key role in initiating adaptive immune responses [2].

In response to HRV infection, affected individuals develop serotype-specific neutralizing immunoglobin G antibodies in their serum, as well as secretory immunoglobin A antibodies in the airways. However, these neutralizing antibodies target the highly variable, surface-exposed regions of the VP1, VP2, and VP3 capsid proteins, which are serotype-specific. Consequently, there is minimal or no cross-neutralization activity between different HRV serotypes [13]. While these antibodies do not appear to contribute significantly to the pathogenesis of HRV infections [1], their lack of cross-neutralization presents a substantial challenge for vaccine development.

Despite the critical role of T cells in immunity, the study of T-cell responses to HRV has been relatively neglected in favor of antibody research. This discrepancy is largely due to methodological limitations, as antibodies are relatively easy to measure, while antigen-specific T-cell responses require more complex cellular assays. Nonetheless, there is compelling evidence of the importance of HRV-specific T cells, which play a crucial role in initiating both cellular and humoral immune responses [14]. Circulating memory $CD4^+$ and $CD8^+$ T cells capable of recognizing HRV-specific antigens have been identified in healthy individuals [15]. HRV-specific $CD4^+$ T cells typically adopt a T helper type 1 phenotype, producing proinflammatory cytokines such as interferon-gamma, IL-2, tumor necrosis factor-alpha, and IL-6. These T helper type 1 cells, in turn, promote the activation and differentiation of HRV-specific cytotoxic $CD8^+$ T cells, which are essential for clearing HRV infections through their ability to recognize and destroy infected cells [16].

Unlike B cells, which can only recognize accessible antigens, T cells can target both exposed and hidden antigenic components. They recognize small peptide fragments of antigens displayed on the surface of antigen-presenting or infected cells, bound to major histocompatibility complex molecules. In humans, major histocompatibility complex molecules are known as human leukocyte antigen (HLA) molecules. Specifically, $CD8^+$ T cells recognize antigens presented by HLA class I (HLA I) molecules, while $CD4^+$ T cells interact with antigens presented by HLA class II (HLA II) molecules [17]. In contrast to the serotype-specific nature of HRV antibodies, T cells have been shown to respond to multiple HRV serotypes, suggesting the presence of conserved epitopes shared across different HRV serotypes [18,19].

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Figure 2. Human rhinovirus entry into the respiratory epithelium. Schematic illustrating human rhinovirus serotypes A, B, and C and their respective viral entry receptors. HRV-A and B primarily bind to the ICAM-1 (CD54) or LDL receptor, whereas HRV-C typically targets the CDHR3 receptor. Upon endosomal entry, TLR receptors 7 and 8 recognize the virus, triggering the release of IFN-γ and pro-inflammatory cytokines. Figure created with Biorender. CD54: cluster of differentiation 54; CDH3: Cadherin-Related Family Member 3; HRV: human rhinoviruses; ICAM-1: intercellular adhesion molecule 1; LDL: low-density lipoprotein; TLR: toll-like receptor.

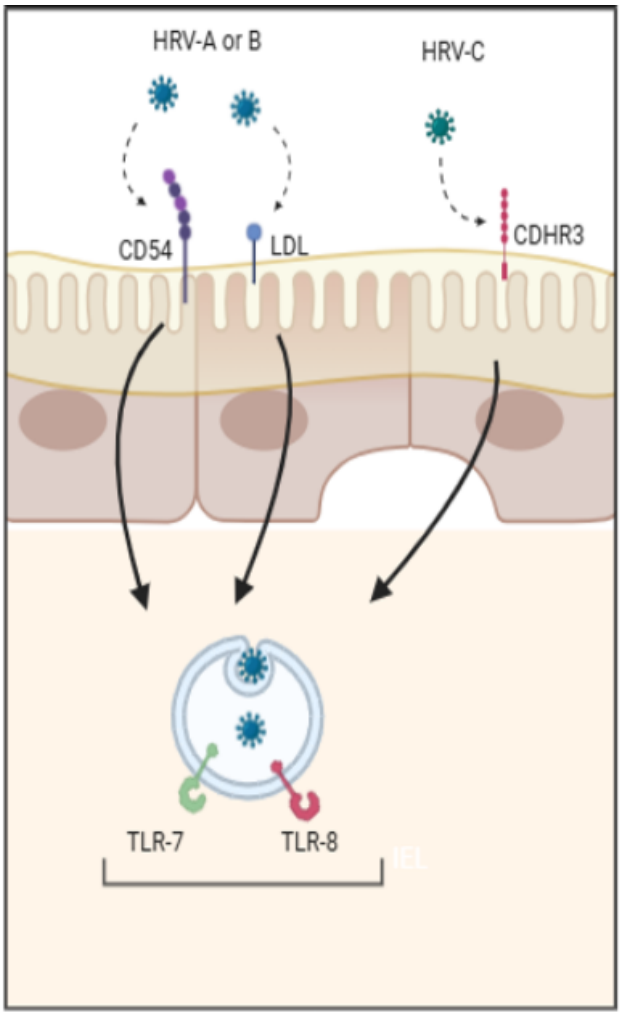

Rationale of the Study

Asthma and COPD are prevalent respiratory conditions that significantly affect public health, leading to increased morbidity, mortality, and health care costs. One of the major triggers of exacerbations in these diseases is infection with the HRV, which is responsible for a substantial number of acute episodes. These viral infections exacerbate the symptoms of asthma and COPD, increasing airflow obstruction, inflammation, and the odds of hospitalization.

The development of a vaccine targeting HRV has the potential to greatly reduce viral-induced exacerbations, improving the quality of life and health outcomes for individuals with asthma and those with COPD. An epitope-based vaccine consisting of conserved viral epitopes offers the possibility of inducing protective immunity against all HRV serotypes.

The final aim of this proposal is to advance the development of an epitope-based vaccine against HRV. To that end, we will explore the role of HRV-specific T-cell immunity in individuals with COPD and asthma, since these two groups will be the main beneficiaries of a potential vaccine. Furthermore, understanding how T-cell responses to HRV differ in these populations could provide valuable insights into the pathogenesis of viral-induced exacerbations and guide the design of future immunotherapies.

Methods

Study Aims

There are primary and exploratory outcomes. The primary outcome of the study is determining population-wide coverage of HRV-specific T-cell responses based on HLA binding profile and high throughput analysis of T-cell recall responses. This aim will help us to determine the responses in the population to viral epitopes across diverse HLA backgrounds, which is a critical step for the rational design of broadly effective T-cell–based vaccines. The exploratory aims of the study are the characterization of HRV-specific T-cell recall responses in the context of obstructive respiratory disorders in comparison to age-matched healthy controls. This exploratory aim will elucidate disease-associated alterations in T-cell immunity and reveal whether impaired or dysregulated T-cell responses contribute to increase disease severity or susceptibility to HRV-induced exacerbations. This aim includes profiling

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cytokine production, T-cell subset distribution, and activation or exhaustion markers. Such biomarkers will be useful for risk stratification for targeted immunomodulatory strategies. In addition, we will also explore comparative T-cell responses elicited by in vitro immunization of HRV epitopes in healthy and patient individuals. This aim will be instrumental for in vitro validation of vaccines aimed at vulnerable populations.

Study Setting and Recruitment

All study visits and associated procedures for both pediatric and adult cohorts will be conducted at the Hospital Clínico San Carlos, located in Madrid, Spain. During the study visit, participants will undergo a series of assessments and blood sample collections, all of which will be carried out by trained medical and research personnel in accordance with standard clinical protocols.

All participants will be enrolled in the study to attend a single visit to the hospital, coinciding with their routine monthly clinical check-up. This visit will serve as the primary data collection point for both pediatric and adult cohorts. Prior to any sample collection, participants (or their legal guardians, in the case of pediatric participants) will be required to review and sign a consent form, ensuring informed consent is obtained. During the visit, comprehensive clinical data will be gathered. In addition, participants will provide biological samples for immunological analysis, including serum and peripheral blood mononuclear cells (PBMCs), as well as blood samples for transcriptomic analysis.

Eligibility Criteria

The inclusion and exclusion criteria for children with asthma and adult participants with COPD enrolled in this study are outlined in Textboxes 1 and 2.

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Textbox 1. Inclusion and exclusion criteria for participants with pediatric asthma.

Inclusion criteria

- Age between 5 and 15 y with a paired sex distribution (ratio 1:1), equivalent age, and BMI.
- Participant who speaks Spanish fluently to ensure a comprehensive understanding of the research project and proposed participation.
- Ability to provide informed consent both individually and parental (parents or legal guardian).
- Awaiting a minor procedure in the case of healthy participants.
- Complete diagnosis and clinical score compatible with the respiratory disorders under study. The asthma diagnosis must have been identified at least 6 mo prior, with well-controlled asthma by a clinical team experienced and familiar with respiratory diseases. Compatible asthma will present the following symptoms: wheezing (current, persistent, or triggered), cough (including nocturnal), shortness of breath, nocturnal symptoms, and diurnal and seasonal variations.
- Asthma positivity thresholds in minors: (1) obstructive spirometry: forced expiratory volume/forced vital capacity (FEV/FVC) ratio less than 70%. Consider forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) with a ratio of less than 80% (or below the lower limit of normal if available) as a positive test for detecting obstructive airway disease (obstructive spirometry). (2) FeNO (fractional exhaled nitric oxide): 35 ppb or higher (3) Bronchodilator reversibility: Improvement in FEV1 of 12% or more. Consider a bronchodilator reversibility test in children and adolescents (5-16 y of age) with obstructive spirometry (FEV1/FVC ratio less than 70%). Consider an improvement in FEV1 of 12% or more as a positive test. (4) Peak flow variability: More than 20%.
- BMI: healthy weight (BMI above the 2nd percentile and below the 85th percentile).

Exclusion criteria

- Inability to provide individual or parental consent. Inability to comprehend reading, visual, or cognitive information that would prevent consent.
- Does not speak or understand Spanish.
- Children under 5 y old or adults.
- Immunocompromised minors or any other disease that leads to altered immunity.
- Inappropriate BMI: (1) Overweight: BMI above the 85th percentile and below the 95th percentile. (2) Obesity: BMI equals or above the 95th percentile. (3) Underweight: BMI below the 2nd percentile.
- Taking medications that may affect the immune system, such as oral steroids, nasal steroid sprays, antibiotics, and disease-modifying antirheumatic drugs.
- Any acute illness – unexplained symptoms in the last 14 d.
- Have received antibiotics, oral steroids, or nasal steroid sprays in the last 28 d.
- More than one asthma exacerbation (as defined by the American Thoracic Society) in the last 12 mo.
- Taking anticoagulants.
- Participating simultaneously in another clinical trial unless it is observational or in a follow-up phase (noninterventional).
- History of significant cardiopulmonary disease (excluding stable hypertension and asthma in treatment steps 2 and 3), or diseases associated with altered immunity, including diabetes, alcohol abuse, malignancies, and rheumatological conditions.
- Pregnancy.
- Taking any medication except those on the “allowed list” (statins, antihypertensives, antidepressants, bisphosphonates, hormone replacement therapy, vitamin supplements, antacids, nicotine replacement therapy, inhaled steroids up to 800 mg equivalent of Beclomethasone dipropinate, inhaled beta-2 agonists, and leukotriene receptor antagonists).
- Not presenting any clinical respiratory condition due to bacterial infection (*Streptococcus pneumoniae*) or viral infection (RSV, SARS-CoV-2, etc) or coinfections requiring hospitalization, and that have not occurred within at least the past month.

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Textbox 2. Inclusion and exclusion criteria for adult chronic obstructive pulmonary disease participants.

Inclusion criteria

- Age between 35 and 75 y with a paired sex distribution (ratio 1:1), equivalent age, and BMI.
- Participant who speaks Spanish fluently to ensure a comprehensive understanding of the research project and proposed participation.
- Ability to provide individual informed consent.
- Awaiting a minor procedure in the case of healthy participants.
- Complete diagnosis and clinical score compatible with the respiratory disorders under study. The chronic obstructive pulmonary disease (COPD) diagnosis must have been identified at least 6 mo prior by a clinical team experienced and familiar with respiratory diseases.
- Smokers or ex-smokers (of at least 10 pack-years).
- COPD positivity thresholds: (1) COPD diagnosis defined by spirometry as forced expiratory volume in 1 second/forced vital capacity (FEV1/FVC) ratio <0.7 (postbronchodilator). (2) Consider FEV1/FVC with a ratio of less than 70% (or below the lower limit of normal if this value is available) as a positive test for detecting obstructive airway disease (obstructive spirometry).
- BMI: Healthy weight (BMI above the 2nd percentile and below the 85th percentile).

Exclusion criteria

- Inability to provide individual or parental consent. Inability to understand reading, visual, or cognitive information that would prevent consent.
- Does not speak or understand Spanish.
- History of or current drug or alcohol abuse (frequent alcohol consumption: men and women should not regularly drink >3-4 units/d and > 2-3 units/d, respectively).
- Immunocompromised patients or any other disease that leads to altered immunity.
- Inadequate BMI: (1) Overweight: BMI above the 85th percentile and below the 95th percentile. (2) Obesity: BMI equals or above the 95th percentile. (3) Underweight: BMI below the 2nd percentile.
- Taking medications that may affect the immune system. For example, oral steroids, nasal steroid sprays, antibiotics, and disease-modifying antirheumatic drugs.
- Any acute illness – unexplained symptoms in the last 14 d.
- Have received antibiotics, oral steroids, or nasal steroid sprays in the last 28 d.
- Taking anticoagulants.
- Participating simultaneously in another clinical trial unless it is observational or in a follow-up phase (noninterventional).
- History of significant cardiopulmonary disease (excluding stable hypertension and asthma in treatment steps 2 and 3), or diseases associated with altered immunity, including diabetes, alcohol abuse, malignancies, and rheumatological conditions.
- Pregnancy.
- Taking any medication except those on the “allowed list” (statins, antihypertensives, antidepressants, bisphosphonates, hormone replacement therapy, vitamin supplements, antacids, nicotine replacement therapy, inhaled steroids up to 800 micrograms equivalent of BDP, inhaled beta-2 agonists, and leukotriene receptor antagonists).
- Not presenting any clinical respiratory condition due to bacterial infection (*Streptococcus pneumoniae*) or viral infection (RSV, SARS-CoV-2, etc) or coinfections requiring hospitalization, and that have not occurred within at least the past month.
- Positive lateral flow test for SARS-CoV-2.
- Acute COPD exacerbation in the last 3 mo or more than 3 exacerbations in the last 12 mo requiring oral steroidsor hospitalization.
- On ambulatory or long-term oxygen therapy.
- If there is evidence of severe obstruction (FEV1 <50% of postbronchodilator predicted), participants will be excluded from the study.

Study Timeline and Duration

This project is planned for 3 years (2023-2026) where the major aims are the following: (1) determination of the population-wide coverage of HRV-specific T-cell responses (2023, first year), (2) characterization of HRV-specific T-cell recall responses in diseases cohorts compared to age-match healthy controls (2024-2026), and (3) comparative analysis and identification of biomarkers of protection and susceptibility within disease cohorts (2025-2026).

Sample Size Calculation

For this exploratory study, the aim is to compare the in vitro immune response between children with asthma or adults with COPD and those without, based on blood samples. Given the exploratory nature of the study and the expected parametric distribution of the population, a sample size of 40 participants

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(20 per group) for each study (asthma and COPD) will be used. The sample size was estimated to detect ~15% differences in HRV-specific T-cell responses between healthy and disease participants at an α level of .05 (2-tailed) and a β value of .2. This sample size is intended to provide preliminary insights into HRV-specific immune responses, serving as a foundational step toward larger, more comprehensive research studies. While the limited number of participants requires cautious interpretation of results, the primary objective is to identify immunological trends and generate testable hypotheses.

Ethical Considerations

This exploratory study protocol has been approved by the Ethical Board Committee of the Hospital Clínico San Carlos (23/799-E). The study will be conducted in accordance with the Declaration of Helsinki and Good Clinical Practice (GCP) guidelines. All participants provided their written informed consent to participate in this study. Participant confidentiality will be maintained throughout the study. All data will be anonymized during processing and stored securely.

Results

Epitope Selection

HRVs are characterized by their great diversity, circulating in nature over 150 antigenically distinct serotypes of HRV. We identified HRV-A and C-specific T-cell epitopes from a reduced set of potential candidates using a computer-assisted strategy (Figure 3). Shannon Entropy was used to assess HRV sequence variability, isolating nonvariable regions for T-cell epitope prediction. Peptides were selected based on predicted binding to at least 3 distinct HLA I or HLA II molecules, using RANKPEP software developed by Reche et al [20]. The immunogenicity of 37 peptides was tested in interferon-gamma ELISPOT recall assays with PBMCs from 14 HLA-typed participants; 25 peptides were positive in at least one participant. Further validation assays led to the first reported HRV-specific $CD8^+$ T-cell epitopes (5 epitopes from HRV-A and 4 from HRV-C) [21]. In addition, 7 HRV-specific $CD4^+$ T-cell epitopes were identified (3 from HRV-A and 4 from HRV-C) [22]. Epitopes will be generated by chemical synthesis, dissolved in dimethyl sulfoxide and combined into pools. Three epitopes' pools will be assembled: HRV $CD4^+$ pool, HRV $CD8^+$ pool, and HRV pool (including all the epitopes; Figure 3A).

Figure 3. Human rhinovirus epitope selection and analysis overview. (A) Computer-aided selection of epitopes. HRV sequence variability was evaluated via Shannon entropy, and peptides were selected based on HLA-I and HLA-II binding affinity using RANKPEP. Epitope peptides were synthesized and validated experimentally. (B) Study design and participant recruitment. Pediatric and adult patients were selected according to predefined inclusion and exclusion criteria. (C) T-cell–specific immune responses will be assessed in vitro through stimulation with epitope pools, followed by flow cytometry and Luminex assays. (D) Transcriptional analysis of blood samples (both unstimulated PBMCs and following epitope stimulation, PBMCs) will be conducted to identify gene expression profiles associated with epitope protective immunity. Figure created with Biorender. BDR: bronchodilator response; CD4: cluster of differentiation 4; CD8: cluster of differentiation 8; CDHR3: cadherin-related family member 3; COPD: chronic obstructive pulmonary disease; FeNO: fractional exhaled nitric oxide; FEV: forced expiratory volume; FEV/FVC: ratio of forced expiratory volume in 1 second to forced vital capacity; FVC: forced vital capacity; HLA: human leukocyte antigen; HRV: human rhinovirus; ICAM-1: intercellular adhesion molecule 1; LDL receptor: low-density lipoprotein receptor; PBMC: peripheral blood mononuclear cells; PFV: peak flow variability.

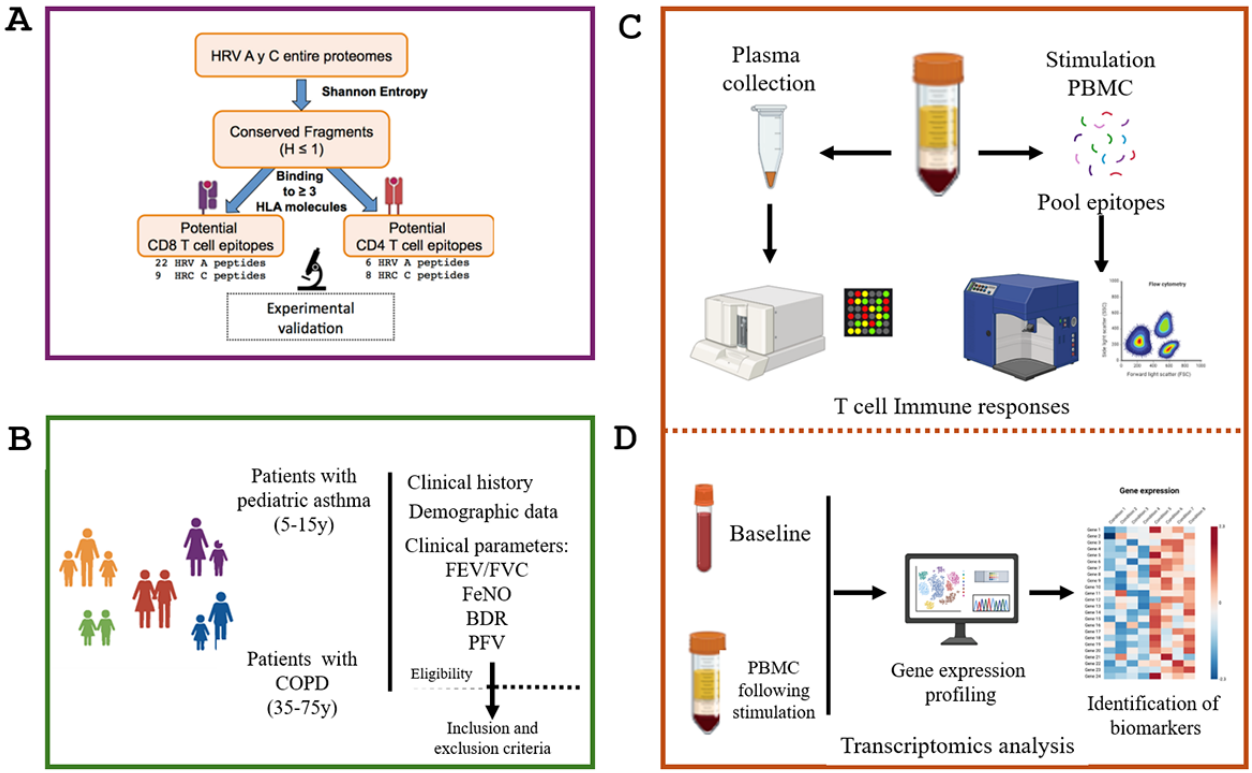

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Clinical Measurements

Comprehensive and demographic medical data will be collected, including exacerbation history, GOLD (Global Initiative for Chronic Obstructive Lung Disease) stage (for COPD), spirometry (forced expiratory volume in 1 second), and current treatment regimen (Figure 3B). This information will be used to correlate immune responses to HRV-specific T-cell epitopes with key demographic and clinical variables such as age, gender, disease severity, and medication, thus enabling a more holistic view of the immune landscape in obstructive respiratory diseases that will provide insights into HRV-related exacerbations across different demographics and clinical parameters between cohorts.

Immune Measurements

Systemic T-cell antigen–specific immune responses will be measured in vitro following exposure to HRV peptide pools (Figure 3C). These responses will be assessed to understand the relationship between immune reactivity and clinical parameters in individuals with asthma and those with COPD. Blood samples, including plasma and PBMCs, will be collected from participants for this analysis. Statistical comparisons of T-cell responses with HRV in disease and healthy participants will be carried out, taking into consideration clinical parameters, sex, age, and potential confounding factors such as medication.

Genetic Measurements

Whole blood samples will be collected from participants at baseline (single visit) to establish a comprehensive profile of individuals with asthma and those with COPD (Figure 3D). In addition, PBMCs isolated from the same participants following stimulation in vitro with HRV peptide pools will be used for RNA sequencing to assess gene expression and regulation in response to HRV-specific stimulation (Figure 3D). This analysis will elucidate key insights into the immune mechanism driving HRV-related disease exacerbations and identify biomarkers that could predict clinical outcomes.

Collectively, from 2023 up to 2025 we have accomplished the primary outcome of the study, and we have recently completed the recruitment of the adult cohort of participants diagnosed with COPD, and their respective age-matched controls. We expect to start the recruitment of the pediatric asthma population cohort during this year and complete the T-cell responses data analysis, from both population cohorts, according to our study timeline.

Discussion

Toward a T-Cell–Based Vaccine Against HRV

HRV is a major contributor to respiratory infections and exacerbations in individuals with obstructive respiratory disorders. Despite the widespread impact of HRV, no licensed vaccine currently exists. This observational and exploratory study proposes an innovative advance in the development of an epitope-based vaccine against HRV in individuals with COPD and asthma. Both vulnerable groups will be the main beneficiaries of a potential vaccine. We hypothesized that a peptide pool consisting of HRV-A and C T-cell epitopes could serve to develop an effective HRV vaccine against all A and C serotypes. This study will allow the exploration and the assessment of systemic T-cell immune responses against a specific pool of selected HRV epitopes, previously identified in silico, and experimentally validated by flow cytometry in vitro [21,22].

HRV-specific CD8+ T-cell epitopes include 8 typical 9-mer peptides and an unusually long 16-mer peptide restricted by HLA-A*02:01 [21], which also induced CD4 T-cell responses [22]. These $CD8^+$ T-cell epitopes induced functional cytotoxic CD8 T-cell responses and could potentially cover up to 87% of the population. The selected HRV-specific $CD4^+$ T-cell epitopes consist of 7 peptides characterized for their promiscuous binding to HLA class II molecules and could potentially be recognized by over 95% of the global population [22]. Collectively, these HRV-specific T-cell epitopes provide a strong foundation for future HRV vaccine development. Other studies also support the potential use of HRV-specific T-cell epitopes for vaccine development.

A previous study in a mouse model identified dominant $CD4^+$ T-cell epitopes in HRV type 1A that were distinct from antibody recognition sites. These epitopes elicited strong proliferative responses and exhibited broad cross-reactivity across HRV serotypes, suggesting their potential inclusion in broadly protective T-cell–based vaccines [19]. In addition, a recent study designed a multiepitope vaccine in silico, targeting conserved regions only on HRV-C, demonstrating strong antigenicity, stability, and solubility [23] with validation via C-ImmSim simulations [24].

Our methodological approach will examine HRV-specific T-cell immunity using peripheral blood samples from individuals diagnosed with obstructive respiratory diseases such as asthma and COPD and correlate those immune responses to clinical parameters and transcriptional signatures. This multiparametric combined analysis will facilitate the potential identification of protectionor susceptibility biomarkers or signatures within those vulnerable population cohorts before and following stimulation with the HRV epitopes. We anticipate that we will be able to identify altered HRV-specific T-cell responses in patients with asthma and those with COPD compared to healthy controls. Presumably, we will also find that factors such as age, disease severity, and medication may influence these responses, potentially revealing biomarkers of susceptibility or protection. Clearly, understanding T-cell responses to HRV within these clinical contexts is key for vaccine development. Furthermore, the study could also provide significant insights into the underlying mechanisms of viral-induced exacerbations as well as guidelines for the development of future immunotherapies.

Strengths and Limitations

This exploratory study will allow the identification of immunological trends and potential biomarkers related to HRV-specific T-cell responses in asthma and COPD, helping to fill a critical gap in current respiratory immunology. The integration of detailed clinical and demographic data such as age, gender, disease severity, and medication use will add translational relevance and may uncover factors influencing susceptibility or protection. However, this study has also

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limitations. The small sample size reduces statistical power and limits the generalizability of the results. Furthermore, this exploratory study may not capture longitudinal changes in the immune responses, which are important to characterize disease progression. Furthermore, potential confounding factors such as varying treatment regimens and comorbidities may hinder potential immune signatures connected to clinical outcomes. Despite these limitations, the study is well-positioned to provide valuable preliminary insights and inform the design of larger more definitive investigations.

Future Directions

The outcomes from this exploratory study will establish a foundation for larger-scale studies including those on mucosal immune responses following stimulation and their correlation to systemic and lung responses. Future studies will focus on expanding the sample size and incorporating both peripheral blood and mucosal samples, alongside longitudinal analyses to evaluate how HRV-specific T-cell responses change over time and correlate with disease progression. Future research will also tackle more diverse and clinically relevant cohorts, including different asthma endotypes and COPD phenotypes across multiple settings. Furthermore, it will deepen the characterization of T-cell subsets and their interaction with other immune cells, using advanced techniques such as spectral flow cytometry, and incorporate multiomics approaches like transcriptomics and proteomics. All together will enable a system-level view of immune responses, enhance our understanding of HRV-driven immunopathology in obstructive airway diseases and facilitate the discovery of novel biomarkers and therapeutic targets.

Acknowledgments

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Authors' Contributions

JR and PAR contributed to study design and experimental design. SAF, RRM, JMG, MCR, JRH, ABP, and SRE performed sample processing. SAF, RRM, JMG, EML, SC, JR, and PAR conducted data analysis. MCR, JLH, JR, and PAR managed ethics submission. SAF, RRM, MCR, JRH, EML, JR, and PAR handled study coordination. MCR, JLH, ABP, and SRE were responsible for clinical cover including on call responsibility. SAF, RRM, JMG, SC, MCR, JH, ABP, SRE, EML, JR, and PAR were involved in writing the protocol SAF, RRM, SC, MCR, JRH, EML, JR, and PAR contributed to manuscript writing. JR (jesus.reine@paediatrics.ox.ac.uk) and PAR (parecheg@med.ucm.es) are co-corresponding authors and have contributed equally as joint last authors on this manuscript.

Conflicts of Interest

None declared.

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Abbreviations

COPD: chronic obstructive pulmonary disease
FEV: forced expiratory volume
GCP: Good Clinical Practice
GOLD: Global Initiative for Chronic Obstructive Lung Disease
HLA: human leukocyte antigen
HRV: human rhinovirus
IL: interleukin
PBMC: peripheral blood mononuclear cell
TLR: toll-like receptor
URI: upper respiratory tract infection
VP: viral protein

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Protocol

Assessment of Individual Exposure to Multiple Pollutants (Noise, Particulate Matter, and Extremely Low-Frequency Magnetic Fields) Related to Daily Life Microenvironments in the Brussels Capital Region: Protocol for a Cross-Sectional Study

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Abstract

Background: Environmental factors are responsible for 13% of annual deaths in Europe. Citizens are constantly exposed to a variety of environmental factors, such as noise, air pollutants, and magnetic fields (MFs), which may interact with one another. To study multiple-pollutant exposures simultaneously, data on individual citizens, collected using portable measuring devices, provide a high level of detail for exposure characterization.

Objective: The aims of this study are to (1) assess the exposure of urban citizens to multiple pollutants (noise, particulate matter [PM], and extremely low-frequency magnetic fields [ELF-MFs]) on a normal weekday, (2) estimate the contribution of each main daily life microenvironment in the multiple-pollutant exposure, and (3) estimate the role of measured exposure in the assessment of perceived personal exposure.

Methods: We collected the exposure levels of 490 individuals to multiple pollutants: PM, ELF-MFs, and noise levels. We used 3 devices per participant (Airbeam 2, EMDEX II or EMDEX Lite, and a smartphone with the Aircasting app for PM, ELF-MFs, and noise, respectively). Participants wore them for 24 hours on a normal weekday. In parallel, they filled out a microenvironment diary and a questionnaire focusing on socioeconomic data, lifestyle, and perceived exposures. The analysis will first describe the exposures as daily averages and aggregated by microenvironment. Several analyses will be conducted: (1) an estimation of the contribution of each microenvironment in the exposure levels of the 3 pollutants studied, (2) a linear mixed model (for each pollutant) to explain the measured levels of exposure, and (3) linear regression to assess the contribution of the measured personal exposure in self-reported perceived exposures.

Results: Data collection was carried out from October 2020 to August 2022, with 490 individuals taking part. The databases have been gathered and cleaned. Future work will focus on data analysis.

Conclusions: The collected data will allow us to describe the daily multiple-pollutant exposures faced by individuals within the general population and to characterize the main microenvironments of their daily lives according to multiple-pollutant exposures. This will help identify precise microenvironments to be targeted in policies aiming to reduce exposure to pollution. Because the sampling method is not probabilistic, it is not expected to be representative of the population of the Brussels Capital Region, but it will provide a first step in the understanding of multiple-pollutant exposures faced by individual citizens.

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KEYWORDS

personal exposure; multiple exposures; noise; particulate matter; PM; extremely low-frequency magnetic fields; ELF-MF; pollutants; microenvironment

Introduction

Background

According to the World Health Organization (WHO), 13% of deaths in the European Union (EU) in 2012 (last update) were linked to environmental factors [1]. This represents 630,000 deaths each year, of which 90% are due to noncommunicable diseases, the main ones being cancer, ischemic heart disease, chronic obstructive pulmonary disease (COPD), and stroke. In addition to deaths, WHO estimates that 20 million healthy life-years are lost worldwide each year due to environmental factors [1]. Since populations are generally exposed to multiple pollutants at once, the European Environment Agency underlines the importance of studying multiple-pollutant exposures and their impacts on health [2]. The 2 main environmental factors negatively impacting human health are air pollution and noise [2].

The main air pollutants are particulate matter (PM), ozone (O_3), and nitrogen dioxide (NO_2). Among these, $PM_{2.5}$ (aerodynamic diameter<2.5 µm) is the largest contributor, with 379,000 of the 400,000 premature deaths attributed to air pollution in the EU-28 (European Union with 28 member states) in 2018 [2]. This is despite a steady decline in PM concentrations in Europe since 1990 [2]. Between 2016 and 2018, more than 74% of Europe's urban population was exposed to $PM_{2.5}$ levels exceeding the WHO threshold. PM affects the human body by causing respiratory problems, cardiovascular diseases, COPD, and even reproductive issues. Concerning indoor air quality, PM is also the first factor responsible for indoor pollutant–related diseases [2].

After air pollution, noise is the second-most important contributor to the environmental burden of disease in Europe [2]. Noise can affect human health either by damaging the auditory system (eg, hearing loss) or by inducing physiological stress (eg, sleep disturbance, impaired concentration with impacts on cognitive development, and metabolic effects potentially leading to cardiovascular diseases) [3,4]. In Europe, the main source of environmental noise is road traffic. Hänninen et al [5] estimated that 400-1500 disability-adjusted life-years (DALYs = years of life with disability + years of life lost) per million people are attributable to traffic-related noise. For example, Basner et al [4] reported that an increase of 10 dB (in LAeq, a weighted equivalent continuous sound pressure level) leads to a 7% increase in hypertension, a 15% increase in strokes, and a 17% increase in myocardial infections.

Extremely low-frequency magnetic fields (ELF-MFs) are fields produced by the movement of electrically charged particles. The "extremely low" range includes 50-60 Hz fields, which are the frequency generated by electricity distribution around the world. These fields, at chronic exposures of 0.3-0.4 µT, have in some studies been associated with an increased risk of childhood leukemia [6-9] and have therefore been classified as "possibly carcinogenic to humans" by the International Agency for Research on Cancer (IARC) [10]. To date, no causal relationship has been concluded, no action mechanism has been identified nor explained, and the Scientific Committee on Health, Environmental and Emerging Risks (SCHEER) 2024 report [11] concludes that evidence of this potential association is weak. ELF-MFs are also suspected to be linked to the development of neurodegenerative diseases, such as Alzheimer's disease or amyotrophic lateral sclerosis (ALS) [12-16], but results are too mitigated and the evidence too weak to conclude a causal association [11,17]. Despite the absence of causal pathways, exposure to ELF-MFs and their potential health effects remain relevant due to an ongoing societal debate on perceived health risks.

Urban citizens are continuously and simultaneously exposed to a wide variety of environmental factors, such as noise, air pollution, and magnetic fields (MFs), that originate from different sources and can enter the human organism in different ways. Little is known about how simultaneous coexposure to multiple types of pollutants leads to interactive, or cocktail, effects. It is hypothesized that the interaction of different exposures may lead to antagonism, synergy, or the cumulation of effects [18]. For example, it has been observed that combined exposure to air pollution and high temperatures leads to higher levels of morbidity and mortality [2].

Urban populations are particularly affected by simultaneous exposures to noise and air pollution. Indeed, road traffic, denser in urban areas, is the main source of both poor air quality and high noise levels [2]. Moreover, both air quality and noise affect similar systems in the human body, such as the cardiovascular and endocrine systems [2].

In 2015, the Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR) underlined the possible role that ELF-MFs may play in interaction with other exposures [19]. Indeed, in the presence of 50 Hz MFs from high-voltage power lines, PM gets electrically charged and becomes "corona ions" potentially more dangerous to human health than nonelectrically charged PM [20]. Moreover, PM is suspected to be associated with similar kinds of diseases than ELF-MFs are, such as neurodegenerative diseases [21,22] or childhood leukemia [23,24].

Most studies on exposures to environmental pollutants (air and noise) use data monitored from fixed stations. They provide average estimates of exposure at the levels of geographical areas (eg, neighborhoods) through extrapolation of measurements at these locations. Although this makes it possible to study potential links between health and exposures via ecological studies, the modeled data reduce the real heterogeneity of individual exposures in each area. Several authors [18,25-27]

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have pointed out that this results in reduced statistical power and increased measurement error.

Collecting exposure data at the level of individual citizens has several advantages. It provides information about exposure levels, detailed to whether the participant is indoors or outdoors, indoors being where people spend up to 90% of the time [2,28]. It also provides insights into exposure at the level of microenvironments (eg, kitchens, living rooms, cars, parks), as has been conducted for air pollution [25,28-30], MFs [31], and noise levels [32]. This allows us to relate exposures to the personal profile of activities of the exposed individuals. As observed by Ma et al [32], the means of exposure (in their case to noise) can be different between citizens from the same neighborhood. Buonanno et al [29] found that women in their sample were more exposed to ultrafine particles than men because they spent more time in kitchens, whereas men were most exposed while in public transport. In addition, this level of detail helps identify potential factors associated with exposure. Sivanantham et al [33] related the multiple-pollutant exposure patterns of different schools to different characteristics, such as the age of the buildings, cleaning habits, or ventilation habits. Finally, individual exposure measurements usually have a higher frequency of measurement (eg, every minute or second), whereas fixed monitors usually measure only once an hour [34].

A literature review on exposure to environmental factors during travel by Poom et al [34] found that 60% of the studies included in their review were published after 2015 and that 65% of those studies used portable sensors to collect data. This shows a growing interest in environmental exposures and in collecting data at the individual level using portable sensors.

However, there are several limitations to individual data that need to be considered. The main challenge is that collecting samples that are representative of the population is nearly impossible. Indeed, participation is voluntary, and as pointed out by Nieuwenhuijsen et al [35], only highly motivated people will agree to wear devices for several hours or days. Canha et al [28] also remind us of the importance of using reliable devices validated by comparisons with reference measurement tools. In the end, despite their imperfections, these methods allow us to improve decision-making, while acknowledging inaccuracies and uncertainties [36].

This data collection at the individual and microenvironmental levels will be insightful for further studies on the impacts of multiple-pollutant exposures on human health, especially given the growing interest in studying exposures to pollution as they occur in real life, with multiple-pollutant exposures that occur simultaneously.

Objectives

ExpoHealth-1 is an observational study collecting data on exposure to multiple pollutants (PM, noise, ELF-MFs) at the individual level for 490 inhabitants of the Brussels Capital Region. To the best of our knowledge, this is the first study of its kind in the region. Our objectives are to (1) assess daily exposures to PM, noise, and ELF-MFs at the individual level for a sample of inhabitants of the Brussels Capital Region, (2) assess the levels of exposure to these 3 pollutants in the main microenvironments encountered on a normal weekday and evaluate the contribution of each microenvironment in the trends of exposure measured, and (3) assess the potential role of real exposure in the reporting of perceived exposure. To this end, we collected (1) individual-level exposure data for PM, noise, and ELF-MFs over 24 hours distributed over 2 normal weekdays, (2) a microenvironment diary for each participant during the 24-hour measurement period, and (3) participant information, such as gender, age, socioeconomic status, perceived health, and perceived exposure via a self-administered questionnaire.

Methods

Recruitment

Areas of Interest

This study is part of the Belgian Bioelectromagnetics Group (BBEMG) [37], a consortium of 7 scientific teams investigating potential health effects of exposure to ELF-MFs. For this multiple-pollutant exposure study (ExpoHealth-1), 3 geographical areas of interest have been identified in the Brussels Capital Region (Figure 1).

Statistical sectors of interest were selected based on 2 criteria. First, they had to have different expected levels of ELF-MF exposures but similar exposure levels to other environmental factors. Indeed, because environmental levels of ELF-MFs are generally low, we decided to target the potential individual exposure to this factor in the selection of areas for the study. To do so, we used data of provisional annual means of load forecast provided by the Belgian electricity system operator ELIA [38] and identified the statistical sectors potentially most and least exposed to ELF-MFs from electricity distribution. Second, each statistical sector had to include a variety of socioeconomic backgrounds to include people from different socioeconomic classes in the investigation. This choice eliminated the income extremes of statistical sectors of the city.

We included 3 environmental factors: (1) access to green spaces, (2) means of exposure to NO_2 and $PM_{2.5}$, and (3) variability of street exposure to ELF-MFs (as measured by a field team). We also included 3 socioeconomic factors: (1) monthly income by inhabitant, (2) employment rate, and (3) age distribution. These data (except for the ELF-MFs on-street measurements) are available in databases from the Brussels Institute of Statistics and Analysis [39]. See Multimedia Appendix 1 for more details of these factors' levels for the selected areas.

To obtain enough volunteers, 3 groups of statistical sectors were chosen. The map (Figure 1) shows the selected areas. It was realized with QGIS 3.34.7, using a base map from Urbis [40].

The sample is nonprobabilistic as recruitment was based on volunteer participation. Invitations to participate in the data collection were made through flyers distributed in each mailbox of the selected areas. Announcements were posted on the websites of the municipal administrations and neighborhood social media groups, such as Facebook and Hoplr (see Multimedia Appendices 2 and 3). Information was also spread by word of mouth between neighbors in the selected areas.

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Figure 1. Map of the selected areas in the Brussels Capital Region.

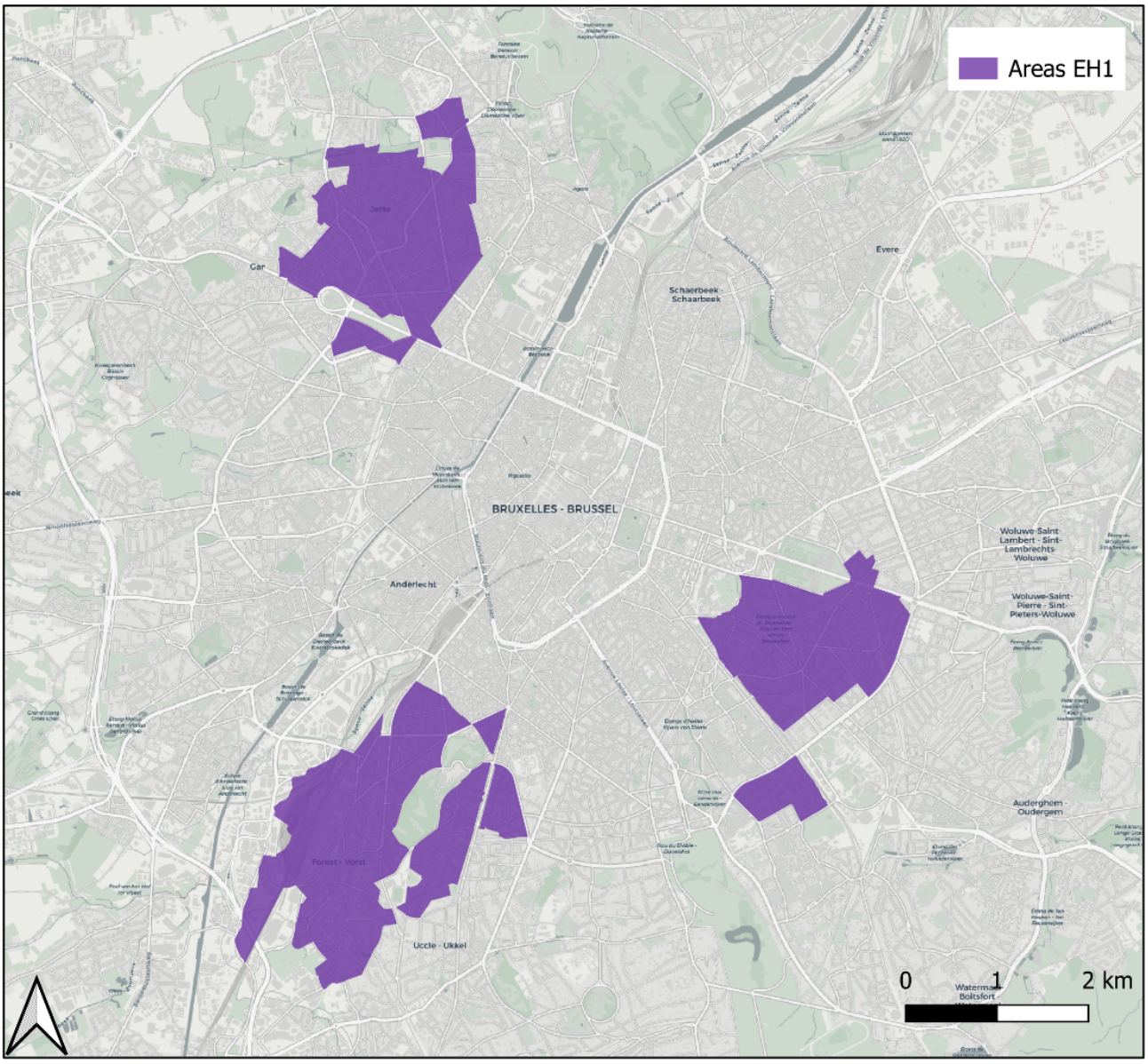

Inclusion and Exclusion Criteria

Participants in the study had to live in the selected areas, be aged between 18 and 65 years, and be nonsmokers or occasional smokers. People from the same household could participate, even on the same day. Indeed, Buonanno et al [29] showed that individuals from the same household have different exposure profiles. Participation was possible in either French or Dutch, the 2 official languages of the region.

Sample Population

Because of the exploratory purpose of this study, the sample size estimated for the data collection was first based on feasibility in terms of the number of devices available, the timing, and the size of the field team. This led to a target of 600 participants. At the end of the data collection, we had enrolled 490 participants.

Data Collection

Data were collected with 3 main instruments: a questionnaire, a set of 3 pollution exposure measurement devices, and a microenvironments diary.

Questionnaire

Participants completed a self-administered questionnaire (Multimedia Appendices 4 and 5), available in French or Dutch, and on paper or online (Limesurvey). This questionnaire contained standardized questions and questions based on a literature review. It focused on socioeconomic aspects, lifestyle, perception of health, and perception and knowledge of environmental exposure. The standardized questions were for:

- Perceived health: Patient Health Questionnaire (PHQ)-9 [41], PHQ-15 [42], Generalized Anxiety Disorder (GAD)-7 [43]
- Physical activity: International Physical Activity Questionnaire (IPAQ)-7 [44]
- Dietary habits: Inspired by the Food Frequency Questionnaire used in the Belgian Food Consumption

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Survey 2014 [45]. Several items were added, based on a literature review, to evaluate the exposure to endocrine-disrupting chemicals through food consumption.
- Modern health worries (MHWs): Inspired by the MHW scale [46]. Several items were added to evaluate the potential worries induced by the COVID-19 sanitary crisis.

We asked the participants to complete the questionnaire a few days before wearing the devices to reduce the priming effect. However, as we would not receive their signed consent until later, on the day they started wearing the devices, they were asked to wait before returning the questionnaire. On the day of the research team's visit, the participants first signed the information and consent form and then received their pseudonym that they added to the questionnaire before submitting it.

Portable Devices

Participants wore 3 different measuring devices (Table 1) at the same time for 24 hours, except when sleeping or showering. The measurements started in the late afternoon with the visit of the field team and ended the next day at the same time plus 15 minutes (24 hours and 15 minutes later). For example, a participant would receive the devices on Monday at 5:00 p.m. and wear them until bedtime. They would leave the devices somewhere in the bedroom in order not to wear them during sleep (for comfort) and put them back on the next morning. The measurements would not be stopped until the field team visited on Tuesday at 5:15 p.m.

Table 1. Main characteristics of the portable devices used in the ExpoHealth-1 study data collection.

Characteristic	EMDEX II	EMDEX Lite	Airbeam 2	Smartphone
Environmental pollutant measured	ELF-MF[a] (frequency range broadband: 40-800 Hz) flux density	ELF-MF (frequency range broadband: 40-800 Hz) flux density	PM[b]$_1$, $PM_{2.5}$, and PM_{10} concentration	Noise levels intensity
Range	0.01-300 µT	0.01-70 µT	0-300 µg/m^3	Pink noise
Unit	µT	µT	µg/m^3	dB
Frequency of data collection (seconds)	3	4	1	1
Duration of measurement	24 hours except sleeping time	24 hours except sleeping time	24 hours	24 hours
Duration of data upload (minutes)	5-10	5-10	5-10	5-10
Dimensions (cm)	16.8 (height) × 6.6 (width) × 3.8 (depth)	11.9 (height) × 6 (width) × 2.5 (depth)	13.2 (height) × 9.8 (width) × 2.8 (depth)	15.6 (height) × 7.3 (width) × 0.8 (depth)
Weight with battery (g)	367	196	176	154
CE[c] pouch (g; for EMDEX Lite only)	N/A[d]	54	N/A	N/A
Shoulder pouch (g; for EMDEX + smartphone)[e]	57	57	N/A	57
Way of wearing	Carried in the shoulder pouch	Carried in the CE pouch, which is in the shoulder pouch	Fixed around the waist	Carried in the shoulder pouch
Duration of wearing	All the time (24 hours) except when in a steamed environment and except during the night (somewhere in the bedroom)	All the time (24 hours) except when in a steamed environment and except during the night (somewhere in the bedroom)	All the time (24 hours) except when in a steamed environment and except during the night (somewhere in the bedroom)	All the time (24 hours) except when in a steamed environment and except during the night (somewhere in the bedroom)
Battery	9 V	9 V	2000 mAh 3.7 V	3020 mAh
Autonomy	Up to 7 days	6 days	10 hours	26-30 hours
Cost by unit (US $)	2950	1525	250	100

[a]ELF-MF: extremely low-frequency magnetic field.

[b]PM: particulate matter.

[c]CE: European Conformity.

[d]N/A: not applicable.

[e]Each participant wore only 1 shoulder pouch (with 1 EMDEX and 1 smartphone inside).

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Airbeam 2 for Particulate Matter

We used Airbeam 2 to collect daily data on exposure to PM_1, $PM_{2.5}$, and PM_{10} (particle diameter<1, <2.5, and <10 µm, respectively). Airbeam 2 is an optical particle sensor (Plantower PMS7003) that uses light scattering to measure the ambient concentrations of PM (maximum diameter 1, 2.5, and 10 µm). The measured data are then sent to a smartphone via the Aircasting Android app through a Bluetooth connection.

Airbeam 2 quality tests were performed independently of this study by the Air Quality Sensor Performance Evaluation Centre (AQ-SPEC) [47]. Their measurements were compared under laboratory conditions [48] with a federal (US) equivalent method device (FEM GRIMM) and under field conditions [49] with several instruments (MetOne BAM, GRIMM, and Teledyne). No correlation with PM_{10} data was found in either situation. PM_1 and $PM_{2.5}$ comparisons with reference instruments under laboratory conditions showed a high correlation (R^2>0.99), but Airbeam 2 underestimated the PM concentrations (accuracy between 62% and 83% for PM_1 and between 51% and 78% for $PM_{2.5}$) [48]. Under field conditions, the correlations of the measurements with the reference instruments were moderate to very strong for $PM_{2.5}$ (0.67<R^2<0.86) and strong for PM_1 (R^2=~0.75). In general, the accuracy was considered moderate in the range between 0 and 300 µg/m^3, with frequent underestimation of the concentrations. Stronger correlations were observed for 24-hour averages (R^2=~0.94 for PM_1 and ~0.91 for $PM_{2.5}$ when compared to GRIMM) [49].

The sensors showed high precision in several combinations of relative humidity and high or low temperature. In addition, there was little variation between the different Airbeam 2 devices used in the tests. This suggests that we can be confident in the precision of the set of 13 different Airbeam 2 sensors used in the data collection.

In conclusion, we will not be mobilizing the data collected for PM_{10} concentrations as we have low confidence in the devices for this. A correction equation will be developed and applied before further analysis of measured data of PM2.5 concentrations. This will tackle the systematic underestimates observed for Airbeam 2 sensors.

Airbeam 2 is worn on the belt, with access to ambient air (Figure 2 and Multimedia Appendix 6). It has an autonomy of 8-9 hours. Participants wore it from the end of the afternoon until the evening, recharged it during the night (sleeping hours), and put it back on during the daytime (sometimes with a small charge of 30 minutes during the day and while still wearing it). Occasionally, the device would stop working and display a flashing red light. Participants were asked to call the team if this happened, in which case they reset the device together over the phone at any time of the day or night to minimize the loss of data. The devices measured exposure continuously over 24 hours, even while Airbeam 2 was charging.

Figure 2. How to wear the portable devices for the ExpoHealth-1 study: EMDEX II or EMDEX Lite + smartphone in a shoulder pouch (either on the front or on the back) and Airbeam 2 at the waist level with access to ambient air.

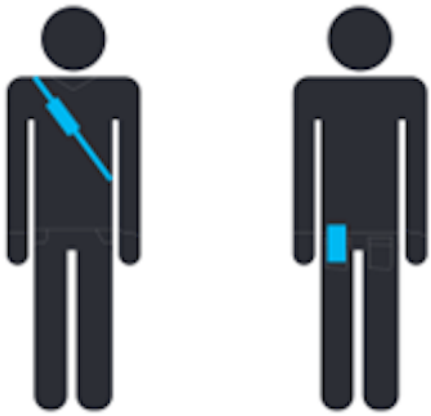

EMDEX II and EMDEX Lite for ELF-MFs

EMDEX II and EMDEX Lite measure the levels of ELF-MFs. They have been used for many years in ELF-MF-monitoring studies. In 2004, Brazzale et al [50] reviewed their quality. They concluded that both instruments provide “reliable measurements of the reference ELF-MFs.” Comparing the 2 devices, they found that the EMDEX II meters showed a consistent underestimation of 0.01 µT, while the EMDEX Lite measurements showed no fixed error, but the authors observed a relative error influenced by the orientation of the instrument. A relative error of 3.5% (95% CI 3.0%-4.0%) was reported for both instruments, which is slightly higher than the 1%-2% indicated by the manufacturer. In 2002, McDevitt et al [51] used EMDEX Lite to assess the measurement quality of the then brand-new MultiWave System III. They reported similar results in terms of the time-weighted average (TWA) but noticed that EMDEX Lite tends to underestimate the maximum exposure measurements.

A calibration control report on EMDEX Lite used in the study showed important relative errors for exposure levels under 0.1 µT [52]. Measurement levels were compared to those of the reference instrument SMP2 Wavecontrol (probes WP400 and WP400-3).

EMDEX II was compared to a Maschek ESM-100 probe by Geuzaine et al [53]. They found similar results: EMDEX II values are too imprecise under 0.1 µT, and values below this threshold should be considered noise.

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Although EMDEX II was developed in 1991, it is still widely used in environmental studies, often for specific microenvironments, such as children's bedrooms and schools [54], residential rooms categorized according to their vicinity to transformer rooms [55], classrooms during digital learning classes [56], and daily microenvironments of adolescents [57], or to assess ELF-MF on land around high-voltage power lines [58] or generated by portable fans [59].

We used both EMDEX II and EMDEX Lite to assess the exposure of individuals to ELF-MFs in each microenvironment they visited during data collection. EMDEX II was calibrated before the start of data collection. Midway through the field experiment, EMDEX II had to be replaced by a set of EMDEX Lite, all of which were then checked in all 3 directions with the testing suitcase (see pictures in Multimedia Appendix 7) and showed values within the acceptable ranges in all 3 directions. As EMDEX Lite is known to be sensitive to radiofrequency (RF) fields that can be generated by a mobile phone within a 30 cm radius, it was carried in a special European Conformity (CE) anti-RF shielding pouch. As we used a smartphone to record noise levels, we needed this shielding pouch to avoid interference. We noted that the shielding pouch did not affect the measurements of 50/60 Hz MFs.

Each participant was asked to wear the device in the same way (ie, over the shoulder), as shown in Figure 2 and Multimedia Appendix 6, and to not leave it lying around (eg, on a desk or couch). This ensured the quality of the measurements.

As participants did not wear the device during their sleeping hours, the data from these periods will not be used.

The fixed error of –0.01 µT in EMDEX II measurements will be corrected when cleaning the data. Measurements below 0.1 µT will be considered background noise.

Smartphones for Noise Levels

Huawei Y6 2019 smartphones (model MRD-LXI) and the Aircasting app were used to (1) measure sound levels in decibels every second, (2) save the data collected with Airbeam 2 and sent to the smartphones via a Bluetooth connection, and (3) record the GPS data of each participant's movements.

The Aircasting app uses a weighting filter (A), which is most commonly used for environmental noise measurements and is close to the range of human hearing. Therefore, we uploaded the data in dB(A).

Although smartphones are not designed for research purposes, they can collect a large amount of data at an individual level and at low cost [25].

Quality control was performed on the smartphones used for data collection by the noise department of Brussels' environmental agency (Bruxelles Environnement/Brussel Leefmilieu). The sound levels collected by the Huawei Y6 2019 smartphones via the Aircasting app were compared to the data collected by a reference sonometer of category 1: the Cube from the 01dB brand. A pink sound was used for comparison because it gathers a wide spectrum of sound frequencies and is therefore similar to environmental noise. The tests were conducted under similar conditions to those of the study: in the shoulder pouch and against the EMDEX device. This quality test concluded that the smartphones tended to underestimate the noise levels by 3 dB in comparison to the reference instrument. Therefore, the data collected will be corrected with +3 dB for each take. Furthermore, there was a maximum difference of 1 dB between the different smartphones.

The mobile phone was placed in the shoulder pouch next to the EMDEX device. The participants were asked to always keep a maximum of 1 m and a minimum of 10 cm between Airbeam 2 and the pouch (smartphone + EMDEX). The maximum distance of 1 m ensures a strong Bluetooth connection between Airbeam 2 and the mobile phone. The minimum distance of 10 cm avoids possible interference of the Bluetooth connection with the ELF-MF measurements by EMDEX II.

Diary of Microenvironments

Participants filled in a paper microenvironment diary (Multimedia Appendix 8) with a code corresponding to the type of environment they were in (eg, kitchen, car, park, restaurant, workplace) for each 15-minute time slot. Each diary was collected and encoded in a digital database, and 10% of the diaries were randomly checked for possible coding errors.

The microenvironments listed were both indoor (kitchen, living room, workplace, car, public transport) and outdoor (green space, walking or cycling in the street).

Organization of the Data Collection

Participants were invited to book an initial appointment between Monday and Thursday afternoons and a second appointment 24 hours later, between Tuesday and Friday afternoons. They were asked to choose a day that was the most representative of their weekly life. Once they had booked an appointment, they received the questionnaire online or on paper (Multimedia Appendices 4 and 5), depending on their preference, and instructions on how to use the measuring equipment (Multimedia Appendix 9).

The research team could meet up to 6 new participants each day and collect up to 6 sets of devices from participants who had started the day before.

Each initial appointment began with a discussion to ensure that all important information was clear to the participant. This was followed by them cosigning the information and consent form. Each participant was given a pseudonym to associate with their filled questionnaire and was asked to submit it immediately. At this point, the devices were started and attached to the participant with explanations to ensure that they were worn correctly: a distance had to be maintained to avoid interference, and the device measuring air pollutants had to always have access to ambient air.

Since part of the data collection took place during the COVID-19 pandemic, hygiene and distance rules were strictly adhered to: Every encounter took place at the doorstep, outside the participants' homes, and the team always wore a mask and disinfected their hands and the equipment before and after every encounter.

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To minimize the environmental impact of data collection, reusable batteries were used throughout the data collection and no more than 20 different 9 V batteries were used in total. Most of the journeys between participants' homes were made by bicycle or on foot.

Data Analysis

Data analysis will be mainly descriptive using R software version 4.2.3 (R Foundation for Statistical Computing). The final database will gather the following data for each participant: (1) exposure levels for noise, $PM_{2.5}$, and ELF-MFs in means per minute over 24 hours, (2) the microenvironment in which each exposure was measured, and (3) answers to the questionnaire, which combines personal information, perceived health, perceived exposure, and several life and home habits.

Description of Exposures by Participants and by Microenvironment

We will first report the central trend of exposures for each pollutant along the 24-hour measurements. We will then report trends by microenvironment to identify potential differences in exposure between microenvironments and by aggregated indoor and outdoor environments. We will present means (SDs) for normal distributions and medians (IQRs) for nonnormal distributions. We will estimate the contribution of each microenvironment in the levels of exposure with a mass-time-ratio calculation [60] and integrate the time spent in each microenvironment with an integrated exposure calculation [61].

Assessment of the Role of Each Microenvironment in the Exposure Levels Measured

Because the data on exposures may be partly dependent (as some data were taken from the same microenvironments of the same participants), we will perform a multilevel analysis (linear mixed model) to evaluate the role of microenvironments in the levels of exposure measured for each pollutant of interest. Control variables, such as gender, age, and period of participation, will be included in the analysis: Y=levels of exposure in means per minute and Xi=microenvironment, gender, age, participation during or after the COVID-19 period.

Assessment of the Role of Measured Exposure in Perceived Exposure

Finally, we will test the potential relationship between measured and perceived exposures for each pollutant of interest with linear models, including several control variables, such as age, gender, participation during or after the COVID-19 period, and MHWs. More advanced methods, such as structural equation modeling, will be used to test for mediation between different kinds of exposures with perceived exposures through MHWs and potential interactions.

Ethical Considerations

The study protocol was approved by the Erasme-ULB Hospital Ethics Committee (approval number P2018/454; approval date November 6, 2018). Consent was obtained from all participants, who signed the information and consent forms. Participants had the option to opt out at any time during data collection. Each participant's data were associated with a pseudonym. A separate table linking each participant's personal information (eg, address and phone number) to their pseudonym was created on a fixed computer and made accessible to the researchers' team only. No compensation was offered to participants.

Results

Data collection was carried out from October 2020 to August 2022, with several interruptions due to the COVID-19 pandemic. In total, 490 people participated in the data collection. The databases have been gathered and cleaned. The next step is the data analysis, as described before. See Table 2 for the composition of the sample (n=459, 93.7%, of 490 participants who sent back the questionnaire).

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Table 2. Description of the sample (N=459).

Variables	Participants, n (%)
Gender	
Female	297 (64.7)
Male	162 (35.3)
Age group (years)	
18-29	24 (5.2)
30-39	143 (31.2)
40-49	151 (32.9)
≥50	141 (30.7)
Equivalized net household income	
<1500 euros (<US $1741)	145 (31.6)
1501-2500 euros (US $1742-$2901)	248 (54.0)
≥2501 euros (≥US $2903)	66 (14.4)
Education	
Secondary school (lower and upper levels)	36 (7.8)
University (bachelor's degree, master's degree, PhD)	423 (92.2)

Discussion

Summary

The objective of this study is to assess personal and simultaneous exposures to multiple pollutants (noise, $PM_{2.5}$, and ELF-MFs) over a normal weekday, with detailed exposure levels for the main microenvironments encountered (home, means of transportation, workplace).

In Brussels, daily averages of exposure to noise and air pollutants are freely accessible from the Brussels environmental agency (Bruxelles Environnement/Brussel Leefmilieu) [62] and the interregional environmental unit IRCELINE [63] websites, respectively. These exposures are measured by several fixed-site monitoring stations distributed in the region and then modeled to estimate levels of exposure in the entire region.

To the best of our knowledge, this study is the first assessment of Brussels' inhabitants' personal exposure to multiple pollutants. The results will provide estimates of personal as well as microenvironmental trends of exposure to noise, $PM_{2.5}$, and ELF-MFs for inhabitants of the areas studied. This is a first step toward a detailed picture of citizens' profiles of multiple-pollutant exposures and toward identifying the main microenvironments affected by these 3 pollutants in Brussels.

The study results will be transmitted to the relevant public institutions: the 3 municipalities in which the data collection took place, the Brussels environmental agency (Bruxelles Environnement/Brussel Leefmilieu), and the federal agency for public health Sciensano.

Every participant in the study has already received their personal results in the shape of averages per 24 hours of measurements. Many of them have shown a strong interest in knowing the levels to which they are exposed in their daily lives. This shows the importance of citizen science.

Strengths

The main strength of this study is that the exposure levels for several pollutants were collected at an individual level, which provides a much higher level of detail than extrapolated data. This, together with the microenvironment diary, the time of the day, and the profile of the participating population, will allow us to identify factors that can influence the levels of exposure, and therefore to highlight concrete targets to reduce exposures. As the measurements were taken during typical days of the week, they reflect the real-life exposures of the participants. Finally, the study focuses on 3 types of daily exposures measured simultaneously. This responds to the needs underlined by the European Environmental Agency to focus on multiple-pollutant exposures [2].

Limitations

The main limitation of the study is the lack of representativeness of the participants due to the nonprobabilistic sampling method. As participation in the data collection was voluntary and without any form of reward, the participating individuals appeared to show similar socioeconomic levels, especially in the level of education received. This makes it impossible to test for differences in socioeconomic status. Moreover, no causal relationship will emerge from this study because of its cross-sectional design.

Second, data collection took place only once, during a 24-hour period, for each participant. This will prevent us from drawing any conclusion about long-term exposure.

Moreover, to gather these many data on multiple-pollutant exposures at the individual level, the best option is often low-cost measuring devices. Although the noise and ELF-MF levels measured will be corrected with a simple correction

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factor, the levels of $PM_{2.5}$ measured with Airbeam 2 will need a corrective equation. Indeed, these devices show systematic underestimations of $PM_{2.5}$ concentrations. A corrective equation adapted to the equipment used in the study is being developed from linear models after colocations of the Airbeam 2 devices and a reference instrument (DustTrak 8534 TSI).

In our data collection for exposure to PM, we did not include a real-time measurement of physical activity, as has been done by other authors [25,64]. This would have allowed us to assess the inhalation rate and therefore the true exposure to air pollutants.

During this data collection, a new model of Airbeam was launched. Airbeam 3 seems to be significantly more efficient and accurate than Airbeam 2. This newer version would have potentially improved our data quality.

Finally, this study focuses on measured exposures and perceived exposures. A cohort design would be more relevant to explore potential links between multiple-pollutant exposures and health impacts.

Conclusion

This paper aims to describe, with a high level of detail, the methodology and protocol for the assessment of individual exposure to noise, PM, and ELF-MFs for 24 hours on a normal weekday, applied to 490 inhabitants of the Brussels Capital Region. We hope that this detailed description of the protocol will make it easily reproducible, foster further improvements to multiple-pollutant exposure methodologies, and permit a wider use of the database produced. The database created will be shared after the publication of the first results. Characterizing the multiple-pollutant exposures faced by individuals in different microenvironments in Brussels could lead to improved understanding of the sources of exposure and contribute to creating better policies to face multiple-pollutant exposures.

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The devices' brands mentioned in this paper are for information purposes only and do not constitute a recommendation on the part of the authors. Sciensano was our main partner among the BBEMG teams and was mainly involved in protocol design. A total of 3 Airbeam 2 devices were loaned from the Université Libre de Bruxelles (ULB) Environment and Mobility Service. Another 10 smartphones were loaned from Telenet. The EMDEX II devices were loaned from the French electricity transmission network Réseau de Transport d'Électricité (RTE France), and Sciensano and the EMDEX Lite versions were loaned from the Walloon Institut Scientifique de Service Public (ISSeP).

We would like to thank everyone who agreed to take part in the data collection, as well as all trainees, job students, and colleagues who helped with the field data collection: Bobin Océane, Brunin Fanny, Ennamsa Zineb, Fernandez Sanchez Javier, Noyer Charlène, Amandt Géraldine, Guadagnin Alexandra, Dzangue Kenne Achille, Van Bellinghen Sybille, Yamsi Noubissie Olive, Courard Antoine, Thuillier Marine, and Permanne Aline. We warmly thank the noise department of Bruxelles Environnement for their help in testing the quality of the smartphones' sound level measurements. Finally, we thank Julie Oppenheimer for her meticulous linguistic corrections.

Authors' Contributions

Conceptualization was handled by CB and ML; methodology by AOS, BV, and ML; investigation, data curation, and writing—original draft by AOS; funding acquisition by CB and EMDC; supervision by BV and CB; and writing—review and editing by AOS, BV, CB, EMDC, and ML.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Table of indicators for populations in the areas of interest: socioeconomic indicators and exposure to pollutants for 2019. PM: particulate matter.
[PNG File , 23 KB - resprot_v14i1e69407_app1.png]

Multimedia Appendix 2
Flyer of invitation in French and Dutch.
[PNG File , 607 KB - resprot_v14i1e69407_app2.png]

Multimedia Appendix 3

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Posts on social media.
[PNG File , 296 KB - resprot_v14i1e69407_app3.png]

Multimedia Appendix 4
Questionnaire for the ExpoHealth-1 study in French.
[PDF File (Adobe PDF File), 1795 KB - resprot_v14i1e69407_app4.pdf]

Multimedia Appendix 5
English version of the questionnaire for the ExpoHealth-1 study.
[PDF File (Adobe PDF File), 887 KB - resprot_v14i1e69407_app5.pdf]

Multimedia Appendix 6
Pictures showing how to wear the devices.
[PNG File , 235 KB - resprot_v14i1e69407_app6.png]

Multimedia Appendix 7
Testing suitcase for the measurement levels of ELF-MFs using EMDEX II and EMDEX Lite meters. ELF-MF: extremely low-frequency magnetic field.
[PNG File , 455 KB - resprot_v14i1e69407_app7.png]

Multimedia Appendix 8
Diary of microenvironments.
[PNG File , 75 KB - resprot_v14i1e69407_app8.png]

Multimedia Appendix 9
Procedure for participants (English).
[PDF File (Adobe PDF File), 198 KB - resprot_v14i1e69407_app9.pdf]

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Abbreviations

BBEMG: Belgian Bioelectromagnetics Group
CE: European Conformity
COPD: chronic obstructive pulmonary disease
ELF-MF: extremely low-frequency magnetic field
EU: European Union
MF: magnetic field
MHW: modern health worry
PHQ: Patient Health Questionnaire
PM: particulate matter
WHO: World Health Organization

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Protocol

Influence of Personal Traits, Social Relationships, and External Resources on the Development of Emotional Resilience in Children From East London: Protocol for an Observational Accelerated Longitudinal Cohort Study

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Abstract

Background: Emotional resilience is a dynamic process by which individuals may prevent, overcome, and thrive following challenging events. Emotional resilience can be defined as absence of negative outcomes (ie, symptoms of psychopathology) and/or the presence of adaptive outcomes (ie, well-being). Despite the wealth of research tracking the nature of and contributions to emotional resilience in adolescence and adulthood, there is a dearth of evidence on the nature of resilience and its development during preadolescent childhood despite this being an important preventative period for later mental health difficulties and a period when emotional experiences change.

Objective: Our primary study objectives are 3-fold: to explore how preadolescent children growing up in deprived areas of London may operationalize resilience, evaluate whether there are differences in the development or trajectories of resilience among our target population, and understand what contributes to resilience pathways over time. Additionally, our research aims to better understand the psychometric properties of resilience measures used in a preadolescent sample and assess the feasibility of developing a longitudinal cohort study of preadolescent children in East London.

Methods: We will conduct an accelerated longitudinal cohort study in primary schools across the broad geographical area of East London. The multimethod approach will span across 3 data collection arms: (1) child cognitive tasks and psychometric questionnaires in classroom settings, (2) teacher ratings, including teacher assessments of school mental health provisions, and (3) parent questionnaires. We aim to recruit approximately 1200 children aged 7-11 years at baseline across UK school years 3, 4, and 5. Our measures will span themes of resilience and mental health, as well as personal, social, and community resources available to the children. We will collect quantitative data via questionnaires from children, their parents, and school staff. We will collect qualitative data from the children through paper-based tasks.

Results: Study recruitment commenced in October 2022 and continued till December 2023. Baseline testing commenced in October 2022 and continued till December 2023; 873 students were enrolled at baseline. Follow-up is anticipated to continue at least annually until June 2027.

Conclusions: This study will assess the feasibility of conducting a longitudinal cohort study on preadolescent children in East London. Alongside evaluating the psychometric properties of resilience measures used in this age group, this study will explore how resilience develops in children across time and relate this to other outcome measures. By identifying how personal, social,

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and community resources may affect resilience in preadolescent children, we will enhance the understanding of how emotional resilience develops in preadolescent children, and future studies will be able to develop interventions to boost resilience by targeting young and diverse populations.

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KEYWORDS

mental health; school; primary school; scholar; student; feasibility; child; mental well-being; youth

Introduction

Background

Resilience is a dynamic process that refers to the capacity of individuals to prevent, overcome, and even thrive following the experience of challenging events [1]. Resilience outcomes can be captured through functioning in different domains, but here, we focus on emotional resilience, which can reflect the presence of an adaptive outcome (well-being, life satisfaction) or the absence of a negative outcome (mental illness) [2] following the experience of stress (internal or external), which can range from adverse childhood events to ongoing chronic stressors. Resilience can be conceptualized as an individual characteristic (eg, grit, perseverance, determination), but it also includes opportunities to harness and navigate access to culturally relevant external resources (eg, contact seeking, participation in community groups) [3]. Although there is a growing body of literature measuring and tracking emotional resilience (good mental well-being and absence of psychopathology following stress) and the factors and resources that contribute toward it in adolescence [4,5] and young adulthood [6,7], there is notably less research on the nature of resilience and how and when it develops at even earlier stages of development such as preadolescent childhood. This phase of development is important because efforts to enhance resilience here have preventative potential; children's emotional experiences are also changing, which may make them more receptive and amenable to acquiring, learning, and consolidating lifelong adaptive strategies for managing emotions.

A study of emotional resilience as it emerges across middle and late childhood into early adolescence and the factors that predict early resilience trajectories would be an invaluable addition to the field for several reasons. First, early signs of reduced emotional resilience could predict reduced well-being and increased mental health problems and their impact in youth, enabling us to identify those who are less well-equipped to manage the challenges and opportunities of adolescence—and in turn, across the lifespan. Second, understanding the factors contributing toward the development of emotional resilience could help with the development of preventative programs and the planning of resources to reduce negative outcomes across the lifespan. Finally, as resilience reflects "the capacity of a dynamic system to adapt successfully to disturbances that threaten system function, viability, or development," it is likely that its nature and core components vary in childhood compared to adolescence and adulthood. More specifically, preadolescent childhood is a period when emotional experiences are becoming more complex, varied, and at times, more intense [8]. These age-based differences may mean that the factors contributing to resilience change between childhood and adolescence, as they begin to stabilize and consolidate. Yet, these more enriched experiences may also allow a more plastic period for children to learn and practice adaptive strategies for managing stronger, more intense emotional experiences.

A better understanding of emotional resilience in mid-to-late childhood would therefore allow us to propose developmentally sensitive theories of resilience. The Youth Resilience Unit is based at Queen Mary University of London—in the diverse and relatively economically deprived area of East London. The university has a commitment to its location and surrounding community, and it is an area that is underresearched; therefore, it has a focus in terms of understanding the development of resilience in this often challenging sociocultural environment. In the 2021 census, East London was found to be much more culturally diverse in relation to the whole of England and Wales, with a much higher proportion of Asian (32.6% vs 9.3%), Black (14.6% vs 4%), mixed (5.6% vs 2.9%), and other (5.1% vs 2.1%) ethnicities and significantly lower in those who identified as White (42.1% vs 81.7%) [9]. In terms of economic activity, East London also has higher levels of self-employment or no employment (10.1% vs 7.9%), students with no employment (9% vs 6.3%), unemployed (4.7% vs 2.8%), and with much lower proportion of retirees (8.6% vs 21.6%). Having a young and the most diverse population in the United Kingdom while also being historically underserved in research makes East London the perfect location for the timely addition of a new cohort study.

The Development of Emotional Resilience (DEER) study is a new (accelerated) longitudinal cohort of preadolescent children (aged 7-11 years at recruitment) residing in East London to address questions relating to (1) the early development of resilience, (2) differences across individuals in resilience trajectories, and (3) factors/resources that contribute toward resilience trajectories.

Objectives

We have 3 primary objectives in the DEER study. These are to explore how preadolescent children growing up in deprived areas of London may operationalize resilience, evaluate whether there are differences in the development or trajectories of resilience among our target population, and understand what contributes to resilience pathways over time. Additionally, our research aims to better understand the psychometric properties of resilience measures used in a preadolescent sample and assess

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the feasibility of developing a longitudinal cohort study of preadolescent children in East London.

Methods

Recruitment and Study Design

Study Design

The DEER study is an observational cohort study that uses an accelerated longitudinal design. An accelerated longitudinal design recruits participants from different aged cohorts and follows them up [10], allowing both a within-time assessment of cross-age differences (cross-sectional age effect) and a cross-time assessment of within-person differences (longitudinal time effect). We will aim to enroll approximately 1200 children across UK school years 3, 4, and 5 (aged 7-11 years at recruitment) attending primary schools in East London. Children will be assessed at least once a year until they reach the end of their first term of secondary school. Parents/carers and teachers will be asked to complete questionnaires to complement children's self-reported measures annually.

Settings and Participants

Schools were contacted from a database containing all schools located in the broad geographical area of East London. Of the schools approached, a total of 10 primary schools in East London across 5 boroughs were recruited. These boroughs (Waltham Forest, Havering, Redbridge, Newham, and Tower Hamlets) include among the most densely populated, socioeconomically, and ethnically diverse areas in London [11].

Consenting Process

Prior to enrolment, research assistants conducted an in-school talk aimed at children from the targeted age group about the DEER study. After the talk, they distributed information sheets to children and their parents/carers. Initially the ethics committee recommended that the consenting process be opt in, that is, in addition to assent collected from children, parents or guardians needed to provide written consent in order for a child to take part. When it became apparent that enrolment was very low (by November 2022, only 6.9% (131/1898) of the consent forms were returned signed) and potentially biased in favor of parents and families who were better resourced, the ethics committee allowed for an opt out process. This means that for the 10 recruited schools, 6 are opt-in only, 1 began with opt-in processes but then agreed to participate using opt-out procedures, and the remaining 3 are opt-out only schools. For opt-out schools, parents were asked to return a form or contact the school or research team to indicate they did not want their child to take part, and then no data were collected from the opted-out children. The team liaised with schools to ensure that only students who met our inclusion criteria were enrolled in the study. Because most of the data are self-reported, some of our measures are not suitable for students who have been diagnosed with an intellectual disability disorder.

Participant Inclusion Criteria

In order to be enrolled in the study, children must be (1) attending a primary school in East London, (2) in school years 3 to 5 (at recruitment), (3) able to understand written and spoken English, (4) willing and able to provide assent, and (5) able to obtain parental/carer consent for opt-in schools.

Participant Exclusion Criteria

To participate in this study, children must not be diagnosed with an intellectual disability disorder.

Sample Size

Based on the planned analyses, the target recruitment was 1200 children in school years 3-5 (age 7-11 years). This sample size provides (1) 94% power to detect correlations as small as 0.10 (2-tailed), $P<.05$ between resilience measures and correlates and (2) the opportunity to compare groups high and low on a psychological or social factors (eg, top and bottom 20% of the sample on attention control) or on a resilience measure and to detect even small effects (eg, Cohen $d=0.30$) at 90% power, 2-tailed, $P<.05$.

Importantly, this sample size will enable us to use novel data-driven analytic approaches to identify subpopulations with different resilience trajectories across time and to assess the predictive value of different psychosocial variables (main effects, interactions, mediation effects) on resilient trajectories by using multinomial logistic regression. This will also allow us to use other advanced quantitative analyses, including structural equation modelling (to explore mediation and moderation effects), a combination of exploratory and confirmatory factor analysis (to verify the factor structure of selected questionnaires), and network analysis to explore associations between individual items of questionnaires.

Ethical Considerations

This study has been reviewed and approved by the Queen Mary University of London research ethics committee (QMERC22.251) on June 27, 2022. The study was prospectively registered in the International Standard Randomized Controlled Trial Number registry (ISRCTN14396374). Written assent from the children was obtained prior to any study procedures being conducted, and written consent was obtained from parents/carers if children were recruited via opt-in procedures. All participating schools gave written consent for participation via the school principals. To ensure anonymity, study data are stored in a deidentified format. Names and other identifying information (eg, addresses, contact details) are replaced by a unique participant ID number. To reduce the risk of disclosure, participant identifying information is stored separately from the research data, which will be saved on a secure server at the Youth Resilience Unit, hosted by Queen Mary University of London. To say thank you to the child's class for taking part, we offer participation in an interactive science show organized by the Centre of the Cell, Queen Mary University of London. The show is aimed at children in primary schools and is educational and fun. Whether the show is offered at the school or the school attends the Centre of the Cell is decided by the school. We compensate parents who complete annual questionnaires £10 (US $13.74) each time.

Procedures

Schools provided the team with students who met the inclusion and exclusion criteria and the students who the teachers felt

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would struggle to complete measures in a group setting. During data collection visits, researchers provide further information about the DEER study to pupils, and pupils provide written assent before completing a battery of validated questionnaires. All assessments intended for the child to complete are done in the classroom, mainly on an electronic tablet or pen and paper depending on the task, in small groups but with privacy. As the baseline assessment took up to 4.5 hours to complete, site visits were often split up across multiple sessions. Detailed information was collected about the demographics as well as the social, personal, and community factors affecting resilience in children. Trained researchers were present throughout all sessions to explain procedures and answer questions. All baseline questionnaires were administered between October 2022 and December 2023. Follow-up will be conducted at least annually until the first term of the secondary school (where possible). Parents or carers complete a set of web-based questionnaires for each year their child is enrolled in the study, for which they received financial reimbursement in the form of e-vouchers worth £10 (US $13.74). Teachers are also asked to complete paper questionnaires for each pupil enrolled in the study and to describe the provision of mental health services at the school.

Measures

Design of Measures

Most outcome measures are completed via tablet computers by using data management applications (eg, Qualtrics, Research Electronic Data Capture [REDCap]). Qualitative measures are completed on paper. A paper-based case report form is used to keep track of the completion of measures for each participant. This study takes place in schools with children, and so the assessment schedule may need to be adapted to fit the practical demands of the environment. As this is a longitudinal cohort, some measures may be dropped, and new measures may be introduced in response to new knowledge, new substudies, or changes to the factors of interest. This may include changing measures that children report to be too time-consuming or onerous to complete within the allocated time. All changes to the measures will be reviewed and approved by the ethics committee prior to implementation.

Measures About Resilience and Mental Health

Table 1 [12-24] shows the measures we used to analyze resilience and the mental health of the children.

Table 1. Measures about resilience and mental health.

Name of the scale	Brief description	Style of administration
Demographics	We will be asking children to report their gender, age, and height and weight will be measured	Tablet
The Stirling Children's Well-Being Scale [12]	Self-report questionnaire used to assess children's emotional and psychological well-being	Tablet
The University of California Los Angeles 3-Item Loneliness Scale adapted to 10-15-year old children and Office for National Statistics, United Kingdom, 1-item Direct Measure of Loneliness [13,14]	Self-report questionnaire used to measure feelings of loneliness and social isolation	Tablet
The Revised Child Anxiety and Depression Scale [15]	Self-report questionnaire providing an overall internalizing score and subscores assessing anxiety (social phobia, panic disorder, separation anxiety, generalized anxiety, obsessive-compulsive symptoms) and symptoms of depression	Tablet
The Children's Revised Impact of Event Scale [16,17]	A self-report questionnaire designed to screen for posttraumatic stress symptoms in children	Tablet
Body Mapping protocol [18]	Body mapping, an arts-based research method, adapted for use to understand how children make sense of their own stress and resilience	Pen and paper
Connor-Davidson Resilience Scale [19]	Self-report questionnaire assessing resilience	Tablet
The Revised Child and Youth Resilience Measure [20]	Self-report questionnaire assessing resilience	Tablet
The Student Life Satisfaction Scale [21,22]	Self-report questionnaire used to gauge an overall level of life satisfaction among children	Tablet
The Somatic Complaints List [23]	Self-report psychosomatic questionnaire used to identify how often children experience and feel pain	Tablet
The Self-Perception Profile for children [24]	Self-report questionnaire used to measure a school-age child's sense of general self-worth and self-competence in the domain of academic skills (scholastic competence, social competence, athletic competence, physical appearance, behavioral conduct, and global self-worth)	Tablet

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Measures About Resources, Psychological, and Social Factors

Table 2 [25-42] shows all the measures used for measuring the psychological factors, social factors, and the resources available to children.

Table 2. List of measures used for measuring the psychological factors, social factors, and resources available to children.

Name of the scale	Brief description	Style of administration
Short version of The Cognitive Emotion Regulation Questionnaire [25,26]	Self-report questionnaire assessing emotional regulation and cognitive copying strategies (self-blame, other blame, acceptance, planning, positive refocusing, rumination or focus on thought, positive reappraisal, putting into perspective, and catastrophizing).	Tablet
Social connectedness questionnaire [27]	A questionnaire exploring children's global social connectedness, within the domains of family, school, peer, and community connectedness.	Tablet
The Advanced Theory of Mind battery [28]	Selected tasks from a task battery used to measure children's ability on social reasoning and recognizing transgression.	Tablet
The Children's Leisure Activities Study Survey [29]	Self-report questionnaire used to gain an understanding about participants' engagement with leisurely activities, hobbies, and exercise.	Tablet
The Youth Spirituality Scale [30]	Self-report questionnaire assessing children's connections to God or higher power as well as their relationship with religious practices. For this purpose, we will look at the Relationship with God and Religious Practices subscales only.	Tablet
The Ambiguous Story Paradigm [31]	A task used to assess children's tendencies to select negative over benign interpretations of ambiguous situations.	Tablet
The Adapted Prospective Imagery Task [32]	A task used to assess children's capacity to imagine past and future positive and negative events in detail.	Tablet
Self-Esteem Matrix Task [33,34]	The task is used to measure how quickly participants can find an accepting face (smiling face) in a matrix of 15 rejecting faces. Slower reaction times on this task may suggest higher sensitivity to social threats.	Tablet
The Five Field Map [35]	Self-report questionnaire used to gauge the size of the children's social network as well as to uncover more details surrounding their relationships.	Pen and paper
The Pictorial Personality Traits Questionnaire for Children [36]	Self-report questionnaire that uses images to explore children's personality traits, underpinned by the Big 5 Personality Traits theory.	Tablet
The approach-avoidance task [37]	A task used to index children's approach and avoidance of emotional faces (angry vs happy).	Tablet
The Youth Life Orientation Test [38]	Self-report questionnaire assessing optimism and pessimism.	Tablet
The Scrambled Sentences Task [39,40]	A task used to assess interpretations of ambiguous sentences.	Tablet
Door Opening Task [41,42]	A computerized response perseveration task aimed at studying reward dominance in children.	Tablet
Words for Feeling Questionnaire	Used to measure children's emotional vocabulary. Children are asked to come up with different synonyms of emotional words (eg, surprised, happy, scared).	Pen and paper

Parents'/Carers' Measures

Table 3 shows the list of measures that parents/carers will complete about their children [43-49].

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Table 3. List of measures that parents/carers will complete about children.

Name of the scale	Brief description	Style of administration
Demographics and socioeconomic status questionnaire	Questions will ask about the child's date of birth, sex, ethnicity, country of birth, and number of siblings. We will also include questions about socioeconomic status, child's religion, family migration status, family structure (ie, foster family, single parent, nuclear family), carers' relationship to the child (ie, biological, foster or adoptive mother or father), household number, the child's birth order, diet type they primarily follow, if the child has ever been in the care of local authority (ie, in foster or residential care), and if the child or anyone in their immediate family has ever been formally diagnosed with a mental health disorder. Socioeconomic status questions will include items relating to the carers' education, occupation, material possessions, whether the child receives free school meals, type of accommodation, and post code (to ascertain material deprivation index).	Online platform
Patient Health Questionnaire 15 [43]	These measures link to physical health problems, including any chronic illness or disability, pain, fatigue, and sleep. For the Patient Health Questionnaire, we will only use questions relevant to physical health problems.	Online platform
Child Health Utility instrument 9D [44]	The Child Health Utility instrument is a pediatric generic preference-based measure of health-related quality of life—we will be using a proxy version for parents to complete. We will also be using questions formulated in-house to ascertain key factors such as hospitalization rates and birth weight.	Online platform
The Strengths and Difficulties Questionnaire [45]	The questionnaire asks about the parents or carers report on their child emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, and prosocial behavior.	Online platform
Arts Council Questionnaire The Taking Part Survey [46]	The survey collects information about children and adults' attendance at a wide variety of arts events, museums, galleries, libraries, and heritage sites. It also asks about participation in creative activities and sport and motivations and barriers to engagement.	Online platform
The Children's Life Events Inventory [47]	Questionnaire used to identify the number of significant life events experienced by the child.	Online platform
The Parenting Styles and Dimensions Questionnaire [48]	Questionnaire used to assess parenting styles that we will be using in the short version of this scale. It measures 3 types of parenting styles: authoritative, authoritarian, and permissive parenting.	Online platform
Parental report of their children social media usage	Questionnaire asking about children's social media use.	Online platform
The Child version of the Eating Disorder Examination [49]	The Child version of the Eating Disorder Examination questionnaire provides assessment of eating disorder psychopathology related to anorexia nervosa, bulimia nervosa, and binge-eating disorder; however, the Child version of the Eating Disorder Examination questionnaire-8 items does not assess symptoms of avoidant/restrictive food intake disorder, pica, or rumination disorder. Originally, this is a self-report questionnaire, but we will use it as a parent/carer report format.	Online platform

Teachers' Measures

Table 4 [45,50] shows the list of measures that teachers will complete about their children.

Table 4. List of measures that teachers will complete about children.

Name of the scale	Brief description	Style of administration
The Strengths and Difficulties Questionnaire [45]	The questionnaire asks about the teacher's report on students' emotional symptoms, conduct problems, hyperactivity/inattention, peer relationship problems, and prosocial behavior.	Pen and paper
Amended: Questionnaire about school resources for mental health support [50]	The questionnaire will ask about all the different resources available to students that are provided by the school for mental health support. Questions about creative arts therapies have been added.	Online platform

Data Analysis

Planned Analyses

This study will explore the association between mental health and resilience in primary school children while assessing the impact of the psychological factors, social factors, and resources available to them. We will also assess the resilience scores in this age group, the psychometric properties, and how these scores might predict mental health problems in relation to the psychological factors, social factors, and resources available. As our dataset will contain multiple possible combinations of the predictors and different ways of operationalizing resilience (even across time), more specific hypothesis-driven analysis

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will be individually preregistered on the Open Science Framework website prior to any analysis. A key analysis will include assessing the impact of the opt-in versus opt-out recruitment process on systematic selection bias. Where relevant and if this overall analysis is significant, we will include this as a sensitivity analysis on a paper-by-paper basis, and this will be stated in the analysis preregistration.

To assess the feasibility (uptake, retention) of developing a longitudinal cohort study of preadolescent children in East London, we will record information on our school recruitment process: (1) number of schools contacted, (2) number of schools who responded with interest, (3) number of schools who had an initial meeting with us, (4) number of schools where we reached out to parents/carers, (4) number of schools where we reached out to children, (5) number of children we spoke to, (6) number of parents/carers who provided consent, (7) number of children who provided assent, (8) number of children who completed at least one assessment, (9) number of parents/carers who completed at least one assessment, and (10) mean number of assessments completed.

Missing Data

Where data are missing, these will either be imputed, or the participant will be removed from the analysis as appropriate for the statistical test being conducted. Because this method will vary according to the nature of the hypotheses and the statistical tests being conducted for any one individual paper, it cannot be stated now, but this will be included in the Open Science Framework preanalysis registration as appropriate (on a paper-by-paper basis). As there is no source documentation for the measures collected directly onto tablets, data cannot be entered during quality assurance checks. Data entry rules will make it very difficult for data to be missed during entry.

Results

Barts Charity awarded a grant to the Faculty of Medicine and Dentistry, Queen Mary University of London, on March 30, 2020, to establish the Youth Resilience Unit. The Unit was established on March 1, 2021. This core funding also provided support for this study. Ethics approval (QMERC22.251) was granted by the Queen Mary research ethics committee on June 27, 2022. Study recruitment commenced from October 2022 and continued till December 2023. Baseline testing commenced in October 2022 and continue till December 2023; 873 students were enrolled at baseline. Follow-up is anticipated to continue at least annually until June 2027. Baseline and follow-up questionnaires will provide evidence regarding the acceptability and feasibility of conducting a longitudinal cohort study in primary schools in East London.

Discussion

Overview

Resilience is the ability to overcome adverse events and experience positive outcomes. Although the development of emotional resilience has been explored in adolescence, there is a dearth of evidence on the nature of and development of resilience among preadolescent populations.

The DEER study aims to explore how preadolescent children define resilience, track the development of resilience, and asses the contributory factors to differences in resilience pathways across time. It is hoped that the results of our study will allow us to work on more developmentally sensitive theories of resilience and propose future interventions to reduce negative outcomes following adverse events in childhood. The core analysis of the study will focus on investigating the trajectories of resilience across time and exploring its links with mental and physical health and other child characteristics. However, as the planned analysis is highly flexible and responsive to changes in the field, it is not possible to speculate meaningfully about this here, but all analyses will be registered on the Open Science Framework website prior to any analysis being conducted.

Strengths of This Study

We believe this is one of the first longitudinal cohort studies exploring the factors associated with the development of emotional resilience in primary school-age children. In our measures, we also assess multiple risk and protective factors from individual traits (including cognitive information processing and lifestyle factors) to social and community resources. We also employ mixed methods, including quantitative and qualitative data, as well as experimental methods in cognitive tasks.

This provides a unique opportunity to understand the factors involved in the early stages of how resilience emerges and develops as well as the impact of these various factors over time. Our sample is also notable in being one that includes children growing up in socioeconomically deprived and marginalized communities. These children are not only typically underrepresented in mental health research, but they may also face multiple chronic stressors (poverty, housing difficulties, discrimination) where resilience—individual traits and external resources—are especially relevant in navigating these daily challenges. The flexible nature of the cohort measures allows us to respond to early findings and new information or data in the field as this is published.

Weaknesses in This Study

This study relies heavily on self-report from young children, and it is not always clear how reliable or valid this method is in children of this age. We have tried to balance this by including measures by teachers and parents. However, parents are notoriously difficult to engage in this process, and this may result in lower levels of data from parents. Teachers also may be less responsive due to their many responsibilities and limited time to complete assessments. The large number of child assessments may also cause participant fatigue, particularly in a school setting. This may lead to nonrandom missingness in the results.

Dissemination Plan

The results of this study will be published in academic journals and presented at academic conferences throughout the life of the project. We will also use the Youth Resilience Unit and the Unit for Social and Community Psychiatry social media accounts to further disseminate the research results. A brief debriefing report will be prepared for all participants,

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parents/carers, and schools, which will be circulated when the results have been prepared. Oral presentations of the key findings will also be offered to all participants, parents/carers, and schools.

All dissemination activities will draw on established research and clinical networks in our partners. Dissemination will be conducted with consideration of the safe data and safe statistical analysis protections. No individual level data will be published that could be linked back to a person or institution, and all output will be assessed to determine if there is a risk of disclosure through things such as single frequency counts in tables or identifying information in any qualitative fragments. In such cases, data will be censored, obscured, or changed to protect individual confidentiality. Where possible, any sensitive or difficult findings will be discussed with the participants or relevant institution if this is about a clinic or similar setting, prior to publication to avoid any inadvertent reputational harm or negative consequences of the findings being made public.

Acknowledgments

We extend our gratitude to the students, parents, and schools who agreed to take part in this study. This work was funded by a Barts Charity grant of £2.8 million (US $3.82 million) awarded to Queen Mary University of London on March 30, 2020, which supported the establishment of the Youth Resilience Unit and covers core costs as well as funding for the cohort study (MRC&U0042). The Barts Charity had no role in the design of the study. The design, conduct, collection, and analysis of the data that will be derived from this research and the preparation of the manuscript are the responsibility of the authors.

Data Availability

Fully anonymized data arising from the study and any other study materials will be available on reasonable request from the study principal investigators (j.lau@qmul.ac.uk and d.ougrin@qmul.ac.uk) governed by a signed data sharing agreement after the publication of the findings of the study by the research team.

Authors' Contributions

Conceptualization: JYFL and DO
Funding acquisition: JYFL and DO
Methodology: JYFL and DO (lead), FvL, MN, DP, IH, AM, EK, JM (supporting)
Resources: JYFL and DO
Supervision: JYFL and DO
Writing – original draft: FvL (lead), MN, and DP (supporting)
Writing – review and editing: FvL (lead), MN, DP, IH, AM, EK, JM, DO, and JYFL (supporting and agreed final version)

Conflicts of Interest

None declared.

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Abbreviations

DEER: Development of Emotional Resilience
REDCap: Research Electronic Data Capture

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Protocol

Ligation of the Pancreatic Stump With Quantified Force During Distal Pancreatectomy for Postoperative Pancreatic Fistula: Protocol for a Single-Center Nonrandomized Controlled Clinical Study

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Abstract

Background: The incidence of postoperative pancreatic fistula following distal pancreatectomy is as high as 30%-50%. Postoperative pancreatic fistula can be a major cause of perioperative morbidity, resulting in prolonged hospital stays and increased health care costs. The management of the pancreatic stump is one of the key factors influencing the occurrence of postoperative pancreatic fistula after distal pancreatectomy, but the optimal management approach remains debatable. The main methods for pancreatic stump closure include manual suturing and stapler closure. However, both methods are associated with a high risk of postoperative pancreatic fistula, which may be related to the balance between providing sufficient pancreatic duct burst pressure and ensuring blood supply to the stump. Ligation of the pancreatic stump has been attempted to reduce the risk of postoperative pancreatic fistula following distal pancreatectomy, but its efficacy remains limited by the challenge of achieving the optimal ligation force.

Objective: This study aims to investigate whether ligation of the pancreatic stump with a quantified force can decrease the risk of postoperative pancreatic fistula following distal pancreatectomy.

Methods: In this nonrandomized controlled clinical study at a tertiary center in China, the major eligibility criterion is the presence of lesions planned for distal pancreatectomy. Sixty patients will be allocated to the experimental or control group according to their choice. Recruitment for either group will be discontinued upon reaching the predefined sample size of 30 participants. In the experimental group, the pancreas will be ligated 5 mm from the pancreatic stump with a quantified force to provide a pancreatic duct burst pressure of approximately 40-70 mm Hg. The ligation force will be provided by a 3.2-mm-diameter silicone ring. During pancreatic stump ligation, this silicone ring will be stretched to 15 mm, generating an applied force of 1.3 N. The pancreas will be severed using energy-based devices before or after the ligation. In the control group, the pancreatic stump will be managed by manual suturing or stapling closure according to the surgeon's clinical judgment and preference. Postoperative regular follow-up examinations will be conducted. The primary outcomes include postoperative pancreatic fistula and postoperative hospital stay, and the secondary outcomes include intra-abdominal infection, incision infection, and postoperative treatment costs. The primary and secondary outcomes of patients in this cohort will be statistically compared using appropriate tests.

Results: This study started in February 2025, and the recruitment period is from February to September 2025.

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Conclusions: This protocol proposes a novel approach for pancreatic stump management aimed at preventing postoperative pancreatic fistula following distal pancreatectomy. The research team established the optimal ligation force for the pancreatic stump to ensure adequate burst pressure for the pancreatic duct while preventing acute stump necrosis, thereby theoretically reducing the risk of postoperative pancreatic fistula.

Trial Registration: Chinese Clinical Trial Register ChiCTR2500097781; https://www.chictr.org.cn/showproj.html?proj=247008

International Registered Report Identifier (IRRID): DERR1-10.2196/74018

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KEYWORDS

pancreatic surgery; distal pancreatectomy; pancreatic stump ligation; quantified ligation force; postoperative pancreatic fistula

Introduction

Distal pancreatectomy is the primary surgical procedure for treating inflammatory lesions as well as benign and malignant tumors in the pancreatic body and tail. Postoperative pancreatic fistula (POPF) is a common and severe complication of distal pancreatectomy, with an incidence rate of approximately 30%-50% [1,2]. POPF can lead to delayed gastric emptying, intestinal obstruction, hemorrhage, wound infection, intra-abdominal abscess, and sepsis. These complications can further increase hospital stay and medical expenses and may potentially result in death [3,4].

To reduce POPF, surgeons have explored numerous strategies, with the aim of achieving better outcomes through improved patient management and advanced techniques [5-10]. The closure technique used for the stump is a crucial factor influencing the occurrence of POPF, and 2 methods are primarily used at present: manual suturing and stapling closure [5,6]. Stapling devices are often used due to their simplicity and convenience, but they may not effectively close the pancreatic stump when the pancreas is hard or thick. In such cases, manual suturing is often the sole option. Additionally, surgeons have investigated techniques such as wrapping the stump with mesh [7], saline-coupled radiofrequency ablation [10], pancreaticojejunostomy [9], preoperative pancreatic duct stenting [11,12], and the application of fibrin patches to the stump [8]. Unfortunately, none of these techniques have significantly reduced the risk of pancreatic fistula. In their expert consensus on the management of the pancreatic stump during distal pancreatectomy in 2022, the International Study Group on Pancreatic Surgery stated that both manual suturing and stapling closure have their respective advantages, and both methods are associated with an equal risk of pancreatic fistula. The use of energy devices or additional biomaterials to seal the pancreas or the combined use of these methods also does not reduce the incidence of pancreatic fistula [13].

Closure of the main pancreatic duct (MPD) is a key step to prevent pancreatic fistula. However, stapling closure may not provide a sufficiently high burst pressure for the pancreatic duct, even when the pancreatic stump is adequately closed. Under physiological conditions, the pancreatic duct pressure ranges from 3 to 31 mm Hg [14,15], but the burst pressures provided by approximately half of the stapling devices for pancreatic duct closure are below 31 mm Hg [16,17], leading to pancreatic fistula in some patients. Manual suturing can provide a burst pressure of up to 400 mm Hg for the pancreatic duct through sutures, but the high pressure on the tissue can cause tissue necrosis and new pancreatic duct proliferation, resulting in pancreatic fistula [17]. Additionally, identification of MPD can be difficult after pancreatic transection in some patients, and empirical suturing increases the risk of pancreatic fistula.

Ligating the pancreatic stump is another technique for the closure of the pancreatic stump. Ligation of the pancreatic tissue proximal to the stump can provide sufficient burst pressure for the pancreatic duct. However, ligation may also lead to acute tissue necrosis and pancreatic duct regeneration, similar to suturing [18]. To address this issue, the project applicant quantified the ligation force to achieve a burst pressure of approximately 40-70 mm Hg for the pancreatic duct. This burst pressure is much higher than the maximum pressure of the pancreatic duct under physiological conditions but lower than the average arterial pressure under physiological conditions. Therefore, theoretically, the use of this burst pressure can avoid the direct leakage of the pancreatic juice from the pancreatic duct while reducing the risk of pancreatic stump acute necrosis by providing partial blood supply to the pancreatic stump, preventing POPF caused by the necrosis-proliferation process of the pancreatic stump.

Thus, we hypothesized that the rate of POPF in patients who undergo pancreatic stump ligation with a quantified force would be lesser than that using other closure techniques. To validate this hypothesis, we launched this clinical trial. According to the Evidence Map of Pancreatic Surgery, this is the first trial of its kind [19].

Methods

Study Design

The methods have been designed and are reported according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) reporting guidelines (Multimedia Appendix 1) [20].

Study Setting

This nonrandomized controlled clinical study is being conducted at a tertiary center in China. The study population consists of patients who are scheduled to undergo distal pancreatectomy. Experienced surgeons will determine the eligibility of the patients and obtain informed consent from the patients (see online supplemental materials). An overview of the protocol is shown in Figure 1.

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Figure 1. Flowchart of the study.

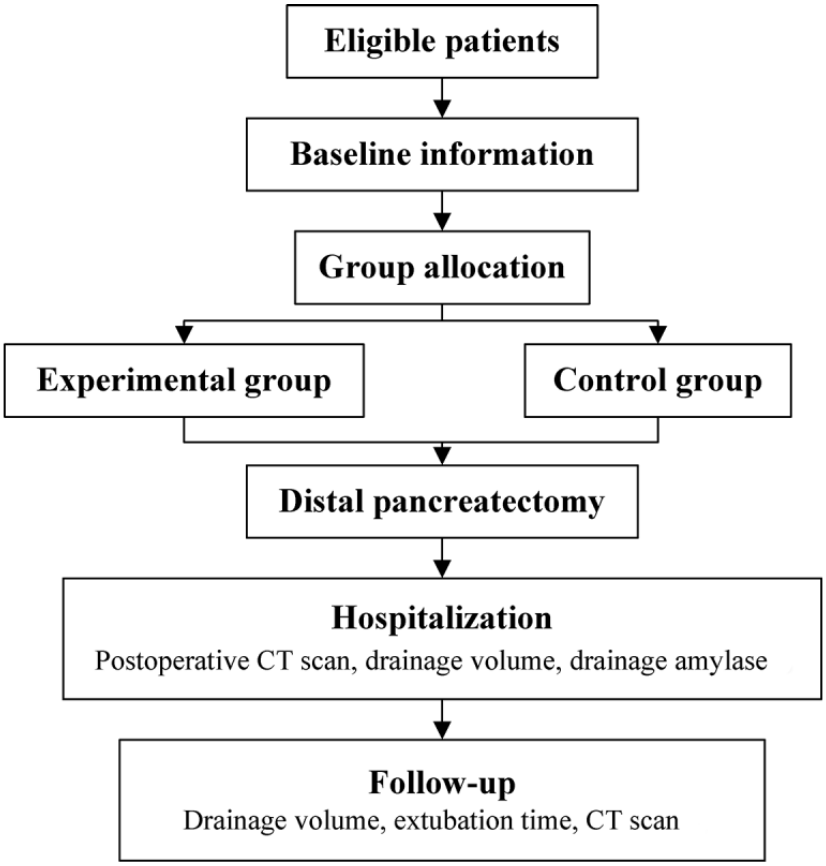

End Points

Primary End Points

The primary end points are POPF and postoperative hospital stay.

Secondary End Points

The secondary end points are intra-abdominal infection, incision infection, and postoperative treatment costs.

Definitions

In this study, POPF will be identified using the definition proposed by the International Study Group of Pancreatic Surgery [21]. Intra-abdominal infection and incision infection will be evaluated on the basis of the Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. Severe adverse events are events rated grade 3 or higher using CTCAE. Postoperative hospital stay refers to the interval from the day of surgery to discharge. Postoperative treatment costs encompass all hospitalization expenses incurred from the patient's return to the ward after surgery until discharge, measured in yuan renminbi.

Patient Eligibility

Inclusion Criteria

The inclusion criteria were as follows.

1. Patients aged between 18 and 75 years.
2. Patients scheduled to undergo distal pancreatectomy (including the body and tail of the pancreas) with the intended pancreatic transection line located on the left side of the portal vein.
3. Patients who fully understand this study, agree to participate in it voluntarily, and sign the informed consent form.

Exclusion Criteria

The exclusion criteria were as follows.

1. Patients with a history of previous pancreatic surgery.
2. Patients requiring additional surgical procedures for the residual pancreas.
3. Patients with proximal pancreatic duct obstruction and planned anastomosis between the residual pancreas and the digestive tract.
4. Patients using long-acting somatostatin analogues during the perioperative period.
5. Patients who are judged by the investigator to be unsuitable for participation in this study.

Group Allocation

Patients will be allocated to the experimental or control group according to their choice. Recruitment for either group will be discontinued upon reaching the predefined sample size.

Study Interventions

Surgical Approach

The laparoscopic approach will be prioritized for all enrolled patients. Open conversion will be initiated upon the surgeon's judgment of laparoscopic feasibility.

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Evaluation of the Texture of the Pancreas

After the baseline visit and admission, eligible participants will be classified by the surgeon and the first assistant in terms of the texture of the pancreas (soft, medium, hard) during the operation. In case of disagreement between the surgeon and first assistant, a third surgeon will be invited to make the decision.

Ligation of the Pancreatic Stump for the Experimental Group

The pancreas will be ligated 5 mm from the pancreatic stump before or after severing the pancreas. To achieve proper ligation force, a predetermined force will be generated with a force device outside the body, and the deformation length of the implantable silicone/rubber will be recorded. When performing ligation in vivo, the specific ligation force will be reproduced by reproducing the deformation length measured in vitro. In this study, the ligation force will be provided by a 3.2-mm-diameter silicone ring composed of silicone and barium sulfate (Gnovo Inc). As shown in Figure 2, this silicone ring will be stretched to 15 mm, generating an applied force of 1.3 N, and the tension will be transmitted to 2 strands of size-0 braided nonabsorbable silk suture (Ethicon, Inc) during pancreatic stump ligation. No additional ligation of MPD will be performed.

Figure 2. The silicone ring and the nonabsorbable silk suture used for the ligation of the pancreatic stump.

Pancreatic Stump Management for the Control Group

The stapler technique will be the preferred method for pancreatic transection. No additional ligation of MPD will be performed. When surgeons determine that stapler use is unsuitable for a particular patient, the pancreatic stump will be managed by manual suturing. Selective ligation of the MPD will be contingent upon its identification following pancreatic transection.

Distal Pancreatectomy

Distal pancreatectomy will be performed according to the standard process.

Postoperative Management

General clinical treatment will be conducted in both groups. The patient's body temperature and drainage volume will be recorded daily. The amount of amylase concentration in the drainage fluid as well as the blood will be routinely measured. Drains will not be removed before postoperative day 3. After postoperative day 3, drains will be left in place until the amylase concentration is less than 3 times the upper limit of normal serum amylase concentration, the output is less than 20 mL/day with an amylase concentration less than 3000 U/L, or the output is less than 5 mL/day.

Follow-Up

For 3 months after surgery, patients will be required to undergo regular follow-up assessments every 2 weeks through outpatient or telephone consultations. The following information will be collected during each follow-up assessment: basic information and the general condition of the patient, whether the patient has been extubated (if the patient has not been extubated, the recent drainage condition will be recorded), and recent medical interventions. Laboratory tests and imaging examinations will be performed at the surgeon's discretion.

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Ethical Considerations

This study was approved by the ethics committee of Union Hospital, Tongji Medical College, Huazhong University of Science and Technology (approval 2024-0833-02). Written informed consent will be obtained from all patients prior to the initiation of study procedures. Participants aged 18 to 75 years will receive a comprehensive explanation of the study's background, objectives, methodology, potential benefits, risks, and any possible inconveniences. Their rights as research participants will also be clearly outlined. All questions will be addressed thoroughly by the research team to ensure full understanding before consent is given. Participation in this study is entirely voluntary. Consent forms must be signed by the participant, or in cases involving minors or individuals unable to provide consent, by a parent or legally authorized representative. A model informed consent form has been provided and uploaded in Multimedia Appendix 2. This study will be conducted in accordance with the approved protocol and the ethical principles set forth in the current version of the Declaration of Helsinki. All participants were provided with surgical accident insurance. The research team will cover all the treatment costs for study-related complications as assessed and approved by the ethics committee. The data collected in this study will be de-identified. The results will be submitted for publication in an international peer-reviewed journal with anonymized data.

Statistical Methods

Hypothesis

Null Hypothesis

The rate of POPF in patients who undergo pancreatic stump ligation is not lesser than that using other closure techniques.

Alternative Hypothesis

The rate of POPF in patients who undergo pancreatic stump ligation is lesser than that using other closure techniques.

Sample Size Calculation

Based on published clinical studies on the incidence of pancreatic fistula [6-8] using other closure techniques, the incidence of POPF was set at 40%. On the basis of the results of previous animal experiments, the expected incidence of POPF in the ligation strategy is 5%. Using the formula $n = 2p\,q\,(Z_\alpha+Z_\beta)^2/(p1-p2)^2$ for sample size calculation with the probability of type I error of .05 and the statistical power of .90, we estimated that 30 participants should be included in each group.

Statistical Analysis

All statistical analyses will be conducted using SAS software (version 9.3; SAS Institute). Normality tests will be conducted for measurement data, describing the mean, standard deviation, median, quartiles, minimum, and maximum values based on the distribution type. Count data will describe the number and percentage of cases in each category. The rate effect indicator will reflect the effective rate and 95% CI. Missing values will not be filled in for research purposes and will not be included in the calculation of percentages unless otherwise specified. Stratified analyses will be conducted on the basis of pancreatic texture. A logistic regression analysis for POPF will be performed to identify its independent risk factors.

Results

The version number and date of the protocol are version 2.0 and January 22, 2025, respectively. Participant recruitment for this study commenced in February 2025 and will conclude when the estimated sample size is achieved (in or around September 2025); thereafter, the follow-up assessments will be completed (in or around December 2025). No specific funding was received for this study.

Discussion

Overview

POPF after distal pancreatectomy remains an unresolved issue [13,22]. The existing stump-closure techniques primarily include manual suturing and stapling, both of which carry a high risk of POPF. Animal studies suggest that the balance between pancreatic duct burst pressure and pancreatic tissue necrosis may be a key factor influencing the occurrence of POPF after distal pancreatectomy. We attempted to address this issue by ligating the pancreatic stump with an appropriate quantified amount of force.

Although suturing MPD has been shown to reduce the risk of POPF [23,24], MPD is difficult to ligate due to its location within the pancreatic parenchyma, and MPD is often difficult to locate during surgery. Therefore, the method adopted in this study involves ligating the pancreatic stump rather than MPD. Through experiments on specimens from patients with pancreatic space-occupying lesions, we found that for pancreas with soft, medium, and hard textures, ligation forces of 2.5 N using 4 strands of size-0 braided nonabsorbable silk suture or 1.3 N using 2 strands of size-0 braided nonabsorbable silk suture were sufficient to achieve a pancreatic duct burst pressure of 40-70 mm Hg. Therefore, we initiated a prospective clinical study on this pancreatic stump treatment technique, which yielded the optimal pancreatic duct burst pressure by quantifying the ligation force. The aim of this study was to determine whether this technique can reduce the risk of POPF and provide new insights into pancreatic stump closure.

Theoretically, potential surgery-related adverse events for participants of the new approach may primarily include pancreatic fistula, hemorrhage, and pancreatitis. All adverse events occurring during both the intervention and follow-up periods will be documented and submitted to the ethics committee regularly. Should the predefined criteria be met, immediate actions will include either termination of an individual participant's trial eligibility or discontinuation of the entire study.

Pancreatic texture and patient age are important factors influencing the occurrence of POPF. To align our study with real-world clinical scenarios, we will not restrict enrollment to patients with specific pancreatic texture characteristics. Instead, we will employ a stratified analysis based on pancreatic texture during data interpretation to mitigate the potential bias arising

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from variations in tissue consistency. Furthermore, to reduce the confounding effect of age on the risk of POPF, we will limit participant enrollment to individuals younger than 75 years [25,26].

Strengths of This Study

The strengths of the study can be summarized as follows. This study uses a prospective design to assess a new strategy for managing the pancreatic stump during distal pancreatectomy. The new strategy will provide a sufficiently high pancreatic duct burst pressure while preserving partial blood supply to the pancreatic stump.

Limitations

One of the primary limitations of this study is its nonrandomized controlled design. Since this study investigates a novel pancreatic stump management technique that has not yet undergone large-scale clinical validation, the institutional ethics committee recommended an enrollment approach based on patient choice to ensure patient autonomy. Furthermore, the involvement of 2 distinct surgical techniques precluded blinding of the investigators. These factors may introduce performance and detection biases into the study. On the basis of the findings of this investigation, the research team will evaluate the need for subsequent randomized controlled clinical trials to address these methodological constraints. The relatively small sample size is another limitation of this study. The inherent variability among the included cases may prevent confirmation of the study hypothesis. We will make a data-driven decision regarding potential sample size expansion.

Acknowledgments

The authors gratefully acknowledge the support for this study provided by the Department of Pancreatic Surgery, Union Hospital, Tongji Medical College, Huazhong University of Science and Technology. No generative artificial intelligence tools, including ChatGPT or similar language models, were used in the preparation or writing of this manuscript.

Data Availability

All data acquired during this trial will be made available to the involved investigators and ethics committee members for monitoring, audits, and inspections throughout the study. The study results will be published in an open-access format. Data will also be available upon reasonable request to the corresponding author via email at shanmiaogou@hust.edu.cn.

Authors' Contributions

Conceptualization: SG (lead), HW (equal), TY (equal)
Data curation: LC
Formal analysis: SG (lead), YY (supporting)
Investigation: JX (lead), MY (equal), TP (equal)
Methodology: LC
Project administration: SG (lead), LC (equal), TP (supporting)
Resources: HW (equal), TY (equal)
Supervision: SG
Validation: LC
Writing – original draft: LC (lead), JX (supporting), MY (supporting), YY (supporting)
Writing – review & editing: SG (lead), HW (supporting), TY (supporting)

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 209 KB - resprot_v14i1e74018_app1.pdf]

Multimedia Appendix 2
Informed consent form.
[DOC File , 56 KB - resprot_v14i1e74018_app2.doc]

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Abbreviations

CTCAE: Common Terminology Criteria for Adverse Events
MPD: main pancreatic duct
POPF: postoperative pancreatic fistula
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Sustained Virological Response as a Surrogate Marker for Mortality, Decompensated Cirrhosis, or Hepatocellular Carcinoma in People With Chronic Hepatitis C Virus Infection Treated With Direct-Acting Antivirals: Protocol for a Bayesian and Causal Mediation Analysis

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Abstract

Background: Sustained virological response (SVR) is commonly used as a marker of treatment success in people with chronic hepatitis C virus (HCV) infection. However, there is uncertainty on whether SVR is a validated surrogate marker of successful chronic HCV infection treatment.

Objective: This research project aims to evaluate whether SVR is a good surrogate for all-cause mortality, decompensated cirrhosis, any specific aspect of liver decompensation (jaundice, ascites, hepatic encephalopathy, hepatorenal syndrome, or variceal hemorrhage), or hepatocellular carcinoma in people with chronic HCV infection eligible to receive direct-acting antiviral drugs.

Methods: We will use two ongoing systematic reviews on the effectiveness of direct-acting antiviral drugs in chronic HCV infection as our data sources. The analysis plan is to estimate the regression coefficients or between-studies correlation between SVR and an event using three different Bayesian approaches with OpenBUGS, as outlined in the guidance by the evidence synthesis unit, and estimate the average proportion of the effect mediated through SVR by causal mediation analysis using R.

Results: As of June 19, 2025, the two systematic reviews (one on randomized clinical trials and one on observational studies) on the effectiveness of direct-acting antiviral drugs in chronic HCV infection are ongoing.

Conclusions: We will use the German Institute of Quality and Efficiency in Health Care criterion for surrogacy for cancer, with at least 50% of the treatment effect mediated through SVR, but the information will be reported in a way that allows people to interpret the information using their own criteria.

(JMIR Res Protoc 2025;14:e68113) doi:10.2196/68113

KEYWORDS

surrogate outcome; chronic hepatitis C infection; HCV; sustained virological response; SVR; direct-acting antiviral drugs

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Introduction

Hepatitis C is a viral infection of the liver that can lead to liver inflammation [1]. Most hepatitis C virus (HCV) infections extend beyond the first 6 months (acute phase) and become chronic infections [1]. An estimated 50 million people have chronic HCV infections globally [2]. Every year, 1 million people acquire new chronic HCV infections [2].

Major clinical complications of chronic HCV infection include cirrhosis, hepatocellular carcinoma (primary liver cancer), and death resulting from the complications [3]. Decompensated cirrhosis refers to jaundice, ascites, hepatic encephalopathy, hepatorenal syndrome, or variceal hemorrhage resulting from cirrhosis [4]. These complications often result in death [4]. Approximately 240,000 people die from chronic HCV infection globally, mainly due to cirrhosis and hepatocellular carcinoma [2].

Direct-acting antiviral drugs are currently the recommended treatment for people with chronic HCV infection [3]. In our Cochrane systematic review of direct-acting antiviral treatment in chronic HCV infection, sustained virological response (SVR; undetectable HCV RNA after treatment completion) was the commonly used indicator of treatment success in 32 of the 138 randomized clinical trials included [5]. While there is no consensus on the time period after treatment completion during which HCV should be undetectable, the European Association for the Study of the Liver mentions that the relapse of HCV infection beyond 6 months is low, implying that SVR can be considered a stable result after 6 months [3]. Most trials in the Cochrane systematic review used undetectable RNA at 24 weeks after treatment completion as the definition for SVR [5].

The risk of decompensated cirrhosis, hepatocellular carcinoma, and death is lower in people who achieve SVR than in those who do not [6,7]. Therefore, some consider SVR as the fundamental goal in HCV treatment [2,3,8]. Cost-effectiveness analyses (used for determining resource allocation policy) of direct-acting antivirals use SVR rather than direct clinical impact in their decision tree models [9-11], indicating that SVR is the key determinant in cost-utility and plays an important role in resource allocation. On the other hand, only 11 of the 138 trials reported all-cause mortality, while HCV-related morbidity such as decompensated cirrhosis was not reported in any of the trials in the Cochrane systematic review [5]. Therefore, others have questioned whether SVR is a validated surrogate marker of successful treatment of chronic HCV infection; SVR may be a good prognostic marker, but it does not meet the criteria for a surrogate marker, as an increase in SVR does not always translate to an increase in life expectancy, and the correlation between SVR and clinical outcomes does not mean that SVR is a sufficiently good surrogate marker [5,12-15].

This project aims to evaluate whether SVR is a good surrogate for all-cause mortality, decompensated cirrhosis, or any specific aspect of liver decompensation or hepatocellular carcinoma in people with chronic HCV infection eligible to receive direct-acting antiviral drugs.

Methods

Data Source

The Cochrane systematic review on the effectiveness of direct-acting antiviral drugs in chronic HCV infection [5] is currently being updated (Professor Goran Bjelakovic, Dr Med Sci, personal communication on June 19, 2025). In addition, a new review on the effectiveness of direct-acting antivirals from observational studies is in progress [16]. As part of these reviews, the information shown in Figure 1 on adjusted treatment effects of the intervention versus the comparator on SVR and event will be collected. In the context of this figure and the protocol, an event is one of the following:

- All-cause mortality
- Decompensated cirrhosis (ie, jaundice, ascites, hepatic encephalopathy, hepatorenal syndrome, or variceal hemorrhage)
- Any specific aspect of liver decompensation (jaundice, ascites, hepatic encephalopathy, hepatorenal syndrome, or variceal hemorrhage)
- Hepatocellular carcinoma

Figure 1. Decision tree. An event is one of the following: all-cause mortality, decompensated cirrhosis, any specific aspect of liver decompensation (jaundice, ascites, hepatic encephalopathy, hepatorenal syndrome, or variceal hemorrhage), or hepatocellular carcinoma. SVR: sustained virological response.

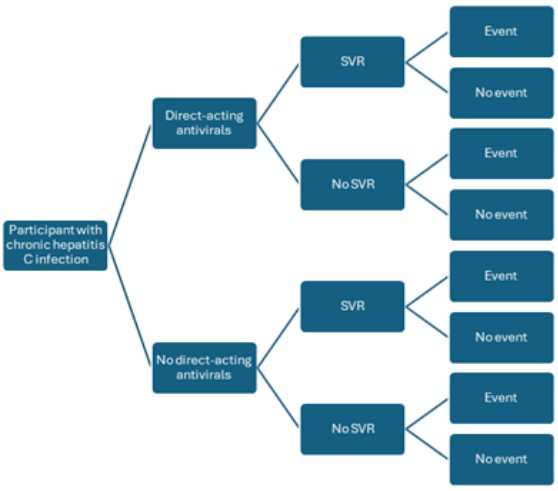

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Analysis

For each outcome, we will evaluate whether SVR is a good surrogate for the clinical outcome. We will reconstruct the individual participant data from the summary data since this is a binary outcome. We will then perform the following to achieve the research objectives.

First, we will estimate the regression coefficients or between-studies correlation between SVR and the event (clinical outcome) using the guidance by the evidence synthesis unit [17] by three different Bayesian approaches using OpenBUGS [18], namely, the standard surrogacy model by Daniels and Hughes [19], bivariate random-effects meta-analysis model [17], and bivariate random-effects meta-analysis in product normal formulation model [20].

We will use three chains and use noninformative priors. We will start with a burn-in of 10,000 iterations and run a further 30,000 iterations to calculate the parameters along with their credible intervals (CrIs). We will check for convergence visually and increase the iterations, using "overrelax" or "thin," as required to achieve convergence. In addition, we will use the Gelman-Rubin statistic (corrected ratio of the pooled variance across chains and within-chain variance or the "potential scale reduction factor") to assess convergence [21]. We will consider an upper bound 5% potential scale reduction factor of more than 1.1 for any variable (to be estimated) as indicative of a lack of convergence [22].

For the treatment effects of SVR and the event, which are required to use for these approaches, we will obtain the adjusted odds ratio when available. If not available, we will calculate the odds ratios and 95% CIs of SVR and the event using the total number of participants and the number of participants with SVR or events, respectively, using R (version 4.5.0; R Foundation for Statistical Computing; package: *meta*) [23]. If there are zero events, we will use a correction factor of 0.01 to obtain these measures.

For estimating the correlation between SVR and the event, we will use the Daniels and Hughes [19] model to base our conclusions. We have provided the reasons for doing so in the Discussion section. For the between-studies correlations estimated from the bivariate random-effects meta-analysis model [17] and bivariate random-effects meta-analysis in product normal formulation model [20], we will use the German Institute of Quality and Efficiency in Health Care (IQWiG) criterion for surrogacy, which requires a correlation with the lower limit of the 95% CI to be above 0.85 [24]. We will use 95% CrIs as we will be using Bayesian methods to indicate that SVR is a good surrogate marker for the clinical event. If this cannot be achieved, we will calculate the 80% CrI and see if the lower limit is above 0.85 [24]. If the lower limit of the 80% CrI is above 0.85 but not the 95% CrI, we will consider that SVR may be a good surrogate marker for the clinical event but that there is uncertainty around this conclusion, and further studies are necessary. For the standard surrogacy model by Daniels and Hughes [19], we will consider whether the 95% CrI of the intercept overlaps 0 and the 95% CrI of the association between the treatment differences on SVR and the clinical outcome is positive and does not overlap 0 as criteria for SVR being a good surrogate outcome.

An alternate approach to regression or correlation coefficients when deciding whether SVR is a good surrogate marker is using the models to predict the clinical outcome from the surrogate marker [17]. This approach uses a "take-one-out" approach to predict the treatment effect of the intervention on the clinical outcome in one study based on the observed treatment effect of the intervention on the surrogate marker and meta-analytical estimate of the correlation between the surrogate marker and clinical outcome in the remaining studies [17]. However, we will not use this approach for the reasons described in the Discussion section. We acknowledge that this might introduce uncertainty in validating the model.

Second, we will perform a causal mediation analysis and estimate the average causal mediation effects and the average direct effects using R (package: *mediation*) [25]. We will estimate the average proportion of the effect mediated through SVR and will consider SVR as a surrogate marker if the lower 95% CI of the proportion of the effect mediated through SVR is more than 0.5.

A summary of our interpretation is available in Figure 2.

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Figure 2. Interpretation algorithm. Criterion 1: 95% credible intervals (CrI) of the intercept overlaps 0. Criterion 2: positive association between the treatment differences in the surrogate and clinical outcomes (95% CrI does not overlap 0). Criterion 3: lower 95% CrI of the between-studies correlations does not overlap 0.85. Criterion 4: lower 95% CI of the effect mediated through the surrogate outcome does not overlap 0.5. If there is a discrepancy between models, we will use the Daniel and Hughes surrogacy model to conclude whether SVR is a good outcome. The between-studies correlations between the treatment differences in the surrogate and clinical outcomes and the proportion of the effect of the direct-acting antivirals will be estimated from the bivariate random-effects meta-analysis model and the causal mediation analysis. For the bivariate random-effects meta-analysis model, if the lower 80% CrI of the between-studies correlations does not overlap 0.85, we will conclude that SVR may be a good surrogate outcome. SVR: sustained virological response.

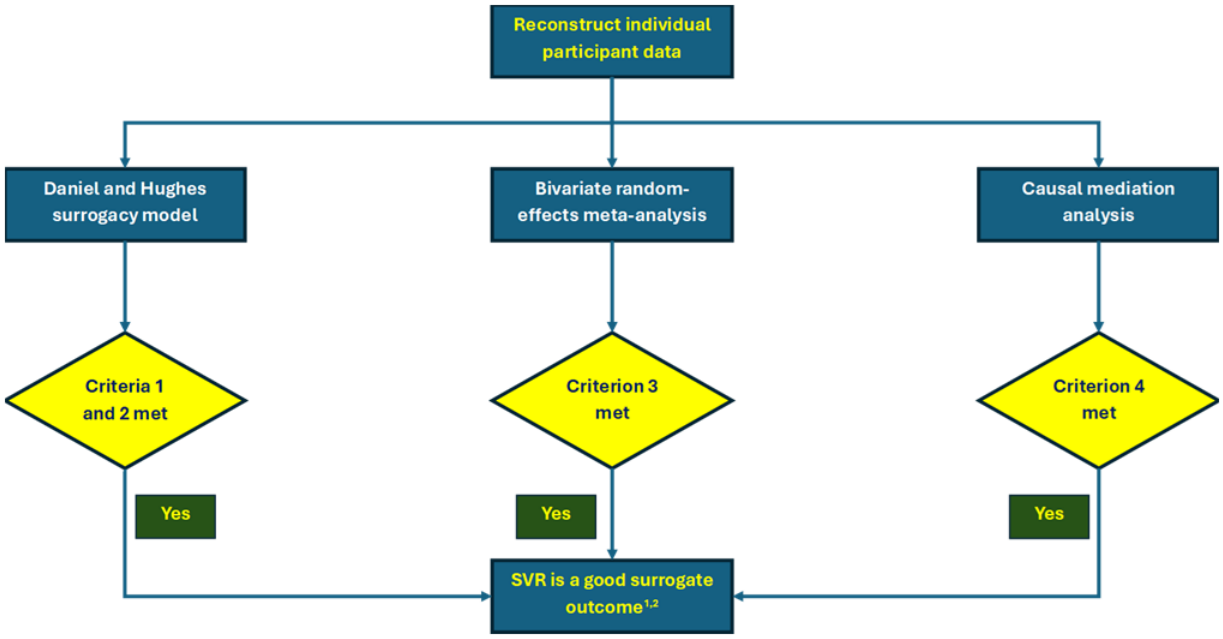

Evidence From Randomized Clinical Trials Compared to That From Observational Studies

We will analyze randomized clinical trials separately from observational studies. If the conclusions based on observational studies are different from those based on randomized clinical trials, we will highlight this difference and indicate the need for corroborating the information from the randomized clinical trials.

Sensitivity Analysis

If possible, we will perform a sensitivity analysis excluding studies with fewer than 10 years of follow-up because of the duration to develop the clinical complications of chronic HCV infection.

Ethical Considerations

Since we will be using summary data available from two systematic reviews, an ethics application was not deemed necessary. All randomized clinical trials and some of the observational studies included in the systematic reviews obtained ethical approval before they launched.

Data Sharing and Reporting

The summary data will be available from the systematic review update, and all authors of the two reviews will be invited to coauthor the results of this research. The data and codes used for this research will be shared via Zenodo. Attempts will be made to publish the report in a journal. If this is not possible, we will share the report of our results through Zenodo.

Results

As of June 19, 2025, the two systematic reviews (one on randomized clinical trials and one on observational studies) on the effectiveness of direct-acting antiviral drugs in chronic HCV infection are ongoing.

Discussion

Justification for Approaches

There is considerable controversy about whether SVR is a good surrogate outcome for clinical outcomes in chronic HCV infection [5,12-15]. However, there has been no previous meta-study evaluating whether SVR is a good surrogate outcome for clinical outcomes in people eligible to receive direct-acting antivirals in the treatment of chronic HCV infection. We will use two different approaches to perform this evaluation. These approaches have been specifically developed to evaluate whether an outcome is a surrogate outcome across a range of medical conditions or whether the effect of an intervention on an outcome is mediated by a surrogate outcome, which is the rationale behind the use of surrogate outcomes. Simpler alternative approaches, such as the association between SVR and the clinical outcomes by odds ratios, establish an association but not a causal association, as a correlation between two variables does not indicate that one variable is a surrogate of another variable [26]. Therefore, we will use the following approaches specifically developed to establish the causal relationship between SVR and clinical outcomes.

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In the first approach, for the bivariate random-effects meta-analysis model [17] and bivariate random-effects meta-analysis in product normal formulation model, we will use correlation coefficients to evaluate whether SVR is a good surrogate outcome. There is no consensus on the thresholds used for interpreting correlation coefficients [17]. We will use the IQWiG guidance on surrogate outcomes in oncology [24] to interpret whether SVR is a good surrogate outcome. If the lower limit of the 95% CrI overlaps 0.85, we will check whether the lower limit of the 80% CrI overlaps 0.85. Therefore, we will highlight this additional uncertainty.

Although the limit of 0.85 for the correlation coefficient has been suggested for cancers, we will use this limit for chronic HCV infection also. When there is a high probability of a clinical outcome, one might want to take a more lenient approach to accept surrogate outcomes and treatments that reduce the surrogate outcome when there is a requirement to act early. In the case of cancer, the proportion of people dying within 10 years is 50% across all cancers [27]. Therefore, one might want to take a more lenient approach in approving treatments based on surrogate outcomes. With HCV infection, the proportion of people dying in about 10 years is around 13% [28]. Therefore, one might argue that much stricter criteria should be used for approving treatments for chronic HCV infection based on surrogate outcomes if the treatments are publicly funded.

Others might argue that because of the longer latency period in chronic HCV infections, there are a lot of factors that might change over time, justifying a more lenient approach to approving treatments based on surrogate outcomes. Public funding of treatments is usually based on the cost-effectiveness of a treatment (ie, incremental quality-adjusted life years per incremental costs) [29]. Besides mortality, we will also obtain features of decompensated cirrhosis and hepatocellular carcinoma, which negatively impact longevity and health-related quality of life. Therefore, we will obtain information on both the mortality and the major factors affecting health-related quality of life, the two components of the quality-adjusted life years. A longer period of latency in chronic HCV infections means that the impact of chronic HCV infection on quality-adjusted life years is likely to be less than that of cancer. This goes against using a more lenient approach (for validating and using a surrogate outcome for funding chronic HCV infection treatments) in an already stretched health care system.

To avoid using some new arbitrary threshold criteria, we decided to use similar criteria used for cancer. Furthermore, we will present the correlation coefficients with the 95% CrI (and possibly 80% CrI) along with the data and the codes used for our analyses. If an individual or an organization is interested in using a different threshold for interpreting whether SVR is a good surrogate outcome for clinical outcomes in people eligible for direct-acting antiviral treatment, they can use the data, codes, and results to guide their decision using an alternate threshold.

We anticipate the bivariate random-effects meta-analysis model (standard form) [17] and the bivariate random-effects meta-analysis (product normal formulation) model [20] to result in similar conclusions since we will use the same noninformative prior distributions of parameters in both models and will include only participants without missing data in both analyses. When the prior distributions of parameters are similar and data are available for both outcomes, the bivariate random-effects meta-analysis in product normal formulation model is equivalent to the bivariate random-effects standard form [17]. However, both these models assume that the treatment effect (of the intervention) on the surrogate outcome is exchangeable, while there is no such assumption in the Daniels and Hughes model [17]. When there is a discrepancy between the Daniels and Hughes [19] model and the bivariate random-effects meta-analysis models, we will use the Daniels and Hughes [19] model, as we plan to obtain data from multiple direct-acting antivirals. The treatment effects on SVR with these direct-acting antivirals may or may not be exchangeable.

For interpretation of the Daniels and Hughes [19] model, we will consider whether the 95% CrI of the intercept overlaps zero and the 95% CrI of the association between the treatment differences on SVR and the clinical outcome does not overlap zero as the criteria for SVR being a good surrogate outcome. This is based on the guidance provided by Daniels and Hughes [19] in interpreting the results. The rationale for this approach is as follows. If the entire effect of the treatment on the clinical outcome is mediated through the surrogate outcome, a treatment that does not have any effect on the surrogate outcome must have no effect on the clinical outcome, resulting in the intercept being zero [19]. Furthermore, if the CrI of the association between the treatment differences on SVR and the clinical outcome overlaps zero, this indicates the possibility that there is no association between the treatment differences on SVR and the clinical outcome.

We will not be able to validate the models using the "take-one-out" approach, as this approach is unlikely to be feasible in our studies. This is because the long-term results of direct-acting antivirals are unlikely to be available from randomized clinical trials. In observational studies, the reason for receiving (or not receiving) treatment with direct-acting antivirals may be correlated with the clinical outcome. For example, in one study, the reasons for not receiving direct-acting antivirals included multiple comorbidities, low health literacy, restricted access to hospitals, nursing home residence, and old age [30]; all of these factors are associated with increased risk of death. This means that confounding could be a major reason for an observed association between no treatment and mortality in the observational studies, and reverse causality (ie, the likelihood of the outcome determining whether a patient receives the treatment) may exist in the association between treatment with direct-acting antivirals and increased survival.

Meta-regression is a statistical method that uses study-level characteristics to provide information on whether the treatment effects are affected by the characteristic and is primarily used to explore statistical heterogeneity in meta-analyses [31]. By using confounding factors as the characteristics, it is theoretically possible to calculate the meta-analytical treatment effects across studies, adjusting for the differences in the confounders, for example, the differences in age or proportion of people with major comorbidities between the studies. However, it is unlikely that the adjusted treatment effects of

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direct-acting antivirals on SVR and clinical outcomes are calculated using the same confounding factors across studies; therefore, it is likely that information on some confounding factors will be missing from some studies. This means it is unlikely that we will be able to use a meta-regression approach to calculate the treatment effects of direct-acting antivirals on clinical outcomes from the treatment effects on SVR, adjusting for the values of the potential confounders. Furthermore, such a meta-regression approach to adjust for study-level characteristics can lead to ecological bias [31,32]. Therefore, we have used the approach of using the regression coefficients and the correlation coefficient to achieve our research objective. However, this is not immune to confounding either, as the regression coefficients may be biased depending on the variables included in the model; this may lead to heterogeneity in the regression coefficients. Furthermore, the regression coefficients do not account for residual confounding. Therefore, the results from the observational studies may be biased.

With our chosen second approach of causal mediation analysis, we will use the lower 95% CI of the proportion not overlapping 0.5 as the criterion for indicating that SVR is a good surrogate marker. This is an arbitrary decision as there is no guidance on the magnitude of the average causal mediation effects that should be considered relevant [33]. We have based the criterion on the rationale that SVR should at least explain most of the effect of direct-acting antivirals on the clinical outcome, if SVR is to be used as the primary objective of treatment or the primary outcome in a clinical trial. Since the 95% CI of the proportion is presented, an individual or organization can use their own criterion for interpreting the information.

As indicated earlier in the Discussion section, there are possible confounding factors explaining the decision to treat (or not to treat) a person with direct-acting antivirals. Therefore, we will analyze the data separately between randomized clinical trials and observational studies.

Limitations of This Study

We will be relying on data from two systematic reviews (update on the Cochrane review of randomized clinical trials [5] and another systematic review on observational studies [16]). The second author of this study is a coauthor in these studies and will provide information on any deviations from the plans for these systematic reviews due to the peer review. We do not anticipate any major revisions to this research due to the peer review of the two systematic reviews, but we acknowledge the uncertainty of relying on the data.

We have included observational studies in this research because of the limited follow-up time usually found in randomized clinical trials. However, this leads to some limitations in our study. We have discussed one of the limitations of using observational studies, confounding, previously, and there are other limitations.

We will be relying on existing publications. The follow-up in the trials may be different between studies. This can lead to heterogeneity. We will perform a sensitivity analysis, including only studies with at least 10 years of follow-up, to assess the impact of the heterogeneity in follow-ups on the conclusions.

We expect the update of the Cochrane review [5] to identify the randomized clinical trials through the trial registry (because of the mandatory prospective trial registration), thereby allowing an assessment of reporting biases by comparing the registered trials and published trials. However, the other systematic review relies on observational studies; there is currently no mandatory registration of observational studies. Funnel plot asymmetry may help with the identification of publication bias, but the power of the tests used to assess funnel plot asymmetry may be limited with fewer than 10 studies in the meta-analysis [34]. Furthermore, the power is reduced in the presence of heterogeneity, and heterogeneity can be one of the causes of funnel plot asymmetry [34]. All these make it more difficult to identify reporting biases in observational studies.

Because of all these limitations in observational studies, if the conclusions based on observational studies are different from those based on randomized clinical trials, we will highlight the need for corroborating the information from long-term follow-ups in randomized clinical trials using record linkage studies.

We will not be able to validate the models using the “take-one-out” approach. We acknowledge that this might introduce bias, but this bias can be corrected only when randomized clinical trials report long-term clinical outcomes.

Data Availability

The datasets generated or analyzed during this study will be available in the Zenodo repository.

Authors' Contributions

KSG wrote the first draft. CG commented and improved the draft.

Conflicts of Interest

The salary and promotions of KSG are dependent on high-quality research.

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Abbreviations

CrI: credible interval
HCV: hepatitis C virus
IQWiG: Institute of Quality and Efficiency in Health Care
SVR: sustained virological response

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Protocol

A Complex Intervention to Strengthen Person-Centered Care and Leadership in Residential Care Facilities (the PERLE Study): Protocol for a Development and Implementation Study

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Abstract

Background: Although the benefits of person-centered care (PCC) are widely recognized, there is a lack of empirical research on how PCC is best developed and implemented by the leaders responsible for driving such initiatives. To achieve meaningful change and ensure the sustainability of PCC practices, it is crucial to understand how leaders can foster care environments rooted in person-centered values while managing operational challenges. This knowledge gap highlights the need for an in-depth exploration of the conceptual foundations, experiences, mechanisms, strategies, and outcomes of person-centered leadership (PCL) to design an intervention for strengthening such leadership.

Objective: The Person-Centered Care and Leadership in Residential Care Facilities (PERLE) study aims to (1) explore and develop tools to measure PCL; (2) develop, test, implement, and investigate the effects of an intervention to strengthen PCL in residential care facilities (RCFs) for older people; and (3) generate knowledge about the process of development and implementation of the intervention.

Methods: The PERLE study builds on the Medical Research Council framework for the development of complex interventions. It includes several studies with exploratory, descriptive, correlational, and quasi-experimental designs and is based on the research group's previous research on PCL. The project is composed of 5 work packages (WPs). Each WP includes research questions with different samples; data collection; and methodological approaches, such as qualitative, mixed methods, and quantitative studies. As this project involves sensitive issues, a high level of ethical awareness was maintained throughout. The primary challenge is the possible interference with participants' work time, which could otherwise be devoted to supporting older people and staff. Nevertheless, the involvement of leaders and staff can lead to valuable knowledge that can improve the quality of PCC. Participants will be provided with both oral and written information about the study and assured of their right to withdraw at any time without providing a reason.

Results: As of July 2025, 6 studies in WP I have been conducted, and one is in progress. The conducted studies address leaders' understanding of PCC, the meaning of PCL in RCFs from the perspective of leaders, the ethical challenges in providing PCC during the COVID-19 pandemic, and the cultural adaptation of the aged care clinical leadership qualities framework.

Conclusions: This project aims to provide new insights into the support that first-line managers need to advance PCC in RCFs, highlight their specific challenges, and create tailored support measures for the implementation of PCL. The intervention could potentially reduce staff turnover and related costs while supporting leadership training and education to benefit future leaders in aged care, which may be important from an international perspective.

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KEYWORDS

person-centered care; leadership; residential care facilities; nursing homes; long-term–care facilities; older people; quasi-experimental intervention

Introduction

Overview

The need for research on person-centered leadership (PCL) stems from the growing recognition of person-centered practices and their well-documented benefits for patients, staff, and care cultures, particularly in the context of care for older people [1]. Despite the theoretical promise of person-centered care (PCC), leading PCC remains challenging because of structural, cultural, and systemic barriers [2]. Leaders often face conflicting demands between focusing on individual needs and meeting organizational goals [3], which can be ethically challenging when leading PCC. This became particularly visible during the COVID-19 pandemic [4]. Furthermore, while PCC has been extensively explored, there is limited empirical evidence on how PCC can be developed and implemented by the leaders who are appointed to steer such processes. Understanding how leaders can support care environments permeated by person-centered values, while balancing operational pressures, is essential for promoting meaningful changes and sustainable PCC practices. This gap in knowledge calls for a deeper investigation into the conceptual meanings, experiences, mechanisms, strategies, and outcomes of PCL. The knowledge gained will facilitate the development of a complex intervention to strengthen PCL. This study protocol describes the conceptualization and design of the Person-Centered Care and Leadership in Residential Care Facilities (PERLE) study.

Background

PCC Approach

The PERLE study is grounded in person-centeredness, originally based on Rogerian psychotherapy [5]. During the 1990s, Kitwood [6] adapted the ideas for dementia care formulated by Rogers [5] to address “malignant social psychology,” a term he coined to describe practices that devalued, dehumanized, and depersonalized persons with dementia. Kitwood [6] emphasized the importance of recognizing personhood as preserved, even amid cognitive decline. Building on the work by Kitwood [6], Brooker and Latham [7] introduced the VIPS framework for PCC, with the acronym representing 4 core components: valuing human life regardless of cognitive ability, individualized care, the perspective of the user, and a supportive environment. The importance of the relationship between the person and the caregiver is emphasized in the conceptual framework for person-centered practice by McCormack [8]. It advocates a holistic, ethical, and humanistic foundation; shared decision-making; and care based on the person’s needs, values, and preferences, ensuring their well-being remains the priority [9]. PCC also involves promoting quality of life by incorporating meaningful activities, social interactions, and cultural elements [10].

Several intervention studies have provided compelling evidence for the importance of PCC, particularly for older people, establishing it as an indicator of high-quality care in residential facilities, especially for persons living with dementia [11]. A systematic review and meta-analysis of PCC interventions revealed several positive outcomes, including reduction in agitation, neuropsychiatric symptoms, and depression, along with improved quality of life among older people in residential care facilities (RCFs) [12]. These findings call for the reshaping of care for older people, making it more tailored and personalized. Essential components of person-centered interventions include social interaction, physical activities, cognitive training, life story work, emotional support, education and support for caregivers, and adjustments to the care environment and organization [13].

These findings offer an understanding of key elements and activities for improving PCC practices. Furthermore, McCormack and McCance [1,14] stress the importance of a supportive organization, competent staff, and an adaptive care environment. A supportive organization fosters creativity, initiative, and collaboration among staff, underpinned by strong leadership. Ultimately, PCC places the person’s preferences and needs at the forefront, guiding decisions and actions. This also means that leadership focusing on person-centeredness has to address the needs of the persons who receive care and create a supportive care and work environment, while balancing organizational goals with person-centered principles.

Leading PCC

Previous research highlights the critical importance of leadership in successfully implementing PCC in RCFs [15]. Leaders play a vital role in shaping a professional vision, acting as role models, and offering support by actively engaging in the implementation process [16]. Stein-Parbury et al [17] emphasize that building trustful relationships through support and active engagement with staff is key to achieving success. Similarly, Chenoweth et al [18] stress that flexibility in work approaches and involving staff in care-related decision-making are pivotal factors in effective implementation. Moreover, Rosemond et al [19] illustrate how leaders can enhance PCC by introducing the approach with responsiveness, inclusivity, and respect. This is reinforced by Jeon et al [20], emphasizing that leadership requires not only listening to staff suggestions but also making necessary adjustments to organizational structures to support person-centered practices. In addition, leadership for PCC practices involves fostering trust through delegation, clarifying roles, considering staff expertise, and creating opportunities for development [21]. Backman et al [22] highlight the leader’s role in supporting staff to provide care tailored to the needs of older persons, while simultaneously focusing on team development and improving workplace cohesion.

Despite the evidence that leadership is important for implementing person-centered interventions, research indicates that practical implementation remains challenging, fragmented, and often not fully person-centered [23]. Cases of unmet goals in person-centered interventions have been attributed to a lack

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of leadership support to continually motivate, coach, and sustain the process [24] or to management's failure to enable necessary organizational changes, leading to unfavorable outcomes [18]. These findings underscore the critical role of leadership in initiating and fostering PCC. In a systematic review, Moenke et al [25] found that most studies on leadership for person-centered practices focus on what leaders should do, rather than on how they can be supported in developing their leadership capabilities. This gap between person-centered theory and practice highlights the need for further research to understand how leaders can be supported in promoting PCC daily over the long term.

Insufficient leadership support has also been linked to challenges for staff to address the unique needs of older people [26], reinforcing the need for targeted leadership development in PCC. In addition, research also emphasizes the importance of restoring humanistic aspects in care to enhance quality, improve staff well-being, and increase job satisfaction [3]. It has been said that leaders who heavily rely on hierarchical structures tend to prioritize tasks and outcomes over the humanistic elements of leadership, often neglecting the development of employees' skills [27]. While leadership is central to PCC, it also introduces new demands and challenges for leaders. The concept of PCL, by contrast, remains largely underexplored, resulting in a significant knowledge gap that needs to be addressed to support leaders in developing their PCL skills.

Leading PCC During the COVID-19 Pandemic

The COVID-19 pandemic highlighted the need for leadership that addresses the needs of both staff and older people [28], underscoring the importance of leadership practices aligning with person-centered principles. PCC involves navigating complex ethical and practical challenges, even under ordinary circumstances. These challenges became significantly greater during the COVID-19 pandemic, as the need to protect populations considered vulnerable introduced restrictions and shifts in care practices. As in many other countries, Sweden faced significant challenges, with early efforts focused on protecting older persons [29]. In RCFs, numerous restrictions were implemented [30], limiting the ability to provide PCC. Leaders struggled to adapt their leadership as care conditions kept changing [31], while staff faced new ethical dilemmas, such as when isolating residents by confining them to their rooms against their will [32]. The restrictions severely impacted residents' autonomy, freedom, participation, and overall well-being [30]. Although the COVID-19 pandemic entailed specific conditions, it also exposed preexisting ethical challenges in delivering PCC and underscored the importance of PCL.

Theoretical Framework of PCL

Skivington et al [33] highlight the importance of using theoretical frameworks in the development of complex interventions. One such framework is the aged care clinical leadership qualities framework (ACLQF), which clarifies clinical leadership, outlines several leadership aspects, and can be used to support the implementation of PCC. PCC forms the foundation of the ACLQF, which emphasizes the importance of staff and managers treating all residents with respect by acknowledging and addressing their unique experiences and needs [34]. A cluster randomized controlled trial evaluating a leadership program based on the ACLQF in the care of older people in Australia [35] showed positive outcomes across all primary measures. These included leaders demonstrating greater individual consideration, increased motivation, stronger role modeling, and more recognition and praise to staff.

Measuring and Evaluating PCL

As PCL is a relatively new concept, validated methods for measuring PCL have so far been lacking. Several instruments measuring different aspects of PCC [36] have been translated and adapted for the Swedish context, for example, the Person-Centered Care Assessment Tool [37,38], person-centered climate [39,40], and PCC in acute settings for older persons with cognitive decline [41]. Several general leadership instruments exist [42,43], but none specifically measure leadership in the context of care of older people or PCC. To enable the evaluation of the effects of leadership interventions with a focus on PCL, a specific instrument measuring these aspects is needed.

Rationale for the Study

Although the benefits of PCC are widely recognized, there is a lack of empirical research on how PCC can be developed and implemented by the leaders responsible for driving such initiatives. To achieve meaningful changes and ensure the sustainability of PCC practices, it is crucial to understand how leaders can foster care environments rooted in person-centered values while managing operational challenges. This knowledge gap highlights the need for an in-depth exploration of the conceptual foundations, experiences, mechanisms, strategies, and outcomes of PCL to design an intricate intervention aimed at strengthening such leadership.

Aims

The PERLE study aims to (1) explore and develop tools to measure PCL; (2) develop, test, implement, and investigate the effects of an intervention to strengthen PCL in RCFs for older people; and (3) generate knowledge about the process of development and implementation of the intervention.

Methods

Context

In Sweden, health care and social care are tax-financed and means-tested, as is placement in an RCF or, using international terminology, in a nursing home, skilled nursing facility, or long-term-care facility. In Sweden, the county councils (regions) are responsible for health care services provided at hospitals and in primary care (health care centers). For people aged ≥65 years, the municipalities are responsible for health and social care, although services may be provided by private actors or nonprofit organizations [44]. The chronological age of 65 years, the former retirement age, is still defined in the legislation as the entry age to an RCF. However, since 2020, a pension age adjustment system has been in place in Sweden, with the present suggested retirement age being 67 years, but with the possibility to retire earlier or to work longer if the employer agrees, meaning that 65 years is no longer a relevant definition of "older

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people." Using chronological age instead of functional age as an indicator for when someone is "older" has also been questioned. In Sweden, the term "older people" is primarily used for people aged ≥75 years.

Because of the growing aging population, the demand for more RCF places is increasing, while the number of available places in RCFs has decreased over time [45]. In 2024, approximately 10% of people aged ≥80 years, mostly women, resided in RCFs [46]. Today, the mean age for moving to an RCF is 86 years [46], and the mean length of stay is 2 years [47]. However, this varies greatly. A large percentage of residents die shortly after admission [48]. Residents often have major health care needs related to aging and frailty when they move into residential care, and the majority have a cognitive disorder [49].

The largest staff groups in municipal care for older people are direct nursing staff, that is, licensed practical nurses (61%) and nursing assistants (32%), while registered nurses (RNs) account for 7% [50]. The majority are women (82%), 42% are foreign-born, and 49% have only temporary employment (ie, employed by the hour and only when the employer needs additional staff) [51].

RNs work in the daytime and are on call evenings, nights, and weekends. Occupational therapists and physiotherapists are employed by the municipality and work on a consultancy basis. Physicians also work on a consultant basis in RCFs and are employed by the primary health care center. Physicians are responsible for medical assessments, while RNs coordinate the residents' medical care. First-line managers are, together with the RNs, responsible for the quality of care, and are responsible for staff management, budgeting, administration, and the work environment [46]. First-line managers mainly have a professional background in social work or nursing. RNs are not subordinate to first-line managers, as they are part of a different organizational structure, often together with occupational therapists and physiotherapists.

During the COVID-19 pandemic, there was no strict lockdown in Sweden, but social distancing was applied, which included visitor restrictions in RCFs [29]. The restrictions were in place for periods between March 2020 and March 2022. The COVID-19 vaccination was introduced in RCFs at the beginning of 2021, and by January 2022, 95% of RCF residents had received a vaccination [52].

Design

The PERLE study includes several studies with exploratory, descriptive, correlational, and quasi-experimental designs and is based on the research group's previous research on PCL [53]. The project is composed of 5 work packages (WPs) whose aims are as follows:

- WP I explores PCC and PCL in RCFs for older people. The knowledge derived from this WP will be used as a basis for the development of tools to measure PCL (WP II) and the development of the intervention (WP III).
- WP II develops tools to measure intervention effects concerning PCL in RCFs for older people. The knowledge derived from this WP will be used as primary and secondary outcome measures when investigating the effects of the intervention (WP IV).
- WP III develops and tests an intervention to strengthen PCL in RCFs for older people. The knowledge derived from this WP will be used as a basis for the implementation of the intervention (WP IV) and will, together with the results of WP II, be used as a basis for the calculation of sample sizes and for determining the methods of randomization.
- WP IV implements and investigates the effects of an intervention to strengthen PCL in RCFs.
- WP V generates knowledge about the process of development and implementation of the intervention. WPs II to IV will contribute to the results of this WP.

For an overview of the 5 WPs and how they are interrelated, refer to Figure 1.

Figure 1. Overview of the different work packages (WPs) and their interrelationships. PCC: person-centered care; PCL: person-centered leadership.

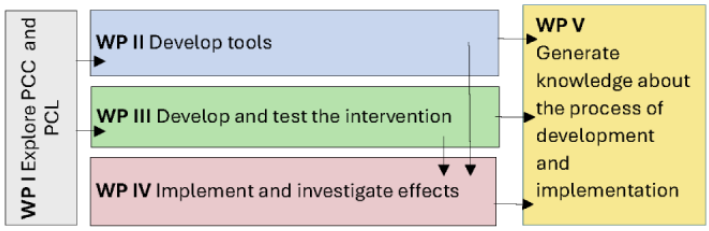

The first studies will, together with the group's previous research, be used as a foundation for the development of a complex intervention for leaders in RCFs. Skivington et al [33] highlight that the possibility of success of an intervention increases if it is adjusted to the specific context and builds on an extensive empirical and theoretical basis. Therefore, it is of utmost importance that the various parts of the intervention are developed for the specific context and target group and are based on theoretical underpinnings. This also applies to the evaluation of an intervention, where it is equally important that the outcome measures are developed for the actual context and in relation to the target group.

The guidelines for the development and evaluation of complex interventions have been updated since they were first published in 2008 by the Medical Research Council [54]. The new guidelines [33] describe four phases: (1) development of the intervention (WP I and II), (2) feasibility assessment (WP III), (3) implementation, and (4) evaluation (WP IV). The studies within the PERLE study will mainly generate knowledge to inform the development of the intervention, while also providing insights into the processes of its development, implementation, and evaluation (WP V). Zwarenstein et al [55] point to the importance of involving the users (eg, staff, leaders, and decision makers) in the phases of development, implementation, and

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evaluation. Most studies and all the WPs in the PERLE study will have a high degree of user involvement.

Skivington et al [33] list six core elements of importance in the intervention development and implementation process:

1. Consider context; contextual factors, such as cultural, social, and economic factors, need to be considered. This is addressed in a process of cocreation with the leaders, especially in WP II and III, ensuring that the intervention is based on the specific context of Swedish residential care.

2. Develop, refine, and test or retest program theory; the program theory should describe how an intervention is expected to lead to effects and under what circumstances. In this project, the program theory is operationalized by a theoretical and empirical evidence base derived from WP I, being developed in WP II, and tested in WP III.

3. Engage stakeholders; stakeholders, in this project being mainly first-line managers, will participate in all stages of the project (WP I-V) in a cocreation process consisting of meetings, workshops, and focus group discussions.

4. Identify key uncertainties; the potential to identify key uncertainties is strengthened by the close involvement of stakeholders and the use of different methods in development and testing (WP II and III).

5. Refine the intervention; the refinement of the intervention components will be done in the feasibility studies in close collaboration with first-line managers (WP III).

6. Identify economic considerations; economic considerations need to be identified and reflected throughout the development and implementation phases to ensure that the intervention is cost-effective. In this project, relevant health economic measures will be developed in WP II, tested in WP III, and used for evaluation in WP IV.

Each WP includes research questions (RQs) with different samples, data collection methods, and methodological approaches. For an overview of the RQs, samples, data collection, and analyses in relation to the different WPs, refer to Table 1.

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Table 1. Overview of the WPs[a], RQs[b], sample, and data collection and analyses.

WPs and RQs	Sample			Data collection				Analyses		
	FLMs[c]	RNs[d]	Direct care staff	Interviews	Questionnaires	Workshops	Literature	Qualitative	Mixed methods	Quantitative
WP I: explore PCC[e] and leadership in RCFs[f] for older people										
RQ 1—What are leaders' understandings of PCC in RCFs?	✓	✓		✓				✓		
RQ 2—Which ethical challenges emerged in the provision of PCC during the COVID-19 pandemic?	✓	✓	✓	✓				✓		
RQ 3—What is the meaning of PCL[g] in RCFs from the perspective of leaders?	✓	✓		✓				✓		
RQ 4—What is the conceptualization of PCL in RCF from the perspective of RCF leaders?	✓	✓				✓			✓	
RQ 5—What is the present evidence base of PCL?							✓	✓		
RQ 6—Is the ACLQF[h] relevant and applicable in a Swedish RCF context?	✓	✓			✓					✓
WP II: develop tools to measure intervention effects concerning PCL in RCFs for older people										
RQ 7—How can PCL (primary outcome) be measured?	✓		✓		✓					✓
RQ 8—What other (secondary) outcome measures concerning staff, leaders, and care quality are relevant?							✓			✓
RQ 9—What health economic outcome measures are relevant, and which economic considerations are needed?							✓			✓
WP III: develop and test an intervention to strengthen PCL in RCFs for older people										
RQ 10—Which intervention components are relevant and can be adopted in a Swedish aged care context?	✓					✓			✓	
RQ 11—Are the intervention components feasible, and how are they experienced by the leaders?	✓			✓				✓		
RQ 12—What are the strengths and challenges of the different parts of the intervention?	✓			✓				✓		
WP IV: implement and investigate the effects of an intervention to strengthen PCL in RCFs										
RQ 13—What are the effects of the intervention?	✓		✓		✓					✓
WP V: generate knowledge about the process of development and implementation of the intervention										
RQ 14—How do the participants experience the process of cocreation of the development and implementation of the intervention?	✓			✓	✓			✓		

[a]WP: work package.

[b]RQ: research question.

[c]FLM: first-line manager.

[d]RN: registered nurse.

[e]PCC: person-centered care.

[f]RCF: residential care facility.

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[g]PCL: person-centered leadership.

[h]ACLQF: aged care clinical leadership qualities framework.

Studies With a Qualitative Approach

The qualitative studies concern leaders' understanding of PCC in RCFs (RQ 1), ethical challenges in the provision of PCC during the COVID-19 pandemic (RQ 2), the meaning of PCL in RCFs from the perspective of leaders (RQ 3), the evidence base of PCL (RQ 5), the feasibility and experience of the intervention components (RQ 11), strengths and challenges of the different parts of the intervention (RQ 12), and the experience of the cocreation process of development and implementation of the intervention (RQ 14).

Samples

The sample for the qualitative studies will be purposively selected to include people who can report relevant experiences and describe the phenomenon being investigated [56]. First, permission from the heads of social services representing municipalities of varying sizes in both rural and urban areas in southern, western, and northern Sweden will be collected. Thereafter, first-line managers, RNs, and direct care staff working in RCFs will be invited to participate in the study. They will receive oral and written information about the study at workplace meetings. Interested persons will be asked to contact a member of the research team. The estimated sample size will range between approximately 15 and 20 participants in each group; to ensure variation in experiences, participants will be drawn from different regions of Sweden, diverse workplaces, and will vary in age and work experience [57].

Data Collection

Individual and focus group interviews will be performed with leaders and direct care staff. Before data collection, pilot interviews will be conducted to test the interview guide and format. Before the interview, the participants will be asked to provide demographic information. Both the individual and the focus group interviews will be guided by a semistructured interview guide. The focus groups will be relatively small (3-5 participants) to enable digital focus group interviews. Focus group interviews will be conducted by a moderator and an observer. The moderator will facilitate the discussion and ensure that all participants are involved, and the observer will take notes and ask complementary questions [58]. All interviews will be audio recorded, transcribed verbatim, and pseudonymized. The interview guides are in Swedish and are available on request.

For the metasynthesis, data will be extracted from empirical studies retrieved from relevant databases. The review (RQ 5) for establishing the evidence base will be conducted by searches across relevant databases for studies on PCL published in English or a Scandinavian language within the past 20 years, ensuring both relevance and accessibility. Abstracts will be systematically reviewed to assess their alignment with the study's objectives. Articles that pass this stage will then undergo a quality assessment, following the established guidelines outlined by the Swedish Agency for Health Technology Assessment and Assessment of Social Services [59]. Only studies demonstrating high methodological quality will be included in the analysis.

Analyses

The interview material concerning leaders' understanding of PCC (RQ 1) will be analyzed using a *discourse analytic approach* with a focus on the question "How do leaders talk about PCC?" The analysis will be guided by constructing discourses on PCC to articulate its various aspects and categorize language use regarding specific ways of talking about PCC [60].

The interview material concerning leaders' experiences of ethical challenges during the COVID-19 pandemic (RQ 2) and the meaning of PCL from the perspective of leaders (RQ 3) will be analyzed using *conventional content analysis*, as described by Hsieh and Shannon [61]. The content analysis will be conducted in several steps: (1) an initial reading of the texts; (2) repeated reading of the transcripts, highlighting text (meaning units) related to the aim; (3) a line-by-line coding of meaning units; (4) grouping of the codes into meaningful clusters; and (5) sorting the clusters by content, grouping content into subcategories, and abstracting to main categories. The analysis will be conducted as a constant iteration between the text, codes, clusters, and possible categories.

The interview material concerning staff experience of ethical challenges in the provision of PCC during the COVID-19 pandemic (RQ 2) and the experience of the cocreation of development and implementation of the intervention (RQ 14) will be analyzed using *thematic analysis*, as described by Braun and Clarke [62]: (1) familiarizing with the data, including multiple readings of the transcripts and a shared discussion of all authors' initial understanding of the data; (2) coding; (3) sorting the codes into preliminary themes; (4) reviewing and validating the themes in relation to the data; (5) compiling an overview (similar to a thematic map) as a basis for defining and naming the themes; and (6) writing a report [62].

The *metasynthesis* (RQ 5) of the included studies from the database search will be analyzed and synthesized into common themes, covering the content of PCL in existing research. This comprehensive approach will allow for the integration of both theoretical perspectives and empirical evidence. The extracted data will be systematically organized into codes and categories to identify recurring themes, patterns, and variations. Codes and categories will be synthesized into overarching themes that connect the findings to a broader theoretical framework [63]. This will result in a comprehensive compilation of existing evidence regarding PCL.

Studies With a Mixed Methods Approach

The mixed methods studies will use group concept mapping (GCM) to explore the conceptualization of PCL in RCFs from the perspective of RCF leaders (RQ4) and to refine the intervention components (RQ10).

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Samples

The sample for the mixed methods studies will likewise be purposively selected to include participants with relevant experience [56]. After permission from the heads of municipal social services has been obtained, RNs (RQ 4) and first-line managers (RQ 4 and RQ 10) will be invited to participate. They will be informed about the study and get in touch with the research team if interested, as is the case with the qualitative studies. The minimum sample size for a GCM study is 20 participants, although a larger sample of 25 to 40 is often used to achieve a more robust result. The sample size for the GCM studies ranges from 30 to 40 [64].

Data Collection and Analyses

Data will be collected and analyzed using GCM. This is a collaborative process that combines qualitative and quantitative data collection and analysis with a specific focus. In RQ 4, the characteristics of PCL are the focus, while the focus of RQ 10 is the identification of intervention components. GCM is a structured method for organizing and "mapping" ideas, needs, and preferences [65]. It involves the following steps: (1) brainstorming with participants using a prompt; (2) organizing the responses (where additional aspects from RQ 3 will be added for RQ 10, if missing) and entering them into the program Groupwisdom (Concept Systems Inc); (3) participants rate the responses in relation to how important and how feasible the response is on a 4-point scale where 1="not at all" and 4="very much"; (4) analyzing the responses based on their relationships (qualitative analysis) and ranking (basis for quantitative analysis); (5) conducting quantitative analysis of the organization and ranking in the Groupwisdom program, resulting in ≥1 visual figures; and (6) interpreting the visual figures together with the participants [66].

Studies With a Quantitative Approach

The studies with a quantitative approach involve the translation and cultural adaptation of the ACLQF (RQ 6); development of an instrument to measure PCL (RQ 7); identification of other relevant outcome measures concerning staff, leaders, and care quality (RQ 8); and identification of health economic outcome measures and economic considerations (RQ 9). The quantitative studies will have correlational (RQ 6 and 7) and descriptive (RQ 8 and 9) designs.

Samples

The sample for the studies with correlational designs will be composed of RNs (RQ 6), first-line managers (RQ 6 and 7), and direct care staff (RQ 7). The estimated sample size for RQ 6 is 30 participants (15 RNs and 15 first-line managers), as the preferred range for calculation of item-level content validity index (I-CVI) is approximately 10 experts from each group [67]. The estimated sample size for RQ 7 is 40 first-line managers participating in the development of the scale and approximately 100 direct care staff for the evaluation of its psychometric properties. The sample size of 100 is preliminary, as it depends on the number of items in the scale and needs to be adequate for the calculation of both internal consistency and test-retest reliability, as well as for exploratory factor analysis [68]. The studies with a descriptive design will be based on literature searches (RQs 8 and 9).

Data Collection and Analyses

The framework will initially be translated into Swedish using forward and backward translation (English-Swedish-English) by 2 independent translators. Thereafter, the participants will be asked to complete a web survey in which they will rate the relevance of the 40 translated statements in the framework on a 5-point scale, ranging from 1="not at all relevant in a Swedish context" to 5="to a high degree relevant in a Swedish context." The test of the prefinal version, the cultural validation, will be examined using the I-CVI, where the number of participants giving the rating "relevant" (3 or 4) for each item will be divided by the total number of participants. When all participants rate an item as relevant, the I-CVI is 1.0. As recommended by Polit et al [67], a scale can be judged as having excellent content validity if the items have an I-CVI of ≥0.78. The cultural adaptation of the ACLQF has already been finalized and published (refer to the Results section).

The development of an instrument to measure PCL in RCFs from the perspective of staff, the PCL Questionnaire, will follow the Consensus-Based Standards for the Selection of Health Measurement Instruments (COSMIN) guidelines [69]. The development will be conducted in four phases: (1) deriving items based on the results from RQ 5, (2) preliminary testing, (3) analysis, and (4) psychometric evaluation [68]. The developed instrument will be used as the primary outcome measure when investigating intervention effects.

In the first phase, relevant statements (items) will be developed through the following steps: (1) formulation of specific items, where statements are carefully crafted to be clear, concise, and easy to understand; (2) face validity testing through cognitive interviews with managers and staff to evaluate the comprehensibility and interpretability of the items and to identify potential issues; and (3) revisions based on feedback, where items are revised for clarity and precision according to the feedback obtained during the interviews.

In the second phase, preliminary testing of the instrument will be conducted using classical test theory to identify and minimize measurement errors. Classical test theory will also be used to reduce the number of items and thus optimize the instrument's efficiency. In the third phase, a 2-parameter item response theory model will be applied to gain a detailed understanding of how individual items function regarding difficulty and discrimination. This model addresses how well each item differentiates between participants with varying degrees of the ability in focus (ie, varying degrees of PCL). In the fourth phase, psychometric evaluations will be conducted to ensure the instrument's reliability and validity. This fourth step will also include a test-retest assessment to examine the instrument's stability over time, as well as refinement and adjustments to the instrument following the results of the psychometric evaluations. The instrument will be freely available for research purposes and academic use. Commercial exploitation and use in business activities will not be permitted without prior written approval from the authors.

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Relevant outcome measures concerning leaders, staff, care quality, and economic measures (RQs 8 and 9) will be identified through a systematic search of the literature, where instruments showing reliable and valid psychometric properties will be selected. The identified instruments will be discussed in the steering group and the reference group regarding quality, feasibility, and the possibility of detecting intervention effects. These instruments will be used as secondary outcome measures when investigating intervention effects.

The Intervention

The insights gained from the earlier WPs (WP I-III; Figure 1) will guide the development of the intervention content, structure, and evaluation methods. A cluster randomized quasi-experimental study will be conducted, focusing on PCL through a complex intervention specifically tailored to support first-line managers in the care of older people. This design will ensure that the intervention is evidence based, relevant, practical, and user-friendly, addressing the unique challenges of—and opportunities within—the aged care context. By systematically incorporating knowledge from the earlier phases, the intervention aims to create a well-considered approach to strengthen PCL practices and gradually impact PCC quality. During the initial phases, the program theory will undergo further refinement. The tentative conceptualization posits that by supporting the leaders in practicing PCL, the implementation and overall quality of PCC will increase. This improvement is expected to positively affect the staff's working environment, working conditions, and work satisfaction, ultimately contributing to the well-being of residents.

As the intervention concerns leaders, an appropriate cluster would be the unit for which each leader is responsible. However, additional information derived from WP III is needed to understand how different units are connected, to estimate the risk of contamination and determine which units should be included in the randomization.

The measurement of intervention effects (RQ 13) will be based on the results from RQs 6 to 9, while the sample will be composed of first-line managers and direct care staff. The sample size will be determined by power analyses based on expected differences in primary and secondary outcome measures.

Timeline

Some studies in WP I started already in 2022 and will be concluded by 2026. WP II will run between 2026 and 2027, WP III will run through 2028, and WP IV is planned to start in 2029. Finally, WP V will run in parallel with WP III and IV (Figure 2).

Figure 2. Timeline for the work packages (WPs).

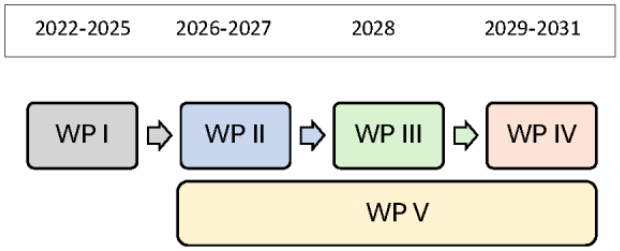

Research Group

The research group is multidisciplinary and represents the subjects of nursing, social work, medicine, geriatrics, rehabilitation, and health economics from 4 different universities: Kristianstad University, Umeå University, and Karolinska Institute in Sweden and the University of Sydney in Australia. The group consists of 4 professors, 1 associate professor, 3 researchers, and 2 doctoral students. Additional postdoctoral and doctoral students will be assigned. The University of Sydney will be involved in WP I only, particularly in relation to the adaptation of the framework, while the remaining WPs will be conducted in Sweden.

Project Organization

The project has a steering group composed of representatives from the municipalities at the government level, the principal investigators, and the coordinators of the 5 WPs, who are responsible for strategic planning and decisions. The project also includes a reference group of direct care staff responsible for ensuring the clinical relevance of the results and the intervention. These groups will meet approximately 4 times a year. The project group will meet every month via a digital meeting forum.

Ethical Considerations

This project involves several sensitive issues that need to be addressed, and we will promote ethical awareness throughout the project. The main ethical challenge concerns the risk of taking up the participants' working time, which would otherwise be dedicated to supporting older people in their care and, in the case of the leaders, the personnel. This may be balanced by the fact that the leaders' participation in the study can contribute to new knowledge, which, in turn, can help improve the quality of care.

In all empirical studies, the participants will receive both oral and written information about the study as well as about their right to withdraw from ongoing participation at any time without needing to state a reason. The participants will report their interest in participating directly to the researchers, thus reducing the risk of pressure from colleagues or managers. All participants will provide written informed consent. Information about the study participants will be coded, with the code list being stored in a safe locker, apart from the data. Only the responsible researchers will have access to the code list. The material will be held in secure custody at Kristianstad University (WP I) and Umeå University B (WP II-V) in accordance with the universities' regulations concerning data storage and

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security. The confidentiality of the participants will be kept in the publications by using pseudonymns. All studies will be performed in line with the Declaration of Helsinki. The studies in WP I have been approved by the Swedish Ethical Review Authority (number 2021-000413). Additional ethics approval applications for WPs III-V will be submitted. The participants will not receive any compensation for their participation.

Results

As of July 2025, a total of 6 studies in WP I have been conducted (relating to RQs 1-3 and RQ 6). Of the 6 studies, 5 are published [70-74] and 1 has been submitted for publication (M Jönsson, unpublished, July 2025). The study related to RQ 4 is in progress.

Leaders' Understanding of PCC

The findings indicate that the leaders recognized the importance of considering older people's autonomy, individual needs, and care environment in PCC. However, their narratives also revealed paradoxes concerning respect for autonomy, the significance of the past and the present, and the shared environment. Leaders play a vital role in emphasizing autonomy while offering practical support to staff navigating these challenges. Achieving PCC involves a delicate balance between meeting residents' needs, respecting their home environment, and ensuring staff well-being. These findings have recently been corroborated (M Jönsson, unpublished, July 2025).

The Meaning of PCL in RCFs From the Perspective of Leaders

Our findings indicate that providing PCL comprises 2 elements: being person-centered by focusing on relationships with employees and leading PCC by prioritizing the older persons [70]. The findings highlight that in a complex and fragmented aged care organization, PCL requires not only skills and abilities but also an embodiment of person-centered principles to convey them to employees and older people simultaneously. PCL is defined by leaders' beliefs, abilities, and actions and not necessarily by their position of authority [71].

Ethical Challenges in Providing PCC During the COVID-19 Pandemic

The findings show that during the COVID-19 pandemic, leaders needed to prioritize the needs and safety of the society and the care facility over individual residents' needs, which impacted the possibility of providing PCC. Moreover, it was difficult to balance protecting the residents from infection while preserving their dignity and autonomy [72]. Among the ethical challenges experienced, staff witnessed older persons being deprioritized and receiving unequal care, which violated their human rights. Staff felt constrained and undervalued, with a deep sense of being abandoned. Their own integrity and autonomy were also severely compromised. Fulfilling their professional duty came at great personal risk, as staff had their lives on the line while working in an atmosphere of pervasive fear [73].

Translation and Cultural Adaptation of the ACLQF

The ACLQF was translated into Swedish, cross-culturally adapted, and validated. It was shown to be useful and suitable for leaders in residential care in Sweden. The framework clarifies the leader's role and identifies leadership attributes and requirements for PCL in residential care, thereby providing support to leaders by framing PCL [74].

Discussion

Anticipated Findings

The PERLE study seeks to achieve an in-depth exploration of the conceptual foundations, experiences, mechanisms, strategies, and outcomes of PCL; develop tools for implementation of a quasi-experimental complex intervention; develop, test, and implement the intervention; and investigate its effects. A further aim is to generate knowledge about the process of development and implementation. So far, several explorative studies have been conducted in WP I; once all studies in WP I are complete, their findings will serve as a foundation for the subsequent WPs.

In WP I, we used a broad definition of "leaders in RCFs," including both RNs, in their role as clinical leaders, and first-line managers as RCF leaders. However, our findings, along with previous research, for example, by Josefsson and Hansson [75], suggest that Swedish RNs in municipal care for older people do not inherently view themselves as leaders per se. This fact requires attention. In the upcoming studies within the PERLE study, our primary focus will therefore be on first-line managers' leadership. Our plan is for subsequent studies to focus solely on RNs and their leadership role in the provision of PCC.

Rigor and Methodological Aspects

There are several methodological aspects to be considered in the outline of the project concerning both the qualitative and quantitative studies. *Qualitative research* is evaluated based on trustworthiness, including credibility, dependability, confirmability, and transferability [76]. One aspect of credibility is accuracy in the selection of participants. In the studies, we will strive for a broad variation in experiences by including direct care staff and leaders representing a range of experience, education, and care contexts. This will also increase the transferability of the findings. Credibility concerns whether the study's findings are correct and accurate [76]. This is the responsibility of the researchers and depends on the research methods used. Credibility will be strengthened by using well-known and established methods, researcher triangulation, and user involvement. The steering group and reference group will further enhance referential adequacy. Dependability refers to the consistency and reliability of a study's results and the possibility for other researchers to replicate the study. Therefore, we will provide a thorough description of the context, sample, data collection, and analysis in each study. The confirmability of a study concerns objectivity, accuracy of the material, relevance, and meaning [76]. We will carefully provide audit trails of each step of the data analysis and present and discuss our preunderstandings of the phenomena in focus. Participant quotes will be provided to support the findings. The entire research group will be involved in the synthesis of data, thereby enabling a multifaceted analysis while also reducing the impact of individual researchers' preunderstanding of the phenomenon. Transferability concerns whether, and to what extent, the results are applicable in other contexts, circumstances, and settings

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[76]. Therefore, we will provide detailed descriptions of the context, participants, and data collection procedures.

Quantitative research is evaluated based on reliability and internal and external validity. Reliability in WP IV will concern the instruments developed or used to investigate intervention effects regarding homogeneity, stability, and equivalence. Each instrument will be critically reviewed for its psychometric properties in line with the COSMIN guidelines [69]. Internal validity embraces aspects of content and face validity, addressing whether the instruments measure what they are intended to measure. In the PERLE study, these aspects will mainly be highlighted in WP II, which has a high degree of user involvement. In WP II, validity—addressing whether a test accurately measures the concept being studied—will be assessed regarding homogeneity, convergence, and theory evidence (construct validity), as well as convergent, divergent, and predictive validity (criterion validity) [56].

The development of the intervention study calls for further attention concerning internal validity. The main potential threats to internal validity will be organizational and economic changes that might affect the outcomes, testing and instrumentation effects as the participants become familiar with the outcome measures, and selection bias in the way the intervention and control units are chosen. As there is a high turnover rate among Swedish RCF staff, aspects of attrition must be considered when calculating the sample size [56]. As leaders and staff in residential care will be closely involved in WP III, there is strong potential to identify risks, especially resistance related to organizational culture, and explore ways to mitigate them.

Plan for Dissemination

The plan for communicating the results involves different target groups: (1) staff and leaders in the care of older people; (2) decision makers at municipal, regional, and national levels; and (3) the scientific community and society at large, as outlined in Textbox 1.

Textbox 1. Strategies for disseminating the research findings.

1. The dissemination of the research results for staff and leaders will take place via established collaborations and forums, such as research breakfasts and seminars.
2. The dissemination of research results to decision makers at municipal and regional levels will be achieved via county-wide management seminars and established channels, such as the project steering group.
3. The scientific community and society at large will be informed via several channels, including the following:
   - Publications in reputable scientific journals to ensure credibility and reach a broad target group, preferably national and international researchers, as well as relevant education at undergraduate, advanced, and doctoral levels
   - National and international conferences, seminars, and workshops where both the research results and the methods and cocreative design will be communicated to, and discussed with, health and care managers in health and care, health care personnel, decision makers in the care of older people, relatives, interest organizations, and international researchers
   - Popular science articles in Swedish to reach key target groups in health care and care of older people, as well as audiences outside academia
   - Course literature, via already established editorial positions and chapter authorship for teaching materials at undergraduate and advanced levels. The knowledge generated by the project can be included in future editions and thus form the basis for training future care and nursing leaders.

Conclusions

Ultimately, this project aims to enhance PCC by focusing on the needs and preferences of older people and to improve their quality of life. The PERLE study addresses a key challenge highlighted during the COVID-19 pandemic: balancing the well-being of staff with the care needs of older people. The project aims to provide new insights into the need to support first-line managers in advancing PCC in RCFs, understanding their specific challenges, and creating tailored support measures for the implementation of PCL. Improving PCL is expected to enhance working conditions and address recruitment, retention, and absenteeism challenges in RCFs. The intervention could potentially reduce staff turnover and related costs while supporting leadership training and education to benefit future leaders in aged care. The results will likely be applicable in an international context, that is, beyond Scandinavian countries, especially in countries with similar health care systems. All instruments will be made available for translation and cultural adaptation for research purposes.

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Data Availability

The datasets generated or analyzed during this study will available in Swedish from the corresponding author on reasonable request.

Authors' Contributions

AKE and AB outlined the paper, and with AKE taking primary responsibility for drafting it. Both authors have approved the final version.

Conflicts of Interest

None declared.

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Abbreviations

ACLQF: aged care clinical leadership qualities framework
COSMIN: Consensus-Based Standards for the Selection of Health Measurement Instruments
GCM: group concept mapping
I-CVI: item-level content validity index
PCC: person-centered care
PCL: person-centered leadership
PERLE: Person-Centered Care and Leadership in Residential Care Facilities
RCF: residential care facility
RN: registered nurse
RQ: research question
WP: work package

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Protocol

Implementing Remote Radiotherapy Planning to Increase Patient Flow at a Johannesburg Academic Hospital, South Africa: Protocol for a Prospective Feasibility Study

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Abstract

Background: Access to timely radiotherapy in resource-constrained environments, particularly low- and middle-income countries (LMIC), is hampered by infrastructure constraints, workforce shortages, and a rising cancer burden. Remote radiotherapy planning (treatment planning as a service [TPaaS]) has the potential to enhance workflow efficiency, reduce wait times, and expand access to treatment. However, its integration and feasibility in LMIC public health systems remain underexplored.

Objective: This study evaluates the feasibility and initial effectiveness of remote radiotherapy planning using the Varian Eclipse system integrated with Elekta Versa HD linear accelerators (LINACs) at the busiest public hospital in South Africa. The primary goal is to determine whether remote planning can maintain plan quality while enhancing efficiency and minimizing treatment delays.

Methods: A prospective, single-site, pilot study is being conducted at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH) in 2 phases. Phase 1 (feasibility) encompasses system commissioning, including beam modeling, computed tomography (CT)-to-electron density calibration, multileaf collimator (MLC) optimization, and dose calculations using the anisotropic analytical algorithm. System performance is validated through gamma index analysis (≥95% pass at 3%/3 mm). Interoperability and workflow readiness are assessed using simulated clinical scenarios and time integration steps. Phase 2 (effectiveness/impact) evaluates operational outcomes in 100 screened adult patients (≥18 years) with cervical, breast, prostate, head and neck, or rectal cancers requiring curative radiotherapy. Patients are grouped by cancer type (25 per group). Time to treatment, plan quality, and system efficiency will be compared with historical in-person planning data. Key workflow metrics include dates of first consultation, CT simulation, planning initiation, plan approval, quality assurance, and treatment start and completion.

Results: The study commenced enrollment in November 2023, with completion anticipated by mid-2025. As of July 2024, approximately 44 patients were screened and are anticipated to complete the remote planning. Initial findings show successful MLC transmission and dosimetric leaf gap optimization through iterative testing. Gamma pass rates exceeded 90% on both clinical and test servers, demonstrating initial accuracy. Results, including planning timelines, quality assurance outcomes, and system

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performance, will be available following comprehensive analysis in the third quarter of 2025. Preliminary findings indicate effective integration of remote planning in a resource-constrained public health sector setting.

Conclusions: This study shows that remote radiotherapy planning is feasible and might improve cancer treatment in LMIC. The integration of commercially available systems, such as TPaaS, was successfully achieved without compromising dosimetric quality and ensured workflow continuity. Remote planning could serve as an effective tool to reduce treatment delays and enhance resource utilization in oncology units facing high demand. These findings offer valuable insights into technical integration, quality planning, and workflow outcomes, which can inform the future implementation of effective strategies in resource-constrained settings.

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KEYWORDS

remote radiotherapy planning services; radiotherapy; remote radiotherapy; feasibility; treatment planning; quality assurance; remote treatment; cancer care

Introduction

Research indicates that there is a growing global demand for cost-effective, high-quality [1-4], and sustainable radiotherapy solutions in low- and middle-income countries (LMIC) to address rising cancer cases [5]. However, existing strategies often lack affordability and adequate support, particularly in LMIC, where cancer incidence is high, staff shortages are severe, and health care resources are constrained [6]. Consequently, 55 countries lack radiotherapy, and 80 countries face significant shortages [5]. Even in high-income countries (HIC), centralized radiotherapy networks limit access, particularly in geographically dispersed populations (for example, in Canada, Australia, and the United Kingdom) [7-10].

The quality of radiotherapy relies on accurate treatment planning that optimally balances effective tumor control with the preservation of surrounding healthy tissues [11]. Technological advances over the past two decades have enhanced the precision the delivery and planning of radiotherapy, yet significant challenges remain [12]. In South Africa, a rising cancer incidence, limited radiotherapy equipment, and critical staff shortages contribute to delays ranging from several months to years (ranging from 3 months to 5 years) [13]. Public sector facilities experience prolonged waiting times, underscoring the need for solutions to optimize radiotherapy workflows [14-16], particularly in LMIC [17].

Access to cancer treatment in LMIC is hindered by limited infrastructure, treatment facilities, planning systems [18], and human resources [19,20]. Although advanced modalities, such as intensity-modulated radiotherapy (IMRT), volumetric-modulated arc therapy (VMAT), and emerging therapies [21], offer significant potential, their implementation is often resource-intensive and time-consuming. In Africa, the cancer burden is expected to rise sharply, with new cases projected to increase from 844,000 in 2012 to over 1.5 million in 2030 [19,22], driving a parallel rise in the demand for radiotherapy services. The World Health Organization (WHO) and International Atomic Energy Agency (IAEA) have provided radiotherapy guidelines to support the development and implementation of radiotherapy services globally [23]. However, many African countries lack comprehensive cancer care infrastructure. As of 2020, the continent had only 430 external beam radiotherapy megavoltage units, with over one-half concentrated in Egypt (119 units) and South Africa (97 units) [19]. Addressing radiotherapy needs in such settings necessitates not only physical infrastructure but also trained personnel, robust quality assurance (QA) protocols, and integration of clinical workflows.

Remote treatment planning, including treatment planning as a service (TPaaS), offers a promising strategy to enhance access and reduce delays in radiotherapy delivery in resource-limited environments. Off-site planning enables the redistribution of specialized expertise without requiring patient relocation, thus optimizing service delivery in under-resourced settings. Although remote radiotherapy planning and artificial intelligence (AI)–based systems are increasingly studied in HIC [24-26], limited research has explored their applicability and impact in LIMC, particularly in the South African public sector. A notable exception is the study by McGinnis et al [27], who surveyed radiation oncology providers across sub-Saharan Africa (SSA; including Botswana, South Africa, and Tanzania) and Central America (Guatemala) regarding their experience with the Radiation Planning Assistant, web-based software aimed at improving radiotherapy planning accessibility and quality in LMIC. Despite its promise, the feasibility of remote planning for reducing overall treatment timelines requires further investigation. Therefore, a comprehensive understanding of remote radiotherapy planning's potential to improve patient flow in LMIC, particularly South Africa, is essential. To evaluate the feasibility of remote radiotherapy planning in resource-constrained settings and commissioning of remote radiotherapy planning, measurement of beams is required.

Given the substantial delays in radiotherapy initiation, ranging from 3 months to 5 years, at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH), the region's largest public sector radiotherapy center, there is a pressing need for workflow innovations. CMJAH primarily manages cervical, prostate, breast, head and neck, and rectal cancers. Delays are exacerbated by a shortage of radiotherapy machines and a critical shortage of radiotherapists and medical physicists. To date, no studies have evaluated the feasibility of remote radiotherapy planning in this context. Therefore, this study presents the implementation of remote radiotherapy in the Radiation Oncology Division at

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CMJAH. This study has two primary aims: The first is to (1) evaluate the feasibility of implementing remote radiotherapy planning to improve workflows, with a focus on integrating the Varian Eclipse treatment planning system (TPS) with Elekta Versa HD linear accelerators (LINACs). This includes assessing workflow integration, QA processes, planning system functionality, and analysis of dose calculation data through comprehensive commissioning in a resource-constrained setting. The second is to (2) explore the impact of remote workflows on key operational metrics, such as time-to-treatment, resource utilization, and workflow efficiency. The study hypothesizes that remote radiotherapy serves as an efficient, cost-effective alternative to conventional planning methods, with the potential to reduce treatment backlogs, enhance throughput, and improve care quality. The study provides critical insights into the feasibility of remote planning in LMIC, with implications for informing future strategies to scale radiotherapy access in resource-constrained settings through digital innovation and clinical workflow optimization.

Methods

Study Design and Sample

A prospective, observational, descriptive study aimed at assessing the feasibility and efficacy of remote radiotherapy treatment planning feasibility will be conducted at CMJAH in Johannesburg, South Africa. The primary focus is on assessing implementation feasibility and workflow impact, rather than achieving statistical significance; no formal power calculations were performed prior to study initiation.

The pilot study aims to enroll 100 adult patients with histologically confirmed cervical, breast, prostate, head and neck, or rectal cancer. This sample size is deemed sufficient to assess operational efficiency feasibility and system integration and to generate preliminary data regarding the clinical usefulness and workflow efficiency of remote treatment in a resource-constrained environment.

Study Settings

CMJAH hosts the busiest radiation oncology unit in South Africa, receiving the highest number of national radiotherapy referrals annually. However, the unit faces significant treatment delays due to severe equipment and human resource constraints. Reported wait times range from 12 months to 18 months for breast cancer and extend up to 5 years for prostate cancer [28].

Evidence from clinical trials demonstrates that delayed initiation of radiotherapy is associated with increased risk of local recurrence across several tumor types in cancer patients [29]. The current patient workflow for treatment planning is shown in Figures S1 and S2 in Multimedia Appendix 1. This pilot study seeks to assess the integration of remote treatment planning to improve efficiency, standardization, and equitable access to quality care objectives aligned with broader global health equity efforts in oncology.

Eligibility Criteria

Inclusion and Exclusion Criteria

To be eligible for participation in this pilot study, patients must meet all the following inclusion criteria: age ≥18 years; histologically confirmed diagnosis of cervical, breast, prostate, head and neck, or rectal cancer; presentation to the Radiation Oncology Division for curative radiotherapy; and provision of written informed consent.

Patients meeting these criteria are informed about the study in a private room, with a trained member of the research team. On-site translators are available to assist where necessary. For interested patients, the consent form will be explained in detail. Upon agreement, patients will provide written consent using documentation approved by the institutional Human Research Ethics Committee.

Exclusion criteria include patients younger than 18 years old, previous history of radiotherapy, and current need for emergency or palliative treatment.

Withdrawal of Participants

Participants have the right to withdraw from the study at any time, without penalty or effect on their ongoing clinical care. Researchers may exclude participants requiring urgent interventions, and those who discontinue participation prior to completing the required study procedures will be censored and excluded from analyses assessing the impact of remote planning on treatment timelines and workflow metrics.

Recruitment Procedures

Recruitment will be conducted in the Radiation Oncology Division at CMJAH. The recruitment and screening process is summarized in a simplified diagram (Figure 1) based on the CONSORT (Consolidated Standards of Reporting Trials) diagram, as described by Ruslin et al [30]. The study aims to enroll up to 100 patients in total; however, as of July 2024, 44 patients had been enrolled. The anticipated final cohort will include approximately equal representation across 4 cancer types, including cervical, breast, prostate, head and neck, and rectal cancers (approximately 25 per group), though final distributions may vary based on real-time patient presentation and eligibility. This sample size is deemed sufficient to evaluate feasibility and generate preliminary efficacy data on remote radiotherapy treatment planning services.

To identify eligible participants, all individuals presenting to the Radiation Oncology Division at CMJAH will be screened by the clinical staff following initial consultation and staging (as illustrated in Figure 2).

Prior to enrollment, participants will receive comprehensive information regarding the risks and potential implications of study participation. Informed consent will be obtained after confirming the participant's understanding and agreement to participate in the study

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Figure 1. CONSORT (Consolidated Standards of Reporting Trials) flowchart of the remote radiotherapy treatment planning service.

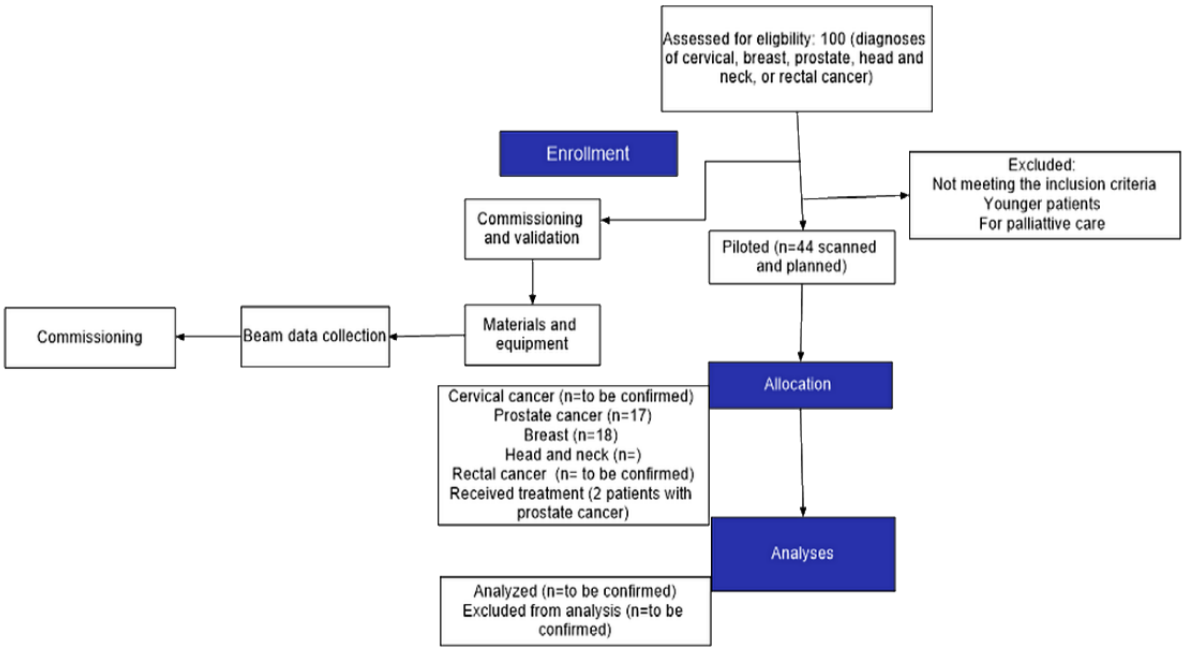

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Figure 2. Critical decision points and corresponding time stamps are meticulously recorded at each stage of the process. QA: quality assurance; RO: radiation oncologist.

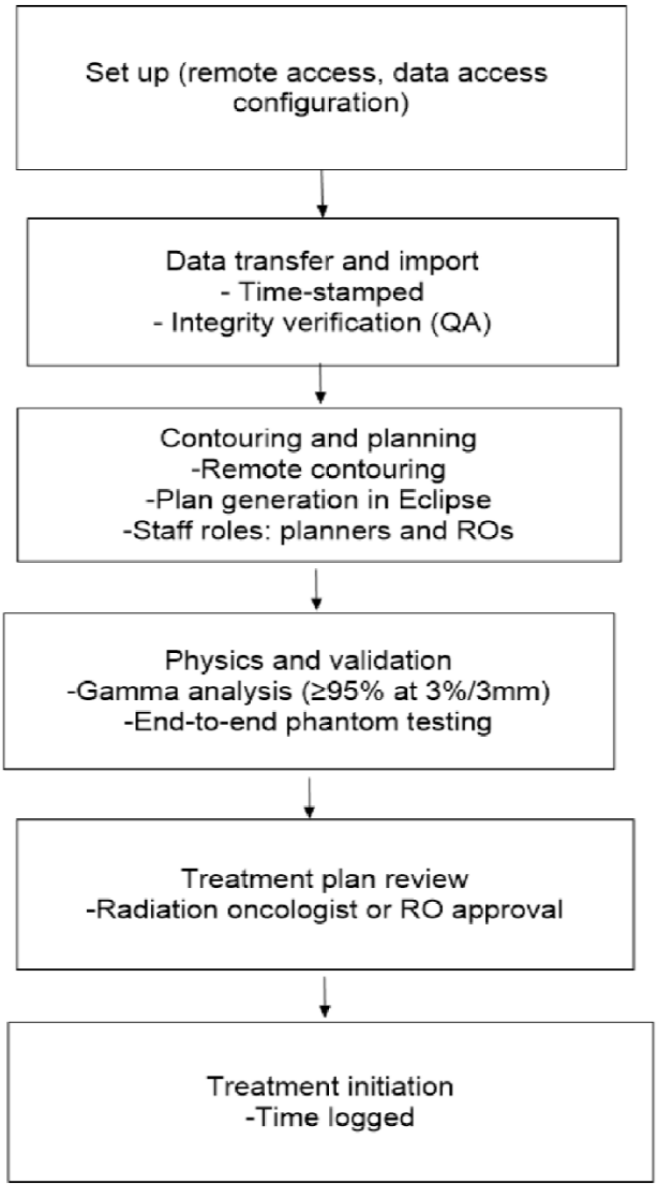

Feasibility and Efficacy Assessment

To evaluate the potential for integrating remote treatment planning within resource-constrained clinical settings, the study was designed in 2 phases: Phase 1 (feasibility assessment) and Phase 2 (efficacy assessment). This study focuses solely on Phase 1, which evaluates the operational and technical feasibility of remote radiotherapy planning. Phase 2, which will assess clinical efficacy outcomes, is planned for future research.

Phase 1: Feasibility Assessment

The feasibility of remote radiotherapy planning was evaluated through strategic modifications to the existing radiotherapy workflow to optimize task execution, enhance data interoperability, and streamline coordination among clinical teams. The components and performance metrics described in the following sections were applied (see Figure 2).

Assessment of Workflow Integration Feasibility

The integration of remote treatment into existing operations was assessed by documenting the time metrics for core planning activities, including remote contouring, treatment plan generation, and review of plans by radiation oncologists. These data will serve to describe the operational characteristics inherent to the remote planning process.

System Integration and Data Integrity

The assessment of system integration and interoperability will involve comprehensive end-to-end testing of the Varian Eclipse TPS with Elekta Versa HD LINACs. This methodical process was designed to ensure seamless integration, reliable data transfer, and technical preparedness for clinical implementation.

Beam Characterization and Integration Validation

Validation of the integration of the remote TPS will be conducted through a comprehensive series of technical assessments. Consequently, qualified medical physicists conducted the comprehensive beam modeling validation, which

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included parameters such as percent depth dose (PDD) curves, beam profiles, and output factors (OFs), with uniformity verified across all 4 LINACs. Additionally, the calibration of computed tomography (CT)–to-electron density calibration curves will be rigorously validated to ensure dosimetric accuracy in patient simulations.

Dosimetric Analysis and Workflow Timing and Logging

The evaluation of dosimetric accuracy will be conducted using gamma index analysis, adhering to a predetermined acceptance threshold of ≥95% at 3%/3 mm criteria, thereby ensuring the clinical safety of remotely generated plans through meticulous timing and logging. Furthermore, time-stamped logs will be used to assess the duration of critical integration processes, encompassing data transfer setup, verification of CT-to-electron density calibration, treatment plan import and export, and QA system configuration.

Operational Readiness and Success Criteria

Feasibility success was defined by (1) accurate and uninterrupted data exchange between the TPS and treatment delivery system, (2) plan acceptability based on dosimetric QA, and (3) uninterrupted clinical operations without the need for manual overrides or unplanned troubleshooting.

Clinical Review and QA Documents

The review and approval of the clinical suitability of autocontours and final treatment plans will be conducted by study radiation oncologists. As such, all validation procedures, comprising beam and imaging data verification, dose calculations, and QA results, will be meticulously documented using standardized forms and institutional standard operating procedures, in accordance with international guidelines (eg, American Association of Physicists in Medicine [AAPM], IAEA).

Training Staff (Future Work)

Systematic training sessions on the TPaaS will be implemented to ensure consistent data collection and workflow adherence. The training will be conducted by a collaborative team that includes personnel from Siemens-Varian alongside the study investigators. The training curriculum will encompass user manuals, live demonstrations, video tutorials, and hands-on workshops meticulously designed for the TPaaS and Eclipse remote planning systems. The 3-day program will encompass methodologies for data collection, strategic planning of workflows, protocols for system access, and processes for ensuring QA. Staff competency will be evaluated through supervised trial runs, with follow-up on-site observation for 1 week to 2 weeks to ensure sustained workflow integration. All training activities will be executed in accordance with ethical standards approved by the institutional review board.

Summary of Phase 1

In summary, successful integration of remote treatment planning will be defined by (1) technical interoperability-reliable transmission of imaging and planning data between LINAC systems; (2) dosimetric reliability and clinical acceptability of remotely generated images confirmed through standardized thresholds, as verified through patient-specific QA metrics; and (3) workflow sustainability, or the demonstrated ability to implement the remote planning workflow within existing clinical operations, without unplanned interruptions or manual interventions.

Phase 2 Efficacy Assessment (Future Work)

In contrast to the technical feasibility focus of Phase 1, Phase 2 will assess the operational effectiveness of the integrated remote planning system for improving clinical workflow efficiency and reducing treatment delays. The operational metrics described in the following paragraph will be evaluated.

For comparative workflow analysis, the impact of remote planning will be evaluated at key workflow stages, including the time from initial patient presentation to scanning, time from scanning to contour approval, time from contour approval to plan acceptance, and total time from patient presentation to treatment initiation. In addition, QA will be timed and quantitatively compared with historical data or matched in-person control cohorts using a 1:1 matching methodology. The primary outcome is reduction in total time to treatment; secondary outcomes include increased patient throughput and reductions in backlogs.

Although radiotherapy planning is hypothesized to reduce delays, its effectiveness for accelerating treatment workflows in resource-constrained settings will be rigorously evaluated. This phase aims to determine whether a remote planning system provides measurable operational benefits in a routine clinical environment.

A detailed analysis of Phase 2, including its methodology and findings, will be presented in future studies.

Proposed Workflow: Remote Radiotherapy Planning

This study uses the Eclipse (Varian) remote radiotherapy planning system, integrated AI-supported tools, and institutionally standardized QA processes. The system adheres to Digital Imaging and Communications in Medicine (DICOM) standards and is designed to facilitate efficient, high-quality treatment planning across distributed teams. Radiation oncologists and dosimetrists can create customized plans, visualize imaging data, and collaborate remotely. Varian's systems ensure the accuracy and safety of patient data.

CT is performed at the CMJAH Radiation Oncology Division. Once acquired, CT data sets are uploaded to a secure server hosted within the facility and accessed remotely via a secure virtual private network connection installed by Siemens-Varian Healthineers in compliance with the South Africa Protection of Personal Information Act.

Organs at risk (OARs) are delineated using the Monaco and Limbus AI auto-contouring systems, as illustrated in Figure 3. These contours are then reviewed and adjusted by an on-site radiation oncologist as needed to ensure anatomical fidelity and protocol adherence.

Remote planners located in the United States and India access patient data sets and proceed to develop treatment plans within the Eclipse TPS. AI-assisted optimization tools facilitate plan

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generation, which is manually verified by dosimetrists before submission for approval.

Collaborative review between radiation oncologists and remote planners is facilitated through encrypted platforms (ie, video calls and secure messaging) for plan finalization. Upon approval, the plans are digitally signed off by the radiation oncologist and transferred for QA in accordance with established clinical protocols.

Following plan generation, medical physicists at CMJAH conduct rigorous beam modeling verification and patient-specific QA checks using the Octavius 4D phantom system. This step confirms dosimetric accuracy and equipment compatibility.

The radiotherapists subsequently verify the preparedness for treatment, schedule sessions, and perform final verification steps. The in-house Monaco plan is used in parallel to safeguard the clinical integrity.

The delineation of roles and responsibilities across clinical staff (radiation oncologists, medical physicists, radiotherapists, and remote planners) is illustrated in Figure 3. This methodical, phased approach ensures patient safety, data confidentiality, and the precision of clinical outcomes during remote planning.

Any implementation of remote planning requires integrating a comprehensive review step without compromising clinical standards. Future studies will focus on incorporating automated review support tools or scheduling adjustments to reduce delays while maintaining rigorous QA protocols, enhanced scheduling algorithms to minimize idle time between planning and treatment, and implementation of remote plan review dashboards for real-time tracking.

This structured, multitiered approach is expected to improve workflow efficiency, preserve safety standards, and provide a scalable model for radiotherapy services in LMIC.

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Figure 3. Remote radiotherapy planning steps. AOS: advanced oncology solutions; AIRC: artificial intelligence companion radiation-based radiotherapy; CT: computed tomography; CTV: clinical target volume; DR: dose rate; LINAC: linear accelerator; Msq: Mosaiq; MU: monitor unit; PTV: planning target volume; QA: quality assurance; TPS: treatment planning system; ToI: tolerance; Tx: radiation treatment or treatment plan; RTT: radiation therapist; VMAT: volumetric modular arc therapy.

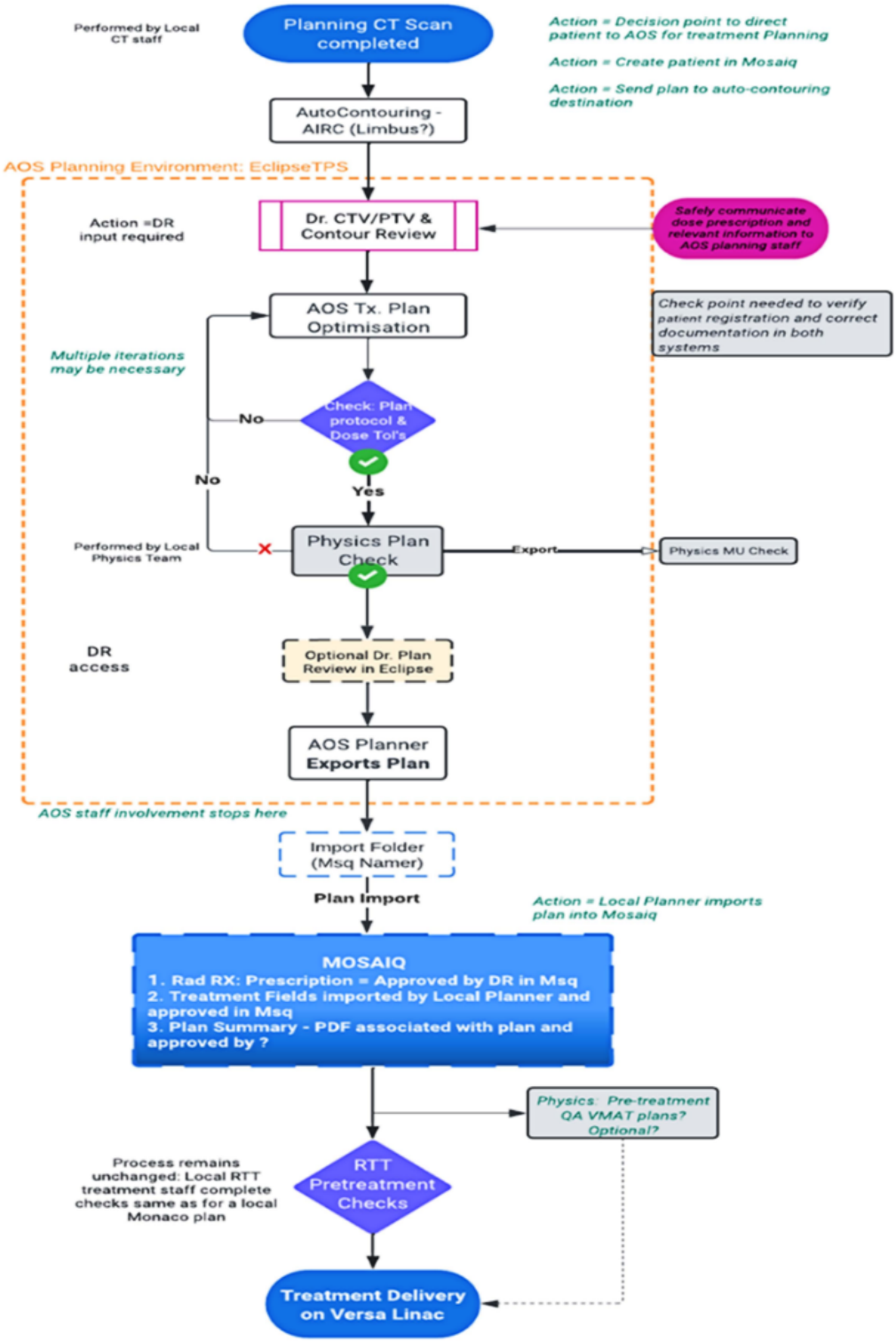

Data Collection

Table 1 shows how the assessments will be conducted.

In this study, a standardized data capture sheet (Multimedia Appendix 2) will be used to collect each participant's clinical and procedural data. Variable recorded will include sociodemographics (age, sex); cancer type; treatment details; treatment planning type; QA metrics; and key dates, including first consultation, CT simulation, treatment planning initiation, treatment plan approval, and treatment completion. Although patient demographics are not directly linked to the primary aims of this study, they will be collected to contextualize the representativeness of the cohort and support post hoc analyses

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examining whether characteristics such as age, sex, or disease-specific characteristics influence workflow efficiency or waiting times. This ensures transparency and enhances the generalizability of findings across diverse patient populations. Including this information allows for a more comprehensive understanding of the clinical applicability and scalability of remote planning systems across diverse patient populations.

Table 1. Assessment of the pilot.

Items	Consent	Protocol	Diagnosis	Volumes	Contouring	Treatment
CT[a] scans	✓	—[b]	—	—	—	—
Cervical	—	✓	✓	✓	✓	✓
Head and neck	—	✓	✓	✓	✓	✓
Rectal	—	✓	✓	✓	✓	✓
Breast	—	✓	✓	—	—	✓
Prostate	—	✓	✓	✓	✓	✓

[a]CT: computed tomography.

[b]Not applicable.

Data Collection on Commissioning and Equipment

This study aims to evaluate the feasibility and operational efficiency of remote treatment planning in resource-constrained settings, specifically for accurate delineation of gross tumor volumes and OARs. Key commission activities include the acquisition and verification of the CT-to-electron density curve, an essential component for ensuring accurate dose calculations. Additional details on the remote planning process are provided in Multimedia Appendix 3.

The commissioning will encompass the integration of 4 Elekta Versa HD LINACs with the Varian Eclipse TPS, supported by a comprehensive beam-matching process to standardize data across machines, enhancing flexibility and accuracy. Key measurements, including PDD curves, profiles, and OFs, will be acquired using PTW's BEAMSCAN water tank in accordance with the AAPM and IAEA guidelines. Focused beam validation will center on photon and electron energies of 6X, 10X, and 6X flattening filter-free photons suitable for Eclipse modeling [31]. Validation of all measurements will be carried out by qualified medical physicists. This includes beam data verification (PDD curves, beam profiles, OFs), end-to-end phantom testing for dose accuracy, patient-specific QA using gamma index analysis (≥95% pass at 3%/3 mm), and review of CT-to-electron density calibration for dose calculation reliability.

Multileaf collimator (MLC) characteristics, including dosimetric leaf gap, and transmission factors will be calibrated using a sweeping-gap technique, with iterative refinements to ensure accuracy across all energy levels [32].

Comprehensive system validation will follow the IAEA's end-to-end methodology, simulating clinical scenarios using phantoms to test dose distribution integrity across various field sizes and geometries [31]. Fine-tuning will continue through QA, including validation using gamma analysis for IMRT/VMAT plans, aiming for a minimum 95% pass rate at 3%/3 mm criteria [32].

The final QA process will confirm the technical readiness for clinical implementation across all 4 LINACs, ensuring reproducibility and dose accuracy for patient treatment under remote planning paradigms.

Quality Control

Prior to pilot study commencement, the research team will receive structured training on TPaaS, QA protocols, administration procedures, and clinical documentation. During the study, attending radiation oncologists will oversee prescription validation for each cancer type. Following CT simulation, imaging data will be securely backed up via Citrix systems, as depicted in the workflow in Figure 2, with audit trails in place for monitoring data access and modification. Reasons for any participant discontinuing treatment will be recorded.

Statistical Analysis

Sociodemographic, clinical, and dosimetric parameters, along with CT images of patients, will be extracted and anonymized, entered into a REDCap (Research Electronic Data Capture) database, followed by exportation into STATA software (v.19) for statistical analysis. Descriptive statistics will summarize patient characteristics, cancer type, and planning timelines. Associations between categorical variables (planning type and treatment delays) will be examined using chi-square and Fisher exact tests [33], and odds ratios and CIs will be calculated. For continuous outcomes (eg, time intervals), *t* tests or nonparametric equivalents will be used where appropriate. Multivariable logistic regression analysis will be considered to adjust for potential confounders (eg, age, sex, cancer type, treatment intent) in outcomes such as plan approval delay or planning method efficacy. Statistical significance will be set at $P<.05$.

Ethical Considerations

This pilot study was approved by the Human Research Ethics Committee (Medical) of the University of Witwatersrand, Johannesburg (certificate number M231076). All participants will provide written informed consent before enrollment.

Participants will receive full information regarding the study procedures, data collection, and voluntary nature of participation before signing the consent form. They are explicitly informed

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of their right to withdraw at any time without facing adverse consequences. No monetary compensation will be provided; however, participants will benefit from free access to treatment and diagnostic services directly related to the pilot study.

Strict privacy protocols ensure that all medical data are exclusively stored on the CMJAH server, with encryption protocols and unique study codes to maintain confidentiality. No participant data will be transferred to or retained on external storage systems. Siemens-Varian will fund the hybrid remote and AI method for 100 patients at approximately R3000 (US $170.51) per plan (total cost R300,000 [US $17,050.60]). Radiation therapy costs will be covered under the Radiation Oncology Syndicate at Wits Health Consortium covering the associated logistical costs such as patient transportation.

Results

The study, which began in November 2023, is currently in the enrollment phase. As of July 2024, more than 44 patients were recruited for radiotherapy planning. Among these 44 patients, 17 (39%) are undergoing planning for prostate cancer, 18 (41%) for breast cancer, and 9 (21%) for head and neck cancer. The project was funded in May 2023, with data collection projected to end in May 2026.

The commissioning and validation of the Varian Eclipse TPS integrated with Elekta Versa HD LINACs involved rigorous assessments to ensure accurate beam modeling and dosimetric reliability. Measurements included profiling PDD curves and OFs across relevant photon energies. The process also entailed CT-to-electron density curve verification, optimization of MLC transmission characteristics, and dose calculations using the anisotropic analytical algorithm.

The validation procedure was led by a team of qualified medical physics and clinical staff. Preliminary results, as summarized in Tables 2 and 3, indicate that transmission of factors of the MLC consistently remained <0.5% across all energy levels, exhibiting a variation ranging from 0.3% to 0.5%, which aligns with the findings of previous studies [32,34] and are significantly well below the 2% threshold set forth by the AAPM Task Group No 50 [35]. The data confirm the LINAC calibration integrity, with dose deviations maintained within clinically acceptable thresholds.

Table 2. Measured dosimetric leaf gap (DLG) and multileaf collimator (MLC) transmission.

Energy level	DLG (mm)	MLC transmission, %
6X	0.31	0.44
10X	0.47	0.45
6X flattening filter free (FFF)	0.38	0.29

Table 3. Reference dosimetry results using an independent chamber.

Energy level	Expected dose (Gy)	Measured dose (Gy)	Difference
6X	1.000	1.0018	–0.18
10X	1.000	1.0164	–1.64
6X flattening filter free (FFF)	1.000	1.02598	–2.60

Minor discrepancies were observed between measured and modeled data, particularly for small field sizes and shallow depths, which were attributed to beam hardening and electron contamination. The measurement results, as outlined in Table 3, validated that the LINACs were accurately calibrated to deliver the correct specified doses. The measured doses closely matched the expected values, exhibiting deviations that remained within acceptable limits, thereby ensuring the accuracy and reliability of the LINAC systems in clinical settings.

Dosimetric validation was performed using QA testing with phantom models and cross-calibration, meeting IAEA standards and achieving dose deviations within acceptable limits. Remote infrastructure testing using mock patient data sets demonstrated technical readiness for clinical application, with gamma index pass rates exceeding 90% (see Table 4).

Detailed results will be included as part of a comprehensive analysis within the complete manuscript, offering an in-depth overview of system performance, workflow efficiency, and preparedness for clinical integration. Preliminary results are anticipated to be published by mid-2025 and disseminated through high-impact peer-reviewed journals (quartile 1 and quartile 2), reports, conference proceedings, and other relevant platforms, providing robust insights and potential recommendations based on the study's outcomes.

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Table 4. Patient-specific quality assurance results for the 5 mock patients with distance to agreement (DTA) of 3 mm and dose difference (DD) of 5%.

Patient	Location	Results, %
VarianTest 1	Prostate	98.90
VarianTest 2	Head and neck	91.90
VarianTest 3	Breast	97.50
VarianTest 4	Prostate	99.20
VarianTest 5	Breast	98.80

Discussion

Key Findings and Interpretation

This study hypothesizes that remote radiotherapy planning can reduce time delays, reduce associated costs, and improve planning efficiency and patient care delivery in resource-constrained settings. As a preliminary evaluation of feasibility and efficacy of remote radiotherapy planning, this study explores an off-site planning service, as an innovative approach to addressing longstanding infrastructural and workforce challenges in radiation oncology in LMIC.

At the time of this study's protocol development, the Radiation Oncology Division at CMJAH experienced considerable diagnostics delays due to limited imaging equipment and increased patient volumes. For example, waiting time for magnetic resonance imaging scans can extend up to 7 months, and CT services were frequently disrupted by technical failures. These delays highlight systemic barriers prevalent across Gauteng public hospitals, where resource constraints and high patient-to-equipment ratios hinder timely cancer care.

Conventional radiotherapy workflows at CMJAH, detailed in Figure S2 in Multimedia Appendix 1 and Multimedia Appendix 4 [36,37], often rely heavily on in-person methods to generate plans. In recent years, off-site treatment services in radiation oncology have gained traction [38], enabling planning expertise to be provided remotely, even across countries [39,40]. In settings like Canada, the United States, the United Kingdom, and Portugal, these approaches have been driven by concerns over SARS-CoV-2 transmission during the COVID-19 pandemic [41], which was associated with heightened mortality rates. These models allowed for interregional and international redistribution of planning expertise and fewer treatment disruptions [42].

Despite this, limited data exist on the performance and scalability of off-site radiotherapy planning services in radiation oncology in LMIC, particularly in SSA [27], where infrastructural limitations and concerns about patient privacy remain significant barriers [43]. Standardization of clinical studies is essential to evaluate the feasibility and quality of these services, especially in resource-constrained settings. Early evidence from remote planning services, such as with Monaco or Eclipse systems, suggests these platforms can potentially reduce backlogs, optimize resources, and maintain plans [44,45]. Previous commissioning studies have shown these services can alleviate treatment delays and improve radiotherapy delivery [45], supporting their investigation in this study. This underscores the need for structured evaluation in LMIC settings, such as CMJAH.

Unfortunately, implementation of remote radiotherapy planning services at CMJAH presented challenges. These included short trial license periods, treatment couch discrepancies requiring re-planning, and the retraining of staff accustomed to in-person systems like Monaco. Technical limitations, such as restricted access for medical physicists, necessitated collaborative workarounds involving therapists and planners. Workflow integration with TPaaS required effective communication among internal and external teams (eg, doctors, medical physicists). Additionally, therapists managed printing, exporting, and preparing treatment data due to limited access to the Eclipse system for medical physicists.

In this study, we anticipate that remote radiotherapy planning services will effectively support treatment planning, as observed in previous studies conducted during the COVID-19 pandemic [41]. Drawing on lessons from the COVID-19 pandemic and remote planning models in HIC, this study aims to quantify parameters and generate insights into the feasibility and early efficacy of the remote planning services, both scientifically and clinically. These findings will inform cancer treatment planning, particularly in resource-constrained settings, and contribute to the broader discourse on modernizing cancer care in LMIC through technology-enabled solutions.

Although remote planning offers a promising strategy to reduce wait times and workflow efficiency, successful implementation demands mitigation of specific technical and systemic barriers. First, reliable and secure data transfer systems are critical to prevent workflow delays and protect patient privacy. Network connectivity and data security protocols must be robust to support real-time collaboration between remote and on-site teams. Second, interoperability between planning systems and software tools must be optimized to ensure consistency in target delineation and dose delivery. Third, effective communication and coordination are essential to streamline decision-making and avoid process bottlenecks, especially when real-time consultation is required.

Finally, training demands must be addressed through structured educational programs to facilitate clinician adaptation to remote workflows. Addressing these challenges requires careful workflow optimization, investment in technology infrastructure, and comprehensive training programs to maintain efficiency and ensure the quality and safety of patient care.

Implementing remote planning to reduce waiting times requires specific workflow changes, which introduce potential barriers

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that must be addressed to ensure feasibility and efficacy. Key workflow modifications include the introduction of secure remote access for data transfer, ensuring seamless integration between remote and local planning systems, and scheduling adjustments to facilitate real-time communication among team members. However, these changes present challenges, such as the need for robust data security measures to maintain patient confidentiality, potential delays due to network connectivity issues, and variations in the performance of different contouring and planning software tools. Additionally, effective communication between remote and on-site staff is critical to avoid workflow disruptions.

To overcome these barriers, investments in secure, high-speed data transfer infrastructure, standardized software compatibility protocols, and comprehensive team training are required. Furthermore, optimizing communication workflows through scheduled review sessions and clearly defined roles can mitigate delays and enhance process coordination. Addressing these challenges is essential to fully realize the benefits of remote planning in reducing waiting times without compromising treatment quality and safety.

Moreover, training demands must be addressed through structured educational programs to facilitate clinician adaptation to remote workflows. Technological variability, internet connectivity limitations, and software licensing constraints can introduce delays, offsetting potential time savings. For instance, routine synchronization of imaging and planning data can add an estimated 5 minutes to 15 minutes per case, depending on case complexity and network bandwidth.

To enhance system readiness, this study implemented proactive measures, including predefined data transfer templates, optimized scheduling, and system configuration protocols. These efforts aim to reduce integration-related delays and ensure that remote planning can be conducted without compromising clinical safety, data security, or overall treatment timelines.

Limitations

This study has several limitations. First, as a single-site pilot study, generalizability may be restricted, and findings may not be immediately transferable to other LMIC or health systems. However, the results provide a critical groundwork for evaluating remote radiotherapy workflows in resource-limited contexts. The adapted data collection tools, although based on validated instruments, require further contextual validation. Additionally, real-time staff engagement data and cross-platform integration (eg, Eclipse and Mosaiq) challenges require further study to support optimization and scale-up. Second, although the data sheet was adapted from validated questionnaires, it has not yet undergone extensive validation within the context of this study. However, this pilot will inform its final version.

Although the assessment of the feasibility and scalability of this model in various LMIC constitutes a primary objective, this study does not incorporate a formal cost analysis. The financial implications associated with integration and implementation are currently ambiguous, potentially constraining the generalizability of findings to other resource-limited environments.

Technical barriers including short-term licensing, planning system discrepancies, and limited access for physicists impacted implementation. Furthermore, the limited study duration may not fully capture longitudinal outcomes such as plan durability or patient satisfaction. Despite these limitations, this is the first study in SSA evaluating the feasibility of a remote (AI and hybrid remote) radiotherapy planning model, which could offer a rare opportunity to document early insights into hybrid and AI-supported planning models in SSA to enhance cancer treatment efficiency, reduce wait times, and improve the patient experience.

Future Directions

Future research should explore AI-generated contouring, plan quality, time efficiency, staff and patient satisfaction, and privacy concerns and incorporate detailed cost-effectiveness analyses and implementation frameworks to assess the economic feasibility, scalability, and sustainability of the model within various health care systems in LMIC. Data collection on staff perspectives and any workflow adjustments observed during the integration process is essential to optimize remote radiotherapy planning. Research should include evaluating workflow adjustments, interoperability challenges, and clinical efficiency during integration of the Eclipse and Mosaiq systems. Such studies should also explore staff experiences and technical requirements to optimize integration, offering valuable insights for broader implementation across similar health care settings. Enhanced understanding of these integration requirements would support improved planning and resource allocation, ultimately contributing to streamlined radiotherapy processes and patient care. Comparative studies of Monaco and Scripting planning systems are needed to evaluate OAR sparing, inverse planning, and efficiency. Insights from these studies will support the broader adoption of remote radiotherapy, optimize workflows, and enhance patient care.

Conclusion

This study introduces and evaluates the feasibility and initial efficacy of remote radiotherapy planning as a tool to improve treatment planning and a solution for workflow inefficiencies in oncology care in LMIC. Targeting high-burden malignancies such as cervical, prostate, breast, head and neck, and rectal cancers, this approach holds the potential to optimize resource use, streamline clinical operations, and enhance care delivery. By leveraging remote infrastructure and international expertise in such environments, remote planning may bridge the gaps in oncology care and improve cancer care delivery where resources are limited. The findings have significant implications for global health care, particularly in advancing equitable access to high-quality radiotherapy services in underserved regions.

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Acknowledgments

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Data Availability

Data from this pilot study will be available from the corresponding author upon reasonable request. Patient data will be deidentified before any sharing requests.

Authors' Contributions

DR, DM, OA, MA, and SN contributed to study conceptualization. DR, J0, TN, DM, and OA contributed to data collection. JO and TN contributed to visualization and project administration. DR and SN contributed to supervision and resources. OA, MA, and DM contributed to the methodology. All authors contributed to writing the original draft as well as reviewing and editing it.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Patient workflows.
[DOCX File , 54 KB - resprot_v14i1e60131_app1.docx]

Multimedia Appendix 2
Data capture in the Radiation Oncology Department, Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).
[DOCX File , 16 KB - resprot_v14i1e60131_app2.docx]

Multimedia Appendix 3
Remote planning process.
[DOCX File , 18 KB - resprot_v14i1e60131_app3.docx]

Multimedia Appendix 4
Conventional radiotherapy workflows at Charlotte Maxeke Johannesburg Academic Hospital (CMJAH).
[DOCX File , 93 KB - resprot_v14i1e60131_app4.docx]

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Abbreviations

AAPM: American Association of Physicists in Medicine
AI: artificial intelligence
CMJAH: Charlotte Maxeke Johannesburg Academic Hospital
CONSORT: Consolidated Standards of Reporting Trials

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CT: computed tomography
DICOM: Digital Imaging and Communications in Medicine
HIC: high-income countries
IMRT: intensity-modulated radiotherapy
LINAC: linear accelerator
LMIC: low and middle-income countries
MLC: multileaf collimator
OAR: organ at risk
OF: output factor
OR: odds ratio
PDD: percent depth dose
QA: quality assurance
REDCap: Research Electronic Data Capture
SSA: sub-Saharan Africa
TPaaS: treatment planning as a service
TPS: treatment planning system
VMAT: volumetric-modulated arc therapy
WHO: World Health Organization

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Protocol

Effect of a Family-Centered Empowerment Model–Based Intervention on the Caregiving Capacity and Preparedness of Caregivers of Children With Malignant Neoplasms: Protocol for a Quasi-Experimental Study

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Abstract

Background: Malignant neoplasms are among the most common causes of disease-related death in children. Long-term chemotherapy often requires a high degree of parental involvement. Family caregivers' preparedness and capacity are critical in reducing the burden of care and improving quality of life. This study looks to examine the impact of a family-centered empowerment model (FCEM)–based intervention on the caregiving capacity and preparedness of family caregivers.

Objective: This study aims to develop and evaluate an FCEM-based intervention to improve caregiving preparedness and capacity among family caregivers of children with malignant neoplasms. It also examines the potential effects of the intervention on self-efficacy and psychological outcomes, including depression, anxiety, and stress.

Methods: This quasi-experimental study focuses on caregivers of children with malignant neoplasms attending our hospital for the first time, implementing a 4-phase FCEM-based intervention program evaluated through questionnaires administered 3 days after admission and 3 days before discharge. Differences in caregiving preparedness, caregiving capacity, self-efficacy, and depression, anxiety, and stress scores will be assessed using independent and paired *t* tests, Mann-Whitney tests, and paired rank-sum tests for both within-group and between-group comparisons preintervention and postintervention.

Results: Recruitment will be conducted in 2 waves (control group: July to December 2025; intervention group: July to December 2026). It is expected that the intervention group will show significantly greater improvements in caregiving preparedness, caregiving capacity, and psychological well-being compared to the control group.

Conclusions: The findings of this study are expected to provide evidence for the development of structured family empowerment in pediatric oncology. In the future, expanding to multiple centers and conducting targeted surveys among caregivers of children with different cancer types would help validate and promote the effectiveness of family empowerment interventions.

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KEYWORDS

caregiving preparedness; family-centered empowerment model; malignant neoplasms; childhood cancer; educational program; depression; anxiety; stress

Introduction

Background

Malignant neoplasms in childhood usually refer to malignant tumors with onset between the ages of 0 and 14 years and are the most common cause of death from childhood illnesses, including leukemia, lymphomas, tumors of the brain and central nervous system, and osteosarcomas [1-3]. Approximately 13.7 million children younger than 15 years are predicted to suffer from tumors by 2050 [4]. In China, approximately 22,000 cases of malignant neoplasms occur in children younger than 15 years each year, and the prevalence rate is estimated to increase annually by 5% [4].

Family caregivers, often parents or grandparents, manage children's daily needs, provide emotional support, and respond to sudden illnesses and other conditions. Since children are in a critical stage of growth and development, and their tumors are characterized by high malignancy, disease complexity, early onset, prolonged chemotherapy cycles, and numerous adverse reactions, family caregivers must provide extensive care. Their preparedness and capacity play pivotal roles in reducing caregiving burdens and enhancing quality of life [4-6].

The family-centered empowerment model (FCEM), developed by Alhani et al [6] in 2003, aims to empower patients and their families by defining essential elements for improving chronic care outcomes [6]. This model builds on the family-centered care philosophy, which emphasizes the child's family as the "center of capacity building" [6].

The FCEM involves a 4-step process. The first step consists of improving knowledge through educational programs using resources, such as posters, models, and handouts, as well as interactive methods, including quizzes and question-and-answer sessions. The second step is self-efficacy enhancement, the third step is the promotion of self-esteem through participation in educational activities, and the fourth step involves evaluating the entire intervention period [6]. By following this structure, FCEM helps caregivers acquire the necessary skills and confidence to manage their child's condition effectively and maintain a balanced family life [6].

This model has also been widely used for patients with chronic diseases in China. Nonpharmacologic interventions based on the FCEM have demonstrated positive effects on the quality of life, knowledge, and self-efficacy of patients with chronic diseases, such as chronic obstructive pulmonary disease, thalassemia major, asthma, and myocardial infarction. These interventions also alleviate stress, anxiety, and restlessness in family caregivers [7,8]. While FCEM was initially developed for chronic illnesses, its structured framework is equally applicable to the caregiving needs of family caregivers of patients with malignant tumors [9].

Although studies highlight the positive impact of FCEM-based interventions on caregivers of patients with malignant neoplasms [7-9], most have focused on primary caregivers of adult patients. Compared with adults, children require more detailed and comprehensive care because of their younger age, longer chemotherapy cycles, and critical developmental stages. This necessitates caregivers with greater preparedness and advanced caregiving skills. The impact of the FCEM on caregiving capacity and preparedness among family caregivers of children with malignant neoplasms remains unclear.

Objectives

This study aims to recruit family caregivers of children with malignant neoplasms to develop a corresponding intervention program based on the FCEM and to evaluate its impact on caregiving preparedness and caregiving capacity. Additionally, the study aims to examine the effects of the empowerment intervention on caregivers' self-efficacy as well as their levels of depression, anxiety, and stress.

Research Hypotheses

This study has the following research hypotheses:

1. Statistically significant differences in caregiver preparedness and caregiving capacity will occur after the FCEM intervention program.
2. Significant differences in self-efficacy, depression, anxiety, and stress will occur in the intervention group after the intervention compared to previous measurements.

Methods

Data Collection

Setting and Participants

This is a quasi-experimental study. This protocol is version 1.0, finalized on July 8, 2025. We will select children with malignant tumors and their family caregivers who were hospitalized at West China Second Hospital, Sichuan University, between July 2025 and December 2026. Family caregivers of the children will be enrolled. The researchers will provide a detailed description of the study's purpose and content to the participants, who must sign an informed consent form.

The QR code for the web-based questionnaire will be distributed after caregivers provide informed consent. The family caregivers recruited for the study will be divided into control and intervention groups. Children will be grouped according to their diagnosis and treatment timeline as follows: children admitted from July to December 2025 will form the control group, and those admitted from July to December 2026 will form the intervention group. The caregivers of the children will be enrolled along with the children. In the intervention group, the intervention program will be implemented after inclusion. For the control group, where routine health promotion is implemented, an intervention program based on FCEM will be offered upon the second admission to the hospital (Figure 1).

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Figure 1. Participant timeline.

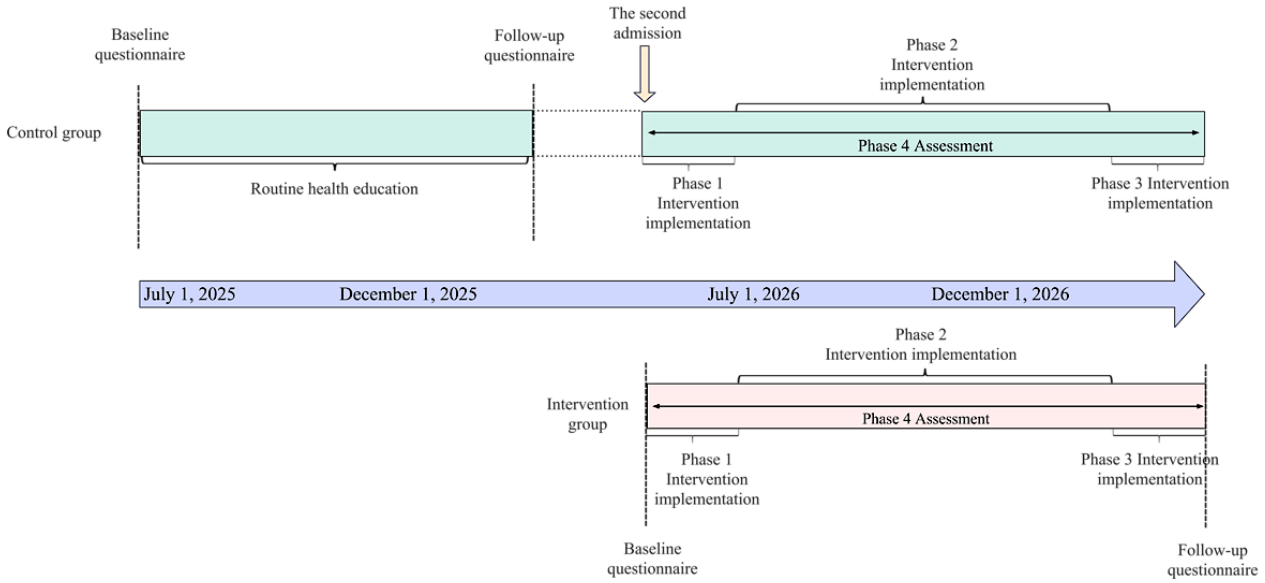

After the family caregivers complete the baseline survey, the researchers will distribute paperwork or provide verbal health promotion with relevant health promotion components and assess the caregivers' knowledge weekly.

The questionnaire will be re-administered 3 days before the child is discharged. One researcher will enter the data, which will be double-checked for errors by another researcher. After all data are entered, the analysis will be performed by a designated specialist who remains unaware of the groupings. Finally, 2 additional researchers will independently review the analyses to ensure accuracy. Family caregivers will be aware of their grouping. If family caregivers prefer to adjust their groupings, appropriate adjustments will be made based on their identified needs.

The inclusion criteria are as follows: (1) children aged 0-18 years, (2) children clinically diagnosed with malignant neoplasms, and (3) first-time visitors to our hospital.

The exclusion criteria are as follows: (1) children diagnosed and treated with radiotherapy or chemotherapy in other hospitals and (2) children undergoing their first treatment in our hospital for recurrence of the disease.

Primary caregiver inclusion criteria are as follows: (1) the caregiver is enrolled along with the child, (2) the caregiver is aged 18 years or older, (3) the caregiver is a member of the child's immediate family, (4) the caregiver has cared for the child for the longest period among multiple caregivers, (5) the caregiver has basic communication and reading skills and is proficient in Chinese, and (6) the caregiver has no previous history of psychiatric illness or consciousness-related disorders.

The sample size was calculated to be 128 using G*POWER 3 software [10] with the parameters α=.05, 1 – β=0.8, and effect size=0.5. Considering a 10% lost-to-follow-up rate, the total sample size required was estimated to be 142, with 71 caregivers in the intervention group and 71 in the control group.

Sociodemographic Variables

Sociodemographic variables in patients (including age, sex, ethnicity, medical payment method, clinical diagnosis, and duration of disease) and their caregivers (including age, relationship with the patient, ethnicity, place of residence, number of children, marital status, level of education, occupation, monthly family income, caregiving experience, number of other persons in need of care, hours of care per day, health status, disease awareness, and access to information) will be recorded. Disease-related variables will be obtained from the consent forms signed by the patients and their guardians.

Dependent Variables

The outcome variables are caregiving preparedness, caregiving capacity, self-efficacy, depression, anxiety, and stress. The tools used to measure these variables are described in Table 1.

The caregiver preparedness scale was developed by Archbold et al [11] to assess parents' caregiving preparedness. This scale consists of 8 items, namely, preparedness for physical needs, emotional needs, service planning, caregiving stress, comfort care, coping with and managing emergencies, accessing medical information resources and help, and overall caregiving preparedness [11]. A 5-point Likert scale was used, with scores ranging from 0-4 indicating "not at all prepared" to "fully prepared," and higher scores reflecting better preparedness for caregiving. Yanjin et al [12] adapted the scale for use in China, demonstrating its good reliability and validity as a suitable tool for assessing preparedness. The Cronbach α of the Chinese version was 0.92 [12].

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Table 1. Measurement tools used to assess outcome variables.

Tool	Dimensions	Items
Caregiver preparedness scale	Physical care, emotional support, in-home support services, and caregiving stress	8
Family caregiver task inventory	Adaptation to caregiving roles, coping and assistance provision, management of personal emotions, caregiving needs, and assessment of family and social resources	25
General self-efficacy scale	Self-efficacy	10
Depression anxiety stress scale-21	Depression, anxiety, and stress	21

Caregiving capacity was measured using the family caregiver task inventory developed by Clark and Rakowski [13] in 1983, which covers 5 dimensions: role adaptation, caregiving assistance, emotional management, life adjustment, and use of social and family resources. It consists of a total of 25 items. The family caregiver task inventory uses a 3-point Likert scale, with 0 indicating "no difficulty," 1 indicating "some difficulty," and 2 indicating "great difficulty." Higher scores represent greater difficulty and poorer caregiving capacity. The Cronbach α of the Chinese version was 0.86 [14].

The general self-efficacy scale was developed by Schwarzer et al [15] in 1981 and subsequently translated into Chinese [15,16]. The general self-efficacy scale assesses the self-efficacy of family caregivers. It contains 10 items within the single dimension of self-efficacy and is scored on a 4-point Likert scale, ranging from 1 ("not at all true") to 4 ("exactly true"), with a total score of 10 to 40. Higher scores indicate better general self-efficacy [15,16]. The Cronbach α coefficient for this scale was 0.91 [15].

The depression anxiety stress scale-21 was developed by Lovibond and Lovibond [17] in 1995 and later translated into Chinese by Gong et al [18]. The depression anxiety stress scale-21 evaluates depression, anxiety, and stress levels in family caregivers. It contains 21 items across 3 dimensions: depression, anxiety, and stress. The depression subscale includes items 3, 5, 10, 13, 16, 17, and 21; the anxiety subscale includes items 2, 4, 7, 9, 15, 19, and 20; and the stress subscale includes items 1, 6, 8, 11, 12, 14, and 18. A 4-point Likert scale is used, with scores ranging from 0 ("did not apply at all") to 3 ("applied most or all of the time"). Higher scores indicate higher levels of depression, anxiety, and stress. The Cronbach α coefficient of the scale was 0.89 [18].

Intervention Program

Intervention Content Development

Through a preliminary search of the literature, the caregiving needs of family caregivers of children with malignant neoplasms were identified to include disease information needs, such as knowledge about the disease, its progression, and prognosis; symptom management needs, including knowledge related to Peripherally Inserted Central Catheter (PICC) or infusion port care; dietary management needs; prevention and treatment of infections; management of daily living activities; prevention and treatment of adverse reactions to chemotherapy drugs; and psychological regulation needs, such as managing anxiety, nervousness, and fear.

We plan to select approximately 17 caregivers of children with malignant neoplasms for interviews using purposive sampling as part of the preliminary research. Face-to-face interviews using open-ended questions will be conducted by experienced interviewers. The interview is expected to last 15-30 minutes. It will be discontinued immediately if the child requires medical attention. The interview outline includes the following questions:

1. What kinds of feelings do you experience during caregiving, and what are your biggest concerns and stresses?
2. What problems or needs have you encountered in the caregiving process, and how have you coped with them?
3. Regarding treatment and care, what kind of health guidance would you like medical workers to provide (including knowledge about diseases, dietary management, daily life activities management, maintenance of PICCs and infusion ports, and knowledge of drug reactions)?

Data collection will be discontinued when thematic saturation is reached. Saturation is defined as the point at which no new themes or codes emerge from at least 2 consecutive interviews. The results of interviews with 17 caregivers will be summarized and refined to determine the main needs of the caregivers. The results of a previous pilot study on parents of children with acute lymphoblastic leukemia showed that the main needs of caregivers were in the following areas:

1. Disease information, including symptoms and manifestations, incidence rate, relapse rate, cure rate, 3-year to 5-year survival rate, and other disease-related details.
2. Infusion port and PICC maintenance, including precautions after infusion port implantation, PICC-related knowledge, and daily observation priorities.
3. Infection prevention, including methods for infection prevention and management.
4. Medication guidance, including common adverse drug effects and steps to observe and manage them.
5. Dietary guidance, including methods for preparing hygienic and appropriate meals for children.
6. Psychological aspects, including methods to alleviate negative emotions, such as anxiety and depression, in caregivers and children.

A draft intervention program will be developed based on the FCEM model, literature review, results of the preliminary research, and the departmental health education manual (Multimedia Appendix 1).

Intervention Revision

After the first draft is finalized, a group meeting is planned for the researchers and team members, all of whom are clinical and nursing experts in pediatric hematology. The group includes a

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hematologist and 5 nursing staff members with more than 5 years of experience. Before the study begins, a group meeting will be held to jointly negotiate the terminology to be used with patients during implementation and to ensure that the terminology used during implementation is harmonized.

Intervention Delivery Process

Intervention Group

The intervention group will be provided with a family empowerment intervention program based on usual care.

Three sessions of approximately 15-30 minutes each will be conducted within 3 days of the child's admission to the hospital, from the fourth day to 3 days before discharge. The timing of the intervention sessions was determined based on evidence from a prior study conducted in China involving caregivers of children with asthma combined with clinical experience [19]. The researcher or charge nurse will assess the caregivers' knowledge every week using uniform evaluation criteria and adjust the topic or number of interventions within each phase based on the knowledge gained, with the final intervention content and timeline remaining unchanged.

During stage 1 (within 3 days of admission), the researchers will explain the use of the facilities in the ward, including the proper use of a hospital bed or laminar flow bed, and outline safety precautions in the ward (including preventing falls, falls out of bed, and avoiding burns). They will also provide information about daily care, infection prevention, dietary considerations (eg, low-fat diets and special diets for children experiencing vomiting), input and output monitoring, the recognition of symptoms for oral and perianal infections and how to gargle and cleanse the perianal area, and disease-related information, including cure rates and recurrence rates. Completing stage 1 will require 15-25 minutes.

During stage 2 (fourth day after admission to 3 days before discharge) the nurse in charge will ask the main caregiver about difficulties and problems encountered during the caregiving process using open-ended questions, such as "In your opinion, what is the most difficult thing right now?" "Do you have difficulties taking care of your children and yourself?" "What kind of information would you like the nurse to provide more of while providing care for your child?" Based on the preinterview, the nurse will conduct adequate communication with the main caregiver in response to their difficulties, listen patiently, and provide positive guidance tailored to their psychological state. A childcare program will be developed, and the following content will be explained to the patient's family, part of which will be presented in written or video form: (1) medication guidance based on the actual use of drugs by the child, including the dosage, frequency, and adverse effects of the drugs; (2) PICC-related knowledge, including daily observation, handling of abnormalities, prevention and identification of complications, and precautions for daily life and exercise; (3) postoperative care for infusion port implantation, including postoperative diet, postoperative medication changes, observation during use, and postdischarge precautions; (4) blood indicators, including an explanation of blood indicators, such as platelets, hemoglobin, and neutrophils, along with precautions to be taken in case of critical values; (5) condition monitoring and emergency treatment, including simple treatments in case of fever or other emergencies; and (6) psychological support, including sharing stories of other successful cases to positively motivate the caregivers. Completing stage 2 will require 20-30 minutes.

Stage 3 (3 days before discharge) will involve the evaluation of outcomes and discharge instructions as well as communication with the patient to address problems related to caregiving abilities and caregiving preparedness, affirm the level of care provided by the family caregiver during the child's hospitalization, boost their confidence, and guide the child's postdischarge medication, nursing care, review, and follow-up chemotherapy plans. Completing stage 3 will require 10-20 minutes.

Stage 4 encompasses the entire implementation process. During program implementation, a dedicated researcher will coach the primary caregiver 1-on-1 to ensure they understand the program content (ie, until they can repeat it independently). Family caregivers will be instructed to record changes in their children's symptoms. The family caregivers' knowledge of the program will be assessed weekly (Multimedia Appendix 2).

Control Group

In the control group, routine nursing care and current health education content will be provided, including the following: introduction to the department's environment, rules, and regulations; admission counseling; examination guidance; ongoing education on daily care, medication management, and health practices during hospitalization; proactive support and communication by medical staff, including resolving questions and sharing caregiver experiences; and discharge instructions with follow-up schedules for chemotherapy (Multimedia Appendix 3).

Participants in the control group will be offered an FCEM-based intervention regimen on their second admission (at the beginning of the second course of treatment), which will be appropriately adapted to the control group's second chemotherapy treatment.

Follow-Up Assessment

To evaluate the sustained impact of the intervention, an additional follow-up will be conducted 1 month after discharge. This will be completed via telephone and web-based questionnaire by the research assistants. The same validated instruments used during hospitalization will be used to measure caregiving preparedness, caregiving capacity, self-efficacy, and depression, anxiety, and stress.

Data Analysis

Data will be analyzed using SPSS version 26.0 (IBM Corporation). For general information, measurement data conforming to a normal distribution will be described by means and SDs, and count data will be described by frequencies and constitutive ratios. Missing data will be removed and will not be included in the analysis. Participants who request to switch groups based on their preferences will be excluded from the primary analysis; however, we will summarize the baseline characteristics of these participants and compare them to those

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who remain in their originally assigned groups. This comparison will include demographics to assess the potential impact of nonrandom attrition on study validity.

Independent-sample *t* tests will be used to compare caregiving preparedness, caregiving capacity, self-efficacy, and depression, anxiety, and stress scores between the 2 groups before the intervention. After the intervention, both within-group and between-group differences in these variables will be analyzed using independent-sample *t* tests, paired *t* tests, Mann-Whitney tests, and paired rank-sum tests.

Ethical Considerations

This study was approved by the Ethical Review Committee of West China Second Hospital of Sichuan University (approval number YXKY2024432). The trial was registered on February 5, 2025, with ClinicalTrials.gov (NCT06810388). Before data collection, the study leader will obtain written informed consent from all participants. Participants will also be informed in advance that they will be contacted for a follow-up assessment approximately 1 month after discharge.

During the study, personal information, such as names, gender, and other identifiers of participants and their children, will be replaced with codes or numbers to maintain confidentiality. Access to this information will be limited to authorized researchers, ensuring the privacy of participants and their children is fully protected. While the study results may be published in academic journals, no personal details of the participants will be revealed.

All participants will be informed of their right to withdraw from the study at any time and that completing the questionnaire will not affect their children's medical or nursing care. All family caregivers in the control group will be asked if they would like to receive the family empowerment intervention program upon their second admission, which the researchers will provide.

Results

Recruitment Progress

The study was approved by the Ethical Review Committee of West China Second Hospital of Sichuan University on January 9, 2025 (approval number YXKY2024432). We plan to recruit participants for the control group from July to December 2025. We will recruit caregivers for the intervention group from July to December 2026. Data collection will occur throughout the recruitment period. Results are expected to be published in late 2027.

Caregiving Preparedness and Capacity

We expect caregivers in the intervention group to have higher preparedness and caregiving capacity than those in the control group. In addition, significant improvement is expected within the intervention group after the intervention.

Self-Efficacy Outcomes

Regarding the self-efficacy outcomes, caregivers receiving the intervention are likely to show increased self-efficacy after discharge. No major change is expected in the control group.

Psychological Outcomes

Caregivers in the intervention group are expected to report significantly lower depression, anxiety, and stress scores after the intervention.

Discussion

Principal Findings

The intervention based on the FCEM model is expected to improve caregiving preparedness, caregiving capacity, and self-efficacy in family caregivers of children with malignant neoplasms. It may also reduce their psychological distress, including symptoms of depression, anxiety, and stress. These anticipated findings will contribute to enhancing the design and implementation of family-centered interventions in pediatric oncology care.

The results of this study will be shared with the Department of Pediatric Hematology and used to refine and improve existing health promotion strategies.

Limitations

This study has several limitations. First, the intervention will be implemented for family caregivers of children with malignant neoplasms rather than targeting a specific cancer type, and caregivers of children with different cancer types may face distinct challenges. Second, the intervention period is relatively short, limiting the ability to observe the long-term effects of the FCEM intervention program on family caregivers. Finally, as this is a single-center study conducted at 1 hospital, the findings will reflect only the situation at this center. Considering geographic variations in the level of medical care, the findings may not be generalizable to primary care settings or populations with different cultural or socioeconomic backgrounds. In the future, the study could be expanded to include multiple centers. To further enhance the evaluation and adaptation of empowerment strategies, it is also recommended that future studies involve caregivers of children with various types of cancer.

Strengths

The methodological strength of this study lies in the establishment of an intervention program tailored to the needs of family caregivers of children with malignant neoplasms. The program includes caregiving knowledge, skills, and psychological coping strategies to enhance the educational content of the family empowerment program. Designed for caregivers of children with various types of malignant neoplasms rather than a single type, the intervention program aims to contribute to a more comprehensive health education system and facilitate future replication.

Future Directions

To further expand the impact of such interventions, future studies may consider integrating emerging technologies into caregiver support strategies. As digital health tools continue to evolve, there is growing interest in leveraging emerging technologies to enhance caregiver support [20,21]. With the rapid development of large language models, future studies may

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consider exploring the integration of large language model–based tools to further support family caregivers.

Authors' Contributions

X Li and YY designed the study, drafted the study protocol, and developed the recruitment plan and data collection materials. QC, JM, FL, and X Luo provided guidance on the methodology of this study and codeveloped the intervention protocol. FL and X Luo guided the study's ethics board's accountability. We would like to include X Luo as one of the corresponding authors, but FL is the primary corresponding author. All authors critically reviewed and edited the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Theoretical framework mapping the family-centered empowerment model to the phases of the intervention.
[PNG File , 503 KB - resprot_v14i1e73304_app1.png]

Multimedia Appendix 2
Family caregiver mastery evaluation form (weekly).
[DOCX File , 18 KB - resprot_v14i1e73304_app2.docx]

Multimedia Appendix 3
Routine health education content for the control group.
[DOCX File , 15 KB - resprot_v14i1e73304_app3.docx]

Multimedia Appendix 4
Sample informed consent form.
[DOC File , 42 KB - resprot_v14i1e73304_app4.doc]

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Abbreviations

FCEM: family-centered empowerment model
PICC: peripherally inserted central catheter

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Protocol

A Peer Support Specialist–Delivered Sexual and Intimate Partner Violence Prevention Program for Women in Substance Use Treatment: Protocol for a Single-Arm Trial

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Abstract

Background: Women in substance use treatment are disproportionately affected by violence. Both a history of violence and substance use place women at risk for cumulative exposure to violence and adverse outcomes, including mental and physical health problems. Interventions are urgently needed to reduce these health disparities by preventing initial and repeated exposure to sexual and intimate partner violence among women with substance use disorders (SUDs). The Healthy Relationships and Interpersonal Violence Education (THRIVE) program adapts evidence-based strategies for this population and is informed by the information, motivation, behavioral skills theoretical model. Topics include the intersection of substance use and violence, consent, risk detection, protective behavioral strategies, and help seeking. THRIVE uses a novel approach by delivering the program via peer support specialists (PSSs), trained advocates in recovery from SUDs who can help overcome barriers to care, including stigma and accessibility.

Objective: The first objective is to determine program acceptability and feasibility. The second objective is to determine the preliminary effectiveness of THRIVE, including its effect on violence-related knowledge and attitudes, protective behaviors, exposure to sexual and intimate partner violence, substance use, and mental health.

Methods: The study entailed a single-arm trial of THRIVE with 71 women in behavioral and medication-assisted substance use treatment, recruited from 3 outpatient and residential treatment sites. Interview data assessing intervention acceptability and feasibility were collected from participants and PSSs. Participants completed assessments at 4 time points over 3 months (baseline, after the intervention, and 1- and 3-month follow-ups). Self-report questionnaires assessed (1) violence prevention knowledge, attitudes, and behaviors; (2) exposure to sexual and intimate partner violence; and (3) substance use and mental health. To determine acceptability and feasibility, both quantitative and qualitative data were collected on feasibility (recruitment and retention), adherence, and acceptability (engagement, perceived usefulness, barriers and facilitators to participation and adoption, and working alliance with PSSs).

Results: Of the 92 women recruited and enrolled, 71 (77%) completed the intervention, 58 (63%) completed the 1-month follow-up, and 44 (48%) completed the 3-month follow-up between June 2024 and March 2025. The mean age of enrolled participants was 35 (SD 9.87) years, and the majority were White (n=79, 86%), followed by Black (n=4, 4%) and other racial and ethnic identities (n=7, 8%).

Conclusions: THRIVE will address critical gaps in the field by (1) expanding violence prevention strategies to SUD treatment settings, (2) integrating sexual and intimate partner violence prevention, (3) incorporating a focus on illicit substance use, and (4) engaging PSSs to overcome barriers to care. The long-term objective of this project is to develop an accessible, scalable, and

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efficacious prevention program that reduces the incidence of exposure to sexual and intimate partner violence, substance use, and violence-related mental health disorders for women in substance use treatment.

Trial Registration: ClinicalTrials.gov NCT06608979; https://clinicaltrials.gov/study/NCT06608979

International Registered Report Identifier (IRRID): DERR1-10.2196/68673

(JMIR Res Protoc 2025;14:e68673) doi:10.2196/68673

KEYWORDS

interpersonal violence; sexual violence; sexual assault; dating violence; partner violence; repeated exposure to violence; intervention; peer recovery coaches; addiction; substance use disorders; drug use

Introduction

Interpersonal Violence History, Substance Use, and Health

A substantial proportion (60%-90%) of individuals in substance use treatment report a history of violence, with women being at greatest risk for initial and repeated exposure to interpersonal violence [1-3]. Interpersonal violence is an overarching term that encompasses both sexual violence (SV) and intimate partner violence (IPV) [4]. SV can be defined as nonconsensual sexual contact through physical force or inability to consent (eg, incapacitation due to drugs or alcohol). It can include harassment, unwanted contact, coerced sex, or attempted or completed rape and more recently has been expanded to include cyber-SV [5,6]. IPV often co-occurs with SV and includes physical violence, SV, stalking, and psychological aggression that occurs in the context of a current or former romantic relationship [7]. Given the high prevalence of interpersonal violence among women with substance use disorders (SUDs), there is an urgent need for interventions to prevent initial and repeated exposure to interpersonal violence in this population.

Interpersonal violence is a critical public health problem associated with a host of physical and mental health outcomes, including posttraumatic stress disorder (PTSD), depression, SUDs, chronic pain, gastrointestinal disorders, and a variety of chronic health conditions [8-10]. In particular, women in SUD treatment with a history of violence are more likely to experience relapse and poor recovery outcomes [11-13]. Both a history of violence and substance use place women at risk for exposure to cumulative interpersonal violence, and two-thirds of women with exposure to SV experience repeated exposure [1,14,15]. Substance use is frequently cited as a coping mechanism for managing posttraumatic stress and the aftereffects of exposure to violence and also places women at risk for exposure to interpersonal violence [1,14]; for example, research has indicated that individuals in treatment for co-occurring disorders such as PTSD and SUD are at greater risk for exposure to violence than individuals with SUD alone [16].

Despite the intersection of trauma and substance use problems, there is a disconnect between trauma-informed services and substance use treatment [17]. Substance use treatment can be defined as behavioral or pharmacological treatment provided by medical and mental health professionals for a range of SUDs (eg, alcohol, opioid, stimulant, polysubstance use) [18]. The Substance Abuse and Mental Health Services Administration (SAMHSA) has proposed a model of trauma-informed care to adopt in behavioral and substance use treatment facilities, further emphasizing the importance of an integrated approach to substance use treatment [19]. Although the acceptance of and evidence for integrated treatments for trauma and SUD have grown, studies indicate that less than half of SUD treatment facilities offer trauma-specific services [17,20,21]. The facilitators of adopting these models include state policies supportive of screening, insurance reimbursement, and evidence-based treatment for trauma [21]. Barriers to implementation include organizational factors such as the logistics of adopting integrated treatments within current service time frames and formats, mental health provider concerns about the timing of trauma treatment initiation or ongoing exposure to violence, lack of mental health provider training, and high case management needs in this population [22]. These studies have primarily focused on the provision of mental health services, and little is known about the promotion of violence prevention programs in SUD treatment settings. Without efficacious violence prevention programs integrated into these settings, women with SUDs will continue to experience trauma-related health disparities.

Barriers to Care

In addition to a lack of access to integrated service delivery models, women with SUDs and a history of interpersonal violence face multiple barriers to engaging in trauma-informed services and mental health care. Barriers include stigma, lack of acknowledgment of violent incidents, mistrust in formal systems, being a member of a group considered oppressed or minoritized, problematic gender role norms, lack of available resources, and fears of negative consequences [23,24]. Studies indicate that individuals with a history of violence frequently experience multiple co-occurring mental health concerns and, in the face of other barriers to care, are unlikely to seek treatment [25]. Furthermore, individuals with a history of violence and substance use face specific barriers such as lack of acknowledgment of substance-involved sexual assaults as rape, perceived lower credibility by health care providers, and fears of facing criminal charges [23]. These barriers inhibit engagement with prevention and recovery, as well as curtail help-seeking behavior. Furthermore, the strain on health care systems to address the current mental health crisis has limited the availability of mental health professionals to deliver preventive care and clinical interventions [26,27].

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Potential of Peer Support Models to Advance Trauma-Informed Care

The SAMHSA model for trauma-informed care highlights the important role of peer support services in overcoming these barriers and in ensuring a continuum of care. Peer support specialists (PSSs) are individuals who have achieved stable recovery from mental health conditions [28]. Although the definitions of recovery differ between peer-certifying organizations, many align with SAMHSA's definition, which describes recovery as a process of change to improve health and wellness and strive toward one's full potential, rather than a symptom-free end state [29]. As such, recovery can be achieved via multiple pathways such as mental health treatment, family and peer support, and faith-based interventions [29]. PSSs use both their lived experience and relevant training to guide and mentor other individuals in treatment or recovery [30]. Peer support programs are based on the principles of mutual respect and support, empowerment, shared responsibility, and an empathy and connection that can be achieved outside of the constraints of a hierarchical (expert and patient) relationship [31]. These programs aim to reduce marginalization and stigma while offering an extension of mental health care beyond the bounds of formal services. PSSs not only offer a means of overcoming resource demands but can also address other significant barriers to care, such as stigma, mistrust in formal systems, and limited availability of mental health providers representing minoritized identities [32]. Peer norms are a significant predictor of substance use as well as both perpetration of and exposure to violence, and the involvement of peers as prevention educators could be especially fruitful in shifting these norms [33,34]. Violence prevention programs are sorely needed in substance use treatment settings, and PSSs can serve as an important resource for offering the tools to prevent initial and repeated exposure to interpersonal violence and the associated mental health sequelae among women with SUDs.

Peer support programs were integrated into formal mental health systems in the 1980s and currently represent one of the fastest growing sectors of the mental health workforce [30]. Research has established the value of PSS models for suicide prevention and the management of mental health conditions [35,36]. In addition, some violence prevention programs have used peers as advocates, with peers being defined as fellow students or adolescents [37,38]. However, studies have yet to evaluate PSS models for offering violence prevention services in various mental health care settings. Our program extends this promising model to implement needed prevention programming via trusted and trained peer facilitators in substance use treatment settings.

Violence Prevention Programs

Numerous evidence-based programs for SV and IPV prevention have been developed and supported by prior research [39,40]. However, they have almost exclusively been delivered in college and school-based settings, and a recent review has indicated minimal changes in the overall prevalence of SV exposure and perpetration over time [41]. A recent meta-analysis showed that campus SV prevention programs have significant impact on rape myth acceptance, knowledge and attitudes toward sexual assault, knowledge of consent, and exposure to SV [39]. By contrast, a similar meta-analysis highlighted limited behavior change, despite changes in knowledge and attitudes [42]. Most of these programs are geared toward a broad audience of individuals at risk of experiencing SV, potential perpetrators, and bystanders. The enhanced assess, acknowledge, act model is one of the few models to show efficacy for specifically addressing risk for exposure to SV among women by using risk recognition, reducing barriers to active resistance, and engaging in protective strategies [43-45]. Participants demonstrated decreased rape myth acceptance, increased resistance strategies, and decreased incidence of completed rape at 6 months [43]. To our knowledge, very few programs address alcohol or other substance use problems in the context of SV prevention. One web-based program, which used normative feedback on drinking behavior significantly reduced SV risk among women with a history of severe SV and also reduced alcohol use among college women with histories of SV and heavy episodic drinking [46]. Our own team has developed and tested college prevention programs, including a digital app (Make a Change) [47] and a web-based program for college athletes (All In) [48] that used education on consent, protective strategies, and alcohol risk reduction. These programs demonstrated reductions in SV risk factors, including violence-supportive peer norms and drinking behavior [47,48].

Prior programs offer guidance in terms of evidence-based prevention content, although none have been tested among populations seeking treatment or individuals with SUDs outside of alcohol use disorders. Although alcohol use is a commonly cited risk factor for exposure to violence, other substances are associated with IPV and SV; for example, perpetrators use illicit substances to exercise control over their partners through coercing use, encouraging the use of greater amounts, and interfering with recovery. Illicit substance use is also associated with transactional sex, stigma that leads to sexual vulnerability, and financial and relationship strain that increases risk for interpersonal violence [49-52]. Researchers describe the need for prevention programs that emphasize connections between illicit substance use and exposure to SV, as well as reducing stigma and offering supportive environments to disclose these experiences [52]. Furthermore, despite the shared risk factors and the concurrence of SV and IPV [53], none of these programs integrate strategies for addressing these co-occurring forms of violence. An integrated approach to violence prevention is particularly relevant to women in SUD treatment, whose histories are characterized by multiple incidents and types of interpersonal violence [54,55].

Theoretical Framework

The Healthy Relationships and Interpersonal Violence Education (THRIVE) program is informed by the information, motivation, behavioral skills model, which posits that three constructs influence behavior change and its consequent effects on health outcomes: (1) information and knowledge about the behavior, (2) motivation to perform the behavior, and (3) the behavioral skills necessary to perform the behavior [56]. Regarding information and knowledge, the literature on interpersonal violence indicates that inaccurate knowledge regarding how to define or label sexual assault, intentions to engage in risky behavior, overestimations of peer engagement in risky sexual

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behavior, acceptance of gender role stereotypes, and endorsement of rape and partner violence myths are positively associated with SV exposure risk [57-62]. Motivational factors associated with protective behaviors and exposure to SV include supportive peer norms, intentions to engage in protective behaviors, and risk recognition related to SV and IPV [63,64]. Behavioral skills and behaviors that reduce the likelihood of exposure to SV include risk recognition, coping and resistance skills for risky situations, self-efficacy to perform these skills, protective behavioral strategies (eg, sexual assertiveness and safety planning), substance use harm reduction strategies, and help seeking [65-67]. THRIVE program components align with each of these theoretical and empirical risk and protective factors as depicted in Figure 1.

Figure 1. Alignment of THRIVE Program Components with the IMB Model.

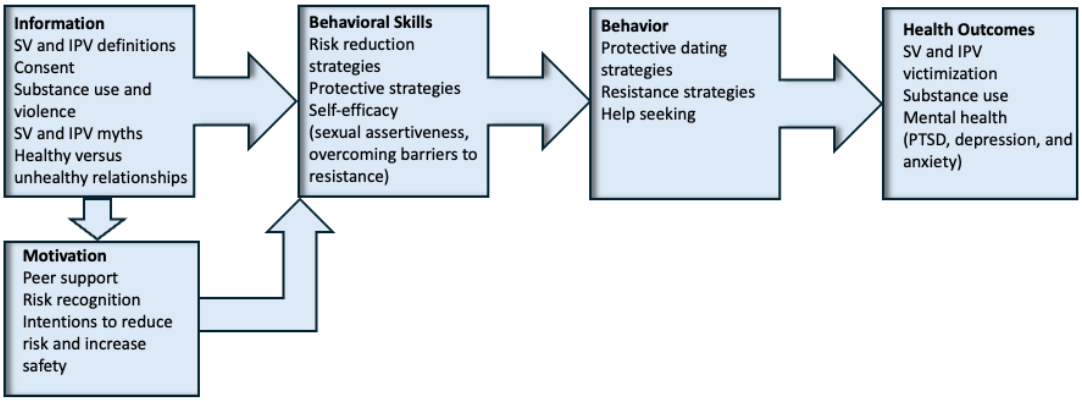

Study Aims

The study will examine the feasibility and preliminary effectiveness of THRIVE, a PSS-delivered interpersonal violence prevention program for women in substance use treatment. The first objective is to determine program acceptability and feasibility. The second objective is to determine the preliminary effectiveness of THRIVE. Proximal outcomes include violence-related knowledge and attitudes, protective sexual and dating behaviors, and help seeking. Distal outcomes include exposure to SV, substance use, and mental health. These objectives will be achieved via a single-arm trial with at least 60 women in outpatient and residential substance use treatment.

Methods

THRIVE Program Development

We conducted preliminary program content development following an iterative process. We first developed content based on evidence-based and theoretically informed strategies from the literature (ie, the enhanced assess, acknowledge, act model and the information, motivation, behavioral skills model), as well as our prior prevention programs with college women [47,48,68]. Second, we adapted and refined the content based on 2 rounds of interviews with 2 expert consultants, 5 health care providers at substance use treatment clinics, 5 PSSs, and 5 women in SUD treatment. The interviews assessed feasibility and acceptability, the strengths and weaknesses of the program, preferred delivery modalities, and suggestions for improvement. Participants unanimously agreed that the content would be useful and appropriate for women in SUD treatment. Participants indicated that a flexible format would be preferred in terms of offering individual versus group sessions. The women in SUD treatment noted that they would respond well and prefer a PSS over a health care or mental health provider to deliver sensitive content related to sexual assault psychoeducation and substance use.

We added components specific to this population based on feedback from the participants. These include risk reduction information focused on drug use (in contrast to the primary focus on alcohol of most prevention programs), the addition of discussions on exchanging sex for drugs, a scenario-based skills-building component, increased engagement (question-and-answer and myths vs facts exercises), and handouts summarizing key takeaways.

Intervention

The intervention consists of two 60-minute sessions delivered in-person by PSSs in either group or individual format. Groups consist of 5 to 10 individuals. The sessions include a combination of information; interactive exercises to fuel discussion on knowledge, attitudes, and behaviors; and skills-building activities. Handouts accompany each session with key takeaways and resources. Topics include (1) definitions of SV and IPV, (2) consent, (3) healthy versus unhealthy relationships, (4) help seeking and resources for trauma-related care, (5) protective behavioral strategies, (6) safe dating, (7) alcohol and drug safety (8) sexual assertiveness, (9) overcoming barriers to protective strategies, and (10) creating a behavior change plan. Table 1 presents the intervention content. In addition to the prevention education program, PSSs screen each participant for PTSD using the Primary Care PTSD Screen for DSM-5 (PC-PTSD-5) [69]. Participants who score ≥3 (indicating a potential PTSD diagnosis) are referred to local mental health providers who provide trauma-informed care. If participants are already enrolled in mental health care, the PSS ensure that the provider is informed of the participant's PTSD symptoms.

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Table 1. The Healthy Relationships and Interpersonal Violence Education program content.

Sessions and topics	Content	Outcome measures	Information, motivation, behavioral skills model components
Session 1: be in the know			
What is sexual assault?	• Definitions and types of sexual violence • Types of perpetrators	Illinois Rape Myth Acceptance Scale	Information
What is drug or alcohol-facilitated assault?	• Definitions and types of drug- or alcohol-facilitated sexual assault • How it occurs	Illinois Rape Myth Acceptance Scale	Information
What is consent?	• What is and is not consent • Enthusiastic consent	ARC3[a] Consent Scale	Information
Red flags	• Intimate partner violence: warning signs of unhealthy relationships	Attitudes Towards Male Dating Violence Scale	Motivation and behavioral skills
What is healthy?	• Healthy relationships	Attitudes Towards Dating Violence Scale	Motivation and behavioral skills
Myths versus facts	• Exercise: myths and facts about interpersonal violence	Illinois Rape Myth Acceptance Scale and Attitudes Towards Male Dating Violence Scale	Information
Resources	• Local and national resources for interpersonal violence	Knowledge of Resources Scale	Information
Session 2: safety skills			
How to respond	• How to respond if someone is pressuring or hurting you	Dating Behavior Survey	Behavioral skills
Alcohol and drug safety	• Reducing risk when substance use is involved	Dating Behavior Survey	Information and motivation
Safe dates	• Safe dating and protective behaviors	Barriers to Resistance Scale	Information and behavioral skills
Be assertive	• Sexual assertiveness	Barriers to Resistance Scale	Behavioral skills
Overcoming barriers	• Barriers to protective behaviors and how to overcome them	Resistance Responses to Sexual Aggression Scale	Motivation and behavioral skills
Skills building	• Recognizing and responding to risk (example scenario)	Resistance Responses to Sexual Aggression Scale	Behavioral skills
Make a plan	• Personalized behavior plan	Resistance Responses to Sexual Aggression Scale	Behavioral skills
Help seeking	• Resources for interpersonal violence	Service Use Scale	Behavioral skills

[a]ARC3: Administrator-Researcher Campus Climate Collaborative.

Study Design

We developed elements for a larger clinical trial by pilot-testing a 2-session program in a single-arm trial with 60 participants. To analyze feasibility and acceptability, we will examine retention, adherence, and survey data from the trial. We also conducted exit interviews with 12 participants (10 completers and 2 noncompleters) as well as the 2 PSSs facilitating the program. To examine preliminary effectiveness, we collected self-report questionnaires at baseline, after the intervention, and at 1- and 3-month follow-ups. We assessed the proximal outcomes of knowledge, attitudes, and behaviors and the distal outcomes of exposure to SV, substance use, and mental health. Although a single-arm trial does not allow for rigorous efficacy testing, it is a first step in determining feasibility and potential efficacy. For a newly developed and exploratory intervention, it offers opportunity to identify areas for improvement and refinement to ensure a robust approach within a future large-scale, randomized controlled trial [70].

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The study has been registered with ClinicalTrials.gov (NCT06608979).

Ethical Considerations

The study was approved by the Prisma Health Institutional Review Board (2042281). Before screening potential participants for eligibility, the research coordinator obtained verbal consent for screening, which included a brief description of the study and reinforced the confidentiality of all survey responses. Interested patients who were eligible for the study after the initial screening provided verbal consent to proceed after reviewing a written informed consent document. The informed consent document reviews the possible risks and benefits of study participation and informs the participants that they may terminate the study at any time without penalty. The participants reviewed the consent document again before proceeding with each self-report survey. The surveys did not record identifying information, and participants were assigned a participant number to link survey data. To minimize social desirability bias, the study procedures emphasized with participants include confidentiality of survey responses and disclosures within the intervention sessions. This is further reinforced with the use of confidential online surveys and reliance on aggregated data for interpretation of the findings. A separate consent process was conducted for the interviews, wherein the research coordinator met with participants to review the study and asked them to provide verbal consent after reviewing the written consent document. Participants received US $30 for each of 4 assessments (a maximum of US $120). Participants completing exit interviews received an additional US $30.

Setting

The study was conducted at 3 sites that provide substance use treatment in Greenville, South Carolina, United States. The first site, Prisma Health Addiction Medicine Center, provides care to >3000 patients with opioid use disorder per year, including medication-assisted treatment, peer recovery support, and counseling. The second site, Phoenix Center, is a comprehensive substance use treatment program with an intensive outpatient program, inpatient detoxification and rehabilitation programs, an outpatient buprenorphine program, and a residential program for pregnant women and mothers (Serenity Place). Phoenix Center serves >2000 individuals per year. PSSs are contracted to work with the patients at Phoenix Center. The third site, Magdalene Clinic at Prisma Health, offers prenatal care, peer support services, and counseling to pregnant persons with SUDs. Magdalene Clinic serves >100 individuals per year and works closely with Prisma Health Addiction Medicine Center and Phoenix Center.

Participants and Procedure

Participants

We recruited and enrolled 92 women (71 completers) in substance use treatment for a single-arm trial of THRIVE. The inclusion criteria include (1) adults (aged ≥18 y), (2) identifying as women, (3) currently enrolled in substance use treatment (behavioral or pharmacological), and (4) willing to accept random assignment to a waitlist (usual care) or THRIVE. The exclusion criteria include (1) having a severe medical or psychiatric disability that could impair ability to perform study-related activities (determined by their substance use treatment provider), (2) unable to independently read and comprehend the consent form or other study materials, and (3) unable to read and speak English. A total of 10 to 20 women as well as the 2 PSSs were selected to complete exit interviews. The inclusion criteria for the interviews included (1) women who completed either the baseline survey only (intervention noncompleters) or the full THRIVE intervention (intervention completers); and (2) for the PSSs, those who delivered the THRIVE intervention.

Recruitment

Participants were recruited via referral from clinicians and research coordinators at the 3 recruitment sites, using flyers, email, and verbal communication. Recruitment occurred during each clinic's operating hours (8:30 AM-5 PM). Recruitment for the pilot trial remained open until at least 60 participants completed the intervention. For the interviews, women who completed either the baseline assessment session only or the full THRIVE intervention were randomly selected and recruited via telephone or email by the research coordinator. Recruitment for interviews remained open until data saturation was achieved, at 12 participants [71].

Screening

The research coordinator enrolled potential participants from the Prisma Health Addiction Medicine Center, Phoenix Center, and Magdalene Clinic by contacting patients who were referred by clinicians and staff at each of these facilities. Potentially eligible participants were given a flyer about the study and asked whether they were interested in considering participation. Potential participants who expressed interest in learning about our study were referred to the research coordinator, who described the study to the participants and initiated the consent process.

Assessment Plan

Research assessments consisted of 20- to 30-minute online self-report questionnaires at 4 assessment points: baseline, after the intervention, and 1- and 3-month follow-ups. Ten completers and 2 noncompleters from the intervention group were selected for the postintervention exit interviews. We also conducted interviews with the 2 PSSs who are facilitating the program. Participants attended baseline, intervention, and postintervention visits in person at 1 of the 3 study sites. The research coordinator or another research team member attended all baseline and postintervention visits (immediately before and after the THRIVE sessions) in person to collect online survey data using a tablet PC. Qualtrics software (Qualtrics International Inc) [72] was used to administer the online surveys and extract the data. Follow-up data were collected via online surveys delivered to participants via SMS text message or email. For the interviews, participants were provided with a copy of the THRIVE prevention program content to review, either via email or in hard copy. Participants then completed a 30-minute semistructured interview assessing program acceptability, feasibility, strengths, weaknesses, and areas for revision or improvement, as well as barriers and facilitators to participation,

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engagement, and implementation. A member of the research team conducted the interviews via teleconference for the PSSs and in person for the women in treatment.

Retention Plan

Beyond the incentive structure for study participation, implemented additional strategies to ensure high retention rates. First, we asked for ≥2 alternate contacts at baseline so that we could continue to reach participants during follow-up. Written consent was also obtained to contact other persons for locating the participant for follow-up. The research coordinator contacted all participants at least once between follow-up assessments to maintain a connection and updated contact information. Participants received at least 3 email or SMS text message reminders to complete surveys. The research coordinator made at least 20 attempts to contact participants who did not respond or complete assessments before considering them lost to follow-up. The research coordinator attempted to make regular contact with participants to collect data at each assessment interval, regardless of whether they attended the intervention. The research coordinator also worked with health care providers to determine when eligible participants had appointments to better facilitate scheduling assessment sessions around already scheduled health care appointment times.

Research team members attended staff meetings at each recruitment site to update the sites on enrollment and retention status and to work with the sites on overcoming barriers to recruitment and retention. A member of the research team was present on site throughout active recruiting periods to connect with health care providers, screen eligible participants, and meet with potential participants around the time of their health care appointments.

Measures

Overview

Table 2 presents a list of outcomes and study measures.

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Table 2. Pilot trial outcomes and measures.

Outcomes and measures	Baseline	Sessions 1-2	After the intervention	1-month follow-up	3-month follow-up	Information, motivation, behavioral skills model components	Health outcome
Acceptability and feasibility							
Feasibility							
Recruitment and retention: enrollment and attendance tracking			✓		✓		
Percentage of assessments completed			✓		✓		
Adherence							
THRIVE[a] adherence scale (rating of PSS[b] fidelity to protocol)		✓					
Acceptability and engagement							
PSS interviews				✓			
Exit interviews				✓			
Satisfaction and engagement scale			✓	✓			
Qualitative survey items: feedback on protocol			✓	✓			
Proximal outcomes: knowledge, attitudes, and behaviors							
Sexual violence attitudes							
Illinois Rape Myth Acceptance Scale–Short Form [73]	✓		✓	✓	✓	✓[c]	
Partner violence attitudes							
Attitudes Towards Dating Violence Scale [74]	✓		✓	✓	✓	✓[c]	
Knowledge of consent							
ARC3[d] Consent Scale [75]	✓		✓	✓	✓	✓[c]	
Sexual self-efficacy							
Barriers to Resistance Scale [67]	✓		✓	✓	✓	✓[e]	
Behavioral intentions							
Dating Behavior Survey [76]	✓		✓	✓	✓	✓[f]	
Resistance Responses to Sexual Aggression Scale [77]	✓		✓	✓	✓	✓[f]	
Knowledge of resources							
Knowledge of Resources Scale (locally adapted) [75]	✓		✓	✓	✓	✓[c]	

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Outcomes and measures	Baseline	Sessions 1-2	After the intervention	1-month follow-up	3-month follow-up	Information, motivation, behavioral skills model components	Health outcome
Help seeking (trauma-related service use)							
Frequency of use of behavioral health services and local and national resources	✓			✓	✓	✓[e]	
Primary distal outcomes: exposure to violence							
Exposure to sexual violence							
Sexual Experiences Survey–Short Form [78]	✓			✓	✓		✓
Exposure to intimate partner violence							
Revised Conflict Tactics Scale–Short Form [79]	✓			✓	✓		✓
Secondary distal outcomes: substance use and mental health							
Substance use							
CAGE-AID[g] [80]	✓		✓	✓	✓	✓[e]	
PTSD [h]							
PC-PTSD-5[i] [69]	✓		✓	✓	✓		✓
Depression							
PHQ-2[j] [81]	✓		✓	✓	✓		✓

[a]THRIVE: The Healthy Relationships and Interpersonal Violence Education program.
[b]PSS: peer support specialist.
[c]Information.
[d]ARC3: Administrator-Researcher Campus Climate Collaborative.
[e]Behavior skills.
[f]Motivation.
[g]CAGE-AID: CAGE Adapted to Include Drugs.
[h]PTSD: posttraumatic stress disorder.
[i]PC-PTSD-5: Primary Care PTSD Screen for DSM-5.
[j]PHQ-2: Patient Health Questionnaire-2.

Demographics

A demographics questionnaire assessed gender identity, race and ethnicity, and age. A participant log recorded recruitment site and intervention format.

Feasibility and Acceptability

The data sources are presented in Textbox 1.

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Textbox 1. Data sources.

- Recruitment and retention: study logs recorded enrollment, attendance, retention rates, and the percentage of assessments completed.
- Adherence scales: completed by research team members for 50% of the sessions, these scales assess peer support specialist fidelity to the protocol.
- Satisfaction and engagement scale: 4 Likert scale survey items from our prior study (eg, "How engaging did you find the program?") assess satisfaction and engagement.
- Qualitative feedback: 2 items on the self-report surveys elicited areas for improvement and strengths of the protocol (eg, "What did you like about the program?" and "How could the program be improved?").
- Interviews: semistructured interviews assessed program feasibility, acceptability, strengths, and weaknesses (eg, feasibility of attending appointments, acceptability of the study location, satisfaction with the research team, and intervention format and modality). The interviews also assessed alliance with peer support specialists and suggestions for improvement (eg, "How appropriate does the program seem for women who are in substance use treatment?" "How did you feel about your interactions with the peer support specialist who delivered the program?" "What barriers or difficulties did you experience in terms of participating in the study?").

Knowledge, Attitudes, and Behaviors

Proximal outcomes were assessed via the self-report surveys presented in Textbox 2 [67,73-77].

Textbox 2. Proximal outcomes and measures.

- The Illinois Rape Myth Acceptance Scale [73] is a 20-item scale assessing acceptance of rape-supportive beliefs and norms (eg, "If a woman was raped while she was drunk, she is responsible for what happened"), with total scores ranging from 20 to 140. Higher scores indicate greater rape myth acceptance.
- The Attitudes Towards Male Dating Violence Scale [74] consists of 15 items assessing acceptance of dating and partner violence myths, including stereotypical gender roles and acceptance of partner violence, (eg, "A girl should always do what her boyfriend or intimate partner tells her to do"), with scores ranging from 15 to 105. Higher scores represent greater acceptance of dating violence myths.
- The Administrator-Researcher Campus Climate Collaborative Consent Scale [75], a 7-item scale ranging from 7 to 35, assesses understanding of consent in sexual situations (eg, "If you and your partner are both drunk, you don't have to worry about consent"), with higher scores reflecting a lower understanding of consent.
- The Barriers to Resistance Scale [67] is a 13-item scale that assesses sexual self-efficacy, sexual assertiveness, and perceived barriers to resisting in sexually coercive situations, including substance use (eg, "I might be too intoxicated to think through a plan to get out of the situation"). Total scores range from 13 to 52, with higher scores indicating greater perceived barriers.
- The Dating Behavior Survey [76], a 15-item scale, with scores ranging from 7 to 105, assesses intentions to engage in risky and protective behaviors, such as using substances on a date, arranging for transportation, and making safety plans (eg, "On the first few dates that we have, I will allow my partner to plan what we do"). Higher scores reflect greater intentions to engage in these behaviors.
- The Resistance Responses to Sexual Aggression Scale [77] is a 16-item scale assessing the perceived likelihood of engaging in resistance responses in sexually aggressive situations, including verbal and physical strategies (eg, "Tell them I like them but I'm not ready"). Total scores range from 16 to 112, with higher scores suggesting a greater perceived likelihood of using resistance responses.
- The Knowledge of Resources Scale [75] was adapted to local context to assess familiarity with local and national resources for trauma-focused care (resulting in 13 items), with total scores ranging from 13 to 65. Higher scores indicate a greater awareness of resources for trauma-focused care.
- Trauma-related service use was assessed as the past-month frequency of accessing a list of local and national resources related to interpersonal violence (13 items). The outcome measures were self-report scales that were summed to create mean and total scores.

Exposure to SV and IPV

Outcomes regarding exposure to SV and IPV were assessed using the Sexual Experiences Survey–Short Form [78] and the Revised Conflict Tactics Scale [79], respectively.

The Sexual Experiences Survey–Short Form is a 7-item scale that assesses self-reported experiences of various forms of exposure to SV (unwanted sexual contact, sexual coercion, attempted rape, and rape) using several tactics (verbal, physical, and drug or alcohol facilitation).

The Revised Conflict Tactics Scale, a 20-item measure of IPV, assesses psychological, physical, and sexual experiences of IPV in the context of a marital, dating, or cohabitating relationship, with total scores ranging from 20 to 100. Higher scores indicate greater frequency of experiences of exposure to IPV. Exposure to IPV will be scored as a dichotomous outcome and will be measured across 2 time frames: lifetime and past 3 months.

Substance Use and Mental Health

A secondary set of distal outcomes was assessed with the CAGE Adapted to Include Drugs Questionnaire [80], the PC-PTSD-5 [69], and the Patient Health Questionnaire-2 [81].

The CAGE Adapted to Include Drugs Questionnaire is a 4-item conjoint screening questionnaire for alcohol and other drug use (eg, "Have you felt the need to cut down on your drinking or drug use?). Scores range from 0 to 4, with higher scores indicating greater risk of problematic substance use.

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The PC-PTSD-5 is a 5-item scale that screens for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, PTSD criteria, with total scores ranging from 0 to 5. Higher scores indicate a greater likelihood of probable PTSD.

The Patient Health Questionnaire-2 is a 2-item scale that screens for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition depression criteria. Total scores range from 2 to 8, with higher scores reflecting greater depressive symptoms.

The distal outcome measures are self-report scales that will be summed to create total scores.

Quality Assurance and Implementation

Two female PSSs were hired for the study. Both were trained as certified PSSs and certified assertive community engagement specialists through the National Association of Alcohol and Drug Abuse Counselors program. They are required to be at least 1 year in recovery from addiction, as defined by SAMHSA. Certified PSSs in South Carolina must have 2 recommendation letters from employers or supervisors attesting to 1 year of recovery to receive certification [82]. Experience with interpersonal violence or recovery from trauma is not specified as a requirement to perform as a PSS in this capacity. PSSs received at least 10 hours of training from the principal investigator (PI), using the PSS training manual and the THRIVE intervention protocol developed in our prior research. As part of the training, PSSs conducted at least 2 mock sessions under observation by the PI. PSSs also met weekly with the PI, a licensed clinical psychologist, for supervision once they began delivering the program. Although not a criterion for the study, PSSs may have a history of interpersonal violence, which was assessed and addressed by the PI to ensure that their own mental health concerns were adequately managed and monitored. If the PSSs had trauma symptoms interfering with the delivery of the intervention that could not be adequately managed via clinical supervision, they would have been referred for mental health treatment and could be removed from their role in the study. PSSs were trained in recognizing adverse events and signs of distress and referring participants to mental health and medical professionals to address these concerns as they arise. Intervention fidelity was monitored with a checklist developed by the research team to assess the completion of each THRIVE component. After achieving reliability with at least one other research team member during initial training sessions, one member of the research team attended and rated each of the sessions using the intervention checklist.

Managing Participant Distress

Facilitators were trained in recognizing signs of distress, intoxication, and overdose. Facilitators were instructed to refer participants in distress, including those expressing suicidal or homicidal ideation, to emergency medical personnel on site. For other mental health concerns, including PTSD and trauma-related symptoms arising during the intervention, facilitators were instructed to refer to their current provider or to a social worker at the Prisma Health Addiction Medicine Center. If a participant appeared to be intoxicated, the facilitator was instructed to contact the patient's provider or recovery program nurse, ensure that a referral is completed, and also ensure that the participant had transportation and was not driving. Participants who were intoxicated would not be allowed to participate in study sessions at that time and would be asked to reschedule. If a participant showed signs of overdose, the facilitator would call 911 or emergency medical services and ask recovery program staff for assistance. They could also escort the participant to the emergency department. If a participant was agitated, the facilitator was instructed to contact security. All participants were given handouts with local and national resources for counseling, shelter, crisis management, and related services. In addition, participants were made aware that the PSSs are available to assist with follow-up needs at the conclusion of the intervention. Site-specific procedures and contact persons were outlined in the facilitator training manuals.

Analysis

Feasibility and Acceptability

Descriptive statistics will be used to describe recruitment and retention rates and to calculate means on survey items assessing feasibility and acceptability. A benchmark of ≥75% of the *agree* and *strongly agree* (equivalent to an average score of ≥4) responses will be used [83,84]. For the satisfaction and engagement scale, qualitative survey items will be coded by 2 research team members. Interviews will be recorded, transcribed, and uploaded to NVivo (Lumivero) [85] for thematic analysis [86]. The research team will conduct a line-by-line reading of transcripts to identify inductive codes that emerge from the data. The team will then collaborate to develop a codebook that includes operationalized definitions of each of these inductive codes as they apply to the topics addressed in the interviews (ie, feasibility, acceptability, strengths, weaknesses, areas for improvement, and barriers and facilitators to implementation). A study investigator and the research coordinator will code a subset of the data, then convene to resolve discrepancies and revise codes until consensus is achieved on the codebook. Two research team members will then code the entire dataset and meet to achieve consensus on the final codes. The results from these analyses will be used to inform further refinement of the THRIVE protocol before proceeding to a larger randomized controlled trial.

Preliminary Effectiveness

Analytic Sample

The primary analytic sample will include all participants who completed the baseline survey; this will serve as the intention-to-treat sample. We will also conduct modified intention-to-treat analyses including only participants who attended 1 THRIVE session.

Missing Data

Every effort was made to minimize missing primary outcome data. However, the primary analytic strategy relies on mixed effects models, which is unbiased under missing-at-random assumptions and is the most frequently accepted approach in longitudinal data analysis [87]. Characteristics of patients who are lost to follow-up will be compared to those who complete the study to assess the degree of any selection bias due to attrition. We will complete a sensitivity analysis to compute

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indices of sensitivity to the nonignorability of missing data. If these analyses indicate evidence that nonignorability will impact model parameter estimation, we will apply fully conditional specification multiple imputation methods, which are applicable to nonignorable missing data [87,88].

Statistical Analyses

To test the effects of THRIVE on primary and secondary outcomes, linear mixed effects model for continuous outcomes and generalized linear mixed effects models for binary outcomes will be used, with subject-specific random intercepts to account for the correlations of longitudinal outcomes measured after the intervention (week 2) and at 1-month and 3-month follow-ups. Covariates, such as recruitment sites, any demographic variables correlated with primary outcomes, type of substance use, and intervention format, will be included as fixed effects in all analysis models. The primary knowledge, attitude, and behavior outcomes will be continuous outcomes, and secondary outcomes such as experience of SV or IPV will be binary outcomes. In addition, with this model, we will also identify postbaseline time points where changes in outcomes from baseline are significant.

Results

Recruitment, enrollment, and data collection from the 3 sites was completed between June 2024 and March 2025. Of the 92 women recruited and enrolled, 71 (77%) completed the intervention and postintervention assessments, 58 (63%) completed the 1-month follow-up assessments, and 44 (48%) completed the 3-month follow-up assessments. Ten completers, 2 noncompleters, and 2 PSS completed exit interviews. Of the 92 enrolled participants, 45 (50%) were from the Prisma Health Addiction Medicine Center, 42 (47%) from Phoenix Center, and 3 (3%) from Magdalene Clinic. Of the 92 participants, 1 (1%) was American Indian or Alaska Native, 4 (4%) were Black, 1 (1%) were Hispanic, 79 (86%) were White, 2 (2%) identified as multiracial, and 3 (3%) identified as “other.” Racial and ethnic distribution is representative of the patient populations at the recruitment sites. The participants’ mean age was 35 (SD 9.87) years. The most commonly reported substances used included tobacco (79/92, 86%), cannabis (58/92, 63%), alcohol (55/92, 61%), amphetamine-type stimulants (58/92, 63%), and opioids (50/92, 54%; Table 3).

Table 3. Types of substances used by enrolled participants (N=92).

Substance types	Participants, n (%)
Tobacco	79 (86)
Alcohol	55 (61)
Cannabis	58 (63)
Opioids (heroin, fentanyl, etc)	50 (54)
Amphetamine-type stimulants	58 (63)
Inhalants	19 (24)
Sedatives	47 (51)
Hallucinogens	32 (35)
Cocaine	44 (48)

Discussion

Summary

This study evaluated an interpersonal violence prevention program for women with SUDs to fill a vacuum in programs with demonstrated efficacy for this population. This will be the first study to test an evidence-based SV and IPV prevention program for women in substance use treatment. It will address the nexus of 2 significant public health problems: interpersonal violence and SUDs. Although a majority of women in substance use treatment have a history of SV or IPV, a history of interpersonal violence and risk for repeated exposure to interpersonal violence are rarely addressed in substance use treatment settings.

Both a history of violence and substance use place women at risk for cumulative exposure to violence and adverse outcomes, including SUDs, PTSD, depression, and physical health problems. For women in substance use treatment, exposure to SV and IPV can lead to escalation of substance use and inability to achieve recovery [11]. However, women face barriers to care in seeking trauma-focused services, and there is a lack of available evidence-based violence prevention programs within substance use treatment settings. Therefore, there is a significant need for research to develop and test violence prevention services that could mitigate the sequelae of initial and repeated exposure to interpersonal violence among women in substance use treatment.

An additional gap in the literature that will be addressed by the THRIVE program is the lack of integrated prevention programming for SV and IPV, despite their shared risk factors. These forms of violence share risk factors such as exposure to childhood adversity, stereotypical gender role conformity, and substance use [53]. An intervention that is both pragmatic and designed to achieve maximum impact will address multiple forms of interpersonal violence simultaneously. The THRIVE program is one of only a few programs to adopt an integrated approach to these 2 co-occurring forms of violence [53,89].

THRIVE will also be the only known program to address the use of illicit substances as a risk reduction strategy for violence prevention. Prior prevention programs have singularly focused

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on alcohol use [46]. However, our data from the program development phase suggested the need to address unique concerns around illicit substance use, such as vulnerability during withdrawal, coercion by dealers, and exchange of sex for drugs.

Furthermore, THRIVE will be the first program to engage PSSs as violence prevention educators. Consistent with recommended models of trauma-informed care in substance use treatment settings [90], we will incorporate trained PSSs as educators who can lift stigma, offer empathy and trust, reduce barriers to engagement, and fill gaps in mental health service provision. While PSSs have delivered prevention programming in the mental health sector [91], this will be the first known study to develop and test a PSS-delivered violence prevention program. In addition, training PSSs in health promotion skills related to violence and substance use will provide them with professional skills and confidence to work with their clientele. A PSS violence prevention model also offers scalable and cost-effective solutions for workforce development and the expansion of mental health services.

Finally, THRIVE places unique emphasis on help seeking and overcoming barriers to care as violence prevention strategies. Encouraging help seeking will promote access to resources that could mitigate mental health conditions and reduce adversity related to exposure to interpersonal violence as a means of both health promotion and risk reduction. Our preliminary research indicates that participants view this content as both necessary and missing from existing prevention programs [48]. One benefit of using PSSs as facilitators is that they are trained and capable of both modeling appropriate resource use and providing warm handoffs to other services.

Conclusions

Upon successful completion of this study, we expect to demonstrate the feasibility, acceptability, and preliminary effectiveness of THRIVE. This program will address gaps in the evidence base by emphasizing the critical intersection of violence and substance use, expanding effective strategies to a population considered high risk, and implementing a novel peer-delivered format to overcome barriers to care. The limitations of this approach include the use of a single-arm trial, underrepresentation of minoritized populations at our recruitment sites, and flexibility in program format that introduces some variability and could limit generalizability. If preliminary feasibility and efficacy are established, we will use the study findings to design future trials that minimize these limitations by using randomized controlled designs, oversampling underrepresented groups, and standardizing the delivery format. Our long-term goal is to develop an accessible, scalable, and efficacious prevention program that reduces the incidence of exposure to SV and IPV, substance use, and violence-related mental health disorders for women in substance use treatment. Ultimately, reducing exposure to SV and IPV is expected to reduce substance use escalation as well as sustain recovery from SUDs over the long term.

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Authors' Contributions

HMZ and IP-V conceptualized the study, and HMZ is the principal investigator. AHL and KYE consulted on study design and serve as recruitment leads for study sites. KS serves as recruitment lead for 1 study site. AS, MS, CG, MGB, and AT assist with data collection and analysis. LS serves as project coordinator and assists with data collection and analysis. All authors reviewed the protocol and manuscript.

Conflicts of Interest

None declared.

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Abbreviations

IPV: intimate partner violence
PC-PTSD-5: Primary Care PTSD Screen for DSM-5
PI: principal investigator
PSS: peer support specialist
PTSD: posttraumatic stress disorder
SAMHSA: Substance Abuse and Mental Health Services Administration
SUD: substance use disorder
SV: sexual violence
THRIVE: The Healthy Relationships and Interpersonal Violence Education

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Protocol

Establishing a Multicenter Active Adverse Events Following Immunization Sentinel Surveillance Network Across 22 Tertiary Care Hospitals in India: Protocol for a Prospective Observational Study

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Abstract

Background: The rapid evolution of immunization programs in low- and middle-income countries (LMICs) has necessitated an augmentation of capacity for postlicensure vaccine safety monitoring.

Objective: This study describes the protocol for establishing a Multicenter Active Adverse Events Following Immunization Surveillance System (MAASS) network in India, which conducted prospective observational surveillance for 12 adverse pediatric outcomes between November 1, 2017, and March 20, 2020.

Methods: A multistage site selection process was implemented, beginning with an initial screening survey followed by in-person visits to assess the suitability of potential tertiary care hospitals for inclusion in the network. We adopted a decentralized, collaborative approach to develop the study protocol, standardize case definitions, establish data collection procedures, and create a common data model for monitoring and analysis. Outcomes selected for surveillance included acute disseminated encephalomyelitis, anaphylaxis, aseptic meningitis, dengue, Guillain-Barré syndrome, Kawasaki disease, malaria, seizure, sepsis, thrombocytopenia, intussusception, and urinary tract infections. We screened all children aged 1-24 months who were hospitalized for more than 24 hours at participating sites to identify suspected or confirmed cases of these outcomes using a structured checklist. Written informed consent was obtained from the parent or legally authorized representative for inclusion in the study. Demographic, socioeconomic, and vaccine exposure information was collected for all included participants. Additional clinical information was gathered to assess the level of diagnostic certainty according to standardized case definitions. The study progressed through 3 distinct phases: network establishment (January-November 2017), active surveillance (November 2017-March 2020), and database analysis (April 2020-March 2024). The dissemination process is currently underway.

Results: A geographically representative data network was established across 15 public and 7 private tertiary care hospitals in 17 states and 1 union territory in India. During the study period, we screened 90,147 age-eligible admissions and confirmed 8362 cases with study outcomes. Using multiple analytic study designs, we generated a database of outcomes and exposures to investigate associations between vaccine-event pairs of interest.

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Conclusions: The MAASS network is unprecedented in its scope and scale among LMICs. While the study is specific to India, the lessons learned in establishing and implementing the network offer valuable insights for developing active surveillance systems and strengthening capacity for benefit-risk evaluations of vaccines in resource-constrained settings.

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KEYWORDS

vaccine safety; pharmacovigilance; multicenter studies; adverse events following immunization; low- and middle-income countries; postlicensure safety surveillance; active surveillance

Introduction

Background

The COVID-19 pandemic highlighted significant health system inequities, including in vaccine safety surveillance. Nearly two-thirds of all active vaccine safety surveillance evaluations were conducted in high-income countries, underscoring the limited capacity for postauthorization vaccine safety monitoring in low- and middle-income countries (LMICs) [1]. To help avert future pandemics, the Coalition for Epidemic Preparedness Innovations' 2022-2026 strategy aims to develop safe and effective vaccines against potential diseases within 100 days [2]. Robust vaccine pharmacovigilance systems are critical for ensuring effective vaccine monitoring, particularly because, even under routine conditions, clinical trials lack the power to detect rare and long-term adverse events following immunization (AEFIs) [3]. Clinical trials do not reflect real-world immunization conditions, where vaccines are administered to diverse populations. Without strong postlicensure surveillance, safety concerns could undermine public trust and disrupt immunization programs [4,5].

As more vaccines are tailored to the needs of LMICs, progress in strengthening vaccine pharmacovigilance capacity has not kept pace with the rapid evolution of immunization programs, despite systematic efforts [6,7]. Most LMICs rely on passive reporting systems that often miss or underreport adverse events [8,9]. These systems also lack comparable data from unvaccinated cohorts. The limited availability of clinical information hampers case verification, making it difficult to confirm potential vaccine-event links [10]. To address these gaps, the World Health Organization's (WHO) Global Vaccine Safety Blueprint documents (versions 1 and 2) call for strengthening capacity for active and hospital-based sentinel safety surveillance at the national, regional, and global levels [11,12]. Active vaccine safety surveillance systems proactively solicit reports of events, enabling the systematic investigation of very rare (ie, fewer than 1 event per 10,000 doses) or long-term sequelae after vaccination [13]. Unlike passive surveillance, which depends on spontaneous reporting, active surveillance uses standardized case definitions and protocols to systematically identify adverse events, allowing for more complete detection of rare or underreported events. In LMICs, where health care infrastructure and routine reporting capacity may be limited, active surveillance helps bridge critical gaps in passive systems, thereby supporting more comprehensive vaccine safety monitoring [12,14]. In 2016, the Ministry of Health and Family Welfare tasked the International Clinical Epidemiology Network (INCLEN) with establishing the Multicenter Active AEFI Surveillance System (MAASS) to complement ongoing efforts to improve the coverage, quality, and safety of the national immunization program. This paper describes the protocol for establishing a prospective observational surveillance network to monitor adverse pediatric outcomes in resource-constrained settings.

Study Objectives

This study aims to establish a sustainable, geographically and socioculturally representative hospital-based sentinel surveillance network capable of identifying and classifying pediatric outcomes and documenting vaccine exposure status to inform benefit-risk evaluations of routinely administered vaccines in India. The specific objectives were to (1) estimate baseline hospital outcome rates (per 100,000 pediatric admissions between 1 and 24 months of age per year) for the study outcomes; (2) characterize the seasonality, as well as the demographic, socioeconomic, and clinical profiles, and the vaccine exposure status of selected study outcomes; (3) assess the applicability of standardized case definitions (eg, Brighton Collaboration definitions for known AEFIs) for study outcomes, using information documented during routine clinical practice and patient care at network sites; and (4) investigate the association between selected vaccine-event pairs using appropriate analytical study designs, including case-control, self-controlled case series, and self-controlled risk interval designs.

Methods

Design

We developed an operational framework to establish an active surveillance network for monitoring AEFIs in tertiary care hospitals across India. The framework aims to estimate baseline hospitalization rates for pediatric conditions and document vaccine exposure in children aged 1-24 months.

Network Governance and Decision-Making

We adopted a decentralized, collaborative approach to governance and decision-making. This included the cocreation of the study design, harmonized data collection, shared responsibility for data quality and management, development of a common data model, and joint formulation of the statistical analysis plan and data interpretation. The study was coordinated and monitored by the Executive Office of the INCLEN Trust International in New Delhi, India. The team at INCLEN developed the zero drafts of the study documents (eg, protocol,

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operating procedures, tools, statistical analysis, and data management plans), organized protocol finalization workshops, conducted training, monitored data quality, and analyzed and interpreted the results. Dedicated research staff (n=2) collected data at each surveillance site, while faculty from the departments of pediatrics, pediatric surgery, and community medicine served as principal and coprincipal investigators. They facilitated all aspects of study implementation and monitored progress throughout the study. The sites served as data custodians; however, in accordance with national guidelines, data ownership remained with the patients [15].

A technical advisory group (TAG)—comprising representatives from the Immunization Division, Ministry of Health and Family Welfare, and the national AEFI committee (n=2), along with an interdisciplinary team of pediatricians (n=4), epidemiologists (n=4), statisticians (n=3), and pharmacovigilance experts (n=3)—provided technical guidance throughout all stages of project implementation.

Network Establishment

Site Selection

We identified potential sites for inclusion in the network through a systematic, multistage process. INCLEN has been conducting large multicentric studies since 1997 and has fostered partnerships with many medical schools and tertiary care hospitals across the country [16-19]. First, a list of 68 large public and private tertiary care hospitals was developed, based on criteria such as geographic and sociocultural representativeness, the availability of pediatric departments, and, where applicable, the performance of hospitals in prior prospective surveillance studies [19,20]. All listed sites were invited to participate in a screening survey to assess eligibility for inclusion based on predefined criteria (refer to Multimedia Appendix 1 for site selection questionnaires). The survey also helped delineate the ethics and regulatory approval processes, data-sharing policies, and timelines at each potential site. Based on the responses, technical experts shortlisted 31 sites for in-person visits. These visits served to validate findings from the screening survey; assess the quality, completeness, and ease of retrieval of patient medical records and diagnostic reports; and gather qualitative feedback regarding institutional support and willingness to participate in the study. The TAG reviewed the findings from the screening questionnaire and site visits during a review meeting in March 2017 and recommended the selection of 24 sites for inclusion in the network. The sites were chosen to ensure that nearly equal numbers of hospitals were represented from each of the 4 geographic zones of the country (north, south, east, and west), with at least one hospital from the private sector, as illustrated in Figure 1. Figure 2 outlines the eligibility criteria and site selection process followed in establishing the network.

Figure 1. Types of facility in the Multicenter Active AEFI Surveillance System (MAASS) network and their geographic distribution. AGMC: Agartala Government Medical College; AMC D: Assam Medical College, Dibrugarh; AMC V: Andhra Medical College, Visakhapatnam; CMC L: Christian Medical College, Ludhiana; GMC M: Grant Govt. Medical College & Sir J. J. Group of Hospitals, Mumbai; GMC N: Government Medical College Nagpur; GMC T: Government Medical College, Thiruvananthapuram; H: Hospital; IGIMS P: Indira Gandhi Institute of Medical Sciences; IMS & SUM: Institute of Medical Sciences & Sum Hospital; IPGMS K: Institute Post-Graduate Medical Education and Research and Seth Sukhlal Karnani Memorial Hospital, Kolkata; KMC: Kasturba Medical College; LHMC: Lady Hardinge Medical College; MAMC: Maulana Azad Medical College; MP SHAH: Shri M. P. Shah Medical College; NEIGHRMS: North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences; PGIMS R: Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak; PSG C: PSG Institute of Medical Sciences and Research, Coimbatore; RIMS: Rajendra Institute of Medical Sciences; SKIMS: Sher-e-Kashmir Institute of Medical Sciences.

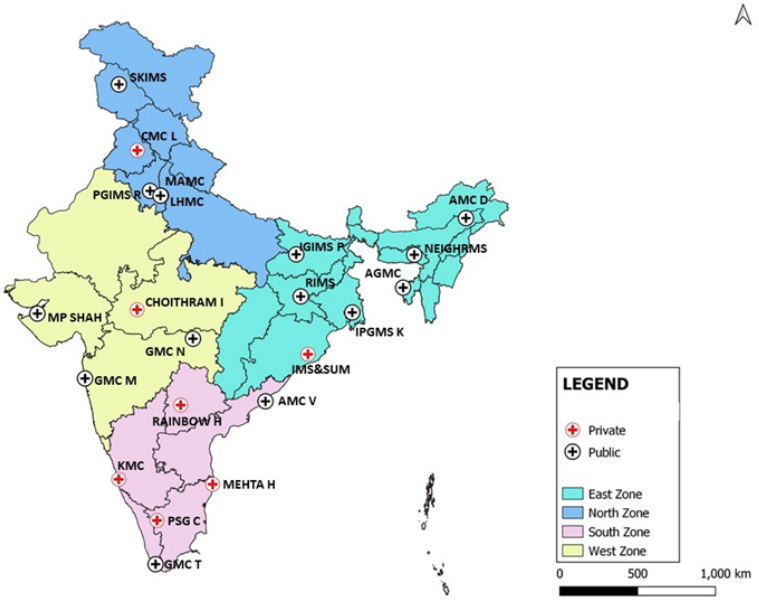

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Figure 2. Site selection criteria.

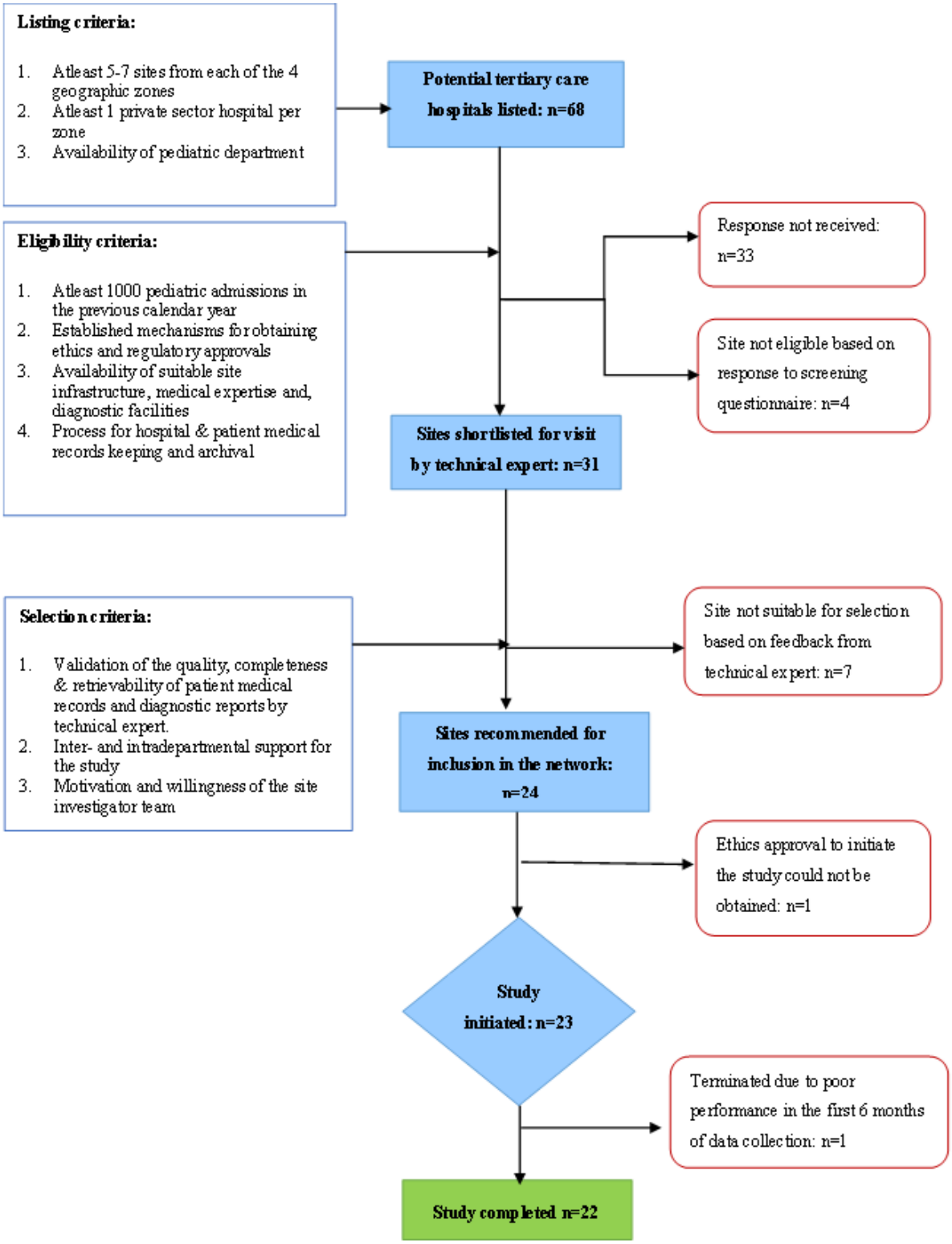

Protocol Development

The central team, TAG, and site investigators codeveloped the study protocol during a 3-day workshop held in New Delhi, India (May 2017). Participants provided feedback on the selection of study outcomes, the standardization of case definitions for assessing the level of diagnostic certainty, data sources, and collection procedures, which informed subsequent revisions to the study protocol. Drawing on clinical experience, site investigators developed dummy patient records to pilot-test the draft study tools. The workshop also helped clarify the anticipated technological and human resource requirements, as well as mechanisms for data quality assurance for the study.

Training and Study Initiation

We developed a standardized training agenda and supporting documents to promote a uniform understanding of the study protocol, data collection tools, use of the electronic data

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collection tool, and related procedures. In October 2017, 3 regional training workshops were conducted at network sites in the north (Lady Hardinge Medical College, New Delhi), east (Institute of Post-Graduate Medical Education and Research and Seth Sukhlal Karnani Memorial Hospital, Kolkata), and south (Government Medical College, Thiruvananthapuram) zones to facilitate hands-on training in data collection. Special role-play sessions helped clarify proper procedures for obtaining informed consent and conducting patient interviews. Each site also listed potential source documents and mapped the flow of data collection within their respective settings in preparation for study initiation.

Sites began data collection once training was complete and the necessary ethics and administrative approvals were in place; 17 of the 23 participating sites initiated data collection in November 2017, followed by 3 more sites in December. The final 3 sites began data collection in January, February, and May 2018, respectively.

Ethical Considerations

Independent ethics committees at INCLEN (2017/IIEC-052) and 23 of the 24 participating sites approved the master study protocol following the May 2017 workshop. Unanticipated delays in obtaining ethics approval from the twenty-fourth site prevented its participation. In accordance with state norms, additional administrative approvals were obtained from the relevant institutional, state, and national departments before initiating data collection.

The study was conducted in accordance with the principles of the Declaration of Helsinki and the National Ethical Guidelines for Biomedical and Health Research Involving Human Participants [21]. Parents or legally authorized representatives of all potential participants were informed about the voluntary nature of participation, and written informed consent was required for recruitment. The study information sheet and informed consent forms clarified that participation would not result in any direct benefit or harm, nor would it alter the routine medical care of patients. Personal identification and contact information were collected for enrolled participants and retained at the respective sites to enable follow-up of patient records across multiple hospital departments. Source documents validating immunization exposure history were also collected. To maintain confidentiality, robust security measures were implemented during data collection, analysis, and archiving. Paper case report forms (CRFs), source documents, and signed copies of study information sheets and informed consent forms were stored in secure locations at both the study sites and the central data center, with access restricted to core investigators. Electronic CRFs (e-CRFs) were stored in an encrypted format on a secure cloud server with backup and safety features. Personal identification information was removed from the database before analysis, and study participants were identified solely by study-generated unique identification numbers. In accordance with national guidelines [21], study data are securely archived for 5 years.

Study Procedures

Study Population

The study population included all children aged 1-24 months who were hospitalized for any reason and for more than 24 hours in the pediatrics and pediatric surgery departments at network sites. This population was screened for the outcome conditions and also served as the denominator for calculating rates. Most vaccines under the Universal Immunization Programme are administered during this period. The neonatal period was excluded, as only a few vaccines are administered during this time, and sampling and diagnostic challenges may arise due to limited access to neonatal intensive care units.

Screening of Study Population for Eligibility

The study population was screened based on the following criteria: (1) patients who met the criteria of at least 1 of the 3 screening checklists, which were based on admission diagnosis and presenting signs and symptoms (refer to the “Data Collection Tools and Procedures” section and Multimedia Appendix 2 for the checklist); (2) confirmation or suspicion of 1 or more study outcomes by the treating team; and (3) absence of any exclusion criteria.

The exclusion criteria were (1) diagnosis of a condition that could bias the participant’s ability to receive vaccines, such as immunodeficiency disorders; (2) undergoing therapies that precluded vaccination, for example, chemotherapy or immunotherapy; (3) diagnosis of a chronic systemic disease (eg, liver, kidney, blood, brain, or heart disease); (4) a known history of allergic reaction or anaphylaxis to a previous dose of vaccine or its components; and (5) prior recruitment in the study for the same condition (refer to Figure 3).

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Figure 3. Systematic overview of patient screening, recruitment, and case confirmation processes. CRF: case report form.

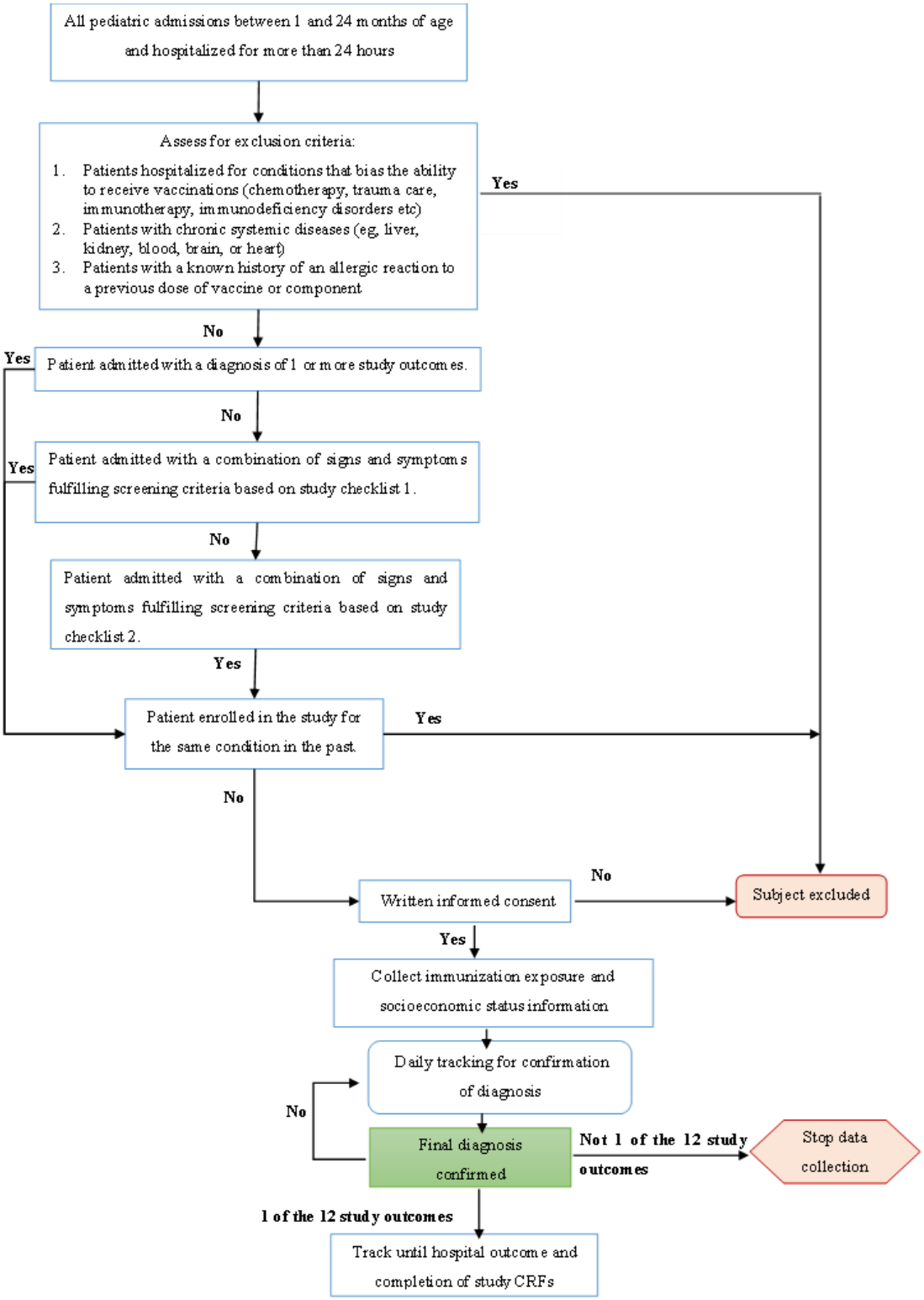

Selection of Study Outcomes

To broaden the scope of analytical designs for investigating vaccine-event associations, 2 categories of study outcomes were selected: 8 case conditions with published literature supporting their temporal association with 1 or more vaccines, and 4 control conditions with established infectious etiologies and no known link to vaccination [22]. These 12 conditions were highly likely to result in hospitalization, and consistent diagnostic criteria and case definitions could be applied. Table 1 lists the case and control outcomes selected for surveillance in the study.

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Table 1. List of adverse pediatric study outcomes (case and control conditions) selected for surveillance.

Case conditions: outcomes with prior evidence establishing a temporal association with 1 or multiple vaccinations	Control conditions: outcomes with established etiology and no known association with any vaccinations
Acute demyelinating encephalomyelitis	Dengue
Aseptic meningitis	Malaria
Anaphylaxis	Sepsis
Guillain-Barré syndrome	Urinary tract infection
Intussusception	N/A[a]
Kawasaki disease	N/A
Seizure	N/A
Thrombocytopenia	N/A

[a]N/A: not applicable.

Standardizing Case Definitions for Assessing the Level of Diagnostic Certainty

We used the Brighton Collaboration standardized case definitions [23] to assess the level of diagnostic certainty for acute demyelinating encephalomyelitis [24], aseptic meningitis [25], anaphylaxis [26], Guillain-Barré syndrome [27], intussusception [28], Kawasaki disease [29], seizure [30], and thrombocytopenia [31].

The methods developed by the Brighton Collaboration [32] were also adapted to establish accepted case definitions and to ascertain levels of diagnostic certainty for the control outcomes. Dedicated working groups, led by subject-matter experts—all members of the TAG—reviewed published and unpublished literature. The working groups then categorized levels of diagnostic certainty with decreasing specificity and increasing sensitivity. Multimedia Appendix 3 specifies the standardized case definitions developed for the control conditions.

Data Collection Tools and Procedures

Data were collected in 2 modes during the study period: paper CRFs from the start of the study to August 2019, and e-CRFs from September 2019 to site closure in March 2020. Initially, paper CRFs were used to ensure uniformity in study processes across all sites, especially in settings with limited digital infrastructure. Furthermore, at the time of study initiation, available electronic data collection applications did not accommodate the complex screening, recruitment, and case confirmation criteria used in this study. Paper CRFs were submitted monthly by sites and, after review and clarification, were digitized using the customized SOMAARTH-I system, which featured built-in double data entry and quality assurance mechanisms [33]. As the study progressed, e-CRFs were deployed to improve data completeness, timeliness, and accuracy, and to facilitate real-time monitoring. To support this, a customized SOMAARTH-III application [34] was developed, featuring built-in validity checks, automated skip patterns, and form activation to digitally replicate the study process. We pilot-tested both the paper and e-CRFs, along with the standardized case definitions for case and control conditions (described above), at 2 sites in New Delhi over a 1-week period. We trained all sites to use SOMAARTH-III during a 2-day workshop in August 2019. Following the training, sites completed a simulation exercise using dummy patient records before receiving clearance to begin electronic data collection.

Figure 3 provides a systematic overview of the participant screening, recruitment, and case confirmation processes in the study. Potential study participants were identified through a daily review of hospital registers and admission records to capture all children aged 1-24 months hospitalized within the previous 24 hours. Upon recruitment, information on socioeconomic status and immunization exposure was collected. The treating team and patient medical records were then consulted to assess the applicability of exclusion criteria. To minimize missed outcomes, 3 screening checklists with increasing sensitivity were developed: the first identified participants diagnosed with or suspected of having study outcomes in admission records, while the subsequent 2 screened for signs and symptoms associated with the study outcomes (refer to Multimedia Appendix 2).

Regardless of immunization exposure status, all participants meeting any of the 3 checklist criteria were eligible for recruitment, pending properly administered and signed informed consent from their primary caregivers.

We considered only documented sources of immunization status—such as mother-child protection cards and immunization registers—as acceptable, due to concerns about the validity of recall-based methods. We aimed to ascertain exposure status as comprehensively as possible, including active outreach to catchment area immunization centers and postdischarge follow-up of primary caregivers of recruited participants.

Concurrently, all recruited participants were tracked daily for diagnosis confirmation, and clinical information was completed once the treating team confirmed a study outcome as the final (primary or secondary) diagnosis. We followed up with recruited participants until the end of their admission—whether death, discharge, or leaving against medical advice—to complete any pending study CRFs.

We followed up with patients after discharge to (1) obtain immunization exposure source documents if these could not be collected during hospitalization; and (2) ascertain the monophasic nature of illness for acute demyelinating

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encephalomyelitis [24] and Guillain-Barré syndrome [27], as required by their respective standardized case definitions.

Data Monitoring and Quality Assurance

We developed a data management plan guided by study policies covering data collection, monitoring, quality assurance, sharing, archival, curation, and dissemination.

The central team remotely reviewed incoming data using structured templates to assess completeness, quality, and adherence to the study protocol and procedures. Any discrepancies were addressed through monthly teleconferences with site teams.

Regular monitoring helped identify sites submitting erroneous, incomplete, or delayed data, enabling targeted support. In the first year, 5 sites were selected for quality assurance visits; in the second year, all sites were visited. During these visits, a team comprising members of the central team and TAG completed a structured questionnaire to assess data quality, evaluate the risk of missing study outcomes, identify challenges and facilitators related to project implementation, and provide recommendations on whether data collection should continue at each site based on their observations. In its June 2018 meeting, the study TAG reviewed findings from the visits and recommended discontinuing 1 site due to significant operational challenges and concerns about the timeliness and completeness of its study data.

Sample Size Determination

No sample size calculations were required to address the first 3 objectives; all age-eligible participants diagnosed with 1 or more study outcomes were eligible, pending fulfillment of the study inclusion and exclusion criteria as described in Figure 3. For objective 4, that is, hypothesis testing, we estimated sample size requirements for an unmatched case-control study as an alternative to case-only analytical designs, which are typically more efficient and require smaller sample sizes [35]. Assuming an exposure rate of 20% among controls, a minimum odds ratio of 1.3, 20% incomplete data, and a case-to-control ratio between 1:2 and 1:4, we calculated a required sample size of 3700-5040 participants to test hypothesized vaccine-event associations with 95% confidence and 80% power [36] (see Table 2). Based on pediatric admission data submitted during site screening and the expected prevalence of case and control conditions, we estimated that this sample size (for a 1:2 case-to-control ratio) would be reached in approximately 2.5 years.

Table 2. Sample size required for an unmatched case-control study assuming 20% exposure in controls, minimum odds ratio of 1.3, and adding 20% incomplete or missing data for a range of case-to-control ratios at 95% confidence and 80% power.

Categories	Case-to-control ratio			
	1:1, n	1:2, n	1:3, n	1:4, n
Sample size for cases	1339	1016	899	840
Sample size for controls	1339	2032	2695	3358
Total sample size	2798	3048	3594	4198
Projected sample size including incomplete/missing data (20%)	3360	3700	4320	5040

Statistical Analysis

For objectives 1, 2, and 3, we analyzed data cumulatively by health outcome using Stata version 15.1 (StataCorp) [37]. Results were stratified by geographic zone. We calculated all 95% CIs using the Clopper-Pearson method [38]. For objective 1, we estimated outcome rates per 100,000 hospitalized children aged 1-24 months per year, with 95% CIs, for each outcome. For objective 2o, we also stratified the cumulative and zone-wise outcome rates by climatological seasons in India, as defined by the Indian Meteorological Department [39]. We calculated the sex and age distribution (with 95% CIs) and the median age (IQR) for all study outcomes. Additionally, we calculated wealth index scores for each participant using a previously standardized method [40]. Based on the calculated wealth score, we classified each case into wealth quintiles using cut-offs from the National Family Health Survey-4 dataset [41]. We calculated the proportion (with 95% CIs) of confirmed outcomes with documented vaccine exposure information. For objective 3, we calculated the proportion of outcomes meeting standardized case definitions stratified by level of diagnostic certainty, as well as reasons for nonclassification to the lowest diagnostic certainty level.

For objective 4, we developed a decision framework to select appropriate primary and secondary analytic designs for each vaccine-event pair by considering relevant exposures (vaccine types), the number of participants recruited, the type of onset (well-defined or insidious), and the expected duration of the risk interval (long or short) for each case outcome based on prior published literature. For case-control analyses, we excluded combinations that tended to co-occur—for example, thrombocytopenia with dengue. The date of hospital admission was used as a proxy for the event date. Sensitivity analyses were conducted based on the date of symptom onset (as recorded in patient medical records), vaccine dose, level of diagnostic certainty for study outcomes, and varying risk intervals.

Results

Site Characteristics

The final network included 15 public tertiary care and 7 private hospitals across 17 states and 1 union territory in India. Of the 7 private facilities, 4 were located in the south zone. Two study sites either could not be activated or were closed after a limited recruitment period (see Figure 1). Wide variations were observed in pediatric and age-eligible admissions across sites: the largest site (Government Medical College, Trivandrum) admitted

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15,527 children, while the smallest site (Assam Medical College, Dibrugarh) admitted 651 children aged 1-24 months during the study period. Data collection at some sites was disrupted due to local operational challenges. Table 3 describes the characteristics of participating sites, including their geographic distribution, pediatric patient load, patient record–keeping mechanisms, and the number of months of data collected.

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Table 3. Study site characteristics.

Zone	State/union territories	Site name	Type of facility	Format in which patient case records are maintained	Number of pediatric admissions of children between 1 and 24 months of age, n	Number of months of data collection, n
North	Punjab	Christian Medical College, Ludhiana	Private	Paper	1304	29
North	New Delhi	Lady Hardinge Medical College	Public	Paper	8709	29
North	New Delhi	Maulana Azad Medical College[a,b]	Public	Paper	5849	26
North	Haryana	Pandit Bhagwat Dayal Sharma Post Graduate Institute of Medical Sciences, Rohtak	Public	Paper	8861	29
North	Jammu & Kashmir	Sher-e-Kashmir Institute of Medical Sciences[c]	Public	Paper	1593	27
East	Tripura	Agartala Government Medical College	Public	Paper	3271	29
East	Assam	AMC D[d]	Public	Paper	4069	26
East	Bihar	Indira Gandhi Institute of Medical Sciences, Patna	Public	Paper	651	29
East	Odisha	Institute of Medical Sciences & Sum Hospital	Private	Paper	2316	29
East	West Bengal	Post-Graduate Medical Education and Research and Seth Sukhlal Karnani Memorial Hospital, Kolkata[e]	Public	Paper	2496	22
East	Meghalaya	North Eastern Indira Gandhi Regional Institute of Health and Medical Sciences[f]	Public	Paper	601	27
East	Jharkhand	Rajendra Institute of Medical Sciences	Public	Paper	3167	29
West	Madhya Pradesh	Choithram Hospitals & Research Center[a]	Private	Electronic	995	28
West	Maharashtra	Government Medical College Nagpur	Public	Paper	3122	29
West	Maharashtra	Grant Government Medical College & Sir J. J. Group of Hospitals, Mumbai[a,g]	Public	Paper	2230	26
West	Gujarat	Shri M. P. Shah Medical College[a]	Public	Paper	8652	29
South	Andhra Pradesh	Assam Medical College, Dibrugarh	Public	Paper	4759	29
South	Kerala	Government Medical College, Thiruvananthapuram	Public	Paper	15527	29
South	Karnataka	Kasturba Medical College	Private	Paper	4736	29
South	Tamil Nadu	Mehta's Hospital	Private	Paper	2821	29
South	Tamil Nadu	PSG Institute of Medical Sciences and Research, Coimbatore	Private	Electronic	2183	29
South	Telangana	Rainbow Children's Hospital	Private	Electronic	2235	29

[a]These 2 sites initiated data collection in December 2017.

[b]Data missing for June and August 2019 due to loss during the transition to electronic data collection.

[c]Data collection was interrupted in August and September 2019, due to government-mandated restrictions, which prevented the research staff from accessing the site.

[d]This site initiated data collection in February 2018.

[e]This site initiated data collection in April 2018. Further, data collection was interrupted in December 2018 due to staff turnover.

[f]This site initiated data collection in January 2018.

[g]No data were collected at this site for November and December 2018 due to staff turnover.

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Study Population and Outcomes

Over the 29-month study period from November 1, 2017, to March 20, 2020, the network admitted 90,147 children aged 1-24 months. Of these age-eligible admissions, 8803 (9.77%) met screening criteria for recruitment, and a final diagnosis was confirmed in 7616 participants. These 7616 participants collectively contributed 8362 confirmed outcomes. Of the 7616 participants, 6959 (91.37%) contributed to only 1 outcome, while the remaining 657 (8.63%) contributed to multiple outcomes. Figure 4 presents the total number of participants and outcomes screened, suspected, recruited, and confirmed. The screening algorithm, based on admission diagnoses and presenting signs and symptoms, identified study outcomes in 7616 of the 8803 suspected participants (86.52%). Immunization documents were available for 6875 of the 8362 participants (82.21%) with confirmed outcomes.

Figure 4. Subjects screened, suspected, recruited, and confirmed cumulatively by Multicenter Active AEFI Surveillance System (MAASS) network sites.

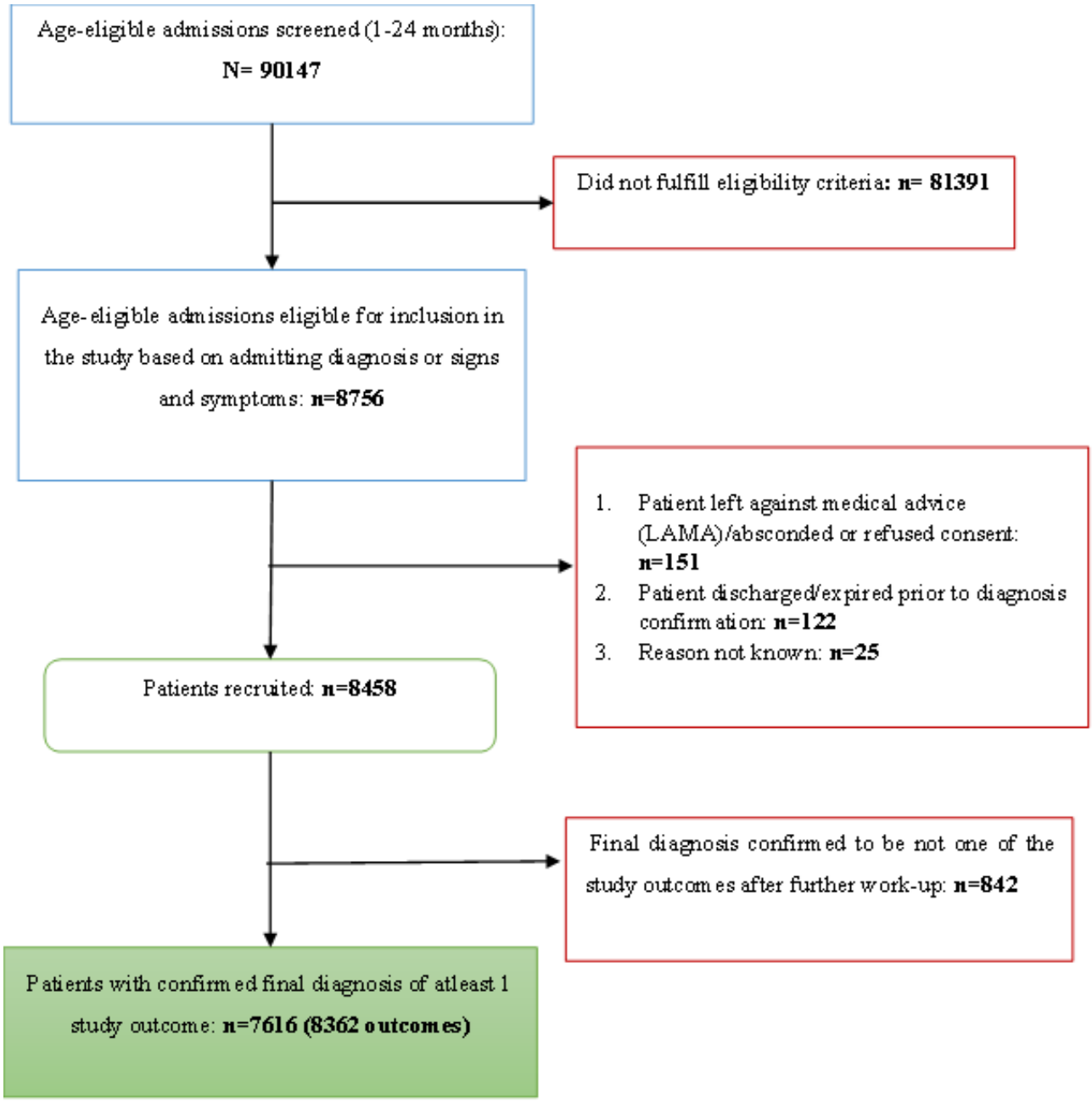

Data Characteristics

Data timeliness and completeness varied significantly across sites, influenced by the mode, complexity, and type of data collected. The timeliness of data submission was especially affected during the paper-based data collection phase, with delays of 2-8 months observed from the site with the heaviest patient load. On the one hand, paper CRFs were more intuitive and beneficial for sites with initially disrupted internet access; on the other hand, they posed significant challenges in study monitoring, as well as in data storage, transcription, and archival. The transition from paper to electronic data collection optimized many aspects, including overall data quality, timeliness (enabling real-time entry), completeness (due to mandatory

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response fields in the software), and the rigor of data monitoring, supported by a weekly feedback system. However, the switch also introduced an unforeseen disadvantage: it eliminated our ability to triangulate data across multiple source documents for verification—for example, comparing age recorded in 3 CRFs (screening form, immunization card, and recruitment CRF). Such discrepancies created challenges in assigning a single definitive value in the final dataset. Age mismatches were observed in over 10% (at least 692 age mismatches out of 6830 confirmed outcomes in the paper dataset) of cases when comparing the 3 forms within the paper dataset. Discrepancies in these mismatches often alerted us to other potential data-entry errors, such as inaccuracies in immunization exposure dates. Similar challenges with source-data mismatches have been reported in previous multicenter studies as a significant barrier to ensuring data quality [19,42]. The use of auto-fill features in the electronic dataset further limited our ability to detect and monitor such source-based data discrepancies. Because of varying capacities in digital data collection, some sites required additional technical support and experienced delays during the initial week of the e-CRF module rollout. Although the paper-based phase lasted nearly 3 times longer than the electronic phase, it was reassuring that the overall pattern of outcome identification remained consistent. We confirmed 6830 outcomes from 70,288 (9.72%) age-eligible participants screened during the paper phase and 1532 outcomes from 19,859 (7.71%) participants during the electronic phase.

Basic demographic data (age and sex) and hospitalization details (date of admission and outcome) were available for all participants, while socioeconomic status information was missing for only 14 of the 7616 participants. By contrast, the completeness of clinical description data varied, depending on the number and complexity of the clinical and diagnostic confirmation criteria. For example, fewer data were missing when assessing simple clinical symptoms such as vomiting in intussusception cases—this symptom could not be evaluated in only 6 of 654 intussusception cases, whereas more responses were missing for criteria requiring complex and invasive diagnostic procedures, such as lumbar punctures to assess pleocytosis in cerebrospinal fluid, which is necessary to confirm aseptic meningitis according to the Brighton Collaboration case definition [25]; this criterion could not be evaluated in 131 of 383 aseptic meningitis cases. A more detailed evaluation of the quality of the reported clinical information will be presented in subsequent manuscripts.

Almost all of the 6875 confirmed outcomes with documented immunization exposure included vaccination dates and the administered antigen(s) (single or combination), although vaccine brand names were not recorded on the immunization cards obtained from public sector hospitals.

Overall Study Timelines and Milestones

Figure 5 summarizes the MAASS study timelines and milestones. The study progressed through 3 distinct phases: (1) network establishment phase (January to November 2017), which included site selection, protocol and study tool finalization, as well as ethics and administrative approvals; (2) active data collection phase (November 2017 to March 2020), which involved the development and deployment of electronic data collection systems; and (3) analysis and result dissemination phase (March 2020 to March 2024), which included transcription of paper CRF data, database finalization, analysis for all 4 objectives, and preparation of study reports and manuscripts.

Figure 5. Multicenter Active AEFI Surveillance System (MAASS) study timelines and key milestones.

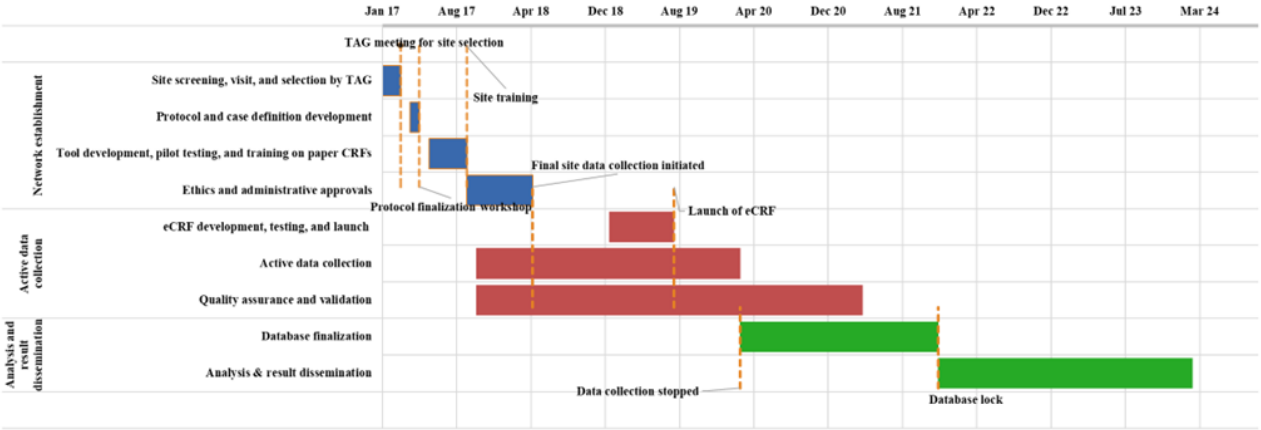

Discussion

Expected Findings

This manuscript describes the operational framework for establishing India's first geographically and socioculturally representative active surveillance network to monitor pediatric health outcomes and vaccine exposure.

The framework's feasibility was demonstrated through successful consensus on governance and procedures, the establishment of a 22-hospital sentinel network, standardized protocols and data collection methods, deployment of electronic data systems with a unified database, rigorous quality control measures, and the capacity to link health outcomes to immunization records in a large study population for robust safety analyses. While the MAASS network demonstrated feasibility, the long-term sustainability of such networks depends on addressing additional challenges, including securing sustained funding for staff training and retention, site maintenance, technical support, and ensuring ongoing commitment from investigators and institutions. Variability in data quality across

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sites necessitated targeted site support, standardized training programs, and periodic quality audits of participating centers.

The initial results from this initiative highlight the potential of hospital-based sentinel surveillance for actively monitoring pediatric outcomes and immunization exposure in resource-limited settings, including LMICs. The network generated a substantial database of 8362 outcomes and documented vaccine exposure for 6875 (82.22%) cases. The size and representativeness of the sentinel hospital network and the population, combined with the established operational framework, provide a strong foundation for future developments and offer a valuable resource for conducting subsequent studies without the need to start from scratch. The variability observed in the database—across data collection modes, complexity, and source documentation—offered valuable insights for enhancing data quality in vaccine pharmacovigilance. The MAASS network has the potential to transform the national surveillance program by complementing existing passive surveillance systems and strengthening the evidence base for the safety of both traditional and new vaccines, thereby bolstering public confidence.

Several operational challenges were encountered in establishing the MAASS study network, offering valuable lessons for future development and for other resource-limited settings aiming to build similar capacity. Complex ethics and administrative requirements delayed the start of data collection by an average of 3.5 months, with the final site taking up to 7 months to obtain approval. National ethics institutions need to develop guidelines specifically for multicentric network studies to streamline and accelerate approval processes, incorporating mechanisms that ensure consistency in core study protocols [15]. This is particularly important to facilitate international scientific collaboration in today's increasingly global public health landscape [5].

Paper-based data collection was resource-intensive and delayed error detection, with quality assurance hindered by a 1-month lag between data collection and review. The introduction of e-CRFs significantly reduced this time lag, minimized errors from repeated data entry, improved overall data quality, and helped ensure closer adherence to the study protocol. Previous experiences comparing paper-based and electronic data collection have demonstrated similar challenges and their resolution [19]. Digital tools improve efficiency by embedding accountability and validation checks and help reduce long-term costs. In our study, limited access to reliable internet connectivity, especially at remote sites, posed a significant challenge to the timely submission of electronic data. This challenge was addressed by incorporating offline data entry capabilities within the software. Moving forward, allocating additional resources to ensure adequate internet access will be crucial for establishing rapid and responsive pharmacovigilance networks, even in resource-limited settings. Furthermore, providing dedicated training to study staff on digital data collection procedures at the outset of the study—including hands-on simulation exercises—can help mitigate challenges encountered during the transition from paper-based CRFs to e-CRFs. Significant operational challenges resulted in temporary disruptions to data collection at 4 network sites (Table 3). At 2 of these sites, data collection resumed only after new or additional research staff were allocated and trained. At another site, operations could recommence only after access to the facility was restored.

Despite these challenges, the MAASS network demonstrated a scalable model that can be adapted to other resource-constrained settings, particularly in light of the rapidly evolving immunization landscape. Passive surveillance alone is often insufficient to provide the comprehensive data needed to evaluate newly introduced vaccines targeting broader age groups and demographics, or to detect long-term and rare adverse events. Integrating both public and private sector health care facilities enables a more comprehensive approach to data collection. Simultaneously, the use of harmonized Brighton Collaboration case definitions and confirmation criteria offers a reliable framework for generating comparable vaccine safety data across diverse geographic settings. The use of a tiered approach to patient screening and outcome confirmation enhances the network's ability to identify complex health outcomes across sites with varying health infrastructure and clinical practices. Future iterations built on the MAASS network infrastructure could leverage advanced analytic approaches—such as machine learning and artificial intelligence—to automate signal detection across disparate data sources and reduce delays in case ascertainment through natural language processing of clinical notes [43].

Limitations

As with most hospital-based studies, ours lacked well-defined catchment populations, limiting the ability to generate true population-based estimates [14]. To address this limitation, we used all hospital admissions of children aged 1-24 months during the study period as the denominator, assuming that referral patterns remained relatively consistent for each participating tertiary care facility. Although the selection of hospitals in our study aimed to ensure geographic representativeness, the identification of outcomes and the estimation of hospital outcome rates were influenced by factors such as the type of facility, the availability of infrastructure and diagnostic resources, and the health care–seeking behaviors of the populations served [44]. Expanding the sentinel network in the future may help reduce regional disparities. Depending on a country's size and other characteristics, both regional and national network–based background rates—as well as deviations from baseline—can be effectively monitored. Linking this information with vaccine exposure data can enhance the quality of risk assessment studies. As new vaccines are introduced targeting broader age groups and geographic areas, establishing community-based background rates will be essential for verifying potential vaccine safety signals.

The study population was restricted to children aged 1-24 months, thereby excluding data on neonatal immunizations and immunizations administered later in childhood. Future studies may consider adjusting or expanding the age range to capture a broader spectrum of immunization-related outcomes. Additionally, the inclusion criterion of hospital admissions exceeding 24 hours excluded cases managed entirely in emergency care settings. For instance, instances of anaphylaxis

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treated and discharged directly from the emergency department were not captured in this study.

Over 90,000 children were hospitalized across participating study sites during the study period. The screening algorithm identified 8803 of the 90,147 (9.77%) children as suspected cases of specific outcome conditions, of which 7616 (86.52%) were subsequently confirmed. However, it remains unknown how many true outcome cases may have been missed among the nearly 80,000 admissions not flagged by the screening tool. This limitation could lead to an underestimation of the true background rates generated by the study.

Variability in the completeness of clinical information—driven by the complexity and type of data collected—and in vaccine exposure data may impact 2 critical aspects of vaccine safety monitoring: (1) the comparability of the level of diagnostic certainty across study outcomes, and (2) the ability to assess associations between adverse outcomes and specific vaccine types or brands. Future safety studies could benefit from more rigorous efforts to collect detailed vaccine exposure information—including brand, batch number, and timing of vaccination—potentially by integrating with administrative immunization data from existing national health management information systems.

Finally, our study highlighted the need to develop additional case definitions and data collection guidelines for a reference set of clinical outcomes (controls) with specific etiologies known not to be associated with vaccine exposure. The standardized case definitions developed for the controls should undergo further field testing before wider application. Although beyond the scope of this study, the sensitivity, specificity, positive predictive value, and negative predictive value of all standardized case definitions related to vaccine safety monitoring need rigorous evaluation and contextual adaptation to ensure precise and reliable outcome identification.

Comparison With Prior Work

The need to establish global frameworks for vaccine safety monitoring is well recognized [11,12]. While adequate methods and methodological frameworks have been developed in some regions, international efforts toward harmonizing vaccine safety assessment are ongoing [45,46]. Efforts in LMICs remain limited, highlighting the need for innovative approaches. Our study builds upon methodological insights from high-income settings as well as selected pilot experiences in LMICs. Previous hospital-based active sentinel surveillance studies for vaccine safety monitoring in LMICs have been limited by the scope of outcomes and vaccine exposures assessed. The Global Vaccine Safety Multi-Country Collaboration study assessed the risk of immune thrombocytopenia and aseptic meningitis following measles-mumps–containing vaccines across 26 sites in 11 LMICs and 5 high-income countries [47]. In India, 2 separate tertiary care hospital–based network studies have evaluated the risk of intussusception following the introduction of the rotavirus vaccine over the past decade [20,48]. All 3 studies used self-controlled case series as the primary analytical design to estimate the relative incidence of selected outcomes following vaccination, using predefined risk intervals [47-49]. In Singapore, a single hospital-based active surveillance study identified a fivefold increase in postvaccination Bacillus Calmette-Guérin vaccine–associated lymphadenitis rates, which prompted further investigation of this safety signal [50]. All studies reported similar operational challenges, notably significant delays due to ethics and regulatory approvals from multiple authorities [19,50,51]. Future research will benefit from streamlining ethics and regulatory processes at global, regional, and national levels to facilitate multicenter studies. Collectively, these studies demonstrate the applicability of hospital-based active sentinel surveillance to address a broad spectrum of postlicensure vaccine pharmacovigilance challenges. These include establishing baseline outcome rates, characterizing the clinical and sociodemographic profiles of rare adverse events, detecting previously unrecognized safety signals, and investigating associations between specific vaccines and adverse outcomes. While the MAASS network offers a scalable model for active vaccine safety surveillance in resource-constrained settings, its long-term sustainability depends on implementing digital solutions tailored to local infrastructure, providing targeted site support, and increasing advocacy for domestic funding of such networks. With the growing ability to leverage additional data sources, such as social media and solicited reports, active vaccine safety surveillance systems can both detect previously unreported safety signals (eg, via cohort event monitoring) and investigate or verify reported signals using hypothesis-testing study designs [52].

Conclusions

The MAASS study, unprecedented in scale, provides a scalable blueprint for active vaccine safety surveillance in resource-limited settings. The adoption of globally standardized case definitions, along with the development of definitions for reference control outcomes, has strengthened the capacity of participating sites and encouraged improved documentation of immunization exposure and diagnostic evaluations in routine patient care. Beyond India, the MAASS framework tackles key questions about the feasibility of active surveillance networks in resource-constrained settings and offers a template to advance global vaccine safety equity. Future networks should focus on long-term sustainability; harness rapidly evolving digital health infrastructure; and broaden the range of conditions, vaccines, and populations assessed to generate robust vaccine safety data from LMICs. The study addresses critical gaps in understanding rare and complex pediatric health outcomes and bolsters ongoing efforts to enhance vaccine pharmacovigilance capacity in India.

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Data Availability

All data are available from the corresponding author of this study. Given the sensitive nature of patient-linked information collected in this study, fully anonymized datasets are available from the corresponding author upon reasonable request, in alignment with India's national ethical guidelines for biomedical research [21].

Authors' Contributions

AS contributed to conceptualization, investigation, methodology, project administration, visualization, validation, formal analysis, data interpretation, writing of the original draft, and writing—review and editing. MKD was involved in conceptualization, investigation, methodology, funding acquisition, formal analysis, and writing—review and editing. APM contributed to data curation, formal analysis, and writing—review and editing. RP was responsible for formal analysis, data curation, validation, and writing—review and editing. NKK contributed to software, data curation, and writing—review and editing. CB, JB, SA, and DP participated in conceptualization, methodology, data interpretation, and writing—review and editing. NKA contributed to conceptualization, methodology, resources, data interpretation, supervision, and writing—review and editing. The MAASS study group contributed to conceptualization, investigation, data curation, data interpretation, validation, and writing—review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Site screening and selection questionnaire.
[PDF File (Adobe PDF File), 436 KB - resprot_v14i1e64050_app1.pdf]

Multimedia Appendix 2
Outcome screening checklists.
[PDF File (Adobe PDF File), 104 KB - resprot_v14i1e64050_app2.pdf]

Multimedia Appendix 3
Standardized case definitions for control conditions.

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[PDF File (Adobe PDF File), 335 KB - resprot_v14i1e64050_app3.pdf]

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Abbreviations

AEFI: adverse events following immunization
CRF: case report form
e-CRF: electronic case report form
INCLEN: International Clinical Epidemiology Network
LMIC: low- and middle-income country
MAASS: Multicenter Active AEFI Surveillance System
TAG: technical advisory group
WHO: World Health Organization

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Protocol

Post–Critical Illness Dysphagia in the Intensive Care Unit (the Dysphagia-ICU Study): Protocol for a Prospective Cohort Study

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Abstract

Background: Post–critical illness dysphagia occurs in about 10% to 62% of patients in the intensive care unit (ICU). Studies focusing on risk factors for dysphagia following endotracheal intubation are scarce and provide conflicting results. More research is required to determine the true prevalence of dysphagia, possible mechanisms, and risk factors.

Objective: The aims of the study are to determine (1) risk factors associated with post–critical illness dysphagia, (2) the prevalence of post–critical illness dysphagia, (3) outcomes of patients with post–critical illness dysphagia, and (4) the diagnostic accuracy of the water sip test compared to fiber-optic endoscopic evaluation of swallowing (FEES).

Methods: We plan to undertake a single-center prospective cohort study of patients with post–critical illness dysphagia admitted to the ICU at Prince Sultan Military Medical City, Saudi Arabia. Our inclusion criteria are as follows: (1) being an adult (age 18 years and older), (2) having undergone invasive mechanical ventilation for >24 hours, (3) having been extubated for >24 hours, (4) being able to participate in a FEES, and (5) being hemodynamically stable. Each day, the research coordinator will screen all patients in the ICU for enrollment in the study. The research coordinator will collect daily data on the use of advanced life support, the need for mechanical ventilation, and outcomes (mortality, duration of mechanical ventilation, ICU length of stay, and hospital length of stay). Enrolled patients will undergo a water sip test in the ICU and FEES performed by a certified speech-language pathologist. Patients will then be followed during a hospital stay truncated for analysis at 30 days as two cohorts: (1) patients that have dysphagia, that is, abnormal FEES results; and (2) patients who have normal FEES results. Logistic regression will identify dysphagia risk factors (eg, age, Acute Physiology and Chronic Health Evaluation II score, and ventilation duration), while sensitivity and specificity tests will be used to compare the results of the water sip test to the FEES. Survival analysis will be used to evaluate 30-day outcomes.

Results: The study anticipates enrolling 200 patients over 18 months. Key outcomes include dysphagia prevalence and risk factors. Final results will be analyzed and reported upon completion of the 30-day follow-up for all participants. As of July 13, 2025, a total of 45 patients had been enrolled, with an average recruitment rate of 7.5 patients per month.

Conclusions: The study findings will promote early intervention for patients with post–critical illness dysphagia, improve multidisciplinary care, and inform policymakers for better resource allocation. This study lays the groundwork for future research and clinical guidelines tailored to Saudi Arabia's health care context.

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KEYWORDS

Dysphagia; intensive care; post–critical illness dysphagia; protocol; cohort study

Introduction

About 20 million patients are admitted to intensive care units (ICUs) globally each year. Those that survive frequently have post–critical illness complications that impair their quality of life [1]. Post–critical illness dysphagia is a well-recognized complication in the ICU [2]; however, it is an area that is under-studied [3]. Dysphagia refers to an impairment of the process of deglutition affecting the oral, pharyngeal, and/or esophageal phases of swallowing; it has been reported to occur in 10% to 62% of patients who undergo invasive mechanical ventilation in the ICU [2,4]. Dysphagia can persist for more than 6 months after critical illness [5].

The cause of post–critical illness dysphagia is unclear, but there are several hypotheses, such as motor and sensory impairment of the tongue [6]; laryngeal injury secondary to endotracheal intubation [7,8]; neuromuscular impairment associated with underlying comorbidities, neuromuscular blockade use, or critical illness neuropathy [5]; and cognitive impairment secondary to critical illness [9]. Post–critical illness dysphagia is associated with delayed oral intake, malnutrition, aspiration, prolonged hospitalization, and death [10,11].

However, several studies have reported that screening occurs in <50% of patients [12,13]. In clinical practice, the detection and management of post–critical illness dysphagia requires a multidisciplinary collaboration between physicians, nurses, speech language pathologists (SLPs), and physiotherapists. Unfortunately, there are no published high-quality studies to describe post–critical illness dysphagia in Saudi Arabia. Donohue et al [14] conducted a systematic review of 51 studies on oropharyngeal dysphagia in critically ill adults during acute and postacute recovery. They found a wide prevalence range—from 15% to 100%. Persistent dysphagia affected up to 74% at discharge and up to 22% at 10 to 17 months. Most studies had serious limitations: high risk of bias, inconsistent assessment tools, and varied outcomes. These flaws weakened the study's conclusions. The authors called for prospective, longitudinal studies using standardized assessments to better define prevalence and long-term impact. Herein, we present a multidisciplinary research project to determine the prevalence and consequences of post–critical illness dysphagia in patients in Saudi Arabia.

The primary objective of this study is to determine the predictors associated with patient-important outcomes. The secondary objective is to determine the prevalence of post–critical illness dysphagia in the ICU of Prince Sultan Military Medical City, a tertiary care center in Saudi Arabia.

Methods

Study Design

This study will be a single-center prospective cohort study carried out in a tertiary care ICU (Prince Sultan Military Medical City) in Saudi Arabia. Recruitment will occur over 18 months, with follow-up truncated for analysis at 30 days after enrollment. Figure 1 illustrates the design of the study.

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Figure 1. Summary of the Dysphagia-ICU Study.

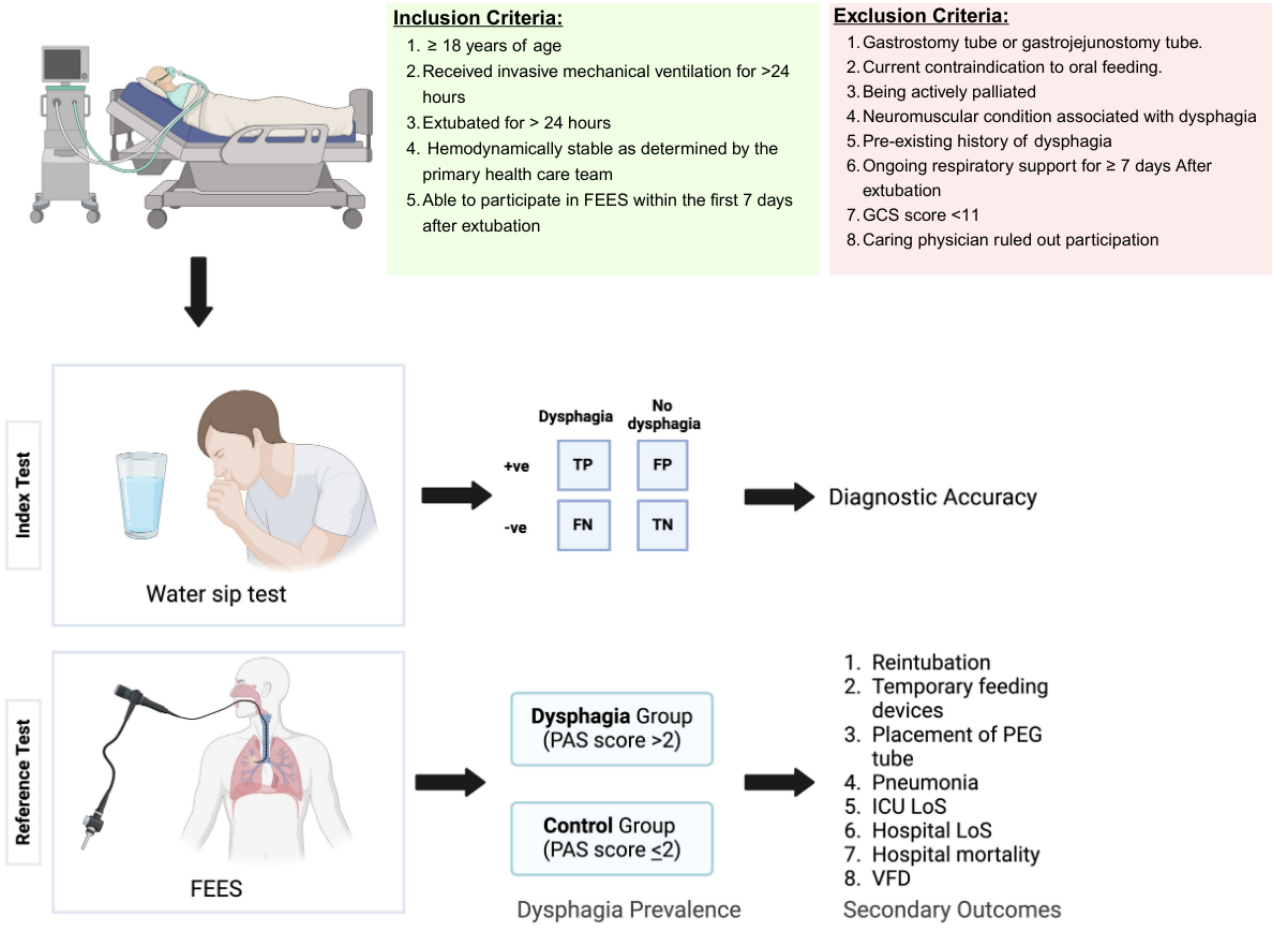

Population

Eligible patients must meet the criteria shown in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Aged ≥18 years
- Received invasive mechanically ventilated for >24 hours
- Have been extubated for >24 hours
- Hemodynamically stable as determined by the primary health care team (ie, not requiring active resuscitation or vasoactive agents)
- Able to participate in fiber-optic endoscopic evaluation of swallowing within the first 7 days after extubation.

Exclusion criteria

- Gastrostomy tube or a gastrojejunostomy tube
- Current contraindication to oral feeding (eg, recent gastrointestinal surgeries as indicated by the surgeon)
- Being actively palliated
- Neuromuscular condition associated with dysphagia (eg, amyotrophic lateral sclerosis, myasthenia gravis)
- Preexisting history of dysphagia
- Ongoing respiratory support (defined as requiring ≥50% oxygen, bilevel positive airway pressure, or high-flow nasal cannula) for 7 days or more after extubation
- Glasgow Coma Scale score <11
- Caring physician ruled out participation

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Feasibility Assessment

We will assess feasibility outcomes after the first 50 patients are enrolled in the study. A successful consent rate will be defined as 70% of substitute decision makers (SDMs) or patients approached to consent choosing to participate in this study. In addition, a successful recruitment rate will be defined as achieving enrollment of 50 patients at a recruitment rate of 2 patients per screening week. Recruitment and consent rate will be reviewed weekly, and the screening records will be reviewed monthly with cases of missed eligible patients reviewed. If applicable, barriers to enrollment will be addressed to maximize recruitment. The recruitment metric will be measured and interpreted once 50 patients have been enrolled.

Dysphagia Assessment

Enrolled patients will undergo a water sip test in the ICU, performed by the study SLP or the bedside nurse. First, the study SLP or bedside nurse will ask the patient to drink 5 ml of water (approximately 1 teaspoon) while sitting upright or at >30°. If the patient tolerates this small volume, the patient will then be asked to drink 90 ml of water from a cup, straw, or syringe. The study SLP or bedside nurse will observe the patient for 1 minute after drinking the water, looking for indirect signs of aspiration, such as coughing, grunting, or change in voice quality. The test is positive when these signs appear or when the patient cannot drink the full volume of water. Other volumes of water can also be used (2 × 5 ml, 2 × 10 ml, 2 × 20 ml, or 90 ml). The patient will be asked to produce the sustained vowel sound /a/ before and after swallowing the water to observe any voice change after swallowing. In addition, a certified study SLP will perform a FEES to assess swallowing. Although video fluoroscopy swallowing studies are another valid diagnostic tool [15,16], we elected to perform a FEES to minimize the risks associated with patient transfer. Previous studies have identified silent aspiration rates ranging upward from 25%, therefore, direct visualization using FEES is important. While the patient is in a sitting or upright position, the study SLP will use a disposable flexible fiber-optic rhinoscope directly passed through the nasal cavity using lubricated nonanesthetic gel down to the level of the soft palate or below. During FEES, the patient will be asked to swallow substances with a variety of consistencies (eg, thin fluids, thick fluids, and purees) colored with a food dye (blue or green) to help in visualization of aspiration and penetration in varying volumes (3 ml, 5 ml, and up to 10 ml). Although FEES is considered a safe procedure, study participants and/or their SDMs will be informed about potential complications during the consent process, which include discomfort, epistaxis (0.3% to 1.1%), swallowing inhalation, vasovagal episodes (6 in 1000), laryngospasm (3 in 1000) and mucosal laceration (a very rare complication). In this study, FEES serves as the reference standard for diagnosing dysphagia.

Interpretation of the FEES

The study SLP will complete the Penetration Aspiration Scale (PAS) after completing the FEES for every patient and classify safety status for swallowing as safe (scores 1 or 2) or unsafe (scores above 2; Table 1) [17] The results will be collectively reported as positive (oropharyngeal dysphagia present, ie, an abnormal result) or negative (ie, a normal result). A PAS score >2 will be considered abnormal and indicative of oropharyngeal dysphagia. This cutoff is based on previously validated thresholds for aspiration risk.

Table 1. Penetration Aspiration Scale (PAS) score interpretation.

PAS score	Description	Safety status
1	Material does not enter the airway	Safe
2	Material enters the airway, remains above the VCs[a], ejected from the airway	Safe
3	Material enters the airway, remains above the VCs, not ejected from the airway	Unsafe
4	Material enters the airway, contacts the VCs, ejected from the airway	Unsafe
5	Material enters the airway, contacts the VCs, not ejected from the airway	Unsafe
6	Material enters the airway, passes below the VCs, ejected from the trachea	Unsafe
7	Material enters the airway, passes below the VCs, not ejected despite effort	Unsafe
8	Material enters the airway, passes below the VCs, no effort made to eject	Unsafe

[a]VC: vocal cord.

Ethical Considerations

This study has been reviewed and approved by the Central Research Ethics Committee of the Ministry of Defense Health Services, Riyadh, Saudi Arabia (H-01-R-096). The study protocol adheres to the ethical principles outlined in the Declaration of Helsinki and complies with local regulations governing research involving human participants.

Informed consent will be obtained from all participants or their legally authorized SDMs prior to enrollment. All collected data will be anonymized and stored securely in accordance with institutional policies to protect participant confidentiality.

The study research coordinator (RC) will screen all patients in the ICU during weekdays to avoid incurring additional weekend on-call costs. Due to the nature of their illnesses, associated life-sustaining treatments, use of sedatives and analgesic medications, and frequency of delirium, eligible patients may not be capable of participating directly in the informed consent process [18-20]. The study RC will approach patients who meet the eligibility criteria and can provide consent for written

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consent after extubation. However, as most patients will be incapable of consenting at the time of enrollment, the RC will approach the SDM to provide a priori consent. If the SDM is not available in person, the RC will use a telephone script to complete the consent procedure.

Data Collection

The study RC will collect patient baseline data, including demographics, illness severity, need for advanced life support, and comorbidities. In addition, they will collect the results of the water sip test and FEES, outcomes (ie, dysphagia, reintubation events, pneumonia, mortality, percutaneous endoscopic gastrostomy tube insertion, and hospital and ICU length of stay), and source documentation that will help with the adjudication of outcomes. A patient's vital status will be recorded at 30 days if the patient was not discharged from the hospital. Mortality, duration of ventilation, and ICU stay outcomes will be truncated for analysis at 30 days.

Data will be collected using electronic case report forms via the REDCap data capture system [21] All personal information, including informed consent forms and subject code lists, will be stored electronically on a secured network drive dedicated to the study that is located in a locked research room and accessible only by designated study staff.

Outcomes

The clinical outcomes are the following (all truncated at 30 days after the FEES assessment):

- Dysphagia, defined as abnormal FEES scores resulting in the need for modification of oral diet texture or non-oral means of nutrition and hydration
- Dysphagia severity, ranging from severe (defined as an abnormal FEES requiring nothing per oral recommendation) to mild or moderate (defined as an abnormal FEES that requires any adjustment to diet texture)
- Reintubation, defined as reintubation within 30 days of the original extubation during initial hospital admission (reasons for reintubation will be recorded)
- Use of temporary feeding devices such as nasogastric or nasoduodenal feeding tubes
- Use of total parenteral nutrition
- Placement of a percutaneous gastrostomy feeding tube
- Pneumonia, defined as new pneumonia after extubation as determined by the treating health care team
- ICU length of stay, recorded as days from ICU admission to discharge from the ICU
- Hospital length of stay, recorded as days from ICU admission to hospital discharge
- Mortality during hospital stay, truncated for analysis at 30 days
- Ventilator-free days, defined as days alive and not receiving invasive mechanical ventilation at 30 days

Statistical Analysis

Sample Size

To estimate the required sample size, we will assume a conservative prevalence of dysphagia of 35%; if we enroll 200 patients (anticipating 70 dysphagia events), this will allow for 6 covariates in a logistic regression model, including age, length of mechanical ventilation, Acute Physiology and Chronic Health Evaluation (APACHE) II score on admission, functional status defined by the Functional Status Score for the ICU (FSS-ICU), use of neuromuscular blocking agents, and use of systematic glucocorticoids.

Feasibility Assessment

After enrollment of 50 patients, we will assess feasibility outcomes. The consent rate will be calculated as the overall proportion of SDMs or patients consenting among those approached (with 95% CI), and the recruitment rate will be calculated as the mean number of recruited patients per active screening month. The target consent and recruitment rates are 70% and 8 patients per month, respectively.

Descriptive Statistics

Descriptive statistics will be used to analyze the baseline characteristics and will be reported as a count (percentage) for categorical variables and mean (SD) or median (IQR) for continuous variables, depending on the distribution. The prevalence of dysphagia will be computed as the number of patients with dysphagia divided by the number enrolled and reported as a percentage with 95% CIs.

Inferential Statistics

A bivariate analysis, such as the χ^2 test or *t* test, will be applied to assess the association between each risk factor and the occurrence of dysphagia. Then, logistic regression will be used to determine the variables associated with post–critical illness dysphagia (defined a priori as length of mechanical ventilation, age, APACHE II score on admission, functional status defined by the FSS-ICU, use of neuromuscular blocking agents, and use of systematic glucocorticoids). Covariates will be entered into the model as a block. Model fit will be assessed using the Hosmer and Lemeshow goodness of fit statistic, with odds ratios and 95% CIs reported. A P value <.05 will be considered significant.

Diagnostic Accuracy

Sensitivity and specificity will be used to check dysphagia screening using a FEES, with the cutoff point for the dysphagia group being a PAS score >2. The sensitivity will present the proportion of true positive results (ie, correctly identified cases) among all patients who have dysphagia. In addition, the specificity will present the proportion of true negative results (ie, correctly identified noncases) among all the patients who do not have dysphagia. In this study, we will focus on sensitivity to avoid missing any positive cases and to determine how well the water sip test can correctly identify dysphagia. Moreover, a receiver operating characteristic curve analysis will be used, and the area under the curve will be calculated, to assess the overall performance of the water sip test.

Survival Analysis

Kaplan-Meier curves will be used to compare time-to-event outcomes (eg, dysphagia resolution, pneumonia, reintubation, or mortality) between patients with abnormal versus normal FEES results. Log-rank tests will assess differences in survival probabilities.

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Timeline

At a predicted recruitment rate of 2 patients per week, we anticipate that 18 months will be required to recruit 200 patients (Table 2).

Table 2. Study timeline and procedures.

Study procedures	Visit 1 (day 0): eligibility/enrollment (eCRF[a]); demographics (eCRF)	Visit 2 (days 1-7): FEES[b] assessment; FEES results (eCRF); daily data collection	Visit 3 (days 2-29): daily data collection	Visit 4 (day 30; final study visit): ICU[c]/hospital discharge (eCRF)
Informed consent	✓			
Eligibility assessment	✓			
Demographics	✓			
Water sip test		✓		
FEES assessment		✓		
Outcome data collection		✓	✓	✓
Dysphagia		✓		
Aspiration		✓	✓	✓
Reintubation			✓	✓
PEG[d] tube insertion			✓	✓
Pneumonia			✓	✓
ICU LOS[e]				✓
Hospital LOS				✓
Mortality (in ICU or in hospital)				✓

[a]eCRF: electronic case report form.
[b]FEES: fiber-optic endoscopic evaluation of swallowing.
[c]ICU: intensive care unit.
[d]PEG: percutaneous endoscopic gastrostomy.
[e]LOS: length of stay.

Results

The Dysphagia-ICU study is currently in the active recruitment phase at Prince Sultan Military Medical City, Saudi Arabia. The study received institutional review board approval on September 25, 2024 (18-2024-04-08-93). As of July 13, 2025, a total of 45 patients had been enrolled. The current recruitment rate averages 7.5 per month, aligning with the projected pace to complete enrollment within the planned 18-month period. All participants to date have undergone the water sip test and FEES within 7 days of extubation, and no adverse events related to the FEES procedure have been reported.

Discussion

Principal Findings

Through implementation of the Dysphagia-ICU study, we aim to generate data on the prevalence of, risk factors for, and outcomes of post–critical illness dysphagia among critically ill patients in Saudi Arabia. Our anticipated main findings include identifying key predictors of post–critical illness dysphagia, determining the prevalence of dysphagia, evaluating the accuracy of bedside screening tools, and assessing the impact of dysphagia on patient outcomes such as ICU length of stay, pneumonia, reintubation, and mortality.

This study aims to establish the prevalence of post–critical illness dysphagia using FEES as the reference standard. We anticipate that post–critical illness dysphagia will be a significant yet underdiagnosed complication among ICU patients, as previous studies have relied on less sensitive bedside screening methods [2,3]. By identifying modifiable and nonmodifiable risk factors, this study will help guide early detection and intervention strategies [4,5].

Post–critical illness dysphagia remains underdiagnosed in ICUs, with its true prevalence often underestimated due to unreliable assessments [2,10]. While international data exist, studies in Saudi Arabia are limited. Dysphagia affects up to 62% of mechanically ventilated patients [4], but inconsistent evaluation methods impact prevalence estimates. Our Dysphagia-ICU study will use FEES for precise detection, bridging this gap by identifying prevalence, risk factors, and outcomes to inform clinical and policy decisions [11].

A key strength of this study is its comprehensive design, incorporating both clinical assessments and instrumental evaluations to accurately diagnose dysphagia. Additionally, the prospective cohort design will enable tracking of patient outcomes over 30 days, providing valuable insights into the short-term impact of post–critical illness dysphagia. However, as a single-center study, the generalizability of the findings may

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be limited. Future multicenter studies are needed to confirm these findings in a broader population.

Despite its limitations, this study promises to establish the foundation for regional guidelines. For patients, identifying dysphagia early can lead to prompt intervention, potentially reducing risks such as respiratory complications and malnutrition. For health care professionals, the study outcomes will strengthen multidisciplinary collaboration, enhancing the recognition and management of dysphagia. For policymakers, a clearer understanding of the burden posed by this condition will facilitate more effective resource allocation and health care planning in Saudi hospitals and ICUs, ultimately improving patient outcomes.

The results of the Dysphagia-ICU study will also lay the foundation for future research and the development of clinical practice guidelines tailored to the needs of the Saudi health care system.

Conclusions

The study's findings will enhance early detection of dysphagia, thereby reducing complications, and provide insights for health care providers and policymakers to develop new guidelines for improving ICU care for critically ill patients.

Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization and study design: WA, KL, HFA, A Alrwais, A Alhomoud, SA, JS
Writing (first draft): WA, KL, RMA
Review and approval of the manuscript: all authors

Conflicts of Interest

None declared.

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Abbreviations

APACHE: Acute Physiology And Chronic Health Evaluation
FEES: fiber-optic endoscopic evaluation of swallowing
FSS-ICU: Functional Status Score for the Intensive Care Unit
ICU: intensive care unit
PAS: Penetration Aspiration Scale
RC: research coordinator
SDM: substitute decision maker
SLP: speech-language pathologist

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Protocol

Pulmonary Function and Sleep-Related Disorders During Cervical Administration of Intrathecal Baclofen in Adults With Spinal Cord Injury (Cervit-B): Protocol for a Multiphase Single-Arm Intervention Trial

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Abstract

Background: The effect and safety of intrathecal baclofen (ITB) on generalized spasticity of the lower extremity have been well described in numerous studies, whereas the safety and effect on spasticity of the upper extremity during cervical administration seems to be less certain.

Objective: We aim to establish the safety of cervical administration of ITB on pulmonary function and sleep-related disorders in adults with a cervical spinal cord injury with functional hindering spasticity. In addition, we aim to explore the effect of cervical ITB on the reduction of spasticity; participant satisfaction; and improvement at the level of function, activities, and participation.

Methods: The study is a multiphase single-arm intervention study. Before the start of the study, participants are screened for the presence of sleep-related disorders, and pulmonary function is assessed using spirometry and a capillary blood gas sample. Participants are allowed to start the first phase of the study if there are no signs of sleep-related disorders or if these are adequately treated. The P_cCO_2 (partial pressure of CO_2 in capillary blood sample) should be between 4.5 and 6.5 kPa. In the first phase of the study, an extracorporeal pump will be used to investigate whether cervical administration of ITB leads to a reduction of spasticity without an adverse effect on pulmonary function and sleep-related disorders. In case of a safe (no adverse effects) and positive (reduction of spasticity) result of the trial, a baclofen pump will be implanted in the second phase of the study. After implantation, the dosage of ITB will be slowly increased, and eventually, the use of oral spasmolytics will be phased out. The dosage will be increased during the monitoring of pulmonary function and sleep-related disorders. In the second phase of the study, a pulse oximetry will be performed, and pulmonary function; spasticity; satisfaction; and the level of function, activities, and participation will be assessed at 3, 6, and 12 months after definitive implantation of the baclofen pump.

Results: The first participant was recruited on May 23, 2023. Data collection and analyses are expected to be completed in 2027.

Conclusions: Currently, little is known about the safety and effectiveness of cervical administration of ITB for the treatment of upper extremity spasticity. We aim to establish the safety and explore the efficacy of this procedure. This paper describes the protocol of this study.

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KEYWORDS

spinal cord injury; spasticity; intrathecal baclofen; upper extremity; pulmonary function; sleep-related disorders

Introduction

Background

Cervical spinal cord injury (SCI) is often accompanied by spasticity of the upper extremity (UE), leading to limited function of the UE, which may negatively influence the quality of life [1]. Therefore, effective treatment of spasticity is of great importance. Neuromuscular blocks or surgery are treatments for focal spasticity. Neuromuscular blocks might be insufficient for generalized spasticity, given the maximum tolerated dose and potential complications [2]. Baclofen therapy is well established for the treatment of generalized spasticity [2]. Baclofen is a strong and selective gamma-aminobutyric acid-B receptor agonist, leading to presynaptic inhibition of reflex activity. Dosing the baclofen directly into the spinal fluid results in a higher drug concentration at the site of action, with fewer systemic side effects compared to oral baclofen. The effect of intrathecal baclofen (ITB) on generalized spasticity of the lower extremity (LE) has been well described in numerous studies, whereas the effect on spasticity of the UE seems to be less certain [2,3]. This difference in effectiveness might be related to the placement of the catheter tip intrathecally and the baclofen gradient in the cerebrospinal fluid [4,5]. In current settings, the catheter tip is usually placed at the thoracolumbar level.

It has been shown that the concentration of baclofen is highest around the tip of the catheter and the concentration rapidly decreases in caudal and rostral direction [4,5]. Furthermore, the rate of decrease depends on the method of infusion (bolus or continuous). There is a faster decrease in concentration in continuous infusion [5].

As the catheter position affects the concentration gradient, the concentration of ITB at the cervical level will be higher if the catheter tip is at the cervical level than if the catheter tip is at the thoracolumbar level. To properly treat spasticity of the UE, the tip of the catheter should be positioned cervically. A cervical catheter tip will probably, in addition to the effect on spasticity of the UE, also have an effect on the spasticity of the respiratory muscles.

Reducing the spasticity of respiratory muscles could improve respiration and pulmonary function [6-8]. However, higher concentrations of ITB at the cervical level may lead to a deterioration of pulmonary function and an increased risk or increased severity of sleep apnea syndrome (SAS) due to respiratory muscle weakness and a central dampening effect [3].

A systematic review by Jacobs et al [9] suggests that cervically administered ITB seems to improve UE spasticity and function, without causing more complications than thoracolumbar ITB. However, the main drug-related complications have not been thoroughly investigated, preventing definitive conclusions [9]. This conclusion is confirmed in a recent study by Mossner et al [10]. Therefore, we propose investigating the safety and exploring the efficacy of this procedure.

Objective

We aimed to extensively describe the design and methodology of the Cervit-B study, in which we will investigate the safety of cervical administration of ITB in adults with SCI. In addition, we will explore the effect of cervical ITB on spasticity; the level of function, activities, and participation; and participant satisfaction. We hypothesize that cervical administration of ITB is a safe procedure without adverse effects on pulmonary function, as measured by spirometry and capillary blood gas, and on sleep-related disorders in the sense of SAS. In addition, we hypothesize that it improves the efficacy of spasticity management, enhances functional abilities and activities, promotes greater social participation, and increases participant satisfaction.

Methods

Study Design

This multiphase single-arm intervention study will contain 2 phases. We will first start with screening and recruitment to determine if there is an indication for, and if it is safe to start treatment with ITB. Phase 1 will be the safety phase, in which an extracorporeal pump will be used to investigate whether cervically administered ITB leads to reduction of spasticity without adverse effect on pulmonary function and sleep-related disorders. In case of a safe and positive test, we will continue to the next phase (phase 2) in which a baclofen pump is implanted. After implantation, the dosage of ITB will be slowly increased to the optimal setting, and if the participant uses oral spasmolytics, these are phased out. The optimal setting varies in accordance with patient conditions. In this phase of the study, we will focus, in addition to pulmonary function and sleep-related disorders, on the reduction of spasticity; improvement of participants' level of function, activities, and participation; and participant satisfaction according to the International Classification of Functioning [11].

All participants will be assessed once before the start of phase 1 (T0A1), at the start of phase 1 (T0A2), and daily during phase 1 (T0B). In the case of a safe and positive test, participants will be assessed at the end of phase 1 (T1). During phase 2, they will be assessed at 3, 6, and 12 months (T2, T3, and T4) after baclofen pump implantation. We chose to start the assessment in phase 2 only after 3 months following the implantation because in the first 3 months, the pump settings will still be regularly adjusted to optimize the daily dosage of ITB.

Setting

The study settings of phases 1 and 2 will be at the Medisch Spectrum Twente (MST) hospital and Roessingh Center for Rehabilitation (RCR), respectively. Both the centers are in Enschede, the Netherlands.

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Study Coordination

RCR is the coordinator of the study and is responsible for the study design, management, data collection, and data analysis.

A data safety monitoring board is involved throughout the study. Once the first 6 participants have completed phase 1, the board will assess the safety and related continuation of the study. Monitored visits by an independent study monitor are planned every 6 months. This is to ensure the continued protection of participants' rights and well-being, assure protocol adherence, and verify that data integrity during the study complies with good clinical practice [12]. All protocol deviations will be filed. In this study protocol, the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) reporting guidelines are used [13].

Ethical Considerations

The study will be conducted according to the principles of the Declaration of Helsinki, (October 2013 version), and in accordance with the Medical Research Involving Human Subjects Act (WMO). Approval of the study has been obtained from the Medical Ethics Committee Oost Nederland (2021-7364) and the Central Committee on Research Involving Human Subjects. The trial is registered in the EudraCT database (2021-004994-30) and is transitioned to the Clinical Trials Information System (2023-508143-51-01). All administrative and protocol-related amendments will be submitted for approval to the Medical Ethical Committee. After receiving their approval, these modifications will be reported via email to the participating centers and the external monitor. The sponsor has both patient and liability insurance, which is in accordance with article 7 of the WMO.

After the nature and possible consequences of the study are explained, informed consent will be obtained from all participants. Participants will be informed that they always have the ability to opt out. Apart from travel expenses, there is no compensation for the participants.

Before the start of the study, a data management plan that covers all aspects of handling data gathered during and after completion of the study was devised.

All documents related to the study and all participants' data will be collected in the investigators' site files. These files, containing personal and contact information, as well as the screening information from potential candidates, will be safeguarded in RCR. All relevant data will be copied from the case report form into a web-based clinical database for case report data (Castor, Castor EDC) by the primary investigator using unique and anonymous participant codes. If necessary, this study identification number can be linked to the participant by the primary investigator only. The primary investigator, the research assistant in RCR, the research nurse in MST, and the monitor will have access to the full dataset.

All coded data will be stored for 10 years within the clinical database.

Participants

Adults with SCI eligible for the study must have generalized or multifocal spasticity in UE and eventually also in the LE. Their spasticity must be refractory to oral drugs or local treatment [14,15].

In the Netherlands, there are 8 rehabilitation centers with a specialized spinal cord unit. These 8 centers work closely together on patient-related content in the Dutch-Flemish Spinal Cord Society. According to guidelines in the Netherlands, all persons with SCI in the chronic phase are seen by a rehabilitation physician [16-18]. The rehabilitation physician involved in the chronic phase is familiar with the Cervit-B study. In case of generalized therapy-resistant spasticity of the UE and eventually also the LE, patients are referred to RCR by their rehabilitation physician. In RCR, they are seen by the principal investigator (EMM) for assessment to check the indication for cervical administration of ITB. Spasticity is assessed using the Perceived Resistance to Passive Movement (PRPM) and the Modified Ashworth Scale (MAS) [19,20].

When there is an indication for cervical administration of ITB, participants will be informed about the study. When participants are interested, an information letter is given to them. After 1 week, the principal investigator (EMM) will contact the participants to determine their interest in participating in the study and to answer possible questions. If interested in participating, a physical appointment with the principal investigator (EMM) is scheduled to obtain informed consent and to complete the screening procedure to check if it is safe to start phase 1. If it is safe, participants will be seen by the skilled functional neurosurgeon at the outpatient clinic in MST before the start of phase 1. The neurosurgeon will check for operative exclusion criteria and will answer questions. The same neurosurgeon will be involved in the study during all surgical procedures and admission at MST.

The inclusion and exclusion criteria for the Cervit-B study are described in Textbox 1 [21-23].

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Aged >18 years
- Spinal cord injury (SCI) with a neurological level at or above Th1
- >1 year after the onset of SCI
- An American Spinal Injury Association Impairment Scale of A to D, according to the International Standards for Neurological Classification of Spinal Cord Injury [21]
- Generalized or multifocal spasticity in UE, and eventually also in LE, refractory to oral drugs or local treatment
- Providing written informed consent

Exclusion criteria

- Pregnancy
- Women of childbearing potential
- Women who are currently breastfeeding
- Baclofen allergy
- Use of oral anticoagulants
- Individuals with active depression, schizophrenia, or bipolar disorders who are still under treatment by a psychiatrist, as exacerbations of these conditions during the use of baclofen have been observed [22]
- Excessive alcohol use according to the Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition [23], because interactions with alcohol are unpredictable [22]
- Progressive disease as the cause of SCI
- Concomitant presence of a terminal disease, such as cancer
- Muscle or nerve blocks carried out in the last 6 months
- Dependent on invasive or noninvasive ventilation other than a Continuous Positive Airway Pressure device
- P_cCO_2 (partial pressure of CO_2 in capillary blood sample)>6.5 kPa or <4.5 kPa
- Not adequately treated sleep apnea syndrome with an Apnea-Hypopnea Index (AHI) >5. The AHI represents the average number of apneas and hypopneas each hour during sleep.

Sample Size

No sample size calculation was performed for this pilot safety study. On the basis of a previous comparable study by Bensmail et al [3] with 11 participants, we decided to include the same number of participants. We expect that we need to screen and recruit 25 participants to retain 11 participants at the start of the phase 1 because of the safety criteria for inclusion (Figure 1).

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Figure 1. Flowchart of the study phases, including settings, sample size, and parameters to be assessed. ITB: intrathecal baclofen; MST: Medisch Spectrum Twente; RCR: Roessingh Center for Rehabilitation; SCI: spinal cord injury.

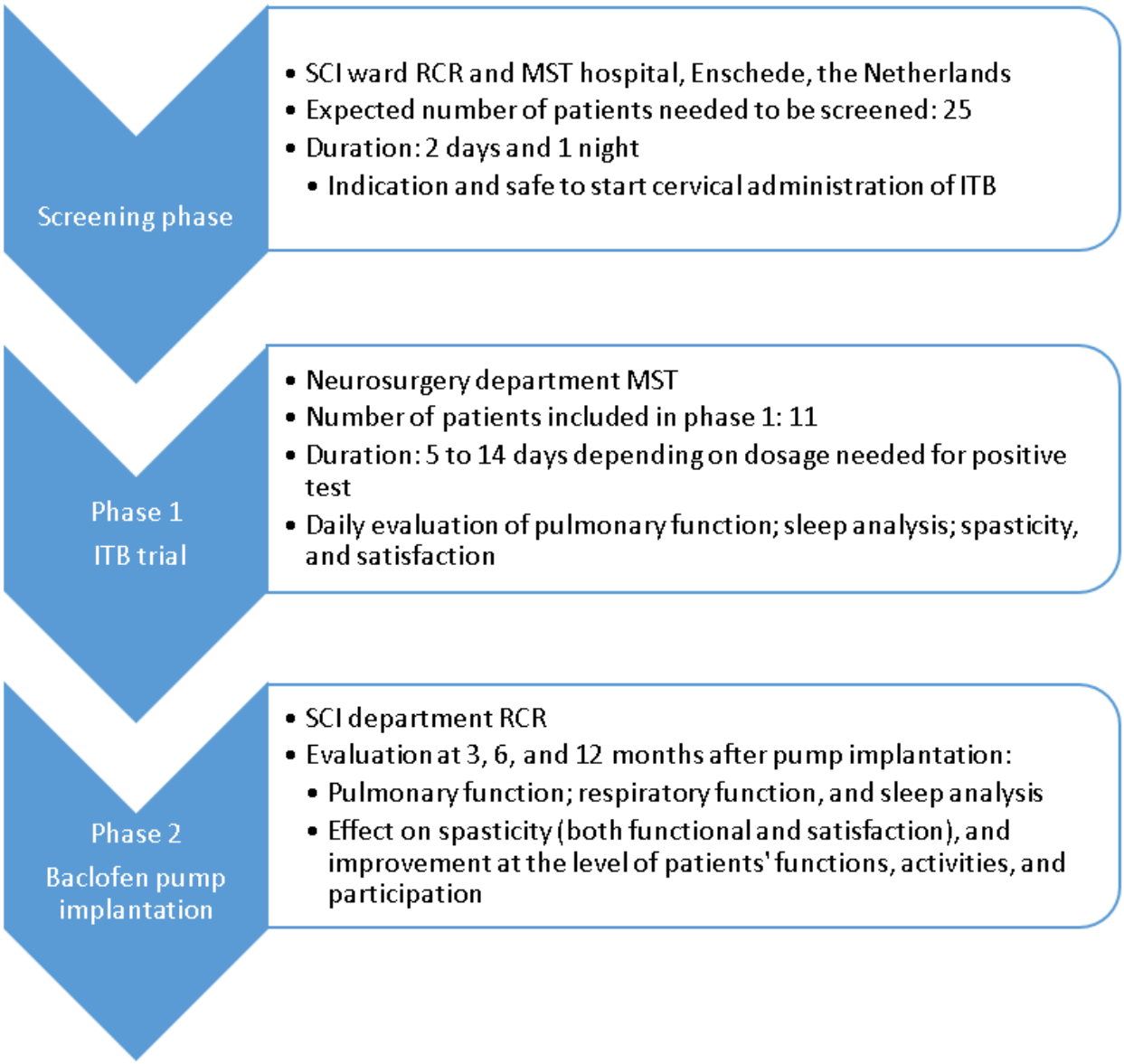

Study Procedures

Screening and Recruitment

Before participants are included in the study, they will be assessed by an experienced SCI rehabilitation physician to check the indication for treatment of their spasticity by ITB. If there is an indication, participants will be screened for the presence of SAS by the use of OSAsense (OSAsense BV) [24]. The OSAsense consists of a validated online questionnaire and a nightly saturation and pulse rate measurement (pulse oximetry). The OSAsense algorithm, based on the questionnaire and pulse oximetry, is able to detect SAS with a sensitivity of 100%, a specificity of 35%, a negative predictive value of 100%, and a positive predictive value of 79.4% [25]. If, according to the algorithm, there is any suspicion of SAS, polysomnography will be performed, and the patient will be set up for SAS treatment if necessary. In addition, a morning capillary blood gas sample will be taken to determine the P_cCO_2. We chose to take a capillary blood gas sample because there is a strong correlation between samples collected from the fingertip capillaries and the arterial blood samples in relation to the analysis of blood [26].

These measurements determine the safety for participants to start the first phase of the study. The start of the first phase of the study will be determined as safe if the participant is stable enough to undergo surgery (defined by neurosurgeon), capillary blood gas shows a P_cCO_2 between 4.5 and 6.5 kPa, and there are no symptoms of SAS or, in the case of SAS, the participant is adequately set to SAS treatment with an Apnea-Hypopnea Index (AHI) <5. These cut-off values have been chosen according to the applicable guidelines in the Netherlands [27].

ITB Trial (Phase 1)

Before definitive treatment with ITB, individuals will undergo an ITB trial by continuous infusion using an extracorporeal pump. We opted for this type of trial treatment based on a study

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by Bensmail et al [3], which demonstrated that a bolus infusion mode gave relatively more increase in the respiratory disturbance index and of central and mixed sleep apneas than the continuous infusion mode.

During phase 1, participants will be admitted to MST in Enschede. A hybrid infusion system consisting of a spinal catheter (Medtronic Ascenda 8781; Conformité Européenne [CE] mark for intrathecal use) and an implantable infusion port (Cellsite spinal; CE mark for intrathecal use) will be implanted under deep sedation. The participant lies in a lateral decubitus position. After marking the incision locations in the midlumbar region and the paraumbilical area, the incision areas will be infiltrated with local anesthesia (bupivacaine). After sterile draping, the lumbar fascia is exposed through a 2- to 3-cm incision, and a 16 T-gauge introducer needle will be placed to access the intrathecal space. Then, the spinal catheter will be placed under fluoroscopic guidance to the cervical level just below the level of injury. Once positioned, an anchor will be placed over the catheter and sutured to the deep fascia of the musculus erector spinae. The catheter will then be tunneled subcutaneously from the midlumbar region to the paraumbilical area and will be connected to the subcutaneous infusion port. Before wound closure, the port will be accessed to document the cerebrospinal fluid flow through the complete hybrid system. Thereafter, an extracorporeal pump (CADD solis infusion pump, CE mark for intrathecal use or application) will be connected percutaneously to the subcutaneous infusion port.

For safety reasons, we chose to start with the lowest possible dose given the concentration of baclofen and the infusion rate of the extracorporeal pump used. The starting dose of the ITB will be 1 µg per hour and is titrated in the following days based on both objective and subjective (participant's experience) change in spasticity. In the literature, no maximum dose of ITB during a trial with an extracorporeal pump is reported. We set the maximum dose at 200 µg per day, based on our extensive previous experiences with the use of an extracorporeal pump in ITB trials.

Daily capillary blood gas samples will be taken, and continuous pulse oximetry during sleep, by use of the OSAsense, will be recorded. If the participant is set on a continuous positive airway pressure (CPAP) device, the CPAP device is read out. The trial will be determined as unsafe and will be stopped if the P_cCO_2 is >6.5 kPa for 2 days in a row, according to hypoventilation rules in adults as mentioned by Berry et al [28]. The trial will also be stopped when participants without SAS, during the trial, will develop complaints matching SAS and the Oxygen Desaturation Index (ODI) is between 5 and 15 [27]. The ODI represents the number of desaturations per hour.

A third reason to stop the trial is when participants during the trial have no complaints matching SAS, but the ODI is >15 [27]. If the participant uses a CPAP device, the setting of the device may be adjusted to stay within the safety margin. This safety margin is set at an AHI <5 [24]. This adjustment will be registered. A fourth reason to stop the study is when, after adjustments of the CPAP device, it is not possible to stay within this safety margin [24]. A fifth reason to stop the study is if there is no effect on spasticity at the maximum dose of ITB (200 µg per day).

If the participant experiences a positive effect of the ITB on their spasticity, with a score between 1 and 3 on the Patient Global Impression of Change (PGIC) [29] without deterioration on functionality (PGIC 5-7) and there is not a clinically relevant deterioration of pulmonary function or SAS, it is considered a safe and positive ITB trial with an indication for intracorporeal pump implantation (phase 2) and treatment with ITB at cervical level. We opted for these cut-off values for assessment of reduction of spasticity according to the algorithm established by the European working group for spasticity in adults [30].

If, during the trial, no effect is observed on spasticity or there is a clinically relevant deterioration of pulmonary function or SAS, the trial will be discontinued. This is considered a negative test in which there is no indication for treatment of spasticity with ITB. The catheter and the subcutaneous infusion port will then be removed (Figure 2).

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Figure 2. Overview of phase 1. CPAP: continuous positive airway pressure; PGIC: Patient Global Impression of Change.

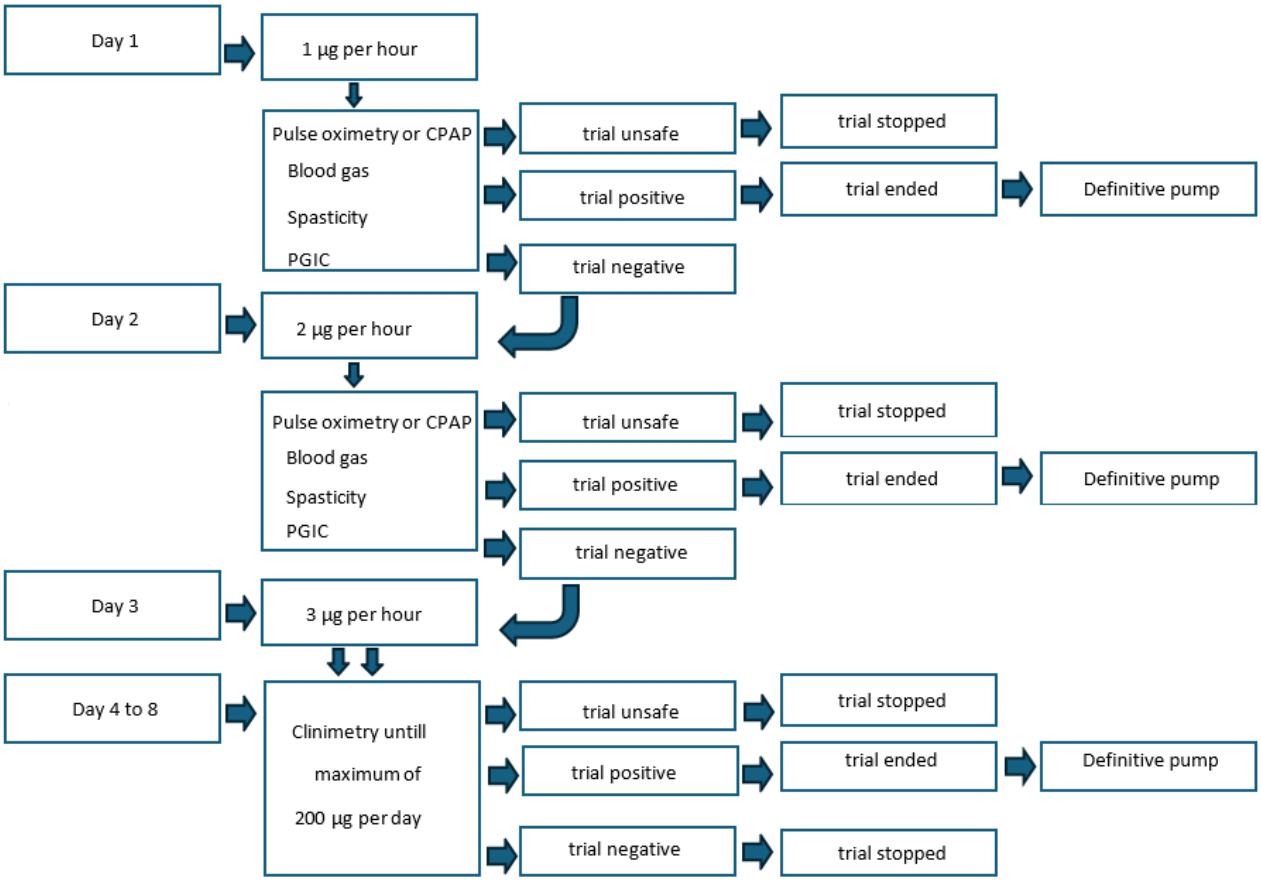

Baclofen Pump Implantation (Phase 2)

In the case of a positive ITB trial phase, the infusion port will be replaced by a definitive pump system. In this procedure, the participant is in a supine position and under deep sedation or local anesthesia. The infusion port is removed from the catheter, and the catheter is connected to a programmable implantable pump (Medtronic SynchroMed II; CE mark) for intrathecal drug delivery.

One day after the pump implantation at the MST, participants will be transferred to RCR. Participants will remain in the rehabilitation center for at least 2 weeks. During admission, the dosage of ITB will be slowly increased, and the oral spasmolytics will be phased out. Spasticity is measured on a daily basis, and for safety reasons, once a week and at discharge, a capillary blood gas sample is taken and a screening with the OSAsense is performed, or CPAP data are checked. The participant will be discharged home when the oral spasmolytics are phased out, the patient is satisfied with the current level of spasticity (PGIC between 1 and 3), and the AHI or ODI and P_cCO_2 are within the safety margins, as indicated previously. The participant will be seen for follow-up at the rehabilitation center at 3, 6, and 12 months after implantation. To promote follow-up, the participants will be called once before their appointment by the primary investigator. In case a participant stops or deviates from the protocol, the reason for this will be recorded.

Outcomes, Characteristics, and Other Variables

Overview

Table 1 shows an overview of the primary and secondary outcome measurements, descriptive variables, and timing of the data collection. At both centers, everyone involved in the measurements is trained in measuring and collecting study data in a uniform and reproducible manner. A training and delegation log will be maintained by the principal investigator (EMM).

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Table 1. Overview of outcome measures and timing.

Construct	Timing							Measures
	Screening	First phase (test phase)			Second phase (after implantation)			
	T0A1[a]	T0A2[b]: before starting the trial	T0B[c]: during the trial	T1[d]: end of the trial	T2[e]	T3[f]	T4[g]	
Primary outcomes								
Respiratory function	✓	✓	✓	✓	✓	✓	✓	Capillary blood gas
Sleep disorder	✓		✓		✓	✓	✓	Pulse oximetry[h]
Pulmonary function	✓	✓		✓	✓	✓	✓	Spirometry[i]
Secondary outcomes								
Patient satisfaction			✓	✓	✓	✓	✓	PGIC[j]
Spasticity	✓	✓	✓	✓	✓	✓	✓	PRPM[k] and MAS[l]
Pinch and grip strength	✓				✓	✓	✓	e-link
Muscle power	✓				✓	✓	✓	MRC[m] scale
Passive ROM[n]	✓				✓	✓	✓	Degrees
Walking ability (if possible)	✓				✓	✓	✓	Timed Up and Go Test and 10-Meter Walking Test
Activity and participation	✓				✓	✓	✓	COPM[o], GRT[p], and QIF-sf[q]
Participants and disease characteristics								
Sex	✓							
Race	✓							
Age	✓							
Level and completeness of the SCI[r]	✓							International Standards for Neurological Classification of Spinal Cord Injury
Etiology of SCI	✓							
Time since injury	✓							
Other treatments against spasticity	✓							
Medication	✓	✓	✓	✓	✓	✓	✓	
Comorbidity	✓	✓	✓	✓	✓	✓	✓	
Vital signs	✓	✓	✓	✓				
Complications and side effects		✓	✓	✓	✓	✓	✓	

[a]T0A1: preassessment screening.

[b]T0A2: start of the extracorporeal pump.

[c]T0B: period during the trial phase.

[d]T1: moment appropriate titration in the trial phase.

[e]T2: 3 months after implantation.

[f]T3: 6 months after implantation.

[g]T4: 1 year after implantation.

[h]If there is any suspicion of sleep apnea syndrome based on the results of the pulse oximetry, additional polysomnography will be performed during the screening and recruitment.

[i]If participants during the trial phase experience dyspnea, spirometry will be performed.

[j]PGIC: Patient Global Impression of Change.

[k]PRPM: Perceived Resistance to Passive Movement.

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[l]MAS: Modified Ashworth Scale.
[m]MRC: Medical Research Council.
[n]ROM: range of motion.
[o]COPM: The Canadian Occupational Performance Measure.
[p]GRT: Grasp and Release Test.
[q]QIF-sf: Quadriplegia Index of Function—Short Form.
[r]SCI: spinal cord injury.

Primary Outcome Measures

The primary objective of the study is to establish whether cervical administration of ITB is a safe treatment for spasticity without deterioration of pulmonary function and possible increased risk or increased severity of SAS. Safety will be determined by use of a capillary blood gas sample and an OSAsense or CPAP screening before and during the first phase of the study. We will use P_cCO_2 and the AHI or ODI as safety markers.

Secondary Outcome Measures

The secondary objective of the study is to explore the effect of cervical administration of ITB on the reduction of spasticity; intermediate and long-term effects on pulmonary function and SAS; and improvement in the level of participants' function, activities, and participation [11]. Participant satisfaction will also be considered.

All secondary outcome measures are carried out in RCR at screening and at 3, 6, and 12 months after implantation of the baclofen pump by an experienced and trained physiotherapist and occupational therapist. Spasticity and satisfaction will also be measured during phase 1.

Spasticity is measured by the MAS [19] and PRPM [20]. Spasticity will be measured in the UE and LE. The PRPM is an ordinal scale that measures and describes perceived resistance against passive motion. The scale ranges from 0 (no increase in resistance) to 4 (limb is rigid in flexion or extension). During testing, the patient is in a relaxed position (the position of the patient is documented). The patient is instructed not to assist or oppose the movement. First, the passive range of motion of the joint is tested by slow flexion or extension. Subsequently, perceived resistance is assessed within the entire range with a faster movement, covering the whole range within 1 second. The movement can be repeated a maximum of 2 times (the lowest score is noted).

The MAS measures the increase in muscle tone and assigns a grade of spasticity from a 0 to 4 ordinal scale. A score of 0 signifies normal muscle tone, a score of 1 signifies a slight increase in muscle tone with a slight catch when the limb is moved in flexion and extension, a score of 1^+ signifies a slight increase in muscle tone with minimal resistance at the end of movement, a score of 2 signifies a more marked increase in muscle tone through the entire movement but the limb is still easy to move, a score of 3 indicates a considerable increase in muscle tone and that passive movement is difficult, and a score of 4 indicates that the limb is rigid in flexion or extension. The position of the patient and the procedure is the same as in the PRPM.

Participant satisfaction will be measured by PGIC [29], which is a 7-point scale ranging from 1 (very much improved) to 7 (very much worse). Using the scale, the participant can rate if the ITB has changed the level and the hindrance of the spasticity according to the situation before cervical administration of ITB.

Muscle strength of the core muscles of the UE and LE will be measured by the Medical Research Council (MRC) scale [31]. The core muscles of the upper extremity are the elbow flexors, the wrist dorsal flexors, the elbow extensors, the deep flexor of digit 3, and the ulnar abductor of digit 5. The core muscles of the LE are the hip flexors, the knee extensors, the ankle dorsal flexors, the extensors of digit 1, and the ankle plantar flexors. The MRC scale is an ordinal scale ranging from 0 to 5. With a score of 0, no muscle activity is seen, a score of 1 indicates muscle contraction is felt or observed but no full range of motion, a score of 2 indicates that there is a full range of motion with gravity eliminated, a score of 3 suggests a full range of motion against gravity, a score of 4 indicates that there is muscle activity against some resistance, and a score of 5 suggests a normal force. During testing, the patient is in supine position and tight or restrictive clothing is removed so the examiner can visualize the muscles being tested and observe for muscle twitch. Muscles are first tested with gravity eliminated so that muscle contraction is perpendicular to gravity. If the participant is unable to engage the muscle with gravity eliminated, the examiner places a hand on the muscle and asks the participant to contract his or her muscles again. This allows the examiner to feel for a muscle twitch, even if a twitch is not visible. This observation would differentiate a score of 0 from a score of 1. When the participant demonstrates the full range of motion with gravity eliminated, the test should be repeated against gravity for the full range of motion. If this is successful, the examiner should challenge the participant by the addition of a small degree of resistance, and then by the maximum resistance to differentiate between a score of 3, 4, or 5.

For the lateral- and cylindrical grip strength, the E-Link Hand Grip Dynamometer and Pinchmeter (Biometrics Ltd) will be used [31]. For the measurement, the participant sits on a chair or in his or her wheelchair at a table with the arm resting on the table with the elbow at a 90° angle. The participant should squeeze as hard as possible and hold this for about 2 seconds. Each hand is measured 3 times and a mean score is calculated.

For the measurement of passive range of motion, a goniometer is used. The participant is in a supine position. This measurement is performed by two physiotherapists, with one therapist moving the joint and the other using the goniometer to record the joint's mobility in degrees. Notation is done via the neutral 0 method [32].

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Walking ability and the ability to safely stand up from a chair will be measured by the Timed Up and Go test [32] and the 10-Meter Walking Test [33].

The Timed Up and Go test measures the time it takes the participant to get up from a chair or a wheelchair, walk 3 meters comfortably (most energetically efficient), turn around, walk back, and sit down. At the start, the participant sits in the chair or the wheelchair with hands on the upper legs. When standing up and sitting down, the armrests may be used. Time is stopped when the participant sits again with their hands on their legs. The participants may use their own walking aid or orthosis, but no physical help should be provided.

The 10-Meter Walking Test measures the speed of comfortable walking and the maximum walking speed over a distance of 10 meters. If necessary, it is permitted to use a walking aid or orthoses, but the patient must be able to walk without physical help.

For the assessment of the level of activities and participation, the Canadian Occupational Performance Measure [34], the Grasp and Release Test [35], and the Quadriplegia Index of Function—Short Form (QIF-sf) [36] will be used.

The Canadian Occupational Performance Measure [34] is a semistructured interview designed to identify and prioritize everyday issues that restrict individuals' participation in everyday living. An occupational therapist determines, together with the participant, which 5 activities of daily living he or she would like to be able to perform better and be more independent. These activities are scored on a 10-point scale for both performance and satisfaction.

The Grasp and Release Test [35] measures unilateral hand performance during the manipulation of 6 objects of different sizes and weights—3 objects with lateral pinch (peg, weight, and fork) and 3 objects with palmar grasp (block, can, videotape). The participant sits on a chair or in a wheelchair in front of a table. The position of the participant in relation to the table and the test is exactly documented so that during repeated measurements, this same position can be maintained. Participants are asked to grasp, lift, and release the objects as many times as possible within 30 seconds. Each object is repeated 3 times and a mean score is calculated.

The QIF-sf [36] is a clinician-administered interview, developed to provide a functional assessment for documenting small but clinically significant gains made by SCI quadriplegics. On the basis of the Quadriplegia Index of Function originally developed in 1980, the QIF-sf assesses only 6 activities of daily living instead of 37 in the original version. Items include washed or dry hair, turning supine to side in bed, LE dressing, opening a carton or jar, transferring from bed to wheelchair, and locking the wheelchair. The QIF-sf is scored on a 4-point Likert scale ranging from totally dependent (score of 0) to independent (score of 4).

Pulmonary function [37] will be mapped by spirometry. In RCR, spirometry is performed by a handheld spirometer. Before starting the test, patient's age, sex, height, and origin are determined for assessment and interpretation of results. The participant is sitting in an upright position, and a nose clip is applied. Thereafter, a mouthpiece is placed into the mouth. The participant is instructed on how to perform the test. The mouthpiece must be surrounded with lips and teeth; the blowhole may not be closed with the tongue. Then, the participant performs a maximum inspiration followed by a fast, forceful, smooth, and full expiration of at least 6 seconds, and finally a rapid, forceful, and complete inspiration.

For the assessment of the spirometry, specific attention is paid to forced vital capacity, forced expiratory volume in 1 second, and peak expiratory flow because of the importance of these parameters on pulmonary function in people with cervical SCI [37]. The forced vital capacity represents the lung capacity when forced to inhale and exhale. The forced expiratory volume in 1 second value shows how much air of the total lung capacity can be exhaled in the first second. The peak expiratory flow concerns the maximum airflow rate during the test.

P_cCO_2 is determined by a morning capillary blood gas sample from the fingertip [24]. Sleep analysis is done by pulse oximetry using the OSAsense. The OSAsense consists of a validated online questionnaire and a nightly saturation and pulse rate measurement by a plaster around a finger [24,25]. In case a participant has a CPAP device, the AHI is determined by analyzing the data recorded by the device.

Baseline Characteristics and Other Factors

Participants characteristics, such as age; sex; race; neurological level of SCI according to the International Standards for Neurological Classification of Spinal Cord Injury [21]; etiology of SCI, time since SCI; vital signs (temperature, blood pressure, pulse rate and saturation); other treatments for spasticity before inclusion; and comorbidity will be registered at baseline. Medication will be registered at baseline and during assessments at phases 1 and 2.

Other factors that will be registered during the study are possible complications and side effects of ITB, such as temporary liquor loss, infection, epilepsy [37,38], and drowsiness. Serious adverse events and Suspected Unexpected Serious Adverse Reactions will be registered according to applicable guidelines.

Statistical Analysis

Because of the small sample size, it is expected that the continuous variables will not be parametrically distributed; therefore, they will be presented as median with IQR. Furthermore, due to the small sample size, pre- and postassessments during the first phase or the ITB trial phase will be compared with descriptive statistics and differences will not be formally tested. In addition, the measurements in the second phase after definitive implantation of the baclofen pump (3, 6, and 12 months after implantation) will be compared with descriptive statistics. Changes over time in the outcome measures within patients will be visually explored.

For categorical variables, we will present numbers and corresponding percentages. To compare pre- and postassessment during the first phase or the ITB trial, cross tabs will be made. Our primary analysis population is the intention-to-treat analysis. Considering the study design, we expect a few missing data. In case of missing data, we will use generalized estimation

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equations analysis (<20% missing data) or multiple imputations (>20% missing data).

Results

The study has started in January 2021. Funding was completed in March 2022. The first participant was enrolled in May 2023. As of June 2025, we have enrolled 6 patients in phase 1 and 3 patients in phase 2. No data analysis has been done yet. We expect data collection to be completed and published in 2028.

Discussion

Anticipated Findings

A literature review [9] on cervical ITB suggests improvement of UE spasticity and function, without causing more complications than thoracolumbar ITB. However, the data prevent definite conclusions. In 2024, a retrospective case series by Mossner et al [10] was performed in children with hypertonia, highlighting the safety and efficacy of using cervical ITB. They concluded that the cervical catheter tip location for ITB was safe, was effective in controlling tone, and should be considered for the treatment of hypertonia. Larger studies with longer follow-up were suggested to further determine upper-limit dosing safety, along with long-term functional benefits in these patients. This study will be the first study that will investigate whether cervical administration of ITB is safe in adults with SCI.

In addition to safety, efficacy will be exploratively assessed before phase 1 and at 3, 6, and 12 months after implantation of the ITB pump. The intermediate and long-term effects of cervical administration of ITB on respiratory muscles affecting pulmonary functions and SAS, as well as the effects of decreasing spasticity of the UE and LE on participants' satisfaction, function, activities, and participation, will be assessed.

Besides the aforementioned direct effect of reduction of spasticity on UE function, reduction of spasticity may have an additional indirect benefit on UE function. At the end of conventional rehabilitation, UE reconstructive surgery is a well-documented and effective treatment in tetraplegia to improve arm or hand function [39]. Spasticity may adversely affect the outcome of this surgery and is mostly considered as a contraindication and must be treated first [40,41]. In case of generalized spasticity, cervical ITB may enable UE reconstructive surgery and thereby indirectly improve UE function.

When cervical ITB seems to be both safe and effective, it will change the usual care of this treatment. The catheter tip position should then be dependent on the localization of spasticity and treatment goals: tip at thoracolumbar level for functionally hindering spasticity of the LE muscles and tip at cervical level for functionally hindering spasticity of UE and LE muscles.

Limitations

This study protocol has some limitations. Although the safety aim of the study is clear, it is important to note that this study is not powered to test for efficacy. It will provide us with the first exploratory data on efficacy, which can be used to power a subsequent study on efficacy. In addition, we anticipate variation in catheter placement relative to the lesion level. Although the catheter tip will deliberately be positioned just below the lesion to maximize sympathetic activity reduction, its proximity to the diaphragm may impact diaphragmatic function and, consequently, safety and efficacy. This variability will be considered when interpreting the results.

Although spasticity is a common complication in all central nervous system disorders with involvement of the upper motor neuron, only adults with SCI in a chronic phase will be included in this study. A potential follow-up study, in which adults with other disorders of the upper motor neuron and adults within 1 year after the onset of SCI can also be included, will focus more on effectiveness. However, the intensity of the current protocol may impact participants' adherence and study feasibility, particularly in larger-scale or multicenter settings. Therefore, in this study, we will evaluate whether the frequency and scope of the postimplantation assessments can be reduced without compromising data quality or participant safety.

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Authors' Contributions

EMM was responsible for the study design and writing the protocol and the manuscript. KHK and JSR were responsible for the study design and providing feedback on the protocol and the manuscript. MGJB-K was responsible for the study's statistical design and providing feedback on the protocol and the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

AHI: Apnea-Hypopnea Index
CE: Conformité Européenne
CPAP: continuous positive airway pressure
ITB: intrathecal baclofen
LE: lower extremity
MAS: Modified Ashworth Scale

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MRC: Medical Research Council
MST: Medisch Spectrum Twente
ODI: Oxygen Desaturation Index
PGIC: Patient Global Impression of Change
PRPM: Perceived Resistance to Passive Movement
RCR: Roessingh Center for Rehabilitation
SAS: sleep apnea syndrome
SCI: spinal cord injury
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
QIF-sf: Quadriplegia Index of Function–Short Form
UE: upper extremity

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Protocol

Harm Reduction Contingency Management for Stimulant Use Reduction and Antiretroviral Therapy Adherence in HIV Primary Care: Protocol for an Implementation Effectiveness Study

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Abstract

Background: Stimulant use disorder has been linked with medication nonadherence and mortality among people living with HIV. Contingency management (CM) is a strategy incentivizing measurable behavior change that is recommended as the first-line treatment for stimulant use disorder and can support antiretroviral therapy (ART) adherence. However, CM is not widely implemented, in part due to feasibility concerns. Although reductions in substance use short of full abstinence can improve health outcomes, CM programs typically target complete abstinence from stimulant use rather than reduction. To optimize care for safety-net populations living with comorbid stimulant use disorder and HIV, we designed a novel CM program incentivizing both stimulant use reduction and ART adherence in the HIV ambulatory setting.

Objective: We aimed to (1) evaluate the feasibility of once-weekly CM in safety-net HIV ambulatory care and (2) assess the acceptability of CM among participants and care providers.

Methods: We will conduct a pilot, single-arm, hybrid implementation effectiveness trial offering a novel CM intervention in 2 low-barrier, ambulatory HIV clinics. Patients with stimulant use disorder and suboptimal ART adherence will be offered 12 weeks of once-weekly CM including incentives for positive-tenofovir and negative-stimulant results on urine point-of-care assays. We will assess stimulant use once weekly using tests with a 4-day detection window, allowing participants to use stimulants during select days of the week but earn incentives by reducing their frequency of use from near-daily use. We will assess feasibility and acceptability using quantitative process methods and qualitative in-depth interviews, guided by the RE-AIM (reach, effectiveness, acceptability, implementation, and maintenance) evaluation framework. We will define preliminary effectiveness by proportion of stimulant-negative and tenofovir-positive urine tests, as well as changes in HIV viral suppression before and after participation.

Results: Recruitment and CM visits have concluded as of September 2024. Quantitative and qualitative evaluation is underway and is expected to continue through October 2025.

Conclusions: This novel CM program offers dual incentives targeting stimulant use reduction and ART adherence. We hypothesize that incentivizing stimulant use reduction is acceptable to our target safety-net population. Demonstration of a feasible, acceptable model may serve as a first step toward wider use of stimulant-reduction CM in the safety-net setting.

Trial Registration: ClinicalTrials.gov NCT06564792; https://clinicaltrials.gov/study/NCT06564792

International Registered Report Identifier (IRRID): DERR1-10.2196/67292

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(JMIR Res Protoc 2025;14:e67292) doi:10.2196/67292

KEYWORDS

substance use disorder; motivation; drug users; central nervous system stimulants; medication adherence

Introduction

Background

Stimulant use disorder continues to rise as a devastating public health issue in the United States, accounting for more than 57,000 deaths in 2022—a near 5-fold increase since 2015 [1] Among people living with HIV, stimulant use is particularly prevalent (>5% to 15% in the general population of people with and 30% in safety-net patient populations living with HIV) and represents a key challenge for maintaining overall health [2-4]. Both methamphetamine and cocaine have been repeatedly associated with antiretroviral therapy (ART) nonadherence, HIV viremia, and progression to AIDS; by some estimates, people living with HIV using stimulants demonstrate double the odds of ART nonadherence compared to those not using stimulants [5-9].

Contingency management (CM) is the first-line treatment for stimulant (methamphetamine and cocaine) use disorder and has also been used to promote ART adherence for people living with HIV [10-15]. This behavioral treatment—in which patients receive tangible incentives for demonstrating abstinence (eg, measured by drug-negative urine)—is highly efficacious, supported by a multitude of randomized controlled trials [10,16,17]. In addition, research suggests that CM can also be efficacious for ART adherence, although these studies were limited by the potential inaccuracy of indirect adherence measurements (eg, electronic pill bottle cap monitoring does not equate to ingested medication) [11-15].

Despite its demonstrated efficacy, the uptake of CM remains limited in both safety-net and ambulatory settings. While these settings represent the main source of medical care for many high-need patients, feasibility concerns have largely impeded CM implementation. Frequently described barriers include insufficient training and awareness, logistic concerns related to program execution, cost and resource intensiveness of programs requiring multiple weekly visits, and staff reluctance to provide financial incentives [18-21]. In addition, addressing syndemic behaviors simultaneously (by incentivizing both stimulant use reduction and ART adherence through a single “multitarget” intervention) is an important opportunity to seize. To effectively reach people living with HIV who are most in need of this treatment, there is an urgent need for feasible CM models that target stimulant use and ART adherence in ambulatory safety-net settings.

Leveraging harm reduction principles will be essential for addressing the needs of safety-net populations with comorbid HIV and stimulant use disorder. Abstinence from stimulants can be an unrealistic, unwanted, or a less proximate goal for people with severe stimulant use disorder, who may be using daily or chronically [22]. Efforts to emphasize stimulant use reduction rather than abstinence have shown promise in promoting overall health; for example, in a secondary analysis of 13 randomized controlled trials, reduced use of methamphetamine and cocaine was associated with global improvement of psychosocial functioning and severity of drug-related problems, as well as improved depression and fewer drug-seeking behaviors [23]. Although CM is traditionally structured to promote abstinence, new models that incentivize stimulant use reduction and other positive health behaviors may be more aligned with patient goals and needs in the safety-net setting.

To optimize care for safety-net populations living with comorbid stimulant use disorder and HIV, we designed a novel CM program incentivizing both stimulant use reduction and ART adherence in the HIV ambulatory setting, called CoMBo (Contingency Management for Both HIV and Stimulant Use Disorder). CoMBo involves point-of-care (POC) tests that detect stimulant use within a 3- to 4-day window and offer once-weekly visits in contrast to traditional CM programs that test urine 2 to 3 times per week to confirm abstinence. In addition, we use a novel POC, a urine-based tenofovir assay that allows for real-time assessment of adherence to tenofovir-based ART [24,25]. This technology enables simultaneous assessment of tenofovir adherence and stimulant use by using one urine sample, facilitating a truly paired intervention.

In this paper, we present a full description of an implementation effectiveness pilot delivering CM with paired incentives in the HIV ambulatory setting and describe a protocol for the quantitative and qualitative evaluation of program feasibility and acceptability (the CoMBo study). We hypothesize that (1) this program will be acceptable to staff and participants and (2) offering once-weekly CM (as opposed to multiple-times per week) to achieve stimulant reduction (as opposed to abstinence) in low-barrier medical homes of people living with HIV will be feasible.

CoMBo Study Objectives

The following are the objectives of this study:

1. To evaluate the feasibility of once-weekly CM in safety-net HIV ambulatory care to decrease stimulant use and improve ART adherence
2. To qualitatively assess the acceptability of CM offered in safety-net HIV ambulatory care to participants and care providers

Methods

CoMBo Study Design

We will conduct a pilot, single-arm, hybrid implementation effectiveness trial of dual-incentive CM targeting stimulant use reduction and improved ART adherence in 2 low-barrier, ambulatory HIV clinics. We use the Behavior Change Wheel framework to tailor this intervention to meet the needs of our target safety-net population (Table 1). This study design will

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allow for the investigation of implementation feasibility in our target setting, while also gathering data on the intervention's impact on target behaviors. The study will occur over a period of 9 months; patient recruitment will occur during the first 6 months of the study on a rolling basis. Following this pilot, we will solicit feedback on intervention acceptability using in-depth qualitative interviews with participants and clinic staff. The study has been registered as a clinical trial (ClinicalTrials.gov NCT06564792).

Table 1. Formative intervention components for targeting behavior change in safety-net ambulatory care, as described by the Behavior Change Wheel framework [26].

Source of behavior	Example of barriers to behavior change	Intervention component	How will intervention component facilitate behavior change?
Motivation (reflective and automatic)	Complete abstinence following a long period of dependence may be unrealistic, intimidating, or unwanted	1. Assess stimulant use reduction using once weekly using point-of-care tests with a 2- to 4-day detection window	Incentivization: create expectation of reward
Motivation (reflective)	Internalized stigma around psychosocial factors (eg, substance use and housing instability) leads to low self-belief in ability to change behavior	2. Engage in motivational interviewing, emphasizing self-talk and goal setting and providing social support	Persuasion: induce positive or negative feelings to stimulate actions
Opportunity (physical and social)	Limited resources to schedule and keep consistent in-person appointments (eg, limited access to phone, transportation)	3. Offer drop-in, one-on-one visits	Environmental restructuring: change physical and social context

Study Setting

This study will be conducted at 2 subclinics at San Francisco General Hospital's Ward 86, one of the oldest HIV clinics in the country serving more than 2600 people living with HIV in the county safety net. Ward 86 provides wraparound care with co-located behavioral health, social work, case management, laboratory, and pharmacy services. The Women's Clinic is an interdisciplinary, team-based model of care providing HIV, substance use disorder, drop-in services, and mental health care to people identifying as cis- or transwomen living with HIV at Ward 86, serving 234 patients as of July 2022. The POP-UP clinic is another interdisciplinary, team-based clinical program within Ward 86 providing low-barrier, drop-in primary care to patients with HIV experiencing homelessness. At least 30% of the Ward 86 population report regular stimulant use, with approximately 40% of Women's Clinic patients and 90% of POP-UP patients reporting stimulant use. By co-locating CM into low-barrier medical homes for vulnerable people living with HIV, we aim to decrease barriers to CM engagement for patients with comorbid stimulant use disorder and HIV.

Study Population and Inclusion and Exclusion Criteria

Recruitment, enrollment, and study procedures will occur at Ward 86, with targeted recruitment from the aforementioned clinics. We aim to recruit participants living with HIV who (1) are on tenofovir-based ART regimens, (2) are diagnosed with severe stimulant use disorder (according to the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria, measured with the Structured Clinical Interview for DSM-5, using at least near daily), (3) have suboptimal ART adherence (defined as at least one instance of HIV viral load over 200 copies/mL in the preceding 18 months or reporting periods of discontinuation within last 18 months), (4) are interested in reducing frequency of stimulant use and improving ART adherence, and (5) speak either English or Spanish [26]. On the basis of the estimated prevalence of comorbid stimulant use disorder and HIV within our target safety net, we aim to recruit approximately 40 participants.

Recruitment and Informed Consent

Primary care providers within the safety net may refer participants via email or direct messaging through the electronic health record system (Epic), and participants may also spontaneously walk-in for enrollment without a referral. Eligibility criteria are assessed via phone (for referrals) or in-person (for walk-ins) and confirmed via the electronic health record (last detectable viral load, confirmation of stimulant use disorder diagnosis, and ART regimen) before enrollment. Participants who meet the eligibility criteria are offered an enrollment visit, in which they provide informed consent and complete baseline assessments.

Intervention

Description

Enrolled participants who have provided informed consent will complete baseline surveys and urine testing (Table 2), then come to the clinic (in-person) once weekly for 12 weeks. During CM visits, participants will engage in motivational interviewing (MI) and provide urine for POC tenofovir and stimulant testing, with escalating incentives for a longer duration of stimulant-free and tenofovir-containing urine (Figure 1) [27]. Of note, incentives will not require both behavioral targets to be met. For example, if a participant's urine tests positive for tenofovir but also for cocaine, they would receive draws for tenofovir but not for stimulants. At the next study visit, the stimulant-related draws would reset to 2 (if no stimulant in urine) with a rapid reset procedure for each target behavior following a lapse in target behavior (or missing sample).

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Table 2. Assessment variables and schedule for dual-incentive contingency management in HIV primary care.

Domain and assessment	Stage of collection	
	Baseline	Study visits
Sociodemographics		
Gender, age, housing status, and race or ethnicity	✓	
Substance use history		
Substances currently using	✓	
Route of use	✓	
Overdose history, from what substances?		
7-d timeline follow-back[a]	✓	✓
Severity of dependence scale[a]	✓	
HIV history		
Last detectable viral load	✓	✓
3-point Medication Adherence Assessment[a]	✓	
"Did you take [medication] more, less, or the same this week compared to last week?"		✓
Point-of-care results		
Tenofovir detected	✓	✓
Stimulants detected	✓	✓
Other substances detected	✓	✓
Visit characteristics		
Length of visit	✓	✓
Number of incentives earned		✓
Amount earned	✓	✓

[a]Use of the validated assessment tool.

Figure 1. Intervention description. ART: antiretroviral therapy; NEG: negative; POC: point of care; POS: positive; SCID-5: Structured Clinical Interview for DSM-5.

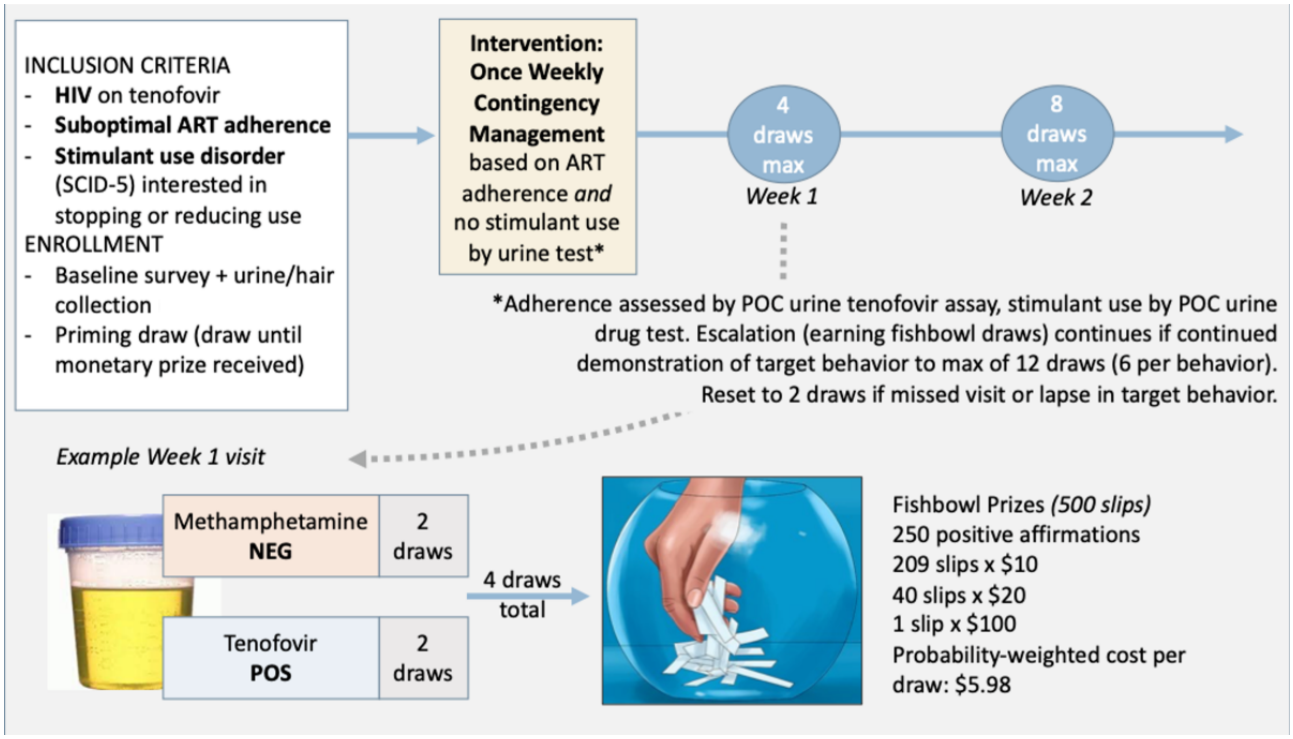

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All visits will occur in-person in clinic on the same day of the week. Participants will be invited to drop-in for study appointments anytime during clinic hours (9 AM to 5 PM). Visits are estimated to last approximately 20 minutes.

The following key tenets of CM will be adhered to: (1) frequently monitoring the behavior of interest (eg, stimulant use and adherence assessed weekly); (2) tangible, immediate positive reinforcement after confirmation of behavior of interest (eg, POC testing allows for immediate provision of incentives if indicated); and (3) positive reinforcement (ie, incentives) withheld if behavior of interest is not demonstrated [21]. We will use the prize method for reinforcement provision (also known as the "fishbowl method," established by CM authority Dr Nancy Petry), in which participants earn an escalating number of draws from a fishbowl containing paper slips with variable monetary value [28,29]. As specified by distribution of paper slips, patients have a 50% chance of drawing a monetary incentive and 50% chance of drawing an affirmation with an encouraging message (no monetary value; Figure 1). In keeping with this method, participants will receive a "priming draw" at their enrollment visit, in which they draw from the fishbowl until they receive a monetary prize, regardless of their POC results. If a participant misses a visit or does not provide evidence for the target behaviors, the number of draws related to that behavior resets to zero (ie, stimulant positive urine will reset stimulant-related draws to zero).

Theory for Formative Components

To customize the CM intervention to our target safety-net population, we used the Behavior Change Wheel framework to identify population-specific barriers to behavior change and created intervention components to address these barriers (Table 1). These formative components are discussed in the subsequent sections.

Incentivizing Stimulant Use Reduction

We hypothesize that incentivizing stimulant use reduction rather than abstinence will be acceptable to our target safety-net population with comorbid stimulant use disorder and HIV. One challenge to incentivizing stimulant use reduction is that no POC tests measure quantitative levels of cocaine or methamphetamine and thus cannot determine if one positive result represents a reduction or increase in use compared to another positive result. To overcome this challenge, we will assess stimulant use once weekly using POC tests with an approximate 4-day detection window. This would theoretically allow participants to continue using substances some days of the week, but still test negative for stimulants on POC tests if they do not use in the days preceding testing. Given that (per inclusion criteria), participants endorse using stimulants most days of the week (if not daily), we theorize that a negative result will constitute a true sign of use reduction.

Offering Drop-In, Individual Visits

The need to adhere with scheduled clinic appointments is a frequently cited barrier to engagement in care for vulnerable populations, including people living with HIV. Emerging models of care have shown that offering low-threshold, drop-in visits without an appointment can circumvent this barrier to achieve robust improvement in care engagement and target health outcomes; one such model is demonstrated in the POP-UP clinic, one of this study's 2 host clinics, wherein more than 50% of enrolled, viremic patients experiencing homelessness achieved viral suppression within 6 months [30,31]. In keeping with low-barrier principles, we expect that offering drop-in visits will optimize engagement for safety-net patients with complex psychosocial factors.

Incorporating MI

MI is a psychosocial interviewing technique that aims to enhance intrinsic motivation by eliciting statements that amplify and reinforce a patient's commitment for behavioral change [32]. Several meta-analyses have shown that interventions using MI have had some effect on reducing substance use (including stimulants) and that pairing MI with CM interventions may lead to more durable behavior change [33]. In addition, integrating MI into CM study visits can help promote relationship building between patients and CM providers, which we expect will be particularly important for cultivating trust among patients with negative past health care experiences related to substance use or HIV-related stigma [33].

CM Provider and Training

One CM provider will be trained to lead all CM activities with supervision by the principal investigator, an addiction medicine specialist. Training includes (1) POC device training; (2) completing the free, virtual "Contingency Management Overview Training" offered by the Recovery Incentives Program at the University of California, Los Angeles; (3) addiction medicine–specific intensive MI through a 2-day training workshop [34].

Materials

At enrollment, participants will receive a visual schema describing the incentive structure and indicating where or when they may come in for CM visits (Multimedia Appendix 1).

The materials required for conducting study visits include fishbowl with paper slip incentives (Figure 1), stimulant POC tests, tenofovir POC tests (Figure 2), gift cards, and sign-out sheets (to confirm receipt of gift cards and record barcodes, as required by our funding mechanism), and timeline follow-back form (Multimedia Appendix 1).

The number of incentives earned during each visit will be automatically calculated via REDCap (Research Electronic Data Capture; Vanderbilt University; calculated field using special functions) after input of POC results.

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Figure 2. Novel point-of-care urine tenofovir test.

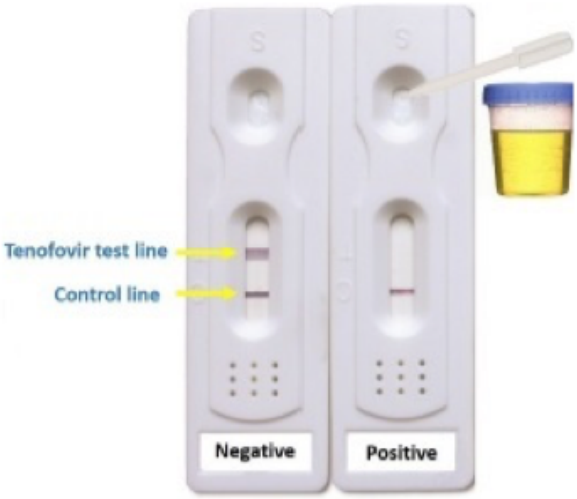

Assessment and Data Collection

All data will be captured and stored using REDCap electronic data capture tools hosted at University of California, San Francisco [35,36]. Most data metrics (described in Table 2) will be extracted from patient interviews during baseline and study visits, although viral loads will be extracted from patient's electronic medical record.

Baseline assessments (Table 2) will extract patient variables relating to sociodemographics, substance use history, and HIV history, including HIV viral load before participation. We will also collect POC results at baseline (although no incentives will be earned from these results), perform 7-day timeline follow-back to assess baseline frequency of stimulant use, and record visit-related characteristics (length of visit and amount in US $ received through a priming draw; Multimedia Appendix 1) [37].

Visit assessments will assess recent stimulant use and ART adherence, capture POC results, and record visit characteristics (including number of incentives earned). At each visit, we will objectively assess each target behavior through POC testing (used to calculate incentives), subjectively assess stimulant use using 7-day timeline follow-back, and subjectively assess ART adherence using a 3-point Likert scale question (Table 2).

Upon intervention conclusion after 12 study visits, we will record the viral load most proximate to the patient's last attended visit.

Evaluation Frameworks and Outcomes

Quantitative Evaluation

We will leverage the RE-AIM (reach, effectiveness, adoption, implementation, and maintenance) framework (Table 3) to quantitatively evaluate feasibility, reach, effectiveness, and intervention implementation.

Per our first study objective, we aim to evaluate the feasibility of implementing this intervention in the safety-net, ambulatory HIV care setting, which we will assess using various domains of the RE-AIM evaluation framework. Our primary outcome will be defined via engagement: 50% CM visit attendance will indicate a threshold for program feasibility. Secondary feasibility outcomes will include number of visits performed, average visit time, and monetary value earned per participant, which map to domains (Table 3). Metrics related to "reach" will assess if the proposed implementation model will be used by a diverse patient population with complex sociomedical needs (as intended), reflecting both the utility and accessibility of this program. "Effectiveness" metrics will seek to establish if the intervention modified the target behavior changes, leading to reduced stimulant use, improved ART adherence, and undetectable HIV viral loads. "Implementation" metrics will describe the costs required to start and maintain this program during the study period (8 months). Our secondary outcome is preliminary effectiveness, which we will determine using proportion of stimulant-negative and tenofovir-positive urine tests, as well as changes in HIV viral suppression before and after participation. We will report missing data and impute missing viral load data as >200 copies/mL.

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Table 3. RE-AIM (reach, effectiveness, adoption, implementation, and maintenance) framework evaluation of dual-incentive contingency management targeting antiretroviral therapy adherence and stimulant use in ambulatory HIV care.

Dimension	Question	Outcomes
Reach	• Will safety-net patients living with HIV and stimulant use disorder enroll in this program? • Will they return after enrollment?	• Sociodemographics • Substance use and HIV histories • Proportion of study visits attended
Effectiveness	• Will participants reduce stimulant use? • Will participants improve tenofovir adherence?	• Weekly point-of-care results and 7-d timeline follow-back
Adoption	• Will offering this program in the ambulatory HIV care setting be acceptable to staff and participants? • What changes, if any, would make the program more or less acceptable?	• Qualitative evaluation
Implementation	• What were the monetary and other resource costs of program implementation?	• Length of visits • Total gift cards provided (amount in US $) • Proportion of incentives earned for stimulant use versus tenofovir adherence • Number of point-of-care tests used • Time spent on participant outreach
Maintenance	• Not assessed in this pilot	__[a]

[a]Not applicable.

Qualitative Evaluation

Per our second study objective, we will qualitatively evaluate program acceptability to participants and health care staff following the Consolidated Framework for Implementation Research (CFIR). Constructs describing acceptability are encompassed by “adoption” and seek to describe circumstances and factors that influence intervention engagement among participants and synergy within the ambulatory HIV care ecosystem.

Sampling and Recruitment

Participants will be asked to engage in the qualitative evaluation following study completion (week 12 from enrollment), during either the end of their final study visit or when they return to the home clinic for routine care. Any participant who enrolled and completed at least one study visit will be eligible to enroll. Eligible staff will be identified by the study coordinator, who will recommend staff who meaningfully contributed feedback regarding the pilot rollout or who interfaced with the pilot’s day-to-day functioning. For example, we anticipate the clinic’s head nurses and primary social workers to meet this criteria.

Data Collection

Interviews will occur at each home clinic during clinic hours. They will be conducted by 1 to 2 trained researchers with extensive experience conducting qualitative interviews and background in HIV or addiction medicine. Participants will be consented by the interviewer before the interview. In-depth interview guides have been developed using the CFIR framework in order to systematically evaluate setting, intervention, individual, and process characteristics influencing program acceptability (Table 4; Multimedia Appendices 2 and 3). All interviews will be recorded; the interviewer will refrain from using identifying language during the record process, for example, by using participants’ study ID numbers instead of their name. Interviews are estimated to last approximately 45 minutes. Each interviewee will receive US $50 worth of gift cards for their participation.

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Table 4. Consolidated Framework for Implementation Research (CFIR) framework for qualitative evaluation of program acceptability in low-barrier, ambulatory HIV care.

Target interviewees, CFIR domain, and CFIR construct	Question examples
Care providers and staff who were involved with study participants (n=10)	
Inner setting	
Compatibility	How compatible was this intervention with existing work processes at the clinic?
Tension for change	Is there a need for this intervention?
Relative priority	How important is it to provide this intervention, compared with other priorities?
Networks and communication	How have you referred participants?
Characteristics of the individual	
Knowledge and beliefs	How do you feel about this intervention being offered at [clinic name]?
Participants who attended >50% of study visits (N=7); participants who attended <50% of study visits (N=7)	
Intervention characteristics	
Relative advantage	How would your experience be different if you had to schedule visits instead of dropping-in?
Process	
Engaging	How easy or difficult was it to participate in the program?
Executing	What did you think about getting urine results for both stimulants and tenofovir?
Reflecting and evaluation	How do you think you benefited from this program?

Participant Interviews

We will create a purposive sample of 14 trial participants, with priority recruitment of at least 7 participants who completed fewer than 50% of CM visits and 7 participants who completed more than 50% of CM visits (Table 4). This sample size will largely depend on the number of participants recruited, but we aim to interview approximately 30% of our total target sample size (ie, 14 participants in a pool of 40). Interviews will seek to (1) understand participant experiences in the primary care–based, stimulant, and adherence-targeted CM intervention and (2) explore how multilevel factors might positively and negatively influence engagement with multitarget CM (eg, role of relationships in the clinic, and concurrent synergistic clinical goals such as gender-affirming surgery, intervention factors such as drop-in visits, and reinforcement schedule, etc). We are secondarily interested in identifying how participant goals for stimulant use reduction are related to HIV management, if at all, and how drivers of stimulant use and additional determinants of health (eg, homelessness, intimate relationships, etc) interact with HIV and stimulant use disorder management.

Care Provider and Staff Interviews

We will also conduct qualitative interviews with 5 to 10 care providers and staff who were involved in participants' care or who interfaced with the intervention's activities (eg, referred participants and assisted with program logistics). This final sample size will depend on how many care providers meaningfully interact with this pilot; we have identified a minimum of 5 care providers whose roles interface with the intervention, and we expect this number to increase as we integrate the problem into the everyday functioning of our target clinics. We seek to investigate perceived appropriateness of dual-incentive CM in the low-barrier HIV care context, elucidating perspectives on (1) the intervention's compatibility with existing clinic processes, (2) how well the intervention met clinic needs and relative importance of these needs, and (3) changes to promote long-term sustainability.

Analysis Plan

Quantitative Evaluation

We will analyze reach and implementation metrics (Table 3) using basic descriptive statistics. For effectiveness, we will use descriptive statistics to describe POC results, including the proportion of negative-stimulant and positive-tenofovir tests each week and cumulatively overall and the number of participants that test negative for stimulants or positive for tenofovir at least once. We will also report the average frequency of use as captured by weekly timeline follow-back and compare average use at baseline versus study visit 12 (ie, the final visit) using a paired 2-tailed *t* test. We will use the McNemar test to compare the proportion of participants with HIV viral loads less than 200 copies/mL before and after CM participation.

Qualitative Evaluation

To analyze our qualitative data, we will follow the main principles of "scientifically descriptive" thematic analysis as defined by Finlay [38] and further elucidated by Braun and Clarke [39]. Audio recordings will be professionally transcribed into Microsoft Word documents and saved on a secure, password-protected, cloud-based folder that is only accessible to the research team. As traditional qualitative coding is a well-documented, lengthy process, we will use the framework analysis approach to efficiently generate findings with a small team [40,41]. We will first develop a spreadsheet in which we plot the key CFIR constructs outlined in Table 4 across the x-axis and individual research participants across the y-axis.

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One of the researchers who conducted both patient and care provider interviews (LS) will then review each transcript and copy and paste individual excerpts into the appropriate columns in the spreadsheet. For example, if a patient mentions that they would have trouble keeping an appointment if that was required for participation in the study, this information will be recorded in the "Relative Advantage" column. To keep with the definition of scientifically descriptive thematic analysis by Braun and Clarke [39] and ensure confirmability of findings, a second researcher on the team (AA) will then cross-check a select subset of transcripts and meet with LS to discuss any discrepancies and reach consensus. To enhance reflexivity, the analysts will maintain awareness of how their academic backgrounds may shape data collection and interpretation, ensuring that participants' experiences with stimulant use disorder and HIV are centered in the analysis.

Ethical Considerations

This study was approved by the Institutional Review Board at University of California, San Francisco (23-38747). Written informed consent will be obtained from participants before enrollment, consenting to study activities, review of electronic medical records by research staff, and secondary analyses using study data. Consents will be available in English and Spanish (Multimedia Appendices 4 and 5). Participants may opt out of the study at any point.

To maintain participant privacy, any data relating to the study will be stored in either REDCap or an encrypted Box folder hosted by the University of California, San Francisco. Only members of the research team will have access to any participant data stored in REDCap. Study data will not be recorded or linked to the patients' electronic medical records. Audit of gift cards will be performed by the San Francisco Department of Public Health, per the Controller's Office protocol. No participants currently incarcerated will be enrolled in this study.

Compensation will be provided for participation in the qualitative evaluation and will consist of a US $50 gift card that can be used at most grocery stores.

Results

As of September 26, 2024, a total of 37 patients have been recruited and they completed 12 weeks of CM. Analysis of quantitative metrics for RE-AIM evaluation has concluded as of June 2025. Qualitative evaluation has begun, with 10 participants and 7 staff interviewed. Interviews concluded as of January 2025, and analysis is underway.

Discussion

This work may demonstrate that once-weekly CM targeting both stimulant use disorder and ART adherence can be feasibly implemented in safety-net ambulatory care settings, as defined by the RE-AIM framework. In addition, we may demonstrate through qualitative analysis that such a program is acceptable to both patients and care providers who work in safety-net ambulatory care settings. We anticipate that this single-arm trial will inform any subsequent larger trials investigating the efficacy of offering CM in the HIV primary care setting.

Implementing CM interventions in real-world settings is a critical first step toward reducing morbidity and mortality from stimulant use disorder. Implementation in safety net, ambulatory HIV care—with targeted sampling among patients experiencing homelessness—will help meet the urgent needs of medically complex individuals at high risk for complications of substance use. This protocol offers the opportunity to address syndemic behaviors through one intervention—namely, the related behaviors of stimulant use and ART nonadherence. The success of this pilot would demonstrate the feasibility of offering this evidence-based treatment in HIV ambulatory care and provide a scalable model for implementation in similar safety-net settings. By assessing acceptability through qualitative interviews, we aim to center community voices and align this program with the goals, needs, and lived experiences of people living with HIV and stimulant use disorder.

While abstinence from stimulant use is thought to provide the most clinical benefit (albeit less feasible), use reduction is emerging as an important and meaningful treatment outcome for patients with stimulant use disorder [42]. Moreover, as the field of addiction is evolving to understand addiction as nuanced and multifaceted, we must offer a wider range of treatment implementation options that meet a diversity of patient goals, which may encompass both abstinence-based and reduction-based approaches. In the HIV space specifically, holistic care should address substance use and its related health behaviors, such as reduced rates of ART adherence. Emphasis on reducing stimulant use for people living with HIV and stimulant use disorder may serve as a vehicle to improve overall health among highly susceptible patients.

The use of tenofovir POC assays represents an important advancement, but the inability to rapidly test other forms of ART limits this program to patients on tenofovir-based regimens. This requirement excludes individuals on long-acting ART that are not tenofovir based, although other incentive structures to support injection adherence could be considered. In addition, no POC tests can rapidly quantify stimulant use, thus we rely on indirect methods for assessing stimulant use reduction. While this study targets the enrollment of patients with severe, frequent stimulant use, this program may not be optimally effective for individuals who desire abstinence or with less frequent stimulant use at baseline. Finally, we rely on participant self-report to establish ART nonadherence, which is subject to bias.

This study describes a novel CM program that (1) offers dual incentives targeting the syndemic behaviors of stimulant use and ART nonadherence, (2) uses a novel tenofovir urine assay for POC ART testing, and (3) incentivizes stimulant use reduction. In addition, we describe a protocol for evaluating implementation feasibility in HIV ambulatory care and acceptability to participants and staff. Demonstration of a feasible model that is acceptable to participants with HIV and stimulant use disorder may serve as a first step toward wider use of CM in the safety-net setting and can help meet critical needs in this population.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
HIV and stimulant use contingency management study details.
[PNG File , 260 KB - resprot_v14i1e67292_app1.png]

Multimedia Appendix 2
Patient-facing interview guide.
[DOCX File , 30 KB - resprot_v14i1e67292_app2.docx]

Multimedia Appendix 3
Staff-facing interview guide.
[DOCX File , 32 KB - resprot_v14i1e67292_app3.docx]

Multimedia Appendix 4
Consent form in English.
[DOC File , 89 KB - resprot_v14i1e67292_app4.doc]

Multimedia Appendix 5
Consent form in Spanish.
[DOCX File , 29 KB - resprot_v14i1e67292_app5.docx]

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Abbreviations

ART: antiretroviral therapy
CoMBo: Contingency Management for Both HIV and Stimulant Use Disorder
CFIR: Consolidated Framework for Implementation Research
CM: contingency management
MI: motivational interviewing
POC: point of care
REDCap: Research Electronic Data Capture
RE-AIM: reach, effectiveness, acceptability, implementation, and maintenance

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Protocol

Ethical Principles Pertaining to the Care of People With Dementia: Protocol for a Qualitative Thematic Synthesis of Legal Documents

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Abstract

Background: The global prevalence of dementia presents profound challenges for health care systems, societies, and legal structures worldwide. While the ethical dimensions of dementia care have been extensively discussed in the literature, limited research addresses how ethical principles are effectively operationalized within legal frameworks governing dementia care.

Objective: We aim to explore how national, European, and international legal instruments integrate and translate ethical principles such as autonomy, dignity, beneficence, and justice into dementia care legal documents, including case law and legislation.

Methods: This study will be conducted by a team of 24 researchers from 15 European countries, within a European Union (EU)–funded European Cooperation in Science and Technology Action on dementia care. The project applies a combined methodological approach, using qualitative thematic synthesis and a legal document review framework. Legal documents published between 2010 and 2025 will be searched and qualitatively analyzed at 3 levels: national, EU, and international, including legislation, case law, and authoritative legal literature explicitly addressing dementia care. Researchers from each country will conduct searches in national legal databases using predefined search terms. At the EU and international levels, databases such as Westlaw, Lexis+, the European Court of Human Rights, and the European Ombudsman will be consulted. Key information from each document will be collected using a standardized data extraction tool, focusing on ethical principles and frameworks. Data analysis will combine deductive and inductive approaches, allowing the identification of ethical principles and the emergence of new

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concepts discussed in the documents. Thematic analysis will follow a 3-stage process: line-by-line coding, grouping codes into descriptive themes, and developing analytical themes to address the research questions.

Results: This study will identify and categorize ethical principles embedded in legal documents, analyzing their expression, interpretation, and variability across jurisdictions. The project is scheduled to be implemented throughout 2025. In January 2025, a pilot test of the data extraction tool was conducted. Between February 2025 and April 2025, a systematic search of legal documents meeting the inclusion criteria was performed, applying a structured 3-level search strategy. Data extraction and initial coding are planned from May 2025 to July 2025, followed by data analysis between September 2025 and October 2025, through iterative coding and collaborative discussion. The final research paper will be drafted in November 2025.

Conclusions: This cross-country thematic synthesis will provide critical insights into how ethical principles guide dementia care and shape its discussion within legal systems. By systematically analyzing legal instruments through an ethical lens, this study aims to bridge the gap between ethical theory and legal practice, offering valuable guidance for future policy development. The findings will contribute to promoting ethically grounded and legally coherent frameworks for dementia care, safeguarding the rights and dignity of individuals living with dementia across diverse legal cultures.

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KEYWORDS

dementia care; legal frameworks; ethical principles; thematic synthesis; cross-country analysis

Introduction

Background

The global prevalence of dementia is rising rapidly, presenting significant challenges for health care systems and societies worldwide. With the number of people living with dementia projected to triple by 2050 [1], there is an urgent need for legal frameworks that effectively address the ethical and practical concerns of dementia care. Ethical issues in dementia care typically arise when conflicting ethical principles or values generate uncertainty about the most appropriate course of action. While such dilemmas may have been less visible in earlier periods characterized by more paternalistic approaches to patient care, contemporary ethical and legal frameworks demand a more explicit and transparent consideration of ethical principles when supporting individuals living with dementia.

In caregiving contexts, these ethical challenges often emerge when individuals with dementia express preferences or make decisions that their caregivers perceive as imprudent or unsafe, for instance, the desire to continue driving despite clear evidence of cognitive decline. In legal or institutional settings, ethical concerns may involve the use of coercion in nursing homes, questions of testamentary capacity, or the individual's ability to manage and dispose of personal property while experiencing progressive cognitive impairment and residing in a health care facility. Although extensive literature exists on the clinical and ethical dimensions of dementia, limited research has explored how legal frameworks operationalize ethical principles, particularly in the context of dementia care.

Legal frameworks, including binding legal instruments, such as international treaties, national legislation and case law, and nonbinding normative instruments, such as, guidelines determining legal relationships, rights, and duties or legal literature, play a crucial role in shaping dementia care, defining the rights and entitlements of individuals, and setting standards for the quality of care provided. These frameworks potentially have an impact on various aspects of life for people with dementia, including their right to receive appropriate care, promote their autonomy and decision-making capacity, maintain their dignity, and participate in society. The legal frameworks may be linked or otherwise include, either explicitly or implicitly, reference to or discussion of ethical principles. Under legal positivism, ethics, which is a subcategory in the discipline of philosophy, is separated and distinguished from law [2,3]. Yet, both ethics and law act as normative systems guiding human behavior. A natural law approach would argue that a law may serve as a formal expression of ethics, enforcing morality and promoting ethical values in society [4]. More generally, a law seeks to guide actions and decisions in many areas, including dementia care. It may establish exclusive rights, such as the right to receive proper care or make care decisions, and inalienable rights, such as the right to respect for human dignity [5]. Aside from and independent of the vast literature discussing ethics of dementia care [6-10], the law can be viewed as translating broad ethical principles into specific, actionable rules and regulations through the language of rights [11], which makes compliance with these principles mandatory. At the same time, by applying ethical principles, legal frameworks may gain more legitimacy and acceptance in their effect and power within society.

Research on the ethical principles underpinning, discussed, or referenced by legal frameworks is very limited, and, to the best of our knowledge, there are no studies systematically appraising ethical principles integrated into law within the field of dementia. Therefore, a thorough exploration and understanding of how and which ethical principles are integrated into laws governing dementia care is much needed and particularly vital in the clinical and policy contexts. Identifying the ethical principles and qualitatively understanding their role in legal regulation will make it possible to discern whether there is consistency between law and recognized ethical principles in dementia care.

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Objectives

This study aims to address this gap by providing a comprehensive cross-country thematic synthesis of the ways in which ethical principles play a role and are integrated into legal frameworks governing dementia care. Specifically, it seeks to comprehensively identify, explore, and categorize the spectrum of ethical principles related to dementia care as reflected in national and international legal frameworks and reported in various legal documents. In addition, this thematic synthesis aims to explore and analyze ethical conceptual frameworks such as the United Nations Charter on Human Rights or other national and international structures referred to in the legal documents. The study results will have the potential to inform policy and ultimately improve care for individuals with dementia.

Methods

Overview

This study aims to explore and examine the qualitative expression and role of ethical principles and ethical frameworks as reported in legal documents, which is described in the subsequent sections. This research project seeks to answer the following key questions:

1. How are ethical principles such as autonomy, dignity, and beneficence operationalized in national and international legal frameworks?
2. What are the most common ethical frameworks referenced in dementia care legislation, and how do they vary across different jurisdictions?
3. How can legal frameworks better harmonize ethical principles across countries to provide consistent care standards for individuals with dementia?

For the purposes of our study, we use the definitions mentioned in subsequent sections, which are also summarized in Textbox 1, along with key examples.

Textbox 1. A tentative summary of ethical and legal perspectives to explore.

Ethical principles

- Autonomy
- Nonmaleficence
- Beneficence
- Justice
- Informed consent

Ethical frameworks

- Human rights
- Principlism ethics
- Justice based

Legal documents

- Legislation
- Case law
- Administrative guidelines
- Literature in legal journals

Moral obligations and duties

- Dignity
- Person centeredness
- Individuality, including political and democratic participation
- Privacy and confidentiality

Principles (Including Ethical Principles)

In this study's context, *principles* should be understood in the broadest possible sense. We define ethical principles as any generic normative claim, that is, claims about what one ought to do or what is good or bad and right or wrong. Thus, ethical principles include the classical principles of biomedical ethics, such as autonomy, nonmaleficence, beneficence, and justice, and encompass broader values, duties, moral obligations, and entitlements (such as dignity, person centeredness, individuality, political and democratic participation, privacy, and confidentiality).

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Ethical Frameworks

In this study's context, ethical frameworks are defined as structured or systematic approaches or an organized set of principles that provide a foundation for assessing ethical issues. Ethical frameworks are meant to assist decision makers (eg, individuals or organizations) in making decisions about what is right or wrong and good or bad in various situations. Examples of such frameworks include the human rights ethical framework, principlism ethics, a justice-based ethical framework, etc.

Legal Documents

For this study, we define legal documents as instruments regulating social aspects of life; establishing rules of behavior in society; disciplining the actions of public administration; resolving legal issues; developing business between people and companies; recording natural and social facts of legal relevance; and, in addition, recording, accumulating, sharing, and preserving theoretical legal knowledge [12]. Examples of these documents include legislation, case law, some administrative guidelines, and the literature published in legal journals.

Design

This study will be conducted by a group of 24 researchers who are members and leaders in a European Union (EU)–funded COST Action on dementia care, representing 15 countries (Albania, Denmark, Estonia, Greece, Israel, Italy, Latvia, Lithuania, Macedonia, Norway, Portugal, Romania, Slovakia, Spain, and Turkey). This multinational team enhances the goals and robustness of the analysis by integrating diverse legal and cultural perspectives on dementia care. In addition, the team's collective expertise in both legal and ethical dimensions ensures a proper understanding of how ethical principles are framed across different legal systems.

To achieve study goals, we will apply the qualitative thematic synthesis (QTS) method, developed by Thomas and Harden [13]. QTS is specifically designed for reviews or other qualitative reports, addressing questions about people's perspectives and experiences that cannot be adequately assessed through traditional statistical analysis. This method is grounded in systematic review principles, combining rigorous search and qualitative coding strategies to formalize the identification and development of themes. It involves 5 consecutive steps. The first step involves *searching* for studies not necessarily to locate every relevant source but in accordance with the range of concepts found in the studies, their context, and whether they are in agreement or not. The second step involves the *quality assessment* of the findings, referring to the quality of reporting the studies' aims, context, rationale, methods, and findings as well as the sufficiency of the strategies confirming the reliability and validity of the data collection tools and methods of analysis. It also refers to the assessment of the appropriateness of the methods at stake. The third step involves *extracting data*, usually including all the data presented under the Findings or Results sections of the studies. The fourth step involves *data synthesis* through coding text and developing themes, including free line-by-line coding and organization of *free codes* into related content areas, to construct descriptive themes. The fifth step includes *generating analytical themes*, that is, making judgments and going beyond the explored content. This last step has been identified as the defining characteristic of synthesis, as it involves conceptual innovation. The choice of QTS methodology for this study is highly appropriate, given the research aims and the types of sources of information to be reviewed, namely legal documents that provide narrations and discussions of ethical issues associated with dementia care. Moreover, QTS has been successfully applied in dementia and the ethics of dementia care [14-17].

Given the legal perspective of this study, we will also apply the framework proposed by Baude et al [18] for conducting a review of legal documents. This framework offers a 4-step process for conducting a review of legal documents. The first step involves *defining the exact question that the subsequent analysis is trying to answer*. Such a question should be precise and legalistic. This step also includes exploring what evidence is required for the question. The second step involves *defining the relevant sample of cases that were analyzed*. This step includes specifically mentioning what process was used to assemble the universe of cases or documents, stating any inclusion or exclusion criteria that were applied to the sample, and documenting the technology of the search process (databases, terms used, etc). The third step involves *stating how the cases in the sample were weighed in the analysis*. Examples of rules establishing proportional weight that are derived from legal doctrine include giving more weight to cases of greater precedential status, which are more recent, cited more frequently or written by more frequently cited judges, or include more analysis on the relevant topic. The fourth step involves *analyzing the sample and answering the question posed*. This step includes mentioning the criteria that were used to analyze the cases or documents, indicating how the cases were analyzed, and stating a conclusion that is supported by the analysis.

The framework by Baude et al [18] helps make legal claims through systematic demonstration of supporting evidence while also referring to the unique elements characterizing legal documents and ensures systematic identification, weighting, and analysis of legal texts. By combining QTS with a structured legal analysis framework, the study rigorously assesses the role of ethical principles in shaping dementia care legislation. This not only substantiates the claim but also allows for the assessment of its certainty or uncertainty, identifies potential disagreements in the referenced sources, reduces the risk of false statements, and helps minimize actual or potential bias, imprecision, subjectivity, and reliance on anecdotal evidence [12,18-20].

Searching, Quality Assessment, and Data Extraction (Stages 1-3 Under QTS)

Our sample will include legal documents discussing ethical principles pertaining to the care of people with dementia following a 3-level systematic search strategy: national, EU, and international.

At the national level, researchers from each of the 15 participating countries will search national legal databases for relevant legal documents in their own languages. The documents

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must constitute either applicable law or rulings, court decisions, and case laws that pertain to dementia care.

At the EU level, the search will include European case law, notably published by the European Court of Human Rights, as well as petitions submitted to and legal decisions published by the European Ombudsman. In addition, the study will include EU regulations that pertain to dementia care. The documents must constitute either applicable law or case law, ensuring that the analysis captures both regulatory frameworks and judicial interpretations. All searched materials at the European level will be in English.

Finally, at the international level, the search will focus on three types of documents: (1) international treaties and covenants as well as rulings and court decisions published by the International Court of Justice or other similar international legal bodies, (2) legal texts from the United Nations and other international organizations that issue binding or influential guidelines and rulings on dementia care, and (3) literature published in international legal databases that can serve as acceptable legal sources and which interpret or apply legal rulings and discuss them. All searched materials at this level will be in the English language only. The inclusion and exclusion criteria for the legal documents are presented in Textbox 2.

Each researcher in the research team will conduct searches in their respective national legal databases according to a table of tasks allocated among members of the group. We will apply the first 2 stages suggested in the framework by Baude et al [18] to conduct a review for legal analysis. This stage will include the substages mentioned subsequently.

The search strategy will include the search terms (in the original language for the national level search and in English for the European and international levels) as presented in Textbox 3.

Textbox 2. Inclusion and exclusion criteria.

Inclusion criteria

- The documents must explicitly but not exclusively mention dementia or conditions that pertain to dementia, for example, dementia care or the rights of people with dementia. The same text may also apply to other conditions, for example, intellectual disabilities.
- The documents must constitute applicable law (actual regulations), case law (rulings, decisions, etc), or the interpretation of it in international peer-reviewed legal literature indexed in legal databases.
- The documents must be published within the past 15 years (2010-2024) to ensure contemporaneity and relevance.

Exclusion criteria

- Gray literature that does not contain legal guidance, such as commentaries, opinions, or policy briefs that do not constitute law or case law, will be excluded.
- Peer-reviewed scientific articles published in nonlegal databases will be excluded.
- Legal documents that do not directly pertain to dementia will be excluded.

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Textbox 3. Search strategy for dementia.

Keywords

- Dement*
- Chronic brain disorder
- Alzheimer
- Neurocognitive impairment
- Cognitive impairment
- Neurocognitive decline
- Cognitive decline
- Neurocognitive loss
- Cognitive deterioration
- Neurocognitive disease
- Cognitive loss
- Neurocognitive dysfunction
- Cognitive disease
- Neurocognitive disorder
- Cognitive dysfunction
- Neurocognitive deficit
- Cognitive disorder
- Neurodegenerative impairment
- Cognitive deficit
- Neurodegenerative decline
- Memory impairment
- Neurocognitive loss
- Memory decline
- Neurodegenerative disease
- Memory loss
- Neurodegenerative dysfunction
- Memory disease
- Neurodegenerative disorder
- Memory dysfunction
- Neurodegenerative deficit
- Memory disorder
- Neurocognitive impairment
- Memory deficit
- Neurocognitive decline
- Neurocognitive loss

The final search strategy will make use of the following databases:

1. European Commission Library and e-Resources
2. Lexis+ (international)—search by country
3. Westlaw International Materials
4. European Court of Human Rights
5. European Ombudsman
6. National case law databases

We selected these databases for their unique characteristics and legal focus. These databases facilitate a comprehensive exploration of ethical principles and frameworks in dementia care that may be reported in legal documents. Texts that are not online or are not indexed under any of the aforementioned databases will not be analyzed.

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The next stage involves reading the retrieved documents to ensure that they meet the inclusion and exclusion criteria. Relevant documents will be collected and cataloged for analysis. Researchers will use a standardized data extraction table to record key information from each document, including the title, publication date, jurisdiction, type of document (law, regulation, and case law), and a summary of the ethical principles mentioned (Multimedia Appendix 1). In addition, the charting form will be based on questions that specifically relate to searching legal documents following the framework by Baude et al [18]. It will allow the researchers to uniformly chart the legal documents for elements relevant to the research question. Moreover, the data charting process will focus on collecting both quantitative and qualitative elements in an effort to facilitate seamless analysis at a later stage. Any research member reviewing the text will be at liberty to add principles or frameworks to the data charting as long as they align with the aforementioned definitions. However, we will maintain detailed records of changes to the list of principles or frameworks, noting when and why a new principle is added or when an existing one is refined. This will enhance transparency and provide a clear audit of the decision-making process of our study. Moreover, we will continually reassess our data, using the updated charting form to check for extensiveness and accuracy in the data.

Data Synthesis and Generating Analytical Themes (Stages 4-5 Under QTS)

Our data analysis process will include data synthesis through coding text and developing descriptive themes referring to the methodology by Thomas and Harden [13] and the framework by Baude et al [18] to conduct QTS.

Overall, to secure a rigorous analysis process, our analysis will use a combination of deductive and inductive approaches [21]. The deductive aspect will involve the use of a list of well-established ethical principles, which may serve as an inspiration for the research analysts (Multimedia Appendix 2). The list has been developed through iterations and in consultation with more general ethical literature discussing dementia, in particular, and care, in general, and following extensive work that has been done in the COST Action [22]. The inductive approach will enable us to identify ethical principles and frameworks without relying on any predetermined conceptual lens. Each analyst will be able to add more principles as the data analysis progresses after agreement on their wording and relevance to the research project among the research group.

The inductive approach will facilitate the identification of ethical principles that meet a predefined threshold of prevalence in our data. In addition, it will enable the reinterpretation of previously analyzed data, as outlined in the charting form. Our qualitative synthesis of the data will take the form of 3 intertwined stages [13]. The first stage is free line-by-line coding of the verbatim findings of the primary collected materials. In this stage, 2 researchers will independently code each line of the text according to its meaning and content at the European and international search levels and, when possible, at the national level. A list of codes will be prepared based on the translation of research principles or concepts put forth by each of the analysts and new principles or concepts added by analysts, when necessary. The second stage is the organization of “free codes” into related areas to construct “descriptive” themes. This process involves constant comparisons between and within codes for the purpose of exploring the similarities and dissimilarities among them. Following that, we will gradually group codes together in hierarchical order, adding and leaving out codes and categories until we establish agreed-upon tree-structured codes. The third stage is the development of “analytical” themes, including making judgment and going beyond the researched content. In this stage, which is regarded as the key characteristic of the synthesis [23], we will refer to the product of our analysis in its capacity to address the research aims and elucidate new concepts, understandings, and meanings concerning the role that ethical principles play in legal documents. Where possible, we will use ATLAS.ti or NVivo software (Lumivero) for the coding process as well as developing descriptive and analytical themes.

Ethical Considerations

Human Participant Ethics Review Approvals or Exemptions

This study involves a QTS of publicly available legal and policy documents and does not involve direct interaction with human participants or include any patient data or personal information. Therefore, formal ethics committee approval was not required, in accordance with international and local guidelines for research involving publicly accessible secondary data.

Informed Consent

As no human participants were recruited or studied directly, informed consent was not applicable. All analyzed materials are legal and policy documents available in the public domain.

Privacy and Confidentiality

This study does not involve the collection or analysis of identifiable personal or sensitive data. All documents analyzed are identified and publicly available. Consequently, there are no concerns regarding privacy or confidentiality.

Compensation Details

No participants were recruited for this study, and no compensation was provided.

Results

We expect to obtain the findings mentioned in the subsequent sections.

Distribution of Ethical Principles

Our analysis will provide a rich description of the distribution of ethical principles of dementia care in legal documents. Such distribution will be made by (1) document type, including the frequency distribution of principles across document types (from most to least prevalent) and the qualitative explorations of each of these principles by document type; (2) chronological trends, identifying evolutionary patterns in the discussion and prioritization of ethical principles; and (3) target population, pointing to the differences, if any, of the discussions of ethical

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principles in documents focusing on persons with dementia compared to formal and family caregivers.

Principle Conflict Identification

We will describe the distribution of cases that address conflicts between ethical principles, for example, autonomy versus beneficence, or professional obligations versus family preferences. Such conflicts will be analyzed by document type, chronological trends, and target population.

Qualitative Analysis of Key Principles

The key principles that will be found across the documents will be qualitatively analyzed by describing and discussing their expected codes and contexts. For example, we believe that concerning the principle of personal autonomy, expected codes may include self-determination, informed consent, capacity assessment, supported decision-making, and advance directives. The expected context of these principles is likely to be framed differently based on the document type, with legal documents emphasizing procedural aspects of autonomy, while clinical literature may focus on relational autonomy concepts.

Resolution Frameworks

Legal documents that will include tensions or conflicts between ethical principles will also be described according to prevalent theories by which they will be resolved, for example, principlism, care ethics, rights-based approaches, consequentialism, casuistry (case-based reasoning), and the like.

Qualitative Analysis of Resolution Strategies

Legal documents that will include tensions or conflicts between ethical principles will also be qualitatively analyzed. Expected codes include balancing tests, best interests assessments, substituted judgment, procedural safeguards, shared decision-making, ethics consultation, and proportionality analysis.

Judicial Analysis

For case law only, we also expect to have additional results pertaining to the (1) significance of ethical principles, referring to the question of how much of a central role ethical principles play in the judicial decisions addressing relevant care situations; (2) judicial disagreement**,** examining the proportion of cases that will show split opinions or dissents specifically related to the interpretation or prioritization of ethical principles; (3) normative hierarchy analysis, assuming that principles with strongest legal protection (legislation and constitutional rights) will typically prevail over principles derived from lower-ranked sources, such as case law or policy documents; and (4) citation analysis, including citation rates, that is, the proportion of documents that include citations to other ethical sources or precedents, the ethical principles receiving most citations, and citation sources of ethical principles**.**

Unexpected Data Patterns and Proposed Timeline

Along these expected results, we will remain alert to unexpected patterns in the data, such as the emergence of newer ethical principles not traditionally emphasized in bioethics literature, significant jurisdictional differences in ethical approaches, or novel resolution frameworks not anticipated in the initial coding structure.

Given the changing and updating nature of law and legal materials, we propose the timeline for this project:

- January 2025; a pilot test of the data extraction tool was conducted.
- February to April 2025; a systematic search of legal documents meeting the inclusion criteria was performed, applying a structured three-level search strategy.
- May to July 2025; data extraction and initial coding are planned.
- September to October 2025; data analysis will be conducted through iterative coding and collaborative discussion.
- November 2025; the final research paper will be drafted.

Discussion

Anticipated Findings

This study seeks to advance our understanding of how ethical principles are embedded within legal frameworks relating to dementia care, within the national legal systems of the participating countries as well as in wider EU and international legal frameworks. We anticipate that our analysis will reveal the extent to which ethical principles, such as autonomy, dignity, beneficence, and justice, are expressed, interpreted, or contested within binding legal texts and normative legal instruments. Moreover, by examining legal materials from 15 countries alongside the European and international instruments, we expect to identify jurisdictional variability and differing interpretations of ethical principles. Provided that we identify such variability in our analysis, this will be reported in the final study.

In addition, we expect to find both direct and indirect references to ethical principles, which may be framed through rights-based discourses, procedural safeguards, or institutional responsibilities. Through this, this study will contribute to a better understanding of the legal translation of ethical norms and the degree to which such norms are enforceable, aspirational, or symbolic in national and supranational regulatory contexts.

While substantial literature exists on the ethical aspects of dementia care, to the best of our knowledge, no studies have explored their concrete integration in legal instruments. The 2009 Nuffield Council on Bioethics report on dementia [24] remains a foundational document, emphasizing the need to uphold values such as respect for autonomy, social inclusion, and balancing risks with potential benefits in dementia-related decision-making. However, the report stops short of exploring how these values are formalized and protected in law across different jurisdictions. Similarly, Strech et al [10] offered a systematic review of ethical issues in dementia care, identifying a broad range of dilemmas, particularly regarding consent, risk management, and personhood, but without addressing the legal codification of these challenges. Finally, Johnson and Karlawish [25] reviewed emerging ethical issues in dementia care but did not examine how these issues and principles are addressed within legal frameworks.

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More recent works [7] have focused on specific areas such as supported decision-making and legal tools for addressing manifestations of dementia, yet there is no comparative, systematic thematic analysis of legal instruments through an ethical lens.

Our study builds on this gap by applying legal and philosophical frameworks in tandem to assess how ethical principles function within regulatory texts, which allows us to explore not only the principles that are present but also how they are interpreted and potentially contested across diverse legal cultures.

Strengths and Limitations

A core strength of our project is its multidisciplinary and multinational design, combining expertise in law, ethics, health policy, and dementia care across 15 countries. This enables robust triangulation of perspectives and enhances cultural and legal contextualization. Methodologically, the integration of QTS with a structured legal review process [18] provides a unique and replicable approach to doctrinal legal analysis grounded in qualitative rigor. Screening and selecting the documents for this thematic synthesis will be systematically conducted by a multidisciplinary team with backgrounds in law, philosophy, psychology, nursing, medicine, and gerontology. Our aim is to promote rigor and replicability in the document screening and selection processes, adhering to the following three-step systematic approach:

1. Initial abstract or ratio decidendi review (when applicable)—at least 2 research group members will independently assess abstracts for study screening in the European and international search levels, and when possible, at the national level as well.
2. Reviewer meetings—regular meetings will be held during the study screening and selection process to discuss and resolve any challenges or uncertainties regarding study selection and ensure relevance to the study objectives.
3. Full document review and analysis—Following the abstract or ratio review, analysts will independently assess the full documents of selected abstracts for final inclusion. Any uncertainties among the researchers will be resolved at team meetings. Where no abstract or ratio decidendi appears, documents will be reviewed in full at the first stage.

However, both inherent and anticipated limitations must be acknowledged. First, the analysis will depend on the researchers' linguistic and legal familiarity with national documents, which may introduce interpretive variation. Moreover, the multidisciplinary composition of the research team, while a major strength, also presents a limitation; not all team members may have previous experience working with legal texts, and some may not be formally trained in identifying ethical principles, particularly from a philosophical or normative standpoint.

To mitigate these risks and enhance quality assessment, we will consider both the limitations of our reporting, given the great variety and subjectivity of the assessment tools and the fluid content, which is subject of the synthesis, and explain the quality assessment process, including the criteria by which cases have been excluded from our synthesis [26]. Moreover, all coding and thematic development will involve structured peer debriefing, collaborative consensus building to the greatest extent possible, and the use of standardized charting forms. These forms will be accompanied by detailed guidance on both their use and the process of identifying and interpreting ethical principles within legal materials. In addition, our report will follow and apply the 21 items put forward in the Enhancing Transparency in Reporting the Synthesis of Qualitative Research statement, referring to 5 main domains: introduction, methods and methodology, literature search and selection, appraisal, and synthesis of findings [27].

Conclusions

This study will provide a comprehensive, cross-country thematic synthesis of how ethical principles, such as autonomy, dignity, beneficence, and justice, are embedded, interpreted, and sometimes contested within legal frameworks governing dementia care. By systematically analyzing legal instruments across national, European, and international contexts through an ethical lens, this study highlights the extent to which these principles are operationalized in law. The integration of ethical norms into legal frameworks is crucial not only for ensuring medically appropriate care but also for safeguarding the rights and dignity of individuals living with dementia. This study's multidisciplinary approach, rigorous methodology, and focus on transparency contribute to bridging the gap between ethical theory and legal practice. Its findings may have important implications for policy makers, legal professionals, and health care providers, offering guidance for the development of more ethically grounded and legally coherent regulatory frameworks.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

DS, SL, RS, and AM were involved in conceptualization. All authors equally contributed to methodology, investigation, data curation, visualization, and formal analysis. DS, SL, RS, MA, AM, and SG were involved in writing the original draft. All authors were equally involved in reviewing and editing the manuscript. DS and AM were involved in project administration and supervision.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Data extraction chart.
[PDF File (Adobe PDF File), 28 KB - resprot_v14i1e71490_app1.pdf]

Multimedia Appendix 2
List of ethical principles.
[DOCX File , 15 KB - resprot_v14i1e71490_app2.docx]

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Abbreviations

EU: European Union
QTS: qualitative thematic synthesis

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Protocol

A Population Health and Lifestyle Survey of a Coastal City in England (Health Counts 2024): Protocol for a Cross-Sectional Study

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Abstract

Background: Health and lifestyle population surveys are important in public health to identify trends, provide data to monitor the effectiveness and reach of public health initiatives and policies, and help allocate health resources more equitably. Surveys are a methodologically robust way of examining the inequalities in health outcomes or access to resources across a number of sociodemographic groups in a defined geographic area. This particular public health survey will provide information that cannot be obtained from other sources.

Objective: The aim of the study is to generate comprehensive public health–relevant data from an adult population in a defined geographic coastal area of South East England.

Methods: A cross-sectional, noninterventional (observational) health and lifestyle population survey was developed using a mobile-first design approach to recruitment, with the content drawing on a previous iteration of the survey in 2012. Previous Health Counts surveys in this region have been conducted approximately every 10 years since 1992 to provide data about trends over time. Extensive rounds of consultation and testing took place between October 2023 and February 2024. The final survey comprised 102 questions structured around 13 contemporary public health-related issues in the United Kingdom. Survey distribution was carried out in 2 rounds of SMS text messaging through all general practices in Brighton and Hove involving all adults registered with a general practice and having a mobile phone who had not opted out of communications. Advertising across a range of public-facing initiatives was also used, as well as targeted outreach activities for potentially marginalized groups, for example, in public libraries and community groups. Enrollment took place between March 18, 2024, and April 28, 2024.

Results: A total of 26,014 eligible people responded. Data analysis has started, and results will be reported later in 2025.

Conclusions: Understanding trends in population inequalities over time as well as gaining insights into new areas for the very first time, Health Counts 2024 data can inform decision-making on strategies to improve health and reduce inequalities by local authorities in not only England and the National Health Service but also potentially across other European cities through the effective dissemination and sharing of promising practices as an integral part of evidence-based public health.

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(JMIR Res Protoc 2025;14:e64001) doi:10.2196/64001

KEYWORDS

health; survey; health inequalities; population; Health Counts 2024; public health

Introduction

Background

Coastal communities in England often face poor public health outcomes due to a combination of socioeconomic, environmental, and health care access factors [1]. Reports have demonstrated that coastal towns and cities have a higher burden of disease across a range of physical and mental health conditions. Life expectancy, healthy life expectancy, and disability-free life expectancy are often lower in coastal areas compared to inland regions [1,2]. One of the key reasons for these inequalities is the relatively higher levels of economic deprivation, which include lower income, higher unemployment, and lower economic activity. Economic deprivation is strongly correlated with health outcomes through multiplicative risk factors, such as smoking, alcohol use, access to healthy food and environments (including housing and recreational space), stress, and anxiety. Some coastal communities experience higher levels of social isolation, which is particularly pertinent among older adults and people aged <24 years [1]. Social isolation is associated with poorer mental health, such as anxiety and depression, and can also negatively affect physical health. Coastal regions more often have a high proportion of residents who are aged >65 years, which is set to increase with time [3].

The city of Brighton and Hove, in South East England, United Kingdom, has many similarities to other coastal regions; however, it has a disproportionate population of young people due to there being 2 universities. It has a diverse population and varied socioeconomic conditions; however, there are significant inequalities in health, well-being, and deprivation across different neighborhoods. Lower layer Super Output Area ranks demonstrate areas that are among the most deprived in England alongside areas that are the least deprived [4,5], making public health initiatives complex. Within Brighton and Hove, there is an inequality gap in life expectancy associated with the most and least deprived areas (10.6 y for male individuals and 6.6 y for female individuals [5]), making it important to fully understand the impact of health inequalities on outcomes [6,7].

There is a lack of granular data at a population level, especially with regard to the impact of social isolation, housing conditions, and neighborhood safety on health and well-being indices. Therefore, health and lifestyle population surveys, such as the one described in this protocol, are an important method of public health research. Their ability to generate robust information by geographical area, capacity to provide trend data, ability to focus on important new issues across the population, and ability to explore health and other inequalities across the population allow us to provide segmented data and identify inequalities across our city.

This protocol describes the development of the 2024 Brighton and Hove Health Counts Survey which was commissioned to better understand the health indices, behaviors, and health concerns of the population in a coastal city in South East England. Health Counts 2024 builds on 3 former surveys conducted in 1992 (as “Health Quest”), 2003, and 2012 (as “Health Counts”). In each case, a random sample of the population was drawn from the city. The most recent Health Counts 2012 drew a random sample of 2.5% of the population aged ≥18 years via the general practice (GP) registration database. The 2012 questionnaire covered physical and mental health, sexual health, self-harm and drug use, a range of other health topics [8], and the Office for National Statistics defined questions for a measure of happiness and personal well-being. More than a decade later, Health Counts 2024 has been commissioned by the Brighton and Hove City Council (BHCC) Public Health Team to develop a new survey that includes similar items to the previous survey (allowing tracking of inequalities over time) while also introducing changes for updates and improvements and changes to reflect local public health priorities and national public health guidance (eg, chief medical officer recommendations).

Objectives

This paper presents the protocol for the Health Counts Survey 2024, which will allow researchers to explore the current health and well-being trends and inequalities across a defined population in a coastal region of South East England, United Kingdom. The overarching aim of this study is to generate comprehensive public health–relevant data from an adult population in a defined geographic area of South East England. Specifically, the research objectives are to (1) obtain a range of data on health and well-being, health behavior, lifestyles, and broader social determinants of health, aiming for a sample that is broadly representative of the city of interest’s adult population; (2) provide comparable data to previous population surveys of the city of interest, enabling changes to public health in the city to be tracked over time; and (3) allow population-level inequalities to be explored both cross-sectionally and longitudinally.

Methods

Design

This is a cross-sectional, noninterventional (observational) health and lifestyle population survey.

Study Population

The study population for Health Counts 2024 was defined as anyone aged ≥18 years residing either temporarily or permanently or registered with a GP within the city council boundaries. There was no sample size calculation for this convenience survey. As of the census of 2021, the population of Brighton and Hove was 277,200 (141,600 female and 135,600 male individuals). The total adult population of Brighton and Hove is estimated at 240,000.

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Inclusion and Exclusion Criteria

The inclusion and exclusion criteria are presented in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Aged ≥18 years
- Currently living in Brighton and Hove permanently or temporarily (eg, students, travelers, refugees, and asylum seekers)
- Living elsewhere but registered at a general practice located within the city of Brighton and Hove

Exclusion criteria

- Aged <18 years
- Responses indicating residence outside of the city of Brighton and Hove and that they are not registered with a general practice in the city of Brighton and Hove

Design of the Questionnaire and Testing

The initial design for Health Counts 2024 was based on 3 previous versions of the survey (Health Quest 1992, Health Counts 2003, and Health Counts 2012). Each of these former surveys was designed to be paper based and self-completed. In the development of Health Counts 2024, the following considerations were discussed:

1. Retaining key topics from previous Health Counts and Health Quest surveys to be able to examine change over time versus replacing or adding new emerging public health topics
2. Keeping questions as close as possible to Health Counts 2012 for comparability versus adjusting questions to improve measurements, modernize language, or take into account changes in licensing of some standardized scales (eg, replacing the 12-Item Short Form Health Survey or 36-Item Short Form Health Survey with the license-free Veterans RAND 12-Item Health Survey [VR-12])
3. Providing an increased number of response options to better reflect people's experience and increase data specificity versus fewer response options (required for a mobile-first approach), which potentially increases ease of completion and later data management
4. Balancing having a longer survey capturing more factors of interest but with potentially increased dropout and partial completion with retaining a representative sample, especially those from underresourced groups

An initial critical review of the previous Health Counts 2012 survey was conducted by the study team (the authors) of Health Counts 2024 in February 2023. This was to identify which questions could potentially be removed, adjusted, or kept. This process considered aspects such as wording and phrasing (eg, outdated language and terminology), questions about topics where good-quality recent local data were already available, emerging topics of interest, and backward comparability with previous surveys to allow for analyses of trends over time.

Following this initial review, an in-person consultation event was held with the BHCC Public Health Team, comprising colleagues with expertise in the areas covered by the survey, to discuss and agree on the items to bring forward from the 2012 version as well as identify additional topics and additional outcome measures for potential inclusion. During this consultation, issues discussed also included the length of the survey (ideally to be completed within a maximum target time of 20 min), balance of topics, acceptability to different populations (eg, items on suicide ideation), as well as which validated scales should be retained and adjusted or new ones included (eg, Global Physical Activity Questionnaire) [9].

After the BHCC consultation, a questionnaire draft was created with the questions structured in conceptual order and arranged in 10 groups: about you (demographics), general health, mental health and well-being (including self-harm and suicide), physical health, diet, smoking and vaping, alcohol, drugs, sexual health, and local area and neighborhood. Information was provided on the source of each item, with any new topics and items highlighted in red. This second consultation was then held, this time by email, with the BHCC Public Health Team; local community and voluntary organizations; and other stakeholders, including representatives from the wider partnership, such as the National Health Service (NHS) Sussex, statisticians, and a wide array of experts in public health population survey design. As a result of this second round of consultation, numerous changes to existing questions were made, with decisions to include or exclude or change items accordingly.

Parallel to these consultation events, several platforms to host the survey were tested. Requirements were to be a secure, General Data Protection Regulation (GDPR)–compliant online platform allowing routing between questions, attractive presentation of the survey, optimization for mobile and other devices, and a "backend" that could be programmed to minimize data cleaning and recoding effort. Three platforms were trialed (in order), including REDcap (Research Electronic Data Capture; Vanderbilt University), Joint Information Systems Committee online surveys (version 2), and Qualtrics (Qualtrics International Inc). Preliminary test versions of sections of the questionnaire (eg, demographic questions) were entered into each platform and prepiloted with people known to the study team of Health Counts 2024. Personal invitations were sent to academic colleagues at the authors' own institutions as well as practitioners from the local government authority's public health team. The purpose of these prepilots was to explore the limits of the software, including mobile design "friendliness"; investigate functionality around routing; and provide

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opportunistic possibilities to test out discrete sections of the questionnaire as they became available, checking for acceptability, completeness, phrasing, and comprehension.

Further pretesting during a planned period of public patient involvement and engagement (PPIE) activities also garnered feedback on the look and feel of the survey on each of these platforms as well as ease of use on various devices (eg, Apple vs Android mobile operating systems on mobile devices, tablets, and PCs). PPIE activities were conducted during September 2023 and October 2023 by Healthwatch Brighton and Hove (a community interest company that represents the views of the people who use health and social care services in the city) with diverse communities, including populations that are often under-resourced and absent from research (eg, older people; those at risk of digital exclusion; homeless people; and Gypsy, Roma, and Traveller communities). As part of these activities, Healthwatch Brighton and Hove was asked to engage with 10 to 15 people individually or in a group setting to include those whose first language was English, people who do not classify themselves as White British (to include Gypsy, Roma, and Traveller communities), a range of gender identities, and people aged >18 years. On the basis of this feedback from 13 people (n=9, 69% individuals and 1 group of n=4, 31% individuals) as well as other practical considerations (eg, functionality), Qualtrics was confirmed as the platform of choice, which includes a dedicated mobile design build optimized for mobile-first design.

A third and final consultation event was held among the research team partners (universities, local authority, and Healthwatch Brighton and Hove) in October 2023 to finalize the questionnaire items. A first full draft of the Health Counts 2024 questionnaire was then developed, representing a compromise between inclusivity and brevity. While prioritizing a mobile-first approach and respondent experience, we nevertheless aimed to make the survey as useful as possible to the largest number of stakeholders.

During November 2023, a second full draft of the survey was developed, which included the proposed introductory text, exit page texts, page and topic headings, details of the prize draw, support organizations, and any additional instructions to participants. At this point, this document was used as the basis to translate into a full online version using Qualtrics. From this point, all pretesting, PPIE, and piloting were conducted using the online version only.

Final Testing and Online Piloting Checks

Given extensive pretesting, the main aim of the pilot in February 2024 was to test the survey in its most complete form and provide sufficient data for validity checking of particular questions. The survey was kept open online for 1 week to collect responses from participants outside of Brighton and Hove who would not be eligible to take part in the final survey. In total, 50 responses were received during the piloting, and no major problems were evident. The piloting highlighted some minor issues that needed attention, including some routing errors, typos, and opportunities to reduce “clutter” in line with the design approach (eg, removal of brackets, full stops, and bold and italics). The pilot dataset was downloaded using SPSS (IBM Corp) and imported into Stata (StataCorp) to generate what would become the syntax during the survey launch itself to allow the team to monitor completions on a daily and weekly basis, thus informing proactive promotion and marketing of the survey across the city.

Final Questionnaire Content

The final version of the questionnaire comprised 102 questions structured around 13 contemporary public health-related issues in the United Kingdom (Table 1). A copy of the final questionnaire is available in Multimedia Appendix 1.

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Table 1. Final questionnaire content of Health Counts 2024.

Categories	Items
Survey eligibility check	• Items assessing eligibility of age, postcode, and general practice
Sociodemographics	• Items about participants' age, disability, ethnicity, marital, civil, and relationship status, religion, gender identity, sexual orientation, carer status, and armed forces status—including family, employment and education, household, and refugee and asylum seeker status
General health	• Items assessing happiness, general health status, as well as long-term conditions and disabilities and their impact • Includes items from the VR-12[a] [10]
Physical health	• Items assessing the impact of health on daily living and activities and the impact of pain, falls, and active and sedentary behaviors • Includes items from the VR-12 standardized scale, the IPAQ[b] [11], and the SALS[c] [12], measuring adult physical activity levels
Mental health and well-being	• Items assessing the impact of mental health on daily living and activities, energy fatigue, social functioning, anxiety, depression, self-harm, suicidal ideation, and suicide attempt • Includes items from the VR-12 [10]
Smoking and vaping	• Items assessing the use of tobacco (smoking and other), addiction, quit attempts, household smoking, and vaping status
Alcohol consumption	• Items assessing frequency of alcohol use, units consumed, binge drinking, and alcohol reduction attempts. • Includes items from the AUDIT[d] [13]
Gambling	• Items assessing gambling participation and gambling impact (own and others)
Drugs	• Items assessing recent drug use and drug type
Sexual health	• Items assessing the number of partners last year, the number of new partners, new partner type, condom use (new partners only), HIV testing (ever and recency), and preexposure prophylaxis to prevent HIV awareness and use
Diet, height, and teeth	• Items assessing fruit and vegetable consumption ("5 a day"), perceived weight status, BMI (height and weight) [14], teeth cleaning frequency, source of dental support, dentist visit frequency, and reasons for attendance or nonattendance
Housing and the cost of living	• Items assessing housing status, housing condition, and the cost-of-living impact
Local area	• Items assessing local area satisfaction, neighborhood belonging, neighbor contact, social support, access to nature (frequency and type), local area safety (day and night), fear of crime, and experienced harassment

[a]VR-12: Veterans RAND 12-Item Health Survey.

[b]IPAQ: International Physical Activity Questionnaire.

[c]SALS: Short Active Lives Survey.

[d]AUDIT: Alcohol Use Disorders Identification Test.

Conceptual Approach to Methodology

The survey was underpinned conceptually by theoretical ideas coming from the theory of planned behavior [15] and other conceptual frameworks, such as the health belief model [16], social cognitive theory [17], and ecological models such as the one by Bronfenbenner [18]. Together, these frameworks emphasize how behavior and lifestyle are influenced by, for example, complex interactions among personal, social, cultural, environmental, and behavioral factors. Furthermore, a mobile-first design approach was also used to underpin the survey development from the outset. This approach goes beyond simply making a survey available online and accessible by any device. Rather, mobile-first research is designed from the bottom up to be conducted on a mobile phone. Such a design entails paying attention to how mobiles are used in day-to-day life and creating the right conditions for participants to engage and complete the survey. For example, the survey should be short, simple, and easy to navigate (minimizing things such as sliders and drop-down boxes that require additional actions by the user, minimizing open text responses, minimizing any horizontal scrolling, keeping instructions short and concise, removing unnecessary wording, being visually engaging, and using short response scales). Therefore, this mobile-first thinking informed all aspects of the Health Counts 2024 design, being balanced against the requirements of a degree of backward comparability with previous paper-based health counts questionnaires.

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Procedure and Recruitment

Health Counts 2024 opened at 7 AM on Monday, March 18, 2024, and ran for 6 weeks until April 28, 2024, 8 PM. The survey was hosted on the University of Brighton landing page [19], containing a call-to-action button to the survey as well as detailed participation information and details of relevant support organizations on issues covered by the survey (eg, sexual health, smoking, drug use, and mental health support).

Previous Health Counts surveys (1992, 2003, and 2012) were conducted as postal self-completion surveys, sent to a random 2% to 2.5% sample of adults aged >18 years registered in GP. The most recent data from NHS Digital [20] and the Office for National Statistics [21] indicate that the number of people registered with GPs in England is higher than ONS population estimates and for Brighton and Hove, where this survey was conducted, the difference is estimated to be 4% to 9% higher than the resident population for various reasons [22]. Due to this relatively high level of registration among adult populations, recruitment through GP services was selected as the main method of enrollment. For the 2012 survey, public health was located within the NHS; therefore, samples could be drawn using the Primary Care Support Services. This meant that patient contact details could be provided directly to researchers, who could then invite them to participate. With the introduction of GDPR, there was no option to generate a random sample for the 2024 survey. Therefore, in discussion with a wide range of stakeholders and partners (eg, the NHS information governance team, the data protection officer for GP, the GP Practice Managers' Forum, the local medical committee, and the Brighton and Hove Health and Care Partnership), a population approach was adopted whereby each GP in the city would be asked to send SMS text messages to eligible registered patients with an invitation to complete the survey. In these discussions, the Practice Managers' Forum suggested that, as there was no way for practices to identify a random sample of patients, all patients aged >18 years should be invited to participate. Such an approach would mean GPs would be able to reach most of the local population (estimated at approximately 98%). This process is compliant with the Data Protection Act 2018, which is the United Kingdom's implementation of the GDPR, provided practices first run the patient list through the Message Exchange for Social Care and Health to remove any patients with a National Data Opt Out (a service that allows patients to opt out of their confidential patient information used for research and planning). We also engaged with the National Institute for Health and Care Research Clinical Research Network to confirm that contacting patients in this way is reasonable and appropriate in terms of offering patients the opportunity to participate in health-related research.

Between November 2023 and March 2024, the Health Counts team liaised either directly with GPs or via the Brighton and Hove Federation to request them to (1) send 2 SMS text messages to eligible patients with a link to the survey (1 initial invitation and 1 reminder) and (2) promote the survey to their patients through the practice (eg, link or QR code on the practice website, electronic poster on a digital screen, and social media channels). Practices were reimbursed by the public health grant for the time taken to run searches and message patients as well as the cost of SMS text messages being paid for.

Practices were asked to send the first text on the first day of the survey launch (March 18, 2024), ideally either between 7 AM and 10 AM or 2 PM and 8 PM. This timing was proposed to maximize potential responses based on the literature suggesting that these are the times patients may be more likely to complete the survey. The second text was requested to be sent on Monday, April 15, 2024, either between 7 AM and 10 AM or 2 PM and 8 PM. These times were indicative, and some practices opted to send messages to batches of patients across the relevant weeks rather than all in one go to minimize potential disruption to reception staff with potential queries.

Community Engagement and Supported Completion

To maximize the potential to engage and support those often underrepresented in research or those who might have challenges in accessing and completing the survey (eg, homeless or not registered with a GP in the city), targeted outreach activities were conducted. Outreach comprised collaborating with community organizations, voluntary sector groups, and charities to share information on their websites and social media platforms and meeting community groups to (1) explain the purpose and nature of the survey and (2) assist people to access the survey by providing digital devices (eg, tablets) and, where necessary, a hard copy or supported completion by a member of the research team, if required. Organizations that already support groups in the following areas were approached directly: young people; learning disability; mental health; sexual health; homelessness; women's support; gender; minority and ethnic communities, including Gypsy, Roma, and Traveller communities; and older people. Two full-day drop-in sessions were also conducted in a local library to support general community engagement. In addition, community outreach by 2 local football clubs facilitated awareness raising at 2 match days. A wide range of organizations supported awareness raising, disseminated information through their own social media platforms and digital networks, and facilitated public engagement and hands-on support with the survey. In addition, other community services used their own digital platforms and digital screens to raise awareness of the survey for their service users. This complemented the general marketing strategy described subsequently by targeting specific groups in the population of Brighton and Hove. Where the research team met with local community groups or was present in the library, support to engage with the survey through a digital device or hard copy survey was offered, or "hands-on" support was offered for individuals to use their own digital device, such as a mobile phone. The intention was to assist individuals in completing the survey themselves and enhance access, address concerns, and support informed consent.

Promotion of the Survey

To help raise awareness about Health Counts 2024 for those receiving SMS text messages from their GP as well as wider opportunities to engage through the outreach activities or independently of these routes (eg, directly via QR codes), a comprehensive marketing and communication strategy was developed in collaboration with an external design contractor

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to provide an attractive, coherent, and augmented visual identity. This strategy included both paid and unpaid promotional activities through the partner organizations as well as a paid social media campaign across the major platforms during the survey launch window. Daily statistical monitoring of the survey completions allowed promotion to be adjusted throughout the campaign to target, for example, those less likely to complete the survey (eg, young people and men) or geographical areas where completion rates differed substantially. The range of promotional activities and their locations were diverse, including, for example, pull-up banners and LED and plasma screens in public spaces (such as libraries, other public buildings, and council offices), posters, radio advertisements, mailers and newsletters, university student alerts, web banners and email signatures, digital bus stop promotions, and hard-copy flyers and posters as well as the use of community apps, forums, and newsletter articles.

Data Cleaning and Analyses

Data were cleaned and checked for eligibility before starting analysis. Attrition, nonresponse, and missing data were examined and dealt with at the appropriate level of analysis. A detailed codebook describing each of the items and response frameworks was used to guide the scoring of each item and construct. For validated scales (eg, the VR-12 [10], International Physical Activity Questionnaire [11], Global Physical Activity Questionnaire [9], and Alcohol Use Disorders Identification Test C [13]), scores will be created following standardized instructions, including instructions for dealing with missing values in the case of the VR-12.

Data analyses will be primarily exploratory and descriptive initially. Descriptive findings will be reported as means and SDs for continuous variables and numbers and percentages for categorical variables. To ensure internal consistency of scales, reliability will be checked with Cronbach α. Where feasible and appropriate, estimates will be compared to values from national surveys, such as the UK Census 2021 and other annual population surveys (eg, the People and Nature Survey for England from April 2023 to March 2024) [23], covering similar time periods. In addition, and again where possible, comparisons will also be made against data generated from previous iterations of the Health Counts survey (1992, 2003, and 2012).

Descriptive analyses will be run in SPSS (version 29.02.0) and include bivariate analysis, including chi-square tests (or Fisher exact test when appropriate) and Mann-Whitney *U* tests, which will be used to determine significant differences between groups for categorical variables, including demographics. Kruskal-Wallis tests will be used for continuous variables. CIs will be reported where relevant.

Given the likely deviations of the sample composition from the population, we will statistically weight our findings accordingly. This will make the data more representative of the population they are designed to represent, that is, Brighton and Hove as a whole. Apart from this form of frequency weighting, we will consider using a poststratification approach to sampling weights, which will provide improved estimates of measures of variation, including SEs. The weights for Health Counts 2024 will be calculated with the help of census data from 2021 and will include age, (binary) sex, and Index of Multiple Deprivation quintiles [24].

While most questions in the survey were closed, a limited number did allow open-ended responses so respondents could elaborate or "specify" if they felt the standard response options did not apply to them. To analyze these qualitative data, we expect to apply content analysis to the verbatim responses given to the open-ended questions. This will ensure text can be systematically categorized to meaningfully quantify the qualitative (descriptive) responses.

Ethical Considerations

Overview

Initial approval for recruitment via GPs (NHS recruitment pathway) was granted by the University of Brighton Pre-Sponsorship Approval Panel and the University of Brighton Sponsorship Approval Panel (2023-11973). The ethics approval was granted by the NHS Health Research Authority (23/LO/0825) and the London—Bromley Research Ethics Committee (23/LO/0825). In this study, GPs were acting as participant identification centers, and each participating GP signed a participant identification center agreement outlining the responsibilities of the practice and study sponsor. The ethics approval for the community enrollment and supported completion pathway was granted by the University of Brighton Cross-School Research Ethics Committee C (2023-12553).

Confidentiality

No personal data (such as names, addresses, and dates of birth) were collected from participants. The survey was completely anonymous; no IP addresses were stored or downloaded, and no information regarding the origin of the "click" was collected. No cookies were installed on the potential participant's computer or device. There was no compensation provided to participants.

Informed Opt-In Consent

Respondents who received an SMS text message invitation to participate in Health Counts 2024 from their GP had to click on the link sent to them in the message, which took them to the survey landing page. This page contained an action button to the survey as well as detailed participation information and details of relevant support organizations on issues covered by the survey (eg, sexual health, smoking, and drug use). The information provided included information about the project, confidentiality of the survey findings, and an outline of what participants were required to do and how long it would take them to complete the questions. A statement was provided regarding data protection, including confidentiality and anonymity. Potential participants were asked to click on a box to confirm that they had (1) read and understood the participant information before proceeding; (2) understood that the survey was voluntary and anonymous and their answers would not be traceable to them; and (3) agreed to take part in the survey.

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Results

Recruitment

Participant enrollment took place between March 18, 2024, and April 28, 2024, with 26,014 eligible respondents. The response rate to the survey is estimated to be 11.2% of the resident population aged ≥18 years based on the July 2024 Office for National Statistics' midyear population estimates release for 2023 (232,971 adults). As expected, there were some incomplete surveys submitted; of the 26,014 submissions, 16,729 (64.31%) were complete, giving a final weighted sample and response rate of 7.2% of the resident population aged ≥18 years. Data analysis will be completed in 2025, with results expected by the end of 2025.

Analysis

Data analysis for the primary outcome paper, along with planned secondary analyses, is currently underway, with the intention of disseminating study findings in peer-reviewed journals. Findings from the analyses will also be disseminated to voluntary and community sector organizations (including the public) through specific accessible summary reports and accompanying presentations as well as representatives of the local government and the NHS. The planning, preparation, and submission of publications will follow the Health Counts 2024 Editorial Board policy, which draws on international guidance for authorship, including the International Committee of Medical Journal Editors [25] criteria. In addition, findings will also be shared with a broad scientific audience through presentations at local, national, and international conferences.

Discussion

Anticipated Findings

Health and lifestyle population surveys are essential in public health to identify trends, provide data to monitor the effectiveness and reach of public health initiatives and policies, and help allocate health resources more equitably. To our knowledge, this study is one of the first internet-based self-completion questionnaire surveys that, in partnership with the local authority, the NHS, primary care, and other partners, has the potential to transform understandings of the health and well-being of the residents of the city of Brighton and Hove. It is expected that results will (in some cases) be able to provide an indication of inequalities over time by comparing with previous versions of the survey and also in other important emerging areas, such as gambling, vaping, community safety, harassment, and hate crime, drawing attention to issues where data are less available. Indeed, by understanding better historical inequalities as well as new emerging public health areas of interest, including threats, the findings are also expected to generate important insights across different local authority departments directly relevant to public health and its social and wider determinants (eg, housing, environment, and transport).

Health Counts 2024 survey data will also be important in helping researchers identify population-level health inequalities and also critically inform decisions about future health and well-being strategies and services to better meet residents' needs. It will thus provide a wealth of information that cannot currently be obtained from other sources and may be of particular relevance for government bodies regionally and nationally as well as in wider international settings (eg, such as the World Health Organization Healthy Cities Network).

There are some limitations to this study, including the cross-sectional nature of the design methodology. Although this survey includes some items linked to the 3 previous iterations of the survey, allowing for the analysis of inequalities over time to be conducted, new items and topics introduced for the first time in Health Counts 2024 (including gambling-related harms, suicidal thoughts and attempts, harassment and hate crime, alongside access to nature and the natural environment) limit the ability to make causal inferences or assess temporal relationships about these items and topics. Moreover, as health and lifestyle surveys cover a variety of issues that are commonly stigmatized and include sensitive topics (eg, alcohol and drug use, physical activity, weight, suicide and suicide ideation, and the fear of crime), there is potential for information bias in the form of social desirability. However, it is also likely that due to the anonymous nature of the survey, the fact that the primary invitation to participate was sent to participants through GP in the city, and also the known fact that the public trust in the NHS and primary care is high, it is possible that social desirability concerns may have been suitably mitigated.

Conclusions

The Health Counts 2024 survey was designed to generate comprehensive public health data from an adult population in a coastal area of South East England. It is expected that our results can be used to inform future public health and other intersectoral policies and interventional campaigns and health care provider–based interventions that introduce new models of care for city residents. Through better understanding the trends in population inequalities over time (where data allow) as well as gaining insights into new areas for the first time, it is hoped that the data can inform decision-making on strategies to improve health and reduce inequalities by local authorities in not only England and the NHS but also potentially across other European cities through effective dissemination and sharing of promising practices as an integral part of evidence-based public health.

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Agency, University of Brighton Communications and Marketing, Brighton and Hove City Council Public Health and Communications teams, Brighton and Sussex Medical School Communications, Brighton and Hove Federation, National Health Service Sussex, Brighton and Hove City Libraries, Albion in the Community, Digital Brighton and Hove, Bridging Change, Families, Friends and Travellers, Refugee Radio, Trust for Developing Communities, Whitehawk FC, Jolloffe Café, Black and minority ethnic Chinese elders' council, Hangleton & Knoll Project, Hangleton & Knoll Western Group, Whitehawk Outreach Group, Oasis Homeless Charity, Arch Healthcare, Acorn, Trust for Developing Communities, Community works, Community Base, Sussex Impact Initiatives, UOK Partnership, Cascade, NHS public engagement involvement in Brighton and Hove, the Peoples' (Digital) Panel, Somerset Centre, Allsorts, Mind out, Older and Out, Clare Project, Speak Out, Amaze Families, Primary Care Network East Central Brighton, East Brighton Food cooperative Baker Street, and the Women's Institute. The authors also wish to thank Professor Dr Thomas Kohlmann (University of Greifswald Department of Medicine) for advising on the calculation of the Veterans RAND 12-Item Health Survey component scores. Health Counts 2024 was funded by Brighton and Hove City Council Public Health Department.

Conflicts of Interest

KG, CMV, and LK are employed by Brighton and Hove City Council and were part of the study team of Health Counts 2024 in collaboration with the University of Brighton, Healthwatch Brighton and Hove, National Health Service Sussex, Brighton and Sussex Medical School, and Brighton and Hove Federation.

Multimedia Appendix 1
Health Counts 2024 questionnaire.
[PDF File (Adobe PDF File), 474 KB - resprot_v14i1e64001_app1.pdf]

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Abbreviations

BHCC: Brighton and Hove City Council
GDPR: General Data Protection Regulation
GP: general practice
NHS: National Health Service
PPIE: public patient involvement and engagement
REDCap: Research Electronic Data Capture
VR-12: Veterans RAND 12-Item Health Survey

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Protocol

Hemodynamic Assessment of Arterial Perfusion by Using the Ultrasonographic Hand Acceleration Time: Protocol for a Cross-Sectional Prospective Descriptive Study

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Abstract

Background: Several noninvasive methods can be used to assess hand perfusion, but none have been standardized for diagnosing chronic upper limb ischemia. One potentially useful diagnostic tool for this purpose is the ultrasonographic hand acceleration time (HAT), although it still requires characterization and validation.

Objective: This study aims to describe the technique for assessing hand perfusion through HAT while quantifying it in patients with chronic upper limb ischemia and healthy volunteers.

Methods: This prospective, cross-sectional, and descriptive study evaluates HAT measurements by using vascular duplex ultrasound (DUS), a novel technique for assessing hand arterial perfusion. This study includes adult patients with chronic upper limb ischemia and healthy volunteers without cardiovascular risk factors. HAT was measured in 4 different hand arteries. A standard descriptive analysis was performed, along with comparisons using the Mann-Whitney *U* test, when applicable. This study received institutional review board approval, and no study-related procedures were performed prior to signing the written informed consent. This research complied with the Declaration of Helsinki, Good Clinical Practice guidelines, and Spanish regulatory requirements.

Results: As of June 2023, 30 participants were enrolled in the study, comprising 15 patients and 15 healthy volunteers, resulting in a total of 15 ischemic and 30 nonischemic hands. Data analyses were concluded in late November 2023, and results were sent for publication in February 2024. The manuscript containing the results was accepted in May 2024 and published online in July 2024, becoming available in PubMed in December 2024. The results have already been made available to the scientific community prior to the submission of this protocol. This study protocol was submitted for publication in July 2024 to enhance transparency and to offer comprehensive methodological insight into the HAT technique. No additional analyses beyond those reported in the published study are planned.

Conclusions: This study presents the first systematic evaluation of HAT measurements by using vascular DUS as a novel diagnostic tool for chronic upper limb ischemia. By comparing ischemic and nonischemic hands, this study aims to establish preliminary cutoff values that may aid clinical decision-making. Although prior studies have only reported HAT measurements in case reports, this study provides quantitative data on its feasibility and potential clinical application. Despite its small sample

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size, which limits subgroup analysis and generalizability, the study serves as a foundation for future research by providing essential data for refining cutoff values and informing sample size calculations for larger studies. Although examiner dependence could introduce systematic bias, the standardized methodology ensures consistency across all measurements. Ultimately, HAT may emerge as a quick, noninvasive diagnostic tool for chronic upper limb ischemia, potentially complementing existing nonstandardized methods such as the digital-brachial index, digital pressures, and plethysmography.

Trial Registration: ClinicalTrials.gov NCT05977725; https://clinicaltrials.gov/study/NCT05977725

International Registered Report Identifier (IRRID): RR1-10.2196/64450

(JMIR Res Protoc 2025;14:e64450) doi:10.2196/64450

KEYWORDS

hand arterial perfusion; hand acceleration time; HAT; acceleration time; chronic upper limb ischemia; duplex ultrasound; arterial; acceleration; upper limb; protocol; cross-sectional study; ultrasound; ischemia; hand; arteries; descriptive analysis; ultrasonographic

Introduction

Different noninvasive techniques can be used for evaluating arterial perfusion in the hand, which include measuring the digital-brachial index (DBI), digital arterial pressures, oxygen saturation, and plethysmographic signals [1]. However, despite their availability, none have become the accepted standard for diagnosing chronic ischemia of the upper extremities, likely due to the rarity and etiological diversity of this condition.

In contrast to its lower limb counterpart [2], upper limb vascular diseases (whether acute or chronic) represent <10% of the consultations in vascular surgery settings [1]. Among these, only a minority (around 4%) ultimately require revascularization procedures [3]. The underlying causes of upper extremity ischemia are varied and include atherosclerosis, thoracic outlet syndrome, different forms of vasculitis (such as Takayasu arteritis, giant cell arteritis, and Buerger disease), connective tissue disorders, trauma, unresolved thrombotic events [3,4], and ischemia secondary to vascular access in patients undergoing dialysis [5].

Particularly noteworthy is hemodialysis access–induced distal ischemia (HAIDI), which affects up to 5%-7% of individuals with end-stage renal disease undergoing dialysis via an arteriovenous access [6]. Although chronic upper limb ischemia is rare overall, HAIDI represents a considerable subset within this population. DBI and digital pressures have been investigated extensively in this context, but no clear consensus exists on their diagnostic thresholds or reliability [7-9]. Furthermore, although adaptations of Fontaine's classification have been proposed for UPPER limb ischemia, corresponding objective testing metrics such as DBI or digital pressure stratification have not been standardized as they have for lower limb disease.

Because of these limitations, imaging modalities such as computed tomography angiography, magnetic resonance angiography, or arteriography are often needed to confirm a diagnosis of upper limb arterial occlusive disease [3,10]. On the other hand, duplex ultrasound (DUS) is a noninvasive, dynamic tool that can visualize the entire upper extremity arterial tree, and prior studies have successfully described the anatomical characteristics of the hand vasculature by using this approach [11].

One specific DUS parameter—acceleration time—has emerged as a potential indicator of distal arterial compromise. Acceleration time quantifies the interval in milliseconds between the onset of the systole and the systolic peak on Doppler waveform analysis, providing real-time insight into arterial compliance and resistance [12]. The diagnostic applicability of acceleration time has been established in different vascular beds, particularly in the pedal arteries for assessing lower limb ischemia (pedal acceleration time) [13-15]. Additionally, acceleration time has been studied in arterial territories such as the carotid arteries [16], pulmonary arteries [17], and the aorta [18]. Some authors have applied this concept to the upper extremity, measuring what is referred to as the hand acceleration time (HAT) [19-21]. However, current data are limited, mostly consisting of small case series or anecdotal reports, and no formal characterization or validation of HAT has been conducted to date.

In light of this, our study aims to describe a reproducible technique for measuring HAT by using DUS and to assess its diagnostic potential by comparing patients with chronic upper limb ischemia to healthy control participants. We hypothesized that HAT is a useful diagnostic tool for chronic upper limb ischemia, considering that ischemic hands would exhibit prolonged acceleration time values due to impaired perfusion, which would broaden the arterial spectral Doppler waveform. This study aims to describe the technique for assessing hand perfusion through HAT while quantifying it in patients with chronic upper limb ischemia and healthy volunteers.

Methods

Study Design

This was a cross-sectional, prospective, and descriptive study of HAT measurements—a hemodynamic assessment technique—with vascular DUS for assessing the hand's arterial perfusion. Notably, vascular DUS with HAT measurements is a new technique that has not been previously described.

Study Population and Setting

The study population consisted of patients with known chronic upper limb ischemia who were observed in the Angiology and Vascular Surgery outpatient clinic or hospitalized in the Vascular Surgery Unit, and they served as the exposed population. In the diseased cohort, we classified chronic upper

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limb ischemia by extrapolating Fontaine's clinical classification of chronic lower limb ischemia [22]: (1) grade I: asymptomatic, (2) grade II: arm claudication, (3) grade III: rest pain, and (4) grade IV: trophic lesions.

The diagnosis of chronic upper limb ischemia in the study participants was primarily clinical based on the presence of characteristic signs and symptoms, including the absence of upper extremity pulses and presence of arm claudication, rest pain, or trophic lesions. Additionally, although we assessed digital pressure reductions in all patients, these measurements were not included in this study due to the lack of standardized DBI criteria for diagnosing chronic upper limb ischemia. To confirm the diagnosis and evaluate arterial involvement, DUS was performed to identify stenotic or occlusive lesions. DBI and digital pressures were not used for clinical staging since they have not been standardized for the upper limb arterial disease and are not a gold standard for comparison. We invited the patients' escorts to participate in the study as healthy volunteers (who served as the unexposed population for comparison purposes). All study-related procedures were performed at the Bellvitge University Hospital.

Eligibility Criteria

Textbox 1 summarizes the eligibility criteria for patients with chronic upper limb ischemia and healthy volunteers. Both must meet all the inclusion criteria and none of the exclusion criteria to participate in the study.

Textbox 1. Eligibility criteria.

Inclusion criteria

- Patients with upper extremity chronic ischemia
  - Adult (≥18 years) patients
  - Either biological sex
  - Diagnosed with chronic ischemia of the upper extremity
  - Who sign the written informed consent
- Healthy volunteers
  - Healthy adult (≥18 years of age) volunteers
  - Either biological sex
  - Who sign the written informed consent

Exclusion criteria

- Patients with upper extremity chronic ischemia
  - Patients deemed unable to understand the study by the investigator
- Healthy volunteers
  - Healthy volunteers deemed unable to understand the study by the investigator
  - Healthy volunteers presenting any known cardiovascular risk factor (eg, smoking habit, arterial hypertension, diabetes mellitus, dyslipidemia)

Study Procedures

All study participants (patients with chronic upper limb ischemia and healthy volunteers) underwent hand DUS at the Bellvitge University Hospital. Participants were instructed to rest in a supine position for a minimum of 10 minutes prior to the ultrasound examination to ensure hemodynamic stability; the environment temperature was set at approximately 22 °C. A clinical assessment was conducted before imaging, with particular attention to distal pulse palpation in the upper limbs. Ultrasound assessments were performed with EPIQ Elite (Philips Healthcare), utilizing a high-resolution linear transducer operating at 22 MHz to measure hemodynamic parameters.

Optimizing ultrasound settings (such as increasing color gain and lowering pulse repetition frequency) is crucial for accurate visualization of small-caliber hand arteries. After locating the artery, the Doppler "acceleration time or time/slope" function was used to assess HAT after adjusting the spectral waveform in the spectral window and measuring the interval from the onset of systolic flow to its peak velocity (Figure 1). In healthy arteries, the waveform typically exhibits a triphasic pattern with a steep upstroke and short acceleration time, whereas in ischemic vessels, the waveform broadens and the acceleration is delayed.

Considering the anatomical variability in the hand's arterial vascularization, we measured HAT in 4 hand arteries and the distal ulnar and radial arteries. HAT1 was measured at the princeps pollicis artery by placing the transducer on the dorsal side of the hand at the level of the first finger (Figure 2A). The radial artery in the hand lies in the anatomical snuffbox between the extensor pollicis longus and extensor pollicis brevis muscles. The princeps pollicis artery arises from this point of the radial artery as it runs ulnarward and dorsalward to the extensor

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pollicis longus. Similarly, HAT2 was assessed by keeping the hand at the same position and placing the transducer on the first commissure on the volar metacarpal surface (Figure 2B)—it was measured at the radial artery of the index finger. HAT3 and HAT4 were measured at the first and third common palmar digital arteries, respectively, through the hand's palmar surface. First, the transducer was transversally over the metacarpal head and distal to the hand fold (Figure 2C). After locating the common palmar digital artery between the extensor muscles and above the metacarpus, we located the common palmar digital artery and measured HAT3 at the first common palmar digital artery and HAT4 at the third common palmar digital artery. Thereafter, the transducer was positioned in a longitudinal view (Figure 2D), and we repeated both HAT3 and HAT4 assessments.

We performed 3 measurements per artery to minimize variability and to ensure consistency during the evaluation.

Figure 1. A normal HAT occurs in the absence of upper limb ischemia (with a narrow triphasic spectral waveform), while an increased HAT arises in the setting of upper limb ischemia (with a decreased systolic up-rise and wide waveform). HAT: hand acceleration time.

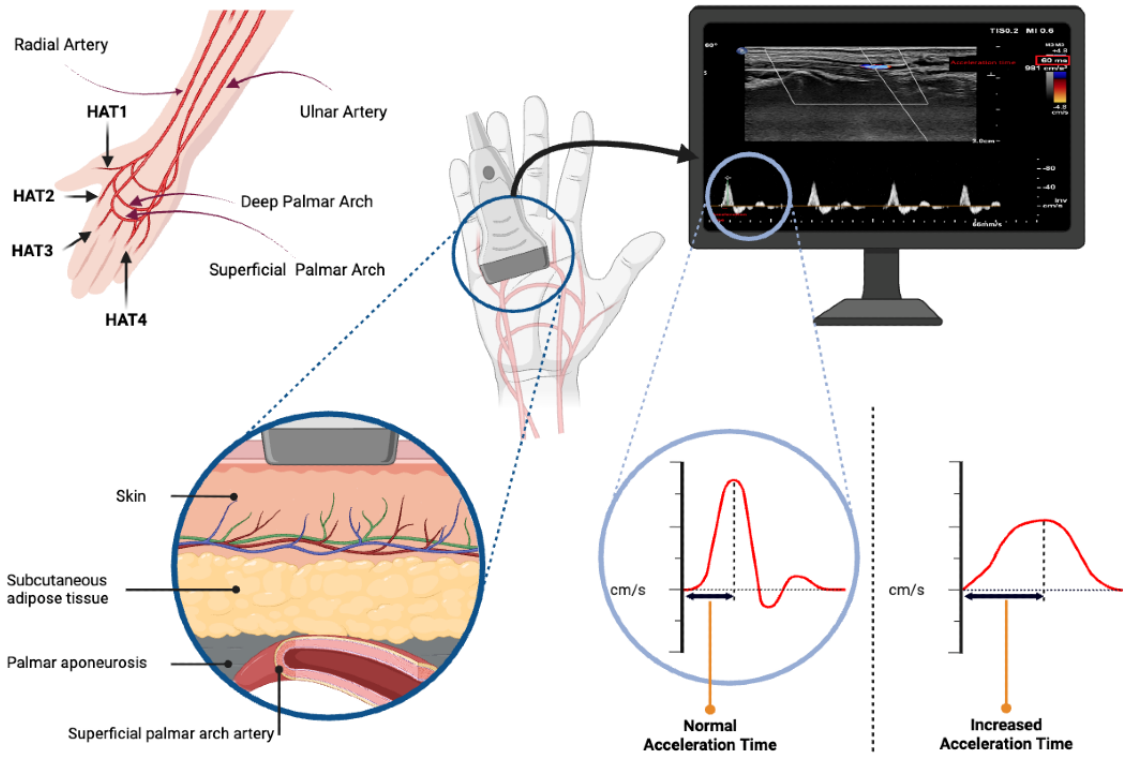

Figure 2. HAT measuring sites. (A) HAT1 measuring site, (B) HAT2 measuring site, (C) HAT3 and HAT4 measuring sites (transversal view), (D) HAT3 measuring site (longitudinal view), and (E) HAT4 measuring site (longitudinal view). Of note, HAT3 and HAT4 are both measured twice with the same views. HAT: hand acceleration time.

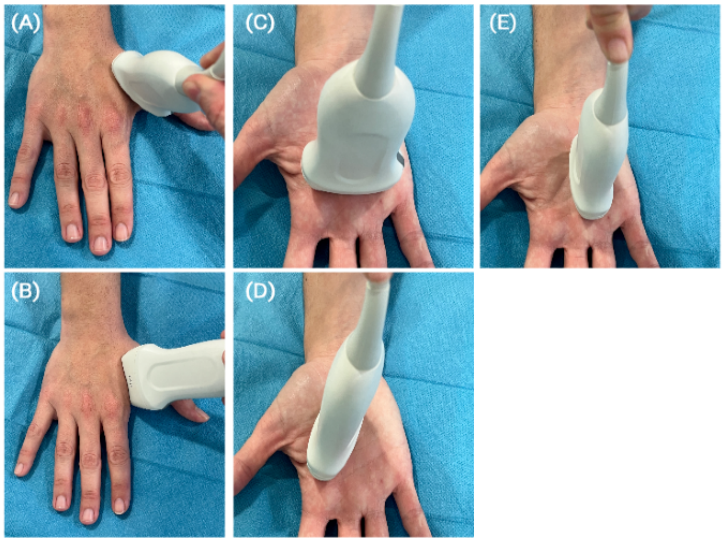

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Outcomes

Our primary variables were HAT measurements (in milliseconds) with DUS in the (1) princeps pollicis artery (HAT1), (2) radialis indicis artery (radial artery of the index finger; HAT2), (3) first common digital artery (HAT3), and (4) third common digital artery (HAT4) (Figure 1).

The secondary variables included (1) the absolute and relative frequencies of baseline and demographic characteristics (age and biological sex), (2) the cumulative incidence of cardiovascular risk factors (eg, smoking habit, arterial hypertension, diabetes, dyslipidemia), (3) the cumulative incidence of diseases of interest (ie, end-stage renal disease, ischemic heart disease, heart failure, chronic obstructive pulmonary disease), (4) the absolute and relative frequencies of each etiology of ischemic upper limb disease (eg, subclavian, humeral, distal stenosis/occlusion, end-stage renal disease-secondary lesions), (5) the clinical stage of upper limb disease (eg, asymptomatic, arm claudication, trophic lesions), and (6) the presence of distal pulses in the upper limb in the physical examination.

Ethical Considerations

This study was approved by the Bellvitge University Hospital's institutional review board (registration ICP013/23) in May 2023. All participants provided written informed consent in accordance with the updated Declaration of Helsinki, Good Clinical Practice guidelines, and applicable Spanish and European regulatory requirements prior to any study procedures. Participation was voluntary, and participants were informed that they could withdraw from the study at any time without providing a reason and without any consequences. All collected data were deidentified prior to analysis, ensuring that no individual could be identified in the published results. Confidentiality was safeguarded in compliance with the current Spanish data protection law (LOPD 3/2018) and the European General Data Protection Regulation (EU regulation 2016/679 of the European Parliament and Council of April 27, 2016). Notably, this publication strictly reflects the version approved by the institutional review board and was not modified either before or after the study results were published elsewhere [23]. Participants, including both patients and healthy volunteers, did not receive any financial or nonfinancial compensation for their participation. This study was prospectively registered on ClinicalTrials.gov (NCT05977725) and adheres to the STROBE (Strengthening the Reporting of Observational studies in Epidemiology) guidelines for reporting observational studies.

Data Sources, Data Collection, and Quality Control

Our data sources were clinical interviews, individual medical histories, and sonographic examinations performed on all study participants. All study-related information was registered in the participant's medical history and in an ad hoc–created database. This database was made up of anonymized data, and only the principal investigator and authorized study team members had access to it. All data were dissociated, and participants were assigned a number (code) upon enrollment. To ensure data accuracy, the principal investigator reviewed all individual medical histories as a quality control measure.

Sample Size and Statistical Analysis

Given the exploratory nature of this study, we did not perform a formal sample size calculation. Considering the aforementioned disease's low prevalence, we intended to include all 15 patients diagnosed with chronic upper limb ischemia and observed in our center's outpatient clinic, as well as the 30 hands of 15 healthy volunteers. We performed a standard descriptive analysis of all the study variables. We summarized categorical variables as absolute and relative frequencies and continuous variables as medians and range. The nonparametric Mann-Whitney *U* test (independent samples) was used for between-group comparisons regarding HAT values in 4 digital locations (princeps pollicis artery, radialis indicis artery, first common digital artery, and third common digital artery) as well as in the distal radial and ulnar arteries [24]. Given the exploratory nature of this study, a formal sample size estimation was not conducted. Notably, we must underscore that this is a preliminary feasibility study with a sample size that is too small to allow analysis adjustments for more than one variable. All statistical analyses were performed with R 4.3 software or higher (R Foundation for Statistical Computing) for Windows.

Results

As of June 2023, 30 participants were enrolled in the study, comprising 15 patients and 15 healthy volunteers, resulting in a total of 15 ischemic and 30 nonischemic hands. Data analyses were concluded in late November 2023, and results were sent for publication in February 2024. The manuscript containing the results was accepted in May 2024 and published online in July 2024, becoming available in PubMed in December 2024 [23]. This study protocol was submitted for publication in July 2024 to enhance transparency and offer comprehensive methodological insight into the HAT technique. No modifications were made to the original protocol used to guide the results, and no further analyses beyond those reported in the published study are planned.

Discussion

This study protocol outlines the design and methodology of a cross-sectional, prospective, and descriptive investigation into HAT as a diagnostic marker for chronic upper limb ischemia. Although the sequence of the publication is atypical (ie, protocol being published after the dissemination of the corresponding results [23]), it reflects the intent to foster transparency and provide guidance for the future applications of this technique.

To date, the clinical application of HAT has been explored only in a handful of case reports. Notably, one series described its application in 4 patients with HAIDI and associated trophic lesions, where HAT values declined after revascularization, coinciding with symptom resolution [19]. In another case report, palmar DUS was used to guide the need for reperfusion in a patient with subclavian artery disruption and scapulothoracic dissociation, accurately assessing the function of an extra-anatomic bypass [20]. Finally, HAT was successfully used to detect early signs of posthemorrhagic shock state [21]. These preliminary findings suggest that HAT may hold promise as a rapid, noninvasive diagnostic tool for assessing upper limb

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perfusion and might potentially complement or even replace other noninvasive techniques such as DBI, digital pressures, and plethysmography (which are currently standardized in this context). Nonetheless, this will require future robust prospective studies addressing the sensitivity, specificity, and predictive values of HAT in comparison to these existing modalities.

Herein, we propose a structured and reproducible method for measuring HAT by using DUS in both patients with chronic upper limb ischemia and healthy volunteers. Although the study was not powered to establish definitive diagnostic thresholds, the reported ranges might serve as preliminary reference for future research. Given its descriptive nature and limited sample size, stratifying HAT values across different types of arterial disease was deemed impractical, as subgroup analysis would likely reduce (if not mislead) interpretability. However, this study does describe the anatomical location of the affected arteries, bearing in mind that HAT values tend to be elevated in ischemic hands regardless of the disease site when compared to healthy limbs.

Markedly, this study might incur information bias since the HAT results, like most sonographic measurements, are examiner-dependent; however, if it were the case, it would be a systematic bias (since the same examiner performed all the measurements), yielding similar probabilities of occurrence in all study participants. The small sample size does not allow analysis adjustments for more than one variable and acts as another limitation. Further, generalizing its results to a broader population requires caution, given these limitations; however, they may serve as guidance for conducting future large-scale studies.

Transcutaneous oxygen pressure ($TcPO_2$) and skin perfusion pressure are valuable tools for assessing tissue perfusion, particularly in the context of lower limb ischemia, and exploring their correlation with HAT in cases of upper limb ischemia would be of interest. However, although $TcPO_2$ has been well validated for lower limb assessments, no consensus currently exists regarding reference values or diagnostic thresholds for hand ischemia. Based on our clinical experience—despite having previously used $TcPO_2$ routinely for lower limb evaluation—we found the test to be time-consuming, technically challenging for the upper extremities, and frequently inconclusive in guiding clinical decision-making. Consequently, we progressively discontinued its use in our daily practice. Given these limitations and the lack of validated upper-limb parameters, $TcPO_2$ was not included in this study. Nevertheless, future research examining the correlation between HAT and alternative perfusion metrics such as $TcPO_2$ or skin perfusion pressure may contribute to further validating HAT as a diagnostic tool for hand ischemia.

On the other hand, the rich collateral circulation of the hand—arising primarily from the radial, ulnar, and interosseous arteries—plays a significant role in modulating perfusion and may influence arterial Doppler waveforms, potentially affecting HAT results. The HAT protocol was intentionally designed to assess the overall arterial supply to the hand and to provide an indirect measure of collateral flow. To ensure consistency and reliability, we selected 4 arterial segments for evaluation: 2 branches from the radial artery and 2 from the ulnar artery. This choice was based on anatomical studies indicating relatively low interindividual variability in these segments, thereby supporting reproducibility across participants while adequately capturing the contributions of both major vascular axes.

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Data Availability

Datasets used and/or analyzed during this study are available from the corresponding author upon reasonable request immediately after publication.

Authors' Contributions

The authorship is based on the International Committee of Medical Journal Editors criteria.
Conceptualization: BG, SV, EI
Methodology: BG, SV, TC, EI
Investigation: BG, JM, CH, EE
Writing – original draft preparation: BG, TC
Writing – review & editing: BG, SV, TC
Supervision: BG, SV, EI

Conflicts of Interest

None declared.

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Abbreviations

DBI: digital-brachial index
DUS: duplex ultrasound
HAIDI: hemodialysis access–induced distal ischemia
HAT: hand acceleration time
STROBE: Strengthening the Reporting of Observational studies in Epidemiology
$TcPO_2$: transcutaneous oxygen pressure

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Protocol

Dance as an Adjunct Therapy for Neurological Rehabilitation – Creative Enrichment for Recovery (DAN-CER): Program Design and Protocol for a Mixed Methods Pilot to Assess Feasibility and Acceptability

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Abstract

Background: Dance is a novel recreational activity that may improve psychosocial outcomes in inpatient neurological rehabilitation; however, adapted dance programs in neurological rehabilitation settings are still emerging.

Objective: This paper describes the co-design process undertaken to develop an adapted dance program for use in neurological rehabilitation. It also presents a study protocol aimed at evaluating the program's feasibility, acceptability, and preliminary efficacy in a subacute hospital setting.

Methods: A 3-phase co-design approach was used to develop the Dance as an Adjunct Therapy for Neurological Rehabilitation – Creative Enrichment for Recovery (DAN-CER) program and protocol, including knowledge seeking, seeking expert input, and refining. Information sources included a literature review, stakeholder meetings, workshops, and focus groups with clinicians and patients. This study has approval from two ethics committees (HREC/2023/QGC/99631 and GU 2023/813).

Results: We undertook 4 workshops with Queensland Ballet, and 2 focus groups were undertaken with staff and neuroscience ward patients. The resultant program was mapped to the Template for Intervention Description and Replication (TIDieR) checklist. A mixed methods design was selected to evaluate the program. Primary outcomes are the feasibility and acceptability of the adapted dance program with data on accrual and attendance collected weekly. Semistructured interviews with patients and staff were conducted postintervention. The secondary outcome is the efficacy of DAN-CER for improving well-being and affect, with impact on fatigue monitored. Adapted dance classes and data collection assessments began in late October 2024, and data collection was completed in late February 2025. At the time of manuscript submission, 14 participants had been recruited. Interviews have been transcribed, and preliminary coding is underway; findings are expected to be submitted for publication in December 2025.

Conclusions: The rigor of the multiphase co-design process enabled the development of an adapted dance intervention capable of accommodating the physical, cognitive, and communication challenges of neurorehabilitation ward patients. The proposed mixed methods protocol will enable multidimensional evaluation of the adapted dance program.

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(JMIR Res Protoc 2025;14:e69452) doi:10.2196/69452

KEYWORDS

acquired brain injury; adaptive dance; adjunct therapy; dance; feasibility; neurorehabilitation

Introduction

Recovery From Brain Injury

After surviving a traumatic brain injury (TBI) or stroke, 35% to 44% of people will require inpatient neurological rehabilitation [1,2]. Many patients during this time report experiencing social dysfunction (eg, reduced ability to function socially and feelings of social isolation) and psychological distress, such as anxiety [3]. Although there are biological (eg, inflammation and disrupted neurocircuitry between the prefrontal cortex and the limbic system) [4,5] and social reasons (eg, role change) for this, the inpatient environment may also be a contributing factor. Specifically, one limitation of brain injury rehabilitation settings is the predominant focus of impairment-driven rehabilitation, delivered in risk-adverse environments that optimize efficiency [6]. Although for good reason, this can be at the expense of elements necessary to support a positive patient experience such as positive distractions [6] and social contact [7]. Further, when not completing intensive rehabilitation, inpatients are often exposed to large amounts of passive, nonstimulating activities such as watching television [8,9], highlighting the need for alternative stimulating experiences in neurological rehabilitation [10].

In the hope of improving patient well-being and therapeutic outcomes, there is now a push to enrich the neurological rehabilitation environment [11]. “Environmental enrichment” can be defined as activities designed to facilitate sensorimotor, cognitive, and social activity by the provision of a stimulating environment [12]. Applying this definition to neurological rehabilitation, such activities should be interesting or engaging to encourage voluntary participation [13].

One environmental enrichment activity suitable for inpatient brain injury recovery is *creative arts*. Using *creative arts*, group-based activities offer two distinct advantages to traditional group therapy in the neurological environment. Although verbal psychotherapy relies on dialogue as the primary mode of communication [14], creative arts instead provide a low-verbal alternative for emotional expression [15,16]. Additionally, creative arts approaches facilitate communication in a unique way, encouraging authentic, natural interactions within the group, which can offer a new way to connect among participants [17] and a potential avenue for peer support [18].

Adapted dance is a novel approach to a group-based creative arts environmental enrichment activity for use in inpatient neurological rehabilitation. Although all creative arts activities aim to foster self-expression and creativity [18], dance also uniquely engages multiple sensory, cognitive, and motor pathways [19] and is typically perceived as a meaningful activity that fosters a sense of agency [20]. Further, certain elements of dance can be strategically used as a pillar in the program to foster a sense of belonging. Specifically, the synchronized movement and social coordination fundamental in group dance have been shown to enhance social connection, elevate mood, and promote pro-social behaviors [21,22]. Together, the multisensory and social elements of dance make it a prime candidate for an enrichment activity.

There is sound empirical support that dance has positive psychosocial benefits for individuals experiencing an array of health conditions. Reviews highlight the positive psychosocial impacts of dance across various clinical populations, including individuals with affective disorders, Parkinson disease, schizophrenia [23], physical disability [24], or physical and mental illness [25] as well as older adults [26]. Although the psychosocial impact has been understudied in people with brain injury, the limited existing research indicates social benefits of dance in both the hospital [27-29] and community [30] settings. However, further research is warranted to explore the potential of dance for enhancing well-being in individuals with brain injury.

Adapted Dance in Neurological Rehabilitation

To systematically evaluate adapted dance in neurological rehabilitation settings, it is essential to take an evidence-based approach to program design and use standardized reporting in publications. Specific methodologies for designing adapted dance programs tailored to neurological rehabilitation are emerging [31]. However, Fortin [32] argues that, across many dance health programs, more research has focused on the outcomes of dance rather than the program itself. Although dance movement therapy is a common therapeutic approach, it can include a variety of components. When tested in a neurologically healthy population, it was found that some elements should be used cautiously due to their negative effect [33]. However, detailed descriptions of the components included in adapted dance programs are rarely reported. For these reasons, Beaudry et al [34] advocated for consistent use of a standardized checklist by dance health program designers to advance the field. One such example is the Template for Intervention Description and Replication (TIDieR) checklist [35], which helps provide a comprehensive description of an intervention facilitating future replication.

Acceptability research is also essential for programs such as adapted dance in neurological rehabilitation. Acceptability in health care interventions refers to the extent to which the intervention is considered appropriate by either the people delivering or receiving the intervention [36]. Examples of acceptability constructs are dropout rates, reasons for discontinuation, side effects, ratings of satisfaction, and feelings toward and perceptions of the intervention [36]. Although several dance studies to date have trialed adaptations, a scoping review found that, in many studies, the acceptability of these programs was not assessed by end users (D Pretty et al, unpublished data, August 2024). However, reviews of community dance programs and other complementary rehabilitation programs have highlighted that exploring

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feasibility and acceptability is a critical phase prior to formal evaluation and implementation [30,37].

Reviews indicate that few adapted dance programs in neurological rehabilitation use a co-design approach. In the review by Kipnis et al [30], only one-half of the programs used movements recommended by therapists. This is similar in adapted dance for people with TBI. Our review found that adapted dance programs were rarely developed with clinician input or through a co-design approach that involved individuals with lived experience of a brain injury (D Pretty et al, unpublished data, August 2024). Collaborative involvement of clinicians and patients in the design process can help to ensure the final program meets safety requirements while also being enjoyable and engaging. Multidisciplinary involvement may also help stakeholders build trust in the program, which will assist in the program running.

In summary, the acceptability of adapted dance programs in neurological rehabilitation has not been thoroughly assessed. For adapted dance programs to align with other neurological rehabilitation practices, the design process should engage end users and be multidisciplinary, and the program should be reported in a systematic fashion.

Current Limitations in Neurological Rehabilitation Assessment

A key challenge evident in the neurological rehabilitation literature is understanding the individual differences in outcomes from interventions [38,39] and the variability from day to day (see [40]). Repeated measurements of psychosocial function, such as in a single case design approach, can reduce the threats to internal validity posed by this variability. This approach allows researchers to better understand the impact of adapted dance at an individual level, which is particularly important given the heterogeneity of brain injuries [41].

An additional priority for patient safety and ethical conduct in neurological rehabilitation research is the adequate monitoring of fatigue throughout adapted dance. Various researchers have identified fatigue as a potential barrier to participation [42] and a potential adverse effect from adapted dance [27,29]. However, fatigue has not been systematically examined in adapted dance studies. Fatigue is a multifaceted issue, including both mental and physical components [43] that must be addressed and monitored throughout the program to ensure patient safety.

The Need for a Mixed Methods Feasibility and Acceptability Evaluation

In study populations that have complex needs, questions of “can it work?” prior to “does it work?” are particularly pertinent [44]. Using mixed methods is beneficial for assessing implementation feasibility, specifically with the inclusion of field notes and observations [45], providing a rich understanding of why the program or methods did or did not work [44].

Summary

Adapted dance could be a novel adjunct therapy in neurological rehabilitation offering physical and cognitive stimulation and encouraging interactions, in addition to providing other health benefits. However, adapted dance in this field requires strategic program development including co-design techniques. For adapted dance to advance within neurological rehabilitation, essential modifications must occur in consultation with clinicians and patients and reported using standardized methods. Moreover, traditional pre-post research designs should be expanded to include repeated measurements to better understand variability in key outcomes and include safety measures such as fatigue monitoring and management.

Aims

The aims of this paper are 3-fold: (1) describe a 3-phase co-design approach used to develop the Dance as an Adjunct Therapy for Neurological Rehabilitation – Creative Enrichment for Recovery (DAN-CER) program, (2) provide a description of the resulting DAN-CER program using the TIDieR checklist [35] to promote completeness of reporting for replication, and (3) describe the mixed methods protocol to assess the feasibility and acceptability of the DAN-CER program and the methods used to evaluate its efficacy for improving well-being in addition to monitoring fatigue.

Methods

Development of the Program

A 3-phase co-design approach was used to develop the DAN-CER program over 2 years (Aim 1). The phases were (1) knowledge seeking, (2) seeking expert input, and (3) refining. Figure 1 provides an overview of the program development phases.

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Figure 1. Program design timeline. GU: Griffith University; GCUH: Gold Coast University Hospital; QB: Queensland Ballet.

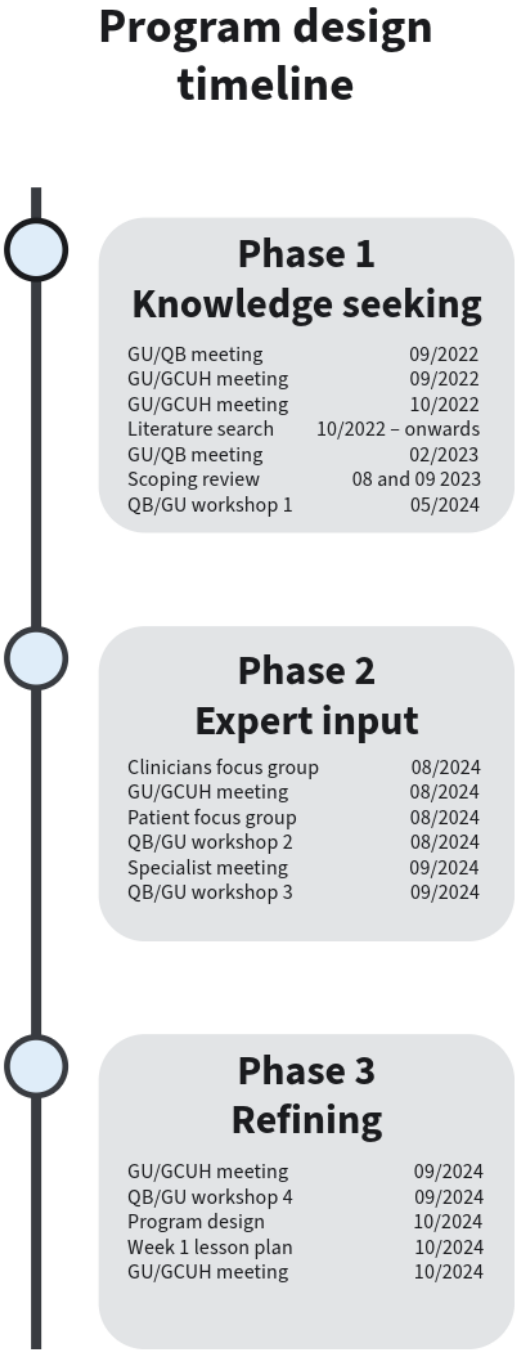

Phase 1: Knowledge Seeking

Phase 1 consisted of discussions, a literature review, reflections on previous pilot adapted dance programs, and a teaching artist workshop.

Collaborator Discussions

Griffith University (GU), Queensland Ballet (QB), and the Gold Coast University Hospital (GCUH) were involved in initial collaborator discussions to propose formative ideas and assess interest. Discussions occurred during face-to-face meetings in September 2022, October 2022, and February 2023. In attendance were members from the medical and research team (including senior and middle management of the organizations and the GU PhD candidate).

Each party discussed their specific requirements. The university included a PhD candidate who had been involved in the earlier community-based proof-of-concept study—Ballet for Brain Injury (BFBI; a collaboration between Citrine Sun Entertainment, QB, and GU). GCUH required a recreation program that could run on Saturday mornings within their recreation activity program (RAP) using nursing staff to assist. The program needed to be designed for a heterogeneous group of people with acquired brain injuries. The neuroscience rehabilitation ward has a high turnover of patients, so each class needed to be independent from previous and subsequent sessions. It was noted that strict procedures for patients to participate would be necessary. For example, the medical team would need a process to determine who can participate and what

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movements they could be asked to do. Their procedures required consistent dance teachers throughout the program, with formalized class plans developed ahead of the sessions.

QB preferred a partnership model rather than being contracted to run the program. They proposed including their physiotherapist and expressed concerns about how ballet might be perceived as elite or daunting in a noncreative environment. As a result, they proposed moving away from the term ballet, rather using the more approachable term "dance."

All collaborators noted resource availability challenges of some nature. Availability of two teaching artists (dance teachers) on a weekend was challenging for QB given their existing weekend program. Similarly, neurosciences ward allied health staffing was restricted on weekends. Funding limitations also restricted the scope and duration of the program.

Literature Insights

The literature was searched for useful evidence to support the design of programs for people with neurological impairments. A meta-analysis by Mogan et al [21] concluded that moving in synchrony is beneficial for positive affect and prosocial behavior. A multisensory experience is beneficial following stroke [46], and meditative movement and mindfulness may reduce fatigue in people with brain injury [47]. Regarding movement function, systematic reviews suggest that movement to the beat is beneficial to facilitate motor movements in people with brain injury [48,49] and action observation (observing an action while performing the action) can lead to improvement in movement function [50]. Thus, these concepts became the initial building blocks of the program.

Available dance literature specifically for people with brain injury was reviewed to determine what techniques were currently being used, how dance was being taught, what modifications were used, and if they were effective. This review identified a scoping review on dance with people with stroke [30], but there were no reviews on dance for people with TBI. Therefore, a scoping review was conducted on this topic (D Pretty et al, unpublished data, August 2024). These reviews identified challenges associated with previous neurological dance programs including difficulties initiating movement [34,51,52], risk taking and disinhibition [52], tailoring the intervention (eg, stimulating a stroke-affected side in a heterogeneous class [34]), inappropriate movements during improvisation [34], and the potential that dance increases fatigue [27,29].

Pilot Project

A proof-of-concept study, BFBI, was conducted in 2021 (D Pretty et al, unpublished data, December 2024). Follow-up questionnaires were sent to all participants with brain injury and their carers post-BFBI program participation. Responses indicated that people with a brain injury and their carers were satisfied with how the pilot program was delivered. The majority agreed it improved their quality of life and their emotional and mental well-being. Perceived benefits included improved perceived fitness and a sense of social connection, which was linked to positive emotion. Participants reported that the classes were well facilitated and scaffolded. They highlighted the usefulness of movement repetition and the tailored speed of the class to suit the needs of people with brain injury. When asked what could improve the program, one person suggested increased options to suit varying ability levels, and another suggested recapping the previous week due to memory limitations (D Pretty et al, unpublished data, December 2024).

The author DP audited the adapted dance classes throughout the proof-of-concept BFBI study and had informal discussions with the participants and therapists following sessions. These observations highlighted a need to reduce the burden on those assisting participants perform the movements. Specifically, helpers struggled with not knowing what movements were coming next. It was also challenging to maneuver participants (eg, changing sides on the ballet barre). Thus, it was decided that the teaching model required slight modifications to support those assisting dancers and ensure less effort was required.

Teaching Artist Workshop

This phase was concluded with a face-to-face workshop in May 2024 with QB teaching artists, research team members including the QB physiotherapist, and the GU researcher/dance teacher (DP). Initial ideas for addressing the program-related challenges were discussed. Optimal approaches for including those with hemiparesis were workshopped. The use of improvisation was also discussed, and consideration was given to how this could be safely implemented.

Phase 2: Seeking Expert Input

The information gathered from Phase 1 shaped design questions that were further explored in Phase 2 where expert opinion was sought from allied health clinicians (n=2) and neurosciences ward inpatients (n=3) during separate focus groups and a speech pathologist through a meeting. Data from the focus groups were analyzed and applied over 3 steps: (1) Content analysis was used to derive key safety and organizational concerns, including barriers and enablers to patient attendance; (2) conclusions were validated through specialist consultations; and (3) QB/GU workshops were conducted to apply the knowledge gained to program design and implementation.

Clinician Input

Two allied health clinicians (a physiotherapist and an occupational therapist) attended a 1.5-hour focus group in mid-August 2024. The clinicians had between 8 years and 19 years of experience in neuroscience rehabilitation, one with and one without previous experience with dance. Example topics in the focus groups were the barriers and enablers to dance, potential benefits of dance, safety concerns, and movements that should be omitted.

Example recommendations made by therapists were that movements be gentle and stay within their base of support (no leaning forwards or sideways) and that exercises avoid the need for arms or legs moving at the same time (eg, feet marching without arms or arms extended without feet marching). The need for modifications to language such as slowed pace of instruction, the additional use of gestures, and using language sensitive to those who have had a limb amputated were suggested. Views on the appropriateness or inappropriateness

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of patients performing movements standing if able were raised, and a safety modification of no passive assistance for those with hemiparesis was recommended.

Concerns were raised regarding dance teachers' lack of medical knowledge or medical training and how this might impact patients. For example, if teachers would instruct patients to "stretch" when this would be contraindicated for them or if they would give unsolicited advice regarding what would be beneficial for patients from a rehabilitation perspective. The onsite location of the dance classes was also discussed. For example, concerns included the impact of using the therapy room on a weekend; logistical challenges such as transporting the patients to and from the location; and equipment safety and staffing limitations on the weekend. These important topics raised were then discussed with the medical team, and a plan of action for each topic raised was devised. This involved medical emergency team call procedures and processes for the research nurse to provide dance teachers with information regarding what movements patients are and are not cleared to do or any specific necessary precautions.

Neurosciences Inpatient Input

A 60-minute focus group was attended by 3 neurosciences ward inpatients with acquired brain injuries (56-77 years old; 2 women, 1 man) in mid-August 2024. Questions pertained to what they wanted to achieve, what would help them feel safe, what type of dance movements and music they wanted, and what barriers there would be to participating. Patients were given the questions earlier in the day to allow time to plan their answers. Issues raised included the desire for simple movements (such as percussion) for inclusivity, repetition, and improvisation. They discussed that having themes would be fun and something to look forward to with certainty. When discussing music, the patients reminisced about music, dance halls, and music from their younger years. It became apparent that music selection from relevant eras could be an important element to the adapted dance classes.

Three other salient topics patients raised included agency, boredom, and safety. Patients discussed that, during inpatient care, every element of their day is chosen for them, from what time they shower to what time they eat. The opportunity to choose and have influence over decisions such as the opportunity to create movements or choose music was important. The desire to break the boredom of "staring at the ceiling" was also relished. Regarding safety, patients discussed the desire for clinicians to be involved in their lessons. They also described potential barriers of fatigue, pain, and sickness.

Specialist Support

Based on clinician opinions regarding the need to tailor communication for people with brain injury, specialist support was sought from a speech pathologist at GCUH through a 60-minute virtual meeting in early September 2024. Suggestions included the use of both verbal cues and gestures to communicate, using repeated simple instructions on repeated movements (eg, arms, arms, arms), and the use of concrete descriptions free of jargon. Suggestions to support attentional processes included having only one main speaker for each section, using a consistent technique to get attention, and keeping distractions to a minimum.

Advice for supporting cognitive disorders included segmenting teaching, where one teaches the more complex version and one teaches a simpler version instead of demonstrating both options and allowing the patient to choose. Given the potential challenges associated with the use of improvisation and movement creation, it was suggested that a contingency plan be developed for the improvisation section including alternative facilitation strategies.

Teaching Artist Workshop

Two workshops were conducted with QB teaching artists, a QB physiotherapist, and the GU researcher/dance teacher (DP) in August 2024 and October 2024 to consolidate all information learned. Together, this information was used to develop the *what* and *how* of the program and classes. Teaching techniques were refined and practiced at these workshops. The structure of the class was determined, and fundamental movements to be included in the movement bank were decided.

Phase 3: Refining

In Phase 3, the aim was to build on and finalize the adapted dance program and the movement bank and to manualize the program (the TIDieR checklist and class plans). The weekly sessions could then be built to these parameters with confidence in safety and consistency in sessions. To enact this, initial concepts were disseminated (via movement and teaching videos and the TIDieR checklist). Feedback was then gathered and implemented in an iterative process, alternating between meetings and workshops. In collaborative meetings (which included further expert support from allied health and a rehabilitation team member), processes for safe participation were further developed where necessary.

Movement Bank

The safety of the preliminary devised movements was assessed through feedback from the medical research team. A video bank, consisting of prototypical movements from each section of the class (ie, mindful warmup, percussion, arms and legs) was shared, along with the corresponding cueing styles. The videos included a range of potential movements of differing degrees of challenge, by difficulty (levels 1, 2, and 3).

GCUH Medical Team Feedback

In late September 2024, feedback on the movement bank was given through an online meeting with members of the medical research team who had also consulted other specialist rehabilitation team members. This feedback was predominately on providing additional modifications for those in wheelchairs and for those with upper limb mobility challenges. Other modifications included the use of headset microphones for the hearing impaired and the requirement of additional stability aids if some patients were to be standing. The expected proportion of patients who would be able to participate in certain exercises or not was also discussed for dance teacher knowledge.

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Teaching Artist Workshop

Final program design based on this feedback occurred in a 2-hour face-to-face workshop in late September 2024. Further cues for the creative section were mapped out, as were the themes and design of the repertoire section. Music options were discussed, and a music bank was initiated for quick selection over the weeks in case any in vivo adaptations needed to be made to the song tempo. Following this, the TIDieR [35] was completed, and preliminary weekly class plans (which included cueing and any precautions) were devised collaboratively online between the QB and GU team members then sent to the hospital team for final approval.

GCUH Medical Team Feedback (2)

Further feedback on the program was given (such as the removal of neck movements (eg, slow looking sideways). Standing exercises were removed for the first week of the program.

Outcomes

At the end of each phase, critical decisions about the program were made. Table S1 Multimedia Appendix 1 reports these decisions. The need for additional processes was also highlighted and devised. For example, to assist with patient eligibility as to who can perform what level of movements, it was agreed that the class plan for the week would be sent to the medical research team on Monday afternoons ready for their Tuesday morning staff discussions. Table S2 in Multimedia Appendix 1 highlights the safety concerns between stakeholders and how these were addressed.

The DAN-CER Program Mapped to the TIDieR Checklist

Following the end of Phase 3, the DAN-CER protocol was finalized. In this section, a description of the DAN-CER program was mapped to the TIDieR checklist to promote completeness of reporting for the purposes of replication (Aim 2). The protocol is described in Table S3 in Multimedia Appendix 1. Using the TIDieR checklist ensured that clinicians, allied health professionals, and dance teachers can replicate or build on research findings.

Protocol for Piloting the DAN-CER Program

This section outlines the protocol to pilot the DAN-CER program (Aim 3). The primary objective is to assess the feasibility and acceptability of DAN-CER in the subacute hospital setting using a mixed methodology. The secondary objective is to pilot a single-case, 1-phase (B phase), nonexperimental case methodology to assess the efficacy of DAN-CER for improving well-being in addition to monitoring fatigue.

Registration

The proposed pilot is not a clinical trial and, therefore, has not been registered. Any future evaluative research on the DAN-CER program will be registered.

The Brain and Enriched Environment Laboratory

This project is a Brain and Enriched Environment Laboratory (BEEHive) project. As described by Norwood et al [11], the BEEHive is a multidisciplinary team situated within The Hopkins Centre, GU, that investigates how an enriched environment can assist neurological rehabilitation. Specifically, the BEEHive aims to develop (using a participatory research approach), test (including piloting and acceptability and efficacy testing), and deliver novel solutions to enrich the neurorehabilitation environment.

Setting

DAN-CER operates at the GCUH neuroscience rehabilitation unit as part of their RAP. This is a 28-bed unit in which the hospital team provides intensive inpatient rehabilitation throughout weekdays and recreational activities occur on weekends. The classes are held on the neuroscience ward on Saturday mornings at 10 AM for 6 weeks and began in mid-October 2024.

Study Design

The study uses a mixed methods design. Mixed methods were chosen to generate comprehensive insights that may be used to inform further adaptations of the DAN-CER intervention and methodology. The mixed methods design includes semistructured interview questions, field notes, and quantitative data (eg, questionnaires and count data). Regarding quantitative data, the study incorporates a single-case, 1-phase (B phase), nonexperimental design with replication across 3 participants. Interparticipant replication is chosen for intensive study at the individual level to capture different characteristics of brain injury. This approach provides a detailed understanding of any potential impact of the program while also assessing how variable outcomes are from day to day and differences between participants. The chosen methodology (as opposed to an A-B or multiple baselines study) is due to a range of contextual factors such as the average patient length of stay, the available time for running the classes, and funding. In addition, restricting enrichment in a group of people that have minimal other activity options (due to delivery of the adapted dance program occurring on the weekend when no therapy is available) could raise ethical concerns in terms of potential negative emotional impacts [53], which we aimed to avoid. Given the pilot nature of the case study methodology, there is no control group and therefore no randomization nor blinding. Results will give an indication of how to proceed with future iterations of the study.

By using a mixed methods pilot, any issues with data collection (eg, due to logistical or communication barriers, time pressures, fatigue) and program implementation can be evaluated and used to inform the design of future research methodology, including outcome measures (for example, determining if a single-case experimental design is feasible) and any further program modifications needed. See Figure 2 for the schematic diagram of the study process and Table 1 for the schedule of assessments.

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Figure 2. Flowchart of the protocol for neuroscience ward patient participants. DAN-CER: Dance as an Adjunct therapy for Neurological rehabilitation – Creative Enrichment for Recovery; SCD: single case design; UBACC: University of San Diego, Brief Assessment of Capacity to Consent.

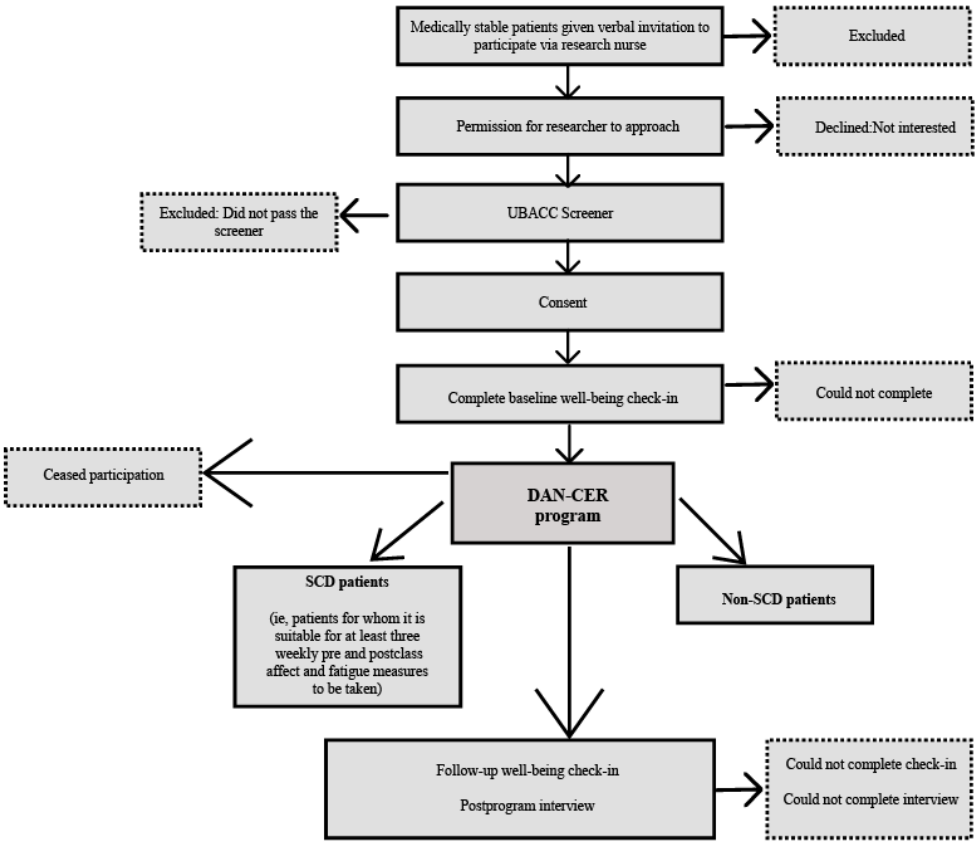

Table 1. Schedule of enrollment, assessments, and adapted dance classes.

Activities	Time (minutes)	B1[a]	Week 1 class		Week 2 class		Week 3 class		Week 4 class		Week 5 class		Week 6 class		F1[b]
			A[c]	B[d]	A	B	A	B	A	B	A	B	A	B	
Consent	30	✓	__[e]	—	—	—	—	—	—	—	—	—	—	—	—
PANAS[f]	5	—	O[g]	O	O	O	O	O	O	O	O	O	O	O	—
VAS-F [h]	5	—	O	O	O	O	O	O	O	O	O	O	O	O	—
DASS-21[i]	5	✓	—	—	—	—	—	—	—	—	—	—	—	—	✓
WEMWBS[j]	5	✓	—	—	—	—	—	—	—	—	—	—	—	—	✓
Exit interview	<30	—	—	—	—	—	—	—	—	—	—	—	—	—	✓

[a]B1: pre-Dance as an Adjunct therapy for Neurological rehabilitation – Creative Enrichment for Recovery (DAN-CER).
[b]F1: post-DAN-CER follow-up
[c]A: pre-adapted dance class assessment.
[d]B: postadapted dance class assessment.
[e]Not applicable.
[f]PANAS: Positive and Negative Affect Scale.
[g]O: option to assess at this time if appropriate (eg, some patients may not be assessed every week).
[h]VAS-F: visual analog scale for fatigue.
[i]DASS 21: Depression Anxiety Stress Scales.
[j]WEMWBS: Warwick-Edinburgh Mental Wellbeing Scale.

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Participants and Recruitment

The study includes 2 groups of participants, as follows: (1) patients at the GCUH who sustained a brain injury and are residing on the neurosciences ward and (2) neurosciences ward staff who assist with program delivery. The group of patients will primarily consist of people who have experienced a stroke, TBI, or neoplasm. A research nurse provides information about the project to the patients. As a pilot study, the adapted dance classes are adjunct to participants' other therapies. For the staff group, any staff member present during the adapted dance sessions receives information about the follow-up interview at the end of the day. All participants are adults (>18 years) who can communicate in English.

Patients residing on the neurosciences ward are considered a special population necessitating additional ethical considerations, as discussed in the following paragraphs.

Regarding cognitive impairments, to be eligible, patient participants must demonstrate sufficient cognitive capacity to understand the study's purpose and provide informed consent. Eligibility requires completion of the University of California, San Diego Brief Assessment of Capacity to Consent (UBACC) [54], with a passing score. Further, a patient consent form modified with assistance from a speech therapist is used to ensure that the language used is appropriate.

For recruitment considering the dependent relationship with hospital staff, eligible patients are approached by a research nurse, who obtains verbal consent to allow a university researcher to provide further information.

Patient data are maintained in accordance with an approved data management plan to ensure confidentiality and security. When required, essential data are securely transferred to co-investigators via password-protected links, granting access to the individual research files stored in a secure system.

Sample Size

The sample size required for the study is not derived statistically but rather determined by feasibility and pragmatic considerations. The sample size is constrained by class size parameters for safety (a maximum of 6 participants per session) and an expected high turnover of patients during the 6-week period (due to discharge from the ward). Accrual data are gathered from all patients on the ward, and qualitative data are gathered from up to 10 patients and nursing staff who participated in the program.

Intervention and Procedures

The intervention is outlined in Table S3 in Multimedia Appendix 1 in accordance with the TIDieR checklist [35]. Several potential challenges to implementation are anticipated and addressed. The most likely concern is staff shortages due to sickness. In such instances, a contingency plan is in place to reduce the number of participants in each class, ensuring that the appropriate staff-to-patient ratio is maintained. Additionally, if logistical issues such as transportation difficulties arise, the class is relocated to the dining room, which is closer to patient rooms.

Another key consideration involves the burden on clinical staff to conduct patient clearances. This challenge is minimized by aligning the clearance process with the existing procedure for granting weekend leave. To facilitate this, the lead author developed a proforma document for completion.

Outcomes

To align the research questions with the quantitative and qualitative data sources, a data source table has been developed. This is presented in Table S4 in Multimedia Appendix 1. Further descriptions are provided in the following sections where necessary.

Primary Objective Measures

Feasibility

Feasibility is gauged through recruitment, retention, and attendance. Here, field notes provide a deeper understanding. For example, if a participant ceased participation during a class, the reason is noted (eg, fatigue, nonenjoyment, conflicting schedule). These data on attendance and field notes are collected by the researcher/dance teacher (DP). Regarding accrual success criteria, ongoing feasibility for the RAP requires at least 6 participants who are deemed safe and interested per week. To justify staffing, a minimum of 4 patients per class is needed. These numbers serve as the feasibility targets. Feasibility assessment also includes any safety concerns such as adverse events or minor harms.

Acceptability

Acceptability is assessed through qualitative analysis of face-to-face interviews with patient participants (target numbers of 6 individuals with acquired brain injury) and neurosciences ward staff (target number of 12). All patients with brain injury who participate in the adapted dance sessions are given the opportunity to provide insight into their experience with the program through a semistructured exit interview. Similarly, all staff involved in the program delivery are invited to provide feedback. Example topics for questions to participants include their overall experiences, likes and dislikes, any challenges and how these were overcome, and whether they perceive any benefits. Example topics for questions to staff include their general observations and experiences; perceived benefits or disadvantages to the participants, themselves, or the operation of the hospital; and any other feedback. Acceptability is also assessed through dance teacher, research nurse, and multidisciplinary team notes.

Secondary Objective Measures

Psychosocial Outcomes and Fatigue

Participants who can complete the repeated assessments have fatigue and affect assessed before and after each adapted dance class for the duration of their participation. It is expected that approximately 3 sets of complete pre and postsession individual data will be gathered across the 6-week program. Fatigue is assessed using the visual analog scale for fatigue (VAS-F) [55], and affect is assessed using the Positive and Negative Affect Scale (PANAS) [56].

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The VAS-F will be used to assess present moment fatigue. On it, participants circle their response (0 to 10) to 18 items indicating how energized and fatigued they feel. Responses range from "not at all" to "extremely." The VAS-F has been found to have convergent validity with the Standford Sleepiness Scale and the Profile of Mood States and has high internal consistency. Cronbach α for a patient group was 0.96 and 0.94 for evening and morning assessments, respectively. Results can be interpreted according to two subscales, an energy subscale and a fatigue subscale. Where necessary, the researcher reads aloud the questions and circles responses on their behalf.

The PANAS [56] asks 20 questions about current mood. It measures 11 specific aspects of mood including enthusiasm, pride, fear, and sadness. Participants indicate the extent that they feel a certain emotion at that present moment. Responders choose from "very slightly or not at all," "a little," "moderately," "quite a lot," or "extremely" (1 to 5, respectively). Positive and negative affect items are then summed, producing a score between 10 and 50. The present moment internal consistency is 0.89 for positive affect and 0.85 for negative affect. The PANAS has been used to measure daily affect changes in individuals with brain injury [40].

All neuroscience ward patient participants recruited for the adapted dance intervention undergo mood and well-being assessments assessed at baseline as a "wellness check-in" using two validated measures. These scales are the Depression Anxiety Stress Scales (DASS-21) [57] and Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS) [58]. Participants are re-assessed if they complete at least 4 of the 6 adapted dance sessions. Completion of both pre and postdata is expected for up to 10 participants.

The DASS [57] asks questions regarding levels of agitation; low mood; apathy; and body sensations related to depression, anxiety, and stress such as dryness of mouth and trembling. Participants respond by circling a response (0 to 3), with 0 representing "did not apply to me at all" and 3 representing "applied to me very much or most of the time." Due to the population, the shorter questionnaire (DASS-21) will be used, as it takes one-half the time but retains validity. The DASS has been validated in a TBI sample [59], with depression and stress subscales showing adequate internal reliability. The test-retest reliability (taken between 1 week and 3 weeks apart) of the depression, anxiety, and stress subscales in a brain tumor sample was 0.77, 0.65, and 0.60, respectively [59]. The tool's validity as a screening measure has also been assessed in a TBI population [60].

The WEMWBS [58] has 14 statements regarding positive feelings and thoughts such as optimism, usefulness, self-efficacy, and feeling loved. Respondents reflect on their experience over the last 2 weeks and respond by circling a response from 1 through 5, with 1 representing that they felt that feeling "none of the time" and 5 indicating "all of the time." It has shown sensitivity to change from hospital-based remediation programs with patients with schizophrenia [61] and has been validated as being responsive at the individual level [62]. Test-retest reliability is 0.83 in the general population [58] and 0.84 in older adults [63]. It has been used with participants with stroke [64].

Data Analysis

Approaches to analysis will differ depending on the data type. Pre- and postsession PANAS and VAS-F will simply be plotted and visually displayed. For the pre-and postprogram well-being data, a reliable change index will be calculated (change score divided by the standard error of the two measurement scores) [65]. Recruitment and attendance will be displayed in a flowchart, showing the total number admitted to the ward during the study period, the number deemed eligible and offered the program, the number consenting to participate, and those who attended. The average number of classes attended over the 6 weeks will also be presented.

Interviews will be transcribed verbatim and deidentified for analysis. Interview transcripts will be analyzed thematically using the method proposed by Braun and Clarke [66] to devise themes concerning participants' perceptions of the adapted dance program. DP and MN will initially read and reread interview transcripts to immerse themselves in the data. Initial codes, along with example raw data, will then be presented in a team meeting for team level discussion and code refinement. Themes will be collaboratively developed by the research team.

Mixed Methods Data Integration

As recommended by Aschbrenner et al [44], a joint display table will be produced where rows represent each aspect of feasibility (ie, accrual, retention, attendance, safety, and acceptability) as well as pilot efficacy and measurement and design feasibility. Columns will represent quantitative data (including count data and reliable change index), qualitative data (stratified via stakeholder) including dance teacher and research nurse notes, and themes raised in the semistructured interviews. The final column will be the point of intersection or integration of quantitative and qualitative data including a comment on where the data diverge or are in agreement.

In the case study write-up, qualitative data will be used to expand on the quantitative data in a side-by-side write-up where the patient-specific qualitative data can add value to the quantitative data.

Ethical Considerations

This study has ethics approval (HREC/2023/QGC/99631 and GU 2023/813). All participants provide written consent and can withdraw at any stage. For their participation, participants are offered entry into a draw to win 1 of 3 gift cards worth 50 Australian dollars (~32 USD).

Files are stored in a secure system, and when required, essential data are securely transferred to co-investigators via password-protected links.

Dissemination

The dissemination plan uses multiple strategies to ensure widespread access of the findings among key stakeholders. All participants will be given the opportunity to receive a summary of the results. In addition to traditional dissemination methods such as peer-reviewed journal publication and conference

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presentations, the results will also be shared with hospital staff internally through the BEEHive laboratory newsletter, online presentations with senior staff, and at The Hopkins Centre events hosting relevant brain injury associations.

Reporting

The SCRIBE (Single Case Reporting Guideline In Behavioural Interventions) reporting guideline was not intended for a nonexperimental, single-case study design; however, as highlighted by Tate et al [67], following the guidance of the items may be useful. Specifically in this case, where assessing the feasibility of a future single-case experimental design study is an aim, reporting relevant items according to the guideline is advantageous. Therefore, where applicable, the proposed study will be reported in line with the SCRIBE guidelines.

Patient demographic characteristics will be reported in detail including clinical characteristics such as the cause or type of acquired brain injury; baseline participant characteristics such as functional status, age, and gender; and baseline DASS and WEMWBS scores.

Results

Data collection for the pilot began on October 21, 2024. The classes ran from October 26, 2024, to December 6, 2024. During this period, 9 patients participated in at least one adapted dance class. Data collection is now complete. Follow-up interviews were conducted with 8 patients and 5 nurses. All interviews have been transcribed, and preliminary coding is now underway, with initial codes being tentatively developed and refined through immersion in the data. The results of the study are expected to be submitted for publication in December 2025. This research received no external funding.

Discussion

Overview

Dance combines physical, cognitive, and social activity, and for many, dance is considered an enjoyable, fun experience, thus making it a potential novel environmental enrichment activity for those in inpatient neurological rehabilitation. However, adapted dance program design, feasibility and acceptability assessment, and efficacy assessment in the neurorehabilitation setting need to be systematic and involve end users throughout development. Thus, there were 3 aims in this paper that address these issues.

Aim 1 was to report the design and development of the DAN-CER program. In Aim 2, the resultant program was mapped to the TIDieR checklist [35] for transparency. The information consolidated from the stakeholders across the 3 phases shaped the design of the DAN-CER program. Each stakeholder contributed uniquely. Input from allied health staff assisted designers with developing strategies to suit participants' learning capabilities (eg, the use of short sequences, hand gestures, attention aids). Input from clinicians assisted with improving patient safety (eg, movement omissions and suggestions) and fine-tuning the operational processes. Input from current patients ensured that future neuroscience ward patients would find the program interesting and manageable (through the use of themes, free choice in music selection, and movement style). By using this inclusive approach, it is hoped that the final program will accommodate the physical, cognitive, and communication challenges patients may face.

Aim 3a related to developing protocols for assessing how appropriate the adapted dance program is in the neurological inpatient setting (primary findings). Teresi et al [45] described that, in diverse populations, it is imperative to assess the feasibility and acceptability of an intervention before scaling up. This is a step that is often missed in adapted dance literature, although see [27,29,34]. Continuing the conscious decision to include all stakeholders' viewpoints, the study protocol is a mixed methods design whereby all perspectives are integrated. Accordingly, insight into what changes need to be made to the classes (or the processes to carry out the classes) is captured from the full range of people that the classes will impact, thus providing a comprehensive indication of whether and how future studies should proceed.

Aim 3b reports the protocol for piloting a single-case, 1-phase (B phase), nonexperimental design methodology to assess the efficacy of DAN-CER for improving well-being (using the WEMWBS and PANAS) in addition to monitoring fatigue. These secondary findings will be used to design future rigorous efficacy studies. To date, no known adapted dance study has investigated positive psychological constructs quantitatively or used a single-case methodology that includes repetitive testing to capture changes in well-being in the context of an adapted dance program and how variable these impacts are in a brain-injured population. Based on the cohort, it is expected that our pilot data will reflect high variability (inter and intraperson), and, for this reason, a single-case methodology will be a suitable approach in future studies. The primary outcomes (feasibility) will assist with the decision-making process regarding whether there is enough interest, consistent attendance and treatment, and minimal to no adverse effects for a more rigorous single case experimental study and what type of design would be appropriate.

Strengths and Limitations

The use of mixed methods is the main strength of the pilot study. This methodology allows for the integration of data sources to highlight where the feasibility and acceptability results diverge or converge stratified by stakeholder and within stakeholder but across different data types (qualitative and quantitative). The main limitation of both the program development and the proposed protocol study is that it uses convenience sampling, consisting of a small sample size. Further, the research protocol is not experimental in the sense that it does not involve randomization, a control arm, or a baseline period. Therefore, interpretation of outcomes will require caution.

Future Studies

In the current DAN-CER program, we consciously designed an adapted dance program that uses simple synchronous movement as its main pillar, in the hope of creating an environmental enrichment activity for the inpatient neurological population to benefit mood and well-being. Beyond further iterations including

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more rigorous efficacy studies, different aspects of dance (eg, cognition, movement, social interaction, rhythm) can be strategically manipulated to assess the impact on neuroplasticity in the damaged brain. Further, questions around the optimal cognitive and physical load in the adapted dance program and timing in the rehabilitation pathway represent valuable future research directions. Before such questions can begin to be answered, there is a need for stakeholder-inclusive design, transparent reporting of program design, and rigorous methodology that assesses outcomes at the individual level.

Conclusion

This paper represents the first step of many, whereby an adapted dance program for use in inpatient neurological rehabilitation is ethically designed, transparently reported, and tested for acceptability. Future studies will assess its efficacy more rigorously.

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Data Availability

Anonymized transcripts of focus groups are available on request. Any identifying comments such as role will be removed.

Authors' Contributions

Conceptualization — DP, TO, MN, EK
Data collection — DP, MN
Formal analysis and data collection — DP, MN
Methodology — DP, TO, MN, EK, KC
Supervision — EK, MN, TO
Writing original draft preparation — DP
Writing review and editing — DP, TO, MN, EK, KC, KD, SJ, ZG

Conflicts of Interest

None declared.

Multimedia Appendix 1
Decisions, resolutions, program details, and data sources.
[DOCX File , 54 KB - resprot_v14i1e69452_app1.docx]

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Abbreviations

BEEHive: Brain and Enriched Environment Laboratory
BFBI: Ballet for Brain Injury
DAN-CER: Dance as an Adjunct therapy for Neurological rehabilitation – Creative Enrichment for Recovery
DASS-21: Depression Anxiety Stress Scales
GCUH: Gold Coast University Hospital
GU: Griffith University
PANAS: Positive and Negative Affect Scale
QB: Queensland Ballet
SCRIBE: Single Case Reporting Guideline In Behavioural Interventions
TBI: traumatic brain injury
TIDieR: Template for Intervention Description and Replication
UBACC: University of California, San Diego Brief Assessment of Capacity to Consent
VAS-F: visual analog scale for fatigue
WEMWBS: Warwick-Edinburgh Mental Wellbeing Scale

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Protocol

Australian Implementation of the Teaching Personal and Social Responsibility Pedagogical Model in Physical Education: Protocol for a Nonrandomized Controlled Trial

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Abstract

Background: Interventions targeting the psychomotor domain of learning have been the most dominant in the physical education (PE) discipline. However, as PE also incorporates a holistic perspective of student development, a gap has emerged where interventions targeting social outcomes are not frequently analysed. Social outcomes have been of particular interest for interventions conducted in PE.

Objective: This study will evaluate the impact of an intervention designed to enhance social outcomes among Australian school students. The intervention will be shaped by the teaching personal and social responsibility (TPSR) framework. This framework has lacked representation within the Australian context, creating a gap and an opportunity to explore its impact on the social behaviors of Australian students.

Methods: This study will use a nonrandomized controlled trial design with a qualitative evaluation to assess feasibility and acceptability. Data will be collected through student surveys, student focus groups, and teacher reflection journals. Two schools in New South Wales, Australia, will participate by implementing the TPSR framework in their programs. Schools will include classes in stages 3 and 4 of the intervention, involving approximately 90 students from each school. Both schools are located in Sydney, New South Wales: one is a government high school, and the other is an independent K-12 school. To address feasibility and accessibility concerns, the intervention will be delivered during regularly scheduled PE classes. It will be facilitated by students' regular PE teachers, who will also participate in ongoing professional development and be involved in a co-design process with the research team. Primary outcomes include reporting on personal responsibility, social responsibility, and leadership behaviors, measured using two tools: (1) the Tool for Assessing Responsibility-Based Education and (2) the Personal and Social Responsibility Questionnaire. A secondary outcome, enjoyment, will be assessed using the Physical Activity Enjoyment Scale–Physical Education version. Feasibility and accessibility will also be examined as secondary outcomes.

Results: This intervention study will demonstrate the impact of TPSR on social outcomes among Australian school participants. Students will also receive a briefing, and parental permission will be sought before intervention commencement. Students will be involved in the intervention for the duration of term 3 (10 weeks).

Conclusions: This protocol paper outlines the approach to implementing and evaluating the TPSR intervention among Australian school participants. One anticipated strength of the intervention is the ability to apply the framework to different settings, including schools, school sport, and community organizations. Longitudinal follow-up assessment will be critical in determining the long-term impact of the intervention on behavioral changes among participants.

Trial Registration: Australian New Zealand Clinical Trials Registry ACTRN12624000858594p; anzctr.org.au/Trial/Registration/TrialReview.aspx?id=387883

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International Registered Report Identifier (IRRID): PRR1-10.2196/67924

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KEYWORDS

teaching personal and social responsibility; social; physical education; intervention; high school

Introduction

Background

The aim of physical education (PE) lessons is to establish lifelong habits and behaviors that lead to positive health outcomes [1]. Benefits of youth participation in PE lessons include improvements in cognitive development and learning [2]; social development [3]; and a range of physiological benefits such as improved coordination, balance, weight loss, and cardiorespiratory fitness [4]. Another benefit of participation in PE lessons is access to subject matter experts such as PE teachers who can correct movement, give feedback, and influence engagement and participation [5]. However, the literature suggests that young people become disengaged in PE as they get older, which may limit the achievement of a range of cognitive, affective, social, and psychomotor outcomes [6]. To remedy this decline, emerging literature suggests that a way to re-engage students in PE may be through an emphasis on interventions with outcomes that enhance student achievement across a range of learning domains [7].

PE interventions conducted in schools have been a leading method used by researchers to analyze emerging trends in the health of young people [4,7,8]. Interventions can be categorized as psychomotor, affective, social, and cognitive, with the psychomotor domain being the most dominant in PE-based research and interventions [7]. This is evidenced by a systematic review conducted by Dudley et al [7], who found that psychomotor interventions embedded in PE settings made up 38% of the included studies. The authors suggested that future research should target other aspects of learning, such as confidence and competence, to further support young people's development and prepare them for adulthood [7]. This argument is also supported by the Australian Curriculum: Health and Physical Education (AC: HPE) as well as its statewide equivalent, the New South Wales (NSW) K-10 personal development, health, and physical education (PDHPE) syllabus, both of which have made amendments to include a stronger emphasis on social outcomes (eg, developing empathy, relationship skills, and connectedness) in conjunction with psychomotor outcomes, which have always been prioritized in PE lessons [9]. The recently revised NSW PDHPE syllabus also features a specific strand targeting social outcomes—respectful relationships—with the sole focus of addressing and strengthening social behaviors of students [9].

Interventions targeting social outcomes in PE are not as prevalent as those targeting psychomotor outcomes, but existing studies, which are scattered within the literature, have demonstrated positive findings [10-12]. In the systematic review by Dudley et al [7], which reported on PE interventions and a range of outcomes, only 25 of the 135 included studies assessed the impact of PE on social outcomes. The study by Dudley et al [7] is important because it not only highlights emerging studies on previously underrepresented interventions targeting social outcomes but also demonstrates the gap in the literature and an opportunity for further research.

Furthermore, interventions targeting social outcomes are reported to have strong associations between student motivation and the development of autonomy through PE lessons [13]. Research suggests that students who develop skills such as leadership and responsibility behaviors experience smoother transitions from school to adult life [14]. Other research has found that student self-esteem and physical self-concept were improved through involvement in interventions targeting social outcomes [15]. However, a criticism of social interventions has been the issue of transfer, that is, whether positive effects last beyond the intervention or are merely a result of a novelty effect, which has been noted in studies featuring PE pedagogical models such as the sport education model and teaching games for understanding. To counter this criticism, the teaching personal and social responsibility (TPSR) framework has been chosen, as it has a domain dedicated to promoting transfer [16]. This framework has been used in the PE context to improve the social skills of participants and may be able to address the gap in the literature by targeting social outcomes with lasting benefits [17,18]. The sport education model and the teaching games for understanding model have been used in interventions targeting social outcomes in a variety of contexts; however, "transfer" underpins all other levels of the TPSR framework and aims to address social outcomes as a life skill, rather than as a tool for PE class [19]. Furthermore, TPSR differs from other social frameworks, as its levels are more fluid and nonhierarchical, allowing students to move in and out of the TPSR domains, rather than following a step-by-step process of development [19].

TPSR is a pedagogical framework designed by Hellison to engage students with low socioeconomic status (SES) from urban communities in PE lessons [10,16]. One of the main goals of the TPSR framework is to encourage students to apply the skills learned throughout the intervention to other key learning areas, as well as life outside the school setting [16]. TPSR aims to promote student autonomy and teach students to take responsibility for their learning [17]. The framework aims to improve skills such as empathy and leadership as well as developing and maintaining relationships, which strongly mirrors the goals and rationale of the NSW PDHPE K-10 syllabus and the AC: HPE [9,16,20]. The framework has been constructed using five levels: (1) respect for the rights and feelings of others, (2) effort and teamwork, (3) self-direction and goal setting, (4) helping and leadership, and (5) transfer [16,17]. There are also four themes for each program—(1) a strong teacher-student relationship, (2) empowering students, (3) integrating responsibility into physical activity, and (4)

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promoting the transfer of responsibility—which align strongly with the AC: HPE and the NSW K-10 PDHPE syllabus [9,16,17,20]. Due to a strong link between the TPSR framework and the Australian curricula, future interventions should aim to plan, implement, and test the effect of TPSR in Australian schools. Australian schools are a desirable setting for interventions using TPSR, given the similarities to the environments identified by Hellison [21] in his work with disengaged students from low-SES backgrounds. Furthermore, schools in the western suburbs of Sydney serve a high proportion of students with low SES and have noted difficulty with engagement and integration from both student and teacher perspectives [22,23]. However, TPSR implementation in Australian schools has seldom been reported, and interventions using social frameworks in PE lessons are scarce.

International research using the TPSR framework has shown promising findings [12,18,24,25]. In a systematic review, a Turkish study found that TPSR-based interventions improved students' efficacy as well as interpersonal interactions and emotional regulation when dealing with other students and adults and in contexts where they were required to recognize and express emotion [18]. Similarly, research from Taiwan found that adherence to the TPSR framework in PE settings improved the self-efficacy and efficacy-like behaviors of middle school students [24]. A study in the United States found that students' socially responsible behaviors, such as emotional regulation, problem-solving, and the promotion of social norms, improved as a result of TPSR-based interventions [25]. TPRS has further demonstrated an increase in motivation for engaging in PE classes, with research in Spain demonstrating that students had more positive perceptions of their athleticism as well as showed improvements in leadership and decision-making skills as a result of participation in the intervention [12]. International literature demonstrates a clear improvement in many social outcomes due to participation in interventions that apply the TPRS framework. In addition, a notable point of difference between TPSR and other social frameworks is the transfer domain, which could be particularly important when implementing a TPSR intervention in the Australian context.

Objectives

The aim of the study is to conduct a research intervention that will reveal the impact of the TPSR framework on students' social outcomes in the Australian context. This research is significant because it will be the first time that TPSR has been tested in NSW high schools. The study will use a nonrandomized controlled trial design to determine feasibility and acceptability aspects.

Methods

Trial Registration

The study has been registered with the Australian New Zealand Clinical Trials Registry (ACTRN12624000858594p) and was approved on June 11, 2024.

Ethical Considerations

This study has been approved by the University of Sydney Human Research Ethics Committee (2024/HE000496).

Students and parents will sign consent forms before taking part in this study. Students who do not want to participate will still attend PE lessons, but no data will be collected from them. Participants may withdraw from the intervention at any time by informing their facilitating teacher.

All participants will be deidentified, and no information about individual students or their school will be disclosed. Data will be password protected and securely stored by the principal investigator.

No compensation will be offered to participants or participating schools.

Study Design

The protocol was developed according to the SPIRIT (Standard Protocol Items: Recommended for Interventional Trials) statement (Multimedia Appendix 1).

The study will use a nonrandomized controlled trial design with a qualitative evaluation to assess feasibility and acceptability. This method has been chosen for several reasons. First, one of the criticisms against the TPSR model is that it favors qualitative studies and has been underresearched using quantitative methodologies [11]. To address this, we will use both qualitative and quantitative methods in this study. The concern regarding the limited use of quantitative approaches was echoed in a systematic review on TPSR interventions that found that only 4 of the 22 included studies used exclusively quantitative methods, questioning the validity of the framework outside of qualitative research [26]. Studies have consistently called for greater use of quantitative analysis of the TPSR framework in research [10,11,26]. Furthermore, to obtain the most accurate representation of the effect of the framework in Australian schools, teachers, and students, this approach is deemed most suitable because it uses both qualitative and quantitative analysis and is able to factor in a complex landscape such as education [27]. In this study, data will be collected through student surveys, focus groups, teacher reflection journals, and the Tool for Assessing Responsibility-Based Education (TARE).

We will recruit at least 6 classes from each school participating in the intervention, which will amount to approximately 3 classes in the control group and 3 in the experimental group (Figure 1).

Upon recruitment of the schools and selection of individual classes by each principal, researchers will collaborate with intervention facilitators to implement the TPSR framework during the intervention "season." Table 1 presents example strategies that can be implemented in a TPSR study and will be shared with teachers during the co-design process.

A timeline of the intervention is presented in Table 2.

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Figure 1. Study timeline.

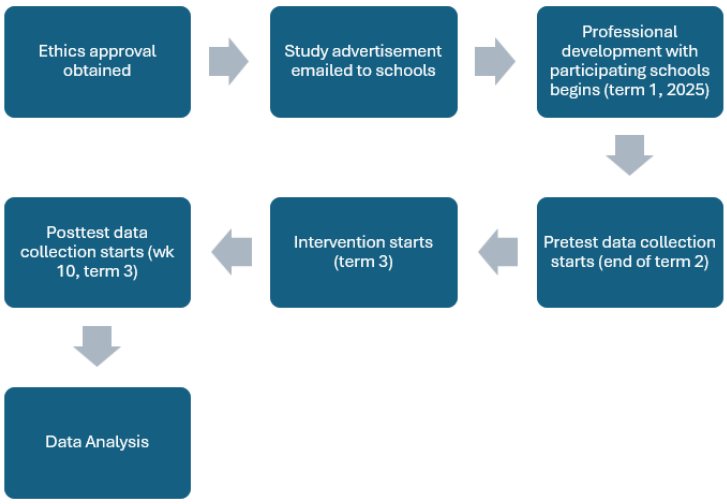

Table 1. Example strategies for implementing the teaching personal and social responsibility (TPSR) framework in physical education (PE) settings.

Levels	Explanation	Social outcomes in New South Wales PDHPE[a] K-10 syllabus	Examples in PE setting
Respect for the rights and feelings of others	Demonstrating empathy for and understanding of other students' feelings	• Interact respectfully with others ("Rationale," page 10) • Stage 4: PD4-2[b]; PD4-3[c]; PD4-10[d]	• Social "theme" of each lesson (eg, cooperation, teamwork, and leadership) • Eye contact • Not raising one's voice during a confrontation
Effort and teamwork	Providing all students, regardless of skill level, the opportunity to be involved and included	• Develop social skills ("Rationale," page 10) • Outcome: PD4-3; PD4-10	• Team huddles • Strategy time • Giving everyone a turn
Self-direction and goal setting	Students' role in the activity, their goals, and the goals of the team; collaboration between the two domains	• Develop self-management skills with self-confident, socially responsible citizens ("Rationale," page 10) • Outcomes: PD4-2; PD4-9[e]	• Discussing strategy • Problem-solving • Giving and embracing roles during games • Students proposing modifications to the games
Helping and leadership	Demonstrating and developing leadership opportunities through play	• Development of interpersonal skills ("Rationale," page 10) • Commitment to lead and promote healthy, safe, and active lives ("Values and attitudes," page 13) • Outcomes: PD4-2; PD4-3; PD4-10	• Equipment roster • Coaching and refereeing responsibilities • Students acquire special roles independent of the teacher • Student-teacher is chosen to instruct the group on the activities for the day instead of the teacher • A new captain is chosen for each lesson
Transfer	How TPSR and the skills learned in lessons can be applied to other facets of life	• Advocate for health, safety, and well-being of themselves and others in the community and beyond school ("Rationale," page 10) • Outcome: PD4-10	• Reflective class discussion on how learning in this setting can be applied to other settings • Student discussions in pairs

[a]PDHPE: personal development, health, and physical education.

[b]PD4-2: a student examines and demonstrates the role help-seeking strategies and behaviors play in supporting themselves and others.

[c]PD4-3: a student investigates effective strategies to promote inclusivity, equality, and respectful relationships.

[d]PD4-10: a student applies and refines interpersonal skills to assist themselves and others to interact respectfully and promote inclusion in a variety of groups or contexts.

[e]PD4-9: a student demonstrates self-management skills to effectively manage complex situations.

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Table 2. Intervention timeline.

Terms and weeks	Tasks
Term 2	
8	• Preintervention testing • PSRQ[a] and PACES-PE[b] surveys administered
9	• Back-up dates for surveys
10	—[c]
Term 3	
1 (athletics)	• Zoom check-in (occurs every week) • "Every name, every day" • Class Goal • HERO concept • "Me time" • "Good Game" at the conclusion of the lesson • "Coaches and Players" in 3-week intervals
2 (athletics)	• TARE[d] analysis
3 (athletics)	—
4 (athletics)	—
5 (athletics)	• TARE analysis
6	—
7	—
8	• TARE analysis
9	—
10	• Postintervention testing • PSRQ and PACES-PE surveys administered • Focus groups completed
Term 4	
Week 5	• Follow-up

[a]PSRQ: Personal and Social Responsibility Questionnaire.

[b]PACES-PE: Physical Activity Enjoyment Scale–Physical Education version.

[c]Not applicable.

[d]TARE: Tool for Assessing Responsibility-Based Education.

Outcomes

The primary outcomes addressed within the intervention are personal responsibility, social responsibility, and leadership, reflecting the levels of the TPSR framework. The secondary outcomes include enjoyment, feasibility, and acceptability. To obtain a comprehensive analysis of the TPSR framework within a school system, the proposed outcomes will provide valuable insights into how the framework influences student behavior and overall intervention effectiveness.

Baseline characteristics will include age, gender, boarding status (boarding vs nonboarding), school type, and SES (via postcode).

Participants

The participants in this study will be students from years 5, 6, and 8. Each intervention group in the study will need to have 77 students and a matched control group of the same size to detect 2-tailed statistical significance ($P<.05$) with 80% power ($1-\beta=0.8$). Two schools in the western suburbs of Sydney have been recruited to participate in the study: one is a government high school, and the other is an independent K-12 school. They have been chosen through professional networks who expressed interest in the TPSR study. Students in NSW generally participate in 1 PE lesson per week, which is where the intervention will take place. PE lessons in NSW high schools are delivered to students from years 7 to 10 and focus on skills development, alongside one or two sport lessons focused on game play.

Consent will be obtained from parents, students, and the school principals in line with the ethics requirements of the University of Sydney. Participants' personal information and school names

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will be deidentified in all publications arising from the study. Students and teachers will also be briefed on the intervention before study commencement and given the opportunity to ask questions. Participants will be allowed to withdraw from the intervention at any time. All data collected, including data from focus interviews, surveys, meeting minutes, and consent forms, will be stored securely and encrypted with a password. If parents request details of intervention results, a lay summary will be provided.

Fidelity and acceptability will be addressed through teacher expertise and training, intervention location, timetabling, and time spent on the intervention. Teachers will participate in a professional development program before starting the intervention. The purpose of this program is to familiarize teachers with the TPSR framework and to facilitate the co-design of strategies and activities to integrate the framework into programs. This approach also means that students do not have to build relationships with or adapt to outside facilitators. Furthermore, it does not incur additional funding for the school or research team. The professional development program will comprise a 3-hour, face-to-face learning block before the intervention and ongoing check-ins with teachers using Zoom (Zoom Video Communications, Inc) for the duration of the intervention.

The intention of the co-design process is to limit disruption to teachers and their practice as well as to create a mutually agreed-upon implementation of the TPSR framework in existing units. The co-design process allows both parties to benefit from sharing information that aims to improve currently established protocols and promotes sustainable practice within the school and with teachers [28]. Co-design principles can be applied at any stage of an intervention but may target three main components: (1) defining the problem, (2) designing a solution, and (3) implementation [29]. Throughout this intervention, teachers will work with researchers to identify social issues at their school; they will then work with researchers to apply TPSR principles to address these issues; and, finally, they will be involved in facilitating PE lessons that implement these principles with students. The co-design process aims to "share power" between the 2 parties taking part in the research with the mutual aim of improving outcomes [29]. This process will enable the research team and teachers to navigate the intervention in a collaborative manner, strengthening the planning process before intervention commencement.

Measurement Tools

The Personal and Social Responsibility Questionnaire (PSRQ) will be used to measure the primary outcomes of the study: personal responsibility, social responsibility, and leadership. This questionnaire has been used in previous TPSR studies and has been deemed valid and reliable [30,31]. It consists of 14 items split into 2 categories (personal responsibility and social responsibility) [30]. Participants will complete the PSRQ in the pretest and posttest phases of the intervention and will be assured that there are no right or wrong responses and that their responses will remain anonymous. The TARE is an observational tool aligned with the TPSR model. The second part focuses on whether teachers have included elements such as modelling respect and setting expectations within their lessons [32]. The secondary outcomes of the study will be enjoyment, feasibility, and acceptability. These outcomes will be measured using the Physical Activity Enjoyment Scale–Physical Education version (PACES-PE), which is an 11-item measurement tool designed to measure enjoyment levels in adolescent children using a Likert scale and revised, student-friendly questions [33]. The PACES-PE has been used in PE-based studies previously and demonstrated positive results in female adolescent populations, particularly through the link between enjoyment and increased rates of physical activity [33].

Recruitment Process

Two schools in NSW expressed interest in participating in the study during the 2025 school year. Upon being are recruited, a brief outlining the intervention design is emailed to principals, including the length of the intervention, its theoretical framework, and requirements for teachers and participating students. Meetings with participating schools will take place, and a co-design plan as well as professional development time will be organized. Consent forms and participation information statements will be distributed to the schools for collection from principals, teachers, students, and parents or guardians.

Eligibility Criteria

Explicit eligibility criteria must be met for participation in the study. Students may participate if they (1) are enrolled in year 5, 6, or 8 at a participating independent or government secondary school in NSW; (2) have completed the pretest questionnaire; and (3) have written consent from parents or guardians.

Intervention Design

This intervention will focus on providing opportunities for students to develop social skills in PE classes. Teachers will act as facilitators, and researchers will codevelop and adapt the intervention programs with them using a co-design process. A teacher professional development program will be administered before intervention commencement to ensure that teachers are familiar with the TPSR framework. Students will take part in focus groups before and after the intervention and will complete surveys measuring social outcomes. The researchers will be available for communication with teachers to maintain intervention integrity and to ensure that issues are addressed efficiently. Teachers will run their PE lessons with the TPSR framework embedded within their existing programs, minimizing additional workload. Examples of TPSR strategies that may be featured within lessons are provided in Table 1.

Before intervention commencement, students and teachers from the participating schools will complete preintervention testing, which will include surveys. Students at each school will then take part in the 10-week intervention and complete a postintervention test similar to the preintervention test. Focus groups will also be conducted during the posttest period. There will be a follow-up 5 weeks after the intervention. In line with the mandated requirements of the schools, students will participate in 1 PE lesson per week, which is standard practice in NSW schools. The duration of each lesson will depend on the school, with 45 to 60 minutes being typical in NSW schools. Social outcomes (personal responsibility and social

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responsibility) will be the primary focus of the intervention, as per the measurement tool.

Data Analysis

This study will use a nonrandomized controlled trial design with a qualitative evaluation of feasibility and acceptability, integrating both qualitative and quantitative data to evaluate the impact of the TPSR intervention.

Quantitative Analysis

Quantitative data from the PSRQ, PACES-PE, and TPSR will be analyzed using SPSS software (version 30.0; IBM Corp). Internal consistency of the scales will be assessed using Cronbach α. The PSRQ will assess students' self-perceived levels of personal and social responsibility, and the PACES-PE will assess enjoyment in PE. ANOVA will be conducted to compare mean scores before and after the intervention for both questionnaires. TARE data will be collected through lesson observations by the research team 3 times during the 10-week intervention period, and interrater reliability will be assessed using Cohen κ. Frequencies and mean scores of the TPSR strategies will be examined descriptively and across time to explore implementation fidelity. A repeated measures multivariate ANOVA will be performed to provide a more complex analysis of the findings and a more comprehensive view of how the intervention affects multiple variables simultaneously.

Qualitative Analysis

Focus group data will be collected from students to capture their experiences and perceptions of the TPSR program. Interviews will be analyzed using NVivo 15 (Lumivero) and the thematic analysis process developed by Clarke and Braun [34]. Representative quotes will be selected to exemplify key themes and bring student voice into the interpretation of the intervention's impact [35].

Fidelity

Fidelity measures are important in intervention studies because they reflect whether the intervention was implemented as intended [36]. Fidelity is also important when considering study replication and future work in related fields [36]. Ginsburg et al [36] argue that 3 common elements (ie, delivery, receipt, and enactment) are important in all fidelity models. This study aims to ensure that fidelity requirements are met through measures such as the professional development program for teachers, ensuring that they not only know and understand the TPSR framework but also know how to apply it in the intervention. This marks the co-design process as significant because researchers and teachers will work together to integrate TPSR elements into already existing PE programs. Fidelity measures will be gathered through both qualitative and quantitative methods, with students and teachers participating in focus groups before and after the intervention. Teachers will also complete a reflection journal at the conclusion of each lesson to assess the framework's impact. This reflection journal will take <5 minutes to complete and will include the following questions:

1. "How would you rate student engagement with the responsibility themes today?" (1=not at all, 5=very highly)
2. "Did you observe any signs of student progress in any of the themes? Comment with dot points below"
3. "What was the most successful part of the lesson? Comment with dot points below"
4. "Any changes for next time?"

A member of the research team will conduct check-ins using Microsoft Teams or Zoom at the conclusion of weeks 1, 3, 5, 7, and 9 to ensure that teachers' questions are answered and implement contingencies if needed or when responses to question 4 in the teacher reflection journal indicate that changes are warranted.

Results

Recruitment for the study concluded in December 2024. Participation in the 10-week TPSR intervention will commenced in term 3 of the 2025 school year. Ethics approval was obtained in 2024 for the commencement of the study in 2025, and participating schools have been finalized. Data collection began in August, 2025, with the analysis scheduled for October 2025. Results are expected to be published in early 2026.

Discussion

Anticipated Findings

This study will be one of the first TPSR-based intervention studies conducted in NSW independent and government schools to evaluate outcomes in PE settings. Its evaluation aligns with the social outcomes articulated in the rationale and aims of the NSW PDHPE K-10 syllabus. The findings will contribute valuable data for future research, enabling comparisons of social interventions, both within Australian contexts and internationally, among similar cohorts. By extending existing research that focuses on psychomotor outcomes, this study aims to explore the broader impact of social interventions in PE, particularly in relation to responsibility, leadership, motivation, and engagement. If effective, the intervention has the potential to enhance students' social development; relationships; and, by extension, academic performance. These improvements may also help address common barriers to participation in PE, including low self-esteem, bullying, and disengagement.

Strengths and Limitations

One of the strengths of this study is that it represents the first TPSR investigation in secondary school settings in NSW, which may prompt further research into social outcomes in Australian schools. This is a significant strength due to the aforementioned benefits of fostering positive social behaviors. Furthermore, as one of the criticisms of past TPSR studies has been the lack of methodological diversity, this study will incorporate both qualitative and quantitative methods, thereby strengthening the literature in this field and addressing known limitations. In addition, positive findings may drastically transform school and classroom culture in the participating schools, potentially increasing participation and engagement in PE, an area that has faced criticism for low student involvement previously.

Predicted limitations of the study include the focus of the intervention solely on PE classes, which may limit the transfer

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of outcomes to other learning contexts. Moving forward, the TPSR framework may evolve to target the overall student experience across all key learning areas; however, given its current application only in PE, the effect of such transfer is difficult to gauge.

Authors' Contributions

SM was responsible for conceptualization, methodology, writing the original draft, reviewing and editing the manuscript, and visualization. WC, LP, and DD were responsible for conceptualization, methodology, reviewing and editing the manuscript, and supervision.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines.
[PDF File (Adobe PDF File), 143 KB - resprot_v14i1e67924_app1.pdf]

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Abbreviations

AC: HPE: Australian Curriculum: Health and Physical Education
NSW: New South Wales
PACES-PE: Physical Activity Enjoyment Scale–Physical Education version
PDHPE: personal development, health, and physical education
PE: physical education
PSRQ: Personal and Social Responsibility Questionnaire
SES: socioeconomic status

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SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TARE: Tool for Assessing Responsibility-Based Education
TPSR: teaching personal and social responsibility

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Protocol

Periodic Assessment of Trajectories of Housing, Homelessness, and Health Study (PATHS): Protocol for a Prospective Cohort Study of People Experiencing Homelessness

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Abstract

Background: The past decade has seen a substantial increase in the number of people experiencing unsheltered homelessness. The unsheltered population faces heightened health and social risks, yet research on their experiences remains limited.

Objective: This paper presents the protocol for the Periodic Assessment of Trajectories of Housing, Homelessness, and Health Study (PATHS), a longitudinal study that leverages mobile phone technology and web-based surveys to track the housing and health trajectories of people experiencing unsheltered homelessness in Los Angeles County.

Methods: Participants were recruited from the Los Angeles County Homeless Count Demographic Survey, an annual representative survey of the county's unsheltered population. Eligibility criteria included being aged ≥18 years, having stayed in an unsheltered location or homeless shelter for at least 1 night in the past month, and residing in Los Angeles County. The study uses a web-based survey platform accessible via mobile phones and provides electronic gift card incentives for participation. Data on housing, health, and social outcomes are collected monthly using trauma-informed, equity-sensitive surveys, designed for diverse literacy levels with a user-friendly interface that includes buffers for sensitive topics.

Results: Since the study launched in December 2021, a total of 2058 individuals have been screened and found eligible. In total, 57.43% (n=1182) of participants completed the baseline survey, of whom 75.47% (n=892) completed at least 1 monthly survey. By December 2024, participants had contributed 7585 monthly surveys (average of 8.5, SD 8.36 per respondent and median of 6, IQR 2-11). Compared to the unsheltered population of Los Angeles County, the PATHS sample overrepresents younger adults aged <40 years (641/1182, 54.23% vs 38.64%) and female participants (507/1182, 42.89% vs 27.74%). Furthermore, the PATHS cohort reports a high burden of health risks relative to the housed population, with 47.3% (422/892) reporting symptoms of anxiety (vs 19.1%), 45.1% (402/892) reporting symptoms of depression (vs 16.4%), 35% (312/892) reporting a disability (vs 12.9%), and 69.4% (619/892) experiencing food insecurity (vs 15.7%).

Conclusions: PATHS offers an innovative platform for real-time monitoring of the housing, health, and service needs of people experiencing unsheltered homelessness in Los Angeles County. By leveraging continuous, in-depth data collection via mobile surveys, PATHS provides valuable insights into the evolving challenges faced by this population. Addressing critical gaps in longitudinal research, PATHS has the potential to drive more informed policy decisions and interventions that improve outcomes for this population considered vulnerable.

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KEYWORDS

unsheltered homelessness; housing instability; digital data collection; mobile phone surveys; longitudinal study; homeless health risks

Introduction

Background

Over the past decade, the number of people experiencing homelessness in the United States has increased substantially [1]. While people experiencing homelessness is widely used as a person-first term in academic and policy contexts, we recognize that some individuals with lived experience prefer terms such as "homeless" or "unhoused." We intend to use respectful, person-centered language while aligning with terminology commonly used in the field. Unsheltered homelessness—defined as sleeping on the streets, in vehicles, in tents, or in other places not meant for human habitation—is a growing phenomenon within this crisis, particularly in the Western United States [1,2]. According to the Point-in-Time Count by the US Department of Housing and Urban Development, the estimated number of unsheltered people experiencing homelessness on a single night in January between 2014 and 2024 rose by 56%, from 175,399 to 274,224 [1].

People experiencing homelessness face numerous health risks, including harassment, physical injury, poor sanitation, inadequate nutrition, and limited health care access [3-7], contributing to higher rates of chronic diseases (eg, obesity, cancer, and depression), earlier onset of geriatric conditions, and a 20-year shorter life expectancy compared to the general population [8-11]. Exposure to unsheltered homelessness is associated with even greater social and health challenges, such as poor sleep, extreme weather, food insecurity, policing, exposure to violence, and substance use, which are likely to further accelerate premature aging and mortality [3,4,9,12-15]. A recent literature review found that most existing studies pointed to associations between unsheltered homelessness and poorer health outcomes compared to those who were sheltered [12]. However, the review also highlighted that few longitudinal studies track the well-being of people experiencing homelessness over time [16,17], whether sheltered or unsheltered, and none have done so at time intervals that highlight the ways in which their lives can change in a short period.

Los Angeles (LA) County is home to the largest population of unsheltered people experiencing homelessness in the United States [18]. In 2024, LA County had approximately 75,000 people experiencing homelessness in a single night, with almost 70% living unsheltered [18], a figure that far exceeds those seen in other major US cities and global urban centers such as London and Tokyo [19]. For comparison, New York City reported approximately 140,000 people experiencing homelessness, but the vast majority (97%) were sheltered [20]. A significant driver of LA County's unsheltered crisis is its jail system, the largest in the world, which has become a central part of an institutional cycle involving homelessness, poverty, substance use, and mental illness [21,22]. Decades of underinvestment in behavioral health services, coupled with rising housing costs, have forced thousands of individuals with untreated psychiatric conditions to live on the streets [22]. In the absence of adequate support systems, jails have become shelters of last resort for many with severe psychiatric needs [22-24]. Upon release, individuals often fall into a revolving door of incarceration and street homelessness, as criminal records create substantial barriers to employment, housing, and public services, further entrenching the conditions that led to their incarceration [22,24]. The convergence of housing insecurity, untreated mental illness, and mass incarceration reflects a systemic breakdown in the health care, housing, and social service systems—one that continues to fail the county's residents experiencing the greatest vulnerability [22,24].

In the past 5 years, the county has invested in various interventions aimed at reducing the size of its unsheltered population, including new supportive services and permanent supportive housing programs [25-28]. However, the lack of real-time data collection of the housing and service needs, as well as other basic metrics of well-being among unsheltered individuals, has hindered the effective delivery of these efforts. Furthermore, amid growing public concerns about livability, LA County, similar to many municipalities nationwide, has introduced new camping ordinances and ramped up efforts to remove homeless encampments through "sweeps" [29,30]. These actions often combine policing with efforts to connect individuals to housing and services [30]. The growing reliance on these more punitive approaches to homelessness management raises concerns about whether these strategies can help individuals transition into stable housing, or whether sweeps merely displace people experiencing homelessness, disrupt their social networks, and expose them to further health risks [31]. Timely tracking of these outcomes can help assess policy impact and inform program development.

The *Periodic Assessment of Trajectories of Housing, Homelessness, and Health Study* (PATHS) aims to address this knowledge gap by following a cohort of predominantly unsheltered people experiencing homelessness in LA County. PATHS overcomes previous challenges of conducting longitudinal research with this highly mobile population by leveraging their widespread use of mobile phones to administer monthly web-based surveys. Mobile phones have become an increasingly important tool in social and behavioral research due to their low cost, ease of use, customizable applications, built-in sensors (eg, GPS and accelerometer), and ubiquity across socioeconomic groups [32,33]. In a sample of people experiencing homelessness in LA County, >90% of adults owned and used mobile phones daily [34]. Mobile phone surveys can be delivered remotely and completed by participants independently, allowing them to respond at their convenience within scheduled time frames. This flexibility makes mobile phones an invaluable tool for capturing the challenges faced by people experiencing homelessness with the frequency needed

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to track the rapid unfolding of critical health and socioeconomic events.

Objectives

This paper reports on our efforts to develop a multipurpose data collection platform designed to enable an action-learning approach to addressing the housing, health, and service needs of people experiencing unsheltered homelessness. We describe our recruitment methodology and the challenges of implementing the study using trauma-informed design principles. In addition, we present initial findings from follow-up surveys, highlighting areas of monthly consistency and variability, which underscore the advantages of a monthly survey model. We conclude by reflecting on the limitations and strengths of our approach, as well as the potential opportunities to expand its reach and impact.

Methods

Study Design Overview

PATHS is a longitudinal cohort study of adults experiencing homelessness who were unsheltered at the time of recruitment in LA County. Using a web-based survey platform and electronic gift card incentives, the study collects recurring data on a broad range of health, housing, and social outcomes. With an ongoing panel, we also regularly update the study questionnaires to incorporate new questions that evaluate emerging issues and initiatives affecting LA County's unsheltered population, such as changes in rehousing efforts, policing, and health care delivery. Participation involves a screening survey, a baseline survey, monthly surveys, and biannual follow-up surveys, distributed in January and July of each year. All survey distribution and data collection are carried out through Qualtrics (Qualtrics International, Inc), a secure platform that meets US federal standards for protecting personal health information as outlined in the Health Insurance Portability and Accountability Act of 1996 [35].

The study is conducted collaboratively by investigators from the University of California, Los Angeles (UCLA) Fielding School of Public Health and the University of Southern California (USC) Dworak-Peck School of Social Work, with human subject protection overseen by the UCLA Institutional Review Board. The study builds on an earlier pilot study in which 136 people experiencing homelessness, who were patients of a Federally Qualified Health Center, were enrolled electronically in a monthly survey, generating actionable research on COVID-19 vaccine uptake and retaining 66% of clients for 3 months [36].

PATHS was codeveloped in collaboration with individuals with lived experience of unsheltered homelessness, who contributed to the survey design and content to ensure cultural relevance. PATHS results are regularly interpreted by lived experts via presentations conducted through the Homelessness Policy Research Institute at the University of Southern California and other community presentations. These sessions have helped to ensure that findings accurately represent the challenges faced by people experiencing homelessness and are accessible and actionable for both people experiencing homelessness and service providers. Throughout the study period, we will solicit feedback more intensively through community presentations and by reporting key findings back to respondents themselves. Insights from these engagements will inform ongoing study improvements and guide the development of dissemination materials.

Recruitment

Launched in December 2021, PATHS has completed 3 waves of annual recruitment, primarily through LA County's annual Homeless Count Demographic Survey (DS), which accompanies the county's official point-in-time count of people experiencing homelessness, as mandated by the US Department of Housing and Urban Development. The DS collects data from a sample of adults experiencing homelessness in unsheltered settings to estimate the characteristics of this population across the county and the number of people living in cars, vans, recreational vehicles, tents, and makeshift shelters captured in the point-in-time count [37].

Each year from December to March, the DS field team deploys approximately 25 trained surveyors to canvas around 500 randomly selected census tracts across the county and administers a short, 1-time DS to approximately 5000 unsheltered adults. Detailed methods are documented in LA County's annual Homeless Count reports [37]. Briefly, DS sampling occurs in 25% of the county's census tracts, using a sample drawn from hot spots and non–hot spots via Neyman allocation. All DS estimates are weighted to account for tract selection, nonresponse, and refusals. Enumerators are trained to collect "perceived" data on age, sex, race or ethnicity, and health status for both surveyed and nonsurveyed individuals. Nonrespondents are represented by the most similar respondents based on nearest neighbor weighting, which accounts for perceived characteristics and spatial proximity. Estimates for the DS are calculated with and without these weights and are closely aligned. Unsheltered adults who completed the DS are invited to participate in PATHS; in 2024, approximately 37.47% (1605/4283) of DS respondents accepted the invitation. Additional recruitment for the study has been conducted through dedicated canvassing in hot spots of unsheltered homelessness annually between April and July.

To enroll, participants must have a valid mobile phone number at the time of recruitment to check for previous enrollment and receive the initial screening survey. Individuals interested in participating are enrolled in 1 of two ways: (1) surveyors collect their mobile phone numbers through a webform, after which participants receive an SMS text message with a link to the study enrollment website on Qualtrics via SMS text message, or (2) surveyors distribute printed study cards with a QR barcode and phone number, allowing prospective participants to scan the code or SMS text message the number to access the study website (Multimedia Appendix 1). The enrollment website provides information about the study and then guides participants through the self-administered informed consent process (Multimedia Appendix 2). Once consent is obtained, participants fill out a brief screening survey to determine whether they meet the study's eligibility criteria: (1) have lived in a homeless shelter or unsheltered setting (eg, street, vehicle,

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tent, or makeshift shelter) for at least 1 night in the past month, (2) live in LA County, and (3) be aged ≥18 years. Continued participation also requires a valid email address to receive electronic gift card incentives. Eligible participants are sent the baseline survey within 2 days of being screened.

Once the baseline survey is completed, participants receive links to follow-up surveys each month via SMS text message or email. All surveys are self-administered over the Qualtrics web interface, accessible via phone or computer, and are available in both English and Spanish.

Ethical Considerations

Ethics approval for the study was granted by the UCLA Institutional Review Board (IRB#21-001148) in September 2021. As noted in the Recruitment section, informed consent was obtained from all participants through a self-administered, online consent process after the nature and potential consequences of the study were explained and before eligibility screening. Ethical standards were maintained for all digital data collection tools used in the study.

Respondents initially received a US $5 financial incentive for each completed survey, which was raised to US $10 per survey in February 2022, and subsequently to US $20 per survey in August 2024. Incentives are provided in the form of an electronic gift card sent directly to their email, which can be redeemed at their choice from among 8 local retail locations. As of December 2024, the gift card redemption rate is approximately 90%.

All reasonable steps are taken to protect the privacy and confidentiality of research participants. Each individual is assigned a unique identifier that is separate from any personally identifiable information (ie, mobile phone numbers and email addresses), ensuring that all study data are deidentified. Raw survey data, including personally identifiable information, remains securely stored on the Qualtrics platform, compliant with the Health Insurance Portability and Accountability Act, until transferred to a password-protected encrypted server. Before any analysis, the data are deidentified and stored in a restricted-access folder on the research server, accessible only to select research staff with appropriate training in research ethics, compliance, and data security.

Retention Strategies

To enhance response rates, starting in March 2023, participants are asked after each survey to indicate their preferred method of contact for future surveys. They can choose to receive subsequent surveys via SMS text message or email, with the option to switch between modes each month based on their preference. In addition, we provide a dedicated hotline, available via email, SMS text message, or phone call, for participants to contact if they experience any issues accessing their surveys or receiving their incentives. Furthermore, to address nonresponse due to changing phone numbers, we recontact participants lost to follow-up (ie, those who have not completed the last 3 monthly surveys) via the email address used for their electronic gift card, allowing them to update their contact information or switch their preferred mode of contact.

Measures

PATHS collects data on various topics related to people's housing and health experiences and the social determinants of health through multiple surveys. The initial surveys were developed and tested by people with lived experience of homelessness to ensure that they were trauma-informed, equity-sensitive, and appropriate to a broad range of literacy levels. In addition, the surveys feature a visually engaging interface to encourage completion and incorporate techniques such as buffers to prepare respondents for potentially difficult, sensitive, or triggering questions (Multimedia Appendix 3).

The core measures collected in this study as of December 2024 are listed in Table 1. The baseline survey captures sociodemographic characteristics and homelessness history. The baseline survey and regular biannual follow-up surveys, conducted in January and July of each year, collect self-reported data on health diagnoses, health care access, social services use, housing and health needs, and disability status. The monthly surveys cover topics related to housing status; service engagement; access to basic necessities; policing; discrimination or violence; and physical, social, and mental well-being. Periodic survey modules have been updated to address the rapidly changing ecosystem of service, policing, and environmental risks, including events such as the wildfires that hit LA County in January 2025. Furthermore, the monthly survey collects participants' geographic location, which they can provide either by sharing exact coordinates through their devices or by self-reporting the address, cross streets, or neighborhood where they are staying, which can be linked to administrative spatial data.

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Table 1. Study measures.

Domains	Measures and their description
Baseline and biannual follow-up surveys	
Sociodemographics (baseline only)	Age, sex at birth, gender identity, sexual orientation, race or ethnicity, veteran status, educational attainment, and history of criminal legal system involvement
Homelessness history (baseline only)	Duration
Self-reported health diagnoses	Chronic physical health conditions (eg, serious heart condition, cardiovascular disease, diabetes, HIV or AIDS, cancer, immunocompromised status, asthma, chronic respiratory disease, chronic kidney disease, blood disorder, liver disease, neurodegenerative disease, and arthritis), neuropsychiatric disorders (eg, major depression, anxiety, bipolar disorder, schizophrenia or other psychotic disorder, personality disorder, and posttraumatic stress disorder), substance use disorders (eg, alcohol use, cannabis or marijuana use, stimulant use, and opioid use), and history of substance use treatment
Coping strategies	PC-PTSD-5[a], 6-item BRS[b], Insignia Patient Activation Measure (4 items), and DERS[c]
Access to resources and services	Health insurance coverage, receipt of government benefits (eg, SSI[d] or SSDI[e], SNAP[f], and unemployment), have a usual source of care, and MNA-SF[g]
Health care needs	Health conditions of greatest concern and quality of care received for the condition, as well as trust in the medical profession [38]
Housing needs	Preferences for types of shelter or housing (eg, safe camping, congregate, bridge housing, and supportive housing), housing needs (eg, storage and accommodations for pets, spouse, and child), and housing concerns (eg, hours or curfew, cleanliness, and safety)
Disability	ACS-6[h] on disability status
Monthly surveys	
Physical health	Self-rated physical health (1 item, PROMIS[i] Global Health Scale version 1.2) and body pain (1 item, Medical Outcomes Study Physical Functioning Scale)
Psychosocial health	PHQ-4[j] for anxiety and depression, PROMIS Sleep Disturbance Scale (2 items), and 5-item UCLA[k] Loneliness Scale
Substance use	AUDIT-C[l], WHO ASSIST[m], overdose, and receipt of treatment
Basic needs	USDA[n] Food Security Module (3 items) and access to sanitation and personal hygiene facilities (ie, clean drinking water, toilets, and showers)
Health care use	Emergency room visits, hospitalizations, unmet health care needs (ever wanted or needed health care but did not obtain it), medication adherence, and type of health care services received
Homeless services engagement	Offers of shelter or housing and contact with a homeless services outreach worker
Housing status	Housing status (last night, at any point in the past month, and most often in the past month), perceptions of safety, and displacement or changes in sleeping locations
Policing and criminal legal system involvement	Police interaction, arrests, move-along citation, exposure to encampment sweeps, and incarceration
Violence and discrimination	National Crime Victimization Survey (2 items: assault and harassment) and Everyday Discrimination Scale (short version, 5 items)
Employment	Work history and income

[a]PC-PTSD-5: Primary care posttraumatic stress disorder screen for Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition.

[b]BRS: Brief Resilience Scale.

[c]DERS: Difficulties in Emotional Regulation Questionnaire.

[d]SSI: Supplemental Security Income.

[e]SSDI: Social Security Disability Insurance.

[f]SNAP: Supplemental Nutrition Assistance Program.

[g]MNA-SF: Mini Nutritional Assessment–Short Form.

[h]ACS-6: 6-item American Community Survey.

[i]PROMIS: Patient-Reported Outcomes Measurement Information System.

[j]PHQ-4: 4-item Patient Health Questionnaire.

[k]UCLA: University of California, Los Angeles.

[l]AUDIT-C: Alcohol Use Disorders Identification Test–Consumption.

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[m]WHO ASSIST: World Health Organization Alcohol, Smoking, and Substance Involvement Screening Test.

[n]USDA: United States Department of Agriculture.

Results

This project is funded by the Conrad N Hilton Foundation, with funding awarded in September 2021. Data collection began in December 2021 and is ongoing. Data analysis is performed on a rolling basis to address specific research questions and stakeholder priorities as they emerge.

Recruitment

Figure 1 shows screening and enrollment statistics for 3 years of PATHS recruitment, covering the period from December 2021 to July 2024. Among the 2155 participants screened throughout the study period, 2058 (95.49%) met the eligibility criteria, with the majority (1840/2058, 89.41%) having spent at least 1 night in an unsheltered location. A total of 1182 (57.43%) participants completed the baseline survey, of whom 892 (75.47%) continued to the monthly survey, officially enrolling in the study. As of December 1, 2024, enrolled participants have contributed a total of 7585 monthly surveys (average of 8.5 surveys per respondent). In the most recent 6-month follow-up period (June to December 2024), 416 (46.6%) of the enrolled participants responded to at least 1 monthly survey (herein referred to as the "recent monthly follow-up sample").

Figure 1. Periodic Assessment of Trajectories of Housing, Homelessness, and Health Study screening and enrollment funnel, by recruitment year (2022 to 2024). Percentages are calculated using the number of participants in the previous stage as the denominator.

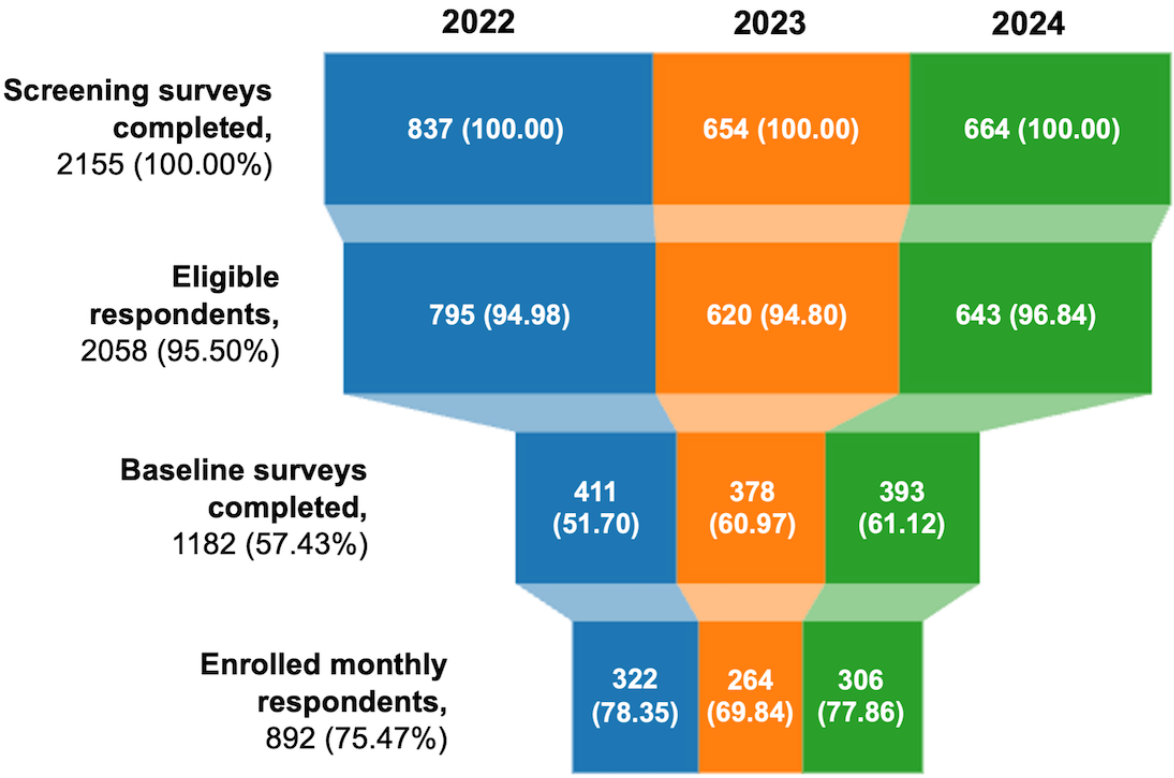

Study Population

To examine the representativeness of the PATHS sample to LA County's unsheltered population, Table 2 compares the sociodemographic characteristics of the PATHS baseline sample and recent monthly follow-up (between July and December 2024) sample respondents to respondents of the LA County Homeless Count DS from 2022 to 2024, which is considered to characterize LA County's unsheltered population.

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Table 2. Comparison of the Periodic Assessment of Trajectories of Housing, Homelessness, and Health Study (PATHS) samples to Los Angeles (LA) County's unsheltered population, 2022 to 2024.

Characteristic	2022 to 2024 LA County unsheltered population[a] (%)	PATHS baseline sample (n=1182), n (%)	PATHS recent monthly follow-up sample[b] (n=416), n (%)
Age (y)			
18-24	4.49	105 (8.88)	49 (11.78)
25-39	34.15	536 (45.35)	176 (42.31)
40-49	23.94	267 (22.59)	99 (23.80)
50-59	21.78	194 (16.41)	60 (14.42)
≥60	15.64	80 (6.77)	32 (7.69)
Sex			
Male	69.14	635 (53.72)	203 (48.80)
Female	27.74	507 (42.89)	199 (47.84)
Neither male nor female	3.12	40 (3.38)	14 (3.37)
Race or ethnicity			
Hispanic or Latinx	40.67	413 (34.94)	169 (40.63)
Non–Hispanic American Indian or Alaskan Native	1.58	12 (1.02)	6 (1.44)
Non–Hispanic Asian	1.33	18 (1.52)	9 (2.16)
Non–Hispanic Black or African American	28.59	315 (26.65)	96 (23.08)
Non–Hispanic Native Hawaiian or Pacific Islander	0.40	8 (0.68)	1 (0.24)
Non–Hispanic White	23.97	325 (27.50)	103 (24.76)
Others or unknown[c]	3.46	91 (7.70)	32 (7.69)
Homeless for >1 y	79.33	947 (80.12)	321 (77.16)
Past treatment for substance use disorder	31.79	372 (31.47)	97 (23.37)

[a]Values for LA County's unsheltered population come from the LA Homeless Count Demographic Survey of adults experiencing homelessness, combined for the years 2022, 2023, and 2024. Approximately 5000 unsheltered individuals in LA are surveyed each year for the Homeless Count. Absolute counts are not reported because values have been adjusted using statistical weighting to improve representativeness and account for sampling design.

[b]PATHS participants who responded to at least 1 monthly survey in the last 6 months.

[c]Percentages for the PATHS samples include respondents who identified as multiracial.

Compared to the county's unsheltered population, participants in the baseline and recent monthly follow-up PATHS samples were slightly younger (641/1182, 54.23% aged <40 y in the baseline sample, 225/416, 54.1% aged <40 y in the recent monthly follow-up sample, vs 38.64% in the county unsheltered population), which may reflect differences between age groups in mobile phone access and technology literacy needed to enroll in the study and consistently respond to the monthly surveys. PATHS also had higher rates of participation in the baseline survey among female individuals than the overall unsheltered population (507/1182, 42.89% vs 27.74%); this overrepresentation was even more pronounced in the recent monthly follow-up sample (199/416, 47.8% vs 27.74%). However, higher female individual participation rates are common in many volunteer-based opinion surveys, given the distinct challenges faced by women experiencing homelessness [39,40]. This response pattern allows us to better examine their specific needs. In comparison to the county's overall unsheltered population, Hispanic or Latinx individuals were underrepresented in the baseline sample (413/1182, 34.94% vs 40.67%), while non–Hispanic White individuals were slightly overrepresented (325/1182, 27.5% vs 23.97%). However, these differences became much more comparable in the recent monthly follow-up sample. On the other hand, non–Hispanic Black individuals were underrepresented in the recent monthly follow-up sample compared to the overall unsheltered population, highlighting differences in retention rates across racial groups. Both samples mirrored the unsheltered population in homelessness duration (ie, having been homeless for >1 y). Finally, a higher proportion of individuals with a history of substance use treatment were recruited into the study compared to the county's unsheltered population. However, this group experienced a drop in the recent monthly follow-up sample, likely due to challenges in retaining individuals facing the complex intersection of homelessness and substance use.

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Retention

To examine participant retention, Table 3 displays the response rate to the monthly surveys during the first 6 calendar months following enrollment: overall and stratified by recruitment year. Overall, 39.2% (350/892) of enrolled participants completed most (5 to 6) of the monthly surveys distributed, while just less than a quarter (205/892, 23%) of participants did not provide any responses after enrollment. Response rates were generally higher among participants recruited in 2023 and 2024 compared to those recruited in 2022. This improvement may be attributed to our decision to allow participants to choose their preferred method for receiving the survey link, either via SMS text message or email.

Table 3. Response rate to the monthly surveys during the first 6 months after enrollment, by recruitment year.

Respondents	Overall (n=892), n (%)	By recruitment year, n (%)		
		2022 (n=322)	2023 (n=264)	2024 (n=306)
0%	205 (23)	89 (27.6)	50 (18.9)	66 (21.6)
0%-34%	193 (21.6)	69 (21.4)	57 (21.6)	67 (21.9)
34%-67%	144 (16.1)	47 (14.6)	43 (16.3)	54 (17.6)
67%-100%	350 (39.2)	117 (36.3)	114 (43.2)	119 (38.9)

Population Health

Table 4 [41-43] characterizes the extraordinarily high burden of poor health and health risk among the entire PATHS monthly survey respondent sample, compared to the housed population of LA County. Almost half (441/892, 49.4%) of the PATHS sample rated their health as fair or poor (vs 16.9% of LA County adults), 47.3% (422/892) had symptoms of anxiety (vs 19.1%), 45.1% (402/892) had symptoms of depression (vs 16.4%), 36.7% (327/892) smoked cigarettes regularly (vs 5.2%), and 35% (312/892) reported having a disability (vs 12.9%). Food insecurity was particularly severe: 69.4% (619/892) of PATHS monthly respondents reported experiencing food insecurity, which is 4 times as high as the rate in the adult population of LA County (15.7%).

Table 4. Comparison of selected health indicators among the Periodic Assessment of Trajectories of Housing, Homelessness, and Health Study (PATHS) monthly respondent sample to the Los Angeles County adult population.

Indicator	PATHS monthly survey respondents (n=892), n%	Los Angeles County's adult population, %
Poor of self-rated	441 (49.4)	16.9
Symptoms of anxiety (GAD-2[a])	422 (47.3)	19.1
Symptoms of depression (PHQ-2[b])	402 (45.1)	16.4
Regular smoking	327 (36.7)	5.2
Food insecurity	619 (69.4)	15.7
Any disability	312 (35.0)	12.9

[a]GAD-2: 2-item Generalized Anxiety Disorder.

[b]PHQ-2: 2-item Patient Health Questionnaire.

Discussion

Anticipated Findings

PATHS addresses multiple gaps in homelessness research and policy, including a lack of representative survey-based data on unsheltered populations, a lack of longitudinal data systems for addressing housing trajectories and well-being of people experiencing homelessness, and a lack of longitudinal evaluations of interventions affecting unsheltered people experiencing homelessness [12,27]. Research from other US cities, such as New York City and Boston, has largely focused on the sheltered population [8]. While these studies offer important insights into service delivery and shelter-based interventions, they often fail to capture the scale and complexity of unsheltered homelessness seen in regions in the Western United States, such as LA, where unsheltered population rates are significantly higher [1]. People experiencing homelessness, especially those living unsheltered, can be conceptualized as part of what Castells [44] describes as the "Fourth World": populations facing extreme marginalization within affluent societies and excluded from housing, health care, and legal protections. This exclusion gives rise to the recurring movement of people experiencing homelessness between the streets, shelters, hospitals, and jails, representing a "revolving door" pattern stemming from fragmented systems of care [45,46]. Repeated institutional contacts can contribute to the "mortification of the self," a concept introduced by Goffman [47] in which individuals experience a loss of identity, autonomy, and social roles through constant surveillance, regulation, and disempowerment [48]. By focusing on unsheltered individuals, who remain critically underrepresented in empirical investigations, our study can provide evidence of this extreme marginalization and institutional cycling, as framed

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by these theoretical concepts. In doing so, we offer valuable insights into the lived, dynamic realities of this population, highlighting the transitory nature of their living situations and the daily health and social challenges they face.

Our study will offer new insights into the relationships between homelessness and health trajectories in a population-based sample—a critical remaining gap in the homelessness and health literature [49,50]. Past longitudinal studies that attempted to follow people experiencing homelessness have generated critical insights into the health experiences of homeless populations, including those transitioning out of shelter systems [10,16,17,51,52]. For instance, in a prospective cohort study of 350 homeless adults aged ≥50 years in Oakland, California, 35% reported persistent or worsening functional impairment over 3 years, compared to the 20% typically seen in the general US older adult population [53]. In a national longitudinal study of 4651 adolescents and young adults in the United States, those who had experienced homelessness faced higher risks of health-limiting conditions and poor self-rated health over an 8-year period [54]. A 2-year study in Ottawa, Canada, found that among 329 single homeless individuals, those who avoided substance use and secured high-quality housing demonstrated better mental health outcomes at follow-up [55]. In a study of 136 women experiencing homelessness in Madrid, Spain, two-thirds reported feeling discriminated against due to their housing status, and this perceived discrimination was linked to poorer mental health at follow-up [56]. Despite these findings, much of the existing longitudinal research on people experiencing homelessness used purposive sampling methods, targeted specific age groups, and lacked the sample size to make reliable inferences about subpopulations. PATHS represents a feasible approach to building on the findings of these studies by collecting monthly data more frequently and examining the impacts of diverse socioenvironmental conditions on the health trajectories of people experiencing homelessness.

Furthermore, our longitudinal data are a crucial tool for examining the impact of recent rehousing and policing initiatives in the LA region. For example, both the city and county of LA have implemented encampment resolution programs in recent years, an effort to resolve longstanding encampments by moving residents into agency-provided motels or hotels [25,26]. While framed as a pathway to stability, it remains unclear whether these shelter and rehousing initiatives actually lead to better housing outcomes for those affected. In addition, some temporary sheltering and congregate housing models have been critiqued for producing what scholars characterize as "shelterization," where institutional routines, surveillance, and loss of autonomy contribute to the erosion of identity, agency, and long-term housing readiness [57]. By surveying participants regarding their housing status and location each month, we will be able to track whether clients have been successfully rehoused and for how long, whether they have done so through provider support or self-resolution, and where they are rehoused. For respondents who remain unsheltered, we will be able to monitor both general health and well-being trajectories over time. These data will help inform local policy and guide the efforts of service providers and government agencies.

Finally, PATHS offers a flexible platform for evidence-based monitoring of other evolving issues in several key ways. First, the study's recruitment and data collection strategies can be adapted to target specific populations of people experiencing homelessness, facilitating further investigations into policy and program development and evaluation. For example, across the United States, "street medicine" has emerged as a response to the inadequacy of traditional clinical models, attempting to deliver medical and psychiatric care directly to people experiencing homelessness in the spaces where they live, such as encampments, sidewalks, or temporary shelters [58,59]. These approaches reflect a growing recognition of the limitations of brick-and-mortar health care systems in reaching highly transient and marginalized people experiencing homelessness [59]. Using our existing recruitment strategy, we have recruited a sample of people experiencing homelessness engaged in street medicine services through interactions with health care providers. This sample will be compared with our representative sample to assess the effect of street medicine engagement on both health and housing outcomes. Our recurring data on a wide range of outcomes will provide valuable insights into the short-term and long-term effects of these programs, helping improve service distribution and informing future intervention strategies. Second, as part of our ongoing panel, we can update our surveys to include new questions, addressing emerging issues, initiatives, and interventions. For instance, in response to the wildfires in LA County that began on January 7, 2025, we added questions about the impact of wildfires on participants' well-being to the monthly survey distributed on January 20, 2025. This rapid assessment will help understand the impact of wildfires and other extreme weather events on the unsheltered population, especially as such events become more prevalent, to guide interventions during these emergencies.

Looking beyond these specific topics, our survey platform can serve as a resource for other investigators, allowing them to invite respondents to participate in separate qualitative and quantitative studies aimed at gaining a deeper understanding of unsheltered individuals' perceptions of and experiences with various policies and programs. Finally, the PATHS approach and technological platform can be extended to other populations considered highly vulnerable facing extreme, recurrent, and overlapping forms of marginalization. We have had discussions with research groups in other municipalities about extending the PATHS model and have begun to explore enrollment of samples in other populations facing overlapping and recurrent adverse exposures, such as precarious workers and people exiting prison [60,61].

Limitations

Despite making significant advancements, the PATHS design has a few limitations. Most notably, PATHS requires mobile phone access at enrollment and an email address, raising concerns about generalizing findings from the cohort to the LA County unsheltered population, lacking digital access or literacy. While previous studies have shown that most of the unsheltered populations have access to a mobile phone at some point [34], the recruitment strategy may still miss individuals with transitory access or those who face difficulties maintaining a phone, such as those with severe cognitive impairments or more severe forms

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of neuropsychiatric disorders. In addition, individuals without internet-enabled phones or those who choose not to participate in research studies because of paranoia, suspiciousness, delusions, and cognitive decline may also be systematically excluded. This may result in the underrepresentation of the most marginalized subgroups of the unsheltered population and introduce selection bias by favoring participants with higher connectivity, potentially skewing findings toward individuals who are already somewhat engaged with services or supports. However, we are able to assess the extent of this sample selection criterion by comparing our respondent sample to the broader unsheltered population in LA County. This comparison allows us to create sampling weights that adjust for this bias in the analysis.

Furthermore, the use of web-based surveys in our study requires people to have internet access to participate, leading to challenges in keeping respondents engaged on a regular basis over a long time frame. Some level of attrition is inevitable, especially because respondents in our study population may lose their phones, run out of mobile data, or lack access to a computer with internet when surveys are distributed. To address these concerns and improve response rates, we introduced a "preferred contact mode" question in our monthly surveys, allowing respondents to choose whether they would like to receive their next survey via email or SMS text message. We also proactively send reminder emails to respondents who have not completed a survey in a while, encouraging them to update their contact information. By taking these steps, we aim to minimize attrition and ensure that our data remain as representative and reliable as possible over the course of the study.

Relatedly, 1 aspect of PATHS that serves as both a feature and a strength is the use of "Prefer not to answer" options on all questions. This trauma-informed approach ensures higher levels of survey completion, but at the cost of higher-than-usual missingness of individual survey items. As a result, many complex analyses of PATHS data require the use of multiple imputation or, at least, careful assessment of the comparability between completed cases and the full sample.

Conclusions

PATHS provides a flexible and comprehensive approach to real-time monitoring of the unsheltered population in LA County, making it a valuable resource for future homelessness and health research and policy development. With PATHS now fully operational, we plan to expand our focus to explore critical areas affecting unsheltered individuals, such as the impact of wildfires and other natural disasters, as well as the effects of environmental stressors such as policing. In addition, we aim to evaluate the effectiveness of current interventions and support services tailored to this group considered vulnerable, assessing their impact on long-term housing stability and overall well-being. Through these efforts, we hope to contribute to more informed, evidence-based policies and interventions that can better address the evolving needs of unsheltered people experiencing homelessness.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

RK and BH initially designed the study that secured funding. All authors contributed to study implementation, data collection, and data management. JC conducted the data analysis for this manuscript. RK, BH, and JC drafted the manuscript, which all authors critically reviewed and revised.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Study enrollment via SMS text message and flyer.
[PNG File , 279 KB - resprot_v14i1e74266_app1.png]

Multimedia Appendix 2
Study enrollment web page.
[PNG File , 345 KB - resprot_v14i1e74266_app2.png]

Multimedia Appendix 3
Survey buffer messages.
[PNG File , 436 KB - resprot_v14i1e74266_app3.png]

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Abbreviations

DS: Demographic Survey
LA: Los Angeles
PATHS: Periodic Assessment of Trajectories of Housing, Homelessness, and Health Study
UCLA: University of California, Los Angeles

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Protocol

Therapeutic Drug Monitoring for Precision Dosing of Janus Kinase Inhibitors: Protocol for a Prospective Observational Study

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Abstract

Background: Janus kinase inhibitors (JAKIs) are small molecules used orally to treat inflammatory and hematological disorders. They have demonstrated impressive efficacy across multiple indications. However, concerns have emerged regarding their safety profile. Despite their growing clinical use, therapeutic drug monitoring is not yet established for JAKIs, but it could help address exposure-dependent efficacy and tolerability issues through individualized treatment approaches.

Objective: This protocol aims to characterize the pharmacokinetics of the 6 most prescribed JAKIs in Switzerland (abrocitinib, baricitinib, fedratinib, ruxolitinib, tofacitinib, and upadacitinib) and identify factors influencing drug exposure. It seeks to explore exposure-response relationships to assess the impact of drug exposure markers on efficacy and safety. Ultimately, these findings will contribute to establishing therapeutic intervals.

Methods: This prospective observational study, conducted throughout Switzerland, was approved by the Cantonal Ethics Committee in August 2023. Consenting adults (aged ≥18 years) who are capable of judgment and who are prescribed JAKIs are enrolled in the study, either for sparse sampling during routine medical visits to collect trough or random plasma concentrations or for a detailed pharmacokinetic substudy involving serial blood sampling over an 8-hour period. The characterization of JAKI pharmacokinetics, including associated variability and the effect of specific covariates, such as age, body weight, BMI, sex, disease type, drug-drug interactions, or concomitant pathophysiological conditions, will be performed using nonlinear mixed effect modeling techniques. Relationships between JAKI exposure and efficacy and safety will be assessed.

Results: By August 2024, a total of 276 blood samples were collected from 107 patients, the majority being female individuals (n=62, 57.9%). The patients had a median age of 51 (range 17-87) years and a median body weight of 69 (range 39-132) kg. Most patients recruited were taking ruxolitinib (n=44, 41.1%), upadacitinib (n=39, 36.4%), or baricitinib (n=11, 10.3%).

Conclusions: The framework of the study will allow the characterization of the pharmacokinetic profiles of JAKIs and their variability in real-world conditions. On the basis of novel therapeutic drug monitoring approaches, we expect to explore the relationship between drug exposure, treatment response, and tolerability, providing essential information for precise dose optimization.

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KEYWORDS

Janus kinase inhibitor; JAKI; abrocitinib; baricitinib; fedratinib; ruxolitinib; tofacitinib; upadacitinib; therapeutic drug monitoring; pharmacokinetics; population pharmacokinetic modeling

Introduction

Background

The substantial progress in managing inflammatory disorders has led to a broad range of therapies for patients with systemic autoimmune conditions. Biological agents, such as monoclonal antibodies, are the standard of care for many autoimmune disorders. However, they are characterized by variable pharmacokinetics and are associated with the production of autoantibodies over time. While biological agents achieve disease control in most patients, practical concerns remain regarding their stability and parenteral routes of administration [1].

Concurrently, the Janus kinase (JAK) and signal transducer and activator of transcription (STAT) signaling pathway plays a key role in cellular signal transduction involved in numerous acute and chronic inflammatory diseases, making the JAK/STAT target an alternative therapeutic approach for their treatment. JAKs are multidomain nonreceptor tyrosine kinases. The JAK protein family includes 4 isoforms (JAK1, JAK2, JAK3, and TYK2), while the STAT family consists of 7 proteins (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6). The broad spectrum of possible combinations between JAK-STAT subunits specifically regulate cytokine signaling through class I and II receptors, resulting in pleiotropic effects on various immune and biological functions [2-4].

JAK inhibitors (JAKIs) are representatives of a novel class of small molecule immunosuppressants interfering with intracellular signaling triggered by the proinflammatory stimuli, such as cytokines [5]. JAKIs are increasingly used for various inflammatory conditions, such as immune-mediated arthropathies (eg, rheumatoid arthritis), immune-driven dermatological diseases, inflammatory bowel disease (IBD), myeloproliferative neoplasms (MPNs; eg, myelofibrosis, polycythemia vera), graft-versus-host disease (GvHD), and in some cases of myelodysplastic syndromes [4]. Compared to biological agents, JAKIs have a more rapid mode of action in acute situations and fewer issues associated with pharmacokinetics inertia [6-13]. Their immunosuppressant profiles are similar, but they offer the convenience of oral administration and lack of autoantibody formation. In Switzerland, the first JAKIs approved were ruxolitinib (2012) and tofacitinib (2013). Several other JAKIs have received marketing approval between 2020 and 2024.

Recently, safety concerns regarding JAKIs were reported in the literature. Across the class, common adverse drug reactions (ADRs) include infections; hematologic abnormalities; and laboratory changes, such as elevations in total cholesterol, low-density lipoprotein, liver transaminases, and creatine phosphokinase. Mycobacterial, fungal, viral, and other opportunistic infections, in particular herpes zoster reactivation, were associated with JAKIs [14-16]. In line with these findings, meta-analyses have reported a significant, dose-dependent increase in the risk of herpes zoster caused by reactivation of the varicella-zoster virus [17,18]. Hematological toxicities, including neutropenia, lymphopenia, anemia, and thrombocytopenia, are also dose-related ADRs and have been reported frequently with ruxolitinib and fedratinib [19-24]. Cardiotoxicity is a major safety concern, with reports of major adverse cardiovascular events, which include cardiovascular death, nonfatal myocardial infarction, and nonfatal stroke. The Oral Rheumatoid Arthritis Trial Surveillance study showed a higher risk of nonfatal myocardial infarction with tofacitinib compared to adalimumab in patients with rheumatoid arthritis aged 50 years or older with at least 1 cardiovascular risk factor [14]. In addition to thromboembolic events, such as deep vein thrombosis, pulmonary embolism, and venous thromboembolism, an increased risk of malignancies, including lymphoma, lung cancer, and nonmelanoma skin cancer, has also been reported [14,25]. These safety concerns emphasize the need for careful monitoring to ensure treatment efficacy while minimizing ADRs.

Therapeutic drug monitoring (TDM) involves measuring drug concentrations and adjusting the dosage to maintain exposure within a target range (ie, to optimize efficacy while limiting toxicity). Drug concentration exposure is the key factor for both drug efficacy and toxicity. However, drugs are mostly prescribed at standard dosage indicated by the manufacturer ("one-size fits all" approach), without accounting for interindividual pharmacokinetics variability. Multiple sources of variability can be identified, including demographic, environmental, clinical, and genetic factors. Besides this explained variability, a certain amount of pharmacokinetics variability remains unexplained, but deserves all the more to be taken into account in dosage individualization, which TDM makes possible. A priori recommended dosages vary sometimes according to the indication (eg, gastroenterologists use 2 to 3 times the dose of upadacitinib compared to rheumatologists) but are not individually adapted according to drug exposure. Holford and Sheiner [26] and Sheiner and Ludden [27] developed the population pharmacokinetics (popPK) approach to analyze TDM data, aiming to characterize and quantify variability, identify underlying sources, such as covariate effects, and simulate dosage adjustment. The popPK method ultimately allows for validating or proposing an alternative dosing regimen.

Drug concentration measurement has been increasingly used to optimize immunosuppressant treatments and is considered mandatory for the follow-up of organ transplantation. Typical drug candidates for TDM have clearly established exposure-response (in terms of efficacy and toxicity) relationships, a narrow therapeutic margin, limited intrasubject pharmacokinetics variability, significant interindividual pharmacokinetics variability, a lack of pharmacodynamic markers that reliably reflect therapeutic response or toxicity, and a sufficient treatment duration [28]. JAKIs fulfill several of these criteria, particularly the exposure-response relationship. An exposure-response relationship of JAKIs is well documented

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for most molecules regarding efficacy [29-41], while associations with toxicity have been reported but remain less consistently characterized across studies [29,32,37,42-45]. Despite relatively low intraindividual pharmacokinetics variability, JAKIs exhibit moderate to significant interindividual pharmacokinetics variability, susceptible to translating into insufficient efficacy in case of suboptimal concentration exposure, or unwanted toxicity in case of overexposure [32,43,46-50]. Several factors contribute to the variability in JAKI exposure, including their oral administration over long treatment periods, which may lead to suboptimal therapeutic adherence. As JAKIs are mainly metabolized by cytochrome P450 (CYP), they are subjected to many drug-drug interactions (DDIs) that may affect blood concentrations and, thus, exposures. Beyond DDIs, the inflammatory state itself may alter drug metabolism, a phenomenon known as phenoconversion, which can modify enzyme function and affect drug clearance [51-53]. On another note, baricitinib is primarily eliminated through renal filtration and secretion. Inflammatory-associated glomerular hyperfiltration may decrease its exposure; therefore, older patients with impaired renal function are at risk of accumulation [54]. Finally, inflammatory diseases and MPNs differ in pathophysiology, cytokine environment, and potential effects on drug metabolism. Higher concentrations of ruxolitinib were observed in patients with GvHD compared to patients with myelofibrosis under the same daily dose, due to a reduced clearance [43,55].

This Study

We hypothesize that JAKIs could benefit from TDM to improve efficacy, safety, and efficiency according to the disease conditions. This exploratory study focuses on abrocitinib, baricitinib, fedratinib, ruxolitinib, tofacitinib, and upadacitinib and aims to investigate the pharmacokinetics characteristics of JAKIs in real-world patient populations. We aim to characterize pharmacokinetics profiles of JAKIs along with their variability based on measurements of circulating blood concentrations, patient characteristics, DDIs, pathophysiological status, and comedications using a popPK approach. In addition, we seek to pioneer the methodological development and clinical implementation of TDM-driven administration of JAKIs in multiple inflammatory states, collecting clinical responses to establish therapeutic intervals with pragmatic recommendations.

Methods

Study Participants

Adult patients (aged ≥18 years) capable of making informed decisions are eligible if they are receiving or about to receive JAKIs for the control of their inflammatory disease. This study includes currently commercialized JAKIs in Switzerland (abrocitinib, baricitinib, fedratinib, ruxolitinib, tofacitinib, and upadacitinib). Participants who wish to withdraw consent at any stage of the study, are incapable of judgment, or are under tutelage are excluded from this study.

Ethical Considerations

The present protocol was approved by the Cantonal Research Ethics Committee of Vaud and transferred to the Ethics Committee of Northwestern and Central Switzerland, Cantonal Research Ethics Committee of Geneva, Cantonal Ethics Committee of Zurich, Ethics Committee of Eastern Switzerland, and Cantonal Ethics Committee of Bern in August 2023 (2023-00904). This research project is conducted in compliance with the protocol, the Declaration of Helsinki [56], the principles of Good Clinical Practice, the Human Research Ordinance [57], and the Human Research Act [58], as well as other locally relevant regulations. Patients are included in the study after signing an informed consent or a general consent. All data are handled in accordance with data protection laws, with participants' identities coded and accessible only to authorized study staff to ensure strict confidentiality throughout the study. Participants undergoing detailed pharmacokinetics substudy investigations receive compensation for their time.

Study Design

This is a prospective observational study conducted in a real-world setting. As presented in Figure 1 [59], this project is divided in 2 main parts: sparse sampling and a detailed pharmacokinetics substudy. Sparse sampling is performed exclusively during routine medical visits, where 1 plasma sample is taken. This part of the study aims to obtain 1 to 3 trough plasma concentration samples (sample collected just before the next dose) and 1 to 3 random samples at unselected times over the entire dosing interval per patient. The detailed pharmacokinetics substudy is performed on specific patients in the Service of Clinical Pharmacology at the University Hospital of Lausanne to enrich the data collected during routine medical visits. It consists of collecting 1 sample before and 7 samples after taking a dose of JAKIs over an 8-hour period. This part of the study can be repeated for specific consenting patients in whom the introduction of an interacting drug raises the question of a DDI, or for those experiencing pathophysiological changes or acute intervention (eg, extrarenal epuration, gastric bypass, or plasmapheresis). In accordance with patient preferences and the study's requirements, participants could either undergo a detailed pharmacokinetics investigation or provide additional sparse samples. Dosing results, including in cases of potential DDIs, are communicated to the treating physician for information purposes only, with any dose adjustment left to their discretion. In addition, pharmacogenetic analysis, which aims to identify genetic variants (ie, single-nucleotide polymorphisms) that affect the activity of drug-metabolizing enzymes or transporters and thereby influence overall drug exposure, will be performed in a subset of patients who provided separate consent for genetic testing. If clinicians consider phenotyping clinically relevant, a metabolic ratio analysis can provide additional medical insights related to JAKI metabolism [60]. The total study duration, including patient recruitment and the pharmacokinetics investigations, is estimated to last approximately 24 months.

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Figure 1. Study design. The study is divided into 2 parts: (A) the sparse sampling, where 1 blood sample can be collected during routine medical visits, and (B) the detailed pharmacokinetics substudy, where 8 blood samples are collected over a period of 8 hours. Cmin: samples collected at trough concentration; Crandom: samples collected at unselected time points over the dosing interval; C1,min: first samples collected at trough concentration; C2 to C7: samples collected at selected time points during the detailed pharmacokinetics substudy; JAKI: Janus kinase inhibitor. This figure was created using BioRender. Tachet, J [59].

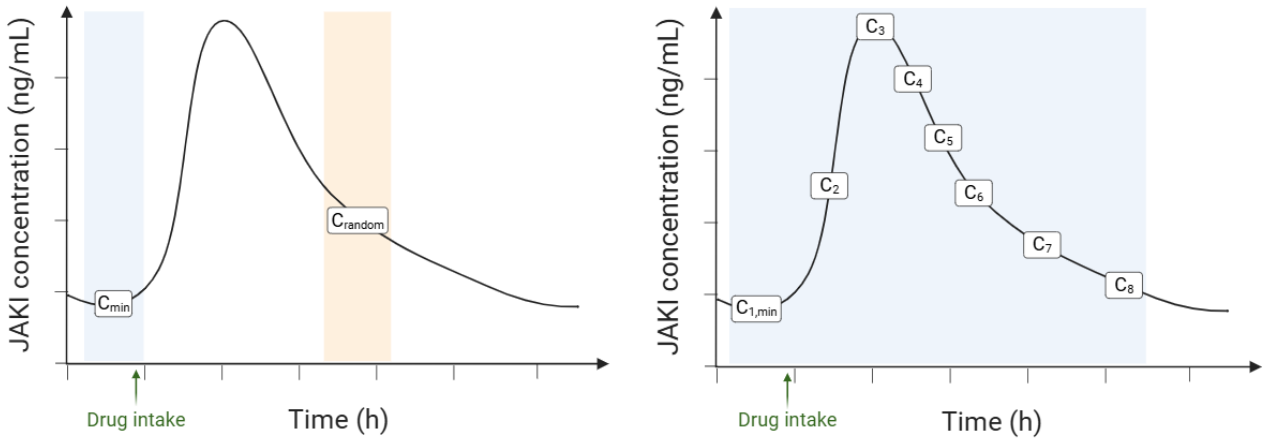

Source Data

The study data are recorded on a dedicated TDM report form and treated confidentially according to Swiss law data protection legislation. The actual times of the last drug intake preceding each sampling, along with the times of blood samplings themselves, are precisely recorded and documented. Specific information is also collected at each sampling time: body weight, height, JAKI (dose amount and administration frequency), diagnosis, comorbidities, list of comedications, clinical scores (eg, Disease Activity Score-28, Bath Ankylosing Spondylitis Disease Activity Index), and any information on organ dysfunction. ADRs reported by the patient during the investigation (Common Terminology Criteria for Adverse Events classification; version 5.0) are also documented through TDM report forms to capture the safety profile of the drugs being studied (Table 1). Other relevant clinical information (concomitant diseases, biomarkers) is extracted from the medical records and recorded with study data. Reasons for treatment interruption are documented in all cases. Adherence to treatment is assessed at the standard visit with physicians and nurses before filling out the TDM form. Information retrieved from each TDM report form and JAKI drug levels is entered into the Research Electronic Data Capture electronic case report form by a study team member. Before any pharmacokinetics or statistical analysis, the data entry is double-checked by the study coordinator.

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Table 1. Data collected for the project.

Data type and subcategory	Unit
General information	
Patient identification number (coded)	Category
Physician name	Category
Clinical justification	
Therapeutic monitoring not otherwise specified	Category
Unsatisfactory response and therapeutic failure	Category
Suspected drug interactions	Category
Dose adjustment for organ failure	Category
Suspected toxicity	Category
Diagnosis	
Indications for treatment with JAKIs[a]	Category
Comorbidities	Category
Clinical response	
Global clinical response	Value
DAS-28-ESR[b]	Value
DAS-28-CRP[c]	Value
ASDAS-ESR[d]	Value
BASDAI[e]	Value
BASFI[f]	Value
DAS68-ESR[g]	Value
DAS68-CRP[h]	Value
EASI[i]	Value
SCORAD[j]	Value
PGA scale[k]	Value
SELENA-SLEDAI[l]	Value
Harvey-Bradshaw	Value
Modified Truelove and Witts Severity Index	Value
Partial Mayo Score	Value
SSCAI[m]	Value
MPN 10[n]	Value
Organ dysfunction	
Heart failure	Category
Renal dysfunction	Category
Liver dysfunction	Category
Support (hemodialysis, CRRT[o], and other)	Category
Sign of toxicity	
Sign of toxicity (CTCAE[p], version 5.0)	Category
Body weight, height, and environmental factors	
Age (year of birth)	Date

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Data type and subcategory	Unit
Gender	Category
Ethnic background	Category
Body weight	kg
Height	cm
BMI	kg/m^2
Smoking habits	Category
Alcohol consumption	Category
Laboratory values	
Creatinine	µmol/L
Erythrocyte	T/L
Hemoglobin	G/L
Neutrophile	G/L
Thrombocyte	G/L
Bilirubin	µmol/L
ALT[q]	U/L
AST[r]	U/L
Inflammatory biomarkers[s]	__[t]
Drug	
Molecule measured (ATC[u] code)	Category
Dosage	mg
Number of daily intakes	Value
Level of therapeutic adherence	Percentage
Blood sampling and last given dose	
Date and time of blood sampling	Date and time
Date and time of the last dose	Date and time
Date of initiation or last change of dosing	Date
Time after dose	Time
Comedications	
Comedication (ATC code)	Category
Concentration measured	

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Data type and subcategory	Unit
Concentration measured	ng/mL

[a]JAKI: Janus kinase inhibitor.
[b]DAS-28-ESR: Disease Activity Score-28 for rheumatoid arthritis with erythrocyte sedimentation rate.
[c]DAS-28-CRP: Disease Activity Score-28 for rheumatoid arthritis with C-reactive protein.
[d]ASDAS-ESR: Axial Spondyloarthritis Disease Activity Score with erythrocyte sedimentation rate.
[e]BASDAI: Bath Ankylosing Spondylitis Disease Activity Index.
[f]BASFI: Bath Ankylosing Spondylitis Functional Index.
[g]DAS-68-ESR: Disease Activity Score-68 for rheumatoid arthritis with erythrocyte sedimentation rate.
[h]DAS-68-CRP: Disease Activity Score-68 for rheumatoid arthritis with C-reactive protein.
[i]EASI: Eczema Area and Severity Index.
[j]SCORAD: Scoring Atopic Dermatitis.
[k]PGA: Physician Global Assessment.
[l]SELENA-SLEDAI: Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index.
[m]SCCAI: Simple Clinical Colitis Activity Index.
[n]MPN-10: Myeloproliferative Neoplasm Symptom Assessment Form.
[o]CRRT: continuous renal replacement therapy.
[p]CTCAE: Common Terminology Criteria for Adverse Events.
[q]ALT: alanine aminotransferase.
[r]AST: aspartate aminotransferase.
[s]Inflammatory biomarkers, for example, C-reactive protein and erythrocyte sedimentation rate.
[t]Units for inflammatory biomarkers depend on the specific markers selected.
[u]ATC: Anatomical Therapeutic Chemical classification.

Drug-Level Measurements

Measurements of total plasma levels of JAKIs are performed by multiplex high-performance liquid chromatography coupled to tandem mass spectrometry as a part of the routine TDM service provided by the Laboratory of Clinical Pharmacology (University Hospital of Lausanne, Switzerland). A multiplex assay was developed and validated according to the French Society of Pharmaceutical Sciences and Techniques and International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use–M10 guidelines (European Medicine Agency) for the simultaneous quantification of JAKIs in plasma (abrocitinib, baricitinib, fedratinib, ruxolitinib, tofacitinib, and upadacitinib). The method was validated over the clinically relevant concentration ranges (0.5-200 ng/mL for abrocitinib, baricitinib, and upadacitinib; 0.5-400 ng/mL for ruxolitinib; 1-400 ng/mL for tofacitinib; and 10-800 ng/mL for fedratinib) [61].

In-house studies indicate that abrocitinib, baricitinib, tofacitinib, and upadacitinib are stable in whole blood at room temperature up to 96 hours, whereas ruxolitinib and fedratinib are stable in plasma (up to 96 hours at room temperature). Whole blood and plasma samples, together with the TDM report form, are shipped at room temperature in a plastic transport protection coffer to the Laboratory of Clinical Pharmacology. Whole blood samples are then immediately centrifuged (2000 g, 10 min, +4°C). The separated plasma is frozen at −80°C until analysis by high-performance liquid chromatography coupled to tandem mass spectrometry.

Pharmacokinetic and Pharmacodynamic Modeling

The comprehensive population-based modeling and simulation of JAKI pharmacokinetics profile rely on nonlinear mixed effect modeling techniques, such as those implemented in the NONMEM (version 7.6.0; ICON Development Solutions) and Monolix (version 2024R1, Lixoft) software. PopPK approaches will enable the characterization of the average pharmacokinetics profile of JAKIs, including absorption, distribution, metabolism, and excretion, based on plasma concentrations and data pooled over all sampled individuals. It also allows for the quantification of inter and intraindividual variability and for the identification of various factors (covariates) contributing to this variability within the population.

For each JAKI, a classical stepwise procedure will be conducted to identify the popPK model that best fits the concentrations [62]. Models with several compartments, different absorption processes, and linear elimination will be compared. Interindividual variability will be sequentially tested on all the parameters, assumed to follow a log-normal distribution. Intraindividual variability will also be assessed. Covariates, such as body weight, age, sex, BMI, genetic polymorphisms, and comedication (eg, CYP and transporter inhibitors or inducers), susceptible to interact with JAKI metabolism will be tested for significance on the base model parameters using appropriate mathematical functions. DDIs will be identified based on concomitant medications reported in TDM report forms using the UpToDate drug interactions tool [63]. Interacting drugs will be classified as weak, moderate, or strong CYP or transporter inhibitors or inducers. As chronic inflammation in autoimmune diseases may alter drug pharmacokinetics, disease type (eg, GvHD, rheumatoid arthritis) and level of inflammation assessed with inflammatory

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biomarkers (eg, C-reactive protein) will also be tested for significance in the popPK model. Covariates will be sequentially tested using forward selection and backward elimination steps. The first phase involves adding each covariate to the base model, followed by combining the significant ones in multivariate analyses to establish an intermediate model. The second step is the one-by-one removal of covariates from the intermediate model to retain only the most significant ones. Significance levels of .05 and .01 will be used to statistically discriminate hierarchical models during the base model building and covariate forward insertion steps, and the backward elimination phase, respectively. Akaike information criterion will serve to discriminate nonnested models. Diagnostic plots and the relative SE will support model selection. Sensitivity analyses will be conducted to assess the robustness of our model by removing outlier patients with extreme parameter estimates or covariates, such as patients receiving CYP-modulating drugs or those with severe disease presentations. Moreover, well-established internal validation methods (prediction-corrected visual predictive checks and bootstrap) will be used to evaluate final model predictive performance and reliability [64-66]. If enough data are collected, cross-validation will be performed with repeated data-splitting, creating random subsets of the dataset, allocating 80% of the data for modeling and 20% for validation.

Treatment efficacy and safety will be ascertained by studying the correlation between drug levels and the occurrence of inadequate disease control and ADRs within the study population. Efficacy-related pharmacodynamics data are collected through clinical outcome scores, while data on ADRs and predictive biomarkers for response, nonresponse, or toxicity (eg, platelet, erythrocyte, hemoglobin, and neutrophil counts) are gathered in parallel (Table 1). Pharmacokinetics and exposure-response or toxicity models will be developed using popPK software. This will enable comprehensive pharmacokinetics and pharmacodynamic analyses for the formal establishment of target trough concentrations or other relevant pharmacokinetics parameters. Findings will be compared with the available literature to identify suitable concentration targets associated with an optimal efficacy and toxicity ratio.

Statistical Considerations

The precision of model estimates depends on both the number of available samples and their distributions across the dosing interval. Data collected throughout the administration interval enhances the ability to develop an adequate model. Drugs with highly variable and complex pharmacokinetics require more samples for an accurate description [67]. Moreover, the identification of covariate effects relies on their distribution and variability within the population of interest. Preliminary popPK analyses showed that abrocitinib, baricitinib, fedratinib, ruxolitinib, and upadacitinib were best described by a 2-compartment model [47,50,68-72], while tofactinib was best described by a 1-compartment model [73,74]. Actually, simulation studies have established that the minimum sample size required for a popPK analysis based on a 2-compartment model to estimate the 95% CI around typical pharmacokinetics parameters, such as clearance and distribution volume within a 50% precision level with a power of 0.8, is at least 50 patients, provided that the study applies an appropriate sampling schedule [75]. More specifically, assuming a 30% intraindividual variability and 50% interindividual variability in clearance, 182 patients would theoretically be needed to demonstrate a 20% difference by adding a covariate, again with due consideration to the sampling schedule [76]. Because the model will be based on rich data from detailed pharmacokinetics substudy, a smaller sample size of at least 50 patients per drugs was considered sufficient to establish popPK parameter values and coefficients for clinically significant covariates with a sufficient degree of precision, as it has already been the case in previous popPK studies that were conducted in similar patients [77-80].

Results

The patient recruitment began in August 2023, following approval from the Ethics Committee. As of August 2024, a total of 107 patients had been recruited and 276 plasma samples analyzed. Most patients recruited were taking ruxolitinib (n=44, 41.1%), upadacitinib (n=39, 36.4%), and baricitinib (n=11, 10.3%). Of these, 23 (21.5%) participants taking either ruxolitinib (n=10, 43%), upadacitinib (n=10, 43%), or baricitinib (n=3, 13%) were enrolled in the detailed pharmacokinetics substudy over a period of 7 to 10 hours. Table 2 presents the overall and drug-specific population characteristics. Patient population was predominantly female individuals (62/107, 57.9%), with a median age of 51 (17-87) years and a median body weight of 69 (39-132) kg.

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Table 2. Summary of characteristics of the patient population (data were extracted in August 2024).

	Abrocitinib	Baricitinib	Fedratinib	Ruxolitinib	Tofacitinib	Upadacitinib	Total
Summary of characteristics of patients included in the study, n (%)							
Patients	2 (1.8)	11 (10.3)	1 (0.9)	44 (41.1)	10 (9.3)	39 (36.4)	107
Samples	3 (1.1)	36 (13)	1 (0.4)	118 (42.8)	11 (4)	107 (38.8)	276
Demographic characteristics							
Age (y), median (range)	38 (29-47)	62 (17-83)	76 (76)	64 (23-87)	53 (25-74)	47 (19-87)	51 (17-87)
Sex, n (%)							
Male	0 (0)	3 (27.3)	1 (100)	25 (56.8)	3 (30)	13 (33.3)	45 (42.1)
Female	2 (100)	8 (72.7)	0 (0)	19 (43.2)	7 (70)	26 (66.7)	62 (57.9)
Anthropometric characteristics, median (range)							
Body weight (kg)	58 (55-60)	70 (47-82)	85 (85)	67 (40-112)	72.3 (46-100)	73 (49-132)	69 (39-132)
Height (cm)	161 (160-162)	165 (152-178)	175 (175)	172 (146-202)	162 (150-190)	165 (157-188)	167 (146-202)
BMI (kg/m^2)	22 (21-23)	26 (16-35)	28 (28)	24 (15-32)	27 (20-34)	26 (18-43)	25 (15-49)
Clinical characteristics							
Pathologies, n (%)							
Atopic dermatitis	2 (100)	0 (0)	0 (0)	0 (0)	0 (0)	3 (8)	5 (4.7)
Vitiligo	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	1 (0.9)
Dermatomyositis	0 (0)	1 (9)	0 (0)	0 (0)	1 (10)	1 (3)	3 (2.8)
Lichen planus	0 (0)	2 (18)	0 (0)	0 (0)	0 (0)	0 (0)	2 (1.9)
Eczema	0 (0)	1 (9)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.9)
Eczema herpeticum	1 (50)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.9)
Alopecia totalis	0 (0)	1 (9)	0 (0)	0 (0)	0 (0)	1 (3)	2 (1.9)
Hidradenitis suppurativa	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	2 (5)	2 (1.9)
Prurigo nodularis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	1 (3)	1 (0.9)
Rheumatoid arthritis	0 (0)	6 (55)	0 (0)	0 (0)	2 (20)	3 (8)	11 (10.3)
Psoriatic arthritis	0 (0)	0 (0)	0 (0)	0 (0)	2 (20)	5 (13)	7 (6.5)
Axial spondyloarthritis	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	11 (28)	11 (10.3)
Juvenile idiopathic arthritis	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	0 (0)	1 (0.9)
Myelofibrosis	0 (0)	0 (0)	1 (100)	10 (23)	1 (10)	0 (0)	12 (11.2)
GvHD[a]	0 (0)	0 (0)	0 (0)	26 (59)	0 (0)	0 (0)	26 (24.3)
Polycythemia vera	0 (0)	0 (0)	0 (0)	3 (7)	0 (0)	0 (0)	3 (2.8)
Essential thrombocytopenia	0 (0)	0 (0)	0 (0)	2 (5)	0 (0)	0 (0)	2 (1.9)
VEXAS[b] syndrome	0 (0)	0 (0)	0 (0)	2 (5)	0 (0)	0 (0)	2 (1.9)
Sarcoidosis	0 (0)	0 (0)	0 (0)	0 (0)	1 (10)	1 (3)	2 (1.9)
APECED[c] syndrome	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)	1 (0.9)
Ulcerative colitis	0 (0)	0 (0)	0 (0)	0 (0)	4 (40)	8 (21)	12 (11.2)
Crohn disease	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	11 (28)	11 (10.3)
Number of comedications, n (%)							
0-4	2 (100)	6 (54.5)	0 (0)	22 (50)	7 (70)	27 (69.2)	64 (59.8)
5-8	0 (0)	5 (45.5)	0 (0)	13 (29.5)	3 (30)	8 (20.5)	29 (27.1)
9-12	0 (0)	0 (0)	1 (100)	9 (20.5)	0 (0)	4 (10.3)	14 (13.1)

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[a]GvHD: graft-versus-host disease.

[b]VEXAS syndrome: vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome.

[c]APECED syndrome: autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome.

Ruxolitinib was primarily prescribed for GvHD (n=26, 59%) and myelofibrosis (n=10, 23%), while upadacitinib was mainly used for IBD (n=19, 49%) and rheumatological conditions (n=19, 49%). In total, 3 patients were treated with ruxolitinib for off-label conditions, such as autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy syndrome (n=1, 2%), or vacuoles, E1 enzyme, X-linked, autoinflammatory, somatic syndrome (n=2, 5%).

Most patients were administered upadacitinib at a dosage of 15 mg once daily and ruxolitinib at 10 mg twice daily (BID). One patient receiving ruxolitinib 10 mg BID exhibited unexpectedly high plasma exposure during the detailed pharmacokinetics substudy.

Inadequate response or treatment failure was reported in 14 (13.1%) of 107 patients. ADRs were present in 17 (38%) and 13 (33%) participants taking ruxolitinib and upadacitinib, respectively. The most frequent ADRs concerned the blood and lymphatic system (anemia, cytopenia, neutropenia, or thrombocytopenia), abnormal laboratory values (transaminases and cholesterol), and dermatological disorders (acne), which accounted for 30% (23/77), 16% (12/77), and 14% (11/77) of the total reported ADRs.

Discussion

Anticipated Findings

This protocol aims to monitor and individualize JAKI concentrations in the treatment of various inflammatory and hematological diseases. To the best of our knowledge, this is the first large-scale study to investigate the pharmacokinetics and pharmacodynamic profile of JAKIs in a real-world population and to develop method for monitoring them.

To date, most participants have been administered ruxolitinib, upadacitinib, or baricitinib, whereas only a limited proportion of participants received abrocitinib, fedratinib, and tofacitinib, reflecting their less frequent use in the study population. One individual diagnosed with GvHD and treated with 10 mg BID of ruxolitinib exhibited elevated concentrations and low elimination over time. Genotyping indicated a normal metabolizer phenotype, whereas phenotyping results revealed a phenoconversion with a reduced activity of the CYP2C19 and CYP3A, the latter likely due to environmental factors. The low activity could explain the abnormally elevated plasma drug concentrations. This patient notably experienced a viral respiratory infection requiring hospitalization shortly before inclusion in this study and was diagnosed with nonmelanoma skin cancer (basal cell carcinoma), documented in the literature as a ruxolitinib-related ADR [20,81-85].

During the first 12 months of inclusion, most patients receiving JAKIs demonstrated an adequate response to their treatment. However, some patients on ruxolitinib mainly experienced hepatic and hematological disorders ranging from mild to severe, while those on upadacitinib primarily reported dermatological ADRs. Dosages were frequently adjusted empirically over time by clinicians to manage toxicity and improve efficacy.

However, there are gaps in knowledge with regard to dosage and administration schemes for nonstandard patients. Significant interindividual variability has been reported for ruxolitinib in the literature [43,55], which may complicate the management of MPN and GvHD, potentially resulting in toxicities or reduced efficacy for some patients. According to published data, drug exposure was also influenced by the type of disease and comedications [43,50]. Current practices are based on drug manufacturers' recommendations, often complemented by empirical decisions that account for patient characteristics, comorbidities, comedications, disease severity, and treatment response. For instance, upadacitinib has been used for a growing range of indications, from rheumatic (rheumatoid arthritis, psoriatic arthritis, and spondyloarthritis) and dermatological (atopic dermatitis, vitiligo, and alopecia) conditions to highly inflammatory diseases such as IBD, which require induction doses up to 3 times higher before transitioning to a maintenance phase [86]. Nonetheless, these approaches have so far been tested in the strict frame of clinical trials, which do not account for the complex real-world situation of many patients. In such cases, our understanding of JAKIs' pharmacokinetics profiles and their impact on chronic disease management remains limited.

A wide range of clinical situations reported by physicians revealed unmet needs regarding the potential interest of TDM for JAKIs. A precision medicine approach, which can be assisted by the Tucuxi program [87,88], could thus help individualize treatments and improve clinical outcomes. JAKI monitoring represents a promising approach to maintain drug concentrations within narrow therapeutic indexes to overcome efficacy and safety concerns, while possibly addressing compliance issues as well. It represents a novel approach to provide an unambiguous benefit for patients and clinicians.

Perspective

On the basis of the gathered pharmacokinetics data, the first popPK models for ruxolitinib and upadacitinib are expected to be developed in early 2025. By that time, the number of recruited patients should be sufficient for this analysis, which is expected to take several months. As a secondary end point, a pharmacokinetics and pharmacodynamic analysis will be conducted using the collected pharmacodynamics data to explore the relationships between drug concentration-response and toxicity. The results will be compared with existing literature to identify an optimal efficacy-toxicity ratio.

Strengths and Limitations

Our patient population sample differs from the one observed in clinical trials due to the demographic characteristics and will enable us to perform robust analyses of pharmacokinetics variability in real-world settings. However, several limitations of the present protocol should be acknowledged. First, to ensure ethical compliance, participants incapable of judgment or who

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were under tutelage were excluded from the study, which may limit the generalizability of the findings. However, based on feasibility analyses, this group represents only a small proportion of patients eligible for JAKI treatment. Our cohort includes patients who are polymedicated with complex clinical situations, such as multimorbidity and altered metabolism, which likely contribute to the pharmacokinetics variability observed in real-world settings.

Furthermore, this study allows for the collection of ADRs not only during routine consultations but also during hospitalizations, when some ADRs may be severe. However, collecting pharmacodynamic data remains challenging. ADRs may be underreported in this study for several reasons. Outpatients typically report ADRs only during routine medical visits, which means that important information that may arise between consultations may be missed. This limitation is exacerbated by the infrequency of these visits, as patients may experience ADRs without the opportunity to communicate them. Health care professionals may also not systematically document reported ADRs due to time constraints. Besides, all clinical data and laboratory values are not always accessible, as patients are followed in different hospitals and cabinets across Switzerland. Finally, some clinical outcomes might also be underreported in our study, as they are not systematically assessed during routine clinical visits.

Conclusions

This protocol aims to bring an original contribution to the monitoring of JAKIs by investigating the characteristics of their pharmacokinetics profile in real-world patients. It addresses an integrated strategy of treatment monitoring of JAKIs, based on relevant demographic and clinical factors, and measurement of circulating blood concentrations. The TDM of JAKIs appears instrumental in streamlining targeted immunotherapy as second- or third-line treatments. In the growing movement toward precision medicine, this novel research initiative is expected to improve the efficacy, effectiveness, tolerability, and long-term safety of JAKIs, and address DDIs and pharmacogenetic issues associated with them as prototypic medications with a narrow therapeutic index.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Disclaimer

On February 28, 2025, Bristol-Myers Squibb announced the withdrawal of fedratinib from the Swiss market. The temporary marketing authorization had expired, resulting in its discontinuation. Fedratinib was initially included in the study protocol before this decision.

Authors' Contributions

JT, MG, LAD, and FRG conceptualized, designed, and supervised the research proposal. JT wrote the paper with input from all the authors. FRG is leading the project. MG is leading the development of the population pharmacokinetics model of Janus kinase inhibitors. LAD is responsible for managing the laboratory and analytic aspects of the project. JT developed and validated the analytic method, coordinates blood sample collection, and is developing the Janus kinase inhibitor population pharmacokinetics model. FRG and LAD are the cosupervisors of JT's PhD. All authors have approved the final version of the paper and agreed to be accountable for all aspects of the work related to accuracy and integrity.

Conflicts of Interest

None declared.

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Abbreviations

ADR: adverse drug reaction
BID: twice daily
CYP: cytochrome P450
DDI: drug-drug interaction
GvHD: graft-versus-host disease
IBD: inflammatory bowel disease
JAK: Janus kinase
JAKI: Janus kinase inhibitor
MPN: myeloproliferative neoplasm
popPK: population pharmacokinetics
STAT: signal transducer and activator of transcription
TDM: therapeutic drug monitoring

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Protocol

Assessing a Person-Centered and Culturally Sensitive Intervention for Arabic-, Turkish, or Urdu-Speaking Individuals With Type 2 Diabetes: Protocol for a Mixed Methods Realist Evaluation Study

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Abstract

Background: Individuals from ethnic minority backgrounds have a 2.5 times higher incidence of type 2 diabetes (T2D) than ethnic Danes. They often face negative experiences with health care professionals, leading to unequal treatment. A person-centered and culturally adapted treatment approach can improve self-care, diabetes management, and treatment adherence.

Objective: This mixed methods realist evaluation (RE) protocol aims to understand how a person-centered and culturally sensitive course of treatment for T2D works, for whom it is most effective, and under what circumstances it is likely to be effective.

Methods: This RE is embedded within a 1-year randomized controlled trial, the Culturally Sensitive Course of Treatment for Individuals With T2D (ACCT2) study, for Arabic-, Turkish-, or Urdu-speaking individuals with suboptimal glycated hemoglobin (HbA_{1c} ; ≥53 mmol/mol) or unmet individual targets at 2 consecutive visits. The RE follows three phases: (1) developing, (2) testing, and (3) refining initial program theories. Data are collected through semistructured interviews at 4 months (visit 4) and at the end of the intervention (visit 6). Survey data are collected at baseline and at the end of the intervention. We aim to recruit 16 to 20 intervention participants, including at least 2 men and 2 women from each language group. Qualitative data will be analyzed thematically using a predefined codebook, and survey data will be analyzed descriptively.

Results: As of December 2024, a total of 13 visits and 4 interviews had been completed. All baseline survey responses have been collected, along with 2 survey responses at the end of the intervention. Data analysis is pending. The results will inform revisions to the initial program theories, refining a comprehensive model that captures interactions between context, mechanisms, and outcomes. We anticipate disseminating the findings in the first half of 2026.

Conclusions: This RE will support the randomized controlled trial by providing insights applicable to real-life clinical settings. The anticipated impact includes aiding the future development and implementation of interventions for the target groups.

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KEYWORDS

immigrants; transients and migrants; minority groups; theoretical models; program evaluation; clinical protocols; public health; health personnel; artificial intelligence; AI; type 2 diabetes

Introduction

Background

Individuals with ethnic minority backgrounds constitute almost 16% of the Danish population, and this percentage is expected to increase [1]. Despite an improved focus on health among individuals with ethnic minority backgrounds, significant health inequity persists [2], and their incidence rate of type 2 diabetes (T2D) is 2.5 times greater that of ethnic Danes [3]. Individuals with ethnic minority backgrounds have an increased risk of developing severe T2D complications [3-6], partly due to

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genetic, environmental, cultural, and social factors challenging diabetes management [7]. The risk is further exacerbated by structural factors, as health information and services are often not adapted to the needs of ethnically diverse groups [8,9].

Previous research indicates that individuals with ethnic minority backgrounds often face negative experiences in consultations with health care professionals (HCPs), leading to mistrust and unequal treatment [10]. These challenges can stem from differing health perceptions [9,11], limited knowledge of the health care system [10,12], and reduced participation in diabetes educational interventions due to language barriers, lack of cultural sensitivity, and difficulties in navigating the health care system [13-15].

A person-centered and culturally adapted approach where HCPs pay attention to knowledge, motivation, individual experiences, values, cultural beliefs, and support from family and socioeconomic resources [16] has proven to support individuals with ethnic minority backgrounds in self-care and greater adherence to treatment plans [17]. This aligns with the realist evaluation (RE) framework proposed by Pawson and Tilley [18], which emphasizes understanding how context influences mechanisms that produce specific outcomes.

Previous studies have primarily focused on developing and testing group-based, culturally sensitive educational programs through randomized controlled trials (RCTs) and RE [19-22]. Although a previous study has developed a structured and person-centered model targeting the general diabetes population across both primary and secondary care sectors [23], there is a significant knowledge gap regarding how person-centered, culturally sensitive diabetes education and treatment work when integrated into clinical consultations for individuals with ethnic minority backgrounds in specialized diabetes care settings.

RCTs rarely address the context-specific factors that influence implementation outcomes or their connection to the underlying program theory [18], which limits the interpretability of findings across different programs and settings. Therefore, an RE is particularly valuable for assessing complex interventions in RCT studies, as it seeks to understand the generative causality between different intervention components and levels through the context-mechanism-outcome (CMO) configuration model, with a strong focus on context [18,24]. This approach enables a more holistic understanding of how and why an intervention works, moving beyond simple "what works" questions to explore "what works, for whom, in what circumstances, and why" [25].

Pawson and Tilley [18] acknowledge that interventions are active, adaptable to change, and embedded in a social reality that shapes both implementation and stakeholders' responses to the intervention. This theoretical foundation is particularly relevant for understanding complex health care interventions targeting populations with ethnic minority backgrounds, where context plays a crucial role in determining effectiveness.

Objectives

We have developed a 1-year, person-centered, and Culturally Sensitive Course of Treatment for Individuals With T2D (ACCT2 study [26]) to improve glycemic control (glycated hemoglobin; HbA_{1c}), health literacy, and overall well-being. The target population includes men and women who speak Arabic, Turkish, or Urdu; have T2D; and have limited access to health care services. The overall purpose of this mixed methods RE protocol is to explore how the ACCT2 study works, for whom it is most effective, and under what circumstances it is likely to be effective. Specifically, we explore which intervention components contribute to specific outcomes by identifying the mechanisms that produce intended or unintended outcomes.

Methods

Study Design

Using a mixed methods design [27], we plan to conduct an RE [18] nested within the ACCT2 study [26]. The RE will follow the Realist and Meta-Narrative Evidence Synthesis: Evolving Standards guidelines [28] and will be reported separately. In the nested integration method, the RCT examines the causal impact of the ACCT2 study, while the RE provides a generative understanding of causality by explaining the intervention's effectiveness through the interaction between mechanisms and context [29,30]. By developing and testing initial program theories of the intervention, we aim to produce robust evidence while maintaining high internal validity from the RCT, achieving both quantifiable outcomes and qualitative insights [31].

In this RE, we understand mechanisms as "unobservable entities that are activated in a specific context to generate one or more outcomes" [30,32], meaning that the hidden mechanisms generate changes within the intervention. Through the RE, we use semistructured interviews and survey data to assess the effectiveness of the ACCT2 study thoroughly. The RE design involves three steps: (1) developing, (2) testing, and (3) consolidating our program theories based on data collection and analysis (Figure 1) [33].

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Figure 1. Study design and methods. CMO: context-mechanism-outcome.

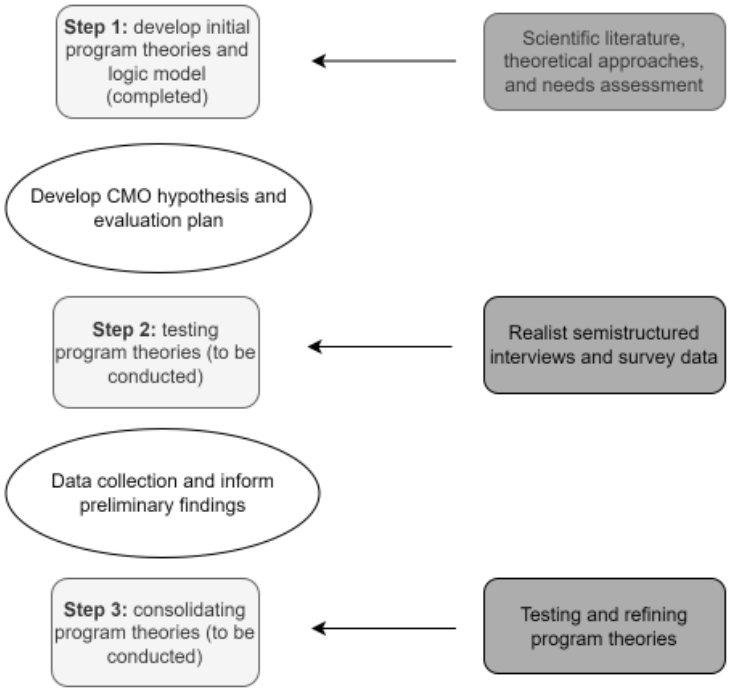

Our RE is guided by initial program theories [34] (step 1), outlining the mechanisms through which the ACCT2 study is expected to be effective within the context of Steno Diabetes Center Copenhagen (SDCC), Denmark. The initial program theories (Table 1) are depicted in a logic model (Figure 2) [18] following the CMO configuration framework and comprise resources; activities; outputs; and short-term, intermediate, and long-term outcomes [18]. The logic model [35] serves as a framework for organizing the theoretical and empirical assumptions underlying the ACCT2 study. It encompasses both the format and content of the designed intervention, and emphasizes that complex interventions possess underlying theories for achieving specific outcomes [36]. The initial program theories enable an examination of how the intervention works, for whom, and under what circumstances, focusing on the mechanisms it triggers and the resulting outcomes [36]. Applying a logic model and CMO configurations ensures a holistic and contextualized evaluation, integrating quantitative and qualitative data. Our initial program theories will guide our data collection and analysis in step 2.

In step 2, we plan to unfold and explore the mechanisms activated by the intervention by conducting semistructured interviews with participants, their close relatives, and HCPs delivering the intervention. We also plan to apply survey data collected during the RCT. By analyzing both qualitative and quantitative data, we will test the initial program theories to gain insights into the experiences and perspectives of participants.

In step 3, we will consolidate our initial program theories, based on our data analysis. Through the RE, we will focus on individual and interpersonal needs and institutional settings to design features that improve HbA_{1c} levels, health literacy, diabetes management, and well-being. This does not consider broader social and economic contexts, although it is based on the local context of SDCC. This study specifically captures behavioral, interpersonal, and social mechanisms that contribute to intervention outcomes.

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Table 1. Initial program theories and rival theories of the culturally sensitive course of treatment for individuals with type 2 diabetes (ACCT2) study and evidence.

Theories	Evidence
Consultations with the same HCP[a]	
Initial: ensuring longer and more consultations with the same HCPs will help build trusting relationships and dialogue. This will create a relaxed environment for the target group, allowing them to ask questions without feeling rushed. HCPs will understand and accommodate individual needs and treatment preferences better. This will lead to improved comprehension, adherence to treatment plans (eg, medication and healthy diet), and diabetes management, leading to better HbA_{1c}[b] levels and enhanced well-being.	[12]
Rival: increasing the frequency and length of consultations will overwhelm the target group with excessive information, lowering retention and engagement, causing them to depend on future sessions to resolve issues, and weakening adherence to treatment plans. Overfamiliarity with the same HCPs can foster complacency rather than enhance communication. Consequently, HbA_{1c} levels and well-being will remain unchanged, and health care resources will be misallocated without improved outcomes.	[12]
Increasing the number and duration of consultations	
Initial: expanding the number and duration of consultations (from 4 to 6 sessions, with an additional 30 min on average) will allow HCPs to thoroughly explain the nature of T2D[c], complications, treatments, medications, and side effects. This will help the target group feel informed about their condition and have their questions addressed. This will increase their level of health literacy and encourage them to adhere to treatment plans (eg, medication, healthy diet, and physical activity) and diabetes management, leading to improved HbA_{1c} levels and enhanced well-being.	[12]
Rival: expanding the number and duration of consultations might overwhelm the target group with information, leading to confusion rather than increased health literacy. Longer sessions could cause disengagement, with the target group burdened by the extra details. This can weaken their motivation to adhere to treatment plans, ultimately resulting in little to no improvement in HbA_{1c} levels or well-being. The extended consultations may also inefficiently use health care resources without significantly improving personal outcomes.	[12]
Providing continuous glucose monitoring technology	
Initial: continuous glucose monitoring sensors will provide the target group with real-time blood glucose level data. These data will be discussed during consultations and used as pedagogic tools to empower and motivate the target group with concrete guidance on how to engage in diabetes management. As a result, the target group will be more likely to adhere to treatment plans (eg, medication, healthy diet, and physical activity), leading to improved HbA_{1c} levels and overall well-being.	[37-42]
Rival: continuous glucose monitoring sensors will provide the target group with real-time blood glucose level data and increase their awareness of fluctuations. However, this heightened awareness may lead to greater anxiety and worry, as the target group becomes overfocused on data and guidance. This can result in poorer adherence to treatment plans and diabetes management, ultimately leading to poorer HbA_{1c} levels and overall well-being.	[37-42]
Culturally adapted communication	
Initial: if HCPs use culturally adapted communication during consultations, such as translated information, tailored dialogue tools, and appropriate nonverbal methods when needed, the target group will better understand their condition. This will motivate them to act on the knowledge, as the materials will be accessible and culturally relevant. Consequently, this increased understanding will enhance health literacy and improve T2D management by aligning with cultural and linguistic backgrounds.	[43-46]
Rival: if HCPs use culturally adapted communication with translated materials and tailored dialogue tools, the target group might not achieve better understanding or improved health literacy. Barriers such as personal beliefs, past experiences, or complex information can still impede comprehension and adherence, potentially limiting diabetes management.	[43-46]
HCPs emphasize a holistic, whole-person perspective and diverse cultural context	
Initial: if HCPs have knowledge about diversity, cultures, and religions, then the target group will be more likely to engage in their treatment because the HCPs can plan and tailor the treatment to individual needs and diverse sociocultural contexts. This will result in HCPs perceiving the target group as more motivated to actively participate in their treatment because the customized treatment respects individual cultural and religious values and practices, which increases trust and willingness to cooperate.	[43,44,47]
Rival: if HCPs have knowledge about diversity, cultures, and religions, the target group can still face barriers to fully engage in their treatment. While tailored care can help, other factors such as language barriers, socioeconomic challenges, or personal beliefs can continue to limit participation. Even with culturally sensitive treatment, the target group may prioritize traditional practices or remain hesitant to trust medical advice due to past experiences. As a result, it may not lead to increased trust, motivation, or willingness to cooperate.	[43,44,47]
Relatives' treatment responsibility	
Initial: if the target group receives individualized treatment and support from HCPs, then the relatives will no longer feel responsible for the treatment, because the target group will have gained the ability to manage their condition. This shift in responsibility occurs as the target group becomes more empowered to take charge of their health, reducing the burden on relatives.	[48,49]

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Theories	Evidence
Rival: if the target group receives individualized treatment and support from HCPs, their relatives may still feel responsible for the treatment, as family involvement is often ingrained in caregiving roles. Despite gaining knowledge and the ability to manage T2D, relatives may continue to provide oversight or support out of concern or habit. This dynamic might persist, as relatives may not fully trust that the target group can manage T2D independently or may feel their emotional support is still necessary, thus maintaining a high level of responsibility.	[48,49]

[a]HCP: health care professional.

[b]HbA_{1c}: glycated hemoglobin.

[c]T2D: type 2 diabetes.

Figure 2. Initial logic model of a culturally sensitive course of treatment for individuals with type 2 diabetes, the Culturally Sensitive Course of Treatment for Individuals With T2D (ACCT2) study. HbA_{1c}: glycated hemoglobin; HCP: health care professional; SDCC: Steno Diabetes Center Copenhagen; T2D: type 2 diabetes.

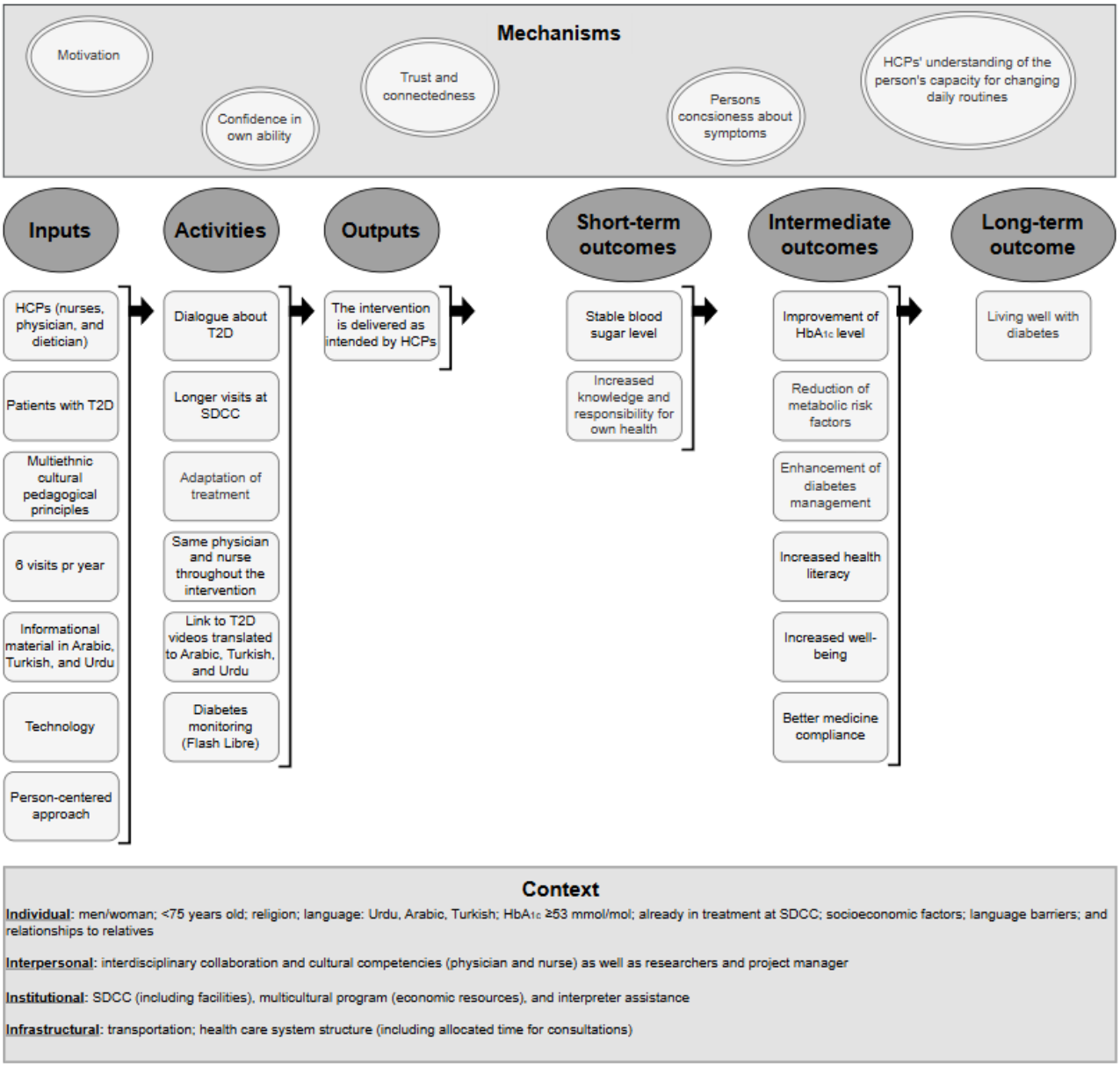

Participants

We aim to recruit a subgroup of 16 to 20 participants from the intervention group (N=48), with at least 2 men and 2 women from each language group to increase representativeness. The eligibility criteria for participants following the ACCT2 study are men and women who speak Arabic, Turkish, or Urdu as their native language; are already undergoing treatment at the outpatient T2D clinic at SDCC, Denmark; and have suboptimal HbA_{1c} levels (≥53 mmol/mol) or have not achieved their individual treatment goal for HbA_{1c} in 2 consecutive measurements [26]. Participants are stratified according to the

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3 native languages included in the RCT (Arabic, Turkish, and Urdu). The final selection of participants for interviews is coordinated according to the timing of their visit 4 (V4). In addition, we plan to interview relatives from each language group (n=15) and HCPs delivering the intervention (physician: n=1 and nurse: n=1).

Intervention Design and Key Components of the ACCT2 Study

The ACCT2 study was developed with the target group and HCPs from the outpatient T2D clinic at SDCC. It consists of three phases: (1) needs assessment, (2) intervention development and element testing, and (3) an RCT.

Phase 1 (needs assessment) involved interviews and workshops with individuals with T2D and non-Western backgrounds (n=18) and HCPs (nurses, physicians, and dieticians; n=18). The findings from this phase suggested adjustments to the standard course of treatment focusing on (1) extended duration and number of consultations, (2) use of technology for diabetes monitoring, (3) awareness of language barriers and use of culturally adapted communication, (4) continuity of care with the same HCPs, and (5) increasing levels of health literacy. A culturally sensitive approach by HCPs was considered vital for enhancing understanding and engagement in diabetes management among the target group, emphasizing a whole-person approach rooted in everyday life. On the basis of the needs assessment and evidence from existing literature, a 1-year intervention was designed and tested on a small scale in phase 2. Phase 3 involves a 1-year pragmatic RCT, including 96 individuals with T2D and an ethnic minority background. The ACCT2 study consists of 6 visits to SDCC (for further description, refer to the study protocol by Bjerre et al [26]). All visits are based on specific values and competencies of HCPs, which are important for the organization, implementation, and completion of the RCT. Educational materials, including written texts, images, and videos, have been translated into Arabic, Turkish, and Urdu. Beyond translation, the content has been culturally adapted to reflect participants' values, food cultures, and visual preferences. Images feature individuals from the relevant ethnic backgrounds and illustrate familiar dietary practices to enhance cultural relevance and engagement [26].

To ensure and monitor intervention fidelity, detailed standard operating procedures were developed for both physician and nurse consultations. These standard operating procedures serve as fixed protocols that outline precisely how each component of the intervention should be delivered. Fidelity monitoring will be conducted through triangulation of data sources: medical records from the consultations are used to document the content and procedures followed, and the duration of each consultation is recorded as an indicator of adherence to the planned structure. In addition, the semistructured interviews included questions about participants' experiences with key elements of the intervention to assess whether they perceived having received the intervention as intended. The CONSORT (Consolidated Standards of Reporting Trials) reporting guidelines were applied (Multimedia Appendix 1 [50]).

Step 1: Developing Initial Program Theories of the ACCT2 Study

The initial program theories produce abstract and plausible explanatory insights into the components of the intervention and focus on how inputs and activities relate to specific responses of our target group (mechanisms), leading to a change in intended or observed outcomes [33,34,51]. Our initial program theories are based on scientific literature, theoretical approaches, and the needs assessment we conducted (Bjerre, N, unpublished data, July 2025). In Table 1, a list of initial program theories and rival theories is detailed and structured according to intervention components, that is, activities. The rival theories offer an alternative explanation that challenges the causal claims of program theories by suggesting other mechanisms that may simultaneously influence outcomes [24]. Rival theories, therefore, allow us to focus on the possible unintended intervention outcomes or harm [24].

Step 2: Testing Program Theory

This step constitutes the core of the investigation, where the initial program theories from step 1 are tested through systematic data collection and analysis. On the basis of a data collection strategy (Table 2), it is specifically examined whether the expected relationships between context, mechanisms, and outcomes actually exist. A combination of quantitative and qualitative methods has been used to document both the occurrence of outcomes and the underlying processes that lead to them. In this process, it is central to investigate whether the theoretically expected mechanisms are activated in practice. This is examined through in-depth interviews to uncover the causal processes underlying the program's effect or lack thereof. Simultaneously, it is systematically investigated how different contextual factors affect the program's mode of operation. This may include demographic, organizational, geographic, or cultural differences that can explain variations in the intervention's effectiveness across different settings. Throughout this process, attention will be paid to mechanisms or relationships that were not anticipated in the initial program theories. These findings are just as important as confirmation of existing theories and can lead to significant revisions in the understanding of how the intervention works [25].

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Table 2. Initial data collection plan for the realist evaluation.

Constructs	Mode of operation	Data source	Participants	Measure	Time of data collection
Mechanisms	• Motivation • Empowerment • Diabetes knowledge • Capacity for change • Trust and connectedness	Individual semistructured interviews	Persons (n=16), relatives (n=15), nurse (n=1), and physician (n=1)	Self-reported understanding of the meeting with health care professionals in the consultation	V4[a], V6[b], and every 6 months during the intervention[c]
Resources	• Person-centered approach and cross-sectoral collaboration (culturally sensitive competencies)	Individual semistructured interviews	Persons (n=16), nurse (n=1), and physician (n=1)	Experience of change in behavior and the intervention process	V4, V6, and every 6 months during the intervention[c]
Activities	• Dialogue of T2D[d] (including diabetes technology) and adjustment of treatment	Individual semistructured interviews and survey data (REDCap[e])	Persons (n=16), nurse (n=1), and physician (n=1)	Self-reported understanding of what has worked in the dialogue, and which factors have been most effective in adjusting the treatment	V4, V6, and every 6 months during the intervention[c]
Outputs	• Intervention delivered as intended	Individual semistructured interviews and survey data (REDCap)	Persons (n=16), nurse (n=1), and physician (n=1)	Self-reported experience with access to diabetes knowledge, blood sugar measurement, and attendance to consultations	V4, V6, and every 6 months during the intervention[c]
Outcome	• Increased knowledge and responsibility for own health	Individual semistructured interviews and survey data (REDCap)	Persons (n=16), relatives (n=15), nurse (n=1), and physician (n=1)	Individual experience of short-term and intermediate outcomes: health literacy, well-being, medication adherence, and diabetes management	V6 and every 6 months during the intervention[c]

[a]V4: visit 4.

[b]V6: visit 6.

[c]Data collected every 6 months during the intervention from nurse and physician.

[d]T2D: type 2 diabetes.

[e]REDCap: Research Electronic Data Capture (Vanderbilt University).

Data Collection

Qualitative and survey data will be collected by the end of 2025.

Semistructured Interviews

To test the initial program theories (step 1), we will conduct semistructured interviews with participants at 2 time points during the RCT; following V4 and at the last visit (visit 6 [V6]). Relatives are invited to participate in one interview, while HCPs delivering the intervention will be interviewed every 6 months of the study period.

The RE interviews aim to explore and expand on various aspects of the program theories. Different interviewguides will be constructed for the target group, relatives, and HCPs to explore experiences during the intervention, assess its acceptability, and identify potential improvements and key factors influencing the effectiveness of the intervention. Before the participants' V4 time point, we will call to schedule the interview to take place immediately after their V4 appointment, during which we will meet them. Before conducting interviews, participants will receive oral information about the interview, and written informed consent will be obtained.

Qualitative researchers will conduct the interviews at SDCC, lasting 20 to 30 minutes.

Survey Data

Quantitative data, in the form of survey data collected using validated questionnaires (for further details, refer to RCT protocol by Bjerre et al [26]), will be gathered at baseline visit 1 and after the end of the intervention (V6; Table 3). The survey data cover well-being, diabetes management, health literacy, medication adherence, and satisfaction with the intervention. Participants can complete the survey in Danish, Arabic, Turkish, or Urdu.

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Table 3. Questionnaires used in the survey at visit 1 and visit 6.

Questionnaires	Baseline (visit 1)	End (visit 6)
Sociodemographic characteristics	✓	
Diabetes distress (PAID-5[a]) [52]	✓	✓
Well-being (WHO-5[b]) [53]	✓	✓
HLQ[c] (3 items) [54]	✓	✓
Diabetes management (PRO[d] scheme diabetes) [55]	✓	✓
MARS-5[e] [56]	✓	✓
Acceptability, retention, and satisfaction [57]	✓	✓

[a]PAID-5: Problem Areas in Diabetes Scale–5.

[b]WHO-5: World Health Organization–Five Well-Being Index.

[c]HLQ: Health Literacy Questionnaire.

[d]PRO: patient-reported outcome.

[e]MARS: Medication Adherence Rating Scale.

Data Analysis

The data analysis will be guided by the initial program theories, which form the foundation for the codebook comprising conceptual categories related to the CMO configurations. The audio records from the interviews will be transcribed verbatim using the artificial intelligence software Viceron27 (Centre for IT and Medical Technology) and subsequently reviewed by qualitative researchers to ensure accuracy. Two researchers will conduct a deductive thematic analysis based on a predefined codebook, with a third researcher consulted in cases of disagreement.

Meaningful text units will be coded in Word (Microsoft Corp) according to the codebook and subsequently organized in Excel (Microsoft Corp) spreadsheets, structured by each initial program theory. CMO components will be extracted from the coded transcripts, accompanied by analytic notes and reflections to explore how context and mechanisms interact to generate specific outcomes.

On the basis of these analyses, revised CMO configurations will be developed to describe how particular mechanisms are triggered within given contextual conditions. These revised CMO configurations will then be compared to the initial CMO configurations based on the initial program theories to assess which patterns were confirmed, refined, or refuted. Particular attention will be paid to the relationships between the following dyads: context-outcome, mechanism-outcome, and context-mechanism dyads.

In parallel, survey data will be analyzed descriptively as part of the RCT [26], with relevant findings integrated into the RE to elaborate on the initial program theories. The statistical analysis is described in detail in the RCT protocol [26].

Step 3: Consolidating Program Theories

In this phase, we will refine and update our initial program theories using the qualitative and quantitative insights from the RE data analysis in step 2 to ensure a robust model that accurately captures the complex relationships between context, mechanisms, and outcomes of the ACTT2 study. This involves refining existing CMO configurations, removing theories not supported by data, and developing new theories based on unexpected findings. Across different datasets and contexts, patterns are identified to develop a broader understanding of which factors consistently affect the intervention's impact. This may reveal underlying principles or "meta-mechanisms" that operate across different specific contexts. Simultaneously, the focus will also be on context specification, with a description of the conditions under which the intervention functions optimally, moderately, or not at all. This often involves identifying configurations of contextual factors that are necessary to activate positive mechanisms [25].

The consolidated CMO configurations are then adapted into the initial program theories. The revised program theories include both strategies for optimizing existing contexts and recommendations for adapting the intervention to different contextual conditions. Finally, the developed theories are positioned in relation to existing research literature and identify how they contribute to the broader understanding of similar interventions and phenomena [25].

Patient and Public Involvement

The intervention was developed in close collaboration with the target group and HCPs, using interviews and workshops (n=18 for each), ensuring that their perspectives and needs were integrated into the research and design process. This active involvement helped highlight key areas for improving health care delivery and emphasized the need for a culturally sensitive approach to enhance engagement and diabetes management. In addition, participants' perspectives are thoroughly considered throughout the evaluation, including potential burdens of the intervention and time requirements. All participants will be invited to seminars where we will present overall findings, allowing them to highlight which results are most critical to share with the SDCC outpatient clinic and the broader public. The participants are covered by the Patient Compensation Association under the Danish Act on the Right to Complain and Receive Compensation in the Health Service.

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Ethical Considerations

The study was approved by the Capital Region of Denmark Ethics Committee (H-387 23042245) and will be conducted in line with the Declaration of Helsinki. It complies with the Danish Data Protection Agency and the General Data Protection Regulation. We will secure adequate blinding of personal data during processing and publication. Participants are covered by the Person Compensation Association. All participants will sign a written informed consent. They will be informed about their right to withdraw at any time and will be guaranteed confidentiality.

Results

As of December 2024, a total of 13 participants have been enrolled, with 13 V4 interviews completed. All baseline survey responses have been collected, along with 2 survey responses at the end of the intervention. Data analysis is pending. The results will inform revisions to the initial program theories, refining a comprehensive model that accurately captures the interactions between context, mechanisms, and outcomes in the ACCT2 study. The study findings will be disseminated in peer-reviewed publications and conference presentations in 2026 or 2027.

Discussion

Anticipated Findings

This protocol presents the design of an RE of the ACCT2 study, aiming to investigate which intervention components contribute to specific outcomes by identifying the mechanisms that produce intended or unintended outcomes. Furthermore, it seeks to understand how the intervention works, for whom it is most effective, and under what circumstances it is likely to be effective.

To our knowledge, this will be the first comprehensive RE to explore how culturally sensitive, person-centered diabetes treatment functions within outpatient consultations for individuals with T2D who speak Arabic, Turkish, or Urdu. We expect that our refined program theory, based on the study findings, will be supported by previous results from other REs and by existing theoretical and empirical evidence in the field.

Strengths and Limitations

A methodological strength of the design is that, before performing this study, the intervention was developed based on a needs assessment involving the target group and HCPs, ensuring an in-depth understanding of their needs, barriers, and potential solutions. In addition, including participants of both genders and from diverse language groups (Arabic, Turkish, and Urdu) will enable us to explore variations in the intervention's effectiveness across these demographics.

To enhance the theoretical rigor of our approach, a subject matter expert in RE supported us in reviewing and refining the initial program theories to ensure that they align with the ACCT2 study's framework.

A limitation of the RE design is its lack of generalizability, largely due to the significant influence of the specific context of the intervention. In addition, potential language barriers among participants are expected and may result in some information being withheld or explanations being shortened.

The target group is known to be grateful and respectful of authority and may hesitate to share negative experiences, which could affect the validity of the data. To address this, participants were encouraged to share both positive and critical feedback to help improve the intervention. Since both interviewers may have interacted with participants during recruitment and data collection, there is a risk of interviewer bias due to power asymmetry and social desirability. This is mitigated by emphasizing openness, triangulating with questionnaires and existing evidence, and encouraging critical reflections. The project manager, who contributed to the development of initial program theories and interview guides due to in-depth knowledge of the intervention, was kept out of data collection and analysis to reduce potential bias. Nonetheless, confirmation bias remains a risk, as the interview guide is shaped by early theories and may overlook alternative explanations, particularly when language barriers are present.

Conclusions

Our RE will elucidate the program theories of the ACCT2 study and address the knowledge gaps highlighted by these theories. This RE is expected to support the RCT by offering insights applicable to real-life clinical settings. The anticipated impact includes aiding the future development and implementation of interventions for individuals with ethnic minority backgrounds and T2D and to minimize inequality in health and T2D treatment.

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Authors' Contributions

MKJ and NB conceptualized the study. MKJ drafted the first manuscript, while both authors contributed to the design and validation of the contents of the study and critically reviewed the manuscript for significant intellectual content. The final manuscript was reviewed, read, and approved by all authors.

Conflicts of Interest

Steno Diabetes Center Copenhagen (SDCC) is a hospital offering health services within the public health care system. SDCC receives partial funding from the Novo Nordisk Foundation through unrestricted grants, with no financial interest in the study. The Novo Nordisk Foundation did not influence (1) the study design; (2) data collection, analysis, or interpretation; (3) preparation of the study or any publications; or (4) the decision to submit the paper for publication. The investigators employed at SDCC will not receive any financial benefit for conducting the study.

Multimedia Appendix 1
CONSORT 2025 editable checklist [38].
[DOCX File , 37 KB - resprot_v14i1e69852_app1.docx]

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Abbreviations

ACCT2: Culturally Sensitive Course of Treatment for Individuals With T2D
CMO: context-mechanism-outcome
HbA_{1c}: glycated hemoglobin
HCP: health care professional

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RCT: randomized controlled trial
RE: realist evaluation
SDCC: Steno Diabetes Center Copenhagen
T2D: type 2 diabetes
V4: visit 4
V6: visit 6

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Protocol

Outcome Evaluation of a Multimodal Suicide Prevention Program Designed Through International Collaboration: Protocol for a Controlled Interrupted Time Series Study

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Abstract

Background: The Coopération Québec-France contre la Dépression et l'Isolement (CQFD-I) initiative represents a collaborative effort between Outaouais, a region in Quebec, and Brest, a metropolitan area in France, to reduce suicide through a multimodal approach. CQFD-I integrates 5 key strategies: a web portal on depression, education of primary care physicians on depression, training for mental health professionals in suicide risk assessment and management, and standardized postcrisis outreach and outpatient monitoring protocols.

Objective: This paper aims to evaluate the effectiveness of CQFD-I in reducing outcomes related to suicidal behavior, namely suicide mortality, hospitalizations due to suicide attempts, and emergency room visits for suicide attempts, across the implementation sites compared to control areas.

Methods: The evaluation will use a controlled, segmented interrupted time series design, spanning 3 distinct phases: preimplementation (2015 to 2020), implementation (2020 to 2022), and postimplementation (2022 to 2024) phases. The outcomes will be (1) suicide mortality, (2) hospitalizations for suicide attempts, and (3) emergency room visits for suicide attempts. Datasets covering September 2015 to August 2024 will be provided by public health organizations in both jurisdictions, that is, the Institut national de la santé publique du Québec and Santé publique France. In Quebec, control sites will consist of the 14 other health regions with a population of at least 50,000, while in France, control sites will include the 18 metropolitan areas with a status comparable to that of Brest Métropole. The analysis will focus on age- and sex-adjusted monthly rates of the specified outcomes, with an emphasis on changes across the study phases to assess the putative effectiveness of the CQFD-I intervention. We hypothesize that each study outcome will decrease by 20% at implementation sites compared to control sites between the preimplementation and postimplementation phases.

Results: This project is funded by the Ministère de la Santé et des Services Sociaux du Québec, with access to data and expertise representing in-kind contributions from Santé publique France and Institut national de la santé publique du Québec. Data collection,

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led by the first author, will take place in September 2027 to allow for the delay required to confirm suicide deaths in official registers, with analysis planned between 2027 and 2028.

Conclusions: To our knowledge, this study will be the first to document the outcomes of a multimodal suicide prevention program targeting geographically defined areas within 2 countries, not limited to the European Union.

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KEYWORDS

suicide; suicidal behaviors; prevention; multimodal program; complex intervention; outcome evaluation; interrupted time series

Introduction

Background

Suicide, defined as the act of deliberately killing oneself, prematurely ends the lives of approximately 700,000 people every year around the globe [1,2]. For every death, it is estimated that there could be up to 20 suicide attempts [1]. A variety of effective strategies exist to counteract suicidal behaviors across diverse populations [3]. Best practices involve reaching as many people as possible by combining several strategies within a more comprehensive suicide prevention program [4], sometimes labeled as a multimodal, multilevel, multicomponent, community-based, or integrated intervention [5]. Multimodal programs are thought to be more effective than single strategies in preventing suicide deaths and attempts [6], especially programs implemented in high schools or targeting groups based on occupation or ethnicity [7,8]. However, current evidence is inconsistent regarding programs targeting the whole population of a geographic area [8].

Much of the available evidence on population-level multimodal suicide prevention pertains to a program named “Optimizing suicide prevention programs and their implementation in Europe” (OSPI-Europe), which provides community and professional training, public education, and direct intervention strategies to prevent suicide across the participating regions [9,10]. The first instance of OSPI-Europe implementation was the Nuremberg pilot in the early 2000s, a pre-post study with a control region that was underpowered to detect changes in suicide mortality but found a decrease of more than 30% in suicide attempts [11]. Building on the Nuremberg pilot and with support from the European Commission, OSPI-Europe was then implemented from 2008 to 2013 in 4 European regions [12], with additional instances of implementation in Germany [13-15] and Hungary [16].

Inspired by ongoing European trials, in 2014, government officials in France and the Canadian province of Quebec started working on an innovative suicide prevention project involving a shared vision of health and social services integration. The resulting Coopération Québec-France contre la Dépression et l’Isolement (CQFD-I) has since involved experts and financial contributions from both jurisdictions in designing and implementing a multimodal suicide prevention program in 2 demonstration sites: the Outaouais region in Quebec, Canada, and Brest Métropole in Brittany, France. The CQFD-I program was structured following the public health model, distinguishing 3 levels of preventive measures: universal, selective, and indicated strategies [17,18]. Interventions are classified as universal when they are relevant for the whole population, selective when they benefit at-risk populations, or indicated when they target people individually at risk. After navigating the lengthy process of designing a program compatible with both jurisdictions, and facing further delays caused by the COVID-19 pandemic, CQFD-I entered the postimplementation phase in September 2022.

OSPI-Europe evaluation studies compare implementation sites to areas chosen by stakeholders [11-13,15,16] or national suicide statistics [13-15]. To our knowledge, only 3 studies have evaluated the outcomes of whole population multimodal suicide prevention programs using formally matched controls, showing mixed results: a 7% suicide reduction in Australia [19]; no effect in New Zealand [20]; and mixed results from Japan’s NOCOMIT-J program, with notable decreases in rural areas [21]. Some studies incorporate time as a covariate [19-21] or use interrupted time series [22-24], which is crucial for understanding the sustained putative impact of such interventions and differentiating real changes from temporary fluctuations. However, evaluation studies of multimodal suicide prevention programs incorporating both a controlled group and interrupted time series in geographically specific programs are lacking.

Objectives

In this paper, we present the protocol for the outcome evaluation of the CQFD-I program, the first instance of an international multimodal suicide prevention program with a non-European implementation. This study aims to determine whether implementing the CQFD-I multimodal suicide prevention program results in lower rates of suicidal behavior–related outcomes, that is, suicide mortality and suicide attempts, compared to matched control sites, and considering the effect of time.

Methods

Study Design

We will conduct an outcome evaluation of the CQFD-I program using a controlled, segmented interrupted time series design [25-27]. The 2 program implementation sites (the Outaouais region in Quebec, Canada, and Brest Métropole in Brittany, France) will serve as cases, each compared against a group of controls identified from geographic areas in the same jurisdictions that have not implemented the CQFD-I program [24]. Retrospective data will be sourced from national clinical

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administrative databases. This paper was written in accordance with the TREND (Transparent Reporting of Evaluations with Nonrandomized Designs) statement [28].

Study Objective

Our objective is to assess whether implementing a multimodal suicide prevention program across 2 countries—encompassing a universal strategy (a web portal focused on depression and social isolation), selective strategies (training for primary care physicians on depression and training for mental health professionals on suicide risk assessment and management), and indicated strategies (standardized postcrisis outreach and outpatient monitoring practices)—leads to a reduction in outcomes associated with suicidal behavior, such as suicide mortality, hospitalization due to suicide attempts, and visits to emergency rooms (ERs) for suicide attempts, compared to control sites and over time. We hypothesize that after 2 years of the CQFD-I program's implementation, there will be a 20% reduction in suicide mortality, hospitalizations due to suicide attempts, and ER visits for suicide attempts compared to control sites. This reduction will be observed when comparing the postimplementation phase (beginning in 2022) to the preimplementation phase (ending in 2020).

Intervention

The CQFD-I program includes 5 strategies rooted in universal, selective, and indicated interventions. We will provide more detailed information on context-specific activities and implementation strategies when reporting the study's results.

The first strategy (universal) is the implementation of a French-language web portal designed and constructed specifically for the CQFD-I program, accessible to the general population [29]. This strategy pertains to promoting public awareness and education, an approach to suicide prevention for which evidence is still scarce at the general population level [8]. The portal aims to increase literacy regarding symptoms of depression and signs of social isolation, raise awareness of the importance of consulting health care professionals, and facilitate help-seeking by sharing contact information on locally available resources. The portal includes written text and short videos (approximately 5 minutes) organized into thematic sections, the form and content of which were designed collaboratively to ensure cultural appropriateness in both countries. Furthermore, the portal provides information on locally available resources for help-seeking when users indicate that they are located in either of the implementation sites. Decisions about the most appropriate strategies to advertise the web portal to the population were left to the purview of local program implementers.

The second strategy (selective) is the promotion of a web-based training program on depression targeting primary care physicians. This strategy is supported by considerable evidence indicating that educating nonpsychiatric physicians and primary care nurses in detecting and treating depression may lead to measurable impacts on suicide rates at the population level [3]. The training program used for CQFD-I aims to improve physicians' skills in early identification and establishing the diagnosis of depressive disorders, assessing the risk of suicide, and determining the appropriate care and services for their patients. Participants can engage with the content of the prerecorded training program at their own pace. Its original version was developed in France by a team led by one of the researchers (MW) several years before its inclusion in the multimodal program and improved following feedback from previous users. One of the researchers (JDC) and a local family physician reviewed the program and requested some modifications to ensure its appropriateness for medical practice in Quebec. While the original version is disseminated in France as a 5-hour activity, adaptation resulted in approximately 1 hour of shared content with some skippable sections replaced by Quebec-specific complementary material. Primary care nurses may also participate in the training program as implemented in Quebec.

The third strategy (selective) is the dissemination of suicidal crisis intervention training targeting social workers and other actors who may have to intervene with at-risk populations. Suicidal crisis intervention training is not based on direct evidence of suicide reduction; however, it constitutes a system-level education initiative targeting people at risk for suicidal crisis [3]. This strategy involves a training program designed by one of the researchers (MS) and disseminated using a train-the-trainer model. Structured as a 2-day workshop, this program covers (1) the epidemiology of suicidal behaviors; (2) current etiological models of suicide; (3) evaluation of the risk, urgency, and danger posed by potential suicidal behaviors; (4) crisis intervention techniques; and (5) safety planning. While the workshop has previously been disseminated to health care workers, notably nurses, it is being extended to social workers for the first time in France in the context of this program. The version of this strategy implemented in Quebec includes the same workshop; however, program implementers also included other training programs targeting suicide prevention recognized by the provincial government.

The fourth strategy (indicated) is the standardization of postcrisis outreach, that is, systematically contacting and providing follow-up for people who have used ambulatory crisis intervention services after calling a helpline or when referred by a third party (eg, friends or family, first responders, health care professionals, or other actors in the community). Evidence supporting this strategy indicates that outreach following suicidal ideation crises may prevent suicidal behaviors [3]. In Brest (France), this strategy leverages the recently implemented VigilanS program designed to provide brief contact interventions to people who attempted suicide [30]. In addition to the usual services of the VigilanS program, additional resources were allocated specifically for postcrisis outreach. In Outaouais (Quebec), this strategy involves adapting and modeling care pathways (in Quebec French: *trajectoires de soins*), a foundation of the management model used in the public health and social services system of the province [31].

The fifth strategy (indicated) is the standardization of outpatient monitoring practices for individuals who have sought medical help after a suicide attempt or who are otherwise deemed acutely at high risk of suicide, based on clinical judgment (eg, a suicidal plan involving accessible means). Despite the lack of clear differentiation between outpatient monitoring and postcrisis

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outreach in the scientific literature [3], these interventions were conceptualized as separate strategies, considering that the target populations are identifiably different and that outpatient monitoring is more intensive. The standardization of outpatient monitoring in France is provided either by the treating general practitioner or psychiatrist (in private or public practice), or by nurse practitioners, according to a decisional algorithm. This algorithm establishes guidelines for the expected intensity and provider of outpatient monitoring, based on whether the patient has previously attempted suicide and whether the current suicidal crisis is psychiatric or psychosocial in nature. In Quebec, similar to postcrisis outreach, the adaptation and modeling of care pathways were used to standardize outpatient monitoring.

Outaouais Region and Control Sites

Outaouais is one of Quebec's 18 health regions (in French: *régions sociosanitaires*), which are administrative divisions used for planning, organizing, and delivering health and social services for the residents of a geographic area. Tables 1 and 2 summarize key characteristics of Outaouais and the 14 other health regions with a population of at least 50,000 individuals that could be included as control sites. We present the most recent data at the beginning of the program's implementation (before September 1, 2020).

Table 1. Key sociodemographic characteristics of the 15 health regions in Quebec with a population of at least 50,000 individuals [32-35].

Health region[a]	Population in 2019, n	Population aged ≥65 years in 2019, n (%)	Population density/km^2, 2019	Living in materially deprived areas in the 2016 census (%)[b]	Living in socially deprived areas in the 2016 census (%)[b]
Bas-Saint-Laurent	197,530	51,153 (25.9)	8.9	58.74	19.16
Saguenay–Lac-Saint-Jean	278,032	63,589 (22.87)	2.8	49.19	27.72
Capitale-Nationale	751,442	159,903 (21.28)	40.4	17.49	42.63
Mauricie et Centre-du-Québec	520,711	123,564 (23.73)	12.3	55.60	33.25
Estrie	489,986	108,984 (22.24)	38.5	43.70	38.71
Montréal	2,066,035	337,071 (16.31)	4140.4	42.86	63.46
Outaouais[c]	*397,007*	*65,561 (16.51)*	*13.0*	*37.74*	*42.62*
Abitibi-Témiscamingue	147,634	28,448 (19.27)	2.6	55.94	28.15
Côte-Nord	90,717	17,767 (19.59)	0.3	61.44	15.80
Gaspésie-Îles-de-la-Madeleine	90,456	24,933 (27.56)	4.5	82.78	11.85
Chaudière-Appalaches	428,969	94,012 (21.92)	28.5	35.97	23.38
Laval	439,583	77,532 (17.64)	1786.9	33.91	30.21
Lanaudière	515,727	95,694 (18.56)	41.9	47.00	25.87
Laurentides	620,648	117,429 (18.92)	30.2	37.24	36.20
Montérégie	1,423,109	266,729 (18.74)	71.4	31.26	33.78

[a]The regions are ordered by official region numbers.

[b]Proportion of the regional population living in dissemination areas that ranked in the bottom 40% (quintiles 4 to 5) of the province for material or social deprivation indices in the 2016 census. Absolute values not included to avoid confusion with 2019 data.

[c]Italics indicate the implementation site.

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Table 2. Key suicide-related characteristics of Quebec's 15 health regions with a population of at least 50,000 individuals [32-35].

Health region[a]	Primary care physician ratio per 1000, 2019 to 2020[b]	Suicide rate per 100,000 (age-adjusted[c]), average of the years 2016 to 2019	Male suicide rate per 100,000 (age-adjusted[c]), average of the years 2016 to 2019	Female suicide rate per 100,000 (age-adjusted[c]), average of the years 2016 to 2019	ER[d] visits for suicide attempt rate per 100,000 (age-adjusted[c]), average of the years 2016 to 2019
Bas-Saint-Laurent	0.85	14.1	22.6	5.7	27.4
Saguenay–Lac-Saint-Jean	0.82	15.7	25.5	5.6	36.7
Capitale-Nationale	0.83	13.7	20.7	6.7	75.1
Mauricie et Centre-du-Québec	0.73	15.1	22.6	7.5	12.9
Estrie	0.78	14.4	21.9	7.0	56.9
Montréal	0.76	10.0	14.3	5.9	42.3
Outaouais[e]	*0.72*	*15.5*	*24.9*	*6.4*	*46.8*
Abitibi-Témiscamingue	0.78	21.8	29.2	14.3	63.8
Côte-Nord	0.73	17.4	26.7	7.9	81.5
Gaspésie-Îles-de-la-Madeleine	1.14	19.0	29.3	8.7	33.7
Chaudière-Appalaches	0.71	17.2	25.3	8.8	31.0
Laval	0.71	7.8	12.6	3.3	46.5
Lanaudière	0.65	13.1	22.2	4.0	30.9
Laurentides	0.65	15.2	23.9	6.5	34.8
Montérégie	0.63	11.7	17.6	5.9	102.7

[a]The regions are ordered by official region numbers.

[b]The financial year starts on April 1 and ends on March 31.

[c]Due to discrepancies between data sources, population structure for age adjustment uses 2011 data for suicide rates and 2016 data for emergency room visits. We will ensure a uniform age adjustment methodology when reporting study results.

[d]ER: emergency room.

[e]Italics indicate the implementation site.

With a population of 397,007 in 2019, Outaouais was Quebec's 10th most populous health region, with the second lowest proportion of residents aged 65 years or more at 16.5% (n=65,561) [32]. Its population density was the seventh lowest [33]. To compare regions' economic and social profiles, we used the 2016 Canadian material and social deprivation indices, which are indicators compiled at the neighborhood level after each national census [36,37]. Material deprivation is based on median income, educational attainment, and employment, whereas social deprivation accounts for the proportion of people living alone; those who are separated, divorced, or widowed; and single-parent households [36]. In 2016, 37.74% (139,740/370,300) of the population of Outaouais lived in more materially deprived neighborhoods (sixth rank), and 42.62% (157,835/370,300) lived in more socially deprived neighborhoods (14th rank) [34].

The public health and social services of Outaouais have been under the jurisdiction of a single regional authority since 2015 [38]. This is also the case for most regions included in Tables 1 and 2, except for the following: Capitale-Nationale (n=2 distinct health authorities), Montréal (n=10), Côte-Nord (n=2), Gaspésie-Îles-de-la-Madeleine (n=2), and Montérégie (n=3). In the 2019 to 2020 financial year, 437 general practitioners billed universal health insurance of Quebec for services provided in Outaouais, with two-thirds using primary care–specific codes (Données de facturation RAMQ des médecins omnipraticiens, unpublished data, December 2023). This corresponds to 0.72 primary care physicians per 1000 residents (sixth rank). From 2016 to 2019, age-adjusted suicide rate of Outaouais averaged 15.5 per 100,000 overall (11th rank), 24.9 per 100,000 among male individuals (11th rank), and 6.4 per 100,000 among female individuals (seventh rank) (l'Infocentre de santé publique, unpublished data, November 2023). The average rate of hospitalizations for suicide attempts in Outaouais was 53.4 per 100,000 from 2016 to 2019 (eighth rank), and the average rate of ER visits for suicide attempts was 46.8 per 100,000 (10th rank) [35].

Brest Métropole and Control Sites

Brest Métropole, located in the Finistère department and the Brittany region, is one of the 21 French metropolises, geographically defined entities described as public institutions for intermunicipal cooperation comprising varying numbers of individual communes [39,40]. Excluding areas that have been given a special status under French law, Brest Métropole is one of the 19 metropolises with a similar status, the others of which will serve as control sites [39]. Given that we are currently

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working with a national public health agency of France, Santé publique France, to extract data at the metropolis level, we could not include it in table form for this paper. In 2019, the population of Brest Métropole was 211,156, making it the least populated among French metropolises [40,41]. The 8 communes of Brest Métropole also represented the lowest number of constituent municipalities compared to other metropolises, which ranged from 12 to 90 [40]. As of January 1, 2020, based on 2019 population and territorial data, Brest Métropole ranked 11th out of 19 for the proportion of inhabitants aged 65 years or more at 18.3% and ninth for population density with 967 inhabitants per square kilometer [42].

Outcomes and Data Sources

Primary outcomes, which include the suicide mortality rates, hospitalization rates for suicide attempts, and ER visit rates for suicide attempts, will be obtained monthly across 3 phases: preimplementation (September 2015 to August 2020), implementation (September 2020 to August 2022), and postimplementation (September 2022 to August 2024) phases. Data will be collected for both the implementation and control sites in both countries.

We will access Quebec data from the Integrated Chronic Disease Surveillance System database available at the Institut national de santé publique du Québec (INSPQ) [43]. In Quebec, suicide deaths are recorded in the Registre des évènements démographiques–Fichier des décès database and correspond to the *International Classification of Diseases, 10th Revision* (*ICD-10*) codes X60 to X84 and Y87.0 [35]. Data on hospitalizations for suicide attempts are recorded in the Maintenance et exploitation des données pour l'étude de la clientèle hospitalière system and correspond to *ICD-10* codes X60 to X84 and Y87.0. We will only consider hospitalization cases when acute care is the documented reason for admission [35]. ER visits for suicide attempts are recorded in the Banque de données communes des urgences, which includes suicide attempts as one of the options that may be selected as the visits' main reason by the nursing staff during triage [35]. For rate calculations, we will use the regional population per calendar year from official data published by the Ministère de la Santé et des Services sociaux du Québec [32]. We will benefit from technical support through collaboration with the INSPQ to ensure access to the most appropriate data sources and validate our data extraction procedures.

We will access France data through the Direction de la recherche, des études et des statistiques, a branch of the French Ministry of Health managing the national health data system (*système national de données de santé*) [44]. In France, suicide deaths are recorded by the Centre d'épidémiologie sur les causes médicales de décès and correspond to *ICD-10* codes X60 to X84 [45]. Data on hospitalizations for suicide attempts are available from the Programme de Médicalisation des Systèmes d'Information and correspond to *ICD-10* codes X60 to X84 [45]. ER visits for suicide attempts are available in the Oscour database of ER data and correspond to *ICD-10* codes X60 to X84, excluding X65 (self-intoxication with alcohol), but including other intoxication-related codes selected by a panel of French experts [45]. For rate calculations, we will use metropolis-level data for each calendar year from the Institut national de la statistique et des études économiques. We will collaborate with Santé publique France for technical support to ensure access to the most appropriate data sources and to validate our data extraction procedures.

Control Sites Selection

Including control sites enables comparison to a counterfactual scenario where the context is similar in all respects except for the CQFD-I strategies. This approach reflects the hypothetical outcomes if the program had not been implemented [24]. Considering that our main hypothesis does not depend on the characteristics of control sites, we will pool all sites within a single control group for the primary analyses. However, we also hypothesized that study results will be sensitive to control site selection. Therefore, we will conduct sensitivity analyses informed by area characteristics expected to influence population-level suicidal behaviors throughout the program implementation. Some relevant area-level data for' the health regions of Quebec are presented in Tables 1 and 2, and similar indicators are being extracted for French metropolises. Several of these indicators have been used as matching variables in previous studies cited in the Introduction section, that is, population size, population density or remoteness, relative socioeconomic disadvantage, general physicians' availability, and past suicide rates [19-21]. Given that some suicide prevention programs have found differences based on age groups and sex, we also considered the proportion of the population aged 65 years or older and sex-specific suicide rates. We included the rates of ER visits for suicide attempts as a potential indication of area-specific differences in service use that would interact with the CQFD-I program's strategies.

Statistical Methods

We will use the software Stata (StataCorp LLC) to analyze data with a segmented time series model in 3 phases (preimplementation, implementation, and postimplementation phases) and 2 arms (intervention and control areas), conforming to the following equation [27]: $Y_t = \beta_0 + \beta_1 T_t + \beta_2 X_i + \beta_3 X_p + \beta_4(T_t - t_i)X_i + \beta_5(T_t - t_p)X_p + \beta_6 G + \beta_7 G T_t + \beta_8 G X_i + \beta_9 G X_p + \beta_{10} G(T_t - t_i)X_i + \beta_{11} G(T_t - t_p)X_p + \varepsilon_{tG}$. In this equation, T_t is the time elapsed since the beginning of the preimplementation period (September 1, 2015); X_i and X_p are dummy variables, respectively representing the implementation and postimplementation phases (X=1 during this phase and X=0 during other phases); t_i and t_p are the first time points of the implementation and postimplementation phases; G=1 for cases and G=0 for controls; and ε_{tG} represents random error that combines ε_{t1} for cases and ε_{t0} for controls.

For all 3 outcome variables (suicide mortality, hospitalizations for suicide attempts, and ER visits for suicide attempts), we will generate monthly rates for each of the cases and control areas throughout the study period (September 2015 to August 2024, n=120 months). For our main analyses, we will adjust monthly rates by age and sex using direct standardization based on yearly data, with the year 2019 serving as the reference population for each implementation site. We will fit the above model using ordinary least square regression, with β_0 through β_5 included

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as pooled values between control areas. We will test for autocorrelation up to 12 lags to account for potential seasonality in our monthly data and adjust the model as per the results. In case of seasonality effect, we will also attempt using Fourier terms or flexible spline functions to fit the data better [46]. In our main analysis for each implementation site, we will treat the implementation phase as a transition period [47] and isolate the program-specific effects: (1) change in rates between the preimplementation and the postimplementation phases ($\beta_8 + \beta_9$), and (2) change in trend between the preimplementation and the postimplementation phases ($\beta_{10} + \beta_{11}$).

For sensitivity analysis, we will replicate the calculations described in this section with various combinations of control areas pooled within the control group. These exploratory analyses will consider various cutoffs for each of the indicators presented in Tables 1 and 2 as potential criteria for control selection. In addition, we will use any information available at the time of data analysis to identify other suicide prevention programs or services that may have differentially impacted the implementation sites or specific control areas, and to justify testing other combinations of control groups. Furthermore, we will test alternative time series models, including 2 phases instead of 3, using bimonthly and trimonthly rather than monthly data, and stratifying by sex and age groups when allowed by power considerations. We will clearly report these analyses as exploratory to avoid distracting from the main study results.

Statistical Power

For the Outaouais region (n=397,007), the statistical power to detect a 20% decrease from the 2016 to 2019 averages at α=.05 would be 33.1% for suicide mortality, 85.7% for hospitalizations, and 80.4% for ER visits [48]. We do not yet have access to suicidal behavior data specifically for Brest Métropole; however, we estimated the statistical power based on its 2019 population (n=211,156) and published data about the Finistère department as a whole: the suicide rate was 23.4 per 100,000 in 2015 and the hospitalization rate was 227.8 per 100,000 in 2017 [45]. From this lower population but considerably higher rates of suicidal behaviors, the statistical power to detect a 20% decrease at α=.05 in Brest Métropole would be 26.8% for suicide mortality and 99.7% for hospitalizations. We did not find a reported rate of ER visits for suicide attempts in Finistère for the same period; however, cursory calculations indicate a base rate approximating 130 per 100,000 and a statistical power higher than 90%.

Given the low incidence of suicide in the general population, statistical power is often an issue when conducting pre-post rate comparisons. This has been reported as a justification to aggregate suicide mortality and suicide attempts in OSPI-Europe [12]. However, the statistical power benefits of variables aggregation would be marginal compared to including hospitalizations and ER visit rates as distinct primary outcomes, both of which can be assessed with satisfactory statistical power. Moreover, interrupted time series will provide additional benefits relating to the statistical power of this study in two important ways: (1) including a high number of repeated observations (n=120 months) [49] and (2) assessing the intervention effect on the outcome slope in addition to their level [50]. Considering the very different implications of death rates and indicators influenced by service use, we will analyze each primary outcome separately.

Ethical Considerations

Evaluation of the *CQFD-I* program was approved by the research ethics board of the Centre intégré de santé et de services sociaux de l'Outaouais in May 2021 (2020-305_171) and by the Comité d'éthique de Brest in March 2023 (B2023CE.18). No consent to participate is required as we will exclusively interact with nonidentifying data in the context of official procedures overseen by governmental bodies in both implementation jurisdictions. We will only extract and report data aggregated at the population level. This outcome evaluation will thus constitute a minimal-risk project for all individuals involved, with no risk to the privacy or confidentiality of any participant. Additional precautions will be undertaken as required by the public agencies providing access to data in Quebec and France.

Results

The CQFD-I program was conceptualized and refined from 2014 to 2020 through a series of meetings and negotiations between the 2 international partners, culminating in a version suited for implementation in Quebec and France despite differences in their medical and psychosocial service structures. The CQFD-I program's timeline includes 3 phases: preimplementation (2015 to 2020), implementation (2020 to 2022), and postimplementation (2022 to 2024) phases. The implementation phase commenced on September 1, 2020, marked by the initial official meetings held within that month to brief stakeholders on the program's strategies. Considering that (1) Brest Métropole was constituted in January 2015 [39] and (2) a law initiating a major health and social services reform was passed in Quebec in February 2015 [51], we define September 1, 2015, as the beginning of the preimplementation phase of the study. This 5-year period for data collection was established to ensure a sufficiently long baseline to reflect changes in policy. All 5 strategies of the CQFD-I program were fully implemented by September 1, 2022, marking the beginning of the postimplementation phase. For evaluation purposes, August 31, 2024, will be the last day of the postimplementation phase.

This project is funded by the Ministère de la Santé et des Services Sociaux du Québec, with access to data and expertise representing in-kind contributions from Santé publique France and INSPQ. Under the responsibility of the first author, data will be collected from public health databases in September 2027 to account for the delays necessary to confirm suicide deaths in official registers. Data analysis will be performed from September 2027 to June 2028.

Discussion

Anticipated Findings

In this paper, we present the study protocol for the outcome evaluation of the CQFD-I program, a multimodal suicide prevention program currently implemented in 2 sites, that is,

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Brest Métropole in Brittany, France, and the Outaouais region in Quebec, Canada. We hypothesize that after 2 years of the CQFD-I program's implementation, there will be a 20% reduction in suicide mortality, hospitalizations due to suicide attempts, and ER visits for suicide attempts compared to control sites. Through this study, we will generate data for the first time on the effects of implementing a multimodal suicide prevention program at the population level in 2 countries not exclusively located in Europe. In addition to its general contribution to currently limited knowledge about the effects of multimodal suicide prevention programs, this study represents a proof of concept of sharing international resources to design a program targeting populations speaking a common language but residing in very different jurisdictions. Accordingly, positive results from this study would have profound implications on the potential to leverage international partnerships to disseminate best practices in suicide prevention, a promising avenue for low-income countries and underserved linguistic minority groups.

One limitation of this protocol is the reliance on administrative databases to ascertain suicide-related outcomes. While this allows for long-term follow-up across implementation phases and ensures comparable data quality between implementation and control sites, it may limit the interpretability of results. For instance, Quebec includes *ICD-10* code Y87.0 (sequelae of intentional self-harm, assault, and events of undetermined intent) for suicide attempts, whereas French databases do not. Even within jurisdictions, definitions differ: in Quebec, suicide attempt hospitalizations are coded with *ICD-10*, while ER visits rely on triage-based clinical judgment. To address these discrepancies, we will avoid assuming data source equivalence. First, suicide attempt rates will only be compared within the same jurisdiction. Second, each outcome—suicide mortality, hospitalizations, and ER visits—will be analyzed separately rather than combined for statistical power. While we expect all outcomes to decrease if the CQFD-I program is effective, reductions in only some outcomes would still be valuable results and warrant further research.

Conclusions

Results may guide future research by offering valuable insights into directing suicide prevention efforts for geographically defined populations. The CQFD-I program created opportunities for participants from 2 distinct jurisdictions to reflect on the unique aspects of the health and social services systems and challenge assumptions that might otherwise limit their ability to innovate in suicide prevention. Program development and implementation benefited from sharing expertise and resources; however, they also highlighted new challenges for researchers to address regarding the operationalization and integration of suicide prevention strategies at the subnational level. Each of the CQFD-I program's components had to be designed and operationalized to accommodate implementation in 2 distinct jurisdictions, a task that involved both anticipated and unforeseen challenges. The web portal required tailored promotional strategies aligned with local information consumption habits, demanding creativity from program implementers. Dissemination of the depression training program had to meet the high continuing education standards of primary care physicians, while suicide assessment and management training needed to be adapted to the staff training approaches of existing organizations. Standardizing postcrisis outreach and outpatient monitoring required a thorough understanding of clinical and managerial practices across multiple disciplines and institutions. The program's implementation will be the topic of an upcoming paper that will go hand in hand with the results of the study described in this protocol.

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Data Availability

The datasets analyzed during this study will be available as permitted and recommended by the public health organizations that will provide access to these data, that is, the Institut national de la santé publique du Québec and Santé publique France.

Authors' Contributions

MS and MW were involved in designing the Coopération Québec-France contre la Dépression et l'Isolement program. JDC and MS conceptualized and wrote the initial proposal for the program evaluation. JDC and MCG wrote the first draft of this paper. MW, KD, MO, SB, and CL contributed to refining the study design through program and methodological expertise. All authors contributed to the revision of this paper and read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CQFD-I: Coopération Québec-France contre la Dépression et l'isolement
ER: emergency room
ICD-10: International Classification of Diseases, 10th Revision
INSPQ: Institut national de santé publique du Québec
OSPI-Europe: Optimizing suicide prevention programs and their implementation in Europe
TREND: Transparent Reporting of Evaluations with Nonrandomized Designs

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Protocol

Effect of Adherence to Oral Semaglutide on Glycemic Control in People With Type 2 Diabetes Treated With Metformin: Protocol for an Open-Label Clinical Trial

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Abstract

Background: Treatment adherence by people with type 2 diabetes (T2D) is overall suboptimal, which can hinder glycemic control. Multiple adherence barriers have been identified, such as the dislike and fear of injections. Several of the recommended antidiabetic drugs are available in oral formulations, which may be a good alternative to injection therapy when possible. However, strict dosing instruction could pose adherence barriers; for example, oral semaglutide requires predose and postdose fasting and restricted water intake at dosing time. Currently, oral semaglutide is the only oral glucagon-like peptide-1 receptor agonist and has only been available for a few years; therefore, limited knowledge exists on adherence to it.

Objective: The aim of this study is to investigate the effect of adherence to oral semaglutide dosing instructions on glycemic control in people with T2D who are dysregulated on metformin and optionally a sodium-glucose cotransporter-2 inhibitor and naïve to oral semaglutide.

Methods: This prospective, noninterventional, open-label, clinical trial with a duration of 12 weeks will be conducted in Denmark. Eligible participants are adults (aged ≥18 years) with dysregulated T2D (hemoglobin A1c of 53-75 mmol/mol) currently treated with metformin and optionally a sodium-glucose cotransporter-2 inhibitor for whom the next natural step in the treatment is to add an antidiabetic drug to the treatment regimen. Potential participants are recruited through announcements on social media and digital mail sent to their official digital mailbox (e-boks). During the trial, 20 participants will be initiated on oral semaglutide and escalated in dosage in accordance with the label. Information on the participants' behavior related to the dosing instructions will be collected using the following devices: a smartwatch to track activity and sleep time, a smart pill bottle to track dosing time, a smart bottle to track time and volume of water intake at dosing time, and a smartphone to take a photo of their breakfast to log time of breakfast. Glycemic control will be assessed using an unblinded continuous glucose monitoring sensor that the participants will wear. Participants are asked to report any cases of nausea or vomiting in terms of time of occurrence, duration, and severity. The primary endpoint is change from baseline to end-of-study time-in-range derived from continuous glucose monitoring data.

Results: The first participant visit was in April 2024. Three months of high frequency temporal data on adherence behavior will be collected, despite the relatively few expected participants included.

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Conclusions: Participants may change their behavior due to awareness of being observed. Regardless, the knowledge gained from this trial might be integrated into a decision support system, providing people with diabetes with guidance on how to increase adherence and potentially improving glycemic control.

Trial Registration: ClinicalTrials.gov NCT06333080.; https://clinicaltrials.gov/study/NCT06333080

International Registered Report Identifier (IRRID): DERR1-10.2196/64899

(JMIR Res Protoc 2025;14:e64899) doi:10.2196/64899

KEYWORDS

medication adherence; continuous glucose monitoring; observational study; oral antidiabetic drug; dosing instructions; oral semaglutide

Introduction

In the adult population worldwide, 10.5% had a diabetes diagnosis in 2021, and an increase in prevalence is expected [1]. A profound majority of people with diabetes, approximately 91%, have type 2 diabetes (T2D). [2]. The goal in diabetes management is to control blood glucose levels to decrease the risk of developing long-term complications [3]. The recommended glycated hemoglobin (HbA1c) level is ≤53 mmol/mol in nonpregnant adults, but the target blood glucose level should be individualized based on each patient according to the American Diabetes Association [3].

The initial antidiabetic drug used is often metformin, although the first-line treatment can be other antidiabetic drugs or a combination of antidiabetic drugs, especially for patients with severe hyperglycemia or some renal and cardiovascular diseases [4]. As T2D progresses, the initial treatment may fail to maintain glycemic control and is therefore often supplemented [4]. The recommended choices of supplemental medication in people with T2D without other comorbidities are glucagon-like peptide-1 (GLP-1) receptor agonists (RAs), dual glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 RAs, sodium-glucose cotransporter-2 inhibitors (SGLT2i), dipeptidyl peptidase-4 inhibitors, sulfonylurea, and thiazolidinedione [4]. According to the American Diabetes Association [4], the choice of antidiabetic drugs should consider both glycemic and weight management goals along with comorbidities, adverse events, and the patient's preferences.

Adherence to the antidiabetic treatment has been reported to be suboptimal [5-8], reducing the effect of the drugs. The patients' preferences on the side effect profile, perceived complexity of the treatment, and the route of administration may all be barriers to good adherence [9-11]. Injection therapy can be associated with discomfort and fear of injection together with the feeling of stigmatization, thus leading to nonadherence [12]. This specific barrier can be removed by choosing a treatment regimen consisting entirely of oral antidiabetic drugs (OADs) for as long as possible based on the recommendations of the American Diabetes Association. As all but the dual GLP-1/GIP RA and insulin are available in an oral formulation, these are potential alternatives to the injection therapies.

The oral formulation of GLP-1 RA, oral semaglutide, has shown promising results for reducing HbA1c and body weight [13]. However, the dosing complexity of oral semaglutide may be perceived as high, as the intake of food both before and after intake of the drug decreases the exposure of semaglutide [14]. In a food-effect study, no or limited semaglutide exposure was observed in participants who had eaten prior to the intake of semaglutide [14]. Similarly, a study on dosing conditions found that food intake shortly after the intake of oral semaglutide decreased semaglutide exposure, whereas a longer duration of fasting resulted in greater exposure [14]. In addition, exposure of semaglutide is affected by the water volume administered with the oral semaglutide [14,15]. These studies resulted in rather complex dosing instructions, namely that oral semaglutide should be administered in a fasting state with up to 120 mL water followed by a postdose fasting period of minimum 30 minutes with no intake of liquids or other medications [16,17]. Furthermore, gastrointestinal adverse events, such as nausea and vomiting, are associated with semaglutide. The occurrence of gastrointestinal adverse events is reported to be most frequent at the time of dose escalation [18]. The rather strict dosing instructions of oral semaglutide combined with the potential occurrence of gastrointestinal adverse events may present a barrier for adhering to the dosing instructions. Poor adherence may result in decreased semaglutide exposure, which may lead to reduced glycemic control.

Knowledge on adherence to oral semaglutide is limited as it is the first and only marketed oral GLP-1 RA and has only been available on the market for a few years [16,17]. Furthermore, adherence to oral semaglutide is not necessarily similar to that of other classes of OADs, as adherence across these drug classes has been found to differ [19]. Thus, a clinical trial investigating the effect of adherence to oral semaglutide dosing instructions on glycemic control is warranted, and to the best of our knowledge, no studies have collected continuous glucose monitoring (CGM) and high frequency temporal data on behavioral patterns of people with T2D on oral semaglutide. Previous reviews on the adherence to OADs, including by the authors of this paper, have based the adherence measurements on pharmacy claims [5-8]. Therefore, it is not possible to ascertain how the adherence behavior of the person with diabetes affects their glycemic level based on existing evidence. An investigation of the effect of adherence to the oral semaglutide dosing instructions on glycemic control, including the influence of side effects, could provide this new knowledge. Thus, the objective of the present trial is to investigate the effect of adherence to oral semaglutide dosing instructions on glycemic control in people with T2D who are dysregulated on metformin and optionally an SGLT2i and naïve to oral semaglutide.

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Methods

Setting and Design of the Study

The study will be conducted at Steno Diabetes Center North Denmark (SDCN) at Aalborg University Hospital, Aalborg, Denmark. This study protocol was based on the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [20].

The trial is a prospective, noninterventional, open-label, clinical trial. As the trial is observational, neither the project group nor the participants will be blinded. The duration of the trial is 12 weeks, during which participants with dysregulated T2D on metformin and optionally an SGLT2i will continue their current treatment, and treatment with oral semaglutide will be initiated 2 weeks after the trial begins (Figure 1).

Figure 1. Study design of the clinical trial. The total duration of the trial is 12 weeks, with oral semaglutide being initiated after the second week of the trial.

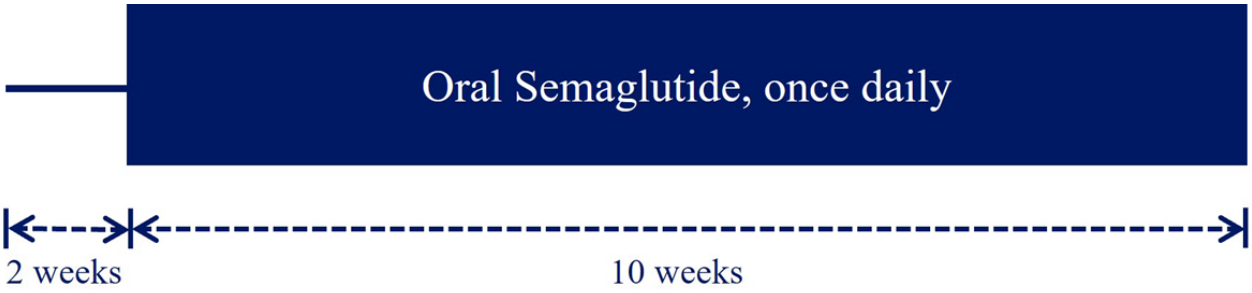

Selection and Screening of Participants

Eligibility Criteria

A total of 20 participants meeting the eligibility criteria will be included in the trial. Eligible trial participants are adults (aged ≥18 years) who for at least 1 year have had a diagnosis of T2D and have been in treatment with metformin and optionally an SGLT2i. A participant will only be eligible if a HbA1c of 53-75 mmol/mol has been recorded less than 3 months prior to trial inclusion. As the participants are not in glycemic control, the next step in the treatment is to add an antidiabetic drug to obtain glycemic control [4], which in this clinical trial is oral semaglutide.

Thus, eligible participants for this study should have an antidiabetic drug added to their current treatment regardless of participation in this study. The participants will continue their current treatment, and treatment with oral semaglutide will be initiated 3 weeks after inclusion in the trial. Furthermore, the participants must be able to understand and read Danish and be able to use a smartphone as well as the devices used in the clinical trial.

Potential participants will be excluded if they previously have received treatment with glucose-lowering medications other than metformin and SGLT2i. Potential participants who are only treated with metformin and have cardiovascular or kidney disease, which would indicate use of other second-line treatments such as SGLT2 inhibitors or subcutaneous GLP1 receptor agonists, are not eligible for inclusion. Participants will also be excluded if any of the following apply: (1) they have other types of diabetes than T2D, (2) they are participating in an interventional trial, (3) they are pregnant or breastfeeding, (4) they have known retinopathy, (5) they have a known allergy to semaglutide, (6) they have major surgery planned during the trial period, (7) they have uncontrolled cancer, (8) they have a personal or family history of medullary thyroid carcinoma, (9) they have multiple endocrine neoplasia syndrome type 2, or (10) they have other conditions that the investigators deem to render the participant unfit for inclusion in the trial, including a physical or cognitive inability to participate in the trial.

Recruitment

Trial participants will be recruited using the following different strategies: (1) telephone calls to a group of potential participants who have agreed to be contacted regarding the initiation of new trials at SDCN; (2) announcements in newspapers, the Danish diabetes magazine, the website of Region North Denmark, social media, and relevant patient organizations; (3) posters and leaflets placed at SDCN, Aalborg University Hospital, and other relevant health centers; and (4) digital mail sent to the official digital mailbox (e-boks) of a list of potential participants (people with T2D on metformin and optionally SGLT2i with high HbA1c obtained less than 3 months ago), which will be obtained from the Business Intelligence Unit at the North Denmark Region.

Informed Consent

A participation information letter describing the trial will be mailed or handed to interested potential participants. An information interview will be held at Aalborg University Hospital with the interested potential participant, an optional companion, and either the investigator, subinvestigator, or a delegated project member with the required professional knowledge. In the information interview, the potential participant will be informed on the voluntary nature of participating in the trial, their right to reflect on whether to participate prior to giving informed consent to trial participation, and their right to withdraw consent at any time, without any explanation. A participant cannot be included in the trial until informed consent has been signed by both the participant and the investigator.

Data Collection

Trial Flow

The trial period starts with the first visit to the trial site and ends 12 weeks later with the second visit to the trial site. A CGM

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baseline reading from each participant will be collected prior to oral semaglutide initiation, corresponding to the first 2 weeks of the trial period. After oral semaglutide initiation, CGM data, physical activity, time of dosing, and water volume intake at dosing time will be collected throughout the remaining trial period. The participants will be asked to report occurrences of nausea and vomiting, including time, duration, and severity (using a scale from 0-10 with 10 being the worst imaginable) in a paper diary. In addition, the participants will be asked to register the time of breakfast at 3 time periods during the trial (Figure 2).

Figure 2. Trial flowchart for each participant. CGM: continuous glucose monitoring.

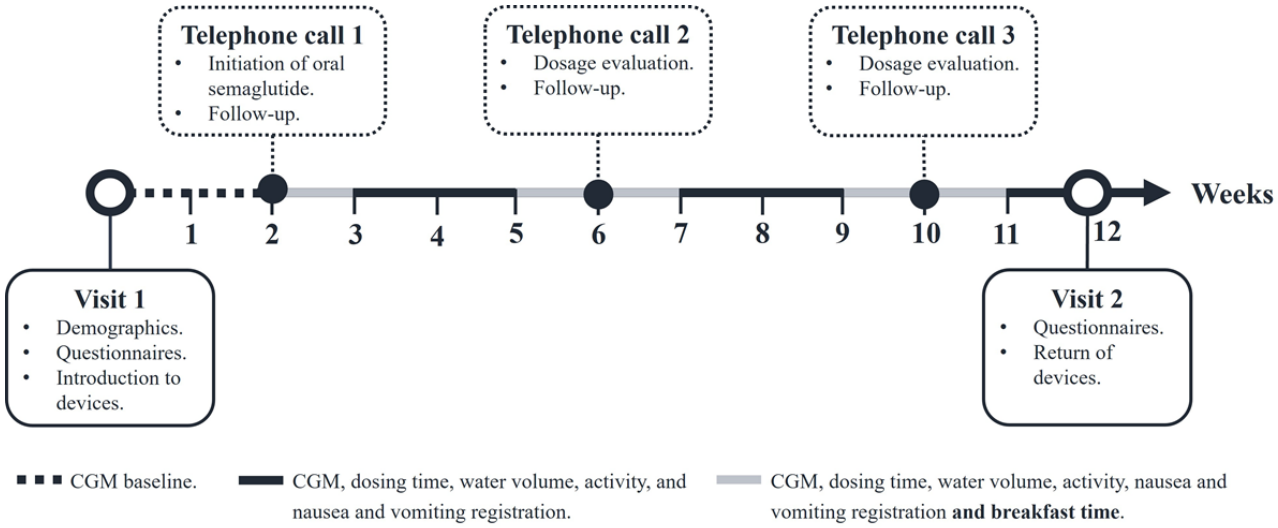

All participants will continue their current treatment throughout the trial period. Additionally, the participants will be started on oral semaglutide 2 weeks after trial initiation, at which time a lab technician from SDCN will contact the participant by phone (Figure 2). The oral semaglutide will be handed out to the participants at the first visit to the trial site. The initiation and dosage evaluation of oral semaglutide will be in accordance with the product information on dose escalation [16,17]. Thus, the initial dosage of oral semaglutide will be one 3 mg tablet once daily (OD), which the participants will be instructed to take in the morning in a fasting state with maximum of a half glass of water, approximately 120 mL. Participants will be instructed to wait at least 30 minutes before the intake of food, liquids, or other medications. After 4 weeks, corresponding to telephone call 2 (Figure 2), the dosage of oral semaglutide will be increased to one 7 mg tablet OD [16,17]. After an additional 4 weeks, corresponding to telephone call 3 (Figure 2), the dosage of oral semaglutide will be re-evaluated and, if needed, increased to one 14 mg tablet OD to reach the glycemic target of the participant [16,17]. The dosage evaluation will be based on the collected CGM data, which the trial staff at SDCN will access remotely in connection with telephone call 3.

Demographic Data

Demographic information on each participant will be obtained at the first visit and includes birth date, biological sex, ethnicity, height and body weight, systolic and diastolic blood pressure, duration of diabetes (defined as the time from T2D diagnosis), diabetes complications, smoking status, alcohol intake, exercise, diet, marital status, housing status, level of education, employment status, and concomitant medications and illnesses.

Questionnaires

The participants' view on their adherence to the treatment and perceived adherence barriers will be captured using previously published questionnaires. Data on health beliefs will be obtained by asking the participants to answer the questionnaire developed by Given et al [21] and adapted by Becker and Janz [22]. The participants will also be asked to answer a questionnaire on social support developed by Sarason et al [23].

The patient-reported adherence to and satisfaction with the diabetes treatment will be assessed using the treatment-related impact measure for diabetes (TRIM-D) questionnaire, which consists of 5 subcategories: treatment burden, daily life, diabetes management, compliance, and psychological health [24]. The participants will be asked to answer the TRIM-D questionnaire at the start and end of the trial. Figure 3 provides a schematic of the trial timeline.

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Figure 3. Schematic overview of participant enrolment, initiation and escalation of oral semaglutide, participation follow-up by telephone, and assessment of baseline variables, demographics, and questionnaires. The schematic overview is based on the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines. TRIM-D: treatment-related impact measure for diabetes.

	STUDY PERIOD					
	Enrolment	Visits and telephone calls				
TIMEPOINT	*Day 0*	*Day 0*	*Day 14*	*Day 42*	*Day 70*	*Day 84*
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
ORAL SEMAGLUTIDE:		◆—	—	—	—	—◆
Initiation			X			
Dose evaluation				X	X	
ASSESSMENTS:						
Baseline variables		X				
Demographics		X				
TRIM-D		X				X
Social support questionnaire						X
Health belief questionnaire						X
Follow-up by telephone tall			X	X	X	

Devices

Throughout the trial, data will be collected by asking the participants to use or wear several devices to collect data. These devices include an unblinded CGM sensor (Dexcom G6 CGM System, Dexcom Inc) to determine the level of glycemic control, a smartwatch (Fitbit Charge 4, Fitbit Inc) worn all hours of the day to track activity and determine time of sleep, a smart pill bottle (MEMS Cap Smart Pill Bottle, Aardex Group) to collect time of dosing, a smart bottle (HidrateSpark Pro, HidrateSpark) to collect time and volume of water intake at dosing time, and a smartphone to take a photo of their breakfast in the week before and after dosage evaluation (Figure 2) to collect time of breakfast data.

Discontinuation Criteria and Adverse Events

Discontinuation From Trial

Completion of the trial is defined as attendance at the final visit regardless of the degree to which the devices of the trial have been used. The entire trial is complete after the final visit by the last participant. In case a participant wants to withdraw from the trial, a visit at the trial site will be offered. All questions the participant may have will be answered and the devices returned.

A participant will be withdrawn from the trial if the participant experiences severe hypoglycemia or hyperglycemia or ketoacidosis that the investigators attribute to the trial, or if the investigators deem the participant unfit to continue the trial. The entire trial will be stopped prematurely if serious adverse events associated with the trial, as judged by the principal investigator or subinvestigators, occur.

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Adverse Events

The disadvantages of participation are considered to be limited. These disadvantages include the inconvenience of trial participation and use of the CGM sensor, which may cause local skin irritation and elevates the risk of infection. As oral semaglutide will be initiated in the trial, side effects due to oral semaglutide may occur. The most frequently reported side effects of oral semaglutide are related to the gastrointestinal symptoms, such as nausea, vomiting, diarrhea, constipation, stomach pain, gastritis, decreased appetite, and gastroesophageal reflux disease [16,17]. Other common side effects include tiredness, hypoglycemia, and complications of retinopathy [16,17]. Uncommon side effects are gall stones, weight loss, and fast pulse [16,17]. Rare side effects include acute pancreatitis and anaphylactic reaction [16,17].

Adverse events occurring during the trial period will be reported, and the investigators will note whether the adverse event in their opinion is related to trial participation in accordance with the guidelines of the National Committee on Health Research Ethics.

Outcome Measures

Primary Endpoint

The primary endpoint is the change from baseline to end-of-study time-in-range (TIR) derived from CGM data calculated in accordance with the International Consensus on Use of Continuous Glucose Monitoring [25].

Secondary Endpoints

Secondary endpoints include the following:

1. Time elapsed from last food intake to dosing time.
2. Time elapsed from dosing time to time of breakfast.
3. Occurrence of nausea or vomiting, including timing, duration, and severity. Nausea and vomiting severity will be reported on a scale from 0-10, with 0 being no nausea or vomiting and 10 being the worst imaginable nausea or vomiting, similar to the scale of nausea severity described by Leere et al [26].
4. Volume of water intake at dosing time.
5. Patient-reported satisfaction and adherence to treatment reported as the total score of the TRIM-D questionnaire.

Exploratory Endpoints

An exploratory endpoint is steps per day. Additionally, qualitative interviews will be carried out with selected participants to explore their adherence to oral semaglutide during the trial period.

Statistical Considerations

Statistical analyses will be performed on the data of all included trial participants, and a statistical significance level of 5% (α=.05) will be used.

Primary Analysis

The primary endpoint (change from baseline to end-of-study in TIR) will be analyzed using a simple linear regression model with the average (in weeks 10-12) of time elapsed from dosing time to time of breakfast.

Sample Size

With 20 participants, there is 80% power to detect a significant correlation of 0.58 between the elapsed time from dosing to time of breakfast and the improvement in TIR.

Missing or Unused Data

CGM-derived metrics such as TIR are only calculated for a specific interval if data have been collected ≥80% of the time in accordance with the International Consensus on Use of Continuous Glucose Monitoring [25]. Missing data will be treated as missing at random, and multiple imputation to impute missing data will be used in the statistical analysis.

Data Management

Biological Material

No biological material will be obtained from the trial participants.

Handling and Archiving Data

Data storage will consist of both paper files and digital files on a computer using Research Electronic Data Capture (REDCap) [27], both of which will be accessible only by the investigator, subinvestigators, and relevant members of the project team. Data related to the trial will be kept stored for the duration reported to the Danish Data Protection Agency. Third-party data use will only occur if agreed upon by the subinvestigators and the primary investigator.

The electronic journal of potential trial participants will be accessed by health care professionals affiliated with SDCN to assess if the potential participant is suitable for trial inclusion by reviewing information including health status, medications, and comorbidities. The electronic journal will not be accessed without the participants' consent. Furthermore, prospective inspection authorities will be given access to the patients' electronic journal in relation to monitoring and quality control of the trial.

Ethical Considerations

The trial has been approved by the Regional Committee on Health Research Ethics of the North Denmark Region (N-20220017) and will be conducted in compliance with the good clinical practice guidelines and the Helsinki declaration. In case changes to the trial protocol are needed, an amendment will be submitted to the Regional Committee on Health Research Ethics of the North Denmark Region for approval. No publications related to this trial will contain information that can identify the trial participants. If future studies based on the data collected in this trial require additional consent from the participants, they will be contacted before any such studies are undertaken. Authorship will be granted based on the Vancouver recommendations [28].

Results

This trial protocol is version 6 and was approved on August 12, 2024. The first participant visit was on April 16, 2024.

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Discussion

The present clinical trial will be conducted with the objective of investigating the effect of adherence to oral semaglutide dosing instructions on glycemic control in people with T2D who are dysregulated on metformin and optionally an SGLT2i and naïve to oral semaglutide. Several previous studies investigating adherence to various OADs based their findings on pharmacy claims data [5-8]. Pharmacy claims data are limited in that it is not possible to know if the medication was administered as per the dosing instructions or at all, and the reasons for potential nonadherence or changes in medication type are unknown.

The main limitation of this study is the relatively low number of trial participants that are planned to be included. However, as high frequency temporal data will be collected for each participant over a 3-month period, each participant will act as their own control over the trial period.

A further limitation of this study is that participants might change their behavior due to their awareness of being observed [29], thus inducing noise in the data. The relatively large number of devices the participants will be asked to use during the trial could lead to the participants feeling burdened, especially participants with low digital literacy, which could result in reduced use of these devices and lowered data quality. This burden has been lowered by asking participants to take photos only of their breakfast and only at certain times of the trial. Additionally, an inclusion criterium of the trial is that the participant is able to use a smartphone and the devices of the trial.

In a study by Babazadeh et al [30], selfcare behaviors such as adherence to antidiabetic drugs and attention to diet were found to affect HbA1c levels in people with T2D. Likewise, studies by Ranjbaran et al [31] and Döbler et al [32] investigated interventions to increase adherence to diet and medication. In both studies, an improvement in HbA1c was observed for the intervention group compared to the control group [31,32], suggesting that delivering these types of interventions can be beneficial for people with T2D to achieve greater adherence.

The knowledge gained from the current trial could be integrated into a decision support system, providing people with T2D with guidance on how to increase their adherence and potentially improve glycemic control. Such a decision support system could, for example, provide people with T2D with a visualization of glycemic control in response to their adherence and automated guidance on how to further increase adherence. Information on glycemic control can be obtained using CGM and the level of adherence can be determined by collecting data on behavioral patterns influencing adherence, such as predose and postdose fasting, water intake at dose time, adverse events, and physical activity, depending on the findings of this clinical trial.

Acknowledgments

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Data Availability

Data related to the trial will be only accessible by the investigator, subinvestigators, and relevant members of the project team and will be kept stored for the duration reported to the Danish Data Protection Agency. Third-party data use will only occur if agreed upon by the subinvestigators and the primary investigator. The electronic journals of potential and included trial participants will solely be accessed by health care professionals affiliated with the SDCN and only after the patients have provided consent. Prospective inspection authorities will be given access to the patients' electronic journal in relation to monitoring and quality control of the trial.

Authors' Contributions

All authors contributed to the design of the trial, provided input to the manuscript, and have read and approved the final version of this manuscript.

Conflicts of Interest

Authors EC, CD, NSH-C, and MHJ are employees and shareholders of Novo Nordisk. PV is Head of Research at Steno Diabetes Center North Denmark funded by the Novo Nordisk Foundation.

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Abbreviations

CGM: continuous glucose monitoring
GIP: glucose-dependent insulinotropic polypeptide
GLP-1: glucagon-like peptide-1
HbA1c: glycated hemoglobin A1c
OAD: oral antidiabetic drug
OD: once daily
RA: receptor agonist
SDCN: Steno Diabetes Center North Denmark
SGLT2i: sodium-glucose cotransporter-2 inhibitor
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
T2D: type 2 diabetes
TIR: time-in-range
TRIM-D: treatment-related impact measure for diabetes

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Protocol

An Everyday Patient-Centered Discussion Model for Primary Care: Protocol for a Feasibility and Acceptability Study of the Zeroing in on Individualized, Patient-Centered Decisions (ZIP) Approach

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Abstract

Background: The Zeroing in on Individualized, Patient-Centered Decisions (ZIP) approach was developed to be a feasible, everyday shared decision-making (SDM) approach to personalizing decisions in primary care. Current SDM models, which require 5 to 10 minutes just to present initial information, are impractical in primary care, highlighting the need for more concise, patient-centered approaches. The ZIP approach preserves core aspects of SDM while offering a more pragmatic framework suited to real-world clinical constraints. This approach includes three key elements: (1) making a personalized recommendation, (2) qualitatively presenting trade-offs, and (3) supporting patient decisional autonomy. Previous work has found this approach to be acceptable. However, little is known about how feasible and acceptable the ZIP approach is during an actual primary care visit.

Objective: This paper aims to describe the protocol for a pilot test of the feasibility and acceptability to both patients and primary care physicians (PCPs) of using a paper-based deployment of the ZIP approach in a primary care clinic.

Methods: Two case studies were examined: lung cancer screening (LCS) and blood pressure (BP) treatment decisions. This study was a multicomponent pilot implementation study involving training PCPs in the ZIP approach and providing them with an encounter-based decision aid supporting the ZIP approach during clinic visits. Eligible patients were either candidates for an initial LCS conversation or a conversation about intensifying BP medication. The patient-PCP medical encounters were audio recorded. Following the appointment, the patient completed a short survey and underwent a semistructured interview. After PCPs completed 2 to 3 study appointments, they underwent a semistructured interview reflecting on their experience with the ZIP approach. Surveys and interviews sought to understand the overall ZIP components presented during the appointment (ie, feasibility) and the extent to which patients and physicians found the approach appropriate (ie, acceptability). Survey data were analyzed to provide an overview of patient and physician demographics. Interviews were transcribed and analyzed through qualitative coding and thematic analysis to identify high-level takeaways of the feasibility and acceptability of this approach.

Results: This study was funded in October 2022 by the Department of Veterans Affairs. We recruited 10 PCPs and 23 patients (n=4, 17% patients undergoing LCS and n=19, 83% patients involved in BP treatment decision-making). Data collection took place from October 2023 to April 2024. Data analysis concluded in December 2024. Planned paper submission will occur in June 2025.

Conclusions: The results from this pilot implementation study will contribute to the ongoing efforts toward integrating a practical approach to SDM into primary care. This pilot will lay the groundwork for an effective and efficient larger-scale trial.

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KEYWORDS

shared decision-making; lung cancer screening; blood pressure treatment; primary care, discussion model

Introduction

Background

During a routine clinic visit, primary care physicians (PCPs) often have only 1 to 2 minutes to discuss a single preventive service [1,2]. While using shared decision-making (SDM) to discuss these preventive care options is often promoted in guidelines, current models of detailed SDM typically require up to 15 to 20 minutes for each decision [1,2]. This creates a clear incongruity between the time available for SDM in primary care and the time needed by current models. To address this gap and make SDM more feasible for primary care, our research team previously developed the everyday SDM approach [1]. This approach was designed to take only 2 to 3 minutes to complete while still focusing on core elements of SDM such as collaborative communication. This makes it a potentially more feasible and practical approach for implementation in the fast-paced primary care setting compared to traditional detailed SDM approaches.

Although initially called "everyday SDM," the approach was renamed to Zeroing in on Individualized, Patient-Centered Decisions (ZIP) based on early feedback from PCPs. The name change was intended to counter widespread physician concerns and perceptions that SDM is not feasible within the constraints of primary care settings [3]. Previous research has shown the ZIP approach's theoretical acceptability through focus groups with patients [2]. Specifically, patients and PCPs who engaged in feedback sessions regarding the ZIP approach felt that the 3-step process was an acceptable compromise approach to SDM: "it provided the patient with a more personalized recommendation" and supported the patient receiving extra information compared to traditional encounters [2]. The ZIP encounter focuses on three key elements: (1) making a personalized recommendation, (2) briefly presenting qualitative information on key trade-offs, and (3) conveying full support for decisional autonomy and desires for more information on the part of the patient.

Objectives

While the concept of ZIP was appealing to patients and a potentially more feasible SDM approach for physicians, it remains unknown how ZIP can be integrated into primary care appointments. Specifically, there are questions about whether it realistically can be completed in 1 to 2 minutes and the extent to which patients and PCPs approves of this approach when carried out in actual clinical practice. To address these gaps, we present the protocol for a single-arm, nonrandomized pilot study testing the feasibility and acceptability to both patients and PCPs of using a paper-based deployment of the ZIP approach in a primary care clinic. The aim of this study was to evaluate the real-world acceptability and feasibility of the ZIP approach during actual primary care visits, focusing on 2 everyday primary care decisions in which a brief, effective, patient-centered approach is necessary—lung cancer screening (LCS) and blood pressure (BP) management.

Methods

Overview

This study was a multicomponent pilot implementation study involving physicians and their patients. The pilot focused on personalizing two decisions through ZIP: (1) how strongly to encourage starting annual low-dose computed tomography LCS for patients meeting current US Preventive Services Task Force eligibility criteria and (2) how strongly to encourage intensification of BP treatment (ie, prescribing a BP medication for the first time, adding another BP medication to the current regimen, or increasing the dose of current medications) for primary prevention of atherosclerotic cardiovascular disease. Importantly, discouraging LCS or BP treatment for low-benefit or ineligible patients was not part of this pilot. Pilot implementation included a physician education session on the ZIP approach, an audio-recorded medical encounter between the physicians and study patients, a postappointment survey and interview with the patient, and a postintervention interview with the physician.

Ethical Considerations

The VA Ann Arbor Healthcare System institutional review board (IRB) initially approved this study on February 9, 2023 (1725106). Any protocol amendments were submitted for IRB approval, and all relevant updates were shared with the study team and documented internally.

Study team members obtained informed consent from all individuals before activities involving human participants. The research team complied with informed consent guidelines and adhered to local, national, and international law and regulations regarding the protection of personal information, privacy, and human rights. Original IRB approval and participant consent cover secondary analysis without additional consent.

All data were deidentified to safeguard participant information. For confidentiality, every eligible patient was assigned a unique patient ID number. The study principal investigator and research team analysts had access to the deidentified dataset.

Patient participants were remunerated with a US $25 Meijer gift card for their time.

Paper-Based Decision Aid Development

The basis for the intervention was to present the physician with tailored guidance based on the intervention's individualized net benefit for the patient—and have the PCP engage in the ZIP approach based on this tailored information. To accomplish

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this, we created a paper-based decision aid to personalize decisions for LCS and BP treatment based on well-validated prediction models and a previously developed web-based tool [4-11]. We generated a personalized paper-based decision aid for each study patient that was presented to the PCPs before the appointment and provided personalized patient information to support the use of ZIP. The decision aid included each patient's relevant risk information (ie, pack years, quit status, and chronic obstructive pulmonary disease or emphysema diagnosis for LCS and high-density lipoprotein and total cholesterol, systolic BP, smoking status, and diabetes for BP treatment). Risk inputs were obtained from the patients' medical records and used to calculate each patient's individualized net benefit for LCS or BP treatment. The tool provided information on how preference sensitive the decision was for the patient (ie, the degree to which net benefit depended on how the person weighed the pros and cons), as well as other personalized risk information (eg, the number needed to screen to avoid 1 death).

On the basis of each person's calculated individualized net benefit, patients were placed along a net benefit spectrum that included a preference-sensitive zone and an encouragement zone (Figure 1). The preference-sensitive zone meant that the patient was eligible for care but their risks and benefits were in fine balance, so neither strong encouragement nor discouragement was warranted, and conditional guidance was best. The encouragement zone, on the other hand, communicated that the net benefit was more clear-cut for the patient due to a high chance of net benefit (ie, the benefits of receiving the intervention likely outweighed the harm). In this case, PCPs were guided to more strongly encourage screening or BP treatment. Table 1 presents the sample 30-second personalized recommendation scripts for patients in the encouragement zone versus the preference-sensitive zone. On the basis of early PCP feedback, scripts were edited and restructured into bullet point format for easier delivery and use during the appointment. Both script versions are shown in Table 1. The recommendation scripts were discussed during the ZIP training and provided to PCPs within the paper-based decision aid during the pilot. These scripts outlined all aspects of the ZIP approach, were tailored based on the recommendation zone (preference sensitive or encouragement), and served as a starting point for dialogue. The personalized recommendation was what the PCP initially shared—and this could include stronger encouragement in cases in which net benefit was very high (eg, smoking cessation). Regardless of the strength of the initial recommendation, the rest of the ZIP conversation incorporated patient input and preferences and emphasized the patient's right to make a final decision.

On the basis of previous work and recommendations in national guidelines [12], LCS patients were included in the preference-sensitive zone if they had <16.2 days of life gained and in the encouragement zone if they had ≥16.2 days of life gained from screening [12,13]. For personalizing decisions about whether to intensify a patient's BP treatment, we categorized patients in the preference-sensitive zone if they had a 10-year atherosclerotic cardiovascular disease risk between 7.5% and 19.9% and in the encouragement zone if they had a risk of ≥20% based on risk thresholds discussed in national guidelines [14-16]. Examples of the full personalized decision aids and further details on how they were created can be found in Figure 1 and Multimedia Appendix 1.

Figure 1. Blood pressure decision aid and net benefit visualization scale example.

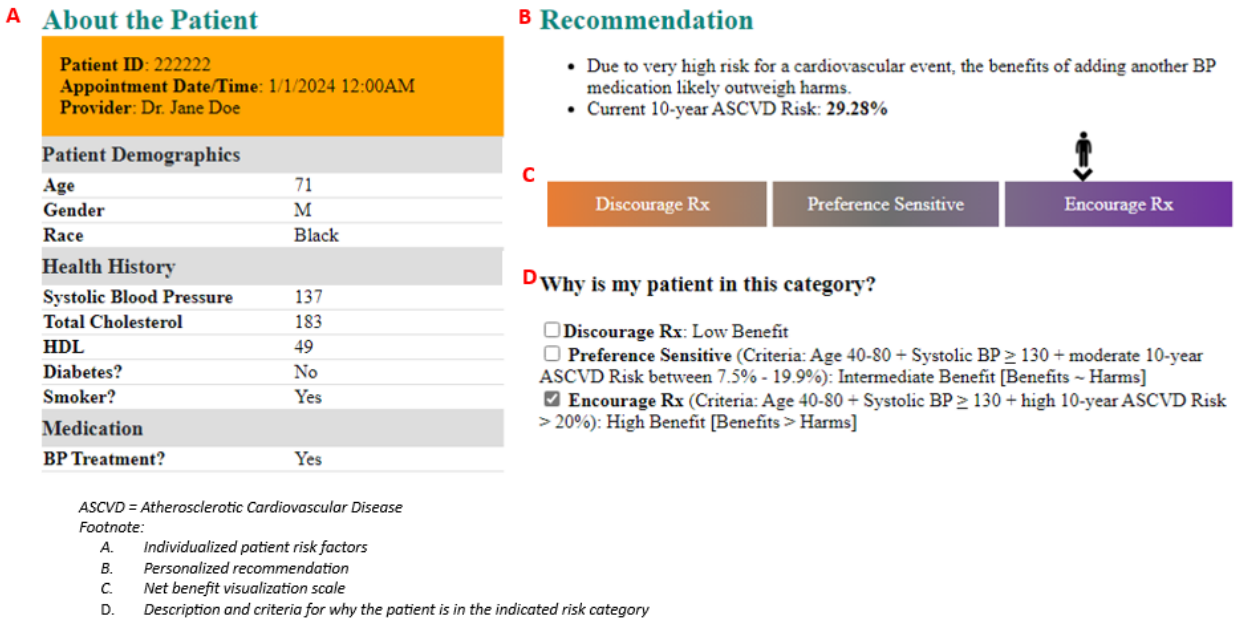

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Table 1. Zeroing in on the Individualized, Patient-Centered Decisions approach recommendation scripts.

	Version 1: narrative	Version 2: bulleted
LCS [a]		
Preference sensitive	"I wanted to talk to you about lung cancer screening. It's something to consider, but for you it's not a clear decision. There's some pros and cons. The big pro is a chance of catching the cancer early and curing it, but there are cons like a risk of false positives, little dots on the CT scan that end up not turning into cancer, leading to more follow-up CTs, with the potential of more risks later on. The good news is you're not at super-high risk.... You know it's a little bit of benefit with a little bit of downside and it's really a personal choice between how you feel about those pros and cons. What are your thoughts?"	• "I wanted to talk to you about lung cancer screening. It's something to consider; for you it's not a clear decision. There are some pros and cons. The big pro is a chance of catching the cancer early and curing it." • "But there are also cons like a risk of false positives which are little dots on the CT scan that end up not turning into cancer. This could lead to follow-up CTs." • "The good news is you're not at super-high risk; it's a little bit of benefit with a little bit of downside. So, it's really a personal choice between how you feel about those pros and cons." • "What are your thoughts?"
Encouragement	"I wanted to talk to you about lung cancer screening. Due to your high lung cancer risk, I think it's a good idea for you, the benefits are fairly high, you can catch the cancer early, but there are some downsides in that we can find false positives, little dots on the CT scan that end up not turning into cancer. This could lead to follow-up CTs, with the potential of more risks later. But in your case, I think it is worth it because you're still in pretty good health, your risk of lung cancer is pretty high, and so overall, I'd recommend it. What are your thoughts about that?"	• "I wanted to talk to you about lung cancer screening. Due to your high lung cancer risk, I think it's a good idea for you." • "The benefits are fairly high, you can catch the cancer early. There are also some downsides in that we can find false positives, little dots on the CT scan that end up not turning into cancer. This could lead to follow-up CTs." • "But in your case, I think it is worth it because you're still in pretty good health and your risk of lung cancer is pretty high. So overall, I'd recommend it." • "What are your thoughts about that?"
BP[b] treatment decisions		
Preference sensitive	"I'd like to talk to you about whether or not we should start an additional blood pressure medicine. I think this is an individual decision that many people may want, and many people may not want. The good news is you have already gotten your blood pressure to where your risk of heart attacks, strokes, and kidney disease is pretty low for your age. But it would be a bit lower with an additional medicine. If you are the type of person that doesn't mind taking another medicine if it will lower your risk of heart attacks, kidney disease, and strokes even a little, I think it is a good thing for you. If you are the type of person that only wants to take another medicine if it is a lot of benefit, I think it would be very reasonable to not and to continue to evaluate and monitor you. What are your thoughts?"	• "I'd like to talk to you about whether or not we should intensify your blood pressure medicine." • "I think this is a personal decision that many people may want to do, and many people may not want to do." • "The good news is you have already gotten your blood pressure to where your risk of heart attacks, strokes, and kidney disease is pretty low for your age." • "But it would be a bit lower with an additional medicine [or a higher dose of your current medicine]." • "So, if you are the type of person that doesn't mind taking another medicine if it will lower your risk of heart attacks, kidney disease, and strokes even a little, I think it is a good thing for you." • "If you are the type of person that only wants to take another medicine if it has a lot of benefit, I think it would be very reasonable to continue to monitor your blood pressure instead." • "What are your thoughts?"
Encouragement	"I'm going to recommend an additional medication. The reason is because your risk of heart attacks and strokes has gone up. It is normal for your risk to go up with age. But we have found that by adding this additional medication it decreases your blood pressure more over the course of the day. What your blood pressure is during today in the office is not important, it is what it is when you are around and active. We have found that by decreasing that we can protect your brain, your kidneys, and your heart. I don't push medicines, but we have great evidence that as we get older our risk for these things increases, and we can decrease this so you are low risk for your age. It's just one additional medication, if you have any side effects, which are rare, we can stop it. So I strongly recommend us trying that. What are your thoughts?"	• "I'm going to recommend we intensify your BP medication. Your risk of heart attacks and strokes has gone up; it is normal for your risk to go up with age." • "But we have found that additional medication can help because it decreases your blood pressure over the course of the whole day. This helps protect your brain, kidneys, and heart." • "What your blood pressure reading is in the office today is not what's most important. What's important is your blood pressure when you are around and active over the course of the day." • "It's one additional medication [or a higher dose of a medication]. If you have any side effects, which are rare, we can stop it. So, I strongly recommend us trying that." • "What are your thoughts?"

[a]LCS: lung cancer screening.

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[b]BP: blood pressure.

Physician Recruitment and Education

We recruited 10 PCPs with at least 50% of their time devoted to ambulatory care from a single US Department of Veterans Affairs (VA) medical center. Purposeful sampling was conducted to ensure representation of sex and a variety of ages. Eligible PCPs were initially asked to participate in the study through email. The recruitment email described the study and included the consent form. If there was no response after initial contact, follow-ups were made through a second email and then Microsoft Teams messaging. Up to 4 contact attempts were made. Once the PCP agreed to participate and electronically signed the consent form, a team member scheduled them for an initial education session.

The initial education session was a 1-hour meeting in which the physicians first watched a 25-minute video created by the study team highlighting the ZIP technique, specific gaps it fills within primary care and preventive care, and how it can specifically be leveraged for LCS and BP treatment decision patients. The 3 steps of ZIP and how they can be completed were highlighted in the video, providing audio clips and example scripts for going through these 3 steps when initiating a ZIP conversation. The video then concluded with an overview of the study and its various aspects. Following the conclusion of the video, the PCPs were given an opportunity to ask questions and discuss the ZIP approach or the study components with the study team. Once all questions were sufficiently answered, and if time remained, PCPs participated in a patient scenario activity where they could practice the ZIP approach with hypothetical patients. These scenarios were also emailed to all participating PCPs before seeing their study patients.

Patient Recruitment

We sought to recruit 2 to 3 patients from each PCP, with a target of at least 1 LCS and 1 BP treatment decision patient. Eligible patients were selected if they had an upcoming primary care appointment and were considered eligible for a conversation on starting LCS or intensifying BP treatment. Patients with missing data were excluded as calculating patient risk and benefit level was not possible with missing inputs.

Specific criteria for LCS and BP treatment decision exclusion were determined based on model input requirements. Eligibility for the LCS cohort was based on the US Preventive Services Task Force criteria, which included patients aged 50 to 80 years with a smoking history of at least 20 pack years. Patients were excluded if they had quit smoking over 15 years before, received LCS in the past, undergone a chest computed tomography in the previous year, or been previously diagnosed with lung cancer. These exclusion criteria helped identify any low-benefit patients. Evaluating smoking status and previous tests and diagnoses helps identify any research participants who will derive limited benefit from screening and focus on those who will derive a high benefit instead.

Eligibility for the BP cohort included patients aged 45 to 80 years with a systolic BP between 130 and 160 mm Hg. These criteria ensured a population that was potentially eligible for our study and had a reasonably elevated BP. Patients were excluded for the following reasons: if, in the previous 5 years, they had had a documented history of myocardial infarction or heart disease, loop diuretic use, dementia, or metastatic cancer and if they had 0 measures in the previous 5 years for high-density lipoprotein and total cholesterol or BP or if their race was unlisted. These exclusion criteria aimed to exclude participants already on BP medication for reasons other than primary prevention. Regarding factors such as dementia and metastatic cancer, our team considered any life expectancy considerations to be more important than BP intensification.

Eligible patients were identified through medical chart review. Every 2 weeks, the research team extracted a cohort of eligible patients with a primary care appointment in the following 2 weeks from the VA Corporate Data Warehouse. For confidentiality, every eligible patient was assigned a unique patient ID number. These patients were mailed a recruitment letter informing them of the study and inviting them to participate, along with a copy of the consent form. A study team member then called each patient 2 to 3 days after the study materials were mailed to assess their interest in participating. Up to 3 attempts were made to contact each patient via phone call. Patients who agreed to participate were called 1 day before their appointment as a reminder. Patients were enrolled in the study between October 31, 2024, and April 24, 2025.

Intervention

PCPs were contacted through Microsoft Teams 1 to 2 days before the appointment to inform them of the upcoming appointment with a study patient and review a copy of the patient-specific decision aid. Patients were asked to arrive 30 minutes before their scheduled appointment, and a study team member met them in the waiting room. The patient's willingness to participate was confirmed, the components of the study were reviewed (ie, audio-recorded medical encounter and postencounter survey and interview), and the patient's signed informed consent was obtained. Participants were informed that they could contact the study team through provided contact information with any questions or concerns. The patient was given a digital voice recorder (DVR) and instructions on its use. Patients were encouraged to practice turning on and off the device and shown how to pause the DVR if they did not want a portion of their appointment to be recorded. Patients were informed that the recording would be used to understand the communication style and language that their physicians used during the appointment. Patients were guided to turn on the DVR at the beginning of their appointment. Finally, the patient was handed the paper-based personalized decision aid, which they were instructed to give to the nurse at the beginning of the appointment to then be given to their PCP. Due to the low risk of patient participation, there were no prespecified criteria for modifying the intervention. In addition, there were no concomitant care restrictions during the study.

During the appointment, PCPs carried out the ZIP discussion as instructed based on the information in the patient-specific decision aid.

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After the appointment, the study team member met the patient in the waiting room and brought them back to a private room within the primary care unit to administer the postencounter survey and interview. The DVR was returned, and the patient was given a copy of their signed consent form for their records. Patients were administered a survey that asked about demographics, general health information, and satisfaction with and general preferences regarding health care (see Multimedia Appendix 2 for the full survey). Questions focused on assessing overall medical trust, the patient-physician relationship, and BP– or lung cancer–specific decision-making during the appointment. After completing the survey, patients participated in a 10- to 20-minute interview focusing on the conversation with their PCP. Specifically, the interview asked about how the conversation went, the strength of the PCP's recommendation, and the patient's final decision regarding screening or medication (see Multimedia Appendix 3 for the full interview guide). LCS patients were asked to compare their perceptions of the benefits and harms of undergoing a screening test and share how worried they were about lung cancer and how helpful they thought screening would be at mitigating this concern. BP treatment decision patients were asked to compare the benefits and harms of BP medication and share how worried they were about myocardial infarction and stroke and how helpful BP medication was in reducing this risk. These interviews were audio recorded. After completing the survey and interview, each patient received a US $25 gift card as remuneration for their time.

Physician Interview

After PCPs completed study visits with 2 to 3 patients, they were contacted to schedule a 30-minute interview and a short demographic survey (see Multimedia Appendices 4 and 5 for the full interview guide and survey, respectively). During these semistructured interviews, the PCPs were asked to reflect on using the ZIP approach in primary care. The PCPs were also asked to provide feedback on the sample 30-second discussion script, specifically on the script's language and how strictly they stuck to the script during the intervention. Physicians were asked how receptive their patients were to this intervention and whether they planned to continue using this method of communication moving forward. PCPs were asked to comment on the most significant benefits and harms of LCS and BP medications and how these benefits and risks compare. PCPs were also asked how worried they were about patients dying from lung cancer without screening and having a myocardial infarction or stroke before starting BP medication. These interviews were audio recorded. Because the physicians were VA employees, they were not eligible to receive compensation for participating.

Analysis Plan

The study principal investigator and research team analysts had access to the deidentified dataset. Analyses included all participants who completed the medical encounter. One patient missed their survey and interview due to a conflict, whereas 3 medical encounters were incomplete—2 (67%) due to technical issues and 1 (33%) because the patient opted out of recording. These data were reported as missing in the analysis.

The medical encounters, patient interviews, and physician interviews were all audio recorded and transcribed verbatim. An internal transcriptionist transcribed patient interviews, whereas the medical encounters and PCP interviews were transcribed through the Microsoft Teams transcription software. Transcripts were analyzed using a deductive approach, and a preliminary codebook was developed based on the interview guide. Transcripts were coded using Microsoft Excel by a team of trained qualitative analysts who individually coded qualitative data and met weekly to address discrepancies and improve interrater reliability. After discrepancies were addressed, a new Microsoft Excel form was populated, a culmination of both qualitative coders' work. Following coding, the team applied a rapid matrix analysis framework to identify common themes and patterns among the data related to how patients and physicians viewed the acceptability and feasibility of the approach and the physician's fidelity to it. This analysis was completed in NVivo (Lumivero). The audio-recorded medical encounters were also used to deduce the length of time of the entire appointment, the length of the initial recommendation, and the length of the entire ZIP conversation. Analysis of the patient and physician survey data was double entered by analysts and included basic descriptive statistics (eg, means, frequencies, and SDs). We analyzed important demographic and clinical characteristics, including age, sex, race, and general health status, to explore variations in responses. The survey used validated tools to assess individual preferences for seeking medical care and how patients perceive SDM. The quantitative results were combined with qualitative themes to offer contextual insights and identify potential differences in the experiences of various subgroups (eg, encouragement vs preference-sensitive zones).

Results

Overview

Data collection began in October 2023 and concluded in April 2024. Data analysis concluded in December 2024. Paper publication is expected in Summer 2025.

Patient and Physician Characteristics

This study was funded in October 2022 by the VA. After obtaining IRB approval for all study procedures and documents, PCP recruitment and enrollment began in July 2023. Patient recruitment then began in October 2023 after recruiting the physicians and engaging them in the education sessions.

A total of 10 PCPs were recruited and enrolled in this study. Half (n=5, 50%) were male, and most (n=8, 80%) reported being either White or Asian individuals. In total, 40% (4/10) of the physicians had completed their medical training more than 20 years before, some (n=3, 30%) were relatively new to the VA (<5 years), and most (n=7, 70%) worked 3 to 4 days a week in the primary care clinic. Complete physician demographics can be found in Table 2.

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Table 2. Patient and physician demographics.

	Total	LCS[a]	BP[b] treatment decisions
Patients			
Sex, n/N (%)			
Male	21/23 (91)	4/4 (100)	17/19 (89)
Female	1/23 (4)	0 (0)	1/19 (5)
Missing	1/23 (4)	0 (0)	1/19 (5)
Race, n/N (%)			
African American	1/23 (4)	0 (0)	1/19 (5)
White	21/23 (91)	4/4 (100)	17/19 (89)
Missing	1/23 (4)	0 (0)	1/19 (5)
Age (y), mean (SD)	69 (6.6)	66 (6.5)	70 (6.6)
Educational level, n/N (%)			
High school	4/23 (17)	0 (0)	4/19 (21)
Some college or trade school	10/23 (43)	3/4 (75)	7/19 (37)
Associate's degree	4/23 (17)	0 (0)	4/19 (21)
Bachelor's degree	2/23 (9)	1/4 (25)	1/19 (5)
Master's degree or higher	2/23 (9)	0 (0)	2/19 (11)
Missing	1/23 (4)	0 (0)	1/19 (5)
Risk zone, n/N (%)			
Preference sensitive	10/23 (43)	0 (0)	10/19 (53)
Encouragement	13/23 (57)	4/4 (100)	9/19 (47)
Physicians, n/N (%)			
Sex			
Male	5/10 (50)	—[c]	—
Female	5/10 (50)	—	—
Race			
African American	0 (0)	—	—
Asian	4/10 (40)	—	—
White	4/10 (40)	—	—
Missing	2/10 (20)	—	—
Hispanic or Latino			
Yes	1/10 (10)	—	—
No	9/10 (90)	—	—
Time since completion of clinical training (y)			
<5	2/10 (20)	—	—
5-10	2/10 (20)	—	—
11-19	2/10 (20)	—	—
≥20	4/10 (40)	—	—
Duration practicing at the VA[d] (y)			
<5	3/10 (30)	—	—
5-10	1/10 (10)	—	—
11-19	6/10 (60)	—	—

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	Total	LCS[a]	BP[b] treatment decisions
≥20	0 (0)	—	—
Average day per week working in primary care			
1-2	3/10 (30)	—	—
3-4	7/10 (70)	—	—
≥5	0 (0)	—	—

[a]LCS: lung cancer screening.
[b]BP: blood pressure.
[c]Not applicable.
[d]VA: US Department of Veterans Affairs.

From the physician panels, 96 patients were identified as eligible for the study: 23 (24%) were eligible for an LCS conversation, and 73 (76%) were eligible for a BP conversation. Within the LCS-eligible cohort, of the 23 patients, 6 (26%) agreed to the study over the phone, 14 (61%) declined to participate, and 3 (13%) were unable to be reached via telephone. Of the 6 patients who agreed, only 4 (67%) consented and participated as 2 (33%) were no-shows to their appointments. Regarding the BP-eligible cohort, of the 73 patients, 23 (32%) agreed over the phone, of whom 19 (83%) were consented and participated (n=2, 9% of the patients were no-shows and n=2, 9% canceled their appointments). Of the 73 eligible BP treatment decision patients, 36 (49%) declined to participate, and 14 (19%) were unable to be reached via telephone. Complete recruitment details can be found in Figure 2.

Figure 2. Consolidated Standard of Reporting Trials (CONSORT) diagram.

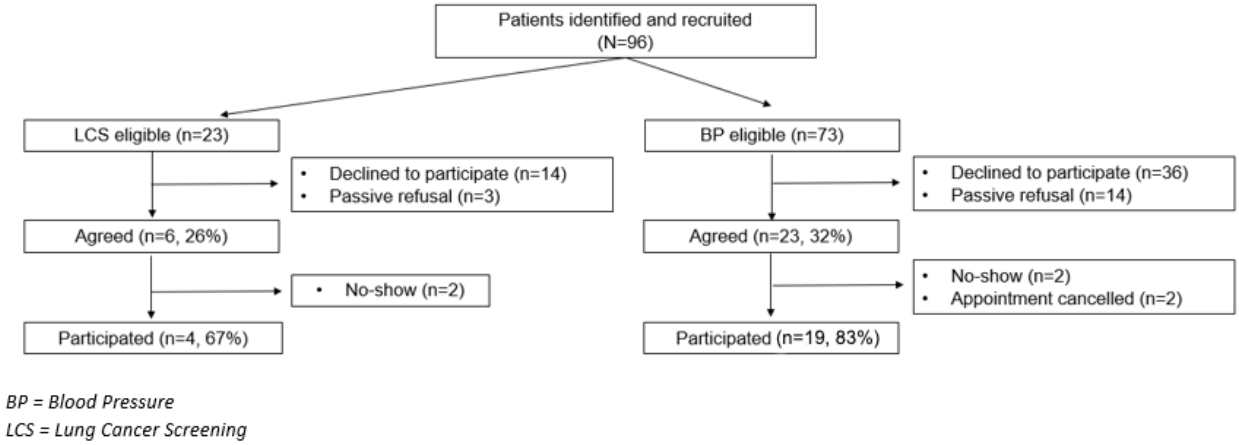

Of the 23 total participants, most were male (n=21, 91%) and White individuals (n=21, 91%), the mean age was 69 (SD 6.6) years, and more than three-quarters (18/23, 78%) completed at least some college. Within the BP cohort, 53% (10/19) of the participants were in the preference-sensitive zone, and 47% (9/19) were in the encouragement zone. All 4 LCS patients were identified in the encouragement zone. Complete demographic details can be found in Table 2.

Not all physicians were able to see an LCS patient. Of the 10 recruited physicians, 4 (40%) saw 3 total patients (n=2, 67% for BP treatment decisions and n=1, 33% for LCS). The remaining physicians saw either 1 or 2 BP treatment decision patients and no LCS patients. Full details on the patient distribution by PCP can be found in Table 3.

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Table 3. Patient distribution by physician.

Physician ID	Number of LCS[a] patients	Number of BP[b] treatment decision patients	Total
1	1	2	3
2	1	2	3
3	1	2	3
4	1	2	3
5	0	2	2
6	0	2	2
7	0	2	2
8	0	2	2
9	0	2	2
10	0	1	1

[a]LCS: lung cancer screening.

[b]BP: blood pressure.

Protocol Challenges

One of the main challenges encountered throughout this protocol was recruitment. A specific challenge was the identification of eligible LCS patients, likely due to long-standing LCS at the site and most patients on these physicians' panels already having started LCS. During each 2-week eligibility pull, there were typically 1 to 3 eligible LCS patients identified, with a high of 6 patients identified in 1 pull. This resulted in a very small pool of recruitable patients, leading to low recruitment numbers and, ultimately, lack of success in recruiting an LCS patient for every recruited physician. In addition, there were several instances in which a recruited patient's appointment was canceled or rescheduled.

Discussion

Principal Findings

This study tested the real-world feasibility of the ZIP approach during primary care visits, aiming to assess whether this novel decision-making approach could help bridge implementation gaps left by more time-consuming and impractical SDM approaches. The results of this pilot study will contribute to the ongoing efforts to integrate a feasible SDM approach into routine primary care encounters, particularly within the time and resource constraints of an appointment. The ZIP approach aims to address the challenges of incorporating SDM into brief primary care visits, where PCPs often have limited time to discuss multiple preventive care options and integrate patient preferences into the decision-making process. While the concept of ZIP appeals to patients, the findings of this study will determine the feasibility and acceptability to both patients and physicians of integrating it into practice.

The mixed methods approach involved medical encounters, postencounter surveys and interviews, and physician feedback sessions. The takeaways found in this pilot can inform the actual time taken to deliver ZIP, patient and physician perceptions of the approach, feasibility of physicians' delivery of the approach, and any specific approach challenges. Findings will be submitted for publication in a peer-reviewed journal. A lay summary will be mailed to research participants.

Implications for Practice

The findings of this pilot feasibility study also offer insights that will inform the development of the PCP education process and patient identification and recruitment strategies for larger-scale projects. Through feedback obtained from participating physicians, we can improve the education session to address specific challenges and enhance PCPs' understanding and confidence in implementing the ZIP approach effectively. Specifically, sending the physician the video before the education session to watch on their own time would help alleviate the time burden and the need to schedule a full hour for an education session. It would also allow the physicians time to process the information within the video and come to the session with more thoughtful questions and comments. In addition, insights gained from patient recruitment and identification strategies, including through electronic health records (EHRs) and targeted patient outreach, can be leveraged to optimize recruitment efforts and assess feasibility for future larger-scale studies, such as engaging the physicians in the patient identification process and adding a second staff member to engage with the patients to reduce scheduling conflicts. By using the results of this pilot to refine PCP education processes and recruitment strategies, larger-scale projects can be better equipped to engage physicians and patients effectively.

Limitations

It is important to acknowledge the limitations of the paper-based prototype used in this study. While effective for the purposes of this pilot project, the final goal is to integrate the decision aid seamlessly into the EHR. Transitioning to an automated tool within the EHR is important as relying on paper-based decision aids that are patient specific and available before clinic visits is unrealistic without additional research staff support. EHR integration can better support providing personalized information to physicians based on the patients' data within decision support tools that can better fit into the usual EHR-based clinical workflows of modern clinical practice.

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Future studies will be needed to complete this integration and study the feasibility of carrying out ZIP guided by the support of EHR-integrated decision aid tools. Although we examined both cancer screening and cardiovascular prevention topics, this study's focus on LCS and BP treatment decisions may not be generalizable to all other preventive care scenarios. Future research can explore the applicability of the ZIP approach across a broader spectrum of preventive care services to assess its versatility and effectiveness in diverse clinical contexts.

Future Directions

The results of this study will show the potential of the ZIP approach to enhance patient-centered care delivery in the primary care setting. Specifically, these findings can inform the physician education process, patient eligibility criteria, and participant recruitment strategies within larger-scale research. If this pilot demonstrates the feasibility and acceptability of the ZIP approach, it will lay the groundwork for further exploration and refinement of this approach to improving patient engagement and personalizing decision-making within the time constraints of primary care.

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Data Availability

The deidentified data sets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization: TJC
Data curation: TJC, JBS, SV, RH, and BY (equal)
Formal analysis: SSD (lead), FBS (lead), JBS (supporting), and TJC (supporting)
Funding acquisition: TJC
Investigation: all authors (equal)
Methodology: SSD, FBS, JBS, and TJC (equal)
Project administration: SSD and FBS (equal)
Resources: SSD, FBS, JBS, and TJC (equal)
Software: BY, RH, JBS, TJC, and SV (equal)
Supervision: TJC (lead) and JBS (supporting)
Validation: all authors (equal)
Visualization: SSD and FBS (equal)
Writing—original draft: SSD (lead), FBS (supporting), and TJC (supporting)
Writing—review and editing: all authors (equal)

Conflicts of Interest

TJC reports holding an Apache License 2.0 for Decision Precision, a freely available, open-source tool to enable personalized shared decision-making for lung cancer screening. He does not receive remuneration of any kind related to this tool. All other authors declare no conflicts of interest.

Multimedia Appendix 1
Example lung cancer screening decision aid.
[DOCX File , 123 KB - resprot_v14i1e64998_app1.docx]

Multimedia Appendix 2
Veteran survey.
[DOCX File , 26 KB - resprot_v14i1e64998_app2.docx]

Multimedia Appendix 3
Veteran interview guide.
[DOCX File , 16 KB - resprot_v14i1e64998_app3.docx]

Multimedia Appendix 4
Physician interview guide.

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[DOCX File , 16 KB - resprot_v14i1e64998_app4.docx]

Multimedia Appendix 5
Physician survey.
[DOCX File , 14 KB - resprot_v14i1e64998_app5.docx]

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Abbreviations

BP: blood pressure
DVR: digital voice recorder

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EHR: electronic health record
IRB: institutional review board
LCS: lung cancer screening
PCP: primary care physician
SDM: shared decision-making
VA: United States Department of Veterans Affairs
ZIP: Zeroing in on Individualized, Patient-Centered Decisions

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Protocol

Understanding the Current and Future States of Behavioural Supports Ontario: Protocol for a Mixed Methods Pilot Study

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Abstract

Background: Behavioural Supports Ontario (BSO) was created in 2010 as a provincially defined and regionally implemented program in Ontario, Canada, to support older adults living with responsive behaviors in long-term care homes, hospitals, and at home, and to also support their family care partners. There are 14 different BSO regions in Ontario, each with its own service delivery model to provide (1) system coordination and management, (2) integrated service delivery, and (3) knowledgeable care teams and capacity building. In 2023, BSO teams across Ontario supported approximately 33,300 older adults with expressions of responsive behaviors, the majority of whom had dementia, and 20,100 family care partners.

Objective: This study aimed to understand how BSO is currently affecting service providers and family care partners across all BSO care settings (ie long-term care, community, and acute care), and how BSO service delivery models can be modified to best meet the current needs of these target populations. This pilot study will be conducted in the western Ontario region, which comprises 4 different BSO regions; this will enable comparison between different BSO service delivery models to identify which service model elements may be best used to support BSO care providers, care recipients, and family care partners in the future.

Methods: Following a 2-phase mixed methods sequential explanatory design, this study will invite BSO staff and leaders to complete an anonymous web-based survey, followed by focus groups and interviews to share their perspectives on BSO's current functioning, areas of weakness, and opportunities for growth. Family care partners will also be invited to complete one-on-one interviews to share information about their experiences with BSO, areas of weakness, and opportunities for growth.

Results: This study began in January 2024; data collection was completed in December 2024. Overall, 360 participants completed the anonymous survey; 51 staff and leaders and 11 family caregivers completed an interview or focus group. Data analysis is anticipated to be completed by September 2025 with results published by December 2025. Quantitative data will be analyzed using descriptive and inferential statistical techniques to identify similarities and differences in the perspectives of BSO staff and leaders across the 4 BSO regions. Qualitative data will be managed and analyzed through descriptive coding and thematic analysis to provide meaningful explanations of BSO staff, leaders, and family care partners' experiences with the program. This study was approved by the Western University Health Sciences Research Ethics Board (124599).

Conclusions: The study findings will support improvements in BSO services across the western region of Ontario. The findings will also be leveraged to support the modernization of the program to better meet the needs of patients and family care partners who depend on the service each year, while also supporting the needs of service providers within the program.

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KEYWORDS

Behavioural Supports Ontario; dementia care; responsive behaviors; family caregivers; health care providers; health care leadership; mixed methods

Introduction

Background

Behavioural Supports Ontario (BSO) is a provincially defined and regionally implemented initiative in Ontario, Canada, that is integrated across multiple care sectors and disciplines. It was created in 2010 to provide health service providers in long-term care (LTC), community-based care, and acute care with a framework to use behavioral interventions to support older adults with complex and responsive behaviors and their family care partners [1]. Expressions of responsive behaviors (ie, crying, moaning, wandering, explicit comments, sexual gestures, threats, screaming, biting, or hitting others) are often present in people living with dementia, substance use and addiction, and other neurological disorders [2,3]. Provincially, in 2023, BSO supported approximately 33,300 older adults with expressions of responsive behaviors and 20,100 family care partners across all care settings [4]. Dementia is the most common reason people receive BSO support, with 76% of residents in LTC and 80% of patients in the community having a formal dementia diagnosis [5]. In addition, patients or residents supported by BSO may also have depression, anxiety disorders, delirium, schizophrenia, and/or other psychiatric diagnoses [5].

BSO Service Delivery Model

When BSO was created in 2010, all 14 of Ontario's Local Health Integration Networks (ie, regional health service authorities) received funding from the Ontario Ministry of Health and Long-Term Care to establish their own regional BSO service delivery model based on local priorities and resources [6]. A single oversight group, the BSO Provincial Coordinating Office (BSO PCO), was created in 2015 to coordinate and manage the program provincially and act as an intermediary between the Ministry and the 14 BSO regional teams. This approach yielded 14 different regional service delivery models, each with its own method to provide BSO's 3 core components: (1) system coordination and management, (2) integrated service delivery, and (3) knowledgeable care teams and capacity building [1]. Despite the Local Health Integration Networks being restructured into 6 Ontario Health (OH) regions in 2019, BSO coordination and delivery still remain within the 14 original regional models.

Regardless of the region, every BSO service delivery model is organized to include the following teams in some form [7,8]: first, a *regional lead or leads* responsible for overseeing BSO service delivery and informing resource allocation and capacity-building opportunities via specialized behavioral intervention training for all BSO staff and clinicians in their region. Second, *LTC teams* that provide behavioral support intervention care to LTC residents and support to their family care partners. LTC teams are interdisciplinary (eg, registered practical nurses, registered nurses, personal support workers, recreation therapists, behavioral therapists, social workers, and social service workers) and support one or more LTC homes, depending on the regional service delivery model. Third, *interdisciplinary multi-sector teams* that provide behavioral support services to patients and family care partners in LTC, community, or hospital. Multi-sector teams are interdisciplinary and can include registered practical nurses, registered nurses, nurse practitioners, personal support workers, recreation therapists, behavioral therapists, social workers, social service workers, occupational therapists, and physiotherapists. In some regions, these teams are managed by the regional lead, while in others, they are managed by schedule 1 hospitals, which are specially designated facilities under the Mental Health Act [9] that can admit individuals involuntarily following specific criteria and assessment from a physician.

Even though each BSO model consists of similar roles, their nature (ie, operation, management, and staff) varies greatly between regions. In addition to the above 3 teams, some regions also provide additional BSO support to patients and family care partners through other dementia-related care services, such as adult day programs or the Alzheimer Society. Despite such variation in service delivery organization, all BSO teams are united under common provincial BSO standards and common core competencies [7].

In addition, BSO service providers receive specialized education to develop the core competencies required to deliver evidence-informed behavioral health care services. Specialized education programs include standardized courses—including PIECES [10], U-First! [11], Gentle Persuasive Approaches [12], and DementiAbility [13]—and education developed by the BSO PCO. BSO health service providers extend their own learning and build capacity with other health service providers who support individuals with responsive behaviors by delivering BSO education and practical hands-on coaching of care techniques. BSO service providers also share this knowledge with family caregivers, equipping them with evidence-informed approaches to reduce the frequency and severity of responsive behaviors. The overall goal of these educational efforts is to strengthen the knowledge and skills of BSO service providers, other service providers, and family caregivers so that they can provide best-practice care to individuals with responsive behaviors.

A previous study [14] focused on the LTC Embedded Team model; however, there have been no published studies highlighting BSO's impact on family care partners and service providers across all sectors. This pilot study will begin to address this gap by engaging with three target populations: (1) BSO service providers (ie, staff and leadership) across all BSO care settings, (2) service providers and specialists (eg, geriatricians and physicians) who are not directly funded by BSO but regularly interact with BSO staff and patients, and (3) family care partners who receive support from BSO teams to care for an older adult with complex and responsive behaviors.

This study aims to understand how BSO is currently affecting service providers and family care partners across all BSO care

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settings (ie, LTC, community, and acute care), and how BSO service delivery models can be modified to best meet the current needs of these target populations. Uncovering the current impacts of BSO will support the modernization of the program to better meet the needs of patients, residents, and family care partners who depend on the service each year, while also supporting the needs of service providers within the program.

Methods

Study Design

This study will use a 2-phase mixed methods sequential explanatory design [15,16]. In phase 1, quantitative data will be collected using an anonymous survey and analyzed by the research team. In phase 2, qualitative data will be collected using interviews and focus groups and analyzed to further explain or expand on the quantitative findings from phase 1. The sequential nature of data collection, with quantitative followed by qualitative, is well suited to provide a general understanding of an issue (the current state of BSO), while also examining nuances of the issue in more depth (family care partner and service provider experiences and areas for program growth). This design aims to use qualitative results to expand on quantitative findings and, occasionally, to understand outliers, thus enhancing interpretation to address the research problem [15,17].

This pilot study will focus on a single OH region (OH West) and its 4 BSO subregions (Erie St Clair [ESC], South West [SW], Waterloo Wellington [WW], and Hamilton Niagara Haldimand Brant [HNHB]; Figure 1). The objective of this study is to understand (1) current state of BSO across the OH West region; (2) How BSO is experienced by family care partners, staff, and clinicians across the OH West region; and (3) areas and opportunities for ongoing growth and development of the BSO program in the OH West region.

Figure 1. Ontario Health West regions. (A) Erie St. Clair; (B) South West; (C) Waterloo Wellington; (D) Hamilton Niagara Haldimand Brant.

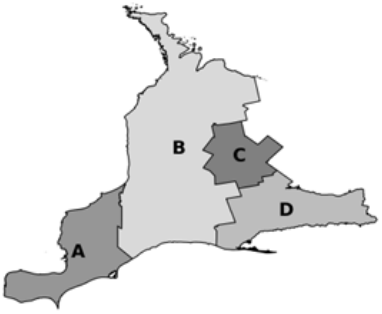

Study Setting

This pilot study will take place in the OH West region, inclusive of its 4 BSO regions. Each BSO region operates different service delivery models (refer to Table 1 for details).

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Table 1. Ontario Health (OH) West Behavioural Supports Ontario (BSO) region service delivery model characteristics.

Characteristic	OH West BSO region			
	Erie St Clair	South West	Waterloo Wellington	Hamilton Niagara Haldimand Brant
Lead agency	• Alzheimer Society of Chatham-Kent	• St Joseph's HealthcareLondon	• St Joseph's Health Centre Guelph	• Hamilton Health Sciences
Community-based care model	• 4 interdisciplinary multi-sector teams managed by BSO lead agency • Interdisciplinary multi-sector teams provide care support to community-based adults living with dementia and their family care partners • Ontario Health atHome leads community-based care to family care partners	• 5 interdisciplinary multi-sector teams managed by Schedule 1 hospitals in the region • Interdisciplinary multi-sector teams provide direct care to community-based adults living with dementia and their family care partners • Alzheimer Society provides care to community-based care partners • Adult Day Programs provide overnight respite	• 1 interdisciplinary multi-sector team managed by lead agency • Interdisciplinary multi-sector teams provide direct care to community-based adults living with dementia and their family care partners • Community-based care integrated within the Specialized Geriatrics Services network • Includes Community Responsive Behavior Team and BSO Transition Team	• Community-based care organized by Alzheimer Society Brant Haldimand Norfolk Hamilton Halton • 1 interdisciplinary multi-sector team supports community-based care for adults living with dementia and their family care partners
LTC[a] model	• Embedded teams at all 36 LTC homes in the region • Each interdisciplinary multi-sector team provides advanced care support to 7-11 homes	• Embedded Teams in all 75 LTC homes in region • Each interdisciplinary multi-sector team provides advanced care support to 8-24 homes	• Embedded Teams in all 34 LTC homes in region • Interdisciplinary multi-sector team provides advanced care support to homes	• 5 Interdisciplinary multi-sector teams managed by BSO Lead Agency • Interdisciplinary multi-sector teams provide direct care to LTC residents with responsive behaviors at 8-26 homes
Acute care model	• Service navigator works with hospital staff at 2 major regional hospitals to support BSO care for inpatients	• None	• Psychogeriatric resource consultant works with hospital staff at 7 acute care sites to support BSO care for inpatients	• BSO clinical leader to support BSO care for inpatients

[a]LTC: long-term care.

Eligibility Criteria

Eligible participants across the OH West region include BSO staff and leadership at any BSO-affiliated site, including the BSO Mobile Team, LTC homes, Alzheimer Societies, adult day programs, regional lead teams, and acute care centers. Other clinicians who engage with BSO staff across the geriatric care pathway (including hospital staff, retirement home staff and leadership, family physicians, nurse practitioners, geriatric medicine specialists, geriatric psychiatry specialists, Ontario Health atHome staff and leadership, and other community-based service providers) are also eligible to participate. In addition, family care partners receiving BSO support in any care setting are eligible to participate (refer to Table 2 for the complete inclusion criteria).

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Table 2. Participant eligibility criteria.

Participant group	Inclusion criteria
All participants	All participants must meet l of the following criteria in addition to their group-specific criteria: • ability to provide consent (either signed and dated consent form, or verbal consent documented on consent form) • willingness and ability to participate in study procedures • can communicate in English
BSO[a] staff and leadership	Must have completed *at least one* of the following BSO-related activities in the past 2 years: • directly or indirectly provided BSO services or care to a patient • participated in delivering BSO supports or services as a provider or care administrator • provided care to patients who have participated in BSO programs or services
Other clinicians that engage with BSO staff	Must have completed *at least one* of the following BSO-related activities in the past 2 years: • referred a patient that has previously utilized BSO services • participated in delivering BSO supports or services as a health care provider or care administrator • provided care to patients who have participated in BSO programs or services
Family care partners	Must meet *at least one* of the following criteria: • are currently caring for or supporting a patient of the BSO program (including patients with late-stage dementia) • previously cared for or supported a patient of the BSO program (including patients with late-stage dementia) within the last 2 years • is currently participating as a care partner in the BSO program.

[a]BSO: Behavioural Supports Ontario.

Sample Size

Phase 1: Anonymous Survey

The sample size calculation is based on data shared with the study team from each BSO regional lead team in the OH West region to estimate the total population of BSO staff and leadership (personal communication, 2024). The following criteria were used to estimate the sample size: a 10% dropout rate, power of 80%, and a statistical significance level of α=.05 [18]. This resulted in a total target sample size of 280 participants to complete the survey in phase 1 of this study.

Phase 2: Focus Groups and Individual Interviews

The target sample size for interviewees and focus group attendees will differ depending on the participant group, with a total target sample of up to 120 participants (up to 24 care partners and up to 96 BSO service providers or leadership) across the OH West region (Table 3).

Table 3. Target sample size for interviews and focus groups in phase 2.

Participant group	Targeted sample size (range)	
	Each BSO[a] region, n	Total OH[b] West region, n
BSO LTC[c] home staff	2-4	8-16
BSO community-based staff	7-14	28-56
BSO leadership	2-3	8-12
Other health care providers	2-3	8-12
Family care partners	4-6	16-24
Total	17-30	68-120

[a]BSO: Behavioural Supports Ontario.

[b]OH: Ontario Health.

[c]LTC: long-term care.

Recruitment

Phase 1: Anonymous Survey

A probability sampling approach will be used in phase 1 to recruit participants. Participant recruitment for phase 1 (anonymous survey) will occur through email and in-person meetings. Each BSO region's regional lead team will distribute a study recruitment email to all BSO staff, leaders, and other eligible participants for whom they have contact information. This email will include details about the study, invite BSO service providers and leaders to participate in an optional brief survey, and inform them that they are able to participate in either phase 1 or phase 2, or both, of the study. In addition, each BSO

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regional lead team will provide brief details about the study and how to complete the phase 1 survey during pre-existing meetings, presentations, and other sessions. Implied consent to participate will be obtained during the initial questions of the survey.

Phase 2: Focus Groups and Individual Interviews

A maximum variation purposeful sampling technique [19] will be used in phase 2 to recruit participants for focus groups and individual interviews. Recruitment of BSO staff, leaders, and other health care providers who work with the BSO program will occur through email and in-person meetings. For BSO staff and leaders, details on how to volunteer for a focus group or interview will be included in the recruitment email distributed by each region's BSO operations team, as described earlier. Staff and leaders will be able to notify the research team of their interest in taking part in a focus group or interview by entering their name, contact information, care setting (ie, LTC, community, or acute care), and whether they are staff or leadership into a contact form; the contact form can be accessed at the end of the anonymous survey in phase 1 or via a direct link. The research team will screen interested individuals and invite those who are eligible to participate in a focus group or individual interview, based on the participant's stated preference, provided that the target sample size has not been filled for their region and participant group type. Before conducting the focus group or interview, participants will complete a brief demographic questionnaire to provide details about their background with BSO. Written consent to participate will be obtained digitally before completing the demographic questionnaire.

Family care partner recruitment for phase 2 interviews will occur in three ways: (1) email, (2) in person, or (3) a recruitment poster. A study recruitment email, including brief details about the study and information on how to participate in an interview, will be sent to BSO family care partners by either the applicable region's BSO operations lead or an associated agency that supports BSO family care partners (eg, Alzheimer's Society and adult day programs). Alternatively, the BSO staff will provide study information and a recruitment poster to eligible care partners. In addition, the study will be advertised by BSO staff using a visual recruitment poster with applicable study information and contact details in locations that BSO care partners frequent (eg, public locations in LTC homes and community offices). In each recruitment method, interested care partners will be required to contact the research team directly to begin study activities. Once contact is initiated, a member of the research team will explain the study in detail to the care partner and answer any questions. If the care partner is interested in participating, the researcher will walk them through the letter of information and consent form and obtain verbal consent. Before conducting the interview, care partners will complete a brief demographic questionnaire to provide details about their background with BSO.

Data Collection

Overview

Data will be collected in three phases: (1) anonymous online survey, (2) focus groups and individual interviews, and (3) secondary data use. Focus groups and interviews with family care partners will occur either off-site (care partners will have the choice of an in-person interview at a local health care area) or in a Microsoft Teams meeting for a period of 9 months. Focus groups and individual interviews with BSO staff, leaders, and other health care providers will be conducted using the Microsoft Teams platform. Data will be collected by the researchers, and the principal investigators will oversee the data collection process. In phase 1, survey data will be collected; in phase 2, focus group and individual interview data will be collected; and in phase 3, secondary data from the BSO PCO will be obtained for analysis.

Phase 1: Anonymous Survey

BSO service providers (ie, staff and leadership) and other health care providers who support BSO from across the OH West region will be invited to participate in an anonymous online survey, hosted by Qualtrics. It is expected that it will take approximately 10 minutes to complete the survey and is accessible from any device with internet access (ie, smartphone, computer, and tablet). Survey participants will be asked demographic questions, including age, ethnicity, gender identity, professional designation (eg, nurse, personal support worker, physician, or management), sector of employment (ie, LTC, hospital, or community), the number of years practicing in their role, the number of years working with BSO, and their BSO region. Participants will also be asked a mix of scale-based and open-ended questions created by the research team to understand their perspectives on several factors related to the BSO program, including support for patients, family care partners, and staff; clarity of the BSO program in general; and relations with other BSO members and the regional lead team in their region. At the end of the survey, participants will be automatically routed to a separate form to sign up for an interview or focus group session, if they are interested. Participants will not be reimbursed or compensated for their time to complete the survey.

Phase 2: Focus Groups and Individual Interviews

BSO staff and leaders and BSO-adjacent health care providers who indicate their interest will be contacted by the research team to participate in an individual semistructured interview or a focus group. Semistructured interviews will take approximately 30 to 45 minutes to complete, and focus group sessions will take approximately 1 to 1.5 hours and include up to 8 participants per focus group. It is expected that 2 members of the research team will attend each interview, while 2 members of the research team will attend each focus group to facilitate the group discussion. All interviews and focus groups will be recorded and automatically transcribed using Microsoft Teams. Before the interview or focus group, participants will be asked to complete a demographic questionnaire to provide information about their age, ethnicity, gender, professional designation (eg, nurse, personal support worker, physician, or manager), sector of employment (ie, LTC, hospital, or community), the number

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of years practicing in their role, number of years working with or collaborating with BSO, and region. During the interview or focus group, participants will be asked about their own experiences with BSO, observations related to the impact of BSO on patients and family care partners, and suggestions for improving BSO in the future.

Family care partners who indicate their interest in the study will be invited to participate in a semistructured interview with a member of the research team, which will take approximately 30 to 45 minutes. Interviews will be conducted over Microsoft Teams, by phone, or in person, based on each participant's preference. Following the verbal consent process and before the interview, participants will be asked to complete a demographic questionnaire to understand their age, gender, ethnicity, and caregiving situation. During the interview, participants will be asked about their experiences with BSO programs and services, observations of how BSO affected the older adult with responsive behaviors, and suggestions for improving BSO in the future. All interviews will be recorded and transcribed using Microsoft Teams.

Secondary Data Collection

To contextualize the findings from phases 1 and 2, the BSO PCO has agreed to provide regional administrative data for the past 5 fiscal years (FY 2019–2020 to FY 2023–2024) for the 4 OH West BSO regions. These data will provide information regarding each BSO region's volumes of family care partners and patients and residents supported in each care sector (ie, LTC, community, and acute care), care coordination, capacity-building efforts, and system navigation support for BSO care recipients.

Data Analysis

Phase 1: Anonymous Survey Analysis

Survey data will be managed and analyzed using SPSS (version 29; IBM Corp). Raw data will be screened before analyses to (1) investigate the integrity and accuracy of the data collected by identifying and removing spam and bot responses [20,21]; (2) identify, examine, and address outliers; (3) identify, examine, and address missing data; and (4) assess the statistical distribution of the data, including measures of linearity, homoscedasticity, normality, and collinearity. Cleaned data will be analyzed using descriptive and inferential statistical techniques. Descriptive statistical analyses will be conducted to create a profile of survey participants, including both personal and professional demographics, and their standing on BSO's impact on staff, patients, and family care partners. Four-way ANOVA and factorial ANOVA will be used to identify interregional differences in continuous variables. Correlational and multiple regression analyses will be conducted to examine the relationships among the variables. Subgroup analyses will include examining differences based on sector and role type (staff or leader). Where possible, data will also be stratified based on participants' recency of BSO interaction and the length of time spent directly or indirectly supporting the provision of BSO services.

Phase 2: Focus Group and Individual Interview Thematic Analysis

Qualitative analysis will be conducted using an interpretive descriptive approach [22]. Interpretive description is an inductive analytic approach used to identify and provide meaningful explanations of thematic patterns in participants' experiences with clinical services, making it a suitable lens for analyzing the experiences of staff, leadership, and family care partners with BSO. All interview and focus group transcripts will be managed and analyzed using NVivo 14 (QSR International). At least 2 researchers will independently analyze the data to ensure reliability in coding. Data analysis will consist of line-by-line coding, followed by the identification of themes using a clustering technique [23,24]. Given the gendered nature of caregiving and health care workers, codes will be created for gender identity in our analysis [25,26], and their relationships with other themes will be examined. In addition, codes will be created for the length of time spent directly or indirectly involved with BSO services to understand the relationship between longevity and recency of a participant's BSO interaction with other themes. If saturation is reached, that is, the point at which few or no new relevant ideas or understandings are generated from participants, no further interviews or focus groups will take place [27].

Secondary Data Analysis

Secondary data provided by the BSO PCO will be analyzed using descriptive and inferential statistical techniques. Descriptive statistical analyses will be conducted to describe BSO activity in the OH West region overall, and the activity of each regional BSO team (ie, ESC, SW, WW, and HNHB). Correlational and multiple regression analyses will be used to examine the relationship among variables. Repeated-measures ANOVA will be used to identify any statistically significant differences in BSO activity over time in OH West and the 4 regions.

Ethical Considerations

Ethics approval was granted by the Western University Health Sciences Research Ethics Board (124599) and Lawson Health Research Institute Research Database Application (R-24-303). This is a nonclinical, noninterventional study and was not registered with any clinical trial registries.

Dissemination

The study data will be published in reports and peer-reviewed journals and presented at appropriate conferences. Deidentified data will be available to all research team members. Program stakeholders responsible for sharing the findings will determine the future scaling of the program's evaluation and quality improvement initiatives. The researchers aim to produce at least 3 peer-reviewed research manuscripts (ie, protocol, phase 1 survey results, and phase 2 interview or focus group results) for publication, to be written by the main research and implementation team.

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Results

This study was initiated in spring 2024 as part of ongoing quality improvement initiatives organized by the SW BSO regional lead team, and was supported by the BSO regional lead teams in ESC, WW, and HNHB. Data collection for the phase 1 anonymous survey concluded in October 2024; a total of 360 participants completed the anonymous survey. Data collection for the phase 2 focus groups and individual interviews concluded in December 2024, with 51 staff and leaders and 11 family caregivers completing an interview or joining a focus group. The results of the study are expected to be published in winter 2025.

Discussion

Anticipated Findings

Recent evidence suggests that because of the country's aging population, the number of Canadian older adults living with dementia may increase by more than 50% by 2030 [28,29]. Such an increase would intensify the dementia-related care demands experienced by staff across all formal health care sectors [30] and family care partners of adults with dementia [28-30]. Understanding how dementia care programs, such as BSO, can be improved to meet the current needs of older adults living with dementia is a necessary step in preparing for the future care demands of Canada's aging population.

This pilot study will provide insight into how different regional BSO service delivery models (ESC, SW, WW, and HNHB) are experienced by BSO staff and leaders, non–BSO funded health care providers who work closely with BSO teams and patients, and family care partners of older adults living with complex and responsive behaviors. Comparative analyses of how staff and leadership across the 4 regions (ESC, SW, WW, and HNHB) and care sectors (LTC, community, and acute care) experienced BSO from the phase 1 survey will be expanded upon with the phase 2 qualitative data to provide rich and nuanced insight into how BSO can be improved to better meet the needs of service providers. By including qualitative data regarding family care partners' experiences with the program, this pilot study will also help BSO to address the current needs of the individuals it supports.

Conclusions

This pilot study offers a first step toward understanding the current needs of BSO and areas for improvement. Collecting this information and sharing it with the appropriate BSO service providers will help prepare the program to meet the increasing dementia-related care demands anticipated during the next decade.

Acknowledgments

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Authors' Contributions

JE and BH designed and will direct the study. BH, DD, JE, and KC contributed to the study protocol and writing of this manuscript.

Conflicts of Interest

None declared.

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Abbreviations

BSO: Behavioural Supports Ontario
ESC: Erie St Clair
HNHB: Hamilton Niagara Haldimand Brant
LTC: long-term care
OH: Ontario Health
PCO: Provincial Coordinating Office
SW: South West
WW: Waterloo Wellington

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Protocol

Quality Improvement of Venous Thromboembolism Prophylaxis in Neurological Surgery: Ochsner Health System Protocol

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Abstract

Background: Venous thromboembolism (VTE) is a common postoperative complication. The perioperative incidence of VTE in patients undergoing neurosurgery on VTE chemoprophylaxis is consistently between 1.7% and 3.5%, excluding patients with trauma. While the majority of VTEs are asymptomatic, symptomatic VTEs may result in serious adverse events or death. There are limited neurosurgery society guidelines making VTE prophylaxis recommendations for patients undergoing cranial or spine neurosurgery. Several societies have published VTE prophylaxis guidelines for neurosurgery, but inconsistent recommendations have led to varied practices based on neurosurgeon preference.

Objective: This study aims to assess whether implementing a single protocol of VTE guidelines at a large hospital system department of neurosurgery would decrease the rate of VTE incidence by 50% within a 12-month period.

Methods: This project uses a department-wide protocol of chemical prophylaxis for admitted patients after neurological surgery. This quality improvement (QI) project has been designed and reported in accordance with the SQUIRE 2.0 (Standards for Quality Improvement Reporting Excellence) guidelines. SQUIRE is the most appropriate framework for reporting system-level interventions aimed at improving health care quality, safety, and outcomes. This manuscript addresses all relevant SQUIRE elements. The primary outcome is the VTE incidence over 12 months following protocol implementation. Secondary outcomes include the incidence of pulmonary embolism, length of hospital stay, and unexpected treatment of patients, such as therapeutic anticoagulation, thrombolysis, or emergency surgical or catheter-directed embolectomy. Balancing measures and process measures are also considered. Interim analyses with department reports will be performed every 3 months, but every VTE event will trigger an analysis of the variables described in this protocol. Analyses will consider barriers to change and adequacy of the protocol to guide protocol modifications and continuous implementation of improvements.

Results: This QI project was approved on February 16, 2023 (protocol ID NEU20230216-01). Adaptation and training began on August 1, 2023. As of May 2024, data collection is ongoing and scheduled to conclude by December 2024. Final data analysis is anticipated in March 2025, with results submitted for publication by the end of 2025.

Conclusions: It is anticipated that this QI project implementing a department-wide protocol for chemical prophylaxis in patients undergoing neurosurgery will improve the rates of VTE in patients on our service. In addition to a discussion of our results, we provide a comprehensive review of the literature and establish a gap in consistent published guidelines for VTE prophylaxis in patients undergoing neurosurgery. Results from this QI project will provide evidence for the effectiveness of a unified protocol of VTE prophylaxis in this patient group. Furthermore, outcomes from this study may be used as the basis for guideline recommendations and will benefit not only our department but may be used for QI of patient care at other hospitals.

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International Registered Report Identifier (IRRID): DERR1-10.2196/57278

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KEYWORDS

chemoprophylaxis; incidence; neurological surgery; neurosurgery; neurosurgery society guidelines; Ochsner Health System; patient-centered; patient-centered care; postoperative care; postoperative complication; quality improvement; venous thromboembolism; venous thromboembolism prophylaxis; VTE

Introduction

Overview

Venous thromboembolism (VTE) is a common postoperative complication. The incidence of VTE in perioperative patients undergoing neurosurgery is consistently between 1.7% and 3.5%, even among patients on pharmacologic prophylaxis, chemoprophylaxis (cPpx), excluding trauma patients [1,2]. A 2015 American College of Surgery (ACS) National Surgical Quality Improvement Program (NSQIP) retrospective analysis [3] of 10,477 patients who underwent cranial surgery across the United States reported an incidence of VTE of 3%-3.4%. Similarly, a single hospital system (Mayo Clinic) analysis of 1622 craniotomies for tumor resections between 2012 and 2017 documented a 3% incidence of VTE [4]. A large retrospective hospital system study (at the University of California) reported the incidence of VTE in patients who underwent spine surgery for nonmalignant versus malignant pathology as 0.5% versus 2.0%, respectively [5]. Incidence of VTE among patients with trauma is, however, much higher. In patients with neurosurgical trauma, the American Association for the Surgery of Trauma (AAST, 2021) cites 20%-30% VTE incidence for traumatic brain injury (TBI) [6,7], while the ACS Best Practices (2022) cites 40%-70% incidence for patients with spinal cord injury (SCI) [8]. As per the North American Spine Society's (NASS) most recent guidelines on antithrombotic therapies in spine surgery, there exists no high-quality study to establish definitively the incidence of VTE in nonelective spine surgery [5,9]. Most published studies assessing VTE incidence are retrospective analyses of NSQIP or other large hospital system data.

In addition, currently there are no published neurosurgery society guidelines making VTE prophylaxis recommendations for patients undergoing cranial or spine neurological surgery, including the Congress of Neurological Surgeons (CNS), American Association of Neurological Surgeons (AANS), or NASS. Multiple non-neurosurgical societies have commented and made a variety of recommendations for the prophylaxis of VTE in patients undergoing neurosurgical procedures. The American Society of Hematology 2019 Guidelines suggest against routine cPpx in patients undergoing neurosurgery in general but suggest all patients should receive mechanical prophylaxis (mPpx) [10]. They highlight that cPpx should be considered in patients at the highest risk, such as patients experiencing prolonged immobility or those undergoing a major neurosurgical procedure and suggest low molecular weight heparin (LMWH) over low-dose unfractionated heparin (UFH). Similarly, the American College of Chest Physicians (ACCP) 9th Edition Guidelines 2012 suggest mPpx with sequential compression device (SCD) over UFH, LMWH, or no prophylaxis for patients undergoing cranial or spine surgery, and cPpx for patients with very high risk of VTE (ie, malignant disease) once hemostasis is obtained and risk of bleeding decreases [11,12]. The ACCP guidelines recommend against an inferior vena cava (IVC) filter use for primary VTE prevention [13]. The new ACCP 2022 revised guidelines do not mention specific anticoagulation for patients undergoing neurosurgical procedures [12]. For patients with central nervous system trauma, including TBI, SCI, and so on, the AAST VTE Ppx in the intensive care unit (ICU) 2021 Guidelines suggest prophylaxis within 24-72 hours of admission pending stability head computed tomography based on Berne-Norwood criteria [14] with either Enoxaparin 30 mg every 12 hours (with Xa target of 0.2-0.4 mg/mL) or UFH 5000 U every 8 hours [7] (Multimedia Appendix 1).

Moreover, most guidelines do not comment on patients with a BMI>30 kg/m^2 and do not include this patient population as a confounder in analyses. Based on our summary of the literature, the most frequently used and recommended methods of VTE prophylaxis include the following:

1. mPpx with sequential compressive devices, which are demonstrated to reduce the risk of deep vein thrombosis (DVT) compared with control treatment (odds ratio [OR] 0.85, 95% CI 0.5-1.50); however, this is based on low-quality evidence [15]. According to a recent Cochrane review, mPpx reduces the incidence of DVT (relative rate [RR] 0.43, 95% CI 0.25-0.73), but cPpx is more effective than mPpx at reducing the incidence of DVT (RR 0.48, 95% CI 0.25-0.95) [16].
2. Chemical prophylaxis with LMWH is considered to reduce the risk of DVT compared to UFH (RR 0.68, 95% CI 0.50-0.94) [15,17]. Patients who received both mPpx and cPpx with LMWH had a lower risk of DVT [16,18]. UFH alone has shown a strong reduction in VTE incidence compared to placebo (RR 0.27, 95% CI 0.10-0.73) [19,20].
3. IVC filter is an alternative prophylaxis for patients at high risk of bleeding in whom cPpx has either been shown ineffective or is contraindicated. Patients receiving an IVC filter had lower incidence of subsequent pulmonary embolism (PE; OR 0.5, 95% CI 1.17-2.48), nonsignificant lower PE–related mortality (OR 0.51, 95% CI 0.25-1.05), and no change in all-cause mortality (OR 0.91, 95% CI 0.70-1.19) [21].

While the majority of VTEs are asymptomatic, symptomatic VTEs may result in serious adverse events or death [4]. Therefore, prophylaxis of VTE plays a major role in reducing adverse events and unexpected mortality in patients undergoing

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neurosurgery. An ACS NSQIP data query for Ochsner Department of Neurosurgery performed on August 1, 2022, for the period of July 1, 2020, to June 30, 2021, yielded incidence rates of VTE as follows: a total of 8 events per 320 total neurosurgery cases for a rate of 2.5%, whereas the predicted rate of VTE was calculated to be 2.83% and the expected rate based on the national average rate of VTE was calculated to be 3.27%. This has resulted in an OR calculation of 0.86 (95% CI 0.52-1.42). When stratified by the type of neurosurgery, the VTE incidence rate was 0.76%, where a VTE event occurred in 1 case out of a total of 132 spine neurosurgery cases. The predicted rate for spine neurosurgery was 1.78% and the expected rate for spine neurosurgery cases was 2.24%, with an OR of 0.77 (95% CI 0.37-1.61). The rate of VTE after neurosurgery for brain tumors at Ochsner was 3.52%, based on 5 cases out of 142 total brain tumor neurosurgery cases. The predicted rate of VTE incidence for patients undergoing neurosurgery for brain tumor was 3.45% and its expected rate was 3.42%, with an OR of VTE incidence among patients after brain tumor neurosurgery of 1.01 (95% CI 0.63-1.63).

Although the incidence of VTE at Ochsner Health Department of Neurosurgery is within the expected range of nationwide data [1-3], the lack of a department- or hospital-based protocol for postoperative VTE prophylaxis results in a heterogeneity of patient care and may contribute to unexpected outcomes. Current practice dictates that individual physicians apply their chosen set of VTE prophylaxis guidelines [17]. This further contributes to a heterogeneity of patient care since most guidelines provide inconsistent recommendations (Multimedia Appendix 1). This creates a gap in patient care that could potentially be bridged through a consistent set of department VTE prevention guidelines, which would aim to diminish patient care variability and reduce the incidence of VTE below the national average rates.

Objective

A department-wide protocol will aim to decrease the rate of VTE by providing a set of consistent guidelines for physicians, physicians-in-training, advanced practice providers, and other clinical staff involved in direct patient care. The objective of this quality improvement (QI) project is to assess the effect of implementing a practice-wide protocol of VTE prophylaxis on the incidence of VTE at Ochsner Health among admitted patients undergoing nonemergent neurosurgery procedures. Implementing a department-wide VTE prophylaxis protocol based on individualized patient risk aims to ensure patient-centered care and enhance the safety and effectiveness of postoperative care. Moreover, we propose that establishing consistent guidelines for VTE prophylaxis in postoperative patients will contribute to efficiency and minimize errors based on heterogeneity of care. A further step to improve patient-centered care is the consideration of both patients' BMI and weight when determining cPpx dosing–a rarely applied approach that is particularly germane for our patient population in the southern United States.

Methods

Overview

This project is well aligned with the Institute of Medicine's 6 domains of quality health care and was designed according to the Institute for Healthcare Improvement steps to a good QI project [22]. It aims to avoid harm to patients while being effective in providing prophylaxis according to a risk-based approach. Specifically, the adaptive design assessing outcomes and process measures and implementing incremental change on a quarterly basis ensure the safety of this QI project. Our protocol follows the Agency for Healthcare Research 2017 guidelines to ensure patient safety while implementing this protocol [23]. This quality improvement project has been designed and reported in accordance with the SQUIRE 2.0 (Standards for Quality Improvement Reporting Excellence) guidelines. SQUIRE is the most appropriate framework for reporting system-level interventions aimed at improving health care quality, safety, and outcomes. This manuscript addresses all relevant SQUIRE elements [24]. Further, this project is patient-centered and aims to ensure equitable care for patients by consistently including all eligible individuals in the protocol without discriminating based on demographics. Finally, it is a timely and efficient protocol, reducing inconsistent application of variable guidelines and thus potentially avoiding supplies and staff waste. The assessment of the impact of this protocol on VTE incidence is at 12 and 24 months post implementation, with interim analyses every 3 months to ensure continuous quality improvement. The goal is a 50% decrease in the overall VTE incidence in patients undergoing neurosurgery from 2.5% to 1.25%, with a greater decrease in incidence of VTE among patients undergoing neurosurgical procedures for malignant pathology (cranial or spine). Targeting a reduction to 1.25% represents an achievable improvement that aligns with outcomes seen in successful QI initiatives with standardized protocols [25-27]. For example, the Mercy Hospital Springfield Neurosurgery VTE quality improvement initiative found that VTE occurrence rates in neurosurgery decreased from 3.97% at the time of protocol initiation to 0.72% in January 2020 [26]. All patients admitted to the neurosurgery service for postoperative care will be managed according to the new protocol after the implementation date. The incidence of VTE among patients admitted during the previous 12 months will serve as a control.

Ethical Considerations

This project did not meet the threshold for institutional review board (IRB) review and approval per Ochsner Health Systems (IRB) guidelines. Human participants were not consented for individual participation in this project. Patient data were stored behind a Health Insurance Portability and Accountability Act (HIPAA)–compliant hospital-wide internet firewall. All patient data are deidentified and anonymized before analysis and dissemination. Participants were not compensated for providing their data or for participation in this project. All staff involved in this protocol adhere to HIPAA. This QI initiative is purely a retrospective study of chart data or similar, and consent was not required for the procedures performed [23,27-31]. As such, it falls under the definition of nonhuman participants research

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according to both the US Department of Health and Human Services (HHS) Office for Human Research Protections (OHRP) and our institutional IRB. This project was reviewed by the Ochsner Health Institutional Review Board and was deemed exempt from IRB approval based on institutional guidelines for QI activities. The key criteria met include the following 4 criteria:

1. The intervention (VTE prophylaxis protocol) was developed and implemented solely for the purpose of improving care within Ochsner.

2. The protocol will be implemented at the department level as a clinical standardization initiative, with all patients receiving care under the new protocol as part of routine care.

3. No patient-identifiable data are used in any dissemination of findings. All data are retrospective, deidentified, and securely stored in a HIPAA-compliant system.

4. There are no additional risks or burdens that were imposed on patients outside of standard care practices. A formal determination of exemption was made under internal protocol ID NEU20230216-01, approved by our department leadership on February 16, 2023.

Ethics approval was not required for this protocol per local IRB requirements. However, all authors strictly adhere to patient privacy and confidentiality according to the US HIPAA.

Outcomes

The primary outcome measure is the rate of VTE. Benchmark data for the primary outcome is derived from ACS NSQIP VTE rates for Ochsner Neurosurgery and the nationwide ACS NSQIP VTE rate. Benchmarks are 2.5% for Ochsner Neurosurgery and 3.27% for the national incidence rate [3]. Secondary outcome measures include the rate of PE, the rate of symptomatic DVT, and the rate of PE-associated mortality.

Process measures have an impact on the primary and secondary outcomes and will include staffing at the time of VTE diagnosis, volume of patients per resident physician, and the percentage of patients at high risk. Balancing measures include the complexity of patients based on VTE risk and history of VTE despite prophylaxis, medication reconciliations, communication with other services, and volume of patients on the neurological ICU. Procedure and patient risk factors of VTE will be included in the analysis as confounding variables. Unintended consequences such as supratherapeutic anticoagulation or bleeding events, delays in mobilization or surgery due to protocol requirements, or variation in adherence will be monitored as well. The mentioned unintended consequences will be monitored through case review and clinical incident reports, and adjustments to the protocol will be made through the Plan-Do-Study-Act cycle framework.

Selecting Change

Two major changes will be implemented. Implementation of a risk-based protocol for VTE prophylaxis for all Department of Neurosurgery patients undergoing elective surgery, and training of direct patient care staff on the protocol across the Departments of Neurosurgery and Neuro Critical Care (NCC). The following steps outline the QI protocol:

1. For all patients admitted to the Neurosurgery or NCC service and undergoing a neurological surgery, use mPpx with SCD intraoperatively and until discharge. An exception is patients in whom mPpx with SCD is contraindicated, such as patients with known DVT or lower extremity injury.
2. For patients with intracranial hemorrhage, we will obtain stability imaging at 24-48 hours before starting cPpx.
3. For all patients admitted to the Neurosurgery or NCC service and undergoing an elective neurological surgery, provide cPpx starting at 24 hours until discharge, unless an absolute contraindication to anticoagulation is present (per #5).
4. Check creatinine clearance (CrCl) and choose cPpx with either enoxaparin if CrCl is >30 mL/minutes or UFH if CrCl≤30 mL/minutes. Dosing for all patients is according to weight and BMI, as obesity is an independent risk factor for hypercoagulability. Small studies have shown an advantage of weight-based dosing in achieving target anti-Xa levels with enoxaparin administration [32,33]. A clinical trial has also demonstrated a reduction in VTE rates for patients on UFH cPpx when using both BMI and weight (weight>100 kg and BMI≥40 kg/m^2) [20]. For weight-based enoxaparin prophylaxis, the standard dose is 40 mg subcutaneously daily. For patients weighing less than 50 kg, the dose is 30 mg subcutaneously daily. Patients with a BMI more than 40 kg/m^2 should receive 40 mg subcutaneously twice daily, and those with a BMI more than 50 kg/m^2 should receive 60 mg subcutaneously twice daily. For weight-based unfractionated heparin prophylaxis, the standard dose is 5000 units subcutaneously every 8 hours. Patients with a BMI more than 40 kg/m^2 and a weight over 100 kg should receive 7500 units subcutaneously every 8 hours.
5. Per AAST VTE prophylaxis in the ICU (2021) [7], an absolute contraindication to cPpx for patients hospitalized with trauma is active hemorrhage or recent spine or intracranial surgery. This is in addition to absolute contraindications to therapeutic anticoagulation, including a prior complication while on anticoagulation therapy or recurrent VTE while on an adequate dose of cPpx, or ongoing risk due to life-threatening bleeding. Risk of life-threatening bleeding includes long-bone fractures, severe pelvic fractures, plus a long-bone fracture, TBI, SCI, and medical conditions predisposing to bleeding. Patients who meet these criteria will be assessed with a stability scan before inclusion in this protocol. Relative contraindications to cPpx include epidural hematoma, risk of wound complications, and neurologic decline. Patients with relative contraindications will be included in the protocol.
6. VTE therapy will be continued until the patient is discharged from the hospital and no longer immobilized.
7. Training on this protocol was provided to all health care providers involved in postoperative neurosurgery patient care. A flowchart is displayed in common work areas

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(Figure 1). This training took place between Inservice in September and October 2023.

Continuous improvement is built with small incremental changes, using a systematic scientific approach to test their impact and feasibility. The Plan-Do-Study-Act cycle will be used as a model on which to structure tests of change. This includes continuous analysis of errors and successes of the protocol and subsequent protocol adaptation for the duration of the project. Dynamic data will be assessed through a run chart with data points added monthly, but with interim analysis every 3 months. Interim analyses will be discussed before changing the protocol for such quality improvement adaptations. A formal statistical analysis will be performed with a *t* test comparing NSQIP and postprotocol end-of-study VTE rates at both 12 and 24 months post implementation. Stratification based on malignancy and cranial versus spine procedures will also be assessed, as will be the confounding process and balancing measures.

Missing data will be handled through checking at each interim review. Any record missing critical outcome or key covariate information will be excluded from regression analyses. In addition, we will conduct sensitivity analyses to assess the impact of any missing data on VTE rates. Discrepancies will be resolved by consensus and reported, if indicated. Interim analyses with department reports will be performed every 3 months, but every VTE event will trigger an analysis of the variables described in this protocol. Analyses will consider barriers to change and adequacy of the protocol to guide protocol modifications and continuous implementation of improvements.

Additional guidance has been incorporated to inform future iterations of the protocol, including considerations for patients with comorbid atrial fibrillation or those already on antiplatelet therapy [34]. Implemented changes will be made based on recent evidence in the literature [35].

Figure 1. Protocol flowchart. BID: twice daily; CrCl: creatinine clearance; DVT: deep vein thrombosis; ICU: intensive care unit; NCC: Neuro Critical Care; NSGY: neurosurgery; Q8h: every 8 hours; qd: daily; SCD: sequential compression device; SQ: subcutaneously.

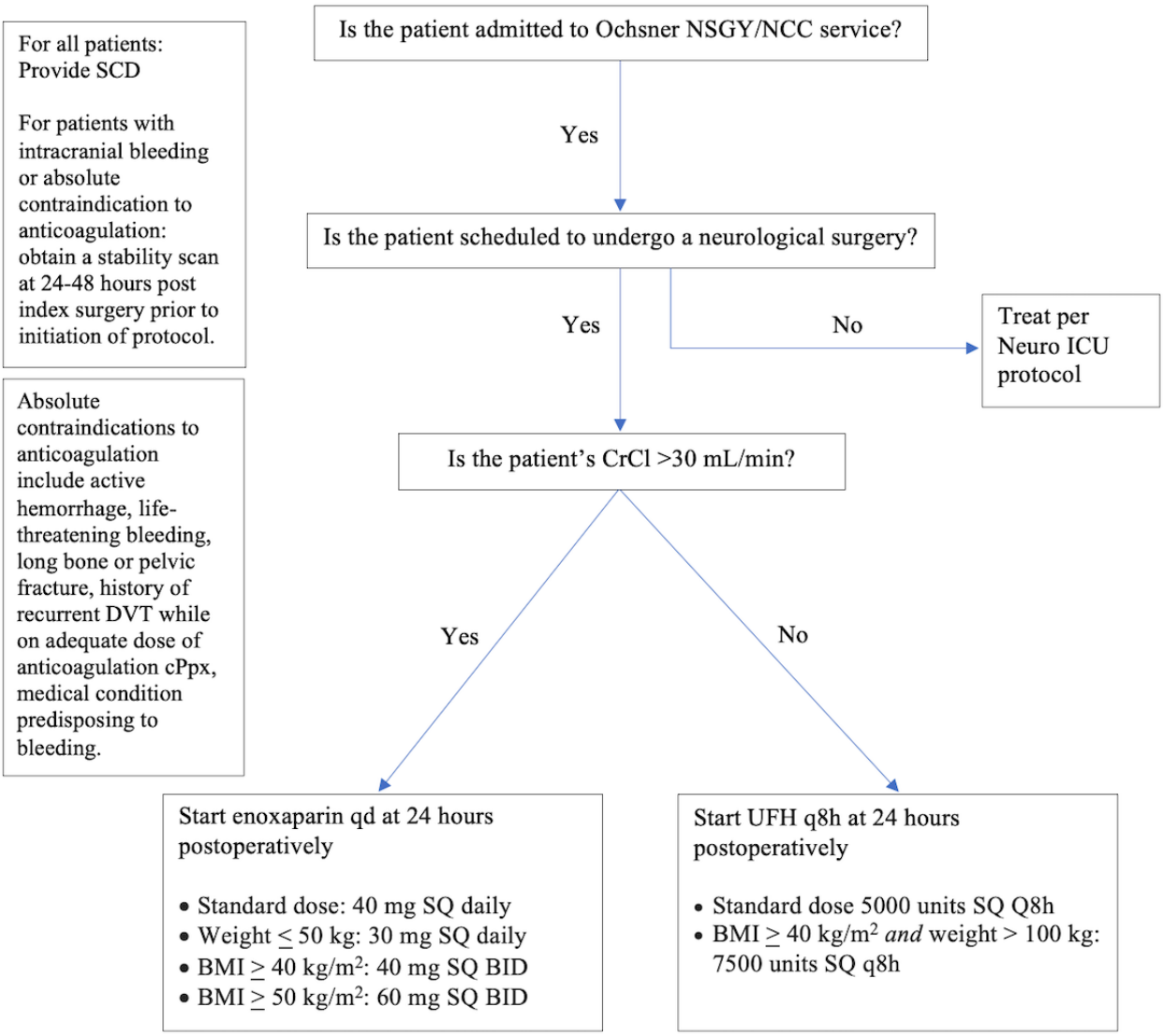

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Results

The desired timeframe for implementing the Neurosurgery VTE prophylaxis protocol is within 6 months of QI project approval, with 1 month of "adaptation time." Adaptation time is defined as the time between training the staff involved in the project and starting the timeline for outcomes assessment. Department project approval occurred on February 16, 2023, and the project adaptation time began on August 1, 2023.

Data collection is scheduled for completion in 2024, with analysis expected by March 2025. We anticipate a 50% reduction in VTE incidence (from 2.5% to 1.25%) following implementation of a standardized department-wide cPpx protocol. The primary outcome is the incidence of VTE. To assess whether implementation of the protocol results in a meaningful improvement compared to the standard of care, we will use a pre-post design comparing outcomes in the 12 months before and 12 months after the protocol implementation. We will evaluate differences in VTE rates using chi-square or Fisher exact test to compare the proportion of VTE events pre-implementation versus post-implementation. The justification for the chi-square test is that it is appropriate for large samples with expected counts ≥5. The Fisher exact test will be used as a backup for smaller subgroup comparisons where expected frequencies are low. In order to mitigate confounding, we will use multivariable logistic regression, using VTE occurrence as the dependent variable, with covariates including patient-level and procedural risk factors such as BMI, malignancy, surgery type (cranial vs spine), and immobility. The justification is that regression modeling will help isolate any independent effects of the protocol on VTE rates. To account for continuous secondary outcomes, we will perform stratified subgroup analyses for patients with malignancy, those undergoing cranial versus spine procedures, and those receiving LMWH versus UFH. The justification for this is that we will protect against or identify subgroups that experience differential VTE risk. A stratified analysis will determine if the protocol is equally effective across populations.

Outcomes of this QI project will be reported to the Ochsner Health Department of Neurosurgery as well as hospital administration. Results will also be shared with the scientific and health care quality improvement community. Consideration of "lessons learned" and suggestions for implementing change in order to improve patient outcomes will be made. In addition, consideration of barriers to change and recommendations for improving patient care will be discussed. This project will provide an evidence base for the implementation of the proposed protocol, and its success or failure to achieve the protocol's aims will be equally important for future hospital patient care quality improvement efforts. Considering there are limited neurosurgical society guidelines on VTE prophylaxis in perioperative patients, results from this project can be used to assess the efficacy of our specific protocol in guiding future guidelines specific for patients undergoing neurosurgery. The overarching objective of this quality improvement initiative is to advance the evidence of the effectiveness of anticoagulation prophylaxis in preventing perioperative VTE morbidity and mortality. As previously identified, the determination of whether implementation of this protocol was a success compared to the current standard-of-care success criteria will be measured against a ≥50% reduction in VTE incidence compared to baseline (from 2.5% to ≤1.25%). Secondary success measures include reduction in symptomatic PE and DVT events, and improvement in protocol adherence across clinical teams.

Discussion

Expected Findings

Our review of the literature (summarized in Multimedia Appendix 1) demonstrated that all published guidelines by non-neurosurgical societies are largely inconsistent. While some suggest against the use of pharmacological prophylaxis in the majority of patients undergoing neurosurgery, others suggest stratifying patients based on risk of VTE, including those with malignancy or immobilization, and providing pharmacological prophylaxis in the high-risk group. Moreover, the choice of anticoagulant is different between published guidelines, and most do not consider weight-based dosing.

In devising our protocol, we borrowed heavily from the trauma and neurocritical care literature when choosing the timing, agents, and dosing for VTE cPpx. NASS working group on VTE prophylaxis [9] notes that the safety and utility of cPpx is controversial, and the literature does not support a specific perioperative start time point nor duration of cPpx. However, the working group acknowledges that LMWH initiated on the day of surgery may be safe for patients undergoing elective spine surgery and makes a consensus-based recommendation for it in their 2009 guidelines [9]. On the other hand, the ACCP recommends initiating cPpx in trauma neurosurgical patients within 24-72 hours of admission pending a stability scan [7]. The NCC guidelines [36] alternatively note that VTE cPpx should be initiated after 24 hours of admission for patients with aneurysmal subarachnoid hemorrhage, after 48 hours for patients with intracerebral hemorrhage, and within 24-72 hours for patients with TBI, but not before. We have elected to initiate cPpx for all admitted patients on the neurosurgery service within 24-48 hours of scheduled surgery. Patients who have a contraindication to anticoagulation or are at a high risk of intracranial bleeding will enter the protocol pending a stable head computed tomography.

In terms of the choice of agent for VTE cPpx, Nyquist et al [36] recommend prophylaxis with UFH for patients after a nontraumatic subarachnoid hemorrhage, and either UFH or LMWH in other patients with intracerebral hemorrhage or patients with neurosurgical trauma. The AAST [7], on the other hand, notes that even though LMWH and UFH have comparable bleeding complications, LMWH results in a lower incidence of PE in trauma neurosurgical patients. Consistent with this, we selected LMWH for our protocol as the primary anticoagulant agent. However, patients with poor renal function, assessed as CrCl<30 mL/minutes, will receive UFH instead.

Another critical aspect of our protocol is the introduction of weight-based dosing. Samuel et al [20] have shown that using 7500 Units of UFH in patients on the neurocritical care service who weigh >100 kg does not lead to increased complications.

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Similarly, Sebaaly and Covert [33] summarize the literature on dose adjustments of LMWH to 30 mg every 8 hours for patients weighing <50 kg or having a BMI of <18 years, reporting comparable complications between higher doses and lower doses of LMWH. The AAST also recommends weight-based dosing for LMWH. Although our study design does not randomize patients, it will allow us to demonstrate the practical challenges of implementing a department-wide VTE prophylaxis protocol in reducing VTE incidence and associated morbidity and mortality.

It is further important to emphasize that VTE cPpx is often used in addition to and not instead of mPpx. Although there is evidence suggesting cPpx may be more effective in reducing the risk of VTE [15,16], all of our patients receive mPpx during their admission unless contraindicated. Consequently, our QI project is not intended to assess the significance of mPpx but rather to assess whether a standardized cPpx protocol may contribute to reducing the overall incidence of VTE and DVT in our patient population.

It is important to consider that a subset of patients may already be on a therapeutic dose of anticoagulation or antiplatelet medications for a history of DVT or PE before hospitalization. Such medications are typically held the evening before a neurosurgical procedure, or in cases of emergency surgery, may be reversed on an individual patient basis. Postoperatively therapeutic dose of anticoagulation or antiplatelet medication may be restarted in these patients. Such patients also continue their regular dose upon discharge. We do not provide a prescription for mechanical VTE prophylaxis other than early mobilization with physical therapy.

Limitations

As this is a nonrandomized pre-post QI design, the project is susceptible to selection bias and performance bias. Examples of such biases include changes in staffing patterns or seasonal admission trends, which may influence VTE rates. We acknowledge this limitation and address it through stratified subgroup analyses and logistic regression to adjust for known confounders. In addition, although we use multivariable regression to control for common risk factors (BMI, malignancy, immobility, and surgery type), unmeasured, or residual confounding may still influence outcomes. We recognize this as a limitation in attributing causality to the intervention. Finally, there is potential for missing or incomplete documentation in retrospective chart review. We aim to address this through predefined rules for data exclusion and sensitivity analysis, as described in the Methods section.

Acknowledgments

All authors whose names appear on the submission (1) made substantial contributions to the conception or design of the work, (2) drafted the work or revised it critically for important intellectual content, (3) approved the version to be published, and (4) agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Generative artificial intelligence, such as ChatGPT or other artificial intelligence, was not used in any portion of this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Guidelines summary.
[DOCX File , 30 KB - resprot_v14i1e57278_app1.docx]

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Abbreviations

AANS: American Association of Neurological Surgeons
AAST: American Association for the Surgery of Trauma
ACCP: American College of Chest Physicians
ACS: American College of Surgery
CNS: Congress of Neurological Surgeons
cPpx: pharmacologic prophylaxis, chemoprophylaxis
CrCl: creatinine clearance
DVT: deep vein thrombosis
HHS: US Department of Health and Human Services
HIPAA: Health Insurance Portability and Accountability Act
ICU: intensive care unit
IVC: inferior vena cava
IRB: institutional review board
LMWH: low molecular weight heparin
mPpx: mechanical prophylaxis
NASS: North American Spine Society
NCC: Neuro Critical Care
NSQIP: National Surgical Quality Improvement Program
OHRP: Office for Human Research Protections
OR: odds ratio
PE: pulmonary embolism
QI: quality improvement
RR: relative rate
SCD: sequential compression device
SCI: spinal cord injury
SQUIRE: Standards for Quality Improvement Reporting Excellence
TBI: traumatic brain injury
UFH: unfractionated heparin
VTE: venous thromboembolism

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Protocol

Attitudes Toward Alternative Tobacco and Nicotine Products and Their Association With Lifestyle Habits: Protocol for the MINERVA International Observational Cohort Study

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Abstract

Background: Traditional smoking is widely recognized as a public health issue, with established risks that include cardiovascular, respiratory, and cancer-related health impacts. Recently, alternative tobacco and nicotine products (ATNPs), such as electronic cigarettes, have gained popularity as potentially safer substitutes for traditional tobacco use. However, there remains uncertainty regarding the health effects of ATNPs, which require comprehensive research to evaluate their risks and potential benefits compared to conventional smoking.

Objective: The aim of this multicenter observational study, MINERVA (My Changing Lifestyles Our Research and Everyone Health), is to examine the interplay between traditional smoking and the potential effect of switching to ATNPs in culturally diverse European countries.

Methods: Data collection will be conducted through a structured web-based questionnaire and administered using a snowball sampling technique, which relies on the referrals and network connections of initial participants. A link will be provided for participants to access the questionnaire. Responders who express a willingness to participate in the study cohort will be recontacted at least twice a year to ensure continuity in their participation, and they will be asked to complete the same questionnaire during these follow-up assessments. This approach allows for the gathering of useful information over an extended period and the assessment of any changes or trends in the data that may emerge over time. Using social media for data collection, the research explores real-time attitudes and experiences related to smoking, with a particular focus on participants' receptiveness to transitioning to nonconventional tobacco products. Statistical analysis will include descriptive statistics, and logistic regression models will examine associations. Nonlinear trends will be assessed using restricted cubic splines. Analyses will be conducted in R software with relevant statistical packages.

Results: The MINERVA study began in June 2023, and data collection is still in progress. As of January 2025, 7535 participants had been enrolled in Italy, of whom 4862 have consented to a follow-up. Preliminary analyses are currently being conducted.

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Conclusions: The study underscores the importance of ongoing research to inform evidence-based policies and interventions, emphasizing the role of social media surveys in capturing diverse perspectives and facilitating longitudinal studies for a deeper understanding of the health implications of transitioning from traditional smoking to ATNPs.

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KEYWORDS

smoking; switch; survey; alternative tobacco and nicotine products; lifestyle

Introduction

Tobacco smoking is a well-known major global public health concern, with well-documented adverse effects on human health [1-6]. Traditional smoking involves inhalation of combusted tobacco, which releases several harmful chemicals, including nicotine, tar, carbon monoxide, and various carcinogens.

Exposure to traditional tobacco products is widely known to be associated with adverse health outcomes, including, but not limited to, cardiovascular diseases, respiratory diseases, cancer, and other health effects (eg, reduced fertility, low birth weight in infants of smoking mothers, increased risk of infections, and impaired wound healing).

In recent years, electronic cigarettes (e-cigarettes or vapes) introduced a new form of nicotine consumption known as e-smoking or vaping. E-cigarettes work by vaporizing a liquid (e-liquid) that typically contains nicotine, flavorings, and other chemicals. E-smoking emerged as an alternative to traditional smoking, often marketed as a less harmful alternative [7]. While e-cigarettes do not involve the combustion of tobacco, they are not without health risks. Studies have shown that e-cigarettes expose users to a different set of chemicals, which can lead to nicotine addiction, respiratory and cardiovascular health problems, and unknown long-term effects [8-10].

However, it is noteworthy that literature has suggested that there could be several advantages of alternative tobacco and nicotine products (ATNPs) over traditional ones. One of the primary advantages of transitioning to ATNPs is the potential for better nicotine dependency management [8]. E-cigarettes allow users to regulate nicotine intake through the choice of e-liquid nicotine concentration and the frequency of use. This can facilitate a gradual reduction in nicotine consumption, aiding smokers in the process of quitting altogether. Compared to traditional smoking, ATNPs significantly reduce the exposure to many harmful chemicals found in tobacco smoke [9]. E-cigarettes do not involve combustion, which eliminates the formation of tar, carbon monoxide, and several carcinogenic compounds. While e-liquids may contain some chemicals, their overall composition is less toxic than that of tobacco smoke. Studies often suggest that transitioning from traditional smoking to ATNPs may lead to improvements in respiratory health [10]. ATNPs also offer potential benefits for nonsmokers and bystanders. Unlike traditional smoking, which emits harmful secondhand smoke, e-cigarettes primarily release water vapor [11]. This reduces the risk of passive exposure to harmful chemicals, thus protecting the health of those around the e-smoker. Furthermore, transitioning to ATNPs may lead to immediate improvements in quality of life [12]. E-smokers often report enhanced taste and smell sensations, as well as reduced coughing and phlegm production. These subjective improvements contribute to an overall sense of well-being [13].

MINERVA (My Changing Lifestyles Our Research and Everyone Health) is an observational international study that encompasses four Mediterranean countries—Italy, Greece, and Turkey—each contributing a distinctive cultural, regulatory, and epidemiological backdrop for evaluating the interplay between traditional smoking and the potential advantages of transitioning to ATNPs.

The objective of the project is to provide a comprehensive profiling of individuals based on their sociodemographic characteristics, lifestyle behaviors, and dietary habits, investigating their association with ATNP use and willingness to switch to alternative nicotine products.

Methods

Study Design and Participants

An observational international cohort study will be conducted. A questionnaire will be administered using a snowball sampling technique, which relies on the referrals and network connections of the initial participants. Snowball sampling was selected due to its ability to efficiently recruit individuals engaged in smoking behaviors and those transitioning to alternative tobacco products, where social networks influence participation. This method also allows for streamlined recruitment without relying on preexisting registries [14].

To be eligible for inclusion, individuals must be aged between 18 and 99 years. This criterion ensures that the study population exclusively consists of adults, encompassing a broad spectrum of age groups, from early adulthood to the later stages of life. This diverse demographic range aims to capture a comprehensive representation of adult participants, allowing for a thorough examination of the intervention's effects across various life stages. The study will be initially conducted in Italy and later in Turkey and Greece.

Participants who consent to be recontacted for inclusion in the cohort will undergo biannual assessments. To ensure continuity in the biannual assessments, participants who consent to follow-up will receive scheduled reminders via email, social media, or phone (if contact information is available). Additionally, engagement strategies such as periodic study updates will be implemented to encourage ongoing participation.

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Individuals who face challenges in accessing and completing the questionnaire and those who experience difficulties reading or responding to the questionnaire will be excluded from participation. Additionally, individuals who are unable to accept the privacy and participation policy will not be eligible for inclusion in this study.

Participants who express their willingness to be recontacted will be part of the cohort for this study. The cohort group will be asked to complete a short version of the questionnaire during these follow-up assessments. This approach permits the gathering of valuable information over an extended period and assessing any changes or trends in the data that may emerge over time.

Ethical Considerations

The study was carried out according to the Declaration of Helsinki guidelines and was approved by the Bioethics Committee of the University of Turin (protocol 0075071) on February 2, 2024.

All participants will provide informed consent before participation, with the option to withdraw at any time. Consent to participate and to collect and process personal data is given electronically (ticking the corresponding box) on the project website, after reading detailed information on data collection and processing, and before accessing the questionnaire, in accordance with the European Commission General Data Protection Regulation (679/2016).

Both the informed consent form for study participation and the data processing consent form have been approved by the institutional ethics committee.

Data will be fully anonymized to ensure privacy and confidentiality. No compensation will be provided for participation. No identifiable personal data will be included in the manuscript or the supplementary materials.

Sample Size

A feasibility assessment was performed using a fixed model multiple regression and correlation analysis approach, parameterized according to a noncentral *F* distribution, which can consider the effect size of the population means. This accounts for differences in expected sample size (ie, a larger effect size requires a smaller sample size to achieve the same level of power). The noncentrality parameter (λ) has been established using the following equation:

$$\lambda = f^2(u + v + 1)$$

Where u indicates the *df* for the numerator (ie, the number of independent variables) and v is the *df* for the denominator (ie, *df* of error variance). This parameter is used to measure the magnitude of the treatment effect. It indicates how far the alternative hypothesis distribution is from the null hypothesis distribution. Since it is possible to describe this scenario as a function of the effect size (f^2) and *df*, everything can be rewritten as an *F* test that involves the λ using the following equation [15]:

Where PV_S represents the proportion of Y (ie, a quantitative dependent variable) variance accounted for by some source (S) in the sample, and PV_E represents the proportion of error variance. Finally, the sample size has been calculated as a function of the unknown λ values in terms of the given power (1 – β), u and v values under the significance criteria of .01 and .05, respectively [16].

To account for multiplicity in answering, the sample size was adjusted by incorporating the design effect by considering the intraclass correlation (ICC) and average cohort size (m).

$$n_{adjusted} = n \times \{1 + (m - 1) \times ICC\}$$

The sample size calculation was based on a noncentral *F* distribution, incorporating the noncentrality parameter (λ) to account for the expected effect sizes. The choice of λ was informed by prior studies on the relationship between smoking behaviors, lifestyle habits, and transitions to ATNPs. Specifically, effect sizes were estimated based on the existing literature examining behavioral and health-related changes associated with smoking transitions. Given the variability in expected effects across different lifestyle factors, a conservative approach was taken in setting λ values to ensure adequate statistical power while minimizing the risk of type 2 errors. Sensitivity analyses were also conducted to assess the robustness of the sample size determination under different assumptions regarding effect sizes and ICC. These considerations strengthen the validity of our study design and ensure that the sample is sufficiently powered to detect meaningful associations.

Therefore, the final sample size is presented in Table 1, with a final choice of 9171 responses, corresponding to a reasonable and common ICC value for such situations.

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Table 1. Required sample sizes across various scenarios based on ICC, power (1 – β), and other model parameters using the Shiny application [17].

ICC[a]	m[b]	(1 – β)[c]	u[d]	v[e]	f^{2}[f]	λ[g]	Sample size, n
0.1	200	0.8	30	Inf[h]	0.2	29	3031
0.15	200	0.8	30	Inf	0.2	29	4473
0.15	250	0.8	30	120	0.2	29	5561
0.25	200	0.8	24	Inf	0.2	22.5	5709
0.2	250	0.8	28	Inf	0.2	22.5	5715
0.15	300	0.8	30	Inf	0.2	29	6648
0.25	200	0.8	30	Inf	0.2	29	7359
0.2	350	0.8	20	Inf	0.2	21	7434
0.2	250	0.8	20	120	0.15	23.7	8026
0.25	250	0.8	30	Inf	0.2	29	9171[i]
0.2	500	0.9	20	Inf	0.25	26.1	10,524
0.3	350	0.8	20	Inf	0.2	21	11,098
0.3	250	0.8	20	120	0.15	23.7	11,961
0.4	300	0.8	20	120	0.2	21	12,663
0.3	500	0.9	20	Inf	0.25	26.1	15,733
0.5	300	0.8	20	120	0.2	21	15,802

[a]ICC: intraclass correlation coefficient.
[b]m: average cluster size.
[c](1 – β): statistical power.
[d]u: *df* for the numerator (number of predictors).
[e]v: *df* for the denominator (residual error).
[f]f^2: Cohen effect size index.
[g]λ: noncentrality parameter.
[h]Inf: infinity.
[i]Final sample size used in the study protocol based on the most realistic and conservative assumptions regarding ICC, effect size (f^2), and power. This combination (ICC=0.25, m=250, f^2=0.2, power=0.80) reflects expected values derived from previous smoking behavior studies in similar populations.

Questionnaire

Overview

The questionnaire has been collaboratively developed with a team of experts from the universities of Torino, Padova, and Ferrara, encompassing expertise in areas such as nutrition, biostatistics, data management, and related disciplines. To ensure clarity and comprehensibility, the development process involved interviews and focus groups with smokers, nonsmokers, and former smokers, focusing on both the overall questionnaire and single-term comprehension and interpretation.

The survey is available on the MINERVA project website [18], where ongoing information (eg, the number of participants enrolled and their age and sex) is updated daily.

The questionnaire is organized into various sections. The first section covers sociodemographic details, including information on education, employment status, income, and the number of children and adults in the household.

The questionnaire also addresses lifestyle habits, such as sports and activities and sleep habits. Another section covers information on dietary behaviors, with questions about meal and snack frequency; fruit, vegetable, and fast-food consumption; and alcohol habits. Finally, one section asks about smoking habits, including the frequency of smoking, past smoking habits, and any smoking withdrawals. The survey also examines feelings after smoking. Additionally, a section is dedicated to understanding participants' attitudes and behaviors toward newer nicotine and tobacco products. This includes knowledge and use of specific products, along with habits associated with these emerging products [19]. The questionnaire items regarding the urge to smoke are adapted from the Brief Questionnaire of Smoking Urges [20]. Furthermore, questions on behavioral intention are derived and modified from McCaffrey et al's [21] study on the development and validation of behavioral intention measures for an e-vapor product, covering intentions to try, use, dual use, and switch. Lastly, the evaluation of health habits is based on the Sport, Movement, Eating Habits, Relationships, and Technologies (SMART) questionnaire [22].

Pilot-Testing and Refinement

The first draft of the questionnaire underwent a pilot test with 12 Italian participants. The sample was characterized by a high

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degree of heterogeneity regarding the distribution of responders according to gender, age, income level, residence (urban, suburban, rural), education level, tobacco consumption status (smoker, ex-smoker, nonsmoker), coconsumption of different types of tobacco, and coconsumption of other substances (alcohol, cannabis, etc).

Individual interviews explored participants' comprehension of key definitions within the questionnaire (eg, smoker, ex-smoker, nonsmoker; cigarettes, electronic cigarettes, heated tobacco products, vaping products; up-switching and down-switching between tobacco products; Multimedia Appendix 1).

Individual interviews explored participant comprehension of key definitions (eg, smoker, ex-smoker, nonsmoker; cigarette types; concepts of up-switching and down-switching). Findings from these interviews were then analyzed in a focus group discussion, leading to a series of modifications summarized in Table 2. Following data collection and analysis, a focus group meeting discussed the interview findings and generated suggestions for refining the final questionnaire. Table 2 describes the summary of findings and proposals for modifications highlighted during both interviews and focus groups.

Table 2. Summary of findings from interviews and focus group, and questionnaire modification suggestions.

Findings	Proposals for modifications
Nationality could be misinterpreted when the aim is to stratify questionnaire answers	• Add country of birth, citizenship, and residence
The open question related to family composition could be difficult to analyze	• Modify and add questions related to different relatives (and frequencies), and ask if they smoke. Add a question related to family's annual income
Nonpublic employee	• Change to private employee
Unemployed	• Add a question related to identifying who is actively seeking employment and who is not
Attitude toward smoking is missing	• Add questions related to social acceptance of smoking, happiness related to smoking or nonsmoking, if the participant would like to quit smoking, if he/she has already tried to quit smoking
Regarding health habits, the survey asks which sport he/she is practicing	• This part of the survey should ask at the beginning if the participant is practicing any sport and any agonistic sport • Add to the question a specification related to the current days • Add multiple answers and revise from open question to closed question
Some questions in the lifestyle habit section of the survey seem related only to young participants or students	• Rethink and modify accordingly the questions
There is a section related to sport and the next section is devoted to physical activity	• The survey section related to physical activity should add a definition and the differences between sport and physical activity
The response options regarding the frequency of physical activity seem to report frequencies that are too low	• Add more answers considering more frequent options
Regarding transportation, something is missing	• Add the number of steps recorded in a day and the use of stairs compared to elevators
Regarding the question related to beverages, something is missing	• Consider adding wine, beer, aperitifs, alcohols, and only water
Related to sleep attitudes, the options available are not suitable for those working in shift	• Modify the options
About the influence of sleep on physical conditions, a 4-point Likert may not be able to capture the differences between participants	• Consider using a visual analog scale

Following these refinements, a second pilot test was conducted to validate the adjustments and ensure logical coherence, branching accuracy, and cultural appropriateness. Table 3 summarizes additional modifications implemented based on the second round of feedback.

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Table 3. Summary of findings provided by questionnaire pilot test and suggested modifications.

Findings	Proposals for modifications
Regarding the required description of the family of the participant, it may not be clear if the participant should be included	• In the question, it should be specified that the participant is included in the description
Some ways of consuming tobacco/nicotine are missing, both conventional and unconventional	• Revise the list of tobacco/nicotine products and add sachets
Some branching logic is not working properly	• Recheck branching logics
The order of questions proposed in the survey can be quite confusing because the leading theme is changing too often	• Some questions should be moved through the survey to place them together according to the different themes/sections
Unconventional employment is missing	• Some kinds of unconventional employment should be added
Discussion on adding or removing ethnicity/race	• Remove ethnicity and race
Semantic differences between smoking at home and smoking inside your home	• The survey focuses on smoking at home
No data is collected on feelings after smoking	• A questionnaire on smoking urges has been added
The survey should also address the perception of participants about the consequences	• The Short Form Vaping Consequences Questionnaire has been added
The survey should try to measure the level of dependency of participants	• Penn State Electronic Cigarette Dependence Index
The survey is not able to check if the participant is reading and accepting GDPR[a] information and if the participant was the minimum age for participating	• Add check about reading and accepting GDPR information and the minimum age for participating
The description of different ways of consuming tobacco/nicotine can be improved by providing pictures	• Add pictures
Waterpipe is missing	• Add waterpipe

[a]GDPR: General Data Protection Regulation.

The development of the final questionnaire involved a process comprising the following steps:

1. Compilation: gathering pertinent questionnaires for each section
2. Translation: translating all questions into Italian
3. Curation: selecting only the pertinent questions for each section
4. Focus group: conducting a focus group session
5. Refinement: fine-tuning the questionnaire based on insights derived from the focus group
6. Testing: assessing the prefinal version
7. Further refinement: tweaking the final version based on testing results
8. Backward translation: conducting a backward translation to English of the entire questionnaire

This systematic approach ensures the comprehensiveness, linguistic appropriateness, and effectiveness of the questionnaire, with iterative refinement occurring (Figure 1).

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Figure 1. The phases of questionnaire development.

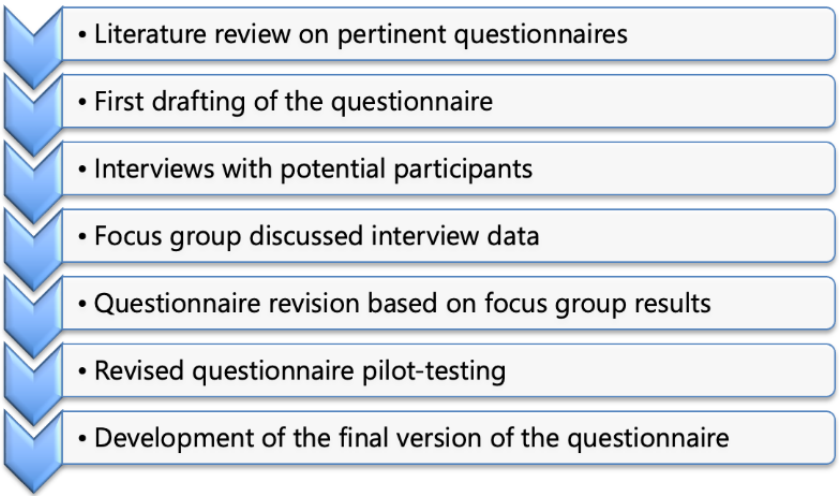

Cultural Adaptation and Cross-Country Comparability

Given the diverse cultural and regulatory landscapes of the participating Mediterranean countries (Italy, Greece, and Turkey), our study acknowledges the potential influence of cultural differences on smoking behaviors and attitudes toward ATNPs. To ensure cultural sensitivity and comparability across populations, linguistic and contextual adaptations were made through multistage expert reviews, focus groups, and interviews involving participants from different cultural backgrounds. Additionally, stratified analyses will be conducted to examine potential variations in smoking behaviors and attitudes across cultural and geographic subgroups. These measures aim to enhance the accuracy and inclusiveness of our findings, providing a comprehensive understanding of the interplay between cultural factors and smoking transitions.

Statistical Analysis

Baseline and demographic characteristics of the study participants will be summarized using medians (IQRs) for continuous variables and absolute and relative frequencies for categorical ones. To examine the associations between smoking habits, dietary patterns, and lifestyle behaviors, univariable and multivariable analyses will be conducted using generalized linear models, with the appropriate distribution selected based on the outcome variables. Confounding variables such as age, gender, and socioeconomic status will be adjusted for using multivariable regression models, informed by prior literature. Interaction effects will be evaluated through interaction terms within models and stratified analyses across demographic subgroups, with likelihood ratio tests used to determine their significance. All analyses will be carried out using R software (R Foundation for Statistical Computing).

Data Collection and Management

Data will be collected using a structured questionnaire administered via LimeSurvey [23]. Once the data is collected, it will be exported in a format suitable for statistical analysis. Data will be securely stored on a private password-protected server with access limited to authorized personnel only. To ensure data security, the server will use encryption protocols and role-based access controls, preventing unauthorized modifications or downloads. Data will be stored in servers located in Western Europe; the data will not be transferred outside of Europe.

Regular backups of the dataset will be made to prevent any loss of data. All data management procedures will comply with GDPR and other applicable data protection and privacy regulations.

Given the longitudinal nature of the study, participant retention and potential changes in behavior over time are key considerations. To address the issue of dropouts, participants who consent to follow-up will be recontacted biannually, with reminders sent by email and social media to encourage continued participation.

Results

The MINERVA study was initiated in June 2023, and data collection is currently ongoing. As of January 2025, the study has enrolled 7535 participants in Italy, with 4862 consenting to follow-up. Preliminary analyses are underway, focusing on sociodemographic characteristics, smoking behaviors, and economic factors. Follow-up assessments will be conducted every 6 months, with results expected to be published at the end of 2025.

Discussion

This protocol outlines the methodology for investigating the association between smoking behaviors, lifestyle factors, and dietary habits, with a particular focus on transitions between conventional tobacco products and ATNPs. By using a longitudinal multicountry approach, the study aims to provide valuable insights into behavioral patterns and factors influencing smoking transitions.

The existing literature highlights the complex interplay between smoking cessation and sociodemographic characteristics. However, gaps remain in understanding how lifestyle factors, particularly dietary habits, influence the use of ATNPs and long-term smoking behaviors across diverse populations [24]. Compared to previous cohort studies, this approach improves

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the ability to capture trends over time and identify predictors of change in smoking behavior.

A key strength of this study is the use of social media–based recruitment and snowball sampling, which facilitates access to diverse populations while ensuring cost-effective and scalable data collection. However, selection bias is a potential limitation, as individuals with higher engagement in digital platforms may be overrepresented. To mitigate this, recruitment strategies will aim to reach a broad demographic, and follow-up analyses will assess the generalizability of findings. Furthermore, self-reported data can introduce recall or social desirability biases; however, the longitudinal design helps to track changes within individuals over time, reducing potential inaccuracies.

Understanding the lifestyle dangers associated with both traditional smoking and ATNPs is essential for public health efforts. Ongoing research is needed to further assess the health risks of ATNPs and to inform evidence-based policies and interventions. Although less harmful than traditional smoking, ATNPs are not without potential risks, and it is important to continue research efforts to fully understand the long-term health implications of ATNPs and to inform evidence-based policies and interventions [11].

Data Availability

The datasets analyzed during this study will be available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guide for questionnaire development.
[PDF File (Adobe PDF File), 45 KB - resprot_v14i1e67163_app1.pdf]

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Abbreviations

ATNP: alternative tobacco and nicotine product
ICC: intraclass correlation
MINERVA: My Changing Lifestyles Our Research and Everyone Health
SMART: Sport, Movement, Eating Habits, Relationships, and Technologies

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Protocol

Social Media Marketing of Non-Evidence-Based Women's Health Interventions: Protocol for a Content Analysis Using Participatory Research Methods

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Abstract

Background: The promotion of non-evidence-based health interventions to women on social media is a growing problem.

Objective: This study aims to explore the use of social media to disseminate and promote health interventions that lack robust evidence and are of current interest and popularity.

Methods: A content analysis of posts on TikTok, Instagram, and Facebook about 5 health interventions targeted at women will be conducted using participatory research methods with consumers. English-language posts that discuss boric acid suppositories, fertility testing, perimenopause and menopause testing, supplements and hormone treatments for menopause, and menopause hormone therapy for disease prevention will be included. Using keyword searches related to each health intervention, consumers will screen the top posts until 100 eligible posts on 2 different social media platforms are identified (1000 posts total across the 5 health interventions). Data from the post's caption, on-screen text, and audio and/or video will be included in the analysis. The analysis of these posts will take both a deductive approach using a prespecified framework and an inductive approach, generating key themes from the post content.

Results: Data on TikTok, Instagram, and Facebook have been searched and screened. Development of the coding framework and analysis is now underway. The findings will be disseminated via publications in peer-reviewed international medical journals and presentations at national and international conferences in 2025 and 2026.

Conclusions: This novel study will provide important insights into how information on various women's health interventions and products, which currently lack robust evidence of benefit, are being disseminated and promoted on social media to women. Understanding this is essential for developing strategies to mitigate potential harm and plan solutions, thus protecting women from the low-value interventions marketed to them, becoming patients unnecessarily, and taking finite resources away from the health care system.

International Registered Report Identifier (IRRID): DERR1-10.2196/76750

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(JMIR Res Protoc 2025;14:e76750) doi:10.2196/76750

KEYWORDS

social media; women's health; evidence-based medicine; overdiagnosis; content analysis; participatory research methods

Introduction

Background

It is now widely acknowledged that the public and patients alike are turning to social media for health information [1]. Conveying health information on social media has both positive and negative impacts [2,3]. Social media, when used as a public communication channel by reliable sources such as health agencies, nongovernmental organizations, health professionals, and communities with chronic health conditions, typically provides greater access to important health information [4]. However, recent studies found stark differences in the accuracy of women's health information across social media [5,6], and the accuracy of information can depend on the creator and their credentials [7]. While different platforms claim to regulate health information, current international regulations may not be geared to respond to the challenges posed by claims and marketing on social media [8,9]. Influencers and companies share health information with their audiences, even though they may not necessarily have relevant knowledge or qualifications to do so, and deliberate agendas for both mis- and disinformation exist. This increases the risk that the information they share can be misleading, incomplete, or inaccurate. Many individuals or companies also have financial conflicts of interest, which can further complicate the quality and neutrality of information [10]. In 2024, influencer marketing drove social media to become the world's leading advertising channel, including the sale of health and wellness products, reaching almost US $250 billion in sales [11].

One particular area of concern for the dissemination of health information on social media is women's health [12]. Women's health has historically been underfunded and underresearched, meaning that large knowledge gaps still exist [13]. In lieu of evidence, influencers, alternative medicine practitioners, and companies are now attempting to fill this space, and social media provides a platform that facilitates the rapid and broad spread of information. Some influencers on social media, including highly influential celebrities with substantial numbers of followers, even have their own women's health brands or businesses, or have vested interests in the interventions. This makes the landscape for sharing health information on social media even more complex because influencers receive significant financial incentives to promote the brand by strongly affirming any underlying health claims [14]. Recent examples include actress Gwyneth Paltrow with her Goop Lab products [15], media personality Kourtney Kardashian's lemme vagina probiotics [16], and the ZOE app for menopausal women [17], which claims to be based on "world-leading science" and has been highly promoted by British television presenter Davina McCall. All of these examples, despite having no robust evidence of health benefits, are successful and seemingly popular among female consumers. However, there is still little evidence on how women's health interventions, such as these, are being marketed to women on social media.

This Study

While previous studies have explored women's health information on social media [5,6], to the best of our knowledge, none have comprehensively analyzed the content and frequency of posts about non–evidence-based health interventions promoted to women and are of interest to women of different ages or life stages. Our team recently analyzed how commercial interests co-opt narratives in women's health to promote non-evidence-based interventions [18]. However, our earlier article did not address the way social media—via influencers, celebrities, and influential companies may endorse or promote non–evidence-based women's health interventions, making it even more difficult for women to know what information is valid and to avoid low-value care [19].

The overarching aim of this study is to explore how social media is used to disseminate and promote health information and sell health products to women, with a specific focus on 5 health interventions that lack robust evidence and are of current interest and popularity. Specifically, this study will assess how balanced the posts are in the discussion of the benefits, harms, and caveats of the intervention; the use of evidence, anecdotes, or appeal strategies in the posts; and whether the financial interests of account holders exist.

Methods

Study Design

A content analysis [20] of social media posts on 5 women's health interventions will be conducted using participatory research methods with consumers. This approach strengthens the research process and improves the effectiveness and relevance of study outputs to women. Using social media platforms (TikTok, Instagram, and Facebook), we will analyze what and how information on these specific interventions is being disseminated and marketed to women. Shorter-content platforms, including TikTok, Instagram, and Facebook, are used because this type of short-form content continues to grow in popularity across all age groups [21]. The study methods follow those of a recent study using content analysis to analyze posts about health tests on social media [22,23], adapted and tailored to address the research aims and questions as outlined earlier, in partnership with consumers. Consumers are women from a diverse consumer panel (Co-SHeLL) [24] based in Australia. Consumers provide a broad range of perspectives to the study, reflecting their age and social media experience. Researchers approached the panel to assess female panel members' interest in being involved as part of the study team, including contributions to the study design, data collection, analysis, and interpretation of the study results. Consumers were compensated AUD $50 (US$32) per hour for their time and will be offered authorship for any resulting empirical publications.

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Eligibility Criteria

English-language posts about the selected interventions were included from accounts on TikTok, Instagram, and Facebook. Each intervention included 2 platforms based on user statistics for the age group where the intervention is typically discussed and marketed, as well as the project's consumer use preferences. The selected interventions met the following criteria: (1) evidence-based concerns that these interventions reflect low-value care (ie, the intervention does not lead to improved health outcomes for generally healthy women and may lead to harm or waste, or reduce the uptake of high-value care) and (2) currently being promoted to generally healthy women on social media. Text-only posts, images, infographics, and videos, including reels, and audio-only posts that explicitly discussed the health intervention in question were all included.

In consultation with consumers of various age ranges identifying what health topics they regularly see on their social media feeds and querying whether certain interventions with no evidence of benefit appear on their feeds, the 5 interventions included: boric acid suppositories to maintain vaginal health, fertility testing, perimenopause and menopause testing, supplements and hormone treatments for menopause, and menopause hormone therapy for disease prevention.

Included Women's Health Interventions

Boric-Acid Suppositories

Boric acid suppositories are marketed on social media as a vaginal health product designed to cleanse and refresh after menstruation, balance pH levels, improve vaginal taste and odor, and prevent and treat yeast infections or bacterial vaginosis [25]. Although boric acid has antibacterial and antifungal properties [26], there is little to no evidence to support these broader claims [26]. In fact, research states that vaginal boric acid suppositories should not be considered a preventive measure [26] and are only recommended as second-line treatment in specific cases of recurrent bacterial vaginosis or treatment-resistant yeast infections [27]. For example, in the United States, it is not a Food and Drug Administration–approved drug [28]. Despite this evidence, many women believe that boric acid is approved and is a natural, effective way to maintain vaginal health [28]. Negative cultural rhetoric that female genitalia are odorous, unattractive, unclean, or a cause for concern [29] may cause boric acid suppositories to be overused in an attempt to self-medicate or prevent perceived problems [28,30]. As there are a considerable number of vaginal boric acid suppository internet retailers [30], this is of particular concern for young women still developing an understanding of their bodies and body image [31], while navigating various influences from social media [32,33] and the new responsibility of making independent health decisions. Boric acid suppositories can cause abnormal discharge, burning, itching, inflammation, and heightened susceptibility to infection [25,29,34] or potentially delay appropriate medical care by masking other issues [30].

Fertility Testing

So-called "fertility" tests claiming to predict women's fertility potential are increasingly being promoted by companies and influencers on social media. These tests can include measuring a range of different hormones, including biomarkers of ovarian reserve, such as the anti-Müllerian hormone or follicle-stimulating hormone. Many of these blood tests can now be ordered online and performed at home without a previous consultation with a physician. Although routinely used when undergoing fertility treatment to inform drug treatment protocols, these tests cannot predict a woman's chance of conceiving, time to pregnancy, or reproductive timeline [35]. Despite lacking diagnostic value, online companies are increasingly selling these tests to women who have not even tried to become pregnant, capitalizing on their anxiety about their fertility [36,37]. Harms that can result from inappropriate testing include unnecessary anxiety about their ability to conceive, sometimes pressuring women to conceive before they are ready, or spending large amounts of money to freeze their eggs [38]. Conversely, it can also lead women to experience a false sense of security about delaying pregnancy.

Perimenopause, Menopause, and Postmenopause Products

Overview

Menopause—typically occurring between the ages of 45 and 55 years—is a normal event for women, characterized by the permanent end of the menstrual cycle caused by the cessation of reproductive hormone production in the ovaries. Before the final period, women undergo a phase of fluctuating ovarian function and hormone levels, known as perimenopause, which generally lasts for several years and may involve menstrual cycles with prolonged or heavy bleeding. Symptoms of menopause vary, but common symptoms include vasomotor symptoms (hot flushes and night sweats) and vaginal dryness. Growing awareness and broadening of acknowledged symptoms could represent positive strides for women's empowerment and health [39]. However, this awareness has also given rise to a lucrative market for menopause-related products and treatments marketed directly to women on social media.

Perimenopause and Menopause Testing

Guidelines recommend that "Women over 45 years presenting with menopausal symptoms are diagnosed with perimenopause or menopause based on their symptoms alone, without confirmatory laboratory tests" [40], as there is no proven benefit to testing. However, biochemical testing and imaging are commonly promoted and undertaken—both through home testing kits and in clinical settings—to identify a woman's menopausal status [41], despite guidelines recommending against such practices. Although such tests may be appropriate in women aged less than 45 years, for example, if premature menopause is suspected or other causes of oligomenorrhea or amenorrhea are excluded, they are considered unreliable, unnecessary, and costly for most women [42].

Menopause Treatments

Menopause treatments advertised on social media include supplements, dietary recommendations, estrogen gels, lifestyle coaching, and more conventional hormone therapies. Although conventional hormone therapies have proven effective in alleviating vasomotor symptoms, they are continuously

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advertised for alleviating other symptoms, such as weight gain, skin dryness, brain fog, and fatigue, for which robust evidence of their effect is lacking [43]. Hormone therapy is also marketed to women beyond what is recommended, potentially leading to unsafe use with serious side effects, such as increased risk of cardiovascular disease, cancer, and dementia [44]. For example, systemic hormone therapy (as opposed to topical therapy) is ineffective for the urinary symptoms of menopause and may in fact worsen the symptoms [45]. Furthermore, women are advertised topical progesterone creams and gels, despite no evidence to support their absorption through the skin [46]. Concerns have been raised about misleading claims regarding the safety and effectiveness of such products, as well as their potential to encourage women to bypass consultations with health care professionals when making treatment decisions [47,48].

Menopause Hormone Therapy for Disease Prevention

Women in their 60s are increasingly using social media [49], leading to increased exposure to fear-based messaging surrounding menopause and its long-term health impacts. Many influencers are promoting the use of hormone therapy not specifically to treat symptoms but for the prevention of dementia and cardiovascular disease, despite no reliable evidence [50] and no guideline recommendations to support the use of hormone therapy for this purpose [40,51]. Such treatment is associated with a long list of side effects and long-term harms, including risk of cancer and cardiovascular adverse events, as well as mood swings and irregular bleeding [52]. Thus, receiving hormone therapy to prevent future diseases is likely to have minimal health benefits and could be dangerous to women's health.

Data Collection

Consumer partners (1-2 across 5 age groups, ie, 20, 30, 40, 50, and 60 years relevant to each intervention target) based in Australia conducted keyword searches using their personal smartphones or tablets. To help account for the impact of the consumer's previous search history and other social media accounts, consumer partners used new accounts matched to their gender and age, created for this study on 2 platforms (TikTok, Instagram, or Facebook). Keywords (Multimedia Appendix 1) related to the intervention were chosen based on the published literature for each health intervention and in consultation with consumers, and then refined through piloting on the social media platforms. The consumers searched using the keywords and then browsed the "For You"-style feed for the top posts, as displayed by the platform, until 100 eligible posts for each intervention on each platform were captured (200 posts total for each intervention). The sample size of the included posts is based on the concept of information power [53] and follows other health- and medical-related social media content analyses using manual searching and coding [22,23]. Posts were bookmarked (TikTok) and saved (Instagram and Facebook) in folders that were included and excluded on the platform. One researcher per intervention then screened the included and excluded posts for eligibility, and a second researcher checked if any disagreement arose between the consumer and the researcher. The links to the eligible posts were then extracted into Microsoft Excel.

Data collected about each social media post includes characteristics such as date posted, type of post (direct advertisement vs not), credentials of the account (eg, influencer or company with expertise health professional or company vs non–health professional), number of followers (ie, nano, micro, macro, midtier, or mega influencer), engagement cues (eg, views, likes, and comments), and target audience, if applicable.

In line with the study aims, we will also collect any information in the post that was related to the intervention's benefits, harms, and caveats, use of relevant evidence, anecdotes, appeal strategies (eg, logos, pathos, and ethos), or narratives (eg, feminism, early detection, wellness, responsibility or moral imperatives), and financial interests of the posts account holders. Specific information relevant to each health intervention was also captured (eg, reference to specific evidence or claims made).

One to 2 weeks following the initial search and screening process, consumers logged into the account again and looked through the first 100 posts on the "For You" page on each platform. They then bookmarked (TikTok) or saved (Instagram and Facebook) any additional content related to the intervention in a separate folder [54]. The purpose of this step was to investigate whether the social media platform's algorithm presented further content on the topics previously searched. As before, the captured posts were then discussed between the researchers to confirm inclusion and exclusion. The additional included posts will not be analyzed further.

Data Analysis

All data from the post's caption, on-screen text, and audio or video will be included in the analysis. The analysis will take both a deductive approach using a prespecified framework and an inductive approach, with independent extraction and review of the data undertaken by researchers and consumers to develop a list of recurring themes. The framework aligns with the study's objectives of understanding how information about the above health interventions will be disseminated and promoted on social media by capturing post and influencer characteristics, references to specific health interventions, the use of scientific and medical claims, and persuasive techniques. The coding tool has been thoroughly tested for reliability and comprehensiveness and is informed by key domains and analysis of other coding tools used in previous media reporting and social media studies [22,23,55,56]. Two researchers will independently apply this coding tool to all the posts (in Microsoft Excel with preset responses, eg, yes, no, or unclear), with any discrepancies discussed and resolved through consensus, consulting a third researcher if necessary. On the basis of our experience with other similar social media content analyses [23], we will not calculate and report the interrater reliability (Cohen κ). As we expect the data to be highly imbalanced for the discussion of the benefits, harms, evidence, etc. (eg, discussion of benefits: 95% yes and 5% no or unclear), this will make the κ unstable and can underestimate true coder agreement [57].

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Previous content analyses of social media have revealed novel perspectives and marketing strategies for health and medical tests [22,23]. This suggests the potential for a supplementary qualitative analysis of the posts to be included in this study. Following an initial familiarization phase to understand the dataset as a whole and its components as per the content analysis described above, the researchers will identify additional preliminary themes for each topic [58]. This will involve inductive qualitative coding of the posts, with preliminary themes identified organically; consumer perspectives will also be sought to help uncover new perspectives. The inductively identified preliminary themes will be applied to a subset of the data by several members of the team with iterative revision to refine the list. Once finalized, these themes will be added to our deductively defined, prespecified framework with the entire dataset double-coded, as described earlier. The coded data will be analyzed using a narrative approach, with frequencies for each category and theme calculated. Illustrative quotes will be included to contextualize the findings [59].

Patient and Public Involvement

Eight consumer partners (1-2 per intervention) are involved in this research. In addition to providing valuable input into the health interventions selected for analysis, they have conducted the searches and will provide input into the analysis and interpretation of the findings. We aim to share a lay summary of the study findings with health consumer groups for dissemination in the wider community.

Ethical Considerations

This study uses unequivocal public data. Data will be largely reported in aggregate form; however, in cases where specific excerpts (eg, quotes) are reported as examples, as is typical with the content analysis method [20], these will be short (eg, a few lines) and nonidentifiable (eg, no personal or professional information or reference will be given). Ethics approval for the study was obtained from The University of Sydney Human Research Ethics Committee, with a waiver of consent granted (2024/HE001041) because of the nonidentifiable nature of the data in any resulting publications.

Results

Progress to Date

Up to 1000 posts across all 5 interventions on TikTok, Instagram, and Facebook were searched and screened (from March to May 2025). One to two weeks after the initial search, an additional 500 posts (100 across each intervention) were screened for further content. Analysis is now underway.

Dissemination

The findings will be disseminated via publications in peer-reviewed international medical journals and presentations at national and international conferences in 2025 and 2026. Deidentified datasets will be made available as per the publishing journals' requirements or upon reasonable request to the study team.

Discussion

Anticipated Results

This study will provide novel insights into how information on various women's health interventions and products, which currently lack robust evidence of benefit, are being disseminated and promoted on social media to women across their lifespan. Although it is acknowledged that the marketing of health interventions, including tests, treatments, and medical devices, currently exists on social media [23,60], specific data on how and by what means this are being disseminated to women across their lifespan are scarce.

This study has important strengths. The use of content analysis combines qualitative and quantitative methods to examine the content and context of social media posts, offering both structured and comprehensive insights into how 5 discrete and topical women's health interventions are being marketed to women. This may then be extended to other non–evidence-based women's health interventions. The analysis may also provide insights into how the algorithm feeds women this type of health information. In addition, consumers of various sociodemographic characteristics, including age, are involved in the study design, data collection, and interpretation of the study findings. Study limitations include the reliance on a small number of search terms to identify the study sample of posts about each intervention. The cross-sectional nature of the study means that we will only capture data at one time, and as is the case with all social media research, the timing of the search limits the reproducibility of the study findings. In addition, as noted in the Methods section, statistical tests of the interrater reliability (eg, κ) will not be calculated because of the expected instability of this measure in our study, which may affect the assessment of coding consistency across researchers. Instead, the reliability will be assessed manually, with any discrepancies discussed and resolved. Although there were no country restrictions on the included posts, they had to be presented in English. Furthermore, post comments and replies will also not be analyzed, which may miss additional information, including how potential misinformation is received, endorsed, or challenged. However, this is not the aim of our study and could be examined further in separate studies.

Conclusions

Promotion of non-evidence-based health interventions to women on social media is a growing problem. Understanding the extent of the problem and the specific marketing strategies used is essential to develop approaches to mitigate potential harm and plan solutions. Findings from this study will provide information that may help women become aware of the issue and resist being unduly influenced or pressured by the marketing of low-value interventions. It will also provide the first comprehensive evidence on how non–evidence-based women's health interventions are marketed across the lifespan using current examples on social media, which may help to inform health regulators of misleading marketing. Together, this will protect healthy women from becoming patients unnecessarily. This work will also help to minimize overuse, which takes health

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care resources from those in genuine need, threatening the sustainability of health systems.

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Data Availability

Data sharing is not applicable to this study as no datasets were generated or analyzed during this study.

Authors' Contributions

BN, TC, and K McCaffery conceived the study idea. BN, TC, EG, JH, CH, K McFadden, KP, JS, MT, AG, BF, and K McCaffery designed the study, with all authors and consumer partners providing input into the design. BN, TC, EG, JH, CH, K McFadden, KP, JS, MT, and AG reviewed the literature on the health interventions. BN, TC, EG, JH, CH, K McFadden, KP, JS, MT, and AG drafted the manuscript, and all authors revised the manuscript.

Conflicts of Interest

BN, EG, and K McCaffery are current members of the International Scientific Committee of Preventing Overdiagnosis. TC is a former member. K McCaffery is a codirector of Health Literacy Solutions Pty Ltd. The Health Literacy Editor is a research tool owned by the University of Sydney. It is sublicensed to Health Literacy Solutions Pty Ltd to enable wider public use. K McCaffery receives no personal income from Health Literacy Solutions Pty Ltd or the Health Literacy Editor. All other authors declare no conflicts of interest.

Multimedia Appendix 1
List of keywords used to search each women's health intervention.
[DOCX File , 25 KB - resprot_v14i1e76750_app1.docx]

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Protocol

Access to a Newly Adapted Diabetes-Specific Multimodal Cross-Sectoral and Interdisciplinary Psychotherapeutic Care Option for a High-Risk Group of Patients With Diabetes Mellitus and Distress: Protocol for the minDBe Pilot Study

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Abstract

Background: Diabetes is a chronic disease requiring daily self-management to regulate physiological parameters like glycemic control. Despite extensive training being available, most patients with diabetes do not meet their target blood sugar levels. Moreover, diabetes-related emotional distress and psychological burden in the form of depressive and anxiety symptoms are very common. Patients with these challenges represent a high-risk group in terms of increased morbidity, mortality, and health care costs as well as decreased quality of life. Hence, in addition to somatically focused standard care, this patient group requires specific treatment options that also address psychosocial aspects. However, these treatments are often not available in routine care. Psychosomatic outpatient clinics (PsIAs) could address this gap by offering multimodal and integrative treatment. However, the indication for treatment in PsIAs and the referral pathways for patients with diabetes from practices or diabetes clinics to PsIAs remain complicated. Moreover, specific treatment options must be adapted.

Objective: This study aims to assess the needs for referral pathways to PsIAs from the patient and service provider perspectives and to adapt the already effective psychosomatic intervention psy-PAD for a group setting (psy-PAD_{Group}), fitting the multimodal PsIA structures.

Methods: This pilot study comprises an explorative qualitative design based on a multilevel approach, using 2 work packages: work package 1 assesses the patient perspective (n=40) using focus groups, as well as the service provider perspective with interviews (n=30). Work package 2 comprises an expert workshop with clinicians and patient representatives (n=10) to adapt the psy-PAD_{Group} manual for the modalities of PsIAs. We will audio-record the patient focus groups and service provider interviews. The audio recordings will be transcribed and analyzed using content analysis within the framework of interpretative text evaluations with MAXQDA.

Results: Outcomes will be (1) the needs regarding referral pathways, (2) short questionnaires to economically assess the acceptance and feasibility of the referral pathways in preparation for the minDBe main study, and (3) the adapted psy-PAD_{Group} intervention for an interdisciplinary multimodal treatment option to be implemented in the structures of PsIAs.

Conclusions: The minDBe pilot study will lay the foundation for the minDBe main study, which aims to evaluate the psy-PAD_{Group} as part of an interdisciplinary multimodal psychotherapeutic treatment program in a randomized controlled trial.

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KEYWORDS

glycemic control; psychological burden; mixed methods; patient perspective; service provider perspective; multimodal treatment

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Introduction

Background

Diabetes mellitus is a highly prevalent, chronic, noncommunicable disease with a global prevalence of 6.2% and 10% in Germany [1,2]. Among other considerations, maintaining quality of life and preventing diabetes-associated secondary diseases is a central goal in diabetes treatment. To achieve this goal, daily diabetes self-management is required to keep glycemic control (hemoglobin A_{1c}; HbA_{1c}) close to or lower than 7.5% [3]. However, in Germany, around 40% of patients with type 1 diabetes and 58% of patients with type 2 diabetes do not achieve their target HbA_{1c} values [4], despite comprehensive diabetes training and structured disease management programs being available.

Factors that have been associated with poor glycemic control are psychological burden as well as diabetes-related distress [5]. A bidirectional relationship between diabetes and depressive and anxiety disorders is widely established [6-9]. Depressive disorders were significantly higher in patients with diabetes compared to those without (type 1: 22% vs 13% and type 2: 19% vs 11%) [10]. The risk of developing anxiety disorders and elevated anxiety symptoms is twice as high for patients with diabetes compared to individuals without diabetes [11]. Moreover, patients with diabetes often experience diabetes-related distress, defined as the general emotional distress of managing diabetes as well as specific diabetes-related worries [12]. While to a certain extent it overlaps with depressive symptoms, diabetes-related distress is a clearly delineated construct [13]. Both depressive and anxiety symptoms and diabetes-related distress are associated with problematic self-management, a lower quality of life, and poor glycemic control [5,13-17]. In addition, they are linked to an increased risk of secondary diseases and diabetes-associated complications [14,18], premature mortality [17,19], as well as significantly increased health care costs [20]. Hence, psychosocial aspects of diabetes are increasingly coming into treatment focus [21].

Given the close association between poor glycemic control, psychological burden, and diabetes-related distress, various studies tried to address this issue by applying psychological, psychotherapeutic, and psychopharmacological interventions to improve both psychological burden on the one hand and somatic outcomes such as glycemic control on the other hand. While some studies have indeed shown the effectiveness regarding psychological outcomes, there are heterogeneous results regarding their effectiveness for glycemic control [22-24]. These findings emphasize that treating psychological burden alone does not generally have a positive effect on glycemic control. Hence, general interventions not considering diabetes-specific challenges, such as diabetes-related distress, do not seem to be enough to improve glycemic control as well. Moreover, addressing psychological burden and somatic specifications (including diabetes-related distress) as part of an integrative treatment seems promising [25]. Internationally, integrative treatment approaches that allow for access to structured, interdisciplinary care concepts integrated into primary care have already proven to be effective for patients with diabetes in reducing psychological burden and also glycemic control [26].

In Germany, neither integrative treatment options with access to structured interdisciplinary care nor interventions addressing psychological burden and diabetes-related distress are usually available in standard routine care. Patients with diabetes are mainly treated by their general practitioner, by their diabetologists, or in specialized diabetes clinics, while individuals with psychological burden usually seek treatment in psychotherapeutic settings (inpatient clinics, day care clinics, or outpatient psychotherapist practices) [27]. This implies that most patients with diabetes receive either somatic or psychotherapeutic treatment, which are not aligned with each other (even if they are received simultaneously). Against the background of this fragmented health care landscape, which generally represents a challenge in the treatment of different patient groups, psychosomatic outpatient clinics (PsIAs) were newly implemented in 2019 in Germany. PsIAs are outpatient treatment options that do not require inpatient or day clinic stay but allow for a higher treatment intensity normally found in inpatient settings. They comprise complex treatment options integrating highly specialized multiprofessional treatment addressing both somatic and psychosocial aspects as well as disease-specific challenges. About the specific requirements of a certain patient group, for example, patients with diabetes, PsIAs can offer indication-specific services that are part of a multimodal and interdisciplinary treatment. A recent randomized controlled trial using an integrated psychosomatic treatment program for patients with diabetes (the psy-PAD intervention) could show effectiveness for this patient group regarding poor glycemic control as well as diabetes-related distress [25]. PsIAs offer the opportunity to implement such an intervention while also offering a more comprehensive multimodal, interdisciplinary, and integrated treatment setting.

Challenges and Objectives

However, for such an implementation, numerous challenges arise. For one, specific adaptations of such a treatment option are necessary to fit the structures of PsIAs. Moreover, the referral pathways to PsIAs pose a challenge, as various specialists are involved. Patients with diabetes need to be identified to also experience psychological burden and diabetes-related distress (usually during standard somatic care by diabetologists), and moreover, they actually need to be diagnosed with a mental disorder by a specialist (usually as part of an additional appointment with a medical specialist for psychosomatic medicine, psychiatry, or psychotherapy). However, such referral pathways are not yet established, and more, they are especially difficult to follow due to the predominantly somatic understanding of their disease. Against this background, the minDBe pilot study has 2 aims. First, developing referral pathways to PsIAs and short questionnaires to economically assess the feasibility of these referral pathways, and second, adapting and further developing the already tested and manualized psy-PAD intervention [25] addressing patients with diabetes and poor glycemic control as well as diabetes-related distress for a group setting (psy-PAD_{Group}).

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Methods

Study Design

The minDBe pilot study comprises a complex intervention by integrating different methodological approaches. Against the background of the medical research council framework published by the UK Medical Research Council [28], the minDBe pilot study encompasses an explorative qualitative research design based on a multilevel approach (patients and service providers) in 2 work packages (Figures 1 and 2). Work package 1 addresses the needs for referral pathways to PsIAs from both the patient and the service provider perspectives. It aims to develop short questionnaires to economically assess the feasibility of these referral pathways in preparation for the upcoming minDBe main study. The patients' and service providers' needs regarding the implementation of a diabetes-specific care option within PsIAs, as well as the referral to PsIAs, will be qualitatively examined with patient focus groups and service provider interviews, respectively. The focus will be on acceptance, feasibility, barriers, and facilitators.

Work package 2 aims to adapt the psy-PAD intervention into the group intervention psy-PAD_{Group}, as a part of the multimodal interdisciplinary setting of PsIAs. Hence, an expert workshop with clinicians from diabetology, psychosomatic medicine, and (psychological) psychotherapy, as well as patient representatives, will be conducted to discuss and adapt the psy-PAD_{Group} manual with a special focus on group psychotherapy aspects. The patient perspective assessed in work package 1 will directly inform the adaptation of the group intervention psy-PAD_{Group}.

Figure 1. Inclusion of the work packages and the planned feasibility and main study in the medical research council framework. psy-PAD group: psy-PAD for a group setting.

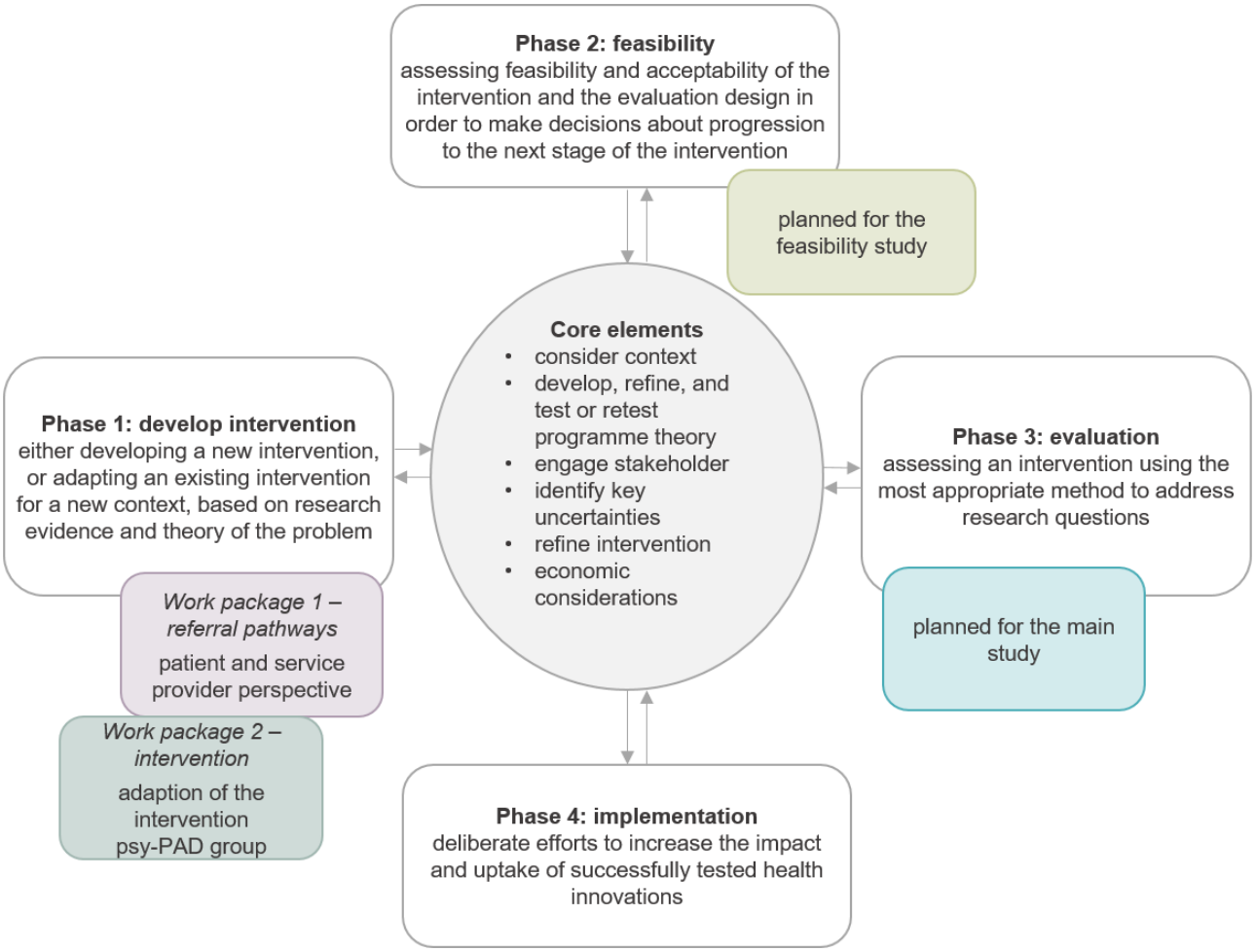

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Figure 2. Study design—overview of the 2 work packages in the overall project and the allocation of the methods used. psy-PAD group: psy-PAD for a group setting.

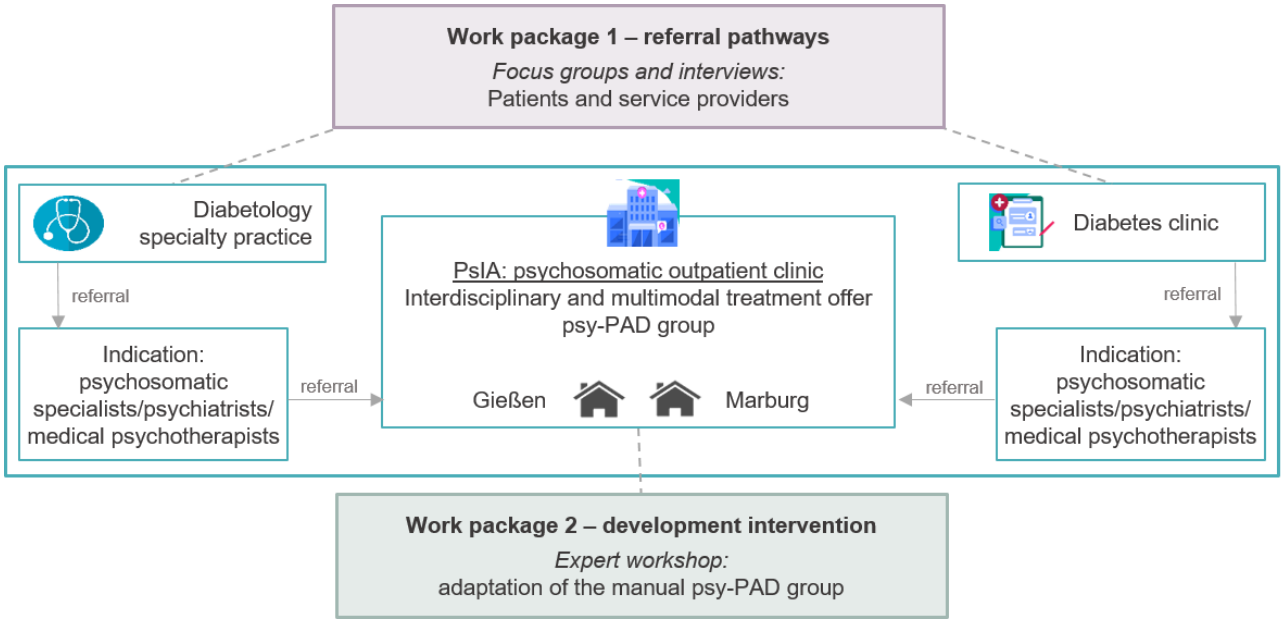

Inclusion and Exclusion Criteria

Work Package 1: Patient Perspective

Patients aged between 18 and 69 years with a medically diagnosed type 1 or type 2 diabetes, an HbA_{1c} ≥7.5%, as well as pronounced diabetes-related distress (determined using the 5-item Problem Areas in Diabetes Questionnaire–short form with values≥11 [29] or clinical impression) will be included in the study to participate in the focus groups. Moreover, sufficient German language skills and cognitive abilities as well as written informed consent to participate in the study, are required. Exclusion criteria comprise a diagnosed type 3 diabetes or gestational diabetes, and severe comorbid diseases (eg, current oncological diseases that modify the indication for HbA_{1c}). Patients will be excluded from the study in case of significant limitations for study participation, for example, dementia, severe depressive episode, psychosis, addiction, being bedridden, or the need for caregiving.

Work Package 2: Service Provider Perspective

Physicians or psychologists working in a diabetes clinic or in an outpatient practice specializing in diabetes will be included in the study to participate in the interviews (psychologists are generally present in diabetes clinics but not in outpatient practices). As it can also be assumed that, in outpatient practices, medical assistants will be involved in any referral processes (eg, handing out a screening form or the referral to established psychosomatic specialists, psychiatrists, or medical psychotherapists), they will also be interviewed about their needs regarding referral pathways. In a diabetes clinic, it is more likely that administrative staff will be involved in the referral pathways; hence, they will be included (independent of profession) to record their needs regarding the referral pathways to PsIAs.

Work Package 2: Expert Workshop

Persons will be included as experts if they belong to the physician or psychologist professions and have a special expertise in diabetology, psychotherapy, or group psychotherapy; have the status of an official patient representative; or experience diabetes themselves while being designated by patient self-help groups to represent the patient perspective.

Sample Size

Work Package 1: Patient Perspective

The planned sample size of the focus groups results from empirically based recommendations for qualitative studies based on focus groups, which postulate a minimum sample size of 40 to achieve saturation [30]. Therefore, 4 focus groups of 10 (25%) patients each are planned.

Work Package 1: Service Provider Perspective

The planned sample size of the service provider interviews is set at 30. This is based on empirically founded recommendations postulating 22 to 24 as the minimum sample size to achieve saturation in individual interviews [31]. Due to the inclusion of various professions, we aimed to conduct 30 interviews: 16 physicians (53%), 4 psychologists (13%), 4 medical assistants (13%), and 6 administrative staff members (20%).

Work Package 2: Expert Workshop

For the expert workshop, the planned sample size is set at 8 clinically and scientifically active physicians or psychologists and 2 patients or patient representatives.

Recruitment and Data Collection

Work Package 1: Patient Perspective

Patients with diabetes will be recruited from specialized diabetes clinics with a flyer containing information regarding the minDBe

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pilot study or by being actively asked to participate by the clinic staff.

Work Package 1: Service Provider Perspective

Service providers will be recruited from specialized diabetes clinics, outpatient practices specializing in diabetes, as well as quality circles for psychodiabetology.

Work Package 2: Expert Workshop

Clinically and scientifically active physicians and psychologists as well as patients or patient representatives will be recruited from the professional networks and quality circles for psychodiabetology as well as patient initiatives and associations for individuals with diabetes.

Assessment and Data Analysis

Work Package 1: Patient Perspective

To assess the patient perspective, focus groups will be conducted based on a semistructured interview guideline. The interview guideline will cover the following topics: (1) current challenges in diabetes treatment, (2) needs and barriers regarding diabetes treatment, (3) referral pathways to PsIAs, and (4) needs regarding the new intervention psy-$PAD_{Group.}$ Each focus group will have a duration of 45 minutes and will be audio recorded.

Work Package 1: Service Provider Perspective

To assess the service provider perspective, interviews will also be conducted based on a semistructured interview guideline. For each service provider profession, a slightly edited interview guideline will be applied. The main topics comprise (1) psychological burden in patients with diabetes, (2) needs and barriers regarding psychological treatment for patients with diabetes, and (3) referral pathways to PsIAs. Each interview will have a duration of 20 to 25 minutes and will be audio recorded.

The audio recordings of both the patient focus groups and the service provider interviews will be transcribed by a professional commercial third party and analyzed using content analysis within the framework of interpretative text evaluations with MAXQDA. In this form of analysis, according to Kuckartz [32], the material is systematically described with regard to the individual categories, which are defined in connection with the research question and differentiated in the course of the analysis, with a particular focus on text comprehension and text interpretation. With the support of the MAXQDA analysis software, a deductive coding and summary of the first overarching main themes is carried out. During the development of the category system, the previously formed main themes are inductively expanded (from the data) by 2 raters, consensually agreed and supplemented by themes that appear to be particularly relevant when analyzing the text.

By recruiting from both cooperation networks and the routine care sector, we explicitly aim to include a broad range of perspectives of patients and service providers. The goal is to understand the typical issues arising in the referral process to PsIAs and how to best address them. Regarding the adaptation of the psy-PAD_{Group} intervention in work package 2, diverging perspectives will be discussed and solved by consensus.

Work Package 2: Expert Workshop

The expert workshop will be conducted as a moderated interactive discussion with a previously outlined set of topics and a duration of approximately 5 hours. The results of the expert workshop will be protocolled. Adaptations of the psy-PAD_{Group} manual as well as the required outline to implement the psy-PAD_{Group} manual in the modalities of PsIAs, will be based on the recommendations derived from the expert workshop.

During the data analysis and the development of the category system, previously formed main themes are inductively expanded from the data. For this purpose, 2 raters will agree consensually upon the categories and complementary themes that appear to be particularly relevant when analyzing the text. Once the category system has been created, the additional content is then classified by just one rater. The second rater can be consulted again if any ambiguities arise. To enhance dependability and confirmability, an audit trail will be maintained, including the key steps of data collection and transcription, coding decisions, and category development. All materials, including transcripts, coding frameworks, and analytic memos, will be securely stored to allow for transparency and traceability of the research process.

Ethical Considerations

This study received ethics approval from the ethics committee of Justus-Liebig University Giessen—Faculty of Medicine (AZ 67/23) and is registered in the German Clinical Trial Register (DRKS00031873).

Data Confidentiality

Work Package 1: Patient and Service Provider Perspective

The data collection of work package 1 comprises patient focus groups and interviews with service providers. The patient focus groups will be conducted in person, and the service provider interviews will be conducted in person or online. Online interviews will be carried out with the program Big Blue Button, which follows the security standards of the Justus-Liebig University. The focus groups and the interviews will be recorded with a suitable audio recording device with no internet connection. The audio recordings will be saved on an SD card or directly on the protected servers of the Justus-Liebig University. The recording device or SD card will be kept double locked and inaccessible to third parties on the premises of the Justus-Liebig University when not in use. The audio files will be transcribed by a professional commercial third party, which has extensive previous experience in conducting studies and research projects and has a comprehensive data protection concept for handling personal data. All references to persons or information that could be used to identify third parties are removed from the transcript during transcription. After these checks, the audio files are destroyed by both the third-party transcription service and the study center, so the data are available in pseudonymized form at this point. Further data processing and analysis of the pseudonymized transcripts is carried out using MAXQDA (VERBI GmbH) and SPSS (IBM Corp) for sample characteristics. In addition, personally

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identifiable data are collected in the form of contact details for planning the patient focus groups and service provider interviews, as well as the informed consent forms. The patient's contact details will remain at the diabetes clinic at all times, and the list of focus group participants will be destroyed immediately after the focus group has been conducted. The contact details of the service providers as well as the informed consent forms, will be stored digitally on protected servers of the Justus-Liebig University or in paper form in the study center in a protected double-sealed manner for the duration of the study.

Work Package 2: Expert Workshop

The data collection of work package 2 comprises personal contact details, including the name and affiliation of the experts. As the participation in the expert workshop is to be made public, informed written consent is required in advance. The names and affiliations of the experts will be made public in the form of publications if informed written consent has been obtained. During the entire duration of the study, the data will be treated as personal data and stored exclusively in digitized form on protected servers and in paper form, double-sealed at the study center.

After completion of the study, all personally identifiable data will be deleted. The transcripts of the focus groups and interviews will be digitized for the required period of 10 years in accordance with data protection regulations and the "Guideline 17 Archiving—Guideline for Safeguarding Good Scientific Practice" [33] and stored on a hard drive specially for the purpose of archiving, double-sealed at the study center. The study will be conducted in accordance with the ethical requirements of the Declaration of Helsinki and in compliance with the standards of the ICH guideline for good clinical practice. Personal data of patients, service providers, and all other confidential information are subject to the provisions of the General Data Protection Regulation and the State and Federal Data Protection Act (Landesdatenschutzgesetz and Bundesdatenschutzgesetz). Participation in the study is voluntary at all times and only takes place after informed written consent.

Results

Work Package 1

Needs from the patient and service provider perspectives regarding referral pathways to PsIAs will be assessed. On the basis of these findings, referral pathways will be developed. Furthermore, in preparation for the upcoming minDBe main study, short questionnaires for patients and service providers will be developed to economically assess the acceptance and feasibility of the referral pathways as well as potential remaining access barriers. This will help determine whether the developed referral routes to PsIAs are successful in routine practice.

Work Package 2

The intervention psy-PAD_{Group} will be adapted and manualized for a group setting to be integrated into the structures of PsIAs as part of an interdisciplinary multimodal treatment option.

Funding was acquired in July 2023. The data collection started in January 2025.

Discussion

Anticipated Findings

The results of the minDBe pilot study will comprise referral pathways to PsIAs using the perspective of patients and service providers, short questionnaires to economically assess these referral pathways, as well as a manual for the psy-PAD_{Group} intervention that can be implemented into the multimodal and interdisciplinary modalities of PsIAs. Given that PsIAs are a new care structure offering outpatient treatment, their role in the psychosomatic care landscape in Germany is yet not fully clear, and research in this regard is scarce. One key aspect of their success is how well PsIAs and their usefulness for both patients and service providers are perceived. By providing referral pathways, the minDBe pilot study is one of the first studies to address the practical challenges patients and service providers face when new care elements are introduced in an already complex health care system. More specifically, the needs of patients with diabetes and psychological burden and their treating physicians or diabetologists, are addressed when interdisciplinary and integrative treatment options are to be planned. Moreover, PsIAs require structured treatment options, which must be specifically designed to fit the modalities of PsIAs. For patients with diabetes and psychological burden, such a tailored treatment option does not exist yet. By adapting the psy-PAD intervention for a group setting, an important gap in the treatment of patients with diabetes and psychological burden is addressed. To date, patients with diabetes are primarily treated by their general practitioner or diabetologist, which tend to be more somatically focused, while psychological burden is treated by a psychotherapist. These treatments are usually not aligned with each other, even when they are received simultaneously. The psy-PAD_{Group} intervention aims to address this issue and presents a comprehensive treatment option integrating both somatic and psychological aspects of diabetes treatment.

The minDBe pilot study specifically aims at laying the foundation for the upcoming minDBe main study, by providing the necessary referral pathways, the short questionnaires, as well as the psy-PAD_{Group} manual. The minDBe main study aims to evaluate the referral pathways to PsIAs and prove their feasibility in clinical practice. Moreover, the main study will evaluate the psy-PAD_{Group} as part of an interdisciplinary psychotherapeutic treatment program in PsIAs by using a randomized controlled trial. The long-term goal of the minDBe overall study is the implementation of a diabetes-specific interdisciplinary multimodal psychotherapeutic treatment option into the new structures of PsIAs. To offer targeted care for the high-risk group of patients with diabetes, inadequate glycemic control, diabetes-related distress, and psychosocial burden, we intend to improve the overall treatment quality of patients with diabetes.

Limitations

Regarding the proposed methodology of this study, several potential limitations should be acknowledged. For one, patients with gestational diabetes, other types of diabetes, or severe

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complications are excluded. Moreover, the diversity of the patient as well as the service provider sample is limited, which may restrict the generalizability of our findings. However, the goal of this qualitative pilot study is not statistical representativeness but theoretical saturation, which can also be achieved with less diverse samples when the research question is narrowly focused [31]. Mixed methods research inherently faces conceptual challenges, including the selection of appropriate methods for a given research question, the meaning of integrating different approaches, and the overall structuring of a mixed methods framework. In addition, qualitative research carries the risk of socially desirable responses, particularly when addressing sensitive topics. Given the time constraints for patient focus groups and service provider interviews, covering all aspects may not be possible.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

SZ wrote the original draft. JK was responsible for the conceptualization and writing—review and editing. HK was responsible for conceptualization, funding acquisition, and writing—review and editing. All the authors approved the final version of this manuscript.

Conflicts of Interest

None declared.

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Abbreviations

HbA1c: hemoglobin A1c
PsIA: psychosomatic outpatient clinic
Psy-PAD$_{Group}$: psy-PAD for a group setting

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Protocol

Implementation of Integrative Nursing for Patients With Cancer Receiving Inpatient Care: Protocol for a Convergent Parallel Mixed Methods Evaluation

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Abstract

Background: Integrative nursing (IN) involves the application of external naturopathic nursing interventions, such as compresses, embrocations, and therapeutic baths and washes. As part of a university hospital project, patients receiving oncology care in participating wards receive IN interventions as supportive care during their hospital stay as part of a consultation service.

Objective: This study aims to investigate the acceptance, feasibility, and contextual conditions of implementing IN in inpatient care and to evaluate perceptions, experiences, and perceived impact of IN interventions from multiple stakeholder perspectives.

Methods: We used a convergent parallel mixed methods approach guided by the Consolidated Framework for Implementation Research. The evaluation consists of 5 substudies reflecting multiple perspectives on the project. Patients, relatives, and hospital staff will participate. Substudies include a single-arm pre-post questionnaire (substudy 1) and semistructured interviews (substudy 2) with patients, a cross-sectional survey of relatives (substudy 3), semistructured interviews with health care professionals (substudy 4), and analysis of project-related documentation (substudy 5). Qualitative data will be analyzed using qualitative content analysis, and quantitative data will be analyzed using descriptive and inferential statistical methods.

Results: Following separate analyses of each substudy, the findings will be integrated and triangulated to generate overarching meta-inferences. The recruitment phase lasted from October 2023 to January 2025. Data collection was completed in March 2025. As of October 2025, after data verification and plausibility checks, data analysis is ongoing. The first results are expected to be published in 2026.

Conclusions: This study presents a mixed methods research protocol aimed at exploring the implementation of IN within a university hospital setting. It is expected to provide a theory-based contribution to IN implementation in inpatient care while also offering insights into its potential effects at the patient level. The study is anticipated to advance understanding of how IN can be sustainably embedded in hospital practice and to provide actionable insights for improving patient-centered supportive care.

Trial Registration: German Clinical Trials Register DRKS00032318; https://drks.de/search/de/trial/DRKS00032318

International Registered Report Identifier (IRRID): DERR1-10.2196/74405

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KEYWORDS

complementary nursing intervention; inpatient care; integrative medicine; integrative oncology; nursing counseling; quality of care; study protocol; supportive care; symptom management

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Introduction

Background

In the following, we differentiate among complementary and integrative medicine (CIM), integrative nursing (IN), and integrative oncology (IO). CIM broadly refers to approaches that combine conventional medicine with complementary therapies [1,2]. IN denotes a nursing-specific framework emphasizing complementary, nonpharmacological, nurse-delivered interventions embedded within conventional care [3]. IO describes the broader integration of such approaches into oncology practice, encompassing medical, nursing, and psychosocial perspectives [4].

Patients with cancer show a significant demand for CIM, which involves both traditional and complementary approaches [5,6]. The global prevalence of CIM use among patients with cancer ranges widely from 16.5% to 93.4%, with an average prevalence of 41.1% reported for Germany [5]. This trend is further supported by findings from a survey conducted at German university hospitals, in which nearly half of the patients surveyed (48%) reported previous or current use of CIM in relation to their disease [7].

IN refers to a care approach that combines conventional nursing practices with evidence-informed complementary methods, aiming to holistically address the physical, emotional, social, and spiritual needs of patients [8-10]. IN interventions include a range of naturopathic, nonpharmacological nursing interventions, such as compresses, embrocations, and therapeutic baths and washes [10-12]. In an oncology setting, these IN interventions aim to prevent and manage symptoms and side effects associated with conventional treatment [10,13]. In recent years, a growing body of research, including reviews and evidence syntheses, has emerged on IN interventions both in general [14-16] and in relation to specific symptoms such as mucositis [17], pain [18], and chemotherapy-induced peripheral neuropathy [19]. In addition, individual studies have investigated specific symptom burdens, such as fatigue [20,21] or sleep quality [22,23], as well as postoperative support during the hospital stay [24,25]. A mixed methods systematic review taking a broader perspective on external applications suggests potential benefits for managing cancer-related symptoms but also identifies limitations, including low study quality and methodological inconsistencies among the included studies [15]. A similar pattern is reflected in an overview of systematic reviews, which indicates a generally positive influence of CIM on patient-reported outcomes in patients with cancer, for example, acupuncture has been associated with pain relief, while also acknowledging methodological limitations and, in part, inconclusive findings [26].

IN therefore plays a relevant role in the field of CIM in oncology [10,27,28], with IN interventions being implemented as part of IO programs [27,29]. Ben-Arye et al [30] highlighted the positive impact of nurse involvement in guiding patients to self-administer IO treatments. However, in this context, the influence of IN interventions at the patient level (eg, patient-reported outcomes) and the institutional level (eg, structural factors) have been examined only as part of multimodal programs [31-33].

In addition, research projects in Germany have focused on implementing IN interventions in health care, particularly in outpatient settings [34-36] and in pediatric inpatient care [37-40]. Recent studies in these contexts have demonstrated the considerable potential of IN interventions to support patients with cancer in managing cancer-related symptoms [41], improving patient activation [42], and enhancing their quality of life [35]. However, these findings are only partially generalizable to adult inpatient populations. Consequently, research on the feasibility, implementation, and evaluation of IN for patients with cancer in inpatient settings remains limited in Germany. Despite the considerable growth of research on CIM and IO in recent years, the specific role of IN is still underrepresented in the literature. Evidence on the systematic implementation and sustainability of IN interventions in inpatient oncology settings remains scarce.

In this context, the IMPLEMENT-UKU (Implementation of Integrative Nursing at the Ulm University Hospital) project offers an IN consultation service for patients on participating wards. The project provides a supportive, complementary care approach that uses external naturopathic nursing interventions to supplement conventional treatments in a patient-centered manner.

Purpose of This Study

This evaluation study is embedded within the IMPLEMENT-UKU project and will examine the implementation of IN through a comprehensive, accompanying scientific investigation that integrates the perspectives of patients, their relatives, and hospital staff. It aims to address the following research questions: (1) To what extent can IN be implemented as intended on the participating wards, including the delivery of IN (eg, number of IN consultations, IN interventions) and its acceptance and perception among patients, relatives, and health care professionals (eg, evaluation of IN, perceptions of IN interventions)? (2) What are the key contextual factors influencing the implementation of IN, including identification of relevant contextual factors and assessment of the implementation process, such as barriers and facilitators? (3) What are the indicators of potential effects of IN at the patient level, with a focus on patient-reported outcomes (eg, well-being, quality of life, self-efficacy, and symptom burden)?

This study aligns with the research priorities outlined in the "German Research Agenda for Nursing Oncology," particularly regarding the management of disease-related symptoms and treatment side effects, as well as the promotion of quality of life across different phases of health and disease [43].

Methods

Project IMPLEMENT-UKU: Setting and Intervention

The IMPLEMENT-UKU project and its accompanying evaluation study are being carried out as a single-center initiative at the University Hospital Ulm. Within the framework of the project, patients with cancer on participating wards receive IN interventions as supportive care during their hospital stay as

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part of a consultation service. Figure 1 illustrates a flowchart of the patient care pathway within the project.

Patients will be referred to an initial IN consultation by nursing or medical staff on the participating wards. Referrals will be based on pertinent and acutely distressing symptoms and problems, such as restlessness, pain, or cancer-related side effects, which are relevant to care and indicate the need for supportive interventions. Following referral, patients will receive an initial IN consultation, which may be followed by additional IN visits and interventions throughout their hospital stay. During the initial IN consultation, the integrative nurse will provide information about IN, the overarching IMPLEMENT-UKU project, and the ongoing evaluation study. The first IN intervention will be conducted directly after this consultation. The number of subsequent IN visits and interventions may vary depending on patient needs and the duration of hospitalization.

Depending on each patient's symptom burden and individual preferences, patient-tailored IN interventions will be offered alongside routine care. To ensure consistent application, these interventions will be guided by a symptom-driven IN intervention catalog (Table 1). The IN catalog was developed through an expert consensus process, drawing on external naturopathic nursing textbooks [11,12,44-47], academic literature [14,15,18,19,48], and recommendations from previous projects and guidelines [36,49-51]. To ensure intervention fidelity, standard operating procedures are available for all IN interventions.

IN interventions are carried out by nurses who are specially trained in IN. These nurses have completed 3 years of vocational nursing education and have extensive professional experience. In addition, they have received training in CIM and hold qualifications in external naturopathic interventions, such as advanced training in compresses and wraps (40 teaching hours), rhythmic embrocation according to Wegman and Hauschka (80 teaching hours), and mindful body care and therapeutic washing (16 teaching hours), provided by the Association for Anthroposophical Nursing in Germany.

Although IN interventions are tailored to individual patient needs, fidelity is ensured through detailed standard operating procedures, structured nursing training, and standardized project-related documentation by nursing staff (substudy 5). This approach enables monitoring of adherence to the intervention catalog and allows systematic examination of variability, including its relationship to patient characteristics and contextual influences.

Figure 1. Flowchart of the patient care pathway within the IMPLEMENT-UKU (Implementation of Integrative Nursing at the Ulm University Hospital) project and in substudy 1.

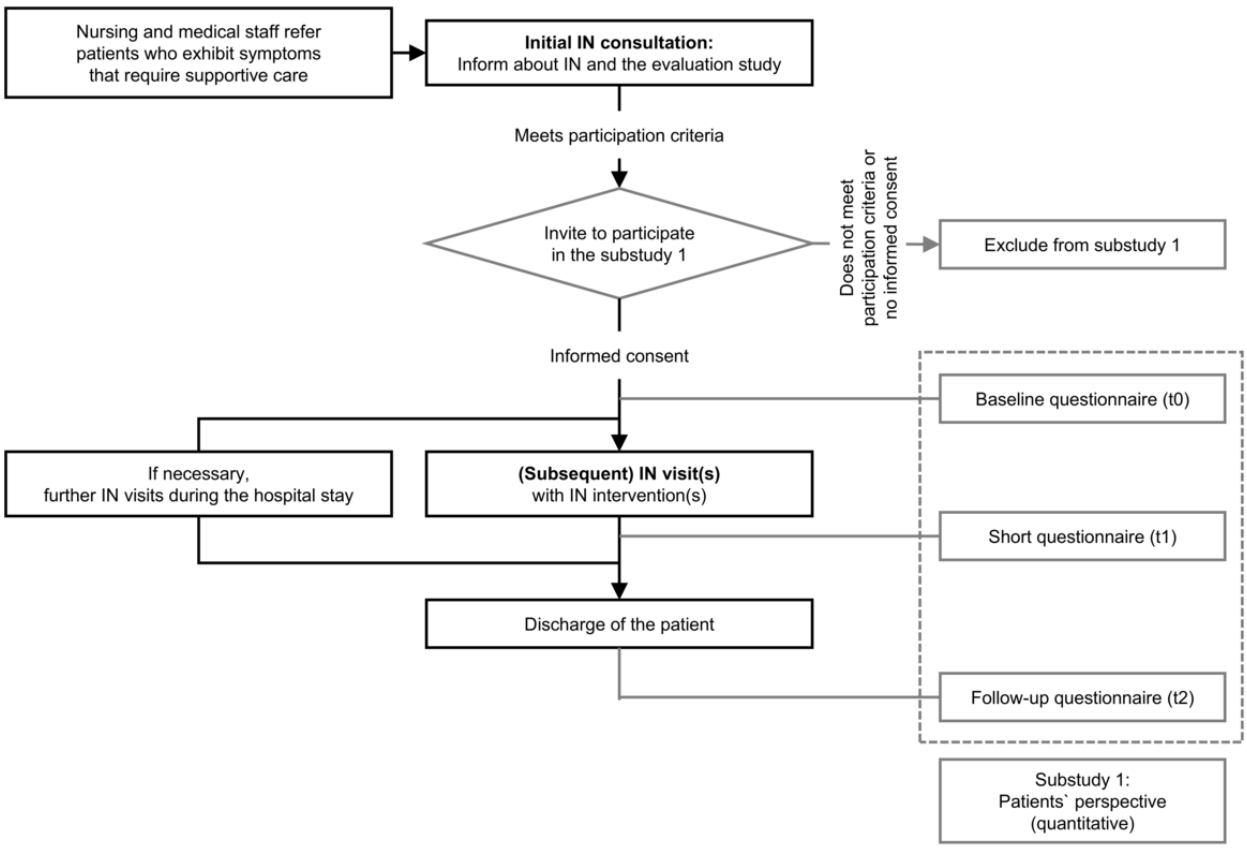

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Table 1. Catalog of integrative nursing (IN) interventions in the IMPLEMENT-UKU (Implementation of Integrative Nursing at Ulm University Hospital) project (as of August 2023).

Symptoms	IN interventions[a]
Appetite loss	• Liver compress with yarrow tea or oil[b]
Respiratory insufficiency and respiratory infections	• Sternum compress with thyme oil[b], plantago bronchial balsam[c] • Embrocation with thyme oil[b], solum oil[c], plantago bronchial balsam[c] • Diaphragm compress with copper ointment[c], thyme oil[b], solum oil[c]
Sleep disorders	• Heart compress with aurum-lavandula ointment[c] • Hand or foot bath with lavender bath milk • Sternum compress with lavender oil[c] • Embrocation with lavender oil[b], solum oil[c], mallow oil[c] • Liver compress with yarrow tea or oil[b]
Exhaustion and weakness	• Hand or foot bath with citrus bath milk, rosemary bath milk • Liver compress with yarrow tea or oil[b] • Therapeutic wash with citrus bath milk, rosemary bath milk, solum oil[c] • Embrocation with mallow oil[c], solum oil[c], rose oil[b]
Depressed mood	• Embrocation with mallow oil[c], rose oil[b], citrus oil[b] • Therapeutic wash with citrus bath milk • Liver compress with yarrow tea or oil[b]
Crisis situation	• Hand or foot bath with lavender bath milk • Embrocation with rose oil[b], solum oil[c], lavender oil[b] • Therapeutic wash with rosemary bath milk
Constipation, meteorism, and irritable bowel syndrome	• Abdomen-embrocation with fennel-caraway oil[b], chamomile oil[b], melissa oil[c], oxalis ointment[c] • Abdomen compress with chamomile oil[b]
Edema and congestion	• Compress with borago essencec, curd, arnica essence[b] • Embrocation with rosemary oil[b], solum oil[c] • Therapeutic wash with citrus bath milk
Polyneuropathy	• Embrocation with aconite oil[c], solum oil[c],
Pain	• Embrocation with aconite oil[c], solum oil[c], arnica essence[c] • Warm or cool compress
Nausea and vomiting	• Abdomen compress with fennel-caraway oil[b], chamomile oil[b], melissa oil[c] • Embrocation with fennel-caraway oil[b], chamomile oil[b], melissa oil[c]
Restlessness, anxiety, and tension	• Heart compress with aurum-lavandula ointment[c] • Liver compress with yarrow tea or oil[b] • Wrist compress with citrus oil[b] • Embrocation with solum oil[c], lavender oil[b], rose oil[b], mallow oil[c] • Sternum compress with lavender oil[b], arnica essence[c] • Hand or foot bath with lavender bath milk

[a]Selected according to the patient's symptom burden and preferences.

[b]Essential oils; for embrocations used with a high-quality carrier oil.

[c]Ready-to-use products as anthroposophical products: aconite oil (*Aconitum napellus e tubere ferm 33c Dil. D9 oleos., D-Campher, Lavandulae aetheroleum, Quarz Dil. D9 oleos.*); arnica essence (*Arnica, montana*); aurum-lavandula ointment (*Aurum metallicum praeparatum Dil. D4, Lavandulae aetheroleum, Aetheroleum extractum e floribus recentibus Rosae damascenae et centifoliae*); borago essence (*Borago officinalis ex herba LA 20%*); copper ointment (*Cuprum oxydulatum rubrum*); mallow oil (*Geranii aetheroleum, Malva arborea e floribus W 5%, Hypericum perforatum, Herba rec., Prunus spinosa e floribus W 5%, Sambucus nigra ex umbella W 5%, Tilia platyphyllos/cordata e floribus W 5%*); melissa oil (*Carvi aetheroleum,*

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Foeniculi amari fructus aetheroleum, Melissa officinalis ex herba W 5%, Origanum majorana ex herba W 5%); oxalis ointment (*Oxalis, folium*); plantago bronchial balsam (*D-Champher, Cera flava, Drosera e planta tota ferm 33c Dil. D3, Eucalypti aetheroleum, Petasites hybridus e radice ferm 33c Dil. D1, Plantago lanceolate e foliis ferm 34 c Dil. D1, Terebinthina laricina, Thymi aetheroleum*); solum oil (*Aesculus hippocastanum e semine LA 25% sicc., Equisetum arvense ex herba LA 20%, Lavandulae aetheroleum, Solum uliginosum*).

Study Design

A mixed methods research design is used, applying a convergent parallel mixed methods design [52,53]. The decision to use a mixed methods approach was made to enable triangulation of quantitative and qualitative data and to integrate diverse perspectives on the implementation of IN, thereby providing a more comprehensive understanding of the phenomenon. In the field of nursing, mixed methods are also essential for addressing implementation research questions, in addition to single-method approaches [54]. In this convergent parallel design, both types of data are collected simultaneously and with equal priority. They are then evaluated independently and subsequently compared, related, and merged after analysis. This process enables the identification of areas where results converge or diverge, which can be then be explored further during the interpretation phase. The protocol follows the principles outlined in the Good Reporting of a Mixed Methods Study guidelines [55].

This study applies the Consolidated Framework for Implementation Research (CFIR) as its theoretical framework [56,57]. CFIR is a comprehensive framework for studying the implementation of complex interventions in health care settings [58]. The updated version of CFIR includes 5 core domains for analyzing the implementation process [57]: innovation, outer setting, inner setting, individuals, and implementation process. These domains are interrelated and collectively influence the success and sustainability of implementation efforts [56]. However, relying solely on CFIR domains may overlook important contextual influences. Maintaining an open and flexible approach during the implementation process is therefore essential to capture additional relevant factors [58].

To address the primary objectives of the study and reflect the multilevel evaluation approach, 5 interrelated substudies will be conducted, incorporating 3 perspectives: those of patients, relatives, and health care professionals. An overview of these substudies is presented in Table 2, with further details provided in the following sections.

Table 2. Study design of the mixed methods approach, comprising 5 interrelated substudies.

Substudy	Aim	Method	Participants
1	To identify perceptions and impact on patient-reported outcomes	Single-arm pre-post questionnaire	Patients
2	To understand how patients experience the IN	Semistructured interviews	Patients
3	To understand how relatives regard the IN	Cross-sectional survey	Relatives
4	To identify facilitators and barriers to the implementation	Semistructured interviews	Nursing and medical staff
5	To demonstrate the feasibility and implementation	Project-related documentation	All project participants

Substudy 1: Patients' Perspective (Quantitative)

The aim is to explore patients' perceptions and experiences with IN interventions, including short-term changes in vitality, sense of warmth and strength, and feelings of calm. The study also seeks to identify the potential impact of IN during the inpatient stay on patient-reported outcomes, such as well-being and associated symptom burden.

Study Design

In this substudy, we will conduct a single-arm, exploratory pre-post study with multiple measurement points.

Participants

Patients who receive IN interventions during their hospital stay as part of the IMPLEMENT-UKU project are eligible to participate. Additional inclusion criteria are age 18 years or older, capacity to provide informed consent, and provision of written informed consent. Exclusion criteria include pronounced cognitive deficits, an imminent dying process, and inability to participate in the survey due to limited communication abilities, such as insufficient language proficiency. Informed consent will be obtained with particular attention to the acute health conditions of inpatients. To minimize participant burden, questionnaires will be concise, and data collection will be scheduled flexibly. In addition, the questionnaire may be completed with support from study staff if required. Participants retain the right to withdraw from the study at any time without providing justification.

The study is designed as a total population survey, aiming to include all patients participating in the project. However, because not all patients may be able or willing to participate, the resulting sample will be classified as a nonprobability convenience sample. Reasons for nonparticipation in the study will be systematically documented in a screening log. Due to the exploratory nature of this substudy, no formal sample size calculation was performed. The final sample size will be determined by the study duration and the number of eligible patients within this timeframe. We anticipate an eligible population of approximately 20 patients per month, with a projected recruitment rate of 30% and an expected dropout rate of 20%.

Data Collection

During the study period, all patients enrolled in the IMPLEMENT-UKU project will be invited to participate on a voluntary basis. During the initial IN consultation, patients will receive detailed information about the study, and the inclusion and exclusion criteria will be reviewed to assess eligibility. If

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the patient agrees to participate, data will be collected throughout the hospital stay until follow-up after discharge (Figure 1). Participants will first complete a baseline questionnaire (t0). A brief questionnaire (t1) will be administered after each subsequent IN visit with interventions. Following discharge, participants will be asked to complete a follow-up questionnaire (t2). In parallel with the ongoing IN visits, project-related documentation of all applied IN interventions will be conducted as part of substudy 5.

Study Outcomes

To comprehensively assess the potential impact of IN on patients' overall experience and functioning, the study incorporates a set of patient-centered outcomes that capture both physical and psychological dimensions of health. The selected instruments are suitable for use in an inpatient oncology setting and designed to cover a time frame of up to 2 weeks. Outcome parameters include well-being, life satisfaction, health status, symptoms, psychological burden, and self-efficacy. In addition, previous use of and interest in CIM, as well as patients' perceptions of and satisfaction with IN and its implementation, will be assessed. These outcomes will be measured at 3 time points, as outlined in Table 3.

Table 3. Outcomes and instruments used in the quantitative pre-post study with patients (substudy 1). Self-developed items underwent pretesting using the think-aloud method.

Outcomes	Instrument	Items, n	t0 (baseline)	t1 (after each IN visit)	t2 (follow-up)
Well-being	WHO-5[a]	4	✓		✓
Life satisfaction	L-1[b]	3	✓		✓
Health status	SRH[c]	2	✓		✓
Symptoms	NRS[d]	15	✓		✓
Psychological burden	PHQ-4[e]	4	✓		✓
Self-efficacy	SES6G[f]	6	✓		✓
Previous use of CIM[g]	Self-developed	7	✓		
Interest in using CIM	Self-developed	7	✓		
Perception of vitality, warmth, strengthening, coming to rest	NRS	4		✓	
Satisfaction with IN[h] and implementation of IN	Self-developed	6			✓
Further comments	Open-ended question	1	✓	✓	✓
Sociodemographic data	Demographic data form	6	✓		

[a]WHO-5: WHO-Five Wellbeing Index.
[b]L-1: Short Scale Life Satisfaction.
[c]SRH: self-rated health.
[d]NRS: numeric rating scale.
[e]PHQ-4: Patient Health Questionnaire-4.
[f]SES6G: Self-Efficacy for Managing Chronic Diseases 6-Item Scale.
[g]CIM: complementary and integrative medicine.
[h]IN: integrative nursing.

Data Analysis

Missing data will be assessed in terms of extent and patterns. Depending on the amount and nature of missing values, either listwise or pairwise deletion will be used for analysis. In cases of substantial missingness, appropriate imputation methods (eg, multiple imputation) will be considered. All procedures for handling missing data will be reported transparently. Descriptive statistics, including frequency, mean, SD, median, and mode, will be used to characterize the sample and outcome variables. To estimate differences between baseline and follow-up scores, a paired *t* test will be applied; the Wilcoxon signed-rank test will be used as a nonparametric alternative. Additionally, subgroup analyses will be conducted based on variables such as gender, age group, diagnosis, previous experience with CIM, and type of IN intervention. Statistical significance will be defined as $P<.05$.

Substudy 2: Patients' Perspective (Qualitative)

This substudy aims to explore how patients perceive and experience IN interventions, as well as their level of satisfaction with the implementation of IN. The primary focus is an in-depth examination of individual perceptions to gain a more nuanced understanding of how IN interventions are received and experienced from the patient's perspective.

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Study Design

In this substudy, we will use a qualitative approach, and semistructured interviews will be conducted.

Participants

Patients who received IN interventions during their inpatient stay will be invited to participate in interviews after discharge. Additional inclusion criteria are age 18 years or older, capacity to provide informed consent, and provision of written informed consent. Exclusion criteria include pronounced cognitive deficits, an imminent dying process, and limited ability to communicate (eg, insufficient language proficiency).

Purposive sampling will be used to identify and select cases that are rich in information [59]. Participants will be selected to ensure variation in factors such as sex, age, and number of IN interventions received, thereby capturing a wide range of perspectives on the implementation of IN. A minimum of 12 interviews is initially estimated to capture sufficient diversity of patient experiences to address the research questions [60]. However, sampling will be flexible and will continue until thematic saturation is reached, defined as the point at which no new significant themes, concepts, or insights emerge from the data.

Data Collection

During their hospital stay, patients will be informed verbally and in writing by study staff. After discharge, they will be contacted by telephone to confirm their interest in participating and to clarify their preferred format and scope of the interview. Upon providing written informed consent, participants will be interviewed online, by telephone, or in person, according to their preference. A semistructured interview format guided by an interview guideline will be used. Each interview will last approximately 45 minutes and will be audio recorded. In addition, the interviewer will take structured notes using a standardized interview protocol to capture relevant contextual details for later analysis. To support sample characterization, the following variables will be recorded: age, sex, marital status, number of children, occupation, and number and type of IN interventions received.

Interview Guideline

The interview guideline was developed based on research interests, following the principle of “collecting, checking, sorting, subsuming” [61], and with consideration of CFIR [57]. The guideline will address the following four main topics: (1) previous experience with and use of CIM and IN, (2) perception and experience with IN at both the physical and psychological levels, (3) satisfaction with the implementation of IN during the hospital stay, and (4) perspectives on the future use of IN, including potential integration into everyday life. At the end of the interview, participants will also be invited to provide additional comments or reflections.

Data Analysis

Audio recordings will be transcribed according to the simple transcription guidelines proposed by Dresing and Pehl [62]. Any personally identifiable information will be anonymized to ensure data protection. Data will be analyzed using structuring qualitative content analysis as proposed by Kuckartz [63], which combines deductive and inductive category development. Deductive categories will be derived from the research questions and CFIR, while additional inductive categories will emerge from the data. The coding system will be redefined iteratively throughout the analysis process. To enhance credibility and reliability, at least 2 researchers will be involved in coding and interpretation. Initially, a subset of transcripts will be coded independently, and the resulting codes and themes will be compared and discussed to reach consensus. The remaining data will then be coded through a consensus-driven approach by the research team. Data analysis will be performed using MAXQDA (VERBI Software). Upon completion of the analysis, all audio files will be permanently deleted to ensure compliance with data protection regulations.

Substudy 3: Relatives’ Perspective

Relatives are considered key stakeholders in exploring the feasibility and relevance of transferring low-threshold IN interventions into the home care setting after hospital discharge. The aim of this substudy is to examine relatives’ perspectives on the use of, attitudes toward, and interest in CIM, as well as their perceptions of IN for inpatients.

Study Design

In this substudy, we will conduct an anonymous, cross-sectional survey using a quantitative descriptive research design.

Participants

The survey will include all relatives of patients who receive IN interventions as part of the IMPLEMENT-UKU project at the hospital. Eligibility criteria for participation are age 18 years or older, sufficient language proficiency, being a relative of a patient received IN interventions, and provision of informed consent.

Data Collection

Relatives will be invited to participate in the survey through information flyers and direct contact by nurses involved in the project, who will provide verbal and written information about the study. Participation in the survey is possible using a paper-based questionnaire or a web-based version. The online survey is administered using the Unipark platform (Tivian XI GmbH). Participants will access the questionnaire using a survey link or QR code, and responses will be submitted anonymously.

Study Outcomes

The questionnaire includes the following domains: sociodemographic data (2 items), caregiving support (3 items), definition of CIM (2 items), previous use of CIM (12 items), interest in using CIM (12 items), perception of IN at the hospital (5 items), involvement of relatives in project implementation (2 items), and space for additional comments (1 item).

Data Analysis

Missing data will be assessed in terms of frequency and distribution across all variables. Cases with missing values will be excluded using listwise or pairwise deletion, as appropriate. Descriptive statistical methods will be used to analyze the data.

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Depending on the level of measurement, absolute and relative frequencies, means, SDs, and medians will be calculated.

Substudy 4: Medical and Nursing Staffs' Perspective

The involvement of health care professionals, including nursing and medical staff on the participating wards, is essential for capturing implementation processes and complementing the perspectives of patients who have received IN interventions. The objective of this substudy is to explore the facilitators and barriers to the implementation of IN from the perspective of health care professionals, as well as their perceptions of its effects and its impact on routine clinical practice.

Study Design

In this substudy, we will use a qualitative approach, and semistructured interviews will be conducted.

Participants

Nursing and medical staff from the wards participating in the IMPLEMENT-UKU project, as well as the integrative nurses delivering the IN interventions, will be invited to participate. Additional eligibility criteria include age 18 years or older, sufficient language proficiency, employed on a participating ward or within the project, and provision of informed consent.

A purposive sampling strategy will be used to identify and select participants who can provide rich and relevant information [59]. The sampling approach will aim for maximum variation in key characteristics such as age, professional background, and years of employment, to capture a broad range of perspectives. This study aims to conduct a minimum of 12 interviews to collect sufficient diverse perspectives to address the research questions [60]. Sampling will continue until thematic saturation is reached, defined as the point at which no new significant themes, concepts, or insights emerge from the data.

Data Collection

Potential participants will be contacted through personal communication, mail, or telephone. Ward managers will serve as gatekeepers during the recruitment process. Nurses and physicians will be informed verbally and in writing by the study staff before the interview. Upon providing written informed consent, interviews will be conducted online, by telephone, or in person, according to the participant's preference. The interviews will be conducted using a semistructured guideline. Each interview will last approximately 45 minutes and will be audio-recorded. Additionally, the interviewer will take structured notes using an interview protocol to capture relevant contextual aspects for later analysis. The sample description will include age, sex, profession, years of professional experience, and additional CIM training.

Interview Guideline

The interview guideline was developed based on research interests, following the principle of "collecting, checking, sorting, subsuming" [61] and with consideration of CFIR [57]. The semistructured interview with nursing and medical staff will cover the following key topics: (1) the process of implementing the IN project, (2) perception and experience with IN on the ward, (3) support and enabling factors to IN implementation, (4) impediments and barriers to IN implementation, and (5) suggestions for future improvements. Participants will also be invited to share additional comments and reflections at the end of the interview.

Data Analysis

Audio recordings will be transcribed using the simplified transcription guidelines outlined by Dresing and Pehl [62]. Any information that could reveal participants' identities will be anonymized during this process. Qualitative data will be analyzed using structuring content analysis according to Kuckartz [63], which combines both deductive and inductive category development. Deductive categories will be derived from the study's research objectives and CFIR, while additional inductive categories will be identified directly from the data. The category system will be refined iteratively during the coding process. A subset of data will be independently coded by at least 2 researchers, after which the code systems and thematic patterns will be compared and discussed. The remaining data will be coded collaboratively using a consensus-driven approach. Analysis will be conducted using MAXQDA (VERBI Software). In accordance with data protection regulations, all audio files will be permanently deleted upon completion of the analysis.

Substudy 5: Project-Related Data

In addition to primary data sources, routinely collected data from the IMPLEMENT-UKU project will be used to complement the analysis and assess the feasibility and real-world implementation of IN. This substudy focuses on key implementation indicators, including acceptance, study participation rate, intervention fidelity, and the number of IN visits and interventions performed. Furthermore, the analysis will support the identification of required resources and potential cost factors associated with implementation in routine care.

Study Design

In this substudy, we will conduct a retrospective analysis using project-related routine data.

Participants

The sample will include all requests for IN consultations and all patients who participated in the project during the study period.

Data Collection

Project-related routine documentation will serve as the data source for all IN consultation requests, as well as the corresponding IN visits and interventions. Data for participants in substudy 1 will be collected pseudonymously, while data for all other project participants will be extracted anonymously.

Study Outcomes

All parameters shown in Textbox 1 will be collected from project-related routine data. This includes sociodemographic and clinical data, details on IN consultation requests and rejections, records of IN visits and interventions performed, and study participation. These data will be used to analyze the acceptance rate of the IN offer, the study inclusion rate, and intervention fidelity, defined as the extent to which the interventions are delivered in accordance with the standard

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operating procedure (eg, duration), and to estimate the resources and costs associated with implementing IN.

Textbox 1. Collection of project-related routine data (substudy 5).

Sociodemographic and clinical data

- Sex, age group, ward, and diagnosis group (*International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* [*ICD-10*])

Integrative nursing (IN) consultation service

- Reason for IN consultation request, acceptance or rejection of the IN offer, and reasons for rejection

IN visits

- Number of visits per patient, duration, notes of preliminary conversation, patient symptoms perceived or reported

IN interventions

- Number of interventions per patient, duration, location (body region), type, substances used, perceived or reported reactions after the IN intervention, and side effects

Study participation

- Study inclusion and reasons for noninclusion of patients

Data Analysis

Where feasible, complete case analysis will be performed; otherwise, pairwise deletion will be applied. Quantitative data will be analyzed using descriptive statistics, including frequencies, medians, means, and SDs, as appropriate. Subgroup analyses (eg, by sex, age group, diagnosis, or type of IN intervention) will be exploratory in nature. Group comparisons will be conducted using independent samples *t* tests for interval-scaled variables and chi-square tests for categorical variables. If the assumptions for parametric tests are not met, nonparametric alternatives such as the Mann-Whitney *U* test and Fisher exact test will be used. The significance level will be set at 5% ($P<.05$). Qualitative data from the open-ended text fields will be categorized using thematic content analysis.

Mixed Methods Analysis

After the separate analysis of each sub-study, the results will be integrated to generate meta-inferences. The ensuing discussion will examine areas of convergence, divergence, complementarity, and the relationships between the quantitative and qualitative findings, as well as different perspectives on the implementation of IN. The interpretation will be grounded in comparisons and correlations [52,64].

Triangulation approaches will be used to compare and integrate data, enabling both cross-validation and enrichment of the findings [65]. Methodological triangulation will enhance the credibility of results by identifying consistencies and discrepancies across different types of data, such as comparing quantitative and qualitative findings on patients' perspectives regarding the implementation of IN. Data source triangulation will be applied by incorporating insights from patients, relatives, and health care professionals, enabling a more comprehensive understanding of the implementation of IN for inpatients.

Integrative data analysis will use joint displays to present and synthesize findings, enabling further conclusions [66,67]. A joint display is a matrix that visually aligns and compares results from different data types to support systematic integration. In this study, which follows a convergent design, a side-by-side comparison will be used [67]. Joint displays will be thematically structured, such as according to the domains of to CFIR [57]. These displays will support the development of new insights and conclusions that extend beyond the individual substudies, serving as a foundation for interpretation, discussion, and stakeholder dialogue.

During the integration process, discrepancies between qualitative and quantitative findings will be systematically examined. Rather than being regarded as limitations, these divergences will be considered opportunities for deeper interpretation. They will be mapped in joint displays and explored through iterative team discussions to generate plausible explanations, including contextual factors or subgroup effects. This process will be transparently documented to ensure rigor.

Ethical Considerations

The evaluation study was conducted in accordance with the Declaration of Helsinki and received ethical approval from the Ethics Committee of the University of Ulm, Germany (144/23). All participants will receive detailed verbal and written information about the project and study objectives as part of the informed consent process. Informed consent will be obtained before participation, ensuring that participation is entirely voluntary. Participants may withdraw from the study at any time without providing a reason and without facing any consequences.

Results

Initially, the results of each substudy will be analyzed independently. Thereafter, the findings will be integrated and triangulated across the substudies, incorporating both quantitative and qualitative data, as well as the perspectives from different stakeholders, to develop comprehensive meta-inferences. The recruitment phase lasted from October

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2023 to January 2025. Data collection was completed in March 2025. As of October 2025, after data verification and plausibility checks, data analysis is ongoing. The first results are expected to be published in 2026.

Discussion

Overview

This study outlines the protocol for mixed methods research aimed at making a theory-based contribution to the implementation of IN for inpatients and examining its potential effects at the patient level. The following anticipated findings are derived from the study's research questions: IN visits and interventions are expected to be implemented as intended, with a moderate to high number of IN consultation requests and repeated IN visits and interventions per patient during the hospital stay. Acceptance rates among patients and staff are likely to be high, with health care professionals perceiving IN as a meaningful complement to conventional care. Contextual, structural, and organizational factors are anticipated to act as key barriers and facilitators in the implementation process. Initial results are expected to show improvements in well-being, reductions in symptom burden, and increased self-efficacy. IN interventions are anticipated to be perceived as supportive and not associated with additional burden. Patients may also report short-term subjective benefits such as enhanced vitality, a sense of warmth and strength, and feelings of calm following IN interventions.

The findings can subsequently be compared and contextualized with studies that have implemented CIM or IN in other settings, such as pediatric care [37,38,40,41,68-70] and outpatient oncology care [35,42,71,72], as well as with studies and programs offering IO for patients [33,73-75]. Situating the findings within the framework of implementation science is essential for advancing both the conceptual development and practical integration of IN into routine care [76]. This research is expected to make a substantial contribution to the implementation of IN as a service for inpatients. Furthermore, the findings will support the German Research Agenda for Nursing Oncology and help establish a scientific foundation for IN in oncology care [43].

The findings of this study will first be shared with the interdisciplinary IMPLEMENT-UKU Steering Committee. The results are expected to be suitable for publication in peer-reviewed journals and for presentation at national and international conferences. As part of the dissemination strategy, the results of the individual substudies will be published separately, followed by an integrative mixed methods publication synthesizing the overall findings. In addition, the results will be shared with the general public through patient forums, information events, and the project website. The findings will also inform the ongoing development and improvement of the IMPLEMENT-UKU project's implementation strategy. The findings may contribute to the development of practical guidelines to support the standardization and facilitation of IN implementation in other hospital settings. Moreover, the study outcomes are expected to inform future research strategies in the fields of IN and implementation science.

Limitations

The monocentric design of this study may limit the generalizability of findings to other settings and reduce external validity, as the results reflect the specific implementation context at Ulm University Hospital. Furthermore, due to the patient-centered and multimodal nature of the IMPLEMENT-UKU project, the delivery of IN interventions is not fully standardized and may vary between patients. To ensure consistency, all IN interventions are guided by a symptom-driven IN catalog, which supports targeted and structured application. In addition, a standard operating procedure is in place, and all applied IN interventions are documented in detail through project-specific documentation, enabling analysis of IN intervention variability and its impact.

As participation in this study is voluntary, there is potential for recruitment bias and corresponding selection bias. Although a convenience sampling approach will be used, several strategies will mitigate these limitations. Recruitment and sampling procedures will be transparently documented, and reflexivity will be maintained throughout the recruitment and data analysis phases. Reasons for exclusion and refusal to participate will be systematically recorded. For the qualitative interviews, efforts will be made to ensure heterogeneity in key participant characteristics.

As the studies rely primarily on self-report measures, risk of response bias, recall bias, and social desirability bias must be considered. In substudy 3, the cross-sectional design and convenience sampling of relatives from a single hospital limit external validity and generalizability. Substudy 1 uses a pre-post design without a control group. While this design enables the observation of intra-individual changes over time, it does not permit causal inference, as observed effects cannot be attributed solely to the intervention, thereby limiting internal validity. Accordingly, only exploratory analyses are planned to generate preliminary insights into potential effects and inform future research directions. Nevertheless, triangulation across multiple data sources within the patient group will enhance the credibility and trustworthiness of the findings, despite the nonprobabilistic sampling.

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Authors' Contributions

Conceptualization: LR (lead), JT (equal), KK (equal)
Funding acquisition: KK (lead), JT (supporting), LR (supporting)
Methodology: LR (lead), JT (supporting)
Project administration: LR
Visualization: LR
Writing – original draft: LR
Writing – review & editing:KK (lead), BSS (equal), JT (supporting)

Conflicts of Interest

None declared.

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Abbreviations

CFIR: Consolidated Framework for Implementation Research
CIM: complementary and integrative medicine
IMPLEMENT-UKU: Implementation of Integrative Nursing at the Ulm University Hospital
IN: integrative nursing
IO: integrative oncology

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Protocol

Association of the Transmembrane Protease Serine 6 rs855791 Variant and Nongenetic Factors With Iron Deficiency Among Female Medical Students in Yogyakarta: Protocol for a Case-Control Study

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Abstract

Background: Iron deficiency is the most widespread nutritional deficiency worldwide, and it is the primary cause of anemia, particularly in low- and middle-income countries such as Indonesia. Iron deficiency has a multifactorial etiology involving complex interactions between genetic factors, especially the transmembrane protease serine 6 (*TMPRSS6)* rs855791 variant, which encodes matriptase-2, a protein involved in regulating hepcidin expression, and nongenetic factors, including sociodemographics, nutritional status, iron intake, and menstrual patterns. Women of reproductive age, including medical students, are susceptible to iron deficiency owing to unhealthy dietary habits, growth requirements, and menstruation. Iron deficiency among medical students may lead to decreased academic performance and productivity. Additionally, as future mothers, women may experience a heightened risk of delivering children with intellectual disabilities and various psychosocial impairments. Owing to the significant consequences of this condition, identifying the underlying causes of iron deficiency is crucial. The high prevalence of iron deficiency in Indonesia poses a challenge in addressing these contributing factors to effectively reduce its occurrence.

Objective: This study aims to investigate the association of the *TMPRSS6* rs855791 variant and nongenetic factors with iron deficiency among female medical students in Yogyakarta, Indonesia.

Methods: This is a case-control study. We will recruit female medical students from the Faculty of Medicine, Public Health, and Nursing of Universitas Gadjah Mada in Yogyakarta, Indonesia. The inclusion criteria are being a final-year female undergraduate medical student who has not entered the clinical clerkship phase, aged 18 to 24 years, not pregnant, providing written consent, and having no history of chronic and inflammatory diseases, congenital diseases, hematological disorders, or blood transfusions during the last 3 months. Participants will be excluded if the C-reactive protein level is higher than 5 mg/L. Participants will be further grouped according to iron status criteria. Profiles of hemogram and iron markers will be compared between the case and control groups using the independent samples 2-tailed *t* test or the Mann-Whitney *U* test, while genotype and allele frequencies will be analyzed using the chi-square test. One-way ANOVA or the Kruskal-Wallis test will be used to assess the impact of different genotypes on iron marker levels. Multivariate analysis will be performed with logistic regression to determine factors independently associated with iron deficiency risk. $P \leq .05$ will be considered statistically significant.

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Results: The study received funding in January 2025. Data collection began in February 2025 and is anticipated to conclude by October 2025. At the time of manuscript submission, 115 participants had been enrolled. The study findings are expected to be published in 2026.

Conclusions: This study will determine the interaction between the *TMPRSS6* rs855791 variant and nongenetic factors that contribute to the risk of iron deficiency among female medical students in Yogyakarta, Indonesia.

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KEYWORDS

transmembrane protease serine 6; rs855791; TMPRSS6; rs855791; nongenetic; iron deficiency; female; women; medical students

Introduction

Background

Iron deficiency is the most prevalent nutritional deficiency globally. It accounts for more than 60% of anemia cases [1,2]. This condition generally affects children younger than 5 years, pregnant women, and women of reproductive age, especially those in low- and middle-income countries (LMICs) [3,4]. The World Health Organization reports that anemia is most widespread in Africa and Southeast Asia [4]. A study conducted across 7 South and Southeast Asian countries found that more than half of women of reproductive age were affected by anemia [5]. Another study, from the Demographic and Health Survey of 46 LMICs, showed that the prevalence of anemia in pregnant (45.2%) and nonpregnant women (39.5%) was higher than the global prevalence [6]. According to the 2018 Indonesian Basic Health Research survey, the overall prevalence of anemia in Indonesia was 23.7% (women: 27.2%; men: 20.3%) [7].

Iron plays a crucial role in several essential biological processes in the body, including electron transfer, oxygen transport, cell growth, aerobic metabolism, DNA synthesis, and enzymatic processes, and functions in muscle and neurological development, nerve fiber myelination, and neurotransmitter production [8-10]. Iron deficiency can affect cognitive development, school achievements, work performance, and productivity [11-13]. Iron deficiency that occurs during essential phases of brain development can cause permanent structural damage [9]. Iron deficiency during pregnancy can result in detrimental effects on infants and children. Many women of reproductive age enter pregnancy with low iron levels and may have no iron reserves whatsoever [2,14].

Several factors contribute to iron deficiency, including environmental factors, nutritional deficiencies, iron intake, sociodemographics, social habits, diet, lifestyle, infections, and blood loss (eg, menstrual bleeding or childbirth among women) [6,15,16]. Studies have also reported the role of genetic variability in an individual's iron status, accounting for approximately 20% to 30% of the variation [17-21]. Genome-wide association studies (GWASs) have demonstrated that single-nucleotide polymorphisms (SNPs) in certain genes are involved in hepcidin hormone regulation pathways that control iron homeostasis. Among these genes, loci on the transmembrane protease serine 6 (*TMPRSS6*) gene are frequently linked to low levels of iron and hematological indices. The most common SNP in the *TMPRSS6* gene that is strongly associated with iron deficiency anemia is rs855791. This gene encodes matriptase-2, which interacts with and promotes the cleavage of hemojuvelin on the cell surface, leading to the release of soluble hemojuvelin and inhibiting hepcidin expression [17,18,21,22]. This gene polymorphism is linked to a reduced ability to decrease hepcidin production, thereby causing increased levels in the circulation despite iron deficiency. Furthermore, matriptase-2 dysfunction is associated with iron-refractory iron deficiency anemia [17,21,23].

Iron deficiency has a multifactorial etiology involving complex interactions between genetic and nongenetic factors. Although GWASs have identified risk alleles for complex genetic characteristics related to iron status, the detected risk alleles did not fully explain heritability. Moreover, the impact of allele frequency and biological adaptation varies across ethnicities owing to environmental and physiological factors. This complexity presents a challenge in effectively addressing the contributing factors of iron deficiency in the population [17,21].

In Indonesia, research on the association of genetic variations and nongenetic factors with iron deficiency remains limited, particularly in vulnerable populations, including female medical students, who are part of the representative population of women of reproductive age. They are susceptible to the risk of developing iron deficiency. Moreover, this group is particularly relevant to study owing to its more homogeneous characteristics. Despite having good knowledge of preventing iron deficiency anemia, they frequently practice unhealthy eating habits, including skipping breakfast, snacking, consuming fast food, and lacking fruit and vegetable intake, and unhealthy lifestyle habits, such as not engaging in physical activity due to heavy study loads and extracurricular activity schedules in college. Furthermore, they experience physiological menstrual blood loss and remain in a growth period that requires adequate nutritional intake [24,25].

This Study

Several studies in India, Pakistan, Iran, and Saudi Arabia have reported a significant rate of iron deficiency and anemia among female medical students, ranging from 16% to 63%, especially among those who live in dormitories and have a low or high BMI [24-29]. However, in Indonesia, only 1 study on female medical students with a sufficient socioeconomic background revealed a relatively low anemia prevalence of 13.6% [30]. The approach to managing iron deficiency has yet to fully consider genetic and nongenetic factors. Consequently, despite efforts to promote the distribution of iron supplements, the prevalence

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of iron deficiency remains high. Identifying the primary determinants of iron deficiency is crucial for more efficient management strategies. By recognizing these determinants, efforts can be made to increase the body's iron reserves and provide appropriate prevention and treatment. Identifying these factors is also valuable in preparing adolescent girls for pregnancy to prevent and reduce the risk of maternal mortality, preterm delivery, low birth weight, and stunting. Therefore, our study aims to analyze the association of the *TMPRSS6* rs855791 variant and nongenetic factors with iron deficiency in apparently healthy female medical students.

Methods

Study Design and Setting

This study will use a case-control design. Cases and controls will consist of medical students at the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada in Yogyakarta, Indonesia. Participants will be selected using purposive sampling according to predefined inclusion and exclusion criteria. The study will specifically target final-year female undergraduate medical students (aged 18-24 years) before entering the clinical clerkship phase; who have provided written informed consent; are not pregnant; and have no history of chronic and inflammatory diseases, congenital diseases, hematological disorders, or blood transfusions within the previous 3 months. Participants with elevated levels of the inflammatory biomarker C-reactive protein (CRP; elevated level defined as >5 mg/L) will be excluded. Study participants will be classified into the control and case groups based on their serum ferritin (SF) and hemoglobin levels. A case-control ratio of 1:1 will be applied. The matching condition will be an age difference of less than 3 years. The control group will include participants with normal hemoglobin (≥12 g/dL) and SF (≥30 µg/L) levels. The case group will include participants with iron deficiency. Iron deficiency will be determined based on SF levels of less than 30 µg/L with or without anemia [10,31].

Sample Size

This study will be conducted from February 2025 to January 2026. The sample size will be determined using the unpaired categorical analytical research sample size formula with a confidence level of 95%, α of 5%, and research power of 80% (with β of 20%). The sample size calculation will use the proportion of exposed controls and the odds ratio of each independent variable for the risk of iron deficiency, yielding a minimum required sample size of 116 participants (58 cases and 58 controls). This sample size will ensure adequate statistical power to examine the influence of sociodemographic characteristics (type of residence and parental income), BMI, menstrual pattern, iron intake, and the *TMPRSS6* rs855791 genetic variant on the risk of iron deficiency.

Data Collection and Analysis

We will use questionnaires for collecting data on the demographics, medical history, and socioeconomic information of the participants. The dietary iron intake of the participants will be assessed using the IRON Intake Calculation-Food Frequency Questionnaire, which has been modified and evaluated for validity and reliability [32]. This questionnaire contains information about the primary sources of iron, which are divided into 12 food groups, including meat, processed meat, eggs, fish, dairy products, cereal products, fruits, vegetables, tubers, oils, nuts, and chocolate products. For each food group included in the questionnaire, participants will be asked to report portion sizes and consumption frequency over the preceding week. The total weekly iron intake calculated from these responses will then be divided by 7 to estimate the mean daily iron intake. The NutriSurvey software will be used for analyzing iron intake [32,33]. Participants' nutritional status will be measured using BMI. Menstrual patterns will be evaluated using a menstrual pictogram for 2 menstrual cycles. Menorrhagia is defined as menstrual bleeding exceeding 80 mL for each cycle [34,35].

Laboratory investigations will be performed as mentioned subsequently. In total, 7 mL of venous blood will be collected under aseptic conditions between 8 AM and 11 AM using 2 different tubes. A total of 3 mL of blood will be collected from each participant using an ethylenediaminetetraacetic acid tripotassium salt tube, with 2 mL of blood allocated for hemogram and reticulocyte profile analysis and 1 mL for genotyping. All laboratory analyses will be performed in accredited laboratories, strictly following the manufacturer's instructions and under Good Clinical and Laboratory Practice conditions with internal quality controls to ensure accuracy and reliability. The hemogram and reticulocyte profile will be analyzed within 1 hour following sample collection using an automated hematology analyzer, Mindray BC-760 (Mindray Corporation). The remaining 4 mL will be collected into plain gel separator tubes and subsequently centrifuged. Serum samples will be stored at –20 °C for CRP and SF examinations and at –80 °C for serum hepcidin examinations. A cobas c 111 analyzer (particle-enhanced immunoturbidimetric assay; Roche Diagnostics), a VIDAS analyzer (enzyme-linked fluorescent assay; bioMérieux), and a sandwich human enzyme-linked immunosorbent assay kit (catalog number EH3221; Wuhan Fine Biotech Co, Ltd) will be used for CRP, SF, and serum hepcidin measurement.

Genotyping Procedure

Genomic DNA will be isolated from 1 mL of ethylenediaminetetraacetic acid–anticoagulated whole blood using a commercially available DNA extraction kit (gSYNC DNA Blood Mini kit; catalog number 51104; Geneaid Biotech Ltd), following the manufacturer's protocol. The concentration of the extracted DNA will be assessed using a NanoDrop spectrophotometer (MaestroGen) to assess the A260/A280 and A260/230 absorbance ratios. All extracted DNA samples will be preserved at –80 °C. *TMPRSS6* genotyping for the rs855791 polymorphism will be conducted using the TaqMan genotyping assay protocol (Applied Biosystems). PCR will be performed using a Taq DNA polymerase kit following the manufacturer's instructions.

Data Analysis Plan

The collected data will be categorized into quantitative and qualitative data. SPSS Statistics (version 22; IBM Corp) will be used for the analysis. The Kolmogorov-Smirnov test will be

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used to assess whether the data follow a normal distribution. If the data are normally distributed, quantitative data will be presented as means and SDs; if not, the data will be presented as medians (minimum and maximum). Qualitative data will be presented as frequencies and percentages.

Parameters measuring hemogram profiles and iron status will be compared between the case and control groups using the independent samples 2-tailed *t* test or Mann-Whitney *U* test. Differences in genotype and allele frequencies between the case and control groups will be evaluated using the chi-square test. To determine the effects of individual SNPs on iron markers, comparison of iron status across the genotyping classes (AA, AG, and GG) will be performed using 1-way ANOVA or the Kruskal-Wallis test. Assessment of bivariate associations between each independent variable and the outcome (dependent variable) will be conducted using the chi-square or Fisher test. Risk factors with a P value of <.25 in the bivariate analysis will be further analyzed through multivariate logistic regression analysis.

All risk factors meeting the aforementioned selection criteria will be entered one by one in the multivariate analysis, starting with the most significant factors from the bivariate analysis. The selection of the final model equation will be based on parsimony, biological interpretability, and statistical significance ($P \leq .05$). This final model equation will be assessed using the Hosmer-Lemeshow test and the area under the curve value obtained through receiver operating characteristic analysis. Subsequently, the results of this final equation will be used for predicting the probability of iron deficiency.

Ethical Considerations

The study protocol has been formally approved by the medical and health research ethics committee of the Faculty of Medicine, Public Health and Nursing, Universitas Gajah Mada in Yogyakarta, Indonesia (KE/FK/0114/EC/2025). Prior to enrollment, written informed consent will be obtained from all participants after they have been fully informed about the study objectives, procedures, potential risks and benefits, and the voluntary nature of their participation. To ensure confidentiality, all collected data will be securely stored with access restricted to authorized members of the research team. As a token of appreciation for their time, participants will receive a snack following the blood draw and reimbursement of Rp 50,000 (US $3.02) for transportation costs.

Results

Data collection commenced in February 2025 and is expected to conclude by October 2025. Data analysis is scheduled for completion by the end of 2025, with the publication of study findings anticipated in 2026.

Discussion

Anticipated Findings

Anemia remains a prevalent health issue in LMICs, with iron deficiency identified as its primary cause. Most anemia cases are preventable and manageable, provided that the underlying causes are identified. Consequently, recognizing the multifactorial etiology of anemia is crucial for developing effective and tailored therapeutic strategies [36]. We anticipate that this study will identify both genetic variations and nongenetic factors impacting the risk of iron deficiency.

Several GWASs have consistently demonstrated a strong correlation between iron status and variants in the *TMPRSS6* gene, particularly the SNP rs855791, across various populations, predominantly in Asia. Despite the significant burden of iron deficiency in Asia, particularly in Southeast Asian nations such as Indonesia, studies focusing on unique gene variants associated with iron homeostasis in humans remain limited [18,21].

Studies by Hamed et al [37] and Elmahdy et al [38] revealed that individuals with iron deficiency or iron deficiency anemia exhibited a significantly increased frequency of the rs855791 variant (both heterozygous and homozygous) compared with the control group. Conversely, Jallow et al [20] and Varikuti et al [39] did not observe any association between this variant and the iron status. Shinta et al [19] investigated children aged 12 to 17 months in the Sasak community of East Lombok regency, West Nusa Tenggara province, Indonesia, and reported that iron intake had a stronger influence on SF levels than the rs855791 polymorphism. Building upon these findings, our study is anticipated to provide further evidence regarding the prevalence and potential role of the rs855791 gene variant in the Indonesian population, particularly among female medical students.

Research results from LMICs have indicated that nongenetic factors, including poor socioeconomic status, illiteracy, lack of formal education, an interpregnancy interval of less than 2 years, excessive menstrual bleeding, living in rural areas, the lack of physical activity, poor nutritional intake, low BMI, obesity, and insufficient knowledge regarding anemia, can all contribute to anemia, particularly iron deficiency–induced anemia [16,25,27,28,36,37]. Most existing research has focused on isolated risk factors, either genetic or nongenetic, with limited investigation into their combined effects. Only a few studies have explored the interaction between genetic factors and a single nongenetic factor. Shinta et al [19] investigated the relationship between *TMPRSS6* gene polymorphism and iron intake on the risk of iron deficiency, whereas Pei et al [22] reported that certain genetic variations have a protective role against iron deficiency anemia among women with menorrhagia. The occurrence of iron deficiency involves a multifactorial interaction between genetic and nongenetic determinants. We aim to identify the interplay between these factors and susceptibility to iron deficiency in the specific context of female medical students. A comprehensive understanding of both genetic and nongenetic contributors will support the development of targeted and evidence-based therapeutic approaches informed by the identified causal factors.

Strengths and Limitations

A notable strength of this study lies in its comprehensive methodology for investigating both genetic and nongenetic factors associated with iron deficiency among female medical students. Iron intake, nutritional status, menstrual patterns, and sociodemographic characteristics will be the nongenetic variables assessed, whereas the genetic aspect will focus on the

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rs855791 variant. In addition, serum hepcidin levels, a key regulator of iron homeostasis associated with the rs855791 variant and other iron-related biomarkers, will be measured. Despite these strengths, several limitations should be acknowledged. First, hemoglobin electrophoresis will not be performed in the case group, thereby limiting the ability to detect coexisting conditions, such as thalassemia trait, in participants with iron deficiency. Second, this study will not include measurements of vitamin D levels. Given vitamin D's role in regulating hepcidin expression, its deficiency may lead to elevated hepcidin levels, thereby reducing iron bioavailability and contributing to iron deficiency [40,41]. Third, the recruitment of participants from a single academic institution may limit the external validity of the findings, potentially constraining their generalizability to the broader population of women in Indonesia. Nevertheless, the conceptual framework and integrated methodological approach addressing both genetic and nongenetic factors may meaningfully contribute to community-based iron deficiency screening strategies, particularly for young, educated women in urban areas.

Further research is recommended to address this study's limitations, including the assessment of hemoglobin electrophoresis and vitamin D levels, which may affect the accuracy of iron deficiency evaluation, by expanding recruitment to a larger, multicenter scale. Moreover, subsequent studies should investigate the efficacy of treatment approaches for iron deficiency based on the causal determinants identified in this study.

Conclusions

Our study aims to elucidate how genetic and nongenetic factors contribute to the risk of iron deficiency in women of reproductive age, especially female medical students in Indonesia. The results are expected to provide valuable insights into the primary determinants contributing to iron deficiency in this population.

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Authors' Contributions

FF designed the study protocol, developed data collection tools, coordinated data collection and analysis planning, and wrote the manuscript. EK, TR, DAAN, JF, and SS reviewed the manuscript and provided significant input. All authors have read and approved the manuscript before submission.

Conflicts of Interest

None declared.

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Abbreviations

CRP: C-reactive protein
GWAS: genome-wide association study
LMIC: low- and middle-income country
SF: serum ferritin
SNP: single-nucleotide polymorphism
TMPRSS6: transmembrane protease serine 6

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Protocol

Emerging Interventions to Improve Health Outcomes for People Aging With HIV: Protocol for a Mixed Methods Implementation Science Evaluation

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Abstract

Background: In 2022, 54% of people with HIV were aged 50 years and older; however, clinical care for HIV in the United States often falls short of comprehensively integrating care for aging-related conditions. In response, the Health Resources and Services Administration HIV/AIDS Bureau Ryan White HIV/AIDS Program funded a new initiative comprising 10 demonstration sites to test emerging interventions to support people aging with HIV, as well as a capacity-building provider and an evaluation provider. NORC at the University of Chicago received an award for the evaluation provider.

Objective: This protocol aimed to describe the application of the Health Resources and Services Administration HIV/AIDS Bureau implementation science (IS) framework to a multisite evaluation, a related evaluation protocol, the technical assistance provided to support the evaluation, and the initiative's dissemination plan.

Methods: Using a theory-based approach, NORC developed a mixed methods evaluation plan using an IS hybrid type 2 study with two main aims: (1) to describe implementation outcomes and (2) to assess client-level outcomes. Implementation outcomes were assessed at the organizational level using tools including a survey of site characteristics, key informant interviews, and documentation of monthly monitoring calls and costs. Client-level outcomes were assessed through a survey and a medical chart abstraction tool. NORC also collected data on the sites' engagement with the capacity-building provider and their satisfaction with the services provided.

Results: The evaluation was funded in August 2022. Organizational-level data collection began upon institutional review board approval in April 2023. All sites were enrolling clients in the intervention and evaluation by September 2023, and 626 clients enrolled by December 2023. Data collection is expected to continue through December 2024. Analysis of the baseline results is currently underway, and comprehensive findings are expected by late 2025.

Conclusions: To the best of our knowledge, this is the first national study to evaluate emerging clinical interventions for people aging with HIV using an IS framework. The findings will build an evidence base for advancing HIV clinical care to meet the needs of the aging population.

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KEYWORDS

implementation science; evaluation; HIV and aging; geriatric care; emerging interventions

Introduction

Background

Advances in HIV treatment have yielded profound improvements in life expectancy and quality of life among people with HIV. More than half of the people with HIV in the United States are now aged 50 years or older [1]. Health Resources and Services Administration (HRSA) HIV/AIDS Bureau (HAB) Ryan White HIV/AIDS Program clients are increasingly older as well. In 2022, 48.2% were aged 50 years and older and 24% were aged 60 years and older [2]. Relative to their younger peers, older adults with HIV are more likely to be retained in care and achieve viral suppression [1], although not all groups benefit equally, and certain populations continue to experience lower viral suppression rates [2].

Current comprehensive HIV care programs often fall short of meeting the variety of co-occurring age-related issues experienced by people aging with HIV. These include comorbidities associated with aging, as people aging with HIV are disproportionately diagnosed with chronic kidney disease, chronic obstructive pulmonary disease, osteoporosis, cardiovascular disease, diabetes, chronic hepatitis, end-stage liver disease, lung cancer, and colorectal cancer relative to other adults of the same age, reducing their overall quality of life [3,4]. Geriatric syndromes such as frailty, falls, and functional impairment are also common in people aging with HIV and are experienced at relatively younger ages compared to the general population [5]. Furthermore, people aging with HIV diagnosed earlier in the epidemic received an array of treatment regimens with varying levels of efficacy. There is evidence that the cumulative toxicity of these various treatments over time may have impacted organ functioning [6]. Despite the complexity of multimorbidity, there exists a nationwide shortage of dually trained HIV and aging specialists who are capable of delivering multidisciplinary care to older adults [7]. The clinics where they work also face persistent challenges in obtaining reimbursement for geriatric assessments, creating structural barriers that limit the integration of geriatric care into standard HIV care visits [8].

In addition to medical conditions, people aging with HIV are more likely to be diagnosed with substance use disorders and mental health challenges compared to the general population and experience psychosocial needs related to social isolation, loneliness, stress, and stigma [9]. These experiences may be related to losses through the untimely death of partners, close friends, and community members during the height of the AIDS epidemic, as well as a lack of informal, peer, or familial support and additional discrimination, rejection, or abuse when they seek long-term care via professional care services, such as home care, retirement homes, or skilled nursing facilities [10,11].

While these medical and psychosocial conditions can be managed using tailored treatment guidance, existing screening measures, and other efforts to integrate HIV care into existing geriatric primary health care delivery services, there remains a notable absence of comprehensive, evidence-based programs to support the medical and psychosocial needs of people aging with HIV. A recent review of efforts in the United States and other high-income countries identified several pilot programs designed to bridge this gap [12]. These programs often featured colocation of geriatric and HIV services, as well as comprehensive geriatric screenings delivered in HIV care exams. Although these initiatives have demonstrated feasibility and have suggested potential benefits to clients, their evidence remains preliminary. Importantly, many of the reported programs have since been discontinued, limiting the ability to assess their sustainability, scalability, or long-term outcomes. Consequently, the current evidence base is insufficient to inform the development of standardized care models. Rigorous evaluation using an implementation science (IS) framework can examine promising approaches to address aging-related issues for people with HIV, further building the evidence base of effective interventions to improve health outcomes and quality of life in this population.

Overview of the Aging With HIV Initiative

To address these identified gaps in comprehensive services for people aging with HIV, the HRSA Ryan White HIV/AIDS Program Part F Special Projects of National Significance (SPNS) program funded the Emerging Interventions to Improve Health Outcomes for People Aging with HIV initiative (also called the Aging with HIV initiative). This initiative supports 10 demonstration sites, an evaluation provider, and a capacity-building provider (CBP) to jointly implement and evaluate emerging interventions to screen and address comorbidities, geriatric conditions, behavioral health, and psychosocial needs of people aging with HIV.

Table 1 lists the demonstration sites of the Aging with HIV initiative, their geographic location, the name of the intervention, the emerging intervention or framework, and a description of their approach. Where applicable, we cited any literature that the demonstration sites used in the development of their interventions. Sites were encouraged to involve patient liaisons as people with lived experience to inform the implementation of their strategy.

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Table 1. Demonstration site name, location, intervention, and program description.

Location	Intervention name	Program description	Reference
Colorado Health Network, Inc, Denver, Colorado	Integrated Care for Healthy Aging and Navigation of Geriatric Effects (iCHANGE)	Implementing patient-centered, integrated geriatric screening, assessment, coordinated care planning, and management approach based on the geriatric 5Ms (mind, mobility, medications, multicomplexity, and matters most to me) framework.	[13]
Empower U Inc, Miami, Florida	Educating and Empowering People Aging with HIV (E&E program)	Enhancing a "one-stop shop" to provide a suite of services, including dental services, nutritional services, social support groups, and cognitive support groups.	[14,15]
Family Health Centers of San Diego, San Diego, California	Intensive Individualized Care Coordination to Enhance Health and Quality of Life for HIV-Positive Older Adults in San Diego, California (I^2C^2)	Comprehensively screening and managing medical and psychosocial comorbidities through improved assessment processes, optimized care coordination, a community advisory board, individualized socialization action planning, and interdisciplinary staff training.	[16,17]
Centro Ararat, Inc, Ponce, Puerto Rico	Platinum Premier Program—integrated care	Implementing a holistic suite of services, including the "friendly hand" of the geriatric health worker, an integrated mental health program, a patient-centered educational and empowerment program, and enhanced health care provider skills in the aging process.	[13]
University of Chicago, Chicago, Illinois	HIV Dementia Champion Training Program—expansion of dementia assessment and management capacity	Expanding dementia assessment and management within care clinics via a staff training program adapted from Scotland's National Dementia Champions Program and the Dementia Resource Champions program on the South Side of Chicago.	[18]
University of Pittsburgh Medical Center Presbyterian Shadyside, Pittsburgh, Pennsylvania	IMPACT (Improving the 6Ms at Pittsburgh Area Center for Treatment) based on the 5Ms model of care: mind, mobility, multicomplexity, medications, matters most, and modifiable	Implementing an adapted version of the 5Ms framework with an added M (modifiable) to improve patient safety, health outcomes, and care satisfaction through health care provider training, patient screening, and workflow improvements.	[19]
Beth Israel Medical Center, New York, New York	Incorporating a community health worker into a comprehensive program of integrated care for older adults with HIV	Expanding and refining an interdisciplinary pilot program offering a practice-within-practice model to create efficiencies and provide comprehensive geriatric assessments to older adults with HIV.	[8,13,20-22]
Boston Medical Center Corporation, Boston, Massachusetts	HIV-Endurance (HIVE) clinic	Establishing a referral-based, integrated infectious disease and geriatric clinic for patients living with HIV to identify, refine, and assess strategies that comprehensively screen and manage comorbidities, geriatric conditions, behavioral health, and the psychosocial needs of people living with HIV aged 50 years and older.	[8,22]
Wake Forest University Health Sciences, Winston-Salem, North Carolina	Targeting Frailty in Persons Aging with HIV	Implementing geriatric screening assessments for people with HIV aged 50 years and older, focusing on people with frailty or prefrailty by the electronic frailty index. Offering interventions to promote successful aging and combat frailty and prefrailty, including a customized activity and nutrition plan.	[23,24]
Yale University, New Haven, Connecticut	Intervention for collaborative care to assess risk and eliminate polypharmacy, falls, and fragility fractures for people aging with HIV (4F)	Developing a collaborative care model using the 4F framework to manage conditions associated with aging in HIV, improving care delivery, and reducing health disparities.	[25-28]

Health Research, Inc., part of the New York State Department of Health, received the CBP award to support sites through various activities, including one-on-one coaching from implementation specialists. The CBP also plans and hosts a 7-session learning collaborative across the first and second years of the initiative to bring sites together in their coaching groups, share progress on their protocols, facilitate peer-to-peer learning, and develop action plans for the upcoming months.

NORC at the University of Chicago received the evaluation provider award. Incorporating the HRSA HAB IS approach, NORC designed a multicomponent evaluation as an IS hybrid type 2 study with two overarching goals to assess the following:

1. Implementation outcomes, including barriers to and facilitators of implementation, costs, integration into practice, and sustainability

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2. Impact of the emerging interventions on client outcomes, including continuum of care outcomes, quality of life, and health care satisfaction

Purpose

This paper describes 10 demonstration sites integrating HIV and aging-related services, the instruments used to evaluate their activities, the technical assistance (TA) provided for evaluation, and plans to disseminate findings to the broader Ryan White HIV/AIDS Program community and the HIV field. The included sites are distributed nationally and include a variety of settings, from community-based health centers to large academic medical centers, acknowledging that aging needs can vary geographically and culturally and are often relative to the available resources within participating institutions. Clients aged 50 years and older with HIV were eligible for enrollment in the intervention and evaluation. Sample sizes for the evaluation are detailed subsequently.

Methods

Overview

NORC will apply 3 complementary IS frameworks to evaluate the Aging with HIV initiative. These are the HAB IS [29]; the reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) [30]; and the Consolidated Framework for Implementation Research (CFIR) [31] frameworks. The HAB IS acknowledges that the uptake and integration of intervention strategies are affected by implementation strategies and broader contextual barriers and facilitators. The HAB IS framework seeks to answer the following core questions:

- Was the intervention strategy successfully implemented in the setting?
- What about the context and environment that shaped its implementation?
- Were the clients successfully engaged in the intervention?
- Were there associated improvements in client outcomes along the HIV care continuum?

The HAB IS calls for integration with other IS frameworks for a more holistic view of implementation outcomes [29]. RE-AIM offers a pragmatic structure to define what constitutes implementation success by assessing the reach and characteristics of participating clients, the degree of organizational and staff adoption, the outcomes of interventions (whether positive, negative, or null), the extent of integration into routine practice, and the sustainability of these outcomes beyond the funding period. The CFIR provides a comprehensive set of constructs across 5 domains—intervention characteristics, inner setting, outer setting, individual characteristics, and process—that enable systematic exploration of the contextual factors shaping implementation.

The combination of these frameworks is uniquely suited to address the gaps identified in aging with HIV interventions, and this combination has been successfully used in other studies. HAB IS provides a solid foundation for testing the intervention and tracking and categorizing the progression of evidence from emerging to evidence-based. RE-AIM defines and measures outcomes from multiple aspects to determine whether those interventions achieve meaningful uptake, effectiveness, and sustainment. CFIR then supplies the theoretical and contextual depth to explain why interventions succeed or fail in particular settings, offering valuable information for replicators to understand potential adaptation. Together, these frameworks allow for the simultaneous testing of implementation strategies, evaluation of client and service outcomes, and systematic identification of contextual determinants, thereby producing actionable knowledge to inform replication and scale-up in diverse care settings.

With a combined framework grounding the evaluation, NORC will design and conduct a hybrid implementation-effectiveness study that dually focuses on implementation processes and implementation, service, and client outcomes [32]. A hybrid study design allows for simultaneous intervention testing and analysis of health data (eg, changes along the HIV care continuum), aligning with the goals of the HAB IS, RE-AIM, and CFIR.

The first objective of NORC's IS approach is to study rapid implementation using a systematic approach to identify effective emerging interventions, determine their core elements, and disseminate them through multimedia toolkits that are easily accessible and facilitate rapid replication. While there are promising interventions to address aging-related issues in people aging with HIV, there is generally a paucity of research on what is effective. Research that has been conducted typically has small to moderate effects or small sample sizes that limit generalizability. Thus, additional research using the HAB IS framework is critical for strengthening the evidence on effective interventions for people aging with HIV and ultimately improving their health outcomes [33].

The second objective of NORC's IS approach is assessing client and implementation outcomes, implementation strategies, and barriers and facilitators. The HAB IS model provides a structure for transforming emerging interventions into evidence-informed interventions and, ultimately, into evidence-based interventions [29].

NORC selected this combination of frameworks to comprehensively capture and describe the factors that influence the implementation of the emerging interventions selected by the demonstration sites. For example, Figure 1 describes how these frameworks were applied to structure the project in 3 phases: preparing for data collection, conducting the evaluation and providing data collection TA, and supporting dissemination and replication. During each phase, the project is guided by a panel of subject matter experts with experience caring for those aging with HIV, individuals who themselves are aging with HIV, and end users of emerging intervention dissemination materials. The HRSA HAB and demonstration sites provided input on the evaluation plan and instruments throughout their development.

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Figure 1. Phases of evaluation. CBP: capacity-building provider; IRB: institutional review board; MSE: multisite evaluation; SSE: specific site evaluation; TA: technical assistance.

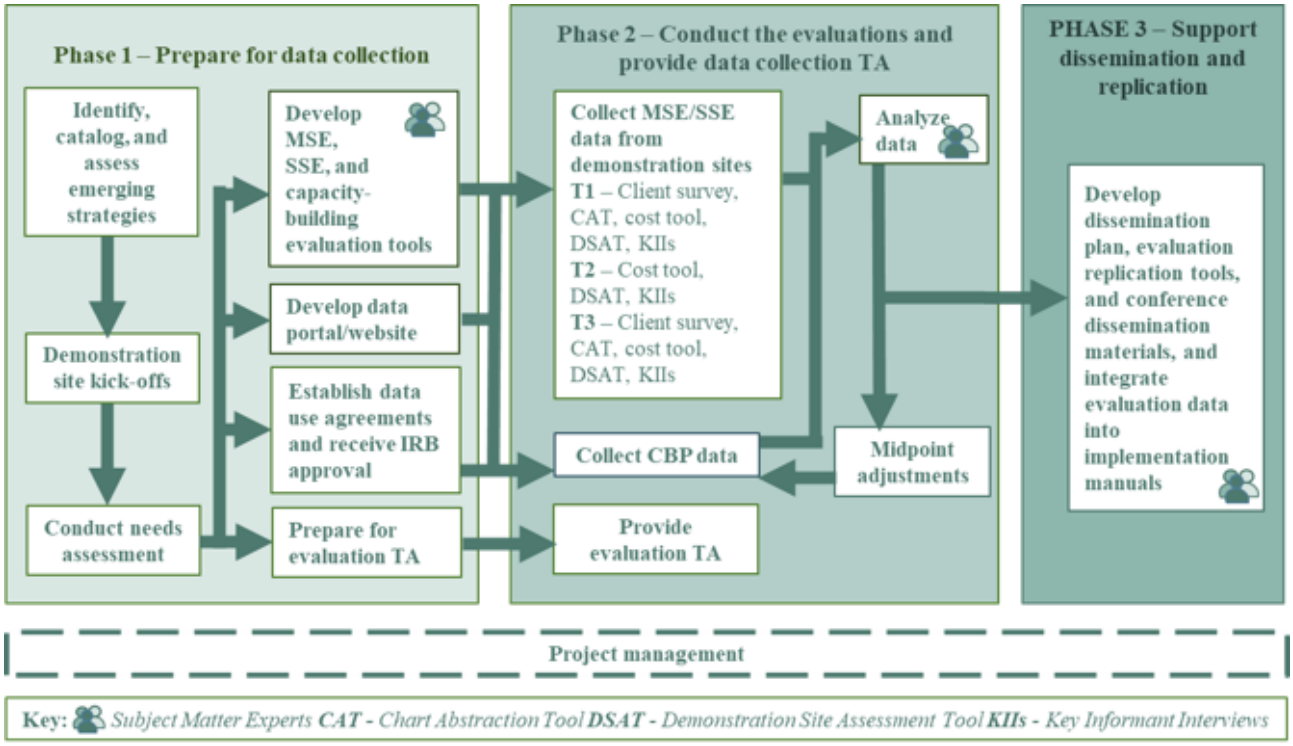

NORC's mixed methods IS evaluation relies on information collected from demonstration sites and clients to inform 3 different aspects of the evaluation, which will be informed by different data collection instruments:

- Multisite evaluation—Demonstration Site Assessment Tool (DSAT) survey, key informant interviews (KIIs), client survey, cost tools, monthly call notes, and a chart abstraction tool (CAT), which relies on sites to abstract chart data describing key outcomes
- Site-specific evaluation—modules added to the client survey upon the site's request
- CBP evaluation—DSAT, KIIs, and a quarterly CBP evaluation survey

The data collection structure was initially based on the protocol and lessons learned from the Implementation of Evidence-Based Behavioral Health Models to Improve HIV Health Outcomes for Black Men who have Sex with Men SPNS initiative [34], which used similar instruments. NORC completed the development and selection of these instruments for the Aging with HIV initiative in conjunction with the demonstration sites, taking into consideration the anticipated client and staff burden, as well as expectations from the funder. Efforts to decrease the burden and promote site buy-in included reducing administration frequency and length of instruments, reducing duplication (eg, client Patient Health Questionnaire scores were not collected in both client-facing and CATs), and aligning administration time points for multiple instruments. Sites were required to participate in the evaluation and support data collection according to the terms of their grant.

Data will be collected at 3 main time points over the course of the initiative. The timing within each site will depend on when the site begins implementation. Baseline data collection will occur at or before the implementation begins, midpoint, and end point. The time point for each instrument is described subsequently.

Needs Assessment

NORC began the evaluation by reviewing all submitted materials to establish the maturity of the intervention and any previous evaluations. NORC also assessed each site's readiness to conduct evaluations based on the plans submitted to HRSA. NORC compiled the results of the needs assessment and met with HRSA to discuss potential barriers to and facilitators of the evaluation, as well as any potential adjustments needed to the evaluation plan.

DSAT Survey

The DSAT documents quantitative, site-level implementation outcomes that are mapped to the overarching research questions. Key domains were built on the RE-AIM and CFIR domains and included staffing, client enrollment in the intervention, client needs for health care and social services, partnerships, organizational culture, leadership, factors influencing implementation, funding sources, and sustainability. NORC encourages sites to meet as a team to complete 1 DSAT response per site at baseline, midpoint, and follow-up to assess how implementation changes over time.

KII Data

KIIs are particularly useful in two contexts: (1) taking an in-depth look at a particular topic that emerged through a TA interaction, and (2) conducting detailed reviews with implementation sites and the CBP to assess emerging quantitative results in a structured way to ensure correct understanding and add richness to the findings. NORC will take detailed notes and conduct rapid thematic analysis for

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site-specific and cross-site themes. Potential respondents for KIIs include principal investigators, project managers, and patient liaisons, with at least 1 respondent per site at baseline, midpoint, and follow-up.

Client Survey

Outcomes related to exposure to interventions, experience with health care services, and quality of life (EQ-5D) must be measured with data from clients. We developed a brief client survey that balances the need for client data while minimizing the burden on intervention clients. Where such measures existed, we included validated measures that have been applied in HIV care settings, including other SPNS projects, as shown in Table 2. The Office of Management and Budget updated the standards for race and ethnicity measurements after baseline, which will be updated for follow-up.

Table 2. Survey domains from validated scales and similar projects.

Item or domain	Source
Race and ethnicity (at baseline)	OMB[a] [35]
Race and ethnicity (at follow-up)	OMB [36]
Quality of life	EQ-5D [37]
Unmet needs for mental health services	Black MSM[b] SPNS[c] initiative [34]
Care satisfaction	Black MSM SPNS initiative [34]
Cultural humility	ESCALATE SPNS initiative [38]
Loneliness	University of California, Los Angeles Loneliness Scale [39]
Acuity	American Community Survey [40]
Frailty	FRAIL[d] scale [41]

[a]OMB: Office of Management and Budget.

[b]MSM: men who have sex with men.

[c]SPNS: Special Projects of National Significance.

[d]FRAIL: fatigue, resistance, ambulation, illness, and loss of weight.

We offered each site multiple approaches to recruit clients and complete the self-administered survey electronically or on paper, with a preference for electronic administration to minimize the staff time needed for data entry. We provided each site with a QR code and survey link that they could share via email, clinic messaging portal (eg, MyChart), or signage. TA coaches asked sites about clients' needs for adaptation, particularly for translation into other languages. As a result, versions of the survey are available in English, Spanish, Haitian Creole, and Arabic, with translations provided by a certified translation company that is tailored to the specific dialects used by demonstration site clients. Adaptations of the paper survey include these translations and a low-vision, high-contrast version in English. These data will be collected at the baseline and at the project conclusion.

NORC offered sites the option to add site-specific questions to the client survey to measure outcomes particular to each emerging strategy. Given that the client survey is comprehensive and already includes many of the site-specific outcomes, only 2 sites requested additional data collection. These include questions on relationship satisfaction, self-care satisfaction, substance use, food insecurity, servings of fruit and vegetables, and exercise frequency.

NORC calculated site-specific baseline enrollment targets based on the number of clients anticipated to be enrolled in each site's intervention, given their capacity for the pilot nature of the interventions and in conversation with the funder. We then accounted for refusals and losses to follow-up to arrive at a site-specific sample capable of producing estimates with an error margin of less than 5% for reasonable effect sizes. The baseline enrollment targets at each site ranged from 30 to 150 participants, with an average of 66 participants per site.

On the basis of the early feedback received from implementation sites to put survey data into action for care improvement, we will compile all completed surveys weekly and share them with sites via a secure platform for their review and follow-up. Given that certain questions can be used in a clinical setting as screening tools, we will calculate each client's score and apply stoplight-style color coding. This will facilitate the clinical staff's review of the client responses and rapid response. We will also highlight any surveys that remain incomplete for 2 weekly downloads and ask the site to follow up with the client.

Cost Tool

Total intervention costs will be assessed by combining the total HRSA-provided funding with other funding sources and in-kind or volunteer supports. Key domains include staffing, intervention-specific space, intervention materials, other direct costs, and indirect costs. We will use this information to calculate the total intervention cost and cost per client served. Should the intervention result in meaningful changes to the client's quality of life, we will assess quality-adjusted life years and cost-effectiveness per US $100,000 saved in societal costs. To assist potential replication sites in estimating the cost of each emerging strategy, we will qualitatively assess the percentage of funding spent on clinical services and other replicable components (eg, client engagement and community partnership) relative to HRSA HAB SPNS initiative requirements (eg, grants

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administration, learning sessions, protocol development, and other dissemination tools) that would not pertain to potential replication sites funded by means other than a SPNS initiative.

Monthly Call Notes

We will evaluate TA calls with each demonstration site on a monthly basis in collaboration with the CBP and the site's HRSA project officer. Each demonstration site will be asked to complete a monthly call form at least 5 days before the joint monitoring call, which will allow time for HRSA, NORC, and the CBP to review the information and prepare for the discussion. During the calls, the demonstration sites will elaborate on the information they provide in the monthly call form related to implementation strategies, activities, ongoing challenges, mitigation strategies, successes, and lessons learned related to implementing their emerging interventions. The HRSA, NORC, and CBP will have the opportunity to ask follow-up questions. During the discussion, NORC evaluation TA coaches will update and annotate the monthly call form so that it is the document of record for sites' activities. Following the call, NORC team will review and finalize the notes and updates in the monthly call form. The evaluation team will use the sites' monthly call forms and DSAT data to tailor the KII guide to each site before conducting the interviews. The monthly call form will also provide a record for noting any client who withdraws, as well as enrollments in the intervention after baseline client data collection has been completed.

CAT Data

Demonstration sites will be asked to abstract client data from their charts or electronic medical record systems and submit this via an Aging with HIV CAT. Clients will be asked to consent to having their selected clinic-level electronic medical record data shared with NORC when they consent to the client survey. This will include data on client screenings, use of services (and what type of services), engagement in care (eg, linkage to care and retention in care), referrals, antiretroviral treatment prescriptions, and viral load. They will provide these data at the same time points as the client survey, that is, baseline and end point.

The data will be used to track the influence of the emerging interventions being implemented at each site on screening and referral of geriatric conditions, as well as typical HIV-related outcomes. NORC will provide each site with a preassigned list of client identifiers. Sites will then assign clients a unique identifier from this at enrollment that will be tied to their chart data, enabling it to be linked to their client survey responses.

The CAT will also collect information on each site's anticipated outcomes to provide data for the site-specific evaluation. This will include data on diagnoses of neurological functioning (which cannot be reliably self-reported), weight, hypertension, cholesterol, referrals for services (including nutrition, oral health, mental health, memory care, physical therapy, and substance use treatment), unplanned hospitalizations, and emergency department visits. In addition, the CAT will collect information on client outcomes related to common HIV and aging comorbidities, geriatric conditions, behavioral health, and psychosocial needs. This will enable us to assess whether the emerging interventions used by the sites improve outcomes for people aging with HIV (goal 2).

As noted earlier, demonstration sites that collect data on sensitive issues related to client safety and require timely follow-up and mandatory reporting will be asked to share these data via a custom tab in the CAT. They will submit deidentified client data through a secure, password-protected, web-based portal and a data repository built in Microsoft SharePoint.

CBP Survey

The CBP evaluation survey is a brief, web-based survey that we programmed in Qualtrics and will be administered to sites' intervention teams on a quarterly basis throughout the preimplementation and implementation phases. The CBP evaluation survey will ask intervention teams to evaluate capacity-building activities that CBP has offered or facilitated with demonstration sites during the 3-month look-back period, such as the learning sessions, affinity group meetings, one-on-one coaching, and peer learning meetings. It will also capture the dosage, perceptions, and needs of implementation teams as related to the capacity-building activities they have engaged in over the previous quarter. We will provide the CBP and HRSA with a topline report on the findings to inform CBP's real-time quality improvement efforts.

Evaluation TA

We will offer TA to sites to support the completion of the abovementioned instruments. We will assign a staff member to be a single point of contact with each site and attend the monthly monitoring calls described earlier. We will also offer a dedicated inbox to receive and track TA requests that arise between calls. We will prepare an evaluation TA checklist to be completed along with the site during an in-person coaching visit. TA requests requiring more than minimal effort, such as responding to an email, will be documented for future analyses. In the first 18 months of the project, there were fewer than 20 such requests.

Ethical Considerations

We will develop study materials and submit them for clearance through NORC's institutional review board (IRB). NORC will implement a business associate agreement with each demonstration site (and the CBP, as appropriate) to facilitate the sharing of datasets for their own individual analyses. NORC will not begin data collection until we receive appropriate human participants' approval and have the necessary business associate agreements in place with the demonstration sites.

We will offer sites the opportunity to rely on NORC's IRB to facilitate obtaining the appropriate clearances for the collection of client data. For those sites that choose to use their own IRBs, we will provide instruments, consent forms, and protocols to support their applications. A total of 6 sites relied upon NORC's IRB. However, NORC's IRB will review and approve the organizational-level data collection instruments and methods for all sites.

NORC operates its own IRB, which is registered with the US Department of Health and Human Services Office of Human Research Protections (Federalwide Assurance 00000142). NORC's IRB follows a formal process for examining all

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research projects to ensure human participants' protections and minimize respondent burden. NORC will develop the IRB protocol to address human participants' protections that includes all study materials, such as recruitment materials, informed consent statements, and data collection instruments. This will include applying for a waiver of written consent for NORC to avoid collecting client names and to mitigate potential concerns of clients who may need to rely on caregivers to consent. Instead, as described in the informed consent, participants will be considered to have consented to the survey after reading the informed consent and clicking next (electronic version) or continuing to the survey questions (paper version). The informed consent will include instructions on how to withdraw consent in the future. NORC will provide TA to sites on ethical data collection standards and report any deviation of the data collection protocol to the IRB immediately. HRSA awarded a certificate of confidentiality automatically as part of the grant-making process, which covers all data collected under the evaluation. NORC did not offer compensation to respondents.

Analysis Plan

To ensure harmonization across the various data systems at the demonstration sites, we will ask a data liaison at each site to enter the data into the standardized tools described earlier. We will offer an evaluation TA to the data liaisons to train them in the tools and completion instructions, and respond to any issues or questions that arise. We will also conduct quality checks of the data as they are submitted, and spot-check a random sample of 10% of the data points during an in-person audit and coaching visit.

Once received, we will clean the data according to accepted data quality standards. We will then analyze and report data on an ongoing basis and, in collaboration with sites and HRSA, will provide data to inform intervention adjustments. Key methods will include unadjusted change in outcomes pre and postintervention and paired 2-tailed *t* tests for continuous outcomes. Because clients are nested within sites, we will also conduct sensitivity analyses using mixed-effects models with random intercepts for each site to account for clustering. Analyses will be conducted using complete case data, with sensitivity checks to evaluate the impact of missingness. Because client survey data are collected during routine program activities, the anticipated rate of missingness is relatively low. As findings emerge, we will review these in collaboration with sites in "data parties," to which the CBP and HRSA will be invited to provide input and contextualization [38]. NORC will make results available to all sites in the form of a master slide deck available on the internal SharePoint site. Sites requiring additional analyses will be able to make requests for NORC's assistance through their TA coach.

Dissemination Planning

Consistent with the IS approach, we will plan for rapid dissemination from the start of the initiative and focus as much on the barriers to and facilitators of implementation as on the resulting client outcomes. The evaluation findings will be part of an initiative-wide effort on dissemination led in partnership with HRSA, the CBP, and the demonstration sites. Expected venues for dissemination include TargetHIV.org, the training and TA repository for the Ryan White HIV/AIDS Program–funded programs, peer-reviewed publications, and professional conferences.

Results

Organizational-level data collection began with monthly call forms starting in April 2023, followed by the administration of the DSAT and then KIIs. The first site began recruitment for their intervention in May 2023 and enrollment in the evaluation in the same month. In all the sites, enrollment was underway by September 2023, and 626 clients were enrolled by December 2023 when baseline data collection ended. Evaluation enrollment and follow-up client data collection is expected to continue through December 2024. Key recruitment challenges included concerns about sharing personal information and challenges encountered in completing the online survey. Facilitators included showing clients how to use a QR code, offering paper surveys as an alternative, and providing incentives for completion. As of February 2024, 136 clients had withdrawn. The most common reason for withdrawing was sites losing contact, although a few clients withdrew their consent. Data submissions have met standards for quality and completeness after provision of evaluation TA, and no data issues were identified in on-site audits. Analysis of baseline data is currently underway and will inform midpoint and end point data collection. Comprehensive findings are expected in late 2025.

Discussion

Anticipated Findings

This paper outlines a protocol for the evaluation of emerging strategies to support people aging with HIV designed to assess key barriers to, challenges to, and facilitators of implementation, along with their potential effect on clients. Currently, HIV care in the United States lacks integration with geriatric care, and many of the pilot programs in this field have not been sustained or replicated [12]. Our nationwide sample of diverse care settings implementing a variety of aging-related supports will offer rich information analyzed with an IS lens to ensure that the findings are applicable to an array of clinical settings in the United States. We expect that the results of our evaluation will advance HIV clinical care nationally by contributing to the evidence base of efforts to integrate HIV care with aging-related care. The interventions we evaluate include general geriatric interventions adapted for people with HIV to best meet the needs of the people served by the various implementation sites. Consequently, providers of health care for people aging with HIV may likely identify relevant aspects that could be applied to their own practice.

Limitations

To the best of our knowledge, our study is one of the first of its kind to evaluate various aging-support interventions for people with HIV in different clinical and community settings nationally through primary data collection, but it is not without limitations. First, our sites include a variety of practices from large, academic medical centers to small, community-based clinics, yet all received grant funding for this initiative; therefore, our

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findings may not be representative of other practice models and health care providers attempting to do this work without additional resources. We will seek to highlight the approaches that show the most promise for implementation in diverse settings, including lower-resourced settings, such as the community health centers included in the initiative. This could include making available screening materials and electronic health record templates used in this initiative. Second, clients participating in the evaluation were largely already enrolled and retained in care by the sites in which they received the integrated services, which may introduce bias into our measurement of satisfaction and retention in care. The number of clients enrolled at each site depended largely on the nature of the intervention being piloted, and subgroup analysis of final data may be limited if participation is low. Finally, given the amount of time necessary to stand up new interventions within a defined initiative period, we may have insufficient time to detect longer-term client outcomes and their economic impact. We will acknowledge these limitations (eg, those related to sample size, temporality, and potential sources of survey error) in the dissemination of the empirical findings.

Despite these limitations, we are confident that our evaluation will yield important insights to inform implementation by other HIV care providers. Consistent with our IS approach, null and negative results are just as important for dissemination as positive results. Should the interventions fail to demonstrate measurable improvements in client health, our implementation information could help explain why that may have happened or what future replicators may need to do differently. We intend to disseminate findings through a peer-reviewed article describing the high-level findings from all demonstration sites, along with topic-specific articles (eg, approaches to addressing frailty) written in collaboration with demonstration sites. To assist practitioners, we will also develop publicly available fact sheets and case studies designed for rapid uptake by health care providers and other interest holders. The resulting dissemination products will provide practical contributions to building the evidence base for integrating an aging perspective into HIV care and will help other HIV care providers identify the strategy that best supports their clients aged 50 years and older.

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Data Availability

The datasets generated or analyzed during this study are not publicly available due to their nature as protected health information from vulnerable populations and corresponding restrictions among participating institutions.

Conflicts of Interest

None declared.

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Abbreviations

CAT: chart abstraction tool
CBP: capacity-building provider
CFIR: Consolidated Framework for Implementation Research
DSAT: Demonstration Site Assessment Tool
HAB: HIV/AIDS Bureau
HRSA: Health Resources and Services Administration
IRB: institutional review board
IS: implementation science
KII: key informant interview
RE-AIM: reach, effectiveness, adoption, implementation, and maintenance
SPNS: Special Projects of National Significance

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TA: technical assistance

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Protocol

Gait Rehabilitation Using Hybrid Assistive Limb in Patients With Lower Limb Amputation: Protocol for a Single-Arm Clinical Trial

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Abstract

Background: Lower limb amputation rates are increasing owing to aging and vascular diseases. However, no standardized rehabilitation protocol has been established for regaining walking ability. Conventional rehabilitation delays prosthetic gait training until 6-8 weeks post amputation, prolonging recovery and increasing medical expenses.

Objective: This study aims to evaluate the impact of neurorehabilitation using the Hybrid Assistive Limb (HAL) for Medical Use Lower Limb Type, developed by Japan's Tsukuba University and the robotics company Cyberdyne, on gait acquisition, improvement in activities of daily living (ADL), and enhancement of quality of life (QOL) in patients with lower limb amputation, and assess the effectiveness of early HAL-assisted gait training before and after amputation.

Methods: This single-arm trial will include 20 patients undergoing unilateral transfemoral or transtibial amputations. HAL-assisted gait training will be performed 5 days per week (30 minutes per session) until postoperative week 8. The primary outcome is a 2-minute walking distance, while secondary outcomes include muscle strength, balance, gait parameters, and ADL/QOL measures. Statistical analyses will be conducted using SPSS (IBM Corp), and results obtained at the following time points will be compared: preoperative, postintervention, and 6-month follow-up.

Results: The planned sample size is 20 patients, calculated using JMP version 12 (SAS Institute) based on an expected 1.5-fold improvement in 6-minute walk distance (effect size 0.8, α=.05, power=0.8). Analyses will be performed using SPSS version 15.0 (IBM Corp). The 2-minute walk test (primary outcome) and secondary outcomes will be compared at baseline, post intervention, and 6-month follow-up using 1-way analysis of variance or Kruskal-Wallis test, and P values <.05 and 95% CIs will be reported.

Conclusions: This is the first study to apply HAL-assisted neurorehabilitation to patients with lower limb amputations. Early gait training may increase prosthetic gait acquisition rates, shorten rehabilitation and hospitalization periods, and reduce medical costs. If effective, this study may contribute to the development of a Japan-originated rehabilitation program and provide clinical evidence supporting broader HAL implementation for patients with lower limb amputations.

Trial Registration: Japan Registry of Clinical Trials jRCTs062200031; https://jrct.mhlw.go.jp/latest-detail/jRCTs062200031

International Registered Report Identifier (IRRID): PRR1-10.2196/76509

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KEYWORDS

gait rehabilitation; Hybrid Assistive Limb; amputation; prosthetics; quality of life, activities of daily living

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Introduction

In Japan, 5.4-6.2 individuals per 100,000 population undergo lower limb amputation annually, whereas the rate is higher in Europe and the United States, ranging from 7.4 to 41.3 per 100,000 population [1]. The causes of amputation include trauma from traffic accidents, tumors, congenital diseases, and peripheral circulatory disorders. Notably, circulatory disorder–related amputations are increasing owing to the rising prevalence of conditions, such as diabetes and arteriosclerosis [2]. In a population-based study of geriatrics with vascular amputations, only 36% achieved successful prosthetic fitting, with advanced age and transfemoral amputation linked to failure [3]. Given the anticipated increase in lower limb amputations due to the aging population, medical and social costs, such as long-term hospitalization, rehabilitation, provision of prostheses, and nursing support, are set to escalate [4]. Therefore, restoring the ability to walk and improving the quality of life (QOL) of individuals with lower limb amputations requires immediate attention.

No established method for training patients to walk following lower limb amputation exists [5]. Traditional rehabilitation protocols after lower limb amputation require approximately 8 weeks for residual limb maturation [6], delaying the start of prosthetic gait training until the maturation period is complete. Furthermore, while active prostheses enable a more normalized gait pattern through neuromuscular control [7,8], passive prostheses are typically restricted to use within 8 weeks postamputation, further slowing the acquisition of a new gait pattern using a prosthetic limb. One of the reasons for the lack of an established method for training patients to walk after amputation is that it takes 6-8 weeks for the stump to mature after amputation, and patients cannot bear weight on the amputated side; therefore, they can only walk on the healthy side. Consequently, training is conducted to strengthen the muscles other than the stump, improve function, manage the condition of the stump, and provide functional training on the stump side [9].

The medical robot “HAL (Hybrid Assistive Limb) for Medical Use Lower Limb Type,” developed by Japan's Tsukuba University and the robotics company Cyberdyne, has been reported to improve the walking ability of patients with 10 slowly progressive neuromuscular diseases, such as spinal muscular atrophy and muscular dystrophy [10]. In April 2016, it became the first medical robot in the world to be covered by medical insurance. The HAL detects weak bioelectrical signals on the skin surface when the user tries to move their muscles and assists their movements. In neurorehabilitation using the HAL for Medical Use Lower Limb Type, neuroplasticity is promoted, and walking is improved by repeating accurate walking movements without errors based on the intention of the wearer [11,12]. However, no studies have documented the application of HAL for Medical Use Lower Limb Type in individuals with lower limb amputations.

Therefore, we aimed to investigate the effect of using the medical robot “HAL for Medical Use Lower Limb Type” for walking rehabilitation before and immediately after above-knee and below-knee amputation surgery on independent walking, activities of daily living (ADL), and QOL in individuals with lower limb amputations, and to help establish new clinical applications of the medical robot HAL for individuals with above-knee amputations. It is expected that “the rate of achievement of walking with a prosthetic limb itself may increase” by “being able to start rehabilitation early.” Elucidating the effect of the HAL for Medical Use Lower Limb Type on individuals with lower limb amputations would enable the establishment of a unique early rehabilitation program for lower limb amputation originating in Japan, aimed at the acquisition of walking ability in individuals with lower limb amputations.

Methods

Study Setting

The study will be conducted in a university hospital setting. Specifically, it will take place at the Department of Rehabilitation Medicine, Hiroshima University Hospital, Japan. All data will be collected within Japan. A list of trial sites is available upon request from the corresponding author.

For participant recruitment, potential candidates visiting the orthopedic department of the implementing facility will be referred to the rehabilitation department, where a rehabilitation doctor will explain the study. After obtaining written consent from the potential participants, the principal investigator (YM) or coinvestigator (KU and TA) will conduct the necessary screening tests to assess eligibility. The participants will be assessed for eligibility based on the inclusion and exclusion criteria. The principal investigator (YM) or coinvestigator (KU and TA) will record the required information on the case registration form and submit it to the registration center. A research subject identification code will be assigned to each participant. This identification code will be arbitrary and contain no information capable of identifying a specific individual. The principal investigator (YM) or coinvestigator (KU and TA) will retain the registration confirmation slips.

Eligibility Criteria

The target population will include individuals scheduled for above- or below-knee amputation, and the inclusion and exclusion criteria are described in Textbox 1.

The inclusion criteria are designed to facilitate rehabilitation after amputation during hospitalization at our hospital. Participants are required to understand the purpose of the study and be able to follow instructions on wearing and walking with the HAL. The minimum age is set at 16 years to ensure that participants can independently provide consent. Furthermore, the height and weight requirements are set to accommodate the HAL S and M sizes. Final participant eligibility will be based on the judgment of the doctor.

The exclusion criteria are set to prevent variability due to participants who have experienced traditional amputation rehabilitation and to exclude participants, considering their safety when conducting this study.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Patients scheduled to undergo unilateral transfemoral or transtibial amputation at our hospital (underlying disease is not specified)
- Patients capable of providing written informed consent
- Patients aged ≥16 years at the time of consent acquisition
- Patients with a height between 150 and 175 cm
- Patients with a body weight between 40 and 100 kg
- Patients deemed by a physician to have the potential to walk postoperatively with a prosthetic limb
- Patients able to comply with the hospitalization and treatment schedule during the treatment period

Exclusion criteria

- Patients with a history of amputation of the contralateral lower limb
- Patients requiring ventilator support, respiratory assistance devices, or oxygen therapy, or those deemed by a physician to require such interventions
- Patients considered unable to participate in walking exercises due to exertional dyspnea, heart failure, or similar conditions
- Patients with severe skeletal deformities (eg, osteoarthritis, spondylosis, and scoliosis) that may hinder walking exercises
- Patients with medical conditions such as bleeding disorders or osteoporosis that could interfere with walking exercises, or those deemed by a physician to be unable to walk postoperatively with a transfemoral or transtibial prosthesis
- Patients with severe hepatic, renal, or cardiovascular diseases
- Patients who are pregnant, may be pregnant, or wish to become pregnant during the study period
- Patients who cannot have HAL-ML05 (developed by Japan's Tsukuba University and the robotics company Cyberdyne) electrodes attached due to dermatological conditions or a short residual limb
- Patients deemed unsuitable for participation in the study by a physician

Ethical Considerations

This study is conducted in accordance with the Declaration of Helsinki and has received ethical approval from the Ethical Committee for Clinical Research of Hiroshima University (approval no CRB6180006). All participants are provided with detailed information about the study's aims, procedures, risks, and benefits, and written informed consent is obtained prior to participation. Informed consent will be obtained by trained investigators or clinical staff who are familiar with the study protocol. The consent process will take place in a private setting at the Hiroshima University Hospital, where potential participants (or their legally authorized representatives, if applicable) will receive detailed verbal and written explanations of the study.

Participants will be given sufficient time to ask questions and consider participation. Participants will be clearly informed that participation in ancillary studies is entirely voluntary and will not affect their involvement in the main study. Participants are informed that participation is voluntary and that they may withdraw from the study at any time without consequences. A separate consent form will be provided and signed before any ancillary data or specimen collection.

If participants agree, additional informed consent will be obtained for the collection and use of their data and biological specimens in ancillary studies related to the main trial. These studies may involve future research on rehabilitation outcomes, genetic markers, or biomarkers, and will be subject to approval by the institutional ethics committee.

Personal data are anonymized to maintain confidentiality. Although the study involves physical activities using the HAL device, comprehensive safety protocols are implemented, and medical staff are present during all intervention sessions to promptly manage any adverse events. Previous studies involving HAL report a favorable safety profile, but potential physical risks such as skin irritation, fatigue, and joint discomfort are explained clearly to participants prior to consent.

While no specific clinical trial insurance is arranged, standard institutional liability coverage applies. In the event of study-related adverse events, participants receive immediate medical attention at no personal cost. This coverage is consistent with the policies of the host institution and meets the ethical requirements for investigator-initiated exploratory research. The study is registered in the Japan Registry of Clinical Trials under registration number CRB6180006.

Interventions

The intervention device used in this study is the HAL for Medical Use Lower Limb Type (HAL-ML05, Cyberdyne Inc; Medical Device Approval number: 22700BZX00366000; Figure 1). This device was developed for patients with slowly progressive neuromuscular diseases to improve walking function through intermittent use of HAL and repeated performance of gait exercises while assisting lower limb movements based on bioelectric signals.

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Figure 1. (Left) Hybrid Assistive Limb (developed by Japan's Tsukuba University and the robotics company Cyberdyne) and (right) walker (All-in-One, Ropox A/S).

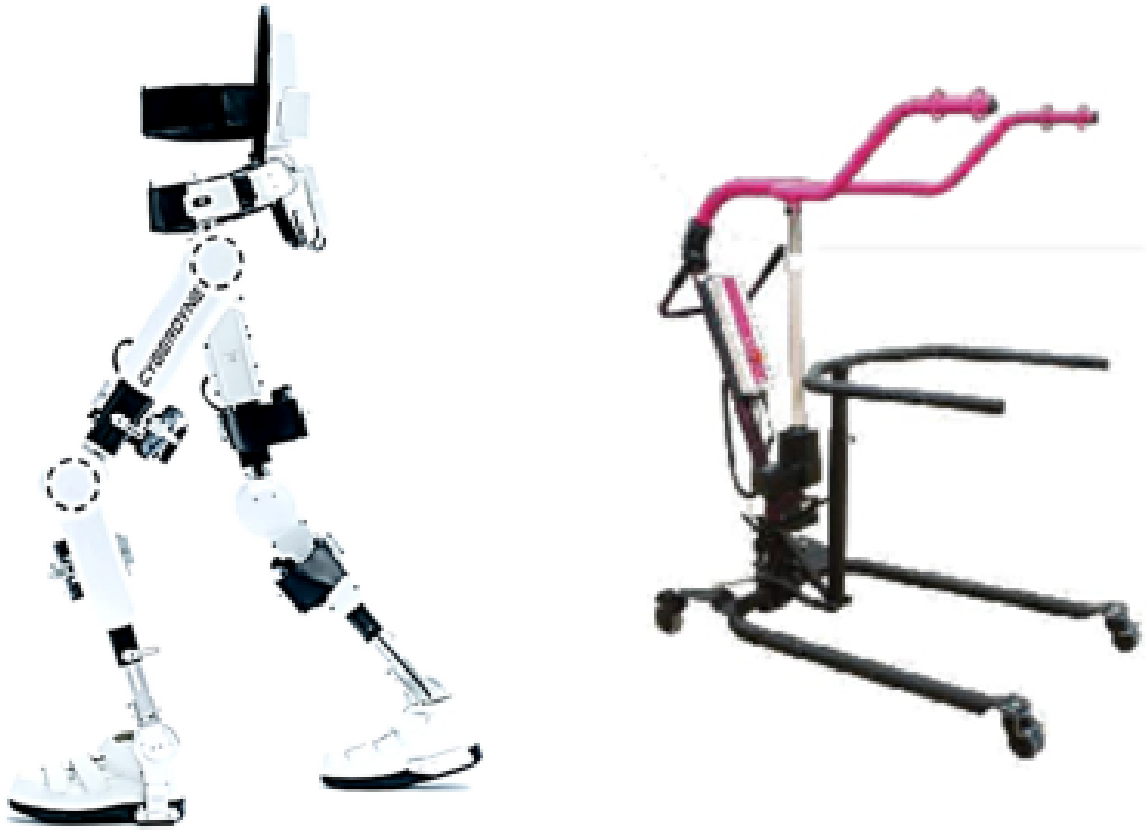

In addition, for patients with unstable standing posture, a walker (All-in-One, Ropox A/S; Figure 1) will be used as a peripheral device for the HAL to aid walking. This walker features a battery-powered unloading lift, enabling a one-touch adjustment of the unloading weight and accommodating users of various body types and training levels. When used in combination with the HAL Lower Limb Type (NON-MEDICAL), it enables safer gait training.

The intervention outline is shown in Figure 2. An explanation of the study will be provided after an initial examination by the principal or coinvestigator. If the patient agrees to participate, they will be registered as a study participant. Before amputation surgery, preoperative assessments will be conducted, and at least one session of HAL-assisted gait training will be performed. Postoperatively, in addition to general rehabilitation exercises, HAL-assisted gait training will commence after the attending physician approves an increased activity level (mobilization clearance). HAL training will be conducted 5 days a week, with one session daily for 30 minutes. In the early postoperative phase, patients may perform HAL-assisted gait training without a prosthesis. Once the residual limb matures sufficiently and is deemed fit by the physician, a temporary prosthesis—customized for each patient but standardized in terms of structure—will be fitted to begin prosthetic-based gait training. The attending surgeon will determine the initiation of HAL training based on each patient's postoperative recovery status, particularly the condition of the surgical wound and residual limb. If adverse skin reactions (such as inflammation, abrasions, or irritation at the electrode sites) are observed, HAL training will be suspended temporarily to avoid complications. The HAL device will be used exclusively for overground gait training during each rehabilitation session. Other tasks, such as sit-to-stand practice, orthotic fitting, and outdoor walking training, will be conducted without HAL support.

As the residual limb matures, prosthetic gait training will begin using a temporary prosthesis. Patients who underwent transfemoral amputations will use a transfemoral prosthesis, whereas those who underwent transtibial amputations will use a transtibial prosthesis. The temporary prosthesis is standardized for gait training and will not differ among patients, whereas the socket will be custom-made to fit the residual limb of each patient. HAL-assisted gait training will continue until postoperative week 8. The hospitalization period will last until the completion of the evaluation at postoperative week 8. At this point, all assessment items will be measured, with a final evaluation conducted 6 months postoperatively.

During gait training, patients may experience significant fatigue, inflammation at the electrode site, abrasions at contact points between the HAL and the body, and adverse muscle or joint pain. If any of these occur, training will be immediately discontinued, and the patient will undergo a medical examination.

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Figure 2. Flowchart for trial. HAL: Hybrid Assistive Limb (developed by Japan's Tsukuba University and the robotics company Cyberdyne).

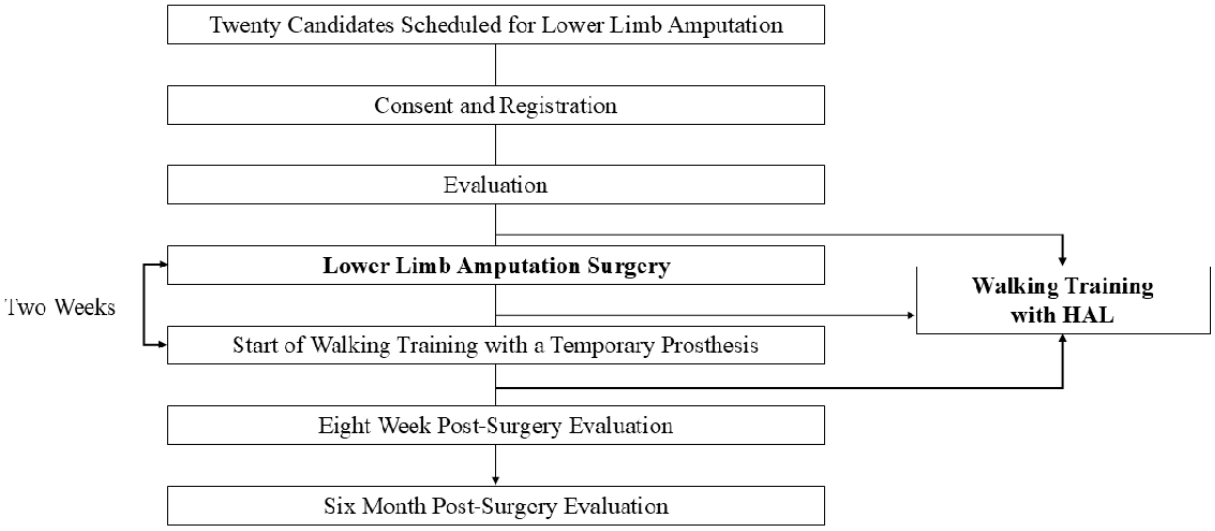

According to the study protocol, criteria for discontinuing or modifying the allocated intervention for individual participants include the following: withdrawal of informed consent; discovery after enrollment that the participant does not meet the eligibility criteria; worsening of the primary disease that makes use of the study device inappropriate; exacerbation of comorbid conditions that hinders continuation; occurrence of adverse events that make continuation difficult; confirmation of pregnancy; significant noncompliance with study procedures; markedly low frequency of intervention use due to postoperative complications; premature termination of the entire study; or any other reason deemed appropriate by the investigator (YM, KU, and TA).

When discontinuation occurs, the reason will be explained to the participant if necessary, and postdiscontinuation care will be provided to ensure the participant is not disadvantaged.

The principal investigator (YM) considers early termination of the study in cases where the planned number of participants cannot be recruited within the designated period; the ethical review board requires protocol changes that are not acceptable; facts or information are discovered that undermine the ethical or scientific validity of the study; the integrity of the study conduct or results is compromised; or critical information emerges regarding the quality, safety, or effectiveness of the study device.

If the ethics committee recommends or instructs discontinuation, the study will be terminated accordingly. In such cases, the reason for termination will be reported in writing to the hospital director, and a study termination report will be submitted without delay. Notification will also be made to the ethics committee and the Ministry of Health, Labour and Welfare within 10 days of termination.

To enhance participant adherence to the intervention (HAL-assisted gait training), the following strategies will be implemented. At the time of enrollment, participants receive thorough explanations and education regarding the importance and expected benefits of the intervention. All intervention sessions are scheduled at times convenient for the participants to minimize dropout due to logistical reasons. Attendance is monitored through structured session logs, and any missed sessions are followed up with a reminder call or consultation by research staff. A fixed staff member is assigned to each participant to ensure continuity of care and to foster trust and motivation. Additionally, participants receive regular positive feedback based on their performance and engagement to support continued participation.

During the trial period, participants are permitted to receive standard medical care and rehabilitation interventions that do not interfere with the objectives or outcomes of the study. Permitted interventions include routine medications for chronic conditions such as antihypertensives and antidiabetic agents, physical therapy sessions unrelated to the study intervention, and participation in nutritional support or general wellness programs. In contrast, prohibited activities include the introduction of new rehabilitation devices or therapies that may affect outcome measures, participation in other clinical trials during the study period, and any medical or therapeutic interventions deemed by the investigator (YM, KU, and TA) to potentially confound the study results.

All concomitant treatments will be documented and monitored throughout the study to ensure they do not compromise data integrity.

If any physical or psychological harm occurs as a result of participation in this study, no financial compensation will be provided. This policy has been reviewed and approved by the institutional ethics committee and will be clearly explained to all participants during the consent process. Participation in the study will only proceed after obtaining their full understanding and written informed consent.

If any adverse effects or harm are observed, appropriate medical care and treatment will be provided without delay. However, the cost of such care under the national health insurance system will be the participant's responsibility.

Since gait training using the HAL device for conditions such as stroke and Parkinson disease falls within the scope of routine rehabilitation care and is not considered to exceed the boundaries of standard clinical practice, we have determined that clinical

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trial insurance is not necessary. Furthermore, no serious adverse events or device malfunctions have been reported in prior clinical research involving HAL.

Participants who choose not to participate in the study will receive standard rehabilitation therapy for patients with lower limb amputation, including exercises targeting the residual limb and other parts of the body.

Outcomes

All gait evaluations at 2 weeks, 8 weeks, and 6 months postoperatively will be conducted without the use of the HAL device. For the primary outcome, assessment will be conducted at 8 weeks postoperatively to evaluate the short-term effectiveness of early HAL-assisted gait training, which is expected to influence the critical period of initial rehabilitation and prosthetic adaptation. Functional recovery may continue beyond this period, particularly up to 6 months; however, the 8-week period was chosen as the primary end point to capture the immediate impact of the intervention. A 6-month follow-up will provide important secondary data on longer-term outcomes. At each time point, walking ability will be assessed under standard conditions using the residual limb or temporary prosthesis, as applicable. A comprehensive examination of various walking-related factors is necessary; therefore, we will collect the items listed in Table 1 extensively. Among these evaluation items, the 2-minute walking distance [13,14] is set as the primary evaluation item, as it is a general indicator of walking ability and is directly linked to ADL and QOL. Other items will be collected as secondary evaluation items. The Locomo 25 is an assessment tool used to evaluate the condition of locomotive syndrome, which indicates a decline in mobility [15].

Table 1. Primary and secondary outcomes.

Assessment item	Description
Physical function	
2-minute walking distance	• Measures the total distance walked in 2 minutes, with pylons placed at 30-m intervals.
Bilateral lower limb muscle strength	• Measured using μ-Tas (ANIMA Corporation) under isometric contraction conditions.
Skeletal muscle mass	• Measured using InBody S10.
Sensory	• Evaluated using a tactile sensory testing device.
Range of motion	• Assessed using the Tokyo University–style goniometer.
Berg Balance Scale	• Evaluates balance ability using a validated assessment form.
Short Physical Performance Battery	• A useful measure combining balance ability and walking performance, assessed using a standard evaluation form.
Gait analysis	• Measures time to complete the TUG and 10-m walk. Gait pattern is analyzed during the 10-m walk using the PhysiGait (CREACT Co, Ltd) gait analysis system, evaluating step length, stride length, weight distribution, gait speed, etc.
Cardiopulmonary function	• Maximal oxygen consumption (VO_2 max): Measured using a respiratory gas analyzer.
Locomo 25	• A questionnaire consisting of 25 items regarding body pain and difficulties in daily activities over the past month. • Responses are scored on a 5-point scale (0-4 points per item). • Locomotive Syndrome Grade 1: Total score ≥7 points. • Locomotive Syndrome Grade 2: Total score ≥16 points.
Muscle activity	• Electromyography (EMG): Measures muscle activity distribution patterns using a multichannel surface EMG system.
Activity	• BI (Barthel Index), FIM (Functional Independence Measure), FAI (Frenchay Activities Index).
Participation	• SF-36, Health Utilities Index, Euro-Qol-5D-5L, Long-Term Care Insurance Certification Level, General Self-Efficacy Scale, WHODAS2.0, Locomotor Capabilities Index (LCI), Prosthetic Evaluation Questionnaire Japan.

All physical function assessments (2-minute walk test) will be conducted without HAL assistance.

In addition, patient background information, including sex, date of birth, age, hospitalization status (inpatient or outpatient), height, weight, comorbidities, past medical history, current medical history, medication status, and residual limb length, will be recorded. Vital signs, such as body temperature, blood pressure, pulse rate, and respiratory rate, will also be

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documented. Furthermore, blood biochemical tests, including white blood cells, red blood cells, hemoglobin, platelets, creatine kinase, albumin, and C-reactive protein, as well as physiological test results, such as electrocardiogram and spirometry, will be collected. The presence or absence of adverse events, including contact dermatitis, abrasions, muscle damage due to overload, and other adverse events, will also be recorded.

The time schedule for participant enrollment, interventions (including pre- and postoperative periods), assessments, and follow-up visits is summarized in Table 2. This table is structured in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 statement and outlines key time points, such as preobservation, surgery, and follow-up phases (2 weeks, 8 weeks, and 6 months postoperatively).

The SPIRIT schedule is presented in table format in the manuscript and is provided to all participants as part of the informed consent process. The schedule includes key components such as enrollment procedures, including informed consent and baseline data collection; interventions, including HAL gait training and prosthesis-based rehabilitation; outcome assessments, which consist of physical function measures, blood biochemistry, and physiological tests; and safety monitoring, including adverse event tracking throughout all phases of the study.

All assessments and interventions are scheduled to ensure consistency and patient safety throughout the clinical trial.

Table 2. Schedule of enrollment, interventions, assessments, and visits (SPIRIT[a]-compliant).

Study period	Enrollment	Preobservation	Day 0	2 weeks postoperative	8 weeks postoperative	6 months postoperative	Withdrawal
Informed consent	✓						
Participant characteristics	✓						
Physical function[b]		✓			✓	✓	
Activities[c]		✓			✓	✓	
Participation[d]		✓			✓	✓	
Blood biochemistry[e]		✓			✓	✓	
Physiological tests[f]		✓			✓	✓	
HAL[g] gait training[h,i]		✓[h]		✓[i]	✓[i]		
Prosthesis gait training[j]					✓[j]	✓	
Adverse event monitoring		✓	✓	✓	✓	✓	✓

[a]SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials.

[b]All physical function assessments (2-minute walk test) will be conducted without HAL assistance.

[c]Activity assessments such as gait tests and activities of daily living (ADL) scales.

[d]Participation measures (social participation scales).

[e]Blood tests: standard biochemical profile.

[f]Physiological evaluations (electrocardiogram and respiratory tests).

[g]HAL: Hybrid Assistive Limb (developed by Japan's Tsukuba University and the robotics company Cyberdyne).

[h]Initial HAL training session presurgery.

[i]Regular HAL training post surgery.

[j]Rehabilitation using a temporary prosthesis.

Sample Size

The calculation was performed with α=.05, a statistical power of 0.8 (80%), and an effect size of 0.8, resulting in a total sample size of 20. The target sample size includes a margin to accommodate potential dropouts. However, if the number of dropouts significantly impacts statistical power or data integrity, we plan to recruit additional participants to maintain the robustness of the analysis.

The sample size will be estimated using data from the 6-minute walk distance (6MWD), as sufficient effect size data for this outcome are available in the literature, and it is a widely recognized measure of functional walking capacity in rehabilitation research. However, performing the full 6MWD may be overly demanding for patients in the early postoperative period following limb amputation; therefore, the 2-minute walk distance (2MWD) will be selected as the primary end point. The 2MWD has been validated as a reliable and less physically demanding alternative to the 6MWD, with strong correlations reported between the two measures in neuromuscular and rehabilitation populations [13,15].

Statistical Analysis

The target sample size was set at 20 patients scheduled for lower limb amputation. Using JMP version 12 (SAS Institute), the sample size was calculated based on a research design assuming

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that the 6MWD would improve by a factor of 1.5, referencing previous studies on gait analysis using the HAL [16]. The calculation was performed with α=.05, power=0.80, and a prespecified effect size.

The primary analysis population for efficacy evaluation will be the Full Analysis Set (FAS), whereas the secondary analysis population will be the Per Protocol Set (PPS).

The FAS includes all study participants who have undergone at least one session of HAL-assisted gait training and have had at least one efficacy-related observation thereafter. However, individuals who fail to meet the eligibility criteria will be excluded. The PPS comprises participants from the FAS who have completed HAL-assisted gait training (5 days per week, 30 minutes per day) without major deviations from the study protocol and for whom the primary evaluation item can be assessed.

Statistical analyses will be conducted using SPSS version 30.0 (IBM Corp). The primary evaluation item, the 2-minute walking distance, will be analyzed using the FAS population, and the mean (SD) [or median (minimum-maximum)] will be calculated. Comparisons between preoperative, postintervention, and 6-month postoperative outcomes will be performed using a 1-way ANOVA or the Kruskal-Wallis test, with a 2-sided significance level of 5%, and a 95% CI will be calculated. In addition, the same analysis will be performed using the PPS as a secondary approach.

For secondary evaluation items, analysis will also be conducted using the FAS population. The mean (SD) [or median (minimum-maximum)] will be calculated for bilateral lower limb muscle strength, skeletal muscle mass, sensory impairment, range of motion, Berg Balance Scale, timed up and go test, gait parameters (step length, stride length, weight distribution, and gait speed during the 10-minute walk test), maximal oxygen uptake, and Locomo 25. Comparisons between preoperative, postintervention, and 6-month postoperative outcomes will be performed using a 1-way ANOVA or the Kruskal-Wallis test, and multiple comparisons will be conducted using the Tukey method (or Steel-Dwass test). A 2-sided significance level of 5% and a 95% CI will be used. The same analysis will also be performed using the PPS as a secondary approach.

Furthermore, for Barthel Index (BI), Functional Independence Measure (FIM), Frenchay Activities Index (FAI), SF-36, Health Utilities Index, EQ-5D-5L (quality-adjusted life years), long-term care insurance certification level, General Self-Efficacy Scale, and WHODAS 2.0, the mean (SD) [or median (IQR)] will be calculated. Comparisons between preoperative, postintervention, and 6-month postoperative outcomes will be performed using a 1-way ANOVA or the Kruskal-Wallis test, with multiple comparisons conducted using the Tukey method (or Steel-Dwass test). A 2-sided significance level of 5% and a 95% CI will be calculated. The same analysis will be conducted using the PPS as a secondary approach.

The primary efficacy analysis will be conducted using the FAS, which includes all participants who received at least one session of HAL-assisted gait training and have at least one postintervention efficacy observation. Participants who are found to violate key eligibility criteria will be excluded from the FAS.

A secondary analysis will be performed using the PPS, which is a subset of the FAS consisting of participants who completed HAL training (5 days per week, 30 minutes per session) without any major protocol deviations and for whom the primary outcome data are available.

For missing data, a descriptive analysis will first be conducted to assess the pattern and mechanism of missingness. If the data are judged to be missing at random, multiple imputation using chained equations will be applied to handle missing values in the primary outcomes. Additionally, sensitivity analyses will be performed by comparing results between complete-case and imputed datasets to evaluate the robustness of the findings.

Results

Sample Size and Participant Flow

Based on previous studies of gait analysis using HAL, we calculated the required sample size using JMP (version 12; SAS Institute), assuming a 1.5-fold improvement in the 6MWD. With an alpha of .05, a power of 0.8, and an effect size of 0.8, the calculated sample size was 20. Considering potential dropouts, we set the final target sample size at 20 participants. The overall flow of the trial, including participant recruitment, consent, evaluation, surgery, intervention, and 6-month follow-up, is planned in accordance with the SPIRIT 2013 statement.

Planned Outcomes and Statistical Analysis

For the primary outcome, the 2MWD, we will compare results at 3 time points: preoperative, post intervention, and 6-month follow-up. Data will be presented as mean (SD) [or median (minimum-maximum)]. Comparisons will be performed using a 1-way ANOVA or the Kruskal-Wallis test, with a P value <.05 and 95% CIs reported.

Secondary outcomes will be analyzed using a similar approach. Descriptive statistics will be calculated for objective measures, like muscle strength, balance, and gait parameters, as well as for subjective scales including ADL/QOL assessments (BI, FIM, and FAI). Multiple comparisons will be conducted using the Tukey method or the Steel-Dwass test, with a P value <.05 and 95% CIs also reported.

For missing data, we will first conduct a descriptive analysis to assess the pattern of missingness. If the data are judged to be missing at random, multiple imputation will be applied to the primary outcomes. Sensitivity analyses will also be performed by comparing results from complete-case and imputed datasets to assess the robustness of the findings.

The primary efficacy analysis will be conducted on the FAS, and a secondary analysis on the PPS.

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Discussion

Principal Findings

This study represents the first attempt at using the HAL for Medical Use Lower Limb Type for neurorehabilitation in individuals with lower limb amputations and also evaluates its effectiveness in early postoperative gait training. By enabling the early initiation of rehabilitation, the success rate of prosthetic gait acquisition is expected to increase. In conventional rehabilitation for individuals with lower limb amputations, active gait training is difficult during the 6-8 weeks required for residual limb maturation, leading to delays in the start of prosthetic walking. We aimed to address this issue by introducing HAL-assisted gait training from an early postoperative stage, with the expectation that it will improve the success rate of prosthetic gait acquisition, shorten the postoperative rehabilitation and hospitalization periods, enhance ADL and QOL, and contribute to medical cost reduction and efficiency. From academic and scientific perspectives, no prior reports on robotic movement therapy and neurorehabilitation based on voluntary movements in individuals with lower limb amputations exist. Consequently, this study will present the first reported findings, highlighting its academic originality and significance.

Comparison With Prior Work

Early neurorehabilitation may facilitate the smooth acquisition of walking patterns. Previous studies on HAL-assisted gait training in patients with cerebrovascular disease have shown that repetitive, precise walking movements help maintain and improve muscle strength and balance ability [16,17]. In addition, early initiation of prosthetic gait training has been reported to enable independent walking even in older women [18]. Thus, implementing early gait training may promote recovery of physical function within the first 8 weeks of postoperative rehabilitation. Furthermore, studies have shown that patients who used a training prosthesis during rehabilitation had shorter hospital stays compared with those who did not [19,20].

Implications for Clinical Practice and Policy

If early HAL-assisted gait training successfully enhances physical function and enables independent walking, it may lead to earlier hospital discharge and reduced medical costs. Currently, no standardized rehabilitation protocol from lower limb amputation to prosthetic gait acquisition exists [5]. If the results of this study prove effective, they may serve as a foundation for establishing a novel rehabilitation program in Japan. Moreover, HAL is currently covered by medical insurance for specific neuromuscular diseases [10], and the potential effectiveness of this study could provide scientific evidence to support the expansion of this insurance to cover individuals with lower limb amputations, potentially benefiting a broader patient population.

Safety Considerations

Previous clinical studies have demonstrated that HAL has a favorable safety profile, with no serious adverse events reported and only minor and transient effects such as skin irritation, pressure discomfort, or fatigue [10,21]. In this study, if complications occur, specific management strategies will be applied. Skin irritation will be managed with local skin care and adjustment of electrode placement or harness fitting. Muscle fatigue will be addressed by reducing training intensity and duration or by introducing longer rest intervals. Joint pain or discomfort will lead to the temporary suspension of training followed by a medical evaluation. HAL training will only be resumed once the attending physician confirms that continuation is safe.

Limitations

A key limitation of this study is the absence of a control group, which restricts the ability to attribute observed improvements directly to HAL-assisted rehabilitation. Moreover, the absence of a conventional rehabilitation control group limits the ability to attribute improvements solely to the HAL intervention. The single-arm design is appropriate for an exploratory investigation; however, future randomized controlled trials will be necessary to confirm efficacy and compare HAL-assisted rehabilitation with conventional rehabilitation protocols.

Second, the sample size is limited to 20 participants. This decision reflects the exploratory nature of the study and anticipates substantial individual variability in residual limb characteristics and rehabilitation backgrounds among transfemoral amputees. Third, the application of HAL is subject to technical constraints related to patient physique and residual limb condition, meaning it cannot currently be applied to all individuals with lower limb amputations. These limitations, arising from narrow eligibility criteria (eg, height, weight, and residual limb conditions), may restrict the generalizability of the findings. However, such strict criteria are necessary to ensure the safe and effective use of the HAL system, which requires specific physical and anatomical conditions for proper fitting and functionality. As the technology evolves, future studies may consider broader inclusion criteria to enhance applicability to the wider amputee population. Ultimately, this research will contribute to the development of guidelines for early rehabilitation following lower limb amputation and facilitate multicenter collaborative studies to strengthen the evidence base.

The 6-month follow-up assessment may be less sensitive in detecting differences attributable to early intervention timing; however, it is intended as a final confirmation of functional walking status. The primary outcome, however, is the 2MWD measured immediately after the 8-week intervention period, which directly reflects the effect of early HAL-assisted rehabilitation. We acknowledge that a 6-month follow-up period may not capture the full extent of functional recovery, particularly for transfemoral amputees. In particular, longer-term adaptations such as neuromuscular reorganization, prosthetic control proficiency, and reintegration into daily activities may require extended periods to fully manifest. While this duration allows for the assessment of short- to midterm effects of early intervention, the decision to limit follow-up to 6 months balances practical feasibility, participant burden, and the exploratory nature of this protocol. Future studies should consider longer follow-up periods to evaluate sustained outcomes and late-phase rehabilitation progress.

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Another limitation is the strict eligibility criteria required for HAL use, including specific height, weight, and residual limb conditions. These requirements may exclude certain patient populations, which could limit the generalizability of the findings. Nevertheless, these criteria are necessary to ensure patient safety and to accommodate the technical specifications of the HAL system.

Conclusions

Early postoperative HAL-assisted gait training can increase the success rate of prosthetic walking, shorten the rehabilitation period, and reduce medical costs. The findings of this study are expected to contribute to the establishment of a standardized rehabilitation program originating from Japan for individuals with lower limb amputations and also serve as a foundation for novel clinical applications of HAL.

Acknowledgments

The authors would like to thank the clinical and administrative staff at Hiroshima University Hospital for their support in conducting this study. We also express our gratitude to all participants who took part in this research.

Data Availability

The datasets generated or analyzed during this study are not publicly available due to privacy restrictions, but are available from the corresponding author upon reasonable request. Requests for access to the data should include the purpose of the request and will be subject to approval by the ethics committee of Hiroshima University Hospital.

Authors' Contributions

MA and YM conceived and designed the study and served as the principal investigators. NO, MS, and YK were responsible for data collection, patient coordination, and preliminary analysis. KU and TA provided expert advice on the use of the HAL system and contributed to refining the intervention protocol. NF offered methodological guidance and statistical support. MA drafted the manuscript. All authors critically reviewed the manuscript for important intellectual content and approved the final version for submission.

Conflicts of Interest

None declared.

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Abbreviations

2MWD: 2-minute walk distance
6MWD: 6-minute walk distance
ADL: activities of daily living
BI: Barthel Index
FAI: Frenchay Activities Index
FAS: Full Analysis Set
FIM: Functional Independence Measure
HAL: Hybrid Assistive Limb
PPS: Per Protocol Set
QOL: quality of life
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Air Pollution Impact on Pregnancy and Early Childhood Development (APiPED) in India: Protocol for a Cohort Study

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Abstract

Background: The impact of air pollution on early childhood development in low-pollution settings is well known. However, comprehensive evidence from high-pollution environments such as the Delhi National Capital Region in India remains limited.

Objective: This maternal-child cohort study aims to investigate the impact of air pollution on pregnancy outcomes and early childhood development, providing critical insights to inform targeted interventions and public health policy.

Methods: This longitudinal maternal-child cohort study will enroll 2500 pregnant women from rural and urban Delhi National Capital Region and follow their children up to 2 years of age. Maternal data on pregnancy complications, delivery mode, parity, and gestational weight gain will be collected from clinical records and structured questionnaires, while newborn outcomes (gestational age, birth weight, anthropometry, and congenital anomalies) will be assessed from birth records and clinical examination. Early childhood development will be evaluated through standardized anthropometry and the Developmental Assessment Scale for Indian Infants. For a 10% subsample, trimester-specific and postnatal indoor and outdoor air pollution exposure (particulate matter with a diameter of less than 2.5 micrometers and particulate matter with a diameter of less than 10 micrometers) will be monitored using portable air quality monitors, along with household surveys and time-activity diaries. Maternal and infant blood samples will be analyzed for inflammatory, oxidative stress, and cardiovascular biomarkers. Exposure estimates will be integrated into personal exposure models, and associations with health outcomes will be examined using multivariable regression and longitudinal mixed-effects models.

Results: As of July 2025, 45% of the planned sample size have been recruited, with baseline data collection completed, and 10% undergoing exposure assessment and sample collection.

Conclusions: This study will provide a comprehensive evaluation of the effects of air pollution on maternal health, pregnancy outcomes, and early childhood development in urban and rural settings in India. This will generate context-specific evidence to support maternal and child health policies, air pollution mitigation strategies, and personal protection measures for pregnant women and infants in polluted environments.

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KEYWORDS

air pollution; pregnancy; longitudinal study; particulate matter; exposure assessment; child development; neurodevelopment cohort studies; India

Introduction

Environmental risk factors, particularly air pollution, contribute to over 2 million deaths annually in India [1]. The source share of household air pollution in these attributable deaths is equivalent to the ambient air pollution. According to the Global Burden of Disease Study 2017, approximately 76.8% of the Indian population lives in regions exceeding the Indian National Ambient Air Quality Standard (NAAQS) for $PM_{2.5}$ (40 µg/m^3), leading to an estimated 1.24 million deaths (95% UI 1.09–1.39 million) attributable to air pollution in 2017 [2]. Older adults, children and pregnant women are particularly vulnerable to adverse effects from air pollution. For women and children, indoor activities and household cooking with solid fuels increase exposure to fine particulate matter and carbon monoxide [3]. Pregnant mothers carrying developing embryos and fetuses, along with newborns and infants, present high and unique susceptibilities to these health risks posed by airborne pollutants. In northern India states such as Delhi, Uttar Pradesh and Haryana, annual $PM_{2.5}$ exposures exceeded 125 µg/m^3 (more than three times the standard) [2]. While the health burden of high exposures in those settings is substantial, evidence on specific long-term outcomes such as child growth or lingering effects from prenatal exposure is still emerging. Several studies suggest that air pollution is associated with low birth weight [4,5], but whether that association persists as children grow remains to be fully elucidated.

In India, the impact of air pollutants on growth and early childhood development is largely unknown. Evidence regarding the impact of the health status of the mother during pregnancy and newborn outcomes is available [6,7]. These studies are restricted to socioeconomic, biological, clinical, and behavioral characteristics in mothers and their effects on birth outcomes. Existing research studies do not adequately address the environmental factors contributing to adverse birth outcomes. The evidence on the association between birth outcomes and air pollution exists in the form of studies correlating cooking fuel type as a proxy of household air pollution with low birth weight outcomes [8,9]. In a few cohort-based studies, the research documents biomass smoke with secondhand tobacco smoke as a determinant for not only low birth weight but also infant mortality and child respiratory morbidity [10]. There is limited quantitative evidence in India linking rural-urban $PM_{2.5}$ exposure to birth weight. Nutritional outcomes and developmental milestones play an important role in child survival and healthy adulthood. A prospective cohort approach is an appropriate way to assess the temporality of association between air pollutant exposure and child health outcomes. Experimental and in vitro studies suggested that endocrine disruption, oxidative stress, inflammatory response, and DNA damage may be contributing to adverse pregnancy and birth outcomes associated with maternal air pollution exposure. Hence, exploring possible metabolic biomarkers using a prospective design and repeated measures becomes important to understand the causal mechanism.

The study aims to understand how long-term exposure to air pollution during pregnancy and early childhood can impact pregnancy and neonatal outcomes, and early childhood development, respectively. The other objectives of the study are to examine the relationship between long-term indoor and outdoor air pollution exposure during pregnancy and pregnancy outcomes among rural and urban populations in the National Capital Region (NCR), India. The study will also analyze the role of blood biomarkers as mediators in the pathway between air pollution exposure and its effects on pregnancy outcomes and early childhood development.

The conceptual framework for this study is structured around 4 core domains. The environmental exposure domain encompasses exposure to PM levels in both indoor and outdoor environments. The biological mediation domain addresses the underlying biological pathways, including oxidative stress and inflammatory responses, and focuses on biomarkers such as interleukin-6 (IL-6), tumor necrosis factor (TNF) alpha, and cardiometabolic indicators such as C-reactive protein. The developmental and health outcomes domain captures maternal and child neurodevelopmental trajectories, while the sociodemographic and environmental modifiers domain considers effect modifiers and potential confounders, including socioeconomic status, diet, breastfeeding practices, parental education, housing conditions, cooking fuel use, access to health care, and prenatal care. The theoretical underpinning of this framework is grounded in the Developmental Origins of Health and Disease [11] theory, which postulates that environmental exposures during critical windows of development, such as gestation and early infancy, can shape long-term health and developmental outcomes. This framework integrates quantitative measures of environmental exposure, biomarker-based mediators, and developmental outcomes, while also explicitly capturing the temporal sequence of exposure, mediation, and outcome, thereby enabling a mechanistic understanding of how early-life environmental exposures influence neurodevelopmental health.

Methods

Overview

The proposed study is a prospective, population-based mother-child cohort that will be assembled in both rural and urban settings. The study population will consist of mother-child pairs from the general population. Part of the sample will come

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from a rural area, and another part will come from an urban site. The study will build on the existing cohort in rural and urban demographic surveillance sites [12]. The rural site is located in the Ballabgarh Block of Faridabad district, and the urban site is located in Dr Ambedkar Nagar of the South-East district of Delhi NCR, India. Both rural and urban study sites have been under demographic surveillance for the last 3 decades by the Centre for Community Medicine of All India Institute of Medical Sciences (AIIMS), New Delhi. Under health demographic surveillance, each birth, death, and other health outcomes of the mother and newborn child are recorded and stored in a computerized health and management information system. This facility will robustly help recruit cohorts. Continued presence of health services from the institutions will ensure maximum community support during the study.

Participants

Study participants will be PW and children (birth to 24 months) born to the recruited PW residing in the study sites. The study population will mostly belong to the middle and low socioeconomic classes living in the stable cohort, both at rural and urban sites. The study has adopted a multipronged strategy to ensure retention in the air pollution impact on pregnancy and early childhood development cohort. As part of the protocol, the inclusion criterion requires participants to have a minimum of 2 years of residence at the demographic sites. Furthermore, retention is strengthened through community engagement mechanisms that leverage existing systems in demographic surveillance sites, that is, through Accredited Social Health Activists and Anganwadi workers. The front-line workers maintain regular contact with the participants through scheduled home visits during pregnancy and postnatal periods, aligning with national health program protocols. The risk of dropouts is further reduced as the study uses flexible scheduling of participant home visits by field workers. Moreover, the visits are strategically aligned with routine community-based events such as Village Health Nutritional Days and immunization schedules at health care centers in both rural and urban sites.

Data Collection

During the initial visit to the households of eligible and consenting PW, detailed residential information (including contact details and geographic coordinates), as well as information about the participant and her household members, will be collected. This baseline information will gather data on the woman's age, education, occupation, lifestyle factors, medical history, and relevant family history. In addition, demographic, socioeconomic, and environmental factors about the household will be collected. For a comprehensive analysis, additional baseline information about PW will be gathered using secondary data available in records. All interview data, secondary information, and monitoring records will be collected using the Kobo Collect App (Kobo Organization) and stored in the KoboToolbox Cloud (Kobo Organization; [13]).

PW will be contacted every 3 months (each trimester) to collect follow-up information on events during pregnancy or hospitalization. One ultrasonography record (possibly in the second trimester) will be retrieved from the recruited PW for assessing fetal well-being. Delivery outcomes will be assessed by visiting PW immediately after delivery. Based on past hospital records, the institutional delivery rate in the study area is nearly 100%. The validity of information on birth outcomes will be checked from the hospital records and during home visits. A detailed list of study forms, along with a brief outline of the content of each questionnaire, is provided in Multimedia Appendix 1. The study plans to undertake exposure monitoring and biomarker analyses in 10% of cohort participants owing to financial constraints and feasibility considerations. In rural sites, participants will be selected using proportionate probability sampling at the village level, while in urban sites, systematic random sampling will be applied to capture heterogeneity. This subsampling strategy ensures representativeness, is resource-efficient, and enables scientifically valid exposure-response assessments. Nested subcohort and case-cohort designs are well established in epidemiological research and have demonstrated that, when sampling is systematic and appropriately stratified, robust estimates of exposure-outcome associations comparable to those from full cohorts can be obtained [14,15].

Personalized exposure assessments to air pollution will be conducted in 10% of the recruited participants, 3 times during pregnancy (once in each trimester) for PW and every 6 months for 2 years for their newborns. Recruited newborns will be visited every 6 months from birth until the age of 24 months for the assessment of childhood outcomes. In addition, pediatricians on the project team will assess various nutritional and physiological outcomes among the recruited children. Blood samples (from 10% of recruited PW and newborns) will be collected at baseline and in the third trimester for PW, and after 6 months and 24 months for the newborns, for the assessment of biomarkers. In total, for both PW and the newborns, 900 blood samples will be taken to have repeated measures of biomarkers. Enzyme-linked immunosorbent assay kits will be used to detect and quantify biomarkers in blood samples, using the in-house facilities at the Department of Laboratory Medicine, AIIMS, New Delhi.

The study design consists of 2 phases. Phase 1 will focus on recruiting PW from rural (n=2000) and urban (n=500) sites, conducting baseline assessments, and performing follow-ups during each trimester to monitor exposure, biomarkers, and pregnancy outcomes. Phase 2 will involve follow-up assessments of children at 6, 12, 18, and 24 months to evaluate growth, health outcomes, exposure, and biomarkers. The study will conclude with an overall assessment and health impact analysis. The study flow, consisting of longitudinal phases, is presented in Figure 1.

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Figure 1. Study flow outlining the longitudinal phases of the air pollution impact on pregnancy and early childhood development (APiPED) dynamic cohort. Phase 1 includes the recruitment of pregnant women (PW) from rural (N=2000) and urban (N=500) sites, baseline assessments, trimester-specific follow-ups, exposure and biomarker assessments, and monitoring of pregnancy outcomes. Phase 2 follows newborns through 4 follow-ups (at 6, 12, 18, and 24 months), assessing growth, health outcomes, exposure, and biomarkers. The study concludes with an overall health impact assessment and analysis.

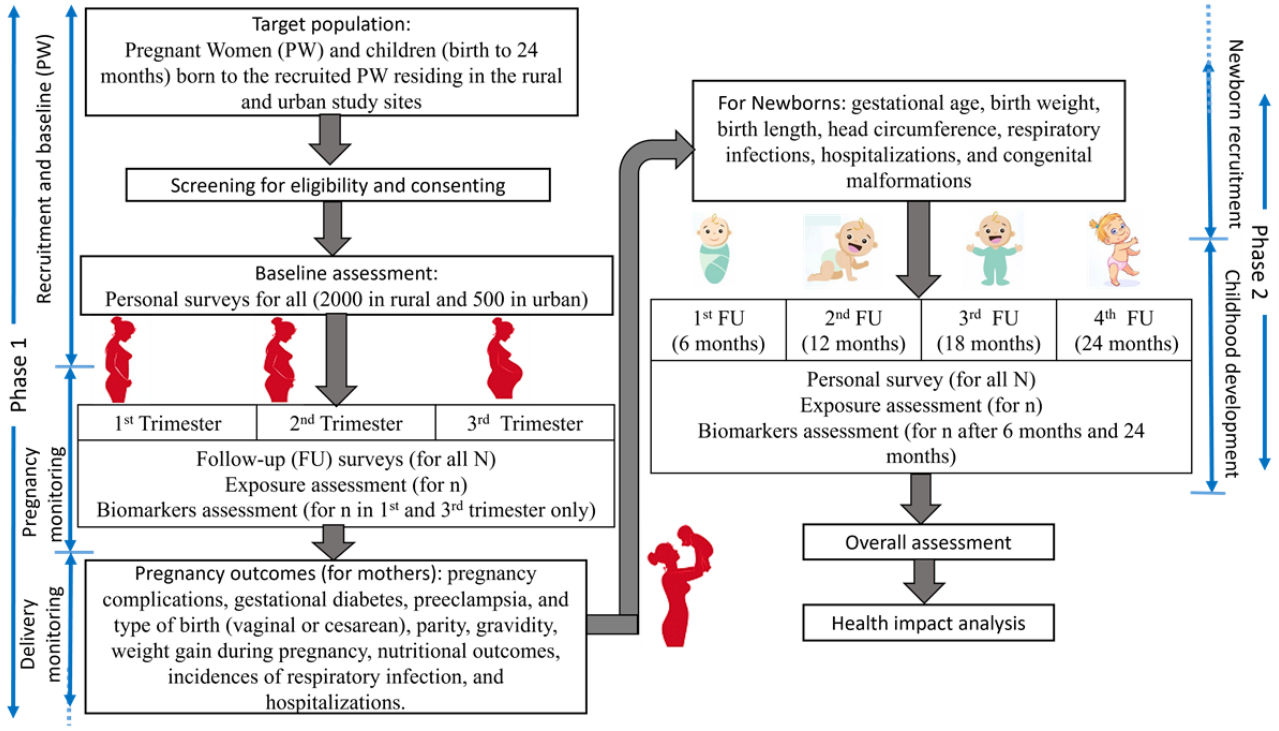

Exposure Assessment

A hybrid exposure model will be developed combining indoor, outdoor, and ambient $PM_{2.5}$ measurements along with satellite-based $PM_{2.5}$ fused with a land use regression (LUR) model to estimate the pregnancy period as well as life course exposure of the children. We will use indoor and outdoor air quality monitors to measure $PM_{2.5}$, temperature, and relative humidity for 10% of PW, assessing their indoor and outdoor air pollution exposure over 24 hours during each trimester. The same monitors will also track the air pollution exposure of newborns for 24 hours across all seasons (every 6 months over a period of 2 years). Personal exposure levels will be reconstructed by combining the participants' time-activity profiles with both outdoor (satellite-derived and ground-based) and indoor measurements.

The levels of PM of various sizes and other pollutants at each study site will be obtained from multiple sources. Using a high-resolution (1-km, 24-hour average) $PM_{2.5}$ database from the satellite-based application for air quality monitoring and management at a national scale (SAANS) project [16]—designed for air quality management, epidemiological research, and public awareness—the spatial patterns of $PM_{2.5}$ for the study sites in the Delhi-NCR area will be evaluated.

Throughout the study, we will collect hourly mean values of air PM_{10} and $PM_{2.5}$ for 24-hour periods from the Central Pollution Control Board website, where open-access data from fixed-site automatic monitors in the Continuous Ambient Air Quality Monitoring Stations network are available [17-19]. In addition, we will gather 5 years (2019-2023) of historical data on daily and annual average PM recorded by Continuous Ambient Air Quality Monitoring Stations and manual gravimetric samplers as part of the National Air Quality Monitoring Program. We will further extract parameters of LUR, such as proximity to line and point source emissions, traffic density, land use pattern, vegetation index, and population density, within a 1x1 km^2 buffer of the cohort using the Arc Geographic Information System following the methodology applied in previous studies [20-22].

In developing our LUR model, we will incorporate a variety of geographic, demographic, and emission source–specific predictor variables sourced from health records, personal surveys, open-access databases, local authorities, and field verification. This will include land use types (residential, industrial, etc), road network characteristics, population density, elevation, and potential emission sources. Satellite-derived aerosol optical depth and meteorological reanalysis data will also serve as predictors. We will use a supervised forward addition linear regression technique for model development and conduct diagnostic tests to ensure the integrity of the regression. The model's performance will be evaluated using a 10-fold cross-validation approach [23,24]. The implementation scheme is presented in Figure 2.

Finally, we will apply this hybrid exposure modeling approach to estimate long-term personal exposure to PM during pregnancy as well as across the life course for all study participants, using geocoded locations and other relevant predictors within the model.

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Figure 2. Implementation scheme for exposure modeling using the land use regression (LUR) method in the air pollution impact on pregnancy and early childhood development (APiPED) cohort study. (A) Extraction of variables from various sources. (B) Screening of selected variables for relevance. (C) LUR model development and validation process, including fitting and cross-validation techniques. PM: particulate matter; RH: relative humidity; Temp: temperature.

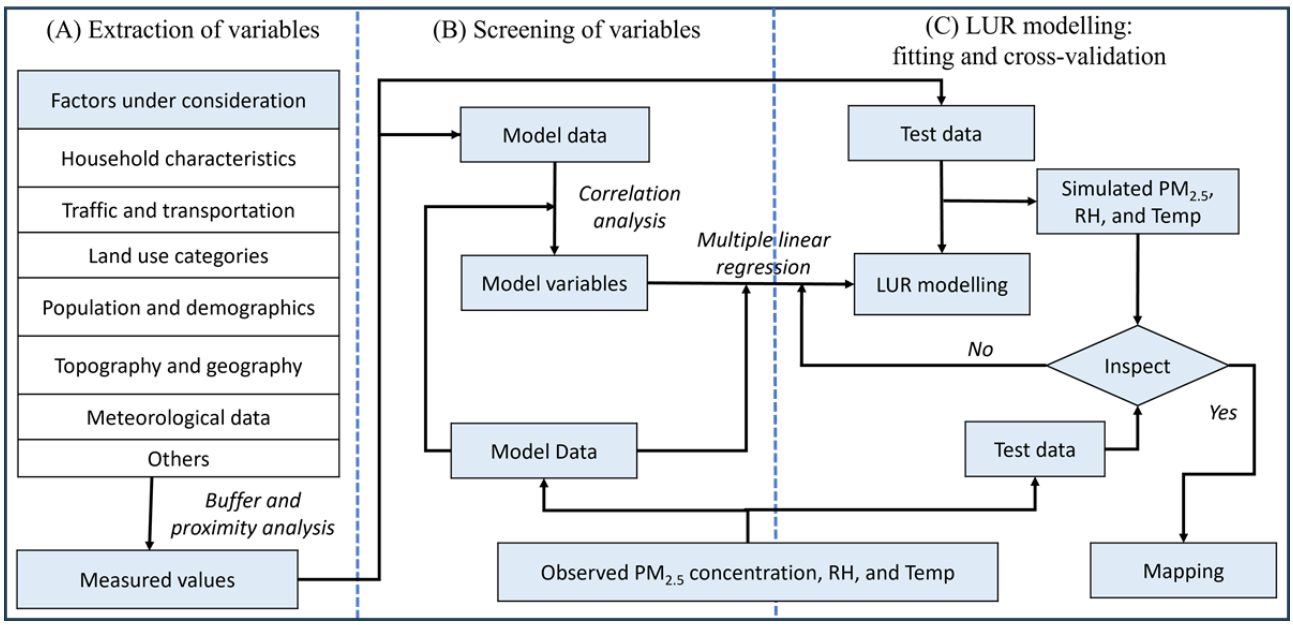

Outcomes

The primary exposure or independent variables examined in this study will be the mean concentrations of $PM_{2.5}$ and PM_{10}, temperature, and relative humidity measured longitudinally using personal indoor and outdoor monitors and centralized sources, as described in the "Exposure Assessment" section.

The primary study outcomes for assessing the impact of air pollution are tabulated in Textbox 1. The study will collect the following pregnancy outcomes for mothers: pregnancy complications, gestational diabetes, preeclampsia, type of birth (vaginal or cesarean), parity, gravidity, and weight gain during pregnancy. For newborns, the following outcomes will be noted: gestational age, birth weight, birth length, head circumference, and congenital malformations. Assessment of developmental milestones will be conducted using the Development Assessment Scales for Indian Infants [25]. This is an Indian adaptation of the Bayley Scales and measures the developmental quotient for the age group 1-30 months. Development Assessment Scales for Indian Infants is the most widely used scale in India, culturally appropriate, and standardized for Indian infants, whereas the Bayley Scales are better suited for the US population. It is an effective, comprehensive, cost-efficient, and practical tool. Three key developmental domains that will be monitored are cognition, language, and motor development. Other developmental outcomes include peak height and weight growth velocities.

Biomarker assessment will be conducted in 10% of the study sample for profiling of inflammation, cardiovascular disease, and oxidative stress [26]. Blood samples from PW (at baseline, 6 months, and 2 years post-pregnancy) and from children (at 6 months and 2 years of age) will be collected. In this study, the role of various inflammatory biomarkers potentially associated with air pollution exposure will be assessed. These include proinflammatory cytokines such as IL-1, IL6, IL-8, TNF-α, anti-inflammatory cytokines (IL-10, transforming growth factor β), anti-infectious (interferon γ, TNF-α), B-cell–activating cytokines (IL-3, IL-4, IL-5, IL-6, IL-21), and T-cells–activating cytokines (IL-2, IL-4, IL-10, IL-13, IL-15) [27]. In addition, the study will evaluate cytokines indicative of cardiovascular risk associated with air pollution, including endothelial adhesion molecules (soluble intercellular adhesion molecule-1 and soluble vascular cell adhesion molecule-1), plasminogen activator inhibitor-1, C-reactive protein, and myeloperoxidase [28].

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Textbox 1. Outcomes for assessing the impact of air pollution in the air pollution impact on pregnancy and early childhood development (APiPED) cohort. The primary outcomes include pregnancy, neonatal, and early childhood development outcomes.

Pregnancy outcomes:

- Pregnancy complications
- Gestational diabetes
- Preeclampsia
- Type of birth (vaginal or cesarean)
- Parity
- Gravidity
- Weight gain during pregnancy

Neonatal outcomes:

- Gestational age
- Birth weight
- Birth length
- Head circumference
- Congenital malformations

Early childhood development outcomes:

- Motor domain (using Developmental Assessment Scale for Indian Infants [DASII]):
  - Neck control
  - Body control
  - Locomotion-1
  - Locomotion-2
  - Manipulation
- Mental domain (using DASII):
  - Cognizance (visual)
  - Cognizance (auditory)
  - Reaching and manipulation
  - Memory
  - Social interaction and imitative behavior
  - Language 1 (vocalization, speech, and communication
  - Language 2 (vocabulary and comprehension)
  - Understanding the relationship
  - Differentiation by use, shape, and movement
  - Mental dexterity
- Peak growth velocities for height
- Peak growth velocities for weight

Study Sample

The rural site consists of a population of 110,000, while the urban site comprises a population of 50,000. This will yield approximately 2000 PW at the rural site and 500 at the urban sites in a year. All pregnant mothers at both sites will be recruited (total 2500 PW). Pregnant women will be followed for birth outcomes such as low birth weight and premature births. The selection of the cohort of PW will be based on continuous monitoring of pregnancies in the rural and urban sites throughout the year using the existing health and demographic surveillance data at study sites during 2024-2025 and periodic screenings. The sampling time frame will be reinforced by conducting household visits to ensure accurate data collection. Newborn children, accounting for a 10% attrition rate of recruited pregnancies, will be followed for 2 years every

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6 months to assess nutritional outcomes, developmental milestones, and psychological assessment. Information on acute respiratory morbidities, biomarker assessment, social determinants, and macroenvironment details will be collected at baseline and follow-up. Only women residing in the study area for at least 1 year and willing to remain in the study area for the study period will be included.

Implementation Strategy

All data collected in the project will adhere to confidentiality and anonymization protocols to protect participant privacy. Personally identifiable information, including names, addresses, and contact details, will be collected at enrollment and stored in a secure, access-controlled database. Each participant will be assigned a unique study identification number, which will be used across all forms, questionnaires, blood samples, and electronic records. This ensures that no personally identifiable information is linked to clinical, exposure, or biomarker data during analysis. Electronic data will be stored on encrypted servers with role-based access control. For dissemination, only deidentified and aggregated data will be reported. For blood samples, the Unique Health Identification system by AIIMS will be used. Samples will be labeled only with the study identification, Unique Health Identification, and collection date. All laboratory personnel analyzing samples will be blinded to participants' identities and exposure status.

For exposure assessment, monitors will be calibrated regularly and rotated to assess drift. In the event of personal monitor malfunction or incomplete capture (<80% valid readings/day), the affected measurements will be flagged, and repeat sampling will be undertaken where feasible. If not feasible, exposures will be imputed using the nearest Central Pollution Control Board station data adjusted for microenvironment or modeled values from the LUR–satellite hybrid framework. In addition, fixed outdoor monitors are deployed at health care centers in both rural and urban sites to provide continuous background reference data. For biomarker analysis, calibrated and quality-checked instruments and high-quality reagents will be used. Research staff will undergo thorough training, and questionnaire-based data collection will rely on standardized tools (KoboToolbox and Google Sheets), with any newly developed tools validated before deployment.

The project's strong urban-rural cohort infrastructure, supported by a multidisciplinary research team comprising experts in public health, social work, pediatric neurology, psychiatry, laboratory medicine, and exposure assessment, will significantly strengthen its ability to collect high-quality data and deliver meaningful outcomes. Standardized protocols and training by subject experts will be provided to the field team to accurately measure environmental exposure and health outcomes, reducing errors and minimizing biases.

For childhood development outcomes, pediatricians in the project team will be engaged to assess various nutritional and physiological outcomes among the recruited children. Developmental assessment at each visit will be done by the trained field worker using valid methods. Training will be provided by a psychiatrist in the investigator team from AIIMS, New Delhi.

Statistical Analysis

Statistical analysis will be carried out in standard statistical software, such as R (R team and the R Foundation), Stata (StataCorp), and SPSS (IBM Corp). The association between air pollution exposure and pregnancy outcomes will be explored using a linear or logistic regression model, depending on the nature of the outcome measure. On the other hand, anticipating a negatively skewed distribution of the score developmental tools, either Beta Binomial regression [29] or logistic regression (after dichotomizing the scores; [30]) will be applied to estimate the impact of air pollution on child development. The association between air pollution and biomarkers will be examined using a linear or log-linear mixed-effects model due to their longitudinal nature. The rural and urban subsamples will be analyzed separately and then meta-analyzed. Continuous and quartile-based analyses of exposure assessment variables ($PM_{2.5}$ and PM_{10}) will be conducted to explore their effects on health outcomes during pregnancy and early childhood.

Confounders and Effect Modifiers

The study will collect the following sociodemographic characteristics: age of parents, family composition, parental education, financial situation, occupation, religion, type and size of home, floor, and exposure to indoor pollution. The study will also collect the following lifestyle factors: breastfeeding, second-hand smoke exposure, alcohol consumption during pregnancy, time spent outdoors, diet, physical activity, heating and cooking modes at home, pets, and nursery attendance. The following physical environmental factors will be collected: pesticides, per- and polyfluoroalkyl substances, phthalates, phenols, stubble burning, and meteorological factors. Finally, data on stressful events during pregnancy and early life of the child, residential and workplace history, information about infectious diseases, and medications will be collected.

Directed acyclic graphs will be used to visualize conceptual models and determine confounders that need adjustment in regression models. All regression models will be adjusted for relevant confounders, including sociodemographic variables (maternal age, education, and income), reproductive history (parity and gravidity), environmental factors (indoor fuel use and season), and lifestyle factors (tobacco smoke exposure, diet, and physical activity). For developmental outcomes, postnatal exposures, such as breastfeeding, recent infections, and nutritional status, will also be included in the adjustment models.

All effect estimates will be reported with 95% CIs. Statistical significance will be defined as a 2-sided $P<.05$. Sensitivity analyses will be conducted to test the robustness of findings, including copollutants, temperature, and stratification by urban or rural setting, sex of the child, or socioeconomic status.

Ethical Considerations

Ethical approval for this study was obtained from the Institute of Ethics Committee of the AIIMS, New Delhi (ref no AIIMSA00452/12.01.2024). All biosafety procedures will be followed in handling and storing the biological samples. The results of blood testing will be communicated to the study participants. Informed consent will be obtained from PW for data collection and dissemination through scientific publications,

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covering both their participation and that of their child. Participant information will be anonymized to ensure confidentiality during data analysis and publication.

Results

The air pollution impact on pregnancy and early childhood development (APiPED) project received approval from the Indian Council of Medical Research, New Delhi, in November 2023. Institutional ethical approval was obtained in January 2024, followed by operative approval in February 2024. The recruitment of project personnel began in April 2024, and the project team includes research scientists and project technical support personnel working under the supervision of project investigators and coinvestigators.

For personal exposure assessment, data collection tools, indoor and outdoor air monitors, and equipment have been procured. In October-November 2024, training sessions for field staff were conducted, along with equipment procurement and monitor calibration. Since project initiation, refresher trainings have been conducted every 4 months for project technical support personnel to maintain consistency and minimize variability in data collection. Participant recruitment began in December 2024. As of July 2025, 45% of the participants have been recruited, and baseline data collection has been completed. In addition, personal exposure assessment and sample collection have been conducted for 10% of the recruited participants.

Discussion

Principal Findings

The proposed study is a prospective, population-based cohort that combines data from rural and urban settings to examine the association between air pollution exposure and outcomes, considering temporal relationships. For pregnant mothers, outcomes include pregnancy results (abortion, stillbirth, premature birth, or normal birth), nutritional status, and incidences of respiratory infections and hospitalizations. For children, outcomes include mortality, birth weight, respiratory infections, hospitalizations, developmental milestones, early childhood development, and nutritional indicators such as underweight and stunting. This study will identify air pollution exposure models and associated blood biomarkers for pregnancy and child health in rural and urban sites of Delhi NCR. While the impact of air pollution on early childhood development is well-documented in low-pollution settings, evidence from high-pollution areas such as Delhi NCR will provide critical insights into its developmental and generational effects. Such findings will support policymakers and industry partners in implementing targeted interventions.

Strengths

One of the key strengths of this study is the use of personalized and portable air pollution exposure assessments. The study will use both indoor and outdoor monitoring of air pollution, which ensures a more accurate evaluation of the exposure levels faced by participants [31]. Integrating satellite-derived, ground-based, and personal exposure measurements to construct 24-hour exposure profiles will enhance the precision of the exposure models [32]. This personalized exposure assessment will be crucial in linking air pollution levels to the health effects observed in the cohort. The study features a comprehensive framework that evaluates a wide range of pregnancy and early childhood development outcomes, alongside exploratory biomarker assessments. Furthermore, integration with ongoing health and demographic surveillance at the study sites will enable long-term monitoring of participants, ensuring comprehensive follow-up into later childhood development.

Limitations

Despite the study's strengths, there are a few limitations. First, the impact of air pollution on pregnancy and early childhood developmental outcomes is primarily considered through $PM_{2.5}$ and PM_{10} effects. Due to limited resource settings, other air pollutants are not measured for personalized monitoring. In addition, while the study will use personal monitors to measure air pollution exposure, these monitors will collect data for a limited duration. Given the variable nature of air pollution, this may not fully capture long-term exposure patterns. Furthermore, the study is subject to the risk of confounding factors such as socioeconomic status, nutrition, and pre-existing health conditions that may influence the observed outcomes. All analyses will account for various confounding variables included in the study.

One of the primary challenges for the proposed study is ensuring consistent and high-quality data collection across both rural and urban sites. Recruitment and retention of study participants can also be challenging, as people in low-resource settings may have limited availability or interest in research participation. Furthermore, variability in air pollution exposure, both spatially and temporally, can make it difficult to assess the precise effects of specific pollutants on health outcomes. This requires careful consideration of the exposure assessment methodology and the need for real-time data to improve the accuracy of exposure models. Another challenge is the collection of comprehensive data over long periods, particularly regarding early childhood development. Regular follow-up visits are planned in the study to track developmental milestones and ensure the accurate assessment of outcomes such as stunting, underweight, and cognitive development. The proposed study will provide standardized protocols and training by subject-matter experts to the field team to accurately measure environmental exposure and health outcomes, thereby reducing errors and minimizing biases.

Practical Implications

The findings from this study will have significant practical applications. By providing robust evidence on the effects of air pollution on maternal and child health, the study will be instrumental for policymakers working toward meeting Sustainable Development Goal 3, which promotes good health and well-being. The study aligns with the priorities of the National Health Mission in India, particularly in addressing environmental factors that contribute to noncommunicable diseases and ensuring the health of vulnerable populations. Moreover, the biomarkers developed through this study will provide a tool for future research on the environmental impacts of air pollution, offering an opportunity to refine epidemiological

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models and improve public health interventions. The project tools, software, and frameworks will be thoroughly documented and shared as open-source resources for other researchers.

Conclusion

The proposed study aims to address a critical gap by providing direct evidence on the impact of air pollution on childhood development in India. A personal exposure model will be developed by integrating participants' time-activity profiles with both outdoor and indoor measurements. In addition, it will offer a framework for personal exposure modeling at the community level in both rural and urban settings. The study will also investigate the potential of biomarkers for predicting the effects of air pollution during pregnancy and early childhood. By investigating both immediate and long-term effects, this study will provide valuable data to inform policy decisions, promote public health awareness, and support the development of effective interventions. The results will not only enhance scientific understanding but also provide actionable insights to mitigate the adverse effects of air pollution on vulnerable populations.

Acknowledgments

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Authors' Contributions

HRS, SD, and AK contributed to the conceptualization of the study. HRS secured funding. All authors contributed to finalizing the methods, data acquisition plan, field activity planning, and training of field staff.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Study forms and questionnaires.
[DOCX File , 931 KB - resprot_v14i1e72683_app1.docx]

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Abbreviations

AIIMS: All India Institute of Medical Sciences
APiPED: air pollution impact on pregnancy and early childhood development

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IL: interleukin
LUR: land use regression
NCR: National Capital Region
PM: particulate matter
PW: pregnant women
SAANS: satellite-based application for air quality monitoring and management at a national scale
TNF: tumor necrosis factor

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Protocol

Registry-Based Assessment of Shunt Operation Methods and Outcomes in Idiopathic Normal Pressure Hydrocephalus (RASHOMON Study): Protocol for a Multicenter Prospective Observational Cohort Study

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Abstract

Background: Idiopathic normal pressure hydrocephalus is an age-related condition characterized by cerebrospinal fluid accumulation and ventricular enlargement, leading to cognitive decline, gait disturbance, and urinary incontinence. Although shunt surgery is the primary treatment, the optimal surgical strategy remains uncertain, and procedure selection is often not tailored to individual patient characteristics. Notably, no prospective study has directly compared the 3 major shunt techniques (ie, ventriculoperitoneal, lumboperitoneal, and ventriculoatrial).

Objective: This multicenter prospective observational study will aim to generate high-quality clinical evidence by evaluating the effectiveness and safety of the 3 aforementioned surgical options in a real-world setting.

Methods: Patients suspected of having this condition will be enrolled based on characteristic symptoms and imaging findings, with a spinal tap test recommended but not mandatory. Eligible patients will undergo one of the aforementioned surgical procedures.

Results: On the basis of recent data from 11 collaborating institutions in Japan, we estimate enrolling 278 cases: 188 (67.6%) surgical, 100 (36%) nonsurgical, and 10 (3.6%) dropouts. Clinical outcomes will be assessed at baseline; after the tap test (if performed); and at 1 week, 3 months, and 12 months postoperatively. The analyses will explore the associations between outcomes and surgical methods, patient backgrounds, and imaging features. As of May 2025, approximately 60 participants have been enrolled from 11 institutions. Data collection is ongoing and is expected to be completed by December 2026. There will be a 1-year follow-up period. The main study results are anticipated to be published in 2028.

Conclusions: Japan is well placed to lead this comparative study with its extensive experience in diagnosing and treating this disease. These findings are expected to provide practical guidance for individualized surgical decision-making and contribute to the global consensus on optimal treatment strategies.

Trial Registration: Japan Registry of Clinical Trials jRCT1040250005; https://jrct.mhlw.go.jp/latest-detail/jRCT1040250005

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International Registered Report Identifier (IRRID): DERR1-10.2196/80678

(JMIR Res Protoc 2025;14:e80678) doi:10.2196/80678

KEYWORDS

idiopathic normal pressure hydrocephalus; ventriculoperitoneal shunt; lumboperitoneal shunt; ventriculoatrial shunt; observational study; registry; cerebrospinal fluid; outcomes; Japan; protocol

Introduction

One disease closely related to aging is idiopathic normal pressure hydrocephalus (iNPH) in an aging society. The cause of iNPH is believed to be a disorder of cerebrospinal fluid (CSF) dynamics [1,2], leading to the accumulation of CSF within the cranial cavity and resulting in characteristic brain morphological changes, including ventricular enlargement. The Primary clinical symptoms include cognitive dysfunction, gait disturbance, and urinary incontinence [2-4]. This condition significantly impairs physical and mental function over several years, even up to decades after its onset, causing disruptions in daily life and shortening life expectancy. One study found that the 5-year mortality rate in untreated older patients with iNPH was significantly higher (87.5%) than in an age-matched healthy population (19.1%) [5]. Individuals aged 60 years and older are at risk of developing iNPH. A Japanese epidemiological survey reported that the population aged ≥65 years is approximately 36.2 million, accounting for 29.3% of the total population in 2024 [6]. In addition, the prevalence of iNPH ranges from 0.37% to 2.9% [7-9]. An estimated 12,900 new patients with iNPH visit health care facilities annually in Japan [10], suggesting that the number of potential patients is even higher.

The world's first guidelines for the management of iNPH were published in Japan in 2004, and several advancements have since been made in the diagnosis and treatment of this condition [11]. The characteristic brain imaging findings are disproportionately enlarged subarachnoid space hydrocephalus (DESH) [11-13]. The tap test, a CSF drainage test, is an important diagnostic tool. These findings also allow for the prediction of treatment efficacy [11,14,15]. Generally, the treatment preferred is shunting, using 1 of the 3 surgical methods: ventriculoperitoneal shunt (VPS), lumboperitoneal shunt (LPS), or ventriculoatrial shunt (VAS). In 2010, the results of the prospective clinical study, Study of Idiopathic Normal Pressure Hydrocephalus on Neurological Improvement (SINPHONI), which investigated the efficacy of VPS for iNPH, were published, demonstrating the effectiveness of VPS [13]. In 2015, the results of the SINPHONI-2 trial, which evaluated the efficacy of LPS for iNPH, showed that LPS surgery yielded results comparable to VPS [16]. However, no prospective studies have reported on the efficacy of VAS for iNPH. Although the third edition of the Japanese iNPH clinical practice guidelines was published in 2020, it does not compare the 3 surgical methods or provide recommendations on which one to choose [17]. Thus, the choice remains at the discretion of individual institutions and surgeons based on their experience and clinical judgment.

This study aims to evaluate and compare the effectiveness and adverse events associated with 3 surgical approaches for iNPH: VPS, LPS, and VAS. It will aim to provide evidence-based guidance for selecting the most appropriate surgical method for iNPH treatment.

Methods

Study Design

This multicenter prospective cohort observational study will be conducted from November 2024 to December 2028. The patient enrollment period is planned to run for approximately 2 years, with a follow-up period of 1 year. This study will evaluate and compare the effectiveness and adverse events associated with 3 surgical approaches for iNPH: VPS, LPS, and VAS. The goal is to provide evidence-based guidance for selecting the most appropriate surgical method for iNPH treatment.

Study Settings

This study plans to register patients from 11 institutions, including Nagoya University Hospital and its collaborating institutions. These institutions were selected through a fair process based on their agreement with the objectives of this study and their capability to provide comprehensive care for patients with iNPH. The iNPH database committee was organized by recruiting core members, including 5 neurosurgeons and 1 neuroradiologist, from Nagoya University Hospital and its affiliated institutions. The committee developed clinical trial plans and will manage and centrally review the data as independently as possible. Specifically, 1 neuroradiologist and 2 neurosurgeons will judge the anonymized images and the observed data of patients who are not involved in their treatment. Timely reminders will be issued to the attending physicians to minimize the risk of missing follow-up data.

Study Population and Eligibility Criteria

This study will include patients who are suspected of having iNPH based on head imaging and clinical symptoms and who undergo a lumbar puncture tap test. Among these patients, those deemed to require surgical treatment for hydrocephalus will be offered the option to choose 1 of the following procedures: VPS, LPS, or VAS. The diagnostic and treatment algorithm generally follows the third edition of the Japanese iNPH clinical practice guidelines. However, based on previous clinical experience, a small number of patients with an Evans index of less than 0.3 may still exhibit features suggestive of iNPH. To allow for the inclusion of such cases, the callosal angle will be incorporated as an additional imaging criterion. Moreover, the criterion of "normal CSF protein levels" described in the guidelines is not a mandatory requirement in this study; values less than or equal to 100 mg/dL are considered acceptable. The inclusion and exclusion criteria are presented in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Aged 60 to 85 years
- Having at least 1 of the following symptoms: gait disturbance, cognitive impairment, or urinary incontinence
- Presents with ventricular enlargement (Evans index >0.3) or a small callosal angle (<90°)
- Head magnetic resonance imaging or computed tomography showing—DESH (disproportionately enlarged subarachnoid-space hydrocephalus) findings, including narrowing of the subarachnoid space in the high-convexity and midline regions

Exclusion criteria

- Informed consent cannot be obtained
- Presence of a clearly identifiable underlying condition known to cause hydrocephalus
- A clearly identifiable space-occupying lesion in the cranium
- Significant brain atrophy observed due to stroke or trauma.
- A history of intracranial surgery for neurological disorders, excluding minor procedures (eg, evacuation of chronic subdural hematoma).
- The presence of systemic diseases (such as heart failure, respiratory failure, liver failure, or kidney failure) or cancer that makes the participant unsuitable
- The participant deemed unsuitable by the principal investigator or study collaborators

Sample Size Calculation

The sample size was calculated based on reports of previous iNPH shunt procedures. On the basis of the iNPH cases at the collaborating research institutions over the past 2 years, 56 (29.8%) VPS, 60 (31.9%) LPS, and 72 (38.3%) VAS procedures are anticipated to be performed, resulting in a total of 188 surgical cases during the 2-year enrollment period. In addition, 100 nonsurgical cases are expected to be included during the same period. Considering a 5% dropout rate during follow-up among the operated cases, the final sample size is estimated to be 278 cases (Figure 1).

Figure 1. Flowchart of the patient enrollment criteria and overall study design in this multicenter prospective observational study of idiopathic normal pressure hydrocephalus (iNPH). Observation cases are determined based on the patient's intention, condition, and need for surgery. Shunt procedures (ie, ventriculoperitoneal shunt [VPS], lumboperitoneal shunt [LPS], or ventriculoatrial shunt [VAS]) are selected according to the patient's clinical status and surgeon's preference. The target numbers for the shunt procedures were estimated from the number of previous surgical cases. DESH: disproportionately enlarged subarachnoid space hydrocephalus.

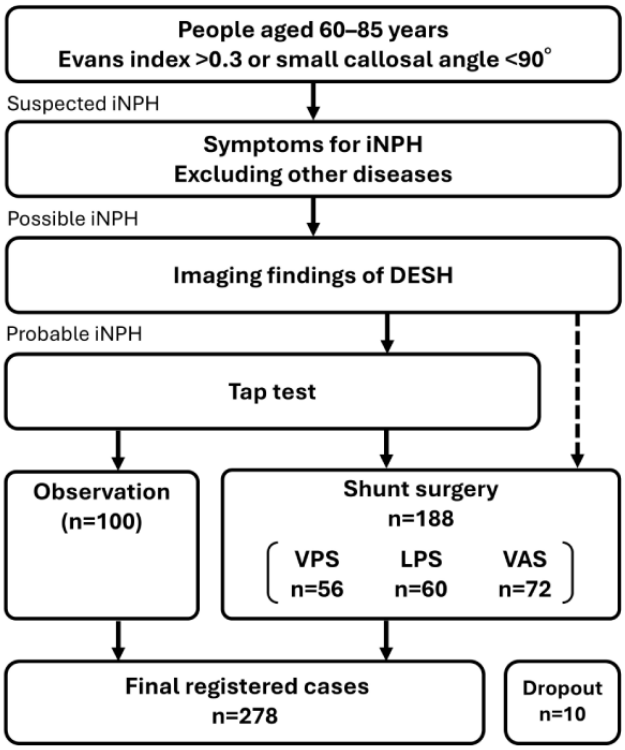

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Outcome Measures

The primary outcome is the change in the Modified Rankin Scale (mRS) score from baseline to 1 year after surgery in the VAS group compared to the VPS+LPS group.

The secondary outcomes are mentioned subsequently. First, the change in the mRS score from baseline to 1 year after surgery in the VAS group will be compared with that in the VPS group. Second, the change in the mRS score from baseline to 1 year after surgery in the VAS group will be compared with that in the LPS group. Third, the change in the mRS score from baseline to 3 months after surgery in the VAS group will be compared with the VPS+LPS group. Fourth, the occurrence of adverse events at 3 months and 1 year after surgery in the VAS group will be compared with the VPS+LPS group. Fifth, the evaluation items influencing treatment decisions in surgical versus nonsurgical cases will be compared.

Data Collection

The attending physicians and supporting medical staff will document the patient data in an electronic file for registration. During the registration process, interviews will be conducted to collect each patient's baseline information, including physical examination findings, comprehensive medical history (with specific items, such as previous abdominal surgery and spinal disease), lifestyle habits, and medication history. These variables will be systematically included in the electronic registration form for all patients, allowing the assessment of whether such factors influenced the choice of shunt procedure (ie, VPS, LPS, or VAS) in subsequent analyses. The information mentioned subsequently will be recorded during the treatment and follow-up.

Physical and cognitive function assessments include mRS, 3-m Timed Up and Go Test, Mini-Mental State Examination, and Idiopathic Normal Pressure Hydrocephalus Grading Scale.

The subjective assessment includes questionnaire survey. The objective assessments include (1) CSF opening and closing pressure and its drainage volume during the lumber tap test, (2) general CSF laboratory data, (3) head computed tomography imaging, (4) head magnetic resonance imaging or magnetic resonance angiography, (5) shunt valve pressure settings, and (6) adverse events.

The questionnaire survey that will be used in this study is an original tool for assessing patient-oriented outcomes. It consists of simple questionnaires regarding gait, cognitive and urinary functions, sleep, activities of daily living, and surgical satisfaction (Figure 2). The questionnaire uses a 4-choice ordinal scale to ensure that people with cognitive impairment can easily and reliably select the options. These forms will be completed as self-assessments by the patients and their family members.

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Figure 2. Patient home assessment form used in this multicenter prospective study of idiopathic normal pressure hydrocephalus. This questionnaire-based assessment tool, completed by patients and their families, enables the evaluation of the subjective changes after the tap test or shunt surgery. The form consists of 6 categories: gait, cognition, urination, snoring, caregiving, and overall satisfaction with the surgery.

Home Assessment Form

Name _____ ID _____ Date ____ / ____ / ____.

- For the following questions 1 to 6, please check the box that applies compared to your condition before receiving the test or treatment. Please select only one box for each question.
- The patient (the person who underwent the test or treatment) and the family member (the caregiver) should review the options together and select the appropriate answer.
- If you notice anything else, please write it in the space below. (Free text)

Question 1. Walking (speed, posture, stability) Example: No longer falling, able to lift feet more easily, able to walk longer distances			
☐ **Improved**	☐ **Slightly improved**	☐ **No change**	☐ **Worsened**
Question 2. Cognitive function (memory, attention, responsiveness) Example: Speaking louder, showing more interest, feeling clearer in the mind			
☐ **Improved**	☐ **Slightly improved**	☐ **No change**	☐ **Worsened**
Question 3. Toilet (frequency of urination, incontinence) Example: Reduced urinary leakage, decreased urgency, fewer nighttime trips to the toilet			
☐ **Improved**	☐ **Slightly improved**	☐ **No change**	☐ **Worsened**
Question 4. Breathing during sleep (snoring, apnea) Example: Snoring has decreased, fewer instances of breath stopping			
☐ **Improved**	☐ **Slightly improved**	☐ **No change** ☐ **Originally not present**	☐ **Worsened**
Question 5. Family (caregiver's) burden (supervision, caregiving) Example: Easier to supervise, caregiving burden has been reduced			
☐ **Improved**	☐ **Slightly improved**	☐ **No change**	☐ **Worsened**
Question 6. Satisfaction with treatment (only if underwent surgery) Example: Whether the surgery was worth it			
☐ **Good**	☐ **Slightly good**	☐ **Neither**	☐ **Not good**
Free text			

Staff Comments Section

☐ Post-tap test	☐ Discharge	☐ 3 months	☐ 12 months

Q1	Q2	Q3	Q4	Q5	Q6	total

Each option should be scored as 2, 1, 0, or -1.

Surgical Decision and Procedures

The decision to perform shunt surgery is comprehensively determined based on the patient's intention, condition, and the need for surgery. The reasons for the decision to undergo surgery will be documented. When shunt surgery is planned, the choice of procedure (ie, VPS, LPS, or VAS) will be determined based on the patient's condition and the surgeon's preference and technique. The type and configuration of the shunt system, including the choice of the catheter, valve, and valve pressure settings, will also be left to the discretion of each surgeon. However, the use of programmable valves equipped with antisiphon or antigravity devices is strongly recommended to minimize the risk of CSF overdrainage. Neither the manufacturer nor the model of the shunt system is specified in the study

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protocol. As CSF overdrainage after shunt surgery reportedly correlates with patient height, the height and weight of all patients will be recorded in the registry to allow for post hoc analysis of the relationship between body size and drainage volume. This study will provide no instructions or guidance regarding the surgical techniques or procedures.

Imaging Analysis

Head computed tomography and magnetic resonance imaging scans will be collected as digital data. The analysis will be conducted under the guidance of the department of radiological sciences at Nagoya University Hospital. These imaging data will be quantitatively evaluated using dedicated image analysis software, including measurements of the DESH score, callosal angle, ventricular volume, and brain center-of-mass displacement. The impact of various factors, including patient background, shunt surgery effectiveness, and adverse events, will be analyzed using imaging findings.

Representative Example of Clinical Protocol

As this is an observational study, there are no restrictions on the clinical guidelines or decisions. However, to avoid variability and confusion among participating institutions, clinical recommendations will be provided to each institution, and actual clinical practice may be conducted based on these recommendations. The recommended protocol was developed in accordance with the guidelines for the management of iNPH published by the Japanese Society of Normal Pressure Hydrocephalus. It incorporates the active use of the tap test. The guidelines recommend evaluating patients before and after the tap test, within 1 week, and at 3 and 12 months after shunt surgery (Figure 3).

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Figure 3. Flowchart illustrating the recommended protocol for diagnosis and assessment in this multicenter prospective study of idiopathic normal pressure hydrocephalus. The evaluation items for clinical symptoms include Modified Rankin Scale (mRS), 3-m Timed Up and Go (3mTUG) test, Mini-Mental State Examination (MMSE), Idiopathic Normal Pressure Hydrocephalus Grading Scale (iNPHGS), and subjective assessments via questionnaires completed by patients and their families. Head computed tomography (CT) imaging, shunt valve pressure settings, and adverse events are also collected and evaluated. The assessment is continued for 12 months after surgery. CSF: cerebrospinal fluid; DESH: disproportionately enlarged subarachnoid space hydrocephalus; LPS: lumboperitoneal shunt; MRI: magnetic resonance imaging; VAS: ventriculoatrial shunt; VPS: ventriculoperitoneal shunt.

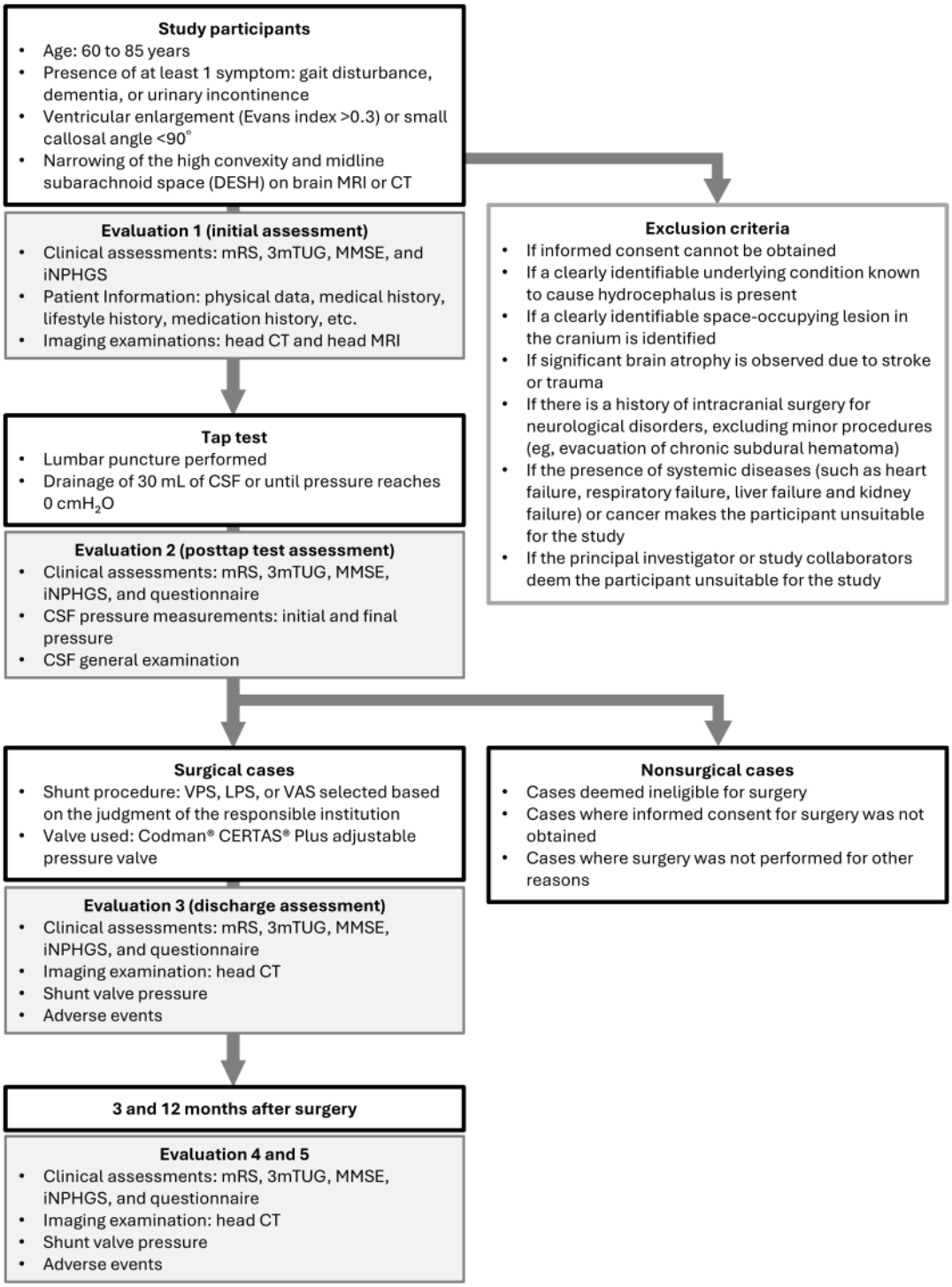

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Study Registration

This study was registered in the Japan Registry of Clinical Trials, operated by Japan's Ministry of Health, Labour and Welfare (jRCT1040250005).

Ethical Considerations

Ethics approval was obtained from the ethical review board for life sciences of Nagoya University (2024-0286-2). The purpose of this study will be explained to the participants, and their participation will be entirely voluntary, with the right to withdraw from the study at any time. In cases where participants lack sufficient decision-making capacity, the information will be provided to a legally authorized representative. Informed consent will be obtained in writing from all participants before data collection. Participants will be assigned a study registration ID, and no personally identifiable information will be collected. All information will be stored in a locked cabinet to ensure confidentiality. Participants will not receive any compensation for their participation. Participants will be asked to provide consent to store their samples and data for future use. The results will be published in international peer-reviewed journals.

Results

The patient enrollment for this study began in November 2024, following approval by the ethics committee. As of May 2025, approximately 60 participants have been enrolled from 11 institutions. Data collection is ongoing and is expected to be completed by December 2026. There will be a 1-year follow-up period. The main study results are anticipated to be published in 2028.

Discussion

Anticipated Findings

This protocol outlines a multicenter prospective observational study designed to comparatively evaluate the effectiveness and safety of 3 shunt procedures (ie, VPS, LPS, and VAS) for iNPH under real-world conditions. Building on the study objective stated in the Introduction section, the registry will standardize clinical assessments (eg, mRS, gait measures, and patient-oriented questionnaires) and incorporate structured imaging evaluations (eg, Evans index, callosal angle, and DESH-related features) while capturing the determinants of surgical decision-making (eg, previous abdominal or spinal surgery, body habitus, and surgeon experience). This design is intended to generate practice-informative comparative data to guide patient-tailored shunt selection.

Interpretation and Comparison With Literature

iNPH has been increasingly recognized as a major neurological disorder in aging societies, alongside Alzheimer and Parkinson diseases, necessitating appropriate clinical management. Unlike other neurodegenerative diseases, no pharmacological treatment has been established for iNPH, making surgical intervention the only therapeutic option [17-22]. Therefore, careful selection of candidates for shunt surgery is essential. Understanding the characteristics of the 3 main shunt procedures is crucial for optimizing treatment outcomes.

Several studies have compared the outcomes of different shunt procedures for iNPH [16,23-27]. These studies generally reported no significant differences in therapeutic efficacy among the VPS, LPS, and VAS procedures. However, variations in complication rates have been observed across studies. Notably, some reports have suggested that VAS may be associated with a lower incidence of complications than VPS and LPS [24,26]. However, complications related to catheter placement in the venous system have also been reported, making the overall evaluation of VAS more challenging [28-30].

VPS is the first procedure that neurosurgeons typically learn and remains the most commonly performed technique among the 3 shunt types. Due to its widespread use, it is considered a reliable procedure for the management of various forms of hydrocephalus. LPS, particularly in Japan, is frequently selected for patients with iNPH, and the number of cases is as large as that for VPS procedures. In contrast, the VAS is less commonly used and is generally reserved for cases in which abdominal surgery is contraindicated or should be avoided. Recently, the cervical approach to VAS placement has become less invasive. The traditional technique of performing a wide-neck incision and cutting down the facial vein for catheter placement has been replaced by a more refined method involving percutaneous puncture and the use of peel-away introducers for internal jugular vein catheterization. This advancement has simplified the procedure, making it easier for neurosurgeons to master. Moreover, this technique is expected to reduce surgery-related complications, leading to a gradual increase in the number of cases for which VAS is actively selected.

This new information regarding VAS highlights the possibility of achieving therapeutic outcomes equivalent to those of VPS and LPS, potentially reducing complication rates. Such findings could position VAS as a first-line surgical treatment for iNPH. A comparative analysis of these 3 procedures may offer critical insights for developing guidelines to tailor surgical approaches based on individual patient backgrounds. To our knowledge, no previous studies have comprehensively compared these 3 procedures, making this investigation a novel endeavor.

Limitations

This is a prospective observational study rather than a randomized controlled trial, making it difficult to compare the results across different surgical methods. One reason for this approach was to investigate the selection of surgical procedures for real-world clinical practice. Another reason was that randomization requires minimization of variability in baseline characteristics, resulting in reduced sample size and prolonged study period. Other limitations should be acknowledged. First, this study cannot completely exclude secondary causes of normal pressure hydrocephalus, such as stroke, meningitis, or collagen vascular diseases. Moreover, certain neurodegenerative disorders, including progressive supranuclear palsy and corticobasal degeneration, may coexist with or mimic iNPH, making clinical differentiation challenging [31,32]. Although the diagnostic criteria for iNPH will be strictly applied, the absence of pathological confirmation remains a limitation. Therefore, the influence of antecedent and comorbid diseases

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must be considered when interpreting imaging findings and clinical outcomes.

Conclusions

By systematically comparing VPS, LPS, and VAS in a multicenter setting, this study is expected to clarify procedure-specific advantages and guide evidence-based surgical decision-making. Incorporating detailed clinical, imaging, and demographic factors may enable the identification of patient subgroups that benefit the most from each procedure. Furthermore, the findings could contribute to the refinement of future clinical guidelines and support the development of personalized treatment strategies for iNPH, ultimately improving long-term outcomes in this growing patient population.

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Data Availability

This paper presents a study protocol. The datasets generated or analyzed during this study not publicly available due to patient privacy and ethical restrictions but are available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization: EO (lead), KT (equal), RS
Data curation: EO
Formal analysis: EO, HM
Funding acquisition: HM
Investigation: EO, KT
Methodology: TT, AH, MO, TN, YA
Project administration: EO (lead), KT (equal)
Supervision: RS (lead), TT (supporting)
Visualization: EO (lead), HM (supporting)
Writing—original draft: EO (lead), KT (supporting)
Writing—review and editing: HM

Conflicts of Interest

None declared.

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Abbreviations

CSF: cerebrospinal fluid
DESH: disproportionately enlarged subarachnoid space hydrocephalus
iNPH: idiopathic normal pressure hydrocephalus
LPS: lumboperitoneal shunt
mRS: Modified Rankin Scale
SINPHONI: Study of Idiopathic Normal Pressure Hydrocephalus on Neurological Improvement
VAS: ventriculoatrial shunt
VPS: ventriculoperitoneal shunt

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Protocol

Registry of Stroke in Korean Medicine Hospital (RoS-KoMH): Protocol for a Prospective, Multicenter, Observational Study

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Abstract

Background: Currently, conventional medicine for stroke treatment remains at a standstill. Korean medicine (KM), which is in high demand in Korea, has been shown to have a therapeutic effect on stroke; however, considering the absence of epidemiological and clinical characteristics of patients receiving KM for stroke in Korea and prospective, large-scale, long-term studies on the efficacy and safety of KM, the acquisition of data from KM treatments on stroke is essential.

Objective: We aimed to collect and analyze data on the major clinical characteristics of patients with stroke receiving KM treatment and investigate the effectiveness and safety of KM in the Korean population.

Methods: The Registry of Stroke in Korean Medicine Hospital (RoS-KoMH) is a prospective, multicenter, observational disease registry aimed at collecting data from 500 sets of patients at multiple timepoints. Eligible adult patients diagnosed with cerebral infarction, cerebral hemorrhage, or subarachnoid hemorrhage who visited 4 KM hospitals as outpatients or inpatients will be continuously registered using the electronic case report form. Baseline data at the first visit; KM treatment, rehabilitation therapy, and concomitant therapy during the visit; stroke evaluation every 4 weeks after the first visit; laboratory findings at discharge or the last visit; and safety evaluation information after each acupuncture or pharmacopuncture treatment will be collected.

Results: The study was funded on August 19, 2020, by the Ministry of Health and Welfare, Republic of Korea, and recruitment for the study started on November 3, 2021. As of September 25, 2024, a total of 410 participants have been recruited.

Conclusions: The RoS-KoMH study is the first and largest multicenter, prospective registry to record comprehensive data on KM treatment of stroke. The results of this study will provide high-quality evidence on the current state of stroke treatment using KM in actual clinical practice, as well as treatment effectiveness and safety, and will consequently contribute to the promotion and standardization of therapeutic interventions for stroke in Korea.

Trial Registration: Clinical Research Information Service KCT0008494; https://cris.nih.go.kr/cris/search/detailSearch.do?seq=23999&search_page=L&search_lang=&class_yn=

International Registered Report Identifier (IRRID): DERR1-10.2196/67850

(JMIR Res Protoc 2025;14:e67850) doi:10.2196/67850

KEYWORDS

stroke registry; Korean medicine; quality improvement; Korean population; rationale and design; acupuncture; herbal medicine

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Introduction

Stroke is the second leading cause of death worldwide and is characterized by high mortality, morbidity, disability, and recurrence [1]. Although the mortality rate is decreasing owing to advances in risk factor control, treatment techniques (eg, thrombolysis), and secondary prevention, the incidence is gradually increasing owing to the rapidly aging population [2-4]. In addition, many survivors experience sequelae, and poststroke disability places a significant burden on patients, caregivers, and society [5].

Current treatments for stroke have made significant progress but still have distinct limitations. Thrombolysis is the recommended first-line treatment for acute ischemic stroke to improve long-term functional outcomes. However, access is limited by narrow time windows, high technical requirements, imaging dependence, and high costs [6]. Antiplatelets are recommended for most patients for the secondary prevention of ischemic stroke [7], but they have a recurrence rate of approximately 10%, have remained flat for decades [8], and carry a high risk of adverse effects, including a bleeding tendency [9]. For cerebral hemorrhage, there are no special treatment options other than blood pressure management unless surgery is indicated [10].

Korean medicine (KM), which includes acupuncture and herbal medicine, is a traditional medicine that falls under the category of traditional East Asian medicine and has a long history in Korea. More than 70% of Koreans experience KM treatment and report high treatment satisfaction [11]. As evidence accumulated on the effectiveness of KM treatment for stroke, the Korean Medicine Clinical Practice Guideline for Stroke was developed in 2021, recommending the use of KM treatments, such as acupuncture and herbal medicine, to improve symptoms, treat, and prevent stroke [12]. However, KM demand for stroke treatment is declining, with stroke as a reason for KM inpatient use decreasing from 20.4% in 2014 [13] to 3.3% in 2022 [11]. This is because the epidemiological and clinical characteristics of patients receiving KM for stroke have not been investigated in Korea, and KM for stroke has been criticized for its low-quality evidence of efficacy and safety. Therefore, there is a need for a large-scale, prospective study on KM in patients with stroke.

A registry is a method for building a unified system by recording and sharing large-scale data in the health care field. Ongoing stroke registries in Korea include the multicenter prospective stroke registry (Clinical Research Collaboration for Stroke in Korea) [14] and a multicenter, prospective cohort study on stroke rehabilitation (Korean Stroke Cohort for Functioning and Rehabilitation) [15]. However, these were both registry studies on Western medicine, and no registry studies on stroke involving KM have been conducted in Korea. In China, a multicenter registry of traditional Chinese medicine for stroke has been organized and is currently enrolling patients [16]. In Taiwan, the characteristics of usage and outcomes of traditional Chinese medicine treatments, such as acupuncture and herbal medicine, for stroke have been analyzed using large-scale, national health insurance data [17,18]. Therefore, there is an urgent need for a stroke registry study of KM in Korea.

We present the rationale and design of the Registry of Stroke at Korean Medicine Hospital (RoS-KoMH). The RoS-KoMH aims to establish a multicenter, prospective registry of stroke in KM hospitals to explore the demographics, clinical presentation, treatment usage status, therapeutic outcomes, and safety of patients treated in KM hospitals and to collect clinical evidence to improve future treatment outcomes.

Methods

Study Design

The RoS-KoMH is a voluntary multicenter, prospective, observational disease registry attempting to explore the demographics, clinical features, treatment status, therapeutic outcomes, and safety of patients with stroke in Korea who are treated using KM in KM hospitals and establish clinical evidence to improve treatment outcomes in the future. A flowchart of the study process is shown in Figure 1. This study will be conducted by the Kyung Hee University Korean Medicine Hospital (KH) located in Seoul, Dongguk University Ilsan Korean Medicine Hospital (DG) located in Gyeonggi-do, Wonkwang University Gwangju Medical Center (WK) located in Gwangju, and Pusan National University Korean Medicine Hospital (PS) located in Gyeongsangnam-do. The protocol was registered with the Clinical Research Information Service (KCT0008494) on June 2, 2023, and reported in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist (Multimedia Appendix 1).

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Figure 1. Flowchart of the study process. Stroke assessments at the initial assessment involve the manual muscle testing (MMT) grading system, modified Ashworth scale (MAS), grasp power, WIN-TRACK, timed up and go (TUG) test, modified Barthel index (MBI), fatigue assessment scale (FAS), fatigue severity scale (FSS), National Institutes of Health stroke scale (NHISS), Korean standard pattern identification (K-SPI) for stroke questionnaire, heart-kidney noninteraction questionnaire, Korean version of the mini-mental state examination (MMSE-K), and patient health questionnaire-9 (PHQ-9). Subsequent stroke assessments involve the MMT, MAS, grasp power, WIN-TRACK, TUG test, MBI, FAS, FSS, NHISS, K-SPI for stroke questionnaire, and heart-kidney noninteraction questionnaire. Korean medicine (KM) treatments include acupuncture, electroacupuncture, bee venom acupuncture, pharmacoacupuncture, indirect moxibustion, direct moxibustion, and cupping. HS, hemorrhagic stroke; IS, ischemic stroke; SAH, subarachnoid hemorrhage.

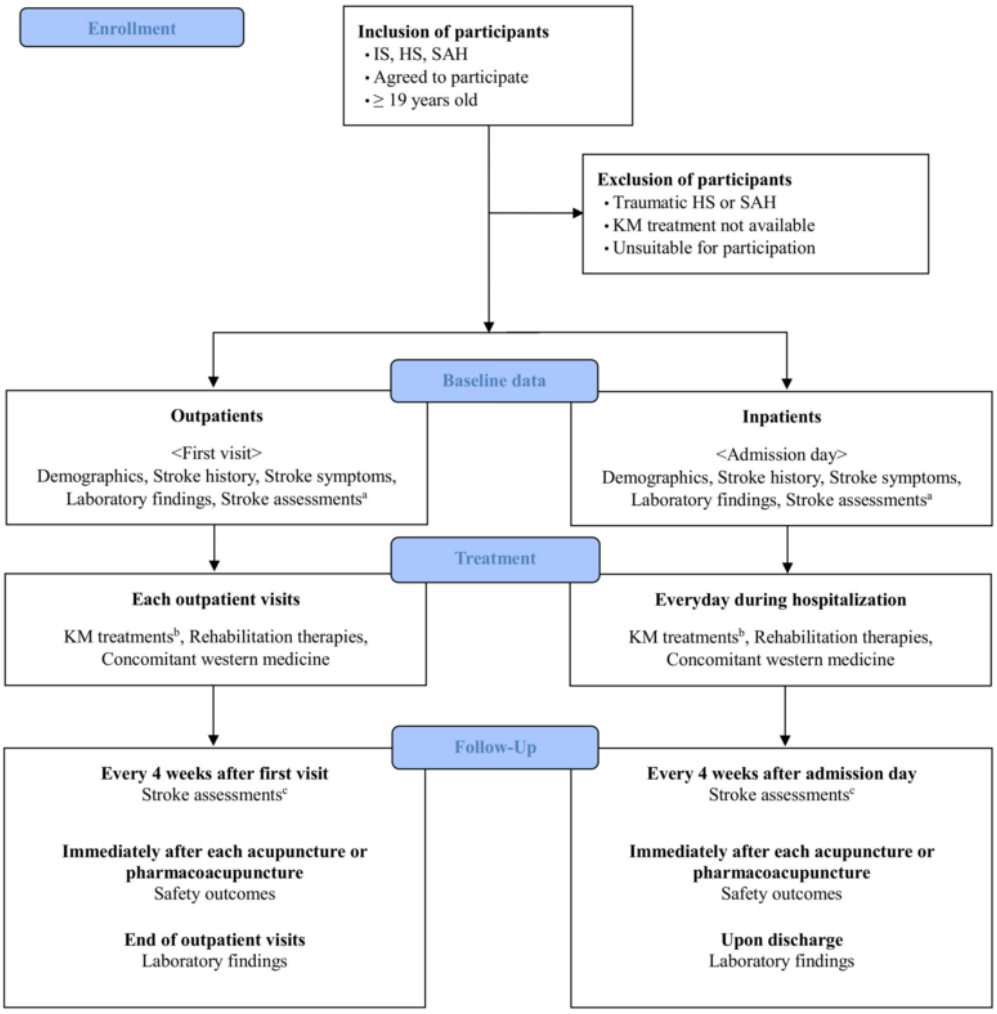

Study Participants

Inclusion Criteria

The inclusion criteria for the study are as follows:

1. Men and women aged 19 years or older.
2. Patients diagnosed with a stroke (including ischemic stroke, hemorrhagic stroke, or subarachnoid hemorrhage; 10th revision of the International Classification of Diseases codes I60-I63) based on the results of clinical examination and radiologic examination and receiving treatment at an outpatient clinic or an inpatient ward of a KM hospital.
3. Patients who understood the purpose and intent of the study and voluntarily agreed to participate through written consent from the patient or their caregiver or representative.

Exclusion Criteria

The exclusion criteria for the study are as follows:

1. Patients with traumatic hemorrhagic stroke or traumatic subarachnoid hemorrhage.
2. Patients who suffer from diseases that can affect acupuncture, electroacupuncture, pharmacopuncture, bee venom injection, moxibustion, or cupping (eg, clinically severe skin diseases and blood clotting disorders) and therefore cannot be treated.
3. Patients judged by the investigator to be physically and mentally unsuitable for participation in the registration study based on examinations and laboratory findings.

Dropout Criteria

The following patients will be considered dropouts:

1. Patients discharged within 4 weeks of admission or lost to follow-up within 4 weeks of the first outpatient visit.
2. Participants who are noncompliant with the investigator's instructions.
3. Participants who withdraw consent or request discontinuation.

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Number of Participants

The purpose of this study was not to statistically verify the intervention effect of KM treatment for stroke but to explore the demographics, clinical aspects, treatment status, and therapeutic efficacy and safety of KM for patients with stroke patients in Korea and to provide clinical evidence to improve the therapeutic effect of KM treatment in the future.

Accordingly, a total of 500 sets of clinical information on patients with stroke will be collected based on the opinions of the researchers, considering the financial resources, the environment in which the study is conducted, and the appropriate number needed to achieve the goal. One set was defined as a stroke patient for whom information was collected at the time of the first outpatient visit or admission, and additional information was collected at any point (4, 8, or 12 weeks) after the first outpatient visit or admission. For example, if information was collected for a single patient once upon admission, once in the fourth week of hospitalization, and once again in the eighth week of hospitalization, 2 sets of information would be considered collected.

Recruitment of Participants

The participants of the study will be patients with stroke who visited as outpatients or were admitted as inpatients to KM hospitals. Patients who are deemed suitable for participation in the study based on the inclusion and exclusion criteria will be recruited by obtaining voluntary written consent from the participants or their caregivers within 7 days of their outpatient visit or hospitalization at a KM hospital after the research staff have provided all information related to the study. All information obtained from patients was collected and recorded using an electronic safety case report form (eCRF) that was developed and validated by the principal investigators and research staff from all institutions participating in the study (KH, DG, WK and PS) over a period of approximately 10 months through multiple face-to-face and web-based meetings, and all assessment tools included in the eCRF were developed, validated, and used in clinical practice.

Baseline Data

Information on participant demographics (age, gender, type of health insurance, and smoking and drinking history), stroke history (stroke onset and initial diagnosis date; the type and date of computed tomography or magnetic resonance imaging used to diagnose the stroke; the site, type and lesion of the stroke; the Trial of Org 10172 in acute stroke treatment classification for cerebral infarction; history of stroke surgery; stroke risk factors; and past medical history), stroke symptoms (hemiplegia, sensory disorder, dysphagia, dysuria, dyspnea, digestive disorder, poststroke depression, poststroke delirium, poststroke insomnia, poststroke cognitive impairment, headache, dizziness, fatigue, and other symptoms), laboratory findings (complete blood count, biochemistry, lipid profile, and endocrine panel), and stroke assessment (hemiplegia with the manual muscle testing grading system, modified Ashworth scale, and grasp power; gait and balance disorders with the WIN-TRACK and timed up and go test; activities of daily living with the modified Barthel index; fatigue with the fatigue assessment scale and fatigue severity scale; stroke scales with the National Institutes of Stroke scale, Korean standard pattern identification for stroke questionnaire, and heart-kidney noninteraction questionnaire; impaired memory and disorientation with the Korean version of the mini-mental state examination; and depression with the patient health questionnaire-9) will be collected from medical records at the time of the first outpatient visit or inpatient admission. Detailed information regarding the collection of each item is presented in Table 1, and the participant timeline is presented in Table 2.

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Table 1. Collecting information from participants.

Item	Information collected
Demographics	Age, gender, type of health insurance (national health insurance, medical benefits, or other), smoking history (status, past and present smoking, and amount of smoking), drinking history (status, past and present drinking, amount of drinking by type, and duration of drinking).
Stroke history	Stroke onset date and initial diagnosis date, the type and date of the imaging test used to diagnose the stroke (CT[a] or MRI[b]), the site of the stroke (cortical area or subcortical area), the type of stroke (cerebral infraction, cerebral hemorrhage, or subarachnoid hemorrhage), the lesion of the stroke (ACI[c], LACI[d], or POCI[e]), TOAST[f] classification for cerebral infarction (LAA[g], CE[h], SVO[i], other causes, or undetermined), history of stroke surgery, stroke risk factors (previous stroke, hypertension, dyslipidemia, diabetes mellitus, atrial fibrillation, or others), and past medical history (date of diagnosis or surgery, name of disease or surgery, and current status).
Stroke symptoms	Hemiplegia (motor disorder), sensory disorder (including central pain), dysphagia (applying L-tube, PEG[j], or dysphagia diet), dysuria (applying foley catheter), dyspnea (applying tracheostomy tube or oxygen), digestive disorder (constipation, dyspepsia, diarrhea, or others), poststroke depression (taking antidepressant or suspected depression on a depression-related scale), poststroke delirium, poststroke insomnia, poststroke cognitive impairment (taking drugs related to cognitive impairment or suspected cognitive impairment on a scale such as MMSE-K[k]), headache, dizziness, fatigue, and other symptoms.
Laboratory findings	Complete blood count (white blood cell; red blood cell; hemoglobin; hematocrit; platelet; differential count, including segmented neutrophils, lymphocytes, monocytes, eosinophils, and basophils; PT-INR[l]; and aPTT[m]), biochemistry (total bilirubin, protein, albumin, AST[n], ALT[o], BUN[p], creatinine, sodium, potassium, chloride, calcium, uric acid, and glucose) , lipid profile (total cholesterol, triglyceride, HDL[q]-cholesterol and LDL[r]-cholesterol), and endocrine panel (hemoglobin A1C).
Stroke assessments	Hemiplegia with the MMT[a], MAS[t], and grasp power; gait and balance disorders with WIN-TRACK[u] and TUG[u] test; ADL[v] with MBI[w] and fatigue with FAS[x] and FSS[y]; stroke scale with the NIHSS[z], K-SPI[aa] stroke questionnaire, and heart-kidney noninteraction questionnaire; impaired memory and disorientation with the MMSE-K; and depression with the PHQ-9[ab]
Korean medicine treatments	Herbal medicine (prescription name, administration purpose and duration, current administration, frequency, single dose, and unit), acupuncture (method, frequency, and duration), electroacupuncture (stimulus method, frequency, and duration), bee venom acupuncture (type and method, frequency, and duration), pharmacopuncture (type and method, frequency, and duration), indirect moxibustion (method, frequency, and duration), direct moxibustion (method, frequency, and duration), and cupping (method, frequency, and duration)
Rehabilitation therapies	Physical therapy, occupational therapy, speech therapy, and swallowing therapy
Concomitant treatment	Western medicine (ingredient name, administration purpose and duration, current administration, frequency, single dose, unit, route of administration)
Safety outcomes	Spot bleeding (bleeding time <10 s), microbleeding 1 (bleeding time 10 s to <20 s), microbleeding 2 (bleeding time 20 s to <30 s), extensive bleeding (bleeding time ≥30 s), massive hemorrhage influencing vital signs or causing other complications, bruising (checked 1-3 hours after removing the needles), edema, faintness or dizziness, fatigue or exhaustion, nausea or vomiting, pneumonia, needle fracture, skin eruption or itching, pain after needling, and other adverse effects after each treatment

[a]CT: computed tomography.

[b]MRI: magnetic resonance imaging.

[c]ACI: anterior circulation infarct.

[d]LACI: lacunar infarct.

[e]POCI: posterior circulation infarct.

[f]TOAST: Trial of Org 10172 in Acute Stroke Treatment.

[g]LAA: large-artery atherosclerosis.

[h]CE: cardioembolism.

[i]SVO: small vessel occlusion.

[j]PEG: percutaneous endoscopic gastrostomy.

[k]MMSE-K: Mini-mental state examination, Korean version.

[l]PT-INR: prothrombin time-international normalized ratio.

[m]aPTT: activated partial thromboplastin time.

[n]AST: aspartate aminotransferase.

[o]ALT: alanine aminotransferase.

[p]BUN: blood urea nitrogen.

[q]HDL: high-density lipoprotein.

[r]LDL: low-density lipoprotein.

[s]MTT: manual muscle testing grading system.

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[t]MAS: modified Ashworth scale.
[u]TUG: timed up and go.
[v]ADL: activities of daily living.
[w]MBI: modified Barthel index.
[x]FAS: fatigue assessment scale.
[y]FSS: fatigue severity scale.
[z]NIHSS: National Institutes of Stroke scale.
[aa]K-SPI: Korean standard pattern identification.
[ab]PHQ-9: patient health questionnaire-9.

Table 2. Participant timeline for the Registry of Stroke in Korean Medicine Hospital.

Item	Outpatient first visit or inpatient admission day	At each outpatient visit or every day during hospitalization	Every 4 weeks after the outpatient first visit or inpatient admission day	Immediately after each acupuncture or pharmacopuncture. therapy	Final outpatient visit or upon discharge
Demographics	●				
Stroke history	●				
Stroke symptoms	●				
Laboratory findings	●				●
Stroke assessments[a]	●		●		
Stroke assessments[b]	●				
Korean medicine treatments		●			
Rehabilitation therapies		●			
Concomitant treatment		●			
Safety outcomes				●	

[a]Hemiplegia with the manual muscle testing grading system, modified Ashworth scale, and grasp power; gait and balance disorders with WIN-TRACK and the timed up and go test; activities of daily living with the modified Barthel index; fatigue with the fatigue assessment scale and fatigue severity scale; stroke scale with the National Institutes of Stroke scale, Korean standard pattern identification-stroke questionnaire, and heart-kidney noninteraction questionnaire; impaired memory and disorientation with the mini-mental state examination, Korean version; and depression with the patient health questionnaire-9.

[b]Impaired memory and disorientation with the mini-mental state examination, Korean version, and depression with the patient health questionnaire-9.

Korean Medicine Treatments

Information on the use of herbal medicines (including herbal decoctions, inpatient pharmaceuticals, and external pharmaceuticals), acupuncture, electroacupuncture, bee venom acupuncture, pharmacopuncture, indirect moxibustion, direct moxibustion, and cupping during outpatient visits and hospitalizations will be collected daily (ie, at each outpatient visit or daily during hospitalization). The start and end dates of each treatment tool will also be investigated. If the use of any treatment tool has been discontinued, the date on which it was discontinued shall be the primary end date, the date the treatment was resumed shall be the secondary start date, and the date the treatment was last used shall be the secondary end date. For herbal medicine and pharmacopuncture, the prescription name will be written separately in the comments section of the eCRF. For herbal medicines, the start and end dates of each prescription will be recorded whenever the prescription is changed.

Rehabilitation Therapies

Information on the use of physical, occupational, speech, and swallowing therapies during outpatient visits and hospitalizations will be collected every day (ie, at each outpatient visit or daily during hospitalization). The duration of each treatment will be recorded in the same way as that for the KM treatment.

Concomitant Treatment

We will also collect information on the daily use of western medications (oral and injection types) every day (ie, at each outpatient visit or daily during hospitalization). For each western medicine, the name of the ingredient, purpose of administration, start date, end date, frequency of administration, dose, unit, and route will be investigated. If the frequency, dose, unit, and route change for the same ingredient, information will be collected separately.

Follow-Up Measures

Stroke assessments (outlined in Table 2) will be conducted every 4 weeks after the first visit for both outpatients and inpatients. Follow-up laboratory findings will be collected at the final outpatient visit or discharge.

Safety Outcomes

During the treatment period, the safety of acupuncture treatments will be evaluated when the needles are removed immediately

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after each acupuncture, electroacupuncture, pharmacopuncture, or bee venom acupuncture treatment. Bleeding events with duration and complications, bruising, edema, faintness or dizziness, fatigue or exhaustion, nausea or vomiting, pneumonia, needle fracture, skin eruption or itching, pain after needling, or other adverse events after each treatment will be assessed. The detailed safety assessment items are listed in Table 1.

Data Analysis

Statistical analyses will be performed with SPSS version 21.0 (IBM Corporation) by our biostatisticians at the RoS-KoMH. Descriptive statistics will be used to analyze the data, and all measures will be presented as means (SDs) for continuous variables and n (%) for dichotomous variables. For variables assessed more than once, the amount or rate of change from baseline to follow-up will be calculated.

Ethical Considerations

The study protocol was approved by the Institutional Review Board of Kyung Hee University Korean Medicine Hospital (KOMCIRB 2021-06-003-001, approved on August 13, 2021), Dongguk University Ilsan Korean Medicine Hospital (DUIOH 2021-10-008-002, approved on August 30, 2022), Wonkwang University Gwangju Medical Center (WKIRB 2021/7-2, approved on September 29, 2021), and Pusan National University Korean Medicine Hospital (PNUKHIRB 2021-11-003-001, approved on December 22, 2021). This study is conducted in accordance with the principles of the Declaration of Helsinki. Participants who wish to participate will receive an explanation of the consent form and must provide written consent of their own free will. All data from participants will be simultaneously recorded in an eCRF with an identification code rather than the participant's name to protect personal information.

Results

The study was funded by the Ministry of Health and Welfare, Republic of Korea (grant RS-2020-KH088006) on August 19, 2020. Recruitment for the registry commenced on November 3, 2021, and is scheduled to end on December 31, 2026. As of September 25, 2024, a total of 410 sets have been collected: 171 from KH, 88 from DG, 125 from WK, and 26 from PS. At this point, no data analysis has been conducted.

Discussion

With increasing interest in the effects, benefits, and adverse effects of various treatments, well-designed, large-scale registries related to the long-term clinical outcomes of patients with stroke should be prioritized by clinicians and researchers [19]. Here, we describe the rationale and design of a prospective, multicenter, registry-based observational study investigating the clinical characteristics, KM stroke management, and outcomes of patients with acute stroke in a real-world setting in Korea. This study is expected to provide comprehensive real-world data on the demographic characteristics, treatment patterns, clinical outcomes, and safety of KM in stroke care across multiple institutions in Korea.

Considering that the current evidence-based guidelines for acute treatment and rehabilitation for stroke still have limitations despite several advances over the last few decades, the need for more effective and safer treatments to improve the prognosis of patients with stroke is constantly increasing [16]. Clinical KM studies on stroke have shown the efficacy of combined herbal treatment for acute ischemic stroke [20], the secondary prevention effect of herbal extracts on ischemic stroke [21,22], the benefits of acupuncture for stroke rehabilitation [23], the prevention effect of acupuncture [24], the improvement of dysphagia following acupuncture [25], the effect of pharmacopuncture on poststroke shoulder pain [26], and the effect of herbal treatment on chronic subdural hemorrhage [27]. The safety of KM treatment for stroke has also been reported, including the safety of combining warfarin with herbal medicine [28], the safety of liver and kidney function with the coadministration of western medicine and herbal medicine in patients with stroke [29], and the safety of combining acupuncture with warfarin [30] and novel oral anticoagulants in patients with stroke [31]. Most of these were retrospective cohort studies, cross-sectional studies, or systematic reviews that evaluated specific treatments or effects, which are common research methods used to generate evidence for KM and have been criticized for the quality of evidence on efficacy and safety. Therefore, it is necessary to improve the quality of evidence for the use of KM for patients with stroke.

Some characteristics of KM have made it difficult to build high-level evidence for it. In other words, KM is an empirical medicine that has accumulated over a long period, and it is difficult to standardize and objectively evaluate treatment because it provides customized treatment according to patient characteristics and requires a long treatment period and long-term follow-up. One way to supplement these points is to collect and use large-scale data [32]. Large-scale data use studies on KM in Korea are rare. In Taiwan, 99% of people are enrolled in national health insurance, and most traditional medicine treatments, including traditional Chinese medicine, are covered by national health insurance and used to generate evidence and improve treatment quality [33]. However, in the case of health insurance databases in Korea, KM is limited in that data cannot be obtained because major treatments such as herbal medicine (with some exceptions), pharmacopuncture, and bee venom acupuncture are not covered by national health insurance. Therefore, we designed the RoS-KoMH to compensate for these limitations by collecting information that can be obtained when treating patients with stroke patients at KM hospitals that actually treat stroke.

The RoS-KoMH protocol has some limitations. Although the RoS-KoMH registry collects longitudinal and multidimensional data, multivariate analyses, such as regression modeling or adjustment for potential confounders, have not yet been applied, which may limit causal inference regarding treatment outcomes given the variability in patient comorbidities and interventions. In addition, since the RoS-KoMH is a real-world, hospital-based, observational registry, it relies on voluntary participation to reflect the natural flow of patients receiving KM treatment for stroke in a routine clinical setting, which may lead to selection bias. The results of this study will provide evidence on the

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efficacy and safety of KM treatment for stroke to facilitate and standardize the optimization of individualized interventions for stroke prevention and treatment in Korea. Therefore, it is suggested that a registry study focusing on KM treatment be conducted using a stratified or consecutive sampling design as a follow-up to this study.

Acknowledgments

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Data Availability

Data sharing does not apply to this protocol, as no datasets have been collected or analyzed.

Authors' Contributions

HGL contributed to the investigation, methodology, writing of the original draft, and review and editing of the manuscript. WSJ contributed to project administration, supervision, and review and editing of the manuscript. SK contributed to conceptualization, project administration, supervision, methodology, funding acquisition, supervision, and review and editing of the manuscript. SL, CHK, DJC, IL, and SKM contributed to project administration, the investigation, and review and editing of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT checklist.
[PDF File (Adobe PDF File), 127 KB - resprot_v14i1e67850_app1.pdf]

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Abbreviations

eCRF: electronic case report form
KM: Korean medicine
RoS-KoMH: Registry of Stroke in Korean Medicine Hospital
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Trust Dynamics and Equity in Public Health in Canada: Protocol for a Mixed Methods Project in the Postpandemic Era

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Abstract

Background: The COVID-19 pandemic impacted trust in public health, medical care, scientific, and governmental institutions; this influenced health, health-seeking behaviors, and adherence to public health measures. Understanding how trust evolves is necessary for informing future public health crisis management and strategies. Rebuilding public trust is key to pandemic preparedness worldwide. This research protocol examines these trust dynamics, their determinants, and their implications.

Objective: This study aimed to investigate the evolution of public trust in scientists, public health and medical care institutions, governments, and social and personal networks during the COVID-19 pandemic. It sought to identify key factors contributing to trust maintenance or erosion, particularly in marginalized and minority communities, and understand the impact of trust level on public health adherence.

Methods: A sequential, explanatory mixed methods approach was implemented, consisting of an initial quantitative survey followed by qualitative interviews. The nationwide representative survey included 5607 Canadian residents as of May 2024. The questionnaire assessed trust in 6 key trust sources before and during the pandemic: provincial and federal governments, public health authorities, medical care providers, health scientists, and social and personal networks. To complement, 41 qualitative interviews were conducted to understand participants' lived experiences, perceptions, and how trust played into both. Data have been analyzed using quantitative statistical techniques and qualitative phenomenological analysis, and the results have been integrated to derive comprehensive insights. All phases of data collection and analysis were finalized by early 2025. The project then advanced to paper preparation, dissemination at national conferences, and knowledge-translation activities, including the report development and public-facing outputs, scheduled for completion in end-2025.

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Results: This Canadian survey included participants from all 10 provinces and 2 territories; the provinces and territories' samples matched the proportions of each in the overall Canadian population. Age and sex or gender were well distributed across the sample. Additionally, 18.6% (1040/5607) identified as an ethnic minority, 12.7% (710/5607) identified as Indigenous, including 7.2% (403/5607) First Nations, 4.8% (270/5607) Métis, and 0.4% (25/5607) Inuit. Fifty-five percent (3094/5607, 55.2%) had received at least 1 dose and planned to stay up to date with booster recommendations, while 36.6% (2052/5607) were vaccinated but did not intend to receive additional doses. A small percentage, 0.7% (39/5607), had not yet been vaccinated but were open to it, whereas 6.4% (359/5607) had not received a vaccine and did not plan to take a vaccine.

Conclusions: The COVID-19 pandemic has underscored the critical role of trust in public health behavior and crisis response. This study explores how consistent, transparent communication and equity-driven policies may contribute to maintaining public trust, particularly among marginalized communities. By examining trust dynamics and identifying potential disparities, this study aims to inform evidence-based public health strategies and improve preparedness for future health emergencies.

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KEYWORDS

COVID-19 pandemic; trust dynamics; Canada; mixed methods; health equity; public health

Introduction

Background

March 11, 2025, marks the five-year anniversary of the official declaration of the COVID-19 pandemic by the World Health Organization, a milestone that reflects the immense challenges faced and the ongoing impacts of this global health emergency. The COVID-19 pandemic, one of the most devastating public health crises in modern history, emerged at a time when the world, including Canada, was largely unprepared. Canada's first confirmed case was reported in Ontario on January 25, 2020, and within weeks, the country recorded its first death from the virus on March 09, 2020. On March 11, 2020, the World Health Organization declared the outbreak a pandemic [1]. In response, Quebec declared a state of public health emergency on March 13, followed by all other provinces and territories by March 27, as the virus spread rapidly across the country [2]. By December 2020, the vaccines had been developed and brought to people, and the rollout began across many countries, including in Canada, marking a critical and definitive turning point in the fight against the virus.

Government Response and Canada in the Global Context

In the early stages of the pandemic, Canada prioritized restricting international travel, based on the belief that limiting travel from the virus's point of origin—Wuhan, China—could help reduce its introduction into the country [3]. Early measures included travel advisories, closure of the Canada-US border, and a mandatory 14-day self-isolation for those entering the country [4]. As COVID-19 transitioned from being a concern primarily for travelers to widespread community transmission, additional public health measures were implemented, including social distancing, hand hygiene, mask mandates, and the closure of schools and daycares [5]. Many workers transitioned to remote work, public gatherings were prohibited, restaurant capacities were limited, and public spaces such as gyms and recreational facilities were closed. While the federal government provided oversight relating to national measures, the pandemic countermeasures closest to people were introduced and enforced by provincial and territorial governments, depending on local conditions [2].

Worldwide, Canada's response in the first 2 years of the pandemic outperformed many other Group of Ten (G10) countries [6]. Canada had the second-lowest infection and mortality rate among the G10, just behind Japan [7]. According to the Oxford Stringency Index, which measures the intensity of governmental responses based on indicators such as travel bans, school closures, and workplace lockdowns, Canada ranked as the second-most stringent country among the G10 during the first 2 years of the pandemic, just behind Italy [4]. Unlike many other nations, Canada's response was characterized by its prolonged and sustained measures, lasting more than 2 years.

Overall Impact of the COVID-19 Pandemic in Canada

The impact of the COVID-19 pandemic on Canadians was profound, affecting nearly every aspect of daily life. Beyond physical health, mental health became a major concern. Canadians experienced heightened anxiety, depression, and stress due to isolation, uncertainty, and economic struggles [8,9]. Alongside psychological distress, alcohol and substance use spiked [8,10], while studies also reported rising rates of self-harm and suicidal ideation compared to prepandemic levels [11-13]. Vulnerable populations—such as children and youth, low-income groups, racial and ethnic minorities, and immigrants—were disproportionately affected, facing even greater mental health challenges [14-18]. The economic impact was also severe, with rising unemployment, government debt, and inflation [7]. Domestic violence and relationship conflicts also increased, particularly among those who experienced job loss or reduction [19]. These economic hardships deepened the existing social inequities, with marginalized communities bearing the brunt of the effects [20,21].

Change in Trust During the Pandemic

Although Canada's COVID-19 outcomes in terms of infection rates and death rates were relatively moderate compared to many countries, especially the United States, it still faced criticism for its pandemic management when compared to exemplars such as Australia, New Zealand, and South Korea [22].

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A key point of contention was the vaccine mandate, which required proof of vaccination for discretionary activities such as dining in restaurants, entering gyms, and cross-border travel. This policy sparked widespread protests, including the "freedom convoy" in early 2022 [23].

Canada initially saw low vaccine uptake, due to supply issues, but once vaccines were acquired in plentiful numbers, Canada's vaccination rates climbed rapidly [7,24]. The vaccine uptake, however, plateaued at a high level, due to growing vaccine hesitancy and refusal, particularly for booster doses in 2021 and 2022 [25,26]. A major contributing factor was declining trust in governments and in public health agencies, which negatively influenced the public acceptability of COVID-19 vaccines [27,28].

The rapid development of COVID-19 vaccines, completed in just 11 months, raised skepticism, as vaccine development typically takes years. In the face of rapidly developing and changing scientific data, trust in government and public health agencies becomes crucial for vaccine uptake [29]. One study showed that public trust in health care providers, public health agencies, and pharmaceutical companies significantly shaped their perception of vaccine effectiveness and safety, and, ultimately, their willingness to get vaccinated [27]. A systematic review and meta-analysis conducted in Canada revealed that in 2021, a total of 1 in 5 people did not want to get vaccinated and that vaccine hesitancy and unwillingness were especially higher among women, rural residents, non-White individuals, and those with lower educational levels [25].

Another key factor that contributed to the erosion of trust was the rapid policy reversals and inconsistent messaging [30]. For instance, the Public Health Agency of Canada initially advised against mask-wearing for asymptomatic individuals, only to later mandate masks in public spaces. A survey in Ontario revealed that more than half of the participants had encountered COVID-19 misinformation and had challenges identifying or appraising COVID-19 information [31]. While provincial leaders, especially in British Columbia and Quebec, were praised for their effective communication, the federal government, as were a few other provincial governments, struggled to provide unified, transparent messaging. The reliance on vague objectives such as "flattening the curve" was widely criticized for lacking clarity and concrete targets, making it harder for the public to rally behind a shared goal. In contrast, countries such as New Zealand and Australia, with clearer and more ambitious targets such as "virus elimination," were more successful in maintaining public support [22].

The 2021 Edelman Trust Barometer revealed that public trust in the Canadian government dropped by 11% between May 2020 and January 2021, alongside a decline in trust in traditional media, social media, and search engines [32]. Additionally, the pandemic and the related restrictions imposed impacted vulnerable communities disproportionately, exacerbating the existing inequalities, which added another layer of complexity to public trust [21].

As of 2025, Canada has largely entered a post-pandemic phase, though COVID-19 continues to circulate. The pandemic not only exposed vulnerabilities in Canada's response but also raised concerns about the government's ability to manage future emergencies effectively. The pandemic's long-term effects, including the erosion of public trust, remain a significant and immediate challenge. Understanding this shift in trust and rebuilding trustworthiness and trust are crucial for Canada's preparedness for future crises.

Trust Dynamics and Equity in Public Health Project

Trust can be conceptualized as a combination of behavioral practices and norms, perceptions and preferences, as well as the functional and institutional properties of interactions between individuals and organizations [33-35]. This conceptual framing informs the types of interventions that may be designed to rebuild or strengthen trust and trustworthiness. The Trust Dynamics and Equity in Public Health Project, a program of interlinked studies, investigates the evolution of public trust in scientists, public health, medical care, and governmental institutions during the COVID-19 pandemic. It sought to understand the extent to which Canadians trusted their own social and personal networks (traditional media, social media, and friends, family, and faith leaders) as sources of information during the pandemic. This research aims to understand how trust was maintained or eroded, particularly among marginalized and minority communities, and how this trust influenced adherence to public health measures and health care–seeking behaviors. Key objectives include (1) investigating the evolution of public trust in scientists, public health authorities, medical care providers, and governments during the pandemic; (2) identifying factors influencing trust, specifically the erosion of trust or maintenance of trust among Canadians at large and in equity-seeking communities; (3) identifying factors that are associated with a change in trust (trust increased, decreased, or stayed the same) in May 2024 compared to before the pandemic (before March 2020); and (4) understanding how Canadians describe trust and trust change during the pandemic, how it impacted vaccine receipt, and how to rebuild trust moving forward.

This study is guided by a concept map (Figure 1) developed through a literature review. This concept map serves as the framework for understanding trust dynamics and their impact on health behaviors. The concept map highlights the multilayered nature of trust in government, scientists, the health care system, public health, social and community networks, and interpersonal trust. It illustrates how different sources of trust interact and influence health behaviors and crisis responses. Trust in these systems is essential for public compliance, effective communication, and improved health care outcomes. The survey questionnaire was designed and structured based on the concepts in the map.

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Figure 1. Concept framework of Trust Dynamics and Equity in Public Health Project. PHAC: Public Health Agency of Canada.

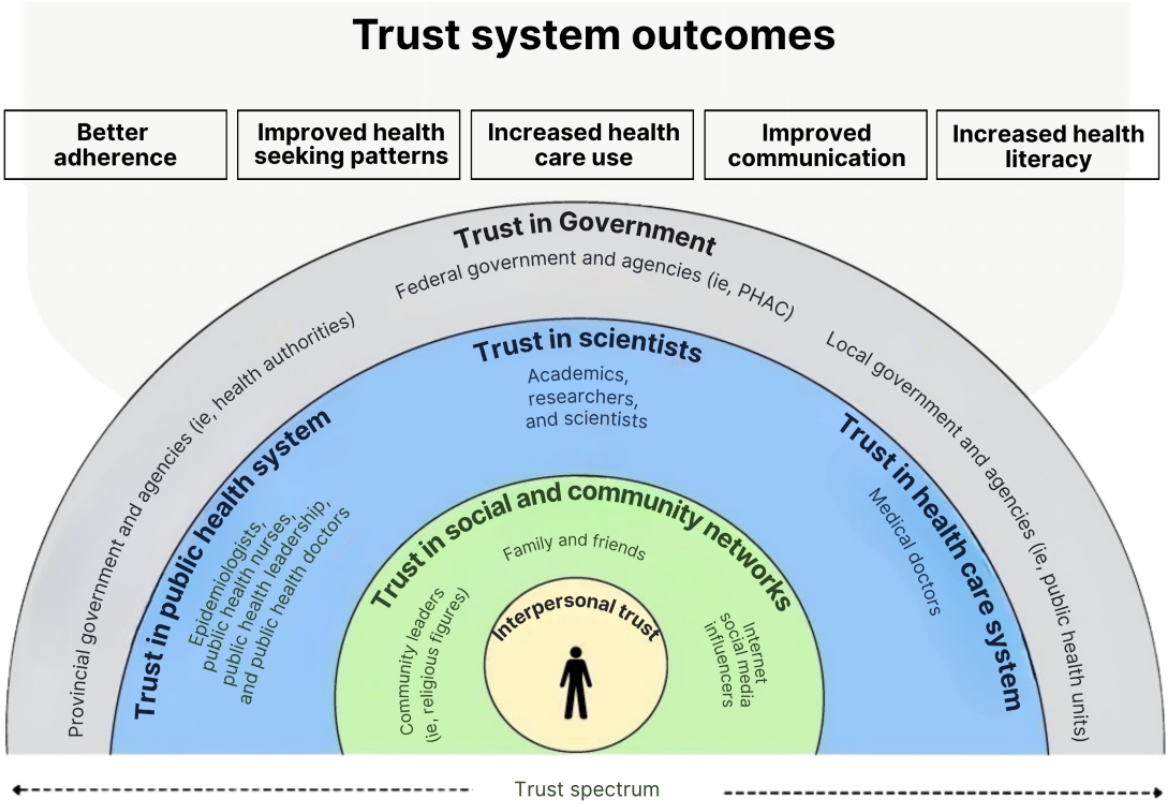

Methods

Study Setting and Design

This study enrolled participants from across Canada, all 10 provinces, and 2 of the 3 territories (a sample from Nunavut was not drawn), capturing a diverse and representative sample of the adult population. The sequential mixed methods approach, quantitative followed by qualitative (sequential quantitative → qualitative), was chosen for this research to provide both breadth and depth in understanding trust dynamics in public health. In the first phase, the national survey of Canadian adults allowed for the collection of large amounts of data, identifying trends and patterns in trust perceptions across diverse demographic groups and places. However, trust is a complex and context-dependent phenomenon that cannot be fully captured through survey responses alone. By incorporating qualitative interviews in the second phase, this study gained deeper insights into the motivations, experiences, and concerns underlying the observed quantitative trends. This methodological combination ensured a comprehensive analysis, strengthening the validity and applicability of the findings for public health policies and interventions.

The recruitment phases have been completed, with a population representative sample of 5607 Canadian adult residents surveyed to assess trust perceptions and attitudes and behaviors related to COVID-19 vaccines. The sample size was informed by precision-based considerations: assuming a conservative prevalence of 50% (where variance is maximal), approximately 2400 respondents would be required to achieve ±2% precision at the 95% confidence level. Our achieved sample of 5607 more than doubles this requirement, yielding national prevalence estimates with a margin of error below ±1.5%. This larger sample also ensured sufficient statistical power (>80%) to detect meaningful subgroup differences—on the order of 5-7 percentage points—across sociodemographic groups (eg, Indigenous vs non-Indigenous respondents, age cohorts, and regions), and to examine changes in trust before and during the pandemic with high precision.

Additionally, 41 in-depth qualitative interviews have been conducted to explore underlying motivations and concerns.

Population Survey

The quantitative phase of this study involved an online survey designed and developed by the University of Saskatchewan team in collaboration with Leger, the largest Canadian-owned research and analytics company. The questionnaire comprised approximately 70 questions, including screening and demographic questions (Multimedia Appendix 1). Three attention check questions were inserted into the survey, approximately every 4-5 screens. Specifically, these directed questions asked participants to give specific answers (eg, “This is a control question. Mark ‘agree’ and ‘move on’”). The survey was translated and programmed in both English and French by Leger, ensuring accessibility for respondents in their preferred language. Respondents were primarily recruited through the LEO (Leger Opinion) panel, Canada’s largest consumer panel with nearly 400,000 active members. For respondents in the Northwest Territories and Yukon, recruitment was conducted through the Hard-to-Reach solution by Leger DGTL (digital), which leverages digital marketing strategies to engage niche populations. A stratified random sampling method was used to ensure representative coverage. The survey targeted Canadian residents aged 18 years and older who had resided in Canada

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for most or all of the COVID-19 pandemic. Additional quotas were implemented to ensure adequate representation of Indigenous Canadians, young adults (18-34 years), and residents of the Northwest Territories and Yukon.

The online survey was conducted between May 1 and May 29, 2024. Respondents received personalized invitation emails containing a unique URL, allowing them to complete the survey at their convenience using a computer, smartphone, or tablet. The average survey completion time was 13 minutes and 23 seconds. Before full deployment, a pretest was conducted on May 1, 2024, with 44 respondents to assess completion time, question clarity, and logical structure. No major revisions were required following the pretest, and the data collected were included in the final dataset. To prevent duplicate entries, LEO assigned unique IDs to each respondent, ensuring that once a survey was completed or terminated, re-entry was not possible. The final sample consisted of 5607 fully completed responses from an initial pool of 7858 invitees. Of these, 710 respondents identified as Indigenous Canadians (“First Nations”: n=403, “Métis”: n=270, “Inuit”: n=25, “Prefer to self-identify”: n=11, and “Don’t know/Refused”: n=1). A 2-step approach was implemented to achieve a representative sample: (1) Recruitment and sampling were monitored and adjusted in real time based on the latest Canadian Census data (2021) to ensure demographic balance, and (2) at the conclusion of data collection, weighting adjustments were applied to align the final dataset with population benchmarks for age, sex, and region.

The questionnaire was designed to assess 6 primary sources of trust, with participants reflecting on their trust levels before and during the COVID-19 pandemic, alongside comprehensive demographic data, as described in Figure 2. Respondents provided insights into their trust in provincial or territorial government, federal government, public health authorities, medical care providers, health scientists, and social and personal networks. These trust dimensions were explored in relation to transparency, communication strategies, decision-making processes, and sources of information. Additionally, demographic questions covered aspects such as age, sex, gender, ethnicity, born in or outside of Canada, education, occupation, parental status, household income, and adherence to spiritual beliefs and practices to provide a detailed understanding of trust variations across different population groups.

Figure 2. Questionnaire content: public trust before and during the COVID-19 pandemic.

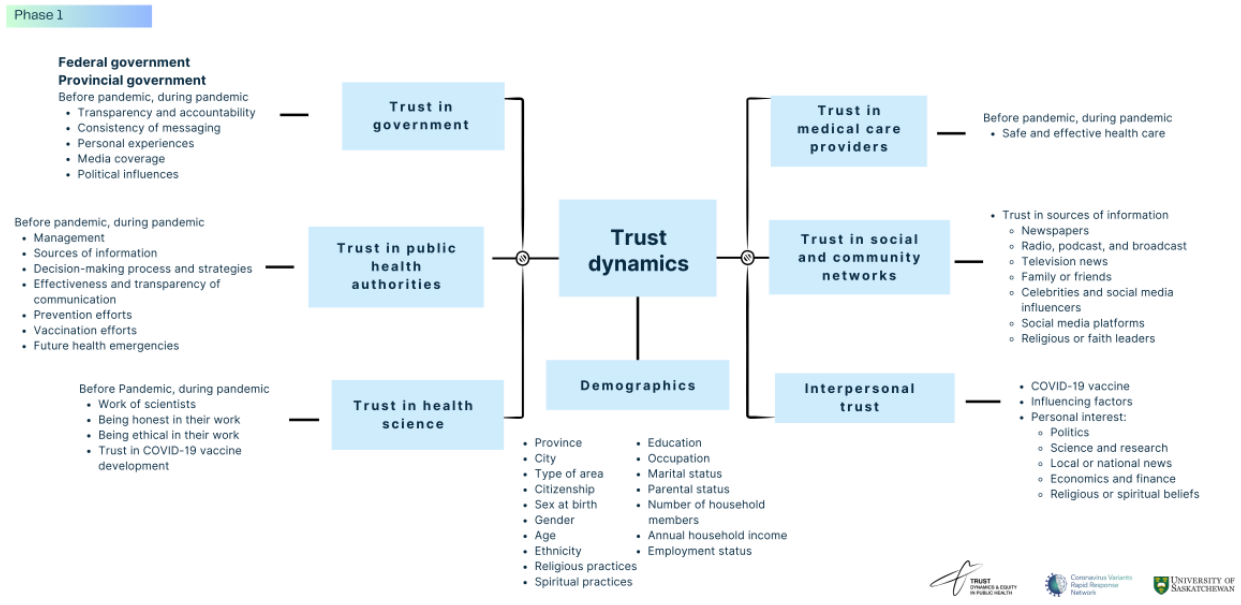

Statistical Methods

The survey data were analyzed using descriptive and inferential statistical techniques in R (The R Foundation for Statistical Computing) and Stata (StataCorp LLC). Descriptive statistics summarized demographic characteristics such as age, gender, ethnicity, education, occupation, household income, adherence to spiritual beliefs and practices, and other socioeconomic factors; geographic factors such as province or territory of residency, rural or urban residence; vaccine related attitudes and behaviors such as trust in the vaccine, willingness to receive the vaccine; and sources of trust such as provincial or territorial government, public health authority, health scientists, and medical care providers. Bivariate analyses using cross-tabulations with chi-square tests examined relationships between trust and trust changes of 6 primary sources of trust and demographic and socioeconomic, geographic, and vaccine-related variables. Multinomial logistic regression then identified factors associated with trust (ie, trust, distrust, preferred not to answer, or neutral), trust change categories (trust increased, decreased, no change, or preferred not to answer), adjusting for demographic and economic factors, geographic and vaccine-related factors. Analysis was conducted using a survey-weighted sample to represent the population benchmarks for age, sex, and region, and statistical significance was set at a 5% level.

In-Depth Interviews

Participants were recruited after completing a quantitative survey. At the end of the survey, participants were allowed to indicate interest in a follow-up qualitative interview. The rationale for this recruitment strategy was both practical (access

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to participants) and by design, to gain further insight into answers given in the survey, though participants' initial survey answers and consequent interview responses were not linkable. The quantitative survey that we first conducted provided a broad set of information for understanding how Canadians experienced trust in public health actors, governments, and their communities. However, we recognized that this quantitative analysis, while providing an overview, required a deeper reading to gain insights into individual experiences of trust during the pandemic. Furthermore, some participants chose the "preferred not to answer" response alternative for certain questions on the quantitative survey, particularly questions dealing with spiritual beliefs, gender, and ethnicity (n=285, n=74, and n=99, respectively). This suggested that a deeper investigation was needed to understand the complex dynamics of public trust during the pandemic. We developed a qualitative interview, both expanding on and responding to information gleaned from the quantitative results. This interview guide was internally reviewed for dependability, and the process and changes made were documented. The main questions we framed the qualitative protocol on were (1) What did participants remember most strongly about the COVID-19 pandemic? (2) How did participants define what trust means to them? (3) How did participants feel about public health interventions from scientists and policy makers during the pandemic? (4) Did participants' trust in government information, health authorities, community leaders, and family change over the course of the pandemic? If so, how? (5) What actions would participants suggest policy makers and public health actors take in future pandemics to increase public trust?

Before beginning the interview process, all members of the interview team spent significant time discussing the volatility of our subject matter. Aware that discussing the pandemic, trust, and vaccination could compound trauma for participants, we were mindful of interviewer and participant safety throughout the interview process. All team members completed the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans certification. The team also undertook a day-long training session on trauma-informed interview practices and was diligent in recognizing their own positionality and bias, as well as preparing themselves to respond to participants' potential trauma [36]. Some concerns were raised regarding interviewee safety, particularly if interviewees chose to keep their cameras on during Zoom (Zoom Communications, Inc) interviews. However, after consulting with the whole interview team, a consensus was reached that, in a project dealing with trust, it was deemed that, as researchers, it was our responsibility to set a base of trust by sharing our names and faces with interviewees.

Before the interview, participants were given a list of questions to consider that were thematically related to, but not direct copies of, the interview questions (Multimedia Appendix 2). Interviews lasted between 20-60 minutes and were conducted either over the phone or via Zoom, according to the participant's preference.

We used a descriptive phenomenological approach in our qualitative interviews, using the frame of trust to understand participants' lived experiences of the pandemic, and how these lived experiences in turn allowed them to make meaning of what "trust" meant during the pandemic, and as it has receded. This approach required the deep analysis of participants' lived experiences, allowing us to investigate their "lifeworld" [37]. As Dahlberg [37] describes, the "lifeworld" is the "essence of that which is already there"—that is, the everyday experiences, realities, and events that underpin how we make sense of our lives. In our interviews, we used the phenomenon of public trust during the COVID-19 pandemic and sought to understand the meaning participants derived from this phenomenon, based on their descriptions of their "lifeworld" [38]. This approach is particularly appropriate to understanding trust, being defined as an experience that is unique to the lived experiences and consequent decisions of the trustor, and how these in turn affect the trustor's relationship with the trustee [35,39]. The phenomenological approach also required the research team to focus fully on participants' perceptions, descriptions, and reflections, and avoid interpreting these results through their own meaning-making frames. To facilitate credibility at all stages of this process, interviews were in-depth, and participants were invited to lead the conversation on topics they felt were important. This contextual richness also allows for transferability—the reader of this study will be able to fully interpret the relevance of the data in further understanding public trust in Canada, through the detailed descriptions provided by the participants, and included in knowledge dissemination activities. Further, team members met frequently to discuss how they made meaning of interview responses, to ensure they were mindful of preconceived biases.

Analysis began during the frequent meetings held by the research team, where emerging themes and patterns were discussed. After the interviews were complete, transcripts were uploaded to NVivo 14 (Lumivero). Adhering to the phenomenological approach, researchers once again "bracketed" their own preconceptions during coding, focusing on themes that emerged about participants' lived experiences as they were described in the interviews [40]. An initial codebook was created based on consensus, and new codes were only added after a meeting where consensus was reached. To ensure confirmability, after the initial coding was completed by 2 team members, a third team member also coded a subset of the interviews a second time, validating the initial codes.

Mixed Methods Approach

To integrate and interpret the 2 datasets, a sequential-explanatory mixed methods approach was applied. This approach required that the quantitative phase be completed first, followed by the qualitative phase, allowing the qualitative phase to expand on findings from the quantitative survey [40,41]. The integration of the quantitative and qualitative data was guided by the thread approach, which requires that researchers review both components of the study at the analysis phase to identify key themes and questions requiring further investigation [42]. These key themes or "threads" are then "followed" across the study [43]. As the threads are followed, more depth and nuance are added to the initial theme, meaning that the research team was able to glean a deeper understanding of these themes by interpreting them across both datasets, instead of in isolation.

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As described in Figure 3, the threads to be investigated were developed collaboratively, with input from both the quantitative and qualitative teams. They were then followed in the data and analyzed collectively to ensure consensus and confirmability.

Figure 3. Timeline showing the points of integration between the quantitative and qualitative data.

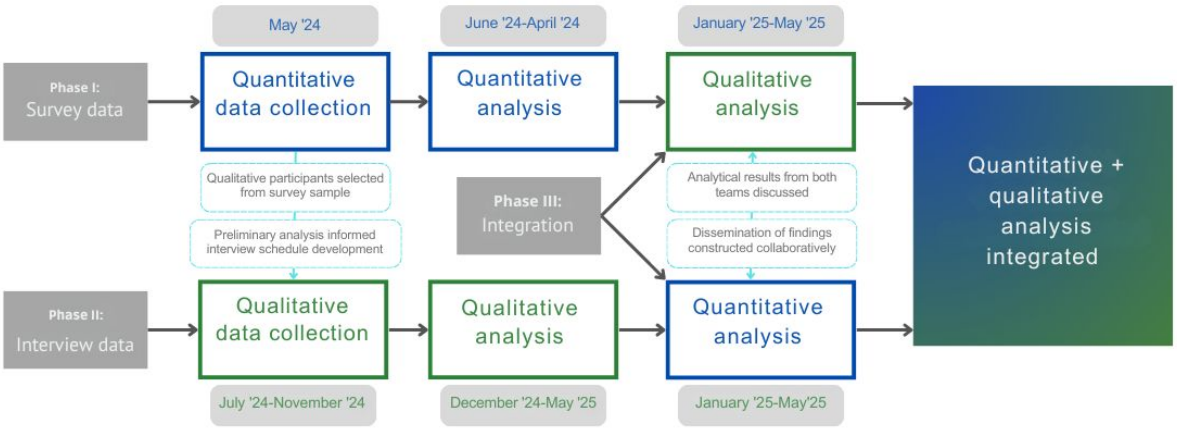

Ethical Considerations

This study, approved by the University of Saskatchewan Research Ethics Board (BEH-4565), follows the Tri-Council Policy Statement on Ethical Conduct for Research Involving Humans. Any protocol changes require Research Ethics Board approval through amendments. Participants gave informed consent for both the quantitative and qualitative phases of this study—for the quantitative survey, they were required to express their consent (either “yes” or “no”) via a query that underlined the voluntary nature of this study, and for the qualitative phase, participants gave informed, verbal consent to be interviewed after being read a consent form that outlined the procedures, policies, and nature of the research project. Participation was entirely voluntary. Raw quantitative data were deidentified before analysis and stored on a secure server accessible only to the research team. All interview transcripts were deidentified before analysis and were stored on a secure server accessible only to the research team. Participants in the quantitative survey were a part of the Leger panel and received points for completing the survey, which could then be collected and redeemed for gift cards. The 1000 points are equivalent to approximately 1 CAD, and participants received 2000 points for their participation in completing the survey. Participants in the qualitative phase received a CAD $25 (US $18) honorarium for their participation in the interview.

Results

Study Progress

Both quantitative and qualitative data collection were completed in mid-2024. Quantitative analyses of survey data and qualitative interviews were transcribed, coded, and analyzed in early 2025. Mixed methods integration was completed in mid-2025. Following data analysis, the project advanced to dissemination and knowledge translation. Outputs include 3 quantitative papers (ready for publication), 1 mixed methods paper (submitted and under review), 1 qualitative paper (published) and a protocol paper (submitted and under review). A scoping review paper and a comprehensive project report are in preparation and scheduled for completion by the end of 2025. In addition, a public-facing website has been developed and launched. Study findings have been presented at various national conferences. Further knowledge-translation outputs are being finalized in 2025 to extend the reach of findings.

Survey Participants

As described in Figure 4, the survey included participants from across Canada, with 32.4% (1816/5607) from Ontario and 25.6% (1433/5607) from Quebec, followed by 13.5% (755/5607) from British Columbia and 11% (618/5607) from Alberta. The Prairie provinces accounted for 2.9% (160/5607) from Saskatchewan and 4.3% (239/5607) from Manitoba, while the Atlantic provinces had 2.2% (123/5607) from New Brunswick, 2.8% (155/5607) from Nova Scotia, 0.3% (19/5607) from Prince Edward Island, and 1.5% (86/5607) from Newfoundland and Labrador. Additionally, 1.8% (100/5607) of participants were from the Northwest Territories and 1.8% (103/5607) from Yukon. With respect to sex assigned at birth, 45.5% (2552/5607) of participants identified as male and 54.2% (3038/5607) as female. Concerning self-reported gender identity, 45.6% (2557/5607) identified as men, 53.6% (3003/5607) identified as women, 0.52% (29/5607) identified as nonbinary, and 0.32% (18/5607) opted not to disclose their gender. Age distribution varied, with 8.1% (454/5607) aged 18-24 years, 19.3% (1080/5607) aged 25-34 years, 16.8% (942/5607) aged 35-44 years, 17% (955/5607) aged 45-54 years, 18.7% (1049/5607) aged 55-64 years, and 20.1% (1127/5607) aged 65 years or older. Additionally, 18.6% (1040/5607) identified as belonging to an ethnic minority, and 12.7% (710/5607) identified as Indigenous, including 7.2% (403/5607) First Nations, 4.8% (270/5607) Métis, and 0.4% (25/5607) Inuit. Educational attainment varied, with 0.7% (39/5607) having completed primary school or less, 19.5% (1094/5607) finishing high school, 9.2% (515/5607) attending trade school, and 69.5% (3905/5607) earning a college or university degree.

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Figure 4. Geographic distribution of study participants by province and territory, Canada; Trust Dynamics and Equity in Public Health Project.

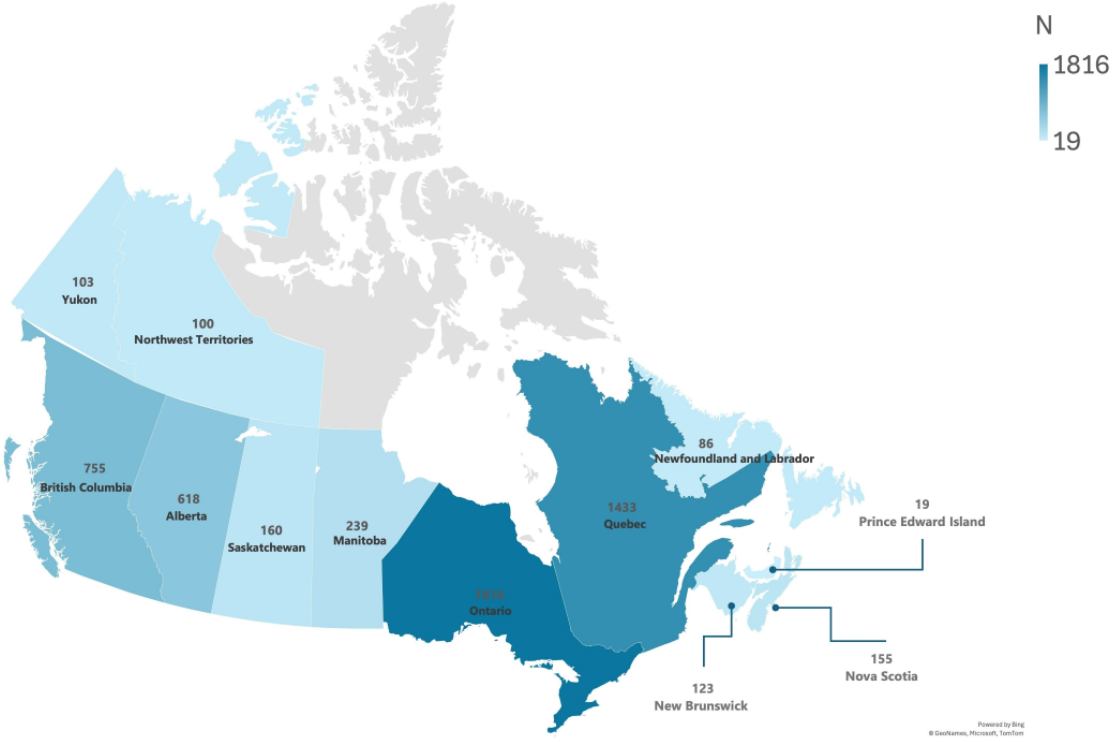

The percent trust in provincial or territorial government, federal government, public health, medical care providers, and health scientists was calculated for the whole sample (n=5607 Canadian adults). These questions specifically were asked about each group: How much did you trust the government (federal and provincial) to take care of the population during the COVID-19 pandemic? How much did you trust Public Health Authorities in their management of the COVID-19 pandemic? Did you trust the work of scientists? Responses were categorized into trust, distrust, neutral, and prefer not to answer.

Regarding COVID-19 vaccination, 55.2% (3094/5607) had received at least 1 dose and planned to stay up to date with booster recommendations, while 36.6% (2052/5607) were vaccinated but did not intend to receive additional doses. A small percentage, 0.7% (39/5607), had not yet been vaccinated but were open to it, whereas 6.4% (359/5607) had not received a vaccine and did not plan to take one.

Interview Participants

We conducted interviews with a subset of individuals (n=41) who indicated interest in being recontacted after completing the initial quantitative survey; however, their original survey answers were not connected to their responses in the qualitative portion, preserving respondent anonymity. Initially, 101 individuals were identified by our survey partner, Leger, who had indicated they wanted to be followed up with and included either an email or phone number where they could be contacted. All 101 participants were sent a follow-up email with a link to a survey asking them for basic demographic data, as well as their availability for an interview. We received 61 responses to this survey, and all of whom were contacted to schedule an interview. Of those contacted, 41 responded and completed their interview. These participants ranged in age between 18-24 years (n=1), 25-32 years (n=7), 35-44 years (n=6), 45-54 years (n=7), 55-64 years (n=12), and 65+ years (n=8), and came from 10 different provinces and territories (Ontario, Alberta, British Columbia, Newfoundland and Labrador, Manitoba, Saskatchewan, Quebec, Nova Scotia, New Brunswick, Prince Edward Island, and Yukon).

Discussion

Five years since the emergence of the SARS-CoV-2 and the COVID-19 pandemic, the world has changed irrevocably. We have experienced mass disruptions to our way of life, lost countless lives, and gained respect for how microorganisms can disrupt our lives, as well as how human ingenuity can counter these threats (by way of novel inventions such as specific vaccines and tests). Through this process, though, we have also seen an erosion of public trust—both worldwide and in Canada [22,29,44]. In Canada, public trust in governments, in particular, was called into question [29]. Canadians indicated that they did not feel the government was being consistent or transparent in its communication—frequent changes in public health messaging only served to bolster this mistrust [29,44]. Further, research suggests that lower institutional trust mirrored vaccine trust, with individuals who did not trust government or public health messaging less likely to accept a vaccine [45]. For instance, individuals who did not trust government warnings about the risk posed by COVID-19 to their communities were shown to be significantly less likely to be vaccinated [46]. This, combined with the proliferation of misinformation that the Canadian government was not fully equipped to address, resulted in many individuals feeling reluctant to take a vaccine [47]. Further, the loss of trust that occurred in both governments and scientists during the pandemic represents a major, ongoing challenge for Canadian public health.

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More worldwide, a recent 23-country survey highlights that challenges of trust and vaccine hesitancy extend well beyond Canada. Conducted in October 2023 with 23,000 participants (1000 per country), collectively representing nearly 60% of the world's population, the study defined vaccine acceptance as having received at least one COVID-19 vaccine dose and hesitancy as not having received any [48]. The results showed a marked decline in intent to receive a COVID-19 booster—from 87.9% in 2022 to 71.6% in 2023—indicating growing pandemic and vaccine fatigue. At the same time, 60.8% of respondents expressed greater willingness to receive vaccines for diseases other than COVID-19, while 23.1% reported being less willing. Trust in vaccine information sources was modest overall, with doctors or nurses (6.9/10) rated highest, while social media and family or friends ranked among the least trusted (typically <5/10). Canada reflected this broader pattern, with health care professionals emerging as the most trusted information source, and social networks rated lower. These international findings reinforce our Canadian results: trust in scientific and medical expertise remains relatively resilient, while institutional and informal sources face greater skepticism. Together, they highlight the global challenge of sustaining confidence in reliable health information while countering mistrust associated with governments and social media.

The project described in this protocol comprehensively addresses this issue. This study's methodological framework demonstrates the importance of capturing both statistical data and in-depth experiential insights to fully understand complex the social phenomena, public trust.

This study will integrate quantitative and qualitative data to facilitate a more rigorous and comprehensive analysis of trust dynamics. A systematic analysis of these data sources will enable a deeper investigation into the underlying determinants of public trust and their implications for health behaviors. Moreover, the dissemination of findings through peer-reviewed academic publications, policy briefs, and targeted community engagement initiatives will be prioritized to ensure that the insights generated inform evidence-based decision-making and contribute to the refinement of public health strategies aimed at strengthening pandemic preparedness and response.

We will compile project findings into various academic outputs, including journal papers, research posters, technical reports, conference presentations, and infographics, which will also be stored in the Saskatchewan COVID-19 Archive.

While the mixed methods design was a distinct strength, it also had limitations. Confidentiality considerations did not allow for linking of survey responses and qualitative interviews. This limitation restricted the ability to analyze individual experiences with corresponding survey outcomes. However, qualitative themes were analyzed to complement and contextualize the overall survey findings, allowing for a broader yet meaningful integration and interpretation of public trust, trust dynamics, and trustworthiness. This approach balanced data privacy considerations while still capturing the depth and complexity of public trust.

Implementation of the quantitative strand, especially self-reported data, may be subject to recall and social desirability biases. Social desirability bias occurs when respondents answer in ways they believe will be viewed favorably, rather than truthfully. This bias can lead to overreporting trust and downplaying mistrust. Although the models adjusted for many theoretically relevant variables, there is still a tendency for the presence of residual confounding because other potential confounders, such as political ideology, media habits, and conspiracy beliefs, were not directly measured.

In conclusion, the observed decline in public trust before and during the COVID-19 pandemic presents a significant challenge for policy makers, public health authorities, and scientific institutions. Rebuilding and maintaining trust necessitates a commitment to transparent communication, accountability, and the mitigation of structural inequities that perpetuate distrust. This research provides critical insights that can inform the development of resilient, equity-driven public health frameworks, ensuring that future public health crises are met with greater public confidence and compliance.

Acknowledgments

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Data Availability

Data collected in this work are archived for preservation and freely accessible online [49]. The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization: NM (lead), CN (equal)

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Funding acquisition: NM (lead), CN (equal), TB (supporting), NA (supporting)
Methodology: NM (lead), KM (equal)
Project administration: NM (lead), CN (equal), KM (supporting), SS (supporting)
Writing – original draft: NM (lead), FB (equal), KM (equal), SR (equal), SS (equal)
Writing – review & editing: NM (lead), CN (equal), KM (equal), FB (equal), SJRR (equal), ZZ (equal), TB (equal), KB (equal), SS (equal), DAA (equal), SR (equal), NA (equal), KH (equal), CB (equal), MJ (equal), TC (equal), KL (equal), ÈD (equal)

Conflicts of Interest

None declared.

Multimedia Appendix 1
Survey questionnaire.
[PDF File (Adobe PDF File), 470 KB - resprot_v14i1e75199_app1.pdf]

Multimedia Appendix 2
Interview topic guide.
[PDF File (Adobe PDF File), 751 KB - resprot_v14i1e75199_app2.pdf]

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Abbreviations

DGTL: digital
G10: Group of Ten
LEO: Leger Opinion

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Protocol

Patients' Preferences Regarding Traditional Chinese Medicine for the Treatment of Chronic Obstructive Pulmonary Disease: Protocol for a Mixed Methods Study

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Abstract

Background: Chronic obstructive pulmonary disease (COPD) is now one of the top 3 causes of death worldwide. Traditional Chinese medicine (eg, herbal prescriptions and acupuncture), which has a long history of managing respiratory diseases, has shown positive effects in COPD management by alleviating dyspnea, improving lung function, and reducing the risk of acute exacerbations. Patients' values and preferences are undeniably important in medical decision-making and may affect treatment outcomes and patient adherence.

Objective: This study aims to investigate the preferences for traditional Chinese medicine of patients with COPD, the clinical outcomes they are concerned about, and the trade-offs involved in evaluating the factors that influence treatment selection, such as clinical effectiveness, cost, and adverse effects.

Methods: We will first update previous evidence through a systematic review of randomized controlled trials, examining the efficacy, safety, cost-effectiveness, and patient satisfaction of traditional Chinese medicines for COPD. Subsequently, an exploratory sequential mixed methods study will be conducted comprising qualitative and quantitative components. In this design, qualitative findings are collected first to inform and guide the subsequent quantitative data collection. Semistructured interviews will be conducted to explore in depth the preferences of patients with COPD for traditional Chinese medicine. Insights from these interviews will then be used to design questionnaires that quantitatively investigate the relative importance of different factors influencing patients' treatment decisions. Data integration will take place by connecting and interpreting the results from both the qualitative and quantitative steps, providing a comprehensive understanding of patient preferences.

Results: This study was approved by the ethics committee of Guangdong Provincial Hospital of Traditional Chinese Medicine on November 6, 2023 (ZM2023-405). A total of 18,188 articles published after 2016 were initially identified in English- and Chinese-language databases. The outline of the semistructured interview guide for this study has been developed. Further clinical evidence updates, qualitative interviews, and discrete choice experiments are still ongoing and will be completed by April 2026.

Conclusions: This mixed methods study might provide important insights into the preferences of patients with COPD for traditional Chinese medicine, assessing trade-offs among efficacy, safety, cost, and other key factors that influence treatment decisions. This study is expected to deepen the understanding of patient-centered decision-making in the treatment of COPD. The findings are anticipated to guide clinical practice, inform policy development, and optimize the integration of traditional Chinese medicine with respiratory care.

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KEYWORDS

traditional Chinese medicine; preference; mixed methods; discrete choice experiment; chronic obstructive pulmonary disease

Introduction

"Patients' values and preferences," as a broad term, is defined as including patient perspectives, beliefs, expectations, and goals for their health and life, including the process that patients go through in weighing the potential benefits, harms, costs, and burdens associated with different treatment or disease management options [1]. Patients' preferences are based on subjective perceptions and values and are influenced by previous experiences, which may affect treatment outcomes and patient adherence; thus, their importance in medical decision-making is unquestionable [2,3].

Many years ago, patients' preferences were suggested to be included in clinical practice guidelines [4]. Patient and public representatives are recommended to engage in the guideline development process. On the basis of the requirements of evidence-based medicine (EBM) and narrative medicine, adequate consideration of patients' needs or understanding of specific treatments is a strong guarantee of scientific and humanized clinical practice guideline development [5]. In addition, understanding patients' preferences is an important expression of respect for the basic principles of medical ethics [6]. However, patient representatives' participation [7,8] is insufficient to reflect individual patients' preferences. Individuals often vary widely in their preferences, even when recommendations are based on rigorous evidence, due to differences in values, experiences, and cultural backgrounds, among other things. Shared decision-making (SDM) is when clinicians and patients participate collaboratively in health decisions after fully discussing treatment options, benefits, and harms, considering the patients' values, preferences, and circumstances [9]. Applying SDM in clinical practice may result an individualized therapeutic regimen for each patient. Achieving active decision-making requires work by the health care provider and patient. The health care provider teams need to be proactive, and the patient needs to be prepared. Patients increasingly want to be active in clinical decision-making, especially younger patients and those with higher educational levels [10,11]. They want to be informed by their physicians and prefer to learn about their treatment options early and discuss the benefits and drawbacks. Knowing this information can help patients weigh the treatment effects, side effects, and costs so that treatment decisions can be matched to their preferences. Therefore, it remains important for health care providers to recognize patients' preferences.

Chronic obstructive pulmonary disease (COPD) is a heterogeneous lung condition characterized by chronic respiratory symptoms due to airway or alveoli abnormalities that cause persistent, often progressive, airflow obstruction. COPD is now one of the top 3 causes of death worldwide, and 90% of these deaths occur in low- and middle-income countries [12,13]. It has resulted in a significant economic and social burden that is projected to increase in the coming decades, with substantial morbidity and mortality worldwide [14]. Medication adherence is a major challenge in chronic disease management. A surprising fact is that medication adherence is lower in patients with COPD than in those with other diseases [15], with an average medication adherence of only 60% reported in several studies [16]. Studies have shown that patients with COPD with higher medication adherence have fewer hospitalizations and spend less on treatment compared to those with lower medication adherence [17]. Most of the drugs available for COPD are delivered via inhalers [18,19]. The use of an inhaler requires several steps and differs by device. Patients should receive additional training and education on the use of inhalers, which significantly increases the burden of their disease management [20,21]. Studies indicate that "convenience-related" attributes, such as ease of use, appropriate shape, and low chance of misuse, are among the factors that influence patient preference for inhalers. Furthermore, according to recent work by the World Health Organization and other organizations, inhaled medications are scarcely available and mostly unaffordable for patients with COPD in low- and middle-income countries [22].

Traditional Chinese medicine (TCM) has been used to manage respiratory diseases for thousands of years and has been comprehensively and systematically evaluated for its clinical effectiveness in treating COPD. Evidence shows that TCM therapies, including acupuncture and tai chi, can help improve clinical outcomes such as lung function, quality of life, breathlessness, and exercise capacity in patients with COPD and are safe and reliable [23-25]. Chinese herbal medicines have shown potential benefits for stable or acute exacerbations of COPD [26-28].

The results of a pilot study conducted by our team suggest that the preference of patients with COPD for TCM may be influenced by factors such as clinical efficacy, side effects, and cost [29]. The findings need to be validated in larger samples. In addition, patient perceptions with regard to specific interventions have not been investigated. In this study, we focus on exploring the preferences of patients with COPD during clinical decision-making. *Preference* is defined as patients' perceptions of TCM for the treatment of COPD, their appraisal of factors for treatment scenarios, and the balance of harms and benefits within or between interventions.

The discrete choice experiment (DCE) is a stated-preference method originating from Lancaster's economic theory of value and McFadden's random utility theory, and it has since been widely applied in health care research [30,31]. DCEs can integrate measures of multiple attributes to obtain results closer to real choices, which can adequately predict actual consumer behavior, being generally used in health care preference surveys today [32,33]. There are currently no studies that have used DCE to investigate the preferences of patients with COPD for TCM. Therefore, we will use mixed methods, including both qualitative and quantitative (DCE) methods to obtain more

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comprehensive information. We hypothesize that clinical practice will be improved by incorporating patients' preferences. Our objective is to investigate patients' preferences for TCM for the treatment of COPD; the clinical outcomes they are concerned about; and the trade-offs for the factors of treatment scenario options, such as clinical effectiveness, cost, and side effects. The main research questions are as follows:

1. What is patients' perception (such as effect, side effects, and treatment duration) of TCM for COPD?
2. Which clinical outcomes are of most concern for patients, and which factors are important for treatment scenario options?
3. Which factors will influence patients' options in terms of the available evidence for specific therapies (eg, efficacy, safety, or economic factors)?

Methods

Study Design

An exploratory, sequential mixed methods study will be conducted involving a qualitative and quantitative study (DCE) [34]. In an exploratory sequential design, data are first collected and analyzed through qualitative investigation, followed by further exploration of themes derived from the qualitative data via a quantitative investigation. The results from both sets of data are then integrated and interpreted [35]. The attributes of the DCE will be identified from a literature review and the qualitative survey based on previous pilot study results [29]. The results of the qualitative and quantitative study phases will be compared to determine the degree of consistency. This study, which is expected to be completed within 1 year, will be divided into three phases, which are illustrated in the procedural diagram (Figure 1): (1) an update of the existing evidence [23] on the efficacy, safety, economic benefits, and patient satisfaction related to TCM in treating COPD (phase 1; 3 months); (2) a qualitative investigation involving semistructured interviews to explore the perception of COPD, expectations of interventions, and attitudes toward TCM, among other aspects (phase 2; 3 months); and (3) a cross-sectional DCE, which aims to understand participants' preferences for the TCM interventions and assess the relative importance of different attributes of treatment scenarios through a questionnaire (phase 3; 4 months).

Figure 1. Procedural diagram of the exploratory sequential mixed methods study on patients' preferences for traditional Chinese medicine in the treatment of chronic obstructive pulmonary disease.

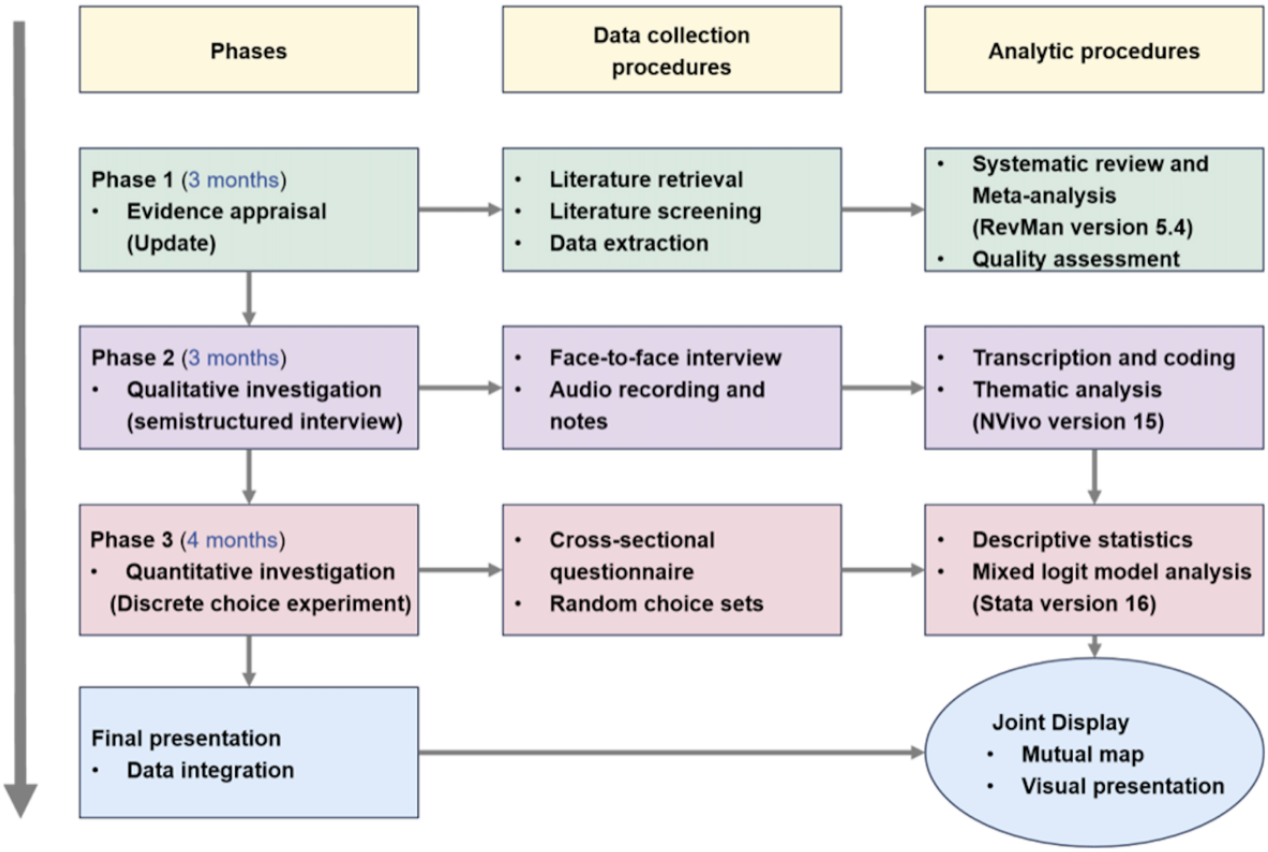

Participants

Patients aged ≥18 years with a diagnosis of COPD based on The Global Initiative for Chronic Obstructive Lung Disease criteria assessed by a clinical specialist [19] who currently prescribes or has previously prescribed TCM and is able to communicate in Mandarin will be included. Patients with evidence of mental illness, who are judged unable to cooperate or complete the survey, or who are receiving TCM to treat other diseases but not COPD will be excluded. There are no restrictions on the stage and severity of the condition, and a broad range of participants is expected to be enrolled to draw comprehensive conclusions.

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Preferences can be diverse in patients from different hospital backgrounds. Recruitment of participants will be conducted based on sufficiently broad background characteristics. Therefore, patients will be recruited from various hospitals. Additional participants will be recruited through newsletters, flyers, or advertisements or when they return for a hospital visit. Participants who have taken part in the interviews will also be invited to take part in the subsequent survey.

All participants will be informed about the study and will sign a consent form before undergoing study procedures.

Setting

This study will be conducted in a private room at the hospital rather than in the clinic so that patients can relax and openly discuss the interview questions or complete the questionnaires.

Sample Size

The sample size for the semistructured interviews will be determined through data saturation, and representative participants will be identified using a purposeful sampling strategy. Data saturation will be reached when no additional novel themes emerge from interviews with participants after data analysis and a sufficient number of participants with different characteristics have been interviewed. Between 10 and 20 potential participants will be included in each site considering the diversity of hospitals.

Multiple factors should be considered in the sample size estimation of the DCE survey, such as the heterogeneity of participants, the structure of the DCE questions, the items of the questionnaire, and the expected precision of the results. A sufficiently large sample size is crucial for capturing significant preference changes in the observed population and distinguishing different preferences among subgroups. However, large-scale studies require substantial resources. The thumb formula is a method proposed by Johnson and Orme [36] to calculate the minimum sample size. Considering the limited resources of this study, we used this formula to calculate the minimum sample size required for the DCE main-effects model. In this formula, 500 is a fixed variable, c is the maximum number of levels in any attribute, t is the number of DCE questions per questionnaire, and a refers to the number of options included in each DCE question:

Data Collection

Phase 1

A systematic review will be conducted following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. We will search 3 English-language databases (PubMed, Embase, and Cochrane Library) and 4 Chinese-language databases (Chinese Science and Technology Journal Database, Chinese Biomedical Literature Database, Wanfang, and China National Knowledge Infrastructure) using the following key search terms: “Chronic Obstructive Pulmonary Disease,” “Chinese Medicine,” and “Randomized controlled trials” (more details on the search strategy can be found in Multimedia Appendix 1). Randomized controlled trials exploring the efficacy, safety, and economic benefits of TCM for the treatment of COPD will be included. The initial screening will be carried out independently by 2 researchers who will read the titles, abstracts, and full texts separately and in strict accordance with the inclusion and exclusion criteria. The inclusion and exclusion criteria will be based on a previous systematic review [23]. Data extraction forms will be predesigned using EpiData (version 3.1; EpiData Association), and 2 reviewers will independently extract data from the included studies, checking the data after extraction and resolving disagreements on the extracted data through discussion or third-party assistance.

Phase 2

Two researchers will conduct the interviews and collect the data. Both have received training on interviewing techniques and data collection procedures and have experience communicating with patients. To ensure objectivity and minimize potential bias, patient recruitment and scheduling will be handled by a separate research coordinator. The interviewers will not be involved in these preliminary stages and will remain blinded to participant identities until the interviews begin. Before the initiation of the interviews, patients will be briefed on the background and main content of the study and promised that the management of the interview audio recordings will protect their privacy to gain their trust. They will also sign an informed consent form. The open-ended interview questions will be designed by the research team based on a comprehensive review of the literature and findings from our preliminary research (Table 1). The content of the interview outline will be flexibly adjusted according to each individual interview, and the participants will be encouraged to actively express their thoughts in a positive way, choices, and expectations regarding the health care process to obtain richer information from the interviews. Participants can also add any new ideas that are important to them but not covered in the current framework. Basic characteristics (gender, age, educational level, and condition duration) will be collected via a questionnaire. The full interview will be audio recorded, and notes will be taken. The interviews will be conducted in a quiet and private venue to ensure that the interview process is not disturbed and will take 60 minutes on average.

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Table 1. Topic guide for the semistructured interview used to investigate treatment preferences for traditional Chinese medicine among patients with chronic obstructive pulmonary disease (COPD).

Topic	Relevant questions
Perception of the disease	• What are your concerns about COPD and what do you want to know about it? • What are your expectations for COPD in the future?
Treatment history	• When and under what circumstances did you start receiving traditional Chinese medicine treatment during the course of your illness?
Perception of the treatment	• What is your perceived effectiveness of traditional Chinese medicine? • Comparing to other treatments you had received throughout the course of illness, what is your perception (such as effect, side effects, and treatment duration) of traditional Chinese medicine for COPD? • What clinical outcomes are you more concerned about?
Factors affecting treatment options	• Which factors are important for treatment scenario options?

Interviewees will be assigned numbers to protect their privacy, and the audio recordings will be transcribed verbatim by the research team within 24 hours after the interview. Transcripts will be individually coded by the interviewers, and potential themes will be elicited accordingly and then entered into a database (NVivo Plus; version 12; Lumivero). The interviewers will be involved in the coding process and check the coding. Major differences in coding will be discussed and resolved by experienced qualitative researchers.

Phase 3

This study's questionnaire is divided into 3 parts. The first part collects basic personal information of the participants, including age, gender, educational level, primary caregiver, per capita monthly family income, and type of health insurance. The second part focuses on disease and treatment information, such as disease type, stage, and duration and treatment plan. The third part includes preference questions based on identified attributes and levels. Using SAS (version 9.4; SAS Institute), choice sets will be generated via efficient design (*D*–efficiency). When there are too many choice sets, they will be evenly distributed across several questionnaire versions to reduce patients' burden. Each choice set offers 2 alternatives (options A and B) plus an exit option. To ensure survey quality, the consistency of patients' pre- and postchoices will be checked by repeating a choice set question and swapping options A and B. Inconsistent choices will be deemed as invalid data.

A pilot survey will be conducted with a small target group to test the comprehensibility of the questionnaire and the rationality of the DCE design. On the basis of this feedback, several discussions will be held to modify and adjust the language and questions of the survey. The same group of participants will then be selected for a second test to gradually improve the reliability and validity of the questionnaire. On the basis of standardized research steps, the research team will strictly control the quality of the questionnaire. The pilot surveys will be completed by the researchers through face-to-face on-site communication to reduce errors and improve the quality of the questionnaire.

Formal research will be carried out in several TCM and Western medicine hospitals. Researchers will distribute and collect paper questionnaires face-to-face to ensure data quality. Before the survey, they will explain the precautions in detail. While patients are filling out the questionnaire, the researchers will answer any questions that arise on the spot.

Data Analysis

Phase 1

A systematic review will be conducted using Review Manager (version 5.4; The Cochrane Collaboration). Risk of bias will be assessed according to the revised Cochrane risk-of-bias tool for randomized trials [37]. The Grading of Recommendations Assessment, Development, and Evaluation system will be used to estimate the certainty of the evidence.

Phase 2

Data analysis and data collection will take place simultaneously. Theoretical saturation will be determined to terminate the interviews when the information from the last interview has been analyzed and no new themes and ideas have been found. The transcribed texts will be read repeatedly for familiarization and line-by-line coding. Initial codes will generate potential themes. The interview transcripts will be analyzed using thematic analysis, which is an inductive method for identifying, analyzing, and reporting patterns within the data [38]. The NVivo qualitative analysis software will be used to facilitate and manage the analysis. After analyzing and processing the interview transcripts, we will provide a subset of participants with the research findings or interpretations to verify whether they accurately reflect the intended meanings of the participants.

Phase 3

The analysis will commence using descriptive statistics, summarizing sociodemographic and clinical characteristics as means and SDs for continuous variables and as frequencies and proportions for categorical variables. The core analysis of the DCE data will used a mixed logit model. This model assesses how the different attributes and levels influence patient choices, with the choice outcome as the dependent variable and the attribute levels as independent variables. The model estimates a regression coefficient (β) for each attribute, where a significant β denotes a meaningful impact on preference, with its sign and magnitude indicating the direction and relative strength of influence, respectively. The associated SD of β quantifies the heterogeneity in preferences for that attribute among

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participants. All analyses will be conducted using Stata (version 16.0; StataCorp).

Data Integration

For the analysis and interpretation of the 2 datasets, a joint display approach will be used to visually integrate and present the mixed methods findings [39]. After all data have been collected, the quantitative results will be mapped onto the qualitative themes to examine both the similarities and divergences between patients' reported experiences and their expressed preferences in hypothetical treatment scenarios. This joint display of qualitative and quantitative findings will facilitate a holistic interpretation, highlighting which factors most strongly influence treatment decisions and how these preferences vary across patient subgroups. The final presentation will include integrated tables and figures illustrating the convergence and complementarity of the quantitative and qualitative data.

Ethical Considerations

This study was reviewed and determined to be exempt from full ethical review by the ethics committee of Guangdong Provincial Hospital of Traditional Chinese Medicine on November 6, 2023 (ZM2023-405). Informed consent will be obtained from all participants.

Results

On the basis of the search strategy we formulated (Multimedia Appendix 1), a total of 18,188 articles published after 2016 were initially identified in the English- and Chinese-language databases. The outline of the semistructured interview guide for this study has been developed (Table 1). Further clinical evidence updates, qualitative interviews, and DCEs are still ongoing and will be completed by April 2026.

Discussion

Expected Findings

In this study, we seek to understand the treatment preferences and needs of patients with COPD regarding TCM. Our findings are anticipated to provide new insights into how patients' personal values and experiences shape treatment choices, helping physicians tailor clinical decisions to individual characteristics and needs.

EBM is defined as "the conscientious, explicit, and judicious use of the current best evidence to make medical decisions for individual patients" [40]. True EBM prioritizes individualized patient care by integrating clinical evidence with the unique contexts, experiences, and preferences of patients [41]. However, over the years, investigators have been committed to addressing patient population and subgroup-specific issues when designing and conducting clinical studies, often at the expense of individual patient differences to achieve more generalized findings and broader application prospects. Nevertheless, contemporary research, guideline development, and even clinical decision-making continue to insufficiently reflect individual patients' values and preferences [42,43].

The personal experience of patients is extremely important and difficult to standardize, and conclusions drawn from studies on general patient populations should not outweigh those drawn by individual patients through their own experiences. Therefore, recent advances in EBM call for a more balanced approach that integrates critical evidence appraisal with patients' values and preferences through SDM [44]. Achieving this integration requires clinicians to invest substantial time and effort in explaining, discussing, and negotiating treatment options with patients.

Previous studies on the treatment preferences of patients with COPD have mainly focused on conventional therapies such as inhalers, pharmacotherapy, and lung transplantation [45,46]. A pilot study by our team suggested that preferences for TCM may be influenced by perceived efficacy, side effects, and cost, but these findings require validation in larger samples [29]. Moreover, previous research has rarely examined patient perceptions of specific TCM interventions or accounted for individual values, experiences, and cultural factors.

This study has several strengths. First, it comprehensively captures the preferences and needs of patients with COPD regarding TCM through an exploratory sequential mixed methods study design that allows for a comparative analysis examining the relationship between patient preferences and individual backgrounds, helping identify patterns of homogeneity or divergence in treatment inclinations. Second, the use of narrative medicine in the interviews enables a deeper exploration of patients' true experiences and perceptions, mitigating biases that arise when patients favor previously used treatments even when there is new evidence suggesting alternatives [47]. Finally, including patients from diverse hospital backgrounds and with diverse treatment experiences ensures that multiple perspectives are represented.

However, several limitations should be acknowledged. Patient preferences may still be influenced by cognitive perceptions, social determinants, environmental factors, or previous experiences, which could limit generalizability. Future multicenter studies with larger samples are needed to validate and extend these findings.

Dissemination

The findings will be shared at national and international conferences focused on respiratory and integrative medicine. For scientific publication, results will be submitted to peer-reviewed journals related to respiratory care, patient-centered medicine, or integrative medicine. To reach patients and caregivers, summaries will be disseminated via patient organizations, hospital newsletters, and social media channels. These efforts aim to ensure that the study results are accessible and understandable to both the scientific community and the wider public.

Conclusions

In conclusion, this exploratory sequential mixed methods study will generate empirical evidence on the treatment preferences of patients with COPD regarding TCM, offering a foundation for SDM and patient-centered COPD care. The anticipated findings will contribute to personalized treatment strategies;

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inform integrative guideline development; support SDM; and, ultimately, improve patient adherence and satisfaction. Future work will extend recruitment across multiple regions and countries to enhance generalizability and explore digital health applications that integrate patient preference modeling into clinical decision support systems.

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during this study. However, collective data from future studies will be made available as supplementary files alongside the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Detailed search strategy.
[DOCX File , 19 KB - resprot_v14i1e75426_app1.docx]

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Abbreviations

TCM: traditional Chinese medicine
COPD: chronic obstructive pulmonary disease
DCE: discrete choice experiment
EBM: evidence-based medicine
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SDM: shared decision-making

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Protocol

Prevalence and Factors Associated With Depression Among Antenatal and Postnatal Women Attending Government Health Clinics in Selangor, Malaysia: Protocol for a Cross-Sectional Study

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Abstract

Background: Maternal mental health concerns either during pregnancy or the postpartum period are a public health challenge. Depression, anxiety, and stress can lead to poorer outcomes in the antenatal and postpartum periods. There is evidence that the effect of stress, anxiety, and depression during pregnancy negatively affects fetal neurodevelopment and children's developmental outcomes. Early diagnosis can improve treatment outcomes and prevent negative impacts on the mother and baby. Identifying risk factors, such as age, socioeconomic status, mental health history, and family dysfunction, and clinical manifestations are important for public health programs.

Objective: This study aims to determine the prevalence of depression and associated risk factors among antenatal and postnatal women attending government health clinics in Selangor.

Methods: A multicenter cross-sectional study will be conducted among antenatal and postnatal women attending government health clinics (*Klinik Kesihatan*) in Selangor, Malaysia, from August 1, 2024, to December 31, 2026. We will perform a simple random sampling in all 9 districts in Selangor to select 1 government health clinic in each district. The inclusion criteria for this study are women aged 18 years and older who are either pregnant or delivered a newborn or stillborn child within the preceding 6 weeks. We will use a published screening tool (Edinburgh Postnatal Depression Scale) to determine the level of depression among antenatal and postnatal women. We will also collect data on sociodemographic characteristics, obstetric factors, and psychosocial support.

Results: We will obtain ethics approval from the relevant ethics boards prior to data collection. Data will be analyzed using SPSS version 26.0 (IBM Corporation) and we will conduct a descriptive analysis to determine the prevalence of depression. We will calculate the level of depression among antenatal and postnatal women and score it based on a previous study conducted in Malaysia, with a score of ≥12 indicating the presence of depression. The association between depression and risk factors will be determined by multiple logistic regression analysis. *P* values less than .05 will be considered statistically significant.

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Conclusions: Depression is one of the mental health complications that may arise following childbirth. Therefore, the findings of this study on the prevalence and associated risk factors of depression among antenatal and postnatal women in Selangor may help women address this challenge and improve maternal mental health during pregnancy and after birth.

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KEYWORDS

prevalence; risk factors; antenatal; prenatal; depression; Selangor

Introduction

Early childhood is a critical period for brain development, and maternal depression can have a detrimental effect during this time. A few studies show that women are particularly susceptible to depression during the antenatal and postnatal periods. Depression can be due to hormonal changes and various psychosocial factors [1]. As a result, depression is more frequently reported in pregnant women than in those who are not pregnant [2]. To help mothers regain their prepregnancy health and well-being, they should receive adequate social support and care after childbirth. The postpartum period is a very important period for women, marked by significant transitions and instability, which require both adjustment and family support. However, some studies have shown that many women experience antenatal and postnatal depression during this period [3,4].

A study has shown that several pregnancies are unplanned or accidental, which can lead to negative attitudes toward pregnancy and increase the risk of prenatal depression in both Western and Asian cultures [5]. This attitude often manifests through symptoms such as exhaustion, anxiety, sleep disturbances, mood swings, irritability, emotional distress, sadness, and decreased self-esteem [4,6]. There is also substantial evidence indicating that maternal depression adversely affects a child's physical health, cognitive development, and emotional well-being [7]. Additionally, women suffering from depression may experience poor prenatal care, which can lead to higher likelihood of obstetric complications, premature birth, and postpartum depression [8]. Even though a strong social support system occurs in many Asian cultures, both antenatal and postnatal depression remain common, with similar findings reported in Western countries [9].

Approximately 9% to 24% of pregnant women experience antenatal depression, while another 10% to 60% suffer from postnatal depression [5,10]. In Asia, the prevalence of antenatal depression stands at 20%, while postnatal depression ranges from 3.5% to 63.3% [5]. In Malaysia, a study found that 13.8% of women experienced antenatal depression and 14.3% reported postnatal depression [5]. These figures underline the need for greater attention to maternal mental health, as the rates of antenatal and postnatal depression are rising worldwide [3].

One of the primary factors contributing to both antenatal and postnatal depression is a lack of family support. Additionally, other factors, such as having more than 2 children, limited social support, conflicts with a partner or family, pre-existing mental health conditions, and experiencing intimate partner violence, may contribute to depression among pregnant mothers [11,12]. These issues can negatively affect personal well-being, marital satisfaction, social relationships, childcare, and child development, and may also prevent mothers from returning to work, which can impact the family's financial stability [3,4,6]. Many working women are expected to return to their jobs within 3 to 6 months after childbirth, and some experience depressive symptoms during this time [13]. Additionally, parental depression has been shown to negatively affect an infant's cognitive development, emotional growth, and behavioral outcomes [9].

Untreated depression can negatively affect both the mother and her unborn child, potentially affecting her ability to perform everyday tasks and damaging her relationships with family, colleagues or coworkers, and society. Prolong depression can also impact the child's physical, social, psychological, and cognitive development [8]. During the postnatal period, the physical and emotional demands on the mother increase, and the disabling effects of postnatal depression may hinder her ability to care for and bond with her newborn and fulfil other maternal responsibilities [14]. In uncommon cases, the mother might become disengaged or even display negative behavior toward her child [7]. Depression during pregnancy and postpartum is a significant public health concern that requires continuous support from family, the community, health care providers, and government agencies. It has gained attention due to its detrimental impact on individuals, families, and child development and the global rise of the condition. Therefore, this study aims to identify the prevalence of depression and the associated risk factors among antenatal and postnatal women attending government health clinics in Selangor, Malaysia.

Methods

Study Design

This is a multicenter cross-sectional study to determine the prevalence of and risk factors associated with depression among antenatal and postnatal mothers attending government health clinics in Selangor, Malaysia.

Study Population and Setting

This study will be conducted among antenatal and postnatal women attending government primary health clinics (*Klinik Kesihatan*) in Selangor, Malaysia from August 1, 2024, to December 31, 2026. The inclusion criteria for this study are women aged 18 years and older who are either pregnant or delivered a newborn or stillborn child within the preceding 6

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weeks. The exclusion criteria are women who are not pregnant or have not deliver any newborn or stillborn child within the preceding 6 weeks. Patients who are diagnosed with a psychiatric illness, such as bipolar disorder, schizophrenia, or depression, during the study period will be excluded from this study. Since this study will not involve any biological sample collection, such as blood or urine, we do not anticipate providing any compensation to participants in the event of harm or loss resulting from their participation in the study. Additionally, all patient data will be kept confidential in both hard and soft copies.

Recruitment and Data Collection

Selangor consists of 9 districts, of which 4 are in urban areas and 5 are in rural areas. In this study, we will identify all the major primary health clinics in each district. We will use a stratified random sampling method to identify 1 clinic in each district; hence, a total of 9 primary health clinics will be included. We will invite the family medicine specialist in the selected clinic to participate in this study.

In each selected primary health clinic, a liaison officer will be appointed to assist in the flow of recruitment of the respondents. We will conduct a training session prior to data collection. We will determine the respondents from the registration counter, and the respondents will be selected using a simple random sampling technique. When a respondent agrees to participate in this study, a face-to-face interview will be conducted by a trained interviewer, which may take 15 to 20 minutes. Verbal consent will be obtained prior to the interview.

Patients with a high score on the Edinburgh Postnatal Depression Scale (EPDS) will appropriately be referred to the family medicine specialist for further assessment and treatment.

Sample Size

We will calculate the sample size using the following formula for estimating a proportion by OpenEpi software version 3.02, where n is the required sample size, Z is the z-score (Z=1.96 for 95% confidence), P is the estimated prevalence (P=0.09 [15]), and e is the margin of error (e=0.8):

A sample size calculation table is provided in Figure 1.

Figure 1. Sample size calculation for the prevalence study using random (not cluster) sampling. FPC: finite population correction.

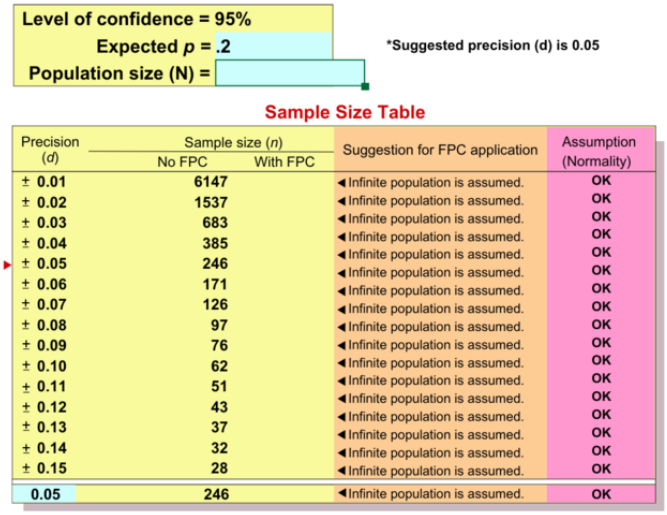

Level of confidence = 95%
Expected p = .2
Population size (N) =

*Suggested precision (d) is 0.05

Sample Size Table

Precision (d)	Sample size (n) No FPC	Sample size (n) With FPC	Suggestion for FPC application	Assumption (Normality)
± 0.01	6147		◀Infinite population is assumed.	OK
± 0.02	1537		◀Infinite population is assumed.	OK
± 0.03	683		◀Infinite population is assumed.	OK
± 0.04	385		◀Infinite population is assumed.	OK
± 0.05	246		◀Infinite population is assumed.	OK
± 0.06	171		◀Infinite population is assumed.	OK
± 0.07	126		◀Infinite population is assumed.	OK
± 0.08	97		◀Infinite population is assumed.	OK
± 0.09	76		◀Infinite population is assumed.	OK
± 0.10	62		◀Infinite population is assumed.	OK
± 0.11	51		◀Infinite population is assumed.	OK
± 0.12	43		◀Infinite population is assumed.	OK
± 0.13	37		◀Infinite population is assumed.	OK
± 0.14	32		◀Infinite population is assumed.	OK
± 0.15	28		◀Infinite population is assumed.	OK
0.05	246		◀Infinite population is assumed.	OK

This gives a required sample size of 39 for each center. We will calculate the design effect using the formula DE = 1 / ICC, where ICC is the intraclass correlation and is estimated at 0.5.

The sample size will be adjusted using a design effect to account for the multicenter study design. We will estimate the nonresponse rate by anticipating that 20% of individuals will not agree to participate in this study. Therefore, we will increase the sample size by 10 to account for the anticipated nonresponse.

Our first objective is to determine the prevalence of depression among antenatal and postnatal women attending government health clinics in Malaysia. The prevalence of perinatal depression among pregnant women was 9% [15]. An expected prevalence of 0.09 and a precision of 0.05 are therefore taken into the calculation. With a 95% confidence level and 20% nonresponse rate, the study requires a minimum of 421 respondents.

Our second objective is to identify the risk factors for depression among antenatal and postnatal women attending government health clinics in Malaysia. Prior data indicate that the percentage of pregnant women with a lack of psychosocial support and who had a history of psychiatric illness were 8.6% and 28.3%, respectively [16]. The percentage of depressed pregnant women who had previous neonatal complications was 10.6% [17]. The proportion of antenatal women with depression who consumed alcohol was 27.8% [18]. Thus, a minimum sample of 372 respondents is needed. With an additional 20% to account for nonresponses, the sample size needed is 445. Therefore, we will use a minimum sample size of 445 respondents for this study (Figure 2).

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Figure 2. Sample size calculation for the associated risk factors among antenatal and postnatal women attending government health clinics in Malaysia.

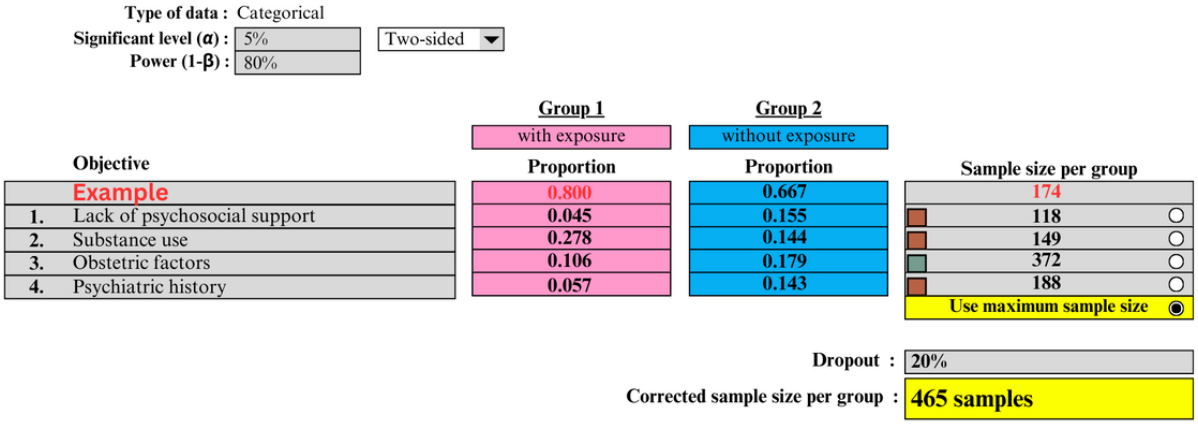

Research Tool

A guided interview by a trained interviewer will be conducted. A standardized web-based questionnaire consisting of 4 sections will be used, the details of which are provided below.

Section A: Sociodemographic Characteristics

This section consists of general information on the respondents' age, education, economic status, marital status, employment, illness, history of substance use, and total current number of children.

Section B: Obstetric Factors

This section consists of information on obstetric conditions such as type of parity, history of abortion and preterm delivery, unplanned pregnancy, history of losing or hospitalization of baby, mode of delivery, place of delivery, pregnancy complications or illness, sex of the fetus, any uncomfortable symptoms faced during the confinement period, and stressful life events and social support during the antennal or postnatal period.

Section C: Psychosocial Support

This section will contain information on psychosocial factors. It includes partner relationship, emotional status (eg, worried, miserable, anxious, or depressed), any mental health concerns, support from other people to manage the baby, and experiences of sexual abuse, emotional, or physical abuse.

Section D: Edinburgh Postnatal Depression Scale

This scale consists of 10 screening questions designed to identify signs of depression and anxiety typical among pregnant and postpartum women. Respondents can select the number corresponding to how they have felt over the past week for each item. The scores for all 10 items are summed to calculate a total score. The EPDS has been previously validated in the Malay language, demonstrating high reliability with a Cronbach α of .86. Using a cutoff score of 11 or 12, the scale showed excellent diagnostic performance, with a sensitivity of 100%, specificity of 98.18%, positive predictive value of 90%, negative predictive value of 100%, and misclassification rate of only 1.56% [19].

In this study, we will use a cutoff score of 12 and above to indicate antenatal or postnatal depression based on the validation study conducted in a Malaysian population, which identified scores between 11 and 12 as indicative of depression [19]. The use of a lower cutoff score may be considered if the aim is to minimize false negatives and identify most patients who meet diagnostic criteria [20]. Prior to the main study, we will conduct a validity assessment, as the previous validation was carried out in a community-based setting, while our study will be conducted in a clinical setting. If respondents score 12 or above, their contact information will be collected and forwarded to the designated liaison officer for referral to the appropriate health care provider.

Statistical Analysis

Data will be entered and organized into a Microsoft Excel spreadsheet by trained investigators. Data cleaning and verification will be conducted prior to analysis using SPSS software version 26.0 (IBM Corporation). We will perform a normality test to observe the distribution of the data. To assess the normality of data, we will plot a histogram to visualize the distribution, which is characterized by a bell-shaped curve for normal distributions, and perform a Kolmogorov-Smirnov test.

Descriptive analysis will be performed to summarize all variables, reporting means and SD. Result from the EPDS will be used to determine the prevalence depression. Chi-square analysis will be used for categorical variables to observe the association between depression and sociodemographic factors, obstetric factors, and psychosocial support. A multivariable logistics regression analysis will be conducted to identify the risk factors associated with depression among antenatal and postnatal women. Depression status (categorized as "depression" or "no depression") will serve as the dependent variable, while associated risk factors, such as sociodemographic characteristics, obstetric factors, or psychosocial support, will be defined as independent variables. The logistic regression will use 3 methods, namely, enter, forward likelihood ratio, and backward likelihood ratio, to assess any differences in outcomes based on the method applied.

Multicollinearity among the predicted variables will be assessed using the variance inflation factor, which measures the strength and extent of correlation between independent variables in the regression model. All *P* values will be 2-sided, and a *P* value of less than .05 will be considered statistically significant.

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Ethical Approval

This study received ethics approvals from the Malaysian Research Ethics Committee (NMRR ID-24-01019-GZX) and Selangor State Medical Department.

We will keep the data on patients anonymized. Patient information will only be accessible to the principal investigator. Data will be kept in a private, password-protected database and will be linked only to a unique study identification number for the purposes of this research. Each patient will be assigned an ID number (eg, KK001) which will appear on all data collection forms. Upon completion of the study, the data will be transferred to an external soft copy, and the original files on the computer will be deleted. Both electronic and physical copies of the data will be securely stored in a locked cabinet that can only be accessed by the principal investigator. These records will be retained for a minimum of 3 years following the conclusion of the study, after which they will be permanently destroyed. The patients will not have access to their individual data, as the information will be integrated into a consolidated database.

Results

Funded by the National Centre of Excellent for Mental Health, this will be a 2-year study (August 1, 2024, to December 31, 2026) from proposal development and data collection to analysis of the findings. Starting in June 2025, we will work with the selected primary health clinics in Malaysia, and we plan for data analysis to start in August 2025. The data will be analyzed using SPSS version 26.0 (IBM Corporation). We will share the findings with the public during a conference and publish the study in a reputable, peer-reviewed journal with a scope for maternal and depression research. This work will determine the prevalence of depression and its associated risk factors among antenatal and postnatal women referred to health care providers in Malaysia.

Discussion

Principal Findings

The incidence of depression among women before and after pregnancy has been steadily rising each year worldwide [11,12]. A study from the National Health and Morbidity Survey reported that 9 out of 10 mothers with depression were undiagnosed [21]. A study has shown that approximately 1 in 6 pregnant women experiences depression, underscoring the need for greater attention to specific risk factors [2]. When left untreated, maternal depression can have significant negative effects on the family members and the baby's development during pregnancy [22] and may lead to preterm birth, low birth weight, and stillbirth [23]. It is also associated with negative health outcomes in children [22].

Antenatal depression significantly increases the risk of postpartum depression, with many postpartum cases being linked to depression during pregnancy [24]. Additionally, women with this condition are also at higher risk for substance abuse, premature rupture of membranes, severe headaches, and hemorrhage [25]. A previous report found that lacking social support; being single, separated, or divorced; having an unplanned pregnancy; being unemployed, experiencing violence, and smoking before or during pregnancy are also significantly associated with antenatal depression [25].

Therefore, understanding the factors contributing to depression are important for determining appropriate treatments or prevention strategies as well as developing awareness programs for pregnant women. Determining the prevalence of maternal depression may also help health care providers and policymakers implement targeted interventions, such as educational programs, psychological evaluation, and mental health assessments.

The findings of this study will be used to inform effective public health programs to reduce the incidence of maternal depression and serve as evidence to inform policy on improving antenatal and postnatal health care. The findings will be presented and published at academic conferences and in international peer-reviewed journals.

Limitations

This is a cross-sectional study where we can only identify factors associated with depression among the population of antenatal and postnatal women. We are unable to make a conclusion with regard to cause and effect. However, due to the limited number of studies conducted within this specific population, our research may provide valuable information on the current state of depression among antenatal and postnatal women, especially in Malaysia.

Conclusions

Depression is one of the mental health conditions that may arise following childbirth. The findings from this study will serve as a platform for the development of maternal mental health programs. These programs can be used for the early detection, prevention, and treatment of mental health conditions like depression, anxiety, and stress during antenatal and postnatal periods.

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This study will be funded by the National Centre of Excellent for Mental Health. The funder has no role in the design of the study, analysis of the data, or preparation or approval of the manuscript and does not have access to the data.

Data Availability

The data generated or analyzed during this study are available from the corresponding author upon reasonable request.

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Authors' Contributions

NAM is the lead investigator of this study. NHM, IAR, NAFNA, NHJ, FNL, TPNTBS, NSM, NHH, NC, NA, and NI are co-leads. NAM, IAR, and NAFNA helped conceptualize the study and design the study methods. NHM wrote the original draft, and NAM critically reviewed and edited various iterations of the manuscript. All authors approve the manuscript in its current form and agree to be accountable for all its contents.

Conflicts of Interest

None declared.

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Abbreviations

EPDS: Edinburgh Postnatal Depression Scale

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Protocol

Newly Designed Optical Coherence Tomography Catheter for Optimizing Bladder Cancer Diagnosis and Treatment: Protocol for a Feasibility Study

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Abstract

Background: Bladder cancer diagnosis relies on cystoscopy and transurethral resection of bladder tumor (TURBT) for histopathological evaluation, but this process is time consuming, costly, and subject to variability. Optical coherence tomography (OCT) offers real-time, high-resolution imaging as a potential alternative.

Objective: This study primarily aims to assess the feasibility of capturing in vivo cross-sectional images of the bladder wall using a novel microelectromechanical systems (MEMS)-based OCT catheter. Secondary objectives include evaluating measurement duration, assessing tumor stage and grade from OCT images in comparison with histopathology, determining the catheter's ability to image resection beds, and comparing OCT-based tumor staging with white light cystoscopy assessments.

Methods: This single-center feasibility study at Amsterdam University Medical Center includes patients undergoing TURBT for suspected bladder tumors. Eligible patients must be aged 18 years or older, have at least 1 cystoscopically accessible tumor, and must be physically fit for TURBT. Exclusion criteria include pregnancy, tumors larger than 2 cm, more than 5 tumors, isolated flat lesions, or tumors solely at the bladder neck. The primary end point assesses the procedural feasibility of OCT imaging, while the secondary end points evaluate tumor staging, grading, and correlation with histopathology. Up to 25 patients will be enrolled, with feasibility achieved if diagnostic images are obtained in more than 60% of the cases. OCT imaging is performed before and after tumor resection, with histopathological results used for comparison. Patients will be monitored for adverse events for 4 weeks after the procedure, after which study participation ends.

Results: As of November 2025, 16 participants have been enrolled, and 13 have successfully completed the study procedure. The projected end date of the study is November 2025, and results are expected to be published in March 2026.

Conclusions: This study is expected to provide key insights into the feasibility and clinical utility of the newly developed MEMS-based forward-looking OCT system for real-time bladder imaging during TURBT. This study will lay the groundwork for a larger trial to evaluate its diagnostic accuracy in staging and grading bladder cancer.

Trial Registration: ClinicalTrials.gov NCT06679920; https://clinicaltrials.gov/study/NCT06679920

International Registered Report Identifier (IRRID): DERR1-10.2196/76644

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KEYWORDS

bladder cancer; optical coherence tomography; OCT; diagnosis; microelectromechanical systems

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Introduction

The current diagnostic process for bladder cancer involves a cystoscopy followed by transurethral resection of the bladder tumor (TURBT) [1]. A TURBT is undertaken to obtain material for histopathology, which is required to confirm the malignant nature of the lesion and, if so, to determine the invasion and grade of the tumor [1]. In some patients, a repeat TURBT is necessary to ensure complete resection and confirm the histopathological stage [1]. Determining the histopathological stage and grade is essential for an appropriate treatment plan. If the tumor is muscle invasive, the available treatment options are radical cystectomy or trimodality therapy [2]. Treatment of non–muscle-invasive bladder cancer comprises TURBT, followed by regular cystoscopy, and, depending on the differentiation grade of the tumor, additional Bacille Calmette-Guérin or chemotherapy instillations [1].

Although the histopathological result is currently regarded as the gold standard, there remains significant interobserver variability, which may have a considerable impact on treatment decisions [3]. Furthermore, the current diagnostic process places a substantial burden on patients with bladder cancer and results in substantial health care costs [4,5]. Both surgical planning and the histopathological process are time consuming as well. Therefore, there is a need for an alternative option to determine the tumor grade and stage in real time.

Such an alternative might be an “optical biopsy,” which uses an optical technique to ascertain the stage and grade of the tumor [6]. An optical biopsy can facilitate the diagnostic process and enable the implementation of alternative treatment options, such as outpatient laser fulguration or active surveillance [7,8]. One technique with the potential to perform such an “optical biopsy” is optical coherence tomography (OCT), which uses infrared light to generate high-resolution, real-time cross-sectional images of tissue [9,10]. OCT was first described in 1991 [11] and has since been used and studied in several tissue types, with encouraging results [12,13]. The OCT catheters typically have a helical-scanning and side-looking design, making them suitable for tubular structures, such as vessels and ureters, but unsuitable for other organs such as the bladder [14,15]. To facilitate the analysis of the bladder wall using OCT, it is necessary to use a forward-looking OCT catheter that has the ability to acquire OCT images within the field of view of the cystoscope.

Three distinct forward-looking OCT catheters have been investigated for use within the bladder in previous studies [16-21]. These studies reported varying results regarding the sensitivity and specificity of both catheters. While some findings were highly promising, others showed no advantage for OCT over white light cystoscopy (WLC). All the studied first-generation time-domain OCT systems used with the catheters had low frames-per-second rates, leading to distorted images and making them highly susceptible to motion artifacts. In addition, the one catheter previously available on the market had to be in contact with the tissue, resulting in a field of view that is only as large as the tip of the catheter (ie, 2.7 mm), limiting its practical use [17,18].

In light of the aforementioned considerations, we developed a novel forward-looking OCT catheter. Interfaced with a fast second-generation OCT system, this OCT catheter has a considerably higher frames per second, while using a wavelength of approximately 1060 nm, which minimizes infrared light absorption by water [22,23]. The new OCT catheter incorporates a microelectromechanical systems (MEMS) mirror combined with a graded index lens that has a focal plane at 10.9 mm (in air) from the OCT MEMS mirror, enabling the generation of an image with a larger field of view than the catheter tip diameter [24].

The primary objective of this study is to investigate the feasibility of capturing in vivo cross-sectional images of the bladder wall in patients with bladder cancer using the newly developed MEMS-based OCT catheter. Secondary objectives are to evaluate the duration of the OCT measurements, determine the tumor stage based on OCT images and test for an association with histopathological results, determine the grade of the tumor based on OCT images and test for an association with the histopathological results, determine if the OCT catheter is able to acquire evaluable images of the bladder wall after resection of the tumor, and compare the tumor grade and stage estimated during WLC with the tumor grade and stage based on the OCT images.

This is a single-group; idea, development, exploration, assessment, and long-term (IDEAL) phase 2a (development) [25]; single-center feasibility study.

Methods

Study Population and Setting

The study population comprises adult patients with a suspected bladder tumor, either non–muscle-invasive bladder cancer or muscle-invasive bladder cancer, planned for a TURBT. This study is performed at the Amsterdam University Medical Center (UMC). The trial has been registered on ClinicalTrials.gov (NCT06679920).

Eligibility Criteria

The eligibility criteria are presented in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Aged older than 18 years
- Have at least 1 suspected bladder tumor seen on cystoscopy
- Have a bladder that is accessible for cystoscopy
- Be in a physical condition to undergo transurethral resection of the bladder tumor
- Must be fully informed about the study and should provide written informed consent before any study-related investigation or intervention

Exclusion criteria

- Pregnant or lactating women
- Only tumor site at the bladder neck
- Tumor larger than 2 cm in diameter
- More than 5 tumors present
- Only flat suspected lesions

Study Procedures

Standard Procedure

The standard procedure is the TURBT. After regional or general anesthesia, a resectoscope is inserted into the bladder through the urethra. First, endoscopic inspection of the bladder wall is performed to identify tumors and suspicious lesions. Then, the identified tumors are resected using a loop wire with electric current. After resection of the tumor and retrieval of the resected tissue, the resection bed and edges are cauterized to ensure hemostasis. Subsequently, the resectoscope is removed, and, in most cases, a catheter will be inserted. Resected tissue is sent to pathology to determine the definitive stage and grade. Figure 1 provides an overview of the standard procedure and the schedule of the interventions.

Figure 1. Schematic overview of the standard procedure and timing of the study interventions during transurethral resection of the bladder tumor.

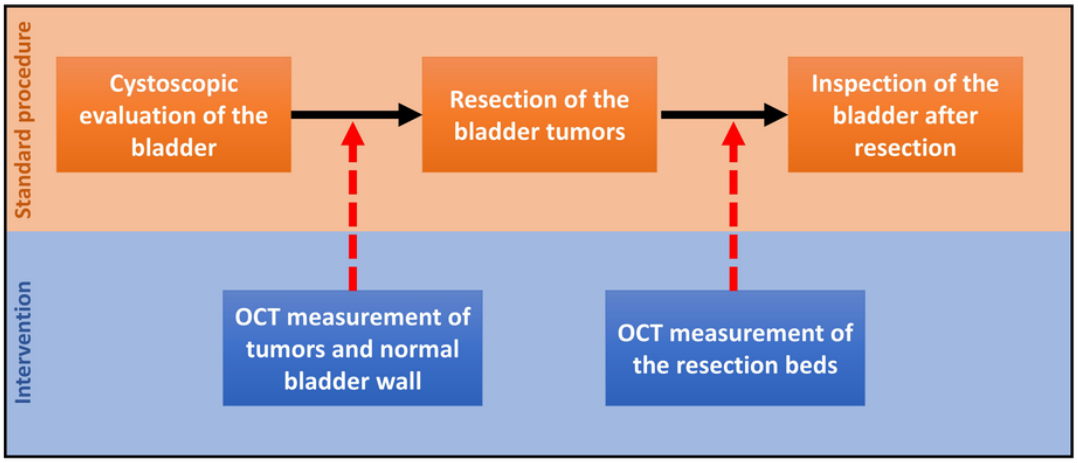

OCT Measurements

During the standard TURBT procedure, the OCT measurements will be performed. After the inspection of the bladder and before the resection of the identified bladder tumors, the OCT catheter will be inserted through the working channel of the rigid resectoscope. The tumors will then be imaged with the OCT catheter tip at approximately 1 cm from the tumor. Approximately 5 measurements will be performed for each suspected lesion and tumor and 3 for a selected region of normal bladder wall. When the OCT measurements are finished, the OCT catheter is removed from the bladder, and the urologist will continue with the standard procedure. The resection of the tumors is performed according to standard care. However, the pathology specimens of each separate tumor will be collected and numbered according to the tumor numbers used during the OCT measurements and sent to the pathologist. After completion of the resection, the OCT catheter will be reinserted through the working channel of the rigid resectoscope, and approximately 3 OCT measurements will be performed on each resection bed. After these measurements, the OCT catheter will be removed from the bladder, and the urologist will continue with the standard procedure (Figure 1).

Study Outcomes

Primary End Point

The primary end point comprises two components:

1. Procedural feasibility of OCT imaging will be determined by the ability to generate images of the normal bladder wall

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and bladder tumors, as assessed by the operating urologist. Procedural feasibility will be achieved if diagnostic images of the tumor and normal bladder are obtained in more than 60% of the patients.

2. Feasibility based on image use will be evaluated as the percentage of images suitable for diagnosis out of the total number of OCT images obtained. A percentage greater than 80% is regarded as feasible.

Secondary End Point

The secondary outcomes include (1) duration of the OCT measurements, (2) concordance between the OCT-based diagnosis of tumor invasion and histopathological diagnosis, (3) concordance between the OCT-based diagnosis of tumor grade and the histopathological diagnosis, (4) the ability of the OCT catheter to acquire evaluable images of the resection bed, and (5) concordance between intraoperative WLC assessments and OCT findings on tumor grade and invasion.

Study Timeline

Patients will be identified at the outpatient clinic, and patients meeting the inclusion and exclusion criteria who provide informed consent will be scheduled for TURBT within 6 weeks of identification. The TURBT and the OCT catheter procedure will be performed as described previously. The procedural timeline of the TURBT is illustrated in Figure 1. After undergoing TURBT, participants will continue with standard treatment. Serious adverse events (AEs) will be monitored and recorded for a period of 4 weeks. Study participation will conclude at the end of this monitoring period.

Sample Size and Enrollment

To date, no human study assessing the feasibility of this new MEMS-based OCT catheter for bladder cancer has been conducted. Therefore, a sample size calculation is not possible. The goal of this study is to test the technical and procedural feasibility of the device in a single-center, single-intervention, small prospective cohort study. In this IDEAL stage 2a study, up to 25 patients who undergo technically successful OCT measurements will be enrolled. Because the feasibility cutoff is set at 60%, inclusion will stop when a feasible procedure is performed in 15 patients. The findings of this study will inform sample size calculations for future investigations.

Data Collection and Management

Data collection and analysis will be conducted in accordance with Good Clinical Practice guidelines to ensure data integrity and reliability. Outcome, baseline, and other trial-related data will be systematically collected from both paper-based and electronic sources, including case report forms completed during TURBT and electronic patient records. All data will be securely stored in Castor Electronic Data Capture, a validated electronic data capture system designed to prevent unauthorized access and ensure compliance with the General Data Protection Regulation. To maintain data completeness and allow for comprehensive analysis, all information collected up to the point of participant withdrawal or protocol deviation, including OCT measurements, cystoscopic video recordings, and histopathological findings, will be retained for subsequent evaluation.

To safeguard participant confidentiality, each enrolled individual will be assigned a unique participant ID code, with a corresponding participant ID code list maintained only when necessary for data traceability. The principal investigator will be responsible for securing the key to this code. In addition, individual OCT measurements will be assigned specific identifiers to ensure structured and organized data management. OCT data and cystoscopic video recordings will initially be stored on the OCT system and subsequently transferred to the local drive of the urology department on the secure Amsterdam UMC computer server using an encrypted external hard drive immediately after acquisition. Access to the local drive will be restricted to study investigators and the study monitor to ensure data security and confidentiality. Once the transfer is successfully completed, the data will be permanently deleted from the external hard drive. Upon completion of the study, all OCT images and cystoscopic video recordings will also be removed from the OCT system.

Robust data management protocols will be implemented to ensure data accuracy, security, and traceability. Data entry, coding, and security procedures will be conducted within Castor Electronic Data Capture, incorporating an audit trail to track all modifications. Paper-based case report forms will be securely stored, signed, and archived, while electronic data will be subject to automated validation procedures. Univariate data validations will be embedded within the Castor system, whereas multivariate validations, derivations, and calculations will be incorporated where applicable and documented in a dedicated data validation and derivation plan. The comprehensive data management strategy is outlined in this study's data management plan. In accordance with regulatory requirements, all participant data will be securely retained for a period of 15 years.

Missing data will be descriptively reported and discussed. Missing OCT measurements will be reported as part of the main outcomes. Missing histopathological data are not expected; in case of missing data, it will be described in the secondary outcomes section.

Statistical Methods

Primary Outcomes

Procedural feasibility will be achieved if images of both the tumor and normal bladder are obtained in more than 60% of the patients. The feasibility based on OCT imaging will be assessed by determining the percentage of images suitable for diagnosis out of the total number of images obtained in all patients. A panel, consisting of 2 urologists and 1 PhD candidate, blinded to clinical information, will individually analyze the OCT images. They will determine if the OCT images are suitable for diagnosis. The OCT measurements will be scored as suitable if (1) tissue is observed on the OCT image, (2) the tissue is within the focus range of the OCT, and (3) no movement artifacts are observed in the image. In case of disagreement, an experienced research fellow will be added to the panel, and the scoring will be discussed within this panel. Consensus will be reached when 3 of the 4 panel members agree. The data will be described and presented as percentages with 95% CIs. No statistical tests will be performed.

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Secondary Outcomes

The duration of OCT measurements (min) will be reported as medians with IQR. Tumor invasion based on OCT images will be determined by a panel of investigators. The panel will consist of 2 urologists, 1 PhD candidate, and 1 pathologist. The panel members will independently score the OCT images and classify them based on (1) whether there is a tumor present and (2) (if present) the tumor stage. In case of disagreement, an experienced research fellow will be added to the panel, and the scoring will be discussed within this panel. Consensus will be reached when 3 of the 5 members agree. The concluding tumor invasions will be descriptively compared to histopathological outcomes, with results presented as percentages with 95% CIs. Attenuation coefficients from OCT data will be analyzed and categorized into tumor grade categories, following the World Health Organization (WHO) 1973 and WHO 2016 grading systems. A descriptive comparison of OCT-based and histopathology-based tumor grades will also be displayed as percentages with 95% CIs. Associations between tumor stage and grade, as determined by OCT and histopathology, will be tested with chi-square or Fisher exact tests, as applicable. In addition, the panel will assess OCT images of the resection beds, reporting the percentage of evaluable images with 95% CIs. Finally, the urologist's WLC-based estimates of tumor invasion and grade will be compared to OCT findings and histopathological results, and the association will be tested with chi-square or Fisher exact tests, as applicable.

Monitoring

Data Monitoring

Data monitoring will be conducted by the Clinical Monitoring Center of Amsterdam UMC. The clinical research associates of the Clinical Monitoring Center operate independently of both the study and the research team, ensuring unbiased oversight. The monitoring committee is responsible for verifying that the rights and well-being of participants are protected; the collected study data are accurate, complete, and verifiable against source documents; and the study is conducted in accordance with the approved protocol, applicable laws, and regulatory requirements. The study-specific monitoring schedule and procedures are documented in a signed monitoring plan.

Safety Criteria and Reporting

AEs will be reported according to the Common Terminology Criteria for Adverse Events (version 5.0). All AEs will be reported up to 4 weeks after the study procedure. Serious AEs will be reported to the ethics committee. Serious AEs that are related to the surgical procedure, without a likely relation to the study intervention, are reported through yearly line listing to the ethics committee. These events are bladder perforation, bladder infection, and hematuria requiring bladder catheterization.

Ethical Considerations

Informed Consent

Patients will be informed about the study by their treating physician at the outpatient clinic. If interested, a second appointment will be planned with one of the investigators. All patients will be fully informed about the aims of this study, possible AEs, and the investigational procedure. Written informed consent is obtained from all participants before enrollment (refer to Multimedia Appendix 1 for the informed consent form). All physicians who may potentially see an eligible patient at the outpatient clinic are informed about the study procedures and criteria to ensure identification of potential participants.

Ethics Approval and Amendments

This study was approved on November 7, 2024, by the institutional review board of the Amsterdam UMC. All substantial amendments will be notified to the medical ethics review committee; nonsubstantial amendments will be recorded and filed by the sponsor. A summary of the trial progress will be submitted to the medical ethics review committee yearly, including information on the date of inclusion of the first participant, the number of participants included, the number of participants who have completed the trial, and serious AEs.

Provisions and Compensation

Provisions for ancillary and posttrial care are not applicable to this study design. The sponsor has insurance coverage for participants that provides compensation for injury or death directly attributable to the study.

Results

As of November 2025, 16 participants have been enrolled, and 13 have already successfully completed the study procedure. The projected end date of this study is November 2025, and results are expected to be published in March 2026.

Discussion

Anticipated Findings

The anticipated principal finding of this study is that the novel MEMS-based forward-looking OCT catheter is safe to use and feasible for generating in vivo cross-sectional images of the bladder wall and tumor during TURBT, with most images suitable for interpretation. This IDEAL phase 2a study represents a critical step in evaluating cystoscopic OCT as a potential imaging tool to aid bladder cancer diagnosis and staging.

The principal findings of this feasibility study will provide critical insights into the utility of the new OCT system in visualizing bladder wall architecture and tumor invasion and grading. Furthermore, this study will provide insights into the clinical and technical obstacles that new devices face when being integrated into the diagnostic process of bladder cancer. In comparison with the current gold standard—histopathological evaluation following TURBT—OCT may enable more immediate, noninvasive diagnostic support, potentially streamlining treatment decision-making. Previously, 3 other forward-looking OCT probes have been studied on bladder tissue and showed that OCT is able to distinguish different layers of the bladder and, in most studies, was able to distinguish malignant tumors from benign tumors [16-21,26,27]. However, the previously studied OCT systems available for bladder wall imaging had, among other constraints, a limited field of view

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and a low frames-per-second rate, limiting their ease of use and the quality of the OCT images [16,21,27]. In contrast, our system has incorporated technical improvements, such as an improved OCT system with an operating wavelength centered at 1060 nm—which is optimal for imaging in water and forward-looking MEMS-based scanning mirror technology—that altogether enhance image acquisition, resolution, and usability. Importantly, this study will also explore secondary outcomes such as measurement duration and the ability to image resection beds.

One strength of the study lies in its integration into the routine clinical workflow without introducing significant treatment delays. However, this study also has important limitations. Most notably, no histopathological samples are taken from areas of the bladder deemed "normal." This choice is deliberate and ethically justified; obtaining such biopsies would require additional surgical interventions that are not part of standard care and would therefore introduce unnecessary risks such as bladder perforation or bleeding. Instead, the assessment of the normal bladder wall will be based on the judgment of an experienced urologist during cystoscopy. Another limitation is the single-center design, which may limit the generalizability of the results because outcomes could be influenced by the urologist's level of experience. However, this limitation is acceptable for an IDEAL phase 2a feasibility study.

Within the IDEAL framework, future studies will aim to validate these findings in larger, multicenter cohorts, with structured training modules for OCT image interpretation, and incorporate learning curves in the study outcomes. Further development may include the integration of artificial intelligence–based image analysis to support real-time diagnosis. In future research, correlation of OCT findings with clinical outcomes such as recurrence or progression could also enhance its clinical relevance. Nevertheless, for integration into clinical practice, the cost-effectiveness of OCT compared to TURBT remains an aspect that should be further studied.

The findings from this study will be published in open-access peer-reviewed journals and will be presented at urology and imaging conferences. In addition, results will be shared with clinical and research communities through institutional networks and multidisciplinary meetings, enabling translation into larger-scale clinical trials and potential clinical implementation if further validated.

Conclusions

This trial aims to demonstrate the feasibility of using a newly designed MEMS-based OCT catheter and OCT system for the acquisition of diagnostic OCT images in human bladders. If the hypothesis is validated, it will lay the groundwork for a larger, multicenter trial to assess the diagnostic accuracy of OCT in staging and grading bladder cancer. The ultimate goal is to evaluate the potential role of this new OCT catheter and system as a real-time, noninvasive adjunct to standard cystoscopic assessment.

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Data Availability

Data sharing is not applicable to this study as no datasets were generated or analyzed during this study.

Authors' Contributions

Conceptualization: MJR, DMdB, JRO, JAN
Funding acquisition: JRO, DMdB
Methodology: MJR, DMdB, JRO, JAN
Project administration: MJR
Supervision: DMdB, JRO
Visualization: MJR
Writing—original draft: MJR
Writing—review and editing: MJR, DMdB, JAN, JRO

Conflicts of Interest

None declared.

Multimedia Appendix 1
Informed consent form.
[PDF File (Adobe PDF File), 265 KB - resprot_v14i1e76644_app1.pdf]

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Abbreviations

AE: adverse event
IDEAL: idea, development, exploration, assessment, and long-term study
MEMS: microelectromechanical systems
OCT: optical coherence tomography
AE: adverse event
TURBT: transurethral resection of the bladder tumor
UMC: University Medical Center
WHO: World Health Organization
WLC: white light cystoscopy

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Protocol

Prevalence of Metabolic Syndrome and Noncommunicable Disease Risk Factors in Andaman and Nicobar Islands, India, and Their Association With Ayurvedic Psychosomatic Constitution (Prakriti) and Socioeconomic Status: Protocol for a Cross-Sectional Study

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Abstract

Background: Metabolic syndrome (MetS) comprises several interrelated conditions, including central obesity, insulin resistance, hypertension, and dyslipidemia—all substantially raise the risk of cardiovascular disease and type 2 diabetes mellitus. National Family Health Survey–5 survey findings indicate that the Andaman and Nicobar Islands has a high risk of MetS due to the high prevalence of obesity, hypertension, and diabetes. Ayurveda highlights that an individual's psychosomatic constitution (Prakriti) plays a key role in determining disease susceptibility, prognosis, and treatment outcomes. Few studies have demonstrated the association and specific Prakriti types with diabetes, hypertension, dyslipidemia, insulin resistance, Parkinson disease, and rheumatoid arthritis. However, the association between MetS and Prakriti remains uninvestigated. Moreover, data on the prevalence of MetS in these islands are limited, and the variations reported in prevalence studies on MetS from mainland India point to challenges in generalizing those findings. Additionally, the unique geography, ethnicity, lifestyle, and health care infrastructure of the Andaman and Nicobar Islands further stress the need for this study.

Objective: This study examines the prevalence of MetS and noncommunicable disease (NCD) risk factors in the South Andaman district and their association with Prakriti and socioeconomic status (SES).

Methods: A cross-sectional study will be conducted with 1000 randomly sampled adult participants from the South Andaman district, Andaman and Nicobar Islands, India. In this study, participants aged 18 years and older who are willing to provide written consent will be included. The exclusion criteria include pregnant women, nonambulant individuals, and those who are unable to undergo Prakriti assessment. MetS will be assessed using the International Diabetes Federation criteria, and NCD risk factors will be recorded via the WHO STEPS (World Health Organization STEPwise approach to noncommunicable disease risk factor surveillance) instrument. Prakriti will be assessed using the Central Council for Research in Ayurvedic Sciences Prakriti Assessment Scale, and SES will be determined using the Modified Kuppuswamy Scale. Data analyses will include descriptive statistics to estimate MetS and NCD risk factor prevalence. Bivariate analyses (chi-square) will explore associations between the variables, quantifying strength with crude and adjusted odds ratios. A multivariable logistic regression will be used to adjust for confounders. Propensity score matching will serve as a sensitivity analysis. Significance is set at an α of .05, using STATA (version 16.1; Stata Corp LLC) software.

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Results: The study started in August 2024; as of June 2025, the survey covered 619 participants.

Conclusions: This study will provide crucial data on the prevalence of MetS and NCD risk factors in the South Andaman population and investigate associations between constitutional Prakriti types and SES with MetS and NCD risk factors. Despite the constraints inherent to its cross-sectional design, the research offers essential baseline information to support future studies on both Prakriti and MetS in this unique population.

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KEYWORDS

ayurveda; IDF criteria; international diabetes federation; metabolic syndrome; noncommunicable disease risk factors; Prakriti; socioeconomic status; WHO STEPS instrument

Introduction

Background

Metabolic syndrome (MetS) is a cluster of conditions that interlink to each other, such as central obesity, insulin resistance, high blood pressure (BP), and dyslipidemia, which substantially increase the risk of cardiovascular disease and type 2 diabetes mellitus [1]. MetS is also a precursor to many clinical disorders and hence plays an important role in the health situations of the present time [2]. The global prevalence of MetS ranges from 12.5% to 31.4% [3]. Population-based studies in India indicated MetS prevalence of 10% to 30% [4]. Systematic reviews on MetS prevalence in India reveal significant variation influenced by demographic factors, gender, ethnicity, urban-rural differences, diagnostic criteria, study settings, and geographic location [4,5]. This heterogeneity among mainland studies emphasizes the limitation in generalizing their findings to all population groups in India. Further, the Andaman and Nicobar Islands vary from mainland India due to their isolated geography, unique ethnic composition, distinct lifestyle patterns, and differing health care infrastructure [6,7]. Therefore, a population-based study on MetS in the Andaman and Nicobar Islands is needed to address these contextual differences and generate relevant public health data.

The Andaman and Nicobar Islands in India comprise 836 islands in the southeastern part of the Bay of Bengal in the Indian Ocean [8]. The islands' population was estimated to be 380,581 (males 202,871 and females 177,710) according to the 2011 census [9]. Most (2,38,142 individuals) of this population reside in the South Andaman district [10]. The proportion of people with overweight and obesity in the Andaman and Nicobar Islands is notably higher compared with many other states and the national average in India [11]. Both male and female overweight/obesity increased in the island between 2015-16 and 2019-20 [11]. Moreover, the prevalence of hypertension (25.3% in females and 30.2% in males) and diabetes (17.5% in females and 17.9% in males) is high in this area, according to National Family Health Survey–05 data [11,12]. Since the components of MetS in the Andaman and Nicobar Islands are high, there is a high possibility of the presence of MetS in this population.

According to the Prakriti concept (Ayurvedic psychosomatic constitution) in Ayurveda, every person has a specific body constitution defined by certain psychosomatic features [13]. As per the distinct physical, physiological, and psychological features, people can be divided into 7 different Prakriti types based on Dosha (Vata, Pitta, Kapha, Vata-Pitta, Vata-Kapha, Kapha-Pitta, and Vata-Pitta-Kapha) [13]. Ayurveda suggests that Prakriti can aid in various clinical scenarios like predicting disease susceptibility, determining illness prognosis, and guiding treatment selection [14]. As per the Prakriti concept, diseases manifest differently according to the individual's constitution [14]. A Pitta-dominant individual is more susceptible to diseases like peptic ulcers, hypertension, and skin disorders [14]. However, a Vata-dominant individual is more prone to musculoskeletal issues like back pain and joint degeneration, and a Kapha-dominant individual faces a higher risk of developing metabolic conditions such as obesity, diabetes, and atherosclerosis [14]. Although Ayurvedic theory proposes that Kapha-dominant Prakriti individuals are inherently more prone to metabolic disorders such as diabetes mellitus, obesity, and insulin resistance, empirical studies are still required to elucidate the potential relationship between Prakriti types and MetS. Based on the concept of Prakriti, several studies have been undertaken to explore the links between specific Prakriti types and various disease conditions. According to Mahalle et al [15], diabetes, hypertension, dyslipidemia, insulin resistance, and inflammatory markers are strongly associated with Vata Kapha and Kapha Prakriti types. Another study by Manyam et al [16] demonstrated a correlation between Vata Prakriti and an increased risk of developing Parkinson disease. Chinthala et al [17] established that those with Vata Prakriti are at a higher risk of rheumatoid arthritis. These findings from research reflect the significance of Prakriti in disease predisposition.

This study examines the prevalence of MetS and noncommunicable disease (NCD) risk factors among the South Andaman population. In addition, the study will also explore the relationship between Prakriti, MetS, NCD risk factors, and socioeconomic status (SES). However, no studies have examined the association between Prakriti and MetS, and no data on the prevalence of MetS in the Andaman and Nicobar Islands is available in the public domain. Hence, the study findings could help develop strategies for preventing and managing MetS and NCDs in the study area. Moreover, the research outcome will guide future research in similar contexts.

Study Objectives

Primary Objectives

The study aims to test whether the prevalence of MetS in the adult South Andaman population is significantly high, and to

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determine whether different Prakriti types are significantly associated with the occurrence of MetS as well as individual NCD risk factors in this population.

Secondary Objectives

The study intends to assess whether the prevalence of major NCD risk factors is significantly high in the adult South Andaman population and to examine whether SES is significantly associated with MetS.

Methods

Study Design

This research uses a cross-sectional approach with descriptive and analytical elements. MetS prevalence and risk factors of NCDs among the study population will be measured as part of the descriptive component. On the other hand, the analytical component examines the associations between Prakriti and SES with MetS and NCD risk factors.

Study Setting

This survey study focuses on the South Andaman district within the Andaman and Nicobar Islands. South Andaman district consists of 30 panchayats and 24 wards, serving as local self-government bodies [18]. The study will select 1000 samples from all these local administrative units (Panchayats and Wards) using a simple random sampling method. The ongoing study was approved and sanctioned by the Central Council for Research in Ayurvedic Sciences (CCRAS) in May 2024, and the total duration of the research is 18 months.

Participants

The study will include adult individuals aged 18 years or older of either sex who are willing to participate and provide written consent. Pregnant women, nonambulant individuals, and persons who are unable to undergo Prakriti assessments will be excluded from the study. Before enrolling in the study, participants will receive clear and comprehensible verbal and written information regarding the study's purpose, procedures, potential risks, and benefits. The investigator will ensure that participants fully understand these details. Participation remains entirely voluntary, and participants can withdraw from the study without facing any adverse consequences. A signed and witnessed Informed Consent form is obtained from participants before initiating any study-related activities.

Variables

The study identifies MetS, NCD risk factors, Prakriti, and SES as outcome variables. MetS is diagnosed based on a combination of waist circumference/BMI, fasting blood glucose, BP, triglycerides (TG), and high-density lipoproteins (HDL) cholesterol levels, following the International Diabetes Federation [19,20]. Central obesity is defined using ethnicity-specific waist circumference thresholds (≥90 cm for males and ≥80 cm for females among Chinese, Malay, and Asian-Indian populations) or a BMI >30 kg/m^2 [20]. Individuals meeting the criteria for central obesity undergo additional laboratory investigations. A diagnosis of MetS is confirmed if central obesity is accompanied by at least 2 of the following conditions: elevated BP (≥130/85 mm Hg or treatment of previously identified hypertension), elevated fasting blood glucose (≥100 mg/dL, or previously diagnosed type 2 diabetes mellitus), elevated TG levels (≥150 mg/dL or specific treatment for this lipid abnormality), or reduced HDL cholesterol levels (<40 mg/dL in males, <50 mg/dL in females, or specific treatment for this lipid abnormality) [20].

Prakriti is classified into 7 distinct types based on Dosha predominance [13]. Three single Dosha-predominant Prakriti types exist: Vata, Pitta, and Kapha [13]. Additionally, there are 3 dual Dosha-predominant types: Vata-Pitta, Vata-Kapha, and Pitta-Kapha [13]. Finally, 3 Dosha-predominant Prakriti types encompass all 3 Doshas: Vata-Pitta-Kapha [13]. Each individual's Prakriti is assigned to one of these 7 categories using the standardized Prakriti Assessment Scale developed by the CCRAS [21].

The WHO STEPS (World Health Organization STEPwise approach to noncommunicable disease risk factor surveillance) instrument [22] includes behavioral and physical measurements. Behavioral measurements comprise tobacco and alcohol use, dietary patterns, physical activity, history of raised BP, diabetes, elevated cholesterol, cardiovascular disease, lifestyle advice, and cervical cancer screening (for women). Physical measurements include BP, height, weight, waist circumference, hip circumference, and heart rate. Due to feasibility constraints, biochemical measurements specified in the WHO STEPS questionnaire that are not diagnostic of MetS (such as urinary sodium and creatinine) were excluded.

SES is determined based on the household head's occupation, education level, and the total family income. Participants are categorized into 5 SES groups: upper class, upper middle class, lower middle class, upper lower class, and lower class. SES is evaluated using the Modified Kuppuswamy Scale [23].

Data Collection

This study enrolment commenced on August 28, 2024, following approval from the Institutional Ethics Committee of the Regional Ayurveda Research Institute, CCRAS, Port Blair, and the district administrative authorities of South Andaman. A research team comprising a primary investigator, a coinvestigator (Co-I), a senior research fellow, and an assistant is actively engaged in data collection. The team received comprehensive training on data collection methodologies and tools to ensure accuracy and objectivity. Participants are surveyed through direct interviews, laboratory investigations, and physical examinations.

The study team is collaborating with Panchayath/Municipal (local governing body) representatives, Tribal council members, local health authorities, and Anganwadi (mother and childcare center) staff for implementing the study. Data collection methods and questionnaires are thoroughly explained to these representatives before the survey to ensure informed consent from all the participants. This ground-level coordination in the community fosters rapport and effective communication with participants, reducing reluctance, misinterpretation, and social stigma related to data collection and Prakriti classification. All the survey participants are being provided with contact information of the local health care workers, Anganwadi staff,

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Panchayath/Municipal representatives, Tribal council captains, and the study Investigators to ensure prompt notification and appropriate medical care in case of any complications from venipuncture.

Venous blood samples are drawn from the participant's forearms. Biochemical parameters, including TG, HDL, and fasting blood sugar, are measured in participants who fast for 12 hours before sample collection. The samples are collected following standard procedures and analyzed using a fully automatic biochemistry analyzer (Snibe Bioassays 240 plus, manufactured in 2021). Standard laboratory procedures are used for all necessary investigations.

BP is measured using an automated BP monitor (Omron digital BP apparatus HEM-8712, manufactured in 2021). Measurements are taken while participants are resting, with their arms placed on a nearby table so the cuff is at heart level. BP is measured 3 times, and the average of the 3 readings is analyzed.

Anthropometric measurements, including height, weight, waist circumference, and hip circumference, are taken using standardized methods. Height is measured with a tension-free, standardized measuring tape, and weight is recorded with a digital weighing machine (Smartcare electronic scale, manufactured in 2021). BMI is calculated by dividing weight (kg) by height squared (m^2). Waist circumference is measured at the end of a normal exhalation in a horizontal plane, halfway between the lower margin of the ribs and the upper edge of the iliac crest. In contrast, hip circumference is measured at the largest circumference around the buttocks.

Bias

This study is susceptible to 2 types of biases: selection bias and information bias. Since the survey team conducts door-to-door surveys during working hours, there is a higher likelihood of sampling bias, as the respondents are more likely to be nonworking or older individuals at home during this time. Interviewer bias may arise because cross-verification or secondary review is not feasible while collecting data related to Prakriti and NCD risk factors. Due to subjective variation in the recalling ability of participants, recall bias is also possible in the study.

Sample Size Calculation

Based on the findings of the Krishnamoorthy et al [4] study, which reported a prevalence of MetS of 30% in Indian adults, a sample size calculation was performed. A relative margin of error of 10% (d=0.03) and a 95% confidence level (α=.05) are adopted.

α=.05; hence $Z_{1-\alpha/2} = 1.96$

p>=(1–q) =30%

n=897

The study considered a 10% nonresponse; hence, the final sample size will be 897 + 90 = 987 (approximately 1000). The study will take 1000 adult participants from the South Andaman district, Andaman and Nicobar Islands, India. Participants will be chosen through random sampling using the area's voter list. The voter list is the electoral roll maintained by the Election Commission of India. Each voter has a unique ID, name, gender, age, and address at the polling station level. For South Andaman, the roll is organized by Assembly Constituency, polling stations, and part numbers. After assigning each voter a number, the entire voter roll will be treated as the population frame. The simple random sampling will be performed to select 1000 participants.

Statistical Analysis

The data will be collected in a single round and subjected to rigorous checks to ensure accuracy and completeness. Any missing or incomplete responses will be addressed through Bayesian imputation, which allows for more robust handling of missingness by incorporating prior information and uncertainty in the estimation process. Following verification and imputation, fundamental descriptive analyses will be conducted to estimate the prevalence of MetS, identify the distribution of NCD risk factors, and describe the baseline demographic characteristics of the study participants. Categorical variables will be summarized as frequency and percentage (n [%]), while continuous variables will be expressed as mean (SD). To explore associations, bivariate analyses will examine the relationship between Prakriti (Ayurvedic constitutional type), NCD risk factors, and SES with the presence of MetS. The chi-square test will be applied to test statistical significance in categorical comparisons. Both crude odds ratios and adjusted odds ratios will be estimated to quantify the strength of associations. A multivariable logistic regression model will compute adjusted odds ratios while accounting for potential confounders. In addition, propensity score matching will be applied as a sensitivity analysis to validate the robustness of the study findings by balancing observed covariates between comparison groups. All statistical tests will be conducted at a 5% level of significance (α=.05). The complete analysis will be performed using STATA software (version 16.1; Stata Corp LLC).

Data Safety and Monitoring

Using Microsoft Excel software, data collected from the field using paper case record forms (CRFs) is converted into electronic CRFs. Both paper and electronic CRFs will be maintained by the principal investigator (PI). Regular monitoring of data collection and data entry processes will be conducted by either the PI or Co-I throughout the project. The electronic CRFs will undergo cross-verification with paper CRFs by the PI or Co-I to ensure data accuracy.

To safeguard participant confidentiality, documents revealing personal information will only be strictly restricted to project staff. Electronic files will be password-protected, and access to the dataset will be limited to authorized individuals. The statistical department at the CCRAS headquarters will analyze the data. Data will be securely stored for a minimum of 5 years upon completion of the study. An external Data and Safety Monitoring Board will oversee the study to ensure ethical conduct and participant safety.

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Ethical Considerations

The study received ethical clearance from the Institutional Ethics Committee on July 16, 2025 (F. No. 11-5/2024/RARI/IMR-Metabolic Syndrome/264). All study procedures adhered to the ethical principles outlined in the ICMR Ethical Guidelines (2017) and the WMA Declaration of Helsinki. The participant information sheet detailed the purpose of the study, procedures for participation, potential risks and benefits, and provided contact information for the Principal Investigator and Co-Investigators. Field staff were instructed to inform all eligible participants that participation was entirely voluntary and that refusal to participate would not impact their access to health care services. Personal data are handled with strict confidentiality to safeguard individual privacy, and no identifiable information was included in publications without prior informed consent.

Results

By June 2025, 619 participants had been enrolled, accounting for 62% of the target sample size, with data entry completed for 480 participants (Figure 1). Of these, 56.46% (n=271) were female, and 43.54% (n=209) were male, with a mean age of 39.88 (SD 14.41) years. Occupational distribution revealed that 40.83% (n=196) were homemakers, while among the employed, 11.25% (n=54) were government employees, 18.54% (n=89) were in the private sector, and 9.79% (n=47) were self-employed. Students comprised 6.25% (n=30) of the sample, and 4.17% (n=20) were unemployed. Educational attainment showed that 42.50% (n=204) had completed primary or secondary education, 24.17% (n=116) had completed high school, and 21.46% (n=103) held a college/university or higher qualification. A small proportion had lower than primary school education (26/480, 5.42%) or no formal schooling (31/480, 6.46%). Marital status analysis indicated that 78.33% (n=376) were married, 16.25% (n=78) were unmarried, and 5.42% (n=26) were widowed.

Figure 1. Flowchart showing the methodology of the study. CCRAS: Central Council for Research in Ayurvedic Sciences; IDF: International Diabetes Federation; MetS: metabolic syndrome; NCD: noncommunicable disease; WHO STEPS: World Health Organization STEPwise approach to noncommunicable disease risk factor surveillance.

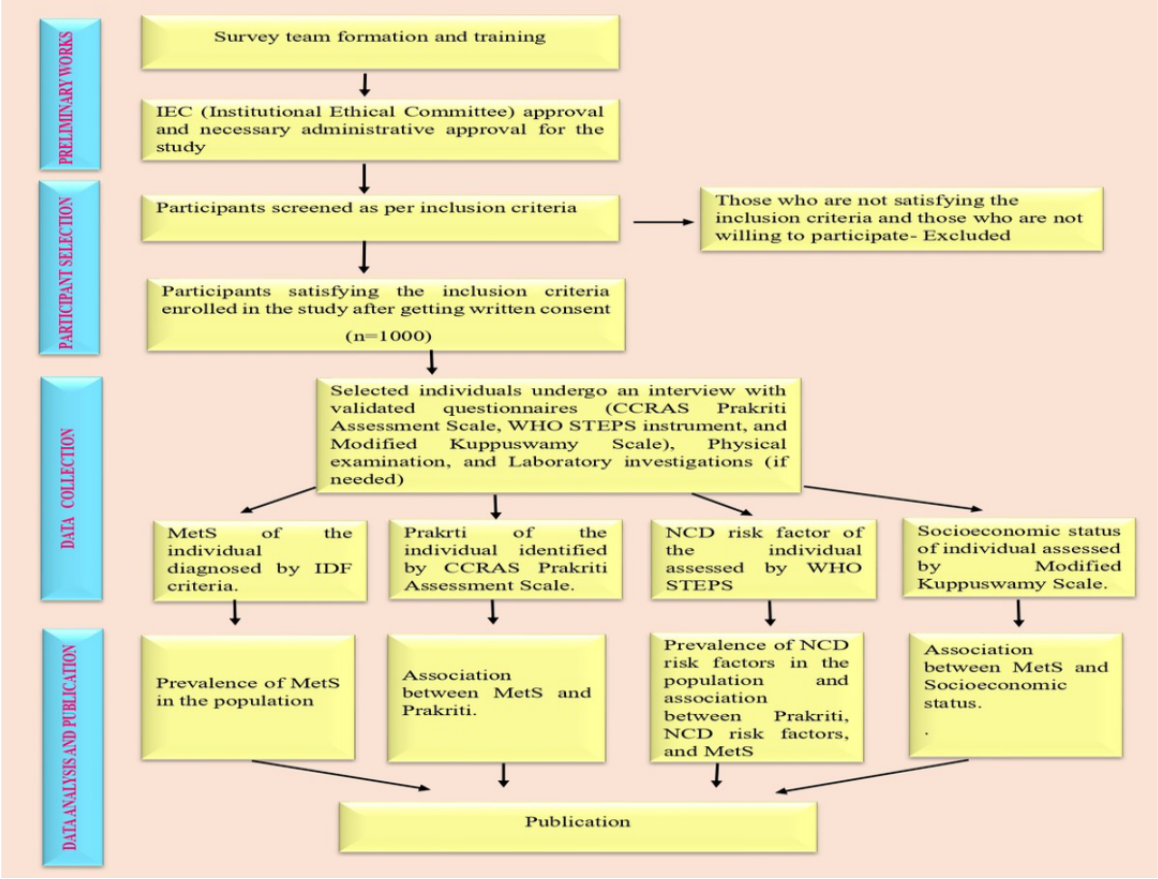

Discussion

Expected Outcomes and Potential Impact

The study is anticipated to provide robust evidence on the prevalence of MetS in the adult South Andaman population, assessing whether it is similar to or higher than in other regions of India. This study's findings thus help further explore inter-regional variations in the prevalence of MetS in India. Further, drawing on previous research by Mahalle et al [15], which demonstrated strong associations of Vata-Kapha and Kapha Prakriti types with diabetes, hypertension, dyslipidemia, insulin resistance, and inflammatory markers, this study is expected to reveal significant associations between specific Kapha-dominant Prakriti types and the occurrence of MetS, as

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well as individual NCD risk factors. Evidence indicating that Kapha-dominant individuals exhibit higher BMI, waist-hip ratio, and fasting blood glucose levels supports the hypothesis of a constitutional predisposition to metabolic disorders, which this study aims to substantiate further [24].

A critical limitation identified in the previous study was the lack of comprehensive dietary and lifestyle data documentation [15]. This study addresses this gap to some extent by using the WHO STEPS questionnaire. This scientifically validated tool systematically captures fruit and salt consumption patterns and physical activity levels. This standardized approach will enable exploration of how dietary and lifestyle factors, which are the determinants of NCDs, influence the manifestation of MetS in this unique population.

The study is expected to reveal a substantial burden of major NCD risk factors, including tobacco use, alcohol consumption, physical inactivity, unhealthy diet, and obesity. This expectation is supported by the findings of Ramu et al [6] from a community-based cross-sectional study in rural South Andaman, which demonstrated an alarmingly high burden of behavioral and clinical risk factors of NCD among adults. The outcomes of this study will explore ongoing trends in NCD risk factor burden and assess changes resulting from public health interventions since the previous assessment. SES is anticipated to positively associate with MetS in higher socioeconomic groups in urban study settings, which is consistent with established literature [25].

These outcomes are expected to provide valuable insights into the epidemiological and Prakriti-based determinants of MetS in the South Andaman population. The comprehensive data will provide evidence for future constitutional medicine research and personalized health care approaches. The study will also establish baseline data for longitudinal monitoring of NCD trends and evaluation of preventive program effectiveness in island populations with unique demographic and environmental characteristics.

Dissemination of Results

A multi-faceted dissemination strategy will be formed to maximize the impact of findings on MetS and Prakriti associations in the South Andaman population. The main manuscript will be submitted to high-impact journals to reach a broad scientific audience. Key results will be presented at national conferences and communicated directly to regional health officials. Information materials like infographics and social media summaries will be created for broader public engagement.

Strength

The study uses standardized and validated questionnaires to collect data on Prakriti, NCD risk factors, and SES to ensure validity and reliability. This research explores the prevalence of MetS in the South Andaman population, a setting with limited existing data. It also examines potential associations between Prakriti, MetS, NCD risk factors, and SES. The study aims to provide novel insights that contribute meaningfully to the existing literature by investigating these relationships within this relatively understudied population.

Limitations

In this study, incorporating an objective parameter, such as a biomarker of MetS, could have further strengthened the acceptance of any identified correlations. However, this study did not include such a biomarker due to feasibility constraints. According to Ayurveda, Prakriti is considered a stable constitutional characteristic since birth in an individual; a cross-sectional design can only reveal associations with MetS and cannot establish causal relationships. Likewise, the expected association between socioeconomic status and MetS in this design is limited by the inability to determine directionality or temporal sequence. Therefore, the findings should be interpreted strictly as associations rather than causal evidence.

Additionally, the study is subject to its inherent limitations of cross-sectional designs, including potential selection and information biases. Although statistical methods will be applied to mitigate potential biases, they should be recognized to ensure a transparent and robust interpretation of the results. While the applicability of the findings may primarily pertain to the Indian population, replication in other populations is feasible since Prakriti is not influenced by race or ethnicity [13]. This study did not include the Particularly Vulnerable Tribal Group population in the South Andaman district due to feasibility constraints. These limitations underscore critical knowledge gaps that warrant further investigation in future studies.

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Data Availability

The datasets used or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

ALM conceptualized the protocol and made a draft article. AZA, ABA, and LSR provided substantial input for the protocol design and edited the article. AT calculated the sample size and made the statistical analysis plan during protocol design. SKD and MM are coordinating the study day-to-day, and both reviewed the article. BCS, NS, and RA reviewed the article and were doing overall coordination and monitoring of the study. All the authors approved the final article.

Conflicts of Interest

None declared.

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Abbreviations

BP: blood pressure
Co-I: coinvestigator
CCRAS: Central Council for Research in Ayurvedic Sciences
CRF: case record form
HDL: high-density lipoproteins
MetS: metabolic syndrome
NCD: noncommunicable disease
SES: socioeconomic status
PI: principal investigator
TG: triglycerides
WHO STEPS: World Health Organization STEPwise approach to noncommunicable disease risk factor surveillance

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Protocol

The White Matter Hyperintensity Shape and Brain Clearance (WHIMAS) Study for Identification of Novel 7T Magnetic Resonance Imaging Markers of Cerebral Small Vessel Disease: Protocol for a Cross-Sectional Study

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Abstract

Background: Sporadic cerebral small vessel disease (SVD) has a heterogeneous underlying pathology, and current SVD magnetic resonance imaging (MRI) markers do not accurately capture this heterogeneity. Novel ultrahigh-field (7T) brain MRI markers provide a window of opportunity to study early changes and potential determinants of SVD. White matter hyperintensity (WMH) shape is a relatively novel MRI marker of SVD and has shown prognostic potential. However, the exact microstructural changes within or surrounding WMHs or potential causes related to WMH shape variations are unknown. Furthermore, impaired brain clearance via the recently discovered brain clearance system may be another early change or potential cause of SVD.

Objective: In the White Matter Hyperintensity Shape and Brain Clearance (WHIMAS) study, we aim to assess the link between WMHs—their shape in particular—and brain clearance and other MRI markers on ultrahigh-field (7T) brain MRI and show whether these markers are associated with cognitive functioning in older adults with memory complaints.

Methods: This is a cross-sectional study conducted at the Leiden University Medical Center. A total of 50 outpatients from the memory or geriatric clinic aged ≥65 years will be recruited for a 3T and 7T MRI scan (including clinical structural scans, eg, 3D T1-weighted, 3D fluid-attenuated inversion recovery), and experimental scans such as cerebrospinal fluid (CSF)–selective T2-prepared readout with acceleration and mobility encoding (CSF-STREAM) and the relationship between blood oxygen level–dependent [BOLD] signals and CSF flow) and magnetic resonance fingerprinting, as well as a standardized neuropsychological test battery (domains: memory, executive function, visuoconstruction, and processing speed). We will assess WMH shape markers (solidity, convexity, concavity index, fractal dimension, and eccentricity) and brain clearance markers (CSF mobility and the relationship between blood oxygen level–dependent signals and CSF flow) and study their relationship to other MRI markers and cognitive functioning using multivariable regression analyses.

Results: Patient inclusion started in January 2023, and study enrollment of patients is expected to finish in the second quarter of 2027, whereas the main results are expected to be published in the first quarter of 2028.

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Conclusions: We aim to understand variations in WMH shape and find their relationship to cerebral SVD and markers of brain clearance and cognitive functioning. WMH shape and brain clearance markers early in the disease process of SVD are extremely important as they may represent a basis for future patient selection for lifestyle interventions or for treatment trials aimed at the prevention of dementia.

Trial Registration: ClinicalTrials.gov NCT06010511; https://clinicaltrials.gov/study/NCT06010511

International Registered Report Identifier (IRRID): DERR1-10.2196/77681

(JMIR Res Protoc 2025;14:e77681) doi:10.2196/77681

KEYWORDS

cerebral small vessel disease; dementia; cognitive impairment; brain clearance; magnetic resonance imaging

Introduction

Dementia is often characterized by a combination of neurovascular and neurodegenerative disease processes, and mixed pathologies are common [1]. The most common mixed pathology is Alzheimer dementia and cerebral small vessel disease (SVD) [2,3]. SVD contributes to the clinical phenotype of dementia in approximately 45% of cases [2-4]. There are 2 main types of SVD in an aging population. One is SVD due to arteriosclerosis, often related to hypertension [5]. The other one is cerebral amyloid angiopathy, characterized by progressive amyloid accumulation in the vessel walls [5]. Current SVD markers such as white matter hyperintensities (WMHs) of presumed vascular origin are unspecific, and they fail to accurately capture the heterogeneity of SVD pathology. Therefore, novel brain magnetic resonance imaging (MRI) markers are needed to identify early changes and potential determinants of SVD. These markers are extremely important early in the disease process of SVD as they may represent a basis for future patient selection for lifestyle interventions or outcome markers for treatment trials such as those currently being developed for cerebral amyloid angiopathy [6] aimed at the prevention of dementia.

WMHs are the key brain MRI manifestation of cerebral SVD [7]. Approximately 92% of all individuals aged >60 years have WMHs [8-10], and a higher WMH burden is a risk factor for occurrence of stroke and dementia [10]. In particular, the volume of WMHs has been extensively studied, but this is a generic and nonspecific marker that only has modest prognostic value [11]. Although there is considerable variation in the shape of WMHs, this marker has received little attention [12]. Recent studies have shown that normal-appearing white matter around WMHs that progressed on follow-up MRI scans already showed changes in structural integrity and hemodynamics at baseline [13,14]. Furthermore, WMHs typically localize at vascular endzones and progress along more proximal parts of the perforating arteries [15]. How the perforating arteries are affected depends on the underlying pathological changes, such as large vessel atheromas at the origin of perforating arteries, small vessel atheromas, or microembolisms [16,17]. These pathological changes may lead to hypoperfusion, defective cerebrovascular reactivity, and blood-brain barrier dysfunction [11], which in turn may be related to increase in WMHs and, thus, also to changes in their shape [12,17]. Previous studies have also indicated that WMH shape may provide a better indication of underlying pathophysiological mechanisms than WMH volume alone and may harbor strong prognostically relevant information [12,18-20].

SVD is a heterogeneous disease with many possible underlying causes. An important factor leading to brain changes in SVD might be impaired clearance of waste products, which has been linked to aging and dementia pathology [7]. The process of brain clearance is postulated to be partly driven by the brain clearance system, where cerebrospinal fluid (CSF) and interstitial fluid “flush” brain tissue and transport waste products out of the brain via perivascular spaces (PVS). Some first studies have shown that, in cerebral amyloid angiopathy and Alzheimer dementia, brain clearance function might be impaired [21]. Currently, brain clearance–related processes can only be studied invasively in humans, for example, through contrast-enhanced MRI following intrathecal injection [22]. This limitation makes it difficult to implement research related to brain clearance dysfunction into clinical study protocols. However, recently developed novel ultrahigh-field (7T) brain MRI markers provide a window of opportunity to study the human brain clearance system in a noninvasive way.

In the White Matter Hyperintensity Shape and Brain Clearance (WHIMAS) study, we aim to study the link between WMHs, and especially their shape, and brain clearance and other MRI markers on high-field (3T) and ultrahigh-field (7T) brain MRI. Furthermore, we aim to study the relationship between WMH shape and brain clearance markers (eg, the relationship between blood oxygen level–dependent [BOLD] signals and CSF flow, also referred to as BOLD-CSF coupling, and CSF mobility) and cognitive functioning (domains: memory, executive function, visuoconstruction, and processing speed).

Studying WMH shape and brain clearance markers in SVD is important because, at an early stage, cerebral SVD is a target for preventive treatment that may postpone or even prevent the occurrence of dementia and stroke. Our study contributes to research into early detection of dementia by first investigating potential markers in a population with the disease to identify markers that might also be relevant in larger studies in healthy older individuals. We specifically strive for early detection of the potentially treatable or modifiable part underlying the dementia phenotype, namely, SVD. Previous studies have already shown that early lifestyle interventions in populations at risk can slow the pathophysiological processes of cerebral SVD [23-25]. However, it is currently impossible to conduct early identification of individuals who have an increased risk of dementia, who may benefit most from available lifestyle

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interventions or from inclusion in treatment trials aimed at prevention. With our study, we aim to pave the way for personalized medicine approaches by finding brain MRI biomarkers that, in the future, can identify these individuals at increased risk of dementia based on SVD burden.

Methods

Study Design

This is an observational cross-sectional study that will be conducted at the Leiden University Medical Center (LUMC). This study involves a whole-day visit to the LUMC for each participant and includes the following procedures: a 3T brain MRI scan of 60 minutes, a 7T brain MRI scan of 60 minutes, a neuropsychological assessment, and questionnaires on demographics and vascular risk factors. An overview of the study procedures can be found in Figure 1. The objectives of this study are as follows: (1) to study the association between a more irregular WMH shape and anatomical, hemodynamic, and white matter integrity abnormalities on MRI; (2) to study the association between WMH shape and cognition or other cerebral SVD markers; and (3) to study the association between novel MRI markers of brain clearance and both cerebral SVD markers and cognition.

Figure 1. Overview of the study procedures. 3D T1: T1-weighted scan; BOLD-CSF: blood oxygen level–dependent signal and cerebrospinal fluid coupling; CSF-STREAM: cerebrospinal fluid–selective T2-prepared readout with acceleration and mobility encoding; DWI: diffusion-weighted scan; FLAIR: fluid-attenuated inversion recovery; MR: magnetic resonance; MRI: magnetic resonance imaging; SWI: susceptibility-weighted scan; T2: T2-weighted scan.

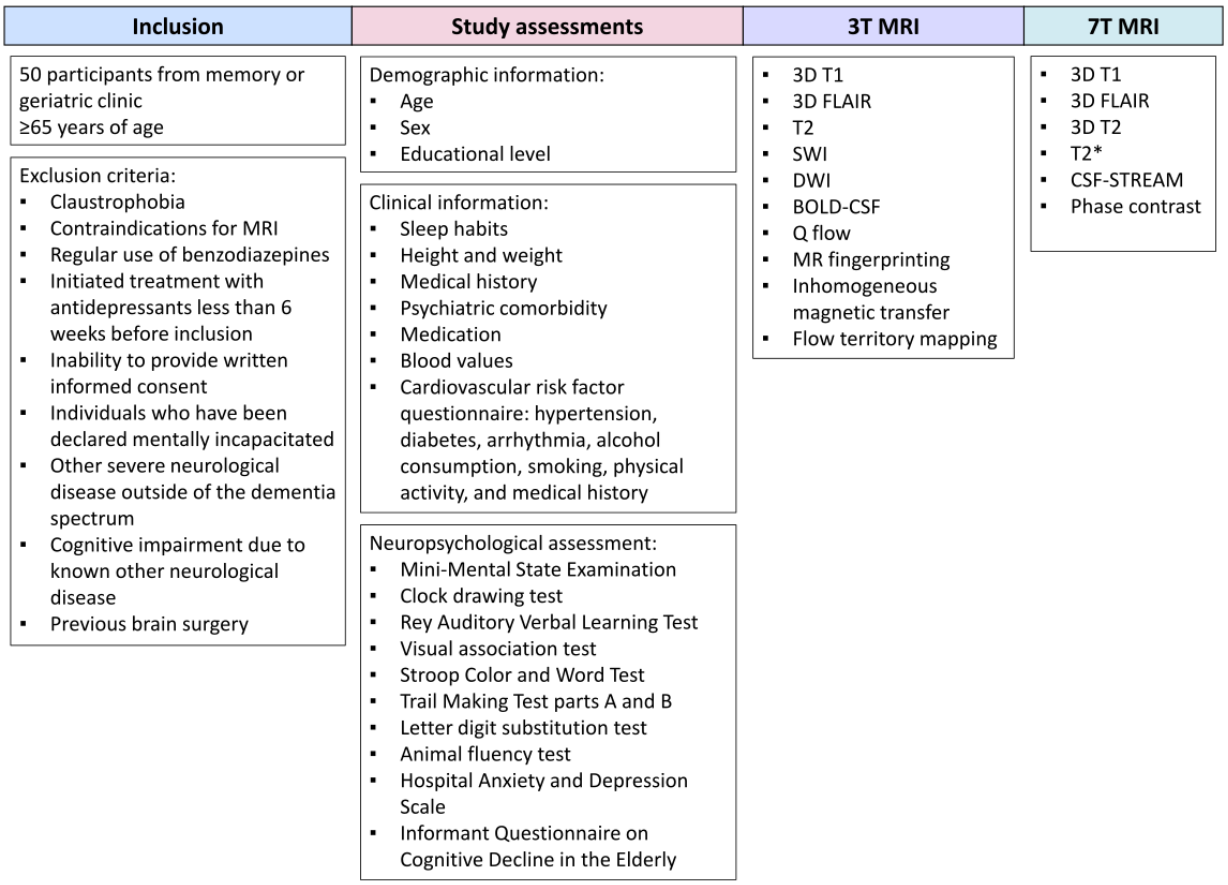

Population

We will prospectively include 50 outpatients aged >65 years with memory complaints from the memory or geriatric clinic in one of their first visits to LUMC (Leiden, the Netherlands), Alrijne Hospital (Leiden, the Netherlands), or Haga Hospital (The Hague, the Netherlands). All participants provide written informed consent before any study procedures. This study involves 3T and 7T MRI and newly developed sequences and markers, especially for brain clearance, which have not been applied in patient populations before. Therefore, we conducted the sample size calculation based on the WMH shape analysis. To provide a frame of reference, we performed a sample size calculation using data from a previous study [26]. The linear regression on hypertension and convexity, corrected for age and sex, was conducted using data from 71 older adults without dementia. The same WMH shape analysis pipeline was used in the previous study as we aim to use it in this study. Using the data from the significant results of the aforementioned study, the sample size calculation conducted in G*Power [27] (input parameters: effect size=0.1; α=.05) showed a result of 79 participants. As the data used in the calculation were obtained from community-dwelling individuals, we expect higher effect sizes in our study, which comprises a memory clinic population. In this population, the prevalence and severity of SVD and, thus, WMHs will be higher, justifying our assumption of

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increased power. At the same time, we do not want to risk an underpowered study. For example, in a case-control study comparing patients with type 2 diabetes with healthy controls, an average effect size of 0.37 for a more irregular WMH shape was found [12]. To illustrate this, we calculated the sample size with 2 different effect sizes that are higher than the one used in the initial calculation (0.2 and 0.3; α remained at .05) but still lower than 0.37 (as found by de Bresser et al [12]). These calculations resulted in a sample size of 42 or 29 participants, which was obtained using the effect sizes of 0.2 and 0.3, respectively. Therefore, 50 participants should provide the necessary statistical power to overcome biological and clinical variation.

To be eligible to take part in this study, a participant must meet all the following criteria: receipt of care in the outpatient memory clinic or the geriatric clinic at LUMC or the memory clinic at Alrijne Hospital or Haga Hospital, age of >65 years, and eligibility for MRI. Moreover, the participants must have native-level proficiency in Dutch due to the requirements of the neuropsychological assessment.

A potential participant who meets any of the following criteria will be excluded from this study: (1) claustrophobia; (2) contraindications for MRI, such as metal implants or pacemakers; (3) regular use of benzodiazepines; (4) initiation of treatment with antidepressants less than 6 weeks before inclusion; (5) inability to provide written informed consent (assessed by the treating physician); (6) individuals who have been declared mentally incapacitated; (7) other severe neurological disease outside of the dementia spectrum; (8) cognitive impairment due to known other neurological diseases; and (9) previous brain surgery.

Clinical Data

We will collect basic demographic information, including age, sex, and educational level. Information about medical history, psychiatric comorbidity, medication, and current blood values are extracted from the clinical files of the participants. Furthermore, a cardiovascular risk factor questionnaire will be used to gather information about hypertension, diabetes, arrythmia, alcohol consumption, smoking, physical activity, and medical history. We will also assess sleep habits using an adapted version of the Pittsburg Sleep Quality Index [28]. The sleep questionnaire will be included because of the influence of sleep on the brain clearance system.

The following tests will be included in the neuropsychiatric assessment: (1) Mini-Mental State Examination [29], (2) clock drawing test [30], (3) 15-Word Verbal Learning Test (immediate and delayed) [31,32], (4) visual association test [33], (5) Stroop Color and Word Test (40-item version) [34], (6) Trail Making Test parts A and B [35,36], (7) letter digit substitution test [37], (8) animal fluency test [38], (9) Hospital Anxiety and Depression Scale [39], and (10) Informant Questionnaire on Cognitive Decline in the Elderly [40].

MRI Scans

All MRI scans will be conducted at the LUMC using a 3T Philips Ingenia Elition and a 7T Philips Achieva MRI scanner (Philips Healthcare). The MRI scan protocols are shown in Table 1.

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Table 1. Magnetic resonance imaging (MRI) scan protocols on the 3T and 7T MRI scanners.

	Purpose	Parameters	Acquisition resolution (mm^3)	FOV[a] (mm^3)	Acquisition time	Additional information
3T MRI						
3D MPRAGE[b] (T1 weighted)[c]	Anatomical information	TR[d]=9.9 ms and TE[e]=4.6 ms	1 mm isotropic	256 × 256 × 170	4 min, 20 s	FA[f]=8°
3D FLAIR[c,g]	WMH[h] and lacunes	TR=4800 ms and TI[i]=1650 ms	1 mm isotropic	220 × 220 × 175	4 min, 48 s	Refocusing angle=40°
2D TSE[j] (T2 weighted)[c]	Perivascular spaces and arteries	TR=4490 ms and TE=80 ms	0.40 × 0.50 × 3.00	230 × 183 × 150	2 min, 15 s	FA=90°
3D SWI[c,k]	Iron, microbleeds, and superficial siderosis	TR=31 ms and TE=7.20 ms	0.60 × 0.60 × 2.00	220 × 182 × 130	2 min, 35 s	FA=17°
2D DWI[c,l]	Acute or recent ischemic lesions	TR=3206 ms and TE=67 ms	1.96 × 2.44 × 5.00	220 × 220 × 148	38 s	b-value=0, 1000
BOLD-CSF[c,m]	CSF[n] hemodynamics coupling	TR=370 ms and TE=25 ms	2.88 × 2.88 × 5.50	230 × 230 × 115	5 min, 7 s	FA=40°
2D phase contrast (Q flow)[c]	Large vessel flow	TR=15 ms and TE=7.2 ms	0.45 × 0.45 × 4.00	230 × 230	1 min, 2 s	Velocity encoding value=80 cm/s; planned using very fast phase-contrast angiograms
MR[o] fingerprinting	White matter structural integrity; myelin water imaging	TR=15 ms and TE=3.0 ms	1.00 × 1.00 × 4.00	240 × 240	5 min	FA range=10.0-60.0°; requires B1+ map
Inhomogeneous magnetization transfer (3D)	White matter structural integrity	TR=90 ms and TE=1.31 ms	2.29 × 2.29 × 5.00	220 × 220 × 96	7 min, 17 s	FA=7°; custom off-resonance parameters
Flow territory mapping	Perfusion territory scan	TR=4550 ms and TE=16 ms	2.50 × 2.56 × 5.00	240 × 240 × 96	4 min, 56 s	pCASL[p]
7T MRI						
MPRAGE (T1 weighted)[c]	Anatomical information	TR=4.2 ms and TE=1.9 ms	0.90 mm isotropic	246 × 246 × 174	2 min, 22 s	FA=7°
3D FLAIR[c]	WMHs and lacunes	TR=8000 ms and TI=2200 ms; TE=252 ms	0.70 × 0.70 × 1.40	240 × 209 × 180	5 min, 12 s	FA=90°
3D TSE (T2 weighted)[c]	Perivascular spaces and arteries	TR=3000 ms and TE=300 ms	0.75 mm isotropic	250 × 250 × 190	4 min, 6 s	FA=100°
T2*-weighted GRE[q]	Iron, microbleeds, superficial siderosis, and veins	TR=1830 ms and TE=25 ms	0.24 × 0.24 × 1.00	240 × 180 × 101	10 min, 32 s	FA=60°
CSF-STREAM[r]	Whole-brain CSF dynamics	TR=3430 ms and TE=497 ms	0.45 mm isotropic	250 × 250 × 190	21 min, 57 s	FA=90°
2D real-time phase contrast (2x)	Blood and CSF flow in and out of the cranium	TR=6.7 ms and TE=3.6 ms	1.72 × 1.72 × 10.0	110 × 110 mm	2 × 2 min, 8 s	Velocity encoding value=10 and 80 cm/s; FA=4°

[a]FOV: field of view.

[b]MPRAGE: Magnetization-Prepared Rapid Acquisition Gradient Echo.

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[c]Default imaging protocol at the scanner using standard Philips software.
[d]TR: repetition time.
[e]TE: echo time.
[f]FA: flip angle.
[g]FLAIR: fluid-attenuated inversion recovery.
[h]WMH: white matter hyperintensity.
[i]TI: inversion time.
[j]TSE: turbo spin echo.
[k]SWI: susceptibility-weighted imaging.
[l]DWI: diffusion-weighted imaging.
[m]BOLD-CSF: blood oxygen level–dependent signal and cerebrospinal fluid coupling.
[n]CSF: cerebrospinal fluid.
[o]MR: magnetic resonance.
[p]pCASL: pseudocontinuous arterial spin labeling.
[q]GRE: gradient-recalled echo readout.
[r]CSF-STREAM: CSF-selective T2-prepared readout with acceleration and mobility encoding.

Conventional (3T) brain MRI scans will be used to determine global and functional markers of cerebral SVD, such as WMH volume and presence of lacunes, microbleeds and superficial siderosis (on a 3D T1-weighted, 3D fluid-attenuated inversion recovery [FLAIR], susceptibility-weighted imaging, and diffusion-weighted imaging scan), and hemodynamics (flow territory mapping [41]). SVD markers will be assessed according to the second iteration of the Standard for Reporting Vascular Changes on Neuroimaging consensus criteria [42]. WMH shape will be calculated in the 3D space using an in-house developed pipeline, as described previously [18]. In brief, WMHs are segmented automatically from FLAIR MRI scans. Lateral ventricles are segmented from T1-weighted scans, and these ventricle masks are inflated by 3 mm and 10 mm. The inflated ventricle masks represent regional references for categorizing WMHs into periventricular, confluent, or deep subtypes. Examples of WMH segmentations and the shape markers are shown in Figures 2 and 3. Convexity, solidity, concavity index, and fractal dimensions will be determined based on the segmentations of the periventricular or confluent WMHs [18]. A lower convexity and solidity and higher concavity index and fractal dimension indicate more irregular shapes. For deep WMHs, fractal dimensions and eccentricity will be calculated [18]. Lower eccentricity indicates a rounder shape, and a higher fractal dimension indicates a more irregular shape of deep WMHs. The formulas of the WMH shape markers are shown in Figure 3. Moreover, total WMH volume, as well as the volumes of periventricular, confluent, and deep WMHs, will be calculated in milliliters.

Figure 2. Overview of the magnetic resonance imaging (MRI) processing pipeline for white matter hyperintensity (WMH) shape. WMHs are automatically segmented from fluid-attenuated inversion recovery (FLAIR) MRI scans. T1-weighted scans are used to segment the lateral ventricles. The lateral ventricle masks are inflated and used to delineate between periventricular or confluent, and deep WMHs. The WMH shape markers are then calculated on individual lesions.

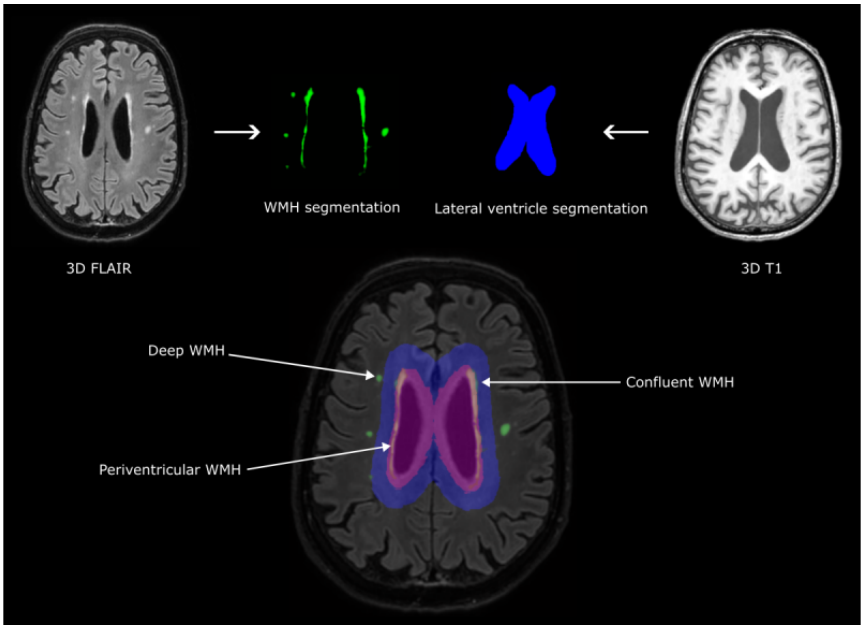

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Figure 3. Examples of shapes with high or low values of different shape markers. Solidity, convexity, concavity index, and fractal dimension are calculated for periventricular and confluent white matter hyperintensities (WMHs). Eccentricity and fractal dimension are the shape markers that are calculated for deep WMHs.

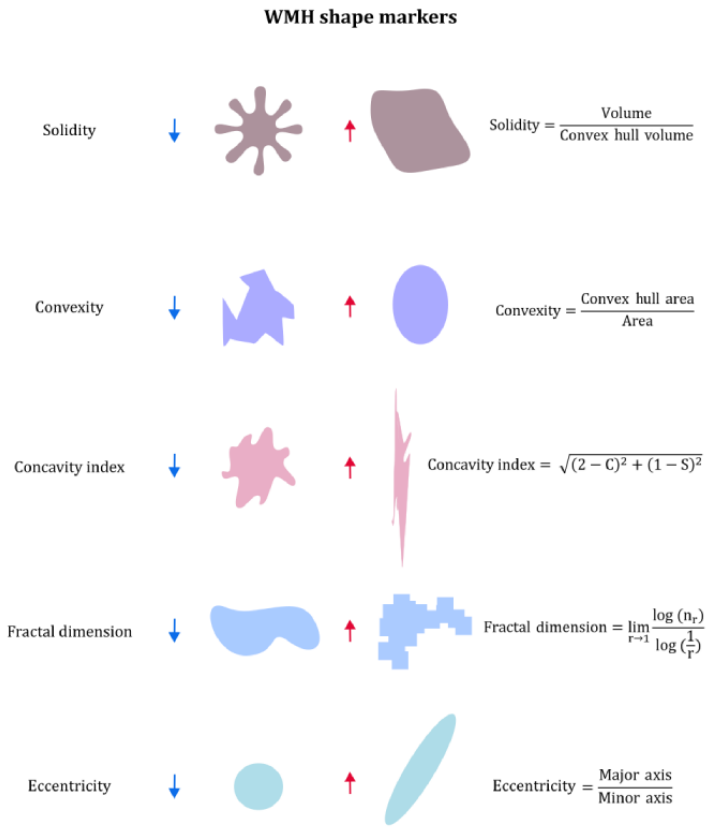

White matter structural integrity will be measured using a magnetic resonance fingerprinting (MRF) sequence [43] and an inhomogeneous magnetization transfer (ihMT) scan [44]. A gradient-spoiled MRF [43] sequence with an optimized flip angle pattern for T1 and T2 quantification [45] was used. The MRF sequence is sensitive to both T1 and T2 relaxation effects in a time-efficient manner. This allows for quantitative T1 and T2 measurements and quantification of underlying magnetization fractions of the tissue present in the brain [46,47]. A 3D gradient echo–based ihMT sequence was acquired in which we used interleaved off-resonance radio-frequency saturation pulses to isolate dipolar effects, which have been linked to myelin [44]. These 2 sequences quantify underlying white matter tissue properties within and outside of the WMHs to better understand their pathological processes in vivo and see whether these are related to a more irregular WMH shape.

A high temporal resting-state functional MRI sequence will be obtained, with its first obtained slice strategically positioned below the fourth ventricle. This will allow for probing of the inflow dynamics of CSF into the brain and correlating these with gray matter BOLD signals [48]. Altered BOLD-CSF coupling might signal impaired drivers of brain clearance activity, such as a decreased driving force of CSF motion due to arteriolar vasomotion, especially when found in relation to lower cognitive scores or more severe SVD burden [49,50].

Phase-contrast sequences will be used, first, to quantify arterial blood flow in the feet-head direction of blood flowing into the brain (Q flow) and, second, as angio-surveys to facilitate the placement of the labeling plane perpendicular to brain-feeding arteries and measure the offset distance between arteries (ie, left-right and anterior-posterior) for flow territory mapping. Q flow can also be used to measure blood flow velocities. Flow territory mapping is achieved through arterial spin labeling MRI. It can demarcate perfusion territories by changing the labeling efficiency within the labeling plane in the right-left and anterior-posterior directions over sequential arterial spin labeling measurements.

Apart from BOLD-CSF coupling, these advanced 3T MRI sequences are secondary to the main aims and will provide additional information on the tissue and perfusion properties of WMHs.

Ultrahigh-field (7T) brain MRI scans will be used to determine WMH shape [18] (solidity, convexity, concavity index, fractal dimension, and eccentricity) and other markers of cerebral SVD in and surrounding the WMHs, such as enlarged PVS, (cortical) microinfarcts, and microbleeds (on a T1-weighted, T2-weighted, FLAIR, and T2*-weighted scan). We will investigate the effect of a higher resolution and increased contrast on the WMH shape calculations. Moreover, a recently implemented MRI technique with high resolution called CSF-selective T2-prepared readout with acceleration and mobility encoding (CSF-STREAM) provides detailed whole-brain imaging of CSF mobility, from subarachnoid spaces down to the level of PVS as a proxy for brain clearance activity [51]. An example of measurements

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obtained using this technique can be found in Figure 4. Moreover, we will measure CSF and blood flow at the level of the foramen magnum using phase-contrast MRI. Heart rate and respiratory signals will be measured during the scans (3T and 7T MRI) using standard vendor-supplied equipment, namely, a respiratory belt and pulse oximeter.

Figure 4. Example of an image obtained using the cerebrospinal fluid (CSF)–selective T2-prepared readout with acceleration and mobility encoding sequence as a measure of brain clearance activity. The image shows an example of a CSF mobility map from a White Matter Hyperintensity Shape and Brain Clearance Study (WHIMAS) patient.

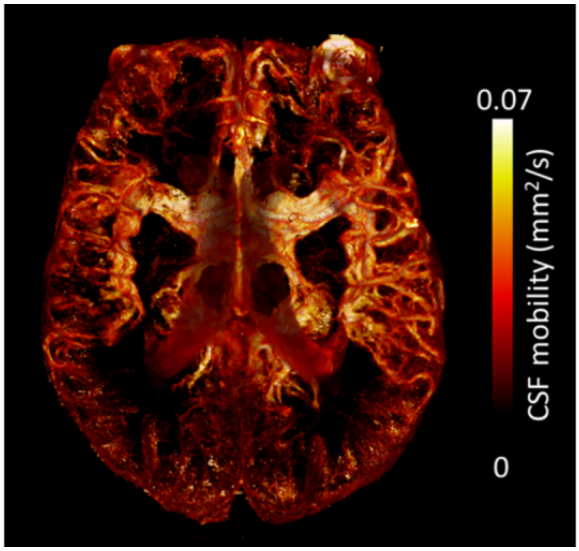

Patients are asked to lie as still as possible during scanning. If any discomfort is felt, they may move that body part slightly during breaks in between acquisitions, but we emphasize that they should not move their head, neck, or shoulders in doing so. Between the 3T and 7T scans, an hour break is planned. Furthermore, patients are asked beforehand if they have neck or back pain that prevents them from laying supine for extended periods. If that is the case, they are excluded as the risk of not completing the MRI scans is high.

CSF-STREAM consists of 7 subscans of 2 minutes, 45 seconds, limiting the effect of motion during each subscan. The 7 subscans will be coregistered with the first scan to correct for motion. If high motion occurs during one of the subscans, resulting in strong image artifacts, the corresponding scans will be excluded from the analysis. BOLD-CSF coupling is a very fast BOLD echo-planar imaging sequence and can be motion corrected retrospectively. The ihMT scan consists of 5 acquisitions with varying on- and off-resonance radio-frequency pulses. These 5 images will be motion corrected to each other similar to the CSF-STREAM strategy or excluded if they show high within-image motion. Furthermore, the large voxel sizes will somewhat mitigate motion blurring.

The T2* gradient-echo readout has a navigator that can prospectively mitigate motion during acquisition.

Statistics

Multivariable regression analyses will be conducted to relate periventricular and deep WMH volume and shape (solidity, convexity, concavity index, fractal dimension, and eccentricity) to brain clearance markers (eg, peak BOLD-CSF coupling magnitude, CSF mobility and flow, and PVS count) and white matter integrity (magnetization transfer ratio and mean T1 and T2 of the white matter maps). Furthermore, the association between WMH shape and brain clearance markers and *z*-transformed cognitive domain scores (memory, executive function, visuoconstruction, and processing speed) will be studied via multivariable regression analyses.

Secondary analyses could include association analyses with other SVD markers (presence of microbleeds, lacunes, and small recent subcortical infarcts).

Potentially confounding demographic variables such as age, sex, level of education, intracranial volume, and vascular risk factors will be included as covariates for subsequent analyses when appropriate.

Statistical assumptions such as linearity and normality of residuals will be checked using *Q*-*Q* plots, histograms, and other distribution measures. If applicable, appropriate nonparametric tests will be used, or the variables will be log-transformed. For the main exploratory analyses, the significance will be set at $P<.05$. Correction for multiple testing will be performed when appropriate.

Ethical Considerations

The WHIMAS study (NL78641.058.21) was approved by the Medical Ethics Committee Leiden The Hague Delft (P21.114) and is registered on ClinicalTrials.gov (NCT06010511). All participants will provide written informed consent before any experiments. Data will be anonymized and, after completion of data collection, transmitted to a secure repository with safeguards in place to protect confidentiality. Participants will receive travel compensation.

Results

Patient inclusion started in January 2023, and study enrollment of patients is expected to finish in the second quarter of 2027. The main results are expected to be published in the first quarter of 2028.

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Discussion

In the WHIMAS study, we aim to study the link between WMHs, and especially their shape, and brain clearance and other MRI markers on ultrahigh- and high-field brain MRI and show whether WMH shape and brain clearance markers are associated with cognitive functioning in older adults with memory complaints. A more irregular WMH shape is defined as lower solidity, lower convexity, higher concavity index, and higher fractal dimension of periventricular WMHs. This more irregular WMH shape can be described as a reduced "smoothness" of the WMH outer border. Our hypothesis is that a more irregular WMH shape is related to brain clearance abnormalities (captured using MRI, eg, altered CSF flow in the fourth ventricle and PVS) and disease severity (captured through other SVD markers). Furthermore, we also hypothesize that a more irregular WMH shape and brain clearance abnormalities are related to reduced cognitive functioning (memory, executive function, visuoconstruction, or processing speed domain). We expect to find the most significant associations in periventricular WMH shape as, in a previous study, a more irregular periventricular WMH shape was associated with cerebral SVD progression and cognition over a 5-year follow-up [52,53], as well as with an increased long-term dementia risk [18].

SVD in an aging population has a heterogeneous underlying pathology that current MRI markers do not accurately capture. Novel 7T brain MRI markers provide a window of opportunity to study early structural changes and potential determinants of SVD. WMH shape is a relatively novel MRI marker, and previous studies have shown prognostic potential [18,19]. However, the exact microstructural changes within or surrounding WMHs or potential determinants related to WMH shape variations remain unknown. Furthermore, impaired brain clearance via the recently discovered brain clearance system may be another early change or potential cause of SVD [54].

The WHIMAS study will generate data that can be used to postulate underlying mechanisms related to WMH shape variations as we will study the association between a more irregular WMH shape and advanced structural and functional markers of cerebral SVD. We expect to gain a better understanding of the structural correlates of WMH shape variation using and combining the advanced measurements of 7T MRI. WMH shape has previously been related to an increased long-term dementia risk [18] and increased long-term stroke and mortality risk [19]. In our study, we expect to find that a more irregular WMH shape will be related to disease severity (captured via other SVD markers) and cognition (memory, executive function, visuoconstruction, and processing speed). Moreover, we expect to capture WMH shape and other structures that may influence shape (such as veins) better through 7T MRI due to an increased spatial resolution. This will allow for a more precise investigation of WMH shape in relation to other SVD markers and structural changes.

Animal studies suggest that dysfunction of the brain clearance system plays a major role in the initiation and progression of not only neurodegenerative pathologies but also SVD [54]. The novel noninvasive markers of brain clearance that we will use in our study will allow us to assess brain clearance in vivo in a noninvasive way. In our study, we expect to find an association between CSF mobility and disease severity. Moreover, the BOLD-CSF coupling has been found to be reduced in patients with Alzheimer disease [50] and cerebral amyloid angiopathy [51]. Therefore, we expect that the BOLD-CSF coupling will be reduced in our patient population and will show an association with disease severity.

Biomarkers early in the disease process of cerebral SVD are extremely important as they may represent a basis for future patient selection for lifestyle interventions and outcome markers of treatment trials aimed at the prevention or treatment of dementia. The results of our study will contribute to the body of evidence for novel brain MRI markers that could hopefully serve as early biomarkers for SVD.

The strengths of our study include the specific patient population and the use of advanced ultrahigh-field 7T state-of-the-art MRI techniques in combination with advanced image processing techniques largely developed within our research group. This study serves to steer future investigations and could be extended into a longitudinal study. This study has several limitations that we would like to address. Undergoing 2 MRI scans of 1 hour each in combination with a neuropsychological assessment can be overwhelming for the targeted patient group. This could limit the inclusion rates and bias our sample toward either healthier or more highly motivated participants. Furthermore, many of the advanced MRI techniques are highly motion sensitive, which may increase the total number of participants needed for the analysis.

In conclusion, in the WHIMAS study, we aim to find brain MRI changes that could represent early determinants of or changes in cerebral SVD and that should be assessed in more detail in future studies in healthy older adults. These markers early in the disease process of SVD could be extremely important as they may represent a basis for future patient selection for lifestyle interventions or for treatment trials aimed at the prevention of dementia.

Data Availability

Only one scan of a single patient was used for this paper as an example of the techniques used. In-house developed magnetic resonance imaging sequences can be shared with interested research groups when proper collaboration agreements are in place.

Acknowledgments

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new participating center in our study. The patient and funding organization Alzheimer Nederland is involved in the conduct and dissemination plans of our study.

Conflicts of Interest

MJPvO reports to be an unpaid member of the steering committee of a clinical trial by Alnylam. The Leiden University Medical Center receives research support from Philips. All other authors declare no other conflicts of interest.

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Abbreviations

BOLD: blood oxygen level–dependent
CSF: cerebrospinal fluid
CSF-STREAM: cerebrospinal fluid–selective T2-prepared readout with acceleration and mobility encoding
FLAIR: fluid-attenuated inversion recovery
ihMT: inhomogeneous magnetization transfer
LUMC: Leiden University Medical Center
MRF: magnetic resonance fingerprinting
MRI: magnetic resonance imaging
SVD: small vessel disease
WHIMAS: White Matter Hyperintensity Shape and Brain Clearance
WMH: white matter hyperintensity

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Protocol

Real-World Efficacy and Safety of Zishenyizhi Pill for Cognitive Impairment Associated With Cerebral Small Vessel Disease: Protocol for a Multicenter Prospective Observational Study

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Abstract

Background: Cerebral small vessel disease (CSVD) is a leading cause of vascular cognitive impairment, contributing to 36% to 67% of vascular dementia cases. Current therapies, primarily cholinesterase inhibitors, offer limited efficacy and significant adverse effects. Traditional Chinese medicine, particularly the zishenyizhi pill, which is a multiherb formulation targeting yin deficiency and blood stasis, has shown promise in preliminary studies but lacks robust clinical validation.

Objective: We designed this study to evaluate the real-world efficacy and safety of zishenyizhi pill combined with conventional Western therapy for CSVD-related cognitive impairment.

Methods: This multicenter, prospective, nonrandomized controlled trial enrolled 246 patients from 4 institutions in Hunan province, China. Participants were stratified into 2 groups: the intervention group received zishenyizhi pill plus standard Western therapy, whereas the control group received conventional integrated Chinese-Western therapy. Cognitive outcomes (Montreal Cognitive Assessment, Mini-Mental State Examination, Vascular Dementia Assessment Scale cognitive subscale, and Trail Making Test parts A and B), traditional Chinese medicine syndrome scores, and safety parameters were assessed over 12 weeks.

Results: Participant recruitment is scheduled to commence in April 2025, with an anticipated enrollment of 246 participants by December 2026. At present, patient recruitment is underway, and preliminary analysis of medical record data is being conducted. Final data collection is expected to conclude by April 2027, with results projected for publication in September 2027.

Conclusions: The anticipated findings suggest that zishenyizhi pill may improve multiple cognitive domains in patients with cognitive impairment associated with CSVD while demonstrating a favorable safety profile. If validated, zishenyizhi pill could serve as a safe and effective adjunctive therapy for CSVD-related cognitive dysfunction.

Trial Registration: International Traditional Medicine Clinical Trial Registry ITMCTR2025000553; https://itmctr.ccebtcm.org.cn/mgt/project/view/-4790836881284495026

International Registered Report Identifier (IRRID): DERR1-10.2196/77661

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KEYWORDS

cerebral small vessel disease; cognitive impairment; zishenyizhi pill; real-world studies; traditional Chinese medicine

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Introduction

Cerebral small vessel disease (CSVD) is a clinical, imaging, and pathological syndrome caused by diverse etiologies affecting cerebral small arteries, arterioles, capillaries, venules, and small veins. Its primary neuroimaging manifestations include recent small subcortical infarcts, perivascular spaces, presumed vascular origin lacunes, white matter hyperintensities, cerebral microbleeds, and cerebral atrophy [1,2]. While patients with CSVD may present with acute-onset symptoms such as lacunar infarcts or hemorrhagic stroke, most exhibit insidious progression characterized by gradual cognitive decline, gait disturbances, affective disorders, and bladder or bowel dysfunction [3,4]. During the acute phase of CSVD evolution, pathological changes predominantly manifest as lacunar infarcts and intraparenchymal hemorrhage, accounting for approximately one-fifth of symptomatic stroke cases [5,6]. In chronic stages, the disease progresses to hemodynamically significant cerebral hypoperfusion, where persistent blood flow dysregulation induces multidimensional neural damage [7,8]. This pathophysiological cascade clinically correlates with progressive cognitive deterioration (encompassing memory, executive function, attention, language, and visuospatial domains), motor coordination deficits, autonomic dysfunction, and neuropsychiatric syndromes. Notably, CSVD represents one of the most prevalent etiologies of cognitive impairment, typically exhibiting a characteristic decline pattern marked by predominant deficits in attention, processing speed, and executive function, with relatively preserved episodic memory [9]. Epidemiological studies indicate that CSVD-related cognitive dysfunction contributes to 36% to 67% of vascular dementia (VaD) cases [10], often leading to severe functional disability, increased mortality, and substantial socioeconomic burdens.

The underlying mechanisms of cognitive impairment in CSVD remain incompletely elucidated. Neuroimaging modalities, particularly magnetic resonance imaging, have provided critical insights into potential pathophysiological correlates. Current evidence demonstrates associations among lacunar infarcts, white matter hyperintensities, cerebral atrophy, and cognitive deficits [11-13], whereas the presence and burden of cerebral microbleeds exhibit modest yet significant impacts on executive function and information processing speed [14,15]. However, the role of perivascular spaces in cognitive decline remains inconclusive based on extant data [16].

Despite the high prevalence and substantial societal burden of CSVD-related cognitive impairment, targeted therapeutic research remains limited. Current interventions predominantly derive from VaD studies, where cholinesterase inhibitors (eg, donepezil, rivastigmine, and galantamine) are used to enhance synaptic acetylcholine levels and mitigate amyloid β protein generation and deposition, thereby ameliorating cognitive dysfunction [17-21]. While these agents demonstrate modest cognitive benefits, they are associated with clinically significant adverse effects, including severe gastrointestinal disturbances (eg, nausea and vomiting), dizziness, and bradycardia [22,23]. Other pharmacotherapies with putative efficacy in vascular cognitive impairment (VCI), such as *Ginkgo biloba* extracts and nimodipine, require further validation through randomized controlled trials (RCTs) [24,25]. Traditional Chinese medicine (TCM) offers a unique therapeutic paradigm for CSVD. The yin deficiency and blood stasis theory constitute the principal TCM pathogenesis framework, positing dual involvement of the kidney and brain. Guided by this theory, the zishenyizhi decoction (nourishing the kidney and enhancing intelligence decoction) has been empirically used to modulate CSVD progression.

Preliminary clinical studies have demonstrated that zishenyizhi decoction significantly improves cognitive dysfunction in patients with CSVD, as evidenced by enhanced scores on the Mini-Mental State Examination (MMSE), Instrumental Activities of Daily Living Scale, National Institutes of Health Stroke Scale, and TCM syndrome evaluation metrics. Preclinical investigations using rodent models of chronic cerebral hypoperfusion further revealed that this formulation ameliorates ischemia-hypoxia–induced pathological changes, enhances spatial learning and memory performance, and reduces hippocampal damage. This prescription has been transformed into the Chinese patent medicine zishenyizhi pill and is widely used in clinical practice due to its clinical efficacy. The zishenyizhi pill is composed of 11 herbs, with the composition and functions shown in Table 1. However, the precise molecular mechanisms underlying its neuroprotective and cognitive-enhancing properties in CSVD are yet to be fully elucidated.

Real-world studies originating from pragmatic clinical trials within the domain of pharmacoepidemiology involve large-scale, long-term evaluations of therapeutic interventions under routine clinical practice conditions. These studies prioritize clinically meaningful outcome measures to assess both efficacy and safety, with a primary emphasis on external validity [26]. In contrast, RCTs focus on internal validity by investigating highly selected populations under strictly controlled experimental settings [27,28]. RCTs are conducted under the premise that findings derived from selected study populations can be generalized to broader target populations. This study design is widely regarded as the gold standard for generating high-reliability evidence, with most clinical guidelines formulating recommendations based on outcomes extrapolated from RCT data [29]. However, a critical limitation stems from the stringent inclusion and exclusion criteria, which may result in study cohorts that inadequately reflect real-world clinical populations and compromise generalizability to broader patient groups. Such restricted participant selection introduces selection bias [30,31]. Due to the particularity and complexity of its theoretical system, through preliminary exploration, we believe that real-world studies are more suitable for the field of TCM. Therefore, we will conduct a real-world study on the treatment of cognitive impairment in CSVD (syndrome of yin deficiency and blood stasis) with zishenyizhi pill. The aim is to clarify the clinical efficacy and medication characteristics of zishenyizhi pill in treating patients with cognitive impairment due to CSVD and provide evidence-based support for its use.

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Table 1. Composition, effects, and pharmaceutical action of the Chinese herbal medicines that constitute zishenyizhi pill.

Chinese name	Latin name	Plant part	Effect (TCM[a])	Pharmaceutical action	Dose (g)
Heshouwu	*Pleuropterus multiflorus*	Fruit	Nourishes essence and blood	Antioxidation, hypolipidemia regulation, and hepatoprotection	5
Gouqizi	*Lycii fructus*	Fruit	Nourishes the liver and kidney	Immunoregulation, anti-inflammation, and liver protection	5
Sangshen	*Mori fructus*	Fruit	Nourishes yin and blood and promotes fluid	Immunoregulation and antioxidation	5
Yinxingye	*Ginkgo biloba*	Leaf	Promotes blood circulation for removing blood stasis and obstruction in collaterals	Antioxidation, neuroprotection, and anti-inflammation	5
Danshen	*Salviae miltiorrhizae*	Root	Promotes blood circulation for removing blood stasis and obstruction in collaterals	Neuroprotection, antioxidation, and improvement of microcirculation	6
Yizhiren	*Alpinia oxyphylla*	Fruit	Nourishes the spleen and kidney	Neuroprotection, memory enhancement, and anti-inflammation	5
Shichangpu	*Acorus tatarinowi*	Tuber	Harmonizes the stomach, resolves phlegm, and opens the orifices	Neuroprotection, anticonvulsion, and antioxidation	5
Yujin	*Curcuma aromatica*	Tuber	Promotes qi circulation, activates blood flow, and alleviates pain	Anticancer, anti-inflammation, and antioxidation	5
Yuanzhi	*Polygala tenuifolia Willd.*	Root	Sedates the heart to stabilize the spirit and resolves phlegm to restore consciousness	Neuroprotection, antidepression, anti-inflammation, and antioxidation	5
Quanxie	Karsch *Olivierus martensii*	Dry body	Dispels pathogenic wind for resolving convulsion	Analgesia, anti-inflammation, and neuroprotection	1
Shanzha	*Crataegi fructus*	Fruits	Harmonizes the stomach and aids digestion	Neuroprotection	5

[a]TCM: traditional Chinese medicine.

Methods

Study Setting

This multicenter prospective observational nonrandomized controlled study (registered at the International Traditional Medicine Clinical Trial Registry; ITMCTR2025000553) enrolled 246 patients with CSVD-associated cognitive impairment of yin deficiency and blood stasis syndrome from 4 institutions—Hunan Provincial Hospital of Integrated Traditional Chinese and Western Medicine, Yiyang First Hospital of Traditional Chinese Medicine, Liuyang Hospital of Traditional Chinese Medicine, and Shimen County Hospital of Traditional Chinese Medicine. Eligible participants were stratified into 2 groups based on zishenyizhi pill use: the intervention group received guideline-based conventional Western medical therapy combined with zishenyizhi pill for 12 weeks, whereas the control group received guideline-based conventional integrated Chinese-Western therapy. Treatment for all enrolled participants was initiated during the stable phase of their outpatient visit or inpatient stay, immediately following the baseline assessment and confirmation of eligibility. Over the 12-week study period, multidomain cognitive assessments (executive function, attention, and processing speed) were conducted to evaluate the efficacy of zishenyizhi pill in CSVD-related cognitive impairment and explore its underlying mechanisms. The trial workflow is summarized in Figure 1. The evaluations and visits will be conducted according to the testing schedule in Table 2.

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Figure 1. Flowchart of the study.

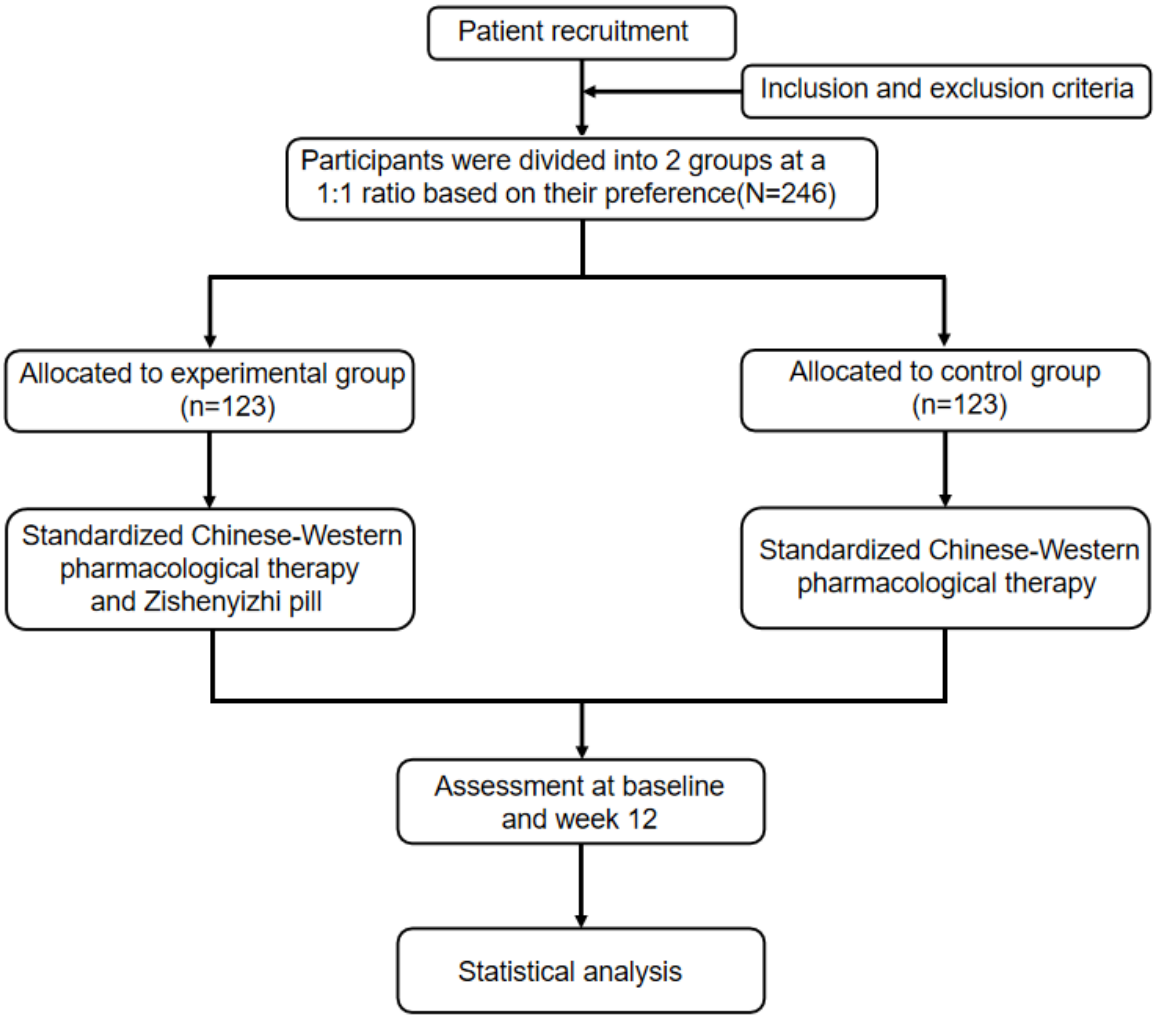

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Table 2. Study timeline.

Assessment	Baseline	Midpoints		End point
	0 wk	4 wk	8 wk	12 wk
Informed consent	✓			
Inclusion criteria	✓			
Exclusion criteria	✓			
General information	✓			
Medical history	✓			
TCM[a] syndrome criteria	✓			✓
Primary outcome measure				
MoCA[b]	✓			✓
Secondary outcome measures				
VaDAS-cog[c]	✓	✓	✓	✓
MMSE[d]	✓	✓	✓	✓
TMT-A[e]	✓	✓	✓	✓
TMT-B[f]	✓	✓	✓	✓
BNT-2[g]	✓	✓	✓	✓
HVLT[h]	✓	✓	✓	✓
CDT[i]	✓	✓	✓	✓
IADL[j]	✓	✓	✓	✓
EQ-5D-5L	✓	✓	✓	✓
NPI[k]	✓	✓	✓	✓
HADS[l]	✓	✓	✓	✓
TCM syndrome criteria	✓	✓	✓	✓
Safety assessments				
Blood, urine, and stool routine test	✓	✓	✓	✓
Liver and kidney function	✓	✓	✓	✓
Coagulation function	✓	✓	✓	✓
Electrolytes	✓	✓	✓	✓
Cardiac enzymes	✓	✓	✓	✓
Lipid profile	✓	✓	✓	✓
Blood glucose	✓	✓	✓	✓
ECG[m]	✓	✓	✓	✓
Efficacy evaluation		✓	✓	✓

[a]TCM: traditional Chinese medicine.
[b]MoCA: Montreal Cognitive Assessment.
[c]VaDAS-cog: Vascular Dementia Assessment Scale cognitive subscale.
[d]MMSE: Mini-Mental State Examination.
[e]TMT-A: Trail Making Test part A.
[f]TMT-B: Trail Making Test part B.
[g]BNT-2: Boston Naming Test–Second Edition.
[h]HVLT: Hopkins Verbal Learning Test.
[i]CDT: clock drawing test.

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[j]IADL: Instrumental Activities of Daily Living Scale.
[k]NPI: Neuropsychiatric Inventory.
[l]HADS: Hospital Anxiety and Depression Scale.
[m]ECG: electrocardiogram.

Training of Assessors and Quality Control

To ensure the consistency and reliability of the cognitive assessments, all neuropsychological evaluators across the 4 centers underwent centralized, standardized training before study initiation. Training sessions covered detailed administration protocols, scoring criteria, and interpretation guidelines for each cognitive tool (eg, Montreal Cognitive Assessment [MoCA], MMSE, Vascular Dementia Assessment Scale cognitive subscale [VaDAS-cog], and Trail Making Test parts A [TMT-A] and B [TMT-B]). Calibration exercises were conducted to minimize interrater variability, and periodic quality checks were implemented throughout the study.

Participants

This study focuses on patients with cognitive impairment due to CSVD with TCM syndrome of yin deficiency and blood stasis treated in the outpatient and inpatient departments of 4 institutions: Hunan Provincial Hospital of Integrated Traditional Chinese and Western Medicine (affiliated hospital of Hunan Academy of Chinese Medicine), Yiyang First Hospital of Traditional Chinese Medicine, Liuyang Hospital of Traditional Chinese Medicine, and Shimen County Hospital of Traditional Chinese Medicine.

Inclusion Criteria

The inclusion criteria are as follows: (1) Western medicine diagnosis meeting the diagnostic criteria for CSVD-associated cognitive impairment, (2) TCM syndrome meeting the yin deficiency and blood stasis syndrome criteria (the Dementia Syndrome Differentiation and Classification Scale is used for syndrome judgment, and the syndrome is established when the score is ≥7; the rating details are shown in Multimedia Appendix 1), (3) age ≥60 years, and (4) agreement from the patients or their family members and signature of an informed consent form.

Exclusion Criteria

The exclusion criteria are as follows: (1) coexisting neurological disorders causing cognitive impairment, including Alzheimer disease, frontotemporal dementia, Lewy body dementia, Parkinson disease, multiple sclerosis, traumatic brain injury, autoimmune disorders, or genetic diseases; (2) impaired consciousness, unstable vital signs (eg, blood pressure, respiratory rate, or heart rate), or life-threatening conditions (such as severe cardiac, hepatic, renal, or endocrine disorders); (3) inability to comprehend or comply with study procedures or follow-up due to psychiatric illnesses, cognitive or emotional disorders, or severe visual or auditory impairments; (4) severe hepatic or renal dysfunction (alanine transaminase or aspartate transaminase of >2 times the upper normal limit; creatinine of >1.5 times the upper normal limit); (5) previous use of kidney-nourishing or blood-activating herbal therapies within 2 weeks before enrollment; and (6) hypersensitivity to any component of the zishenyizhi pill.

Recruitment of Participants

All participants will be recruited through posters from inpatients and outpatients of 4 institutions: Hunan Provincial Hospital of Integrated Traditional Chinese and Western Medicine (affiliated hospital of Hunan Academy of Chinese Medicine), Yiyang First Hospital of Traditional Chinese Medicine, Liuyang Hospital of Traditional Chinese Medicine, and Shimen County Hospital of Traditional Chinese Medicine.

Interventions

All participants were stratified into 2 groups based on zishenyizhi pill administration: the intervention group and the control group, each comprising 123 patients. Both groups received standardized Western pharmacological therapy, including antihypertensive treatment, antiplatelet therapy, and lipid-lowering therapy. The intervention group additionally received the zishenyizhi pill at a dosage of twice daily for 12 consecutive weeks.

Outcomes

Primary Outcome

The MoCA assessed the degree of global cognitive function at baseline and 12 weeks after the intervention.

Secondary Outcomes

The VaDAS-cog assessed the degree of attention, executive function, and related cognitive domains at baseline and 12 weeks after the intervention. The MMSE assessed the degree of orientation, memory, and calculation ability at baseline and 12 weeks after the intervention. The TMT-A assessed the degree of visuospatial ability, psychomotor speed, and visual attention at baseline and 12 weeks after the intervention. The TMT-B assessed the degree of executive function, processing speed, and cognitive flexibility at baseline and 12 weeks after the intervention. The Boston Naming Test–Second Edition assessed the degree of language function (naming ability) at baseline and 12 weeks after the intervention. The Hopkins Verbal Learning Test assessed the degree of memory function (verbal memory) at baseline and 12 weeks after the intervention. The clock drawing test assessed the degree of visuospatial skills and executive function at baseline and 12 weeks after the intervention. The Instrumental Activities of Daily Living Scale assessed the degree of functional independence in daily living at baseline and 12 weeks after the intervention. The EQ-5D-5L assessed health-related quality of life at baseline and 12 weeks after the intervention. The Neuropsychiatric Inventory assessed the severity of neuropsychiatric symptoms at baseline and 12 weeks after the intervention. The Hospital Anxiety and Depression Scale assessed the severity of anxiety and depressive symptoms at baseline and 12 weeks after the intervention. The TCM syndrome criteria assessed the severity of TCM syndromes at baseline and 12 weeks after the intervention.

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Safety Evaluation and Adverse Events

Safety assessments included electrocardiogram, blood routine tests, liver function tests, renal function tests, cardiac enzyme level, blood glucose level, lipid profile, urine test, and stool routine test. Adverse events were comprehensively documented in case report forms (CRFs) throughout the study period. Serious adverse events—defined as those resulting in disability, operational incapacity, life-threatening conditions, or death—required immediate notification to both the investigators and the ethics committee. The research team provided clinical guidance and therapeutic interventions to affected participants while determining their eligibility for continued study participation.

Sample Size

The primary objective of this trial was to evaluate the therapeutic efficacy of zishenyizhi pill in patients with CSVD-related cognitive impairment. The sample size was estimated based on an anticipated superiority in the MoCA score among the intervention group compared to the control group. On the basis of previous pilot data and clinical judgment, we assumed a mean difference (δ) in MoCA score change of 0.5 between the 2 groups, with a common SD (σ) of 1.52. A 2–independent-sample *t* test was used for the calculation. With a significance level (α; 2-sided) set at .05, a desired power ($1-\beta$) of 90% for detecting this difference, and an allocation ratio (K) of 1:1, the required sample size per group was calculated using the following formula for a superiority trial: . As a result, 98 participants were needed in the experimental and control groups. Accounting for a 20% anticipated dropout rate, we planned to enroll 123 participants per group, totaling 246.

Combination Medications

Throughout the trial duration, all concomitant medications will undergo comprehensive monitoring. Additional use of TCM formulations with kidney-nourishing and blood-activating properties is strictly prohibited to ensure protocol compliance and minimize confounding effects.

Statistical Analysis

All statistical analyses will be conducted using the SPSS software (version 25.0; IBM Corp). The primary analysis will follow the intention-to-treat principle. Measurement data that adhere to a normal distribution will be expressed as means and SDs and compared between groups using the independent-sample *t* test. For intragroup comparisons (eg, baseline vs 12-week follow-up), paired *t* tests will be used. Data that do not follow a normal distribution will be expressed as medians and ranges, and the Mann-Whitney *U* test will be used for intergroup comparisons. Count data and categorical variables will be expressed as numbers and percentages and compared using the Pearson chi-square test or Fisher exact test as appropriate.

For the primary outcome analysis, the change in MoCA score from baseline to 12 weeks will be compared between groups using an analysis of covariance adjusting for the baseline MoCA score to enhance precision. A similar analysis of covariance approach will be applied to analyze changes in secondary continuous outcomes (eg, MMSE, VaDAS-cog, and TMT-A and TMT-B scores), with respective baseline scores included as covariates. To explore independent factors associated with cognitive improvement, significant variables identified in univariate analyses will be included in a multivariate linear regression model. All tests will be 2-tailed, and a *P* value of <.05 will be considered statistically significant.

Data Management and Quality Control

Data will be primarily collected using paper-based CRFs. To ensure data quality and accuracy, all data from the CRFs will be independently entered into a designated electronic database by 2 researchers. This process of double data entry and cross-verification will help minimize input errors. In case of inconsistent entries or identified omissions, the original CRFs will be rechecked for clarification and correction. To protect participant confidentiality, all personal identifiers will be removed and replaced with unique coded identification numbers in all electronic databases and analysis reports. The original paper CRFs will be securely stored in locked file cabinets at the principal investigator's institution. The electronic database will be stored on a password-protected computer, with access restricted to authorized research personnel only. Participant personal information will not be disclosed under any circumstances without their written consent. After the database is locked, no further alterations will be permitted.

Ethical Considerations

This study was approved by the Medical Ethics Committee of the Hunan Academy of Traditional Chinese Medicine Affiliated Hospital ({2025}29). This study will be conducted in accordance with the ethical principles of the Declaration of Helsinki. Informed consent will be obtained from all participants or their legal guardians before their enrollment in the study (informed consent is displayed in Multimedia Appendix 2). To protect participant privacy, all personal identifiers will be removed and replaced with a unique code; the list linking codes to identities will be stored separately under strict security measures.

Results

This study was funded by the National Natural Science Foundation of China General Program (grant 8237153821). Participant recruitment commenced in April 2025 across the 4 participating centers and is projected to be completed by December 2026. Final data collection, including all 12-week follow-up assessments, is anticipated to conclude by April 2027. As of November 2025, a total of 47 participants have been enrolled, 28 of whom have completed the follow-up assessments. Data analysis will commence following the completion of data collection. The primary results of this study are expected to be submitted for publication in September 2027.

Discussion

Rationale and Context

VCI is a recently recognized clinical entity primarily caused by cerebrovascular diseases [32,33]. Diverse etiologies contribute to VCI, including CSVD, large artery atherosclerosis,

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intracerebral hemorrhage, cardioembolism, and other less common stroke mechanisms [34,35]. VCI encompasses a spectrum of cognitive deficits, ranging from mild cognitive impairment to VaD, which arises from ischemic or hemorrhagic vascular pathologies either independently or synergistically with neurodegenerative processes such as Alzheimer disease [36]. Epidemiological projections estimate that the global burden of VCI will escalate to 100 million cases by 2050, incurring economic losses approaching US $4 trillion [37]. Although the current prevalence of VCI remains relatively low in low- and middle-income countries undergoing early demographic transitions, the most rapid growth rates in incidence are occurring there, suggesting a significant future disease burden [38]. CSVD represents a critical subtype of VCI and is the most prevalent etiological contributor to VaD in clinical practice [39]. Despite the high incidence and substantial societal burden of CSVD-related cognitive impairment, targeted therapeutic research remains scarce. Current interventions predominantly focus on VaD populations, with limited studies addressing subcortical VCI. However, TCM has long been associated with dementia treatment, supported by extensive research on TCM-based interventions [40]. TCM offers distinct advantages, including fewer adverse effects, cost-effectiveness, suitability for long-term use, and preventive potential [41], positioning it as a significant complementary and alternative therapeutic option for CSVD-related cognitive dysfunction.

The zishenyizhi pill, an empirical formula rooted in TCM theory, targets the core pathogenesis of CSVD by addressing yin deficiency and blood stasis. Preliminary clinical observations suggest its safety and efficacy in managing CSVD-related cognitive impairment; however, there is a lack of robust evidence from high-quality studies. To rigorously evaluate the zishenyizhi pill's therapeutic impact, this study uses the MoCA as the primary end point due to its superior sensitivity and specificity in detecting cognitive deficits compared to the MMSE. Secondary outcomes will assess multidimensional cognitive domains and functional efficacy through validated neuropsychological scales.

Limitations

Nevertheless, this study is subject to several methodological limitations. The nonrandomized observational design carries an inherent risk of selection bias and confounding. Despite stratification based on zishenyizhi pill use, baseline differences in patient characteristics—such as disease severity, comorbidities, and socioeconomic status—may persist between the intervention and control groups, potentially influencing outcome interpretation. The absence of randomization compromises internal validity as unmeasured confounders, including genetic predispositions and lifestyle factors, could independently affect cognitive trajectories.

Although real-world studies prioritize external validity, the limited control over confounding variables constrains the ability to establish causal inferences regarding the therapeutic efficacy of zishenyizhi. In addition, the sample size, while feasible for this preliminary investigation, was not derived from a formal superiority test calculation and was based on a conservative effect size estimate. Consequently, this study may be underpowered to detect differences smaller than 0.5 points on the MoCA, which could represent clinically meaningful but more modest treatment effects, particularly for secondary outcomes. This also limits the potential for meaningful subgroup analyses to explore personalized treatment responses.

Furthermore, the reliance on neuropsychological scales as primary end points without incorporating neuroimaging biomarkers such as magnetic resonance imaging–based quantification of white matter hyperintensity volume or microbleed burden restricts mechanistic interpretation. Objective biomarkers are essential to determine whether cognitive improvements correspond to structural or molecular changes in CSVD pathology. Finally, the 12-week observation period may be insufficient to evaluate the long-term efficacy, safety, and sustained cognitive benefits of zishenyizhi given the chronic and progressive nature of CSVD. Short-term assessment could miss delayed treatment effects, disease progression patterns, or late-emerging adverse events, which are critical in the context of vascular cognitive disorders.

Future Directions

Despite these constraints, this study represents a pivotal step in bridging TCM paradigms with modern clinical research methodologies. The limitations identified herein provide a clear road map for future research. To definitively establish the efficacy of zishenyizhi, subsequent studies should prioritize a multicenter RCT design to overcome the selection bias inherent in this observational approach. This RCT should be explicitly powered for superiority testing, with a sample size calculated based on a formally justified effect size for a prespecified primary cognitive end point. To elucidate the neurobiological mechanisms and move beyond reliance on neuropsychological scales alone, future trials should incorporate multimodal neuroimaging and fluid biomarkers. Furthermore, given the chronic progression of CSVD, extended intervention and follow-up periods are essential to evaluate the long-term sustainability of cognitive benefits and the intervention's impact on disease progression. Finally, leveraging larger cohorts will enable subtype stratification based on clinical, imaging, or biomarker profiles to identify patient subgroups most likely to benefit from zishenyizhi, thereby advancing toward personalized medicine in CSVD. These concerted efforts will be crucial in robustly validating this TCM intervention and advancing its integration into global therapeutic strategies for CSVD.

Conclusions

This ongoing multicenter real-world study represents a critical effort to evaluate the integrative use of zishenyizhi pill with conventional therapy for cognitive impairment in CSVD. By combining TCM principles with modern clinical methodologies, this trial aims to address the unmet need for targeted therapies in CSVD-related cognitive decline. While the nonrandomized design and reliance on neuropsychological end points may limit causal inferences, this study's pragmatic approach provides valuable insights into TCM's applicability in real-world settings. Pending completion, the findings will lay the groundwork for future randomized trials to validate efficacy, elucidate mechanisms (eg, through neuroimaging biomarkers), and optimize personalized treatment strategies. This protocol

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highlights the potential of TCM as a complementary paradigm in global dementia research, bridging traditional knowledge with evidence-based practice.

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Data Availability

Currently, no data have been generated. Relevant data will be available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization: XS, LX, DW
Data curation: XS
Investigation: XS, YX, SZ, SL, JT, TH, XT, YZ
Methodology: YX, RF, LX, DW
Software: XS
Supervision: LX, DW
Writing—original draft and writing: XS, LX, DW

Conflicts of Interest

None declared.

Multimedia Appendix 1
Dementia Syndrome Differentiation and Classification Scale.
[DOCX File , 20 KB - resprot_v14i1e77661_app1.docx]

Multimedia Appendix 2
Informed consent form.
[DOCX File , 28 KB - resprot_v14i1e77661_app2.docx]

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Abbreviations

CRF: case report form
CSVD: cerebral small vessel disease
MMSE: Mini-Mental State Examination
MoCA: Montreal Cognitive Assessment
RCT: randomized controlled trial
TCM: traditional Chinese medicine
TMT-A: Trail Making Test part A
TMT-B: Trail Making Test part B
VaD: vascular dementia
VaDAS-cog: Vascular Dementia Assessment Scale cognitive subscale
VCI: vascular cognitive impairment

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Protocol

Coronary Artery Disease Prevalence in an Executive Population at a Tertiary Medical Center: Protocol for a Retrospective Cohort Study

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Abstract

Background: Coronary artery disease (CAD) is a leading cause of global morbidity and mortality. Although CAD prevalence in the general population is well-documented, its occurrence among executive patients remains largely unexplored. An executive is an individual in a major leadership role, such as a C-suite officer, senior manager, board member, trustee, founder, or business owner, responsible for high-level decision-making and strategic direction. These roles often involve demanding schedules and significant stress. Despite their influence and better access to health care, this demographic faces unique challenges such as demanding work schedules, chronic stress, frequent travel, and reduced control over lifestyle. To address executives' unique health needs, many health care organizations offer specialized programs emphasizing preventive cardiovascular care, using advanced tools such as lipid panels, stress tests, and coronary calcium scans not typically included in primary care, to detect risks early and to promote long-term wellness.

Objective: This protocol aims to design a study to determine the prevalence of CAD in executive patients and compare it to the established prevalence in the US general population with the overarching goal of improving screening and care of CAD among executive patients.

Methods: This protocol proposes a retrospective review of medical records for patients with CAD seen at the Mayo Clinic's Executive Health Program from January 1, 2020, to December 31, 2023, with the aim of determining the prevalence of CAD in executive patients. The primary outcome is CAD prevalence, which will be identified through clinical diagnoses in the electronic medical records. Secondary outcomes include demographics, cardiovascular medications, social determinants of health, laboratory and diagnostic results, coronary calcium scores, and treatment interventions. The prevalence of CAD will be calculated as the proportion of patients with a documented CAD diagnosis relative to the total number of patients in the study cohort.

Results: A total of 24,272 patients were seen in the executive health clinic between January 1, 2020, and December 31, 2023. After applying the inclusion criteria, 6466 executive patients were eligible, with 3290 identified as having a potential CAD diagnosis pending confirmation through a detailed chart review.

Conclusions: In this protocol, we outline a research design and methodology to address a critical gap in understanding the prevalence of CAD among executive patients. This demographic is often overlooked despite their unique risk factors such as high stress and lifestyle choices.

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KEYWORDS

coronary heart disease; executive patients; prevalence; risk factors; age stratification; gender stratification; cardiovascular risk

Introduction

Coronary artery disease (CAD) is a major global health issue, significantly contributing to both illness and death [1,2]. In the United States, heart disease is the leading cause of death, with CAD being the primary contributor [3]. CAD significantly impacts overall health care expenditure and incurs additional costs beyond direct medical expenses, such as lost productivity from premature death and disability [4,5]. Key risk factors for CAD include hypertension, diabetes, dyslipidemia, smoking, and physical inactivity [6,7]. These factors accelerate atherosclerosis, a complex condition involving endothelial dysfunction, abnormal lipid metabolism, and inflammatory mechanisms, leading to the accumulation of low-density lipoprotein and other inflammatory particles that form fatty streaks and plaques prone to rupture [6-8]. There are notable disparities in CAD prevalence across different demographics. For example, CAD prevalence increases with age, with only 1% of adults aged 18-44 years reporting CAD, compared to 24.2% of adults aged 75 years and older [9]. Gender differences are also significant, with men reporting higher rates of CAD than women [10]. From 2009 to 2019, 7% of men reported CAD in 2019 compared to 4.2% of women [10]. Black and Hispanic populations face greater risks, partly due to higher rates of hypertension, diabetes, and obesity [11].

Socioeconomic factors also play a critical role; individuals from lower socioeconomic backgrounds often have limited access to health care, nutritious food, and opportunities for physical activity, increasing their risk for CAD [12,13]. Although insurance coverage is not reported to influence CAD prevalence, factors such as education level and income are reported to have a significant impact [14].

In recent decades, many health care organizations have launched executive health programs tailored specifically for the medical care of professionals in leadership roles [15-17]. Unlike traditional primary care, these programs place a stronger emphasis on preventive care, particularly cardiovascular screening with advanced lipid testing, cardiac stress testing, and coronary artery calcium scan, which are not routinely implemented in primary care [15-17]. Some programs also offer access to emerging disease screening technologies, including predictive genetic testing, pharmacogenomic screening, blood-based multi-cancer screening, and whole-body magnetic resonance imaging [16]. The overarching goal of these programs is to identify health risks and diseases early, promote overall wellness, and provide efficient, accessible health care with a strong focus on disease prevention [15-17].

The target demographic for these executive health programs are typically individuals who hold major leadership positions in corporations, businesses, and trusts, including business owners and entrepreneurs, who often face demanding and stressful professional schedules, such as C-suite executives, senior management, board members, trustees, founders, and business owners, all of whom collectively drive economic activity and contribute significantly to the overall health of the economy [15-17]. Although executives generally have better access to health care, higher incomes, and higher educational levels compared to the general population, they also face high-stress work environments that often interfere with their ability to maintain healthy lifestyle habits [15-19]. Additionally, there are demographic variations between this population and the general population. For instance, in terms of race and ethnicity, executive health program participants often reflect a more homogeneous group, frequently from higher socioeconomic backgrounds, which can influence health outcomes [20]. Gender disparities are notable as well, with a predominance of male participants, aligning with the typical gender distribution in executive roles [20]. The age group of these individuals typically ranges from 40 to 60 years—a period during which the risk for CAD significantly increases [14].

This combination of factors underscores the need to investigate CAD prevalence among executives to develop targeted interventions tailored to their unique needs. However, there are currently no published data on these factors or the prevalence of CAD among executives, representing a critical gap in the literature. We aim to conduct a retrospective cohort study to determine the prevalence of CAD among individuals enrolled in an executive health program at a large medical center.

Methods

Study Design

The design of this study is a retrospective chart review of executives who received care at The Executive Health Program at Mayo Clinic in Rochester, Minnesota, from January 1, 2020, to December 31, 2023. This study protocol was developed in accordance with STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines for observational research (Multimedia Appendix 1) [21,22].

Recruitment

Participants

The population for this proposed study includes executive patients who were enrolled in the Executive Health Program at the Mayo Clinic in Rochester site between January 1, 2020, and December 31, 2023. We define executive patients as individuals holding major leadership positions in corporations, businesses, and trusts, including business owners and entrepreneurs. This group encompasses C-suite executives, senior management, board members, trustees, founders, and business owners who collectively drive economic activity and significantly contribute to the overall health of the economy.

Inclusion Criteria

This protocol proposes to include patients aged 21 to 75 years who sought care at the Executive Health Program between January 1, 2020, and December 31, 2023; provided prior research authorization; and have a CAD diagnosis. We propose screening the medical records of the patient cohort who

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presented during this period by using the codes of the International Classification of Diseases, Ninth Revision; International Classification of Diseases, Ninth Revision, Clinical Modification; International Classification of Diseases, Tenth Revision; and International Classification of Diseases, Tenth Revision, Clinical Modification, as described in Table 1, in addition to keywords such as coronary artery, coronary artery disease, and atherosclerosis. We will utilize an institutionally developed, validated, and research-approved electronic search tool, Mayo Data Explorer, for the screening. Medical records that pass the screening process will be reviewed in detail to confirm CAD diagnosis within a clinical note and/or documentation of CAD through a radiology/cardiology clinical test. Conflicts that arise regarding medical records with an unclear diagnosis will be resolved through group discussions. The details of the complete screening and inclusion are outlined in Figure 1.

Table 1. ICD[a] codes used for patient prescreening.

ICD codes	Description
ICD-9[b] and ICD-9-CM[c] code	
414.00	Coronary atherosclerosis of unspecified type of vessel, native or graft
414.01	Coronary atherosclerosis of native coronary artery
ICD-10[d] and ICD-10-CM[e] code	
I25.10	Atherosclerotic heart disease of native coronary artery without angina pectoris
I25.110	Atherosclerotic heart disease of native coronary artery with unstable angina pectoris
I25.111	Atherosclerotic heart disease of native coronary artery with angina pectoris with documented spasm
I25.118	Atherosclerotic heart disease of native coronary artery with other forms of angina pectoris
I25.119	Atherosclerotic heart disease of native coronary artery with unspecified angina pectoris

[a]ICD: International Classification of Diseases.

[b]ICD-9: International Classification of Diseases, Ninth Revision.

[c]ICD-9-CM: International Classification of Diseases, Ninth Revision, Clinical Modification.

[d]ICD-10: International Classification of Diseases, Tenth Revision.

[e]ICD-10-CM: International Classification of Diseases, Tenth Revision, Clinical Modification.

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Figure 1. Complete screening and inclusion process. ICD-9: International Classification of Diseases, Ninth Revision; ICD-10: International Classification of Diseases, Tenth Revision.

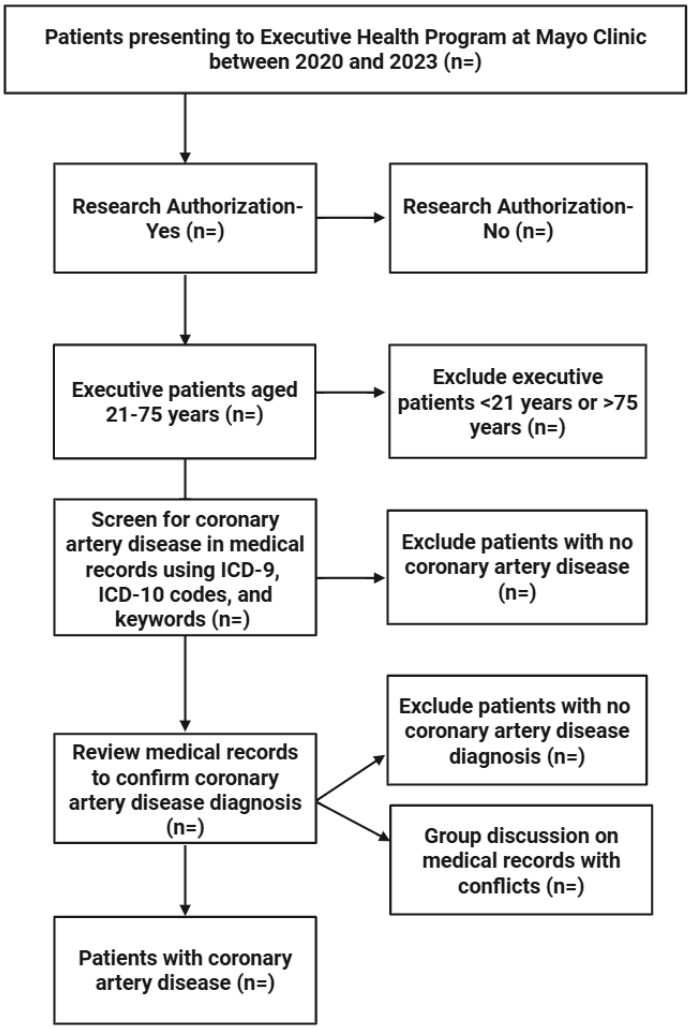

Sample Size Calculation

Study entry criteria will include being an empaneled patient in the Mayo Clinic Executive Health Program, having provided authorization for research, and aged 21 to 75 years. Based on clinical experience, we anticipate that approximately 5%-10% of the executive patients seen during that time period will meet the inclusion criteria. With as estimated denominator of 25,000 and an expected CAD prevalence of 5%-10%, the margin of error for a 95% CI is expected to be less than SD 0.5%. This is based on using nQuery Advisor 7.0 (confidence interval for a proportion using the normal approximation).

Record Review and Data Collection

Primary Outcome Variables to be Abstracted

The primary outcomes of the prevalence of CAD will be determined by a review of medical records of executive patients who presented within this time frame to identify patients with a CAD diagnosis within the clinical notes. Data will be collected and categorized as either binary or continuous into a Research Electronic Data Capture (REDCap) database, as detailed in Table 2.

Table 2. Primary outcome variables to be abstracted.

Key outcomes variables	Source	Variable type
Record ID	Chart review	Identifier
Were they diagnosed with coronary artery disease?	Chart review	Binary
Age at coronary artery disease diagnosis	Chart review	Continuous

Secondary Outcome Variables to be Abstracted

The secondary outcome variables to be abstracted will include baseline demographic characteristics, cardiovascular-related medications, responses to the Social Determinants of Health Questionnaire (covering exercise, nutrition, and alcohol habits), laboratory test results, diagnostic tests, coronary calcium scan results, and treatment interventions (Tables 3-8). Data will be

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collected and categorized as binary, continuous, or categorical into a REDCap database as detailed in Tables 3-8.

Table 3. Secondary outcomes: baseline demographic variables to be abstracted.

Variable	Source	Variable type
Gender	Chart review	Categorical
Race	Chart review	Categorical
Ethnicity	Chart review	Categorical
Level of education	Chart review	Categorical
Marital status	Chart review	Categorical
Medical history	Chart review	Binary, categorical
Hypertension		
Chronic kidney disease		
Hyperlipidemia		
Diabetes		
Stroke		
Obstructive sleep apnea		
Peripheral vascular disease		
Heart failure		
Family history	Chart review	Binary, categorical
Coronary artery disease		
Hypertension		
Chronic kidney disease		
Hyperlipidemia		
Diabetes		
Stroke		
Obstructive sleep apnea		
Peripheral vascular disease		
Heart failure		
Physical measurements		
Height (cm)	Chart review	Continuous
Weight (kg)	Chart review	Continuous
BMI	Chart review	Continuous

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Table 4. Secondary outcomes: medication use at the time of coronary artery disease diagnosis to be abstracted.

Medication use	Source	Variable type
Are they taking lipid-lowering agents? If yes, which ones?	Chart review: medications	Binary, categorical
Are they taking angiotensin-converting enzyme inhibitors? If yes, which ones?	Chart review: medications	Binary, categorical
Are they taking angiotensin II receptor blockers? If yes, which ones?	Chart review: medications	Binary, categorical
Are they taking β-blockers? If yes, which ones?	Chart review: medications	Binary, categorical
Are they taking calcium-channel blockers? If yes, which ones?	Chart review: medications	Binary, categorical
Are they taking diuretics? If yes, which ones?	Chart review: medications	Binary, categorical
Are they taking antiplatelet agents? If yes, which ones?	Chart review: medications	Binary, categorical
Are they taking anticoagulants? If yes, which ones?	Chart review: medications	Binary, categorical
Are they taking vasodilators and cardiac medications? If yes, which ones?	Chart review: medications	Binary, categorical
Are they taking α-blockers? If yes, which ones?	Chart review: medications	Binary, categorical
Are they taking colchicine?	Chart review: medications	Binary
Are they taking supplements? If yes, which ones?	Chart review: medications	Binary, categorical

Table 5. Secondary outcomes: social determinants of health to be abstracted.

Variable	Source	Variable type
Exercise habits		
On average, how many days per week do you engage in moderate to strenuous exercise (like a brisk walk)?	Social Determinants of Health Questionnaire	Continuous
On average, how many minutes do you engage in exercise on this level?	Social Determinants of Health Questionnaire	Continuous
Type of exercise (cardio, strength training, other)	Social Determinants of Health Questionnaire	Categorical
Dietary habits		
On average, how many servings of fruits and vegetables do you eat each day (serving size equal to 1 tennis ball)?	Social Determinants of Health Questionnaire	Continuous
Do you use extra virgin olive oil as your main source of fat in your diet?	Social Determinants of Health Questionnaire	Binary
Alcohol consumption		
How often do you have a drink containing alcohol? (times per week)	Social Determinants of Health Questionnaire	Continuous
How many drinks containing alcohol do you have on a typical day when you are drinking?	Social Determinants of Health Questionnaire	Continuous
How often do you have 6 or more drinks on one occasion?	Social Determinants of Health Questionnaire	Continuous
Smoking habits		
Smoking (any form of tobacco products, eg, chewing): if yes, which type?	Chart review	Binary, categorical
Did they do smokeless tobacco such as chew or snuff?	Chart review	Binary
Total packs per year and current packs per day	Chart review	Continuous
If former smoker, the date they quit smoking or smokeless tobacco	Chart review	Date
Number of packs per year they used to smoke	Chart review	Continuous
e-Cigarette and vaping use	Chart review	Binary

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Table 6. Secondary outcomes: laboratory test results to be abstracted.

Variable	Source	Variable type
Total cholesterol	Chart review: labs[a]	Continuous
High-density lipoprotein cholesterol	Chart review: labs	Continuous
Low-density lipoprotein cholesterol	Chart review: labs	Continuous
Triglycerides	Chart review: labs	Continuous
Lipoprotein(a)	Chart review: labs	Continuous
Apolipoprotein A1	Chart review: labs	Continuous
Apolipoprotein B	Chart review: labs	Continuous
Fasting glucose	Chart review: labs	Continuous
Hemoglobin A_{1c}	Chart review: labs	Continuous
Fibrinogen	Chart review: labs	Continuous
C-reactive protein	Chart review: labs	Continuous
High-sensitivity C-reactive protein	Chart review: labs	Continuous
Myocardial infarction–heart ceramide risk score	Chart review: labs	Continuous

[a]Labs: laboratory test results.

Table 7. Secondary outcomes: diagnostic test information variables to be abstracted.

Variable	Source	Variable type
Diagnostic tests		
Did the patient undergo an exercise stress test?	Chart review	Binary
Did the patient undergo an echocardiogram?	Chart review	Binary
Did the patient undergo an electrocardiogram?	Chart review	Binary
Did the patient undergo a nuclear stress test?	Chart review	Binary
Did the patient undergo a heart computed tomography?	Chart review	Binary
Did the patient undergo a cardiac catheterization?	Chart review	Binary
Calcium scan		
Was a calcium scan done?	Chart review	Binary
Date of calcium scan	Chart review	Date
Total score of calcium	Chart review	Continuous
Left anterior descending artery measurement	Chart review	Continuous
Circumflex measurement	Chart review	Continuous
Left main vessel measurement	Chart review	Continuous
Right coronary artery measurement	Chart review	Continuous
Percentile	Chart review	Continuous

Table 8. Secondary outcomes: procedures and treatment interventions related to coronary artery disease that have to be abstracted.

Variable	Source	Variable type
Did the patient undergo angioplasty?	Chart review: procedures	Binary
Did the patient receive a stent?	Chart review: procedures	Binary
Did the patient undergo coronary artery bypass grafting?	Chart review: procedures	Binary

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Abstractor Training

Prior to the commencement of data extraction, a comprehensive training reference guide will be developed to delineate the specific objectives of the project. This guide will serve as an essential resource, with any updates or modifications promptly incorporated and communicated to the team. Training sessions will be conducted for each new abstractor to ensure thorough preparation for the extraction process.

Quality Assurance

To ensure the accuracy and reliability of the extracted data, we will implement random spot checks on the REDCap dashboard. Our goal is to achieve a 10% spot-check rate, equating to approximately 10 checks per page, with each page containing 100 patient records. These checks will be assigned randomly to minimize bias and will be conducted by reviewers independent of the initial data extractors. This dual-review approach is crucial for identifying any discrepancies or errors that may have been initially overlooked. If errors are detected, they will be promptly corrected, and the responsible individuals will receive retraining to address any gaps in their understanding.

Statistical Analysis Plan

Patients will be initially categorized into those with established CAD and those without. The prevalence of CAD among executive patients will be calculated, along with age- and gender-adjusted incidence rates. The prevalence of CAD will be estimated by calculating the proportion of individuals diagnosed with CAD out of the total sample. Confidence intervals for the prevalence estimates will be calculated using the Wilson score method. All secondary variables collected will be summarized using descriptive statistics. For binary variables, frequencies and percentages will be reported. For continuous variables, means, standard deviations, medians, and interquartile ranges will be calculated. Chi-square tests will be used for categorical variables, and 1-sided *t* tests or analysis of variance will be used for continuous variables. Logistic regression models will be employed to adjust for potential confounders and to identify independent predictors of disease prevalence. Statistical analysis will be conducted using SAS software (version 9.4; SAS Institute Inc) [23].

Ethical Considerations

Patient or public involvement was not incorporated in the design, conduct, reporting, or dissemination plans of this research. Ethical principles have and will continue to be carefully considered and adhered to, and only patients who previously consented to the use of their data for research purposes will be included in this cohort. All data will be deidentified prior to analysis to ensure patient privacy and confidentiality. All procedures are in accordance with the Declaration of Helsinki, and this study underwent expedited review procedures and was determined to be exempt from institutional review board approval (ID 24-005576; 45 CFR 46.104d, category/subcategory 4[iii]).

Results

A total of 24,272 patients were identified as having been seen in the Executive Health Clinic at Mayo Clinic in Rochester between January 1, 2020, and December 31, 2023. After confirming research authorization and executive status and excluding individuals younger than 21 years or older than 75 years, 6466 patients met the inclusion criteria. Of these, 3290 patients had a mention of CAD in their medical records. This subset of medical records will undergo a secondary review to confirm the diagnosis of CAD and abstract variables as outlined in the study protocol.

Discussion

This study seeks to address a significant gap in the literature by evaluating the prevalence of CAD within an executive health population—a group that has been largely understudied despite its unique risk profile. Although CAD prevalence is well-characterized in the general US population, its burden among executives remains unclear [14,24]. Given the distinct demographic, occupational, and lifestyle characteristics of this group, we hypothesize that CAD prevalence may differ meaningfully from that of the broader population. Executives often experience elevated levels of work-related stress, irregular schedules, and limited time for physical activity, all of which are known contributors to cardiovascular risk [19,20]. These factors suggest a potential for higher CAD prevalence in this population. Conversely, patients in executive health programs typically have enhanced access to preventive services than what is offered in routine primary care, including routine cardiovascular screening and personalized education, which may facilitate early detection of subclinical disease or even reduce overall disease burden through proactive risk management [15-17]. As such, the observed prevalence may reflect a complex interplay between increased risk exposure and improved access to care.

Two recent studies have described the prevalence of CAD in the US population by using different methodologies. In the first study, Lee et al [14] evaluated CAD prevalence in the United States from 2011 to 2018 by using data from the Behavioral Risk Factor Surveillance System, where individuals self-reported CAD via telephone surveys. The authors reported an overall CAD prevalence of 5.8%-6.2% in the US population [14]. The prevalence was higher in men compared to women (7.7% vs 4.6%, respectively) and in adults older than 65 years compared to those younger than 45 years (7.4% vs 1.6%, respectively) [14]. Notably, there was a clear discrepancy based on income, with lower CAD prevalence in higher-income individuals compared to those with lower incomes (4.1% vs 8.9%, respectively) [14]. In the second study, Khalid et al [24] used data from the Centers for Disease Control and Prevention's National Center for Health Statistics to evaluate CAD prevalence trends from 2019 to 2022. They reported an overall CAD prevalence of 4.6%-4.9% in the US population, with higher prevalence in males compared to females (6.4% vs 3.6%, respectively) and in adults older than 75 years compared to those aged 65-74 years, 45-64 years, and 18-44 years (19.7%

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vs 12.3% vs 4.1% vs 0.5%, respectively) [24]. Both studies [14,24] reported disparities in CAD prevalence among different racial and ethnic groups. Lee et al [14] highlighted American Indian or Alaska Native individuals as having the highest prevalence, while Khalid et al [24] found White adults had the highest prevalence. Both studies relied on self-reported data (telephone and interview surveys) to determine CAD presence, which could result in missed diagnoses among individuals who did not participate in the survey, who were unaware of their diagnosis, or who did not engage in primary and preventative care [14,24]. Compared to these 2 studies, although our proposed study focuses only on executives and not on the general population, our proposed methodology is superior in that it relies on documentation in medical records, reducing the likelihood of missed diagnoses. Additionally, our patient population participates in routine cardiovascular prevention beyond what is typically offered in primary care, further lowering the chance of undiagnosed CAD. This distinguishes our methodology and underscores the significance of our study.

This proposed study is crucial for several reasons. Given the lack of literature on CAD within executives, our study aims to address this significant gap and may be the first to evaluate CAD prevalence within this population. If our findings show a higher prevalence of CAD among executives, it may indicate that our executive health program provides superior screening or that executives face higher CAD risks due to stress and lifestyle factors. Conversely, a lower prevalence might reflect the benefits of enhanced care in executive health programs. Additionally, there are limited data on health conditions specific to executives, and this research could prompt further studies on executive health profiles. Finally, understanding CAD prevalence among executives can help health care providers tailor screening practices and optimize interventions for this group, especially if the prevalence is higher than in the general population.

As with other retrospective cohort studies, our study has several limitations. First, there is the potential for missing or inconsistent data, as medical records may be incomplete or vary in documentation quality. Second, selection bias may be present, as the cohort reflects only those executives who chose to participate in our program and may not be representative of the broader executive population. Additionally, our sample characteristics may differ substantially from those of a community-based medical sample or the US general population. As a result, any observed differences in CAD prevalence may reflect the self-selected nature of our cohort rather than true population-level differences. Third, we recognize that stress may be a predictive variable for CAD. However, data related to stress are not routinely collected in the executive health population and are therefore not readily available in the medical records. This limitation may affect our ability to fully assess the role of psychosocial factors in CAD prevalence. Fourth, the retrospective nature of the study limits our ability to control for the confounding variables, which may influence both the quantitative and qualitative aspects of the data collected. Despite these limitations, our study has several notable strengths. It leverages real-world clinical data collected at a world-class medical institution, offering valuable insights into how CAD is diagnosed and managed in routine executive practice. The inclusion of 3 years of data enhances the robustness of our findings by capturing patients who may not attend annually and increasing the likelihood of identifying CAD diagnoses that may have been missed in a single year. Additionally, our reliance on clinician-documented diagnoses, rather than self-reported data or survey responses, improves the accuracy and clinical relevance of our findings.

This proposed study aims to fill a critical gap in health literature by evaluating CAD prevalence among executives, potentially guiding tailored screening practices and interventions to improve cardiovascular outcomes in this unique population. Our study findings will be submitted to a peer-reviewed journal to ensure rigorous academic dissemination. If the opportunity arises, the results will also be presented at national and international conferences to reach a broader academic and clinical audience.

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Authors' Contributions

Conceptualization: MD, BK, AV, IC, BD, JA, RH, SN, AP
Methodology: MD, BK, AV, DL, AP
Writing – original draft preparation, review, and editing: MD, BK, AV, IC, BD, JA, RH, SN, DL, AP
Supervision: AV, IC

Conflicts of Interest

None declared.

Multimedia Appendix 1
STROBE reporting checklist.
[PDF File (Adobe PDF File), 207 KB - resprot_v14i1e72451_app1.pdf]

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Abbreviations

CAD: coronary artery disease
REDCap: Research Electronic Data Capture
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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Improving the Reporting Quality of Studies on Information Extraction From Clinical Texts: Protocol for the Development of a Consensus-Based Reporting Guideline

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Abstract

Background: Information extraction (IE) from clinical texts is increasingly important in health care; yet, reporting practices remain inconsistent. Existing guidelines do not fully address the unique challenges of IE studies. IE methods vary widely in their design, ranging from rule-based systems to advanced large language models, contributing to heterogeneity in reporting. While several reporting frameworks exist for applications of artificial intelligence in health care, they primarily focus on prediction modeling or clinical trials and associated protocols rather than text-based IE.

Objective: This study aims to develop the Clinical Information Extraction (CINEX) guideline, a consensus-based reporting guideline for studies on clinical IE.

Methods: The CINEX guideline is developed following an established guideline methodology, including a 3-round electronic Delphi (eDelphi) study with domain experts and a final in-person consensus meeting. The eDelphi process includes feedback loops and predefined consensus thresholds, with items rated on a 10-point scale for both relevance and maturity. The final consensus meeting is held as a hybrid workshop at the MEDINFO 2025 conference and focuses on finalizing the items that reached consensus.

Results: Our results will provide a validated reporting guideline for studies on clinical IE. A preliminary set of 28 reporting items was drafted from a scoping review and existing frameworks. The draft guidelines include 5 key dimensions: information model, architecture, data, annotation, and outcome. This draft guideline will be refined through the eDelphi process. It is designed to be technology-agnostic and applicable across diverse IE approaches, including not only large language models but also traditional machine learning methods and rule-based and hybrid systems.

Conclusions: The CINEX guideline provides structured, expert-validated guidance for reporting clinical IE studies, improving transparency, reproducibility, and comparability. The final guideline will be disseminated alongside an explanatory document to support adoption and implementation.

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KEYWORDS

reporting guideline; information extraction; artificial intelligence; natural language processing; consensus-based approach; eDelphi study

Introduction

Information extraction (IE) refers to techniques that automatically identify and structure key information from unstructured text. These methods enable efficient reuse of clinical narratives, supporting decision-making, research, and automation in electronic health records. Specific use cases include phenotyping (eg, extraction of specific diseases), drug-related tasks (eg, dosage IE), and clinical workflow optimization (eg, adverse event detection) [1]. Furthermore, IE can reduce the burden of manual chart review, enable large-scale epidemiological studies, and support real-time decision support.

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Recent advances in natural language processing (NLP), especially through large language models (LLMs), have improved IE capabilities. However, this rapid technical evolution has introduced fragmentation in methods, terminology, and evaluation. We identified this heterogeneity during a scoping review of studies describing IE specifically from radiology reports. Studies vary widely in defining the target information, annotating reference standards, evaluating system performance, and disclosing implementation details [2]. Without standardized reporting, it becomes difficult to interpret results, compare systems, replicate experiments, or translate the developed effective algorithms into clinical practice. This suboptimal reporting quality had already been identified in a systematic review conducted by Davidson et al [3] in 2021.

To address reporting variability in artificial intelligence (AI) studies, several guidelines have emerged. The CONSORT-AI (Consolidated Standards of Reporting Trials–Artificial Intelligence) extension provides a checklist for reporting clinical trials that include AI-based interventions [4]. Its counterpart, SPIRIT-AI (Standard Protocol Items: Recommendations for Interventional Trials–Artificial Intelligence), focuses on protocol reporting for such trials, ensuring clarity and completeness before trial execution [5]. More recently, TRIPOD+AI (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis–Artificial Intelligence) [6] and TRIPOD-LLM (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis Or Diagnosis specifically tailored for large language models) [7] have extended the original TRIPOD (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis Or Diagnosis) [8] guidelines to include the application of regression and machine learning methods as well as LLM-based approaches for prediction model studies. These guidelines promote transparency and reproducibility for studies describing AI-based interventions and prediction models. However, none are applicable to the reporting needs of IE from clinical text, which involves distinct tasks, input-output structures, and evaluation methods as compared to diagnostic modeling or intervention and their associated trials.

This paper presents the protocol for the development of the Clinical Information Extraction (CINEX) guideline, a consensus-based reporting guideline for clinical IE studies. This protocol outlines the methodology behind the CINEX guideline, including a 3-round modified electronic Delphi (eDelphi) process with domain experts. The development of this guideline follows best practices for health research reporting and includes steps for item refinement, a final in-person consensus meeting, and the publication of an explanation and elaboration (E&E) document. The CINEX guideline aims to close the reporting gap in clinical IE research, promoting rigor, transparency, and harmonization across diverse methodological paradigms.

Methods

Overview and Preliminary Guideline Development

The planned development process of the CINEX guideline was registered and publicly listed with the EQUATOR (Enhancing the Quality and Transparency Of Health Research) Network as a reporting guideline under development in August 2024 prior to its official start in October 2024 [9]. The EQUATOR Network is an international initiative that promotes transparent and accurate reporting of health research to improve the reliability and value of the published literature [10]. The CINEX guideline follows the methodological guidance outlined by Moher et al [11] for developing health research reporting guidelines. Throughout this protocol, references to Moher's checklist items are indicated in angle brackets (< >).

The need for this guideline was identified during a scoping review of studies on LLM-based IE from radiology reports <1> [2]. The review aimed to assess the current state of the art in terms of performance, training and modeling approaches, clinical use cases, datasets, annotation methods, and commonly reported challenges. Derived from the review's aims, a data extraction table was drafted and populated by one author. The scoping review revealed important barriers to study comparability, including untransparent performance metric calculations, lack of external validation, and limited availability of source code. These problems hinder transparency and reproducibility in the field. Based on the data extraction table as well as inspired by existing reporting guidelines, an initial set of 28 candidate reporting items was drafted and published <2> [12].

eDelphi Study

To refine the preliminary guideline, a 3-round eDelphi study was planned between May and July 2025 <5,6>. The Delphi method was chosen as a structured, iterative process to achieve expert consensus, in line with the recommendations of Moher et al [11] for reporting guideline development.

We designed the eDelphi process based on the methodological principles of Häder [13], Nasa et al [14], as well as Trevelyan and Robinson [15]. We aim to recruit between 20 and 30 participants <4>. Minimum response rates are set at 30% for the first round and 70% for the following rounds, consistent with Häder's [13] guidance.

Eligible participants include the authors of studies identified in the preceding scoping review, as well as domain experts with regard to clinical IE, recruited through the personal and professional networks of the executive committee. Interested individuals will be invited via email to join the study. The survey itself will be conducted using the open-source tool LimeSurvey [16].

The eDelphi study will comprise exactly 3 rounds [13]. Consensus for the inclusion of an item in the guideline will be defined as a mean rating of 8 or higher on a 10-point scale, with an SD of 2 or less. Exclusion will be defined as a mean rating of 3 or lower, also with an SD of ≤2. Items falling outside these thresholds will be revisited during a final consensus meeting held after the eDelphi process. Response stability is recorded but not used to assess early termination. Only in the first round, panelists have the possibility to add additional items for each domain. Exclusion as well as finalization due to consensus of items is only conducted after rounds 2 and 3. Rephrasing of items and descriptions is conducted after each round based on the panelists' comments.

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In the first round, participants will be presented with the draft reporting items, including any proposed value sets where applicable. They will be asked to assess the relevance and maturity of each item using a 10-point scale with labeled endpoints only ("not at all relevant" and "not at all mature" to "very relevant" and "very mature"). Each item additionally includes a default "No answer" option. To approximate interval-level data, a larger number of anchor points was selected instead of a classical 5-point scale based on methodological recommendations [17]. To exclude or include (finalize) an item, the abovementioned mean and SD thresholds must be met for both relevance and maturity.

Feedback will be proactively provided by the executive committee for each new round (active feedback loop): participants re-evaluate items that were not excluded, assisted by aggregated ratings of the whole panel (as histograms), moderated anonymized comments from the previous round, and their own previous ratings. This format enables reflection and informed re-evaluation.

Besides participating in the eDelphi panel, each expert completes a self-disclosure of their expertise in clinical IE. Consistent with Häder [13], no demographic data will be collected beyond gender and country of affiliation. Anonymity among participants will be preserved throughout the eDelphi panel. At the end of the first round, participants will be invited to indicate whether they wish to participate in the final consensus meeting taking place after the completion of the third round and to contribute to the final publication of the CINEX guideline and the explanatory document.

A pretest of the first-round survey will be conducted among the executive committee (comprising authors DR, HM, and KD) to ensure clarity and functionality. These individuals will not participate in the actual eDelphi rounds.

Consensus Meeting, Finalization, and Outlook

For the final step of the guideline development process, a face-to-face hybrid consensus meeting is conducted, organized as a workshop at the MEDINFO conference in August 2025 <6,7,8>. During the workshop, the results of the Delphi process are presented, and items that achieved consensus are reviewed for resolving minor ambiguities and final phrasing. Items without prior agreement are discussed and, if needed, resolved by open voting. Consensus is defined as ≥80% agreement. The meeting is considered quorate if ≥50% of the panelists of the first round of the eDelphi panel are present. Persistent disagreements will be documented and reported transparently in the publication of the final guideline. The workshop shall result in the formal finalization of the CINEX guideline; thereafter, the guidance statement is finalized <9>, complemented by an E&E document <10>, and both are made available as publication <11>. The guideline development process will be reported in a structured way in accordance with the Accurate Consensus Reporting Document (ACCORD) reporting guideline [18].

Responsibilities for postpublication activities <12‑18> are divided among the contributing authors: the CINEX guideline will be hosted on an open access online platform for ongoing feedback <12,14,16>, will be pilot-tested by panelists, and its impact on reporting quality will be evaluated. To ensure durability, an executive group will review the CINEX guideline at regular 3-year intervals, evaluating its impact <15> and issuing updates when new evidence or methods make a revision necessary <18>. We seek endorsement from journals and societies <13>. Translation is not planned for the initial release <17>. By following these postpublication activities, we aim at establishing a long-term relevance of the CINEX guideline.

Ethical Considerations

This study was granted an exemption by the competent ethics committee of the canton of Bern on April 29, 2025 (ID: Req-2025‑00587). All eDelphi study participants gave electronic informed consent prior to participation.

Results

A preliminary guideline comprising 28 items and 5 dimensions (information model, architecture, data, annotation, and outcome) was published in August 2024 [12]. These items will be presented in the first round of the eDelphi study.

Discussion

Principal Results

This protocol presents the development of the CINEX guideline, a reporting guideline specifically developed for clinical IE studies. The CINEX guideline addresses key challenges in the field—including inconsistent terminology, reporting, and evaluation—by providing a structured, technology-agnostic framework tailored to IE tasks in health care. By design, the CINEX guideline accommodates both rule-based and data-driven approaches, including LLM-based methods by focusing on essential reporting dimensions (eg, data sources, annotation strategies, information model, and evaluation metrics) that apply across paradigms. This ensures that differences in implementation, such as rule-based extraction pipelines or end-to-end architectures, can be transparently described and compared within a shared reporting structure. To facilitate adoption, we will pursue parallel endorsement of the CINEX guideline by multiple journals in biomedical informatics, promote its use by providing an online website (inspired by TRIPOD-LLM [7]), and invite panelists to apply the CINEX guideline in their own research.

Limitations

Our approach has several limitations. First, the development process for the CINEX guideline is based on guidance for reporting guideline development in health research as outlined by Moher et al [11]. While the CINEX guideline addresses health-related research, it also intersects significantly with the computer science domain. Currently, however, there are no methodological frameworks for reporting guideline development in computer science. Given this gap, we adopted the framework of Moher et al [11], which is well-established and has informed the development of most reporting guidelines endorsed by the EQUATOR Network, including guidelines with a technical focus (eg, CONSORT-AI). Nonetheless, we acknowledge that

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this choice may not fully capture disciplinary nuances outside the health sciences. The CINEX guideline will therefore be developed with input from the computer sciences as well as clinical disciplines and be tested for clarity and relevance in both contexts.

Participant recruitment relies partly on professional networks, which may limit diversity. While consensus thresholds and item rating methods are clearly defined a priori with this protocol, they remain subjective to a certain degree. The final in-person consensus meeting, although valuable for discussion, may introduce social influence and new opinions from participants that have not participated in the eDelphi panel. Additionally, the CINEX may require future updates to accommodate rapid developments in LLMs and multimodal approaches.

Comparison With Prior Work

The CINEX guideline builds on the methods used in guidelines like CONSORT-AI, SPIRIT-AI, and TRIPOD-LLM and is the first to focus specifically on clinical IE. Our study design incorporated detailed feedback loops and a 10-point scale instead of a 5-point scale aiming to improve rating precision. While existing AI guidelines address broader study types, none are tailored to the unique needs of clinical text-based IE, underscoring the CINEX guideline's distinct contribution. Furthermore, we seek to address the challenges faced by prior reporting guidelines: first, adoption and enforcement by journals have often been inconsistent, thus limiting their impact; to mitigate this, we will accompany the CINEX guideline with an online template checklist for authors and actively engage journals to encourage endorsement. Second, ambiguity in checklist items has been a barrier to compliance; therefore, the CINEX guideline will be supported by a detailed E&E document. Third, the CINEX guideline will include example items tailored for computer science as well as medical audiences, supporting broader adoption across disciplines.

Conclusions

The CINEX guideline fills a critical gap in the reporting of clinical IE studies by offering a dedicated, consensus-driven framework. It aims to improve reproducibility, comparability, and transparency in this growing area of clinical NLP. Continued community involvement and iterative updates will be essential to ensure its ongoing relevance.

Acknowledgments

The CINEX (Clinical Information Extraction) guideline is part of a PhD project at the University of Geneva. No dedicated funding was obtained. Generative AI (ChatGPT [GPT-4o and GPT-5] OpenAI) was used to assist with language editing of the manuscript draft and improve clarity and formatting of responses to peer review comments. No artificial intelligence tool was used to generate original scientific content. All content was reviewed and approved by the authors.

Authors' Contributions

Conceptualization: DR and KD
Methodology: DR
Supervision: HM and KD
Writing—original draft: DR
Writing—review and editing: DR, HM, and KD

Conflicts of Interest

None declared.

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Abbreviations

ACCORD: Accurate Consensus Reporting Document
AI: artificial intelligence
CINEX: Clinical Information Extraction
CONSORT-AI: Consolidated Standards of Reporting Trials–Artificial Intelligence
E&E: explanation and elaboration
eDelphi: electronic Delphi
EQUATOR: Enhancing the Quality and Transparency Of Health Research
IE: information extraction
LLM: large language model
NLP: natural language processing
SPIRIT-AI: Standard Protocol Items: Recommendations for Interventional Trials–Artificial Intelligence
TRIPOD+AI: Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis–Artificial Intelligence
TRPIOD-LLM: Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis Or Diagnosis specifically tailored for large language models

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Protocol

Development and Validation of the "Basic Oral Health Assessment Tool" (BOHAT) for Nondental Health Care Professionals to Use With the Indian Adult Population: Protocol for a Mixed Methods Study

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Abstract

Background: Oral health is a significant indicator of general health, well-being, and quality of life. The prevention of oral health problems requires periodic inspection of the oral cavity. Routine oral health examinations at the individual level appears to be one way to deliver quality oral health care but are too often missed as an opportunity for improved oral health in the nondental health care setting in India. This is because of limited training and inaccessible or lack of specialized oral health assessment tools.

Objective: This study will focus on the development, validation, and implementation of the Basic Oral Health Assessment Tool (BOHAT) to improve the oral health assessment capabilities of nondental health care professionals and thus contribute to improved overall health outcomes of the Indian adult population.

Methods: This study will be a mixed methods, multistage study conducted in 3 stages. The study will be conducted with 708 nondental health care professionals in 33 Primary Health Centers (PHCs) of Mangalore Taluk, Karnataka. Ethical approval was sought from the institutional ethics committee of Manipal College of Dental Sciences Mangalore. Informed consent will be obtained from every participant prior to the study. A literature review and qualitative interviews will be used for item and domain generation with respect to BOHAT, and an expert panel review and pilot testing will be used to refine the items and domains. Finally, statistical analyses will be conducted to validate the reliability and consistency. The second phase will involve capacity building and user experience exploration through comprehensive training for nondental health professionals using audio and visual aids, with hands-on learning methodologies including relevant feedback processes in the form of focus group discussions. The third stage will check the effectiveness of BOHAT regarding the changes in knowledge, attitudes, and practices through pre- and posttraining questionnaires, which will then be followed by a retention analysis 3 months later.

Results: As of January 20, 2025, the study is in its preliminary phase: "Substage A: Item and Domain Development." We have received institutional ethics committee and Institutional Protocol Approval Committee approval for the study. Data collection procedures have not started yet. The study is progressing as per the planned timeline.

Conclusions: The BOHAT study holds considerable potential to promote oral health care through collaborative and interdisciplinary approaches. It will facilitate early diagnosis, timely referrals, and comprehensive care by integrating assessment actions for oral health into routine practices of nondental primary health care professionals.

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KEYWORDS

oral health assessment tool; oral health; screening; nondental health care professionals; primary health centers; India; tool validation; health care training; mixed methods research

Introduction

Oral health is a significant indicator of general health, well-being, and quality of life [1]. The functioning of the oral cavity, teeth, and orofacial structures, which enables people to perform fundamental bodily activities like eating, respiration, and speaking, is commonly referred to as oral health, and it undergoes changes throughout the various stages of life, from early childhood to advanced age [2,3]. Oral health problems can have a significant effect on people's quality of life, interpersonal connections, general well-being, and self-esteem [4]. Therefore, emphasizing the importance of preventive measures and early detection of oral diseases becomes crucial in mitigating the likelihood of developing subsequent challenges impacting both oral and overall health.

Oral health assessments serve as a good indicator of disease risk, the proper management of existing disease, and even the improvement of health outcomes because of appropriate oral health care [5]. Prevention of oral health problems requires periodic inspection of the oral cavity. Routine oral health examinations at the individual level appear to be one way to deliver quality oral health care but are too often missed as an opportunity for improved oral health in the nondental health care setting [6]. Health care professionals, from the allopathic doctor (physician and surgeon) to Ayurveda, yoga, naturopathy, Unani, Siddha, and homeopathy (AYUSH) practitioners; nurses; auxiliary nurse midwives; and community health workers (CHWs) [7], are very essential for the delivery of holistic health care but have limited capacity to comprehensively assess oral health issues and subsequently intervene because of significantly limited training on its own as well as inaccessible or lack of specialized supportive tools adapted to suit the population. This might ultimately delay the diagnosis and institution of appropriate interventions for oral health conditions in such patients and increase the possibility of further disease progression, which will then compromise overall health outcomes.

The separation between oral health and general health care practices may contribute to the insufficient integration of oral health assessments into routine health care protocols, limiting the overall effectiveness of health care delivery. Screening of oral health, early detection and triage of oral health issues, and immediate referral to dental specialists ultimately require the integration of frontline health care professionals [8]. Several instruments for health care providers to evaluate oral health have been developed over time. A few of these tools are the Holistic Reliable Oral Assessment Tool (THROAT) [6], Revised Oral Assessment Guide [9], Oral Health Assessment Tool (OHAT) [10], and Oral Assessment Guide [11]. However, the tools in current use lack reference pictures, challenging the completeness, relevance, and clarity of wording [12]. The Federation Dentaire Internationale and International Consortium for Health Outcomes Measurement collaboration developed a preliminary standard core set of oral health outcome measures for adults with a primary focus on periodontal disease and caries. The subsequent action is to conduct a validation and feasibility study in different clinics seeking to fine-tune the Adult Oral Health Standard Set more, and studies to do that are ongoing [13].

To bridge this gap, this research aims to develop, validate, and implement a Basic Oral Health Assessment Tool (BOHAT) that is tailored for use by nondental health professionals working with populations aged 18 years and older in India. BOHAT will be a screening tool for health professionals who are not dentists, to enable rapid identification of the need to refer patients for dental consultation. This tool will further empower nondental health care professionals to perform effective oral health assessments, thereby addressing an emerging critical need for holistic health care approaches at large. This study will focus on the development, validation, and implementation of BOHAT to improve the oral health assessment capabilities of nondental health care professionals and thus contribute to improved overall health outcomes of the Indian adult population.

Methods

Stages

This study will be a mixed methods, multistage study conducted in 3 stages. Stage 1 focuses on the development and validation of the tool. Stage 2 involves capacity building and user experience exploration, and stage 3 aims to check the effectiveness of BOHAT using a pre-post intervention study (Figure 1).

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Figure 1. Multiple stages of the study. BOHAT: Basic Oral Health Assessment Tool.

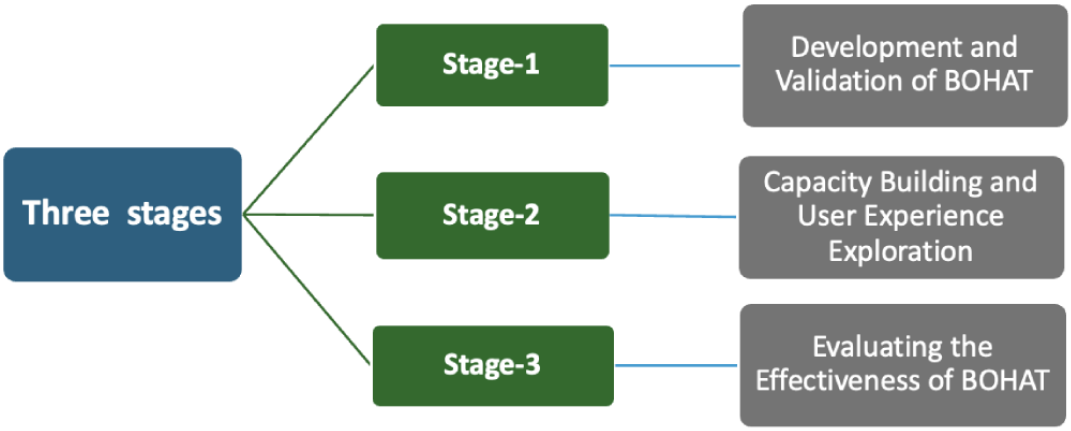

Study Setting

The study will be carried out in Primary Health Centers (PHCs) located within Mangaluru Taluk of Dakshina Kannada District. This selected study setting will enable insights into the applicability and effectiveness of the developed tool, BOHAT, under Mangaluru Taluk's health care infrastructure. In this approach, oral health assessment practices will be examined more precisely and contextually in relevance to the geographic area selected. PHCs in this region will be the primary sites for data generation, data collection, pilot testing, validation studies, and execution of training programs for nondental health professionals. Approval to conduct the studies in PHCs will be obtained from the District Health Officer, Dakshina Kannada, Karnataka.

Sampling Technique and Sample Size

The sampling technique used in this study is census sampling or complete enumeration, which includes all 708 nondental health care professionals working in the 33 PHCs of Mangalore Taluk. This covers professionals from both urban (10 PHCs) and rural (23 PHCs) areas, ensuring that this target population is widely and appropriately represented.

Nondental health care professionals, including allopathic doctors (physicians and surgeons), AYUSH practitioners, nurses, auxiliary nurses, midwives, and CHWs [7]. Within the urban PHCs, there are 216 nondental health care and allied health care professionals, while the rural PHCs have a workforce of 488 nondental health care and allied health care professionals. The inclusive nature of this study aims to involve all 708 nondental health professionals across all 33 PHCs in Mangalore Taluk who provide their consent for participation.

Study Framework

BOHAT will be designed as a paper-based instrument with the inclusion of reference pictures. These reference images serve as visual aids to enhance and facilitate the oral health assessment process**.**

Stage 1: Development and Validation of BOHAT

Stage 1 has 4 substages (Figure 2).

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Figure 2. Conceptual framework for the development and validation of the Basic Oral Health Assessment Tool (BOHAT).

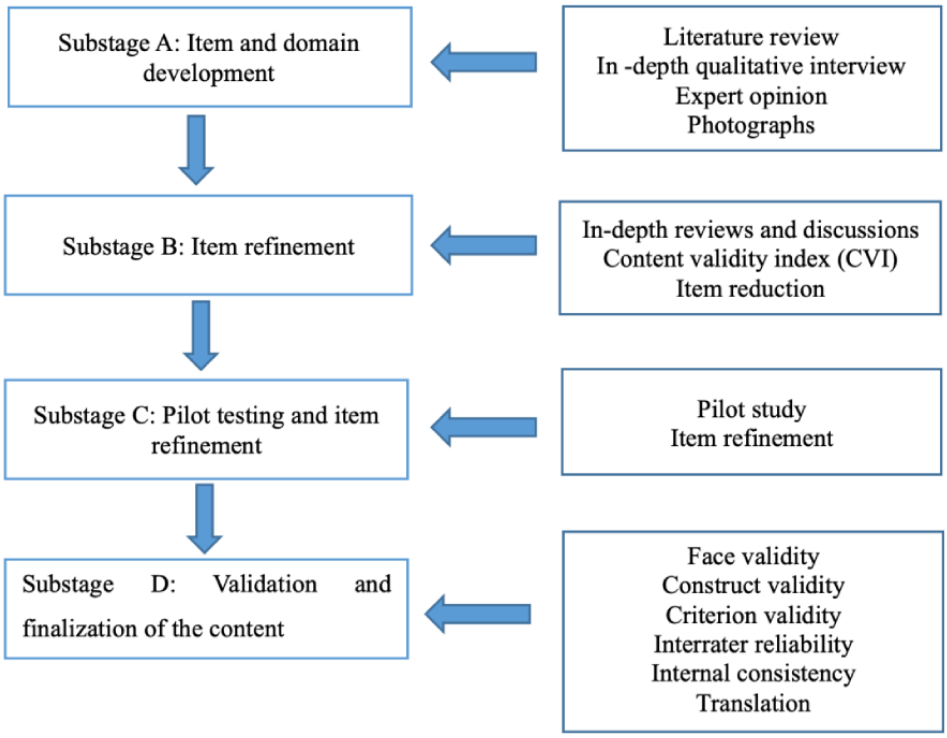

Substage A: Item and Domain Development

A literature search will be conducted to obtain data on oral health, oral hygiene, and common dental problems among Indian adult population. An in-depth qualitative interview will be undertaken with nondental health professionals to explore the challenges and complexities inherent in oral health assessment. Additionally, this approach aims to identify key domains that should be incorporated into the BOHAT. Collaboration with oral health care experts from public health dentistry, oral medicine and radiology, oral pathology, oral surgery, periodontics, endodontics, and prosthodontics will identify relevant and essential oral health problems specific to the Indian adult population.

Photographs for BOHAT will be sourced from patients availing of camps organized by the Department of Public Health Dentistry, Manipal College of Dental Sciences, Mangalore. These photographs will cover a vast spectrum of conditions and scenarios pertaining to oral health, thereby presenting a sample of what nondental health professionals might encounter during their assessments. Prior to photographing, proper ethical consent will be obtained from the patients. The photographs will be taken personally by the principal investigator after completing training in intraoral photography. This will help maintain uniformity so that image collection and image capture follow standardized procedures.

The photographic setup for the intraoral photos will include a Canon EOS 90D camera with a Canon EF 100mm f/2.8L Macro IS USM lens. Adequate lighting in the mouth will be provided using a Canon MR-14EX II Macro Ring Lite, which provides lighting without any harsh shadows and gives the best chance of even illumination. The images will have a resolution of 32.5 megapixels and will be saved in both RAW and JPEG formats. This ensures they will provide sufficient detail and can be modified to suit the intended use. The minimum and maximum ISO standards will be set between 100 and 200, aperture will be set at f/22 to ensure enough depth of field, and the shutter speed will be set between 1/125 and 1/200 seconds in order to minimize motion blurs. The custom white balance will be by intraoral light. Each photo will be captured from a distance between 30 cm and 40 cm, and since the ring flash will be used, a fixed distance will be sustained. Each file will be numbered, kept in encrypted digital storage, and secured to ensure data integrity.

Images will be identified and selected by subject matter experts according to the relevance, clarity, and appropriateness of content in relation to the goals of BOHAT. Each image will be critically evaluated to ensure that the wide spectrum of oral health conditions and scenarios that the nondental health care professionals may come across during assessment is captured. This includes ensuring there is sufficient detail and contextual setting in the images for both normal and pathological conditions. Images will further be categorized based on the diagnostic significance, such as specific oral issues like dental caries, periodontal diseases, or mucosa lesions. Selected images will then be further checked for quality assurance to ensure they are educationally valuable, appropriate for educational purposes, and meet ethical standards.

Substage B: Item Refinement and Item Reduction

The items on the BOHAT will undergo rigorous examinations, review, and engagement with the expert panel so that remarks on issues related to clarity, relevance, and appropriateness are captured. Items will also be subjected to systematic refining through discussions of the panels with respect to clarity, relevance, and appropriateness. To evaluate the test's content validity, the content validity index (CVI) will be computed to

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measure the relevance of each item. Items with a low CVI (eg, item-level CVI<0.78) will be revised to improve their validity, or only the most relevant items will be retained. There will also be feedback from various stakeholders to enhance the contextual and functional appropriateness of the tool.

Substage C: Pilot Testing and Item Refinement

We will approach 20 nondental practitioners to pilot test the tool for its usability and clarity. This feedback will be used to provide input on the validity and reliability of the tool. Based upon the results of the pilot testing, these improvements will fill in the gaps before formal validation occurs. Descriptive statistics along with qualitative coding of each feedback will be used for initial evaluation of the tool's performance.

Substage D: Measurement Properties and Finalization of the Content

Consensus-Based Standards for the Selection of Health Measurement Instruments Taxonomy

Development and validation will be based on the COSMIN (Consensus-Based Standards for the Selection of Health Measurement Instruments) taxonomy [14]. The COSMIN framework will ensure that this newly developed tool adheres to high methodological standards and permits a rigorous assessment of its primary measurement properties including validity, reliability, and responsiveness.

Validity Testing

For face validity, feedback will be obtained from dental professionals, nondental health professionals, and other stakeholders to establish whether the tool is easy to read, accurate, and relevant. A qualitative assessment will follow, to ensure that the tool is fit for purpose and feasible for end users.

For content validity, content experts will assess the CVI of each item for relevance, clarity, and representativeness. These experts will provide CVI scores as a basis for revision, ensuring objectivity through systematic thresholds, for instance, an item-level CVI≥0.78.

Construct validity of BOHAT will be thoroughly assessed to confirm the extent to which the measure assesses oral health assessment capacity for nondental health care professionals. Exploratory factor analysis will be conducted to determine the underlying structure of the tool by grouping items into the dimensions of knowledge, attitudes, and practices (KAP) of oral health assessments. The appropriateness of the factor structure will be considered with the help of statistical tests such as the Kaiser-Meyer-Olkin test as well as the Bartlett test of sphericity. Confirmatory factor analysis will then validate the identified structure. A root mean square error of approximation ≤0.08 and comparative fit index ≥0.90 will be used to assess fit.

To determine criterion validity, each BOHAT item will be assessed against standardized criteria derived from the World Health Organization (WHO) oral health survey [15]. Each item will be directly mapped to the corresponding items or domains in the WHO oral health survey. For instance, the items measuring dental caries, periodontal health, and oral hygiene status will be benchmarked against the WHO criteria on such conditions. BOHAT and the WHO oral health survey will be administered to the same sample of participants. The sensitivity and specificity parameters will be determined as a statistical measure or estimate of validity for each considered BOHAT item in comparison with the WHO criteria for oral health conditions. Sensitivity and specificity values will show the diagnostic accuracy of the items.

Positive and negative predictive values will provide measures representative of usable or functional utility for each variable under study. Reference variables that form a strong connection with either a positive or negative outcome might be derived from those that create the curves and an area under them in the receiver operating characteristic (ROC) curve using the area under the curve (AUC) as an overall measure of accuracy, such that AUC values ≥0.8 indicate good performance. Items with low sensitivity or specificity will either be reconsidered or removed to obtain the most diagnostically relevant and accurate items.

Reliability Testing

For internal consistency, the Cronbach α will be computed and used as a measure of internal consistency with respect to the degree to which something is being measured as intended. The Cronbach α ranges from 0 to 1. An α near 1 indicates a high internal consistency of the items. Standardization of the scoring criteria for BOHAT, on a consensus basis through collective opinion and expert opinion on subject matter issues, will allow uniformity and objectiveness in assessments.

For interrater reliability, different nondental health professionals will independently use BOHAT with the same patients, and the scores will be checked for their agreement. The ratings proposed by different raters may be statistically analyzed using metrics like the Cohen kappa or the intraclass correlation coefficient (high values [≥0.75] represent excellent agreement).

For test-retest reliability, BOHAT will be evaluated among the same participants at specific intervals to estimate score stability. This will be done using metrics reflecting continuity across time intervals such as intraclass correlations.

Responsiveness of BOHAT

Evaluating the responsiveness of BOHAT will be a vital element in determining the validity of the training for augmenting the oral health assessment skills of nondental health professionals. Differences in scores before and after the training will be assessed using the pre- and posttraining questionnaires as compared with the participants' self-reported changes in confidence and competence of conducting oral health assessments. Focus group feedback will also be analyzed to obtain a sense of perceived skill improvements by participants. Distribution-based methods will be used to evaluate changes in pre- and postintervention scores, including calculation of the effect size (Cohen *d*) to measure the magnitude of change and the standardized response mean to evaluate BOHAT responsiveness to detect clinically meaningful changes. Statistical comparisons of pre- and posttraining scores will be conducted using paired *t* tests or Wilcoxon signed-rank tests. Additionally, minimal clinically important differences will be

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determined using ROC curve analysis to interpret thresholds of change in the BOHAT that are considered clinically significant.

Translation of BOHAT

Although BOHAT is primarily in the English language, compliance will ensure proper adaptation of BOHAT for application in Kannada-speaking regions. Adjustments could include providing explanations on linguistic and cultural settings whenever there is a need for clarification. The procedure will likely correspond to the systematic approach provided for the back-translation model by Brislin [16] and comprise the steps outlined in the following sections.

Forward Translation

The test items will be in English; however, key instructions, terms, and technical language will be translated into Kannada by a well-trained bilingual expert who is a native Kannada speaker. This step will provide nondental health care professionals who are comfortable with Kannada the capacity to understand the use and purpose of the tool with ease.

Review by an Expert Team

To ensure cross-cultural equivalence, all translated versions will be reviewed by a multidisciplinary team. A total of 3 oral health experts and nondental health care professionals who have experience with oral health assessments will check the cultural relevance of the terms and concepts with the research team. We will consult 5 nondental health care professionals for practicality and relevance of the tool in the Kannada-speaking health care setting. Any semantic and conceptual changes required will be undertaken based on their feedback, resulting in a first Kannada version of BOHAT.

Back-Translation

A second professional bilingual translator will then back-translate the preliminary Kannada version into English. This translator will be blinded to the original English version to avoid bias.

Comparison and Revisions

The back-translated English version of BOHAT will be compared with the original English version, during which contradictions or deviations will be detected. Revisions will be made when necessary to ensure that the Kannada clarifications correspond to the meaning of the original English version, hence preserving the integrity of the tool items.

Pilot Testing

A refined version of BOHAT in Kannada will be pilot tested with 20 nondental health practitioners in rural and urban PHCs. Each participant will pilot test the tool and provide feedback on items that appear to be unclear or culturally insensitive. The feedback for clarity and utility of additional Kannada content will help determine whether they can understand and use BOHAT properly. The participants will rate each item on a scale from 1 to 5 for relevance, clarity, and specificity. The feedback from this phase will guide further adaptation toward achieving semantic and content equivalence.

The English version will be the final version of BOHAT, supplemented by additional explanatory material in Kannada for users needing language support. This will ensure that the original tool stays in the intended format in English while remaining culturally relevant and accessible to Kannada-speaking health care professionals in the setting.

Stage 2: Capacity Building and User Experience Exploration

Process

The training modules will have details on the purpose of BOHAT, administration procedure, and interpretation of the results. Experts will be given this module, and for content and face validity, they will be invited to classify the need for each question according to a 3-point Likert scale: “necessary,” “useful but unnecessary,” and “unnecessary.” Depending on the experts’ opinion, the content will be modified. The BOHAT training module will adopt a multimodal mode of learning: audio, visual, and audiovisual modes. This will ensure maximum benefits from training sessions so that better understanding and actual application in oral health assessment practices can be achieved.

The module for the training will include how to navigate the tool, interpret the results, and communicate the findings efficiently to patients. Hands-on training sessions will be conducted regarding using the tool. A focus group discussion will be conducted with nondental health professionals to explore the experiences of the participants, challenges faced by them, and perceptions about BOHAT’s usability.

Training Module

This training module is 4 hours long and will be delivered using a combination of audio, visual, and audiovisual aids. The comprehensive training on common problems of oral health among the adult population in India shall draw upon a variety of subjects to provide the necessary background to a health professional. The module will start with an overview of the role of health professionals in disseminating awareness regarding oral health problems and the importance of dental health in relation to overall health. The epidemiology of oral health in India will be presented with data on the most common oral health problems among adults.

The module will consider specific oral health problems often seen in adults. It will cover in-depth the processes of dental caries, periodontal diseases, and tooth sensitivity; the association between tobacco and oral health; potentially malignant disorders and oral cancer; other oral lesions; and the risk factors and lifestyle factors, like diet and lifestyle, affecting oral health. At the same time, emphasis will be placed on early detection and prevention. The module will cover potential solutions to improve access and further incentivize health professionals to incorporate oral health discussions into their practice. The training will be completed with key takeaways underscoring the importance of oral health awareness and preventive measures. An interactive question-and-answer session will be conducted, and participants will have time to share their experiences and discuss special concerns.

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Stage 3: Evaluating the Effectiveness of BOHAT

A validated questionnaire will be used by each nondental health professional before the training session to gauge their baseline KAP regarding oral health assessments. The same questionnaire administered after training will help assess the impact and effectiveness of BOHAT on the KAP of nondental health professionals. The scores obtained from the posttest of BOHAT will be compared with benchmarks as observed by dentists. This comparative assessment aims to establish the effectiveness of BOHAT through the tool's degree of conformance with existing standards in dental practice. Retention analysis 3 months after the posttest will evaluate and measure the retained knowledge and acquired skills from the training sessions. Results of the retention analysis will rate how effective the training was when applied and in the long run to help modify or reinforce the practice of oral health assessment.

Statistical Analysis

Chi-square tests will be used to compare the number and percentage of oral health problems detected in a timely manner by nondental health care professionals before and after the training. Referral frequencies before and after training will be used to measure the changes in early referral behavior. Paired *t* tests or Wilcoxon signed-rank tests will be used to analyze any differences found. We will create a reflected quantitative summary of baseline knowledge, and improvement in the KAP of oral health will be evaluated using validated pre- and posttraining questionnaires. Thematic analysis of the qualitative data obtained through the semistructured interviews and focus group discussions will help provide insights into improvements in collaboration with dental and health professionals.

Data from the training assessment and improvements in competence will be analyzed using paired *t* tests, and the reliability of BOHAT will be assessed using the Cronbach α. Referral logs will subsequently be analyzed to gauge increased accessibility to dental care, and trends over time will be evaluated using longitudinal data analysis methods such as linear mixed-effects models. Finally, retention analysis will be conducted 3 months after the training to examine the sustainability of acquired knowledge and skills measured using KAP questionnaires, and time effects will be analyzed using repeated measures ANOVAs.

Ethical Considerations

The Declaration of Helsinki principles will be followed while conducting the research [17]. Ethical approval was sought from the institutional ethics committee of Manipal College of Dental Sciences Mangalore, Manipal Academy of Higher Education (reference number: 24023). Additionally, the Institutional Protocol Approval Committee of the Manipal Academy of Higher Education provided approval for the study (2300400101). Informed consent will need to be provided by every participant after verbal and written information regarding the study is given to them.

All participant data will be anonymized: Names, addresses, or any other forms of unique characteristic directly identifiable in any data collected will be removed from the data set prior to its analysis. In preparation for data coding, all participants will be allocated an ID code that links to personal details using a secure key held separately. For sensitive data that cannot be anonymized, such as qualitative responses or images, access to identifiable data will be strictly limited to authorized research team members. Electronic data shall be stored on secured, encrypted, password-protected devices. Physical records shall be kept in locked cabinets. There shall be no sharing of identifiable data beyond the research team, and the data shall be used only for research.

Participants will not receive monetary compensation for this study, but they will be compensated for any travel costs associated with their involvement in the study. No identifiable characteristics of the participants will be described in the manuscript, supplemental materials, or images.

Results

Study Status

As of January 20, 2025, the study was in the preliminary phase (Substage A: Item and Domain Development). The study will be carried out for a period of 42 months. We have received institutional ethics committee and Institutional Protocol Approval Committee approval for the study. The research team had a meeting with the District Health Officer, Dakshina Kannada District on January 10, 2025, and the study protocol was submitted to the District Health Officer for review. Data collection procedures had not started yet. The study was progressing as per the planned timeline.

Dissemination

This study will be complemented by in-depth qualitative and quantitative analysis. The results of the study will then be presented at relevant scientific conferences and professional meetings as oral presentations and published in academic journals.

Expected Outcomes

The expected outcomes of the study include timely identification of oral health problems and an increase in early referral behavior. This will improve oral health assessments by nondental primary health care providers and oral health KAP of these nondental primary health care providers, leading to enhanced collaboration with dental and other health professionals and improved training and competency. Increased access to dental care is also expected.

Discussion

Overview

Oral health problems can have a significant effect on people's quality of life, interpersonal connections, general well-being, and self-esteem [4]. It is therefore important to address the role of preventive techniques and early diagnosis of oral pathologies in reducing the risk of developing further oral-health-related complications affecting not just oral but also general health. Therefore, oral health assessments are an important part of estimating disease risk, monitoring existing conditions, and improving oral health [5].

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The current educational frameworks for these practitioners do not sufficiently cover oral health topics, leading to gaps in knowledge and practice [18]. Health care providers face problems effectively assessing and addressing oral health issues in the population because of a lack of adequate training and inaccessibility of tools specialized for the Indian population.

The Brief Oral Health Status Examination allows carers to monitor the dental health of patients in aged care institutions who are cognitively challenged as well as those who are not. However, the study was conducted in only one nursing home, and the sample size was small [19]. THROAT is another instrument for the oral evaluation of hospitalized older adult patients with medical conditions [6]. OHAT is an assessment tool designed for people with cognitive impairment and is easy to use by nondental staff, such as nurses and caretakers. Nonetheless, OHAT has drawbacks, including nonsignificant and weak correlations and percent agreements for the saliva, oral cleanliness, and dental pain categories [10]. The Oral Health Screening Tool for Nursing Personnel (OHSTNP) evaluates the functioning of the mouth as well as oral health status for inhabitants in long-term care homes. Although the OHSTNP had high specificity for screening the lips, tongue, gums, tissues, saliva, and oral cleanliness, its sensitivity is low, indicating the need for further improvements in these categories [20].

The Minimum Data Set (MDS) is a standardized assessment tool used extensively in long-term care settings that includes an oral health component. Nevertheless, studies have indicated that oral and dental items in the MDS 2.0 lack validity and often underdetect oral health problems among residents of nursing homes [21]. This limitation highlights the importance of developing an instrument like BOHAT, which can both assess oral health conditions with relative accuracy and, most importantly, provide actionable findings for nondental health care workers. The Dental Hygiene Registration (DHR) is a dental hygiene assessment scale suitable for nurses working in institutions [22]. The DHR index requires individual judgment and attendance by a dental professional. The DHR is not an alternative to examinations by dental professionals but an aid for nurses and other caregivers in their daily work [22]. The Oral Assessment Sheet aims to improve the oral health of older adults who require nursing care using 3 items in each of the following 3 categories: oral hygiene, biting and chewing, and oral function [23]. However, challenges concerning its use for oral assessments by care workers have been highlighted [23]. BOHAT seeks to fill these gaps by providing a more credible and valid assessment framework

Within nondental health care settings in India, a critical issue has emerged surrounding the insufficient attention given to oral health due to a lack of adequate training, lack of tools, and underutilization of health care providers for oral care [24]. The role of AYUSH practitioners as nondental health professionals is often underappreciated or even underutilized in the Indian health care setting. Josyula et al [25] pointed out the discrepancies in role perceptions among various health system actors, indicating that AYUSH practitioners are not fully integrated into the public health framework, which limits their ability to effectively contribute to oral health promotion. This lack of integration is echoed in the findings of Kharbanda et al [18], who emphasized that AYUSH professionals, when appropriately empowered with training, can go a long way in promoting oral health. CHWs have a role in addressing oral health issues, but their effectiveness is hindered by poor training and inadequate resources.

According to Najmunnisa et al [26], CHWs can be empowered to serve as oral health literacy workers, but actual knowledge and attitudes toward oral health are often insufficient for promoting preventive behaviors. Reddy and Singh [27] also noted that a comprehensive spectrum of health-promoting behaviors, including oral health, is central to community well-being. The necessity of integrating oral health education in the training of CHWs has thus been demonstrated by these studies, which have shown positive results after CHWs had appropriate structured training [28]. Promotion of oral health by professionals not trained as dentists and by nurses and midwives has also been documented. Villarosa et al [29] discussed how indigenous health workers promote oral health while a woman is pregnant, and their findings suggest that nondental professionals could positively impact maternal oral health. Likewise, only one study conducted by Garry and Boran [30] considered that, to improve the care of older adult patients, enhanced oral health training needs to be incorporated within the nursing curriculum. With a more concrete educational foundation, oral health outcomes could be improved across a variety of demographics.

The challenges that nondental health care providers face in India are not unique to that country. International studies conducted by McGrath et al [31] and Scrine et al [32] showed that health professionals from all disciplines acknowledge their role in oral health, yet they lack the training and resources to effectively develop programs. Therefore, there is a universal demand for cross-disciplinary collaboration and training to ensure that oral health receives adequate emphasis in broader health initiatives.

Insufficient research has been conducted to determine how oral health assessment tools can be integrated into the routine practice of nondental health care professionals. Furthermore, the existing literature does not adequately address the training needs to attain effective tool use among these professionals. Evidence pertaining to the validation of the oral health assessment tools in varying clinical scenarios and patient populations is also lacking. Finally, there is a lack of literature investigating the effectiveness of enhanced oral health assessments on overall patient outcomes and preventive care. These gaps in research provide the rationale for the development and validation of BOHAT to fill these gaps with a culturally appropriate tool that can be efficiently used by nondental health care professionals in India.

Beyond dentistry, oral health is important for general well-being and good health [33]. Unfortunately, the absence of specialized instrumentation for nondental health care providers often creates a barrier to early detection and treatment of oral health diseases. This calls for a comprehensive and easy-to-use instrument; hence, the need exists for BOHAT. It allows nondental health care professionals to conduct effective oral health assessments, thus addressing the need for holistic approaches to health care.

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Challenges and Solutions

A major challenge can be a lack of awareness of the importance of oral health care among nondental health professionals. There is a need to conduct an awareness drive with campaigns aimed at professional groups and the community. Conducting a media campaign on television, radio, print media, and social media regarding the importance of oral health and its interlinkage with general health will be very useful. Another challenge is resources and funding. A possible solution for this challenge can be the exploration of grants aimed at health care innovations and public health improvements. Integration into current health care systems presents yet another possible obstacle. Integration issues can be identified and dealt with by working closely with health care administrators to ensure the integration of BOHAT into existing workflows, developing clear protocols and guidelines on implementation, then piloting the program in a few centers prior to a wider area. There can be difficulties relating to the collection and management of data. These may be overcome by ensuring strong systems for data management and error-free and effective data collection, training health professionals in data entry and management, and digitizing tools for data collection and analyses. For its sustainability, this program will require a long-term sustainability plan that includes periodic training and follow-up support for health professionals. A monitoring and evaluation framework should also be developed to check the program's impact, make necessary adjustments, and create community ownership and involvement to help sustain interest and participation.

Strengths of the Study

The BOHAT study fosters holistic health care that is interdisciplinary in nature by its inclusion of nondental health care professionals, therefore providing the basis for oral health to become part of general health assessments. It builds the capacity of nondental health professionals with training and education for better health outputs. This study aims to enhance the capacity of nondental health professionals in relation to the identification and referral of oral health conditions and increase access to dental care, particularly in underserved areas. This way, early identification and intervention will help prevent the progression of these oral diseases and reduce the health care system burden—improving the quality of life of patients. The research conducted here contributes to many sustainable development goals (SDGs) that pertain to good health, quality education, reduced inequalities, and effective partnerships.

Link to SDGs

Oral health assessments are crucial for identifying problems early and preventing more severe oral and general health conditions [34]. Therefore, BOHAT is linked with many SDGs. BOHAT will support the attainment of several health and well-being SDGs. It will help support SDG 3: "Good health and well-being" by providing a systematic approach for performing oral health assessments [35]. It will help with the early diagnosis and prevention of oral diseases by building the capacity of nondental health professionals, hence promoting health and well-being. This study aligns with SDG 4: "Quality education" by training nondental health care professionals on the use of BOHAT and promoting continued education and capacity building, ensuring that health care professionals have the proper skills to manage oral health [36]. The study will help reduce inequalities in oral health, working in concert with SDG 10: "Reduced inequalities" [37]. Hence, it will reduce health disparities in oral health outcomes but ensure equitable access to quality health care. This will add depth to the exploration of oral health practices within a specified region, like Mangaluru Taluk, and establish ways to reduce health inequalities. Thus, working with the main stakeholders—nondental health professionals, PHCs, and people within the community—shall further stress the importance of partnership in line with SDG 17: "Partnership for goals" [38]. This will help underscore the indispensability of collaborative efforts in securing SDGs.

Research Timeline

Figure 3 shows the research timeline for the proposed study including the order of the main activities and the study milestones over time. The developed timeline spans a duration of 42 months, making sure that each of the stages of implementing such a research project takes place in a highly systematic, organized, and timely manner, making it easy to adapt to changes and solve eventual problems.

Figure 3. Research timeline.

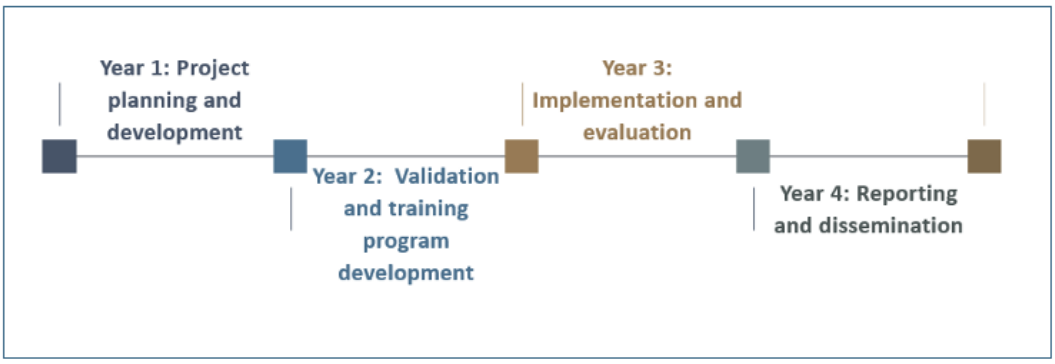

Conclusion

The BOHAT study holds considerable potential for promoting oral health care through collaborative and interdisciplinary approaches. It will facilitate early diagnosis, timely referrals, and comprehensive care by integrating assessment actions for oral health into routine practice by nondental primary health care professionals. This work is a large step toward the

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integration of oral health into general health care, by emphasizing general health and well-being and the reduction of health disparities. This study can, therefore, serve as a model for similar efforts elsewhere in the world and help to ensure good oral health outcomes and excellent quality of life for diverse populations.

Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

AUC: area under the curve
AYUSH: Ayurveda, yoga, naturopathy, Unani, Siddha, and homeopathy
BOHAT: Basic Oral Health Assessment Tool
CHW: community health worker
COSMIN: Consensus-Based Standards for the Selection of Health Measurement Instruments
CVI: content validity index
DHR: Dental Hygiene Registration
KAP: knowledge, attitude, and practice
MDS: Minimum Data Set
OHAT: Oral Health Assessment Tool
OHSTNP: Oral Health Screening Tool for Nursing Personnel
PHC: Primary Health Center
SDG: sustainable development goal
THROAT: the Holistic Reliable Oral Assessment Tool
WHO: World Health Organization

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Protocol

Assessing Preparedness for Self-Management of Oral Anticoagulation in Adults With the PERSONAE Scale: Protocol for a Development and Validation Study

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Abstract

Background: Optimal anticoagulation using vitamin K antagonists prevents strokes associated with atrial fibrillation and heart valve replacements. Preparedness for self-monitoring and self-management could improve outcomes, but this remains a challenge.

Objective: This study aimed to outline the methodology for developing and validating the PERSONAE scale, a self-report measure designed to assess the preparedness for self-monitoring and self-management of oral anticoagulation in adult patients.

Methods: This study comprises 2 main phases, and it adheres to the "COnsensus-based Standards for the selection of health Measurement INstruments" (COSMIN) guidelines for instrument development. The first phase involved the conceptualization of the PERSONAE scale, where a comprehensive literature review and a consensus meeting among experts were conducted to draft the initial items. Face and content validity were then established through an expert panel review. In the second phase (ongoing), a detailed sampling methodology will be used, targeting adult Italian patients on long-term oral anticoagulation. According to a performed simulation-based power analysis, the study aims to recruit a sample size of approximately 500 participants by using a combination of convenience and snowball sampling. Data collection will be facilitated through web-based surveys distributed through social media and patient networks, ensuring a wide and representative sample. Analytical procedures will include Mokken scaling analysis for item selection and confirmatory factor analysis to validate the scale's structure. In addition, internal consistency will be assessed using Molenaar Sijtsma statistics.

Results: The scale's content derived from phase 1 (process completed in December 2023) is grounded in a comprehensive literature review and based on the assessments of a panel of 12 health care expert professionals. The PERSONAE scale derived from phase 1 encompasses 20 items reflecting essential behaviors needed to assess the preparedness for self-monitoring and self-management of oral anticoagulation. Each item obtained a content validity ratio higher than 0.67, which is the critical content validity ratio indicating the minimum level of agreement among the experts for an item to be considered essential beyond the level of chance at a significance level of .05 for a 1-tailed test. From January 2024 to May 2024, we conducted the initial round of data collection and use Mokken scaling analysis to select items. A second round of data collection for confirmatory factor analysis was scheduled from June 2024 to September 2024, which will validate the scale's unidimensional structure. We expect to achieve robust psychometric properties, including high internal consistency and validated constructs.

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Conclusions: The PERSONAE scale will be a valuable tool to assess patients' preparedness for self-monitoring and self-management of oral anticoagulation. The study's insights into technology-assisted learning preferences will inform the design of future educational interventions to enhance preparedness in adult patients.

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KEYWORDS

self-monitoring; self-management; oral anticoagulation; vitamin K antagonists; preparedness; validation

Introduction

Vitamin K antagonists (VKAs), such as warfarin, are a group of medicines used to thin the blood, preventing the formation of harmful blood clots that can lead to stroke [1]. They function by inhibiting Vitamin K-dependent coagulation factors, which are essential for blood clotting. This class of medications is particularly vital for reducing the risk of stroke associated with atrial fibrillation and heart valve replacements, especially when direct oral anticoagulants are unsuitable for certain individuals, such as adults with multiple morbidities [1]. The use of oral anticoagulants globally is on the rise, reflecting an increasing need to manage conditions predisposing individuals to increased thromboembolic risks. Currently, about 2 out of every 100 Italians are on oral anticoagulants [2], including both direct and indirect agents [3]. This increasing prevalence underscores the necessity for regular monitoring of prothrombin time and appropriate dose adjustments, as inadequate monitoring and dose management could lead to serious adverse reactions and complications. Several studies have highlighted the risks associated with insufficient monitoring in the last 2 decades [4,5]. For instance, it was highlighted that patients on warfarin who did not have their prothrombin time regularly monitored were at a higher risk of major bleeding complications [4]. A meta-analysis published in 2020 confirmed that with the rising number of patients on oral anticoagulants, there is a proportional increase in adverse events related to inadequate monitoring [5].

People on long-term oral anticoagulation can use point-of-care testing equipment (POCT) to monitor their blood clotting time, typically measured by the international normalized ratio (INR) [6]. In managing their anticoagulant medication, these individuals have 2 primary options: self-management, where they adjust their medication dosage based on a predetermined dose-INR schedule, allowing them greater autonomy and immediate response to INR readings, or self-monitoring, where they measure their INR levels independently but consult health care providers to make dosage adjustments [7]. This distinction is crucial as self-management empowers patients to take full control of their therapy, potentially improving their adherence and outcomes, while self-monitoring still relies on professional guidance for dose adjustments [8,9].

Numerous studies and systematic reviews have demonstrated that these self-testing approaches are equally effective, if not superior, to routine physician-managed anticoagulation monitoring, providing evidence that patient-led monitoring can enhance therapy management and patient satisfaction [8,9]. For instance, a systematic review reported that patients who self-managed their oral anticoagulation therapy had significantly better control over their INR levels and fewer thromboembolic events than those who relied on professional monitoring [10]. In this context, a solid randomized controlled trial found that self-management was associated with higher patient satisfaction and better quality of life due to increased control over their health [11]. However, the choice between self-management, self-monitoring, and physician-managed care should be individualized based on patient characteristics. Recent researches highlight that health-related quality of life in anticoagulated patients varies significantly, indicating how some patients may benefit more from self-management while others may find self-monitoring or physician-managed care more suitable [9,12,13]. In addition, the quality of anticoagulation control, traditionally assessed by the time in the therapeutic range (%TTR), is enhanced by using recommended coagulometers like CoaguChek XS, which are globally endorsed, particularly in response to the COVID-19 pandemic [14,15].

While self-monitoring and self-management approaches have garnered strong evidence for their effectiveness and cost-effectiveness, a Cochrane review highlighted the need for further research into factors influencing individuals' preparedness for self-testing [8]. These factors include both psychological preparedness and preparedness in terms of objective equipment. Psychological preparedness encompasses patients' self-management knowledge, motivations for medical attention, health literacy, self-efficacy, and perceived and actual support systems [13,16]. Specifically, patients' knowledge about self-management affects their ability to understand and manage their treatment, while motivations for seeking medical attention could influence their commitment to regular monitoring. Health literacy impacts their ability to comprehend medical instructions and make informed decisions, and self-efficacy relates to their confidence in performing self-testing tasks [17]. Finally, perceived and actual support systems are crucial in providing the necessary resources and emotional support for effective self-management. Preparedness in terms of objective equipment involves access to and familiarity with POCT devices and other necessary tools. Evaluating preparedness for self-management and self-monitoring is therefore crucial in tailoring health care delivery, enhancing efficiency, and adequately preparing patients for self-testing [18]. The interaction between psychological preparedness and preparedness regarding objective equipment is critical. Patients who are psychologically ready but lack the necessary equipment, or vice versa, may not effectively self-manage their condition. Therefore, both aspects must be

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addressed to ensure successful self-management and self-monitoring.

In Italy, for instance, adopting self-testing is complicated by organizational and professional barriers, such as the cost of POCT devices and concerns regarding the loss of direct control over treatment management [12]. Addressing this gap is essential, as enhancing patient preparedness through targeted interventions could substantially improve the effectiveness and patient outcomes of self-management programs, ultimately transforming anticoagulation therapy practices globally. The PERSONAE scale specifically addresses these gaps by assessing domains of preparedness and providing its comprehensive measure for self-management and self-monitoring. Thus far, no measures of the preparedness for self-monitoring and self-management exist in relation to this population. Therefore, the aim of this protocol is to outline the methodological steps for the development and validation of the PERSONAE scale, a self-report measure intended to assess the preparedness for self-monitoring and self-management of oral anticoagulation in adult patients. The study is currently focused on the Italian adult patient population, carefully considering the scalability and adaptability of the PERSONAE scale for diverse age groups and international settings. In addition, it aims to pinpoint the most favored technology-assisted learning options among patients undergoing anticoagulation therapy. The PERSONAE scale is expected to improve existing self-management protocols and practices by identifying areas where patients may need additional support or resources after a detailed assessment of patient preparedness. The findings from this pioneering research will lay the groundwork for innovative technology-assisted educational programs designed specifically to boost preparedness for self-monitoring and self-management of oral anticoagulation, marking a significant advancement in patient-centered health care solutions.

Methods

Study Design

This methodological, multiphase study comprises 2 main phases to develop and validate the PERSONAE scale for assessing the preparedness for self-monitoring and self-management of oral anticoagulation in adult patients. The protocol adheres to the "COnsensus-based Standards for the selection of health Measurement INstruments" (COSMIN) guidelines for instrument development [19].

Phase 1 focused on conceptualizing the PERSONAE scale through a developmental methodological approach involving 3 primary steps. First, a literature review was conducted to identify all relevant elements related to the preparedness for self-monitoring and self-management of oral anticoagulation (anticipated between May 2023 and July 2023). This review was recently published elsewhere [13]. Second, a consensus meeting among developers was held to examine the findings of the literature review and endorse its synthesis (anticipated time: September 2023). Finally, the situations representing patients' preparedness will be operationalized, and an external panel of experts, including nurses, physicians, and pharmacists, will determine the face and content validity of the newly developed scale (anticipated time: October 2023). Phase 2 focused on the validation procedures. Initially, the PERSONAE scale, containing items with acceptable content validity, was used for cross-sectional data collection from January to May 2024. The Mokken scaling analysis (MSA) procedure will be used to assess how the items in the first version of the scale behave in response to varying levels of the theoretical latent trait (preparedness). MSA is preferred over exploratory factor analysis in this study as it allows selecting items with the highest scalability, leading to a brief, unidimensional measure computed in a single score. Once a stable unidimensional PERSONAE scale is developed, a second round of cross-sectional data collection was performed from June to September 2024 to cross-validate the plausible unidimensional structure of the scale.

Participants and Procedures

In phase 1, a panel of 8-12 experts, comprising nurses, physicians, and pharmacists, evaluated the relevance and clarity of the proposed items derived from the literature review (content validity). The experts provided written consent to use their sociodemographic and professional characteristics for scientific reporting, as content validity is closely linked to the characteristics of the involved experts. This phase cannot be anonymous to ensure transparency, and variables such as sex, age, academic title, experience in studies testing content validity, and experience in oral anticoagulation were collected.

Once adequate content validity was established (December 2023), data collection commenced at the IRCCS (Istituto di Ricovero e Cura a Carattere Scientifico [Institute for Research and Healthcare]) Policlinico San Donato, using 2 cross-sectional data collection rounds using web surveys. A convenience sampling procedure was used, disseminating the web surveys through social media campaigns, newsletters, and flyers of associations involving anticoagulated patients, such as "Associazione Italiana Cardiopatici Congeniti" (AICCA). Participants for the second round were selected based on the same approach, with communication to prevent overlapping responses from participants who completed the survey.

Quality control measures have been implemented to ensure the integrity and quality of the data collection process: automatic data validation checks are included in the survey software to ensure that all responses are complete and adhere to the required format; unique identifiers were used for each participant to prevent duplicate responses in the dataset; and after data collection, statistical analyses were performed to identify any outliers or inconsistencies in the responses, which were then reviewed for accuracy.

Sampling Procedure

The sampling procedure will use a cloud-data recording system and web surveys disseminated through social media campaigns, newsletters, and flyers. The local study coordinator and the principal investigator will manage the sampling procedure following good clinical practice principles. An expected response rate of approximately 60% is anticipated, which is considered adequate [20]. This expectation is based on several considerations, including using targeted engagement strategies such as precontacting potential participants and leveraging

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multiple dissemination channels. In fact, this rate aligns with the upper bound of the confidence interval from a recent meta-analysis, which reported an average response rate of 44.1% across 1071 studies in educational research [20]. Studies achieving similar response rates are those that have successfully implemented strategies to engage participants actively.

Sample Size

The sample size for phase 1 will be 8-12 experts. The sample size required for phase 2 to perform the Mokken scaling analysis was determined considering the 20 items derived from phase 1 (content validity phase). A simulation-based power analysis was performed in R (R Foundation for Statistical Computing; library "Mokken"), as shown in Multimedia Appendix 1. The aim of the simulation was to estimate a sample size that would provide sufficient statistical power, set at 0.8, to detect a minimum H coefficient of 0.3, indicative of a moderate scale according to Mokken's hierarchy. The H coefficient in Mokken scaling analysis measures the strength of the hierarchical relationship among items in a scale as it quantifies the extent to which items form a cumulative scale. A custom simulation function was created using R statistical software, with the following parameters defined: 20 items, initial sample (n= 200), number of simulations=100, desired power=80%, minimum H coefficient=0.3, and maximum number of iterations=30. For each simulation iteration, the function generated a matrix of binary data representing responses to the 20 items, with responses simulated under a simple random model (ie, the probability of success was 0.5 for each item). The results from the simulation suggested that a sample size of 500 patients would be needed to achieve the desired power of 0.8 for our MSA. The MSA procedure will help reduce the number of items to the first 10-15 items that define the preparedness for self-monitoring and self-management of oral anticoagulation in adult patients. The required sample size for the second round of data collection will be determined through Monte Carlo simulations, aiming to achieve a power of 0.8 for the confirmatory factor analysis (CFA) model.

Eligibility Criteria

In phase 1, experts must have at least 1 year of experience in managing patients with VKAs, hold at least a master's degree in nursing, pharmacy, or an MD degree, and have proficiency in the Italian language. Exclusion criteria for experts include conflicts of interest regarding the topic. In phase 2, patients aged 18 years and older will be included under oral anticoagulation treatment in an anticoagulation clinic for at least 3 months, with appropriate cognitive functioning and the ability to provide informed consent. Patients will be excluded based on more specific criteria to ensure the homogeneity and reliability of our data: those with a high Charlson Comorbidity Index (CCI>4), indicating severe concurrent medical conditions that could confound the study outcomes; patients undergoing any other experimental treatment affecting coagulation; and those with a history of noncompliance with medical regimens as reported by their health care providers.

Study Procedures for Cross-Sectional Data Collections

Patients who agree to participate will access a web-based survey (SurveyMonkey) through social media channels, mobile messages, or emails. The invitation will include all relevant information about the study's aim, methods, and tasks required for participation. Patients will confirm the inclusion and exclusion criteria during the initial access, and those who do not meet the criteria can opt out.

The data collection tools will include the PERSONAE scale derived from the content validity phase, a sociodemographic and clinical data form, and a graphic rating scale for assessing patients' preferences for technology-assisted learning options. Sociodemographic data will include age, sex, marital status, educational level, and occupation, while clinical variables will encompass time in oral anticoagulation, clinical indication for anticoagulation, %TTR, and history of thromboembolic or bleeding complications in the last 3 months. These clinical variables are consistent with previous research, such as the studies that developed measures of knowledge in the same population [21,22], which examined similar sociodemographic and clinical factors to assess anticoagulation knowledge in the Italian population. This alignment ensures that our data collection is grounded in established theoretical frameworks and allows authors to generate hypotheses relevant to our target population.

Data Analysis

The data analysis will involve the use of various statistical methods to develop and validate the PERSONAE scale.

For the first data collection round, MSA will be conducted using the "mokken" package in R [23]. MSA allows for the hierarchical evaluation of items, and the most relevant items that measure preparedness for self-monitoring and self-management of oral anticoagulation will be selected for the PERSONAE scale [24]. Loevinger's coefficient of homogeneity function will be used to assess the scalability of the items. Monotonicity violations will be checked, and violations below 80 will be consistent with the requirements of a Mokken scale [23,25]. Loevinger's coefficients of homogeneity (H) at the scale, item, and pairs of items level will be computed, where H values equal to or greater than 0.3, 0.4, or 0.5 indicate weak, moderate, or strong scales, respectively [23,25]. Item pairs violating monotonicity will be excluded, and floor and ceiling effects in data distribution will be assessed. Invariant item ordering (IIO) will be performed to further narrow down the pool of questions based on monotone homogeneity [25]. The IIO procedure will remove items one at a time until no significant violations are found. The Htrans (H^T) coefficient will express the accuracy of the IIO selection, and H^T>0.3 will denote proper IIO process and consistent Mokken scales. The final set of questions will be used to calculate ρ coefficients for reliability using the Molenaar-Sijtsma technique [26]. This approach is particularly adequate for assessing reliability in MSA because it provides a robust estimate of the internal consistency for nonparametric scales. The Molenaar-Sijtsma technique is well-suited for evaluating the scalability and reliability of the items within the scale, ensuring that the

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PERSONAE scale reliably measures the construct of preparedness for self-monitoring and self-management of oral anticoagulation.

CFA will be used to cross-validate the plausible unidimensional structure of the PERSONAE scale derived from the MSA, theoretically containing 10-15 items, using Mplus 8.1 (Muthén and Muthén, 2017). An unrestricted and unspecified model will be used with a maximum likelihood robust estimation of parameters. A confirmatory factor analysis with covariates will be used to estimate measurement invariance between subgroups if linear relationships between participant characteristics and the scale's total score are detected [27]. Modification indices will be explored to identify items causing a violation of invariance. Items causing invariance will be evaluated for possible deletion from the final scale. The adequacy of confirmatory factor analyses in explaining sample statistics will be assessed using various fit indices, such as chi-square, chi-square/degree of freedom, comparative fit index, Tucker-Lewis index, and root mean square error of approximation [28]. Invariance testing based on different levels of CCI and other potential confounders will be considered if needed and is feasible to ensure that the scale functions equivalently across groups with varying levels of comorbidity and demographics.

Missing data will be managed using an available-case approach for missingness lower than 5% or regression imputations for missingness equal to or higher than 5%, assuming missing at random. The significance level for all analyses will be set at 5%. The software used for the analysis will include Mplus (version 8.1, Muthén and Muthén), IBM SPSS Statistics for Microsoft Windows version 27, and R (version 4.2.1, R Foundation for Statistical Computing).

Ethical Considerations

The present protocol was approved by the Ethical Committee of Ospedale San Raffaele (protocol number 52/INT/2023). Ethical considerations will be carefully adhered to throughout the research process.

In the first stage of the study, which involves experts assessing the content validity [29,30], written informed consent will be obtained from each expert. They will be fully informed about the study's objectives and their voluntary participation in the process. During the second part of the study, data collection will be carried out through anonymous web surveys. As per European Regulation 2016/679 and Legislative Decree 101/2018, this type of study ensures anonymity and does not require individual written informed consent from the participants [31]. However, to ensure transparency and participant understanding, a simple and clear presentation page will be provided to patients before they proceed to complete the web-based questionnaire. This page will explain the study's purpose, the voluntary nature of their participation, and the anonymity of the survey.

The research team will prioritize the confidentiality and privacy of all participants involved in the study, adhering to the ethical principles outlined in the Declaration of Helsinki. Personal data will be handled with utmost care, and all data collected will be stored securely and accessible only to authorized personnel involved in the study. Any potentially identifying information will be removed from the dataset to ensure complete anonymity. Throughout the study, participants' rights and welfare will be protected, and any potential risks will be minimized. The study findings will be reported and disseminated in a manner that preserves anonymity and confidentiality. Researchers will act responsibly, maintaining the highest ethical standards and ensuring that the study is conducted with integrity and respect for the participants' rights and well-being.

Results

The PERSONAE scale development and validation protocol has been fully funded by the "Fondazione Insieme per Vita agli Anni" with additional support from the Ricerca Corrente funding by the Italian Ministry of Health in 2023 (no specific grant number). The summary of the results is shown in Textbox 1.

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Textbox 1. Results summarized per main categories.

Conceptual framework

- Defined by the literature summarized in a literature review published elsewhere, describing self-care behaviors in patients on oral anticoagulant therapy [13].

Focus of PERSONAE measure

- Assess how ready patients feel about undertaking and managing the tasks associated with their anticoagulation therapy by translating the behavioral content identified in the review into terms of preparedness (refer to Multimedia Appendix 1).

Item pool drafting

- November 2023

Expert panel for validation

- Date of content validation: December 2023.
- Median age: 36 (IQR 29-45) years.
- Education qualifications: 25% (n=3) with a master of science, 25% (n=3) with a doctor of philosophy, and 50% (n=6) medical doctors.
- Specialties: 16.67% (n=2) in cardiology, 50% (n=6) in nursing, 16.67% (n=2) in pharmacy, and 16.67% (n=2) in internal medicine.
- Experience: All experts with more than 6 years in oral anticoagulation.
- Sex distribution: 66.67% (n=8) females.
- Conflict of interest: None reported (100%, n=12).
- Content: 50% (n=6) in nursing, 16.67% (n=2) in pharmacy, and 16.67% (n=2) in internal medicine.
- Experience: all experts with more than 6 years in oral anticoagulation.
- Sex distribution: 66.67% (n=8) females.
- Conflict of interest: none reported (100%, n=12).
- Content validity ratio (CVR): All 20 items obtained adequate CVR (refer to

  Multimedia Appendix 1

  for additional details).

Scale question

- "How prepared do you feel to independently monitor and manage your oral anticoagulation therapy for each of the following statements?"

Rating scale

- A 5-point Likert scale ranging from 1 (not at all prepared) to 5 (extremely prepared).

Data collection for phase 2

- Ongoing, anticipated completion by September 2024.

Impact of PERSONAE scale

- The PERSONAE scale will offer a comprehensive and validated tool to assess the preparedness of patients for self-monitoring and self-management of oral anticoagulation, aiding clinicians in tailoring interventions. Health care providers can empower patients to take an active role in their anticoagulation therapy, potentially improving treatment outcomes and reducing health care costs by encouraging safe and effective practices of self-monitoring and self-management.

Dissemination of results

- Upon successful validation, the results will be disseminated through peer-reviewed publications and presentations at international conferences. The research team plans to engage with professional societies and patient advocacy groups to promote the implementation of the PERSONAE scale in clinical practice globally.

The conceptual framework was defined by the literature summarized in a literature review published elsewhere, describing self-care behaviors in patients on oral anticoagulant therapy [13]. The focus on preparedness encapsulates the ability to perform specific self-care tasks and integrates the confidence and knowledge necessary to manage treatment proactively. In other terms, the version of the PERSONAE measure derived from phase 1 aims to assess how ready patients feel about undertaking and managing the tasks associated with their anticoagulation therapy by translating the behavioral content

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identified in the review into terms of preparedness (Multimedia Appendix 1). Once the pool of items was drafted (November 2023), an expert panel for validating the PERSONAE scale was involved, and it consisted of 12 professionals with diverse qualifications and backgrounds in health care. The process of content validation was performed in December 2023. The median age of the experts was 36 (IQR 29-45) years. Regarding higher education qualifications, 25% (3/12) held a master of science degree, another 25% (3/12) had earned a doctor of philosophy degree, and the remaining 50% (6/12) were medical doctors. Expertise among the panel members varied, with representation from multiple disciplines critical to managing oral anticoagulation therapy. Specifically, 16.67% (2/12) specialized in cardiology, the majority, 50.00% (6/12), were from nursing, 16.67% (2/12) practiced pharmacy, and 16.67% (2/12) were from internal medicine. When considering potential conflicts of interest, it was noted that 100% (12/12) of the experts reported none. All experts had substantial experience with oral anticoagulation, with each member having more than 6 years of experience in the field, which provided a solid foundation for their evaluative contributions. Regarding sex distribution, the panel was predominantly female, with 66.67% (8/12) of the members being women. All content validity ratio (CVR) of the 20 items obtained adequate content validity based on the evaluation of the experts (Multimedia Appendix 1; all observed CVR were equal or higher to the critical CVR, indicating the minimum level of agreement among the experts for an item to be considered essential beyond the level of chance at a significance level of .05 for a 1-tailed test).

The question guiding the self-report assessments derived from phase 1 is: “How prepared do you feel to independently monitor and manage your oral anticoagulation therapy for each of the following statements?” Therefore, the scale is designed for the patients. In the current form of the scale, patients are asked to rate their level of preparedness on a 5-point Likert scale ranging from 1 (not at all prepared) to 5 (extremely prepared). Therefore, the scale prompts patients to consider their proficiency across a spectrum of 20 activities (items) vital to the effective self-management of their treatment, from medication adherence to lifestyle adjustments and the use of technology.

The data collection for phase 2 is ongoing, and it is anticipated to be completed in September 2024. The PERSONAE scale will fill a critical gap by offering a comprehensive and validated tool to assess the preparedness of patients for self-monitoring and self-management of oral anticoagulation. Clinicians will be able to use this scale to identify patients who may benefit from self-testing approaches and tailor interventions accordingly. Health care providers can empower patients to take an active role in their anticoagulation therapy, potentially improving treatment outcomes and reducing health care costs by encouraging safe and effective practices of self-monitoring and self-management.

Upon successful validation, the results will be disseminated through peer-reviewed publications and presentations at international conferences. The research team plans to engage with professional societies and patient advocacy groups to promote the implementation of the PERSONAE scale in clinical practice globally.

Discussion

Principal Findings

This study outlines a methodological approach to developing and validating the PERSONAE scale, a self-report measure aimed at assessing the preparedness for self-monitoring and self-management of oral anticoagulation in adult patients. This novel scale aims to help health care providers discern patients’ preparedness for autonomous oral anticoagulation management, potentially leading to customized treatment strategies that enhance patient independence and treatment adherence. High scorers on the PERSONAE scale might be suitable for self-testing and adjusting their medication. At the same time, those with lower scores could benefit from targeted educational programs to improve their management capabilities, pending further research to establish specific scale cutoffs for optimal outcomes. It is important to note that the practical application of this scale and its cutoff points require empirical testing in future research to assess criterion validity and establish effective thresholds for different patient outcomes.

Phase 1 of the research protocol, based on a developmental methodological approach, was based on a literature review [13], followed by a consensus meeting among developers who have operationalized the literature into 20 measurable items of preparedness, leading to the initial version of the scale as per previous research focused on developing new self-report measures [32,33]. An expert panel consisting of 12 professionals from diverse health care disciplines (cardiology, nursing, pharmacy, and internal medicine) validated the content of the PERSONAE scale in December 2023. The experts, who brought a wealth of experience from their respective fields, ensured that the scale’s content was relevant and applicable to various professionals involved in anticoagulation management. This multidisciplinary approach enriched the scale’s content validity, ensuring comprehensive coverage of the necessary competencies for effective self-management. This phase was instrumental in creating a scale that is scientifically sound and clinically meaningful. This initial phase set a solid foundation for the subsequent validation phase, aiming to confirm that the scale accurately measures preparedness in a way that is predictive of patients’ ability to manage their anticoagulation therapy effectively.

In phase 2, validation procedures will be conducted to ensure the reliability and validity of the scale, and it is anticipated to end in September 2024. This process will require 2 cross-sectional data collections among Italian adult patients currently undergoing oral anticoagulation treatment. The collected data will be used to assess the scale’s psychometric properties and determine its performance in measuring preparedness for self-monitoring and self-management of oral anticoagulation [34]. More precisely, the first cross-sectional data collection will provide the needed power to perform the MSA procedure and determine item behavior in response to varying levels of the theoretical latent trait (preparedness) [35]. The second data collection will be based on the version of the scale updated from the analytics of the first data collection, and a CFA will be used to cross-validate the unidimensional

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structure of the PERSONAE scale. Cross-validation helps assess the generalizability of the scale's results and allows researchers to determine if the validity holds true beyond the initial sample used for scale development [36].

Limitations

Several limitations should be acknowledged. First, the sample size for the validation phase was based on a power-based simulation and Monte Carlo simulations, which may have inherent assumptions that could affect generalizability. Expanding future studies to include larger and more diverse populations could enhance the scale's validity across varied demographics and age groups. Second, the use of web surveys for data collection may introduce response biases, particularly biases associated with self-reporting, such as recall bias and social desirability bias. Although measures such as ensuring participant anonymity and confidentiality are planned to mitigate these issues, the influence of these biases cannot be entirely eliminated. In addition, further exploration into potential sources of bias, including sampling biases due to nonrandom selection methods and the impact of the data collection medium on participant engagement and accuracy, is necessary. Limitations stemming from the analysis methods, such as potential confounding factors not accounted for in the statistical models, should also be critically evaluated. Future research should aim to address these limitations by adopting more robust sampling frameworks, using mixed methods for data collection, and applying comprehensive analytical techniques to provide a deeper understanding of the scale's applicability and accuracy.

Comparison With Previous Work

While previous studies have explored various components of oral anticoagulation therapy, such as patient knowledge, health literacy, and self-efficacy in self-management, the PERSONAE scale introduces a unique comprehensive measure [2,7-9,17]. It is the first self-report tool designed to assess both self-monitoring and self-management preparedness among adult patients on oral anticoagulation therapy. This distinction sets the PERSONAE scale apart from existing scales that typically focus on isolated aspects of anticoagulation management. Existing measures often independently evaluate patient knowledge or health literacy, which does not necessarily translate to practical, actionable patient readiness. In contrast, the PERSONAE scale encompasses a broader spectrum of preparedness, integrating aspects of knowledge, self-efficacy, and practical application capabilities into a single measure. This integrative approach not only aids health care providers in identifying well-prepared patients but also pinpoints those who might benefit most from targeted educational interventions. Furthermore, the development methodology of the PERSONAE scale enhances its robustness and applicability. The scale was crafted to ensure scientific soundness and clinical relevance through a rigorous, multiphase approach that included a literature review, expert consensus, and external validation. This methodological solidity supports its potential for widespread adoption and use in clinical settings, distinguishing it further from other tools that may lack such comprehensive validation.

Conclusions

The PERSONAE scale represents a significant advancement in the management of oral anticoagulation therapy. It is the first comprehensive self-report measure specifically designed to assess the preparedness of adult patients for self-monitoring and self-management. This tool will enable health care providers to better identify patients ready to manage their treatment autonomously, possibly enhancing patient outcomes and optimizing therapy adherence. Our study aims to determine the scale's robust psychometric properties, which underscore its reliability and applicability in clinical settings. The PERSONAE scale's ability to encompass a broad spectrum of preparedness, from patient knowledge to self-efficacy and practical application skills, sets it apart from existing tools focusing on narrower anticoagulation management aspects. Looking forward, the PERSONAE scale has the potential to transform patient management in clinical practice globally. By facilitating the identification of patients suited for self-testing, the scale supports tailored educational interventions that can improve self-management skills among those less prepared. This approach promises to enhance patient autonomy and aims to reduce health care costs by improving treatment efficiency and satisfaction. Future research should focus on validating the scale across diverse patient populations to ensure its broader applicability. In addition, integrating the PERSONAE scale into routine clinical practice will be crucial for evaluating its impact on long-term patient outcomes and health care systems. Ultimately, the scale is poised to play a pivotal role in advancing patient-centered health care solutions in anticoagulation therapy.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Additional information.
[DOCX File , 27 KB - resprot_v14i1e51502_app1.docx]

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Abbreviations

%TTR: time in the therapeutic range
AICCA: Associazione Italiana Cardiopatici Congeniti (Italian Association of Congenital Heart Disease Patients)
CCI: Charlson comorbidity index
CFA: confirmatory factor analysis
COSMIN: COnsensus-based Standards for the selection of health Measurement INstruments
CVR: content validity ratio
IIO: invariant item ordering
INR: international normalized ratio
IRCCS: Istituto di Ricovero e Cura a Carattere Scientifico (Institute for Research and Healthcare)
MSA: Mokken scaling analysis
POCT: point-of-care testing
VKA: vitamin K antagonist

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Protocol

Developing a Multisensor-Based Machine Learning Technology (Aidar Decompensation Index) for Real-Time Automated Detection of Post–COVID-19 Condition: Protocol for an Observational Study

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Abstract

Background: Post–COVID-19 condition is emerging as a new epidemic, characterized by the persistence of COVID-19 symptoms beyond 3 months, and is anticipated to substantially alter the lives of millions of people globally. Patients with severe episodes of COVID-19 are significantly more likely to be hospitalized in the following months. The pathophysiological mechanisms for delayed complications are still poorly understood, with a dissociation seen between ongoing symptoms and objective measures of cardiopulmonary health. COVID-19 is anticipated to alter the long-term trajectory of many chronic cardiovascular and pulmonary diseases, which are common among those at risk of severe disease.

Objective: This study aims to use a single, integrated device—MouthLab, which measures 10 vital health parameters in 60 seconds—and a cloud-based proprietary analytics engine to develop and validate the Aidar Decompensation Index (AIDI), to predict decompensation in health among patients who previously had severe COVID-19.

Methods: Overall, 200 participants will be enrolled. Inclusion criteria are patients in the US Department of Veterans Affairs health care system; “severe” COVID-19 infection during the acute phase, defined as requiring hospitalization, within 3-6 months before enrollment; aged ≥18 years; and having 1 of 6 prespecified chronic conditions. All participants will be instructed to use the MouthLab device to capture daily physiological data and complete monthly symptom surveys. Structured data collection tables will be developed to extract the clinical characteristics of those who experience decompensation events (DEs). The performance of the AIDI will depend on the magnitude of difference in physiological signals between those experiencing DEs and those who do not, as well as the time until a DE (ie, the closer to the event, the easier the prediction). Information about demographics, symptoms (Medical Research Council Dyspnea Scale and Post-COVID-19 Functional Status Scale), comorbidities, and other clinical characteristics will be tagged and added to the biomarker data. The resultant predicted probability of decompensation will be translated into the AIDI, where there will be a linear relationship between the risk score and the AIDI. To improve prediction accuracy, data may be stratified based on biological sex, race, ethnicity, or underlying clinical characteristics into subgroups to determine if there are differences in performance and detection lead times. Using appropriate algorithmic techniques, the study expects the model to have a sensitivity of >80% and a positive predicted value of >70%.

Results: Recruitment began in January 2023, and at the time of manuscript submission, 204 patients have been enrolled. Publication of the complete results and data from the study is expected in 2025.

Conclusions: The focus on identifying predictor variables using a combination of biosensor-derived physiological features should enable the capture of heterogeneous characteristics of complications related to post–COVID-19 condition across diverse populations.

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Trial Registration: ClinicalTrials.gov NCT05220306; https://clinicaltrials.gov/study/NCT05220306

(JMIR Res Protoc 2025;14:e54993) doi:10.2196/54993

KEYWORDS

Aidar Decompensation Index; AIDI; biophysical biomarkers of worsening health; biosensor-based physiological monitoring; cardiorespiratory, metabolic, renal, and neurological complications after COVID-19; early warning signs of clinical decompensation; long COVID; noninvasive monitoring of physiology; postacute sequelae of COVID-19; PACS; rapid assessment tool; risk triaging related to long COVID

Introduction

Severe complications of postacute COVID-19 infection like thrombosis, respiratory failure, and cardiac and vascular damage increase the likelihood of future morbidity and mortality in recovered patients. In one study of individuals who had been hospitalized with COVID-19, nearly a third (14,060/47,780, 29.4%) of individuals who were discharged from the hospital after acute COVID-19 were readmitted, and more than 1 in 10 (5875/47,780, 12.3%) died over a follow-up period of 140 days after discharge [1]. These events occurred at rates 4 and 8 times greater, respectively, than in the matched control group from the general population. In another study, the 6-month incidence of a new hospitalization among patients previously hospitalized with COVID-19 was found to be 29.8% [2]. SARS-CoV-2 infection can also lead to postacute development of substantial cardiac cellular abnormalities and cardiovascular clinical sequelae, including dysrhythmias, ischemic heart disease, heart failure, pericarditis, myocarditis, and thromboembolic disease [3]. Glycometabolic abnormalities are also evident in many survivors of acute COVID-19 and, in some cases, manifest as overt new-onset diabetes mellitus [4].

Risks of complications are higher among patients with comorbidities like congestive heart failure, chronic obstructive pulmonary disease, asthma, chronic kidney disease, diabetes, and hypertension [1,5,6]. Thus, although the current rate of new COVID-19 infection has dropped, the risk of morbidity, mortality, and organ dysfunction among the survivors of COVID-19 infection is high, especially among those with preexisting illnesses. Compelling evidence suggests that the pandemic may lead to new-onset kidney disease (and other noncommunicable chronic diseases including diabetes, cardiovascular disease, and neurological disease) in the millions. Given the scale and the chronic nature of several of its sequelae, post–COVID-19 condition (also known as “long COVID” or “postacute sequelae of COVID-19”) will reverberate with us for decades and will have broad and deep social and economic impact long after the COVID-19 pandemic abates [7]. Thus, it would be appropriate to infer that the next wave related to COVID-19 may not necessarily be a new strain but rather the surge of hospitalizations due to postacute complications. Developing strategies to prevent decompensation among high-risk survivors of COVID-19 has emerged as an unmet need.

One approach to the prevention of decompensation is to monitor for worsening in physiological parameters after hospital discharge. However, collecting such data longitudinally for prediction poses several challenges. First, only a limited number of parameters can be easily collected (eg, blood pressure, heart rate, oxygen saturation, etc), although additional parameters such as heart rate variability and lung function may provide additional prognostic data. Second, even if patients or families are able to collect these parameters longitudinally, there is no automated, validated method to analyze those data concurrently and provide a quantitative assessment of decompensation risk over time. These limitations hinder the sensitivity and thus the utility of current approaches to using physiologic parameters to predict decompensation risk among patients after COVID-19.

The overall objective of this study (trial registration: ClinicalTrials.gov NCT05220306) is to use a handheld, multisensor device—MouthLab, which measures 10 vital health parameters in 60 seconds—and a cloud-based proprietary engine to develop and validate the Aidar Decompensation Prediction Index (AIDI). MouthLab measures oral temperature, single-lead electrocardiogram, heart rate, breathing rate, heart rate variability, respiratory flow morphology, oxygen saturation, pulse rate, and basic lung function (forced expiratory volume in the first second and peak expiratory flow rate). The study will collect MouthLab data from patients previously hospitalized with COVID-19 (“severe COVID-19”) in order to identify decompensation predictor variables. These variables will be used to develop the AIDI to accurately predict decompensation events (DEs) related to post–COVID-19 condition. Index development will follow best practices in machine learning and algorithmic development, where the main outcome is any COVID-19–related event that leads to an emergency department (ED) visit, hospitalization, or the need for escalated care (new diagnosis or change in intervention to manage the chronic conditions). These DE cases will help inform the final set of predictor variables to develop the AIDI. In the future, early prediction and real-time risk triaging using the AIDI may support better clinical decision-making, thus preventing complications, controlling disease progression, and improving outcomes. The aim of this paper is to describe the protocol for this study to develop and validate the AIDI.

Methods

Study Design

This is a national, longitudinal, observational study. Potentially eligible patients will be identified using the US Department of Veteran Affairs (VA) Corporate Data Warehouse (CDW) and the COVID-19 Shared Data Resource. A total of 200 patients who have a history of “severe” COVID-19 infection in the previous 3-6 months and at least 1 of the specified comorbidities will be recruited. Severe COVID-19 is defined as requiring hospitalization for acute COVID-19 or its complications.

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Participants will be required to use the MouthLab device twice daily and to complete monthly surveys administered remotely either by phone or through a web portal. Data will be used to develop a machine learning–based algorithm to detect DEs among patients in the postacute COVID-19 phase.

Study Setting

The VA is the largest integrated health system in the United States, with over 9 million patients enrolled. VA delivers care to US military veterans across 171 VA Medical Centers and 1113 outpatient care sites across the United States and Puerto Rico, Guam, and other US territories [8]. Nearly 50% of enrolled veterans are aged 65 years or older; 91.1% are male and 8.9% are female; and overall, veterans bear a greater burden of physical and mental health comorbidities than nonveterans [9,10].

Sample Size

To develop the AIDI algorithm, the study will collect longitudinal parameters that lead up to a DE with the MouthLab device. Because the actual multiparametric changes are unknown and are, in fact, the outcome of the study, the study aims to obtain as much data as possible from those who experience a DE. For this study, we estimate that 100 individual DEs would be sufficient to create a statistical algorithm to predict decompensation. The ultimate goal is to have the algorithm produce no false negatives (ie, if someone is at risk of decompensation while the algorithm says that they are not) and less than 10% false positives (ie, if someone is *not* at risk of decompensation while the algorithm says they are). That is, we do not want to miss any DEs at the cost of having some nonevents classified as being risky.

Al-Aly Z et al [11] observed that the risk and associated burden of pulmonary and extrapulmonary manifestations increase across the disease spectrum of acute COVID-19 infection (from nonhospitalized individuals to hospitalized individuals and then to those admitted to intensive care). The study implemented a comparative approach to examining postacute sequelae in individuals who are hospitalized with COVID-19 versus individuals with seasonal influenza (using a high-dimensional approach and through examination of prespecified outcomes). Results suggested that there is a substantially higher burden of a broad array of postacute sequelae in the individuals who are hospitalized with COVID-19, which provides features that differentiate post–COVID-19 condition (both in the magnitude of risk and the breadth of organ involvement) from postinfluenza viral syndrome [11]. A study by Mainous et al [2] demonstrated a hospitalization rate of 29.8% among survivors of “severe COVID-19.” Given that the AIDI study has defined “decompensation” more broadly than hospitalization alone, we anticipate higher decompensation rates among our study population. Conservatively estimating 1 DE per any participant, with an event rate of 60%, we would need 168 participants to complete the study in order to capture 100 DEs. Since we anticipate up to 15% dropout, we will aim to recruit 200 participants.

Eligibility Criteria

The inclusion and exclusion criteria are shown in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Aged 18 years and older
- Were hospitalized for treatment of acute COVID-19 or its complications in the prior 3-6 months
- At least one of the following comorbidities:
  - Hypertension
  - Asthma
  - Chronic obstructive pulmonary disease
  - Heart failure
  - Chronic kidney disease
  - Diabetes mellitus
- English fluency
- Comfortability with using technology
- Basic literacy with electronic platforms

Exclusion criteria

- Any motor disability that would impede the use of the MouthLab device as required with the left hand
- Pregnancy
- Cognitive deficits that would impede the ability to provide informed consent
- Alzheimer disease or other dementia
- Pacemakers and implantable cardioverter-defibrillators

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Recruitment

This study will recruit participants from across the country who receive care at the VA. A waiver of the Health Insurance Portability and Accountability Act (HIPAA) and informed consent for screening will be obtained for recruitment. Three modes of recruitment will be used. First, eligible patients will be identified via the CDW and sent letters with information about the study and a number to call if they are interested in learning more. Second, those who have authorized the VA through any partnership programs (eg, COVID-19 research volunteer registry) to receive communication on research opportunities may be contacted for this study. Third, study flyers will be posted at three of the VA's post–COVID-19 condition clinics. The selection process will include best efforts to ensure equitable inclusion of different races, ethnicities, and age groups among the participants.

Ethical Considerations

The protocol was approved by the Central Institutional Review Board of the Veterans Healthcare Administration, on December 21, 2022 (1720625-1). Since this is a multisite study, individual institutional review boards at the VA Bedford Healthcare System and the VA Providence Healthcare System also reviewed and approved the study. Informed consent will be obtained from all eligible participants prior to shipping the MouthLab device, administering baseline surveys, and collecting any patient data. Upon obtaining consent, the research team will also obtain HIPAA authorization. No study-related tasks will be performed before obtaining both consent and HIPAA authorization. A member of the research team will send the informed consent form (ICF) to the patient via DocuSign and read through the form with the participants on the WebEx (Cisco) consent call. The person obtaining consent will review the ICF in depth and solicit all questions before the participants sign the ICF via DocuSign. Participants will receive an executed copy via email, and those who prefer to sign a physical copy will be mailed a consent form. This approach will allow participants sufficient time to follow up with questions and discuss before officially signing the consent form. Participants will receive US $85 at the end of months 1-5. At the end of month 6, upon the completion of study tasks (survey and device return), participants will receive US $175. The total potential compensation is US $600, paid by check.

Study Timeline

The timeline of the study is provided in Table 1.

In addition to MouthLab and survey data (Table 2), data will be collected from the CDW on patient demographics, comorbidities, medications, and potential DEs. The main DEs of interest are any COVID-19–related events that lead to an ED visit, hospitalization, or the need for escalated care (new diagnosis or change in intervention to manage the chronic conditions).

The study will collect information about the index hospitalization, related to COVID-19 either as a primary or secondary diagnosis, from the CDW. This information will include medications (including oxygen therapy), vitals, and the use of mechanical ventilation. Additionally, the index hospitalization will be classified as an intensive care unit–level admission or not.

Table 1. Timeline of patient data collection for the Aidar Decompensation Index study.

	Phone screening	Consent	Patient intake form	Training on the MouthLab device	MRC[a] Dyspnea Scale [12]	Post-COVID-19 Functional Status Scale [13]	VR-12[b] [14]	User experience survey
First contact and screening	✓							
Consenting and HIPAA[c] authorization		✓						
Baseline and BP[d] calibration				✓				
Monthly follow-ups and data collection			✓[e]		✓[f]	✓[f]	✓[e,g]	✓[g]
Termination								

[a]MRC: Medical Research Council.

[b]VR-12: Veterans RAND 12-Item Health Survey.

[c]HIPAA: Health Insurance Portability and Accountability Act.

[d]BP: blood pressure.

[e]First month: patient intake form and first VR-12.

[f]Monthly: MRC Dyspnea Scale and Post COVID-19 Functional Status Scale.

[g]Sixth month: second VR-12 and user experience survey.

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Table 2. Survey data to be collected for Aidar Decompensation Index study.

Survey data	Instrument or measure	Time points
MRC[a] Dyspnea Scale (score 1-5)	A 5-point scale that has been used to classify dyspnea, mainly used in grading COPD[b] progression	Every 4 weeks
Post-COVID-19 Functional Status Scale (0-4 grade scale)	Functional status questionnaire that measures the impact of post–COVID-19 condition on ADL[c] along with psychological symptoms	Every 4 weeks
VR-12[d] Quality of Life Assessment	Patient self-report	At the start and end of study
MouthLab Usability Survey	MCQs[e] to ascertain the information of the physical and usage aspects of the MouthLab device	Study conclusion
User feedback on remote physiological monitoring technology	General perception about remote monitoring technologies (wearable and spot-check)	Study conclusion
Index hospitalization	Collected laboratory data, diagnoses, investigation report, medications, oxygen therapy, clinical notes, and vital signs data	Study conclusion

[a]MRC: Medical Research Council.
[b]COPD: chronic obstructive pulmonary disease.
[c]ADL: activities of daily living.
[d]VR-12: Veterans RAND 12-Item Health Survey.
[e]MCQ: multiple-choice question.

Evaluation of DEs

Data on outcomes (DEs) will be collected at the end of the data collection period via the CDW, records obtained from non-VA hospitalizations and ED visits, and monthly and end-of-study surveys.

A DE is defined as a complication related to organ dysfunction induced by SARS-CoV-19 that establishes the need for a change in treatment or intervention. To identify these events, we will first identify all new diagnoses and treatments, including medications, health care visits, and changes in level of service (eg, outpatient, inpatient, and hospital at home), for each patient during the study period using national CDW data. The data reviewed will be limited to those linked to relevant service types (eg, emergency care, urgent care, primary care, cardiology, and pulmonology). A study staff member will review these outcomes with guidance from the principal investigator or other team member with medical training to establish which are highly likely, somewhat likely, and not likely to be related to COVID-19. The full set of outcomes (Table 3) will be used as one outcome in one approach to the development of the predictive algorithm, and the subsets of highly likely and somewhat likely DEs will be used in a second approach to development.

Table 3. Study outcomes.

Outcomes	Instrument or measure
Primary outcomes	
All-cause, higher-level health care use (hospitalization, ED[a], or urgent care visits within the VA[b] system)	Participant self-reporting, confirmed through EMRs[c]
All-cause health care use (within and outside the VA system)	Participant self-reporting, confirmed through record requests and EMRs
Highly likely COVID-19–related health care use	As evaluated by the PI[d] and subinvestigators
Highly likely and somewhat likely COVID-19–related health care use	As evaluated by the PI and subinvestigators
Secondary outcomes	
Highly likely and somewhat likely COVID-19–related health care use	As evaluated by the PI and subinvestigators
Highly likely COVID-19–related diagnoses, treatment, use, and medication	As evaluated by the PI and subinvestigators and confirmed in EMRs

[a]ED: emergency department.
[b]VA: Department of Veteran Affairs.
[c]EMR: electronic medical record.
[d]PI: principal investigator.

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Data Blinding

Participants and physicians are blinded to the data from the MouthLab device. Participants will be informed that they are not restricted from seeking any level of care. There will be no medical intervention provided during or after the study as a consequence of any unfavorable trends in the MouthLab data, as these data are not being surveilled during the study.

Participant Data Protection

The confidentiality of participants will be maintained throughout the study. All participants will be assigned a unique subject ID by the data analyst. The crosswalk that matches the participant ID to the participant's name will be secured behind the VA firewall. Any data that may be published in abstracts and scientific journals or presented at medical meetings will reference the unique participant ID or will be aggregated, so to not reveal the participant's identity. Patient identifiable information such as name, address, email address, and phone number will only be used to support device shipment and return–related activities. Participants' unique identifiers, rather than personal information, will be connected to their device and survey data as well as any other data obtained from the electronic medical record. To protect participants' privacy, the Aidar Connect dashboard will not collect any patient identifiable information during registration, and pairing of MouthLab devices will be performed against the participants' IDs.

Safety Monitoring

During the monthly health surveys sent via the VA Office of Research and Development Qualtrics platform, participants will report any potential adverse events (AEs) that are possibly related to their COVID-19 diagnosis, as well as to any hospitalizations or medical care use. Study coordinators will follow up with participants to gather more information and have participants sign a Release of Information if needed. The investigator or study coordinator will determine whether the AE or serious AE meets the criteria for reporting; submit to the sponsor and VA Central Institutional Review Board all associated information and documentation related to each AE or SAE; and execute corrective actions as necessary.

Statistical Analysis

Feature Engineering and Selection

For each patient, baseline readings will be based on their first few MouthLab measurements. The number of observations used to establish the baseline will depend on the variability in each patient's reading. We will then summarize the patient's parameters obtained from the MouthLab data collection. At each time t, we will include the most recent observations, changes since the last reading, trends, variability in values, and comparison to the patient's baseline. Additionally, we will include information about demographics, symptom scores, other clinical characteristics, as well as key comorbidities. We anticipate that variable interactions will be important. Given the cohort size and the number of different features, regularization will be applied to avoid overfitting.

Outcome Modeling

We will define the outcome as patients experiencing a DE within τ time units (DEτ). For different values of τ, we will deploy a series of more sophisticated models in order to explore the predictive ability of different approaches, as detailed below. We will split up the data into training and testing datasets based on the time of enrollment. We anticipate an 80:20 split; in other words, we will set aside 20% of the data to evaluate the model performance. For each τ, we will construct a training dataset consisting of multiple overlapping time segments for each patient, which we refer to as the observation period (eg, 2 weeks), and multiple nonoverlapping time segments leading up to the outcome for the patients that experience the outcome, one of which contains the outcome.

Second, we will explore several other machine learning algorithms, including classification trees, random forest, and boosting approaches, to understand whether these more flexible modeling approaches have an advantage over the logistic regression approach. The output of any of these approaches is a predicted probability of a DE occurring within the following τ days given observations of a fixed observation interval (eg, up to 30 previous measurements, or ~2 weeks). As stated earlier, the goal is to develop the AIDI to predict worsening health. The detailed analysis laid out above will allow us to understand the ability of early prediction, that is, the critical time frame just prior to decompensation during which the probability of hospitalization becomes increasingly predictive.

The initial exploratory analysis will inform the selection of proper features for the analysis. We will model the patient's risk of hospitalization as a function of their physiological values, short-term changes in those values, changes from the baseline, etc. The initial exploratory analysis will inform features such as the appropriate time ranges (eg, should short-term changes be captured since the last reading or over the last 24 hours).

Performance Evaluation

In case of a lower-than-expected number of observed outcomes, or smaller differences than expected between those who experience the outcome and those who do not, we may revert from our 80:20 split to use cross-validation to measure performance. In that case, we will evaluate the algorithm using the leave-one-out cross-validation technique. We will implement this approach by leaving out one patient at a time (corresponding to potentially multiple observation periods to avoid fitting the model on data from the same patient as the model is being evaluated). The leave-one-out cross-validation technique facilitates cross-validation evaluation of the algorithm structure to assess its robustness to changes. This validation step will remake the algorithm for every patient left out of the algorithm development iteration. In short, this approach fits each algorithm using all available data except for (in our case) the data of one patient and then summarizes whether the algorithm predicts the correct classification of decompensation or nondecompensation for each observation period. This process is repeated over all available patients. For each τ, we will summarize the accuracy, false positives, and false negatives.

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The resulting predicted probabilities of decompensation will then be translated into the easy-to-communicate AIDI, where there is a linear relationship between the risk score and the AIDI. At the conclusion of phase 3, the final COVID-19 DE detection performance of the AIDI will be evaluated using standard measures including sensitivity, specificity, and positive predictive value across a wide range of risk cutoff values. Overall, AIDI DE detection performance and lead time statistics will be examined across study populations as well as within subgroups. If necessary, to improve prediction accuracy, data may be stratified based on biological sex, race, ethnicity, or underlying clinical characteristics into subgroups to determine if there are differences in performance and detection lead times among the groups.

Results

Recruitment began in January 2023, and the first patient was enrolled in January 2023. At the time of manuscript submission, 204 patients have been enrolled. Publication of the complete results and data from the study is expected in 2025.

Discussion

Expected Findings

The AIDI study seeks to address a substantial challenge, that is, to develop an affordable, scalable, technology-assisted remote monitoring solution to facilitate early identification of abnormalities and timely intervention by clinicians to improve quality of life, functional status, and health outcomes and, ultimately, to reduce the burden of post–COVID-19 condition in the United States and elsewhere. We hypothesize that monitoring participants for 6 months and capturing critical cardiorespiratory parameters on a daily basis in conjunction with subjective and clinical data will enable the development of an index, the AIDI, that will empower high-quality clinical care using the MouthLab device as a rapid and early assessment tool. The outcomes of this research have the potential to redefine the care delivery for COVID-19 and potentially other conditions in the future, as well as push the boundaries of prevention and care beyond traditional care settings into the home.

Limitations

Self-selection bias may be a limitation of this study as participation is voluntary, and participants already comfortable with using technology might be especially motivated to participate in digital intervention studies. Patients who are particularly ill may not enroll due to difficulty managing the device, and those without cellular service will not be able to participate.

Strengths

Fully remote study procedures will enhance the accessibility of eligible research participants living in rural or remote locations away from large metropolitan areas. The MouthLab device has built-in SIM cards offering cellular data, thus requiring no other accessory, such as mobile phones, to transmit data to the Aidar Cloud. Using a web application dashboard will allow easier visualization of MouthLab data from all participants, providing us with the opportunity to intervene immediately in the event of absent data or noncompliance.

Conclusions and Future Work

The findings from this study will result in a predictive algorithm (AIDI) to predict decompensation among high-risk patients who previously had severe COVID-19. In the short term, this could be applied to monitoring such patients during the hospital-to-home transition or for longer periods at home. In the long term, we will adapt and validate the AIDI for monitoring other conditions. Our work will generate insight and guidance for scalable and easy-to-use digital monitoring solutions for remote management of chronic diseases to control disease progression, limiting the impact of comorbidities and, ultimately, improving health outcomes among high-risk populations.

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The content is the sole responsibility of the authors and does not necessarily represent the official views of the VA, the National Institutes of Health, the Department of Health and Human Services, or the US Government.

Data Availability

Datasets generated or analyzed during the study described by this protocol may be made available from the corresponding author on reasonable request.

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Authors' Contributions

JM and SE acquired the funding. JM and SE conceptualized the study with input from VGV. JM, JAP, and VGV drafted the paper with input from LKW, KL, and AJL. All authors contributed to reviewing and editing the final version.

Conflicts of Interest

Two authors (JM and SE) are employees of Aidar Health, Inc., which is the company that manufactured the technology being used in the research study (device and the software platform).

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Abbreviations

AE: adverse event
AIDI: Aidar Decompensation Index
CDW: Corporate Data Warehouse
DE: decompensation event
ED: emergency department
HIPAA: Health Insurance Portability and Accountability Act
ICF: informed consent form
SIM: Subscriber Identity Module
VA: Department of Veteran Affairs

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Protocol

Educational Needs in Geriatric Medicine Among Health Care Professionals and Medical Students in COST Action 21122 PROGRAMMING: Mixed-Methods Survey Protocol

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Abstract

Background: The European Cooperation in Science and Technology (COST) Action 21122, PROmoting GeRiAtric Medicine in countries where it is still eMergING (PROGRAMMING) developed an online open survey to assess the educational interests and needs of health care professionals and final-year medical students across participating countries. This survey aims to establish a current baseline for developing educational content on geriatric medicine for nongeriatricians and a framework for its delivery.

Objective: This paper describes the aim, development, structure, content, and dissemination of this survey.

Methods: The mixed methods electronic survey, initially developed in English through a cocreation process with key stakeholders, was subsequently translated into 24 languages. It received ethics approval from multiple participating countries. Within- and cross-country analyses of the survey data will be conducted using descriptive and inferential statistics for quantitative data and content analyses for qualitative data. National and international teams will conduct analyses in parallel exploring responses within a specific country or region, professional category (or among medical students), or setting of work. Basic descriptive statistics and chi-square tests will evaluate differences in knowledge, relevance, and interest in geriatric topics across countries, professions, and settings of work. The effectiveness of formal education in geriatric medicine and clinical rotations in geriatric settings versus the lack thereof in promoting higher self-perceived knowledge on geriatric medicine topics will be explored using binary logistic regression. We will provide basic descriptive statistics (frequencies) of reported barriers to receiving further training in geriatric medicine and the effectiveness of various teaching methods as rated by the respondents and explore differences across countries, professions, and settings using chi-square tests. We will conduct qualitative content analyses of free-text responses to the questions exploring professionals' and medical students' thoughts on caring for older people and medical students' thoughts on becoming geriatricians.

Results: The survey included the following sections: Informed Consent, Demographics, Topics and Skills, Medical Students vs. Professionals, Current Profession (for professionals), Previous Education in Geriatric Medicine (for professionals), Education in Geriatric Medicine (for medical students), Interest in Care of Older People or Geriatric Medicine, Suggestions for Courses in Care for Older People or Geriatric Medicine, and Closure. The survey was disseminated between October 9, 2023, and June 5, 2024, and received 6099 responses; after cleaning, there were 5922 (97.1%) responses (n=5474, 92.43% from professionals and n=448, 7.57% from medical students).

Conclusions: This survey's findings will inform educational projects across the PROGRAMMING countries. We will share these findings with national and international stakeholders, including professional societies, medical schools, and other relevant organizations. We will advocate for professional educational curricula to include geriatric topics rated as relevant by the survey respondents and promote clinical rotations in geriatric settings and teaching methods rated as effective by the survey respondents.

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KEYWORDS

geriatric medicine education; open online survey; questionnaire design; teaching methods; health care professionals; qualitative research; emerging geriatric medicine

Introduction

Background

The world's population is aging, with an estimated 703 to 829 million adults aged ≥65 years, accounting for almost 10% of the global population [1,2]. In Europe, as of June 2024, there were 153 million adults aged ≥65 years, or 20.6% of the population [2]. In the last few decades, both the number and proportion of older adults have increased in most areas of the world due to increasing life expectancy and declining birth rates [1,3]. The European Union (EU) statistics showed a decline in life expectancy in 2020 after the COVID-19 pandemic compared with 2019 [4]. In 2022, the EU life expectancy at birth was 80.6 years, whereas that at the age of 65 years was 19.5 years [4,5]. Moreover, men and women aged 65 years in the EU may expect to live a further 9.5 and 9.9 healthy, disability-free years, respectively, while facing disability in the remaining years [6]. Indeed, multimorbidity and disability become more common with age [7]. The health care complexity and needs of older adults differ from those of younger adults [8,9]. Older adults experience age-related changes in their physiology and may face age-associated diseases, multimorbidity, disability, and geriatric syndromes such as frailty [8,9], which are relevant to all health care professionals participating in the care of older adults.

The needs of older adults place demands on both the health care and social welfare systems. However, there is a global shortage of health care workers, which is projected to reach 10 million health care workers by 2030, equivalent to approximately 20% of the workforce needed [10]. This shortage will occur mostly in low- and middle-income countries while also affecting the EU [11]. In 2021, there were approximately 1.82 million practicing physicians and 2.8 million nurses in the EU but with an unequal distribution across countries [11]. In particular, there is a shortage of physicians and nurses in many Eastern European countries [11]. Moreover, the health care workforce is aging across many EU countries as the baby boomer generation

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reaches retirement age. In 2021, nearly 40% of all physicians in the EU were aged ≥55 years [12].

This shortage is especially striking in the case of health care workers with training and expertise in the care of older adults [11]. In addition, there is significant heterogeneity in the practice and recognition of geriatric medicine as a medical specialty [13,14]. Currently, geriatric medicine is still not recognized as a medical specialty in several European countries, leading to a lack of not only clinicians but also educators.

In view of the growing aging population, every health care professional should ideally receive basic education and training in the care of older adults [15-18]. Most health care professionals will deal with older adults in their clinical practice in most clinical settings [15-18]. The care of older adults should integrate person-centered assessments of their intrinsic capacity—pertaining to all physical, sensory, cognitive, and psychological capacities of an older person—and functional ability [8,9].

Minimum geriatric competencies have been set for graduating medical students in Europe, the United States, and Japan [15,17,19]. In 2007, the Association of American Medical Colleges developed 26 minimum geriatric competencies for medical students, all of which were performance-focused competencies [17]. Later, learning objectives in geriatric mental health were proposed for medical students [18]. Moreover, core competencies and educational training requirements have been established for medical doctors specializing in geriatric medicine across Europe [20,21]. Geriatric training for dental students is included in the European College of Gerodontology undergraduate curriculum guidelines [22], whereas, recently, core competencies in oral health assessment and promotion of older adults have been established for all nondental health care professionals [23]. Further research has addressed the curricula of specialized nurses [24]. However, there is not yet a recommended set of core geriatric competencies for nongeriatrician physicians and surgeons or other health care professionals.

The European Cooperation in Science and Technology (COST) is a funding organization for research and innovation networks [25]. COST Actions help connect research initiatives across Europe and beyond and enable researchers and innovators to grow their ideas in any science and technology field by sharing them with their peers [25]. COST Actions are bottom-up networks with a duration of 4 years that boost research, innovation, and careers [25]. COST recognizes the importance of education in geriatric medicine across Europe. As a result of this and the quality of the proposal suggested, COST decided to allow funding for the PROmoting GeRiAtric Medicine in countries where it is still eMergING (PROGRAMMING) COST Action CA21122 proposal [26]. The European Geriatric Medicine Society (EuGMS) is the grant holder of PROGRAMMING [27].

PROGRAMMING CA21122 aims to reach a consensus about the basic content of geriatric educational programs for a broad range of health care professionals that would consider local contexts, needs, and assets of stakeholders and the constraints of individual settings [26]. Ideally, minimum geriatric competencies should be established for a broad range of health care professionals. We envisage further objectives that go beyond PROGRAMMING but could be facilitated by its outputs. The first is to not only to educate and train graduating health care professionals but also provide curricula for professional education for postqualified and practicing professionals in several countries. Many of these professionals have received little or no education in the care of older adults, and the few that have often require up-to-date education and training in emerging topics and skills such as deprescribing medications or managing delirium [16]. Second, we need to explore how digital education, which has been increasingly used since the COVID-19 pandemic, may promote effective, harmonized, affordable, and accessible education of health care professionals in countries with different income levels and infrastructure [28]. We hope that European countries where geriatric medicine is traditionally well established may share their experience with European countries where geriatric medicine is still emerging.

In February 2025, PROGRAMMING included 355 participants from 43 countries [26]. It comprised a leading core group, a coordinating managing committee (MC) with representatives from most participating countries, and 5 working groups (WGs; Figure 1) [26]. WG 1 aims to map the educational needs in the field of geriatric medicine across participating countries. WG 2 and WG 3 focus on the content of training of health care professionals working in community and primary care settings (WG 2) and acute care hospitals and long-term care institutions (WG 3). WG 4 aims to create a framework for training methods. Finally, WG 5 is responsible for communication, dissemination, and impact maximization of the activities of the other WGs. Additional leadership positions include the gerodontology coordinator, the qualitative research methodology advisor, the accreditation procedure advisor, and the translation coordinator.

As part of its activities, WG 1 developed an open online survey to map the educational interests and needs of health care professionals and final-year medical students across PROGRAMMING countries. This survey aims to describe the "current baseline" on which the WGs will construct the educational content in geriatric medicine and the framework of training methods for its delivery. This survey serves as a starting point to reach an evidence-based agreement on shared core competencies in the care of older adults in Europe. It will inform a competence-based core curriculum, which will be launched together with recommendations for educational frameworks in the future. In this paper, we describe the aim, development, structure, content, and dissemination of the survey. The complete survey is presented in Multimedia Appendix 1.

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Figure 1. Structure of the European Cooperation in Science and Technology Action PROmoting GeRiAtric Medicine in countries where it is still eMergING (PROGRAMMING) CA21122. MC: managing committee; WG: working group.

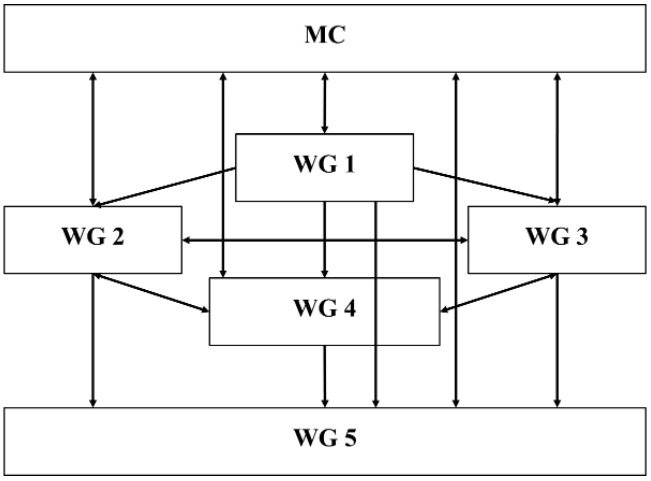

We hypothesized that health care professionals and final-year medical students will report (1) poor self-perceived knowledge, high relevance for clinical practice, and high interest in receiving further education and training in emerging geriatric topics such as delirium and deprescribing; and (2) higher self-perceived knowledge on most geriatric topics in case they had formal undergraduate education in geriatric medicine and clinical rotations in geriatric settings (ie, geriatric medicine acute care hospital wards and outpatient clinics, rehabilitation settings, and nursing homes) compared to not having had it. If the survey's results confirm these hypotheses, we will advocate for the inclusion of emerging geriatric topics in professional educational curricula and for clinical rotations in geriatric settings. Furthermore, we hypothesized that (1) the educational interests and needs, (2) the barriers to receiving education and training in geriatric medicine, and (3) the preferred mode of delivery (ie, in person, online, or hybrid) of courses and the teaching methods will vary by country of education, country of current work, and setting of work. In addition, we hypothesized that different clusters of countries may emerge with respect to the educational needs of health care professionals in geriatric medicine based on previous undergraduate and postgraduate geriatric education and different health care system organizations. By obtaining insights into this diversity, we will be able to tailor our educational efforts to the needs of specific countries and settings of work.

Objectives

This paper outlines a mixed quantitative and qualitative approach that was used to evaluate educational needs in geriatric medicine. This methodology could also be of value in other specialty areas that are seeking to improve understanding of knowledge gaps and needs for health care professionals and medical students.

Methods

Development of the Survey

The survey was created by members of WG 1 and the core group, who are experts in the care of older adults from a variety of health care and non–health care professional backgrounds and from several European and neighboring countries. It was developed through a cocreation process of discussions and feedback that started in October 2022 and was completed in May 2023 (Figure 2).

Figure 2. Development of the PROmoting GeRiAtric Medicine in countries where it is still eMergING (PROGRAMMING) survey. COST: European Cooperation in Science and Technology; MC: managing committee; WG: working group.

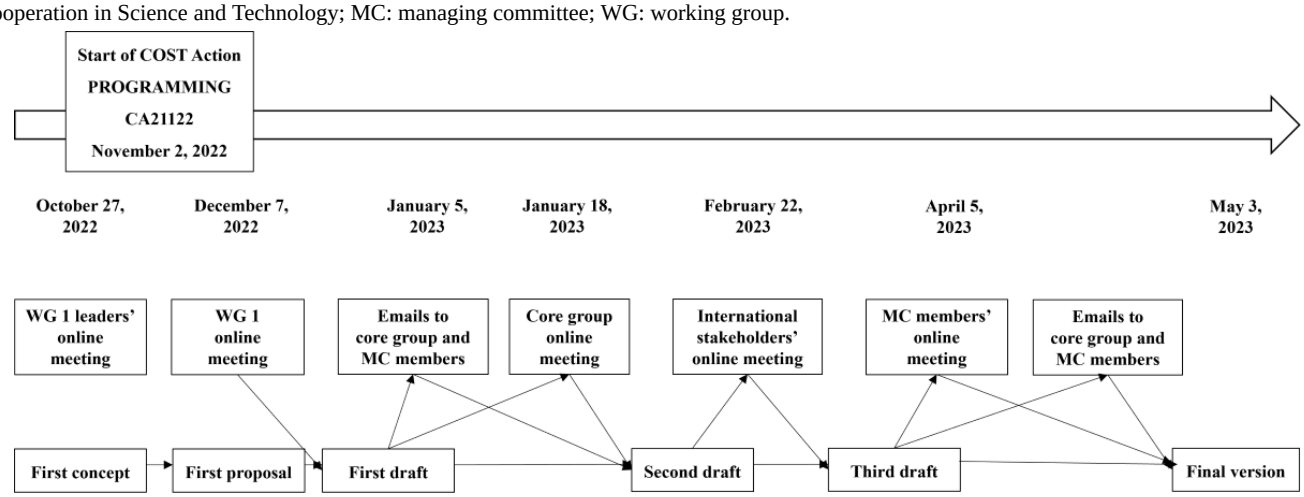

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In October 2022, just before the start of PROGRAMMING, a few WG 1 members conceived the first survey proposal. They discussed this in the first online meeting of WG 1 members in December 2022. In January 2023, they created and emailed a first draft to the core group and MC members. The core group provided feedback during an online meeting in January 2023, and a second draft was created. In parallel, the MC members were asked to identify stakeholders—health care professionals or policy makers with interest and expertise in the care of older adults—in PROGRAMMING-involved countries. They created a panel of 68 international stakeholders from 24 countries (Multimedia Appendix 2) who gave feedback on the survey during an ad hoc online meeting in February 2023. After the meeting, individual stakeholders emailed further feedback to WG 1 members. On the basis of this, a third draft was developed and presented to the MC members in an online meeting in April 2023, and strategies for dissemination of the survey were also discussed. Following further revision and testing of the online version, the final version of the survey was created in English in May 2023 (Multimedia Appendix 1).

WG 1 did not apply a rigorous Delphi process to the development of the survey; for instance, the feedback was not anonymous. However, in line with the Delphi process, WG 1 assumed group judgments to be more valid than individual judgments [29,30]. On the basis of feedback from the international stakeholders, WG 1 adopted the phrase "care for older people" instead of "geriatric medicine" in the survey as the former was deemed more inclusive of health care professionals other than physicians or surgeons. On the basis of the feedback, WG 1 decided to delete, add, or modify specific questions, response options, or entire sections of the survey. For instance, the management of heart failure was initially included and then excluded from the list of topics and skills relevant to the care of older adults. A question on extracurricular volunteer work with older adults was added as this may promote more positive attitudes of medical students toward older adults [31,32].

Content of the Survey

Overview

The survey targeted a broad spectrum of health care and non–health care professionals and final-year medical students, as detailed in the *Informed Consent* section (Multimedia Appendix 3). The survey sections are described in the following manuscript sections and summarized in Multimedia Appendix 3 and Figure 3.

Figure 3. Structure of the PROmoting GeRiAtric Medicine in countries where it is still eMergING survey.

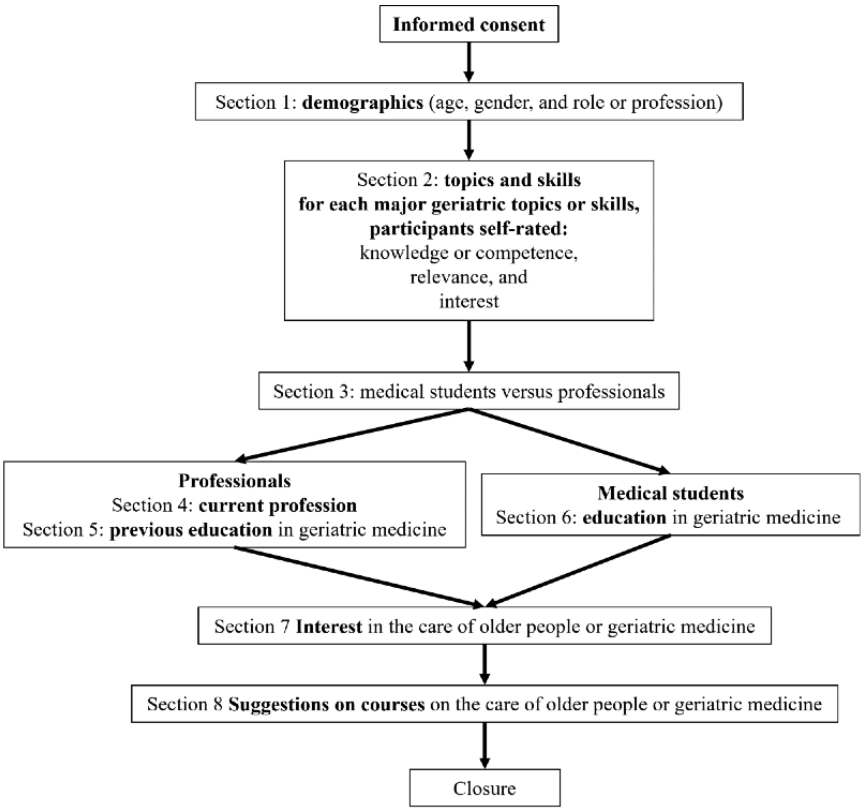

Informed Consent

This section informed the potential participants of the aim of the survey and that it was part of the PROGRAMMING CA21122 funded by the EU. It also stated that the EuGMS is the grant holder of PROGRAMMING. The "Disclaimer" informed the potential participants of the EuGMS privacy policy in compliance with the General Data Protection Regulation (GDPR; EU 2016/679) and of the expected duration of the survey (10-15 minutes). It informed them that they could provide their email address in case they wished to receive information or educational material relevant to PROGRAMMING and the EuGMS. To comply with the national ethics regulation, the German version of the survey did not include the option to provide an email address.

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Section 1: Demographics

This section included 3 questions on gender (man, woman, and "prefer not to say"), age (16 years to ≥100 years or "prefer not to say"), and role or profession. For role or profession, the participants could only choose one of the options in the list or the option "other" and describe in free text their current role or profession. For example, retired or unemployed professionals and professionals with more than one occupation could choose "other." The question on gender was included to explore gender differences in attitudes toward caring for older adults.

Section 2: Topics and Skills

The longest section of the survey started with an explanation of its aim and then included 33 questions related to major geriatric topics and skills, as detailed in Multimedia Appendix 1. For each topic or skill, the participants rated their knowledge or competence on a 5-point Likert scale as very low, low, fair, high, or very high. Then, using the same scale, they rated the relevance of this topic or skill to their current or future work or clinical practice and then their interest in receiving further education or training on each topic or skill. The final question asked the participants to rate their "overall knowledge and competence in care of older people" in relation to what was needed for their role or profession.

Section 3: Medical Students Versus Professionals

This section was meant to divide professionals and final-year medical students. Professionals were directed to sections 4 and 5 and then sections 7 and 8. Final-year medical students were directed to sections 6, 7, and 8.

Section 4: Current Profession (Professionals)

This section inquired about the main qualification or degree, the year when it was obtained, and the country or main country of qualification. These questions considered the developments in teaching and training that took place in the relevant country over the years and the heterogeneity of teaching and training between countries.

Further questions asked whether medical doctors had a medical specialty and, if so, the country and the year in which this was obtained. Another question asked about additional specialties or subspecialties. Question 4.8 asked health care professionals other than physicians or surgeons whether they had a specialty or subspecialty or competency in the care of older adults. Question 4.9 asked all health care professionals in which country they currently worked. Questions 4.10 to 4.13 explored the settings of current work. Question 4.14 asked about the years of experience caring for older adults. Question 4.15 asked about the proportion of older adults among the patients of the clinical health care professionals.

Section 5: Previous Education in Geriatric Medicine (Professionals)

It was important to explore whether health care professionals had previous formal training in the care of older adults for many reasons. First, exposure to geriatric medicine and role models in this specialty may influence health care professionals to choose the specialty or subspeciality of geriatric medicine in countries where it exists [33]. It may also reflect their self-perceived knowledge on major geriatric medicine topics. Therefore, this section asked the health care professionals whether they attended specific courses or lectures on the care of older adults or geriatric medicine.

Then, it inquired about clinical rotations in each of the following settings: a geriatric medicine acute care hospital ward, a rehabilitation setting, and a care home or nursing home or a geriatric medicine outpatient clinic. Care homes or nursing homes have recently been advocated as training settings, although this is uncommon in many countries [34]. Finally, this section asked about volunteer work with older adults and research in the field of geriatric medicine.

Section 6: Education in Geriatric Medicine (Medical Students)

The first 4 questions in this section targeting medical students were intentionally similar to those in section 5, which targeted professionals. Medical students were asked about specific courses or lectures, clinical rotations, volunteer work, and research related to geriatric medicine. Questions 6.5 and 6.6 asked them about the country (or main country) and university where they were studying. Question 6.7 asked them whether they wanted to become geriatricians. Question 6.8 explored the potential obstacles to becoming a geriatrician. In question 6.9, medical students were asked about their "thoughts on becoming a geriatrician" and given the option of writing free text. Finally, they rated how prestigious it is to be a geriatrician in their country or selected that "there are no geriatricians" in their country.

Section 7: Interest in the Care of Older People or Geriatric Medicine

In this section, both professionals and medical students rated their "satisfaction and feeling comfortable when interacting with older adults in both professional and non-professional settings." Health care professionals also rated these feelings specifically "in a professional setting." Both professionals and medical students were then asked about their "thoughts on caring for older people" and given the option of writing free text. Finally, they rated how prestigious it is to care for older people in their country.

Section 8: Suggestions on Courses on the Care of Older People or Geriatric Medicine

This section asked professionals and medical students about the acceptability and perceived effectiveness of a variety of educational and training methods. It asked them to rate their interest in attending courses on the care of older adults and whether they would prefer in-person, online, or hybrid courses. It explored the barriers to attending these courses. Finally, it asked the respondents to rate the effectiveness of various teaching methods, including A to Z textbook such as lectures on a topic, teaching of clinical tools for screening or diagnosis and evaluation, question-driven teaching, clinical cases, role-plays, short presentations by the participants as a learning tool, and assignment of group activities. Question 8.6 gave them the option to suggest any other teaching methods.

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Final Section

The last section gave the participants the option to provide a contact email address. This option was deleted in the German version of the survey.

Translations of the Survey

The survey was originally developed in English and then translated into Albanian, Bosnian, Bulgarian, Croatian, Czech, Danish, Dutch, French, German, Greek, Hebrew, Hungarian, Italian, Latvian, Lithuanian, Macedonian, Polish, European Portuguese, Romanian, Serbian, Slovak, Spanish, Swedish, and Turkish. The translations aimed to promote participation among those who did not have English as their first language and adopt an inclusive attitude toward diversity within health care.

The translations followed specific guidelines by WG 1 (Multimedia Appendix 4). The survey was directly translated only from English into each of the other languages. Each translation required at least a translator and a proofreader. In most cases, the translators were PROGRAMMING members with a health care background who translated from English into their own native language. All proofreaders were PROGRAMMING members and mostly MC members. For each translation, a form was created and tested by providing mock responses that were checked for alignment with the English-language version. Random errors were corrected, and mock responses were deleted before dissemination.

Identification of Stakeholders

WG 1 and WG 5 aimed to identify relevant stakeholders who could promote the dissemination of the survey to specific countries or internationally (Figure 4). WG 5 developed a framework to identify and categorize potential stakeholders and a guide to facilitate discussion group meetings held for identifying the stakeholders internationally and at the country level [35].

Figure 4. Dissemination of the PROmoting GeRiAtric Medicine in countries where it is still eMergING (PROGRAMMING) survey. EuGMS: European Geriatric Medicine Society; SCC: science communication coordinator; WG: working group.

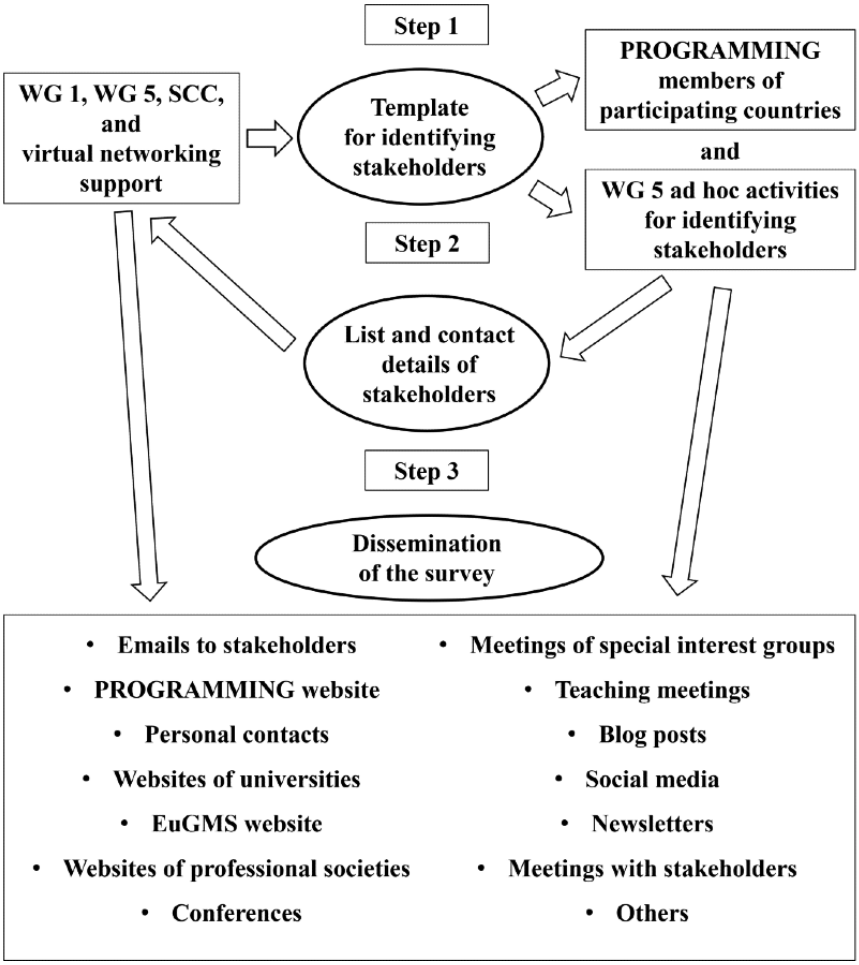

The MC members or, in countries with no MC members, PROGRAMMING members were asked to identify relevant stakeholders from their country and create lists of these using an official template [35]. On this template, the stakeholders were classified as those related to education (including undergraduate and postgraduate education and continuous professional development), policy, nongovernmental nonprofit societies, scientific societies, educational societies, professional societies, student organizations, charities, and research. The same stakeholder could be named in more than one section, and their publicly available contact details were included. WG 1 and WG 5 asked the stakeholders to forward the survey to the members of their organizations without obtaining direct access to their contact lists.

WG 1 and WG 5 encouraged the adoption of this template, although it was not mandatory, and the creation and completion

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of a list of stakeholders per country before October 2023. At the same time, until April 2024, WG 1 and WG 5 accepted new lists as well as any later corrections or additions. The number of stakeholders varied between a few (<10) and a few hundred per country. WG 1 and WG 5 encouraged the identification of international stakeholders such as European professional or scientific societies.

Strategies of Dissemination

The survey was disseminated exclusively online and through several strategies (Figure 4). A specific page was created and dedicated to the survey on the PROGRAMMING website, making the online survey forms openly accessible to the website visitors [36]. The Action awarded a Virtual Networking Support grant to the EuGMS secretariat for the online dissemination of the survey. The EuGMS secretariat contacted international and national stakeholders via emails that described the aim of the survey, the compliance with the GDPR, and the categories targeted by the survey. These emails included direct links to the survey in one or more chosen languages (Multimedia Appendix 5). They were written in English and then adapted and translated into national languages, as deemed appropriate for local contexts. Later, simplified versions were created, and the official poster for dissemination was attached to them (Multimedia Appendix 6 and Figure 5). In a few countries, such as Belgium, France, Portugal, and Finland, the MC members contacted the stakeholders directly without the help of the EuGMS secretariat.

In parallel, in all countries, WG 1 and WG 5 encouraged dissemination through social media and professional contacts (Figure 4). In December 2023, WG 1 and WG 5 held a webinar on the potential strategies for dissemination of the survey with approximately 30 PROGRAMMING members. A few blog posts were posted on the websites of professional scientific societies. We publicly thanked the academic institutions and professional societies that contributed to the dissemination of the survey (Figure 6).

Figure 5. Official poster for the dissemination of the PROmoting GeRiAtric Medicine in countries where it is still eMergING (PROGRAMMING) survey.

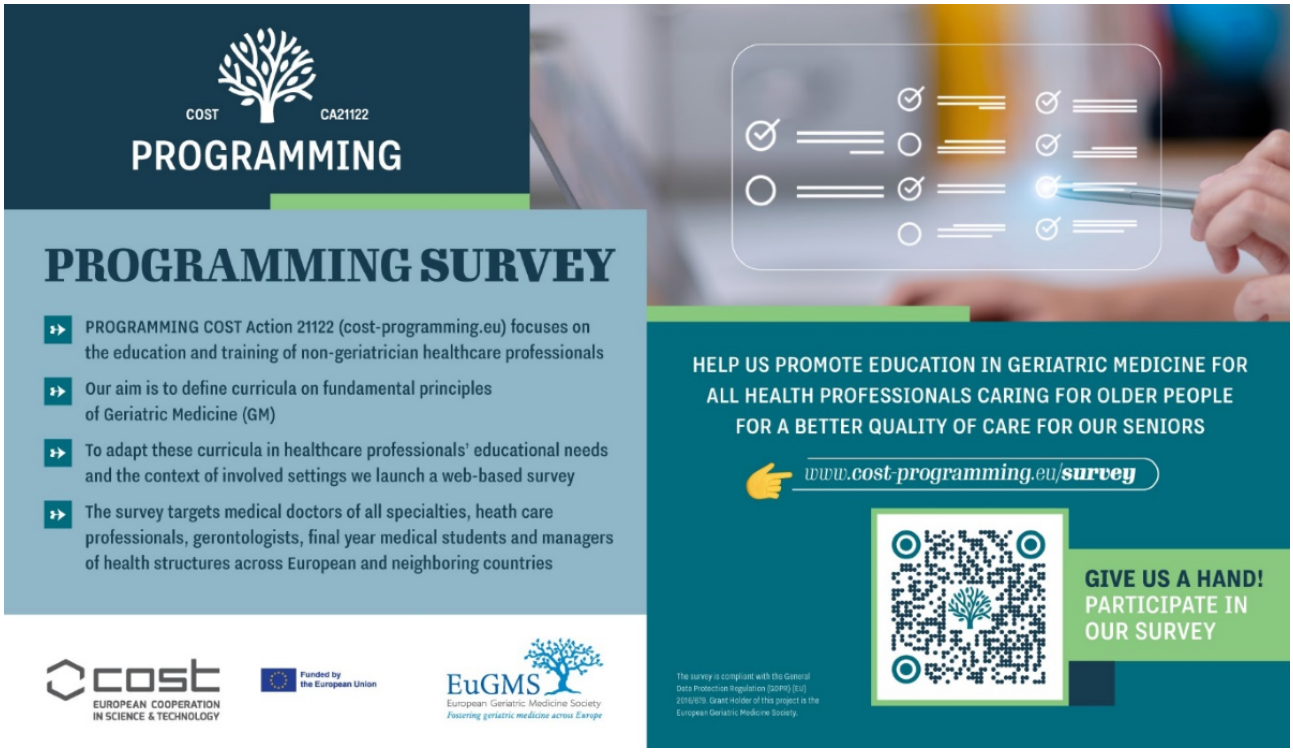

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Figure 6. Academic institutions and professional societies that contributed to the dissemination of the survey.

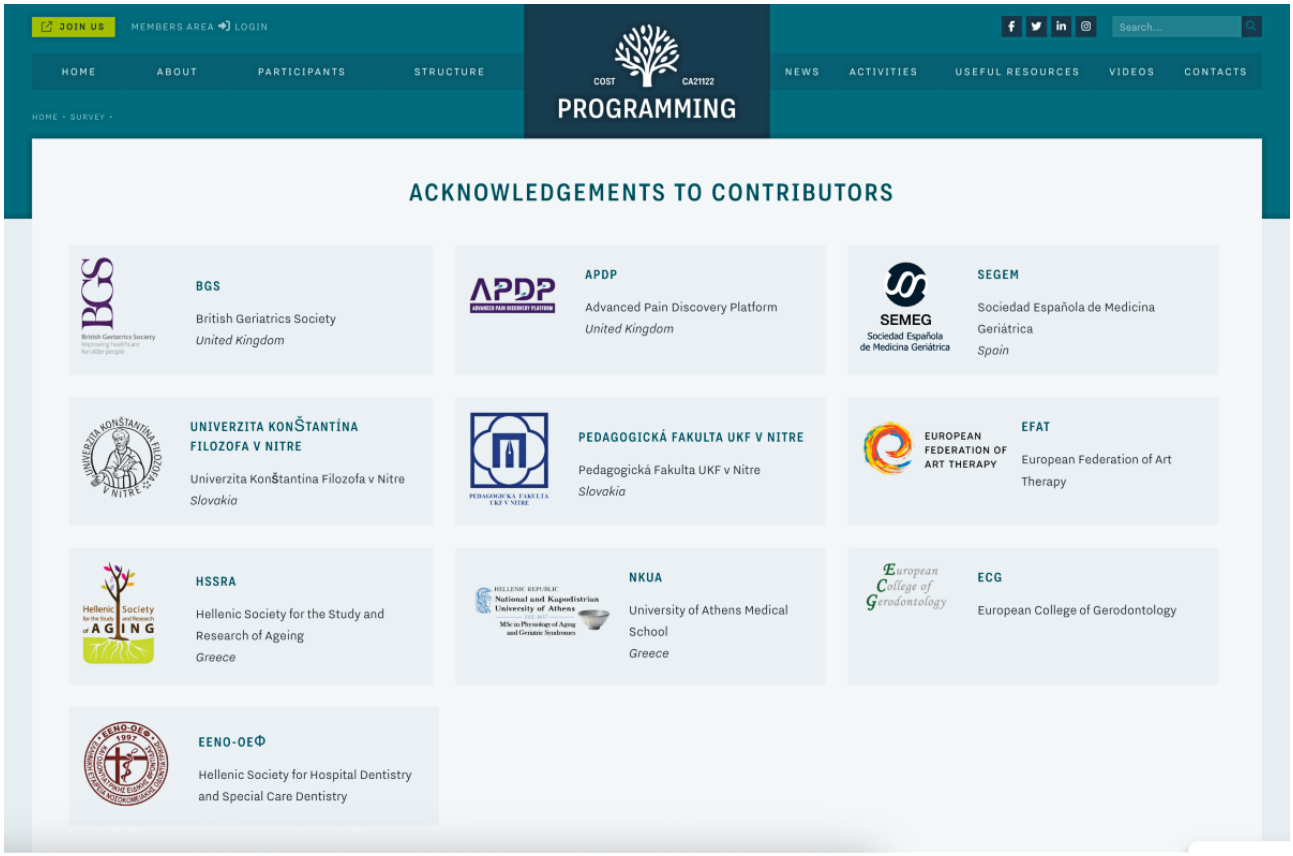

Ethical Considerations

Ethics approval was obtained in the countries where local regulations necessitated review by an ethics committee. The approval numbers and specific institutional review boards overseeing the study are documented in Multimedia Appendix 7. In countries where ethical review was not required, local regulations and institutional policies were followed.

The survey protocol received ethics approval from the Jagiellonian University ethics committee, Kraków, Poland (118.6120.61.2023; request submitted on May 26, 2023; approval by the ethics committee on June 5, 2023); the Ethics Committee for Human Research, Faculty of Medicine, Ss. Cyril and Methodius University in Skopje, Republic of North Macedonia (03-338211; dated August 7, 2023); Medical University of Graz, Austria (35-373 ex 22/23; voted and approved on September 15, 2023); the Faculty of Medicine, Health, and Life Sciences Research Ethics Committee of Queen's University Belfast, United Kingdom (23_123; September 27, 2023); Jerusalem College of Technology, Jerusalem, Israel (014_23; September 2023); the ethics committee of the Faculty of Dental Medicine, University of Belgrade, Serbia (36/42; dated October 16, 2023); the Committee of Bioethics and Deontology, School of Medicine, National and Kapodistrian University of Athens, Athens, Greece (762; October 23, 2023); Istanbul Faculty of Medicine Clinical Research Ethics Committee, Istanbul, Türkiye (application 2023/2339; decision 26; dated December 29, 2023); and the Ethics Commission of the Faculty of Medicine of the University of Cologne, Germany (application 23-1439; letter from the Ethics Commission dated March 11, 2024). The Research Ethics Committee of "Carol Davila" University of Medicine and Pharmacy, Bucharest, Romania (12996; dated May 10, 2023); the Central Denmark Region Committees on Health Research Ethics, Denmark (request 173/2023; outcome letter dated November 10, 2023); the secretariat of the Umbria Regional Ethics Committee, Italy (email dated September 13, 2023); and the Research Ethics Committee of Rīga Stradiņš University, Latvia, stated that the study may be conducted without an approval from the committees. The ethics committee of Constantine the Philosopher University in Nitra, Slovakia, approved the project implementation and questionnaires, including documentation (UKF/370/2025/191013:006). The Ethics Committee of General Hospital "Prim. Dr. Abdulah Nakas," Sarajevo, Bosnia and Herzegovina, approved the project implementation and questionnaires, including documentation (26-213-139/25; Sarajevo, March 3, 2025). According to the Republic of Lithuania's Law on Ethics of Biomedical Research (May 11, 2000; VIII-1679) and the assessment of the Lithuanian Bioethics Committee, the permission of the Lithuanian Bioethics Committee was not required for this survey targeting professionals; medical students were not targeted in Lithuania. According to the Swedish Ethical Review Authority, the Act on Ethical Review of Research Involving Humans (2003:460) states that "If you have designed a study in such a way that sensitive personal data will not be collected ethical review is not required." In Albania, ethics approval was not required for this survey with deidentified data (law 80/2015, "On Higher Education and Scientific Research in Higher Education Institutions of the Republic of Albania"). In Belgium, Bulgaria, Croatia, the Czech Republic, France, the Netherlands, Portugal,

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and Spain, ethics approval was waived as the survey collected data that were deidentified, there were no interventions, informed consent was obtained by proceeding with the survey, and participants were informed of the use of their data in accordance with the GDPR (EU 2016/679), ensuring compliance with the applicable regulations.

Participants were required to provide informed consent before completing the survey. The first section of the survey, "Informed consent," included the following: "Disclaimer If you continue, you are giving your informed consent to this survey and you are accepting the EuGMS privacy policy. The EuGMS is compliant with the GDPR (EU) 2016/679." It provided a link to the EuGMS website for further information on "how the EuGMS collects, keeps, and processes private information in compliance with GDPR" and the contact email of the EuGMS secretary. The participants could opt out of the survey while filling it out, and their responses were not recorded. In addition, they may contact the EuGMS secretary to opt out of the survey as specified on the survey web page of the PROGRAMMING website [26]. As of February 2025, no participant has contacted the EuGMS secretary asking for their data to be deleted.

All survey responses were anonymized to prevent identification of individual participants. Data were stored securely on password-protected servers, with access restricted to authorized researchers. No personally identifiable information was collected, ensuring compliance with data protection regulations such as the GDPR.

No monetary or material compensation was provided to participants. Participation was entirely voluntary and based on professional and academic interest. We believe that the benefit to participants will be indirect and in the long term as we hope that our research will promote geriatric medicine across Europe and beyond. We publicly thanked the participants on the PROGRAMMING website [26].

Quantitative Analyses

We are planning quantitative and qualitative analyses in parallel (Figure 7). Various national and cross-country teams have volunteered to conduct quantitative analyses of the survey data in parallel following approval of their research proposals. There are national teams that will analyze the data of their own countries and share them with national stakeholders and professional societies (eg, in Greece, Portugal, Serbia, and Türkiye), as well as broader regional teams (eg, German-speaking countries and Nordic countries). Teams with members from at least 3 different countries will run analyses of data from across Europe and beyond, focusing on the responses from 1 specific professional category (eg, nurses, pharmacists, and physiotherapists) or from medical students. WG 1 members will conduct global summary analyses of the section 2 findings to create "benchmarking" and mapping data. Finally, WG 2 will explore the responses of professionals working in ambulatory settings as defined on the PROGRAMMING website [26]. In parallel, WG 3 will analyze the responses of professionals working in inpatient settings, including acute care general and psychiatric hospitals, rehabilitation hospitals, long-term care psychiatric hospitals, and long-term care institutions such as residential and nursing homes [26].

The statistical analyses will include basic descriptive statistics such as frequencies (and percentages) for categorical variables (eg, role or profession and self-perceived knowledge on each geriatric topic) as well as means with SDs and medians with ranges and IQRs for continuous numerical variables such as age. We will test for differences in self-perceived knowledge on each geriatric topic between different categories of health care professionals (eg, nurses vs all other professionals) by using chi-square tests, as well as for perceived relevance to clinical work and interest in receiving further education on each geriatric topic. In view of cross-country differences in health care and educational systems, we will conduct sensitivity analyses within countries (at least in those with enough responses). Furthermore, we will explore differences in knowledge on each geriatric topic and overall across countries and settings of work using chi-square tests.

We will conduct analyses within the same professional category (eg, nurses) to test for the role of previous formal education in geriatric medicine (or rotations in geriatric clinical settings) in promoting knowledge on each geriatric topic. Previous formal education in geriatric medicine will be the determinant. Self-reported knowledge on a specific geriatric topic (eg, delirium) will be the dichotomous outcome (poor vs good). In our survey, self-reported knowledge on each geriatric topic was measured using a 5-point Likert scale (from "1=very low" to "5=very high"). In the chi-square analyses, we will show the full descriptive statistics of our data and the 5 categories of self-reported knowledge. For summary purposes, we will then dichotomize self-reported knowledge as either poor (very low or low knowledge) or good (fair, good, or very good knowledge).

We will conduct binary logistic regression analyses with previous formal education in geriatric medicine as the determinant and self-reported knowledge of delirium as the outcome only in the sample of a single professional category; these analyses will be adjusted for age, gender, and country. We expect that those with previous formal education in geriatric medicine will report good knowledge of delirium more frequently than those without it. We will repeat these analyses for each of the geriatric topics of section 2. Similarly, we will conduct binary logistic regression analyses with previous rotations in geriatric settings (acute care geriatric ward, outpatient clinic, rehabilitation ward, and nursing home) as the determinant and knowledge on each geriatric topic as the outcome. We expect that, within each professional category, those with previous rotations in geriatric settings will report good knowledge on geriatric topics more frequently than those without them. Binary logistic regression is a statistical analysis that is suitable for binary outcomes such as poor versus good self-reported knowledge.

We will organize meetings between WG 1 experts in quantitative and qualitative analyses and national and cross-country researchers to ensure consistent data analysis protocols. At the same time, we will welcome adaptations of the analyses to national needs. We are not planning any weighted analyses; we

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welcome sensitivity analyses and particularly within-country analyses in view of the disproportionate number of responses in a few countries.

Figure 7. Analyses of the survey data. EuGMS: European Geriatric Medicine Society.

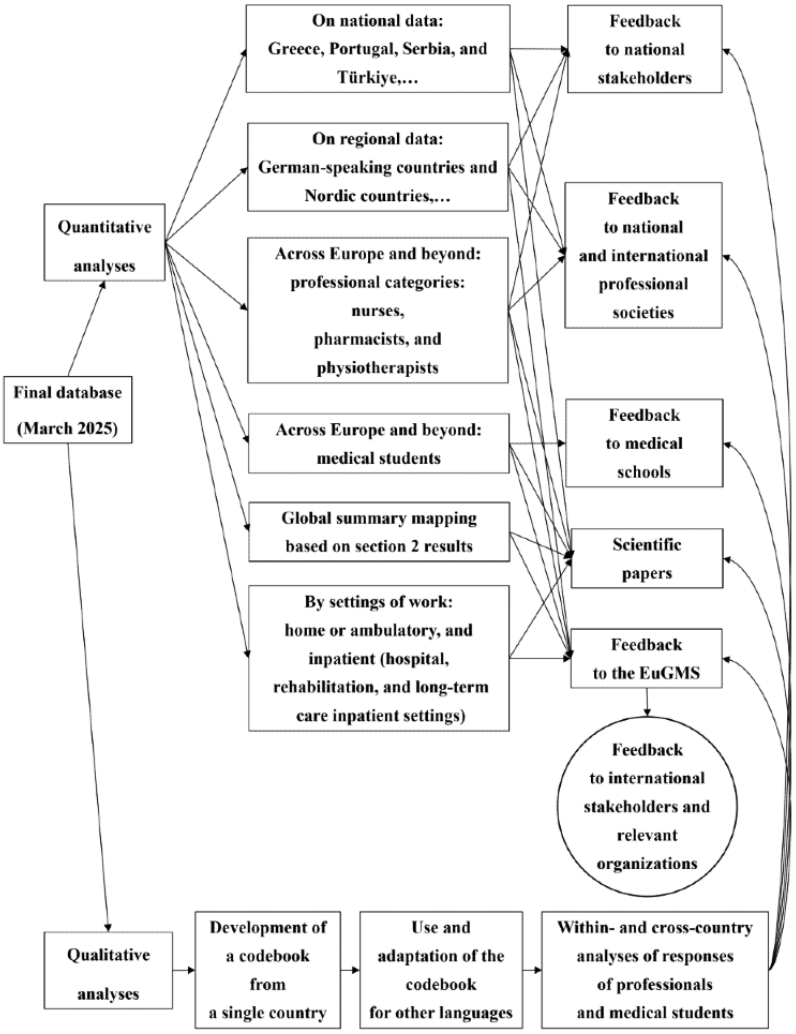

Qualitative Analyses

We are planning qualitative content analyses of the free-text responses to the questions exploring professionals' and medical students' thoughts on caring for older people and medical students' thoughts on becoming geriatricians. Undertaking qualitative analysis for such linguistically diverse data presents challenges and dilemmas [37]. The responses are in >20 languages. Some concepts may not be easily translatable, and capturing nuances of terminology between languages, perhaps reflecting cultural and professional particularities, may generate significant time and resource demands. The responses may also be interpreted differently depending on the professional background of the researchers.

There is a further tension between having a standardized approach but also one that is inductive and can cope with the full richness and context of the sentiments expressed. Across Europe and beyond, broad emotions and sentiments have emerged from the responses, ranging from respect and admiration to sarcasm and feeling that older people are discriminated against by society or family members. Caring for older people is described as both rewarding and challenging. Words such as "enriching" and "gratitude" are mentioned, but also "ageism," "discrimination," and "cuts."

To overcome these multi-language challenges, we developed the following analysis process based on content analysis. Content analysis aims to identify and interpret meaning within recorded communication through labeling smaller data pieces and organizing them in a way that describes or explains a phenomenon [38]. It was originally used to quantitatively describe the manifest content of communication but was adapted to include more qualitative approaches to analysis to understand deeper meanings [39]. In total, 2 coders fluent in the response language will independently code the responses using Microsoft Excel. Coding will be conducted in the coders' native language; bilingual and culturally knowledgeable researchers will ensure both linguistic accuracy and cultural nuances. A standard coding framework will be developed and iteratively refined through cross-cultural discussions to maintain comparability across languages. Discrepancies will be resolved through consensus meetings incorporating responses from native speakers and subject matter experts. To mitigate linguistic and cultural biases, coding checks and double validation will be conducted across diverse linguistic contexts.

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The focus will be on manifest content, but latent content will also be coded as responses tend to be fairly brief but can contain emotive words open to interpretation (eg, “must”). To ensure that multiple possible interpretations of any latent sentiments are explored and consistently applied, 2 coders will be involved and will discuss any disagreements by consulting qualitative experts and the wider WG 1 as needed. This will also help address the issue that the coding researchers may bring biases associated with their own professional background and understanding, and they will be encouraged to be reflexive regarding this throughout coding and discussion.

Multiple codes will be applied where needed; for example, “Perkujdesje, respekt, dashuri, mirenjohje, dhembshuri” (Albanian), which translates to “Care, respect, love, gratitude, compassion,” will generate 5 codes. The codebook will be agreed upon between 2 researchers, and logical category groupings will be applied. Bearing in mind the limited data per person, categories rather than themes will form the main basis of analysis [40], focusing on describing similarities and differences on a manifest and descriptive level related closely to the original responses but including latent data where relevant. Frequencies will be applied to demonstrate the prevalence of views within these categories, especially where there are larger numbers of free-text responses, in addition to textual description. The process will be initially piloted on the Albanian-language responses and will be refined as needed.

The Albanian-language coding process will be conducted in the Albanian (native) language to preserve linguistic and cultural nuances. In total, 2 independent researchers will code the data separately, ensuring reliability, under the guidance of a qualitative research expert. It is planned that teams working in other languages will be able to use the Albanian-language codebook, which will be translated into English, as a basis for coding. Any language- or culture-specific concepts will be described as clearly as possible in English, with the original-language words retained in brackets for clarity. The Albanian-language codebook will serve as a basic framework and applied deductively where relevant codes already exist to maximize comparability between languages for larger-level analysis but taking an inductive approach to ensure that any new data are captured. Inductive coding will be applied for emerging or unique data that do not fit into existing categories. New codes will be discussed in consensus meetings and incorporated into the codebook through an iterative refinement process.

New codes will be added to the codebook iteratively for each country’s analysis following the same principles mentioned previously. Other countries can choose to use the original or adapted codebooks and will be encouraged to discuss new codes with the Albanian-language team and the wider WG 1, particularly if they are unclear on the meaning and comparability of certain codes or definitions. WG 1 will store a copy of all codebooks and will review and refine the initial codebook with the Albanian-language team. Quotes will be translated into English for publication.

Results

Timeline

The dissemination of the survey started on October 9, 2023. Although the initial aim was to have the same time window for dissemination for all languages and countries, this proved to be not possible. The ethics applications in a few countries required long periods, and other countries joined this initiative after the start of dissemination. Dissemination ended on April 30, 2024, for most countries, whereas it was prolonged until June 5, 2024, for the German and Hungarian surveys.

Social Media Metrics

The survey was posted on the PROGRAMMING website and on the social media of the EuGMS and other professional societies. In 2023, the PROGRAMMING website [26] had 30,252 visits from <15,674 unique visitors; in 2024, it had 94,784 visits from <38,019 unique visitors. In addition, Multimedia Appendix 8 presents some metrics that are an underestimation of the overall dissemination.

Final Database

As of February 2025, WG 1 is merging and coding the survey data from multiple electronic forms into a unique database using SPSS (version 29; IBM Corp) [41]. This database will include all the responses that were collected by the survey; it will retain the open-ended responses in the original languages and then add their translations. From June 2024 to January 2025, WG 1 conducted preliminary analyses and developed examples of visual presentation of preliminary data.

As of April 2025, WG 1 has finalized the cleaning of the database. The survey received 6099 responses; as of April 2025, the final cleaning has led to 5922 responses, including 5474 (92.43%) from health care professionals and 448 (7.57%) from medical students. Preliminarily, it included responses from dieticians (3%), dentists (8%), medical doctors in training or not in training (37%), medical students (7.5%), nurses (14%), pharmacists (6%), physiotherapists (6%), and other categories. Responses were excluded from the final database in case the respondent was not a professional or a medical student (eg, responses from dental or nursing students or students other than medical students were excluded), the respondent was a professional who erroneously filled in the student section 6 rather than sections 4 and 5 for professionals, the respondent was a medical student who erroneously filled in the professional sections 4 and 5 rather than the student section 6, there were multiple entries from the same individual, or there were serious inconsistencies across the responses from the same individual.

WG 1 researchers carried out log file analyses to prevent multiple entries from the same individual by checking for duplicates in the optional email addresses provided and by comparing the responses of participants with exactly the same demographics using the tool for identifying duplicate cases in SPSS. When duplicates were found, only their first entry was retained in the final database, whereas the most recent one was excluded, except in the case of a medical student and cases in which the responses in the likely native language were kept instead of those in English.

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WG 1 researchers also checked the internal consistency of the responses by creating cross-tables for variables such as profession (question 1.3: “Role or profession”) and main qualification (question 4.1: “Main qualification or degree”) and by checking the age of the respondent against the year of main qualification or degree and the year of medical specialty (in the case of medical specialists). WG 1 sought clarification from national PROGRAMMING members. In case of serious and multiple inconsistencies, the entire set of responses was excluded from the final database. In case of isolated unrealistic entries (eg, the year of medical specialty was the expected one), this was highlighted as unrealistic with a note within the coded or translated response. WG 1 researchers conducted an extensive cross-checking of the consistency of the responses on the settings of work of professionals (questions 4.10 to 4.13).

There were practically no incomplete questionnaires. All questions in the survey were intentionally made mandatory to avoid incomplete or partially completed questionnaires. Even questions with free-text responses were made mandatory, and the respondent was invited to write “blank” or “not applicable” as appropriate.

We cannot measure the time that each respondent needed to fill out the questionnaire; the variable “time stamp” refers to the date and time of submission of the questionnaire. We cannot exclude questionnaires that were submitted too soon, but no respondent could submit the questionnaire unless all mandatory questions were answered. It is likely that many potential respondents started to fill out the questionnaire but then abandoned it; their responses were not recorded. We cannot estimate the completion rate of the survey.

No response was deleted. The responses that were excluded from the final database were deidentified for confidentiality and retained in separate files for documentation.

Discussion

Expected Findings

We developed a web-based survey to map the educational interests and needs of health care professionals and final-year medical students across the countries of the COST Action PROGRAMMING CA21122. This paper describes the development, structure, and dissemination of the survey in line with current guidelines [42]. We have attached the original English-language version of the survey (with a few technical instructions) to facilitate future replication or adaptation of our work (Multimedia Appendix 1).

Through the implementation of our survey, we collected responses on the educational needs in geriatric medicine from 5474 health care professionals and 448 medical students across Europe and beyond. We achieved this by organizing a dissemination strategy that involved recognized leaders in health science education, following appropriate ethics regulations, and offering translated versions of the survey into several European languages to overcome language barriers that could limit self-expression of needs. In addition, we managed to have significant representation from many categories of health care professionals comprising the geriatric interdisciplinary team across the PROGRAMMING countries (ie, the health care professionals from different disciplines who collaborate to provide comprehensive and coordinated care to older adults). This will allow us to adapt our suggested geriatric educational curriculums to the different needs of health care professionals and across the widely diverse health care landscape across Europe and beyond.

Our survey adds to previous literature exploring the attitudes toward caring for older people and choosing career pathways in this field [43-48]. For example, previous surveys have explored the interest in geriatric psychiatry of Canadian psychiatry residents [43]; the knowledge on and attitudes toward geriatrics of medical students, internal medicine residents, and geriatric medicine fellows at an American academic medical center [44]; and the attitudes toward older adults of medical students at a US medical school [45], clinical pharmacists from a Canadian province [46], dentists from a Brazilian city [47], or physiotherapists [48]. The novelty of our survey is the targeting of a broad range of health care professionals, including those who will not specifically work in geriatric medicine but will encounter older adults in their clinical practice. We acknowledged that most older adults will receive care from medical doctors who are not geriatricians, as well as other members of multiprofessional teams [49]. While previous surveys have focused on a single health care professional category, a single country or academic center, and limited geriatric topics, our survey targeted multiple professional categories across Europe and beyond and explored a wide range of topics. Furthermore, we surveyed professionals and medical students in countries where geriatric medicine is still emerging and included this as a barrier. Similarly to most previous surveys, our survey was cross-sectional and could not capture any changes over time in medical students’ attitudes towards older people; in contrast, previous research conducted at a medical school in the United States described changes in medical students’ attitudes towards older people [45].

This study has several strengths. One of the major strengths is the broad geographic and professional representation, which enhances the relevance and generalizability of our findings. The use of a mixed methods approach also allows for a more comprehensive understanding of both quantitative trends and qualitative insights. A further strength was the harmonization and dissemination of the survey across several European and neighboring countries. One of the crucial points of discussion was whether the survey should be identical between nations or vary to reflect differences between states’ health care needs and systems. While many argued that the survey should be adapted to local contexts or tailored to respondents from different professions, others pointed out that comparisons can be made only when surveys are harmonized. In the end, the consensus was that the survey should be harmonized and include the same sections, questions, and response options across all countries. However, the way in which data are collected will allow for subgroup analyses for different countries and professions. While most sections were the same for both health care professionals and medical students, 2 sections specifically targeted health care professionals, and another one targeted medical students. Second, the survey was developed based on previous research

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on geriatric medicine education, including a recent literature review undertaken by PROGRAMMING members [16]. Third, the survey was developed through many rounds of discussion between professionals from different countries and professional backgrounds. Fourth, it was translated into >20 languages. In our view, this favored participation in the survey of potential respondents who are not fluent in English. In this way, our survey was more inclusive than surveys disseminated only in English or a specific national language. Fifth, it provided a detailed characterization of the educational background of the respondent. It collected data not only on the main qualifications of the respondents but also on the specific year and country of education. In this way, it identifies temporal trends in educational needs as well as cross-country variation. Sixth, it included questions on subjective or self-perceived knowledge on or competence in major geriatric topics alongside objective questions on courses and clinical rotations during formal education. In this way, it may detect gaps in self-perceived knowledge and explore their correlations with various types of training. Seventh, our survey targeted a broad range of health care professionals, which reflected the broad interdisciplinary and interprofessional approach required by contemporary geriatric medicine. Finally, our survey included open-ended questions (eg, on "thoughts about caring for older people") with the possibility of free-text responses; a qualitative content analysis of these responses is planned, preferably in the original languages.

Some limitations should be acknowledged. First, the survey was not developed through a rigorous Delphi process, which may have influenced the selection of topics. Nevertheless, the iterative cocreation process with international stakeholders helped ensure relevance and comprehensiveness. Moreover, the survey was one exploratory step within the broader context of the PROGRAMMING initiatives, which included qualitative focus groups on areas not covered in the survey. A Delphi process would certainly be a necessary approach to final curricula and policy drafting. Second, selection bias may be present as participants with a strong interest in geriatrics may be more likely to complete the survey. To quantify this selection bias, we will calculate the proportion of medical students who would like to become geriatricians among our respondents and compare it with those reported in the literature. Previous studies in the United States have shown that approximately 4% of medical students would choose geriatric medicine as their medical specialty [50]. Third, the survey had a relatively long duration (10-15 minutes), which may have discouraged potential respondents and hindered a potentially wider dissemination. Fourth, the staggered dissemination of the survey may have limited participation in a few countries, but we do not expect this to affect the content of our findings as no major event with an impact on medical practice or education occurred in the few months of dissemination. Fifth, we disseminated our survey primarily in Europe. Consequently, the findings of our survey may not be generalizable to countries in other continents.

The findings of this study will inform the development of targeted educational curricula and professional training programs. We anticipate that insights from the survey will be shared with medical schools, professional societies, and policy makers to advocate for improved geriatric education. Future research should focus on validating these findings through objective assessments of knowledge acquisition and measuring the impact of educational interventions over time.

The goal of PROGRAMMING is to promote education on geriatric medicine to every health care professional caring for older adults in a way that is tailored to the professional roles, clinical settings, and country or region specificities.

At the same time, it is essential that the curricula of health care professionals be harmonized between countries for 2 main reasons [16]: first, to spread up-to-date scientific knowledge, evidence-based recommendations, and good clinical practice models so that older adults across Europe and beyond may receive appropriate care and, second, to remove barriers to the international mobility of health care professionals. Indeed, many high-income European countries are increasingly relying on the recruitment of health care professionals who were trained abroad within or outside Europe [10]. In 2019, one-third of the UK medical doctors were trained internationally [51,52]. The World Health Organization Global Code of Practice on the International Recruitment of Health Personnel (2010) recommended that all countries should train and retain sufficient physicians to meet demand rather than rely on immigration [10]. It supported circular migration of health care personnel so that skills and knowledge can be transferred to the benefit of both source and destination countries [10].

We plan to analyze the findings of the survey using both quantitative and qualitative techniques. We aim to identify the geriatric topics and skills in which health care professionals feel less competent, and we aim to explore patterns associated with lower self-perceived knowledge and competence, for example, in relation to country and qualification or professional role. Furthermore, we aim to explore gender differences in attitudes toward caring for older adults and, among medical students, in choosing geriatric medicine as a specialty. We also aim to investigate barriers, including gender-specific barriers, to choosing geriatric medicine as a specialty and attending courses on care for older adults. By conducting qualitative content analyses, we aim to obtain a deeper insight into the thoughts about caring for older adults of a broad number of health care professionals from diverse professional backgrounds in many countries in and beyond Europe.

One section of the survey explored the effectiveness of a broad range of teaching methods by asking health care professionals and medical students to rate them. Its findings may inform and guide the efforts of WG 4 of PROGRAMMING toward the implementation of education and training in the care for older adults in PROGRAMMING countries.

Furthermore, the survey collected detailed information on the settings in which health care professionals worked. This will allow for subgroup analyses on the educational needs of health care professionals by setting of clinical practice, including community settings, acute secondary care hospitals, and long-term care institutions. This will inform the activities of WG 2 and WG 3, which focus on developing the content of training of health care professionals.

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Conclusions

In conclusion, the findings of our survey will be used to inform educational projects across PROGRAMMING countries. We hope that similar surveys will be disseminated in countries that we did not cover, such as African, American, Asian, and Oceanic countries. We encourage policy makers and medical educators to use our survey or to draw inspiration from it to promote further development of geriatric medicine education (Multimedia Appendix 1).

Acknowledgments

The European Cooperation in Science and Technology (COST) Action 21122 PROmoting GeRiAtric Medicine in countries where it is still eMergING (PROGRAMMING) CA21122 has received funding from COST under grant agreement AGA-CA21122-1-15351. The funder had no role in the study design; collection, analysis, and interpretation of the data; writing of the paper; or decision to submit it for publication. The authors acknowledge the Collaborators of the PROGRAMMING survey on educational needs (see Multimedia Appendix 9). The authors also thank all those who contributed to the translation and dissemination of the survey and all those who completed the survey. They thank Mrs Benedetta Bellotti and Mrs Sabrina Silvani for their administrative support. They thank all the academic institutions and professional societies that contributed to the dissemination of the survey and are listed [53] and in Figure 6. The authors thank the panel of 68 international stakeholders from 24 countries who provided feedback on the survey during an ad hoc online meeting in February 2023. Preliminary data from the PROGRAMMING survey on educational needs were presented at the Top 10 Value-Based Geriatric Care Models and Interventions: Towards a Sustainable Healthcare System, Improving Older Adults' Quality of Life joint event by the PROGRAMMING COST Action CA21122 and the Ordem dos Medicos (the Order of Physicians of Portugal), Lisbon, Portugal, on April 17 to 19, 2024; the European College of Gerodontology 34th Annual Congress: New Frontiers in Gerodontology in Belgrade, Serbia, on June 6 to 7, 2024; the European Society of Cardiology Congress 2024 in London, United Kingdom, on August 30 to September 2, 2024; during the Presentation of the preliminary results of the big Pan-European survey of PROGRAMMING COST Action open session at the 20th European Geriatric Medicine Society Congress in Valencia, Spain, on September 19, 2024; during the Joining efforts to develop geriatric medicine across Europe – the experience of EU-funded projects joint webinar with other European projects on ageing (PROGRAMMING CA21122, ICARE 4 OLD (Individualized CARE for Older Persons with Complex Chronic Conditions at home and in nursing homes) project, and AFFIRMO [Atrial Fibrillation Integrated Approach] project) on July 2, 2024; during the Orthogeriatrics – a model of care towards improving outcomes in older patients with hip fracture and promoting Geriatric Medicine training webinar organized by PROGRAMMING CA21122 in collaboration with the Fragility Fracture Network on October 24, 2024; at the conference within the framework of COST Action 21122 PROGRAMMING entitled Optimal care models for older adults: bridging community care and Geriatric Medicine in Krakow, Poland, on January 23 and 24, 2025; and in the abstract PROmoting GeRiAtric Medicine In Countries Where It Is Still EMergING (PROGRAMMING) CA21122: The Survey on Educational Needs at the 20th European Geriatric Medicine Society Congress in Valencia, Spain, on September 18 to 20, 2024.

Data Availability

The English-language version of the Promoting Geriatric Medicine in Countries Where It Is Still Emerging (PROGRAMMING) survey is available in Multimedia Appendix 1. The datasets generated by the survey may be made available upon request by following the appropriate procedure. Any member of PROGRAMMING can propose research or policy questions to be explored within the survey data following a specific set of recommendations on how to access them. We have created 2 proposal forms for the analyses of data, which are published on the PROGRAMMING website and available in Multimedia Appendices 10 and 11.

A review committee will assess each proposal and decide whether access to the data should be granted based on the following criteria: expertise of the leading proponents, relevance of the proposal's question, informative background and convincing rationale, soundness of the proposed methods, significance of the expected novelty or impact, and feasibility of the proposed timeline. We encourage every member of PROGRAMMING to submit a specific and structured proposal form to the review committee, which will supervise and coordinate the various proposals, to promote cooperation and prevent duplication of efforts. New applications to join the European Cooperation in Science and Technology Action PROGRAMMING CA21122 are possible for the entire duration of the Action, and the process for this it outlined on the Action website [25,26].

Authors' Contributions

GO, TM, AMH, TP, MP, and M Kotsani contributed to the study concept. GO, TM and WM drafted the manuscript. AMH, TP, AWE, KP, SD, AB, NB, SB-G, AK, M Koca, EK, NM-V, RF, RR-W, SS, MV, TY, MP, and M Kotsani critically revised the manuscript for intellectual content. GO and Collaborators of the PROGRAMMING survey on educational needs (see Multimedia Appendix 9) contributed to methodology and data acquisition. All authors read and approved the final manuscript.

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Conflicts of Interest

GO, TM, AMH, TP, AWE, KP, SD, AB, MP, and M Kotsani are members of the review committee of the European Cooperation in Science and Technology (COST) Action PROmoting GeRiAtric Medicine in countries where it is still eMergING (PROGRAMMING) CA21122. TM, AMH, TP, AWE, KP, SD, AB, NB, SB-G, RF, M Koca, AK, EK, NM-V, RR-W, MV, TY, MP, and M Kotsani have leadership positions within the COST Action PROGRAMMING CA21122.

Multimedia Appendix 1
The PROmoting GeRiAtric Medicine in countries where it is still eMergING (PROGRAMMING) survey on educational needs.
[PDF File (Adobe PDF File), 477 KB - resprot_v14i1e64985_app1.pdf]

Multimedia Appendix 2
Composition of the international panel of stakeholders.
[DOCX File , 34 KB - resprot_v14i1e64985_app2.docx]

Multimedia Appendix 3
Sections of the PROmoting GeRiAtric Medicine in countries where it is still eMergING (PROGRAMMING) survey.
[DOCX File , 23 KB - resprot_v14i1e64985_app3.docx]

Multimedia Appendix 4
Translation guidelines.
[DOCX File , 30 KB - resprot_v14i1e64985_app4.docx]

Multimedia Appendix 5
Email to the stakeholders from Belgium.
[DOCX File , 30 KB - resprot_v14i1e64985_app5.docx]

Multimedia Appendix 6
Simplified email to the stakeholders from Norway.
[DOCX File , 29 KB - resprot_v14i1e64985_app6.docx]

Multimedia Appendix 7
Ethical considerations.
[DOCX File , 29 KB - resprot_v14i1e64985_app7.docx]

Multimedia Appendix 8
European Geriatric Medicine Society social media metrics.
[DOCX File , 11207 KB - resprot_v14i1e64985_app8.docx]

Multimedia Appendix 9
Collaborators of the PROGRAMMING survey on educational needs.
[DOCX File , 21 KB - resprot_v14i1e64985_app9.docx]

Multimedia Appendix 10
Extended proposal form.
[DOCX File , 27 KB - resprot_v14i1e64985_app10.docx]

Multimedia Appendix 11
Simplified proposal form for analysis of the PROGRAMMING survey data on educational needs.
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Abbreviations

COST: European Cooperation in Science and Technology
EU: European Union
EuGMS: European Geriatric Medicine Society
GDPR: General Data Protection Regulation
MC: managing committee
PROGRAMMING: PROmoting GeRiAtric Medicine in countries where it is still eMergING
WG: working group

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Protocol

Generative Artificial Intelligence Tools in Medical Research (GAMER): Protocol for a Scoping Review and Development of Reporting Guidelines

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Abstract

Background: The integration of artificial intelligence (AI) has revolutionized medical research, offering innovative solutions for data collection, patient engagement, and information dissemination. Powerful generative AI (GenAI) tools and other similar chatbots have emerged, facilitating user interactions with virtual conversational agents. However, the increasing use of GenAI tools in medical research presents challenges, including ethical concerns, data privacy issues, and the potential for generating false content. These issues necessitate standardization of reporting to ensure transparency and scientific rigor.

Objective: The development of the Generative Artificial Intelligence Tools in Medical Research (GAMER) reporting guidelines aims to establish comprehensive, standardized guidelines for reporting the use of GenAI tools in medical research.

Methods: The GAMER guidelines are being developed following the methodology recommended by the Enhancing the Quality and Transparency of Health Research (EQUATOR) Network, involving a scoping review and expert Delphi consensus. The scoping review searched PubMed, Web of Science, Embase, CINAHL, PsycINFO, and Google Scholar (for the first 200 results) using keywords like “generative AI” and “medical research” to identify reporting elements in GenAI-related studies. The Delphi process involves 30-50 experts with ≥3 years of experience in AI applications or medical research, selected based on publication

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records and expertise across disciplines (eg, clinicians and data scientists) and regions (eg, Asia and Europe). A 7-point-scale survey will establish consensus on checklist items. The testing phase invites authors to apply the GAMER checklist to GenAI-related manuscripts and provide feedback via a questionnaire, while experts assess reliability (κ statistic) and usability (time taken, 7-point Likert scale). The study has been approved by the Ethics Committee of the Institute of Health Data Science at Lanzhou University (HDS-202406-01).

Results: The GAMER project was launched in July 2023 by the Evidence-Based Medicine Center of Lanzhou University and the WHO Collaborating Centre for Guideline Implementation and Knowledge Translation, and it concluded in July 2024. The scoping review was completed in November 2023. The Delphi process was conducted from October 2023 to April 2024. The testing phase began in March 2025 and is ongoing. The expected outcome of the GAMER project is a reporting checklist accompanied by relevant terminology, examples, and explanations to guide stakeholders in better reporting the use of GenAI tools.

Conclusions: GAMER aims to guide researchers, reviewers, and editors in the transparent and scientific application of GenAI tools in medical research. By providing a standardized reporting checklist, GAMER seeks to enhance the clarity, completeness, and integrity of research involving GenAI tools, thereby promoting collaboration, comparability, and cumulative knowledge generation in AI-driven health care technologies.

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KEYWORDS

generative AI; chatbots; reporting guidelines; transparency; Delphi method; large language models; ChatGPT

Introduction

Generative artificial intelligence (GenAI)–based tools and chatbots have been widely applied in medicine, facilitating interactions between users and AI through virtual conversational agents and thereby presenting new opportunities for enhancing health care practice and research methodology [1,2]. The increasing use of GenAI tools linked to chatbots in medical research brings numerous opportunities and supports innovations, but it also poses many challenges and creates issues. For example, the use of large language models may raise ethical concerns and data privacy issues [3,4]. Additionally, the generation of false content using large language models can constitute academic fraud [5]. These problems have detrimental effects on the academic community. Therefore, transparent and standardized reporting of the use of GenAI tools is extremely important. Although many journals and academic institutions have their own guidelines or suggestions on how to use GenAI tools [6-10], there are currently no universally recognized reporting guidelines on how to transparently and scientifically report the use of GenAI tools in medical research.

The Generative Artificial Intelligence Tools in Medical Research (GAMER) project aims to establish comprehensive and standardized guidelines for reporting essential elements of studies involving GenAI-based tools. The GAMER guidelines will delineate key aspects, such as whether GenAI tools were used in the study and in the writing of the paper, which tool and version were used, which sections of the paper it was applied to, the specific content areas it was used for, whether it was used for language editing or content generation, and whether any manual testing was performed. By providing recommendations for what information should be reported for each section, GAMER seeks to create reporting guidelines that streamline the reporting process, allowing researchers, practitioners, and policymakers to critically assess the quality and validity of studies involving GenAI tools in medical research [3].

The development of GAMER draws inspiration from established reporting guidelines in the field of medical research, such as the CONSORT (Consolidated Standards of Reporting Trials) statement for clinical trials [11] and the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) statement for observational studies [12]. Adhering to GAMER will not only enhance the clarity and completeness of reporting in GenAI-related research but will also foster collaboration, comparability, and cumulative knowledge generation in the rapidly evolving field of AI-driven health care technologies. This article describes the methods and processes involved in the development of GAMER, providing a guarantee for the smooth completion and promotion of GAMER in the future.

Methods

We will follow the methodology recommended by the EQUATOR (Enhancing the Quality and Transparency Of Health Research) Network [13] to develop the GAMER reporting guidelines, using methods such as scoping reviews and expert Delphi consensus to formulate the GAMER reporting checklist. We have registered this protocol with the EQUATOR Network [14].

Project Administration

The GAMER reporting guidelines were initiated by the Evidence-Based Medicine Center of Lanzhou University, the Chinese EQUATOR Center, and the WHO Collaborating Centre for Guideline Implementation and Knowledge Translation. Authors YC and JE are the co–project initiators, and author XL serves as the lead investigator and the main contact for communication.

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Funding Sources

The project is funded by research project funds from the Research Unit of Evidence-Based Evaluation and Guidelines (2021RU017), Chinese Academy of Medical Sciences; and the School of Basic Medical Sciences, Lanzhou University, with no involvement of pharmaceutical companies or other third-party entities. The funding is used solely for relevant services, materials, travel, and publication expenses during the development process of GAMER.

Scope and Target Audience

The scope of GAMER is to assist stakeholders such as researchers, clinicians, editors, authors, peer reviewers, and other relevant parties in the smooth and barrier-free use and evaluation of GenAI tools and similar chatbots for the purpose of composing medical research.

Development Process

The development of the GAMER reporting checklist has 3 stages (Figure 1). The first stage is the preparatory phase, involving the formation of an expert group, collection of initial items, and discussion of these items. The second stage primarily includes 1 to 2 rounds of Delphi survey and online, face-to-face discussions, as well as multiple rounds of optimizing items. The third stage involves the publication of the checklist, as well as testing, dissemination, and promotion of the GAMER reporting guidelines.

Figure 1. The 3 stages of development of the GAMER (Generative Artificial Intelligence Tools in Medical Research) reporting guideline.

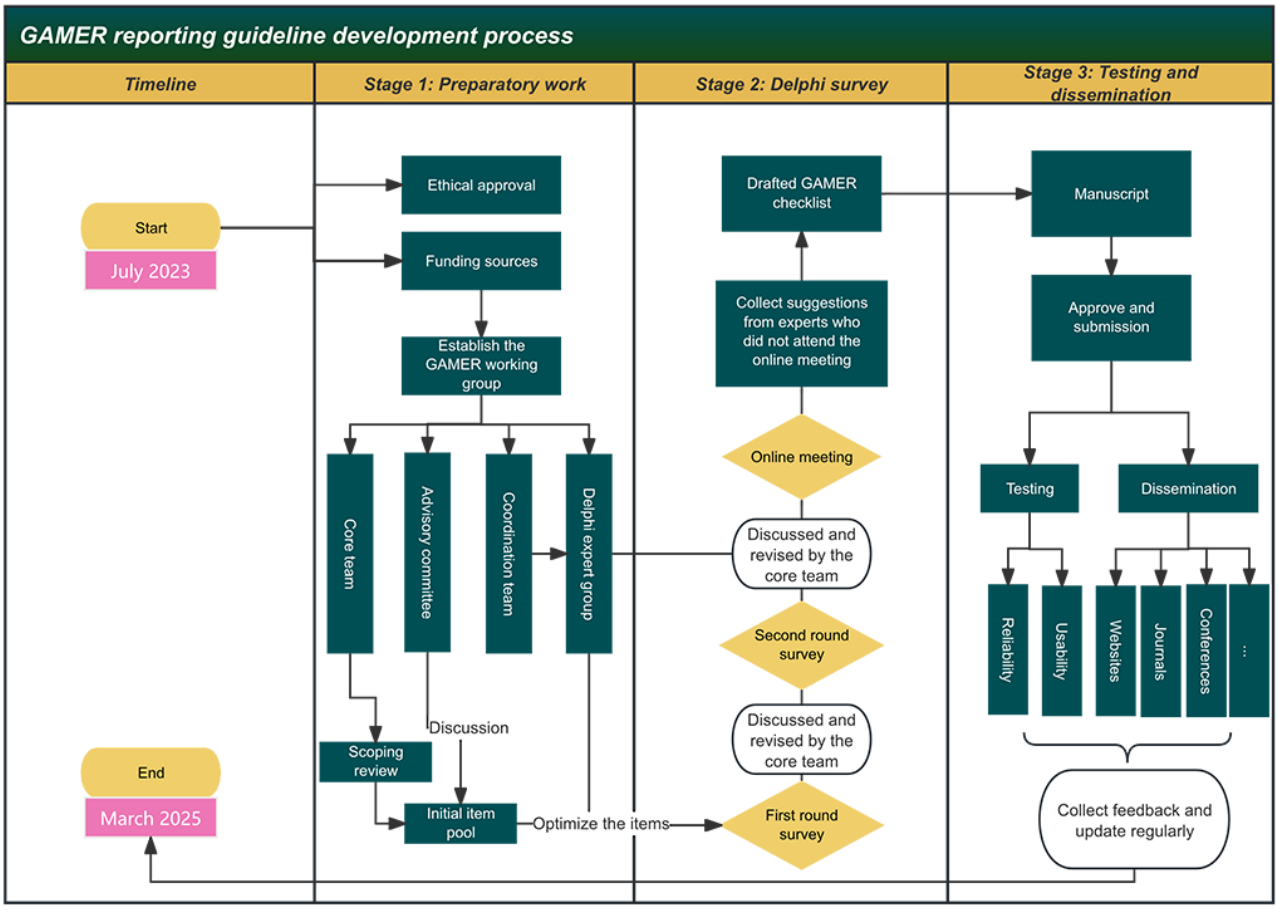

Stage 1: Preparatory Work

Establishment of the Expert Panel

We plan to establish 4 expert groups. The first is the advisory committee, consisting of 3 to 5 authoritative experts familiar with GenAI tools and experienced in the formulation of reporting guidelines. Their main responsibility is to provide advice on issues arising during the development of reporting guidelines. The second is the core team, primarily composed of members from the Evidence-Based Medicine Center at Lanzhou University. This group is responsible for conducting scoping reviews, generating the initial pool of items, revising the items, and drafting the final document. This group is the leading team for GAMER development. The third is the Delphi expert group, comprising experts with experience in a broad range of relevant disciplines from around the world. The inclusion criteria for invitation to this group are (1) participation in the publication of GenAI-related papers (obtained by searching PubMed for corresponding authors of relevant papers), supplemented by snowball sampling (experts recommending peers); (2) expertise (defined as ≥3 years of experience in AI applications or medical research) in medical-related disciplines (eg, bioinformatics, epidemiology, clinical science, data science, ethics); (3) willingness to participate in and support the development of GAMER; and (4) having no severe academic

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or financial conflicts of interests. We aim for 30 to 50 participants, targeting representation across disciplines (eg, including clinicians, data scientists, and ethicists) and regions (Asia, Europe, and the Americas). The Delphi expert group's responsibilities include proposing modifications to the GAMER checklist, voting, and determining the final modifications to the full document. The fourth expert group is the coordination team, which will include 3 to 5 members. This group is responsible for coordinating the development work, communicating with experts, organizing the meetings, sending emails, and organizing materials.

Scoping Review

We conducted a scoping review to identify key reporting elements in studies involving GenAI tools in medical research. The primary research question was as follows: What are the essential elements that should be reported when using GenAI tools in medical research? We searched PubMed, Web of Science, Embase, CINAHL, PsycINFO, and the first 200 results of Google Scholar using keywords such as "generative AI," "chatbots," "ChatGPT," "large language model," and "reporting guidelines." We included existing AI-related reporting guidelines that address the use of GenAI tools in medical research. Studies were eligible if they focused on the application of GenAI tools in a medical context and provided reporting recommendations or considerations. Two reviewers independently screened titles and abstracts, followed by full-text review for eligibility. Data were extracted with a focus on reporting elements and synthesized thematically to identify common themes and recommendations. The review identified key themes, such as the need to specify the GenAI tool and version used, the purpose of its application, and verification processes, which formed the initial pool of items for the Delphi survey and informed subsequent stages of GAMER development. The scoping review was submitted for publication in November 2023 and as of June 2025 is currently under review. The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist is provided in Multimedia Appendix 1.

Stage 2: Delphi Survey

We will follow the Accurate Consensus Reporting Document (ACCORD) guidelines for the Delphi survey [15]. Once the preliminary items are completed, a survey will be disseminated through SurveyMonkey to reach consensus using a modified Delphi method [15,16]. We anticipate conducting 1 to 3 rounds, but there is no limit, and the decision on the number of rounds will depend on whether consensus is reached in the first round. Each initial item will be assigned a survey option ranging from 1 to 7 points, with 1 indicating strong disagreement, 4 indicating neutrality, and 7 indicating strong agreement. All statistics will be based on median scores. If the median score is between 1 and 3, the item will be excluded. If the score is 4 or 5 (or higher with substantial comments on the content), the item will be discussed and entered into the next round of the Delphi survey or the consensus meeting. If the score is 6 or 7 without any substantial comments, the item will be included in the final checklist. Items unresolved after 2 rounds will be discussed in the consensus meeting for final resolution. Participants can propose new items via free-text comments. New items receiving ≥50% support from the core team will enter subsequent rounds. Abstentions are allowed. Forced responses will not be used to avoid bias. Online meetings will be held after the Delphi survey to collect the experts' opinions and optimize and formulate the final checklist. All opinions and suggestions will be documented, and responses to each expert's suggestions will be provided through email. Qualitative data will undergo thematic analysis. Key themes will inform item revisions, with examples provided in supplementary materials. The initial Delphi survey included 10 items derived from the scoping review, covering aspects such as the specific GenAI tool used, the version of the tool, the sections of the manuscript where GenAI was applied, the purpose of GenAI use (eg, language editing or content generation), and whether manual verification was performed.

After the Delphi survey and virtual consensus meeting, we will refine and optimize the final items included. Once approved by the experts, we will prepare the manuscript for submission.

Stage 3: Testing and Dissemination

After the GAMER checklist is finalized, we will conduct a real-life implementation testing phase. Authors of medical research papers involving GenAI tools will be invited to apply the checklist during manuscript preparation and provide feedback via a structured questionnaire developed to assess clarity, completeness, and ease of use. Concurrently, experts from various medical disciplines will evaluate reliability and usability. For reliability, multiple experts will independently apply the checklist to a sample of GenAI-related papers, with interrater agreement measured using the κ statistic. For usability, experts will record completion time and rate item difficulty on a 7-point Likert scale. Feedback from both authors and experts will be analyzed thematically and quantitatively to identify areas for improvement, guiding revisions to the checklist's items, explanations, or examples for enhanced clarity and applicability. Public input will also be sought to ensure broader relevance. Explanatory documents and examples will accompany the final checklist.

Furthermore, we plan to invite the consensus expert group members to translate GAMER into their local languages and promote the dissemination of the checklist. Additionally, we will actively reach out to journals, inviting them to feature GAMER in authors' instructions. Finally, we aim to establish a GAMER website to regularly update users on the latest developments and research findings related to the GAMER reporting guidelines.

Timeline

The process and anticipated timeline for developing the GAMER reporting guidelines are shown in Table 1.

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Table 1. Timeline for the development of the GAMER (Generative Artificial Intelligence Tools in Medical Research) reporting guidelines.

Tasks	2023 (month)						2024 (month)												2025 (month)		
	7	8	9	10	11	12	1	2	3	4	5	6	7	8	9	10	11	12	1	2	3
Launch the project	✓																				
Registration	✓																				
Recruit members		✓	✓																		
Scoping review		✓	✓	✓	✓																
Draft the preliminary items				✓	✓																
First round of Delphi survey					✓																
Revise, discuss, and refine the checklist						✓	✓	✓													
Second round of Delphi survey									✓	✓	✓										
Online meeting											✓										
Collect feedback												✓	✓	✓							
Draft full text															✓	✓	✓				
Refine and approve full text																		✓	✓	✓	
Submission																					✓
Test																					✓
Dissemination																					✓

Ethical Considerations

This study was approved by the Ethics Committee of the Institute of Health Data Science, Lanzhou University (HDS-202406-01). All participants in the Delphi survey and testing phase provided informed consent, with the option to opt out at any time. Data collected from participants were anonymized to ensure privacy and confidentiality, with no identifiable information stored. No compensation was provided to participants. This manuscript includes no images or data that could identify individuals; thus, no consent for image use was required.

Results

The expected outcome of the GAMER project is a reporting checklist, accompanied by relevant terminology, examples, and explanations, to guide stakeholders in better reporting the use of GenAI tools. The GAMER project commenced on July 1, 2023, and concluded in July 2024. The scoping review was completed in November 2023 and submitted for publication. The Delphi process, involving 44 experts from 23 countries, was conducted from October 2023 to April 2024, yielding a 9-item checklist (Multimedia Appendix 2). The testing phase began in March 2025 and is ongoing, with authors and experts providing feedback. The final GAMER guideline is anticipated to be published in the second half of 2025, with dissemination to follow via journals and a dedicated website.

Discussion

We will follow the EQUATOR Network's recommended methodology to develop the GAMER reporting guidelines [13], inviting experts from various disciplines and with a broad geographical distribution to ensure the panel's representativeness. We hope that GAMER can guide and assist those who use GenAI tools in their research to report and apply these tools transparently and scientifically, thereby ensuring the integrity of the research. Additionally, we hope that GAMER will guide reviewers and editors in identifying and assessing manuscripts that have applied GenAI tools, ensuring that manuscripts meet journal requirements for transparent reporting.

The development of GAMER is not only a response to the current use of GAI tools in medical research but also a forward-looking initiative. As AI technologies continue to evolve, the standardization introduced by GAMER will serve as a foundation for future advancements. The checklist's scope, targeting various stakeholders, including researchers, clinicians, editors, peer reviewers, and authors, positions GAMER as a versatile tool with far-reaching implications. GAMER will guide reporting in studies using GenAI for tasks like data synthesis, manuscript drafting, and image generation. The methodology, drawing from the EQUATOR guidelines, ensures a rigorous and evidence-based approach, further solidifying the credibility of GAMER.

The outlined plan for the dissemination and promotion of GAMER demonstrates a comprehensive strategy to ensure widespread adoption of the reporting guidelines. By involving authors of medical research papers, collecting feedback, and actively engaging with journals, the GAMER project aims to integrate the checklist seamlessly into the publication process. The creation of a dedicated website further emphasizes the commitment to transparency and continuous improvement. This multifaceted approach is essential for the successful

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implementation of reporting guidelines, as it addresses both the supply side (researchers and authors) and the demand side (journals and users).

However, this study also has some limitations. First, we did not conduct a pilot test before the Delphi survey, as we considered that the items had been thoroughly discussed within the core expert panel. Second, we did not include patient and public representatives in the Delphi survey due to their limited knowledge of AI and medical topics. However, we will invite patient advocacy representatives to the advisory committee and include public feedback during the testing phase.

In conclusion, the GAMER project holds promise not only to address the immediate needs of standardizing the reporting of GenAI tool use, but also to shape the future landscape of medical research. The meticulous planning, expert involvement, and strategic approach to dissemination position GAMER as a valuable resource for researchers, practitioners, and policymakers in the dynamic realm of AI-driven health care technologies.

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Data Availability

Data are not available to share due to Department of Veterans Affairs and ethical retractions; however, annotation instructions and vocabulary are available upon request..

Authors' Contributions

XL, ZB, YC, and JE designed this protocol. XL and YC drafted the manuscript. YCT, MD, YC, and JE critically reviewed the manuscript. All authors approved the final version for submission to the journal.

YCT (thamyc@nus.edu.sg), YC (chevidence@lzu.edu.cn), and JE (Janne.Estill@unige.ch) are co-corresponding authors of this paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-ScR checklist.
[DOCX File , 87 KB - resprot_v14i1e64640_app1.docx]

Multimedia Appendix 2
Nine-item checklist for the GAMER (Generative Artificial Intelligence Tools in Medical Research) reporting guidelines.
[DOCX File , 16 KB - resprot_v14i1e64640_app2.docx]

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Abbreviations

ACCORD: Accurate Consensus Reporting Document
CONSORT: Consolidated Standards of Reporting Trials
EQUATOR: Enhancing the Quality and Transparency Of Health Research
GAMER: Generative Artificial intelligence Tools in Medical Research
GenAI: generative artificial intelligence
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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Protocol

Factors Affecting the Receptiveness of Chinese Internists and Surgeons Toward Artificial Intelligence–Driven Drug Prescription: Protocol for a Systematic Survey Study

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This is a corrected version. See correction statement: https://www.researchprotocols.org/2025/1/e83537

Abstract

Background: Recently, we developed and tested an autonomous artificial intelligence (AI) agent for prescribing a drug to prevent severe acute graft-versus-host disease in patients receiving human leukocyte antigen haplotype–mismatched hematopoietic cell transplants in a prospective clinical trial. Our experience in this proof-of-concept study suggests that physicians and patients can be receptive to autonomous AI prescription. However, the generalizability of our conclusion requires testing in additional clinical settings. Before broadening the scope of study of AI-driven drug prescriptions, it is important to quantify the factors that influence a physician's receptiveness to AI prescription.

Objective: We aim to systematically interrogate physicians' receptiveness to AI prescription in China.

Methods: We have designed a research protocol to survey a diverse range of factors that may affect physicians' receptiveness to AI prescription systems, including the physicians' personal attributes and their perceptions of the importance of various technological, institutional, and governmental attributes. The survey will be conducted in 2 phases. In phase 1, the survey will be limited to the Tianjin metropolitan area, enlisting >250 physicians from approximately 2 tier-1, 3 tier-2, and 3 tier-3 hospitals. In phase 2, we will survey metropolitan areas in ≥10 additional province-level administrative divisions, enlisting >1250 additional physicians from >15 tier-1, >15 tier-2, and >15 tier-3 hospitals. We hypothesize that physicians can be broadly classified into distinct psychological profile types, and furthermore, that these types are plausibly mediated by the locales where the physicians are employed and the physicians' demographics, educational and job experience, clinical subspecialties, and previous knowledge of and experience with AI. Clustering methods, including *t*-distributed stochastic neighbor embedding and hierarchical clustering, will be performed on respondent data to identify the distinct psychological profile types of the physicians. Multiple-variable

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regression and mediation analyses will be conducted to identify potential underlying mechanisms mediating physicians' receptiveness to AI prescription.

Results: At the time of submission of the manuscript, no subjects have been recruited. The survey study was approved by the institutional ethics committee and funded in May 2025, and we started recruiting respondents in May 2025. We plan to complete phase 1 by September 30, 2025, and phase 2 by November 30, 2025. Anonymized survey results and their analyses are expected to be published in a peer-reviewed journal in fall 2026.

Conclusions: We anticipate that data and analytical insights generated from this study will assist policy makers and AI researchers in prioritizing a data-informed sequence of developing and promoting AI prescription tools in successive regions, disciplines, and clinical use cases and inform policy makers to match resource allocation with "AI readiness."

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(JMIR Res Protoc 2025;14:e76009) doi:10.2196/76009

KEYWORDS

artificial intelligence; conditional autonomy; prescription; receptiveness; systematic survey

Introduction

Background

There is growing interest in using autonomous artificial intelligence (AI) in clinical practice [1]. However, most prospective trials of autonomous AI have investigated image-based diagnosis, radiation therapy planning, behavioral nudges, or chatbots, rather than drug prescriptions [2-16]. Previously, AI models for recommending drug prescriptions have been constructed, but they have rarely been used prospectively in clinical settings [17,18]. Recently, we developed and tested an autonomous AI agent for prescribing a drug to prevent severe acute graft-versus-host disease in patients receiving human leukocyte antigen haplotype–mismatched hematopoietic cell transplants, in a prospective clinical trial (ClinicalTrials.gov [NCT05600855]) [19,20]. Our proof-of-concept study suggested that both physicians and patients can be receptive to autonomous AI prescription in the studied setting. However, the generalizability of our conclusion requires testing in additional clinical settings. We submit that, before broadening the scope of studying autonomous AI in drug prescription, it is important to systematically canvass and quantify potential factors that might influence a physician's receptiveness to using autonomous AI in drug prescription.

Objectives

We hypothesize that physicians can be broadly classified into distinct psychological profile types and that these psychological profile types are at least partially mediated by the locales where the physicians are employed and the physicians' demographics, educational and job experience, clinical subspecialty, and previous knowledge of and experience with AI. Here, we report a survey protocol that we have designed to systematically interrogate physicians' receptiveness to AI prescription in China.

Methods

Ethical Considerations

The proposed survey study has been approved by the ethics committee (QTJC2025047-EC-1) at the Institute of Hematology, Chinese Academy of Medical Sciences (IHCAMS) on May 15, 2025. Only respondents who provide informed consent with e-signatures will be granted access to the survey website. All entered data will be stored in password-protected secure servers. All data will be anonymized before analyses, and no write-up of survey results resulting from this study will contain information that can be used to identify any respondent. No incentives—either monetary or nonmonetary—will be offered to participants taking part in the survey.

Questionnaire Design

Lists of covariates that may affect physicians' acceptance of medical AI, including physicians' personal attributes and perceptions of the importance of self-autonomy, multiple technology attributes, institutional attributes, and governmental attributes, have been compiled in the literature [21-24]. Social influence, perceived ease of use, computer anxiety, and other factors may also play important roles [25-27].

Building on the foundation of previous work related to technology acceptance, we have designed a questionnaire (Multimedia Appendix 1 [English translation] and Multimedia Appendix 2 [original Chinese version]) to interrogate physicians' receptiveness to AI prescription, encompassing 4 dimensions of covariates (Table 1).

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Table 1. Surveyed covariates[a].

Dimensions and covariates	Questions
Personal attributes	
Demographics	Q1. Birth year
	Q2. Sex
	Q3. Highest educational degree
	Q4. Clinical practicing experience
	Q5. Current rank in the professional ladder
	Q6. Clinical specialty
Knowledge of AI[b]	Q7. I am knowledgeable in AI technology in general.
	Q8. I am knowledgeable in medical AI technology.
	Q9. I am experienced with using AI in work and daily life.
	Q10. I am experienced with using medical AI in my clinical practice.
Perception of AI	Q11. I believe AI will eventually transform the health care industry.
	Q12. I believe AI will eventually augment physicians' capabilities.
	Q13. I believe AI will eventually improve health care quality.
	Q14. I believe AI will eventually improve health care equity.
	Q15. I believe medical AI will eventually facilitate physician training.
	Q16. Which is more important to me: AI efficacy versus my autonomy?
Perception of AI prescription	Q17. I believe AI prescription might be useful in ____ situations.
Perceived importance of technological attributes	
Vetted efficacy	Q18. I think an AI prescription model's efficacy needs to be vetted in _____ manners.
Expediency	Q19. I think an "expedient" AI prescription model needs to have _____ properties.
Transparency	Q20. I think technical details regarding how an AI prescription model was built and validated need to be transparent before I start using the model in my own clinical practice.
Explainability	Q21. I think an "explainable" AI prescription model needs to have _____ properties.
Governance and stewardship	Q22. I think ____ aspects of governance and stewardship are the most important for successful adoption of an AI prescription model in my own clinical practice.
Trade-offs	Q23. Rank the perceived importance of these technological attributes: (1) vetted efficacy, (2) expediency, (3) transparency, (4) explainability, and (5) governance and stewardship.
Perceived importance of institutional attributes	
Culture	Q24. I think ___ aspects of institutional culture will be the most crucial for successful adoption of AI prescription.
Change management	Q25. I think ___ aspects of change management will be the most crucial for successful adoption of AI prescription at my institution.
IT and data science	Q26. I think ___ aspects of information technology and data science resource availability and access will be the most crucial for successful adoption of AI prescription in my clinical practice.
Differentiation	Q27. I think my institution will need to improve ____ to maintain or further its edge compared to other medical institutions after adoption of AI prescription systems.
Perceived importance of governmental attributes	
Nation-wide commitment	Q28. I think ____ aspects of governmental policy will be the most crucial for successful adoption of AI prescription in my clinical practice.
AI standards	Q29. I think ____ should set the standards for AI prescription systems.

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Dimensions and covariates	Questions
Remuneration policy	Q30. I think ___ should be remunerated when an AI model is used to prescribe a drug.
To sum up	
__[c]	Q31. I anticipate ≥1 physician (possibly, including myself) at my hospital will become ready to use AI to prescribe a drug within _____ years. Q32. I anticipate I myself will become ready to use AI to prescribe a drug within _____ years.

[a]The abbreviated version of the list of surveyed covariates is displayed here. The full questionnaire that will be used for conducting the survey is provided in Multimedia Appendices 1 and 2.

[b]AI: artificial intelligence.

[c]Not applicable.

The survey questions are structured under each of the 4 dimensions. The first dimension includes the physician's personal attributes, including demographic information (eg, age, sex, education level, clinical practicing experience, seniority, and clinical subspecialty); self-assessed level of confidence in making informed judgments regarding AI technologies; self-assessed level of experience with using AI in work and daily life; self-assessed probability of the success of using medical AI to induce beneficial transformation of the health care industry, augment physicians' patient care capability, improve equity in health care, and facilitate physicians' training; and the physician's attitude toward the trade-off between AI model efficacy and the sanctity of the physician's own autonomy.

The second dimension includes the physician's perceived importance of various aspects or attributes of AI technology, including how an AI prescription model's clinical efficacy should be vetted and which organizations are endorsing the AI model; how the AI model might impact clinical workflows, workload, throughput, cost-effectiveness, risk of making errors, and physician-patient relationship; whether the AI model's technical details are transparent and readily accessible to the physician; whether the physician fully understands and agrees with the model's input variables, input-output relationship (ie, the underlying algorithm), the reasoning or justification behind the model's drug prescription, and how easy it is for the physician to explain the model's mechanistic details to their colleagues and patients; and how stewardship of the AI prescription model would be administered after the model's initial deployment in clinical settings, particularly, regarding model upgrades, safety monitoring, and data privacy and security.

The third dimension includes the physician's perceived importance of various institutional attributes, including workplace culture (eg, whether the institution encourages introduction of new technology and values innovation, interpersonal relationship, team collaboration, transparent communication, talent development, result orientation, and agility); mechanisms for catalyzing changes in the organization (eg, an enlightened leadership team, a dedicated team of local champions "owning" the implementation of new AI technologies, a collaborative and transparent modus operandi of implementing new technologies within the organization, or an on-boarding plan for educating and training staff members to leverage new technologies); in-house IT expertise; access to third-party IT expertise; and how the institution should or could differentiate itself from other medical institutions once new AI technologies are introduced.

The fourth dimension includes the physician's perceived importance of various governmental attributes, such as governmental policies to encourage exploration of new use cases for AI in clinical medicine, governmental efforts to improve technological infrastructure for medical AI, governmental commitment to investment in educational programs cultivating new talents specializing in medical AI, publicization and institution of governmental standards for use of AI for drug prescription, and reimbursement policies for using an AI prescription model.

At the end of the survey, we will ask the respondents to answer 2 forced-choice questions (Q31 and Q32), as presented in Textbox 1.

The questionnaire has been tested internally on 20 physicians at the IHCAMS and modified and improved based on their feedback.

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Textbox 1. Forced-choice questions in the survey questionnaire.

I anticipate ≥1 physician (possibly, including myself) at my hospital will become ready to use AI to prescribe a drug within _____ years.

- ≤1
- 1.1 to 3
- 3.1 to 5
- 5.1 to 10
- >10
- Never

I anticipate I myself will become ready to use AI to prescribe a drug within _____ years.

- ≤1
- 1.1 to 3
- 3.1 to 5
- 5.1 to 10
- >10
- Never

Stratified Sampling of Metropolitan Areas, Hospitals, and Physicians

To ensure that survey takers will be a balanced representation of the physician population in China, the survey will not be open or based on a convenience sample. Rather, we will conduct a stratified sampling of Chinese physicians.

Setting type-I error α=.025 and type-II error β=.1 (without correction for multiple-hypotheses testing), to achieve 90% power to observe the squared correlation coefficient ρ^2>0.1 between independent covariates (with up to 120 df) and the 2 dependent covariates (Q31 or Q32) while the true value of ρ^2 is 0.16, we estimated that ≥1515 physicians will need to participate in the survey.

We plan to conduct the survey in a diverse set of metropolitan areas in >10 of the 31 province-level administrative divisions of the Chinese mainland, with diversity defined in terms of per capita gross domestic product and geography (Figure 1). For each sampled metropolitan area, we will conduct the survey in representative tier-1 (*yiji*; lowest level), tier-2 (*erji*), and tier-3 (*sanji*; highest level) hospitals (a tier-1 hospital in the Chinese mainland is equivalent to a community clinical service center in the United States, while a tier-2 hospital is a midsized hospital and a tier-3 hospital is a larger-sized hospital or an academic medical center). Hospitals with higher patient volumes will be preferentially selected.

For each selected hospital, we will sample a diverse subset of internists and surgeons. Physicians invited to participate in the survey will represent the full range of clinical subspecialties within internal medicine or surgery and the 3 successive seniority ranks, including “chief physician” (*zhuren yishi*), “associate chief physician” (*fuzhuren yishi*), and “junior attending physician” (*zhuzhi yishi*).

The survey will be administered in 2 phases.

In phase 1, the survey will be limited to Tianjin, a municipal administrative area adjacent to Beijing with 13.6 million residents [28] and under direct administration of the central government of the People’s Republic of China. We anticipate surveying approximately 2 tier-1, 3 tier-2, and 3 tier-3 hospitals, enlisting >250 physicians. This pilot study will allow us to fine-tune the logistics and survey administration before rolling out the survey to additional metropolitan areas. We do not anticipate modifying the questionnaire based on experience in phase 1.

In phase 2 of the study, we will survey metropolitan areas in ≥10 additional province-level administrative divisions, with a balanced representation of the Pacific coast (which is economically better developed) and less developed regions, and collect returned questionnaires from >1250 physicians from ≥15 tier-1, ≥15 tier-2, and ≥15 tier-3 hospitals.

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Figure 1. Stratified sampling of metropolitan areas, hospitals, and physicians.

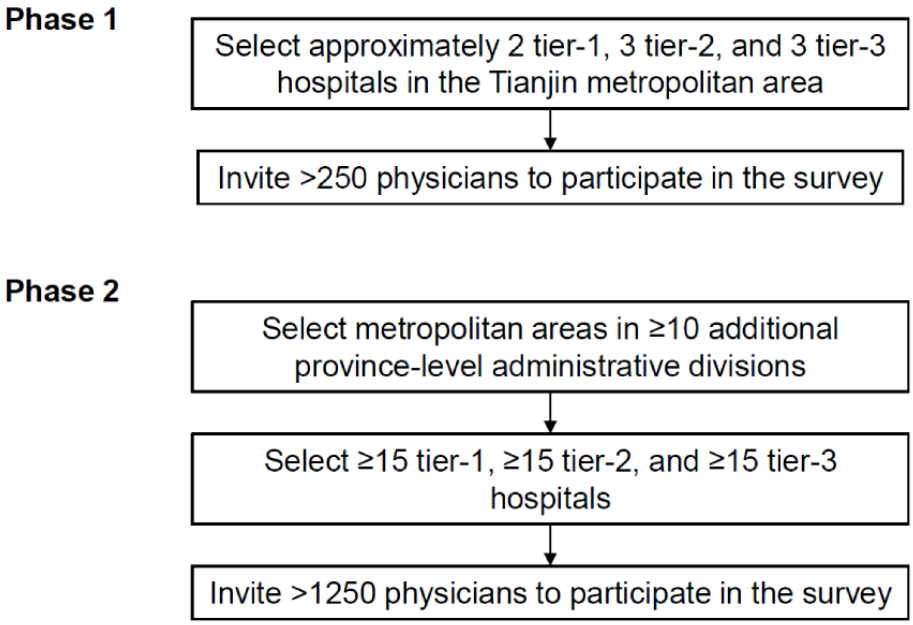

Contact Mode and Privacy Protection

For each sampled hospital, the research team will request the hospital administration to assist in the sampling of their internists and surgeons and to make initial contact with the potential participants on behalf of the research team. The hospital administration will be instructed to ensure that the physicians invited to participate in the survey are a balanced representation of the range of clinical subspecialties and the 3 successive seniority ranks. Participation will be entirely voluntary (the Chinese Academy of Medical Sciences will have no authority over promotion, bonus decisions, or any other aspect of personnel evaluation at any of the sampled hospitals). No incentives—either monetary or nonmonetary—will be offered to the physicians agreeing to participate in the survey.

Once the administration of the sampled hospital identifies a date or dates for survey taking, the research team will dispatch representatives to be physically present at survey-taking sessions to serve as moderators, whose primary goal will be to ensure that there will be no technical errors or misunderstanding of the survey questions. Therefore, the respondents will not be anonymous, in the sense that the hospital administration will know who will attend the survey-taking sessions and that the moderators will see the respondents in person, unlike in most e-surveys wherein the identity of respondents is unknown to the researchers. Nevertheless, the identity of the respondents will be strictly protected in this study. Only anonymized data that cannot be used to identify the respondents will be used for data analyses. Furthermore, when the survey results are disseminated, the respondents will remain anonymous in accordance with the directive of the IHCAMS Ethics Committee.

Informed Consent and Survey Administration

Each separate survey-taking session will have a separate survey website hosted on Alibaba Cloud secure servers. Each separate survey website will have its own preset live period and expiration time. All survey-taking sessions will use an identical user interface, which was developed by the authors.

Respondents in a survey-taking session will first scan a QR code with their personal smartphones to access the survey website. Once connected, the respondents will be prompted to enter their mobile phone number. The message “I understand the purpose of this survey and agree to participate” will be displayed on the phone screen. Concurrently, individualized verification codes will be sent to the respondents via SMS text messages, and to confirm their consent to participate in the survey, respondents will reply with the code (Figure 2). Each phone number can be used only once for participating in the survey. Because “burner” devices are uncommon in the Chinese mainland, the verified phone number will serve as the e-signature for each respondent. The verified phone numbers are protected and will not be used for future communications with the respondents. In other words, the researchers will not call any of the respondents during the follow-up analyses. All entered data, including phone numbers and answers to survey questions, will be stored in password-protected secure Alibaba Cloud servers, and data access will be limited to 4 of the coauthors.

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Figure 2. Procedure for participating in the survey.

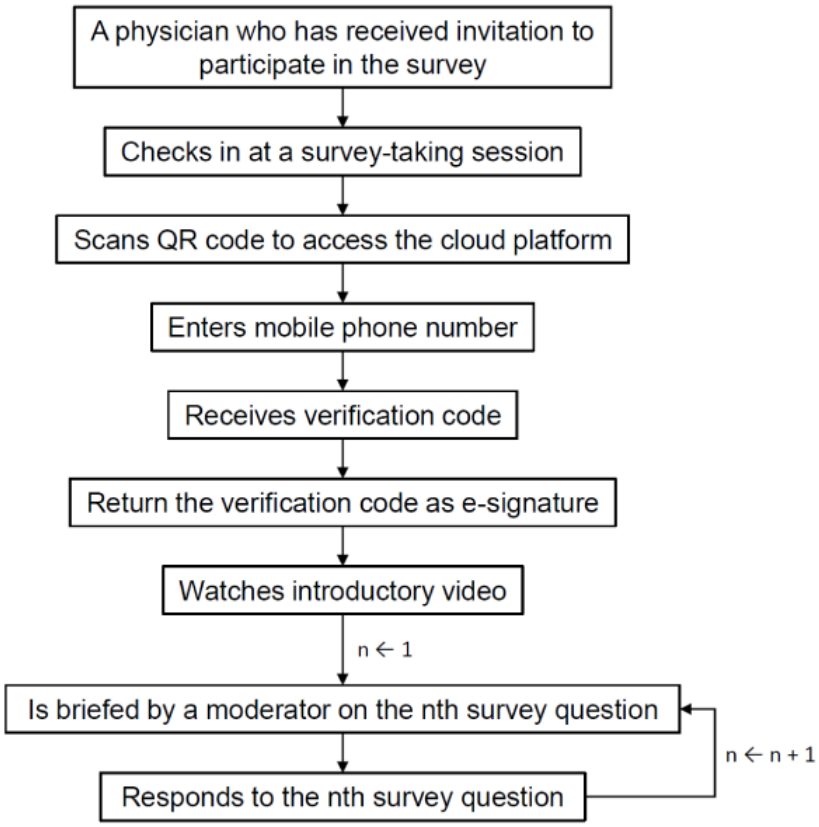

After providing their informed consent, respondents first watch a 50-second-long video (Figure 3 [screenshot] and Multimedia Appendix 3 [original video with English captions]) to be reminded of the purpose of the survey, with the following script:

> *As artificial intelligence (AI) technology progresses, more tasks are executed or assisted by AI. For example, drafting of a press release, automated parking, image-based diagnosis, and surgical robots. According to the 15th Five-Year Plan, China will focus on AI+ for national development, in particular, exploring new use cases for AI. This survey aims to understand physicians' attitudes towards AI prescription. "AI prescription" entails the following steps: First, AI considers multiple factors of a patient; then, AI prescribes medication based on a pretrained model. If the physician thinks the AI prescription is safe, reasonable, and economical, then the AI prescription is automatically executed. AI prescription might not be without risk, but it might also unleash new productivity gains. Your inputs are highly valued.*

The 15th Five-Year Plan is a national economic development plan of the People's Republic of China for 2026-2030 that will emphasize AI and is known to most Chinese residents, including physicians. As of the time of writing this paper, the 15th Five-Year Plan has not spelled out a detailed road map for using AI in clinical practice, and the phrase "AI prescription" is not mentioned in official statements.

Afterward, respondents will proceed to take the survey (Figure 1). Each page will display only one question. Moderators will be present to explain the intent of a survey question if the respondents request clarification. Items in multiple-choice questions will not be randomized, and we will not scramble the order of the questions for different respondents because many questions are Likert-scale questions, and there is a natural progression of the themes asked by the questions. Survey questions will not be "adaptive," and each respondent will be expected to answer all the survey questions. Proper answering of forced-choice rank-order questions will be enforced by the survey website (eg, if a respondent chooses more than 3 items when they cannot select more than 3, they will not be able to submit their answer). The respondent's answers to survey questions are stored sequentially and cumulatively, and if they accidentally exit the survey before completing it, they can reenter the survey using their mobile phone number (with SMS code verification), and their previous data entries will be automatically restored. The respondent cannot click "Final submission" unless they answer all the survey questions. The respondent will be able to switch between questions and modify their answers as long as they have not clicked "Final submission." However, once "Final submission" has been clicked, the respondent cannot reenter the survey to modify their answers.

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Figure 3. Screenshot of the introductory video. The title is "Purpose of this study: to understand physicians' attitudes toward AI prescription". The text on the left translates (from top to bottom) to "AI evaluates a patient based on multimodal data"; "AI prescribes a drug or drugs"; "The physician does not veto after reviewing"; and "The prescription is executed by default". The text on the right translates (from bottom to top) to "Generating a prescription"; "Safe? Reasonable? Economical?" AI: artificial intelligence.

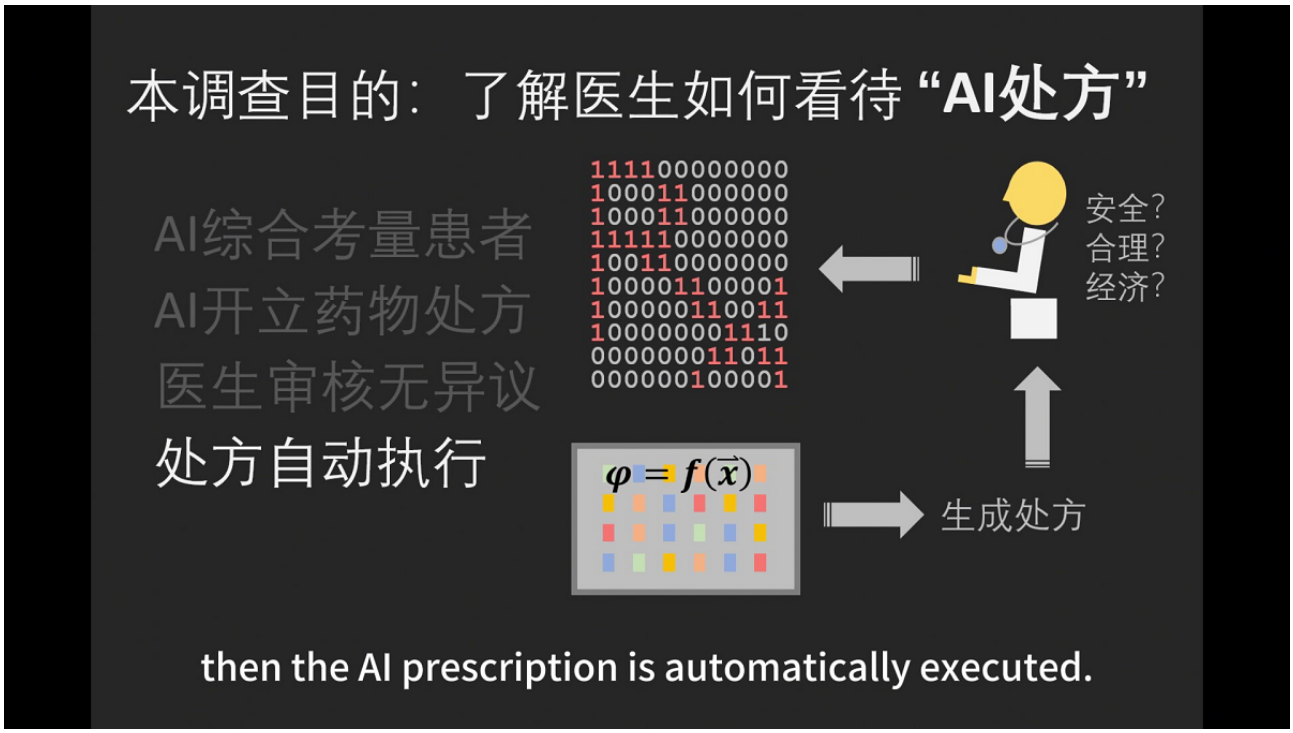

Analyses

Each unique respondent will be distinguishable by their unique mobile phone number. The completion rate will be quantified by the number of people who click "Final submission," divided by the number of people who provide informed consent. Questionnaires filled out in too short a time will be treated as bad responses and excluded from further analyses. Bad response rates will be reported. A balanced representation of hospitals in different tiers and physicians with different specialties and levels of experience will be confirmed by inspection of respondent statistics.

Answers to all survey questions will be converted to numerical values before analyses. Responses to Likert-scale questions will be converted from 5 (highly agree) to 1 (highly disagree). Responses to forced-choice rank-order questions will be coded in two ways: (1) a respondent's first-, second-, and third-choice items will be coded 3, 2, and 1, respectively (if the question asks the respondent to select their ≤3 top choices), and unselected items will be coded 0; (2) alternatively, all the selected items of a respondent will be coded 1 regardless of their rank orders, while all the unselected items will be coded 0.

One of our main hypotheses is that physicians can be broadly classified into distinct psychological profile types characterized by distinct patterns of their answers to Q11 to Q32, and clustering methods, including *t*-distributed stochastic neighbor embedding and hierarchical clustering, will be used to uncover the psychological profile types. We anticipate that distinct types of physicians will have different criteria for evaluating an AI model (eg, one type of physicians may think they need to be able to explain to their patients the inner workings of an AI prescription model before they are willing to adopt it in their clinical practice) and different clinical needs (eg, one type of physicians might particularly welcome the use of AI prescription to expedite outpatient care of persons with chronic diseases who require periodic prescription refills, while another type might think that AI prescription models are the most useful for early intervention of adverse events in complex situations, such as hematopoietic cell transplantation), and—most importantly—different psychological profile types of physicians may have different levels of receptiveness to AI prescription. Geospatial analysis will be performed to map the composition and variance of psychological profile types across the metropolitan areas and provinces.

Our second main hypothesis is that physicians' psychological profile types are at least partially mediated by the locales where they are employed and their demographics, educational and job experience, clinical subspecialty, and previous knowledge of and experience with AI, characterized by their answers to Q1 to Q10. Multiple-variable regression and mediation analyses will be conducted to infer the potential mechanisms underlying the formation of distinct psychological profile types. For example, suppose we learn that clinical subspecialty X and geographic region Y are strong mediators of high receptiveness to AI prescription; then, we could be confident in prioritizing the development of AI prescription tools serving subspecialty X in geographic region Y.

Robustness of analytical results will be assessed via bootstrapping (ie, sampling with replacement).

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Dissemination Plan

Anonymized survey results and their analyses will be published in a peer-reviewed journal. Separate analytical reports that continue to uphold respondent privacy but will focus on subsets of hospitals in subsets of regions may also be produced and disseminated to select hospital administrations for more targeted, locally focused considerations. Respondent identity will not be disclosed in any—published or unpublished—report.

Results

We plan to complete phase 1 of the survey by September 30, 2025, and phase 2 by November 30, 2025. Analyses of the survey results will be completed by January 31, 2026.

Discussion

Anticipated Findings

We anticipate that our survey will reveal that a sizable portion of physicians in China are receptive to AI prescription and, furthermore, that in-depth analyses will shed light on potential mechanisms underlying their AI optimism. This knowledge, in turn, can inform us how to "nudge" physicians that are less receptive to AI prescription to become more receptive. Lessons learned from the resultant "map" of Chinese physicians' minds or psychological profile types will be a useful addition to the medical AI literature.

However, we caution that the lessons learned from our China-focused study might not extrapolate to physicians in other countries. Many people in BRICS (Brazil, Russia, India, China, and South Africa) countries (representing approximately a quarter of the world economy) are considerably more receptive to medical AI and more willing to trust in medical AI systems compared with people in other countries, such as France, Germany, Japan, the United Kingdom, and the United States [29]. Because there is wide variance in receptiveness to medical AI across different countries, it will be imperative to interpret the results of our China-focused survey from a global perspective.

The data collected in the proposed survey study will allow us to construct high-granularity profiles of respondents' psychology with respect to receptiveness to AI prescription. For example, one plausible outcome might be that physicians are broadly classified into 2 psychological profile types, optimists and pessimists, with the former more receptive to the use of AI prescription in their clinical practice while the latter more resistant to the adoption of AI prescription. Physicians with different profile types might have different criteria for evaluating the acceptability of an AI agent. For example, one profile type might value clinical efficacy, while the other profile type might emphasize the sanctity of their own autonomy or job security. Different profile types might also have different expectations for their employers' role in promoting AI prescription. For example, one profile type might think it is of utmost importance that the hospital invests heavily in AI infrastructure while the other profile type might believe it is more important that the hospital administers a staff training program for AI use.

We also anticipate using the survey data to identify the key mediators that underlie the variance in physicians' receptiveness to AI prescription. For example, survey data may reveal that physicians who already have on-the-job experience with medical AI have less AI anxiety and higher receptiveness to AI prescription. Alternatively, it is also plausible that it is the locale where the physician is employed (eg, a tier-3 hospital in an economically developed urban area vs a tier-1 hospital in a less developed region) that predominantly determines their receptiveness. We also anticipate learning that some mediators of receptiveness to AI prescription are more modifiable than others. For example, suppose survey data indicate that previous knowledge of AI is a very strong mediator of receptiveness; then, we can potentially shift the distribution of psychological profile types of physicians toward higher receptiveness by investing in graduate-level and postgraduate educational and training programs that will familiarize more medical students and physicians with AI and the science behind it. Identification of these enablers and blockers for technology adoption will be instructive for prioritizing a data-informed sequence of developing and promoting AI prescription tools in successive regions, disciplines, and clinical use cases, and inform policy makers to match resource allocation with AI readiness.

Future Directions

We anticipate that future directions after the conclusion of the survey study will encompass 2 important parallel paths. First, it will be imperative to incorporate AI and additional novel informatics tools in clinical practice to further reduce human errors and improve patient care whenever and wherever there is AI readiness [30,31]. Second, we will champion a research program focusing on when it is appropriate and beneficial to "nudge" physicians toward higher AI readiness in treatment decision-making [32,33].

Acknowledgments

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Data Availability

Anonymized survey data will be made available to other researchers upon request in accordance with the People's Republic of China regulations on data privacy and security.

Authors' Contributions

JC is the corresponding author. JC conceived the study. JC and JW co-led the study and are co-senior authors. JC, QS, XG, WZ, and YH designed the questionnaire, the accompanying introductory video, and the cloud platform for delivering the survey. ZR and SL assisted in questionnaire preparation. JW, JC, XG, YM, and ZS designed the strategy for sampling physicians to participate in the survey. JC, QS, XG, WZ, and YH generated the tables and figures. JC prepared the manuscript with contributions from RPG. All the authors reviewed the manuscript, agreed to submit it for publication, and take responsibility for the content.

Conflicts of Interest

RPG is a consultant to Antengene Biotech LLC; a consultant to Shenzhen TargetRx, Inc; medical director at FFF Enterprises, Inc; a speaker for Janssen Pharma, BeiGene, and Hengrui Pharma; a member of the board of directors at the Russian Foundation for Cancer Research Support; and a member of the scientific advisory board at StemRad Ltd. All other authors declare no conflicts of interest.

Multimedia Appendix 1
Questionnaire (English translation).
[DOCX File , 42 KB - resprot_v14i1e76009_app1.docx]

Multimedia Appendix 2
Questionnaire (original Chinese version).
[DOCX File , 46 KB - resprot_v14i1e76009_app2.docx]

Multimedia Appendix 3
Introductory video.
[MP4 File (MP4 Video), 9446 KB - resprot_v14i1e76009_app3.mp4]

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Abbreviations

AI: artificial intelligence
BRICS: Brazil, Russia, India, China, and South Africa
IHCAMS: Institute of Hematology, Chinese Academy of Medical Sciences

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Protocol

Fermented Food Consumption Across European Regions: Protocol for the Development and Validation of the Web-Based Fermented Foods Frequency Questionnaire (3FQ)

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Abstract

Background: Fermented foods vary significantly by food substrate and regional consumption patterns. Although they are consumed worldwide, their intake and potential health benefits remain understudied. Europe, in particular, lacks specific consumption recommendations for most fermented foods.

Objective: This project, which is under the framework of the Promoting Innovation Of Fermented Foods (PIMENTO) Cooperation in Science and Technology (COST) Action (CA20128), aims to develop a validated tool to quantitatively estimate fermented food intake across 4 European regions.

Methods: The Fermented Food Frequency Questionnaire (3FQ) was designed to quantify fermented food intake in terms of frequency and quantity. Fermented foods were categorized into broad groups (eg, dairy, plant-based, meat, beverages) based on product classifications, ensuring that the foods included were genuinely fermented through ingredient analysis according to the International Scientific Association for Probiotics and Prebiotics consensus for fermented foods as a guide. For each main fermented food group, subcategories were determined after detailed discussions by a scientific expert panel that provided country-specific examples. For example, for hard cheeses, Parmigiano was chosen in the Italian version, and Graviera in the Greek version. The questionnaire was developed in English (universal version) and then translated into multiple languages using the back-translation method. Each version was pilot-tested for clarity, and data for the prospective validation were gathered. This included two key steps: (1) assessing repeatability by having participants retake the questionnaire after 6 weeks and (2) confirming accuracy by comparing 3FQ results against 24-hour dietary recalls from a subsample of participants. Statistical analyses will be used to confirm agreement between the methods. Representative sample calculations were performed for 4 groups by biological sex and age group (between 18 and 49.9 years and 50+ years). To ensure representative sample obtainment, participants aged

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18+ years were recruited via the internet using multiple strategies, including social media platforms in all countries, snowball sampling, and potential supplementation with panels provided by the survey platform. Prior to all responses, participants were asked to provide informed consent and agree to data collection under ethical guidelines using a General Data Protection Regulation–compliant platform.

Results: A representative sample of 1536 participants per European region was targeted, ensuring diversity in age and sex, with the goal of achieving a 60% response rate. A multilingual questionnaire was developed and pilot-tested for clarity. The upcoming steps will include final validation for accuracy and repeatability using 24-hour dietary recalls and specific statistical techniques of analysis to ensure reliability.

Conclusions: The validated web-based 3FQ aims to address the current gaps in fermented food intake to help improve future research in this important area.

International Registered Report Identifier (IRRID): DERR1-10.2196/69212

(JMIR Res Protoc 2025;14:e69212) doi:10.2196/69212

KEYWORDS

fermented foods; consumption data; intake; human health; European regions

Introduction

The fermentation process involves the action of microorganisms indigenously present in the food (raw) material or added as starter cultures under adequate environmental conditions [1]. In the past few years, the potential health benefits of fermented foods, microorganisms contributing to the fermentation process, and the resulting fermentation metabolites, vitamins, and bioactive compounds have raised great interest [2,3] due to their potential for improving human health [4,5] in children and adults [6]. Nevertheless, assessing the potential health benefits of fermented foods remains a challenge since over 5000 fermented foods and beverages are produced globally [7], and many remain understudied. Moreover, there are no specific recommendations for their consumption in Europe [8] since specific consumption data are limited and addressed mainly in overall dietary assessments.

It is important to consider the variety of substrates, products, and microorganisms involved to understand the diversity of fermented foods and beverages [9]. For instance, although the same substrate, milk, can be the basis for most of the available fermented dairy products (eg, yogurt, kefir, and cheese) [10], the final products differ considerably in terms of nutritional composition and bioactive compounds. Additionally, the fermentation process may involve the action of one or more microorganisms that are either indigenously present in the raw material, added as starter cultures, or introduced via back-slopping and grown under appropriate environmental conditions that may or may not be alive at the time of consumption [1,11]. Moreover, the microorganisms used for fermentation are associated with different metabolic pathways and reactions involved in the process, leading to various physicochemical transformations in the final products. For example, different groups of microbes may produce different end products (metabolites), including organic acids (eg, lactic, acetic acid) through various metabolic pathways under different conditions [12]. Additionally, while some microorganisms are known for their capacity to synthesize specific vitamins (folate, riboflavin, and cobalamin) from various precursors in plant and dairy foods [13], others do not influence or even consume vitamins [14]. Furthermore, various fermented foods have been reported to contain a series of bioactive peptides derived through the action of proteases synthesized by fermenting microorganisms [8]. Consequently, it is not surprising that fermentation from a nutritional perspective is also associated with the reduction of antinutritional factors and an improvement in the overall nutritional value and digestibility of fermented foods [15].

Despite their potential health benefits, fermented foods are generally not recommended as a category in dietary guidelines; in fact, there are no specific recommendations for their consumption in Europe [8,13]. A challenging factor is the fact that the type of fermented food consumed varies by region and country [8]. Differentiation by main food substrate is necessary to understand and assess the potential health benefits of fermented foods and acquire ample information to make specific recommendations. As aforementioned, these food substrates may vary significantly regarding nutritional composition and products formed during fermentation; therefore, population-based consumption data are necessary to understand their role in human health.

To date, there remain limited quantification methods specifically developed for assessing fermented food intake in populations. A recent study identified and estimated fermented foods consumed in Japan using dietary recalls by season and found 1396 unique fermented foods consumed [16]. In the Dutch observational cohort (NQplus) that used a food frequency questionnaire (FFQ), an estimated 17% of foods consumed were fermented, and another 13% were included in composite dishes [17]. The validation results showed that FFQs could effectively estimate foods and beverages that are regularly consumed, such as coffee, bread, and cheese, since the mean difference between recalls and the FFQ was small. However, this was not the case for fermented foods consumed more sporadically [17]. Both studies support the hypothesis of the variety of fermented foods available, regardless of the food substrate, and highlight the importance of developing a tool to assess the intake of these food substrates and their main byproducts. This represents a crucial first step toward understanding their effects on human health.

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In this context, another recent study evaluated food intake biomarkers for various fermented foods to discriminate the dietary patterns of fermented foods [18]. Although this is of great value, many biomarkers could be affected by human metabolic rates (concentration biomarkers) and therefore do not accurately reflect absolute food intake. Therefore, estimating frequency and quantifying fermented food intake using validated dietary assessment methods remains necessary [19], along with developing tools that minimize their potential limitations [20].

One of the main limitations is accurate quantification, which can be addressed using validated color food atlas pictures, where each icon refers to a specific portion size (by weight), allowing the individual to select their usual portion from a series of pictures rather than relying on subjective quantity estimates [15]. This process [21], combined with using food models or selected house measures when no valid food picture is available, has been found to increase intake accuracy [22]. Nevertheless, because fermented foods represent a specific type of food intake, a tool that explicitly evaluates their consumption—providing specific examples by substrate and potential subcategories—can help overcome the limited information reported for these foods. Assessing intake in a representative population may help validate types of biomarkers for further research on fermented foods and health.

The primary aim of this questionnaire is to collect and analyze data on fermented food consumption, using predefined food groups and their substrates, in the 4 main European regions, as defined by EuroVoc [23]. The project is carried out as part of the Promoting Innovation of Fermented Foods (PIMENTO) Cooperation in Science and Technology (COST) Action (CA20128) [24], with the aim of creating a universally validated tool for recording the intake of fermented foods among European consumers.

Methods

Ethical Considerations

This research protocol was approved by the Ethics Committee of the Agricultural University of Athens (27/05.05.2023). The study process abides by the ethical principles for research involving humans, as reported by the Declaration of Helsinki [25].

Identification and Classification of Fermented Foods

Identifying and classifying fermented foods can be challenging because there are multiple definitions and perceptions of what constitutes a fermented food. To address this, in 2019, an expert panel by the International Scientific Association for Probiotics and Prebiotics defined fermented foods as “foods made through desired microbial growth and enzymatic conversions of foods” [23]. This definition encompasses a wide range of products that may or may not contain live microorganisms and is the basis of the definition used for this questionnaire.

Considering the wide variety of fermented foods available in the marketplace and consumed by different European populations, fermented foods were first stratified in the Fermented Food Frequency Questionnaire (3FQ) into broad food groups: plant-based products, dairy products, legumes, meat and/or fish, vegetables, cereal products, chocolate, nonalcoholic beverages, vinegar, coffee, tea, chocolate beverages, beer and/or cider, wine, and spirits. These food groups were defined a priori, based on the classification of product categories used for mapping fermented foods within the activities of Working Group 2 from the PIMENTO CA20128.

Fermented foods within each food group were then aggregated into subgroups. A series of exclusion criteria was also applied to ensure that the studied foods were indeed fermented. Foods that were traditionally fermented but are no longer fermented because of contemporary food processing (such as pickled vegetables) or foods that were partially fermented (such as green or black teas that are typically oxidized rather than post fermented) were included or eliminated based on the ingredient lists of commonly consumed grocery store products. With the exception of chocolate and some plant-based alternatives, partially fermented foods (ie, salad dressings) and composite dishes (ie, chocolate-based confectionery) were not considered. For example, sauerkraut is made from cabbage, water, and salt and its sour taste and preservation are achieved through lactic acid fermentation by live bacteria, which aligns with this study's definition of a fermented food, whereas pickled gherkins made from cucumbers, water, vinegar, salt, and sugar get their sourness and acidity directly by the added vinegar, not by microbial activity. Therefore, this product was excluded as it is pickled but not fermented.

Study Sample

The study aimed to include a representative sample for each of the 4 European regions. A predefined sampling frame was formulated, and the World Health Organization STEPwise procedure was followed. The minimum sample size required for each European region was calculated to achieve 80% study power at a 95% confidence level. A response rate of 60%, as reported by many epidemiological studies, was accounted for, along with a potential 10% attrition rate. The goal was to achieve a representative sample for 4 groups: males and females, young adults (between 18 and 50 years), and older adults (≥50 years of age). Based on a 5% margin of error and a conservative approach of 50% for the indicators to be assessed, a total sample of 1536 from each European region was required (for 4 groups). This translated to a target of 2560 contacts, based on the 60% anticipated response rate. The representativeness by group was monitored (quota monitoring) throughout the study process based on European Region population distribution response rates. In situations where representativity for certain quotas (region, age group, sex) was not achieved, the web-based platform selected provided the option to use predefined panels from specified areas and required characteristics. Specifically, the platform could be used to target sampling from predefined panels in underrepresented areas and specific age groups. The predefined panels could also be used to rectify imbalances in the sex distribution, as evaluated during the development of the sampling frame and assessment of representatives for each European region. Responses obtained through this method were integrated with the originally collected data, ensuring a cohesive and representative final data set that aligns with our study aims. However, sensitivity analyses will be conducted (with and

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without the extra data from the panels) to evaluate potential response differences that can also impact the results. Initially, a comprehensive comparison of the essential demographic, socioeconomic, and lifestyle attributes of participants recruited from the internet versus those from predetermined panels will be performed to assess whether there are substantial variations in parameters that could affect the primary outcomes—documented consumption patterns of fermented foods—between the 2 groups. A primary analysis using the complete, integrated data set will be performed, followed by a secondary analysis using exclusively the nonpanel sample. The 2 results will be compared to ascertain whether the incorporation of panel data significantly modifies the study's conclusions. The outcomes of these sensitivity studies will be fully disclosed in the publication.

Inclusion/Exclusion Criteria

Individuals were considered eligible for participation in the study when they were above 18 years of age at the time of recruitment and agreed to sign the informed consent form. The survey was conducted over the internet, and the questionnaire was hosted on the Conjointly platform. Participants were recruited through the use of many channels: (1) the PIMENTO website [26]; (2) social media (ie, LinkedIn, Facebook, X, Instagram); (3) emailing past survey participants for whom we have contact information; (4) through information from notified sites and nonprofit organizations; and (5) through snowball sampling where respondents were encouraged to forward the invitation to any interested parties.

Conjointly is a web-based research platform used in this study to recruit participants and administer the 3FQ. It is General Data Protection Regulation (GDPR) accredited and offers an option not to maintain IP addresses, thereby increasing the study's confidentiality. It was chosen since it provides researchers with integrated tools to build and customize surveys using a wide range of question formats, from simple scales to complex experimental designs. It also generates QR codes automatically and is accessible through smartphones (iOS and Android). The platform codes responses automatically as uploaded, and it provides the total database coded and with summary statistics for rapid data evaluation during the recruitment phase and sample data collection, reducing selection bias. It also supports advanced analytical methodologies, which are used to statistically measure consumer preferences.

Each participant was asked to provide informed consent before proceeding with the survey. The informed consent included a detailed explanation of the study's main aim, including how data would be collected, stored, and used, and the potential risks associated with web-based questionnaires. It also underlined that the participants are not obliged to respond to all questions and that they can leave the study with no consequences at any time. For the validation process (second part of the study), which asked for personally identifiable information, participants were required to provide consent again in order to be contacted. Additionally, participants selected from predefined panels participated in the primary survey only and were ineligible for the validation phase of the 3FQ, thus segregating the validation outcomes from this possible source of bias. The study protocol has been preregistered in the Open Science Framework, a registry that accepts observational studies as recommended to help decrease publication bias [27].

Study Questionnaire

Respondents were initially asked to answer general questions, including self-reported anthropometric data. They also answered basic questions regarding their health state and any allergies, as these parameters may affect knowledge and behavior related to fermented food consumption. Participants were then presented with the 12 fermented food categories and asked to choose whether they consume each of these food categories and, through visualizations, report their usual consumption portion. The included fermented food categories were plant-based meat alternatives, dairy products, legumes, meat, fish, vegetables, cereal products, chocolate (bars), nonalcoholic and alcoholic beverages (beer and/or cider, wine, and spirits), vinegar, and beverages (coffee, tea, and chocolate beverages). Although this classification is rather extensive, as discussed earlier, some food groups included in the 3FQ structure may not be widespread or frequently consumed in all countries, which is the main challenge as well as the necessity of this multi-European region study to identify differences in the amount and type of fermented foods consumed in each region.

Questionnaire Development and Validation

The questionnaire was first developed in English by experts in food science and technology, nutrition, nutritional epidemiology, and consumer science. Up to 2 National Contact Points (NCPs) from each country were responsible for translating the questionnaire into their respective languages, ensuring it matched the originally derived international tool (English version). However, each country used nationally available food examples per main food group question to personalize the questionnaire (eg, in the cheese group, Greece used feta and Italy used mozzarella as soft/semisoft cheese examples). Countries with more than 1 national language translated the questionnaire in all (eg, Switzerland translated it into French, Italian, and German, along with other national translations from the respective countries). A standardized translation methodology was followed, which included two steps: (1) translation to the national language by an individual fluent in both the national and English languages and (2) back-translation from the national language to English, with the individual responsible for the second step being blinded to the primary international questionnaire. The back-translated questionnaire was compared to the international questionnaire, and necessary corrections were made.

The clarity of the questionnaire was assessed through pilot testing. This was performed through the Conjointly platform, using a sample of 50 individuals from various age groups and educational backgrounds. The participants were asked to note any difficulties they faced when accessing or responding to the questions and/or potential clarifications required. These were reviewed by the NCP members, and corrections were included in the final version.

The 3FQ will also undergo validation, a process that includes 2 parts. The first part aims to ensure the repeatability of the 3FQ

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across all European regions, and the second part assesses overall accuracy. For repeatability, participants were asked if they would be willing to repeat the same questionnaire approximately 6 weeks after their first response. Those who agreed were asked to provide consent and provide an email address and or phone number for further contact at a later stage. A minimum of 200 responders from each European region was calculated as necessary to meet the commonly used rule of thumb of 5 respondents per question.

The second part of the validation will assess the accuracy of the 3FQ using a harmonized methodology. This process will involve participants from the total sample across the participating countries. To ensure a harmonized process, NCPs who agreed to act as interviewers were trained by a dietitian specializing in nutritional research methods through two 2-hour web-based sessions and 1 on-site workshop. A specific Excel (Microsoft Corp) file using drop-down menus was developed and shared with all interviewers to be used during the recall process for each individual.

For the actual procedure, participants were asked if they agreed to share their communication details (as previously described) and to be contacted for a web-based interview about their usual dietary habits. Individuals who shared either a phone number or email address were contacted no later than 2 weeks after completing the web-based 3FQ to undergo a 24-hour phone-based recall. The validation process included one or two 24-hour phone-based recalls, using the Automated Multipass Method, from a representative sample of the study's target population [28]. A total of 265 to 371 individuals were required for this process, as per the rule of thumb (between 5 and 7 participants per survey question).

The study's power calculation was performed for the Spearman correlation analysis using G*Power software (Heinrich Heine University Düsseldorf). Specifically, the sample size needed to achieve 90% power, assuming a low correlation of ρ_o=0.4 (the null hypothesis H_o) with the potential for no correlation (the alternative hypothesis H_1=0.2), at α =5% (2-tailed exact test), was calculated to be 218 participants. Since only 1 recall was expected from most participants, and because Bland-Altman analysis requires more data, a larger sample based on the 7 participants per question rule was targeted to reduce random error. The higher number (371) was chosen as the optimal target, as it ensures adequate power to assess the accuracy of the subproducts of each food group.

Participants who did not provide dietary assessment data or complete at least 1 recall were excluded from the validation data set. At least 1 recall was required (and up to 2 were performed) for the validation of the 3FQ's accuracy. This criterion was chosen since the aim was not to assess overall usual intake but to validate the 3FQ through a meaningful measure of fermented food intake. Permitting the collection of recalls on 1 or 2 days can help reduce participant burden, thereby decreasing selection bias among working individuals. Additionally, it was clearly communicated that the recall would be interview-based to help reassure and decrease selection bias among older participants, who are generally more hesitant with web-based processes.

Moreover, measures were taken to ensure a representative sample for the 3FQ responses, specifically including an older age group that was 50+ years, for representativeness of the 3FQ responses. For the questionnaire's validation, demographics will be disclosed to depict the population to which the results may be justifiably generalized. After merging the 3FQ and 24-hour recall data, the population sample will represent the validation subsample for further analyses.

Data on fermented foods from the 3FQ and recalls will be identified and aggregated into conventional food groups. Percent differences in mean intakes, quintile cross-classification, Spearman correlations, and Bland-Altman analyses will be used to evaluate the agreement between the 2 dietary assessment methods.

Results

This project is part of the PIMENTO COST Action (CA20128) but did not receive specific funding, other than member travel and accommodation costs during on-site working groups. The questionnaire has been developed, translated, and pilot-tested, with the main data collection phase beginning in October 2023 and concluding in May 2024. The validation phase, which will include repeatability testing and 24-hour dietary recalls, was completed in December 2024. Data analysis was set to start in January 2025, with the results anticipated for publication 4 months after the analysis commences, estimated in September 2025.

Discussion

Overview and Important Considerations

The study project handles a variety of operational, methodological, and ethical concerns, particularly in relation to the use of web-based surveys. A significant limitation is the exclusion of susceptible demographics like children, adolescents, and individuals without legal capacity, reducing the generalizability of the results. Furthermore, there are advantages and disadvantages to performing web-based surveys. An important advantage that is an asset pertaining to the study's aim is the ability to reach a sizable, geographically diversified sample at a reasonable cost. Web-based surveys also offer flexibility, allowing respondents to finish the survey at their convenience. The GDPR-certified platform enables automated data collecting and processing, helping minimize human error and misclassification.

However, internet surveys have certain drawbacks that must be considered, such as selection bias. For example, people without internet access or low technological proficiency may not be included, resulting in the underrepresentation of certain demographic groups. Furthermore, response rates might be lower than in-person techniques due to possible difficulties in understanding the question.

To address these challenges, different forms of pilot testing were conducted before the study launch. First, the survey was shared with a panel of food science researchers and nutritionists, who completed it and provided feedback on areas requiring correction and/or clarification. The feedback received was

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reviewed by the study's coprincipal investigators, discussed with the NCPs, and used to make improvements/adjustments. Next, each NCP also conducted a pilot phase using a convenience sample from the general population in their country. Issues encountered during this phase were discussed, and further adjustments were made to improve clarity.

Privacy issues pertaining to the management of anthropometric, health, and personal data are also of great importance, especially when creating profiles. Data will be anonymized and securely stored, with restricted access to authorized personnel. Only the absolutely necessary anonymized personal data will be stored for a maximum of 4 years at the Agricultural University of Athens. After this period, the principal investigators will carefully dispose of the data.

In cases where predefined panels were used because representativity and certain quotas were not met, sensitivity analyses will be conducted. Any significant differences between the 2 groups (based on the collection method) found from comparisons and tests performed will be highlighted. If the results are consistent across groups, this will strengthen the study's validity. If the results differ, the data will not be combined; instead, the results will be separately presented, and a detailed discussion on the implications will be derived as necessary. A weighted approach to balance the influence of each data source may be used if differences are minimized. The results will be ethically handled and disseminated to safeguard participant confidentiality while effectively informing interested parties, including the public, academics, and policy makers. Finally, despite the challenges recognized, careful planning and ethical supervision are in place to ensure that the study significantly contributes to the field of nutrition and food science, paving the way for necessary future actions.

Limitations

While we cannot fully eliminate the potential for social desirability bias, especially for foods perceived as "healthy," the methodology used aimed to mitigate reporting errors. Specifically, the Automated Multipass Method for the 24-hour recalls was used to minimize misreporting and improve recall accuracy through systematic probing, and the 3FQ was designed with a hierarchical structure that included broad food groups followed by specific fermented subgroups. This was used as a "filter" to systematically guide participants' responses and help reduce perception errors.

Furthermore, fermented foods like kefir, kombucha, and kimchi are distinctive and often consumed intentionally or due to cultural reasons. This may lead to more accurate reporting compared to more commonly consumed items.

The potential underrepresentation of individuals with lower literacy levels or those without computer or internet access should also be considered. The platform selected was accessible through a smartphone—either Android or iOS—and easily accessible through a QR code, potentially mitigating the selection bias of individuals with no computer access.

Regarding the effect of literacy levels, it is plausible that the subject matter itself—fermented foods consumption—may have an inherent selection effect towards a more literate population, hence potentially reducing the bias introduced by a web-based survey tool compared to a survey on a more general topic. Future analyses could address this by statistically weighing the data against national census statistics using demographics on literacy levels. This information has been included in the Methods section (where the Conjointly platform is described) and the limitations section (for the literacy level and prospective possibilities).

Conclusion

The web-based 3FQ is designed to address existing research gaps in assessing the frequency and quantity of fermented food consumption across all food groups. This will enable researchers to gain deeper insights into dietary patterns involving fermented foods and support more robust analyses of their potential associations with health outcomes, while also enhancing the accuracy and comparability of data in future studies. This tool is also capable of addressing consumption data of less frequently consumed fermented foods that are regularly missed in usual food frequency questionnaires, thereby minimizing systematic consumption errors.

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Data Availability

The study protocol has been uploaded to the Open Science Framework [29]. Data collected will also be included and open after an embargo period of 3 years. Any database used for publication will be made available, without details on individual patient data, after manuscript acceptance.

Authors' Contributions

MS and GV were responsible for the conceptualization of the study. EM developed the study methodology. EM, SK, TS, and MS contributed to the formulation and writing of the study protocol. SK, SA, KJB, VKS, ML, VM, TS, GV, BV, and CC reviewed the protocol.

Conflicts of Interest

None declared.

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Abbreviations

3FQ: Fermented Foods Frequency Questionnaire
COST: Cooperation in Science and Technology
FFQ: food frequency questionnaire
GDPR: General Data Protection Regulation
NCP: National Contact Point
PIMENTO: Promoting Innovation of Fermented Foods

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Protocol

Development of the SCI-BodyMap—Measuring Mental Body Representations in Adults With Spinal Cord Injury: Protocol for Item Generation, Reliability, and Validity Testing

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Abstract

Background: Approximately 69% of Americans with spinal cord injury (SCI) have neuropathic pain. Research suggests that impairments in mental body representations (MBRs; ie, representations of the body in the brain) likely contribute to neuropathic pain. Clinical trials in adults with SCI, focused on restoring MBR, led to improvements in sensation and movement as well as neuropathic pain relief. Scales measuring aspects of MBR exist, but none of them assess SCI-related MBR impairments.

Objective: As our first aim, we will generate items for a new MBR scale for adults with SCI (the SCI-BodyMap). As our second aim, we will assess the interrater reliability, test-retest reliability, concurrent validity, face validity, and utility of the SCI-BodyMap.

Methods: Our preliminary work will encompass initial item generation by SB, an Italian physical therapist (PT) specialized in cognitive multisensory rehabilitation, which is a therapeutic approach that focuses on restoring MBR in adults with neurological disorders and chronic pain. Further item refinements will be carried out by Italian PTs (n=7) and Brazilian PTs (n=3) specialized in cognitive multisensory rehabilitation. In aim 1, American PTs or occupational therapists (n=8) and adults with SCI (n=8) will provide feedback on the SCI-BodyMap. Next, American PTs or occupational therapists (n=3) will administer the SCI-BodyMap to adults with SCI (n=3) and provide more feedback during an in-person visit. In aim 2, four assessors will administer the SCI-BodyMap to adults with SCI (n=30) for interrater reliability. The self-report items will be administered at 2 separate time points to assess test-retest reliability. We will also administer the SCI-BodyMap to uninjured adults (n=30) to identify whether healthy adults score statistically different on the scale than adults with SCI. We will assess concurrent validity through correlations between the MBR scale, the Revised Body Awareness Rating Questionnaire, and the Multidimensional Assessment of Interoceptive Awareness-2.

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Results: As of August 2025, we have enrolled 8 PTs or occupational therapists and 8 adults with SCI for aim 1 as well as 29 adults with SCI and 13 uninjured adults for aim 2.

Conclusions: A reliable and valid MBR scale is needed to identify MBR deficits and evaluate intervention effects on MBR outcomes in adults with SCI. Improving MBR can lead to safer, more efficient day-to-day activities (eg, transfers); promote functional independence and quality of life; reduce neuropathic pain and spasms; and improve sensorimotor function.

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KEYWORDS

spinal cord injury; mental body representations; body awareness; visuospatial body map; reliability; validity

Introduction

Background

There are approximately 308,620 adults with spinal cord injury (SCI) in the United States, with approximately 18,421 new cases of SCI every year [1]. Pain is one of the most common secondary conditions of SCI and the most difficult to treat [2]. This is especially true for chronic neuropathic pain, present in 69% of adults with SCI [3]. Neuropathic pain is described as sharp, shooting, stabbing, electric, or burning and is sometimes experienced as excruciating pain at, below, or above the level of spinal injury [2,4].

When parts of the body are paralyzed and have impaired or absent sensation after an SCI, the brain can no longer identify where those parts are in space and how the body parts relate to each other. Therefore, aside from sensory and motor impairments, adults with SCI also experience mental body representation (MBR) deficits [5,6]. Body awareness and visuospatial body maps, both generated in the brain, are types of MBRs. Body awareness refers to an attentional focus on and awareness of internal body sensations, which includes whole-body awareness as well as awareness of body parts in relation to each other [7,8]. Visuospatial body maps help the brain understand where the body and specific body parts are situated in space. An example of altered visuospatial body maps can be empirically seen during the International Standards for Neurologic Classification of Spinal Cord Injury American Spinal Injury Association Impairment Scale neurologic examination [9], used in the clinic to quantify changes in sensory and motor function in adults with SCI; for example, people feel a touch with a cotton ball at the bottom of their foot as if it is on the top of their foot, or people feel a touch on the lower leg as being touched on their upper leg. In sum, deficits in body awareness and altered visuospatial body maps are referred to as MBR deficits. Body awareness and visuospatial body maps are situated in different parts of the brain—insular-parietal opercular cortex and posterior parietal cortex, respectively—which continuously interact with each other [6,10]. The visuospatial body maps are updated in real time at each moment to guide movements.

Whole-body awareness is developed by synthesizing information from all our senses. This integration occurs within the multimodal integration network of the brain, which includes regions such as the insula and parietal operculum [6,10]. The integration of senses involves not only perceiving which part of the body is being touched but also accurately determining the direction of auditory signals; for example, when we hear a car approaching, we instinctively look in that direction and wait for it to pass before crossing the street. To create a comprehensive understanding of whole-body awareness, the positions of body parts relative to other body parts, and our body position in space, the brain must be aware of the size, location, and dimensions of our body. Consequently, evaluating these aspects is crucial for identifying any potential MBR deficits a person may have [6,10-13].

Our previous research and that of others identified deficits related to MBR in adults with SCI [5,6,10,13-15]. MBR deficits are also thought to contribute to the production or maintenance of chronic neuropathic pain because the insula and parietal operculum are also key areas for chronic pain perception [5,14,16-19].

The Revised Body Awareness Rating Questionnaire (BARQ-R) [6,15,20,21] and the Multidimensional Assessment of Interoceptive Awareness-2 (MAIA-2) [22] were originally designed to address bodily awareness in adults with chronic pain and mindfulness in healthy adults, respectively. However, these scales do not identify awareness of body parts relative to other body parts, nor whole-body awareness; rather, they focus on interoceptive and emotional awareness, such as the person's perception of tension and pain in their body, whether digestion impacts how they feel, or whether they show to others how they feel [6,15,20-22]. To the best of our knowledge, there is no measure available that assesses SCI-specific MBR deficits. In addition, psychometric assessment, such as interrater reliability, test-retest reliability, feasibility, utility, face validity, concurrent validity, and other relevant analyses, is important before using the scale in the clinic or for research.

Therefore, our overall aim is to develop an MBR assessment for individuals with SCI (ie, the SCI-BodyMap) and to assess its psychometric properties. We will also assess the SCI-BodyMap in uninjured adults (n=30) to identify whether healthy adults score statistically different on the scale than adults with SCI.

In addition, other factors may further influence MBR. Therefore, we will determine correlations between the SCI-BodyMap and age, time since SCI, levels of neuropathic pain, functional mobility level, and percentage of time spent using a wheelchair. In addition, we will conduct exploratory secondary analyses to determine whether there are significant differences in MBR deficits, assessed with the SCI-BodyMap, between adults with paraplegia versus those with quadriplegia, complete versus

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incomplete SCI, presence versus absence of spasms, and presence versus absence of current and past body awareness training.

Purpose of This Study

The purpose of this study is twofold: (1) to develop the SCI-BodyMap for adults with SCI with neuropathic pain and those without neuropathic pain; and (2) assess the interrater reliability, test-retest reliability, concurrent validity, feasibility, utility, and face validity of the new SCI-BodyMap.

Aim 1

We will generate and refine items for the SCI-BodyMap for adults with SCI through iterations based on feedback from physical therapists (PTs) or occupational therapists (OTs) and adults with SCI.

Aim 2

Interrater reliability will be evaluated through in-person testing with the first author (SC) and 3 PTs not involved in initial item generation. For the self-reported items in the scale, test-retest reliability will be performed. Concurrent validity will be evaluated by correlating the SCI-BodyMap with the BARQ-R [13,20,21] and the MAIA-2 [22]. Feasibility, utility, and face validity will be assessed using the QQ-10 [23] after an in-person assessment of the scale with a PT or OT and an adult with SCI. We will also administer the SCI-BodyMap to uninjured adults (n=30) to identify whether healthy adults score statistically different on the scale than adults with SCI.

Secondary Analysis

We will also calculate correlations between the SCI-BodyMap and age, time since SCI, levels of neuropathic pain (the Numeric Pain Rating Scale [24]), functional mobility level, and percentage of wheelchair use. In addition, we will determine whether there are significant differences in MBR deficits, assessed with the SCI-BodyMap, between adults with paraplegia versus those with quadriplegia, complete versus incomplete SCI, presence versus absence of spasms, and presence versus absence of current and past body awareness training.

Methods

Overall Study Design

This study uses a cross-sectional observational design. Aim 1 will include item generation and refinement. Aim 2 will include interrater reliability, test-retest reliability, concurrent validity, feasibility, utility, and face validity analyses. Table 1 displays the study timeline.

Table 1. Scheduling of enrollment and assessments.

	Study period			
	Aim 1		Aim 2	
	Wk 1: enrollment+visit 1 (Zoom)	Wk 1: visit 2 (in person)	Wk 1: enrollment+visit 1 (Zoom)	Wk 2-3: visit 2 (in person)
Eligibility screen	✓		✓	
HIPAA[a]-compliant electronic consent	✓		✓	
Enrollment	✓		✓	
Demographic and clinical information	✓		✓	
Item-generation feedback survey	✓			
SCI[b]-BodyMap+in-person feedback		✓		✓
SCI-BodyMap in-person testing				✓
SCI-BodyMap self-report testing	✓	✓		✓
QQ-10 survey		✓		✓

[a]HIPAA: Health Insurance Portability and Accountability Act.

[b]SCI: spinal cord injury.

Study Setting

Surveys will be distributed remotely through the University of Minnesota (UMN) REDCap (Research Electronic Data Capture; Vanderbilt University) platform. In-person visits will be conducted at the Brain Body Mind Lab at the UMN.

Participants and Recruitment

For aim 1, we will recruit PTs or OTs who are board-certified neurologic clinical specialists with experience in working with adults with SCI or with experience in cognitive multisensory rehabilitation (CMR) [10,13]. We will recruit PTs and OTs through collaborations within the Minnesota Regional Spinal Cord Injury Model System and through collaborations with the Brain Body Mind Lab at the UMN.

For aim 1 and aim 2, we will recruit English-speaking adults with SCI, at least a year after SCI onset, with or without neuropathic pain. There is no restriction regarding race, ethnicity, age, level of injury, or completeness of injury. We will exclude adults with cognitive impairments, those who are pregnant, or those with deep pressure sores hindering prolonged sitting or lying down. For aim 2, we will also recruit English-speaking uninjured adults (aged ≥18 y). Uninjured

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adults and community-dwelling adults with SCI will be recruited through a contact list of participants identified via ClinicalTrials.gov, hospitals, StudyFinder, Research Match (a UMN registry for volunteers), and rehabilitation centers affiliated with the Minnesota Regional Spinal Cord Injury Model System, as well as individuals who have expressed interest in participating in research conducted at the Brain Body Mind Lab.

Demographic and Clinical Outcomes

For healthy adults, we will gather demographic information such as age, sex assigned at birth, gender identity, race and ethnicity, and type and amount of current and past body awareness training (eg, martial arts, Pilates, yoga, tai chi, or qigong).

In addition, for PTs and OTs, we will collect professional information, including their title, profession, and credentials; whether they provide care for patients hospitalized in the clinic (inpatient) or whether these patients have appointments with them as outpatients; location of employment (eg, hospital and private practice); number of years working with adults with SCI; description of any certifications related to CMR (if applicable); and any other relevant information that they may want to add.

For adults with SCI, we will collect the same demographic information as well as SCI-specific information, including the cause of SCI; time since SCI (in months); completeness of injury (International Standards for Neurologic Classification of Spinal Cord Injury American Spinal Injury Association Impairment Scale grade [9]); level of SCI; highest, average, and lowest levels of neuropathic pain in the prior week (Numeric Pain Rating Scale [24]); location of pain; whether they have paraplegia, quadriplegia, or Brown-Séquard syndrome; spasm frequency and severity (Penn Spasm Frequency Scale [25]) and sensorimotor function (National Institute of Neurological Disorders and Stroke–Common Data Element Spinal Cord Injury Functional Index/Assistive Technology [26]), which addresses levels of difficulty in performing basic mobility, self-care, fine motor function, and ambulation; type and percentage of wheelchair or other ambulatory assistive device use; and, if applicable, type and amount of prior or current body awareness training and rehabilitation (eg, qigong or CMR).

Item Generation and Refinement

The study flowchart (Figure 1) shows the progression of the generation and refinement of items for the SCI-BodyMap. As preliminary work, an Italian PT specialized in CMR, MBR, and SCI will develop the initial items for the SCI-BodyMap (Figure 1: iteration 1). The first author (SC) will then standardize the items. Seven Italian PTs specialized in CMR and 3 Brazilian PTs specialized in CMR will jointly provide feedback so that the items can be refined (Figure 1: iteration 2).

Figure 1. Study flowchart: item generation of the SCI-BodyMap. The flowchart illustrates the development process of the SCI-BodyMap. BARQ-R: Revised Body Awareness Rating Questionnaire; CMR: cognitive multisensory rehabilitation; MAIA-2: Multidimensional Assessment of Interoceptive Awareness-2; OT: occupational therapist; PT: physical therapist; SCI: spinal cord injury.

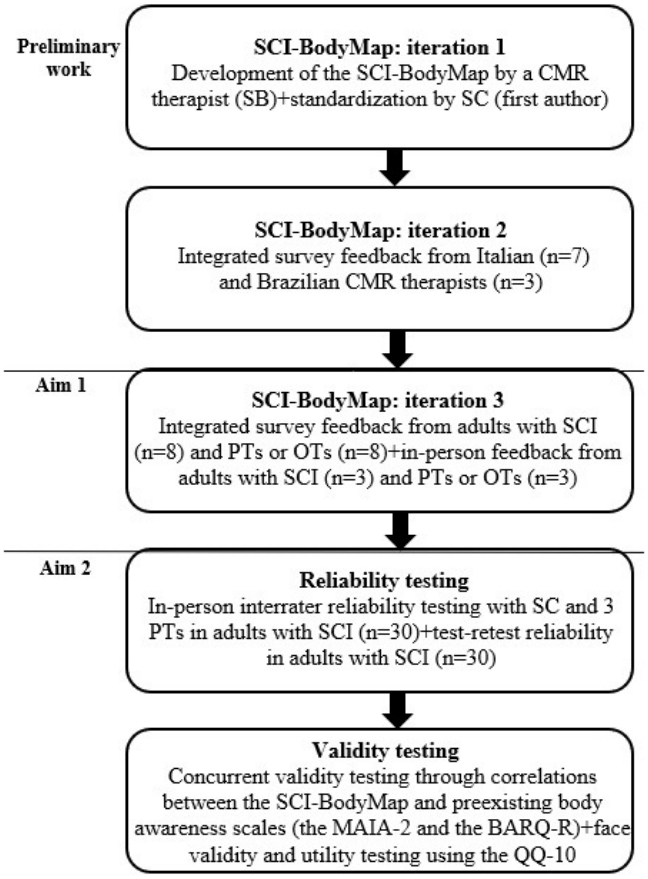

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Once feedback is integrated, 8 PTs or OTs who are board-certified neurologic clinical specialists and 8 adults with SCI will provide feedback on iteration 2 through a survey sent via email. Next, SC and 3 PTs will assess 3 adults with SCI with the SCI-BodyMap during an in-person visit (Figure 1: iteration 3), who will provide additional feedback. Decisions to retain, modify, or eliminate items can be made based on qualitative feedback from the CMR therapists, PTs, OTs, and adults with SCI in relation to the ease of use, feasibility of logistics, and clarity and delivery of instructions. We will incorporate feedback and propose solutions for conflicting suggestions to reach consensus.

Scoring and Interpretation and Description of the SCI-BodyMap

The SCI-BodyMap will consist of 2 sections that will be scored and administered independently. The first section will include 4 items, which will be administered in person by a PT or OT to produce a total score. Scoring for these 4 items will be rated as incorrect or correct for each movement.

In item 1, participants will be instructed to estimate, without physically measuring, how many of their own hands would be required to measure specific body parts if they were to place their hands sequentially on these body parts. To answer accurately, participants need an intact body image and a clear visuospatial body map to understand both the size of their own hands and relate this to the dimensions of each body part.

In item 2, participants will sit with their feet flat on the floor. The PT will move the participants' feet back and forth and then position one foot in a specific way. With their eyes closed, participants must determine the location of their foot in space, how this position relates to their other foot, and how it corresponds to an external object (eg, a marker placed on the floor in front of their feet). Answering this item accurately requires participants to have an understanding of their body's position in relation to the environment and the positioning of both feet.

In item 3, the PT will hold the participant's hand and slowly move it 6 to 8 inches above different body parts. With their eyes closed, participants must determine whether their hand would touch or miss a body part if their hand were to be lowered as well as which body part it would touch. Answering this item correctly requires participants to have a good sense of where their body is in space, an understanding of their body's dimensions, and an awareness of how their hand interacts with other body parts.

In item 4, the PT will make snapping sounds at various locations around the participant's body, approximately 2 feet away. With their eyes closed, participants must identify whether the sound is coming from the front or back of their body at head or foot level. In addition, with the snapping sound presented on the side of the body, they must determine whether the sound is at head, hip, or foot level. Answering this item correctly requires participants to have a strong awareness of their body's position in relation to external auditory stimuli.

The second section contains 4 self-report items, scored separately. In item 1, participants will color the body parts on an image of a blank figure according to statements related to their perception of sensation, body awareness, and neuropathic pain. The score is based on the colored areas, sectioned into multiple body regions, corresponding to differing degrees of sensation (eg, numbness; ranging from 0=complete loss of sensation to 2=complete ability to sense touch and pressure), body awareness (ranging from 0=lack of bodily awareness or connection to the body to 2=complete bodily awareness and connection to the body), and neuropathic pain (ranging from 0=no neuropathic pain to 2=neuropathic pain perceived as stabbing, burning, or painful pins and needles).

For items 2, 3, and 4, scores are assigned for each body region based on the frequency of neuropathic pain (ranging from 0=no neuropathic pain to 4=neuropathic pain experienced 100% of the time), duration (ranging from 0=no neuropathic pain to 4=neuropathic pain experienced 100% of the time), average pain intensity (ranging from 0=no neuropathic pain to 4=excruciating neuropathic pain), and highest pain intensity (ranging from 0=no neuropathic pain to 4=excruciating neuropathic pain). The self-report section of the SCI-BodyMap focuses on how participants perceive their own bodies concerning sensations, pain, and body awareness, reflected here by their emotional or physical connectedness and awareness of their body.

The cutoff values and interpretation of scores for the SCI-BodyMap will be determined after assessing the scoring range in uninjured adults.

Interrater Reliability Testing

To assess interrater reliability, SC (the first author) and 1 of the 3 PTs not involved in developing the SCI-BodyMap will administer the SCI-BodyMap to 30 adults with SCI [27]. In addition, SC will evaluate 30 uninjured individuals with the SCI-BodyMap.

Feasibility, Utility, and Face Validity Testing

Upon completion of the SCI-BodyMap, each participant with SCI will fill out the QQ-10 [23]. This survey consists of 10 questions that assess the feasibility, utility, and face validity of the items and the scale as a whole. Respondents will rate their answers on a 5-point Likert scale ranging from strongly agree to strongly disagree. In addition, there are 3 open-ended questions regarding the relevance of the SCI-BodyMap, its ease of use, the time it takes to complete, and the emotions experienced during the process. We will incorporate qualitative data in the form of direct quotes in the manuscript reporting on the study results.

Statistical Analyses

The sample calculation for aim 2 (n=30 participants for interrater and test-retest reliability) is based on the recommended sample size for pilot studies [27].

For both aims 1 and 2, we will summarize descriptive statistics for all demographic information collected. In aim 2, interrater reliability of the SCI-BodyMap (scores assigned by SC and 1 of the 3 PTs) will be evaluated with the Cohen κ coefficient and intraclass correlation coefficient (ICC). We will consider an ICC value of at least 0.75 as good interrater reliability and

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0.90 as excellent interrater reliability [28]. We will consider the Cohen κ agreement of 0.60 as a moderate agreement and 0.80 as a strong agreement [29].

Test-retest reliability, also analyzed with the ICC, will be assessed within a 2-week period, a time frame commonly used in similar studies. Concurrent validity will be assessed using Spearman correlation coefficients between the SCI-BodyMap and the BARQ-R [21] and MAIA-2 [30]. A Spearman ρ correlation of 0.70 is a high correlation, and 0.90 is a very high correlation [31]. To assess feasibility, utility, and face validity, the QQ-10 Likert scale section will produce both "value" and "burden" scores ranging from 0 to 100, with higher "value" scores closer to 100 and lower "burden" scores closer to 0 indicating greater feasibility, utility, and face validity [23]. To be consistent with previous research, we will interpret mean "value" scores of at least 72.6 as high value and mean "burden" scores of ≤27.7 as low burden, indicating greater feasibility, utility, and face validity of the SCI-BodyMap [23,32]. We will also report responses to open-ended questions as direct quotes.

For our secondary analyses, we will determine associations between the SCI-BodyMap and age, time since SCI, levels of neuropathic pain, functional mobility level, and percentage of wheelchair use with Pearson or Spearman correlation coefficients, depending on the level of measurement and whether or not the data is normally distributed. In addition, we will conduct a Mann-Whitney *U* test to identify possible differences in MBR deficits, assessed with the SCI-BodyMap, between adults with paraplegia versus those with quadriplegia, complete versus incomplete SCI, presence versus absence of spasms, and presence versus absence of current and past body awareness training.

We will also perform a Mann-Whitney *U* test to evaluate whether there are significant differences in SCI-BodyMap scores in adults with SCI versus uninjured adults.

Ethical Considerations

This study will be conducted in accordance with the ethical guidelines of the Declaration of Helsinki and was approved by the UMN institutional review board (IRB; STUDY00020888). The Health Insurance Portability and Accountability Act (HIPAA)–compliant REDCap electronic consent form is delivered via a secure survey link emailed to participants. We will take special precautions to protect confidentiality (ie, verify the participant's email over the telephone, send a "test email," and wait for an email reply before sending the HIPAA-compliant electronic consent form through REDCap).

The participants will have the same consent discussion with the researcher via telephone or Zoom (Zoom Video Communications, Inc) that they would have had in person (including the researcher asking questions to gauge comprehension and answering the participants' questions).

The consent form will provide information regarding the study design, procedures, potential risks and benefits, alternatives to participation, voluntary nature of participation, and confidentiality. Participants will receive US $20 upon completion of the aim 1 email survey, an additional US $20 for the aim 1 visit, and an additional US $20 for the aim 2 visit. The first author (SC) will ensure participants' understanding of the materials discussed and secure informed consent as well as ensure that they are aware of the voluntary nature of study participation and that they understand all potential benefits, risks, and alternatives to study participation as part of the informed consent process.

A PDF file of the HIPAA-compliant electronic consent form signed by both parties will be emailed to the participants for their records. The first author (SC) will document the consent process in a separate note, which will be stored in the UMN Box Secure Storage. Study procedures will not begin until all aspects of the remote consent process are complete. A copy of the HIPAA-compliant electronic consent form will not be included in the participant's electronic health record, but the signed PDF file will be stored securely in the UMN REDCap platform and in the UMN Box Secure Storage. REDCap uses a MySQL database via a secure web interface, with data checks to ensure data quality during data entry. All UMN IRB and HIPAA rules will be followed.

The principal investigator (AVdW) will oversee the safety of the study at the UMN site. We anticipate minimal risk, given that the assessments conducted with the SCI-BodyMap are similar to those conducted in the clinic or rehabilitation centers. The questionnaires will be completed over the secure UMN Zoom system. The only risk here would be the sensitivity of some questions related to SCI-related symptoms. There are minimal potential risks associated with data privacy and confidentiality, and care will be taken to avoid them, for example, by setting up a waiting room for the Zoom meetings. All data are stored on HIPAA-secure servers (REDCap and UMN Box Secure Storage). Although adverse events are unlikely, given the nature of the study, all participants will be encouraged to contact the principal investigator or study staff if they experience any side effects or adverse events. In such cases, applicable policies and procedures of the UMN IRB will be followed.

Results

At the time of manuscript submission, the study is being conducted under the approved UMN IRB protocol version 3.0. We do not anticipate further changes. Recruitment started on November 18, 2024, and we estimate that we will complete data collection by the end of September 2025. As of August 2025, we have enrolled 16 participants (PTs or OTs: n=8, 50%; adults with SCI: n=8, 50%) for aim 1 and 42 participants (adults with SCI: n=29, 69%; adults without SCI: n=13, 31%) for aim 2. The results of this study will be reported and submitted as a manuscript to scientific journals as well as disseminated through presentation at national and international conferences in the fields of SCI and complementary and integrative medicine.

Discussion

Summary

This project aims to develop a new scale to measure MBR deficits, called the SCI-BodyMap. The items on this scale will be designed with, and tailored to the experience of, adults with

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SCI. We expect the SCI-BodyMap to demonstrate good to excellent interrater reliability, test-retest reliability, and concurrent validity.

Previous studies have used body awareness scales to assess MBR in adults with SCI. However, they are no scales specifically designed to address MBR deficits in adults with SCI [33,34]. Some of the existing body awareness or pain scales share similarities with our self-report measure, such as aspects related to coloring [35]; statements addressing feelings of disconnectedness or self-perception of awareness [36]; or tasks related to the visuospatial map, such as the Body Image Task [33]. Nevertheless, there is currently no scale that specifically targets both types of MBRs (eg, body awareness and visuospatial map) in individuals with SCI. Moreover, the SCI-BodyMap includes both an objective section administered by PTs or OTs and a self-report section.

Limitations

Given the small sample size, meaningful associations for some of our secondary analyses may be difficult to detect, limiting generalizability.

Future Directions

The next psychometric steps for the SCI-BodyMap are assessing reliability, validity, and responsiveness to change and calculating the minimal clinically important difference in a larger sample of adults with SCI. Given that this scale will be validated in English, future studies should aim to validate the scale in different languages.

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Authors' Contributions

SC, AVdW, and SB played key roles in the development of the SCI-BodyMap scale and the design of the project, working alongside physical therapists and adults with spinal cord injury. AVdW is the principal investigator of the project and supervises the study. SC is in contact with the University of Minnesota Clinical and Translational Science Institute and submits any necessary protocol modifications. The Italian cognitive multisensory rehabilitation therapists' group (NC, DdP, IG, MR, FR, BP, and MZ) and the Brazilian cognitive multisensory rehabilitation therapists' group (MC, JG, and MM) contributed significantly to the further development and refinement of the SCI-BodyMap. SC and three physical therapists not involved in the design of the SCI-BodyMap collected the data. SC authored the initial draft. All authors made significant contributions to various sections of the manuscript and approved the final version. They collectively agree to be accountable for the accuracy and integrity of the research.

Conflicts of Interest

None declared.

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Abbreviations

BARQ-R: Revised Body Awareness Rating Questionnaire
CMR: cognitive multisensory rehabilitation
HIPAA: Health Insurance Portability and Accountability Act
ICC: intraclass correlation coefficient
IRB: institutional review board
MAIA-2: Multidimensional Assessment of Interoceptive Awareness-2
MBR: mental body representation
OT: occupational therapist
PT: physical therapist
REDCap: Research Electronic Data Capture
SCI: spinal cord injury
UMN: University of Minnesota

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Protocol

Application of the ADAPT-ITT Model to Develop Trauma-Focused Cognitive Behavioral Therapy for Interpersonal and Racial Trauma and Racial Socialization: Protocol for a Mixed Methods Study

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Abstract

Background: Black youth experience higher rates of interpersonal and racial trauma than other youth, yet they are less likely to use and benefit from evidence-based mental health services. These disparities highlight the need for culturally responsive adaptations of existing interventions.

Objective: This study integrated racial socialization (RS)—a protective process for Black youth—into trauma-focused cognitive behavioral therapy (TF-CBT) using the ADAPT-ITT framework (assessment, decision, adaptation, production, topical experts–integration, training, and testing) to improve treatment engagement, acceptability, and outcomes for Black youth and their families.

Methods: Adaptation followed the 8 phases of the ADAPT-ITT model. During *assessment*, a literature review and previous studies identified racial discrimination and socialization as salient risk and protective factors for Black youth, underscoring the need for culturally responsive interventions. In the *decision* phase, TF-CBT was chosen given its evidence base and gaps in addressing racial trauma. The *administration* phase embedded RS messages such as racial pride, barriers, spirituality, and extended family involvement into TF-CBT's components (psychoeducation, relaxation, affect modulation, cognitive coping, trauma narrative and processing, in vivo mastery, conjoint sessions, and enhancing safety) to enhance psychoeducation, coping, trauma processing, conjoint sessions, and safety planning. In the *production* phase, manuals and fidelity checklists were drafted to preserve TF-CBT's core elements while embedding RS content. To ensure clinical and cultural relevance, the *topical experts* phase included interviews with 10 Black caregivers and 12 Black youths (aged 12-18 years) who had completed TF-CBT, as well as focus groups with 15 clinicians. Thematic analysis identified adaptations to increase feasibility and acceptability. During *integration*, a racial trauma task force of faculty, graduate, and undergraduate researchers refined the model and produced *The C.A.R.E. Package for Racial Healing*, a culturally informed workbook. In the *training* phase, 28 clinicians from 13 community organizations participated in a Substance Abuse and Mental Health Services Administration–funded learning community, receiving 2 days of training and 12 months of consultation on delivering TF-CBT that integrates RS (TF-CBT-RS). Role-plays, demonstrations, and case discussions supported fidelity and cultural responsiveness. Finally, during *testing*, surveys and feedback indicated that TF-CBT-RS was feasible, acceptable, and associated with improved clinician efficacy, greater treatment engagement, and positive client perceptions of support. Preliminary outcomes suggested reductions in trauma symptoms and improved coping, supporting the need for larger randomized trials.

Results: Integrating RS into TF-CBT enhanced cultural relevance, engagement, and preliminary effectiveness for Black youth and their families.

Conclusions: TF-CBT-RS offers a culturally responsive adaptation of trauma treatment that validates racial stressors, incorporates cultural strengths, and promotes engagement. Broader dissemination of the TF-CBT-RS manual and further testing may reduce disparities in trauma outcomes for Black youth.

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KEYWORDS

ADAPT-ITT model; Black youth; racial trauma; trauma-focused cognitive behavioral therapy; TF-CBT; racial socialization

Introduction

Black Youth and Trauma

Black youth experience disproportionately high rates of trauma and its negative consequences. While adverse events affect approximately 67% of all youth [1], Black youth are up to 38% more likely than other racial groups to experience interpersonal trauma and polyvictimization—defined as exposure to more than one type of traumatic event [2-9]. Such exposure is associated with adverse emotional and behavioral outcomes, including poor mental health [2], lower well-being [10], substance misuse [11,12], and unsafe sexual behaviors [13,14].

In addition to the disparities in trauma exposure, nearly 40% of Black youth face racism and discrimination—directly (eg, being told that their hair is not professional) and indirectly (eg, witnessing police brutality on social media)—which constitute significant sources of stress [15-20]. These experiences may contribute to negative health outcomes similar to those of trauma exposure, such as depression, anxiety, hypertension, heart rate variability, and calcification of arteries [21-28]. Comas-Díaz et al [29] propose that severe and prolonged stress reactions due to racism-related stressors constitute *racial trauma.* Jernigan and Daniel [30] demonstrate that these symptoms can be akin to those of posttraumatic stress disorder (PTSD) as defined by the American Psychiatric Association [31] *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* [32,33]. Racial trauma can co-occur with other trauma exposure, compounding the symptoms and their impact [2,11,13,14,30,34,35].

In light of recent and ongoing sociopolitical events such as the COVID-19 pandemic and the heightened visibility of racial injustice, the number of Black youths exposed to interpersonal and racial trauma may be increasing [8,36-42]. This presents a growing health concern for clinicians and caregivers alike, underscoring the need for intervention and treatments that are cognizant of these disparities to address high rates of trauma, both racial and interpersonal, in Black youth.

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Figure 1. Table 1: ADAPT-ITT Fidelity List.

1. Assessment *Who will be the primary audience for the EBI?*	Black youth are at risk of experiencing compounding forms of trauma. a. Culturally relevant practices and strengths are emphasized in addressing the identified trauma in Black youth.
2. Decision *What EBI Will Be Used and Will It Be Adapted?*	TF-CBT was chosen as the therapeutic approach to be adapted and integrated with racial socialization. TF-CBT has not been applied specifically to Black youth and their families. a. Racial trauma and racial socialization literature can be combined with cognitive behavioral therapy techniques to result in a reduction of symptoms and adverse outcomes for Black individuals.
3. Administration *What components of the selected EBIs should be adapted?*	The core elements of TF-CBT (P.R.A.C.T.I.C.E.; psychoeducation and parenting, relaxation, affect identification, cognitive restructuring, in-vivo exposure, conjoint parent-child sessions, enhancing safety) should be maintained to preserve treatment fidelity.
4. Production *How do you adapt and document adaptations?*	Racial socialization was integrated into P.R.A.C.T.I.C.E. components of TF-CBT to help youth explore their racial identity, process feelings related to racial stressors, address maladaptive behaviors linked to racial stress and trauma, and utilize proactive, culturally responsive coping strategies.
5. Topical Experts *Who can assist with adaptation?*	Black caregivers and youth with experience receiving trauma treatment and mental health professionals familiar with TF-CBT were consulted for their input, and their feedback was incorporated into the initial adaptation of TF-CBT.
6. Integration *What is going to be included in the adapted EBI?*	Adaptations were made to the application to include culturally specific content, and suggestions were provided for delivering the content through guided text.
7. Training *Who needs to be trained?*	A two-day training was conducted by Masked for Review and focused on incorporating self-reflection on experiences, identities, and expectations concerning clinician's professional roles in treating racial trauma and its symptoms. a. Participants learned about and actively engaged with strategies to effectively apply racial socialization in a culturally affirming and validating manner.
8. Testing *Was this adaptation successful?*	Data were collected on clinician self-efficacy and preliminary client outcomes following TF-CBT-RS training and delivery. a. Provide an overview of the major findings and the steps that can be taken moving forward as a community.

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Figure 2. Table 2: TF-CBT with RS Fidelity List.

PRACTICE Component		TF-CBT Focus	Integrated Racial Socialization Messages
PRAC: Coping skills	*P*sychoeducation and *p*arenting	Inform clients and caregivers about rates of adverse childhood experiences and trauma, discuss common reactions and symptoms post-exposure, and review the structure and process of engaging with TF-CBT.	Incorporate the definition of racial trauma, and explore how RS messages impact racial identity formation. Emphasis on *Racial Pride* and *Racial Barrier* messages.
	*R*elaxation	Provide the client with necessary skills and strategies, depending on the environment and context, to engage with relaxation and de-stressing.	Identify messages of having to work harder (*Racial Achievement*), and how clients should both work twice as hard and rest/restore twice as much. Incorporate messages of finding support in *spirituality* as relevant/necessary.
	*A*ffective expression and modulation	Identify the feelings and reactions as they emerge during and post-exposure to stressors in clients. Develop the vocabulary necessary to identify, discuss, and regulate these experiences as appropriate for the context.	Revisit common reactions and physical responses (e.g., feelings) to racism and discrimination. Identify emotions that are tied to previous exposures and provide tools to recognize racial stressors as they are happening– including how the client is responding in the moment.
	*C*ognitive coping	Discuss the link between thoughts, feelings, and behaviors (the cognitive triangle), and use client reactions as a real-world example. Explore how clients can discuss this link with caregivers and their support system.	Restructure common reactions and practice proactive, value-based responses to discrimination. Challenge internalized racism that the client may experience or accept (e.g., colorism).
T: Trauma narrative and processing	*T*rauma narration and processing	Explore distressing trauma-related memories to identify unhelpful or inaccurate cognitions that need to be processed and reframed. Reframe by validating the experience and put the trauma exposure into context (future hopes and the good outside of that moment). As appropriate/comfortable, invite caregivers to discuss and share in this narrative.	In addition to standard trauma narratives, incorporate *creative narrative exercises rooted in racial identity* (poems, music, art, photography) to encourage engagement, expression, and healing in ways that feel most relevant to the client. Include discussion of client's experiences with racism, RS, and identity development
ICE: Treatment consolidation and closure	*I*n vivo exposure	Separate harmless reminders or triggers of the trauma from the learned fear and anxiety response. Practice exposure to trauma-related memories and cues to reduce avoidance of these harmless triggers.	Practice with clients and caregivers how to respond to discrimination and stressors, like role-playing what to say and do in the face of microaggressions. Incorporate in-vivo exposures to RS messages and experiences e.g., going to a Black History Museum
	*C*onjoint sessions	Invite caregivers into the space to share praise, support, and love with the client. Encourage open and honest discussion between caregiver and child.	Revisit *Racial Pride* and identity affirmation messaging during conjoint sessions with caregivers to encourage the discussion of race. Utilize RS to identify and validate experiences with racial stressors, and to encourage coping.
	*E*nhancing safety	Provide clients and caregivers with psychoeducation about revictimization. Develop a safety plan with strategies to identify unsafe situations, people, and places, and how to respond to these events. Role-play responses to ensure clients and caregivers feel equipped to use the safety-plan.	Provide resources, scripts, and plans for navigating racial stressors in ways that maximize safety (physical and emotional) to the client. For example, discuss what to do when stopped by police officers, or if someone weaponizes the N-word. Provide resources for caregivers and youth to continue engaging in RS.

Trauma-Focused Cognitive Behavioral Therapy

Evidence-based strategies that address trauma exposure and its consequences for youth do exist, yet Black youth are 3 times less likely to initiate care, be retained in treatment, and remain engaged [19,28,43]. Issues with attrition may be attributed to ongoing systemic issues that deter clients from treatment, such as a lack of diverse practitioners, historical medical racism, and long wait times [44]. Issues with treatment sustainability may also be attributed to the fact that there is often a lack of formal acknowledgment of racial stress and trauma. Without explicit discussion of discrimination (eg, defining microaggressions in an effort to identify them) or culturally relevant coping strategies such as spirituality or creativity, care may feel less relevant or engaging to Black communities [44].

Trauma-focused cognitive behavioral therapy (TF-CBT), for example, is the gold-standard evidence-based trauma treatment for youth aged 3 to 18 years, comprising 8 to 25 sessions [45,46]. This treatment program consists of 8 components: psychoeducation, relaxation, affect modulation, cognitive coping, trauma narrative and processing, in vivo mastery, conjoint sessions, and enhancing safety (PRACTICE). The

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components are designed to help youth identify stressors and their effects, restructure unsafe or unhelpful responses to stressors, and engage support systems into care to build sustainability. Compared to other clinical treatments for addressing trauma, TF-CBT significantly reduces traumatic stress symptoms and the likelihood of a PTSD diagnosis [45,47,48]. However, despite the treatment's strengths and efficacy, it does not include culturally specific risk or protective factors for Black youth, such as recognizing racial trauma or discussing common strategies that are used for coping, healing, and navigating racial stressors (eg, preparing for police encounters). This lack of tailored care in TF-CBT—and many other treatment plans—may contribute to the ongoing disparity in the efficacy of treatment and in retaining and engaging Black clients and caregivers in treatment [49-52]. This leaves clinicians to adapt treatment on their own without standardized evidence-based guidance.

Although TF-CBT has been previously adapted for Latinx, Asian American, and American Indian or Alaska Native groups and demonstrated increased therapist self-efficacy and client engagement with the intervention [53-56], none of these adaptations incorporate the experiences of racial stressors and coping specific to Black youth. As such, considering the higher rate of trauma exposure and the compounding nature of interpersonal and racial trauma, it is necessary to develop strength-based treatments that leverage protective factors specific to Black youth [28,53,57].

Racial Socialization

Racial socialization (RS) is the protective process of transmitting cultural behaviors, attitudes, and values to prepare youth to cope with stressors associated with their ethnic minority status and is associated with positive outcomes, including increased resilience, coping abilities, and decreased problem behaviors and anxiety in Black youth [14,58,59]. There are 6 types of RS messages often represented in the literature, which can be communicated verbally or through modeling relevant behaviors. The most popular socialization messages in the literature are racial barriers, equality, promotion of mistrust, and racial pride [58]. Racial barrier messages prepare youth for instances of racism and discrimination, often by teaching coping mechanisms for dealing with them. Racial equality messages shape children's attitudes and behaviors toward issues of social justice, discrimination, and inclusivity. Promotion of mistrust aims to caution Black children when interacting with other people from different racial backgrounds. Racial pride messages focus on the positives of one's racial group, including heritage, history, culture, and the successes of others with a shared identity. These messages can encourage a sense of community and address experiences with racism by helping youth identify the strengths and positives of their racial group. In addition, parents often share messages related to coping through religion or spirituality, finding social support through extended family involvement, and achievement (such as needing to work twice as hard to excel) [1,10,18,60].

Adaptation of treatments to integrate RS as a culturally relevant tool may provide opportunities to increase the efficacy and sustainability of treatment for Black clients. These messages are critical experiences for racially and ethnically marginalized groups who must prepare to face discrimination [61]. Existing interventions that incorporate RS are promising [50,62,63] but have not yet been applied to trauma-focused treatments such as TF-CBT to improve therapists' self-efficacy, increase client engagement, and directly mitigate the impact of interpersonal and racial trauma for Black youth. There are stand-alone in-person RS interventions [50,64,65]; however, given the benefit of RS in addressing both interpersonal and racial stressors, it is necessary to integrate it into trauma treatments (eg, TF-CBT) for Black youth and do so through evidence-based techniques.

The ADAPT-ITT Model

The ADAPT-ITT (assessment, decision, adaptation, production, topical experts–integration, training, and testing) model [66] is an evidence-based process for adapting interventions to be more efficacious for marginalized communities. The ADAPT-ITT model is conducted in 8 stages: assessment, decision, administration, production, topical experts, integration, training, and testing. Each phase of the ADAPT-ITT model focuses on maintaining the original evidence-based intervention's (EBI's) core elements and theoretical foundations while assessing whether to enhance (eg, provide supplemental materials) or adapt (eg, fundamentally change) aspects of the intervention to better address population-specific needs. The ADAPT-ITT model has been used in many studies, and its repeated success suggests that it is beneficial to use in adapting trauma-focused interventions for racially and ethnically marginalized youth [67-71]. The ADAPT-ITT model provides an optimal framework for clinicians to implement interventions in a culturally sensitive way by calling in population-specific risk and protective factors and ensuring that treatment approaches are most suitable for clients' cultural backgrounds. Using the ADAPT-ITT model allows for the creation of a formal model for clinicians to consider racism and RS for Black youth in TF-CBT.

Objective of This Study

TF-CBT and RS have independently been shown to effectively mitigate the negative consequences of trauma, increase youth resilience, and teach healthy coping mechanisms. However, TF-CBT's lack of systematic consideration and integration of culturally relevant factors (eg, RS techniques) for Black youth and their families may prevent these clients from remaining engaged in and benefiting from treatment. Culturally enhanced treatments may resonate more deeply with Black families and youth by validating cultural identities and normalizing mental health outcomes within these communities. This study acknowledges that Metzger et al [61] were the first to incorporate RS into TF-CBT for Black youth to increase resilience, coping, and communication between youth and their caregivers. Their work has been successfully integrated into a formalized treatment manual [56].

This study builds on the previous work by Metzger et al [56,61] by detailing how the ADAPT-ITT model was used to create a modified application of TF-CBT that integrates RS (TF-CBT-RS) for Black youth and their families and the importance of culturally relevant care for Black clients. The goal and expectation of the adaptation is to boost treatment

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engagement and use, enhance support for clients experiencing culturally relevant issues (such as racial stress), and reduce associated internalizing and externalizing symptoms. In addition, the adaptation aims to bolster training and support for mental health care providers in culturally competent practice, enabling clinicians to more effectively support Black youth in treatment.

Methods

Overview

The ADAPT-ITT model [66] allows for the modification of existing evidence-based treatments by maintaining the integrity of the core elements of a treatment while also addressing and integrating population-specific factors that support the treatment's relevance, acceptability, and sustainability. This process of adapting existing treatments consists of 8 phases. Table 1 summarizes the 8 steps of the ADAPT-ITT model and how fidelity was maintained within the context of this project.

Table 1. ADAPT-ITT (assessment, decision, adaptation, production, topical experts–integration, training, and testing) model steps and significant findings.

Steps	Significant findings
1. Assessment: who will be the primary audience for the EBI[a]?	Black youth are at risk of experiencing compounding forms of trauma. • Culturally relevant practices and strengths are emphasized in addressing the identified trauma in Black youth.
2. Decision: what EBI will be used, and will it be adapted?	TF-CBT[b] was chosen as the therapeutic approach to be adapted and integrated with RS[c]. TF-CBT has not been applied specifically to Black youth and their families. • Racial trauma and RS literature can be combined with cognitive behavioral therapy techniques to result in a reduction of symptoms and adverse outcomes for Black individuals.
3. Administration: what components of the selected EBIs should be adapted?	The core elements of TF-CBT (PRACTICE[d]; psychoeducation and parenting, relaxation, affect identification, cognitive restructuring, in-vivo exposure, conjoint parent-child sessions, and enhancing safety) should be maintained to preserve treatment fidelity.
4. Production: how do you adapt and document adaptations?	RS was integrated into PRACTICE components of TF-CBT to help youth explore their racial identity, process feelings related to racial stressors, address maladaptive behaviors linked to racial stress and trauma, and use proactive, culturally responsive coping strategies.
5. Topical experts: who can assist with adaptation?	Black caregivers and youth with experience in receiving trauma treatment and mental health professionals familiar with TF-CBT were consulted for their input, and their feedback was incorporated into the initial adaptation of TF-CBT.
6. Integration: what is going to be included in the adapted EBI?	Adaptations were made to the application to include culturally specific content, and suggestions were provided for delivering the content through guided text.
7. Training: who needs to be trained?	A 2-day training was conducted by masked for review practice and focused on incorporating self-reflection on experiences, identities, and expectations concerning clinicians' professional roles in treating racial trauma and its symptoms. • Participants learned about and actively engaged with strategies to effectively apply RS in a culturally affirming and validating manner.
8. Testing: was this adaptation successful?	Data were collected on clinician self-efficacy and preliminary client outcomes following TF-CBT-RS[e] training and delivery • Provide an overview of the major findings and the steps that can be taken moving forward as a community.

[a]EBI: evidence-based intervention.

[b]TF-CBT: trauma-focused cognitive behavioral therapy.

[c]RS: racial socialization.

[d]PRACTICE: psychoeducation, relaxation, affect modulation, cognitive coping, trauma narrative and processing, in vivo mastery, conjoint sessions, and enhancing safety.

[e]TF-CBT-RS: trauma-focused cognitive behavioral therapy that integrates racial socialization.

Phase 1 (Assessment): Who Will Be the Primary Audience for the EBI?

Specifically, phase 1 asks researchers to determine the risk and protective processes specific to the target group. The literature identifies Black youth as at risk of experiencing layered and compounding forms of trauma (eg, interpersonal and racial) that need addressing through culturally relevant practices and use of specific cultural strengths (eg, RS). The existing literature shows that Black youth are more likely to be exposed to and experience traumatic events; however, they are 3 times less likely to initiate and complete trauma treatment [19,28,43]. As

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such, there is a need for new strategies to reach this underserved population. The first author conducted previous studies that explored the role of racial discrimination and socialization as risk and resilience factors in Black youth, demonstrating that there may be a benefit to including RS within clinical treatment to address racial stressors [2,61,72-74]. To address the need for treatment components specific to Black youth, the identified target population was trauma-exposed Black youth. Building on this assessment, the next step involved deciding on the most suitable existing intervention to adapt for this population.

Phase 2 (Decision): What EBI Will Be Used, and Will It Be Adapted?

As observed in the literature, incorporating culturally specific risk and protective processes within treatment components contributes to improved treatment engagement, sustainability, and efficacy [4,30,37,43,53,64,65,67,68,75]. Due to its recognized effectiveness and recommendation as a treatment for families and children navigating traumatic experiences, TF-CBT was chosen as the therapeutic approach to be adapted and integrated with RS [20,76]. While TF-CBT is an EBI that is effective in addressing externalizing and internalizing trauma-related outcomes and has been previously adapted for specific populations (eg, Latinx and lesbian, gay, bisexual, transgender, and queer populations [53-55]), it has not been adapted and applied in a culturally appropriate manner for Black youth and their families.

As such, it was decided that TF-CBT-RS would be developed to address the needs identified in phase 1. We combined the literature on trauma, racism, and RS with the techniques used in cognitive behavioral therapies. By integrating RS into TF-CBT, Black youth and their families may experience a reduction in the severity and frequency of symptoms and other adverse outcomes associated with experiencing racial trauma. With the intervention identified, the process moved into determining exactly which components of TF-CBT should be adapted to meet the cultural and clinical needs of the target population.

Phase 3 (Administration): What Components of the Selected EBI Should Be Adapted?

To ensure that the essential mechanisms of change were maintained in the adapted model, researchers ensured fidelity to the original treatment model. Population-specific and necessary culturally specific risk (discrimination) and protective (socialization) mechanisms were applied to each of the PRACTICE components that guide the implementation of TF-CBT. Following the PRACTICE model allows clinicians to support Black clients in gaining the essential psychoeducation and coping skills necessary to later process the discrimination experienced before engaging in important dialogue necessary to restructure their responses to racial stressors to be more value based and proactive [61]. Within the PRACTICE components, RS was operationalized using the 6 most referenced messages in the literature: racial pride, racial barriers, racial equality, achievement, spirituality, and extended family involvement [58]. Table 2 shows how RS was integrated while maintaining fidelity to TF-CBT. These messages were validated through interviews with caregivers and youth that confirmed the relevance of these RS messages to this sample.

RS was integrated into early drafts of the *psychoeducation and parenting* component by providing specific coping strategies and knowledge of discrimination and racial trauma to help youth identify and deal with racial trauma and stressors. Resources were also provided to help caregivers foster a positive sense of racial identity in their Black youth. RS was also integrated to help equip caregivers with the tools to talk about race and racism with the Black youth, educate caregivers on how experiencing racial stressors can impact behavioral outcomes, and identify strategies to help youth build self-esteem. RS was integrated into the *relaxation* component by identifying the cultural messages (eg, “strong Black women don’t ask for help”) and values (the need to work twice as hard as one’s counterparts) that surround the concept of rest and relaxation. For instance, if spirituality was an RS component endorsed by the client, listening to gospel music and prayer were suggested by study participants as possible ways to relax, and *giving thanks* could be used as an exercise in mindfulness. The administration phase allows for suggestions for clients to relax and release their stress in a way that is more accessible and relevant than traditionally taught therapeutic skills.

Within the *affect modulation* component, RS was incorporated to help Black youth identify feelings associated with previous experiences with racial discrimination. For example, youth were guided in scanning their bodies to help them practice attuning themselves to physiological responses to their emotions (described as feelings), such as muscle tension or stomach aches. This provides an opportunity to establish awareness of racial stressors and the psychophysical responses that arise. Integrating RS into the *cognitive coping skills* component helps identify and correct negative, inaccurate, and maladaptive thoughts, emotions, and behaviors following experiences with racial stressors. In this area, youth can be guided to reduce self-blame as a response to racism—such as practicing the thought, “I did not do anything wrong. That person said something racist because that’s their belief, not my *fault*.” Adaptations were also made to provide coping skills toward restructuring clients’ *responses to* racial stressors rather than their *perceptions of* these incidents, as traditional TF-CBT may indicate. This change was because it would be invalidating and inappropriate to imply that a youth’s experience of racism and discrimination is false or not as damaging as it feels to them. Instead, it is more beneficial to ensure that a youth knows that they *did* experience racism and that its effects are real and harmful and encourage control over the situation through proactive and safe responses to the stressor. Specifically, the adaptation to the cognitive coping skills component allows youth to process and role-play proactive (rather than reactive) and value-based techniques in response to hypothetical situations. The *trauma narrative and processing* component integrated RS to support youth in processing their racial trauma–related memories and other symptoms, such as intrusive thoughts, flashbacks, and nightmares. The study team encouraged youth to engage creatively with their experiences of identity and racial stressors. Youth were prompted to express themselves through poetry, music, art, and other outlets to allow for cultural expression and

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autonomy in creating their own story and understanding of themselves. Moreover, integrating RS into this component provides the opportunity for youth to discuss and understand their feelings regarding their racial identity, cultural traditions, and values and discuss family values and beliefs with regard to responding to racial stressors.

The research team also integrated RS into the *in vivo mastery* component. With the integration of RS, in vivo mastery can help Black youth overcome and address any avoidant behaviors that may have emerged as a response to experiencing racial stressors. In phase 3, developed clinical scripts were designed to use RS by including messages focused on racial pride, spirituality and achievement, traditional forms of social support, and racial barriers and incorporating relevant vocabulary (such as naming racist comments as microaggressions) to help validate and empower youth to approach rather than avoid potentially beneficial situations, experiences, people, and relationships. The *conjointchild-parent sessions* component incorporated RS to assist in fostering an environment where youth can openly communicate their racial encounters and experiences of racial stressors with their caregivers. This provides youth and caregivers with a chance to discuss and apply RS messages together and for youth to share successes of RS activities with their caregivers. The final component, *enhancing safety*, used RS to develop culturally responsive safety plans. Families were encouraged to have an open dialogue about potential future racial stressors, for example, how to respond when stopped by police officers, being followed in a store, and being called a racial slur. Incorporating RS into the enhancing safety component may help Black youth and their caregivers identify stressful and potentially harmful situations and prepare them with proactive ways to respond to future racial stressors, such as harassment and microaggressions. After operationalizing RS within TF-CBT's structure, the next task was to formally document these changes and create a version of the treatment that could be shared, reviewed, and refined.

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Table 2. Racial socialization (RS) integration in trauma-focused cognitive behavioral therapy (TF-CBT) via psychoeducation, relaxation, affect modulation, cognitive coping, trauma narrative and processing, in vivo mastery, conjoint sessions, and enhancing safety (PRACTICE) stages.

PRACTICE component	TF-CBT focus	Integrated racial socialization messages
PRAC: coping skills		
Psychoeducation and parenting	Inform clients and caregivers about rates of adverse childhood experiences and trauma, discuss common reactions and symptoms after exposure, and review the structure and process of engaging with TF-CBT	Incorporate the definition of racial trauma and explore how RS messages impact racial identity formation; emphasis on *racial pride* and *racial barrier* messages
Relaxation	Provide the client with necessary skills and strategies, depending on the environment and context, to engage with relaxation and destressing	Identify messages of having to work harder (*racial achievement*) and how clients should both work twice as hard and rest or restore twice as much; incorporate messages of finding support in *spirituality* as relevant or necessary
Affective expression and modulation	Identify the feelings and reactions as they emerge during and after exposure to stressors in clients; develop the vocabulary necessary to identify, discuss, and regulate these experiences as appropriate for the context	Revisit common reactions and physical responses (eg, feelings) to racism and discrimination; identify emotions that are tied to previous exposures; and provide tools to recognize racial stressors as they are happening, including how the client is responding in the moment
Cognitive coping	Discuss the link between thoughts, feelings, and behaviors (the cognitive triangle) and use client reactions as a real-world example; explore how clients can discuss this link with caregivers and their support system	Restructure common reactions and practice proactive, value-based responses to discrimination; challenge internalized racism that the client may experience or accept (eg, colorism)
T: trauma narrative and processing		
Trauma narration and processing	Explore distressing trauma-related memories to identify unhelpful or inaccurate cognitions that need to be processed and reframed; reframe by validating the experience and putting the trauma exposure into context (future hopes and the good outside of that moment); invite caregivers to discuss and share in this narrative as appropriate or comfortable	In addition to standard trauma narratives, incorporate creative narrative exercises rooted in racial identity (poems, music, art, and photography) to encourage engagement, expression, and healing in ways that feel most relevant to the client; include discussion of clients' experiences with racism, RS, and identity development
ICE: treatment consolidation and closure		
In vivo exposure	Separate harmless reminders or triggers of the trauma from the learned fear and anxiety response; practice exposure to trauma-related memories and cues to reduce avoidance of these harmless triggers	Practice with clients and caregivers how to respond to discrimination and stressors, such as role-playing what to say and do in the face of microaggressions; incorporate in-vivo exposures to RS messages and experiences, for example, going to a Black history museum
Conjoint sessions	Invite caregivers into the space to share praise, support, and love with the client; encourage open and honest discussion between caregiver and child	Revisit racial pride and identity affirmation messaging during conjoint sessions with caregivers to encourage the discussion of race; use RS to identify and validate experiences with racial stressors and encourage coping
Enhancing safety	Provide clients and caregivers with psychoeducation about revictimization; develop a safety plan with strategies to identify unsafe situations, people, and places, and how to respond to these events; role-play responses to ensure clients and caregivers feel equipped to use the safety plan	Provide resources, scripts, and plans for navigating racial stressors in ways that maximize safety (physical and emotional) to the client, for example, discuss what to do when stopped by police officers or if someone weaponizes the N-word; provide resources for caregivers and youth to continue engaging in RS

Phase 4 (Production): How Does One Adapt an Intervention and Document Adaptations?

In phase 4, the lead author produced the next version of the existing treatment to maintain fidelity to the TF-CBT model and integrate RS to better address the needs of Black youth. The integration of RS into TF-CBT was documented, and the fidelity checklist outlined by Metzger et al [61] in 2021 was used.

In phases 1 to 4, RS was integrated into TF-CBT by providing a framework to address the unique needs and challenges of Black youth who have been exposed to trauma, particularly racial trauma. TF-CBT-RS can assist clinicians and youth in identifying and modifying maladaptive thoughts, feelings, and behavioral responses associated with the experience of racial trauma. In addition, incorporating RS can enable youth to explore and make sense of their racial identity and address their thoughts regarding their experiences with racial stressors. This was allowed for through the production of the foundational manuscript, "Healing Interpersonal and Racial Trauma" [61]. With a documented adaptation in hand, the project was ready to seek input from experts and those with lived experience to ensure that the intervention was both clinically sound and culturally relevant.

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Ethical Considerations

All study procedures received institutional review board approval (Pro00062769) from the University of Georgia, a Research I institution in the Southeastern United States and were funded by the National Institute of Mental Health from 2016 to 2019. Caregivers and youth were contacted through clinician referrals or flyers, and consent or assent was obtained before participation. Youth, caregivers, and clinicians were compensated for their time, and all identifying information was kept confidential and stored in password-protected files.

Results

Phase 5: Topical Experts

To ensure the cultural and clinical relevance of the materials, topical experts were defined as individuals from communities of interest and professionals familiar with the treatment. To aid in the relevance and sustainability of the adapted treatment, we sought out the opinions of individuals who had the lived experience of receiving and delivering trauma treatment (content experts). Specifically, we conducted interviews with 10 Black caregivers (eg, supportive and nonoffending guardians, biological parents, or foster parents of youth) and 12 Black youths (aged 12-18 years) who had previously engaged in TF-CBT due to experiences with interpersonal trauma. We also organized and facilitated focus groups with 15 diverse Master's- and doctoral-level clinicians familiar with and knowledgeable about the TF-CBT framework and who provided services to Black youth and their caregivers.

Participants were recruited through community-based organizations (ie, children's advocacy centers) with whom the lead author had ongoing partnerships. Eligibility criteria for caregivers and youth included identifying as Black or African American, having completed or partially completed TF-CBT, and willingness to provide feedback on the treatment adaptation. Caregiver and youth interviews were conducted via Zoom (Zoom Video Communications) and audio recorded. Clinicians were invited to participate in in-person focus groups after indicating interest and eligibility (having been previously trained in TF-CBT and completed at least 3 TF-CBT cases). Recordings were transcribed using Otter.ai (Otter.ai Inc) [25] and uploaded into NVivo (QSR International) [6] for qualitative analysis.

To complete this phase, youth, caregiver, and clinician participants viewed the initial treatment application and gave feedback on how feasible and acceptable implementation might be in a clinical setting. These experts reviewed the TF-CBT-RS manual for content accuracy, developmental appropriateness, and cultural relevance. As context experts, caregivers and youth provided feedback on experiences with TF-CBT and how it could have been improved (eg, adding consideration of racial trauma into progressive muscle relaxation exercises, making images depict Black youth, and restructuring responses to racism rather than reactions to racism). Furthermore, caregivers described their experiences with RS and racial stressors and how they mapped onto each treatment component. Thematic analysis was used to identify patterns in the feedback guided by the 6-phase framework by Braun and Clarke [77]. Two coders independently reviewed the transcripts to develop an initial codebook, and discrepancies were resolved through discussion with a third team member. Emergent themes related to feasibility, cultural relevance, and needed adaptations were synthesized and mapped onto specific TF-CBT components for integration into revisions of the materials [61], and this iterative process enhanced the clinical applicability and cultural sensitivity of the intervention. In addition, the first author worked with content experts in TF-CBT, cognitive behavioral therapy, and RS to incorporate culturally relevant components while maintaining treatment fidelity. These experts reviewed drafts of the initial manuscript and fidelity checklist and contributed to developing the revised intervention. With expert feedback from both lived experience and professional perspectives, the adaptation process then moved into integrating these recommendations into the applied intervention in a systematic and sustainable way.

Phase 6 (Integration): What Is Going to Be Included in the Applied EBI?

To complete this phase, the first author created a racial trauma task force at a Research I university in the Southeastern United States. This task force consisted of the lead author, 1 doctoral-level licensed clinical faculty member, 3 laboratory staff, 11 graduate students, and 10 members enrolled in undergraduate social science programs. Over 4 months, the graduate students met weekly to receive formal training in TF-CBT. During these weekly meetings, graduate students and the first author discussed RS and racial trauma. They brainstormed how related skills and resources could be integrated into each component of TF-CBT (eg, psychoeducation, relaxation, and cognitive restructuring) based on the findings of the previously collected data with context experts (youth and caregiver clients) in phase 5 (refer to Table 2 for integration).

On the basis of the data from content experts, the task force and first author applied recommendations into a translational material that guided both clinicians and clients in the adapted treatment. The resource, titled *The C.A.R.E. Package for Racial Healing*, is a psychoeducation and skill-based workbook detailing the RS-adapted psychoeducation, relaxation, affect modulation, and cognitive coping components of TF-CBT, which helped guide the final application of TF-CBT-RS. While a resource primarily for clinicians and their clients, this workbook can also be more broadly disseminated to be used by Black youth and their caregivers outside of treatment to encourage healing. To create this resource, the task force collaborated with the first author to incorporate the culturally specific content suggested by Black youth and their caregivers, which included relevant examples and exercises for clients to use under the direction of clinicians and other trusted adults who can provide emotional and tangible support. In addition to providing suggestions on how to effectively use coping strategies via guided text in the *C.A.R.E. Package* workbook, members of the task force worked with a graphic designer to include culturally relevant images and activities in the workbook. Once integration was complete, the next step was to ensure that the clinicians delivering TF-CBT-RS were properly trained to maintain fidelity while effectively engaging with clients in a culturally responsive way.

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Phase 7 (Training): Who Needs to Be Trained?

In 2022 to 2023, the lead author led a 2-day training followed by 12 sessions of ongoing consultation for a Substance Abuse and Mental Health Services Administration–funded learning community composed of 28 practitioners and supervisors currently delivering child-and-family treatment at 13 community-based organizations nationwide. Clinician training focused on understanding how interpersonal and racial stress and trauma impact the lives of Black youth; examining extensive research on the barriers to and facilitators of service use for Black youth, families, and Black adults; emphasizing the protective role of RS in shaping Black youth's behavioral and mental health outcomes; and making culturally informed decisions on engagement, assessment, and treatment of Black youth. Clinicians were provided with resources and information on interpersonal stressors, racial trauma, and using RS as a culturally specific coping strategy. During these learning community calls, the first author guided clinical practitioners and clinical supervisors working with Black youth and caregivers on the integration of RS into the PRACTICE components of TF-CBT. Clinicians raised questions about incorporating skill-based activities such as role-playing, demonstrations, examples, and client discussions, allowing them to connect their lived experiences with training and further their ability to integrate RS into their delivery of TF-CBT.

In addition, the 2-day training and subsequent sessions provided guidance and opportunities to practice leveraging one's identity to establish rapport and trust with Black youth, ultimately empowering clinicians to serve as effective allies within the therapeutic space. The training also focused on preparing mental health care providers with the skills and knowledge to successfully carry out the adapted treatment using role-plays, demonstrations, scripts, and ongoing consultation. The training focused on effective techniques and available resources for implementing RS as a cognitive behavioral intervention in a culturally supportive and affirming way for Black youth, families, and adults healing from interpersonal and racial stress and trauma. A significant advancement to support training more culturally competent clinicians is the integration of RS training on the TF-CBT website, which provides national certification for therapists. The manual, which has been widely used by clinicians since its development, is available for download online and offers strategies for implementing TF-CBT and RS (TF-CBT-RS) [56] for Black youth aged 3 to 18 years and their caregivers who experience stress or trauma related to their race or other significant trauma. Once training was completed and clinicians were equipped with the adapted approach, the logical final phase was to test the intervention's feasibility, clinician efficacy, and preliminary outcomes in real-world practice.

Phase 8 (Testing): Was the Application Successful?

The first author conducted a series of internet-based learning community sessions focused on TF-CBT-RS over the course of a year. The first author and collaborators (treatment developers Judith Cohen and Anthony Mannarino) gained feedback from practitioners and clinical supervisors who participated in the learning community by delivering a survey following the completion of the learning community to assess feasibility in delivery, therapist efficacy, and the accessibility of the language of the adapted intervention. During the *testing* phase, data were also collected to assess youth outcomes and determine whether TF-CBT-RS successfully reduced youth PTSD symptoms and other mental health problems. Preliminary evidence revealed promising results, including increased clinician efficacy, treatment engagement and use, and client perceptions of support and reduced internalizing and externalizing symptoms [56]. The next steps of testing include conducting a more robust randomized controlled trial to assess the effectiveness of the adapted model in comparison to TF-CBT as typically delivered.

Discussion

Expected Findings

This paper describes the process of using the ADAPT-ITT model to integrate RS into TF-CBT to improve treatment engagement and mental health outcomes for Black youth and their families. Although TF-CBT is an effective, evidence-based treatment for trauma-exposed youth aged 3 to 18 years, it does not adequately address the unique impact of racial stressors on Black youth and their families. This paper outlines how the ADAPT-ITT model was used to create TF-CBT-RS, meeting the need for culturally relevant applications of trauma treatment. Such integration and development has the potential to significantly transform the efficacy and sustainability of healing interventions by increasing relevance to, access for, and engagement and retention of Black clients. By using a culturally adapted framework, we propose that TF-CBT-RS will not only increase access for underserved youth but also provide a more comprehensive focus on addressing stressors associated with the lived experiences of Black youth and their families. This work integrates evidence-based tools for mental health treatment—TF-CBT and RS—using a well-validated approach (the ADAPT-ITT model) to address critical areas of risk specific to Black youth. RS is an established cultural strength and presents the opportunity to enhance the utility and delivery of TF-CBT for Black youth and their families who have experienced racial stress and trauma. To address and identify the ways in which racial stress impacts the trauma development of Black youth, it is imperative to research and incorporate the current barriers to and facilitators of such service use for Black youth and their families [56].

During the final phases of development, the first author provided training to multidisciplinary practitioners within a learning community that addressed how to integrate RS strategies into TF-CBT to improve mental health and wellness outcomes. These clinicians received ongoing consultation on the delivery of clinical cases with Black youth who received the integrated treatment and demonstrated promising results. Preliminary findings support the use of RS in TF-CBT, suggesting that this application may improve clinician efficacy and the competence of culturally relevant tools, bolster client perceptions of support, and increase engagement with treatment [50,62-65]. These outcomes also back the use of the ADAPT-ITT model for the adaptation of evidence-based practices for population-specific needs [66-71].

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Nonetheless, there remains a need for additional literature to explore how integrating RS into trauma-focused care can improve clinician efficacy, increase client engagement, and improve outcomes related to chronic exposure to racism and discrimination. Larger randomized controlled trials are needed to rigorously compare TF-CBT-RS with standard TF-CBT, examining not only symptom reduction but also engagement, retention, training and implementation, and satisfaction across diverse clinical and community settings.

Limitations

Although an evidence-based approach was used in making this treatment adaptation and was shown to be beneficial to the participants in the learning community described herein, there are some limitations to consider pertaining to this application of TF-CBT. Clinicians of different experience levels and training backgrounds, as well as youth of varying ages, geographic locations, and cultural identities and their families, may have different perspectives and experiences from those of the participants included in this study. It is important to consider the complexities of Black Americans' intersecting identities, cultural context, and sociopolitical positioning when assessing feasibility and sustainability. In addition, Black youth who have experienced racial trauma and other forms of trauma, such as sexual abuse, may also respond differently to the adapted treatment. While RS psychoeducation can be modified with examples more relevant to the client themselves, this variability in practice requires oversight to determine its impact on the sustainability and outcomes of the adapted manual—especially as intersectionality (such as lesbian, gay, bisexual, transgender, or queer identity; religion; or immigration status) may influence experience of discrimination and related symptoms, perceptions of support, and the acceptability of the application.

Conclusions

This study is the first to apply the ADAPT-ITT model to highlight the additive contribution of RS to manualized trauma treatment for youth through a cultural asset lens. The development of more culturally inclusive research in established trauma treatments, greater accessibility to care and facilitation of racial trauma treatment, and more dialogue on the effects of racism in Black communities is a promising future for evidence-based treatment. Integrating RS into prevention and intervention efforts can equip Black youth with the necessary skills to heal from experiences with pervasive racial stressors, which reinforces the need to include cultural assets such as RS in clinical practice. Continued testing of the TF-CBT-RS model can help refine the quality of research and further the value of this work for underserved, ethnically minoritized populations, particularly Black youth and their families.

Conflicts of Interest

None declared.

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Abbreviations

ADAPT-ITT: assessment, decision, adaptation, production, topical experts–integration, training, and testing
EBI: evidence-based intervention
PRACTICE: psychoeducation, relaxation, affect modulation, cognitive coping, trauma narrative and processing, in vivo mastery, conjoint sessions, and enhancing safety
PTSD: posttraumatic stress disorder

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RS: racial socialization
TF-CBT: trauma-focused cognitive behavioral therapy
TF-CBT-RS: trauma-focused cognitive behavioral therapy that integrates racial socialization

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Protocol

Creating Compassionate Spaces for End-of-Life Care for Older People Experiencing Homelessness: Protocol for an Environmental Assessment of Hospice Settings

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Abstract

Background: With current data supporting an increasing population of older people experiencing homelessness (OPEH) requiring unique spatial and placemaking considerations in end-of-life care, understanding the environmental factors that influence their well-being is crucial.

Objective: This protocol paper provides a comprehensive overview for evaluating hospice environments tailored to the needs of OPEH.

Methods: The Aging in the Right Place study aims to address this gap by developing and implementing the Aging in the Right Place-Hospice Environmental Assessment Protocol (AIRP-HEAP) and AIRP-HEAP secondary observation tools. The AIRP-HEAP tool evaluates the built and natural environment within hospice settings. Adaptations were made to ensure alignment with the unique needs of OPEH, such as reconceptualizing spiritual care and expanding the definition of family accommodation. Additionally, the AIRP-HEAP secondary observation tool supplements this by capturing contextual data on the surrounding neighborhood of the hospice site, providing a holistic understanding.

Results: Data were collected at Maggie's Lodge hospice between November and December 2024 using the AIRP-HEAP and AIRP-HEAP secondary observation tools. The dataset is currently being cleaned, with analysis planned between May and December 2025. The anticipated results will highlight the importance of considering environmental factors in hospice environments and inform recommendations to improve end-of-life care for OPEH.

Conclusions: Data collected using these audit tools can guide environmental modifications in hospice settings to facilitate aging and end-of-life care in the right place. Thus, this protocol paper aims to promote the adoption of best practices in hospice design to better support this marginalized population.

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KEYWORDS

end-of-life; homelessness; hospice; older adults; protocol

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Introduction

Homelessness is a growing social problem in Canada, especially among older adults. According to a point-in-time survey, which provides a glimpse into the minimum number of people experiencing homelessness in a 24-hour period, 4821 people were experiencing homelessness in Vancouver [1]. This number marks a stark 32% increase from the point-in-time survey conducted in 2020 [1]. The proportion of older people experiencing homelessness (OPEH) has also risen, comprising 22% of the homeless population [2]. Safe and stable housing is instrumental in facilitating the physical, mental, and emotional well-being of older adults [3,4]. As the homeless population ages, and as the aging population experiences greater housing insecurity, their demands on medical services, home care, and end-of-life care increase [5]. Research on the Vancouver homeless population reveals the population experiences higher rates of premature death and physical illness [6], while broader research on homelessness demonstrates increased rates of cancer [7] and chronic illnesses [8] compared to the housed population. Moreover, individuals experiencing homelessness often require access to health care services 10-20 years earlier than the housed population due to frailty and age-related conditions [9].

Despite an increased need for palliative care, OPEH face barriers not experienced by the general population. The built environment has been demonstrated to include or exclude OPEH from palliative care. For example, many community-based palliative care programs often deny care to OPEH because the services deem them as not having a physical space to provide medical care [10,11], or because the buildings or neighborhoods they live in are deemed unsafe [11,12]. The built environment also facilitates or hinders OPEH access to institutional palliative care programs. Physical and aesthetic features of these built environments signal to OPEH their acceptance or rejection into the space [13]. Similarly, institutional environments mirroring Indian residential schools or Indian hospitals indicate to Indigenous people that the space is unsafe or traumatic [12,13]. The built environment plays a key role in meeting the end-of-life needs of OPEH.

The concept of “end-of-life care in the right place” emphasizes the importance of providing appropriate housing that aligns with individuals’ unique needs and lifestyles as they approach the end of their lives. This concept holds particular importance for OPEH, a demographic whose palliative needs are shaped by experiences of marginalization, colonialism, and trauma [14]. Conceptualizations of key palliative care tenets, such as safety and autonomy, are shaped differently within this community. Discrimination and abuse experienced when accessing health care greatly influence the meaning of safety within a health institution [13,14]. Similarly, higher rates of substance use and mental illness translate into unique spatial and placemaking needs for OPEH at end-of-life [12,13].

Within the Canadian landscape of end-of-life care, hospice care plays an essential role. The term “hospice” can refer to either a philosophy of care or a physical care facility providing end-of-life care to people. The former definition expresses a philosophy of care that offers medical, social, and emotional support at the end of life, which can be provided at home or within a care facility [15]. The latter definition represents an integral space-based approach where a hospice philosophy is used to address the end-of-life care needs of individuals within a purpose-built facility. Given the barriers to palliative care due to the built environment, specialized hospice facilities for OPEH hold the potential to address this population’s end-of-life care needs.

The spatial understanding of hospices fits with the historical development of the concept, dating back to physical buildings that provided care to sick and dying individuals [16]. Understanding hospices as physical facilities for end-of-life care allows us to examine how their physical make-up either facilitates or inhibits effective care for individuals at the end of life. This understanding is crucial for enhancing our knowledge of how the built environment influences end-of-life care in the right place. For OPEH, the built environment of hospice facilities is especially significant, as research underscores the critical role that space plays in their access to end-of-life care [10,17]. Environmental audits (also referred to as environmental observations or assessments) are useful in evaluating the built environment and can identify ways to improve the environment and placemaking characteristics in different types of housing, including hospice settings. Canham and colleagues [3] reported findings from an environmental audit of a temporary housing program for OPEH, which highlighted the integral role of spatial and placemaking aspects to aging in the right place. In this study, we extend this previous research by applying a therapeutic goals lens [18] to evaluate the extent to which spatial and placemaking factors (eg, spatial configuration, design and layout, connections to nature, access, and scope of personalization) can promote comfort, privacy, sociability, control, dignity, and spiritual expression in hospice setting to understand whether these settings are appropriate for aging and end-of-life care in the right place for OPEH. To examine the built environment of this specialized hospice care (Maggie’s Lodge), we developed an Aging in the Right Place-Hospice Environmental Assessment Protocol (AIRP-HEAP) tool.

End-of-life in the right place is an extension of the Aging in the Right Place (AIRP) project, which emphasizes the significance of secure and optimal housing that assists an individual’s unique vulnerabilities [12]. The concept of AIRP acknowledges that what constitutes the right place for an older adult to age will vary from person to person [19]. Canham et al [3] devised an AIRP project framework drawing on insights from experts in aging, homelessness, and housing services, as well as older adults with lived experience of homelessness. The AIRP project’s framework comprises 6 subcategories, which are indicators for aging in the right place for OPEH. These subcategories are (1) built environment of the housing unit and surrounding neighborhoods, (2) off-site and on-site health and social services and resources, (3) social integration, (4) stability and affordability of space, (5) emotional place attachment, and (6) broader political and economic context. This protocol paper’s focus is on the built environment audit, thus the first indicator of the framework, which is the built environment of the housing unit and the surrounding neighborhoods. An unsupportive built environment can have damaging effects on the quality of life

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of OPEH. Given that this paper is based on the development of an environment audit tool, the built environment identifies notable features of the building, such as amenity rooms, green spaces, security cameras, etc [3]. The AIRP project documents and evaluates "promising practices" of shelter and housing that support aging in the right place for OPEH. Promising practices are understood as novel models that have not gone through rigorous evaluation but hold the promise of supporting aging in the right place for OPEH [18]. One such promising practice for the Vancouver site of the AIRP project is Maggie's Lodge, a 6-bed hospice with a home-like setting and 24-hour nursing care embedded in a socioeconomically marginalized neighborhood in Vancouver, and the only hospice in British Columbia (and one of a select few in Canada) with a mandate to provide end-of-life care for OPEH [18].

Methods

Audit Tool Development

The AIRP-HEAP tool is an adapted version of the Hospice Environmental Assessment Protocol (HEAP) tool developed by Kader [20] as part of her doctoral dissertation. The HEAP tool was developed following the conceptual framework of the Professional Environmental Assessment Protocol (PEAP), a widely recognized, evidence-based tool for evaluating the quality and therapeutic potential of long-term care and dementia care environments [21,22]. The HEAP tool was developed as a standardized method for evaluating whether the spatial and placemaking characteristics of hospice buildings support the following 11 therapeutic goals: (1) continuity of self, (2) access to nature, (3) privacy, (4) social interaction, (5) safety and security, (6) autonomy, (7) stimulation and sensory therapies, (8) spiritual care, (9) family accommodation, (10) support after death, and (11) support for staff [20] (see Textbox 1 for definitions of each goal). Each goal includes several design objectives and subobjectives that operationalize the respective goal, and each objective includes specific environmental items that are observable within the hospice environment, totaling 295 items. For example, the therapeutic goal of "continuity of self" has the following two design objectives: (1) creating a noninstitutional environment or home-like environment and (2) scope for personalization, which each have specific environmental items. The "scope for personalization" objective includes wall shelves present to display personal belongings, and adequate space in individual rooms is provided to bring personal belongings. We adapted these 11 therapeutic goals for the AIRP-HEAP tool to be conceptually linked to domains within the AIRP project's framework [3]. The AIRP project's framework was developed to provide a practical conceptualization of 6 indicators that contribute to aging in the right place for OPEH, and the AIRP-HEAP tool domain was based on this framework [3]. Based on this framework, the AIRP-HEAP tool domains are (1) built and natural environment; (2) housing access and home modification; (3) emotional place attachment; (4) social support, participation, and inclusion; and (5) safety and security. The synergy between the AIRP framework's concepts and the therapeutic goals of the AIRP-HEAP tool helps to ground the environmental characteristics of hospice sites within the conceptual discussion of aging and end-of-life care in the right place. Each audit domain is intentionally structured to theoretically align with the AIRP framework, as illustrated in Textbox 2. This bridging of theory and measurement allows the audit to focus on the environmental elements that support the distinct needs and vulnerabilities of older adults in the hospice setting.

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Textbox 1. Eleven therapeutic goals of the Hospice Environmental Assessment Protocol tool.

Provide continuity of self

- Environmental characteristics that help preserve or support patients' past activities, preferences, and awareness

Provide access to nature

- Environmental characteristics that provide opportunities for visual and physical access to nature

Provide privacy

- Environmental characteristics that facilitate patients' choices in various levels of privacy through regulation of visual and auditory stimuli

Facilitate social interaction

- Environmental characteristics that facilitate and enable meaningful interaction between patients with staff, their family, and other patients

Maximize safety and security

- Environmental characteristics that maximize safety and security of patients, staff, and families

Provide autonomy

- Environmental characteristics that enable patients to exercise choice and personal preference about their environment and everyday life

Regulate stimulation and support sensory therapies

- Environmental characteristics that contribute to an appropriate quantity and quality of sensory experience, and support sensory therapies (palliative therapies)

Provide spiritual care

- Environmental characteristics that facilitate opportunities for patients' spiritual care; religious, philosophical, and existential or personal beliefs, values, practices, and preferences

Provide family accommodation

- Environmental characteristics that facilitate patients' family accommodation and support control, functional independence, comfort, privacy, recreation, and spiritual care

Provide support after death

- Environmental characteristics that support care and dignity for patients and their families during the moment of death, body removal, bereavement, and remembrance

Maximize support for staff

- Environmental characteristics that support staff (care providers) for better communication, observation, efficiency, satisfaction, and well-being

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Textbox 2. Link between the Aging in the Right Place conceptual indicators and the Aging in the Right Place-Hospice Environmental Assessment Protocol tool therapeutic goals.

Built and natural environment

- Goal 1: provision of access to outside view and nature
- Goal 2: regulate stimulation and support sensory therapies

Housing access and home modification

- Goal 3: continuity of self
- Goal 4: culturally appropriate, relevant, and supportive spiritual care

Emotional place attachment

- Goal 5: provision of privacy
- Goal 6: provision of autonomy

Social support, participation, and inclusion

- Goal 7: facilitate social interaction
- Goal 8: accommodation for loved ones
- Goal 9: support after death
- Goal 10: maximize support for staff

Safety and Security

- Goal 11: maximizing safety and security

Audit Tool Revision

The AIRP-HEAP audit tool is designed to collect data on the presence or absence of environmental features with the options: "Yes," "No," or "N/A." According to Kader [20], when a majority of these items are present in a hospice setting, it suggests that the therapeutic goals are being achieved. For this study, Kader's original HEAP tool [20] was revised to better align with the needs of AIRP study participants, as the original tool was initially designed to evaluate hospice sites for the general population. With input from relevant partners, the team, consisting of the principal investigators and master's students, made several adaptations to Kader's [20] tool to include considerations for the unique needs of OPEH in hospice. For example, the goal "spiritual care" was reconceptualized as "culturally appropriate, relevant, and supportive spiritual care" to align with the needs of the Indigenous population, who are overrepresented in homeless counts in Metro Vancouver [1] and elsewhere in Canada [23]. In addition, the definition of "family accommodation" was expanded from "family members" to "loved ones" to represent the diverse support networks of OPEH who receive care and support from friends and close nonkin loved ones [24]. To adopt a less biomedical approach, we replaced "patient" and "nurse" with "staff," "individuals," and "people." Furthermore, we added an open-ended comment section for each goal to allow auditors to provide detailed notes for additional context as needed.

While the AIRP-HEAP tool captures data about the indoor space of hospice sites, a separate, complementary tool, the AIRP-HEAP secondary observation tool, is used to capture contextual data on the neighborhood surrounding the hospice site. The AIRP-HEAP secondary observation tool was adapted from the qualitative observation section of the Stakeholders Walkability/Wheelability Audit in Neighborhoods (SWAN) tool [25], which is a user-led audit tool that evaluates the environmental barriers to walkability and wheelability of neighborhoods for diverse older adults and persons with disabilities. The AIRP-HEAP secondary observation tool consists of 6 open-ended questions about land use, area characteristics, quality of public space and amenities, feelings of safety, travelling on foot or wheeling, and overall traffic volume, speed, and noise.

Data Collection

The 2 trained master's-level research assistants will independently audit the hospice sites using the AIRP-HEAP and AIRP-HEAP secondary observation tool. The data collection will take around 2 hours to complete. The audit data will be subsequently exported and organized into a Microsoft Excel file, separated by hospice site for analysis. The raw data will be checked to identify blank entries. If blank entries are identified, they will be discussed with the research assistant who conducted the audit to identify the reason and will be subsequently addressed. Given that 2 research assistants will independently audit each site, raters' answers will be compared to determine if each response is the same ("=TRUE") or different ("=FALSE"). The discrepancies will be identified and discussed to understand the reason behind the differences, which will then be resolved by consensus. The final data used for analysis will be a consensus of answers between both research assistants. The "N/A" responses will be omitted from scoring due to their lack of applicability. For instance, if the primary question (eg, room present to accommodate family and loved ones) is answered "No," then the subquestions (eg, about the

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size of that room) would be considered not applicable ("N/A"). Qualitative data collected with the AIRP-HEAP secondary observation tool will be imported into NVivo (version 14; Lumivero) [26] for analysis.

Data Analysis

After a consensus is reached on the presence and absence ratings for each item ("Yes" and "No"), the data will be converted into quantitative scores (Yes=1; No=0). Quantitative data will be summed, and a total score (%) for each subobjective will be calculated. A 5-level Likert scale will be created to rate each design objective and follow a scoring system where 0%-20%="Unusually poor," 21%-40%="Poor," 41%-60%="Moderate," 61%-80%="Strong," and 81%-100%="Exceptional." An overall goal score will not be calculated, as each goal has differing design objectives and subobjectives, thus having inequivalent denominators, which would result in an unbalanced interpretation of the data. Therefore, scoring and interpretation will be performed based on the design objectives within each therapeutic goal. Using NVivo (version 14), the qualitative AIRP-HEAP secondary observation data will be coded line-by-line and subsequently collated to form conceptual categories. Two or more trained research assistants will code the qualitative data to ensure rigor and reach consensus. This will initiate the development of a codebook for the AIRP-HEAP secondary observation data that will be derived from the AIRP theoretical framework, which consists of the 6 indicators of aging in the right place. Coders will meet regularly with the principal investigator to discuss any discrepancies or challenges that arise during the coding process to come to a consensus. Coders will conclude coding when no new themes arise and thematic saturation has been reached.

This protocol is reported in accordance with the Consolidated Criteria for Reporting Qualitative Research (COREQ) checklist to improve transparency, ensure full alignment with qualitative reporting standards, and facilitate the peer-review process. A completed COREQ checklist is provided in Multimedia Appendix 1, where each criterion has been addressed in the manuscript.

Significance Score Versus Total Score

Within the AIRP-HEAP tool, certain items were noted as "significant" design objectives based on Kader's [20] original HEAP tool. The significance of items was determined through literature review, expert consultation, and case evidence [20]. For example, some criteria, such as private rooms, are significant and must achieve an optimal level of environmental quality. These are typically well-established, appearing across all 3 phases of data collection or consistently in case studies. Other criteria serve as optional best practices, noted by a few experts or present in select case studies, and can improve overall scores. Some considerations address building layout (eg, distribution of social spaces), while others concern design quality (eg, use of natural materials like wood and stone). Because each criterion is unique, evaluation patterns vary and depend on the nature of the design feature. To further confirm the significance of these items for aging and end-of-life care in the right place for OPEH, we performed an in-depth review of relevant literature.

In Multimedia Appendix 2, the values under "Significant score" will factor in the weight of these significant scores (as a percentage), while the values under "Total score" will consider all items without accounting for significance (as a percentage). "Significant score" will be calculated by dividing the number of significant objectives that are marked present at the hospice site by the total number of significant objectives as labeled in the HEAP tool. This score will allow us to focus only on those characteristics of the hospice that have broader implications (eg, are mandatory) for aging and end-of-life care in the right place for OPEH. "Total score" will be calculated by dividing the number of objectives that are marked present at the hospice site by the total number of objectives, including the significant objectives. This score will allow us to calculate the overall rating of the hospice site based on the Likert scale, and comparisons between hospice sites will mainly be based on this score. Comparing the "Significant score" and "Total score" provides a comprehensive assessment of the quality of the built environment at the hospice sites.

Reliability and Validity of the Tool

The HEAP was developed following the conceptual framework of PEAP, which is one of the most widely used environmental evaluation tools. Early conceptual work by Weisman [21] and later scholarship on person-centered environmental assessment [22] positioned the PEAP as a framework for understanding how the built environment influences residents' well-being and daily function. Its reliability has been demonstrated through strong interrater agreement and consistent scoring across trained evaluators [27,28]. The tool's validity is well supported. Its content aligns with key therapeutic domains, such as safety, comfort, accessibility, social engagement, and cognitive support, while construct validity has been confirmed by associations between PEAP scores and resident outcomes, including functional performance, agitation reduction, and overall satisfaction [29]. More recently, related research has expanded the field of environmental evaluation, with tools such as the Environmental Audit Screening Evaluation further validating evidence-based design approaches [30] and contemporary reviews emphasizing the enduring value of person-centered frameworks for dementia care [31]. Collectively, these studies confirm that HEAP remains a reliable and valid method for guiding design evaluation and improvement in long-term care and dementia-supportive environments.

Ethical Considerations

The protocol for AIRP under the title "Aging in the Right Place: Building Capacity for Promising Practices that Support Older People Experiencing Homelessness in Montreal, Calgary, and Vancouver" was approved by the University of British Columbia (UBC) Rise system through the UBC and Simon Fraser University Research Ethics Board at Simon Fraser University (H24-01268), McGill University (20-09-008), and the University of Calgary (REB20-1229) ethics boards. All study sites provided informed consent.

Results

The results based on the findings will contribute to the understanding of the significance and influence of environmental

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factors in the end-of-life care of hospice residents with experiences of homelessness. Data collection using the AIRP-HEAP and AIRP-HEAP secondary observation tools was conducted at Maggie's Lodge between November and December 2024. The collected data are currently being organized and cleaned, with analysis and interpretation expected to take place between May and December 2025. As this protocol focuses on environmental audits rather than participant recruitment, no human subject enrollment data are reported. Ethics approval was obtained prior to data collection.

The analysis is expected to generate several key outputs. Quantitatively, the study will produce detailed environmental feature scores for each of the tool's therapeutic goals. The AIRP-HEAP's scoring system will allow comparisons between total scores and significance-weighted scores, helping to identify which design objectives are most critical to resident well-being. These findings will highlight both strengths and gaps in the built environment that influence the quality of end-of-life care for residents with experiences of homelessness. Qualitatively, open-ended observations and field notes captured through the AIRP-HEAP secondary observation tool will provide contextual insights into how neighborhood and site-level factors affect the hospice experience. These observations are expected to reveal environmental facilitators and barriers that shape residents' sense of autonomy, dignity, and inclusion within the hospice setting. Drawing from these insights, the study will generate recommendations for equitable hospice design, focusing on features that promote comfort, belonging, and person-centered care.

Discussion

Overview

This protocol aims to provide a comprehensive methodology for conducting a study focused on assessing hospice settings for OPEH in Metro Vancouver. Through this study, new insights into the environmental aspects that influence OPEH's ability to age and receive end-of-life care in suitable settings will be gained, ultimately contributing to the well-being of this population. Thus, this study allows us to discover information regarding AIRP concepts related to HEAP goals for end-of-life care and identify the environmental facilitators and barriers to improvements in hospice settings in the neighborhoods.

For capturing data and information on this protocol, the AIRP-HEAP tool (for indoor space) includes 295 items categorized into 11 therapeutic goals pertaining to the built and natural environment of hospice sites, and the AIRP-HEAP secondary observation tool (for surrounding neighborhoods) will be used. The most detailed questions in the AIRP-HEAP tool domains are related to the inside of the building and will be asked through a questionnaire in order to evaluate the quality of end-of-life care space. These tools will be used to assess the indoor built environment and the outdoor environment surrounding Maggie's Lodge hospice in the Metro Vancouver area. Built environment factors that enhance safety, reduce stress, and have spiritual significance will be audited to evaluate the quality of the built environment. For instance, assessing the amount of natural light in the building, ensuring security and privacy measures, providing spiritual and counseling spaces, and creating areas that facilitate social communication are included in the audit tool. Additionally, elements like accessible and wheelable sidewalks, traffic calming features, sufficient outdoor spaces, support services, and social amenities in the surrounding environment are included in the secondary observation tool, as these factors are known to promote potential for social and outdoor engagement for OPEH and their loved ones.

To ensure that the solutions recognized through this protocol can be extended to other hospice centers, we will develop a set of recommendations based on the findings. These recommendations will outline the best practices and actionable steps for improving the built environment and surrounding neighborhoods of hospice settings catering to OPEH. A recent analysis of Canadian homelessness and palliative policy documents highlighted that there is limited guidance for services to provide end-of-life care for OPEH [32]. Additionally, we will share the results of the study, along with the developed guidelines, with relevant stakeholders, including policy makers, urban planners, architects, and health care providers. By disseminating this information widely and encouraging its implementation in other hospice centers, we can promote the adoption of similar improvements across different locations, thereby extending the benefits to a broader population of OPEH. Findings from this study will be context-specific to the selected hospice site, limiting generalizability. However, the adapted AIRP-HEAP tool and conceptual approach can be transferable and applicable to other hospice contexts. By providing a structured framework for examining spatial and organizational dimensions of hospice environments, the tool may support other sites in identifying ways to create more compassionate and inclusive spaces for OPEH.

Limitations

This study will be conducted exclusively at Maggie's Lodge hospice during a specific time frame to evaluate the quality of its built environment and the surroundings of the building. While the findings based on the audit tool are expected to contribute to addressing gaps in the literature, the study will be subject to several limitations. First, as the audit will take place at a single point in time, the data will not capture environmental changes that occur over time. Future studies will be able to examine temporal factors and weather impacts on the outdoor spaces of hospices over time. Additionally, while the AIRP-HEAP tool will offer valuable insights into hospice environments, its adaptation from an existing tool may overlook certain unique needs of OPEH. The study's focus on Maggie's Lodge hospice site in Metro Vancouver will limit the generalizability of the findings to a broader geographical and cultural context. Finally, findings may not accurately depict the available resources to the hospice, as it omits staff interviews.

Conclusions

The development of the AIRP-HEAP and AIRP-HEAP secondary observation audit tools adds diversity and detail to existing hospice environment assessment methods by incorporating the unique needs of OPEH. Defining therapeutic goals and creating a design checklist for each goal establishes

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a milestone for theory and practice. The findings from these tools will help identify spatial design and placemaking features within hospice environments that either promote or deter end-of-life care for this population. By aligning the AIRP-HEAP goals to AIRP-related concepts, this research is expected to strengthen the connection between design-related therapeutic goals and research-based conceptualizations of aging and end-of-life care in the appropriate setting. The anticipated findings of the audit are expected to provide guidance for identifying environmental improvements in hospice settings, as well as inform future planning and design guidelines for hospice settings that support OPEH.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
COREQ checklist.
[PDF File (Adobe PDF File), 1157 KB - resprot_v14i1e73356_app1.pdf]

Multimedia Appendix 2
Example of design scores across 11 therapeutic goals.
[DOCX File , 19 KB - resprot_v14i1e73356_app2.docx]

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Abbreviations

AIRP: Aging in the Right Place
AIRP-HEAP: Aging in the Right Place-Hospice Environmental Assessment Protocol
COREQ: Consolidated Criteria for Reporting Qualitative Research
HEAP: Hospice Environmental Assessment Protocol
OPEH: older people experiencing homelessness
PEAP: Professional Environmental Assessment Protocol
SWAN: Stakeholders Walkability/Wheelability Audit in Neighborhoods
UBC: University of British Columbia

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Improving Experimental Designs for Interventions to Reduce Intimate Partner Violence: Protocol for Refinements to Single-Case Experimental Design for a Safety Planning Intervention in Ontario, Canada

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Abstract

Background: Intimate partner violence (IPV) affects 2 in 5 women in Canada, leading to both physical and mental health consequences. Safety planning is a secondary prevention intervention designed to assist those experiencing IPV in taking steps to increase their safety and decrease contact with their abusive partner. Safety planning has been shown to help survivors mitigate the negative mental health effects of IPV and encourage actions to increase safety, but evaluation outside the United States remains limited.

Objective: Our team plans to evaluate the use of single-case experimental design (SCED) to assess the effectiveness of a web-based safety planning app (*WITHWomen Pathways*) for women experiencing IPV in the Greater Toronto Area. The study also explores whether women can be safely engaged for intense follow-up.

Methods: SCED evaluation will involve multiple baseline and postintervention assessments of a small number of women experiencing IPV (n=6). Participants will be recruited from IPV service organizations across the Greater Toronto Area. SCED will allow for rigorous within-subject comparison, using repeated measurements at multiple time points for 3 primary outcomes (decisional conflict, empowerment to take safety actions, and use of safety strategies) and 2 secondary outcomes (mental health and IPV recurrence). The evaluation will include 5 phases: recruitment, eligibility screening, multiple baseline interviews, intervention (web app delivery), and multiple postintervention assessments. In this paper, we also discuss the development of rigorous protocols for maintaining safety and flexible data collection methods (in person, via telephone, or online).

Results: Recruitment began on July 3, 2024. As of December 2025, a total of 4 participants have been recruited and have completed multiple baseline assessments. Data analysis has been completed for 4 participants, and results are expected to be published in spring 2026.

Conclusions: The SCED approach may offer a novel and ethical evaluation method for IPV interventions. If effective, the WITHWomen Pathways web app could significantly improve help-seeking and safety planning among women experiencing IPV in the GTA. This study may serve as a model for future IPV intervention evaluations, demonstrating robust evaluation data and participant safety.

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(JMIR Res Protoc 2025;14:e67450) doi:10.2196/67450

KEYWORDS

single-case experimental design; intimate partner violence; safety planning; mHealth; safety; experimental design; partner violence; violence; protocol; planning intervention; Ontario; Canada; North America; web based; effectiveness; mental health; depression; anxiety; domestic violence

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Introduction

Two in five women in Canada have experienced some form of intimate partner violence (IPV) in their lifetime [1]. Such experiences include aggressive, coercive, controlling, or abusive behaviors resulting in physical harm (eg, inflammatory conditions, self-harm, HIV, miscarriage, traumatic brain injuries) and nonphysical harm (eg, anxiety, posttraumatic stress disorder) [2-4]. While IPV occurs across populations and outside male-female relationships, the most widespread form of IPV is violence perpetrated against cisgender women by current or former cisgender male intimate partners [5,6].

Although some women can extricate themselves from violent relationships on their own, most require assistance and support to either leave the relationship or work with the partner to end the violent behavior. Liang et al's [7] theoretical framework of IPV help-seeking addresses 2 main forms: formal and informal. Formal help-seeking includes assistance from legal, medical, religious, or social services, while informal help-seeking refers to assistance sought from family, friends, other survivors, and trusted confidantes [7]. Both formal and informal help-seeking are shown to improve the mental health of those experiencing IPV, often by enhancing the survivor's own coping abilities and social support [7].

Safety planning is a secondary prevention intervention designed to empower survivors to begin the help-seeking process by taking independent actions to maximize their own safety. Similar to household safety plans for natural disasters or house fires, an IPV safety plan takes into consideration an individual's available resources, living arrangements, and needs before recommending individualized, concrete actions that can prevent a violent event or mitigate its damage. To assist women experiencing IPV to begin the formal help-seeking process, this team created *WITHWomen Pathways*, a web-based safety planning app localized to the Greater Toronto Area (GTA; the metropolitan area encompassing Toronto, Ontario, Canada and the regional centers of Durham, Halton Peel, and York). This hyperlocal app is adapted from *MyPlan*, an existing safety planning mobile app in the United States [8] and Canada [9] that has shown effectiveness in reducing decisional conflict and promoting safety planning behaviors for women experiencing IPV in traditional randomized controlled trials (RCTs). Additional details on the creation of WITHWomen Pathways and its features are published elsewhere [10,11].

Safety planning interventions are commonly evaluated via their ability to jumpstart survivors' help-seeking processes by (1) reducing decisional conflict (a state of uncertainty when faced with choices that represent loss or conflict with personal or cultural values), (2) empowering people who experience IPV to take actions to improve their safety, and (3) providing concrete, self-directed actions that align with their goals and needs [12-14]. While there is evidence from the United States to suggest that safety planning can help improve decisional conflict and mitigate future psychological and physical violence, there have been few evaluations of safety planning interventions outside the United States [9,14-16] and only 1 in Canada [17]. This review found no differences in depressive symptomatology or posttraumatic stress disorder symptoms between users of a static, generic safety planning app and one that is more tailored to their specific circumstances. However, the tailored app (which is more similar to the WITHWomen Pathways approach) did show meaningful effects on these mental health outcomes for subgroups of women—especially those who had children in the home, those who were experiencing more severe physical or sexual abuse, or those who lived in a large or medium-sized city [9]. The latter finding may be a function of the additional resources available to women in more urban areas, which a tailored app may be more helpful at recommending.

While evaluation of safety planning interventions is key to improving effectiveness and widespread implementation, RCTs in this space are exceedingly complex due to the important safety considerations and privacy concerns regarding women who are currently experiencing IPV [16-18]. Moreover, RCTs are expensive, complex studies that require large numbers of participants, and people experiencing IPV constitute a hard-to-reach population [19]. This places them out of reach for many community-based organizations that wish to evaluate innovative, survivor-centered programming but lack the scientific expertise and resources to conduct fully powered clinical trials. Moreover, many RCTs of safety planning interventions show null effects between intervention and control groups, which is hypothesized to be due (in part) to an intervention effect in the control group—that is, asking women in the control group about their IPV constitutes an intervention in and of itself, potentially blunting the true effect of the safety planning intervention [20,21].

Single-case experimental design (SCED) is a methodology that allows us to build on findings in a cost-effective and ethical way without unnecessary duplication via another large-scale, expensive RCT. As funding for research continues to decrease in many countries, such RCTs can be a drain on finite resources and impede scholarly progress [22,23]. To overcome some of the challenges posed by traditional evaluation methods, we are interested in using a potentially more rapid and efficient evaluation method that adapts the SCED clinical methodology, alongside novel safety protocols, to the evaluation of WITHWomen Pathways. SCED uses multiple observations in the same participant at short intervals (the time between observations depends on the outcome of interest) both before and after the introduction of the intervention (see Figure 1) [9,24]. Statistically nonsignificant differences in the outcome measures of interest between preintervention visits indicate stability and establish a preintervention baseline that is then compared to the subsequent postintervention time points [25-29]. After the intervention—which may be a single session or consist of multiple sessions [30,31]—is delivered, data collection over multiple postintervention time points allows for the establishment of behavioral trajectories that illustrate when and how change happens. In other words, the participant's baseline measures act as the control. When multiple SCED cases are aggregated, SCED can explain small but meaningful causal variations in intervention effects using fewer participants than an RCT [28].

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Figure 1. Overview of a typical single-case experimental design study flow.

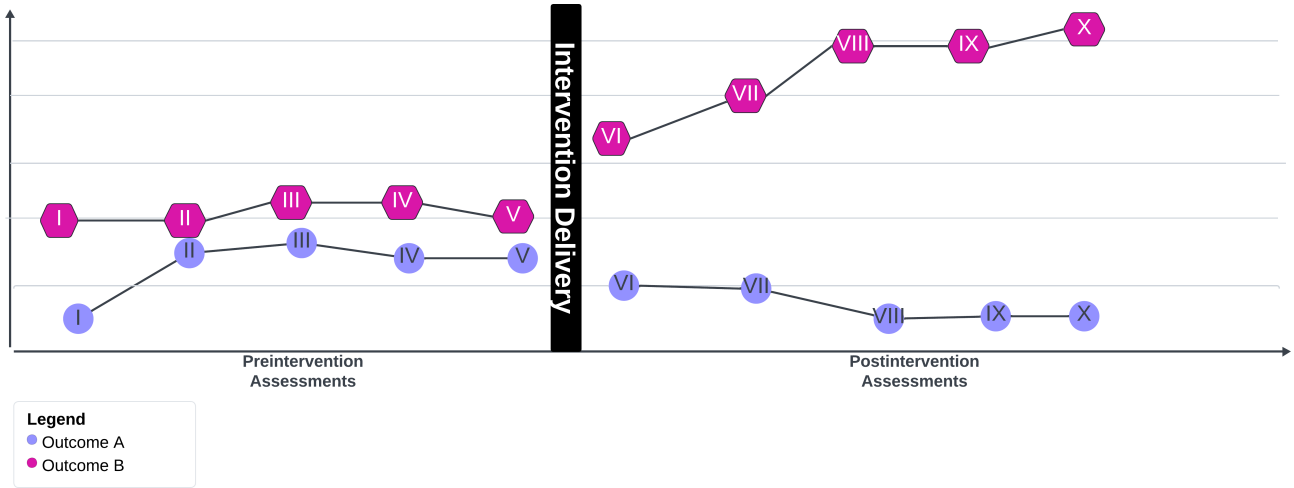

SCED has been used in medical, psychological, and behavioral research for decades to better understand the mechanisms of intervention effects. Recently, it has also been used to assess the effectiveness of technology-based interventions in other areas [32], for example, in vulnerable populations such as adolescents experiencing psychological distress [33], individuals with serious mental illness [34,35], adults with severe autism spectrum disorder [36], and young children [37]. The extant literature suggests that SCED is a viable alternative to RCTs, especially for sensitive outcomes, because it allows for closer observation of individuals [38]—something which is critical for ensuring the immediate safety of participants living with IPV [26,27]. However, to the best of our knowledge, this will be the first adaptation of the methodology to IPV studies [32].

To gauge whether SCED is a viable approach for evaluating a web-based safety planning tool for English-speaking women in the GTA, we have established the following study objectives:

1. To understand whether women who are living with or have recently experienced IPV can be safely engaged for intense follow-up for the purpose of evaluating a safety planning intervention
   a. We hypothesize that our safety protocols and individualized approach will allow for safe participation in the study, as measured by a lack of reportable or adverse events.
2. To examine the preliminary effectiveness of WITHWomen Pathways and our novel safety protocols on 3 primary and 2 secondary outcomes of interest
   a. We hypothesize that within-person changes to decisional conflict and depressive symptoms will show a decrease, whereas empowerment to take safety actions will demonstrate an increase.

Methods

To our knowledge, SCED has never before been applied to IPV evaluation; therefore, the methods in this study involved developing novel safety protocols for women engaging with high-touch research while at high risk for IPV, as well as data collection and analysis procedures.

Ethical Considerations

This study and all relevant protocols were reviewed and approved by the St Michael's Hospital Research Ethics Board (REB; #20 - 120). All study procedures comply with the ethical standards of the St Michael's Hospital REB and follow the principles outlined in the Declaration of Helsinki and relevant Committee on Publication Ethics (COPE) and JMIR guidelines. Further details on informed consent, privacy, and confidentiality are provided in the following sections. Below, we review the development of safety protocols before describing the evaluation of the WITHWomen Pathways app.

Universal Safety Considerations

In-person interviews will be conducted in complete privacy, except for participants who are accompanied by children younger than 2 years. If privacy cannot be ensured, interviewers will reschedule the interview for a different time or place, allowing participants the flexibility to choose a safer or more convenient option. For telephone interviews, interviewers will confirm before beginning the interview that participants can talk privately and safely. Interviewers will be trained to detect whether someone else is present or listening in on the call, using cues such as speech hesitations or background noises, and offer to call back if needed. If a participant is not alone, the interviewer will switch to asking nonsensitive, health-related questions as a safety measure. The online surveys will contain a preamble with online browsing safety tips, including specific recommendations to ensure the participant is alone before beginning the survey and instructions on how to use a private or incognito browser and how to quickly exit the survey. Furthermore, the WITHWomen Pathways app itself has safety features that participants can use should their abusive partner be made aware of their use of the app. As a mobile-friendly web app, WITHWomen Pathways is not physically downloaded, making it easier and quicker to remove any traces of its use. It also contains a quick exit button, which links to an innocuous website (currently hgtv.ca). In addition to these in-person and asynchronous safety measures, all participants completing the screenings by phone will be asked to confirm whether they feel that they are in a safe space, before moving forward. As rollout continues, the safety of completing interviews online will be considered and adjusted as necessary.

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Safely Contacting Participants

Safety protocols are of paramount importance in this study and necessitate bespoke approaches to safety strategies. To develop these strategies, we first consulted the literature and drafted a tentative protocol. These strategies include maintaining a general conversation during phone calls before discussing the research study until it is confirmed that the participant is in a safe environment, conducting regular check-ins to ensure the participant's comfort and well-being, and sending an email prior to making phone calls to confirm that the scheduled time is still safe for the participant.

Our team's peer advisory committee (comprising survivors and IPV advocates) provided feedback on the draft protocol and recommended changes to recruitment and contact procedures (eg, specifically mentioning IPV on recruitment flyers). During the consent process, participants will also be provided with an optional safe contact form where they can list up to 3 "safe contacts" who will only be contacted if the researcher cannot reach the participant. The purpose of this form will be communicated to participants as a standard procedure to ensure their safety if they cannot be reached. Safe contacts will be informed that the participant is part of a women's health study and has given permission for the researcher to contact them if needed. Participants will be encouraged to inform their safe contacts about the possibility of being contacted by St Michael's Hospital in the future. The participants will be asked to sign the safe contact form at baseline to ensure a thorough understanding and to provide written consent for contacting the listed individuals. Information requested for each safe contact includes name, relationship, phone number, and email. Participants will be asked to prioritize whom to contact first and to specify the preferred method of communication. The safe contact form will be reviewed and updated with participants at baseline and during follow-up to maintain accurate information.

Follow-Up Communication Model

A communication protocol will be established between researchers and each participant, specifying when to expect contact from staff, ranking the preferred modes of safe contact (eg, email, phone, and mail), and choosing a code word to end communication if the environment is not private or safe. This information will be reviewed with participants at the first baseline and first follow-up assessments in case their situation changes. At each contact point, participants will be assured that their safety and confidentiality are prioritized and that the research team cares about them as individuals.

Recruitment

While previous app-based safety planning interventions have attempted to reach women experiencing IPV who are unready to be connected with formal services [24], our community partners are interested in using WITHWomen Pathways as a complementary resource for those who present to formal services but are either unready (eg, ambivalent) or unable (eg, due to the presence of pets, male children, or substance use) to avail of temporary housing services or those who are unsure whether they need formal services. Therefore, participants will be recruited through a network of nearly 2 dozen organizations that provide violence against women services across the GTA. Prior to recruitment initiation, the research coordinator (SR) sent emails to staff at each organization about the purpose of this research and ensured that we were in agreement and alignment on participant safety and protocols for safety management, as well as the inclusion criteria. The organizational leadership has agreed to take part in the SCED evaluation study, allowing us to move forward with the recruitment process. To recruit participants, the research coordinator will share flyers and information sheets with the leadership, who will then share the materials with clients and others in their network via their own email listservs and social media accounts.

Eligibility Screening and Informed Consent

Once a woman engages with recruitment material, the research coordinator will reach out using the participant's preferred mode of contact (ie, email or phone) to invite her to learn more about the study and complete the eligibility screener. At the start of this discussion, participants will be provided with a "quick exit" strategy whereby the topic of conversation can quickly move to a safe subject in case privacy is breached. For example, study staff will inform potential participants that if either she or the interviewer notices that privacy is breached, they can quickly switch to talking about a "safe" topic of choice as determined by the participant (eg, shopping, cooking, children, sports, or movies).

The screener consists of questions about basic sociodemographic information (eg, age, residence, and sex), and the level of current or recent IPV is determined via the 9-item WITHWomen screener [39]. The target population for the SCED evaluation of the WITHWomen Pathways safety planning app is 6 self-identified women in the GTA who are currently experiencing physical, sexual, or emotional IPV or controlling behaviors or had these experiences in the past 12 months. Participants will be eligible if they are able to read, write, and speak English; identify as a woman; are 18 years or older; and reside in the GTA. Women who have custody of children younger than 13 years will also be eligible; this age was chosen to reduce the likelihood of multiple abusive partners (eg, presence of dating violence among adolescents) and better understand how women with young children make safety decisions. Men, individuals living outside the GTA, those with children older than 13 years, and those who are experiencing no IPV will be ineligible. Women who do not meet the eligibility criteria but who are experiencing IPV will be immediately referred to formal sources of support (eg, a domestic violence shelter, a hotline, or law enforcement). A separate safety protocol (available upon request) has been created, containing additional information on participant safety measures.

The eligibility screener can be completed in private interview rooms at study offices in downtown Toronto, using an online screener, or via telephone. For telephone-based screeners, the study staff will be instructed to keep the initial communication with potential participants as vague as possible until there is some assurance that they are in a private and safe location to hear more about the study.

Once a potential participant is deemed eligible to participate, the study staff will ask her whether she desires to continue to

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learn about the study and, if so, they will request her to provide informed consent to enroll. They will indicate that this process will take about 10 minutes. Informed consent can be provided immediately in person, via telephone, or via an electronic informed consent form. Staff can also arrange for a phone call at a later time to further discuss the study. The informed consent form outlines all study processes, including (1) study description, (2) a description of what is required of participants, (3) study duration, (4) expected time commitment from participants, (5) compensation, (6) data confidentiality, and (7) any potential risks or benefits of participation. Then, any questions the potential participant has will be answered by the study staff member (via telephone/in person). For electronic informed consent, contact information for the research coordinator and principal investigator will be provided in the event that participants have questions prior to providing their verbal consent or electronically signing the form. Participants will then be asked if they would like a copy of the form.

Preintervention Assessments

As previously discussed, SCED requires the establishment of stability in a given outcome measure prior to intervention delivery [40]. We plan to assess 3 primary outcome measures that align with those assessed by previous RCT safety planning evaluations and are the direct targets of the intervention's activities: safety self-efficacy, decisional conflict, and confidence in planning (see Table 1). These speak to the goals of safety planning, which are to *prime* those who are currently experiencing IPV to take action to improve their safety, which reflects the often nonlinear paths and ambivalence women feel about extricating themselves from a violent relationship [41,42]. Additionally, we plan to measure 2 secondary outcomes: IPV recurrence and mental health. IPV itself is a secondary outcome because changes in IPV exposure are not necessarily expected, for the reasons mentioned above. While mental health is not directly targeted by intervention activities in WITHWomen Pathways, participation in the intervention may secondarily lead to improvements in mental health through help-seeking actions.

Table . Outcome variables for evaluation of *WITHWomen Pathways*.

Outcome measured	Primary/secondary	Instrument	Reference
Use and perceived helpfulness of safety strategies, service use	Primary	Intimate Partner Violence Strategies Index (adapted)	Goodman et al (2003) [43]
Empowerment related to safety	Primary	MOVERS[a]	Goodman et al (2014) [13]
Decisional conflict	Primary	Decisional Conflict Scale	O'Connor (1995) [12]
Anxiety and depression symptoms	Secondary	PHQ-4[b]	Kroenke et al (2009) [44]
Intimate partner violence	Secondary	Composite Abuse Scale-Short Form	Ford-Gilboe et al (2016) [45]

[a]MOVERS: Measure of Victim Empowerment Related to Safety.

[b]PHQ-4: Patient Health Questionnaire-4.

The baseline interview is designed to last approximately 15 to 20 minutes and will end with a reminder that the participant will complete some of these same measures every 3 to 4 days for the next 2 to 3 weeks until stability is reached. Participants will receive CAD $10 (US $7.15) as an online gift card or through electronic money transfer upon finishing each preintervention interview. Following the established safety protocols for working with those experiencing IPV described above, preintervention baseline assessments can occur via telephone, in person, or via an online survey, using the mode that seems the safest for the participant [46]. For telephone-based assessments, we will also ask the participant before beginning each session if she is in a private space. Whether collected remotely or in person, the SCED data will be recorded via Zoho Survey (Zoho Corporation) and saved directly to a secure Zoho server.

After each participant's fifth baseline interview, the research team will assess the overall score for each outcome measure. If the participant achieves stability, measured using previously cited criteria wherein at least 85% of preintervention data fall within a 15% range of the median for at least 1 primary outcome measure (Patient Health Questionnaire-4 [PHQ-4], Measure of Victim Empowerment Related to Safety [MOVERS], and Decisional Conflict Scale), they will progress to the intervention interview [47,48]. If stability is not reached after 5 assessments, baseline measurements will continue for 2 more weeks (3 additional baseline measures with CAD $10 (US $7.15) compensation at each assessment) and reassessed. If, at this point, the participant's outcome measures are deemed stable, they will proceed to the intervention interview. If not, they will still advance to the intervention visit, but their data will not be included in the effectiveness evaluation. Using the standard SCED protocol, these assessments will result in at least 5 but no more than 8 baseline measurements, ensuring that every participant receives the intervention as soon as possible [49].

Intervention Interview

The intervention visit is an in-person session that may last up to 90 minutes and provides detailed instructions on the WITHWomen Pathways app and its features using a study-provided tablet. During this visit, the research coordinator will inform the participant that it differs from previous visits and that an interview or survey will take place at the end of the session, featuring different questions from those asked previously. In a private, mutually agreed-upon, safe location, such as a conference room or unoccupied office either at St Michael's hospital, at one of our partner agencies, or in the community (eg, private meeting room at a public library), the research coordinator will provide instructions on how to use the tablet and engage with the WITHWomen Pathways web app. The participant will then be allowed to explore the web

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app freely, with the coordinator stepping back to provide privacy. The participant will be encouraged to spend a significant amount of time (up to 30 min) exploring the web app. This includes working through all service prioritization activities and creating an individualized safety plan. The coordinator will check in periodically to answer questions. It will be explained to the participant that each time she uses the web app, it is considered a new session, and that for safety reasons, the web app does not store or restore data previously entered. After she has explored each section of the web app, the research coordinator will ensure that the participant is able to access the WITHWomen Pathways app on her own device and is comfortable using and exiting the web app from that device as well. Once the participant is comfortable and familiarized with the app, the session can be concluded. Then, the intervention visit survey will be administered using the interview guide and visual aid (available upon request). Finally, the interviewer will schedule the first remote follow-up interview and thank the participant for her time and input. Participants will be allowed and encouraged to use the web app as often as they like during and after the follow-up period.

Postintervention Interviews

Following standard SCED protocols, the postintervention assessments use the same questionnaires and intervals as the preintervention assessments [28]. At the first postintervention assessment (scheduled during the intervention interview), the participants will complete the same outcome measures at the same intervals (every 3‑4 days) as in the preintervention assessments. Participants with children will also complete the perceived child well-being questionnaire at the final visit. All participants will complete the same number of postintervention assessments (n=8) over the course of 4 weeks after their intervention interview. Postintervention interviews can be conducted in person, via telephone, or using the online survey.

Strategies to Prevent Attrition

Given the high participant burden of SCED and the potentially precarious position in which many women experiencing IPV find themselves, attrition from the study is likely. However, the research team has devised strategies to safely encourage participants to remain in the study. First, the study is designed to be as convenient for participants as possible, offering several modes of contact (in person, via telephone, and online), evening and weekend assessment options, and face-to-face interviews at partner organizations convenient to the participant. Compensation will also be given at the point of assessment, within a day following each check-in, and each assessment will be scheduled at the end of the preceding visit. For those who do not attend previously scheduled assessment visits, researchers will first reach out via the safe contact methods indicated by the participant at different times of the day. They will then search for updated information or attempt previously disconnected phone numbers before reaching out to the safe contacts listed by the participant. While resource limitations prevent us from overenrolling to guard against attrition, sample size is only one of several levers that SCED studies (as opposed to traditional evaluation designs) can use to improve statistical power. Should attrition become an issue, we will explore using additional baseline and follow-up measures in the remaining participants, simulating power using different effect size estimates, and assessing the number of outlier scores to understand its effect on generalizability [50].

Managing Minor Emotional Distress

Given the topic of IPV, study population, and sensitivity of the assessment questions, researchers will undergo training on how to handle situations where participants experience emotional distress during interviews. Sufficient time will be allocated during the initial interview to address any questions or concerns, including the potential for anxiety. For telephone or in-person surveys, researchers will help participants devise a step-by-step strategy to manage various scenarios, such as how to respond if they start crying or feel uncomfortable answering a question. Participants will also discuss options for managing anxiety during the interview ahead of time, such as deep breathing or temporarily discontinuing the interview. For online links, participants will be asked to complete the survey only when they are alone, and all participants will be provided with links to mental health resources at the end of the survey. The research coordinator will be in regular contact with all participants. Researchers will also note the PHQ-4 scores of all participants and those with elevated depressive and anxiety symptoms, making sure to carefully monitor these participants specifically and provide contact information for community mental health resources. Any adverse events beyond minor emotional distress will be immediately reported to the Research Ethics Board and integrated into our assessment of the safety of using SCED for IPV interventions.

IPV Reporting Requirements

Health care professionals and staff affiliated with St Michael's Hospital or the University of Toronto are not legally or professionally obligated to report suspected or verified partner violence. However, reporting child abuse is mandatory under Ontario's Child and Family Services Act, Section 125 [51]. Participants will be informed during the interview's informed consent instructions that the interviewer is obligated to report child abuse, allowing them to control the disclosure of any such incidents.

Data Analysis Plan

Following the SCED technical guidance published by the What Works Clearinghouse (WWC) of the US Department of Education's Institute for Education Sciences [49], we will begin by computing descriptive statistics for each outcome measure, stratified by participant and intervention phase. For each scale, we will calculate the number of observations, mean, SD, SEM, minimum, and maximum, separately for the preintervention and postintervention periods. This will allow us to summarize overall patterns and assess changes in central tendency and variability over time.

The WWC also recommends visual inspection of data points and trend lines to gauge preintervention and postintervention effects [52]. To visualize the within-person patterns over time, we will create scatterplots for each participant and outcome measure, overlaying fitted linear trend lines for both the preintervention and postintervention phases. This will allow for

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visual inspection of potential shifts in level and trend following the intervention. A vertical reference line will denote the point of intervention onset.

Internal consistency will be assessed using Cronbach α, calculated on the basis of the preintervention responses for each scale described previously. These estimates will provide an indication of scale reliability prior to any intervention effects.

To quantify the pre-post changes in outcomes for each participant, we will follow the WWC guidance by calculating Tau-U, a nonparametric effect size metric. Tau-U allows for the estimation of intervention effects while accounting for trends that may be present during the baseline (preintervention) phase [53,54]. For each outcome and participant, we will compute (1) Tau (preintervention, A), to evaluate baseline trend; (2) unadjusted Tau-U (A vs postintervention, B), which compares data points between the baseline and postintervention phases without adjusting for baseline trend; and (3) adjusted Tau-U (A vs B), which corrects for any nonrandom trends in the baseline phase. Consistent with Fingerhut et al [54], our primary aim is not to assess statistical significance, which would be unreliable in small sample size designs such as SCED, but instead to interpret the direction and magnitude of observed effects. We will use previously validated benchmarks to classify effect sizes as small (0.20 - 0.59), moderate (0.60 - 0.79), or large (≥0.80) [53]. Even small effect sizes will be considered potentially meaningful when supported by consistent patterns observed through visual inspection of the data (see Table 2).

Table . Five visual analysis measures of comparison typically used for single-case experimental design evaluation.

Measure	Definition
Nonoverlap of all pairs (NAP)	Values from baseline and intervention time points are paired, and a percentage of pairs whose values do not overlap is calculated.
Extended celeration line (ECL)	An NAP that controls for positive trends in the preintervention phase by calculating the proportion of postintervention data points that are above the median trend line plotted from preintervention data.
Improvement rate difference	It is calculated as the difference in the rates of increase in outcome variable data between the preintervention and postintervention phases by dividing the number of "improved data points" by the total number of data points in that phase.
Tau-U	Tau-U adjusted pairs each preintervention and postintervention observation to make n pairs. The number of positive-change, negative-change, and tied pairs is calculated for each outcome variable
Percentage of nonoverlapping data, corrected (PNDC)	Particularly useful when anticipating an increase in the outcome variable postintervention, PNDC locates the highest data point in the preintervention phase and calculates the percentage of postintervention data points that exceed it. A data correction procedure is used to control for an upward preintervention trend.

Handling Missing Data

SCED requires multiple data collection points with each participant, increasing the likelihood that one of these data collection opportunities will be missed. In the event of interim missing assessments (ie, a missed data point from an enrolled participant), we will still attempt to establish stability. To do so, we will leave a break in the time-series line for visual analysis; data points will not be connected across a missing observation. For the nonparametric effect size calculation (Tau-U), comparisons will be made using all available preintervention and postintervention data pairs, as the statistic does not require an uninterrupted series.

Data Variability

To address potential variability in the data, our visual analysis will systematically examine the stability of data points within each phase, in addition to the level and trend. This will be supplemented by our calculation of SD for each outcome per participant in both preintervention and postintervention periods. This allows us to assess not only the occurrence of a change but also the consistency of the intervention's effect, even with variable data in the preintervention or postintervention periods.

Results

Recruitment commenced on July 3, 2024. As of December 2025, a total of 4 participants have completed the study. Data analysis has been completed for the 4 participants. Additional recruitment is underway, and results are expected to be published in spring 2026.

Discussion

The aim of this study is to assess the viability of an innovative evaluation approach for a localized safety planning web app among English-speaking women currently (or until very recently) experiencing IPV in the GTA. To the best of our knowledge, this study will be the first to evaluate an IPV resource using SCED, and the small sample size will allow the research team to ethically monitor women in precarious situations while still collecting robust data.

Other Alternatives to RCTs

SCED is not, however, the only alternative to RCTs for gauging the effectiveness of app-based safety planning interventions. We also considered whether stepped wedge designs [55] and interrupted time series (ITS) designs could feasibly be used to

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assess WITHWomen Pathways. We decided against a stepped wedge study given that it requires more participants and longer preintervention baseline phases for some participants versus others. Because our second aim is to understand how to more quickly establish baseline stability to provide the intervention as quickly as possible, we believe that it would be unethical to withhold the intervention from some participants given our inclusion criteria. Similarly, ITS designs either require the use of a control group with which the intervention is compared (controlled ITS) or the use of a counterfactual, which assumes that the outcome measure in the group exposed to the intervention would have remained the same in absence of the intervention [56]. We consider the use of a control group for those experiencing IPV as potentially ethically dubious and therefore did not consider a controlled ITS. Furthermore, ITS studies are best suited to understand population-level effects, which—while making them potentially more generalizable—reduces the ability to understand how an intervention impacts the safety planning behaviors of an individual and the IPV experienced by them. For hyperlocal interventions such as WITHWomen Pathways, we believed that a more individualized approach would provide more helpful information on how local community members might be aided by the intervention. Therefore, while stepped wedge and ITS studies may be helpful in future larger trials, understanding the feasibility of SCED is an important step toward improving the rigor of IPV intervention evaluation.

Study Limitations

There are some notable limitations to this study. First, research activities require that women be able to speak and read English, which excludes non-English speakers and women with visual impairment. Second, with its multiple points of intervention and smaller sample size, SCED has safety and statistical limitations. First, having multiple contact points with each participant increases the chance that the abusive partner could become aware of her participation, increasing the risk of IPV. To address this, we have developed strict safety protocols and can promptly leverage our connections with local service providers should emergencies arise. SCED approaches also have multiple measurements in close temporal proximity, increasing participant burden. To help limit attrition, we will clearly communicate with potential participants about the time involved at the outset; invest in training for study team members to promote friendly, empathetic connection with participants; and provide fair compensation for the demands on participants' time. Statistically, SCED carries four major risks: (1) the potential for a lack of variability in the preintervention and postintervention measures because measurements are completed at short intervals, (2) limited generalizability due to a small number of cases, (3) threats to internal validity due to test bias and social desirability bias [40], and (4) potential confounding effects due to the lack of randomization. To address risk 1, we will use the WWC recommendations for conducting sensitivity analyses and reporting multiple effect size estimators (eg, multiple visual analysis methods). Regarding risk 2, although multiple-case SCED (when rigorously evaluated) can be generalizable in many of the same ways as RCTs, this necessitates replication, which requires additional resources [57]. We do not anticipate this preliminary trial to be generalizable. Rather, it is intended to better identify the potential utility of SCED protocols in the evaluation of IPV-related interventions and adaptations that may be necessary. Regarding risk 3, we will use the percentage of nonoverlapping data, corrected (PNDC), to ascertain patterns of preintervention increase, as recommended by the WWC (see Table 2). Regarding risk 4, once this preliminary trial is complete, we intend to introduce randomization to different permutations of the WITHWomen Pathways app in future studies.

Research Plans

Should SCED show the promise for rigorous evaluation of IPV interventions that we anticipate, we intend to conduct a rigorous, multiple-baseline SCED to measure the impact of WITHWomen Pathways on the primary outcomes of interest in this study before integrating the app into existing collaborations with GTA IPV service organizations. Our network of more than 2 dozen such service providers in the area allows for the rapid scale-up of WITHWomen Pathways for overburdened agencies who currently have no evidence-based safety planning tools to recommend to women who feel unsafe, but who are unwilling or unready to leave their relationship. Alongside the scale-up of the English version, we plan additional SCED evaluations of the Spanish and French versions of WITHWomen Pathways, as are adaptations for recent immigrants and asylum seekers who may also be reticent to engage with formal services [58]. This stepped approach allows us to move forward with implementation while creating stand-alone, tailored versions of the tool for women in the GTA who cannot easily avail of the current version of WITHWomen Pathways. Additionally, we anticipate that this study will facilitate a more widespread use of SCED in IPV intervention evaluation.

Conclusions

The findings of this study could have important implications for women and domestic violence service organizations in the region. Improved safety planning is a key marker of future help-seeking for IPV and may help extricate women in violent relationships prior to the escalation of violence to more serious and life-threatening actions [24]. Using WITHWomen Pathways in conjunction with other domestic violence services could also improve service delivery for organizations whose resources and staff are thinly stretched, allowing these organizations to assist more women by providing safety planning resources to women who cannot or choose not to engage with more formal services (eg, law enforcement). By testing the viability of using SCED to assess the effectiveness of WITHWomen Pathways, we may be able to assist women currently navigating violent relationships, by providing rigorously tested safety planning information that is safe to use, tailored to the local context, and self-directed.

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Data Availability

While the data are deidentified, the small sample size and limited geographic area of the study preclude the authors from ethically depositing data in a public repository. However, the authors are happy to consider data requests to the corresponding author.

Authors' Contributions

Conceptualization: POC (lead), NM, ARY
Data curation: NM
Funding acquisition: POC (lead), NM, ARY
Investigation: POC (lead), PB, SR
Methodology: NM
Project administration: PB
Resources: POC (lead), PB
Supervision: POC (lead), PB
Validation: POC (lead), NM
Writing – original draft: NM (lead), PB, SR
Writing – review & editing: POC, NM (lead), PB, SR, ARY

Conflicts of Interest

None declared.

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Abbreviations

COPE: Committee on Publication Ethics

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GTA: Greater Toronto Area
IPV: intimate partner violence
ITS: interrupted time series
MOVERS: Measure of Victim Empowerment Related to Safety
PHQ-4: Patient Health Questionnaire-4
PNDC: percentage of nonoverlapping data, corrected
RCT: randomized controlled trial
REB: Research Ethics Board
SCED: single-case experimental design
WWC: What Works Clearinghouse

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Elderly Activity Life-Space Envelopes (EASE): Development and Feasibility of a Comprehensive, Integrated Protocol for Life-Space Mobility Research in Population Health

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Abstract

Background: Life-space mobility (LSM) refers to the movement of people over time and the areas through which they move to achieve life goals of health, employment, security, and participation for active aging.

Objective: The Elderly Activity Life-Space Envelopes program is a large interdisciplinary mixed methods LSM study in older adults of 50 years and above. The overarching aims were to discover why, where, and when older adults travel and how they get to their destinations.

Methods: In this paper, we focus on the methodology of the main quantitative phase. This community-based study comprised an in-person multidomain geriatric assessment with physical performance measures, followed by a 14-day travel diary. For the multidomain geriatric assessment, we structurally underpinned important population health constructs including the WHO International Classification of Functioning, Disability and Health, Frailty, and Intrinsic Capacity. We also described home meso-environments by incorporating authoritative open-source environmental attributes. These facilitated the categorization of LSM determinants into health, social, and environmental domains. The LSM outcomes include self-reported and objective geographical information science LSM measures. We further developed a suite of geographical information science LSM outcomes in alignment with our overarching aims. Quota sampling based on age groups, housing typology, and frailty status was applied. A customized, smartphone-based digital travel diary was designed, and barometric sensors were enabled to capture 3D LSM in capable smartphones.

Results: We recruited 1131 older adults with an average age of 63.8 (SD 7.6) years. The large majority (n=1062, 95%) successfully documented their travel diary on their smartphones with the rest on paper-based travel diaries. For the digital data, a total of 88,166 node points were recorded. There were 76,741 trips and 106,323 trip legs documented through the e-travel diary platform. Valid vertical LSM data were obtained from 228 participants. The majority (n=842, 75%) lived in public apartments, and 29% (n=326) were prefrail or frail.

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Conclusions: We provide a practical, feasible yet comprehensive protocol integrating LSM within important population health themes. Also, the development of an objective, systematic outcomes framework will form the basis for future LSM studies in the field. We aim to analyze the interactions between LSM outcomes, explore its diverse determinants, and identify senior travel phenotypes. We hope to develop interdisciplinary policy−driven interventions to ultimately improve the quality of life in older adults.

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KEYWORDS

community mobility; community participation; geospatial analysis; preventative health; travel behavior

Introduction

Life spaces (LS) are areas through which people move over a specified time period [1-3]. More recently, the study of LS incorporates active aging concepts [3-7]. Active aging models optimize opportunities for health, participation, and security to enhance quality of life (QoL) in older adults [8,9]. Accordingly, the descriptions of LS also include these opportunities and environmental experiences beyond simpler spatial quantifications. Thus, the movement within these activity spaces is termed life-space mobility (LSM). A full, contemporary definition of LSM is the movement of people over time and the total areas through which they move to achieve life goals of health, employment, security, and participation for active aging. This movement is often described as the individual's mobility capital within these envelopes [10-13]. Examples of activities carried out in particular LS are dining, shopping, recreational, health care, social, or religious activities, and these are subsequently recorded into trip or travel diaries in LSM studies [11,14-16].

LSM is an important biomarker and determinant of population health [3,17-19]. Restricted LSM is associated with higher mortality risks and reduced QoL [5,10,20,21]. It also predicts the development of geriatric syndromes including dementia and falls [5,10,22,23]. Diminished LSM is further linked to future hospitalizations, readmissions, and increased risk of nursing home admissions [24,25].

Multiple varied factors impact LSM itself. The WHO International Classification of Functioning, Disability and Health (WHO-ICF) provides a comprehensive framework, whereby LSM can be considered a measure of participation [26-29]. LSM represents not merely mobility capacity but actual community mobility performance [29-31]. Many diseases, impairments, activity limitations, and environmental, social, and personal factors can restrict LSM (Figure 1) [7,8,10]. Examples of influential diseases include stroke and hip fracture and key impairments such as declines in hearing, strength, or cognition. Poor performance on the activities of daily living can restrict LSM, as can limitations in participation, such as lack of employment. Both environmental contextual factors such as lower neighborhood walkability and personal contextual factors such as poor social network or loneliness can also reduce LSM.

The most established measure of LSM is the self-reported University of Alabama at Birmingham Life-Space Assessment (UAB-LSA) instrument [2,10,32]. Recently, emerging technologies in geographical information sciences (GIS) also provide more detailed and objective measures of LSM [3,9,13,33]. These include smartphone- or wearable-based advanced GPS platforms and accurate, open-source application programming interfaces (API) for environmental mapping [6,16,34].

For the reasons above, the study of LSM is a broad interdisciplinary science in health and medicine. It further integrates diverse sciences including sociology, geography, computer sciences, architecture, urban planning, and the environmental sciences [6,8,15].

There is a significant gap in the literature as contemporary LSM research is conducted mainly in scientific silos and published on diverse platforms. For example, most LS studies in medicine or sociology do not include geographical or built environmental attributes [8,21,27,35-37]. This reduces the impact of the transdisciplinary nature of LSM sciences on both risk assessments and eventual interventions.

The Elderly Activity Life-Space Envelopes (EASE) project is a large interdisciplinary mixed methods study. We first developed a set of LSM outcomes based on biopsychosocial and environmental constructs that underpin the study. The first phase included a large, comprehensive quantitative cross-sectional study on LS and their determinants in older adults. Selected participants from this cohort subsequently underwent an ethnographic qualitative study exploring their travel behaviors. Subsequently, phase 2 integrated phase 1 findings and comprised community design workshops and comparative testing in community locations of the built environment and space usage patterns to provide translational recommendations to improve LSM.

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Figure 1. Life-space mobility (LSM) is a participation measure in the WHO International Classification of Functioning, Disability and Health (WHO-ICF) framework. Assessments performed in the Elderly Activity Life-Space Envelopes (EASE) map to the WHO-ICF domains and illustrate the breadth of the potential factors that may impact LSM outcomes. PTAL: public transport accessibility level; UAB: University of Alabama; UCLA: University of California, Los Angeles.

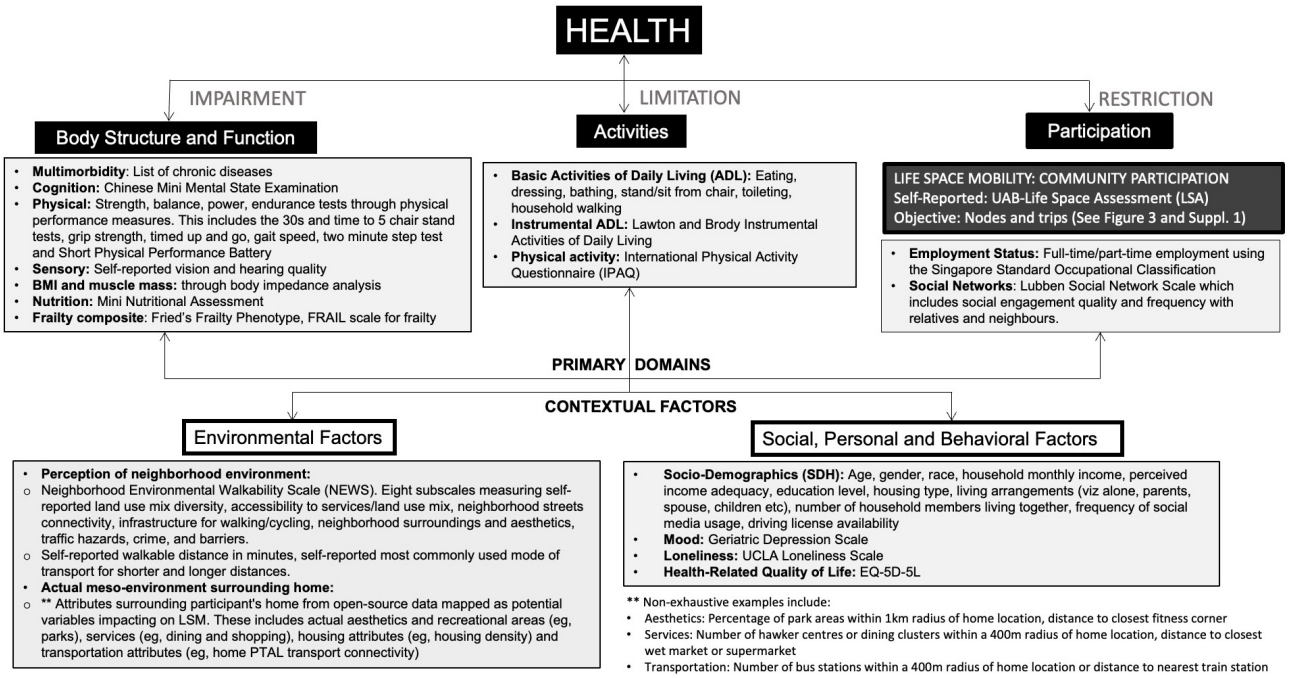

We focus on the main quantitative study methodology in this study. The overarching aims are to determine why, where, when, and how older adults travel in their LS and the health, social, and environmental determinants of these spaces.

In line with national health and urban priorities, we developed 3 primary hypotheses. First, age and LSM are inversely related [13,15,19]. Next, that a state of prefrailty or frailty results in diminished LS [10,38,39], and third, that the participants' home (housing) typology results in significantly different LSM [40,41].

Methods

Ethical Considerations

The SingHealth Centralized Institutional Review Board reviewed and approved the ethics of this study (CIRB Reference Number: 2021/2566). Interviewees signed informed consent forms before participating in the study. All participants were given a 20-SGD (US $15) shopping voucher for finishing the initial in-person assessment and an additional 130 SGD (US $100) on completion of the 14-day e-travel diary [5,16].

Sampling Frame and Sample Size

We recruited inclusively to capture the broad diversity of mobility among community-dwelling older adults in the Central and Eastern regions of Singapore. The key inclusion criteria were minimal. Participants had to be 50 years old or above and reside within the specified geographical area. This geographical boundary was necessary to concentrate and streamline the analysis of environmental attributes rather than having participants scattered countrywide. In addition, SingHealth is the largest health care provider in Singapore, and by working through its community partner arm, these regions fall within the SingHealth catchment area. This facilitated the necessary publicity and center liaison work while enabling us to reach out to a significant proportion and sufficiently wide distribution of Singapore's older population described further below.

We did not specifically restrict participants based on their existing level of community mobility, aiming to capture the full spectrum of LSM ranging from older adults with high mobility to older adults with frailty. Exclusions were refusal or the inability to complete a consecutive 14-day period for GIS tracking and medically unstable participants, for example, older adults with poorly controlled medical, psychological, or behavioral issues.

We first performed a sample size calculation utilizing the UAB-LSA Instrument with age as the primary correlate. The correlation between increasing age and LS, based on a separate cohort of about 800 older adults recruited at community-based senior centers, was −0.21 [26,39]. Comparatively, in a similar study of 1000 older adults in the United States, this is approximately −0.36 [42]. Thus, power calculations indicate that with a sample size of 783, there will be 80% power (β=.20), with a type 1 error rate of 5% to detect a correlation as small as 0.1 between age and LS.

We also factored in a 10% drop-out rate to provide a buffer as participants may not complete the full 2-week period for a valid participation count. Thus, a total recruitment target of 900 older adults was reasonable and practical given our prior experience with community-based research [26,39,43].

For these 900 older adults, we performed quota sampling, that is, the selection of participants based on preset attributes into representative subgroups. These attributes were aligned with the primary hypotheses as having the largest impact on LSM

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and agreed by consensus within the interdisciplinary research team and supporting agencies.

These sampling categories are as follows: (1) two age brackets of 50 to 62 years old and 63 years or older, with a ratio of 40 (“younger-old”) to 60 (“older-old”) in the subgroups. The 63-year-old cutoff corresponds to the retirement age of Singapore citizens and is an age proxy for employment status [44]. (2) Public versus public housing with participants in a 20 (private):80 (public) ratio. This is in line with the nationwide housing type distribution [40]. (3) Frailty status categorized dichotomously by prefrail and frail versus robust seniors. We aimed for a distribution ratio of 30 prefrail and frail: 70 (robust) participants, in line with current Singapore community prevalence rates estimates [26,39,45].

To achieve this broad yet population-representative cohort, we deployed a comprehensive, 2-pronged strategy to ensure wide reach across the SingHealth catchment area. The first prong involved direct recruitment, primarily executed through online registration forms, to capture independent and digitally connected older adults. The second prong focused on community outreach and leveraged collaborative partnerships established through the multi-institutional research team and SingHealth’s community partner arm. This strategy involved working with more than 10 dedicated community partners, such as senior activity centers, which provided essential access to older adults who may not be as digitally active. Wide publicity was further achieved via the investigators’ institutional and community networks, using custom-designed publicity media (Multimedia Appendix 1). This combined approach successfully supported the quota sampling method to ensure representation aligned with the primary hypotheses and local community prevalence rates.

All successfully recruited older adults participated in a community-based, in-person comprehensive assessment, followed by an electronic travel diary tracking of LS over 14 days. The 14-day recording of the e-travel diaries was decided by several factors. Previous research recommends at least a 7-day consecutive period to capture 2 weekend days [7,11,46]. Some investigators suggest that a 14-day period is ideal to account for within-person variability, especially for the nodal extent measures [9,16,47]. A 2-week period may also better corroborate to the UAB-LSA self-reported measure [33]. This balances against the significant participant burden, compliance, and privacy concerns in longer time frames [7,18,30,34].

In-Person Assessment Phase

Overview

This phase comprised a comprehensive multidomain geriatric assessment (MDGA) including a set of physical performance measures [39]. This custom-designed assessment itself was developed based on the overarching biopsychosocial constructs of the WHO-ICF, Frailty, and Intrinsic Capacity (Figures 1 and 2) [26]. These variables were also selected based on their prior usage in previous LSM literature and interventional potential to increase LSM [8].

This also drew on our previous work in Individual Physical Proficiency Test for Seniors, a community-based frailty and sarcopenia screening platform that has been implemented and tested for feasibility [26,39,43,45]. We modified the Individual Physical Proficiency Test for Seniors MDGA for EASE to also include environmental determinants, while keeping the length of assessment itself manageable for both the researchers and the older adults. Figure 2 shows the domains and variables in the MDGA underpinned by the intrinsic capacity–external environment construct.

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Figure 2. Life-space mobility (LSM) as the interface between the WHO-Intrinsic Capacity construct and the external environment. Intrinsic capacity encompasses the 5 key domains: locomotion, cognition, psychosocial, sensory, and vitality. Assessments performed in Elderly Activity Life-Space Envelopes (EASE) map into intrinsic capacity domains. SPPB: Short Physical Performance Battery; UCLA: University of California, Los Angeles.

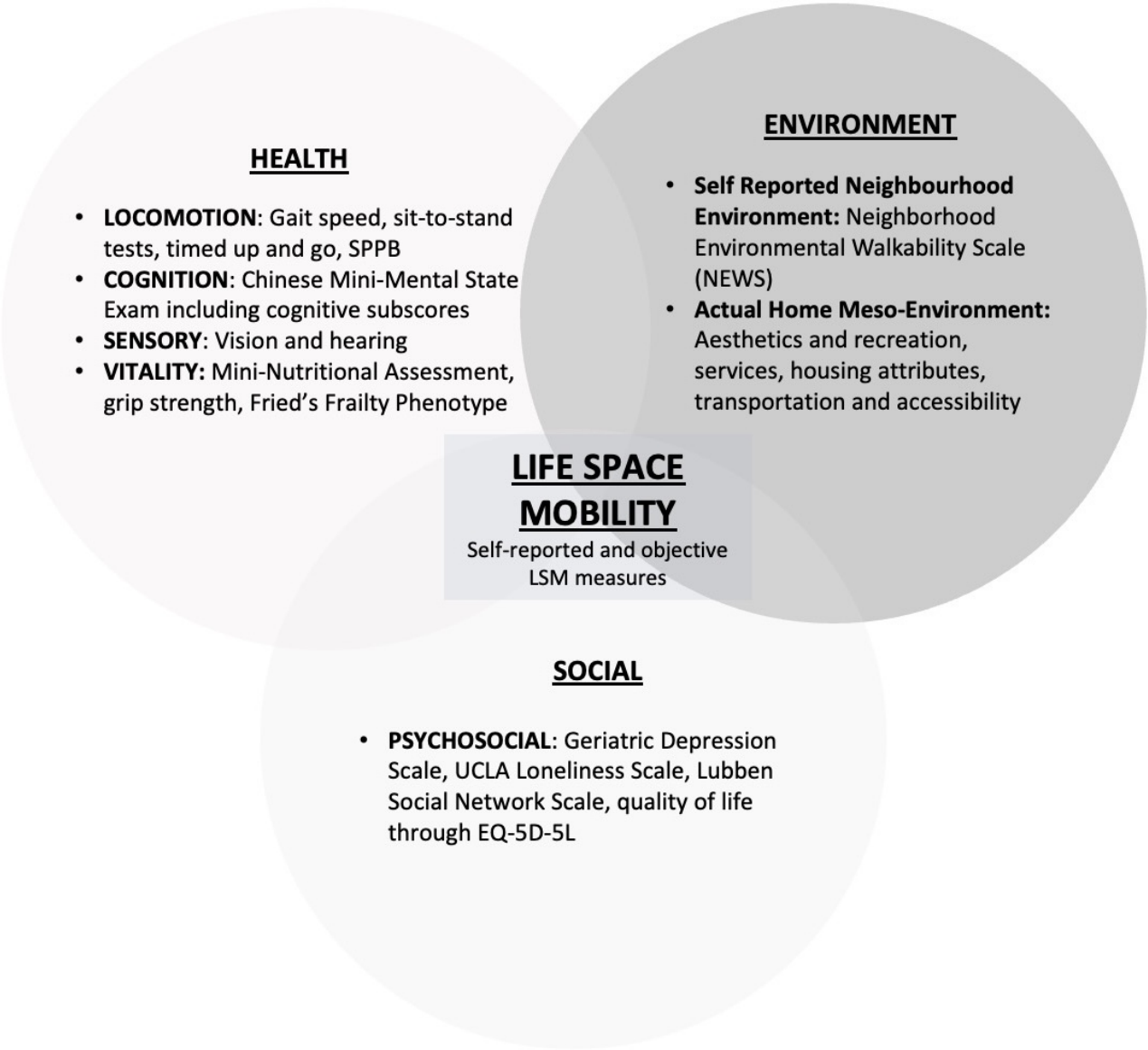

University of Alabama at Birmingham's Life Space Assessment

The UAB-LSA was used to measure self-reported LS in this study [32]. It is the most widely used questionnaire worldwide and is internationally validated [2,10]. It provides a composite measure by combining the level of life space attained, degree of independence, and frequency of attainment over the past 4 weeks. The levels have been adapted for relevance to the local context as more than 95% of the population lives in public or private apartment blocks [26,39]. These are as follows: (1) level 1: rooms of the home, other than the bedroom; (2) level 2: an area outside the home, but within the block; (3) level 3: places in the neighborhood, other than the block; (4) level 4: places outside the neighborhood, but within their residential estate or township; and (5) level 5: places outside their residential district or town.

The maximum score is 120, and scores of less than 60 are categorized as restricted LS with a difference in 10 points being significant [35,48]. Recent summative reviews indicate that the global LSA is 66.8 with 42% having restricted LSM [24].

Frailty State

We aligned EASE with the National Frailty Strategy for Singapore to provide translational relevance [38,49]. Accordingly, we screened for frailty with the Fried's Frailty Phenotype and the FRAIL (Frailty, Resistance, Ambulation, Illness, Loss of weight) scale. The 5 components of the Fried's Frailty Phenotype are weight loss, exhaustion, physical activity, walk time, and grip strength [50]. The FRAIL scale consists of the 5 questions on fatigue, resistance (strength), ambulation, illness (multimorbidity), and loss of weight [51].

For both of these instruments, the summative score of 0 indicated a robust status, 1 - 2 points indicated a prefrail status, and 3 - 5 points indicated a frail status. Where available, the criteria were adjusted based on established local or Asian norms [43,45].

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Quality of Life

Health-related QOL was measured using the EuroQol 5-Dimension 5-Level [52]. Five dimensions are assessed, that is, mobility, self-care, usual activities, pain or discomfort, and anxiety or depression, with 5 response levels per dimension (1=no problems to 5=unable to or extreme problems).

Five-digit profiles, ranging from 11111 (full health) to 55555 (worst health), were generated by concatenating scores across the dimensions. These 5-level profiles were then converted to index values using a crosswalk calculator, applying Singapore's 3-level value set [53,54]. Participants also rated their overall health on the EuroQol Visual Analogue Scale, a 0 - 100 visual analog scale (worst to best imaginable health) [52].

Chinese Mini-Mental State Examination

The Chinese Mini-Mental State Examination is an established screen of general cognitive function that is locally validated and deployed in LSM studies [49,55,56]. It consists of 28 questions assessing the 6 cognitive domains of orientation, registration, attention, calculation, recall, language, and praxis. One point is given for a correct answer, and a Chinese Mini-Mental State Examination score of <21 indicates cognitive impairment.

Geriatric Depression Scale-Short Form

The Geriatric Depression Scale-Short Form is a validated, sensitive, and specific 15-item self-report questionnaire to screen for depression in older adults [14,57,58]. It evaluates the emotional and cognitive symptoms rather than the physical signs of depression. "Yes" responses to negatively worded questions and "no" responses to positively worded questions are given a score of 1. A total score of 5 - 9 points suggests depression, and ≥10 was almost always indicative of depression.

Lubben Social Network Scale

We used the Lubben Social Network Scale-Revised instrument to measure the strength of social network and assess social isolation [59,60]. This 12-item scale measures the network size, closeness, and frequency of contact with family members and friends. The score for each item ranges from 0 to 5 with a maximum score of 60. A score of <20 indicates restricted social networks and a high risk of social isolation.

University of California, Los Angeles Loneliness Scale

Loneliness was assessed using the University of California, Los Angeles 3-item loneliness scale [20,58,60,61]. It measures 3 dimensions of loneliness: lack of companionship, being left out, and feeling isolated. A 5-point frequency scale, ranging from "never" (0 point) to "always" (4 points), was used to evaluate responses to the 3 items. Higher scores indicated a higher level of perceived loneliness.

The Neighborhood Environment Walkability Scale

The Neighborhood Environment Walkability Scale (NEWS) is the most used measure of the perceived neighborhood environment worldwide [62,63]. We adopted the NEWS-Abbreviated (NEWS-A) version for practicality as it has been used successfully in older populations [64]. The NEWS-A assesses the key environmental dimensions of a person's subjective experiences of their neighborhood environment.

These domains are accessibility to services, land use mix (the diversity of destinations), street connectivity, infrastructure for walking, neighborhood esthetics, traffic, and personal safety [15,64]. All items in these domains are rated on a 4-point Likert scale ranging from 1 ("strongly disagree") to 4 ("strongly agree"). Due to the length and complexity of the questionnaire, responses of "do not know" were allowed.

International Physical Activity Questionnaire-Short Form

Weekly physical activity was estimated using the International Physical Activity Questionnaire-Short Form, which weights the time spent in each activity intensity with the estimated metabolic equivalent of task (MET) [49,65,66]. MET minutes per week were calculated by multiplying the respective MET values ("vigorous"=8.0, "moderate"=4.0, and "walking"=3.3) with the number of minutes the activity was carried out and the number of days the activity was carried out. Participants were asked to estimate the number of hours they spent sitting on an average weekday serving as an indicator of time spent in sedentary activity [65]. The products across the 3 levels of activity were summed to derive the total MET minutes per week.

Physical Assessments and Performance Measures

Physical assessments performed include the BMI and muscle mass through multifrequency segmental bioelectrical impedance analysis (MC-780 MA P, Tanita). Physical performance measures included the handgrip strength test, 5 times and 30-second sit-to-stand tests, Timed Up and Go test, 10-m walk test for gait speed, Two-Minute Step Test, and the Short Physical Performance Battery [8,21,34,37,67]. Cut-off thresholds for these measures prioritized local and Asian norms, frailty, and sarcopenia guidelines where appropriate and available [26,39,43,49,68].

Objective Life Space Measures

Overview

Objective LSM measures through GIS systems have distinct advantages over self-reported LSM. These include enabling assessment of older adults with cognitive challenges, reducing recall bias, and documenting the duration and type of travel modes and the places participants go to [1,18,34,69].

However, there is no consensus on what constitutes these objective measures [47]. Classification frameworks exist; however, these constructs tend to be technical with terms such as nonexclusivity and stability [1,3,5,9,33,70]. This can be challenging to investigators in fields such as health and sociology.

We developed a focused, easy-to-understand framework of life-space GIS indicators to bridge the interdisciplinary nature of the EASE project (Figure 3). We considered measures with availability of comparative data in the literature, their known impact on health or relation with sociodemographics, their importance in future interventions, and the capacity of

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present-day smartphone-based apps to obtain these data [1,18,30,71,72]. Figure 3 is a brief description of this framework.

Figure 3. Framework of objective geographical information sciences (GIS) life-space mobility (LSM) measures based on Elderly Activity Life-Space Envelopes (EASE) primary aims of "where older adults go to" and "how they get there."

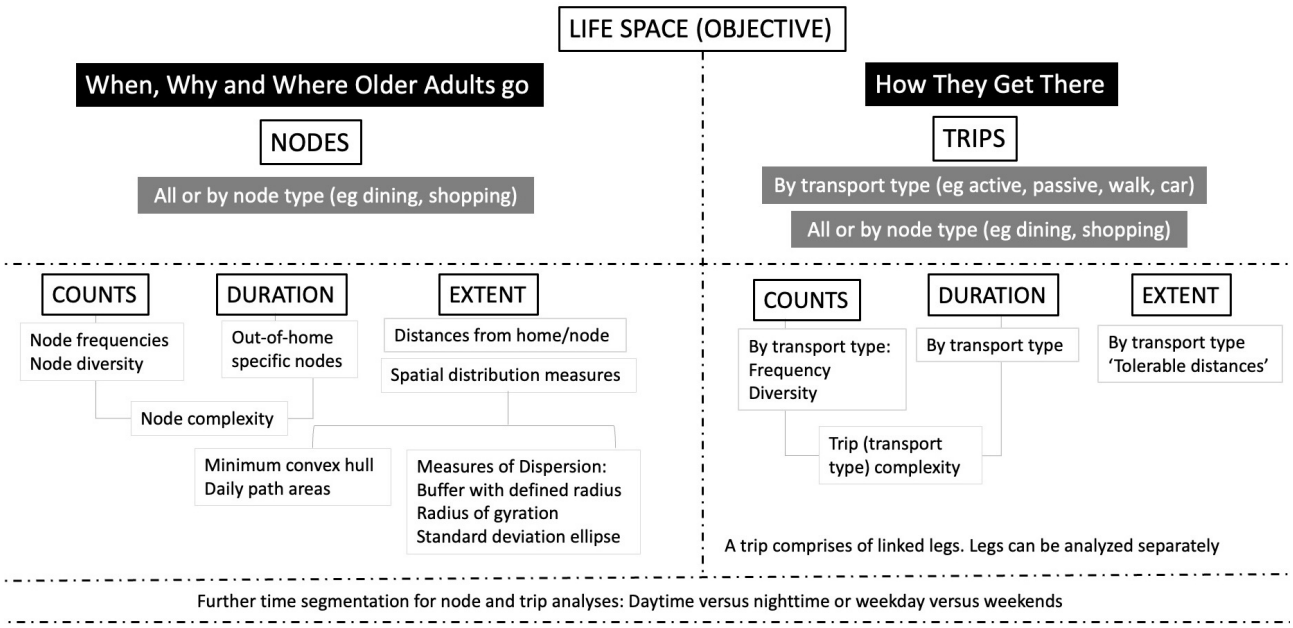

We first classified measures into the primary aim of this project articulated previously of "where do older adults go to" and "how do they get there."

For measures in the first group, we adopted the neutral term "nodes" to describe where the participants went or what they did there. We use the term "nodes" consistently throughout the EASE study for this purpose. Nodes have been variously termed attributes, opportunities, staypoints, stops, locations, and activity points in other research based on their underlying study aims or construct [6,16,33]. We defined 14 types of nodes for this study based on large local surveys, existing literature, and conceptual models categorizing nodes by activity importance [5,7,11,14,33,40,53]. This list of nodes is given in Figure 4.

Figure 4. Trip diary interface. Snapshots of the customized X-ING Future Mobility Survey (FMS) app showing selection for activity or nodes, selection for travel type, trip, and trip legs.

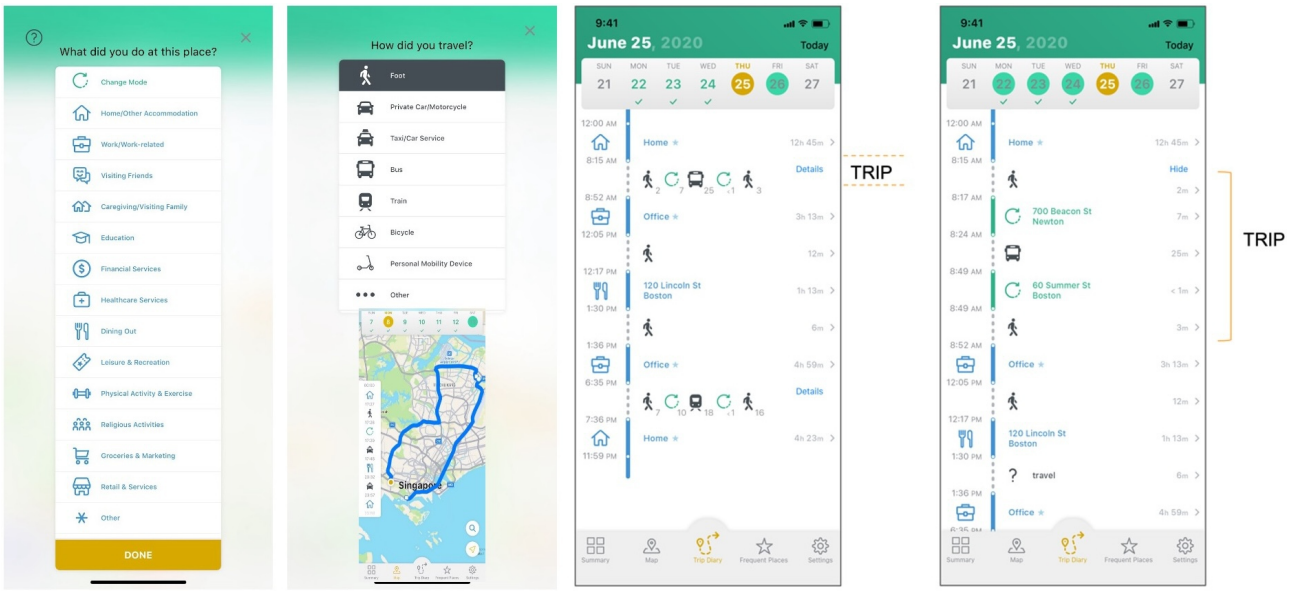

Node Characteristics

Node measures are divided into counts, durations, and extent. They can be analyzed as a whole or by a specific node type. Node counts include the *frequency* of the nodes visited and the count of the number of different node types (node *diversity*) visited [1,18,33,53]. The node *duration* is the time spent at a node [16,31,53]. A composite of these measures is node *complexity*, partially based on entropy concepts [33,34,73]. Higher complexity indicates greater variability in either frequency, type, or duration spent at the nodes when time periods are compared.

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The node extent refers to the distribution of these nodes in the geographical space. This is measured by distances from home or between the nodes. Subsequently, a count of nodes can be done within a defined radius from home or a specified (eg, work) node [5,74,75]. Weighted or unweighted spatial metrics that encompass the nodes can also be obtained, including the minimal convex or concave hull, standard deviation ellipse, daily path area, and radius of gyration [1,7,13,19,30,56]. Additional detailed descriptions of objective LSM measures are available in Multimedia Appendix 2.

Trip Characteristics

In the second group of measures, we defined the term "trip" to represent how older adults get to the nodes. Trips are variously termed moves, excursions, trajectories, or paths in the GIS literature, but we believed "trips" are clearer and more distinctive in interdisciplinary research [1,9,33,34].

Trips are analyzed by their type (mode) of transport. A single trip can be further divided into trip legs with different modes of transport. A common example is a 3-leg trip to a shopping center comprising a walk from home to a bus stop, then a bus ride, and finally a walk from the bus stop to the shopping center. Like nodes, these trips can be analyzed as a whole or to specified node types. Individual legs within trips can also be analyzed.

Trip measures are also divided into counts, duration, and extent. Trip count would be the frequency of trips on a specified type of transport. Trip count (diversity) is the count of different transport modes used [1,72]. The trip duration is the length of time spent on a trip by a transport type [6,19]. We distinguished between active and passive transport modes as there are better health outcomes when more time is spent on active modes like walking and bicycling [5,6,33,76].

A higher trip complexity then represents a greater variability in trip frequency, type, or duration by transport modes between time periods. The trip extent refers to the trip mode as a function of the node extent as described above [5,9,16,77]. For example, walking is the most common mode of transport within 2 km from home. In other words, 2 km is a tolerable walking distance [6,31].

For all the trip and node measures, further insights can be obtained by segmenting data between day or night, or weekday or weekends [19,20,33,69,71]. Both linear and actual (GPS) distances were collected in EASE. Although GPS distances are more accurate, this is often limited by technical challenges due to reception issues in built-up or enclosed areas, or hardware issues like battery life on smartphones [75].

Smartphone Travel Diary Survey System

Our GIS application, X-ING, is based on Mobile Market Monitor's Future Mobility Survey (FMS) architecture [16,78,79]. This is a smartphone-based, automated mobility data collection system that has been field-tested and deployed worldwide to measure LSM and community travel patterns [16,77,79]. It is compatible with Android and iOS systems and has been designed to collect accurate travel data from the phone sensors in a nonintrusive manner while minimizing battery consumption [78]. Briefly, the FMS system consists of 4 interconnected components:

1. The X-ING app that unobtrusively records and integrates the relevant GIS sensor data. This includes GPS, GSM cell tower, Wi-Fi network, accelerometer, and barometric data acquired in the user's smartphone.
2. The dedicated server hosting the database as well as the data processing and machine learning algorithms. To maintain data robustness where GPS signals may be weak (eg, indoors or underground), these algorithms perform multisensor fusion, integrating all raw GIS sensor data (GPS, GSM cell tower, Wi-Fi, and accelerometer) for continuous and accurate location inference. These algorithms detect stops (nodes) and infer travel modes based on the user's GIS sensor data, local contextual data such as public transport network locations, and the user's previous validated trip diary.
3. Trip diary interface within the X-ING app that allows users to verify their daily travel including mode of travel, node activities, and locations (Figure 4). The interface also prompts users to provide supplementary trip details such as whether the participant was the driver or passenger in car transport modes.
4. The data management system used by the researchers to monitor, manage, and quality control incoming data throughout the entire study duration.

The X-ING app was customized for the EASE project, taking into consideration local geography, transportation networks, and GIS infrastructure [16]. All data were encrypted and secured both in transmission and within storage and anonymized in compliance with Singapore's Personal Data Protection Act and the institutional review board [80].

The details of the data processing are provided elsewhere, and a summary is as follows [16,77-79]. Raw data were first filtered to remove clearly invalid points or nodes that occur, especially when there is a paucity of GIS sensor data. Examples include distance errors or high altitudes that are incongruent with Singapore's geographical attributes.

Next, candidate stops are generated through a clustering algorithm where GPS data indicate that participants have been within an area of a 50-m diameter for at least 1 minute. These stops are then verified against sensor place signatures that the user visits frequently. New candidate stops are checked against these signatures, and if a match is found, the stop is moved to the recorded home, office, or nodal activity location. Stops are further consolidated and merged by integrating other sensor information including GSM cell tower, Wi-Fi, and accelerometer data to eliminate phantom trips or location jumps caused by data noise. For example, Wi-Fi signatures are used to determine if participants are in the same indoor location when GPS data are unavailable.

Movement trajectories were then segmented into active or passive transport modes by integrating smartphone data sources like accelerometry and GPS to provide better precision to the transport type. The app further incorporates information of local transport network data (eg, to observe that routes coincided with train routes or bus stops) and user-validated input. Algorithms

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include decision trees to classify shorter stops within a trip into potentially important stops like changing of travel modes or pick-up or drop-off activities versus unimportant ones.

These processed data were then presented on the trip diary interface (Figure 4) where the participant confirms the node locations and trip-related information including the type of vehicular transport used. The FMS platform has learning attributes; thus, the participant burden to verify the data diminishes as the algorithm learns LSM patterns based on its existing databases and preceding user validations. Where possible, we also addressed ambiguity by recoding activities and travel modes. Specifically, we examined all linked free-text entries when the "Others" option was selected, created a free-text dictionary, and successfully recoded 2086 (34.2%) of the 6084 free-text entries across the dataset to the appropriate travel mode or activity. Backend data monitoring was performed, and check-ins were done if there were no valid data for 3 or more consecutive days [33].

For older adults who did not have, or declined using, smartphones, manual paper logs were used. Researchers then input these data into a web-based diary entry system, which is subsequently integrated into the same FMS project database to ensure data consistency.

Home Locations and Built Meso-Environments

Overview

The home location was defined as the majority of overnight stays at a node [9]. In EASE, home nodes are represented by the local 6-digit postal codes. Validation checks were done by first geolocating participants' self-declared postal code home address (self-declared node, SDN) with the OneMap API [81]. We next determined the GPS location (GPS node, GPN) of the participants at 0300 hrs (defined as overnight stay point) on the majority of nights [9]. We subsequently evaluated the similarity of each participant's SDN and GPN location by using a set of guidelines of average block dimensions and spacings to account for deviations [82]. All GPN or SDN deviations more than 100 m were visually inspected on OneMap, and GPNs were snapped to the closest postal code location if this was deemed to be the likelier home location. The large majority (98.7%) of the final home points were SDNs [34].

We next proceeded to describe their unique meso-environments around the participants' home up to a 1-km radius buffer by loading open-source environmental attribute layers into QGIS [6,70,76]. We prioritized using sources based on authoritativeness and accuracy [75].

First, we included GIS data from the government agencies. These include OneMap, Data.gov.sg, and the LTA DataMall [81,83,84]. Next, we applied layers from established GIS providers, and these were OpenStreetMap (through Quick OSM) and the Google Maps API. Finally, any further data needed were obtained from known reputable local websites, particularly data on private housing attributes.

We used OneMap as the basemap and applied 4 groups of environmental attributes as vector layers, merging where appropriate.

Esthetics, Recreation, and Activity Areas

This included National Parks and Reserves (GovTech, Singapore 2025), complemented by "Parks" and "Playgrounds" [85]. We further added layers of activity areas and fitness corners in the community [83,85].

Services

Dining vector layers include hawker and food Centers [83] and dining establishments [85]. Marketing layers include (wet) markets and supermarkets [83,85]. Shopping mall vectors were also layered, as were senior activity centers [14,76,85].

Housing

We obtained public and private apartment buildings and landed housing attributes [83,85]. Consistent factors documented were the age of these buildings and the number of dwelling units within a building reflecting housing density [76].

Transportation

These metrics include geospatial vectors of public transportation location such as bus stops and mass rapid transit train stations [84]. We also added a road layer to calculate both connectivity and density metrics. This layer contains both vehicular road networks, as well as designated cycling paths and park connectors vectors [83,84].

Accessibility

We determined the Public Transport Accessibility Level (PTAL) for each participant's home node. The PTAL itself is a well-known metric of transport connectivity, and we used an established algorithm adapted for the Singapore context [86]. The determinants in the PTAL score include the walking distance from home to bus stops and mass rapid transit stations and the count and frequency of different buses or train services at each of these transport nodes [86].

Vertical Life Spaces

We also incorporated advancements in smartphone technology to record vertical LSM [87]. We utilized an algorithm that integrated both GPS and barometer sensors, whereby the GPS signals identify horizontal location entry points, while the barometric data detect relative changes in atmospheric pressure during rapid vertical movements. This building infrastructure–independent method has shown good accuracy rates previously [87]. We primarily focused on vertical trips at home locations in this pilot exercise to balance the significant burden required to validate many vertical movements in other locations such as workplaces or shopping malls.

Standardization and Quality Assurance of the 14-Day Life Space Tracking Window

To ensure the consistency, integrity, and quality of the objective LSM data collected, the 14-day tracking period was strictly standardized across the 3 phases of preparation, in-field data collection, and final data standardization.

In the preparation and commencement phase, the tracking period officially commenced the day immediately after the in-person comprehensive baseline assessments. This ensured a consistent starting point and minimized recall bias. All patients underwent

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a mandatory training session by the research team members on the use of the X-ING smartphone app or the corresponding manual data log, including assistance with installation and a show-back demonstration on its use.

During the in-field data collection phase, there were 2 key quality assurance measures. First, there was the integration of daily prompted recall via the FMS/X-ING system. At the end of every day, all participants were prompted and required to validate the automatically inferred data in their trip diary, including node locations and travel modes as described previously. This validation process served as the essential check to capture ground truth information that the X-ING app inferred. Second, the research team rigorously contacted participants every 2 - 3 days if compliance appeared low or if data quality issues were flagged by the backend system. For older adults who could not or had difficulty using the app, a paper-based travel diary was provided to ensure continuity of data collection and actively prevent missing days.

The final standardization phase involved rigorous backend processing to ensure 14 full days of valid travel logs for inclusion in the cohort for analysis. This included invalid day removal where days were flagged as invalid if participants did not carry their smartphones during community travel, made trips outside of Singapore, or voluntarily declared the day as invalid. Further, only participants who completed the full 14 days of valid electronic or paper-based travel diary data were retained for the final analysis of objective LSM measures. Those with insufficient data were ultimately withdrawn from the study cohort used for these specific analyses.

Statistical Analysis

A combination of coding and statistical tools was used in EASE. R version 4.3.2 (R Core Team) and SPSS version 29 (IBM Corporation) were the primary quantitative analysis software, and QGIS version 3.34 was the primary spatial software used [13,30,56,71]. Python version 3.12 (Python Software Foundation) and its PyQGIS variant (QGIS Development Team) were used to extract, aggregate, and transform data from multiple sources, develop spatial metrics, and analyze spatial data [13]. As this paper focuses on the background and methods in EASE, we primarily employ descriptive statistics only. This includes means (SD) and medians (IQR) to provide overviews of central tendencies and data variability.

For the 3 primary hypotheses on relationships between age, frailty status, and housing typology on LS, we will first define the LS outcomes, which include both self-reported (UAB-LSA) and objective GIS LSM measures (Figure 3). We will initially explore these associations using bivariate analysis, such as Pearson correlations (for continuous variables like age) and independent samples *t* tests or analysis of variance for categorical variables (frailty status and housing typology) against the LS outcomes.

To test the hypotheses while controlling for confounders, we will develop multivariate regression models. Multiple linear regression will be the primary method for continuous LSM outcomes (eg, LS spatial measures such as mean convex hull or standard deviation ellipse), while for count data (eg, node frequencies, trip counts), a generalized linear model, such as Poisson or negative binomial regression, will be employed to handle the non-normal distribution of these variables.

Covariate selection will be guided by both extant literature and clinical or multidisciplinary consensus, drawing from the comprehensive set of EASE variables categorized by intrinsic capacity (eg, physical performance measures like grip strength) and external environment (eg, neighborhood walkability scores from NEWS-A), or by health, social, and environmental characteristics. Specifically, models will be adjusted for essential confounders including important sociodemographics (eg, education, income, private car availability).

Prior to model interpretation, assumptions will be rigorously assessed, including analyses of the normality of the residuals and linearity of the relationship between continuous variables. Variables will be mathematically transformed if distributional or linearity assumptions are substantially violated. Given the 3 primary, prespecified hypotheses, a 2-sided significance level will be set at P=.05.

Further statistical methods will depend on the specific hypotheses of future studies.

Quality of Trips and Life-Space Activity

We also acknowledge the importance of understanding the subjective experience and quality of these trips—often referred to as semantic attributes of mobility or captured via Ecological Momentary Assessment in travel diaries [7,15,16]. However, for the projected large quantitative sample of over 1000 participants, requiring detailed, self-reported text descriptors on smartphones for trip purposes, meaning, or satisfaction for every journey poses an onerous burden on older adults, potentially increasing recall bias, non-response rates, and necessitating substantial staff training and daily support. Instead, our quantitative protocol prioritized accuracy and objective data capture of transportation and nodal activity by requiring participants to validate automatically inferred trip information daily, minimizing self-reported text input as described above.

The issues of trip purpose and quality, and the meaning of places (placemaking) were comprehensively addressed by the study's mixed methods design through a significant qualitative component that used ethnographic methods. A subset of 60 participants from the main cohort was purposively selected based on the key quantitative stratifications (age group, housing type, and health or frailty status) to ensure representation across the main study hypotheses. These participants underwent a 2-session qualitative assessment: a semistructured in-depth interview involving cocreation of a mental map to explore the meaning of places and travel inclinations, followed by a "go-along" interview. During the "go-along" interview, researchers accompanied the participants on a self-selected typical route, using a combination of participant observation and dialogue to document the real-time social context, pleasurable attributes, and environmental facilitators or barriers that contribute to the quality and satisfaction of their community mobility. This in-depth approach, analyzed using principles of thematic analysis, provides a rich, granular, and controllable dataset on the subjective experience of travel that the

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high-volume quantitative travel diary could not achieve. It also strongly complements the quantitative LSM measures by offering contextual, explanatory data, for example, identifying environmental barriers for older adults or older adults with frailty with restricted LSM [5,31].

Results

We recruited 1131 older adults at 7 community-based sites in Singapore. A total of 13 (1.1%) participants did not complete the 14-day electronic or paper-based travel diary and were withdrawn, leaving 1118 successfully completed participants who were included in this study.

The large majority (n=1062, 95%) successfully documented their travel diary on their smartphones, with the rest using paper-based travel logs. A total of 88,166 node points were recorded, excluding nodes due to a change in transport mode between trip legs, but including home nodes. There were 76,741 trips and 106,323 trip legs documented through the e-travel diary platform. Valid vertical LSM data were obtained from 228 participants.

The average age was 63.8 (SD 7.6) years, and there were 634 (57%) "Old-Old" older adults. About two-thirds (n=760, 68%) were female, 74% (n=1025) were of Chinese ethnicity, and 68% (n=759) were married. A significant proportion of the cohort was still either in part-time (n=221, 20%) or full-time (n=257, 23%) employment. The most common housing typology was public apartments (n=842, 75%). Around 62% of the older adults had a valid driving license. Healthwise, 326 (29%) were prefrail or frail by the criteria listed above. Demographic distribution data are available in Multimedia Appendix 3.

On average, the linear distance from home to the nearest dining option was 118 (SD 92) m, 1.8 (SD 1.5) km to a hawker center, 309 (SD 220) m to a supermarket, 688 (SD 422) m to a shopping mall, and 713 (SD 603) m to a senior activity center. The median PTAL score was 4 (IQR 3). The mean score of the UAB-LSA LSM was 90.2 (SD 18.13), and average convex hull was 101.7 (SD 84.6) km^2.

Discussion

To the best of our knowledge, EASE is the most comprehensive, large-scale LS study that we are aware of with its holistic assessment of multiple domains and the range and complexity of LSM measures. We had included both objective and perceived measures of LSM and believe they complement each other in providing different information on activity spaces. The lack of significant associations between GPS and self-reported data suggests that they measure different LSM dimensions [18,34,53,66].

The EASE study's dataset is also wide-ranging and rigorous due to its foundational underpinning of potential predictors of LSM through contemporary aging and disability biopsychosocial frameworks. This notably includes the WHO-ICF; abbreviated comprehensive geriatric assessments models (MDGA); and population health constructs encompassing social, behavioral, and environmental determinants [6,8,15,28]. This meticulous approach ensures alignment with critical population health issues such as frailty, sarcopenia, disability, physical fitness, and intrinsic capacity in older adults [26,71]. Consequently, our dataset positions itself as a valuable minimum dataset, aligned with national priorities, to advance understanding and interventions in these domains.

In this light, we had considered the time required to complete the in-person assessment prior to participant fatigue. Several LSM GPS studies have minimal, if at all any, in-person contact [13,18,19,88]. However, the in-person assessment permitted the assessment of cognition, physical performance measures, and muscle mass for the health-related constructs [37,67,69]. Overall, participants took about 2 hours to complete this phase. We alternated the physical performance measures, questionnaire portions, and information about the app usage where necessary to retain focus and minimize fatigue. We believe that this assessment set was feasible and practical as all recruited participants completed the in-person phase.

The proportion of the older adults (n=13, 1%) who dropped out from the 14-day travel diary was significantly lower than the expected 10% buffer [18,34]. This positive finding reflects the effectiveness of several strategies and the cohort's characteristics. The participants' general "tech-savviness" facilitated their engagement with the travel diary system, while the comprehensive in-person app demonstration reduced uncertainty and user errors. Open bidirectional communication was also pivotal [33]. Participants were encouraged to clarify concerns throughout the study, complemented by the research team's proactive data management, including backend reviews and timely reminders to participants. The study's methodological design, which incorporated tiered completion incentives, also contributed to the high retention rate [16,18,19,67]. Furthermore, the low dropout and missing data rate was a direct result of the study's robust, multilayered quality assurance framework. This integrated system, combining the X-ING app's automated algorithmic inference and daily participant-driven validation with rigorous human monitoring and data cleaning, effectively maintained data quality and completeness for the entire cohort, negating the need for complex, post hoc imputation methods for activity or travel modes.

Potential research areas include relationships between objective LSM measures (eg, trip length and dining nodes) or between self-reported and objective LSM measures (eg, between the UAB-LSA and the minimum convex hull) [18,34,53,73]. A second research avenue will investigate the demographic, health, social, behavioral, and environmental factors influencing LSM measures [47,53]. This would involve studying how various population health themes like aging, frailty, intrinsic capacity, mental health, and QoL relate to each other and impact LSM [1,20,31,53,71].

We also aim to develop participant LSM phenotypes and profiles through cluster analyses [33,73,79]. These include identifying characteristics of the older adults who predominantly travel during the day versus night, those who use various transportation modes, or those exhibiting specific travel node patterns such as home-work-home or home-dining-shopping-home [16,77,79].

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Further, utilizing unique meso-environmental attributes derived from open-source data offers an unexplored but promising research opportunity. By adopting a "bottom-up" and "top-down" approach, researchers can investigate how individual movements within the environment ("bottom-up") align with broader urban planning and transport policies ("top-down") [76,89]. This includes exploring correlations between elements like the PTAL transport connectivity and actual LSM or assessing if housing density and road infrastructure relate to mental health aspects such as depression [6,7,75,86].

We hope to translate the work through important integrative themes. We highlight 2 important themes of walkability and food behaviors [13,47,76,90]. Walkability is linked to enhanced health and social outcomes, aligning with Singapore's urban design goals of a walkable city and the WHO Healthy Cities blueprint [91]. Similarly, dining activities hold significant health and social implications, influencing government planning that promotes social dining spaces such as hawker centers [16,90]. The baseline dataset serves as a foundation for qualitative research and phase 2 exploration, ultimately guiding city planning interventions toward active aging and community well-being.

Finally, an advancement in EASE is the pioneering mapping of 3D LS as a further LSM outcome measure. In our study, only 20% (n=228) of the older adults had smartphones with barometers capable of measuring vertical movement, but this will increase with advancements of cell phone technology incorporating sophisticated sensors and algorithms [87]. This is particularly relevant in densely urbanized settings where LSM involves vertical movement within multifunctional buildings, a situation further intensified by the COVID-19 pandemic, which has blurred lines between home and workplace environments [91].

A potential limitation of the EASE study is its focus on older and community-dwelling participants, which may limit the generalizability of the findings to other demographic groups. However, this represents the tight balance against the (already) significant resources required to conduct such an extensive study. To mitigate this, the quota sampling frame allowed us to concentrate on the most relevant variables and ensure representation of the key characteristics within the cohort. Additionally, our focus on community-dwelling participants was intentional, as we aim to establish LSM measures as an effective screening tool before individuals develop adverse health outcomes. We could also have further included accelerometry data to measure step counts or physical activity [19,34,47]. However, we prioritized GIS information due to battery life limitations and the reluctance of participants to use another wearable [73].

Another established limitation is the reduced measurement accuracy of GPS systems for highly granular movement within dense urban infrastructure, basements, or underground transport systems, such as train tunnels. However, the methodology of the EASE study was deliberately balanced with its central research goal: characterizing LSM, which focuses on the extent and complexity of travel and activity between distinct community nodes (eg, home, parks, shops, clinics). Consequently, we considered the short duration of activity loss experienced in these sheltered areas a minor trade-off, which is offset by the robustness gained in accurately mapping the overall extent and frequency of out-of-home activity, which forms the core of LSM assessment. Furthermore, to address a common gap in 2D mobility studies, our comprehensive data fusion protocol incorporated signals from GPS, cellular networks, and Wi-Fi, in addition to barometric sensors, in capable smartphones to explicitly capture 3D life-space mobility, such as ascending floors within a building, and to supplement location data in areas where GPS signals are attenuated, like indoors or underground structures.

A further potential limitation of the EASE study is that the project is conducted entirely in Singapore, within its specific societal and environmental context. However, the core strength of this protocol is its high replicability and generalizability across diverse international contexts. This is achieved through the use of universal biopsychosocial constructs (like WHO-ICF, Frailty, and Intrinsic Capacity), deployment in a high-density urban testbed, the development of a novel and universally translatable objective construct for trip or node measures, and a commitment to sharing a comprehensive research toolbox with the global community.

The integration of big data into LSM studies like EASE presents both promising opportunities and significant challenges for future research [25,92,93]. Big data, characterized by its high volume, velocity, and veracity, enable a detailed analysis of LSM through GPS, accelerometry, wearable technology, RFID, and infrastructural sensors [16,19,20,34,58,88]. This can be further enhanced by integration with sophisticated social media platforms within the Internet of Things ecosystem [94]. The fusion of electronic health and social records with LS analytics through artificial intelligence also allows for precision medicine, providing personalized health interventions and comprehensive community participation profiling through self-biofeedback and risk monitoring [17].

However, the EASE research team also believed that we were approaching a ceiling on the amount and granularity of data participants would be prepared to give [66,88,95]. As LSM research becomes more pervasive, safeguarding privacy through coherent governance and legislation is paramount. Researchers have to navigate varying personal thresholds for data sharing, often leading to participation rejections and smaller sample sizes [71]. This is an evolving challenge that must involve the consensus between the interdisciplinary stakeholders in future LSM research.

In conclusion, the EASE study incorporates a comprehensive methodology, integrating LSM within population health themes through a holistic health, social, and environmental framework. By utilizing both self-reported and objective LSM measures, EASE not only deepens the understanding of LSM but also introduces an interdisciplinary language for objective LSM markers, enhancing cross-disciplinary communication and research integration. The feasibility and practicality of the study are highlighted by its low drop-out rate and use of open-source software and public data, providing a minimum dataset that establishes a robust foundation for future research. This

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framework opens several avenues for innovative exploration, from analyzing diverse determinants that impact LSM to developing practical, policy-driven interventions. We hope that the methodology and future findings in EASE significantly contribute to the development of LSM sciences, and further to active aging, urban planning, and public health, ultimately aiming to improve the QoL of older adults.

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Data Availability

The datasets generated or analyzed in this study are not publicly archived or available due to the highly sensitive and identifiable nature of the integrated data. Specifically, the combined dataset includes high-resolution geospatial information including the participant postal codes, which map to exact address locations, the home meso-environments, alongside comprehensive individual-level demographic, health, and functional assessment metrics. The triangulation of these detailed data points presents a significant and unavoidable risk of participant reidentification, which would violate the terms of ethical consent and contravene Singapore's Personal Data Protection Act.

However, to ensure the full transparency and replicability of the methodology, all self-report instruments and derived objective measures, structured according to the WHO International Classification of Functioning, Disability and Health and Intrinsic Capacity frameworks, are fully detailed in the study's figures (Figures 1-3), and the LSM objective measures construct is detailed in Multimedia Appendix 2. The final, deidentified datasets are available from the corresponding author upon reasonable, non-commercial request, subject to the necessary ethical approvals and formal data use agreements.

Authors' Contributions

Conceptualization: AC, AM, BY, LYCH, LT, SL, YSN, YYD
Data curation: FZ, SCJ, SL, TL, YSN
Formal analysis: FZ, RKB, SL, YHP, YSN
Funding acquisition: AC, BY, DS, ES, JT, LYCH, LT, YSN, YYD
Investigation: AL, FZ, SL, SC, SCJ, TL, XY, YW, YSN
Methodology: AM, BY, DS, LYCH, SL, YSN, YYD
Project administration: LLL, SL, YSN
Resources: JT, LLL, YSN
Software: DS, FZ
Supervision: AC, BY, HMH, JT, YSN, YYD
Validation: LYCH, RKB, YHP, YSN
Visualization: FZ, SL, YSN
Writing – original draft: FZ, SL, YSN
Writing – review & editing: AC, AM, BY, DS, ES, FZ, HMH, JT, LYCH, LLL, LT, RKB, SC, SCJ, TL, SL, XY, YHP, YJW, YSN, YYD

Conflicts of Interest

None declared.

Multimedia Appendix 1
Publicity materials for Elderly Activity Life-Space Envelopes in the 3 national languages of Singapore.
[PDF File, 1031 KB - resprot_v14i1e79308_app1.pdf]

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Multimedia Appendix 2
Table of objective geographical information sciences life-space mobility (LSM) measures used in Elderly Activity Life-Space Envelopes to describe node extent, with examples (nonexhaustive) from LSM literature.
[PDF File, 736 KB - resprot_v14i1e79308_app2.pdf]

Multimedia Appendix 3
Tables of ethnic distribution, educational level, and socioeconomic status of participants.
[PDF File, 71 KB - resprot_v14i1e79308_app3.pdf]

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Abbreviations

API: application programming interface
CMMSE: Chinese Mini-Mental State Examination
EASE: Elderly Activity Life-Space Envelopes
EQ-VAS: EuroQol Visual Analogue Scale
FMS: Future Mobility Survey
GIS: geographical information science
GIS: geographic information science
GPN: GPS node
LS: life spaces
LSM: life-space mobility
MDGA: multidomain geriatric assessment
MET: metabolic equivalent of task
NEWS: Neighborhood Environment Walkability Scale
NEWS-A: NEWS-Abbreviated
PTAL: Public Transport Accessibility Level
QoL: quality of life
SDN: self-declared node
UAB-LSA: University of Alabama at Birmingham's Life Space Assessment
WHO-ICF: WHO International Classification of Functioning, Disability and Health

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Cultural Adaptation and Evaluation of the Namaste Care Program for Home-Dwelling People With Dementia and Their Caregivers : Protocol for a Mixed Methods Study

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Abstract

Background: The Namaste Care program is a person-centered intervention that has been shown to improve the quality of life of people with dementia and to alleviate caregiver burden. However, its application in China remains underexplored. Given China's unique sociocultural norms, cultural adaptation is essential to ensure feasibility, acceptability, and contextual fit.

Objective: The primary objective is to culturally adapt the Namaste Care Home Program to the Chinese community context. The secondary objective is to evaluate the feasibility and acceptability of the adapted program (qualitative analysis), and to explore its preliminary effects (quantitative analysis) on quality of life and related outcomes for people with dementia and their family caregivers.

Methods: A 3-stage, 11-step mixed methods design is used in this study. The process includes a baseline stage for community assessment and stakeholder consultations, a formulation stage for adapting the intervention and training materials, and an execution and evaluation stage in which trained family caregivers deliver the intervention. A 1-group, pretest-posttest design will be used, with quantitative assessments at baseline (T0), immediately after intervention (T1), and at the 3-month follow-up (T2), complemented by qualitative process evaluations.

Results: The study was approved in April 2025 (2025-NZY-4‐01) and registered on April 18, 2025 (ChiCTR2500101042). Recruitment occurred from January to April 2025, enrolling 15 caregiver–people with dementia dyads. As of April 2025, baseline data collection is complete, and analysis is ongoing. Primary results are expected in mid-2026.

Conclusions: The cultural adaptation of the Namaste Care Home Program is a critical step toward advancing person-centered, home-based dementia care in China. Findings will provide evidence on feasibility and cultural appropriateness and will inform the design of future large-scale trials to test effectiveness in cross-cultural settings.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2500101042; https://www.chictr.org.cn/showprojEN.html?proj=216440.

International Registered Report Identifier (IRRID): DERR1-10.2196/78449

(JMIR Res Protoc 2025;14:e78449) doi:10.2196/78449

KEYWORDS

Namaste Care; dementia; caregivers; cultural adaptation; China; home-based care; nonpharmacological interventions; mixed methods

Introduction

Dementia affects over 55 million individuals globally and is projected to triple by 2050 [1,2], with more than 60% of people with dementia living in low- and middle-income countries (LMICs). China alone accounts for approximately 20% of global cases, posing a major public health challenge [3]. Dementia leads to cognitive decline, behavioral and psychological symptoms of dementia, progressive dependence, and reduced quality of life (QoL) for people with dementia and their families [4-6].

In China, caregiving is predominantly family based under the influence of filial piety, with over 96% of care provided by family members who often lack formal training [7,8]. Consequently, more than 80% of caregivers experience anxiety,

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depression, and high strain [9,10]. Institutional care exists but is costly and often viewed as temporary, reinforcing reliance on home-based care [11].

Nonpharmacological interventions such as cognitive stimulation therapy [12] and reminiscence therapy [13] are widely used, yet benefits concentrate in the early to middle stages; their reliance on cognitive abilities limits feasibility for advanced dementia and may not align well with China's family-care context [6,14]. In contrast, Namaste Care requires minimal verbal ability, can be delivered by trained family caregivers at home, is a relatively low resource, and targets comfort and behavioral and psychological symptoms of dementia through multisensory engagement—priorities for moderate-to-advanced dementia in China's predominantly home-based care [6,12-16].

Developed in Western settings, Namaste Care emphasizes emotional- and sensory-focused engagement and has shown promise in improving QoL among people with moderate-to-advanced dementia [15,16]. However, the existing evidence is primarily from Western contexts, and there is no culturally adapted Namaste Care model that has been evaluated in China [9,17]; thus, the applicability, feasibility, and effectiveness under China's family-based caregiving norms remain uncertain. Accordingly, this protocol outlines the cultural adaptation of Namaste Care for China and a mixed methods feasibility evaluation to inform subsequent multicenter testing.

The primary objective is to culturally adapt the Namaste Care Home Program (NCHP) for the Chinese community context. The secondary objectives are to: (1) evaluate feasibility (eg, recruitment, retention, and adherence) and acceptability from family caregivers' perspective (qualitative analysis); (2) explore preliminary effects on QoL among people with dementia (quantitative analysis); and (3) explore preliminary effects on caregivers' outcomes, including QoL, caregiving burden, caregiving abilities, attitudes toward dementia, and positive aspects of caregiving (quantitative analysis).

Methods

Study Design

This protocol uses a 3-stage mixed methods design guided by the 11-step adaptation framework proposed by Escoffery [18]. This structured approach ensures a systematic process, from community needs assessment to intervention implementation and evaluation, as illustrated in Figure 1.

Figure 1. Framework for evidence-based adaptation of interventions. EBIs: evidence-based interventions; NCHP: Namaste Care Home Program.

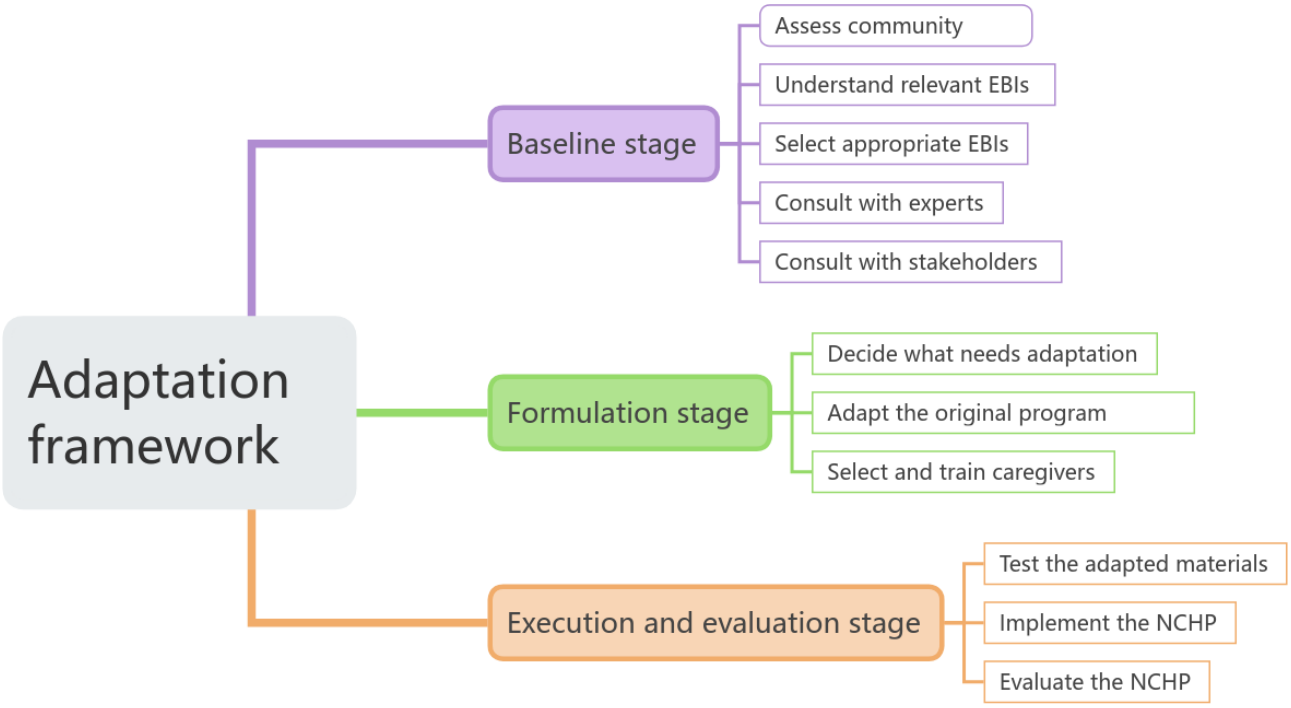

Stage 1: Baseline Stage (Steps 1-5)

Step 1: Assess Community

We selected Lianyungang, Jiangsu (Chaoyang Community Health Service Center) based on facility readiness, participant engagement, and transport accessibility, aligned with the local priority of aging in place [19] (ethics approval: 2025-NZY-4 - 01; refer to the Ethical Considerations section). The detailed steps are shown in Figure 2.

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Figure 2. NCHP adaptation and implementation framework. EBI: evidence-based intervention; NCI: Namaste Care International; NCHP: Namaste Care Home Program.

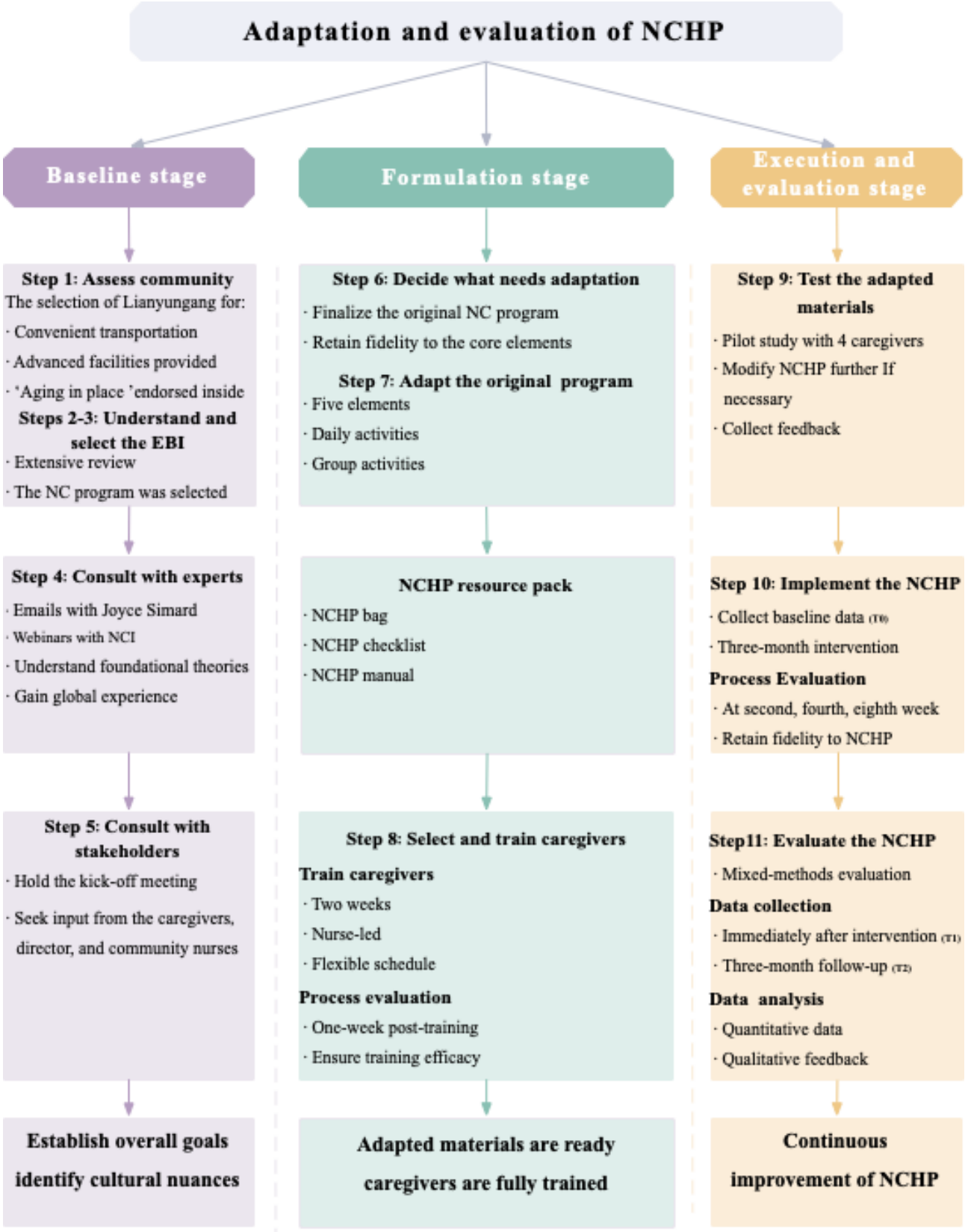

Steps 2-3: Understand and Choose the Evidence-Based Intervention

A comprehensive review of nonpharmacological interventions for moderate-to-advanced dementia informed evidence-based intervention (EBI) selection under resource constraints in LMICs [1]. We selected Namaste Care for its sensory- and emotion-focused components, home deliverability by family caregivers, and stage appropriateness. In addition to these practical considerations, its philosophy, embodied in the

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respectful *namaste* greeting, aligns with the Chinese cultural values, such as compassionate caregiving and filial piety. A brief comparative rationale versus cognitive stimulation therapy or reminiscence therapy is provided in the Introduction section.

Step 4: Consult with Experts

We consulted Joyce Simard (founder of Namaste Care) and Rishi Jawaheer (Honorary Chair, Namaste Care International) through webinars and email exchanges to draw on global adaptation experience and to delineate core components, identify adaptable elements, and gather guidance on community implementation [20].

Step 5: Consult with Stakeholders

We conducted structured meetings with caregivers, community directors, and nurses to map care challenges, knowledge gaps, and preferred delivery formats, thereby generating an initial context, mechanism, and outcome specification for adaptation. We anticipate engaging approximately 12 to 18 stakeholders (eg, 8 - 12 family caregivers, 2 - 3 community directors, and 2 - 3 nurses), sampling will continue until information power is adequate for decision-making.

Stage 2: Formulation Stage (Steps 6-8)

Step 6: Decide What Needs Adaptation

The team will identify China-specific modifications while preserving the NCHP's core objectives, principles, and theoretical foundations. Drawing on initial stakeholder feedback and a review of implementations in other regions, we will specify changes to setting, materials, and training so that activities are practical for home use and can be integrated into daily routines. Community nurses, caregivers, and family members will be convened to finalize these adaptations, ensuring alignment with Chinese caregiving values and practice norms. Outputs will include a China-adapted specification that distinguishes core from adaptable elements.

Step 7: Adapt the Original Program

We will complete the conceptual translation and simplify and standardize procedures to support delivery by community nurses and family caregivers. Daily activities will be tailored to the capabilities of people with dementia, and brief group sessions will be scheduled twice weekly to encourage regular participation (Textbox 1).

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Textbox 1. Adapted Namaste Care Home Program (NCHP) delivery schedule (daily routines and twice-weekly group activities).

Daily activities

Morning sessions

- Preparatory work
- Food and drink preparation: seasonal availability, individual preference, swallowing condition
- Personal care items: NCHP bags (eg, hand cream, face cream)
- Room setup: soft lighting, soothing aromatherapy, relaxing music
- Life care and activities
- Morning greetings
- Facial care: facial cleansing, applying face cream, and rubbing face
- Hand care: hand cleaning, hand cream massage
- Traditional Chinese medicine health care: swallowing exercises, finger exercises, meridian tapping, head soothing, finger combing hair, tooth tapping
- Nutritional supplements
- Snacks: lotus root powder, sesame paste
- Intermittent hydration: water, Chinese floral teas, soy milk

Noon sessions

- Abdominal massage (Fairy kneading manipulation)
- Nap for 20‑30 minutes

Afternoon sessions

- Activities
- Creative activities: paper cutting, painting, colorful doodling, reminiscence therapy, doll therapy
- Games: tossing game, card game
- Traditional Chinese cultural activities: listening to opera, crosstalk, and storytelling
- Outdoor activities: low-angle sunbathing (3‑5 PM) and walking
- Nutritional supplements
- Food: fruit platter or fruit puree
- Intermittent hydration: water, milk (avoid drinks that affect sleep)

Evening sessions

- Life care
  - Foot care: warm water foot soak, foot massage
  - Sleep care: Chinese herbal aromatherapy for sleep aid (Acorus calamus, Albizia Flower, etc), applying body lotion
- Finish work
- Touching the back of the hand and patting the back
- Praising the people with dementia for their cooperation throughout the day
- Document the people with dementia's activity preferences and complete the NCHP checklist

Group activities (twice weekly)

- Competitive activities: marble grabbing and ring toss game
- Cultural and social gatherings: Red Song parties and tea parties

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- Creative activities: horticultural therapy, flower arrangement, DIY handicrafts, and creating a family calendar
- Festival Activities: making rice dumplings and sachets, making mooncakes, paper cutting, and making dumplings

The adapted package will retain the program's core principles while addressing 5 elements (Figure 3): (1) applicability to daily life (affordable, familiar items, eg, Pechoin SOD emulsion; Tong Ren Tang vitamin E lotion and selected traditional Chinese medicine–informed practices such as head soothing and finger combing; food choices that meet nutritional and swallowing needs); (2) group activities that foster social and cultural engagement (eg, paper cutting, Red-Song gatherings, and tea parties); (3) blending with fun through enjoyable and functional games (eg, tossing and card games) to stimulate cognition and mobility; (4) family involvement via tasks that promote participation and strengthen bonds (eg, family calendars and joint activities); and (5) traditional festival participation to increase relevance and feasibility.

Figure 3. Five elements of the adapted Namaste Care Home Program (NCHP) are depicted here.

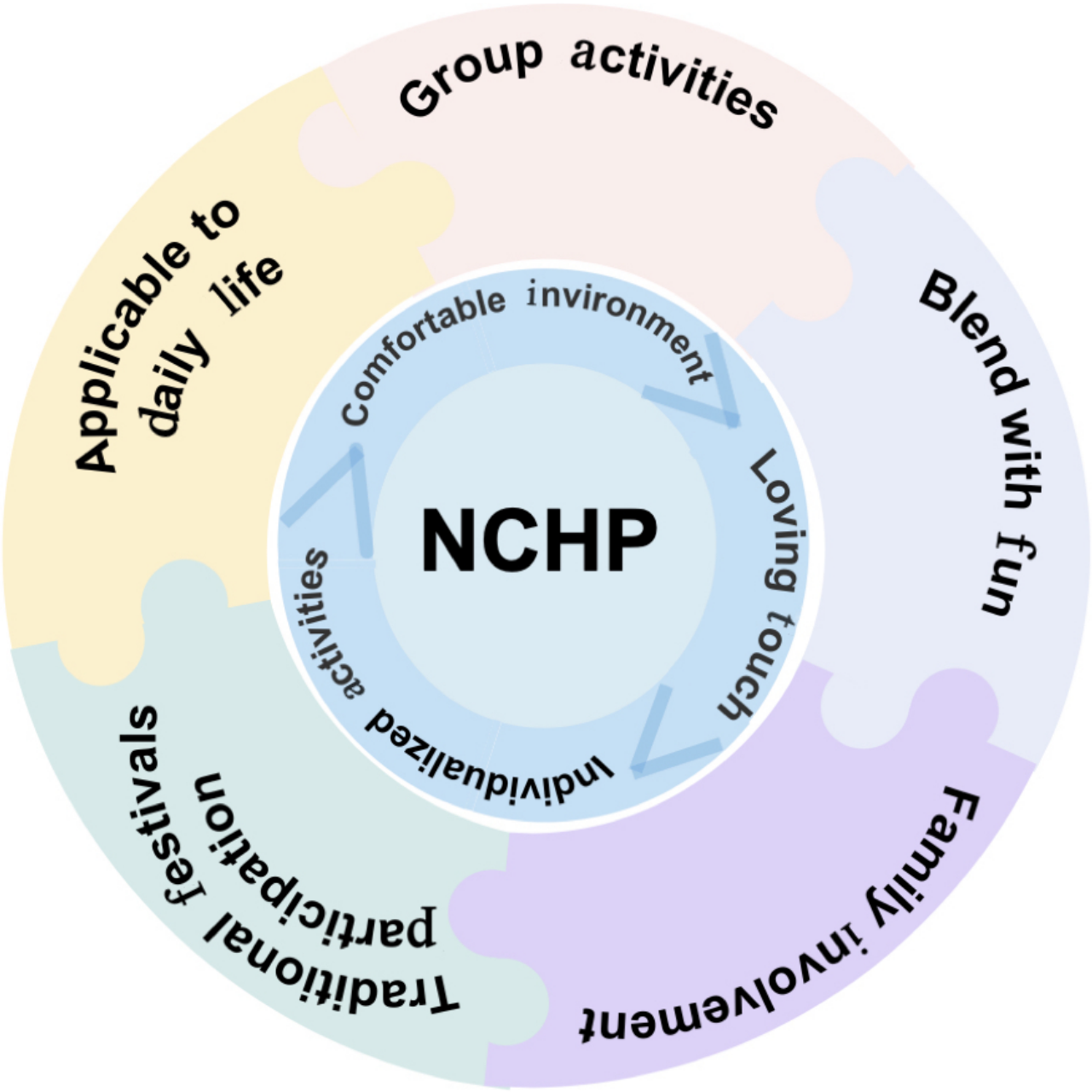

The adapted materials will be reviewed by Joyce Simard to ensure fidelity to the core principles. To assess acceptability and practicality, we will conduct 2 to 3 focus group (6‑8 participants each) discussions with community nurses, caregivers, and family members [20], guided by the Bowen feasibility framework and acceptability theory [21,22]; interview guides (Table S1 in Multimedia Appendix 1) will be used to structure data collection [23]. Additionally, 10 to 15 semistructured caregiver interviews will be conducted, and data collection will continue until adequate information power and

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evidence of theme saturation are reached. Semistructured interviews will also elicit feedback on the activity checklist and item list to finalize personalized NCHP checklists and NCHP bags, and caregivers will review the NCHP manual.

Step 8: Select and Train Caregivers

We will use criterion sampling [21] to recruit eligible dyads. Eligibility criteria for people with dementia include (1) age 60 years or older; (2) moderate-to-severe dementia as determined by the Mini-Mental State Examination [22], clinical symptoms, and caregiver report, confirmed by a trained evaluator; (3) medically stable; and (4) community-dwelling (noninstitutionalized). Caregiver eligibility criteria include (1) age 18 years or older; (2) provision of continuous, 24-hour in-home care for at least 3 months; and (3) ability to communicate effectively.

We will recruit a feasibility sample of 10 to 15 dyads to assess recruitment, retention, adherence, and acceptability rather than to test hypotheses [23]. Previous feasibility studies of Namaste Care and similar interventions have used comparable sample sizes [24], and Bowen et al [25] recommend using small sample sizes for exploratory feasibility objectives. Eighteen dyads were screened, and 3 were excluded, 4 dyads completed a 2-week pilot test, and all 15 dyads then proceeded to the 3-month intervention. (See Figure 4 for participant flow).

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Figure 4. CONSORT-style participant flow for the 1-group feasibility protocol.

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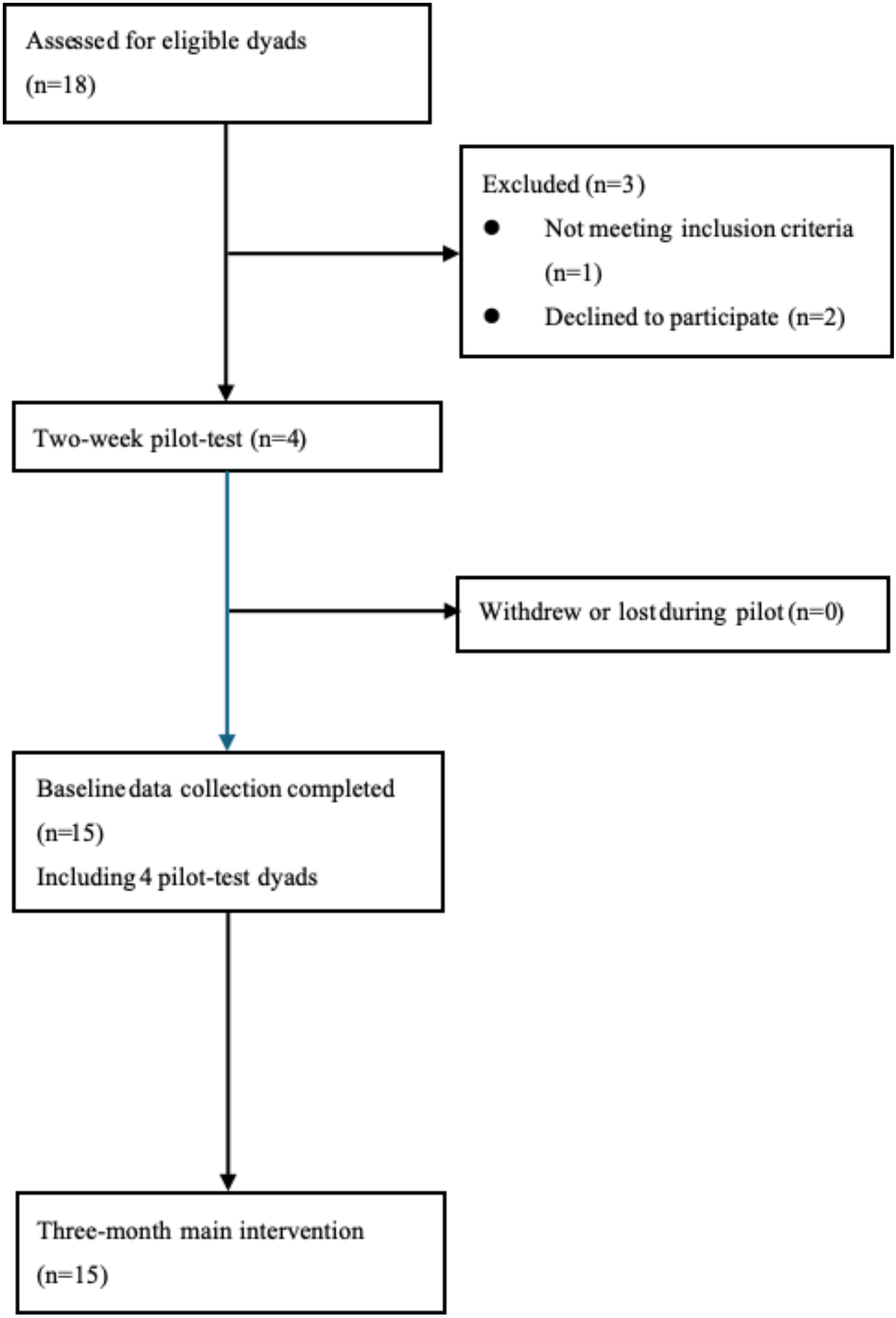

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Pilot Sample-Size Justification

This feasibility study prioritizes estimation precision over hypothesis testing. Therefore, we adopt a precision-based rationale for 10 to 15 dyads. For feasibility proportions (eg, 3-month retention and weekly adherence), a sample of 15 dyads yields an approximate 95% CI half-width of about +22 or –22 percentage points when the true rate is around 75% (and about +27 or –27 percentage points for n=10), which is sufficient to judge performance against feasibility thresholds. For continuous outcomes, a sample of 10 to 15 dyads provides approximately 24% to 19% relative precision for the SD ($RSE(\sigma)\approx\sqrt{[1/(2(n-1))]}$), which is adequate to inform sample-size calculations for a subsequent trial. Regarding safety, if no adverse events (AEs) are observed, the "rule of three" places the upper 95% confidence bound on per-dyad AE risk at approximately 3/n (ie, no more than 20% for n=15), providing an acceptable early-phase safety screen. Taken together and consistent with previous feasibility studies of Namaste Care and related dementia interventions, a sample of 10 to 15 dyads is sufficient and appropriate to estimate key feasibility metrics and guide the design of a larger study.

Training Plan

Training will be led by the principal investigator (a Namaste Care regional champion) with the support of community nurses [26]. Sessions will be delivered on weekends across 2 consecutive weeks, approximately 2 hours per day, supplemented by online modules to enhance access and optional individualized follow-ups for emerging challenges. The curriculum will cover the program's history and core practices; practical use of the NCHP checklist and NCHP bag; assessment of pain, mood, and agitation; and illustrative activities (eg, memory books and dementia-friendly gardening). A concise NCHP manual will be provided before training and will be used as an ongoing reference. Following training, caregivers will apply skills at home with ongoing support, and a process evaluation 1 week after training will assess engagement and inform iterative updates to the manual and training [26].

Stage 3: Execution and Evaluation Stage (Steps 9 - 11)

Step 9: Test the Adapted Materials

We will recruit 4 people with dementia–caregiver dyads for a 2-week pilot to test the adapted NCHP in home settings [27]. After providing written informed consent, caregivers will implement the NCHP at home and use a daily checklist to record activities, task completion, and any tailoring (including adjustments to the NCHP bag as needs evolve). Upon completion, the principal investigator will conduct a focus group discussion with caregivers to collect feedback on feasibility, acceptability, and procedural clarity [28]; field notes will inform refinements prior to full implementation.

Step 10: Implement the NCHP

The adapted NCHP will then be implemented over 3 months in Lianyungang, with the research team providing ongoing supervision and responsive adjustments as needed. Baseline (T0) data will be collected using structured questionnaires before the intervention. For people with dementia, outcomes will include QoL and self-perceived burden; for caregivers, outcomes will include QoL, caregiver burden, caregiving capacity, attitudes toward dementia, and positive caregiving feelings. The purpose, instruments, and assessment schedule for both groups are specified in Tables 1 and 2.

Table . Data collection for people with dementia.

Data collected and tool used	Primary purpose	Time points of data collection		
		Baseline (T0)	Immediately after intervention (T1)	3-month follow-up (T2)
Sociodemographics	Age, gender, ethnicity, medical conditions, and access to social support such as family, friends, or formal care resources	✓	—[a]	—
QOL-AD[b]	Assess quality of life of people with dementia	✓	✓	✓
SPBS[c]	Assess the self-perceived burden of people with dementia	✓	✓	✓

[a]Not applicable.

[b]QOL-AD: Quality of Life-Alzheimer Disease scale; increased score reflects improved quality of life; the total score ranges from 13 to 52.

[c]SPBS: Self-Perceived Burden Scale; decreased scores reflect less perceived burden; total score ranges from 10 to 50.

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Table . Data collection time points for caregivers.

Data collected and tool used	Primary purpose	Time points of data collection		
		Baseline (T0)	Immediately after intervention (T1)	3-month follow-up (T2)
Sociodemographics	Age, gender, educational level, family structure (eg, relationship to the patient and presence of children or other dependents), living situation (eg, cohabiting with the patient, living alone, or in a care facility), and caregiving experience (eg, duration of caregiving)	✓	—[a]	—
WHOQOL-BREF[b]	Assess quality of life of caregivers	✓	✓	✓
C-ZBI[c]	Assess caregiver burden	✓	✓	✓
CTI-25[d]	Assess the caregiving capacity	✓	✓	✓
FAS-C[e]	Assess attitudes toward dementia	✓	✓	✓
C-PAC[f]	Assess positive feelings toward caregiving	✓	✓	✓

[a]Not applicable.

[b]WHOQOL-BREF: World Health Organization Quality of Life Scale- Brief Form Questionnaire; increased scores reflect improved quality of life; total score ranges from 0 to 100.

[c]C-ZBI: Zarit Burden Interview, Chinese version; decreased scores reflect less caregiver burden; total score ranges from 0 to 88.

[d]CTI-25: Caregiver Task Inventory-25; decreased scores reflect less complexity of caregiving tasks; total score ranges from 0 to 50.

[e]FAS-C: Family Attitude Scale, Chinese version; decreased scores reflect less adverse relational effects; total score ranges from 0 to 150.

[f]C-PAC: Positive Aspects of Caregiving Scale; increased scores reflect more positive caregiving emotions; the total score ranges from 0 to 55.

The NCHP coordinator will conduct regular check-ins with caregivers; during the first 2 weeks, reviews will be intensified to identify scheduling or checklist issues and enact immediate adjustments. Process evaluations will be conducted at weeks 2, 4, and 8 [29]. All protocol deviations (eg, withdrawal of consent and discontinuation) will be documented.

Step 11: Evaluate the NCHP

We will use a mixed methods approach that integrates quantitative and qualitative data to assess the feasibility, acceptability, and preliminary effects.

Process 1: Data Collection

This feasibility study will use a 1-group pretest-posttest design. We acknowledge potential threats to internal validity (eg, history and regression to the mean), noting that this design is standard in feasibility research preceding more rigorous trials.

Feasibility Metrics

Feasibility benchmarks will be based on prior work [30] and will include the following: (1) NCHP application frequency (goal: ≥3 days per week, with ≥4 hours on at least 1 of those days); (2) retention over 3 months (goal: ≥75%, consistent with dementia-care feasibility studies [31]); and (3) incidence of AEs (goal: 0%; potential AEs include skin breakdown and falls). Although we aim for 0%, any AE will be closely monitored and addressed per protocol [32]. These thresholds will guide go, modify, or stop decisions for a subsequent trial: ≥75% for both retention and adherence=proceed; 60% - 74% for both=proceed with modifications; <60% for either metric=redesign, conditional on safety (no serious adverse events [SAEs] and all AEs appropriately managed).

Qualitative Acceptability

Postintervention (T1) interviews will explore acceptability and caregiver experience, including perceived advantages and disadvantages, satisfaction with implementation, barriers and facilitators, and suggestions for improvement [33]. The interview guides are provided in Table S2 in Multimedia Appendix 2.

Quantitative Outcomes

Quantitative assessments will be conducted at baseline (T0), immediately after intervention (T1), and 3-month follow-up (T2). The primary outcome will be QoL, assessed using the Quality of Life-Alzheimer Disease scale for people with dementia (caregiver-report form; Cronbach α=0.87 [34]) and the World Health Organization Quality of Life Scale-Brief Form Questionnaire (WHOQOL-BREF) for caregivers (validated Chinese version; Cronbach α=0.70 - 0.88 [35]). Secondary outcomes will include the Self-Perceived Burden Scale (Cronbach α=0.91 [36]) for people with dementia and the Positive Aspects of Caregiving Scale, Chinese version (Cronbach α=0.89 [37]), the Caregiver Task Inventory-25 (Cronbach α=0.93 [38]), the Zarit Burden Interview, Chinese

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version (Cronbach α=0.87 [39]), and the Family Attitude Scale, Chinese version (Cronbach α=0.93 [40]) for caregivers.

All measures have published psychometric support in Chinese samples; detailed properties and assessment schedules are shown in Tables 1 and 2. Where available, instruments show acceptable test–retest reliability and sensitivity to change; where evidence is limited, we will prioritize feasibility signals and effect-size estimation to guide outcome selection for the subsequent trial.

Process 2: Data Analysis

Quantitative Analysis

We will summarize demographics with descriptive statistics and analyze repeated measures using linear mixed-effects models at T0, T1, and T2 under a missing-at-random assumption for incomplete follow-up. Given the small pilot and feasibility focus, models will be parsimonious (time as a categorical fixed effect; random intercept only), estimated by restricted maximum likelihood with Satterthwaite small-sample degrees-of-freedom corrections in SPSS software (version 26; IBM Corp). We will report marginal means and effect sizes with 95% CIs, with primary emphasis on precision estimates; any *P* values will be descriptive. Diagnostics (eg, residuals) will be reviewed, with simple transformations or robust SEs applied if needed. Sensitivity analyses will use generalized estimating equations with small-sample-corrected robust SEs and complete-case paired summaries. We will also report variance components (random-intercept variance and intraclass correlation) to inform the design of subsequent, adequately powered trials.

Qualitative Analysis

With written consent, interviews will be audio-recorded and analyzed using Braun and Clarke reflexive thematic analysis [41]. To enhance trustworthiness, we will use investigator triangulation (2 independent coders, consensus meetings, and third-reviewer adjudication), member checking with a subset of participants (conducted after preliminary theme maps to verify clarity and interpretability rather than enforce agreement), and an audit trail comprising decision logs, codebook versioning, theme maps, analytic memos, and meeting minutes. Coding will be managed in NVivo (version 14; Lumivero), with analysis proceeding concurrently with data collection. A codebook will be developed iteratively (initially seeded from focus-group responses); discrepancies will be resolved by consensus rather than interrater coefficients, consistent with reflexive thematic analysis. We will document researcher reflexivity through brief positionality statements and reflexive journals. Sampling sufficiency and stopping will be guided primarily by information power, with evidence of theme saturation used to corroborate stopping decisions. Codes will be organized into themes and subthemes, and a final member check will confirm the interpretations.

Mixed Methods Integration

Quantitative and qualitative findings will be triangulated to generate meta-inferences about feasibility, acceptability, and contextual fit, thereby informing final refinements to the NCHP and the design of subsequent larger-scale studies [41,42].

Ethical Considerations

The study was approved by the Nanjing University of Chinese Medicine Ethics Committee in April 2025 (2025-NZY-4 - 01) and was registered at the Chinese Clinical Trial Registry on April 18, 2025 (ChiCTR2500101042). The study protocol adhered to the principles of the Declaration of Helsinki [43] and Good Clinical Practice guidelines. All participants provided written informed consent before participation.

Given the nature of the population involved (people with dementia), special consideration was given to obtaining informed consent. Although dementia leads to cognitive decline, it does not automatically imply a loss of decision-making capacity. People with dementia may retain the ability to understand simplified consent forms and express their preferences, especially in the early stages. The study respected the residual autonomy of participants, and information was adapted to accommodate their cognitive abilities. Consent was continuously monitored throughout the study. In cases where a participant could not provide valid consent, a legally designated representative was involved, but the participant's willingness to participate was always considered through a "double consent" approach. Participants had the right to withdraw at any time without any consequences. As compensation for their time and effort, each participating dyad received a 100 RMB (US $14.07) gift package upon completion of assessment. This was clarified during the consent process to avoid undue influence.

AEs include skin breakdown, falls, or activity-related discomfort, defined as any unfavorable and unintended sign, symptom, or event occurring during participation. SAEs are defined as events that result in death, life-threatening conditions, hospitalization or its prolongation, significant disability, or other medically significant conditions. Caregivers will be trained to recognize and document AEs and to report them immediately to the NCHP coordinator. The research team will assess severity and relatedness, determine whether an event is intervention-related, and take appropriate action. SAEs will be reported to the principal investigator and the ethics committee within 24 hours; nonserious AEs will be documented within 72 hours and summarized in periodic safety reports. Immediate first aid will be provided when necessary, and participants will be referred to community health services if required. If repeated or severe intervention-related AEs occur, the intervention may be paused, or the participant withdrawn; study-level suspension will be considered if predefined safety thresholds are exceeded. An independent safety officer will conduct an independent safety review at regular intervals to oversee AE logs and corrective actions.

Personal data collected during the trial will be handled and stored in accordance with applicable data protection laws, including the General Data Protection Regulation and the Personal Information Protection Law of China. Data will be pseudonymized upon study completion, and access to identifiable data will be restricted to authorized study personnel. All data and related documentation will be securely stored in compliance with regulatory requirements, and the use of study data will be controlled by the principal investigator.

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Results

Recruitment was conducted from January to April 2025 and yielded 15 caregiver–people with dementia dyads (n=30). Caregivers had a mean age of 65.7 (SD 11.7) years; 60% (9/15) were women, 66.7% (10/15) were married, and 73.3% (11/15) were retired or not working. People with dementia had a mean age of 83.5 (SD 6.8) years; 60% (9/15) were men, 66.7% (10/15) were in the moderate stage of dementia, 33.3% (5/15) were in the late stage, and 46.7% (7/15) were married, while 53.3% (8/15) were widowed. Recruitment is now closed, baseline assessments are complete, and data analysis is ongoing. Detailed participant characteristics are presented in Tables 3 and 4.

Table . Characteristics of caregivers (n=15).

Characteristics	Participants, n (%)
Age (years)	
45 - 59	4 (26.7)
60 - 74	6 (40)
≥75	5 (33.3)
Gender	
Men	6 (40)
Women	9 (60)
Nonbinary	0 (0)
Marital status	
Married	10 (66.7)
Widowed	2 (13.3)
Divorced	3 (20)
Employment status	
Working	4 (26.7)
Not working or retired	11 (73.3)

Table . Characteristics of people with dementia (n=15).

Characteristics	Participants, n (%)
Age (years)	
75 - 79	4 (26.7)
80 - 84	6 (40)
≥85	5 (33.3)
Gender	
Men	9 (60)
Women	6 (40)
Nonbinary	0 (0)
Marital status	
Married	7 (46.7)
Widowed	8 (53.3)
Stage of dementia category	
Moderate	10 (66.7)
Late	5 (33.3)

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Discussion

Anticipated Findings

This protocol describes the systematic cultural adaptation and feasibility evaluation of the NCHP for Chinese families. By tailoring this EBI to local cultural values and practical realities, we aim to deliver a feasible and acceptable program that enhances QoL for people with dementia and reduces caregiver burden.

The use of a structured adaptation framework provides a transparent, replicable roadmap for modifying EBIs to new contexts and may inform similar work in other LMICs. Integrating culturally relevant elements (eg, traditional Chinese medicine–informed practices and locally meaningful activities) is expected to support engagement and acceptability. The feedback-driven, iterative process is designed to keep the intervention person-centered while maintaining fidelity to the core components.

Findings from this feasibility study will inform the design of future larger studies. Feasibility estimates (recruitment yield, 3-month retention, session adherence, and variance of primary outcomes) will inform sample-size calculations and site-level targets; fidelity and workload data will help determine training dose, supervision cadence, and acceptable fidelity thresholds; and process metrics (eg, time on task, missed visits, and data-capture completeness) will guide whether to standardize phone-based or brief digital assessments at scale.

Although this study is expected to provide valuable insights, several limitations must be considered. First, the one-group pretest-posttest design limits our ability to draw causal inferences, as observed changes may reflect history, regression to the mean, or the Hawthorne effect. Second, the small sample size and single-site design will constrain generalizability. Additionally, measurement bias is possible (eg, caregiver-reported outcomes), and blinding will not be feasible. To mitigate these issues, we will prespecify outcomes and assessment time points (T0, T1, and T2), monitor fidelity and AEs, integrate qualitative data for triangulation, and place primary emphasis on effect sizes with 95% CIs rather than hypothesis testing. Subsequent studies will adopt comparative designs (eg, waitlist, cluster randomized, or stepped-wedge trials) to strengthen causal inference and external validity.

Anticipated Challenges and Methodological Contingencies

We anticipate risks related to caregiver adherence, participant attrition, and resource constraints (eg, time, staffing, and materials), as well as potential intervention contamination within community settings. To address these risks, we plan to (1) provide scheduled check-ins and just-in-time coaching to sustain adherence; (2) use practical supports (brief manuals and NCHP bags) and flexible scheduling to reduce burden; (3) monitor fidelity with brief checklists and remedial feedback; (4) prospectively document protocol deviations and reasons for missing data; and (5) apply analysis plans suitable for small feasibility samples (eg, parsimonious linear mixed-effects models under a missing-at-random assumption, descriptive *P* values, and sensitivity analyses). If adherence or retention falls below predefined feasibility thresholds (eg, ≥3 days per week, with ≥4 hours on ≥1 day, and ≥75% retention), we will implement prespecified adjustments, such as increasing remote support frequency, simplifying activity menus, or modifying data-collection modes (eg, phone-based or brief digital questionnaires), while documenting all changes in the audit trail. These contingencies will inform modifications for a subsequent adequately powered multisite evaluation.

Conclusions

The findings of this study will be crucial for informing future research. Specifically, data on feasibility (recruitment and retention rates), acceptability (caregiver feedback), and preliminary effect sizes will provide foundational insights for the design of larger-scale, multicenter, randomized controlled trials. Such a trial would offer definitive evidence of the effectiveness and cost-effectiveness of the adapted NCHP, paving the way for its broader dissemination and integration into the Chinese community-based long-term care system.

This culturally adapted NCHP holds significant potential in addressing the unique challenges faced by Chinese family caregivers of people with dementia, offering a holistic, person-centered intervention that aligns with local caregiving practices. The outcomes of this study will contribute valuable knowledge on the feasibility and acceptability of the program, setting the stage for future studies to confirm its effects. These efforts will ultimately strengthen the evidence base for nonpharmacological dementia interventions in China and other resource-limited settings.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

Conceptualization: MJ, DM

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Formal analysis: GX, YS
Funding acquisition: DM, YS
Investigation: CS, QS, YB
Methodology: MJ, DM, CS, QS, YB, GX, YS
Project administration: SW, HC
Resources: HC
Supervision: SW
Writing—original draft: MJ, DM
Writing—review and editing: SW, HC, MJ

Conflicts of Interest

None declared.

Multimedia Appendix 1
Personal interview guide and focus group guide for the formulation stage.
[DOCX File, 21 KB - resprot_v14i1e78449_app1.docx]

Multimedia Appendix 2
Personal interview guide for the execution and evaluation stage.
[DOCX File, 18 KB - resprot_v14i1e78449_app2.docx]

Checklist 1
SPIRIT checklist.
[PDF File, 122 KB - resprot_v14i1e78449_app3.pdf]

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Abbreviations

EBI: evidence-based intervention
LMIC: low- and middle-income country
NCHP: Namaste Care Home Program
QoL: quality of life
WHOQOL-BREF: World Health Organization Quality of Life Scale-Brief Form Questionnaire

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Using Mobile Assessments to Characterize Mental and Physical Health Behaviors in Youth: Protocol for a Pilot Intensive Longitudinal Study

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Abstract

Background: Promoting healthy behaviors including adequate sleep, regular physical activity, balanced diet, and abstinence from substance use, alongside nurturing affective functioning, may crucially support physical and mental well-being in youth. Yet, little is known about how these domains interact dynamically in their daily lives.

Objective: This pilot study evaluates the feasibility of prolonged, multiwave ambulatory assessment in school-recruited adolescents as well as in clinical and school-recruited preadolescents. In addition, it will examine the dynamic interplay of different health behavior domains and affective functioning in adolescent samples recruited in schools.

Methods: The initial target sample size was 100 youths (ages 9 - 17 years) across 2 assessment protocols. Adolescents complete three 3-week waves with 4 daily ecological momentary assessments and parallel actigraphy, and preadolescents follow two 10-day assessment waves. Feasibility aims will be assessed via equivalence tests targeting an a priori level of missing data and dropout at 70% each. Dynamic modeling in adolescent datasets will be addressed by a planned multilevel analysis leveraging idiographic effects as predictors of symptom outcomes, as well as state-of-the-art exploratory frameworks.

Results: By July 2025, we enrolled 113 school adolescents and 27 school preadolescents exceeding the a priori target. Recruitment and data collection are still ongoing in the clinical preadolescent group of currently 13 preadolescents.

Conclusions: This concise, intensive longitudinal protocol provides the basis for examining the feasibility of long-term intensive longitudinal paradigms in youth and lays a critical foundation for future large-scale studies aimed at unpacking the evolving interplay of health behaviors and emotional well-being.

Trial Registration: OSF Registries osf.io/s2jm6; https://osf.io/s2jm6

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KEYWORDS

mobile assessment; adolescents; intensive longitudinal study; feasibility; mental health; sleep; physical activity; dietary habits; health behaviors

Introduction

Addressing Health Behavior Domains in Youth Mental Health Research

Late childhood and adolescence represent critical developmental windows characterized by significant physiological, psychological, and social transformations. During this period, youth respond to these numerous biopsychosocial challenges with increasing personal autonomy, manifesting profound shifts across multiple health behavior patterns, including sleep [1-3], physical activity [4,5], dietary habits [6-8], and substance use [9]. Across these health behavior domains, research has made major advances in how health behaviors shape somatic health [10-14], but their role in the development of mental disorders during late childhood and adolescence remains poorly understood [15]. Nonetheless, the importance of modifiable health behaviors for mental health is gaining public awareness, and stakeholders are advocating their integration into public mental health strategies, including primary prevention [16], positive psychology [17,18], and nonpharmacological interventions for youth [19].

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Extant research focused on the prospective and causal relationship of individual health behavior domains, including sleep, physical activity, dietary habits, and substance use, and regarding the onset and severity of diverse mental disorders, including depression, anxiety, bipolar disorder, and attention deficit hyperactivity disorder [20]. However, these isolated lines of research consistently show that the same behavior often relates to multiple disorders, and conversely, the same disorder associates with multiple behaviors. This lack of specificity limits our ability to infer which particular behavior underlies which symptom constellation [21]. In other words, 2 adolescents with the same health behavior profile at a single point of measurement may follow divergent clinical trajectories in terms of type and severity of symptoms over time. Such multifinality of risk factors underscores the need to move beyond domain-specific studies and toward integrative, intraindividual investigations that capture the temporal interplay of multiple behaviors and affective states within each person [21,22].

In this integrative approach, affective functioning, including momentary emotional reactions, mood fluctuations, and emotion-regulation processes [23], is particularly important, as it constitutes the critical interface linking health behaviors to the emergence of psychiatric symptoms. Taken together, these health behaviors and affective states form a dynamic regulatory system characterized by numerous pairwise interdependencies. For example, exercise improves sleep [24], which, in turn, affects activity levels [25] and eating preferences [26]. Emotions also influence physical activity [27,28] and sedentary behaviors [29], which subsequently impact eating behaviors, such as emotional eating [30,31]. Though these investigations remain limited to bivariate group-level associations. To capture the complexity of these interacting regulatory systems, research should adopt an intraindividual, multivariate paradigm that models complementary characteristics of their temporal dynamics [32-35]. Longitudinal studies confirm that adolescents exhibit distinct, person - specific trajectories and intraindividual dynamics in sleep [36], physical activity profiles [37,38], eating habits [39,40], and affective functioning [41]. In sum, we posit that the interdependencies among these health behavior domains reflect dynamic, regulatory adjustment processes to life circumstances that are both specific to the individual and continuously evolving over time.

Providing evidence for the interrelated nature of these health behavior domains and their intraindividual dynamics is crucial for a holistic approach to youth health and requires advanced technical solutions for field research. Mobile digital technologies used for ambulatory assessments [42], such as actigraphy and frequently repeated self-reports collected via ecological momentary assessment (EMA; or experience sampling method), enable real-time monitoring of multiple health domains in naturalistic settings [43-45]. EMA has been widely used to track smoking, alcohol, and drug use [43], and emotional states [44] in youth, whereas actigraphy has been used primarily to assess patterns of sleep and, eventually, activity patterns [45]. Combining EMA and actigraphy allows investigating the temporal dynamic interactions between health domains over different timescales, for example, by investigating the temporal fluctuation of affective functioning and sleep disturbances from the daily [46] to the monthly timescale [47]. However, the inclusion of preadolescent children in EMA data collection depends on their access and autonomy in using a smartphone or similar connected mobile device. Moreover, the adequacy of this method remains subject to a normative ethical consideration regarding the inherent burden of intensive longitudinal designs as well as the role of parental involvement [48].

Taken together, to detect early signs of maladaptive health behaviors, etiological research should embrace a multivariate, intraindividual, and temporally sensitive approach. While large-scale epidemiological evidence requires significant resources, pilot studies can pave the way by examining the feasibility of intensive longitudinal protocols and unraveling the dynamic interplay between health domains and youth mental health.

The Current Study

This study aims to pioneer future intensive longitudinal designs for epidemiological research by addressing both feasibility and across different variations of a modular intensive longitudinal paradigm, as well as preliminary investigations of the dynamic links between health behaviors and mental health among youths. Our methodological ambition was to flexibly adapt a multiwave multitimescale paradigm to different target populations by adapting the intensity of data collection as well as the composition and modality of assessments. First, adolescents recruited in schools will monitor their sleep, physical activity, dietary behavior, substance use, and affective functioning across three 3-week assessment waves over a timeframe of approximately 1 school year. This protocol will be investigated for both feasibility targets as well as preliminary findings in the dynamic interplay among the target domains and mental health.

Second, the developmental and clinical imperative to understand how health behaviors influence youth mental health highlights the need for intensive longitudinal studies in preadolescent age groups, especially as they undergo critical clinical transitions. However, the substantial burden of such designs raises questions about their feasibility in these settings. It even raises ethical challenges to potentially overburden vulnerable youth without prior ground for assuming the feasibility of the essential design characteristics. Therefore, we extended this pilot study with a reduced intensive longitudinal protocol in 2 preadolescent settings: school - recruited participants and psychiatric patients transitioning from intensive outpatient treatment to follow - up care. For both preadolescent groups, we reduced the protocol to 2 waves spanning 10 days each. Further group-specific adaptations are described in the respective protocol descriptions.

For both the adolescent and preadolescent protocol, feasibility outcomes focus on participation metrics of response compliance (ie, the percentage of all answered among all planned EMA surveys) and participant retention. We will test the hypothesis that both remain at an acceptable level (ie, both at 70% or above) and stable across the different groups and waves. Achieving the required sample sizes for the evaluation of these outcomes represents a prerequisite for the evaluation of these outcomes (see “Sample size rationale”). Consequently, the corresponding number of invited youth and schools and the acceptance rate provide information on the feasibility and efficiency of the

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recruitment. Not achieving the targeted sample sizes or rates of retention and compliance will therefore lead to thorough reconsideration of central design parameters. Irrespective of the obtained outcome, we will collect feedback on the subjective experience and opinion of participants and young partners to identify weaknesses and barriers of the protocols that can orient future modification of the design.

Beyond assessing feasibility, we will leverage our comprehensive adolescent protocol and use advanced statistical approaches specifically designed for intensive longitudinal data to examine further dimensions of the bidirectional dynamics linking health behaviors and mental health. By complementing feasibility-related findings with these analytical techniques, we aim to strengthen methodological frameworks and optimize both the design and implementation of future research. Insights gained from this pilot study will therefore guide and refine the scope of subsequent epidemiological cohort studies, ultimately enhancing our understanding of how health behaviors influence youth mental health trajectories.

Methods

Design

The design of this study closely aligns with the methods promoted by the mobile Motor Activity Consortium for Health (mMARCH), a collaborative international network coordinated by the National Institute of Mental Health, Intramural Research Program (ZIA MH002954), that was created to facilitate the coordination of procedures, analyses [49], and data sharing among research groups collecting mobile technology data. As an essential resource for intensive longitudinal research, the consortium provides a modular assessment framework that we followed to implement 2 age-specific assessment protocols, one for adolescents and one for preadolescents. The study is currently in data collection and continues to recruit participants. This study protocol for a pilot intensive longitudinal investigation follows the reporting guidelines for cohort studies as required by the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement [50] as well as the adapted STROBE Checklist for Reporting Ecological Momentary Assessment Studies [51] (CREMAS). The following sections will introduce the methods for the adolescent and the preadolescent protocol separately. For the entire project, the initial goal was to enroll a total of 100 participants from the French-speaking region of Switzerland. Enrollment started in November 2022, and data collection will end in September 2025. Each assessment protocol is adapted and implemented to best meet the respective educational or clinical context, while respecting the capacity of each age group to engage in an intensive longitudinal study.

Adolescent Protocol

Participants

For the adolescent protocol, we planned to recruit 60 participants between the ages of 14 and 17 years from 4 private secondary and high schools. All schools opted for delivering invitations to the entire cohort meeting the respective age range. To this end, the research team held presentations, either during class sessions or in school assemblies.

Eligibility

Inclusion criteria are as follows: adolescents must be in possession of a smartphone and participants are able to speak French or English. We will exclude participants with severe motor or cognitive disability that involves deficits in core activities of daily living, and participants with a disorder of intellectual development or with a potential developmental learning disorder.

Procedures

An overview of the planned data collection timeline, following the guidelines recommended by the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) [52] is presented in Figure 1 and Table 1. Participants will complete a baseline evaluation, followed by repeated waves of parallel EMA and actigraphy monitoring. The adolescent protocol consists of 3 waves, with each wave lasting 3 weeks. In addition, each assessment wave is accompanied by periodically repeating retrospective questionnaires, administered at the beginning of each period, as well as on a weekly basis. Finally, at the end of the study, participants will respond to a final psychopathological follow-up and an assessment of study acceptability and measurement reactivity. The protocol ends with personalized feedback delivered during group in-class sessions. All self-report measures, including EMA surveys, will be administered online via personal access links transmitted via SMS or email using REDCap (Research Electronic Data Capture; Vanderbilt University) [53,54]. All participants receive training sessions with live demonstrations of the EMA procedure in small groups. To prevent missing data due to technical failure or silent dropouts, the study team is contacting participants approaching the two-thirds limit to assist with any technical issues and remind them of the study protocol and its rationale.

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Figure 1. Timeline of assessment protocols. EMA: ecological momentary assessment.

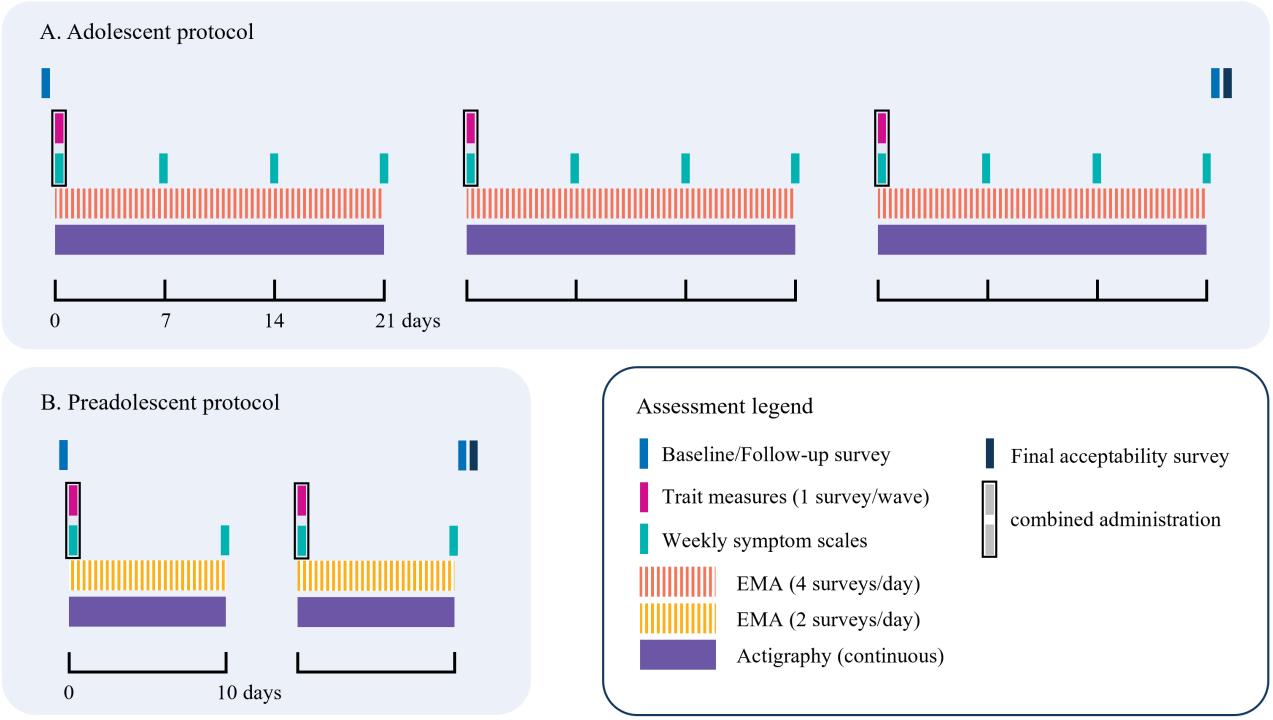

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Table . Multi-informant assessment plan for the participants by group.

Occasions	Adolescents	Preadolescents		
	All self-reported	Participant interview	Self-reported	Reported by the parent
Baseline	• Demographic • PPS[a] • CRISIS[b] • FERS-C[c] • MESC[d] • YSR[e] • PEARLS[f]-TEEN • FFQ[g]	• Demographic • PPS • CRISIS • FERS-C • MESC	• CBCL[h] • PEARLS-CHILD • FFQ	
Start of each wave	• SDQ[i]-social • PAQ-A[j] • ESEA[k]	• SDQ-social • PAQ-C • ESEA	—[l]	—
Weekly[m]	• CES-DC[n] • STAIC[p]	• CES-DC[o] • STAIC[o]	—	—
EMA[q]	• Morning • Noon • Afternoon • Evening	—	• Morning • Evening	—
Follow-up	• YSR	—	—	• CBCL
Round-up session	• Acceptability+ Reactivity	—	• Acceptability+ Reactivity	—

[a]PPS: Peterson Puberty Scale.
[b]CRISIS: Coronavirus Health Impact Survey.
[c]FERS-C: French version of Emotional Regulation Scale for Children.
[d]MESC: Morningness-Eveningness Scale for Children.
[e]YSR: Youth Self-Report.
[f]PEARLS: Pediatrics Adverse Childhood Events and related life events screener.
[g]FFQ: Food Frequency Questionnaire.
[h]CBCL: Child Behavior Checklist.
[i]SDQ: Strengths and Difficulties Questionnaire.
[j]PAQ: Physical Activity Questionnaire.
[k]ESEA: Sleepiness Scale.
[l]Not applicable.
[m]The first weekly assessment of each wave is included in the initial assessment battery of each wave.
[n]CES-DC: Center for Epidemiological Studies Depression Scale for Children.
[o]Preadolescent participants in schools self-report the weekly assessment at the end of their 10-day wave.
[p]STAIC: State-Trait Anxiety Inventory for Children.
[q]EMA: ecological momentary assessment.

Adolescent participants (Figure 1A) engage in three 3-week ambulatory assessment waves with 4 daily EMA surveys. Preadolescent participants (Figure 1B) take part in two 10-day waves with 2 daily EMA surveys. Intervals between waves range from 2 to 3 months depending on the school calendar. The initial trait measure and weekly symptom assessment of each wave are administered as one combined survey.

EMA

Adolescents receive 4 EMA surveys per day on their personal smartphone. Fixed delivery times are adapted to the respective schedule of each school to deliver surveys (1) on mornings before class (eg, 07:45 AM), (2) during lunch break (eg, 12 PM), (3) after the last class in the afternoon (eg, 3:45 PM), and (4) on evenings (eg, 7:30 PM). In case of nonresponse, participants receive 2 reminders in intervals of 20 minutes, and surveys remain accessible for either 3 hours for the first 3

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surveys and 4 hours for the evening survey of each day. The design of the EMA surveys includes the choice of an individual avatar who will guide the participant through his or her "lifestyle journal," as well as a gamified puzzle presented each evening to provide feedback on the progress and approximate compliance with their EMA schedule (Figure 2).

Figure 2. Screenshots of ecological momentary assessment surveys.

In Figure 2, example screenshots showing the welcome screen of the morning survey with the participant-chosen avatar (picture A), items on sleep timing (picture B), mood items (picture C), and the gamified compliance puzzle (21 pieces across 21 days of the adolescent protocol, picture D).

Actigraphy Recordings

During the whole period of each assessment wave, participants are continuously wearing a triaxial accelerometer (GENEActiv, Activinsights Ltd) around their nondominant wrist. Recordings are configured with a 30 Hz sampling frequency starting the afternoon preceding the first EMA morning delivery. Data are downloaded using the manufacturer's software. Preprocessing will be conducted using the GGIR package [49,55,56] in R (R Core Team) and the pyActigraphy package [57] in Python to obtain readouts of physical activity and sleep patterns as implemented by the respective software.

Self-Report Measures

As part of our rationale to cover the dynamic interplay of health behavior domains and mental health, we implemented measures assessing target constructs across different timeframes spanning from static characteristics (eg, sex assigned at birth) over malleable traits (eg, depressive symptom severity and social functioning) to momentary states (eg, sad vs happy mood). The questionnaires are therefore administered and repeated in groups of baseline measures, wave-level measures, weekly symptom monitoring during each wave (Table 1), and EMA surveys (Table 2; Table S1 in Multimedia Appendix 1). For all measures, we sought psychometrically validated scales that are available in French and English whenever possible, favoring measures used by previous data collections of the mMARCH consortium [45,58]. We also considered brevity of instruments, especially for those scales that were added for this study. Two measures, the Pediatrics Adverse Childhood Experiences (ACEs) and related life events screener for parents of children (PEARLS-CHILD) and for teenagers (PEARLS-TEEN) [59], and the Physical Activity Questionnaire for Older Children (PAQ-C) and for Adolescents (PAQ-A) [60,61] were forward translated by 2 blinded members of the research team and synthesized in discussions supervised by a senior researcher.

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Table . Ecological momentary assessment measures.

Section	Range of number of items
Sleep[a]	4
Activities and context	4 - 6
Emotional and somatic states	12
Beverage intake	1 - 11
Food intake	1 - 5
Substance use[b]	1 - 9
Physical activity	1 - 2
Social media use[b,c]	2
Daily major events and emotion regulation[c]	10 - 11
Physical health[c]	3 - 6

[a]Only administered at the first active response of each day.

[b]Only administered to adolescent participants (Group 3, 14 - 17 years).

[c]Only administered in the evening survey.

Baseline and Follow-Up Measures

Baseline assessments mainly serve for descriptive purposes and between-person covariates in longitudinal analyses. Instruments are presented in the order they are administered to the participants.

First, participants report on sociodemographic characteristics (eg, gender, age, and family composition) and their medical history (eg, presence of chronic disease, past surgical interventions, and psychiatric treatment) with items adapted from the CoLaus study [58]. To operationalize an indicator of pubertal maturation, we administer the Peterson Puberty Scale (PPS) [62]. Worries related to a COVID-19 infection of the participants themselves or of significant others are assessed by the COVID-19 worries subscale Coronavirus Health Impact Survey (CRISIS) based on 5 items [63]. Participants further rate their habitual emotional awareness, interpretation effort, and reactions based on the 15 items of the French Emotional Regulation Scale for Children (FERS-C), with English item wordings made available through the published validation study [64]. Chronotype represents a crucial bioregulatory trait for the target domains of this study [65]. We, therefore, assessed the preference of being more active and performant at earlier versus later hours using the 10 items of the Morningness-Eveningness Scale for Children (MESC) [2,66].

To examine a dimensional psychopathological profile across participants, we use the Youth Self-Report (YSR) of the Achenbach System of Empirically Based Assessment (ASEBA) [67,68]. This measure is at the end-of-study follow-up, allowing us to relate the within-person dynamics measured across the full study period to changes in broadband symptom severity. The YSR operationalizes psychopathology across a set of 119 behavioral and emotional problems covering 8 different dimensions: anxious-depressed, withdrawn-depressed, somatic complaints, social problems, thought problems, attention problems, rule-breaking behavior, and aggressive behavior.

Addressing a putative transdiagnostic risk factor, the PEARLS-TEEN [59] inquires about the presence of 10 potential traumatic events, such as abuse, neglect, and family violence. As the last measure of the baseline assessment, a Food Frequency Questionnaire (FFQ) specifically developed for the Swiss population of the Lemanic region [69,70] provides a past-week food intake recall across a wide range of 97 food and beverage items. Taken together, the reported frequencies allow estimation of latent dietary profiles (eg, Mediterranean diet) among the sample. The final end-of-study survey inquiring about study acceptability and measurement reactivity was adapted from a previously published feasibility study [71].

Wave-Level Measures

At the beginning of each assessment wave, participants provide a retrospective report on malleable traits we consider susceptible to change across periods of multiple weeks to multiple months. As part of this “moving baseline” for each assessment wave, participants fill the prosocial subscale of the Strengths and Difficulties Questionnaire (SDQ) [72-74]. This scale operationalizes social functioning indicated by 5 items on prosocial efforts, attitudes, and empathy. In addition, participants report habitual daytime sleepiness using the French Sleepiness Scale adapted to children and adolescents (Échelle de Somnolence adaptée à l’Enfant et à l’Adolescent [Somnolence Scale for Children and Adolescents]; ESEA) [75]. More specifically, respondents estimate the chances of dozing off or falling asleep across 10 different example activities.

In addition, participants are asked to recall their physical activity and exercise during the past 7 days based on the PAQ-A [60,61,76]. This measure incorporates a list of popular sports disciplines among youth, which we adapted to match the disciplines favored by a representative Swiss sample of adolescents [75].

Weekly Measures

Each assessment wave is accompanied by weekly monitoring of depressive and anxiety symptoms, allowing us to relate

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momentary fluctuations in mood and health behaviors to changes in retrospective self-reports. The Center for Epidemiological Studies Depression Scale for Children (CES-DC) assesses depressive symptoms [77-79], and the State-Trait Anxiety Inventory for Children (STAIC) [80,81] inquires symptoms of anxiety, both scales consisting of 20 items each.

EMA Surveys

Items incorporated in the EMA protocol were selected to balance multiple considerations, including the broad scope of the study, survey duration, sensitivity to youth-specific processes, and, finally, relevance for local youth. First, we adapted a subset of the item catalog harmonized by the mMARCH consortium [82]. Second, we included 2 additional items on emotional overload and loss of control used in a prior project [83]. Third, 7 items assessing distinct emotion-regulation strategies (eg, reappraisal and distraction) were adapted from another published study [84]. Finally, the substance use section (including vaping for both nicotine and tetrahydrocannabinol) was tailored to local adolescent consumption patterns. The resulting item catalog yields a technical range of 20 - 68 items depending on skip-logic (see Table 2 for an overview of sections and Multimedia Appendix 1 for the full EMA item catalog). Preliminary piloting resulted in response durations between 2 and 7 minutes maximum.

Participant Involvement

Participants from all groups are invited to feedback sessions at the end of the study, giving them the opportunity to express their honest opinion about the study. In addition, we will invite motivated adolescent participants to become young partners and contribute to a dedicated in-depth discussion session on the research project.

Preadolescent Protocol

Our presentation of the preadolescent protocol primarily concentrates on differences relative to the adolescent protocol and eventual differences between the school-recruited and clinical subgroups among preadolescent participants. Design characteristics that are not explicitly specified for preadolescents align with the description of the adolescent protocol.

Participants

For the preadolescent protocol, we intended to include 20 preadolescents between the ages of 10 and 13 years from private secondary schools, as well as 20 preadolescent patients between the ages of 9 and 12 years from an intensive outpatient treatment program. Patients commonly present with behavioral disturbances (eg, oppositional defiant behavior and emotion-regulation difficulties), communication or language disorders (eg, speech delays), specific learning disorders (eg, reading or writing impairments), and socialization problems (eg, limited peer interactions). Patients and their families receive intensive psychiatric care to sustain the psycho-affective and social development of the patient and to construct a therapeutic project for ambulatory follow-up care. Recruitment of eligible preadolescent patients is organized on an individual basis and is still ongoing.

Eligibility

Most eligibility criteria of the adolescent protocol also apply to the preadolescent protocol. The sole difference consists of preadolescents having to have access to a smartphone of one of their parents or legal representatives instead of being in possession of their own smartphone.

Procedures

The preadolescent protocol entails 2 waves of parallel EMA and actigraphy monitoring, with each wave lasting 10 days. During each ambulatory assessment wave, preadolescent participants respond to 2 EMA surveys per day (morning and evening) via their parents' smartphones. Morning deliveries are scheduled individually to allow families to be at the same place before heading off to school or work. Preadolescent participants recruited from schools receive EMA training in small groups, whereas clinical participants and their parents receive individual training. Instead of repeating retrospective symptom reports at exactly 7-day intervals as in the adolescent protocol, preadolescents respond to these measures at a 10-day interval, once at the beginning and end of each assessment wave. Actigraphy recordings are configured as described in the adolescent protocol, with recordings interrupted at the end of the 10-day period upon return of the device.

Participant Involvement

The design adaptations for the clinical preadolescent group were informed by discussions with parents of the clinical target population. This feedback was particularly influential in the design of the preadolescent clinical protocol. Participants recruited in the school setting will be invited to feedback sessions, whereas participants from the clinical setting will be invited to individual feedback sessions with their parents.

Self-Reported, Parent-Reported, and Clinician-Administered Measures

To reduce participation burden for preadolescent participants, we adapted the specific choice of instruments and modality of data collection (Table 1) to best meet their capacities of needs as well as those of their parents.

Baseline and Follow-Up Measures

During baseline assessments, the majority of instruments, more specifically the sociodemographic and medical history instruments [58], as well as the PPS [62], CRISIS [63], and FERS-C [64], are administered in an interview setting. Baseline self-reports from preadolescents were limited to the MESC [2,66], which uses adequate language for this age group (eg, "Imagine school is canceled. You can get up whenever you want to. When would you get out of bed?"). Parents responded to the respective parent-report versions for the general psychopathology assessment by means of the ASEBA Child Behavior Checklist (CBCL) [67,68] followed by the parent-report version of the ACEs screener (PEARLS-CHILD) [59]. Parents also report on baseline dietary habits of their participating child (FFQ) [69,70], with alcoholic beverage items omitted for this age group. Consistent with the follow-up planned for adolescent participants, parents repeat the CBCL

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at the end of the protocol, while their children respond to the final questions on study acceptability and measure reactivity.

Wave-Level and Weekly Measures

At the beginning of each wave, preadolescent participants respond to the retrospective assessments of social functioning (SDQ-social) [72-74], daytime sleepiness (ESEA) [75], and physical activity in an interview setting. For the physical activity questionnaire, a dedicated children's version was available (PAQ-C) [60,61,76]. Retrospective self-reports of symptoms of depression (CES-DC) [77-79] and anxiety (STAIC) [80,81] were administered in self-report format for school-recruited preadolescents and in interview format for clinical participants, respectively.

EMA Surveys

Preadolescents complete a reduced set of EMA items compared to adolescent participants (Table 2; Multimedia Appendix 1). Due to the negligible likelihood of psychotropic substance exposure in this age group [85], we exclude items related to substance use in their EMA prompts. Similarly, questions concerning alcohol consumption are omitted from the EMA surveys for preadolescents. In addition, the item addressing current menstruation is presented exclusively to female participants who report having experienced the start of menarche at baseline or at the onset of the second assessment wave.

Statistical Analyses

The targeted feasibility outcomes of acceptable and stable participation metrics will be examined by appropriate tests of equivalence regarding compliance and dropout against a priori benchmarks for both protocols [86]. We will further examine the stability of participation metrics by means of separate equivalence tests. We will also explore potential determinants of missing data and problematic response behaviors such as careless responding that might be clinically informative and that span different timescales as we test predictions from the retrospective baseline level (eg, ACEs) to the momentary level (eg, sedentary behavior).

To comprehensively address the inherent temporal and mechanistic complexity of dynamic interactions among health behaviors and affective functioning, multiple complementary statistical frameworks will be applied to data from the adolescent protocol. Each analytical model targets distinct characteristics of this interplay. We coregistered a first set of hypotheses claiming substantial heterogeneity in the daily within-person couplings of sleep patterns and daytime mood among adolescents [75,76]. Building upon prior research on internalizing etiology [87,88], we further hypothesize that the intensity of mood-sleep couplings is associated with levels of internalizing symptoms within the subclinical spectrum. These analyses apply Bayesian multilevel modeling [89,90].

To further contrast the relation between interindividual and intraindividual variability, time-series data will be analyzed to identify average and individual variability in motor activity, sleep patterns, eating habits, and associations with emotional states over different time periods (1 vs 2 vs 3 weeks; time of the day; day of the week; month and season). In order to provide preliminary findings on the different dynamic features of the interplay between health behaviors and mental health in youth, stability of sleep, physical activity, eating, and emotional states and their interrelationships will be assessed via different statistical approaches: (1) fragmentation analysis will be used to quantify subject-specific stability [91]; (2) functional principal component analyses and other machine learning approaches, such as the Joint and Individual Variance Explained (JIVE) [92] will be applied on the rich actigraphy dataset to explore the key components of sleep and physical activity, including average intensity, variability, and timing [93]; (3) Generalized Estimating Equations and network modeling [94] will be used to test the conditional estimate of the stationary dynamic associations between sleep, physical activity, eating, and emotional states, incorporating the lagged associations between these domains. Collectively, these approaches provide complementary rather than competing perspectives to deepen understanding of the dynamic interrelationships between health behaviors and mental health in youth.

Psychometric properties of the in-house translated scales (ie, PEARLS-CHILD, PEARLS-TEEN, PAQ-C, and PAQ-A) will be assessed based on internal consistency and construct validity. We will examine criterion validity by correlating ACEs with general psychopathology and self-reported physical activity with objectively recorded actigraphy. In addition, we will assess the test-retest reliability of the PAQ-C and PAQ-A scales across the 3 assessment waves based on changes observed in actimetry recordings.

Sample Size Rationale

Regarding the mixed populations and protocols within the present pilot study, we plan to balance data availability and statistical robustness for our feasibility targets and within-person effects. With respect to the limited annual intake of patients in the outpatient treatment who are eligible for group 1 (approximately 15 per year), our intention was to test feasibility per protocol with the combined preadolescent group reaching a sample size of 40 (ie, 20 each). Targeting the feasibility of the present multiwave design, we calculated statistical power for frequentist equivalence tests supporting the stability of response compliance rates across assessment waves. Based on equivalence bounds covering change scores within 70%±10%, a nominal alpha level of .05, and modest variability in change of response compliance (SD 0.1), statistical power of results in favor of stable compliance rates was considered adequate for the preadolescent protocol (power=0.87, n=40). This was also the case for the adolescent protocol (power=0.97, n=60), even under conservative Bonferroni correction accounting for 3 wave-specific equivalence tests (α=.015, power=0.91; see Figure S1 in Multimedia Appendix 1).

The rationale for determining sample size in the adolescent protocol, with regard to registered Bayesian multilevel models, was based on a reliability metric [95] for within-person effects between sleep patterns and daytime mood. A detailed explanation of this precision-oriented sample size calculation is available in the openly registered analysis plan [96]. Of note, precision-oriented determination of sample size aligns with principles of Bayesian analysis, emphasizing the accuracy of

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parameter estimates when comparing evidence for competing hypotheses [97].

Missing Data Handling

Given the intensive longitudinal design and the likelihood of both intermittent and monotone missingness, our complementary analytic approaches will use listwise deletion or full-information maximum likelihood estimation to accommodate unbalanced data under a missing-at-random assumption. Where missingness may be informative, such as dropout being related to symptom severity, school holidays, or duration of participation, we aim to extend these models to jointly estimate the missingness mechanism and outcome trajectories using selection models within a structural equation modeling framework [98] or via joint multilevel survival models [99]. For variables exhibiting sporadic missingness under missing-at-random, we will perform multiple imputation by chained equations, generating at least 20 datasets. Finally, sensitivity analyses will compare these results to complete-case analyses to evaluate the robustness of our findings.

Ethical Considerations

The study was approved by the Ethics Committee of the Vaud Canton, Switzerland (Project-ID 2021‑01821) and is in accordance with the Declaration of Helsinki. All participants received oral and written information about the study and received enough time to ask any questions. Adolescent participants provided written consent. Parents of adolescent participants received written information and were invited to reach out to the research team in case of any questions. Parents of preadolescent patients are met in person to explain the study and provide information letters and informed consent forms, whereas participants recruited in schools are asked to transmit information letters to their parents and return signed forms to the school staff or to the research team. Parents of both groups were encouraged to ask any questions regarding the study.

Adolescent participants will receive gift vouchers at a technology and culture retail chain of CHF 30 (US $37.72) at the end of the first and second, and CHF 40 (US $50.29) at the end of the third wave, respectively, when completing at least two-thirds of the self-report measures. Preadolescent participants receive gift vouchers of CHF 20 (US $25.15) and CHF 30 (US $37.72) at a technology and culture retail chain at the end of each respective wave, when completing at least two-thirds of the self-report measures.

During the ethics review, the local ethics committee recommended that such exclusion be avoided, noting that it could be perceived as unfair by students who had shown interest in participating. Participating schools opted to present the study to entire age cohorts, making oversampling a foreseeable outcome. This approach was formally documented in an amendment and received prior ethical approval.

Results

As of July 2025, we enrolled 113 adolescent and 27 preadolescent students, 13 preadolescent patients from the outpatient unit. The overrecruitment observed in the school-based samples, particularly among adolescents, reflects our ethical consideration to avoid excluding students solely based on the achievement of the predefined sample size.

Recruitment and data collection are still ongoing in the clinical setting. Every group in the school setting received feedback sessions with dedicated time to discuss the participants' experience of being involved in the study. Furthermore, we held one participatory session with 4 adolescent students from one school to discuss the strengths and limitations of the study in more detail.

Discussion

Principal Research Targets

This research highlights and attempts to capture the developmental dynamics of mental and physical health during emerging adolescence, using assessments across multiple timescales for in-depth, longitudinal analysis. Our feasibility-related findings will be crucially informative for future field research, especially in epidemiological paradigms. By examining the complex interplay between health behaviors across varying stages of late childhood and adolescence, we will gain preliminary insights into the transition from healthy states to those with mental health problems. This approach is pivotal for promoting health literacy, for developing age-appropriate early detection and prevention strategies, including transdiagnostic interventions in community and in clinical settings [100]. Using mobile technologies enables the creation of school-based programs for promoting healthy behaviors and discreetly identifying at-risk youth, particularly in older children and adolescents before the onset of many psychiatric disorders [101]. Because the study of these multiple health domains in youth using methods such as EMA and actigraphy is still struggling to converge on coherent frameworks of developmental psychopathology [102], the present methodological groundwork is essential across different clinical contexts and age groups.

Limitations

Despite its commendable attributes, notably the rich and multifaceted longitudinal data, this research project has inherent limitations that need to be addressed. First, clinical participants were drawn exclusively from a single intensive outpatient treatment unit for preadolescents, and school‑recruited youth attended private institutions, resulting in unbalanced and unrepresentative sampling, which impedes group comparisons. Populations recruited from private schools likely differ systematically from public schools and community clinics in socioeconomic profile [103], access to beneficial environments (eg, parental support and calm and safe sleep environment) [104], and development of health behaviors [105]. For example, private‑school adolescents, who typically come from higher socioeconomic status (SES), have been shown to select healthier snacks and consume more fruits and vegetables than their public‑school peers [106], and high‑SES adolescents generally engage in greater levels of physical activity compared to lower‑SES youth [107]. Conversely, clinical patients represent a subgroup characterized by greater symptom severity and comorbidity, with adolescents accessing specialty mental health services tending to have more severe and persistent

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disorders than those in community settings [108]. Consequently, the temporal dynamics of sleep, activity, diet, and mood we characterize may not extend to adolescents in lower - resource environments, public school settings, or clinical engagement. Our unbalanced design impeded corresponding group comparisons. Future large - scale studies should purposively sample across diverse sociodemographic and educational contexts, including public schools, community mental health centers, and underresourced regions, to evaluate whether the longitudinal dynamics we observe hold across the broader population of youth. Second, while we aimed for a comprehensive evaluation of relevant health behavior domains, some areas may have been missed, such as interpersonal relations and peer dynamics. Third, the lack of detailed data on stressors and significant life events such as relationship break-ups or familial loss during the study is a limitation. Anticipated events, such as final school examinations, were also not examined. Fourth, the translation of selected questionnaires without formal validation due to the multilingual study cohort may be a limitation. Fifth, the reliance on self-reported measures, including both retrospective trait questionnaires and in situ EMA surveys, introduces potential biases such as recall error [109], social desirability [110], and measurement reactivity, which may affect the accuracy and generalizability of our findings. Although EMA minimizes recall intervals [111], participants' awareness of ongoing monitoring can alter their responses. Future work should consider the most direct and unbiased assessment modalities available or under development (eg, passive dietary sensors and ecological smartphone usage logs) [102] or multimethod approaches to mitigate these self-report biases.

Despite these limitations, the comprehensive exploration of key health behavior domains and mental health in developing youth holds promise as a foundation for future studies. These findings can inform interventions and training programs to enhance prevention and intervention strategies for individuals.

Clinical and Research Implications

The present multimodal ambulatory monitoring paradigm can be seamlessly embedded within routine therapeutic care by choosing the specific domain most relevant for a given clinical situation. At treatment initiation, EMA and actigraphy can be used collaboratively by patient and clinician to coconstruct a personalized case formulation, providing an "additional eye" on day-to-day symptom dynamics and functional patterns [112,113]. By repeating these assessments at midtherapy and during key care transitions (eg, stepping down from intensive support), clinicians and patients can discuss their perceptions in front of the changes captured between sessions to refine formulations, adjust treatment targets, and evaluate response in real time [6, 114,115].

Going forward, research should thoroughly test the validity of temporal and digital markers that emerge from fundamental psychopathology studies and translate into practical, in-session tools [113]. Such work will determine which patterns of sleep, activity, stress reactivity, or digital engagement most reliably map onto clinical processes (eg, remission and relapse) and other consequential outcomes, and how to present these markers to clinicians [116]. Ultimately, this line of research will bridge ambulatory assessment science and everyday practice, enhancing transparency, engagement, and, hopefully, the effectiveness of youth mental health interventions.

Conclusions

This research aims to strengthen the investigation of the intricate dynamics between mental and physical health during adolescence by investigating the interplay between health behaviors and affective functioning across multiple timescales. The findings will not only contribute to methodological advancements but also inform future large-scale epidemiological studies and interventions aimed at early detection and prevention of mental health issues, highlighting the importance of idiographic approaches in youth health research.

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Authors' Contributions

KD, SU, KJP, and JG conceptualized the study and contributed to the acquisition of schools. KD wrote the manuscript of the study supervised by SU, KJP, and JG. All authors reviewed the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Ecological momentary assessment items and power curves.
[PDF File, 474 KB - resprot_v14i1e70990_app1.pdf]

Checklist 1

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STROBE checklist.
[PDF File, 92 KB - resprot_v14i1e70990_app2.pdf]

Checklist 2
CREMAS checklist.
[PDF File, 85 KB - resprot_v14i1e70990_app3.pdf]

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Abbreviations

ACE: Adverse Childhood Experiences
ASEBA: Achenbach System of Empirically Based Assessment
CBCL: Child Behavior Checklist
CES-DC: Center for Epidemiological Studies Depression Scale for Children
CREMAS: Checklist for Reporting Ecological Momentary Assessment Studies
CRISIS: Coronavirus Health Impact Survey
EMA: Ecological Momentary Assessment

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ESEA: Échelle de somnolence chez l'enfant et l'adolescent [Sleepiness Scale]
FERS-C: French version of Emotional Regulation Scale for Children
FFQ: Food Frequency Questionnaire
MESC: Morningness Eveningness Scale for Children
mMARCH: Mobile Motor Activity Consortium for Health
PAQ-A: Physical Activity Questionnaire for Adolescents
PAQ-C: Physical Activity Questionnaire for Older Children
PEARL-TEEN: Pediatrics Adverse Childhood Events and related life events screener for teenagers
PEARLS-CHILD: Pediatrics Adverse Childhood Events and related life events screener for parents of children
PPS: Peterson Puberty Scale
REDCap: Research Electronic Data Capture
SDQ: Strengths and Difficulties Questionnaire
SES: socioeconomic status
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
STAIC: State-Trait Anxiety Inventory for Children
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
YSR: Youth Self-Report

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Designing an AI-Enhanced Public Health Care Platform for the Rapidly Aging Population in South Korea: Protocol for a Mixed Methods Study Based on the Design Thinking Approach

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Abstract

Background: South Korea is undergoing one of the world's fastest demographic shifts toward an aging society, with projections indicating that by 2047, half of all households will be led by older adults. While digital health technologies such as mobile health apps and telemedicine offer promising solutions for promoting healthy aging and reducing health care expenditures, their adoption among older Koreans remains limited. To address these challenges, this study will use a user-centered design thinking approach to develop a public health care platform tailored to the needs of South Korea's older adults.

Objective: The primary objective of this study is to develop and evaluate a user-centered digital health care platform tailored to older adults in South Korea, with the aim of overcoming key barriers, such as low digital literacy, interface complexity, and mistrust in artificial intelligence–driven systems, and ultimately bridging the digital divide in health.

Methods: This mixed methods study will integrate qualitative and quantitative research within a design thinking framework, progressing through 3 operational phases: empathize and define, ideate, and prototype and test. In phase 1, a scoping literature review, field observations at 5 community centers for older people and in-depth interviews with 29 older adults and 15 stakeholders were conducted to identify behavioral barriers and user needs. In phase 2, an open idea contest and expert focus groups were used to generate and prioritize innovative features for the platform. Phase 3 involves co-design workshops, minimum viable product development using a no-code platform, and usability testing with 8 to 10 older adults.

Results: The research received a grant (HI22C1477) from the Korea Health Industry Development Institute (2023-2025) and ethical approval (2023-01-014) from Sungkyunkwan University. As of July 2025, data collection for phase 2 is ongoing, and preliminary findings are expected by late 2025.

Conclusions: By adopting an inclusive design thinking approach, this study aims to produce a practical and user-centered platform for older adults. The findings will contribute to research on digital health equity and offer actionable insights for community-centered technology design.

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KEYWORDS

aging society; design thinking; digital literacy; digital health care platform; participatory research; digital inclusion; older adults; user-centered design

Introduction

South Korea is experiencing one of the most rapid demographic shifts toward an aging population in the world, with official statistics indicating a steadily increasing proportion of older adults [1,2]. In 2020, the number of single-person households headed by older adults surpassed 1.66 million, constituting more than one-third of all such households [1]. Projections suggest that by 2047, half of all Korean households will be headed by an older adult [2]. While this demographic change reflects advances in health care and socioeconomic development, it also raises urgent questions about maintaining older adults' health, well-being, and quality of life [3]. Many older Koreans live with multiple chronic conditions and face substantial health care costs, and approximately 9.5% require long-term care [1]. In response, the government has emphasized policy-level interventions and the development of innovative service models for healthy aging [2,3]. Among these, digital health technologies, such as mobile health apps, telemedicine, and remote monitoring, are considered promising strategies for reducing the burden on the health care system [2]. However, actual

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adoption among older adults remains low, hindered by barriers such as limited awareness, low digital literacy, and skepticism toward technology-driven interventions [4-6].

This discrepancy underscores a broader "digital divide" in health—a gap in access to, and effective use of, digital resources that often correlates with age, socioeconomic status, and technological proficiency [7-9]. Digital literacy plays a pivotal role in bridging this divide, encompassing not only the ability to operate devices but also to critically evaluate and apply digital information [4,7,9]. While younger cohorts in South Korea frequently acquire digital competencies through daily life and formal education, older adults have had fewer opportunities to develop such skills [6,10]. Although many own smartphones, use is often limited to basic communication rather than health management tasks [5]. Additional hurdles include text-heavy interfaces, foreign-language prompts, and frequent software updates that can further deter sustained use [11,12].

Against this backdrop, design thinking offers a user-centered, iterative approach to creating digital health solutions that genuinely reflect the needs and preferences of older adults [13-15]. Characterized by 5 key stages—empathize, define, ideate, prototype, and test—design thinking actively engages end users, reframes problems from their perspectives, and iterates solutions based on real-world feedback [13,14]. In this study, we group these 5 stages into 4 operational phases to streamline the design process: (1) emphathize and define, (2) ideate, and (3) prototype and test. Prior studies have shown that co-designing technology with older adults not only increases adoption but also fosters a sense of ownership and comfort in using platforms that aligns with their cognitive and physical capabilities [6,16,17]. These findings suggest that participatory, empathy-driven methodologies can narrow the digital divide by identifying context-specific user requirements early in the design process [16,18].

In this study, we use a design thinking framework to develop a public health care platform tailored to older adults in South Korea. Our goal is to create a mobile- or web-based platform that connects older adults to essential health information and services, such as chronic disease management, medication reminders, and social welfare resources, in a user-friendly and contextually relevant manner. We hypothesize that a co-designed, user-centric platform will demonstrate enhanced usability and acceptance, potentially leading to better health management behaviors and reduced health care costs [2,3]. By integrating older adults throughout the design process, we aim to address their unique barriers, mitigate the digital divide, and ultimately contribute to a more inclusive health care system.

Methods

Overview

This study uses a participatory, mixed methods approach grounded in design thinking [13-15] to create a user-centered digital public health care platform for older adults in South Korea. We apply the 5 classical stages of design thinking—empathize, define, ideate, prototype, and test—grouped into 3 operational phases over a 36-month period (January 2023 to December 2025). While the design thinking process is structured into phases, these phases are not implemented in a strictly linear order. Insights from earlier activities are continuously cycled back into later stages, allowing for iterative refinement across the project timeline.

Although this study is organized into 3 distinct operational phases, the activities within these phases are conducted iteratively and concurrently rather than strictly sequentially, reflecting the inherent flexibility and iterative nature of the design thinking methodology [13,14,16]. Thus, these phases permit ongoing feedback loops and dynamic adjustments based on user insights and emergent findings. Figure 1 provides a schematic diagram illustrating how qualitative (eg, interviews and observations) and quantitative (eg, System Usability Scale; SUS) data converge to refine the platform's design.

Figure 1. Five key stages of the design thinking process.

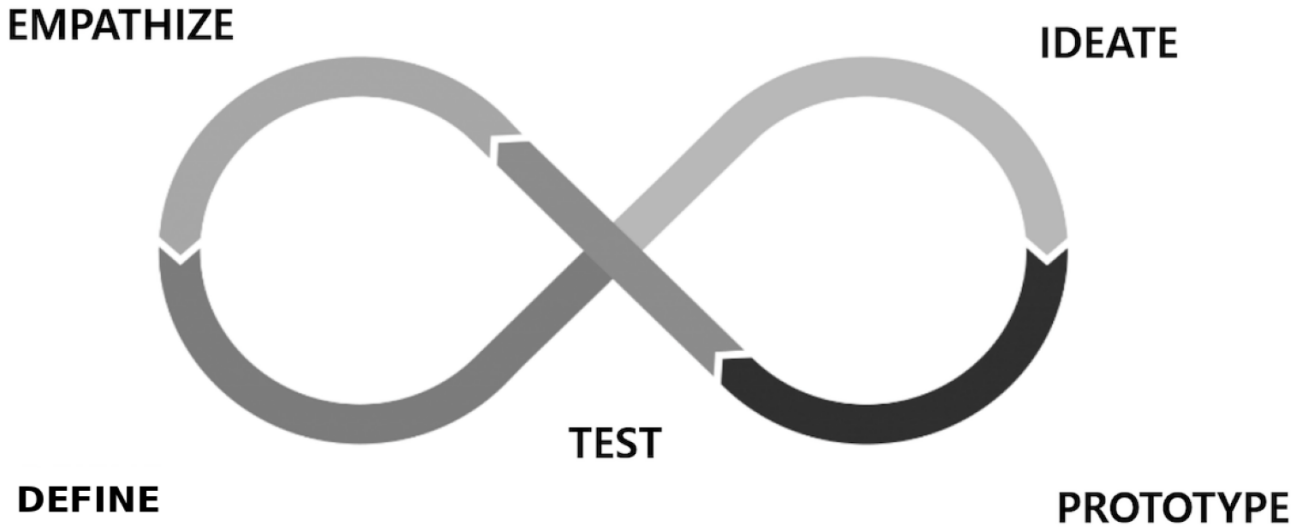

The design thinking process adopted in this study consists of 5 iterative stages: empathize, define, ideate, prototype, and test [13-15]. *Empathize* involves understanding users' needs, preferences, and behaviors through methods such as interviews, observations, and field immersion. This helps uncover deeper insights that inform problem framing [13,14]. *Define* focuses

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on synthesizing user insights to identify key challenges and articulate a clear problem statement. A well-defined problem sets the direction for ideation and solution development [13]. *Ideate* encourages the generation of diverse ideas in response to the defined problem, often through creative techniques such as brainstorming and mind mapping [13]. *Prototype* refers to building tangible representations of promising ideas. These prototypes help visualize concepts and gather early feedback before full development [13,15]. *Test* involves evaluating prototypes with real users to identify usability issues, gather insights, and refine solutions iteratively. This stage ensures the solution is feasible, desirable, and aligned with users' needs [14,15]. Together, these stages provide a user-centered and flexible framework that will guide the platform development process in this study.

To facilitate transparency in the mixed methods design, Table 1 summarizes how each design thinking stage integrates qualitative and quantitative insights [13,16,19] and Table 2 shows the mixed methods flow across the design thinking stages.

Table . Overview of study phases, activities, and outputs.

Phase	Timeline	Primary activities	Outputs
Phase 1: empathize and define	Jan 2023 to May 2025	Scoping review, field observation, semistructured interviews	Personas, scenario maps, problem statements
Phase 2: Ideation	Jan to Mar 2023 (students), fall 2025 (experts)	Idea contest, expert focus group discussions	Ranked ideas, priority features, technical feasibility roadmap
Phase 3: prototype and test	Jun to Dec 2025	Co-design workshops, minimum viable product development, usability testing	Functional prototype, usability metrics, user feedback

Table . Mixed methods flow across design thinking phases.

Design thinking stage	Input (qualitative and quantitative)	Process	Output
Phase 1: empathize and define	Scoping review (qualitative), interviews (qualitative), field notes (qualitative)	Persona creation, scenario mapping	Problem statements, user archetypes
Phase 2: ideate	Idea contest entries (qualitative), expert focus group discussions (qualitative)	Thematic coding, feasibility scoring	Ranked feature sets, concept clustering
Phase 3: prototype and test	Usability survey (quantitative: System Usability Scale), posttest interviews (qualitative)	Triangulation, sprint revision	Usability dashboard, minimum viable product refinement plans

This structure aligns with the mixed methods approach of Creswell and Plano Clark [19], ensuring both methodological rigor and iterative design adaptability.

Phase 1: Empathize and Define Scoping Literature Review

Overview

A scoping review was conducted in accordance with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines [20] and the Arksey and O'Malley [21] framework to investigate how older adults interact with digital healthcare platforms, focusing on human information behavior and associated barriers. Four major academic databases (PubMed, Scopus, Web of Science, and gray literature repositories) were searched using Boolean combinations of "eHealth," "digital literacy," "elderly," and "technology adoption," covering the period from 2010 to 2023. Two independent reviewers screened titles and abstracts and then the full texts. Data extracted included study design, population characteristics, technology type, behavioral frameworks, and outcome measures. Previous studies indicate that older adults' acceptance of digital health tools can be influenced by factors such as interface complexity and perceived ease of use [22,23]. From this review, we identified 4 prominent behavioral barriers: interface complexity, low digital literacy, emotional resistance, and lack of contextual support [5,6,11]. These findings informed the design of subsequent interview protocols, field observation criteria, and participant personas. They also shaped the problem statements and discussion prompts used during the ideation phase (contest and expert focus groups).

In-Depth Interviews: Participants and Recruitment

We aimed to recruit approximately 29 older adult participants (aged 65 years or older) from Seoul and Suwon, balancing factors like digital experience level and living situations to ensure thematic saturation (Textbox 1). Previous gerontological research suggests that samples of around 20 to 30 participants can capture major themes while allowing demographic variability [24].

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria
Korean-speaking, cognitively able to participate, with or without prior smartphone experience
Exclusion criteria
Diagnosed dementia or psychiatric disorders impeding informed consent or interview participation

Stakeholders included social workers, care coordinators, nurses, and program administrators, each with at least 1 year of experience delivering services to older adults. The sample size (n=15) aimed to represent the range of professional roles relevant to care of older people and welfare service systems [3]. Recruitment occurred through program referrals at community centers for older people and snowball sampling. Interested individuals received a study information sheet and provided signed informed consent [6].

In-Depth Interviews: Interview Procedure

Interviews were conducted in Korean, typically lasting 40 to 90 minutes. Depending on participant preference and mobility, interviews were held face-to-face or by phone from September 2024 to May 2025. A semistructured guide (Multimedia Appendix 1) covered topics such as older adults' digital device use, barriers, support needs, safety concerns, and impacts on quality of life. Interviews were audio-recorded, transcribed verbatim, deidentified, and uploaded to a secure server.

In-Depth Interviews: Data Analysis

Data were analyzed using reflexive thematic analysis [25]. The process is outlined in Figure 2.

Coding was facilitated by NVivo (version 14; Lumivero). To enhance the credibility of findings, the research team used member-checking with selected participants, peer debriefing sessions for code refinement, and triangulation with field observation data and the scoping review outcomes [16,25].

Figure 2. Data analysis process using reflexive thematic analysis

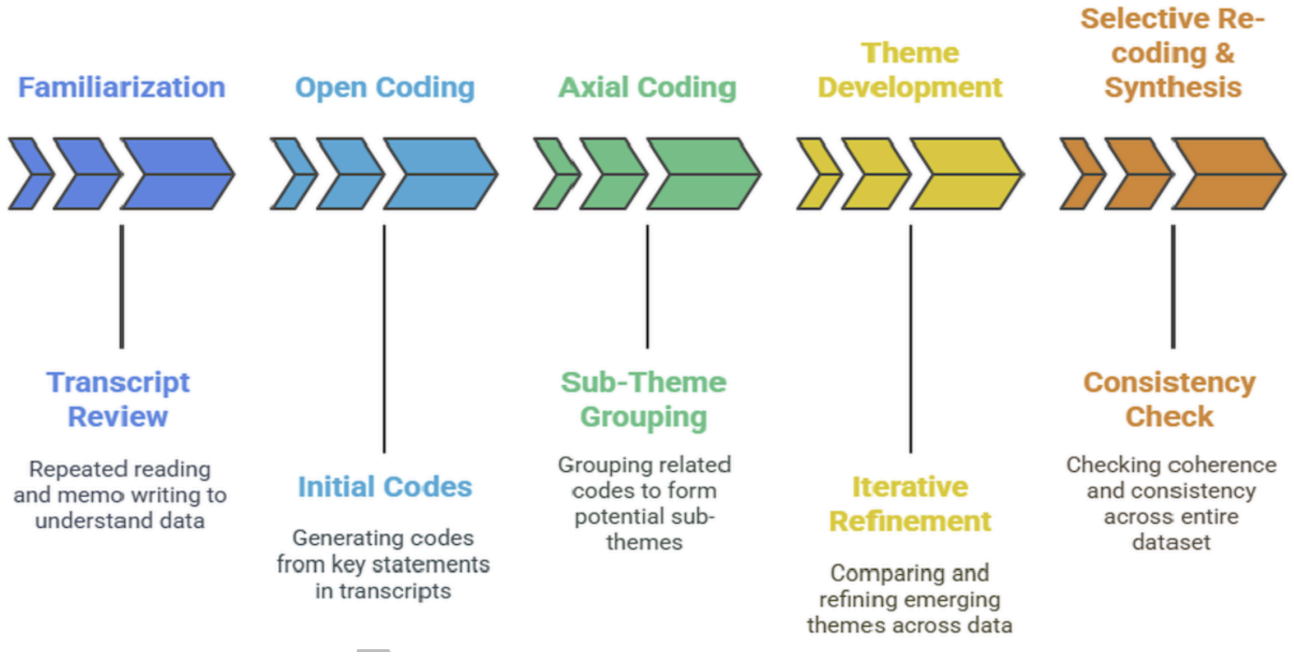

Phase 2: Ideate

Student Idea Contest

In January 2023, we launched an open idea contest titled Social Welfare+Digital Technology to gather innovative solutions targeting older adult health care needs. Promotion was conducted via online university platforms (Everytime and Instagram). We enrolled students or recent graduates in social welfare–related fields. The submission requirements were a 5-page proposal outlining the problem background, a proposed digital solution, and an implementation plan. The review criteria were innovation (25% weight), user-centeredness (25% weight), feasibility (20% weight), alignment with eldercare goals (20% weight), and clarity/scalability (10% weight). The review criteria and weights were determined by the research team based on relevance to digital eldercare innovation and user-centered design principles.

We received 24 proposals, and 6 won awards based on feedback from an expert panel (including a social worker, physician, and technology entrepreneur). Notable ideas, such as a voice-based health assistant, were prioritized for prototype development [15,16].

Expert Focus Group

Scheduled for late 2025, focus groups will involve 8 to 10 professionals with expertise in user experience and user interface design, geriatrics, and public health. This range (n=8 to 10) was chosen to ensure multidisciplinarity while maintaining an optimal group size for in-depth discussions [26]. Using the

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personas and problem statements derived from phase 1, participants will evaluate the feasibility of the idea contest winners, prioritize key features and components (via dot-voting and feature scoring), and discuss integration paths with existing public systems (eg, the National Health Insurance Service). Outputs from this stage will inform a minimum viable product (MVP) blueprint for development [15,16].

Phase 3: Prototype and Test

Co-Design and Development

Between June and September 2025, we will adopt an agile co-design process. Two older adult advisors will collaborate with user experience designers, front-end developers, and back-end engineers to create a functional MVP. Low- to medium-fidelity wireframes will be generated using Figma, and the MVP will be implemented with Bubble.io (a no-code platform) for rapid iteration [16]. Initial core features include simplified login and intuitive navigation, medication reminders with optional voice prompts, and an "ask a nurse" chatbot interface for basic health queries.

Usability Testing

A subset of 8 to 10 older adult users from the interview cohort will be recruited for usability testing, following the heuristic of Nielsen and Landauer [27] that testing with 5 to 10 users can uncover 80% to 90% of major usability problems [5,23]. Testing will occur in October to November 2025 through scheduled on-site sessions (Textbox 2) . Participants will perform key tasks on the MVP, including logging into the app, setting or modifying medication reminders, and using the chatbot for health-related questions.

A think-aloud protocol will capture real-time user reactions, and screen recordings will log errors or confusion points.

Textbox 2. Usability testing data collection and analysis.

System Usability Scale (SUS)

After completing the tasks, participants will fill out the SUS questionnaire. Results will be analyzed via descriptive statistics (mean and SD) using SPSS (version 28; IBM Corp), with a score ≥68 considered "acceptable."

Posttest interview

Participants will provide open-ended feedback on overall design, satisfaction, and suggested improvements. Thematic coding will be used to identify common pain points [25].

Mixed Methods Integration

To ensure robust triangulation and iterative refinement, we integrate qualitative and quantitative data at 2 critical junctures [13,16,19] through interpretive convergence. Themes from phase 1 interviews and field observations are mapped against usability bottlenecks detected in phase 3 (SUS scores and error logs) to deepen our understanding of how older adults' perceptions and attitudes translate into actual platform interaction challenges.

By weaving together data from multiple sources, this approach strengthens the ecological validity of our findings and ensures that the final platform design is both technically sound and responsive to real-world user contexts [13,16,19].

Ethical Considerations

This study was approved by the Institutional Review Board of Sungkyunkwan University (2023-01-014). Prior to participation, all participants were provided with both written and verbal explanations of the study objectives, procedures, potential risks, and benefits. Written informed consent was obtained from every participant. To maintain confidentiality, no personal identifiers were collected; audio recordings and transcripts were stored on password-protected devices. All participants received KRW 30,000 (US $21.83) as compensation for their participation.

Results

As of April 2025, phase 1 (empathize and define) had been completed, including 29 older adult interviews and 15 stakeholder interviews. These insights will directly inform phases 2 and 3, which are planned to be carried out in the latter half of 2025.

During the scoping review, we screened publications from 2010 to 2023 and identified key barriers to older adults' engagement with digital health tools, including interface complexity, low digital literacy, emotional resistance, and insufficient contextual support. These categories informed the initial interview protocol and guided the creation of personas. Preliminary qualitative analysis suggests three recurring themes: (1) interface anxiety, (2) family-mediated use, and (3) trust in artificial intelligence (AI)–driven systems. First, participants reported anxiety when confronted with unfamiliar buttons, icons, or English terminology. They often deferred to family members or care workers to handle advanced features. Second, many older adults rely on adult children or relatives to set up smartphones, download health apps, and troubleshoot technical issues. This reliance creates both a support system and a dependency, potentially limiting independent engagement. Third, several older adults expressed skepticism about chatbot-based health advice, citing concerns over accuracy, privacy, and data misuse. Stakeholders stressed the importance of transparent data governance and easy-to-understand consent processes.

The observed difficulties and reported anxieties underscore the need for simplified interfaces. These insights will shape the concept brief for the co-design sessions, ensuring that user-friendly layouts and robust support features (eg, step-by-step tutorials) are prioritized. The findings on mistrust of AI will be crucial in determining the extent to which automated health recommendations are integrated into the MVP and how transparency in data handling is communicated. The research received a grant (HI22C1477) from the Korea Health

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Industry Development Institute (2023-2025) and ethical approval (2023-01-014) from Sungkyunkwan University. Recruitment progressed smoothly through community partnerships, though ongoing efforts are required to ensure a balanced representation of older adults with varying degrees of digital literacy.

Discussion

Principal Findings

This research protocol outlines a design thinking–based approach to address the ongoing challenge of low digital health care adoption among older adults in South Korea. By combining a scoping review, field observations, and in-depth interviews, the study seeks to uncover barriers such as interface anxiety and trust in AI-driven systems. These insights are expected to inform the design of a user-centered platform that is both inclusive and usable.

Comparison to Prior Work

The proposed co-design process builds upon prior participatory approaches, but places a stronger emphasis on iterative feedback loops with older adult participants. While the participatory framework is anticipated to improve alignment with user needs, its actual impact will depend on successful implementation and engagement throughout the design phases.

Strength and Limitations

A potential strength of this study lies in its planned integration of multiple qualitative and quantitative methods across iterative design stages. However, certain limitations, such as the initial focus on urban participants and a relatively short MVP evaluation period, may restrict early generalizability. These limitations will be addressed in subsequent phases by expanding to rural communities and implementing longer-term follow-up activities.

Future Directions

Future work will explore scaling the platform to different demographic groups and health care contexts, including collaborations with local clinics and nonurban community centers. Usability evaluation in real-world settings will be prioritized to ensure long-term adoption.

Dissemination Plan

Upon completion, the study aims to provide a transferable model of digital health engagement that can inform future interventions. Planned dissemination includes academic publishing, stakeholder workshops, and the development of publicly available co-design toolkits. Overall, this protocol contributes to growing efforts to bridge the digital divide by centering older adults as active agents in the design of inclusive health care technologies.

Conclusions

This study will generate practical and theoretical insights into inclusive platform design by engaging older adults in a human-centered participatory process. The expected outcomes will inform digital health policy and community-based intervention models for aging societies.

Disclaimer

Generative AI (ChatGPT) was used for grammar and formatting edits after full manuscript drafting. No content generation or interpretation involved AI assistance.

Authors' Contributions

The author is solely responsible for the conceptualization, methodology design, data collection planning, and drafting of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Development of a smart care service platform model based on the Digital Literacy for Older Adults Interview Questionnaire.
[DOCX File, 27 KB - researchprotocols_v14i1e63094_app1.docx]

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Abbreviations

AI: artificial intelligence
HCI: human-computer interaction
MVP: minimum viable product
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
SPSS: Statistical Package for the Social Sciences
SUS: System Usability Scale

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Protocol

Evaluation of the Transition-to-Practice Arrangements for Novice Perioperative Nurses: Protocol for a Mixed Methods Study

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Abstract

Background: Transitioning into the first year of clinical practice as a nurse or changing specialties in the nursing career presents a critical phase for novice nurses characterized by excitement, apprehension, and the phenomenon of “transition shock.” Within perioperative nursing, this transition phase takes on distinctive challenges. However, there is a lack of empirical evidence on transition programs and arrangements.

Objective: This study aimed to evaluate the current transition-to-practice (TTP) arrangements available to new graduate and novice nurses within Australian perioperative nursing settings.

Methods: This study uses an exploratory mixed-method, multilevel triangulation with a sequential phase design to address 4 research questions. Phases 1 to 3 will use document analysis, surveys, and semistructured interviews to establish the findings of the research questions. Phase 4 will use meta-inference and triangulation to aggregate and analyze the data from all preceding phases. These findings will be the foundation for developing a framework to inform future TTP arrangements. This robust framework will embed empirical evidence, existing literature, and sound learning and teaching pedagogy. Results emerging from this study will be reported using the Good Reporting of Mixed Methods Study guidelines.

Results: This project received approval in June 2023. Following this, Human Research Ethics Committee approval was sought for phases 1 and 2, and recruitment began. As of August 2024, phase 1 has collected 50 responses and phase 2 has collected 69 responses. Data collection for phase 3 is projected to commence in May 2025 once data from phases 1 and 2 have been analyzed. Phase 4 is projected to occur in 2026. Each phase is anticipated to have a results manuscript submitted for publication once data are analyzed and written up.

Conclusions: The findings of this study will provide an in-depth exploration of TTP arrangements within perioperative nursing in Australia and provide a framework to guide the future development of TTP arrangements.

Trial Registration: OSF Registries osf.io/zm432; https://osf.io/54s36

International Registered Report Identifier (IRRID): DERR1-10.2196/64970

(JMIR Res Protoc 2025;14:e64970) doi:10.2196/64970

KEYWORDS

transition to practice; perioperative nursing; novice nurses; nurse educators; mixed methods research; protocol; document analysis; semistructured interviews; pedagogy

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Introduction

Transitioning from undergraduate nursing studies or other nursing specialties into perioperative nursing is a pivotal phase in a nurse's career journey. This critical period in a novice nurse's career is often filled with excitement, nervousness, and apprehension. It is not uncommon for novice nurses to experience transition shock during this period, a term that describes a state of emotional and physical shock [1]. Novice nurses often describe transition as feeling like they are "drowning", "terrified," or "scared to death" [1]. Within the specialized field of perioperative nursing, transition challenges take on a unique dimension. Perioperative nurses play a vital role in surgical settings, where precision, attention to detail, and seamless care coordination are paramount. Professional health care organizations recognize the unique nature of critical care environments, such as perioperative nursing, that require specialized clinical competence and an understanding of the environment [2,3].

Transition shock in novice nurses arises from the sudden shift from a structured, academic environment to the complex and high-pressure demands of real-world practice, which often differ greatly from their expectations [1]. Without the support systems novice nurses rely on as students, novices can feel isolated, anxious, and insecure in their abilities. The disconnect, paired with high responsibility and fear of making mistakes, contributes to self-doubt, stress, and sometimes burnout in the early months of their job [1].

It is common practice for novice nurses to gain employment opportunities that offer the prospect of completing structured transition-to-practice (TTP) arrangements [4]. TTP arrangements serve as vital conduits connecting the theoretical knowledge acquired during undergraduate nursing education with the knowledge and skill requirements of real-world clinical practice. TTP arrangements play a pivotal role in nurturing the growth of novice perioperative nurses by providing mentorship, tailored training, and a supportive environment where new graduates can gain hands-on experience and develop the competence and confidence necessary for successful nursing practice [5,6].

A lack of empirical evidence regarding TTP arrangements within the perioperative nursing setting was noted during the literature search [7]. Transition arrangements and the impacts of transition shock are well defined within the literature [5,6]; however, there was a paucity of empirical literature that discussed the perioperative TTP arrangements. Most of the literature identified were discussion pieces [7]. Second, the "Educating the Nurse of the Future" report described the significant variability between TTP arrangements and their providers [8]. In this report, it was identified that there is no set standard for the length of transition arrangements, the content taught, how the content is taught, or the other supporting mechanisms available to novice nurses.

This study will address the 2 critical gaps in the literature and transition practices, as identified above. This paper provides a detailed overview of the methods to be used and a discussion of how the study will systematically investigate current practices in transition arrangements and the efficacy of these arrangements. It seeks to explore the perspectives of novice perioperative nurses and perioperative nurse educators regarding transition arrangements.

Methods

Study Aim

The proposed research study aims to evaluate the current TTP arrangements available to new graduate and novice nurses (hereafter referred to both groups as novice nurses) within Australian perioperative nursing settings and draw on these findings to develop recommendations and a theoretical framework to guide the design, development, and implementation of future transition arrangements within the perioperative nursing specialty.

Study Objectives

The following research objectives stem from the research aim and have been used to guide the development of the research questions. The research objectives are (1) to develop an understanding of the transition to practice arrangements in the perioperative environment; (2) to engage key stakeholders to share their opinions, expertise, and experiences on transition arrangements within the perioperative nursing environment in Australia; (3) to undertake critical analysis of the transition arrangements available in Australia to support novice nurses entering perioperative nursing; and (4) and to develop a framework and model that provides evidence-based educational, social, and holistic transition arrangements for novice nurses entering perioperative nursing.

Research Questions

The following research questions (RQs) are designed to meet this study's aims and objectives:

- RQ1: What are the current TTP arrangements available to novice perioperative nurses within Australian health care organizations?
- RQ2: What are the content, methods, and educational philosophies used within these TTP arrangements?
- RQ3: How effective are TTP arrangements in supporting novice perioperative nurses and guiding them throughout the transition period?
- RQ4: What support do novice perioperative nurses undertaking TTP arrangements require to become competent and confident clinicians?

Design

This study uses an exploratory sequential mixed-method, multilevel triangulation design (Figure 1). This methodology combines both qualitative and quantitative data to yield a deeper understanding of the research questions [9]. By mixing qualitative (subjective) and quantitative (objective) research, the researcher is provided with the flexibility to explore complex issues and answer multifaceted research questions, thus bridging the divide between the 2 individual research approaches [10]. Several multifaceted research questions need to be answered within this study, which would not be feasible by using only quantitative or qualitative data sources.

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Figure 1. Overview of the exploratory mixed-method, multilevel triangulation design with sequential phases.

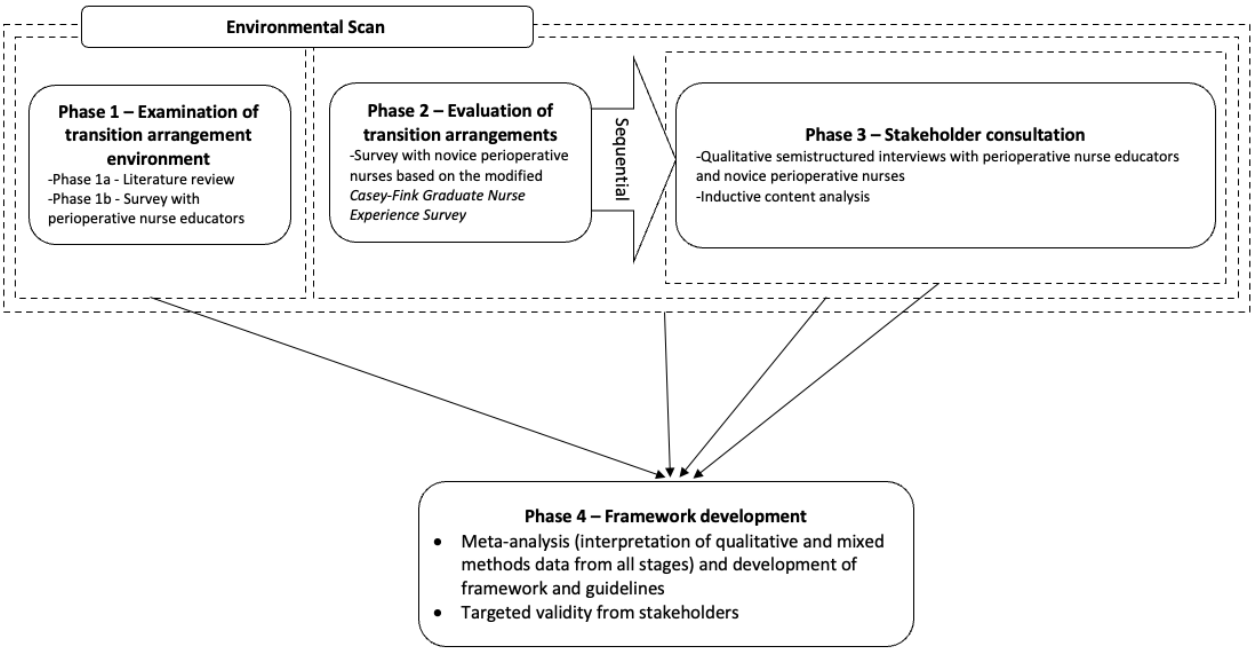

This research study has 4 phases (Figure 1). The sequential design will be applied between phase 2 and phase 3 [11]. Phase 1 involves document analysis and surveys to establish the existing TTP arrangements for perioperative nursing in Australia. Phase 2 involves surveys with novice perioperative nurses to determine the effectiveness of TTP arrangements. The findings from these phases will inform the development of interview questions for phase 3. Phase 4 of this study will involve a meta-analysis of all the data collected, which will be used in the development of a framework. An overview of this research design is represented in Figure 1, illustrating the research questions being addressed and the primary method used at each phase. Ethics approval will be sought for phases 1 and 2, as these will run concurrently, and for phase 3.

Phase 1: Transition-to-Practice Arrangement Analysis

The first phase of the study will address RQ1 (what are the current TTP arrangements available to novice perioperative nurses within Australian health care organizations?) and RQ2 (what are the content, methods, and educational philosophies used within these TTP arrangements?) using document analysis techniques and a mixed methods survey. As most health care organizations do not publicly publish their transition arrangements, a survey was designed to collect data about TTP arrangements from perioperative nurse educators. The research team had access to their local TTP arrangements; however, surveying perioperative nurse educators will ensure that this study is not geographically confined. Using 2 data collection methods ensures sufficient results are obtained to understand the TTP arrangements used within the Australian perioperative environment.

Participants, Sample Size, and Recruitment

Data will be collected from 2 separate sources. First, the document analysis, which seeks to explore and understand TTP arrangements from within Australia. These TTP arrangements will be purposefully selected to ensure completeness and that they are currently used in novice perioperative nurses' training and transition support.

Second, a survey will be undertaken with a convenience sample of Australian perioperative nurse educators. Sample size calculations indicate an ideal sample size of 28 participants will be required using a confidence level of 95% and a margin of error of 5%) [12] to capture adequate responses to generalize TPP arrangement practices in Australia. Perioperative nurse educators who participate in this survey must be currently used within an Australian perioperative department in a role that allows them to provide nursing education, management, or support to novice perioperative nurses. Participants will be recruited through snowball sampling techniques and social media such as LinkedIn, Facebook (Meta), and Twitter (rebranded as X) [13]. In addition, professional nursing organizations and peak bodies for perioperative nursing will be approached to disseminate the survey.

Data Collection and Analysis

Manual searching of gray literature search engines, professional organizations, and health service websites will be used to identify suitable TTP arrangements for the document analysis component of this phase. Data collection for the document analysis and survey will be completed using a fit-for-purpose online survey. The survey tool was designed based on the authors' scoping literature review findings [7]. The survey instrument will collect data regarding the duration of TTP arrangements, modality, pedagogy and content taught, assessments, efficiency, and barriers. The survey will remain open until the required sample size is reached, or until all recruitment strategies have been used.

The document analysis tool and survey will collect both qualitative and quantitative data. Qualtrics StatsIQ will be used for descriptive statistical analysis and frequencies for quantitative data. Qualitative data will be analyzed using Braun [14] and Clarke's [15] 6-step guide to thematic analysis. NVivo

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(Lumivero) software will be used for data management and coding of qualitative data. The findings from this phase will be used to inform the semistructured interviews for phase 3.

Phase 2: Survey Phase

Phase 2 of the project will use an online survey to address RQ3 (How effective are TTP arrangements in supporting novice perioperative nurses and guiding them throughout the transition period?) by exploring the effectiveness of TPP arrangements within perioperative nursing from the novice nurse perspective. By doing this, the researcher will understand the efficacy of TTP arrangements within perioperative nursing. Understanding transition practices, particularly from the novice nurse experience, is essential as novice nurses are integral to transition arrangements. Transition arrangements should be designed around novice nurses' learning and organizational needs and resources.

Participants, Sample Size, and Recruitment

A convenience sample of novice perioperative nurses who have recently completed a TTP arrangement within perioperative nursing will be sought for this study phase. It is anticipated these participants will be familiar with the transition arrangement they undertook. A 3-year inclusion criterion is set based on Benner's Novice to Expert Theory [16]. Nurses within the perioperative specialty with over 3 years of experience are often considered competent and an expert and no longer novices [16].

Significant missing data were noted when attempting to calculate sample sizes for this phase. An accurate estimate of the current population of novice perioperative nurses in Australia was unable to be achieved without making several assumptions that may lead to inaccurate sample size calculations. As the purpose of this phase is to inform the interview development of the next phase (interview phase), therefore a purposive, convenience sample will be the aim for this survey, where all reasonable recruitment strategies will be undertaken and the survey will remain open for 12 months.

Recruitment will be conducted through social media and snowballing, through professional organizations such as the Australian College of Perioperative Nurses, at conferences, and through university contacts to disseminate to graduate perioperative nursing students.

Data Collection and Analysis

Data will be collected using the revised Casey-Fink Graduate Nurse Experience Survey [17]. The survey tool was modified with the written permission of the survey tool authors. Adjusting the survey allows contextualization to the Australian perioperative nursing setting and enables the inclusion of further questions relating to participants' experiences during the transition. The Casey-Fink Graduate Nurse Experience Survey examines novice nurse transition across 8 domains, these being Role Confidence, Organize and Prioritize Care, Support, Role Satisfaction, Stress and Burnout, Resilience, and Organizational Commitment and Preceptorship [17].

Data will be analyzed using SPSS (IBM Statistics) software [18]. Descriptive and inferential statistics will be completed, including reliability testing (Cronbach α), linear regression, and factor analysis (varimax rotation) [19,20]. The NVivo software [15] and Braun and Clarke's [14] 6 steps of thematic analysis will be used to analyze the open-ended qualitative survey questions. The findings from this phase will be used to inform the semistructured interviews for phase 3.

Phase 3: Interview Phase

In phase 3, semistructured interviews will be conducted to address RQ4 (What support do novice perioperative nurses undertaking TTP arrangements require to become competent and confident clinicians?). These interviews will involve 2 cohorts: novice and perioperative nurse educators. The aim of phase 3 is to comprehensively examine the components of transition arrangements essential for success from the perspective of these 2 sample groups. This approach will also facilitate an exploration of the similarities and differences in the perspectives of the 2 cohorts.

Participants, Sample Size, and Recruitment

A total of 8-12 participants from each cohort will be sought to complete semistructured interviews. Purposive sampling techniques will be used to ensure a suitable breadth of participants. Continuous comparative analysis will be used throughout the interview process to examine data saturation. Participants must meet the eligibility requirements of novice perioperative nurses and perioperative educators, as defined in the above phases, to participate in phase 3.

Recruitment for phase 3 will commence in the previous 2 phases. Both cohorts will have the option to express their interest in participating in follow-up interviews after the completion of their survey. To maintain the confidentiality of participants and their survey responses, participants who choose to enroll for follow-up interviews will be redirected to a separate survey to collect their names, contact details, and cohort group. The study will use social media and snowball if insufficient participants are recruited through this method.

Data Collection and Analysis

A data collection instrument will be developed for phase 3, following the sequential completion of phases 1 and 2. The findings from these earlier phases will inform the development of the interview tool and semistructured interview questions. Before delving into a detailed exploration of TTP arrangements, a comprehensive understanding of the content, methods, and philosophies within TTP arrangements and the experiences of novice perioperative nurses must be obtained.

The interviews will be audio recorded and transcribed verbatim before data analysis is undertaken. NVivo software [15] will be used for thematic analysis using Braun and Clarke's [14] 6-step guide. This process will be applied to both cohorts, and the results will be compared and triangulated to uncover the experiences and perspectives related to TTP arrangements of novice perioperative nurses and experienced perioperative nurse educators. Differences and similarities between the cohorts will be carefully examined and presented.

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Phase 4: Meta-Inference and Framework Development

The final phase involves the analysis of data and findings from the previous 3 phases. Data will undergo meta-inference analysis and triangulation to establish the findings directly aligned with the research aims, objectives, and questions. These findings will form the foundation for developing a framework to guide the design, development, and implementation of future perioperative nursing TTP arrangements. This framework will be embedded in the empirical evidence uncovered by this study, existing literature, and adult learning principles. Targeted validity checking will be used to ensure rigor and congruence of the research findings.

Peer Reviews

This study has completed 2 peer reviews. The initial review occurred during the confirmation of candidature milestone for Doctor of Philosophy students. This review encompassed 2 independent reviews from experts in their field. The second review was conducted as part of the approval process by the CQUniversity Human Research Ethics Committee for both phases 1 and 2 of the study.

Ethical Considerations

As this study spans 4 phases, ethics approval will be obtained in 2 applications. The initial ethics application encompasses phases 1 and 2 and has been approved by the CQUniversity Human Ethics Research Committee under approval number 0000024139. The subsequent ethics application will be submitted once data analysis from phases 1 and 2 is completed and a semistructured interview protocol has been developed for phase 3.

Results

This project received approval in June 2023. Following this, Human Research Ethics Committee approval was sought for phases 1 and 2, and recruitment began. As of August 2024, phase 1 has collected 50 responses and phase 2 has collected 69 responses. Data collection for phase 3 is projected to commence in May 2025 once data from phases 1 and 2 have been analyzed. Phase 4 is projected to occur in 2026. Each phase is anticipated to have a results manuscript submitted for publication once data is analyzed and written up.

The results from this study will be disseminated locally and at relevant national and international conferences. The findings from this study will also be disseminated in peer-reviewed nursing journals. Media releases will be undertaken as opportunities arise. In addition, this study will be published and disseminated as a thesis document to meet the requirements of the Doctor of Philosophy program.

Discussion

International Significance

In examining the international implications of this study, it is evident that the findings should hold significant relevance on a global scale, reflecting the shared challenges encountered by novice nurses worldwide as they transition into specialized fields [21].

Identifying and exploring gaps in empirical evidence regarding TTP arrangements within perioperative nursing is not unique to Australia; many countries grapple with similar challenges in standardizing and evaluating TTP programs [7]. By addressing these gaps, this study will offer insights that extend beyond national borders, providing a comparative perspective on the effectiveness of transition practices.

Furthermore, the development of a framework and model based on evidence-based educational, social, and holistic transition arrangements has implications beyond Australian perioperative nurses. Components of the framework could be used to inform the development of TTP arrangements internationally. In addition, aspects of this study can be replicated internationally to identify common trends and differences between countries in TTP arrangement practices. The challenges novice perioperative nurses face are likely shared globally, making a well-informed framework adaptable and applicable in different countries to enhance the quality of transition programs.

Available Evidence

It could be argued that TTP arrangements from other specialty areas could be used within the perioperative nursing realm to support novice nurse assimilation; however, perioperative nursing requires a unique skill set and specialized knowledge that is incomparable to other nursing contexts [3,22]. For this reason, a rigorous literature review was undertaken to establish the existing body of literature related to TTP arrangements within perioperative nursing. The literature review identified a paucity of empirical evidence, with most research on perioperative TTP arrangements consisting of discussion and editorial papers [7]. In addition, most papers described the TTP arrangement they offer rather than provide an evaluation of the TTP arrangements. Papers that evaluated TTP arrangements frequently measured efficacy by participant retention postcompletion [7]. In addition, an Australian national report also identified that TTP arrangements are unregulated and unmonitored [8]. This has led to significant variability between TTP arrangements and their providers.

The lack of empirical evidence and the variability between TTP arrangements provide the rationale and justification of this study. The aims, objectives, and RQs developed are aimed to address these gaps and limitations. It will also provide a guiding framework for TTP arrangement design, development, and implementation within perioperative nursing.

Methodological Discussion

Integration (with or without method integration) is an essential element within mixed methods methodology [10]. This differs from multimethod research, where various methods are used, but data or data analysis are not required to be integrated [10]. Within this study, mixed methods are adopted as the methodology for a multitude of reasons. Mixed methods are frequently used in evaluation research as the research questions are often multifaceted, such as phases 1 and 2 within this study [9]. The third phase of this project requires data collection from multiple sources, as novice perioperative nurses and

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perioperative nurse educators are key participants in this topic. The mixed methods methodology is well suited to collecting and mixing multiple data sources from various participant cohorts [9,10].

The mixed methods methodology uses significant formalization approaches to ensure rigor and accuracy of results [10]. Numerous mixed-method designs are available for the researcher to use to provide a pragmatic and appropriate approach to their research. This study uses an exploratory mixed-method, multilevel triangulation design with sequential phase design to achieve the desired research aim and objectives [9,10]. Using this design, the researchers can collect data in distinct phases and sequentially. Each phase of this study requires a differing method due to the lack of perioperative nursing TTP literature. In addition, phase 3 of this study relies on the findings from phases 1 and 2. The findings from phases 1 and 2 are related to the characteristics of TTP arrangements and the experiences and efficacy of these arrangements. Using these findings, an interview tool can be developed for phase 3 to explore TTP arrangements in great depth.

Implementation Challenges and Limitations

The researchers have identified several potential challenges and limitations that may affect this study. The use of online surveys, generalizability, and the methodology will be discussed herein. By identifying these challenges and limitations in the early phases of the study, mitigation strategies can be enacted to prevent or minimize their impact.

The use of online surveys presents a potential implementation challenge. It is estimated that online surveys attract response rates anywhere from 15% to 60% [23]. Regarding this study, it may suggest that the surveys of phases 1 and 2 may not receive the desired number of participants. The implication of this challenge is minimized as sound plans for participant recruitment have been included in the research methods. In addition, the survey will remain available online until an appropriate number of participants is reached. It is also observed within online surveys that some responses may be fraudulent [23]. Fraudulent refers to multiple responses from the same participant, or the tool might be inappropriately and opportunistically used. This may cause misrepresentation in the data collected and affect the findings. This study overcomes this challenge by ensuring that participants must complete a reCAPTCHA before accessing the survey, placing a cookie on participants' browsers to prevent surveys from being completed more than once by the same participant, and preventing search engine indexing [12].

Sample size and generalizability considerations have been incorporated into this study and the methods. However, capturing all potential demographic participants and participant experiences in a study is difficult. Furthermore, it is difficult to ascertain the population sizes of the participant cohorts within this study. The researcher used their own experiences to establish an estimated total population size that was used for sample size calculations. Therefore, the components of this study may not apply to all perioperative novice nurses. Generalizability has been addressed by ensuring accurate sample size calculations for the relevant phases of the study. In addition, it has been addressed by the recruitment strategies and analysis strategies.

Finally, the mixed methods methodology presents some unique challenges. In particular, the length of the study can be greater than a single-method study [10]. This is particularly relevant within this study as phase 3 is sequential from phases 1 and 2; therefore, the project length will be increased. In addition, there is potential difficulty in reconciling and triangulating differences in data. Data sets that may emerge from this research could be noncongruent. However, this will lead to further discussion possibilities [10]. A delimitation of this method is that data sets from each phase can often be cross-validated and confirmed, adding to the validity and trustworthiness of the research.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during the preparation of this protocol.

Authors' Contributions

NN contributed to the conceptualization, methodology, validation, and writing (original draft). PC, AS, and LJ performed conceptualization, methodology, validation, supervision, and writing (review and editing).

Conflicts of Interest

None declared.

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Abbreviations

RQ: research question
TTP: transition to practice

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Protocol

Feasibility of a Progesterone-Modified Natural Protocol for Frozen Embryo Transfer: Protocol for a Pilot Cohort Study

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Abstract

Background: With the existence of various frozen embryo transfer (FET) methods currently used in the field of assisted reproductive technologies, the debate surrounding which of these is superior remains. All FET protocols aim to prime the endometrium and time embryo transfer during the window of implantation. Current methods include the true natural cycle FET (tNFET), modified natural cycle FET, artificial cycle FET, and ovulation induction. Each of these harbors, distinct advantages and disadvantages, namely, surrounding the timing of transfer and flexibility conferred through this process. More recently, a newer approach has been used whereby the need to monitor or trigger ovulation is circumvented, with luteal phase support commenced once a certain follicle diameter and endometrial thickness criteria are met but before ovulation. However, the research into this protocol has certain important limitations that our study seeks to address.

Objective: This study aims to assess the feasibility of a progesterone-modified natural cycle protocol for FET. The primary outcome will be the presence of a corpus luteum on ultrasound scans on the day of embryo transfer. The secondary outcomes will include the number of clinic visits required per patient undergoing the protocol, biochemical pregnancy rate, and clinical pregnancy rate.

Methods: We will conduct a prospective cohort study, recruiting 20 women undertaking FET at the Public Fertility Care of The Royal Women's Hospital in Melbourne, Australia. These women will be matched to a control group who have undergone the tNFET protocol within the preceding 12 months of the study start date.

Results: This project received ethics approval on July 17, 2024, with commencement of the study in September 2024, aiming for a duration of completion of 9 months. The completion of the follow-up and submission of the study for publication are anticipated for September 2025.

Conclusions: After this preliminary study, the aim would be to progress to a noninferiority randomized controlled trial to compare the progesterone-modified natural cycle protocol for FET to the tNFET.

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KEYWORDS

frozen embryo transfer; fertility care; reproductive health; infertility; progesterone-modified natural cycle protocol; in vitro fertilization

Introduction

Frozen embryo transfer (FET) has been increasingly used over recent decades in Europe [1,2] and Australia [2]. With advancements in cryopreservation techniques and increasing use of FET, debate still exists around the optimal method of endometrial preparation to achieve the best possible pregnancy rates and improve various maternal and neonatal outcomes. The most widely used protocols for endometrial preparation include the natural cycle FET (NFET), artificial cycle FET (AFET), and ovulation induction methods [3], with the latter two protocols usually reserved for anovulatory women. While the true NFET (tNFET) relies on monitoring for a surge of endogenous luteinizing hormone (LH) and rise in progesterone (P4) as markers of ovulation to time P4 supplementation start and embryo transfer, the AFET protocol involves exogenous hormone (estrogen, followed by P4) administration to mimic the natural cycle and prime the endometrium. Furthermore, while the AFET confers greater flexibility in terms of timing FET precisely, there is evidence to suggest lower overall implantation rates and higher miscarriage rates from this technique [4]. The literature also suggests there may be a higher rate of obstetric complications for both mother and fetus, including pre-eclampsia [5] and fetal macrosomia [6]. Therefore, the advantage of tNFET centers on avoiding excessive exogenous hormone administration and the resulting adverse events (AEs) linked to AFET. However, the inflexibility conferred by the tNFET in terms of the need to closely monitor endometrial thickness, follicle size, and hormone levels may require multiple blood tests and 7-day in-vitro fertilization clinic availability. Further, the ovulation induction protocol involves the expense and invasiveness of using medication without removing the need for a 7-day service or the need for blood tests. Therefore, a protocol that achieves ovulation and gives a degree of flexibility to the timing of embryo transfer would be highly appealing to both patients and in-vitro fertilization clinics.

To address these challenges, some clinics use the modified NFET (mNFET) protocol where exogenous human chorionic gonadotropin (hCG) is administered to trigger ovulation when a dominant follicle of typically 17 mm or more is detected, thereby conferring some flexibility in scheduling FET while still relying on the woman's natural cycle [7]. Retrospective cohort studies have shown favorable outcomes in both the tNFET and mNFET as compared to the AFET [8]. Notably, two recent randomized controlled trials (RCTs) showed similar rates of pregnancy in the mNFET as compared to the tNFET, with higher implantation rates in the mNFET cohort [7,9]. However, at least one study has reported better outcomes with tNFET [10], and the most recent Cochrane systematic review on cycle regimens of FET did not compare tNFET and mNFET [3].

To further explore the potential flexibility conferred by the mNFET method while mitigating the lack of flexibility in scheduling the transfer, a prospective case series proof-of-concept study by Weiss et al [11] has trialed a novel approach whereby timing the FET to the endogenous LH surge is circumvented. Instead, P4 luteal phase support (LPS) via vaginal pessary is commenced once a mature follicle of >12 mm is identified in ultrasound scans and the lining of the endometrium is sufficiently thick at >7 mm, with FET scheduled 2-5 days from this point, depending on the stage of the embryo at the time of cryopreservation. It appears that this P4-modified natural protocol for FET (P4mNFET) provides a simultaneous advantage of both retaining a natural cycle, with authors suggesting ovulation took place regardless, as well as conferring greater flexibility for the scheduling of embryo transfer without compromising clinical pregnancy rates. It should be noted that the authors report a degree of variation in the timing of P4 initiation in relation to the last ultrasound scan without any further blood tests. Importantly, no AEs were reported from this study of 42 participants. A more recent retrospective cohort study comparing this method to AFET demonstrated comparable outcomes in terms of clinical pregnancy, miscarriage, and live birth rates between the methods [12]. A further single-center retrospective cohort study reported similar results when comparing outcomes from patients undergoing FET cycles within the natural and artificial protocols, as compared to a P4mNFET protocol [13]. Taken together, P4mNFET may confer greater flexibility to clinicians and patients in timing FET, negating the requirement to await ovulation, with comparable outcomes.

Overall, this study aims to provide greater flexibility in timing transfer by providing participants with vaginal pessaries of P4 to be used before FET and, subsequently, confirming the absence of elevated endogenous P4 on the day of P4 supplementation start and confirming the presence of a corpus luteum on an ultrasound scan. It is hypothesized that the potential advantages of this P4mNFET protocol, over triggering and manipulating ovulation, may include the increased flexibility in the timing of commencing P4 without the requirement of a large follicle, the elimination of the importance of pinpointing the exact timing of ovulation, and the potential cost-saving to the patient and clinic as a result of these components. It is anticipated that the outcomes of this pilot cohort study may inform the planning and development of a subsequent noninferiority RCT to further reinforce the utility of such a protocol.

Methods

Study Type

The proposed study will adopt a pilot cohort methodology consisting of 12 weeks of intervention and follow-up monitoring of participants for primary and secondary outcomes. Secondary outcomes will be compared with retrospective data from the tNFET control group.

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Participants

The study population will consist of 20 women undertaking FET cycles at the Public Fertility Care of The Royal Women's Hospital (RWH), Melbourne, Australia. The recruitment process will commence at this location, whereby clinicians and nursing teams will be invited to screen the patients they interact with for eligibility for the study. These staff members will be trained on appropriate screening according to the study protocol and will be delegated by the principal investigator. Eligible patients will then be approached for study by team members who are not directly involved in potential participants' clinical care and, therefore, will not have had any clinical interactions with the participant. All patients will be provided with a patient informed consent form (Multimedia Appendix 1) to ensure they are familiar with the protocol requirements and understand their rights as participants. Additionally, they will be provided with a patient information document created by the research team (Multimedia Appendix 2) to assist with patient education surrounding the use of the P4 pessary during the study.

Inclusion criteria consist of women with regular cycles defined as 21-35 days, women younger than 40 years at the start of a cycle, and women whose BMI ranges from 18 to 35, inclusively.

The exclusion criteria include anovulatory women, women who are 40 years or older at the start of the cycle, and women who have preexisting contraindications to exogenous P4 supplementation, such as those with liver disease or thromboembolic disease. The exclusion criteria will also include the use of additional LPS (eg, subcutaneous), women with uterine pathology, including congenital malformations of the female reproductive tract, endometrial polyps, intrauterine adhesions, adenomyosis, and leiomyoma. Regarding the retrospective element of the study, patients for whom inclusion criteria information is lacking will not be included in the study.

The control group will consist of retrospective data from 20 women, matched against inclusion and exclusion criteria, within the Public Fertility Services of the RWH data bank. These controls would have undergone tNFET at the service provider within the preceding 12 months of the study start date.

All participant data will be stored securely in the database of the RWH Reproductive Services Unit (RSU), ensuring the security of patients' confidential information. Furthermore, on completion of the study, all patient information will be securely stored within the hospital server with restricted access for a minimum of 15 years, with custodial responsibilities given to the principal investigator.

Outcome Measures

The primary outcome will be the presence of corpus luteum with a characteristic "ring of fire" appearance on the transabdominal ultrasound on the day of embryo transfer.

The secondary outcomes consist of the number of clinic visits required per patient undergoing this protocol, the biochemical pregnancy rate defined as the detection of βhCG in serum or urine [14], and the clinical pregnancy rate defined as the ultrasonographic visualization of one or more gestational sacs [14].

Randomization

This is a pilot prospective cohort study without randomization.

Intervention: P4mNFET Protocol

Participants will undergo active treatment for 2-8 weeks, with a follow-up period of up to 12 weeks or gestation. For a patient with a 28-day menstrual cycle, on days 10-12 (Figure 1), a transvaginal ultrasound will be performed to evaluate for an appropriate endometrial thickness of 7.0 mm and a mean follicle diameter of 14.0 mm. If these ultrasound criteria are met, the patient will undergo blood tests for estrogen, LH, and P4 on the same day; should levels of P4 be under 5 nmol/L, exogenous P4 supplementation via vaginal pessary will then commence on the same day, with FET scheduled 120-125 hours post P4 administration. P4 pessary, ORIPRO (Orion Laboratories Pty Ltd T/A Perrigo Australia, Balcatta, Western Australia), at a dose of 200 mg twice daily, will be the only form of LPS for patients undergoing P4mNFET. Following FET, serum hCG will be taken 10 days later. If positive, LPS via P4 pessary at 200 mg twice daily will continue to 8 weeks' gestation with a pregnancy scan between 6-7 weeks. If negative, the patient will be advised to cease LPS. In the instances where P4 levels are greater than 5 nmol/L, the patient will be removed from the study.

Figure 1. Visual representation of the patient journey with P4mNFET protocol. FET: frozen embryo transfer; hCG: human chorionic gonadotropin; P4: progesterone; P4mNFET: progesterone-modified natural cycle protocol for frozen embryo transfer; TVUS: transvaginal ultrasound.

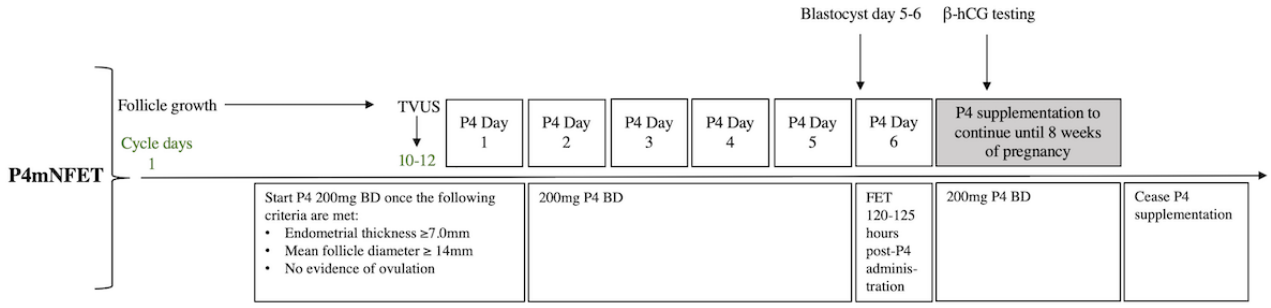

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Control: tNFET Protocol

The control group will consist of patients, matched to the inclusion and exclusion criteria, who would have undergone tNFET at the RWH RSU. Patients undertake an ultrasound on days 10-12 of their cycle for those with a 28-day cycle. Upon detection of a dominant follicle of 18 mm or more and an endometrial thickness of 7 mm or more, serum LH and P4 are taken. An LH surge is defined as >25 IU/L in the context of P4 <5 nmol/L. Ovulation is defined as a P4 >5 nmol/L. LPS, in the form of a vaginal ORIPRO 200 mg pessary (Orion Laboratories Pty Ltd T/A Perrigo, Australia), is commenced on day 1 post ovulation, and embryo transfer is carried out 6 days post LH surge.

Statistical Analysis and Sample Size

Given the qualitative and binary nature of the primary outcome, no statistical testing is proposed for this. Secondary outcomes will undergo *t* tests and Mann-Whitney *U* tests for data that are normally and not normally distributed, respectively. Should there be significant variation in the key baseline variables between the study and the control group, a multivariate analysis will be performed.

Safety Monitoring and Reporting

Safety oversight for the study will be carried out under the direction of the independent safety monitor working within the framework of the Data and Safety Monitoring Board Charter to ensure an objective assessment of the safety and efficacy of the study. AEs deemed secondary to the administration of the pessary will be monitored and reported accordingly by either the investigators or the independent safety monitor, from administration to the end of follow-up. Relevant physical examinations or investigations will then be carried out to ensure the effects of the AE are managed accordingly. The primary investigator will record the AE appropriately into the patient's medical record or study shadow file.

Integration and Dissemination of Findings

On completion of the study, primary and secondary outcomes will be disseminated to investigators, ensuring the confidentiality of patient information. Findings will be synthesized and communicated to colleagues of the RWH RSU and Human Research Ethics Committee, as well as in further peer-reviewed publications related to the RCT that may be conducted following the completion of this cohort study. Additionally, findings will be communicated confidentially in potential presentations at national and international conferences.

Results

This project was conceived in November 2023. It was subsequently approved by the RWH Human Research Ethics Committee on July 17, 2024. Local governance approval was granted on August 28, 2024.

Commencement of the study began in September 2024, aiming for a duration of completion of 9 months, and completion of follow-up and submission of the study for publication in September 2025.

Discussion

Overview

We have designed a pilot cohort nonrandomized study to assess the feasibility of a novel P4mNFET protocol that circumvents the need to monitor for an endogenous LH surge to pinpoint ovulation to schedule FET. This protocol, therefore, may combine the advantages of the tNFET, AFET, and mNFET into one protocol that provides greater flexibility for the timing of transfer with fewer requirements for surveillance and no impact on pregnancy outcomes.

Anticipated Challenges

As with any study of this kind, some challenges are anticipated with patient recruitment. The research team aims to mitigate this via appropriate counseling and use of our patient informed consent form, which is in a question-and-answer format.

The second challenge may be the accuracy of the retrospective data for the control group. This is an inherent issue with all retrospective studies. However, it is anticipated that key secondary outcomes will be accurately reported.

Limitations

As with any study, there are limitations to acknowledge. First, cohort studies lack the same level of rigorous methodology as an RCT. However, based on the results of this pilot, we aim to proceed with a noninferiority RCT to compare this novel protocol to tNFET. Second, the retrospective nature of the control group may be associated with issues related to data entry.

Implications

The implications of this study are that it may inform the future of FET. If primary outcomes are met such that the presence of the corpus luteum is maintained with P4mNFET, then a noninferiority RCT will be carried out to formally compare the two methods. Moving forward, this P4mNFET protocol may provide clinics the opportunity to perform FET with greater scheduling flexibility and comparable outcomes to established methods while potentially leading to cost-saving and increased efficiency.

Acknowledgments

Generative artificial intelligence was not used in the writing or conceptualization of this protocol.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

AC was involved in the project conceptualization, literature search, and writing of the original draft. EG was involved in the conceptualization, reviewing and editing, project administration, and supervision. VA was involved in the protocol development and study coordination. AP was involved in the study conceptualization and writing of the protocol. WTT was involved in the study conceptualization and writing of the protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Patient informed consent form for recruitment of patients to undergo the progesterone-modified natural cycle protocol for frozen embryo transfer at the Reproductive Services Unit of The Royal Women's Hospital, Melbourne.
[PDF File (Adobe PDF File), 289 KB - resprot_v14i1e66579_app1.pdf]

Multimedia Appendix 2
Participant information sheet for use of progesterone pessary during progesterone-modified natural cycle protocol for frozen embryo transfer.
[PDF File (Adobe PDF File), 95 KB - resprot_v14i1e66579_app2.pdf]

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Abbreviations

AE: adverse event
AFET: artificial cycle frozen embryo transfer
FET: frozen embryo transfer
hCG: human chorionic gonadotropin
LH: luteinizing hormone
LPS: luteal phase support
mNFET: modified natural cycle frozen embryo transfer
NFET: natural cycle frozen embryo transfer
P4: progesterone
P4mNFET: progesterone-modified natural cycle protocol for frozen embryo transfer
RCT: randomized controlled trial
RSU: Reproductive Services Unit
RWH: Royal Women's Hospital
tNFET: true natural cycle frozen embryo transfer

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Protocol

Early Detection of Type 1 Diabetes in First-Degree Relatives in Saudi Arabia (VISION-T1D): Protocol for a Pilot Implementation Study

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Abstract

Background: Type 1 diabetes (T1D) is a growing global health concern, with a notable rise in incidence in Saudi Arabia. Despite the potential benefits of early detection through screening programs, such initiatives are currently lacking in Saudi Arabia and other Arab countries.

Objective: This study aims to evaluate the feasibility, acceptability, and cost-effectiveness of a T1D-screening program targeting high-risk individuals, specifically children with a first-degree relative diagnosed with T1D.

Methods: The VISION-T1D program is a prospective cohort study focused on the early detection of presymptomatic T1D by screening children aged 2-18 years. The primary screening method involves testing for islet autoantibodies, including insulin autoantibodies, glutamic acid decarboxylase autoantibodies, insulinoma associated-2 autoantibodies, and zinc transporter-8 autoantibodies. Optional genetic testing, including human leukocyte antigen phenotyping and the genetic risk score, is offered. Outcomes include the feasibility of the screening process, prevalence of early-stage T1D, psychological impacts, educational intervention effectiveness, progression rates to stage-3 T1D, and economic viability.

Results: The VISION-T1D program began in May 2024. As of December 2024, a total of 176 families have been enrolled. Data collection will continue until April 2025, with final data analysis projected for mid-2025.

Conclusions: The VISION-T1D study provides a practical approach to T1D screening tailored to the health care landscape of Saudi Arabia. The insights gained from this pilot program will inform the development of a national, population-based screening initiative designed to reduce diabetic ketoacidosis at diagnosis, improve long-term outcomes, and alleviate the economic burden of T1D. The VISION-T1D initiative could also serve as a scalable and sustainable model that can be adopted internationally, contributing to global efforts to manage and prevent T1D.

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International Registered Report Identifier (IRRID): DERR1-10.2196/70575

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KEYWORDS

islet autoimmunity; type 1 diabetes mellitus; T1D; screening program; antibody detection by agglutination–polymerase chain reaction; PCR; ADAP; human leukocyte antigen; genetic risk score

Introduction

Background

The incidence of type 1 diabetes (T1D) is rising globally, with Saudi Arabia reporting a surge to 31.4 per 100,000 youths annually, making a nearly 9-fold increase over the past decade [1,2]. This trend is compounded by high rates of diabetic ketoacidosis (DKA) at diagnosis [3], ranging from 40% to 77%, the highest in the Arab region [4,5]. DKA at T1D onset is associated with significant morbidity, mortality, and long-term complications [6-9]. DKA also imposes a substantial economic burden through direct and indirect medical costs [10-12]. Early detection by T1D screening is crucial in reducing DKA incidence and mitigating the health and economic impacts [13,14].

T1D pathogenesis involves a complex interplay of genetic predisposition and environmental factors, resulting in the autoimmune destruction of pancreatic β-cells [15,16]. Individuals with a first-degree relative (FDR) affected with T1D have a 15-fold higher lifetime risk of developing T1D compared to the general population [13]. Screening for islet autoantibodies identifies presymptomatic stages (stages 1 and 2) at least in children, adolescents, and young people, enabling timely interventions that may alter disease progression [13,17-19]. Individuals with multiple positive islet autoantibodies have a 99% lifetime risk of progressing to clinical stage-3 T1D, with 84% developing insulin-dependent diabetes within 15 years of seroconversion [18-20]. Screening programs in several countries have successfully reduced DKA at diagnosis, improved long-term outcomes, and lowered health care costs [13,14].

Despite successful screening initiatives in other countries, Saudi Arabia and neighboring Arab countries lack such programs. Moreover, most prior efforts have been confined to research settings, leaving a gap in knowledge about real-world implementation in health care settings [14,18,20,21]. The VISION-T1D protocol (NCT06513247) aims to bridge this gap by evaluating the feasibility and cost-effectiveness of a pilot, T1D-screening program for FDRs of individuals with T1D in Saudi Arabia. Aligned with Saudi Arabia's National 2030 Vision, which prioritizes health improvement and the reduction of chronic disease burden, the VISION-T1D initiative aims to establish a robust framework for broader, population-based, T1D-screening implementation in Saudi Arabia. Furthermore, it could also serve as a scalable and sustainable model for international adoption, thereby contributing to global efforts to manage and prevent T1D.

Study Objectives

Primary Objectives

The primary objectives are as follows:

- Evaluate the feasibility of implementing a pilot, T1D-screening program for early detection in FDRs of patients with T1D in Saudi Arabia.
- Determine the prevalence of stages-1, -2, and -3 T1D among FDRs of patients with TID in Saudi Arabia.

Secondary Objectives

The secondary objectives are as follows:

- Examine the psychological impacts of T1D screening on caregivers, including changes in anxiety, depression, distress level, and health-related quality of life before and after receiving screening results.
- Evaluate the effect of early detection on reducing DKA incidence at stage-3 T1D onset.
- Analyze the cost-effectiveness of implementing a T1D-screening program in Saudi Arabia.
- Evaluate the natural history of T1D progression in identified presymptomatic individuals, tracking time to clinical onset and changes in health outcomes over time.
- Examine the effectiveness of educational interventions on caregivers' knowledge of T1D screening and early identification.
- Investigate the genetic predisposition to T1D within our population through human leukocyte antigen (HLA) testing and validate the genetic risk score (GRS) 2 in the Saudi population.

Methods

Study Design and Setting

The Vision-T1D study is a prospective cohort designed to screen children aged 2-18 years who have an FDR with T1D (index case). Participants are recruited from the University Diabetes Centre (UDC) at King Saud University Medical City (KSUMC) in Riyadh, Saudi Arabia. The diagnosis of T1D in index cases is based on the American Diabetes Association criteria [22], and T1D classification is determined by a clinical diagnosis from a specialized endocrinologist, with or without confirmatory islet autoantibodies testing. Exclusion criteria included index cases diagnosed with other forms of diabetes and non-Saudi children due to different ethnic and genetic backgrounds.

Ethical Considerations

The study was approved by the Institutional Review Board of King Saud University Ethics Committee (approval: E-248566). The pilot phase began in May 2024, with 1 year dedicated to recruitment and screening. All procedures were conducted in accordance with the ethical standards of the Declaration of Helsinki and national research ethics guidelines.

Informed consent was obtained from all participants or their legal guardians prior to data collection. Privacy and confidentiality were maintained according to GCP standards. Participants identified as at risk or presymptomatic for T1D

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will enter a 4-year clinical follow-up phase, culminating in a total study duration of 5 years.

Participants did not receive financial compensation for participation. However, We have received funding for the project as described in the acknowledgment section.

Study Process and Interventions

The VISION-T1D study consists of 3 well-structured phases: screening, results communication and counseling, and long-term clinical follow-up. Each phase is designed to provide tailored interventions, ensuring appropriate care, monitoring, and education for children and their families (Figure 1).

Figure 1. The study flowchart. CGM: continuous glucose monitoring; HbA_{1c}: hemoglobin A_{1c}; MODY: maturity-onset diabetes of the young; OGTT: oral glucose tolerance test; T1D: type 1 diabetes; T2D: type 2 diabetes.

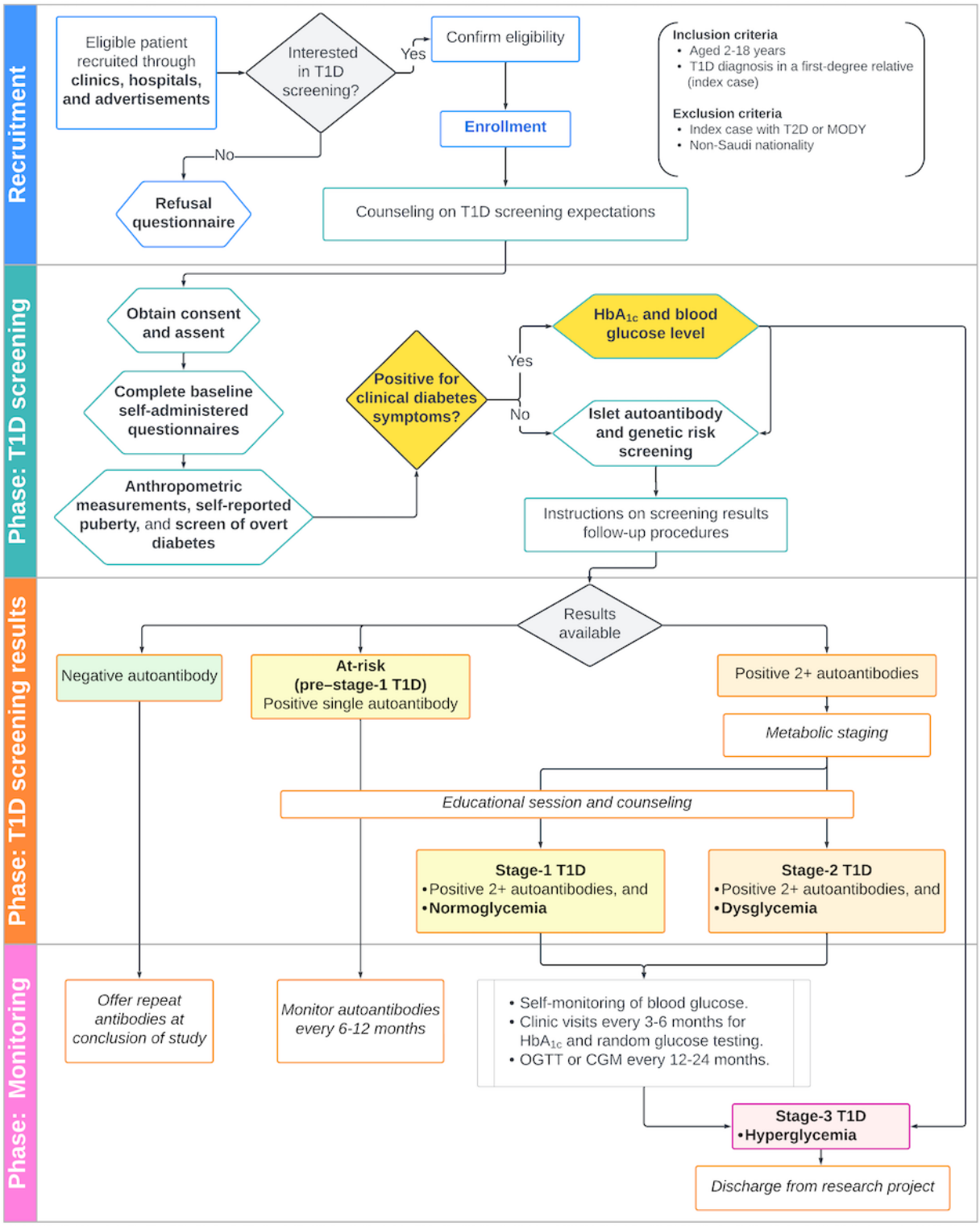

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Phase 1: T1D Screening

Families are recruited and scheduled for an enrollment and screening visit, where they receive comprehensive counseling about participation and education on T1D screening. Upon obtaining informed consent and assent, participants undergo baseline assessments, including completion of questionnaires and the collection of blood samples for islet autoantibody testing. Optional genetic screening for HLA phenotyping and GRS analysis is also offered to evaluate genetic predisposition to T1D. To enhance recruitment, a home testing option is provided, allowing families to conveniently perform finger-prick testing and data collection at home.

Phase 2: Results Communication, Education, and Metabolic Staging

After screening results are available, a research physician reviews the findings. Participants who test positive for islet autoantibodies are invited to a follow-up visit that includes personalized counseling, targeted educational interventions, and additional metabolic staging to determine their T1D stage. Participants with negative islet autoantibody results are notified by the research staff and are invited for repeat autoantibody screening at the conclusion of the long-term follow-up period (approximately 4-5 years later).

Phase 3: Long-Term Clinical Follow-Up

Participants identified as having presymptomatic T1D (stage 1 or 2) or those at risk based on autoantibody markers enter a 4-year clinical follow-up phase. During this period, regular monitoring of disease progression is conducted through metabolic assessments and psychological evaluations. Participants receive continuous support tailored to their risk level and diagnosis.

This systematic, 3-phase approach ensures that participants receive appropriate care, counseling, and monitoring based on their screening outcomes.

Phase 1: T1D-Screening Procedures and Data Collection

Recruitment and Enrollment

Active and passive recruitment strategies are used. Research staff identified potential participants by reviewing patient lists from KSUMC diabetes clinics and pediatric endocrinology inpatient records. Recruitment materials, including advertisements with QR codes, are shared via the UDC and on social media platforms. The QR codes were linked to an introductory video explaining the study and eligibility criteria, along with a contact submission form. Families who decline participation are asked about the reason for refusal.

Informed Consent

Eligible families are scheduled for T1D-screening visits, where informed consent and assent are obtained. A comprehensive educational approach was developed to ensure participants receive standardized information and fully understand the T1D-screening process. This included an animated video and an educational booklet. The video, in Arabic, explains the screening program and key concepts, such as T1D pathophysiology, its stages, and clinical presentation. It emphasizes the benefits of early detection in preventing DKA and improving long-term outcomes; outlines the screening process; and provides an overview of current and emerging T1D treatments, including insulin therapy and disease-modifying interventions. The educational booklet complemented the video, using infographics to illustrate T1D pathophysiology, stages, symptoms, and benefits of screening. It also outlined study expectations and provided key study contact information.

Intervention: T1D Screening

Islet Autoantibodies Screening

The program uses antibody detection by agglutination–polymerase chain reaction (ADAP) assay, a cutting-edge technology developed by Enable Biosciences. The assay measures islet autoantibodies [23-27], including insulin autoantibodies, glutamic acid decarboxylase autoantibodies, IA-2 autoantibodies, and zinc transporter 8 autoantibodies, using dried blood spots on filter paper. The ADAP assay offers notable advantages over other assays for large-scale analysis, such as cost-effectiveness, high sensitivity and specificity, and minimal sample volume requirements. These features make it suitable for large-scale applications, including home testing [25-27].

Genetic Risk Screening

This pilot study integrated optional HLA phenotyping and GRS testing to deepen the understanding of T1D pathogenesis in the Saudi population. Analyses will be conducted by Enable Biosciences, the Barbara Davis Center for Childhood Diabetes, and delegates [28,29]. These tests are used for research purposes only.

HLA Phenotyping

Testing focuses on identifying high-risk HLA genotypes associated with T1D, particularly variants in the HLA region (MHC class II alleles), which account for over 50% of T1D heritability [13]. This approach aims to provide insights into T1D risk associations in the Saudi population, especially in participants with negative islet autoantibodies. HLA typing is performed using oligonucleotide probes for *HLA-DRB1*, *DQA1*, and *DQB1* alleles as previously described [30].

GRS Testing

The GRS aggregates the cumulative contribution of multiple genetic variants into a single score estimating an individual's genetic predisposition to T1D [29,31-33]. This study uses GRS2, an advanced version that incorporates HLA haplotypes, non-HLA loci, and interactions between HLA variants [34]. Testing is conducted using a Kompetitive allele-specific polymerase chain reaction (PCR) assay, as described earlier [35,36]. The Kompetitive allele-specific PCR assay is a cost-effective and efficient alternative to the traditional DNA array and imputation-based methods. It successfully genotypes 60 of the 67 single nucleotide polymorphisms in GRS2, with the remaining single nucleotide polymorphisms excluded due to genotyping challenges. This study represents one of the first applications of GRS2 in FDRs of patients with T1D and the first validation of its use within the Saudi population.

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Specimen Collection

Blood samples are collected via fingerstick or venous sampling onto dried blood spot filter paper, based on participant preference. For families opting for home testing, parents collect sample cards and detailed instructions from the clinic, perform the testing at home, and return the samples for processing. All collected samples are stored at –80 °C before being batched and shipped to the United States for analysis.

Measures

Demographics and Clinical Characteristics

Families complete a self-administered questionnaire upon enrollment to collect baseline demographics and clinical characteristics. Information includes the age, sex, medical history, and current medications of the participating child, as well as family demographics such as parental age, marital status, number of siblings, education levels, family income, residential region, and family medical history focused on diabetes or autoimmune diseases among FDR and any self-reported parental comorbidities. For the index case with T1D, the questionnaire captures clinical details, including the relationship to the participant, age at diagnosis, current age, insulin regimen, history of DKA at onset or recurrent DKA, and diabetes-related complications. If multiple FDRs have T1D, similar information is collected for each.

Clinical T1D Screening

Participants are screened for overt diabetes symptoms, such as polyuria, polydipsia, polyphagia, and unexplained weight loss. Research staff conduct point-of-care hemoglobin A_{1c} (HbA_{1c}) and random blood glucose tests if any symptoms are reported. Participants with abnormal blood sugar levels are referred to a research physician for further evaluation, which may include an oral glucose tolerance test (OGTT) and counseling. Those meeting the diagnostic criteria for stage 3 T1D will receive standard medical care and education for new-onset diabetes.

Health Literacy

The Single-Item Literacy Screener tool evaluates parental health literacy using a 5-point Likert scale. A score of 4 or higher indicates adequate health literacy, while a score of 3 or lower suggests limited literacy [37-39].

T1D-Screening Acceptability Assessment Scale

This self-administered tool evaluates caregivers' acceptability of the T1D-screening program through 10 items rated on a 5-point Likert scale. Domains include affective attitude, the ethicality of the screening, perceived effectiveness, self-efficacy, opportunity costs, communication, burden, and general and cultural acceptability. Total scores range from 10 to 50, with higher scores indicating greater acceptability [40].

Psychological Measures

A set of validated Arabic tools assess caregiver stress, anxiety, depression, and quality of life at baseline, after results disclosure, and during long-term follow-up.

Anxiety Symptoms

The Generalized Anxiety Disorder 7-item scale screens for generalized anxiety over the past 2 weeks using a 4-point Likert scale. A score of 8 or more indicates possible generalized anxiety disorder, with 92% sensitivity and 76% specificity [40,41].

Depressive Symptoms

The Patient Health Questionnaire-9 screens for depression. A score of more than 10 suggests possible major depressive disorder, with a sensitivity and specificity of 88% [42-44]. Research staff will screen responses indicating suicidal ideation and prompt immediate referral to emergency care.

Health-Related Quality of Life

The EQ-5D-5L tool from the EuroQol Group measures health across 5 dimensions—mobility, self-care, usual activities, pain or discomfort, and anxiety or depression—each rated on 5 levels. The EuroQol Visual Analogue Scale allows participants to rate their overall health from 0=worst to 100=best [45]. The results are scored using a value set specific to Saudi Arabia, providing a comprehensive quality of life score [46].

Distress

The Subjective Units of Distress Scale measures anxiety and discomfort on a 0-100 scale, with higher scores indicating greater distress. The Subjective Units of Distress Scale is widely used and validated in clinical settings for assessment and monitoring of changes over time [47-49].

Anthropometric Measurements

Baseline assessments will include weight, height, BMI, and self- or parental-reported pubertal status [50].

Phase 2: Result Disclosure, Education, and Metabolic Staging

Results Disclosure

Participants receive written reports explaining the results, estimated risk of progression, long-term follow-up recommendations, and key contact information. The process of sharing results varies based on screening outcomes:

Participants With Negative Results

Families of participants who test negative for islet autoantibodies are contacted by the research staff to receive their results report. They are instructed to contact the research team if T1D develops in the future and are invited for repeat antibody testing at the end of the follow-up phase.

Participants With Positive Results

Families of participants who test positive for multiple islet autoantibodies are invited to a one-to-one counseling visit with a research physician to discuss the result, followed by a group education and metabolic staging to determine their T1D stage.

Participants With Equivocal Results

Families of participants with a single autoantibody are invited for a one-to-one counseling session with a physician to discuss the result. They then join the same group educational session as those with positive results.

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Genetic Testing Disclosure

Genetic testing results are shared with families only upon request to avoid unnecessary alarm given the elevated baseline risk among FDRs and the lack of validated Saudi population–based genetic risk estimation. When shared, these results are presented in a dedicated educational session designed to help families understand the complexities of genetic predisposition to T1D.

Educational Curriculum for Participants With Positive or Equivocal Results

The educational curriculum was developed based on a comprehensive robust educational framework and expertise [51]. It is delivered in small group sessions by experienced endocrinologists, diabetes educators, and dietitians. The curriculum covers key topics such as T1D pathophysiology, disease progression stages, and the importance of early detection. Participants learn to identify their specific stage and risk of progression and recognize factors that influence clinical diabetes onset. The curriculum highlights insulin's role as the primary treatment for clinical T1D (stage 3), addressing common concerns and misconceptions. Participants are also trained to monitor their condition by recognizing early T1D symptoms, performing blood glucose checks, interpreting results, and determining when insulin therapy or medical advice is needed.

The program underscores nonpharmacological strategies for reducing the risk of T1D progression through healthy eating and lifestyle modifications and provides an overview of current and future T1D research. The psychological and emotional aspects of receiving T1D screening results are also addressed, and access to support is provided.

Psychological Support

The psychological and emotional impact of T1D risk disclosure is carefully addressed throughout the process. Families experiencing significant psychological burdens are offered counseling sessions and access to professional psychological support. Additionally, all families can self-refer to these services as needed. These measures are designed to alleviate stress, promote resilience, and ensure families feel supported during the follow-up period.

Metabolic Staging

Participants with multiple positive islet autoantibodies undergo metabolic staging to determine their T1D stage. This includes HbA_{1c} measurement, fasting glucose, 2-hour OGTT, or continuous glucose measurement (CGM) if OGTT is not feasible.

OGTT Measurement

Performed after an overnight fast of at least 8 hours. Participants consume a glucose solution dosed at 1.75 g/kg (up to 75 g). Serum glucose levels are measured at fasting baseline and 120 minutes after ingestion.

HbA_{1c} Measurement

Serum samples will be processed in the laboratory per American Diabetes Association–recommended standards.

CGM Measurement

Used as an alternative for participants unable or unwilling to complete an OGTT. CGM glucose profiles over a 2-week period will be reviewed for staging.

Phase 3: Long-Term Monitoring and Clinical Follow-Up

Monitoring for Disease Progression

Participants with positive single or multiple autoantibodies will enter a 4-year follow-up phase. During this period, regular assessments are performed to monitor T1D disease progression, track time to clinical onset, and observe any changes in metabolic staging. Monitoring intervals vary by stage and risk level [18,20]. Participants progressing to stage-3 T1D will transition to standard care.

Self-Monitoring of Blood Glucose

All participants with multiple positive islet autoantibodies results will be instructed to perform self-monitoring of blood glucose testing at home twice over a 2-week period after receiving their results, including one fasting test and one 2-hour postprandial test after a heavy meal. This testing should be repeated every 1-3 months and during any illness. Participants will be provided with contact information and guidance on when to seek medical advice.

Stage-1 Monitoring

Participants categorized as stage-1 T1D (positive autoantibodies with normal glycemia) will have clinic visits every 6 months for HbA_{1c} and random glucose testing. An OGTT or CGM will be performed every 24 months or earlier if there is a 10% or more rise in HbA_{1c} from baseline.

Stage-2 Monitoring

Participants categorized as stage-2 T1D (positive autoantibodies with dysglycemia) will have more frequent clinic visits every 3 months for HbA_{1c} and glucose testing. An OGTT or CGM will be performed annually or sooner if there is a 10% or more rise in HbA_{1c} from baseline.

Monitoring for Single Autoantibody Results

Participants with a single autoantibody undergo metabolic assessment only if symptoms develop. For children younger than the age of 6 years, autoantibody screening will be repeated within 6 months for confirmation, then annually throughout the study. For children aged 6 years or older, annual screening will be conducted for the duration of the study. Autoantibody monitoring will be discontinued if a participant seroconverts to a negative status. No physician visits are required, and families are encouraged to contact the research team if T1D symptoms arise in the future.

Monitoring for Participants With Negative Autoantibodies

All participants who test negative for autoantibodies will undergo follow-up autoantibody testing at the conclusion of the 5-year study period.

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Other Monitoring Measures

Clinical Measurements

Weight, height, and BMI are assessed annually for participants with positive autoantibodies.

Psychological Assessment

Parents of children with positive autoantibody results will undergo psychological assessment within one week of receiving screening results. Assessments are repeated during follow-up at 6 and 12 months to track changes over time.

Outcome Definitions and Metrics

Feasibility Metrics

The feasibility of the screening program will be evaluated using the following key metrics.

- Recruitment rates: The proportion of eligible participants successfully recruited into the study.
- Screening refusal rates: The percentage of eligible participants who decline participation.
- Completed screening visit rates: The percentage of participants completing the initial screening visit (phase 1).
- Completed counseling visit rates: The percentage of participants with positive autoantibody results who complete the counseling session and educational curriculum (phase 2).
- Completion of long-term follow-up: The percentage of participants with presymptomatic T1D who complete their monitoring visits during the 4-year follow-up period (phase 3). Participants progressing to clinical T1D before the study conclusion will transition to standard clinical care and be considered as having completed follow-up.

Prevalence of Presymptomatic T1D at Screening

Metabolic staging performed during the screening results visit (phase 2) will classify participants into the following stages.

- Stage-1 T1D: Presence of two or more islet autoantibodies with normal glycemia. Criteria include HbA_{1c} <5.7%, fasting blood glucose <100 mg/dL, and a 2-hour OGTT <140 mg/dL. For CGM users, values >140 mg/dL should be less than 10% of the time over 10 days of continuous wear.
- Stage-2 T1D: Presence of two or more islet autoantibodies with dysglycemia. Criteria include HbA_{1c} between 5.7% and 6.4%, fasting blood glucose between 100-125 mg/dL, and a 2-hour OGTT between 140-199 mg/dL. For CGM users, values more than 140 mg/dL should be between 10% to less than 20% of the time over 10 days of continuous wear.
- Stage-3 T1D: Clinical onset of T1D marked by one or more islet autoantibodies and hyperglycemia. Criteria include HbA_{1c} 6.5%, fasting blood glucose levels 126 mg/dL, and a 2-hour OGTT 200 mg/dL. For CGM users, values >140 mg/dL must occur at least 20% of the time over 10 days of continuous wear.
- At risk (pre–stage-1 T1D): Defined as the presence of a single islet autoantibody with normal glycemia.
- Isolated genetic predisposition: Defined as the presence of positive genetic risk markers without accompanying islet autoantibodies.

Incidence of DKA

The incidence of DKA at the clinical onset of T1D will be tracked during the long-term follow-up phase (phase 3). DKA occurrences will be captured from clinical records and follow-up visits.

T1D Progression Rate

The annual progression rate to stage-3 T1D will be tracked in participants testing positive during the follow-up phase (phase 3) and categorized based on their initial stage.

Effectiveness of Educational Interventions

The effectiveness of the educational curriculum will be evaluated using pre- and postintervention tests completed by caregivers. These tests are developed to measure changes in knowledge related to the curriculum's objectives, providing a comprehensive assessment of the intervention's effectiveness in preparing caregivers for presymptomatic T1D management.

Health Care Resource Use for Cost-Effectiveness Analysis

Health care resource use will include both program-related and external health care resources. Program-related costs will encompass autoantibody testing, metabolic profiling, results notification visits, and educational or follow-up visits. Non–program-related costs will include diabetes clinic visits (eg, consultations with physicians, educators, nutritionists, or psychologists), emergency department visits for diabetes or DKA, hospitalizations for diabetes, laboratory and imaging studies, and prescription medications for diabetes management either inpatient or outpatient.

Statistical Analyses

Sample Size

The target enrollment is 1300 participants (or 322 families), based on the feasibility of recruiting 70% of eligible families from the UDC clinic cohort. The estimated seropositivity rate for islet autoantibodies among children with an FDR diagnosed with T1D is estimated at 5% to 15%, with a 90% significance level and 80% power. Considering that the UDC serves approximately 450-500 children with T1D, and that the typical Saudi family has 4-6 children younger than the age of 18 years, this sample size is calculated to be sufficient. Recruitment will be expanded to FDRs outside the UDC cohort if the family target is met without reaching the participant's goal.

Statistical Analysis

Descriptive statistics will report continuous data as mean (SD) for normally distributed variables and categorical data as frequency and percentage (N, %). Feasibility metrics and T1D stages will also be summarized as percentages.

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To evaluate the psychological effects of T1D screening on caregivers, pre- and postscreening levels of anxiety, depression, and distress will be compared using paired 2-tailed *t* tests or Wilcoxon signed-rank tests, depending on data distribution. The effectiveness of educational counseling will be analyzed similarly, comparing pre- and postintervention test scores. Longitudinal changes in the psychological measures will be evaluated using repeated-measures ANOVA or mixed effects models to track patterns over time.

For participants with presymptomatic T1D, progression rates to stage 3 will be analyzed using Kaplan-Meier survival analysis. Time to event will be calculated from screening age to age at stage-3 T1D diagnosis or last follow-up. Cox proportional hazards models will assess factors associated with disease progression, such as baseline autoantibody titers, genetic risk scores, and demographic variables.

At the 1-year follow-up, cost-effectiveness will be assessed by reporting total costs for all screened participants, cost per child screened, and cost per case detected. The incremental cost-effectiveness ratio calculations will compare outcomes for screened children with controls diagnosed with stage-3 T1D in the general population. The incremental cost-effectiveness ratio will incorporate potential benefits, such as reduced DKA incidence and improved HbA_{1c} levels, while adjusting for control characteristics like age and FDR status.

Results

The VISION-T1D pilot screening program was funded and launched in May 2024, with the initial screening phase scheduled to conclude in April 2025. As of November 2024, a total of 176 eligible families had enrolled, representing approximately 39.1% of the target sample size of 322 families. Final data analysis for the initial screening phase is projected for mid-2025.

Discussion

The VISION-T1D protocol outlines a comprehensive approach to assess the feasibility and impact of a T1D screening among FDRs of individuals with T1D in Saudi Arabia. This model is tailored to address the unique demographic, cultural, and health care characteristics of the Arab region, aiming to deepen understanding of the prevalence and patterns of autoimmunity in at-risk populations. The data generated will provide valuable epidemiological insights to inform future health care policies and targeted interventions.

A key strength of this study is its focus on translating screening programs from the research setting to practical, real-world implementation. It provides a detailed roadmap for integrating T1D screening into health care systems, addressing scientific and operational complexities, particularly within the Arab region. The use of culturally sensitive consent materials, diverse educational methods, and clear protocols ensures that participants and caregivers are well informed, supported, and empowered to manage their health proactively. Additionally, the adoption of the ADAP assay—a cost-effective, sensitive, and low-sample-volume technology—enhances scalability and operational efficiency, making the program accessible for large-scale applications.

This study addresses significant unmet needs in T1D care and research in the Middle East, offering critical insights into genetic predispositions and disease progression in the Saudi population. One of the program's pivotal contributions is the early identification of candidates for T1D prevention therapies. Early detection through screening will facilitate timely intervention with disease-modifying therapies that can delay or prevent the onset of clinical T1D. This proactive approach aligns with global health strategies advocating for prevention and early intervention to mitigate the long-term burden of chronic diseases. Furthermore, this initiative lays the groundwork for the future of prevention trials in Saudi Arabia, contributing to the development of a sustainable infrastructure for T1D research and management.

The study also tackles logistical challenges, such as recruitment, sample analysis, and generalizability, through a combination of recruitment strategies, robust educational tools, and systematic follow-up procedures. While reliance on international laboratories for sample analysis introduces potential delays, the program is designed with long-term sustainability in mind, including plans to establish a centralized laboratory for the ADAP assay in Saudi Arabia.

Despite its strengths, the study has limitations. Focusing on FDRs may restrict generalizability to the broader population, as prior exposure to T1D within the family could influence the acceptability of the screening program. Additionally, cultural and social factors specific to Saudi Arabia may shape perceptions and behaviors related to T1D screening and management, potentially affecting intervention outcomes. Furthermore, the relatively short follow-up period, constrained by funding, limits the ability to assess long-term outcomes and the program's sustainability. Extended follow-up would provide a deeper understanding of the enduring effects of early detection and educational interventions on disease progression and management. Future extensions of this study are based on funding availability or collaborations with national screening programs may allow for prolonged follow-up.

In conclusion, this study represents a critical advancement in addressing the challenges of T1D screening and management of presymptomatic T1D. By integrating innovative screening technology with a robust educational framework and systematic follow-up, this program demonstrates the potential to enhance health outcomes while offering a scalable and sustainable approach to managing presymptomatic T1D. The outcomes garnered from this research will provide a foundation for implementing practical T1D-screening programs and establishing a framework adaptable to similar initiatives in neighboring Arab countries. By addressing both scientific and operational challenges, this study serves as a valuable resource for policy makers, health care providers, and researchers striving to integrate effective T1D management strategies into routine health care practice, ultimately improving the quality of care for at-risk populations.

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Authors' Contributions

The study was conceptualized by ISA and RAA, who also led the design of the protocol framework, supervised the research process, and provided overall research direction. Methodology, data curation, and formal statistical analysis plans were developed collaboratively by RAA, ISA, and YA, with additional contributions from JS and KA. Data collection plans, strategic guidance, and investigation, including participant recruitment and data collection, were carried out by ISA, MM, KA, MA, SA, AAA, and RAA. DS and CTT were responsible for the provision of laboratory technology and the analysis of blood samples. Funding was secured by RAA, ISA, JS, and MM. ISA and RAA collaborated on the literature review, drafting, revisions, and final submission of the manuscript. All authors reviewed and approved the final version of the manuscript.

Conflicts of Interest

The authors declare that there is no conflict of interest regarding the publication of this paper. DS and CTT were employed by Enable Biosciences. DS and CTT are shareholders of Enable Biosciences. CTT are inventors of the antibody detection by agglutination–polymerase chain reaction (ADAP) patent licensed from the University of California, Berkeley to Enable Biosciences. The ADAP assay used in this study is a product in development. This does not alter our adherence to journal policies on sharing data and materials.

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Abbreviations

ADAP: antibody detection by agglutination–polymerase chain reaction
CGM: continuous glucose monitoring
DKA: diabetic ketoacidosis
FDR: first-degree relative
GRS: genetic risk score
HbA_{1c}: hemoglobin A_{1c}
HLA: human leukocyte antigen
KSUMC: King Saud University Medical City
OGTT: oral glucose tolerance test
PCR: polymerase chain reaction

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T1D: type 1 diabetes
UDC: University Diabetes Centre

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Original Paper

Effectiveness of The Umbrella Collaboration Versus Traditional Umbrella Reviews for Evidence Synthesis in Health Care: Protocol for a Validation Study

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Abstract

Background: The synthesis of evidence in health care is essential for informed decision-making and policy development. This study aims to validate The Umbrella Collaboration (TU), an innovative, semiautomatic tertiary evidence synthesis methodology, by comparing it with Traditional Umbrella Reviews (TUR), which are currently the gold standard.

Objective: This study aimed to evaluate whether TU, an artificial intelligence—assisted, software-driven system for tertiary evidence synthesis, can achieve comparable effectiveness to TURs, while offering a more timely, efficient, and comprehensive approach. In addition, as a secondary objective, the study aims to assess the accessibility and comprehensibility of TU's outputs to ensure its usability and practical applicability for health care professionals.

Methods: This protocol outlines a comparative study divided into 2 main parts. The first part involves a quantitative comparison of results obtained using TU and TURs in geriatrics. We will evaluate the identification, size effect, direction, statistical significance, and certainty of outcomes, as well as the time and resources required for each methodology. Data for TURs will be sourced from Medline (via PubMed), while TU will use artificial intelligence—assisted informatics to replicate the research questions of the selected TURs. The second part of the study assesses the ease of use and comprehension of TU through an online survey directed at health professionals, using interactive features and detailed data access.

Results: Expected results include the assessment of concordance in identifying outcomes, the size effect, direction and significance of these outcomes, and the certainty of evidence. In addition, we will measure the operational efficiency of each methodology by evaluating the time taken to complete projects. User perceptions of the ease of use and comprehension of TU will be gathered through detailed surveys. The implementation of new methodologies in evidence synthesis requires validation. This study will determine whether TU can match the accuracy and comprehensiveness of TURs while offering benefits in terms of efficiency and user accessibility. The comparative study is designed to address the inherent challenges in validating a new methodology against established standards.

Conclusions: If TU proves as effective as TURs but more time-efficient, accessible, and easily updatable, it could significantly enhance the process of evidence synthesis, facilitating informed decision-making and improving health care. This study represents a step toward integrating innovative technologies into routine evidence synthesis practice, potentially transforming health research.

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KEYWORDS

tertiary evidence synthesis; The Umbrella Collaboration; umbrella reviews; health research methodology; AI-assisted synthesis; AI-assisted; evidence-based decision making; machine learning; ML; artificial intelligence; AI; algorithms; models; analytics; digital health; digital technology; digital interventions

Introduction

Background

The synthesis of evidence in health care is a knowledge-acquisition process designed to transform extensive volumes of data into manageable information to support decision-making based on the best possible evidence. It aims to integrate information from multiple sources on complex topics in a comprehensive, precise, transparent, and easily understandable manner. These principles ensure that synthesized evidence is accessible and useful to all stakeholders, including health care professionals, policy makers, and patients [1].

Evidence synthesis plays a pivotal role in knowledge translation (KT) [2], serving as a bridge between research and health care. Consequently, evidence synthesis is essential for the development of health policies and informed decision-making [3].

The role of all stakeholders in health decision-making underscores the importance of their ability to access, understand, and evaluate health information adequately [4]. A persistent challenge in KT is the low level of statistical and health literacy among the general population and health professionals, which significantly complicates effective health management [5,6]. Therefore, it is crucial to democratize access to high-level health information and to promote active participation of all stakeholders in decisions affecting health care [7].

The evolution of evidence synthesis methodologies has led to the development of tertiary synthesis, designed to condense knowledge from multiple systematic reviews with or without meta-analyses (SR/MA). This synthesis, often referred to as Umbrella Reviews now referred to as Traditional Umbrella Reviews (TUR) to distinguish them from the experimental methodology under study, The Umbrella Collaboration (TU), builds upon the concept of primary studies (individual studies with participant samples) and secondary studies (systematic reviews and analysis of those primary studies). Tertiary synthesis represents a third level, named with other terms such as overviews, meta-epidemiological studies, meta-analyses, meta-synthesis, and meta-reviews also describing this approach [8,9]. Tertiary synthesis has gained prominence in contexts where broad research questions are posed, rapid results are needed, and resources for extensive systematic reviews are limited. TURs follow a structured methodological process that involves several clearly defined stages [9-14]. Although organizations like Cochrane Collaboration [14] and the Joanna Briggs Institute (JBI) [11] have developed and continually updated detailed methodologies for these reviews, there remains considerable divergence in how TUR authors implement these steps in practice. This methodological freedom leads to significant variations among different TURs in terms of rigor and approach.

The urgency for high-quality, timely information during crises like the SARS-CoV-2 pandemic has highlighted the critical need for faster evidence synthesis methods, even if it means accepting certain limitations in comprehensiveness, detail, and precision [15]. This demand has driven the development of innovative approaches such as TU, which leverages artificial intelligence (AI)-assisted software to facilitate tertiary evidence synthesis under human oversight. While AI tools such as PICO (Population, Intervention, Comparison, and Outcome) Portal, DistillerSR, Covidence (Veritas Health Innovation), and Rayyan (Rayyan Systems Inc) have already improved secondary evidence synthesis by streamlining data management and analysis [16], technologies like large language models (LLMs), including ChatGPT, are beginning to demonstrate potential for conducting systematic reviews autonomously, though human supervision remains essential to mitigate risks such as errors and hallucinations [17]. Despite these developments in secondary synthesis, the application of AI and software engineering in tertiary synthesis is still in its early stages, with no dedicated software currently available. TU is at the forefront of this field, pioneering the integration of AI and software engineering with human oversight to ensure accuracy and minimize technology-induced errors. As AI continues to evolve, it is likely that fully automated processes for both secondary and tertiary synthesis will emerge, potentially revolutionizing clinical research and practice. However, building confidence in these technologies will require ongoing development and rigorous validation.

The Umbrella Collaboration (Patent Pending)

TU is primarily a software-driven system engineered to streamline tertiary evidence synthesis, relying on programmed algorithms to automate the majority of its functions. The core of the system is built on a software infrastructure that processes and synthesizes data from SR/MA abstracts stored in MEDLINE. While AI plays a crucial role, particularly through the use of LLMs and machine learning (ML), it is used selectively within the broader software framework to enhance specific tasks.

LLMs are used in generating related search terms, expanding upon human-generated queries to enhance the comprehensiveness of literature searches. Any LLM can be adapted to TU software, up to date we have used ChatGPT 4 [18]. This function is crucial in broadening the scope of the searches while ensuring that the results remain relevant and precise. The AI component is designed to support, not replace, human oversight, ensuring that the final selection of literature is both accurate and comprehensive [19]. To mitigate the risk of AI-generated hallucinations due to insufficient data, TU

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primarily operates as a stable, auditable software system. The use of AI is limited to the search term expansion phase, where it suggests synonymous terms for the keywords provided by the human reviewer.

All AI-generated search terms are subject to human validation before being incorporated into the search strategy. The human reviewer evaluates the relevance and appropriateness of each AI-suggested term, ensuring that only those that align with the research objectives are retained. This manual oversight serves as a critical safeguard against inaccuracies or misleading AI-generated suggestions, maintaining the methodological integrity of the evidence synthesis process.

As the TU database grows, ML will be integrated to further refine and optimize the software's performance. Training the system on an expanding dataset is expected to enhance its ability to select, categorize, and analyze relevant research, thereby improving both efficiency and accuracy over time. This approach allows TU to evolve, continuously improving its utility in evidence synthesis through the iterative learning process [20].

Overall, TU represents a hybrid model where traditional software engineering and targeted AI applications work in tandem. This balance ensures that while the software performs most functions automatically, AI enhances specific tasks, such as search term generation and future predictive analysis, under strict human supervision. This strategic integration of AI elements within a primarily software-driven system ensures the reliability and precision of the evidence synthesis process.

The outcomes generated by TU will be presented through an interactive web application designed to enhance accessibility and comprehension for a broad range of stakeholders, including those without advanced statistical expertise. The use of graphical formats and clear language aims to facilitate the interpretation of findings by diverse audiences.

In addition, the platform supports continuous updates, automatically integrating new SR/MA data every 24 hours, thereby ensuring the most current and reliable evidence synthesis. This approach aligns with the concept of Living Systematic Reviews (LSRs) [21], which advocate for frequent updates to maintain relevance in rapidly evolving fields. While Cochrane Collaboration recommends updating LSRs monthly [22], TU is designed to surpass this standard by ensuring updates are incorporated daily, providing near real-time evidence synthesis.

The daily updates provided by TU are expected to enhance its efficiency, allowing for a more dynamic and continuously updated evidence synthesis process. Pilot tests have demonstrated TU's capability to complete tertiary evidence synthesis projects within hours, a significant reduction in time compared to traditional methods (unpublished data). If validated by the upcoming research, this advancement could demonstrate TU's potential to streamline the synthesis process, delivering rapid yet reliable results while upholding the highest standards of accuracy. Should these findings be confirmed, TU may emerge as an invaluable tool for accelerating the pace of evidence-based research.

TU is designed to maximize computational efficiency while maintaining methodological rigor. Unlike TURs, which require extensive manual data extraction and synthesis over months, TU automates critical steps in the tertiary synthesis process, significantly reducing execution time.

In terms of computational complexity, TU does not perform direct statistical meta-analyses but instead extracts and synthesizes pre-existing systematic reviews and meta-analyses. This approach ensures that the computational load remains minimal compared to methodologies that require full-scale meta-analyses or real-time data processing. The most computationally intensive process within TU is the search term expansion using AI, which is constrained to generating synonymous terms based on human-input keywords. This AI function operates on a lightweight model that does not require high-performance computing resources.

A key distinction of TU is that it assists in the entire tertiary review process, rather than being limited to isolated stages. Compared to existing approaches such as DistillerSR, Covidence, and Rayyan, which focus on specific tasks like study screening or data extraction, TU integrates a complete methodology for tertiary evidence synthesis. This includes search term expansion, literature retrieval, synthesis automation, and structured result visualization. While other tools provide assistance in certain steps, TU ensures a fully automated, structured, and reproducible workflow for umbrella reviews.

To our knowledge, there are currently no automated systems specifically designed for tertiary evidence synthesis that comprehensively address and assist in the entire synthesis process. While several tools exist for systematic review automation—such as DistillerSR, Covidence, and Rayyan—these primarily focus on secondary evidence synthesis (ie, systematic reviews) and are not designed to facilitate tertiary synthesis methodologies like umbrella reviews.

In addition, no previous tool has undergone a formal assessment or validation for automated tertiary synthesis, as TU is the first system explicitly developed for this purpose. Unlike existing software, TU does not merely automate isolated steps (such as literature screening or data extraction) but provides a structured, end-to-end approach for tertiary evidence synthesis. This distinction highlights the novelty of TU and underscores the need for this study to formally assess its performance compared to TURs.

A schematic diagram is provided to clearly illustrate TU's workflow, showing the process from data acquisition to the generation of synthesized results. Abstracts of SR/MA, retrieved from the MEDLINE database via PubMed, form the foundation of the analysis. The decision to use MEDLINE via PubMed as the sole database for literature retrieval in TU is based on its strong coverage of systematic reviews and meta-analyses, as well as the feasibility of leveraging LLMs for search term expansion. Recognizing the potential limitation of relying on a single database, we conducted preliminary assessments to estimate the impact of this decision. Specifically, we evaluated the ability of TU to retrieve references from TURs and analyzed the proportion of systematic review and meta-analysis references found in MEDLINE. Our results showed that TU was able to

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retrieve 81.1% (414/511) of TUR references using its AI-assisted search methodology in Medline alone. In addition, an independent assessment of 511 references from 22 TURs found that only 11 references were not indexed in MEDLINE. While some loss of relevant studies is inevitable, these findings suggest that the methodological approach used in TU remains sufficiently comprehensive for tertiary evidence synthesis, balancing feasibility and completeness (unpublished data). The data obtained are processed through a range of techniques, including natural language processing (NLP), sentiment analysis (SA), web scraping (WS), and ML. The expected results comprise synthesized evidence on intervention effectiveness and risk exposures, presented in a graphical and visual format. These results are conveyed in plain language, making them easily understandable by all stakeholders, regardless of their statistical literacy.

The project is continuously updated through automated and on-demand searches, with data from new studies seamlessly integrated into the existing body of evidence. Each inclusion restarts the synthesis process, creating a dynamic, cyclical workflow that ensures the results of the project remain up-to-date (Figure 1).

The implementation of new methodologies in the scientific field requires a comparative validation process with established methods to ensure their reliability and effectiveness. TU, being an innovative methodology still in its theoretical-conceptual stage, must be evaluated against established methodologies. Therefore, the aim of this study is to validate TU by comparing its performance and outcomes with the gold standard, TURs, to establish its credibility and potential superiority.

Figure 1. The Umbrella Collaboration workflow. NLP: natural language processing; LLM: large language models; SA: sentiment analysis; SR/MA: systematic reviews with or without meta-analyses.

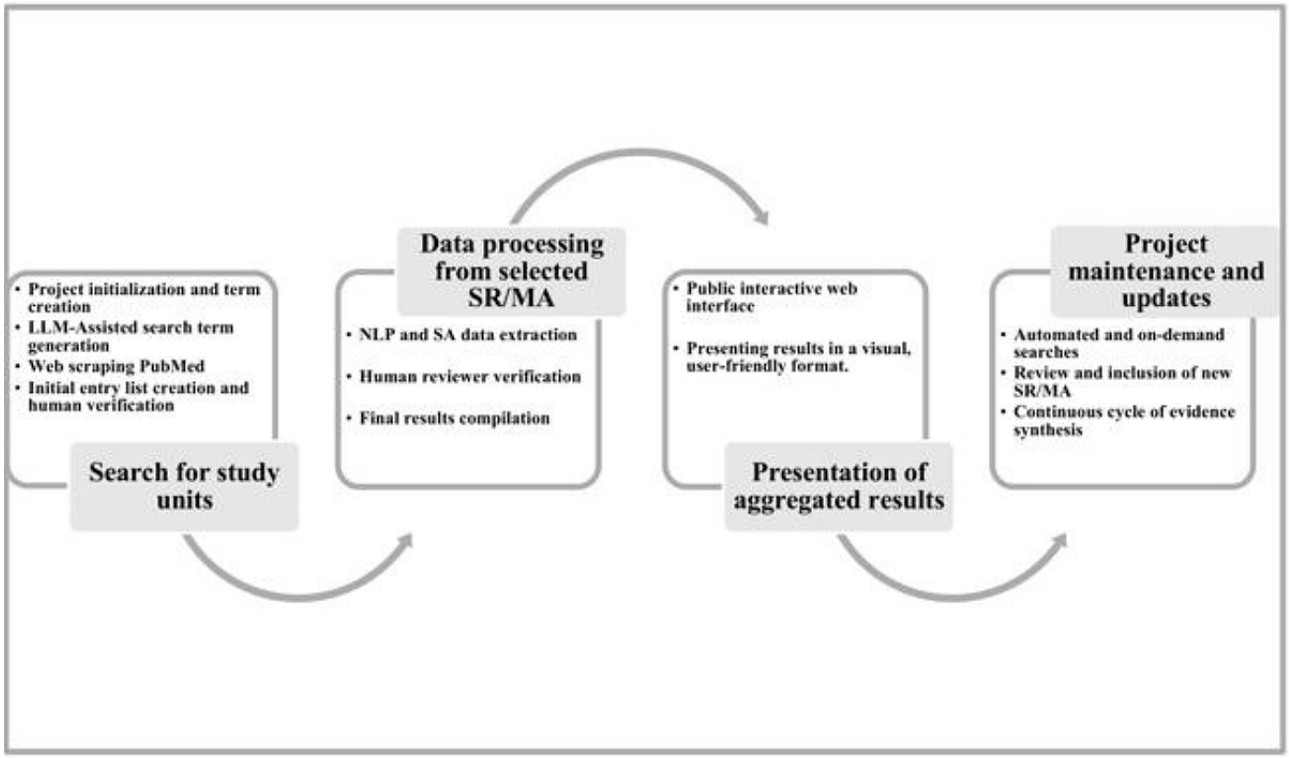

Objectives

The primary objective of this study is to assess whether a software-driven AI-assisted system of evidence synthesis, TU, can match the effectiveness of traditional methods of tertiary synthesis, providing a potentially more timely, efficient, and comprehensive approach while remaining open to findings that could demonstrate superior performance. To support the primary objective of evaluating the effectiveness of TU compared to traditional methodologies, this study also aims to assess the accessibility and comprehensibility of TU's outputs as a secondary objective.

Methods

Study Design

Part 1: Quantitative Comparison of Methodologies

Overview

Figure 2 provides an overview of the study design. The study follows a structured comparative approach in which selected TURs in geriatrics serve as the gold standard for validation. Using the same research questions, projects are conducted in parallel with TU to assess its performance. Data from both methodologies are systematically collected and compared, focusing on key variables such as the identification of outcomes of interest, effect size, effect direction, statistical significance, certainty of evidence, and execution time. The figure illustrates

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the step-by-step workflow of the study, from the selection of umbrella reviews in geriatrics as reference models to the comparison of results obtained using TU and TURs.

The first part of this study focuses on a quantitative comparison between the 2 tertiary synthesis methodologies. To facilitate this comparison, a targeted search in PubMed will identify relevant TURs in geriatrics, focusing on representative reviews rather than an exhaustive search. Our approach will involve a focused search in PubMed, using specific terms relevant to geriatrics, to find suitable TURs that serve as a benchmark for this comparative analysis. This targeted search is sufficient for our methodological comparison and does not require the comprehensive search strategy typical of systematic reviews, as our goal is not to cover the entire scope of available literature but to enable a parallel evaluation of synthesis methodologies. Therefore, while the search strategy may appear basic, it is intentionally designed to fulfill the specific needs of our project without aiming for exhaustive literature retrieval, which is beyond the scope of this project.

Figure 2. Study design overview. TU: The Umbrella Collaboration; TUR: Traditional Umbrella Reviews.

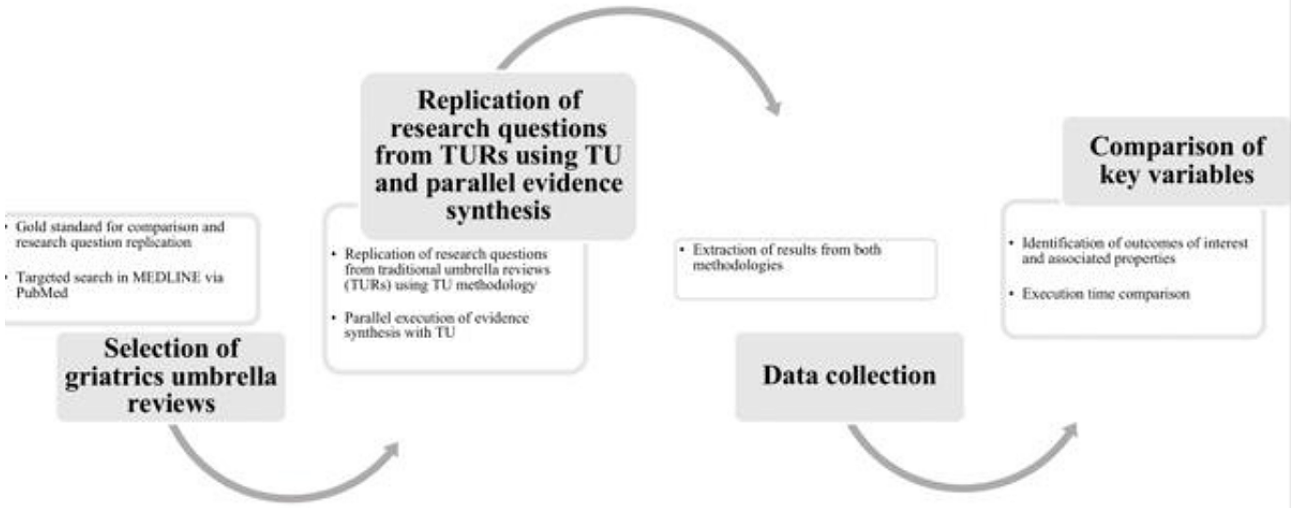

Study Variables

In the quantitative comparison, several critical variables will be analyzed. Key among these is the identification and evaluation of outcomes of interest (outcomes). This includes assessing the degree of concordance between the methodologies in identifying outcomes and using a concordance matrix to document and compare the outcomes identified by TU and TURs. In addition, we will analyze the total number of outcomes identified by each methodology, providing a descriptive and statistical comparison. It is essential to define the concept of an "outcome of interest" within the context of tertiary evidence synthesis. An outcome of interest refers to specific aspects identified and evaluated by systematic reviews with meta-analyses that examine the same research question. These outcomes are critical for understanding the overall impact of various interventions on health conditions or the effects of exposure to risks.

A crucial aspect of this analysis involves the comparison of effect sizes for the identified outcomes. TU uses an automated approach for standardizing effect sizes using a custom-designed metric (R_{TU}). This metric transforms all commonly used effect size statistics in evidence synthesis (eg, standardized mean difference [SMD], mean difference [MD], relative risk [RR], odds ratio [OR], hazard ratio [HR], and others) into a single weighted composite measure. The R_{TU} metric enables the aggregation of heterogeneous effect size measures across different systematic reviews supporting a given outcome of interest in tertiary evidence synthesis.

Since this process is fully automated, accuracy is assessed through comparisons with TURs. By replicating research questions from TURs in TU, we compare whether the R_{TU}-derived effect sizes align with those obtained using traditional methodologies. This validation step ensures that the automated transformation process does not introduce systematic distortions and maintains consistency with established effect size estimation methods. Given the diverse metrics used in TURs, such as SMD, MD, RR, OR, and HR, and the unique metric used by TU, we will standardize all effect sizes, used in TURs, to Cohen *d*. This standardization facilitates a direct comparison, ensuring consistency in the interpretation of results.

We will also examine the direction of the effects for each outcome, categorizing them as favorable, unfavorable, or unknown for interventions, and as increasing, decreasing, or unknown for exposures to risks. The statistical significance of the outcomes will be compared by analyzing *P* values and CI, assessing whether the results are statistically significant across both methodologies.

Furthermore, the certainty of the evidence (LoE) associated with each outcome will be evaluated. To assess the LoE within TU, we use sentiment analysis as a NLP technique. This approach allows for the automated classification of certainty indicators extracted from systematic review abstracts. Regarding the concern about the training data for sentiment analysis, at this stage, TU uses a sentiment analysis model initially trained on X (formerly known as Twitter) data. While we acknowledge that this is not highly optimized for medical texts, it provides a cost-effective starting point for sentiment classification without incurring additional expenses. Cloud-based solutions, such as

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Azure cognitive services, offer more specialized sentiment analysis models for health care, but these are paid services that exceed our current budget.

We fully recognize the limitations of using general sentiment analysis for LoE, as traditional GRADE (Grading of Recommendations Assessment, Development, and Evaluation)-based approaches consider multiple factors such as study limitations, inconsistency, indirectness, publication bias, and confounders. However, our primary aim is to determine whether a simplified approach, using abstract-level sentiment classification, can yield reasonable agreement with traditional methodologies. TU does not claim to replace the rigor of full-text GRADE assessments but instead seeks to evaluate whether an alternative automated method can provide valuable insights with lower resource demands. We are actively working toward developing our own custom sentiment analysis algorithm tailored to medical literature, trained on validated medical datasets. This will enhance precision and improve TU's ability to evaluate LoE more effectively in the future.

For TURs, this will be done using the GRADE system [23], which categorizes evidence into very low, low, moderate, and high levels. TU applies an SA-based scoring system on a scale from –1 to +1. Both scales will be normalized to a similar quantitative range (0-1) to facilitate comparison. To align the 2 systems, the SA scores are normalized using the following transformation formula: X=(SA score+1)/2. Where X represents the normalized certainty score, ensuring that SA values originally in the range of –1 to 1 are mapped to a 0 to 1 scale. The GRADE ordinal levels are mapped onto the 0-1 scale as follows: very low=0.00-0.25, low=0.26-0.50, moderate=0.51-0.75 and high=0.76-1.00. This process allows TU and TUR certainty ratings to be compared in a standardized manner, enabling statistical concordance analyses between the 2 methodologies.

Finally, the execution time of each methodology will be assessed, with TU providing exact time measurements and TURs relying on an estimated timeframe of 6 to 12 months based on existing literature.

Data Collection and Research Question Replication

Data collection will begin with a targeted search in PubMed to identify TURs in geriatrics, using the search terms "umbrella" AND "geriatric." The identified TURs will serve as benchmarks for our comparative analysis. The research questions from these selected umbrella reviews will be directly replicated in TU without modification, ensuring a precise comparison of outcomes generated by each methodology. TU will be configured to replicate these questions, using automated searches and synthesis through NLP, WS, SA, and ML, with human reviewers verifying and extracting data as necessary. This approach allows us to assess the comparative effectiveness and efficiency of TU relative to traditional methods, particularly in identifying and analyzing outcomes critical to evaluating health interventions and exposure risks. Data from both TURs and TU will be systematically collected and recorded in a database to facilitate precise comparisons of outcomes, effect sizes, and other critical variables, ensuring a thorough evaluation of both methodologies.

The decision to rely solely on abstracts for data extraction in TU was driven by practical and methodological considerations. First, this approach was chosen due to budgetary constraints, as full-text access to all systematic reviews and meta-analyses would require extensive licensing fees or institutional subscriptions, which are beyond the scope of this project. Second, abstracts help mitigate language bias, since all systematic review abstracts indexed in MEDLINE are available in English, regardless of the original language of publication. This ensures a broader and more internationally representative evidence base.

While it is acknowledged that abstracts often contain limited methodological details and may lack comprehensive information on certainty of evidence, outcome effect sizes, or risks of bias, the core objective of TU methodology is to assess whether robust conclusions can still be drawn based on abstracts alone. Recognizing the inherent limitations of abstracts, TU incorporates structured extraction criteria to capture the most relevant information while acknowledging the potential risks of missing key methodological details. The validation process of TU explicitly includes a comparison with full-text TURs to evaluate whether synthesis based on abstracts alone yields comparable conclusions.

Part 2: Evaluation of Ease of Use and Comprehension

Overview

The second part of the study focuses on evaluating and comparing the ease of use and comprehension of the results generated by TU with those from TURs. This evaluation will be conducted through an anonymous and voluntary online survey directed at health professionals, designed to assess their experience with both methodologies.

The survey, developed using Google Surveys for ease of access and data analysis, comprises 16 items. The initial 6 items gather demographic information about the survey respondents, while the subsequent 10 questions directly compare the usefulness and clarity of the results produced by TU and TURs, using a Likert scale ranging from 1 to 5. This scale will measure respondent's perceptions of the clarity, comprehensibility, and ease of use of the results provided by both methodologies (Table 1).

To ensure a thorough evaluation, informational sessions will be held in geriatric departments of university hospitals in Madrid (Spain). During these sessions, the concept of tertiary evidence synthesis and the functionality of TU will be introduced. Health professionals, including those from geriatrics and other rotating specialties, will be given access to the TU platform and guided through its use by an expert. This hands-on experience will be complemented by providing the participants with TUR result tables to facilitate a direct comparison.

Participants will be able to access the survey via a QR code, provided during the sessions, allowing them to complete it either immediately or at their convenience. The survey's responses will be analyzed descriptively, focusing on the overall user experience with TU and its potential advantages in terms of ease of interpretation and presentation compared to traditional methods.

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Table 1. Survey questions on the utility of The Umbrella Collaboration.

	Question	Answer Likert scale
1 - 6	Respondent affiliation data	
7	Do you consider that the interactive interface of the "TU"[a] methodology facilitates the understanding of results compared to the static tables of TURs[b]?	• 1: Strongly disagree • 2: • 3: • 4: • 5: Strongly agree
8	Do you believe that the visualization of results using bubble plots in "TU" helps to quickly identify the most relevant outcomes?	• 1: Strongly disagree • 2: • 3: • 4: • 5: Strongly agree
9	Does the graphical representation of the outcomes (illustrated by figures, colors, and sizes) in "TU" enhance your ability to assess the clinical relevance of the results?	• 1: Strongly disagree • 2: • 3: • 4: • 5: Strongly agree
10	Do you find that access to detailed data by clicking on the figures of the outcomes in "TU" interface enhances your evidence analysis experience?	• 1: Strongly disagree • 2: • 3: • 4: • 5: Strongly agree
11	Do you think that "TU" methodology allows for a quicker interpretation of data compared to TUR?	• 1: Strongly disagree • 2: • 3: • 4: • 5: Strongly agree
12	Is the information provided by "TU" useful in your field of work (clinical, research, or educational) for evidence-based decision-making?	• 1: Strongly disagree • 2: • 3: • 4: • 5: Strongly agree
13	Does the ease of use of "TU" interface facilitate greater data exploration compared to traditional methods?	• 1: Strongly disagree • 2: • 3: • 4: • 5: Strongly agree
14	Do you consider the historical evolution of evidence provided by "TU" methodology to be useful?	• 1: Strongly disagree • 2: • 3: • 4: • 5: Strongly agree
15	Does "TU" methodology require less statistical knowledge to interpret the results compared to TUR?	• 1: Strongly disagree • 2: • 3: • 4: • 5: Strongly agree
16	Overall, are you satisfied with "TU" methodology as a tool for tertiary evidence synthesis?	• 1: Strongly disagree • 2: • 3: • 4: • 5: Strongly agree

[a]TU: The Umbrella.

[b]TURs: Traditional Umbrella Reviews.

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Statistical Analysis: Data Analysis and Statistical Methods

The quantitative analysis will compare the results obtained by both methodologies. Contingency tables will be constructed to contrast the identification of outcomes, the size effect, the direction of the effect, and the statistical significance, ensuring statistical congruence between the methods. For the evaluation of certainty levels, TU scores will be normalized to a scale comparable to the GRADE levels, which will also be transformed into a numerical scale between 0 and 1.

The chi-square test will be used to determine significant differences between the methodologies. In addition, Pearson and Spearman correlation analyses will be conducted to quantify the relationship between TU certainty levels and GRADE certainty levels of the TURs. Pearson correlation analysis is useful for quantifying the strength and direction of a linear relationship between 2 continuous variables. Moreover, the analysis will be complemented with Spearman correlation analysis due to potential violations of normality assumptions in the data.

Statistical analysis will be performed using IBM SPSS Statistics (version 26), with an alpha level of .05 to determine statistical significance.

Ethical Considerations

This study does not involve human participants, personal data, or animals. All data will be sourced from published materials, and the analyses will be conducted in accordance with established ethical standards for secondary data analysis. In addition, the survey component will be conducted anonymously and on a voluntary basis. Given these considerations, we do not deem it necessary to seek approval from an ethics committee, as the study adheres to standard ethical practices for research of this nature [24].

Results

We will focus on evaluating the effectiveness of the experimental methodology in accurately identifying and analyzing relevant outcomes. Among the results, we will include detailed assessments of effect sizes, the direction of effects, statistical significance, and the certainty of evidence for each outcome. We will compare these findings with those derived from TUR to determine if the experimental approach yields results that are at least equivalent in quality and comprehensiveness.

Finally, the efficiency of the experimental methodology will be evaluated by recording the time taken to complete the synthesis process. While the time required for TUR is estimated to range between 6 and 12 months based on existing literature, we will document the actual time taken by the experimental approach. This will provide a practical measure of the potential time savings offered by the software-driven AI-assisted method, highlighting its feasibility and effectiveness in a real-world context.

To evaluate the ease of use and comprehension of TU within its environment, a detailed survey will be specifically designed. Survey respondents will have access to the TU platform, where they can interact with various interactive screens displaying the results of the synthesis process across different projects completed to date.

Discussion

Principal Findings

The anticipated findings of this study are expected to demonstrate that TU, a semiautomated tertiary evidence synthesis tool, can produce results that are methodologically comparable to TURs while significantly improving efficiency. By leveraging AI-assisted methodologies, TU may streamline the synthesis process, reducing the time and effort required for evidence aggregation. In addition, the study aims to assess whether tertiary evidence synthesis can be effectively conducted using only systematic review abstracts, balancing feasibility with methodological rigor. If successful, these findings could support the broader adoption of AI-driven approaches in tertiary synthesis, potentially transforming the landscape of evidence-based decision-making in health care.

The primary objective of this study is to evaluate whether TU, a software-driven system designed to facilitate tertiary evidence synthesis with AI-assisted methodologies, can match the effectiveness of TURs. TU integrates with its software development advanced technologies such as NLP, SA, WS, and ML to enhance the efficiency of evidence synthesis.

The semiautomated processes implemented by TU could signify a significant advancement in making evidence synthesis more accessible and timely, with the potential for continuous updates as new data becomes available. The study's findings could pave the way for broader adoption of AI-driven methodologies in evidence synthesis, potentially reducing the time and resources needed for comprehensive reviews. TU's integration of software engineering projects and AI with traditional methods could streamline the review process, enabling faster aggregation and interpretation of data across various research domains.

Several software tools assist in systematic and umbrella review processes, such as DistillerSR, Covidence, and Rayyan. These platforms improve efficiency in evidence synthesis by automating tasks such as study screening, data extraction, and literature management. However, they do not offer a fully structured and automated methodology for tertiary evidence synthesis, which remains a predominantly manual process. In contrast, TU is designed to support the entire tertiary synthesis workflow, rather than focusing on isolated stages. TU integrates (1) AI-assisted search term expansion, which enhances literature retrieval by suggesting synonymous terms for human validation; (2) automated data extraction from systematic review abstracts, allowing for a structured and efficient synthesis process; (3) a dedicated framework for tertiary synthesis, unlike other tools that primarily assist in secondary synthesis (systematic reviews); and (4) interactive and visual result presentation, providing stakeholders with an accessible interpretation of findings, rather than traditional tabular outputs.

Ongoing Project Status

Once created, projects in TU remain active indefinitely, preventing obsolescence. This continuous updating of evidence

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synthesis is a key feature that differentiates TU from static review methodologies. The system conducts literature searches every 24 hours or on demand by the human reviewer responsible for the project. This allows for real-time incorporation of newly published studies, ensuring that the synthesis remains current and reflective of the latest scientific evidence. While TUR requires manual updates, often years apart, TU transforms the synthesis process into a living evidence system, ensuring that the latest research is incorporated seamlessly. This eliminates the need for reinitiating entire projects and allows researchers to work with continuously updated data.

One similarity between TU and existing platforms is the incorporation of automation to enhance efficiency. However, TU distinguishes itself by providing a fully integrated tertiary synthesis methodology with a self-updating mechanism, ensuring both methodological rigor and computational efficiency in umbrella reviews.

By offering a platform that supports real-time updates and provides accessible synthesis outputs, TU has the potential to enhance the utility of tertiary synthesis for a wide range of stakeholders, including those with limited statistical expertise. However, a key limitation of TU is its reliance on a single database (MEDLINE via PubMed), which might not capture all relevant studies. This study will examine whether this limitation can be mitigated by the system's other capabilities. Ultimately, the timely and comprehensible evidence synthesis provided by TU could facilitate more informed decision-making in clinical settings, particularly in rapidly evolving areas of medical research.

Future research will be essential to further validate and refine TU. Planned next steps include expanding the sample size of included TURs to increase representativeness, conducting blinded validation studies to minimize potential biases, and testing the tool across different reviewer profiles to assess usability beyond expert users. In addition, TU's methodology should be applied to other medical and nonmedical disciplines to evaluate its versatility. A critical aspect of future validation will also involve independent expert review, ensuring that TU's findings align with established methodological standards. Finally, economic feasibility studies comparing TU with traditional synthesis approaches will be necessary to assess its cost-effectiveness and scalability in real-world implementation.

Limitations

The decision to use only one database, MEDLINE via PubMed, in TU is both a recognized limitation and a deliberate choice shaped by resource constraints and technical considerations. While systematic reviews typically require searching multiple databases to capture all relevant literature [25], our approach focuses on testing whether TU can achieve outcomes comparable to TURs despite these limitations. While the pilot study provided preliminary evidence of PubMed's strong coverage, further validation through TU is necessary to confirm its applicability across different domains.

Furthermore, while searching multiple databases is often recommended to avoid language and indexing biases, especially those related to non-English literature [26,27]. TU mitigates some of these biases by focusing on abstracts in English, as all PubMed abstracts are provided in this language regardless of the original publication's language. However, the absence of Chinese databases in our approach is a notable limitation, given that only a small proportion of Chinese journals are indexed in MEDLINE.

The decision to rely exclusively on abstracts rather than full texts in TU is a deliberate methodological choice aligned with the core objective of this study: to evaluate whether tertiary evidence synthesis can be conducted efficiently, with fewer resources, and without requiring extensive methodological expertise from the reviewer, while still producing results comparable to TURs.

We acknowledge that abstracts may lack key methodological details, including certainty of evidence assessments, effect size calculations, and risk of bias evaluations. However, the fundamental hypothesis of TU is that an automated, structured approach to abstract-based synthesis may still yield clinically useful conclusions, particularly when applied under standardized and reproducible conditions. Moreover, relying on abstracts offers two key advantages: (1) minimization of language bias: all systematic review abstracts in MEDLINE are available in English, regardless of the original publication language, which ensures that non-English studies are not automatically excluded due to language barriers, a common issue in traditional systematic reviews; and (2) feasibility and accessibility: full-text access to all systematic reviews requires extensive licensing fees and institutional subscriptions, which may not always be feasible. Abstracts provide a universally accessible data source, allowing for broader implementation of evidence synthesis methodologies.

While TU does not claim to replace the depth of full-text review, this study aims to evaluate whether a structured synthesis based solely on abstracts can yield results that are sufficiently coherent and robust to serve as a complementary or alternative approach. If validated, this methodology could provide an efficient solution for synthesizing evidence in settings where full-text access is restricted or when rapid evidence synthesis is needed.

While we acknowledge the potential benefits of testing TU across multiple medical domains, this study is a pilot study designed to assess the feasibility of our methodology in a single, well-defined field, geriatrics. At this stage, limiting the scope to geriatrics is a strategic choice, ensuring that the study maintains clarity, feasibility, and methodological rigor in its initial validation phase. This focused approach allows for a controlled evaluation of TU against TURs, ensuring that the initial validation is conducted under clearly defined conditions. If the results demonstrate that TU can produce findings comparable to TURs, future studies will expand its application to other medical fields, such as cardiovascular medicine and psychiatry, as well as nonmedical domains, including education, sociology, and other disciplines with abundant systematic reviews. This stepwise approach ensures a methodologically sound progression, allowing TU to be tested and refined incrementally before broader implementation.

In this initial phase of the study, we have prioritized clinical health professionals as the primary participants for the ease of

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use and comprehension surveys. This decision is based on the primary objective of TU, which is to facilitate evidence synthesis for clinicians and health care professionals who may not have extensive expertise in systematic review methodologies. Given that TU is designed to enhance the accessibility and usability of tertiary evidence synthesis in clinical practice, it is essential to first evaluate its clinical utility and interpretability among end-users.

We fully acknowledge the importance of a rigorous methodological review by epidemiologists and research methodologists, as well as the need to assess the validity of results produced by TU. However, this will be addressed in a subsequent phase of research, where surveys will be extended to other key stakeholders, including epidemiologists and research methodologists, to evaluate the methodological robustness of TU. Health care policy makers and hospital administrators, assess TU's potential role in decision-making. Patients and caregivers, to explore how synthesized evidence can be communicated effectively to the general population. This stepwise approach ensures that TU is first assessed from a clinical perspective before expanding to other critical stakeholders in future validation studies.

Another limitation of this study is the potential for response bias in the ease-of-use and comprehension survey. Given that most participants will complete the survey immediately after structured demonstrations of TU, their responses could be influenced by the context of the presentation. This could lead to a more favorable assessment of TU than what might be observed in an independent evaluation setting. This halo effect can impact the perceived usability and effectiveness of TU. Future studies should aim to validate these findings through independent assessments in settings where TU is used without direct guidance from the research team.

Conclusion

This study aims to validate TU as a tool for tertiary evidence synthesis in health. If this methodology proves to be as effective as TURs, but more efficient in terms of project execution time and more accessible in terms of ease of use and comprehension, it could significantly enhance the way evidence synthesis is conducted, facilitating informed decision-making, and improving health outcomes. The results of this study may represent a step toward the integration of innovative technologies into the routine practice of evidence synthesis, with the potential to transform the field of health research.

Acknowledgments

This project has received a research grant from the Fundación Alfonso X el Sabio.

Conflicts of Interest

The authors BC, MR-C, JP-M, AP-L, and BC-R were involved in the development of The Umbrella Collaboration (TU) software. In addition, BC and MR-C are owners of the software and may have financial or intellectual property interests in its future applications. While this study was conducted with the aim of validating TU as an evidence synthesis tool, the authors have taken all necessary precautions to ensure that the study design, data analysis, and interpretation of results remain as objective and methodologically rigorous as possible. To mitigate potential biases, comparisons were conducted against gold-standard Traditional Umbrella Reviews (TURs), and statistical methodologies were used to ensure transparency and replicability of findings. Furthermore, the affiliations of the authors did not influence the study design, execution, data analysis, or interpretation of results. All research activities were conducted following rigorous methodological standards to ensure impartiality and scientific integrity.

While this study was conducted with the aim of validating TU as an evidence synthesis tool, the authors have taken all necessary precautions to ensure that the study design, data analysis, and interpretation of results remain as objective and methodologically rigorous as possible. To mitigate potential biases, comparisons were conducted against gold-standard TURs, and statistical methodologies were used to ensure transparency and replicability of findings.

Furthermore, the affiliations of the authors did not influence the study design, execution, data analysis, or interpretation of results. All research activities were conducted following rigorous methodological standards to ensure impartiality and scientific integrity.

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Abbreviations

AI: artificial intelligence
GRADE: Grading of Recommendations Assessment, Development and Evaluation

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HR: hazard ratio
JBI: Joanna Briggs Institute
KT: knowledge translation
LLM: large language model
LoE: certainty of the evidence
LSR: Living Systematic Review
MD: mean difference
ML: machine learning
NLP: natural language processing
OR: odds ratio
PICO: Population, Intervention, Comparison, and Outcome
RR: relative risk
RTU: custom-designed metric
SA: sentiment analysis
SMD: standardized mean difference
SR/MA: systematic reviews with or without meta-analyses
TU: The Umbrella Collaboration
TUR: Traditional Umbrella Reviews
WS: web scraping

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Protocol

Resource-Oriented Case Management to Implement Recommendations for Patients With Chronic Pain and Frequent Use of Analgesics in General Practices (Project RELIEF): Protocol for a Single-Arm Exploratory Feasibility Study

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Abstract

Background: Chronic noncancer pain (CNCP) is a frequent reason for counseling in general practice. Current German guidelines emphasize its biopsychosocial etiology and the importance of self-care and nonpharmacological treatment strategies such as education, physical and social activity, and psychological approaches. Comprehensive assessments are necessary to individualize treatment maximally and monitor appropriate use of pain medication. General practitioners face many challenges in implementing holistic pain management, which considers biological, psychological, and social aspects. In project RELIEF (resource-oriented case management to implement recommendations for patients with chronic pain and frequent use of analgesics in general practices), a case management program was developed to facilitate implementation of guideline recommendations on pain management regarding medical assessment and monitoring, patient and practice team education, promotion of self-care strategies, and rational pharmacotherapy.

Objective: We evaluated the feasibility of the intervention and study procedures before applying them in a larger cluster randomized controlled trial. Our secondary objective is to estimate potential effects of the complex intervention.

Methods: A single-arm trial with general practices and patients with CNCP and analgesics use will be conducted, accompanied by a mixed methods process evaluation. The intervention comprises 5 components, including software-supported medical pain history, 3 scheduled structured appointments, e-learning on CNCP for general practitioners and medical assistants, educational material for patients, toolbox with information on (regional) resources for patients and practice teams. Participating practices will be located in the federal state of Baden-Württemberg, Germany, and will recruit eligible patients (adults with CNCP for more than 3 months, with at least moderate pain-related disability, permanent or on-demand use of analgesics or co-analgesics in the previous 4 weeks, and practice team assessed ability to participate actively in the trial). A questionnaire given to the first 150 adult patients entering the practice in February 2025 will help screen eligible patients. The primary objective will be measured

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by a set of predefined indicators. The key secondary outcome is pain-related disability measured by the Pain Disability Index German version. All participants will be asked to participate in the process evaluation. Outcome evaluation data will be gathered by paper-based and digitally provided questionnaires to be completed by participants. Process evaluation data will be gathered in surveys and a qualitative study. Descriptive analyses will be performed.

Results: Recruitment occurred between October and December 2024. Targeted sample size was 6 practices and 50 patients. The intervention period will be February-June 2025. It is expected that eligible patients will benefit from the intervention and that improved medication management and intensified use of nonpharmacological treatment strategies will reduce pain-related disabilities and other patient-reported outcomes.

Conclusions: This study will provide valuable information regarding feasibility and potential effects before testing the intervention in a confirmatory cluster randomized controlled trial.

Trial Registration: German Clinical Trials Register DRKS00034831; https://www.drks.de/search/de/trial/DRKS00034831

International Registered Report Identifier (IRRID): PRR1-10.2196/66335

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KEYWORDS

chronic noncancer pain; case management; primary care; general practice resource-oriented; chronic pain; analgesics; pharmacological treatment; pain medications; holistic approach; feasibility; single-arm; exploratory; pilot study; screening; questionnaire; survey; protocol

Introduction

Background

About 20% of the patients in German general practices are affected by chronic pain [1], defined as pain that persists for more than 3 months or reoccurs [2]. Classification systems distinguish between chronic primary pain which cannot be explained by a detectable tissue damage (eg, fibromyalgia, unspecific low back, and psychosomatic pain disorders) and chronic secondary pain which is likely to have been caused at least initially by an organ or tissue damage (eg, degenerative or inflammatory diseases of the joints or spine and nerve damages) [2]. While cancer-related pain has characteristics of continuous or intermittent pain [3], chronic noncancer pain (CNCP) comprises any painful condition not associated with malignant disease and persisting for at least 3 months [4]. It interferes with activities of daily life and has a negative impact on quality of life and physical function [5]. CNCP is considered to be a major public health problem and one of the most common reasons why patients seek medical care [6,7]. The understanding of chronic pain pathogenesis has become more differentiated in recent years and there is consensus that chronic pain is always maintained or influenced by an interaction of biological, psychological, and social factors. Furthermore, psychological comorbidities such as depression, anxiety, or posttraumatic stress disorder are frequently associated with chronic pain [8]. Depending on which factors or comorbidities prevail, different treatment strategies are effective. Thus, comprehensive medical pain assessment is necessary in order to individualize treatment as best as possible.

Guidelines emphasize the importance of holistic pain management and nonpharmacological and noninvasive treatment strategies such as education, physical activity, social activity and support, relaxation techniques, or cognitive behavioral therapy. Analgesics should only be used temporarily and supportively until nonmedical treatments show an effect [9]. However, about two thirds of patients with chronic pain take analgesics [10] which may have severe adverse effects. Particularly alarming is the high percentage of patients taking nonsteroidal anti-inflammatory drugs (NSAID) which are also available as over-the-counter drugs. In a large telephone survey, 72% of German respondents with chronic pain stated using nonprescribed NSAID [10]. If taken on a long-term basis, NSAID may lead to renal insufficiency, gastrointestinal damages and cardiovascular events. Furthermore, the rise of opioid prescriptions for CNCP is observed with concern in Germany, even though there are no signs for an opioid epidemic [11]. The majority of opioid prescriptions are issued for CNCP, although it is well known that opioids are frequently not or little effective in this indication and associated with a high risk for adverse events such as obstipation, falls, cognitive impairments, or addiction [12]. If analgesics are applied, it is vital to perform thorough medication management and to adhere to monitoring recommendations. The German guideline for long-term use of opioids in chronic noncancer pain (LONTS) gives clear recommendations for safe opioid management [13]. However, adherence to guidelines might be impacted by factors such as personal attitudes, preferences, and experiences [14] and General practitioners (GP) might be less likely than other specialists to follow a guideline since they favor their own experience [15,16], or might not be aware of guidelines. Suboptimal pain management does not only result in unnecessary suffering of the affected patients but also in high costs for the health care system: patients with pain-related disabilities have a 6-fold higher rate of sick leaves and 4.5-fold higher rate of physician visits [17].

In Germany, patients with CNCP are mainly treated in ambulatory care by GPs and specialists such as orthopedists, neurologists, or rheumatologists. Only 10% have ever seen a pain specialist or received multimodal pain therapy [18]. GPs frequently know their patients and the patient's family for many years. They often act as coordinators of care and are frequently the main prescribers of all medications. Therefore, they play a crucial role in the care of patients with chronic pain. In spite of these good preconditions, it remains challenging for GPs to

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implement structured and holistic pain management in their daily practice [9].

Within the project RELIEF (Resource-oriented case management to implement recommendations for patients with chronic pain and frequent use of analgesics in general practices), a case management program was developed to support GP in implementing guideline-based pain management. The program focusses on patients with CNCP and 4 essential areas of pain management: medical assessment and monitoring, practice team and patient education, self-care, and rational pharmacotherapy.

Overall Aim of the Study

The main objective of this pilot study is to test the developed program in a small number of practices with a small number of patients to assess the feasibility of the developed intervention components (eg, assessment and e-learning) and methods used for recruitment (eg, screening process) and data collection. Thus, a control group (no intervention) will not be involved. The evaluation of the program's potential effectiveness and data generation on the prevalence of the programs' target group in German general practices are secondary objectives. Based on findings of this study, the program and evaluation concept will be adapted where applicable and applied in a subsequent confirmatory cluster randomized controlled trial (not described in this protocol).

Methods

Study Design

A single-arm, exploratory pilot study with accompanying process evaluation will be conducted to pilot the case management program. Conducting a pilot study provides a good opportunity to assess feasibility of a full-scale study and can be considered an essential prerequisite to enhancing likelihood of success of the main study. Pilot studies should be well designed with clear feasibility objectives, and explicit criteria for determining feasibility [19]. Figure 1 details the design for the RELIEF pilot study.

Figure 1. The design of the pilot study in RELIEF. Yellow box (circles): intervention components; blue box (star): outcome evaluation; purple box (diamond): process evaluation. GP: general practitioner; MA: medical assistant; RELIEF: resource-oriented case management to implement recommendations for patients with chronic pain and frequent use of analgesics in general practices.

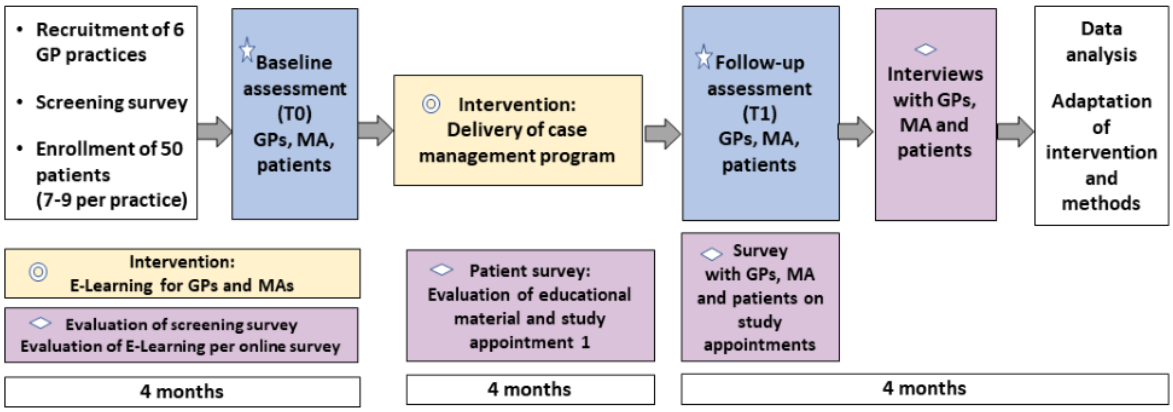

Intervention

The RELIEF intervention consists of five key components: (1) medical pain assessment and monitoring using a module specifically developed for the RELIEF intervention to be applied within an established case management software (CareCockpit) [20], (2) 3 scheduled structured appointments with GPs and medical assistants (MA), (3) e-learning on chronic pain management for GPs and MA, (4) educational video- and paper-based material for patients, and (5) a toolbox with a collection of resources for pain management for patients and practice teams. GP and MA will receive financial compensation for their additional efforts related to participation in the study (€200 [approximately US $216] per GP, €400 [approximately US $432] per MA) and number of included patients (€80 [approximately US $86] per included patient). GPs can apply for a total of 8 continuing medical education points upon completing the e-learning modules.

It is expected that patients participating in the case management program will benefit from the intervention. It is hypothesized that improved medication management and intensified use of nonpharmacological treatment strategies will result in a reduction in pain-intensity and pain-related disabilities, improved patient activation, more self-care activity and less use of analgesics. Figure 2 describes the assumed effect mechanism of the developed intervention.

It is assumed that adherence to guideline recommendations for CNCP by practice teams (green boxes) will improve if the intervention components (yellow boxes) effectively reduce identified barriers or make use of identified enablers respectively (blue boxes). Improved adherence to guideline recommendations will result in improved health outcomes or health behavior, respectively (gray box). Primary and secondary outcomes (gray box) focus on the effects of improved guideline adherence while adherence as well as assumed linkages between interventions and barriers are assessed within the scope of a comprehensive process evaluation.

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Figure 2. The assumed effect mechanism of the intervention. GP: general practitioner.

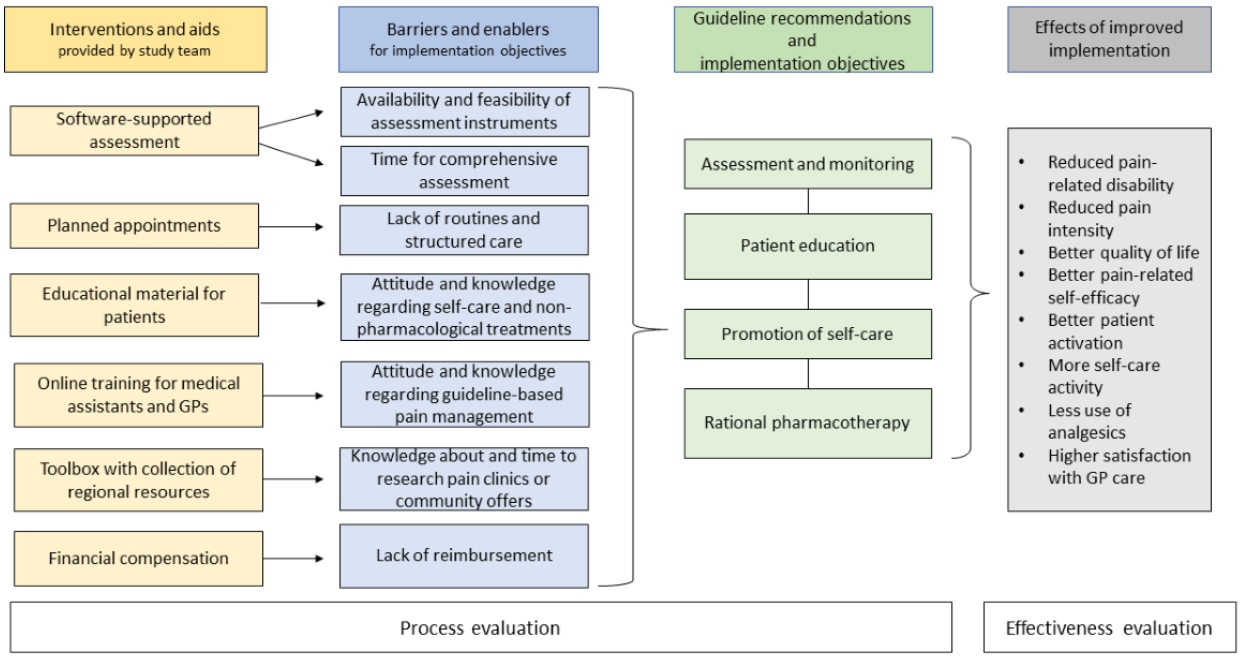

After enrolling in the pilot study, patients will complete a pain assessment through a browser-based proprietary app available to study participants only (TeleVital app linked to CareCockpit) at home on their own digital device (smartphone, tablet, computer, etc). The assessment focusses on various aspects of pain and mental comorbidities. Within 2 weeks, patients will have a scheduled structured appointment (study appointment 1) with their GP during which the patients' specifications in the assessment will be discussed and complemented by an open pain history taking. For this purpose, GPs or medical assistants will perform a manual import of the assessment data into the software CareCockpit, an established case management software currently used by about 800 general practices in Baden-Württemberg, Germany, for the case management program PraCMan [20]. This is a care model for patients with multimorbidity insured by the statutory health insurance AOK Baden-Württemberg. The data import will only be started when the patient is present in the practice to ensure that GPs are able to react immediately on critical information such as severe depression. Practice teams will receive the data in 2 versions: the original version with all items and patients' responses and, in addition, a summary of the assessment with automatically calculated scores.

At the end of study appointment 1, educational material on chronic pain (a booklet and links to educational videos tailored to patient's self-efficacy, to be used as often as patients want, and at their own speed) will be handed out to patients and the date for study appointment 2 will be set for about 2-4 weeks later. During study appointment 2, patients and GPs or patients and medical assistants will reflect on the educational material provided and agree on treatment goals related to daily activities (eg, to be able to do some gardening) and self-care activities (eg, physical activity or relaxation techniques). If necessary, medication is prescribed and therapies outside the general practice are initiated (eg, physiotherapy, multimodal pain therapy, psychotherapy, and rehabilitation), and monitoring activities (diagnostics, amendments to therapy plan, discussion of possible adverse effects, pain management, medication, self-care, etc) are planned. A treatment plan containing all this information will be issued by the responsible GP through the CareCockpit software and the date for study appointment 3 will be set for 4-6 weeks later. During study appointment 3, practice teams will check whether activities could be applied as planned. If necessary, the treatment plan will be adapted. The activities performed during study appointments 1-3 will briefly be documented by the practice teams through a checklist in the CareCockpit module. The intervention period will end with a follow-up assessment 4 weeks after study appointment 3.

A webinar will be offered by the study team to go over study organization and measures with all participating practice teams. Participating GPs and MAs will complete an e-learning on chronic pain management with 4 modules covering the pathogenesis of chronic pain, self-care activities (relaxation technics, physical activity, and topical applications), analgesics and interprofessional and interdisciplinary pain therapy. The e-learning is expected to be completed before the first patient receives study appointment 1. A website with a toolbox containing useful links and information on chronic pain as well as a collection of regional resources (eg, hospitals providing multimodal pain therapy and counseling centers etc.) will be provided by the study team. Table 1 summarizes the planned course of the RELIEF case management program.

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Table 1. The course of the case management program in the RELIEF[a] pilot study.

Who	Where	What
Week 0		
MA[b]	Practice	• Enrollment into study
Patient	At home	• Structured pain assessment through TeleVital appT0 baseline assessment through a paper-based questionnaire
Week 2		
GP[c]	Practice	• Study appointment 1: • Discussion of the results of the structured pain assessment • Open pain history taking • Patient receives educational material
Patient	At home	• Reading educational material or watching educational videos, respectively
Week 5 to 6		
• MA • MA or patient • GP	Practice	• Study appointment 2: • Reflection on educational material • Agreement on treatment goals and self-care activities • Treatment plan is issued
Patient	At home	• Applies treatment plan
Weeks 10 to 12		
• MA • GP	Practice	• Study appointment 3: • Monitoring if treatment plan and self-care could be applied as planned; if necessary, adaption of the treatment plan
Patient	At home	• Applies (adapted) treatment plan
Week 16		
Patient	At home	• T1 follow-up assessment; end of pilot study

[a]RELIEF: resource-oriented case management to implement recommendations for patients with chronic pain and frequent use of analgesics in general practices.

[b]MA: medical assistant.

[c]GP: general practitioner.

Recruitment

General practices will be recruited through known contacts such as the established practice network of about 800 practices that use a particular case management system for chronically ill patients (PraCMan) [21] and a network of teaching and research practices affiliated with the Department of Primary care and Health Services Research, University Hospital Heidelberg. The target is to include 6 practices. Based on previous experiences, it can be assumed that about 10% of the practices approached are interested in participating in research projects. Therefore, 60 practices in a predefined region will be randomly drawn and an invitation to participate in the pilot study will be sent to them by postal or electronic mail together with a declaration of interest form. Practices that declare interest in participation will receive written information about study aims and procedures. In case the recruitment target is not met, another random sample will be drawn.

To identify eligible patients and to gather information on the prevalence of the target group in primary care, a screening survey will be conducted (see Data Collection and Outcomes section below). Eligible for participation will be adult patients with CNCP for more than 3 months, with at least moderate pain-related disability (minimum 4 points on a scale from 0-10), permanent or on-demand use of analgesics and co-analgesics in the previous 4 weeks, and practice team assessed ability to participate actively in the pilot study (sufficient cognitive abilities and internet access). Patients with cancer pain or in palliative care will be excluded. Recruitment target for each practice is 7-9 patients. If more than 9 patients agree to participate in the piloting, the practice team will select 7-9 patients who are according to their assessment likely to benefit from the program. Specific reasons for their choices will be explored in the process evaluation.

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Data Collection and Outcomes

For the screening survey, each participating practice will hand out a screening questionnaire to the first 150 adult patients entering the practice from a defined date on. The practice team will collect the questionnaires, check eligibility with a provided template and invite all patients meeting the inclusion criteria to participate in the pilot study by handing out the study information material. The practice team will add information regarding reasons for nonparticipation, known CNCP diagnosis, known use of analgesics, and prescription of analgesics during the last month on the screening questionnaires of all patients meeting the inclusion criteria (regardless of whether they agree to participate in the study or not) by checking the patient file. The practice team will deidentify all questionnaires (also of patients without chronic pain) by cutting the lines for name and birthdate and send them to the study center for evaluation purposes regarding prevalence of patients in a primary care setting who meet the inclusion criteria.

Data collection related to medical pain history (used by practice teams only, not by researchers) comprises the following steps: patients receive a weblink from their GP practice leading to a browser-based app called TeleVital and complete the assessment through the app on their own digital device. TeleVital is a proprietary development of the Department of Primary Care and Health Services Research, University Hospital Heidelberg, and facilitates structured data collection in studies which use the CareCockpit. Data generated in the TeleVital app data will be stored on a secure server located at the University Hospital Heidelberg, Germany until it is transferred to the CareCockpit software installed in the GP practice. Data import will be initiated manually by the practice team at the next patient contact. Thus, practice teams will receive the assessment data only when the patient is present in the practice. Practice teams will use the assessment data for the purpose of diagnostics and treatment. It contains information on pain history, pain characteristics, use of analgesics, use on nonpharmacological measures, treatment targets, and items from validated screening questionnaires such as the Pain Detect questionnaire on neuropathic pain [22] and on mental comorbidities such as posttraumatic stress disorder [23].

Data collection for the outcome evaluation comprises the following steps: primary objective of this pilot study is to assess the case management's feasibility, measured by a set of predefined feasibility indicators. Regarding the intervention components, feasibility indicators refer to the software-supported medical pain history, study appointments, educational material for patients, and e-learning for GPs and MA. Feasibility of study procedures will be measured for the patient recruitment and enrollment process, completion of T0 and T1 questionnaires and drop-out rate. To facilitate this assessment, transfer of partial documentation from the CareCockpit to the study center will be used either electronically or paper-based, depending on preference and available resources in the participating practices. Table 2 describes the feasibility indicators in relation to the intervention components, and Table 3 details the feasibility indicators for study procedures.

Table 2. The feasibility indicators for intervention components in the pilot study.

Interventions	Data source	Indicator	Rating
Software-supported medical pain history	CareCockpit data process evaluation	Percentage of patients with pain assessment transferred to practice computer	• ≥80%: feasibility given • <80%, but reasons solvable by modification: feasibility likely • <80% and reasons not solvable by modification: feasibility not given
Planned appointments	CareCockpit data	Percentage of patients who received all 3 study appointments	• ≥80%: feasibility given • <80%, but reasons solvable by modification: feasibility likely • <80% and reasons not solvable by modification: feasibility not given
Educational material for patients	Evaluation questionnaire and patient interviews	Percentage of patients who perceived the provided content relevant and comprehensible	• ≥80%: feasibility given • <80%, but reasons solvable by modification: feasibility likely • 80% and reasons not solvable by modification: feasibility not given
E-Learning for GPs and medical assistants	Evaluation questionnaire and general practitioner and medical assistant interviews	Percentage of health care professional who perceived the e-learning relevant and comprehensible.	• ≥ 80%: feasibility given • <80%, but reasons solvable by modification: feasibility likely • 80% and reasons not solvable by modification: feasibility not given
Toolbox	Survey and general practitioner, medical assistant, and patient interviews	Percentage of participants who perceived the toolbox as relevant	• ≥80%: Feasibility given • <80%, but reasons solvable by modification: feasibility likely • 80% and reasons not solvable by modification: feasibility not given

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Table 3. The feasibility indicators for study procedures in the pilot study.

Study procedure and data source	Indicator	Rating
Patient recruitment		
Screening questionnaire	Percentage of patients who agreed to participate in the screening survey	• >80%: feasibility given • <80%, reasons solvable by modification: feasibility likely • <80% and reasons not solvable by modification: feasibility not given
Screening questionnaire	Percentage of patients in screening survey meeting all inclusion criteria	• >10%: feasibility given • <10%, but reasons solvable by modification: feasibility likely • <10% and reasons not solvable by modification: feasibility not given
Screening questionnaire	Percentage of practices that enrolled 7-9 patients	• >80%: feasibility given • <80%, reasons solvable by modification: feasibility likely • <80% and reasons not solvable by modification: feasibility not given
Outcome evaluation		
T0 and T1 questionnaires	Percentage of patients who completed T0 and T1 questionnaires	• >80%: feasibility given • <80%, reasons solvable by modification: feasibility likely • 80% and reasons not solvable by modification: feasibility not given
General practitioner report	Patient drop-out rate	• <20%: feasibility given • >20%, but reasons solvable by modification: feasibility likely • >20% and reasons not solvable by modification: feasibility not given

A range of secondary outcomes will be determined to gather information on potential effects of the program. All secondary outcomes are participant-reported and will be collected before (T0) and after (T1) the intervention by paper-based questionnaires which participants will complete at home and send directly to the study center.

Outcome measures on patient level comprise the German versions of the following validated instruments: Pain Disability Index German version (PDI-G) [24] (key secondary outcome), Patient Activation Measure [25], Short Form 12 Health Survey scale for health related quality of life [26], De-Jong-Gierveld loneliness scale [27], Pain Self-Efficacy Questionnaire German version [28], Avoidance-Endurance Fast Screening instrument [29], Pain-Catastrophising Scale [30], selected items of the European Project on Patient Evaluation of General Practice Care (EUROPEP) questionnaire on evaluation of GP care [31,32], and pain intensity (numeric analogue scale). Further study-specific items will be used to assess the use of self-care such as physical activity (3 items), relaxation techniques (1 item) and use of topical applications (1 item) and patients will be asked to document their pain medication (over-the-counter and prescribed). Secondary outcomes on GP and MA level refer to quality indicators for ambulatory pain management developed in the RELIEF project. Data for the process evaluation will be collected at various points in time as detailed in Figure 1.

During patient recruitment, practice teams will be asked to send the deidentified patient screening questionnaires to the study center for evaluation purposes. The e-learning for GPs and MA will be hosted on the platform Moodle on the server of the aQua Institute, Göttingen. After completion of the e-learning GPs and MA will be asked to fill in a short digitally provided survey to evaluate the training regarding aspects such as subjective knowledge increase, appropriateness of required time, appropriateness of didactical methods, and usability of the platform. The survey will be conducted through the survey tool Lime Survey hosted at a server of the University Hospital Heidelberg. Survey data will be linked through a pseudonym to the following meta-data gathered by the e-learning platform (e-learning completed or not completed, time needed to complete the e-learning (minutes), and number of logins necessary to complete the e-learning).

Patients will complete a paper-based pseudonymized questionnaire focusing on use and perceived usefulness of the provided educational material and experiences with study appointment 1. Patients will complete the questionnaire after going through the content provided and within 4 weeks after study appointment 1. At the end of the intervention period, patients will be asked to fill in a second questionnaire focusing on their experiences with study appointment 2 and 3 as part of the T1 follow-up survey.

All participating GPs and medical assistants will be invited to report their experiences during the pilot in a telephone interview. All patients will be invited to an interview after completing study visit 3. Depending on the response rate, a purposive sample of patients will be drawn. Written informed consent to participate will be obtained using separate information documents and agreement forms. Key questions on the interview guides will refer to intervention feasibility with regards to specified feasibility indicators, usefulness of provided material and tools, perceived effectiveness of the case and care management program, and suggestions for modifications from the perspective of health care providers and patients. Interviews will be recorded and transcribed verbatim. Transcripts will be pseudonymized and stored on secure servers at the Department of Primary Care, University Hospital Heidelberg. All audio files will be deleted after completion of data analysis.

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Data Analysis

A plan for the primary analysis will be finalized before data bank closure. All analysis will be performed in R (version 4.2.0 or higher; R Foundation for Statistical Computing) or in SPSS (version 28.0.1.0; IBM Corp) in a validated environment. The final analysis will be done as soon as the database has been declared to be complete and accurate and has been locked. Descriptive statistics will be provided to summarize demographics and baseline characteristics. In general, continuous variables will be described using number of observations, mean, SD, median, Q1, Q3, minimum, maximum, 95% CIs and, if existing, number of missing values at T0, T1 and for T0-T1 if appropriate. For categorical variables, absolute and relative frequencies will be given with missing values being reported as a separate category at T0 and T1. A CONSORT (Consolidated Standards of Reporting Trials) flow diagram will be created to display the progress of all participants through the trial. This includes the number of patients assessed for eligibility and the number of patients excluded because they did not meet inclusion criteria, declined to participate, or any other reason.

Primary Outcome Analysis

For each objective of the intervention components and study procedures, a descriptive analysis will be performed to assess feasibility. For each objective, 95% CIs will be given based on the Wilson Score interval for binary measures [33]. Reasons for not fulfilling an indicator will be categorized and evaluated descriptively.

Secondary Outcomes Analysis

As one of the aims of the study is to estimate the effect size, the 95% CI (2-sided) of the PDI-G percent change from baseline to T1 (T0-T1), which is planned to be the primary outcome in a subsequent cluster randomized trial and therefore of major interest in this pilot study, will be given. Only questionnaires with at least 6 out of 7 answered items will be considered. Missing items will not be imputed. Questionnaires with less than 6 answered items will not be considered.

As a sensitivity analysis, missing values of the PDI-G will be replaced on item level using multiple imputation based on predictive mean matching using the variables age, sex, center, and pain intensity at baseline as potential predictors. Missing scores and differences can then be calculated using the imputed items. Furthermore, a best- and worst-case scenario will be looked at, where missing values will be imputed by the highest and lowest observed value for T0 and T1 in the best case scenario and vice versa in the worst case scenario (lowest and highest observed value for T0 and T1, respectively). As another sensitivity analysis, a mixed linear regression model for the dependent variable PDI-G score at T1 will be performed including age, sex, and PDI-G at T0 as fixed effects and center as random effect. Descriptive analysis at item level and for the total number of pain-related patients at T0 and T1 will be done. Descriptive analysis of the item and score level will be done for all remaining secondary outcomes. For differences in scores between baseline and follow-up, 95% CIs will be reported. Missing values for secondary outcomes will not be imputed.

No sample size calculation was performed, as the main purpose of the pilot study is to investigate feasibility of the applied interventions and study procedures. Considering the exploratory nature of the pilot study, and based on experiences from previously conducted research, a total of 50 patients is considered sufficient to provide an initial estimate of the potential effect of the intervention measured by the PDI-G percent change from baseline to T1 (T0-T1), which is the key secondary endpoint. Assuming a SD of 13.7 and 15.4 score points [34] corresponding to a SD of 19.6% and 22% score points respectively, a sample size of 50 patients and a 2-sided 95% CI would yield the following: assumed SD 19.6: [x-5.6, x+5.6]; assumed SD 22: [x-6.3, x+6.3], where x is the point estimate of the PDI-G percent change from baseline to T1 (T0-T1).

Analysis of Process Evaluation Data

Analysis of the qualitative data collected in the process evaluation will use an inductive approach based on the themes covered in the interview guide (including unintended effects). Data management will be done in MAXQDA (Verbi Software). Written surveys will be conducted digitally through the survey tool Lime Survey hosted on secure servers of the Heidelberg University. All quantitative survey data and data from free text fields will be analyzed descriptively using SPSS and visualized in Excel (Microsoft). In addition, data entered by the practice teams into the CareCockpit software to document activities performed during the study appointments will be transferred to the study center and analyzed within the scope of the process evaluation. All data will be deidentified before analysis. All data generated in the process evaluation will be triangulated for classification of intervention and program feasibility. Final assessment of feasibility will be performed by 2 researchers in a consensus process.

Ethical Considerations

The pilot study in RELIEF received ethics approval from the Ethics Committee of the Medical Faculty at University Heidelberg, Germany (S-329/2024; June 05, 2024) and the state medical association of Baden-Württemberg (B-F-2024-057; July 02, 2024). The study will be conducted in accordance with the Declaration of Helsinki. All participants will give written consent before participation.

Results

The recruitment for this pilot study started in October 2024 and was open until end of December 2024. The targeted sample size was 6 practices and 50 patients. The intervention period began in February 2025 and will run until June 2025. Findings are expected to provide an indication of potential patient benefits as well as feasibility of the interventions and study procedures. First evaluation results regarding potentially necessary adaptations of intervention components and study procedures are expected to be available in July 2025. Publication of findings and necessary adaptations are expected for the second and third quarters in 2025.

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Discussion

Principal Findings

Findings in this exploratory pilot study will provide a clear indication regarding intervention feasibility and applied study procedures. It is expected that eligible patients will benefit from the intervention and that improved medication management and intensified use of nonpharmacological treatment strategies will result in a reduction of pain-related disabilities and other patient-reported outcomes. Potentially necessary adaptations of intervention components and study procedures will be finalized before testing the intervention in a randomized controlled trial which is planned to begin late in 2025. The evidence base regarding the chosen combination of intervention measures for patients with CNCP in German primary care is still limited. The expected effects appear to be plausible; however, they are not certain, so this pilot study can provide an important contribution.

The common belief that pain is a normal part of aging may explain why chronic pain is often underestimated and underreported [35]. Studies found that older adults tend to adopt a stoic attitude toward experiencing pain and prefer to use self-reliance–based coping strategies, though these may not always be effective [35,36]. A study in Italy explored coping strategies used by older adults to manage chronic pain and found that frequently coping self-statements, resting, task persistence, and guarding were described, while the least used strategies were relaxation and exercise or stretching [37]. The latter are clearly recommended in German guidelines [9]. Other studies also explored life experiences and needs of older adults with chronic pain and strategies they use to cope with and manage pain [38,39] or aimed to promote effective and tailored pain self-management interventions [36,40]. The RELIEF case management program contains innovative elements: GPs, MAs, and patients may benefit from the more structured care processes and patient activation which in turn can provide room and time for open discussion with patients on their needs. Meticulously obtained pain history for example, provides important information for pain assessment regarding onset and course, pain episodes, quality, intensity, activity impairment, and any stress factors in a patient's personal life [41]. Some elements of the innovative program can be assigned to medical assistants, for example reflecting on the educational material or setting individual treatment targets with patients. Thus, MA will be more involved in CNCP care than usual, which may increase their competences, strengthen their role in the care process, and support sharing of the workload in team-based care [42].

Educational components will be used as an explicit treatment strategy anchored directly in the general practice setting. Care programs for disease management usually offer patient education outside of the GP practice which has the disadvantage of GPs being unfamiliar with the presented content which makes it difficult to refer to and pick it up in the course of treatment [9]. Combining therapies with delivering content remotely through the internet or mobile devices is increasingly used to promote and improve self-management of chronic conditions. And complement face-to-face pain treatments [43]. On the other hand, some elements of the RELIEF program may cause additional burden: patients will be asked to provide detailed information about their pain history, mental condition and personal goals and receive comprehensive information about chronic pain. This may provoke adverse effects such as negative, stressful emotions, yet also has the potential for reflection about perhaps still unused self-care potential and possible behavior adaptation. Participation in the case management program will require additional appointments and therefore be associated with an additional time burden for patients and practice teams alike. This pilot study will assess thoroughly whether the assumed effect mechanisms are plausible and whether the potential benefits outweigh potential harms.

Strengths and Limitations

This study is a single-arm exploratory pilot study which leaves room for bias. Primary and secondary outcomes are based on self-reported data. In the multifaceted program, the potential impact of the various components might be difficult to separate. Strong aspects will be the program's closeness to daily practice and the exploration of implementation outcomes in the accompanying process evaluation which adds value to this study. The analysis of components of the complex implementation program using predefined feasibility indicators contributes to the transparency of the implementation program.

Dissemination Plan

After completing this feasibility study, findings will be disseminated through oral and poster presentations at scientific conferences as well as in a scientific article in a peer-reviewed journal.

Conclusion

This study will provide valuable information regarding potentially necessary adaptations before applying the intervention in a confirmatory cluster randomized controlled trial.

Acknowledgments

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Data Availability

In line with the obtained ethics approval, all data sets that will be generated and analyzed during this pilot study and the process evaluation will not be publicly available due to data protection laws. They will be stored on secure servers at the Department of Primary Care and Health Services Research, University Hospital Heidelberg. Deidentified sets of these data can be made available by the corresponding author on reasonable request.

Authors' Contributions

RPD, CS, and SB designed this pilot study and the intervention components and drafted and revised this study protocol. AB provided expertise on statistical analysis and critically revised the manuscript. CS and RPD shared the project management. All authors provided input and critical feedback and approved the final version of the manuscript.

Conflicts of Interest

The principal investigator CS is member of the guideline commission of the German Society of General Practice and Family Medicine (DEGAM). SB is a doctoral candidate in RELIEF. All authors declare no conflict of interest.

Multimedia Appendix 1
SPIRIT checklist.
[PDF File (Adobe PDF File), 190 KB - resprot_v14i1e66335_app1.pdf]

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Abbreviations

CNCP: chronic noncancer pain
CONSORT: Consolidated Standards of Reporting Trials
EUROPEP: European Project on Patient Evaluation of General Practice Care
GP: general practitioner
LONTS: German guideline for long-term use of opioids in chronic noncancer pain
MA: medical assistant
NSAID: nonsteroidal anti-inflammatory drug
PDI-G: Pain Disability Index German version
RELIEF: resource-oriented case management to implement recommendations for patients with chronic pain and frequent use of analgesics in general practices

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Protocol

Diabetic Retinopathy Screening Among at Risk Populations: Protocol for Distributional Cost-Effectiveness Analysis

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Abstract

Background: Diabetic retinopathy (DR) remains the primary vision complication of diabetes and the leading cause of blindness among adults, with up to 30% prevalence among low-income populations. Tele-retina is a cost-effective screening alternative to vision loss prevention, yet there is an adverse association between screening and income. Intersectionality theory notes that barriers to achieving health equity result from the intersection of personal and social characteristics. Experiences at this intersection are influenced by interpersonal and structural systems of oppression. Studies have found that tele-retina is the preferred strategy over standard of care screening for at-risk populations. No study has assessed the economic equity impact of DR screening using a theoretical foundation.

Objective: This study aims to address shortcomings related to the utilization of intersectionality theory in the economic evaluation of DR screening. We propose conducting a distributional cost-effectiveness analysis (DCEA) of the tele-retina program.

Methods: The study will be undertaken using a deductive theoretical drive sequential multimethod approach, consisting of two studies: (1) a modified Delphi study and (2) DCEA. The Delphi panel (patient partners, field experts, and decision makers; N=35-50) will select the social constructs (eg, age, gender) for at-risk populations and potential trade-offs between health maximization and equity. The research will be guided by a social theory framework (intersectionality theory) to understand the impact of social constructs on economic outcomes. Social constructs that are selected by the Delphi panel will be integrated into the validated tele-retina cost-effectiveness analysis model, which will serve as a case study for DCEA.

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Results: We have submitted the research ethics board application to the University Health Network Research Ethics Board and are expecting to begin recruitment for the Delphi study in Spring 2025. We anticipate beginning work on the model in the summer of 2025 and completing it by early 2026.

Conclusions: The Delphi study will provide an understanding of which social factors are deemed necessary by the stakeholders for guiding the inequity in care access. Study results will offer information related to the net health benefit of the intervention and the health equity impact of the tele-retina program, hence providing a more comprehensive valuation of the tele-retina program, which is informative to policy makers and governments whose goal is to mitigate the drivers of health inequities. We anticipate that each of these drivers will raise important questions regarding the implications for decision-making that may have not yet been addressed by Canadian health technology assessment bodies, such as the Canada Drug Agency. This is the first Canadian study to (1) have social constructs for DCEA selected by the Delphi panel, (2) mainstream how health equity framework and social constructs are used in economic assessment, (3) improve DR screening programs by using health equity lens, and (4) scale and adopt "de-novo" integration of social constructs in economic models for program evaluation.

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KEYWORDS

diabetic retinopathy; equity of care; distributional cost-effectiveness analysis; health equity; health care disparities; intersectionality; telehealth; telemedicine; retinopathy screening

Introduction

Social and Economic Impacts of Diabetes

Every 3 minutes, someone in Canada is diagnosed with diabetes, while 11 million are living with diabetes or prediabetes [1]. About 6.1% of Canadian adults aged 20-79 years have prediabetes, putting them at high risk of developing type 2 diabetes [1]. The prevalence of diabetes is expected to increase to 5 million (12.1%) by 2025 [1]. Ontario has more people living with diabetes than anywhere else in the country. Rates of type 1 and type 2 diabetes have increased by 42% since 2009 [1]. There are now an estimated 4,424,000 people with diabetes or prediabetes in Ontario [1]. Diabetes Canada states that the costs of treating diabetes have surpassed CAN $30 billion [2] (a currency exchange rate of US $0.70). Goeree et al [3] have estimated that the excess attributable cost per incident case per person of diabetes in Ontario is CAN ~$2930 in the first year after diagnosis and CAN $1240 in the following years [3]. In Canada, diabetes disproportionately impacts First Nations and Métis people, and people of African, East Asian, and South Asian ethnic backgrounds, who experience higher rates of type 2 diabetes compared to the general population [4]. Inequities in the social determinants of health (eg, income, education, and housing), resulting from the impacts of systemic racism, intergenerational trauma, and colonization, are associated with higher rates of type 2 and gestational diabetes in priority populations [4].

Equity in Health Service Delivery and Intersectionality Framework

Health equity is created when individuals have a fair opportunity to reach their fullest health potential. It is directly correlated with the distribution of resources within any setting [5]. Low socioeconomic groups with multiple health conditions and limited access to resources have decreased access to achieving health equity [5]. Intersectionality (Figure 1) is a theoretical framework in which consideration of heterogeneity across different intersections of social positions is critical to the conceptualization of health and social experiences [6]. The framework was published by Crenshaw [7] and developed within Black feminist theory to better explicate the situation of Black women in the United States [8]. It encompasses a wide range of intersections of ethnoracial groups, gender, socioeconomic status, sexual orientation, and other social identities and positions [7]. The framework notes that social positions exist on a hierarchy of social power and are not independent [7] but rather that they shape human experience jointly. As social positions intersect at the individual level (eg, income, age, and rurality), experiences at those intersections are influenced by larger interpersonal and structural systems of oppression, such as racism and sexism [9]. The synergies of oppression are created through the intersections of three domains: (1) socioeconomic status (ie, income), (2) identity-isms (eg, race), and (3) geography (segregation). Intersectionality in this conceptual framing (Figure 1) is an intersectional categorical axis where social determinants of health, systems of oppression, and environmental factors are integrated and three categories or framings within the context of the synergy of oppressions, specifically the outcomes of increased marginalization through oppressions and intersections of social determinants of health. This synergy is further compounded with access to health equity [7-9].

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Figure 1. Intersectionality or synergies of oppression. SDH: social determinants of health.

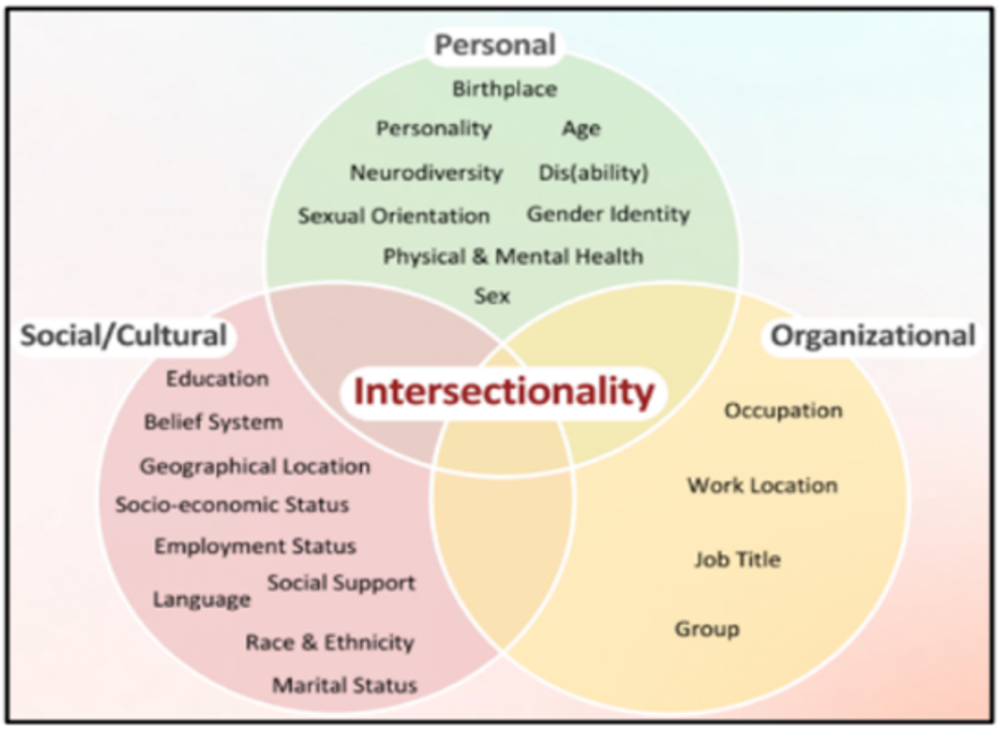

Social and Economic Impacts of Diabetic Retinopathy and Screening

Diabetic retinopathy (DR) is the primary vision complication caused by diabetes [10] and is the leading cause of new cases of blindness in adults aged 20-65 years [11], yet it is often asymptomatic in the initial stages [12]. The prevalence of DR in Canada ranges from 20% to 30% [12]. In 2016, more than a million Ontarians were affected by DR [6]. The prevalence of vision loss in Canada is expected to increase by nearly 30% in the next decade [13]. Lower income and type 2 diabetes are associated with increased odds of visual impairment [14]. In 2007, the cost of vision loss in Canada was estimated at CAN $15.8 billion and is projected to grow to CAN $30.3 billion by 2032 [12]. In addition to these costs, the Canadian National Institute for Blindness estimated the cost of associated complications of vision loss: falls CAN $25.8 million, depression CAN $175.2 million, hip fractures CAN $101.7 million, and nursing home admissions CAN $713.6 million [12]. Early detection ensures that treatment or intervention can decrease the incidence of vision impairment or blindness. Evidence notes that one-third of adult patients with diabetes did not receive an eye examination for DR within 2 years [6], and more specifically, 25.3% of people with diabetes over 60 years had not seen an eye care provider in the last year [12]. Tele-retina is one of the DR screening modalities that can be used to bring the testing to community settings. It is focused on reducing eye care disparities that lead to avoidable vision loss. Tele-retina is a branch of telemedicine that delivers eye care remotely. Retinal images and data are collected and transferred via telecommunication technology to eye specialists [15]. Previous research has noted that it is a more cost-effective alternative than the standard screening in detecting DR among lower-income individuals with limited access to eye care [15]. Specifically, the cost per case correctly detected was CAN $281.10 with tele-retina and CAN $982 with the standard of care (SOC) screening (note, the standard of care screening for DR entails walking into an optometrist or ophthalmologist office to get the eyes checked), and the cost per case correctly diagnosed was CAN $82.21 and CAN $314.14, respectively. For both pilot and pan-Ontarian sensitivity analyses, tele-retina remained the dominant strategy (ICER <0). Unfortunately, screening rates among at-risk populations remain below 60% [12,15].

For DR screening, we know that socioeconomic status is the primary driver of risk for DR screening and that systemic societal barriers, for example, ageism, racism, and sexism [7,8], have had a detrimental impact on eye health and vision. Lack of education or information, social role and identity, competing priorities (getting time off work or study to attend appointments), language barriers, and lack of family and clinical support [9,10] are noted by patients as barriers associated with access to DR screening.

Differential access to retinopathy screening was evident when we evaluated the designed tele-retina model of DR screening. We found that only 50% of low-income individuals living with diabetes with limited access to vision care would get screened through SOC screening (walking into an optometrist or ophthalmologist office to get their eyes checked, which may be even more challenging in remote and rural areas), whereas 80% of the same population would get screened with the tele-retina program [11]. Screening percentage was the major driver of tele-retina's economic dominance. This further suggests the need to elucidate social factors associated with the inequity of screening, as ignorance of these remains a major factor in perpetuating lack of access to equitable care.

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Overall Objective

In collaboration with patient partners, the primary objective of this project is to assess the equity impacts of tele-retina screening in populations that experience systemic social and economic disadvantages with limited access to conventional eye care.

More specifically, we will:

- Create an inventory of social constructs that could be used in subsequent (economic) analysis when tackling inequity in the health care setting
- Apply a novel methodological theoretically guided framework for undertaking a distributional cost-effectiveness analysis (DCEA) to combine the objectives of maximizing health and minimizing unfair variation in health when evaluating population health interventions using a case study of DR screening

Understanding the equity impact of the tele-retina program will contribute to the creation of socially and culturally acceptable economic milieu in line with the multicultural Canadian context, with the ultimate purpose of improving the screening rate for DR, augmenting the quality and access to DR care, and decreasing the incidence of severe vision loss ultimately leading to blindness.

Methods

Study Design

This study will build on our current intersectionality work for DR screening access among those who identify as women of low socioeconomic status [16]. Meanwhile, combining the advantages of multiple designs and enabling a comprehensive understanding of social complexities related to the implementation context, we propose the deductive theoretical drive sequential multimethod approach. Multimethod design entails conducting two or more research methods rigorously and completely in one project, where the major research question drives the study, but the approach consists of 2 interrelated studies. The deductive theory-driven approach indicates that we begin with an (intersectionality) theory, develop a hypothesis from that theory, and then collect and analyze data to test our hypotheses. The sequential approach indicates quanàQUAN, encompassing two quantitative methods used sequentially, one of which is dominant (in capital letters) [17,18]. The two components of this study are (1) modified Delphi and (2) DCEA study. Once the first project (modified Delphi) is completed, we will use the results to provide details for the DCEA (Figure 2).

Figure 2. Illustration of the study design.

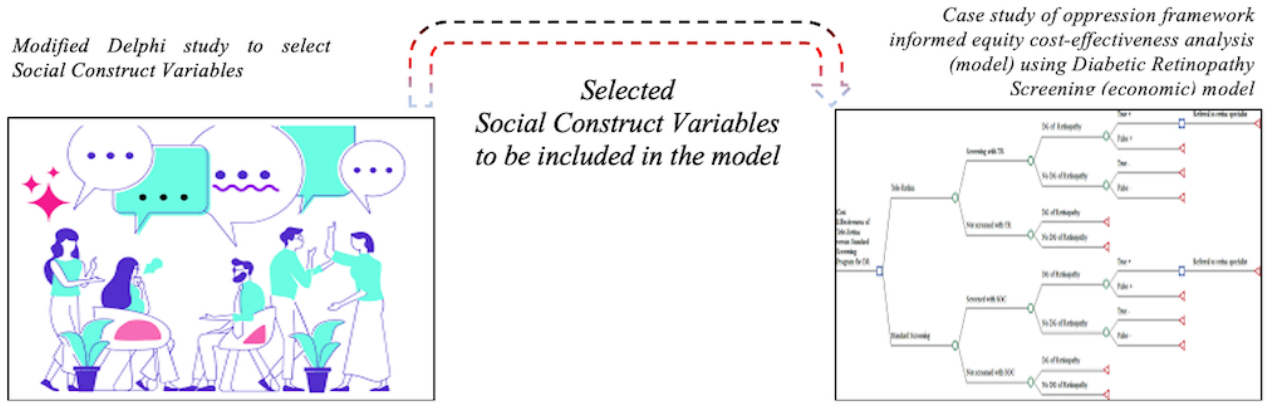

Stage 1: Modified Delphi

In the modified Delphi, we are seeking the opinion of participants as to whether social constructs may dictate one's health (seeking) behavior. The Delphi will guide us in developing the set of social construct variables to be integrated into the tele-retina screening economic model. We anticipate 35-50 participants (patient representatives: n=20-25; field experts, including in health technology assessment [HTA], and clinicians: n=5-10; decision and policy makers: n=10-15) who will be purposely selected based on experience, training, and specialized areas of knowledge (Table 1). Please note that there is no standard size of the Delphi panel members, and it varies from 10 to 1000 (typically between 10-100) in published studies. However, due to data management difficulties and logistic issues (rounds of the survey), a panel with a 3-digit sample size is unusual [1,2]. Generally, a double-digit number close to 30-50 is considered optimal in concluding rounds for a homogenous Delphi [3,4]. Appropriate size depends on the complexity of the problem, homogeneity (or heterogeneity) of the panel, and availability of the resources. Apart from panel members with knowledge, some studies recruit members from diverse academic and practice backgrounds or involve end users in the process [5]. Delphi participants are all members of the Diabetes Action Canada (DAC) Network. Potential participants, who will be invited via Network email to participate [19], will consist of patient partners, researchers, diabetes specialists, primary care practitioners, nurses, pharmacists, data specialists, and health policy experts committed to improving the lives of persons with diabetes. The team has successfully partnered and collaborated with DAC to plan, execute, and evaluate research projects to improve patient outcomes and experiences [20]. Before joining the Delphi panel, each participant will be approached by a qualitative researcher and study lead to sign a consent form.

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Table 1. Modified Delphi general categories of expertise.

General categories of expertise	Experts, n
Patient representatives	20-25
Field experts, including in health technology assessment, and clinicians	5-10
Decision and policy makers	10-15

Below is a summary of the modified Delphi, as it is a well-established approach to answering a research question by identifying a consensus view across subject experts.

Approach to Analysis

Overview

Social construct selection (income, education, area-level deprivation, ethnicity, area-level ethnic diversity, sex, and gender) is guided by the constructs' baseline distribution and will be presented to the Delphi participants by patient partners and qualitative researchers. The baseline distribution informs on one's physical, mental, and emotional health. It is shaped by one's medical, social, and family history, and is continuously influenced by factors affecting everyday life factors [17,18,21]. Relevant population characteristics include dimensions of direct equity concern (eg, income, area-level deprivation, and ethnicity or area-level ethnic diversity) and characteristics that are necessary to estimate expected costs and effects and generate further equity concern (eg, sex and gender) [17,18,20,21]. We will undertake a 2-round process to assess the importance of each variable (social construct) on a 0-5 Likert scale (not at all important, low importance, neutral, moderately important, and very important) [22].

Area-Level Deprivation

The construct allows for rankings of neighborhoods by a socioeconomic disadvantage in a region of interest (eg, at the state or national level). It includes factors for the theoretical domains of income, education, employment, and housing quality.

Area-Level Ethnic Diversity

Based on the Statistics Canada census the diversity index is a measure of the racial and ethnic diversity of residents based on 7 major racial and ethnic or political groups (Asian American, Black, Latinx, Pacific Islander, mixed or other race, Native American, and White) identified by the census. The value of the area-level ethnic diversity ranges from 0 to 0.93. A diversity index of 0 means that every person in the area belongs to the same ethnic group. The highest possible index of 0.93 (based on the current census) corresponds to a perfect mixture of ethnic groups, with an equal proportion of each ethnic group in the region.

Round 1

At a workshop, information about variables will be presented to panelists, and subsequently, the panel will answer the Delphi questionnaire (Multimedia Appendix 1). Questionnaire responses will be entered into Microsoft Excel; frequencies will be calculated; and after Round 1, a summary report will be prepared. The report will be distributed to panel members. The need for further consideration of each social construct will be reviewed and confirmed through discussion at the meeting.

Round 2

The Delphi web-based questionnaire will be submitted 4 weeks following the workshop. The median score and range will be estimated for Likert scale questions per guidelines [22]. A proportion of 70% or higher viewing each domain and topic as "moderately important" versus "highly important" will be considered as an indication of the stability of participants' consensus concerning face validity [22]. SAS 9.4 (SAS Institute) will be used to analyze the data.

Case Study of Oppression Framework–Informed Equity Cost-Effectiveness Analysis

Once Delphi participants have selected the most relevant social constructs or variables to be included in the distributional cost-effectiveness model, we will rank them and select the 5 social constructs with the highest ranking to be considered for inclusion in the model.

In the following, the modified Love-Koh et al [19] and Asaria et al [23,24] approaches (stages A and B as described in detail below), directed by a senior health economist, will evaluate which DR screening intervention has the best "social value" based on selected social constructs in the modified Delphi, as these are deemed important to the participants in health care resource allocation. We will investigate how these fit with the implicit value judgments inherent in the original cost-per-quality-adjusted life years model formulation of the tele-retina screening program. Note that quality-adjusted life years are a measure of disease burden, including both the quality and the quantity of life lived [25]. The case study is based on the Toronto tele-retina screening program offered in partnership with 7 primary care organizations with a population focus on those located in low-income urban and rural communities with a high prevalence of diabetes and low DR screening rates, with more details described in Figure 3 [15]. The Toronto tele-retina model was selected because it is a validated economic model but does not provide information on equity in the distribution of costs and effects. Please note that the case study population includes individuals residing in Ontario who are unable to obtain government insurance coverage (non–Ontario Health Insurance Plan [OHIP]–insured patients), including those residing illegally, those new to Canada awaiting coverage, and those so marginalized that they may struggle to obtain the identification and home address required to receive OHIP.

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Figure 3. Decision tree of tele-retina versus standard of care screening (SOC) for diabetic retinopathy (DR). Decision tree illustrating the possible consequences, the chance of event outcomes, resource costs, and utility of using tele-retina (TR) versus in-person standard of care screening to measure diabetic retinopathy [15].

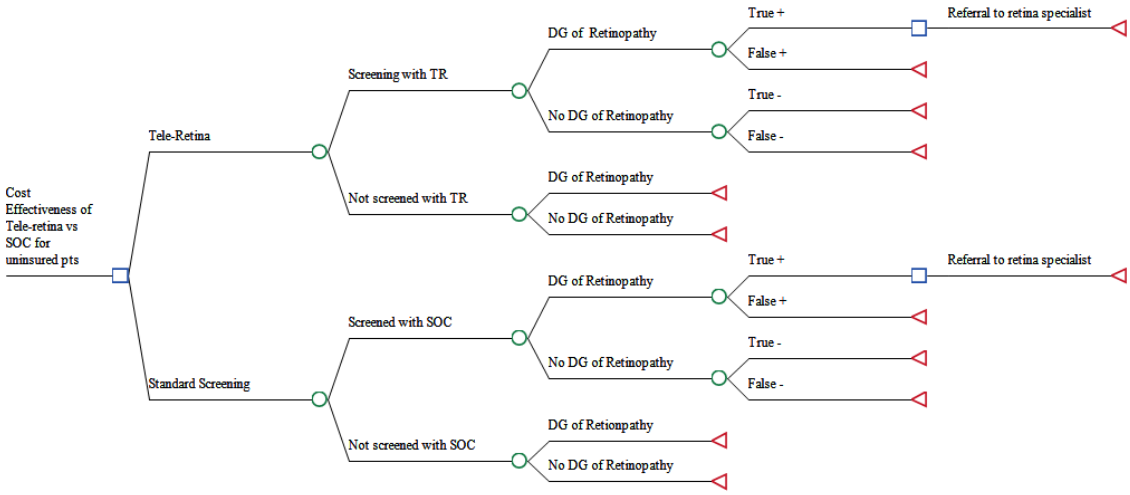

Distributional Cost-Effectiveness Analysis

Stage A: Model Social Distributions of Health

Estimating the Baseline Health Distribution

We will describe the baseline distribution of health among the study population (length and health-related quality of life). Baseline distribution will need to include the full general population and not just the population receiving the intervention (tele-retina and SOC). This is important for 2 reasons. First, the general population is typically the relevant population for characterizing policy concerns with health inequality. Second, within a national, budget-constrained system, additional resources used by recipients of the intervention may displace activities that could have been provided to anyone within the full general population. This baseline distribution of health will describe variation in health among multiple different subgroups in the population as defined by relevant population characteristics, allowing for a correlation structure among these various characteristics. The relevant population characteristics include not only dimensions of direct equity concern (eg, income and ethnicity) but also characteristics necessary to estimate expected outcomes and costs that may generate further equity concern (eg, sex, gender). In consultation with the senior health economist, we will select the most appropriate health metrics ensuring that they are measured on an interpersonally comparable ratio scale suitable for use within a cost-effectiveness analysis [24] and their data availability. To obtain health metrics, we will consult with data from published literature based on individual studies, a systematic review to pool the data, published literature dealing with administrative data, and access to DR screening data from the Alliance for Healthier Communities, which includes data on uninsured patients.

Estimate the Distribution of Health Changes Due to the Interventions

To evaluate changes in the baseline health distribution that could be attributed to the use of alternative interventions, it is necessary to know how the outcomes and costs of the intervention differ between the relevant subgroups, and how the opportunity costs of any change in resource use differ by those same subgroups. After we estimate a baseline health distribution, we will model how this health distribution is affected by the tele-retina screening program and alternative ways of promoting increased uptake of the tele-retina screening. We do this by using an existing cost-effectiveness analysis Toronto tele-retina screening model [15] for the DR screening (Figure 3) that simulates the natural history of the disease and the impact of screening. The model compares in-person examination for DR screening (SOC) versus the tele-retina program [15]. The model has been conceptualized for patients residing in neighborhoods with limited access to ophthalmologists and optometrists at high risk for diagnosis of DR. The SOC is a fundus examination with pupil dilation performed by a primary eye care specialist (optometrist or ophthalmologist). Patients with positive results would be referred to a retina specialist, as coordinated by the primary care provider for comprehensive eye examination with angiography and optical coherence tomography. The model (Figure 3) illustrates pathways of care, possible consequences, chance of event outcomes, resource costs, and utility of using tele-retina versus in-person SOC to measure DR. The published tele-retina model ends with severe vision loss following screening alternatives. However, we have conceptualized and presented to the decision-making organization a complete model containing treatment effects. We will use the model with treatment effects for the case study.

We note that there are parameters in the model that can vary, including the following:

1. Disease prevalence, severity, mortality rate, and natural history: We assume in our case study that DR-specific parameters may be constant across our population subgroups (may need to confirm with expert)
2. Uptake of the intervention: The impact of DR screening uptake by subgroup is the key difference between the various implementations of the screening program's success. We will estimate this parameter for each subgroup.

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3. Direct costs associated with the intervention: We assume the direct costs related to treating a given stage of DR do not vary by subgroup (although the chance of incurring these costs and the screening-related costs by subgroup may vary under the different implementations of the screening program). This seems to be a plausible assumption without more detailed cost data at the subgroup level.
4. Opportunity costs from displaced activities: We assume that opportunity costs in the base case analysis are shared equally among all population subgroups; this assumption may be explored in sensitivity analyses.
5. Other-cause mortality: The mortality rates may vary by subgroup in the same way as discussed when deriving the baseline health distribution. In calculating these rates, we remove diabetic-specific mortality (assuming this is constant across subgroups) and apply this separately in the model.

Adjusting for Social Value Judgments About Fair and Unfair Sources of Inequality

The distributions of health estimated thus far would represent all variations in health in the population. We may perceive that some variation in health seems "fair," or at least "not unfair," perhaps because it is due to individual choice or unavoidable bad luck. Then, before measuring the level of inequality, we will first adjust the health distributions to only include health variation deemed "unfair." We need to make social value judgments about whether health variation associated with each of the population characteristics is deemed fair. We will adjust our modeled health distributions for this value judgment by using the direct standardization method [26].

Stage B: Evaluating Social Distributions of Health

Once we have estimated the appropriate health distributions, we can characterize the distributions in terms of the twin policy goals of improving total health and reducing health inequality.

Comparing Interventions in Terms of Total Health and Unfair Health Inequality

We will use a specific index to compare the interventions in terms of total health and unfair health inequality. One useful piece of information for decision makers produced at this step of the analysis is the size of the health opportunity cost of choosing an intervention that reduces health inequality; this is simply the difference in total health between the intervention and a comparator. However, we can go further than that and provide information about the size of the reduction in health inequality in terms of the difference in one or more suitable inequality indices between the intervention and a comparator. The selection of appropriate inequality indices requires further value judgments about the nature of the inequality concern. There are a number of commonly used indices to measure inequality that can be broadly grouped into those measuring relative inequality (scale-invariant index) and those measuring absolute inequality (translation invariant). We can calculate the range of relative and absolute inequality measures for the quality-adjusted life expectancy distributions associated with our interventions. A higher value for each measure typically indicates a higher level of inequality between the healthiest and the least healthy. We will select the inequality measure in consultation with a senior health economist.

Ranking Interventions Using Dominance Rules Accounting for the Level of Inequality

To rank distributions based on mean health and the level of health inequality, we may use economic dominance rules provided by Atkinson [27] and Shorrocks. Dominance rules apply when mean health is higher and inequality is lower for almost any measure of inequality. Both rules are based on the Lorenz curve, which will be used to analyze relative inequality constructed for health distributions. We will do this by ordering the population from least healthy to most healthy and plotting the cumulative proportion of population health against the cumulative proportion of the population. Regarding Atkinson's theorem tests for Lorenz dominance between distributions, this means that the Lorenz curves for the distributions do not cross, and the more equal distribution has at least as much mean health as the less equal distribution. In other words, a distribution is dominated if it has higher inequality and the same or lower amount of mean health. On these criteria, the standard screening strategy is dominated by the targeted reminder. Shorrocks' theorem tests for generalized Lorenz dominance, wherein the Lorenz curve is multiplied by the mean health. We will consider that distribution is dominated if the generalized Lorenz curve [28] lies wholly below that of an alternative intervention. Under this criterion, the targeted and universal reminder strategies dominate the no-screening option. This leaves us to compare the universal reminder and targeted reminder strategies. However, if the generalized Lorenz curves for two distributions cross, we cannot use Shorrocks' theorem to rank the distribution and will use Atkinson's [27] theorem test for Lorenz dominance.

Analyzing Trade-Offs Between Total Health and Health Inequality Using Social Welfare Indices

We need to rank strategies to fully specify an underlying social welfare function. We will specify the nature of inequality aversion and the level (or value) of inequality. The inequality aversion parameters in these functions describe the trade-off between total health and health inequality (ie, the amount of total health that a decision maker would be willing to sacrifice to achieve an equal distribution). As inequality aversion parameters are difficult to interpret on a raw scale, we will use a more intuitive scale by combining a specific parameter value with a specific health distribution to derive the equally distributed equivalent (EDE) level of health. The difference between the mean level of health in that distribution and the EDE level of health represents the average amount of health per person that one would be willing to sacrifice to achieve full equality in health, given that specific value of inequality aversion. We will use two social welfare indices closely linked to the dominance rules applied above: the Atkinson index [27] to evaluate the distributions in terms of relative inequality and the Kolm index [29] to evaluate the distributions in terms of absolute inequality to estimate the EDE level of health for all strategies. We will visualize our findings using the equity-efficiency impact plane (Figure 4) [30].

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Figure 4. Equity-efficiency impact plane.

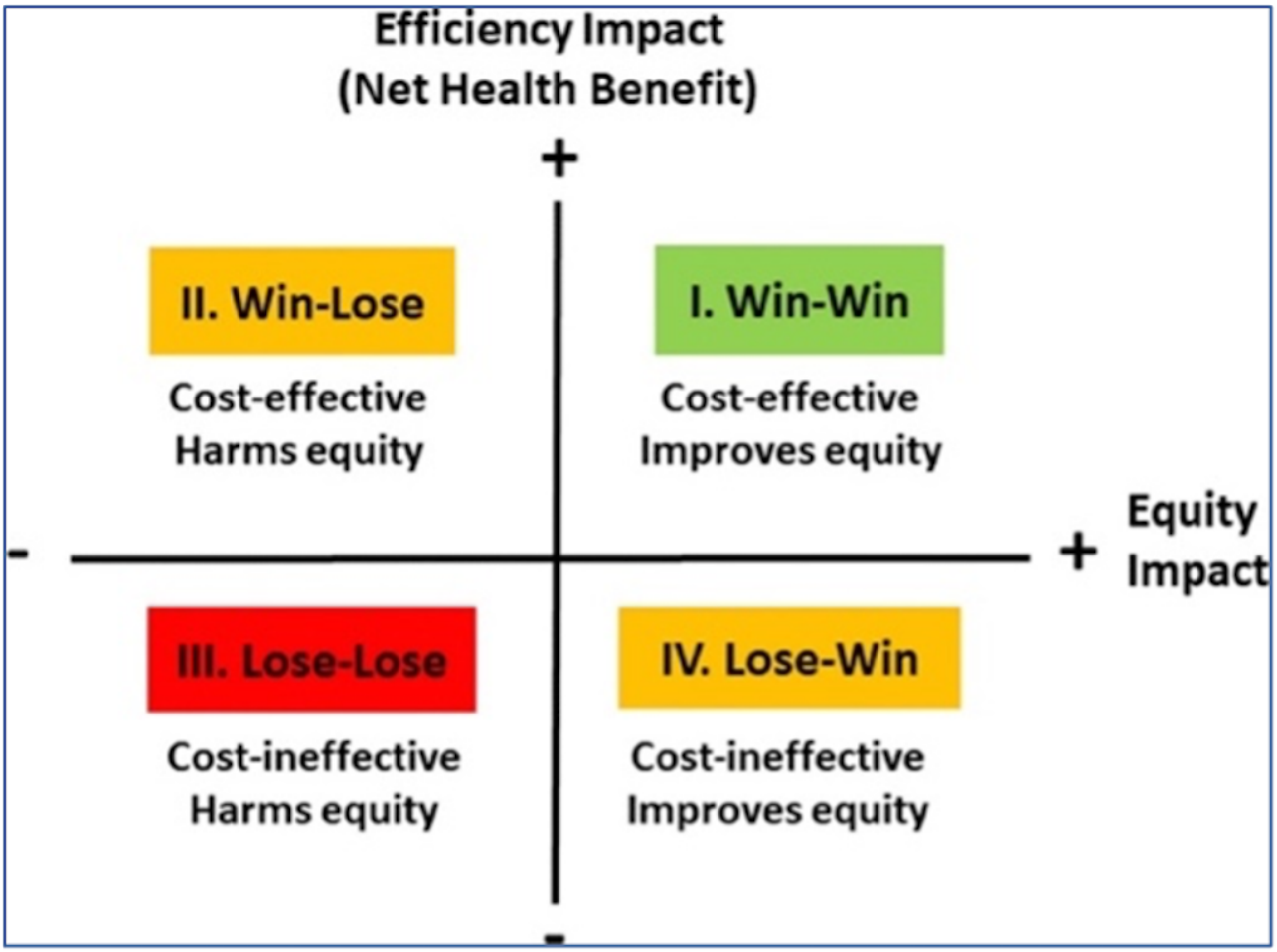

Sensitivity Analysis

We may run several sensitivity analyses to explore the impact of making alternative assumptions in our modeling on the choice of preferred strategy. We can explore (1) the impacts of alternative assumptions around the distribution of opportunity costs and (2) the impacts of alternative social value judgments about which inequalities are considered unfair.

Ethical Considerations

The study is under review (24-6035.0) by the University Health Network (UHN) Research Ethics Board (REB). Please note that in accordance with the UHN REB will report any protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REB, trial participants journals, and regulators). As indicated in the earlier section of the manuscript, before joining the Delphi panel, each participant will be approached by a qualitative researcher and study lead to sign an informed consent. Data in the Delphi study will be deidentified and individuals will be identified using a unique study ID. In the compensation process of patient partners, we follow the regulations and protocols of DAC.

Results

We have submitted the REB application to UHN REB and are expecting to begin recruitment for the Delphi study in the spring of 2025. We anticipate beginning work on the model in the summer of 2025 and completing it by early 2026.

Discussion

The Delphi study will offer insights into which social factors are perceived as necessary by the stakeholders for guiding the inequity in care access. We may input all social factors into the DCEA model or create distinctive context-dependent scenarios. The findings of this study will provide relevant information on the distribution of the patient population eligible for DR screening, the net health benefit of the intervention, and the health equity impact of DR screening. Applying the DCEA approach will reveal key social factors and drivers that undermine health equity. We anticipate that each of these drivers will raise important questions regarding the implications for decision-making that may have not yet been addressed by Canadian HTA bodies, such as the Canada Drug Agency. We will compare our findings with the relevant literature focused on DCEA.

Distributionally sensitive economic evaluations are expected to result in a more comprehensive valuation of interventions, which is informative to policy makers and governments whose goal is to mitigate health inequities. In our analysis, we will not only assume that all eligible patients receive treatment. This assumption may not hold true in clinical practice, as uptake varying across income quintiles has been observed across many

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interventions (eg, cancer screening and diabetes complications) [31]. Instead, we will create diverse scenarios where the screening uptake will vary from 25% to 100%. We will apply the "staircase of inequality," which is a framework used in DCEA to identify the stages of a health program where inequalities may result in costs and health effects varying between equity-relevant subgroups [32].

Our study has several limitations. The study is an illustrative example of applying a DCEA approach based on data available in published literature. Hence, the analysis may only offer a ballpark estimate of the size and direction of the impact on equity and societal welfare, which could be larger or smaller or in the other direction depending on the actual data.

We know that DCEAs are data intensive. This may result in relying on assumptions or a tendency to ignore gradients in model inputs to address data gaps, potentially resulting in uncertainty in the estimates. The introduction of additional analyses as standard practice into the evidence requirements of HTA bodies may increase the burden for those submitting and those appraising the evidence.

Conclusion

This protocol outlines a study designed to provide information on the inequality impacts of tele-retina screening programs in at-risk patient populations. Understanding the equity impact of the tele-retina program will inform decision makers and program administrators of what may be necessary for creating a contextually and culturally acceptable screening program in line with social context, with the ultimate purpose of improving the screening rate for DR and thus decreasing the incidence of severe vision loss for the at-risk populations. This will be the first study in collaboration with patient partners to mainstream how we assess the economic impact of screening programs and interventions with respect to inequality and access to care for women, people from lower socioeconomic groups, or people from certain cultures or racial backgrounds while remaining focused on economic analysis and the best use of care resources. The study has substantial external validity as the social construct-guided economic model (DCEA) can be applied across disciplines and domains and a range of care settings when evaluating large-scale public health programs that have an explicit goal of tackling health inequality. The "de-novo" integration of social constructs into economic models may be transferred to other screening programs (breast, colon, etc), care settings (primary, secondary, and tertiary), and models of care. We plan to expand this approach to different stroke initiatives.

Acknowledgments

This protocol would not have been possible without the support of Diabetes Action Canada.

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Data Availability

Data will be presented in the main manuscript.

Authors' Contributions

AS, TF, and VER have conceived the study design and will be heavily involved in data collection and analysis, interpretation of findings, and the broader discussion. JMB, SI, S Meera, S Mathew, and AP have participated in conceptualization of the study design and will be responsible for data collection, interpretation of findings, and the broader discussion. All authors contributed to the manuscript write-up.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Social construct variables to be presented to Delphi participants and relative and absolute indices.
[DOCX File , 16 KB - resprot_v14i1e60488_app1.docx]

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Abbreviations

CDA: Canada Drug Agency
DAC: Diabetes Action Canada
DCEA: distributional cost-effectiveness analysis
DR: diabetic retinopathy
EDE: equally distributed equivalent
HTA: health technology assessment
OHIP: Ontario Health Insurance Plan
REB: Research Ethics Board
SOC: standard of care
UHN: University Health Network

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Protocol

Acceptability of the Expert Standard for Oral Health Care in Older Adult Patients Among Nursing Staff in German Hospitals and Care Facilities: Protocol for a Cross-Sectional Study

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Abstract

Background: The aging population and increasing prevalence of natural teeth among older adults have escalated the demand for oral health care, especially in nursing settings. Impaired oral health in older individuals is closely linked to systemic conditions such as diabetes and cardiovascular diseases. The expert standard “promoting oral health in nursing” was developed in Germany to enhance the quality of oral care and address future challenges in geriatric nursing. It comprises a series of recommended interventions targeting oral health promotion in nursing care. However, significant barriers, including high patient-to-nurse ratios and staff shortages, often result in missed or rationed nursing care, limiting the feasibility and implementation of such interventions. Evaluating the acceptability of this standard is critical to its successful integration into routine nursing practice.

Objective: We aim to assess the acceptability of the expert standard among nursing staff providing care for older individuals, identify factors influencing its adoption, and examine the relationship between nursing competence, care rationed or missed (CROM), and the standard’s acceptability.

Methods: This quantitative cross-sectional study will collect data from nursing staff in 25 hospitals and long-term care facilities in North Rhine-Westphalia, Germany, using standardized survey instruments. Based on the template of the generic theoretical framework of acceptability, a questionnaire to measure the acceptability of interventions across 7 domains was created. Oral health knowledge will be assessed using the Oral Health Literacy Profile and competence in mouth care using the questionnaire developed by the DNQP (Deutsches Netzwerk für Qualitätsentwicklung in der Pflege [German network for Quality Development in Nursing]). Barriers to implementation will be evaluated according to the acute care nurses’ questionnaire on oral hygiene and CROM using the oral care–related question from the Basel Extent of Rationing of Nursing Care instrument. Statistical analyses consist of first calculating the mean acceptability with a 95% CI for each recommended intervention of the expert standard. Second, repeated measures ANOVA is used to examine mean differences in acceptability between these interventions. Third, linear regression analyses are used to test the impact of nursing competence on acceptability and lastly chi-square tests of independence are used to compare CROM with already published rates in German-speaking countries.

Results: The results are anticipated to provide insights into the acceptability of the expert standard and its determinants, including nursing competence and perceived barriers. Data collection will commence in June 2025 and is expected to be completed by October 2025.

Conclusions: This study evaluates the acceptability of the expert standard for oral health in nursing. The findings will support evidence-based strategies to enhance feasibility, reduce CROM prevalence, and improve oral health in older adults. By focusing on acceptability as a prerequisite for implementation, this study emphasizes the need to align interventions with the realities of nursing care to achieve effective outcomes.

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KEYWORDS

oral health; nursing standards; acceptability; competence; missed nursing care; health intervention feasibility; long-term care; interprofessional collaboration; implementation science

Introduction

Background

The ongoing demographic shift toward an older society presents growing challenges for health care systems [1,2]. Poor oral health in older adults is closely associated with systemic diseases, such as diabetes and cardiovascular disease, which require special attention [3,4]. Advances in dental prophylaxis have significantly reduced edentulism among older adults, leading to a new generation of toothed care recipients [1]. The combination of a growing older adult population and more natural teeth leads to increased demand for oral health interventions and associated nursing care. This progress highlights the increasing complexity and cost intensity of dental care, requiring greater attention and resources.

In response to these challenges, an interdisciplinary group of dentists and nurses in Germany established evidence-based interventions aimed at improving oral health in nursing care [5,6]. The resulting consensus-based expert standard, "promoting oral health in nursing," aims to improve the quality of oral care and overall health while addressing the future challenges of nursing care. There is evidence that the use of care standards can lead to improved quality in the care of older people [7]. However, significant barriers arise from the workload of nursing staff, making the effective execution of additional measures challenging [8-12].

Current studies highlight the strain on nursing personnel caused by high patient-to-nurse ratios. Time constraints and staff shortages often lead to care rationed or missed (CROM) [8-12].

For example, in cross-sectional studies, 31% of nurses in Austrian hospitals [13], 35% in German hospitals [12], and 22% in Swiss long-term care facilities [11] reported that they had omitted oral care within the last 14 or 7 days, respectively, at least sometimes or frequently, according to a Likert-type rating scale. According to Schubert et al [10], there is no universal intervention that can reduce the CROM for all care procedures. They have found evidence that interventions can help to reduce the CROM in selected measures only [10]. These findings underscore the urgent need to consider CROM phenomena when establishing new standards.

Ensuring the feasibility of interventions under current working conditions is critical, as even the best-designed standards are ineffective if they are not adopted or executed. According to Proctor et al [14] and Skivington et al [15], acceptability is a key prerequisite for feasibility and should, as recommended by the UK Medical Research Council (MRC), be assessed prospectively. Mirbeth [16] found initial evidence that acceptance is crucial for sustaining expert standards. Acceptability of future interventions and also acceptance of interventions that have already been implemented determine whether nursing staff will adopt and apply an intervention.

Assessing the acceptance of the expert standard is therefore of central importance, particularly in the context of overburdened nursing staff [17,18].

The expert standard for oral health has been pilot-implemented in 18 stationary facilities in Germany. Nine residential long-term care facilities and 9 hospitals with capacities ranging from 275 to 3000 beds were examined; further, 8 outpatient care services were included [6]. However, 5 facilities discontinued the implementation at an early stage, with reasons cited as challenges such as staffing shortages due to the COVID-19 pandemic, high staff turnover, and temporary staff absences [6].

Following a 6- to 8-week period of implementation of the interventions, a self-administered evaluation was conducted in each facility, in which patient medical record analyses revealed that assessments of oral health by nursing staff were infrequent, particularly in residential long-term care facilities (73%) and hospitals (79%), compared to outpatient care (94%) [6].

Preliminary audit findings of the implementation process highlight the need for further research to enable a comprehensive evaluation of the implementation process, to understand how the standard is received by nursing staff, and to identify factors that influence implementation [5].

The audit results also indicate that acceptance is generally rated as satisfactory; however, significant differences exist across various care settings [6]. While some facilities successfully completed the implementation, others had to discontinue it prematurely. This highlights the variability in acceptance and implementation, which is influenced by factors such as the type of facility, available resources, and the specific patient population [6]. Such differences in acceptance and implementation effectiveness suggest that further research is necessary to understand the reasons behind these disparities and to develop strategies for overcoming them.

The Expert Standard for "Oral Health in Nursing"

This expert standard, "promoting oral health in nursing," was created by an interprofessional team of experts, comprising professionals from nursing, dentistry, and self-help organizations, to enhance oral health, particularly for older adult care–dependent individuals. Based on a systematic literature research, the group formulated consensus-based and practical recommendations [5].

The expert standard is conceptualized as a multicomponent intervention, comprising a set of distinct recommended interventions to be anchored in nursing practice. Each

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intervention is associated with a specific domain of action defined by the standard and should be assessed for its acceptability and feasibility before implementation [6,15].

These recommended interventions are as follows:

1. Standardized oral care procedure: regular oral care constitutes a pivotal measure for the promotion of oral health. It encompasses cleaning rituals twice a day, including tooth brushing, the use of toothbrushes, interdental cleaning tools, and mouthwashes, as well as the cleaning of dentures. Nurses bear the responsibility of implementing or providing assistance with these measures, particularly for patients who are incapable of performing them independently. The objective of regular oral care is to prevent the accumulation of plaque and the development of caries, thereby reducing the risk of infections.
2. Systematic assessment of oral health: it is recommended that systematic screenings and assessments of oral health be conducted at the beginning of the care process and as needed. Regular evaluations ensure that oral health is continuously monitored and addressed according to the identified needs.
3. Training and continuing education: nursing professionals must receive comprehensive training to adequately perform oral hygiene tasks. Regular continuing education ensures that nursing staff apply up-to-date methods and knowledge. This supports professional and patient-centered care practices, which are essential for preventing oral health problems.
4. Interprofessional collaboration: close cooperation with dentists is recommended to ensure comprehensive and interdisciplinary care. Coordinating this collaboration is essential for providing holistic care and treatment.
5. Promoting oral health in specific conditions, such as dry mouth: while specific measures to address conditions such as dry mouth are not explicitly outlined, the recommendations include general measures to promote oral health. These also encompass the treatment and management of specific issues such as dry mouth.
6. Establishment of an oral hygiene manager: although not explicitly included in the expert standard, Dr Elmar Ludwig, a co-author of the expert standard, proposed the introduction of an oral hygiene manager during the interdisciplinary symposium “Day of Senior Dental Medicine” on January 27, 2024, in Düsseldorf, Germany (personal communication by Dr Elmar Ludwig, Committee for Gerodontology, German Dental Association, Berlin, Germany, on January 27, 2024). This role would serve as a central coordination point within care facilities, overseeing all aspects of oral care and ensuring that nursing staff are adequately trained and equipped. The oral hygiene manager would also coordinate collaboration with dentists and other professionals, ensuring consistent and high-quality implementation of oral health standards, ultimately improving care for those in need.

The current state of research reveals that, despite the evident importance of interprofessional approaches to promoting oral health in older patients within clinical settings, specific data on the effectiveness and acceptance of such programs remains scarce [19]. The concept of the expert standard for oral health, introduced in Germany, was primarily developed through consensus decisions rather than empirical data [5]. Although this standard has been implemented as a pilot in a variety of facilities, studies confirming its acceptability, feasibility, and effectiveness are still lacking [6].

Theoretical Framework of Acceptability

The theoretical framework of acceptability (TFA), developed by Sekhon et al [20], offers a multidimensional definition of acceptability. It assesses how individuals involved in delivering or receiving a health intervention perceive its suitability, considering their expected or actual emotional and cognitive responses. The TFA identifies 7 key components [20]: affective attitude (describing the emotional state toward the intervention), burden (measuring the perceived effort involved), intervention coherence (reflecting the level of understanding of the intervention), ethicality (examining the compatibility with personal values), opportunity costs (assessing necessary sacrifices), perceived effectiveness (estimating the expected success of the intervention), and self-efficacy (gauging confidence in one’s ability to perform the intervention; Figure 1).

Acceptability is potentially critical in settings where interprofessional approaches are required, as different professional groups often have varying perspectives and expectations of an intervention. This diversity can either facilitate or hinder implementation, depending on how well the intervention aligns with the needs and workflows of the different groups [5].

Moreover, it is essential to understand acceptability not as a 1-time act but as a continuous process [20]. The sustainability of an implementation depends on whether the intervention can be integrated into the daily routines of users and whether it continues to be perceived as useful and relevant.

Figure 1. The TFA model with 7 key components [20]. TFA: theoretical framework of acceptability.

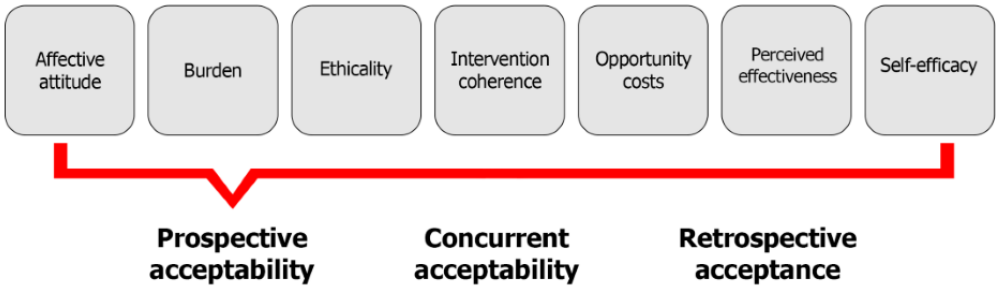

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Nursing Competence as a Predictor for Acceptability of the Expert Standard

In this work, competence is understood as the ability to apply learned knowledge in a professional context, act in a self-organized manner, and make independent decisions [21]. According to Erpenbeck [22], competence is more than a mere qualification. It encompasses cognitive as well as action-oriented, social, and normative dimensions. While the cognitive dimension refers to knowledge and understanding, the action-oriented dimension focuses on the application of skills. The social dimension includes communication skills and responsibility, and the normative dimension describes the internalization of values, rules, and norms. These dimensions form the foundation for actions that are both professionally and morally sound, as well as self-organized [22].

The inclusion model proposed by Erpenbeck provides a framework for assessing and developing competencies (Figure 2 [23]).

The question arises as to whether a high level of nursing competence, specifically oral care competence, is a contributing factor to the greater acceptability of the expert standard intervention.

It can be argued that a higher level of competence positively influences the domains of the TFA. Competence development through practice and knowledge acquisition not only enhances self-efficacy [24] but is also expected to have a positive impact on coherence and perceived effectiveness [25]. Furthermore, the authors speculate that competent actions are likely to reduce the perceived burden.

Therefore, the hypothesis is proposed that nursing competence, measured in terms of qualification level, oral health literacy, and oral care competence, has a positive effect on the acceptability of the intervention (Figure 3).

Figure 2. Inclusion model based on Erpenbeck et al [23].

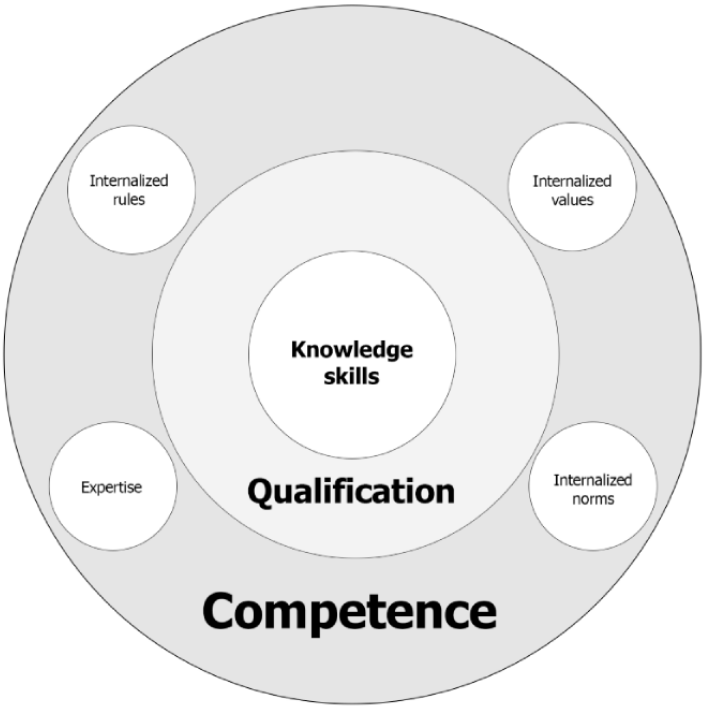

Figure 3. Combined acceptability model.

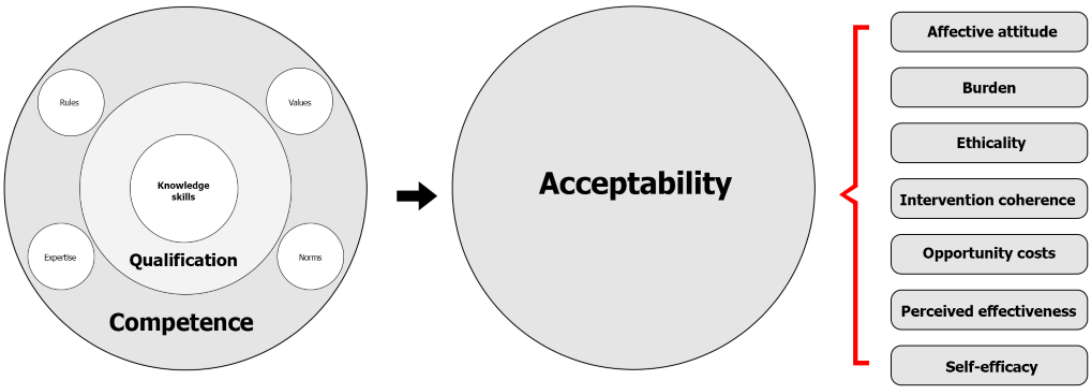

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Research Objectives and Questions

This study pursues 3 objectives: first, to determine the rate of acceptability of the several interventions derived from the expert standard. Second, to examine the influence of competence (knowledge, qualifications, and skills) on acceptability. Third, to assess the extent of CROM in oral health care and its relationship to the acceptability of new interventions.

The successful implementation of new measures requires broad acceptance among recipients. Currently, there is a lack of empirical data on this topic, which represents the first research gap. The authors assume a relationship between competence and acceptability. Several interdisciplinary theories describe potential influences of competence on the domains of the TFA.

Primary objective: estimate the acceptability rate and level for the interventions of the expert oral health care standard in various residential long-term care facilities and hospitals.

Primary Research Questions

Question (Q; Q1): what is the acceptability (in terms of acceptability rate and level) of the individual interventions from the expert standard for promoting oral health among nursing staff in residential long-term care facilities and hospitals?

Q2: which specific interventions from the expert standard are particularly acceptable, and which are not?

Q3: are there differences in the acceptability rate and level between long-term care facilities and hospitals?

Secondary objective: assess the competence of nursing staff and determine the relationship between competence level and the acceptability level of the interventions.

Secondary Research Questions

Q4: what influence does the competence level of nursing staff have on their acceptability of interventions?

Q5: what obstacles are perceived in the implementation of interventions to promote oral health in older adult care?

Q6: how important is oral care in the care of older individuals?

Q7: is there a relationship between the severity of subjectively perceived obstacles and the acceptability of interventions?

Tertiary objective: measure CROM in oral health care and identify the relationship between the CROM phenomenon and the acceptability level of interventions.

Tertiary Research Questions

Q8: how do CROM rates in oral care in Germany differ from already published CROM rates in Austria [13] and Switzerland [11]?

Q9: is there a relationship between the nursing staff's acceptability of new interventions and the CROM rate in oral care?

Hypotheses

The formulation of the hypotheses is based on prior observations and theoretical considerations suggesting that variations in the implementation of standards and the competence of nursing staff are critical factors influencing the acceptability of health interventions. Additionally, it is assumed that both structural and individual differences within facilities can have a significant impact on the outcomes. By clearly defining these assumptions, the hypotheses can be systematically tested, highlighting the practical relevance of this study's results and their implications for further research.

Hypotheses for the Primary Research Questions

Without hypothesis: the estimation of the acceptability rate and level of the interventions from the expert standard will be conducted without additional hypothesis formulation.

Hypothesis (H; H1): the interventions from the expert standard differ in terms of their acceptability level.

H2: the acceptability level of the interventions varies between the types of facility (different residential long-term care facilities and hospitals).

Hypotheses for the Secondary Research Questions

H3: there is an association between the competence of nursing staff in oral care and the acceptability level of interventions from the expert standard.

H4: there are differences in the severity of obstacles perceived as barriers to oral care.

H5: there is an association between the subjectively perceived severity of obstacles to performing oral care measures and the acceptability level of interventions from the expert standard.

Hypotheses for the Tertiary Research Questions

H6: there is an association between CROM in oral care and the acceptability of interventions from the expert standard.

H7: there are differences in the CROM rate for oral care between Germany and already published CROM rates in Austria [13] and Switzerland [11].

Methods

Study Design

This is a quantitative cross-sectional study in which data are collected from nursing staff in hospitals and long-term care facilities at a specific time using standardized survey instruments. This study protocol was created based on SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 Guidelines [26]. According to the MRC Framework for Developing and Evaluating Complex Health Interventions, this research is part of the feasibility evaluation [15]. The first phase—identifying or developing the interventions of the expert standard—has already been completed [5]. The third and fourth phases—implementation and evaluation—are the focus of this research and have yet to be conducted.

Setting and Study Population

This study is conducted in North Rhine-Westphalia, Germany's most populated federal state, with 18.2 million residents [27]. It includes various care facilities, such as hospitals and university clinics with geriatric wards, as well as long-term care facilities.

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This study population consists of nursing staff working in the mentioned facilities. The following inclusion criteria are applied: nursing staff who perform or oversee daily oral care for older adults. Exclusion criteria are trainee or voluntary staff.

Outcome Measures and Data Collection

Acceptability

The TFA questionnaire is an assessment tool developed to measure the acceptability of health interventions. It consists of 7 items, each representing 1 dimension of intervention acceptability: affective attitude, burden, intervention coherence, perceived effectiveness, self-efficacy, ethical acceptability, and opportunity costs. Additionally, the questionnaire includes 1 item assessing the overall acceptability of the specific expert standard intervention [20,28].

Each item on the TFA questionnaire is typically rated on a 5-point rating scale, allowing quantitative measurement of agreement or disagreement with each statement. The questionnaire is specifically designed to capture the multidimensional aspects of acceptability, which is crucial for understanding how and why certain interventions are accepted or rejected by health care professionals [20,28].

For our study, the TFA questionnaire was specifically adapted to evaluate the acceptability of each intervention within the expert standard for promoting oral health in nursing care. Each specific intervention—including regular oral care, assessment and evaluation of oral health, training and continuing education for nursing staff, collaboration with dental professionals, and specialized measures to address dry mouth—is assessed through the 7 specific items in the TFA questionnaire. This adaptation results in a total of 35 items. The items were formulated according to the guidelines suggested by Sekhon et al [28].

The TFA questionnaire can be applied to assess both prospective acceptability (before implementation) and retrospective acceptance (after implementation), evaluating how interventions are perceived before and after their introduction [20,28]. Our planned study will investigate the prospective acceptability of these measures. This means that the survey will be conducted in institutions where the interventions from the expert standard have not yet been introduced.

For each specific intervention of the expert standard, a descriptive text was created detailing the content, core elements, and specific tasks. This was included to provide nursing staff with clear guidance and support in understanding the content of the specific expert standard.

Furthermore, it was decided to use a 6-point rating scale instead of a 5-point scale as the response format. The rationale for this decision is explained in the section on adjustment of rating scales.

Nursing Competence

According to Erpenbeck [22], qualification involves the interplay of knowledge, skills, and abilities [22]. Building on Erpenbeck model, oral health knowledge is assessed using the Oral Health Literacy Profile (OHLP), nursing qualification is gathered through a sociodemographic survey, and nursing competence in oral care is measured using the questionnaire from the DNQP (Deutsches Netzwerk für Qualitätsentwicklung in der Pflege [German network for Quality Development in Nursing]). The data collection instruments used are described as follows.

About OHLP

The OHLP is a tool developed to assess an individual's knowledge and behavior related to oral health. For our study, the Oral Health Knowledge module consisting of 10 questions was used [29]. These questions aim to evaluate respondents' knowledge of various aspects of oral health, including the impact of diet on dental health, the importance of fluoride, general oral hygiene practices, the connection between oral health and systemic diseases.

Each question is presented in a single-choice or multiple-choice format.

Participants receive 1 point for each correct answer. Incorrect answers or the option "I don't know" are not scored. Scores from the questions are combined into an overall score, normalized on a scale from 0 to 100, with higher values indicating better oral health knowledge [29].

Nursing Competence in Oral Health

The audit tool: questionnaire 2 (DNQP-FB2 [Deutsches Netzwerk für Qualitätsentwicklung in der Pflege Fragebogen 2]) from the DNQP includes a specialized questionnaire designed to assess the knowledge level and further educational needs in mouth care practices [6].

The questionnaire comprises 5 items, each rated on a 5-point rating scale ranging from "very good" to "poor." Additionally, respondents are asked whether further training is needed for each topic, with a simple "yes" or "no" response option [6].

The items cover a wide range of areas: assessing risks and problems related to oral health, planning and coordinating interventions, providing information, training, and counseling, performing nursing interventions, and evaluating the effectiveness of these interventions. This structured approach helps identify specific knowledge gaps and facilitates targeted training to enhance the quality of oral care in nursing facilities [6].

The response scale for this questionnaire was also adapted to a 6-point rating scale to provide more nuanced feedback.

Subjectively Perceived Importance of Oral Care Measures

It is assumed that the evaluation of oral care measures as highly important can be defined as an expression of competence. This information is collected using a question adapted from the questionnaire by Gibney et al [30]. To determine the perceived importance of oral hygiene, respondents are asked to rate the importance of oral hygiene on a 5-point rating scale. The scale ranges from "not important" (anchored by "cleaning glasses") to "extremely important" (anchored by "wound care").

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Barriers to Performing Oral Hygiene Measures

In the acute care nurses' questionnaire on oral hygiene by Gibney et al [30], barriers to performing oral care are assessed by asking respondents to rank 8 potential obstacles from most to least significant [30]. To reduce the likelihood of invalid responses in a web-based survey, this ranking system was adapted. Instead of ranking, each of the 8 barriers is rated using a slider on a scale from 0 to 100, allowing participants to subjectively assess the severity of each barrier.

About CROM

To measure CROM, a question regarding oral and dental hygiene from the first module, "activities of daily living" in the Basel Extent of Rationing of Nursing Care Assessment Questionnaire [31], is used. The question is:

> *How often in the last 7 working days did it happen that you could not perform necessary oral or dental hygiene for a patient?*

This question is typically answered on a 4-point scale (never, rarely, sometimes, or often). For consistency with the response format across the survey, the scale was adapted to a 6-point format. The revised scale ranges from "very rarely" to "very often."

Both Zuniga et al [11], who used the Basel Extent of Rationing of Nursing Care Assessment Questionnaire [31], and Cartaxo et al [13], who used the MissCare Survey [32], dichotomized the responses to determine the proportion of nursing staff who rationed or omitted care. In the study by Zuniga et al [11], categories 3-4 were combined, while Cartaxo et al merged categories 4-6.

To ensure comparability with the national studies conducted in Austria [13] and Switzerland [11], this study includes the question with 2 timeframes: 7 days and 14 days, accommodating differences in data collection periods.

Sociodemographic Data

Sociodemographic data collected includes age, gender, years of practical experience, employment type, work shift, qualification level, and specific competency roles such as nursing aide, nurse, and nursing management. Additionally, data on facility size, unit type and size, setting (urban or rural), and legal status of the institution are gathered.

The age of nursing staff is considered a confounding factor in the acceptability of new interventions. Nurses of different ages often exhibit varying attitudes. Older nurses have been found to show lower acceptability toward the introduction of modern measures in nursing compared to younger colleagues [33]. However, older nurses often possess greater practical competence due to extensive professional experience [7].

The work shift (morning or evening) is also considered a factor influencing the acceptance and level of new nursing measures. Morning and evening shifts differ significantly in terms of workload and priority setting. While the morning shift involves a tightly packed schedule of nursing services and organizational and documentation tasks [34-36], the evening shift focuses on administering medication and serving meals [37,38]. These differences in workload could influence the perception of the usefulness and importance of new measures.

Exploratory Questions

Additional questions are included to determine whether the interventions from the expert standard are already known to the nursing staff and whether they are currently being applied.

Translation and Adaptation of Questionnaires

The existing questionnaires by Sekhon et al [28] and Gibney et al [30] were translated by the authors into German and culturally adapted. As prescribed by Sekhon et al [28], the TFA was tailored to ensure that its wording and semantics correspond to the topic of the research. Experts in nursing science and oral health were consulted to ensure the appropriateness of the questions.

The TRAPD (Translation, Review, Adjudication, Pretesting, and Documentation) method was applied for the translation process. This team-based approach ensures the quality and cultural relevance of the translation through review, resolution of discrepancies, pretesting, and detailed documentation [39,40].

The translated and adapted questionnaires were initially reviewed in a small team consisting of a dentist, a statistician, a psychologist, and a nursing scientist. Using the Think Aloud Method [41], the questionnaires were tested for clarity and feasibility refined.

Adjustment of Rating Scales to Optimize Data Quality

In our study, a modification was made to the originally used rating scales in the questionnaires by Sekhon et al [28], Gibney et al [30], and DNQP [6], replacing the 5-point scale with a 6-point scale. Each item is considered a Likert-type item, and the mean of such items represents a Likert scale [42].

This adjustment, based on the elaborations of Moosbrugger and Kelava [41], aims to enhance the scale's ability to differentiate between responses and to reduce ambivalent answers by removing the neutral middle category. This increases the precision and validity of the data. Expanding the response options also improves the reliability of the measurement instruments and minimizes response biases by encouraging participants to take a clearer stance [41].

Study Procedure

Selection of Hospitals

A total of 25 hospitals and long-term care facilities in North Rhine-Westphalia, Germany, will be selected. These are sites where the interventions of the expert standard have not yet been implemented.

Recruitment of Participants

The nursing management of the selected hospitals will be contacted to gain support for participant recruitment. Information sessions will be held to inform nursing staff about this study and encourage participation. Direct communication will be established with facility management or human resources departments to foster cooperation. Participation will be voluntary and anonymous.

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Recruitment Communication Tools

A QR code linking to the web-based survey will be included with the nursing staff's pay slips. Additionally, a flyer explaining the importance of this study and encouraging participation will accompany the pay slips. The QR code will be distributed repeatedly over a 3-month period, along with reminders to participate, until the desired number of participants is reached.

Data Collection

Data will be collected exclusively through an web-based survey. To minimize potential bias and ensure representativeness, the sample will reflect institutional diversity by surveying Germany's most populous state. This approach ensures a representative range of institutions and captures ethnic diversity.

Ethical Considerations

This study follows the ethical principles outlined in the Declaration of Helsinki and was reviewed and approved on January 14, 2025, by the Research Committee for Scientific Ethical Questions of the UMIT Tirol (Private University for Health Sciences and Health Technology) in Tirol, Austria (reference number 3512).

The selection of nursing staff, as well as the storage, transmission, and access to collected data, will be anonymized and accessible only to authorized personnel.

Participation in this study is entirely voluntary, and written informed consent will be obtained after participants have been fully informed about this study's purpose, procedures, and any potential risks.

As an incentive, 30 gift cards valued at €20 (US $22.74) each will be raffled among participants. To enter the raffle, participants will be asked to provide their email addresses. In compliance with ethical committee requirements, participants' contact information will be stored separately from their survey responses to maintain confidentiality and data protection.

Statistical Analysis

Overview

This study protocol outlines the statistical considerations for this study. Categorical variables will be described using absolute frequencies and percentages. For variables measured on at least an interval scale, mean, median, SD, minimum, and maximum values will be calculated.

The assumptions for applying statistical methods will be examined in advance, and appropriate alternative methods will be used if assumptions are violated. In the case of the planned repeated measures ANOVA, specific attention will be given to testing sphericity for within-subject factors, homogeneity of variances for between-subject factors, and the absence of outliers. For regression analyses, the homoscedasticity of residuals and the absence of outliers will be assessed.

Identified confounders will be accounted for in the statistical models, with particular attention paid to multicollinearity among predictors.

The statistical analysis plan has been reviewed and approved by a certified statistician for its accuracy and suitability to address the research questions.

The data analysis will be performed using IBM SPSS Statistics (version 30.0; IBM Corp).

Primary Research Question: Acceptability Rate and Level

Calculation of Acceptability Rate and Level

The first objective of this study is to estimate the acceptability rate and level for each intervention within the expert standard. The items from the TFA questionnaire [28] serve as the basis for calculating these acceptability parameters.

The acceptability rate is determined by evaluating how many respondents selected a value of 4 or higher on a 6-point rating scale. Values 4-6 are considered indicators of higher acceptability, while values 1-3 represent lower acceptability. The rate is calculated by dichotomizing responses and determining the proportion of participants selecting the top 3 categories (4 to 6). A 95% CI will be generated for the acceptability rate. Each of the interventions of the standard will be analyzed separately.

For this analysis, frequencies (counts) and percentages (rates) will be reported separately for each TFA domain. Domains 2 (burden) and 7 (opportunity costs) will be reversed, as lower burden and lower opportunity costs indicate higher acceptability.

The acceptability rate for each intervention of the expert standard will be averaged across all 7 TFA domains. Similarly, for each TFA domain, the acceptability rate will be averaged across all 6 interventions, yielding a marginal distribution.

For every mean value calculated, a 95% CI will be provided.

Analysis of Differences in Acceptability Levels Across Domains and Interventions

A repeated measures ANOVA will be used to identify differences in acceptability levels between interventions and across the TFA domains. These calculations aim to test H1.

In a first step, the 6 interventions from the expert standard will be used as a within-subject factor to compare the average acceptability levels across the 7 TFA domains. Bonferroni-corrected post hoc analyses will be conducted to perform pairwise comparisons, identifying interventions with particularly high or low acceptability values.

In the second step, the model will be extended to include an additional within-subject factor representing the 7 TFA domains of acceptability. This will allow for analysis of differences in acceptability levels across the TFA domains and interactions of domains and interventions. This 2-step approach facilitates an in-depth examination of the acceptability structure.

Group Comparisons Regarding Acceptability Levels

The above-described repeated measures ANOVA model will be further expanded to include an additional independent variable to test H2. The variable "facility type" (hospital vs nursing home) will be added to the model to assess whether

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differences in acceptability levels are associated with the type of facility.

Secondary Research Questions: Competence and Barriers

Influence of Competence on Acceptability Level

To statistically analyze H3, a multiple linear regression analysis will be conducted (Figure 4). In our planned study, nursing competence in oral health will be operationalized using 2 measurement instruments, which will serve as predictors in the regression model. The first predictor is the sum score of the OHLP items, and the second is the mean index of the items from DNQP. Additionally, the subjectively perceived importance of oral health in the nursing process will be tested as a mediator to determine whether it mediates the relationship between knowledge or competence and acceptability.

The goal of these analyses is to examine the impact of these predictors on the acceptability level. First, an overall acceptability level will be calculated as the mean across all domains and interventions and used as the criterion in the regression model. Subsequently, the analysis will be repeated at the domain and intervention levels to calculate the impact of competence on each individual TFA domain and each intervention separately. This 2-step approach aims for a nuanced understanding of the influence of competence on acceptability.

Figure 4. Regression analysis modelling acceptance using oral health knowledge and competence in nursing as predictors and perceived importance of mouth care as mediator.

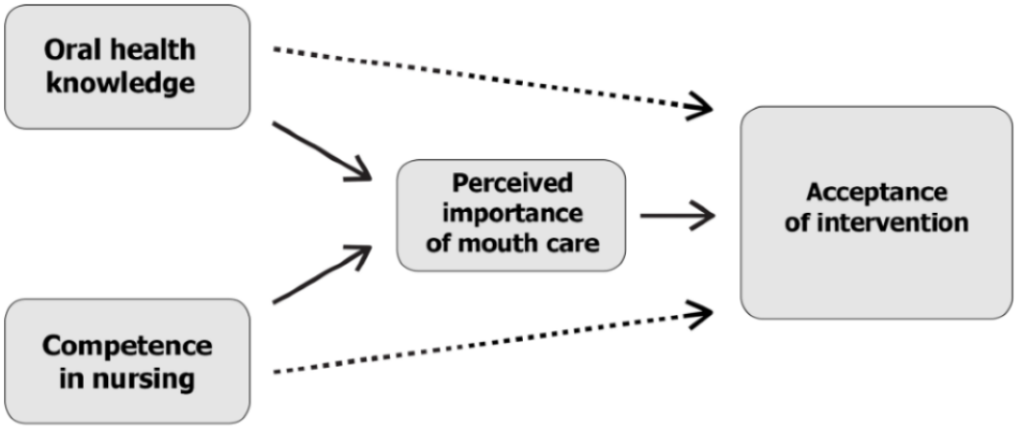

Identification of Barriers to Implementing Mouth Care Interventions in Older Adult Care

The 8 identified barriers will be assessed using a rating scale. Absolute and relative frequencies for each barrier will be calculated, along with the mean and a 95% CI.

Influence of Barriers on Acceptability

A multiple linear regression analysis will be conducted, with the severity of the 8 identified barriers serving as predictors. Consistent with prior analyses, the overall acceptability level will first be calculated as a criterion and included in the regression. Subsequently, the analysis will be repeated at the domain and intervention levels to determine the influence of barrier severity on each TFA domain and each intervention separately.

Determining the Importance of Mouth Care

The subjectively perceived importance of mouth care will be analyzed by calculating absolute frequencies and percentages for each of the 5 levels on the rating scale. Additionally, the analysis will include a mean or median value to summarize the distribution of responses.

Tertiary Research Questions: CROM

Estimation and International Comparison of the CROM Rate in Oral Care

The CROM rate for oral care will be calculated by assessing how many participants selected at least category 4 on a 6-point rating scale. Categories 4 to 6 will be used as indicators of rationed or omitted oral care, while categories 1 to 3 indicate no CROM. Through this dichotomization, the proportion of participants selecting the upper 3 categories will be calculated.

A 95% CI will be calculated for the CROM rate estimation.

To test H7, a chi-squared test of independence will be performed. The CROM rate for oral care identified in this study will be compared with previously published data from studies conducted in Austria [13] and Switzerland [11].

Exploratory Analyses

A multiple linear regression analysis will be conducted to examine the influence of sociodemographic characteristics on the acceptability level. The educational level of nursing staff will be included as a third predictor or mediator to explore whether educational qualification provides insight into knowledge, competence, and the perceived importance of oral health.

Significance Level for Hypothesis Testing

The significance level for all hypotheses is set at 5%. A Bonferroni correction will be applied when multiple statistical tests are conducted as part of hypothesis testing. Specifically, this is planned for post hoc analyses following repeated measures ANOVA and for the regression analysis that includes more than 1 predictor to assess the impact of nursing competence.

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Due to the exploratory nature of this study, all results, particularly those related to interactions, will be treated as preliminary insights for this research area. These findings are intended to guide future studies with confirmatory designs for validation.

Sample Size Calculation

This study aims to estimate the acceptability rate of interventions from the expert standard with a precision of ±5 percentage points and a statistical confidence level of 95%. In the absence of specific assumptions about the acceptability proportion, a conservative estimate of 50% is used.

According to the BARMER Nursing Report [43], approximately 479,000 nursing staff were used in residential care facilities in Germany. However, the report does not provide a detailed breakdown of the proportions of skilled versus auxiliary staff [43].

Based on the large population size, the required sample size for estimating a proportion in the population is approximately 385 participants. The calculation for determining the sample size for population proportion estimation of nursing staff is as follows:

Additional calculations for statistical power will be performed to ensure that this study is sufficiently sensitive to detect the expected effects.

To address the second research question, a power analysis was conducted to evaluate the ability to detect a relationship between nursing competence and acceptability. Assuming a correlation coefficient (r) of 0.3 (explaining 9% of the variance), the power is calculated to be 99.9%, indicating a high likelihood of detecting such a correlation if it exists in the population.

Even with a smaller correlation of r=0.15 (explaining 2.3% of the variance), statistical significance is achievable, with a power of 84% to detect this correlation if present.

Thus, the sample size can be considered sufficient to address all research questions effectively.

Data Preparation

The data preparation process will be thoroughly documented. If response patterns in individual datasets suggest erroneous or intentionally inaccurate questionnaire completion, the respective participant will be excluded from the analysis, and the exclusion will be documented.

Such cases may include: clearly implausible responses (eg, a person indicates an age of 20 years while claiming 40 years of professional experience), inability to understand the questionnaire (eg, due to insufficient language proficiency), deliberately false answers (eg, intentional misinformation), uniform responses across all items, regardless of the content of the rating scale items.

All statistical analyses will be conducted following the available case analysis approach. Participants who do not complete the entire questionnaire will not be excluded from this study. Instead, only fully completed modules will be included in the corresponding analysis.

Results

This study received approval from the Research Committee for Scientific Ethical Questions of the UMIT Tirol, Austria, in January 2025. Recruitment will commence in June 2025. Data collection and analysis are expected to be completed within 6 months. This study's results will be submitted for publication in peer-reviewed scientific journals and presented at expert conferences. Additionally, it is planned to get in contact with decision makers.

Discussion

Principal Findings

This study aims to address a critical gap in the research surrounding the acceptance of the expert standard "promoting oral health in nursing" in German care facilities. By investigating the factors that influence the acceptance of this standard among nursing staff, this study provides essential insights into optimizing its implementation. The anticipated findings will highlight how the standard can be better integrated into routine practice, ultimately reducing the prevalence of CROM and improving the quality of oral health care for older populations. Furthermore, this research emphasizes the role of acceptability as a key determinant of feasibility, as interventions that are not acceptable are unlikely to be implemented effectively.

This study is expected to identify specific barriers and facilitators to the acceptability of the expert standard, such as nursing staff's competence levels, workload, and the organizational support provided by care facilities. These findings will inform targeted strategies for enhancing the acceptability and feasibility of new health care standards, such as tailored training programs and interprofessional collaboration initiatives. Additionally, this research will contribute to a better understanding of how nursing staff perceive oral health interventions and the factors that impact their willingness to adopt new practices.

By focusing on acceptability as a prerequisite for successful implementation, this study also offers broader implications for the development of health care standards in nursing settings. The findings will support the creation of evidence-based policies that align with the realities of nursing care, addressing the unique challenges posed by high patient-to-nurse ratios and the increasing care needs of aging populations.

Limitations

This study is limited by its reliance on self-reported data, which may be influenced by social desirability bias. Additionally, the cross-sectional design precludes an analysis of how acceptance changes over time or in response to specific interventions. Another limitation is that this study focuses on German care facilities, which may limit the generalizability of the findings to other health care systems or cultural contexts. Finally,

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resource constraints may impact the representativeness of the sample, as this study relies on voluntary participation.

Furthermore, the absence of qualitative methods is a limitation. While this study focuses on quantitative measurement, qualitative approaches could have revealed individual motivations and helped identify barriers to acceptability not captured by structured survey items.

However, qualitative approaches were used by the DNQP in the development of the expert standards. In the current phase of implementation according to the MRC framework, it is assumed that quantitative data collection will provide helpful and practice-relevant results. The quantitative method allows a large number of participants to be involved with the available resources. As the expert standard is to be widely implemented, the authors considered it important to achieve a large sample.

Conclusion

This study will provide valuable insights into the factors influencing the acceptability of the expert standard for oral health in nursing care. By identifying barriers and facilitators, it aims to optimize the implementation of the standard, reduce the prevalence of CROM, and improve the quality of oral health care for older adult patients. The findings will not only contribute to the advancement of this specific standard but also offer important implications for the broader implementation of health care standards in nursing settings. Emphasizing the importance of acceptability and feasibility, this research underscores the need for evidence-based approaches to standard development and implementation, ultimately improving patient outcomes and supporting overburdened nursing staff in their critical roles.

Acknowledgments

We would like to express our sincere gratitude to Mark Mussner, MSc, for evaluating and approving the statistical analysis plan.

Data Availability

The datasets generated during this study will not be publicly available until this study is completed and results are published. Upon reasonable request, data may be shared for scientific purposes. Requests can be directed to the corresponding author.

Authors' Contributions

DP worked on the conceptualization, methodology, formal analysis, writing of the original draft, and project administration. HS handled the supervision, review and editing of the writing, and validation. All authors have read and agreed to the published version of this paper.

Conflicts of Interest

None declared.

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Abbreviations

CROM: care rationed or missed
DNQP: Deutsches Netzwerk für Qualitätsentwicklung in der Pflege (German network for Quality Development in Nursing)
DNQP-FB2: Deutsches Netzwerk für Qualitätsentwicklung in der Pflege Fragebogen 2
MRC: Medical Research Council
OHLP: Oral Health Literacy Profile
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TFA: theoretical framework of acceptability
TRAPD: Translation, Review, Adjudication, Pretesting, and Documentation
UMIT: Private University for Health Sciences and Health Technology

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Protocol

Feasibility of Digitally Identifying and Minimizing Stressors in Palliative Care Workplaces by Measuring Stress Continuously for Nurses Through Wearable Sensors (DiPa): Protocol for a Prospective Cross-Sectional Study

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Abstract

Background: Nursing in palliative medicine combines primary patient care with the special challenges of this medical field (eg, handling the processes of dying, grief, and death). These cause high stress levels and burden on the nursing staff, resulting in an early exit from working life because of physical or psychological disorders like burnout.

Objective: DiPa (digitally identifying and minimizing stressors in palliative care) is a prospective study investigating the feasibility of measuring burden and its causes in palliative care using methods of subjective and objective stress detection. Based on these results, stress-reducing interventions are to be deduced and evaluated. In this paper, we present our study protocol.

Methods: The nursing staff of an inpatient university palliative hospital ward gathered data over 6 weeks. Each was equipped with a smart wristband and a smartphone that continuously measure physiological and ambient parameters throughout their working day. These objective data were enriched by subjective measurements: a questionnaire at the beginning of the study that assessed multiple potential stressful situations and constellations in the private and working environment as well as ecological momentary assessments (EMAs) during the workday. The EMAs were prompted by scanning near-field communication (NFC) tags placed at different locations on the ward. The ongoing data analyses will be processed using computer algorithms partly programmed specifically for this study and partly drawn from existing libraries, such as toolboxes for neurophysiological signal processing for Python. Comparisons between subjective and objective measures and group comparisons between variables of interest will be made using inferential statistics, including regression analyses and analyses of variance. Data analysis using machine learning algorithms will be implemented once sufficient data are gathered.

Results: The study was funded in October 2019. As of July 2025, 12 of 18 nurses in the palliative care unit consented to participate in our study. We expect to start detailed data analysis in in the third quarter of 2025 and to finish and publish our results in 2026.

Conclusions: The DiPa study aims at testing the feasibility of measuring and merging subjective and objective stress parameters for palliative care nurses.

Trial Registration: German Register for Clinical Studies DRKS00024425; https://drks.de/search/en/trial/DRKS00024425/details

International Registered Report Identifier (IRRID): DERR1-10.2196/63549

(JMIR Res Protoc 2025;14:e63549) doi:10.2196/63549

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KEYWORDS

stress; wearables; psychological distress; psychological health; work-life balance; smartphones; ecological momentary assessment; workplace mental health

Introduction

Background

Chronic and severe diseases are increasing in importance and require sufficient medical treatment and well-educated specialists in the field to provide medication, help with personal hygiene, and offer counselling. In 2020, 1.7 million nursing staff worked in nursing and older adult care in Germany [1], which reflects a growing shortage of skilled workers in view of the aging population. The reasons are manifold, but the reasons found in the working environment include the 3-shift system, time pressures, and heavy physical and emotional burden, leading to dissatisfaction or even leaving the profession [2,3]. These factors can be found in almost all hospital departments but are exacerbated in areas with a high level of physical and interpersonal care. Palliative medicine is one of these particularly sensitive areas.

Palliative Medicine

Palliative medicine is a specialty for the treatment of people with critical diseases like advanced cancer or higher-grade cardiac, renal, or lung diseases with limited life expectancy. Palliative care is a challenging discipline, not only due to the required medical care but also due to the psychosocial and spiritual aspects in the interaction between nursing staff and patients or their relatives, especially given the aim of improving quality of life in the last months and weeks of the patients' lives. The main tasks of nursing staff in the palliative field include life support for the terminally ill and relieving their suffering from commonly experienced severe symptoms. These include pain, shortness of breath, and nausea, as well as anxiety and depression, which are also highly prevalent, as Sewtz et al [4] showed in their study.

Burden in Palliative Caregiving

Palliative nurses face many work-related stressors (like interruptions, time pressures, interpersonal conflicts, or shift work, as aforementioned) that are also experienced by other professions in addition to stressors that are unique to taking care of patients who are terminally ill or close to dying. Additionally, they are not able to express their needs, which can also lead to burden as Seibel et al [5] have published in 2024 (see Table 1, adapted from [6]). It is an imminent part of the job—physicians and palliative nurses are confronted with the end of a patient's life and with patients and relatives facing this stage. Even though nurses in this field choose this sensitive job after careful consideration, it still is an emotional burden to cope with the dying and death of patients for 54% to 68% of nurses in palliative care [6], which is moderated by circumstances (eg, age of the patient, patient and caregiver agony).

Table 1. Examples of potential stressors in a palliative care unit (PCU).

Factors	Examples
Team-associated factors	• Staff fluctuation among physicians in the PCU • Lack of support • Lack of appreciation by other professional groups
Patient-associated factors	• Young patients' ages • High care effort due to symptoms (eg, wounds, nausea, breathlessness, restlessness) • Insufficient symptom control (eg, therapy-resistant pain, insatiable bleeding)
Structural factors	• Understaffing • High amount of documentation • Inadequate education of patients and relatives about the palliative setting by the referring doctor
Personal factors	• Ethical conflicts • Feeling of being overwhelmed • High expectation of one's own work

Only a few studies have investigated this topic [6-12]. Diehl et al [11] surveyed and compared strains and resources for 149 nurses (34.5% response rate) working in the field of palliative care (in hospitals, hospices, or outpatient care in Germany). In their study, more than one-half of the nursing activities were perceived as heavy burdens, including transferring patients, time pressures, having to care for too many patients per day, handling patients with severe symptoms, and dealing with grief and death. Being surrounded by these topics every working day, nurses are at risk of psychiatric disorders that can accumulate to result in burnout syndrome in 15% to 20% of palliative nurses in home care [12,13].

Clinicians and researchers demand more studies, as urged by Pereira et al [10] in their systematic review of burnout syndrome in palliative care. Further evaluations of palliative care nurses throughout Europe could ensure better positioning of any results in the transnational context of the palliative care area and reveal further deficits in the care structure [9].

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Digitally Identifying and Minimizing Stressors in Palliative Care Study

The DiPa (Digitally Identifying and Minimizing Stressors in Palliative Care) study was conceptualized to use digital technologies ("Di") to assess the working conditions of and burden on nurses in palliative settings ("Pa"). The study is a joint project of the Fraunhofer Institute for Computer Graphics Research (IGD) Rostock and the University Medical Centre Rostock (UMR) and funded by the State Office for Health and Social Affairs Mecklenburg-Western Pomerania. The study aims to identify correlations between measured objective physiological parameters and subjective perceptions of stress in everyday situations in the palliative care unit (PCU). Therefore, the primary goal is demonstrating the feasibility of identifying stressors in palliative care and measuring stress reactions with wearable devices. With these initial results, stressors and stress can be reduced by developing preventive measures.

Physiological Stress Model

To explain our rationale for using wearable devices to measure stress in humans, we present the physiological stress model. The autonomic nervous system is responsible for all vital functions, regulating breathing, digestion, and the cardiovascular system as well as influencing the heart and glands [14]. The autonomic nervous system is divided into the sympathetic nervous system (SNS) and parasympathetic nervous system, which often act antagonistically. Although the SNS is activated by stress, the parasympathetic nervous system supports resting states. "Stress" occurs when the demands of the environment exceed the individual's ability to cope [15]. It is defined as an individual's reaction to burden and is caused by triggers that are called "stressors."

Three phases of the physiological reaction can be distinguished. The phases were first described as part of the "general adaptation syndrome" by Selye and Köbcke [16]: The first phase is called the "alarm phase" and appears immediately after the stimulus.

The SNS reacts to a stressor by releasing catecholamines like noradrenalin and adrenalin from the adrenal medulla [17] and, simultaneously, adrenocorticotropic hormone from the cortical part of the brain [18]. In their paper, Chodan et al [19] described how the different physical changes interact during the alert: The muscles require oxygen for the oxidation of glucose and fat into energy. To provide this surplus of oxygen, breathing rate and heart rate (HR) increase. Empirical knowledge and experiences with handling data from biomedical parameters gathered with wearable devices have been accumulated in prior studies [19-21]. In particular, HR and heart rate variability (HRV) have been identified as valid stress markers [22,23].

To facilitate chemical reactions to provide energy (ie, the oxidization of glucose and fat), body temperature rises. At the same time, to protect the body from overheating, the sweat glands are also targeted by the SNS, increasing skin conductance and lowering skin resistance, which can be measured between 2 electrodes placed onto the skin [24]. Thus, measuring sweat secretion is an important method to investigate the activity of the SNS and to determine stress reactions.

Directly after the alarm phase, the "resistance phase" ensures and is biochemically characterized by increased cortisol liberation. Cortisol passes through the blood-brain barrier to the hippocampus, which then lowers the activity of the hypothalamic-pituitary-adrenal axis via negative feedback mechanisms. This serves to regulate stress reactions and prevent exhaustion of stress hormones.

Only in chronic stress (eg, when the available resources are insufficient to relieve stress or when the stressor is present over a long period of time), a third phase, "exhaustion phase", follows, with symptoms of exhaustion and a dangerous weakening of the immunological system [25].

The DiPa study aims to test the feasibility of measuring and merging subjective and objective stress parameters in palliative care nurses.

In addition to physiological models of stress, various psychological frameworks have been developed to explain the conditions under which stress occurs in the workplace. One of the most widely known is the Job Demand-Control (JDC) model, originally proposed by Karasek [26]. This model posits that stress results from the interaction between the psychological demands of a job and the individual's decision latitude, or control, over their work tasks. According to the model, high job demands combined with low control are particularly detrimental, leading to increased strain and adverse health outcomes.

It is important to acknowledge that the JDC model—and other cognitive-behavioral stress frameworks—can be meaningfully integrated with our somatic approach. All major stress models, despite differing in their conceptual emphasis (eg, cognitive appraisal, social support, or organizational structure), converge on the notion that stress elicits a biological stress response. Our focus on this common somatic end point allows for alignment with a broad range of theoretical models, including the JDC model. Specifically, job conditions characterized by high demands and low control, as described in the JDC framework, are likely to be present in the workplace of palliative care nurses and are thus likely to activate the very physiological stress pathways that are measured in this study.

Methods

Study Design

To assess the working conditions of and burden on nurses in palliative settings, preliminary tests were executed to investigate the functionality of and user experience with wearables, including handling in a hospital environment and resistance to the hospital's disinfection routines.

The study design (Figure 1), a prospective cross-sectional approach with continuous measurements throughout each workday, allows for assessing both the current manifestation of stressors and current level of perceived stress load both objectively and subjectively. Participants were split into groups, and each group conducted the measurements for 6 weeks, thus expanding the span of the measurement across all participants (to increase the time frame depicted in the data), while individual

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participants were not burdened with the additional workload for longer than necessary.

Figure 1. Study design. EDA: electrodermal activity; HR: heart rate; HRV: heart rate variability; NFC: near-field communication; UMR: University Medical Centre Rostock.

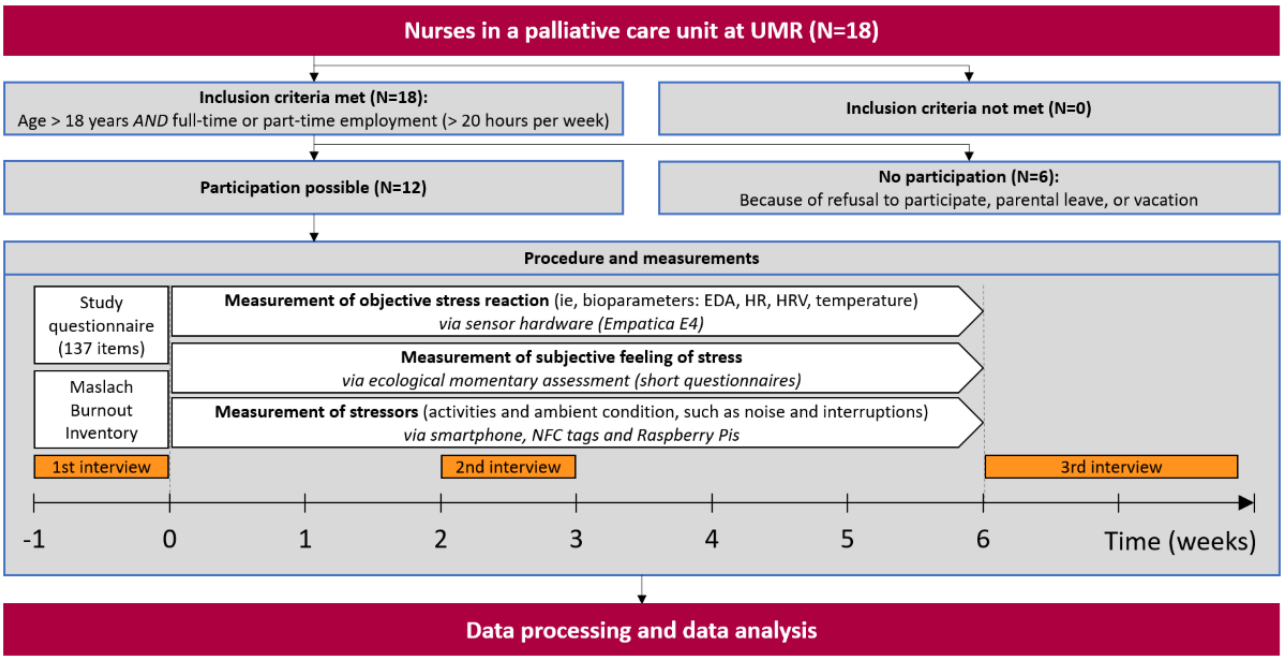

Apparatus

Overview

Stress level was measured both objectively (physiological stress reaction) and subjectively (appraisal of the perceived stress in ecological momentary assessments [EMAs]). Possible stressors were also identified both as subjective perception via questionnaires and objectively by matching physiological stress responses to concurrent ambient conditions, such as noise, interruptions, or specific activities. We compared the objective stress levels to the daily staffing, occupancy level, and other daily changing factors of a hospital ward.

To this end, a combination of wearable and ambient sensors that can measure the physiological (objective) stress reaction as well as possible stressors (causes of stress) is being used. The prototypical setup consisted of a smart wristband, a smartphone, near-field communication (NFC) tags, and Raspberry Pis equipped with microphones to record interruptions (incoming telephone calls) and unexpected tasks (calls from patients). The setup can be seen in Figure 2 and Figure 3. At the end of the study, it will be possible to characterize a normal working day of a palliative caregiver more precisely in terms of physical and psychological stress. The perceived burden will be correlated with bed occupancy and the numbers of patient admissions, discharges, and deaths per day as well as influence of the duty roster design (including the staffing) and frequency of interruptions by telephone or a patient's bell.

Figure 2. To assess possible stressors, near-field communication (NFC) tags have been programmed and placed in numerous positions on the ward.

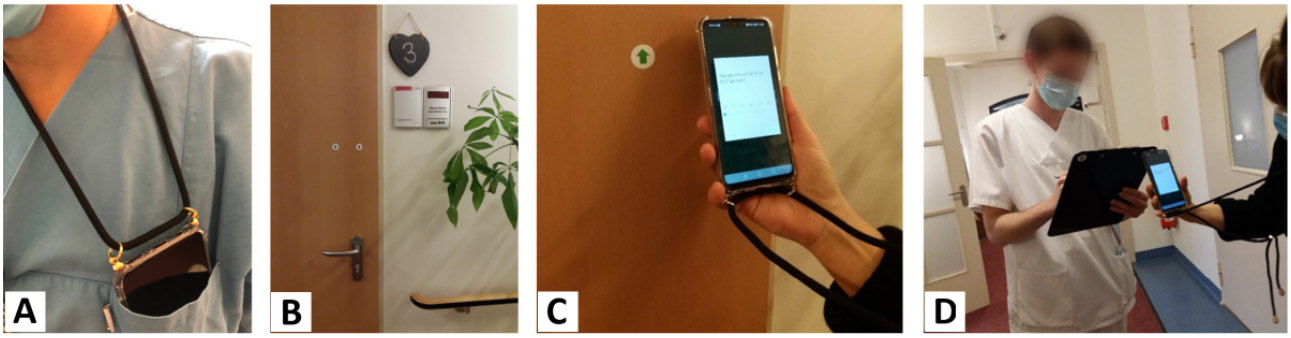

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Figure 3. Electrodermal activity, heart rate, and skin temperature are recorded with the Empatica E4 research wristband.

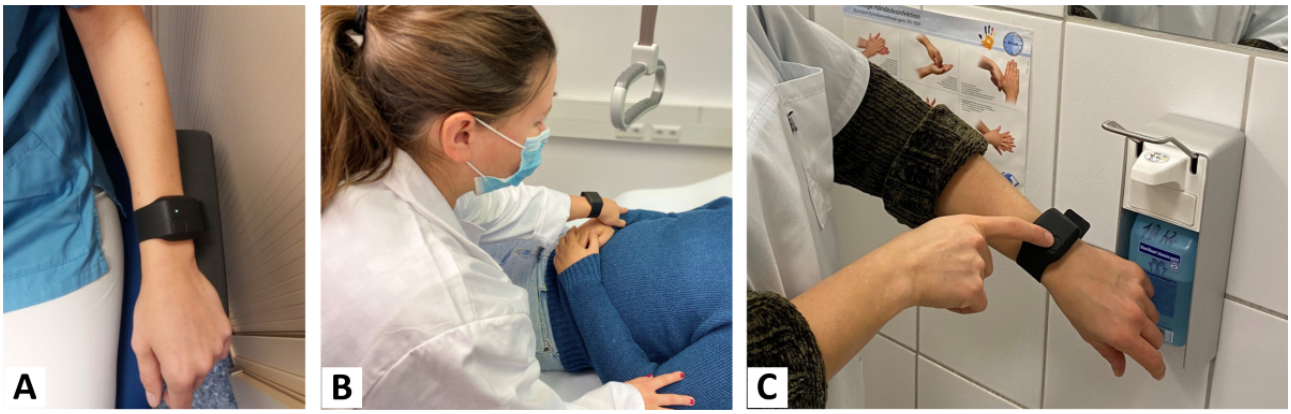

Body-Worn Equipment

The results of measured electrodermal activity (EDA), HR, and skin temperature should provide information about an SNS reaction to stress [14]. All these parameters are recordable with the Empatica E4 (Empatica Inc) research wristband. Thus, to measure the physiological stress reaction, we used the commercially available Empatica E4 wristband [27]. The E4 wristband possesses a photoplethysmography sensor and 2 electrodes to measure the galvanic skin response at the wrist. It was used to measure pulse, HRV, EDA, and body temperature (surface). The automatic data preprocessing was bypassed, since this would require sending the sensitive data to an alien server. To circumvent these international servers for reasons of data protection, the code of the E4 had been altered, allowing the extraction of raw data. Raw data were then sent to the smartphone, which is also part of the study's setup, and stored on the phone's memory until transferred to a local server. The E4 had no display and thus provided no feedback to the participants that could interfere with or distort the measurement. LEDs provided the necessary feedback on the functionality of the wristband, and additional feedback on functionality (and connectivity) was given in the corresponding smartphone app.

In addition to the LED, allowing event marking (ie, a real-time annotation) via tapping the button deposits a record in the session file. The record included the time of the button press (expressed as a Unix time stamp in UTC), which was synchronized with the initial time of the corresponding session. Feedback on the button press was given both visually (illuminating the LED) and audibly (beeping). The button press was used for 2 purposes: (1) logging an event of subjectively perceived stress (a single button press) and (2) logging the event of disinfecting one's hands (as this can alter the EDA; 2 consecutive button presses).

Preparation of the Hospital Ward

To assess possible stressors, NFC tags (Figure 2C) had been programmed and placed in numerous positions on the ward. The NFC tags were used to log the activity of the participants, such as NFC tags placed on the doors of the 9 patient rooms to log when a participant entered or left a specific patient room. Other activities that were logged included the beginning and ending of meetings (medical rounds; daily, weekly, and monthly team meetings; and daily handovers at the beginning or end of a shift), the beginning and ending of conversations with patients or their relatives, and relaxation.

Furthermore, in addition to pressing the wristband button, as aforementioned, a stressful event could also be marked by scanning the NFC tags, which offered the possibility to communicate a challenging situation by entering a short description of the current event using a Huawei smartphone P30 lite. This smartphone, which hangs by a cord around the participants' necks and can be stored conveniently in their gowns' pockets with the microphone poking out (see Figure 2A), was also used to measure ambient noise.

Last, 2 types of interruptions were measured, each with a microphone attached to a Raspberry Pi 4 Model B. The first was an interruption by telephone calls (eg, outsiders calling to reach patients or to retrieve information about the patients such as family physicians or calls from within the hospital, eg, calling about referrals). The second kind of interruption was a distress call (from a patient) or an emergency call (from a fellow nurse or physician), both broadcast through the hospital ward's bell system.

Questionnaires

Two types of questionnaires were used to assess subjective stress levels. An extensive study questionnaire with 137 items (101 of which ask for specific stressors) was handed out at the beginning of the study. It asked about the subjectively perceived frequency and participant's rating of different stressors (ie, how often does this event take place and how stressful does one find it). A multiplication of the 2 parameters allowed for an evaluation of the perceived stress. Although an event could be labeled as very stressful, it was not necessarily a meaningful stressor if it rarely ever occurred. Thus, a stressful event that seldom took place or a frequent event that barely stressed the participant were both considered less harmful than an event that was both frequent and (moderately or highly) stressful. The study questionnaire was designed specifically for this study by a psychologist and a nurse with longstanding work experience, incorporating known stressors from the literature as well as stressors mentioned in a survey carried out in a palliative ward and an outpatient palliative care facility.

In addition, the Maslach Burnout Inventory [28] was handed out to assess further burdens (or possible sequelae of the stress).

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It is a standard questionnaire that will allow for interstudy comparisons of this study's findings with those in the literature.

In addition to these 2 questionnaires that were only completed once at the beginning of the measurements, the subjective stress level was also assessed throughout the workday and accompanied the continuous ambulatory measurements using EMAs. EMAs are short questionnaires asking for self-reported information that documents the perceived subjective experience of stress at a certain moment (ie, a *momentary* appraisal of their *current* stress level) [29]. The questionnaires popped up on the participants' smartphones whenever an NFC tag was scanned that indicated the end of an activity (eg, end of rounds, leaving a patient room, end of a meeting, end of speaking with a patient or his or her relatives) and asked, for example, "How stressed do you feel right now?" with a continuous slider from 0% to 100%, labeled in increments of 20%. In addition, the questionnaire could also be accessed at any time by scanning a designated NFC tag called "open questionnaire." Additional EMAs popped up when the participant put the setup on at the beginning of a shift (greeting the participant, asking for the subjective sleep quality of the night before, and asking about his or her current stress level) and when the setup was removed and shut down at the end of the shift (asking for the current stress level, asking how many patients were looked after throughout the day, and wishing the participant a pleasant recreational time).

Sample and Recruitment

The PCU at UMR, with its 14 beds, is the largest PCU in Mecklenburg-Western Pomerania, Germany. It employed 13 full-time nurses and 5 part-time nurses who work in a 3-shift system during the study implementation in 2021. Study participants had to be older than 18 years, their working time had to have a minimum of 20 hours per week, they had to have proficiency in written and spoken German, and they had to be employed at the palliative care unit at the Rostock University Medical Centre (inclusion criteria). Exclusion criteria comprised of nonconsenting capacity and nonfulfilment of all inclusion criteria. For the DiPa study, all 18 nurses working in the UMR PCU, who partly specialize in palliative care, were invited in December 2020 to participate in the study by presenting the procedure and aims of the project in a lecture as well as in a written inquiry. The measurement period for each participant was 6 weeks allowing for a total measurement duration of 3 months.

A power analysis was not conducted as the population was prespecified (N=18), rendering the need for an accruing sample. In the end, 12 nurses agreed to participate, resulting in a participation rate of 67% (12/18).

Patient and Public Involvement

Patient involvement was not directly part of our study design because of the focus on nursing staff in palliative care. However, analogous to patients, our study participants were included in selected questions when we created the study design. As an example, preliminary tests could be used to compare measuring instruments with different measuring methods with regard to their wearing comfort and manageability. Furthermore, before starting the measurements, the nursing staff were shown a list of possible stressors in their work area. Anyone who had an additional suggestion could add it anonymously to this list. After the study design was developed further, the study was presented to the potential participants in an on-site presentation, as aforementioned. There was also the opportunity for questions and answers. Each nurse was free to take part in the study after having detailed knowledge of the study objective and carrying out the measurements on a daily basis.

Apart from our study participants, the public was not especially included in the planning phase. The expected results could affect the public and especially nurses in palliative care or other medical departments indirectly by identifying stress factors and their possible reduction.

Procedures

After enrollment, each participant received thorough instruction on how to use the technical equipment. On the same day, each participant was interviewed separately to define their expectations and attitudes toward the DiPa study. Interviews were conducted by UMR staff who were not involved in the study (ie, a research assistant or a member of the central research center of the UMR). The answers were recorded during the interview and transcribed afterward to allow for an evaluation by independent raters to reduce bias and ensure data privacy. In addition, the participants completed the questionnaire on their perception of stressors and stress, including patient-associated stressors, working environment, team-associated stressors, and resources.

Participants were instructed to conduct the measurements during every shift. At the beginning of the shift, the participants gathered their equipment from their locker, put on the wristband, and picked up the smartphone. By turning on the wristband, a digital questionnaire appeared automatically on the smartphone's display, welcoming the participant and asking for their current stress level as well as sleep quality of the previous night. Further free-text annotations were also possible. Participants then stored the smartphone in the pocket of their scrubs and began their workday.

Participants were instructed to use the smartphone to scan the corresponding NFC tag whenever entering a patient's room. To this end, a green NFC tag with an arrow was placed on each patient room door. This event was thus recorded on the smartphone. Analogously, a red NFC tag was scanned when leaving the room. This not only recorded the event but also prompted a short questionnaire that was displayed on the smartphone's screen, asked for their current stress level, and included a free-text space.

Special recurring processes on the PCU like daily visits, weekly and daily team meetings attended by nurses and physicians, and patient interviews had their own individual NFC tags denoting the start and end.

In parallel to data recording by the wristband and smartphone, the study team collected and analyzed data about the nurses (eg, how many worked in the ward per shift, length of work experience in years, and if they had the additional designation of "palliative care nurse," as we expected an influence of

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workload for each participant). The second focus was patient-associated factors, especially the average, minimum, and maximum patient age and number of occupied beds per day. Because the PCU treats many critical ill patients with life-limiting diseases, we also thought it could be important to analyze the number of deaths per day.

Data Analyses

Every participant received a pseudonym so that data from the different sources (interviews, questionnaires, physiological data from the E4, EMAs from the smartphone) can be grouped. Raw data analyses and analyses of data on an individual level are being conducted by the Fraunhofer IGD, an institution that is independent of UMR, ensuring data privacy. The UMR will receive the preprocessed, averaged data for further evaluation processes.

The experimental setup consisted of a local server that, via a locally installed network, only ensured the station's data flow by transmitting data from smartphones and the wristbands. Local access to the server was limited by password-protected log-in. Data were also stored in pseudonymized form, so that no clear names could be found in the files. Data were automatically forwarded from the smartphone once a day to a server within the UMR via Wi-Fi connection. There, the collected information initially remained locally on the hard drive. At regular intervals, a Fraunhofer Institute employee brought along an encrypted data storage device on which he or she created a local backup copy on and transferred it to a computer within the Fraunhofer Institute. This prevented unauthorized access by unauthorized people.

The participants were informed in advance about the guarantee of data security, including the scope of the data collected and the duration of data storage, in their written consent form. These aspects were explained to an ethics committee and confirmed by a positive ethics vote.

The raw data were collected with the Empatica E4 device and stored in CSV files. Each parameter was sampled at the maximum available rate provided by the Empatica E4 firmware. The parameters included interbeat intervals (IBI) sampled at 1/64 second, blood volume pressure sampled at 64 Hz, EDA sampled at 4 Hz, temperature sampled at 4 Hz, and acceleration sampled at 32 Hz.

All parameters were stored with a Unix time stamp to allow the proper selection of intervals.

The EDA data were decoupled using the NeuroKit2 Python library so that the tonic component (skin conductance level) and the phasic component (skin conductance response) could be extracted.

Since the Empatica E4 wristband saved IBI only when the signal quality is sufficient, IBI data can include missing values. The IBI data were used to determine the HRV and HR by applying the following equation:

The acceleration data were fused to a 3D vector by applying the following equation:

All algorithms for data extraction were written in Python using Jupyter Notebooks and the *Pandas*, *Numpy*, *SciPy*, *Matplotlib*, and *NeuroKit2* libraries.

For stress detection analysis, all stress events marked with a button press will be identified, and windows surrounding this event will be extracted and averaged, leading to one value per stress event per participant. Analogously, the windows surrounding a scan of the NFC tag "relaxation" and the baseline windows will be extracted and averaged as well. Descriptive and inferential statistical analyses will be applied using IBM SPSS Statistics 30. Weighted ANOVAs for correlated samples will be computed to compare the stressful events and the baseline for each physiological parameter.

To examine the predictability of experiencing stress, the subjective ratings given in the EMA will be used as ground truth. Surrounding the EMA, data windows will be extracted from the data for each physiological parameter. A linear regression will be computed with the subjective stress level (EMA) as the dependent variable and entering the means of the physiological variables (HR, HRV, tonic EDA, phasic EDA, temperature, and acceleration) as independent variables. Artificial intelligence approaches will be used to analyze the data where appropriate.

With the data for daily occupancy of patients and the total number of nurses on the same day, we will be able to calculate the relationships of these 2 variables with stress. The minimum occupation level according to the recommendation from the German Society for Palliative Medicine (*Deutsche Gesellschaft für Palliativmedizin*) on staffing in palliative wards [30] of 1.4 nurses per patient will be used as a cutoff to create two subgroups of "well-staffed" and "under-staffed."

Usage of Study Guidelines

We structured our study protocol using the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [30].

Ethical Considerations

The ethics committee of the University of Rostock approved the study (approval A 2020-0295). Data protection is ensured by providing participants with their own lockers to store their devices, gathering data using pseudonyms only, and analyzing raw data at the Fraunhofer IGD exclusively (sharing only group means with the UMR, which employs the participants).

All possible participants received information in writing assuring them that participation was voluntary, that the choice of not participating would yield no harmful consequences, and that they could withdraw from the study at any time if they no longer wished to participate. Each participant had the possibility to ask further questions. They were asked by a study nurse, so the inviter and the participant were on the same hierarchy level, lowering any possible pressure that the nurses might have felt to participate. They were assured in speech and writing that they did not have to fear professional consequences or disadvantages if deciding against participating in the study.

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Results

The DiPa study was funded in October 2019; received ethics approval on December 18, 2020; and was registered in the German Register for Clinical Studies on February 10, 2021. As of January 2021, the devices were assembled, and the stationary equipment (eg, the server, the NFC tags) was placed on the ward. Recruitment to the trial is finished, with a total of 12 participants having signed the written consent form by June 12, 2021. The measurements were initiated by giving out the first questionnaires.

The data assessment algorithms have been programmed, and the data assessment has been finished.

We expect to finish data analysis and publish the final results at the end of 2026 or beginning of 2027. We aim to publish the data and summary findings in academic journals and at conferences. For the participants, these will be presented accessibly in a staff meeting.

Discussion

Potential Outcomes and Impact

We aim to achieve results that provide deeper insights into the stress levels of nursing staff on the palliative care ward. A central focus is on identifying the causes of this stress. An essential part of the study deals with the investigation of various stressors, which include patient care, contact with relatives, working conditions, and the collegial working environment. Based on the studies by Diehl et al [6,11,31-33], we assume that the challenging task of dealing with seriously ill, dying patients and their death is a significant source of stress. In addition, based on the preliminary discussions with the participants, we expect that a considerable part of the stress is triggered by contact with the patients' relatives. As a third important factor, we assume that the working conditions, including duty rosters, interaction with colleagues, and the number and timing of meetings, have a significant influence on the participants' experience of stress. In order to record these and other relevant factors such as air quality or activities, a complex test design is required. Although questionnaires can ask about subjective feelings at a particular point in time, they are not able to take sufficient account of the day's events as a whole or capture aspects that the participants may not be aware of—a well-known problem with the use of questionnaires.

To our knowledge, the DiPa project is the first innovative project addressing the burden on nursing staff in palliative care using wearable devices to collect objective data in combination with subjective measurement instruments such as questionnaires.

Since this project is the first of its kind, it aims to measure the feasibility of generating data with the abovementioned technology as a primary outcome. As secondary outcomes, we want to identify correlations between the recorded bioparameters and parameters of the work environment (time, telephone, temperature, etc) as well as subjective well-being, especially in handling sensor technology in a normal working day—which could be a potential stressor by itself.

Strengths and Limitations

The content-related strengths lie mainly in two aspects: the multitude of measurements and the continuous measurement. As for the multitude of measurements, the study can assess all three aspects of the stress phenomenon: the stressors that elicit stress (activities, ambient conditions, noise, and interruptions—measured via smartphone, NFC tags, and Raspberry Pis), the stress reaction in the sense of subjective appraisal and feelings (measured via EMAs on the smartphone), and the stress reaction in the sense of the objective stress reaction (bioparameters, EDA, heart rate, HRV, and temperature measured via sensor hardware).

In addition, the study also features a methodological strength in the unobtrusiveness, interaction, and automation of the measurement devices: the smartphone and the sensor hardware were worn by the participants and were easily accessed. The sensor hardware was linked to the smartphone and sent data automatically; the smartphone in turn sent these data automatically to the server during the times when it was stored and charged in the lockers. This allowed for smooth data acquisition and increased motivation of the participants to collect data over such a long period and while working.

The study apparatus, for example, the use of smartphones or the scanning of the NFC tags, introduces a potential for user fatigue or confusion. The feasibility of sustained use was not assessed in this study, as the study did and does not intend sustained use of the apparatus. The assessment was deliberately limited to a duration of weeks to gain insights on the status quo of perceived stress, with a long-term goal of deducing provisions to reduce stress. However, the level of perceived fatigue caused by the interaction with technological devices, as well as the level of acceptance of technology and skill level when interacting with technology, could be assessed in future studies with a larger sample to allow for analyzing potential influences of these factors.

In the same line, introducing repeated prompts during the workday (the EMAs)—together with the aforementioned use of technology—can act as a further stressor. While this method enabled us to capture real-time self-reports of perceived stress and contextual factors, it may have inadvertently increased participants' cognitive load or interfered with task performance, thus acting as an additional stressor. This reactivity to the assessment process itself could potentially amplify or confound the stress responses we aimed to measure.

Nonetheless, EMA offers critical advantages that justify its use. Unlike retrospective questionnaires, EMA minimizes recall bias and allows for the assessment of stress as it unfolds in the natural work environment, providing high ecological validity. This approach also enabled us to capture dynamic fluctuations in stress levels across the workday and to relate them temporally to physiological stress markers. Importantly, the combination of EMA and physiological measures enhances our ability to understand the complex interplay between subjective experience and somatic stress responses.

Still, the potential reactive burden introduced by the method should be treated as a confounding variable. To mitigate its

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potential confounding effect, the EMA protocol was designed to be minimally intrusive. The number of mandatory EMA prompts were limited to two per shift: one at the start and one at the end of the workday. Additional EMA entries were linked to the scanning of the NFC tags, enabling context-specific data collection while reducing the need for separate prompts. These intermediate assessments were optional and could be skipped without consequence if participants felt rushed, overwhelmed, or otherwise unable to respond at the moment.

Furthermore, we actively monitored the acceptability and perceived burden of the EMA procedure through qualitative feedback. Participants were interviewed midway through the assessment period and again at the end, where they were asked about the extent to which the EMA prompts were experienced as disruptive or burdensome. While a detailed analysis of this qualitative feedback is beyond the scope of this paper, these data are being prepared for publication in a separate manuscript focusing specifically on participants' subjective stress perception, including their experiences with EMA in high-demand clinical settings.

Regarding the study population, the final sample (n=12) includes no stratified analysis plan based on shift, age, or prior burnout, limiting subgroup insights as a result of the study design. There is also a self-selection bias risk. Participants volunteered, likely introducing selection bias; for example, more tech-savvy nurses participated. However, we do not believe that only more resilient nurses participated in the study. Indeed, it is likely that interest in the study results and the resulting reductions in stress led to increased participation among a group of nurses who demonstrated even lower levels of resilience to stress.

Nurse shortages and the high emotional and physical demands of palliative care contribute to chronic workplace stress, which can undermine both staff well-being and patient care quality. Yet, traditional methods of stress assessment (eg, surveys and end-of-shift reports) often fail to capture the real-time, fluctuating nature of stress in these settings. By using digital monitoring tools such as EMA and physiological sensors, we aim to better understand the moment-to-moment stress patterns nurses experience during their shifts. This approach not only captures stress more accurately but could inform future targeted interventions or adaptive support systems, especially in the strained setting of palliative care where staffing and resilience are critical. The effects of these targeted interventions could then be evaluated by using similar methods to ensure comparability while adding measures for practical relevance such as stress-related attrition (eg, burnout or leaving the profession).

Future Directions

In the near future, the results are to be used to derive preventive measures to reduce stress. While it is a scientific end in itself to gain knowledge on the stressors, we would like to use this knowledge to help enhance the working conditions and the well-being of the nursing staff.

For example, structural processes can be questioned and adjusted to reduce stress and its impact. The effectivity of these interventions will be part of further studies.

Parameters that measure stress have trained a multidimensional model. Based on the known input parameters (HRV, tonic and phasic EDA, and NFC labels) and knowledge of their correlation with stress (from the literature), it is possible to determine which factors primarily influenced the decision or outcome by visualizing the activation of neurons within the network. For regression, the architecture of a fully connected (dense) neural network will be used, with the goal of building a regression model that targets a value between 0 and 100%.

Acknowledgments

The DiPa (Digitally Identifying and Minimizing Stressors in Palliative Care) study has been funded by the State Office for Health and Social Affairs of Mecklenburg-Western Pomerania, Germany (Landesamt für Gesundheit und Soziales Mecklenburg-Vorpommern, Friedrich-Engels-Platz 5-8, 18055 Rostock; grants LAGuS/MV-6-S150-0005/19 and LAGuS/MV-6-S150-00029/19). The LAGuS had no other role than funding.

The interdisciplinary steering committee gave input for the study design and ethical considerations. The University Medical Centre Rostock (UMR)—as the coordination center—played a key role in developing the study design, implemented the study, and provided access to the study participants. The Fraunhofer Institute for Computer Graphics Research—as the data management team—co-designed the study, preprocessed data, and analyzed and interpreted data. The central study office of UMR helped conduct the interviews with the study participants and enhanced the openness to share sensitive information while protecting the participants' privacy. They also store the consent forms.

The authors attest that there was no use of generative artificial intelligence technology in the generation of text, figures, or other informational content of this manuscript.

Data Availability

Because of our small number of study participants, it might be possible to draw conclusions about a particular person by publishing the detailed data. In our study consent form, the participants were informed about the data dissemination: "The data collected as part of the study will be processed and evaluated in cooperation with the Fraunhofer Institute. The data will only be passed on to other institutions or persons and published cumulatively (for example, averaged over the entire group of all participants), i.e. conclusions about individual persons are excluded." Thus, we are not allowed to publish our data due to our own privacy policy.

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Authors' Contributions

All authors were part of study conceptualization. WC and AS drafted the protocol. Content additions in the sections of technical equipment and data evaluation were done by FH. Having a comprehensive experience in working in palliative care, CS delivered further information concerning the clinical environment. CJ, HME, SF, and MA acquired financial resources. They also reviewed and edited the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Abbreviations

DiPa: Digitally Identifying and Minimizing Stressors in Palliative Care
EDA: electrodermal activity
EMA: ecological momentary assessment
HR: heart rate
HRV: heart rate variability
IBI: interbeat intervals
IGD: Institute for Computer Graphics Research
JDC: Job Demand-Control
NFC: near-field communication
PCU: palliative care unit
SNS: sympathetic nervous system
UMR: University Medical Centre Rostock

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Protocol

Exploring the Time to Onset and Early Predictors of Poststroke Spasticity Combined With Surface Electromyography: Protocol for a Nested Case-Control Study

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Abstract

Background: Poststroke spasticity (PSS) is a frequent sequela in patients who have experienced stroke. This form of paralysis is more prevalent compared to other poststroke sequelae and is among the most challenging and complex symptoms to manage. Surface electromyography (sEMG) can reflect the physiological information of muscles in real time and is highly beneficial in diagnosing neuromuscular diseases in clinical medicine.

Objective: This study aimed to investigate the timing of poststroke limb spasms using a nested case-control study combined with sEMG and to identify and predict factors of PSS at an early stage.

Methods: This was a nested case-control study. Participants were assessed within 24 hours of the onset of hospitalization using a standardized case report form to evaluate general patient information and clinical data related to cerebral infarction and imaging. Upon inclusion, patients were assessed after 1, 2, 4, 8, and 12 weeks, using the Modified Ashworth Scale (MAS) for spasticity severity, root mean square values from sEMG for limb spasm severity, and the simplified Fugl-Meyer (S-FM) Assessment for limb motor function. Patients who experienced spasticity within 12 weeks were assigned to the spasticity group, whereas those who did not experience spasticity were assigned to the control group. Unmatched case grouping was implemented. Data with normal distribution were analyzed using the *t* test, while data with nonnormal distribution were analyzed using the rank-sum test; categorical data were analyzed using the chi-square test, rank-sum test, or Fisher exact test. Logistic regression analysis was used to investigate factors affecting treatment outcomes. Data processing, analysis, and visualization were conducted using Statistical Package for the Social Sciences software (version 26.0; IBM Corp).

Results: This study is funded by the Chinese Association of Ethnic Medicine and began participant recruitment and registration in November 2023. The study is currently ongoing, with 66 participants enrolled as of March 2025.

Conclusions: This study selected a diagnostic method combining sEMG and subjective scales to determine PSS, aiming to eliminate diagnostic errors caused by subjective assessments. This study adopted a nested case-control study method, which has minimal information bias, allowing for the inference of causal relationships between exposure and disease.

Trial Registration: Chinese Clinical Trial Registry ChiCTR2300077121; https://www.chictr.org.cn/showproj.html?proj=205037

International Registered Report Identifier (IRRID): DERR1-10.2196/65829

(JMIR Res Protoc 2025;14:e65829) doi:10.2196/65829

KEYWORDS

nested case-control study; poststroke spasticity; stroke; surface electromyography; early predictor

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Introduction

Stroke is currently the leading cause of disability and death in China, with a high incidence, high disability rate, high mortality rate, and high recurrence rate [1]. In China, approximately 3 million new patients with stroke are diagnosed annually, and 70%-80% of stroke survivors experience residual limb paralysis, which prevents them from living independently. Poststroke spasticity (PSS) is the most prevalent of these disabilities [2]. PSS is the result of stroke-induced damage to upper motor neurons, causing the loss of basic voluntary motor control by the advanced motor centers of the cerebral cortex and the inhibition of the primitive functions of the lower motor centers, resulting in a spastic state [3]. Muscle tone is the force generated by the interaction of muscle cells, typically measured by the resistance experienced during passive muscle stretching. However, these methods are unable to quantify muscle tone objectively [4].

Related researches suggest that surface electromyography (sEMG) can reflect muscle tone mechanisms through the threshold of muscle reflex electromyography, enabling direct, objective, timely, and accurate descriptions of spastic muscle tone [5]. Many studies also demonstrate that sEMG is crucial for investigating muscle contraction status and evaluating the degree of spasticity [4,6,7]. It quantitatively detects and evaluates the synchronization and contraction levels of different muscle groups involved in activities, thereby enhancing its utility in disease in the diagnosis and evaluation of diseases [8].

It is estimated that approximately 25% of patients experience spasticity within 2 weeks after cerebral infarction based on existing observational data. A total of 9 recent studies were reviewed and summarized by Sunnerhagen et al [9], which evaluated the spasticity status at different stages after stroke. The research findings emphasize the necessity of conducting follow-ups with patients at an increased risk of severe spasticity to facilitate the initiation of appropriate spasticity treatment and prevent adverse outcomes. Therefore, this clinical study aimed to improve the prognosis of patients with PSS by exploring the time of PSS occurrence through a nested case-control (NCC) study, early identification, and prediction of PSS factors. Our research plan and informed consent form were submitted to the Ethics Committee of the Affiliated Hospital of Hunan University of Chinese Medicine. Ethical approval was obtained on June 25, 2023. The results were to be published after the conclusion of the trial.

Methods

Study Design

The research methodology used in this study was an NCC with a specific emphasis on PSS. The research cohort consisted of approximately 72 patients admitted to the Hunan Integrated Traditional Chinese and Western Medicine Hospital (Hunan University of Chinese Medicine Affiliated Hospital) due to cerebral infarction. A standardized case survey form was designed to gather general information, clinical data about cerebral infarction, and imaging data for both patient groups. Relevant scale assessments were conducted within 24 hours of admission. The root mean square (RMS) values of sEMG, Modified Ashworth Scale (MAS), and Fugl-Meyer Assessment Scale (S-FM) were assessed on the bilateral biceps brachii, abductor pollicis brevis, tibialis anterior, and gastrocnemius muscles of patients at 1, 2, 4, 8, and 12 weeks in both active and passive flexion states upon inclusion. The patients who developed limb spasticity during the 12-week follow-up period were categorized as the spasticity group, while those who did not were the control group. The study flowchart is illustrated in Figure 1. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) schema is depicted in Table 1 (checklist provided in Multimedia Appendix 1).

Figure 1. Trial flowchart. Triangles represent the root mean square evaluation of surface electromyography, Modified Ashworth Scale score evaluation, and simplified Fugl-Meyer Assessment Scale score evaluation. NPSS: non-poststroke spasticity; PSS: poststroke spasticity.

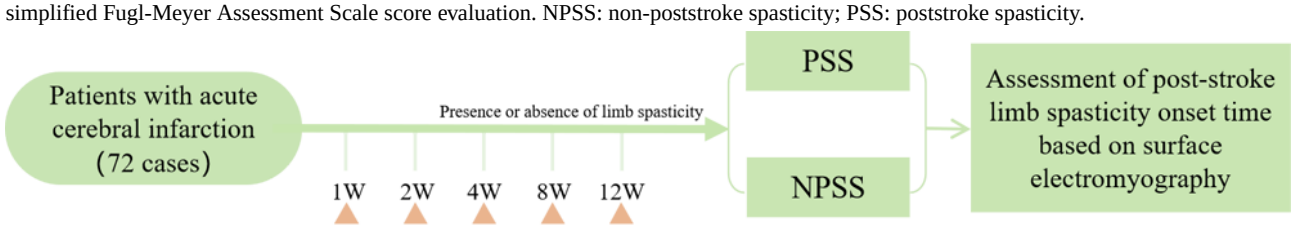

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Table 1. Study visit schema.

Research content	Screening period (D_{-5}-D_0[a])	Observation period (1 week)	Observation period (2 weeks)	Follow-up period (4 weeks)	Follow-up period (8 weeks)	Follow-up period (12 weeks)
Signing an informed consent form	✓					
Reviewing inclusion and exclusion criteria	✓					
Demographic data	✓					
Collecting medical history	✓					
Internal medicine assessment (vital signs)	✓	✓	✓	✓	✓	✓
12-lead electrocardiogram	✓					
MAS[b] score evaluation		✓	✓	✓	✓	✓
RMS[c] evaluation of surface electromyography		✓	✓	✓	✓	✓
S-FM[d] score evaluation		✓	✓	✓	✓	✓

[a]D_{-5}-D_0: day –5 to day 0.

[b]MAS: modified Ashworth scale.

[c]RMS: root mean square.

[d]S-FM: simplified Fugl-Meyer.

Steps for sEMG

Materials and Equipment

The sEMG collection and analysis system used in this study was manufactured by BTS (model FreeEMG 300, serial number: 2106-F7 60 0E; Figure 2).

Figure 2. Surface electromyography device.

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Collection Sites

sEMG signals from the biceps brachii, flexor pollicis brevis, and tibialis anterior and gastrocnemius muscles during different states of elbow flexion, thumb flexion, index finger abduction, and ankle dorsiflexion, and plantarflexion were collected [10,11]. EMG waveforms were displayed on the screen in real time during the collection process, allowing the experimenter to verify signal quality and record data.

Collection Method

Overview

1. Patient preparation: The patient was held lying or sitting for 30 minutes. The strenuous activity was prohibited to prevent muscle fatigue, potentially impacting the experimental results.
2. Skin preparation: The measured area was wiped with a 75% alcohol swab to remove surface oils, increase conductivity, and minimize data error.
3. Electrode configuration: Ag/AgCl surface electrodes (10 mm diameter, 20 mm interelectrode distance) were used and positioned according to the Surface ElectroMyoGraphy for the Non-Invasive Assessment of Muscles (SENIAM) guidelines. Channel A (left side) and Channel B (right side) corresponded to the target muscles: biceps brachii, flexor pollicis brevis, tibialis anterior, and gastrocnemius. The active electrode was placed at the point of maximal muscle belly thickness, with an interelectrode spacing of approximately 1.5-2 cm.
4. Steps: The participant was settled in a sitting or supine position for optimal comfort. The participant was directed to relax completely, ensuring no EMG signals were observed on the oscilloscope. During active and passive muscle contractions, signs were collected from the biceps brachii, flexor pollicis brevis, tibialis anterior, and gastrocnemius muscles. The patient was instructed to perform the movements with the utmost effort and complete them uniformly within 2 seconds. After the signal stabilized, the position was maintained for 3-5 seconds before the movement was repeated. A 25-second cycle was used to collect EMG signals from the muscles on both sides in active and passive states. The participant was permitted to rest after completing 1 cycle. The collection process was repeated 3 times, using the average of the 3 measurements as the final indicator.

Biceps Brachii Collection

The examiner fixed the participant's elbow joint using his left hand and instructed the participant to perform elbow flexion, ensuring the movement was completed uniformly within 2 seconds. Once the signal stabilized, it was maintained for 3-5 seconds and the operation was repeated. EMG signals from both biceps brachii in an active state were collected using a 25-second cycle. The participant's biceps brachii were fully relaxed. The examiner fixed the participant's elbow joint using his left hand and instructed him to refrain from applying force. The examiner then used his right hand to move the participant's elbow, adjusting resistance as necessary to ensure the motion was completed uniformly within 2 seconds. Once the signal stabilized, it was maintained for 3-5 seconds before the action was repeated. A 25-second cycle was implemented to collect EMG signals from both biceps brachii in a passive state. Following 1 cycle, the participant was allowed to rest and the collection was repeated 3 times, using the average of the 3 measurements as the final indicator.

Flexor Pollicis Brevis Collection

The examiner fixed the ventral side of the participant's thumb distal segment with his left hand and instructed the participant to perform thumb flexion, ensuring the movement was completed uniformly within 2 seconds. After the signal stabilized, it was maintained for about 3-5 seconds and the action was repeated. The EMG signals from both flexor pollicis brevis muscles in an active state were collected using a 25-second cycle. The participant's flexor pollicis brevis muscles were completely relaxed. The examiner fixed the ventral side of the participant's thumb distal segment using his left hand and instructed the participant not to exert force. The examiner then moved the participant's thumb using his right hand, adjusting the resistance as necessary to complete the motion uniformly within 2 seconds. After the signal stabilized, it was maintained for 3-5 seconds and the action was repeated. A 25-second cycle collected EMG signals from both flexor pollicis brevis muscles in a passive state. After 1 cycle, the participant was allowed to rest and the collection was repeated 3 times, using the average of the 3 measurements as the final indicator.

Tibialis Anterior Collection

The examiner fixed the participant's tibialis anterior using his left hand and instructed the participant to perform dorsiflexion and plantarflexion, ensuring that movement was completed uniformly within 2 seconds. After the signal stabilized, it was maintained for about 3-5 seconds and the action was repeated. The EMG signals from both tibialis anterior muscles in an active state were collected using a 25-second cycle. The participant's tibialis anterior muscles were completely relaxed. The examiner fixed the participant's tibialis anterior with his left hand and instructed him not to apply force. The examiner then moved the participant's foot with his right hand, adjusting the resistance as necessary to complete the motion uniformly within 2 seconds. After the signal stabilized, it was maintained for 3-5 seconds and the action was repeated. A 25-second cycle collected EMG signals from both tibialis anterior muscles in a passive state. After 1 cycle, the participant was permitted to rest and the collection was repeated 3 times, using the average of the 3 measurements as the final indicator.

Gastrocnemius Collection

The examiner fixed the participant's gastrocnemius using his left hand and instructed the participant to perform dorsiflexion and plantarflexion, ensuring the movement was completed uniformly within 2 seconds. After the signal stabilized, it was maintained for about 3-5 seconds and the action was repeated. The participant's gastrocnemius muscles were fully relaxed. The examiner fixed the participant's gastrocnemius using his left hand and counseled him to refrain from exerting force. The examiner then moved the participant's foot using his right hand, adjusting resistance as needed to complete the motion uniformly within 2 seconds. After the signal stabilized, it was maintained for 3-5 seconds and the action was repeated. The EMG signals

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were collected from both gastrocnemius muscles in a passive state using a 25-second cycle. Let the participant rest after 1 cycle and the collection was repeated 3 times, using the average of the 3 measurements as the final indicator.

Participants and Sample Size

Well-experienced occupational therapists on the team were responsible for appointing potentially eligible patients and individuals interested in this study for further evaluation and consent. If the eligible participants were willing to participate, the project leader (XL) must obtain their signed informed consent.

Eligibility Criteria

The eligibility criteria of this study are listed in Textbox 1.

Textbox 1. Eligibility criteria.

Inclusion criteria

- The Western medical diagnosis was consistent with the diagnostic criteria for cerebral infarction (refer to the diagnostic criteria for ischemic stroke in the second edition of the Clinical Management Guidelines for Cerebrovascular Diseases in China, organized by the Chinese Stroke Association in 2023): (1) acute onset; (2) focal neurological deficits, with a few cases showing global neurological deficits; (3) symptoms and signs persist for more than 24 hours; (4) exclusion of nonvascular brain lesions; and (5) brain computed tomography or magnetic resonance imaging excludes hemorrhage and other lesions, with responsible ischemic lesions identified.
- Age>18 years old, regardless of gender.
- Patients who were conscious and had stable vital signs.
- Muscle strength grading was strictly limited to a level of 4 or below.
- The onset of symptoms occurred within 7 days in all patients.
- Patients or their family members needed to sign the informed consent form.

Exclusion criteria

- Patients who have been diagnosed with poststroke spasticity.
- Any history of motor dysfunction, such as rheumatoid arthritis, limb surgery, joint deformities, multiple sclerosis, spinal cord injury, or neuromuscular disorders that affect limb movement.
- Inability to comply with the research procedures or follow-up due to mental illness, cognitive impairment, or emotional disorders.
- Women who were pregnant or lactating.
- Severe cognitive impairment caused by noncompliance with treatment.

Discontinuing criteria

Withdrawal was a consideration for:

- Those who did not meet the inclusion criteria after enrollment.
- Those who did not attend follow-up visits on time were lost to follow-up, possessed incomplete data, or could not determine treatment efficacy.
- Those who developed severe comorbidities or experienced a recurrent stroke during the trial.

Sample Size

This study pre-assumed an effect size relative risk (RR) of approximately 4. By using unmatched case grouping with a case-to-control ratio of 1: 1, assuming a control group exposure rate of 40%, α=.05 (2-sided test), and power (1β)=0.8, the estimated sample size was as follows: the sample sizes for the case group and control group were calculated to be N1=N2=33 using power analysis and sample size software (PASS 15.0; NCSS, LLC). The formula is calculated based on the sample size of the unmatched case-control study:

Among them, , , , and c=1 (the control number: the number of cases).

We inflated the total sample size to 72 after considering a nonresponse rate of 10% among the study participants.

Unmatched Case Grouping

Patients were selected that met the inclusion criteria were selected. Patients who experienced spasticity events within 12 weeks of follow-up were assigned to the spasticity group. Patients who did not develop spasticity within 12 weeks of follow-up were assigned to the control group based on the spasticity group. Those who did not meet the criteria were excluded.

Outcomes

Primary Outcome: MAS

The MAS is user-friendly, requires no additional tools, and is highly reliable and valid. It is currently the most frequently used tool for assessing muscle tone in research and clinical settings [12]. The MAS grading results were categorized into 6 levels ranging from mild to severe: 0, 1, 1+, 2, 3, and 4. These were quantified as 0, 1, 2, 3, 4, and 5 points, respectively. It is primarily used to evaluate muscle spasticity. The lower the

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score, the closer it is to normal. If the score is higher, it indicates higher muscle tone and more severe spasticity. Currently, there is no consensus regarding the diagnostic criteria for PSS. Many international studies use the criterion of a modified MAS score of ≥1 to diagnose the PSS [13]. The primary outcome of this study was assessing limb spasticity using MAS within 3 months (Multimedia Appendices 2 and 3).

Secondary Outcomes

Secondary outcomes included the evaluation of limb spasticity using the RMS of sEMG and the assessment of limb motor function using the S-FM.

RMS

sEMG can reflect the physiological information of muscles in real time, rendering it a powerful tool for rehabilitation assessment, training plan formulation, and monitoring rehabilitation effects. The RMS is the most commonly used time-domain indicator. It is the square root of the mean of the squares of the instantaneous EMG amplitude over a specific period. The larger the RMS value, the greater the muscle strength or tension, which increases its physical significance. Therefore, this research selected RMS as the research indicator.

S-FM

The S-FM scale can provide an accurate quantitative assessment of limb function in patients with hemiplegic stroke, with a comprehensive evaluation that includes upper and lower limb movements. There are 6 assessment items for each limb section. Each item is assigned a score of 2 points for full completion, 1 for partial completion, and 0 for no completion. The total score for upper limb movement is 12 points, and the total score for lower limb movement is 12 points, making a combined total of 24 points. The evaluator can evaluate the severity of motor impairment based on the participant's final score.

Demographic information was collected. These included (1) demographic characteristics, (2) medical history, (3) unhealthful lifestyle history, (4) stroke history, (5) lesion location, and (6) lesion size (Multimedia Appendix 4).

Statistical Analysis

The variables from the case investigation form were organized in Microsoft Excel and subsequently imported into SPSS software (version 26.0; IBM Corp) for further statistical analysis. For measurement data that adhered to a normal distribution, the results are expressed as mean and SD, and an independent sample *t* test was used to compare the groups. Measurement data that did not follow a normal distribution are expressed as median (minimum to maximum), and the rank-sum test was implemented for group comparisons. Count data are expressed as numbers (percentages). The rank-sum test was used to compare ordered categorical variables, while unordered categorical variables were compared using the Pearson chi-square test. A P value of <.05 indicated statistical significance. The significant data variables identified through the correlation, as mentioned in earlier analyses, were then assigned values appropriate for data processing and subjected to multivariate logistic regression analysis to explore the independent risk factors for spastic paralysis following cerebral infarction (with α=.05 as the test standard).

Data Collection and Storage

Subsequently, the significant data variables identified through the correlation as mentioned above analyses were assigned values that were appropriate for data processing and subjected to multivariate logistic regression analysis to investigate the independent risk factors for spastic paralysis following cerebral infarction (with α=.05 as the test standard). These paper data were transferred to Microsoft Excel 2020 and EpiData 3.1 software (IBM Corp) for proper management. A total of 2 independent researchers were responsible for double data entry and verification to ensure the data's accuracy and authenticity. If there were inconsistent data entries or omissions, the original data were rechecked for further verification. After being entered and verified, all data were prohibited from being altered.

Personal data were kept strictly confidential. The participants' original paper case report forms (CRFs) were securely stored in file cabinets at the research site. Coded identification numbers were used in all reports, data collection, processing, and administrative forms to guarantee participant confidentiality. All paper records with names or personal identification codes were stored separately from documents containing coded numbers. The data were stored on a computer at the research site with a password set by the project leader that was only accessible to the study's staff. Participants' personal information was not disclosed without their written consent.

Trial Status

The trial is in progress and recruiting patients with PSS.

Quality Control

This study collected all medical records following a standardized CRF to prevent subjective bias. The research process ensured the authenticity, completeness, and consistency of medical record collection. Trained physicians were responsible for collecting all pertinent cases to ensure data accuracy. (1) Patients were informed of the pertinent survey items before data collection. Data collection was initiated only after obtaining the patient's consent. A professional explanation of terminology was provided to patients during the survey to avoid using suggestive language. (2) The meticulous and precise recording process guaranteed the data's authenticity. Any required modifications were documented, along with the rationale behind them. (3) All MAS and sEMG assessments in this study were conducted by 2 therapists from our research team, each with over 3 years of experience in neurorehabilitation assessment. (4) Data were entered into an Excel database. Information was promptly recorded, and all indicators were verified to ensure accuracy during each data collection session. (5) Regular validation of research data records was conducted, and the study's authenticity, safety, and progress were assessed.

Ethical Considerations

The study was registered in the Chinese Clinical Trials Register (registration number: ChiCTR2300077121) and was approved by the Ethics Committee of the Affiliated Hospital of Hunan Academy of Traditional Chinese Medicine (approval number

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202371). Each participant signed a written informed consent form (informed consent is displayed in Multimedia Appendix 5). We strictly adhered to the Declaration of Helsinki. The investigation findings were to be published in a peer-reviewed journal and presented at national or international academic conferences.

Results

This study was funded by the Chinese Ethnic Medicine Association in October 2023 and is scheduled to conclude in October 2025. Recruitment and enrollment began in November 2023 and are currently ongoing. The study is designed to assess MAS, S-FM, and RMS values at weeks 1, 2, 4, 8, and 12. An increase in MAS and RMS values accompanied by a decrease in S-FM values is considered indicative of the onset of spasticity. Patients who develop limb spasticity are categorized into the spasticity group, while those without spasticity serve as the control group. As of March 2025, a total of 66 participants have been enrolled, with 56 of them having completed the 12-week follow-up assessments of MAS, S-FM, and RMS. We expect to complete patient enrollment and data analysis in December 2025 and aim to publish the results in 2026.

Discussion

Anticipated Findings

This clinical study aims to investigate the onset timing of PSS through an NCC design, with a focus on the early identification and prediction of PSS-related factors, ultimately to improve patient prognosis. Stroke is one of the most prevalent causes of long-term disability worldwide [1]. Despite the active rehabilitation treatment, the severity of motor disorders in many patients with stroke continues to vary [14,15]. Limb disharmony is a common symptom of motor dysfunction primarily caused by spasms. This condition impedes the patient's motor function recovery and increases his economic burden [16]. The data reveal that PSS patients' medical expenses are increasing 4-fold. Therefore, the onset time of PSS can provide a deeper understanding of its development [17]. sEMG signals can reflect neuromuscular activity to a certain extent due to the varying degrees of correlation between signals and the functional and active states of muscles [18,19]. The sEMG continuously measures the muscle activity in a stationary state and monitors changes in muscle activity during movement [20]. The alterations in sEMG signal characteristics are highly consistent with physiological and pathological changes, which facilitates inference of neuromuscular pathology [21,22] and provides a significant reference value for assessing efficacy in rehabilitation medicine. Studies have demonstrated a significant correlation between the MAS assessments and RMS values in patients with increased upper limb muscle tone post stroke [23]. The assessment of spasticity-related functional impairment largely relies on highly subjective scales. Consequently, we used sEMG to investigate the onset of spasticity within 3 months after a stroke to eliminate errors such as missed diagnoses resulting from subjective assessments.

This study used an NCC design, a hybrid method that integrates features of both traditional case-control and cohort studies. Specifically, it involves conducting a case-control analysis within a previously established cohort under longitudinal observation [24]. The NCC design combines the strengths of cohort and case-control approaches while mitigating the limitations of traditional case-control studies. It offers higher statistical power and testing efficiency, and allows estimation of disease incidence [25]. Compared with conventional case-control studies, NCC studies require a smaller sample size, are easier to conduct, and yield quicker results. Moreover, they enable investigation of multiple etiological factors for a single disease. Since both cases and controls are selected from the same cohort, the comparability between groups is improved, reducing selection bias. In addition, exposure data are collected before disease onset, ensuring temporal causality and minimizing recall bias [26]. Therefore, this study adopted an NCC design to investigate the timing and risk factors of poststroke spasticity.

Currently, there is no internationally recognized standardized treatment regimen for poststroke spastic hemiplegia due to its unclear pathological mechanism [27]. The prognosis of spastic paralysis following cerebral infarction is related to biological factors, pathological factors, and psychosocial factors [28]. Therefore, the treatment and prevention of spastic paralysis following cerebral infarction require comprehensive consideration of multiple factors, including etiology, clinical manifestations, and the specific circumstances of the patient. This study developed a CRF to collect relevant patient data during admission. The spastic hemiplegia occurrence and prognosis following cerebral infarction are influenced by various factors, including age, gender, etiology, infarct location, scale scores, and early treatment. These factors should be comprehensively considered during treatment to develop individualized treatment plans that are aimed at improving the prognosis of patients with spastic hemiplegia following cerebral infarction. Currently, there is a lack of conclusive evidence regarding the risk factors for patients with spastic hemiplegia, and the impact of these factors on clinical treatment remains uncertain. Future research should investigate the mechanisms of these factors further and explore relevant treatment strategies to direct clinical practice more effectively.

Existing evidence-based studies indicate that poststroke spasticity typically emerges gradually within 1 to 3 months after stroke onset. However, in some cases, it can be observed as early as 1 to 3 weeks, depending on the location and severity of the brain lesion. The incidence increases with disease progression, with approximately 30% to 40% of patients developing spasticity within the first 3 months [29]. Wissel et al conducted a prospective observational study in which a cohort of 103 patients with stroke was followed up at a median of 6 days, 6 weeks, and 16 weeks post stroke. The results showed that 24.5% of patients exhibited increased muscle tone within 2 weeks after stroke, and approximately 19% to 39% developed spasticity within 3 months after onset [30]. Lundström et al conducted a 5-year follow-up study on patients with stroke and found that the incidence of spasticity peaked within the first year poststroke, ranging from 25% to 40%, and then stabilized thereafter [31].

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According to the 2018 "China Stroke Prevention and Treatment Report," the geographical distribution of stroke in China shows a pattern of "higher in the north, lower in the south, and prominent in the central regions." From 1990 to 2017, the number of stroke-related deaths in Hunan province increased annually, and the overall disease burden of stroke in the province has shown an upward trend. The monitoring data from Hunan's cerebrovascular disease population indicated that the incidence and prevalence of transient ischemic attack in Hunan are higher than the national average. However, as the study sample was exclusively drawn from the Hunan Provincial Hospital of Integrated Traditional Chinese and Western Medicine, the homogeneity of the sample limits the ability to perform regional comparative analyses. To enhance the generalizability of our findings, we have initiated the establishment of a multicenter clinical research network. Letters of intent have been signed with several tertiary hospitals across different regions, and the second phase of data collection is being planned accordingly.

Conclusion

This nested case-control study investigates the onset timing and predictive factors of PSS within the critical 3-month window using objective sEMG assessment. If key predictive factors and the early onset window are identified, this approach could provide an objective basis for timely clinical intervention in PSS, ultimately improving functional recovery and reducing the significant associated health care burden.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

SS conceived and designed the study, contributed to the intervention design, and secured funding. SW and SZ contributed to the evaluation protocol and participant recruitment plan. WW and LW contributed to the intervention and evaluation design. XT, XS, and DW drafted the initial version of the manuscript. LX contributed to the manuscript revision and was also responsible for funding acquisition.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 109 KB - resprot_v14i1e65829_app1.pdf]

Multimedia Appendix 2
Muscle strength measurement.
[DOCX File , 12 KB - resprot_v14i1e65829_app2.docx]

Multimedia Appendix 3
Modified Ashworth Scale.
[DOCX File , 12 KB - resprot_v14i1e65829_app3.docx]

Multimedia Appendix 4
Simplified Fugl-Meyer Scale.
[DOCX File , 15 KB - resprot_v14i1e65829_app4.docx]

Multimedia Appendix 5
Clinical information collection form.
[DOCX File , 15 KB - resprot_v14i1e65829_app5.docx]

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Abbreviations

CRF: case report form
MAS: Modified Ashworth Scale
NCC: nested case-control
PSS: poststroke spasticity
RMS: root mean square
RR: relative risk
sEMG: surface electromyography
S-FM: simplified Fugl-Meyer
SENIAM: Surface ElectroMyoGraphy for the Non-Invasive Assessment of Muscles
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Improving Data Integrity in Samples Obtained From Web-Based Recruitment: Protocol for the Development of a Novel System for Assessing Participant Authenticity in a Remote Longitudinal Cohort Study of Polysubstance Use

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Abstract

Background: Remote recruitment for human participant research is increasingly popular due to its speed, cost-effectiveness, and accessibility for participants. However, in some cases, it can be particularly difficult to authenticate participants recruited remotely, which, unless adequately addressed, may pose a threat to data integrity and validity.

Objective: This protocol aims to outline authenticity concerns encountered via remote recruitment for a longitudinal cohort study of adults reporting polysubstance use. Stemming from these concerns, we describe the development of a novel system of participant authenticity checks, designed with the goal of maximizing data integrity and minimizing the introduction of additional barriers to participating in the research. Finally, we examine rates of passing each active authenticity check among participants recruited via web-based advertisements.

Methods: Participants were recruited through one of several modalities, including via electronic health records and a third-party company managing a web-based advertising campaign. All participants enrolled in the longitudinal study completed a screening survey, followed by a baseline assessment (involving a survey and an interview) before completing up to 4 weekly interviews and follow-up assessments at 4, 8, and 12 months after baseline. The authenticity check system described here was implemented for all participants recruited via web-based advertising. In addition to passive authenticity checks (ie, randomized online survey passwords), we describe a five-step active authentication protocol: (1) reviewing interest forms for duplication (interest form duplication review), (2) an attention check at screening (attention check), (3) reviewing personal information after completion of the screening survey for duplicates or inconsistencies (personal information verification), (4) a verbal identity confirmation at baseline (verbal identity confirmation), and (5) a review of participant responses for inconsistent reporting at baseline (consistent reporting review).

Results: In total, 178 (6.85%) of the 2598 active authenticity checks administered were failed, leading to the exclusion of 119 unique potential participants due to fraudulent, inconsistent, or ineligible submissions. The 119 unique exclusions represented 11.13% (119/1069) of the potential participants identified via web-based advertising. Reviewing personal information provided at screening for inconsistencies (personal information verification) accounted for the largest number of failed checks (100/178,

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56.2%), whereas reviewing interest form entries for duplicate personal information (interest form duplication review) yielded the fewest failures (7/178, 3.9%).

Conclusions: The system presented provides an example of how researchers may increase confidence in the authenticity of participants recruited remotely, while avoiding the introduction of potential barriers to participating in research, such as requiring photo ID, online video call verification, or in-person verification. Such additional requirements for participants may systematically bias samples, especially when conducting research with populations that have been historically marginalized or those with stigmatized health conditions or behaviors.

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KEYWORDS

authentication; web-based recruitment; remote recruitment; research barriers

Introduction

Background

Use of fully remote or web-based methods for human participants research is becoming increasingly popular [1,2]. With a range of options, including phone- or SMS-based contacts, social media, or web-based advertising, either driven by the research team or through contracting recruitment companies that manage online advertisement campaigns [3], remote recruitment has been shown to be reliable and effective [4-7].

Remote recruitment provides study teams with several important benefits. First, these methods appear to be cost-effective, providing research teams with the ability to recruit relatively large samples without excessive expense [8-10]. Second, these large samples can be recruited quickly, such as by using mobile apps and websites [11] or via social media and web-based advertisements [8,12,13]. The ability to recruit geographically diverse samples that would otherwise not be feasible to recruit in person contributes to this speed and potential benefit [6]. Third, remote recruitment may simultaneously reduce the burden on the study team and reduce participant-level barriers for participating in the research [9,11,14]. For example, rather than requiring participants to travel to a physical laboratory space to determine their eligibility for a research study, research staff may instead administer screening assessments over the phone or via online platforms. Fourth, remote recruitment methods may be particularly effective tools for democratizing research participation among communities that have been historically excluded, including rural communities [15-17], racial or ethnic minority groups [18,19], sexual and gender minority groups [15,19,20], or individuals with stigmatized health conditions (eg, HIV and opioid use disorder) or behaviors (eg, substance use) [17-21]. Removing the requirement to participate in person removes a sizable barrier to participating, and the anonymity often afforded by remote participation can reduce biases based on social desirability [19].

Remote recruitment may be particularly effective for reaching groups that have been marginalized and stigmatized, such as participants who engage in substance use, including polysubstance use (PSU). Individuals with substance use disorders or who engage in PSU behaviors experience substantial stigma from health care providers [22,23] and the general public [24-26], which may reduce their trust in medical and research institutions. Remote recruitment methods may increase accessibility and help increase research representation among this population, as well as aid in recruiting members of rural or other underserved communities and individuals with stigmatized identities, who may face additional disparities in substance use disorder treatment. To effectively engage individuals reporting stigmatized PSU behaviors with remote recruitment, researchers must be able to quickly and accurately authenticate participants, without adding substantial barriers or burden to participation in the research that may systematically bias the sample.

Despite the potential benefits, remote or web-based recruitment may also pose several key limitations to study teams. First, remote recruitment can be inconsistent in terms of quality of responses, cost, and completion rates [14,27]. This variability may make it difficult for study teams to accurately estimate costs or require multiple remote recruitment avenues to ensure sampling goals are met. Second, it is considerably harder to verify a remote participant's identity and authenticate that they are participating in good faith compared to traditional face-to-face recruitment [28-30]. Bots and fraudulent submissions via online platforms may be difficult to detect and require rigorous quality checks to preserve data integrity [28,31-35]. Across the literature, there are numerous examples of remote fraudulent submissions affecting data integrity, including among samples collected from crowdsourcing websites [36] and social media [37].

To combat these potential threats to validity, researchers have examined IP addresses [30,38-41]; compared names and email addresses to identify potential duplicate submission attempts [34,40]; required participants to enter study-designated passwords; updated web page identifiers to prevent repeated or automated responding [33,34,42]; or have implemented verification protocols for email addresses, phone numbers, and other forms of contact information to prevent multiple sign-ups with the same contact information [43,44]. In addition, studies sometimes capture similar information at multiple data points and then examine those responses for inconsistencies or unlikely responses [34,35,44,45] or use attention checks embedded within surveys to help ensure the validity of self-report data [46]. Although these strategies have been used across multiple study settings and populations, to the best of our knowledge, no studies have systematically implemented these checks as a means to

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enhance the rigor of remote recruitment methods when using third-party companies.

Remote recruitment companies have become increasingly popular and accessible to research teams, as evidenced by the multitude of options (eg, Prolific, Respondent, CloudResearch, User Interviews, Positly, and many others). Partnering with these companies yields many of the same advantages listed previously, along with the added benefit of outsourcing day-to-day management of the advertisement campaign to experts who may use data-driven tailoring to maximize visibility. However, little is known about the integrity of samples generated by these companies, especially considering the wide variety of options and approaches available. As evidenced by the increased popularity of new third-party companies, the remote recruitment space continues to rapidly change. Consideration of established remote authenticity strategies along with novel protocols may be necessary for research teams to adapt to the ever-changing authentication demands of remote research studies.

Objectives

In this paper, we outline a novel system for authenticating participants recruited remotely via a third-party recruitment company for a longitudinal cohort study examining trajectories of opioid-involved PSU and other health outcomes. Given that individuals with PSU can experience marginalization from health care and research institutions, especially if they hold more than one stigmatized identities, this authentication process was also designed to avoid adding substantial barriers for potential research participants.

The aims of this paper are threefold: (1) to describe common participant authenticity concerns encountered by our research team during remote recruitment conducted using a third-party recruitment company; (2) to describe the gradual development and testing of a remote participant authentication check system put in place on an ongoing longitudinal cohort study of PSU trajectories, including 5 passive and 5 active steps; and (3) to examine rates of passing and failing each active check.

Methods

Study Methods

The ongoing longitudinal cohort study aims to better understand predictors and trajectories of opioid-involved PSU through 3 primary avenues. First, research suggests that there are individual-, social-, and community-level influences on substance use behaviors and overdose risk [47]. Synthesizing data at each of these levels may inform strategies for facilitating health care access and reducing overdose risk. Second, there are many motives for engaging in PSU [48], but research examining between- and within-person variation in these motives is currently lacking. Third, research suggests that alterations in reward and decision-making may be an important maintaining factor of substance use [49-51]. By examining individual decision-making and PSU choice preference through behavioral economics, the results of this study may inform the development and tailoring of interventions for PSU.

Variables of particular interest include quantity and frequency of substance use (eg, opioids, stimulants, cannabis, and alcohol), health care use, and experimental online tasks. Key covariates include demographic information, measures of mental and physical health, and barriers to accessing care. Participation lasts 12 months and consists of several surveys and interviews. Before continuing to the longitudinal portion of the study, participants complete a screening survey, followed by a baseline assessment (comprising a survey and an interview). During the longitudinal portion of the study, participants finish 4 intensive weekly interviews and then complete an assessment 4, 8, and 12 months after baseline. The selection of assessment time points served 2 key purposes aligned with balancing participant burden and staffing resources while being able to evaluate our research questions. First, the more intensive weekly interviews allow us to investigate episodic PSU in detail, given the recency of the assessments to the behaviors. Second, the 4-, 8-, and 12-month assessments were evenly spaced over 1 year to allow for consideration of longitudinal and longer-term trends in substance use patterns and health care use, as well as to maintain consistent contact with participants, facilitate retention, and minimize participant burden. Surveys may be completed online, over the phone, or in person (excluding the screening survey). Interviews include timeline follow-back (TLFB) assessments and must be completed over the phone or in person. Surveys and interviews both yield quantitative data. Interview-based TLFB assessments require participants to recount the events of a specific period and, using a calendar and these events to guide them, recall their alcohol and substance use during that period [52] to yield quantitative estimates of substance use. These interviews result in detailed data reflecting frequency and quantity of substance use consumption, categorically coded motives for use and routes of use, and information about the number of episodes of use a participant engaged in. Interview-based TLFB assessments have strong validity support for capturing detailed substance and alcohol use count data [52,53] and can be compared to survey-based measures of substance use for accuracy (details provided in Consistent Reporting Review section).

Out of 400 planned participants, as of October 16, 2024, the study team had enrolled 279 (69.8%) participants in the longitudinal portion of the study. Strategies to retain participants throughout the course of the study include providing monetary incentives for confirming follow-up assessment appointments, collecting multiple forms of contact information, and providing study activity reminders. We will impute data missing through skipped questions or attrition. We will investigate mechanisms underlying missingness to the greatest extent possible and evaluate the missing at random (MAR) assumption. If MAR is plausible, we will use multiple imputation by chained equations [54]. If the MAR assumption, which is not statistically checkable, is questionable, we will consider alternatives such as pattern-mixture models [55] or complete case analysis [56].

Eligibility criteria include past-month illicit opioid use or nonmedical use of a prescription opioid, use of another substance (ie, alcohol, cannabis, cocaine, crack, methamphetamine, ecstasy, lysergic acid diethylamide, mushrooms, or synthetic cannabis; nonmedical use of

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benzodiazepines or sedative anxiety and sleep medication; and nonmedical use of stimulant medication), and age between 18 and 75 years at screening. Eligible participants must also report having reliable access to a phone to complete study assessments and reside in the United States. Participants are excluded if they do not speak English or have medical conditions that preclude informed consent (eg, acute psychosis or severe cognitive deficits) as determined through a chart review (for participants recruited via electronic health records [EHRs]) or by research staff observation, including a brief cognitive impairment screening if required.

Ethical Considerations

The study protocol was approved by the University of Michigan Medical Institutional Review Board (HUM00229563), including a University of Michigan participating site (HUM00234294). Waivers of Health Insurance Portability and Accountability Act authorization were requested and approved for recruitment and full study procedures. Waivers of documentation of informed consent were requested and approved for study consent to offer participants multiple options for providing consent (eg, self-administered online and verbally over the phone with a research staff member). All data presented in this report are deidentified, and this research is covered by a Certificate of Confidentiality from the National Institutes of Health.

Participants consent separately to participate in the screening survey and the longitudinal portion of the study. Study staff are available to answer questions about participation and ensure participants can describe the main components of the study, and participants are provided a copy of the longitudinal study consent form.

Participants are compensated US $15 for completing the screening survey, US $25 for each of the 4 weekly interviews, US $60 for the baseline assessment, US $60 for 4-month assessments, US $65 for 8-month assessments, and US $75 for 12-month assessments. To incentivize retention, participants can also earn up to an additional US $30 for confirming each study follow-up assessment (4, 8, and 12 months) appointment. Incentives are distributed as gift cards.

Recruitment

Recruitment for this study has spanned several modalities. Methods have included using relevant diagnostic codes (eg, opioid use disorder) and other keywords to identify potentially eligible participants and then reviewing EHR, recontacting participants from other research studies focused on substance use, and in-person recruitment of inpatients at a large health care system. In addition, the research team has partnered with a third-party company to run a targeted, web-based advertising campaign. Advertisements appear on social media platforms, medical websites, and as part of Google Ads. Potential participants who click an online advertisement are directed to a landing page where they can briefly learn more about the study. The study team worded advertisements and the study landing page to mask specific eligibility criteria while still providing information about the purpose of the study. From the landing page, our team worked with our third-party partners to create an online interest form that allows interested individuals to answer several questions and provide contact information. Upon successful completion of the form, the individual's contact information is provided to the study team on a private dashboard only accessible to the team, allowing research staff to initiate recruitment for eligibility screening.

Importantly, recruitment via the third-party company's remote advertising campaign has presented challenges in participant authentication that were not commonly observed in other avenues of recruitment for this project (eg, EHR review). Duplicate contact information, the completion of several interest form entries from the same IP address within the span of 1 or 2 minutes, and inconsistent reporting from individuals recruited via this source necessitated additional protections for the integrity of data collected from remotely recruited participants. Consequently, the following passive and active authentication protocol was designed specifically for use on the remote advertising sample, and descriptive results reflect checks and findings only from this group (N=1069).

Development of the Authentication Protocol

In the following authentication protocol, active checks are defined as those that involve direct effort and attention by a research staff member and result in a pass or a failure. Passive checks are those that are either automated or are study design decisions and do not directly result in a pass or a failure. Consequently, we present passing and failing rates only for active checks. The following protocol integrates strategies previously outlined in published work as well as novel authenticity checks.

In addition, as this protocol was developed during an ongoing study, some strategies were implemented earlier or later than others. Consequently, new checks were retroactively applied to participants who had already progressed past the intended checkpoint. This developmental process resulted in some instances wherein participants failed multiple active checks. Multimedia Appendix 1 includes the date each check was added to the study protocol.

Passive Authentication Strategies by Third-Party Group

Overview

Passive authentication strategies were implemented before individuals who completed the interest form were invited to complete screening for study eligibility. For each check, we present the primary authenticity concern the check was meant to address, as well as a brief procedure for implementation. Multimedia Appendix 1 provides a complete breakdown of this protocol. Figure 1 provides a diagram outlining when in the study flow these passive checks occur.

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Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram and authenticity checks administered as of October 2024. CONSORT diagrams for participants recruited via electronic health record or other non–web-based recruitment sources and for participants recruited via web-based advertisement are presented separately. The authenticity protocol is outlined for the web-based advertisement diagram. These diagrams do not list other reasons for ending participation not related to authenticity concerns, such as ineligibility or voluntary withdrawal. In the web-based recruitment diagram, arrows denote the timing of each authenticity check within the study flow. Italicized authenticity check names represent passive checks. Bolded authenticity check names represent active checks and include the number of failed checks resulting in withdrawal from the study.

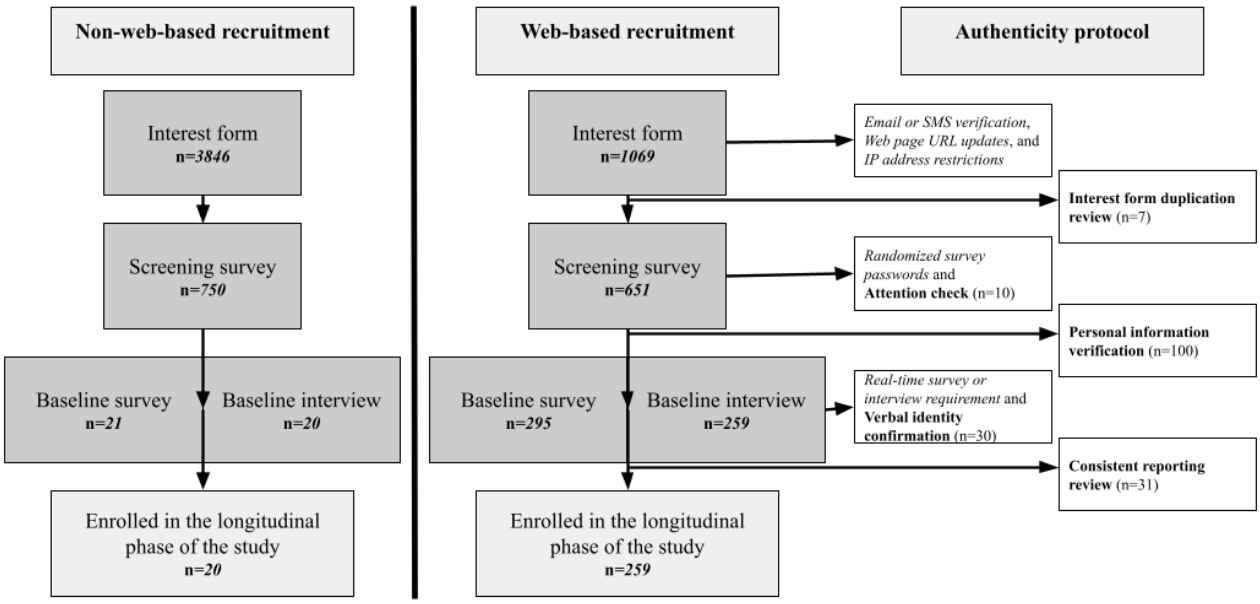

Email and SMS Verification

The purpose of the email and SMS check was to prevent bots from submitting interest forms, as well as to certify that an email address was valid and that the participant had access to the account. Our third-party partner is responsible for verification, which involves sending the individual an email with a unique link that they must click on within the next several minutes. Verification via the unique link constitutes a pass, whereas a lack of verification constitutes a failure.

Similar to email verification, participants must complete verification of their cell phone number via SMS text verification (given that the study inclusion criterion is access to any type of phone [eg, inclusive of landlines and other phones incapable of texting], this authenticity check adds an additional requirement to have a text-capable device. This decision was made for several reasons. First, participants recruited from nonremote sources can still participate without a text-capable phone. Second, the intention of providing a phone-based option to complete study assessments was to provide an avenue for participation for individuals without internet access. Given that participants recruited via web-based advertisements by definition have internet access, the study team considered the addition of this authenticity check acceptable to increase data integrity).

Our study involves several phone-based assessments, as well as texting and calling to confirm study sessions, making it essential for participants to have reliable phone access. Requiring SMS verification helps confirm that the phone number is real and connected to cellular service and that the participant has access to the phone.

After submitting their interest form, participants are texted a code by our third-party partners that they must enter into the study web page to demonstrate their access to that phone number. Without completing verification, participants' interest forms are not completed and are not sent to the study team.

Web Page URL Updates

Working with our third-party partner, we changed the URL of our study landing page (from which potential participants could fill out an interest form) several times. Updating the landing page link reduces the likelihood that the interest form will be distributed in ways our study team cannot control (eg, via an online forum), which could reduce the quality of leads and increase study staff burden. Rather than being a pass or fail authenticity check, outdated versions of the study landing page are simply not accessible.

IP Address Restrictions

Early in recruitment, our team weighed the benefits of restricting interest form submissions by IP address. Although potential participants using the same internet network (eg, family members and roommates) would be unable to participate, we determined that the more pressing concern was that some individuals were completing multiple screening submissions under different names from the same IP address. Fraudulent submissions reduce the quality of interest forms, substantially increase study staff burden, and threaten data validity. Consequently, we opted to only allow a single interest form submission from each IP address. Attempts to submit additional interest forms are not processed. In addition to restricting interest form submissions by IP address, we also ensure that submission attempts from outside of the United States are blocked, given that US residence is an eligibility criterion.

Before automatic IP address restrictions were implemented, research staff completed a 1-time IP address review of all remotely recruited participants who had completed the interest

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form, including those who had already been screened. If multiple submissions were associated with a single IP address, study participants associated with all of those submissions were excluded. Individuals excluded for this reason are listed in Table 1 as part of the personal information verification active check. With the automation of these IP address restrictions, it was no longer necessary for staff to review this piece of information manually. Table 1 provides a breakdown of the total number of failed active authenticity checks. Table 2 provides a breakdown of the total number of unique participants withdrawn due to authenticity concerns.

Table 1. Number of active authenticity checks administered to and failed by potential participants recruited via web-based advertisements, as of October 2024[a].

Check	Administered (N=2598), n (%)	Failed (n=178[b]), n (%)
Interest form duplication review	942 (36.3)	7 (3.9)
Attention check	517 (19.9)	10 (5.6)
Personal information verification[c]	424 (16.3)	100 (56.2)
Verbal identity confirmation	340 (13.1)	30 (16.9)
Consistent reporting review[d]	375 (14.4)	31 (17.4)

[a]Data are presented on the administration and rate of failure of active authenticity checks on the portion of our sample recruited via web-based advertisement. For the personal information verification and consistent reporting review, we present additional granularity on the reason for a failed check. This table provides the total number of checks administered and failed, inclusive of instances in which 1 individual failed multiple checks.

[b]Of the 2598 active authenticity checks administered, 178 (6.8%) failed.

[c]Reasons for failure of personal information verification include name consistency (33/100, 33%), duplicate contact information (14/100, 14%), address verification (43/100, 43%), and duplicate IP address (10/100, 10%; the study staff completed a 1-time review of duplicate IP addresses before this process was automated by our third-party partner; details in IP Address Restrictions section).

[d]Reasons for failure of consistent reporting review include date of birth (8/31, 26%) and data inconsistency (23/31, 74%).

Table 2. Number of unique participants recruited through web-based advertisements who were withdrawn due to authenticity concerns, as of October 2024 (N=119)[a].

Number of failed checks	Participants, n (%)
5	1 (0.8)
4	2 (1.7)
3	6 (5)
2	30 (25.2)
1	87 (73.1)

[a]Data are presented on the number of unique participants who were withdrawn from the study due to failed active authenticity checks. These data represent only the portion of our sample recruited via web-based advertising.

Passive Authentication Strategies Through Study Design

We included 2 additional passive authentication strategies through the design of the study that occur after individuals complete interest forms (Multimedia Appendix 1 provides details).

Randomized Survey Passwords

Because remote participants complete some study assessments online, each participant is assigned a unique identifier and password. Initially, passwords were the intended recipient's unique identifier. However, early on in recruitment, our team noticed that some screening surveys were completed by individuals not assigned to a given identifier (eg, a 20-year-old man completing a screening survey using an identifier or password assigned to a 60-year-old woman). This was due to individuals guessing passwords to complete multiple screening surveys, which are remunerated US $15 for completion. To rectify the issue, our team began assigning each unique identifier a 10-digit password consisting of randomized strings, significantly reducing the likelihood that a password could be guessed and used by an unauthorized individual.

Real-Time Assessment Requirement

Built into our study design, all participants complete some real-time assessments (ie, over the phone or in person, with almost all participants thus far choosing the phone option). The baseline interview must be completed over the phone or in person, and participants can opt to complete the screening survey or baseline survey over the phone as well. Our team made this design choice to deter individuals from completing multiple submissions, as our team believed individuals would be less likely to submit fraudulent surveys if they knew the study would not be able to be completed entirely asynchronously.

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Active Authentication Checks

Overview

Once a potential participant completes the interest form, the study team receives their contact information and interest form results. Through the process of a 5-step active authentication protocol, study team members complete additional verification checks before a participant can be enrolled in the longitudinal portion of the study. We present each check, including the primary authenticity concern that the check addresses, the stage in the study flow when the check occurs, a brief protocol for implementing the check, and definitions of passed and failed checks. A failed check results in withdrawal from the study. Multimedia Appendix 1 provides a complete breakdown of the protocol. Figure 1 provides a diagram outlining when in the study flow these active checks occur.

Interest Form Duplication Review

Although passive checks prevent many duplicate or fraudulent interest form submissions, others are identified manually. Due to the multitude of recruitment streams on the project, it is possible that a participant recruited in person (eg, from the EHR) could also come across the online advertisement and mistakenly fill in the interest form. Furthermore, an individual could complete multiple interest forms using different names but with a duplicate phone number or address.

The interest form duplication review occurs after completion of the interest form and before participants are invited to complete the screening survey. For each new potential participant, research staff compare recruitment logs against the individual's primary contact information and address. If the primary contact information or address is duplicate, the check fails and the individual is not invited to complete the screening survey.

Attention Check

If a submission passes interest form duplication review, the individual is invited to complete the screening eligibility survey. Several items on the screening survey require respondents to select yes or no regarding their substance use history. Through review of responses on the screening survey and baseline assessment, the study team noticed a pattern of affirmative answers to all substance use items on the screening survey, but at baseline, the same participant would report use of fewer substances during the same period. Consequently, the team added an attention check item to the screening survey in the section asking about substance use, which instructs the participant to select "no" on the item. Failing the attention check results in an end to participation, as this may indicate that a participant is inattentive or was selecting "yes" to all substance-related questions.

Personal Information Verification

Research staff then examine personal information reported by individuals who are eligible at screening, checking for inconsistencies before inviting them to complete the baseline assessment. Staff review the name, contact information, and address. Staff also reviewed the IP address before this process was automated. Comparing the name participants provide at the screening with the name associated with their interest form allows staff to identify surveys completed by someone other than the intended participant, as well as instances in which someone has guessed the password to a survey. Changes in contact information among individuals experiencing financial strain or housing instability may be common. However, duplicate contact information may indicate that an individual has submitted multiple interest forms, facilitating identification of potential fraudulent efforts to enroll in the study. Consequently, staff check contact information provided at screening against all recruitment records. If this newly provided contact information matches information entered in other study records, both records are withdrawn. For address review, we noticed that many individuals who completed the interest form provided incomplete or blank addresses. We believe that this tendency may be due to initial mistrust and that participants are more trusting of the study after they have interacted with a member of the study team (eg, received an email from a real person inviting them to complete the screening survey). Rather than comparing the address provided at screening to the one provided on the interest form, we chose to verify the existence of the address provided at screening using public online records. Determining that an address was nonresidential (eg, a bank) constituted a failed check unless a participant had previously indicated that they were experiencing housing instability.

Verbal Identity Confirmation

Once all postscreening survey authenticity checks are passed, participants are invited to complete the baseline assessment. Because the interview portion of the assessment must be completed over the phone or in person, participants must speak to a staff member before they are able to continue to the longitudinal portion of the study. The first time staff speak with a participant over the phone or in person, the participant must confirm their name, date of birth (DOB), and zip code before proceeding. This check identifies fraudulent submissions and inaccurate information and ensures that staff are speaking with the intended participant. If the respondent accurately provides the information when prompted, they pass the check. If the participant does not provide the correct information, refuses to answer, or does not provide the information when prompted (eg, hangs up and calls back later in the day to provide the information), they fail the check and are withdrawn from the study. For participants enrolled before this check was implemented, staff administered the identity confirmation check at their next phone-based or in-person assessment.

Consistent Reporting Review

After completion of the baseline assessment, at least 2 study team members (including at least 1 principal investigator [PI] or study coordinator) review a participant's responses on all assessments for inconsistent reporting. First, DOB is reviewed for inconsistent reporting across study assessments. Research staff observed that submissions determined to be fraudulent often included discrepancies in reported DOB. Thus, DOB is assessed at screening and at baseline for comparison. Inconsistent reporting of DOB constitutes a failure and removal from the study.

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In addition to DOB, at least 2 study team members (including at least 1 PI or study coordinator) also review responses on each assessment for indications of poor-quality responses. Poor-quality submissions may stem from fraudulent reporting or honest mistakes, but regardless, low-quality reporting is a threat to data validity. Research staff members may initiate this check if they observe highly unlikely or conflicting information reported by a participant. Examples of reasons to initiate this review include unusual routes of using substances (eg, snorting cannabis), significant and unexplained changes in substance use patterns over a very short time span (eg, reported using fentanyl every day in their screening survey but reported no lifetime opioid use in their baseline survey), or other cues from interactions with the participant (eg, participant A references an email sent to participant B as if the email had been sent to participant A).

Baseline inconsistency reviews begin with examination of the dates of the screening survey and baseline assessment to establish which items, based on response window (eg, past week, past year, or lifetime use), are expected to overlap. Next, research staff review each response to items with overlapping time frames from the screening and baseline surveys. For example, if a participant reported no lifetime use of cannabis in the baseline survey but then reported weekly cannabis use in the baseline interview completed 2 days later, that would be recorded as an inconsistency. Of course, it is reasonable that a participant could make errors in reading and answering survey questions; therefore, we set a threshold for the number of inconsistencies required to prompt the next stage of review. Specifically, if it is determined that there are ≥4 inconsistencies across the screening survey and baseline assessment, the research staff member prepares a formal report of all potential inaccuracies for the project PIs and coordinator to review. The PIs and coordinator examine all inconsistencies to determine if any can be explained more parsimoniously. If the PIs and coordinator deem at least 4 inconsistencies to be due to poor-quality reporting (ie, not otherwise reasonably explainable), the check is considered failed and the participant is withdrawn from the study. If ≤3 inconsistencies are deemed to be due to poor-quality responses, the check is passed and the participant may continue in the study.

The criterion of 4 inconsistent responses was based on a preliminary review of data from participants who had passed all other checks (ie, high likelihood that they were genuine and eligible participants). Among these authenticated participants, the maximum number of inconsistencies was 3.

Data Analyses

We computed descriptive findings (eg, frequencies and proportions) regarding the active authentication system, including passing rates for each.

Results

Non–web-based recruitment for this study began in fall 2023. Web-based recruitment, facilitated by a third-party recruitment company, began in January 2024. Results of the recruitment process are presented through October 2024 in Figure 1, divided by recruitment source (web-based recruitment vs non–web-based recruitment). A timeline of the date each strategy was implemented can be found in Multimedia Appendix 1. Of the 4915 interest forms completed, 1069 (21.75%) were completed by participants recruited remotely using web-based methods. Of the 1401 screening surveys completed, 651 (46.47%) were completed by participants recruited remotely using web-based methods. A total of 259 participants recruited using web-based methods were eligible and completed the baseline assessment, resulting in 39.8% (259/651) of the participants screened from this recruitment method completing the baseline assessment and continuing to the longitudinal portion of the study. A total of 20 participants recruited from non–web-based recruitment sources were eligible and completed the baseline assessment, resulting in 2.7% (20/750) of the participants screened from this recruitment method completing the baseline assessment and continuing to the longitudinal portion of the study. Of the 279 participants currently completing the longitudinal phase of the study, 259 (92.8%) were recruited using web-based methods.

The authentication protocol has been applied to the 1069 individuals completing interest forms who were recruited via web-based avenues managed by a third-party recruitment company. The total number of active authentication checks administered to this sample as of October 2024 is presented in Table 1, along with the number of failed checks. Altogether, 2598 active authenticity checks were administered to the 1069 individuals recruited remotely. In total, 6.85% (178/2598) of those checks failed. Because some checks were applied retroactively, individuals could fail multiple checks (Table 2 provides a complete breakdown). Consequently, 11.13% (119/1069) of unique individuals recruited by web-based methods were withdrawn from participation due to failed checks.

The largest source of failed active checks was personal information verification, which comprised 100 failures. Of those 100 failures, most were due to either providing a different name on the screening survey than on the interest form (n=33, 33%) or providing a nonresidential address in the absence of reporting housing instability (n=43, 43%). The consistent reporting review and verbal identity confirmation accounted for the second and third largest sources of failed active checks, comprising 31 and 30 failures, respectively. Alternatively, the interest form duplication review had the lowest rate of failure at 0.7% (7/942) and accounted for the fewest failures.

Discussion

Summary

This report describes the development and initial implementation of authenticity checks for remote recruitment procedures in a sample of individuals reporting opioid-involved PSU. We discuss findings and conclusions related to the success of web-based recruitment methods for this population, the utility of the authenticity protocol designed for this study, the use of third-party web-based recruitment companies for conducting human participant research, and avoiding the introduction of barriers to participation when choosing and implementing authentication systems.

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Web-Based Recruitment

Consistent with previous work examining the utility of web-based recruitment methods in substance use research, the preliminary results of our investigation suggest that these methods are effective [17,21]. In addition, these methods appear to be considerably faster than non–web-based recruitment avenues [8,12,14]. Despite far fewer completed interest forms compared to those recruited via non–web-based methods, the vast majority of our sample has been recruited from a web-based advertisement campaign managed by a third-party recruitment company. There are several possible reasons for this success. First, as has been observed in previous studies, web-based recruitment has the benefit of reaching a much larger pool of possible participants (eg, national recruitment) [6]. This breadth, combined with the tailoring of our advertising campaign, likely contributed to the high rate of eligible participants observed in the data. Second, remote research methods have been shown to be effective when recruiting participants based on stigmatized health behaviors, including substance use [17,21]. Third, participants responding to targeted advertisements are self-selecting into the study, whereas reaching participants through some non–web-based methods, such as EHR review, requires the study team to initiate contact with the participant.

Takeaways From the Authenticity Protocol

The finding that study design and automated integrity protocols (eg, IP address verification) alone were not sufficient for deterring fake or fraudulent submissions is consistent with the recommendation to use both active and passive authentication strategies [30]. Considering the passive strategies, research suggests that email or SMS verification [43,44], IP address review [30,40], and requiring participants to input unique passwords each contribute to increasing data integrity [33,34]. It was highly feasible to implement these passive strategies, primarily due to the services provided by the web-based recruitment company.

Regarding the active authenticity checks, the interest form duplication review was considerably less efficient in this study compared to previous research [34,40]. As presented in Figure 1, this active check occurs after participants have already completed email and SMS verification and met IP address restrictions. The finding that very few potentially fraudulent submissions were detected with this check may be evidence that these passive strategies have been effectively dissuading or detecting these submissions, thus decreasing the necessity of checking interest forms for duplicate entries.

Although the attention check during screening identified very few instances of inattentive or automatic responding, the ease with which such a check can be added to a survey-based assessment adds to its utility as part of an authentication protocol. There are several possible explanations for the very low failure rate. First, it is possible that the attention check was too simple and did not sufficiently distinguish between attentive and inattentive or automatic responding. We used an instructed response item as an attention check [46], so it is possible that different attention check items could result in different failure rates. Second, it is possible that most inattentive participants or those using automatic response patterns were prevented from continuing in the study due to the previous passive strategies.

Similar to the findings of other studies [34,40], assessing similar constructs at different time points and examining responses for consistency (ie, personal information verification) appeared to be a particularly effective authentication strategy. Because it is possible that some participants, especially those who may have had negative previous interactions with research teams or who were concerned about the possibility of internet data breaches, did not provide entirely accurate information on the interest form due to a lack of trust, we recommend assessing these demographics once research teams have more personalized interaction (eg, email, phone, or in-person contact). In addition, in some instances, participants may make typographical errors or misremember personal information, so it is important to have staff carefully review and understand verification procedures (eg, if someone enters their DOB as September 10, 1986 instead of September 10, 1989, this may or may not be an indication of fraudulent reporting). Although personal information verification requires considerable staff time and effort, our results support its continued implementation.

When implementing the verbal identity confirmation check, our team did not expect many participants to fail it. However, our results suggest that this check was surprisingly effective at identifying fraudulent participation attempts. Anecdotally, most failures of the verbal identity confirmation occurred when participants refused to provide identifying information when prompted or simply hung up the phone without responding. One possible explanation for the unexpected utility of this active check is that it is the first time participants are prompted in real time to verify their identity. Because administering a verbal check can be completed remotely over the phone relatively quickly, we recommend the use of this check when possible.

In accordance with previous research, the consistent reporting review was also effective at identifying fraudulent or poor-quality submissions [34,35,44,45]. In particular, this active check acted as a catch-all as the final step of the authenticity protocol before the longitudinal portion of the study. Of note, reviewing data from multiple study time points is time consuming. Research teams may elect to adapt decision rules for when to conduct this check to increase feasibility.

Overall, the active checks appeared feasible to implement. Creating clear protocols for administering and interpreting each check reduced staff burden and increased standardization. Throughout the course of the study, we attempted to increase automation of these checks to further reduce staff burden, such as automatic IP address verification and automatic logging of attention check outcomes. Study teams conducting similar research may elect to implement some or all of these checks to tailor to their specific research goals, as well as further automate to reduce required staff effort.

Data Integrity and Third-Party Recruitment Companies

Importantly, the results of this report suggest that previously established strategies for participant authentication can be successfully adapted and integrated for use in conjunction with

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web-based recruitment companies. However, as with all web-based or remote recruitment efforts, our results suggest that working with a third-party recruitment company to manage and tailor an advertising campaign is not enough to ensure data integrity. A sizable proportion of research participants identified by the company our team worked with did not pass authenticity checks and were withdrawn from the research study. However, this proportion of fraudulent submissions may still be lower than what is expected from other web-based recruitment sources [36].

Authenticity Protocols and Barriers to Participation

Consistent with findings from other web-based studies, our results suggest that at least some fraudulent or inconsistent research submissions can be identified primarily using information provided as part of regular participation (eg, survey responses) [33,34,44,45]. We considered several additional authentication strategies for this study that were eventually deemed to be too high of a risk for introducing substantial bias into our sample, including requiring video sessions (ie, inaccessible for individuals without video-capable devices or reliable internet service), requiring photo ID (ie, inaccessible for individuals without this form of ID), and verifying address using physical mail (ie, time consuming and excludes individuals who are unstably housed). The ability to identify these invalid responses with information already typically required of participants is promising and may help to ensure that a broad spectrum of experiences is represented in the research. Research teams must weigh the added burden to participants and potential addition of barriers to participation when selecting authenticity strategies to limit sampling bias.

Strengths and Limitations

The primary strength of this report is the formative approach to establishing an authenticity verification system for use in the context of remote recruitment, particularly openly recruited through online advertisements that are particularly vulnerable to fraudulent attempts to enroll in research studies. An additional strength is the effort to consider and balance the goals of maximizing data integrity and validity while minimizing barriers to participation (eg, requiring photo ID or an in-person study visit). Despite the introduction of this protocol, participants recruited remotely were only required to have a valid email address and text-capable phone, and the verification procedures did not unduly increase the time or effort of participation. The use of active authentication checks has also allowed our team to continue to improve our authentication system over time, as we developed many of our checks in response to ambiguous or nuanced situations we encountered.

However, as with any in-depth protocol, implementing an authentication system requires some staff effort. Authentication methods that are more likely to introduce barriers to participation may require less staff effort, and consequently, study teams will need to continue to weigh the costs and benefits of the processes they choose based on resources and potential for bias within the study population of interest. In addition, strategies for automating some of the more time-intensive elements (eg, using an automatic data-driven approach to flagging data inconsistencies for closer inspection) may enhance the efficiency of such approaches.

The authentication steps themselves also have several limitations. First, regarding the personal information verification, it is possible that these methods restrict study sign-ups among family members or individuals living in the same household. Some households may share phone numbers or emails, and many more likely share networks and devices that can access the internet. IP address verification may be most effective when examining attempts for repeat responses close in time. Second, address verification (part of personal information verification) is reliant on publicly available information. Newer construction or redistricting may not be accurately reflected in these datasets, causing the check to be inaccurate in rare cases. Third, our team encountered several instances wherein verbal identity confirmation was difficult to interpret. When prompted to provide their information, some individuals would hang up the phone, pause for a long time before responding, or call back later to provide the information. Many instances of failure for this check were more ambiguous than for other checks, requiring our team to establish the strict definition of failure reported when prompted. Fourth, we developed cutoffs for inconsistency reporting (part of consistent reporting review) based on preliminary data from approximately 30 individuals who had already passed all other checks. Because some room for error is to be expected in self-report data, particularly in TLFB interviews when participants are asked to recall events of up to the past 30 days, our selected cutoff of 4 inconsistencies should not be interpreted as a standard. Fifth, the introduction of automatic SMS verification for participants recruited remotely may prevent individuals without text-capable devices (eg, landlines) from joining the study. However, participants recruited through more traditional methods (eg, EHR review) are still able to participate without a text-capable phone.

Conclusions

The authentication protocol presented, including both passive and active authentication strategies, provides an example of how research teams can increase confidence in the validity of data collected from remotely recruited research participants. Importantly, the system displays how authentication can occur while minimizing the introduction of barriers to participating in research, which may be of particular concern when conducting research with populations that have been historically marginalized or on highly stigmatized health behaviors (eg, opioid-involved PSU). Initial descriptive data indicate that web-based methods may be particularly effective for recruiting participants reporting PSU and other populations that have been highly stigmatized and that working with third-party web-based recruitment companies can be valuable for tailoring advertisement campaigns. Considering the utility of different authentication strategies, those that examine responses for inconsistencies across study activities may be particularly effective (ie, personal information verification, verbal identity confirmation, and consistent reporting review). Protocols to detect fraudulent or inconsistent reporting are important for assessing the validity of data collected remotely, and research teams will need to continue to adapt and tailor these strategies as remote recruitment methods evolve.

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Data Availability

The datasets generated or analyzed during this study will be available in the Helping to End Addiction Long-term Data Platform after the conclusion of study activities [57].

Authors' Contributions

CRR contributed to this study through conceptualization, methodology, investigation, writing the original draft, reviewing and editing the manuscript, visualization, and project administration. MC contributed to this study through conceptualization, methodology, investigation, reviewing and editing the manuscript, visualization, and project administration. EEB, JEG, and MAW contributed to this study through conceptualization, methodology, reviewing and editing the manuscript, supervision, and funding acquisition. LAL and LNC contributed to this study through conceptualization, methodology, investigation, reviewing and editing the manuscript, supervision, and funding acquisition.

Conflicts of Interest

LAL has consulted for the Peterson Health Technology Institute.

Multimedia Appendix 1
Remote recruitment identity authenticity protocol.
[DOCX File , 18 KB - resprot_v14i1e69956_app1.docx]

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Abbreviations

DOB: date of birth
EHR: electronic health record
MAR: missing at random
PI: principal investigator
PSU: polysubstance use
TLFB: timeline follow-back

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Protocol

Guideline-Based Clinical Decision Support Framework for Multimorbidity: Protocol for a Formulation and Testing Study

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Abstract

Background: The burden of multimorbidity is increasing globally, which complicates the use of guidelines in clinical practice and health care: practitioners may need to increasingly refer to multiple guidelines with potentially conflicting recommendations.

Objective: We aim to develop a guideline-based decision support framework for the management of patients with multimorbidity to help clinicians efficiently evaluate, select, and adapt recommendations focusing on the different comorbidities and aspects of multimorbidity.

Methods: We will conduct the project using the following steps: (1) needs assessment (searching published literature and documents on guideline use in multimorbidity care through the study initiators, and assessing the necessity of developing a comprehensive decision-making framework focusing on multimorbidity in a broad sense), (2) establishing international working groups (a coordination team, an evidence support group, and a consensus group) by leveraging existing participants' networks and inviting experts with relevant academic publications or activities, (3) conducting literature reviews of multimorbidity guidelines and original qualitative research involving interest-holders in multimorbidity care and/or guideline development to formulate an initial draft framework, (4) a consensus process including an expert survey and a consensus meeting, (5) formulating and releasing the final framework, and (6) testing the framework (collecting feedback through educating health professionals in different settings and applying the framework in practice to evaluate and improve it). We plan to complete the project within 3 years.

Results: The project has started in March 2024 and is due to conclude in June 2026. As of May 2025, we have finished the literature reviews and qualitative studies and are currently conducting the first round of the expert survey.

Conclusions: This framework will help clinicians from all levels of health care institutions to make decisions in the management of patients with multimorbidity based on the latest available evidence, and to reduce potential health risks to their patients. One limitation of this framework is that such a broad framework may not fully fit all disease combinations or realistic situations. To reduce the degree of inapplicability, after completion of the framework, we will continue to monitor its use with regular updates as needed.

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KEYWORDS

multimorbidity; comorbidity; clinical decision support; protocol; burden; health care; support framework; consensus; inapplicability; monitoring

Introduction

An increasing number of people, especially older adults, are experiencing multimorbidity, a situation where the patient has multiple (chronic) conditions at the same time [1]. As a result, multimorbidity is becoming a defining challenge for health systems [2]. Interactions among drugs, interventions, and diseases can impair the patients' quality of life and physical functioning [3,4], while health care providers also face challenges in managing the increasingly complex health situations of patients with multimorbidity [5].

Health care providers should generally refer to clinical practice guidelines or guideline-like documents such as expert consensus statements to ensure that their decisions are based on the latest evidence [6]. In multimorbidity practice, the choice of recommendations becomes, however, challenging. Due to the complex health situation of the patients, health providers may need to consult a large number of guidelines, including traditional clinical practice guidelines focusing on the target conditions and guidelines related to multimorbidity in a broader sense. Multimorbidity guidelines can further be divided into health-centered guidelines that address the condition and management of patients with multimorbidity in general, and disease-centered guidelines that address specific diseases and their combinations. Only few health-centered multimorbidity guidelines have so far been published: a systematic search conducted in 2018 identified only 8 [7]. Recommendations in the identified guidelines covered a broad spectrum of aspects of clinical and self-management, beyond the realms of traditional disease-centered guidelines [7]. Such guidelines are usually developed based on the concept of patient-centered care; however, they still face many challenges in implementation [8]. Although the use of multiple single-disease guidelines may seem to be a feasible approach, this approach does not consider the interactions or special conditions related to the coexistence of multiple diseases and may further lead to potentially hazardous side effects, overtreatment, and high costs [9]. Therefore, in the care of patients with multimorbidity, it is crucial to consider carefully which guideline recommendations are chosen and how they are applied to support clinical decision-making.

To our knowledge, no uniform standards exist yet for the use of guidelines for multimorbidity-related decision-making in clinical practice. Our project therefore aims to develop a framework to clarify the process of guideline-based multimorbidity decision-making. This framework can help clinicians evaluate, choose, and adapt recommendations from guidelines focusing on the different comorbidities and aspects of multimorbidity efficiently.

Methods

Overview

The framework we plan to develop in this project will be formed as a tree or graph. The target users include clinicians and other health care professionals at all levels of the health care system. The user will first answer questions related to the setting, patient, target condition or problems, and possibly other details depending on the final framework, which will lead to various steps to detailed instructions on how to select the recommendations from different guidelines considering also the potential interactions. We will conduct the project using methods similar to the development of reporting checklists. David Moher and colleagues from the EQUATOR (Enhancing the Quality and Transparency of Health Research) network [10] have published guidance for developing health research reporting guidelines [11]. The guidance divides the development process into initial steps, premeeting activities, face-to-face consensus meetings, postmeeting activities, and postpublication activities. The entire development can be summarized as a series of background studies and a consensus process. Based on this guidance, we plan to conduct our project with the following steps: (1) needs assessment, (2) establishing working groups, (3) formulating an initial draft framework, (4) consensus process including expert survey and consensus meeting, (5) formulating and releasing the final framework, and (6) testing the framework. The steps of the development process are illustrated in Figure 1.

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Figure 1. The detailed development process.

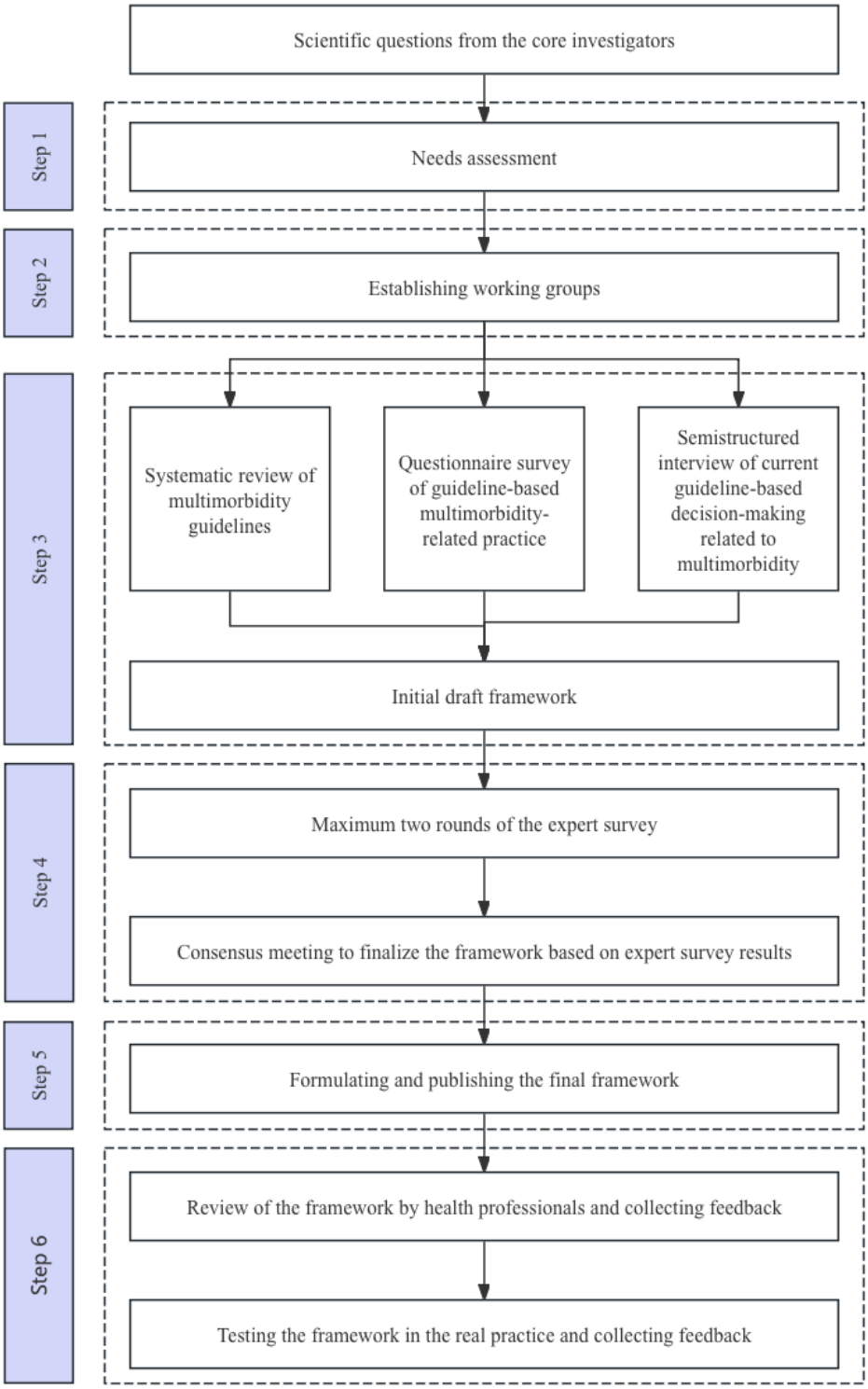

Needs Assessment

To identify the need for this new framework, we searched the published literature and documents on improving the use of guidelines in multimorbidity practice. We searched PubMed from its inception until March 2024 using terms "Multimorbidity," "Guideline," "Framework," "decision support," and their derivatives. A supplementary search in Google was also performed. We found a limited number of decision-making frameworks for multimorbidity [9,12-16], but we have various reasons to believe they are not sufficient to comprehensively guide the care of patients with multimorbidity. First, the aim of all frameworks we identified was to solve problems arising from the use of multiple single-disease guidelines, while multimorbidity guidelines (both disease- and health-centered) were usually ignored. Second, most frameworks were published at least 5 years ago without being updated thereafter. Third, many of the frameworks focused on the

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management of comorbidities rather than multimorbidity in general. Although these concepts are closely related, their perspectives are different. The concept of comorbidity includes the idea of focusing on a primary target disease and its interactions with other conditions, whereas multimorbidity refers to the patient's health condition as a whole [17]. Finally, many frameworks were restricted to specific diseases or their combinations, such as type 2 diabetes and hypertension, and their scope of application is thus very narrow. Therefore, based on the current literature, there is a clear need for a comprehensive decision-making framework that focuses on multimorbidity in the broad sense.

Establishing Working Groups

Three working groups will be established for this project: the coordination team, the evidence support group, and the consensus group.

The coordination team will consist of the 3 members who initiated the study (ZW, YC, and JE). They will lead and coordinate all steps of the project and ensure its timely completion. The coordination team is responsible for forming the initial draft framework with the help of the evidence support group, responding to the suggestions and opinions of experts during the consensus process, revising the framework, and collecting feedback through testing process of the framework. In addition, they will support the consensus group and seek advice from external parties when necessary throughout the whole process.

The evidence support group will be composed of 5-6 members with experience in evidence-based medicine and guideline methodology. This group will support the coordination team in forming the initial draft framework by (1) systematically gathering, summarizing, and/or evaluating the relevant literature and guidelines and (2) collecting the results of the questionnaire survey and interviews and performing preliminary analyses of the results.

The consensus group will be composed of 20-30 experts with experience in multimorbidity research or practice and/or guideline development or methodology. Members of the consensus group will be recruited worldwide through three pathways: (1) through contact networks of the coordination team, (2) by contacting authors of key articles relevant to the topic, and (3) by attending academic conferences related to the topic and inviting attendees to participate. Individuals who agree to participate in the consensus group will be asked to recommend additional members (the snowball method). We will continue the recruitment until at least 20 experts with sufficient diversity in terms of fields of expertise, geographical region, and other characteristics have agreed to participate. The consensus group will participate in a web-based survey and consensus meetings, provide their views during the formulation process, and approve the final version of the framework.

Formulating the Initial Draft Framework

The coordination team will formulate the initial draft framework in 2 steps.

First, the evidence support group will collect data and ideas through a series of studies under the supervision of the coordination team (Table 1): 2 systematic reviews of guidelines, a questionnaire survey, and semistructured interviews of key experts. The 2 systematic reviews will focus on health-centered and disease-centered multimorbidity guidelines, respectively. The former review aims to include all published guidelines on how multimorbidity should be taken into consideration in health care; for the latter, we have selected diabetes, coronary heart disease, and stroke as an example, and will search all guidelines that have recommendations on any combination of these conditions. We will systematically search 6 literature databases and 9 guideline platforms for both reviews. Official websites of selected relevant societies and/or associations will also be searched for systematic reviews of disease-centered multimorbidity guidelines. Due to the expected low number of guidelines, the systematic review of health-centered multimorbidity guidelines will include all guidelines published until the date of the search. For the systematic review of disease-centered multimorbidity guidelines, we will include guidelines published in 2020 or later, which contain recommendations addressing at least 2 of the target diseases. Both reviews will collect and qualitatively analyze the recommendations and assess the methodological and reporting quality of the guidelines using the AGREE II (Appraisal of Guidelines for Research and Evaluation II) instrument and RIGHT (Reporting Items for Practice Guidelines in Health Systems) checklist, respectively. The protocols of both reviews with more details have been registered on Open Science Framework (osf.io/ymk7u and osf.io/b8ecp, respectively).

In the second step, the coordination team will discuss the findings based on their own experience to reach a consensus on the format of the framework. We will also refer to the Ariadne principle when forming the nodes of the framework. The Ariadne principle categorizes multimorbidity-related decision-making in primary care into 5 steps [19]. The Ariadne principle was formed to serve as a basis for multimorbidity management in primary care but can also give directions for multimorbidity care in general. A draft version of the framework will be built after the discussion.

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Table 1. Summary of the studies conducted to collect the pool of key information.

Research questions	Study type	Source of information (data or participants)	Methods
What are the characteristics of current multimorbidity guidelines?	Systematic review	• Health-centered multimorbidity guidelines (eg, guidelines for the care of patients with multimorbidity regardless of the diseases) • Disease-centered multimorbidity guidelines (eg, guidelines for the management of hypertension in combination with other diseases)	Qualitative content analysis
How are guidelines used in multimorbidity-related practice at present?	Questionnaire survey	• Individuals with experience in multimorbidity management (particularly frontline workers)	Descriptive analysis, qualitative analysis (see questionnaire in Multimedia Appendix 1)
What should we pay attention to when making multimorbidity decisions?	Semistructured interview	• Individuals with experience in multimorbidity research (experts, especially guideline developers, and methodologists)	Thematic analysis [18] (see interview guide in Multimedia Appendix 2)

Consensus Process and Formulation of the Final Checklist

We will first conduct web-based expert surveys among the consensus team, following a procedure similar to the Delphi process. During the first round of the survey, all members of the consensus group will receive a draft version of the framework through email. In this draft version, the framework will be shown as a decision tree or graph with some supplemental information about the factors that are likely to influence the choices the users make in each step. Participants will vote on 2 parts: the factors that influence the choices at each step and the rationality of the decision-making process (provided as a list of all steps from the framework). The participants will anonymously rate each factor/step on a 7-point Likert scale to indicate their level of agreement with the importance of the factor/step to be included in the framework [20]. Free-text boxes will be included in the survey to collect comments (both on the overall structure and on factors influencing each step) or propose additional factors/steps. The scale and definitions of the consensus results are shown in Table 2. The factors/steps that achieve agreement are included in the final version and removed from subsequent rounds, factors/steps with disagreement are removed from the framework (subsequent step will be modified accordingly), and factors/steps rated as ambivalent will be revised to reflect points raised by the consensus group and be included in the next round of survey. In addition, the coordination team may propose some new factors/steps based on the free-text comments. All members who participated in the first round are asked to rate the new factors/steps and factors/steps on which no consensus was reached. Free-text boxes will again be available for comments. If there are only few factors/steps that need discussion, we may consider skipping the second round and proceed directly to the consensus meeting. After a maximum of 2 rounds of survey, we will formulate a revised version of the framework, which will be discussed in the next step (consensus meeting).

We will organize a consensus meeting either on the web, in person, or in a hybrid format. All members of the coordination team and consensus group will be invited to attend and discuss the revised version of the framework. If web-based format is chosen, multiple meetings can be arranged to keep the number of attendees to a manageable level to and accommodate participants from different time zones. The meetings will be recorded and transcribed. The coordination team will review all feedback and suggestions given during the meetings and send the final version of the framework together with responses to the main suggestions to the consensus group.

Table 2. The 7-point Likert scale and definitions of consensus.

Score and interpretation	Definitions of conclusions regarding consensus
• 1=strongly disagree • 2=disagree • 3=somewhat disagree	"Disagreement": more than 80% of the participants choose scores of 1 to 3
• 4=neither agree nor disagree (neutral) • 5=somewhat agree	"Ambivalent": the conditions for neither "agreement" nor "disagreement" are fulfilled
• 6=agree • 7=strongly agree	"Agreement": more than 80% of the participants choose a score of 6 or 7, and there are no major comments suggesting a revision

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Testing

We will evaluate the practical usability of the framework through 2 steps of testing. Health professionals from different types of facilities (eg, hospitals, community health centers, or nursing homes) who commonly manage patients with multimorbidity and who were not involved in any step of the development (including the surveys and interviews) will be invited to take part. In the first step, we will give an introduction of the framework to the participants and educate them how to use it. To help participants understand and try to use this framework to make decisions, we will provide a specific case (patients with diabetes and those with coronary heart disease) as an example. The participants will be asked to comment on the usability and integrity of the framework based on their experience.

In the second step, the participants will be asked to use this framework in their daily practice related to multimorbidity management and provide feedback on the applicability and feasibility of the framework, barriers, and facilitators to this process, as well as opportunities that should be explored further to refine the framework. Feedback from these 2 steps will be collected through focus group discussions. The discussions will be recorded and analyzed using the topic analysis method.

We will compare the feedback from both steps and form suggestions and directions for future improvements to the framework. The coordination team will continue to meet twice a year to discuss any feedback from users, recent developments in multimorbidity research and policies, and the need of updating the framework or developing extensions for specific situations. Further details about the testing process are still under discussion and will be gradually determined in the future.

Patient and Public Involvement

This study will not involve the participation of patients or the public.

Ethical Considerations

The project has been approved by the Institute of Health Data Science Ethical Commission, Lanzhou University (reference HDS-202404-01). The framework will be disseminated through scientific articles and international conferences. All individuals who participate in different steps of the project (consensus group members, survey respondents, interviewees, and professionals involved in the testing step) will be required to provide informed consent, either in writing or via other means (such as video recording). Data from questionnaires and interviews will be treated anonymously. Participants will not receive any financial compensation.

Results

The project started in March 2024 and is due to conclude in June 2026. The proposed schedule is shown in Figure 2.

As of May 2025, we have formed all 3 working groups. The coordination team consisting of the 3 lead investigators (ZW, JE, and YC) was formed prior to the project. The evidence support group comprises 8 members with a background in evidence-based medicine. The consensus group comprises 20 experts with experience in various disciplines and from different regions of the world. In addition to the 3 groups, we have decided to invite 2 experienced clinicians specializing in multimorbidity management and guidelines as external advisors to complement the gaps in experience among the coordination team members. The coordination team and advisors will discuss the feedback from all steps of the consensus process before revising the framework.

Figure 2. Timeline for the development of framework.

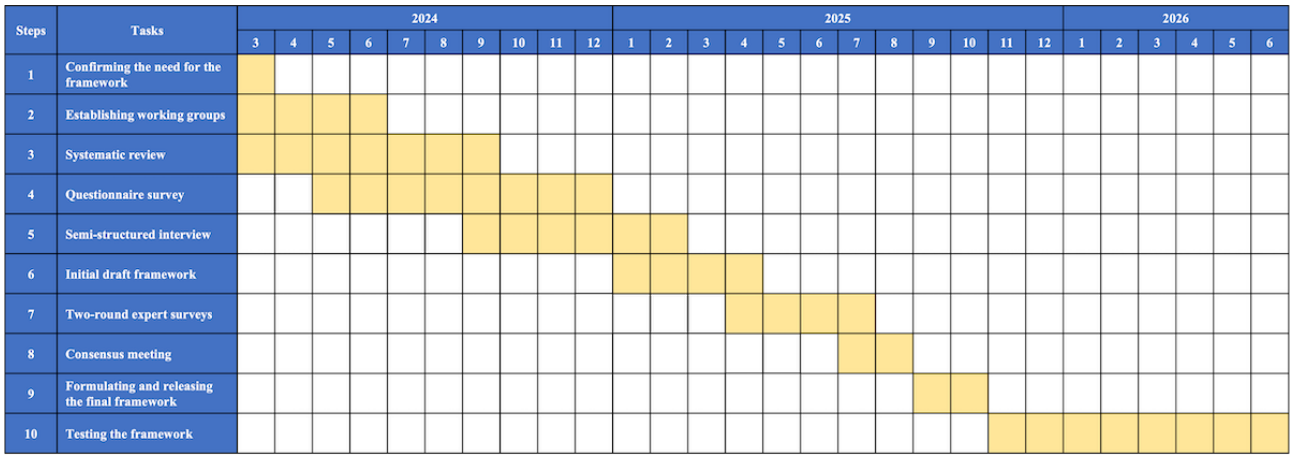

We have, so far, finished the 2 planned systematic reviews of guidelines, a questionnaire survey, and semistructured interviews of key experts. The systematic review of health-centered multimorbidity guidelines included 19 guidelines and consensus statements and was published in November 2024 [21]. The systematic review of disease-centered multimorbidity guidelines included 82 guidelines and consensus statements with recommendations on drug therapies on combination of diabetes, coronary heart disease, and/or stroke (manuscript currently in preparation). The global survey among medical professionals with clinical experience has also been completed, with 311 valid responses (manuscript submitted for publication). Fifteen experts in multimorbidity research and guideline development with more than 10 years' experience in the field were interviewed; the contents have been analyzed, and a manuscript is under preparation. The results with the 4 abovementioned studies were

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discussed and used to formulate an initial version of the framework, which consists of a decision graph with 12 nodes, explanations for each node, and for 2 nodes, also a set of factors influencing the decision to be made in the node. The first round of the consensus survey started on May 14, 2025. All members of the consensus group received a survey link including the draft version of the framework and its explanation, with a request to complete the survey in 2 weeks.

Discussion

The main output of this project will be a framework to support guideline-based decision-making related to multimorbidity, as well as an explanatory document. This framework will help clinicians make well-informed decisions in the management of patients with multimorbidity and thus reduce potential health risks to their patients. The framework not only is limited to the selection of recommendations from disease-specific guidelines but also considers the use of general multimorbidity guidelines. The framework will cover all levels of health care from community facilities and residential homes to referral hospitals, including tailored instructions for different facility types and clinical situations. All above advantages make up for the shortcomings in the applicability and comprehensiveness of current guideline-based multimorbidity decision frameworks. The existing decision support frameworks have a very disease-specific focus and essentially only integrate recommendations from single disease guidelines [9,12-16]. These may be helpful for some decision-making in clinical practice, but they largely ignore the patient-centered model of care that is an essential part of multimorbidity management. Treating patients with multimorbidity not only consists of selecting the optimal therapy based on the clinical situation but also requires considering factors like the patient's preferences and values, practical issues related to the social situation and daily activities, and the quality of life in general [22-24]. Health-centered multimorbidity guidelines focus on these issues, but these guidelines are usually not addressed by the existing tools, and clinicians may not be aware of the existence of such recommendations. In contrast, our framework will cover all aspects of patient care, including also the challenges related to multimorbidity itself.

There are several potential limitations to our framework. First, multimorbidity is a highly complex issue, and management policies and the availability of applicable guidelines vary across countries, regions, and health care settings. This diversity makes it challenging to fit such a broad topic into a simplified decision tree. As a result, our framework may have limited applicability in certain contexts. Second, implementing the framework in clinical decision-making requires specific resources and expertise. For instance, during the development the framework, we may assume that all relevant guidelines are readily available. However, in practice, access to these guidelines may be restricted due to differences in hospital levels or institutional policies. Third, a persistent challenge in multimorbidity research and clinical practice is the lack of strong direct evidence. Consequently, even if the framework is implemented, final decisions may still rely on expert judgment rather than strong recommendations based on high-quality evidence. Fourth, shifting clinical attitudes, particularly among specialists, may be difficult. While we are committed to refining the framework for practical use, we cannot guarantee its seamless integration into clinical practice. We can mitigate the influence of these limitations by continuously revising the framework based on feedback from users. With the help of partners across the world, we will adapt the framework to the local contexts of different settings and consider developing extension versions for specific situations where the core framework alone is not sufficient. Ultimately, we hope this framework will lead to a more standardized approach in the care of patients with multimorbidity in different situations, guiding the way toward more personalized and patient-centered health care.

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Authors' Contributions

Conceptualization: ZW, YC, and JE
Validation: LW, BW, HH, ZL, DZ, JZ, HZ; major contribution from LW
Writing—original draft: ZW and JE
Writing—review and editing: ZW, LW, BW, HH, ZL, DZ, JZ, HZ, YC, and JE

Conflicts of Interest

None declared.

Multimedia Appendix 1
Questionnaire.
[DOCX File , 19 KB - resprot_v14i1e63339_app1.docx]

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Multimedia Appendix 2
Interview guide.
[DOCX File , 21 KB - resprot_v14i1e63339_app2.docx]

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Abbreviations

AGREE II: Appraisal of Guidelines for Research and Evaluation II
EQUATOR: Enhancing the Quality and Transparency of Health Research
RIGHT: Reporting Items for Practice Guidelines in Health Systems

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Original Paper

Small Extracellular Vesicles as Biomarkers in Sarcoma Follow-Up: Protocol for a Prospective, Multicentric Pilot Study

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Abstract

Background: Sarcomas are rare cancer with a heterogeneous group of tumors. They affect both genders across all age groups and present significant heterogeneity, with more than 70 histological subtypes. Despite tailored treatments, the high metastatic potential of sarcomas remains a major factor in poor patient survival, as metastasis is often the leading cause of death. Currently, metastatic risk assessment relies mainly on histological grading; yet, this method has limitations due to the disease's heterogeneity. Advances in genomic and transcriptomic research have identified potential molecular signatures, but these approaches lack reproducibility and prognostic reliability. Therefore, new biomarkers are essential for improving risk prediction and therapy adaptation. Recent studies highlight that sarcoma cells secrete extracellular vesicles, particularly small extracellular vesicles (sEVs). These nanovesicles, abundant in bodily fluids such as blood, urine, and saliva, play a crucial role in tumor development, growth, and metastasis. sEVs contain proteins and nucleic acids that mirror tumor characteristics. Given their presence in blood, sEVs offer a promising avenue for noninvasive molecular cancer analysis via liquid biopsy. Preliminary studies in Ewing sarcoma have shown substantial alterations in sEV-derived transcripts, underscoring their potential in tracking disease progression and treatment efficacy.

Objective: This study aims to investigate whether sEVs can serve as reliable biomarkers for monitoring sarcoma progression and predicting recurrence risk.

Methods: This prospective, multicentric pilot study will enroll adult patients diagnosed with localized or metastatic liposarcomas, leiomyosarcomas, or undifferentiated pleomorphic sarcomas at 3 French cancer centers. The study's primary goal is to quantify sEVs and analyze their protein and RNA content in the blood of patients with localized or metastatic sarcomas before and after

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the treatment. sEVs will be isolated from plasma samples, and protein and microRNA concentration will be determined. Research will last, on average, 6 months for patients with localized sarcoma and 4 months for patients with metastatic sarcoma.

Results: We expect to identify differences in exosome levels based on disease stage and observe correlations between exosome dynamics and treatment response. If confirmed, these findings could establish sEVs as noninvasive biomarkers for monitoring therapy effectiveness and disease progression in patients with sarcoma.

Conclusions: This study could establish a novel, noninvasive biomarker for sarcoma prognosis and treatment monitoring. If successful, a nationwide study will be launched to confirm findings in a larger patient cohort, potentially revolutionizing sarcoma management and improving patient outcomes.

Trial Registration: ClinicalTrials.gov NCT03800121; https://clinicaltrials.gov/ct2/show/study/NCT03800121

International Registered Report Identifier (IRRID): DERR1-10.2196/63718

(JMIR Res Protoc 2025;14:e63718) doi:10.2196/63718

KEYWORDS

pilot study; liquid biopsy; small extracellular vesicle; sarcoma; cancer monitoring

Introduction

Sarcomas are rare cancers representing 1%-2% of all adult cancers with more than 5000 cases per year in France recently [1]. They affect men and women of all ages and constitute a heterogeneous group of tumors, with more than 70 different histological types and subtypes [2]. Despite adapted therapies, the metastatic risk of these diseases currently has a major negative impact on patient survival. Metastatic dissemination of tumor cells is responsible in most cases for patient death. The estimation of sarcoma's metastatic risk is complex, given the histological heterogeneity of this pathology. It is therefore essential that, at diagnosis, a reliable evaluation of metastatic potential may be determined to better adapt the therapeutic strategy. Currently, the estimation of this risk is based essentially on histological criteria, namely the tumor grade. In recent years, large-scale genome and transcriptome analyses have allowed the identification of tumor molecular signatures predictive of prognosis. However, results reproducibility can be discussed, and the biological and prognostic significance remains limited. It is therefore necessary to find new biomarkers.

It has recently been found that sarcoma tumor cells secrete extracellular vesicles (EVs) [3] including small EVs (sEVs). In this study protocol, we will use the term exosomes to refer to small EVs. Exosomes are nanovesicles secreted by all the cells of the human body and found in abundance in different biological fluids such as blood, urine, saliva, and breast milk. Recently, the role and involvement of exosomes in sarcoma [4,5] development have been demonstrated [6]. Indeed, exosomes seem to play an important role in tumorigenesis, growth, tumor progression, and metastases appearance. Exosomes contain many proteins and nucleic acids (DNA, RNA, and microRNA), reflecting tumor characteristics. It has been shown that the amount of exosomes can be correlated with the grade of tumor malignancy [7,8]. Present in the blood, they offer the possibility of a noninvasive analysis of cancer cell molecular information by liquid biopsy. Recent preclinical studies have demonstrated strong changes in more than 1200 transcripts present in exosomes derived from Ewing sarcoma cells. Therefore, the study of plasma-derived exosomes in patients with sarcoma has a high potential to evaluate cancer pathogenesis, progression, and treatment efficacy.

The aim of this study is to demonstrate the potential of exosomes as biomarkers for monitoring disease progression and predicting treatment response in patients with both metastatic and nonmetastatic sarcoma.

Methods

Study Population

Adult patients with a diagnosed sarcoma, such as liposarcomas, leiomyosarcomas, or undifferentiated pleomorphic sarcoma (UPS) and managed at Georges-François Leclerc Center in Dijon or at Jean Minjoz Center in Besançon or CHU Poitiers.

Study Objectives and Endpoints

The main objective of this pilot study is to quantify exosomes from plasma and to analyze protein and RNA content in patients with sarcoma, with localized or metastatic disease. Analysis will be performed before and after surgery in localized disease and before and after first-line chemotherapy in metastatic sarcoma. Some patients may have received neoadjuvant chemotherapy with or without radiotherapy.

The secondary objectives are to:

1. Determine whether the initial exosome concentration, protein, and RNA profile vary in the plasma with localized or metastatic stage of the disease.
2. Determine whether the exosome concentration as well as protein and RNA profile varies upon treatment.
3. Determine whether the initial exosome concentration (T0) is associated with a response to treatment.
4. Determine whether changes in exosome concentration before and after treatment are associated with a response to treatment.

The primary endpoint of the study is the quantification of exosome concentration in the blood, as well as the measurement of protein and RNA levels after exosome lysis. Measures will be performed before and after surgery in case of localized disease and before and after chemotherapy in case of metastatic disease.

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The secondary endpoints will be exosome blood concentration, as well as protein and RNA concentrations measured after exosome lysis. Treatment response and tumor progression (locoregional or appearance of metastases) will be assessed by magnetic resonance imaging (MRI) or computed tomography (CT) scan using RECIST (Response Evaluation Criteria in Solid Tumors) V1.1 criteria.

Study Design

Pilot, prospective, multicentric, nonrandomized study, without direct individual benefit. The study is supported by the Institut National du Cancer (INCa) platform CLIP² (Certified Early-Phase Clinical Trial Centers) at the Georges-François Leclerc Center in Dijon, CHU Poitiers, and Jean Minjoz Center in Besançon. The study inclusion period will be 48 months and the total study duration will be 60 months. Study design is depicted in Figure 1. Research will last an average of 6 months for patients with localized sarcoma and 4 months for patients with metastatic sarcoma.

Investigators receive an informative notice on the EXOSARC (Study of Exosomes in Monitoring Patients With Sarcoma) study and will be provided samples of eligible patients. Upon written patient consent, serology to HIV, hepatitis C virus, and hepatitis B virus will be tested (Figure 1). Only patients with negative serology for these infectious agents will be included, to protect technicians from biological risks, in agreement with laboratory procedures. Exact inclusion and exclusion criteria are available in Textbox 1.

Figure 1. Study design. EDTA: ethylenediaminetetraacetic acid; EV: extracellular vesicle; HBV: hepatitis B virus; HCV: hepatitis C virus.

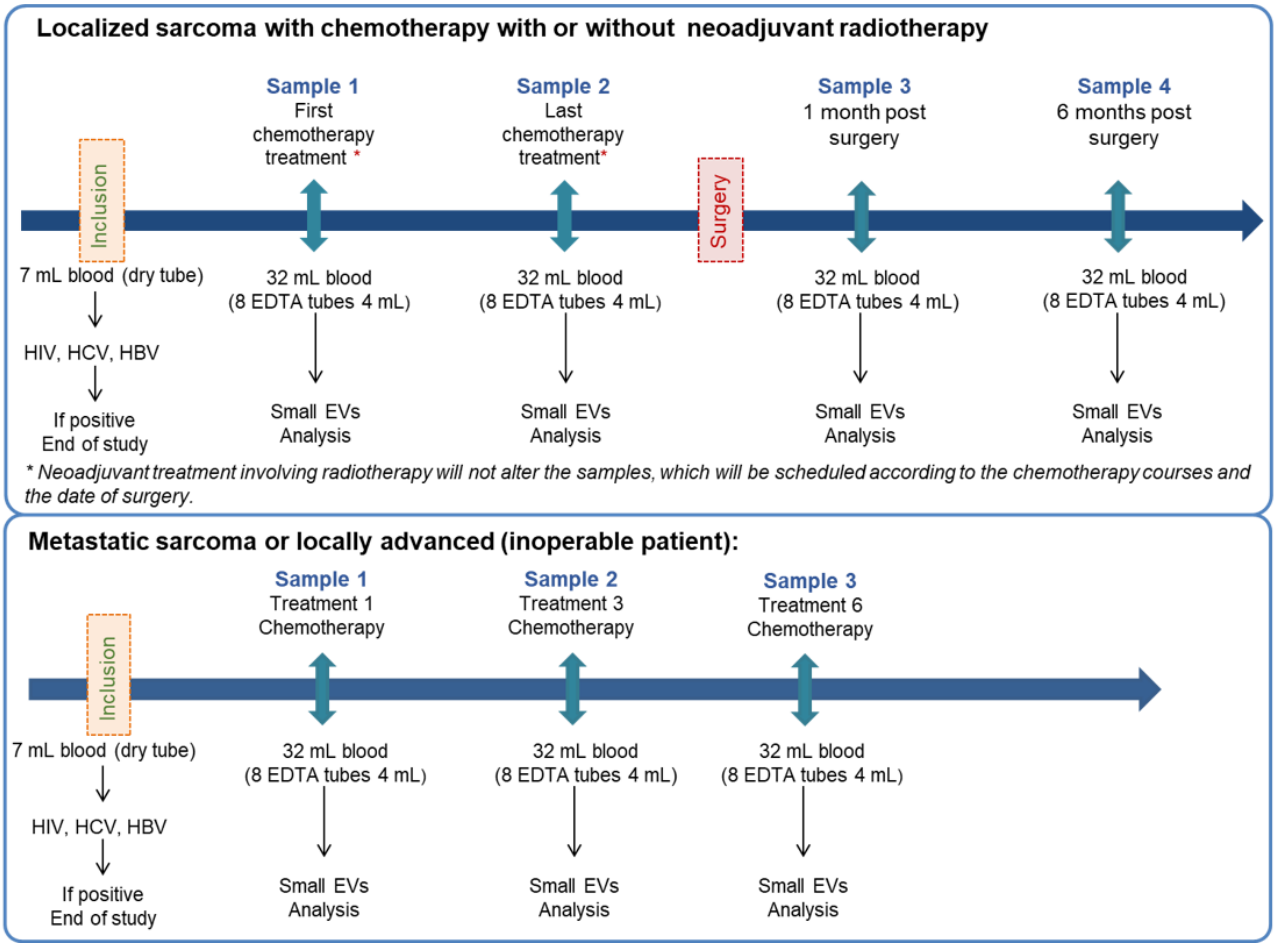

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Textbox 1. EXOSARC (Study of Exosomes in Monitoring Patients With Sarcoma) inclusion and exclusion criteria.

Inclusion criteria

- Men and women diagnosed with localized or metastatic soft tissue sarcoma (liposarcoma, leiomyosarcomas, or undifferentiated pleomorphic sarcomas [UPS]).
- Adult patients (≥18 years old) with histologically confirmed sarcoma, including but not limited to liposarcomas, leiomyosarcomas, and UPS.
- Previous treatment of the disease with chemotherapy, radiotherapy, or surgery is allowed if it has been completed for more than 12 months at the time of inclusion.
- Age ≥18 years old.
- For metastatic or locally advanced (inoperable) sarcoma, patients for whom first-line metastatic chemotherapy is indicated.
- Affiliated to French social security or beneficiary of such a regimen.
- Written informed consent.

Exclusion criteria

- Patient with other synchronous tumors
- Patient with sarcoma in irradiated tissue.
- Patient with a history of cancer other than sarcoma in the 5 years preceding sarcoma diagnosis.
- Patient unable to undergo medical follow-up for geographical, social or psychological reasons,
- Person benefiting from an adult protection system (including guardianship and trusteeship).
- Positive serology to HIV or hepatitis B virus or hepatitis C virus.
- Pregnant or lactating woman.
- Patients unable to understand, read, or sign an informed consent.

Patient Identification and Recruitment

Patients will be identified and recruited from participating oncology centers through:

- Diagnosis codes (*ICD-10* [*International Statistical Classification of Diseases and Related Health Problems 10th Revision*]) and pathology reports from hospital databases.
- Referral by treating oncologists and multidisciplinary sarcoma teams based on eligibility criteria.
- Screening during routine clinical visits for patients with newly diagnosed sarcoma or those scheduled for treatment.

Sampling

A total of 32 mL of blood (8× 4 mL EDTA [ethylenediaminetetraacetic acid] tubes) will be collected at each sampling for exosome analysis in both cohorts.

- For cohort 1 (patients with localized sarcoma and undoing neoadjuvant chemotherapy), blood samples will be collected before surgery at cure 1 (sample 1) and at the last cure preceding surgery (sample 2). Then, at 1 month (sample 3) and 6-8 months post surgery (sample 4).
- For cohort 2 (patients with metastatic or locally advanced inoperable sarcoma), a blood sample will be collected before initial chemotherapy administration (sample 1). Then, at the third (sample 2) and at the sixth chemotherapy treatment (sample 3).
- Note that sample collection will take place before chemotherapy treatment even if the cure schedule is changed or postponed. Samples will be kept for a maximum of 2 hours at 4 °C.

Blood Collection and Storage

Plasma will be collected by centrifugation of blood samples (EDTA tube; 2200 rpm for 15 minutes at 4 °C). All the 3 components obtained will be aliquoted and stored on site at −80 °C.

Extracellular Vesicle Analysis

Thawed plasma samples will be processed to centrifugation at 2000 g at 4 °C for 20 minutes. Exosomes will be extracted with Total sEV Precipitation Reagent (4484450, Thermo Fisher Scientific) for 10 minutes following homogenization. Part of the EVs will be used to determine their concentration and distribution profile using Nanotracking Analysis (NS300, Malvern). The data will be analyzed using Nanosight NTA 3.2 Analytical Software (Malvern Instruments). The other part will be used for the analysis of EV contents (proteins and RNA) and stored at –80 °C. Content analysis (proteins and RNA) will be performed using Western blot analysis, enzyme-linked immunosorbent assay, and RNA sequencing (Illumina) approaches. It is expected that all collected blood will be used for extracellular vesicles and content analysis.

Data Collection

The following data will be collected during the study, at the time of inclusion, and during medical follow-up: demographic and clinical data (age, sex, weight, height, performance status, etc), medical history, date of diagnosis, first-line treatment, disease evaluation reports (biological, imaging, etc), exosome analysis data (total exosome concentration, HSP70 exosome

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concentration, and multiple miRNA dosing). These data will be sent as a standard report from the laboratory in charge of these analyses (Inserm UMR1231). All data will be recorded in a Case Report Form (CRF).

Sample Size

A total of 30 patients, for whom all samples required for the study have been collected, should be included, distributed as follows:

1. Group 1: 15 patients with localized disease, for whom the 4 samples required for the study were collected.
2. Group 2: 15 patients with metastatic disease, for whom the 3 samples required for the study were collected.

These numbers will provide preliminary data before considering a larger study. The primary objective of this study is to measure the markers of interest in patients. Given that the study focuses on rare cancers and that statistical analyses are only secondary objectives, no statistical power calculation has been performed for this study. Patients for whom the total number of required samples was not achieved will be replaced.

Statistical Analysis

Plasma exosomes as well as exosomal protein and RNA concentrations will be described by their mean (SD) and their median (with extent). Comparison of baseline concentrations of participants with localized disease versus metastatic disease will be performed using nonparametric Wilcoxon tests. Comparison of pretreatment and posttreatment (surgical or drug) concentrations will be performed using nonparametric tests for matched data. Analyses will be carried out by subgroup (metastatic and localized) and on the whole population. Relative exosome variation before and after treatment will be compared in responders and nonresponders using nonparametric Wilcoxon tests. A Bonferroni correction will be applied to the *P* value to adjust the significance threshold during multiple comparisons.

The area under the receiver operating characteristic curve (AUC) modeling the response to treatment in function of initial exosome concentration will be plotted. AUCs with 95% CI values will be provided. The model will be adjusted to the type of disease (localized or metastatic). An exosome concentration threshold, predictive of response to treatment, will be determined. Performance (ie, sensitivity, specificity, and predictive values) associated with this threshold will be calculated. A similar approach will be followed concerning exosome concentration after treatment and delta between initial and posttreatment values. Different protein and RNA-derived markers will be analyzed. Performance associated to the absence or presence of these markers to predict response to treatment will be determined for each of the markers. Analyses will be performed under the software SAS 9.4 (SAS Institute).

Patient and Public Involvement

The patient committee of the National League Against Cancer (“Comité de patients en recherche clinique en cancérologie de la Ligue contre le cancer”) was consulted on the information notice that will be given to patients asked to participate in this trial. This committee brings together patients, former patients, or patient relatives who have a shared interest in oncology medical research. The purpose of this consultation was to read and improve the patient information notice on the design and aim of the study, so that patients can clearly understand and decide whether to participate, in agreement with the principle of informed consent.

Ethical Considerations

This study was approved by the local ethics committee and was authorized by the French Health Agency (ANSM [Agence Nationale de la Sécurité du Médicaments et des produits de santé], number 2018-A01393-52) in May 2018, and by the French Ethical Research Committee (CPP [Comité de Protection des Personnes], Ile de France 1) in October 2018. The clinical trial has been registered at ClinicalTrials.gov with the identifier NCT03800121. Last version of the study protocol dated May 19, 2021, is 1.4. Participants must provide informed consent in agreement with the Declaration of Helsinki. Participants will be informed of the objectives of the project and the risks and benefits of the explorations to be carried out. None of the tests will pose risks that could endanger participants’ lives. Confidentiality of participant data will be guaranteed at all times in agreement with the **National Commission on Informatics and Liberty** MR01 reference methodology registered for CGFL (1878714v0, July 30, 2015).

Results

This study is expected to provide valuable insights into the role of exosomes in sarcomas, both in localized and metastatic stages. We anticipate that exosome concentration, as well as protein and RNA profiles, will differ between localized and metastatic disease, reflecting distinct tumor biology. Furthermore, we expect to observe variations in exosome concentration and content before and after treatment, potentially correlating with treatment response. A higher baseline exosome concentration may be associated with a poorer or more aggressive disease profile, while changes in exosome levels following treatment could serve as predictive biomarkers for therapeutic efficacy. The integration of exosome analysis with imaging-based assessments (MRI or CT scan using RECIST V1.1 criteria) will help establish correlations between exosome dynamics and tumor progression. If confirmed, these findings could pave the way for the use of exosomes as noninvasive biomarkers for monitoring sarcoma treatment response and disease progression, ultimately improving patient management.

Discussion

Anticipated Findings

As of 2025, despite the strong diagnostic and prognostic potential of exosomes in sarcomas [3,7-10], no prospective study has yet demonstrated the feasibility and clinical relevance of this concept. Our team has recently patented a technique to detect exosomes in various biological fluids, such as blood and urine [5] (patent WO/2015189395A1, Inserm Transfer). We have also launched a study on exosomes from solid tumors, analyzing their protein content and microRNA (Exodiag, NCT02662621), which has confirmed the technical feasibility of exosome research in humans. Notably, this study is currently

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the only ongoing clinical trial on sarcomas listed on ClinicalTrials.gov. Consistent with preclinical findings, we believe that studying plasma exosomes in rare cancers like sarcomas could significantly improve therapeutic management.

Looking ahead to 2030, our innovative approach has the potential to offer a noninvasive method for predicting treatment response and disease progression. If our pilot study yields positive results, we plan to conduct a nationwide study to validate these findings in a larger cohort.

Conclusion

This pilot study proposes an innovative approach to monitoring patients with sarcoma by evaluating the potential of sEVs as noninvasive biomarkers. By analyzing the concentration and molecular content (proteins and RNA) of circulating exosomes, the study aims to improve our understanding of sarcoma biology in both localized and metastatic settings and to correlate these markers with treatment response. The expected outcomes could enhance prognostic assessment and therapeutic monitoring, ultimately enabling more personalized patient management. If successful, this pilot study will lay the groundwork for a larger nationwide clinical trial, with the potential to significantly advance the clinical care of patients with sarcoma.

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Data Availability

The investigator undertakes, on behalf of himself and all individuals involved in the conduct of the trial, to ensure the confidentiality of all information provided by the Centre Georges – François Leclerc until the publication of the trial results. This confidentiality obligation shall not apply to information that the investigator is required to disclose to patients as part of their participation in the trial, nor to information that has already been published. The investigator commits not to publish, disclose, or use, in any manner whatsoever, directly or indirectly, any scientific or technical information related to the trial. Any partial or total reproduction of this document is prohibited without the authorization of the Centre Georges François Leclerc. However, in accordance with Article R 5121-13 of the French Public Health Code, the center and the investigator may provide information related to the trial to: the Minister of Health, public health inspector physicians, public health inspector pharmacists, the Director General and inspectors of the ANSM (French National Agency for Medicines and Health Products Safety). The trial shall not be subject to any written or oral comments without the sponsor’s approval (CGFL); all information communicated or obtained during the trial shall be the exclusive property of the sponsor, who shall have full discretion over its use. At the end of the study, research-related documents (Investigator File, completed and validated CRFs, and other research documents) will be archived by the sponsor and the investigator sites in accordance with Article 2 of the decree of August 11, 2008, which sets the retention period at 15 years.

Authors' Contributions

JG and NI contributed to supervision. AB assisted with methodology. JG, NI, CCB, VV, ER, AH, and IN handled writing–original draft. JG, IN, SC, ID, and LC contributed to writing–review and editing.

Conflicts of Interest

None declared.

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Abbreviations

ANSM: Agence Nationale de la Sécurité du Médicaments et des produits de santé
AUC: area under the receiver operating characteristic curve
CLIP²: Certified Early-Phase Clinical Trial Centers
CPP: Comité de Protection des Personnes
CRF: Case Report Form
CT: computed tomography
EDTA: ethylenediaminetetraacetic acid
EV: extracellular vesicle
EXOSARC: Study of Exosomes in Monitoring Patients with Sarcoma
ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision
INCa: Institut National du Cancer
MRI: magnetic resonance imaging
RECIST: Response Evaluation Criteria in Solid Tumors
sEV: small extracellular vesicles
UPS: undifferentiated pleomorphic sarcoma

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Protocol

A Group-Based Telehealth Intervention for Birth Trauma: Protocol for a Pilot Feasibility and Waitlist Control Trial

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Abstract

Background: Traumatic childbirth experiences affect almost half of Australian women giving birth and can lead to significant mental health impacts, including postpartum depression, anxiety. and posttraumatic stress disorder (PTSD). Despite evidence supporting psychological interventions for birth trauma, there are prominent gaps in the accessibility of these treatments, particularly for postpartum women in regional or rural areas, who face long waitlists, geographical isolation, and high financial costs. Although narrative approaches hold promise for addressing birth-related trauma, no research study to date has specifically trialed a narrative-informed, group-based telehealth intervention in this space.

Objective: This study aims to assess the acceptability and feasibility of a narrative-informed, group-based telehealth intervention for postpartum women in reducing the mental health impacts of having experienced a traumatic childbirth.

Methods: This pilot feasibility trial with a waitlist control design evaluated a six-session narrative-informed, group-based intervention delivered weekly via telehealth to postpartum women who experienced a traumatic childbirth within the past 6 months. The intervention incorporated narrative therapy techniques, such as externalization, double-listening, and outsider witnessing. Participants from a specific catchment area of predominantly rural towns in New South Wales in Australia were randomly assigned to either an intervention group (IG) or a waitlist control group (WCG). Quantitative measures assessing mental health symptoms of postpartum depression (Edinburgh Postnatal Depression Scale [EPDS]), anxiety (Perinatal Anxiety Screening Scale [PASS]) and posttraumatic stress (City Birth Trauma Scale [City BiTS]) were administered prior to, in between, and at the end of treatment, and measures of client satisfaction (Client Satisfaction Questionnaire [CSQ-8]) and group cohesion (Group Cohesiveness Scale [GCS]) were administered on completion of the intervention.

Results: The project was funded in March 2024. Recruitment was completed between July and August 2024. Eleven pretreatment sessions were held in August 2024. Of the 33 expressions of interest (EOIs) received by August 2024, 9 participants were recruited and randomized to the IG (n=4, 44.4%) and the WCG (n=5, 55.6%). The IG completed the six-session program between September and October 2024, with data collection finalized for pre-, mid-, and postintervention timepoints. The WCG began receiving the intervention mid-October 2024, with the final data collection in December 2024. Key feasibility and acceptability metrics include attendance rates, participant retention, and group cohesion scores. Data analysis is ongoing, with manuscript preparation planned for mid-late 2025.

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Conclusions: This study addresses a critical gap in evaluating scalable, accessible mental health interventions for birth trauma recovery. By using narrative approaches in a telehealth group format, this intervention directly responds to the barriers around accessibility and affordability highlighted in recent policy recommendations. Thus, findings from this pilot study could provide important directions in reducing the burden on perinatal mental health services in regional and rural Australia.

Trial Registration: Australian New Zealand Clinical Trials Registry ANZCTR12624000460505p; https://www.anzctr.org.au/Trial/Registration/TrialReview.aspx?ACTRN=12624000460505p

International Registered Report Identifier (IRRID): DERR1-10.2196/69051

(JMIR Res Protoc 2025;14:e69051) doi:10.2196/69051

KEYWORDS

birth trauma; telehealth; group therapy; narrative therapy; early intervention; postpartum mental health

Introduction

Background

Childbirth is a significant life event following on from pregnancy; however, almost half of the Australian birthing population (45.5%) reports having had a birth experience that they describe as traumatic and distressing [1]. Initially limited to physical injury during the birthing process, the current definition of a traumatic birth experience (interchangeably referred to as “birth trauma”) is “a woman’s experience of interactions and/or events directly related to childbirth that caused overwhelming distressing emotions and reactions, leading to short- and/or long-term negative impacts on a woman’s health and wellbeing” [2]. The risk of experiencing a traumatic childbirth increases when there is a history of previous trauma (including sexual trauma or birth trauma from a preceding birth experience); a history of mental health conditions; pre-existing disability; younger age; a lack of continuity of care (with respect to the availability of health professionals); having a lesbian, gay, bisexual, transgender, queer (or questioning), intersex, asexual, and other (LGBTQIA+) identity; living in a regional, rural, or remote area; and having a culturally or linguistically diverse background [3].

A wealth of literature links traumatic childbirth experiences or birth trauma to poorer mental health outcomes in postpartum women, including childbirth-related posttraumatic stress disorder (CB-PTSD), depression, and anxiety [4-9]. Further, the consequences of traumatic childbirth experiences have been shown to extend far beyond the immediate postpartum period and can also impact child outcomes [10]. Experiencing trauma symptoms postchildbirth has been linked to difficulties in breastfeeding [3,11] and, specifically, disruptions in mother-infant attachment and bonding [12-14]. These can have long-term adverse impacts on children’s socioemotional development [15,16] and long-term mental health [17], demonstrating the far-reaching impacts of traumatic childbirth experiences, if left unaddressed.

Given its widespread ramifications, the Parliament of New South Wales (NSW) formed a Select Committee in 2023 to conduct an inquiry into birth trauma. This is the first time in the world a parliamentary committee examined and reported on birth trauma. After reviewing over 4000 submissions from the community, the committee released a detailed report summarizing the submissions and hearings, as well as providing recommendations to reduce the likelihood of birth trauma and its adverse consequences [3]. Among various aspects pertaining to birth trauma, the report highlighted a dearth of adequate mental health services available for postpartum mothers, particularly in regional Australia, with long waitlists to see psychologists and expensive out-of-pocket costs for new parents [3]. This emphasized a critical need to offer accessible, cost-effective mental health services for postpartum mothers with traumatic childbirth experiences.

To address some of these barriers to accessing psychological interventions, such as long waitlists and higher costs, group-based interventions are a viable option for addressing mental health challenges in postpartum mothers, and have additional benefits of providing social support in the form of reducing feelings of isolation, having their feelings and experiences normalized and validated, and through modeling [18]. There has also been an increasing focus on telehealth interventions, necessitated by the COVID-19 pandemic. Research (including a systematic review and meta-analysis) has found that telehealth interventions are a feasible and effective option for supporting postpartum women with mental health diagnoses [19-21]. Taken together, group-based telehealth interventions have demonstrated increased attendance and comparable mental health outcomes to interventions delivered in person when treating mood and anxiety disorders in the general population [22,23] and have been successfully implemented to decrease symptoms of depression and posttraumatic stress in postpartum mothers as well [24]. This is significant, as psychological interventions that are group based and delivered via telehealth will greatly improve access to mental health services by overcoming established barriers to treatment, including affordability, availability, and convenience. For postpartum mothers in particular, such an intervention would further address additional barriers around time management, arranging for childcare, and needing to tend to their infants in an unfamiliar environment [25]. To date, no psychological intervention involving a telehealth group format for women with traumatic birth experiences has been studied.

Two systematic reviews [26,27] collated data from several studies that focused on the effectiveness of interventions to prevent CB-PTSD following birth trauma, ranging from primary prevention (antenatal education) to secondary prevention (hours to weeks following a traumatic childbirth) and tertiary prevention (when CB-PTSD is indicated). Most of the early

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intervention trials (ie, secondary prevention) focused on debriefing within 48-72 hours following birth or within 10 weeks postpartum, with no treatment effect on CB-PTSD [27]. The trauma-focused interventions reviewed included trauma-focused cognitive-behavior therapy (TF-CBT), individual or group based, predominantly with mothers whose infants were admitted to the neonatal intensive care unit or those with preterm infants, and eye movement desensitization reprocessing (EMDR) with women exhibiting symptoms of CB-PTSD [26,27]. A large proportion of these trauma-focused interventions demonstrated a positive treatment effect on CB-PTSD, with some of them reducing symptoms of postpartum depression or anxiety [26-28]. Specifically, for women at risk of or diagnosed with CB-PTSD, two Swedish studies trialed internet-based TF-CBT, with one study finding a positive treatment effect on CB-PTSD, depression, and anxiety [29] and the other finding no significant differences postintervention [30]. However, interventions such as TF-CBT and EMDR are required to be delivered by practitioners with specialized training in these modalities and therefore may be less available for postpartum mothers, particularly in rural areas. Further, these interventions have been predominantly trialed on women who are at risk of developing CB-PTSD or meet the diagnostic criteria for CB-PTSD versus women who report having experienced a traumatic childbirth, with or without symptoms of posttraumatic stress.

Women who report having had a traumatic birth experience frequently attribute their trauma to a lack or loss of control or sense of powerlessness [31], and birth storytelling has been found to be therapeutic for postpartum women, especially first-time mothers [32,33]. Therefore, a therapeutic approach incorporating narrative therapy techniques, such as externalizing the problems and reauthoring one's story [34], which emphasizes self-empowerment, is likely to benefit this target population. Narrative therapy differs from other therapeutic modalities by explicitly acknowledging the social, cultural, and political contexts in which problems arise that ultimately shape the stories we tell ourselves [34]. As women's childbirth experiences can be significantly impacted by sociocultural factors, political factors, and other practical concerns outside their control (eg, workforce shortages), a narrative-informed approach could be ideal in cultivating a strengths-based perspective on narratives. Narrative-informed interventions have been successfully used to address trauma delivered in group settings [35,36]. Linked to a narrative approach, a series of studies in Italy explored the use of a single instance of expressive writing within 48-96 hours postpartum, where women were asked to write about their labor and delivery experiences, focusing on their thoughts and feelings, the purpose of which was to develop a coherent narrative of their birth experience [37-39]. All studies indicated that expressive writing results in reduced psychological distress (depression and CB-PTSD) at 2-3 months postpartum [37-39].

Although curricula exist internationally for therapy groups for traumatic birth experiences [40], these have not been empirically evaluated. Therefore, this research will overcome this critical gap by assessing the acceptability and feasibility of a narrative-informed, group-based telehealth intervention for postpartum women in reducing the mental health impacts of having experienced a traumatic childbirth.

Hypotheses/Research Question

Our first hypothesis is that a narrative-informed, group-based early intervention for postpartum women who have had a traumatic birth experience will be feasible and acceptable. Our second hypothesis is that the intervention will decrease symptoms of postpartum depression, postpartum anxiety, and/or postpartum post-traumatic stress disorder (PTSD) in women with traumatic birth experiences.

Methods

Study Design

This study is a pilot feasibility trial with a parallel design. Eligible participants will be randomly assigned to either an intervention group (IG) or a waitlist control group (WCG), with both arms delivered online and in group format. A WCG was included to ensure that all interested participants would have access to the intervention offered. This project was prospectively registered with the Australian New Zealand Clinical Trials Registry (ANZCTR12624000460505p) on March 26, 2024 (universal trial number U1111-1305-9340).

The pilot trial will be conducted entirely online using the videoconferencing software Zoom. Participants will be sent a password-protected URL to enter the videoconferencing room.

Participants

The inclusion criteria were as follows:

- Women residing in a catchment area in Northern NSW, Australia, of predominantly rural towns spanning 131,785 km, with an estimated population of 962,390 residents as of 2021.
- Up to 6 months postpartum.
- Aged 18 years and above.
- Proficient comprehension of spoken and written English.
- Subjectively reporting having had a traumatic birth experience with their most recent birth.
- Having had a live birth with a gestation of at least 34+ completed weeks. (Births after 34 weeks of gestation are considered late preterm births, and infants may or may not require intensive care. Births prior to this gestation would likely require infants to be hospitalized and remain in intensive care and, therefore, would constitute a specific type of trauma. Such participants would likely benefit from a more homogenous group for increased group cohesion and support.)

The exclusion criteria were as follows:

- Women residing outside of the defined catchment area described earlier (Hunter New England Local Health District, NSW, Australia).
- Nulliparous, pregnant, or more than 6 months postpartum.
- Under 18 years of age.
- Not proficient in English.
- Do not subjectively report having had a traumatic birth experience with their most recent birth.
- Most recent delivery involving a still birth or a live birth with a gestation of under 34 weeks.

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- Endorsing item 10 on the Edinburgh Postnatal Depression Scale (EPDS; pertaining to suicide risk) or have a total score of more than 13.
- Having serious mental health concerns that impinge on their ability to provide informed consent (eg, an intense mood or psychotic episode associated with bipolar disorder or schizophrenia).

Sample Size

The study aimed to recruit 16 participants, which was deemed feasible within the project's funding budget and timelines and is within the recommended size for group-based teletherapy [41]. As a pilot feasibility and acceptability study, should the study be deemed feasible and acceptable, the study findings may help inform estimates for sample size calculation for a larger trial. Consequently, no formal power calculation was performed for this study.

Procedure

Recruitment

Recruitment took place in July and August 2024 and was completed by the start of September 2024. Participants were recruited through the following:

- Midwives and lactation consultants in public and private health care systems who aid postpartum mothers in recovery and breastfeeding.
- Child and family health nurses who provide free health and developmental checks on growth and development throughout infancy and early childhood. These nurses are also responsible for organizing local mothers' groups for first-time mothers within a region.
- Perinatal Infant Mental Health Services (PIMHS), a free mental health service for women up to 2 years postpartum.
- Local referral hospitals (Armidale and Glenn Innes), who put the recruitment flyers in the personal health record books given to parents of all newborns born within that recruitment period.
- General practitioner obstetricians providing postpartum checks.
- Targeted advertising on social media (Facebook).
- Australian Facebook groups on birth trauma, breastfeeding, etc.
- Pamphlets with information about the study given to health care providers, including a QR code linking to an expression-of-interest survey.

Ethical Considerations

This study will be conducted in compliance with all stipulations of this protocol, the conditions of the University of New England Human Research Ethics Committee approval (approval number HE24-054, valid till June 1, 2025), with site-specific approval granted to recruit from Hunter New England Health sites in the towns of Armidale and Glenn Innes; the National Health and Medical Research Council (NHMRC) National Statement on Ethical Conduct in Human Research; and the Australian Code for the Responsible Conduct of Research. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 checklist was followed when writing this protocol [42].

Potential participants who expressed interest were emailed a detailed information sheet by the research assistant and then invited to a pretreatment session. There was at least a week's duration between receiving the information sheet and the pretreatment session for potential participants to consider participating. The pretreatment session included an introduction to the chief investigator (CI; author CS), who delivered the intervention and who presented screening questions to determine participant eligibility. The scope of the group therapy and guidelines for participation were explained (eg, telehealth etiquette, the need to be respectful, maintaining confidentiality of other group members, and distress management within sessions). At each individual pretreatment telehealth session, the information sheet was presented again, and participants got an opportunity to ask questions and clarify concerns, leading to the informed consent process. The clinician then gathered personal contact information and emergency contact details from the participants and explained the circumstances in which they would be used (ie, a participant leaves a group session abruptly, and one of the psychologists on the research team needs to do a telehealth welfare check to ensure safety). If deemed eligible, participants then signed the informed consent form, which could be done via an e-signature and sent as a file attachment within the password-protected Zoom Meeting or via email. The pretreatment session concluded with an assessment of the participants' preferences for the session day and time. Additionally, participants also provided online implied consent before completing the pretest survey. Participants had the right to withdraw at any point without needing to provide a reason. Their identity was only known to the CI (CS) and the research assistant (author HM) to safeguard their privacy. All participants were remunerated with gift vouchers at designated intervals (to a total of AU $200, or ~US $130 at an exchange rate of AU $1=US $0.65, per participant) across the intervention to promote retention.

All data collected will be electronic and kept on the University of New England's (UNE) centrally managed cloud server, as well as on a password-protected computer. Only the research team will have access to the data. All audio/video files recording the sessions will be deleted upon completion of the transcription process. Quantitative and qualitative data will be deidentified using numerical identifiers. The deidentified data will be stored in the UNE's online research repository indefinitely and can be made available upon reasonable request.

Allocation and Concealment

This pilot trial included an IG (who received the intervention immediately after recruitment) and a WCG (who were allocated to a waitlist during the same observation period as the intervention. Although there were no restrictions on outside care for the WCG, no intervention or support was actively offered to these participants. HM monitored the mental health of participants in the WCG (across the outcome measures administered at various timepoints; see Table 1) and alerted the team to any observed deterioration. A recent pilot feasibility trial conducted in Australia noted that people typically wait 6 months or longer to access mental health services [43]. Once the study with the IG concluded, the WCG received the full

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intervention, which involved a wait time of 6 weeks, significantly less than the typical waitlist.

A randomization sequence in alternating block sizes of 4 and 6 was generated from an online sequence generator by author PJT. The randomization sequence was revealed to the research assistant (HM) and only after completion of the baseline and eligibility measures. At that time, the research assistant informed participants of the intervention start date based on their allocation to either the IG or the WCG.

Table 1. Data collection timeline.

Measure	IG[a] timepoints				WCG[b] timepoints			
	T1[c]	T2[d]	T3[e]	T4[f]	T1	T2	T3	T4
City BiTS[g]	X[h]	X	X	__[i]	X	X	X	X
EPDS[j]	X	X	X	—	X	X	X	X
PASS[k]	X	X	X	—	X	X	X	X
GCS[l]	—	—	X	—	—	—	—	X
CSQ-8[m]	—	—	X	—	—	—	—	X

[a]IG: intervention group.
[b]WCG: waitlist control group.
[c]T1: prior to session 1 for the IG.
[d]T2: after session 3 for the IG.
[e]T3: after session 6 for the IG.
[f]T4: after session 6 for the WCG.
[g]City BiTS: City Birth Trauma Scale.
[h]X: applicable.
[i]Not applicable.
[j]EPDS: Edinburgh Postnatal Depression Scale.
[k]PASS: Perinatal Anxiety Screening Scale.
[l]GCS: Group Cohesiveness Scale.
[m]CSQ-8: Client Satisfaction Questionnaire.

Blinding

Participants were blinded to whether they were in the IG or the WCG. The CI was not involved in the randomization sequencing, nor in communicating intervention start dates to participants, depending on their group membership. However, as the CI was the clinician delivering the telehealth intervention, this was partial blinding. Participants filled in the measures at pre-, mid-, and postintervention timepoints using a unique identifier (generated by HM), so the survey data collected will be anonymous to the statistician.

Pre- (baseline), mid-, and postintervention measures were administered to the IG and WCG according to the schedule depicted in Table 1. The group-based intervention was conducted via telehealth to assess the feasibility and acceptability of a program that is likely to be cost-effective and accessible. The telehealth platform used in this study was a Zoom Conference Room, which was password-protected, so only individuals with the password (ie, study participants who met the eligibility criteria) were able to join in. For added security, all participants were sent two separate modes of communication, one with the Zoom Meeting link and another with the password to this meeting. Email reminders on the 2 days preceding each scheduled session were sent out to all participants. All sessions were recorded with informed consent. These were then transcribed verbatim for qualitative analyses to identify the key themes of healing from traumatic birth experiences.

Intervention Details

The intervention was a group-based early intervention incorporating techniques and ideas from narrative therapy, roughly based on a modified version of the six-session trauma narrative recovery model developed by Lane and Lane [44]. The CI and one of the coauthors (HF) reviewed existing group-based and narrative-informed trauma-based interventions [40,44] and outlined each of the six sessions. A detailed treatment guide is freely available on an online repository for reproducibility of this intervention [45]. Each session ranged from 60 to 120 minutes; a large time range was deliberately proposed to enable participants to take breaks in the session, as needed, to attend to the needs of their babies (eg, a feed, nappy change). The intervention was conducted via a password-protected Zoom Conference Room. Table 2 provides an overview and brief description of each of the six sessions.

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Table 2. Overview of the six sessions of the intervention.

Session number	Title	Description
1	Introduction and Psychoeducation	The first session introduces group members, recaps group guidelines, provides psychoeducation on birth trauma, and encourages reflection on personal experiences and coping strategies.
2	Sharing Birth Stories and Narrative Techniques	Participants commence sharing birth stories, with the clinician facilitating externalizing language use and implementing the "outsider witnesses" technique to enrich narratives.
3	Sharing Birth Stories and Narrative Techniques	Birth story sharing continues, focusing on externalizing problems and identifying unique outcomes in participants' narratives.
4	Sharing Birth Stories and Narrative Techniques	This is the final session of birth story sharing, guiding participants to retell their stories with new perspectives and identified unique outcomes.
5	Reflection and Reauthoring	Participants reflect on shared experiences, rewrite or redraw their birth stories with new insights, and plan for the final session.
6	Integration and Closure	The group reflects on changes and emotional shifts, explores future directions, revises personal definitions, and completes a finishing ritual.

The designed intervention was carefully reviewed by an advisory group that consisted of a perinatal clinical psychologist, a narrative therapy clinician (experienced in working with women and trauma), a midwife, a doula (with lived experience from several years prior), and a person with recent lived experience. The group met twice (June and July 2024) and provided recommendations to modify the proposed intervention. Some of these recommendations were suggestions around the language used with participants (eg, changing the commonly used term "group rules" in group therapy to "group guidelines" to make it less authoritative and more collaborative), as well as activities participants could engage in during specific sessions (eg, ideas for "finishing rituals" to commemorate the end of the intervention). The advisory group met again on completion of the pilot trial to discuss findings, implications, and future directions.

Detailed Description of Sessions

Session 1: Introduction and Psychoeducation

The first group session (60-120 minutes) opened with introductions and ice-breaking activities to foster a comfortable atmosphere. The clinician presented the group guidelines to ensure a safe and supportive environment. Psychoeducation on trauma and birth trauma followed, with a specific focus on the postpartum period. The clinician then led a discussion on common trauma responses and their neurobiological basis, introducing the concept of healing from trauma through language and memory systems. Participants were encouraged to share coping strategies for triggers. The session included a reflection on personal definitions of "me" and "my space." As an optional activity, participants engaged in a writing exercise to begin exploring their birth story.

Sessions 2-4: Sharing Birth Stories and Narrative Techniques

These sessions (60-120 minutes each) were dedicated to sharing birth stories, with 1 or 2 participants narrating their birthing experiences per session. Through careful questioning, the clinician helped participants use externalizing language to describe their problems (as separate from their personhood versus inherent in them). The clinician then implemented the "outsider witnesses" technique. This is a structured process wherein group members, acting as an audience to the story shared, are invited to reflect on and respond to a person's story. This involves highlighting significant aspects that stand out, relating them to their own experiences, and describing how the story has impacted them, thereby potentially revealing alternative narratives or overlooked strengths. It usually involves a four-step process (identifying resonant expressions, recognizing values, making personal connections, and acknowledging impact) that validates the storyteller's experience, while extracting moments of agency and resilience within their narrative. A key focus is the identification of unique outcomes in participants' stories. The storyteller is then guided through a retelling of their story, incorporating new perspectives and the identified unique outcomes.

Session 5: Reflection and Reauthoring

The fifth session (60-120 minutes) began with completing any remaining story sharing, if needed. Participants were then guided to reflect on how their stories felt after sharing and witnessing others' experiences. The clinician provided them with an opportunity to rewrite or redraw their birth stories, incorporating new insights. Next, the group collaboratively decided on the content for the final session and chose one or more finishing rituals to symbolize consolidation and the end of treatment.

Session 6: Integration and Closure

The final session (60-120 minutes) focused on instilling hope by reflecting on changes observed within oneself and others. The clinician guided a reflection on the evolution of birth stories and any emotional shifts experienced (if participants wrote down their birth story after session 1, this was used to facilitate this comparison). The discussion then turned to future directions, exploring values and sources of social support. Participants could revisit and potentially revise their personal definitions of "me" and "my space." The chosen finishing ritual was completed, providing a sense of closure to the group experience. If desired, participants were given an opportunity to exchange contact information.

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Outcomes

The following measures were administered according to the schedule depicted earlier in Table 1.

Treatment acceptability was assessed using the Group Cohesiveness Scale (GCS) [46] and the Client Satisfaction Questionnaire (CSQ-8) [47].

The GCS is a 7-item self-report measure assessing the level of cohesiveness in group therapy settings. The scale has strong psychometric properties and is a brief measure of group cohesiveness that can be used in psychiatric settings [46]. The CSQ-8 is a widely used 8-item scale measuring client satisfaction with mental health services. It is a subscale of the original Client Satisfaction Questionnaire-18, which has robust psychometric properties and, combined with its brevity, is a useful brief measure of client satisfaction [48]. The CSQ-8 has been used successfully in the provision of psychological interventions via telehealth (ie, videoconferencing) for conditions such as depression [49].

Treatment feasibility was assessed using indicators of treatment adherence and retention. Based on Wright et al's [24] research on a virtual psychotherapy group for postpartum mothers, a rate of 70% was set to determine feasibility with respect to individual participant attendance across all the six sessions of the intervention, as well as overall retention (determined by the completion of all postintervention measures after session 6).

Postpartum depression was assessed using the EPDS [50], a 10-item self-report questionnaire widely used to screen for postpartum depression. It assesses symptoms experienced in the past 7 days, with higher scores indicative of a greater endorsement of depressive symptoms. The EPDS has demonstrated good reliability and validity in postpartum women [51] and has been validated for routine postnatal screening in Australia [52].

Postpartum anxiety was assessed using the Perinatal Anxiety Screening Scale (PASS) [53], a 31-item self-report questionnaire designed to screen for anxiety in both antenatal and postpartum women. Developed and validated for use in Australia [53], PASS provides cutoffs for differentiating between minimal, mid-moderate, and severe anxiety [54]. Its strong psychometric properties have led to its cross-cultural use and translation to other languages.

Posttraumatic stress symptoms were assessed using the City Birth Trauma Scale (City BiTS) [55], a 29-item self-report questionnaire specifically designed to measure postpartum PTSD following childbirth. It assesses symptoms based on the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5) diagnostic criteria for PTSD. The scale has shown good reliability and has been validated for use among Australian postpartum women [56].

Data Analysis

Quantitative Data

All analyses will be based on the intention-to-treat principle. The quantitative data analyses will involve repeated-measures ANOVA entering the main effects for group, time, and group×time interaction, assuming $\alpha<.05$ to denote a significant effect between the IG and the WCG for continuous study outcomes (City BiTS, EPDS, PASS). Assumption testing will examine normality using the Shapiro-Wilk test and sphericity using the Mauchley test of sphericity. Transformation and Huynh-Feldt correction will be applied, respectively, in the case of violation of these assumptions. The therapy process measures will be analyzed for between-group differences to determine the acceptability of the group intervention. As a feasibility and acceptability study, testing the proof of principle, our analyses will provide an estimate of mean (SD) change data and effect sizes to inform a larger trial in the future. The assessment of acceptability and feasibility postdelivery of the intervention, in both the IG and after the last session of the WCG, will afford the trial more quantitative data to identify aspects of the intervention that were perceived as beneficial and preferred.

Qualitative Data

Audio recordings of all group sessions were transcribed verbatim for qualitative analyses to identify the key themes salient in the treatment of traumatic birth experiences. The transcribed data from the six intervention sessions across both the IG and the WCG will be subjected to qualitative data analysis in order to better understand therapeutic processes that support change. Specifically, comprehensive process analysis (CPA) [57] will be adopted. CPA is an interpretive, qualitative research method used for analyzing therapy and is specifically designed to identify elements that could facilitate or hinder therapeutic progress [57]. The analysis will encompass three broad domains: context, key responses, and effects. Elliot et al [57] described four levels of *context* that must be explored: background (factors bringing participants into treatment, which in this study include experiences of birth trauma, previous coping styles, etc), presession context (referring to relevant events that could occur between sessions, eg, preparing a narrative of one's birth story), session context (eg, therapeutic alliance and session tasks such as sharing one's birth story, outsider witness), and, finally, episode context (conversational episodes pertaining to a significant event in therapy). An analysis of *key responses* relates to therapist or client responses perceived to be most helpful [57]. This analysis can include actions by the clinician or client, the style adopted, the nature of the content, and the quality of delivery. Finally, *effects* will be documented, aiming to track immediate and delayed consequences of the events within a session or across treatment.

Two coauthors will serve as CPA analysts (CS and HF), the former of whom is also the intervention facilitator. Both CS and HF are experienced in qualitative data analysis. Each analyst will independently review session transcripts (looking at the two initial sessions together, the two second sessions together, and so on) to identify significant process events and extract meanings with respect to context, key responses, and effects. The analysts will also maintain a reflective journal through this process. Once this step is complete, the analysists will meet in the presence of another coauthor (SC), also experienced in qualitative data analysis and not part of the intervention, who will assist in developing consensus through open dialogue, while ensuring that all perspectives are considered and discussed adequately. The multiauthor discussion and review, alongside

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considerations in the reflective journal, will support the trustworthiness and rigor of the analysis and ensure the analysis best reflects the data and process elements. With this process, we aim to produce a comprehensive understanding of which narrative intervention elements that effectively support birth trauma recovery in a telehealth group setting and which require modification, directly informing intervention refinement for the future. The embedded mixed methods design will allow details of the processes of change in the intervention to complement qualitative findings around feasibility and effectiveness. Outcome data will also be used to triangulate qualitative findings to further support which elements of change were and were not acceptable or useful for participants.

Results

This project was funded in March 2024 through the Peregrine Centre Rural Mental Health Partnerships Small Research Grants (AU $26,707.68, or US $17,406.86) and was prospectively registered with the Australian New Zealand Clinical Trials Registry on March 26, 2024. Recruitment was completed between July and August 2024, and 33 expressions of interest (EOIs) were received, of which 12 (36.4%) booked in pretreatment sessions (n=17, 51.5%, did not respond to the invitation to join a pretreatment session, and n=4, 12.1%, replied but were ineligible to participate either due to age of the infant or location). In total, 11 pretreatment sessions were held in August 2024, and 9 (81.8%) participants returned signed informed consent forms (n=2, 18.2%, participants were deemed ineligible due to gestation at birth and age of the infant). These 9 participants (demographic details reported in Table 3) were randomly assigned to the IG or the WCG (see Figure 1). The IG completed the six-session program between September and October 2024, with data collection finalized for pre-, mid-, and postintervention timepoints. The WCG began receiving the intervention mid-October 2024, with the final data collection (timepoint 4) in December 2024. Data analysis is ongoing, with manuscript preparation planned for mid-late 2025. The study is proceeding according to protocol without significant deviations.

Table 3. Participant demographic information.

Participant	Group	Age (years)	Education level	Annual household income (AU $; US $)[a]	Parity	Age of infant (months)
P1	IG[b]	36	College certificate or diploma	160,000-169,999; 104,281-110,798	1	3
P2	IG	36	Undergraduate degree	60,000-69,999; 39,105-45,622	2	2
P3	WCG[c]	26	Year 12	80,000-89,999; 52,140-58,657	2	1
P4	WCG	Not disclosed	Not disclosed	Not disclosed	1	3
P5	IG	30	Postgraduate degree	170,000-179,999; 110,754-117,268	1	4
P6	WCG	20	Year 11	<10,000; 6515	1	2
P7	WCG	28	Undergraduate degree	130,000-139,999; 84,694-91,209	1	2
P8	IG	26	Year 10 or less	$100,000-$109,999; 65,152-71,014	1	<1
P9	WCG	Not disclosed	Not disclosed	Not disclosed	1	<1

[a]An exchange rate of AU $1=US $0.65 has been applied.

[b]IG: intervention group.

[d]WCG: waitlist control group.

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Figure 1. Flowchart of the pilot trial procedure. IG: intervention group; WCG: waitlist control group.

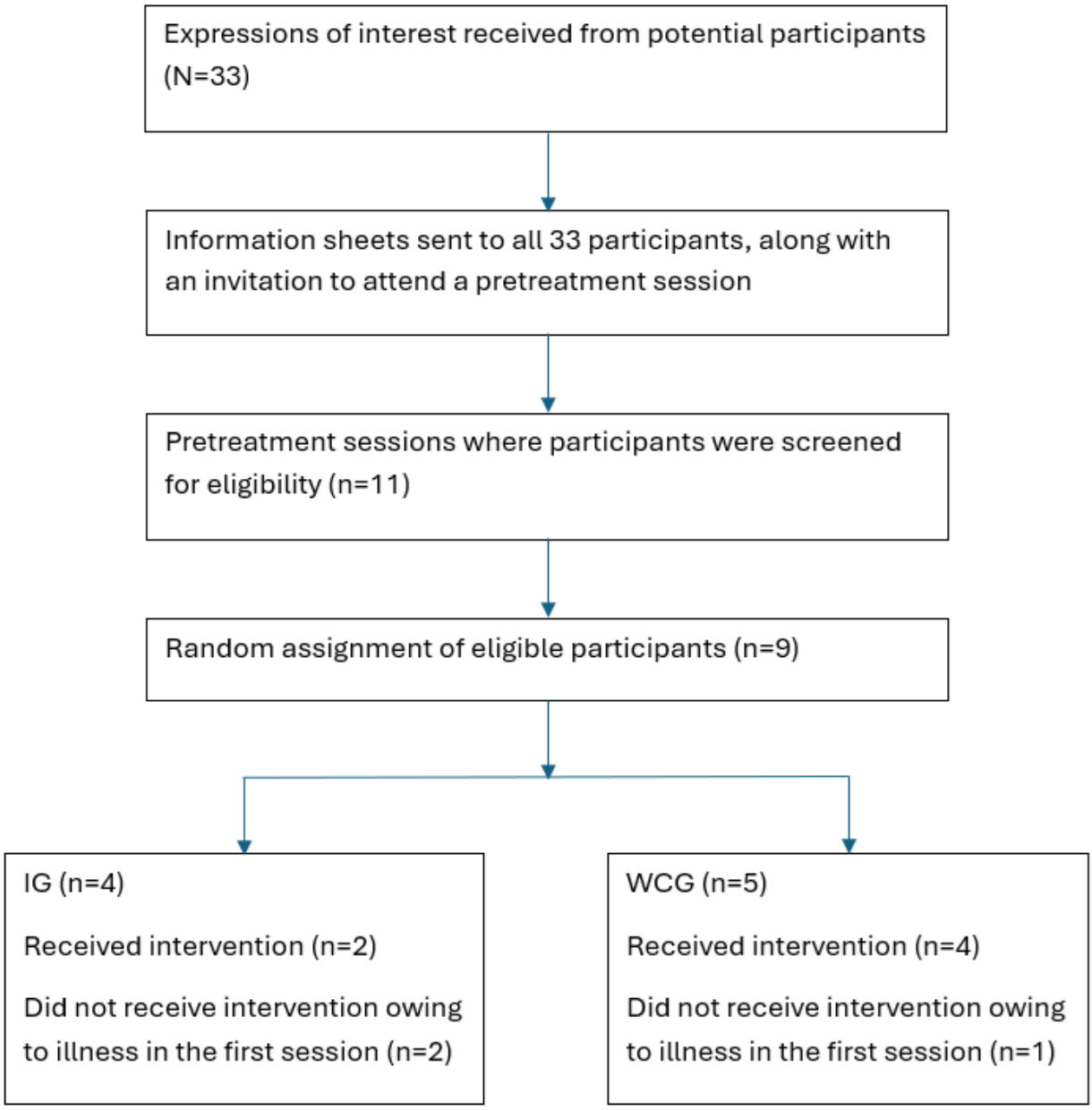

To determine treatment acceptability, GCS-7 and CSQ-8 scores will be totaled for each participant, and a range of scores will be examined, including the central tendency score for each group. Higher scores will indicate greater treatment acceptability on both measures. Treatment feasibility will be determined by using attendance and retention metrics, with a threshold of 70% established as the criterion for feasibility drawn from recent research on virtual psychotherapy groups for postpartum mothers [24]. This threshold will apply to both individual participant attendance across all six sessions and overall retention, as measured by completion of postintervention measures across both groups. These predetermined benchmarks will provide clear criteria for determining whether the intervention warrants investigation in a larger trial.

The mental health outcome measures (EPDS, PASS, and City BiTS) will be scored according to the developer instructions. The last observation carried forward (LOCF) approach will be used to deal with any missing values, which involves replacing each missing value of a participant with the last observed value for that participant. The LOCF was chosen for its simplicity and frequent use in clinical trials [58]. As this is predominantly a feasibility and acceptability pilot study whose sample size is insufficiently powered to demonstrate statistically significant treatment effects, the LOCF was chosen over other more complex imputation methods that may not offer substantial benefits at this early stage. The average scores will be compared across the IG (who had these measures administered prior to, during, and after the intervention) and the WCG (who completed measures while they were on the waitlist, as well as after they received the intervention).

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Discussion

Summary

This pilot trial will evaluate the acceptability and feasibility of a narrative-informed, group-based telehealth intervention specifically designed for postpartum mothers who have experienced birth trauma in the previous 6 months, and explore its potential impact on mental health symptoms of depression, anxiety, and posttraumatic stress. The findings from this study will have important implications for clinical practice, future research, and policy development in maternal mental health care.

Although research supports the use of psychological interventions in the postpartum period for mothers who are at risk of CB-PTSD, the majority of these studies tend to be individual based and in person [26,27]. Our intervention approach addresses the important barriers of accessibility and affordability by offering a group-based telehealth intervention that spans 6 weeks. Further, although narrative approaches, in the form of expressive writing, have been found to be useful in reducing psychological distress postpartum [37-39] and have been used in other trauma-focused group interventions [35,36], this is the first application of a narrative-informed group intervention for postpartum mothers specifically delivered through telehealth.

This pilot intervention also responds to some of the recommendations outlined following the NSW parliamentary inquiry, specifically pertaining to the need for more accessible and affordable psychological support services for people who experience traumatic childbirth experiences [3]. Currently, organizations in Australia that offer free postpartum mental health support report that their service capacity is restrained due to limited resources, with the main national helpline for postpartum mental health reporting that it has a capacity to attend to only 20%-30% of “live calls” on any given day [3]. Further, although the government does offer funding to access psychological services via Medicare rebates, there are several barriers and limitations; for instance, postpartum mothers cannot self-refer for these services (they require a referral from a general practitioner and other administrative procedures to be completed first), the funding is limited to 10 sessions per calendar year, and it is usually only sufficient to cover part of the costs [3]. Our telehealth delivery with a group format responds directly to address some of these accessibility barriers.

Apart from the cost of treatment, another frequently reported barrier among the perinatal population is the difficulty in attending mental health appointments due to varying reasons, including time constraints, childcare responsibilities, geographic distances (particularly in regional areas), transportation, and scarcity of qualified providers [59]. Providing an opportunity for postpartum women to access a telehealth psychological intervention mitigates several of these barriers, allowing them to access services from qualified professionals in a timely manner from the comfort of their own home.

As mentioned earlier, group-based interventions offer social support, normalization, and validation to participants [18]. However, this is not without disadvantages. Individual therapy can offer more privacy, individualized attention, and flexibility in scheduling (or rescheduling) sessions [18]. Mitigating some of these disadvantages should be the focus of future research.

Dissemination and Scalability

Several avenues for dissemination have been planned, with some already implemented. The intervention was presented at numerous conferences, including those with practitioners and academic audiences both nationally and internationally. The treatment protocol was also presented to a group of psychologists in the public health sector in NSW, Australia, with further practitioner presentations planned into the future. A treatment guide has been developed in consultation with the advisory group, and this has been made available freely for practitioners to access [45]. Further avenues of dissemination will also be provided by the funding body. Finally, the authors will present a summary of the findings to participants who completed the intervention and will publish their findings in an academic journal.

The intervention was also designed to be scalable, and on reflection and in consultation with the advisory group, a practitioner treatment guide has been developed. For evaluating this intervention in larger samples (ie, multiple groups) in order to have statistical power, multiple clinicians will need to be familiarized with this treatment modality. The current intervention is designed such that anyone with training in mental health (ie, psychologist, psychotherapist, counsellor, narrative therapist, psychiatric social worker, or mental health nurse) will be able to implement it referencing the treatment guide, provided they have some experience and knowledge of group therapy, perinatal mental health, and narrative therapy techniques. Scaling up this intervention in a future study will require regular peer supervision for the clinicians involved, wider recruitment strategies, and robust screening and referral pathways for potential participants.

Study Limitations and Future Directions

This study has several limitations that warrant consideration. First, the statistical power for detecting significant changes in the mental health outcome measures is limited owing to the small sample size (n=9) in this pilot trial, and the use of single imputation methods (eg, LOCF) to deal with missing values is generally not recommended as it is based on the assumption that outcomes do not change if a participant does not fill in a specific measure [58]. However, the primary aim of this project is to examine the feasibility and acceptability of delivering such an intervention, not to comment on significant treatment effects. Further, as we are adopting an embedded mixed methods approach, it is anticipated that the qualitative data will provide a rich understanding of the processes facilitating change as a result of the intervention. If feasibility and acceptability are demonstrated in this study, then future research can look at using this intervention in large-scale trials with a priori power calculations to evaluate statistical significance. In this instance, multiple imputation methods would be recommended to deal with missing values in order to provide more robust estimates.

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Second, it is possible that there has been a selection bias owing to recruitment through social media and health care professionals. Potential participants were to send in an EOI if they wished to participate in the study and could have had higher digital literacy, less perceived stigma, and greater help-seeking tendencies than other eligible persons who did not submit an EOI. Further, postpartum women outside of the geographical region under study, and those with infants older than 6 months of age, were not eligible to participate in this study, which meant that the intervention could not be offered even when they reached out (sent an EOI). Participants who were deemed ineligible were provided with alternate mental health support resource options that they could access. This recruitment strategy also potentially limited the cultural diversity in potential participants. Future research with larger trials could seek to deliberately recruit participants from culturally diverse backgrounds, which could speak to this intervention's broader applicability.

Third, the CI (CS) of this research project also delivered the intervention, given the resource constraints and need for a qualified professional to implement the intervention. To mitigate potential bias, CS was blinded to the random assignment of participants to the IG and the WCG; the research assistant (HM) handled all participant communication with respect to group allocation and the administration of outcome measures; and the coauthor (PT), who was not involved in the intervention delivery, will conduct the statistical data analysis.

Finally, our study does not involve long-term follow-ups beyond the intervention period, which limits our understanding of sustained effects of the intervention. This extended follow-up was not included in the study design, as the primary aims of the study were to assess feasibility, acceptability, and immediate impacts on mental health measures. However, future research with larger samples would benefit from including follow-ups a few weeks or months after the intervention to determine whether any changes in symptoms were sustained.

Conclusion

This pilot feasibility trial aims to address significant barriers in mental health support services available for women who experience a traumatic childbirth experience by evaluating a narrative-informed, group-based telehealth intervention delivered within 6 months postpartum. Although this study is preliminary and limited by some aspects of methodology (including a small sample size, partial blinding, and the lack of follow-up), it still establishes the groundwork for developing a scalable, evidence-based intervention that can be integrated into existing perinatal mental health pathways to mitigate the impacts of traumatic childbirth experiences.

Our research directly responds to some of the recommendations from the NSW Parliamentary Inquiry into Birth Trauma [3] specifically addressing the urgent need for accessible and affordable psychological support for postpartum mothers, particularly in regional and rural areas. The uniqueness of its contribution lies in its application of narrative therapy principles within a telehealth group format, specifically using technology to overcome geographical, logistic, and financial barriers that postpartum women in regional and rural Australia face. It is also an intervention that various mental health clinicians could relatively easily learn to implement (versus other trauma-focused interventions that require delivery by psychologists with additional training), which in turn could contribute to reducing the disease burden and the drain on the health system, currently plagued by long waitlists and a limited number of clinicians able to offer mental health services. Finally, if feasibility and acceptability are demonstrated, future research can look at larger, adequately powered randomized controlled trials to evaluate efficacy, including long-term follow-ups and exploring implementation in diverse populations.

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Data Availability

Deidentified data and materials will be placed in an online research repository, which will be made available upon reasonable request on completion of the pilot trial.

Authors' Contributions

CS was the chief investigator responsible for leading the project, project design and conceptualization, adaptation of the intervention, intervention delivery, data analysis, and supervising the research assistant. SC was responsible for mentorship, project design and conceptualization, sharing expertise in qualitative research methodology, and data analysis; AL for mentorship, project design and conceptualization, and data analysis; and HF for adaptation of the intervention and data analysis. HM was the research assistant on the project and assisted with recruitment, participant correspondence, and survey administration. MK, JC, and JT were responsible for sharing professional health care expertise on perinatal and postpartum care for women and recruitment of participants; AS for offering advice as an additional resource if there are significant mental health concerns or crisis; and PJT for mentorship, project design and conceptualization, sharing expertise in quantitative research methodology and clinical trials, randomization sequence generation, and data analysis.

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Conflicts of Interest

None declared.

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Abbreviations

CB-PTSD: childbirth-related posttraumatic stress disorder
CI: chief investigator
City BiTS: City Birth Trauma Scale
CPA: comprehensive process analysis
CSQ-8: Client Satisfaction Questionnaire
EOI: expression of interest
EMDR: eye movement desensitization reprocessing
EPDS: Edinburgh Postnatal Depression Scale
GCS: Group Cohesiveness Scale
IG: intervention group
LOCF: last observation carried forward

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NSW: New South Wales
PASS: Perinatal Anxiety Screening Scale
PTSD: posttraumatic stress disorder
TF-CBT: trauma-focused cognitive-behavior therapy
WCG: waitlist control group

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Protocol

Piloting Digital Navigators to Promote Acceptance and Engagement With Digital Mental Health Apps in German Outpatient Care: Protocol for a Multicenter, Single-Group, Observational, Mixed Methods Interventional Study (DigiNavi)

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Abstract

Background: In Germany, patients often have to wait several months for psychotherapeutic treatment. Digital therapeutics (DTx) offer a promising approach for timely mental health support, but their use remains limited. Digital navigators (DNs) are specially trained medical assistants who support other health care professionals (HCPs) in selecting and using DTx. This can improve digital health literacy, increase engagement, and reduce the burden on HCPs.

Objective: The DigiNavi study is the first pilot study that aims to test the feasibility of implementing DNs in general practice and outpatient psychiatric care in Germany.

Methods: This mixed methods study took place at six study sites (three psychiatric outpatient clinics, three general practices) in Germany. In the prestudy, patients and HCPs participated in semistructured interviews and focus groups concerning their acceptance and expectations of DNs (phase I). The Harvard Digital Navigator Training (HDNT) was adapted, and medical assistants were trained as DNs (phase II). During the intervention, 8 patients per site (N=48) diagnosed with a mental disorder were recruited via convenience sampling and supported by DNs in using DTx for mental health for 12 weeks (phase III). Patients' (N=48) and HCPs' (N=18) digital health literacy, digital and technical literacy, readiness and ability to change, and clinical symptom severity were assessed before and after 12 weeks of DTx prescription and support by DNs. Patient engagement with the DiGAs (usage duration and intensity) was measured after the intervention. Quantitative data were analyzed using a pre-post design. Finally, qualitative interviews were conducted with HCPs, patients, and DNs to explore their experiences with DNs, including perceived implementation barriers.

Results: The study received funding in July 2024. The prestudy including 35 participants was conducted from August to October 2024. HDNT adaptation and DN training were conducted from October to December 2024. Recruitment and quantitative baseline data collection started in December 2024, and 48 participants were enrolled by the end of March 2025. The intervention study

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ended in June 2025. Result dissemination and the development of strategies for the long-term implementation of DNs into the German health care system are planned until September 2025. We hypothesize that the provision of support by DNs will enhance patients' and HCP' digital and technical literacy, patient engagement with DiGAs, and readiness and ability to change. In addition, patients' mental health is expected to improve after the end of the intervention.

Conclusions: This is the first study to examine the feasibility and effects of DNs in German health care. The study will provide significant insights into the acceptability and feasibility of human-facilitated competency development for mental health apps in multiprofessional health care teams and their patients. The successful implementation of DNs can promote the use of DTx in Germany and thus enhance access to and the provision of health care for individuals affected by a mental disorder.

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KEYWORDS

digital therapeutics; digital health; digital health applications; digital health app; digital health apps; digital navigator; digital navigators; digital intervention; digital interventions; eHealth; mHealth; mobile health; digital health literacy; mental health; psychiatric care

Introduction

The prevalence of mental health conditions is increasing worldwide [1]. Mental health disorders, such as depression and anxiety, have a significant impact on an individual's quality of life and, if left untreated, can become chronic [2]. This can result in a burden on health care systems and society as a whole [3]. Effective treatment typically involves psychological interventions. However, there is a significant treatment gap, particularly in low- and middle-income countries [2,4]. Lack of psychotherapy and the resulting long waiting times are structural barriers to treatment [2]. In addition, general practitioners (GPs) often do not have the resources to provide adequate treatment, even when mental disorders are recognized [5]. Personal attitudes toward psychotherapy also contribute to this gap, as many patients have a high threshold for seeking treatment and may not recognize their condition as requiring professional intervention [5].

Low-threshold digital services, such as digital therapeutics (DTx), for mental health offer scalable, evidence-based, and easily accessible solutions that can reduce waiting times and provide initial relief [6-10]. International studies indicate the great potential of digital mental health tools to improve the quality of and access to care [11]. An increasing number of countries have already introduced the possibility to prescribe DTx or financially support the purchase of mental health apps [12-14]. However, despite the growing availability of mental health apps, the use of DTx internationally remains below expectations [15,16].

The reasons for low engagement are complex [17]: A user-friendly design and interface are essential for app adoption [18]. However, a significant proportion of users lack the digital and technical literacy to use the apps intuitively and effectively [11,19]. According to a recent study, patient digital literacy represents the biggest barrier to virtual care adoption, with 71% of health care organizations identifying it as a major challenge [20]. This so-called digital divide particularly affects already underserved patient groups, such as older adult or educationally disadvantaged patients [21,22]. In addition, many patients often do not have sufficiently modern smartphones or the necessary digital health literacy to use digital mental health apps effectively [23]. However, even among populations that frequently use technology, adoption remains low. Key barriers include resistance to change and concerns about data privacy, shared by both patients and medical staff [24]. Acceptance of digital health services by health care professionals (HCPs) is an important factor influencing the adoption of digital interventions by patients [11,25]. In addition to the general concerns that HCPs may have about integrating DTx into their medical practice, they often lack the time to keep abreast of developments in DTx and how to effectively integrate them into treatment processes [7,8,24,26]. Furthermore, both HCPs and patients frequently perceive digital apps as inadequate for addressing mental health problems [23], and patients often do not adhere to the intended use and stop using the app after initial installation due to a lack of motivation [16,27]. However, research suggests that human guidance—defined as personal assistance in the selection, installation, and use of DTx—can improve both acceptance and engagement with DTx and achieve lasting positive health outcomes [28-32]. A promising approach in this context is to train selected HCPs in medical teams to become so-called digital navigators (DNs) [33-35]. The core tasks of DNs are threefold: first, to increase digital competence within psychiatric and GP treatment teams through training initiatives; second, to expand the knowledge base of HCPs and patients regarding DTx for mental health; and third, to support and accompany patients in the use of DTx. The guided use of DTx is intended to improve the care of the target group of people with mental health conditions.

In Germany, DTx are called *Digitale Gesundheitsanwendungen* ("digital health apps" [DiGAs]) and have been available since the implementation of the Digital Health Care Act (*Digitale-Versorgung-Gesetz*) in December 2019 [36]. This legislation established the framework for the approval and reimbursement of digital mental health apps. These apps must meet specific standards set by the German Federal Institute for Drugs and Medical Devices (BfArM) to ensure safety, quality,

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functionality, privacy, data security, and effectiveness [37]. Once approved, DiGAs can be prescribed by physicians and psychotherapists and are reimbursed by statutory health insurances. Currently, there are 72 DiGAs available, of whom 29 (40.28%) focus on mental health conditions (eg, n=7, 24.14% on depression; n=7, 24,14% on anxiety). All approved DiGAs can be found in the publicly available German DiGA directory of the BfArM [38].

Although DNs have been successfully implemented in several countries [11,32], no such role or training program currently exists in Germany. In addition, evidence from abroad cannot be easily transferred to Germany since the introduction of new roles, such as DNs, must align with existing structures, including statutory health insurance and professional licensing laws. As a result, the best practices from other countries must first be adapted to the German legal, financial, and organizational framework [39].

An exploratory pilot trial is therefore needed to gather preliminary information about the implementation of DNs in the German health care system and the feasibility of conducting a full-scale trial. The aim of this study is to (1) explore the acceptance and expectations of HCPs and patients in Germany toward DNs (2); adapt the Harvard Digital Navigator Training (HDNT) for the German health care system; (3) evaluate the trial implementation of DNs, including their impact on patients and other HCPs; and (4) investigate options for perpetuating DNs in the German health care system.

Methods

Study Setting

This study protocol was developed in accordance with SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [40]. The SPIRIT checklist was used to ensure completeness and transparency in the reporting of key methodological aspects (see Multimedia Appendix 1 for the SPIRIT checklist).

Within the framework of the DigiNavi study (duration: July 2024-September 2025), DNs will be piloted in GP practices (n=3) and psychiatric outpatient clinics (n=3) in different rural and urban regions of the federal state of Brandenburg, Germany, based on the DN model of the Harvard Medical School [41,42]. Specifically, study centers are located in the Brandenburg districts of Märkisch-Oderland, Oder-Spree, Barnim, Brandenburg an der Havel, and Dahme-Spreewald. Study sites were selected to ensure proximity between a primary care practice and a psychiatric outpatient clinic to facilitate networking.

Role of Digital Navigators

According to Perret et al [11], DNs have at least three distinct roles (see Figure 1): First, it is their task to keep their knowledge of available mental health apps up to date and to evaluate these apps based on the available evidence. For this purpose, DNs can refer to the MindApps database of Harvard University. In this way, DNs can advise HCPs on the selection of suitable health apps and provide ongoing assistance to patients in using the app. Second, DNs are responsible for teaching the multiprofessional care team the technical and digital basics and skills, as well as informing team members about available mental health apps and their specific features. This requires constant availability to team members and patients in the case of questions or problems (troubleshooting). Third, it is the DNs' responsibility to process the data generated by patients' use of the mental health apps and prepare the data for the HCPs in a way that is useful for treatment.

Figure 1. Role and tasks of DNs adapted from Wisniewski and Torous [34]. DN: digital navigator.

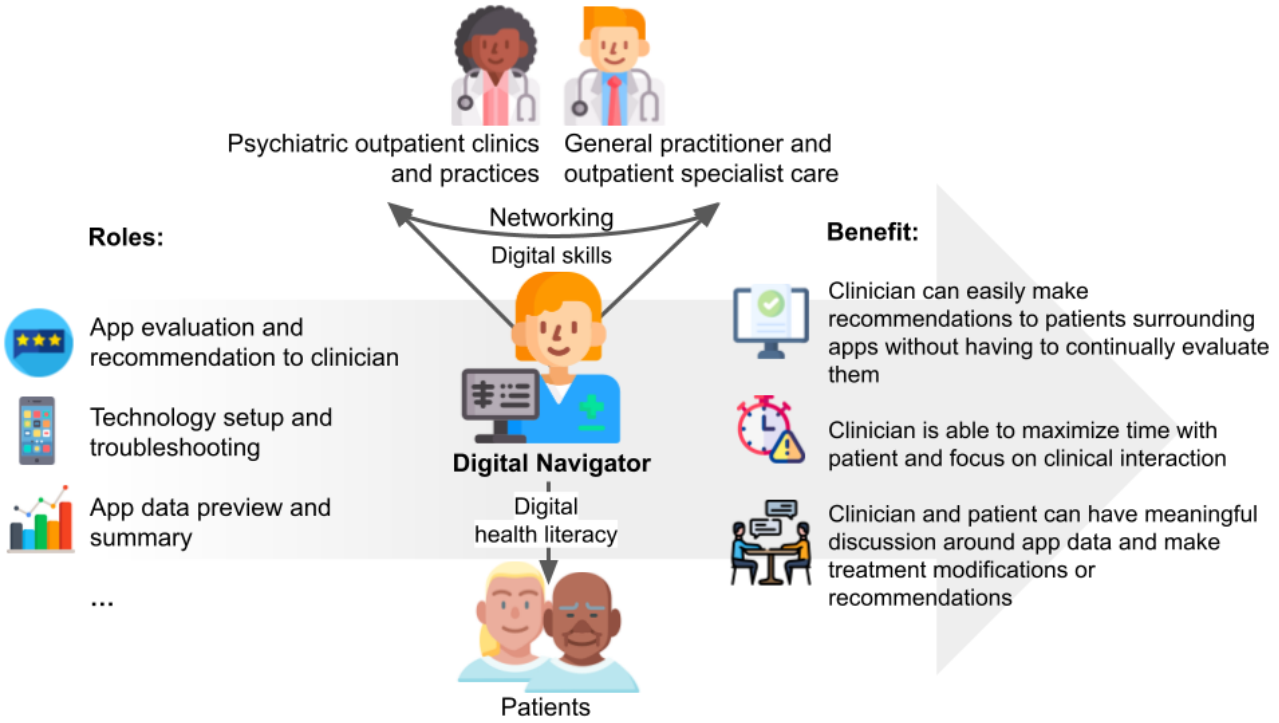

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Complex Health Care Intervention

The methodological implementation is strictly based on the UK Medical Research Council (MRC) guidelines for the evaluation of complex interventions [43]. A complex intervention is defined as a health care intervention or program that consists of a number of interacting components, each of which may contribute to the overall outcome in different ways [44]. The impact of the intervention typically depends on the interaction between these different components. The use of DNs in multiprofessional care teams is a complex intervention with several interacting components, as the role of DNs comprises several components in terms of content (see Figure 2) and requires evaluation at multiple levels. In this regard, its evaluation must include questions about digital health literacy, implementation conditions, the role and function of DNs, treatment processes, and impact factors, in addition to clinical endpoints. Furthermore, the evaluation process should consider the perspectives of patients, HCPs, and DNs themselves.

Figure 2. Research phases of the DigiNavi study. DN: digital navigator; DTx: digital therapeutics; HCP: health care professional; HDNT: Harvard Digital Navigator Training.

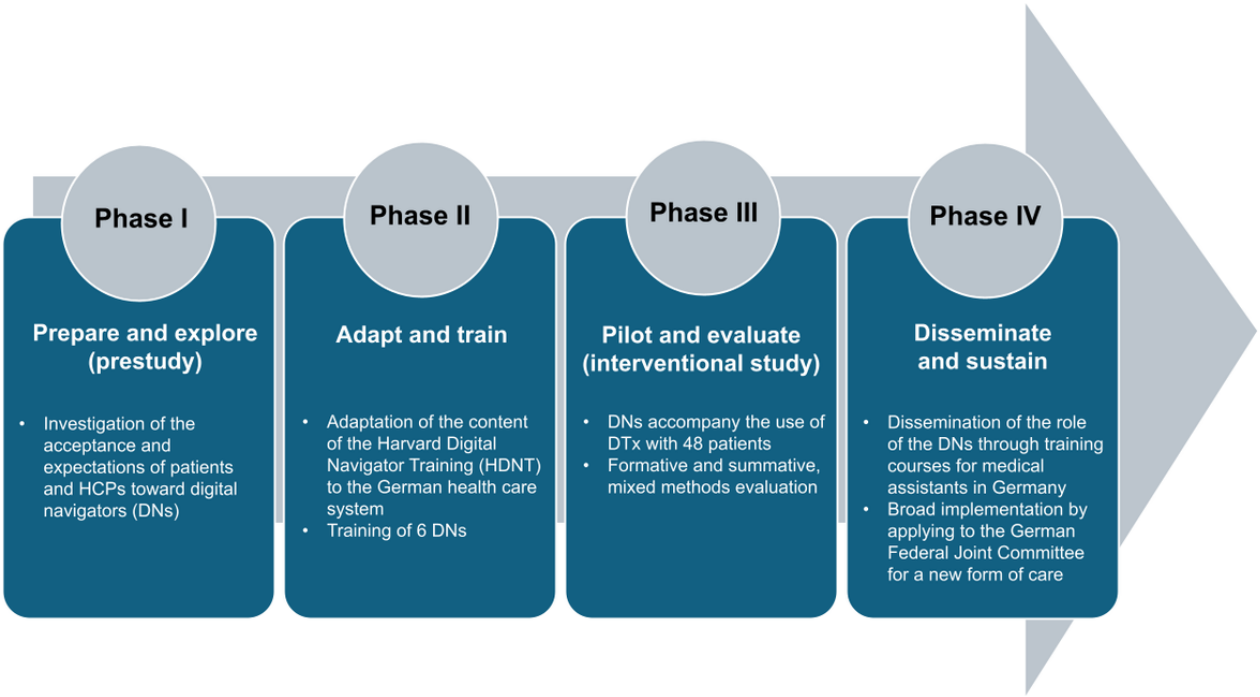

Process Evaluation

To evaluate complex interventions, such as the pilot of DNs, and to gain insight into the impact of the intervention in practice, elements of process evaluation were incorporated into the study design [44]. In this sense, the design of this study follows the fundamental recommendations of the UK MRC for process evaluation [43]. Accordingly, the intervention, any prior assumptions, contextual factors, implementation processes, influencing factors, and outcomes were carefully observed, analyzed, and described in order to facilitate an informed interpretation of the study results [43]. A mixed methods approach was adopted, using both quantitative and qualitative methods for data collection and analysis to provide a comprehensive picture of the implementation of the intervention. In our analysis, we will integrate quantitative and qualitative data to examine, for instance, how different local implementations are related to the implementation experiences.

Study Population

Recruitment

Both patients and HCPs (GPs, outpatient psychologists and psychiatrists, medical assistants) collaborated with DNs and were therefore considered as relevant stakeholders and included in this study.

HCPs and DNs (usually medical assistants at each study site) were recruited by the study team. In addition, raters (n=6, typically psychologists) were assigned to each study site to conduct data collection. Future DNs and raters were approached by members of the study team and informed about the study, as well as the compensation for their work. DN candidates and raters were then employed as part of the study team.

Patients were approached by their HCPs and informed about the DigiNavi study, including their compensation. Interested patients received further written and verbal information from the respective DNs at the study site and were enrolled into the study upon providing written informed consent. New participating patients were recruited in each phase of the study, and the pool of previously recruited participants was used in subsequent phases. For the intervention study, each center screened subjects until the target population was achieved (n=8 patients/site).

Sampling

A report on DiGAs by the German Association of Statutory Health Insurance Funds (GKV-Spitzenverband) indicates that in Germany in 2023, users of DiGAs for mental health

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conditions were on average 43 years old and 70% female [45]. Internationally, sociodemographic factors appear to be similar, as shown by a study examining diversity in clinical trials of DTx, which found that the median reported mean age across studies is 43.3 years, with 65% of participants being female [46]. To better address the specific needs of younger, older, and male patients, convenience sampling with a balanced gender ratio was used for all patient-related surveys conducted as part of this study. In addition, marginalized groups in the German health care system were prioritized for recruitment to address inequalities in mental health care through the use of DNs [47]. This included the selection of at least 1 individual who was non-White (n≥1); nonnative German-speaking (n≥1); lesbian, gay, bisexual, transgender, queer, questioning, intersex, asexual, and other identities (LGBTQIA+; n≥1); and older than >65 years (n≥1) [48] for study participation. The sample size for each study phase was not derived statistically but determined based on feasibility considerations. As this is a pilot study with an exploratory character, the primary objective is not to achieve statistical power for hypothesis testing but to gather preliminary data on the intervention's implementation, acceptability, and potential effects. Given the focus on the practical implementation of the intervention in a real-world setting, nonrandomized allocation using a convenience sample was chosen for the intervention group.

Eligibility Criteria for Patients

Patients provided written informed consent before any study procedures occurred (see Multimedia Appendix 2 for a sample informed consent form). Patients eligible for the trial had to comply with all the following inclusion and exclusion criteria listed in Textbox 1.

Textbox 1. Inclusion and exclusion criteria for this study.

Inclusion criteria:

- Diagnosis according to the *International Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10) codes F01-F06.x or F06.7
- Ability to provide informed consent
- Minimum age of 18 years
- Absence of significant cognitive deficits, as indicated by severe organic brain disease
- Sufficient language skills to complete an interview in German
- Sufficient modern hardware (eg, smartphone, tablet, or personal computer) available
- Basic knowledge of how to use a smartphone

Exclusion criteria:

- Ongoing or recent (≤3 weeks) qualified psychiatric or psychotherapeutic treatment
- Acute danger to self or others
- Disturbance of orientation or reference to reality
- Diagnosis of intellectual impairment

Eligibility Criteria for Health Care Practitioners

Participating HCPs must be at least 18 years of age and provide informed consent to participate. HCPs must be either GPs or psychologists or physicians employed in psychiatric centers. We therefore assumed basic psychological expertise in order to diagnose mental disorders. DNs are HCPs who were recruited from resident medical assistants at the study centres. In Germany, these occupational groups often work as receptionists, who usually work at the registration desk of health care facilities and perform mainly administrative and partly nursing tasks (eg, administering depot medication or carrying out treatments ordered by a medical practitioner). The medical assistants know the patients well and work closely with other HCPs, which predestines them to take on the role of a DN.

Study Design

The DigiNavi study is designed as a multicenter, single-group, observational, mixed methods interventional study, incorporating elements of participatory design. This study consists of four research phases (see Figure 2): a prestudy (phase I), training of DNs (phase II), a 12-week intervention where DNs support the use of DiGAs (phase III), and steps toward integrating the DN role into the German health care system (phase IV). The following research questions will be addressed in the four phases:

- Phase I: What are the levels of acceptance and expectations of HCPs and patients toward DNs?
- Phase II: What responsibilities and specific skills should DNs have in the German health care system? How can these findings contribute to the need-based introduction of this new role?
- Phase III: What impact does the advice and support provided by DNs have on the digital health literacy of patients and HCPs? What impact does the increased integration of DiGAs into treatment have on their use and the therapeutic relationship between patients and HCPs?

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What are the challenges and barriers that arise when piloting DNs?

- Phase IV: What measures are necessary to ensure the long-term implementation of DNs in the German health care system?

Data Collection and Analysis

The following sections provide a concise overview of the data collection procedures (primary and secondary measures). All primary and secondary outcomes will be assessed before and after the 12-week intervention (pre- and postassessment). For an overview of enrollments, interventions, and assessments, see Multimedia Appendix 3. The subsequent sections offer a comprehensive description of the specific data collection procedures that were implemented in each phase of the study.

Primary Outcome Measures

One primary outcome measure will be the impact of DNs on patients' and HCPs' digital health literacy. Digital health literacy will be assessed with two validated instruments, the Revised German eHealth Literacy Scale (GR-eHEALS) [49,50] and the Digital Health Literacy Index (DHLI) [51], which can already detect changes in smaller samples [52], before and after the 12-week intervention. The eHealth Literacy Scale (eHEALS) is the most widely used international questionnaire for the assessment of digital health literacy. It is a self-assessment tool that focuses on digital information–seeking skills [50]. We used the GR-eHEALS instead of the original eHEALS to ensure linguistic and cultural appropriateness for our German-speaking target group, since it is an adapted and validated version that considers language nuances and health care system specifics relevant to Germany [49]. The DHLI complements the GR-eHEALS in assessing interactive skills, such as the use of (web-based) health apps [51]. Further important primary outcome measures were the digital and technical literacy of patients and HCPs, their readiness and ability to change, as well as patients' engagement with DiGAs. The following self-assessment instruments were used for this purpose: the information and communication technology (ICT) Self-Concept Scale [53], the Brief Scale of Technological Readiness [54], and the Digital Use survey from Harvard University and the Readiness for Change survey [55]. Engagement with DiGAs was assessed via structured interviews conducted by the study team.

Secondary Outcome Measures

As a secondary outcome measure, the severity of the patient's disease was assessed and compared before and after the intervention using validated scales. This measure allowed for a comprehensive evaluation of the symptom burden, functional status, and overall clinical improvement.

The Global Assessment of Functioning (GAF) [56] and the Clinical Global Impression (CGI) [57] scales are brief clinician-rated tools that capture the clinician's view of the patient's overall functioning and treatment response and are widely used to evaluate symptom severity and improvement. To assess specific symptom domains, the following instruments were used: the Hamilton Anxiety Rating Scale (HAM-A) [58], which is an instrument that measures the severity of anxiety symptoms, and the Hamilton Depression Rating Scale (HDRS) [59], which evaluates depressive symptomatology across multiple dimensions, including mood, sleep, and somatic complaints. These clinician ratings were complemented by the Beck Depression Inventory-II (BDI-II) [60], a widely used self-report questionnaire that captures the patient's subjective experience of depressive symptoms. Additionally, sleep quality was assessed using the Insomnia Severity Index (ISI) [61], a brief self-report measure that evaluates the nature, severity, and impact of insomnia, which often co-occurs with mental health conditions and may influence treatment outcomes.

Table 1 provides an overview of the instruments used for data collection and analysis. The specific methodological details for each study phase are described in the following sections.

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Table 1. Construct and data collection used for pre- and postassessment of the interventional study.

Outcome and participants	Construct	Data collection instrument
Primary outcomes		
Patients and staff	Digital health literacy	• DHLI[a] (online self-assessment survey) • GR-eHEALS[b] (online self-assessment survey)
Patients and staff	Digital and technical literacy	• ICT[c] Self-Concept Scale (online self-assessment survey) • Brief Scale of Technological Readiness (online self-assessment survey) • Digital Use survey (online self-assessment)
Patients and staff	Readiness and ability to change	• Readiness for Change survey (online self-assessment)
Patients	Engagement	• Duration and frequency of DiGA use (observer rating)
Secondary outcomes		
Patients	Severity of disease	• GAF[d] (observer rating) • CGI[e] (observer rating) • HAM-A[f] (observer rating) • HDRS[g] (observer rating) • BDI-II[h] (online self-assessment survey) • ISI[i] (online self-assessment survey)

[a]DHLI: Digital Health Literacy Index.
[b]GR-eHEALS: Revised German eHealth Literacy Scale.
[c]ICT: information and communication technology.
[d]GAF: Global Assessment of Functioning.
[e]CGI: Clinical Global Impression.
[f]HAM-A: Hamilton Anxiety Rating Scale.
[g]HDRS: Hamilton Depression Rating Scale.
[h]BDI-II: Beck Depression Inventory-II.
[i]ISI: Insomnia Severity Index.

Research Phases

Phase I: Prepare and Explore (Prestudy)

A first exploratory prestudy examined the acceptance of and expectations of DNs from the perspective of patients and HCPs. This qualitative study involved 7 GPs, 11 outpatient psychiatrists/psychologists, and 17 of their patients from the service areas of the study sites. Specifically, 17 semistructured interviews (n=4, 57.1%, GPs; n=4, 36.4%, outpatient psychiatrists/psychologists; and n=9, 52.9%, patients) and 4 focus groups were conducted. Two focus groups with patients (n=8, 47.1%), one focus group with GPs (n=5, 71.4%), and one focus group with outpatient psychiatrists/psychologists (n=7, 63.6%) were conducted. The interview guidelines were developed based on knowledge gaps identified through an extensive literature review. The questions related to what opportunities and barriers patients and professionals saw in the implementation of DNs, how it might change the HCP-patient relationship, and what they think should be considered when introducing DNs (see Multimedia Appendix 4 for the prestudy interview guideline for patients). In addition, the sociodemographic characteristics of the participants were collected [62].

The developed survey instruments and interview guides were pretested before implementation. As part of the pretest, one interview was conducted with a patient and one with an HCP. The collected qualitative data were transcribed, pseudonymized, and analyzed using MAXQDA software following a thematic analysis to elaborate stakeholders' acceptance and expectations of DNs [63].

Phase II: Adapt and Train

German Version of the Harvard Digital Navigator Training

Three researchers from the study team participated in a multiday training and coaching program on the implementation of DNs during field visits at Harvard Medical School [64]. Furthermore, the content of the certified HDNT was translated into German and adapted to the German context based on the findings from the focus groups and interviews. Depending on the results of the qualitative data (eg, information about the skills that are particularly important for DNs), the HDNT was adapted. If necessary, new modules were developed and added. Additionally, there was a participatory process in terms of a modified Delphi study [65] that involved patients (N=9) and HCPs (N=17) in discussion groups at three time points, following the levels of the European Commission's Digital Competence Framework for Citizens (DigComp 2.0) [66].

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During these discussion groups, selected components of the HDNT were presented and evaluated for their suitability in the German context. The content of the conversation was documented by a member of the study team in the form of field notes, which were subsequently presented to the entire study team and discussed within the team. Based on these insights, the study team developed an adapted version of the HDNT and designed the training sessions for the German DNs.

Training the Digital Navigators

Subsequently, clinical staff (preferably medical assistants who participated in phase II; n=6, 35.3%) were trained with the adapted HDNT as DNs in three training sessions. Each session lasted for 3 hours and took place over 3 consecutive weeks. The first session was held in person at the study site in Rüdersdorf. The following two sessions were web based. According to the predefined roles of DNs, the training entailed general knowledge about existing DiGAs and how to keep the knowledge of available DiGAs up to date. The DNs were provided with a study smartphone and a test account for each of the mental health DiGAs available. As part of the training sessions, all DiGAs available at the time of training were introduced and tested together, ensuring that all DNs could become familiar with the DiGAs, both theoretically and practically. This process enabled the DNs to gain a comprehensive overview of all available DiGAs, thus allowing them to recommend the most suitable one later. Additionally, technical issues and difficulties could be identified and resolved immediately.

Beyond the knowledge about the DiGAs, the DNs also received mental disorder–specific training. Currently, DiGAs are available for the following mental illnesses: anxiety disorders, depression, and eating disorders. The DNs were provided with an overview of the diagnosis, prevalence, and treatment of these mental illnesses. The main sources were the *International Classification of Diseases and Related Health Problems, 10th Revision* (ICD-10) [67] for diagnosis and the Association of Scientific Medical Societies (AWMF) level S3 treatment guidelines for mental illnesses [68]. This contributed to raising awareness and knowledge of mental health disorders, particularly among DNs working in GP settings, enabling them to assess these disorders competently.

Furthermore, DNs were instructed on how to deliver training on DiGAs to their multiprofessional teams in their workplace and how to use and process data generated by patients by using the DiGAs. Additional training content entailed recruitment of participants, technological troubleshooting, or the conduction of motivational check-in appointments with participants.

A key reference for DNs was the DIGAnavigator website, which we will develop based on the model of MindApps, the platform created by Harvard University. This new website will focus on integrating and evaluating German DiGAs. Initially, all DiGAs for mental health approved by the BfArM [38] in Germany will be listed on the website. In addition, detailed psychoeducational content on the use of DiGAs for mental health conditions will be developed and incorporated into the website.

Training the Raters

In addition, 6 psychologists were trained as raters to conduct participant recruitment and data collection. The training session was conducted at the study site in Rüdersdorf and lasted 3 hours. During the training session, the raters learned more about the data collection process in the study. Specifically, they learned which instruments are used for pre- and postassessment, how data for self-assessment are collected, and what to consider when conducting an interview about the patients' severity of disease. This training aimed to standardize testing and to promote consistency in data collection.

Phase III: Pilot and Evaluate (Interventional Study)

In the intervention phase, the trained DNs trained the multiprofessional teams at the six study sites to select and integrate DiGAs for mental health into the treatment of 48 patients (n=8, 16.7%, per site). The DNs provided at least one training session for their teams. A guideline for this training was provided by the study team. Based on the findings from phases I and II, the content and structure of the intervention were finalized. It was established that selected patients would use a DiGA for 12 weeks and receive guidance and support from trained DNs during these 12 weeks, encouraging regular use of a DiGA tailored to their individual needs. To enhance adherence, participants were regularly asked about any challenges they encountered during check-up appointments with their DNs. To promote engagement, DNs suggested practical strategies, such as integrating DiGA use into daily routines or identifying suitable time frames for engagement. The study team supported the DNs through monthly web-based meetings. In these meetings, DNs received up-to-date information about the study progress, got an opportunity to ask questions, and exchanged experiences. During the intervention phase, DNs contacted the study team at any time if they had questions or encountered any issues. In addition, process data, such as the number and duration of contacts between patients and DNs, were collected during the intervention to enable the identification and validation of any qualitative differences in implementation at the different study sites.

The trained raters (n=6) conducted data collection with patients (N=48) and HCPs (N=18; n=3, 16.7%, per site) at each study site at two timepoints: before the 12-week intervention (preassessment), and directly after completing the intervention (postassessment). The end of the intervention phase was defined as the date of DiGA activation plus a 3-month DN support period. The study team also met with the raters once a month in a web-based meeting to discuss the progress of the preassessments and later postassessments. During these meetings, raters got an opportunity to ask questions and receive assistance with any issues or challenges they may have encountered.

All patients and HCPs received an online self-assessment form (administered by the online survey service LimeSurvey), assessing sociodemographic parameters (eg, age, gender), digital health literacy, digital and technical literacy, readiness and ability to change, and severity of disease (see Table 1). Additionally, patients were interviewed on the severity of their disease and app engagement.

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The collected sociodemographic characteristics were analyzed using descriptive statistics and presented in an appropriate format, such as age distribution and gender ratio. Quantitative primary data collected (eg digital health literacy, severity of disease) were analyzed using descriptive statistics in a pre-post comparison using paired *t*-tests or Wilcoxon signed-rank tests, depending on the distribution of the data. Effect sizes were reported to assess the magnitude of changes, and multiple linear regression models were used to control for potential confounders. Analyses were performed using SPSS with a statistical significance set at α=.05.

After the intervention, the study team conducted qualitative semistructured interviews and focus groups with 25 participants in total (n=13, 52%, patients; n=6, 12.5%, DNs; and n=6, 12.5%, HCPs) to assess the opportunities and implementation barriers to implementing DNs, as well as the effects of counseling and support by the DNs. The collected qualitative data were transcribed, pseudonymized, and analyzed using qualitative content analysis according to Kuckartz and Rädiker [69]. The diverse and complex narratives of the participants were recorded and explored using a multistage approach. The formation of categories and subcategories enabled the content of the information to be structured. The iterative procedure increased the comprehensibility of the information generated but also allowed flexibility and an interpretative approach. To ensure high-quality reporting, the COREQ (Consolidated Criteria for Reporting Qualitative Research) checklist (Multimedia Appendix 5) was followed [70].

Phase IV: Disseminate and Sustain

This study phase includes the dissemination of the study results, as well as the development of strategies to ensure the long-term integration of the pilot innovation into the German health care system. This includes the continuation of the pilot project beyond the end of the study by maintaining the DiGAnavigator website, training medical assistants at the Federal State of Brandenburg's Medical Association (LAEKB), and preparing the accreditation of the training program for medical assistants to become DNs through the LAEKB. Preliminary scenarios for the remuneration of DN activities are currently being formulated. Results of the study will be disseminated regardless of the magnitude or direction of the effect.

Ethical Considerations

The study was approved by the Ethics Committee of the Brandenburg Medical School (MHB) (reference number: 218062024-BO-E). The study was registered at the German Clinical Trials Registry (DRKS00034327) and at ClinicalTrials.gov (NCT06575582). The DNs or HCPs introduced the study to patients. Patients also received information sheets. The DNs or HCPs discussed the trial with patients in the light of the information provided in the information sheets. All participants were informed about the possibility to withdraw their consent at any given time. Afterward, the DNs or HCPs obtained written informed consent from the participants of the study. If a patient chose to discontinue during the intervention phase, the DN or HCP conducted an informative discussion to explore the underlying reasons in order to understand potential barriers to the use of digital mental health interventions. For their participation in either the preliminary study or the intervention study, patients received 25 euros (US $23.92).

All self-assessments were conducted using LimeSurvey, a web-based platform. This approach reduced the risk of data loss or unauthorized access, as no local storage on individual devices was required. It also allowed the study team to monitor data entries in real-time, enabling timely detection of incomplete or erroneous submissions. If necessary, raters could be informed so they could follow up with participants.

To ensure data protection, each participant was assigned a pseudonymized study code that does not allow identification. Qualitative data, such as transcripts from focus groups and interviews, were securely stored on the study team's local, password-protected computers. In accordance with data protection regulations, all data collected were pseudonymized to safeguard participant information and will be deleted after 10 years, ensuring compliance with legal and ethical requirements, while allowing sufficient time for scientific evaluation.

Results

The study received funding in July 2024. The prestudy, including the collection of qualitative data, was conducted from August to October 2024. The adaptation of the HDNT and the training of the DNs took place from October to December 2024. Data analysis was completed in March 2025, and the data are being prepared for publication. Recruitment of participants and collection of quantitative data (preassessment) commenced in December 2024 and continued through March 2025. By the end of March 2025, a total of 48 participants had been enrolled. The intervention study, in which participants used DiGAs and received support from the DNs, started in December 2024 and ended in June 2025. The second collection of quantitative data (postassessment) began once the first participant completed the intervention phase (March 2025) and continued until early June 2025. The qualitative data collection was conducted in June 2025.

Dissemination of results and the development of strategies for the long-term integration of this pilot innovation into the German health care system have been planned between March and September 2025. The study will provide important insights into the acceptability and feasibility of human-facilitated competency development for mental health apps in multiprofessional health care teams and their patients.

Discussion

Summary

International studies indicate the great potential of digital mental health tools to improve the quality of and access to care [11]. However, the actual use and integration of these apps is still limited, even in an international context, partly due to a lack of relevant technical and digital literacy among HCPs and patients alike [34]. DNs have the potential to mitigate these barriers, promote digital health literacy, and ultimately lead to improved care outcomes [11,33].

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The study will provide important insights into the acceptance of DNs by HCPs and patients (phase I), which, in combination with the participatory adaption and piloting of the German DN training, will contribute to a target-oriented implementation in the pilot region (phase II) and beyond. The open access publication of the adapted and field-tested manual and all training materials for the DN training (including the MindApps database) in German will facilitate the independent implementation of the innovation by outpatient care providers and enable its extension to other disciplines and settings (eg, day clinics or even inpatient care). To ensure a broad implementation and continuation of the innovation, the project team is preparing the accreditation of the training program for medical assistants to become DNs by the LAEKB. At the end of the project period, a roll-out phase is planned, during which the innovation will be transferred to the member practices of the Brandenburg General Practitioners Association.

The role of DNs in multiprofessional medical teams is a novel approach within the German health care system, which is why it has not yet been researched. The DigiNavi study will adapt, pilot, and evaluate the role of DNs in a participatory manner for the German health care system. The planned study will provide valuable insights into the acceptance, expectations, challenges, and opportunities associated with the role of DNs in improving health care.

Limitations

This study is limited by the size and composition of the sample, which was selected based on convenience rather than random sampling. Due to the small sample size, the study is not powered to detect statistically significant effects. However, it reveals trends of potential changes that should be further explored and tested in future randomized studies. Furthermore, the small sample size increases the risk of type II errors and limits the generalizability and transferability of quantitative findings. The nonrandomized sampling constrains the ability to draw causal inferences, and the findings cannot be generalized to the entire population of patients with mental health conditions in Germany. Although the study is designed to assess feasibility, not effectiveness, we recommend that future research include a randomized controlled design to evaluate causal effects more robustly.

Moreover, patients treated in psychiatric outpatient clinics often have more severe mental health conditions compared to those in general outpatient psychotherapy, further limiting the generalizability of the results. In addition, the focus on patients with mental health conditions is a limitation in itself, so the results cannot be generalized to patients with somatic conditions or to individuals without illnesses. Furthermore, it can be assumed that the study will attract a larger number of technologically proficient HCPs and patients (self-selection). This may result in overrepresentation of this particular patient and HCP group.

Additional limitations arise from the outpatient setting of the study. In inpatient care, the ability to prescribe DiGAs is restricted. These contextual conditions, in combination with the exploratory nature of the pilot study, do not allow for the integration of these aspects into the present investigation.

In addition, the study is being conducted without a comparison group (ie, with only one condition). This makes it difficult to identify and control for confounding factors and to attribute observed changes, such as in digital literacy or psychological health, clearly to the intervention. However, the primary goal of the DigiNavi study is to investigate the feasibility of the innovation, not to provide evidence of its effectiveness. The sample size and composition chosen are therefore justified by the exploratory nature of the planned study and are appropriate for a pilot project. The implementation of a larger randomized controlled trial may be a future goal for research efforts to assess effectiveness and causal relationships.

Furthermore, the limited funding period of only 14 months has resulted in the intervention phase being constrained to a duration of 3 months per patient. As a result, the study design does not include a follow-up component, precluding any assertions regarding the evolution of the outcomes of interest over a 6- or 12-month period.

Further studies are needed to test DNs in inpatient and outpatient settings, or in the somatic field, to determine whether the hypothesized effects of DNs can be confirmed in other settings and patient groups and whether DNs can be established as a sustainable tool for improving the care of patients with mental health conditions. In addition, further international studies involving different health care systems would be of great value. The findings of this study, together with the easily accessible training materials on the project website [71], should encourage and facilitate further research.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study will not be publicly available but will be available from the corresponding author upon reasonable request.

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Authors' Contributions

JS designed the study and applied for funding. DS and EMD were involved in developing the main documents regarding ethical approval. JS, EMD, and LU drafted the study protocol. Successive drafts were revised by LU, EMD, JT, and JS. All authors have approved the submitted version. All authors have agreed both to be personally accountable for their own contributions and to ensure that questions related to the accuracy or integrity of any part of the work, even ones in which the authors were not personally involved, are appropriately investigated and resolved and the resolution documented in the literature.

Conflicts of Interest

JT is the editor-in-chief for *JMIR Mental Health*. The remaining authors have no conflicts to declare.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 194 KB - resprot_v14i1e67655_app1.pdf]

Multimedia Appendix 2
Sample informed consent form.
[PDF File (Adobe PDF File), 274 KB - resprot_v14i1e67655_app2.pdf]

Multimedia Appendix 3
Schedule of enrollments, interventions, and assessments. DN: digital navigator; HDNT: Harvard Digital Navigator Training.
[PDF File (Adobe PDF File), 65 KB - resprot_v14i1e67655_app3.pdf]

Multimedia Appendix 4
Prestudy interview guideline for patients.
[PDF File (Adobe PDF File), 78 KB - resprot_v14i1e67655_app4.pdf]

Multimedia Appendix 5
COREQ (Consolidated Criteria for Reporting Qualitative Research) checklist.
[PDF File (Adobe PDF File), 419 KB - resprot_v14i1e67655_app5.pdf]

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Abbreviations

BDI-II: Beck Depression Inventory-II
BfArM: German Federal Institute for Drugs and Medical Devices
CGI: Clinical Global Impression
DHLI: Digital Health Literacy Index
DiGA: digital health app
DN: digital navigator
DTx: digital therapeutics
eHEALS: eHealth Literacy Scale
GAF: Global Assessment of Functioning
GP: general practitioner
GR-eHEALS: Revised German eHealth Literacy Scale
HAM-A: Hamilton Anxiety Rating Scale
HCP: health care professional
HDNT: Harvard Digital Navigator Training
HDRS: Hamilton Depression Rating Scale

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ICD-10: International Classification of Diseases and Related Health Problems, 10th Revision
ICT: information and communication technology
ISI: Insomnia Severity Index
LAEKB: Federal State of Brandenburg's Medical Association
MRC: Medical Research Council

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Protocol

Feasibility of Hemolytic Disease of the Fetus and Newborn Case Ascertainment and Assessing Its Impact on Prenatal and Postnatal Outcomes: Protocol for Observational Studies

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Abstract

Background: Hemolytic disease of the fetus and newborn (HDFN) is a rare but serious condition caused by maternal-fetal red blood cell antigen incompatibility. In an affected pregnancy, maternal immunoglobulin G antibodies cross the placenta and target fetal or neonatal red blood cells, leading to hemolysis, hyperbilirubinemia, and anemia. Although routine screening and alloimmunization prevention programs have contributed to the decline in HDFN in the United States, further understanding of its epidemiology is still needed.

Objective: This protocol aims to provide an overview of the study design, methodology, and analytical approach used to investigate the epidemiology, treatment, and health care resource use of HDFN within a large integrated health care system.

Methods: We conducted a retrospective cohort study of pregnant women who received obstetric care in the Kaiser Permanente Southern California (KPSC) health care system from January 1, 2008, to June 30, 2022. To identify HDFN cases, we used a novel methodology developed by KPSC researchers combining structured data and detailed clinical information extracted from unstructured records via a natural language processing–assisted chart review process. Chi-square and Wilcoxon rank sum tests were used to compare the distributions of maternal and infant demographic characteristics, as well as medical and perinatal conditions, by HDFN status. We also evaluated the association between HDFN and adverse perinatal outcomes using logistic regression models. Planned analyses using this unique cohort will include describing the annual prevalence, health care resource use, and treatment patterns of mothers and infants by HDFN status.

Results: The study population consisted of 464,711 pregnancies, of which 136 (0.03%) were HDFN cases confirmed by chart review, resulting in 138 (0.03%) births (n=137, 0.99% live births and n=1, 0.01% stillbirth). The mean age at pregnancy was 29.8 (SD 5.7) years, and the population was racially and ethnically diverse.

Conclusions: We present an overview of the methodology developed by KPSC clinicians and researchers on the epidemiology, treatment, and health care resource use of HDFN within a large and demographically diverse population of pregnant women. Our novel methodology, combining both structured and unstructured data and a natural language processing–assisted chart review process, ensures the successful identification of true cases to carry out pharmaco-epidemiological studies.

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KEYWORDS

hemolytic disease of the fetus and newborn; HDFN; hemolytic disease; fetus; newborn; protocol; epidemiology; treatment use; electronic health record

Introduction

Hemolytic disease of the fetus and newborn (HDFN) is a rare disease caused by maternal-fetal red blood cell antigen incompatibility. HDFN occurs when maternal immunoglobulin G antibodies cross the placenta and destroy the fetal or neonatal red blood cells, leading to perinatal morbidity and mortality if left untreated [1-4]. Numerous alloantibodies are implicated in HDFN, including anti-D, anti-E, and anti-C, with anti-D being the most common and clinically significant cause [1,5]. The clinical presentation of HDFN varies widely, ranging from mild immune reactions to more serious forms of HDFN, such as severe anemia, congestive heart failure, or intrauterine death [1,5-7]. Other complications, including hyperbilirubinemia, cholestasis, and kernicterus [8-10], and long-term complications, such as neurodevelopmental impairments and cardiovascular disease, have been reported [1,8,11-13].

Due to inconsistencies in the definitions and criteria used to ascertain HDFN, there is wide variability in the reported annual prevalence of HDFN, with estimates ranging from 3 to 80 cases per 100,000 births [1,14]. This variability is influenced by differences in diagnostic practices, population characteristics, and the availability of prophylactic interventions such as Rh immunoglobulin [1]. Prior approaches to defining HDFN in electronic health record (EHR) data have often relied on either a single indicator, such as HDFN-specific diagnostic codes [15], or a combination of indicators, such as laboratory results suggestive of HDFN (eg, maternal alloantibody titers), fetal complications stemming from HDFN (eg, hyperbilirubinemia, neonatal anemia, and fetal hydrops), or maternal-fetal treatment for HDFN (eg, exchange transfusion and intrauterine transfusion) [16-24]. While using a combination of indicators improves the accuracy of HDFN case identification, prior studies have varied widely in the specific set of indicators selected, limiting the generalizability of their findings. In addition, several studies have taken a narrow approach by concentrating on antigen-specific alloimmunization [16,17], which may not capture the full spectrum of HDFN cases; therefore, the estimates provided in such studies do not accurately represent the broader epidemiology of the disease. Finally, studies describing other important components of the epidemiology of HDFN, including treatment plans and health care resource use, have not received enough attention in the literature. Considering these limitations, improved clarification of the epidemiology and perinatal complications of HDFN is warranted. Therefore, we plan to conduct retrospective cohort studies to address knowledge gaps in the epidemiology, treatment, and health care resource use of HDFN. Using a combination of structured and unstructured data collected at the point of care over the proposed study period, Kaiser Permanente Southern California (KPSC) developed a natural language processing (NLP)–assisted chart review process to accurately identify and characterize this rare condition [25]. This paper presents an overview of the study design and characteristics of the study population, as well as the methodology developed by KPSC researchers to define and establish an HDFN cohort. It also outlines our strategy to investigate the epidemiology, treatment, and health care resource use associated with HDFN in a large, diverse, and integrated health care system.

Methods

Study Design, Setting, and Data Sources

This retrospective cohort study was performed at KPSC, an integrated health care delivery system that serves more than 4.8 million members across 15 hospitals and more than 235 medical offices. KPSC membership is broadly representative of the socioeconomic, racial, and ethnic diversity of Southern California's population [26-28], with long-term retention of its members, exceeding 95% at 2 years and 87% at 5 years, which supports the generalizability and longitudinal strength of research conducted within this population. Data for this study were extracted from the KPSC's comprehensive EHR system, which contains detailed patient-level data, including diagnostic and procedural codes, pharmacy and laboratory records, and member demographics and behavioral information from patients receiving inpatient and outpatient care. In addition to structured data, KPSC's EHR database contains unstructured data, which include free-text clinical notes, radiology, pathology, imaging reports, and clinician-patient communications.

The KPSC EHR databases comprise a comprehensive and longitudinal data infrastructure that includes health plan enrollment information, inpatient and outpatient clinical encounters, external claims, laboratory results, and pharmacy dispensing records. The inpatient database captures all inpatient hospitalization visits and records admission and discharge dates; *International Classification of Diseases*, ninth and tenth revisions; clinical modification diagnosis, procedure, and discharge codes; and *Current Procedural Terminology* codes. The outpatient database captures all primary care outpatient clinic visits, urgent care, and emergency room visits, with corresponding *International Classification of Diseases* and *Current Procedural Terminology* codes. The external claims database captures all outpatient (clinic, urgent care, and emergency room) and inpatient visits by KPSC enrollees to non-KPSC facilities where KPSC is financially responsible for the care of the patients. The pharmacy database captures medications dispensed and refilled to KPSC enrollees with a pharmacy benefit plan at KPSC-owned pharmacies. All databases are linked through a unique medical record number assigned to each enrollee for life, precluding multiple counts of the same health event for individuals across sources. To enhance case identification and characterization of rare conditions, additional relevant information was extracted from the unstructured data via NLP. This approach has been validated

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in prior KPSC studies and shown to substantially improve the accuracy of case identification compared to diagnosis codes alone [25].

Study Population and Selection Criteria

Medical records of pregnant women and their children born between January 1, 2008, and June 30, 2022 (n=572,328), were included in this study. We excluded pregnancies without KPSC health plan membership (n=89,254, 15.59%), those ending in elective abortion (ie, abortion done not for medical reasons; n=921, 0.16%), and pregnancies with ABO alloimmunization of the newborn without the diagnosis of HDFN (n=17,442. 3.05%). After applying the exclusions, a total of 464,711 (81.19%) pregnancies remained for analysis.

Study Outcome

We identified HDFN cases through a novel, systematic approach that began with the selection of HDFN-specific diagnostic and related codes. Next, we assembled a range of candidate HDFN indicators from structured EHR data, including positive indirect Coombs laboratory test results, abnormal maternal antibody titer results (anti-Kell ≥4; other antibodies ≥8), HDFN diagnosis codes, receipt of blood transfusion or intravenous immunoglobulin treatment, neonatal jaundice and phototherapy, and rho (D) immune globulin injection. To enhance case detection, we then developed an NLP approach, in conjunction with detailed medical record reviews, to detect these candidate indicators from clinical notes. Details of our HDFN identification process, including the NLP-assisted chart review process, have been published previously [25].

Data Analyses

Completed Analyses

We aimed to describe the epidemiology of HDFN, including the demographics and clinical presentation of the disease among those with pregnancy outcomes over the study period (January 1, 2008, to June 30, 2022). The demographic and clinical presentation at the time of pregnancy were compared between HDFN cases and controls, as defined by our criteria. Descriptive statistics were calculated for the variables of interest, both overall and stratified by predefined categories. For continuous variables, the mean (SD) and median (IQRs) were computed. All missing data were treated as a separate category (dummy variable), and no imputation was performed. Categorical variables were compared using chi-square tests, while continuous variables were analyzed using the Wilcoxon rank sum test.

Planned Analyses

In future studies, we will report trends in the prevalence of HDFN-associated pregnancies over the study period, with 3-year rates standardized to the age, race, and ethnicity distribution of pregnant women from 2014 to 2016. This standardization will allow for meaningful comparisons across time by accounting for demographic shifts in the underlying population. We will also compare health care resource use patterns between pregnancies and infants affected by HDFN and those without the condition, focusing on key use metrics, such as maternal length of hospital and intensive care unit stays, neonatal intensive care unit stays, emergency room visits, and urgent care visits.

Furthermore, we will use logistic regression models to estimate both crude and adjusted odds ratios to evaluate the association between HDFN and a range of adverse maternal, fetal, and neonatal outcomes. These outcomes will include, but are not limited to, fetal death, preterm birth (defined as delivery before 37 weeks of gestation), low Apgar score (<7 at 5 min), and neonatal jaundice. To account for potential confounding, the models will be adjusted for a comprehensive set of covariates, including demographic characteristics (eg, age, race and ethnicity, and socioeconomic status), behavioral factors (eg, smoking status and substance use), clinical comorbidities (eg, diabetes and hypertension), obstetric history (eg, parity and prior cesarean delivery), and health care use patterns (eg, number of prenatal visits and hospitalizations during pregnancy) [29].

Ethical Considerations

The Institutional Review Board of KPSC approved the study and granted an exemption from the requirement for patient informed consent (13503). The proposed study involves analyses of existing EHR data (ie, secondary data analysis); therefore, no compensation was provided to study patients. All data created for this project are fully anonymized to ensure patient confidentiality. The resulting research database is password protected and accessible only to authorized research staff responsible for data management and analysis.

Results

Demographic Data

The study population comprised 464,711 pregnancies, among which 136 (0.03%) were identified as HDFN pregnancies, resulting in 138 (0.03%) births (n=137, 0.99% live births and n=1, 0.01% stillbirth). This corresponds to a prevalence rate of 29.3 per 100,000 pregnancies (Table 1).

Pregnancies affected by HDFN were significantly more likely to involve women who were aged ≥35 years (P=.003), from non-Hispanic White racial-ethnic group (P=.01), multiparous (P<.001), multigravida (P<.001), and covered by Medicaid or private insurance (P=.04; Table 1).

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Table 1. Distribution of maternal demographic, medical, and obstetric characteristics based on HDFN[a] status.

Maternal characteristics	Total (N=464,711)	HDFN (n=136)	Non-HDFN (n=464,575)	*P* value[b]
Age at index date (y), mean (SD)	29.8 (5.7)	31.8 (5.3)	29.8 (5.7)	<.001
Age at index date (y), n (%)				.003
<20	21,437 (4.6)	3 (2.2)	21,434 (4.6)	
20-29	193,523 (41.6)	40 (29.4)	193,483 (41.6)	
30-34	152,571 (32.8)	51 (37.5)	152,520 (32.8)	
≥35	97,180 (20.9)	42 (30.9)	97,138 (20.9)	
Race or ethnicity, n (%)				.01
Asian or Pacific Islander	62,045 (13.4)	17 (12.5)	62,028 (13.4)	
Hispanic	213,525 (45.9)	57 (41.9)	213,468 (45.9)	
Non-Hispanic Black	36,344 (7.8)	10 (7.4)	36,334 (7.8)	
Non-Hispanic White	126,026 (27.1)	52 (38.2)	125,974 (27.1)	
Missing	1159 (0.2)	0 (0)	1159 (0.2)	
Other or multiracial	5794 (1.2)	0 (0)	5794 (1.2)	
Unknown	20,977 (4.5)	0 (0)	20,977 (4.5)	
Insurance type, n (%)				.04
Medicaid	44,583 (9.6)	22 (16.2)	44,561 (9.6)	
Commercial	386,724 (83.2)	101 (74.3)	386,623 (83.2)	
Private	27,385 (5.9)	11 (8.1)	27,374 (5.9)	
Other or unknown	6019 (1.3)	2 (1.5)	6017 (1.3)	
Parity, n (%)				<.001
Multiparous	264,887 (57)	120 (88.2)	264,767 (57)	
Nulliparous	140,722 (30.3)	11 (8.1)	140,711 (30.3)	
Unknown	59,102 (12.7)	5 (3.7)	59,097 (12.7)	
Gravidity, n (%)				<.001
Multigravida	326,956 (70.4)	126 (92.6)	326,830 (70.4)	
Nulligravida	136,049 (29.3)	10 (7.4)	136,039 (29.3)	
Unknown	1706 (0.4)	0 (0)	1706 (0.4)	
Gestational weight gain (kg), mean (SD)	12.5 (7.2)	11.6 (7.1)	12.5 (7.2)	.19
Renal disease, n (%)				<.001
No	456,372 (98.2)	128 (94.1)	456,244 (98.2)	
Yes	8339 (1.8)	8 (5.9)	8331 (1.8)	
Chronic hypertension, n (%)				.045
No	455,405 (98)	130 (95.6)	455,275 (98)	
Yes	9306 (2)	6 (4.4)	9300 (2)	

[a]HDFN: hemolytic disease of the fetus and newborn.

[b]*P* values were obtained using chi-square test for categorical variables and 2-tailed Student *t* test for continuous variables.

Clinical Data

HDFN-affected pregnant women were more likely to have a higher prevalence of renal disease (*P*<.001) and chronic hypertension (*P*=.045; Table 1). Their offspring were more likely to be born preterm (<37 weeks of gestation; *P*<.001) and to have low birthweight (≤2499 g; *P*<.003), smaller head circumference (*P*=.01), and neonatal jaundice (*P*<.001) compared to offspring from a pregnancy that was not complicated by HDFN (Table 2).

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Table 2. Distribution of infant characteristics based on HDFN[a] status.

Infant characteristics	Total (N=446,499)	HDFN (N=138)	Non-HDFN (N=446,361)	*P* value[b]
Preterm birth, n (%)				<.001
No	402,035 (90)	97 (70.3)	401,938 (90)	
Yes	42,280 (9.5)	40 (29)	42,240 (9.5)	
Missing	2184 (0.5)	1 (0.7)	2183 (0.5)	
Birthweight (g), n (%)				<.001
<1500	5982 (1.3)	4 (2.9)	5978 (1.3)	
1500-2499	25,780 (5.8)	18 (13)	25,762 (5.8)	
2500-3999	366,607 (82.1)	110 (79.7)	366,497 (82.1)	
≥4000	38,773 (8.7)	4 (2.9)	38,769 (8.7)	
Missing	9357 (2.1)	2 (1.4)	9355 (2.1)	
Head circumference (cm), mean (SD)	34.0 (2.7)	33.5 (2.3)	34.0 (2.7)	.01
Neonatal jaundice, n (%)				<.001
No	283,942 (63.6)	48 (34.8)	283,894 (63.6)	
Yes	162,557 (36.4)	90 (65.2)	162,467 (36.4)	

[a]HDFN: hemolytic disease of the fetus and newborn.

[b]*P* values were obtained using chi-square test for categorical variables and Student *t* test for continuous variables.

Laboratory Data

While specific laboratory parameters are not detailed in this summary, the study includes data extracted from the KPSC EHR system, which captures antibody types associated with HDFN. Among these, anti-D was the most frequent identified antibody (47/95, 50%), followed by anti-E (26/95, 27%), anti-C (16/95, 17%), and anti-K (7/95, 7%). Notably, 100% (7/7) of antibodies among non-Hispanic Black individuals were anti-D. Anti-D prevalence was also observed in non-Hispanic White individuals (22/39, 56%), Hispanic individuals (16/39, 41%), and Asian or Pacific Islander individuals (2/10, 20%). Anti-E was most common among Asian or Pacific Islander individuals (7/10, 70%), followed by non-Hispanic White individuals (10/39, 26%) and Hispanic individuals (9/39, 23%). Anti-C was found in 21% (8/39) of non-Hispanic White individuals and 18% (7/39) of Hispanic individuals, while anti-K was identified in 8% (3/39) of non-Hispanic White individuals and 10% (4/39) of Hispanic individuals. Additionally, serologic and hematologic markers relevant to the diagnosis and monitoring of HDFN, such as hemoglobin levels, hematocrit, reticulocyte counts, and total bilirubin, were extracted from laboratory records for further analysis.

Study Timeline and Dissemination Plan

The study was funded in October 2022. Initial data extraction started in February 2023 and was completed in November 2023. Our final analysis, which focuses on trends in the prevalence of HDFN and patterns of health care resource use, including costs associated with pregnancies and infants affected by HDFN, is expected to be completed in early 2026. We plan to disseminate these findings through peer-reviewed, open-access journals; presentations at professional societal conferences; and meetings with key stakeholders by late 2026.

Discussion

Anticipated Findings

We presented an overview of the methodology used to establish a cohort of patients with HDFN, along with a description of the epidemiology, study design, characteristics of the study population, and health care resource use associated with HDFN. Our comprehensive approach successfully identified an HDFN prevalence of 29.3 per 100,000 among a cohort of more than 450,000 pregnancies. We found that pregnant women affected by HDFN tended to be older, non-Hispanic White, insured through Medicaid or private insurance, multiparous, and multigravida. Furthermore, these pregnancies were associated with a higher prevalence of renal disease. Finally, infants born from HDFN-associated pregnancies had a higher likelihood of preterm birth, low birthweight, small head circumference, and neonatal jaundice. Among HDFN cases, anti-D was the most frequently identified antibody, followed by anti-E, anti-C, and anti-K. Notable heterogeneity in the distribution of antibodies associated with HDFN was observed across racial and ethnic groups. This variation highlights potential disparities in immunologic profiles and may have implications for targeted screening and management strategies.

There is currently no standardized approach to reporting the incidence rates of HDFN, with recent studies showing considerable variation in prevalence estimates. A retrospective cohort study of US birth data between 1996 and 2010 reported a prevalence of 1695 cases per 100,000 births [7]. Although this estimate is substantially higher than our observed prevalence of 29 per 100,000 births, critical difference in case ascertainment methods may explain the discrepancy.

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The majority of alloimmunized women in our cohort were multiparous and older than 30 years, which aligns with findings from previous studies [30]. It is important to note that this demographic trend may reflect an increased cumulative exposure to immunizing events, such as prior pregnancies or blood transfusions, as well as potential age-related changes in immune function that heighten susceptibility to alloimmunization [31]. These observations underscore the importance of early screening and targeted monitoring strategies in high-risk pregnancies, particularly among older and multiparous women.

In our study, the integration of structured data with unstructured data through an NLP algorithm was critical for accurately identifying HDFN cases. However, the rarity of the disease presented several challenges during the cohort development phase, including the need for manual validation and expert adjudication to ensure diagnostic accuracy.

As there are no straightforward diagnostic codes to identify HDFN cases, selecting the appropriate isoimmunization codes to accurately identify HDFN cases was a major challenge. To overcome this, we adopted an inclusive approach, using a broad range of isoimmunization diagnostic codes to minimize the risk of missing true cases. Furthermore, extracting laboratory data for antibody screening and indirect Coombs tests often required careful manual review of medical records, as this information was not always readily available in the test result fields. Further challenges arose during the medical review phase, where conclusively ascertaining often proved difficult for cases, even after reviewing both maternal and infant records. In some instances, we found that isoimmunization codes had been incorrectly assigned to infants based solely on maternal antibody test results. Moreover, several HDFN-related symptoms and treatments, such as jaundice, kernicterus, and hydrops fetalis, overlap with symptoms of other unrelated medical conditions. Therefore, a thorough review was critical to accurately determine true cases. Overall, we resolved most of these challenges through expert clinician review of ambiguous cases.

In future studies, we plan to compare health care resource use between pregnancies and infants affected by HDFN and those without, focusing on maternal hospital and intensive care unit stays, neonatal intensive care unit stays, and emergency and urgent care visits. We will also assess the association between maternal comorbidities and the development of alloimmunization, as well as examine the links between HDFN and adverse maternal and infant outcomes, including, but not limited to, stillbirth and preterm birth. Additionally, we plan to examine whether the prevalence of alloimmunization varies across racial and ethnic groups and explore the potential influence of sociocultural and genetic factors. As all pregnant women in our study are part of the same integrated health care system, disparities in access to care are unlikely to explain any observed racial or ethnic differences. This supports further investigation into other contributing factors, such as biological predispositions, cultural practices, and environmental exposures.

Strengths and Limitations

A major strength of this study is the comprehensive approach to defining HDFN within the EHR, which combined structured and unstructured data with extensive chart reviews. This novel methodology enabled effective case ascertainment and facilitated both prevalence estimation and more complex epidemiological analyses. As noted in previous research, reliance on diagnostic codes alone, especially for rare and complex conditions, may provide inaccurate estimates [32]. In our analysis, fewer than 6% of true HDFN cases were appropriately coded as such, while more than 15% of confirmed HDFN cases lacked any HDFN-specific diagnostic codes. Even with our novel HDFN case ascertainment methodology, there are a few limitations to acknowledge. First, we used data from member patients of a large integrated health care system in Southern California, and although comparable to the overall residents of Southern California [26,28], our findings may not reflect national HDFN rates. Second, the accuracy of data hinges on the completeness of information recorded in the EHR system, which may introduce some degree of bias.

Overall, the database compiled for this study and the methodology described to ascertain HDFN cases provide the opportunity to conduct pharmacoepidemiological studies on rare conditions such as HDFN. Our study cohort represents a large, socioeconomically diverse population, and the results of this study will provide updated epidemiological data regarding the prevalence, temporal trends, and health care resource use associated with HDFN.

Conclusions

This study established a robust methodology and comprehensive cohort for identifying HDFN cases, enabling future pharmacoepidemiological research on rare conditions. By leveraging a large, socioeconomically diverse population, the findings offer updated insights into HDFN prevalence, trends, and health care use. There is considerable heterogeneity in the characteristics of pregnancies associated with HDFN compared to those without HDFN, reflecting variations in maternal demographics, clinical profiles, and pregnancy outcomes, underscoring the clinical significance and health care burden of HDFN. The approach described may serve as a foundation for generating evidence to inform clinical guidelines and support future drug development, including clinical trials.

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Conflicts of Interest

This study was supported by Johnson & Johnson, Pennsylvania, United States. The opinions expressed are solely the responsibility of the authors and do not necessarily reflect the official views of the funding agency. Authors employed by the sponsor (CM, MM, and IL) participated in the study design, interpretation of data, the writing of the report, and the decision to submit the manuscript for publication.

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Abbreviations

EHR: electronic health record
HDFN: hemolytic disease of the fetus and newborn
KPSC: Kaiser Permanente Southern California
NLP: natural language processing

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Protocol

Perinatal Cannabis Use, Depression, and the Mother-Child Dyad: Protocol for a Prospective Multimethod Study

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Abstract

Background: Postpartum depression (PPD) rates in the United States are among the highest globally, and PPD can pose significant, long-term risks to families. Concurrently, perinatal cannabis use is increasing in prevalence and may exacerbate PPD. Although evidence links cannabis use with PPD, little is known about its impact on immediate depressive symptoms or depression trajectories across the perinatal period. Moreover, the potential impact of cannabis use on mother-child attachment, bonding, and emotional availability could intensify the effects of cannabis on PPD.

Objective: This protocol study is a longitudinal investigation aimed at detecting initial signals of the daily and long-term associations between cannabis use, PPD symptoms, and the mother-infant relationship.

Methods: Participants (N=20) were individuals carrying a singleton pregnancy who reported using cannabis at least twice weekly. Recruitment was through community outreach and online advertisements. Study participation began with a baseline laboratory assessment during pregnancy, which included surveys on mental health and substance use. Follow-ups were conducted virtually at 6 weeks post partum and in the laboratory at 6 months post partum and included additional surveys on infant development, aspects of the mother-infant relationship (eg, attachment), as well as behavioral interaction tasks. Each assessment was paired with a 2-week ecological momentary assessment burst, resulting in three bursts. To support retention, brief check-in visits were completed during the second and third trimesters (depending on gestational age at enrollment), and a postdelivery phone call was conducted within 2 weeks of delivery. A 2-level linear mixed-effect models will be used to examine both event-level and person-level associations of cannabis use with momentary negative affect, PPD symptoms, and attachment, bonding, and emotional availability. Interaction models will test whether these characteristics of the mother-child relationship intensify the association between cannabis use and PPD symptoms.

Results: This project received institutional review board approval on December 19, 2022, and was awarded funding on February 1, 2023. The recruitment goal of 20 participants was reached on September 4, 2024. Recruitment challenges were encountered early in the study, leading to successful adaptations in recruitment and data collection protocols. Follow-up data collection is ongoing, with completion expected by October 2025 and results anticipated by April 2026. Retention rates approach 100% at follow-up, and ecological momentary assessment compliance rates exceed those observed in nonpregnant samples (ie, >80%).

Conclusions: This protocol study demonstrates our ability to collect momentary and longitudinal data to examine the daily and cumulative impact of cannabis use on PPD and the mother-infant relationship. These data are well-positioned to provide preliminary evidence on how cannabis use may shape depressive symptoms during a particularly high-risk period for maternal mental health. The findings will inform a larger-scale study and advance understanding of the potential effects of cannabis use on perinatal mental health.

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KEYWORDS

postpartum depression; PPD; perinatal cannabis use; mother-infant relationship; ecological momentary assessment; EMA; maternal mental health

Introduction

Background

Rates of postpartum depression (PPD) in the United States are among the highest in the world [1-3]. It is estimated that one in 7 birthing individuals experiences perinatal depression (depressive episodes that occur during pregnancy or the first postpartum year) which can pose profound, protracted risks to the mother, child, and family [4,5]. PPD is the leading complication related to childbearing, and suicide rates in the postnatal period may be as high as other times in a woman's life [6,7]. Further, PPD is a chronic, relapsing disease; those who experience PPD are 300 times more at risk of experiencing PPD in subsequent pregnancies and twice as likely to experience depression within 5 years post partum relative to those who do not experience PPD in the first 12 months after birth [8]. An additional consequence of PPD may be disruption to the mother-child relationship, which can result in a developmental cascade of unhealthy outcomes for the child [9].

Perinatal Cannabis Use

Perinatal cannabis use is increasing in prevalence [10] and may worsen PPD over time. Relative to pregnant people without depression, pregnant people with depression are at least 3 times as likely to use cannabis during pregnancy and at least 2 times as likely to use cannabis while breastfeeding [11]. Pregnant people report that cannabis use helps them cope with depressive symptoms [12]. While cannabis use may reduce depressive symptoms, such as negative affect in the moment [2], it may increase these symptoms over time, as has been demonstrated in nonpregnant samples [13]. Also, in nonpregnant samples, using cannabis to cope is linked to cannabis dependence and increased depression [14]. There is initial evidence that those who engage in prenatal cannabis use experience higher levels of PPD and anxiety [15,16], but the impact of prenatal cannabis use on longitudinal patterns of PPD have not been assessed, which is essential to mitigate PPD and inform treatment. Examination of longitudinal trajectories are important, as PPD persists at 6 months post partum in 50% of mothers [17].

Although this directional association (cannabis use leading to PPD) is theorized and is the focus of this study, a bidirectional relationship may exist. As such, research is needed on both the momentary and long-term effects of cannabis use on PPD. Intensive longitudinal designs that capture momentary associations as well as long-term changes in symptoms can offer a rigorous approach to inform hypothesized directionality and momentary impact of cannabis use on PPD symptoms.

Postpartum Cannabis Use, Depression, and the Mother-Child Relationship

Maternal well-being is essential for attentive, responsive, and emotionally available parenting [18], and both substance use and depression can interfere with a mother's ability to provide this level of care. The relationship between a mother and their offspring begins before birth, with maternal-fetal attachment reflecting a pregnant person's emotional bond and cognitive representations of the developing fetus (eg, imagining interactions or future scenarios). This attachment often translates into behaviors that convey care for the fetus, including nurturance (eg, abstaining from harmful substances), comforting (eg, touching or holding the belly), and preparing physically and emotionally for the baby's arrival [19]. Evidence indicates that maternal-fetal attachment is strongly associated with both depressed mood and substance use during pregnancy [19,20], but the literature on cannabis use and maternal-fetal attachment is lacking.

After delivery, early relational processes evolve into measurable aspects of the postnatal mother-infant relationship, including bonding and emotional availability. Bonding refers to a mother's emotional connectedness toward their child, and is evidenced by the provision of protection, comfort, and care [21]. Emotional availability is a dyadic construct capturing how well caregiver and child can respond to each other's emotional cues in ways that foster a healthy relationship [22]. A dyadic system that is not functioning well may present with a restricted range of emotion or lack of interest or sustained pleasure [22]. Thus, bonding reflects the caregiver's inner emotional experience, and emotional availability may reflect the manifestation of these feelings or the quality of the observed relationship in action. These constructs are central to healthy relational development and may be particularly vulnerable to disruption in the context of maternal cannabis use and PPD.

There is overlap in the neurobiological and psychological systems that are implicated in substance use and mother-infant interactions (eg, emotional responsivity, reward processing, and executive functioning [23]). Consequently, substance use can lower intensity of maternal feelings toward the infant, which can result in less responsivity to infant cues [24]. Systematic reviews and meta-analyses [24-28] consistently demonstrate the significant negative consequences of PPD on various aspects of the mother-infant relationship. Depression-related anhedonia and low or dysregulated affect can interfere with a mother's attunement to their infant and disrupt both bonding [29] and emotional availability [30]. For example, there is evidence that depressed (vs nondepressed) mothers engage in less communication and smiling toward their infants [31], as well as less physical touch during social interactions [32]. There are likely bidirectional associations between depression and mother-infant interaction quality that can be probed with momentary data. None of this work, to our knowledge, has focused on prenatal cannabis use, specifically. Given what is established for the use of other substances, cannabis use may operate similarly, via mechanisms like affect blunting, disrupting emotional regulation and sensitivity, increasing withdrawal or distraction, or via neurobiological impacts of tetrahydrocannabinol on mood and cognition. Extending this work to cannabis use is a critical next step, as the rapidly evolving status of cannabis legalization is tied to increased

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access and decreased perceived harm, both of which predict increased use among pregnant people [33]. Moreover, research has yet to examine how cannabis use affects the developing relationship between mother and child, and how the interactions between the 2 influence PPD. There is the strong potential for a cyclical relationship, such that disrupted interactions may perpetuate a negative feedback loop such that PPD leads to negative mother-infant interactions, which exacerbates PPD. Research is needed to test this hypothesized effect as well as factors that may exacerbate PPD.

Another opportunity lies in multimethod approaches (ie, behavioral, self-report, and ecological momentary assessment [EMA]) that yield the most comprehensive data on maternal-child interaction quality, as maternal perceptions and observational assessments may capture different aspects of the mother-infant relationship [34]. Cannabis use is common in the postpartum period, but controlled cannabis administration cannot be studied due to ethical concerns. The use of EMA is therefore feasible as it facilitates the understanding of the impact of cannabis on mother-child interactions as they naturally occur.

Use of Ecologically Valid Methods for Studying Perinatal Cannabis Use

EMA methods are ecologically valid and ideal for studying cannabis use, PPD, and mother-child interactions during the perinatal period, as they limit recall bias and allow for low-burden assessment within an individual's typical context [35,36]. Further, EMA methods are essential for examining the impact of cannabis use in a pregnant sample for whom administration of substances is not possible, but allows for the harnessing of the frequent cannabis use already occurring in this sample. Finally, these intensive longitudinal data collection methods allow for the examination of within- and between-person sources of variation that exist for cannabis use across the perinatal period. While cross-sectional research has been beneficial in unearthing associations among cannabis use, maternal health outcomes, and mother-infant interactions, there remains a gap in our understanding of these naturalistic relationships. EMA capture of parenting is essential to bolster laboratory and self-assessment and capture mother-infant interactions as they occur in the real world; yet no studies have used EMA methods to examine how cannabis use and PPD impact the mother-child relationship. This study answers a call for the use of ecologically valid methods to study caregiver-child interactions in the natural environment [37].

Current Study

Despite mounting evidence that cannabis use cooccurs with PPD, we have very little understanding of the impact of cannabis use on the immediate experience of PPD symptoms (such as negative affect) or trajectories across the perinatal period. Further, the influence of cannabis use on attachment, bonding, and emotional availability in the mother-child relationship may be profound and may exacerbate the effect of cannabis use on PPD. The first objective of this study is to gather pilot data to examine initial direction of effects for the event-level and longitudinal impact of cannabis use on PPD symptoms. It is hypothesized that (1) cannabis use will result in decreased negative affect in the moment, and (2) more frequent cannabis use will increase depression symptoms across the postnatal period. The second objective is to evaluate the impact of cannabis use on mother-infant relationship and PPD via multiple methods, and it is hypothesized that (3) cannabis use will be associated with less bonding and lower emotional availability at the day-level and across the perinatal period (assessed both in the natural environment and laboratory), and (4) lower-quality mother-child relationships are expected to exacerbate the association between maternal cannabis use and PPD across the postpartum period.

Methods

Design Overview

Study participation involves a baseline laboratory assessment in pregnancy (before 28-week gestation period; Time 1), a virtual assessment at 6 weeks post partum (Time 2), and a laboratory assessment at 6 months post partum (Time 3). Each Time 1-3 assessment is followed by a 2-week EMA burst for a total of 3 bursts. In addition, up to 2 prenatal retention visits occur in trimesters 2 and 3, such that those enrolled during their first trimester of pregnancy completed follow-ups in both the second and third trimesters, while participants enrolled in their second trimester completed a single follow-up in the third trimester. Participants also completed a brief phone call within 2 weeks post partum, for retention purposes (study flow mentioned in Figure 1).

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Figure 1. Study flow. EMA: ecological momentary assessment.

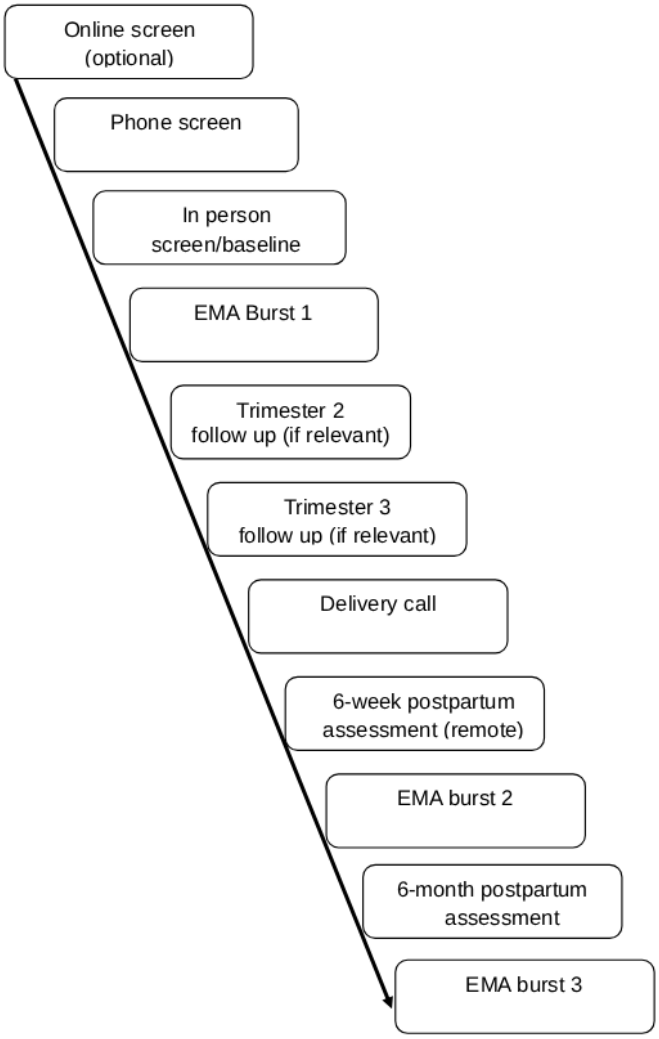

Participants

Eligibility

Eligibility criteria include (1) participants older than 18 years of age; (2) English-speaking; (3) report cannabis use at least twice weekly over the past 60 days; (4) pregnant with one child with a gestational age no more than 28 weeks (to allow time for scheduling of baseline); (5) not currently in substance use treatment; (6) no current (past month) mania, psychosis, or active suicidal ideation; (7) no substance use other than cannabis, tobacco, or alcohol; and (8) own a personal smartphone to accommodate the data collection app. For revisions to eligibility criteria to address initial recruitment challenges, see Results section.

Recruitment and Screening

Participants were recruited through social media, community flyers (posted in locations such as playgrounds, Women, Infants, and Children offices [supplemental nutrition program for women, infants, and children], and obstetrics/gynecology clinics), and via BuildClinical, a platform that identifies potential research participants using online advertising campaigns and conducts initial eligibility screening. Respondents to flyers or online advertisements accessed an online screener hosted on Qualtrics via a clickable link or the QR code. This screener included questions aligned with the study's inclusion and exclusion criteria. Those meeting initial eligibility criteria were prompted to complete a contact form specifying their preferred method and time for follow-up. Study staff then contacted these individuals to confirm eligibility through a telephone screener. Alternatively, prospective participants could reach out directly via call or text to schedule screening. Eligible participants were invited to an in-person baseline assessment and instructed to abstain from using cannabis for at least 15 hours prior to the visit.

Procedures

In-Person Screening

After verifying identity and age via government-issued ID (eg, driver's license), participants complete the informed consent process, which was presented via PowerPoint (Microsoft Corp) to facilitate comprehension. After consent is obtained, participants provide biochemical verification of eligibility. Biochemical verification includes a commercially available pregnancy test to confirm pregnancy and a 5-panel iCup urine drug screen which screens for amphetamines, cocaine,

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methamphetamine, opiates, and tetrahydrocannabinol, as well as validity and specimen integrity checks, including oxidants, pH level, and specific gravity, to confirm cannabis use and no other drug use. Tetrahydrocannabinol is detected at 50 ng/mL. If participants tested negative for tetrahydrocannabinol at 50 ng/mL, a tetrahydrocannabinol dipstick with a greater sensitivity of 5 ng/mL was administered. A saliva test is also conducted to ensure that the participant has not used cannabis in the past 15 hours, with a cut-off threshold of 40 ng/mL of tetrahydrocannabinol. This test was conducted to ensure no intoxication was experienced at study sessions.

Following bioverification of eligibility, the Mini-International Neuropsychiatric Interview (MINI [38]) is administered to rule out past month mania, psychosis, or active suicidal ideation, and the Timeline Followback (TLFB) is administered to rule in twice weekly cannabis use and rule out substance use other than alcohol and nicotine. The MINI is administered by a PhD-level study staff member or a student currently enrolled in an MPH program; both are supervised by a licensed clinical psychologist. Participants deemed ineligible are compensated US $15 and provided psychoeducational resources on cannabis and mental health. These resources are provided to all who were screened and enrolled in the study.

Baseline (Time 1) and EMA Burst 1

The baseline assessment lasts approximately 3-4 hours. Participants complete baseline surveys on substance use patterns and psychosocial factors that may influence maternal health. Finally, participants view a PowerPoint presentation and receive hands-on training to familiarize themselves with completing EMA surveys. This training ensured they were comfortable using MetricWire, the EMA mobile app, on their smartphones to report real-time data on daily substance use, mood, and other contextual factors. Participants are subsequently enrolled in the EMA burst procedures, which begin the day following the baseline assessment and last for 2 weeks.

Trimester Follow-Ups

Each trimester follow-up assesses recent (30-day) substance use, as well as current depression and anxiety symptoms.

Delivery Call

A 5- to 10-minute phone call is conducted 0-14 days post delivery to gather basic information about the newborn. Participants are asked to text research staff upon the delivery of their baby. If staff do not receive a text, they refer to the participants' estimated delivery date and send text and email reminders to let study staff know when they deliver.

6 Weeks Post Partum (Time 2)

A 30-minute virtual visit occurs at approximately 6 weeks post partum. Participants self-report on substance use, mother-infant bonding, birth experience, infant development, and parental substance use. Participants were refamiliarized with the EMA procedures and are enrolled in EMA burst 2, which begins the day after the Time 2 assessment.

6 Months Post Partum (Time 3)

The participant and their infant attend a 90-minute laboratory assessment at approximately 6 months post partum. The birthing person reports on their substance use, depression, and anxiety. Dyads also complete behavioral tasks, which are video-recorded for later behavioral coding. Following the mother-infant interaction tasks, study staff debrief with the parent to review their experience in the paradigm and ensure mother and baby are comfortable. Participants are refamiliarized with the EMA procedures and are subsequently enrolled in the third and final burst, which begins the day following the 6-month assessment.

Ecological Momentary Assessment

EMA data are collected via MetricWire, enabling individualized data collection via participants' smartphones. At baseline, participants are trained to use the mobile app, including specific instruction on responding to prompts and measurement of cannabis quantity. Participants are instructed to self-initiate reports just before using cannabis (begin cannabis report), which assesses for the formulation of cannabis being used, current reasons for using cannabis, and current mood. After participants complete a begin cannabis report, they are instructed to complete an end use report, and follow-up reports are triggered at 30-minute intervals to assess for the end of the cannabis use event if not self-initiated. Once the end use report is completed, cannabis use event details are assessed, including context, any other substance use, as well as impact on mood and infant presence (postpartum bursts only). Participants also complete random prompts throughout the day (sent randomly within three 3-hour blocks each day) to capture mood during noncannabis use events and cannabis use that is not self-initiated. Participants also complete morning reports, which assess overall sleep quality, mood symptoms, intentions to use cannabis that day, and summarize the prior day's substance use. Bedtime reports capture mother-child interactions from the day (postpartum bursts only) and any additional use since the last report. Assessments are designed to be less than 2 minutes. Similar methods have been used by Gunn et al [39].

Compensation

Participants could earn up to US $595, dispersed on reloadable debit cards. The compensation schedule is outlined in Tables 1 and 2. Payments are provided following each assessment. Compliance is maximized in the EMA study phase by compensating participants by increasing USD amounts based on compliance rates. EMA compliance rates are calculated following the completion of each burst and compliance is compensated following completion of each burst.

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Table 1. Compensation schedule for non–ecological momentary assessment. Participants deemed ineligible at screening were compensated US $15.

Non-EMA[a] activities	Compensation amount (US $)
Baseline (in person)	100
Trimester follow-up 1 (if indicated)	25
Trimester follow-up 2 (if indicated)	25
Postdelivery call	10
6-week post partum (virtual)	50
6-month post partum (in person)	85
Study completion bonus[b]	40

[a]EMA: ecological momentary assessment.
[b]Participants receive the completion bonus if they complete all study sessions and at least 50% of surveys across all mobile surveys.

Table 2. Compensation schedule for ecological momentary assessment activities.

Percent surveys complete	Burst 1 (US $)	Burst 2 (US $)	Burst 3 (US $)
<25%	10	15	20
25%-49%	30	40	50
50%-74%	60	70	80
75%-89%	70	80	90
90%+	75	85	100

Measures

A list of constructs assessed and an administration timeline can be found in Tables 3 and 4. Before administering these measures, participants reported their preferred term for cannabis. When applicable, we used the participant's chosen term in place of "marijuana" throughout the measures.

Table 3. Schedule of ecological momentary assessment measures.

EMA[a] measures	Start	FU[b]	Random	AM[c]	PM[d]
Cannabis form and quantity	✓	✓	✓	✓	✓
Cannabis intoxication		✓	✓		✓
Motives	✓				
Social context		✓	✓		✓
Other substance use		✓			
Mood	✓	✓	✓	✓	✓
Sleep				✓	
Mother-child relationship					✓

[a]EMA: ecological momentary assessment.
[b]FU: follow-up
[c]AM: morning survey.
[d]PM: bedtime survey.

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Table 4. Schedule of measures.

Construct	Screen	Baseline	Time 2 and Time 3[a]	Delivery	6 Weeks PP[b]	6 Months PP
Eligibility						
Mental health	✓					
Substance use (past 90-day use)	✓					
Acute THC[c] intoxication	✓					
Urine drug screen	✓					
Pregnancy	✓					
Demographics		✓			✓	✓
Substance use		✓	✓		✓	✓
Cannabis use beliefs and behaviors		✓				
Mental health		✓	✓		✓	✓
Social support		✓				
Feeding intentions		✓				
Attachment		✓				
Child development				✓	✓	✓
Birth experience					✓	
Parenting stress					✓	✓
Bonding					✓	✓
Mother-infant interaction tasks						✓

[a]Time 2 and Time 3: trimester follow-ups.

[b]PP: post partum.

[c]THC: tetrahydrocannabinol.

Screening

Mental Health: Current Mania, Psychosis, or Suicidal Ideation

The MINI is a short structured diagnostic interview designed to assess major *DSM-IV* (*Diagnostic and Statistical Manual of Mental Disorders* [Fourth Edition]) and *ICD-10* (International Statistical Classification of Diseases and Related Health Problems, Tenth Revision) psychiatric disorders [38]. The MINI assesses for current (past month) mania, psychosis, and suicidal ideation, all of which were exclusion criteria in this study. In addition to these screening data obtained to inform study eligibility, the MINI includes assessments of current and past psychiatric diagnoses, including major depressive disorder, panic disorder, agoraphobia, social anxiety disorder, obsessive compulsive disorder, posttraumatic stress disorder, alcohol and substance use disorder, anorexia nervosa, bulimia nervosa, binge eating disorder, generalized anxiety disorder, and antisocial personality disorder.

Substance Use

Participants self-report their substance use with the TLFB, a structured, calendar-based interview tool used to collect detailed retrospective data on substance use [40,41]. Participants are guided to recall daily activities and contextual cues to enhance the accuracy of their reports. The TLFB is included as part of the in-person screening to identify use of cannabis (eligibility), alcohol, tobacco, as well as to capture the use of other substances (ineligibility). Participants also report mode of cannabis use. Duration covered by the TLFB varies by assessment, such that the reporting period was either past 90-day (Time 1) or past 30-day (trimester follow-ups, Time 2, and Time 3) use.

Baseline

Demographics, Household, And Pregnancy Context

Participants report on their demographics (eg, age, biological sex at birth, gender identity, race, ethnicity, income, government assistance), as well as contextual information about the home environment, including the number of children and relationship status. Date of last menstrual period and trimester of pregnancy are queried to determine gestational age. Additional questions probe prenatal care, including the number of prenatal appointments attended and how pregnancy has been confirmed.

Other Substance Use

Participants report on their use of nicotine or tobacco products (cigarettes, e-Cigarettes, or nicotine vaporizers, other tobacco or nicotine products) and alcohol use, as well as the frequency and quantity of use for each trimester. Participants report on parallel information about their partner's substance use (alcohol,

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cannabis, cigarettes, other tobacco products, and other drugs) since the participant found out they were pregnant.

Cannabis Use Characteristics

Participants are asked if they have a medical card, if they use the card to purchase cannabis, and for what conditions they have been provided a medical card. Moreover, they report on their current level of cannabis use (ie, if they use the same, less, or more than when they found out they were pregnant), if they have quit or temporarily stopped using cannabis since finding out they were pregnant, and if so, why.

For each trimester, participants report number of days of cannabis use per week, average times per day of cannabis use, average number of hours high per cannabis use day (presented on a visual analog scale from 0 to 24 hours), how high they felt when using cannabis (visual analog scale ranging from 0=not at all high to 100=as high as possible). Amount of tetrahydrocannabinol versus cannabidiol in cannabis used was assessed (mostly or entirely cannabidiol/no tetrahydrocannabinol, roughly equal parts cannabidiol or tetrahydrocannabinol; mostly or entirely tetrahydrocannabinol or no cannabidiol, or unsure). Finally, participants indicate the number of days (0-7) that they used each of the following: join, hand pipe, bong, blunt, concentrates or dabs, edibles, tetrahydrocannabinol-infused alcoholic beverages, tinctures, and cannabidiol-only products (eg, lotions) [42].

Symptom Management Motives

Participants are provided a list of 10 physical symptoms common in pregnancy (ie, stomach or digestion problems, physical pain, neurological symptoms, sleep, fatigue, bleeding, Braxton-Hicks contractions, dyspareunia, hot flashes, and appetite) and 13 emotions (ie, sad or depressed, happy, nervous or anxious, excited, decreased pleasure or motivation, angry, optimistic, lack of energy, fidgety or restless, scared, irritable, and boredom stress). Participants indicated if they did or did not use cannabis for managing each symptom or emotion, and if they reported using cannabis to manage the symptom, they were asked how helpful cannabis was at managing that symptom (response options were did not help, helped somewhat, helped a lot). This measure was developed for this study.

Cannabis Consequences

The Brief Marijuana Consequences Questionnaire [43] assesses the negative consequences, grouped into 5 categories: interpersonal, health, academic or occupational, legal, and psychological, associated with cannabis use since the participant found out they are pregnant. Respondents rate how frequently they have experienced each consequence on a 5-point Likert scale (ranging from 0=never to 4=often).

Perceived Harms of Substance Use

Participants report on how harmful they think their cannabis use is to their own health, to the health of their baby during pregnancy, and to the health of their baby after they give birth. An additional question probes how harmful they think it is to breastfeed while using cannabis. All questions are presented with separate visual analog scales ranging from 0 (not at all harmful) to 100 (very harmful). In addition, participants are asked the extent to which they agreed or disagreed with statements about the perceived harms of alcohol use, nicotine or tobacco use, and use of other drugs to the developing child. Items were adapted from Nordeng et al [44].

Sources of Information and Disclosure About Cannabis Use

Participants are asked where they sought information about substance use and who provided them with information, including unsolicited advice. Response options included physician, midwife, nurse, other health care provider, internet, pregnancy groups, family or friends, dispensaries, or other. A follow-up, open-ended question assessed the type of information received from these sources. Participants also reported if they disclosed their cannabis use to their provider (yes or no), how comfortable they are in discussing their cannabis use with their provider (4-point Likert scale from not at all comfortable to very comfortable), and how honest they have been with their provider about their cannabis use. This measure was developed for this study.

Cannabis Stigma

Participants are also asked how much they agree or disagree on a 5-point Likert scale, including a “not sure” option, with the following statements: “there is negative stigma around using cannabis” and “there is negative stigma around using cannabis during pregnancy.” Additionally, participants reported how acceptable or unacceptable they find both medical or therapeutic and recreational cannabis use.

Protective Behavioral Strategies

The Protective Behavioral Strategies for Marijuana Scale is a self-report tool designed to assess how often individuals use strategies to minimize potential harms from cannabis use [44,45]. The scale consists of 17 items (eg, “Only use once during a day/night”), each measuring the frequency of specific protective behaviors (response options are never, rarely, occasionally, sometimes, usually, and always). To our knowledge, this is the first application of this measure in a pregnant sample. Together with the developers of the measure, we made 3 modifications to the scale. First, the question stem specifies the use of protective behavioral strategies during pregnancy. Second, replaced “marijuana” with the individual’s preferred term. Finally, we included the following open-ended question to probe for protective behavioral strategies that were not captured in the initial measure: “What other things do you do to help you avoid some of the not so good things about using [preferred cannabis term] while you are pregnant?”

Depression

The Edinburgh Postnatal Depression Scale [46] was used to screen symptoms of depression and has been validated in pregnant and postpartum samples [47]. The Edinburgh Postnatal Depression Scale consists of 10 items (eg, “I have felt sad or miserable”) scored on a 4-point Likert scale (0-3), reflecting the frequency or severity of symptoms over the past week. Scores range from 0 to 30, with higher scores indicating greater severity of depressive symptoms.

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Anxiety

The Perinatal Anxiety Screening Scale (PASS [48]) is designed to screen for a broad range of anxiety symptoms in pregnant and postpartum individuals. The PASS consists of 31 items scored on a 4-point Likert scale ranging from 0 (not at all) to 3 (almost always). The PASS includes four subscales, including excessive worry and specific fears (eg, "Fear that harm will come to the baby"), social anxiety (eg, "Fear that others will judge me negatively"), perfectionism and control (eg, "Needing to be in control of things"), and acute anxiety and trauma. Total scores can range from 0 to 93, with higher scores indicating more severe anxiety symptoms. Anxiety thresholds are defined as low (0-20), moderate (21-41), or high (42+).

Social Support

Two questions query social support in pregnancy; the first asked if participants have been adequately supported in their pregnancy (1=never to 5=always), and if they have or would be willing to attend a support group for pregnant individuals. Items were developed for this study.

Feeding Intentions

Participants report their intended primary method of feeding their infant during the first 6 months (options: breastfeeding or chestfeeding, pumping, formula-feeding, milk sharing or milk bank, or other). They also complete a check-all-that-apply item listing all feeding methods they planned to use during this period. Participants indicated whether they believe cannabis can pass through breast or chest milk (response options: yes, no, or I don't know). Items were developed for this study in collaboration with an International Board Certified Lactation Consultant.

Attachment

The Maternal-Fetal Attachment Scale is a self-report questionnaire designed to measure the emotional bond that a mother develops with their unborn child during pregnancy [49]. The Maternal-Fetal Attachment Scale assesses the extent to which a pregnant person engages in behaviors that reflect attachment to their fetus. The scale consists of 24 items with four response options (definitely yes, yes, no, and definitely no). The Maternal-Fetal Attachment Scale includes 5 subscales: differentiation of self from fetus, interaction with fetus, attributing characteristics to fetus, giving of self, and role taking. Higher scores indicate stronger maternal-fetal attachment.

Delivery Call

Newborn information included date of birth, height, weight, Appearance, Pulse, Grimace, Activity, and Respiration scores, head circumference, neonatal intensive care unit admission (yes or no and duration), and sex.

6 Weeks Post Partum

Demographics and Substance Use Environment

Demographic information collected included the number of children and adults in the home, as well as adult substance use within the household. Participants were presented with a table reflecting the previously reported number of adults in the home and were asked to indicate if any adult had used cannabis, alcohol, cigarettes, other nicotine products, or other drugs since returning home after delivery.

Birth Experience

The Childbirth Experience Questionnaire [50] provides a comprehensive assessment of a birthing person's perceptions and feelings about their labor and birth experience. The measure includes 19 items rated on a 4-point Likert scale ranging from 1 (totally agree) to 4 (totally disagree). The measure consists of 4 key domains: own capacity (eg, I felt strong during labor and childbirth), professional support (eg, my provider understood my needs), perceived safety (eg, I felt scared during labor and birth), and participation (eg, I felt I could have a say in deciding my birthing position).

Child Protective Services Involvement

Participants reported on whether or not the family has had Child Protective Services involvement since the birth of the baby.

Neonatal Intensive Care Unit

Participants were asked if their baby spent any time in the neonatal intensive care unit, and if so, the number of days.

Parenting Stress

The Parental Stress Scale [51] is an 18-item questionnaire assessing parents' feelings about their parenting role, exploring both positive (eg, emotional benefits and personal development) and negative aspects of parenthood (eg, demands on resources and feelings of stress). Respondents agree or disagree on a 5-point Likert Scale in terms of their typical relationship with their child or children. Example items include "I am happy in my role as a parent" and "I sometimes worry whether I am doing enough for my child(ren)."

Infant Temperament

The very short form of the Infant Behavior Questionnaire [52] is a widely used parent-report tool designed to assess temperament in infants aged 3 to 12 months. The measure includes 37 items with response options of 1 (never) to 7 (always), including a not applicable option. Multiple dimensions of temperament are assessed, including activity level, distress to limitations, fear, smiling and laughter, duration of orienting, soothability, and falling reactivity or rate of recovery.

Infant Development

Participants completed developmentally appropriate Ages and Stages Questionnaires [53] at 6 weeks and 6 months post partum. This measure is a widely used developmental screening tool designed to assess young children's developmental progress and identify potential delays or concerns. The 2-month questionnaire (which covers babies ages 1 month 0 days to 2 months 30 days) assesses a child's development across 5 domains: communication (eg, ability to respond to sounds and voices), gross motor skills (eg, large muscle movements), fine motor skills (eg, hand-eye coordination and small muscle control), problem solving (eg, early cognitive skills), and personal-social skills (eg, social interactions and self-regulatory behaviors). Each domain includes 6 questions that parents answer based on their own observations of their child. Similarly, the 6-month questionnaire assesses a child's development across

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the same 5 domains as the 2-month version, but with milestones appropriate for a 6-month-old infant.

Bonding

Parents completed 2 questionnaires to identify potential issues in bonding and early signs of difficulties, such as maternal distress or postpartum mood disorders. The Postpartum Bonding Questionnaire [54] includes 25 items that are designed to assess the quality of the emotional bond between a parent, typically the mother, and their newborn. The measure includes 25 items, rated on a 6-point Likert scale from "always" to "never." Four subscales assess: impaired bonding (eg, "I feel distant from my baby"), rejection and pathological anger (eg, "I feel irritated by my baby"), anxiety about care (eg, "I feel anxious when my baby is with me"), and risk of abuse (eg, "I feel like I might hurt my baby"). The Mother Infant Bonding Scale [55] includes 8 items that reflect aspects of maternal feelings toward the infant (eg, "I feel loving toward my baby") on a 4-point Likert scale ranging from "Very Much" (0) to "Not at All" (3).

6 Months Post Partum

Background

Mental health, substance use, parenting stress, bonding, and child development are reassessed at 6 months. Additionally, participants complete 2 behavioral tasks that are video recorded using a 3-camera mounted recording system. This system includes one camera focused on the mother, one on the infant, and one capturing a wide-angle view of the entire room. Video signals from the two cameras are transmitted through a digital mixer to generate a split-screen recording of the mother and infant. The recording process is managed by a research assistant stationed outside the laboratory.

Still-Face Paradigm [56] is a laboratory-based assessment in which a caregiver's unemotional face is used to evoke pronounced behavioral reactions in the infant. Mothers are seated 18-36 inches from their infants, at eye level with their infants, who are placed in an infant seat by the mother. The paradigm involves three phases of mother-child interaction: (1) Baseline: in the first interaction, mothers are instructed to interact normally with their infants. (2) Still-face: after the mother returns from a break, they are told to keep eye contact but maintain a neutral expression, remain still, and do not touch or interact with their infant. (3) Reunion: after the second break, the mother is instructed to respond to their baby in any way they feel is appropriate. Each episode lasts 120 seconds, and the onset of each episode is cued by a research assistant who is seated in the room, out of sight of the infant.

Mother and infant behaviors are coded using the Infant and Caregiver Engagement Phases framework [57], which includes a set of mutually exclusive phases of interactive engagement and additional regulatory codes based on facial expressions, direction of gaze, and vocalization. The Infant and Caregiver Engagement Phases coding scheme has been applied to the paradigm conducted with substance-exposed infants [57] and infants of mothers experiencing psychiatric symptoms and stress [58]. For infants, engagement codes include passive-withdrawn, protest, object-environment interaction, social monitoring, and social positive engagement. Caregiver engagement codes consist of hostile-intrusive, withdrawn, social monitoring without vocalizing, social monitoring with positive vocalizing, and social positive engagement. Additional infant behaviors coded involve oral self-comforting (eg, mouthing), self-clasping, distancing or turning away, and autonomic stress indicators such as hiccups or spitting up. For caregivers, additional codes capture rough touches and deviations from still-face instructions, including speaking to or touching the infant during the designated still-face period. Infant and mother phases will be coded in two separate viewings of the videotape, with a third viewing dedicated to coding of infant regulatory actions, autonomic stress indicators, mother intrusions, and procedural violations.

Free Play

Mothers are instructed to play with a standardized set of developmentally appropriate toys as they normally would at home for 5 minutes. The research assistant is seated outside the room. The free play interaction will be coded using the Emotional Availability Scales [59], based on global judgements from the observers, and designed to assess the emotional connection between parent and child.

EMA Measures

Cannabis Formulation and Quantity

For all assessments, cannabis use is assessed by asking participants whether they used flower, concentrate, or edible (with "select all that apply"), followed by the quantity of cannabis used based on formulation. (ie, flower=grams of flower, concentrate=number of hits, and edible=milligrams of tetrahydrocannabinol). Additionally, participants report the potency of cannabis consumed and the level of intoxication or "high" ("rate how high you feel from 0=not at all high to 10=as high as possible").

Motives for Use

Participants selected all that apply: "to be social," "to feel less anxious," "to feel less depressed," "to relieve physical pain," "to sleep better," "to relax," "to enjoy the effects," "to increase appetite," and "other."

Social Context

Participants are prompted to report the context in which they consume cannabis, indicating the number of people they were with, the specific people they were with (eg, friend, partner, and family), and whether or not those individuals were also consuming cannabis at the time.

Other Substance Use

Participants are prompted to report any other substance use (ie, "Did you/are you using any other substance?"), reporting these substances via a select all option for alcohol, cigarettes, nicotine vaporizers, other tobacco or nicotine products, simulants, opiates, sedatives, hallucinogens, and other, if applicable.

Mood

Participants report on their current mood with an adapted version of the NIH Patient Reported Outcomes Measurement Information System adult depression short [60] form on a 5

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point scale: “Rate how much you currently feel this way” from 1=not at all to 5=very much, for depressed, hopelessness, helpless, worthless, anxious, irritable, happy, excited, and relaxed.

Mother-Child Relationship

For Time 3 only (ie, post partum), surveys assessed for the following mother-child questions, all reported on a 10 point scale from (not at all to as much as possible): “How bonded did you feel to your child today?” “How emotionally connected did you feel with your baby today?” “How sensitive did you feel toward your baby today?” “When your baby needed something today, how responsive were you to their needs?” “Did you provide the comfort and care that your baby needed today?”

Data Analysis Plan

Regarding the first objective of this study, to examine the event-level and longitudinal impact of cannabis use on PPD, 2-level linear mixed-effect models (LMEM) will be used to test hypothesis 1, that cannabis use will be associated with reduced negative affect in the moment. Longitudinal regression will be implemented to test hypothesis 2, that greater cannabis use will be associated with greater depression symptoms via the Edinburgh Postnatal Depression Scale across the postnatal period. Cannabis use and PPD symptoms will be modeled as person-level aggregates at each time point. Regarding the second objective of this study, to evaluate the impact of cannabis on mother-infant interactions and depression, LMEM will be used to test hypothesis 3, that cannabis use frequency will be associated with poorer mother-child interaction quality at the day-level, as well as longitudinally using person-level aggregates of cannabis use and laboratory-assessed measures of mother-child interactions. LMEMs will also be used to examine hypothesis 4, that poorer mother-child interaction quality, assessed via the still-face paradigm and free play, will amplify the association between cannabis use and depression, by adding an interaction term to hypothesis 3 models. For all LMEMs, variation in time-varying covariates will be modeled at the event level (level 1). Between-person effects, including aggregates of level 1 predictors and between-person covariates, will be modeled at level 2. Covariates will include EMA compliance (level 2), demographics (level 2), anxiety (level 2), other substance use (level 1), sleep (level 1), birth experience (level 2 postpartum models), and psychotropic medication use (level 2).

Ethical Considerations

Overview

The University institutional review board completed and approved human subjects’ ethics review (approval number 2022003468). Research procedures have been conducted in accordance with the Declaration of Helsinki. All participants provided informed consent, during which a research assistant reviewed all aspects of the study protocol, and knowledge checks were conducted before each participant gave consent. Participants are provided with the opportunity to opt out. Participants have received monetary compensation, outlined below, which was deemed appropriate for the time required to complete study procedures.

Relationship to the Parent Research Award

This project is supported by Brown University’s Center for Addiction Disease Risk Exacerbation (CADRE), funded through NIH’s Centers of Biomedical Research Excellence. All projects supported by CADRE benefit from the resources of three cores: the Clinical Laboratory Core, the Recruitment, Engagement, and Community Health Core, and the Administrative Core. The Clinical Laboratory Core provides essential research infrastructure and resources to advance CADRE-funded research. A key objective of this core is to create a database of factors (biological, environmental, social, and behavioral) associated with the development and progression of substance use disorders and chronic disease. In alignment with this objective, the current project incorporated the CADRE Core measures into its data collection process. A complete list of these measures is provided in Multimedia Appendix 1. These measures were administered at the baseline session after the study-specific measures listed below. For the purposes of this report, we focus on the research activities and measures specifically relevant to the aims of the current research.

Results

This project received institutional review board approval on December 19, 2022, and was awarded funding on February 1, 2023. The recruitment goal of 20 participants was reached on September 4, 2024. Table 5 summarizes the demographic characteristics of the sample. Follow-up data collection is ongoing. At the time of submission, 18 participants completed the full protocol. Retention rates were 100% for trimester follow-ups (20/20), 100% for the delivery call (20/20), and 95% for the 6-month assessment (19/20). One participant was lost to follow-up at the 6-week assessment, indicating a retention rate of 95% (19/20). One participant was pending the final 6-month EMA burst. Data collection is expected to be completed by October 2025, and initial results related to study aims are expected in April 2026. EMA compliance at all 3 bursts was also strong: 80% at burst 1, 81% at burst 2, and 83% at burst 3.

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Table 5. Participant demographics (N=20).

Demographic variables	Values
Age (years), mean (SD), range	30.15 (5.03), 20-39
Race[a], n (%)	
White	12 (60)
African American or Black	2 (10)
American Indian	1 (5)
Other[b]	1 (5)
Multiple	4 (20)
Ethnicity (Latinx), n (%)	6 (30)
Trimester at recruitment, n (%)	
First	4 (20)
Second	10 (50)
Third	6 (30)
Cannabis frequency (past 60-day use), mean (SD), range	50.74 (15.87), 14-60

[a]Check all that apply.

[b]One participant (self-identified as Puerto Rican).

A CONSORT (Consolidated Standards of Reporting Trials) flow diagram is presented in Figure 2. We faced significant recruitment challenges upon the initial launch of the project. A total of 3 notable revisions were made to the study procedures and inclusion criteria on April 8, 2024, to alleviate these challenges while retaining the scientific integrity of the project. The first change pertained to the current depression inclusion criteria. At the time of study launch, participants were required to report elevated depression levels, defined as a score of 3 or higher on the Patient Health Questionnaire-2 [61]. We decided to remove this inclusion criterion to allow for the potential capture of depression symptom onset in participants who did not initially screen positive for elevated depression. One participant was recruited prior to changing the depression criterion.

The second change was related to gestational age. Recruitment was initially limited to individuals in their third trimester of pregnancy. This criterion proved challenging because many pregnant individuals we screened reported reducing cannabis use as they approached delivery. The eligibility criterion was expanded to include participants as early as 8 weeks' gestation. However, this change introduced a significant risk of attrition for those recruited in the first trimester, as their next assessment would not occur until the delivery call. To address this, we incorporated up to 2 retention assessments during the second and third trimesters for participants recruited in the first or second trimester, as applicable. Third, the recruitment platform BuildClinical was implemented in April 2024, which expanded recruitment.

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Figure 2. CONSORT (Consolidated Standards of Reporting Trials) flow diagram. CU: cannabis use; LFU: lost to follow up.

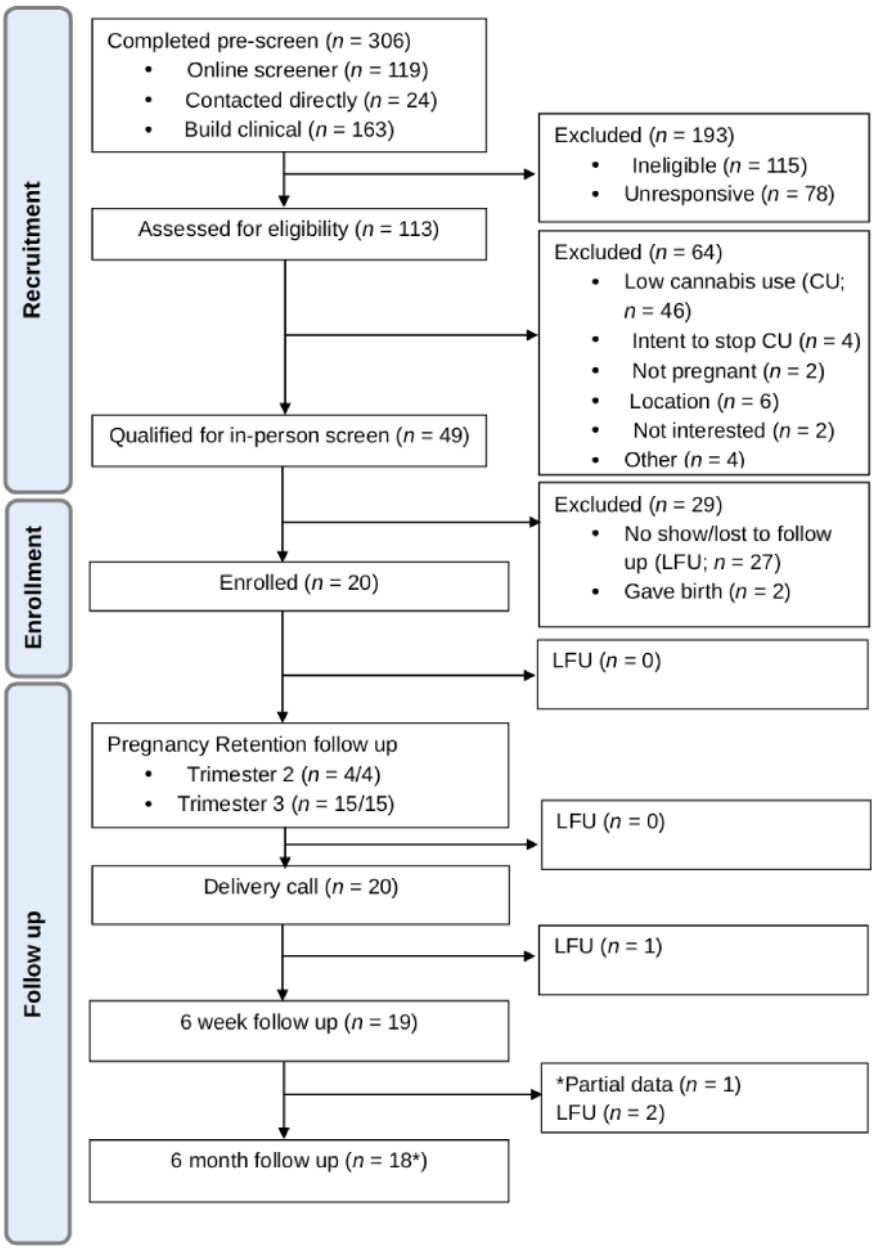

Discussion

Overview

This protocol study used a multimethod approach to examine the daily and longitudinal impact of perinatal cannabis use on PPD and the mother-infant relationship. Perinatal cannabis use is increasingly common [62] yet has been linked to heightened risk of adverse maternal mental health outcomes [15]. Similarly, PPD remains one of the most prevalent complications of childbirth, with implications not only for maternal well-being but also for early caregiving and infant socioemotional development [5]. Obtaining repeated measures across the prenatal and postpartum periods allows for a rigorous evaluation of the longitudinal impact of cannabis use on depressive symptoms during a time of heightened vulnerability for maternal mental health.

Preliminary results indicated that retention rates approached 100% and EMA compliance rates exceeded those observed in nonpregnant populations (ie, >80% across all EMA bursts). These high rates, suggestive of strong feasibility and acceptability, demonstrate the ability to successfully implement a rigorous study procedure that captures both momentary and cumulative associations between cannabis use and PPD, as well as downstream effects on the mother-infant relationship. Pending analyses resulting from these data are thus well-positioned to provide preliminary evidence on how cannabis use may shape depressive symptoms in-the-moment and over time across the postpartum period.

Study Implications

This study advances current research by introducing several key innovations that enhance our understanding of the relationship between cannabis use, PPD, and mother-child bonding or interactions. First, the study uses an ecologically

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valid methodology by using EMA to investigate the impact of cannabis use on PPD and mother-child interactions within real-world environments. Traditional between-person designs are not suited to capturing dynamic, within-person effects across varying contexts and over time, as is possible here. By adopting EMA methods, this study addresses calls for research that explores caregiver-child interactions in natural settings, offering a more authentic and nuanced perspective [37]. Further, we identified compliance rates higher than standard substance use EMA studies [63], suggesting excellent feasibility of these methods in perinatal populations. Second, this study is the first to explore the impact of cannabis use on key markers of quality of the mother-infant relationship and how these may contribute to maternal depression in a potentially cyclical manner. Understanding this directional association will provide essential preliminary data to inform future longitudinal research examining these dynamics over extended periods of child development. Finally, the study integrates a multimethod assessment approach by combining ambulatory assessment with laboratory and self-reported measures to evaluate mother-child interactions comprehensively. This approach captures the complexity of parenting behaviors in real-world contexts, which has not been achieved in previous studies. Together, these innovations will generate critical insights into how cannabis use and PPD influence mother-child interactions, laying the groundwork for future research and potential interventions.

Limitations

This study has limitations that should be considered. First, the inclusion of participants who use other substances, such as alcohol and tobacco, may complicate the parsing of individual substance effects. However, since the study does not focus on substance-specific outcomes (eg, metabolism), this approach aligns with the reality of perinatal polysubstance use and improves generalizability. Second, the lack of a comparison group is a limitation driven by the scope of the current project. Inclusion of a control group, which is the next step for this work, would allow for direct comparisons between mothers who use cannabis and those who do not, providing a clearer understanding of the specific impact of cannabis use on PPD and the mother-child relationship. This comparison would help isolate the effects of cannabis from other confounding variables, such as general perinatal stress. Third, the study does not assess parenting behaviors while mothers are acutely under the influence of cannabis. While this research provides valuable insights into the momentary relationship between cannabis use, PPD, and eventual mother-child interactions, it does not directly examine the immediate, short-term effects of cannabis use on maternal behavior and caregiving in real-time. For instance, cannabis may affect emotional regulation, attentiveness, and responsiveness during critical caregiving moments, which could have important implications for child development and maternal mental health. Future research could address this gap by investigating how acute cannabis use influences maternal behaviors and interactions with the infant, in real-time, as well as the potential for short-term disruptions in mother-child bonding or engagement during cannabis intoxication. Fourth, the large battery of assessments related to the parent study may limit generalizability to samples for whom this level of observation may represent a significant burden. Future studies expanding this work should consider the population of interest fully when determining study assessments. Finally, we opted not to exclude participants using prescribed antidepressants. The inclusion of participants using antidepressants may make it challenging to disentangle the effects of medication from those of cannabis use on PPD. However, excluding these participants would significantly limit the generalizability of the findings to real-world populations in which antidepressant use is common.

Conclusions

This study offers a significant step forward in understanding the relationship between cannabis use, PPD, and critical aspects of the mother-child relationship in real-world contexts. By using naturalistic and laboratory methods, the study captures both the dynamic and nuanced nature of maternal behavior and mood in natural environments, as well as in tightly controlled settings. Ultimately, this work lays the groundwork for developing targeted interventions to support maternal well-being and healthy early relationships between mothers and their children.

Acknowledgments

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Data Availability

Data will be deposited in a publicly available repository.

Authors' Contributions

LM contributed to conceptualization, data curation, funding acquisition, investigation, methodology, project administration, and writing the original draft. LH contributed to project administration and writing the original draft. CB and JM contributed to

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funding acquisition, investigation, methodology, and reviewing and editing the original draft. RLG contributed to conceptualization, data curation, funding acquisition, investigation, methodology, project administration, and writing the original draft.

Conflicts of Interest

LM is a founder of Ember Therapeutics, which is developing digital therapeutics to prevent postpartum smoking relapse. This work does not conflict with the research described here. All other authors declare no conflicts of interest.

Multimedia Appendix 1
CADRE Core measures administered in this project.
[DOCX File , 24 KB - resprot_v14i1e71302_app1.docx]

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Abbreviations

CADRE: Center for Addiction Disease Risk Exacerbation
CONSORT: Consolidated Standards of Reporting Trials
DSM-IV: Diagnostic and Statistical Manual of Mental Disorders (Fourth Edition)
EMA: ecological momentary assessment
ICD-10: International Statistical Classification of Diseases and Related Health Problems, Tenth Revision
LMEM: linear mixed-effect model
MINI: Mini-International Neuropsychiatric Interview
PASS: Perinatal Anxiety Screening Scale
PPD: postpartum depression
TLFB: Timeline Followback

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Protocol

Student Acceptance of Digital Entrustable Professional Activities: Protocol for a Cohort Study

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Abstract

Background: Integrating digital entrustable professional activities (EPAs) and simulations in medical education represents a substantial shift toward competency-based learning. This approach focuses on developing specific skills through manageable units and enhancing proficiency in high-stakes environments. The technology acceptance model provides a framework to evaluate the adoption of these educational technologies, emphasizing the roles of perceived usefulness and ease of use.

Objective: This cohort study aims to investigate the acceptance of digital EPAs among medical students within simulated training environments. It seeks to understand how perceived usefulness and ease of use influence this acceptance, guided by the principles of the technology acceptance model.

Methods: The cohort study will involve medical students in the clinical phase of their education at Ludwig Maximilians University Munich. The survey, distributed through the Module-6 distributor, will capture their perceptions of digital EPAs. The data will be analyzed using regression analysis.

Results: Data collection is anticipated to be complete by April 2025, with analysis concluded by May 2025. The results will provide insights into students' attitudes toward digital EPAs and their willingness to integrate these tools into their learning.

Conclusions: This study will contribute to the understanding of digital EPAs' role in medical education, potentially guiding future design and implementation of these tools. While highlighting the importance of perceived usefulness and ease of use, the study also acknowledges limitations in sample size and recruitment methodology, indicating the need for further research with more diverse and larger groups. This research is poised to shape future medical training programs, aligning with the evolving landscape of medical education.

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KEYWORDS

medical education; entrustable professional activities; EPAs; digital EPAs; technology acceptance model

Introduction

Background

The concept of entrustable professional activities (EPAs) has changed the approach to medical education, shifting the focus toward competency-based learning. They cover core functions like educational theory, curriculum design, and assessment while also addressing emerging areas such as self-development and technology use in health care education [1]. EPAs are designed to break down complex medical skills into manageable units, allowing learners to gain proficiency in specific tasks progressively [1]. This methodology has been instrumental in ensuring that medical trainees are adequately prepared for the responsibilities they will face in their professional lives while empowering teaching staff to maximize the learning outcomes of their students [2].

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Complementing EPAs, the use of simulations in medical training has become increasingly important. These simulations provide realistic, interactive environments where students can practice and hone their skills without the risks associated with real-life clinical settings. As highlighted by Chernikova et al [3] and Smetana and Bell [4], computer-based simulations, in particular, offer dynamic representations of real-world medical scenarios. These tools are invaluable for developing both the cognitive decision-making and motor skills essential in the medical field.

However, despite the advancements in and the separate explorations of EPAs and simulations, the combination of these two into a digital format, more specifically digital EPAs, remains largely unexplored. While both EPAs and simulations have been part of extensive research efforts individually, their integration into a digital EPA format offers a new development for these two teaching methods [1,3,4]. Yet digital EPAs and their acceptance among learners and educators remains largely unexamined [5].

In understanding the adoption and effectiveness of these educational technologies, the technology acceptance model (TAM) offers valuable insights. Introduced by Davies [6] and further explored by Marangunić and Granić [5], the TAM posits that perceived ease of use and usefulness are critical factors influencing the acceptance and integration of new technologies in learning environments. This model has been widely applied in various contexts to understand how users come to accept and use technological tools in their work.

The aim of this study is therefore to identify how well students perceive the usefulness of digital EPAs as well as their ease of use. In addition, we will investigate whether this perception influences students' intention of using digital EPAs in their studies.

EPAs in Medical Education

EPAs, as a didactic concept, focus on competency-based curricula to help students acquire specific competencies, potentially contributing to a more flexible duration of training [1]. They are characterized by a gradual reduction of supervision until learners can perform tasks completely independently [7]. This development occurs over five stages, starting with mere presence and observation to the independent guidance of younger learners [1,8]. EPAs represent specific professional activities distinguishing them from conventional learning objectives [2]. A competency-oriented teaching method could reduce the training duration for faster-learning medical students without compromising the quality of education [9]. Such a system could benefit not only medical students but also the teaching staff, program developers, and medical institutions, as well as other employees, by clearly defining which tasks can be performed with what degree of autonomy [1,2,10].

Digital EPAs

Simulations, as interactive representations of real-world scenarios, play a crucial role in the acquisition of complex skills. Simulation-based learning, as demonstrated by Chernikova et al [3] in their 2020 meta-analysis, is a highly effective approach to designing learning environments in higher education and can be beneficial from the beginning of study programs for students at all levels. Simulations provide an effective medium for developing complex skills, such as those required in surgery, combining theoretical knowledge with practical expertise, such as seen in spinal surgery [11]. In combination with the concept of EPAs, as gradually increasing levels of clearly defined competencies, this suggests complementing real-life training with training in simulations. These simulations would need to precede real-life training by allowing students to practice the same competencies (digital EPAs). Systematic use of these digital EPAs could potentially substantially increase the quality of and reduce the time required for real-life training, which is often cost-intensive or requires rare and critical situations (eg, high-stakes operations).

However, such a shift in education would need to be accepted by all stakeholders (ie, medical educators, medical students, and patients).

The TAM

The TAM has significantly influenced the understanding of technology adoption and use [5]. This model's foundation was built on two critical factors: perceived usefulness and perceived ease of use [5]. These factors are pivotal in shaping users' attitudes and intentions toward adopting technology. Davies' [6] original model proposed that users' motivation to use a system is influenced by these two beliefs [5]. Perceived usefulness reflects the degree to which a person believes that using a specific system would enhance their job performance [12]. Perceived ease of use refers to the belief that using a particular system would be effortless [12]. The interaction between these two beliefs plays a critical role in determining the user's attitude toward the system and, consequently, their actual use behavior [6].

The significance of the TAM extends beyond traditional technologies and has proven to be indispensable, especially in designing user-friendly and effective technology-based learning systems. In a world where digital technologies are increasingly coming to the forefront, TAM remains a critical framework for researchers and practitioners to predict and understand user behavior toward new technological advancements.

This Study

In this cohort study, we will focus on medical students, investigating how well they perceive the usefulness of digital EPAs as well as their ease of use in medical education. In addition, we will investigate whether this perception influences students' intention of using digital EPAs in their studies. Since this teaching concept is largely unfamiliar to students, they are first presented with a written EPA, followed by a digital version, which the questionnaire will refer to. The example EPA, as well as the digital EPA, can be accessed via Open Science Framework (OSF) [13].

Methods

Recruitment Plans and Study Population

The study population for this cohort study will consist of medical students in the clinical phase of their studies. This cohort is optimally suited for the application of digital EPAs,

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as these are aimed at learning specific skills, which is the core of the clinical phase of medical studies. The plan is to distribute the survey link through the major study distribution lists of Ludwig Maximilians University Munich, such as the Module-6 distributor. This would ensure that only students in the clinical phase participate in the survey. In addition, students would have the flexibility to complete the questionnaire at their convenience.

Inclusion Criteria

Medical students must be at least in their third year of medical training. This ensures that the preclinical foundational subjects, such as macroscopic and microscopic anatomy, physiology, biochemistry, and medical psychology, have already been completed. In addition, they must have passed their first medical state examination.

Exclusion Criteria

Reasonable command of the German language is required to participate in this study.

Data Analysis Plans

A regression analysis will be performed assuming a moderate effect size. Furthermore, an α level, common in social sciences, of .05 was chosen. The statistical power of the study was set standardly at P=.80. To calculate the necessary sample size for these specific parameters, the software G*Power 3.1 [14] was used. This calculation indicated that a sample size of 68 participants is required to meet the above criteria. To provide additional security and account for possible dropouts, a margin of 10% will be added to the calculated sample size. This means that a total of 75 participants should be recruited for the study. Assuming a response rate of approximately 25% (based on previous experiences), we will contact 300 students (about 25% of all viable students at Ludwig Maximilians University Munich) via email.

Questionnaire and Hypotheses

Overview

The basis for the conception of the questionnaire is the research work by Abdul Ghani et al [15], which used the TAM as a foundation for evaluating digital game-based learning. The questionnaire was only adapted to the context of digital EPAs. The entire questionnaire can be found on OSF [13]. Both the German translation shown to the participants and an English version of the questionnaire can be found there. The hypotheses below were formulated based on the TAM and are to be explored through the questionnaire.

Construct: Perceived Usefulness

Operational Definition

Perceived usefulness [6] reflects students' perception of whether the use of digital EPAs in a simulated environment will enhance their performance (independent variable).

Hypothesis

The more useful medical students find digital EPAs in medical simulations, the higher their behavioral intention to use this technology as part of their studies will be.

Construct: Perceived Ease of Use

Operational Definition

Perceived ease of use [6] refers to a student's perception that using digital EPAs for learning skills during their medical studies will require minimal effort (independent variable).

Hypothesis

The easier medical students find the operation of digital EPAs in medical simulations to be, the greater their behavioral intention to use this technology will be.

Construct: Attitude

Operational Definition

Attitude [6] refers to student's judgment on whether the use of digital EPAs is beneficial to them (independent variable).

Hypothesis

The more positive the attitude of medical students toward digital EPAs in medical simulations is, the higher their behavioral intention to use this technology will be.

Construct: Behavioral Intention (Operational Definition)

Behavioral intention [6] refers to a student's intention to theoretically use digital EPAs for their studies during the clinical phase of medical school if they were to be offered.

Due to the construct of the TAM, "Behavioral Intention" is highly influenced by "Perceived Usefulness" and "Perceived Ease of Use," making it the dependent variable.

Digital EPAs

Due to the unfamiliar teaching concept of EPAs for students, as well as the digital EPAs, a formulated EPA and its digital counterpart were created based on a paper by Ten Cate and Taylor [1]. The digital EPA merely represents a theoretical implementation of the previously formulated EPA for students in the future. It cannot yet be tested digitally in this form and can, therefore, only be presented to students conceptually in the form of continuous text. The complete description of the EPA and the digital EPA can be found on OSF [13]. Additionally, there is both a German and an English version for the same reasons as with the above questionnaire.

Ethical Considerations

Ethics approval by the host university is pending. The study will only be conducted once it is granted.

Results

The data collection of this study is expected to be completed by the end of April 2025. Following this, data analysis is to take place, which is to be completed by May 2025, following the reporting standards of the *Journal of Medical Internet Research* for statistics.

All data, in anonymized form, and the code for analysis will be uploaded to the project's OSF repository.

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Discussion

This study hypothesized that the higher students' PU and PEU are, the higher their behavioral intention to use will be and that this relationship would lead to higher actual system use [6].

The basis for our study is, on the one hand, the increasing emergence of EPAs in medical curricula as well as in specialist training and continuing education and, on the other hand, the widespread use of digital simulations [1,3,4]. The merging of both concepts remains relatively unexplored and can only be considered a successful development of traditional EPAs if this concept is also accepted by the learners themselves. Using the tried and tested TAM model, a meaningful evaluation of this situation will be made [5]. Since digital EPAs can increasingly contribute to medical training improvement, our findings are to be considered as a starting point for the design and implementation of these didactic tools so that more effective implementation and more engaged use among learners can be promoted in the future.

Nevertheless, our study must be viewed in light of some limitations. The sample size and the methodology of recruitment could limit the generalizability of the results. Future studies should involve larger and more diverse groups of medical students to gain a more comprehensive understanding of acceptance factors. In addition, investigating the long-term effects of digital EPAs on learning outcomes could provide valuable insights.

In summary, this study should serve as a starting point for more extensive research projects so that factors influencing the acceptance of digital teaching technologies in medicine, particularly digital EPAs, can be comprehensively investigated. By emphasizing the importance of usefulness and ease of use for the acceptance and use of digital EPAs, our study opens new perspectives for the design of effective and engaging medical training programs that meet both the needs of the students and the requirements of a constantly changing medical training landscape.

Acknowledgments

MD has received funding during the research for this paper from the "Promotionsstipendium" of the medical faculty of the Ludwig Maximilians University Munich.

Data Availability

All data will be made available in anonymized form on the Open Science Framework repository after completion of the study.

Authors' Contributions

MD was responsible for the visualizations and writing of the initial draft, including substantive translation. CR and MS extensively contributed to the writing process by reviewing and editing the initial draft. Further, MS had the role of supervisor for the project as well as project administration. All authors read and approved the final manuscript.

In preparing this manuscript, a generative artificial intelligence (AI) tool (ChatGPT-4o, version February 2024, OpenAI) was used solely for language enhancement and stylistic refinement. No content generation, data analysis, or research-related functions were performed by AI. The authors retain full responsibility for the originality, accuracy, and integrity of the scientific content presented in this paper. All intellectual contributions and findings are the result of the authors' independent work.

Conflicts of Interest

None declared.

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Abbreviations

EPA: entrustable professional activity
OSF: Open Science Framework
TAM: technology acceptance model

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Corrigenda and Addenda

Correction: Disaster Preparedness Intervention for Older Adults (Seniors' Positive Involvement in Community Emergencies): Protocol for a Quasi-Experimental Study

Sharon White-Lewis[1*], RN, MSN, PhD; Joseph Lightner[1*], MPH, PhD; Julia Crowley[1*], AICP, PhD; Amanda Grimes[1*], MCHES, PhD; Kathleen Spears[2*], PhD; Steven Chesnut[1*], PhD

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Related Article:

Correction of: https://www.researchprotocols.org/2024/1/e58895

(JMIR Res Protoc 2025;14:e71160) doi:10.2196/71160

In "Disaster Preparedness Intervention for Older Adults (Seniors' Positive Involvement in Community Emergencies): Protocol for a Quasi-Experimental Study" JMIR Res Protoc 2024;13:e58895) the authors made one correction.

The last name of author JC, "Crowely", has been revised to "Crowley".

The correction will appear in the online version of the paper on the JMIR Publications website on January 16, 2025 together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: Methodology for the Positive Voices 2022 Survey of People With HIV Accessing Care in England, Wales, and Scotland: Cross-Sectional Questionnaire Study

Janey Sewell[1*], PhD; Carole Kelly[2*], MSc, PGCert; Adamma Aghaizu[2], PhD; Hannah Kitt[2*], MSc; Annegret Pelchen-Matthews[1], PhD; Veronique Martin[2], PhD; Amal Farah[2]; Colette Smith[1], PhD; Alison Brown[2], PhD; Clare Humphreys[2], MSc; Alex Sparrowhawk[3], BA; Valerie Delpech[2,4], Dr Med; Alison Rodger[1,5], Prof Dr Med; Fiona Lampe[1*], Prof Dr; Meaghan Kall[2*], MSc

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Related Article:

Correction of: https://www.researchprotocols.org/2025/1/e58531

(JMIR Res Protoc 2025;14:e72512) doi:10.2196/72512

The paper "Methodology for the Positive Voices 2022 Survey of People With HIV Accessing Care in England, Wales, and Scotland: Cross-Sectional Questionnaire Study" published in JMIR Res Protoc 2025;14:e58531) had a few errors. Hence, the following edits have been made (changes italicized).

In the **Abstract,** the following subsections had a few sentences modified, as follows:

- Objectives: "This paper aimed to describe the methodology, recruitment strategies, and *key demographic* features of participants…"
- Methods: "…At the start of 2023, due to under-recruitment mainly due to the impact of the monkeypox (Mpox) outbreak, a separate sequential recruitment strategy was initiated in *14 of the largest clinics* to increase participant numbers."
- Results: "…The median age of participants was 52 years, 3428 of participants were men, 2991 were *White*, and 1121 were *Black*."

In the **Introduction** section, the following paragraphs have been revised, as follows:

- "High levels of perceived and internalized stigma associated with *HIV status are experienced* by people with HIV, impacting their mental health…
- PV is a cross-sectional *questionnaire study of people with HIV who receive HIV specialist care in England, Wales, and Scotland, which is carried out every 3-5 years…*
- Our paper aims to describe the methodology and study design of the second round of the *study: Positive Voices 2022 (PV2022)."*

In **Methods** section, the first column of ***Table 1*** has been edited to improve readability and clarity.

The following incorrect values were updated in ***Table 2***:

- The number of Positive Voices 2022 participants was changed from *4620* to *4622*.
- "Age group (years)" category: The percentage of participants in the 55-64 subcategory was changed from *30.2* to *30.3*.

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- "Gender" category: The number and percentage of participants in the "Prefer not to say *and unknown*" subcategory was changed from *34 (0.7)* to *36 (0.8)*.
- "Ethnic group" category: The number and percentage of participants in the "Other (including prefer not to say and unknown)" subcategory was changed from *176 (3.8)* to *178 (3.9)*.
- "Year of diagnosis" category: The number of participants in the "2019-2023" subcategory was changed from *213* to *214*.
- "Year of diagnosis" category: The number of participants in the "2014-2018" subcategory was changed from *800* to *801*.
- Footnote "a" was assigned to the "Age group (years)" category and was updated from *Missing sociodemographic information for 2 participants* to *Age was missing for 2 participants.*

A few abbreviations have been introduced for better readability. These have also been added to the abbreviations list at the end of the article.

A few additional changes have been listed below:

- Under Study Design:
  "The questionnaire data were linked to clinical data on antiretroviral therapy (ART), HIV viral load, and CD4 *lymphocyte* count from the HIV and AIDS reporting system (HARS)…"
- Under Setting:
  "178 HIV clinics in the country, returned an expression of interest, *98* % of whom were in England (99/101)…"
- Under Sample Size:
  "HARS was used as a sampling frame to *provide a representative*, random sample of people with *HIV within each participating clinic, who* could be approached to participate in the PV2022 survey. HARS is a surveillance database held at the UKHSA that consists of pseudonymized data on the demographic, clinical, and *treatment characteristics* of people with HIV that is reported each quarter year by all HIV service providers in England…
  …Therefore, considering this, a sample list of 17,121 patients was created *with the assumption* that approximately 14,400 would be recruitable. …the PV2022 response rate was expected to be between 30% and 50%, resulting in 4320 *to* 7200 participants being recruited. … ±1.4% and ±1.1% *(with 95% confidence)* for the response rates of 30% and 50%, respectively."
- Under Study Management:
  "PV2022 was a collaboration between the University College London (UCL) NICHE *team, the UKHSA HIV national surveillance team, and a NICHE Patient and Public Involvement representative. "A Person-Centered Needs Informed Model of Care for People with HIV" (NICHE)* is a National Institute for Health Research (NIHR) funded program..."
- Under Questionnaire Development:
  "…These included demographic and socioeconomic factors, HIV related factors, comorbidities, met and unmet health, social and welfare *service* needs, quality of life measured by EQ-5D-5L, *height and weight*, smoking and alcohol status *by the Alcohol Use Disorders Identification Test-Consumption (AUDIT-C)*, recreational drug use and general practice (GP), and HIV clinic satisfaction, enabling assessment of trends over time in these factors…
  …New items included in the PV2022 questionnaire included… a modified version of the *Duke-UNC (University of North Carolina)* Functional Social Support Questionnaire…
  Questions on stigma and discrimination were expanded to take account of internalized *and other* stigma and included an adapted validated stigma scale [27]. In addition, participants *who* completed the study online in PV2022 were able to opt-in to complete "Positive Outcomes," an HIV Patient Reported Outcome Measure (PO-PROM), a tool designed for use in clinical settings to assess *the needs and concerns of* people with HIV…"
- Under Study Documents:
  "...a password-protected study log that listed each clinic's sample list of *randomly selected* participants. ... and unique identifier displayed on the outside, as well as the patient information leaflet, *questionnaire*, a freepost..."
- Under Linkage:
  "Data on ART *use*, the most recent CD4 lymphocyte count,..."
- Under Ethical Considerations:
  "All participants received a digital gift voucher for 5 GBP (*equivalent to* US $6.50)..."

In the **Results** section, the following sentences have been edited:

- Under Response Rate:
  "...the original preselected participant recruitment strategy (*49%*, Figure 1). Of the 930 sequentially recruited participants, 906 were able to be matched to HARS: 222 (*25%*) of these had initially been preselected to take part in the survey.
  Men had a higher response rate (60%) (3428 completed out of 5715 accepted or declined) compared with women (1124/2580, 44%) and *White people* had a higher response rate (2991/4724, 63%) compared with *Black African people* (983/2380, 41%) *or those of* other ethnicities (648/1158, 56%)."
- Under Age, Gender, *and Ethnic* Distribution of PV2022 Participants:
  "The median age of PV2022 participants (n=4620) was *52 (IQR 43-60) years, and about* 3 quarters of participants had been diagnosed with HIV more than 10 years ago (Table 2). Nearly a quarter of participants were women (24%) and over a fifth (21%) of participants were *Black African people* (Table 2).
  A total of *67* PV2022 participants identified as transgender or gender diverse...
  Compared with the national population of people accessing HIV care, *Black African individuals were underrepresented in the PV2022 sample (10% lower)*, and *White* participants were overrepresented (13% higher; Figure 2)...

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Participants from the sequential recruitment route were younger compared to the preselected random recruitment strategy (median age 49 (IQR 39-57) years versus 53 (IQR 45-60) years, for sequential versus random recruitment respectively), overrepresented men (85% vs 72%) and White people (67% vs 64%) and underrepresented Black African people (14% vs 23%).

A higher proportion of *participants who completed the online questionnaire were White compared to participants who completed the paper questionnaire (67% online vs 63% paper*; Figure 1 and Multimedia Appendix 2)."

In the **Discussion** section, the following edits were made:

- Under Principal Findings:
  "…The pandemic exacerbated inequalities in health and access to health care, particularly amongst those living in economic hardship [38] and for *Black African individuals and those of other* minority ethnic groups [39], and the HIV population consists of a high proportion of these groups.
  Strengths of PV2022 include the large sample size, the inclusion of a broadly representative sample of 1 in 20 people with HIV in *England, Scotland and Wales* (as evidenced by comparison with the national HARS database) and the linkage of participant self-reported questionnaire data to HIV clinical data from HARS.
  ..., whose mental and physical health, and experiences of *health* care, may be different and valuable for informing and improving HIV specialist services.
  Findings from PV2022 informed the development of the intervention for the "Psycho-Social Intervention for People With HIV–Evidence From a Randomised Evaluation" *(SPHERE)* trial, which commenced in United Kingdom HIV clinics in August 2024."

The correction will appear in the online version of the paper on the JMIR Publications website on February 27, 2025, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: ENABLE—App-Based Digital Capture and Intervention of Patient-Reported Quality of Life, Adverse Events, and Treatment Satisfaction in Breast Cancer: Protocol for a Randomized Controlled Trial

Thomas M Deutsch[1], Dr med; Léa L Volmer[2], Dr med; Manuel Feisst[3], Dr sc hum; Laura Bodenbeck[1], Dr med; Kathrin Hassdenteufel[1], Dr med; Lara Tretschock[1], Dr med; Christiane Breit[1], MD; Stefan Stefanovic[4], Prof Dr med; Armin Bauer[5], PhD; Carolin Anders[6,7], MSc; Lina Weinert[6,8], MSc; Tobias Engler[2], Dr med; Andreas D Hartkopf[2], Prof Dr med; Nico Pfeifer[9,10], Prof Dr; Pascal Escher[9,10], Prof Dr; Marc Mausch[9,10,11], Dipl Phys; Oliver Heinze[12], Prof Dr; Marc Suetterlin[4], Prof Dr med; Sara Y Brucker[2], Prof Dr med; Andreas Schneeweiss[13,14], Prof Dr med; Markus Wallwiener[15], Prof Dr med

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Related Article:

Correction of: https://www.researchprotocols.org/2025/1/e69855

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In “ENABLE—App-Based Digital Capture and Intervention of Patient-Reported Quality of Life, Adverse Events, and Treatment Satisfaction in Breast Cancer: Protocol for a Randomized Controlled Trial” (JMIR Res Protoc 2025;14:e69855) the authors noted one error.

The following affiliation of authors Carolin Anders and Lina Weinert:

> *"Rhein Main University of Applied Sciences, Wiesbaden, Germany"*

Has been revised to:

> *"Institute of Medical Informatics, Heidelberg University, Heidelberg, Germany"*

The correction will appear in the online version of the paper on the JMIR Publications website together with the publication of

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this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: Optimizing a Personalized Health Approach for Virtually Treating High-Risk Caregivers of Children With Neurogenetic Conditions (Project WellCAST): Protocol for a Randomized Controlled Trial

Bridgette Kelleher[1], PhD; Kaleb Emerson[1], BS; Lyndsey N Graham[1], PhD; Veronika Vozka[1], MS; Anne Wheeler[2], PhD; William Fadel[3], PhD; Daniel Foti[1], PhD; Isha Metzger[4], PhD; Mandy Rispoli[5], PhD; Wendy Machalicek[6], PhD; Laurie McLay[7], PhD; Sean Lane[8], PhD; Wei Siong Neo[1], PhD; Allie Carter[3], MS; Lisa Brown[1], MS; Jennifer Brown[1], PhD; Laura Lee McIntyre[6], PhD; Elizabeth Salwitz[1], BS; Gloria Dietz[1], BS; Riley Naughton[1], BS; Katlyn Peek[1]; Nicole Hollins[5], PhD; Emma Woodford[9], PhD

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Related Article:

Correction of: https://www.researchprotocols.org/2025/1/e64360

(JMIR Res Protoc 2025;14:e80023) doi:10.2196/80023

In "Optimizing a Personalized Health Approach for Virtually Treating High-Risk Caregivers of Children With Neurogenetic Conditions (Project WellCAST): Protocol for a Randomized Controlled Trial" (JMIR Res Protoc 2025;14:e64360) the authors noted one error.

In Table 1, "Study" column, reference 55 was mistakenly cited as

Kanady and Harvey [55]

This has now been corrected to

Durand [55]

The correction will appear in the online version of the paper on the JMIR Publications website, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Correction: Optimizing a Personalized Health Approach for Virtually Treating High-Risk Caregivers of Children With Neurogenetic Conditions (Project WellCAST): Protocol for a Randomized Controlled Trial
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Corrigenda and Addenda

Correction: Associations Among Diet, Health, Lifestyle, and Gut Microbiota Composition in the General French Population: Protocol for the Le French Gut – Le Microbiote Français Study

Chloe Connan[1*]; Sébastien Fromentin[1*]; Mourad Benallaoua[2]; Anne-Sophie Alvarez[1]; Nicolas Pons[1]; Benoît Quinquis[1]; Christian Morabito[1]; Julie-Anne Nazare[3]; Elise Borezée-Durant[1,4]; Le French Gut Consortium[5]; Florence Haimet[1,6]; Stanislav Dusko Ehrlich[1]; Karine Valeille[1]; Alexandre Cavezza[1]; Hervé Blottière[1,7]; Patrick Veiga[1,4]; Mathieu Almeida[1]; Joël Doré[1,4]; Robert Benamouzig[2]

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Related Article:

Correction of: https://www.researchprotocols.org/2025/1/e64894

(JMIR Res Protoc 2025;14:e80127) doi:10.2196/80127

In "Associations Among Diet, Health, Lifestyle, and Gut Microbiota Composition in the General French Population: Protocol for the Le French Gut – Le Microbiote Français Study" ([JMIR Res Protoc 2025;14:e64894]) several errors appeared in the published version related to the group authorship of Le French Gut.

1. The affiliations of contributors from public institutes and private companies were omitted in the published version and have been included in the corrected version as:

> *Monique Axelos (INRAE), Sylvie Binda (Lallemand Health Solutions), Pierre Cressard (Nahibu), Anne-Marie Davila-Gay (Université Paris-Saclay, AgroParisTech, INRAE, UMR PNCA), Christophe d'Enfert (Institut Pasteur, INRAE), Assia Dreux-Zigha (Greentech), Erik Eckhardt (DSM-Firmenich), Etienne Formstecher (GMT Science), Maiana Houssaye (INSERM), Milan Lazarevic (APHP), Sophie Legrain (Lesaffre), Oana Bernard (Biocodex), Benoît Fouchaq (Biofortis), Pedro H. Oliveira (Génomique Métabolique, Genoscope, Institut François Jacob, CEA, CNRS, Université d'Évry, Université Paris-Saclay), Raish Oozeer (Danone Nutricia Research), and Karine Roget (NexBiome Therapeutics).*

2. The list of names under the Le French Gut Consortium in the "Authors' Contributions" section were revised as follows:

> *Françoise Levacon and Marie-Emmanuelle Le Guern*

were replaced with

> *Benoît Fouchaq and Oana Bernard, respectively*

3. The location "Gif-sur-Yvette" was incorrectly listed in the affiliation for the Le French Gut consortium and has been removed in the corrected version.

The correction will appear in the online version of the paper on the JMIR Publications website, together with the publication

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of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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©Chloe Connan, Sébastien Fromentin, Mourad Benallaoua, Anne-Sophie Alvarez, Nicolas Pons, Benoît Quinquis, Christian Morabito, Julie-Anne Nazare, Elise Borezée-Durant, Le French Gut Consortium, Florence Haimet, Stanislav Dusko Ehrlich, Karine Valeille, Alexandre Cavezza, Hervé Blottière, Patrick Veiga, Mathieu Almeida, Joël Doré, Robert Benamouzig. Originally published in JMIR Research Protocols (https://www.researchprotocols.org), 14.07.2025. This is an open-access article distributed under the terms of the Creative Commons Attribution License (https://creativecommons.org/licenses/by/4.0/), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work, first published in JMIR Research Protocols, is properly cited. The complete bibliographic information, a link to the original publication on https://www.researchprotocols.org, as well as this copyright and license information must be included.

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Corrigenda and Addenda

Correction: Effect of Live Environmental Music Therapy and Prerecorded Music on State Anxiety, Stress, Pain, and Well-Being Levels of Patients and Caregivers in the Emergency Department Waiting Room: Protocol for a Multicenter Randomized Clinical Trial

Angélica Hernández[1,2], MagMT; Ana María Díaz[2,3], MMT; Ornella Fiorillo Moreno[3], PhD; Raúl Suárez[2,3]; Moshé Amarillo[4], MS; Ana María Moreno[1], MA; Bryan Alonso Ríos Suarez[1], BA; Lina Marcela Gómez González[1], BA; Guiselle Alexandra Cristancho Olaya[1], MD; Mark Ettenberger[1,2], PhD

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Related Article:

Correction of: https://www.researchprotocols.org/2025/1/e69131

(JMIR Res Protoc 2025;14:e80077) doi:10.2196/80077

In "Effect of Live Environmental Music Therapy and Prerecorded Music on State Anxiety, Stress, Pain, and Well-Being Levels of Patients and Caregivers in the Emergency Department Waiting Room: Protocol for a Multicenter Randomized Clinical Trial" (JMIR Res Protoc 2025;14:e69131), the authors noted one error:

In the originally published paper, reference 27 appeared as:

> *Reger DL, Little CA, Rheingold AL, Lam M, Liable-Sands LM, Rhagitan B, et al. A synthetic, structural, magnetic, and spectral study of several [Fe[tris(pyrazolyl)methane]2](BF4)2 complexes: observation of an unusual spin-state crossover. Inorg Chem. 2001;40(7):1508-1520. doi: 10.1021/ic001102t. Medline: 11261958*

This has been corrected to:

> *Chlan L, Savik K, Weinert C. Development of a shortened state anxiety scale from the Spielberger State-Trait Anxiety Inventory (STAI) for patients receiving mechanical ventilatory support. J Nurs Meas. 2003 Winter;11(3):283-93. doi: 10.1891/jnum.11.3.283.61269. PMID: 15633782*

The correction will appear in the online version of the paper on the JMIR Publications website, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: Factors Affecting the Receptiveness of Chinese Internists and Surgeons Toward Artificial Intelligence–Driven Drug Prescription: Protocol for a Systematic Survey Study

Qiujin Shen[1,2*], PhD; Xiaowen Gong[1,2*], MS; Wei Zhang[1,2*], MS; Yu Hu[1,2*], MD; Yueshen Ma[1,2], MS; Ziyi Ren[1,2], MPH; Sichang Liu[1,2], MD; Zhen Song[1,2], MS; Robert Peter Gale[3], MD, PhD; Jinyu Wang[1,2*], MD; Junren Chen[1,2*], MD, PhD

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Related Article:

Correction of: https://www.researchprotocols.org/2025/1/e76009/

(JMIR Res Protoc 2025;14:e83537) doi:10.2196/83537

In “Factors Affecting the Receptiveness of Chinese Internists and Surgeons Toward Artificial Intelligence–Driven Drug Prescription: Protocol for a Systematic Survey Study” (JMIR Res Protoc 2025;14:e76009) the authors noted one error.

In Textbox 1, under both forced-choice questions, the first option:

≤1 to 3

Has been revised to:

≤1

And the following option has been added underneath the first option:

1.1 to 3

So that Textbox 1 now reads as follows:

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Textbox 1. Forced-choice questions in the survey questionnaire.

I anticipate ≥1 physician (possibly, including myself) at my hospital will become ready to use AI to prescribe a drug within _____ years.

- ≤1
- 1.1 to 3
- 3.1 to 5
- 5.1 to 10
- >10
- Never

I anticipate I myself will become ready to use AI to prescribe a drug within _____ years.

- ≤1
- 1.1 to 3
- 3.1 to 5
- 5.1 to 10
- >10
- Never

The correction will appear in the online version of the paper on the JMIR Publications website together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: Developing a Core Outcome Set and a Core Outcome Measurement Set for Studies Evaluating Interventions to Minimize Physical Restraint Use in Adult Intensive Care Units: Protocol for a Modified Delphi Study

Ziad Alostaz[1], PhD; Wendy L Ellis[1], PhD; Sangeeta Mehta[2], MD; Mohammed Aldalaykeh[3], PhD; Nasrin Alostaz[4], PhD; Raajpreet Sekhon[1], MSc; Abeer Omar[5], PhD; Craig Dale[6], PhD; Louise Rose[7], PhD

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Related Article:

Correction of: https://www.researchprotocols.org/2025/1/e76405/

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In “Developing a Core Outcome Set and a Core Outcome Measurement Set for Studies Evaluating Interventions to Minimize Physical Restraint Use in Adult Intensive Care Units: Protocol for a Modified Delphi Study” [1], the authors noted an error in the affiliation of one of the co-authors.

The affiliation for Craig Dale was incorrectly listed as:

> *Interdepartmental Division of Critical Care Medicine, University of Toronto, Toronto, ON, Canada*

This has been corrected to:

> *Lawrence S. Bloomberg Faculty of Nursing, University of Toronto, Toronto, Ontario, Canada*

The correction will appear in the online version of the paper on the JMIR Publications website, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

Reference

1. Alostaz Z, Ellis WL, Mehta S, Aldalaykeh M, Alostaz N, Sekhon R, et al. Developing a Core Outcome Set and a Core Outcome Measurement Set for Studies Evaluating Interventions to Minimize Physical Restraint Use in Adult Intensive Care Units: Protocol for a Modified Delphi Study. JMIR Res Protoc 2025;14. URL: https://doi.org/10.2196/76405

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Protocol

Validation of the Nociception Level Index for the Detection of Nociception and Pain in Critically Ill Adults: Protocol for an Observational Study

Céline Gélinas[1,2], PhD; Shiva Shahiri T[1,2], MScA; Han Ting Wang[3,4], MD, MSc; Maria Cecilia Gallani[5,6], PhD; Walid Oulehri[7,8], MD, PhD; Denny Laporta[9,10], MD; Philippe Richebé[11,12], MD, PhD

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Abstract

Background: In the intensive care unit (ICU), many patients are unable to communicate their pain through self-reporting or behaviors due to their critical care condition, mechanical ventilation, and medication (eg, heavily sedated or chemically paralyzed). Therefore, alternative pain assessment methods are urgently needed for this vulnerable patient population. The Nociception Level (NOL) index is a multiparameter technology initially developed for the monitoring of nociception and related pain in anesthetized patients, and its use in the ICU is new.

Objective: This study aims to validate the NOL for the assessment of nociception and related pain in critically ill adults in the ICU. Specific objectives are to examine the ability of the NOL to: (1) detect pain using standard criteria (ie, self-report and behavioral measures), (2) discriminate between nociceptive and nonnociceptive procedures, and (3) generate consistent values when patients are at rest.

Methods: The NOL will be monitored in three ICU patient groups: (1) Group A, participants able to self-report their pain (the reference standard criterion using the 0-10 Faces Pain Thermometer) and express behaviors; (2) Group B, participants unable to self-report but able to express behaviors (the alternative standard criterion using the Critical-Care Pain Observation Tool); and (3) Group C, participants unable to self-report and express behaviors. The NOL will be tested before, during, and after two types of standard care procedures: (1) nonnociceptive (eg, cuff inflation to measure blood pressure, soft touch) and (2) nociceptive (eg, tube or drain removal, endotracheal or tracheal suctioning). Receiver operating characteristic curve analysis of the NOL will be performed for Groups A and B using pain standard measures as reference criteria. Mixed linear models for repeated measures

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will be used to compare time points, procedures, and their interaction in each group (A, B, and C). Based on power analyses and considering an attrition rate of 25%, a total sample size of 146 patients (68 in Group A, 62 in Group B, and 16 in Group C) is targeted.

Results: This study was funded in April 2020 but could not be launched until 2022 due to the COVID-19 pandemic. Recruitment and data collection began at the primary site in July 2022 and has been implemented at the secondary sites in 2023 and 2024 and is planned to continue until 2026.

Conclusions: The primary strength of this study protocol is that it is based on rigorous validation strategies with the use of pain standard criteria (ie, self-report and behavioral measures). If found to be valid, the NOL could be used as an alternative physiologic measure of pain in critically ill adults for whom no other pain assessment methods are available.

Trial Registration: ClinicalTrials.gov NCT05339737; https://clinicaltrials.gov/study/NCT05339737

International Registered Report Identifier (IRRID): DERR1-10.2196/60672

(JMIR Res Protoc 2025;14:e60672) doi:10.2196/60672

KEYWORDS

validation; NOL; Nociception Level; nociception; pain; intensive care unit; ICU; critical care; protocol

Introduction

Background

Patients in the intensive care unit (ICU) are exposed to many noxious stimuli as part of standard care, which may involve nociception and pain. Although nociception and pain are interrelated, they are distinct concepts. Nociception involves the neural processes of encoding noxious stimuli that lead to autonomic (eg, increased vital signs) and behavioral responses, which may or may not imply the sensation of pain [1,2]. Pain is a personal and multidimensional phenomenon influenced by biological, psychological, and social factors [1-3]. Appropriate detection of nociception and pain is key to providing adequate analgesia during critical illness in order to reduce the risk of adverse outcomes such as prolonged mechanical ventilation, longer ICU stay, and chronic pain development [4,5].

Many ICU patients experience pain at rest, and this pain is significantly increased during nociceptive procedures as part of standard care (eg, drain or tube removal, endotracheal suctioning, line insertion, wound care, and turning) [6-9]. Behavioral responses such as grimacing and muscle rigidity are commonly observed in ICU patients during standard care procedures and have been associated with their self-reported pain [10]. While the patient's self-report (the reference standard) is the preferred method of pain assessment, it is unsuitable for patients unable to rate their pain due to a combination of several factors affecting their capacity to communicate, such as mechanical ventilation (>33% of Canadian ICU patients) [11], sedation, or an altered level of consciousness. In such situations, behavioral assessment tools such as the Behavioral Pain Scale (BPS) [12] and the Critical-Care Pain Observation Tool (CPOT) [13] are alternative standard measures of pain in patients unable to self-report with minimal motor function to exhibit behavioral responses [14]. However, these behavioral assessment tools cannot be used in heavily sedated patients or those receiving neuromuscular blocking agents as they become unresponsive to stimulation [15].

Alternative methods for pain assessment are necessary when none of the pain standard criteria (ie, self-report or behavioral measures) can be used. Although individual vital signs (eg, heart rate, blood pressure) are easily accessible through continuous bedside monitoring, they are not valid for ICU pain assessment due to inconsistent findings across studies and clinically insignificant variation in their values (<20%) [14,16]. However, research in the field of pain and anesthesia has shown that the combination of physiologic parameters is superior to their individual values [17]. Inspired by initial data from healthy subjects exposed to tonic heat stimuli inducing different pain levels [18], the Nociception Level (NOL) index (Medasense Biometrics Ltd) is a multiparameter technology, which was further developed for nociception monitoring and related pain in anesthetized patients [19-21]. In our recent review [22] of 6 studies in anesthetized patients, the NOL index outperformed single physiologic parameters for the detection of nociception during standard care procedures and experimental stimuli [17,20,23-25].

Although the validity of the NOL is supported in anesthesia, its use in the ICU is new. To our knowledge, we are the first research team to have pilot-tested the use of the NOL for nociception and pain assessment in the ICU. We conducted 2 pilot studies in 15 mechanically ventilated [26] and 54 cardiac surgery ICU patients [27] able to self-report their pain. In both studies, discriminative validation of the NOL was supported with higher index values during nociceptive procedures (ie, chest tube removal, endotracheal suctioning) compared with rest and a nonnociceptive procedure (ie, noninvasive blood pressure [NIBP] using cuff inflation). The NOL values were positively associated with self-reported pain and CPOT scores during nociceptive procedures, providing initial evidence of criterion validation with pain standard criteria [26,27]. Also, a NOL cutoff >25 was found to adequately classify patients with moderate to severe self-reported pain intensity (>4/10) [27]. However, these pilot validation studies of the NOL were limited to 2 nociceptive procedures as part of standard care and were solely conducted in ICU patients who were able to self-report. Further validation of the NOL during various standard care procedures in critically ill adults with different levels of consciousness or sedation and in response to analgesic treatment is necessary to confirm its validity for the assessment of nociception and related pain in the ICU.

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Study Rationale, Goal, Objectives, and Research Hypotheses

An instrument can only be shown as valid for a specific purpose in a given population and context [28]. The NOL index was initially developed and validated for nociception monitoring and related pain in anesthetized patients [17,19-25]. Therefore, validating its use for nociception (primary purpose) and pain assessment (related purpose) in critically ill adults admitted to the ICU (different population and context of care) is necessary. Inspired by our pilot work, strategies for this larger validation study include: (1) criterion validation (ie, NOL's ability to detect pain according to pain standard criteria) and (2) discriminative validation (ie, NOL's ability to discriminate between nonnociceptive and nociceptive procedures) [28]. Considering that reliability is a necessary condition for validity [28], test-retest reliability of the NOL's ability to generate consistent values in similar conditions (eg, at rest) will also be examined.

Research Question: Is the NOL a valid method for the assessment of nociception and pain in critically ill adults in the ICU context?

In order to answer this research question, specific validation objectives are to examine the NOL's ability to:

1. Detect pain in ICU patients able or not to self-report using appropriate pain standard criteria (ie, criterion validation);
2. Discriminate between nonnociceptive and nociceptive procedures part of standard care as well as before and after the administration of a breakthrough opioid dose (ie, discriminative validation);
3. Generate consistent values in similar conditions (ie, pre- and post-nonnociceptive and nociceptive procedures) when ICU patients are at rest.

Our research hypotheses to be tested include:

H1. The NOL index adequately classifies ICU patients with pain based on either their self-reported pain intensity or CPOT scores.

H2. The NOL index produces higher values during nociceptive procedures compared to nonnociceptive procedures and lower values post- versus preopioid administration.

H3. The NOL index generates consistent values pre- and post-nonnociceptive and nociceptive procedures when ICU patients are at rest.

Methods

Study Design

A prospective observational design was selected as it is appropriate for validation purposes using ICU standard care procedures in critically ill adults. The Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) Statement: Guidelines for Reporting Observational Studies is used for the description and reporting of the study [29].

Settings

This study is conducted in the ICUs of 3 tertiary-level university-affiliated health centers in Montréal, Québec, Canada. These ICUs have a total capacity ranging from 16-59 beds, and each ICU admits, on average, 1000-2750 patients annually.

Participants

A consecutive sampling method is used to approach all eligible patients or their representatives during the study period. This sampling method aims to capture a representative sample of ICU patients able or not to self-report. Eligible ICU patients (Textbox 1) are assigned to one of the following groups:

1. Group A can communicate their self-report of pain and can exhibit behaviors (conscious and alert with Glasgow Coma Scale [GCS] [30] score of 13 to 15 or Richmond Agitation Sedation Scale [RASS] [31] score of 0);
2. Group B cannot communicate their self-report but can exhibit behaviors (altered level of consciousness with GCS score of 6 to 12 with a score ≥4 on the motor subscale or RASS score of –1 to –3); and
3. Group C cannot communicate their self-report or exhibit behaviors (unconscious with GCS score of 3 to 5 with a score ≤3 on the motor subscale or RASS score –4 or –5 or receiving neuromuscular blocking agents).

Exclusion criteria were selected to control for potentially confounding variables that may affect the NOL signal or pain standard measures. Patients assigned to Group A who screen positive for delirium are excluded as this condition is likely to affect the reliability of their self-report of pain [32]. Patients with conditions that may seriously influence perfusion of the hands, heart rate, heart rate variability, blood pressure, repetitive or high movements due to agitation or behavioral responses (eg, agitation, cognitive, or psychiatric conditions) are also excluded, thereby strengthening the internal validity of the study. Finally, patients with *Clostridium difficile* must be excluded because the required disinfection product (ie, sodium hypochlorite 5000-6000 ppm) could damage the NOL device, according to the manufacturer.

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Textbox 1. Eligibility criteria of intensive care unit (ICU) patients.

Inclusion criteria:

- Admitted to the ICU >24 hours
- Aged >18 years
- English or French speaking

Exclusion criteria:

- Delirium (Group A only)
- Lack an available finger
- Severe peripheral vascular disease affecting the upper limbs
- Uncontrolled cardiac arrhythmia (eg, atrial fibrillation)
- Pacemaker with paced rhythm
- Severe edema in upper limbs
- Hypoperfusion state or shock and receiving norepinephrine (>14 mcg/min) or equivalent vasopressors to maintain a systolic blood pressure >90 mmHg or a mean arterial pressure >65 mmHg
- Agitated (Richmond Agitation Sedation Scale +1 to +4)
- Psychosis
- Cognitive deficits (eg, Alzheimer)
- Positive for Clostridium difficile
- Pregnancy

Recruitment and Consent Procedures

ICU patients are screened for eligibility by the research staff in collaboration with the medical and nursing team. Potentially eligible ICU patients able to self-report and consent, if they agree to participate, are assigned to Group A. Other potentially eligible ICU patients unable to self-report and consent are assigned to either Group B or C. According to Article 21 of the Quebec Civil Code for minimal risk studies, a significant person qualified to consent to care required by the state of health of the person of full age is asked to provide consent on their behalf for the research study.

Group A: Potentially eligible ICU patients able to self-report are approached for participation by their responsible nurse or physician. If interested, the research staff provides information about the study to the patient and obtain written informed consent.

Group B and Group C: For potentially eligible ICU patients unable to self-report, the person qualified to consent on their behalf is approached by their responsible nurse or physician. If interested, the research staff provides information about the study to the significant person and obtain written informed consent. If a patient participant who was previously unable to consent regains the ability to consent at any time, the research staff provides them with the informed consent form, allowing them to decide on their continued participation in the study. If a patient participant decides to withdraw from the study and requests their research data be removed, all collected information will be deleted.

Study Procedures

Before starting data collection, the group assignment of the participant is confirmed by the research staff. Then, the research staff sets up the NOL device at the bedside, places the finger probe on the participant's finger, and proceeds with calibration (requires less than 5 minutes). The screen of the NOL device is faced away from the patient and family members present in the room to reduce potential bias. Research staff also installs a video camera on a tripod at the foot of the bed to capture the face and the upper body in order to allow for interrater reliability examination of CPOT scores with another trained research staff not present at the bedside.

Participants are assessed at rest before, during, and 15 minutes after nonnociceptive and nociceptive procedures that are part of ICU routine care. Whenever possible, 15 minutes postprocedure are respected to allow for the resolution of the release, reaction, and elimination of stress hormones (ie, epinephrine and norepinephrine) and stress-activated responses that may be present following noxious stimulation [33]. The nonnociceptive procedures are ideally performed prior to nociceptive procedures and include soft touch (ie, research staff touching the patient's arm for 1 minute) and cuff inflation for blood pressure measurement (NIBP), which were empirically shown to be painless in previous studies [34], including our pilot NOL studies [26,27]. In the sequence of nonnociceptive procedures, soft touch is performed first and cuff inflation last. Then, the goal is to observe up to two nociceptive procedures per participant (Textbox 2). Nociceptive procedures are selected according to the standard care required by the patient's condition. These procedures do not involve mobilizing the patient out of bed, as important movements may introduce

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artifacts in the NOL data. When possible and as required by the patient's condition, participants are also assessed before and 15 minutes postadministration of a breakthrough dose of an opioid such as fentanyl, morphine, or hydromorphone through a parenteral route (mainly through intravenous or subcutaneous routes) to capture onset or peak of action. The decision to administer an opioid is made as per local practice and based on an assessment performed by the ICU nurse or physician. Within a window of 48 hours after obtaining informed consent, a total of 10 to 12 time points of data collection is completed with each participant during their ICU stay (Table 1).

The NOL index is continuously monitored during the data collection time period, and values are extracted in a standardized manner as done in previous clinical studies for NOL data analysis purposes [24-27]. CPOT assessments (one-minute observation or duration of the procedure) are performed on participants from Groups A and B by research staff, and then conscious patients able to self-report (Group A) are asked to provide their self-report of pain intensity at each time point. Video recording is stopped before participants provide their self-report to avoid possible bias by the research staff, who will view the videos for CPOT scoring at a later time. Finally, demographic and clinical information is extracted from the participants' medical files. At the end of data collection, the study equipment (ie, video camera, tripod, NOL device, and keyboard) is disinfected according to the prevention control infection procedures of each institution before being used for another patient.

Textbox 2. List of nociceptive and nonnociceptive standard care procedures in the intensive care unit.

Nociceptive procedures

- Chest tube removal
- Drain removal
- Mouth, endotracheal, or tracheal suctioning
- Arterial line insertion
- Peripheral intravenous line insertion
- Subcutaneous injection
- Wound care
- Bed turning or repositioning

Nonnociceptive procedures

- Soft touch of the patient's arm
- Noninvasive blood pressure cuff inflation (NIBP)

Table 1. Assessment time points and pain variables to be measured in each group (A, B, and C).

Measure	Nonnociceptive procedures				Nociceptive procedure 1			Nociceptive procedure 2			Analgesic[a]	
	Pre	Soft touch	Cuff inflation	Post	Pre	During	Post	Pre	During	Post	Pre	Post
NOL[b]	A[c], B[d], C[e]	A, B, C	A, B, C	A, B, C	A, B, C	A, B, C	A, B, C	A, B, C	A, B, C	A, B, C	A, B, C	A, B, C
Behaviors	A, B	A, B	A, B	A, B, C	A, B	A, B	A, B	A, B	A, B	A, B	A, B	A, B
Pain level	A	A	A	A	A	A	A	A	A	A	A	A

[a]Administration of an analgesic as required by the patient's condition.

[b]NOL: Nociception Level Index.

[c]Group A: Patients are able to communicate their self-report of pain and can exhibit behaviors.

[d]Group B: Patients are unable to communicate their self-report of pain but can exhibit behaviors.

[e]Group C: Patients who cannot communicate their self-report of pain or exhibit behaviors.

Variables and Measurement Tools

Primary Measure: The Nociception Level (NOL) Index–All Groups (A, B, and C)

The Pain Monitoring Device-200 (PMD-200; Medasense Biometrics Ltd; Figure 1) is used in this study. PMD-200 offers the multiparametric NOL index (0-100) and was approved by Health Canada for clinical use in September 2017. The NOL captures several physiological parameters simultaneously through a finger probe and disposable sensor, which includes 4 small sensors, sampled 50-500 Hz: (1) accelerometer, (2) photoplethysmograph, (3) galvanic skin response, and (4) peripheral temperature. From these 4 sensors, the following physiological parameters are extracted: heart rate, heart rate

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variability, photoplethysmography pulse wave amplitude, skin conductance level, number of skin conductance fluctuations, skin temperature, and their time derivatives. All these parameters are integrated and analyzed simultaneously using a Random Forest machine learning model approach to provide the NOL index, which can range from 0 to 100 [17]. A NOL cutoff value >25 for the detection of self-reported pain was found in our pilot study with ICU cardiac surgery patients [27].

Figure 1. Nociception Level (NOL) index.

The PMD-200 device allows the documentation of each event (ie, beginning and end time of rest and procedure assessment) or any contextual information (eg, interruption during a procedure), which is facilitated with the use of a wireless keypad. All NOL data are electronically collected every 5 seconds by the PMD-200 monitor.

Reference Standard Measure of Pain–Group A

The Faces Pain Thermometer (FPT) was selected to measure pain intensity as it can accommodate adult patients of various ages. It consists of an enlarged visual thermometer including 6 faces with a numeric rating scale scoring from 0="no pain" to 10="worst possible pain" (Figure 2). The validity and reliability (test-retest) of the tool were established in ICU patients [35]. The FPT was used in many previous validation studies led by the primary investigator [13,34,36] and pilot NOL studies [26,27].

Figure 2. The 0-10 Faces Pain Thermometer (FPT)[35].

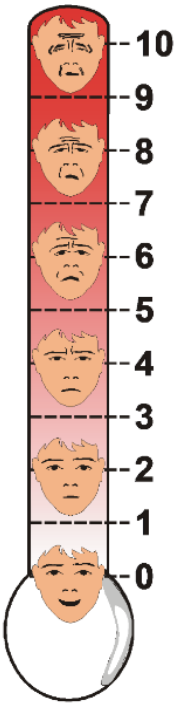

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Alternative Reference Standard Measure of Pain–Groups A and B

The Critical-Care Pain Observation Tool (CPOT) [13] was selected for behavioral pain assessment in critically ill adults. The CPOT was used in our NOL pilot studies [26,27], and it is 1 of the 2 behavioral scales suggested as alternative reference standard measures of pain by the Society of Critical Care Medicine [14] and has been implemented in clinical practice in the 3 study ICUs. The CPOT includes 4 behavioral items: (1) facial expressions, (2) body movements, (3) muscle tension, and (4) compliance with the ventilator (for mechanically ventilated patients) or vocalization (for nonintubated patients). Each item is scored from 0-2, and the total score can range from 0-8. The CPOT has been validated in 47 studies with more than 3900 ICU patients with surgical, trauma, and medical diagnoses from various countries [34]. Consistent findings of good interrater reliability (interclass correlation coefficient [ICC] >0.60 between research staff and ICU nurses) and ability to discriminate between various nociceptive and nonnociceptive procedures were found across studies. Criterion validation of the CPOT was also supported by positive correlations (r>0.40) with ICU patients' self-reported pain intensity [34]. A CPOT score >2 was found to adequately identify patients with self-reported pain (AUC>0.80) [34,36].

The research staff of all sites have been trained to use the CPOT using a standardized training session previously described [37]. Briefly, this 60-minute training session covers the description of the CPOT content and its scoring process. Patient videos are viewed to practice scoring with the tool with the goal of reaching consistent CPOT scores between raters within a total score difference of no more than 1 point.

Demographic and Clinical Information for ICU Patient Participants

Demographic information (eg, age, sex, gender, and ethnicity) is collected from the patient or their representative. Information related to the patient's clinical condition (ie, ICU admission diagnosis, mechanical ventilation, the severity of illness [Acute Physiology and Chronic Health Evaluation; APACHE II] [38], level of consciousness [GCS] [30], sedation level [RASS] [31], delirium screening with the Confusion Assessment Method-ICU [39] or Intensive Care Delirium Screening Checklist [40], according to the respective tool used at each site), as well as medication information (ie, morphine equivalent doses [41] received within 4 hours before and during the entire data collection, sedative agents, vasopressors, and use of opioids before ICU admission) is extracted from the medical records by the research staff. The following clinical information is collected at the time of obtaining consent and performing data collection: mechanical ventilation status, GCS score, RASS score, and delirium screening.

Sample Size Calculation

The primary objective is to validate the NOL using pain standard criteria (ie, self-report and CPOT scores). Therefore, ROC is considered our primary analysis and guides the sample size calculation for Group A and Group B. Power calculations were based on our pilot findings [26,27] and results from previous ICU studies considering a clinically acceptable AUC of 0.75 [42] (using a null hypothesis of AUC=0.50) with a power of 80% and an adjusted α of .025 (2 ROC curves for each procedure in each group). For Group A in whom the self-report of pain is obtained and using a ratio of 2:1 in pain:no pain cases according to self-reported pain intensity scores of <4 and >4, a sample of 54 patients is required. For Group B in whom only the CPOT scores are available and using a ratio of 1.5:1 in pain:no pain cases according to CPOT scores of <2 (no pain) and >2 (pain), a sample of 50 patients is necessary. For Group C (unable to self-report and express behaviors), we will not be able to use any pain standard criterion. Therefore, our main objective is to test whether the NOL can discriminate between a nociceptive procedure and a nonnociceptive procedure. In order to detect a minimal mean increase of 10 in the NOL value during the nociceptive procedure (with a standard deviation of 10 as found in our pilot findings), a minimal sample size of 13 patients is required to run paired t tests with a power of 80% and an α of .01 (to account for multiple test comparisons). Considering an attrition rate of 25% (data collection was completed in 73% of consenting patients in our pilot work), recruitment targets include 68 patients in Group A, 62 patients in Group B, and 16 in Group C for a total of 146 ICU patients. Power calculations were performed by a statistician using Power and Precision 4 (Biostat Inc).

Data Analysis

SPSS software (version 29; IBM) and SAS (version 9.4; SAS Institute) will be used for data analysis. Descriptive statistics will be computed to characterize the study samples and outcomes. The NOL signal quality will be checked for all enrolled patients to ensure the accuracy of the data. As done in previous studies, NOL values will be averaged within 15 seconds before and after the peak value obtained after the start of each nonnociceptive procedure (7 NOL values total around the peak for soft touch and NIBP) and nociceptive procedure. In addition, NOL values will be averaged over a 1-minute period at rest before and after the procedure. CPOT scores will be obtained independently by 2 trained raters, one at the bedside and one who will view the patient videos at a later time. Intraclass correlation coefficients (ICC) will be calculated between the CPOT scores of both raters during procedures. ICC>0.80 will confirm excellent interrater reliability [28].

For objective 1 (criterion validation), the receiver operating characteristic (ROC) curve [43] will be performed to examine the ability of the NOL to adequately classify patients with pain. In patients able to self-report (Group A), an established pain intensity score >4 based on participants' self-reports as the reference standard criterion indicating moderate to severe pain will be used [10,44]. This criterion is also commonly used in practice to support clinical decisions in the administration of opioids. A ROC curve will be obtained for each nociceptive procedure (a total of 2 procedures per patient). In patients unable to self-report but in whom behaviors can be observed (Group B), we will use the determined CPOT score >2 as the alternative reference criterion, which is associated with the presence of moderate to severe pain [44]. Again, for Group B, a ROC curve will be obtained for each nociceptive procedure (total of 2 procedures per patient) [45]. As a supplementary analysis, we

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will perform ROC curves for repeated-measures design in each group (A and B) and compare them [46]. In addition, considering that the CPOT will be available in Group A and Group B, ROC curves will be performed in each group separately to compare the AUC of independent curves for each of the 2 procedures [45]. The NOL cutoff value that will optimize both sensitivity and specificity will be determined.

Discriminative validation (objective 2) is our main objective to test in Group C, and paired *t* tests comparing the NOL values of each nociceptive procedure with the nonnociceptive procedure will be obtained. Generalized linear mixed model for repeated measures will allow us to compare the NOL index values across time points (pre, during, and post), procedures (nonnociceptive vs nociceptive), and their interaction in each group (A, B, and C). The generalized linear mixed model technique incorporates the full-information maximum likelihood procedure, which allows parameter estimation for missing data [47]. NOL values are expected to be significantly higher during nociceptive procedures in all 3 groups. Covariates (eg, sex, gender, morphine equivalent doses, opioid use before ICU admission) may be added if appropriate. Finally, NOL data obtained at pre- and postadministration of an opioid dose will be tested separately using paired *t* tests as not all patients will be candidates for these assessments.

For test-retest reliability (objective 3), paired *t* tests will be performed between pre and post-nonnociceptive and nociceptive procedures in all 3 groups. Nonsignificant paired *t* tests are expected to support the stability of NOL values when the patients are at rest.

Ethical Considerations

Ethical approval was submitted in February 2022 and approved by the Medical and Biomedical Research Ethics Committee of the primary site in June 2022 (project # MP-05-2022-2988). A first amendment of the research protocol (version 2) was approved in June 2023 regarding the addition of pacemaker as an exclusion criterion as it affects the generation of the NOL signal. A second amendment of the research protocol (version 3) was approved in September 2024 for the addition of a third study site and revision of the sample size. According to our pilot studies [26,27], participating in this study is not associated with any known risks; however, participants will be informed that if they find the finger probe uncomfortable, they can choose to switch fingers or hands or have it removed to stop data collection. Participation in this research project is completely voluntary. Participants or their representatives have the freedom to decline or withdraw from the study at any time without providing a reason, with no consequences. Opting not to participate or withdrawing will not affect the quality of care and services they are entitled to receive. Participants or their representatives can also choose not to answer specific questions or decline video recording if they prefer.

The confidentiality of collected data, video recordings, and contact information will be maintained. Electronic folders will be saved on the secure server of the institution and their access will be restricted to only the research team members with their own username and password. Mechanisms to ensure confidentiality will include the assignment of numeric codes and the removal of personal identifiers. The code key linking the participants to their research file will be kept in a file protected by a unique password, stored separately from the coded research data, and only accessed by the research team. Informed consent forms will also be stored separately from the coded research data. The REDCap (Research Electronic Data Capture; Vanderbilt University) [48] web application licensed by the primary site will be used to create the data collection forms and to facilitate data storage and management between the study sites.

For monitoring control, safety and security, the research files may be examined by a person mandated by Canadian or international regulatory authorities, such as Health Canada, as well as authorized representatives of the study sponsor (the institution) or the research ethics board. The data will be permanently destroyed after 15 years. All participants have the right to access their study files at any time to verify and correct the information if necessary. They are informed and consented to the fact that summarized deidentified data will be presented in scientific conferences and publications.

Results

This study was funded in April 2020 (see the funding report in Multimedia Appendix 1) but could not be launched until 2022 due to the COVID-19 pandemic. It was registered to ClinicalTrials.gov (NCT05339737) in April 2022. Recruitment and data collection began at the primary site in July 2022 and has been implemented at the secondary sites in 2023 and 2024. Recruitment and data collection will be ongoing until 2026.

Discussion

In alignment with our pilot findings [26,27], we anticipate that the NOL will be able to detect pain according to pain standard criteria and to discriminate between nociceptive and nonnociceptive procedures. The enrollment of critically ill adults with various clinical conditions and the capacity to communicate will allow us to better generalize our validation findings to the ICU population.

Methodological Strengths

The selection of rigorous validation strategies according to methodological guidelines in health measurement is the main strength of this study. With the participation of conscious ICU patients able to self-report, we can use the reference standard of pain, that is, self-reporting, for criterion validation. Furthermore, this validation strategy is reinforced by using the alternative reference standard, that is, the CPOT. Regarding discriminative validation, 2 strategies were selected, that is, discrimination between nonnociceptive and nociceptive procedures as well as before and after opioid administration. Test-retest reliability pre- and post-nonnociceptive and nociceptive procedures will allow us to examine the stability of the NOL values when patients are at rest. Both reliability and validation strategies are necessary to confirm the validity of an instrument [28].

In order to reduce potential bias related to pain scoring, Group A participants who are able to self-report will be blinded to the

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NOL values screen during the procedures. CPOT scoring will be completed by research staff before obtaining the patient's self-report (ie, Group A participants) so raters are not influenced by self-reported pain intensity scores. Interrater reliability of CPOT scores will also be examined.

Our study lies in its foundation built upon the robust pilot work of the NOL conducted in the ICU setting. Our previous pilot studies have provided valuable insights and preliminary data to inform and support the research hypotheses and methodological decisions made in this study protocol. By expanding a rigorous validation process of the NOL to patients who are representative of the broader ICU population, the knowledge gained could contribute to identifying an alternative measure of pain in the most vulnerable critically ill adults.

Potential Limitations and Mitigation Strategies

Recruiting ICU patients or obtaining written consent from the persons qualified to consent for them is challenging. This requires daily screening of eligible patients and close follow-up. Support from the nursing staff and physicians is key to identifying eligible patients and approaching those qualified to consent for them. Our research team has developed efficacious recruitment procedures, trained competent research staff, and established close collaboration with ICU care teams in all sites, which facilitate the implementation of this study. The feasibility of recruitment was also demonstrated in our pilot work. A screening log will be completed at each site to compile eligibility criteria and reasons for refusals, losses, or withdrawals. In our pilot studies [26,27], we were unsuccessful in obtaining data from some participants mainly due to missing the procedure, either because temporary fellows forgot to inform the research team or the procedure occurred after ICU discharge. Chest tube removal and endotracheal suctioning were the sole nociceptive procedures included in our pilot studies. Broadening the selection of nociceptive procedures may reduce the number of missed observations of these events. However, we may still miss some procedures due to urgent situations. Also, data collection will be planned as soon as possible after obtaining written consent to minimize losses. In addition, we will document any challenges related to the use of NOL (eg, absence or loss of signal) and troubleshooting strategies. Finally, CPOT raters cannot be blinded to the procedures they will view on the videos. As a result, they may anticipate patients' behavioral responses to the procedure, which may influence their ratings. The examination of interrater reliability of CPOT scores involving trained research staff from different settings and using 2 methods of rating (bedside and video) may help minimize this potential bias.

Conclusion

The validity of the NOL has been supported in anesthetized patients, but its use in the ICU context is still new. Its validation in the ICU is relevant as many critically ill adults may be unable to self-report or express pain behaviors. As part of the validation process, it is key to validate the NOL with patient groups in whom pain standard criteria can be used as well as during nociceptive and nonnociceptive procedures in order to support its validity for both nociception and related pain assessment in the ICU. If found to be valid, the NOL could be used as an alternative measure to detect nociception and pain and to guide pain management decisions in the most vulnerable, critically ill adults.

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Medasense Biometrics Ltd has not been involved in any part of this NOL validation protocol.

Data Availability

The dataset generated during and analyzed during this study is not publicly available due to ethical agreement but may be available from the corresponding author on reasonable request.

Authors' Contributions

CG, PR, SST, DL, MCG, and HTW contributed to conceptualization. CG, PR, SST, DL, MCG, and HTW handled funding acquisition. CG, PR, SST, DL, MCG, HTW, and WO contributed to the methodology. CG and PR performed supervision. CG, SST, and PR contributed to writing the original draft. CG, PR, SST, DL, MCG, HTW, and WO contributed to writing–review and editing.

Conflicts of Interest

None declared.

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Multimedia Appendix 1 [PDF File (Adobe PDF File), 75 KB - resprot_v14i1e60672_app1.pdf]

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Abbreviations

APACHE: Acute Physiology and Chronic Health Evaluation
BPS: Behavioral Pain Scale
CPOT: Critical-Care Pain Observation Tool
FPT: Faces Pain Thermometer
GCS: Glasgow Coma Scale
ICC: interclass correlation coefficient
ICU: intensive care unit
NIBP: noninvasive blood pressure
NOL: Nociception Level
NRS: Numeric Rating Scale
RASS: Richmond Agitation Sedation Scale
REDCap: Research Electronic Data Capture
ROC: receiver operating characteristic
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology

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Proposal

Development of a Framework for Youth- and Family-Specific Engagement in Research: Proposal for a Scoping Review and Qualitative Descriptive Study

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Abstract

Background: Youth and families play an indispensable role in health research, given their unique lived experiences and expertise. Aligning research with patients' needs, values, and preferences can significantly enhance its relevance and impact; however, recent research has highlighted various challenges and risks associated with youth and family engagement in health research. These challenges encompass the perils of tokenism, power imbalances and dynamics, questioning the motives behind engagement, and limited accessibility to patient-friendly training for patient partners, as well as inadequate training on patient engagement for researchers and the absence of equitable engagement tools. To address these risks and challenges, different patient engagement models, theories, frameworks, and guiding principles have been developed and adopted; to date, however, their transferability to youth- and family-specific engagement in research has been limited.

Objective: The objectives of this project are (1) to determine the extent of the literature on the application of patient engagement models, theories, frameworks, and guiding principles in the context of youth-specific research; and (2) to determine how meaningful the key components and constructs of these models, theories, frameworks, and guiding principles are to youth and their family members.

Methods: This project will use an integrated knowledge translation approach and consists of 2 phases: (1) a scoping review to identify patient engagement models, theories, frameworks and guiding principles in youth research; and (2) a qualitative descriptive study using one-on-one semistructured interviews with youth and family members to understand their conceptualization of meaningful engagement in health research. For phase 1, the following databases were searched: Medline, CINAHL, EMBASE, PsycINFO, and the Cochrane Central Register of Controlled Trials. Literature from 2013 to August 28, 2024, was captured. Primary studies using a patient engagement in research model, theory, or framework, or guiding principles, in youth will be included. The risk of bias of included studies will not be assessed. Extracted data will be quantitatively summarized using numerical counts and qualitatively using content analysis. For phase 2, we will recruit 9 to 17 youth and 9 to 17 family members. Transcripts will be analyzed using an inductive approach outlined by Braun and Clarke.

Results: The project has received funding from the Canadian Institutes of Health Research. A 9-member integrated knowledge translation panel consisting of 6 youth and 3 family members has been established.

Conclusions: The findings from this study will identify what is currently known about the application of patient engagement models, theories, frameworks, and guiding principles in youth-specific research and the important components of these models, theories, frameworks, and guiding principles from the perspective of youth and their families. These findings will be instrumental to developing a youth- and family-specific engagement in research framework called the UNITE framework and subsequently, a validated measure.

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KEYWORDS

youth and family engagement; frameworks; implementation science; scoping review; qualitative

Introduction

Background

Patients play an essential role in health research, given their unique lived experiences and expertise, which can significantly enhance the quality, relevance, and impact of research by aligning it with patient needs, values, and preferences [1,2]. The overarching objective of patient engagement in health research is to generate research that contributes to improved health care service delivery, clinical outcomes, and population health [3]. Recent research has highlighted the myriad benefits and positive outcomes associated with patient engagement for patient partners, investigators, and research endeavors [4-8]. For example, engaging patients has influenced initial research priorities, study designs, interpretation of findings, health care interventions, and knowledge mobilization strategies, resulting in outcomes that more closely align with patient perspectives [7,9]. When patient engagement is characterized as meaningful and authentic, it provides a rewarding experience for patients and researchers alike [10].

However, other recent research has highlighted various challenges and risks associated with patient engagement in health research. These challenges, which include tokenism [11-14], power imbalances/dynamics [12,15], limited accessibility to patient-friendly training for patient partners [16], and the absence of equitable engagement tools [17], can have lasting effects on patient partners, including mental and physical exhaustion, deteriorating health, doubts about the value of

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engagement, and a sense of having personally failed both the team and the broader patient community [18]. A recent article by patient partners led by Richards et al [18] on how patient engagement can falter highlighted key themes, including "patient partners as a checkmark," "unconscious bias towards patient partners," "lack of support to fully include patient partners," and "lack of recognizing the vulnerability of patient partners" [18].

To address these challenges and risks, various patient engagement models, theories, frameworks, and guiding principles (eg, the strategy for patient-oriented research [SPOR], the patient engagement in research [PEIR] framework, and "ways community members can participate in the stages of research" from the Ontario Brain Institute) have been developed and adopted within the research community [10,19,20]. For example, the PEIR framework [10] includes eight key components, which collectively contribute to meaningful patient engagement in research: (1) procedural requirements, (2) convenience, (3) contributions, (4) support, (5) team interaction, (6) research environment, (7) feeling valued, and (8) benefits. A subsequent measure of meaningful patient engagement in research from the patient perspective has been developed, the Patient Engagement in Research Scale (PEIRS-22) [21,22]. This measure is designed to be completed by adult patients and family caregivers who partner with researchers on projects.

It is important to acknowledge that existing frameworks often predominantly emphasize the benefits of patient partners to the research project and team, sometimes overlooking the reciprocal benefits that may occur between the research team and patient partners, especially youth partners [23]. This skewed approach fails to fully consider the potentially extractive nature of research collaboration, as aptly described by Metz and Damschroder [23], where the research process can unintentionally exploit the knowledge and contributions of youth without adequately reciprocating in terms of personal and professional development opportunities. This issue takes on particular significance when crafting an engagement framework tailored for youth, as research teams have the potential to foster skill development, positively impact their life and career trajectories, and contribute to their holistic growth [23].

Despite the significant contribution of the PEIR framework [10] and the PEIRS-22 [21,22], they lack the incorporation of a comprehensive review of the evidence on existing frameworks, and their development was based on participants with limited diversity in terms of gender, race, education, primary diagnosis (all had arthritis), and age [10,21,22]. These limitations impede the transferability of this framework and measure to youth- and family-specific engagement in health research.

Furthermore, there is a model of engagement specifically designed for use with youth called the McCain model of youth engagement [24]. However, it was developed solely in the context of youth mental health systems research for youth and young adults aged 15 to 29 years [24], limiting transferability (ie, across different contexts and family members) and highlighting the need to develop a broader framework. Accordingly, our research seeks to directly address these specific gaps in existing engagement models, theories, and frameworks by developing a youth and family-specific engagement in research framework, the UNITE framework.

Research Objectives

This proposal has two objectives: (1) to determine the extent of literature on the application of patient engagement models, theories, frameworks, and guiding principles in the context of youth- and family-specific research; and (2) to understand how meaningful the key components and constructs of these models, theories, frameworks, and guiding principles are to youth and their family members. Collectively, these findings will be foundational to the development of the UNITE framework and a subsequent validated measure.

Methods

Study Design

This study will be conducted in 2 phases, with phase 1 consisting of a scoping review and phase 2 consisting of a qualitative descriptive study.

Integrated Knowledge Translation Approach

Integrated knowledge translation (iKT) is defined as a collaborative relationship between researchers and relevant knowledge users as partners that facilitates mutually beneficial decision-making related to a study or research program [25]. Youth aged 10 to 24 years in Canada and their family members who have engaged in health research (ie, as patient partners) in the last 3 years were recruited as iKT panel members via Holland Bloorview Kids Rehabilitation Hospital's Youth Advisory Council and Family Leader Program, professional networks, social media pages, and email lists. A sample of diverse youth advisors who have participated in our previous research on best practices in youth engagement were also approached, including youth with disabilities or developmental differences [26]. A total of 6 youths and 3 family members were recruited to be part of the iKT panels. The lead youth representative will lead the iKT panels. The lead youth representative and research team decided to hold separate iKT panels (ie, having a youth panel and a family panel with the opportunity to mix panels when needed). This approach will ensure that both groups feel comfortable and can freely express their unique perspectives. Activities of the panels have included planning study activities, and may include participant recruitment, data collection and analyses, and knowledge mobilization. Panel discussions will be conducted in a manner that respects diverse perspectives and experiences. A reflective exercise on equity, diversity and inclusion developed by the Strategy for Patient-Oriented Research Evidence Alliance will be conducted with iKT panel members to encourage dialogue and understanding around equity, diversity and inclusion [27].

Phase 1: Scoping Review on Patient Engagement Models, Theories, Frameworks, and Guidance in Youth Health Research

The methodology for the scoping review will follow the methodological frameworks of the Joanna Briggs Institute (JBI) [28] and Khalil et al [29]. The scoping review protocol has been registered on the Open Science Framework Registries [30] and

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was guided by and reported according to the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols (PRISMA-P) [31]. The completed PRISMA-P checklist can be found in Multimedia Appendix 1. The results of the scoping review will be reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR) checklist [32].

Stage 1: Developing a Search Strategy

The population, concept, and context (PCC) framework was used to guide the search strategy (population: World Health Organization [WHO] definition of "young people" as those aged 10-24 years [33]; concept: patient engagement in research; context: models, theories, frameworks, and guiding principles). With the assistance of a research librarian, literature search strategies using Medical Subject Headings and text words related to patient engagement and models, theories, frameworks, and guidance or guiding principles were developed. The search strategy combined structured database-specific subject headings (as available) and keywords or synonyms. An information specialist with expertise in conducting searches for systematic and scoping reviews drafted the search strategy using OVID Medline (Multimedia Appendix 2) and worked with the research team to refine and finalize the search. The final search strategy also underwent peer review using the Peer Review of Electronic Search Strategies (PRESS) statement checklist with another librarian/information specialist [34].

The following databases were searched: Medline, CINAHL, EMBASE, PsycINFO and Cochrane Central Register of Controlled Trials. Searches were limited to English. Literature from 2013 to August 28, 2024 was captured, consistent with when the term "patient engagement" became frequently used [35]. We will also search the gray literature in specialized databases like OpenGrey, Grey Literature Report, and GreyNet International, platforms like arXiv, bioRxiv, and SSRN, and databases such as ProQuest Dissertations and Theses.

Stage 2: Evidence Screening and Selection

All primary studies using a model, theory, or framework for patient engagement in research among young people will be eligible for inclusion. Studies with a model, theory, or framework may have also reported on guiding principles. We define young people as those aged 10 to 24 years, consistent with the WHO definition [33]. We define a model as the essential elements or variables of a phenomenon or a specific aspect of a phenomenon; a theory as "a set of analytical principles or statements designed to structure our observation, understanding and explanation of the world"; and a framework as an explanation of a phenomenon by organizing it into a collection of descriptive categories and the relationships between them [36]. Systematic reviews, meta-analyses, editorials, commentaries, and nonspecific conference proceedings will be excluded to focus on including primary results and not preliminary findings or ongoing research; however, the reference lists of such articles will be hand-searched for relevant articles.

Removal of duplicates as well as level 1 and level 2 screening will be managed through Covidence. To increase reliability, the level 1 screening form will be piloted on a random sample of approximately 50 articles. Eligibility criteria descriptions will be revised if deemed necessary by the team, or if low agreement (ie, <70%) [37] is observed, to improve the consistent application of the selection criteria. Agreement will be measured using Cohen κ [38]. A pilot test of the level 2 screening will also be performed on approximately 25% of the articles, similar to the process for level 1 screening. For studies that are excluded at level 2, the reason for exclusion will be recorded. All screening will occur in duplicate and independently. When necessary, another reviewer will be sought to resolve conflicts.

Stage 3: Data Extraction

A standardized data extraction form will be developed by the research team and iKT panels based on the *JBI Manual* data extraction recommendations [28] and those recommended for the extraction, analysis, and presentation of results in scoping reviews [28,39]. Extracted data will include study characteristics (eg, study design, year of publication, geographic location), youth and family participant characteristics (eg, age of the youth), and details of the engagement models, theories, frameworks, and guiding principles (eg, components or values and principles and how they were enabled or enacted in the study), as well as study results. Additional categories for data extraction identified through discussions with the research team and iKT panels will be added to the final data extraction template as applicable. The data extraction template will be piloted for 2 to 3 articles to ensure all relevant results are extracted. All data will then be extracted in duplicate by 2 independent reviewers. Discrepancies in the extracted data will be discussed and resolved by the 2 reviewers. Quality and risk of bias will not be assessed, as this is not required in scoping reviews [32].

Stage 4: Data Analysis

The extracted data will be quantitatively summarized using numerical counts and qualitatively summarized using content analysis [40]. The data will be grouped by the main components of the model, theories, frameworks, guiding principles (and how they were enabled or enacted), study designs, and associated methods (eg, one-on-one interviews). We will also synthesize data on how youth and family members were engaged throughout the research process, the types of outcomes collected, and results. Depending on the available data, subgroup analyses may be conducted by health condition, sex, gender-related variables, and other PROGRESS-Plus characteristics (PROGRESS-Plus is a term meaning "place of residence, race/ethnicity/culture/language, occupation, gender/sex, religion, education, socioeconomic status, social capital") [41]. If feasible, we will contact the study authors of the included studies to confirm that all the data collected were included in the published article (ie, nothing was excluded due to word count limitations of a journal).

Phase 2: Qualitative Study to Understand Key Components and Constructs for Development of a

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Framework for Youth- and Family-Specific Engagement in Research

Study Design

Phase 2 will adopt a qualitative descriptive approach [42,43]. Findings from the scoping review will inform the development of the interview guide for phase 2, such as identifying what aspects of the included models, theories, frameworks, and guiding principles resonate with youth and family members and which do not.

Recruitment

We will recruit Canadian youth (aged 10-24 years) and their family members who have had experience in youth engagement in health research (eg, as partners of a research project) within the last 3 years. Participants will be recruited via our professional networks, including those of the iKT panel members (eg, the Kids Brain Health Network, the Bloorview Research Institute Family Engagement Office, and the SickKids Patient and Family Engagement Office), social media pages, and email lists. We will also enlist the help of a diverse group of youth advisors who have participated in our research team's previous research for recruitment [26,44,45]. We aim to recruit 9 to 17 youth and 9 to 17 family members; this is consistent with the sample size in qualitative studies to reach thematic saturation [46].

Data Collection

Youth and family participants will take part in separate, one-on-one, semistructured telephone or online interviews with a member of the research team with expertise in qualitative research methods [47,48]. All interviews will be digitally recorded and transcribed verbatim for data analysis. The interview guides will consist of questions focused on youth and family members' conceptualization of meaningful engagement in health research. The interview guide will be pilot-tested with various members of the research team and iKT panel. We will use probes or recursive questioning during interviews to explore issues in greater depth and verify the interviewer's understanding of the collected information [49,50].

Data Analysis

We will use inductive thematic analysis, as described by Braun and Clarke [51,52], which is consistent with the pragmatic orientation of this research [53]. Codes and themes will be refined through discussion with the larger research team. The software program NVivo (version 14; Lumivero) will be used during the analysis of the transcripts to help organize the codes. Multiple aspects of trustworthiness will be used [54]. For example, we will demonstrate credibility via peer debriefing with various members of the research team and the iKT panels. Transferability will be accomplished by describing the study samples. Independent analysts will review the data and contest the themes to ensure dependability. Finally, confirmability will be accomplished by providing decision trails between data and interpretation [54].

Ethical Considerations

Ethics approval for phase 2 of this project will be obtained from the first author's primary institution (Holland Bloorview Kids Rehabilitation Hospital, Bloorview Research Institute). Informed consent will be obtained from participants prior to the start of the interview. Transcripts from the interviews will be deidentified to ensure privacy prior to data analysis. Participants will be compensated for their time in the form of gift cards. The amount compensated will be consistent with the Canadian Institutes of Health Research (CIHR) Patient Partner Compensation Guidelines (CAD $50 [US $34.96] per participant) [55].

Results

This work is supported by a CIHR Healthy Youth Catalyst Grant received in March 2024 (HEY- 192883; Multimedia Appendix 3). A 9-member iKT panel consisting of 6 youth and 3 family members has been established and has been actively involved in the study. We anticipate that phase 1 of the study will be completed in March 2025. Ethics approval for phase 1 was not required as it did not involve collecting or using data from participants. Ethics approval for phase 2 of the study will be applied for in winter 2025. Phase 2 of the project is anticipated to be completed in August 2025. A detailed timeline of the project can be found in Multimedia Appendix 4.

Discussion

Anticipated Findings

The findings from this study will allow us to identify what is currently known about the application of patient engagement models, theories, frameworks, and guiding principles, which are often designed for adults, in the context of youth-specific research, and to understand the importance of the components that make up these models, theories, and frameworks from the perspective of youth and their families.

Dissemination Plans

We will use a variety of passive and active end-of-grant knowledge mobilization approaches to disseminate our findings, which will be codeveloped with our iKT panels. We will ensure youth and family voices are heard to develop flexible communication plans that will suit diverse needs. Traditional knowledge translation will include dissemination through meetings locally, nationally, and internationally (eg, PxP and For Patients, By Patients) and publications in peer-reviewed journals. Members of the research team are affiliated with and situated within pediatric institutions where the UNITE framework will be disseminated and implemented. We will codevelop plain language summaries with youth and family partners with clear, simple, and individualized messages for patients and family and community service organizations to augment the accessibility of the information. Finally, members of the research team will also discuss and distribute the UNITE framework within their expansive training curriculum and a planned youth-focused engagement in research course.

Future Directions

This project lays the foundational work for developing a patient engagement framework called the UNITE framework, which will include equity, diversity, and inclusion considerations, and

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the subsequent development and validation of an associated measure of engagement. Future research will involve the implementation of the UNITE framework and a subsequent measure in a learning health system context within pediatric institutions that our research teams are associated with. The UNITE framework and associated measure will contribute to meaningful and sustained engagement of youth and their families in health research by addressing gaps in current patient engagement frameworks.

Strengths and Limitations

A strength of this study is the inclusion of gray literature (eg, reports and policy literature) for phase 1 (the scoping review). This will provide a more comprehensive understanding of the concept (patient engagement in research) and context (models, theories, frameworks, and guiding principles) that we are interested in, as well as mitigate publication bias [56]. In addition, the search strategy for phase 1 has been reviewed by the iKT panel and undergone peer review using the PRESS statement checklist [34], which further strengthens the relevance, comprehensiveness, and quality of the search strategy. One limitation of this project is the potential for selection bias (specifically for phase 2), where individuals who had either very positive or very negative experiences with patient engagement in research may be more likely to participate in the study, which may limit the applicability of the study's findings. However, the adoption of the iKT approach and having the iKT panels (consisting of youth and their families) assist in the recruitment for phase 2 of the study should result in the recruitment of a variety of individuals with diverse interests.

Conclusions

The current proposal will lead to the development of a youth- and family-specific engagement in research framework, UNITE, with future research focused on the development of an associated validated measure. The UNITE framework and measure will lay the foundation for meaningful and sustained engagement in health research by youth and their families, ultimately contributing to enhanced health care service delivery, improved clinical outcomes, and increased overall well-being and quality of life for youth and their families [1-3].

Data Availability

The data collected during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

SEPM, AT, and CJ conceptualized the overall study design and methods, wrote the manuscript, and approved the final manuscript as submitted. CJ, SEPM, and AT informed the design of the study engagement approach and coordinated the knowledge user engagement. SEPM, CJ, and AT contributed to the design of the study knowledge mobilization strategies. All authors provided input and guidance on the study design and approved the final manuscript as submitted.

Conflicts of Interest

SEPM is the editor-in-chief of *JMIR Rehabilitation and Assistive Technologies*.

Multimedia Appendix 1
PRISMA-P checklist.
[PDF File (Adobe PDF File), 149 KB - resprot_v14i1e65733_app1.pdf]

Multimedia Appendix 2
Medline search strategy.
[PDF File (Adobe PDF File), 95 KB - resprot_v14i1e65733_app2.pdf]

Multimedia Appendix 3
Peer-review report by the Catalyst Grant: Healthy Youth competition, Canadian Institutes of Health Research (Canada).
[PDF File (Adobe PDF File), 281 KB - resprot_v14i1e65733_app3.pdf]

Multimedia Appendix 4
Timelines and milestones for the youth- and family-specific engagement in research (UNITE) project.
[PNG File , 73 KB - resprot_v14i1e65733_app4.png]

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Abbreviations

CIHR: Canadian Institutes of Health Research
iKT: integrated knowledge translation
PCC: population, concept, and context
PEIR: patient engagement in research
PEIRS-22: Patient Engagement in Research Scale-22
PRESS: Peer Review of Electronic Search Strategies
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PRISMA- ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Extension for Scoping Reviews
SPOR: strategy for patient-oriented research
WHO: World Health Organization

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Protocol

Examining Quality of Work Life in Atlantic Canadian Long-Term Care Homes: Protocol for a Cross-Sectional Survey Study

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Abstract

Background: The Canadian long-term care (LTC) workforce cares for increasingly complex residents. With greater care needs come greater demands. Despite this, LTC staffing and resources are largely unchanged and underresearched over the last decade. The Atlantic provinces are home to the oldest population in Canada, indicating a high need for LTC. The health and well-being of the LTC workforce are critical components of care quality, yet only in Western Canada are such data routinely and systematically collected. Translating Research in Elder Care is a 2-decade research program studying the LTC work environment and has found strong links between the working conditions of LTC staff and resident outcomes. We draw upon their success to generate the evidence needed to understand, support, and manage the LTC workforce in Canada's four Atlantic provinces.

Objective: This study aims (1) to assess the quality of work life among staff in LTC homes in Atlantic Canada; (2) to examine the effects of the work environment on the quality of work life; and (3) to build capacity for research in the LTC sector in Atlantic Canada among knowledge users, researchers, and trainees. The objective of this paper is to describe the approach needed to examine the quality of work life and health of care staff in LTC homes.

Methods: Stratified random sampling will be used to recruit homes in Atlantic Canada. The sampling frame was designed to recruit 25% of the LTC homes in each of the 4 provinces with proportional representation by size; ownership model; and, if applicable, region or language. Key outcome variables include measures of mental health and well-being, quality of work life, intention to leave, workplace context, and missed or rushed care. Primary data will be obtained through structured interviews with care aides and web-based surveys from registered nurses, licensed practical nurses, managers, and allied health providers. Eligible participants were from an LTC home with at least 25 residents, 90% of whom were aged 65 years or older, and had worked in the home for at least 3 months. Multivariate analyses include regression analysis for explaining predictors of quality of work-life outcomes and multilevel modeling for more complex relationships of staff outcomes by provinces and LTC home characteristics.

Results: Data collection and cleaning are complete as of October 2024 (N=2305). Care aides (n=1338), nurses (n=724), allied health providers (n=154), and managers (n=89) from 53 homes make up the sample. Data analysis is ongoing. Initially, individual reports will present descriptive data for each participating LTC home. Concurrent analysis is planned for publication in peer-reviewed journals.

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Conclusions: This peer-reviewed research protocol lays the foundation for a comprehensive analysis of the effects of the work environment on the quality of work life of LTC staff in Atlantic Canada.

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(JMIR Res Protoc 2025;14:e66338) doi:10.2196/66338

KEYWORDS

residential long-term care; care staff; Atlantic Canada; quality of work life; work environment; health and well-being

Introduction

Background

This protocol is for a collaborative investigation that aims to address profound deficiencies in data to understand, support, and manage the long-term care (LTC) workforce in Canada's 4 Atlantic provinces. In Canada, LTC homes are funded by provincial governments and provide a range of health and personal care services to predominantly older adults who require 24-hour nursing, personal, and support care [1]. Residents of LTC have higher levels of acuity and have more complex care needs than in the past decade as a result of increased life expectancy and delayed entry due to an increased emphasis on home care [2]. Approximately 81% of residents in Canadian LTC homes live with mild to severe cognitive impairment, 27.1% have seven or more chronic conditions, and 51.5% have extensive limitations in activities of daily living [3]. As the care needs of residents become greater, so do the demands placed on the LTC workforce. Despite this, LTC staffing and resources have remained largely unchanged and underresearched over the last decade [4,5].

The LTC workforce cares for residents with complex needs, but their work environments are strained by heavy workloads, inadequate resources, and critical staffing shortages [4,5]. The health and well-being of the LTC workforce are critical components of care quality [5], and yet only in the Western Canadian provinces of British Columbia, Alberta, and Manitoba are such data routinely and systematically collected [6]. In Atlantic Canada, no data are available on workforce characteristics or the work experiences of LTC care providers (ie, indicators of health, well-being, or burnout). LTC in Canada is provincially regulated, meaning policies, regulations, and practices differ among provinces; fundamental differences in how LTC is organized between Western provinces and Atlantic Canada influence how staff work and care for residents, including staffing models and ratios, and education and training requirements of staff. While many other Canadian provinces have continuously relied on internationally trained care workers to supplement the domestic workforce, this is a relatively new phenomenon in the Atlantic Canadian provinces of Nova Scotia, Prince Edward Island, Newfoundland and Labrador, and New Brunswick. Chamberlain et al [7] reported in 2018 that only 35% of care aides working in Alberta LTC homes spoke English as a first language in comparison to 95% of LTC care staff in a Nova Scotian 2021 pilot study [8]. Additionally, according to the 2021 census, between 96% to 99% of the population in Nova Scotia, Prince Edward Island, Newfoundland and Labrador spoke English as a first language, and as a bilingual province, nearly 70% of the New Brunswick population spoke English as a first language while the remaining 30% spoke French [9]. While recent efforts from governments in Atlantic Canada to bring internationally educated workers into LTC have been largely deemed successful from a recruitment perspective [10-12], little is known about how the changing composition of the workforce impacts the LTC environment. More specifically, it is unknown if, and to what degree, domestic and international staff feel supported as they adjust to a more diverse workplace. Further, the combined population of all 4 Atlantic provinces is fewer than 2.5 million [13] and far fewer staff are trained internationally. These differences limit the ability to generalize workforce data from the Western provinces to Atlantic Canada.

Given the relationship between work and care conditions [14,15], data on the LTC workforce are important as they allow policy makers to identify and address workforce issues that compromise resident care and the health and well-being of care staff. Understanding the work environment will assist in future workforce planning and the strategies designed to improve work conditions and ultimately care conditions.

Translating Research in Elder Care

Translating Research in Elder Care (TREC) is a program of research spearheaded by Carole Estabrooks and a group of researchers from Alberta Canada who have been studying the LTC work environment in the Western Canadian provinces for nearly 2 decades [6]. TREC has analyzed the impact of the LTC work environment on staff quality of work life, mental health, and well-being outcomes in 7 waves of data collection [5,7,16-18]. These data enable in-depth longitudinal analysis that demonstrates the impacts of policy changes, interventions, and events such as COVID-19 [19-21]. The TREC research program also links the staff survey data within a clinical microsystem to resident outcomes using data from the Resident Assessment Instrument for LTC [22]. Evidence of strong links between the working conditions of LTC staff and resident outcomes is reported. For example, significant relationships were found between the use of best practices and care staff's social capital and organizational slack (time and staffing) [23]. In examining the demographic profile of the LTC workforce, staff who provide the majority of direct resident care had little formalized training, were racially diverse, and had high rates of English as a second language [7]. More recently, TREC has designed and delivered interventions to enhance the work environment in LTC, such as Safer Care for Older Persons in (residential) Environments [21] and Improving Nursing Home care through Feedback on Performance [24], and a coherent breathing intervention to decrease stress, insomnia, and anxiety [25].

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The TREC measurement system, including the care aide structured interview and the regulated staff web-based survey, were consistent with the instruments used in this study in Atlantic Canada. The minor exceptions were because of localized staff job titles and translation of survey instruments to enable staff in designated French LTC homes in New Brunswick to participate in their French language. The goal of our team is to build upon the work of TREC and to use their comprehensive data collection tools to build an Atlantic Research Collaboration (ARC) and to generate the evidence needed to understand, support, and manage the LTC workforce in Canada's 4 Atlantic provinces. Ultimately, we will identify work environment areas that are amendable to intervention so that targeted interventions can be designed and delivered at the regional, provincial, institutional, and unit levels to enhance the quality of the LTC work environment.

Study Purpose and Objectives

This ARC on LTC (ARC LTC) involved researchers and collaborators form 4 provinces to describe and examine the relationship between the health and quality of work life of LTC staff and their work environment (organizational context). The research aims are as follows.

- To assess the quality of work life among staff in LTC homes in Nova Scotia, Prince Edward Island, Newfoundland and Labrador, and New Brunswick.
- To examine the effects of the work environment on quality of work life.
- To build capacity for research in the LTC sector in Atlantic Canada among knowledge users, early career researchers, and trainees.

Methods

Study Design

This is a cross-sectional, multilevel survey study with an integrated knowledge translation approach with knowledge users (ie, representatives from LTC homes, health authorities, provincial ministries, and key sector organizations) embedded throughout the project. We use the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) reporting guidelines for web-based or internet surveys as a framework for our approach [26]. A detailed description using the CHERRIES checklist is present in Multimedia Appendix 1. Our methods are consistent with the established recruitment and data collection protocols used by TREC [23,27] and will enable comparison of data not only across the Atlantic Canadian provinces but also with the Western Canadian provinces.

Study Context

The LTC sectors in Atlantic Canada are diverse with variations in names assigned to LTC homes, regulatory oversight, ownership models, and titles given to unregulated care staff (Table 1). The study's design is sensitive to these differences with some modifications made to the sampling frame to reflect the uniqueness of individual provinces. In this protocol, we use the terms LTC home and care aide to describe the facility where care staff work or residents live, and the unregulated staff, respectively.

Table 1. Characteristics of homes by province in 2023.

Characteristics	Nova Scotia	New Brunswick	Newfoundland and Labrador	Prince Edward Island
Name of LTC[a] homes	Nursing home	Nursing home	LTC homes	Manors or nursing homes
Government responsible	Department of Seniors and LTC	Department of Social Development	Department of Health and Community Services	Department of Health
Legislative framework	Homes for Special Care Act	Nursing Home Act	Health and Community Care Services Act	Community Care Facilities and Nursing Homes Act
Ownership model	Public, private for-profit, and not-for-profit	Private corporations run by boards of directors	Public	Public, private for-profit, and not-for-profit
Title for unregulated care staff or care Aides	Continuing care assistant	Resident aide	Personal care attendant	Resident care worker
Regulated nursing staff	Registered nurses and licensed practical nurses	Registered nurses and licensed practical nurses	Registered nurses and licensed practical nurses	Registered nurses and licensed practical nurses
Allied health providers presence of these providers varies by province and LTC home	Recreation therapist, aide social worker, dietitian physiotherapist, aide occupational therapist, and aide	Recreation therapist, aide social worker, dietitian physiotherapist, aide occupational therapist, and aide	Recreation therapist, aide social worker, dietitian physiotherapist, aide occupational therapist, and aide	Recreation therapist, aide social worker, dietitian physiotherapist, aide occupational therapist, and aide

[a]LTC: long-term care.

Theoretical Framing

The critical socioecological framework [28] is used to guide this research. This framework depicts how behaviors are influenced by characteristics of, and interactions between, the individual and immediate social network (microsystem), local environment or community (mesosystem), and the larger system (macrosystem). The ecological framework supports the bidirectionality of this influence (eg, the work environment may affect individual staff feelings of well-being and vice versa). The framework highlights the complexity of staff's experiences

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and agency within the LTC environment and their ability to engage in change to enhance resident care. It acknowledges how the work environment is shaped and buffered by factors in the micro, macro, and meso levels. Embedding our research in the critical socioecological framework will enable us to examine the inter-relationships among individual experiences, the work environment, and the larger provincial and regional LTC policy context.

We will examine LTC at the macro, meso, and micro levels (see Multimedia Appendix 2 [29-39] for how the survey content is organized at the meso and micro levels). At the macro level, all 4 Atlantic provinces provide public funding to LTC. Although regulations, guidelines, and staffing ratios differ by province, individual homes vary in how they operationalize them internally. At the meso level, institutional practices, policies, and work culture, along with heavy workloads associated with complex LTC residents have a major impact on staff. About 80% of resident care in Canada is provided by unregulated care aides who have little, if any, formal education [7]. Despite their pivotal role in LTC, care aides may not receive the recognition they deserve, nor do they always feel like valued members of care teams [23]. Contextual factors in work environments such as leadership, culture, and social capital, influence individual staff at the micro level and account for greater job satisfaction, empowerment, and autonomy [40,41]. The critical socioecological framework can facilitate our understanding of the multilayered influencers on LTC staff's quality of work life, and ultimately, resident care and quality of life in LTC homes in Atlantic Canada.

The dynamic nature of the LTC environment including things such as changes in the complexity of resident care needs and the increasing number of staff who speak English as a second language, could prompt changes in workplace policies and culture. Changes in both policies and culture can impact how staff work at the micro level as well as how organizations operate at the meso level. The nature of these bidirectional relationships affects how staff work, how they experience their work, and their perceived ability to support the changes needed in the work environment.

Sampling

Facility Sampling and Eligibility

A stratified random sampling technique will be used to recruit homes from each of the 4 provinces. The sampling frame was designed to recruit 25% of the LTC homes in each province (Table 2) with proportional representation by size (large: >120 beds; medium: 70-119 beds; and small: 25-69 beds); ownership model (eg, public, not-for-profit, and private for-profit); and, if applicable, region or language. These strata have been previously associated with residents' quality of care [42,43]. Oversampling will be done in Newfoundland and Labrador and Prince Edward Island to ensure a minimum of 8 homes in these provinces and a sufficient sample to enable cross-tabulation. Because Prince Edward Island only has 1 health region, and New Brunswick is a bilingual province with designated English and French homes, the region strata will not be used in Prince Edward Island, and linguistic designation will be used in New Brunswick.

To be eligible to participate, homes need to provide 24-hour, on-site housing and health care services for older adults by professional (nursing) staff, be stand-alone facilities (ie, not attached to an acute care hospital), and have a minimum of 25 LTC beds with at least 90% of the resident population aged 65 years or older. Homes will be ineligible if they are hybrid care homes integrated with an acute care facility or hospital, or share central services (eg, human resources and laundry) with an acute care facility or hospital.

Table 2. Number of LTC[a] homes included in the sample and strata by province (2023 estimates).

Characteristics	Nova Scotia	New Brunswick	Newfoundland and Labrador	Prince Edward Island	Total
Total number of LTC homes, n	92	73	43	19	227
Eligible homes, n (% of total)	81 (88%)	71 (97.3%)	27 (62.8%)	15 (78.9%)	194 (85.5%)
Sample (25% of eligible), n	20	18	8[b]	8[b]	54
Strata	Region ownership size	Language size	Region size	Ownership size	__[c]

[a]LTC: long-term care.

[b]Newfoundland and Labrador and Prince Edward Island were oversampled.

[c]Not applicable.

Staff Sample and Eligibility

Our sample will include senior administrators, managers, regulated nursing staff, unregulated care staff, and allied health providers (Table 3). All staff must have worked at the LTC home for 3 months or longer. In addition to the 3-month criteria, managers must work a minimum of 50% of the time at the LTC home, nurses must work a minimum of 6 shifts a month at the LTC home, care aides must be able to identify a unit they work on more than 50% of the time and work a minimum of 6 shifts a month on that unit, and allied health must provide at least one-third of their services that equals 6 days a month at the LTC home. Senior administrators who hold executive positions in LTC, such as chief executive and operation officers, will be required to provide the standardized facility (eg, physical design) and unit-level data (eg, staffing models).

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Table 3. Estimated number of care staff in LTC[a]—both regulated and unregulated by province.

Characteristics	Nova Scotia	New Brunswick	Newfoundland and Labrador	Prince Edward Island	Total by staff group
All registered nurses or licensed practical nurses in LTC, n	1611	2625	1278	299	5813
Sample pool from LTC homes (25%), n	322	656	320	150[b]	1448
Desired sample (60% of eligible staff), n	193	394	192	90	869
All care aides, n	3866	4875	962	710	10,413
Sample pool from LTC homes (25%), n	773	1219	241	355[b]	2588
Desired sample (60% of eligible staff), n	464	731	144	213	1553
Desired care staff (registered nurses, licensed practical nurses, or care aides) sample total, n	__[c]	—	—	—	2422

[a]LTC: long-term care.

[b]Prince Edward Island was oversampled (50%).

[c]Not applicable.

Sampling Procedures

With the exception of Prince Edward Island, each province will have a team of staff responsible for recruitment and data collection. Due to the size and resources in Prince Edward Island, recruitment and data collection will be assigned to the Nova Scotia team. Each provincial research team will create a database of their LTC homes that includes information on each stratum, along with the name and contact information of facility administrators. The stratified proportional random sampling procedure will be performed centrally by a project manager who will then inform provincial teams of the randomly selected LTC homes to recruit. Homes identified in the randomization procedure will be emailed a letter of invitation from the province's lead investigator and if necessary, a follow-up phone call from a member of the research team. Meetings via Microsoft Teams will be held with homes who express interest in the study. During these meetings, the nature and purpose of the study will be explained along with details of what participation entails. Homes that agree to enroll in the study will be asked to sign a facility agreement form that outlines the expectations of participation. If approval of an operator is required for facility participation the operator is asked to sign an operational approval form prior to the home signing a facility agreement.

Once a home agrees to participate, research staff will conduct orientation meetings (one in-person visit and MS Team or telephone meetings as needed) with administrators and site liaisons to (1) verify the eligible participant pool for completing staff surveys; (2) identify the number and types of care units, staff assignment, and shifts; and (3) discuss the logistics of data collection (eg, dates for data collection, promotion and recruitment strategies, interview flow and schedule, contact information for a site liaison).

Measures

Data will be collected using TREC's suite of survey instruments. TREC data collection tools have been administered in Western Canada at several points in time [5,7,18,23] and in Nova Scotia in 2021 with 10 LTC homes [8]. A key component of the surveys is the Alberta Context Tool (ACT), which was developed to measure 10 dimensions of the organization context within health care settings (eg, leadership, culture, feedback, staffing). The ACT contains slight variations for each category of staff and was developed and refined for use in LTC [44]. In addition to the ACT, other surveys will be used to collect data on staff demographics, their perceptions of physical and mental health, well-being, burnout, job satisfaction, as well as missed and rushed care. Permission to access and use these tools has been obtained. Minor revisions to the survey instruments have been made with permission to reflect Atlantic Canada–specific context (eg, provincial term used for care aides). Details of these tools, including their psychometric properties, are outlined in Multimedia Appendix 2 [29-39].

Translation

Many of TREC's suite of tools are only available in English, which means they have to be translated to French to accommodate the New Brunswick French LTC homes. The quality of these translations is critical in maintaining the integrity of the data collected, and the comparability of data across provinces. The TREC research team has a preexisting rigorous translation protocol that was modified by Hoben et al [45] and is based on international best practices [46]. The first step in the process is to identify the proprietary rights of each survey and to establish which tools are available in French. Of the tools in the suite, 6 tools have existing French versions, and 2 of these cannot be altered. We will obtain permission to translate the remaining 6 tools from English to French (Multimedia Appendix 2).

Translation of these 6 tools and the full TREC survey will involve a rigorous systematic process of forward translation from English to French, back translation from French to English, and cognitive debriefing. Once the forward and back translation processes are completed, additional reviewers will examine the changes for accuracy and precision and, if necessary, make recommendations for the final translation.

We will recruit 4 LTC staff members to complete the translated surveys to verify the understanding, clarity, and appropriateness

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of the items. This step is for language, comprehension, and cultural issues only; these pilot data will not be included in the study's sample.

Additional translations will also be required for other research materials, such as demographic questionnaires, consent forms, standardized instructions, and explanations of items within individual surveys.

Data Collection Procedures

Based on TREC's experience, data to determine care home units for the study and the number of eligible staff will be collected during the initial in-person meeting between a member of the research team and an LTC care home administrator. Data collection for staff will not begin until these data are obtained. Meetings will take approximately 1 hour and will include a tour of the LTC facility and will allow research staff to build a relationship with care home administration.

A staff member at each care home will be designated as the site liaison by the LTC administrator. The site liaison will work with research staff on promotion, participant recruitment, and scheduling of data collection. An individualized data collection schedule will be cocreated for each home that allows for maximum access to eligible staff and minimum disruptions to the home. Data collection will take place during days, evenings, nights, and weekends. Data collection will be scheduled over a 1-week period, but, if necessary, more time will be provided.

Informed consent will be obtained from all staff prior to data collection. Staff survey data will be collected through a self-administered web-based survey or during a structured interview using Microsoft Teams. Regulated staff will be provided with a link to the closed web-based survey and instructed to complete it voluntarily and independently on the web using the Nooro research platform, on which the survey was thoroughly tested by project staff prior to data collection. Codes given to staff can be used to leave and reenter the survey without losing progress; once the survey is submitted, the code can no longer be used to access the survey thus preventing duplicate entries.

Care aides (unregulated staff) will be scheduled to meet in a private and quiet space with a trained data collector via Microsoft Teams. The data collector will administer the surveys using Computer Assisted Personal Interviewing (CAPI) techniques; survey questions will be read to the participant in a structured interview format using standardized language, and the data collector will enter responses directly into the Nooro research platform. In the event of a staff member becoming upset during data collection, interviews will be paused, and a support protocol will be initiated, including the provision of a list of local mental health resources. The variation in data collection procedures between regulated staff and care aides is based on previous feasibility testing conducted by the TREC team which determined structured interviews are more effective than self-administered web-based surveys for care aides and can be conducted in less time [27].

Facility- and Unit-Level Data

One facility profile survey will be completed for each participating LTC home, and unit profile surveys will be completed for each unit in the LTC home. These surveys collect data such as the size, ownership model, unit information (ie, number and size of resident care units), types of units (eg, dementia and psychiatric), human resources (eg, physicians and nurse practitioners), care staff complement (eg, type and number of staff on each unit on a given shift), quality improvement activities, and access to programs and services. These surveys will be completed by research staff with LTC administrators or their designate (eg, a director of care or unit manager) through Microsoft Teams during or shortly after the staff data collection period.

Staff Data

Surveys or interviews can be completed during work time and will take approximately 35 minutes. Multimedia Appendix 2 details the measures that will be collected. Survey item totals varied by staff survey type: care aide surveys have 154-169 items depending on responses to adaptive questions and are answered continuously in the interview format; nurse surveys have 207-219 items across 50 pages; allied health surveys have 138-149 items across 37 pages; and manager surveys have 209-229 items across 53 pages. Items or scales were not randomly ordered. Regulated staff completing the web-based survey could review and change their answers if desired before submission. There are no automatic completion checks alerting participants if their web-based survey contains missed items. Data collectors administering the care aide survey are to check for completion, however, it is not obligatory for care aides to answer missing items.

Data Collector Training

Training will be in accordance with TREC's training program for quality assurance purposes and to ensure consistency. Data collectors will receive in-depth standardized CAPI and survey interview training, which will be done in collaboration with TREC's field coordinator and the ARC LTC staff who have experience with implementing the TREC Survey.

Data collectors will participate in 3 training sessions followed by a quality assurance test. The 3 sessions will be 2-3 hours long and delivered in-person or using Microsoft Teams meetings. These web-based sessions will be recorded for onboarding additional staff at later points in time. The sessions will include didactic teaching, group discussion, and survey practice with peers. Topics will include project background, survey overview, CAPI administration, accessing the survey platform, consent process, shift schedules and resources, and strategies for challenging interviews (eg, technology issues, managing participant distress, keeping participants on track). In addition to survey practice during the 3 sessions, data collectors will be instructed to practice on their own or with friends and family.

During the quality assurance testing, each data collector will complete a minimum of 2 surveys. Data collectors must meet all criteria (eg, obtaining proper consent, reading questions verbatim, appropriate use of scales, proper flow, correctly

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inputting responses, acting professional, answering or navigating participant questions, managing technology issues, managing participant distress, keeping participants on track). If necessary, additional training will be provided to data collectors on an individual basis to ensure they are able to conduct quality interviews meeting all quality assurance criteria.

Upon completion of training, each data collector will complete at least 1 practice interview with an ARC LTC staff member. Data collectors must receive approval from the ARC LTC staff before being cleared to conduct interviews. Ongoing quality assessment will continue throughout the data collection phase to ensure proficiency in administering surveys using CAPI, consistency between data collectors, and consistency across time ensuring high-quality data.

Ethical Considerations

Ethical approval for this protocol was obtained from the research ethics boards of the academic institutions of each of the investigators. The study was first reviewed and approved by the Research Ethics Board at Mount Saint Vincent University, Nova Scotia (2023-039), and then subsequently reviewed and approved by ethics boards at Dalhousie University, Nova Scotia (2023-6887); University of New Brunswick (2023-133); Memorial University of Newfoundland (2023.212 or 2024.1112); and Health Prince Edward Island (2023-10-19 or 2024-02-12). Care staff participation will be voluntary, and the information collected will be completely confidential. Data collection with care staff will be held in a private location and no names will be stored with study data. Potential participants will be sent a copy of the consent form prior to the interview, and it will be reviewed just prior to initiating an interview. Informed consent including the purpose of the study, approximate length of completion, data storage and privacy, research team, and ability to opt-out at any time prior to survey completion will be obtained prior to starting the survey. After each care aide survey, the data collector will complete an interview checklist which will capture feedback on the interview and rate its quality. Biweekly data quality reports will be compiled and the number of interviews completed and in progress, time to complete interviews, and occurrence and nature of missing data or extreme scores will be reviewed by investigators and staff. Any unexpected issues will be reviewed with data collectors on a regular basis. Data collectors may be observed conducting interviews for ongoing quality assurance purposes. Data are anonymized upon survey entry, and as such, there is no way to identify or remove participants' responses once the survey has been submitted. Study reports at the unit level will only be available if more than 8 staff from the care unit participate; in cases where fewer than 8 staff from 1 care unit participate, reports will only be available at the facility level to protect participants from being identified. No data will be presented unless the cell size is 5 or more. The identities of the LTC homes that participate will also be held in confidence; sites will only be described by their province, size, region, and language. All the data and the results will be kept indefinitely on a secure server in the Health Research Data Repository that resides in the Faculty of Nursing, University of Alberta. The nominated principal investigator JMK is the data custodian for these data. Contingent on subsequent ethics reviews, its access will be highly restricted. The Health Research Data Repository will support storage, data analysis, and access control for all ARC LTC team members and trainees. Research team members may access the data remotely using unique usernames and strong passwords. Users are unable to download any data or access the internet while logged into the repository. Identifiable data and personal information will be stored separately from their deidentified counterparts to ensure participant confidentiality. Any print documents will be stored securely in locked file cabinets by the project lead in each of the provinces. All staff who participate in the study will receive a CAD $10 (US $7.55) coffee gift card as a token of appreciation. These cards will be supplied to the facility liaison who will hand out cards to staff who agree to participate on survey completion. In addition, LTC homes that participate will be provided with a small stipend at the completion of the study to compensate for any work associated with their participation; the stipend will be based on the size of the home (ie, small, medium, or large). All staff will be given an opportunity to obtain a copy of the study's findings.

Knowledge Translation

As part of the feedback process, tailored reports will be generated for each individual care home. These care home reports will be shared with the home administrator. Staff participants will be given the opportunity to receive a generalized report on the study's findings. If they wish to receive results, they will be asked at the end of the survey to provide an email address. Email addresses for feedback purposes will not be linked to any data provided by participants.

Data Analysis Plan

To assess the quality of work life among staff working in LTC homes in Atlantic Canada, data will be analyzed by home, by province, and in combination to identify and assess associations, interactions, and predictors of health and work-life outcomes. No correction methods will be calculated. Regression analysis and statistical modeling techniques will be used to explain how work environments within LTC homes are impacting the quality of work life and health of staff. For example, is the work environment (an independent variable) correlated with job satisfaction and burnout? In what way do demographic variables, such as age, or English as a second language mediate the effect of work environment on quality of work life and intention to leave? Multimedia Appendix 3 shows the proposed statistical approaches. Multilevel modeling will be conducted to explore the complex interplay among characteristics at the micro (eg, LTC staff), meso (eg, unit and facility), and macro (eg, province) levels and their effects on indicators of quality of work life and health. Early careers researchers, trainees, and knowledge users will be involved in all aspects of data analysis to help build capacity for research in the LTC sector in Atlantic Canada.

Results

Data collection occurred between November 2023 and June 2024 and is complete. Between July 2024 and September 2024, data were cleaned and organized for analysis. Data analysis is underway. Initially, individual reports will present descriptive data for each participating LTC home comparing their staff responses to mental health and well-being by occupational group

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with those of staff from all other facilities participating in their province. A series of three reports are proposed: (1) demographics and perceptions of work life (eg, burnout, job satisfaction, and intention to leave); (2) personal health and well-being (eg, general anxiety, posttraumatic stress disorder, and insomnia); and (3) organizational context (including the 10 dimensions of the ACT [44]; eg, leadership, culture, feedback, and staffing). Concurrent with this descriptive analysis, analytical analysis is planned for publication in peer-reviewed journals.

Discussion

Overview

This study aligns with Canadian and global priorities related to creating a sustainable health workforce and improving service delivery for those residing in LTC [47]. Specifically, our study builds on the influential research of the TREC group in Western Canada who developed and refined a comprehensive methodology for understanding the context of LTC and more notably, identifying solutions for enhancing the work environment and improving the quality of resident care [15,20]. Such work has been proven effective in enriching the work life of staff and improving system efficiency [15,16]. To date, a key finding of TREC's work is the importance of organizational context to support the implementation of interventions to improve staff outcomes. Given the difference in the organization and delivery of LTC services across Canadian provinces [4], this study will generate much-needed data for enhanced and targeted planning and decision-making in the Atlantic LTC sector. Findings from this study will support a greater understanding of our LTC work environment and workforce, and to use these regional data to determine where knowledge users can introduce interventions to improve staff quality of work life.

Expected Findings

Concerns about the LTC workforce have existed for some time, but these have heightened since the COVID-19 pandemic [41]. The pandemic brought unprecedented challenges to LTC and staff were forced to navigate these stressors while maintaining the highest standards of care under difficult and often unsafe conditions. We expect to verify the extent to which these conditions continue to impact staff's health and well-being, including stress, anxiety, and quality of work life, and assess whether care aides continue to report a poorer quality of work life than other LTC staff as reported in a Nova Scotian study in 2021 [48]. This Nova Scotian study's finding is significant as it underscores the distinct struggles care aides face in LTC. These struggles may stem from providing direct care to increasingly complex residents or they may be associated with undervaluing of their work within an LTC work environment (eg, low pay, limited education), or both.

Should our research findings, across LTC settings and geographical locations, be consistent with those of the study by Keefe et al [48], it will provide further evidence to advocate for tailored supportive interventions specifically designed for care aides. For instance, our findings could inform policies related to the minimum educational requirements of care aides, which are currently lacking in some Atlantic Canadian provinces. Research findings could also support the need for job redesign, particularly efforts to provide care aides with more formal interaction within the workplace. Enhancing care aides' inclusion into decision-making processes, providing mentorship programs, or enriching team-based care in a way that acknowledges and values the perspective that care aides bring will enable greater connection to their workplace [16,49,50]. Such approaches could recognize the vital contributions of care aides, affirming their roles as essential members of care teams, and enhancing their status within the workplace.

We are confident that our study will provide data to assess recent policy initiatives within Atlantic Canada regarding the recruitment of internationally educated nurses to address the staffing shortage in LTC. These efforts include targeted recruitment campaigns, streamlined credentialing processes, and both professional and personal support programs. In the short term, these efforts appear to be successful as evidenced by the increasing number of nurses who have migrated to the region from targeted countries. However, despite these short-term successes, little is known about the long-term sustainability and effectiveness of these recruitment strategies, especially in terms of retention and overall job satisfaction. This gap is important because the long-term success of these initiatives is crucial for ensuring that Atlantic Canada can maintain a stable and skilled health care workforce in the face of ongoing human resource challenges. Our data will offer valuable insights not only into the work patterns of these migrant workers but also into their work integration experiences, including job satisfaction, relationships with colleagues, and their intentions to leave their current roles. Such information will be crucial for understanding the true impact of international recruitment efforts and for identifying areas where improvements can be made to enhance retention and overall workforce stability in our region.

It is also expected that our findings will be able to provide recommendations for how to address the deficits in the LTC system that have been exposed during the COVID-19 pandemic [51]. As the Atlantic provinces are home to the oldest population in Canada, policy makers require region-specific data to ensure sustainable and quality LTC is available for those who need it. Efforts to provide quality LTC must recognize that work conditions are care conditions, and consider the context where care takes place. The results of this study will support workforce planning and provide much-needed data on the LTC sector's current and future capacity. Study findings promise to identify elements in the work environment that are amendable to change and enable policy makers to develop strategic responses needed to support care staff, enhance worker health and well-being, and ultimately create the conditions that maximize staff's ability to provide quality care.

Limitations

The study has a number of limitations. While it is anticipated that there will be great interest among the LTC sector to participate in this research, it is possible that some homes may still be recovering from the pandemic or have human resources challenges that preclude them from participating in the study.

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We are using a stratified random sample to ensure provincial representation but the strata used in the sampling frame need to be adapted to reflect the uniqueness of each province. For example, language (French and English) is a stratum used only in the sample of LTC homes in New Brunswick, and the ownership model (ie, public, private for-profit, and not-for-profit) is only being used with the LTC homes in Prince Edward Island and Nova Scotia. While the decision to modify these strata was made to ensure adequate representation of subgroups within each province, we recognize the need for our data analysis procedures to account for these differences. We will perform rigorous comparisons between provincial data to identify and account for differences in strata. If necessary, we will use statistical techniques such as multilevel modeling to account for differences across provinces. We will also acknowledge any potential threats to external validity that may arise as a result of our sampling plan during our dissemination activities.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are not publicly available due to limited access to the University of Alberta Health Research Data Repository where they are housed. Data are available from the corresponding author on reasonable request.

Authors' Contributions

JMK is the lead researcher and nominated principal investigator who received Canadian Institute of Health Research, Research Nova Scotia, and Health Prince Edward Island funding. CAE is the principal investigator of the Translating Research in Elder Care research program whose surveys are used in the study. CAE and RM are co–principal investigators and RM received funding from Research New Brunswick. LEW, CM, AM, and MJH are coinvestigators on the research proposal. RM and JMK drafted the manuscript. MJH and CAE provided input into the statistical analysis for the study. All authors contributed to the manuscript and approved the submitted version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Checklist for Reporting Results of Internet E-Surveys (CHERRIES).
[PDF File (Adobe PDF File), 162 KB - resprot_v14i1e66338_app1.pdf]

Multimedia Appendix 2
Overview of instruments used to measure micro- and meso-level concepts in the Atlantic Canada long-term care study: Translating Research in Elder Care survey.
[PDF File (Adobe PDF File), 336 KB - resprot_v14i1e66338_app2.pdf]

Multimedia Appendix 3
Analytic Plan.
[PDF File (Adobe PDF File), 123 KB - resprot_v14i1e66338_app3.pdf]

Multimedia Appendix 4
Peer review report.
[PDF File (Adobe PDF File), 832 KB - resprot_v14i1e66338_app4.pdf]

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Abbreviations

ACT: Alberta Context Tool
ARC LTC: Atlantic Research Collaboration on Long Term Care
CAPI: Computer Assisted Personal Interviewing
CHERRIES: Checklist for Reporting Results of Internet E-Surveys
LTC: long-term care
TREC: Translating Research in Elder Care
HRDR: Health Research Data Repository

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Protocol

Effect of an Online Mobility Self-Management Program on Walking Speed in Older Adults With Preclinical Mobility Limitation: Protocol for a Randomized Controlled Trial

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Abstract

Background: Walking difficulties are a common and costly problem. However, disability associated with the decline in walking ability is not an inevitable consequence. With an aging population, it is increasingly important to establish strategies to help older adults preserve the capacity to live independently and function well in late life. Preclinical mobility limitation (PCML), which is characterized by subtle changes or limitations in mobility that precede disability, manifests as changes in how daily tasks such as walking are performed. Persons with PCML are at increased risk for the onset of disability and chronic disease. For that reason, PCML is a critical stage in the natural history of functional change when there is the opportunity for primary prevention interventions.

Objective: To evaluate the effect of a 12-week online mobility self-management program (Stepping Up) on mobility outcomes, including walking speed, aerobic exercise capacity, dual-task cost, physical functioning (balance and strength), balance confidence, extent of community mobility, self-management of mobility, and quality of life in older adults with PCML.

Methods: This randomized controlled trial (RCT) will recruit 249 older adults (aged 55-75 years) screened for PCML. Participants will be assigned to the Stepping Up program, a telephone-based coaching walking program or an online chair-based yoga program.

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Programs will be delivered over 12 weeks and participants will undergo virtual assessments with a blinded physiotherapist at baseline, 12, 24, and 36 weeks. An economic evaluation will be conducted alongside this RCT.

Results: A total of 253 participants were enrolled in the trial. Data collection commenced in August 2021 and will be completed in October 2025. Data analysis will begin in November 2025 and results will be published in the Summer of 2026.

Conclusions: To our knowledge, PCML has not been addressed by primary prevention interventions that incorporate both task-oriented motor learning exercise and mobility self-management sessions. Results will establish if the Stepping-Up program has the potential to serve as a model for sustainable, accessible, and cost-effective programming for individuals with early mobility limitations.

Trial Registration: ClinicalTrials.gov NCT04368949; https://clinicaltrials.gov/study/NCT04368949

International Registered Report Identifier (IRRID): DERR1-10.2196/72585

(JMIR Res Protoc 2025;14:e72585) doi:10.2196/72585

KEYWORDS

mobility; self-management; task-oriented motor learning; preclinical mobility limitation; walking speed

Introduction

Background

In 2024, 1 in 5 Canadians is older than 65 years and many of these individuals are experiencing some change in their walking ability [1]. Sufficient walking speed is a cardinal indicator of the mobility required to fulfill most tasks that humans undertake. Slowing of walking speed is associated with increasing age and has been associated with both survival [2,3] and independence [4,5]. Walking difficulties represent a common and costly problem [2]. However, disability associated with a decline in walking ability is not an inevitable consequence of aging [6]. With an aging population, it is increasingly important to establish strategies to help older adults preserve the capacity to live independently and function well later in life. The development of cost-effective interventions for primary prevention of mobility limitation is of paramount importance to the health care system. Health care costs in a US Medicare sample were US $2773 per year higher for persons who report difficulty walking half a mile and US $3919 higher for persons who were unable to walk this distance [7]. Further studies have estimated that over a one-year period, persons who developed mild walking difficulties had higher health care costs (US $1128 per person), which has been estimated at a societal cost of US $3.6 billion for the 22% of older persons who report incident walking difficulties annually [8,9]. There is currently no comparable Canadian cost data available.

Mobility, the ability to move within one's environment, is essential to maintaining independence [6]. Importantly, changes in mobility are frequently the first indication of functional decline [10,11]. The onset of mobility decline is characterized by frequent transitions between states of mobility independence and mobility limitation and represents a highly dynamic process that is often indicative of health status [10,12,13]. Mänty (2007) [14] hypothesized that major mobility disability develops through stages, beginning with preclinical mobility limitation (PCML) which is characterized by subtle changes or limitations in mobility.

PCML manifests early in the process of declining mobility and is not typically identified or acted upon by clinicians. The prevalence of PCML in community dwelling samples ranges 20%-40% [15] and 31%-55% in adults over 75 years [16]. These mobility limitations manifest as changes in how daily tasks such as walking are performed (slower speed and lower endurance). Persons with PCML are at increased risk for the onset of disability and chronic disease [17,18]. Persistent deterioration in mobility is a predictor of mortality and has been reported even in the absence of changes in activities of daily living over a two-year period [19]. Further, older persons with mobility limitations, including reduced gait speed, are at risk for falls [4,20]. Thus, PCML is a critical stage in the natural history of functional change with aging when there is the opportunity for primary prevention interventions [21,22].

Interventions to improve walking (gait) are usually impairment-focused, aimed to address issues such as strength, flexibility, and endurance [23]. However, recent evidence suggests that interventions aimed to optimize mobility in older adults must also address task-oriented motor sequence learning to improve walking skills [23]. Motor skill-based exercise needs to address several components to optimize benefits to walking ability that include (1) an identified movement goal, (2) movement that provides feedback about muscle ability, posture, and movement awareness, (3) repetition and practice to correct errors, and (4) altering the environment and practice conditions to select an optimal motor plan [23].

Two randomized controlled trials (RCTs) examining the effect of task-oriented motor learning (TOML) exercise on mobility delivered to older persons (mean age 77.2, SD 5.5 years) showed greater improvement in energy cost of walking, gait quality, walking confidence, and physical function compared with persons who participated in impairment-focused exercise [24,25]. A recent large scale RCT (n=298) in senior residential apartments found a significant difference between an intervention focused on coordination and timing versus a seated strength and flexibility control. The between-group difference on the 6MWT was 17 m (P=.03) and between-group difference on gait speed measured using an instrumented walkway was 0.05 m/second (P=.02) [26]. Using a TOML approach facilitates the re-education of basic functional movement patterns to a wide variety of dynamic activities and targets more integrated aspects of balance and mobility.

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Self-management (SM) has been promoted to increase healthy behaviors and manage symptoms for persons with chronic conditions [27]. Studies have examined the use of SM to deliver rehabilitation-based principles and manage musculoskeletal issues associated with chronic conditions [27-29], but SM has not been used to address changes in mobility.

According to our research, PCML has not been addressed by tailored primary prevention interventions that incorporate both TOML and SM. From 2014-2016, we undertook a pilot RCT (n=89) to compare an intervention that combined TOML exercise and mobility SM principles (Stepping Up) to an existing community-based fall prevention program. In the pilot, we established the feasibility and acceptability of the intervention as well as preliminary effects [30]. We now propose a fully powered RCT to demonstrate that the Stepping Up program will improve walking in persons with PCML.

Objectives

Our primary objective is to determine if a 12-week mobility program called Stepping Up is more effective than a telephone-based coaching walking program or a chair-based yoga program at improving walking speed, assessed using the Four-Meter Gait Speed (4MGS) test. Secondary objectives are to compare the effectiveness of the Stepping Up program to the telephone-based coaching walking program and the chair-based yoga program for the following outcomes: (1) gait speed at 24 and 36 weeks and (2) aerobic exercise capacity, dual-task cost, physical functioning (balance and strength), balance confidence, extent of community mobility, SM of mobility, and quality of life at 12, 24, and 36 weeks.

We will compare the cost-effectiveness of the Stepping Up program to the telephone-based coaching walking program and the chair-based yoga program with respect to health care usage costs (including hospitalizations and physician visits) and program-related costs over 36 weeks.

Focus groups will be conducted to discover how participants in the Stepping Up program develop their mobility skills in comparison to those in the telephone-based coaching walking program and chair-based yoga program.

Methods

Trial Design

This is a pragmatic RCT [31,32], evaluating a complex intervention and reflecting the heterogeneity of individuals living in the community with PCMLs who might benefit from this intervention. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist is available in Multimedia Appendix 1. Both outcome assessors and data analysts will be blind to group allocation. Participants will be evaluated at 4 time points: baseline (0 weeks), at the end of the intervention (12 weeks), and at follow-up (24 and 36 weeks).

Study Setting

The Stepping Up and chair-based yoga interventions will be delivered in synchronous online classes, and the telephone-based coaching walking intervention will be delivered by phone. This trial was initially planned for in-person delivery but switched to online delivery due to COVID-19 restrictions.

Eligibility Criteria

Potential participants will initially be screened by phone and subsequently via videoconferencing by the research coordinator (RC) who is a physiotherapist. Inclusion criteria include (1) community-dwelling, (2) age ≥55-75 years, (3) PCML as assessed using a questionnaire that requires respondents to self-report difficulties with their mobility (walking 2 km). Respondents will be considered in a stage of PCML if they report no task difficulty but report modification of task performance (ie, modify frequency, method, or time to complete the task) [14], (4) understanding of spoken and written English, (5) own a laptop, computer, or tablet and have an email address and the internet capabilities of running the videoconferencing platform, Zoom (Zoom Video Communications). We will exclude persons (1) with a score of <11 on the Montreal Cognitive Assessment 5-minute telephone screen [33], (2) with a major illness that would prevent participation, (3) who are not residents of Ontario, and (4) receiving active physiotherapy treatment.

Following screening by telephone, each potential participant will be emailed a copy of the information letter and consent form. During an introductory Zoom session with each participant, the RC will review the information letter, answer all questions, and obtain verbal consent. The RC will keep a verbal consent log and participants will be mailed a signed copy of the consent form, indicating that verbal consent was provided. Ongoing consent will be implied unless participants withdraw from the study. Participants will be asked not to participate in other studies delivering an exercise intervention during enrollment in the trial.

Interventions

The Stepping Up program is a 12-week, multicomponent intervention that includes tailored TOML exercise and a mobility SM program developed for the pilot study. Participants will attend two 1-hour synchronous online sessions (1-hour exercise and 1-hour SM) per week using Zoom. The exercise component includes a variety of stepping sequences that are intended to enhance timing and coordination and improve automatic control of walking. Timing and coordination problems impact walking efficiency and contribute to age-related decline in physical function for older adults. [24] The exercise program begins with simple stepping patterns and progresses over 12 weeks. Each participant has a card which indicates the tailoring to address individual difficulties and mastery of each stepping pattern, as well as the progression to increase the complexity. Progression involves introducing more complex stepping tasks (ie, diagonal patterns that require stepping across midline), as well as increasing speed and varying the base of support. Once a stepping pattern is mastered, a dual task is introduced (ie, carrying an object in one or both hands and performing a cognitive task). The online class will be led by a fitness instructor and monitored by a physiotherapist who will provide feedback and individually tailor the exercises for each participant. The mobility SM component, facilitated by a physiotherapist, will aim to enhance participants' understanding

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of (1) changes in mobility with aging [17,34], (2) active SM of mobility including self-monitoring [27,28,34], (3) preclinical disability [17,18,35], (4) the importance of walking speed [2,23], (5) fall prevention [36], (6) exercise and TOML to improve mobility [25,37], (7) strategies to optimize sleep [38-40], (8) managing pain and physical discomfort [41,42], (9) conserving energy and minimizing fatigue [43], (10) better breathing [44], (11) posture to promote mobility [45,46], and (12) environmental barriers to walking and mobility [47,48]. The SM sessions were developed based on research evidence, discussion in an online forum with physiotherapists and researchers in mobility and aging, and in consultation with older adults. The SM component aims to increase self-efficacy through collaborative goal setting and action planning. A study website will allow participants to view short videos of the walking patterns being performed and review the SM sessions.

We will incorporate two control groups to establish the true effect of the Stepping Up intervention. The telephone-based coaching walking program will act as a comparative effectiveness control group. A review of interventions to increase walking behavior found that telephone interventions as brief prompts appeared to be as effective as in-depth counseling supporting walking prescriptions of 5-7 days per week versus 3-5 days per week [49]. In these studies, telephone interventions were often added as an adjunct to the primary intervention and mobility was not always measured as an outcome. Telephone counseling, compared with no intervention, has been shown to increase physical activity in low-activity older persons recruited from primary care [50,51]. However, it is unclear whether telephone-delivered interventions are cost-effective compared with face-to-face interventions for improving walking in persons with PCML [52].

The telephone-based coaching walking program will be delivered by a physiotherapist. The frequency, duration, and intensity of walking will be determined based on the individual's current level of physical activity and an end target level of physical activity (minimum of 150 minutes of moderate-intensity aerobic exercise per week) [53]. The physiotherapist will engage participants in goal setting and action planning, which will include discussion of coping, planning, identifying support systems, and evaluating self-efficacy. The initial telephone contact will last 20-30 minutes, and subsequent weekly calls will last approximately 10 minutes. Therapists will help participants evaluate their action plans, assist with problem-solving, discuss program progression, and help develop new action plans. This group will also receive written material about the benefits of walking and the importance of walking speed.

The chair-based yoga program will act as an attention control group. Chair-based yoga programs are typically reserved for older adults who are unable to participate in regular exercise or standing yoga programs. An RCT evaluating an 8-week chair-yoga program for older adults with lower extremity osteoarthritis who could not participate in standing exercise found that participants experienced a reduction in pain and an increase in gait speed compared with those in a health education program [54]. These improvements were not sustained postintervention. Chair-based yoga has not been evaluated for effectiveness in improving mobility outcomes for higher-functioning older adults with PCML.

Participants in the chair-based yoga program will undertake chair-based yoga sessions that include breathing control, seated poses, standing poses, and relaxation exercises, led by a fitness instructor. Participants will join a synchronous online class for 1 hour, twice per week for 12 weeks.

Outcomes

Demographic information (birth date, sex, gender, marital status, living accommodation, employment status, education, ethnic origin, and household income) and comorbid conditions (identified using the Self-Administered Comorbidity Questionnaire) [55] will be collected at baseline. Primary and secondary outcomes will be assessed virtually at baseline, 12 weeks, 24 weeks, and 36 weeks. Health care usage data will be collected during follow-up assessments only.

Primary Outcome: Walking Speed

The primary outcome measure is walking speed. The 4MGS test [56] is a performance-based measure of walking speed. The 4MGS test will be performed from a standing start at both a self-selected (usual) and fastest walking speed [57]. Although usual walking speed is more commonly reported in the literature [58], there has been some evidence in which maximum walking speed outperforms usual walking speed in identifying preserved exercise capacity [59]. Furthermore, maximum walking speed has been found to be a better predictor of future dependence in activities of daily living (eg, bathing, dressing, walking, and eating) in individuals aged 65-74 years and usual walking speed to be a better predictor of future dependence in activities of daily livings in individuals older than 75 years of age [60]. The 4MGS test has excellent test-retest reliability (intraclass correlation coefficient [ICC] 0.96) in healthy older adults [56]. 4MGS is responsive to clinically meaningful changes with 0.05 m/second denoting a small change and 0.1 m/second indicating a substantial change [61].

Secondary Outcomes

Dual Task Cost

Dual task cost will be measured using the dual-task Timed Up and Go (TUG) [62]. This test requires individuals to stand up from a chair, walk 3 m at usual speed, cross a line marked on the floor, turn around, walk back, and sit down while counting backward by threes from a randomly selected number between 20 and 100 [62]. Dual task cost is calculated as the difference in time (in seconds) between the TUG and the Dual-Task TUG. A systematic review identified that changes in gait speed over varying distances (3, 5, and 25 m) under dual-task rather than single-task conditions were associated with fall risk in community-dwelling older adults [63-65]. It has strong interrater reliability (ICC 0.94) and concurrent validity with the Berg Balance Scale (r=–0.66) [64]. There are no reports on the minimal detectable change for the Dual-Task TUG, but the minimal detectable change for the TUG is between 3.5 and 4.1 seconds [66,67].

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Exercise Capacity

The 2-minute step test is a test of exercise capacity that can be used as an alternative to a timed long-distance walking test when assessment space is limited [68]. Individuals are required to march in place as quickly as possible for 2 minutes while lifting their knees to a height midway between their patella and iliac crest when standing [69]. Both knees must be raised to the correct height to be counted. The score is the total number of times the right knee reaches the minimum height target. Rikli and Jones [69] found the 2-minute step test demonstrated good test-retest reliability (ICC 0.90) and convergent validity relative to 1-mile walk time (r=0.73) in older adults.

Balance

The Unipedal Stance Test is used to assess static balance [70]. Individuals are asked to stand barefoot on the limb of their choice with arms at their sides until they (1) use their arms (ie, move their arms away from their sides), (2) use their raised foot (ie, move it toward or away from the standing limb or touch the floor), (3) move the weight-bearing foot to maintain their balance (ie, rotate foot on the ground), or (4) maintain the position for a maximum of 45 seconds. The procedure is repeated 3 times, and the best and average time (s) of the 3 trials is recorded. The UPST has excellent inter-rater reliability for both the best of 3 trials ICC 0.994 (95% CI 0.98-0.996) and the mean of 3 trials ICC 0.951 (95% CI 0.926-0.969) in older adults [70].

Lower Extremity Strength

The 30-Second Chair Stand Test is used to assess lower body strength and power and is measured by the number of chair stand repetitions in a 30-second period. It has excellent test-retest reliability (r=0.89, 95% CI 0.79-0.93), interrater reliability (r=0.95, 95% CI 0.84-0.97), and concurrent validity with leg press performance (r=0.77, 95% CI 0.64-0.85) [69].

Self-Perceived Mobility

The Mobility Assessment Tool-Short Form (MAT-sf) is a video-animated tool for assessing mobility. It consists of 12 animated video clips that assess an individuals' perceived level of proficiency in performing each mobility task [71]. Participants are asked to estimate their ability to perform each task by responding yes or no, or by indicating the number of minutes or number of times they can complete the task. The possible range of scores is from 30 to 80 with higher scores indicating better mobility. The MAT-sf demonstrates excellent test-retest reliability (ICC 0.93, P<.001) and evidence of known groups validity (older adults who were able to complete the 400-m walk test have higher MAT-sf scores than those who failed the test, P<.001) [71].

Change in Mobility

The Global Mobility Change Rating consists of a single question: "Since your last visit, has there been any change in your mobility?" The response will be made on a 11-point self-reported Likert scale: –5=very much worse, 0=unchanged, and 5=very much better [72]. These scales have excellent test-retest reliability (ICC 0.90) and a minimally clinically important difference (MCID) of 2 points on an 11-point scale [72].

Preclinical Mobility Limitation

The PCML Scale allows for categorization into 4 groups of self-reported mobility limitation based on participants' ability to walk 2 km: (1) no mobility limitation, (2) PCML, (3) minor manifest mobility limitation, and (4) major manifest limitation [14]. The risk ratio for the development of major manifest mobility limitation in walking 2 km for persons with PCML at baseline compared with persons with no mobility limitation at baseline was 5.8 (95% CI 2.6-12.9) [14]. The PCML Scale will be administered at 12, 24, and 36 weeks and changes in the level of mobility limitation will be evaluated between time periods using chi-squared tests.

Physical Activity Level

The International Physical Activity Questionnaire (IPAQ) is a 27-item self-administered questionnaire that is used for monitoring physical activity and inactivity [73]. It collects information about the frequency and duration of sitting, walking, moderate and vigorous activity during a 7-day period. It has excellent test-retest reliability for overall score (ICC 0.81) and physical activity (ICC 0.84). It has excellent concurrent validity (correlations of time spent in vigorous physical activity compared with accelerometer monitoring [ρ=0.71]) and adequate concurrent validity (correlations of time spent in physical activity at home and during leisure time compared with logbook monitoring [ρ=0.47, ρ=0.58, respectively]) [74].

Self-Reported Balance Confidence

The Activities-specific Balance Confidence Scale is a self-report measure of balance confidence [75]. Individuals are asked to rate their confidence in completing 16 common tasks without losing balance, on a scale from 0% (no confidence) to 100% (complete confidence). The Activities-specific Balance Confidence Scale has demonstrated excellent test-retest reliability (r=0.92) and has been shown to have better scale responsiveness than the Falls Efficacy Scale when used with community-dwelling older people aged 65-95 years [75].

Pattern of Mobility

The Life-Space Assessment measures a person's usual pattern of mobility during a 1-month period, documenting mobility based on how far and how often a person travels and any assistance required [76]. The Life-Space Assessment has excellent test-retest reliability (ICC 0.96) [77] and has been used in longitudinal studies of aging [76] to assess mobility frequency and distance. It will be used to determine baseline levels of self-reported mobility and to track changes that occur with the interventions.

Knowledge, Skill, and Confidence for SM

The Patient Activation Measure is a 13-item measure of the patient's level of knowledge, skill, and confidence for SM [78]. Raw scores (13-52) are converted into activation scores (0-100) with higher scores indicating greater patient activation. The Patient Activation Measure has a MCID of 0.5 points [79] with high test-retest reliability (ICC 0.85) and evidence of validity

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against a classification of individuals' level of activation (κ=0.8-0.9) [80].

Quality of Life

The EQ-5D-5L is a generic utility-based health related quality of life questionnaire [81] with an MCID of 0.056 [82]. It consists of 5 questions covering the dimensions of mobility, self-care, usual activities, pain and discomfort, and anxiety and depression with 5 response options indicating no, mild, moderate, severe, and extreme problems for each dimension [83]. The EQ-5D-5L can define a total of 3125 health states which can be converted to a utility index anchored at 0 for a state being equal to dead, and 1 for full health using the Canadian Scoring function [84]. The utility index combined with life expectancy allows for the estimation of quality-adjusted life years (QALYs), a recommended generic outcome measure in health economic evaluation in Canada and other countries [85-87].

Self-Efficacy for Physical Activity

Participants will be asked to rate how confident they are that they could participate in moderate intensity physical activity for 150 minutes per week using a single question on a scale of 1 (not at all confident) to 10 (completely confident) [88].

Health Care Usage

Health care usage data to assess service use and cost effectiveness of the trial will be collected using administrative data accessible at the Institute for Clinical Evaluative Sciences (ICES) at McMaster University. Specifically, usage data will be obtained through the following databases: Ontario Health Insurance Plan, National Ambulatory Care Reporting System, and the Discharge Abstract Database, which are all housed at ICES McMaster. We will use standard person-level costing approaches established by ICES [89] to capture the formal component of direct health care costs. Health care usage data will also be collected using a case report form (CRF) to complement the ICES administrative data. If a variable is not available in an administrative database, the CRF will capture the variable and be included in the economic analysis using standard micro-level costing approaches. Health care usage variables that will be collected using the administrative databases and CRF are direct costs, including health care facility visits, hospitalizations, family doctor visits, specialist visits, tests and procedures, other health care services, and falls. The project leads will work with ICES scientists, a health economist, and an ICES Research Analyst. The administrative databases will be accessed once all of the clinical data has been collected.

Focus Groups

Our pilot study demonstrated perceived transformative aspects of the intervention that require further exploration and explication. Focus groups, following an interpretive descriptive approach, will be conducted [90] to identify possible aspects that enable participants to improve their mobility and become more successful self-managers and explore how these may differ in the Stepping Up intervention compared with the telephone-based coaching walking program and chair-based yoga program. Gender considerations will be explored to describe how changes in mobility self-efficacy and SM are related to gendered environments and gendered role expectations. Virtual focus groups (4-6 per group) will be conducted by a qualitative researcher. Participants will be invited to take part in the focus groups at the end of the 12-week intervention period. There will be a total of 4 focus groups for each of the 3 interventions for a total of 12 focus groups over the course of the study. Interviews will be audio-recorded, transcribed, and deidentified. Refer to Multimedia Appendix 2 for the interview guide.

Sample Size

The sample size calculation is based on the primary outcome measure, the 4MGS test. Small clinically meaningful change is 0.05 m/second on the 4MGS test in older adults [2]. We expect to observe minimal to no change in the chair-based yoga group (0 m/s), small but meaningful change in the telephone-based coaching walking group (0.05 m/s), and a large change in the Stepping Up group (0.12 m/s) [61]. Assuming a correlation between baseline and 12-week scores of 0.5, a mean baseline gait speed of 1.14 m/second, and a common SD of 0.22, a sample size of 66 per group (N=198) will have 80% power at the 0.05 significance level. To account for dropouts (20%), the planned total sample size is 249 (or 83 per group). Sample size calculations were performed using SAS (version 9.4; SAS Institute).

Recruitment

Participant recruitment will occur from August 2021 to January 2025, and follow-up assessments will be completed by October 2025. Refer to Figure 1 for the SPIRIT schedule of enrolment, interventions, and assessments. Participants will be recruited through advertisements in local newspapers and social media sites (ie, Facebook and Instagram, Meta). We will send out promotional material about the study in e-Newsletters of agencies that cater to older adults (ie, senior research centers, university retiree groups, and local Councils on Aging), and advertise on the websites of local libraries and Active Aging Canada. Posters and postcards will be displayed in local Young Men's Christian Associations (YMCAs), helping to spread the word and raise awareness for the study. The ads will be created using design elements that appeal to older adults and will include information about how to contact the research team. We will recruit over a period of 42 months (recruitment rate of 6-8 participants per month), and we will deliver the interventions to groups of 5-7 participants in 12-week sessions.

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Figure 1. SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) schedule of enrollment, interventions, and assessments. SM: self-management; PA: physical activity.

	STUDY PERIOD					
	Enrolment	Baseline	Allocation	Post-allocation		
TIMEPOINT	*0*	*0*	*0*	*12w*	*24w*	*36w*
ENROLMENT:						
Eligibility screen	X					
Informed consent	X					
Allocation			X			
INTERVENTIONS:						
STEPPING-UP			◆——	——◆		
TELE			◆——	——◆		
YOGA			◆——	——◆		
ASSESSMENTS:						
Walking Speed		X		X	X	X
Dual-task cost		X		X	X	X
Exercise capacity		X		X	X	X
Balance		X		X	X	X
Lower extremity strength		X		X	X	X
Self-perceived mobility		X		X	X	X
Change in mobility				X	X	X
Self-reported difficulty walking 2 km	X			X	X	X
Self-reported balance confidence		X		X	X	X
Pattern of mobility		X		X	X	X
Physical activity level		X		X	X	X
Knowledge, skills and confidence for SM		X		X	X	X
Quality of life		X		X	X	X
Self-efficacy for PA		X		X	X	X
Healthcare utilization				X	X	X

Randomization

The unit of randomization will be the participant, and the randomization process will use computer generation of group assignment using the REDCap (Research Electronic Data Capture; Vanderbilt University) randomization module. REDCap is a secure web application designed to support data capture for research studies [91]. Participants will be stratified by age (55-64 years or 65-75 years). An allocation table will be created and uploaded to the REDCap randomization module by a statistician not involved in the RCT. Using a 1:1:1 allocation ratio, we will block the randomization with variable block sizes of 3, 6, and 9. The RC will not have access to the allocation table. Once participant consent is obtained and the baseline assessment is complete, the RC will access the randomization module in REDCap to enter the participant strata value (age category) and receive the group allocation.

Data Collection and Management

During an introductory Zoom session with each participant, the RC will discuss space requirements and setup for the assessments and review emergency procedures should an adverse event occur. Written instructions will be sent by email before each assessment. The instructions will describe the setup required for the assessment and a list of equipment needed (measuring tape, chair, and masking tape to mark distances). If the participant is unable to secure these items independently, they will be mailed to them before their baseline assessment.

The same physiotherapist blinded to group assignment will perform baseline and follow-up assessments for a given participant. All trial assessments will be conducted virtually using the Zoom platform. During the assessments, assessors will use screen-sharing to administer patient-reported questionnaires and enter participant responses directly into

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REDCap. For the performance measures, assessors will use screen-sharing to play a video clip to demonstrate how the participant is expected to complete each of the physical tests that will be administered. Participants will then complete each test with the assessor observing by video, and scores will be entered into REDCap.

We have estimated the rate of loss to follow-up in our sample size calculation as 20%. We will attempt to minimize loss to follow-up in the trial by using a 2-stage screening process and by having the RC follow-up with participants after 2 consecutive unreported absences. Participants who drop out of their intervention will be given the opportunity to complete follow-up assessments. Those participants who complete follow-up will also be offered a personalized report that provides them with a summary of their results.

Intervention-specific data will be entered into REDCap by trained study staff or by survey. The physiotherapist delivering the telephone-based coaching walking intervention will enter data pertaining to the participant's goals and action plans during the weekly telephone sessions. Participants in the Stepping Up intervention will receive weekly REDCap surveys and will record their goals, action plans, and practice minutes. The RC will perform regular checks to ensure completeness and will follow-up on any missing data.

Personal information will be collected directly from each participant by the RC during the introductory Zoom session. Personal information (name, address, phone number, and phone number of an emergency contact) will be shared with the assessors using a private Google Calendar and with the study staff delivering the interventions using encrypted email. Participant data will be deidentified using a study ID number. A password protected electronic file linking participant identifiers to their study ID number will be stored on a secure server. Only the Primary Investigators and the RC will have access to this file. Additionally, only the primary investigators and authorized users will have access to the project in REDCap. User rights will be configured to ensure that users only have access to the data essential to their role.

Analysis

Baseline characteristics will be analyzed using descriptive statistics reported as mean (SD) or median (first quartile {Q1}, third quartile {Q3}) for continuous variables, depending on the distribution and count (%) for categorical variables. All analyses of primary and secondary outcomes will follow the intention-to-treat principle. The results will be reported as relative risk or odds ratio for binary outcomes or mean difference for continuous outcomes, with corresponding 95% CI and associated *P* values. All *P* values will be reported to 3 decimal places with those less than .001 reported as $P<.001$. All analyses will be performed using SAS 9.4. We will use multiple imputation to handle missing data [92].

To assess the effect of the intervention on the primary outcome (4MGS), we will conduct an analysis of covariance adjusting for age as a stratification variable and baseline value of 4MGS as a covariate. Secondary outcomes will also be analyzed using analysis of covariance, again using age as a stratification variable and baseline value for each outcome as a covariate. No interim analysis is planned.

We will conduct exploratory subgroup analysis for both the primary and secondary outcomes by including an interaction term between the subgroup variable (sex and age) and the treatment group variable. The multiple measures subgroup analyses will not be adjusted for multiple testing since they are exploratory.

Our hypothesis is that there will be reduced hospitalizations and physician visits for the intervention group compared with the control groups. Cost data is usually treated as nonparametric. Therefore, a Poisson or negative binomial distribution will be used to model the number of hospitalizations and physician visits by counts to determine the difference between the groups on relative intervention cost.

Analysis of the qualitative interview transcripts will follow an interpretive descriptive approach [90], an approach used in applied health disciplines to inform practice. A member of the research team will lead the analysis involving: (1) multiple line by line readings of the data to ensure a deep understanding of the data; (2) an inductive and deductive coding process based on the research questions and the emerging analysis; (3) the use of a data matrix to facilitate the manipulation of coded data and exploration of patterns, variations, and discrepancies, as well as comparisons within and among the participant groups in the data; and (4) finally, asking questions of the data to understand aspects of intervention and to answer the research questions. Rigor will be enhanced by the maintenance of a detailed record of all steps [93], inclusion of multiple perspectives in the analysis [94], guidance of a methodological framework [90], and use of the NVivo qualitative data analysis software (Lumivero) [95].

The cost-effectiveness analysis will compare the Stepping Up program with the telephone-based coaching walking program and the chair-based yoga program from the public health care payer's perspective. The main effectiveness measure for the cost-effectiveness analysis will be the incremental cost per QALY gained over 36 weeks. We consider 36 weeks' sufficient time to capture the potential cost-effectiveness of Stepping Up. As this cost-effectiveness analysis is conducted alongside the trial, nonparametric bootstrap will be used to calculate the 95% CI around the incremental cost per QALY ratio. The decision uncertainty will be presented using cost-effectiveness acceptability curves, which show the probability of the intervention being cost-effective compared with the telephone-based coaching walking group and the chair-based yoga group.

Oversight and Monitoring

A steering committee will be established comprised of all central study team members, older adults from the community, and partners from the YMCA. The steering committee will review study progress and monitor recruitment, data quality and completeness, and general study conduct. The steering committee will monitor the rate of adverse events and will be responsible for the dissemination of results and will meet every

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6 months. Given that this trial presents minimal risks, we will not have a data monitoring committee.

We do not anticipate any safety risks to the participants. However, it is possible that they might experience muscle stiffness, soreness, falls, or injuries. Since the interventions will be delivered remotely, each participant will provide the name and telephone number of a friend or family member that the research staff can contact should the participant be alone at home and an emergency arises. If the adverse event is deemed to be the result of the intervention, an Adverse Event Form will be completed by a member of the trained research staff and appropriate medical attention will be sought as necessary.

Ethical Considerations

This study has received final approval from the Hamilton Integrated Research Ethics Board (HiREB Project #10663). Participants will provide informed verbal consent to participate. Ongoing consent will be implied by continued involvement in the trial. Participants will be informed that they may withdraw at any time with the option of removing their data from the study by notifying study staff.

Results

Recruitment for the trial concluded in January 2025 with a total of 253 participants enrolled. Data collection commenced in August 2021 and will be completed in October 2025. Data analysis will begin in November 2025 and results will be published in Summer 2026. Refer to Figure 2 for the CONSORT flow diagram. Data supporting this study will be openly available from the Open Science Framework repository [96].

Figure 2. CONSORT (Consolidated Standards of Reporting Trials) flow diagram.

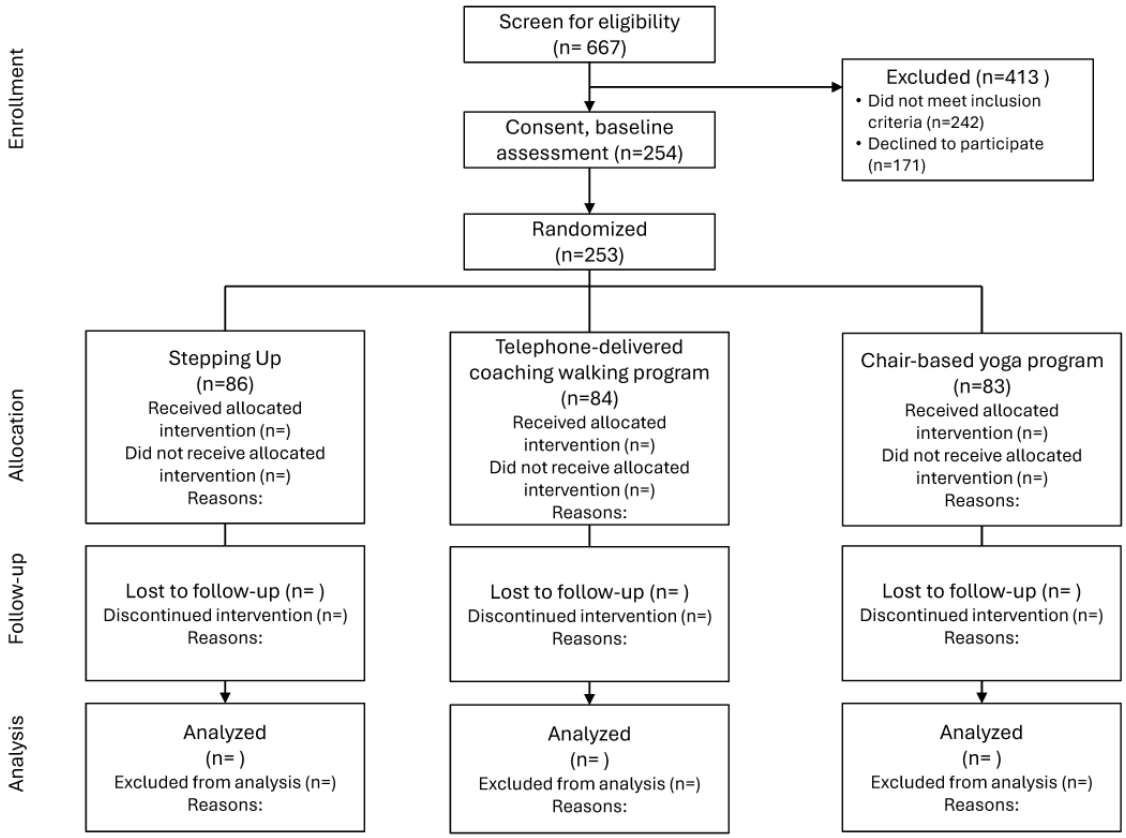

Discussion

Principal Findings

Approaching functional decline from a primary prevention perspective by targeting individuals with PCML is important. Online community-based mobility programs have the potential to reach large groups of older adults to improve quality of life and to maintain or enhance physical function [97]. Such programs may also translate to lower health care system costs [98]. There have been several other rehabilitation programs successfully delivered online with positive results, including a multicomponent rehabilitation program to frail older adults during the pandemic [99], a cardiac rehabilitation program [100], and stroke [101] and cancer [102] rehabilitation programs. A recent survey showed that 71% of the 184 pulmonary rehabilitation programs surveyed were delivered remotely [103].

The results of this trial will inform future research and clinical practice. We will integrate knowledge translation activities such as the synthesis, exchange, dissemination, and application of knowledge to provide more effective health care services

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through complex interactions between researchers and knowledge users [104]. We will collaborate with the YMCA, with whom we have a long-term relationship, and they will be actively involved in the ongoing delivery of the study. LiveWell is a strategic partnership between McMaster University, the YMCA, and Hamilton Health Sciences whose mission is to promote health through community access to innovative, evidence-based wellness programs. This partnership will allow us to share our results with other YMCAs whose core business involves the promotion of activity, mobility, and healthy communities. Furthermore, the program will be available in an open-source format. Knowledge users, with the capacity to promote adoption of the results, will be closely involved in the project and include a member of the McMaster Optimal Aging Portal Expert Advisory Committee (JR) and the Senior Regional Manager of the YMCA of Hamilton, Burlington and Brantford, Health and Fitness Division. The Nominated Primary Investigator (JR) has a strong network within primary care provincially and nationally, and as a member of the Primary Care Advisory Committee to the Ontario Physiotherapy Association, she will lead dissemination within this sector. We will also share results through the McMaster Optimal Aging Portal and through publications that target older adults who may be experiencing preclinical mobility problems, as well as through high impact internationally peer-reviewed journals. We have 3 older adult community members who are collaborating on this project and who have been involved in the development of this intervention. These individuals will continue to consult on the execution of the study and will be involved in the development of knowledge translation materials and the dissemination of results.

Limitations

There are some limitations that might be encountered during this trial. The delivery of the intervention virtually rather than in person may result in problems detecting when a participant is having difficulty and requires correction. The ability to provide individual tailoring or to determine if a participant has achieved mastery of an exercise will be challenging in an online group format since participants will be progressing at different rates and 1-1 interactions will disrupt the flow of an online class. To mitigate these issues, we will have the physiotherapist observing and providing feedback and tailoring recommendations to the participants at the end of the class.

Conclusions

This trial will evaluate the impact of the Stepping Up program on walking speed, as well as on aerobic exercise capacity, dual-task cost, physical functioning (balance and strength), balance confidence, extent of community mobility, SM of mobility, and quality of life. We will also examine the cost-effectiveness of the STEPPING UP program. Results will establish if this evidence-based initiative, which has modest resource demands, has the potential to serve as a model for sustainable, accessible, and cost-effective programming for individuals with early mobility limitations.

Acknowledgments

This study is funded by the Canadian Institutes for Health Research (project grant PJT-169034).

Data Availability

The datasets generated and analyzed during this study are available in the Open Science Framework repository.

Authors' Contributions

JR contributed to the conceptualization, funding acquisition, investigation, methodology, project administration, supervision, and drafting of the original manuscript. AK was involved in funding acquisition, investigation, methodology, project administration, and review and editing of the manuscript. SS contributed to data curation, investigation, and drafting of the original manuscript. MB and AT provided review and editing of the manuscript. AC provided resources and participated in review and editing. SD was involved in methodology, review, and editing. ED performed formal analysis and contributed to review and editing. JM contributed to methodology and participated in review and editing. LT provided resources and software and contributed to review and editing. FX was involved in methodology development and review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 86 KB - resprot_v14i1e72585_app1.pdf]

Multimedia Appendix 2
Interview guide.
[DOCX File , 43 KB - resprot_v14i1e72585_app2.docx]

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Abbreviations

4MGS: Four-Meter Gait Speed
CRF: case report form
ICC: intraclass correlation coefficient
ICES: Institute for Clinical Evaluative Sciences
IPAQ: International Physical Activity Questionnaire
MAT-sf: Mobility Assessment Tool-Short Form
MCID: minimally clinically important difference
PCML: Preclinical mobility limitation
QALY: quality-adjusted life year
RC: research coordinator
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SM: self-management
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TOML: task-oriented motor learning
TUG: Timed Up and Go
YMCA: Young Men’s Christian Association

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Proposal

Health System Leadership for Psychological Health and Organizational Resilience During the COVID-19 Pandemic: Protocol for a Multimethod Study

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Abstract

Background: Since the World Health Organization declared COVID-19 a global pandemic, health systems and health system leaders have faced unprecedented challenges through the various stages of the crisis. Canada and other health systems were largely ill-prepared to handle this crisis. The longevity of the pandemic has profoundly affected health care systems and compounded the rates of negative psychological outcomes in health systems' leaders and staff, rates of emotional exhaustion, and burnout.

Objective: The purpose of this study is to investigate the experiences of health system leaders and nurses during COVID-19 and to develop recommendations to inform pre-, during-, and postcrisis leadership strategies and practices for health system leaders, which address leaders' and nurses' psychological health and well-being, as well as organizational resilience.

Methods: A 3-year multimethod approach will be adopted and include a qualitative exploratory inquiry informed by Geerts' 4-stage framework of imperatives for health system leaders to guide data collection and analysis. We will then conduct semistructured individual interviews with health system leaders in 3 provinces in Canada and hold focus group interviews (FGIs) with nurses from the same organizations. Data from the interviews and FGIs will be integrated to determine how health system leaders promoted their own health and how their leadership shaped nurses' psychological health and contributed to building organizational resilience. We will engage knowledge users using a nominal group technique in a 1-day forum to discuss how findings can be applied in professional contexts. We will conduct a thematic analysis of the aggregated data to identify and analyze themes to provide an interpretive explanation of health system leaders' experiences and organizational resilience during the COVID-19 pandemic, and how the leaders promoted nurses' psychological health and well-being. The protocol has been reviewed and approved by the University of Manitoba institutional review board (IRB), the University of Alberta IRB, and McMaster University Ontario IRB.

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Results: As of September 6, 2024, this study has made significant progress. Data collection has been completed for individual interviews with health leaders in Alberta and Manitoba, and has commenced in Ontario. FGIs will be completed by the fall of 2025, data integration in early 2026, nominal group technique in the spring of 2026, and the final report will be written in the summer of 2026.

Conclusions: The findings will support practices that health system leaders can implement to foster their own and nurses' psychological health and well-being and build organizational resilience. The benefits of this study aim to include evidence for effective health system leadership and support for nurses, crisis preparedness, and lessons from the pandemic to address leadership practices to operationalize the imperatives within the 4 stages of the crisis model.

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KEYWORDS

health system leadership; COVID-19; psychological health; organizational resilience; crisis leadership; crisis model

Introduction

Background

Since the World Health Organization declared COVID-19 a global pandemic [1], health systems and health system leaders have faced unprecedented challenges through the various stages of the crisis. Dr Theresa Tam, Canada's Chief Public Health Officer, warned of the threat of pandemics and the need to prepare more than 15 years before COVID-19 [2], and yet, health systems worldwide, including Canada's, were largely ill-prepared to respond effectively to this crisis [3-5]. COVID-19 placed novel and extreme demands on health care systems and their leaders by exceeding regional and organizational capacity for detection and outbreak containment, rationing of the supply chain and required resources, infodemic management, and the health care workforce to maintain operations [6-8].

Given the certainty of future pandemics and health care crises, there is a pressing need for immediate action to bolster national, regional, and organizational emergency preparedness and to safeguard the welfare of the health care workforce [9]. Nurses make up a significant proportion of the health care workforce worldwide, and in Canada and elsewhere, this profession was in crisis before the COVID-19 onset [8]. A global shortage of almost 6 million nurses was driven by an ageing population and increased care needs, retirements, high turnover, and low retention, including many leaving the profession altogether, and an ageing workforce [9]. One Canadian study found 93% of nurses had symptoms of burnout and almost 1 in 3 had clinical levels of burnout requiring medical attention [10]. The pandemic has exacerbated this situation for nurses, causing further deterioration of their mental health [11] and rates of burnout [12-16]. This is attributable to the demoralizing work conditions in which nurses have worked with severely inadequate resources and overwhelming workloads at the front lines of care [8,9]. A survey of 1705 frontline nurses in Canada in 2020 found high chronic fatigue, lower work satisfaction, and higher intention to leave their organization for those caring for patients with COVID-19, which resulted in poor quality of care provision [17-19]. Similarly, for health system leaders, despite their extensive experience navigating forces influencing organizational change, the prolonged and chaotic COVID-19 situation exposed leaders to unique leadership challenges [20]. The longevity of the pandemic profoundly affected health care.

Leadership is critical in a crisis and affects organizational performance and resilience [14,21-23]. Organizational resilience is a multidimensional concept that refers to the ability of individuals and groups to maintain operations and stability during situations of uncertainty, including how an organization reacts to and recovers from major disruptions, with minimal disturbance [24-27]. The leader's role is to anticipate potential problems in the environment, secure resources, make and guide others in making good decisions regarding priorities and strategies, and take action, and minimize the negative impact of a disturbance [28]. These are key leadership capabilities that increase the organization's awareness and adaptive capacity [29]. In a crisis, despite intense pressure, complexity, and uncertainty, leaders must be decisive, obtain and allocate stretched resources, and communicate clearly with employees, often under a spotlight [30-32].

Few empirical studies exist on health system leadership in crises, and what is available is often either limited to anecdotal summaries of lessons learned by senior leaders and their corresponding suggested strategies [30,33,34] or is restricted to disaster preparedness [26] and acute emergency response [27]. Although COVID-19 involved waves of intense emergency periods, which required a decisive reaction, it also presented distinctly different crisis subcontexts, such as the escalating warning period before the first local impact, as well as postemergency but prefinal resolution phases of eerily uncertain length [28]. The unique characteristics and demands facing leaders in each of these situations require customized leadership priorities and strategies. To the best of our knowledge, there is a dearth of evidence-informed leadership guidance for each stage of a crisis.

The scale of the COVID-19 pandemic and the corresponding challenges it presented, such as the infodemic, supply chain inefficiencies, and massive leader and staff shortages, absenteeism, burnout, and turnover, severely overwhelmed hospitals, many of which were notably overburdened before the pandemic [35,36]. The pandemic has taken a toll on health system leaders and nurses, including on the deterioration of nurses' well-being and their capacity to be engaged and provide compassionate care, which compromises the quality of care that they can provide to patients, and their ability to tackle the backlog of surgeries and other services that have been paused over the past 5 years. Consequently, the need to improve leader

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and nurse psychological well-being [9,13,35,37], and the need for organizational resilience [7] have been identified as urgent research priorities.

Study Purpose and Objectives

The purpose of this study is to investigate the experiences of health system leaders and nurses during COVID-19 and to develop recommendations to inform pre-, during-, and postcrisis leadership strategies and practices for health systems leaders. The specific objectives are as follows:

1. Examine health system leadership challenges, enablers, and effective strategies at the organizational level in response to the evolving COVID-19 pandemic.
2. Examine nurses' (registered nurse [RN] and registered psychiatric nurse or licensed practical nurse) experiences during COVID-19, their perceptions of leaders' support for them and their working conditions, and the impact on their psychological health and well-being.
3. Investigate health system leaders' promotion of their own health and how their leadership shaped nurses' psychological health to mitigate strain and burnout.
4. Examine how health system leaders have fostered organizational resilience and how that may be shaped by gender.
5. Generate recommendations of leadership strategies to foster leader and staff psychological health and well-being and enhance organizational resilience.

An in-depth understanding of the factors facing leaders and staff throughout the pandemic and corresponding leadership strategies could provide several benefits. It could form the basis for individual, team, and organizational reflection, debriefs, and reviews of performance during the COVID-19 response. It also has the potential to inform emergency preparedness training, as well as guide crisis leadership practice during the ongoing pandemic and postpandemic context, as well as for future crises. Finally, the recommendations of strategies and practices based on this study's findings could contribute to enhanced leadership and organizational performance and resilience more generally, partly by prioritizing leaders' and nurses' psychological health and well-being. Given the central role that health systems leaders played in the COVID-19 response and in advising government, with public health, and given the commonality of challenges that leaders in other sectors faced during this time, there is potential for this study's recommendations to extend to other professional domains [38,39].

Methods

Study Design

To achieve this study's objectives, we will use a qualitative exploratory inquiry [40] to explore the experiences of leaders and nurses. This design will enable us to answer the "what" and "how" associated with improving and advancing postcrisis leadership strategies and practices in hospital settings across 3 provinces. We will collect data from over 3 years across urban centers in 3 Canadian provinces using a multimethod approach consisting of individual semistructured interviews, focus group interviews (FGIs), data integration, and a nominal group technique to synthesize findings and develop recommendations.

Conceptual Framework

To ground our work, we draw from the evidence- and expertise-informed framework of imperatives for health system leaders conceptualized by a coinvestigator (JMG; Figure 1) [28]. This novel framework organizes the context of a crisis into four dynamic, progressive stages: (1) escalation, (2) emergency, (3) recovery, and (4) resolution [28], with defining characteristics and leadership imperatives presented for each stage. For example, leadership capabilities in the escalation stage involve rapidly gauging the nature, scale, and scope of an imminent threat, and preparing leaders and staff to implement preplanned organizational response protocols and gathering requisite resources [41,42]. The emergency stage is marked by focusing exclusively on urgent priorities, putting all nonessential operations on pause, maximum staff dedication, consistent adherence to emergency protocols using a command and control approach, balanced with frontline adaptive autonomy [42]. The recovery stage requires the greatest range of leadership capabilities because this stage involves balancing intense competing priorities, maintaining staff engagement, and minimizing burnout, within a prolonged and highly stressful, uncertain, volatile, and complex environment [28]. Finally, the resolution stage is marked by the leader's focus on organizational learning and a willingness to share lessons learned with other organizations, while reconsidering how to build back and to address the toll the crisis has taken on people [41,42]. Our approach highlights how health system leaders can create conditions for a psychologically healthier workforce that can be sustained beyond the crisis.

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Figure 1. Geerts' framework of 10 leadership imperatives during the recovery stage of a crisis.

The framework developed by Geerts et al [28] serves as the basis for gathering and organizing data about how health systems leaders implemented key leadership imperatives across the 4 stages during the COVID-19 pandemic, as well as how leaders sustained their own health and how their leadership shaped nurses' psychological health and well-being and strengthened organizational resilience. The concepts of well-being and organizational resilience align with the leadership imperatives central to the framework, which guides leaders before, throughout, and following crises. Leaders who can implement these imperatives are ideally situated to anticipate and respond to urgent needs and collaborate with nurses to cocreate organizational conditions across all 4 stages that best serve nurses and the patients entrusted to their care.

Management and Administrative Structure

This study will be led by SU and PEB, with support from study coauthors (also termed the "core team"). The team will also be supported by a study advisory committee ("AC"), composed of senior health care leaders, directors, middle managers, frontline managers, nurses, and stakeholder representatives from urban academic and community hospitals from each province (Alberta, Manitoba, and Ontario). They will be involved in assisting with the recruitment of participants, providing consultation, particularly about initial study recommendations, and facilitating knowledge dissemination. The administrative team will be made up of a research coordinator (RC), a data manager (DM), and a graduate research assistant.

Settings

To increase the potential for variations in health care settings and transferability of findings, we purposefully selected 3 provinces with wide variations in COVID-19 incidence rates (Alberta 598,813, Manitoba 147,329, Ontario 1,163,243, as of August 13, 2022; Government of Canada) [43]. Additionally, the 3 provinces were among the 6 provinces in Canada with the lowest distribution of RNs per 100,000 population in 2021, whereby Ontario is at the bottom of the list with only 690, Alberta with 835, and Manitoba with 1037 RNs/100,000 population [44]. Similarly, the 3 provinces were among the top 5 provinces with the highest COVID-19–related mortality in 2021, with 10,206, 3263, and 1420 cumulative deaths for Ontario, Alberta, and Manitoba, respectively [45]. We will purposively select 1 academic and 1 community hospital from each of the 3 provinces to investigate how different provinces and leadership roles were enacted and how various factors (including unit overcapacity issues, leadership decision-making, administrative structures, and personal characteristics) may shape the work environment and the overall effects on the health and well-being of the leadership and nursing workforce. We will compare leader responses across provinces and compare leader responses with those of nurses from their same hospital

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to assess whether there is a disconnect in the frequency or effectiveness of leader practices.

Participants and Sample Size

The sample will consist of 66-84 leaders (objectives 1 and 3) and 30-63 nurses (objective 2) as illustrated in Tables 1 and 2, and Table 3, respectively. When and how data saturation (ie, when new data adds only minor variations to categories) [46] can be achieved is difficult to determine before the onset of this study, as it depends on the volume and complexity of the data [40,47]. Based on similar qualitative studies with leaders, the proposed sample size should achieve saturation and will be robust enough to allow exploration within and across groups.

Table 1. Sample size of leaders to be interviewed per province by category and hospital type.

Hospital type	Category of leaders to be recruited			Total
	Senior leaders	Directors or middle managers	Frontline managers	
Academic	3-4	4-5	4-5	11-14
Community	3-4	4-5	4-5	11-14

Table 2. Total (Alberta, Manitoba, and Ontario) sample size of leaders to be interviewed by category and hospital type.

Hospital type	Category of leaders to be recruited			Total
	Senior leaders	Directors or middle managers	Frontline managers	
Academic	9-12	12-15	12-15	33-42
Community	9-12	12-15	12-15	33-42
Total	18-24	24-30	24-30	66-84

Table 3. Sample size of nurses to be interviewed during focus group interviews by province.

Province	Nurses per FGI[a] session	FGI sessions	Total nurses
Alberta	5-7	2-3	10-21
Manitoba	5-7	2-3	10-21
Ontario	5-7	2-3	10-21
Total	15-21	6-9	30-63

[a]FGI: focus group interview.

For the purposes of this study, we defined categories of leaders as follows: senior leaders are executive-level decision-making management personnel responsible for achieving organizational goals and strategic plans within the day-to-day operational management of the organization. Directors or middle managers are supervised by an organization's senior leaders, supervise frontline managers, and have a role in practical improvements in health care delivery. These leaders can be registered nurses, allied health professionals, or other health-related disciplines. Frontline managers (who are registered nurses or other health-related disciplines) have patient, operational, and fiscal responsibility for their units and oversee direct care nurses and other care providers.

For objectives 1 and 3, through criterion sampling [42], the three levels of leaders who have an experiential knowledge of working in the COVID-19 crisis will be recruited. We will engage the AC to assist in maximum variation sampling with the aim of creating a demographically diverse sample across age, gender, and racial identity from each leader group per province.

Recruitment

In consultation with the core team, this study's principal investigators (PIs) will extend personal invitations to candidates to join the AC, ensuring that diversity, diversity of expertise, perspective, and geographical location are represented [48-51]. To recruit leaders and nurse participants (objectives 1, 2, and 3), we will use multiple recruitment strategies, including drawing on the core team networks and working closely with the AC in their respective provinces to invite participation of senior hospital administrators within the selected hospitals. We will provide representatives from potential sites with information about this study, including participant requirements, which can contribute to gaining hospital ethics approval and access approval. Once committed, each site representative will email prospective participants based on a template that we provide. Interested personnel will then contact this study's PI or RC, who will respond with a consent form and participant demographic questionnaire. The consent form explains that participants agree to include their responses in published results in anonymized or aggregate forms, with no identifying information included that would compromise their anonymity. Once these forms are completed, the participant will be officially enrolled in this study, and we will schedule interviews.

To recruit knowledge users (objective 5), we aim to recruit 30 knowledge users in health care systems from the 3 provinces, and an additional 10 knowledge users from across Canada identified by the team and AC. Knowledge users are health

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leaders (senior, director, and frontline) from hospitals in urban, rural, or remote regions, nurses, policy makers, and health service researchers who will be able to make informed decisions about the research findings and apply them to programs or policies.

Data Collection

A multimethod approach, informed by the conceptual framework of imperatives for health systems leaders, will guide the development of an integrated coding framework and data analysis. Individual interviews will be conducted using a semistructured interview guide (Multimedia Appendix 1) and will consist of questions centering on the organizational context (barriers, policies or guidelines, and resources), leadership strategies and practices (eg, communication or decision-making) that were effective (or not), and organizational resilience (leader or nurse well-being, and organizational learnings). Each interview will begin with exploring how the COVID-19 pandemic was perceived by the individual, followed by standardized questions and prompts, and will conclude with an open-ended question regarding final insights to generate further meaning and gain more clarity and understanding (objectives 1 and 3).

FGIs will be conducted with nurses from the included hospitals. There will be 2 to 3 FGIs in each province, as indicated in Table 3, each lasting approximately 90 minutes. A core team member will lead discussions in each group and concerning 3 areas informed by the conceptual framework: context (eg, their work conditions, their ability to provide safe, and quality care), perceptions of leadership effectiveness (eg, decentralized decision-making, communication, and level of engagement), and organizational resilience (eg, psychological health, ability to be innovative, and learnings). Concomitantly, the RC will document interactions among participants and observations of group dynamics, noting language, tone of voice, and nonverbal body language, including whether these appear to be consistent among genders. At the conclusion of each FGI, the lead researcher will summarize the main points and seek clarity on areas of ambiguity.

Data will be integrated from individual interviews with leaders and FGIs with nurses and will be used as a foundation for the 1-day forum. Following data integration, we will engage knowledge users from across Canada in a 1-day online forum (objective 5). The integrated data from individual interviews with leaders and FGIs with nurses will be used as a foundation for the forum. The nominal group technique is designed to obtain qualitative data from knowledge users to bring about consensus for promising postcrisis leadership strategies and practices [52,53]. This technique will be facilitated by engaging knowledge users in a 1-day online national forum via video technology (MS Teams [Microsoft Corp] or Zoom [Zoom Video Communications]) with the goal of achieving consensus for what should be shared and promoted nationwide. This technique has been proven effective in bridging the gap between researchers, policy makers, and practitioners [54-56]. Finally, an e-handbook will be developed for publication in collaboration with and mobilized by the AC and knowledge users.

Ethical Considerations

This study is of low risk, and the participants are not considered vulnerable. This protocol has earlier been peer-reviewed prior to award (Multimedia Appendix 2); additionally, this protocol has been reviewed and approved by the University of Manitoba institutional review board, Office of Human Research Ethics (HE2023-0193), the University of Alberta institutional review board (Covenant Health Research Center, Pro-00136740), and the Hamilton Integrated Research Ethics Board at McMaster University in Ontario (Panel B 16790). Additionally, operational approvals have been granted by Shared Health (the provincial health regulatory body for the province of Manitoba) and Alberta Health Services, the provincial health authority. At the time of drafting this paper, we obtained operational approval from 2 hospitals in Ontario. All participants who agreed to participate in this study have signed written informed consents. The informed consent document has clearly explained this study's procedure, the risk involved (minimum risk), and the right of the participant to withdraw from this study at any point. Participants' privacy is fully protected by deidentifying participants, anonymization, and full delinking. Participants were compensated for their time with a CAD $20 (US $14.41) e-gift card (Walmart, Tim Hortons, or Amazon).

Data Management, Analysis, and Quality and Security

The interviews and FGIs will be recorded, and verbatim transcripts will be generated. The RC and graduate research assistant will compare the transcripts against the recordings to ensure accuracy, and we will use a transcript-based analysis to increase rigor. We will allocate anonymous identifiers to transcripts, field notes, audit trail information, and demographic data. Data will be managed using MAXQDA (MAXQDA - Distribution by VERBI GmbH) qualitative software.

Thematic analysis will be used to identify and analyze themes (patterns of meaning) within the data to provide an interpretive explanation of health system leaders' experiences during the evolving COVID-19 pandemic. This analysis will also enable us to understand how leaders promoted their own psychological health and well-being, and that of the nursing staff. We will apply Braun and Clarke's [57] 6-phase approach to thematic analysis to enhance scientific rigor and ensure the research team is open to emerging codes and categories as analysis continues. Coding of responses will be deductive and organized according to the stages and imperatives within the conceptual framework; however, a complementary inductive approach will be used to capture important themes not represented in the framework. We will code line-by-line and supplement this with fieldnotes and analytic memos. After an initial independent review of a sample of the first transcripts by the coprincipal investigators and consultation with the creator of the framework (JMG), an initial coding framework will be developed. This initial coding framework will then be applied to an initial subsample of seven transcripts by the RC and the DM for two reasons: (1) to get a sense of the kinds of themes that are emerging in the data and to streamline the framework by removing redundant codes [58], and (2) to report preliminary results of the data to the rest of the core research team.

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After the coding of the initial subsample is complete, the PIs, RC, and DM will meet and discuss any discrepancies or understanding of codes to achieve consensus, as well as suggestions for how to modify and optimize the coding framework. The final coding framework will then be applied to all transcripts. Constant comparison will be used to pay attention to the experiences of leaders across 3 levels and nurses from the same hospitals. The coding framework helps organize participants' responses regarding effective leadership strategies and practices in the context of the 4 stages of a crisis, with a focus on promoting leaders' and nurses' psychological health and well-being and building organizational resilience. Contextual factors will be considered, including similarities or differences of leader experiences across provinces and across hospitals that include unit size, specialties (medicine or surgery, emergency department, and intensive care unit), academic or community hospitals, and available resources. We will create an audit trail to identify and justify early themes or codes, and decisions made to modify the framework to generate desired data.

We will share initial raw data findings, early themes, and corresponding qualitative responses with the research team and AC, including overarching similarities and differences, and data alignment (or not) with the conceptual framework, as well as any proposals or modifications that researchers have already made to the data collection instruments or coding framework. This discussion is to ensure that there is consensus in the analytical approach to bolster the robustness and quality of the results and study recommendations. Although consistency in data collection is important, equally so when researching a dynamic social phenomenon is adapting the methods based on initial responses when it appears that doing so will address the research objectives more effectively [47]. Consequently, the researchers will review field notes following each FGI and consider which emerging issues should be discussed and explored in subsequent FGIs, as the diversity of contexts (province and type of hospital), experiences, and perceptions of nurses attending the FGIs will likely enable unanticipated but important themes to emerge which are worthy of further exploration.

Objective 4 involves integrating data collected to address objectives 1, 2, and 3, in which each set (interviews, FGIs, and field notes) will be given equal weighting in the analysis [57]. Data will be combined and threaded into a visual summary of effective leadership strategies and emerging themes of how health systems leaders promoted their own health, and how their leadership shaped nurses' psychological health and well-being in the workplace to mitigate strain and burnout, while building organizational resilience. To begin, we will review each dataset and identify "promising" lead codes for further analysis [59], which will then be reapplied in an iterative way to the data.

To uphold study rigor, we aim to establish trustworthiness through transparency and several other tactics [60]. Credibility includes inviting participants to review postinterview transcripts to ensure accuracy and completeness and incorporating any requested changes to review their transcripts, and providing comments on preliminary findings to strengthen the accuracy of interpretations, and through rich description and using illustrative quotes. Reflexivity will be logged by the PI, the RC, and DM to enhance their self-awareness of the phenomenon and improve the quality of this study. Transparency and dependability will be established by creating an audit trail documenting detailed records of the data collection process, details of coding, interpretive decisions, theme development, methodological decisions and modifications, meeting minutes, and data triangulation by interviewing a variety of participants.

Confirmability and objectivity will be met by independent coding and analysis of a portion of the data by the team (noted above) [61,62] and by several stages of incorporating an iterative feedback process until consensus is reached. Finally, given the ongoing pressures on health system leaders and nurses, we will strive to be flexible in accommodating participants' contributions.

Data security and management will comply with institutional ethics and provincial privacy requirements.

Results

As of September 6, 2024, this study has made significant progress in line with the approved timelines. Data collection has been completed for objectives 1 and 3 in Alberta and Manitoba and has commenced in Ontario. Table 4 shows the distribution of the interviewed from the 3 study provinces.

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Table 4. Distribution of leaders interviewed.

Category of leaders	Academic	Community	Total
Alberta			
Senior leaders	3	2	5
Directors or middle managers	0	1	1
Frontline managers	5	3	8
Total	8	6	14
Manitoba			
Senior leaders	0	1	1
Directors or middle managers	3	2	5
Frontline managers	4	2	6
Total	7	5	12
Ontario			
Senior leaders	0	0	0
Directors or middle managers	0	3	3
Frontline managers	2	0	2
Total	2	3	5
Total for the 3 provinces (Alberta, Manitoba, and Ontario)			
Senior leaders	3	3	6
Directors or middle managers	3	6	9
Frontline managers	11	5	16
Total	17	14	31

FGIs began in November 2024, and we anticipate interviews will be completed by the fall of 2025 in all provinces. Data will be integrated from individual interviews with leaders and FGIs with nurses and will be used as a foundation for the 1-day forum (nominal group technique). We anticipate beginning data integration in the fall of 2025 and extending into early 2026. The nominal group technique will be conducted in the spring of 2026, and the final report will be written in the summer of 2026.

Discussion

Principal Findings

Although there is available literature on disaster preparedness [26] and leadership strategies in emergencies [27], to the best of our knowledge, there is a dearth of guidance for leaders during all 4 stages of a crisis, as described by Geerts [28]. Furthermore, few empirical studies exist on preparing health systems leaders following a major crisis, and what is available is often based on anecdotal lessons learned and proposed strategies for senior leaders [30,33,34]. The various waves of COVID-19 severely overwhelmed hospitals worldwide, many of which were notably overburdened before the pandemic [35,36], resulting in more than 7 million reported global casualties [63] and the most severe health human resources crisis of our generation [28]. The latter involved massive staff shortages and turnover, unrivalled rates of staff absenteeism, burnout, and psychological distress and trauma. Along with ramifications on nurses' well-being, the destructive impact of these conditions depleted their engagement and ability to provide compassionate, quality care to patients, and compromised their capacity to address the surgical and diagnostic backlog. Health systems leaders have a "duty to care for their workforce" [9] and are tasked with prioritizing their people, while reimagining what leadership, staffing, and health provision should look like for systems transformation in the evolving global, national, and regional contexts.

A review of the literature identified several knowledge gaps. First, there is a limited understanding of how leadership strategies and practices apply and adapt across all 4 distinct stages of a crisis. Second, there is limited knowledge of how health system leaders sustain themselves and their staff, including nurses, through an extended crisis, and whether this is shaped by the gender of leaders and nurses. Third, there is limited understanding of how health system leaders can influence workplace contexts to sustain their own and their staff's well-being and how they can ultimately bolster organizational resilience. Finally, there is a lack of understanding of how the crisis-resilience relationship provides direction in how health care organizations can prepare for, respond to, and rebuild stronger following the evolving and future health care crises. Similarly, although there is strong empirical support indicating that leadership development interventions can facilitate outcomes at individual and organizational levels [39,64], there is limited available evidence to guide the design, delivery, and evaluation of crisis-specific

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training programs. This information could also be applied to increase individual, team, and organizational adaptability, resilience, and innovation more generally.

Developing a deeper understanding of how leaders at different levels experience and perform effectively during various stages of a crisis is an underresearched priority area. Validating the evidence- and expertise-informed conceptual framework is an important foundation for addressing this research gap. This is the first study to apply the Geerts model [28] to guide primary data collection, analysis, and recommendations for all 4 stages. From this foundation, a qualitative exploratory inquiry [6] is a suitable research approach to elicit a detailed understanding of a range of experiences and behaviors [65], in this case, those of health care leaders and nurses related to effective leadership strategies to promote psychological health and well-being and build organizational resilience. This approach will allow us to explore new areas of inquiry while also providing a credible structure within which to organize findings and optimize strategies for health system leaders.

Our study aligns with developing and implementing a comprehensive, multifaceted approach to integrated knowledge translation and end-of-grant knowledge translation strategies [63]. Integrated knowledge translation has been the primary strategy for building relationships with our AC partners from the outset of the project to assist in the uptake of results to inform decision-making for hospital leaders, managers, and policy makers, and thereby, positively impacting nurses and patients [66]. We will aim for a broad impact of context-relevant approaches, coordinated planning, leveraging relationships, and technology to support dissemination and application of our findings to practice [67,68]. The AC has committed to providing input into preliminary and end-of-study findings for interpretation, relevance, and clarity, and to cocreating critical implementation strategies. Senior leaders will be consulted regarding dissemination strategies, including how to reach diverse audiences and different leader groups [69].

Finally, this study's results will provide health systems leaders access to evidence-based strategies to strengthen and optimize their own psychological health and well-being and those of the nursing workforce, which can contribute to improved clinical outcomes. Additionally, the findings will directly inform and improve crisis preparedness, given anticipated future health crises, and prepare health systems leaders to be more effective across all 4 stages of a crisis, equipping them to ensure that patients receive high-quality care by nurses and other health care professionals in workplaces that prioritize their health and well-being.

Conclusions

The results of this study will make an important contribution to the crisis leadership literature, as this is the first study aimed at providing evidence-informed effective leadership strategies framed within the Geerts model [28]. The findings will support practices that health system leaders can implement to foster their own and nurses' psychological health and well-being and build organizational resilience. The benefits of this study will include evidence for effective health system leadership and support for nurses, crisis preparedness, and lessons from the pandemic to address leadership responses in the 4 stages of the crisis model. End-of-study dissemination strategies have been planned to broaden the impact of context-specific approaches to relevant stakeholders to support dissemination of findings to practice. Overall, this study will generate practical and potentially transferable strategies to contribute to how health system leaders can more effectively lead during a crisis that can improve nurse outcomes and the patients entrusted to their care.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview and focus group interview guides.
[PDF File (Adobe PDF File), 122 KB - resprot_v14i1e66402_app1.pdf]

Multimedia Appendix 2
Peer-reviewer report from the Health Policy & Systems Management Research/Recherche sur la gestion des systèmes et la politique de la santé (Canadian Institutes of Health Research; CIHR/IRSC).
[PDF File (Adobe PDF File), 39 KB - resprot_v14i1e66402_app2.pdf]

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Abbreviations

AC: advisory committee
DM: data manager
FGI: focus group interview
IRB: institutional review board
PI: principal investigator
RC: research coordinator
RN: registered nurse

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Protocol

Engaging Older Adults With Cognitive Impairment in Digital Health Technologies: Protocol for a Scoping Review

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Abstract

Background: The aging of the population is a major issue in Canada, particularly in Quebec. For people older than the age of 65 years, aging is often associated with both mild and severe cognitive impairment. The management of these disorders increases the pressure on health care systems. Digital health technologies could be used to promote the cognitive health of older people living with cognitive disorders. However, to reap the full benefits of using digital health technologies, it is critical that older people with cognitive disorders engage with these technologies. A dose-response relationship has been demonstrated between the level of engagement with digital health technologies and the effectiveness of interventions in older people. It is thus important to understand how older people with cognitive impairment engage with digital health technologies and how this engagement can influence the success of digital health interventions.

Objective: This study aims to describe how the engagement of older adults with cognitive impairment with digital health technologies is conceptualized and assessed, and how this engagement relates to the effectiveness of digital health interventions.

Methods: We will use the scoping review method outlined by Arksey and O'Malley. We will apply a systematic approach following the Joanna Briggs Institute guidelines and the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist to ensure reproducibility of the scoping review. A search strategy, created with a medical information specialist, will be applied to MEDLINE, Embase, CINAHL, Web of Science, and Google Scholar, without time restrictions. Two reviewers will independently select titles, abstracts, and full texts. Data extraction will be conducted by the research team and validated by a senior member, resolving disagreements by consensus or a third party if necessary. Descriptive analyses will be done using concept mapping for a narrative synthesis of the results by themes related to the research questions.

Results: The development of the search strategy and the completion of the selection phases of the review were completed in July 2024. Data extraction and analysis began in August 2024, and results are expected to be available in November 2024.

Conclusions: The results of this scoping review will provide a comprehensive overview of the different conceptualizations of engagement with digital health technologies in older people with cognitive impairment, as well as the tools to measure it. This will contribute to a better understanding of the relationships between levels of engagement and the effectiveness of digital health interventions in older people living with neurocognitive disorders.

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KEYWORDS

engagement; older adults; cognitive disorders; digital health technologies; scoping review

Introduction

People aged 65 years and older represent 19% of the Canadian population and are expected to reach 25% by 2030 [1]. With the accelerated aging of the population, the prevalence of both major and mild cognitive disorders is increasing [2]. Cognitive disorders correspond to an alteration in one or more cognitive functions, regardless of the mechanism involved, its origin, or reversibility, and may be neurological, psychiatric, drug induced, and so on [3]. The prevalence of major cognitive disorders, such as Alzheimer disease, doubles every 5 years after the age of 65 years [4]. In 2015-2016, a total of 87% of residents in Canadian nursing homes had some type of cognitive impairment, 69% had dementia, 50% had behavioral disorders, and 31% had depression [5]. Of these residents, 82% required assistance with their care or were dependent on all care related to activities of daily living [5]. At the same time, the proportion of older people with dementia living outside a long-term care facility or nursing home was 61%, including 69% of those aged younger than 80 years and 58% of those aged 80 years and older [6]. The consequences of these cognitive disorders, which manifest themselves as a decline in performance in one or more cognitive domains [7], are often far-reaching for the individual, his or her family, health care professionals, and society. In Canada, the economic burden incurred by the health care system for caring for people with cognitive impairment was around CAD $10.4 billion (equivalent to US $7.2 billion) in 2016 and would reach CAD $16.6 billion (equivalent to US$ 11.5 billion) by 2031 [8].

Such a picture calls for mechanisms to maintain cognitive health in older adults. There are 2 main ones: vascular health and cognitive reserve [9]. Some of the protective factors acting on these mechanisms have been identified. First, physical activity contributes to maintaining vascular health and developing cognitive reserve, making it a preferred intervention for preventing cognitive impairment or delaying its progression [10]. Second, social participation, either direct or indirect contact between individuals in which information, attitudes, and norms are shared, has been shown to be a protective factor against cognitive decline [11].

Finally, cognitive engagement is associated with an increase in cognitive reserve [12]. This factor has 2 components: cognitive stimulation and cognitive training. On the one hand, cognitive stimulation is achieved through individual or group activities that involve different cognitive functions and consist of new learning activities, such as learning a new language [12]. Cognitive training, on the other hand, is based on the repetition of standardized tasks that target specific cognitive functions, such as the use of sophisticated video games [12]. These key protective factors (eg, physical activity, social participation, and cognitive engagement) can be promoted in a variety of ways, notably through the use of digital health technologies.

According to Health Canada, digital health technologies include stand-alone software applications as well as integrated software systems and instruments that can be used with platforms such as computers, smartphones, tablets, wearable devices, and environmental sensors [13,14]. Digital technologies for older adults, also known as gerontechnologies, have been used in many aspects of health care for older adults [2]. For example, mobile apps used to stimulate cognitive functions, connected devices to monitor physical activity, and digital platforms to facilitate communication with loved ones or consultation with health care professionals can be found among older people living with neurocognitive disorders [15]. Several studies have demonstrated the positive impact of digital health technologies on various aspects of an older person's life, such as health, housing, services and transactions, mobility and transportation, access to information, communication and work, leisure, and personal fulfillment [16]. These technologies can improve access to health information, enable faster diagnosis and treatment, and improve access to care and services for older people with cognitive impairment at home, in health care facilities, and in rural and remote communities [13,17].

However, the potential benefits associated with the use of these technologies cannot be realized without the engagement of the people who use them. Thus, despite the growing interest in digital health technologies and the availability of evidence on the feasibility and effectiveness of health interventions using these technologies in a cognitively impaired population [18], little is known about the engagement of older people with cognitive impairment with these tools. Nevertheless, the success of digital health interventions depends on their adoption and optimal use, which implies an experienced and ongoing engagement of the people who use them. For example, some people may have access to the technology and possess the skills to use it but choose not to engage with a digital health service [19]. Other people engage with these technologies and then decide to abandon them. A systematic review and meta-analysis of attrition and adherence in smartphone-based interventions for mental health problems found attrition rates as high as 30% and very low adherence rates ranging from 2% to 10% [20]. Several factors could influence attrition in digital health interventions. In their study of barriers to adoption of mobile phone–based mental health interventions by older adults, Pywell et al [21] highlighted factors that may lead older adults to disengage. For example, participants felt that if they did not make sufficient progress while using digital health technologies, if they did not gain a better understanding of their symptoms and how they might affect them, or if they had to invest a lot of time and effort, then they would give up. These findings underscore the importance of increasing engagement, as there is evidence that higher levels of engagement are associated with better cognitive health [20].

For older people living with cognitive impairment, engagement with digital health technologies can be particularly challenging,

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and even more so for people from cultural or linguistic minority groups. Indeed, digital health technologies may contribute to increasing health inequalities due to systematic differences and people's ability to engage with digital platforms [19].

The engagement of older people with cognitive impairment with digital health technologies is therefore a key factor in maximizing the benefits of these tools. This engagement can be influenced by conditions related to the design of digital health technologies, data security and confidentiality, and support for older people with cognitive impairment. However, other factors may also influence the level of engagement with digital health technologies in this population. Indeed, it is essential to understand the concept of engagement, how it is assessed, and how it relates to the effectiveness of digital health interventions for the prevention and management of cognitive disorders in older people. This understanding can inform the development and implementation of digital health interventions that are better adapted to this population, thus contributing to their health and well-being.

The purpose of this scoping review is to describe how the engagement of older adults with cognitive impairment with digital health technologies is conceptualized and assessed, and how this engagement relates to the effectiveness of digital health interventions.

Our key synthesis questions are as follows: (1) How is engagement conceptualized and operationalized in the context of studies of digital health technologies for older adults with cognitive impairment? (2) What measures are used to assess the level of engagement of older adults with cognitive impairment with digital health technologies? (3) What facilitates or limits the engagement of older adults with cognitive impairment with digital health technologies? and (4) What are the relationships between the level of engagement and the effectiveness of digital health interventions for older adults with cognitive impairment?

Methods

Overview

We will use the scoping review method based on the framework of Arksey and O'Malley [22], as improved by Levac et al [23]. In addition, we will use a systematic approach to conduct the scoping review, following the Joanna Briggs Institute recommendations for this type of review [24]. We will also follow the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews Extension for Scoping Reviews) [25] to guide the scoping review approach and ensure reproducibility.

Eligibility Criteria

Inclusion and exclusion criteria are listed in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- We will include all types of evidence that meet the PCC (Population, Concept, Context) criteria.
- Participants or population: we will include all studies of people aged 65 years and older with cognitive impairment and their family caregivers.
- Concept: we will consider engagement with digital health technologies as a central concept in this scoping review.
- Context: we will include studies that address engagement with digital health technologies in all types of contexts (care setting, retirement home, community, etc) without geographic limitations.

Exclusion criteria

- We will exclude studies that address the concepts of use, adherence, compliance, participation, and adoption, which are often used interchangeably with the concept of engagement in studies.

Search Strategy

The search strategy (Multimedia Appendix 1) was developed in collaboration with a librarian experienced in systematic reviews (FB). The research team conducted an iterative review, and all relevant comments on the research strategy were incorporated into the final version. The final version was approved by all members of the research team. A specific search strategy (Multimedia Appendix 1) combining concepts related to engagement and digital health was formulated for each of the following databases: MEDLINE (Ovid), Embase, CINAHL, and Web of Science, in addition to the Google Scholar search engine. The search strategy (Multimedia Appendix 1) was not restricted by time constraints. Gray literature, including government websites and documents, dissertations or theses, and conference abstracts, may be consulted as needed to supplement information from scholarly articles. The search will also include a manual search, and bibliographies of pertinent studies will be reviewed for additional relevant references.

Data Collection

All search results in the various databases were exported to Covidence [26], a collaborative knowledge synthesis management software that automatically eliminates duplicates. This software allows double-blind evaluation at both stages of study selection. Independent and blind assessment of inclusion and exclusion criteria will be performed by at least 2 reviewers, first based on titles and abstracts, and second based on full texts. Any conflict will be resolved by consensus and finally by the principal investigator. For included studies at this stage, reviewers will read the full texts to further assessment of eligibility for the final inclusion. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart will be used to describe the identification of studies,

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the selection process, and the application of inclusion and exclusion criteria [27].

Data Extraction

A preformatted data extraction grid will be developed by the research team. It will be used to compile the results extracted from the selected relevant studies. The extraction itself will be performed independently by two members of the research team and then validated by a senior member (MPG or MS). Disagreements will be resolved by consensus within the research team or, if necessary, by a third party. Data to be extracted include study characteristics (ie, title, year of publication, authors, and country where the study took place), intervention (type of engagement conceptualization and type of engagement measurement tools), context (care setting and community characteristics), participants (target population, stage of cognitive impairment, number of participants, and sample size), methods (study design, inclusion and exclusion criteria, and methodological quality), and outcome measured (qualitative and quantitative). We will highlight specific outcomes related to sex, gender, and other identity characteristics documented in the selected studies in line with the PROGRESS-Plus (place of residence; race, ethnicity, culture, and language; occupation; gender and sex; religion; education; socioeconomic status; social capital–personal characteristics associated with discrimination; features of relationships; and time-dependent relationships) health equity framework [19].

Data Summary

We will conduct descriptive analyses using concept mapping to provide an overview of the information contained in the selected documents. We will first perform a narrative synthesis, grouping the findings by topic according to the initial research questions of the scoping review. We will then produce graphical representations of the results, depending on the nature of the information analyzed.

Results

The development of the search strategy and the completion of the selection phases of the review were completed in July 2024. Data extraction and analysis began in August 2024, and results are expected to be available in November 2024.

Discussion

Overview

The results of this scoping review should provide evidence on how engagement with digital health technologies by older people with cognitive impairment is conceptualized, measured, and related to the effectiveness of digital behavior change interventions.

Main Contributions of This Scoping Review

Several literature reviews have explored the concept of engagement [28-31]. Kelders et al [29] showed the variety of areas in which engagement has been studied. These include areas such as work, society, commerce, digital, and health. On the one hand, some authors have focused on conceptualizing engagement with digital behavior change interventions and tools for measuring engagement [30], while others have focused on patient engagement with digital health [31]. On the other hand, it should be noted that one review examined digital engagement among older people but focused on barriers and facilitators and was not specifically targeted at older people with cognitive impairment [16]. Another review examined the effectiveness of digital health solutions among older people with cognitive impairment [15], without focusing on their engagement with digital health technologies. Thus, to our knowledge, our review is the first attempt to examine the engagement of older people with cognitive impairment with digital health technologies. Beyond descriptive data, the synthesis of evidence by study type, intervention, context, methods, and outcomes will provide beacons to support the development of innovative interventions that promote the engagement of older people living with cognitive impairment with digital health technologies. In addition, our review will provide guidance for the evaluation of the effectiveness of these interventions through an analysis of tools for measuring the engagement of older people living with cognitive impairment toward digital health solutions.

Potential Benefits and Next Steps

Engaging patients in the responsible management of their health is widely recognized as a means of overcoming challenges in the health care sector [28]. For this reason, it is generally accepted that some level of engagement is necessary for interventions to be effective [30]. However, it should be noted that patient engagement in the development, adoption, use, and evaluation of digital technologies in health care is not as advanced as in the traditional area of patient engagement in health care service delivery [31]. In the field of digital health, particularly in the case of older people with cognitive impairment, there is a lack of clarity in how engagement with digital technologies is conceptualized [32]. The results of this scoping review will provide a better understanding of the conceptualization and operationalization of engagement with digital technologies in health care by focusing on the experiences of older people living with cognitive impairment. The approach will promote the production of rigorous results while being adapted to the needs of older people with cognitive impairment, their caregivers, or the groups or institutions using this knowledge. The results of this scoping review will identify priority needs for knowledge users that can serve as a basis for the development of strategies to promote the engagement of older people with cognitive impairment with digital health technologies. The knowledge gained will inform further research for the development and implementation of digital health technologies that are better adapted to older people with cognitive impairment, thereby fostering their engagement and achieving the expected benefits for their health and well-being.

Conclusion

The results of this scoping review will provide a comprehensive mapping of the conceptualization and measurement of engagement of older people with digital health technologies. Such evidence will enable technology providers to develop digital technologies that focus on engagement, and policy makers and practitioners to develop engaging digital health

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interventions that promote cognitive health and prevent cognitive impairment in older people.

Acknowledgments

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Data Availability

Data on the search strategy for this review are available in Multimedia Appendix 1. All data generated or analyzed during this study (including the PRISMA [Preferred Reporting Items for Systematic Reviews and Meta-Analyses] flowchart) will be included as multimedia appendices. Databases created during the data extraction process will be made available upon reasonable request.

Authors' Contributions

PG performed funding acquisition and supervision. SMARD, MS, and MPG contributed to conceptualization. SMARD, FB, and MPG were responsible for the methodology. SMARD wrote the original draft.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 21 KB - resprot_v14i1e65515_app1.docx]

Multimedia Appendix 2
PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist.
[DOCX File , 49 KB - resprot_v14i1e65515_app2.docx]

Multimedia Appendix 3
Peer review report from the Brain Health and Reduction of Risk for Age-related Cognitive Impairment - Knowledge Synthesis and Mobilization Grants Committee (Canadian Institutes of Health Research, Canada).
[PDF File (Adobe PDF File), 37 KB - resprot_v14i1e65515_app3.pdf]

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Abbreviations

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
PROGRESS-Plus: place of residence; race, ethnicity, culture, and language; occupation; gender and sex; religion; education; socioeconomic status; social capital–personal characteristics associated with discrimination; features of relationships; and time-dependent relationships

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Protocol

Identifying and Taking Action on the Protective and Risk Factors of Black Maternal Mental Health: Protocol for Community-Based Participatory Study

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Abstract

Background: Maternal mental health disorders are associated with adverse maternal and infant health outcomes. Despite advances in screening and treatment, disparities in maternal mental health disorders continue to disproportionately affect Black mothers and birthing persons. While there are studies that have examined maternal mental health, a gap in research remains in understanding the protective and risk factors of Black maternal mental health in Canada. Identifying the risks and protective factors is critical for advancing equitable and inclusive policies and practices that promote maternal well-being and optimal outcomes for Black perinatal populations.

Objective: This paper presents an outline of a study protocol that seeks to identify the protective and risk factors of Black maternal mental health and to engage Black mothers and birthing persons from the Greater Toronto Area in codesigning a culturally safe and inclusive best practices model to inform policy and interventions.

Methods: The proposed study will use an exploratory 3-phase sequential mixed methods approach underpinned by the principles of health equity and community-based participatory research. Phase 1 will involve engaging Black mothers and birth persons (n=300) in a survey to examine the psychosocial determinants of Black maternal mental health, including depression, anxiety, discrimination, strong Black women trope, attitude toward seeking mental health, support, and stigma. In phase 2, we will conduct 6 focus groups and individual interviews (n=60) to explore the stressors in the context of Black mothers and birth persons' everyday lives, psychosocial and support needs, and conditions that promote their resilience. Finally, phase 3 will engage Black women and birthing persons (n=30) in a codesign session using the concept mapping method to identify priority areas for action to inform policy and programming. We will use SPSS version 26 (IBM Corp) to analyze the survey data, drawing on both descriptive and inferential statistics. NVivo (Lumivero), a qualitative data analysis software, will be used to organize the data from phase 2 into meaningful themes informed by Braun and Clarke's thematic analysis approach.

Results: Ethics approval was granted in July 2024. Data collection for phase 1 started in December 2024 and will be completed in April 2025. Findings from phase 1 will inform phases 2 and 3 of this study, which will be conducted in the third quarter of 2025. We will disseminate the results of this study in the second and third quarters of 2025.

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Conclusions: The findings will generate the much-needed knowledge to shift policy, practice, and research and support capacity building among Black mothers and birthing persons. In addition, the proposed study will contribute to informing policy initiatives and interventions at the health system and community level to advance mental health equity and build capacity among service providers to provide culturally safe and equitable mental health care.

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KEYWORDS

Black mothers; Canada; community-based research; maternal mental health; mixed methods

Introduction

Background

Maternal mental health (MMH) disorders before and after birth are a major public health concern associated with poor pregnancy and mental health outcomes for parents [1-3]. Research also shows that poor MMH undermines the development of secure infant attachment, which in turn affects the development of socioemotional skills of children [4,5]. While all populations can be affected by poor MMH, research has consistently shown that Black mothers and birthing persons are at a higher risk of MMH disorders, including postpartum depression and anxiety before and after childbirth [6-8]. Despite advances in perinatal mental health care, racialized health disparities continue to exist within and across countries. Evidence from the United States suggests that 40% of Black mothers and birthing persons are more likely to experience MMH issues compared with White women [9]. In Canada, 23% of all women experience MMH disorders [1] with Black, Indigenous, and other racialized people accounting for 40% of all reported cases [10]. Despite the highly preventable and treatable nature of MMH disorders, only 15% of those who experience symptoms of depression and anxiety receive the required care [10]. MMH disorders cost the Canadian health care system an estimated CAN $6.7 billion (US $4.9 billion).

Few studies have explored MMH disorders among Black populations in Canada, but disparities in diagnosis, delivery of care, and their relationship to health outcomes for Black women have been well documented in the United States [11,12]. Black mothers and birthing persons are known to be at increased risk of MMH disorders before and after childbirth, and these have been associated with complex socioenvironmental factors, including anti-Black racism, discrimination, low socioeconomic status (SES), neighborhood disadvantage, inadequate social support systems, and stressful life circumstances [7,8,13-17]. Even after accounting for known risk factors such as a history of depression, anxiety, and substance use, Black mothers and birthing persons are still at an increased risk for MMH disorders [7,16]. They face unrelenting gendered racial stress, and this structural disadvantage coupled with emotional and hormonal changes increases their risk of postpartum mood and anxiety disorders [15].

MMH disorders can lead to adverse effects before and after childbirth [7,18]. High levels of stress and anxiety related to untreated MMH disorders can interfere with fetal development and increase the risk of adverse pregnancy outcomes including preterm birth, low birth weight, and risk of infant mortality in the first year of life [9,19]. Furthermore, MMH disorder affects the health and psychosocial functioning of Black mothers and birthing persons and undermines their capacity to care for themselves and their infants [20]. This in turn can interfere with a mother's responsiveness to infant needs and ability to engage in infant caregiving [4,21-23], thereby affecting the child's emotional and cognitive development potentially leading to social and behavioral issues [21,22].

Black mothers and birthing persons face significant barriers accessing mental health support. They are less likely to receive treatment due to challenges such as fear of stigma, involvement in child welfare services, and limited financial support [9,13,14,18]. Limited understanding of MMH disorders along with a lack of support among partners and family members can further isolate Black mothers and birthing persons and affect their ability to seek care. The stigma of mental illness and the expectation to demonstrate strength in the face of these negatively perceived issues can also create barriers for Black mothers to openly discuss their mental health and reinforce their hesitancy to seek care [11,12,24]. These factors are exacerbated by inadequate universal screening, low mental health literacy, lack of culturally relevant, gender-responsive care, systemic racial discrimination, microaggressions, and a fractured health system [7,11,12,24,25]. Untreated postpartum mental health disorders are known to increase the risk of maternal infanticide [26] and most recently have been identified as the leading cause of direct maternal death during pregnancy and within the first year of childbirth [27]. This is highly concerning given the already limited social support, lack of culturally responsive services, and overstrained community resources [9,11,12,28].

Research has shown that identifying and strengthening protective factors including coping resources and support systems can decrease the risk of postpartum depression among Black mothers and birthing persons [11]. While these findings from the United States provide valuable insights, they cannot be directly extrapolated to the Canadian context because the 2 countries differ fundamentally in terms of their social, structural, environmental, and health care systems. Some studies in Canada have explored perinatal mental health among women [29], but very few studies have specifically examined the protective and risk factors of MMH among Black mothers and birthing persons in the first year postpartum. In addition, there were significant gaps in Canadian literature on the cross-cultural considerations in response to and treatment of MMH disorders [29]. This limited evidence on Black MMH in Canada constitutes a significant barrier to promoting and advancing mental health

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equity. Given the significant public health concerns related to MMH disorders among Black mothers and birthing persons and the downstream impacts on infants before and after birth, it is crucial to identify and act on the risk and protective factors. Black mothers and birthing persons face complex intersectional issues and unique stressors that increase their risk of MMH disorders in the first year of postpartum [7,11,15]. Our project will contribute to increasing awareness and understanding of the protective and risk factors of MMH disorders for Black mothers and birthing persons and identify priority areas for action to advance MMH equity.

Objectives

The overall goal of this study is to examine the protective and risk factors for MMH disorders among Black mothers and birthing persons and to critically engage them in identifying priority areas for action to advance MMH equity in Ontario and across Canada. The specific research objectives (RO) are:

- RO 1: Identify the protective and risk factors related to MMH disorders among Black mothers and birthing persons in the first year of postpartum
- RO 2: Explore the stressors in the context of everyday life, psychosocial and support needs, and conditions that promote resilience
- RO 3: Identify the factors that facilitate or impede MMH support
- RO 4: Engage Black women and birthing persons in identifying priority areas for action to inform policy and programming

Theoretical Framework

This proposed study is underpinned by the principles of health equity as it relates to health outcomes of systematically marginalized and racialized communities. It is also informed by intersectionality [30] and socioecological frameworks [31]. Intersectionality is based on the understanding that (1) social identities constructed through power relations are not distinct and unidimensional but rather multiple and intersecting; (2) the experiences of historically oppressed and systematically marginalized groups are the focus of understanding; and (3) multiple social identities such as race, gender, and SES intersect and interlock with structural factors such as sexism, racism, and poverty to create disparities in health outcomes [30]. Intersectional analysis is based on the understanding that disparities in health outcomes do not occur in isolation but are a combination of complex interlocking conditions that contribute to inequality and inequity within society. Intersectional analysis enables researchers to analyze how racism, gender, economic marginalization, sexism, education, and neighborhood shape experiences and vulnerabilities associated with MMH disorders. In addition, we will draw on the socioecological framework to examine how individual, interpersonal, community, and societal conditions interact to influence MMH outcomes [31]. The socioecological framework situates the analysis of social and structural determinants of health across multiple levels to determine their effect on health and mental well-being and to identify areas for creating change [30]. Together, these frameworks will help the team identify the sociocultural, contextual, and structural conditions that shape the MMH of Black mothers and identify target areas for creative and sustainable intervention programs to strengthen protective factors and reduce risk factors to improve health outcomes.

Methods

Overview

The proposed study will use an exploratory 3-phase sequential mixed methods approach [32]. The approach outlined in Figure 1 will be used to identify and explore the protective and risk factors of Black MMH and to co-create best practices framework and policy action. The determinants of MMH disorders are complex and are shaped by broader social and political conditions at the individual, community, and societal levels. Therefore, understanding and taking action to reduce risks and strengthen protective factors requires a research approach that fosters collaboration and meaningful community engagement. The study will be guided by tenets of community-based participatory research. As an innovative and transformative research approach, community-based participatory research aims to generate understanding and action on issues affecting communities to reduce disparity and advance health equity [33]. Community-based participatory research draws on the principles of empowerment and meaningful engagement with communities, researchers, and interest holders in cocreating culturally transformative, sustainable, and equity-driven action to create change [34,35]. A combination of quantitative (sociodemographic survey and validated scales) and qualitative (focus group and in-depth interviews) methods and a participatory process of group concept mapping will be used to generate a new understanding of the complexities of Black MMH.

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Figure 1. Sequential mixed methods approach.

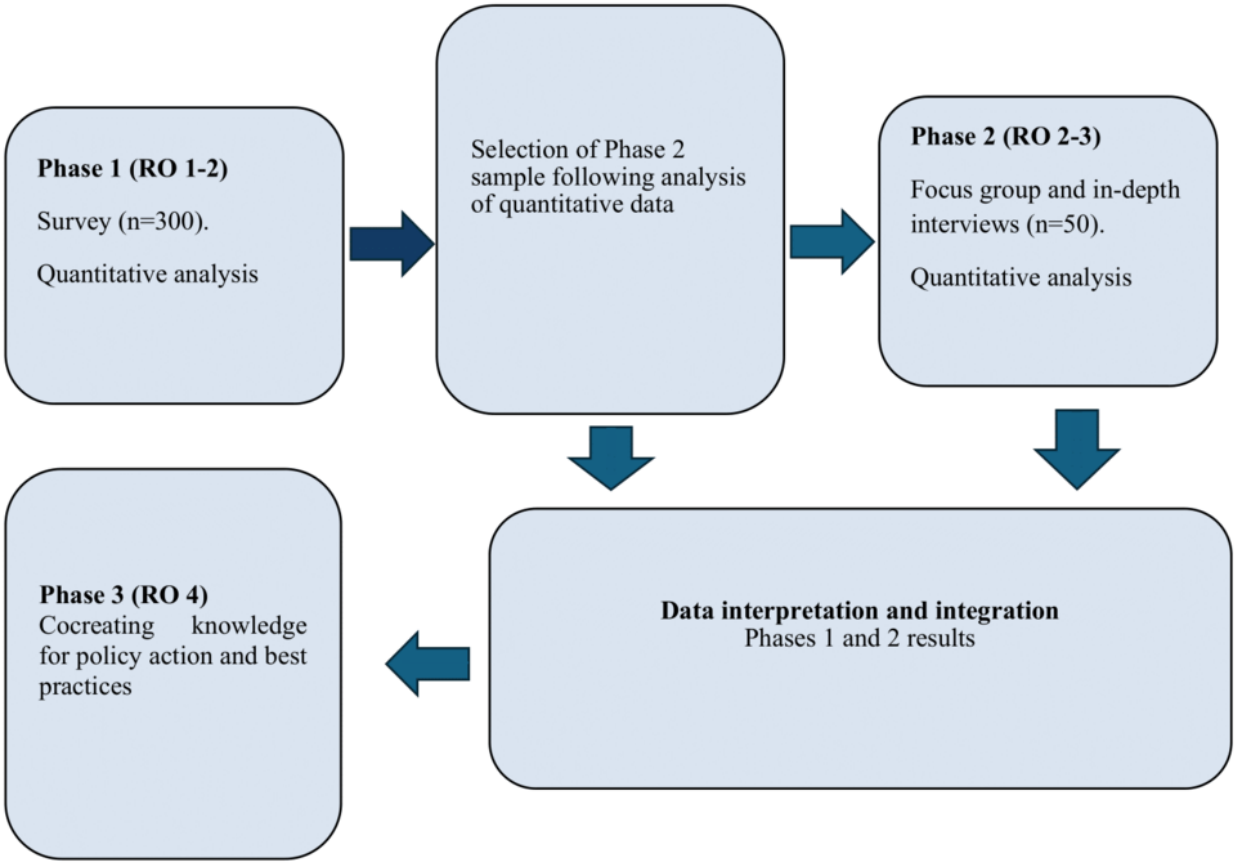

Sample and Setting

We will foster meaningful community engagement by working with formal and informal collaborators in Black communities made up of Black mothers and birthing persons, community advocates, service providers, and faith leaders in Toronto, Canada. The inclusion criteria for participation are Black mothers and birthing persons who (1) self-identify as Black, (2) have biologically conceived and given birth within the past 12 months, (3) are caring for an infant 1 year or younger, and (4) speak English and reside in the Greater Toronto Area, Ontario. To enhance the efficiency of the data collection, we will purposively recruit 300 eligible Black mothers and birthing persons of all gender and sexual identities (self-identified as heterosexual, lesbian, bisexual, queer, cisgender, transgender, intersex, nonbinary, etc) and relationship and family compositions (same sex, intergenerational, sole parenting, etc). Recruitment will be supported by community partners across the study site and facilitated by the use of the study flyer in addition to using multiple approaches, including local public health agencies, diverse Black parenting groups, faith-based organizations, and a wider network of interest holders in the Black communities to promote participation and engagement (Black businesses, salons, Black churches, mosques, community, and neighborhood associations, etc). We will leverage social media platforms to ensure representation and will engage local public health agencies to disseminate information and recruitment flyers about this project.

Phase 1: Objectives 1 and 2: Surveys on Mental Health Status and Coping

In this phase, an e-survey (n=300) will be used to collect data on the participants' demographic (age, racial and ethnic identities, immigration status, educational status, SES, gender identity, housing, neighborhood, employment, relationship status, and household income along with obstetric information including gestational age at birth (full or preterm), admission to neonatal intensive care unit, and infant health issues or concerns. The following validated scales will be used to assess experiences of Everyday Discrimination Scale (EDS) [36], stress in the context of their everyday lives using the Parental Stress Scale (PSS) [37], mental health status using the 7-item Generalized Anxiety Disorder (GAD-7) [38] and Center for Epidemiological Studies-Depression (CES-D) [39], emotional support using Multidimensional Scale of Perceived Social Support (MSPSS) [40], attitude toward help-seeking mental health [41], and endorsement of the Strong Black Woman Archetype [42]. As an exploratory study with a Black population that is geographically spread out across the Greater Toronto Area, we will use convenience sampling techniques to reach our target population.

Quantitative Data Analysis

Descriptive and inferential statistics will be used to analyze the data from the surveys. To identify risk and protective factors, stepwise linear regression analysis will be used to examine the impact of parental age, racial and ethnic identities, gender

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identities, educational status, SES, housing, neighborhood, employment, relationship status and family composition, discrimination, support, gestational age at birth on parental stress, anxiety, and depression. Intersectionality will be explored by examining interaction terms in the regression analysis, such as sexuality and SES, and race and SES.

Phase 2: Objectives 2 and 3: Exploring the Experiences and Perspectives of Participants

In phase 2, we will conduct focus groups and in-depth individual interviews to explore the unique and common experiences of Black mothers and birthing persons (n=60) in the context of physical, emotional, psychological, social, and economic needs and overall well-being. We will engage 40-50 Black mothers and birthing persons in focus groups. We will determine the sample size based on the ontological and epistemological assumptions of qualitative research and purposive sampling [43]. We will use purposive matrix sampling [43], which allows us to reach the maximum diversity of participants specific to the study population and the intended study outcomes. We will conduct 5-6 focus groups (8-10 Black mothers and birthing persons per group) across the study site. These focus groups will provide opportunities for participants to share and exchange information, leading to the generation of deeper, comprehensive, and collective understanding. Participants will be drawn from phase 1, and we will also use a matrix to guide recruitment to enrich the diversity of all focus groups in terms of relationship status, family composition, gender identities, neighborhoods, and SES. We also plan to conduct 8-10 individual interviews with some participants to further explore their experiences, including sensitive topics that may be difficult to discuss in a group setting [44]. We expect that combining focus groups and interview methods will lead to a more comprehensive understanding through the triangulation of data collection methods, ultimately contributing to the trustworthiness of the findings [45].

Qualitative Data Analysis

We will use thematic analysis [46] drawing on both inductive and deductive processes to analyze the data. The analytic process will be organized using NVivo. We will draw on intersectionality and socioecological frameworks to analyze the complex ways by which race, gender, class, and other factors intersect to affect the mental health, coping, and resilience of Black mothers and birthing persons. We will develop a codebook based on the research objectives and questions (deductive), as well as ideas and perspectives generated by the participants (inductive). A systematic and iterative process will include (1) familiarizing and sorting the data, (2) generating a coding template to guide the analysis, (3) assigning codes to the dataset, (4) categorizing similar phrases and statements into clusters, (5) identifying and defining themes and relationship between the themes, and (6) creating a narrative to describe the data interpretation [46]. The analytic process will be conducted in collaboration with the project team members to ensure broader and collective interpretation and understanding is achieved. The combined results of phases 1 and 2 along with relevant evidence from existing literature will be used to inform digital integrated knowledge translation (iKT) and the team will collectively work with participants to translate the findings into practical solutions relevant to the contexts of their experiences and community realities to co-create a best practices framework.

Phase 3: Objective 3: Cocreating Knowledge for Policy Action and Best Practices

Phase 3 of this study is guided by the principles of meaningful community engagement and iKT [47]. In this phase, we will use concept mapping to engage Black mothers and birthing persons in cocreating an inclusive best practices model to inform policy and programming to promote mental well-being and resilience among Black mothers and birthing persons. We will use the Groupwise software (OpenText) to support the concept mapping activities. Concept mapping is an innovative community-based research method that has been used successfully to explore health and social issues from the perspective of affected individuals and communities [47,48]. Concept mapping has been used to understand and develop equity-driven best practice guidelines and models to improve the health of communities [49]. As a strategy for iKT and knowledge cocreation, concept mapping will facilitate the uptake of evidence generated in phases 1 and 2 and engage Black mothers and birthing persons to collectively translate the evidence into actionable strategies.

Sampling

We will use purposive matrix sampling to recruit diverse Black mothers and birthing persons (n=30). According to the researchers who developed the Group Concept Mapping methods and software, 20-30 participants are adequate for effective use of concept mapping [49]. We will draw from the lists of phase 1 and 2 participants who have indicated their wish to participate in phase 3. In addition, we will engage Black mothers and birthing persons who are interested but not able to take part in phases 1 or 2. Using the matrix methods, we will recruit a group of diverse Black mothers and birthing persons based on their relationship status, family composition, ethnic ancestry, gender identities, neighborhoods, and SES.

Concept Mapping: Data Collection, Map Analysis, and Interpretation

As a structured process, concept mapping captures participants' responses and ideas on a given issue and translates them into an interpretable visual representation (concept map). All ideas are displayed through the concept map, which shows the relationship between the ideas and the degree of significance and importance. When engaging participants in developing the best practices framework, we will apply intersectionality as a guiding framework to integrate gender- and sex-based analysis with race and class or SES-based analysis. The concept mapping process with Black mothers and birthing persons will involve 4 meetings via Zoom, and we will use the Groupwise software and group discussion to support data collection, analysis, and interpretation. The concept mapping process allows for consensus building and collaboration with participants:

Session 1: Knowledge Exchange

The combined results of phases 1 and 2 along with relevant evidence from existing literature will be presented by the

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research team, and participants will be invited to respond to these findings in relation to their lived experiences. Both research teams and participants will engage in dialogue to further explicate the social determinants and intersectional experiences of Black mothers and birthing persons. This dialogue will prepare participants to co-create a best practices framework in subsequent sessions.

Session 2: Brainstorming

Drawing on the study results presented in session 1, participants will engage in brainstorming ideas for best practices to meet the needs of Black mothers and birthing persons. They will be given a prompt, "What needs to be done by various stakeholders (individuals, families, service providers, community organizations, and government and policymakers) to promote the MMH of Black mothers and birthing persons," and work individually to generate as many ideas as they can based on the prompt. We anticipate that participants will generate statements of ideas on effective and culturally safe programs and services, community support and resources, health service delivery, policy actions, and socioenvironmental conditions that promote or hinder resilience. The research team will refine the statements generated to remove redundant statements, and these will be entered into the Group Concept Mapping computer program to be aggregated based on similarities.

Session 3: Sorting and Rating

In this session, each member will be given a list of statements generated by the Group Concept Mapping program. They will work individually to sort the itemized ideas into stacks according to similarity and provide each stack with a name. Participants will also be given a list of items to rate based on importance using a scale of 1-5, with 5 being the most important. Responses from participants' input will be entered into the Group Concept Mapping program to generate concept maps for interpretation.

Session 4: Analysis and Interpretation of Concept Maps

The analysis includes (1) multidimensional scaling to generate point maps; (2) hierarchical cluster analysis to generate 3-dimensional cluster maps, individual items (statements) are collated into thematic maps to show the relative importance of each theme; (3) pattern matching analysis is used to compare importance and feasibility ratings for each cluster of strategies (statements); and (4) go zone plots and analyses will be used to show the graphical representation of the mean values obtained for all the individual statements in order of importance and feasibility rating scales. We will facilitate discussion with participants, assess the degree of alignment of the concept maps with their experience, and work collaboratively to make sense of these maps. After the initial large group interpretation of the clusters, participants will work in small groups of 4-6 to translate the maps into practical solutions relevant to the contexts of their experiences and community realities. They will then return to the large group, share their ideas, and work collectively to integrate all group ideas into a best practices framework. After completing the 4 sessions of group concept mapping, the research team will finalize the best practices framework and translate it into audience-specific products to promote effective dissemination and uptake.

Team Expertise

Our team consists of a multidisciplinary team of researchers with outstanding track records in community-based action research in the areas of mental health and health equity. The team comprises senior and early career researchers in academic institutions and clinical and community-based settings, many of whom have experience working with Black women in the prenatal and postnatal periods in addition to scholarship on anti-Black racism and health inequities experienced by Black communities. Collectively, the team brings diverse expertise and experience including quantitative research, qualitative, and mixed methodologies; cultural psychiatry, and sociocultural issues in mental health; community-based action research and knowledge translation and exchange; and implementation science. The research team also includes community partners and collaborators with grassroots connections with our population of interest, who will support the successful implementation of this project.

Ethical Considerations

The protocol for this study has been reviewed and approved by the Toronto Metropolitan University Research Ethics Board (REB 2024-126). Data will be collected over a period of 1 year starting December 2024 to May 2025. The team will collectively adhere to ethical principles and guidelines governing the study protocol during phases of the project implementation including informed consent, privacy and confidentiality, and rights of participants. Participants will be asked to provide written informed consent before completing the survey, focus groups, in-depth interviews, and concept mapping sessions. Data from the focus groups and in-depth interviews will be purged of any identifiable information before being stored in an institutional repository. Each participant will receive CAN $30 (US $22) for completing the survey, and those who will be invited to participate in the focus groups and interview will receive CAN $50 (US $36).

Results

This study received ethics approval from a Canadian institution in July 2024, and data collection for phase 1 started was December 2024 and was completed at the end of April 2025. A total of 329 participants completed the e-survey. The data is currently being processed for analysis using SPSS version 26, and the findings will be used to inform the development of the focus group guide for phase 2 and the co-creation process for phase 3. We anticipate the results of this study will be available in the third and fourth quarters of 2025.

Discussion

Overview

This research seeks to examine the protective and risk factors for Black MMH in the Canadian context. The new evidence will contribute to addressing the long-standing research gaps and inform change in policy, research, and practice to advance

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health equity. While research on risk factors of MMH among Black women is well documented [24], very few studies have identified factors that promote resilience and protect against perinatal mood disorders [50,51]. Moreover, maternal mental disorders are shaped by complex interactions of social and structural determinants. This proposed project will be among the first few studies to identify the risk and protective factors of MMH among Black mothers and birthing persons in Canada. Reducing the risk associated with MMH disorders and strengthening protective factors are critical to addressing the disparities in mental health outcomes that disproportionately impact Black women during pregnancy and after childbirth. Based on this understanding, we will use a mixed methods study design (quantitative and qualitative methods) informed by the principles of a community-based participatory research approach to engage Black mothers and birthing persons, interest holders, community leaders, service providers, decision makers, policy and mental health advocates, and parent champions to co-create best practices framework to reduce MMH disparities and advance equity. The involvement of different stakeholders contributes to narrowing the knowledge gaps on the experiences and mental health needs of Canadian Black mothers and birthing persons and offers evidence to advance inclusion. We will discuss the findings of this study in the context of current evidence, highlighting the similarities and contrasting perspectives.

Dissemination of Findings

The findings of this study will be disseminated widely through conferences and community networks. We will disseminate the evidence to researchers through peer-reviewed publications and presentations at local, national, and international conferences. The findings will also be translated into policy briefs, infographics, and e-posters to be disseminated to policy makers, share knowledge with the public through media interviews (eg, CBC Metro Morning, Black community) and social media to communicate to wider stakeholders to stimulate policy priorities and change. We will also present our findings to Black community groups and organizations to identify needs and priorities for meaningful action.

Strengths and Limitations

The proposed study has strengths. First, the integration of quantitative and qualitative methods will contribute to a comprehensive understanding of the protective and risk of Black MMH. In addition, using a mixed methods approach provides multiple and contextual insights that will enhance the knowledge cocreation and identify priority areas for action and programming. Potential limitations include those that can be complex and challenging to reconcile. We also anticipate that recruitment may be challenging given that the Black mothers and birthing persons are geographically dispersed throughout our research study setting. However, we have established a network of collaboration with community partners and collaborating organizations to facilitate recruitment.

Conclusion

This project is well positioned to shift the deficit approach to understanding Black MMH, generate the much-needed critical knowledge, and increase awareness of the protective factors of MMH. Using an innovative concept mapping approach as an engagement and research tool, this study will contribute to the development of an effective policy and culturally relevant best practices model, and guide the design of interventions to optimize and promote equitable access to mental health support for Black mothers in Canada and beyond.

Acknowledgments

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Data Availability

The data to be generated by the study will be encrypted and stored securely in an institutional repository located at the Toronto Metropolitan University for a period of 5 years and will be available to other researchers upon reasonable request.

Conflicts of Interest

CC declares CIHR funding Consultant for Seven Starling and Biogen. All other authors declare no conflicts of interest.

Multimedia Appendix 1 [PDF File (Adobe PDF File), 39 KB - resprot_v14i1e70076_app1.pdf]

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Abbreviations

CES-D: Center for Epidemiological Studies-Depression
EDS: Everyday Discrimination Scale
GAD-7: 7-item Generalized Anxiety Disorder
iKT: integrated knowledge translation

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MMH: maternal mental health
MSPSS: Multidimensional Scale of Perceived Social Support
PSS: Parental Stress Scale
SES: socioeconomic status

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Protocol

Evaluation of the Implementation of an Outreach Clinic for Opioid Use Disorder: Protocol for a Participatory Cocreation and Implementation Study

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Abstract

Background: The opioid overdose crisis currently affecting Canada has resulted in thousands of deaths, and the COVID-19 pandemic has exacerbated the consequences of this crisis, particularly through the instability of the unregulated drug market. The province of Quebec is observing a similar pattern: the opioids consumed are more dangerous, and the number of overdoses is rising. Opioid use disorder (OUD) therefore represents a major public health issue. Offering appropriate interventions, such as opioid agonist therapy integrated into primary care, is one strategy to reduce the risk of death from overdose.

Objective: The aim of this research is to evaluate the implementation of an outreach clinic offering a low-threshold treatment program for OUD in Quebec. The secondary objective is to identify the factors that foster the participation in primary care research of people who are socially excluded and have current or past lived experience of OUD.

Methods: This study is being conducted in the Montérégie region of Quebec and comprises 3 phases: exploratory, photovoice, and participatory evaluation. The qualitative research adopts a participatory approach by involving people who are socially excluded and targeted by the outreach clinic's services (eg, people experiencing homelessness and living with OUD). A committee of peer researchers, made up of experts with current or past lived experience of OUD, will be set up and will hold 10 meetings at various stages of the research. Two participant profiles will be involved: (1) health care professionals and community workers, who will take part in semistructured interviews; and (2) people with current or past lived experience of OUD, who will take part in the photovoice sessions or peer researcher committee meetings.

Results: The peer researcher committee was formed in winter 2024, and 10 meetings had been held as of June 2025. As of August 2025, 4 photovoice sessions had been conducted, and 14 health care professionals and community workers had participated in the semistructured interviews. This study was funded in September 2022, with funding available through March 2025. Data were collected from September 2022 through June 2025. The analysis was finished in spring 2025. Results of the study are expected to be published in winter 2026.

Conclusions: The anticipated outcome is the establishment of an outreach clinic for OUD outside a major urban center, with a range of services tailored to the needs of people who are socially excluded and living with OUD. The coconstruction of this clinic in collaboration with people with current or past lived experience of OUD will enable an adequate response to the targeted population's overall health needs and help reduce the barriers to access that they may face in conventional care structures.

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KEYWORDS

opioid use disorders; people who use drugs; people who inject drugs; participatory research; outreach clinic; low-threshold treatment program; primary care; photovoice

Introduction

Background

Over the last few years, the prevalence of opioid abuse has increased in North America [1], and tens of thousands of people have died from opioid overdoses in the United States [2] and Canada [3]. Since the global COVID-19 pandemic, Canada has experienced a worsening opioid crisis [4,5]. Fentanyl and the emergence of fentanyl analogs—extremely potent opioids with a high risk of overdose—contribute to this situation [3,6]. In Canada, an 89% increase in deaths from these substances was reported between April and December 2020 compared with the same period the previous year [3,7]. Since this marked increase, the number of deaths per quarter has continued to fluctuate around the 2020 peak and could be even higher in 2024 [7]. In the province of Quebec, the situation follows a similar pattern: the opioids consumed are more dangerous, and the number of overdoses is rising [6]. Problematic opioid use also involves other risks that should not be overlooked [8,9], such as the sharing of injection equipment among people who inject drugs, which is associated with an increased risk of blood-borne infectious diseases such as HIV, hepatitis B, and hepatitis C [9-11]. The overdose crisis in North America is mainly driven by the introduction of synthetic opioids into the unregulated drug market [12]. Managing the opioid crisis, and more specifically opioid use disorder (OUD), is a major public health issue in Canada [13], including within Quebec [6,14-16], given that OUD is a chronic, recurrent disorder with personal, societal, and economic consequences that are preventable through appropriate primary care interventions [17-19].

Populations That Are Socially Excluded and Access to Opioid Agonist Therapy

Management of OUD must include opioid agonist therapy (OAT) using buprenorphine-naloxone or methadone, which should be offered as first- and second-line treatment, respectively [18,20-23]. OAT has been shown to reduce cravings associated with opioid use, lower the risk of opioid overdose, and significantly improve quality of life for people with OUD [17]. However, few people with OUD have access to OAT in Quebec [17]. In Montreal, the most recent statistics on local services indicated that, in 2016, the targeted coverage rate for people with OUD was 70%, while the actual coverage rate was only 36% [24]. This discrepancy is associated with the fact that populations that are socially excluded, such as people who inject drugs and people experiencing homelessness and living with OUD, often encounter obstacles in accessing services due to the high threshold requirements of OAT programs (eg, abstinence from drug use and complex administrative procedures), which do not match the needs and realities of these individuals [24-26].

Accessibility of Services Outside Major Urban Centers

The opioid overdose crisis is not confined to the downtown areas of major urban centers [27,28]. The same progression is observed all over Canada, particularly in the Montérégie region, the second most populous administrative region in Quebec [29], where deaths increased during the COVID-19 pandemic [30]. One of the particularities of this mixed urban-rural region close to the Montreal metropolis is that, while the needs of people experiencing OUD are very much present, programs offering OAT, as well as adapted addiction treatment programs for people who are socially excluded, are scarce, with most addiction treatment programs concentrated in downtown Montreal (A-A Paré-Plante and Y Chertouk, unpublished data, 2017). This concentration forces people with OUD to move to the metropolis, where exposure to an environment unfavorable to their condition (eg, availability of substances) could exacerbate it [31]. Having to leave their community to receive care increases the precariousness of their situation [27,28]. Moreover, a survey by the Direction de la santé publique (directorate of public health) of the Montérégie region regarding fatal overdoses recommends creating user committees to develop new awareness approaches that would better reflect the on-the-ground reality of people who use drugs [30]. Montérégie faces a lack of services, particularly in the spheres of community resources, mental health, and postdetoxification transition, which considerably compromises continuity of care [32].

An Outreach Clinic to Improve Access to Services

An outreach clinic offering a low-threshold treatment program for OUD has been established in the Longueuil area, located in the Montérégie region. The opioid crisis and the current situation in Montérégie make it necessary to evaluate the implementation of such a clinic, coconstructed with users and adopting a holistic approach to meeting their needs. It also responds to the need to improve overall health care and services for people in the most vulnerable situations in and around Longueuil and, indeed, elsewhere in Quebec and Canada. This need has been described on several occasions [32]. The results obtained will enable us to improve access to health and social care and services on an ongoing basis according to the needs expressed by the target population. As such, this intervention and project will improve health equity, a benefit that aligns with the United Nations' Sustainable Development Goal 3 of ensuring well-being and healthy lives for all.

Montérégie's addiction treatment programs do not adequately meet the needs of its community, and we have little data on participatory evaluations of implementations similar to this intervention. This study will support the evaluation of the implementation of an outreach clinic outside the major Canadian

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centers (Montreal, Vancouver, or Toronto), coconstructed by and for people who are socially excluded and living with OUD.

Research Objectives

The aim of this project is to support a participatory evaluation of the implementation of an outreach clinic offering a low-threshold treatment program for OUD that opened in Longueuil in 2022. The secondary objective is to identify the factors that foster the participation in primary care research of people who are socially excluded and have current or past lived experience of OUD.

Methods

A Participatory Approach

This research project is based on a participatory approach that promotes the active and voluntary involvement of people who are socially excluded (eg, people experiencing homelessness, people who use drugs, and people who inject drugs) at all stages of the research process [33]. The populations for whom health services are intended should be at the heart of the implementation process [34]. The participatory approach allows for the genuine inclusion of people who are socially excluded. In this study, it will also foster partnership between researchers and community members while stimulating knowledge development and empowerment [35-37]. Moreover, participatory methods contribute to enhancing the scientific quality and transferability of research [37].

This research approach promotes the active involvement of all stakeholders, including people who are socially excluded, in the health care system throughout the research process [38,39]. It fosters the codevelopment of new knowledge and innovative practices that integrate academic and experiential knowledge and reflect the real needs of the community [38-42]. It enables the inclusion in the research process of the traditionally excluded voices of people in the most vulnerable situations [42-44], thereby fostering their empowerment and presenting them with the opportunity to exert an influence on the care and services that concern them [40,45]. Such involvement also helps align health and social services research with the needs expressed by the community [39,40]. Community-based research enables the development of initiatives that improve the quality-of-care delivery and diversify the range of services offered to better meet community needs [42,45,46]. This protocol has been developed in accordance with qualitative study guidelines and the ObsQual checklist for qualitative protocols [47].

Study Population and Sampling

Three different groups of participants will be involved. Group 1 (n=15-20) will consist of health care professionals and community workers, recruited through convenience sampling in connection with their work at the outreach clinic and partner organizations. Group 2 (n=10) will consist of people who are socially excluded and whose profiles correspond to those of the outreach clinic's users (eg, people experiencing homelessness and living with OUD who would otherwise be in an addiction treatment program in Longueuil). These participants will also be recruited through convenience sampling, with the help of the Direction de la santé publique of the Montérégie region and partner community organizations. Group 3 (n=4) will consist of members of the peer researcher committee, who have current or past lived experience of OUD and homelessness or other marginalized conditions. They will be recruited directly by the research team.

Participant Selection Criteria

The inclusion criteria for health care professionals and community workers are as follows: participants must be adults, able to provide consent, and able to speak either English or French. In addition, they must be working in services or within a community organization that serves people who use the outreach clinic.

The inclusion criteria for photovoice participants and members of the peer researcher committee are as follows: participants must be adults, able to provide consent, and able to speak either English or French. They must also meet the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* criteria for OUD (current or past). Furthermore, their profile should correspond to that of the outreach clinic's target population for OUD.

There are no exclusion criteria.

Data Collection

This study comprises three phases: (1) exploration with partners and creation of a committee of peer researchers with current or past lived experience of OUD, (2) photovoice with people who are socially excluded and living with OUD, and (3) participatory evaluation of the clinic.

Phase 1: Exploration With Partners and Creation of the Peer Researcher Committee

Phase 1 involves 2 preliminary meetings with the collaborators involved in setting up the outreach clinic. These preparatory meetings are not part of the project but will be used to determine research methods, analyses, and the knowledge transfer strategy. The committee of peer researchers with current or past lived experience of OUD (n=4) was formed to reflect the timeline under the leadership of 2 citizen partners (peer researchers: n=4) and will meet approximately once a month for 2 hours to discuss various topics and carry out project-related tasks.. The planned schedule of meeting topics is detailed in Multimedia Appendix 1. The peer researcher committee is limited to 4 members to ensure active, meaningful, and safe participation by all members and to reflect the team's capacity to accomplish this objective throughout the study.

Phase 2: Photovoice With People Who Are Socially Excluded and Living With OUD

The photovoice process aims to explore how the services implemented when the clinic first opened meet the needs of the population served and to adapt these services to the needs expressed by the population. Photovoice is a visual participatory research method that has been used in a number of health research projects. One advantage of this method is that it encourages introspection, the acquisition of knowledge, and the promotion of critical dialogue. The research question, which will be refined with those involved, is as follows: how do the

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services provided by the clinic meet the needs of the people it serves? For photovoice participants, this question will be phrased in the first person (eg, How do the services I receive at this clinic meet my needs?).

Using voluntary convenience sampling, we will recruit 10 people who could benefit from the clinic's services to participate in 5 sessions, as detailed in Textbox 1.

Textbox 1. Photovoice sessions.

Session 1

A preparatory meeting for the photo-taking activity (statement of research question, ethical considerations, and reflections on poverty)

Sessions 2 and 3

Discussions on the presentation of 5 photos each, responding to the research question (2 h each), which will be recorded and cofacilitated by an experienced researcher (C Loignon) and a family physician (AAP-P)

Session 4

A meeting to validate the data analysis resulting from the discussions, as summarized by the researchers and reviewed by the participants (1 h)

Session 5

A meeting to present the results (1 h)

The target number of participants is 10, as the research team believes that this will provide data representative of the people benefiting from the services offered by the clinic, which is expected to eventually serve 100 to 200 people. A peer researcher will be present at the preparatory photo-taking meeting to help participants with their questions and photo-taking needs. Participants are expected to use their smartphones to take photos, but the research team will lend a digital camera to participants who are unable to use a personal device. Over a 4-week period between the first and second meetings, participants may take as many photos as they wish; however, they will select 5 photos to present at the discussion sessions. If they wish, they can be accompanied by a member of the research team during the photo-taking process. The research team's observations during the photovoice sessions, the data collected in the logbook, and participants' spontaneous discussions with the peer researchers will help address the secondary research objective: identifying the factors favoring the participation in a research project of people who are socially excluded and have current or past lived experience of OUD.

Phase 3: Participatory Evaluation of the Outreach Clinic's Low-Threshold Treatment Program

A participatory evaluation of the clinic's low-threshold treatment program will be conducted from the start of the project. The evaluation will use multiple qualitative methods, including field observations and individual semistructured interviews (n=15-20) with health care professionals and community workers, supported by a research logbook of observations of clinic activities and informal interviews with field actors. The sample size for the targeted semistructured interviews is 15 to 20 participants or until data redundancy is achieved [48]. In addition, the research team will conduct meetings with the peer researcher committee on various topics; for example, the committee will validate the interview guide with health care professionals and community workers, provide feedback on the analysis of the interviews, and offer input on the results of the photovoice sessions. Members of the peer researcher committee will also conduct observations over the course of the project. During these sessions, they will observe the facilities, the services offered, the atmosphere in the clinic for both users and professionals, and any other relevant aspects. No confidential information will be collected. The peer researcher committee will analyze these observations and then make recommendations for improvements to the clinic. Finally, based on the results obtained across all phases of the project, the committee will choose a method to disseminate the results it deems relevant and organize the dissemination activity. The interview guide for professionals is provided in Multimedia Appendix 2.

Data Analysis and Interpretation

A thematic analysis will be conducted iteratively, following the approach formulated by Braun and Clarke [49], to enhance rigor and credibility. Trustworthiness [50] (confirmability, dependability, credibility, and transferability) will be ensured through an audit trail (study logbook), validation of our interpretations with peer researchers, and multidisciplinary peer debriefing sessions to address the researchers' personal reflexivity and methodological limitations [49,51].

The data will be organized through coding, which will consist of labeling the various elements addressed in the interviews or photovoice discussions. These interviews and discussions will be recorded. Data analysis will be iterative: each interview or discussion (individual or group) will be coded as soon as verbatim transcription is completed, and the data will then be integrated into the research team's coding tables. NVivo software (Lumivero) will be used to facilitate the data analysis. The validity of the analyses and interpretations will be ensured through triangulation at all stages of the research. Triangulation will also apply to the formulation of hypotheses and the development of conclusions. The findings from interviews and discussions will be triangulated with data from observations, the research team's logbook, and informal interviews with key actors. To this end, members of the research team, including a peer researcher (C Loignon, AAP-P, and LF), will meet regularly to participate in interpretations and facilitate the analysis of multiple data sources. The peer researcher committee will validate the data interpretations at meetings, where summary tables of the data will be presented. All data collection and analysis procedures will be described in the research reports, enabling a rigorous methodological evaluation.

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Ethical Considerations

Ethics Approval

The research protocol was approved by the ethics committee of the Centre intégré en santé et services sociaux de la Montérégie-Centre–Hôpital Charles-LeMoyne (project number: MP-04-2022-698).

Informed Consent

A consent form for the research project was created, setting out all risks and benefits of participation. Potential participants will have time to review the form before providing consent and may withdraw from the project at any stage.

Privacy and Confidentiality

The interviews and the content of the photovoice discussions will be depersonalized using digital codes for each participant. No recordings will be disseminated outside of the research team. Information that could lead to the identification of participants will be removed during the transcription of the interviews and discussions (individual or group).

Compensation Details

To acknowledge the expertise of individuals with lived experience of OUD, homelessness, or other marginalized conditions, participants in the peer researcher committee and the photovoice project will be compensated for their time. Members of the peer researcher committee will receive CAD $40 (US $29.08) in the form of a grocery store gift card and CAD $60 (US $43.62) in cash for each 2-hour meeting, along with a meal and drinks. Photovoice participants will receive CAD $20 (US $14.54) in cash at each meeting, along with snacks and drinks.

Results

Phase 1

Two preliminary meetings were held with a dozen collaborators. Representatives from 3 different community organizations working with people experiencing OUD, homelessness, or other marginalized conditions attended, along with 5 health care professionals who offer OAT services. The committee of peer researchers was formed in winter 2024, and the 10 meetings were held until June 2025.

Phase 2

As of August 2025, 4 sessions had been completed with 12 individuals who are socially excluded and whose profiles correspond to those of the outreach clinic's users. Preliminary results were presented at the 2023 North American Primary Care Research Group conference as part of a doctoral student project. In addition, a presentation on the initial impressions of using photovoice as an innovative research method to engage individuals who are socially excluded and use opioids was delivered at the 2024 International Society for the Study of Drug Policy conference. Analysis was completed in the spring of 2025.

Phase 3

As of August 2025, 14 health care professionals and community workers had participated in the semistructured interviews. In addition, members of the peer researcher committee conducted 2 observation sessions at the outreach clinic in Longueuil. Preliminary results from the interviews were presented at the 2024 North American Primary Care Research Group conference as part of a medical resident project. Publication of the results of this phase, along with final and integrated results of phases 1 and 2, is expected in winter 2026.

Table 1 outlines the progression of the study.

Table 1. Study timeline.

Study phase	Time frame
Preparatory phase (preparatory meetings and interview guide)	Fall 2022
Phase 1: peer researcher committee	Fall 2023 through winter 2025
Phase 2: photovoice	Fall 2022 and fall 2023; analysis: winter 2025
Phase 3: interviews with professionals	Fall 2023 through winter 2025
Knowledge transfer phase	Spring 2024 through winter 2026

Discussion

A Service Adapted to User Needs

This project aims to evaluate the participatory implementation of an outreach clinic for OUD, with services adapted to the needs of its users. This innovative service offering will be coconstructed by involving people who are socially excluded and living with OUD (experiencing homelessness, with severe mental health disorders or in other vulnerable circumstances causing them difficulty in accessing basic addiction-related services), together with primary care or addiction care providers. The implementation of the primary care clinic with integrated OUD treatments that address overall health needs (eg, access to mental and physical health services, housing search assistance, and adapted employment integration) will be analyzed, and the service offering will be adapted to the needs of people living with OUD in the most marginalized conditions. This project will lay the foundation for a rigorous participatory evaluation process of this innovative intervention, following the example of another clinic in Montreal [52].

Strategies to Ensure Rigorous Qualitative Research

The participatory approach presents specific challenges. Unequal power between the people involved in the study can lead to

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power and influence dynamics, often unconsciously [42], which can contribute to tensions and conflicts and undermine the participatory and collaborative nature of the approach [42,43,45]. Our research team will set up a committee made up exclusively of peers with current or past lived experience of OUD and will provide ongoing support to encourage their active participation in the project and the exploration of power-related topics [39,40,43]. Most of the partners in this project already have an established relationship of trust with the research team. We will also take the time to clarify the role and responsibility of each partner involved from the beginning of the research process [42] and then continually revalidate them with feedback and readjust them as necessary [42,45]. A logbook maintained by the research team will enable this process to be monitored.

The proposed research meets the rigorous criteria of qualitative research in a number of ways. First, with regard to the credibility and accuracy of the results, 3 coresearchers are involved in the clinic's addiction treatment program, which enables the results to be enriched with nuances and extensive observations. After each interview, a debriefing between the research assistant performing the transcription and one of the coresearchers is scheduled to improve the process and enable verification of the interview report. In addition, after the initial analysis, a meeting is scheduled with the interview participants to verify the results of each interview and ensure the credibility of the interpretations. Second, to ensure the transferability of the results, the study team includes several coresearchers with clinical backgrounds. Their in-depth knowledge of the setting will enable a rich and detailed description of the research site. Although theoretical saturation may not be fully achieved, data redundancy is expected with the planned sample. Finally, the reliability of the results will be ensured by the careful application of procedures at each stage: during the interviews, using an interview guide and interview report; during transcription, performed by an experienced research assistant; and during analysis, with coding conducted by multiple research team members to enhance the neutrality of the interpretations.

Conclusions

The results will provide decision-makers with coherent, evidence-based data for users and the community regarding the quality of care and services as well as their relevance and efficiency (improving value for money) and their ability to improve the health of the local population living with OUD and in precarious situations (improving population health). Thus, the process leading to the development of an outreach clinic for OUD outside major Canadian urban centers, as well as its subsequent evaluation and adaptation, will help improve health equity for all. The advantages of this project are that the intervention is coconstructed and monitored and that the evaluation process is initiated simultaneously. This project will provide useful data on the implementation of an addiction treatment program for people who are socially excluded in a semiurban context. Such data are essential for decision-makers because this population is the most difficult to reach in addiction treatment programs and has the least access to regular services due to multiple barriers [25,26]. This project could therefore help demonstrate to decision-makers the importance of developing such services in an appropriate way, particularly in the context of the dual crises of the COVID-19 pandemic and opioid overdoses.

In this project, the knowledge transfer strategy is based on the application of integrated knowledge. This approach is inherent to participatory research and enhances the potential for direct and immediate benefits for the organizations and partners involved. The community organizations, clinicians, and health care administrators involved will be able to apply the results in their respective environments. All team members will participate in disseminating the results. Peer researchers and people from community organizations will be called upon to present the results in dissemination activities.

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Authors' Contributions

All authors contributed to the conception of the study. AAP-P, CL, LF, IW, BDAN, CP-T, C Langlois, and SP collected the data, as per submission of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Schedule of topics for peer-researcher committee.
[DOCX File , 14 KB - resprot_v14i1e72457_app1.docx]

Multimedia Appendix 2
Interview guide for professionals.
[DOCX File , 23 KB - resprot_v14i1e72457_app2.docx]

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Multimedia Appendix 3
Peer review reports from the Catalyst Grant: Quadruple Aim and Equity Committee, Canadian Institutes of Health Research (CIHR).
[PDF File (Adobe PDF File), 45 KB - resprot_v14i1e72457_app3.pdf]

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Abbreviations

OAT: opioid agonist therapy
OUD: opioid use disorder

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Proposal

Developing Recommendations to Improve Crisis Line Supports for Public Safety Personnel in Canada: Protocol for a Multimethod National Study

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Abstract

Background: Public Safety Personnel (PSP) in Canada experience disproportionately high rates of mental distress and suicidal thoughts and behaviors. PSP mental health is a critical public health issue with far-reaching implications for both individual well-being and the effectiveness of emergency response systems. Crisis lines are an evidence-based public health intervention; however, knowledge gaps remain regarding PSP crisis line use, barriers to accessing services, and the appropriateness of crisis line service models for meeting PSP mental health needs.

Objective: This study aims to address these knowledge gaps using a participatory approach to better understand the crisis line needs and preferences of PSP communities. We also aim to apply our learnings and co-design actionable recommendations for crisis line service improvements and to support PSP who may wish to contact a crisis line.

Methods: This Canada-wide study uses multiple methods across three iterative phases. Phase 1 involves community engagement with PSP to better understand their crisis needs and existing supports. Instrumental to our engagement ethic is the formation of a co-researcher group, composed of PSP with lived experience, who will guide the research process. We will review deidentified crisis line interactions to identify patterns in service use and call outcomes to identify possible points of intervention to enhance

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service efficacy. We will launch a national web-based anonymous survey to understand the crisis line needs, barriers, and preferences of PSP. Phase 2 focuses on deepening our understanding of PSP experiences with crisis lines through in-depth interviews with those who have accessed or thought about accessing crisis lines and those without crisis line experience who wish to share their views. We will conduct focus groups with crisis sector staff to learn about desired training and resources for improving service delivery to PSP. Phase 3 focuses on developing and conducting co-design workshops to generate evidence-based recommendations with PSP, crisis line responders, researchers, and clinicians. Collaborating across sectors will allow us to codevelop feasible strategies for improving crisis line services to better meet the needs of PSP in crisis who may be inclined to access crisis lines for support.

Results: As of December 2024, the crisis line dataset has been identified and study recruitment for the national survey was completed. Data collection for all other research activities is expected to conclude by May 2025. We anticipate that study findings will be available by the end of 2025.

Conclusions: By identifying barriers to crisis line use and codeveloping solutions, this research will inform policy, service design, and training to enhance services. Ensuring PSP can access crisis line supports that are equitable, evidence-based, and integrated within mental health care systems is crucial to fostering a resilient public safety workforce and emergency response capacities at a societal level.

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KEYWORDS

public safety personnel; crisis lines; suicide prevention; participatory; co-design

Introduction

Background

Urgent attention has been called to the mental health and suicide prevention needs of public safety personnel (PSP; eg, law enforcement, paramedics, and search and rescue) [1] as a critical public health priority. PSP routinely face occupational exposures to potentially traumatic events (PTE) [2-4], operational and organizational stressors [5-8], higher rates of mental health symptoms and disorders [9-12], and higher rates of suicidal thoughts and behaviors than are observed in the general population [13-17].

Much work has been done to develop and evaluate interventions to reduce the mental health impacts of public safety work [18] and mitigate potentially traumatic stress injuries [19] for PSP, with some interventions demonstrating potential benefit. For example, evidence-based psychotherapy (eg, narrative therapy and cognitive behavioral therapy) and resilience training have been associated with reductions in mental health symptoms in PSP [20-24]. Crisis-focused interventions such as critical incident stress management and critical incident stress debriefings [25,26] yield mixed evidence supporting their effectiveness in reducing mental health symptoms. Suicide prevention interventions, however, have rarely been studied among PSP [21,27].

We are aware of three studies (conducted in Canada, South Africa, and the United States) that have sought to evaluate suicide prevention programs for PSP [28-30]. These programs combined multiple intervention components (eg, awareness training, peer support, and critical incident stress management) and included crisis line support services. Of the 3 suicide prevention programs for PSP, 1 study reported longitudinal evidence suggesting a suicide prevention program that included a crisis line for Montreal police was associated with reduced suicide rates over time [28,31]. The contributions of specific program components to reduced suicide rates remain unclear. Peer support programs tailored to police have also been described in the literature, including a helpline for police to access in-person peer support services [32], and a New Jersey-based COP2COP hotline with composite narratives illustrating service user experiences [33].

Given the essential role PSP play in maintaining public safety and emergency response, their mental well-being is a workforce and public health concern, with implications for service continuity, response effectiveness, and broader community health outcomes. Further work is needed to identify and develop appropriate crisis and suicide prevention supports for PSP. There is little research exploring the experiences, needs, or preferences of PSP who are experiencing a mental health or suicide-related crisis. For example, a recent review of qualitative research on first responder well-being found that organizational factors contributed to a decline in well-being rather than exposures to specific events [8]. This suggests there is a knowledge gap about how mental health challenges in PSP arise and develop over time. This knowledge gap is amplified when we consider the numerous barriers to care PSP may face when accessing mental health services, including stigma [24,34-36], mental health literacy, confidentiality concerns, and unsupportive work cultures [37]—factors that may also increase the acuity of a crisis. In summary, there is a dearth of research exploring what PSP need in times of crisis and what supports are most appropriate for PSP experiencing suicidal thoughts and behaviors and mental health crises.

Crisis Lines and the Launch of 9-8-8: Suicide Crisis Helpline

The primary aim of this study is to identify and address gaps in understanding the experiences of PSP in Canada in crisis and to collaboratively improve available crisis line supports. The launch of Canada's 9-8-8: Suicide Crisis Helpline on November

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30, 2023, represents a significant policy advancement aimed at improving crisis line service availability nationwide [38].

Crisis lines are a key component of Canada's National Suicide Prevention Action Plan [39,40] and a cornerstone of public health suicide prevention efforts, providing an accessible, scalable, and evidence-based intervention to mitigate mental health crises. They are a readily available intervention with growing evidence supporting their effectiveness at reducing short-term mental distress and suicidal urgency [41-43]. While crisis lines offer an alternative to workplace-based mental health resources, there remains a gap in understanding their accessibility and effectiveness for PSP. Given the structural and attitudinal barriers that PSP may face when seeking mental health support, including stigma, confidentiality concerns, and organizational culture, there is an urgent need to assess whether crisis services meet the acute mental health needs of this population and to ensure that they align with broader public health strategies for suicide prevention.

We aim to generate evidence that informs public health and policy-driven improvements to crisis line services for PSP in Canada. Specifically, we aim to explore the following research questions:

1. What are the needs, experiences, and preferences of PSP related to crisis line services?
2. What are the experiences of crisis line responders when providing services to PSP, and what training and resource supports might improve service provision?
3. What fit-for-purpose tools, strategies, and recommendations can be developed to improve services to provide better support for PSP?

Through a collaborative knowledge translation process, we aim to develop tools, strategies, and policy-relevant solutions to optimize crisis line service delivery for PSP, ensuring that services are accessible, effective, acceptable, and integrated within the broader public health and emergency response system.

Study Design

To explore the crisis line needs of PSP, we designed a participatory [44], multimethod study. Figure 1 provides an overview of the study design, including research questions, iterative phases, and methods used.

Figure 1. The components of the proposed project. PSP: public safety personnel.

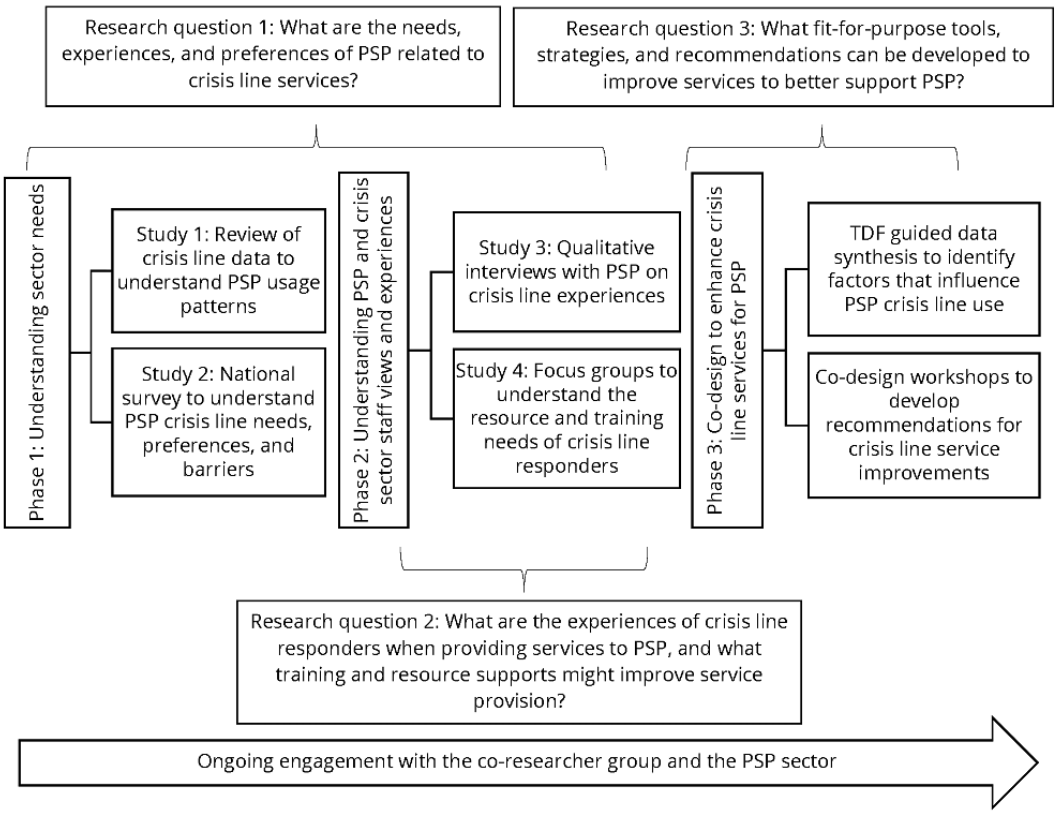

Population of Interest

For this study, PSP refers to those who are in professions entrusted with ensuring the safety and security of people in Canada (ie, municipal and provincial police, Royal Canadian Mounted Police, firefighters, paramedics, correctional employees, border services personnel, operational and intelligence personnel, search and rescue personnel, Indigenous emergency managers, and dispatch personnel) [1]. For all research and engagement activities, we include adults (18 years or older) who are current, former, retired, or trainee PSP.

Participatory Approach

To ensure that our research process is informed by those most affected by our work and leads to meaningful service improvements [45], we are working with a co-researcher group composed of PSP with lived experience with mental illness, suicidal thoughts and behaviors, suicide bereavement, and peer crisis support. Our work is guided by a participatory approach

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aligned with the public health principles of equity, community engagement, and lived experience leadership, which have been shown to improve the relevance, effectiveness, and implementation of mental health interventions [46,47]. Co-researchers were recruited at the outset of this project by circulating an invitation to collaborate through PSP networks. Specifically, we asked researchers working in the PSP mental health space and PSP mental health organizations to share our invite with their networks. We successfully identified and recruited 5 co-researchers through this approach. An additional co-researcher was recruited through snowball sampling, and the final member was purposively recruited from the crisis sector. In total, 7 co-researchers were onboarded to the team, representing various public safety sectors (law enforcement, fire services, paramedicine, corrections, and the crisis sector) and regions in Canada.

The co-researcher group is an instrumental component of this work, as they provide guidance and feedback on the goals and conduct of the study. Co-researchers collaborate on study design and data collection tools (eg, survey and interview questions), recruitment strategies (eg, text, images, channels), and data interpretation, ensuring that the research reflects the realities of PSP in crisis. Co-researchers are actively involved in interviewing participants, cofacilitating workshops, and developing knowledge translation outputs, including publications and conference presentations. Their contributions strengthen the study's ability to generate actionable insights that inform policy, crisis service delivery, and public health strategies for suicide prevention. Regular co-researcher meetings will continue throughout the project to promote collaboration, accountability, and lived-experience leadership [48].

Beyond our co-researcher group, we will also engage directly with national, provincial, and municipal PSP organizations (eg, employers, unions, professional associations, and PSP mental health associations) as part of a systems approach to crisis intervention. PSP organizations will be identified through web searches and snowball sampling methods. Outreach meetings and activities will focus on building relationships in the sector, identifying available mental health programs and crisis services for PSP, system-level strengths, gaps, and priorities, refining recruitment strategies, and enhancing knowledge exchange. Outreach activities also support effective knowledge mobilization, allowing findings to be translated into policy and practice improvements at multiple levels of the crisis response system [49].

Overarching Analytic Framework

This work is guided throughout by the Theoretical Domains Framework (TDF) [50-52]. The TDF synthesizes constructs from 33 theories into 14 domains known to influence behavior: knowledge; skills; social or professional role and identity; beliefs about capabilities; optimism; beliefs about consequences; reinforcement; intentions; goals; memory, attention, and decision processes; environmental context and resources; social influences; emotion; and behavioral regulation. The TDF has been widely used in a health care context to surface barriers and enablers to behavior change [53,54]. The TDF will guide the synthesis of lessons across study phases to facilitate the redesign of crisis interventions by providing a framework with which to identify targets for behavior change. We aim to develop theory-driven strategies that address the identified factors to support behavior change. The strategies will be refined in collaboration with various stakeholders to coproduce recommendations in pursuit of making crisis line services more accessible, appropriate, effective, safe, and equitable for PSP.

Methods

Phase 1: Understanding System and Community Needs

Study 1: Review of Crisis Line Data to Understand PSP Usage Patterns

To begin exploring questions about the needs, preferences, and experiences of PSP with crisis lines, we first seek to understand PSP crisis line usage patterns, including reasons for contact and interaction outcomes. To this end, we are conducting a retrospective review of existing crisis line data. By reviewing existing crisis line interaction transcripts, we aim to explore and understand the stated reasons that PSP provide for contacting a crisis line, the psychosocial context contributing to their distress in that moment, what they hope to achieve by contacting a crisis line, the narrative of their mental health experience discussed during interactions, the nature of the interventions provided during the interaction (eg, safety planning and resource provision), and the outcomes of interactions (eg, connecting to external resources, follow-up calls, and engaging emergency services).

Setting and Background

Talk Suicide Canada was a national suicide prevention crisis line service that provided crisis support to callers and texters. As of November 30, 2023, Talk Suicide Canada was expanded and recreated to become 9-8-8: Suicide Crisis Helpline. Our research team began working in partnership with Talk Suicide Canada to conduct a review of deidentified crisis line call and text interactions that were recorded by Talk Suicide Canada. Per service terms and conditions at the time, it was possible to share deidentified Talk Suicide data with researchers with research ethics approval. The terms of service governing data use came into effect in September 2018. As of November 30, 2023, they were replaced with 9-8-8's terms of service.

Data Characteristics

During crisis line interactions with Talk Suicide Canada, crisis line responders used a client record management system to document text and phone crisis line interaction information. Data that were routinely collected included the date and time of contact, communication modality, length of interaction, phone number, age, gender, province, suicide risk assessment outcomes, reasons for reaching out, responder notes detailing actions taken, and transcripts of interactions. Between May 2022 and April 2023, crisis line responders also had the option of indicating whether interactions were from PSP within the client record management system by selecting "yes," "no," or "N/A" to the question "Is the service user a First Responder or Public Safety Personnel?" Based on data retention policies, data for text interactions were available dating back to December

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2018, and data for call interactions were available dating back to May 2022.

Search Strategy

To identify eligible text interactions between December 2018 and May 2022, Talk Suicide staff were trained to search for applicable text interactions using a set of words related to PSP professions (refer to Multimedia Appendix 1). Applicable call and text interactions occurring between May 2022 and April 2023 were identified based on crisis line responder responses to the question "Is the service user a first responder?" that was embedded in the client record management system. Records identified through these means were reviewed by Talk Suicide staff who were trained to apply the inclusion and exclusion criteria outlined in Textbox 1 to crisis line records.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Text interactions were recorded by Talk Suicide Canada in English between December 2018 and April 2023.
- Phone interactions were recorded by Talk Suicide Canada in English between May 2022 and April 2023.
- The texter or caller self-identified as current, former, retired, or a trainee of the public safety personnel (PSP) workforce.

Exclusion criteria

- The caller or texter was younger than 18 years.
- Interactions were not initiated by PSP.
- Interactions were initiated by PSP on behalf of someone else (third-party calls).

Interaction data that met eligibility criteria were deidentified by Talk Suicide staff by removing personal identifiers and unique details (eg, phone numbers, names, locations, and details that may become identifying through internet searches). Deidentified transcripts and data were then shared with the research team for analysis via secure file transfer.

Planned Analyses

Quantitative crisis line data will be analyzed descriptively to generate frequencies, means, and proportions of demographic data (eg, gender, age, and province) and suicidal behaviors and to examine the distribution of suicidal behaviors across PSP groups. Chi-square tests will be run to determine whether there are differences in the rates of suicidal behaviors (ie, current thoughts, past attempts, and current plans) across demographic variables (ie, gender, age, and province), and modality (ie, text or phone) and across PSP groups.

To qualitatively understand the interaction patterns of PSP who contacted the Talk Suicide crisis line, a team of analysts will conduct an inductive content analysis [55] to describe and characterize PSP experiences based on antecedents, behaviors, and experiences during the interaction, and outcomes. Data analysis will be conducted in 6 stages. In stage 1, analysts will read transcripts fully to familiarize themselves with the data. This will be followed by stage 2, an open coding process where descriptive labels will be attached to phrases. Stages 3 and 4 involve reviewing codes for their content (stage 3) and grouping them according to shared characteristics (stage 4). During stage 5, the team of analysts will generate broad categories that describe the interaction process. The research team will meet regularly to discuss different approaches to coding data and to iteratively develop a codebook that outlines the codes and categories generated during stages 3-5. The codebook will both document the analytic process and, once finalized, will represent a shared understanding of the major codes and categories that capture the data [56]. Stage 6 will involve synthesizing and abstracting information from codes and categories to represent the crisis line experience for PSP captured in this sample [57]. The results of this analysis will allow us to describe and characterize how crisis line interactions have unfolded when PSP contacted Talk Suicide Canada. We aim to generate insights on areas for possible service improvements and future research directions based on our findings.

Study 2: National Survey to Understand PSP Crisis Line Needs, Preferences, and Barriers

Overview

To better understand the needs, preferences, and experiences of a broader sample of PSP, we will conduct a national web-based survey. Crisis lines are an existing suicide prevention and mental health resource that is readily available to all PSP in Canada. However, there may be many reasons why PSP may or may not choose to contact a crisis line during a time of need. We aim to identify what aspects of a crisis line service are most important and meaningful to PSP and to identify barriers and enablers to PSP accessing crisis lines when needed. Using the TDF to identify modifiable factors associated with crisis line use will facilitate the identification of theory-driven strategies [58] to address barriers and enablers to crisis line use. Therefore, we aim to answer the research question: What are the behavioral determinants (TDF domains) of intent to use crisis lines? Based on our understanding of the research literature, we hypothesized (1) social influence, beliefs about consequences, knowledge, and environmental resources and context will be the strongest TDF predictors of whether survey respondents intend to use crisis lines; (2) gender will be associated with intent to use crisis lines, such that men will be less likely to intend to use crisis lines than women or other genders; (3) professions that experience more stigma will be less likely to intend to use crisis lines; and (4) other demographic variables will not be associated with intent to use crisis lines.

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Survey Development

To identify barriers and enablers to PSP accessing crisis lines, we developed survey questions based on the TDF [59,60]. The TDF domains represent theoretically modifiable factors that influence behavior. Identifying which TDF domains predict behavior, in this case, intent to use crisis lines, can suggest avenues for behavior change interventions. Some TDF domains are more influential than others, depending on the context and behavior in question. Based on outreach meetings with public safety personnel, we know that concerns over engaging emergency services are a major deterrent to accessing crisis line services. Based on existing research, we know that stigma, confidentiality concerns (including concerns that colleagues will find out), not knowing where to get help, and schedule conflicts are common barriers to accessing mental health supports [24,34,35,61].

Therefore, we developed a survey to assess barriers and enablers that correspond to 11 of the 12 original domains (knowledge, skills, beliefs about capabilities, beliefs about consequences, social or professional role and identity, social influences, emotion, memory, attention and decision-making, environmental context and resources, motivation and goals, and intention), as they were the most relevant to this study. The TDF-based questions were designed to reflect the barriers and enablers that have been identified both anecdotally and in the research literature. We also crafted questions about preferences (eg, anonymous, recorded, call answered by peer supporter, and preferred modalities) based on what we learned through outreach meetings with PSP.

To ensure we obtained a comprehensive understanding of the survey sample, we included demographic questions (eg, gender, age, race and ethnicity, and province of residence), work history questions (eg, role, tenure, and status), items exploring past experiences with suicidal thoughts and behaviors, and questions regarding past access to various mental health care services (refer to Multimedia Appendix 2 for the full survey). To ensure items were relevant and understood by PSP and that the length was acceptable, we piloted and tested the survey with co-researchers and research staff before launching.

Inclusion and Exclusion Criteria

The national survey was open to all current, former, and trainee members of the Canadian PSP workforce. The survey was available in French and English.

Recruitment

The survey was launched in April 2023. To recruit PSP survey participants across Canada, we worked with PSP-serving organizations identified through outreach efforts to disseminate recruitment materials digitally and in person. A variety of tools and strategies were used, including sharing print materials at events and advertising through social media.

Sample Size

Our goal was to collect a sufficient number of survey responses to run regression analyses with up to 35 independent variables (ie, TDF domains, demographic variables, and preferences). A minimum required sample size of 277 survey respondents was calculated using the G*power sample size calculation software (version 3.1.9.7; Heinrich-Heine-Universität Düsseldorf), assuming a .05 error probability, .95 power, medium effect size (f^2=0.15), and 35 degrees of freedom [62]. Based on previous research with PSP samples [9], we expect that approximately 70% of those who begin the survey will complete all sections. Based on this estimated attrition rate, a minimum sample size of 500 survey respondents would yield approximately 350 fully completed surveys, which would allow us to run our planned regression analyses. This estimate aligns with other guidance available for calculating sample size for regression analyses [63,64].

Analyses

We will conduct a series of simple linear regression analyses to determine which TDF variables are the strongest predictors of intent to access a crisis line during a time of need. The dependent variable will be based on participants' responses to a single Likert-scale item: "I would contact a crisis line during a time of need." Independent variables will include items reflecting the TDF domains (eg, items relating to skills, knowledge, and beliefs about consequences) [59,60]. Simple linear regression will be used to examine the relationship between TDF variables and intent to use crisis lines. Demographic variables will be entered into regression models to control for any potential effects on associations.

This work will allow us to identify possible targets for theoretically derived behaviors and changed strategies.

Phase 2: Understanding the Views, Experiences, and Practices of PSP and Crisis Sector Staff

Study 3: Qualitative Interviews With PSP to Understand Crisis Line Experiences

We seek to conduct in-depth qualitative interviews with PSP who have used or considered using crisis lines to better understand what these experiences mean to PSP and what they see as crucial to change about crisis line services. Semistructured interviews are the preferred method to explore first-person narratives of sensitive topics, as they provide a confidential space for participants to articulate their experience, engage in sense-making, and offer reflections and insights on the phenomena in question [65,66]. Working from a social constructivist paradigm that seeks to understand participant experiences and meaning-making [65], interviews will explore participant thoughts, behaviors, experiences, and sense-making related to mental health crises and the accessibility and adequacy of crisis line services in those pivotal moments.

Inclusion and Exclusion Criteria

We are conducting interviews with PSP who have accessed or thought about accessing a crisis line or helpline when experiencing a mental health crisis. We will also seek to conduct semistructured interviews with PSP who may not have any experience accessing crisis lines or helplines but wish to share their views on barriers and enablers to crisis line use and ideas for service improvements.

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Interview Guide Development

A total of 3 guides have been developed to explore experiences from the following groups: (1) PSP who have contacted a crisis line, (2) those who considered but chose not to contact a crisis line, and (3) those who have not accessed or thought about accessing crisis lines but may have insights to share (refer to interview guide in Multimedia Appendices 3-5). The guides prompt participants to share the chronology, meaning, reflections, and learnings from experiences that can be applied to service improvement considerations. The interview guides have been pilot tested with PSP co-researchers and members of the research team to ensure the questions and interview process are feasible, safe, accessible, and acceptable [67].

Recruitment

Interview participants are being recruited by providing a link within the national survey where survey respondents can indicate interest in participating in further research. Additional participants will be recruited by working with PSP-oriented organizations to share posters and advertisements notifying PSP across Canada about this opportunity.

Sample Size

Given the specificity of the experiences and views we are sampling, we expect that a small to medium sample size will provide sufficient information power to derive meaningful insights about the data regarding the gaps, barriers, and mental health needs of PSP who access or may want to access crisis lines [68]. Therefore, to achieve sufficient information power, we will conduct 60-80 interviews with PSP across the three groups (accessed a crisis line, thought about accessing a crisis line, and neither accessed nor thought about).

Planned Analyses

Interview data will be analyzed using an inductive, reflexive thematic analysis [69-72]. Reflexive thematic analysis allows for the identification of patterns in the data to generate themes that capture participant experiences and sense-making, situating crisis line use in sociocultural contexts, and allows for organizing thematic statements into actionable implications for practice [72]. Analysis will involve generating initial codes, identifying relationships between codes and categories, and generating interpretive themes related to PSP crisis line use, barriers to accessing and using crisis lines, and possible avenues for improving crisis line services. To ensure rigor in the analytic process, a team of analysts will be trained in reflexive thematic analysis and will meet regularly to discuss the coding process and emerging themes. Rather than seeking consensus on coding, the goal of these meetings will be to sense-check, interrogate assumptions, and explore alternative interpretations to enrich the developing analysis [73]. As analyses progress, we will compare emerging themes and findings across the 3 groups to better understand how experiences with crisis lines shape perceptions of mental health resources and the likelihood of contacting a crisis line in the future. Reflections on possible service improvements will also be examined and compared across the 3 groups.

Study 4: Focus Groups to Understand the Resource and Training Needs of Crisis Line Responders

Overview

Online focus groups are an effective method of data collection when seeking to capture a range of ideas from geographically dispersed participants [74,75]. We will conduct online focus groups with crisis sector personnel connected to the 9-8-8 network to better understand the experiences of crisis line staff when providing services to PSP. We also aim to learn what types of support or resources crisis line responders may need to bolster their capacity for quality service provision to PSP communities.

Inclusion and Exclusion Criteria

Participants are required to be 18 years or older and have at least 2 months of experience providing crisis line services. Prior experience providing services to PSP is not required, given that this may be an uncommon experience.

Focus Group Guide Development

Focus group participants will be asked about their views and experiences in providing crisis services to PSP, whether additional training and supports tailored to PSP service users would be helpful, and their perspectives on improving services for first responders (refer to the focus group guide in Multimedia Appendix 6).

Recruitment

To better understand the views of crisis sector personnel, we aim to recruit a convenience sample of crisis line responders, trainers, and supervisors (volunteer or paid) who work within the 9-8-8 crisis line network. Crisis sector staff will be recruited through an email invitation to be sent out to the 9-8-8 mailing list.

Sample Size

We expect crisis line responders working for 9-8-8 to be a more homogenous group, requiring fewer focus groups to generate insights from diverse perspectives. As recommended in the literature, we will aim to conduct between 3 and 5 focus groups with 5-8 participants in each group to ensure sufficient data is collected for the planned analyses [74,76].

Planned Analyses

Crisis sector focus groups will be analyzed using an inductive-deductive content analysis [55,57,77,78]. The primary analysis will involve an inductive coding of content categories that describe the perspectives, attitudes, perceived barriers and enablers, sense-making of preliminary data, and ideas for service improvement that each group generates. Data will also be deductively analyzed using the TDF as a guiding framework. The coding and analytic process will be guided by the recommended phases of initialization (initial reading, coding, and abstraction), construction (labeling, classifying, and defining codes and categories), rectification (identifying relationships between codes and categories and with the existing knowledge base, stabilizing themes), and finalization (developing the storyline) to generate meaningful, descriptive themes [78]. We will use a similar approach to the inductive content analysis as

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described for the crisis line data analysis. The research team will meet to discuss coding and theme generation and will develop a codebook to document the coding and analytic process.

Phase 3: Co-Design to Enhance Crisis Line Services for PSP

Theory-Guided Data Synthesis to Identify Factors That Influence PSP Crisis Line Use

Using the TDF as a guiding framework, results from across all study activities will be analyzed and synthesized according to TDF domains to allow the identification of factors to target for the development of behavior change and implementation strategies. Domains that are consistently represented across crisis line transcripts, survey data, and interview and focus group findings will be prioritized for consideration. Exploration of possible strategies and solutions to TDF-based barriers and enablers will take place during co-design workshops that aim to bridge study findings with actionable recommendations.

Study 5: Co-Design Workshops to Develop Recommendations for Crisis Line Service Improvements

Co-design is a dynamic, collaborative, and creative approach to generating solutions to problems identified by communities of interest [47,79]. We will use the generative co-design framework [80] to guide a series of co-design workshops where we will engage project stakeholders in codeveloping recommendations for tools, supportive resources, training modules, and policy changes in support of PSP who may wish to access crisis line services and in support of crisis sector staff who deliver services.

Co-design workshop participants will be engaged in framing the issue so that it reflects a mutual understanding of lived experiences and a vision for the way forward. They will be invited to use generative techniques to surface explicit and latent needs, challenges, and experiences, and to envision alternative future possibilities to address identified issues and challenges. Following the workshops, data from the co-design activities will be analyzed, synthesized, and translated into actionable items. Results from the project will be shared back with participants, and next steps will be articulated and actioned.

Participants

We aim to hear a wide range of perspectives during our co-design workshops to ensure that recommendations are grounded in the experiences and needs of those most affected by mental health crises. To achieve this, we will invite PSP with lived experience, mental health care providers, advocates, researchers, and policy makers to ensure that possible recommendations generated reflect the diverse voices and priorities of those impacted by crisis line services and policies. The co-researcher group will play a critical role in the process, contributing to workshop development, facilitating small group discussions, and actively participating as key stakeholders. This inclusive approach is essential for fostering public health solutions that are equitable, relevant, and sustainable.

Recruitment

We will advertise co-design workshops to PSP and other contacts who were identified through initial outreach efforts. PSP outreach contacts will receive an email invitation and a request to share the invitation with other PSP in their networks. We will also share newsletters, posters, and advertisements with clinicians and researchers who are known to work with PSP (eg, researchers who are associated with the Canadian Institute for Public Safety Research and Treatment) and with the 9-8-8 network.

Sample

We aim to host 3-6 online co-design workshop sessions with 10-30 participants in each session. Hosting multiple sessions will allow us to iteratively build on the insights and recommendations shared in previous sessions. Given that the topic of discussion is highly focused on brainstorming solutions based on study results, we anticipate needing fewer sessions to arrive at a fulsome list of recommendations that reflect the views of various stakeholders [68].

Planned Analyses

Similar to focus groups, we will use an inductive-deductive content analysis, guided by the TDF, to summarize findings from co-design workshops and synthesize recommendations.

Privacy and Confidentiality

Crisis line, interview, focus group, and co-design data will be deidentified. For crisis line data, Talk Suicide staff manually redacted identifying information from transcripts and quantitative data. Deidentified files were shared with the study team using a secure file transfer system that met institutional privacy requirements. The study team assigned unique study numbers to each transcript file. Interview, focus group, and co-design data will be deidentified by transcriptionists and assigned unique study numbers by the study team. Deidentified study data will be kept separate from any identifying source data (ie, recordings and consent forms). The study team will keep a password-protected master log that links study numbers with participant information. Survey data is completely anonymous. Participants were not required to provide any identifying information (eg, name) as part of their participation.

Compensation Details

For study 1, there was no compensation as there was no direct contact with crisis line callers or texters. For study 2, survey participants were given the option of entering a draw for the chance to win 1 of 5 electronic gift cards valued at CAD $50 (approximately US $36.50). To enter the draw, participants had to provide a valid email address—this information was collected separately from survey data so that personal information remained unlinked to survey data. Once the survey was closed, the study team used a random number generator to identify winners. Participants were then contacted and provided with an e-gift card. For studies 3-5, all participants are provided with a CAD $50 (approximately US $36.50) e-gift card in appreciation of their participation.

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Ethical Considerations

This study has received ethics approval and receives ongoing ethical review from the Centre for Addiction and Mental Health Research Ethics Board (2022-058). All eligible research participants (studies 2-5) will undergo a consent process according to the research ethics board policies. For study 1, deidentified crisis line data was obtained directly from Talk Suicide Canada under the terms of service, which permitted third-party researchers to access and analyze crisis line data if the following conditions were met: (1) the data were deidentified, (2) results were reported in aggregate, (3) research ethics approval was obtained, and (4) the research contributes to improving the quality of crisis line services.

When contacting Talk Suicide Canada, each service user interaction began with a prerecorded greeting, the option to select their language of preference, and a standardized message regarding the potential collection and use of their data for quality improvement before the service user was routed to a responder. The prerecorded voice message, implemented as of August 2019, about data stated, “Your privacy is important to us. Calls may be monitored or recorded for quality control. For more information, visit our website.” Service users who accessed the text service were similarly provided with a link to the Talk Suicide Canada terms of service, which informed users of the potential collection and use of their data for quality improvement and research purposes (implemented as of December 2018).

Given the terms of use, the Centre for Addiction and Mental Health’s legal and privacy offices and the Research Ethics Board determined that additional consent was not necessary for a review of deidentified crisis line data.

Results

This research project was funded in March 2022. As of December 2024, the crisis line dataset had been identified. In total, 118 crisis line interactions (54 text messages and 64 call interactions) were eligible for inclusion in the study. Data analysis of the crisis line interactions is designed to map out what happens during interactions with PSP so we can identify possible avenues for intervention. The analysis of crisis line transcripts is expected to be completed by July 2025.

Study recruitment for the national survey was launched in April 2023 and concluded on December 31, 2024, with a total sample of 1073. Analysis of survey data has begun and is expected to be completed by July 2025. We facilitated a total of 4 focus groups with crisis sector staff in November 2024. Analysis of the focus group data will commence in March 2025 and will be completed by August 2025. Interview recruitment began in May 2024. As of March 5, 2025, a total of 38 interviews had been conducted. Data collection for all research activities (interviews and co-design workshops) is expected to conclude by June 2025. We anticipate that study findings from all data collected will be available by December 2025 and published in the winter of 2026.

Discussion

Summary

To our knowledge, this is the first Canadian study investigating the experiences of PSP with crisis line services on a national scale, addressing a critical gap in the public health literature. This multimethod study will contribute multiple perspectives drawn from community engagement, a review of deidentified crisis line data, a national survey, qualitative interviews, focus groups, and co-design workshops. By leveraging a broad range of data sources, our study will inform both local and national public health strategies to improve access to suicide prevention and crisis line services for PSP and consider whether alternative suicide prevention resources are needed.

Through our collaboration with the co-researchers and other key stakeholders, we will cocreate evidence-based recommendations that reflect the needs of PSP. This participatory, human-centered approach will ensure that our findings resonate with PSP and address their unique challenges. By involving PSP and crisis service providers in every phase of the study, we aim to produce public health interventions that are grounded in equity, accessibility, and effectiveness. The resulting knowledge will guide the development of services that meet the diverse mental health needs of PSP, contributing to system-level improvements in public health and crisis care.

In addition to its national relevance, this study aims to contribute to global suicide prevention efforts by providing an example of how community-engaged research can inform public health interventions. By showcasing a participatory approach that includes PSP as active partners in research, we hope to inspire similar efforts in other countries and settings. This research approach could also be applied across different occupational groups that face exposures to PTE and increased mental health concerns (eg, nurses and physicians) to better understand their crisis line needs and preferences. Our work will provide critical insights into how health care systems can integrate crisis line services for at-risk populations and advance the global public health agenda for suicide prevention and mental health support.

Limitations

We hope to learn about PSP crisis line needs and preferences through the outlined research. However, we anticipate there will be potential limitations to the data gathered. First, our crisis line data search strategy requires that PSP identify their profession during the crisis interaction. Not all PSP who use the crisis line will reveal their professional backgrounds. Thus, any estimates of call and text frequencies from PSP groups will likely be an underrepresentation. To address this, we have trained responders on the crisis service to more actively take note of when the caller or texter is a PSP. Second, we are focusing PSP contacts on one crisis service, albeit one with many partners and with a national reach, which has an explicit suicide prevention mandate. It may be that other, more general helplines and services, particularly those run by peer supporters, are contacted by PSP more frequently.

Third, our survey and interview data may be susceptible to response bias. Those who take the survey or elect to participate

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in an interview may overrepresent those with high mental health literacy, awareness of crisis lines, and favorable views toward mental health, help-seeking, and crisis lines. To address this limitation, we will make it explicit during our outreach and engagement efforts that we aim to hear from a diversity of PSP and encourage hearing opposing views and experiences, including those with potentially negative views of mental health and crisis lines. This consideration will also be directly addressed during co-design workshops by acknowledging that the data must be understood with this caveat in mind. Co-design participants will be invited to consider and brainstorm alternative approaches to addressing the crisis and suicide prevention needs of PSP, given that crisis lines may not be used as frequently as other mental health resources. By taking these measures as we conduct our work, we aim to begin building an evidence base from which we can make informed decisions about whether crisis lines are an appropriate resource for PSP communities, whether they need adaptations for these groups, or whether PSP needs are best met through other means. We are confident that even within these constraints, we will gain useful data in an underexplored area.

Conclusion

PSP play a vital role in maintaining community well-being, yet they face disproportionate mental health risks due to occupational stressors and exposures to potentially traumatic events. Despite the critical need for accessible and effective crisis supports, little is known about how PSP engage with crisis line services, what barriers they face, and how these services can be optimized to meet their needs. This study will generate essential evidence to bridge these gaps, using a participatory, multimethod approach that centers the voices of PSP, crisis line responders, and key stakeholders.

By leveraging community engagement, co-design methodologies, and a robust public health lens, this research will produce actionable, evidence-based recommendations to enhance crisis line services and suicide prevention supports for PSP. Our findings will inform not only service improvements but also broader suicide prevention strategies, ensuring that crisis interventions are accessible, equitable, and responsive to those who need them most. Moreover, by embedding knowledge translation into the research process, we aim to drive real-world change, strengthening crisis response systems, informing policy, and advancing public health efforts to reduce suicide and mental health crises among PSP and supporting the mental well-being of those who serve and protect our communities.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

A Crawford led the conceptualization of the study, with equal contributions from CC and supporting contributions from NA, RNC, JH, SH, FH, BM, ES, DRS, MS, KV, and JZ. Data curation was led by FA, with support from TR and AD. Formal analysis was led by A Crawford, with supporting roles from CC, GC, TR, FA, and AD. Funding acquisition was co-led by A Crawford and CC. GC led the investigation, with support from TR, FA, AD, MC, A Crawford, and DD. Methodology was developed by A Crawford (lead) and CC (equal), with support from GC, TR, FA, MC, A Crewdson, DD, MG, CH, CT, and YW. Project administration was led by GC, with support from A Crawford, CC, SA, TR, FA, and AD. SA contributed resources. Supervision was led by A Crawford, with support from CC, SA, and GC. Validation was led by TR, with support from FA. GC led the visualization effort, supported by TR, FA, and A Crawford. GC led the writing of the original draft, with support from A Crawford and CC. GC also led the review and editing process, with supporting contributions from A Crawford, CC, TR, FA, SA, AD, NA, RNC, MC, A Crewdson, DD, MG, JH, CH, SH, FH, BM, ES, DRS, MS, CT, KV, YW, and JZ.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Talk suicide search terms.
[DOCX File , 13 KB - resprot_v14i1e75285_app1.docx]

Multimedia Appendix 2
National online survey.
[DOCX File , 603 KB - resprot_v14i1e75285_app2.docx]

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Multimedia Appendix 3
Interview guide 1.
[DOCX File , 27 KB - resprot_v14i1e75285_app3.docx]

Multimedia Appendix 4
Interview guide 2.
[DOCX File , 160 KB - resprot_v14i1e75285_app4.docx]

Multimedia Appendix 5
Interview guide 3.
[DOCX File , 23 KB - resprot_v14i1e75285_app5.docx]

Multimedia Appendix 6
Focus group guide.
[DOCX File , 21 KB - resprot_v14i1e75285_app6.docx]

Multimedia Appendix 7
Peer review report from the Operating Grant Research and Coordination Hubs for Post-Traumatic Stress Injuries in Public Safety Personnel (PTSI in PSP) Committee, Canadian Institutes of Health Research (CIHR, Government of Canada).
[PDF File (Adobe PDF File), 38 KB - resprot_v14i1e75285_app7.pdf]

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Abbreviations

PSP: public safety personnel
PTE: potentially traumatic event
TDF: Theoretical Domains Framework

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Protocol

An Internet-Delivered Sexual Assault Resistance Intervention for Undergraduate Women (The IDEA3 Trial): Protocol for a Multisite Randomized Controlled Efficacy Trial

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Abstract

Background: Sexual assault (SA) is a serious problem at universities. It is estimated that 1 in 5 women students will experience SA before they graduate.

Objective: The primary aim of this randomized controlled trial is to test whether a synchronous web-based facilitated adaptation of an efficacious intervention (the Enhanced Assess, Acknowledge, Act [EAAA] program) can reduce the 1-year incidence of rape among first- and second-year undergraduate women. Secondary aims will assess the impact of the Internet-Delivered EAAA (IDEA^3) on other forms of SA (attempted rape, attempted and completed coercion, and nonconsensual sexual contact). Tertiary aims will evaluate effects of the program on (1) survivor self-blame in the event of an assault, (2) 6 known mediators of the intervention effect to guide revision of IDEA^3 if necessary, and (3) 2 exploratory outcomes measuring acceptance of sexualized aggression and sexual empowerment.

Methods: In this multisite open-label randomized controlled trial, 1920 diverse women students at 2 Canadian and 4 US universities will be randomly assigned to receive either the 12-hour IDEA^3 (intervention arm) or standard of care (control arm: 60-minute, web-based, live-facilitated consent workshop). Outcomes are measured at baseline, 1 week, 6 months, and 12 months post intervention. SA will be assessed using the Sexual Experiences Survey-Short Form Version. Survivor self-blame and outcomes known to be mediators of EAAA's reductions in SA will also be measured.

Results: Funding was received in October 2022. Recruitment began on October 2, 2023, and the first participant was randomized on October 23, 2023. As of August 2025, a total of 683 participants have been enrolled and randomized. Data collection will end in May 2027.

Conclusions: If efficacious, IDEA^3 will be made available to universities in Canada and the United States. To date, 6 provinces in Canada and the Campus SaVE Act in the United States require institutions to provide SA prevention programming. An evidence-based, cost-effective option that can be delivered remotely via the internet has the potential to become the gold standard. The research, therefore, has the potential to impact women's health and safety internationally.

Trial Registration: ClinicalTrials.gov NCT06058455, https://clinicaltrials.gov/study/NCT06058455

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education; intervention; resistance; sexual assault; universities; women

Introduction

An estimated 1 in 5 undergraduate women experience sexual assault (SA) before graduation, driving depression, anxiety, and negative educational outcomes in survivors [1-3]. Unfortunately, few interventions designed for college students have been proven effective in reducing perpetration or victimization [4]. The Enhanced Assess, Acknowledge, Act (EAAA) SA resistance program is the only intervention proven in a randomized controlled trial (RCT) to reduce SA victimization and sustain these benefits beyond 6 months [4]. Compared with participants in the control arm of the trial, attempted and completed rape was reduced by 50% in female undergraduates who took EAAA, with effects lasting at least 2 years [5]. An implementation effectiveness trial of female-identified students at 5 implementing universities replicated the reductions in completed rape and all mediators for students beyond the first year in a more diverse sample [6]. The program also appears to have effects that generalize to reduce nonsexual intimate partner violence by over 50% for at least 12 months [7].

The EAAA SA resistance program consists of four 3-hour units led by 2 trained near-peer facilitators with a group of up to 20 women [8]. The program uses games, mini-lectures, facilitated discussion, and application and practice activities to facilitate knowledge and skill acquisition. Unit 1 (assess) focuses on improving women's assessment of risk for SA involving male acquaintances and developing problem-solving strategies to reduce perpetrator advantages. Unit 2 (acknowledge) assists women in acknowledging the inherent danger in situations that have become coercive and exploring ways to overcome emotional barriers to resisting known men. Unit 3 (act) offers instruction and practice of various effective resistance options, focusing on common acquaintance SA situations. It also includes 2 hours of self-defense training based on Wen-Do Women's Self-Defence, which teaches techniques designed to be successful against larger, stronger perpetrators. Unit 4 (relationships and sexuality) includes sex-positive sexual education adapted with permission from the Our Whole Lives program [9,10]. Activities build on what women have learned from the previous 3 units and apply this knowledge to longer-term romantic and sexual relationships. More detail is provided elsewhere [8,11].

Despite its efficacy and availability since June 2016, implementation of EAAA on campuses has been limited, with ongoing and new implementations interrupted during the COVID-19 pandemic. Interest has been high despite the absence of marketing efforts, and demand for training has been strong (15 trainings between 2016 and 2024 for 193 staff), with high satisfaction ratings. Nevertheless, relatively few universities send their staff for training, and the number of campuses implementing the EAAA intervention remains small. Some US administrators have expressed reticence due to the belief that a Canadian RCT is insufficient evidence of efficacy for US students. Resource issues have been an obstacle to the wider scale-up of EAAA despite institutional interest. Local implementation costs roughly US $232 per participant in the first year and US $200 in subsequent years [12]. Only 13 participants need to complete the program for one fewer attempted or completed rape to be experienced [5]. However, on campuses where resources are limited, this cost has been prohibitive. This estimate also does not include the cost and logistical burden of assigning an existing staff member as a Campus Trainer who must be trained and subsequently recruit, hire, train, and supervise a team of near-peer facilitators to offer the intervention on campus. Near-peer facilitators are often graduate students, which generates high turnover among facilitators if they are in 1- or 2-year master's degree programs, and it can be difficult to recruit facilitators at undergraduate-focused institutions. Adapting EAAA for web-based delivery, which could be delivered to any campus by a centralized pool of peer facilitators, would eliminate the need to have trained staff locally. We estimate that this could reduce intervention costs to an institution by as much as 30%-40%.

In addition to reductions in cost and local implementation burden, a web-based version of EAAA offers key benefits for timing, fidelity, and accessibility of the intervention. Unlike in-person EAAA, students could more easily take the intervention remotely via web-conferencing before arriving on campus or in the preorientation "move in" week, addressing the issue that on many campuses, the highest-risk period for SA is in the first semester [13]. A centralized pool of full-time facilitators would likely enhance intervention fidelity over campus-specific facilitation models, as supervision quality of facilitators at a given institution may vary; further, small institutions where facilitators only offer 1 or 2 sessions per year may not be high enough frequency for facilitators to truly gain expertise with the intervention [14]. Centralization and web-based facilitation should therefore theoretically improve the effectiveness of the intervention across sites. A version of EAAA delivered via the internet would also increase the reach and coverage of the intervention to students at universities where intensive campus-run primary prevention programming is not offered due to a lack of institutional resources, which may disproportionately affect students who attend religious, rural, commuter, tribal, or small campuses.

Our adaptation of EAAA, called Internet-Delivered EAAA (IDEA^3, pronounced "IDEA Cubed"), retains the synchronous, live-facilitated group learning format over videoconferencing and retains all of the core content of the theory- and evidence-based EAAA. We conducted a rigorous and systematic adaptation for internet delivery using the ADAPT-ITT

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framework [15]. This is a substantial innovation compared with existing web-based options, which are most commonly click-through or asynchronous trainings (eg, the popular sexual assault prevention for undergraduates training by Vector Solutions; formerly called Haven by Everfi). Asynchronous, individual web-based interventions have failed to reliably change even knowledge or attitudes about SA [16-18] or have had equivocal short-term effects on victimization [19]. Key advantages of the synchronous group format over individual click-through programs include learning from and with peers and peer facilitators, longer duration (at 12 hours) than other web-based programs, and the ability to address comments and questions that emerge from participants, allowing for meaningful integration of the material. Our 2-year adaptation process included extensive consultation with the University of Windsor's Office of Open Learning staff with expertise in online education, pedagogy, and technology. A theatre test on a small number of first-year students (N=8) led to further revision followed by a single-arm pilot trial (N=65), which provided preliminary evidence of IDEA^3's feasibility, acceptability, and effects on the validated intermediary outcomes shown to mediate the effect of in-person EAAA on SA victimization [20]. The pilot study demonstrated the feasibility of the intervention, with strong recruitment and retention. The acceptability of the intervention was high, with participants reporting enjoyment (mean 8.2 out of 10) and willingness to recommend the training to others (mean 8.5 out of 10). Qualitative data from open-ended survey questions and focus groups indicated that within a short follow-up period, many participants had already used information and skills they learned in the program to detect coercive behavior and remove themselves from situations where they felt unsafe. Preliminary indicators of potential efficacy showed that the program increased self-defense self-efficacy and perceived risk of acquaintance rape while reducing acceptance of rape myths and beliefs about female participation in rape, echoing the changes found in these mediators of intervention effect in the in-person EAAA trial [21].

EAAA is part of a broader group of empowerment and resistance interventions developed in the field, but it has the strongest evidence base for efficacy in reducing victimization in North American university contexts. Other high-quality programs for university women had been developed since the late 1980s and were promising, but generally did not work to reduce victimization reliably for survivors or for the longer term [22]. A much longer empowerment self-defense program was found to be effective in reducing sexual violence in a propensity-matched quasi-experiment [23]. Unlike most other interventions in this space, EAAA is effective at reducing victimization in women with and without previous sexual victimization experiences [5,24]. EAAA was developed based on a decade of empirical evidence and theory [25] and, with pedagogical attention to the reality that survivors would always be present in the group, to address the difficult social and emotional context women face in society when the risk of SA is highest from people they should be able to trust (eg, male friends, intimate partners, and other acquaintances) in situations that should be safe (eg, parties, studying with classmates, and dating). EAAA is the only resistance program evaluated in North American universities with a rigorous RCT [4].

We focused on developing a web-based version of EAAA for scale-up, as it is the intervention with the strongest evidence base for yielding immediate, durable, and substantial reductions in assault victimization. While comprehensive prevention of sexual violence will involve ending perpetration and dismantling structural sexism, no existing interventions have been rigorously shown to durably reduce campus sexual violence perpetration, and a cultural shift is a long-term effort. In the meantime, EAAA prevents 1 attempted or completed rape for every 13 women who take the program, while reducing self-blame in the event of an assault [5,24]. An adaptation of EAAA for internet delivery would prevent imminent threats to safety and reduce sexual violence for women now and at scale, as work to end perpetration continues [26].

The next step is an RCT whose aim is to test whether IDEA^3, when compared against a brief control workshop ("usual care," ie, consent education), can deliver reductions in SA victimization of sufficient size to warrant scale-up to campuses in North America. Given that web-based interventions sometimes fail to produce benefits as strong as in-person ones [27], we have powered our trial to detect an intervention effect that is 80% as large as the effect size of in-person EAAA. We hypothesize that IDEA^3 will reduce the 1-year incidence of completed rape by 37.75% (absolute difference of 3.7%) among first- and second-year undergraduate women in the United States, as compared with a consent workshop control condition. If successful, this trial of a web-based adaptation of the only intervention proven to prevent campus sexual violence and sustain those benefits in the longer term has the potential to revolutionize the fight against campus SA.

Methods

Study Design

This is a multisite, open-label, RCT.

Inclusion and Exclusion Criteria

A total of 1920 first- and second-year undergraduate students will be enrolled in Canada and the United States. To be eligible, participants must (1) identify as women, (2) be between the ages of 17 and 24 years, (3) be first- or second-year undergraduate student, (4) be available during one of the intervention schedule blocks, (5) provide the contact information for another woman undergraduate who they would be willing to participate in the intervention with or express willingness to being partnered with another woman undergraduate at their university, (6) have access to internet and be willing to use the videoconferencing software ZoomPro (Zoom Video Communications, Inc) for the intervention, (7) provide informed consent, including to be recorded while participating, and (8) complete the baseline survey and be randomized with a partner who also meets all the criteria. At one site (University of Central Florida), participants must be 18-24 due to state law. Participants whose partners drop out within 24 hours of the first intervention session or do not show up for their assigned intervention after

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randomization will be permitted to participate alone. There are no exclusion criteria.

Recruitment

Recruitment began on October 2, 2023, at 4 sites: the Universities of Windsor and Guelph in Canada and the Universities of Michigan and Nebraska-Lincoln in the United States. In year 2 of the trial, recruitment was ended at the University of Nebraska and paused at the University of Michigan due to the departure of the site principal investigators (PIs) from those institutions. In year 3 of the trial, recruitment is planned at the University of Guelph, the University of Michigan, the University of Maryland, and the University of Central Florida. The 6 total sites represent diverse students, sizes, and contexts (eg, rural vs urban, proportion of students in residence, racial, and geographic diversity). Recruitment will only take place during the academic year when classes are in session. Multiple methods are used to attract participants to the study, including (1) recruitment emails through the registrar, faculties, or departments to all eligible students, (2) research participant pools, (3) social media ads or posts to relevant Facebook groups (eg, groups for students at a particular university), and (4) flyers will be distributed at on-campus events, posted in women's bathrooms on campus, and sent digitally to student newsletters/newspapers, student organizations, or student-specific listserves at the sites of Universities. Not all recruitment methods will be used at all sites (eg, emails are permitted through the Registrar at certain sites but not others).

Prescreening Survey

Links or QR codes in advertising materials (emails, flyers, and ads) take potential participants to a website that has the semester's updated survey link or directly to the prescreening survey in REDCap (Research Electronic Data Capture; Vanderbilt University) to determine eligibility. The screener begins with a brief description of the study, followed by the screening survey.

Participants give their initial consent to provide demographic information in the screener to determine their eligibility for this research. Demographic information provided (eg, sexual identity and race/ethnicity) also allows us to see whether recruitment strategies are working to reach diverse students. If participants (1) do not consent to provide demographic information or (2) are ineligible based on the screening criteria, they are sent to a page thanking them for their interest.

Participants attend the IDEA^3 program in pairs for support and in order to adequately practice and learn the self-defense tactics in the third unit with a partner. Using the same protocol we used in our pilot trial [20], after completing the screening survey, eligible participants are sent to an additional page where they are asked a series of questions about the partner with whom they would be willing to participate. Partners must meet study eligibility criteria. Students can either participate with a friend or consent to be partnered with another undergraduate woman by the study staff. Potential participants must also indicate which one of the intervention session blocks scheduled for that semester they are available for. Although the control arm intervention condition only meets once (see below), participants must state they are available for the 4 dates allotted for the IDEA^3 program in case they are assigned to the intervention arm of the trial.

Students who wish to participate with a friend are asked to provide their own contact information and the first and last name of their friend. If they are willing to provide the friend's email address, they can personalize an email invitation sent directly through REDCap, or if they prefer to communicate with their friend first, we send them an email they can forward to that friend with a link for them to sign up. If that friend is not interested, students have the option of proceeding in the study with a match done by the research team or discontinuing their involvement. If they believe their friend has already signed up for the study, they can indicate this and, if verified, that person is contacted to ensure they are willing to be matched with the student. Participants who do not provide the name for a potential program partner and are unwilling to be partnered with another student by study staff are sent to a page thanking them for their interest, as they are not eligible for the study. Referred program partners progress through a similar prescreening process via an emailed REDCap link. Once both partners have completed the prescreening survey and have screened as eligible for the study, they are "matched" and their ID numbers are linked in REDCap.

Partnered participants are introduced (if they were not already friends) by email and invited to get in touch to discuss where they will get together to participate. Further, they are provided with a link where they can schedule their individual screening interview or request further information.

Screening Interview and Informed Consent

Interested students who meet the initial prescreening criteria and have been successfully matched with a partner receive an email with a link to book a 30-minute screening interview using Calendly. Up to 5 reminder emails/texts are sent over a 10-day interval until the student schedules an interview or is presumed to be no longer interested in the study. When potential participants book, they are sent a confirmation of their interview time and date, a Zoom link with instructions on how to use Zoom, and the full consent form to review before the interview. The main points from the consent form are reviewed aloud with the participant by the study staff, and questions are answered. Participants provide consent verbally at the start of the scheduled interview (or, if not given, participants are thanked, and the interview is ended). The screening interview is conducted by an intervention facilitator and potential participants are required to turn on their camera for the interview as (1) this allows additional screening for age and gender eligibility and (2) participants are required to come to intervention sessions with cameras on, and using a camera during the screening interview confirms they have a working camera that they can use during intervention sessions.

Facilitators review the format of the intervention with participants to make sure the participant is willing and able to meet in person with the partner and that they have a suitable and safe space to participate together. Facilitators assess any physical limitations that might affect participation in the self-defense portion of the program (to inform adaptations for

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accessibility if they are assigned to the intervention arm), ensure participants feel comfortable using Zoom, and ensure participants have a stable Wi-Fi connection. They are asked if they are willing to sign up for a GroupMe account and be included in group messages to other participants assigned to their intervention block using this app. GroupMe is a messaging app designed for multi-person chats. Facilitators use this app to send messages to participants in the IDEA^3 arm (after they come to the first session and learn their assignment), about upcoming program sessions, resources, etc. Participants do not have to have a GroupMe account to receive these messages, but they need one to chat with other participants. For participants who have requested to be partnered with someone they do not know, this interview allows them to discuss any concerns/reservations about this process and go over where they need to meet their partner before their first or only program session. Both partners in each participant pair will be required to individually complete this one-on-one interview and provide informed consent before being allowed to enroll in the study.

Randomization

When participants have completed their screening interview, they receive an email inviting them to complete the baseline survey (see section below on assessments for more details). The baseline survey must be completed no less than 24 hours before their first program session (or only program session for control participants). The email contains an individualized URL taking them directly to this first survey, which takes 30-45 minutes.

Randomization of the pair will occur once both participants in the pair complete their screening interview and baseline survey, and no later than 24 hours before the first (or only) session. If one member of the pair fails to complete the baseline survey, the other member of the pair will be given the choice of continuing in the study with a different partner (time permitting), rescheduling for a later intervention session, or discontinuing the research. In rare circumstances, that is, if the participant has been re-paired once or more, there is insufficient time to re-pair, or no one else is available for a new pairing, she will be individually randomized and permitted to complete the intervention by herself. Once the pair is randomized, they are sent a Zoom link for the session through REDCap. This link does not identify their random assignment. The facilitators/research assistant (RA) reveal the assignment once everyone is present in the Zoom room at the scheduled time.

The trial biostatistician is responsible for setting up the randomization protocols in REDCap. Randomization is stratified by site using permuted block sizes of 2 and 4, and participant pairs are randomized 1:1 to the IDEA^3 program or control. Randomization occurs after baseline completion so that participation in the trial cannot be affected by knowledge of intervention assignment. The site coordinators generating the random assignment for a participant pair are not able to view the random allocation sequence.

Interventions

Both Arms

After providing informed consent in the screening interview and before the first (or only) session, a Program Resource Kit is delivered to participants by mail (if time permits) or hand-delivered by study staff. Kits include some sealed envelopes (marked unit 1-4) with resources necessary for both the control and intervention arms, with instructions not to open the envelopes until they are instructed to do so at their first intervention session. Kits also include some snacks and small “swag” items. Both arms receive identical kits. Receiving gifts and snacks before the first session also encourages attendance at the first session.

Intervention Condition

The IDEA^3 SA resistance program follows the same structure as EAAA, with four 3-hour units led by 2 near peer-facilitators with content designed to help women more quickly and effectively recognize and resist coercion (see the *Introduction* section for more detail). IDEA^3 retains the interactive modality of EAAA by using games, discussions, and other activities.

This intervention is presented by a pair of highly trained woman-identified “near-peer” program facilitators (ie, a few years older than the participants). Unlike the original in-person intervention, a tech facilitator is present at all sessions to facilitate the Zoom technology, troubleshoot participant technical difficulties, assign breakout rooms, provide participants with links to external games/group apps, record sessions, and perform other technical duties before, during, and after each session. The presence of the tech facilitator allows the program facilitators to focus on content delivery and facilitating participant discussion and engagement.

Participants receive the intervention in pairs via Zoom in a private room with enough floor space to practice basic self-defense techniques, and where they know they will not be disturbed. If a pair of participants does not have an appropriate room available to them, a university-sponsored space for each pair is arranged. These Zoom sessions include a minimum of 1 and a maximum of 8 pairs of participants (16 women total) taking part in the intervention together.

Control Condition

Participant pairs assigned to the “usual care” control arm will receive one 60-minute session. The workshop focuses on (1) defining consent, including what components need to be present for consent to be meaningful, and (2) expanding the ways in which participants feel comfortable giving, refusing, and asking for consent. The control condition was selected to mimic what is currently available, “usual care” on typical college campuses, which is a brief consent workshop. The content is therefore based on the common components of consent workshops held at the study sites and community-based consent workshops (confirmed with participating campus materials and in consultation with the Ontario Coalition of Rape Crisis Centres).

As with the intervention arm condition, participants receive the consent workshop in pairs via Zoom in a private room (their

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own or provided to them on campus). These Zoom sessions include up to 8 pairs of participants (16 max) taking part in the workshop together. The control workshop is given by a well-trained RA. Participants who are assigned to the control arm will be informed of the importance of the control group to the study and their ongoing participation. They are made aware that they will be contacted in a year and offered the opportunity to take the full IDEA^3 program.

Training of Facilitators and Research Assistants Conducting Interventions

IDEA^3 has been manualized for program facilitators and tech facilitators and, as is the case for the in-person version of the program, includes scripts, instructions on how to conduct activities, and troubleshooting advice. An EAAA lead trainer delivers the theory and program content-based 5-day facilitator training. Training also includes a certified Wen-Do Women's Self-Defence instructor leading an in-person 15-hour Wen-Do Women's Self-Defence Basic Course and another day of instruction in how to safely teach the self-defense content remotely over videoconferencing. Tech facilitators attend a portion of this training and have additional training in their tasks. Program facilitators and tech facilitators receive additional training to perform their research tasks (eg, screening interviews and tracking attendance in REDCap) from PIs. RAs are trained to conduct the control intervention by PIs. Research training of Site/Country Coordinators and RAs is conducted by the Trial Project Manager and PIs.

Feasibility/Acceptability

Postsession Evaluations

At the end of each IDEA^3 session and at the end of the control arm workshop, participants are given a link to an anonymous 5-minute REDCap survey with closed- and open-ended questions on their evaluation of the session to assess feasibility and acceptability, and allow the chance to offer feedback on the program. Participants are asked to complete the survey immediately to minimize recall bias, and to increase response rates, participants only receive entries into the two $25 raffles for the session if they fill out the evaluation form.

Attendance/Dose and Fidelity

Attendance at the assigned intervention/control sessions will be recorded by the tech facilitator/RA to allow us to examine the effects of dose and attrition. All sessions in both arms will be recorded, and a randomly selected 25% of these recordings will be assessed for facilitators'/RAs' fidelity to the protocols for that arm of the trial. Consent for video recording of each program session is a requirement of participation in the research, is included in the Consent Form, and is discussed in the screening interviews.

Outcome Assessments

Web-based surveys will be administered to participants at 4 time-points as explained in the following subsections.

Baseline Survey

After completing the screening interview and giving consent, participants are invited to complete the baseline survey. The survey includes a number of demographic questions (eg, year of study, age, ethnicity, sex assigned at birth, gender identity, sexual identity, sexual orientation, current relationship status, number of sexual partners, and age of first sexual contact), primary outcome assessment (Sexual Experiences Survey-Short Form Victimization [SES-SFV]) [28], secondary outcomes scheduled for the baseline (Self-defense Self-efficacy Scale) [29], perceived risk for acquaintance SA [30] (1 item), the Perceived Causes of Rape Scale [31], and the Updated Illinois Rape Myth Acceptance Scale [32], and tertiary outcomes (Acceptance of Sexualized Aggression Scale [33], 13 items from the Sexual and Reproductive Empowerment Scale [34]).

Postintervention Survey

One week after the completion of the final session for participants in the intervention arm, participants in the same recruitment cohort in both arms of the trial will be invited by email to complete the postintervention survey via the web-based REDCap platform. This survey includes the same measures used in the baseline, excluding demographic questions. It includes additional secondary outcome measures: (1) a measure of Risk Assessment and Resistance developed by Testa et al [35] built on items from Norris et al [36] and Davis et al [37], and (2) an open-ended question measuring knowledge of effective resistance strategies and willingness to use them if a man they knew tried to force them to have sex when they did not want to. It also contains "contamination questions" to determine whether and to what extent participants in the intervention arm shared information with those in the control arm, or control arm participants had IDEA^3 content shared with them. Participants who indicate on the postintervention SES-SFV that they experienced a completed or attempted rape will also be asked follow-up questions relating to the first (and the most recent if more than one) SA (eg, the date the assault happened, her relationship to the perpetrator, etc) and these same participants will also be asked to complete the Rape Attribution Scale [38] to assess self-blame.

6- and 12-Month Follow-Up Surveys

Participants will be invited to complete the 6- and 12-month follow-up surveys approximately 6 and 12 months after completing their baseline survey. The timing is adjusted to avoid the summer months when response rates are much lower (based on the research team's previous research). These surveys will consist of the same measures used in the postintervention survey, except that the risk assessment and resistance measure is replaced with 2 different versions of a risk perception task [39], one at each time period, as the risk assessment and resistance measure is not designed for repeat use.

All Surveys

At each follow-up point, participants will receive an email invitation through REDCap to complete each of the surveys. A combination of text and email reminders (up to 5) to complete each survey will be sent every 24-48 hours to any participants who have not yet completed them. This is fewer than Dillman

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et al's [40] recommended number (7 reminders), but we have found 5 sufficient to maximize survey completion rates. Participants are reminded of the study structure and reconsented at 6- and 12-month time points via an introductory page to the survey before progressing to the questions.

At the end of the postintervention and 6-month surveys, participants are asked to provide updated, detailed contact information (primary and secondary cell phone numbers and email addresses) so that we can contact them for subsequent follow-ups. For use in the event that an email or text is unable to be delivered, we will ask for (1) permission to contact the Registrar's Office in case the contact information they have provided us is out of date and (2) contact information for 2 people who would know how to get in touch with them in case they have not updated their contact information with the Registrar. If text messages or emails are undeliverable at the 6- or 12-month surveys, we will ask the Registrar or the provided contacts for updated contact information only for those participants who have given us permission to do this. If we reach out to the participants' nominated contacts, we will not share any information about the research study when we do so. We will only ask these individuals to ask the participant to contact us for those participants who have given us permission to do this.

Incentives

In the second year of recruitment, the incentive for the 20- to 30-minute screening interview was increased from $5 to $10, based on attrition between preliminary screening/matching and the interviews. This change is reflected in the description of incentives that follows. For participation in this research, participants receive incentives (preloaded gift cards) of up to $105 or receive up to $70 and 2.5 course bonus points for those recruited from Participant Pools. Specifically, nonpool participants receive $35 for completing the screening interview, baseline, and 1-week postintervention surveys ($20 for screening and baseline alone if they do not complete both surveys), $30 for the 6-month survey, and $40 for the 12-month surveys. Pool participants receive 2.5 bonus points for completing the screening interview, baseline, and postintervention surveys (combined) which occur in the same semester in which they are registered for the participant pool (1.5 pts if they do not complete both surveys), and the same monetary incentives as nonpool participants for the remaining 2 follow-up surveys (which occur outside of that semester).

For each session attended and postsession evaluation completed, participants (in both trial arms) are entered into a postsession raffle for two $25 draws among the people who attended their session that day (max 16 participants). Participants assigned to IDEA^3 are therefore eligible for up to $100 in session-end raffles (depending on how many sessions they attend) compared with $25 for control group participants, to compensate them for the longer time commitment involved. Further, for each intervention session attended, all participants (in both trial arms) receive a ballot for an end-of-term $250 raffle at each site.

Increasing incentives for each survey completed encourage students to stay in the trial for its full duration after the intervention is complete and maximizes response rates for follow-up surveys within a range supported by the published literature [41], our previous RCT [5], and our implementation trial [6]. The use of various incentives is standard in psychological research and, increasingly, in clinical trials, providing the size of the payment does not put "undue" pressure on individuals to participate, and the sample is not drawn from a "vulnerable population" [42,43]. Our survey incentives ($105 over the course of multiple surveys for a year) are well within the range considered acceptable (adjusted for inflation) by authors publishing in Contemporary Clinical Trials [44].

Every intervention arm participant who completes all 4 sessions of the IDEA^3 program will receive a certificate of attendance for their resumé.

Outcome Measures

Primary Outcomes

The primary aim of the trial is to test whether IDEA^3 can reduce the 1-year incidence of completed rape among women attending university in Canada and the United States. Completed rape will have occurred when a participant indicates she has had at least one experience of threatened, forced, or drugged completed (not attempted) sexual activity (oral, anal, or vaginal intercourse)—answered "once" or more to any of 9 items (2c-e, 3c-e, and 4c-e) in the period between the last outcome measurement and the current day (SES-SFV). Dates of occurrences will be recorded using a calendar function to allow time-to-event analyses. The SES-SFV has been used in very large university and college and community samples and is considered the gold standard. We use the gender-specific version (male perpetrator) due to the focus of the intervention. Responses on the scale are stable across administrations [28] and are comparable to those received through interviews [45]. The validity of the scale has been demonstrated in many published studies [28,47]. Predictive validity has been demonstrated with correlations between sexual victimization and variables predicted to be influenced by it, such as trauma symptoms [28].

Secondary Outcomes

The secondary aim of the trial is to test the hypotheses that IDEA^3 can reduce the 1-year incidence of: (1) attempted rape; (2) attempted or completed sexual coercion; and (3) forced sexual contact (nonpenetrative SA). Attempted rape will have occurred when a participant answered she has had at least one experience of attempted, threatened, forced, or drugged completed sexual activity (oral, anal, or vaginal intercourse)—answered "once" or more to any of 9 items on the SES-SFV (5c-e, 6c-e, 7c-e) in the same period. Sexual coercion will have occurred when a participant reports one or more incidents of verbally coerced (excluding threats of physical harm) nonconsensual oral, vaginal, or anal intercourse—answered "once" or more to any of 6 items (2a-b, 3a-b, 4a-b). Attempted sexual coercion is assessed when a participant reports that sexual coercion was attempted but did not occur—answered "once" or more any of 6 items (5a-b, 6a-b, 7a-b). Forced sexual contact will have occurred when a participant indicates she has had an experience of threatened,

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forced, or drug-facilitated sexual touch (excluding intercourse)—answered "once" or more to any of 3 items (1c-e). Dates of occurrences for the first reports in any period will be recorded using a calendar function to allow time-to-event analyses.

Tertiary Outcomes

The main tertiary aim is to test the hypothesis that IDEA^3 can positively affect the 6 outcomes shown to be mediators of decreases in SA victimization [47]: (1) increase women's ability to detect risk in hypothetical situations, (2) increase women's knowledge of and willingness to use the most effective self-defense strategies, (3) increase women's confidence that they could defend themselves if confronted with a SA situation, (4) increase women's perception of their own risk of SA by male acquaintances, (5 and 6) reduce rape myth beliefs and woman-blame that hamper risk detection.

The expanded cognitive appraisal model [48] upon which the intervention is built proposed a process through which changes to the primary outcome of rape victimization would be accomplished. Chained mediation analysis of the original RCT data supported this theory and showed that 3 measures (risk detection, knowledge, and willingness to use effective strategies, and self-defense self-efficacy) were primary mediators that explained 95% of the decrease in completed rape and 76% of the decrease in attempted rape [47]. Other attitudes and beliefs (perceived risk of one's own SA risk from male acquaintances, general rape myth beliefs, and belief in female precipitation of rape) were more distal mediators that led to improvements in the primary mediators. Measurement of mediators (common to the original EAAA RCT) will allow targeted revision to the IDEA^3 program if necessary to strengthen program material meant to impact the mediators that were not significantly affected by the intervention.

Tertiary aims additionally include testing the hypothesis that IDEA^3 can, (7) reduce women's self-blame if a rape occurs, as previously demonstrated with the in-person version of EAAA, as well as exploratory hypotheses related to whether IDEA^3 can, (8) reduce attitudes related to acceptance of sexualized violence using the Acceptance of Sexualized Aggression scale [33] and, (9) increase sexual empowerment, using 13 items drawn from the Sexual and Reproductive Empowerment Scale [34].

Methods for Protecting Against Sources of Bias

Selection Bias

Randomizing a large number of participants is expected to minimize selection bias, that is, minimize baseline differences between the intervention and control groups. Selection bias is further minimized by concealing the random assignment to participants until they complete the baseline assessment and arrive at the virtual intervention session.

Outcome Assessment Bias

Blinding is not possible in this trial. However, bias in outcome assessment is minimized by having the primary outcome, SA, collected with the best measure of coercive sexual experiences available (SES-SFV) [45]. This measure will be applied equally to all study participants. The measure has been tested on tens of thousands of undergraduates, and it has high reliability and validity [28,45]. Self-report through the SES-SFV has been the gold standard for assessing SA experience, as external adjudication is not possible and allows comparison to the original RCT. The instrument follows best practice for not using terms like "sexual assault" directly but instead assessing by describing the behavior (eg, "A man put his penis into my vagina, or inserted fingers or objects without my consent by using force, for example, holding me down with his body weight, pinning my arms, or having a weapon"). This measure, therefore, avoids issues with survivors not labeling their experience as "assault" despite it meeting the definition as intended.

Differential Dropout

Our pilot testing prior to the original EAAA RCT indicated that dropouts are minimized by having follow-up times coincide with the school year rather than with holiday breaks. We use the same follow-up timing in this trial. As we have done previously, we use frequent reminders (sent out by RAs at each site and automated within REDCap) for those who have not responded to maximize response. For students who have not completed a 6- or 12-month follow-up survey within 2 weeks after the final reminder, we invite them to complete a shorter survey that just includes the SES-SFV (primary and secondary outcomes) at 6 months and 12 months. Taken together, these methods reduce the attrition rate considerably. There is a possibility that women in the control arm may not feel as connected to the research and drop out of the study as a result. We have reduced the likelihood of differential dropout by providing a brief intervention (consent workshop) rather than using a no-contact control, a participant kit including snacks and resources mailed to the home of control participants as well, increasing incentives and personalized email/text contact, as well as offering the opportunity for control participants to receive IDEA^3 at the end of the trial. Recruitment materials present both intervention and control programs as valuable to participants. As evidenced by our past research, these maximize the connection to the trial to reduce or eliminate differential attrition.

Between-Group Contamination

While our own and others' research show that significant contamination is not likely to occur for an intervention of this length [49], as we have done previously, we will ask all participants at 1-week, 6- and 12-month follow-up the following questions: "Do you have any friends who were assigned to the other program in this study?" If the answer is "yes," they are asked, "Did she/they share anything with you about what they learned in their program?" or "Did you share anything that you learned in your workshop with her/them?" depending on their group assignment. An open text box asks them to enter what was shared. We will describe the amount of contamination occurring and discuss its possible influence on the findings.

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Noncompliance and Loss to Follow-Up

Noncompliance (aka "no show") is defined as not attending the assigned intervention after randomization. Lost to follow-up is defined as not being able to ascertain participants' SA status at 1 year.

To minimize attrition, participants' sessions will start close to the beginning of the term or closely following midterms (rather than during final assignment and examination season when participants have competing priorities). We will use incentives, reminder emails, and texts 1 week and 1 day prior to the first session, and reminder texts by facilitators for those in the IDEA^3 arm for subsequent sessions. Using a similar level of incentives, we attained full EAAA attendance from more than 78% of participants in the previous RCT and over 90% in the IDEA^3 pilot trial.

Nonresponse on follow-up surveys will be defined as refusing to complete one or more follow-up surveys. We use a number of procedures known to maximize response rates for follow-up surveys [40], such as confirmation of contact information at each follow-up and multiple reminder emails/texts. We use increasing incentives ($10 baseline, $15 1-week, $30 6-month, $40 12-month surveys) within a range supported by the published literature [41] and our previous RCT [5] and implementation trial [6] to maximize response rates. We have found that web-based surveys (with all appropriate security and privacy measures taken) improve the ease with which women can participate. The follow-up outcome surveys take less than 30 minutes to complete, which maximizes response rates [40].

Sample Size Considerations

In calculating the sample size for the proposed trial, we used estimates of the 1-year incidences and difference in completed rape from the previous trial (9.8% control vs 5.2% EAAA=4.6% difference [5]). However, we conservatively powered the trial so we can still detect meaningful differences even if IDEA^3 is less efficacious than in-person EAAA, that is, it achieves 80% of the previously observed difference (80% of 4.6%=3.7%). Therefore, assuming 1-year incidences of completed rape in the proposed trial of 9.8% in the control group versus 6.1% in the intervention group, a sample size of 1676 will have 80% power to detect an absolute difference of 3.7% (relative risk reduction of 37.75%) at a 2-sided 5% level of significance. As participants in the IDEA^3 sessions will be in pairs, the sample size is further inflated by a design effect of 1.031, based on a within-pair correlation of 0.031 from the previous trial. Including an estimated maximum 10% lost-to-follow-up, a total of 1920 participants will be enrolled in the trial (1920=1676×1.031/0.90). Using estimates for the secondary outcomes from the previous trial [5] and similarly, assuming 80% efficacy compared with the in-person intervention, the proposed sample size yields 97% power for comparing 1-year differences in attempted rape (9.3% vs 4.6%), 92% power for sexual coercion (22.6% vs 16.1%), and 99% power for sexual contact (39.1% vs 28.5%). Using estimates for the tertiary outcomes from the previous trial [21] and similarly, assuming 80% less efficacy, the proposed sample size yields > 99% power for comparing 1-week postintervention group differences in risk perception (Cohen *d* 0.58), rape myths (Cohen *d*=0.48), risk detection (Cohen *d*=0.54), and self-defense self-efficacy (Cohen *d*=0.64).

Statistical Analyses

Analyses will be performed after all participants have completed their 1-year follow-up survey. Following a modified intention-to-treat principle, a participant will be included in the analyses if they are randomized and complete one or more postrandomization surveys. The analyses will compare the incidence (ie, first occurrence) of each primary and secondary outcome between the IDEA^3 and control groups with Kaplan-Meier failure curves (indicating the cumulative percentage of first outcomes among women in the respective groups) and log-rank tests. Participants who are lost to follow-up or drop out will have their data censored at the time of last contact. To account for the correlation between the paired observations, variance estimates will be appropriately inflated for within-pair clustering with the use of estimates of the design effect [50]. In case of baseline imbalances in participant characteristics, Cox proportional hazards regression models with a robust sandwich covariance matrix to account for the clustering will be used to compare the IDEA^3 and control groups while controlling for the confounding factors. The literature [24,51,52] suggests that prior SA can be a modifier with respect to the effectiveness of SA resistance interventions. Therefore, intervention effects will be compared for women with and without SA histories at baseline by adding a cross-product term to the Cox regression model and testing for statistical significance. For the tertiary outcomes, which are all continuous, linear mixed models will be used to analyze the data that mirror a multilevel repeated-measures study design. A random intercept will be included in the models to account for the correlation between the paired observations, and a first-order autoregressive covariance structure will be used to characterize the interdependence of the repeated measures over time. A cross-product term between group and time will also be included in the models. Participants who are lost to follow-up or drop out can affect the validity of the group comparison if (1) the outcome is related to being lost or dropped, and (2) it is differential between groups. Therefore, baseline characteristics of women who are lost and drop out will be compared with women who complete the trial. In addition, the missing data mechanism will be formally tested [53] to determine whether it is Missing Completely at Random or missing at random. For completeness in assessing the effect of missingness, 2 additional analyses will be conducted: (1) a "per-protocol" analysis among participants who attend all sessions and respond to the 1-year SES-SFV questions; (2) multiple imputation of 5 data sets using a discriminant function for binary outcomes and Markov chain Monte Carlo for continuous outcomes, assuming the missing data mechanism is missing at random.

Ethical Considerations

Ethical approval for the trial was received from the University of Windsor Research Ethics Board (reference number 42876). Other university sites (eg, University of Guelph, University of Michigan, University of Maryland, University of Nebraska-Lincoln, and University of Central Florida) ceded ethical review to the Windsor Research Ethics Board.

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Our ethics and safety protocols have been developed and refined over many pilot studies and 2 trials. There are limited risks related to the content of the intervention and the survey questions on SA. Women know the topic of the intervention and the study prior to volunteering and therefore can evaluate their readiness to participate. Informed consent is fully voluntary, and participants can opt out or leave the study at any time. Participants provide verbal informed consent in the screening interview, which is documented by study staff. Brief emotional discomfort may still occur for participants, particularly if they have an assault history. Session evaluations demonstrate that survivors rate participation in EAAA positively, and our own [25] and others' [54,55] research confirms that survivors perceive research on these topics as beneficial and important. The self-defense instruction adds a limited physical risk. Risks are minimized through protocols associated with the research (eg, internet and local resources and referral lists provided at every time point), intervention (eg, trauma-informed intervention content and process, screening interviews to assess physical safety of space and participants' physical limitations, clear safety instructions for self-defense practice, extra-large external monitors for clear view of participants to monitor their safety), and training (eg, extensive facilitator training including on dealing with disclosures, providing referrals, and monitoring the safety of self-defense practice). None of the women participating in the original RCT (N=893) or implementation effectiveness trial (N=603) reported adverse events. Consultation with Deb Chard, Senior Wen-Do Women's Self-Defense instructor, during the adaptation process enhanced our facilitator training and participant safety monitoring for the virtual environment and the theatre, and a pilot trial of IDEA^3 confirmed their efficacy.

Participants receive up to $105 for study activities, with the possibility of winning additional raffle incentives. Identifiable data are stored on a secure REDCap database at the University of Windsor. All survey data will be reported in the aggregate and deidentified; identifiable data will be deleted at the end of the study after all the data are cleaned and merged across time points. Video recordings of the screening interviews will be deleted at the end of the semester, and video recordings of the intervention sessions will be deleted once the project is over and all fidelity ratings have been completed.

Steering Committee and Trial Oversight

The Steering Committee includes the PIs and 4 coinvestigators. Our psychosocial educational interventions do not require a data safety monitoring committee. Research decisions for all sites are made by the trial project manager, and weekly communication with the Site Coordinators during active recruitment and intervention periods will ensure consistency on trial issues. Integrity of the trial at each site is the responsibility of the Site Coordinators. The trial project manager is supervised by the PIs; the site coordinators are supervised by the site investigators. Weekly virtual meetings are held between the trial project manager, site coordinators, PIs, and coinvestigators during recruitment semesters, and meetings between the trial manager and all investigators (virtually) monthly and (in-person) annually.

Results

This trial was funded in October 2022. Recruitment began on October 2, 2023. The first participant pair was randomized on October 23, 2023. A total of 683 participants had been enrolled in the ongoing trial by August 2025. Recruitment will end by May 2026, and data collection will end in May 2027. Results are expected to be published in 2028.

Discussion

Key Findings

Findings from this trial will determine if IDEA^3 can successfully reduce sexual violence against undergraduate women as compared with a consent workshop control condition. In addition to its unique contribution to the published literature as what may be the first synchronous web-based program shown in a randomized trial to reduce SA victimization, the results of the trial will be used to (1) produce a maximally effective manualized IDEA^3 intervention manual and facilitator training protocol for implementing the intervention in universities across North America or (2) provide direction for further research into which aspects of the intervention need to be strengthened before it can be widely disseminated. The data will also be used to indicate how long the effects of the intervention last and whether refresher sessions are necessary.

Findings from the trial will be disseminated in peer-reviewed publications as well as products such as briefs and infosheets designed for campus decision makers and students.

Strengths and Limitations

Strengths of the trial include the randomized design against an active control, use of validated measures for outcome assessment, a 1-year follow-up period, and the use of multiple sites in 2 countries to enhance external validity. Limitations of this trial include the restriction of recruitment sites to 2 Canadian (both in Ontario) and 4 US campuses that are all large public institutions, which may limit generalizability. However, campuses were thoughtfully selected for diversity in geographic regions of the United States (Midwest, mid-Atlantic, and Southern) and class and racial diversity. While a 12-month follow-up period is meaningful and beyond what is typical for more campus SA prevention intervention evaluations [19,56], a 2-year follow-up period would allow for more assessment of the durability of intervention effects.

Future Work

The results of this trial will also be used to provide a foundation for further adaptation work for high-risk minority populations with unique vulnerabilities for SA. If the intervention is effective, we will use the intervention as the foundation for our work to adapt IDEA^3 for trans and other gender-diverse students, where the smaller proportion of identifying students within one campus population would make the web-based intervention more feasible than an in-person version at every university. As compared with in-person EAAA, where implementation was in the hands of a specific university for its students alone, IDEA^3 may also provide an opportunity for wider dissemination to

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young women aged 17-24 years who are not enrolled in or even living near a university and who are at as high or higher risk of SA [57].

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Data Availability

Data will be made available upon reasonable request from the authors.

Authors' Contributions

SP and CS conceptualized the study and co-led the writing of the paper. ME designed the randomization and data analysis plan and reviewed and approved the final version of the paper. PB, KE, and LJP contributed to the conceptualization of the study and reviewed and approved the final version of the paper. KH helped draft portions of the paper and reviewed and approved the final version of the paper.

Conflicts of Interest

None declared.

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Abbreviations

EAAA: Enhanced Assess, Acknowledge, Act
IDEA^3: Internet-Delivered EAAA
PI: principal investigator
REDCap: Research Electronic Data Capture
RCT: randomized controlled trial
RA: research assistant
SA: sexual assault
SES-SFV: Sexual Experiences Survey-Short Form Victimization

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Protocol

Advancing Health Equity Through Primary Care: Protocol for the Spread, Scale, and Multimethod Developmental Evaluation of the Deep End Canada Network

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Abstract

Background: The social determinants of health are “the conditions in which people are born, grow, live, work and age,” such as housing, employment, and race. Canadian primary health care organizations are increasingly looking for ways to systematically and routinely collect demographic and social needs data from patients to increase appropriate and responsive care by attending to the social determinants of health. The SPARK (screening for poverty and related determinants to improve knowledge of and links to local resources) tool is a standardized tool for use in primary health care settings that was developed, pilot-tested, refined, and validated in primary health care clinics across Canada. General Practitioners at the Deep End is a network of primary health care general practitioners working in the 100 most socioeconomically deprived areas in Scotland with the goal of connecting practitioners and advocating for better training, policies, and resources. Primary Health Care at the Deep End Canada or Soins primaires en milieux défavorisés Canada (Deep End Canada) was launched in June 2024 to offer guidance and resources to the growing number of primary health care teams interested in collecting and using demographic and social needs data.

Objective: Our primary objective is to spread the sustainable implementation of the SPARK tool to systematically and routinely collect and use demographic and social needs data to respond to the social determinants of health in 20 to 25 primary health care organizations across Canada through the creation of Deep End Canada.

Methods: Deep End Canada is a network of primary health care teams, including health professionals, researchers, and patient partners, working in areas with high rates of poverty. This project will use a multimethod developmental evaluation approach guided by the reach, effectiveness, adoption, implementation, and maintenance framework. Web-based surveys will capture the reach and adoption of demographic and social needs data collection, and network activities will be evaluated using qualitative analysis of focus groups, interviews, and meetings.

Results: The study was funded in February 2022. Recruitment to the network commenced in June 2024 and included 10 organizations as of submission of the manuscript. Web-based survey data collection commenced in September 2024. Implementation of the network will be assessed from June 2024 to December 2025, with expected findings available in June 2026 and published in the fall of 2026.

Conclusions: Efforts to systematically and routinely collect and use demographic and social needs data and address structural issues in Canadian primary health care have grown significantly in the last 10 years. This increased commitment involves using

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data to develop evidence-based interventions that can reduce health inequities and address local community needs at the individual, organizational, and policy levels. This study will demonstrate how the Deep End Canada network contributes to achieving those aims by fostering collaboration among practitioners to promote health equity and tackle the structural and social determinants of health.

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KEYWORDS

spread; scale; primary health care; innovation; developmental evaluation; demographic data; social needs; health equity

Introduction

Background

The social determinants of health are "the conditions in which people are born, grow, live, work and age" [1], such as income, educational level, housing, employment, social support, food security, race, and gender. These determinants are pivotal in shaping health across the life span and contribute to health inequities. There is a growing recognition that health care should address the social determinants of health to achieve better and more equitable health outcomes and meet health system goals such as the quadruple aim [2]. Major health organizations, including the World Health Organization [3], British Medical Association [4], Canadian Medical Association [5], College of Family Physicians of Canada [6], and Registered Nurses' Association of Ontario [7], have called on health systems to play a greater role in tackling the social determinants of health. However, a recent review of the literature on addressing social determinants in health care settings found that evidence supporting such interventions remains limited [8]. Addressing the social determinants of health directly and going "upstream" of illness and disease remains uncommon in health systems, including in Canada [9].

In Canada, primary health care is typically the first contact that a patient has with the health care system and offers a strong opportunity to address patients' social needs. Primary health care is community based; focused on long-term patient relationships; and comprehensive, with a focus on systematically addressing broader social, economic, environmental, and individual determinants of health [10]. Indeed, the last decade has seen a major advancement in the involvement of primary health care teams in direct interventions on the social determinants of health [6,11-13]. Initiatives encompass clinical tools, educational sessions, and clinical guidelines for medical trainees and physicians, as well as medical-legal partnerships addressing housing, employment issues, immigration, citizenship, and social benefits [14-18]. A central priority of primary health care is commitment to health equity, the ability of everyone to achieve their full health potential without disadvantage regardless of their social position [19].

Despite advances, primary health care organizations and primary care providers face barriers to identifying and addressing social needs, including a lack of time, a lack of expertise, limited knowledge of community resources, education and training focused on a biomedical understanding of health and disease, and funding directed to "downstream" and acute health concerns [20-22]. Moreover, there is a lack of individual-level patient data necessary to accurately screen patients' needs and develop targeted interventions [8,9,23]. Demographic and social needs data collected through routine and systematic screening paired with interventions to meet identified social needs could help further address the social determinants of health in primary health care [23-27]. Among health organizations that collect demographic and social needs data, many do not link the data to their electronic medical records (EMRs), and when they do, the quality is demonstrably variable [24,28]. Robust demographic and social needs data linked to EMRs could support quality improvement, the development of new care pathways at the organizational level, and planning and resource allocation at the system level [29,30]; bolster public health [22]; and advance research on health inequities [9,31,32].

While several screening tools to collect individual-level demographic and social needs data have been piloted [33-36], most have been tested in a specific setting, mainly in the United States, and little research has focused on how these tools can be effectively implemented, spread, and scaled in diverse primary health care practices. The SPARK (screening for poverty and related determinants to improve knowledge of and links to local resources) tool is a standardized tool for use in primary health care settings developed, pilot-tested, refined, and validated in primary health care clinics across Canada over the past decade building on health equity questions developed in 2012 [37-41]. The SPARK tool includes 17 questions that assess demographics (language, immigration status, Indigenous identity, race, disability status, gender identity, and sexual orientation) and social needs (educational level, income, food security, medication access, housing status, transportation, phone and internet access, cost of utilities, social isolation, and precarious employment) plus 2 optional questions (ethnicity and religion). The spread and scale of demographic and social needs data collection requires an organizational commitment to collecting and using such data to inform care provision that can respond to the social determinants of health and reduce health inequities.

General Practitioners at the Deep End is a network of primary health care general practitioners (GPs) working in the 100 most socioeconomically deprived populations in Scotland with the goal of facilitating connections between practitioners working in deprived regions [42]. It uses Julian Tudor-Hart's swimming pool analogy for the inverse care law to highlight how patients living in the most deprived regions (in the "deep end") often have the highest health care needs but the lowest availability and quality of health care resources [43]. Since its inception in

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2009, General Practitioners at the Deep End has grown beyond a peer support network to include 20 networks in 9 countries that advocate for better training, policies, and resources for their communities and patients. Deep End projects have propagated across the United Kingdom and the world, with networks in Ireland, Australia, and Japan, among other locations [44,45]. While some follow the original model of inviting practices from regions with the highest deprivation scores, others are open to all GPs with an interest in addressing health inequities. Deep End activities can include regular meetings for physician networking and support, policy and advocacy initiatives, and fellowship programs to support physicians working in areas of socioeconomic deprivation [44-46].

Primary Health Care at the Deep End Canada / Soins primaires en milieux défavorisés Canada (Deep End Canada) was launched in June 2024 (Figure 1), joining the Deep End international network [47]. The network builds on growing interest among Canadian primary health care in collecting and using demographic and social needs data to address social determinants of health by offering resources and guidance. Deep End Canada offers clinics over 25 resources to guide demographic and social needs data collection and use (eg, a copy of the SPARK tool in English and French and patient and staff informational materials), regular coaching meetings with Deep End Canada coordinators, and the opportunity to meet with other clinics across Canada. Deep End Canada's mission is to advocate for addressing health inequities in primary health care at the individual, organizational, and policy levels through the collection and use of demographic and social needs data and develop, share, and collaborate on clinic-level initiatives and projects. The network consists of primary health care teams, including health professionals, researchers, patient partners, and decision-makers, working with patients who may face social or economic disadvantages.

Figure 1. Primary Health Care at the Deep End Canada / Soins primaires en milieux défavorisés Canada logo.

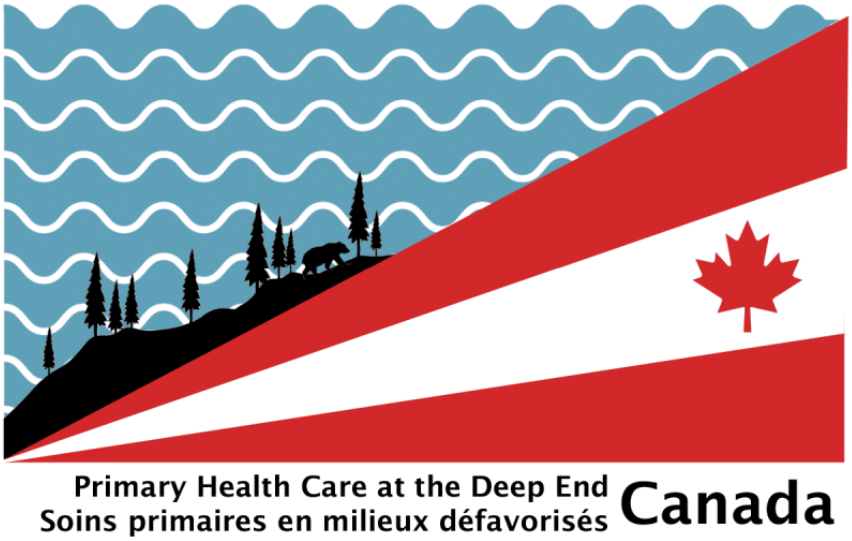

Objectives

By establishing Primary Health Care at the Deep End Canada, our primary objective is to assist 20 to 25 primary health care clinics or organizations across Canada attend to their patients' social determinants of health through the sustainable implementation of the SPARK tool to systematically and routinely collect and use demographic and social needs data. Our secondary objective is to facilitate community engagement in the collection and use of demographic and social needs data to identify and address inequities.

Research Questions

The research questions (RQs) for this study are as follows:

1. What is the reach, effectiveness, adoption, implementation, and maintenance of the SPARK tool and other demographic and social needs data collection efforts in primary health care settings across Canada?
2. What factors influence the use of social needs data to advance individual-, organizational-, and policy-level interventions addressing social determinants of health for clinics part of Deep End Canada?
3. How does Deep End Canada facilitate community and key actor engagement between and beyond members? How do these activities support the collection and use of demographic and social needs data?

Methods

Overview

Primary Health Care at the Deep End Canada is a network of primary health care teams, including health professionals, researchers, patient partners, and decision-makers, working in underresourced areas of Canada with patients who may face social or economic disadvantages [48]. Their central goal is the same: to advocate for addressing health inequities in primary health care at the individual, organizational, and policy levels and develop, inform, and share strategies that can support data collection, data use, and related local health equity initiatives. Deep End Canada members engage with the network in 3 ways. First, they attend quarterly network meetings to share opportunities for collaboration, challenges, and strategies related to health equity with other clinics across Canada. Second, they participate in regular implementation coaching sessions to

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support their use of the SPARK tool, analysis of demographic and social needs data, and the use of demographic and social needs data to develop health equity interventions. Third, they receive resources and materials to support demographic and social needs data collection in primary health care [37]. Network activities may include, for example, summarizing evidence of primary health care interventions to tackle social determinants (eg, environmental scans of best practices), supporting local spread and scale efforts (eg, helping clinics expand demographic and social needs data collection to other local sites and advocating for regional or provincial expansion), and responding to new opportunities or policies (eg, supporting demographic and social needs data collection integration into new EMR systems).

Overall Design and Approach

This project aims to gain a better understanding of what factors can support the development and maintenance of a network of primary health care clinics focused on the systematic and routine collection and use of demographic and social needs data, with an overarching aim of addressing patients' social determinants of health at the individual, clinic, organizational, community, and policy levels. This project will use a multimethod developmental evaluation approach guided by the reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) framework [49-53], as described in Table 1.

Table 1. Developmental evaluation guided by the reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) framework.

RE-AIM outcome [54,55]	Key pragmatic priorities to consider	Answers
Reach	• Who is intended to benefit and who actually participates or is exposed to the "project" or policy?	• Primary health care settings focused on tackling social determinants of health and patients with social needs
Effectiveness	• What is the most important benefit one is trying to achieve and what is the likelihood of negative outcomes?	• Adoption and implementation of routine and systematic collection and use of demographic and social needs data at the individual level and planning for use at the clinic level
Adoption	• Where is the project or policy applied? • Who applies it?	• Primary health care settings at the clinic or organizational level • Primary care providers, clerical staff, operations staff, clinic leadership, and quality improvement teams
Implementation	• How consistently is the project or policy delivered? • How will it be adapted? • How much will it cost? • Why will the results come about?	• Regular coalition meetings as determined by the coalition and demographic and social needs data collection as determined by the clinic • Web-based (eg, manual or software EMR[a] integration, EMR survey, or public URL survey) or on paper • Cost of implementation depends on the clinic setting and implementation strategy • Results will come about as per data collection outlined in this protocol
Maintenance	• When will the project become operational, how long will it be sustained (setting level), and how long are the results sustained (individual level)?	• June 2024 until June 2026 • Sustainment at the individual and setting level will vary by clinic due to local factors (eg, clinic size, number and availability of staff and primary care providers)

[a]EMR: electronic medical record.

Reach and Adoption: Pan-Canadian SPARK Survey (RQ 1)

The study team will use a combination of the SPARK reach and adoption survey and follow-up survey to learn about the reach and adoption of the SPARK tool and demographic and social needs data collection efforts across Canada. We will use a short electronic survey to collect background and contextual information from each primary health care clinic interested in using the SPARK tool or collecting demographic and social needs information (Multimedia Appendix 1). Information collected will include, for example, name and email address, location, type of organization, role, size of clinic or organization, familiarity with demographic and social needs questions, and intended or actual adoption of the SPARK tool. A follow-up survey at 6 months will include an assessment of perceptions and actions related to demographic and social needs data collection and participation in Deep End Canada after a 6-month period. The spread and scale of primary health care innovations has been previously evaluated using surveys at multiple time points [56]. Furthermore, clinics not already part of Deep End Canada may develop an interest in joining the network after they complete the survey. Draft copies of the 2 surveys are available in Multimedia Appendix 2.

Effectiveness, Implementation, and Maintenance: Deep End Canada Activities

The effectiveness, implementation, and maintenance components of the RE-AIM framework will be used to evaluate other potential Deep End Canada activities identified by members.

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Deep End Canada members will generate potential ideas for implementing and evaluating their local efforts to collect demographic and social needs data and use them to support care responsive to the social determinants of health, as well as other local, regional, provincial, or national efforts to advance health equity at the individual, organizational, and policy levels. These discussions will support the development of measures that Deep End Canada can apply to evaluate both the effectiveness, implementation, and maintenance of its network and the network's ability to support clinic activities. Furthermore, implementation and evaluation ideas will develop and grow alongside changes and growth in Deep End Canada membership, which may include clinics in different urban and rural areas, clinics focused on health care for different priority groups (eg, homelessness, addiction medicine, newcomers, and refugees), or Indigenous health clinics.

Demographic and social needs data collection will be one of several activities that Deep End Canada members may implement as part of their work on addressing social determinants of health. Many patients may not feel comfortable sharing personal demographic or social needs information or feel that it is relevant for their primary care providers. Deep End Canada facilitators will make relevant resources available to help make patients feel comfortable, including key messages for clerical staff and primary care providers to emphasize why the clinic is collecting demographic and social needs data, that the tool is voluntary, that responses are only visible to the health care team and protected by law like all health information, and that researchers will not be able to identify patients. As facilitators of Deep End Canada, we also have resources that emphasize the importance of community engagement and data governance to facilitate appropriate collection and use of data, especially if organizations plan to ask questions regarding Indigenous identity. Resources may be shared directly with clinics during or following coaching sessions or widely distributed to the network depending on interest and need.

Other activities of Deep End Canada could include system-level efforts to support demographic and social needs data sharing between organizations or collective policy advocacy for advancing health equity. For example, Deep End Canada members may choose to engage in initiatives such as creating a pan-Canadian set of demographic and social needs data; identify opportunities for collective policy advocacy; or facilitate deliberative dialogues with policymakers, patients, and other key stakeholders to identify system-level opportunities for advancing health equity.

Deep End Canada Evaluation: Meeting Minutes and Tracking Sheet (RQs 2 and 3)

As a starting point, the developmental evaluation of Deep End Canada activities will first involve analyzing quarterly meeting minutes using the RE-AIM framework to share back to all network members at Deep End Canada meetings and inform discussions about potential activities, lessons for other clinics, and ongoing challenges at specific clinics or for the entire network. Second, we will use a tracking sheet to evaluate engagement with prospective and current Deep End Canada members after implementation coaching sessions and email communications. This sheet will also help us understand the implementation and effectiveness of the network in helping clinics set and achieve goals related to demographic and social needs data collection and use and health equity interventions (drawing on quality improvement methodology such as cycles of planning, doing, checking, and acting).

Deep End Canada Evaluation: Focus Groups and Interviews (RQs 2 and 3)

Throughout the evaluation, we will engage Deep End Canada members to identify indicators of the effectiveness, implementation, and maintenance of their health equity activities, focus groups, or interviews. A draft copy of the focus group and interview guide is available in Multimedia Appendix 3. The study team will use focus groups and interviews with staff from various Deep End Canada member clinics to collect information on participants' involvement in data-driven local solutions (eg, demographic and social needs data collection), community and key actor engagement (eg, involvement with Deep End Canada members and local communities), and social action and advocacy (eg, support for pan-Canadian campaigns related to primary health care). Focus groups were chosen as they offer the opportunity for people who share similar experiences and identities (eg, as primary health care staff) to discuss their experiences and opinions and learn from each other in a supportive, nonjudgmental, and neutral setting. Focus groups and interviews will last 45 to 90 minutes.

Recruitment

Initial recruitment to Deep End Canada will involve self-selection of clinics that operate in underresourced areas of Canada with patients who may face social or economic disadvantages and are committed to tackling social issues to improve the health of their patients and communities. Survey participant recruitment will involve convenience sampling of staff at primary health care clinics in Canada who contact the authors for information about the SPARK tool or those who contact Deep End Canada or access the Deep End Canada website pages to download SPARK tool–specific implementation resources [57]. We are sharing information about the Deep End Canada website with representatives from primary health care teams who contact the coauthors about the SPARK tool given over a decade of published work on demographic and social needs data collection in primary health care [27,30,37-41], public health [22], and hospital settings [31,32]. We will use purposive sampling to contact clinics and organizations across Canada engaged in demographic and social needs data collection efforts either directly using publicly available contact information on their websites (or contact information provided when they contact us) or through relevant listserves and mailing lists (eg, the Canadian Institute for Health Information mailing list). In addition, clinics may be referred by other clinics involved (snowball sampling).

Sample Size Rationale

The total sample size is 250 organizations. For the SPARK reach and adoption survey, the sample size (n=200) is based on an estimate of how many organizations across Canada expressed interest in using the SPARK tool previously and those we

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anticipate would be interested in learning more about it. For the meeting minutes, tracking sheet, focus groups, and interviews, the sample size (n=50 participants) is based on data from 2 to 4 participants from each of the 13 Deep End Canada member organizations at the time of writing.

Inclusion and Exclusion Criteria

Survey participants will include staff from health clinics that indicate an interest in pursuing and supporting demographic and social needs data collection or health equity interventions in primary health care settings in Canada when contacting us. We will exclude participants who are under the age of 18 years.

The meeting minutes, tracking sheet, focus group, and interview participants will include Deep End Canada members at the time of recruitment (which involves meeting with the coordinating team and attending a network meeting at least once). At the time of writing, Deep End Canada has 13 member organizations representing over 25 primary health care clinics in 8 provinces (British Columbia, Alberta, Saskatchewan, Ontario, Quebec, Prince Edward Island, Nova Scotia, and Newfoundland and Labrador). Organizations include family health teams, university health centers, community health centers, primary care networks, community pharmacies, research teams, and clinical trial teams. Members include primary health care professionals, researchers, patient partners, and administrators supporting patients who may face social or economic disadvantages.

Analysis

We will calculate descriptive statistics (frequencies and percentages and means and SDs) to summarize clinic characteristics from the reach and adoption surveys, such as geographic representation, types of clinics represented, or types of professions represented. The initial survey and optional follow-up survey will be linked to examine changes in perceptions and actions related to demographic and social needs data collection over 6 to 12 months. Surveys will be designed so that identifying information about the clinic is kept separately from the responses; however, a code will be embedded in the surveys to allow researchers to link the responses for analyses. We will analyze the differences between respondents who participate in one or more Deep End Canada network meetings or coaching sessions and those who do not. We may also examine how level of engagement (eg, regularly attending network meetings and coaching sessions vs engaging with Deep End Canada a single time) impacts responses.

We will transcribe interviews and focus groups verbatim. We will apply content analysis to the qualitative data, including interviews, focus group discussions, survey responses, or meeting minutes [56]. Using an initial codebook informed by the RQs (eg, RE-AIM framework, use of social needs data, and community engagement), we will analyze transcripts deductively and inductively. We will iteratively refine this codebook using the RE-AIM framework and other relevant activities of Deep End Canada members (eg, experiences designing and implementing health equity interventions or engaging in advocacy).

As a developmental evaluation, combining qualitative and survey data will provide a richer understanding of implementation outcomes and an in-depth understanding of context for and barriers to and facilitators of the implementation and maintenance of the SPARK tool or initiatives to respond to social determinants of health in primary health care, including system-level advocacy. This approach will also enable us to better understand participants' perspectives of participating in a pan-Canadian network focused on health equity.

The sources of data collected in this study will help answer the overarching RQs and be combined to provide insights on the role of Deep End Canada in Canadian primary health care. First, survey data will allow us to understand the role of demographic and social needs data collection in building a foundation of health data and provide concrete examples of how clinics plan to or currently draw on such data when designing health equity interventions at the individual, clinic, organizational, or policy levels. Second, focus group and interview data will provide insights into how various activities broadly focused on reducing health inequities can be integrated and shared across a pan-Canadian network to support similar activities in other contexts. Finally, qualitative data, analyzed together with survey data, meeting minutes, and the tracking sheet as part of this overall study, will demonstrate how Deep End Canada serves as a basis not only for discussing specific activities such as demographic and social needs data collection and use but also for collaboration and mutual support across jurisdictions to identify and address system- and policy-level challenges within primary health care.

Advisory Group

Our advisory group will include 4 to 6 patient partners from multiple provinces who have experience receiving primary health care in Canada or were involved in various phases of the SPARK study and development of the SPARK tool. Their role will include, for example, providing input on Deep End Canada member activities, participating in quarterly meetings, reviewing evaluation feedback to clinics, reviewing proposed initiatives to respond to social determinants of health from a patient perspective, interpreting findings, and helping develop recommendations for advancing the mission of Deep End Canada. This could include discussing the design and wording of patient-facing materials and ensuring the clarity of the network's mission.

Ethical Considerations

We will obtain informed consent and provide the option to opt out of the study for all study participants. All interviews, focus groups, and surveys will be deidentified before being aggregated for analysis. No participants will be identifiable when the findings are published. Focus group and interview participants will be offered a CAD $30 (US $21.71) honorarium for their time. The first survey was approved by the Unity Health Toronto Research Ethics Board (REB) on July 2, 2024 (24-094). At the time of writing, a REB amendment is under review to include the other data collection activities described in this protocol in the REB approval (follow-up SPARK reach and adoption survey, Deep End Canada evaluation activities, and focus groups and interviews).

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Results

Recruitment to the network commenced in June 2024 and included 10 organizations as of submission of the manuscript. Data collection using a web-based survey commenced in September 2024. Implementation of the network will be assessed from June 2024 to December 2025, with expected findings available in June 2026 and published in the fall of 2026 (Figure 2).

Figure 2. Schematic of project workflow. SPARK: screening for poverty and related determinants to improve knowledge of and links to local resources.

Discussion

Anticipated Principal Findings

The anticipated findings of this study will include a cross-sectional view of the reach, effectiveness, adoption, implementation, and sustainability of the collection and use of demographic and social needs data across Canada (using the SPARK tool and other tools), highlighting the role of Deep End Canada in supporting and expanding such work to promote equitable health care. Other findings will include factors that influence the use of such data by members of Deep End Canada to advance individual-, organizational-, and policy-level interventions and community and key actor engagement to address social determinants of health.

Comparison With Previous Work

Previous research on the development of Deep End networks provide peer support to members and have established policy and advocacy initiatives, and fellowship programs to support GPs working in areas of socioeconomic deprivation [44,45]. However, no Deep End networks have made an explicit commitment to building the capacity of primary health care to systematically and routinely collect and use demographic and social needs information alongside other health equity interventions. Deep End Canada will help build such capacity while also facilitating other activities associated with Deep End networks internationally, such as supporting the primary health care workforce and promoting education, advocacy, and research [45,58].

Strengths and Limitations

The strength of this study is the use of an established international model for building collective identity and facilitating opportunities for social action in primary health care to improve patient care and health outcomes, especially for those experiencing poverty and who face social or economic disadvantages. This study will provide a realistic view of how a network of primary health care clinics committed to a common mission will facilitate the implementation and sustainability of health equity interventions, including the collection and use of demographic and social needs data. The focus of our study, in addition to describing an effort to expand demographic and social needs data collection across Canadian primary health care, is to generate “more uncertain answers to broader, more complex questions” [59]—we hope to provide a space for members to collaboratively discuss topics and develop interventions related to health equity that align with their interests and needs while acknowledging challenges associated with supporting patients experiencing poverty-related hardships and providing mutual support [43].

Limitations of this study include potential discrepancies between the goals of individual members and their vision for the network (eg, discussing ideas to address the social determinants of health of their patients) compared to the aims of the developmental evaluation (eg, reach of the SPARK tool and understanding the influence of the network on health equity interventions). For example, if members feel an imbalance where they are unable to address their interests or gain something from the network due to a greater emphasis on a particular topic or on collecting

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data to inform the evaluation (eg, structuring meeting agendas to discuss the SPARK tool), they may opt to leave the network and seek support elsewhere. Such challenges may preclude a full understanding of the network's potential influence on members who may have joined for reasons other than collecting and using demographic and social needs data. Second, our approach to recruitment (ie, self-selection) may limit the involvement of clinics in rural settings or those with limited capacity to participate in activities that do not involve addressing the day-to-day clinical needs of patients or that do not know about the network as we primarily engage clinics actively seeking support.

Future Directions

Future directions for Deep End Canada beyond helping build a foundation of demographic and social needs data from which to address social determinants of health across Canadian primary health care should include initiatives that address national issues in primary health care. Aligned with the workforce, education, advocacy, and research framework and adopted by several Deep End networks internationally [43,45,48], one priority that Deep End Canada could support is the national adoption of the OurCare standard, which represents "the collective aspirations of all people in Canada for a more sustainable, high-quality and equitable" primary health care system [60,61]. Future research could involve studying the factors that facilitate the implementation of the standard and how implementing it potentially reduces burnout in the primary health care workforce. Other future directions could include advocating for policies that reflect the standard and address issues in primary care and educational activities to share lessons from other networks internationally to support Deep End Canada and related initiatives [62,63]. Deep End Canada will continue to facilitate meetings for members to shape the network's direction, with a focus on reducing health inequities [43].

Policy Implications

Policy implications include the potential for Deep End Canada to provide ongoing mutual support for primary health care professionals supporting patients experiencing hardships related to poverty, with potential financial or human resources support from professional bodies such as the College of Family Physicians of Canada or the Canadian Medical Association. Evidence generated from this study could also lead policymakers to seek opportunities for encouraging the systematic and routine collection of demographic and social needs data, as was done for public health units in Ontario as part of the provincial COVID-19 response [22]. Finally, evidence generated from this study could offer insights into ways to conduct research, education, and patient and community engagement with primary health care clinics that are closely supporting patients experiencing poverty and other social needs in other contexts.

Conclusions

Efforts to implement systematic and routine demographic and social needs data collection and use and address other structural issues in Canadian primary health care have grown significantly in the last 10 years. Researchers developed the Primary Health Care at the Deep End Canada national network of primary health care teams to not only collect but also use such data to develop evidence-based health equity interventions that aim to reduce health inequity and address needs within the local community at the individual, organizational, and policy levels. This study will demonstrate how the Deep End Canada network contributes to achieving those aims, drawing on national survey and qualitative data. Deep End Canada is based on an established international model born of the collective organizing of GPs in Scotland to build social connections to offer mutual support and collaborate to systematically address the health impacts of poverty on their patients and communities. It is in this spirit that the Deep End Canada network seeks to foster Canada-wide collaboration among multidisciplinary practitioners to promote health equity and tackle the structural and social determinants of health.

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Data Availability

The datasets generated or analyzed during this study (where not already included in the published article with the study findings) will be available from the corresponding author on reasonable request.

Authors' Contributions

JJO, MAS, IF, LK, and ADP contributed to study conception and design. JJO, IF, MAS, and ESA contributed to data collection and data analysis. JJO, MAS, and IF drafted the manuscript. All authors reviewed, revised, and approved the final version of the manuscript.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
The SPARK (screening for poverty and related determinants to improve knowledge of and links to local resources) tool.
[PDF File (Adobe PDF File), 1751 KB - resprot_v14i1e75732_app1.pdf]

Multimedia Appendix 2
SPARK reach and adoption survey 1 and 2.
[PDF File (Adobe PDF File), 933 KB - resprot_v14i1e75732_app2.pdf]

Multimedia Appendix 3
Draft focus group and interview guide.
[PDF File (Adobe PDF File), 587 KB - resprot_v14i1e75732_app3.pdf]

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Abbreviations

EMR: electronic medical record
GP: general practitioner
RE-AIM: reach, effectiveness, adoption, implementation, and maintenance
REB: Research Ethics Board
RQ: research question
SPARK: screening for poverty and related determinants to improve knowledge of and links to local resources

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Protocol

Evaluating the Effectiveness of a Family-Based Lifestyle Intervention for Managing Childhood Overweight: Protocol for a Randomized Controlled Trial

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Abstract

Background: Family-focused interventions promoting lifestyle behaviors such as physical activity and healthy eating can be effective strategies for obesity management in children. To maximize public health impact, there is an urgent need to develop innovative solutions to improve the scalability of childhood obesity management interventions. Stand-alone web-based interventions are easily administered but may be hindered by low participant engagement and limited support. A blended intervention that includes both facilitated web-based group sessions and self-guided resources may enhance engagement, thereby optimizing improvements in children's health outcomes. However, the long-term effectiveness of stand-alone versus blended web-based interventions to manage childhood obesity has not yet been evaluated.

Objective: The primary objective of this randomized controlled trial is to evaluate the long-term effectiveness of a blended, web-based, family-focused healthy living program (Family Healthy Living Program [FHLP]) compared to an active control (self-guided web-based educational resources) in lowering BMI *z* scores in children with overweight or obesity over 12 months. The secondary objective is to examine intervention effects on children's physical activity, dietary behaviors, and health-related quality of life as well as parental self-efficacy and motivation to support children's lifestyle behaviors.

Methods: This single-blind 2×4 trial aims to recruit 278 parent-child dyads across Canada to be randomly assigned to the FHLP intervention group or an active control group (1:1 ratio). The 10 weeks of FHLP activities have been designed based on the multiprocess action control framework to support children and parents in learning behavioral change skills that will enable them to improve their healthy lifestyle behaviors, and the FHLP delivery has been piloted previously. Families in the intervention group will receive weekly web-based synchronous group sessions and access to additional resources and suggested activities. Families in the control group will receive access to 10 weeks of self-guided web-based educational resources only. Outcomes,

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including child's height and weight, daily physical activity, dietary behaviors, health-related quality of life, and parental support, will be measured via questionnaire at 4 assessment time points over 1 year (ie, baseline, 10 wk, 6 mo, and 12 mo). Intervention engagement and attrition will also be recorded. Multiple linear regression models will be used to examine the effectiveness of the FHLP intervention compared to stand-alone web resources only.

Results: This study was funded in 2020, with 270 participants enrolled between January 2021 and May 2024. The 12-month data collection period ended in June 2025 and data analysis is currently underway. Study results are expected to be published in winter 2025. Results will be disseminated via conference presentations, peer-reviewed publications, and other media channels.

Conclusions: The blended web-based FHLP intervention has the potential to become a scalable solution for the prevention of obesity and related health conditions.

Trial Registration: ClinicalTrials.gov NCT06777888; https://www.clinicaltrials.gov/study/NCT06777888

International Registered Report Identifier (IRRID): DERR1-10.2196/76837

(JMIR Res Protoc 2025;14:e76837) doi:10.2196/76837

KEYWORDS

childhood obesity; web-based intervention; family-based intervention; health behavior change; obesity and overweight; physical activity; child behavior; parental support of child behavior

Introduction

Background and Rationale

Childhood obesity is a prevalent pediatric health issue linked to a range of physical and psychological problems, including type 2 diabetes, hypertension, sleep apnea, and low self-esteem, all of which contribute to a diminished quality of life during childhood [1-3]. In Canada, more than 30% of children are classified as overweight, defined based on BMI ≥85th percentile for their age and sex [1]. Without effective interventions, these children have a high risk of remaining overweight into adolescence and adulthood [4]. As a result, fostering healthy eating habits and encouraging physical activity during childhood has become a central focus for policymakers and public health initiatives at the global, national, and provincial levels [5-7].

Family-focused behavioral obesity management interventions that include both parents and children as corecipients have been shown to be an effective approach for promoting healthy lifestyles and achieving weight control in children [8,9], particularly when the intervention content is grounded in behavioral theory [10]. Several randomized controlled trials have demonstrated that family-focused behavioral interventions delivered in person can be effective strategies in improving children's lifestyle behaviors and reducing BMI *z* scores [11-13]. However, to enhance their public health impact, such interventions must be delivered through scalable and accessible methods.

Leveraging the internet to deliver these interventions can be an innovative strategy to enhance program accessibility and scalability, making it easier for families to participate regardless of their geographic location [14]. Previous studies have shown that internet-based programs can be effective in improving lifestyle behaviors and clinical outcomes, including BMI [15,16]. However, a limitation often observed in self-guided, asynchronous web-based interventions (with no human support) is reduced engagement over time [17]. By contrast, synchronous web-based sessions (delivered using video chat) may provide distinct advantages, such as fostering engagement through real-time interaction, personalized support, and opportunities for families to connect and share experiences. These sessions retain the scalability and flexibility of internet-based interventions while offering live interaction, which may enhance motivation, promote accountability, and improve adherence to the program [18]. This could make synchronous delivery a powerful and adaptable option for managing childhood obesity effectively.

Drawing on the evidence supporting the effectiveness of family-based interventions and use of the internet for program delivery, the research team partnered with stakeholders (the Childhood Healthy Living Foundation and the British Columbia Ministry of Health) to develop a 10-week early intervention lifestyle management program (Family Healthy Living Program [FHLP]) that combines web-based resources with weekly live, interactive group sessions led by trained facilitators. This intervention targets families with children aged 8 to 12 years who are above the healthy weight trajectory (BMI ≥85th percentile for age and sex). Interventions aimed at this age group are particularly impactful, as prepubertal children have a greater potential to return to a healthy growth pattern [19,20]. Extensive stakeholder consultation was conducted with more than 100 health care professionals to develop an evidence-based 10-week family-focused intervention involving both parent- and child-specific interactive activities. The FHLP intervention was designed to align with existing best practices in the clinical and public health setting, complement an existing childhood obesity management clinical intervention in British Columbia, and meet the needs of diverse families and communities [21]. The FHLP aims to support children who are off the healthy weight trajectory by managing overweight and preventing progression to obesity through targeting 5 behavioral domains: physical activity, healthy eating, sleep, media use, and mental well-being.

The FHLP was designed using the multiprocess action control (M-PAC) framework, a meta-theoretical behavior change framework emphasizing a social cognition approach to intention formation (reflective processes), the adoption of action control through self-regulation (regulatory processes), and the action control maintenance phase once a behavior becomes habitual and self-identified (reflexive processes) [22,23]. One advantage

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of the M-PAC framework is its ability to address the intention-behavior gap, which poses a particular challenge for childhood obesity interventions because almost all families enter these programs already intending to adopt a healthy lifestyle but often struggle to translate this intention into sustained behavior change [22,24,25]. Addressing this intention-behavior gap can therefore improve the effectiveness of physical activity interventions [23,26]. Thus, the FHLP curriculum begins with intention formation (physical and mental health benefits of physical activity as well as perceived capability), then moves into action control adoption (restructuring the physical and social environment to create opportunities for physical activity, goals and planning, and feedback and monitoring), and concludes with action control maintenance (habit formation and identity formation).

The FHLP intervention was initially piloted in 2018 [21] and delivered in person at community sites across British Columbia. The content has since been adapted for delivery as a blended web-based intervention, and previous evaluation showed a positive impact on children's lifestyle behaviors and parental support in the short term [27,28]. However, the FHLP intervention has yet to be evaluated in a randomized controlled trial, and the long-term effectiveness of the intervention and its impact on children's anthropometry have not been examined.

Objectives

The primary objective of this study is to evaluate the effectiveness of the synchronous web-based FHLP intervention compared to an active control group in lowering BMI *z* scores in children (aged 8-12 y) with BMI ≥85th percentile for age and sex over a 12-month period. The secondary objectives include evaluation of the effectiveness of FHLP compared to the active control in improving lifestyle behaviors and health-related quality of life in children (aged 8-12 y) with BMI ≥85th percentile for age and sex, as well as parental self-efficacy and motivation to support their child's healthy living behaviors. The trial hypotheses are that the FHLP intervention will result in significantly greater reduction in BMI *z* scores than the active control and that intervention participants will show greater improvements across all domains than those in the control group.

Methods

Trial Design

This study is a single-blind randomized controlled trial (ClinicalTrials.gov NCT06777888) with a 2×4 design (Figure 1). Participating households will be randomly assigned in a 1:1 ratio to 2 groups: FHLP intervention and control. Data will be collected at 4 assessment time points: baseline (wk 0), after the intervention (wk 10), 6-month follow-up (wk 26), and 12-month follow-up (wk 52; Figure 1). The intervention will be delivered via video chat in 3 regions across Canada (British Columbia, the prairie provinces, and Ontario), with the central site located at the University of Victoria in British Columbia.

Figure 1. Overview of the study design and assessment timeline. FHLP: Family Healthy Living Program.

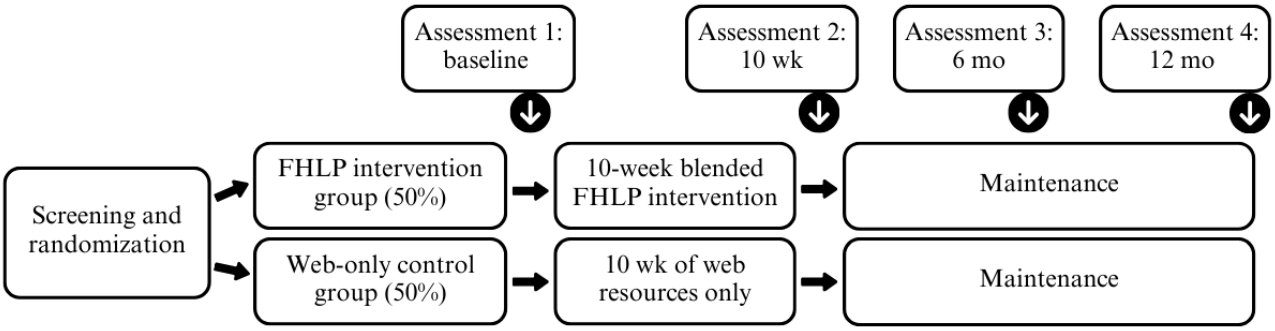

Trial preparation, implementation, and evaluation will adhere to the CONSORT (Consolidated Standards of Reporting Trials) criteria [29], and the trial protocol will adhere to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [30]. Data collection began in January 2021 and was completed in June 2025.

Eligibility Criteria

Child participants must be aged 8 to 12 years, have BMI ≥85th percentile for age and sex, and have at least 1 primary caregiver (parent or guardian) who agrees to participate in the study along with the child. Exclusion criteria will include the inability to communicate (speak, read, and write) in English and any conditions that prevent children from being physically active.

Recruitment

Participants will be recruited from 3 regions across Canada (British Columbia, the prairie provinces, and Ontario) using advertising via social media; local community newsletters; posters and rack cards within communities; and direct mailings to physician offices, health clinics, and allied health professionals. Interested parent-child dyads will be screened for eligibility by a trained research assistant at the central site (University of Victoria in British Columbia).

During the consent process, participants will be made aware of the differences between the 2 groups and informed that they will be randomly assigned to either the full intervention or the web resources only. Participants from both groups will be offered technical support from the research coordinator if needed for viewing web-based content, using the Fitbit Inspire tracker, or accessing the web-based questionnaires.

Assignment of Interventions and Blinding

Participating households will be randomly assigned to the FHLP intervention or the active control group. To reduce selection

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bias, the centralized randomization process will be managed by a research coordinator not directly involved with intervention delivery. The research coordinator will use computer-generated random numbers to assign the participants to either the intervention or control group. Participants will not be stratified because the population is assumed to be inherently homogeneous with respect to location due to the web-based nature of the program delivery. After randomization, data will be collected electronically via REDCap (Research Electronic Data Capture; Vanderbilt University) automated invitations to reduce response bias. Other research team members, including the principal investigator, coinvestigators, and data analysts, will be blinded to group assignment to minimize detection bias and ensure impartiality in decisions regarding trial activities.

Participant Timeline and Data Collection

The intervention period will be 10 weeks; the full assessment duration will be 12 months. Web-based questionnaire assessments will be completed at baseline and at 10-week, 6-month, and 12-month intervals after randomization (Figure 1). The assessments will include self-reported height and weight measurements and 7 days of step counts for each child as measured by Fitbit Inspire activity trackers. Questionnaire data will be collected and managed using SurveyMonkey and REDCap tools hosted at the University of Victoria. REDCap is a secure, web-based software platform designed to support data capture for research studies [31,32]. Survey responses will be stored on a secure network drive at the University of Victoria. Participants may choose to discontinue their participation at any point; data completion will be encouraged by multiple personalized email reminders and compensation at each assessment time point.

Sample Size

The parameters used for sample size calculation are based on the results of a published randomized controlled trial evaluating the effectiveness of a family-based intervention in reducing BMI *z* scores compared to control [33]. The required sample size was estimated at 232 children, using a 2-arm, parallel-group design with 80% power. On the basis of previous research [17,33], the attrition (loss at follow-up) is expected to be similar between the groups (20%). In sum, the trial aimed to recruit a study population of 278 participants, which accounts for an attrition rate of 20%. In practice, 270 participants were successfully enrolled.

Intervention

The FHLP intervention aims to target children who are off the healthy weight trajectory, with the goal of managing overweight and preventing progression to obesity. FHLP curriculum activities have been designed to support children and parents in learning behavioral change skills that will enable them to improve their health-related lifestyle behaviors. The details of the intervention content have been previously published [21]. Families attend weekly 2-hour web-based healthy living group sessions comprising family-based and parent-only components. Family-based components consist of interactive lessons and active games to keep children engaged in learning and enhance the reflexive processes that lead to habit formation. For the final 30 minutes of each session, parent-only components focus on food- and physical activity–related practices and strategies for improving the home environment.

The FHLP intervention will be delivered by a team of 2 facilitators with backgrounds in nutrition or physical education. These individuals will receive training from the centralized research team (based at the University of Victoria), including attending FHLP sessions delivered in British Columbia via video chat by the Childhood Healthy Living Foundation. The facilitators will be participants' main point of contact during the 10-week intervention and will call each enrolled family (via telephone or video chat) individually before the first group session to orient them to the program. They will send weekly email reminders for group sessions and reach out to participants following absences.

During the 10-week intervention, the facilitators will deliver 1 individual orientation call and 9 weekly group sessions over Zoom (Zoom Video Communications, Inc). Weekly group sessions will follow the FHLP curriculum with modules on healthy eating, physical activity, behavior change skills, mental health, parenting practices, sleep routines, and media use. Participants will be provided with a physical kit containing hard-copy binders of the session handouts along with materials to use during session activities (eg, jump ropes, water bottles, juggling scarves, and hacky sacks). Throughout all sessions, the facilitators will accentuate behavioral change skills (cognitive and behavioral regulation processes) such as goal setting and monitoring. One group session will include a "healthy eating Q&A" led by a registered dietitian in addition to the facilitators; participants will also have the option to attend up to 3 web-based live cooking classes led by a registered dietitian and child assistant.

In addition to the facilitated weekly sessions and cooking classes, participants in the intervention group will have access to a self-guided web-based family portal offering additional resources and information, healthy recipes, articles for parents, videos, and suggested healthy eating and physical activities. The portal will also serve as a repository of materials covered in each session, maximizing flexibility in terms of participants interacting with intervention content.

Active Control Group

It is an ethical imperative for long-term trials of health promotion interventions to ensure that the control group also receives essential information, which in this case would be education about childhood obesity management. To match the weekly intervention delivery frequency, the active control group will be given access to a similar secure portal where they can view weekly educational content aligned with the FHLP topics. This information is based on the FHLP curriculum and relevant information and resources from Canadian public health agencies (eg, Canada's Guide to Healthy Living, Canada's Food Guide, and Canada's Physical Activity Guide). These materials are guideline based, user-friendly, and visually appealing; in addition, they include child-specific content.

At baseline, a member of the research team will meet with each control participant for a 10- to 15-minute video meeting to orient

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parents to the portal and ensure that they have sufficient internet literacy to access the resources. However, the control group will not receive other personal contact, such as the FHLP facilitated group sessions, physical kits, web-based cooking classes and Q&A sessions, regular check-ins, or email reminders to access the resources. All families in both study groups will maintain the same delivery schedule (10 weeks in total; Figure 1).

Primary Outcome

Each child's BMI *z* score will be calculated based on the World Health Organization criteria [34]. Height and weight will be self-reported at each time point via questionnaire, with parents provided with instructions to accurately measure their child's height and weight at home [35].

Secondary Outcomes

Child Physical Activity Behaviors

Changes in physical activity will be measured using accelerometry via Fitbit Inspire wrist-worn activity trackers. Seven consecutive days of daily step counts will be measured at each assessment time point. Changes in physical activity predilection and adequacy as well as perceived intrinsic motivation and competence in physical activity will be measured using the motivation and confidence subscale of the Canadian Assessment of Physical Literacy-2 [36]. Physical activity self-report will be measured using the Physical Activity Questionnaire for Older Children [37] and the Canadian Assessment of Physical Literacy-2 [36]. Changes in physical activity confidence, sedentary behavior, and family support for physical activity will be assessed using the Patient-Centered Assessment and Counseling for Exercise Plus Nutrition adolescent psychosocial measures [38]. Physical activity and screen time self-efficacy will be measured using the Family Life, Activity, Sun, Health, and Eating (FLASHE) questionnaire [39].

Child Dietary Behaviors

Changes in dietary behavior will be assessed using the 7-day recall questionnaire retrieved from the Behavioral Risk Factor Surveillance System survey questionnaire [40]. Healthy eating outcome expectations will be assessed using the Power Play! survey [41]. Dietary behavior self-efficacy will be assessed using the Patient-Centered Assessment and Counseling for Exercise Plus Nutrition adolescent psychosocial measures [38]. Healthy eating motivation will be assessed using the FLASHE and modified child nutrition questionnaires [39,42], and perceived cooking skills will be assessed using the Cooking with Kids questionnaire [43].

Child Mental Well-Being and Quality of Life

Changes in a child's self-reported self-esteem, gratitude, and self-compassion will be measured using the self-esteem measure from Project EAT [44], the Gratitude Adjective Checklist [45], and the Self-Compassion Scale for Children [46], respectively. Children's self-reported sleep quantity will be measured using the FLASHE questionnaire [39]. Changes in a child's health-related quality of life will be assessed by parents (proxy report) using the Pediatric Quality of Life Inventory [47].

Parent Support for Healthy Family Lifestyle Environment

Parents will complete a questionnaire assessing changes in parental support, habit, role identity, and behavioral regulation in supporting their child's physical activity and healthy eating practices using the Parent Support of Child Physical Activity and Eating Behaviors questionnaire [48], the Exercise Identity Scale [49], the Activity Support Scale for Multiple Groups [50], and the Perceived Behavioral Control Over Child Physical Activity Support Scale [51]. Changes in parental feeding practices and food preparation self-efficacy will be assessed using the FLASHE-EAT survey [52]. The structure of the home food environment and parents' habits and dietary behaviors will be assessed using the Fruit and Vegetable At Home Survey for Parents [53]. Family eating habits and family physical activity habits will be measured using the Self-Report Habit Index [54].

Intervention Engagement and Attrition

For the control group, engagement with web content will be assessed based on the number of portal log-ins, the percentage of content accessed, and time spent viewing pages. For the FHLP intervention group, engagement will be assessed based on the number of Zoom-based group sessions attended as well as portal use (log-ins, the percentage of content accessed, and time spent viewing pages). Attrition will be recorded when a family withdraws from the study.

Data Analysis

Overview

All analyses will be intention to treat and will include all participants with available data. Patterns of missing data in the study groups will be examined, and multiple imputations will be applied to address missing data if data are missing at random. Generalized linear mixed models will be used to compare the effectiveness of the 2 treatments in improving the primary outcome, BMI *z* score, over time. The models will include fixed effects for treatment group, time, and group×time interaction; in addition, they will adjust for baseline BMI *z* score and child's sex. A random intercept will be included to account for within-participant correlations across repeated measures. Similar to the primary outcome analysis, generalized linear mixed models will be used to examine changes in secondary outcomes over time. Models will adjust for the baseline value of the outcome, child's sex, and parent's relationship to the child; in addition, a random intercept will be included to account for repeated measures.

Previous research has shown that parental involvement in child interventions can differ in ways that affect behavioral and weight-related outcomes [55]. Including this variable makes it possible to control for these potential sources of variability in the generalized linear mixed models.

In line with the sex- and gender-based analysis framework of the Canadian Institutes of Health Research [56], which encourages the thoughtful integration of sex and gender into health research, we have taken steps to reflect sex and gender considerations in our analysis plan. Specifically, we will adjust for child sex assigned at birth where biological differences may

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be relevant to health outcomes (eg, BMI trajectories). In the exploratory analysis, descriptive analyses will be conducted to explore whether intervention effectiveness differed between children's gender or sex in the treatment group.

Engagement metrics will primarily be examined in subgroup and dose-response analyses. However, engagement may play a role in treatment effectiveness. Therefore, its potential inclusion as a covariate in secondary models will be explored. These exploratory analyses will help clarify the mechanisms underlying intervention impact.

Subgroup Analyses

Analyses will be performed to (1) describe intervention engagement and attrition to explore potential differences by parental income and education, study site, and ethnicity; (2) conduct descriptive analyses to explore whether intervention effectiveness differed between children's gender or sex in the treatment group; and (3) evaluate the dose-response relationship in the intervention group and improvements in children's health-related outcomes at 10 weeks, 6 months, and 12 months. Intervention dose will be defined by level of intervention engagement.

Data Safety Monitoring

The University of Victoria Human Research Ethics Board considers this trial to be a minimal-risk behavioral intervention; therefore, a data safety monitoring committee will not be established.

Ethical Considerations

Ethics Approval

This study has been approved by the BC Harmonized Ethics Platform (H20-00759).

Informed Consent and Assent

During the screening process, a research assistant will speak with parents and caregivers by telephone to inform potential participants about the trial. The research assistant will explain that a consent form will be provided along with the first set of research questionnaires. All participants will be provided with the research team's contact information and will be encouraged to reach out if they have any questions or concerns after reading through the consent form.

Parent consent and child assent will be obtained electronically through the REDCap survey delivery system (refer to Multimedia Appendix 1 for the study consent form). To document ongoing consent, participants will be required to review and sign a copy of the consent form before accessing the parent and child surveys at each assessment time point (ie, baseline, 10 wk, 6 mo, and 12 mo). Participants may choose to discontinue their involvement at any time.

Compensation Details

Participants will receive grocery cards valued at CAD $25 (approximately US $18) for completing all questionnaires at each assessment point, for a total of CAD $100 (approximately US $72) incentive value over the study duration.

Harms or Risks to the Safety of Participants Involved in the Trial

The FHLP intervention is designed as a lifestyle behavior intervention. Participants will be exposed only to activities and information that are already readily available. The University of Victoria Research Ethics Board considers this trial minimal risk because it involves potential benefits for participants, with risks of harm that do not exceed those encountered in daily life.

Potential risks include emotional discomfort for children, such as stress or embarrassment related to research participation, particularly during weight measurement. To mitigate this, the research team will normalize the measurement as a "healthy growth check." Research team members will also complete Balanced View BC training on minimizing weight bias and using sensitive language when discussing weight and measurements associated with weight and lifestyle behaviors [57]. In addition, research team members will receive training on scope of practice and appropriate referral procedures when issues are raised that fall outside the scope of practice of the FHLP (eg, signs of disordered eating or serious physical health concerns). Participants with such concerns will be encouraged to contact clinical health professionals.

To ensure that participants can safely participate in the physical activity component of the program, each parent or guardian will complete the Canadian Society for Exercise Physiology Get Active Questionnaire at enrollment. This is an evidence-based self-administered tool that will guide each participant's caregiver to make an informed decision about the appropriateness of increasing their child's physical activity [58].

Privacy and Confidentiality

Data collected will be deidentified for program evaluation, with participant names replaced by study ID numbers. Participants' confidentiality and the confidentiality of the data will be protected by having no participant names on any of the data during analysis. Electronic files will be stored using participants' unique ID numbers (ie, study ID) on a secure network drive at the University of Victoria that is accessible only to the principal investigator and research staff. Participant data will be destroyed 5 years after the final study publication.

Results

This study was funded in January 2020, and recruitment began in January 2021. A total of 270 participants were enrolled. Data collection was completed in June 2025 and analysis is currently underway. Results are expected to be published in winter 2025.

Discussion

Anticipated Findings

This study aims to evaluate the effectiveness of the FHLP intervention compared to an active control group in improving BMI *z* scores and related health outcomes in children aged 8 to 12 years. On the basis of the study objectives, it is hypothesized that children in the FHLP intervention group will show greater reductions in BMI *z* scores than those in the control group over the 12-month period. In addition, improvements in secondary

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outcomes are anticipated, including healthier lifestyle behaviors, enhanced quality of life for children, and increased parental self-efficacy and motivation to support their child's healthy living. The blended delivery model, which combines self-guided resources with web-based synchronous sessions, is likely to foster greater engagement and adherence, promoting sustainable behavior changes.

Comparison to Previous Work

The FHLP intervention was designed based on the M-PAC framework for supporting behavior change through reflective, regulatory, and reflexive processes. Several previous randomized controlled trials, including studies focusing on families with children in the target age range, have demonstrated that the M-PAC framework can be applied to promote a healthy lifestyle in community-based interventions [26,59-62].

Compared to existing family-based lifestyle interventions, the FHLP curriculum addresses a key gap by targeting 5 different behavioral domains to support healthy living (ie, physical activity, healthy eating, sleep, media use, and mental well-being). This has been identified as a strength because the majority of family-based childhood obesity interventions address only activity and nutrition [63].

Previous studies have found that eHealth behavior interventions can be effective for childhood obesity management, with technology-based delivery increasing intervention reach and accessibility [64,65]. However, participant engagement has been noted as a challenge for remote delivery [66]. This trial proposes engagement strategies that include weekly live sessions with a group facilitator, branded kit materials, frequent communication with participants, and personal check-ins from delivery staff to mitigate retention challenges.

This trial is one of the first to examine the long-term impact of blended web-based family-based behavioral interventions for childhood obesity. A recent randomized controlled trial of a 10-week web-based lifestyle intervention found it effective in improving short-term health outcomes for children with overweight or obesity, including decreasing BMI *z* scores and increasing quality of life, diet, and daily physical activity immediately after the intervention; however, long-term effectiveness has yet to be investigated [67].

Strengths and Limitations

The study has several strengths. First, the innovative blended intervention design combines the scalability and flexibility of internet-based programs with the benefits of real-time support through web-based synchronous sessions. This hybrid approach has the potential to address common challenges in traditional in-person or self-guided web-based programs, such as limited accessibility and engagement, respectively. Second, the program was developed in collaboration with community stakeholders and informed by feedback from pilot participants, ensuring its relevance and practical applicability. Third, the intervention is grounded in the M-PAC framework, a robust theoretical model that emphasizes intention formation, action control, and maintenance, supporting sustained behavior change. Fourth, the rigorous trial design, which follows best practices for real-world randomized controlled trials [68,69], including pediatric-specific recommendations applied to reduce the risk of bias [70], enhances the validity and reliability of the findings. Finally, the study incorporates comprehensive outcome measures, providing a holistic understanding of the program's impact on both children and parents.

However, this study also has limitations. The reliance on parent-reported home measurement data for height, weight, and dietary behaviors may introduce error due to variation between different scales. Protocols for parent-report measure for child height and weight were adopted due to COVID-19–related restrictions at the start of the trial. Previous research has shown that parent measurements of height and weight can be effective in classifying child weight status in the absence of professional measurements [71] and that providing instructional guides may improve accuracy [72]. Therefore, participating parents will be instructed to measure children as accurately as possible and provided with a link to a US Centers for Disease Control and Prevention guide titled "Measuring Children's Height and Weight" [35].

Despite these limitations, this study has the potential to significantly advance the field of childhood obesity management by providing evidence on the effectiveness of an internet-based intervention. The results will offer valuable insights into how web-based synchronous sessions can enhance engagement, support behavior change, and improve health outcomes. These findings will inform policymakers, health care providers, and community organizations on the development and implementation of scalable, flexible, and effective interventions for managing childhood obesity.

Dissemination Plan

This study is founded on the principles of integrated knowledge translation with an actively engaged academic, community, and public health partnership guiding the development of the intervention, the research and evaluation questions, the interpretation of results, and dissemination [73].

It is anticipated that the group-level deidentified results of this trial will be shared through conference presentations, reports to community stakeholders, and academic publications. A range of knowledge translation tools will also be developed for the general public, including dissemination of the resulting publications and general study information via web-based platforms, including the University of Victoria Digital Health Lab website, and official social media channels.

Future Directions

The research team is already working closely with a community partner (the Childhood Healthy Living Foundation) and will continue to collaborate with knowledge users to ensure that research outcomes are responsive to shifting community and knowledge translation needs. Trial findings regarding the content and methodology of stand-alone and blended web-based interventions will be used to support evidence-informed policy decisions in future.

Conclusions

The FHLP represents an innovative, scalable, and family-focused intervention designed to address the growing

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public health challenge of childhood obesity. Leveraging feedback from community stakeholders and pilot participants has allowed tailoring of the FHLP to meet the diverse needs of families while maintaining flexibility and accessibility. By integrating self-guided resources with web-based synchronous group sessions, the FHLP aims to enhance engagement, promote sustainable behavior changes, and improve BMI *z* scores and related health outcomes in children aged 8 to 12 years.

This trial will provide critical insights into the relative effectiveness of blended versus stand-alone web-based interventions, addressing a key gap in current literature. The findings from this study may inform future program development and implementation strategies, offering a practical, evidence-based solution to support families in adopting healthier lifestyles. Ultimately, the FHLP has the potential to make a meaningful contribution to public health efforts aimed at reducing childhood obesity and improving quality of life for children and their families.

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Data Availability

Anonymized group-level data as well as the statistical analysis plan and data dictionary will be available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization: SL (lead), PJN (equal), KS (supporting), GDCB (supporting), LCM (supporting), RER (supporting), XZ (supporting), RPN (supporting), SZ (supporting), VR (supporting)
Data curation: RRJ (lead), SL (equal)
Formal analysis: SL (lead), RRJ (supporting)
Funding acquisition: SL (lead), PJN (equal), KS (supporting), GDCB (supporting), LCM (supporting), RER (supporting), XZ (supporting), RPN (supporting), SZ (supporting), VR (supporting)
Investigation: SL (lead), RRJ (equal)
Methodology: SL (lead), PJN (equal), RRJ (supporting)
Project administration: RRJ (lead), SL (supporting)
Resources: SL (lead), KS (equal)
Supervision: SL (lead), RRJ (equal)
Writing—original draft: RRJ (lead), SL (equal)
Writing—review and editing: RRJ (lead), SL (equal), PJN (supporting), KS (supporting), GDCB (supporting), LCM (supporting), RER (supporting), XZ (supporting), RPN (supporting), SZ (supporting), VR (supporting)

Conflicts of Interest

None declared.

Multimedia Appendix 1
Research consent form.
[PDF File (Adobe PDF File), 46 KB - resprot_v14i1e76837_app1.pdf]

Multimedia Appendix 2
Peer review report from the Psychosocial, Sociocultural & Behavioural Determinants of Health Committee / Déterminants psychosociaux, socioculturels et comportementaux de la santé Comité - Canadian Institutes of Health Research (CIHR) / Institutsde recherche en santé du Canada (IRSC) (Canada).
[PDF File (Adobe PDF File), 137 KB - resprot_v14i1e76837_app2.pdf]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
FHLP: Family Healthy Living Program
FLASHE: Family Life, Activity, Sun, Health, and Eating
M-PAC: multiprocess action control
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Effectiveness of an Education Toolkit Delivered by Soap Operas Among Communities Living in Extreme Poverty in Improving Vaccination Confidence in the Philippines: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: Measles and polio pose significant public health challenges globally, particularly in low-resource settings such as the Philippines, where vaccine coverage falls short of the World Health Organization's (WHO's) targets, with hard-to-reach populations contributing to the "last mile." This research addresses the "last mile" challenge in routine immunization efforts by bridging the vaccination gap in marginalized populations.

Objective: We describe the implementation of a cluster randomized controlled trial to evaluate the impact of an education toolkit aimed at improving confidence in measles and polio vaccines among communities living in extreme poverty in the Philippines.

Methods: Developed with local stakeholders, our intervention consists of a 10-minute video and vaccination reminders delivered by health trainers. It is embedded within the Soap Opera Trial, a large cluster randomized controlled trial conducted by the International Care Ministries that evaluates a 15-episode soap opera series combining drama with aspirational messages on hope, self-worth, and education, aimed at improving participants' knowledge and practices in health, hygiene, nutrition, and livelihood. A total of 180 communities with 5400 participants will be randomly assigned to the intervention and control arms. By leveraging an existing community-based education program on health and livelihood run by our local partner, the proposed intervention will be delivered to participants in the intervention arm of the existing program, while those in the control arm will receive standard participatory adult learning sessions on health education. The primary outcome is the first-dose measles-containing vaccine coverage among participants' children aged 1 year. Secondary outcomes include the 2-dose measles-containing vaccine coverage among children aged 2 to 6 years, polio vaccination coverage among children aged 1 year, and participants' knowledge of measles and polio vaccines. The absolute differences in these outcomes between the intervention and control arms will be estimated using generalized estimating equations while adjusting for baseline levels and covariates. In addition, we will conduct a process evaluation.

Results: Between January 31 and February 29, 2024, we recruited 66.9% (3613/5400) of the participants for the trial. Data collection is ongoing at the time of manuscript submission.

Conclusions: Findings from this trial will provide critical insights into effective strategies for enhancing vaccine confidence and uptake in marginalized populations. By leveraging community-based approaches and local partnerships, this study aims to improve public health responses to vaccine-preventable diseases and contribute to global efforts to eradicate measles and polio. Furthermore, the findings will inform scalable interventions that can be adapted to similar contexts, potentially reducing health disparities and advancing global health equity.

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KEYWORDS
measles; polio; vaccination; education intervention; randomized controlled trial

Introduction

Background

Measles and polio are highly contagious diseases that can lead to outbreaks with serious public health consequences and strain health systems. Over the past century, measles incidence and mortality have dramatically declined due to advancements in nutrition, health care, socioeconomic conditions, and the introduction of a safe and cost-effective vaccine in the 1960s. From an annual incidence of approximately 4 million cases in 1981, measles cases dropped to under 150,000 by 2016, sparking renewed efforts toward global eradication [1]. However, stagnation in global measles vaccination coverage over the past decade has been a cause of concern. With first-dose measles-containing vaccine (MCV) coverage hovering around 86% and <70% for the second dose MCV, these figures fall short of the World Health Organization's (WHO) recommended 95% coverage necessary to achieve herd immunity and prevent outbreaks [2]. The Global Polio Eradication Initiative's extensive vaccination campaigns have been remarkably successful since 1988, reducing polio cases worldwide by 99%. This effort has averted an estimated 20 million cases of paralysis in children. Two primary vaccines are used in this global endeavor: the oral polio vaccine (OPV) and inactivated polio vaccine (IPV), with IPV administered through injection. OPV, the more widely used of the two, plays a crucial role in areas with limited access to sanitation and handwashing facilities [3]. As of 2022, global vaccination coverage for polio stood at 84%, with infants receiving 3 doses of the vaccine. Similarly, in countries that continue to use OPV, 84% of infants had received their first dose of IPV. Targeted for global eradication, vaccines have stopped the spread of wild poliovirus in all countries except Afghanistan and Pakistan. Until poliovirus transmission is interrupted in these countries, all countries remain at risk of the importation of polio, especially vulnerable countries with weak public health and immunization services and travel or trade links to endemic countries [3].

In the Philippines, measles and polio vaccines are provided as part of the routine immunization schedule. For vaccination against measles, monovalent measles vaccine (targeting measles alone at 9 months) and measles-mumps-rubella vaccine (providing immunity against measles, mumps, and rubella at 12 months) are primarily offered as part of the national immunization program [4]. For polio vaccination, the national immunization program includes both OPV and IPV, with OPV administered at 6, 10, and 14 weeks to prevent transmission and IPV administered at 14 weeks to provide systemic immunity [5]. Despite aiming for a 95% vaccination rate, the Philippines experienced a decline in measles vaccine coverage before the 2018-2019 measles outbreak [6,7]. The measles vaccine was introduced in 1983, with a second dose added in 2009 [6,7]. The Philippines' first-dose MCV coverage peaked at 92% between 2004 and 2008 but dropped to 80% in 2016 and 75% in 2018, with measles outbreaks occurring from 2010 to 2011 and in 2013 [8]. In addition to measles, a polio outbreak was declared in the Philippines in 2019, prompting the Department of Health (DOH) and its partners to initiate a comprehensive outbreak response, including mass polio immunization campaigns starting in October 2019. However, polio vaccination rates reported in 2020 and 2021 were around 70%, which is still substantially below the DOH's target of 95% [9,10].

Despite the DOH's continuing efforts to improve vaccination coverage through mass immunization campaigns and annual public health initiatives aimed at increasing awareness, challenges persist in fully reaching the WHO targets, especially in the most remote and underserved communities, often referred to as the "last mile" [11-13]. Specifically, vulnerable populations residing in hard-to-reach communities pose a significant challenge for the delivery of vaccination campaigns and services. These populations are also often those living in poverty or of low socioeconomic status [11]. Although data specifically from the Philippines are sparse, studies from various low- and middle-income countries consistently report lower vaccination rates among households with lower socioeconomic status [14-17]. This inequality in vaccination is often observed in rural areas or urban slums, where public health campaigns and interventions are difficult to implement [14]. Another challenge to vaccination programs is vaccine hesitancy, which largely stems from concerns about vaccine safety, importance, and effectiveness. In the Philippines, vaccine hesitancy has been exacerbated by the controversy surrounding the Dengvaxia scandal in 2016, which involved a dengue vaccine that was prematurely introduced by the Government of the Philippines and the WHO and was associated with several deaths among vaccinated children, fueling skepticism and fear among the public regarding the safety and efficacy of vaccines in general [18]. Moreover, the unprecedented disruption caused by the COVID-19 pandemic has temporarily halted routine immunization schedules, further complicating the delivery of essential vaccination services [19,20]. The pandemic's impact on health care systems has diverted resources and attention, causing delays in routine vaccinations against diseases such as measles and polio, and reversing gains made in previous years [19,20].

Objectives

To facilitate successful vaccine delivery to the "last mile" in the Philippines, we will implement an education toolkit that was codeveloped with local stakeholders. The toolkit will be implemented in partnership with an existing community engagement intervention, with the aim of enhancing confidence

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in measles and polio vaccines. The project will evaluate the education toolkit's feasibility and effectiveness among households in extreme poverty in the Philippines. Specifically, we will assess (1) the effectiveness of the toolkit in improving measles and polio vaccination rates, knowledge, and attitudes concerning measles and polio and (2) the relevance, applicability, and feasibility of the toolkit in the local context.

Methods

This protocol is reported according to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines.

Study Design

We will use a pragmatic, parallel, cluster randomized controlled trial to assess the effectiveness of an education toolkit in improving public confidence in measles and polio vaccines in the Philippines.

Setting

International Care Ministries (ICM) is a faith-based nongovernment organization in the Philippines that operates community-based programs focused on poverty alleviation with individuals and households experiencing extreme poverty [21]. Leveraging its organizational strengths in community engagement and outreach, its network of churches and communities, and close partnership with local government units and national government departments (eg, the DOH), ICM delivers its programming through 12 bases across the Philippines. Each base is led by an area head who supports 3 branches staffed by a branch head, health coordinators and trainers (focused on health education, promotion, referrals, and services), livelihood coordinators and trainers (focused on addressing socioeconomic needs), and pastor coordinators (focused on identifying potential partner communities) who provide services in communities [21]. The ICM's core program is called the Transform Program, which consists of 15 weeks of education sessions on health and livelihood delivered by partner pastors and health and livelihood trainers through participatory adult learning sessions in communities. The intervention delivery timeframe of 15 weeks aligns with the Soap Opera Trial and the delivery structure of ICM's Transform Program, in which weekly sessions are consistently delivered across communities. Within this framework, our vaccine education toolkit is introduced during weeks 12 to 15, with messages focused on measles and polio vaccination. In addition, this 15-week intervention timeframe allows us to build on participants' sustained engagement with the transform sessions and ensures that the intervention is delivered in a feasible and standardized manner across clusters. A total of 30 participants from households that meet the criteria for extreme poverty will be selected to participate in the Transform Program in each community [22,23].

Our toolkit will be embedded in an ongoing cluster randomized controlled trial, called the Soap Opera Trial, which is designed and run by the ICM, leveraging its community-based Transform Program at 4 bases (Bohol, Cebu, Dumaguete, and Dipolog). The Soap Opera Trial aims to evaluate the impact of a variation of its standard Transform Program, which uses aspirational videos to deliver information to improve food security, livelihood, and health. The health education sessions include information on general hygiene, nutrition, childhood growth and development, and prevention of sexually transmitted infections and tuberculosis. The soap opera video is entitled "First Light" and was produced by the ICM's media team. It includes drama and plot twists like a typical television show, but highlights lessons about hope, sense of control, self-efficacy, self-worth, and aspirations for children's education and future income, as well as on downstream economic outcomes such as income, consumption, and food security, which are key behaviors and outcomes that can help people living in poverty take a step out of poverty. ICM is conducting a cluster randomized controlled trial to assess the impact of these soap opera videos on outcomes such as aspirations about the future, investments in children's education, social capital, health, hope, and economic outcomes. In this trial, the intervention arm receives the soap opera video for 15 sessions in 15 weeks, while the control arm receives the same information through standard lectures over 15 weeks. The "soap operas" were produced by ICM (which wrote the scripts, hired local actors, videographers, and directed the soap operas) and funded by the Global Innovation Fund. The entire series was filmed on location and in the language of the intended audience. The content of the narratives was developed primarily by ICM staff in consultation with the primary investigators of that study and aimed to embed behavioral nudges within the storyline [24]. Table 1 summarizes both trials and illustrates how our Vaccine Confidence Trial will be embedded in the Soap Opera Trial. Our vaccine confidence toolkit and video are introduced to participants in the intervention arm for 4 weeks (wk 12-15), while the participants in the control arm receive standard education in the form of participatory adult learning, which does not contain vaccine confidence education specified in the intervention arm.

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Table 1. Summary of Soap Opera Trial and Vaccine Education Toolkit trial.

	Soap Opera Trial	Vaccine Confidence Trial
Intervention aims	• To evaluate the impact of a variation of their standard Transform Program, which uses aspirational videos to deliver education about food security, livelihood, and health.	• To improve the knowledge of and confidence in measles and polio vaccines in communities living in extreme poverty in the Philippines.
Intervention content	• The soap opera, which will be shown in a total of 15 episodes, each lasting 15 min, is entitled "First Light" and was produced by ICM's[a] internal media team. It includes drama and plot twists such as a typical television show but highlights lessons about hope, sense of control, self-efficacy, self-worth, and aspirations for children's education and future income, as well as downstream economic outcomes, such as income, consumption, and food security, which are key behaviors and outcomes that can help people living in poverty take a step out of poverty.	• The vaccine education intervention contains two components: (1) an educational toolkit on measles and polio vaccination in the form of a 10-min video and (2) reminder messages regarding vaccination. • The video includes information on (1) a comprehensive introduction of measles and polio, (2) vaccine safety and efficacy, (3) measles and polio vaccination guidelines and schedules, and (4) myths and misconceptions. In the toolkit video, we will provide information on (1) the definitions of measles and polio, (2) the importance of measles and polio prevention, (3) the side effects of the vaccines, and (4) locations where vaccinations are provided.
Intervention delivery	• A total of 15 soap opera videos will be shown alongside the standard Transform Program over 15 wks.	• The intervention will be delivered from wk 12-15 of the Transform Program.
Study participant eligibility	• The same participants will be screened using a poverty scorecard, loosely based on PPI[b] developed for the Philippines (by Innovations for Poverty Action, 2014) and self-reported household income. Participants in households that meet the definition of extreme poverty by income (<22 PHP [US $0.38] per person per day) are prioritized for recruitment into the Transform Program. Participants are eligible if they (1) reside in the participating communities where ICM recruits for the Transform Program and (2) meet the criteria and definition of living in extreme poverty based on ICM's screening. Those who refuse to participate will not be included in the trial.	• The same participants will be screened using a poverty scorecard, loosely based on PPI developed for the Philippines (by Innovations for Poverty Action, 2014) and self-reported household income. Participants in households that meet the definition of extreme poverty by income (<22 PHP [US $0.38] per person per day) are prioritized for recruitment into the Transform Program. Participants are eligible if they (1) reside in the participating communities where ICM recruits for the Transform Program and (2) meet the criteria and definition of living in extreme poverty based on ICM's screening. Those who refuse to participate will not be included in the trial.
Outcome measures	• Outcomes on aspirations about the future, investments in children's education, social capital, health, hope, and economic outcomes.	• Primary outcome measures • First-dose MCV[c] coverage among participants' children aged 1 year • Secondary outcome measures • First-dose MCV coverage at the family level • Coverage of 2-dose MCV among participants' children aged 2-6 years • Polio vaccination coverage (IPV[d] or OPV[e]) among participants' children aged 1 year • Polio vaccination coverage at the family level • Participants' mean knowledge score on measles and polio vaccines, which will be assessed using a 10-item questionnaire, 6 mos after the Transform Program
Evaluation methods	• Preintervention and postintervention survey	• Review of individual immunization records for the children in the participants' immediate family from the Department of Health, before and after the intervention. • Preintervention and postintervention surveys (survey questions will be embedded in the Soap Opera Trial survey questionnaire) • Semistructured interviews

[a]ICM: International Care Ministries.

[b]PPI: Progress out of Poverty Index.

[c]MCV: measles-containing vaccine.

[d]IPV: inactivated polio vaccine.

[e]OPV: oral polio vaccine.

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Eligibility and Recruitment

Participants are eligible to be included in our trial if they (1) reside in the participating communities where ICM recruits for the Transform Program, (2) meet the criteria and definition of living in extreme poverty based on ICM's screening, and (3) give informed consent to participate in the health-education sessions, which include the delivery of our toolkit. Those who refuse to participate will not be included in the trial. Participants will be recruited and screened with an ICM poverty scorecard that uses asset-based scoring loosely based on the Progress out of Poverty Index developed for the Philippines and self-reported household income [25]. The items used for computing the score are elicited through in-person enumeration and home visits. Participants in households that meet the definition of living in extreme poverty by income (<22 PHP [US $0.38] per person per day) are prioritized for recruitment into the Transform Program. There are 30 eligible participants in each community to start the ICM Transform Program. In previous programs, 27% of transform participants went to bed hungry at least once per week. All participants are women with specific parental education levels and have an illiteracy rate of 15%. On average, there are 3.3 children per participant's immediate family, and 1 child per family falls within the vaccination age for measles and polio, which is between 12 months and 6 years. Children in the household are often malnourished. Economic deprivation is a common unifying factor across households.

Randomization and Blinding

Recruited communities will be randomized into the intervention and control groups in a 1:1 ratio using computer-generated random numbers developed by a research statistician. A total of 180 communities with all eligible participants (≥30 participants per community) will be randomly assigned to the intervention and control arms in a ratio of 1:1. No blinding will be performed because of the nature of our intervention. As our intervention is integrated into the Soap Opera Trial conducted by the ICM, we will adhere to the trial's established randomization assignments.

Process

Intervention Arm

All participants of the existing trial (ie, 30 participants per community) in the intervention arm will receive a series of 15 soap opera videos, 1 for each week, to complement the 15-week Transform Program's education sessions, which are the core intervention of the Soap Opera Trial developed and run by ICM. The 15 episodes were designed to be consumed as a series, with the storylines for each character extending throughout the 15 videos. The characters were developed to reflect situations and contexts comparable to those of the audience, increasing the likelihood that they will relate personally to the story and messages. The videos were shown on televisions brought into the communities (ICM also tested projectors, but the screen setup and lighting proved too logistically challenging). Speakers were also brought into each "watch-session," and a variety of tests were conducted to ensure that the audience would be able to engage properly with the videos. The soap opera is a popular medium in the Philippines and is widely consumed by the target population. According to NGP, a Filipino-based agency, soap operas are important media sources for Filipinos. Given that the eligible participants live in extreme poverty, the soap operas are a strategic medium for health messaging [24,26]. In addition, all participants in the intervention arm will receive our education toolkit intervention from weeks 12 to 15.

The intervention in our Vaccine Confidence Trial contains two components: (1) education on measles and polio vaccination in the form of a 10-minute video and (2) reminder messages regarding vaccination. The education toolkit will contain information and messages about the following four aspects of measles and polio vaccines: (1) a comprehensive introduction to measles and polio, (2) vaccine safety and efficacy, (3) measles and polio vaccination guidelines and schedules, and (4) myths and misconceptions. In the toolkit, we will provide information on (1) the definitions of measles and polio, (2) the importance of measles and polio prevention, (3) the side effects of the vaccines, and (4) vaccination provision locations. The education toolkit will be presented in local languages using a 10-minute video converted from Microsoft PowerPoint slides. The PowerPoint slide deck and accompanying script were collaboratively developed with health educators from ICM. Professional translators have translated the finalized English version of the slide deck and script into the local languages. Subsequently, ICM produced a video featuring a health worker presenting the toolkit, synchronized with the voiceover and PowerPoint slides.

Following the delivery of the video, participants will also receive reminder messages regarding vaccination from health educators from ICM in the savings groups program running in communities for 4 months. For participants whose children are not yet vaccinated, the health educators will remind them about the importance and benefits of measles and polio vaccination. This process will serve as a reminder for parents about the importance of measles and polio vaccination. In the typical Transform Program, approximately 40% to 50% of participants will self-select to form a savings group, which ICM will support for 2 years. In these groups, participants will receive weekly reminder messages about measles and polio vaccination in their meetings for 4 months.

Control Arm

In the control group, participants will attend the standard 15-week Transform Program, with education sessions delivered through standard participatory adult learning sessions by health educators from ICM on the topics of income creation, education, food security, health, and resilience, with key messages consistent with the soap opera videos. No specific educational information will be provided regarding measles and polio vaccination, and no specific reminders regarding measles and polio vaccinations will be provided.

Outcomes

The primary outcome will be the coverage of the first dose of any MCV among the participants' children aged 1 year. This will be measured at 6 months after completing the Transform Program. Eligible children must be legal dependents of Transform Program participants and reside in the same

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household. MCV coverage will be calculated as the proportion of children who have completed at least 1 dose of MCV among the total number of eligible children.

Secondary outcomes will include (1) the first-dose MCV coverage at the family level, which will be determined by the number of participants whose eligible children have completed at least 1 dose of MCV by age 1 year (a family will not be considered covered if any eligible child does not receive the vaccine); (2) coverage of 2-dose MCV among children aged 2 to 6 years; (3) the rate of 2-dose MCV coverage at the family level; (4) polio vaccination coverage, calculated as the proportion of children aged 1 year who will have received at least 3 doses of polio vaccines (IPV or OPV); (5) the polio vaccination coverage at the family level; and (6) participants' mean knowledge and attitudes score toward measles and polio vaccines, which will be measured by a 10-item questionnaire administered at the beginning and end of the Transform Program. Outcomes 1 to 5 will be assessed 6 months after the completion of the Transform Program. We will conduct subgroup analyses by children's sex and by province. In addition, we will conduct a process evaluation to assess its relevance, applicability, and feasibility using qualitative research methods.

Sample Size

The first-dose MCV coverage in the control arm is estimated to be 80% in 2023 based on the WHO report [27]. We estimate that the rate will increase by at least 10% after the intervention. To detect this difference with 90% power using 2-sided testing at the 5% significant level, assuming a mean cluster size of 5 children aged 1 year per cluster and an intracluster correlation coefficient of 0.12, we estimate that at least 156 clusters (communities; 78 per arm) will be needed to detect the proposed effect size. To maximize the statistical power, we will recruit all 180 clusters participating in the Soap Opera Trial. We assume that 900 children aged 1 year (450 per arm) will be evaluated for the primary outcome. Because there are 30 participants (ie, parents or grandparents) in each community, we will include them all for a total of 5400 participants in the trial activities.

Data Collection

To collect primary and secondary outcome data, we will review the individual immunization records of children issued by the DOH for both the baseline and endline periods. To supplement the data retrieved from immunization records, we will also conduct pre- and postintervention surveys using structured, closed-ended questions to collect data on study participants' sociodemographic information, self-reported vaccination status of their children, and their knowledge and attitudes toward measles and polio vaccines.

To assess the self-reported knowledge and attitudes toward measles and polio vaccination, we will distribute a survey to all participants before and after the intervention. In this survey, 2 items with 5-point Likert-scale responses will be used to assess vaccination attitudes, yielding a total score ranging from 1 to 10. The two items are (1) How much do you agree with the statement "Measles and polio vaccines are safe and effective"? and (2) How much do you agree with the statement "My concerns about vaccine-related side effects deter me from getting my children vaccinated"? All the Transform Program participants in both arms will participate in the pre- and postprogram survey. The ICM team will conduct primary data collection as part of their trial operations, and all personally identifiable information will be removed before sharing it with the study investigators. The survey questions will be administered by ICM staff through in-person interviews. In addition, to enhance the accuracy of the data collected, survey administrators from ICM will verify the vaccination status of the participants' children by inspecting their vaccination cards. All participants of the Transform Program will be asked to complete the survey before and after the Transform Program as part of the ICM's standard evaluation process. Preintervention surveys will be completed in February 2024, and postintervention surveys will be completed in August 2024. Vaccination data collection will be validated with local government vaccination records by June 30, 2025.

The ICM surveys will be conducted using SurveyCTO, which stores uploaded data on Amazon Web Services servers. All data will then be backed up using Boxcryptor, which encrypts cloud-based files. Personal identifiable data will be shared only after encryption and will be password-protected. Survey participants will provide consent through the ICM's survey and data collection processes. The ICM's survey team will conduct primary data collection as part of their program operations, and all personally identifiable information will be removed before being shared with the investigators of this study. The data will only be analyzed at the group and subgroup levels, and individuals will never be isolated during the process.

Statistical Analysis

The data will be analyzed following an intent-to-treat approach and at the individual level. Sociodemographic characteristics of community members will be summarized descriptively using means (or medians) or proportions. For the primary and secondary proportion-based outcomes, the absolute differences in vaccination coverage between the intervention and control arms 6 months after the end of the Transform Program will be estimated using the generalized estimating equation models with a logit link while adjusting for baseline vaccination levels and covariates, including sex, age, and province. The odds ratio and 95% CI will be calculated to express the treatment effect. Preintervention and postintervention survey scores in knowledge and attitudes toward measles and polio vaccines will be calculated for the 2 arms, respectively. Generalized estimating equation models will be used to assess the effect of the toolkit on the postintervention knowledge and attitude scores, while adjusting for baseline level and covariates. Subgroup analyses by the 4 bases will be performed. Analyses will be conducted using either Stata (StataCorp) or R software (R Foundation for Statistical Computing). A 2-sided $P<.05$ will be considered statistically significant for the primary outcome analysis. For other analyses, P values will be computed and interpreted as the level of statistical evidence against prespecified null hypotheses.

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Process Evaluation

The relevance, applicability, and feasibility of our education toolkit will be assessed using qualitative research methods. In the intervention arm, we will purposively identify and recruit relevant toolkit end users, including the health educators and participants of the Transform Program. We will purposively select 30 stakeholders to participate in semistructured interviews within 2 weeks after the end of the Transform Program as in Multimedia Appendix 1. The interview will aim to understand the accuracy and appropriateness of the toolkit content, user perceptions of the relevance of the toolkit, and overall satisfaction with the toolkit.

Interviews will be conducted in person, online, or by phone, depending on the availability and preference of interviewees, by members of the Canadian research team or research staff from ICM. Interviews will be conducted in the preferred language of the interviewee. In cases where interviews are not conducted in English, an interpreter will be hired to assist with interview facilitation. Each interview will begin with an explanation of the study, followed by the delivery of a verbal consent script and signing of the consent document. Consent will be obtained for both study participation and audio recording (the consent process is described in detail in the subsequent section). Each interview is expected to last 40 to 60 minutes with the aid of an interview guide. Interviews will be audio recorded. For participants who consent to study participation but not to audio recording, we will seek consent to take notes during the conversation. Data collected from the interviews will be transcribed from the recordings. We will use a thematic analysis approach following the 6-phase framework of Braun and Clarke: (1) data familiarization through repeated reading of transcripts and noting initial ideas, (2) systematic coding of meaningful features across the dataset, (3) collating codes into initial themes and subthemes, (4) reviewing and refining themes against coded data and the entire dataset, (5) defining and naming themes to capture their essence, and (6) producing the final analytic report [28]. Transcripts will be coded inductively by 2 researchers, with discrepancies discussed and resolved through consensus. The analysis will be performed using NVivo (Lumivero). Throughout the analysis, we will maintain reflexive memos to document assumptions, positionality, and decision-making throughout the analytic process, ensuring transparency and minimizing bias [29]. To strengthen transferability, we will provide descriptions of the study setting, participant characteristics, and contextual factors, enabling readers to assess the applicability of the findings to other contexts [29].

Ethical Considerations

Ethics approval for this trial was obtained from the Office of Research Ethics at the University of Toronto, Canada (45722) and the ethics committee of ICM (2024-001). Informed consent will be obtained from participants before trial enrollment. The data will be deidentified before analysis. No compensation will be provided to participants.

Trial Management

The trial will be co-led by XW (University of Toronto) and LL (ICM, Philippines), who will have full access to the trial dataset. To protect the safety and privacy of participants and to ensure that data are collected ethically, stored correctly, and used solely for research, we will establish a data management committee that will be led by external and independent members. In addition, we will form a trial steering committee to oversee the trial design and implementation. Teleconference meetings will be held for both the data management committee and the trial steering committee at the start and midpoint of the study, with the option of additional meetings as necessary. Protocol modifications will be discussed during these meetings.

Results

This study was funded in 2021 and registered at ClinicalTrials.gov (NCT06218368) on January 23, 2024. Participant recruitment was launched on January 31, 2024, and completed on February 29, 2024. A total of 3613 participants have been recruited for the trial. Data collection is ongoing and is expected to be completed by June 30, 2025, and we plan to disseminate the results by September 30, 2025. We will disseminate the trial results through research articles and policy briefs. We aim to publish our results in leading international medical journals and present them at national and international conferences. The total lifespan of the study will be 23 months, as shown in Table 2.

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Table 2. Study timeline.

	Study period (months)					
	1-3	4	5-8	9-10	11-20	21-23
Preparation						
Study design	✓					
Development of research tools	✓					
Ethics evaluation	✓					
Interventions						
Enrollment		✓				
Intervention arm		✓	✓			
Control arm		✓	✓			
Evaluation						
Primary outcome data collection		✓	✓	✓	✓	
Process evaluation data collection		✓	✓	✓	✓	
Data analysis and results dissemination						✓

Discussion

Anticipated Findings

Our trial aims to assess the effectiveness and feasibility of an education toolkit developed in collaboration with local stakeholders to enhance confidence in measles and polio vaccines among communities living in extreme poverty in the Philippines. Conducted in partnership with ICM, the trial will use a cluster randomized controlled design across 4 bases in the Philippines. Eligible participants from communities participating in the Transform Program of ICM will receive either the intervention, consisting of a 10-minute educational video about the efficacy and safety of measles and polio vaccines and vaccination reminders, or standard program sessions delivering health education through participatory adult learning sessions. Primary outcomes will include measles vaccination rates among the children of the participating families, and secondary outcomes will include polio vaccination rates, participant knowledge, and attitudes toward vaccines. In addition, the feasibility of the intervention will also be assessed.

Our intervention aims to address the last mile challenge of reaching WHO vaccination targets by improving knowledge and awareness of measles and polio vaccines among the communities living in extreme poverty in the Philippines and to complement the continuing efforts of the DOH to improve measles and polio vaccination coverage. By adopting a community-based approach and embedding our intervention within an existing community-based program run by our local partner, we leverage the established trust between community members and health educators. This approach is expected to enhance the acceptability and effectiveness of our intervention, as community members are more likely to engage with familiar and trusted sources of information, namely, pastors and the nongovernmental organization facilitating the program. In addition, using local health educators and staff who have long-standing working relationships with these communities will facilitate cultural competency and help ensure that interventions are tailored to meet the unique needs of the target population. Evidence on the impact of the intervention and the factors influencing its impact will be generated from the trial, and local stakeholders will be informed about the sustainability and scalability of this intervention to other regions of the Philippines. By systematically documenting the outcomes and lessons learned, we seek to contribute valuable insights that can guide the development and implementation of future community-based interventions aimed at improving vaccination coverage and addressing health disparities among marginalized populations.

Strengths and Limitations

Our trial has the following strengths. First, the use of a cluster randomized controlled design enhances the validity of the study, providing a rigorous framework to evaluate the effectiveness of the intervention. This design will enable us to draw robust conclusions about the impact of the education toolkit on vaccination rates and knowledge. Second, using an implementation science approach will offer valuable insights into the facilitators and barriers encountered during the implementation of the intervention. By understanding the contextual factors influencing the success of the intervention, local stakeholders will be able to make informed decisions about its implementation and sustainability. Finally, this trial leverages our strong ties with our local partners in the Philippines, which strengthens the relevance and impact of our findings. By prioritizing equitable collaboration and engaging local partners from the development phase of the intervention, we aim to ensure that the benefits of the intervention extend to the most vulnerable populations. This approach is expected to foster vaccine confidence and support inclusive vaccination programs that address the needs of all community members.

However, while the vaccination status will be retrieved from the DOH, there is a possibility of missing data on the children of study participants. In such cases, relying on self-reported vaccination status may introduce recall bias, potentially affecting the accuracy of the data. Due to constraints on survey length,

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only 10 questions related to measles and polio vaccines will be included in the assessment of participants' knowledge and attitudes. This limited scope may not fully capture the complexity of participants' beliefs and understanding regarding vaccination. Despite this limitation, careful selection of survey questions based on key indicators will help ensure that essential information is obtained, balancing the depth of inquiry with practical considerations. Second, our intervention will be implemented alongside the soap opera intervention of the Transform Program. If the soap opera intervention is effective, participants in the intervention arm may make greater investments in children's education, social capital, health, hope, and economic conditions, which would positively impact their children's vaccination rates. Because the control arms will receive the traditional Transform Program, which includes the same content, any additional effect would be attributable to the soap opera delivery method, which is part of our intervention. Finally, participants in both arms may miss the health education and vaccine sessions due to other commitments, which could reduce their level of engagement with the intervention and its overall effectiveness.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

SW, QD, SP, MK, LL, and XW contributed to the conception and design of this study. SW drafted the paper. SW, QD, ZZ, SP, KT, MK, VH, LL, and XW critically revised the paper. SW, QD, ZZ, SP, KT, MK, VH, LL, and XW provided final approval for the submitted version. XW and LL are co-corresponding authors. LL can be reached via email: lincoln.lau@utoronto.ca, phone: +63-2-470-4008, or address: Unit W-1701, Philippine Stock Exchange Center, Exchange Road, Ortigas Center, Pasig City, 1605 Philippines.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guides.
[PDF File (Adobe PDF File), 162 KB - resprot_v14i1e77022_app1.pdf]

Multimedia Appendix 2
SPIRIT checklist.
[PDF File (Adobe PDF File), 97 KB - resprot_v14i1e77022_app2.pdf]

Multimedia Appendix 3
Peer-review report from the Operating Grant: COVID-19 Vaccine Confidence Committee, Canadian Institutes of Health Research (CIHR).
[PDF File (Adobe PDF File), 115 KB - resprot_v14i1e77022_app3.pdf]

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Abbreviations

DOH: Department of Health
ICM: International Care Ministries
IPV: inactivated polio vaccine
MCV: measles-containing vaccine
OPV: oral polio vaccine
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
WHO: World Health Organization

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Protocol

Effectiveness and Cost-Effectiveness of a Stepped Model of Care for Musculoskeletal Disorders: Protocol for a Multiarm Randomized Controlled Trial (Edu-First Trial)

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Abstract

Background: Musculoskeletal disorders (MSKDs) are a leading cause of pain and disability, placing a substantial burden on health care systems. Optimizing resource use through innovative interventions is essential. Evidence from randomized controlled trials suggests that not all individuals with MSKDs require ongoing follow-up with a health care provider; for many, education alone is sufficient for symptom resolution. A stepped care model, which prioritizes patient education as a first-line intervention and reserves usual care for those with persistent symptoms, may enhance health care efficiency and reduce costs.

Objective: The primary objective of this randomized controlled trial is to evaluate the effectiveness of a stepped care model compared to the 2 most common approaches for managing MSKDs: usual medical care and usual rehabilitation care. A secondary objective is to assess cost-effectiveness.

Methods: This pragmatic, noninferiority, multiarm, parallel-group randomized controlled trial will enroll 369 adults with MSKDs, randomly assigned to one of three 12-week intervention groups: stepped care, usual medical care (physician-led), or usual rehabilitation care (physiotherapist-led). Participants in the stepped care group will first complete a 6-week education program. Those with persistent symptoms after 6 weeks will receive rehabilitation interventions, while participants whose symptoms have resolved will receive no further intervention. The primary outcome is functional limitations at 24 weeks. Secondary outcomes include pain severity, health-related quality of life, pain-related fear, and pain self-efficacy, assessed at baseline and at 6, 12, and 24 weeks. Linear mixed models will be used for group comparisons, and incremental cost-effectiveness analyses will evaluate cost-effectiveness. The ethics committee of the CIUSSS-CN approved the project (#2024-2982). Findings will be shared through clinical and community platforms, peer-reviewed publications, and conference presentations.

Results: The Edu-First trial is funded by a project grant from the Canadian Institutes of Health Research (grant #495615). Recruitment began on January 31, 2025. As of September 2025, a total of 65 participants have been enrolled. Recruitment is expected to continue for up to 3 years, targeting approximately 10 new participants per month, and is anticipated to be completed by Winter 2028.

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Conclusions: We anticipate that the stepped care model will be noninferior to usual medical care and usual rehabilitation care in terms of treatment effectiveness. Furthermore, it is expected to be cost-effective by reducing reliance on expensive resources, such as provider consultations and medical investigations. By emphasizing education and self-management as the initial approach, the stepped care model may enhance access to care without compromising quality, while empowering patients to actively manage their condition. Findings from this study could inform systemic changes in MSKD care delivery, improving treatment accessibility and reducing the average cost per care episode.

Trial Registration: ClinicalTrial.gov NCT06832852; https://clinicaltrials.gov/ct2/show/NCT06832852

International Registered Report Identifier (IRRID): DERR1-10.2196/77574

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KEYWORDS

education; cost-effectiveness; rehabilitation; shoulder pain; low back pain; anterior knee pain; neck pain.

Introduction

Musculoskeletal disorders (MSKDs) have become a global epidemic, with their prevalence steadily rising over the past decades [1]. This trend is expected to persist due to aging populations and ongoing exposure to environmental and occupational risk factors [1,2]. MSKDs significantly impact individuals by limiting activities and restricting participation while also placing a heavy burden on society through work absenteeism, disability pensions, early retirement, and increasing demands for social support [3,4]. While some individuals experience short-term symptoms, others endure persistent or recurrent pain, leading to impaired daily functioning and substantial health care costs [5-7]. MSKDs are among the most common reasons for seeking primary care, with up to 20% of adults consulting their family physician for an MSKD-related issue annually [8]. Ensuring timely and appropriate care for individuals with MSKDs remains a challenge, even in countries with universal health care [9].

A major barrier to health care access for individuals with MSKDs is prolonged wait times [10-12]. In addition, significant gaps and disparities in access to publicly funded health care persist across several countries [11,13-15]. A systematic review reported significant declines in health-related quality of life and psychological well-being among those experiencing treatment delays [16]. Longer wait times have also been associated with increased health care use, delays, or restrictions in work participation [17]. To address these challenges, health care services must be redesigned to reduce wait times and promote more equitable access. A systematic review examining strategies to reduce waiting times in outpatient rehabilitation services for adults with MSKDs found that several service redesign approaches—such as referral management strategies and alternative models of care—effectively decreased waiting times while better meeting patients' needs [18]. Given the negative consequences of prolonged delays, implementing efficient and effective strategies to improve timely access to care for individuals with MSKDs is essential.

In 2 randomized controlled trials, we demonstrated that not all patients with chronic MSKDs require close follow-up by a health care provider, as for a large proportion, patient education alone was sufficient to achieve significant improvement or even resolution of their condition [19,20]. As a first-line approach in primary care, patient education is cost-effective, widely accessible, and adaptable [11,21], and in some cases, it is as effective as usual care [22,23]. It can be delivered by various health care providers in multiple formats, including self-administered options, depending on the context and individual needs [24]. The primary goals of education are to improve patients' understanding of their condition, dispel myths and misconceptions, promote healthy lifestyle choices, and optimize self-management [25-27]. A better understanding of the condition and its psychological factors enables individuals to manage their symptoms more effectively [28,29]. As health care costs rise, a stepped care model—where patient education and advice are offered first, with usual care provided only to those whose symptoms persist—could improve access to health care by reducing the number of visits with a health care provider without compromising quality of care.

The primary objective of this randomized controlled trial is to determine whether a stepped care model is as effective as the 2 most common care models—usual medical care (led by a family physician) and usual rehabilitation care (led by a physiotherapist)—in individuals with MSKDs at 24 weeks post allocation. The primary outcome will be functional limitations at 24 weeks. Secondary outcomes will include functional limitations at 6 and 12 weeks, as well as pain intensity, health-related quality of life, region-specific symptoms and functional limitations, pain-related fear, pain catastrophizing, pain self-efficacy, and satisfaction with care at 6, 12, and 24 weeks. The secondary objective is to investigate the cost-effectiveness of a stepped care model compared to usual medical care and usual rehabilitation care for managing MSKDs in Canadian adults over a 24-week period. We hypothesize that the stepped care model will be noninferior to usual medical care and usual rehabilitation care in terms of effectiveness. In addition, we expect health care costs to be significantly lower for the stepped care model due to a reduction in the use of costly resources, such as consultations with health care providers and medical investigations (eg, laboratory tests and medical imaging).

Methods

Study Design

A pragmatic, noninferiority, multiarm, parallel-group randomized controlled trial will be conducted in the Quebec

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City area, Canada, targeting individuals with 1of the 4 most common MSKDs encountered in primary care: low back pain, neck pain, rotator cuff–related shoulder pain, or anterior knee pain [30,31] (see Figure 1). This pragmatic trial will reflect real-world clinical practice, as participants will receive care in routine medical and rehabilitation settings [32-37]. The trial is registered at ClinicalTrials.gov (NCT06832852), and follows the multiarm extension of the Consolidated Standards of Reporting Trials (CONSORT) guidelines [38], as well as the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines [39,40]. Interventions in each arm are described according to the Template for Intervention Description and Replication (TIDieR) checklist [41].

Figure 1. Study flow diagram.

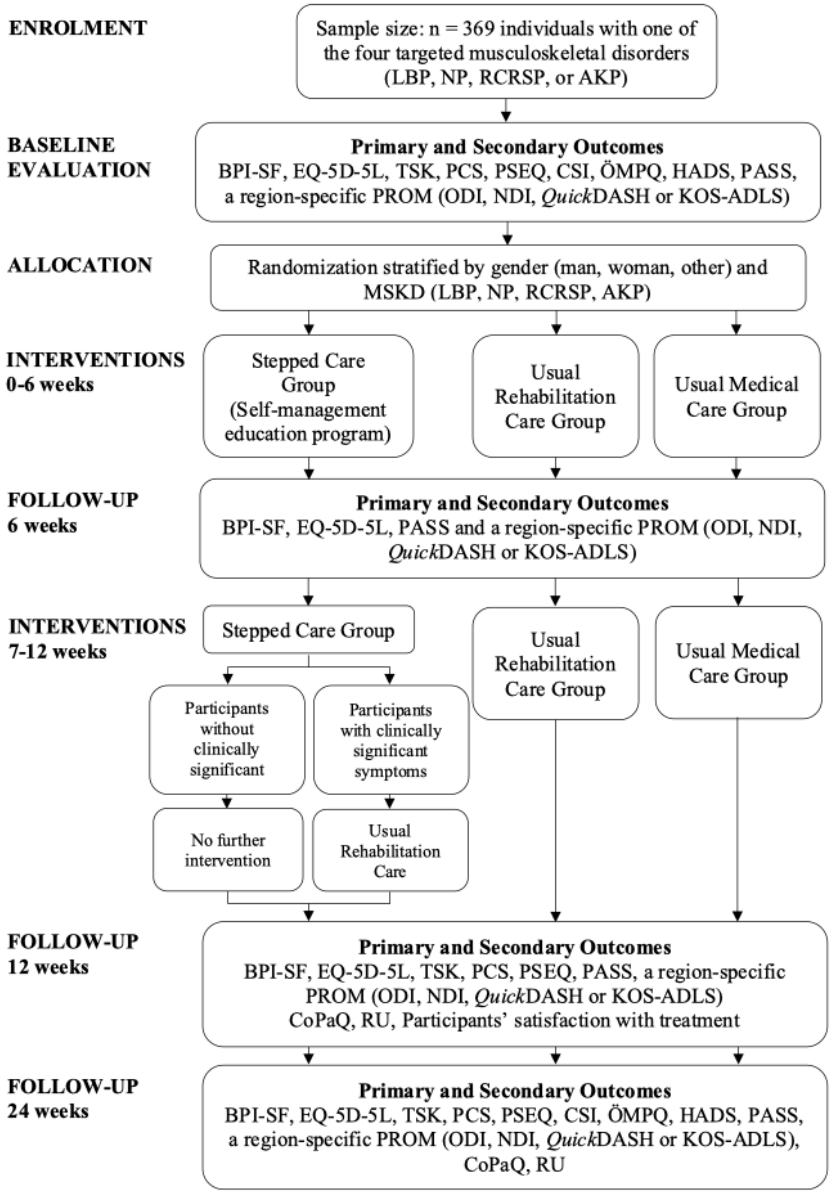

Participants will be recruited through a convenience sample using various channels, including social media platforms (Facebook, LinkedIn, and Instagram), electronic mailing lists of students, employees, and retirees at Université Laval, and advertisements in local newspapers. Interested individuals will be invited to contact the research team by email or phone. Initial eligibility screening will be conducted online using a web-based questionnaire through REDCap (Research Electronic Data Capture; Vanderbilt University) platform [42]. During this process, potential participants will receive information outlining the nature and objectives of the study. A follow-up phone interview with a team member will provide further eligibility screening and an opportunity to discuss the study details.

Individuals who meet the initial criteria will be asked to provide electronic informed consent, complete the primary and some secondary outcome measures using web-based patient-reported outcome measures within REDCap (see Figure 2), and attend an in-person meeting at the Center for Interdisciplinary Research in Rehabilitation and Social Integration (Cirris), a research center affiliated with Université Laval in Quebec City. During this meeting, an experienced physiotherapist will confirm eligibility using standardized screening questionnaires and, for certain diagnoses (eg, rotator cuff–related shoulder pain and

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anterior knee pain), additional physical tests. All screening questionnaires used throughout the recruitment process are provided in Multimedia Appendix 1.

Figure 2. Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) diagram of enrolment, interventions, and assessments. BPI-SF: Brief Pain Inventory–Short Form; CoPaQ: Cost for Patients Questionnaire; CSI: Central Sensitization Inventory; HADS: Hospital Anxiety and Depression Scale; KOS-ADLS: Knee Outcome Survey Activities of Daily Living Scale; NDI: Neck Disability Index; ODI: modified Oswestry Disability Index; ÖMPQ: OREBRO musculoskeletal pain questionnaire; PASS: Patient Acceptable Symptom State; PCS: Pain Catastrophizing Scale; PSEQ: Pain Self-Efficacy Questionnaire; QuickDASH: shortened version of the Disabilities of the Arm, Shoulder, and Hand; TSK: Tampa Scale of Kinesiophobia.

	Enrolment		Allocation	Post-Allocation		
TIMEPOINT	**Before in-person meeting**	**In-person meeting**	**T_0**	**T_6**	**T_{12}**	**T_{24}**
ENROLMENT						
Eligibility screen	X	X				
Informed consent	X					
Allocation			X			
INTERVENTIONS						
Stepped Care			◆—	——	—◆	
Usual Rehabilitation Care			◆—	——	—◆	
Usual Medical Care			◆—	——	—◆	
ASSESSMENTS						
Baseline characteristics		X				
Expectations of recovery		X	X			
BPI-SF: pain interference	X			X	X	X
BPI-SF: pain severity	X			X	X	X
EQ-5D-5L	X			X	X	X
TSK	X				X	X
PCS	X				X	X
PSEQ	X				X	X
CSI		X				X
ÖMPQ		X				X
HADS		X				X
ODI, NDI, *Quick* DASH or KOS-ADLS	X			X	X	X
PASS	X			X	X	X
CoPaQ					X	X
Resources use					X	X
Satisfaction with intervention					X	

During the in-person meeting, enrolled participants will also complete the baseline evaluation, which includes questionnaires on sociodemographic characteristics (including sex at birth and gender identity), medical history, symptom onset context, work restrictions, recovery expectations (participants' expectations regarding the intervention's potential effectiveness on their pain,

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work capacity, and ability to engage in leisure activities) [43], and treatment preferences (eg, preferred health care provider, desired duration and frequency of consultations) [44,45]. Finally, the remaining secondary outcome measures will be evaluated on-site using web-based patient-reported outcome measures in REDCap. Participants will then be randomly assigned to one of three 12-week intervention groups: stepped care, usual rehabilitation care, or usual medical care. Recovery expectations will be reassessed immediately after participants receive an explanation of their assigned intervention.

Primary and secondary outcome measures will be reassessed online using web-based patient-reported outcome measures in REDCap at 6, 12, and 24 weeks post allocation (see Figures 1 and 2).

Population and Sample Size

Participants must be aged between 18 and 65 years, present with 1 of the 4 targeted MSKDs (low back pain, neck pain, rotator cuff–related shoulder pain, and anterior knee pain), and have experienced pain for at least 6 weeks. Potential participants will be excluded if they: (1) are unavailable for the 12-week intervention; (2) cannot understand or read French or English; (3) have a diagnosis of rheumatoid, inflammatory or neurodegenerative diseases; (4) have signs of upper (eg, bilateral paresthesia, hyperreflexia, or spasticity) or lower (eg, decreased sensation or strength in dermatomes and myotomes, hypotonia, or hyporeflexia) motor neuron lesions; (5) have received a corticosteroid injection or any other type of injection (eg, platelet-rich plasma, prolotherapy, and hyaluronic acid) in the past 3 months for their current condition; and (6) have cognitive impairments interfering with participation (mini—mental state examination administered if doubts arise; score must be ≥24) [46,47]. Participants who previously received conservative management will be eligible if at least 6 weeks have passed since their last intervention (including prescribed condition-specific exercises or medication). Specific inclusion and exclusion criteria for each MSKDs are the following.

Low Back Pain

Inclusion criteria are (1) nonspecific low back pain with or without radiation to the lower limbs, (2) minimum score of 15/100 on the modified Oswestry Disability Index (ODI; 1.5 times the minimally clinically important difference [48], to ensure participants have clinically significant symptoms). Nonspecific low back pain is defined as low back pain that cannot be attributed to a specific condition. Exclusion criteria are (1) low back pain related to specific conditions (eg, vertebral fracture, infections, and neuropathic pain, with a score of ≥4 on the DN4 [Douleur Neuropathique 4, a screening questionnaire used to identify neuropathic pain] questionnaire [49]) and (2) history of spine surgery.

Neck Pain

Inclusion criteria are (1) nonspecific neck pain with or without radiation to the upper limbs and (2) a minimum score of 21/100 on the Neck Disability Index (1.5 times the minimally clinically important difference [50]) to ensure participants have clinically significant symptoms). Exclusion criteria are (1) neck pain related to specific conditions (eg, vertebral fracture, infections, and neuropathic pain; ≥4 on the DN4 questionnaire [49]), (2) history of spine surgery, or (3) signs of upper or lower motor neuron lesions.

Rotator Cuff–Related Shoulder Pain

Inclusion criteria are (1) shoulder pain attributed to rotator cuff–related shoulder pain (pain over the deltoid or upper arm region, pain associated with arm movement [painful arc of movement], and familiar pain reproduced with loading or resisted testing during external rotation of the arm) [36,51], and (2) a minimum score of 15/100 on the shortened version of the Disabilities of the Arm, Shoulder, and Hand (QuickDASH; 1.5 times the minimally clinically important difference [52], to ensure participants have clinically significant symptoms). Exclusion criteria are (1) history of shoulder surgery, dislocation, or fracture; (2) presence of severe osteoarthritis, symptomatic acromioclavicular joint pathology, or adhesive capsulitis (defined as restriction of passive glenohumeral movement of at least 30% for two or more directions); and (3) full thickness rotator cuff tear, identified by imaging or clinical tests (lag signs and gross weakness) [53,54].

Anterior Knee Pain

Inclusion criteria are (1) anterior knee pain during walking, running or going up or down stairs, or during at least two activities among: kneeling, squatting, and resisted knee extension [55] and (2) maximum score of 79/100 on the Knee Outcome Survey Activities of Daily Living Scale (1.5 times the minimally clinically important difference [56], to ensure participants have clinically significant symptoms). Exclusion criteria are (1) history of knee surgery or patellar dislocation, and (2) pain believed to originate either from the meniscus [57] or any knee ligament based on clinical tests.

The primary objective is to assess the equivalence between the stepped care model and the 2 usual care models. With 123 participants per group, we will have 80% power to test the noninferiority of the stepped care model compared to usual rehabilitation care and usual medical care, using a noninferiority margin of 2.0 (out of 10) points on the primary outcome measure. This margin is based on the highest suggested minimally clinically important difference for the Pain Interference subscale of the Brief Pain Inventory—Short Form (BPI-SF) [58]. The sample size calculation assumes a true mean difference of 0 between groups, and an SD of 1.8 in the usual care groups [59], a 15% dropout rate at the 24-week follow-up [20,60-62], and a 1-sided alpha level of .025.

Randomization and Blinding

Randomization lists (1:1:1) were generated using a computer-based random number generator by an independent research assistant not involved in the project. Blocked randomization (with random block sizes of 3, 6, and 9) was used to ensure balanced group allocation. Given that randomization was stratified by gender (men, women, and other) and MSKD (low back pain, neck pain, rotator cuff-related shoulder pain, and anterior knee pain), 12 separate lists were generated. The randomization lists were integrated into the REDCap randomization module, eliminating the need for sealed envelopes. After the baseline evaluation, the research associate

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will enter the participant's gender and MSKD type into REDCap, which will then generate the assigned group. The allocation will appear in a secure, concealed table within REDCap, preventing any modifications. The research associate will then inform the participant and the medical or physiotherapy clinic of the assigned group to schedule the participant's first appointment.

Blinding of treatment providers and participants is not feasible due to the nature of the interventions. However, the statistician conducting the analyses will remain blinded to group allocation. Since all study outcomes are self-reported and collected via REDCap, an outcome assessor is not required. Participants will interact with a research associate only at baseline, before randomization. Participants will be informed that they are enrolled in 1 of 3 groups, that all groups receive high-value, individualized care, and that the number and frequency of follow-up sessions may vary. However, they will not be told whether they are assigned to a stepped care, usual rehabilitation care, or usual medical care, thereby maintaining partial blinding regarding group allocation. They will only be informed about the interventions received by participants in the other groups after completing the 24-week follow-up. To minimize potential contamination, each group will receive treatment in separate clinics: Usual medical care in medical clinics, while stepped care and usual rehabilitation care will be provided in different physiotherapy clinics. Co-interventions will be monitored at each follow-up using a questionnaire on REDCap.

Intervention

Usual medical care will be provided by family physicians practicing in family medicine groups or university-affiliated family medicine groups, while usual rehabilitation care and stepped care will be provided by physiotherapists practicing in physiotherapy clinics across the Quebec City area. To enhance the generalizability of findings to the broader health care workforce, family physicians and physiotherapists with varying levels of experience, from early-career to experienced clinicians, will be included. Each intervention will have a maximum duration of 12 weeks. All consultation fees with the family physicians and physiotherapists related to the study will be covered by the research team.

Stepped Care Group

During the first 6 weeks, participants in the stepped care group will engage in a web-based self-management education program, supplemented by 2 individual educational sessions with a physiotherapist. The first session (60 minutes) will begin with a clinical evaluation by the physiotherapist responsible for the educational intervention, followed by an education session covering the anatomy, function, and diagnosis of the affected area, basics of pain neuroscience, and condition-specific guidance on load management [27]. Participants will also receive strategies for pain and activity (pacing) self-management, optimal sleep and work positions, and key lifestyle factors such as stress management and nutrition [19,63]. The importance of physical activity will be emphasized, with recommendations aligned with World Health Organization guidelines (ie, 150-300 minutes of moderate-intensity activity per week), and adapted to each participant's condition and physical capacity. Throughout the session, physiotherapists will foster open dialogue, personalizing discussions to address each participant's needs and goals, answering questions, dispelling myths or misconceptions, providing reassurance, and discussing prognosis. An educational website, developed in collaboration with 7 patient partners, will also be introduced. It offers additional resources, including educational videos, summaries of key topics, and supplementary material for reference. Participants will be encouraged to explore these resources independently during the following weeks. The research team will have access to data on time spent on the website throughout the study.

The second educational session (30 minutes), scheduled 2 to 4 weeks later, will focus on reinforcing key concepts and providing long-term recommendations. The physiotherapist will begin by reviewing the participant's condition and assessing their understanding of the material from the first session and the website. They will verify whether the participant has engaged with the educational website's online content, address any remaining questions, offer personalized guidance, and provide recommendations for long-term self-management. While the second educational session will be preferably conducted in person, it may also be held via telehealth, depending on the participant's preference. Following each session, the physiotherapist will complete a brief REDCap questionnaire documenting the topics discussed.

At the 6-week follow-up evaluation, participants in the stepped care group will be assessed using a region-specific patient-reported outcome measure to determine if their condition has resolved. Participants who no longer experience clinically important symptoms at the 6-week follow-up will be classified as "resolved" and will not receive further intervention. Those with scores exceeding the minimal clinically important difference thresholds on their region-specific patient-reported outcome measure (low back pain >10 on the ODI; neck pain >14 on the Neck Disability Index [NDI]; rotator cuff-related shoulder pain >10 on the QuickDASH; and anterior knee pain <86 on the Knee Outcome Survey Activities of Daily Living Scale [KOS-ADLS]) will be considered "unresolved" and will receive follow-up rehabilitation interventions. This dichotomization approach between "resolved" and "unresolved" MSKDs was chosen because, while an improvement greater than the minimal clinically important difference would be indicative of clinically significant improvement, participants may still experience substantial symptoms and limitations if their total score remains above the minimal clinically important difference threshold [64]. Participants classified as "unresolved" will undergo a rehabilitation intervention supervised by a physiotherapist over the following 6 weeks. This intervention will mirror the usual rehabilitation care group's approach but will be condensed into a maximum of 5 sessions within a 6-week period. To prevent bias in patient-reported outcome measures responses, participants will not be informed during the first 6 weeks that they may be eligible for additional physiotherapy sessions if their symptoms remain clinically significant at the 6-week follow-up. Similarly, participants classified as "resolved" will not be informed at the 6-week mark that additional treatments could have been offered if their symptoms

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had persisted after the educational intervention. This information will only be disclosed at the end of the study, at the 24-week follow-up.

Usual Rehabilitation Care Group

Participants will engage in a pragmatic 12-week rehabilitation intervention led by a physiotherapist, consisting of up to 10 individualized sessions, each lasting 30 minutes (except for the initial 60-minute session), along with an individualized home exercise program. During the first session, the physiotherapist will conduct an initial clinical evaluation. Given the pragmatic nature of the intervention, its structure and modalities will remain flexible, shaped collaboratively by the physiotherapist and the participant. This approach will take into account the participant's goals and preferences, as well as the observed disabilities and the severity of the condition. Exercises may be used to improve strength, endurance, flexibility, the ability to sustain mechanical load, and dynamic control, as needed. In addition, participants may receive educational information related to their painful area, along with advice on pain and load management, activity modification, and any other relevant topics as determined by the treating physiotherapist. Manual therapy techniques (eg, massage, mobilization, or manipulation) and other passive interventions (eg, electrotherapy, heat, ice, dry needling, or any type of taping) may be used during sessions based on pragmatic clinical decision-making [65]. At the end of each supervised session, participants may receive individualized exercises, with progression, to perform at home between sessions.

If participants become symptom-free before completing the 10 sessions, or if the participant and physiotherapist determine that no further sessions are needed, treatment will be discontinued. Participants will then receive advice, recommendations, and home exercises as appropriate. If needed, they will have the option to resume the intervention within the 12-week period. Participants will not be restrained from using over-the-counter medications for pain relief if deemed helpful. If pain persists, the physiotherapist may refer participants to a family physician for further medical evaluation and management, which may include diagnostic tests (clinical, laboratory, or imaging), pharmacological pain management, and corticosteroid injections. Participants may also be referred to other health care providers (eg, psychologists, occupational therapists, and kinesiologists). However, these referrals will not be managed by the research team, and the associated costs will be the participant's responsibility. After each supervised session, the physiotherapist will complete a short REDCap questionnaire detailing the intervention modalities used, exercises prescribed, any referrals made, and the follow-up plan.

Usual Medical Care Group

Participants will take part in a pragmatic 12-week medical intervention led by a family physician, consisting of up to 3 consultations during this period. The initial in-person meeting at the medical clinic will involve a comprehensive evaluation by the family physician, which may include diagnostic clinical tests, laboratory tests, and medical imaging if necessary. Based on this assessment, the family physician and participant will collaboratively determine the most appropriate management approach. Interventions may range from reassurance and patient education on pain management strategies to pharmacological treatments and corticosteroid injections. If needed, the family physician may refer participants to a physiotherapist, medical specialist, or other health care providers (eg, psychologists, occupational therapists, kinesiologists, acupuncturists, or chiropractors). However, these referrals will not be managed by the research team, and the associated costs will be the participant's responsibility.

During the 2 potential follow-up meetings, the participant's condition will be reassessed, and the intervention will be adjusted accordingly. While these meetings are preferably conducted in person, they may also be held by phone or via telehealth, depending on the participant's preference. If a participant becomes symptom-free before completing the 3 sessions, or if the participant and family physician decide that no further sessions are required, treatment will be discontinued, and appropriate advice and recommendations will be provided. However, they will have the option to resume the intervention within the 12-week period if needed. Given the pragmatic nature of the intervention, its structure remains flexible, allowing for adaptation based on the participant's goals and preferences and clinical presentation. Following each session, the family physician will complete a brief REDCap questionnaire documenting the management approach used (eg, education, medication, and injection), any imaging or laboratory tests ordered, any referrals made, and the follow-up plan.

Training of Treatment Providers

Given the pragmatic nature of the interventions in the usual medical care and usual rehabilitation care groups, the physiotherapists and family physicians in these groups will not receive specific training related to the intervention. However, they will attend a 60-minute meeting outlining the study objectives and relevant procedures (eg, maximum number of consultations, the brief questionnaire to be completed in REDCap, and the expectation that they provide care according to their usual practices).

Physiotherapists delivering the educational intervention were selected based on their expertise in a clinic specializing in educational approaches for MSKDs. They will participate in a 2-hour in-person training session led by 3 members of the research team. This training will emphasize the educational components to be delivered and the importance of establishing a strong therapeutic alliance with participants. The study's educational website will also be presented and explained during this session. To ensure consistency, follow-up meetings will be held twice a year to discuss strategies for maintaining standardization and to address any challenges that arise.

It should be noted that physiotherapists and family physicians providing usual medical care and usual rehabilitation care will not have access to the educational website, nor will it be presented to them.

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Primary and Secondary Outcome Measures

Overview

The study outcomes will be assessed online using web-based patient-reported outcome measures on REDCap [42]. Patient-reported outcome measures integrated within REDCap are designed to prevent incomplete submissions, ensuring that all questionnaires are fully completed. The primary outcome will be functional limitations at 24 weeks, as measured with the Pain Interference subscale of the BPI-SF. Secondary outcomes include pain severity as measured with Pain Severity subscale of the BPI-SF, health-related quality of life (HRQoL) as measured with the EQ-5D-5L, pain-related fear as measured with Tampa Scale for Kinesiophobia (TSK), pain catastrophizing as measured with Pain Catastrophizing Scale (PCS), pain self-efficacy as measured with Pain Self-Efficacy Questionnaire (PSEQ), symptoms related to central sensitization using the Central Sensitization Inventory (CSI), risk of long-term disability and poor recovery as measured with the short version of the OREBRO musculoskeletal pain questionnaire (ÖMPQ-sf), and anxiety and depressive symptoms as measured with Hospital Anxiety and Depression Scale (HADS). Furthermore, region-specific symptoms and functional limitations will be assessed at all time points using the modified ODI for participants with low back pain, the NDI for those with neck pain, the QuickDASH for participants with rotator cuff–related shoulder pain, and the KOS-ADLS for those with anterior knee pain. Finally, participants' satisfaction with the treatment will be assessed at the end of the intervention period (week 6 for the stepped care group, and week 12 for the "unresolved" participants in the stepped care, usual rehabilitation, and usual medical care groups). Validated French or English versions of all questionnaires are available. The psychometric properties of all patient-reported outcome measures have been established in populations with MSKDs [66-70]. Given the number of patient-reported outcome measures assessed at baseline, their completion will be divided into 2 sequences. The first sequence (BPI-SF, EQ-5D-5L, TSK, PCS, PSEQ, and region-specific patient-reported outcome measure) will be completed before the in-person meeting, while the second sequence (CSI-9, ÖMPQ-sf, and HADS) will be completed during the in-person meeting. Although most outcomes will be assessed at all measurement time points, some secondary outcomes will only be reassessed at 12 or 24 weeks to minimize the burden on participants. Figure 2 provides an overview of when the patient-reported outcome measures will be assessed at the different measurement time points.

Primary Outcome: Functional limitations

The BPI-SF is an 11-item questionnaire comprising two subscales: the 4-item Pain Severity subscale and the 7-item Pain Interference subscale. It has been shown to be valid, reliable, and responsive for MSKDs [71-74]. The Pain Interference subscale, measured at the 24-week follow-up, will be the primary outcome measure, assessing the extent to which pain disrupts daily functioning [73,74]. Its minimally clinically important difference ranges from 1.3 to 2.0 out of 10 points [58].

Secondary Outcomes: Generic Patient–Reported Outcome Measures

Secondary outcomes comprised pain severity, HRQoL, pain-related fear, pain catastrophizing, pain self-efficacy, symptoms related to central sensitization, risk of long-term disability, and anxiety and depressive symptoms. Pain severity: The Pain Severity subscale of the BPI-SF consists of 4 items that assess pain intensity [75]. HRQoL: The EQ-5D-5L is a 5-item generic HRQoL questionnaire evaluating five dimensions: mobility, self-care, usual activities, pain and discomfort, and anxiety and depression. These dimensions define 55=3125 possible health states, which can be converted into a Canadian weighted index score [76]. The weighted index scores at each time point will be used to calculate the quality-adjusted life years for each participant. Quality-adjusted life years will be the primary outcome measure for the cost-effectiveness analysis and will be used to estimate the incremental cost-effectiveness ratio (ICER) [66]. Pain-related fear: The TSK is a questionnaire assessing beliefs and behaviors related to pain, with a focus on the perception that pain is damaging [77]. The 13-item version will be used. Pain catastrophizing: The PCS is a questionnaire designed to identify catastrophic thoughts about pain [78]. The 13-item version will be used. Pain self-efficacy: The PSEQ measures a patient's confidence in performing daily activities despite pain [79]. The 10-item version will be used. Symptoms related to central sensitization: The CSI evaluates the frequency of common symptoms associated with central sensitization [80,81]. The 9-item version will be used. Risk of long-term disability: The ÖMPQ-sf is a questionnaire that assesses psychosocial and pain-related factors to predict the risk of long-term disability and delayed return to work in individuals with MSKDs [82]. The 10-item version will be used. Anxiety and depressive symptoms: The HADS is a 14-item questionnaire used to screen the presence of anxiety and depression [70].

Secondary Outcomes: Region-Specific Symptoms and Functional Limitations Patient-Reported Outcome Measures

Participants will only complete the region-specific patient-reported outcome measure relevant to their condition. Low back pain: the modified ODI (minimal detectable change=10 points and minimally clinically important difference=10 points) is a 10-item questionnaire assessing the impact of low back pain on activities of daily living [48,83-86]. Neck pain: NDI (minimal detectable change=10 points and minimally clinically important difference=14 points [50,87]) is a 10-item questionnaire measuring self-reported disability related to neck pain [50]. Rotator cuff-related shoulder pain: QuickDASH (minimal detectable change=11 points and minimally clinically important difference=10 points) is an 11-item questionnaire, validated in individuals with rotator cuff–related shoulder pain [88], that assesses difficulty in performing daily activities and the severity of the upper limb symptoms [89]. Anterior knee pain: KOS-ADLS (minimal detectable change=8.3 points and minimally clinically important difference=14 points) is a 14-item knee-specific questionnaire that evaluates symptoms and functional limitations [90].

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Secondary Outcomes: Participants' Satisfaction

Participants' satisfaction with their condition will be assessed at each evaluation time point using the Patient Acceptable Symptom State [64,91]. This measure asks patients whether they consider their current state acceptable and requires them to rate their satisfaction on a 0-100 numeric scale [73]. At the end of the intervention, participants will also evaluate their satisfaction with various aspects of the treatment received. They will rate their overall satisfaction ("not satisfied," "satisfied," and "very much satisfied"), the adequacy of treatment duration ("too short," "long enough," and "too long"), treatment frequency, and the time spent with the health care providers during sessions ("not enough," "just right," and "too much") using a 3-item Likert scale [73,75,92].

Secondary Outcomes: Health Care Resource Use and Health Costs

At the 12-week (covering weeks 0 to 12) and 24-week (covering weeks 13 to 24) follow-up assessments, participants will complete 2 questionnaires: one assessing resource use from the perspective of both public health services and private insurers, and another capturing out-of-pocket costs incurred by participants. For the latter, the Cost for Patients Questionnaire (CoPaQ) will be used, a validated tool that measures patient-related costs, including those incurred by informal caregivers [93,94]. The CoPaQ covers expenses such as copayments, transportation to treatment sessions, childcare, time off work, and lost income. The resource use questionnaire will collect data on health care use, including visits to family physicians, physiotherapists, and other health care providers, as well as medical imaging, laboratory tests, and indirect costs. It will also collect information on each participant's private health insurance and the extent of coverage for each resource used, where applicable. The average cost of consultations with each type of provider will be determined based on reimbursement rates from both the public and private payers.

Data Integrity and Analysis

All collected data will be securely stored on a server hosted at Université Laval, with access restricted to the research team. Data will be retained for 7 years after the study's completion to support planned publications, after which it will be permanently deleted. Given the low-risk nature of this trial, a Data Monitoring Committee is not required, and no interim analysis will be conducted.

Statistical Analysis Plan

Descriptive statistics will be used to summarize participants' characteristics and outcome measures at the different measurement times. Participants who withdraw from the study and the reasons for withdrawal will be analyzed. Any harm or unintended effects will be recorded by both the treating family physician and physiotherapist at the beginning of each consultation, as well as by the participants during the follow-up evaluations on REDCap. If a participant experiences an adverse event, the principal investigator will report it to the Ethics Committee. However, since the interventions included in this trial are commonly used in clinical practice and are generally well tolerated, no major adverse events directly related to the intervention are expected, except perhaps a temporary increase in pain.

For each of the primary and secondary patient-reported outcome measures, repeated measures analyses will be performed using linear mixed models with a random effect by participant to account for the correlation present in repeated measures within individuals. The model allows assessment of the group and time effects, as well as the group-by-time interaction. An intention-to-treat analysis will be used. Gender and type of MSKD will be used to test the interaction between the group effect and the strata in order to test whether the comparison across interventions depends on gender or type of MSKD. Residual analysis will be performed to verify that the assumptions of normality and homoscedasticity are met. If not, the model will be extended to a generalized linear mixed-model framework. Effect sizes will be presented as the standardized differences between treatment groups in the mean weekly improvements over 12 and 24 weeks. Satisfaction will be compared using chi-squared tests, Mann-Whitney tests, or independent *t* tests.

For economic analyses, the total cost of an episode of care will be calculated from the perspectives of the public health service, the participants, and private insurers. ICERs will then be computed from 3 perspectives: the public health service, the participant, and society. The ICERs will be measured as the difference between the mean costs divided by the difference in effectiveness at 24 weeks between the stepped care model and each of the usual care models [95].

Mitigation Plan

As with any clinical trial, maintaining adherence to the intervention and follow-ups may be challenging for some participants. To encourage compliance, several strategies will be implemented. Medical and rehabilitation interventions will be held in clinics offering both daytime and evening appointment options. Follow-up assessments will be conducted online to minimize travel requirements. Automated reminders will be sent via email as needed, and research associates will be available to provide assistance via email or phone. In addition, participants will receive CAD $40 (approximately US $28.50 as of October 2025) at the baseline evaluation to cover travel expenses and another CAD $40 (approximately US $28.50 as of October 2025) at the end of the project to compensate for time spent completing follow-up questionnaires.

Ethical Considerations

Ethics approval has been granted by the Comité d'éthique de la recherche sectoriel en réadaptation et intégration sociale du CIUSSS de la Capitale-Nationale (Rehabilitation and Social Integration section; #2024-2982). All participants will receive a comprehensive information and consent form outlining the nature and objectives of the study.

Participation is entirely voluntary. Participants may decline to take part or withdraw from the study at any time, without providing a reason, by informing the principal investigator or a member of the project staff. They may also request that any data collected from them be withdrawn.

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Electronic informed consent will be required before enrollment. Participants' confidentiality will be maintained by the research team throughout the project in accordance with current regulations. Participants' identities will be coded, and all data will be stored in secure folders within the research team's offices or in password-protected files. It will not be possible to identify participants in any publications.

Patient and Public Involvement

The website used during the first six weeks of the stepped care intervention was co-created with seven patient-partners living with chronic MSKDs (mean age 49.4 y, SD 14.7 y; 71% women). The website underwent iterative development until it received approval from the patient-partners. They also provided feedback on the selected set of patient-reported outcome measures to ensure that the completion burden was acceptable and that all important constructs were adequately assessed. Additionally, a patient partner contributed to the design of the study protocol to ensure its relevance and alignment with patient needs.

Results

The Edu-First trial is funded by a project grant from the Canadian Institutes of Health Research (grant #495615), with funding spanning from October 2023 to September 2028.

Recruitment began on January 31, 2025, with the first participants enrolled in February 2025. As of September 2025, a total of 65 participants have been enrolled. Recruitment is expected to continue for up to 3 years, aiming for approximately 10 new participants per month, and is anticipated to be completed by Winter 2028. Data analysis and manuscript preparation are projected to take up to 6 months, with the first manuscripts anticipated for submission by Fall 2028.

Discussion

Principal Findings

We anticipate that the stepped care model will be noninferior to usual medical care and usual rehabilitation care in terms of treatment effectiveness. In addition, we expect this model to reduce health care costs by limiting the use of expensive resources, such as consultations with health care providers and medical investigations. As health care costs for MSKDs continue to rise, implementing a stepped care model—where patient education and self-management advice are prioritized initially, and usual care is reserved for those whose symptoms persist—could improve access to care without compromising quality. This approach also empowers patients to take an active role in managing their condition, overall health, and well-being from the outset.

MSKDs are among the most common reasons for primary care consultations, with up to 20% of adults seeking care for these conditions annually [8], and approximately 30%-40% of individuals with MSKDs reporting contacting their family physician for these complaints [30]. Despite their high prevalence, MSKDs remain difficult to treat effectively beyond the acute phase [96-98]. Given the significant impact of MSKDs on individuals' activities and participation, as well as their contribution to societal burdens such as work loss, disability pensions, early retirement, and increased demand for social support [3,4], it is crucial to explore innovative care models to address these challenges.

The findings from this study could inform systemic changes in care delivery, improving access to treatment while reducing the average cost per care episode. Ultimately, this study aims to provide robust evidence supporting more efficient, patient-centered care models for a prevalent and costly set of conditions.

Strengths and Limitations

This study is designed as a pragmatic randomized controlled trial, reflecting real-world clinical practice and enhancing the generalizability of its findings. Key strengths include the direct comparison of the stepped care model with 2 of the most widely used care models, the inclusion of cost-effectiveness analyses, and the focus on patient-centered outcomes. Potential limitations include the reliance on patient-reported data for some outcomes, which may introduce reporting bias, and the heterogeneity of MSKD presentations, which could influence treatment response. In addition, given the pragmatic nature of the trial, variability in usual care practices may impact the consistency of comparator interventions.

Future Directions

If the stepped care model proves to be noninferior in effectiveness and superior in cost-effectiveness, the results could guide systemic improvements in the delivery of MSKD care. Wider implementation of this model may improve access to health care services, particularly in primary care settings, while reducing the economic burden on both patients and the health care system. Future research could explore long-term outcomes, patient adherence to self-management strategies, and the applicability of this model to other musculoskeletal conditions or health care systems.

Dissemination Plan

At the conclusion of the project, targeted materials will be developed for patients, clinicians, managers, and decision-makers. These will include infographics, podcasts, webinars, presentations, and videos, which will be shared through a variety of clinical and community platforms, including the websites and social media channels of professional associations and key partners. Academic dissemination will include peer-reviewed manuscripts and conference presentations to ensure broad visibility within the scientific community.

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Authors' Contributions

Conceptualization: J-SR, HM-A, M-OD, F Desmeules
Methodology: J-SR, HM-A, F Desmeules, M-OD, JT, AMP, M Lamontagne, M Laberge, F Dupuis, FF, IN, GS
Formal analysis: EM
Investigation (participant recruitment and data collection): JT, F Dupuis, FF, IN
Project administration: JT
Supervision: J-SR
Writing – original draft: J-SR
Writing – review & editing: J-SR, HM-A, M-OD, AMP, M Lamontagne, GS, JT, M Laberge, F Dupuis, FF, IN, EM, F Desmeules

Conflicts of Interest

ML is a member of the scientific advisory board and a speaker for PendoPharm. None declared by the other authors.

Multimedia Appendix 1
Recruitment process.
[DOCX File , 34 KB - resprot_v14i1e77574_app1.docx]

Multimedia Appendix 2
Peer-review report by the Project. Grant / Subvention Projet - Clinical Investigation - B 2 / Investigation clinique B 2 - Canadian Institutes of Health Research (CIHR) / Instituts de recherche en sante´ du Canada (IRSC).
[PDF File (Adobe PDF File), 30 KB - resprot_v14i1e77574_app2.pdf]

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Abbreviations

BPI-SF: Brief Pain Inventory – Short Form
CoPaQ: Cost for Patients Questionnaire
CONSORT: Consolidated Standards of Reporting Trials
CSI: Central Sensitization Inventory
HADS: Hospital Anxiety and Depression Scale
HRQoL: health-related quality of life
ICER: incremental cost-effectiveness ratio
KOS-ADLS: Knee Outcome Survey Activities of Daily Living Scale
MSKD: musculoskeletal disorder
NDI: Neck Disability Index
ODI: modified Oswestry Disability Index
ÖMPQ: OREBRO musculoskeletal pain questionnaire
PCS: Pain Catastrophizing Scale
PSEQ: Pain Self-Efficacy Questionnaire
QuickDASH: shortened version of the Disabilities of the Arm, Shoulder, and Hand
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TIDieR: Template for Intervention Description and Replication
TSK: Tampa Scale of Kinesiophobia

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Protocol

Multilevel Estimation of the Relative Impacts of Social Determinants on Income-Related Health Inequalities in Urban Canada: Protocol for the Canadian Social Determinants Urban Laboratory

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Abstract

Background: Two decades of research have highlighted persistent income-related health inequities in Canada across municipal, provincial, and national levels. While there is broad consensus among researchers, advocates, and health professionals that social determinants are the primary drivers of health, the empirical foundation supporting this remains relatively limited. A current renaissance in health system data access offers an opportunity to assess the multilevel impact of social factors on health inequalities, yet this potential remains underused.

Objective: This project aims to examine how social, economic, and political conditions shape health inequalities and investigate how structural and intermediate determinants explain disparities across national, provincial, city, neighborhood, and individual levels.

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Methods: We will create the Canadian Social Determinants Urban Laboratory (CSDUL), a multilevel, longitudinal, virtual data environment that integrates 15 existing databases from Statistics Canada, the Canadian Institute for Health Information, the Canadian Urban Environmental Health Research Consortium, and DMTI Spatial. Guided by the World Health Organization social determinants of health framework, CSDUL will initially cover 2011 to 2015 due to data completeness and expand as additional years become available. CSDUL builds on Statistics Canada's Canadian Population Health Survey and will link survey data to administrative and health records, including hospital discharges, ambulatory care, mortality, cancer registries, and longitudinal tax files. Area-level indicators will be added using historical postal codes and geospatial boundaries. Organized through a hub-and-node model, CSDUL includes a central hub and 5 research nodes. We will develop and validate area-based indicators to study social determinants at micro (individual), meso (neighborhood, city, and province), and macro (national) levels. A core deliverable is to assess the strengths and limitations of survey and administrative data for health research and derive variables accordingly. After developing CSDUL, we will replicate World Health Organization Regional Office for Europe income-related health inequality analysis for urban Canada and analyze the impact of social determinants on outcomes. We will apply a 2-fold Oaxaca-Blinder decomposition between the lowest and highest urban income quintiles. A major strength of CSDUL is its capacity to analyze how diverse determinants shape health across subgroups (eg, gender), identifying key drivers of health outcomes.

Results: The indicators to be used in CSDUL are being developed and validated by the contributing nodes. In collaboration with node 3, we are constructing measures of social capital using DMTI Spatial Points of Interest data. A prototype version of CSDUL incorporating a limited set of indicators has been developed in Statistics Canada's Research Data Centre. We anticipate receiving the finalized indicators from the nodes by August 2025 to September 2025 and aim to complete the decomposition analysis by December 2025.

Conclusions: Multisectoral interventions are most effective when they are customized to meet the unique needs of specific subpopulations using robust and multilevel data sources such as CSDUL.

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KEYWORDS

social determinants of health; health inequity; data linkage; decomposition analysis; multilevel model

Introduction

Background

Despite a mounting consensus among researchers, advocates, and health professionals that social determinants are the primary drivers of the health of Canadians, the empirical basis for this claim remains thin. Studies from several European countries have shown that income and social security are primary drivers, with social determinants of health (SDOHs) explaining up to 89% of the variation in self-reported health in these countries [1]. A similar trend is observed in the United States, where socioeconomic factors tend to be the strongest predictors of health outcomes [2]. One of the very few flagship reports describing health disparities across Canadian cities, *Reducing the Gaps in Health: A Focus on Socio-Economic Status in Canada*, championed by the Urban Public Health Network (UPHN), found that income-related health inequalities have remained largely unchanged since the early 2000s and vary considerably between cities and indicators [3-5]. Many of these inequalities persist at municipal, provincial, and national levels and are direct consequences of individuals' socioeconomic disadvantages [3,6]. As SDOHs are many and their interactions are complex [7,8], a more in-depth account of how social determinants impact health is needed to identify the highest-impact targets for interventions that can reduce these inequalities and improve health outcomes.

Considerable data are required to measure different aspects of the SDOHs, and these data have to be combined, motivating calls for more significant investments in linkages between health and social data [9-12]. During the past 2 decades, Canadian research data access centers have developed a new way of conducting health and social research using nationally representative linked surveys and administrative data [13]. However, despite offering a significant amount of data on the various SDOHs, the advanced knowledge of these data sources that is needed to work with them is limited among researchers and academics [14]. Considerable disparities also exist in the capacity of local health units to survey regional differences in population health and health equity, with some units having no capacity at all [15,16], and becoming familiar with large and complex data sources such as those in the Research Data Centres (RDCs) is costly. Even among units that do have the capacity to make these investments, work tends to be carried out in isolation, and no national standards exist to ensure that research is carried out in ways that support comparative learning [17-19].

This paper presents an innovative protocol for the world's first fully integrated virtual, multilevel, and longitudinal social determinant laboratory environment, entitled Canadian Social Determinants Urban Laboratory (CSDUL). CSDUL aims to facilitate multilevel statistical analyses of how social and structural determinants of health impact the overall health of Canadians—achieved by creating a set of programs, algorithms (statistical codes and syntaxes), and data components accumulating information from at least 15 primary data sources within the secure research environment of the RDCs. The project will further use CSDUL to replicate the decomposition analysis of income-related inequalities in self-reported health carried

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out by the World Health Organization (WHO) Regional Office for Europe (WHO/Europe) [20] for urban Canada. Decomposition analysis is a method used to investigate changes in specific indicators by breaking them down into various contributing factors, enabling us to identify the underlying drivers of these changes [19].

In short, this project will allow us to determine how much of the variation in income-related health inequalities in Canada can be attributed to the various SDOHs (ie, report on the relative impact of social determinants on health inequities). In addition to replicating previous studies that have illustrated the contribution of SDOHs in determining health status, the CSDUL environment will allow us to examine how different categories of SDOHs operate on health at different levels and bridge the gap between the WHO's conceptual and action frameworks. Our research will adopt a slightly modified version of the WHO *Conceptual Framework for Action on the Social Determinants of Health* [21]. The WHO SDOH framework illustrates how social, economic, and political mechanisms give rise to environmental and socioeconomic conditions and how these, in turn, shape access to important determinants of health status [21]. One of the innovations of the SDOH framework is that it also conceptualizes the health system as a social determinant. However, the WHO's separate but complementary framework for action on tackling SDOH inequalities identifies 4 levels of *mechanisms*—global, macro, meso, and micro—that motivate different kinds of policy actions to improve population health and reduce inequalities [21].

Objectives

The specific research aims of this project will be to work with Statistics Canada's integrated Canadian Population Health Survey (CPHS) data [22] and other leading social determinant data to (1) develop and distribute the world's first fully integrated virtual, multilevel, and longitudinal social determinant laboratory environment, which we will call CSDUL; and (2) replicate the decomposition analysis of income-related inequalities in self-reported health carried out by the WHO/Europe for urban Canada and report on the relative impact of social determinants.

Methods

Data

Overview

The backbone of CSDUL's data structure will be Statistics Canada's CPHS [22], which researchers can access via RDC programs. The CPHS consists of linked survey, administrative, and registry data among the Canadian Community Health Survey (CCHS) [23], the Discharge Abstract Database [24], the National Ambulatory Care Reporting System [25], the Canadian Vital Statistics–Death database [26], the Canadian Cancer Registry [27], and 20 years of Canada Revenue Agency personal and familial tax records [22]. These data will be merged with area-level indicators using historical postal codes in the CPHS, Canada Post's Postal Code Conversion File Plus [28], and census boundary files [29] provided by Statistics Canada. Additional data sources include the Canadian Classification of Functions of Government [30], data from the Canadian Urban Environmental Health Research Consortium [31], DMTI Spatial Enhanced Points of Interest [32], and Statistics Canada's Canadian Social Environment Typology (CanSET) [33]. Table 1 provides a brief description of the datasets. The period with existing data for all these sources is 2011 to 2017. This will be the initial observation window for CSDUL, but we aim to extend it in future studies as new data become available. The CCHS samples approximately 65,000 Canadians each year, and we will add new years as they become available, resulting in an overall N of approximately half a million individual Canadians and a number of health events (eg, hospitalizations or deaths) that is an order of magnitude greater.

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Table 1. Description of the datasets.

Data source	Description
CCHS[a]	The CCHS is a cross-sectional self-reported survey providing provincial and subprovincial (health region or combined health regions)–level estimates of health status, health care use, and health determinants [23]. The CCHS comprises 2 types of surveys: an annual component survey on general health administered to all the sample and focused surveys on specific health topics from which the provinces and territories can opt out [34].
CPHS[b]	The CPHS links various Canadian datasets, including the CCHS annual and focus content, CVSD[c], DAD[d], NACRS[e], CCR[f], and 20 years of personal and familial tax records, providing researchers with analytical datasets that contain integrated data on mortality, hospitalization, historical postal codes, cancer, tax data, and censuses [22].
CanSET[g]	A qualitative measure of the social environment in Canadian cities entitled CanSET was created using 30 socioeconomic, demographic, and ethnocultural variables derived from the 2016 census [33]. Aggregated at the dissemination area level, CanSET clusters portray a comprehensive picture of urban social and health inequalities in Canada [33].
CVSD[c]	The CVSD is a comprehensive, cross-sectional census that collects demographic and medical data, including causes of death classified according to the World Health Organization's ICD[h], from all provincial and territorial vital statistics registries on a monthly and annual basis [26].
CCR[f]	The CCR is a national population-based registry that provides person-level information on the type and characteristics of each new primary cancer diagnosed among Canadian residents since 1992 [27]. It includes information provided by the 13 Canadian PTCRs[i] except Quebec (since 2018) and Nova Scotia (since 2020) [27].
Canadian Census of Population	The Canadian Census of Population is conducted every 5 y and includes a short survey administered to every Canadian and a long-format survey administered to roughly 25% of the subsample (replaced by the National Household Survey in 2011) [35]. The census database contains detailed demographic and socioeconomic data on the Canadian population living in its provinces, territories, and municipal areas [35].
CCOFOG[j]	The CCOFOG classifies areas of government spending according to international standards, allowing for comparisons of government expenditures across jurisdictions [30]. Covering the years between 2008 and 2020, the CCOFOG illustrates the total expenditure by the various government units (federal, provincial and territorial, and local) in 10 categories: general public services, defense, public order and safety, economic affairs, environmental protection, housing and community amenities, health, recreation, culture and religion, education, and social protection [36].
CANUE[k]	The CANUE provides a comprehensive and easily accessible set of national urban exposure metrics from 1980 onward [31]. It has assembled several datasets capturing built and natural environmental exposures at the postal code level across the country [31]. This includes variables describing greenness, proximity to water bodies, proximity to roads, walkability, noise, light and air pollution, and gentrification [31].
Census boundary files	Statistics Canada releases census boundary files each census year in 3 types of geographic areas: administrative boundaries (eg, provinces and territories, health regions, and federal electoral districts), statistical boundaries (eg, census metropolitan areas and census agglomerations, census tracts, and dissemination areas), and nonstandard boundaries (eg, population ecumene) [29]. In addition, boundary files for the intercensal years containing only CSD[l] boundaries are also released, and CSDUL[m] will use both of these types of files to link multiple datasets [37].
CIHI[n]	The CIHI collects and reports comparable pan-Canadian data on various aspects of the health system, such as health care access, appropriateness, and quality at the health region level on the Your Health System online portal [38]. We will use this portal to create a suite of ready-made and documented area-level health system indicators for inclusion in CSDUL.
DAD[d]	The DAD[d] is collected and reported by the CIHI, containing detailed administrative, clinical, and demographic information on hospital discharges, including deaths, sign-outs, and transfers, at the provincial and territorial levels except for Quebec [24]. This database can be used to calculate various population health indicators, providing important insights into regional health inequities, including hospitalizations for opioid overdoses, alcohol-related harm, attempted suicide, and various injuries [24].
DMTI Spatial EPOI[o]	The EPOI file, produced by DMTI Spatial Inc, is a national database that contains >1 million business and recreational locations across Canada [32]. This resource allows users to view and analyze point-of-interest data within a specific geographic area, facilitating applications such as market research and business analysis [32]. We are measuring social capital based on this data source.
NACRS[e]	The NACRS[e] data are sourced directly from participating facilities, regional health authorities, or health ministries [25]. It includes information on hospital-based and community-based ambulatory care services (eg, day surgery, outpatient services, and emergency department services) [25].
CRA[p] tax records	CRA tax records contain information about taxes, benefits, and related details for most Canadian provinces and territories, such as income tax records [22].

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Data source	Description
PCCF+[q]	The PCCF+ file serves as a connection among 6-digit postal codes from the CPC[r], standard census geographic areas (including dissemination areas, census subdivisions, and census tracts) created by Statistics Canada, and supplementary administrative areas and neighborhood income quintiles [28].

[a]CCHS: Canadian Community Health Survey.
[b]CPHS: Canadian Population Health Survey.
[c]CVSD; Canadian Vital Statistics–Death database.
[d]DAD: Discharge Abstract Database.
[e]NACRS: National Ambulatory Care Reporting System.
[f]CCR: Canadian Cancer Registry.
[g]CanSET: Canadian Social Environment Typology.
[h]ICD: International Statistical Classification of Diseases and Related Health Problems.
[i]PTCR: provincial and territorial cancer registry.
[j]CCOFOG: Canadian Classification of Functions of Government.
[k]CANUE: Canadian Urban Environmental Health Research Consortium.
[l]CSD: census subdivision.
[m]CSDUL: Canadian Social Determinants Urban Laboratory.
[n]CIHI: Canadian Institute for Health Information.
[o]EPOI: Enhanced Points of Interest.
[p]CRA: Canada Revenue Agency.
[q]PCCF+: Postal Code Conversion File Plus.
[r]CPC: Canada Post Corporation.

Furthermore, at this time, we will restrict CSDUL to Canada's cities and towns because our aim is to estimate a fully articulated model of the SDOHs, and these factors are not as well understood or measured in rural and remote regions [39-41]. We will classify communities as cities and towns if they qualify as census agglomerations or census metropolitan areas—that is, communities with a core population of at least 10,000 [42]; these entities can be made up of multiple municipalities (eg, the census metropolitan area of Montreal includes Laval, among others). This was the same approach used by Statistics Canada in creating CanSET [33].

In their raw form, most of the databases that will be included in CSDUL are not user-friendly and not readily usable for health analysis. Thus, many of the primary research deliverables of this project will be to critically analyze and document the strengths and limitations of these databases for supporting health research and create and validate the best methods for deriving variables from them. By combining all these data elements, our project will create a multilevel and longitudinal virtual laboratory environment that can be used to examine the operation of SDOHs at micro, meso, and macro levels and study income-related health inequalities. This approach builds on previous studies that could only demonstrate the contributions of SDOHs to health across a limited subset of the WHO SDOH framework elements [2,43].

The development of CSDUL will be organized using a hub and multidisciplinary node teams across Canada and organized around the WHO SDOH framework. Figure 1 provides an overview of the CSDUL project and its mappings between data sources and hub and node activities.

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Figure 1. Stylized overview of the Canadian Social Determinants Urban Laboratory, its data structure, and its organizing nodes. CanSET: Canadian Social Environment Typology; CANUE: Canadian Urban Environmental Health Research Consortium; CCHS: Canadian Community Health Survey; CCOFOG: Canadian Classification of Functions of Government; CIHI: Canadian Institute for Health Information; CPHS: Canadian Population Health Survey; DAD: Discharge Abstract Database; EPOI: Enhanced Points of Interest; LAD: Longitudinal Administrative Databank; NACRS: National Ambulatory Care Reporting System; RDC: Research Data Centre; T1FF: T1 Family File.

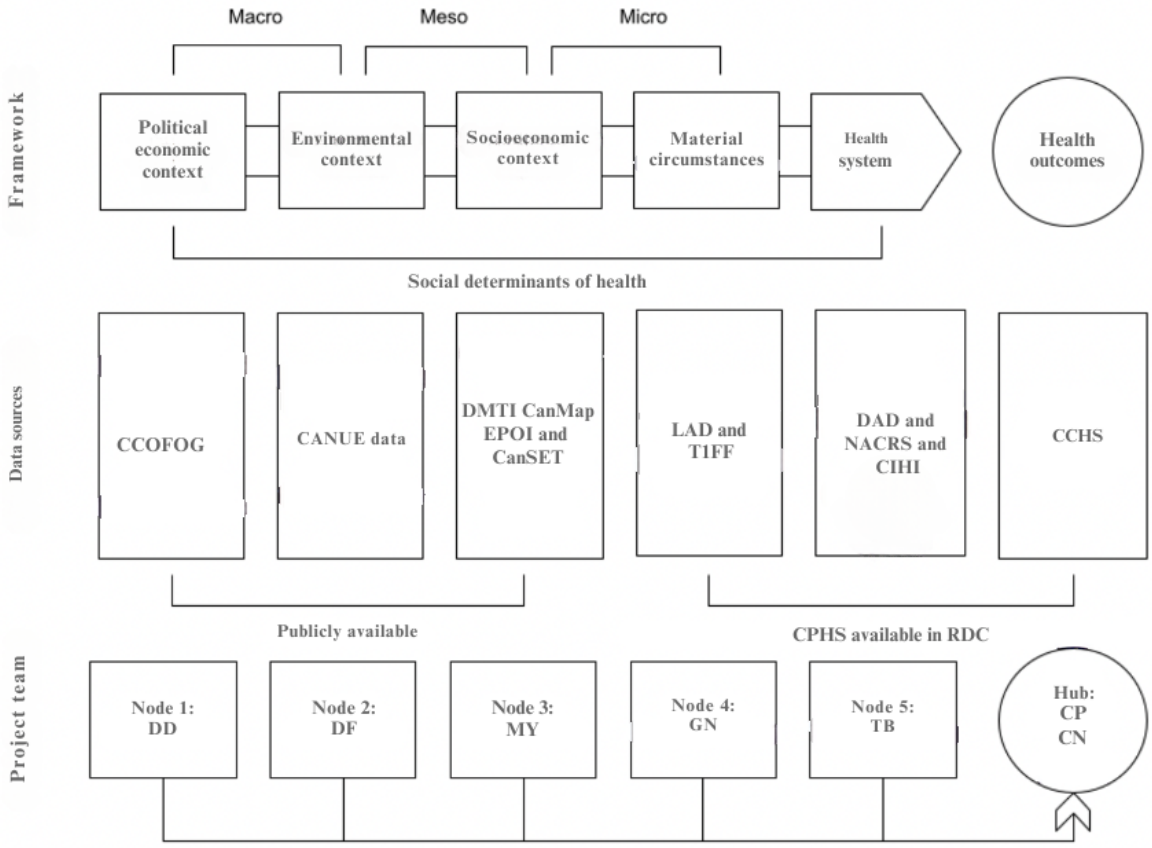

Outcome Variable

Self-reported health will be the primary outcome variable of interest for the decomposition analysis. Drawing on validation work by our team using the Health Utilities Index [44,45], we will categorize self-reported health based on whether respondents reported having health that was at least better than *fair*. Self-rated health is a widely used indicator of overall health status, and multiple studies have validated its usefulness as a subjective proxy for a number of objective health measures [46-49].

Predictor Variables

Each node will contribute tables of predictor variables to the decomposition analysis based on their work on developing CSDUL. To achieve this, working group nodes will conceptualize, operationalize, and link constructs from the WHO conceptual and action social determinant frameworks. Hub individual-level variables will include demographic variables (eg, gender and age), family income, health behaviors [50], health comorbidities [51,52], health system access [38], and health history [53,54]. Political and economic context variables will include economic indicators (eg, macroeconomic policies and Gini coefficient), social indicators (eg, policies on social welfare and land and housing), social spending [55], and health spending [55] at the health region and provincial levels. Environmental context variables will include green space [56], walkability [57], gentrification [58], urban sprawl [59], and air pollution [60] at the dissemination area level in urban areas. Socioeconomic context variables will include the social environment, such as stress and different types of available social capital, including what Klinenberg [61] refers to as *social infrastructure*. Material circumstances will include area-based income and deprivation. Health system indicators will include health care access, health care quality, health care appropriateness, and public health systems. Figure 2 provides an overview of the planned construction of the CSDUL environment, its elements, and its variables.

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Figure 2. Description of the Canadian Social Determinants Urban Laboratory data components and their relationships. DA_ID: dissemination area identification number; Env.: environmental context; Health syst.: health system; HR_ID: health region identification number; Mat. circ.: material circumstances; Pol. econ.: political and economic context; PROV_ID: province identification number; Socioecon.: socioeconomic context; STC_ID: Statistics Canada identifier.

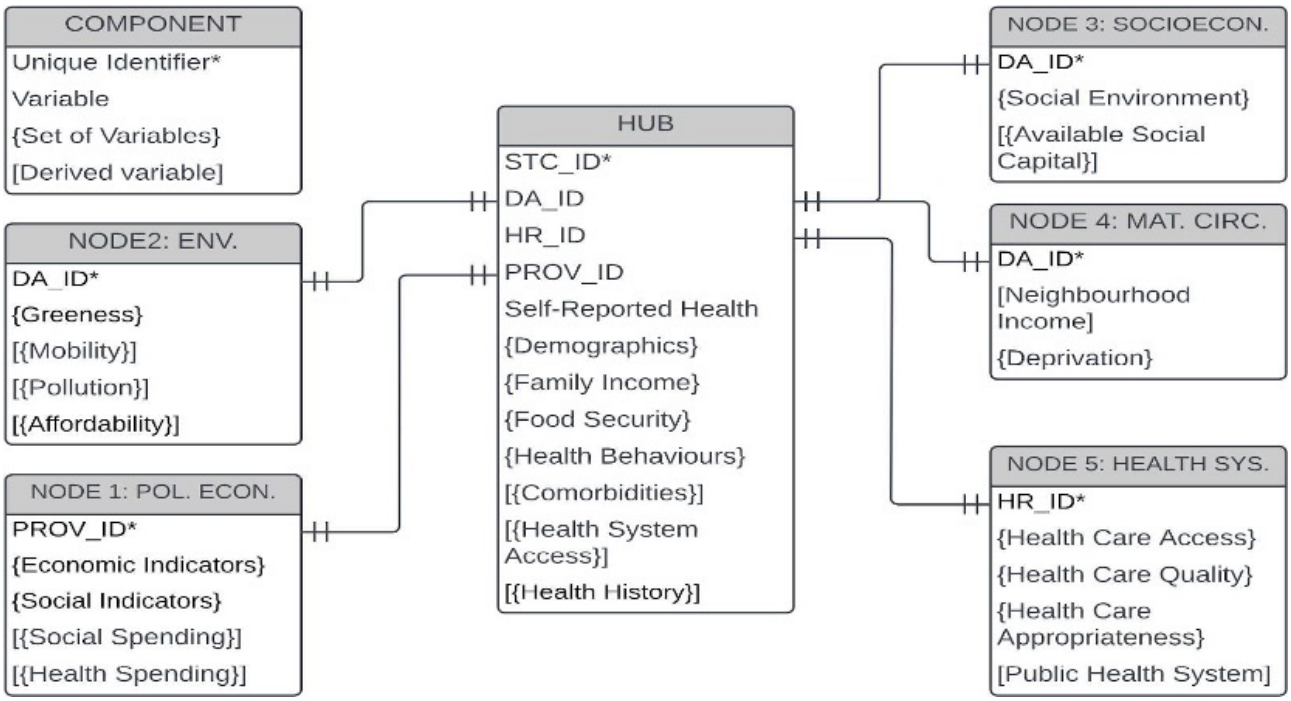

CSDUL Development

Overview

A central hub operating out of the UPHN Research Group and based at the University of Saskatchewan (hereinafter referred to as the Hub) will assemble data in collaboration with partners, combining them with individual-level indicators of health behavior, history, system access, system use, and outcomes in the CPHS. The Hub will also coordinate the project and ensure that the primary objectives are met. Under the Hub, CSDUL will have 5 project nodes led by different investigators, who will create and validate area-based indicators at the macro and meso levels that will be integrated with CSDUL and the decomposition analysis (objective 2). The nodes are political and economic context (node 1), environmental context (node 2), socioeconomic context (node 3), material circumstances (node 4), and health systems (node 5). In addition, the Hub will assemble and disseminate this virtual environment, which will operate on individual-level data within Statistics Canada's RDC. The project will be advised by a senior advisory group composed of experts in the field of population health and secondary data development and use. In addition, CSDUL will be advised by a knowledge user group operating as part of the UPHN's unique Integrated Knowledge Translation Collaborative [62], which brings together academic researchers, national data stewards, and local public health practitioners eager to advance measures and tools that can be used for effective local-level evidence-based decision-making.

Node 1: Political and Economic Context

The primary objective of this node will be to study and document the effect of macroeconomic factors and government policy on health outcomes using the new Canadian Classification of Functions of Government data [36]. Statistics Canada has recently updated its Consolidated Government Revenue and Expenditures tables to align with international government revenue and spending practices. This update brings a significant amount of detail, particularly in the areas of health and social spending. This node will create a simplified version of these data (spanning 2008 to 2018) and a set of guidelines for CSDUL. Several macro-level variables from Statistics Canada's *The Daily* indicator series (eg, Gini coefficients, gross domestic product, and unemployment rate) will be included.

Node 2: Environmental Context

Node 2 aims to measure the impacts of environmental factors (ie, walkability, bikeability, food environments, transit accessibility, gentrification, and housing affordability) on health outcomes in Canada's cities since 2010. The measures already developed are walkability, urban sprawl, bikeability, food environments, transit accessibility, and gentrification. It will also create new neighborhood-level indicators of environmental context using the Canadian Urban Environmental Health Research Consortium data specifically related to housing affordability, as well as validate these measures. CSDUL will be one of the first large-scale validation studies explaining how environmental factors can be combined in population health research with population health outcomes, including self-reported health.

Node 3: Socioeconomic Context

Node 3 will expand on the existing theoretical and methodological work conducted on the area-based available social capital in rural communities in Canada [63,64], classifying it into 4 normative types: market, bureaucratic, communal, and associative for urban Canada. This work will be expanded by

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integrating recent approaches to capturing the social infrastructure in residential areas [61,65,66]. This node will also make use of the UPHN work with the Health Analysis Division of Statistics Canada, which produced a new *qualitative* measure of the social environment—the CanSET [33]. The key purpose of node 3 is to investigate the connection between the availability of family-friendly resources from DMTI Spatial (see the study by Young et al [65] and Young and Singh [66] for an overview) and health outcomes using data from the CCHS. Node 3 will also use leading indicators of population health in Canadian cities starting from 2010 from DMTI Spatial and other sources.

Node 4: Material Circumstances

The primary objectives of node 4 will be to develop and support the distribution of improved dissemination area–level median after-tax income measures for the CSDUL project and the decomposition analysis. In Canada, income-related health inequalities at the area level have traditionally been measured using income data collected once a year by the census. However, in recent times, social scientists have preferred to use median after-tax income as a more accurate measure of disposable income [67,68]. Canada also has a Longitudinal Administrative Databank that provides longitudinal data on income at the dissemination area level since 1982, but it has not been widely used in health science research. Node 4 extends the use and distribution of a new after-tax income area-level indicator based on the Longitudinal Administrative Databank. It aims to assess the consequences of implementing a new indicator to explore health inequalities associated with income and study how our preference for area-level income or deprivation impacts our research on health inequalities.

Node 5: Health System

Node 5 research activities will focus on developing and deploying a suite of area-level (primarily at the health region level) health system indicators to quantify system-level access and quality of care that can be integrated with CSDUL [62,69]. This will involve deriving health system indicators that are available at the subprovincial level and identifying and assessing individual-level indicators of health system access and use from the CCHS.

Senior Advisory Group and Knowledge User Group

The knowledge user group and the senior advisory group, integral parts of the UPHN Integrated Knowledge Translation Collaborative around the CSDUL project, are composed of the UPHN membership, which includes the country's top public health medical leadership and the country's top experts in population health research, respectively. These 2 groups will receive regular updates from the Hub and will provide valuable advice on the design and dissemination of CSDUL related to their areas of expertise and advanced experience. They will also play a key role in facilitating knowledge mobilization within their organizations and among their affiliate health leadership agencies. Figure 3 shows how we plan to operationalize the WHO SDOH framework.

Figure 3. Operationalizing the social determinant of health framework. CCHS: Canadian Community Health Survey; CIW: Canadian Index of Wellbeing; GDP: gross domestic product.

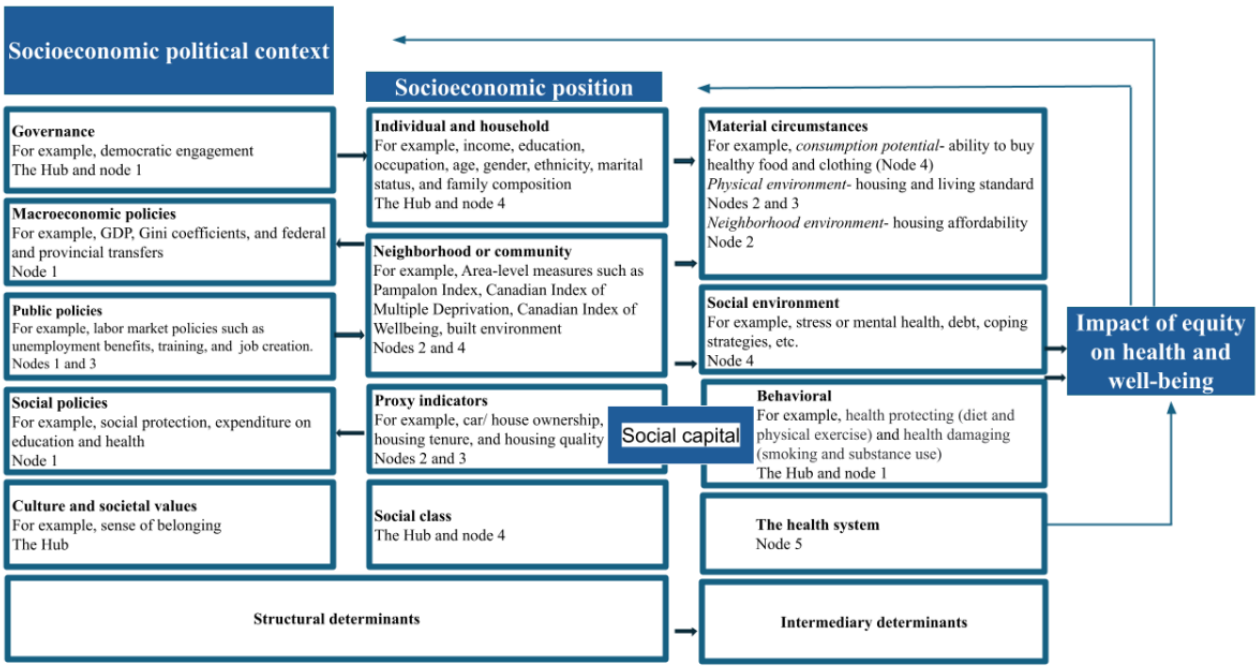

Decomposition Analysis

Our study will follow the WHO/Europe [20] and use a *2-fold* Oaxaca-Blinder decomposition [70-72] to identify the primary drivers of self-reported health. We are mindful that the CCHS has been redesigned multiple times (most recently in 2015); we will follow best practices [73] and only work with variables that have been measured in the same way over time as we have done in previous work [74]. As was done by the WHO/Europe, we will also report on the distribution of social determinants

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and health outcomes in the cities and towns we include and replicate our analysis for additional self-rated outcomes—mental health and life satisfaction.

The decomposition analysis will be conducted as follows. If y_q is a vector of observations of dichotomized self-reported health in quintile q and X_q is a matrix of observed social determinants and a constant, then the difference between average self-reported health in the lowest quintile, $_1$, and the highest quintile, $_5$, can be fit using linear regression and broken down into 2 components: first, a component that is attributable to differences in X_q between the quintiles (ie, differences in their composition) and, second, a component that is attributable to differences in associations between y_q and X_q, captured by the coefficients in the linear model, β_q. If we use the associations of the fifth and richest quintile, β_5, as our benchmark for *best health*, then the estimated difference in average self-reported health between that quintile and the worst-off quintile, β_1, is decomposable as follows:

If social determinants in X_q are indexed by m, then the estimated proportional contribution of determinants $m \in G$ is as follows:

We will estimate equation 2 for each group of categories of social determinants and levels. Our baseline estimates of β_q will use pooled multilevel logistic regression with mixed effects and include all predictors in X_q identified by our nodes (use of logistic regression will slightly modify the aforementioned notation, but the interpretation will remain the same [75,76]).

Data will be pooled to ensure sufficiently large local sample sizes (in previous work [74], we have found that pooling ≥5 years is needed—at this time, we only have 7 years, which is not enough for two 5-year pooled intervals). We will include indicators for year to control for period effects. Provincial effects will be set to fixed, and meso-level variable effects (ie, health region and metropolitan area or municipality) will be set to random. As this is the first study of its kind, we will explore different model specifications and document the implications of these choices for our decomposition results [77,78].

All statistical estimates will be calculated using probability weight, and SEs will be calculated using bootstrapping to account for the complex survey design of the CCHS [79].

Interaction and Effect Modification Analysis

We will also examine the impacts of accommodating interaction and effect modification [80] between certain predictors—specifically, self-reported gender (ie, male; female; and, when possible, nonbinary) and different categories of non–White-identifying (eg, Black-identifying) individuals—and fitting random effects at lower levels (eg, aggregate dissemination area or census tract). This would allow us to see, for instance, whether the impact of education is more significant for women than for men [81,82].

Ethical Considerations

The University of Saskatchewan Research Ethics Board deemed this study exempt (E486). All datasets used in this study are covered under existing data sharing agreements within the RDC network and provided to researchers in a controlled research environment. The required data linkages have already been completed by Statistics Canada. Furthermore, the datasets are internally deidentified, harmonized, and thoroughly documented by Statistics Canada and its partners, ensuring secure and consistent use for research purposes. No monetary compensation was paid.

Results

We have used our bridge funding to hire a research specialist full time to obtain ethics approval and data access, complete environmental scans, and begin assembling the linked individual-level data components that are accessible within the RDC (roughly, the preliminary work proposed for the Hub). A prototype version of CSDUL incorporating a limited set of indicators has been developed in a Statistics Canada RDC. We anticipate receiving the finalized indicators from the nodes by August to September 2025 and aim to complete the decomposition analysis by December 2025. In addition, in the beginning year of the project, the Hub will take primary responsibility for integrating the work and components completed by the nodes in the RDC and creating and disseminating CSDUL. It will also work with the nodes simultaneously to create and validate social and environmental area-based indicators at the macro and meso levels that will be merged with the survey and administrative data. It will also construct individual-level demographic variables, health behavior indicators, and health history and health system use indicators. Individual health behaviors (ie, smoking, drinking, physical activity, and frequency of fruit and vegetable consumption) will be operationalized in the CCHS using established methods developed by Statistics Canada [50]. Demographic variables, including age, gender, ethnicity, marital status, family composition, level of education, family income, employment status, and occupation, will be added. For health history and health system use, Discharge Abstract Database and National Ambulatory Care Reporting System data combined with *International Classification of Diseases* coding will be used to identify comorbidities (ie, the Charlson Comorbidity Index). In the second and third years of the project, the Hub will complete the decomposition of the income-related inequalities in self-reported health.

Discussion

Expected Findings

The WHO Commission on Social Determinants of Health has called for a *third wave* in population health research, which "makes explicit that health systems and the people who use them exist within a social context that can powerfully determine people's chances to be healthy—not only through access to health services, but also through access to a range of other resources, opportunities, and rights" [83]. There are numerous social determinants that can impact health outcomes, and the

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way in which these factors interact with each other is complex [8,84]. For example, *political and economic context* refers to a broad set of structural and functional aspects of society that cannot be directly measured at the individual level but have an immense influence on the patterns of social stratification and, therefore, on the health of populations [21]. The environmental conditions in which populations live, work, and play have a profound influence on their health and well-being [21]. Exposure to harmful elements of the built environment—pollution, low-quality housing, and low amounts of green space, for example—can differ within cities and across subpopulations, leading to environmentally mediated health disparities in specific conditions and overall health status [85]. Biological factors, which include age and sex, also need to be considered when examining the impact of SDOHs in health inequality research [21]. Material circumstances are the direct factors that determine an individual's ability to live a healthy life [21]. These factors include income, education, employment status, and food security, among others. These factors are proximate measures of socioeconomic position that provide insights into the level of resources available to individuals to enable health-promoting conditions and behaviors [21]. In contrast, contextual determinants such as the socioeconomic environment provide individuals with the opportunity to live a healthy life [21]. The health system is considered an intermediary SDOH, and improving equity in health care requires addressing not only access but also the appropriateness and acceptability of care. Promoting intersectoral action to enhance these aspects can improve overall health outcomes and reduce differential quality of care [21,86]. The WHO SDOH framework has evolved, drawing on various models developed for different purposes, including public education and advocacy, to better understand the complex interrelationships between social factors. It is important to note that these models, including the aforementioned Commission on Social Determinants of Health, have limitations. For instance, they often fail to account for critical aspects emphasized in Indigenous communities, such as the roles of culture and land. Our work aims to contribute to the ongoing evolution of SDOH frameworks, offering a more comprehensive and inclusive perspective that reflects current research.

CSDUL will be the first of its kind that will bridge the gap between the WHO's conceptual and action SDOH frameworks in a data-driven way and clarify our understanding of what are the factors most likely to drive health outcomes in Canada (ie, what makes Canadians sick or healthy). We will operationalize the WHO SDOH framework, which considers the health system as a social determinant. In addition, by linking multiple leading databases that provide information at the micro, meso, and macro levels, CSDUL will also help researchers see how the various categories of determinants operate on health at different levels, as conceptualized by the WHO's separate but complementary framework for action on tackling SDOHs. It will also allow us to explore interaction effects with identifiable groups (including by gender) to understand how social determinants impact their health differently. Moreover, the data and decomposition methods used in our study will allow us to combine or differentiate among associations between social and structural determinants and more effectively link their conceptualization with the levels at which decisions are made and actions are taken.

CSDUL will also provide a framework and data components that can augment existing microsimulation tools such as Statistics Canada's Population Health Model [87], which are used to forecast the impacts of health policy decisions. Crucially, the development and future maintenance and dissemination of CSDUL will ensure that Canadian researchers are able to collaboratively use, build on, and learn from the work of others in the RDC. Researchers who are new to the RDC, including health system researchers, will no longer have to start from scratch, thus dramatically reducing the costs of conducting population health and health equity analysis using Canada's linked health and social data.

Conclusions

Health inequities and inequalities are common in Canadian cities, but they are not equally distributed across various population groups. Due to data limitations, it has been difficult to conduct large-scale comparative research on health disparities in Canadian cities in the past. However, this situation is rapidly changing, and with the introduction of CSDUL, it will be possible to investigate SDOHs at both the individual and area levels simultaneously and seamlessly. Decomposition analysis is a method for understanding what contributes to health inequities by estimating associations among health inequalities, populations, and correlated determinants, such as those that our hub and nodes will identify, and analyzing the relative impact of each. Our work will go beyond the WHO/Europe analysis by providing data-driven relative contributions of individual-level variables, political and economic context, environmental context, socioeconomic context, material circumstances, and health systems.

Acknowledgments

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conducted in partnership with the University of Saskatchewan. This research was funded in part by the UPHN, the College of Medicine of the University of Saskatchewan, and the Canadian Institutes of Health Research (Multimedia Appendix 1).

Authors' Contributions

CP and CN conceived and designed the research protocol and secured funding. SDG and CP drafted the protocol manuscript, while members of the CSDUL team, including DF, DD, GN, MY, CB, BR, LL, CC, DB, TB, DY, and AM critically reviewed both the protocol and manuscript for methodological rigor and academic quality.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the Public, Community & Population Health Committee (PH1), Canadian Institutes of Health Research (CIHR).
[PDF File (Adobe PDF File), 84 KB - resprot_v14i1e71929_app1.pdf]

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Abbreviations

CanSET: Canadian Social Environment Typology
CCHS: Canadian Community Health Survey
CPHS: Canadian Population Health Survey
CSDUL: Canadian Social Determinants Urban Laboratory
RDC: Research Data Centre
SDOH: social determinant of health
UPHN: Urban Public Health Network

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WHO/Europe: World Health Organization Regional Office for Europe
WHO: World Health Organization

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Protocol

Enrichment of the Canadian Partnership for Tomorrow's Health Study: Protocol for Administering Multiple Online Dietary and Movement Behavior Assessment Tools in a Longitudinal Cohort Study

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Abstract

Background: Suboptimal diet quality and physical inactivity are key risk factors for chronic disease and disability in Canada. However, the lack of high-quality population-level data hinders the development of evidence-based strategies to support improvements in diet quality, movement behaviors (physical inactivity, activity, and sleep), and health. The lack of data is also a barrier to developing capacity in diet and physical activity assessment and epidemiology in Canada.

Objective: This protocol describes the development of the largest known repository of dietary intake and movement behavior data in Canada by drawing upon an existing longitudinal cohort study, the Canadian Partnership for Tomorrow's Health (CanPath). In the short-term, the data will be used to examine associations between system factors (eg, retail food environments) and dietary intake. In the longer-term, data will be available to pursue a range of research questions, including longitudinal associations between diet, movement behavior, and health outcomes.

Methods: Participants in CanPath (>330,000 adults) who can complete online questionnaires are eligible and will be asked to complete a baseline web-based questionnaire including questions on demographic characteristics and screeners capturing dietary intake and movement behaviors. Subsequently, participants will be invited to complete an online 24-hour dietary recall using the Automated Self-Administered 24-Hour Dietary Assessment Tool (ASA24-Canada-2018) and an online 24-hour activity recall using Activities Completed Over Time in 24 Hours (ACT24). Repeat recalls will be administered 1-2 weeks later. A subset of

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participants will be invited to complete 2 additional ASA24-Canada-2018 and Activities Completed Over Time in 24 Hours recalls 6 months later. One year after baseline, participants will be invited to complete past-year diet and movement behavior questionnaires. In Québec, dietary intake and movement behavior data are from 3000 CanPath participants enrolled in the NutriQuébec study. Participant addresses will be linked to geospatial data on the food, built, and social environment.

Results: Data collection began in 2025. As of manuscript acceptance (November 4, 2025), 3171 participants had been recruited. Data processing and cleaning will be completed in 2027, and analyses will occur in 2028. It is anticipated that dietary intake and movement behavior data will be available for up to 100,000 adults.

Conclusions: This protocol outlines the collection of detailed data on dietary intake and movement behavior in a large cohort spanning all provinces in Canada. In addition to allowing examination of a range of research questions related to diet, movement behavior, and health, the combination of assessment tools will support methodological research, including expanding analytical strategies to mitigate the effects of error in dietary and movement behavior data. This effort will also build capacity in the collection, processing, and harmonization of dietary and movement behavior data among cohorts and provide a training ground for emerging researchers.

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KEYWORDS

dietary intake; movement behavior; environments; population cohort; nutrition; web-based assessment

Introduction

Consumption of high-quality diets rich in fruits and vegetables, whole grains, dairy, and plant-based foods and low in refined grains, added sugars, and sodium is essential for overall health and chronic disease prevention [1-3]. Most adults in Canada consume diets that do not meet dietary guidelines [4-7], with little evidence of improvement over time [5,8]. Accordingly, poor diet quality is the leading cause of death and disability in Canada [9]. Healthy movement behaviors—including engaging in physical activity, muscle strengthening, and standing; limiting sedentary time; and getting good quality sleep—are also critical for health and chronic disease prevention [10,11]. Most adults in Canada do not meet guidelines for movement behavior, with variation according to sex, age, family arrangement, and health status [12].

As part of the first-ever Food Policy for Canada, the federal government announced approximately US $35.4 million investment in local infrastructure to improve access to healthy foods in communities [13]. However, large gaps in population-level evidence on the retail food environment (RFE) and overall dietary intake make it unclear how to achieve the desired outcome of improving diet quality. Evidence has shown that improving access to healthy foods, for example, by introducing new grocery stores or stores selling a wide variety of healthy food in a neighborhood, has a null or modest impact on dietary intake [14-16]. Proximity to fast food outlets is linked to (poor) diet quality, although not consistently [16]. Methodological limitations within studies, including lack of standardized measures of the RFE, sparse dietary intake data (typically confined to fruit and vegetable consumption), and absence of consideration of individual-level factors that interact with dietary intake (eg, sex, gender, income, family structure, education, and sedentary behavior), hinder the ability to draw firm conclusions [15]. Research and policy efforts to improve the RFE seldom consider the multidimensionality of factors within which eating patterns emerge and the complexity of neighborhood environments where built and social environment and individual-level factors interact with the RFE to affect dietary intake. For example, a new grocery store may have a limited impact on food consumption in low-income neighborhoods unless there is adequate walkability (eg, sidewalks), public transit access, and social support, and individuals have adequate income to purchase food at the new store. Similarly, the federal government developed “A Common Vision for Increasing Physical Activity and Reducing Sedentary Living in Canada: Let’s Move” [17]. A Common Vision recognizes the complex system of factors that contribute to movement behavior, including neighborhood-level factors such as social environments and physical environments.

To inform interventions to improve diet quality, physical activity, and health, we need high-quality comprehensive data on dietary intake and movement behaviors that reflect individuals in Canada and the diverse environments in which they live. Existing population-level surveys such as the Canadian Community Health Survey and Canadian Health Measures Survey [18,19] do not provide contemporary estimates of dietary intake and overall diet quality. Comprehensive dietary data have only been collected (using a single 24-hour recall for most participants) twice in recent decades in the Canadian Community Health Survey [20,21], with the most recent data collected in 2015. The annual component of the Canadian Community Health Survey is limited to querying fruit and vegetable intake. In the Canadian Health Measures Survey, dietary data are limited to intake of select food groups [22]. Movement behavior is surveyed as part of the annual component of the Canadian Community Health Survey, providing data at the health region level every 2 years [23]. The lack of concurrent measurement of dietary intake and movement behavior in the Canadian Community Health Survey and the limited ability to link to information on health outcomes constrain the use of these existing data to inform interventions. Established population health cohorts are ideal for the collection of high-quality dietary intake and movement behavior data, given the ability to leverage existing infrastructure. The longitudinal follow-up of participants and the ability to link with administrative health data, including

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on health outcomes, within cohorts allow the use of the dietary and movement behavior data to address a broad range of research questions.

This protocol describes the enrichment of the Canadian Partnership for Tomorrow's Health (CanPath) [24] to create the largest known repository of dietary intake and movement behavior data in Canada. In the short-term, the newly collected dietary intake data will be used to examine associations between built, social, and RFE and dietary intake as part of the Healthy Eating and Supportive Environments (HEAL) study. Specifically, HEAL aims (1) to evaluate associations between the RFE and diet quality as measured by the Healthy Eating Food Index-2019 and (2) to evaluate whether associations between the RFE and diet quality vary by environmental factors (such as built and social environmental characteristics) and individual-level factors (such as gender identity and income). Beyond the HEAL-specific aims, this rich resource of data will enable addressing timely research questions on dietary intake, including how it is associated with food security, discrimination, and financial stress. In the longer term, the dietary intake and movement behavior data collected as part of HEAL—in combination with the wealth of information already held by CanPath—will make it possible to pursue a range of questions including how dietary and movement patterns are associated with health outcomes such as mortality and incident chronic disease. The combination of assessment tools administered in HEAL will support methodological research, including expanding strategies to mitigate the effects of error in dietary intake and movement behavior data on observed associations with health. Finally, this effort will build capacity in the collection, processing, and harmonization of dietary intake and movement behavior data among cohorts and provide a training ground for emerging researchers.

Methods

Data Sources

Overview

HEAL is leveraging 4 national resources: CanPath [24], the NutriQuébec study [25], the Canadian Urban Environmental Health Research Consortium (CANUE) [26], and the Canadian Food Environment Dataset (Can-FED) [27] (Figure 1).

Figure 1. Overview of the data sources comprising the Healthy Eating and Supportive Environments study [23-26]. Can-FED: Canadian Food Environment Dataset; CanPath: Canadian Partnership for Tomorrow's Health; CANUE: Canadian Urban Environmental Health Research Consortium.

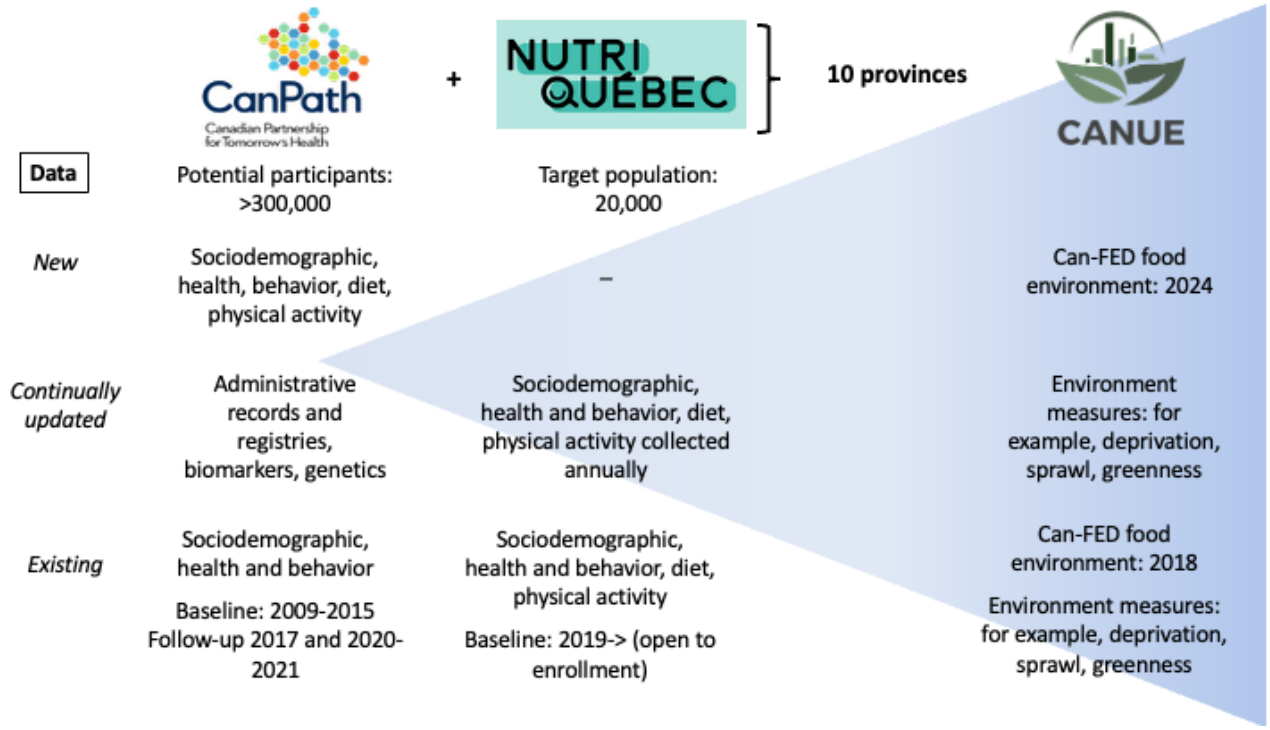

Canadian Partnership for Tomorrow's Health

CanPath is one of the world's largest prospective health research platforms, bringing together data from 7 regional cohorts including over 330,000 adults living in 10 provinces [24]. The CanPath regional cohorts include Alberta's Tomorrow Project (n=~55,000, recruited from 2000 to 2015) [28,29], the BC Generations Project (n=~30,000, recruited from 2009 to 2016) [30,31], the Atlantic Partnership for Tomorrow's Health (n=~35,000, recruited from 2009 to 2015) [32,33], the Ontario Health Study (n=~225,000, recruited from 2009 to 2017) [34,35], the Manitoba Tomorrow Project (n=~10,000, recruited from 2019 to 2024) [36], and Healthy Future Sask (n=~7000, recruited from 2022 to present) [37]. CanPath also includes CARTaGENE (n=43,000, recruited from 2009 to 2015) [38,39], which is participating in HEAL via study participants who have subsequently enrolled in NutriQuébec [25]. Broad eligibility criteria, encompassing adults aged 30 to 74 years who were able to complete surveys in English or French, were applied within the CanPath regional cohorts to achieve recruitment of a participant base that is generalizable [40], as almost half of adults in Canada fall into this age group [41].

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CanPath is a rich resource of epidemiological data with multiple waves of follow-up data collection [40,42]. In addition to completing questionnaires on sociodemographic characteristics and a range of health-related measures, participants have provided physical measures and biological samples, including blood, urine, saliva, and toenails at baseline [40]. Consent has been obtained for passive follow-up via linkage to administrative health records and for inviting participants to complete additional measures within regional cohorts, along with coordinated efforts such as a cohort-wide COVID-19 questionnaire in 2021 [40,42]. Data are collected within each regional cohort and subsequently undergo a rigorous harmonization process [43].

NutriQuébec

In 2023 (prior to the funding of the HEAL study), CARTaGENE agreed to invite a subset of its participants to enroll in NutriQuébec. Thus, CARTaGENE is participating in HEAL via NutriQuébec, an ongoing open cohort of adults older than 18 years of age living in the province of Québec with a target enrollment of 20,000 participants and specific recruitment and retention strategies for low socioeconomic status populations [44]. NutriQuébec was launched in 2019 with the primary goal of providing essential data for the evaluation of the first-ever Government Health Prevention Policy in Québec [45]. The prevention policy was launched to influence factors that lead to better health status and quality of life and reduced social inequalities in Québec [45].

Participants are invited to complete yearly online questionnaires that query age, ethnicity, sex, gender identity, body weight, household composition, main occupation, education, annual income, global health status, household food security status, and 6-digit postal code for their place of residence [44]. NutriQuébec is collecting information on dietary intake and other measures using methodology similar to HEAL, described below [44].

Canadian Urban Environmental Health Research Consortium

The mission of CANUE is to advance knowledge on how characteristics of urban form, such as land use, physical infrastructure, and socioeconomic conditions, interact to affect health [46]. At its core is the collation and generation of standardized social and built environment data for every postal code in Canada [46]. CANUE is widely recognized as the premier source of urban environmental exposure data in Canada. CANUE's established partnerships with CanPath and NutriQuébec provide the ability to access CANUE data linked to participants' data through the established cohort data access procedures [47].

Geospatial exposures are captured with ArcGIS (Esri), which associates single-link DMTI Spatial postal codes to Statistics Canada dissemination area boundary files. Dissemination area identifiers will be used to join Census data with postal codes for participants within CanPath and NutriQuébec. Available variables include sprawl, population density, walkability, and social environment constructs such as gentrification, the Canadian Marginalization Index, and social and material deprivation [48].

Canadian Food Environment Dataset

Can-FED is the first high-quality geographic-based set of measures that represent spatial access to food in communities across Canada. Can-FED was developed through collaborations between researchers and Statistics Canada [27,49] and has been updated as part of HEAL. Can-FED measures are included in CANUE's data platform, are linked to CanPath data, and are linkable to NutriQuébec. Can-FED uses existing microdata from the Business Register, an administrative dataset maintained by Statistics Canada, to develop measures of the RFE [49]. The resultant database provides standardized measures that can be applied to assess the RFE across jurisdictions in Canada at the dissemination area level.

Food outlets are extracted and classified from the Business Register based on an exhaustive list of 19 categories (eg, grocery stores and convenience stores) [49]. Food outlets are then mapped in a geographic information system using their addresses. RFE measures are calculated at the absolute (eg, counts per kilometer within a buffer of 1 and 3 km around the centroid of each dissemination area in Canada) and relative (eg, proportion of food outlets that sell a wide selection of fresh and nutritious food) levels [49]. Two relative density measures reflecting availability include the modified RFE index (the proportion of food outlets that sell a wide selection of fresh and nutritious food) and fast-food restaurant mix (the proportion of fast-food outlets relative to fast-food outlets and full-service restaurants) [49,50]. In total, 19 continuous measures, including densities of chain supermarkets, convenience stores, grocery stores, fast-food outlets, and fruit and vegetable markets, are calculated [49]. Validity of Can-FED has been examined in comparison with "gold standard" criteria, such as Enhanced Points of Interest data by DMTI Spatial Inc and data from a municipal health inspection list [49]. Geographic conversion tools, such as the Postal Code Conversion File [51], are used to link Can-FED to CanPath and NutriQuébec participants.

Study Governance

The HEAL study included a 16-month planning period to facilitate coordination across the regional cohorts and engagement with external experts, knowledge users, and participants to refine the study design. The study design was informed by consultations with CanPath operational staff, a HEAL Working Group, a HEAL Scientific Advisory Committee, and participants. Decision-making rests with the Working Group, with oversight from the Scientific Advisory Committee.

The HEAL Working Group is comprised of the HEAL principal investigators, the scientific and operational leads from CanPath and the regional cohorts, the scientific lead of NutriQuébec, statistical experts, and representation from Maelstrom Research, which oversees data harmonization within CanPath and NutriQuébec. The Working Group is engaged approximately quarterly to discuss issues such as ethics applications, harmonizing the demographic data collected in HEAL with data already held by the regional cohorts, and specifications for the dietary intake and movement behavior assessments.

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The Scientific Advisory Committee is comprised of experts in nutrition, dietary and movement behavior assessment, health policy and promotion, and biostatistics and epidemiology. The Committee includes knowledge users—including representatives from Health Canada and the Canadian Cancer Society—and CanPath, NutriQuébec, and Can-FED investigators. The Scientific Advisory Committee is engaged at least twice yearly to help ensure the relevance of the study, including the utility of the data collected beyond addressing the HEAL study objectives.

Alberta's Tomorrow Project has a Participant Advisory Committee comprised of 30 participants who advise and inform decision-making on activities related to the design of ancillary studies, data collection tools, and communication materials. The Committee members are diverse with respect to sex, gender identity, age, geographic location in Alberta, and occupational backgrounds. The Participant Advisory Committee is engaged 2 to 3 times per year and has provided feedback on the HEAL study design, baseline questionnaire, and participant materials, including invitation letters and consent forms. The development of the participant materials was supported by CanPath's national communications staff.

Data Collection

Overview

Data collection tools and procedures are first described for the regional cohorts aside from CARTaGENE, followed by a description of the NutriQuébec study, that is, the source of dietary intake and movement behavior data for a subset of CARTaGENE participants.

CanPath regional cohorts hold email addresses for respective cohort participants. All regional cohort participants with an email and who can complete online questionnaires are eligible to participate in HEAL. Invitations to complete questionnaires and assessments are sent via email, and all assessments are completed online on desktop or laptop computers or on mobile devices, with responses entered manually by participants. All questionnaires use adaptive questioning, with some questions displayed based on the responses to other items. Participants are asked to complete a baseline questionnaire and a combination of tools to capture dietary intake and movement behavior over approximately a 1-year period per participant (Figure 2). To mitigate challenges with digital literacy, participants' frequently asked questions and instruction guides for completing the questionnaires were adapted or developed. Call center staff at regional cohorts are available and are provided with frequently asked questions to assist participants. Data are collected regionally, integrated, and held by regional cohorts and the CanPath National Coordinating Centre [52].

Figure 2. Collection of dietary intake and physical activity data within the HEAL study. ACT24: Activities Completed Over Time in 24 Hours; ASA24: Automated Self-Administered 24-Hour Dietary Assessment Tool; CDHQ-III: Canadian Diet History Questionnaire-III; HEAL: Healthy Eating and Supportive Environments; PYTPAQ: Past-Year Total Physical Activity Questionnaire.

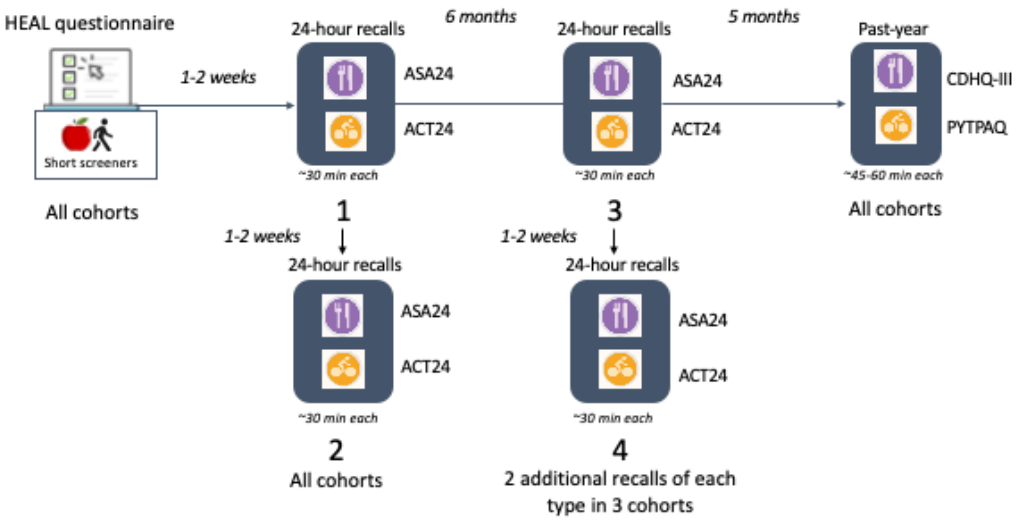

HEAL Baseline Questionnaire

At baseline, participants in each regional cohort are invited to complete a web-based questionnaire. The questionnaire content (Table 1) was informed by the HEAL Working Group and Scientific Advisory Committee and reflects measures from different levels within the socioecological model [53] that are associated with dietary intake, movement behaviors, and chronic disease. Information collected includes gender identity, household income, financial stress, self-rated health, household food security status, and 6-digit postal code of residence and place of employment (if applicable). Participants are asked to provide their date of birth for verification purposes. The questions were drawn from prior CanPath questionnaires whenever possible to facilitate longitudinal analyses (eg, demographics, anthropometrics, physical and emotional health, and food security), along with established tools and measures used in other population cohort studies (eg, functional status and activities of daily living; Table 1).

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Table 1. Content included in the Healthy Eating and Supportive Environments study baseline questionnaire.

Question category	Description	References
Demographics	Date of birth, sex, gender, pregnancy, breastfeeding, residential postal code, marital status, employment status, employment postal code, household income, household structure (number of children and adults living in household).	[54]
Financial stress	Feelings of stress due to finances.	[54,55]
Food security	Food situation in participants' household in the prior year.	[56]
Experiences of discrimination	Experiences of discrimination as a result of sex, gender, ethnicity or culture, race or color, physical appearance, religion, sexual orientation, age, disability, language, or another reason.	[57]
Anthropometrics	Weight, height, waist, and hip measurement (self-measured).	[54]
Food timing	Timing of eating occasions over the prior year.	[58]
Diet quality (dietary screener)	Alignment of dietary intake to the 2019 Canada's Food Guide healthy food choices recommendations over the past month.	[59,60]
Physical activity questionnaire	27 Questions on job-, transportation-, housework-, and recreational-related physical activity, as well as time spent sitting.	[61]
Questions cohorts may choose to include		
Functional status	14-Item scale on upper body limitations, lower body limitations, and dexterity limitations.	[62]
Physical and emotional health	The Patient Health Questionnaire, Generalized Anxiety Disorder, and self-reported health.	[63,64]
Activities of daily living	20-Item scale capturing activities of daily living, for example, Can you dress and undress yourself without help?	[62]

Dietary Intake and Movement Behavior Assessment Tools

Participants who complete the baseline questionnaire are asked to complete various web-based dietary intake [65] and movement behavior assessments [66,67] over approximately a 1-year period (Table 2). The baseline questionnaire includes short dietary intake and movement behavior screeners, including the Canadian Food Intake Screener [59,60] and the long-form International Physical Activity Questionnaire, which queries movement behaviors over the past 7 days [61]. The Canadian Food Intake Screener [59,60], which provides a rapid assessment of dietary intake over the past 30 days in relation to the 2019 Canada's Food Guide, is included to allow the regional cohorts to develop scoring algorithms based on comparison of the screener data to 24-hour dietary recall data [68]. Such scoring algorithms may be useful for improving the quality of dietary intake data from the screener for future data collections that do not include more intensive dietary assessment. Regional cohorts have previously used the International Physical Activity Questionnaire in baseline data collections, providing an opportunity for longitudinal analyses, while the Canadian Food Intake Screener has been administered in Alberta's Tomorrow Project and will be newly administered in the other regional cohorts.

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Table 2. Dietary intake and movement behavior assessment tools administered to participants within the Canadian Partnership for Tomorrow's Health (CanPath) regional cohorts as part of the Healthy Eating and Supportive Environments (HEAL) study.

Assessment tool	Description	Administration considerations	Psychometric properties
Dietary intake			
Canadian Food Intake Screener [59,60]	• 16-Item screener that rapidly assesses alignment of intake with the 2019 Canada's Food Guide healthy food choices recommendations. • Application of the scoring algorithm results in a total score that ranges from 0 to 65, with higher scores reflecting higher alignment with the guidance.	• Requires ~5 minutes to complete. • Available in English and French. • Can be programmed into any survey platform.	• A similar level of construct validity as observed for other multidimensional screeners has been shown in a sample of adults [60].
Automated Self-Administered 24-Hour Dietary Assessment Tool (ASA24[a]-Canada-2018) [65,69]	• Allows web-based self-administration of 24-hour dietary recalls, and auto-codes reported foods and beverages, eliminating the need for trained interviewers and coders. • Includes multiple passes adapted from the United States Department of Agriculture's Automated Multiple-Pass Method to enhance the accuracy and completeness of recall. • Output includes all foods and beverages reported and estimates of energy and nutrient intake per food and per recall.	• Requires 30 to 60 minutes to complete a recall. • Available in English and French. • Single sign-on can be used to integrate ASA24-Canada-2018 into an existing survey platform, eliminating the need for participants to sign in to a separate platform.	• Feeding studies have shown that ASA24 captures intake with a high level of accuracy relative to true intake, ascertained through weighing of amounts served and plate waste, among samples of US adults [70].
Canadian Diet History Questionnaire-III [71,72]	• Past-year food frequency questionnaire that asks participants to recall intake of over 140 foods and beverages over the past year, including typical portion size and frequency of intake. • Adapted from the US Diet History Questionnaire-III to reflect the Canadian food supply using data from the 2015 Canadian Community Health Survey—Nutrition.	• Requires 45 to 60 minutes to complete. • Available in English and French.	• The US Diet History Questionnaire has been shown to have similar or better assessment of nutrients versus other food frequency questionnaires [73].
Physical activity			
International Physical Activity Questionnaire-Long Form (IPAQ-LF) [61,74]	• 27-Item questionnaire that asks participants to report the frequency and duration of vigorous and moderate intensity physical activity, as well as walking, in the prior 7 days across occupational, transportation, household, and recreation or leisure domains.	• Requires 10 to 15 minutes to complete. • Available in English and French. • Can be programmed into any survey platform.	• Strong associations observed with data from an activity monitor and total and vigorous activity estimated by the IPAQ-LF among adults [74].

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Assessment tool	Description	Administration considerations	Psychometric properties
Activities Completed Over Time in 24 Hours (ACT24) [66,75]	• Allows web-based self-administration of 24-hour activity recalls capturing a range of sedentary behaviors, including screen time, as well as low-intensity physical activity, daily activities, and activity intensities over time. • Output includes total energy expenditure, physical activity energy expenditure, physical activity level, physical activity time, sedentary time, and measures of sleep.	• Requires 30 to 60 minutes to complete among individuals aged 50- to 74-years (the predominant age range in CanPath) [76]. • Available in English and undergoing translation to French for the HEAL study. • Personalized participant links can be used, eliminating the need for participants to sign in to a separate platform.	• Good agreement with total energy expenditure based on doubly labeled water and activPAL accelerometer values [76]. • Higher correlations with doubly labeled water-measured physical activity energy expenditure compared to other questionnaires [76]. • Higher correlations with accelerometer (activPAL) active and sedentary time compared to other questionnaires [77]. • Mean difference in sedentary time of 1.9% between ACT24 and accelerometry [77].
Past-Year Total Physical Activity Questionnaire [67]	• Past-year frequency questionnaire that captures type, duration, frequency, and intensity of physical activities in the previous 12 months, including employment and volunteer activities (including walking or biking to and from); household, childcare, and do-it yourself activities; and recreation and leisure activities. • Output includes total hours per week spent in each activity; total physical activity quantified in metabolic equivalent hours per week; and frequency, duration, and perceived intensity of activities reported over the past year.	• Requires 30 to 60 minutes to complete. Available in English and undergoing translation to French for the HEAL study.	• Similar reliability and validity for measuring past-year physical activity relative to accelerometer and 7-day activity logs as other self-administered activity questionnaires [67].

[a]ASA24: Automated Self-Administered 24-Hour Dietary Assessment Tool.

A total of 1 to 2 weeks following completion of the baseline questionnaire, participants are invited via email to complete an online 24-hour dietary recall using the Automated Self-Administered 24-Hour Dietary Assessment Tool (ASA24-Canada-2018) [65,69] and a 24-hour physical activity recall using Activities Completed Over Time in 24 Hours (ACT24) [66,75]. Participants are invited to complete a second set of recalls 1 to 2 weeks later. A subset of cohorts, including Alberta's Tomorrow Project, Manitoba's Tomorrow Project, and Atlantic Partnership for Tomorrow's Health, invites participants to complete another 2 sets of ASA24-Canada-2018 and ACT24 recalls 6 months later. The 24-hour dietary recalls aim to collect information on all foods, beverages, and supplements consumed the prior day from midnight to midnight. Similarly, the 24-hour activity recall queries all activities in the prior day, including time spent in bed, sedentary behavior, and physical activity. One year after baseline, participants are asked to complete past-year food and physical activity frequency questionnaires. These include the Canadian Diet History Questionnaire-III (CDHQ-III) [71,72] and the Past-Year Total Physical Activity Questionnaire (PYTPAQ) [67]. Prior versions of the Canadian Diet History Questionnaire have been administered in Alberta's Tomorrow Project and CARTaGENE [38,72], and the PYTPAQ was included in the Alberta's Tomorrow Project baseline questionnaires administered from 2000 to 2008 [29]. The ASA24 has been administered to subsets of participants in the BC Generations Project (unpublished) and Alberta's Tomorrow Project [78], while the ACT24 is being newly administered to CanPath participants as part of HEAL.

The 24-hour recalls are the primary source of dietary intake data used to address the objectives of the HEAL study. The CDHQ-III is administered to broaden possible applications of the data in the future. Using data from dietary recalls and frequency questionnaires in epidemiological research leverages the strengths of each, increasing power and precision for estimation of associations with dietary intake [79-81]. Validation studies comparing self-report data to recovery biomarkers have shown that systematic error (ie, bias) in estimates of absolute intake is greater in food frequency questionnaires (FFQs) versus recall data [81-85], raising concerns about the use of FFQ data alone [86]. Comparatively, data from 24-hour recalls are affected to a larger extent by random error, largely due to within-person day-to-day variation [87,88], which can be addressed using repeat measures and statistical modeling [89,90]. Nonetheless, 24-hour recalls may not adequately capture infrequently consumed components, such as fish, whereas this is a strength of FFQs, given their focus on a longer period [91]. Overall, the 24-hour recall data will provide estimates of total intake of foods and nutrients, whereas the FFQ data will lend insights into less

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frequently consumed foods. The 2 tools can be used together in future research, for example, using regression calibration to mitigate bias in estimates of diet-disease associations [92].

Data Collection Procedures

The data collection approach was informed by prior feasibility work in Alberta's Tomorrow Project [78] and an expert advisory committee that provided guidance to Alberta's Tomorrow Project in 2019. The regional cohort was planning a comprehensive diet and movement behavior assessment that was interrupted by the COVID-19 pandemic. Data collection will be staggered across cohorts (eg, one cohort starts in January, another in April to facilitate sharing of "lessons learned" and adjustment to implementation as needed). The study was announced to CanPath participants through existing CanPath and cohort communication channels, including websites, newsletters, and heads-up emails notifying participants of the study in advance of the invitation. Within each cohort, emails inviting participants to complete the baseline questionnaire are sent in waves, with the aim of spreading the subsequent 24-hour recalls over the months of the year to minimize the effects of seasonality. Phased rollout across cohorts across the months of the year further minimizes the effects of seasonality at the population level. Each participant completes their data collection activities over about a 1-year period, with full data collection for all participants in each regional cohort expected to last from 1.5 to 2 years.

Participants enter the study by completing the HEAL baseline questionnaire. Participants are able to return to prior questions to change their answers, but not to advance in the questionnaire without providing a response. Up to 2 email reminders to complete the questionnaire will be sent to participants who have not responded after receiving the initial email invitation. The reminders will be sent 14 and 21 days after the initial invitation.

Participants who complete at least the demographic section of the HEAL baseline questionnaire are invited within approximately 2 weeks to complete their first ASA24-Canada-2018 and ACT24 recalls. To reduce participant burden, personalized hyperlinks or single sign-on methods are used. These methods will enable participants to access the recall systems directly from their email invitation or their regional online participant platform without being required to enter unique usernames and passwords for ASA24-Canada-2018 and ACT24. Automated batching of output files from ASA24-Canada-2018 and ACT24 can be used by cohorts to facilitate tracking participants' completion status and sending reminders.

Invitations to complete ASA24-Canada-2018 and ACT24 recalls are sent in the morning, prompting participants to report their intake and activity for the prior day from midnight to midnight. The unannounced recalls are intended to reduce reactivity [91]. Participants are encouraged to complete the recalls on the day they receive the invitation. The recalls can be completed at any time during the day (up to 8 AM the following day for ASA24-Canada-2018) and in multiple sittings if needed. Nonresponders receive up to 3 reminders every 3 days. Once the first set of recalls has been completed, participants are invited to complete another set of 2 recalls (1 diet and 1 activity, for a total of 2 of each type) within 3 to 10 days. Approximately 6 months later, participants in Alberta's Tomorrow Project, Manitoba's Tomorrow Project, and Atlantic Partnership for Tomorrow's Health are asked to repeat the recall protocol for a total of 4 of each type (Figure 2). The additional recalls will contribute data to better estimate the usual diet and movement behavior.

Approximately 1 year after completing the baseline questionnaire, participants are invited via email to complete the CDHQ-III and PYTPAQ. Nonresponders receive up to 3 reminders 7, 14, and 25 days later.

The time to complete the baseline questionnaire and all diet and physical assessment tools is approximately 4 to 5 hours for participants who complete 2 ASA24-Canada-2018 and 2 ACT24 recalls and 6 to 7 hours for participants who complete an additional 2 ASA24-Canada-2018 and an additional 2 ACT24 recalls. The ASA24-Canada-2018, ACT24, and CDHQ-III systems all have researcher platforms that allow for monitoring of completion status. These platforms provide an indication of whether the recalls and questionnaires have been completed by each participant. Data cleaning will be conducted to consider whether recalls and questionnaires are sufficiently complete even if participants did not make it all the way to the end or alternatively, whether some recalls and questionnaires that appear to be complete do not represent high-quality data. For example, for the dietary recalls, established steps include checking for outliers in estimated nutrient intakes [93].

NutriQuébec

NutriQuébec uses an online 24-hour dietary recall platform, Rappel de 24 h Web (R24W), that was developed for use in Québec [44,94,95]. Like ASA24 (Table 2), participants report foods and beverages consumed the previous day by browsing or using the search engine. Additionally, prompts query the context of consumption (time, place, and presence of others) and remind participants about potentially forgotten food categories. The R24W can be used on a phone, tablet, or computer. NutriQuébec participants receive unannounced email invitations to complete 2 to 3 recalls using R24W on nonconsecutive days over a 30-day period [96,97], with up to 5 reminders for nonresponders. The NutriQuébec study is collecting movement behavior data using the Physical Activity and Sedentary Behavior Questionnaire, developed by the PULSAR's *Comité Activité physique et sédentarité* [98]. The questionnaire includes items from the Godin Leisure-Time Exercise Questionnaire [99], the European Prospective Investigation into Cancer and Nutrition physical activity questionnaire [100], and the Québec Population Health Survey [101]. A recent study among 48 female and 20 male population in Québec found that data generated from 2 R24W and 2 ASA24-Canada dietary recalls were comparable, with no meaningful differences in estimated intake of energy, proteins, lipids, saturated fatty acids, carbohydrates, fibers, sodium, and vegetables and fruits [94].

Data Integration and Harmonization

Data from the HEAL baseline questionnaire and dietary intake and movement behavior assessment tools will be transferred to

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Maelstrom Research [102] for cleaning and integration with existing CanPath and NutriQuébec data. Each participant has a unique study ID, which facilitates data integration with earlier waves of data collection within each respective regional cohort. Existing CanPath data are already connected to Maelstrom's platform. Cleaning procedures include those specifically developed for 24-hour dietary and movement behavior recalls, which encompass examination and assessment of incomplete recalls, as noted previously [43,93]. The 6-digit postal code of participants' residence and work (if applicable) allows linkage to geospatial environment data from CANUE and Can-FED [67]. Collection of data using the same tools and data dictionaries across cohorts (aside from NutriQuébec) minimizes the need for harmonization. Harmonization of data between CanPath and NutriQuébec will follow best practices outlined by Fortier et al [43] including defining target variables and harmonization potential, processing of data, and estimating the quality of the generated harmonized dataset.

Data Access

All data generated via HEAL will be available within the CanPath researcher access platform using existing access request procedures detailed on the CanPath website.

Statistical Analysis

The association between a given food environment characteristic (ie, density of fast food outlets) with diet quality will be evaluated using generalized linear mixed models, both unadjusted and adjusted for possible confounders as fixed effects. A random intercept representing the dissemination area (unit of measurement of the food environment) will be included. The mixed component of the generalized linear mixed model will contain random effects to account for the correlation of participants within dissemination areas. Unexplained variation will be partitioned into between- and within-area components and between-area heterogeneity in the effects of environmental exposure variables. Effect modification will be used to determine whether associations between the food environment and diet quality vary by environmental- and individual-level chronic disease risk factors.

Ethical Considerations

Ethics approval for HEAL was granted by the University of British Columbia/BC Cancer Institutional Review Board (H23-02478). Each CanPath regional cohort study will also obtain local ethics approval for its respective data collection. Participants in CanPath provide consent to be recontacted for research purposes and for secondary analysis of data in the future. Participants are recontacted and asked to provide informed consent if they wish to participate in HEAL. The consent process included details on the purpose of HEAL, study investigators, the length of each survey, and data storage and retention. The regional cohorts retain personal identifiers. For verification purposes, participants are asked to provide their birthdate for questionnaires completed, but the HEAL research team will not receive this information. Only deidentified data will be accessible to the HEAL research team and to investigators who receive approval for use of the data. Participants do not receive compensation for participation.

Results

Participant recruitment and data collection began in spring 2025 in 2 regional cohorts: Manitoba's Tomorrow Project and the BC Generations Project. Participant recruitment in the remaining cohorts will occur until fall 2026. Data collection is expected to conclude by the end of 2027. As of manuscript acceptance (November 4, 2025), 3171 participants had been recruited. Data cleaning and harmonization will occur on a rolling basis. Linkage of data collected within HEAL to CANUE and Can-FED data occurs twice per year to coincide with the transfer of cleaned or harmonized data from Maelstrom to the regional cohorts. Analysis of the main study aims pertaining to dietary intake and the food environment is planned for 2026. It is anticipated that dietary intake and movement behavior data will be available for up to 100,000 participants and accessible to researchers in 2029. At the end of the study, participants will receive a report summarizing the diet and movement behavior information they provided.

Discussion

Principal Findings

This protocol outlines the extensive planning and coordination required for the collection of detailed dietary and movement behavior data that will be linked to rich environmental data, along with the wealth of information already held by regional cohorts in Canada. The approach of embedding data collection within ongoing cohorts is resource sparing, drawing on the significant investments already made in the CanPath and NutriQuébec infrastructure. In addition to an existing pool of participants, CanPath is a research platform, meaning that data collected by the regional cohorts are available for use by the broader research community in Canada and internationally. This protocol may inform the design and collection of detailed dietary and movement behavior assessments using web-based tools in other epidemiologic and surveillance studies.

The comprehensive data collection, including sociodemographic data and completion of multiple dietary and movement behavior tools, will enable us to address the aims of HEAL, improving our understanding of how environmental factors are associated with dietary intake among adults in Canada. The HEAL study thus shifts focus from individual-level behaviors and choices to the broader structural environment, recognizing the complexity of factors that shape dietary intake. The new dietary and movement behavior data collected within HEAL have implications more broadly as CanPath is designed to facilitate collaboration with large-scale international cohorts, including the UK Biobank [103] and the European Prospective Investigation into Cancer and Nutrition study [104], both of which hold detailed dietary and movement behavior data.

Strengths and Limitations

This work will provide a platform for addressing a wealth of research questions as the largest detailed assessment of dietary intake and movement behavior in Canada. The study population, which spans all 10 provinces of Canada and includes structurally excluded groups, is a major strength. The large sample will

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allow consideration of how factors such as gender identity and income interact with environmental factors in relation to diet. The combination of assessment tools will support methodological research, including expanding strategies, to mitigate the effects of error in dietary intake and movement behavior data on observed diet-disease associations. The collection of data using multiple tools in a large population is uniquely possible because of the advent of web-based systems that enhance the feasibility of recalls by eliminating the need for interviewers and coders and that allow for automated batching of output to facilitate participant tracking and reminders.

A limitation is the further introduction of self-selection in this volunteer sample of participants through the baseline questionnaire, which serves as a gateway to the HEAL study. Given the time commitment and collection of data over a 1-year period, participant nonresponse is also anticipated. However, a prior substudy in Alberta's Tomorrow Project, in which participants were asked to complete 4 ASA24 recalls and an online frequency questionnaire within 4 months, suggests that our approach will have reasonable uptake. Of participants who consented to the Alberta Tomorrow Project substudy (~50% of those invited), 70% completed at least 1 tool and half completed more than 1 recall [78].

The lack of comprehensive data in Canada is a barrier to training emerging researchers in the areas of diet and movement behavior assessment and epidemiology. The enrichment of CanPath through HEAL provides a valuable opportunity to expand capacity in these areas in Canada, which is crucial given that diet and movement behavior patterns are not aligned with guidance [1,105], with substantial implications for morbidity and mortality [9,106].

Conclusions

In the immediate term, the data newly collected in HEAL will lend insights into how features of the built, social, and RFE are associated with dietary intake in a large population of adults in Canada. In the longer-term, data collected in HEAL will provide an unprecedented opportunity to advance research on nutrition and movement behavior. For instance, data from the recalls and past-year questionnaires can be leveraged to examine associations with long-term outcomes through linkage to administrative health data including vital statistics, hospital records, and cancer registry data. This effort will also build capacity in the collection, processing, and harmonization of dietary intake data among Canadian cohorts and provide a training ground for emerging researchers.

Acknowledgments

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Data Availability

Data generated through this protocol will be available upon approval from the data access committee of the Canadian Partnership for Tomorrow's Health.

Authors' Contributions

Conceptualization: RAM, JEV, BL, SIK
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Methodology: MW, BL, DS, RAM, JEV, SIK
Writing—original draft: SIK, RAM, ADM, JEV
Writing—review and editing: GF, BL, CEM, LMM, DS, ES, MW, MJW

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report by Nutrition, Food & Health/Nutrition, aliments et santé Committee, Canadian Institutes of Health Research (CIHR).
[PDF File (Adobe PDF File), 39 KB - resprot_v14i1e71680_app1.pdf]

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Abbreviations

ACT24: Activities Completed Over Time in 24 Hours
ASA24: Automated Self-Administered 24-Hour Dietary Assessment Tool
Can-FED: Canadian Food Environment Dataset
CanPath: Canadian Partnership for Tomorrow's Health
CANUE: Canadian Urban Environmental Health Research Consortium
CDHQ-III: Canadian Diet History Questionnaire-III
FFQ: food frequency questionnaire
HEAL: Healthy Eating and Supportive Environments
PYTPAQ: Past-Year Total Physical Activity Questionnaire
RFE: retail food environment
R24W: Rappel de 24 h Web

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Protocol

IMplementation of Physical Activity for Children and adolescents on Treatment (IMPACT) for Cancer Diagnoses in Alberta: Protocol for a Single-Arm, Mixed-Methods, Hybrid Effectiveness-Implementation Trial

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Abstract

Background: Physical activity (PA) is feasible, safe, beneficial, and recommended for pediatric patients with cancer. Nevertheless, PA levels remain low due to treatment-related effects (eg, fatigue, pain), isolation and immunosuppression, geographic and transportation barriers, and limited access to population-specific programming. Delivering PA by videoconference may address some of these barriers. Thus, IMplementation of Physical Activity for Children and adolescents on Treatment (IMPACT) was developed. IMPACT is an individualized, tailored PA intervention delivered by an exercise professional over videoconference and is being evaluated in a hybrid effectiveness-implementation trial.

Objective: The objectives of this trial include (1) assessing the effectiveness of IMPACT on participants' device-measured PA (primary effectiveness outcome) and secondary effectiveness outcomes, including participant- and caregiver-reported PA and participant- and caregiver-reported quality of life, symptoms, cognitive function, resource use, and participant physical fitness outcomes (ie, participants' aerobic endurance, lower body flexibility, shoulder flexion range of motion, balance, functional mobility); and (2) assessing the implementation of IMPACT and the trial through evaluating recruitment, indices of feasibility, delivery time, expertise, cost, fidelity of intervention delivery, and adverse events.

Methods: A single-arm, mixed-methods, type II hybrid effectiveness-implementation trial is being conducted, and the RE-AIM (reach, effectiveness, adoption, implementation, maintenance) framework is guiding evaluation. Pediatric patients with cancer and blood disorders diagnosed between 5 and 18 years of age are being recruited in Alberta. Following informed consent/assent and baseline assessments (ie, participants' device-measured PA, participant- and caregiver-reported outcomes, participant physical fitness outcomes), participants receive individualized, tailored PA sessions up to 3 times/week for 15-45 minutes/session over

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12 weeks from an exercise professional via videoconference. Assessments are then completed postintervention (with the addition of a participant and caregiver interview) and at 6- and 12-month follow-ups. With respect to RE-AIM, reach covers referral and participation rates, participants' and caregivers' personal and medical information, and the proportion of participants from rural versus urban locations. Effectiveness includes participants' device-measured PA, participant- and caregiver-reported outcomes, and participant physical fitness outcomes. Adoption covers sources of referral. Implementation includes recruitment, feasibility, delivery time, expertise, cost, fidelity of intervention delivery, and adverse events. Maintenance includes participants' and caregivers' desire for ongoing access to PA, and participant- and caregiver-reported PA levels at 6- and 12-month follow-ups. Throughout the trial, quality improvement cycles occur every 6 months.

Results: Funding was obtained in April 2022. Participant recruitment began in March 2022 and will conclude in December 2025. Interim analyses and additional analyses of selected trial data have been conducted, and publications are forthcoming. Full trial results will be analyzed and published following trial cessation.

Conclusions: This work will provide insights into the effects of, and factors influencing, the implementation of an individualized, tailored PA intervention delivered by videoconference. Findings may support continued exploration of videoconference delivery as a strategy to ensure that more pediatric patients can access and benefit from PA.

Trial Registration: ClinicalTrials.gov NCT04956133; https://clinicaltrials.gov/ct2/show/NCT04956133

International Registered Report Identifier (IRRID): DERR1-10.2196/59302

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KEYWORDS

exercise; movement; pediatric oncology; neoplasms; internet-based; online; remote

Introduction

Background

Cancer among children and adolescents (ie, cancers diagnosed at <18 years) is relatively rare [1]. Recent estimates suggest that approximately 400,000 children and adolescents are diagnosed with cancer each year globally [2], representing <3% of all new cancer diagnoses annually [3]. Nearly 90% of children and adolescents diagnosed with cancer are anticipated to survive 5 or more years, and >70% will survive 10 or more years [4]. Despite this relatively positive prognosis, the disease remains a leading cause of morbidity and mortality among children and adolescents in North America [1,5], and is associated with negative effects in both the short term [6-8] and long term [9-14].

In the short term, children and adolescents on treatment for cancer (ie, pediatric patients with cancer) experience negative effects spanning physical (eg, pain, nausea [6]), psychological (eg, depression, anxiety [7]), social (eg, isolation [7]), and cognitive (eg, difficulty thinking and remembering [8]) domains of functioning. In the long term, children and adolescents living beyond treatment for cancer (ie, pediatric cancer survivors) may experience poorer physical (eg, decreased strength, increased fatigue [14]), psychological (eg, posttraumatic stress, fear of cancer reoccurrence [10,14]), social (eg, challenges in relationships with family and friends [10]), and cognitive (eg, reduced processing speed, impaired executive functioning, lower academic performance [9,15]) outcomes. This cohort is also at greater risk for secondary cancers, morbidity, and premature mortality [16-20]. Thus, identifying strategies to improve outcomes in both the short and long term is important.

Physical activity (PA; any bodily movement produced by skeletal muscles that requires energy expenditure [21]) may enhance physical, psychological, social, and cognitive domains of functioning among pediatric patients with cancer [22-24]. PA may reduce the severity of many of the negative effects experienced during treatment and enhance the overall quality of life among pediatric patients with cancer [25-27]. Indeed, systematic reviews have found that individualized, supervised PA during treatment—even during the intensive treatment phase—is safe and may improve a range of health outcomes [28,29]. Further, PA during treatment is associated with reductions in morbidity, secondary cancers, and premature mortality [30]. Recent reviews underscore the beneficial role of PA for pediatric patients with cancer [28,29,31,32], and guidelines and recommendation statements have been published suggesting that all pediatric patients with cancer *move more* [33].

Despite the documented benefits of PA and existing guidelines and recommendation statements [33], the desire and motivation of pediatric patients with cancer to engage in PA varies widely [34], and many stop engaging in PA during treatment [35,36] or take part in significantly less PA than their healthy peers [37]. This may be due to many of the barriers pediatric patients with cancer face when seeking to engage in PA, including adverse treatment-related side effects (eg, pain, nausea, fatigue), variable treatment timelines that differ significantly from child to child and include periods of isolation and immunosuppression [38,39], and the lack of pediatric cancer-specific PA opportunities (eg, interventions or programs) for this group [40]. Of the PA interventions and programs that are available, most are delivered at or near the hospital, which could pose an additional barrier to participation [41,42] and further disadvantage those who live in rural locations or farther from the hospital. Additionally, given that pediatric patients with cancer and their caregivers desire PA to be delivered close to or at home, the dominant focus on hospital-based delivery overlooks important preferences for PA within this population [41,42].

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Exploring home-based PA delivery may be one way to address some of the barriers pediatric patients with cancer face when trying to engage in PA. However, relying solely on home-based PA programs may not successfully promote the adherence required to realize PA-related outcomes among this group [43]. Synchronous supervision of PA sessions by videoconference from exercise professionals may better support adherence to PA [40,43], ensure safe PA engagement, and reach more pediatric patients with cancer—a small and dispersed population [44]. Emerging evidence from recent trials suggests PA delivered by exercise professionals over videoconference is feasible and may improve physical outcomes (eg, physical fitness, flexibility, strength) among pediatric cancer survivors (ie, those off-treatment) [45,46]. This is bolstered by findings from videoconference-delivered (ie, telehealth) interventions focused on rehabilitation for pediatric patients with cancer and pediatric cancer survivors, which have found significant improvements in outcomes spanning PA limitations, participation restrictions, and quality of life [47,48]. In addition to being feasible and conferring benefits, videoconference delivery of PA may address another important interrupter to supervised in-person PA delivery—namely, circumstances such as cold and flu season or pandemics that limit access to pediatric patients with cancer (eg, ward closures) [45-48]. Finally, videoconference delivery of PA to this cohort could ensure that more pediatric patients with cancer have access to support from trained exercise professionals (eg, kinesiologists, clinical exercise physiologists, certified personal trainers), filling a gap within the Canadian context where exercise professionals (beyond physiotherapists and occupational therapists) are rarely, if ever, embedded within the pediatric cancer care system.

Indeed, in Alberta, there are no exercise professionals embedded within the pediatric cancer care system. However, there is support for providing PA in this cohort, positioning supervised videoconference PA delivery as a viable modality. Considering a desire to implement and evaluate a PA intervention with potential for sustainability and scalability in this context, a single-arm, type II hybrid effectiveness-implementation trial [49] is ideally suited to generate data assessing both the impacts of PA delivered by videoconference and the factors influencing implementation. This trial design has also been recommended by international experts to advance the field of pediatric exercise oncology [50]. Though videoconference delivery is a relatively novel approach, forgoing traditional feasibility and comparative designs is suitable given: (1) face validity for PA and its acceptability for pediatric patients with cancer [31,51]; (2) a growing evidence base from different, but related, populations (eg, young adults affected by cancer, adolescents with intellectual and developmental disabilities, adolescents with congenital heart disease) supporting the delivery of PA by videoconference [52-55]; (3) minimal risk associated with individualized, tailored PA for pediatric patients with cancer—with evidence to date supporting the safety of PA during this phase and of videoconference delivery (ie, few adverse events) [24,28,29,56]; and (4) rationale to gather more data on the effectiveness of PA interventions for pediatric patients with cancer [50] and on implementation metrics [47,48].

Purpose and Study Objectives

The co-primary aims of this trial are to (1) assess the effectiveness of the videoconference-delivered PA intervention on participants' device-measured PA (primary effectiveness outcome), as well as secondary effectiveness outcomes including participant- and caregiver-reported PA and participants' quality of life, symptoms, cognitive function, resource use, and physical fitness outcomes (ie, aerobic endurance, lower body flexibility, shoulder flexion range of motion, balance, functional mobility); and (2) assess implementation of the PA intervention and the trial through evaluating recruitment, indices of feasibility, delivery time, expertise, cost, fidelity of intervention delivery, and adverse events.

Methods

Overview

This protocol paper was prepared following the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [57] and the TIDieR (Template for Intervention Description and Replication) checklist [58] (see Multimedia Appendix 1). The trial was registered with ClinicalTrials.gov [59] on July 09, 2021, and started at Stollery Children's Hospital on March 1, 2022, and at Alberta Children's Hospital on September 28, 2022 (see the "Ethical Considerations" section). This paper details the PA intervention and trial to enhance transparency in reporting and will serve as a reference for forthcoming papers. The CONSORT (Consolidated Standards of Reporting Trials) for eHealth interventions [60], the StaRI (Standard for Reporting Implementation Studies) statement [61], and the GRAMMS (Good Reporting of a Mixed Methods Study) checklist [62] will be followed when preparing and reporting the full trial results.

Trial Design

A single-arm, mixed-methods, type II hybrid effectiveness-implementation trial is being conducted, and the RE-AIM (reach, effectiveness, adoption, implementation, maintenance [63,64]) framework is being used to guide evaluation. As above, a single-arm trial design was selected with consideration for the local Alberta context and the desire to develop and test an intervention that could be sustained and scaled into a routine care pathway. Mixed methods are being used to gather both qualitative and quantitative data to provide a more comprehensive understanding of the effectiveness and implementation of this novel mode of delivery. Quantitative and qualitative data are collected from participants, caregivers, and those involved in trial conduct (ie, health care providers, exercise professionals) at several time points, outlined in greater detail throughout the "Procedures" and "Data Collection" sections.

Ethical Considerations

The research ethics application for this trial was submitted to the Health Research Ethics Board of Alberta (HREBA) on December 16, 2020, and approval was granted on February 16, 2021 (HREBA.CC-20-0364). Administrative approval was obtained from Stollery Children's Hospital on February 12, 2021, and from Alberta Children's Hospital on May 15, 2021.

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Due to delays related to the COVID-19 pandemic and hospital restrictions, recruitment opened at Stollery Children's Hospital on March 1, 2022, and at Alberta Children's Hospital on September 28, 2022. The first health care provider referral was received from Stollery Children's Hospital on March 16, 2022, and from Alberta Children's Hospital on October 19, 2022. Finally, research ethics board approval was granted by the Human Research Ethics Board at the University of the Fraser Valley on January 23, 2023 (approval number 101287). This approval was sought as the co-principal investigator (AW) moved institutions and onboarded additional local trial team members to support interview conduct and quality improvement cycle data collection.

In accordance with the principles of the Declaration of Helsinki and the ethics boards named above, all patients provide informed consent or assent to participate in this trial online via the web-based platform Research Electronic Capture (REDCap; Vanderbilt University) [65,66]. The designation of a Mature Minor, endorsed by Alberta Health Services, is being followed (ie, typically minors 14 years and older who can understand and appreciate the nature, risks, and consequences of participating in proposed procedures and are able to provide consent without the input of their legal guardian [67]). Caregivers also provide informed consent and, where indicated, provide consent on behalf of their child via REDCap. Health care providers and exercise professionals provide informed consent via REDCap to participate in semistructured interviews at regular intervals (see the "Quality Improvement Cycles" section).

Of note, all trial data are being deidentified and are accessible only to members of the trial team directly involved in trial conduct. Financial compensation is not provided to participants, caregivers, health care providers, or collaborators referring to the trial. Exercise professionals involved in PA sessions and assessment delivery are compensated for their time delivering PA sessions and conducting assessments of physical function, but do not receive compensation for completing interviews or data collection as part of the quality improvement cycles.

Recruitment and Participants

Patients are recruited through referral from health care providers at Alberta Children's Hospital or Stollery Children's Hospital, via consent-to-contact forms, posters, self-referral documents, emails from the Kids Cancer Care Foundation (a local support organization), and word of mouth. Children and adolescents are eligible to participate if they (1) are between 5 and 18 years of age at enrollment; (2) have been diagnosed with any cancer or blood disorders; (3) are scheduled to receive, are currently receiving, or have completed treatment within the past 3 months; (4) are medically cleared to participate in PA; (5) have a caregiver (ie, an individual responsible for providing care to a child or adolescent diagnosed with cancer or a blood disorder) willing to complete assessments and be present during the PA sessions; and (6) are able to participate in English.

The decision to include pediatric patients with blood disorders was made considering that, in this Canadian context (ie, Alberta), pediatric patients with cancer and blood disorders are typically treated on the same unit/ward; the supervised, tailored, and low-risk nature of the PA delivered in IMplementation of Physical Activity for Children and adolescents on Treatment (IMPACT); early evidence suggesting the safety and benefits of PA in this cohort (ie, pediatric patients with blood disorders [68]); and consultations with clinical trial team members who supported, including pediatric patients with blood disorders.

Sample Size

The trial sample size was set at 76. This estimate was based on the primary effectiveness outcome of device-measured PA (ie, steps per day over 7 days). A meaningful difference in PA was defined as an average increase of 1000 steps/day between baseline (week 0) and postintervention (week 12), based on prior literature [69]. Setting α=.05 and power=0.80, and accounting for 25% attrition, a target of 76 participants between the ages of 5 and 18 years, along with one of their caregivers, from Alberta Children's Hospital or Stollery Children's Hospital (approximately 38 per site) was established. This sample size also provides sufficient power to explore secondary effectiveness outcomes while accounting for covariates (eg, sex, gender, and other factors) and offers the opportunity to stratify the sample to examine changes by cancer versus blood disorder diagnoses and across age ranges.

Regarding qualitative data, all participants and caregivers are invited and encouraged to complete an interview at postintervention (week 12) to capture their experiences and perspectives. This approach was chosen to gain a comprehensive understanding of participants' and caregivers' experiences within IMPACT. Perspectives from those involved in implementation are also being collected. In these cases, health care providers who refer participants and exercise professionals involved in intervention and trial conduct are recruited purposefully, with no predetermined sample size. Instead, the principle of theoretical saturation is applied, wherein participants are recruited until no new insights emerge or specific quality improvement cycle questions have been addressed [70].

Procedures

Following referral (health care provider or self-referral), a member of the trial team contacts the caregiver via their preferred method (ie, email, phone call, or text message) to describe the PA intervention and trial, ascertain interest, confirm eligibility, and share the link to the participant consent or assent, and caregiver consent forms via REDCap. Once consent (or assent, as appropriate) is provided by the patient (henceforth referred to as the participant) and caregiver, the participant is scheduled for a baseline (week 0) assessment, which includes the collection of the participant's device-measured PA through a 7-day Fitbit (Google LLC) wear period and tracking log. Caregivers also complete a questionnaire covering personal and medical information, and participants and caregivers complete a series of questionnaires via REDCap assessing participant- and caregiver-reported PA as well as the participant's quality of life, symptoms, cognition, and resource use. Participants additionally complete a physical assessment via videoconference, measuring aerobic endurance, lower body flexibility, shoulder flexion range of motion, balance, and functional mobility. Once baseline assessments are completed, participants are matched with an exercise professional and begin

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the 12-week, individualized, 1:1 PA intervention. Following the PA intervention, participants and caregivers complete the same assessments as at baseline (with the exception of personal and medical information, which is collected only at baseline) and are invited to complete a postintervention interview via videoconference. At 6- (week 24) and 12-month (week 52) follow-up time points, participants complete the same assessments as at baseline (week 0) and postintervention (week 12), with the exceptions of personal and medical information, which is collected only at baseline, and the interview, which is conducted only postintervention. To enhance data completeness, notifications of assessments are sent via REDCap, and reminders are sent every 3 days for up to 2 weeks if assessments are not completed at baseline, postintervention, and follow-up time points. See Figure 1 for the CONSORT diagram.

Figure 1. CONSORT flowchart.

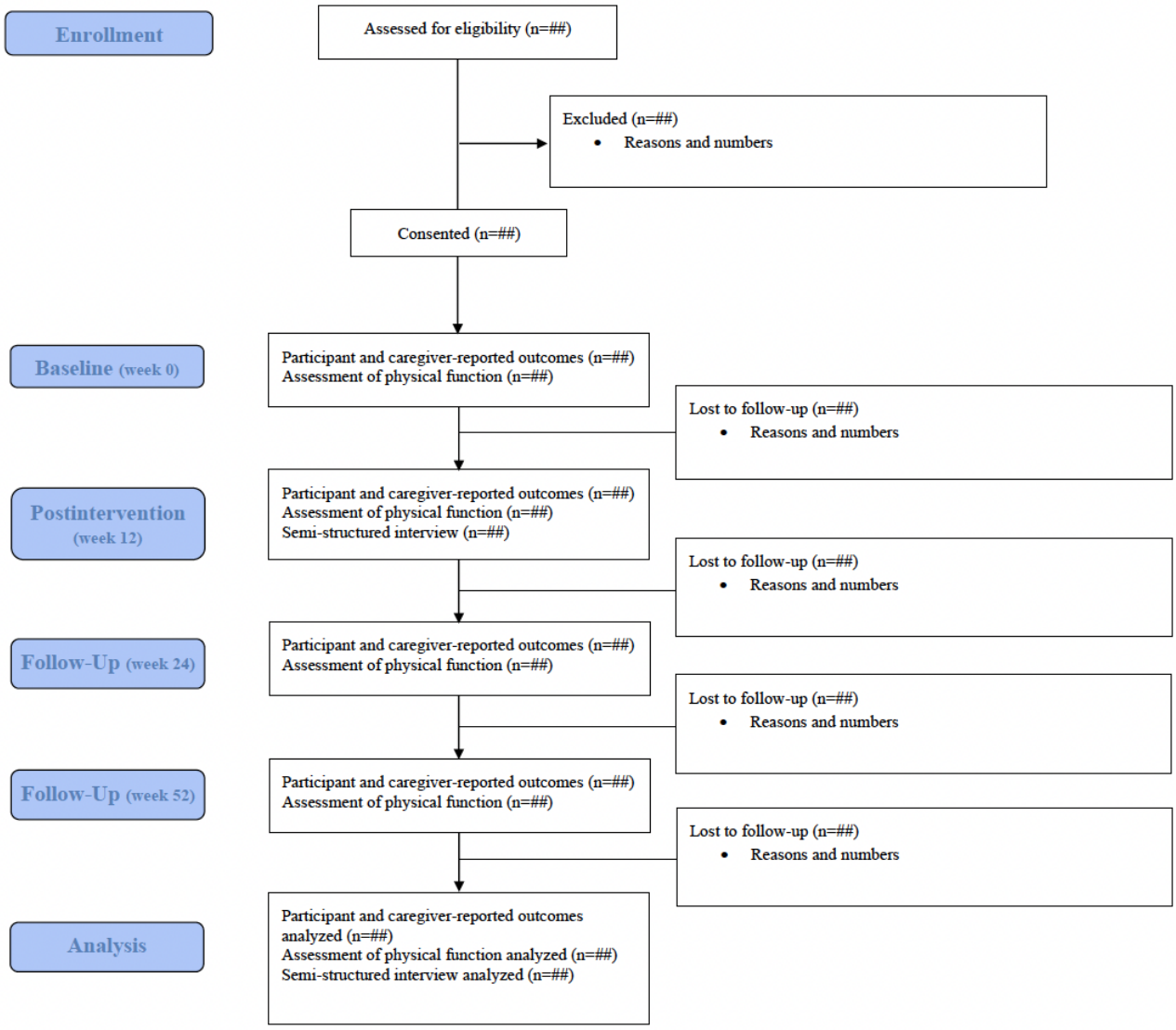

Throughout the trial, additional data aligned with the RE-AIM framework are being collected. Specifically, *reach* (ie, referral rate, number of participants excluded and reasons for exclusion, participation rate, participant and caregiver demographics, and medical information); *effectiveness* (ie, participants' and caregivers' perceptions of the IMPACT intervention and trial); *adoption* (ie, sources of referral and differences in referrals across hospitals); *implementation* (ie, indices of feasibility [trial retention, adherence, percentage of missing data, and participants' and caregivers' perceptions of feasibility], intervention delivery time, trial delivery time, expertise, cost, fidelity of intervention delivery, and adverse events); and *maintenance* (ie, semistructured interviews with participants and caregivers to explore their desire for ongoing access to the PA intervention, and the proportion of participants who continue to engage in PA through the 2 follow-ups). All data are collected by trial staff. Finally, quality improvement cycles to review and optimize the implementation of the intervention and trial are conducted every 6 months (see the "Quality Improvement Cycles" section). Data covering participants' and caregivers' personal and medical information, intervention fidelity, and perspectives from health care providers and exercise professionals involved in referral and trial conduct are collected. These data are collated and reviewed during meetings with an advisory board comprising participants, caregivers, trial staff, health care providers, and community partners (see the "Participant and Caregiver Involvement" section). Further information on data collection and quality improvement cycles

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is provided in the relevant subsections within the "Data Collection" and "Quality Improvement Cycles" sections, respectively.

The Intervention

The PA intervention was developed over 24 months with funding support from the Strategy for Patient-Oriented Research Evidence Alliance [71] and followed a patient-oriented approach [72]. The intervention was informed by relevant literature [28,29,31,32], existing pediatric exercise oncology resources (eg, the Pediatric Cancer Patients and Survivors Engaging in Exercise for Recovery program [73,74] and the Pediatric Oncology Exercise Manual [75]), and recently developed PA guidelines and recommendation statements for pediatric patients with cancer and pediatric cancer survivors [33]. This was integrated with perspectives gathered through semistructured interviews with 11 international experts who had successfully implemented PA with pediatric patients with cancer [69,76] and 16 local health care providers (eg, oncologists, nurses, physiotherapists, child life specialists) and staff from children's hospitals in Alberta. Semistructured interview guides were developed with support from an implementation science expert (Kelly Mrklas) and were informed by the Consolidated Framework for Implementation Research and the Theoretical Domains Framework [77]. Questions explored barriers and enablers to implementing PA with pediatric patients with cancer and examined factors spanning intervention characteristics, outer setting, inner setting, characteristics of individuals, and process. Additionally, during the interviews, context-specific implementation strategies were explored. Relevant literature, resources, and perspectives were integrated, and a team of researchers, exercise professionals, and health care providers (ie, the trial team) collaboratively developed and refined the PA intervention.

The resulting 12-week PA intervention, delivered via videoconference, includes sessions offered 3 times per week for 15-45 minutes and incorporates a combination of aerobic, resistance, balance, core, and flexibility exercises. Videoconference delivery allows participants to join whether they are at home or in the hospital. The intervention is tailored for each participant based on the frequency (ie, how often each exercise is completed and the number of PA sessions per week), intensity (ie, the difficulty of exercises or PA sessions), time (ie, duration of each exercise and each PA session), and type of exercise (ie, aerobic, resistance, balance, core, and flexibility). Each aspect of the intervention is modified based on participants' needs, preferences, medical factors, age, and abilities, including how they are feeling and managing treatment-related side effects, their treatment schedules, and other considerations (eg, school or extracurricular commitments). PA sessions are provided regardless of whether participants are in the hospital or at home. Select behavior change techniques (eg, goal setting, feedback and monitoring, social support, self-monitoring) are embedded within PA sessions and discussed in an age-appropriate manner. Behavior change topics are also selected based on participant choice and ongoing conversations throughout the PA sessions. As noted above, participant autonomy is prioritized throughout. See Multimedia Appendix 2 for an overview of the PA intervention.

Of note, caregivers are required to be present for each PA session, either at home or in the same room as the participant, depending on the participant's age, functional characteristics, and preferences (see the "Safety" section). If caregivers wish, they may participate in the PA sessions after completing the Get Active Questionnaire to ensure readiness and safety for engaging in PA, although the primary focus remains on the participant [78].

All PA sessions are delivered by a trained exercise professional who has completed a comprehensive >30-hour training program comprising both educational (eg, cancer and treatment protocols) and practical components (eg, exercise prescription, delivery, behavior change support, motivational communication skills). This training included the Thrive Health Cancer and Exercise program [79], as well as pediatric cancer and exercise [80] and adolescent- and young adult–specific modules [81]. Exercise professionals also attended trial-specific training covering topics such as oncology treatment and side effects, modifying PA based on treatment-related side effects, supporting movement, and intervention processes, delivered by the trial team. Finally, they completed a scenario-based competency training session, shadowed an existing group-based PA program in the community (ie, Pediatric Cancer Patients and Survivors Engaging in Exercise for Recovery [73,74]), and practiced delivering PA via videoconference to children aged 5-14 years without a history of cancer [82].

Safety

To ensure safe delivery of the intervention and trial, several precautions are taken. Specifically, participants are medically cleared by one of their health care providers (eg, oncologist, nurse, physiotherapist) to confirm they can safely participate in PA sessions and physical function assessments. Participants' personal and medical information is collected as part of baseline (week 0) participant- and caregiver-reported outcomes and reviewed by the trial team, including assessors and exercise professionals. If additional information is required, the trial team consults the participants and their caregivers, the participants' health care team, and an exercise professional with >20 years of experience delivering PA to this cohort to provide safe exercise alternatives and modifications. PA sessions are led by trained exercise professionals (see the "The Intervention" section for their training). The exercise professionals follow a detailed protocol designed to support safe delivery of PA and enable necessary modifications. During sessions, they regularly check in with participants to ask how they are feeling and whether they wish to continue exercising, and they quickly adapt exercises based on participants' responses. Additionally, exercise professionals have participants' full address, phone number, and emergency contact information readily available, and follow established protocols in the event of a medical emergency. Two members of the trial team (AW, CCV, or Julia T Daun) also review 10% of PA sessions for each participant—see the "Implementation (Throughout)" section—using a standardized checklist covering multiple categories, providing comments specifically on safety. During assessments of physical function, see the "Assessments of Physical Function (week 0, week 12, week 24, and week 52)" section, similar safety strategies are followed. Specifically,

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assessors have experience conducting videoconference-based assessments with young adults and adults living with and beyond cancer [53,83,84], and have received study-specific training and practice assessing children without a history of cancer. As noted above, caregivers are present during assessments, assessors have access to participants' medical and personal information, and 2 assessors are present to support data collection and implement emergency protocols if required.

Data Collection

Assessment Timeline and Data Collection

As described above, assessments occur at baseline (week 0), postintervention (week 12), and 6- (week 24) and 12-month (week 52) follow-ups. See Table 1 for an overview of outcome measures and time points. Following the RE-AIM framework, multiple types of information are collected.

Table 1. Outcome measures and time points.

Reach (throughout)	Effectiveness (weeks 0, 12, 24, and 52)	Adoption (throughout)	Implementation (throughout)	Maintenance (weeks 12, 24, and 52)
• Referral rate (numbers and sources) • Number of participants excluded and reasons for exclusion • Participation rate (number of participants consenting to participate divided by the number of eligible individuals referred) • Personal and medical information (ie, sex, gender, and other factors [eg, age, cancer diagnosis, sexual orientation, race/ethnicity, cultural background, and socioeconomic status]) of participating participants and caregivers (collected through caregiver-reported outcomes at baseline only) • Proportion of participants from rural versus urban locations	• Device-measured PA[a] levels • Participant and caregiver questionnaires (PA, quality of life, symptoms, cognitive outcomes, and resource use) • Assessments of physical function (aerobic endurance, lower body flexibility, shoulder flexion range of motion, balance, and functional mobility) • Interviews with participants and caregivers to explore the benefits of the PA intervention (at week 12 only) • Resource use • Direct and indirect costs (costs of intervention delivery and trial management)	• Sources of referral • Differences in referrals across referring sites	• Trial retention • Adherence to the PA intervention • Percentage of missing data • Interviews with participants and caregivers to explore their perceptions of feasibility (at week 12 only) • Intervention delivery time and cost • Trial delivery time and cost • Expertise of exercise professionals • PA session fidelity • Adverse events (safety)	• PA levels at 6- and 12-month follow-ups • PA referral into community programs • Access/use of maintenance offerings • PA referral implementation

[a]PA: physical activity.

Reach (Throughout)

Reach is assessed using data on referral rate (numbers and sources), number of participants excluded and reasons for exclusion, participation rate (number of participants consenting divided by the number of eligible individuals referred), personal and medical information (ie, sex, gender, and other factors such as age, cancer diagnosis, sexual orientation, race/ethnicity, cultural background, and socioeconomic status) of participating participants and caregivers, and the proportion of participants from rural versus urban locations. Where possible, information is also gathered from nonparticipating individuals via the consent-to-contact form and emails to assess reasons for trial refusal and to inform understanding of barriers to participating in the PA intervention and trial.

Effectiveness

Device-Measured Physical Activity (Week 0, Week 12, Week 24, and Week 52)

Device-measured PA (ie, step count) is assessed by having participants wear a Fitbit Charge HR activity tracker and complete a tracking log for 7 days. Participants are mailed the Fitbit and sent account information (generated by trial staff) via email. They are instructed to wear the Fitbit for 7 consecutive days, for at least 10 hours per day. Along with the Fitbit, participants complete a tracking log to record wear times (eg, when they put on or removed the Fitbit, and any PA performed throughout the day). At the end of the 7-day period, participants sync their Fitbit with their account, and caregivers scan or photograph the tracking log and send a copy to trial staff via email. Participants may wear the device between assessment periods if they wish, but these data are neither collected nor analyzed. Fitbits are returned once participants complete all assessments. The participant's step count from the 7-day period is retrieved from their Fitbit account by the trial team and

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averaged for each time point. Fitbits have been shown to be a reliable and valid method for collecting device-measured PA data in pediatric populations with and without chronic conditions [85-88] and have been used successfully in pediatric participants with cancer [69,89].

Participant and Caregiver Questionnaires (Week 0, Week 12, Week 24, and Week 52)

Personal and medical information is collected at baseline (week 0) from both participants and caregivers to describe their characteristics. This includes participants' biological sex, gender, race, ethnicity, location, age, diagnosis, and year of diagnosis, as well as caregivers' highest level of education, employment status, and annual household income. The questionnaire was developed by the trial team.

Self-reported PA at weeks 0, 12, 24, and 52 is assessed using a modified version of the Godin-Shephard Leisure-Time Exercise Questionnaire (m-GLTEQ) to capture frequency and duration of aerobic, resistance, flexibility, and balance training [90]. Participants complete the m-GLTEQ for themselves, regardless of age, and caregivers complete the m-GLTEQ based on both their own PA and their child's PA behavior. Specifically, participants and caregivers report the number of times per week they (and, in the case of caregivers, both themselves and their child) engage in mild, moderate, and strenuous PA during leisure time for a minimum of 10 minutes. At baseline, they also report PA levels before their (or their child's) cancer diagnosis, and at all other time points, they report PA over the past month. The m-GLTEQ is scored by calculating the total amount of PA (time × intensity) for each intensity and type of activity and summing the totals. Intensity is weighted using metabolic equivalents of 3, 5, and 9 for light, moderate, and strenuous PA, respectively. Higher scores indicate greater PA behavior. Reports will include total moderate-to-vigorous PA as well as total PA. The m-GLTEQ has demonstrated high reliability and validity in pediatric populations with cancer [91,92].

Quality of life at weeks 0, 12, 24, and 52 is assessed by both participants and caregivers using the Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales and PedsQL 3.0 Cancer Module [93,94]. Participants aged 5-7, 8-12, and 13-18 complete the Young Child Report, Child Report, and Teen Report versions of the PedsQL 4.0 Generic Core Scales and PedsQL 3.0 Cancer Module, respectively. Caregivers also complete a proxy report evaluating their child's quality of life using the corresponding PedsQL 4.0 Generic Core Scales and PedsQL 3.0 Cancer Module. Caregivers of participants aged 5-7, 8-12, 13-18, and 18+ complete the Caregiver Report for Young Children, Caregiver Report for Children, Caregiver Report for Teens, and Caregiver Report for Young Adults, respectively. The PedsQL 4.0 Generic Core Scale includes 23 questions across 4 domains of functioning: physical, emotional, social, and school. Items are scored on a 3-point scale for the Younger Child version (5-7 years): 0 (not at all), 2 (sometimes), and 4 (a lot), and on a 5-point scale for the Child (8-12 years) and Teen (13-18 years) versions, ranging from 0 (never) to 4 (almost always). After reverse scoring, items are linearly transformed to a 0-100 scale (0=100, 1=75, 2=50, 3=25, 4=0) and averaged to generate domain and total scores. Higher scores indicate a better quality of life. The PedsQL 3.0 Cancer Module participant and caregiver reports for young children (5-7 years) include 26 items across 8 domains: pain and hurt, nausea, procedural anxiety, treatment anxiety, worry, cognitive problems, perceived physical appearance, and communication. Items are scored on a 3-point scale: 0 (not at all), 2 (sometimes), and 4 (a lot). For participants and caregivers of children aged 8-12 and teens aged 13-18, the module includes 27 items across the same 8 domains, scored on a 5-point scale ranging from 0 (never) to 4 (almost always). For both versions, items are reverse-scored, linearly transformed to a 0-100 scale, and averaged, with higher scores indicating better quality of life and fewer problems or symptoms. Both the PedsQL 4.0 Generic Core Scale and PedsQL 3.0 Cancer Module have been previously used to evaluate quality of life among pediatric participants with cancer in PA interventions [51,94], and their scores have demonstrated high reliability and validity in this population17.

Symptoms at weeks 0, 12, 24, and 52 are assessed by both participants and caregivers using the Symptom Screening in Pediatrics Tool (SSPedi) and mini-SSPedi, which were developed for children receiving cancer treatment and undergoing hematopoietic stem cell transplant [95]. These tools capture symptoms that are currently bothering the participant, or that bothered them in the past day. The mini-SSPedi is used for participants aged 5-7 years [95], and the SSPedi is used for participants aged 8-18 years. The mini-SSPedi includes 15 items scored on a 3-point scale ranging from 0 (not bothered at all) to 2 (extremely bothered). The SSPedi includes 15 items scored on a 5-point scale ranging from 0 (not bothered at all) to 4 (extremely bothered). For both versions, item scores are summed, yielding a total score ranging from 0 (no symptoms) to 60 (worst possible), with higher scores indicating greater symptom impact. In both versions, participants and caregivers are also asked a final (16th) open-ended question to report any other issues that have recently bothered them (or, in the case of caregivers, their child). Additionally, caregivers of participants aged 5-18 years complete a proxy report SSPedi [95], which includes the same 15 items scored on a 5-point scale from 0 (not bothered at all) to 4 (extremely bothered). Similar to the participant versions, the caregiver proxy report SSPedi sums the 15 items to yield a total score ranging from 0 (no symptoms) to 60 (worst possible), with higher scores indicating greater symptom impact. The SSPedi has demonstrated reliability and validity for assessing symptoms among pediatric participants undergoing cancer treatment or hematopoietic stem cell transplant [95].

Cognitive executive functioning at weeks 0, 12, 24, and 52 is assessed by caregivers using the Behavior Rating Inventory of Executive Function, Second Edition (BRIEF-2) [96]. The parent proxy report form is used for all children and adolescents [97]. The BRIEF-2 includes 9 items covering major areas of executive function—behavior, emotion, and cognitive regulation—scored on a 3-point scale: 1 (never), 2 (sometimes), and 3 (often). Caregivers indicate how often their child has experienced each problem behavior over the past 6 months. Raw scores are calculated and summed to generate a score for each subscale. Additional scoring is applied for the inconsistency, negativity,

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and infrequency scales. The t scores and percentiles are also calculated for each raw scale score, and 90% CIs are computed to estimate the measurement error associated with the clinical scale, index, or t scores. Higher scores indicate greater cognitive impairment. The BRIEF-2 has been used with pediatric participants with cancer [98] and has demonstrated reliability and validity in this population 94.

Resource use at weeks 0, 12, 24, and 52 is assessed by caregivers using a modified version of the Pathways in Autism Spectrum Disorder, Phase III Resource Use Questionnaire for Adolescents (RUQ-A; November 30, 2016) [99]. Items have been adapted to the context of this trial and population. The modified RUQ-A assesses 7 types of resources that participants may use: (1) school; (2) mental health and psychological interventions; (3) rehabilitative services (eg, occupational therapy, physiotherapy); (4) child-focused recreational activities; (5) medications; (6) additional services; and (7) caregiver time associated with treatment and care. Caregivers are asked to indicate the frequency of use and costs associated with each resource their child accessed over the past 3 months. A final open-ended question allows caregivers to report any additional resources and associated costs not captured in the listed categories. The RUQ-A is not scored, and information on validity, interrater and test-retest reliability, and responsiveness is not summarized or statistically reported [99]. The RUQ-A is flexible, allowing questions to be adapted for the population of interest [99]. Although the RUQ-A has previously been used with caregivers of children with autism [99], to our knowledge, this is the first adaptation of the modified RUQ-A for pediatric participants with cancer.

Assessments of Physical Function (Week 0, Week 12, Week 24, and Week 52)

Each physical assessment is conducted by 2 trained exercise professionals via videoconference at the participant's convenience, with a caregiver present. The assessments were selected based on their prior use with pediatric patients with cancer in person and for pragmatic reasons related to the feasibility of videoconference delivery [100].

Aerobic endurance at weeks 0, 12, 24, and 52 is assessed using the 2-minute step test [101]. Participants position themselves perpendicular to the camera, with their right leg facing the camera, and march in place for 2 minutes. They are instructed to lift their knees to hip height, so that their thighs are parallel to the floor. Assessors count the number of steps completed with the right leg (ie, the leg facing the camera). Participants also report their perceived exertion on a scale from 0 (nothing at all) to 10 (very, very hard; maximal; extremely strenuous exercise) [101]. A greater number of steps indicates higher aerobic endurance. Although this test has not previously been used with pediatric participants with cancer, it has been validated in young adults and adults living with and beyond cancer [52,53,83] and was deemed suitable due to the ease of videoconference administration.

Lower body flexibility at weeks 0, 12, 24, and 52 is assessed using the sit-and-reach test [102]. Participants begin by sitting on the edge of their chair and stretching each leg twice for 20 seconds. Next, they position the chair perpendicular to the camera, sit on the edge, and extend 1 leg at a time, keeping the ankle bent at 90°. Participants then hold a measuring device (eg, ruler or measuring tape) with both hands and lean forward as far as possible, reaching toward the toes of the extended leg while keeping the leg straight. Participants hold the maximum flexion position for 3 seconds, then measure the distance from the measuring device to the tip of their toes, recording the measurement to the nearest 0.5 cm. The test is performed twice on each leg, and the best score for each leg is recorded. Higher scores indicate greater lower-body flexibility. The sit-and-reach test has previously been used to assess flexibility among pediatric participants with cancer in person 108,109.

Shoulder flexion range of motion at weeks 0, 12, 24, and 52 is assessed using the shoulder flexion test [103,104]. Participants position their chair perpendicular to the camera, sit upright with feet flat on the floor, and face forward so that the shoulder being assessed is perpendicular to the camera. The camera is adjusted to capture the area from the participant's belly button up to the height their hand would reach when extended overhead. Participants begin with their arms at their sides, palms facing inward (toward the hips), and thumbs pointing upward (toward the ceiling). While keeping the arm straight, participants raise it in forward flexion within the sagittal plane, avoiding compensatory movements (eg, arching the back or moving the arm away from the ear). Once the participant reaches their full range of motion, they hold the position while the assessor takes a screenshot. This procedure is repeated twice for each arm, and the average of both trials is calculated. After the assessment, the assessor measures the range of motion in degrees using a goniometer and anatomical landmarks (head of the humerus, midline of the humerus, and mid-axillary line). Higher scores indicate a greater range of motion. Although this test has not previously been used with pediatric participants with cancer, it has been validated in young adults and adults living with and beyond cancer [52,53,83] and was deemed suitable for videoconference administration.

Balance at weeks 0, 12, 24, and 52 is assessed using the flamingo balance test [105]. Participants stand barefoot with their arms crossed over their chest, placing each hand on the opposite shoulder. When ready, the assessor instructs the participant to stand on a leg of their choice while lifting the opposite leg, bending the knee so that the foot is behind them and not touching the standing leg. Timing begins when the foot is lifted and continues for a maximum of 45 seconds or until the participant loses balance. If balance is lost within the first 3 seconds, a second trial may be completed, with the better time recorded. The test is performed once on each leg unless a second trial is required. Longer times indicate better balance. The flamingo balance test has previously been used to assess balance among pediatric participants with cancer in person [106].

Functional mobility at weeks 0, 12, 24, and 52 is assessed using the 30-second sit-to-stand test [105] and the timed up and go test [107]. For the 30-second sit-to-stand test, participants sit on a chair with their arms crossed over their chest, hands on opposite shoulders. From this position, participants rise to a full standing position (knees straight) and return to a seated position, ensuring full contact with the seat before standing again. When the assessor says "ready-set-go," participants complete as many

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sit-to-stand repetitions as possible within 30 seconds, and the total number is recorded. This test is completed only once. Higher scores indicate greater functional mobility. The 30-second sit-to-stand test has previously been used to assess functional mobility among pediatric participants with cancer in person [69,108-110]. The timed up and go test [107] is also used in this trial to assess functional mobility. Participants, with the help of their caregivers, set up a chair and measure 3 m (10 feet) from the chair, marking the distance with an object or piece of tape. Participants sit with their backs against the chair. On the "ready-set-go" cue, they stand up without assistance, walk as quickly as possible (without running) past the 3-m mark, turn around, and return to the chair. The assessor stops the timer once the participant's back touches the back of the chair. Participants complete 1 practice trial, followed by 2 counted trials, the results of which are averaged. Lower times indicate greater functional mobility. The timed up and go test has previously been used to assess functional mobility among pediatric participants with cancer in person [106,111,112].

Interviews (Week 12)

Participants and their caregivers are invited to complete semistructured interviews. Interviews are conducted either one-on-one or as a dyad, depending on the participant's and caregiver's preference, by trained members of the trial team who are not involved in delivering the intervention. A semistructured interview guide is followed, in which the interviewer asks a series of open-ended questions with follow-up probes to elicit detailed responses. The interviews aim to gain a deeper understanding of participants' and caregivers' experiences with the PA intervention, including what they liked and disliked, its acceptability (satisfaction), feasibility, barriers and facilitators to participation, and plans for continued or future engagement in PA. The Capability, Opportunity, Motivation, and Behavior (COM-B) framework informed selected questions in the interview guide [113]. In addition, questions explore participants' and caregivers' desire for ongoing access to the PA intervention and other PA opportunities—see the "Maintenance (Week 12, Week 24, and Week 52)" section. Multimedia Appendix 3 presents the semistructured interview guide. All interviews are audio-recorded using a Sony ICD-PX240 or Sony ICD-PX470 recorder and transcribed verbatim.

Adoption (Throughout)

Adoption is assessed by tracking referral sources. Differences in referral rates are monitored across channels (eg, referral vs self-referral) and between the 2 sites, Alberta Children's Hospital and Stollery Children's Hospital.

Implementation (Throughout)

Implementation is being evaluated using data on indices of feasibility, including intervention delivery time, trial delivery time, required expertise, cost, fidelity of intervention delivery, and adverse events. Feasibility is defined by participant retention in the trial (ie, completion of assessments), adherence to the PA intervention (ie, percentage of PA sessions attended out of those offered), overall percentage of missing data, and participants' and caregivers' perceptions of feasibility, which are collected via qualitative interviews. For intervention delivery, the time required for delivering the PA intervention, conducting PA assessments (including administrative tasks), health care provider referral time, and the costs associated with implementation (eg, delivery and administrative support costs) are being tracked. Fidelity refers to the extent to which the intervention is delivered as intended and is assessed by randomly selecting 10% of PA sessions for each participant. These sessions are recorded and reviewed by 2 trial team members (AW, CCV, or Julia T Daun) who are not involved in delivering the PA or conducting assessments. Trial team members review the recorded sessions using an established checklist covering various categories, including safety, exercise tailoring and modifications, and adherence to the protocol. This process provides a percentage of sessions delivered as intended—meaning the PA program is followed with appropriate modifications, behavior change components are embedded, and delivery remains autonomy-supportive and tailored to each participant's preferences. Fidelity checks also offer an opportunity to provide feedback to individual instructors if improvements are needed. Adverse events are tracked using a standardized reporting form capturing details such as date, timing, site/location, duration, severity, action taken, and outcome, following the Common Terminology for Adverse Events (CTCAE) version 5.0 [114]. Participants, caregivers, and exercise professionals may report adverse events; however, the responsibility for documenting each adverse event lies with the exercise professional and trial staff.

Maintenance (Week 12, Week 24, and Week 52)

Maintenance is assessed via semistructured interviews—see the "Interviews (Week 12)" section—to explore participants' and caregivers' desire for ongoing access to the PA intervention or plans (or both) for continued engagement in PA. In addition, participant- and caregiver-reported PA levels will be collected at follow-ups through the m-GLTEQ via REDCap, enabling exploration of sustained PA levels.

Quality Improvement Cycles

Quality improvement cycles are one way to explore and refine implementation strategies so that, by the end of the trial, there is an optimized approach (including all required resources; [115]). Within this trial, the Consolidated Framework for Implementation Research has been fully operationalized and is used to categorize the data collected [116]. Quality improvement cycles are conducted every 6 months, during which the trial team reviews participants' and caregivers' personal and medical information, as well as intervention fidelity data, to ascertain the necessity of potential additional recruitment strategies to further diversify the sample. Additionally, a purposefully recruited subset of health care providers and exercise professionals who have been involved with the intervention and trial are selected to participate in 1:1 semistructured interviews, based on their role in referring to or delivering the PA intervention, respectively. These interviews are not conducted during every quality improvement cycle but are scheduled based on conversations among the trial team. Additional individuals are recruited during quality improvement cycles when there have been new health care providers who have referred, and exercise professionals involved in PA session delivery or

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conducting assessments of physical function (or in both scenarios). Interviews are conducted by trained members of the trial team who are not involved in intervention delivery. A semistructured interview guide is followed. The interviewer asks a series of open-ended questions, with follow-up probes, to gain a better understanding of whether additional resources are required to facilitate recruitment or whether further training is needed to support the delivery of the intervention by the exercise professionals. The semistructured interview guide can be found in Multimedia Appendix 3. All interviews are audio-recorded using a Sony ICD-PX240 or Sony ICD-PX470 recorder and transcribed verbatim. Data from quality improvement cycles are analyzed using descriptive statistics, examining recruitment rates and participants' personal and medical information (eg, sex, gender, and other factors), as well as content analysis for interviews. These data are being used to optimize implementation by exploring whether additional resources are required to support recruitment (eg, posters, brochures, emails), to support health care providers to refer, and whether further training is needed to support exercise professionals.

Any modifications identified during quality improvement cycles are carefully considered by the trial team and advisory board (see the "Participant and Caregiver Involvement" section) and are implemented only when deemed necessary to enhance recruitment, increase participant diversity, support health care provider recruitment, or improve training for trial staff and the exercise professionals (or in all of the aforesaid scenarios). No modifications are made to PA session delivery, assessments of physical function, or other aspects of the intervention or trial that could influence effectiveness data.

Participant and Caregiver Involvement

Participants' and caregivers' perspectives are deemed critical within this work. As such, an advisory board was developed 1 year into the trial, in August 2023, after several participants had completed the intervention. Currently, the advisory board comprises 1 participant (of note, initially 2 past participants comprised the board; however, 1 passed away), 2 caregivers, 1 health care provider, 1 community partner, and 4 trial team members (including the 2 coprincipal investigators). The advisory board meets quarterly by videoconference to discuss data collected in the quality improvement cycles (when relevant), provide advice regarding potential challenges, gaps, and opportunities within the PA intervention and trial implementation, advise on current and future dissemination opportunities, and contribute to adaptation and scaling discussions. At trial cessation, advisory board members will have the opportunity to review and comment on all data and will work with the trial team to contextualize the findings. All members have also contributed to, reviewed, and approved this manuscript.

Data Analysis

Data will be analyzed and disseminated through conference presentations and manuscripts at multiple time points, including interim and trial cessation. To date, interim analyses have been conducted covering implementation metrics within the first 30 months, descriptive information, and individual changes in selected secondary outcomes pre- to postintervention [117]. No predetermined stopping rules were set within the context of the interim analyses.

At trial cessation, the full dataset will be analyzed. Single proportion inference tests and CIs will be used to determine the proportion of eligible participants who provided informed consent (or assent where appropriate) and adherence rates to the intervention components. Initial plans to analyze effectiveness data included generalized linear mixed models to examine changes over time in participants' device-measured PA (primary effectiveness outcome) and in secondary effectiveness outcomes, multilevel modeling to examine site differences in relation to the primary and secondary outcomes, and inclusion and stratification of covariates (sex, gender, and other factors) to explore changes between cancer and blood disorder diagnoses and across age ranges (if sufficient power). Given the information presented in the "Sample Size" section, this trial is well below the sample size target. Thus, at trial cessation, alternative data analysis approaches will be considered. It is anticipated that the analysis will emphasize individual (idiographic) patterns and trajectories rather than relying solely on the more aggregated approach described above. Implementation data related to reach (referral rate, participation rate, participant personal and medical information, caregiver personal information, proportion of participants from rural vs urban locations), adoption (sources of referrals, differences in referrals across referring sites), implementation (trial retention, adherence to the PA intervention, percentage of missing data, intervention delivery time, expertise, PA session fidelity, trial delivery time, adverse events), and maintenance (participants' and caregivers' desire for ongoing access to the PA, participant- and caregiver-reported PA levels at follow-up time points) will be assessed using descriptive statistics via SPSS (IBM Corp) or R (R Foundation). The CONSORT diagram ([60]; Figure 1) will be completed to illustrate participant recruitment and retention in the trial.

All interviews will be transcribed verbatim, and transcripts will be managed and analyzed in NVivo (Lumivero) using conventional content analysis [118]. Each transcript will be read several times so the authors conducting the analysis can familiarize themselves with the data. Next, the transcripts will be coded. Labels (ie, codes) will be created to reflect key ideas. Codes will then be organized into groups and higher-order categories [118]. Interviews with participants and caregivers will be analyzed to explore participants' and caregivers' experiences within the intervention; acceptability, barriers, and facilitators to participation; feasibility; and their desire for ongoing access to the PA intervention, plans for continued engagement in PA; or all of these.

With respect to integrating quantitative and qualitative data, the initial plan included an embedded mixed-methods approach. Quantitative data will be reviewed, and qualitative data will be layered over to expand and provide further context to the situation, thereby complementing the findings [119]. This integration is an important component of mixed-methods research and will provide a more comprehensive understanding of the effects of the intervention, enhancing the depth and context of the findings [120]. Should the target sample size not

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be met, as noted above, the embedded mixed-methods approach may shift to feature the qualitative data; this will be determined via consultation with the trial team.

Additional analyses of selected trial data are planned and will cover health care providers' experiences referring and not referring to the IMPACT intervention and trial, as well as exercise professionals' experiences delivering the 1:1 PA sessions, conducting assessments of physical function, or both. These data will be analyzed using the fully operationalized Consolidated Framework for Implementation Research and conventional content analysis. These analyses will be conducted and published separately from the main trial results. Finally, given the amount of data collected within this trial, additional exploratory analyses may be conducted; these analyses will seek to answer additional research questions and will occur only after the interim and main analyses described above, based on discussion and agreement among the trial team.

Results

This trial received funding in April 2022, and funding extensions were sought (due to slower and lower than anticipated recruitment) until March 2026. Participant recruitment commenced in March 2022 and will conclude in December 2025. Interim analyses were conducted in February 2025 and submitted in November 2025 [117]. As of October 2025, 105 patients have been referred (health care provider referral; n=90, 85.7%) or self-referred (n=15, 14.2%). Of the 105 referred participants, 42 (40%) scheduled a phone call with the trial team to receive more information, of which 26 (62%) provided informed consent; 16 enrolled in and completed the intervention, and 1 is currently actively in the intervention.

Discussion

Summary

PA is feasible, safe, beneficial, and recommended for pediatric patients with cancer [28,31]. Indeed, PA can improve physical, psychological, social, and cognitive outcomes, as well as overall quality of life [25-27,91,121-123]. Yet, pediatric patients with cancer face many barriers that make engaging in PA during treatment challenging. As a result, pediatric patients with cancer may not be active enough during treatment to accrue benefits [35,36]. To date, most PA interventions for pediatric patients with cancer have required participants to attend in-person PA sessions [31], which may be challenging due to treatment-related side effects, periods of isolation, variable treatment timelines, lack of PA opportunities, and geographical location [38-42]. PA delivered by videoconference may help overcome common barriers and be one way to offer PA to a small and geographically dispersed population [43]. However, only a few PA interventions have been delivered by videoconference for this population [45,46], and the effectiveness and factors influencing implementation for this population remain relatively unknown.

Strengths

This manuscript details the protocol for our trial evaluating a PA intervention delivered by videoconference to pediatric patients with cancer (and pediatric patients with blood disorders) treated at the children's hospitals in Alberta. Notable strengths of the PA intervention and trial include the following: first, the development process, which utilized an evidence-based [31,33] and patient-oriented approach [72], wherein extant data and resources were integrated with perspectives gathered through semistructured interviews with international experts and local health care providers; and second, the pragmatic nature of the intervention and trial, which could support a more rapid translation of findings to practice. Third, the broad eligibility criteria for participants ensure that all have access to PA, a recommended health behavior [124] and a basic right for all children and adolescents [125], and could help advance the field by including data from the range of cancers diagnosed. Fourth, by including patients with blood disorders, it is possible that evidence will be generated for the effectiveness of PA for pediatric patients with blood disorders, which is limited to date [68]. Relatedly, by offering PA to both pediatric patients with cancer and those with blood disorders—who are often treated on the same ward—this intervention and trial may support a shift toward a culture in which movement is supported and more readily available during treatment. Fifth, recruitment from 2 sites may overcome the often-reported limitation in this field of small sample sizes [50], enhancing the statistical power to further understand the relationship between PA and domains of functioning while exploring covariates (sex, gender, and other factors). Finally, the mixed-methods approach will provide a more comprehensive and nuanced understanding of both effectiveness and implementation by incorporating more than 1 perspective (ie, input from participants and caregivers) [126].

Limitations

Notwithstanding the strengths of this work, there are some anticipated challenges. First, challenges in collecting device-measured PA data from participants during the 7-day Fitbit wear are foreseen (eg, forgetting to wear the Fitbit, forgetting to complete the tracking log). Although steps to minimize this have been taken (ie, additional reminders), it is plausible that the device-measured PA data may have high levels of missing data. Second, the volume of assessments may be burdensome to participants and caregivers. The decision was made to collect data for outcomes at various time points to help generate evidence for PA delivered by videoconference and its potential lasting impacts (ie, maintenance) in a field lacking research to date. Third, recruiting participants from multiple sites is an advantage, but it may increase the amount of time required for coordination and overall trial costs. Strong communication is required to ensure ongoing referral and engagement with health care providers at both children's hospitals in Alberta. Fourth, although the heterogeneous nature of the population is a distinct advantage in terms of representing the breadth of cancer (and blood disorders) diagnoses, the variability could make it challenging to detect changes when analyzing data based on different disease trajectories, treatments, and treatment-related side effects. Relatedly, the single-arm design and varied treatment timelines of participants mean that some may receive the PA intervention during a time when they are on treatment and experiencing high symptom burden, and therefore, results may not be reflective of PA engagement alone.

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Without a control or comparison group, interpretation of findings will be cautious. However, alternative data analysis strategies may be beneficial to truly understand the impact of IMPACT, such as collecting, analyzing, and integrating both the quantitative and qualitative data to provide context for findings. Finally, although individualized and tailored PA sessions are important to ensure safety, support participants' autonomy, and enhance the likelihood of behavior change, challenges in succinctly reporting what was done in each session are anticipated. While exercise professionals are keeping detailed tracking logs for each participant on the components delivered, behavior change techniques used, participants' fatigue and energy before/during/after PA sessions, and other notes (eg, side effects reported and what the participant liked/did not like), it may be difficult to distill and report the details of the PA sessions in a way that ensures they can be replicated by others. The decision to offer a tailored intervention ensures personalized care and the potential to optimize benefits for each participant.

Conclusions

Although PA is feasible, safe, beneficial, and recommended for this cohort, little is known about the effectiveness and implementation of PA via videoconference (see [45,46] for notable exceptions). Results from this trial may provide real-world data and insight into factors influencing the implementation of a PA intervention delivered by videoconference for pediatric patients with cancer and blood disorders. In particular, findings may support the use of videoconferencing to deliver PA to support pediatric patients to move more and experience the benefits of PA during treatment.

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Data Availability

The datasets generated or analyzed from the trial described may be available, upon reasonable request (AW), from the corresponding author at trial cessation.

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Authors' Contributions

Conceptualization: SNCR, AW
Investigation: EM, SNCR, AW
Methodology: EM, SNCR, AW
Resources: SNCR, AW
Supervision: SNCR, AW
Visualization: SNCR, AW
Writing – original draft: EM, SNCR, AW
Writing – review & editing: EM, SNCR, CCV, BW, SF, GMTG, BP, JW, LW, AW

Conflicts of Interest

EM, CCV, BW, SF, GMTG, MP, BP, JW, and LW declare that they have no competing interests. SNCR is a co-founder of Thrive Health Services Inc, which provides preliminary training (Cancer and Exercise) for the qualified exercise specialists and physical assessors involved. AW developed the pediatric cancer and exercise module that is available on Thrive Health.

Multimedia Appendix 1

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Reporting checklists.
[PDF File (Adobe PDF File), 258 KB - resprot_v14i1e59302_app1.pdf]

Multimedia Appendix 2
Physical activity intervention program.
[PDF File (Adobe PDF File), 710 KB - resprot_v14i1e59302_app2.pdf]

Multimedia Appendix 3
Interview guide.
[PDF File (Adobe PDF File), 115 KB - resprot_v14i1e59302_app3.pdf]

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Abbreviations

BRIEF-2: Behavior Rating Inventory of Executive Function, Second Edition
COM-B: Capability, Opportunity, Motivation, and Behavior
CONSORT: Consolidated Standards of Reporting Trials
CTCAE: Common Terminology for Adverse Events
GRAMMS: Good Reporting of a Mixed Methods Study
HREBA: Health Research Ethics Board of Alberta
IMPACT: IMplementation of Physical Activity for Children and adolescents on Treatment
m-GLTEQ: modified version of the Godin-Shephard Leisure-Time Exercise Questionnaire
PA: physical activity
PedsQL: Pediatric Quality of Life Inventory
RE-AIM: reach, effectiveness, adoption, implementation, maintenance
REDCap: Research Electronic Capture
RUQ-A: Resource Use Questionnaire for Adolescents
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SSPedi: Symptom Screening in Pediatrics Tool
StaRI: Standard for Reporting Implementation Studies
TIDieR: Template for Intervention Description and Replication

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Protocol

Developing Guidelines for Conducting Stigma Research With Transgender and Nonbinary Individuals: Protocol for Creation of a Trauma-Informed Approach to Research

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Abstract

Background: Transgender and nonbinary individuals have received increasing attention within HIV research, with studies documenting the pervasive role stigma plays in creating and sustaining health inequities. However, the proliferation of HIV stigma research with this population has also raised concerns about research practices that may unintentionally stigmatize or retraumatize the very communities they are designed to benefit. Conducting stigma research is critical for generating accurate information about HIV epidemiology, risk and protective factors, and intervention strategies for transgender and nonbinary individuals. Yet, little research has directly examined the experiences of transgender and nonbinary individuals when participating in these studies or identified specific research practices (eg, recruitment materials or study framing, choice of specific survey measures, data collection protocols, and researcher behaviors) that may influence study participation, retention, and data quality. Equally important, research has not adequately examined the potential for unintended harm due to emotional distress experienced by participating in such research and what specific strategies might mitigate against potential distressful research experiences.

Objective: This study aimed to develop a set of empirically based trauma-informed guidelines for conducting HIV-related stigma research with transgender and nonbinary individuals to increase researchers' capacity to recruit and retain transgender and nonbinary individuals in HIV-related stigma research, enhance the quality of data collected, and reduce unintentional harm in stigma research methodology.

Methods: The study will engage in primary data collection using both qualitative and quantitative methodology. First, we will use in-depth qualitative interviews with 60 participants representing 3 participant groups: researchers, mental health clinicians, and transgender and nonbinary individuals who have participated in HIV-related and sexual health research. Second, the qualitative findings will be used to develop an initial set of survey items representing a preliminary set of guidelines. Third, we will engage 75 participants in a 3-round modified Delphi method, to refine the guidelines and promote their acceptability among key stakeholders.

Results: The study is funded by the National Institute of Mental Health starting in July 2022 and data collection began January 2023. The study's findings underscore the critical importance of adopting a trauma-informed approach to HIV stigma research with transgender and nonbinary individuals.

Conclusions: To make meaningful strides in stigma research, it is imperative to examine experiences of stigma that may happen within the research context and identify strategies for improving data quality and reducing unintentional harm in study recruitment, methodology, implementation, and dissemination.

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KEYWORDS

transgender; non-binary; HIV prevention and treatment; stigma research; trauma-informed

Introduction

Background

Over the past 2 decades, transgender individuals, particularly Black and Latina transgender women, have received increasing attention within HIV research [1-9]. Such research has consistently documented the pervasive role stigma plays in creating and sustaining health inequities among this population. However, this research proliferation has also raised questions about practices that may unintentionally stigmatize or retraumatize the very communities they are designed to benefit [4,10-15]. One area of particular concern is the measurement of stigma as part of HIV-related research with transgender and nonbinary individuals. First, there is concern that specific items within commonly used measures may unintentionally recreate or activate stigma. For example, many stigma and minority stress scales [16-19] include items that may be experienced as stigmatizing (eg, "Being transgender is disgusting to me") [19] or ask participants to recount and relive traumatic experiences (eg, history of physical and sexual violence, family rejection, and experiences of discrimination and harassment) to document their association with negative affect or health behavior [2]. There has been considerable debate within the larger field of trauma-related research as to whether recalling and answering questions about past trauma has negative or positive consequences for study participants [20-29]. However, there is surprisingly limited research within HIV science on the potential emotional impacts of participating in stigma research. Second, there are no evidence-based guidelines for person-centered, trauma-informed, and actively destigmatizing implementation of HIV stigma research. Conducting stigma research is critical for generating accurate information about HIV epidemiology, risk and protective factors, and intervention strategies for transgender and nonbinary individuals. Yet little research has directly examined the experiences of transgender and nonbinary individuals when participating in these studies, or identified specific research practices (eg, recruitment materials or study framing, choice of specific survey measures, data collection protocols, and researcher behaviors) that may influence study participation, retention, and data quality [30]. Equally important, research has not adequately examined the potential for unintended harm due to emotional distress experienced by participating in such research and what specific strategies might mitigate against potential distressful research experiences.

Impact of Stigma on HIV-Related Outcomes

Research documenting multiple and intersecting structural factors, including racism, sexism, transphobia, homophobia, and other systems of stigmatization, oppression, and traumatic victimization that contribute to the disproportionately high rates of HIV infection and HIV-related morbidity in this population [2-4,6,7,14,31-35]. One of the strengths of HIV research in this area has been its intersectional focus, [36] as well as the acknowledgement that stigma operates at individual, interpersonal, and structural levels. Intersectional approaches demonstrate the ways in which HIV-stigma and other sources of stigma occur simultaneously and interact to impact transgender and nonbinary individual's daily experience, health outcomes, and engagement with care. Research suggests that transgender and nonbinary individuals may experience this impact as traumatic, and support trauma-informed approaches that seek to mitigate retraumatization within the provision of care [37-43]. Transgender and nonbinary individuals health disparities have been directly linked to intersectional and multidimensional stigma processes [37,41,44,45], underscoring the extent to which this approach is essential for advancements in transgender and nonbinary individual–specific stigma frameworks, measurement, and intervention development.

Potential for Unintentional Harm

Within the fields of clinical psychology and neuroscience, there has been intense debate about the impact of research about traumatic experiences on study participants [20-29]. Some evidence suggests that such research might lead to traumatization or cause further harm to those with previous exposure to violence or abuse. One meta-analysis of studies about traumatic events found that approximately 25% (IQR 4.3%-50%) of adult participants reported distressing impacts (ie, unexpected upset, negative emotions, unwanted thoughts, or distress) as a result of research participation. Although, most people find that participating in trauma research is distressing, they also report that they find it worthwhile and meaningful [28]. Neuroscience research on memory reconsolidation suggests that the context and content of memory reactivation may determine its harmful or therapeutic impact. Data indicate that research participants anticipate or attribute negative impacts to study participation; in 1 large-scale study of traumatic experience, 94% of participants rated their participation as more than minimal risk, with participants that had greater previous exposure to trauma reporting higher levels of distress [46]. However, limited research within the field of HIV has directly examined the potential impact of stigma research itself on transgender and nonbinary participants.

Impact on Engagement in HIV Prevention and Care

Growing recognition of the importance of community partnership for HIV research with transgender and nonbinary individuals has led to a rise of studies that rely on community health centers or other service agencies for research recruitment and implementation [47-50]. It is well established that experiences of stigma within these settings may negatively impact transgender and nonbinary individual's willingness to receive needed health care, including HIV testing, treatment, or pre-exposure prophylaxis [37-39,51,52]. If stigmatizing or harmful research is conducted within these settings, there is the potential to reduce transgender and nonbinary individual's trust in the very organizations upon which they depend to access life-saving services. As such, it is essential to understand

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whether and under what conditions HIV stigma research may result in unintentional harm or stigmatization of transgender and nonbinary individuals, and how harmful impacts can be reduced.

Impact on Recruitment, Engagement, and Data Quality

Evidence indicates that mistrust of research projects, study teams, or settings leads to difficulties with recruitment and retention of study participants and may be associated with false or misleading responses to study measures. Studies indicate that research mistrust is particularly strong among transgender and nonbinary participants, who may report feeling used or mistreated within HIV research contexts [53-55]. In 1 study, transgender women reported that research scripts and procedures can be experienced as microaggressions [55]. Critical HIV-related stigma research is likely to underperform and fail to provide much needed data on stigma processes if participants are discouraged from participating or alienated from the research enterprise by perceptions that stigma research is itself stigmatizing [56].

Need for Empirically Grounded Research Guidelines

Many HIV stigma studies report incorporating intentionally affirming components into their research practice, such as measures of self-esteem, community-connectedness, or other resilience factors [57,58]. However, there has been no systematic compilation of these strategies, or analysis of their potential use in reducing stigma experiences. This research gap results in a lack of consensus of what is meant by trauma-informed HIV stigma research, as well as gaps in how to best implement and evaluate stigma-reducing measures in HIV research practice. Outside of HIV research, there are models for patient-centered, trauma-informed health research [59] that could be adapted to better inform implementation strategies, but such adaptation needs to be grounded in empirical data from participants, researchers, and practitioners with direct experience in the field.

Theoretical Frameworks

This study is based on an interdisciplinary integration of minority-stress and trauma-informed theoretical frameworks to explain health inequity. Minority stress theory [60] is a strong epidemiological framework for explaining disparity but is less precise in specifying mechanisms of an individual stigmatized person's behavior, feelings, or experience. To complement this theory, we incorporate a conceptual framework developed specifically to support the mental health of TGNB individuals [61], which combines 2 trauma-informed care models to guide our research questions and analysis. The first, developed by Fallot & Harris [62,63], emphasizes five principles of interaction: safety, trustworthiness, collaboration, choice, and empowerment. The second, guiding principles of trauma-informed care created by the Substance Abuse and Mental Health Services Administration within the US Department of Health and Human Services, focuses on attention to cultural, historical, and gender issues that impact power relationships, privilege, and oppression [64]. This trauma-informed theoretical approach attends to the potential presence of trauma-related symptoms on the thoughts, feelings, needs, and reactions of TGNB research participants, and aims to actively disrupt retraumatization through the creation of interpersonal processes and settings that emphasize safety, trust, collaboration, empowerment, and choice. Rather than focusing on isolating and describing stigmatizing internal and external experiences that happen to a marginalized person, a trauma-informed approach to stigma research centers how those marginalizing experiences thwart a survivor's wellness, healing, and resilience [65]. Trauma-informed approaches are, therefore, inherently person-centered, and strengths-based in that they entail recognition of the signs and symptoms of trauma in an individual's behavior and guide clinical responses to minimize negative impact on the survivor's natural recovery process [64]. These characteristics are likely to support greater engagement, quality, and benefit of HIV research among transgender and nonbinary individuals [55].

Study Aims

The primary aim of this study is to develop empirically informed, trauma-informed guidelines for conducting HIV-related stigma research with transgender and nonbinary individuals. This work seeks to address critical gaps in the field by improving recruitment, retention, and data quality while reducing the potential for harm during research participation. Specifically, the study focuses on the following aims. First, this study aims at understanding participant experiences by conducting in-depth interviews with transgender and nonbinary participants who have engaged in HIV or sexual health-related research to explore their experiences, including factors that contribute to or mitigate distress, stigma, and harm. This aim seeks to uncover the nuanced challenges and opportunities for designing research that supports participant well-being. Second, this study aims to gather stakeholder perspectives by conducting in-depth interviews with researchers and mental health clinicians to identify current practices, challenges, and strategies for implementing trauma-informed and person-centered approaches in HIV stigma research. This aim emphasizes understanding the perspectives of professionals who interact with transgender and nonbinary populations in research and clinical settings. Third, this study aims to develop and refine trauma-informed guidelines by using findings from the first and second aims to create a preliminary set of trauma-informed research guidelines. These guidelines will be refined through a modified Delphi process involving transgender and nonbinary individuals, researchers, and mental health professionals to ensure their relevance, acceptability, and applicability across diverse research contexts.

By integrating qualitative interviews with a structured consensus-building approach, this study aims to establish actionable and evidence-based recommendations. These guidelines will enhance the ethical rigor and methodological quality of HIV stigma research, contributing to improved health equity and reducing unintentional harm in research practices.

Methods

Study Objectives

Our study is designed to address a critical gap in existing HIV stigma research with transgender and nonbinary individuals by examining experiences of stigma within the research context

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and identifying strategies for improving data quality and reducing unintentional harm in study recruitment, methodology, implementation, and dissemination. This study will engage in primary data collection using both qualitative and quantitative data collection methodology. To accomplish the study aims we will first, conduct in-depth interviews with transgender and nonbinary individuals (n=30) to better understand how they understand and experience participation in HIV-related stigma research, including willingness to respond to questions about stigma and factors that may contribute to or mitigate potential distressing or stigmatizing experiences within the research context. Second we will conduct in-depth interviews with 2 groups: investigators who conduct HIV-related stigma research with transgender and nonbinary individuals, to better understand perceptions of and experiences with conducting stigma research with transgender and nonbinary individuals and compile existing strategies for mitigating harm (n=15) and mental health professionals (n=15) who provide care to transgender and nonbinary individuals to better understand ways in which experiences of stigma can be measured and studies can be conducted in a manner that is person-centered, trauma-informed, and actively destigmatizing. Third, we will develop a set of empirically informed guidelines for conducting HIV stigma research with transgender and nonbinary individuals. We will use a modified Delphi technique to engage a panel of transgender and nonbinary individuals, mental health providers, and researchers in a consensus building process to identify practical recommendations for person-centered, trauma-informed recruitment, measurement, and conduct of HIV-related stigma research with transgender and nonbinary individuals.

The sample sizes for this study were designed to ensure robust data collection and meaningful analysis across all phases. For aims 1 and 2, the sample size was chosen based on recommendations for similar qualitative inquires to ensure thematic saturation and demographic diversity [66-69]. In aim 3 the Delphi panel will consist of 75 participants (25 transgender and nonbinary individuals, 25 researchers, and 25 clinicians), aligning with best practices for achieving reliable consensus and providing robustness against attrition [68,70,71]. These sample sizes ensured methodological rigor, demographic representativeness, and the capacity to develop empirically informed, trauma-informed research guidelines.

Qualitative Interviews

Aim 1: Semistructured Qualitative Interviews With Transgender and Nonbinary Individuals

Overview

In aim 1, we will conduct a series of in-depth semistructured qualitative interviews with 30 transgender and nonbinary individuals.

Participants

Our sample will be stratified by gender identity and HIV status. We will ensure that >40% of participants will be aged 18-29 years and at least 70% people of color, due to the disproportionately high HIV infection rates among these populations and lack of access to HIV prevention and treatment services. Eligible participants will be aged >18 years; identify as transgender, nonbinary, or gender diverse; and have participated in an HIV prevention or treatment related research study.

Recruitment

Participants will be recruited through existing research panels, transgender health-related social media and listservs, and word of mouth. Interested participants will fill out an eligibility screener survey. For those who are deemed eligible, they will be provided a link to the study website [72] to schedule their interview at a day and time of their choice, with the study team member of their choice. Participants will be provided with a link to an electronic consent form on the study website, as well as the interview guide before the interview. The interviewer will review the consent form with the participant and obtain verbal consent before conducting the interview.

Interview Procedures

Interviews will be designed to last no longer than an hour and a half, and participants will be compensated US $80 for their time. All interviews will contain a core set of questions to assess how transgender and nonbinary individuals understand and experience participation in HIV-related stigma research, including decision-making processes around participation, perceptions of study purpose, risks and benefits, participants' willingness to respond to questions on stigma, factors that may contribute to or mitigate potential distressful or stigmatizing experiences within the research context, and opinions of the research after participation. Participants will also be asked to identify specific strategies to enhance researcher's capacity to design and implement stigma research that is person-centered, trauma-informed, and actively destigmatizing.

Aim 2: Semistructured Qualitative Interviews With Researchers and Mental Health Professionals

Overview

In aim 2, we will conduct a series of in-depth semistructured qualitative interviews with 2 groups, investigators who conduct HIV-related stigma research with transgender and nonbinary individuals (n=15) and mental health providers who provide care to transgender and nonbinary adults (n=15).

Participants

Investigators (n=15) will be stratified by career stage: early (n=5), middle (n=5), or late (n=5) stage investigators to represent a range of perspectives and experiences with conducting stigma research with transgender and nonbinary individuals. Our sample of mental health professionals (n=15) will include mental health clinicians with a master's degree in either social work, marriage and family therapy, or mental health counseling or a doctoral degree in clinical psychology (PhD or PsyD) who provide individual or group therapy to transgender and nonbinary adults (aged 18 years or older) and have training in providing trauma-specific or trauma-informed clinical practice.

Recruitment

Early, middle, or late-stage investigators with existing HIV-related transgender health research will be identified by Google Scholar and the National Institutes of Health (NIH) RePORTER. Investigators will be contacted by a study team

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member by email and invited to participate in our study. Mental health professionals will be recruited through professional networks and word of mouth. Interested participants will fill out an eligibility screener survey. For those who are deemed eligible, they will be contacted by a study team member to schedule their interview. Participants will be provided with a copy of the study consent form. The interviewer will review the consent form with the participant and obtain verbal consent before conducting the interview.

Interview Procedures

Aim 2 will consist of 30 semistructured interviews with 2 groups, investigators who conduct HIV-related stigma research with transgender and nonbinary and mental health clinicians who provide counseling to transgender and nonbinary adults (aged 18 years or older). Interviews are designed to last no more than an hour and a half, and participants will be compensated US $50 for their time. *Interviews with investigators* will assess understanding experiences of conducting HIV-related stigma research with transgender and nonbinary individuals, including perceptions of study purpose, risks and benefits, question and measurement selection and creation, and factors that may have contributed to or mitigated against distressful or stigmatizing experiences within the research context. *Interviews with mental health professionals* will focus on identifying ways in which experiences of stigma can be measured in a manner that is person-centered, trauma-informed, and actively destigmatizing, including suggestions for using person-centered, trauma-informed language when developing questions or measures, and strategies to assist researchers around developing protocols and procedures to assess for and address potential distressful situations within the research context.

Development of Interview Guide (Aims 1 and 2)

The interview guide was developed through a collaborative, trauma-informed approach to ensure that all protocols and procedures reflected the study's goals and minimized potential harm to participants. This process involved a 3-step methodology with the transgender-identified research team. First, the team conducted an in-depth review of existing trauma-informed care models and adopted the framework developed by The Institute on Trauma and Trauma-Informed Care (ITTC) at the University of Buffalo, which emphasizes the principles of safety, choice, empowerment, collaboration, and trustworthiness. Second, components from ITTC's Trauma-Informed Organizational Change Manual [73] were adapted and integrated into the research procedures, including participant recruitment, consent, interview data collection, and analysis, to align all research activities with a trauma-informed approach. Third, the interview questions, prompts, and scripts were mapped to the ITTC framework to minimize risks of retraumatization and ensure a supportive environment for participants. Interview questions were refined to align with the study's 4 overarching research questions and tailored to the perspectives of the 3 participant groups, researchers, community stakeholders, and mental health clinicians, ensuring comparability and analytic integrity across the study phases (Multimedia Appendix 1).

Qualitative Analysis Plan (Aims 1 and 2)

Data collected in aims 1 and 2 will be analyzed using rapid qualitative analytic methods, [74-77] to identify key themes that best reflect the research decision-making process, perceptions and experiences of transgender and nonbinary individuals. We will assign four trained team members to summarize a subset of the interview transcripts independently, extracting key data into a summary template based on our framework and interview guide; triangulate key themes in the transcript through documenting observations, quotations, and reflections into the summary template; meet to compare and combine templates for each interview; and create a comprehensive matrix identifying common themes and contrasts across and within stakeholder groups.

Application of Knowledge Gained in Aims 1 and 2 to Aim 3

In preparation for aim 3, we will use the themes that were identified in the qualitative interviews to develop a preliminary list of survey items for use in the first stage of the modified Delphi process (aim 3) [78]. The use of qualitative interviews in a pre-Delphi phase [78-80] allows for all relevant stakeholder groups to guide the Delphi process by contributing to the development of the first round Delphi survey. To ensure that the Delphi survey items describe and capture the perceptions and experiences of all the stakeholder groups participating in aim 3, we will develop items using the language and narratives participants use during their interviews [78,80,81]. For example, the language used to describe and the meaning behind core concepts within stigma research may differ distinctly between stakeholder groups and could contribute to inaccurate measurement and interpretation of research findings. By integrating language from each stakeholder group into the Delphi survey we hope to better reflect the experiences of all relevant stakeholders involved in this process [79,82,83]. We will then compare the themes and associations derived from Aims 1 and 2 to better understand areas of concordance and discordance between stakeholder groups [78-81,84]. For example, it is possible that interview findings highlight similar domains across participant groups that are key to understanding and improving stigma research procedures, yet what is important to address within these domains may differ by stakeholder group. The use of qualitative interview findings will help further parse out and include survey items that address this complexity.

Aim 3: Development of Empirically Informed Guidelines for Conducting Stigma Research With Transgender and Nonbinary Individuals

Overview

To accomplish aim 3 we will use a 3-round modified Delphi method [85] to develop a set of empirically informed guidelines for conducting HIV-related stigma research with transgender and nonbinary individuals. The modified Delphi method will include 4 structured steps: panel formation, quantitative survey development, data collection and analysis, and guideline development [68,69,85,86].

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Panel Formation

We will recruit 75 participants from the following 3 stakeholder groups, transgender and nonbinary individuals (n=25), researchers (n=25), and mental health professionals (n=25). Our sample size is based on previous studies which demonstrate that this sample size provides stable results robust to participant attrition or inconsistent responding [68,70,71]. Individuals who participated in aims 1 and 2 will be recruited to participate in aim 3.

Survey Development

Survey development will occur in 3 steps. First, the transcripts and codes from aims 1 and 2 will be reviewed to draft the initial survey items based on the most salient themes and domains pertinent to all aspects of the research process, including recruitment, measurement, retention, and dissemination. Each survey item will be designed to capture a single idea and be easily understood by participants. Second, we will develop a rating scale for the Delphi survey items that best capture the original content from aims 1 and 2. Third, we will finalize the items and organize the survey into the following 3 sections, Trauma-Informed Principles for Research Practice, Trauma-Informed Research Standards, and Trauma-Informed Research Competencies.

Quantitative Data Collection and Analysis

A survey will be administered online by REDCap (Research Electronic Data Capture) [87,88] at 3 time points (rounds 1-3). Participants will be compensated US $40 for their time after the completion of each survey. In each round, participants will be asked to rate each item on a 5-point scale indicating whether the item should be included in the research guidelines. Survey items will be categorized according to the decision matrix in Textbox 1, which has been widely used in previous studies [85,86]. In round 1, all items created by our study team will be included in the survey. At the end of each survey section in round 1, participants will be encouraged to provide feedback on items (ie, how to improve wording or messaging) and suggest novel items to include [68,85,86]. After round 1, we will analyze survey responses, including participant comments, and edit existing or draft new items to be included in the round 2 survey based on participant suggestions. In the second-round survey, participants will rerate items that receive a near miss in the first round and rate new items the research team crafted based on suggestions from participants in round 1. At the end of rounds 1 and 2, participants will be sent a report outlining survey results. Statements to be rerated will be displayed with the overall percentages for each rating and then by stakeholder group so participants can compare their response with others' responses. The report will allow participants to consider whether to retain or change their ratings in the next round. Finally, in round 3, only items rated for the first time in round 2 or received a near miss rating will be included in the final survey (Textbox 1).

Textbox 1. Decision matrix for developing expert consensus.

Endorsed

- If between 80%-100% of participants of each group rate a statement as either essential or important, it will be endorsed as a guideline.

Re-rated (near miss)

- If between 80%-100% of participants of each group rate a statement as either essential or important, it will be endorsed as a guideline.

Rejected

- If none of the above conditions are met, a statement will be rejected for inclusion as a guideline.

Guideline Development

At the end of round 3, the research team will create a document comprised of the endorsed items to be widely disseminated. Once the document is completed, participants will be invited to attend a 1-day virtual convening where we will present and discuss the final guidelines document as well as the goals and next steps for dissemination and implementation.

Ethical Considerations

Ethics Approval

The study received expedited approval from the City University of New York Human Research Protection Program (#2022-0280-Hunter).

Informed Consent

Participants were electronically sent a consent form and interview guide in advance to review at their own pace once their interview was scheduled. Before the start of each interview a trained study team member reviewed the consent form with participants and obtained verbal consent to participate. Before completing the Delphi survey participants affirmed that the agreed to participate.

Privacy and Confidentiality

All data were anonymized to protect participant identities.

Compensation

Participants were compensated US $40- US $80, depending on the study phase, to ensure fairness.

Results

The study was funded by the National Institute of Mental Health from July 1, 2022, to June 30, 2024. The study successfully achieved its specific aims. We successfully completed data collection and analysis for aims 1 and 2 recruiting 30

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transgender and nonbinary participants (aim 1) and a total of 34 participants in aim 2 (17 researchers and 17 clinicians). As outlined above, we directly applied the knowledge gained to the development of the preliminary set of guidelines voted on in aim 3. The Delphi process for aim 3 is entering its final survey round, and we are actively preparing the finalized guidelines for dissemination (Table 1).

Table 1. Study timeline and progress by aims.

Phase	Planned timeline	Current progress
Aim 1: interviews	January 2023-June 2023	Completed (30 participants)
Aim 2: interviews	July 2023-December 2023	Completed (34 participants)
Application of knowledge gained from aims 1 and 2	January 2024-March 2024	Completed
Aim 3: Delphi survey	March 2024-June 2024	Ongoing (final survey round)

Discussion

Principal Findings

This study addresses a critical gap in HIV-related stigma research by developing trauma-informed guidelines to improve the quality of research involving transgender and nonbinary individuals. HIV stigma research has historically documented the pervasive role of stigma in shaping health inequities but has largely overlooked the unintended harms participants may experience within the research process itself. By using an interdisciplinary, trauma-informed approach grounded in qualitative data collection and a modified Delphi method, this study emphasizes principles of safety, trustworthiness, collaboration, empowerment, and cultural sensitivity. The findings aim to enhance participant engagement, reduce emotional distress, and improve data quality, thereby advancing ethical and effective research practices. Through active collaboration with community members, researchers, and clinicians, this project provides a model for addressing stigma while centering participant well-being and resilience.

The study's findings underscore the critical importance of adopting a trauma-informed approach to HIV stigma research with transgender and nonbinary individuals. Interviews with community members, researchers, and clinicians revealed the significant benefits of trauma-informed principles for enhancing participant trust, retention, and engagement while also improving the quality of collected data. Key findings include the following.

Higher Data Quality and Participant Engagement

Stakeholders across all groups emphasized that trauma-informed practices create safer and more supportive environments for participants, leading to more honest and comprehensive data. For instance, researchers noted that flexible interview formats and clear communication protocols increased participant willingness to share sensitive information.

Improved Team Dynamics and Research Outcomes

Researchers and clinicians reported that adopting trauma-informed principles, such as trustworthiness and collaboration, not only benefits participants but also enhances team cohesion and efficiency in implementing study protocols.

Ethical and Methodological Standards

The findings contributed to the development of trauma-informed research standards, including guidelines for ethical recruitment, harm minimization, and culturally sensitive data collection protocols. These standards prioritize participant autonomy and recognize the compounded effects of intersecting identities, such as race, gender, and sexual orientation.

Institutional Support Needs

Participants consistently highlighted the necessity of institutional support for implementing trauma-informed practices. Recommendations include increased funding, researcher training, and revisions to institutional review board protocols to ensure systemic integration of these practices into research frameworks.

Guidelines for Trauma-Informed Research

Preliminary guidelines developed through this study emphasize the integration of trauma-informed principles into every aspect of the research process. These include ensuring safety and dignity, using affirming language, and providing participants with opportunities for feedback and choice throughout their involvement in studies.

The findings collectively highlight the transformative potential of trauma-informed approaches for improving HIV stigma research practices. By addressing participant needs and mitigating harm, these practices ensure ethical rigor and enhance the impact of research on health equity for transgender and nonbinary populations.

Comparison to Previous Work

Previous research on HIV stigma has predominantly focused on documenting stigma and its health impacts without critically examining research practices themselves. Our study extends the NIH's Stigma and Discrimination Toolkit [89] by addressing the need for guidelines to reduce stigma within the research context. This complements existing frameworks and fills a critical gap. By focusing on the process rather than outcomes alone, this research provides a novel contribution to the field.

Strengths and Limitations

The study's strengths include a diverse, multidisciplinary research team with significant community representation, innovative use of the Delphi method, and the integration of trauma-informed principles. Limitations include the absence of a bioethicist on the team and potential challenges in generalizing findings to other populations beyond transgender and nonbinary individuals. Future research could explore the applicability of these guidelines in other contexts and populations.

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Future Directions

Key next steps include developing researcher training modules and advocating for institutional review board and institutional policies that mandate trauma-informed practices. These guidelines could extend to other areas of health inequities research.

Dissemination Plan

This study prioritizes transparency and community engagement in disseminating findings. The dissemination plan aligns with trauma-informed principles by emphasizing accessibility, mutuality, and collaboration with the community and stakeholders.

Community-Focused Dissemination

A dedicated study website was created to provide participants and stakeholders with clear and accessible information about the study aims, process, and team. This platform has been instrumental in sharing updates, progress, and findings during the study period.

Two newsletters were distributed to participants and posted on the website to update stakeholders about study progress and preliminary findings. These newsletters ensured continuous engagement with the community and maintained trust.

Final study findings will be summarized in community-friendly formats, such as infographics and plain-language reports, and shared through newsletters and the website. This ensures that findings are accessible to diverse audiences, including those with varying levels of education and technical expertise.

Academic and Professional Dissemination

Findings have been shared at national and international conferences, ensuring visibility within academic and professional circles. Future presentations will focus on engaging institutional review boards, research institutions, and policy makers.

The trauma-informed research guidelines will be published in academic journals and policy briefs, targeting audiences involved in HIV research, social work, and public health.

Workshops and webinars will be conducted for researchers and community health organizations to facilitate the implementation of the guidelines. These sessions will provide practical strategies for adopting trauma-informed practices.

Collaborative Dissemination

The final guidelines will be shared during virtual or in-person gatherings with study participants and community members. These sessions will include opportunities for participants to provide feedback and discuss the next steps for implementation.

Findings will be disseminated through partnerships with community-based organizations and health centers. This approach ensures that the guidelines reach the people and institutions directly involved in HIV stigma research and care.

Sustainability and Long-Term Impact

Recommendations for integrating trauma-informed practices into institutional review board review processes, funding applications, and researcher training will be disseminated to key institutions. This will include targeted briefings and resource-sharing with institutional review boards and funders to encourage systemic change.

Training materials, including video tutorials and toolkits, will be developed to help researchers and institutions adopt the guidelines. These materials will be shared through academic and community networks. By using these dissemination strategies, this study aims to ensure that its findings are accessible, actionable, and impactful across diverse audiences, including researchers, policy makers, and the communities at the center of the research.

Conclusion

To make meaningful strides in stigma research, it is imperative to examine experiences of stigma within the research context and identify strategies to improve data quality while reducing unintentional harm in study recruitment, methodology, implementation, and dissemination. This study addresses these critical needs by developing empirically informed trauma-informed guidelines for conducting HIV-related stigma research with transgender and nonbinary individuals.

Grounded in interdisciplinary theoretical frameworks and extensive collaboration with transgender and nonbinary participants, researchers, and clinicians, this study highlights the transformative potential of trauma-informed approaches. These guidelines emphasize the principles of safety, trustworthiness, collaboration, empowerment, and cultural sensitivity, demonstrating their capacity to enhance participant engagement, foster trust, and mitigate risks of retraumatization. Findings further underscore the importance of systemic institutional support, including training programs, funding mechanisms, and policy revisions at the institutional level, to ensure the widespread adoption of these practices.

The study achieved its goals by developing and refining these guidelines through rigorous qualitative analyses and a modified Delphi process. By embedding trauma-informed principles into research methodologies, this work sets a new standard for ethical and effective research practices. These guidelines have the potential to increase researchers' capacity to recruit and retain transgender and nonbinary participants in stigma research, improve the quality of collected data, and reduce the unintended harms of research participation.

Next steps include broad dissemination of the guidelines through community-friendly formats, workshops, and academic publications. These efforts will ensure that the findings are accessible to a diverse range of stakeholders, including researchers, clinicians, policy makers, and community organizations. By reshaping HIV stigma research methodologies, this work contributes to advancing health equity and ethical research practices, with implications for other high-priority populations and fields of health disparity research.

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Data Availability

The datasets generated during and analyzed during this study are not publicly available to protect the identity of the participants, as some of the details mentioned in the qualitative interviews include information that could help identify the individual. Data are available from the corresponding author on reasonable request.

Authors' Contributions

AK contributed to conceptualization, methodology, writing original draft, writing review and editing, supervision, and funding acquisition. SAG managed methodology, writing review and editing, supervision, and funding acquisition. DB handled methodology and writing review and editing. ERC contributed to writing review and editing, project administration.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guide for Aims 1 and 2 by participant group.
[DOCX File , 480 KB - resprot_v14i1e66800_app1.docx]

Multimedia Appendix 2
Peer-reviewer report from HIV/AIDS Intra- and Inter-personal Determinants and Behavioral Interventions Study Section, Risk, Prevention and Health Behavior Integrated Review Group (HIBI) (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 143 KB - resprot_v14i1e66800_app2.pdf]

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Abbreviations

ITTC: Institute on Trauma and Trauma-Informed Care
NIH: National Institutes of Health
REDCap: Research Electronic Data Capture

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Protocol

Cardiometabolic Health Intervention Using Music and Exercise (CHIME) Delivered via Telehealth to Wheelchair Users: Protocol for a Randomized Controlled Trial

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Abstract

Background: Wheelchair users live predominantly sedentary lifestyles and have a substantially higher risk for cardiometabolic disease and mortality compared to people without disabilities. Exercise training has been found to be effective in improving cardiometabolic health (CMH) outcomes among people without disabilities, but research on wheelchair users is limited and of poor quality.

Objective: The primary aim of this study is to examine the immediate and sustained effects of a 24-week, telehealth, movement-to-music cardiovascular (M2M-C) exercise program on core indicators of CMH among adult wheelchair users compared to an active control group. The secondary aim is to explore the beneficial effects of M2M-C exercises on cardiovascular capacity, physical activity, and quality of life. Intervention components include tailored exercises and remote performance monitoring, delivered via live videoconference training by a telecoach and asynchronous videos.

Methods: This study's design is a parallel-arm randomized controlled trial enrolling 132 physically inactive adult wheelchair users with poor cardiometabolic profiles. The M2M-C intervention group involves 24 weeks of virtual live and monitored home exercise training (3×/wk, 15-40 min/session), followed by a 12-week maintenance period where participants have access to an online media library of exercise videos. The control group involves 36 weeks of self-guided exercise through access to a media library of exercise videos, including videos for range of motion, muscle strength, and balance. The primary outcomes are cardiometabolic indicators of health, and assessors are blinded.

Results: Recruitment procedures started in January 2024 with the first participant enrolled on March 18, 2024. All data are anticipated to be collected by November 2027, and the main results of the trial are anticipated to be published by February 2028. Secondary analyses of data will be subsequently published. A total of 16 participants have been recruited as of paper submission.

Conclusions: The knowledge obtained from this trial will provide evidence to inform exercise prescriptions aimed at improving CMH among adult wheelchair users.

Trial Registration: ClinicalTrials.gov NCT05606432; https://clinicaltrials.gov/study/NCT05606432

International Registered Report Identifier (IRRID): DERR1-10.2196/57423

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KEYWORDS

exercise; physical activity; wheelchair user; telehealth; disability

Introduction

Background

People with physical disabilities have higher risks of cardiometabolic disease than the general population. For example, studies have reported that as many as one-third of people with spinal cord injury (SCI) may be diagnosed with cardiometabolic disease (ranging from n=41, 29% to n=222, 34.1%), which is nearly twice as prevalent as reported in people without SCI [1-3]. Another study found that adults living with cerebral palsy or spina bifida are 52% more likely to experience any type of cardiometabolic morbidity than adults without cerebral palsy or spina bifida (n=15,302) [4]. Meta-analyses have demonstrated that conventional aerobic exercise, such as running, walking, and cycling at a moderate-to-vigorous intensity, are effective in managing indicators of cardiometabolic health (CMH) in the general population [5-9]. However, people with physical disabilities, particularly wheelchair users, are typically unable to engage in conventional modalities of exercise long enough to obtain CMH benefits. Wheelchair users include users of any wheeled devices for their primary means of mobility, such as manual and powered wheelchairs or motorized scooters, and may include individuals in a variety of disability groups, including those with SCI, cerebral palsy, spina bifida, multiple sclerosis, or limb loss. A total of roughly 5.5 million wheelchair users in the United States would benefit from an accessible aerobic exercise program to reduce their cardiometabolic disease risk [10].

However, there is limited evidence that aerobic exercise improves CMH among wheelchair users. Most evidence is observational and nearly all randomized controlled trials (RCTs) have small sample sizes limited to a single population (eg, those with SCI). There are no large confirmatory RCTs that demonstrate that aerobic exercise improves CMH in adult wheelchair users. A recent meta-analysis of 3 RCTs, with samples of 15-21 adults with SCI, determined that 6-weeks of aerobic exercise improved CMH among adults with SCI (ie, decreased fasting glucose and insulin and increased fasting high-density lipoprotein cholesterol fraction) [11]. Another meta-analysis of 16 pre-post and controlled trials with sample sizes of 5-20 adults with SCI determined that vigorous exercise training improved cardiorespiratory fitness in adults with SCI [12] (ie, increased peak power output, muscular strength, and time to fatigue) but did not improve CMH risk factors, such as blood pressure (BP), cholesterol, and insulin sensitivity. Noted limitations of these studies included small sample sizes, inclusion of participants already within healthy ranges for CMH at baseline, lack of a control group, use of laboratory-based training, and inclusion of a single population (those with SCI). Therefore, the finding that CMH measures did not improve must be interpreted with caution.

Interventions that have sought to improve physical activity levels have also failed to improve CMH among wheelchair users. The largest physical activity trial among wheelchair users (n=128), Workout on Wheels, increased self-reported physical activity by 17 min/wk, with no significant between-group differences in cardiorespiratory fitness or CMH measures [13]. Other recent lifestyle interventions (eg, behavioral coaching) have similarly failed to elicit significant CMH benefits among people with disabilities, even while achieving large sample sizes [14]. Thus, the exercise doses or intensity studied may be suboptimal for improving CMH among people with physical disabilities. Despite failures to improve CMH, many of these physical activity trials have informed the creation of the most recent guideline related to CMH for people with SCI [15,16]. Collectively, there is an urgent need for well-designed interventions that can provide an effective exercise dose for people with disabilities, including wheelchair users, while obtaining evidence for improving CMH through physical activity.

Rationale for Telehealth Exercise Program

A telehealth exercise program was developed to overcome the barriers of participation in exercise requiring individuals to leave their homes and use expensive equipment. This study uses an exercise program that includes various movement patterns that are coupled with elements of music and imagery, referred to as movement to music (M2M) [17]. The M2M program uses a range of different muscle groups allowing for a safer form of exercise than arm ergometry. Moreover, M2M incorporates a theory-driven telehealth delivery protocol that removes the most common barriers to participation in community and clinical exercise training studies (ie, cost, transportation, and time) [18,19]. The design of the movement-to-music cardiovascular (M2M-C) intervention is based on four key elements of social cognitive theory: self-efficacy, self-regulation, outcome expectations, and social support. These components are essential for promoting positive health behavior change. To effectively integrate these principles, the M2M-C program provides a structured, individualized, and progressively challenging exercise routine. Participants receive regular feedback and personalized guidance from M2M-C instructors and telecoaches, which helps build confidence and maintain motivation. In addition, the incorporation of music enhances movement quality and motor coordination [20] while serving as a powerful motivational tool [21]. By increasing enjoyment and improving mood, music makes exercise more appealing and engaging. This approach is consistent with the broader goal of promoting sustained physical activity among wheelchair users by addressing both psychological and physical barriers to exercise adherence.

To test whether the M2M program can improve CMH outcomes among wheelchair users, this study uses a parallel-group RCT with blinded assessors. The intervention group will use the M2M program, composed primarily of cardiovascular exercises (M2M-C), which will be compared to an active control condition using prerecorded non-M2M exercise videos. The M2M-C exercises were informed by disability exercise guidelines and reviews of relevant studies [22]. This study is referred to as the Cardiometabolic Health Intervention Using Music and Exercise

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(CHIME) study. The primary aim is to examine the effects of a 24-week, synchronous M2M-C program on core indicators of CMH in adult wheelchair users with ≥2 cardiometabolic risk factors. The secondary aim will explore the beneficial effects of M2M-C exercises on cardiovascular capacity, physical activity, and quality of life. We hypothesize the M2M-C intervention will yield both immediate and sustained CMH outcomes among adult wheelchair users with poor cardiometabolic profiles.

Methods

Study Design

This study's protocol follows the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines [23,24].

Aims and Design of this Study

This study's design includes three aims. The primary aim examines the immediate effect of a 24-week, synchronous M2M-C training protocol compared to a 24-week, asynchronous activity control on core indicators of CMH among 132 adult wheelchair users with ≥2 cardiometabolic risk factors. The secondary aim examines the immediate effect of M2M-C training compared to the active control condition on cardiovascular capacity, physical activity, and quality of life. The first tertiary aim evaluates the sustained effects of M2M-C training (24 to 36 wk) on physical activity participation. A second tertiary aim evaluates the potential response heterogeneity in CMH, cardiovascular capacity, and physical activity outcomes using prespecified moderator variables (eg, age, sex, body composition, diet, or ethnicity) to understand for whom the intervention is most effective.

This study's aims will be tested using a parallel-group, assessor-blinded RCT design. For primary and secondary aims, we hypothesize that a telehealth M2M-C program will lead to significantly greater improvements in CMH outcomes, peak oxygen consumption (VO_{2peak}), physical activity level, and quality of life from baseline to 24 weeks compared to controls. For the tertiary aim 1, we hypothesize that M2M-C participants will maintain physical activity levels from week 24 to week 36.

Participants

Recruitment

We are recruiting participants who receive health care from a large medical center residing in the southern United States through direct referrals from health care professionals (eg, physicians or therapists) and distribution of study materials (eg, flyers, newsletters, or advertisements) to various clinics, hospitals, and medical rehabilitation service providers.

Eligibility Criteria

Adult wheelchair users who do not participate in health-enhancing volumes of exercise [16] and have ≥2 cardiometabolic risk factors are recruited for this study. Potential participants are prescreened for the eligibility criteria via telephone screening, medication list review, and physical screening. The onsite, physical screening to confirm eligibility occurs in the baseline visit.

Textbox 1 lists the specific participant eligibility criteria. Participants undergo a 2-stage screening process. The first stage, eligibility screening, is undertaken during a scripted phone screening by the project coordinator. The presence of CMH risk factors [25] is initially screened based on the self-reported height and weight to estimate the BMI and waist circumference, as well as the physician-prescribed medications that are relevant to CMH risk factors (eg, are you taking any medications related to increased BP? Has your doctor ever expressed concerns about your cholesterol level?).

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Full-time or part-time use of a wheelchair device (manual wheelchair, power wheelchair, or electric scooter) self-reported as the primary means of mobility
- Aged ≥18 years
- Able to use arms to exercise
- Obtaining <90 minutes of moderate-to-vigorous intensity exercise per week in the last month
- ≥2 cardiometabolic risk factors:
  - Elevated waist circumference: ≥102 cm in men and ≥88 cm in women
  - Elevated triglycerides: ≥150 mg/dL
  - Reduced high-density lipoprotein cholesterol fraction: <40 mg/dL in men, <50 mg/dL in women
  - Elevated blood pressure (BP): ≥130 mm Hg systolic BP or ≥85 mm Hg diastolic BP
  - Elevated fasting glucose: ≥100 mg/dL
- No contraindication to participate in moderate-to-vigorous intensity exercise as informed by physician's medical clearance for exercise
- Not currently participating in a structured exercise program
- Able to converse and read in English

Exclusion criteria

- Medically unstable to perform the prescribed home exercise as determined by their physician
- High-level tetraplegia and unable to use arms to exercise
- No internet access was determined via self-report and internet speed test
- Positive pregnancy test
- Other physical conditions that can potentially prevent them from participating in an exercise routine (eg, pressure sore and open wound)

Justification for exclusion criteria

- Exclusion of pregnant individuals: The use of dual-energy x-ray absorptiometry for body composition analysis involves minimal radiation exposure. However, to eliminate any potential risk to the fetus, pregnant individuals will be excluded.
- Exclusion of individuals with medical instability: To minimize the risk of adverse events during the intervention, participants must be medically stable and have clearance from a health care provider to engage in moderate-to-vigorous intensity exercise.
- Internet access requirement: As the intervention is delivered via a tele-exercise platform, participants must have reliable internet access to ensure they can fully engage in the program, participate in live sessions, and receive remote monitoring and feedback.

The second screening stage involves a review of participation medications (self-reported) and a physical examination by laboratory staff. The medication list is obtained before the baseline visit using a secure electronic survey, and this study's staff reviews and verbally confirms them during the baseline visit. If the potential participants currently take ≥2 medications related to CMH risk factors, then they can proceed to the baseline physical examinations. Otherwise, they proceed to physical screening in the following order: manual BP, tape-measured waist circumference, and fingerstick blood sampling for triglycerides, high-density lipoprotein cholesterol fraction, and glucose using the lipid analyzer (Cholestech LDX, Abbott). If the potential participants meet the eligibility criteria with BP and waist circumference, fingerstick blood sampling is omitted.

Ethical Considerations

Ethical approval for this study was obtained from the University of Alabama at Birmingham Institutional Review Board on December 22, 2022 (IRB-300009718). This study's protocol adheres to all relevant ethical guidelines for research involving human participants, including medical records and patient information.

Informed consent will be obtained from all participants before the baseline visit or during the baseline visit. During the consent process, participants will receive detailed instructions about this study, including its objectives, procedures, potential benefits, and any associated risks or discomforts. They are also informed of their rights, including the ability to withdraw from this study at any time, to ensure that their participation is completely voluntary. This comprehensive approach is designed to ensure that all participants fully understand this study before providing their consent.

To protect participants' privacy, all data collected will be anonymized by assigning each participant with a study number to ensure that no personally identifiable information is directly linked to the data. Demographic, personal, and exercise test

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data will be securely stored in REDCap (Research Electronic Data Capture; Vanderbilt University) and Box (Box, Inc), which are secure, password-protected databases. Access to these data will be limited to authorized research personnel, and all information obtained during this study will be used for research purposes only.

Participants will receive up to US $830 for their participation in this study. Compensation will be provided in stages, with participants receiving US $150 at the baseline assessment, US $200 at the 12-week assessment, US $250 at the 24-week assessment, and US $150 at the 36-week assessment. In addition, participants will receive US $40 for each of the two interview sessions to ensure fairness and transparency in recognition of their time and effort.

Power Analysis and Sample Size

We plan to recruit 132 participants into this study (66 per treatment group), with the expectation that at least 100 (50 per group) will complete this study. We anticipate an attrition rate of 23% based on the average attrition rate between the largest home-based behavioral interventions among wheelchair users (33%) [13] and our scoping review of exercise trials for people with various disabilities (13%) [14]. Due to the nature of the proposed exercise training involving one-on-one training and supervision, we believe that the role of exercise training coaches in this study will lead to lower attrition rates as it has in our past studies [26].

Power calculations were performed using nQuery (version 8.5; Statsols). For the primary outcome of CMH, we obtained SDs of biomarkers of this outcome from our pilot study among individuals with SCI (6-wk arm crank exercise training), including SDs of 43 mg/dL for total cholesterol, 4.3% for body fat, and 22.4 mg/dL for triglycerides [27]. Assuming a final sample size of 50 participants per group, a 2-sided 2-group *t* test (2-tailed), and a significance level of .05, we will have at least 80% power to detect differences of 24.4 mg/dL for total cholesterol, 2.5% for body fat, and 12.7 mg/dL for triglycerides (and greater) between the intervention and control groups as being statistically significant. This is equivalent to detecting an effect size (Cohen *d*) of 0.566 (a moderate effect size) as statistically significant between the two groups.

Outcomes

Outcomes are assessed at baseline, midintervention (12 wk), postintervention (24 wk), and follow-up (36 wk) time points. Physiological outcomes are assessed by anonymous-to-treatment assessors. The assessors are not involved in random assignment or the intervention delivery and do not directly communicate with the M2M instructors and assistant health coaches about participants. Data collection with physiological outcomes is conducted at a local research facility affiliated with a major medical center. Self-reported outcomes are administrated via a secure electronic database, referred to as REDCap. Online platform analytics are used to assess heart rate (HR) and video minutes viewed and stored in the cloud. Figure 1 shows the schedule of assessments.

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Figure 1. Example template of recommended content for the schedule of enrollment, interventions, and assessments. CMH: cardiometabolic health; M2M-C: movement-to-music cardiovascular; SET: standard exercise training.

	Study period					
	Enrollment	Allocation	Postallocation			Closeout
Time point	$-t_1$ (Week -2)	0 (Week 0)	t_1 (Week 1)	t_2 (Week 12)	t_3 (Week 24)	t_x (Week 36)
Enrollment:						
Eligibility screen	X					
Informed consent	X					
Allocation		X				
Interventions:						
M2M-C training			◆——	——	——◆	
SET control			◆——	——	——◆	
Assessments:						
CMH blood specimen or pressure	X			X	X	
Body composition	X			X	X	
Cardiovascular capacity	X			X	X	
Pulmonary function	X			X	X	
Grip strength	X			X	X	
Self-reported physical activity	X			X	X	X
Self-reported health	X			X	X	X
Exercise behavior	X			X	X	X
Self-reported diet	X			X	X	X
Exercise enjoyment or satisfaction				X	X	
Intervention analytics			X	X	X	X

Primary Outcome Measures

CMH outcomes are assessed via venipuncture blood specimen, brachial cuff BP, and body composition.

- High sensitivity C-reactive protein (hsCRP; mg/L): hsCRP is a critical marker of inflammation that contributes to proinflammatory and prothrombotic elements of cardiovascular risk. A single hsCRP measure is a strong predictor of myocardial infarction or coronary heart disease mortality and several other diseases of the circulatory system in people without a history of such conditions [28]. Changes in hsCRP may occur from as early as 8 weeks of exercise [29].
- Hemoglobin A1c (HbA1c, mmol/mol): HbA1c is a measure of red blood cell mean hemoglobin glycation over the previous 3 months. Exercise interventions without a dietary

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component should yield a small to moderate effect on HbA1c after a month of training [30].

- Fasting insulin (μIU/mL): A high fasting insulin level indicates the presence of insulin resistance and whether an individual shows glucose intolerance. Exercise interventions without a dietary component should yield a small beneficial change in fasting insulin levels after a month of training [30].
- Fasting glucose (mmol/L) and homeostatic model assessment of insulin resistance: This is calculated as [fasting insulin (μU/mL) × fasting glucose (mmol/L)]/22.5 [31].
- Fasting triglycerides (mg/dL): A triglyceride level >150 mg/dL, is largely supported as an indicator of cardiovascular risk [32,33]. Exercise interventions without a dietary component should yield a small beneficial change in triglyceride levels after a month of training [30], even among people with normal triglyceride levels [34].
- Fasting cholesterol (mg/dL): Abnormalities in the lipid profile, including elevated total and LDL cholesterol as well as decreased HDL cholesterol, are predictors of future cardiovascular disease among young and middle-aged people [35,36]. Exercise interventions without a dietary component should yield a small effect after 1 month [30].
- BP (mmHg): Moderate-intensity exercise has been shown to reduce BP [37].
- Waist circumference (cm): The waist circumference is measured at the level of the superior border of the iliac crest, above the umbilical level, and at the midline level [38] using a Gulick tape.
- BMI (kg/m^2): Dual-energy x-ray absorptiometry (DXA) scan is used to measure weight-adjusted BMI, in addition to total mass, lean mass, and fat mass. It is evident that people with SCI often have elevated waist circumference (≥94 cm), but their BMI is less than 30 kg/m
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[39].

Secondary Outcome Measures

Secondary outcomes include cardiovascular capacity, pulmonary function, grip strength, and self-reported physical and psychosocial health outcomes.

- VO_{2peak} (ml/kg/min): VO_{2peak} is measured during a graded exercise test as an indicator of cardiovascular capacity using an arm ergometer (Lode) and open circuit spirometry with a metabolic cart (TruOne, ParvoMedics). Arm ergometers are considered the gold standard modality for exercise testing among people with disabilities who use wheelchairs or cannot run or cycle for prolonged periods [40,41]. Before starting the test, participants rest for 3-5 minutes. They are then instructed to maintain a pace between 55 to 65 revolutions per minute throughout the testing period. The participant starts their test with 2 minutes of warm-up without any resistance, and then the resistance is increased every minute by 10 watts until the participant reaches volitional fatigue or subjective discomfort (eg, shortness of breath and chest pain) or achieves 2 or more of the following termination criteria: age-predicted maximum HR of more than 85%; rate of perceived exertion (RPE) of 8 or more on a 0-10 scale; respiratory energy exchange ratio of 1.1 or higher; or plateau in oxygen consumption [42]. HR and oxygen consumption is measured continuously.
- FEV1 (forced expiratory volume over 1 second) and FVC (forced vital capacity; liters): Pulmonary function is measured by (1) how much air the participant exhales quickly, and (2) how much air can be expelled after taking a full breath via a portable spirometer (MIR Spirobank). These will be measured 3 times, with a 1-minute resting period between each trial during the testing session.
- Grip strength (kg): Grip strength is measured using a hand-held dynamometer (Jamar Hydraulic Hand Dynamometer, Lafayette Instruments) for both hands, with 3 trials conducted for each hand and a 1-minute resting period between each trial.
- Self-reported physical activity (min/wk): The volume of physical activity is measured using the Leisure-Time Physical Activity Questionnaire for SCI [43].
- Self-reported physical and psychosocial health: Various aspects of physical and psychosocial health are measured using standardized questionnaires by the National Institutes of Health PROMIS (Patient-Reported Outcomes Measurement Information Systems) [44]. This includes Pain Intensity, Pain Interference, Fatigue, Sleep Disturbance, Global Health, Ability to Participate in Social Roles and Activities, Depression, Anxiety, and Physical Function.

Moderating Outcome Measures

The moderating outcome measures are as follows:

- Demographics and clinical characteristics of participants (eg, age, sex, ethnicity, diagnosis, or medications)
- Exercise behavior measured by Exercise Self-efficacy Scale [45,46], and Exercise Goal Setting and Planning Scale [47] based on Social Cognitive Theory constructs
- Self-reported diet using the Rapid Eating Assessment for Participants Shortened Version [48,49]
- Exercise enjoyment using the Physical Activity Enjoyment Scale [50] and satisfaction via qualitative, semistructured one-on-one interview
- Exercise session duration based on attendance rate and video minutes viewed via online platform analytics
- Exercise intensity based on minutes exercised at moderate-to-vigorous intensity using an optical HR monitor (Polar Verity Sense, Polar) and RPE scale 0-10: The RPE is periodically asked during the exercise session to adjust the intensity and at the end of the exercise session to obtain the overall exertion level. The talk test is used as a secondary measure, primarily to ensure that participants stay in the moderate-to-vigorous intensity training zone and that RPE is related to aerobic strain as opposed to anaerobic. Additionally, this is an important indicator of exercise intensity, especially for individuals with a blunted exercise HR response.

Random Assignment

After participants are determined eligible and all baseline assessments are complete, they are randomized into 1 of the 2

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groups, M2M-C or control (n=66 per group), with a 1:1 allocation ratio. The randomization sequence is generated and only known by the project statistician using a computer-generated random schedule in permuted block (SAS; version 9.4; SAS Institute Inc). The block size is unknown to intervention staff.

Intervention Arm—Home-Based, Synchronous Aerobic Exercise Training Using M2M

The prescriptive exercise guideline in this proposed study was generated through a critical review of the relevant literature. To determine an appropriate exercise dose, we used data from 16 studies of moderate-intensity aerobic exercise included in a recent meta-analysis on CMH effects of exercise training in the general population [22]. Specifically, we calculated the total prescription (average prescription per week × intervention duration) for each study and the overall average. We determined that an aerobic exercise training dose of approximately 2400 minutes (40 h) over 6 months would be necessary for CMH benefits. We then spread the minutes across a 24-week intervention period for this trial with wheelchair users to ensure adequate time to safely and progressively reach the prescribed dose. The session structure and exercise minutes for each week are presented in Table 1, and the intervention components are summarized in Table 2.

Table 1. Movement-to-music cardiovascular session structure and exercise in minutes for each week.

Week	1	2	3	4	5	6	7	8	9	10	11-24
Checking in	5	5	3	3	3	3	3	3	2	2	2
Range of motion	5	5	5	5	5	5	5	5	5	5	5
Aerobic	15	15	20	20	25	25	30	30	35	35	40
Cool down	5	5	5	5	5	5	5	5	5	5	5
End discussion	5	5	5	5	5	5	5	5	3	3	3
Exercise min/session	25	25	30	30	35	35	40	40	45	45	50
Total min/session	40	40	45	45	50	50	55	55	60	60	60

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Table 2. Summary of movement-to-music cardiovascular program features.

Feature	Description
Prescription	• 2400 minutes of exercise across 24 weeks • Progressive • Individualized
Frequency	• 3 times per week
Session duration	• 25 to 50 minutes
Intensity	• Moderate-to-vigorous • Maximum heart rate at or above 70% • Rate of perceived exertion between 3 and 7
Intervention length	• 24 weeks
Setting	• Home
Exercise mode	• Aerobic using M2M[a]
Supervision	
Who	• M2M instructors • Assistant telecoaches
Mode	• Remote telecoaching
Oversight	• Zoom (Zoom Communications, Qumu Corporation) and TeleRehab app (JNP Enterprises LLC) • Live, instruction sessions with M2M instructors • Monitoring sessions with assistant health coaches using recorded live session videos
Meeting with the instructor or coach	
Weeks 1-8	• 1× M2M instructors • 2× assistant telecoaches
Weeks 9-16	• 1× M2M instructors • 1× assistant telecoaches • 1× self-guided with no supervision
Weeks 17-24	• 1× assistant telecoaches • 2× self-guided with no supervision
Equipment provided	• Computer tablets • Tablet stand • Polar heart rate monitor
Intervention safety	• Zoom oversight • Adverse event or serious adverse event reporting

[a]M2M: movement to music.

During the 24-week training phase, the M2M-C group receives 1:1 synchronous training from M2M-trained exercise instructors and assistant health coaches within a remotely coached, home-based setting using telehealth monitoring platforms (ie, Zoom, TeleRehab app). The intervention is administered 3 times per week, starting at 25 minutes per session and increasing by 5 minutes every 2 weeks to a maximum of 50 minutes. The exercise program focuses on improving cardiorespiratory fitness using a series of movement patterns accompanied by music. The program is tailored to an individual's functional abilities (eg, use lower limb if able, slow vs fast tempo, level of trunk control) and preference of musical themes, including classical, country, decades (oldies), international, jazz or blues, and pop.

For the first 8 weeks of the training phase, participants attend 1 instructional session with an M2M instructor per week, and the live session is video-recorded via Zoom. Participants attend 2 monitoring sessions in the same week to repeat the exercise using the prerecorded video of the week with assistant telecoaches. For the second 8 weeks (wk 9-16), participants continue to attend 1 instructional session with an M2M instructor per week, and the live sessions are video recorded. Participants attend 1 monitoring session with assistant telecoaches and 1

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self-guided session without any supervision. For the third 8 weeks (wk 17-24), participants no longer meet with M2M instructors. Using the recorded videos between weeks 11 and 16 (ie, 40 minutes per video; archived with no instructions), participants attend 1 monitoring session per week with assistant telecoaches and 2 self-guided sessions in the same week.

Telehealth Monitoring Platform

The exercise intensity is prescribed at a moderate-to-vigorous intensity level, which is monitored through a web-based platform with physiologic devices to support remote telehealth supervision of the intervention. The platform, referred to as TeleRehab, includes an Android (Google LLC) app that is installed on a computer tablet with Bluetooth capability (Samsung FE S7, Samsung USA), which sends data and allows 2-way communications to a secure web server. HR data are recorded and transmitted for real-time viewing by both the user and research staff using an optic HR sensor (Polar Verity Sense, Polar). The device instructions from the manufacturer state that the sensor can be worn on the head, forearm, or upper arm. For the M2M-C exercise intervention, the HR sensor is placed on a thin, elastic sports headband and worn on the temple of the head. Based on internal testing among research staff (nonpublished findings), the head placement resulted in more accurate readings during intervention exercise than when the device was worn on the forearm or upper arm. The head placement avoided signal disruption caused by the rapid and consistent arm movements required for the exercise intervention. At the end of each session, the platform provides the summary of exercise minutes (ie, light or moderate-to-vigorous) based on the predetermined HR zone. For participants with blunted HR, RPE is used. The TeleRehab app was an upgraded version of one used previously in a tele-monitored feasibility exercise study among people with SCI [51].

Control Arm—Home-Based, Asynchronous Standard Exercise Training

For ethical and engagement purposes, the control group receives access to a YouTube playlist of standard exercise training (SET) videos adapted for people with physical disabilities. They are advised a similar prescription as the intervention group of 3 exercise sessions per week. The SET program is based on the National Center on Health, Physical Activity, and Disability 14-Weeks to a Healthier You program launched in 2008. It involves various exercises that are performed in both standing and seated positions, including the upper and lower extremity range of motion (2 videos, 5 min each), muscle strength (3 videos, 5 min each), aerobic fitness (1 video, 5 min; 2 videos, 10 min each), balance (1 video, 2 min; 2 videos, 5 min each), and a cool down (1 video, 5 min) [52].

Procedure

This study's procedure is administered by a project coordinator with oversight by the principal investigator (PI) and coinvestigators and monitored through a fidelity monitoring plan. Our intervention fidelity plan is based on the best practices and recommendations from the Behavior Change Consortium [26]. These recommendations are intended to link theory and application across 5 primary study phases, including study design, provider training, monitoring and improving the delivery of the intervention, and monitoring and improving the enactment of intervention skills.

The project coordinator, who is specific to participant engagement, contacts interested participants via telephone, describes this study and its requirements, and conducts the screening based on this study's inclusion and exclusion criteria. For eligible individuals, the project coordinator then obtains physician approval. Upon approval by the physician, the project coordinator then distributes the informed consent document electronically as a final step in enrollment. After completing the informed consent, a baseline self-report questionnaire packet and a current medication list form are sent electronically. The project coordinator follows up with a telephone call to schedule a baseline data collection visit and provide verbal and written instructions regarding the baseline testing procedure, completion of the questionnaire packet and medication list, and directions with parking information. The project coordinator contacts the participant by telephone 24 hours before the appointment as a reminder. Upon arrival at the adaptive human performance laboratory, the project coordinator reviews this study's procedures with the participant and then initiates the baseline data collection. The baseline data collection is undertaken by treatment-anonymous research staff who will administer the second level of eligibility screening based on CMH indicators. The eligible participant then undertakes a series of physiological tests, and the composition of those measures takes approximately 2 hours.

Once the baseline assessment is completed, participants are randomly assigned to either the intervention or control conditions using a random numbers sequence with concealed allocation. The project coordinator unfolds the allocation information via this study's database, communicates the condition of assignment with the participant and, if allocated to the M2M-C intervention, prepares the necessary equipment for program participation. The participant will also meet with instructors and assistant telecoaches. If allocated to the control condition (SET), the project coordinator prepares the tablet with access to the SET videos. Lastly, the project coordinator will schedule a goal-setting session to be completed within 2 weeks between the participant and PI. This is carried out for both groups.

Participants in both intervention and control groups receive a 15-minute, individual goal-setting session at each time point from the PI, who is trained in physical activity counseling. They discuss participant's outcome expectations from the program and review the goal of the program based on the given exercise prescription. The participants are prompted to share any foreseen barriers to complying with the program and guided to develop a relapse prevention plan (eg, identifying activities and social support to reactivate participation; outlining consequences for continuing and discontinuing the program). Additionally, the participants are prompted to share additional health goals and receive guidance on making them specific, measurable, attainable, relevant, and time-bound.

The intervention and control participants complete the same measurement procedures at the 12-week (midintervention) and

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the 24-week (postintervention) time points. There is no physiological data collection at the 36-week follow-up, as the aim to be addressed is sustaining physical activity behavior.

Participants receive up to US $830 for completing the measures per assessment period, including baseline as well as 12-, 24-, and 36-week assessments, and 12- and 24-week interviews. Semistructured exit interviews are conducted at the 24-week assessment for the first 30 participants to identify opportunities for intervention improvement and refinement.

Data Analyses

All data will be exported into and analyzed using SAS software (version 9.4 or later). Statistical tests will be 2-sided and will be performed using a significance level of 5%. Data analyses will follow intent-to-treat principles. Data will be initially examined for variations, outliers, errors, and patterns of missing values. Missing data will be inputted using multiple imputation techniques where necessary based on the assumption that the missingness mechanism is at random. Descriptive statistics, such as means, SDs, frequencies, and proportions, will be obtained for this study's variables.

Primary and Secondary Aims

We will analyze between-group differences (differences between the intervention and control groups) and within-group changes from preintervention to the 12-week midintervention (immediate effects of the intervention) time point. "Clinically significant improvement" was defined for each risk factor based on the minimum change deemed clinically important; for our purposes, "clinically significant improvement" equates to the following: approximately 10% decrease in total cholesterol, 30% reduction in triglycerides, and 5% reduction in body fat from the beginning of care to the most recent measure.

Tertiary Aims

Our analyses will focus on only the within-group changes from the preintervention to the 12-week midintervention to the 24-week postintervention (sustained effects of the intervention) time point. For all 3 aims, comparisons of cardiometabolic indicators, measures of fitness, and scores of self-reported questionnaires between and within the 2 groups will be performed using generalized linear mixed model techniques, including mixed models repeated measures analyses. The specific covariance matrix, such as the unstructured covariance matrix, will be selected based on the final data. The Tukey-Kramer multiple comparisons test will be used as the post hoc test for pairwise comparisons of means. These models will allow us to assess the between-group effect, the within-group effect, and the group-by-time interaction. Covariates of scientific interest such as wheelchair use status (full-time vs part-time), medication use (use vs nonuse), and participant characteristics (eg, age, sex, race, and severity of disease) may be included in some of these models. Pearson (or Spearman, if needed) correlation analyses will be performed between pairs of study variables. Analyses of categorical variables will be performed using the Pearson chi-square test (or Fisher exact test, if needed). Baseline characteristics will be evaluated using the 2-group *t* test for continuous variables or the chi-square test for categorical variables. For all aims, missing data that is not rectified through ongoing review of source documents may be managed with multiple imputation, and the influence of the missing data assessed with sensitivity analysis. Continuous variables will be examined for normality of distribution using graphical techniques and tests of normality. Transformations will be performed for continuous variables that are not normally distributed, or nonparametric methods will be used for these variables.

Adherence and compliance data are logged onto the online training platform. Adherence and compliance rates will be assessed as proportions and their corresponding exact 95% CIs will be obtained. These rates will be obtained overall and separately by age, sex, body composition, and ethnicity. These rates will be compared separately for age group, sex, body composition, and ethnicity using the chi-square test or Fisher exact test if the assumptions for the chi-square test are not met.

We will consider the suggested outcomes as potential moderators and test effect modification by including appropriate interaction terms in our repeated measure of mixed models, including the severity of motor impairment (ie, PROMIS Physical Function 12a), clinical diagnosis (eg, SCI vs multiple sclerosis vs stroke), psychosocial metrics specific to readiness to change (eg, self-efficacy and goal setting skills), and other factors, such as wheelchair use status (full-time vs part-time), medication (use vs nonuse), and diet quality (healthy diet vs less healthy diet).

Results

Recruitment procedures started in January 2024 with the first participant enrolled on March 18, 2024. All data are anticipated to be collected by November 2027, and the main results of the trial are anticipated to be published by February 2028. Secondary analyses of data will be subsequently published. A total of 16 participants have been recruited as of August 20, 2024.

Discussion

Principal Findings

The CHIME study proposes a parallel-group RCT for examining the 24-week effects of an evidence-based M2M program compared with a control condition for yielding immediate and sustained CMH outcomes among adult wheelchair users with poor cardiometabolic profiles. This study anticipates that after 24 weeks, participants in the M2M-C intervention group will show significant improvements in key cardiometabolic risk factors, such as reduced HbA_{1c} levels; lower fasting glucose and triglycerides; and decreased BP, waist circumference, and body fat percentage, compared to the control group. Furthermore, the M2M-C intervention is expected to improve health-related physical fitness, including measurements such as VO_{2peak}, FEV1, FVC, and grip strength, in line with self-reported psychosocial health outcomes. In addition to the improvements in CMH and physical fitness, we anticipate that these benefits will be sustained during the maintenance phase (up to 36 wk). This suggests that wheelchair users may be able to adhere to telehealth-based exercise programs over the long

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term. If successful, this study will be the largest and sufficiently powered confirmatory RCT trial targeting CMH outcomes in this population. The prescribed exercise dose was informed by the review of the relevant literature [22]. If successful, this study will establish an evidence-based recommendation of adequate exercise dosing for adult wheelchair users with poor CMH profiles.

Strength and Limitations

This study uses an evidence-based M2M program with modifications to focus on aerobic training and telehealth delivery [53,54]. The M2M program has been specifically designed and tested for safety and effectiveness for balance, walking endurance, and volume of physical activity among people with various disabilities (eg, multiple sclerosis, stroke, and SCI) [17,55,56]. Studies involving fitness training and traditional modes of exercise, such as riding a stationary bike and lifting weights, often result in low adherence rates for many people due to a lack of enjoyment or social interaction [57,58]. Several studies have reported that adding music improves exercise adherence [59] and enjoyment [60,61]. The enjoyment was a highlighted component of the M2M program in addition to its safety and effectiveness, and it has the potential to improve aerobic fitness and CMH when the exercise intensity is regulated by trained instructors.

This study has been designed to deliver quality exercise interventions in the convenience of the participant's home with minimal exercise equipment. However, many exercise interventions often fail to be made available after research trials due to a lack of resources and support. To support the sustained exercise behaviors and gains, postintervention resources will be provided to study participants for their maintenance period (wk 25-36) and can be used after that time. The M2M-C intervention participants will have access to an online library of exercise videos, including their 24-week M2M-C videos, and the control participants will have access to the SET exercise videos. In addition, all participants will be introduced to the National Center on Health, Physical Activity and Disability (to receive continuous support through various health-related programs that are specifically designed for people with disabilities. Participants will be given the center's website and email addresses, in addition to their toll-free hotline.

Limitations

One of the major limitations of this study is that it relies on self-reported data for certain outcomes, such as physical activity, exercise behavior, and diet. Self-reported data can sometimes overestimate or underestimate actual behavior and can be affected by recall bias, where participants may not accurately recall their physical activity or exercise habits [62]. In addition, the time frame for these questionnaires is limited to a 1-week period, which may not fully capture participants' typical physical activity and exercise patterns over time. To address these limitations, future studies could incorporate objective measures, such as wearable devices and activity trackers, to supplement self-reported data. These tools would provide a more comprehensive and accurate understanding of physical activity patterns and engagement, helping to mitigate the biases associated with self-reported data. An additional limitation of the trial is that participants are not blinded to treatment due to the nature of the intervention being an online exercise program.

We may experience problems with the participants adhering to this study's protocol due to the requirement of onsite physiological data collection. Transportation is a well-documented barrier for people with disabilities, especially our target population who may require assistance with transferring in and out of a vehicle or obtaining accessible public transportation. To overcome this barrier, we have arranged a ride service that contains accessible vehicles. In addition, there may be some attrition during the maintenance period (wk 25-36) wherein there is no planned coaching and contact. Potential attrition is expected from this study but we have developed a plan to minimize it using the taper-down approach of coaching and contact during the 24-week training period.

Lastly, the current design of the trial involves intensive supervision of training by the M2M instructors and assistant health coaches, which is approximately 43 hours per participant over the 24-week training period (ie, 19, 16, and 8 hours for each 8-wk phase). The high volume of staff time to implement this study may hinder the scalability of the program in its current form.

Clinical and Practical Implications

The M2M-C intervention has potential clinical and practical implications if proven successful. First, the M2M-C program would demonstrate the feasibility of delivering a structured, individualized tele-exercise platform. This approach effectively addresses common barriers faced by wheelchair users, such as transportation challenges, limited access to fitness facilities, and a lack of tailored exercise programs. The M2M-C program offers a convenient and accessible solution for engaging in physical activity from the comfort of one's own home. Its adaptability makes it suitable for various settings, including rural or underserved areas where traditional exercise programs may not be available. The use of telecoaching also allows for regular interaction and personalized support, which are essential for maintaining motivation and long-term adherence. Moreover, if the M2M-C intervention proves successful, there is the potential for it to be expanded to serve a broader range of clinical populations. The program's emphasis on individualization—adjusting exercises to align with each participant's physical capabilities and fitness level—makes it adaptable. With appropriate modifications, the M2M-C program could be extended to other groups, including individuals with different types of mobility impairments and older adults with physical disabilities. This flexibility highlights the M2M-C intervention as a versatile tool for promoting physical activity on a larger scale, potentially reaching diverse populations in need of accessible exercise solutions.

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Data Availability

The data generated as part of this study will be made available through a data repository. Additionally, deidentified datasets will be made available as supplementary material with each relevant publication.

Authors' Contributions

All authors contributed to the final draft of this paper and project design. JW and Yumi K created the initial manuscript draft. All authors contributed to either this study's design or procedures.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the National Institute of Child Health and Human Development Special Emphasis Panel Home and Community-Based Physical Activity Interventions to Improve the Health of Wheelchair Users (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 241 KB - resprot_v14i1e57423_app1.pdf]

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Abbreviations

BP: blood pressure
CHIME: Cardiometabolic Health Intervention Using Music and Exercise
CMH: cardiometabolic health
FEV1: forced expiratory volume over 1 second
FVC: forced vital capacity
HbA1c: hemoglobin A1c
HR: heart rate
hsCRP: high sensitivity C-reactive protein
M2M: movement to music
M2M-C: movement-to-music cardiovascular
PI: principal investigator
PROMIS: Patient-Reported Outcomes Measurement Information Systems
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
RPE: rate of perceived exertion
SCI: spinal cord injury
SET: standard exercise training
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
VO2peak: peak oxygen consumption

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Protocol

Harnessing Human-Centered Design for Evidence-Based Psychosocial Interventions and Implementation Strategies in Community Settings: Protocol for Redesign to Improve Usability, Engagement, and Appropriateness

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Abstract

Background: Although substantial progress has been made in establishing evidence-based psychosocial clinical interventions and implementation strategies for mental health, translating research into practice—particularly in more accessible, community settings—has been slow.

Objective: This protocol outlines the renewal of the National Institute of Mental Health–funded University of Washington Advanced Laboratories for Accelerating the Reach and Impact of Treatments for Youth and Adults with Mental Illness Center, which draws from human-centered design (HCD) and implementation science to improve clinical interventions and implementation strategies. The Center's second round of funding (2023-2028) focuses on using the Discover, Design and Build, and Test (DDBT) framework to address 3 priority clinical intervention and implementation strategy mechanisms (ie, usability, engagement, and

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appropriateness), which we identified as challenges to implementation and scalability during the first iteration of the center. Local redesign teams work collaboratively and share decision-making to carry out DDBT.

Methods: All 4 core studies received institutional review board approval by June 2024, and each pilot project will pursue institutional review board approval when awarded. We will provide research infrastructure to 1 large effectiveness study and 3 exploratory pilot studies as part of the center grant. At least 4 additional small pilot studies will be solicited and funded by the center. All studies will explore the use of DDBT for clinical interventions and implementation strategies to identify modification targets to improve usability, engagement, and appropriateness in accessible nonspecialty settings (Discover phase); develop redesign solutions with local teams to address modification targets (Design and Build phase); and determine if redesign improves usability, engagement, and appropriateness (Test phase), as well as implementation outcomes. Center staff will collaborate with local redesign teams to develop and test clinical interventions and implementation strategies for community settings. We will collaborate with teams to use methods and centerwide measures that facilitate cross-project analysis of the effects of DDBT-driven redesign on outcomes of interest.

Results: As of January 2025, three of the 4 core studies are underway. We will generate additional evidence on the robustness of DDBT and whether combining HCD and implementation science is an asset for improving clinical interventions and implementation strategies.

Conclusions: During the first round of the center, we established that DDBT is a useful approach to systematically identify and address chronic challenges of implementing clinical interventions and implementation strategies. In this subsequent grant, we expect to increase evidence of DDBT's impact on clinical interventions and implementation strategies by expanding a list of common challenges that could benefit from modification, a list of exemplary solutions to address these challenges, and guidance on using the DDBT framework. These resources will contribute to broader discourse on how to enhance implementation of clinical interventions and implementation strategies that integrate HCD and implementation science.

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KEYWORDS

implementation science; human-centered design; evidence-based psychosocial interventions; mental health

Introduction

Background

Psychosocial clinical interventions such as psychotherapy, counseling, and case management are a preferred mode of treatment by most people seeking care for mental health problems [1-5]. Access to evidence-based clinical interventions remains variable among diverse groups, leading to mental health disparities across racial and ethnic, geographic, and socioeconomic status [6-16]. Furthermore, implementing clinical interventions in nontraditional and integrated settings (eg, primary care, telehealth platforms, and schools) has shown mixed success. These settings can serve as a *safety net* for accessing mental health treatment when traditional options are inaccessible [17-20]. Addressing barriers to implementing clinical interventions in these settings is vital to promote more equitable access to mental health services for all.

Poor availability of clinical interventions is often due to intervention complexity and suboptimal fit with many settings where clinical interventions are deployed [21]. Implementation strategies—"systematic intervention process(es) to promote the uptake of evidence-based health innovations into usual care"—have often taken the form of complex tools and processes (eg, train the trainer, booster training, incentive models, and decision supports) [22,23]. However, these often fall short because they can be excessively costly and cumbersome [22,24]. Different needs of recipients and settings can lead to high rates of reactive adaptations of clinical interventions and implementation strategies by their intended users in many settings where they are deployed. Reactive adaptations are unplanned or improvised changes during an implementation process in response to unanticipated challenges [25]. While reactive adaptations can compromise clinical potency, those that are proactively tailored to different care settings can improve sustainability and impact [26-29]. A systematic review of cultural adaptations to health and mental health services highlighted how adaptations motivated by cultural sensitivity are not guaranteed to demonstrate increased efficacy [30]. Instead, patient-centered approaches that account for individualized needs and barriers to service are recommended to guide adaptations [30,31].

Human-Centered Design and Implementation Science

Human-centered design (HCD) and the closely related discipline user-centered design offer a suite of methods to develop useful, compelling, intuitive, and enjoyable products, services, and tools based on people's needs [32,33]. HCD relates to the evolution of human-computer interaction (HCI), a multidisciplinary field that incorporates computer science, cognitive science, and human factors engineering as a response to personal computing, collaborative work, and interconnected technologies in everyday life [34]. While HCD's origins are rooted in technology, it has been used beyond the context of digital technologies to address therapeutic elements and implementation supports [35]. HCD has been applied to improve usability, reduce burden, and increase the contextual appropriateness of clinical interventions and implementation strategies [36-40].

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The fields of HCD and implementation science share common objectives and offer complementary methods that can support clinical interventions and implementation strategies innovation and redesign [41-44]. HCD techniques are particularly well positioned to help with redesign, which we define as adaptations to clinical interventions and implementation strategies while preserving effective components (ie, fidelity-consistent adaptation) [45]. HCD's traditions of situating problem discovery and solutions in user needs, usability, engagement, innovation, and rapid exploration are core strengths that align with implementation science's goal of improved adoption, fidelity, reach, and adaptation of clinical interventions and implementation strategies [41]. Combining HCD and implementation science traditions for clinical intervention and implementation strategy redesign grounds novelty in empirical evidence.

Integrating HCD and Implementation Science Through the Discover, Design and Build, and Test Framework

The University of Washington Advanced Laboratories for Accelerating the Reach and Impact of Treatments for Youth and Adults with Mental Illness Center (UWAC), which is funded by a grant from the National Institute of Mental Health (NIMH), is a multidisciplinary team of experts from the fields of mental health, implementation science, and HCD focused on improving usability, engagement, and appropriateness of clinical interventions and implementation strategies in diverse and nonspecialty settings (eg, rural, urban, low-income, primary care, and schools). Drawing on strengths from different disciplines, UWAC developed the Discover, Design and Build, and Test (DDBT) framework (Figure 1) at the start of the center (ie, "UWAC 1.0"). The current DDBT framework guides teams in redesigning clinical interventions and implementation strategies to improve usability, engagement, appropriateness, and implementation outcomes while preserving clinical interventions' core components [46]. Key principles underlying this model include the following: (1) not all clinical interventions and implementation strategies are designed for all settings; (2) "there is no implementation without adaptation" [47]; (3) unchecked, reactive adaptations have the potential to exclude essential active ingredients [48,49]; and (4) reactively adapted clinical interventions and implementation strategies can negatively impact implementation and clinical outcomes.

Figure 1. Discover, Design and Build, and Test (DDBT) redesign framework.

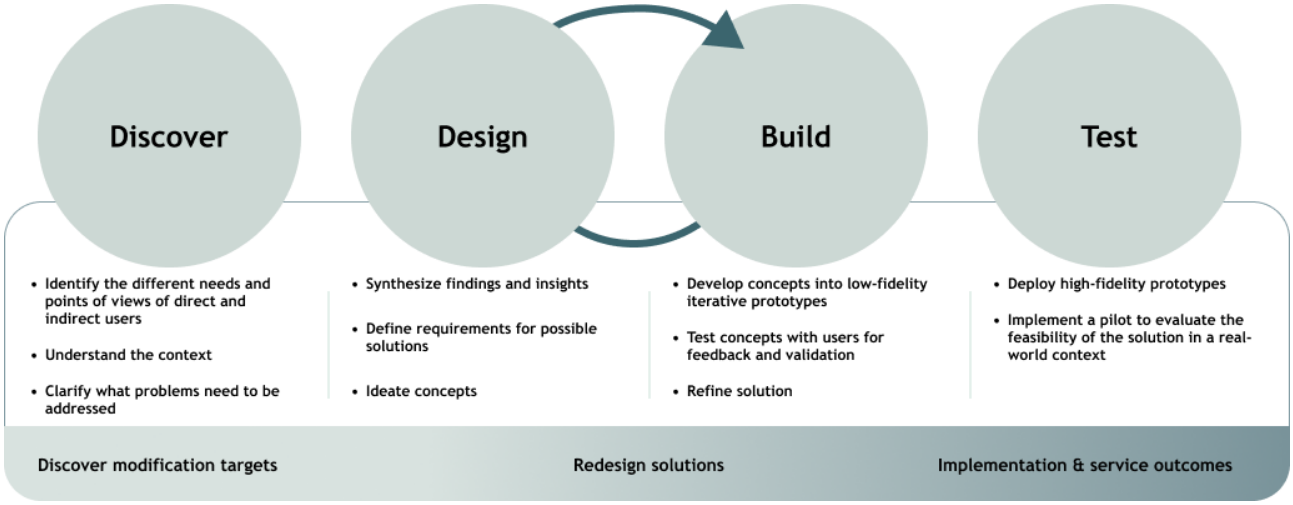

The DDBT framework is modeled after existing HCD frameworks [50] and is an iterative stepped approach to systematically (1) understand usability constraints of existing clinical interventions and implementation strategies, (2) iteratively design solutions for usability challenges with redesign teams of direct and indirect users, and (3) test and refine prototypes. We define direct users (also known as "primary users") as people who directly interact with the clinical intervention and implementation strategy and indirect users (also known as "secondary users") as people affected by the clinical intervention and implementation strategy. HCD places a strong emphasis on explicitly identifying relevant community collaborators and users to ensure that new products effectively meet their needs [51,52]. DDBT starts by identifying multilevel factors that drive clinical intervention and implementation strategy usability problems, engagement challenges, and problems with contextual appropriateness (Discover phase). Once problems and challenges are identified, modifications are iteratively created between the design team and practitioners and clients, until a new version of the clinical interventions and implementation strategies is developed to address crucial issues and enhance usability, engagement, and appropriateness (Figure 2; Design and Build phase). Early prototypes of clinical interventions and implementation strategies are assessed with small samples (eg, 5-25 participants) to answer design questions using paper or other "low-fidelity" (ie, sufficient to communicate a concept but potentially lacking functionality, some content, and look and feel of final materials) versions of modifications, which reduces waste of unnecessary investment in programming and development until as late in the process as possible. Findings from the Design and Build phase are incorporated to develop high-fidelity prototypes, which are tested against the unadapted version to ascertain if the modified clinical interventions and implementation strategies result in improved implementation (eg, increased adoption, fidelity, reach, and reduced reactive adaptations) and equivalent or better mental and behavioral health outcomes because of the changes to usability, engagement, and appropriateness (Test phase). Additional details

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on the DDBT framework are outlined in our UWAC 1.0 protocol paper [46].

All UWAC research uses the DDBT framework, which is applied flexibly based on project needs and allows us to evaluate the extent to which incorporating HCD and implementation science methods impacts clinical interventions and implementation strategies. Since 2018, DDBT has been used in >18 UWAC studies and 16 National Institutes of Health (NIH)–funded awards external to UWAC. During UWAC 1.0, we originally assessed impact of DDBT on 3 mechanisms: learnability (ie, extent to which users can understand or facilitate use) [46], usability (ie, extent to which users can achieve specified goals of effectiveness, efficiency, and satisfaction) [50], and sustained quality of care (ie, extent of treatment fidelity and impact on target outcomes) [46]. Analysis of UWAC 1.0 projects resulted in (1) identification of common usability issues in clinical interventions and implementation strategies that could benefit from modification (ie, "typology of modification targets") and corresponding heuristics to guide their design [53], (2) reflections on potential exemplary solutions to these challenges (ie, library of clinical interventions and implementation strategies redesign solutions), and (3) guidelines for using the DDBT framework [46].

Figure 2. University of Washington Advanced Laboratories for Accelerating the Reach and Impact of Treatments for Youth and Adults with Mental Illness Center (UWAC) theory of change for clinical intervention and implementation strategy redesign. DDBT: Discover, Design and Build, and Test.

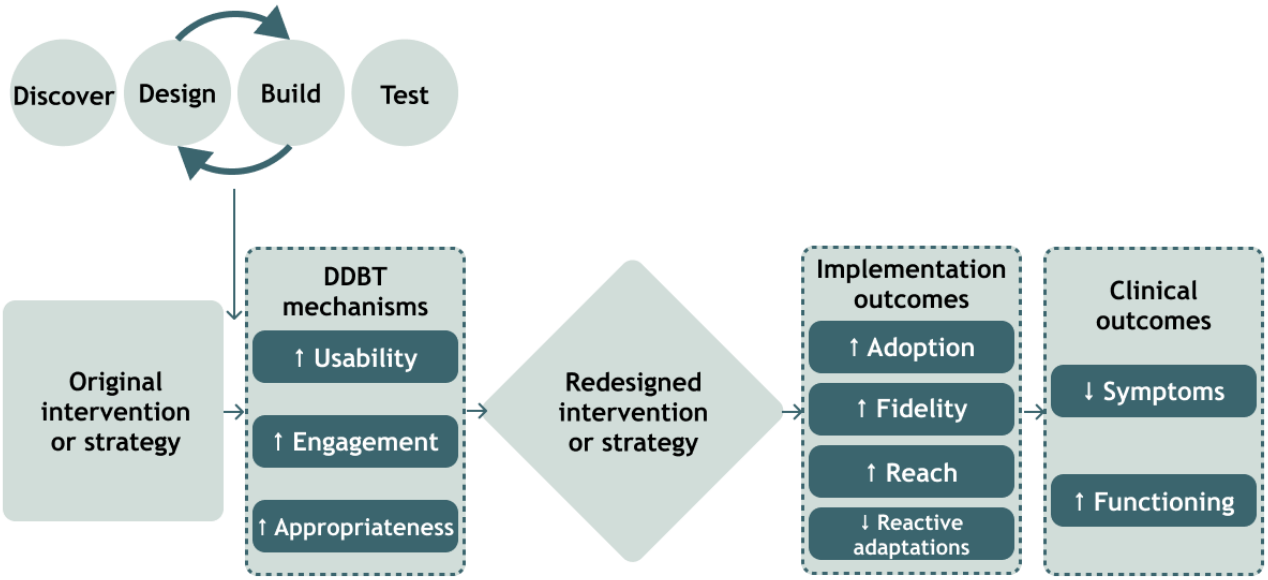

UWAC Theory of Change for Clinical Intervention and Implementation Strategy Redesign

Our UWAC 1.0 findings and the implementation literature [21] outline how limited availability and the use of clinical interventions and implementation strategies are persistently attributable to organizational and system characteristics (eg, readiness to adopt, resources and culture, and leadership), clinician and adopter characteristics (eg, appropriateness and perceived efficacy of clinical interventions and implementation strategies for patients) [28,54,55], and incentives to engage in clinical interventions and implementation strategies [29,56].

As a result, we updated DDBT's underlying theory of change to highlight how adoption of clinical interventions and implementation strategies are largely due to usability (eg, extent to which clinical interventions and implementation strategies can be used to achieve specified goals with effectiveness, efficiency, and satisfaction) [53]; engagement (eg, degree of user participation and enthusiasm for the aspects of clinical interventions and implementation strategies that require user involvement) [57]; and appropriateness (eg, perceived fit, relevance, or compatibility of clinical interventions and implementation strategies for a given practice setting, practitioner, or consumer) [58] (Figure 2). These mechanisms are direct targets of DDBT-driven redesign and the focus of the new iteration of funding between 2023 and 2028 (ie, "UWAC 2.0"). We ultimately expect DDBT to result in changes to proximal implementation outcomes (adoption, fidelity, reach, and reactive adaptation) and clinical outcomes.

DDBT Mechanisms

Usability

Usability is an underlying outcome at all stages of the HCD process. Understanding the extent to which designs are unusable and opportunities to increase an existing solution's usability can inspire innovation and adoption [53]. Deployment of clinical interventions and implementation strategies will continue to be subpar unless usability can be addressed, the historically unidirectional relationship between developers and users can be overcome, and insufficient incorporation of user perspectives can be remedied [59]. Usability is assessed through usability evaluations and usability testing, where prototypes are evaluated using established heuristics [60] and observing users complete critical tasks [61]. Usability assessment methods stem from evaluating technologies; however, these techniques have been used to improve usability, decrease burden, and increase contextual appropriateness of nontechnological mental health clinical interventions and implementation strategies [5,36,39,53].

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Approaches to assessing usability frequently couple interview-type questions with surveys and observation [62]. As a form of usability evaluation, metrics such as the System Usability Scale (SUS) [63] are questionnaires that assess perceived usability. The SUS is a widely used instrument to measure usability of technologies by industry. Task-based usability testing involves asking participants to complete tasks while using a prototype or product. This method can be used to gather baseline usability data for an existing clinical intervention and implementation strategy and assess usability of clinical intervention and implementation strategy prototypes [53]. The think-aloud protocol (TAP) involves participants verbalizing thought processes as they use clinical interventions and implementation strategies [39] to complete assigned tasks, including actions they consider taking and reactions to materials as they encounter them. Similarly, the Cognitive Walkthrough for Implementation Strategies (CWIS) is a 6-step method for evaluating clinical interventions and implementation strategies usability, which can include interviews as part of task-based usability testing [39].

UWAC 1.0 projects assessed usability through usability questionnaires, CWIS [39], and TAP [64,65]. We developed the Intervention Usability Scale (IUS) [37] and Implementation Strategy Usability Scale (ISUS) [39] to better measure clinical intervention and implementation strategy usability; these scales are closely aligned with SUS. SUS scores of ≥70 out of 100 are considered adequate usability, and we anticipate a similar threshold for IUS and ISUS. Cross-project usability data informed the typology of modification targets: 12 unique categories of clinical intervention and implementation strategy usability issues of varying severity. These categories help researchers understand common barriers to clinical intervention and implementation strategy use that can be prevented and addressed during clinical intervention and implementation strategy redesign [53].

Engagement

Engagement, and adaptations to improve engagement, relates to clinical interventions fidelity and clinical outcomes [66-69] and is a defining feature of quality of care [70-72]. Engagement describes user connection to clinical interventions and implementation strategies and their capacity to sustain a connection [57]. Engagement is distinct from common health concepts of compliance, adherence, and coverage because it incorporates a dimension of quality and welcomes the possibility that different people may engage differently with different parts of clinical interventions and implementation strategies based on varying needs. Typical users include the practitioners who deliver them (eg, clinicians, implementation practitioners, and intermediaries) and the individuals who receive them (eg, clients, practitioners, and service system administrators). Our work has found that engagement can be negatively impacted by insufficient buy-in, components that are inaccessible to different users, little support for communication or rapport building, and requirements or constraints that inadvertently shift one user's responsibilities to another (eg, practitioners completing client tasks) [53].

Engagement is a common focus in HCI literature [57,73-75], where there is an active conversation around how to best assess the quality of interactions rather than quantity of interactions. Multidisciplinary UWAC project teams present an opportunity to incorporate different approaches to improving engagement in translational research [76-78]. We conceptualize engagement as a multifaceted construct focused on interaction quality (ie, participation and enthusiasm) that is enhanced by clinical interventions and implementation strategies that are well designed and result in improved adoption, fidelity, reach, and adaptations. There are subjectivity-oriented and objectivity-oriented approaches to measuring engagement [57]. Subjectivity-oriented measures are self-reported and include questionnaires, observation, perceived task outcomes, and interviews. Objectivity-oriented measures minimize researcher involvement and can include behavior logging, psychophysiological measurements, or telemetry. Within HCI, objectivity-oriented measures such as user data—logs, time, number of interactions, and frequency of log-ins—are commonly used.

Appropriateness

Appropriateness captures perceived fit between clinical interventions and implementation strategies and the settings to which they are deployed [58]. Client needs and therapeutic style drive how mental health practitioners modify clinical interventions and implementation strategies in practice [26]. During UWAC 1.0, we observed how practitioners and recipients felt that exciting innovations can be inappropriate for specific contexts (eg, schools) or for users facing challenges with identifying and selecting goals or implementation plans. Challenges included clinical interventions and implementation strategies' excessive time demands in their delivery, incompatibility with existing workflows or roles, unavailable system infrastructure requirements, overreliance on digital technology, and, importantly, practitioner perceptions of the fit of the clinical interventions and implementation strategies to specific client problem types. These issues are well documented as multifaceted factors that influence clinical intervention and implementation strategy adaptations [29,45]. During UWAC 1.0, we used the Intervention Appropriateness Measure (IAM) [79] across projects to assess appropriateness.

Study Purpose

Center Aims and Structure

Our goal is to overcome obstacles that prevent quality mental health interventions from reaching historically marginalized groups through addressing critical clinical intervention and implementation strategy problems with the DDBT framework. Building on learnings during the first iteration of the center, UWAC 2.0 focuses on addressing longstanding problems with *usability*, *engagement*, and *appropriateness* of clinical interventions and implementation strategies that result in high rates of reactive adaptations in settings where they are deployed. Within UWAC, the Methods Core team provides methodological and technical support to all projects and maintains cross-cutting project data on UWAC outcomes to determine the impact of DDBT on clinical interventions and implementation strategies. These data will be used to refine and expand UWAC's typology

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of modification targets and library of redesign solutions. This iteration of the center emphasizes increased leadership and application of DDBT methods by local project redesign teams (eg, administrators or champions) that receive methodological training and supports from the Methods Core team to work alongside investigators, increasing their decision-making at all stages of the design process. This is a shift from the previous centralized model, where projects engaged users, but project principal investigators (PIs) and UWAC Methods Core team members often led the design process. The Methods Core team will address the subsequent aims during UWAC 2.0.

Aim 1: Identify Clinical Intervention and Implementation Strategy Modification Targets to Improve Usability, Engagement, and Appropriateness in Accessible Nonspecialty Settings (Discover Phase)

Known determinants of successful clinical intervention and implementation strategy use exist at several levels, including clinical interventions (eg, complexity); practitioner and client (eg, training, attitudes, and intention to use); and organizational (eg, climate, leadership, resources, and supervision). Historically, adaptations of clinical interventions and implementation strategies have been driven by academics rather than the lived experiences of recipients. Using the Consolidated Framework for Implementation Research (CFIR) [80] as our guide in the Discover phase of each UWAC project, we support project redesign teams to use HCD methods to identify targets within our typology of modification targets [53]. Qualitative analyses will allow us to compare targets identified via local DDBT, characterized by user involvement in redesign teams and shared decision-making about target prioritization and solutions, with those derived from our original, centralized application of DDBT [46]. Aim 1 outcomes will inform typology revisions and allow for comparisons between the original, centralized DDBT and the local DDBT. An updated typology will be broadly disseminated to inform future research.

Aim 2: Develop Redesign Solutions With Local Teams to Address Clinical Intervention and Implementation Strategy Modification Targets (Design and Build Phase)

Using rapid, iterative design principles, we are supporting research project teams in redesigning clinical interventions and implementation strategies to enhance usability, engagement, and appropriateness. We will systematically catalog these design solutions using the Framework for Modifications and Adaptations of Evidence-Based Interventions (FRAME) or FRAME for Implementation Strategies (FRAME-IS) [26,29,45]. We will examine solutions and the populations, organization types or structures, practitioner types, and clinical interventions and implementation strategies in which they work, identifying solutions that transfer across different contexts or are uniquely suited to specific contexts. Aim 2 outcomes will be compared with centralized DDBT outputs, resulting in an updated library of redesign solutions organized by target and redesign method (ie, localized vs centralized), and shared with the interested community.

Aim 3: Determine If Redesign Affects Changes in Usability, Engagement, and Appropriateness (Test Phase)

Each project conducting a Test phase will include a hybrid effectiveness-implementation trial [81,82] with a primary comparison between the original clinical intervention and implementation strategy and the DDBT-adapted version on theorized mechanisms (usability, engagement, and appropriateness), implementation outcomes (adoption, fidelity, reach, and adaptations), and client outcomes. Projects will apply FRAME or FRAME-IS [29,45] to examine the extent to which DDBT decreases reactive adaptations to the clinical intervention and implementation strategy (ie, unplanned or due to unanticipated obstacles) during implementation. We hypothesize that DDBT-informed, prospective, and planned adaptations will reduce the number and extent of reactive adaptations. The Methods Core team will systematically integrate new data from the UWAC projects with existing data in an integrated cross-project analysis of how redesign affects theorized mechanisms, implementation outcomes, and patient outcomes. Aim 3 outcomes will be disseminated to the field and inform new projects designed to test which redesign strategies best improve DDBT mechanisms and outcomes.

Methods

Overview

Composed of an interdisciplinary team and advisory board with experience in HCD, implementation science, psychosocial clinical interventions, and research methods and data, the Methods Core team supports one large hybrid effectiveness-implementation study (NIH R01), 3 exploratory pilot studies (NIH R34s; Multimedia Appendix 1), and at least 4 pilot projects (NIH R03s) during UWAC 2.0. These projects aim to improve clinical intervention and implementation strategy access and scale in diverse settings. The R01 Problem Solving Treatment-Aid (PST-Aid; NCT06494384; PIs: IB, PR, and SAM) will test a DDBT-designed decision support tool for Problem Solving Treatment (PST) in a large network of primary care clinics. R34 Research Units on Behavioral Intervention in Educational Settings (RUBIES; NCT06508515; PIs: KB and JL) will create a novel implementation strategy to support the delivery of evidence-based classroom supports for students with autism. R34 Trauma-Focused Cognitive Behavioral Therapy (TF-CBT; PIs: ARL and DW) will redesign and test an evidence-based clinical intervention for youth trauma for use in education settings. R34 Brief Intervention for School Clinicians (BRISC; PIs: EB, JVD, and Elizabeth McCauley) will adapt an existing set of effective implementation strategies to enhance delivery of a school-based engagement, assessment, brief mental health intervention, and triage strategy. Funding for all core projects began in 2023. Multimedia Appendix 2 outlines key details (eg, study design and sample) of each study. PST-Aid and RUBIES were part of UWAC 1.0 as R34 and R03 projects, respectively, highlighting how UWAC 2.0 activities build on previous accomplishments. UWAC funds pilot projects through a competitive solicitation process, with a particular focus on supporting and mentoring investigators from

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historically marginalized groups. All projects use the DDBT framework to address clinical intervention and implementation strategy usability, engagement, and appropriateness in partnership with local community collaborators. UWAC provides projects direct support for integrating methods and measurement approaches and professional development that centers diversity, equity, and inclusion (DEI) values.

DDBT Constructs

Projects collect common data on DDBT mechanisms and constructs to determine the impact of modifying clinical intervention and implementation strategy targets. The Methods Core team maintains a list of recommended and required measures for projects to gather at each DDBT phase ("Center Measures and Guidance"; Multimedia Appendix 2). We developed Center Measures and Guidance to facilitate DDBT hypothesis testing and data management across UWAC, help teams select methods based on project design objectives, and satisfy NIMH reporting requirements. Center Measures and Guidance include 15 constructs with 26 quantitative and qualitative measures across DDBT phases. The Methods Core team provides project teams support with integrating and adapting these measures for projects through a consultation model. This is a shift from our approach in UWAC 1.0, where the Methods Core team provided more personalized measurement support to project teams. Multimedia Appendix 3 [83] outlines each construct with a description of related measures and activities, and relevance to each DDBT phase. The Methods Core team provides data management for all projects, maintains survey instruments in REDCap (Research Electronic Data Capture; Vanderbilt University), and conducts cross-project analyses. Each project is responsible for conducting its own analyses. The Methods Core team provides guidance on ensuring recruitment, data analysis, and dissemination practices incorporate diverse perspectives and accurately represent the lived experiences of participants to inform clinical intervention and implementation strategy redesign.

DDBT Theory of Change Mechanisms

Usability

All projects are expected to report usability issues on existing or redesigned clinical interventions and implementation strategies and standardized usability metrics to the Methods Core team. Because interviews alone can be limiting for identifying usability issues because of issues with recall or challenges with describing behavior, UWAC projects are encouraged to combine interviews with other methods such as CWIS and TAP. This helps projects learn what a participant is considering doing next and why, better understand their in-the-moment goals, and identify misconceptions. For example, R34 BRISC will use TAP and a cognitive walk-through methodology with users to identify opportunities for redesign and improve implementation based on user needs [39]. The Methods Core team supports projects with adapting surveys (eg, SUS, IUS, and SUS) and implementing cognitive walkthroughs and usability testing for projects.

Engagement

We expect all projects to assess engagement quantitatively using the User Responsiveness Scale and qualitatively (ie, thematic findings from observation or other chosen methods) during the Discover and Test phases of existing and redesigned clinical intervention and implementation strategy. The Methods Core team developed the User Responsiveness Scale based on the Patient Responsiveness Scale [66]. The User Responsiveness Scale has 10 statements that cover participation and enthusiasm for a clinical intervention and implementation strategy that participants rate on a Likert scale. The original Patient Responsiveness Scale has demonstrated strong internal consistency (Cronbach α=0.86) and construct validity.

Appropriateness

R01 and R34s are expected to administer the IAM [79] or revised goodness-of-fit interview [84] during the Discover and Test phases of existing and redesigned clinical interventions and implementation strategies to probe areas of alignment and misalignment on goals and expectations, roles, etc. IAM is a 4-item survey and the leading instrument for measuring clinical intervention and implementation strategy contextual fit with good internal consistency (Cronbach α=0.87) and adequate test-retest reliability (r=0.73). The goodness-of-fit interview is particularly well-suited to probe on clinical intervention and implementation strategy appropriateness issues identified through IAM. We will use content analysis to analyze goodness-of-fit interview data. For example, R34 RUBIES will conduct goodness-of-fit interviews to explore the appropriateness of the RUBIES implementation strategy ("RUBIES-Team") for the school environment using the CFIR domains to drive questioning.

Proximal Implementation Outcomes

Adoption and Reach

Adoption and reach are implementation outcomes specified in the CFIR [58] and Reach, Effectiveness, Adoption, Implementation, and Maintenance [85] frameworks. We expect projects to report on adoption and reach as part of the Design (if feasible) and Test phases. All projects will report adoption and reach of the intervention. For redesigned implementation strategies, the approach to measuring adoption and reach depends on the project. For example, R34 RUBIES defines adoption as educators' first use of the RUBIES-Team at any point during the study and will measure reach for both RUBIES-Individual (ie, an original implementation strategy) or RUBIES-Team in three ways: (1) the number of other educators with whom trained educators share RUBIES strategies; (2) the number of other students with whom trained educators share RUBIES strategies; and (3) the number of other contexts and settings in which they applied RUBIES strategies.

Intervention and Implementation Strategy Fidelity

Fidelity is a core implementation outcome [58]. We expect projects to report on fidelity as part of the Design (for existing clinical interventions and implementation strategies) and Test phases. Teams choose an approach to measuring fidelity based on redesign goals. For example, R34 RUBIES rates paraeducator fidelity to treatment (eg, weekly ratings of the paraeducator's

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homework completion and behavior support plan implementation). R34 TF-CBT will code session recordings using the Therapy Process Observational Coding Scale [86] and the Therapy Process Observational Coding Scale–Self-Reported Therapist Intervention Fidelity for Youth [87] at baseline, 3 months, and 6 months. Finally, R01 PST-Aid will measure initial and sustained fidelity using a PST Fidelity Scale. Initial fidelity will be measured as the number of sessions it takes providers to get certified; providers must have 2 sessions rated as "satisfactory" on the PST Fidelity Scale to receive certification. Sustained fidelity will be measured as the number of "satisfactory" sessions during the 6 months after certification, as measured by the PST Fidelity Scale.

Planned Adaptations

Characterizing adaptations, or redesign solutions, is key to all 3 Methods Core team aims to better understand and address challenges to clinical interventions and implementation strategies. We expect projects to characterize adaptations with FRAME or FRAME-IS [29] as part of the Design and Build phase, where planned and proactive changes will be made as a part of the redesign process. For example, R34 BRISC will analyze recorded intervention sessions using FRAME or FRAME-IS. The R01 PST-Aid will code randomly selected session audio recordings per client for fidelity and adaptations using FRAME or FRAME-IS. Projects will share adaptations made with the Methods Core team and describe whether these adaptions were made proactively (eg, as part of the redesign process in the design and build phases) or reactively (eg, unplanned or due to unanticipated obstacles in the test phase). Across projects, the Methods Core team will systematically categorize adaptations to examine solutions and the populations, organization types or structures, practitioner types, and clinical interventions and implementation strategies in which they work. Our objective is to identify transferable and unique solutions to different contexts and clinical interventions and implementation strategies. This information will ultimately inform an updated version of the library of redesign solutions.

Unplanned or Reactive Modifications

Reactive or unplanned modifications during the Test phase will be measured using a 17-item Center-developed measure based on the FRAME or FRAME-IS to assess the nature of modifications. Providers will self-report any changes they made while they administer the intervention.

Distal Service Recipient Outcomes

During the Test phase, projects are expected to collect clinical and functional outcomes. Teams will administer standardized assessments (eg, Patient Health Questionnaire [88], Quality of Life in Neurological Disorders [Neuro-QOL] [89], Satisfaction with Social Roles for adults [90], and the Neuro-QOL Social Relations Scale for youth [91]). The Neuro-QOL measures are widely used to assess functioning in usual social roles, activities, and responsibilities. The scales have been evaluated with thousands of participants from the general population of the United States and in clinical inpatient and outpatient settings who have a wide variety of presenting problems [89-91]. All projects will also use idiographic (ie, individualized) client outcome monitoring based on the Top Problems Assessment [92], an approach informed by goal attainment scaling [93,94] that has been found to be highly sensitive for monitoring clinical intervention outcomes and thus is preferred over standardized or nomothetic assessments by both practitioners and clients [95].

Demographic and Process Measures

Demographics

All projects are expected to collect participant demographic data mandated by the NIMH at all phases. Teams collect additional demographic data on the basis of the project needs. For example, the R34 RUBIES collects required educator and student demographics (eg, age, gender, and race) and additional data on school characteristics (eg, school size, percentage eligible for free or reduced lunch, racial and ethnic composition, percentage of English language learners, percentage in special education, annual funding for external resources, and per capita number of community-based organizations). Data will be tabulated to satisfy federal demographic and data reporting requirements as well as cross-project meta-analyses and comparisons.

User Needs and Experience

All projects are expected to clearly identify direct and indirect users and incorporate methods that address user needs. Explicit user identification produces more usable products and ensures that the design team does not underestimate user diversity [96] or create designs based on the team's own needs [36,97,98]. clinical intervention and implementation strategy users should include the deliverers (eg, providers of clinical interventions) and recipients (eg, clients and implementation strategy targets such as administrators or clinicians). Identification of users for a clinical intervention and implementation strategy includes (1) generating a preliminary user list, (2) articulating the most relevant characteristics that reflect anticipated users, (3) describing and prioritizing main user groups, and (4) selecting typical and representative users [96]. For example, in R34 TF-CBT, direct users are school counselors and social workers who provide mental health services, as well as public school students with histories of traumatic stress. Potential indirect users in this project include caregivers of students. We included users who are diverse with respect to characteristics such as age (eg, students), race and ethnicity (eg, students and practitioners), culture (eg, students and practitioners), and clinical domain experience (eg, practitioners), which are features known to impact experiences of usability, engagement, or appropriateness [53,99-101].

Projects will use interviews to identify key challenges that users might face when applying clinical interventions and implementation strategies. Interviews consist of questions derived from HCD principles such as organizational and community culture, values, and challenges in applying clinical interventions and implementation strategies. For example, in R34 RUBIES, the team will interview educators about their existing opportunities to learn behavioral management strategies for students with autism who exhibit challenging behavior. Interviews will identify promising professional development approaches and areas to improve the existing RUBIES

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multifaceted implementation strategy. Additional interviews with school administrators or lead special educators are likely to surface critical organizational factors that can serve as design constraints for any subsequent redesign solution [102,103].

As described earlier, interviews can be supplemented through observation methods to better understand interactions in real-world settings. Projects can use an adapted form of TAP, where participants (eg, clinicians or clients) and researchers watch recordings of sessions while the participant explains what they were thinking in the moment. This approach can offer additional suggestions for improvement on the design of a clinical intervention or offer ideas for tools that could support the clinician during implementation. Interviews can also supplement comparative testing (eg, A/B testing) to explore and evaluate a broader landscape of design options and reach more robust solutions. A/B testing is an evaluation method in which ≥2 versions of a prototype are compared sequentially or in parallel to determine which version is easier to use and better meets user needs [104]. For example, R34 BRISC will build prototypes of digital asynchronous learning modules for novel users as well as posttraining support tools; initial prototypes will undergo comparative testing to finalize solutions to be evaluated in the Test phase. The pragmatic applicability and match of potential designs to the targeted service environments and resource constraints will be systematically addressed.

Participant Research Burden, Incentive Appropriateness, and Research Satisfaction

At the end of the Test phase, projects are expected to measure the burden of participation in the study. This instrument includes 6 questions to understand participants' perceived burden of participating in the study, appropriateness of the level of compensation offered, and overall satisfaction with the study experience. This information will be used to help improve future protocols. Response frequencies will be tabulated for the 4 close-ended responses and themes will be summarized from open-ended responses.

Adherence to DDBT Process (DDBT Fidelity and Cost Measure)

All projects are expected to complete a Fidelity and Cost survey in REDCap about their application of HCD techniques at the end of each DDBT phase. We are developing the survey to systematically collect data on how the DDBT framework guides clinical intervention and implementation strategy redesign and link design activities with project goals. To facilitate teams in drawing on a range of methods, the Fidelity and Cost survey focuses on understanding which goals of each DDBT process teams completed (Figure 1) and the methods they used to support each goal. We will conduct descriptive statistical analyses and content analysis of data to understand the frequency of goals completed and HCD strategies used, links between strategies and goals, and modifications made to strategies during their use.

We will measure the costs of applying DDBT to help understand the resource requirements involved in its use, which can be a major challenge of HCD and coproduction methods [105]. Projects are expected to report total costs of redesign, reported through a Fidelity and Cost Survey in REDCap at the end of each phase (this is optional for R03 projects). We will aggregate activity-based costs (eg, time to create, complete, and analyze each activity; participant payments or time) across individuals, use budgets or other institutional records to assign hourly costs by role, and then add in any fixed costs (eg, materials and activity-specific software). We will calculate total DDBT costs, as well as phase-specific and activity-specific DDBT costs. Analyses will follow best practices by placing all US dollar values onto the same metric, including an index year to account for inflation; local or national average cost-of-living values to account for geographic variation in prices; and discounting of costs from different years due to preferences for delayed over immediate costs. We will conduct sensitivity analyses to examine the robustness of our cost estimates [106,107] by identifying areas of uncertainty in measuring units and prices for our ingredients, and then calculating costs across a range of plausible values (eg, we can substitute limits of 95% CIs for uncertain prices).

Team Collaboration, Trust, and Respect

At the end of each DDBT phase, R01 and R34s team members are expected to complete a survey that assesses satisfaction with the collaboration, impact of collaboration, trust, and respect. This survey is modeled after the Transdisciplinary Tobacco Use Research Center's measure of Team Collaboration and Transdisciplinary Integration, which assesses satisfaction with the collaboration, impact of collaboration, trust, and respect [108]. Continuous review of outcomes will allow for critical assessment and course correction as needed and recommended by these bodies. Participation is confidential, and teams will receive an aggregate report of the number of team member participants and average scores for each item. Any free-response comments are additionally summarized. We will encourage teams to discuss results to improve their projects.

Community Participation in Research

The collaboration survey questions described earlier will be administered with additional questions to characterize the extent to which redesign teams engage users in a localized DDBT process. This instrument is based on an existing measure of community participation in research [109,110], which has been modified to target the design of clinical interventions and implementation strategies across 6 dimensions: identification of design issues, design activities, use of resources, design methods, indicators of success, and sustainability. Redesign teams will complete the measure at or near the end of each DDBT phase and then discuss ratings in an interview.

Investigator Satisfaction With the Support They Receive From the Center

At the conclusion of projects, we will ask investigators to share their level of satisfaction with support from UWAC through a 5-item Likert survey adapted from a survey used by the University of Washington IMPACT Center [111]. We intend to use these data to improve how the Methods Core team provides projects technical support.

Data Analysis

The Methods Core team provides data management and guidance on all DDBT constructs. For Aim 3, fundamental

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comparisons are the differences in DDBT mechanisms (usability, engagement, and appropriateness) and implementation outcomes (adoption, reach, adaptation, and fidelity [and sustainment for the R01 PST]) for the original (unadapted) clinical intervention and implementation strategy versus the DDBT-informed (localized) clinical intervention and implementation strategy. We will conduct a (1) qualitative multiple case study analysis and (2) quantitative meta-analysis across projects. Case studies will examine each project's context, implementation, mechanisms, and outcomes.

For each project, we will also develop analytical summaries to facilitate between-project comparisons. Using the constant comparative method [112], we will compare projects to group common and divergent themes. The meta-analytic synthesis will increase our inferential ability by combining results from the underpowered R34s. For the meta-analysis, each project's mechanism and outcome will be summarized as a Cohen *d* effect size comparing localized DDBT with original clinical intervention and implementation strategy and corresponding 95% CI, using random effects weighting by the inverse of the within- and between-studies variance. Standard data screening and adjustments will be made to the data (eg, to limit the effect of outliers, they will be winsorized). Each project will be additionally advised on how to address possible confounders in analysis and reporting. For instance, projects will be encouraged to use naive participants in the Design and Build and Test phases, recognizing that adaptations of smaller elements of complex clinical interventions may require the participation of experienced participants during the Design and Build phase. In addition, randomization will occur at appropriate levels to avoid contamination by intralevel communication. Nonmonotonic missing data will be addressed via inverse probability weighting or multiple imputation, as appropriate [113]. The Methods Core will aggregate these data across projects into a series of working meta-analyses of the effectiveness of DDBT on each mechanism and outcome.

Finally, determining whether a DDBT-modified clinical intervention and implementation strategy leads to better implementation and clinical outcomes is ultimately a question of mediation. Although the initial R34 and R03 studies are not likely to yield large sufficient sample sizes to meaningfully test such an implementation mechanism question, the R01 PST will provide a direct test of the DDBT theory of change (Figure 2). Aggregating project data over time will allow us to eventually test a range of mediation-focused hypotheses via multivariate network meta-analyses.

Incorporating DEI

During UWAC 2.0, we are improving the integration of DEI initiatives throughout Center activities. Projects selected for UWAC 2.0 and pilots must demonstrate potential substantial impact on clinical or public health outcomes, especially for historically marginalized communities. The Methods Core team provides mentorship on incorporating and adapting methods so that teams are positioned to conduct research that respects diverse populations and maximizes community benefits. Project teams will be provided training and consultation on the Adapting strategies to promote implementation reach and equity method, a 3-step process for adapting implementation science to promote equity, and expertise in methods for explicitly incorporating equity into the measurement of implementation outcomes [114]. We will also collaborate with projects to ensure diverse representation and decision-making during the DDBT phases, crucial stages where diverse viewpoints and demographically representative samples are essential. To facilitate diverse engagement, we will offer resources on building equitable research-practice partnerships, contextualizing implementation science to specific communities, and enhancing community collaborator capacities for community-engaged research. Consultation on quantitative critical research [115] will be provided to examine the treatment of race within quantitative methods and support equity testing through disaggregation, moderator exploration, and mixed methods triangulation.

UWAC additionally supports faculty and staff as part of its DEI work. The center team engages with historically marginalized investigators in planning and conducting center activities so that DEI efforts are integrated throughout center mentoring, pilot funding, methods support, and support for investigators planning future proposals. These measures include enhancing communication strategies based on team science [77] and avoiding a "minority tax," which refers to assigning additional responsibilities to marginalized or underrepresented team members to promote diversity [116,117]. The Methods Core team also advises investigators on using patient-centered and nonstigmatizing language when reporting findings.

Ethical Considerations

The University of Washington Institutional Review Board (IRB) approved materials and procedures for all 4 core projects and deemed projects minimal risk by June 2024 (PST-Aid: STUDY00017272; RUBIES: STUDY00017261; TF-CBT: STUDY00017262 and STUDY00019451; and BRISC: STUDY00017263 and STUDY00019682). All studies follow best practices across studies: review and collect informed consent and Health Insurance Portability and Accountability Act authorizations (when not waived) from participants; collect parental assent for individuals <18 years of age; compensate participants financially for their time and, when appropriate, with continuing education credits; and ensure participants are aware that they may opt out or leave the study at any time. When personal health information (eg, name, date of birth, and contact information) is collected, we preserve participant privacy and confidentiality by storing those identifiers separately from the study data and only linking them to study data via a code. The Methods Core team will provide support to pilot project teams on institutional review board applications after studies are funded.

Results

Overview

UWAC 2.0, including the 4 core projects detailed in Multimedia Appendix 3, received funding in June 2023. We provide a brief synopsis of each study's progress as of January 2025 in the subsequent sections. Across studies, as well as the to-be-funded R03 pilots, we anticipate DDBT will result in changes to the clinical intervention and implementation strategy mechanisms,

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proximal implementation outcomes (ie, adoption, fidelity, reach, and adaptation), and clinical outcomes.

R01 PST-Aid

This study began in the Design and Build phase, as the Discover phase was completed during an R34 in UWAC 1.0. For the Discover phase, the study team has completed a codesign workshop and user testing with patients and providers from a nonprofit, health informatics network with independent community-based health centers. The study is beginning the Test phase, and the team is recruiting the first cohort of providers. Providers will be randomized to receive training in either PST implementation as usual (ie, training and sessions supported by paper worksheets for practitioners and clients to use as they complete PST) or PST-Aid (ie, a web-based app that promotes practitioner-client collaboration in the use of PST for goal setting and action planning).

R34 TF-CBT

At the time of submission, the study team has completed a task analysis of unadapted TF-CBT to prioritize components to develop scenarios for testing with students and school-based mental health practitioners. The study has finalized TF-CBT user-testing scenarios and are actively recruiting students and practitioners to begin the first of 3 waves of testing for the study. These data will then inform the redesign of TF-CBT, which aims to be more usable in school settings.

R34 RUBIES

Discover and Design and Build phase study activities, including focus groups, cognitive walkthroughs, and user testing with paraeducators and other school personnel (eg, principals and teachers), are complete. These data are being used to inform the Test phase where the study team is recruiting paraeducators and students and their caregivers to begin RUBIES training. Once recruited, this Test phase will include a 2-year randomized controlled trial enrolling paraeducators and students who will then be randomized to 1 of 2 implementation strategies: RUBIES-Individual or RUBIES-Team.

R34 BRISC

This study is scheduled to begin in April 2025, and the study team has received institutional review board approval.

Discussion

Charting New Research Directions

Our vision is to address persistent issues with usability, engagement, and appropriateness that are barriers to clinical intervention and implementation strategy use by drawing from the fields of HCD and implementation science. The first iteration of the center advanced our understanding of how DDBT can guide clinical intervention and implementation strategy adaptations for uptake in historically marginalized communities. During UWAC 2.0, we aim to continue serving as a multidisciplinary incubator to find viable solutions for improving implementation of clinical interventions and implementation strategies using DDBT through the R01, R34s, and pilot projects. Table 1 summarizes potential outputs and future directions by aim. Focusing on usability, engagement, and appropriateness and providing and testing ways to measure engagement in a clinical intervention and implementation strategy context is particularly novel. UWAC 2.0 will further test the robustness of the DDBT theory of change, expand the potential evidence base for its utility in combining HCD and implementation science for clinical intervention and implementation strategy redesign, and add to the field's understanding of how to apply DDBT to a variety of clinical intervention and implementation strategies and contexts.

Our experiences underscore a benefit of developing additional resources for DDBT, HCD, and implementation science. UWAC 1.0 outputs contributed to foundational conversations on the intersection of HCD and implementation science and produced potential pathways to address conceptual overlap and distinctions [43] and terminology [42]. We additionally developed resources such as CWIS [39], IUS [37], the ISUS [39], and a typology of modification targets and usability issues [53]. We have accumulated substantial experience adapting common HCD methods for different contexts and communities, and we hope these adaptations can support future teams in their use these methods. We plan to build on these methodological advancements, which have been used beyond the UWAC team by a broader research community interested in HCD and implementation science methods and measurement. As we learn with UWAC 2.0 project teams, we will continue to identify and develop additional resources for UWAC project teams and the broader research community on specific methods, team science, equity-oriented design practices, and grant writing. Developing additional resources aligns with the Methods Core team shifting to a consultation model on using the DDBT framework during UWAC 2.0. UWAC projects receive technical support from the Methods Core team with greater emphasis on building local capacity to apply DDBT rather than having the Methods Core team members conduct some of the DDBT activities.

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Table 1. Expected center-level outputs and future directions by aim.

Aim	Expected outputs	Potential future work
Aim 1: identify clinical intervention and implementation strategy modification targets to improve usability, engagement, and appropriateness in accessible nonspecialty settings (Discover phase)	• Updated Typology of Modification Targets that expands the previously identified usability issue categories [53] • New insights on engagement and appropriateness issues in clinical intervention and implementation strategy redesign	• Incorporate additional findings from non–UWAC[a]-funded projects that have used the typology of modification targets
Aim 2: develop redesign solutions with local teams to address clinical intervention and implementation strategy modification targets (Design and Build phase)	• Updated Library of Redesign Solutions	• Recommendations on how to approach measuring engagement and appropriateness with a focus on clinical intervention and implementation strategy redesign
Aim 3: determine if redesign affects changes in usability, engagement, and appropriateness (Test phase)	• Integrated cross-project analyses to demonstrate the impact of DDBT[b]-informed redesign	• Further expansion of DDBT and associated methods to new domains in health and social services

[a]UWAC: University of Washington Advanced Laboratories for Accelerating the Reach and Impact of Treatments for Youth and Adults with Mental Illness Center.

[b]DDBT: Discover, Design and Build, and Test.

Limitations

UWAC 2.0 and the DDBT framework represent a robust effort to integrate HCD with implementation science, although several methodological limitations merit consideration. The standardized measures we are using to assess usability, appropriateness, and engagement have evidence of psychometric soundness, but these measures have not yet been evaluated in all the contexts in which they will be applied. Redesign solutions developed by local teams may rely primarily on context-specific adaptations, which may not generalize to other settings and may not address systemic barriers that impact usability or accessibility. Therefore, reactive modifications (ie, primary outcome) needed to address additional barriers may not be reduced. In this work, there is a tension between our desire to standardize DDBT phases and measures, to facilitate center-wide learning, with promoting the adaptability and flexibility to adapt to specific goals, contexts, and populations that is necessary for good design projects. This, combined with the variability of research project contexts, the small sample sizes of redesign teams and subjective nature of the proposed mechanisms may impede our ability to make inferences across projects.

Conclusions and Impact

There is a pressing need to ensure that clinical interventions and implementation strategies are easily implementable and meet the needs of the communities they aim to help. Integrating HCD and implementation science offers promising approaches to tackle this challenge. UWAC 2.0 expands and strengthens our efforts to ensure that accessible community service settings and marginalized communities see the benefit of decades of research on effective clinical interventions and implementation strategies.

Acknowledgments

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Data Availability

Clinical outcome data for the R01s and R34s will be made publicly available through the National Institute of Mental Health National Data Archive. The quantitative datasets generated and analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

All authors contributed to conceptualizing the study. ARL, SAM, and MDP led funding acquisition and created the protocol with support from the team on methodology. MDP led plans for data curation and formal analysis. ARL, SAM, BM, and TA wrote the original draft with review and editing support from all authors. BM and KPO oversaw project administration.

Conflicts of Interest

KB reports royalties from Oxford University Press.

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Multimedia Appendix 1
Peer-review report by the National Institute of Mental Health Special Emphasis Panel - National Institute of Mental Health - Advanced Laboratories for Accelerating the Reach and Impact of Treatments for Youth and Adults with Mental Illness (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 211 KB - resprot_v14i1e65446_app1.pdf]

Multimedia Appendix 2
Summary of projects.
[DOCX File , 32 KB - resprot_v14i1e65446_app2.docx]

Multimedia Appendix 3
Center measures and guidance.
[DOCX File , 29 KB - resprot_v14i1e65446_app3.docx]

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Abbreviations

BRISC: Brief Intervention for School Clinicians
CFIR: Consolidated Framework for Implementation Research
CWIS: Cognitive Walkthrough for Implementation Strategies
DDBT: Discover, Design and Build, and Test
DEI: Diversity, Equity, and Inclusion
FRAME: Framework for Modifications and Adaptations of Evidence-Based Interventions
FRAME-IS: Framework for Modifications and Adaptations of Evidence-Based Interventions for Implementation Strategies
HCD: human-centered design
HCI: human-computer interaction
IAM: Intervention Appropriateness Measure
ISUS: Implementation Strategy Usability Scale
IUS: Intervention Usability Scale
Neuro-QOL: Quality of Life in Neurological Disorders
NIH: National Institutes of Health
NIMH: National Institute of Mental Health
PI: principal investigator
PST: Problem Solving Treatment
PST-Aid: Problem Solving Treatment-Aid
REDCap: Research Electronic Data Capture
RUBIES: Research Units on Behavioral Intervention in Educational Settings
SUS: System Usability Scale
TAP: think-aloud protocol
TF-CBT: Trauma-Focused Cognitive Behavioral Therapy
UWAC: University of Washington Advanced Laboratories for Accelerating the Reach and Impact of Treatments for Youth and Adults with Mental Illness Center

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Protocol

Investigation of Information Overload in Electronic Health Records: Protocol for Usability Study

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Abstract

Background: Electronic health records (EHRs) have been associated with information overload, causing providers to miss critical information, make errors, and delay care. Information overload can be especially prevalent in medical intensive care units (ICUs) where patients are often critically ill and their charts contain large amounts of data points such as vitals, test and laboratory results, medications, and notes.

Objective: We propose to study the relationship between information overload and EHR use among medical ICU providers in 4 major United States medical centers. In this study, we examined 2 prominent EHR systems in the United States to generate reproducible and generalizable findings.

Methods: Our study collected physiological and objective data through the use of a screen-mounted eye-tracker. We aim to characterize information overload in the EHR by examining ICU providers' decision-making and EHR usability. We also surveyed providers on their institution's EHR to better understand how they rate the system's task load and usability using the NASA (National Aeronautics and Space Administration) Task Load Index and Computer System Usability Questionnaire. Primary outcomes include the number of eye fixations during each case, the number of correct decisions, the time to complete each case, and number of screens visited. Secondary outcomes include case complexity performance, frequency of mouse clicks, and EHR task load and usability using provided surveys.

Results: This EHR usability study was funded in 2021. The study was initiated in 2022 with a completion date of 2025. Data collection for this study was completed in December 2023 and data analysis is ongoing with a total of 81 provider sessions recorded.

Conclusions: Our study aims to characterize information overload in the EHR among medical ICU providers. By conducting a multisite, cross-sectional usability assessment of information overload in 2 leading EHRs, we hope to reveal mechanisms that explain information overload. The insights gained from this study may lead to potential improvements in EHR usability and interface design, which could improve health care delivery and patient safety.

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KEYWORDS

electronic health records; information overload; eye-tracking; EHR usability; EHR interface

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Introduction

Electronic health records (EHRs) can be a source of information overload for providers; however, the mechanisms that explain overload and their link to patient safety are not understood. Information overload in the EHR is associated with missing critical information that affects the decision-making process [1-3]. Studies have relied on secondary data analysis or subjective measures to assess the effect of information overload on decision-making processes; however, the use of physiological and objective data to study information overload has shown great potential in other domains [4]. We propose using eye-tracking approaches coupled with objective patient safety measures to investigate current EHR design flaws [5-9]. These methods reveal mechanisms that explain overload, such as fatigue and degradation in performance. Furthermore, poor EHR interface design contributes to inefficiencies [10], frustration [11], and medication errors [12].

Although advantageous over paper-based documentation, EHR use is associated with new physician-related challenges that may increase medical errors [13]. EHR interface design can lead 50% of providers to make an error when ordering medication tapering [12]. In addition, too much information contributes to patient safety risks, such as 30% of providers missing test results in the EHR, leading to care delays [2,14]. Information overload increases cognitive load and error rates among physicians during clinical simulations. Common issues contributing to information overload included an overabundance of clinically irrelevant information, poor data presentation, and excessive alert notifications [15]. However, we have limited knowledge of the relationship between information overload and EHR usability.

Our study uses objective eye-tracking data along with self-reported task load and usability surveys to better understand the challenges Intensive care unit (ICU) providers face in using EHRs to provide patient care. By measuring providers' performance, information seeking load, and information processing load, we aim to characterize information overload in the EHR by examining decision-making and usability outcomes.

Methods

We conducted a multisite, cross-sectional usability assessment of information overload in 2 leading EHRs among medical ICU providers in 4 US medical centers. Between the 4 sites, 2 leading EHR systems are used. The ICUs at the medical centers vary in terms of the catchment area; however, all 4 medical centers in the study are considered level I trauma centers, each with level 3 ICU support. The number of ICU beds between the 4 medical centers ranges from approximately 74 to 200 ICU beds each.

Providers will be recruited by the individual study site teams at each medical system using emails, flyers, and word of mouth. Interested providers will be asked to complete an initial screening survey before scheduling a session to ensure that they are an ICU provider or, if they are a resident, that they have completed at least one ICU rotation.

The sessions will occur in a simulation laboratory or private space that mimics the ergonomics of natural inpatient settings. Our team used the standard computer screen in each practice setting, with ICU-like ergonomic placement, ambient lighting, and seating. To ensure standardization among the cases, the lead investigators at each site met via Zoom (Zoom Video Communications) to determine a rubric for patient records to be included in the study. The study team created 4 ICU patient cases for inclusion, based on reviews of our 2 domain experts. Next, the domain experts created a set of universal experimental questions and tasks for providers to complete for each patient.

Before each session, the usability specialist explained the study and consent forms to providers, assuring them that the goal is to assess EHR usability rather than clinical knowledge. Participants are informed that their participation is voluntary and that they can decline to participate at any time. After the informed consent has been obtained, each provider will be asked to complete 3 pages of paper surveys.

We then ask providers to complete a basic calibration exercise while looking at the monitor which allows the eye-tracking software to be calibrated to each provider's eye shape and eye size. We record pupil diameter and fixation points on the screen continuously during the study session. All sessions used the same screen-based eye tracker.

Each provider was then logged in to their institution's EHR environment, where 4 simulated ICU patient records are presented in random order to eliminate selection bias. Providers reviewed 1 patient case at a time and were encouraged to review the patient chart as if they were prerounding on this patient, using their typical workflow. The provider then indicated to the research assistant (RA) when they completed their chart review and were ready to begin a series of question-and-answer activities about that specific patient. The RA asked the provider a series of questions in which the provider responded verbally, and the RA recorded the answers using both audio and written recordings. Providers were allowed to navigate through the EHR to answer these questions. After completion of question-and-answer activities, the provider then reviewed the next patient record. A process map detailing the study procedure from enrollment to usability session can be seen in Figure 1.

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Figure 1. Process map illustrating the various study steps from recruitment to completion of the usability session. CSUQ: Computer System Usability Questionnaire; ICU: intensive care unit; NASA-TLX: National Aeronautics and Space Administration–Task Load Index; Q and A: question and answer.

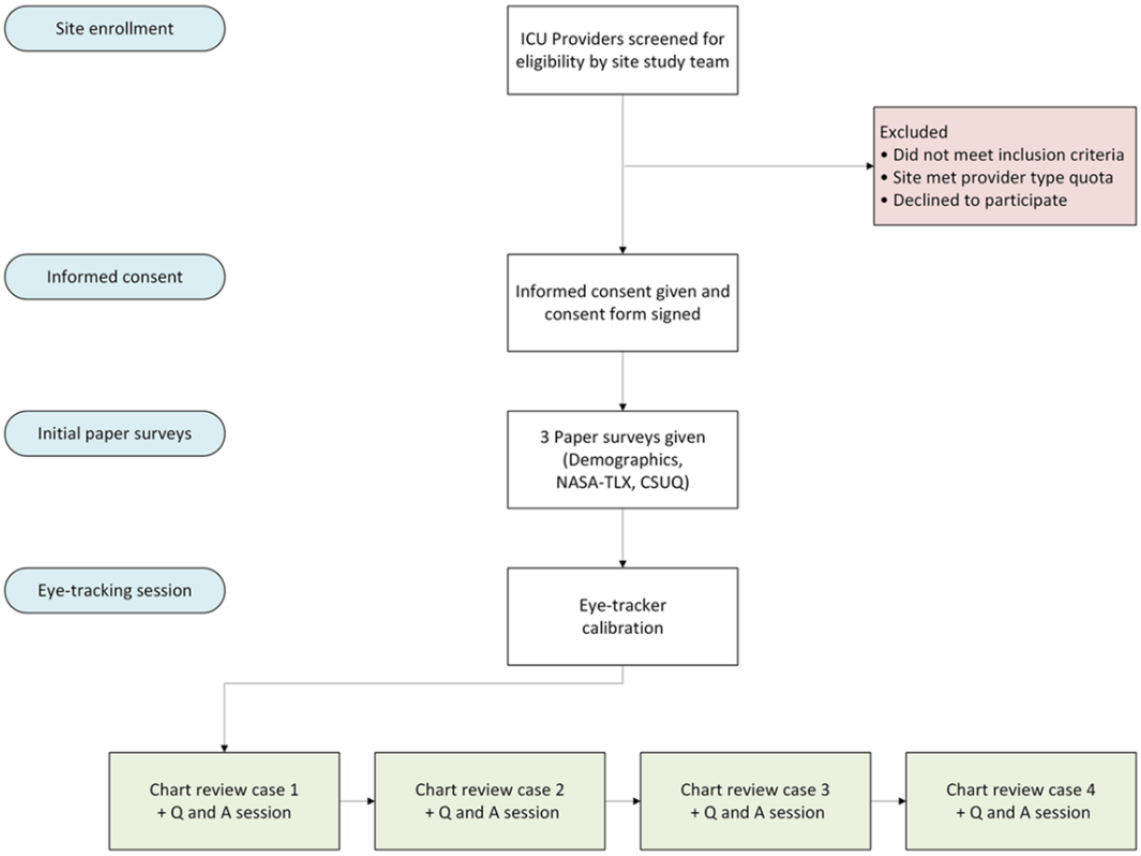

Patient Cases

A team of critical care physicians created 4 patient cases. Each patient was representative of a patient that could be hospitalized in an ICU setting. Of the 4 patients, 2 were considered basic or "standard" ICU patients while 2 were considered to be complex patients. The 2 basic patients were less critically ill, not currently ventilated, on fewer medications, and had fewer abnormal laboratory values. The 2 complex patients were critically ill with many abnormal laboratory values, on the ventilator with poor oxygenation, and on complicated medication regimens.

The nurse informatician on the study team worked with the primary investigator and each site's study team to build the patient cases in their institution's EHR test environment. The same 4 cases were used at all study sites, and the nurse informatician monitored case builds to ensure consistency and accuracy across study sites.

Case Questions

Providers were asked 5 questions for each patient following their preliminary chart review. These questions were created by a critical care physician (TB) and reviewed by a critical care physician team before data collection. Questions were written to ensure the answer is present within the EHR and that providers at different levels of experience can realistically locate the answer. While some questions were considered more basic and only needed 1 EHR screen or data point to answer, other questions were more complex and required synthesizing multiple data points or locating information not frequently accessed. This approach allows us to analyze the time it takes to answer these questions and how many EHR screens and mouse clicks each provider uses before answering a question. Questions were scored as either correct, partially correct, or incorrect by the team nurse informatician. Alternate answers will be reviewed by a critical care physician (SC) for scoring.

Sample

Our initial goal was to recruit 80 ICU providers, 20 at each site, with the following distribution: 15 physicians and 5 advance practice providers (APPs). The physician group will be divided into 3 subgroups: 5 attending physicians, 5 fellow physicians, 5 resident physicians, and 5 APPs including nurse practitioners and physician assistants. Our actual recruitment was 81 ICU providers, comprised of 53 physicians and 28 APPs. Each study team's local RAs circulated departmental emails and flyers at each site. They provided interested individuals with a link to an online calendar showing available time slots to facilitate appointment scheduling. Once an appointment was scheduled, the RA emailed each participant their appointment time and location with a map, as well as a contact number for same-day inquiries or cancellations. Inclusion criteria: ICU physicians and APPs on active full-time ICU service OR Residents who have completed at least 1 ICU rotation, use an institutional EHR, and speak English.

Statistical Power

The design effect arising from the clustering within-person inherent to the study's design is estimated using the following formula: $D_{eff}=1+(m-1)$, where m=average cluster size (4 cases)

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and *P*=intraclass correlation coefficient (ICC). Assuming an ICC of .6 (a common ICC for similar intensive repeated measures designs), the application of this equation results in D_{eff} of 1.09, for an effective sample size of 294 (320/2.8). In a multivariable linear regression context assuming N=114, 5 person-level effects, 3 case level effects, a 2-tailed critical *P*=.05, and 80% power, the minimum detectable effect size is represented by a Cohen f^2 of 0.10, which is considered a small effect. In a multiple logistic regression with 2 tailed critical *P*=.05 and 80% power, the minimum detectable odds ratio is 3.23, which is considered a medium-sized effect.

Materials and Software

To measure the extent and effect of EHR information overload, we used several tools during the 1-hour sessions.

Providers were asked to complete 3 paper surveys before the eye-tracking session. The first survey asked basic demographic questions, including age, gender, years since graduation (medical school or APP schooling), years of experience with their institution's EHR, and the estimated number of hours they use their institution's EHR each week. We also asked the providers if they are on service that day (pre- or post-usability session) and to rate their level of sleepiness and stress on a Likert scale. The second paper survey used was the NASA (National Aeronautics and Space Administration) Task Load Index (NASA-TLX) which asked providers to rate the task load of their institution's EHR, including how mentally and physically demanding it is to use and their level of satisfaction and confidence with using the EHR [16]. The third and final paper survey was the Computer System Usability Questionnaire (CSUQ) which asked providers to rate their satisfaction with their institution's EHR system including questions about usability, ease of use, the system interface, and overall functionality [17].

Our study used a noninvasive screen-based eye tracker to provide further insights into a provider's cognitive processing during the sessions. The Tobii Pro Fusion is an advanced eye-tracking system with 2 eye-tracking cameras taking up to 250 images per second to ensure accuracy. The Pro Fusion mounts onto the bottom of any monitor, allowing us to record eye-tracking data seamlessly. The Tobii eye-tracker was used with Tobii Pro Lab software to create a seamless recording that includes eye-tracking data and screen recording. Used by renowned researchers in medicine and psychology [18,19], the Tobii eye-tracker and software will provide us with fixation points, gaze areas, and eye movement type. These measures will provide us with insight regarding providers' information processing behaviors, in particular, the relationship between fixation points (a measure of concentration) and the outcome variable (decision-making accuracy). We have expertise in analyzing large and complex data sets from Tobii, considered the most accurate eye-tracking device manufacturer in the world.

Outcomes

Primary outcomes are cognitive overload (ie, fixation points), usability (clicks and completion time), and performance score. Secondary outcomes are the provider reported EHR workload and usability using the NASA-TLX and computer system usability questionnaire surveys.

To characterize information overload, we will explore under what conditions providers experience EHR information overload. We will accomplish this by determining which patient cases create the highest level of information overload, indicated by the least number of eye fixations, meaning a loss of concentration. We also want to understand the consequences of a lack of concentration as it relates to decision accuracy and time. Understanding the underlying factors and the consequences of information overload will fill a significant gap in the literature.

Analytical Plan

Each participant will receive a single score for each question determined by the domain expert (0: incorrect, 0.5: partial, and 1: correct). Correct decisions are the aggregate of the correct answers, and errors are the aggregate of the incorrect answers. For each participant, we will compute a score for each patient case and a total score for all the patient cases. Case scores will depend on the number of questions asked, such that if a case has 5 questions to be answered, the total score of this case will be equivalent to the highest possible points (5).

Our past work will inform ways to compute case scores [10,12]. Responses and scores will be assigned by 2 domain experts (the site-Principal Investigator and a senior ICU provider).

Eye-tracking data gives the frequency and duration of fixations for each participant. We will calculate participants' fixation points based on (1) total fixations for the study, (2) total fixations per patient case, and (3) total fixations per EHR screen visited.

We will compute descriptive statistics for patient and case characteristics, employing chi-square tests, *t* tests, and ANOVAs to examine between-group differences, where appropriate. We will examine differences between provider types (physicians and APPs), as well as between sites. Given the nested nature of the data (ie, repeated case assessments nested within providers), we will use multilevel modeling as the primary analytic approach. Each patient case will be coded based on the days of ICU stay and the presence or absence of key characteristics such as vent settings and intake and output, to determine the level of complexity. Case variables will be entered into the model as case-level (Level 1) predictors. Models will also account for person-level (Level 2) factors such as participant gender, age, clinical role, site, and years of EHR experience. We will use SAS (version 9.4; IBM Corp) using PROC MIXED for continuous outcomes and SAS PROC GLIMMIX for binary and count outcomes.

Ethical Considerations

Recruitment and site testing occurred sequentially, such that the study was implemented at one site at a time, allowing the study team to be present on site to add organization to the data collection process. Each participant was required to read and sign a consent form specific to their medical center, witnessed by a representative of that medical center. Participants were allowed to opt out of the study at any time. We used one

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screen-based eye-tracker device for data collection at each site. We recruited through flyers and departmental email communications at each site. Participants were compensated with a US $100 gift card for their participation. All data collected were deidentified and study participants and their data were assigned a unique identification number. Study data entry and management systems are secured and password protected to ensure participant privacy and confidentiality. The University of North Carolina at Chapel Hill's institutional review board (IRB) approved this study (IRB #20-3384).

Results

This EHR usability study was funded in 2021. The study was initiated in 2022 with a completion date of 2025. Data collection was completed in December 2023 with a total of 81 provider sessions recorded. The primary analysis is ongoing and expected to be published in early 2025.

Discussion

Study Significance and Strengths

This study aims to characterize information overload in the EHR and uncover possible improvements to EHR interfaces and user skills. We will deploy a mixed methods approach to better study providers' reactions to information overload in the EHR. We will use usability evaluation metrics, eye-tracking, and surveys to assess the aforementioned relationship. The use of physiologic data, namely eye-tracking, will produce new knowledge about providers' cognitive performance during EHR interaction. Eye-tracking will allow us to quantify fixation points, a measurement of cognitive overload, as providers interact with basic and complex ICU patient cases. In this study, we examine the 2 most prominent EHR systems in the US, which will generate reproducible and generalizable findings that can be applied to clinical settings using an EHR system. Another strength of this study is the inclusion of different professional roles, including residents, APPs, fellows, and attending. This diverse sample will enable subgroup analysis to test if information overload has similar effects on different professional roles.

Examining information overload within EHRs will demonstrate the critical impact of EHR usability on clinical decision-making, especially in high-pressure environments like ICUs. By measuring and assessing information overload, we can identify design opportunities in EHRs that may improve providers' ability to access and process vital information. This knowledge enables health systems to enhance patient safety and the quality of care by tailoring training and support systems that address specific challenges faced by providers. Future research needs to involve longitudinal studies to evaluate the long-term effects of information overload on clinical performance and patient outcomes. Incorporating qualitative methods, such as interviews with providers, will complement our quantitative findings to create a comprehensive understanding of EHR interactions. Potential interventions may include the implementation of information visualization within EHRs to facilitate information processing, implementing tailored training programs for providers, and developing integrated decision support tools. These research goals aim to enhance EHR usability, reduce the cognitive burden on health care professionals, and promote a safer and more efficient health care delivery system.

Limitations

Although we proposed adequate recruitment numbers, we understood that recruiting the exact number of participants in each professional role may be challenging. Alternatively, we expanded recruitment to include medical ICUs in other affiliated hospitals within the same health care system. All study sites include multiple hospitals to enable expanding recruitment within the same system and under the same IRB. Potential bias may occur from recruiting participants who are technology enthusiasts. We attempted to mitigate this bias by predefining a quota for every professional role to ensure we have representation from junior and senior providers. This mix of roles was done to include persons with varying degrees of technological astuteness.

Variations in EHR design and performance may affect the study findings. We account for this limitation by including the 2 most prominent EHR systems and 4 different medical centers, leading to more generalizable findings. The study protocol was not published earlier to keep the study design and the components of the patient cases undisclosed to avoid introducing bias to potential participants.

Future Directions

We will use our findings from this study to guide future research on information overload in the EHR. Observations of the current opinions and functionality of each of the 2 institutional EHRs will be used to prepare for a randomized controlled trial using the same 4 US medical centers. This randomized controlled trial will compare the current institutional EHR's interface with a visualization dashboard, examining the differences in provider efficiency and fatigue.

Conclusions

Our study aims to characterize information overload in the EHR by examining decision-making and usability outcomes among medical ICU providers. By conducting a multisite, cross-sectional usability assessment of information overload in leading EHRs, we hope to reveal mechanisms that explain overload, such as fatigue and degradation in performance. Through the use of eye-tracking approaches coupled with objective patient safety measures, we aim to investigate current EHR design flaws and their impact on decision-making processes. The insights gained from this study will contribute to a better understanding of the relationship between information overload, EHR usability, and patient safety, ultimately leading to potential improvements in EHR interface design and health care delivery.

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Acknowledgments

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Data Availability

The data that support the findings of this study are not openly available due to reasons of sensitivity and are available from the corresponding author upon reasonable request. Data are located in controlled access data storage at the University of North Carolina at Chapel Hill.

Authors' Contributions

All authors contributed to the conceptualization, methodology, and design of the study and established the hypothesis. SK and JM wrote the first draft of the manuscript. All authors contributed to the writing review & editing. All authors were invited to revise the manuscript and approved the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

APP: advance practice provider
CSUQ: Computer System Usability Questionnaire
EHR: electronic health record
ICC: intraclass correlation coefficient
ICU: intensive care unit
IRB: institutional review board
NASA-TLX: National Aeronautics and Space Administration–Task Load Index
RA: research assistant

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Protocol

Digital Mental Health Screening, Feedback, and Referral System for Teens With Socially Complex Needs: Protocol for a Randomized Controlled Trial Integrating the Teen Assess, Check, and Heal System into Pediatric Primary Care

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Abstract

Background: Teens with socially complex needs—those who face multiple and potentially overlapping adversities—are disproportionately affected by several barriers to mental health screening and treatment. Pediatric primary care (PPC) is a typically low-stigmatized setting for teens that is visited at least annually. As such, implementing digital mental health tools (DMH), as low-intensity treatments in PPCs may increase the reach of such tools for teens with socially complex needs.

Objective: This study aimed to evaluate the Teen Assess, Check, and Heal (TeACH) System in comparison to a control condition while integrated into PPCs at 2 Medical Centers serving teen patients in Chicago, Illinois. Through collaboration with key players throughout the design and implementation planning phases, the TeACH System is hypothesized to increase teen patient self-reported engagement with DMH and address specific individual-level barriers to mental health care, compared with a digital psychoeducation control condition.

Methods: Eligible participants will be recruited through PPC clinics housed within the University of Illinois Chicago (UIC) and Rush University Medical Center (RUSH). Recruitment involves invitations from research staff members and primary care clinicians and staff members, as well as posting flyers with QR codes at the specified clinics. All participants complete a brief demographic survey, baseline survey, and Kiddie-Computerized Adaptive Tests Anxiety Module. Participants are randomized to receive either the control condition (digital evidence-based workbook) or the intervention (TeACH System Feedback and Resources). All randomized participants will then be invited to complete an immediate and 1-week follow-up survey. The primary outcomes assess changes in engagement with DMH (ie, likelihood to use DMH for anxiety and actual DMH use) and individual-level barriers to mental health care (ie, symptom understanding and confidence to act). Descriptive analyses will be conducted to characterize the sample and usability ratings of the TeACH System. Linear or generalized linear mixed effects regression models will examine differences in primary outcomes over time.

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Results: Recruitment began in July 2024 and data collection is expected to be completed by August 2025. To date, 122 teens have assented to complete study activities, 80 have been randomized (an additional 24 teens have had subthreshold anxiety symptoms and were therefore not randomized), and 42 teens have completed the 1-week follow-up assessment.

Conclusions: This study will provide preliminary feasibility data that may inform how the TeACH System and other DMH low-intensity treatments might better engage and support teens with socially complex needs.

Trial Registration: ClinicalTrials.gov NCT05466929; https://clinicaltrials.gov/study/NCT05466929

International Registered Report Identifier (IRRID): DERR1-10.2196/65245

(JMIR Res Protoc 2025;14:e65245) doi:10.2196/65245

KEYWORDS

teens; primary care; digital mental health; low intensity treatments; disparities

Introduction

Background

Even before the multiple endemics occurring since 2020, pediatric mental health disorders and symptoms were the leading causes of disability and negative sequelae for youth [1]. For some time, mental health disorders have been the most common disease of childhood in the United States, surpassing the *combined* rates of multiple pediatric conditions (eg, cancer and diabetes) [2-4]. Despite the tremendous impact of mental health disorders on teens, millions do not receive mental health care [2]. Anxiety is particularly untreated, as up to 80% of youth with a diagnosable anxiety disorder do not receive mental health care [2,3,5]. Most exposed to this failure of mental health care are teens with socially complex needs, those who face multiple and potentially overlapping adversities, such as (1) enduring adverse childhood experiences, (2) residing in a systemically excluded community that experiences disproportionate disparities in health outcomes and health care access, or (3) being minoritized due to socioeconomic status as well as racial, ethnic, gender, or sexual identity or identities [1,6-8]. Teens with socially complex needs have multiple barriers placed between them and mental health care, which the current system is failing to address [9-15]. As such, traditional methods for reaching such teens are not working, resulting in life-long health disparities and a significant public health impact [2,6,7,16,17].

Digital Tools Implemented in Primary Care to Extend Care Capacity

Pediatric primary care (PPC) is one setting with strong potential as an environment to engage and screen teens with socially complex needs. Indeed, nearly all youth visit a PPC office annually for well-child visits as well as illnesses or injuries that necessitate care (eg, ear infection) [18]. As such, PPC is a centralized and typically low-stigmatized setting for teens of all backgrounds. Mental health care is increasingly warranted in PPC, with the American Academy of Pediatrics recommending universal anxiety screening for all children and adolescents, aged 8-18 years, during PPC visits [19]. However, PPC providers report variable administration of standardized assessment measures [20] and multiple barriers to mental health screening, broadly [20-22]. Further, when mental health needs, such as anxiety, are screened or arise in PPC, pediatricians report multiple barriers to assessing mental health needs and connecting patients to therapy [23,24], adding to the obstacles to care noted above. Even in the case of using a collaborative care model for depression in primary care [25], a pragmatic approach for anxiety that embraces the logistical realities that providers face in delivering mental health screening and ensuing recommendations is lacking [26,27]. A potential solution to these barriers is to incorporate digital mental health tools (DMH) as a low-intensity treatment (LIT) into PPCs. LITs are patient-facing tools that may provide screening, psychoeducation, resources, or combinations of these items. Given the long-standing efficacy of LITs in digital and other delivery mechanisms for mild to moderate symptom presentations (eg, self-help books) [28], DMH LITs have been proposed as a scalable and strategic first-line model of care in PPC and similar care environments [29].

Integrating DMH LITs into spaces that teens already visit, such as PPC, has the potential to increase mental health care reach. However, uptake and subsequent clinical outcomes will not be impacted if teens do not engage with DMH in their daily lives [30]. One problem is a lack of implementation planning early on in the design processes for DMH [31,32]. Also implicated in poor engagement is a failure to address the range of multilevel implementation barriers, spanning from individual-level barriers (eg, problem recognition, stigma, and confidence to act), intervention barriers (eg, usability and relevance), and systemic barriers (eg, accessibility and cost) [24-27,33]. Interventions such as incorporating motivational interviewing [34] and usage incentivizes [35-37] have improved DMH engagement, but diminish scalability [38]. As such, means to target barriers must be identified and harnessed to address poor engagement, the perennial failure of DMH deployment to date.

Objectives

In this study, human-centered design methodologies and an implementation science framework [39-41] were used to guide the development and implementation of the Teen Assess, Check, and Heal (TeACH System). Through the use of these methodologies and frameworks, the TeACH System was designed to target individual-level barriers to care (eg, feedback to directly respond to problem recognition, stigma, and confidence to act on symptoms), DMH intervention barriers (eg, human-centered design methodologies to optimize usability and relevance), and systemic barriers to care (eg, increase accessibility by integrating in a space already visited by teens, remove cost barrier by providing a freely accessible service and resources) [24-27,33]. Our primary aim was to increase DMH

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engagement for teens with socially complex needs through: (1) engaging teens and caregivers from the systemically-excluded and underserved communities of Chicago, Illinois, to refine the TeACH System to be engaging, appropriate, and in line with cultural and user needs; and (2) integrating the TeACH System into PPCs serving teens on the West Side of Chicago. The West Side of Chicago was selected for initial implementation planning and integration evaluations as part of a larger body of research focusing on adapting DMH LITs for and with teens living in communities disproportionately inflicted with health disparities, violence exposure, and higher economic hardship (eg, [42]). Through collaboration with key players throughout the design and implementation planning phases, the TeACH System was hypothesized to increase teen patient self-reported engagement with DMH and address specific individual-level barriers to mental health care, compared with a digital psychoeducation control condition. This hypothesis is being evaluated through a pilot feasibility randomized controlled trial in Chicago PPCs, comparing engagement outcomes for teens with anxiety randomized to use the full TeACH System to those who are provided access to a publicly available, digital evidence-based workbook for teens (psychoeducation control) [43,44].

Methods

Positionality

Positionality influences all aspects of a research study and is connected to the researchers' personal and philosophical views [45]. In recognition of this influence, the positionality of the lead author of this study has been reported elsewhere [23] and is similarly described: (1) author CSS is a lifelong Chicagoan, (2) trained social worker, and (3) a pediatric psychologist who believes that engaging youth with DMH and in health environments they already frequent maybe 1 path to get more resources directly to youth to use as they need and want, but that DMH will not become a panacea to disparities. As a monolingual, White woman trained in health care settings, she has biases and experiences that may impact her interpretation of findings (eg, she is comfortable in health settings; DMH has primarily been tested with individuals who have overlapping identities with her [eg, college-educated and White women] [46]). To minimize bias, author CSS partnered with key players, by establishing interdisciplinary mentor and peer collaborator teams, to learn with teens, caregivers, and providers about their wants and needs for DMH in health care settings.

Procedures

Study Design

The study design is a pilot feasibility randomized controlled trial. The participant focus is teen patients in PPCs with anxiety. While universal anxiety screening is recommended [19], pediatric anxiety has a long-standing history of being underrecognized and often untreated [47-49]. Participants first answer initial screening eligibility questions (ie, age, clinic location, and ability to complete and read surveys in English), followed by completing a digital assent. While a waiver of guardian consent was obtained from the institutional review board, participants are able to "opt in" to have a guardian provide consent in English or Spanish, should they elect to do so. Following assent and optional guardian permission, participants complete a brief demographic survey, indicate their preference for future contact (ie, text message or email), and complete a brief assessment of the primary outcomes (Measures section). All participants then complete the Kiddie-Computerized Adaptive Tests (K-CAT) Anxiety Module [50] to ensure eligibility (ie, a score >29 and indicating mild or greater anxiety symptoms). Participants who do not meet these criteria are excluded and offered access to a publicly available, digital evidence-based workbook for teens [43,44]. Participants who do meet the criteria for mild or greater symptoms of anxiety are randomized into either the control arm (digital evidence-based workbook [43,44]) or the Intervention Arm (TeACH System Feedback and Resources). Randomization is automated through the Research Electronic Data Capture (REDCap, Vanderbilt University) platform, and study staff members are blind to allocation. Following a review of these resources, all participants are invited to complete an immediate follow-up survey. One week following this interaction, participants are invited to complete the same follow-up survey. Figures 1 and 2 display the study design flow.

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Figure 1. Participant flow through TeACH system trial in pediatric primary care K-CAT: Kiddie-Computerized Adaptive Tests.

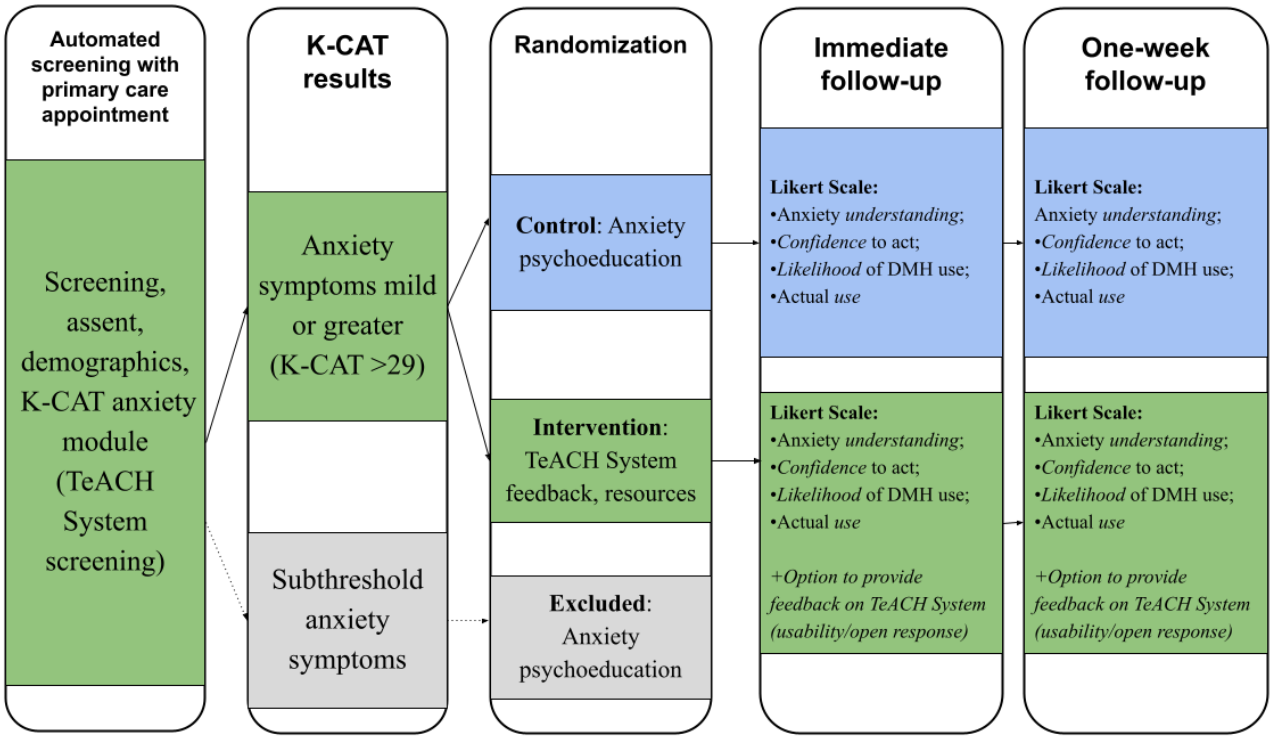

Figure 2. Study flow diagram.

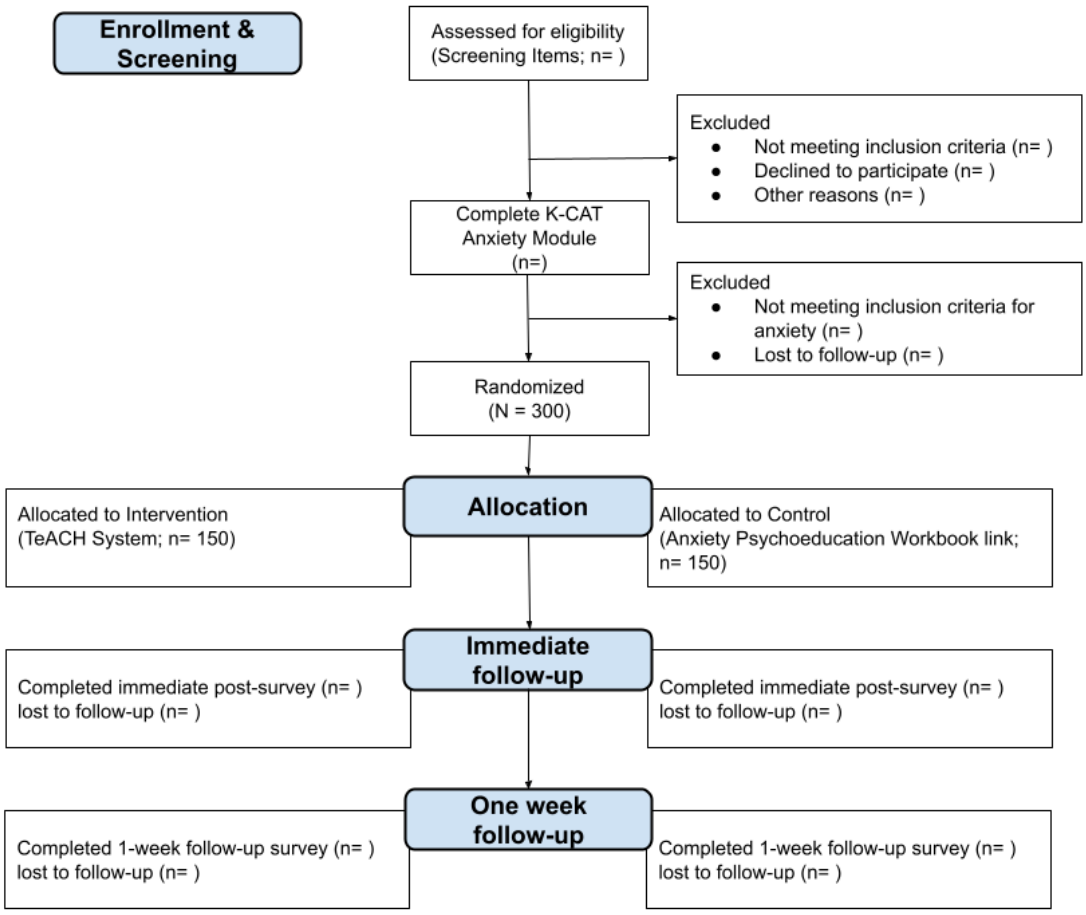

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Setting and Recruitment

Eligible participants are being recruited through PPC clinics housed within the University of Illinois Chicago (UIC) and Rush University Medical Center (RUSH). Both hospital systems' primary campuses are situated on the West Side of Chicago and serve diverse patient populations [51,52]. Eligible participants are being recruited in clinics through (1) QR codes on displayed and circulated flyers, including sharing of the flyer by PPC pediatricians, trainees, and staff; and (2) invitation from research staff (ie, offered tablet in the clinic waiting room or while waiting in an exam room) or PPC clinicians and staff members.

Inclusion and Exclusion Criteria

For study inclusion, participants must be (1) receiving care at the specified clinics at UIC or RUSH; (2) between 13 and 17 years of age; and (3) able to speak and read in English. These inclusion criteria are determined by teen self-report (ie, answering 3 screening questions based on these criteria). Following assent and completion of a demographics and engagement survey (Measures section), final inclusion criteria are assessed based on responses to the K-CAT Anxiety Module. Namely, to be randomized, participants must also meet criteria for mild or greater symptoms of anxiety (ie, K-CAT Anxiety Module score >29) [50]. There are no assessments for comorbidities, nor any exclusion criteria beyond not meeting the inclusion criteria noted above.

TeACH System

The TeACH System is a DMH LIT that includes teen patient-facing brief assessment, feedback, and resources for symptoms of anxiety (sample screenshots displayed in Figure 3. Increasing DMH engagement for teens with socially complex needs is the primary aim of the current iteration of the TeACH System. The mechanism to achieve this outcome includes the use of key player involvement throughout the design and implementation planning processes. Consistent with a broad spectrum of community-engaged research practices [53], involvement of teens and caregivers from the West and South Side Communities of Chicago have ranged from 1-time interviews and focus groups to co-design activities, with plans to form a community advisory board for the broader line of research led by this team [42,54,55]. Most relevant to the design of the current iteration of the TeACH System (eg, direct quotes described below), formative usability testing sessions were completed remotely with 10 teens (mean age 15.9, SD 0.99 years; female: n=8, 80.0%; Hispanic or Latino: n=6, 60.0%; Middle Eastern of North African: n=1, 14.3%; White: n=6, 60.0%) and 7 parents of teens (mean age 41.86, SD 8.7 years; female: n=5, 71.4%; Hispanic or Latiné: n=1, 14.3%; Middle Eastern or North African: n=1, 14.3%; Black or African American: n=4, 57.1%) from the West and South Side Communities of Chicago.

Figure 3. Sample screenshots of the TeACH system.

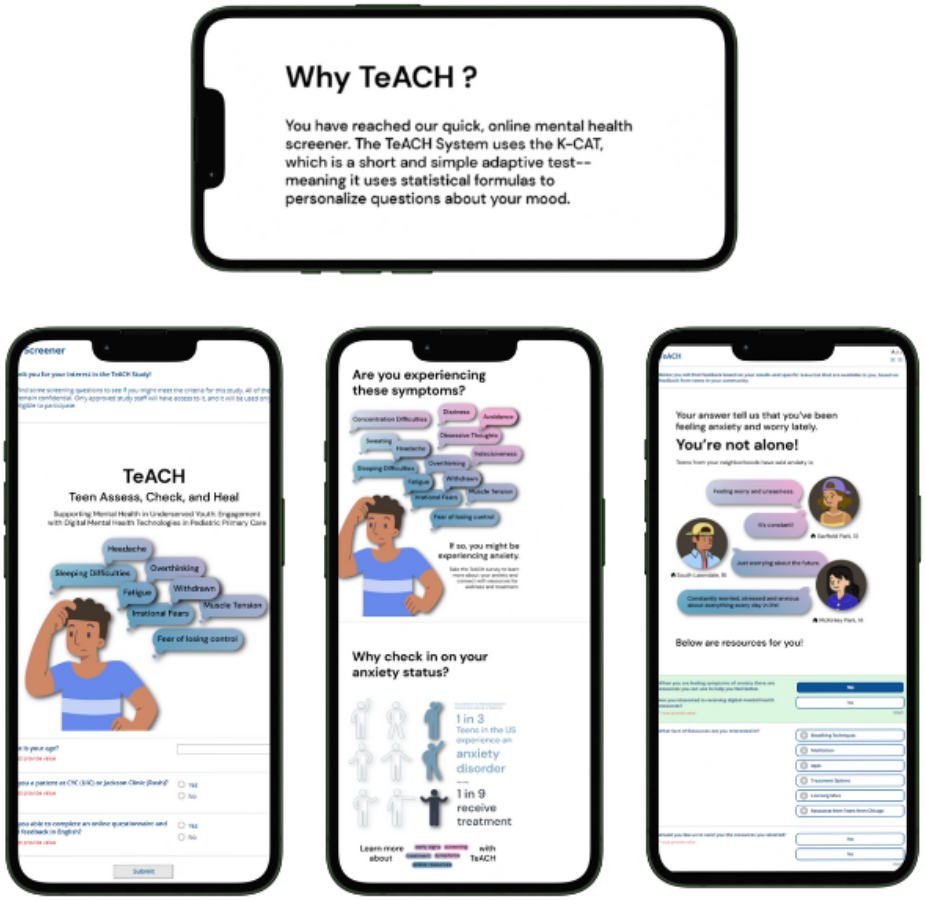

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TeACH System Assessment

The TeACH System uses the Kiddie-Computerized Adaptive Tests (K-CAT) Anxiety Module to assess teen patient anxiety symptoms [50]. The K-CAT Anxiety Module (youth report; ages 7 to 17 years) uses an item bank of more than 200 items, typically offering 10 questions to a teen user to predict the likelihood of a diagnosis of generalized anxiety disorder (area under the receiver operating characteristic curve=0.83). However, the module is not limited to generalized anxiety disorder and may also be used for general anxiety screening in youth [50]. Future iterations of the TeACH System may use the full K-CAT (ie, assessing anxiety, depression, substance misuse, oppositional defiant disorder, attention-deficit/hyperactivity disorder, mania, conduct disorder, and suicidality), but the current version of the TeACH System is solely assessing anxiety. This decision was driven by input from PPC clinicians and staff members who expressed concern about follow-up mental health care, safety, and workflow disruptions around more expansive digital mental health assessments [23]. Participants in the current study are eligible for randomization with a score greater than 29 on the K-CAT Anxiety Module, indicating mild, or higher anxiety symptoms [50].

TeACH System Feedback

Following the completion of the K-CAT, the TeACH System informs users that they will be provided feedback and specific resources that were informed by feedback from "teens in your community." The feedback provides an infographic that starts by stating: "Your answer tells us that you've been feeling anxiety and worry lately," followed by the validation that "You're not alone!" Following this, 4 quotes from Chicago teens describe anxiety as: "feeling worry and uneasiness"; "It's constant!"; "Just worrying about the future"; and "Constantly worried, stressed, and anxious about every day in life!" before proceeding to viewing resources, users are prompted that "When you are feeling symptoms of anxiety, there are resources you can use to help you feel better." In sum, the feedback section aims to briefly address multiple individual barriers to care, including problem recognition (ie, "Your answers tell us that you've been feeling anxiety and worry lately."), stigma (ie, "You're not alone!" and quotes from "Teens from your neighborhoods"), and confidence to act (ie, "When you are feeling symptoms of anxiety, there are resources you can use to help you feel better") [24-26].

TeACH System Resources

Following the feedback, users are asked if they would like to receive DMH resources. The resources are all freely accessible online and are presented to participants through both sample screenshots and links to their direct sources (eg, App Store, YouTube, and TikTok). All resources are grounded in evidence-based skills (eg, progressive muscle relaxation and diaphragmatic breathing) and psychoeducation (including brief videos from teens and young adults with lived experience with anxiety). If participants indicate that they do not wish to receive DMH resources, they are asked to provide a reason as to why. If they would like to receive DMH resources, they are asked what types of resources they would prefer (eg, "Breathing Techniques," "Apps," and "Learning More"). This checkbox selection allows teens to view the content they wish, as opposed to getting all options at once, which can be overwhelming. Users may also opt to have the resources sent to them at their preferred method of contact (ie, email or text message).

TeACH System Platform

The TeACH System is intended to be adaptable and scalable. As such, using a simple but secure platform that may be easily edited at minimal cost was ideal. UIC's instance of REDCap was therefore selected as the platform to build and manage the TeACH System [56]. REDCap is housed and managed by the University, as is common across multiple university and health care systems. To enhance the aesthetic appeal and engagement of the TeACH System for teen users, the UIC Innovation Center collaborated on its development within REDCap. An interdisciplinary team of researchers applied human-centered design techniques and analysis frameworks to effectively present the survey and maintain participant interaction throughout. They used user journey maps and extensive user testing to ensure a smooth and intuitive survey flow. The team also crafted a distinct visual language for the TeACH System, incorporating contemporary graphic elements inspired by popular social media platforms, calming color choices, and clear, simple language to appeal to the teen audience and put users at ease.

Control Condition

Following screening, assent, demographic characteristic assessment, and completion of the K-CAT Anxiety Module, participants randomized to the control condition receive different feedback and resources than those allocated to interact with the full TeACH System. The control condition includes immediate feedback about anxiety symptoms (ie, "Your answers tell us that you've been feeling anxiety and worry lately."). Following this, participants are queried whether they would like access to a digital resource. If they respond negatively, they are prompted to provide their reasoning. If they respond positively, they are provided with a direct link to a free download of an evidence-based workbook for teens with anxiety [43,44].

Measures

Demographics

Following assent, teens are asked to report the following demographic information: name, age, ethnicity (Hispanic or Latiné and Middle Eastern or North African), race, pronouns, gender, preferred language, the reason for visiting primary care, and preferred method for contact (ie, email or text message).

Primary Outcomes

The primary outcomes are administered within REDCap and are assessed at 3 time points for all participants: (1) baseline: following assent and before administration of the K-CAT; (2) post interaction: immediately after receiving the allocated feedback and resources; and (3) maintenance: 1 week following the interaction. The primary outcomes are discrete variables focusing on individual-level barriers to mental health care (ie, symptom understanding, confidence to act [24-26]) and engagement with DMH (ie, likelihood to use DMH for anxiety, actual DMH use). Namely, through a questionnaire created for this study, participants rate on a Likert scale (1=not at all to

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5=completely): (1) anxiety *understanding* (ie, "I understand what anxiety is."); (2) *confidence to act* (ie, "I feel confident I can do something if I feel anxiety."); and (3) *likelihood* to use digital tools for anxiety (ie, "If I feel anxiety, I would use a digital tool to help (app, website, and reel or video)."). Following this, participants indicate whether they have used a digital tool for their anxiety before (ie, yes, no, and unsure).

Usability

Usability of the TeACH System and its control arm are assessed post interaction (ie, immediately after receiving the allocated feedback and resources) and 1 week after the interaction through the After Scenario Questionnaire, a 3-item measure of usability [57].

Data Analyses

Overview

Descriptive analyses will be conducted to characterize the sample, primary outcomes, and usability ratings of the TeACH System. To assess changes in the engagement outcomes over time and account for missing data, linear or generalized linear mixed effects regression models will examine differences in responses to the baseline, postinteraction, and maintenance questionnaires. Demographic variables and existing DMH use, as well as their interactions with time, will be examined as covariates to assess differential engagement outcomes based on these variables.

Sample Size and Power

Power and sample size computations were based on previously published work [58,59]. Conservative estimates of sample sizes were estimated (ie, anticipating a 15% attrition rate on the follow-up survey), which indicated that 300 patients were deemed appropriate to examine the initial TeACH System use (ie, K-CAT Anxiety module, feedback, and resources) after being invited during their PPC appointment. With an expected 15% attrition rate for the follow-up questionnaire 1 week later, we would be adequately powered for within-subjects (pre vs post using the main effect of time) and between groups comparisons (TeACH System vs Control condition using treatment by time interaction). For within-subjects comparison, our proposed sample size is overpowered such that we should exceed 90% power to detect differences generally considered to be moderate in size (d=0.5) with a sample size exceeding approximately 70 participants. To detect within-subjects differences from baseline to endpoint equivalent to d=0.34 for the engagement outcomes, we would require a sample size of approximately 136 for 95% power. As such, our proposed sample is more than adequate for the planned within-subjects comparisons. For between-group comparisons with the anticipated 15% attrition rate, we should have 95% power to detect differences generally considered moderate in size (d=0.5) with 240 participants. With our proposed sample size of 300 participants, we will have 80% power to detect smaller differences equivalent to d=0.34.

Ethical Considerations

All procedures were approved by the institutional review boards of the University of Illinois Chicago (2024-0252) and Rush University Medical Center (20051313). Further, ongoing study monitoring is being overseen by an independent Data Safety and Monitoring Board. All participants complete a digital assent and are compensated for completing a follow-up assessment with a US $15 Amazon e-gift code (see the section Study Design below).

Results

This study received funding from the National Institute of Mental Health on September 13, 2021 (K08 MH125069), and began recruiting at UIC in July 2024 and at Rush in August 2024. Earlier funded activities informed the design and implementation planning for the current trial [23,32,42,54]. To date, 122 teens have assented to complete study activities, 80 have been randomized (an additional 24 teens have had subthreshold anxiety symptoms and were therefore not randomized), and 42 teens have completed the one-week follow-up assessment. We expect data collection to be completed by August 2025.

Discussion

Overview

The current feasibility study aims to evaluate the TeACH System in terms of (1) increasing engagement with DMH and (2) addressing individual-level barriers to mental health care. These outcomes are being examined in the context of integration in urban PPC clinics and in comparison to a control condition (ie, access to a digital workbook). The design and implementation plan for the TeACH System involved collaborative input from key players (ie, teens, caregivers, and PPC staff and clinicians) to increase the likelihood of teen engagement and acceptability in a dynamic health care setting [23,42,54].

The TeACH System stands as one of a growing number of DMH LITs being evaluated and implemented in care settings (eg, [60,61]). DMH LITs have demonstrated promise in increasing engagement for minoritized teens, compared with more intensive digital and traditional care models [37]. Amid this landscape, some unique aspects of the TeACH System situate it to adapt and scale well based on user and setting needs. First, the TeACH System is housed on a secure, stable, and editable platform (ie, REDCap [56]) and may therefore be adapted across iterations and for differing populations and settings. For example, screening may be expanded from self-reported anxiety only (current version) to up to 8 diagnostic categories assessed through the K-CAT (ie, anxiety, attention-deficit/hyperactivity disorder, conduct disorder, depression, mania, oppositional defiant disorder, substance use disorder, and suicidality [50]). Second, infographics and other design features may be changed to reflect the language and design preferences of different target groups. Similarly, resources may be edited or changed based on availability (eg, open access removal of a video), population preferences, and platform safety and availability (eg, if a "TikTok ban" results in higher teen use of a different platform). Finally, the TeACH System–and any future iterations are grounded in human-centered design with input from key players to target DMH engagement. Such targeting is hypothesized to serve as a mechanism of DMH to ultimately impact clinical

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outcomes [62]. In sum, the TeACH System has been designed for teens with both anxiety and socially complex needs while visiting primary care. However, future iterations may be easily adapted at any level for integration in settings youth visit regularly and trust.

Future Directions

The scope of this study is associated with specific limitations and caveats, all of which inform future research directions. First, the current iteration of the TeACH System focuses solely on anxiety. While originally aimed to include the full K-CAT assessment, the scope was limited to anxiety to meet the implementation needs of PPC clinicians and staff members [23]. Anxiety was also selected to establish proof of concept for this first iteration, as anxiety is highly prevalent and socially minimized by clinicians and the public, making it less likely to be effectively screened and treated. Once the TeACH System establishes initial feasibility, it can be broadened to address multiple disorders through a larger study. Second, the K-CAT demonstrates the strongest accuracy when the parent proxy report and child self-report are integrated [50]. While the current iteration of the TeACH System is solely teen-facing, there is the potential for the TeACH System to have both caregiver and teen-facing elements in the future. Alternatively, summative feedback from this study may indicate that teens or families prefer for this to be a teen-facing tool, but with the option to inform trusted adults in their life about the indication of anxiety from the K-CAT. Further, the K-CAT is available and validated in both English and Spanish. As such, future iterations may also include cultural and linguistic adaptations to serve teens and caregivers who speak Spanish. Finally, while PPC is typically visited annually by most teens, integration in this care setting does not ensure that all teens will be reached. PPC was selected to establish feasibility for reasons detailed above, but future iterations may be adapted and integrated in other community spaces in which teens and families spend their time (eg, schools, parks, libraries, and churches).

Conclusions

LITs have a long-standing history of benefiting individuals with mild to moderate mental health symptoms [28], implicating DMH LITs as a promising first-line approach in care settings [29]. The TeACH System represents 1 possible DMH LIT that may provide brief assessment, feedback, and resources for teen patients without unduly burdening a busy health care environment nor requiring the approval of a guardian to use. This study will provide preliminary feasibility data that may inform how the TeACH System and other DMH LITs might better engage and support teens with socially complex needs.

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Authors' Contributions

CST led all aspects of this work, including conceptualization, funding acquisition, methodology, and writing the original draft of the manuscript. GB, KR, and ML conducted project administration and supervision. DLS led formal analysis. CF, CA, GD, RMC, NM, GM, AT, and KMW completed visualization and design activities. ELG, WAJ, and NSK provided additional supervision.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report from the Mental Health Services Study Section, National Institute of Mental Health Initial Review Group (NIH).
[PDF File (Adobe PDF File), 92 KB - resprot_v14i1e65245_app1.pdf]

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Abbreviations

DMH: digital mental health tools
K-CAT: Kiddie Computerized Adaptive Test
LIT: low-intensity treatment
PPC: pediatric primary care
REDCap: Research Electronic Data Capture
RUSH: Rush University Medical Center
TeACH System: Teen Assess, Check, and Heal System
UIC: University of Illinois Chicago

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Protocol

Integration of a Patient-Centered mHealth Intervention (Support-Moms) Into Routine Antenatal Care to Improve Maternal Health Among Pregnant Women in Southwestern Uganda: Protocol for a Randomized Controlled Trial

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Abstract

Background: Mobile health (mHealth) interventions that leverage social support (SS) can improve partner involvement and pregnancy experiences and promote antenatal care (ANC) attendance and skilled births. In our previous studies, we used behavioral frameworks to develop a user-centered mHealth-based, audio SMS text messaging app to support pregnant individuals to use maternity care services in rural Uganda (Support-Moms app). In our pilot study, we observed high intervention uptake, acceptability, and feasibility, as well as increased ANC attendance and skilled births.

Objective: With the promising pilot data, we propose a type 1 hybrid implementation-effectiveness trial to test if this novel patient-centered automated and customized mHealth-based SS intervention is effective and cost-effective enough to warrant future large-scale implementation into Uganda's routine maternity care.

Methods: We will physically recruit 824 pregnant women at <20 weeks of gestation living in Mbarara and Mitooma districts, southwestern Uganda, and randomize them (1:1) to receive standard of care or the Support-Moms app, with at least 2 of their identified social supporters. Our primary outcome will be the proportion of skilled births. Secondary outcomes will include number of ANC visits, institution-based delivery, mode of infant delivery, preterm birth, birth weight, SS, obstetric complications, and deaths (maternal, fetal, and newborn). We will assess other implementation, service, and client outcomes through study records, the mHealth platform, and questionnaires with all women in the intervention, their social supporters, health care providers (HCPs), and managers from participating facilities. We will conduct face-to-face in-depth exit interviews with 30 purposively selected intervention participants and 15 facility HCPs and managers to explore implementation strategies for scale-up. Annual maternity resource allocations, costs, number of ANC visits, and deliveries will be assessed from facility records up to 36 months after implementation. We will estimate incremental cost-effectiveness ratios concerning cost per additional HCP-led delivery, per death averted, and per quality-adjusted life year gained as cost-effectiveness measures.

Results: This study was funded in September 2023. Ethics approval was obtained in February 2024, and actual data collection started in March 2024. As of January 2025, 75% (618/824) of all projected study participants provided consent and were recruited into the study. Participants are expected to be followed up until delivery, and 15% (124/824) have so far exited. Data analysis for the trial is expected to start as soon as the last participant exits from the study. The qualitative interviews will start in April 2025, and data will be analyzed and published as soon as data collection is done, which is expected in March 2027.

Conclusions: We are testing the feasibility, acceptability, and cost-effectiveness of implementing Support-Moms into routine maternity care from individual and facility perspectives. We hypothesize that Support-Moms will be an effective and cost-effective strategy to improve maternity service use for women in rural Uganda and similar settings.

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International Registered Report Identifier (IRRID): DERR1-10.2196/67049

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KEYWORDS
social support; intervention development; maternal health; antenatal care attendance; skilled births; Uganda

Introduction

Background

While maternal mortality has fallen over the last 20 years, an estimated 300,000 women die each year from preventable causes related to pregnancy and childbirth, and 99% of the deaths occur in low- and middle-income countries (LMICs) [1]. Over 99% of infant deaths also occur in LMICs [2,3]. Persistently high maternal mortality ratios (MMRs) in LMICs are partly attributed to challenges accessing care, with undiagnosed or poorly managed pregnancy-related complications from direct or indirect causes [1]. Recurrence risks of fatal episodes increase exponentially among women who survive previous fatal episodes unless preventive measures for early detection and monitoring throughout the perinatal period are adopted [2,4-6]. Antenatal care (ANC) prevents perinatal and maternal morbidity and mortality by early detection and treatment of prenatal complications and identifying women at high risk to ensure delivery in skilled settings [7-11]. ANC supports women, their families, and communities to navigate challenges at a critical time during pregnancy; debunks misconceptions; increases information transfer; and can motivate women to seek facility delivery and care [9]. The World Health Organization (WHO) and other authorities have called for urgent evaluation of adaptable and context-specific health solutions to promote ANC uptake and maternity services to reduce maternal and early childhood mortality and morbidity [9,11-14]. Identifying and scaling up interventions that improve access to and the use of available health care in pregnancy and childbirth has the potential to prevent 823,000 stillbirths, 1,145,000 neonatal deaths, and 166,000 maternal deaths annually in the 75 highest-burden countries [2,4-6].

Despite expanded capacity to increase the number of skilled birth attendants at community facilities, Ugandan women still have low rates of ANC use and skilled births, resulting in one of the highest MMR (189/100,000) and perinatal mortality rates (34 deaths/1000 births) in the world [15]. Women's lack of information, social support (SS), financial independence for emotional and economic provisions, decision-making autonomy regarding childbirth, birth preparedness, and perceived need for maternity care services are important challenges to using available maternity services in these settings [1,16-19]. One analysis showed that women at risk of unskilled home births needed relevant and context-specific strategies to encourage ANC attendance and skilled delivery [20]. The high cost of MMR highlights the need for adaptable interventions that boost ANC and maternity services use to reduce MMR and early childhood deaths [12].

SS is an important pillar of health promotion that has been directly linked to health care–seeking behavior, infant care practices among mothers, and HIV care in sub-Saharan Africa (SSA) [21-25]. SS can mitigate structural and physical barriers to health care access at individual and societal levels, including facilitating self-efficacy to complete positive health behaviors [26-28]. Spouses, relatives, and friends have been the sources of SS among individuals living with HIV in SSA [23-25]. Community health workers (CHWs) can provide or promote additional SS during pregnancy, leading to better health outcomes [29,30]. Village health teams (VHTs), which comprise community members identified by their community who are trained on major health programs, improve timely care seeking for facility delivery [31-35]. VHTs have historically focused on the treatment of infectious diseases, such as malaria, pneumonia, and tuberculosis [35]. Their role as an additional resource for peripartum women has not been harnessed. Therefore, social network involvement not only addresses individual but also family- and societal- or community-level barriers to care in a setting with modest availability of health centers (HCs) providing needed services [17,25,36-38].

Mobile health (mHealth) interventions can be practical, effective, and scalable tools to improve maternal health care delivery and outcomes. Many SMS text messaging and other mHealth interventions can help individuals internalize risks and potential impact of various medical conditions as well as the needs and benefits of health services [11,13]. mHealth approaches can empower individuals to seek help, address specific health concerns, strengthen informed decision-making, and improve outcomes in the perinatal period [14,39]. Scheduled SMS reminders and telephone voice messaging approaches can enable people to increase control over their health by improving knowledge transfer, learning, and comprehension. These gains may improve the perceived need to use available services, especially when interventions are well directed and executed to provide accurate and relevant information on the promoted behavior [11,13,14,25,39-42]. Several studies have found that mobile phone–based messages can be motivational as a source of individual or family SS [43], cues to action [44], or to challenge societal negative beliefs [45]. Mobile phone interventions have also been shown to increase ANC attendance [46,47], institutional delivery [48,49] and vaccination rates (such as tetanus toxoid) [11,49].

mHealth interventions that specifically bolster SS can improve pregnancy experiences by decreasing anxiety and depression [50-53] and increasing perinatal bonding [52] and communication within social networks [53]. These benefits are mediated by promoting existing family structure and social networks, which in turn foster financial and emotional coping mechanisms to enable women to overcome socioeconomic and

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physical barriers to care, such as food insecurity, transportation, and provision of delegated service to overcome competing priorities [25,53-55]. Community and social network engagements toward mobilization of resources to enable health care access are practical, scalable, and sustainable approaches toward participatory health care financing and use [56]. Although SMS alone is a convenient and lower cost approach to support health care interventions with higher delivery success, the provision of multiple messaging options, such as voice messages and social networks involvement, has been crucial to extend reach beyond the individual literate personal phone owners in SSA [57,58].

Health awareness and motivating health care use are key elements of developing effective behavior change interventions [59]. However, mHealth interventions are not always effective in improving health care and use. Whereas the failure of impact has been attributed to a mismatch between the function, adaptability, and need for mHealth interventions in some settings [11,14], end-user designs that use iterative approaches in app development can improve health care service use [60]. In a formative study, we observed that knowledge gaps influenced women's past and future decisions to not attend ANC and pursue unskilled home births [17,20]. Women were also largely dependent on their significant others for economic provisions, which, together with the existing gender and traditional norms, limited women's ability and freedom to make family or health decisions to seek skilled care. Therefore, we developed an mHealth-based SS intervention (the Support-Moms intervention) using the health care use model by Andersen [61] that incorporates predisposing-, enabling-, and need-based factors to improve intervention uptake and service use. We then considered the framework by Bendixen et al [62] to personalize the information and tailor the system for our targeted end users. Our novel mHealth app was developed as part of a career development award (NIH-K43TW011004). This app or intervention was compatible with local regular mobile phone types, providing varying text and audio delivery mediums for individuals who were literate and who were not. In a randomized 3-arm pilot study (N=120) pregnant women who had not presented for ANC by their second trimester were equally randomized to receive (1) standard of care, which is the routine ANC information given at the maternity centers (control); (2) scheduled SMS audio messages from the final messaging prototype (scheduled messaging [SM]); and (3) SM, plus social supporter engagement through SMS (SS) [63].

We observed high intervention acceptability and feasibility, with >80% of women receiving ≥85% of intended messages within 1 hour. Over 95% of women found the app easy to use and compatible with their existing messaging programs; they also reported that the messages were useful and engaging and would strongly recommend the intervention to others. Nearly all women in the SS arm (39/40, 98%) had a skilled delivery compared to 78% (31/40) and 70% (28/40) of the women in the SM and control groups, respectively. All women whose social supporters were engaged on the app (SS arm: 40/40, 100%) attended ≥4 ANC visits, compared to 83% (33/40) and 50% (20/40) of the women in the SM and control groups, respectively. Fewer women (8/40, 20%) in the SS arm missed any visits due to the lack of transportation compared to 58% (23/40) and 68% (27/40) of the women in the SM and control groups, respectively. In addition, fewer maternal or fetal complications (3/40, 8%) were reported in the SS arm compared to 13% (5/40) and 25% (10/40) complications in the SM and control groups, respectively. Using the Duke-University of North Carolina (UNC) Functional Social Support scale [64], women in the SS arm reported improved SS (median 3.4, IQR 2.8-3.6) compared to 2.8 (IQR 2.6-3.2) and 2.4 (IQR 2.2-2.8) in the SM and control arms, respectively (score ranges from 1 to 4, and 4 indicates high levels of SS). In qualitative interviews, all women described the intervention as useful, actionable, and easy to use; tailored health information helped them to learn, internalize, and comprehend ANC and skilled delivery benefits, strengthening their informed decision-making as they were reportedly able to easily share and discuss information with their significant others, who in turn committed to providing them the needed support to prepare and seek help. Women also expressed that the involvement of their significant others within a friendly, trusted, and familiar environment helped them to mobilize needed support during pregnancy. Involving both health care providers (HCPs) and end users in characterizing, developing, and formulating the mHealth intervention allowed its tailoring to their preferences. Given the success in our pilot work where 78% (93/120) of the women used feature phones and promising preliminary efficacy data presented earlier [36,63], the next logical step was to assess the effectiveness, implementation, and scalability of such multiple messaging strategies to improve care access in SSA, where the contextual factors that drive successful interventions differ, but the public health impact of such interventions is likely to be the greatest [65].

Objectives

We now propose a type 1 hybrid implementation-effectiveness trial to evaluate and implement this intervention into routine care. We will test the effectiveness of the intervention in a randomized controlled trial (aim 1). We will apply the implementation outcomes framework by Proctor et al [66] to evaluate implementation, service, and client outcomes and conduct in-depth interviews with users and key stakeholders to contextualize or clarify these outcomes as well as explore implementation strategies for future scale-up using the Consolidated Framework for Implementation Research (CFIR; aim 2). We will then assess the costs and cost-effectiveness of implementing the Support-Moms intervention into routine care (aim 3). We hypothesize that implementing Support-Moms will be an effective and cost-effective strategy to improve maternity service use.

Methods

Study Overview

We propose to evaluate the effectiveness and implementation of the Support-Moms app into routine care. We hypothesize that Support-Moms will improve maternity service use and reduce the MMR when integrated into routine care. We will test the effectiveness of the Support-Moms intervention in a randomized controlled design (aim 1); evaluate intervention

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implementation using the implementation outcomes framework by Proctor et al [66], as outlined in Figure 1 (aim 2); and then refine implementation strategies for future scale-up using the CFIR, as outlined in subsequent sections [67]. We will assess the cost and cost-effectiveness of implementing this intervention into routine care and its implication for sustainability (aim 3). These outcomes will serve as indicators of implementation success or necessary preconditions for attaining desired service outcomes for women in rural, resource-limited settings. This will enable us to identify practical, context-specific, and actionable strategies for achieving optimal implementation effectiveness at a low cost. The intervention strategies were developed in our pilot work together with facility HCPs. In the cost-effectiveness analysis, if Support-Moms and standard of care are found to have equivalent effectiveness, we will conduct a cost-minimization analysis where only the cost of Support-Moms per participant will be estimated and reported (no incremental cost-effectiveness ratios [ICERs] will be calculated). This alternative approach would remain informative to the policy makers and stakeholders in maternity service use. Notably, simultaneous assessment is warranted given the (1) strong preliminary evidence, (2) relatively low investment needed for costing, and (3) overall efficiency of our proposed type 1 hybrid effectiveness-implementation trial approach.

Figure 1. Modified conceptual framework by Proctor et al [66] for implementation and evaluation.

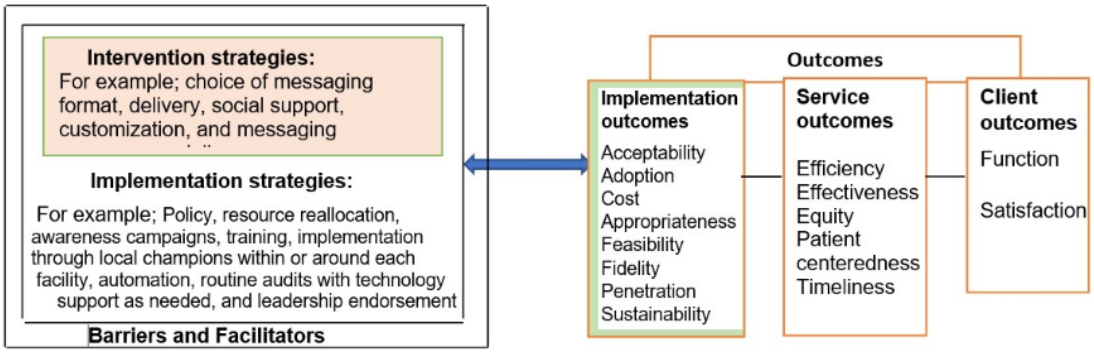

Study Setting

Uganda's public health system is organized into 7 tiers with national and regional referral hospitals, general district hospitals, and 4 levels of community HCs. Staffing and available services vary across the 4 levels; HC3 carry out vaginal deliveries, whereas HC1 and HC2 serve as low-resource referral units. HC4s and hospitals conduct normal and cesarean deliveries and have ambulances and blood transfusion services [68]. Private HCPs operate in parallel to the public health system to provide maternal health care. Mbarara District is located approximately 270 km southwest of the capital, Kampala [69]. Mbarara District hosts a regional referral hospital that serves the southwestern region (Mitooma district inclusive); most deliveries are high risk [70]. Mitooma District borders Congo and is situated approximately 370 km southwest of the capital [71]. These 2 sites were selected for this research based on their geographic, sociocultural, and institutional diversity and high maternal mortality and morbidity data (Table 1 presents more details). Both districts have publicly funded and operated facilities with an active maternity care unit. Participants may be seen at any of the maternity sites in these 2 districts or other neighboring districts (Table 1), with recruitment and follow-up organized through CHWs. This consideration, plus the diversity of the settings and the study population, has potential for generalizability to similar settings. The local economy of these 2 districts is also largely based on subsistence agriculture, with both food and water insecurity being common [72,73]; ANC attendance of ≥4 visits is still at 58%, and the skilled facility delivery rate is approximately 70%. Maternity services, including delivery, are largely provided free of charge through public HCs.

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Table 1. Mbarara and Mitooma district statistics 2019.

Characteristics	Mbarara, n	Mitooma, n
Total population	Approximately 250,000	Approximately 185,000
Annual registered ANC[a] visits	31,200	18,350
Annual public facility deliveries	14,800	4450
MMR[b] per 100,000 live births	328	412
Hospital availability	5 (4 are private)	0
Publicly funded HC4s[c]	2	1
Publicly funded HC3s	10	6
VHTs[d]	246	143
Other private facilities providing maternity services	34	12
Total HCPs[e]	253	104

[a]ANC: antenatal care.
[b]MMR: maternal mortality ratio.
[c]HC: health center.
[d]VHT: village health team.
[e]HCP: health care provider.

Aim 1: Testing the Effectiveness of the Novel Support-Moms Intervention in a Randomized Controlled Trial

We will enroll a cohort of 824 adult pregnant individuals with gestational ages ≤20 weeks at enrollment (determined by last normal menstrual period or ultrasound scan where available). Consenting participants will be randomized 1:1 at enrollment to standard of care (Ministry of Health [MOH] guidelines–based routine care and information giving, n=412, 50%) versus the Support-Moms (intervention) group (n=412, 50%). We will identify, screen, and enroll people through the existing CHWs or VHT structure from areas within a 10 km radius of all publicly funded maternity centers across Mbarara and Mitooma districts, who have not yet presented for ANC by the beginning of their second trimester. We will power the study to test the superiority of the Support-Moms intervention for our primary effectiveness outcome: HCP-led skilled birth delivery. Secondary outcomes will include (1) number of ANC visits, (2) institution-based delivery, (3) SS, (4) mode of infant delivery, (5) all deaths (maternal, fetal, and newborn), (6) preterm birth, (7) birth weight, (8) breastfeeding, (9) completion of postnatal care, and (10) complications of pregnancy and childbirth (eg, obstructed labor, ruptured uterus, need for neonatal or maternal resuscitation or assisted ventilation, severe preeclampsia or eclampsia, postpartum hemorrhage, maternal or newborn sepsis, and other infections).

Recruitment and Enrollment of Study Participants

We will include individuals who (1) are in the first trimester of pregnancy and have not yet presented for ANC, (2) reside in the catchment area of a study HC, (3) are emancipated minors and adults aged ≥18 years, (4) report access to a cell phone with reception in their home, (5) are able to identify at least 2 social supporters living within the study districts, and (6) are able to provide consent. Notably in our pilot study, >95% of screened individuals had access to a cell phone, and all were able to identify at least 2 social supporters living within their communities [63]. We will track the exclusion rates to inform generalizability. CHWs will notify study research assistants (RAs) about potentially eligible participants, who will then contact and seek written informed consent and assent for emancipated minors (ie, those aged <18 years and pregnant) before enrollment into the study. Participants will be asked to identify 2 individuals from their existing SS network with whom they have had stable, long-term relationships and believe they would be available to help them during the pregnancy and study follow-up period. Eligible social supporters will include spouses, relatives, CHWs, and friends [23-25] aged ≥18 years; who are aware that the study participant is pregnant; and who own a cell phone for personal use with reported reliable reception. Potential social supporters will be excluded from the study if they are unable to use SMS or are unwilling to receive SMS notifications, as this was identified as a barrier in the pilot study. In the pilot study, one of the eligible social supporters identified by women included a spouse (75%), friend (38%), sibling (10%), parent (53%), and a CHW (25%), and we expect a similar distribution in the trial. There will be no gender exclusion criteria for social supporters. We will emphasize the selection of an existing partner, who is aware of the pregnancy, as one of the social supporters. This was not a problem in our pilot study, as most women were able to suggest a partner as a potential social supporter, alongside a friend, sibling, parent, or CHW. A few partners were excluded because they did not own a cell phone for personal use (5/40, 13%) or were not aware of the pregnancy (5/40, 13%). All other eligible social supporters that were identified by participants in the social supporter arm (80/80, 100%) were successfully enrolled and completed study procedures. RAs will contact social supporters from the intervention arm within 2 weeks of the enrollment of pregnant women to confirm an active relationship at the time of their

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enrollment. Eligible social supporters will be offered an explanation of the study procedures and an opportunity to participate in informed consent. The study nurse will inform consenting social supporters about the objectives of ANC and skilled delivery as well as danger signs during pregnancy using standard MOH and WHO guidelines [9,74].

Randomization

Before the study initiation, the study statistician will generate a randomization table, inaccessible by other study team members, and lock it and store it in the REDCap (Research Electronic Data Capture; Vanderbilt University) study database. Participants will be stratified according to district and HC level and randomly assigned to either intervention or control arms in a ratio of 1:1 in blocks of 10. RAs will be informed of the arm assignment by the REDCap module after consent and at the time of enrollment. Study participants in the control group will receive MOH guidelines–based routine care and information giving. The intervention group will receive the intervention described in the next section.

Intervention Delivery and Components

The final messaging prototype that includes tailored SMS and audio health information (described earlier) will be delivered by the Support-Moms app developed through a partnership with iStreams-Uganda, an app development company based in Mbarara that developed the app, and with an existing mHealth platform [75]. The unique multimedia design allows women to be registered on the platform and be tracked throughout pregnancy and the postpartum period. Enrolled women receive automated and scheduled SMS text messages, reminders, and notifications about upcoming appointments as well as informational voice messages in their preferred language. The app includes a data collection platform and stores information submitted in real time directly from the participant's phone, thus allowing managers to access up-to-date data on process measures (eg, automated SMS text messages sent and accessed) as well as intervention delivery and health outcomes. Fixed SMS data are stored in a secure cloud, which is Health Insurance Portability and Accountability Act (HIPAA) compliant. iStreams-Uganda works in partnership with Africa's Talking, a platform that facilitates access to a telco infrastructure that uses automated SMS, voice, airtime, and other application programming interfaces—mechanisms tested and successfully used during our pilot study. This automated technology for SMS [23,25] and calls [36,63] has also been used for other studies in Uganda.

Both SMS and audio messages will be delivered at participants' preferred time and day of the week for free to optimize intervention delivery. A weekly SMS reminder on the impending ANC appointment and expected date of delivery at their preferred time and day of the week, plus a day before the scheduled ANC visit, will be sent to study participants. Social supporters will receive weekly SMS notifications to motivate the pregnant women participants to be present for scheduled ANC visits during the pregnancy as well as for delivery. Notifications to the 2 preidentified social supporters will provide information about the upcoming ANC visits and delivery due date during the study follow-up period. ANC appointment dates will automatically be generated based on the provided LNMP and MOH guidelines [74] at enrollment. Social supporters will be able to personalize the SMS content at enrollment (the default message will be "This is your reminder to assist your friend [XXX] attend her upcoming ANC visit due soon"). They will also be advised to assist study participants with problems that may affect ANC attendance or facility delivery. The intervention is designed to build on existing supportive relationships of study participants within their communities. All women and their social supporters will receive all accredited messages included in this app for at least 4 months, including the standard routine care provided at the community maternity centers.

Data Collection

Baseline participant characteristics will be collected from study participants from both arms as well as among the social supporters in the intervention arm physically (Table 2). Data collected through participant questionnaires will be conducted in the local languages, Runyankole and Rukiga. We will collect outcome data in two ways: (1) through medical record review of the routinely provided ANC cards, postnatal discharge forms (where available), and records at the relevant HCs and (2) through participant exit interviews 2 to 4 weeks following delivery to enhance data completion, particularly for people who did not deliver at a facility.

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Table 2. Baseline questionnaire items for study participants and social supporters.

Topic	Details of measure
Individual level	
Individual characteristics	Age, education, employment, socioeconomic status, marital status, religion, and self-efficacy[a]
General and mental health[a]	We will assess psychological symptoms using validated Hopkins Symptoms Checklist for depression and anxiety [76,77].
Alcohol or substance use	We will assess alcohol use using the 3-item consumption subset of the AUDIT-C[b] [78,79] due to its association with adherence and health outcomes.
Reproductive history	Gravidity, parity, gestational age, prenatal and antepartum high-risk morbidities, and NCDs[c]
Pregnancy and childbirth perceptions	Health beliefs, knowledge and risk awareness, need for skilled delivery, and childbirth practices
Relationship level	
Reproductive goals and motivation	We will adopt the 6 items used in Uganda to assess personal and partner pregnancy desires [80-82], In total, 18 questions or statements reflect 6 parenthood motives [83].
Relationship power and gender-based violence[a]	We will assess gender-based violence [84] and relationship power [85-87] given its relationship with home births in Uganda [17].
Social support[a]	We will adopt and measure social support using a version of the Duke-UNC[d] Functional Social Support Scale [26], a tool that has been widely used in Uganda [64].
Community level	
Service availability[a]	Distance to the nearest health facility, availability of midwives, history of home or facility birth, community support for alternative birthing choices, and relationships with HCPs[e]
Societal level	
General health and food insecurity[a]	We will assess the general health of women, including diagnosed NCDs, and measure food insecurity using the HFIAS[f] [88]
Societal norms[a]	Beliefs about pregnancy, childbirth, birth order, twin delivery, facility delivery, and fatality
Quality of life[a]	Improved Short Form-6 Dimension version 2 survey by Brazier et al [89] to assess the quality of life

[a]Collected at exit interviews.

[b]AUDIT-C: Alcohol Use Disorders Identification Test-Consumption.

[c]NCD: noncommunicable disease.

[d]UNC: University of North Carolina.

[e]HCP: health care provider.

[f]HFIAS: Household Food Insecurity Access Scale.

To additionally reduce the risk of missing data, for participants who cannot be contacted, we will conduct home visits and interview the next of kin for those who are lost from observation or who die during the study period. These survey data will include the date and location of the birth; whether there was a skilled birth attendant present; mode of delivery (ie, vaginal vs cesarean delivery); birth outcome, including preterm birth, maternal, fetal, and newborn deaths, and any other complications of the birth (eg, obstructed labor, ruptured uterus, need for neonatal or maternal resuscitation, severe preeclampsia or eclampsia, postpartum hemorrhage, maternal or newborn sepsis, and other infections); weight and height of the newborn; number of ANC visits completed; use of breastfeeding; and attendance at postnatal care. Finally, we will administer the Duke-UNC Functional Social Support Questionnaire to measure reported SS received by women during pregnancy and childbirth.

Aim 1: Analysis Plan and Sample Size Calculations

We will first summarize health-related and sociodemographic data between arms. For our primary effectiveness outcome, HCP-led skilled birth delivery, we will fit a multivariable logistic regression model, with study arm as the predictor of interest, and age, high-risk pregnancy, and health facility at enrollment as a priori additional variables in the model, due to their strong association with the selected outcome [70,90,91]. In our primary intention-to-treat model, we will consider women with missing outcome data, after home visits and next of kin interviews, as presumed to have not received skilled birth (ie, there will be no missing outcome data in our primary analysis). In sensitivity analyses, we will (1) repeat the analysis after excluding women with missing outcome data and (2) include additional potential confounders in the model that may have persisted despite individual randomization (eg, number of previous deliveries at a facility, socioeconomic status, distance to facility, history of facility delivery, food insecurity, alcohol

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use, and depression). Although not designed to detect a difference, we will also explore additional secondary outcomes, including (1) number of ANC visits completed, (2) mode of infant delivery, (3) institution-based delivery, (4) presence of one or more birth complications, (5) child mortality, (6) maternal mortality, (7) preterm birth, (8) birth weight, (9) completion of postnatal care, (10) SS, and (11) initiation of breastfeeding. Both our pilot data and other similar studies estimate that 70% of the women in Uganda deliver with a skilled attendant [15,48,49]. Finally, we will explore the role of SS as a moderating effect of the intervention through a prespecified stratified analysis among women in the upper versus lower half of SS in the cohort, as measured by the Duke-UNC Functional Social Support Scale [64]. To test our primary effectiveness hypothesis, allowing for a 2-sided type I error of 5%, 90% power, and assuming a 5% loss to follow-up, we will require 824 participants to detect a 10% difference in HCP-led skilled birth delivery between arms. Data analysis will be conducted using Stata (version 17; StataCorp LLC). The findings will be presented as descriptive statistics, scatter plots, and graphs; statistical significance will be considered at $P \leq .05$. While we will ensure completed data are collected through timely cleaning and REDCap prompts, we will still be able to detect the same effect in the primary outcome with the power of 85% in the unlikely event that we lost up to 18% of the records due to missing data.

Aim 2: Evaluating Intervention Implementation

We will evaluate intervention implementation using the framework by Proctor et al [66] (Figure 1) and plan for future scale-up per the CFIR [67] (Table 3). While the effect of the Support-Moms intervention on HCP-led skilled birth delivery, ANC attendance, and other secondary outcomes in aim 1 is critical, the translation of its potential benefit into routine care impact requires understanding the implementation process. We chose the evaluative framework by Proctor et al [66] because it consists of essential implementation science outcomes with attention to both services and clients, which will be critical for uptake and long-term use of Support-Moms in routine care (Figure 1 and Table 4). Then, we will consider and refine implementation strategies for future scale-up using the CFIR as a determinant implementation science framework (Table 3) [67].

Table 3. Consolidated Framework for Implementation Research (CFIR) constructs that will guide data collection on intervention challenges, facilitators, and potential strategies by care users, health care providers (HCPs), and payers and managers.

CFIR construct	Interview topic	Possible questions to elicit implementation strategies from users and implementers
Intervention characteristics	Intervention-setting fitness, automation, and auditing	On the basis of the reported or presented acceptability, effectiveness, patient centeredness, satisfaction, and function outcomes, how can the intervention be improved for increased implementation?
Outer setting	Existing policy, resources, and MOH[a] willingness and capacity to support increased demand for services and adopt the intervention	On the basis of the presented adoption, penetration, and other outcomes, as well as existing policies and resource commitments, what rollout strategies will be most effective in overseeing intervention implementation?
Inner setting	Facility adaptive reserve, leadership endorsement, and resource reallocation	On the basis of the identified cost-effectiveness, how can existing resources be reallocated to promote intervention uptake?
Individual characteristics	Patient centeredness, support, and community referrals	On the basis of acceptability, satisfaction, and function, what potential support will be needed for individuals using Support-Moms to improve uptake, enthusiasm, and retention?
Implementation process	Experience of HCPs on app enrollment, patient interaction, and increased demand and implementer's intention to "try," budgeting, sustainability, timing, execution, and scale-up	Explore implementers' support and satisfaction of the app to improve service use; approaches to publicizing and dissemination; engaging CHWs[b], focal HCPs, and social supporters as champions; long-term funding, potential impact; and "leading" or "lagging" indicators of the implementation success

[a]MOH: Ministry of Health.

[b]CHW: community health worker.

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Table 4. Application of the framework by Proctor et al [66] to evaluate implementation, service, and client outcomes.

Outcomes and domain	Specific intervention measures	Data source
Implementation outcomes		
Acceptability	• Reported ease of use and performance expectancy, effort expectancy, social influence, facilitating conditions, self-efficacy, and behavioral intention to use the app in the future • Overall user acceptability per the tool by Weiner et al [92] • Qualitative: For example, participants: How was it for you to use these SMS, messaging, or calls? and HCP[a]: How was it for you using the messaging app?	• Exit interviews • Exit questionnaire
Adoption	• Initiation and use of the app over time • Percentage of eligible and participating social supporters	• mHealth[b] platform • Study records
Appropriateness	• Relevance (for setting) and compatibility • Overall appropriateness with the tool by Weiner et al [92] for both HCPs and end users • Qualitative: For example, participants: What happened when you received SMS or voice calls? and HCP: What happened or what did you observe when you enrolled people on the app?	• Exit interviews • Exit questionnaire
Cost	• Refer to aim 3: Evaluating the Cost and Cost-Effectiveness of Implementing the Support-Moms Intervention Into Routine Care and Its Implication for Sustainability section	• Refer to aim 3
Feasibility	• Percentage of users willing to participate; percentage of women, spouses, and social supporters meeting eligibility criteria; recruitment or participating rates, and reason for not participating. • We will use the tool by Weiner et al [92] to measure feasibility for both HCPs and end users.	• mHealth platform • Study records • Exit questionnaire
Fidelity	• Percentage of HCs[c] with capacity and integrity to deliver intended service (ANC[d], skilled deliveries, and admissions), percentage of accessible cell phones, and percentage of messages automatically sent out • Percentage of SMS or voice calls received by the participant over anticipated per protocol • Percentage of network, dead battery, phone losses, and phone functionality issues encountered	• Study records • mHealth platform • Facility audits
Penetration	• Number and type of HCs and HCPs engaging with the app • Percentage of eligible participants and social supporters enrolled	• Facility audits • Study records
Sustainability	• Use of the app over time, social supporter engagement over time, and user retention • Percentage of participants lost to follow-up and percentage of additional staff needed • Qualitative: All, for example, what challenges did you experience or face while using this app?	• Facility audits • Study records • Exit interviews
Service outcomes		
Efficiency	• Time spent on enrolling participants on the app, time spent on deliveries, timely delivery of needed supplementary or reference information, cost of delivery • Qualitative: All, for example, what do you think about this intervention?	• mHealth platform • Exit interviews
Effectiveness	• Refer to aim 1	• Refer to aim 1
Equity	• App use by facility type, participant type, and demographics	• Study records
Patient centeredness: accomplished during the formative and pilot work [36,60]		
Timeliness	• Perceived impact on ANC attendance and skilled deliveries • Qualitative: How was your experience attending ANC and preparing for birth and delivery?	• Exit interviews
Client outcomes		
Function	• Perceived quality, impact on maternity care, use, and life (survey by Brazier et al [89]) • Qualitative: How did this intervention help you in your pregnancy or work as an HCP?	• Exit questionnaire • Exit interviews

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Outcomes and domain	Specific intervention measures	Data source
Satisfaction	• Satisfaction with intervention content, delivery, and credibility (Client Satisfaction Questionnaire) [93] for both HCPs and end users • Qualitative: What concerns do you have about using this technology to support you?	• Exit questionnaire • Exit interview

[a]HCP: health care provider.

[b]mHealth: mobile health.

[c]HC: health center.

[d]ANC: antenatal care.

Data Collection

Implementation Metrics

A trained RA will administer interviewer-led questionnaires at the trial exit (Table 4 presents outcomes and data sources) to (1) all intervention arm postpartum women, (2) all intervention arm social supporters, (3) all HCPs from participating facilities who enroll and deliver participants within the study sites, and (4) MOH key stakeholders and managers expected to inform rollout and adoption by the MOH. We will use a standardized checklist to conduct facility audits during implementation to document ANC visits and deliveries registered; maternity admission data; maternal mortality; disease cases managed; prescription data; laboratory data; and resource allocations at baseline, 12, 24, and 36 months following the implementation of the intervention for all study sites. A facility inventory will be done to inform our understanding of baseline conditions and set up for maternity and reproductive health services at the hospital and HC4 and HC3 public maternity centers.

We will use quantitative data on reported acceptability, appropriateness, effectiveness, function, and satisfaction to purposively select a subset of up to 15 postpartum individuals for exit in-depth interviews (or until saturation is met [94]), 15 social supporters, and up to 10 HCPs (approximately 2 for each facility level or district; refer to Table 1) involved in participant app enrollment and facility deliveries to clarify or contextualize observed outcomes based on the framework by Proctor et al [66] as outlined in Table 4. We will ask participants to describe actual events and experiences wherever possible (eg, for postpartum individuals, what worked well or poorly with receiving the messages and the challenges experienced during the study) to not only ensure coverage of specific areas but also allow unanticipated themes to emerge. We will further explore the feasibility, appropriateness, acceptability, patient centeredness, and sustainability of involving social networks in this intervention, as well as relationship dynamics, which have been shown to influence social supporter interventions [23-25] (eg, the social supporter's specific role, their relationship throughout pregnancy, routine communication, the type of voluntary and requested SS given or received during pregnancy toward improving her experience, ANC visits, birth preparedness, childbirth, and the app-related challenges and opportunities). We will schedule these interviews between 4 and 6 weeks post partum. HCPs will also be interviewed at the end of the study to clarify potential opportunities and problems that were experienced with the intervention and its delivery. These will facilitate appropriate conclusions about effectiveness and implementation success.

Implementation Strategy Development

Using CFIR, we will develop guides to further interview these postpartum individuals, social supporters, and HCPs on the intervention, individual, and inner settings to inform our implementation strategies and optimize intervention delivery (Table 3). We will develop some initial implementation strategies based on these findings and the literature (eg, awareness campaigns in the community and dissemination or publicizing the app, implementation in facilities through local champions within or around each facility to maintain enrollments, training, choice of messaging format, automation, and routine audits with technical support as needed). At the end of the implementation period, we will present data on outcomes and cost-effectiveness of the framework by Proctor et al [66] (refer to aim 3), along with the preliminary implementation strategies to the facility, district, and national MOH managers and stakeholders who have key roles in budgeting and policy or service implementation and are expected to evaluate or endorse the app. Using CFIR-informed interview guides (Table 3), we will interview 5 to 10 of these key MOH managers and stakeholders for feedback and refine our initial implementation strategies for testing in a subsequent study. All qualitative interviews will be audiotaped with the participant's permission and transcribed verbatim. RAs will be trained on the interview guides. All HCP and MOH interview guides will be piloted with 3 staff managers at Mbarara Hospital to ensure optimization, comprehension, and appropriateness.

Intervention Fidelity

Intervention fidelity plays a key role in assessing intervention effectiveness [95,96]. An RA will ensure participants know how to use the phone to retrieve information. CHWs and HCPs from the targeted public HCs will be trained to enroll participants onto the app, with technical support from the study research teams, led by ECA and GRM. We will measure the 3 elements of implementation fidelity as outlined in Table 4. Notably, 13% of the women enrolled in our pilot study missed some app messages because of lost phones or phone functionality issues. To minimize dead battery and charging issues, solar chargers will be given to study participants to charge their phones as needed during enrollment. These chargers are readily available and inexpensive, and we will be tracking their cost. Phone losses will be assessed on a case-by-case basis, replaced sparingly, and costs will be determined accordingly. Outgoing SMS and voice messages will be monitored daily by the data management team. The times and lengths of individual outgoing calls and engagements will be recorded and transmitted to the server. Message deliveries during periods of inadequate cellular reception will be stored for later transmission. Although

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2-way messaging has been found to be useful in other settings [11,14], our key factors in this proposal are to provide scheduled, targeted information and catalyze SS for women seeking maternity care, a mechanism that showed promising results in our pilot preliminary data. Moreover, 2-way messaging creates a burden on the health system that may not be sustainable. However, we will assess the need for this type of feature in the exit interviews for further exploration. In addition, contact numbers of the VHT and CHWs attached to the neighboring public HC will be provided to address any questions, referrals, or emergencies that may arise. SMS and voice call delivery or reception will be considered as proxies for accessing information to alter existing predisposing factors (such as negative health beliefs and low awareness) that could enable and improve perceived need to seek care with the help of available social networks, factors that will be assessed during exit interviews (Table 2 presents more details).

All quantitative data will be collected using a web-based database that will be developed in REDCap to improve data completeness, management, and quality control monitoring. Errors or out-of-range entries are reported immediately on the website so the original interviewer can reconcile the problem in a timely manner. Data entry verification will include algorithms that automatically check completed forms for missing, out-of-range, or inconsistent values before a form can be saved on the website.

Aim 2: Quantitative Analysis Plan

We will summarize implementation outcomes for Support-Moms users and implementers using descriptive statistics. Success in the implementation survey data will be identified qualitatively and by the top tertile of relevant scales (eg, acceptability, feasibility, satisfaction, and appropriateness). We will explore similarities and differences across HCs and districts over time as well as potential associations between implementation outcomes and effectiveness at HCs and district levels. We will summarize all findings and present them through a Delphi process or technique [97], with a final meeting involving key MOH managers and stakeholders. We will describe the ranked implementation strategies selected by app users and key MOH managers and stakeholders after the dissemination process.

Aim 2: Qualitative Analysis Plan

In-depth interviews will be digitally recorded and transcribed. The first set of exit interviews will be conducted to understand participants' or stakeholders' experiences and perspectives of the Support-Moms intervention and clarify the implementation, service, and client outcomes outlined in Table 4. The goal of the CFIR-informed interviews will be to refine and inform implementation strategies for integrating the Support-Moms intervention into routine maternity care. Qualitative analysis will be inductive [98], and categories will be derived from the different study textile participants, HCPs, and MOH manager and stakeholder interviews. These responses will be transcribed into English, if needed, and coded using NVivo (version 13; Lumivero). Data analysis will be jointly performed. The study coordinator and research fellow will double code 5 sampled transcripts from each category and, together with the principal investigator, resolve any coding disagreements to ensure consistency in the codebook. Dyadic analysis will also be performed between pregnant individuals and their social supporters. Categories will then be developed and presented with illustrative quotes from data to explain experiences, challenges with the intervention, and recommendations to improve its implementation into routine maternity care.

Aim 3: Evaluating the Cost and Cost-Effectiveness of Implementing the Support-Moms Intervention Into Routine Care and Its Implication for Sustainability

The incremental cost and the cost-effectiveness of the Support-Moms intervention or program will be estimated from HCP and health system and societal perspectives to guide the decision makers on continuation, incorporation, integration, sustained use, and routinization—a method that has previously been used in a Ugandan context [99]. We will measure and record the cost of developing and implementing the intervention (program costs), the cost to HCPs from increasing demand for or use of services, and costs to users (intervention participants and their social supporters). The cost of developing and delivering the intervention will be estimated in consultation with the app developers, data from the pilot study, the maintenance team, time and motion studies conducted at representative sites over a 2-week period, as well as administrative records during implementation. The costs of maternity service use to access care will be collected from all aim 1 participants and HCPs at exit; all intervention users and HCPs will provide the cost of care seeking and intervention involvement. We will identify comprehensive tasks required by both users (eg, time used to seek care) and HCPs (eg, training and staff time) and quantify public-sector resource use during the use and provision of the HCP-led service during the 3 years of implementation. Routine and additional public-sector unit costs will be collected from the health management information system [100] and administrative records at the facility and district levels, MOH, and other safe motherhood implementing partners. Direct and indirect costs to intervention users and HCPs because of involvement in the intervention (such as trainings, time used to seek care, and time used by HCPs to enroll users on the app) will be collected from participant exit interviews and administration records. The costs of providing user phones and solar chargers will be explored.

Cost-Effectiveness Analysis

Cost analysis will include estimating program costs, costs to HCPs, and costs to users as described above. We will also develop a decision tree model to assess the potential impact of economic, clinical, or health outcomes of the Support-Moms intervention against routine care [101,102]. The model will incorporate cost items, relevant clinical probabilities, and case outcomes, allowing a cost-effectiveness evaluation. We will combine the costs and outcomes for each branch of the tree using branch possibilities to simulate the expected costs and outcomes of the intervention and routine care. We will hypothesize service users using routine maternity services or enrolled on the Support-Moms app (per trial arm) as they pass through different health states over time and within acute and chronic health states of 3 key maternal morbidities of sepsis,

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postpartum hemorrhage, and hypertensive disorders [70,103-105]. Our cost-effectiveness evaluation will account for the outcomes for both the mother and the infant throughout their lifetime at the annual discounting rate of 3% [106]. The clinical and cost outcomes for the infant (eg, low birth weight and stillbirth or intrauterine fetal deaths) will be incorporated in the decision tree. We will use 1-way and probabilistic sensitivity analyses to quantify the confidence level or robustness in this model analysis output in relation to the outputs and the payer's willingness to pay thresholds [101,107]. We will estimate ICERs in terms of cost per additional HCP-led skilled birth delivery and per death averted. In addition, we will estimate ICERs per disability-adjusted life years averted and quality-adjusted life years (QALYs) gained (QALYs derived from the collected SF-6Dv2 data) as the main summary measures of cost-effectiveness [108] in line with the country's gross domestic product per capita (GDPpc) [109], to assess the value for money of adopting or providing the Support-Moms app long-term compared to routine care. If ICERs per QALY or per disability-adjusted life years <300% of GDPpc, Support-Moms will be deemed cost-effective, highly cost-effective for ICERs <100% of GDPpc, and not cost-effective otherwise. The decision tree and cost-effectiveness analyses will be programmed in TreeAge (TreeAge Software, LLC).

Ethical Considerations

The ethics approval was obtained from the Mbarara University of Science and Technology Research Ethics Committee (MUST-2022-631) and Uganda National Council for Science and Technology (HS3366ES). Study site administrative permission was obtained from the Mbarara district health officer, Mbarara City Health Officer, Mitoma District health officer, and the director of clinical services at the MOH. We are continually seeking and obtaining written informed consent from all study participants before enrolling in the study. The participants can withdraw from the study at any time. Participant data are anonymized at all times. The study was registered at ClinicalTrials.gov (NTC05940831). The research outcomes from this study will be published in international peer-reviewed journals and presented to the Ugandan MOH as policy briefs and at selected national and international conferences.

We are making firm attempts to adequately explain study purpose, schedule, expectations at the time of enrollment, and data collection and continually updating residence and phone details at each visit to minimize loss to follow-up. We are using appropriate means of contact based on participant preference and information on the best telephone network for the time of the day to telephone or send text messages, with emphasis that participation in this study is voluntary. However, reasons for decline or withdrawal from the study are being sought and documented. Participants are reimbursed for their study visits; a small compensation for their transport worth approximately UGX 20,000 (US $5.50) altogether is given at the end of each of the 2 planned baseline and exit interviews. Participating HCPs are reimbursed with US $5 as compensation for their time after every interview. The estimated time needed for interviews and other study procedures per visit is approximately 1.5 hours.

Results

This study was funded in September 2023. Ethics approval was obtained in February 2024, and actual data collection started in March 2024. As of January 2025, 75% (618/824) of all projected study participants have consented and been recruited into the study. Participants are expected to be followed up until delivery, and 15% (124/824) of the participants have exited to date. Data analysis for the trial is expected to start as soon as the last participant exits (expected in March 2026). The qualitative interviews will start in April 2025, and data will be analyzed and published as soon as data collection is done. Data collection is expected to be completed by March 2027.

We are currently recruiting at least 60 women or individuals and their social supporters per month. We have registered no loss to follow-up so far.

Discussion

We are targeting to recruit 824 pregnant women or individuals who have not yet presented for ANC by their second trimester, residing in Mitooma and Mbarara districts, with self-reported access to a cell phone with reception in their home for personal use, and are able to identify at least 2 social supporters living within the study districts. Uganda has approximately 30 million people who access mobile phones (most adult Ugandans), and 71% of users are connected using a basic feature phone [110]. Women or individuals are being identified by CHWs and VHTs, who then notify the study RAs to contact and seek written informed consent before enrollment into the study. Eligible social supporters who own a cell phone for personal use with reliable reception and know the study participant is pregnant be asked to provide consent and will be recruited within the first 2 weeks preceding enrollment of the pregnant women or individuals to ensure an ongoing relationship at the time of their enrollment. Adult HCPs who conduct deliveries within the study sites and MOH facility managers and stakeholders who participate in budgeting, procurements, or funding for facilities are being identified and offered enrollment into the study.

We developed an intervention aimed at improving communication of targeted, health-related information, motivating and mobilizing SS for pregnant women to use maternity services in rural southwestern Uganda (Support-Moms) [36]. Through an iterative approach, we (1) identified preferred key ANC topics from stakeholder interviews with 30 women and 5 HCPs and characterized a preferred messaging intervention; (2) developed content for SMS text and audio messages with 4 medical experts based on identified topics; (3) designed an app prototype through partnership with an mHealth development company (iStreams); and (4) pilot-tested the prototype and sought user experiences and feedback to refine the intervention through 3 different sets of 10 iterative exit interviews, 2 focus group discussions, and 5 cognitive interviews.

We are currently conducting a type 1 hybrid effectiveness-implementation trial [111] to test if this novel patient-centered mHealth-based SS intervention is effective and

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cost-effective if implemented into routine care from individual and facility perspectives. We will simultaneously assess other implementation, service, and client outcomes per the framework by Proctor et al [66] and refine implementation strategies for future scale-up using the CFIR (individuals, intervention, inner and outer settings, and process). We hypothesize that this intervention will be an effective and cost-effective strategy to improve maternity service use for women in rural Uganda and similar settings. Data collection is underway. Our results will present the functionality of our mHealth intervention, its ability to stimulate and encourage routine health care use, and improve maternal-fetal health outcomes among all rural women, including those with limited education. The results of our work will be usable for other groups designing similar interventions to promote perinatal health in resource-poor settings. Results of this study will also provide requisite data for maternal health policy change and lay the groundwork for evaluation for a regional implementation of the intervention.

Notably, our study will have some strengths. Unlike in many studies, we used conceptual frameworks to characterize and develop patient-centered content and design aimed at making findings more relevant and generalizable to rural communities where the impact of such interventions is likely to be the greatest. This approach is often lacking in mHealth development, most of which is often led by developers and investigators, with limited input from end users [11,14,112]. While many mHealth interventions have been developed in Uganda [113-115], very few have been in the reproductive health field [114,116], and fewer have been evaluated at scale in the public sector [115,117]. Therefore, our study will be among the first ones to test mobile maternal health apps in a randomized controlled trial in Uganda, concurrently assessing effectiveness and other implementation metrics, information that is critical for guiding ultimate use and integration of this intervention in routine care. In this study, we are studying a high-risk population, in which <70% of women deliver with a skilled attendant [15], <58% attend at least 4 ANC visits (of the 8 recommended by the WHO), and thus are likely to benefit from this intervention. We believe that our grounded approach, using appropriate implementation science models and partnering with key regional stakeholders to evaluate an intervention in a rural low-resource setting, will enhance the likelihood of uptake, adoption, and integration into routine care.

We are leveraging existing CHWs, social networks, and resources to encourage uptake, retention, and adoption within a community that largely depends on family and community networks to thrive [42]. This approach is hypothesized to improve pregnancy experiences, partner involvement, support, communication, and mental health during and after pregnancy, ultimately offsetting the downstream cost of avoidable maternal morbidity and mortality [50-53]. We are also building on our pilot, promising preliminary data, and it will provide vital evidence about effectiveness, uptake, and sustained use of this tailored mHealth approach designed to address common individual, family, and community or societal barriers to health care use in Uganda.

We are building on our experience from our previous work done within a typical public health facility setting to recruit and follow up participants. Many people in Uganda move frequently in search of stable work or new settlements, including pregnant individuals [25]. In addition, some change or lose their mobile phones or phones could be inaccessible at times due to network issues. We are using our previous clinical research experience in conducting similar trials to maximize the feasibility of our mHealth intervention and retention in care. SMS distribution is controlled, and women are routinely scheduled for ANC randomly and independently. Consequently, the risk of contamination (eg, discussing and sharing information) at the facility level is minimized. To minimize potential contamination in the community, we are making an effort to clearly explain the study procedures to CHWs or HCPs and intervention women who may learn about different arm allocations through casual conversations, an approach that worked well during our pilot. We have developed and administered a quality control checklist for a few randomly selected control participants so far to assess contamination between arms every 3 months.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study will also be available from the corresponding author on reasonable request.

Authors' Contributions

All authors conceptualized the project and participated in the research protocol writing. ECA wrote the first draft. All authors reviewed the manuscript and approved it for submission.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
Peer review report from the SIHH - Science of Implementation in Health and Healthcare Study Section, Eunice Kennedy Shriver National Institute of Child Health and Human Development (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 129 KB - resprot_v14i1e67049_app1.pdf]

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Abbreviations

ANC: antenatal care
CFIR: Consolidated Framework for Implementation Research
CHW: community health worker
GDPpc: gross domestic product per capita
HC: health center
HCP: health care provider
HIPAA: Health Insurance Portability and Accountability Act
ICER: incremental cost-effectiveness ratio
LMICs: low- and middle-income countries
mHealth: mobile health
MMR: maternal mortality ratio
MOH: Ministry of Health
QALY: quality-adjusted life year

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RA: research assistant
REDCap: Research Electronic Data Capture
SM: scheduled messaging
SS: social support
SSA: sub-Saharan Africa
UNC: University of North Carolina
VHT: village health team
WHO: World Health Organization

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Protocol

Unintended Prolonged Opioid Use: Protocol for a Case-Controlled Trial

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Abstract

Background: Misuse of prescription opioids remains a public health problem. Appropriate short-term use of these medications in opioid-naive patients is indicated in selected settings but can result in unintended prolonged opioid use (UPOU), defined as the continuation of opioid therapy beyond the period by which acute pain would have been expected to resolve. Clinical strategies aimed at preventing UPOU are lacking due to the absence of information about how this poorly understood clinical phenomenon actually develops.

Objective: In this research project, 3 Clinical and Translational Science Awards (CTSA) programs (Mayo Clinic, University of Michigan, and Yale University) leveraged the conceptual framework for UPOU to investigate how patient characteristics, practice environment characteristics, and opioid prescriber characteristics facilitate or impede UPOU. All data management and analyses were conducted at a fourth CTSA program (University of Minnesota). This work was accomplished by pursuing 3 specific aims.

Methods: In aim 1, opioid-naive adults receiving an initial opioid prescription were recruited for study participation. Opioid prescriptions were identified longitudinally, and patterns of use were categorized as short-term, episodic, or long-term use using established criteria. Using a prospective case-control design, patients progressing to UPOU were matched 1:1 with patients who did not develop UPOU, and differences in patient characteristics were assessed. In aim 2, clinicians who prescribed opioids to patients in aim 1 were identified and recruited for prospective assessments. Institutional and individual practice environments were assessed using a validated self-report survey. In aim 3, structural equation modeling was used to evaluate data collected in aims 1 and 2, and identified interactions were further evaluated in a large national administrative claims database.

Results: Patient recruitment began on August 1, 2019. However, due to the COVID-19 pandemic, patient recruitment was slowed and intermittently interrupted over the ensuing 3-year period. As a result of regional variations in the impact of the COVID-19 pandemic on research activities, the majority of patient and clinician recruitment occurred at the Mayo Clinic site.

Conclusions: Following complete data analyses, it is anticipated that electronic health record systems will be leveraged to help clinicians identify at risk patients and to develop direct-to-patient educational materials to raise awareness of the risk factors for developing UPOU.

Trial Registration: ClinicalTrials.gov NCT04024397; https://clinicaltrials.gov/study/NCT04024397

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International Registered Report Identifier (IRRID): DERR1-10.2196/72032

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KEYWORDS

opioid use; case-control; unintended opioid use; prolonged opioid use; prospective

Introduction

Background

Misuse of prescription opioids remains a public health problem [1]. Appropriate short-term use of these medications in opioid-naive patients is indicated in selected settings but can result in a previously underrecognized segue to unintended prolonged opioid use (UPOU), defined as the continuation of opioid therapy beyond the period by which acute pain would have been expected to resolve [2,3]. Clinical strategies aimed at preventing UPOU are lacking due to the absence of information about how this poorly understood clinical phenomenon actually develops.

Investigators at Mayo Clinic previously organized a group of thought leaders to develop a conceptual framework for understanding the broad array of factors potentially contributing to UPOU [4]. A conceptual framework is essential both to guide the study of this clinical problem and to identify potential targets for interventions aimed at mitigating the development of UPOU. The framework is comprised of 3 domains, including patient characteristics, practice environment characteristics, and opioid prescriber characteristics that interact to either facilitate or impede UPOU (Figure 1) [4].

Figure 1. The conceptual framework for unintended prolonged opioid use.

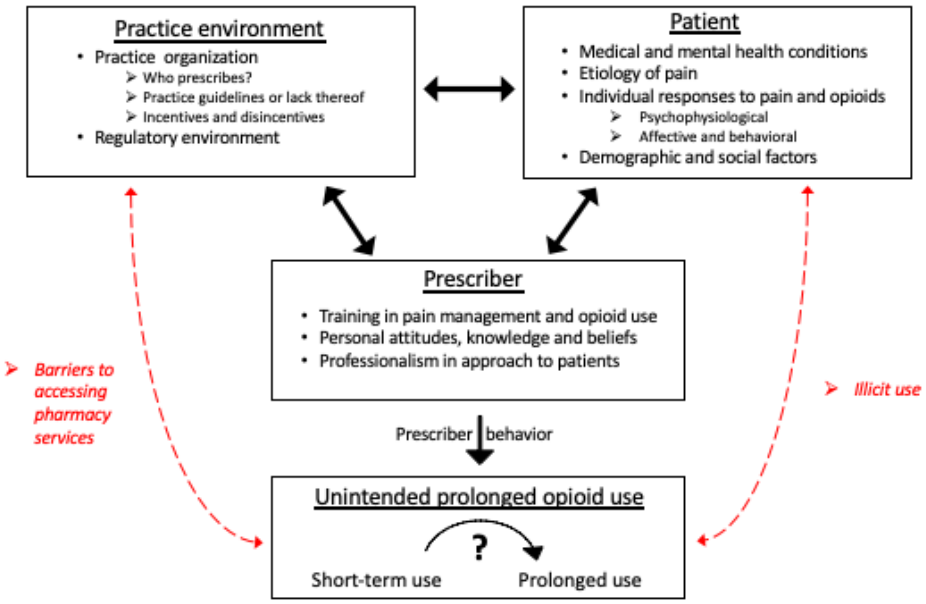

Within each domain, potential factors, drawn from the relevant literature, moderate or mediate the influence of each domain. However, the necessary evidence within each of these domains is frequently lacking. This is critically important because 25% of patients in a population who received an initial opioid prescription proceeded to UPOU [3]. This work relied on a medical records linkage system unique to the geographically defined region, limiting the ability to perform larger studies across different patient populations. It also did not perform prospective assessment of several factors important to evaluate the proposed conceptual framework.

Study Objectives

In this research project, 3 Clinical and Translational Science Awards (CTSA) programs (Mayo Clinic, University of Michigan, and Yale University) leveraged the conceptual framework for UPOU to investigate how the patient characteristics, practice environment characteristics, and opioid prescriber characteristics facilitate or impede UPOU. All data management and analyses were conducted at a fourth CTSA program (University of Minnesota). This work was accomplished by pursuing three specific aims.

Specific Aim 1

The first aim was to identify incident cases of UPOU and prospectively assess their characteristics in comparison to new opioid users who did not progress to UPOU. At each site, opioid-naive adults receiving opioid prescriptions were enrolled. Opioid prescriptions and self-reported opioid use were followed, and patients progressing to UPOU were identified in real time. A matched sample of patients who did not develop UPOU were recruited for assessment of framework elements, including biochemical confirmation of opioid use, pain-related measures of physical and emotional functioning, and medical and social histories.

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Specific Aim 2

The second aim was to assess clinicians prescribing opioids to incident cases of UPOU and new opioid users who did not progress to UPOU. Clinicians treating patients recruited in aim 1 were recruited for prospective assessment of prescriber characteristics including questions about past training in pain management, and attitudes and beliefs about pain and opioid use. The practice environment was assessed including practice organization, practice size, and estimated proportion of patients receiving pain management services.

Specific Aim 3

The third aim was to evaluate the conceptual framework. Using the information gathered in aims 1 and 2, structural equation modeling (SEM) was used to evaluate the associations between framework elements in each domain. Identified interactions were further evaluated in a large nationally representative administrative claims database.

Methods

Study Settings and Participants

Overview

In specific aim 1, opioid-naive adults receiving an opioid prescription (n=780 at each site) were identified at each clinical site (Mayo Clinic, University Michigan, Yale University) and recruited for study participation. A research coordinator assisted in activating a mobile platform on each patient's personal smartphone for purposes of providing informed consent and completion of study outcome measures. Opioid prescriptions were identified longitudinally by review of each patient's electronic health record (EHR). Patients progressing to UPOU were identified in real time, and patterns of opioid use were categorized as short-term, episodic, or long-term use using the Consortium to Study Opioid Risks and Trends (CONSORT) criteria [5]. Patients meeting criteria for episodic or long-term use were considered to have progressed to UPOU. Characteristics associated with UPOU were used to assess framework elements, including biochemical confirmation of opioid use; pain-related measures of physical and emotional functioning; and medical, surgical, psychiatric, and social histories.

In specific aim 2, clinicians who prescribed opioids to patients in aim 1 were identified and recruited for prospective assessments. Institutional and individual practice environments were assessed using a self-report survey validated in a national sample of physicians [6].

In specific aim 3, SEM was used to evaluate data collected in aims 1 and 2 to identify the associations between framework elements in each domain. Identified interactions were further evaluated in a large national administrative claims database (OptumLabs Data Warehouse [OLDW]).

Study Settings

Each CTSA clinical site leveraged established resources and clinical infrastructure.

Mayo Clinic

Olmsted County residents who previously consented to have their medical records used for research purposes were identified using the Rochester Epidemiology Project (REP) medical records linkage system [7,8]. The REP provides access to all medical records for Olmsted County residents. The indications for opioid use in these patients were both surgical and nonsurgical pain. Patients recruited from this site reflected the characteristics of UPOU as it developed in a geographically defined population.

University of Michigan

The surgical specialty clinics at the University of Michigan were used to identify opioid-naive patients receiving an initial opioid prescription following common surgical procedures, including knee and hip arthroplasty, inguinal hernia repair, intra-abdominal procedures, and thoracic and breast procedures [9]. The indication for opioid use in these patients was acute surgical pain. Patients recruited from this site reflected the characteristics of UPOU as it developed in a surgical setting.

Yale University

Yale New Haven Health is a large health care delivery system that provides services to individuals residing in the greater New Haven, Connecticut area. The EHR was leveraged to identify opioid-naive adults receiving an initial opioid prescription. These individuals were contacted using the patient communication portal of the EHR to assess their interest in participating in the research project. The indication for opioid use among these patients was surgical and nonsurgical pain. Patients recruited from this site reflected the characteristics of UPOU as it developed in a large health care delivery system.

Study Participants

A total of 780 patients were approached for recruitment at each site (N=2340), and eligibility criteria for study participation are outlined in Textbox 1. Patients meeting these eligibility criteria were further categorized based on CONSORT criteria [5]. Criteria for the long-term CONSORT category included episodes of opioid prescribing lasting longer than 90 days and including 120 or more total days of supply or 10 or more prescriptions [5]. Criteria for the episodic CONSORT category included episodes lasting 90 days or longer, with total days of supply being fewer than 120 and the total number of prescriptions filled being fewer than 10. Criteria for the short-term CONSORT category included episodes of opioid prescribing lasting 90 days or fewer [5]. Although study participation was limited to adults who own a smartphone, recent data from January 2018 demonstrated 77% of US residents own a smartphone [10].

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Textbox 1. Eligibility criteria.

Inclusion criteria:

- Age ≥18 years
- No use of opioids for 6 months before the issuance of the initial opioid prescription as confirmed by review of the electronic health record and patient self-report
- Willingness to participate in all aspects of the study including use of the mobile platform on their personal smartphone

Exclusion criteria:

- Cancer-associated pain
- Concurrent treatment for cancer (eg, chemotherapy and radiation therapy)
- Residence in an extended care facility
- Any surgery or hospitalization within the past 6 months
- Mental health disorders that could impede functioning in an ambulatory care setting (eg, schizophrenia and dementia)
- Non–English-speaking individuals
- No smartphone; although study participation was limited to adults who own a smartphone, recent data from January 2018 demonstrated that 77% of US residents own a smartphone [10]

Specific Aim 1

Overview

At each of the 3 sites, a total of 780 opioid-naive adults receiving an initial opioid prescription were approached for enrollment. Subsequently issued opioid prescriptions were monitored by reviewing the EHR, and patients progressing to UPOU were identified in real time. Time-matched samples of patients who did and did not develop UPOU were recruited for assessment of outcome measures.

Participant Recruitment

Participant recruitment was site specific. For example, the Mayo Clinic site leveraged the resources of the REP to identify a population-based cohort of potential patients who had previously provided informed consent for the use of their medical records for research purposes. Since 2002, Mayo Clinic and Olmsted Medical Center have used a proprietary software system to document and manage all prescriptions including prescriptions for opioids [11]. These two institutions provide a vast majority of medical care for Olmsted County residents [7,8,12,13]. The electronic prescription system was used to identify previously opioid-naive Olmsted County residents receiving an initial opioid prescription as previously described [3]. These individuals were contacted by telephone and invited to participate in the study. The Michigan site used resources associated with the University of Michigan Analgesic Outcomes Study (AOS) [9]. The AOS is a prospective, observational cohort registry of postsurgical acute and chronic pain outcomes. Previously opioid-naive patients in the AOS registry were invited to participate in study. The Yale University site used the EHR to identify previously opioid-naive patients receiving an initial opioid prescription. More specifically, the EHR was screened by study personnel for the issuance of any opioid prescription, and previously opioid-naive patients were contacted using the EHR patient portal system and invited to participate in the study.

Mobile Smartphone Platform

All study participants were assisted by study personnel in downloading the smartphone platform (CareEvolution). The smartphone platform complied with the security and privacy controls defined by the National Institute of Standards and Technology SP 800 53 Rev 5 as designated by the Federal Information Security Modernization Act. The platform was granted authorization to operate by the National Institutes of Health and is Health Insurance Portability and Accountability Act compliant [14]. The smartphone platform was used to obtain informed consent and to collect all outcome measures.

Timeline for Establishing Consortium to Study Opioid Risks and Trends Criteria for Opioid Use

The timeline of the study was governed, in part, by the temporal requirements for applying CONSORT criteria (Figure 2). The beginning date of an episode of opioid use was defined as the date that the initial prescription was issued, with no previous opioid prescriptions issued for the preceding 6-month time period. The end date of an episode was the date that the last dispensed medication supply was exhausted, based on the days of supply as documented in the prescription instructions with no opioid dispensing in the ensuing 6 months. Patients who continued to use opioids on day 90 following issuance of the initial opioid prescription were invited to participate in the study assessment. Although it was not possible to accurately apply CONSORT criteria for episodic or long-term use on day 90, the study assessment was performed at this time point to ensure patients were captured at the earliest stages of episodic or long-term use. The status of opioid use in these patients was monitored every month by reviewing the EHR. This approach to follow-up limits the time interval between establishment of CONSORT criteria for episodic or long-term use and the final study assessment.

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Figure 2. Flow diagram for establishing Consortium to Study Opioid Risks and Trends (CONSORT) criteria for opioid use.

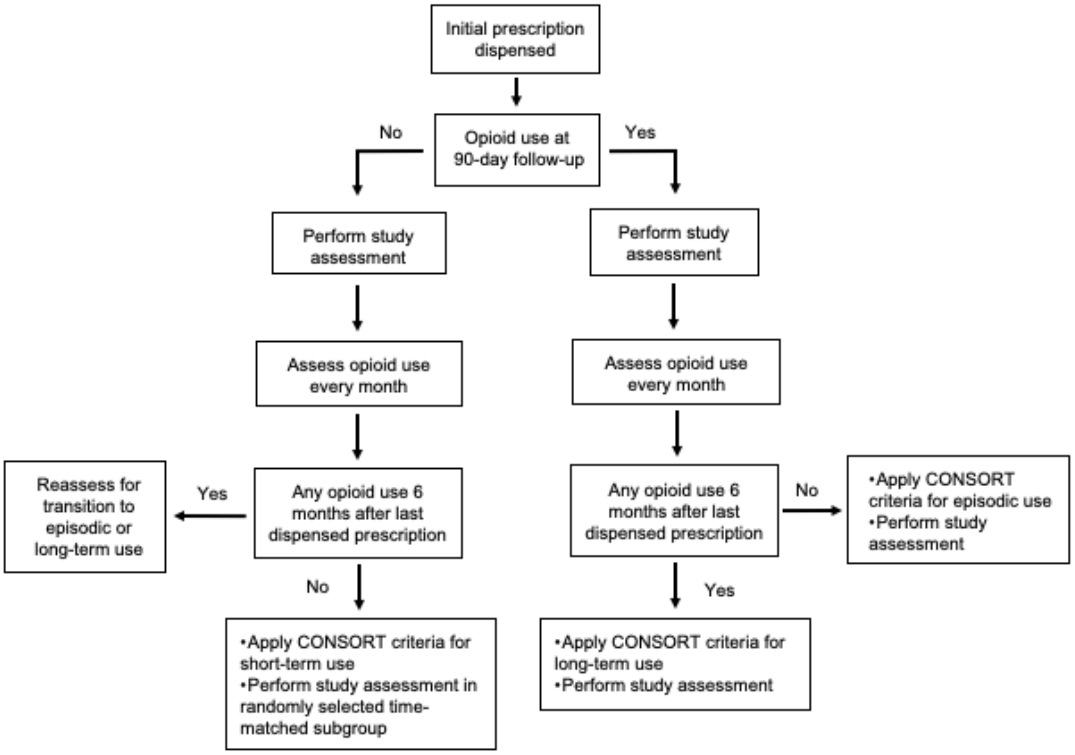

A randomly selected group of patients meeting criteria for short-term use at day 90 were invited to participate in the study assessment. This group of patients was selected to be time-matched 1:1 to patients continuing to use opioids at day 90 (initial issue date ±2 weeks) Although it was not possible to accurately apply CONSORT criteria for short-term use until month 6 following issuance of the last prescription, the study assessment was performed at this time point to ensure that patients were captured in the earliest stages of short-term use. Because it was anticipated that the majority of the cohort would meet criteria for short-term use, it was not feasible to invite all patients to participate in the study assessment.

Study Assessments

Assessments were performed at 2 time points: 3 months following dispensing of the initial opioid prescription and 9 months following dispensing of the initial opioid prescription.

Demographics and Clinical Characteristics

Demographic and clinical characteristics were assessed including age, sex, ethnicity, marital status, education, employment status, BMI, and past medical and surgical histories including chronic pain.

Verification of Opioid Status and Dose

Opioid use and dose were verified by review of pharmacy and medical records. Opioid doses were converted to daily morphine equivalents using a conversion calculator as previously reported [15-17]. The opioid status was biochemically verified with a urine toxicology screen.

Occurrence and Risk of Opioid Misuse

The occurrence and risk for opioid misuse was assessed using 3 instruments. The Alcohol, Smoking, and Substance Involvement Screening Test (ASSIST) was administered. The ASSIST is validated [18] and used in the National Institute on Drug Abuse Quick Screen [19]. The Prescribed Opioid Difficulties Scale [20] was used to assess for substance use disorders associated with use of prescribed opioids [21]. The Opioid Risk Tool is a brief questionnaire that is validated [22] and was used to assess the risk of opioid misuse.

Symptoms of Opioid Withdrawal

Symptoms of opioid withdrawal were assessed using the Clinical Opiate Withdrawal Scale, which is an observer-rated instrument [23,24].

Opioid Craving

Opioid craving was assessed using responses (0 to 100 on a visual analog scale) to 3 questions: (1) How much do you crave opioids? (2) How often do you think about the next dose? and (3) How strong is your urge to take more medication than prescribed? This approach is validated [25] and was used to assess opioid craving [26-28].

Pain Intensity

Pain intensity was assessed using the 11-point verbal pain rating scale. The validity of the verbal pain rating scale is well established [29-31].

Michigan Body Map

The Michigan Body Map (MBM) is a self-report measure to assess body areas where pain is experienced. The MBM has demonstrated utility, reliability, and construct validity [32,33]. The MBM measure has been used to assess pain in a broad range of clinical settings [34-41].

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Pain-Related Psychosocial Functioning

The Multidimensional Pain Inventory (MPI) measures the psychosocial impact of chronic pain [42]. The MPI has proven reliability and construct validity [43].

Negative Affect

Depressive symptoms and pain catastrophizing are key components of negative affect [44]. The Center for Epidemiologic Studies-Depression scale provides a validated measure of depressive symptoms [45] in patients with chronic pain [46,47]. The Pain Catastrophizing Scale provides a measure of negative cognitions and emotions associated with actual or anticipated pain experiences [48].

Baseline Smoking Status

Baseline smoking status was assessed using the techniques used by the Behavioral Risk Factor Surveillance System: (1) Have you ever smoked a cigarette, even a puff? (Yes or No); (2) Have you smoked at least 100 cigarettes in your entire life? (Yes, No, or Not sure); and (3) Do you now smoke cigarettes every day, some days, or not at all? (Every day, Some days, or Not at all) [49].

Quantitative Sensory Testing

Heat pain perception was quantified using the Computer Aided Sensory Evaluator IV (WR Electronics). This quantitative sensory testing device is validated [50-52], and we have used it to quantify opioid-induced hyperalgesia [15,16] and to study other pain-related states associated with altered heat pain perception [53-56].

Concomitant Treatments

Use of concomitant treatments for pain were assessed (eg, nonopioid medications, supplements, acupuncture, physical therapy, and chiropractic).

Sample Size Estimates

Based on our preliminary work [3,9,57-62], we estimated the rate of episodic opioid use would be 20% and the estimated rate of long-term use would be 7%. This would yield approximately 200 (780 × .27 = 210.6) patients developing some form of UPOU at each site. The analysis for specific aim 1 involved examining a wide variety of predictors of UPOU rather than 1 specific exposure. As a result, the minimum detectable odds ratios across a range of sample sizes were calculated. Setting the power at 0.8 and α at .05 (2-tailed), a total sample size of 1200 (600 cases and 600 controls) allowed detection of an odds ratio of 1.38 with a predictor that had a prevalence of 0.5 in controls and zero correlation in exposure between cases and controls. The detectable odds ratio (OR) goes up as the correlation between cases and controls becomes positive (detectable OR=1.48 with r=0.3), and it also increases as the prevalence of the exposure in the control group increases (detectable OR=1.55 with r=0.3 and prevalence of exposure=0.7 in controls).

Data Analysis Plan

The primary research question for specific aim 1 was to identify patient characteristics associated with UPOU. A case-control design was used with controls time matched to cases. The expectation was that multiple patient characteristics would be associated with UPOU. Descriptive statistics (means, medians, and ranges) were generated to compare cases and controls on all patient characteristics. Differences in patient characteristics between cases and controls were assessed using bivariate tests including the McNemar test for categorical variables and paired 2-tailed t tests (or Wilcoxon signed rank test, if needed) for continuous variables. The results of the bivariate analyses were used to select variables for conditional logistic regression analyses to regress UPOU on all variables identified as potentially associated with the UPOU. The regression models were constructed in stages by incorporating predictors in conceptual blocks and using standard selection methods to retain variables. All models included a fixed effect for site. ORs and 95% CI were used to evaluate the magnitude and statistical significance of the association between predictors and outcome.

Specific Aim 2

Overview

Clinicians prescribing opioids to patients in specific aim 1 were recruited for assessment of prescribing characteristics.

Clinician Recruitment

Clinician recruitment was site specific, but a similar stepped approach was used. First, an email message was sent to each clinician briefly explaining that they had issued an opioid prescription to a patient participating in the observational study. The email note contained a link to a validated self-report survey regarding clinician attitudes and beliefs about opioids, and clinicians were asked to complete the survey [6]. Clinicians who did not respond were sent a reminder email 1 week later. Clinicians who did not respond to the reminder email after an additional 1-week period were sent a final email. After a 2-week period, all clinicians not responding to the email messages were sent a paper version of the survey using each site's intracampus mail system. Clinicians not responding to the mailed survey after a 4-week period were considered nonresponders.

Study Assessment

Clinicians were assessed using the Clinicians' Attitudes and Beliefs About Opioids Survey (CAOS) [6]. The validity and test-retest reliability of the CAOS has been reported [6]. The CAOS also assesses clinician demographics and practice characteristics including sex, age, years in practice, professional training (physician surgeon, nonsurgeon physician, nurse practitioner, and physician's assistant), organization of practice (single specialty, partnership, solo, or multispecialty), practice structure (academic or university versus clinic or hospital based), proportion of weekly patient appointments involving management of chronic pain, and proportion of patients with chronic noncancer pain currently receiving opioids.

Sample Size Estimates

There was no information available to predict how many unique clinicians prescribe opioids to patients in aim 1. A 2013 meta-analysis of provider surveys estimated a survey response rate among health professionals of 53% [63]. Thus, we conservatively estimated the response rate would be between

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35% to 65% and anticipated between 410 and 760 clinicians would complete the survey.

Data Analysis Plan

The primary research question for specific aim 2 was to identify clinician and practice environmental characteristics associated with UPOU. The analysis plan was similar to the plan described for specific aim 1. Descriptive statistics (means, medians, and ranges) were generated to compare cases and controls on all clinician and practice environmental characteristics. Differences in clinician characteristics between cases and controls were assessed using bivariate tests including the McNemar test for categorical variables and paired 2-tailed *t* tests (or Wilcoxon signed rank test, if needed) for continuous variables. The results of the bivariate analyses were used to select variables for conditional logistic regression analyses to regress UPOU on all variables identified as potentially associated with UPOU. The regression models were constructed in stages by incorporating predictors in conceptual blocks and using standard selection methods to retain variables. All models included a fixed effect for site. ORs and 95% CI were used to evaluate the significance of the associations between predictors and outcome.

Specific Aim 3

Overview

Using the data generated in aims 1 and 2, SEM was used to evaluate the associations between framework elements in each domain. Identified associations were further evaluated in a large national administrative claims database.

SEM Analysis

The primary goal of aim 3 was to combine the results from aims 1 and 2 and extend these by building a statistical model that synergistically integrated the three domains of the UPOU conceptual framework. The UPOU framework has a number of complexities that limit the use of regression including multiple correlated predictors and outcomes, unobserved constructs that are difficult to directly measure, and nesting of patients with clinicians who are nested within sites. SEM can estimate latent variables and include them as both exogenous and endogenous variables in the same model, use multiple observable and quantifiable indicators to estimate latent variables from the shared variability of these indicators, and accommodate multiple endogenous variables (ie, dependent variables or outcomes) in 1 model. Multilevel SEM can estimate latent variables at 1 or more levels (eg, patient and clinician levels) and appropriately test associations at and across these different levels for categorical and continuous outcomes.

The SEMs were developed in several steps. The number of measurement models were estimated for all constructs that potentially used latent variables. Descriptive statistics were examined including means, medians, SDs, ranges, measures of central tendencies, and normality of the distributions. Extensive preliminary analyses were conducted to evaluate possible inconsistencies in the data, outliers, and variations in the data, and clinically and statistically relevant cutoff points that may facilitate the analyses were identified. The primary outcome measure was UPOU, measured as a dichotomous variable of cases and time-matched controls. The predictors of interest were grouped into 3 domains: patient characteristics, practice environment, and clinician characteristics. Each of these domains contained a number of directly observable and directly unobservable constructs. Examples of directly observable variables in the patient characteristic domain included age, sex, and employment status. Examples of directly unobservable constructs in the patient characteristic domain included symptoms of opioid withdrawal, opioid craving, and the psychosocial impact of chronic pain. Analyses (eg, coefficient α, principal components analysis, and factor analysis) were conducted to determine how to optimally combine scale items into reliable measures.

After all measurement models were established, a comprehensive structural model describing the conceptual framework was developed. In the first step, models were fitted separately by domain. For example, a parsimonious model relating patient characteristics to UPOU was developed. This first step involved a model-testing approach to trim a saturated model containing all patient-level constructs to develop a final parsimonious model that maximally explained UPOU with the least number of parameters. The results from aim 1 analysis directly informed this stage, but models varied due to the use of latent variables and a different statistical model. The Akaike information criterion, Bayesian information criterion, and the root mean square error of approximation were used to guide decision model trimming and refinement. This process was conducted separately for all 3 domains. The second step combined the parsimonious, domain-specific models into an integrated model. This involved multilevel SEM with a patient-level outcome (eg, UPOU) and predictors at the patient level, the clinician level, and the practice environment level. This model started with the 3 parsimonious, domain-specific models but then was expanded to test for possible cross-level interactions. For example, the effects of pain management training on UPOU varied by patient age. The conceptual model, previous research, and empirical findings were used to guide the model-building process, particularly with regard to the direction of association and what interactions were tested. This was not a process for testing all possible interactions; rather, only specific indicated effect modifications were tested.

Missing data were evaluated to determine if the pattern was missing completely at random (MCAR) or missing at random (MAR). If missing data were MAR or MCAR, SEM techniques were used to estimate missing values using either full information maximum likelihood or multiple imputation. If missing data did not fit an MAR or MCAR pattern, other options were explored including pattern mixture models. To the extent possible, potential bias due to attrition and missing data over time were assessed. All analyses were conducted using Stata (version 15, StataCorp) or MPlus (version 7, Muthén & Muthén).

Sample Size Estimates

Common algorithms do not exist for assessing power for complex SEM; however, 3 aspects of sample size were considered. First, because of the iterative and complex nature of SEMs, it was important to verify that the sample size was

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sufficiently large to produce stable model estimates. There are simulation studies suggesting that for models of the size and complexity proposed, minimum sample sizes for model stability would likely be in the hundreds [64]. Second, comparing models requires a certain sample size. Published estimates of model degrees of freedom suggest that sample sizes in the hundreds would be sufficient to discriminate competing models [64]. Finally, given a set sample size, an expected detectable effect size was estimated. Setting statistical significance at =.05 (2-sided tests) and power at 80%, a sample size of 500, for example, would allow detection effects of approximately 0.13 SD units across time (ie, considered a small effect). Even accounting for losses due to missing data, which can become an issue when combining multiple sources of data at multiple levels, the proposed sample size of 1200 patients, and the smaller number of clinician and practice environments in which they were nested, should be sufficient to estimate stable, comprehensive models and detect relatively small associations between constructs.

National Administrative Claims Database Analysis

The data collected prospectively on clinicians and patients at the 3 clinical sites provided detailed data on patients and clinicians from varied settings but were necessarily limited in sample size and derived from institutions affiliated with academic medical centers. As a result, a large national claims database was used to explore the findings of this study in a much larger and more diverse population.

The OLDW is an open, collaborative research and innovation center founded in 2013 [65]. The core linked data assets include deidentified claims data for privately insured and Medicare Advantage enrollees and deidentified EHR data from a nationwide network of provider groups. The database contains longitudinal health information on enrollees and patients, representing a diverse mixture of ages, ethnicities, and geographical regions across the United States. The EHR data are sourced from provider groups and reflects all payers, including uninsured patients.

The OLDW was used to estimate a structural model similar to that used in the analyses of clinical data from aims 1 and 2. The latent factors representing clinician, patient, and environmental factors associated with patients developing OPOU were estimated using OLDW data, and the results were compared with those estimated in the clinical data. The OLDW contains beneficiary characteristics including gender, age, race and ethnicity, household income, and geography (ie, state, county, or zip code). For beneficiaries submitting health insurance claims, a broad range of information is available including pharmacy claims (ie, prescribing clinician, drug type and date dispensed, days of supply), clinician and facility claims (ie, Current Procedural Terminology 4 codes, *International Classification of Diseases* [*ICD*]-*9* or *ICD-10* procedure codes, and *ICD-9* or *ICD-10* diagnoses), dates and place of service, cost data (ie, charges and patient and insurance amounts paid), and clinician type and specialty. In addition, OLDW includes laboratory data for 30% to 40% of patients whose clinicians have contracted with laboratories that provide data to OLDW.

Many of the concepts to be tested with clinical data were approximated using administrative claims data. Diagnostic codes were used to measure comorbidities including depression, anxiety and substance use disorders. Procedure and diagnostic codes were used to infer pain etiology from surgery, trauma, and other causes. Place of service and clinician specialty codes were used along with prescription fill information to determine the source of opioid prescriptions. Patient geographic information and prescription fill information were used to determine regulations governing the use of prescription drug monitoring programs.

Ethical Considerations

The Mayo Foundation Institutional Review Board served as the reliant international review board (IRB) of record for all participating institutions including Mayo Clinic, the University of Michigan, Yale University, and the University of Minnesota. Written informed consent, using a mobile platform, was obtained from all study participants before study participation. Use of the mobile platform to obtain informed consent and collect study outcomes was IRB approved (#18-010484). All patient-related research information was deidentified before data analysis. All patients were remunerated US $50 for the initial screening, US $150 for the first clinical assessment, and US $100 for the second clinical assessment.

Reporting Guidelines

The reporting of study methods and results adhered to the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) guidelines [66].

Results

Study Recruitment

Overview

The research proposal was funded on January 3, 2019, and patient recruitment began on August 1, 2019. However, due to the COVID-19 pandemic, patient recruitment was slowed in March 2020 and halted in April 2020 for a 4-month period. Over the next 2-year period, patient recruitment was slowed or interrupted at each clinical site based on the regional impact and the individual health care system response to the COVID-19 pandemic. Compared with the more urban setting of the University of Michigan and Yale University, the impact of COVID-19 pandemic on the rural catchment area of Mayo Clinic was less disruptive and associated with fewer interruptions. As a result, the majority of patient and clinician recruitment occurred at the Mayo Clinic site. Due to the unanticipated effects of the COVID-19 pandemic on clinical research activities, two 6-month, no-cost extensions were granted by the funding agency, and all recruitment and data collection were completed by August 2024.

Patient Recruitment

Table 1 depicts the total number of cases and controls recruited at each site. The Mayo Clinic site recruited 83% (855/1030) of the cohort, the Yale University site recruited 14.3% (147/1030), and the University of Michigan site recruited 2.7% (28/1030). Data analysis of patient characteristics associated with UPOU

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has been completed and the manuscript is under active development.

Table 1. Patient recruitment by study site.

Study site	Patients, n (%)		
	Total (n=1030)	Cases (n=513)	Controls (n=517)
Mayo Clinic	855 (83)	422 (82.3)	433 (83.8)
University of Michigan	28 (2.7)	15 (2.9)	13 (2.5)
Yale University	147 (14.3)	76 (14.8)	71 (13.7)

Clinician Recruitment

A total of 148 clinicians completed the CAOS survey. The Mayo Clinic site recruited 146 (98.6%) clinicians, and 2 (1.4%) clinicians were recruited at the University of Michigan site. Recruitment of unique clinicians at the Mayo Clinic site was limited, in part, by clinicians who prescribed opioids to more than 1 patient. Due to unanticipated administrative barriers at Yale University, no clinicians were recruited at this site. The data analysis of clinician characteristics associated with UPOU has been completed and the manuscript is under active development.

SEMs and National Administrative Claims Database Analysis

The SEMs are under active development, and the results of the SEMs based on the case-control data will be submitted for publication in a peer-review journal. The administrative claims database from OLDW has been successfully retrieved and is actively being prepared for data analysis using the SEMs developed from the case-control data. The results of the SEM and OLDW analysis will be submitted for publication in a peer-review journal.

Discussion

Principal Findings

The anticipated results of this prospective, case-control study should provide ample data to understand how patient, clinician, and practice environment characteristics facilitate or impede development of UPOU. More specifically, multivariate logistic regression models will elucidate the individual influence of each domain (eg, patient, clinician, and practice environment) on UPOU and multilevel SEMs will provide an estimate of latent variables and test associations at and across these different levels for categorical and continuous outcomes. Widespread dissemination will be facilitated by the results derived from the broader analysis of the OLDW.

The results of this study will further build existing knowledge about the clinical characteristics associated with UPOU. For example, in a systematic review and meta-analysis of 33 studies comprised of 1,922,743 individuals, patient-level characteristics associated with UPOU after surgery included female sex; high school level education; previous mental health diagnosis of depression, anxiety, or posttraumatic stress disorder; cocaine or alcohol use disorder; tobacco use; and preoperative use of prescription opioids, antidepressants, benzodiazepines, or antipsychotic medications [67]. In addition, a history of back and neck pain, fibromyalgia, and migraine headache were associated with UPOU after surgery [67]. However, interpretation of these findings was limited by varying definitions opioid naivety and UPOU, clinical and statistical heterogeneity, and varying approaches for establishing baseline clinical characteristics. The imprecision of the meta-analysis was due, in part, to the use of large administrative and insurance claims data by studies included in the systematic review, which limited the number of studies that were available for inclusion in the subgroup analysis of patient characteristics. The results of our study will extend these findings by including surgical and nonsurgical patients and using uniform definitions of opioid naivety and UPOU. Finally, due to imprecision associated with establishing previous psychiatric diagnoses [68,69], the severity of current depressive symptoms, the presence of positive and negative affect, and the level of pain catastrophizing were included as study outcomes.

The clinical and research implications of the study results are important for 2 reasons. First, this study leveraged a conceptual framework and a case-control design to identify patient and clinician characteristics associated with UPOU. It is anticipated that the patient characteristics will have an immediate and significant impact on the clinical care of opioid-naive adults receiving appropriately indicated opioid prescriptions for short-term use. The identified clinician characteristics will provide the opportunity to develop and deliver targeted educational content to clinicians to raise awareness of UPOU. Second, development of SEMs and secondary testing in the much larger and more diverse cohort derived from the OLDW will facilitate the design of future research projects aimed at reducing development of UPOU.

Limitations

The timeline of the research project was disrupted by the COVID-19 pandemic, but data collection was facilitated by no-cost extensions and leveraging the rural catchment area of Mayo Clinic. This produced an imbalance in the number of patients and clinicians recruited between the 3 clinical sites. While the overall target sample size was largely attained and therefore target statistical power was met, the imbalance potentially limited generalizability and precludes site-specific analyses for Yale University and University of Michigan. The opioid use status of cases and controls were based on the number of prescriptions issued by clinicians. As a result, discrepancies could exist between the number of prescriptions issued compared with the number of prescriptions dispensed by pharmacies. Finally, the CONSORT criteria were adapted to categorize opioid use 3 months following the initial prescription.

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Although it is possible that the status of opioid use could change over time, all patients were followed an additional 6 months to assess the stability of the opioid use category in cases and controls.

Conclusions

Following completion of data analysis, the study results will be immediately available for widespread dissemination in clinical practice and for use in ongoing research projects. It is anticipated that EHR systems will be leveraged to identify at risk patients receiving an initial opioid prescription and to send alert messages to members of the care team. This preemptive approach could also be used to develop direct-to-patient educational materials to raise awareness of the risk factors for developing UPOU.

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Data Availability

The study data will be presented in the main results sections of peer-review journals and as supplemental files when indicated.

Authors' Contributions

WMH, DJE, JFW, CMB, and MMJ contributed to conceptualization. WMH, DJE, MC, NAS, and MMJ handled data curation. WMH, DJE, MC, NAS, and MMJ conducted formal analysis. WMH, DJE, JFW, CMB, and MMJ managed funding acquisition. WMH, MC, JFW, CMB, and MMJ contributed to investigation. WMH, DJE, MC, NAS, and MMJ. WMH, DJE, and NAS managed project administration. WMH, DJE, MC, JFW, CMB, and MMJ handled resources. WMH, DJE, MC, NAS, and MMJ managed software. WMH, DJE, MC. JFW, CMB, and MMJ contributed to supervision. WMH, DJE, MC, and NAS managed validation. WMH, MC, NAS, and JJM handled visualization. WMH, DJE, MC, NAS, JFW, CMB, and MMJ wrote the original draft. WMH, DJE, MC, NAS, JFW, CMB, and MMJ conducted review and editing.

Conflicts of Interest

WMH has received funding from the National Institutes of Health (NIH) and the US Food and Drug Administration (FDA). DJE, MC, and JFW have received funding from the NIH. CMB has received funding from the NIH and he has served as consultant for Merck Pharmaceuticals and Vertex Pharmaceuticals, and he has provided expert medical testimony. MMJ has received funding from the FDA, NIH, Centers for Disease Control and Prevention, American Cancer Society, and Agency for Healthcare Research and Quality.

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Abbreviations

AOS: Analgesic Outcomes Study
ASSIST: Alcohol, Smoking, and Substance Involvement Screening Test
CAOS: Clinicians' Attitudes and Beliefs About Opioids Survey
CONSORT: Consortium to Study Opioid Risks and Trends
CTSA: Clinical and Translational Science Awards
EHR: electronic health record
FDA: Food and Drug Administration
ICD: International Classification of Diseases
IRB: institutional review board
MAR: missing at random

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MBM: Michigan Body Map
MCAR: missing completely at random
MPI: Multidimensional Pain Inventory
NIH: National Institutes of Health
OLDW: OptumLabs Data Warehouse
OR: odds ratio
REP: Rochester Epidemiology Project
SEM: structural equation modeling
STROBE: Strengthening the Reporting of Observational Studies in Epidemiology
UPOU: unintended prolonged opioid use

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Protocol

Examining the Efficacy of the Telehealth Assessment and Skill-Building Kit (TASK III) Intervention for Stroke Caregivers: Protocol for a Randomized Controlled Clinical Trial

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Abstract

Background: Stroke is a leading cause of serious, long-term disability and has a sudden onset. Upon discharge to the home setting, families are thrust into providing care, often without sufficient training from health care providers. Aligned with current patient and caregiver guidelines, the Telehealth Assessment and Skill-Building Kit (TASK III) is a nurse-led intervention designed to empower caregivers to address their own needs and those of the survivor using innovative skill-building strategies.

Objective: This study aims to test the short-term (immediately after the intervention at 8 wk) and long-term (12, 24, and 52 wk) efficacy of the TASK III intervention, compared with an information, support, and referral (ISR) group, to improve caregiver life changes (ie, changes in physical health, physical functioning, emotional well-being, and general health) as a result of providing care.

Methods: A randomized controlled clinical trial design will be used with baseline data collection from 296 family caregivers by telephone after the stroke survivor is discharged home. Caregivers randomly assigned to the ISR group (n=148, 50%) will receive information from the American Heart Association about stroke family caregiving. Caregivers randomly assigned to the TASK III group (n=148, 50%) will receive a TASK III resource guide and information from the American Heart Association. Both groups will receive 8 weekly calls from a nurse, with a booster call a month later. Outcomes will be assessed by blinded data collectors at 8, 12, 24, and 52 weeks. The primary outcome (at 8 wk) is caregiver life changes measured by the Bakas Caregiving Outcomes Scale. Secondary outcomes are depressive symptoms; other symptoms (eg, stress, fatigue, sleep, pain, and shortness of breath); unhealthy days; diet; exercise; and self-reported health care use. Mediators are task difficulty, threat appraisal, and self-efficacy. Program evaluation outcomes (satisfaction and technology ratings) will also be analyzed.

Results: The trial was registered on March 10, 2022. Enrollment and random assignment of the first participant was on November 30, 2022, with an anticipated completion of recruitment by November 30, 2025. Completion of the primary end point data analysis

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is anticipated by August 31, 2026, with results expected to be reported on ClinicalTrials.gov by April 1, 2027. As of October 9, 2024, a total of 198 (66.9% of the proposed total sample of 296) family caregivers have been enrolled and randomly assigned to the TASK III group (n=98, 49.5%) or the ISR group (n=100, 50.5%). The last update was performed on January 25, 2024.

Conclusions: If the TASK III intervention is shown to be efficacious in the proposed randomized controlled clinical trial, our next goal will be to translate TASK III into ongoing stroke systems of care, providing a tremendous public health impact.

Trial Registration: ClinicalTrials.gov NCT05304078; https://clinicaltrials.gov/study/NCT05304078

International Registered Report Identifier (IRRID): DERR1-10.2196/67219

(JMIR Res Protoc 2025;14:e67219) doi:10.2196/67219

KEYWORDS

stroke; family caregivers; depressive symptoms; health-related quality of life; clinical trial; intervention study; protocol; nursing

Introduction

Background and Rationale

Each year, approximately 795,000 Americans experience a stroke, which is a leading cause of serious, long-term disability [1]. Because of disability, approximately 68% to 74% of stroke survivors require the care of family members [2,3], who are suddenly thrust into providing care without receiving proper training from health care providers [4-6]. The lack of training contributes to difficulty with caregiving tasks and high threat appraisal, defined as caregiver perceptions of ability to provide future care [7-10]. These stressful experiences place caregivers at risk for depressive symptoms and major life changes as a result of providing care (eg, physical health, physical functioning, emotional well-being, and general health) [7-15]. Finally, stressful caregiver experiences have been reported to impede the survivor's rehabilitation [16-18] and to increase costs from premature long-term institutionalization [11,19,20].

Major scientific and policy statements from the American Heart Association [17,21-25] and other guidelines [26-30] recommend (1) assessment of stroke family caregiver needs and concerns; (2) education on stroke-related care; (3) attention directed toward caregivers' physical and emotional health; and (4) individualized caregiver interventions that combine psychoeducational strategies with skill building (eg, problem-solving, stress management, and goal setting). Aligned with the American Heart Association recommendations and other published guidelines [17,21-30], the Telephone Assessment and Skill-Building Kit (TASK) II is a nurse-led intervention enabling caregivers to build skills based on the assessment of their own needs [31-38]. Unlike existing stroke caregiver interventions that require costly face-to-face interactions [22,23,33,39-41] and that focus primarily on the survivor's care [22,23,39-41], TASK II is delivered completely via telephone and empowers caregivers to address both their own and the survivor's needs using innovative skill-building strategies (eg, problem-solving, stress management, realistic expectations, time management, and communication with health care providers) using a mailed TASK II resource guide and calls with a nurse. Evidence has been published regarding content validity [32], treatment fidelity [36], caregiver satisfaction [32], and efficacy of the TASK II program with 254 stroke caregivers in a randomized controlled clinical trial (R01; R01NR010388; ClinicalTrials.gov ID: NCT01275495) [34]. TASK II, in comparison with an information, support, and referral (ISR) group, reduced depressive symptoms up to a year after baseline (in caregivers with mild to severe depressive symptoms) and reduced unhealthy days, a reflection of caregiver's physical and mental health at 8 weeks [34]; however, further enhancements were needed to improve caregiver life changes (ie, physical health, physical functioning, emotional well-being, and general health) and to provide additional telehealth modes of delivery based on caregiver preferences [34,38,42-44].

Through a funded R21 (R21NR016992; ClinicalTrials.gov ID: NCT03635151) feasibility study, the Telehealth Assessment and Skill-Building Kit (TASK III) version has been optimized for delivery via various modes of technology [38] and provides a stronger emphasis on caregiver self-management [37,45,46] of their own symptoms and health care needs to sustain positive life changes and health outcomes over time. Caregivers can now choose how they want to access the TASK III resource guide (mailed hard copy, e-book, USB drive, or website) and how they would like to interact with the nurse (telephone, FaceTime, or web-based videoconferencing). Our published findings demonstrate the usefulness, ease of use, convenience, feasibility, and acceptability of our new TASK III telehealth technology [38]. Our published findings have also shown content validity, accuracy, feasibility, and acceptability of our new skill-building tip sheet on goal setting to enhance caregiver self-management of symptoms and health [37]. As part of the R21 feasibility study, a pilot study with 74 stroke caregivers randomly assigned to the TASK III (n=36) or ISR (n=38) group revealed successful recruitment, retention, treatment fidelity, high satisfaction ratings, and positive data trends.

In this larger randomized controlled clinical trial (R01NR020184; ClinicalTrials.gov ID: NCT05304078), we plan to enroll 296 caregivers to test the efficacy of the TASK III program (n=148, 50%), in comparison with the ISR group (n=148, 50%) for improving stroke caregiver life changes, symptoms, and health outcomes. The TASK III group will receive the TASK III resource guide along with information from the American Heart Association about stroke family caregiving. The ISR (attention control) group will only receive information from the American Heart Association. Both groups will receive 8 weekly calls from a nurse with a booster call a month later. The nurse calls for the TASK III group to focus on assessing and addressing stroke caregiver needs and concerns using the TASK III resource guide, along with information from

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the American Heart Association; support through active listening; and provide referrals to their own health care providers. The nurse calls for the ISR comparison group to focus only on information from the American Heart Association, support through active listening, and provide referrals to their own health care providers. The ISR group procedures have been used successfully as a comparator for our previous trials (eg, R01 and R21). Data will be collected at baseline and at 8, 12, 24, and 52 weeks after randomization.

Objectives

Specific Aim 1

This study aims to test the short-term (immediately after the intervention at 8 wk) and long-term (12, 24, and 52 wk) efficacy of the TASK III intervention, compared with the ISR group, in improving the *primary outcome* of caregiver life changes (ie, physical health, physical functioning, emotional well-being, and general health) as a result of providing care.

Specific Aim 2

This study also aims to test the short-term (immediately after the intervention at 8 wk) and long-term (12, 24, and 52 wk) efficacy of the TASK III intervention, compared with the ISR group, in improving *secondary outcomes* including caregiver depressive symptoms (in caregivers with mild to severe depressive symptoms); other symptoms (stress, fatigue, sleep, pain, and shortness of breath); unhealthy days; self-management of diet and exercise; self-reported health care use; *mediators* (caregiver task difficulty, threat appraisal, and self-efficacy for exercise and diet); and *program evaluation outcomes* at 12 weeks (caregiver satisfaction and technology ratings).

Methods

Trial Design

An experimental, 2-group, randomized controlled clinical trial design based on a superiority framework will be used to test the efficacy of the TASK III program compared with an ISR group using an intention-to-treat design. We will randomly assign 296 stroke caregivers using a 1:1 allocation ratio to either the TASK III intervention group (n=148, 50%) or the ISR attention control group (n=148, 50%) following baseline data collection by telephone after the stroke survivor is discharged home (Figure 1). Follow-up data collection by telephone will occur by blinded data collectors after the 8 weekly TASK III or ISR calls, after the booster call at 12 weeks, and then at 24 and 52 weeks. Program evaluation by telephone will occur at 12 weeks after all the calls from the nurse have been completed while maintaining blinding of the data collectors.

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Figure 1. Study flow diagram. ISR: information, support, and referral; TASK III: Telehealth Assessment and Skill-Building Kit.

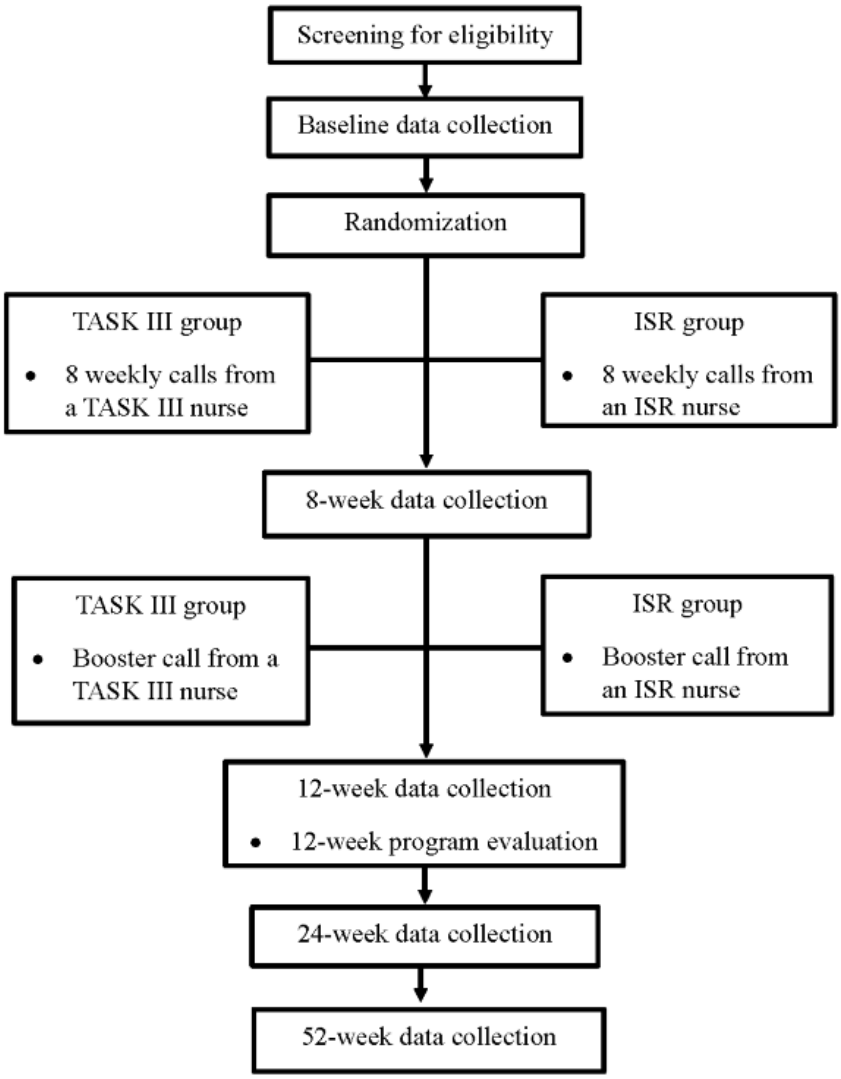

Participants, Interventions, and Outcomes

Study Setting

Data will be collected from family caregivers living in the community caring for stroke survivors after discharge to the home setting. Recruitment sites are acute care and rehabilitation hospitals that provide care for stroke survivors located in the United States Midwest region. A list of our recruitment sites as of October 7, 2024, is provided in Multimedia Appendix 1. Further details regarding recruitment are provided in the *Recruitment* section.

Eligibility Criteria

Inclusion and exclusion criteria for stroke family caregivers are summarized in Textbox 1.

Eligibility criteria for the nurse interveners for both the TASK III and ISR groups include having a registered nurse license; strong interpersonal skills; and proficiency with technology, including Zoom (Zoom Communications) and Teams (Microsoft Corp) videoconferencing and basic computer skills. Blinded data collectors are required to have a high school diploma (college education preferred); strong interpersonal skills; and basic computer skills including the ability to type and enter data.

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Textbox 1. Inclusion and exclusion criteria for stroke family caregivers.

Inclusion criteria

- Primary caregiver (family member or a significant other providing care for a stroke survivor at home)
- Fluent in the English language (ie, able to read, speak, and understand English)
- Access to a telephone or computer
- No difficulties hearing or talking by a telephone or computer
- Scores ≥4 on a 6-item cognitive impairment screener
- Willing to participate in 9 calls from a nurse and 5 data collection interviews (baseline, 8, 12, 24, and 52 wk)

Exclusion criteria if the following were true for the survivor

- Had not had a stroke
- Did not need help from the caregiver
- Resides in a nursing home or long-term care facility

Exclusion criteria if the following were true for the survivor or caregiver

- Aged <18 years
- Prisoner or on house arrest
- Pregnancy
- Terminal illness (eg, late-stage cancer, end-of-life condition, or renal failure requiring dialysis)
- History of Alzheimer disease, dementia, or severe mental illness (eg, suicidal tendencies, schizophrenia, severe untreated depression, or manic depressive disorder)
- History of hospitalization for alcohol or drug abuse within the past 5 years

Ethical Considerations

The study was approved by the University of Cincinnati Institutional Review Board (IRB; study 2022-0180). Lists of contact information for stroke survivors and next of kin will be obtained from each recruitment site. Approximately 1 week after study flyers and informed consent forms are mailed, stroke caregivers will be contacted via telephone by the TASK III study research staff to determine their interest in the study and to screen for eligibility. Flyers with response cards and informed consent forms may also be distributed by staff employed at each recruitment site.

The informed consent process will take place via telephone. The informed consent form is provided in Multimedia Appendix 2. The process will be explained to interested family caregivers, and if they are eligible and provide verbal consent, a baseline interview will be scheduled. All caregivers will be provided with full information about the nature, purpose, and possible risks and benefits of the study. Furthermore, caregivers will be informed that participation in the study is voluntary, and they are free to discontinue participation at any time. The principal investigator (PI) or research staff trained by the PI will obtain initial and ongoing consent. Training of research staff will include reading the informed consent and role-playing the consent process with the PI. All research staff having contact with the caregivers in the study will be trained on this process. The telephone calls to explain the consent will be scheduled at a time that is convenient for the caregiver using a telephone number provided by the caregiver. The PI or trained research staff will make the calls from a private location to protect the confidentiality of the caregiver. At the beginning of the baseline interview, the informed consent form will be reviewed again with caregivers, with verbal consent being verified before baseline data collection. Caregivers who are eligible, have provided verbal consent, and have completed baseline data collection will be enrolled and randomly assigned into either the TASK III or ISR group. Because this is a minimal risk study, the IRB has approved a waiver of written documentation of consent. We have previously conducted 4 IRB-approved studies using the same recruitment strategies as detailed in the current protocol [7,31,34,37,38]. Our procedures have not been found to be coercive by the IRB, and we have been successful in recruiting and retaining caregivers in our previous studies. In fact, we believe that approaching caregivers in person while the survivor is still hospitalized may be more coercive than requesting their participation by mail and telephone. Caregivers receiving their informed consent by mail approximately a week in advance have more time to read it and consider participation than if they were approached in person.

Only authorized study personnel will have access to the database or contact information for potential family caregivers, as well as family caregivers enrolled in the study. Study identification numbers will be generated to protect the identity of the participants. Participants will not be identified in any manner in reports or manuscripts from the study. Data from all data collection interviews and nurse calls will be audio recorded. Audio recordings will be uploaded to a secure password-protected OneDrive (Microsoft Corp) folder at the University of Cincinnati and then deleted from the digital recorders. Once the audio recordings are monitored for

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adherence to the protocol or transcribed (deidentified), they will be deleted to protect the anonymity of the participants. Data entered on paper forms will be entered into REDCap (Research Electronic Data Capture; Vanderbilt University) by trained research staff using a secure log-in. Deidentified paper forms will be stored in a locked file cabinet accessible only to study personnel or shredded once data entry into REDCap is complete. REDCap is backed up nightly by the institution. Only authorized study personnel will have access to REDCap. All data collection calls to participants will be made to a telephone number provided by the participant at a time that is convenient for the participant. The TASK III and ISR group calls will be made via telephone, FaceTime, or Zoom videoconference using a secure link that is protected by the Health Insurance Portability and Accountability Act (HIPAA) based on caregiver preference. Research staff will make calls from a private location to protect confidentiality. All research staff will be trained in procedures to protect the confidentiality of the participants, including referring to caregivers using only their study ID numbers while communicating with the PI, project manager, or other approved research staff. Procedures for tracking completed interviews, determining the appropriate dates for follow-up interviews, and providing reminders for missed interviews will be specified and tracked in REDCap.

Although no compensation is provided for this study, participants are permitted to keep any study materials mailed to them, including a pedometer, Amazon Fire Tablet, USB drive, and a hard copy binder with either the TASK III or ISR content.

Interventions

Explanation for the Choice of Comparators

The comparator for this study will be the ISR program that has been used and validated as an attention control group in our previous studies testing the TASK, TASK II, and TASK III programs [31,32,34-36]. Caregivers randomly assigned to the ISR group have expressed high satisfaction ratings (ie, usefulness, ease of use, and acceptability) [32] with low attrition [31,34] and high fidelity of procedures [36]. Stroke caregivers randomly assigned to the ISR group for this study will receive a mailed copy of an American Heart Association brochure about stroke family caregiving and 8 weekly phone calls from a nurse with a booster call at 12 weeks. Calls will focus on providing ISR via the use of active listening strategies [31,32,34-36]. The ISR group can access the American Heart Association brochure through its website, which offers publicly available guidelines and web-based information for family caregivers. In addition, caregivers will receive a pedometer to track their daily steps, an Amazon Fire Tablet and a USB drive for use in the ISR program, and a unique username and password to log in to the ISR group on our TASK III website, which contains links to the American Heart Association materials for stroke family caregivers. Caregivers in the ISR group can choose to receive calls from their nurse via telephone, FaceTime, or Zoom videoconferencing. The length of each ISR session will vary based on the needs of the caregiver. As in our previous study with the TASK II program [34], our R21 feasibility trial showed that the total number of minutes on the ISR calls averaged about 17 minutes for each of the 9 ISR calls (mean 156, SD 103 min).

Intervention Description

Stroke caregivers randomly assigned to the TASK III intervention will receive a mailed copy of the TASK III resource guide, a mailed copy of an American Heart Association brochure about stroke family caregiving, a TASK III USB drive, and instructions for accessing a TASK III e-book and the TASK III interactive website. Screenshots of TASK III website are provided in Multimedia Appendix 3 [47].

TASK III Resource Guide

In a mailed binder with numbered tabs, the Caregiver Needs and Concerns Checklist (CNCC) [4] addresses 5 areas of needs: finding information about stroke, managing the survivor's emotions and behaviors, providing physical care, providing instrumental care, and dealing with personal responses to providing care (along with 35 corresponding tip sheets addressing each CNCC item) [4,32,34,35]. The Bakas Caregiving Outcomes Scale (BCOS) [7] with corresponding tip sheets addresses caregiver life changes, which is our primary outcome. Six skill-building tip sheets address the following: (1) strengthening existing skills, (2) screening for depressive symptoms, (3) maintaining realistic expectations and time management, (4) communicating with health care providers, (5) problem-solving, and (6) stress management [32,34,35]. The guide also includes (7) a new self-management skill-building tip sheet on goal setting designed for this study [37]. We will measure several key social determinants of health factors [48,49] at baseline, which will be useful in training caregivers on how to use skill-building strategies to address their needs and concerns within the context of their own social determinants of health. For example, 2 instrumental care tip sheets address managing finances and covering costs (financial strain is a key social determinant of health factors). The problem-solving skill-building tip sheet will help caregivers identify barriers and create new solutions to further mitigate financial strain. The goal-setting tip sheet helps caregivers set realistic goals to improve their own health (eg, setting a walking goal that considers neighborhood characteristics as another social determinant of health factor). Our original TASK, TASK II, and TASK III tip sheets have a large 14-point Arial font that is easily readable across all age groups. In our previous TASK II and TASK III studies, caregiver ages ranged from 21 to 83 years, representing a wide range of ages across the life span [34,38]. Our positive satisfaction data demonstrate that our materials are acceptable for a wide range of younger and older caregivers [38]. The TASK III resource guide is constructed to be appealing to both sexes. Male caregivers expressed high satisfaction ratings in our TASK II trial (>4.0 on a scale of 1 to 5), with positive qualitative comments (eg, "It's been such a help to me. It gave me an outlet that I could express my feelings."). Female caregivers also expressed high TASK II satisfaction ratings (>4.0) with positive TASK II qualitative comments (eg, "They're not just there for the person that's had the stroke, they're there for the caregiver too."). Our TASK II [34] and TASK III trials showed minority group representation consistent with the demographics of our Midwest populations, with 24.8% (63/254) in TASK II and 24% (18/74) in TASK III being Black or African American. When seeking input for the goal-setting tip sheet and technology preferences for our TASK

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III program, we purposefully enrolled 50% Black or African American caregivers to ensure that our ratings and qualitative data reflected their views [34,35]. In our TASK III R21 feasibility trial, we employed a diverse research team, with our project manager, one of the TASK III nurses and one of the ISR nurses who identified as Black. We believe that these efforts enhanced the success of our TASK II and TASK III trials. Although not as well represented in our area, we will welcome other minority and ethnic group individuals.

TASK III USB Drive

A USB drive containing a searchable PDF file of the entire TASK III resource guide and separate PDF files of each of the TASK III tip sheets will be mailed to caregivers. Instructions and links to download the TASK III e-book and access the TASK III interactive website will also be provided on the USB drive.

Amazon Fire Tablet

In addition to the USB drive, we will provide all stroke family caregivers enrolled in the study with an Amazon Fire Tablet to access our materials. For the TASK III group, we will load the TASK III tip sheets as PDF files and provide links for the TASK III e-book, the TASK III website, and Zoom videoconferencing.

TASK III e-Book

An interactive multitouch e-book for the TASK III resource guide has been designed using Kotobee software [50] and tested for feasibility for use on multiple devices (eg, desktops, laptops, phones, tablets, and e-book readers). A download link automatically installs Kotobee Reader [50] and the TASK III e-book onto any Mac or PC laptop or desktop. The TASK III e-book will also be installed on the Amazon Fire tablets given to caregivers.

TASK III Interactive Website

We engaged the expertise of Oohology [51] to create in WordPress a searchable TASK III PDF library with TASK III tip sheets that appear on the website based on caregiver responses to an automated assessment process containing the CNCC and BCOS. Infrastructure for backend support of these technologies was provided during our TASK III R21 feasibility study, with continued support and ongoing hosting of the website provided by Oohology [51]. Most importantly, the tip sheets can be viewed on any laptop, tablet, or smartphone. Caregivers are instructed by research staff on how to access the TASK III interactive website through a unique username and password. *All materials created for the TASK III USB drive, e-book, and website are based on our TASK III resource guide.* Embedded within the TASK III resource guide tip sheets are links to additional resources available on the internet. We will ensure that the links are active and checked regularly during project implementation. Similar to the ISR group, the TASK III group can access the American Heart Association brochure through the American Heart Association website, which offers publicly available guidelines and web-based information for family caregivers. In addition, TASK III caregivers will receive a pedometer to track their daily steps.

TASK III Telephone Calls

The TASK III intervention calls will take place via telephone or videoconferencing using FaceTime or Zoom per caregiver preference [38]. Similar to the TASK II intervention [34-36], caregivers will receive 8 weekly calls from a nurse, with a booster call at 12 weeks. Caregivers will be assigned to a specific nurse for consistency. Nurses will train caregivers on how to assess and prioritize their needs, concerns, and life changes, then help them select corresponding content and skill-building tip sheets. The new goal-setting tip sheet will be used during each call to promote caregiver self-management of their symptoms and health.

TASK III FaceTime

Caregivers may receive calls using FaceTime [52]. Over Wi-Fi, FaceTime is accessible on iPhone 4 (Apple, Inc) or later, iPad 2 (Apple, Inc) or later, or iPad Mini (all models; Apple, Inc). Android-accessible apps such as Facebook Messenger (Meta Platforms, Inc), Google Duo (Google LLC), or Skype (Skype Technologies) will be considered.

TASK III Zoom

Caregivers can receive calls using Zoom videoconferencing [53]. Zoom unifies cloud videoconferencing, simple web-based meetings, and a software-defined solution into 1 easy-to-use platform, offering the best video, audio, and wireless screen-sharing experience across Windows, Mac, Linux, iOS, Android, and Blackberry devices [53]. Zoom allows real-time screen-sharing of TASK III resource guide materials during calls. The university has purchased secure Zoom links for research purposes to ensure the privacy of participants, which will be used in this TASK III R01 study. The length of each TASK III session will vary based on the needs of the caregiver. As in our previous study with the TASK II program [34], our R21 feasibility trial showed that the total number of minutes on the TASK III calls averaged about 43 minutes for each of the 9 TASK III calls (mean 389, SD 198 min).

Differences and Overlaps Between TASK III and ISR Groups

Both the TASK III group and the ISR group will receive the American Heart Association brochure, access to the American Heart Association website, a pedometer, an Amazon Fire Tablet, a USB drive, and 8 weekly phone calls from a nurse with a booster call at 12 weeks. Only the TASK III group will receive the TASK III resource guide that contains the CNCC and BCOS to assess caregiver needs, concerns, and life changes, as well as skill-building and content tip sheets that correspond to the CNCC and BCOS items. In the TASK III group, the nurses will train caregivers on how to assess and address their own needs, concerns, and life changes using the TASK III resource guide. This guide (containing the BCOS) informs our primary hypothesis that the TASK III group, compared with the ISR group, will have greater improvements in life changes (measured by the BCOS) from baseline to 8 weeks (after the intervention). We expect that these improvements will be sustained for a longer term from baseline to 12, 24, and 52 weeks. Including the BCOS as part of the TASK III intervention will enhance

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the power to detect an effect on caregiver life changes as measured by the BCOS.

Criteria for Discontinuing or Modifying Allocated Interventions

Participation in the study is completely voluntary, and caregivers may withdraw at any time. Caregivers who ask to withdraw from the study will be given the option for a partial or full withdrawal. For example, participants may complete the rest of the calls with the nurse and withdraw from the remaining data collection interviews or participants may withdraw from the calls with the nurse and choose to complete the remaining data collection interviews. Participants may choose to completely withdraw from all study-related activities. Previously collected data from the participants will be withdrawn if specifically requested by the participant. Otherwise, collected data will be retained and analyzed, particularly for an intention-to-treat design. Participants will be withdrawn from the study if they are unable to be contacted after up to 10 attempts. A letter will be mailed to the participants notifying them that they have been withdrawn from the study.

Strategies to Improve Adherence to Interventions

Adherence to protocols for both ISR and TASK III groups will be a high priority for this study. The Treatment Fidelity Checklist [54] addressing design, training, delivery, receipt, and enactment will be used to maintain and track treatment fidelity for both TASK III and ISR procedures [36,54]. Training for the nurses will include detailed manuals and podcasts, training booster sessions, self-evaluation of recordings, evaluation by supervisors, quality checklists, and frequent team meetings [36]. TASK III nurses will attend an 8-hour training session to learn the intervention content and delivery processes and to role-play sessions with each other. The role-play sessions will be recorded and checked for competency before caregiver interaction. Beyond initial training, TASK III nurses will be monitored weekly during team meetings and asked to complete a self-evaluation of their recordings for adherence to the protocol on a monthly or bimonthly basis. Then, supervisors (ie, the PI or coinvestigator) will listen to recordings, analyze self-evaluations, and provide individualized feedback and retraining when necessary. ISR nurses will undergo a similar process, but the initial training session will last for 4 hours. Protocol adherence for the TASK II study was excellent at 80% (37.6/47) for the TASK II group and 92% (43.2/47) for the ISR group, and for common items on the checklist, 90% (42.3/47) in the TASK II group and 92% (43.2/47) in the ISR group [36]. Focus groups with nurses yielded further evidence for treatment fidelity [36]. The same procedures were used to track treatment fidelity in the TASK III R21 feasibility trial; this TASK III R01 study will follow the same rigorous treatment fidelity procedures with the nurses. Caregivers will be monitored for treatment fidelity regarding receipt (eg, the number of minutes spent on the calls with the nurse; ratings of the helpfulness of each call; the number of minutes of viewing TASK III or ISR materials; and the types of materials viewed, such as TASK III tip sheets or American Heart Association brochures or the website). Enactment will be monitored by asking caregivers whether their problems discussed with the nurse were unresolved, making progress, or resolved. In the TASK III group, the enactment will be further monitored by having caregivers evaluate their own progress on their goals to improve their own health based on our new TASK III goal-setting tip sheet [37].

Relevant Concomitant Care Permitted or Prohibited During the Trial

The trial will not interfere with any concomitant care or interventions that caregivers or their stroke survivors receive. No concomitant care or interventions are prohibited during the trial.

Provisions for Posttrial Care

There are no provisions for ancillary or posttrial care. This is a minimal risk study where the risk is not expected to be more than one would have in daily life.

Outcomes

Outcomes were selected based on a conceptual model derived from our previous research on caregiver needs and concerns [4,35]; our stroke caregiver outcomes work [8-10,31,34] informed by the transactional approach to stress proposed by Lazarus [55-57]; and our conceptual model that has empirical support from our previous research [8-10,31,34], including the original TASK and TASK II programs [31-36]. We added concepts from the self-efficacy theory based on the works by Bandura [58-60] and Lorig et al [61,62] to improve caregiver health. Our outcomes are clinically relevant, particularly our primary outcome of caregiver life changes (eg, physical health, physical functioning, emotional well-being, and general health) because of providing care [7]. Caregivers are known to neglect their own health needs while providing care [4-6,35,37], making them the hidden patients in our health care system. Difficulty with tasks threatens caregivers' ability to provide future care (ie, threat appraisal) [7-10] and is strongly associated with caregiver depressive symptoms and major life changes as a result of providing care (eg, physical health, physical functioning, emotional well-being, and general health) [7-15,17,39]. Finally, stressful caregiver experiences have been reported to impede the survivor's rehabilitation [16-18] and to increase costs from premature long-term institutionalization [8-11,19,20]. In addition to our primary outcome of caregiver life changes, we have included several secondary outcomes, such as caregiver depressive symptoms, other symptoms, unhealthy days, self-management of diet and exercise, and self-reported health care use. Further outcomes include our mediators of caregiver task difficulty, threat appraisal (ie, ability to provide future care), and self-efficacy for maintaining a healthy diet and exercise, as well as program evaluation outcomes. As listed on the ClinicalTrials.gov website (NCT05304078), Multimedia Appendix 4 [7-10,31,32,34,48,49,63-86] details measures and time points for our primary outcome, secondary outcomes, mediators, and program evaluation outcomes.

Participant Timeline

Table 1 provides the time schedule of enrollment, interventions, and data collection interviews for participants. Screening for eligibility and data collection interviews will take place via telephone. TASK III and ISR calls with the nurse will take place

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via telephone or videoconference (eg, FaceTime or Zoom) based on caregiver preference. Data collection will take place at screening; baseline; and 8-week (after the 8 weekly calls with the nurse), 12-week (after the ninth booster call with the nurse), and 24- and 52- week follow-ups. Randomization will occur after the completion of the baseline interview.

Table 1. Schedule of the study period, including enrollment, interventions, and assessments.

Time point	Enrollment	Allocation	Postallocation period					Close out
	Screen	Baseline	8 weekly nurse calls	8 wk	9th nurse call	12 wk	24 wk	52 wk
Enrollment								
Eligibility screen	✓							
Informed consent	✓	✓						
Allocation		✓						
Intervention								
TASK III[a] group			✓		✓			
ISR[b] group			✓		✓			
Assessments								
Demographics, comorbidities, and other social determinants of health		✓						
Survivor impairment		✓		✓		✓	✓	✓
Primary, secondary, and other outcomes (mediators)		✓		✓		✓	✓	v
Program evaluation outcomes						✓		

[a]TASK III: Telehealth Assessment and Skill-Building Kit.

[b]ISR: information, support, and referral.

Primary, secondary, and other outcomes (ie, mediators and program outcomes) are detailed in the *Outcomes* section. Further information about these measures, as well as demographics, comorbidities, social determinants of health, and survivor impairment, is provided in Multimedia Appendix 4.

Sample Size

Sample size is based on the change in the total BCOS [7] scores from baseline to 8 weeks for the primary outcome of caregiver life changes because of providing care (ie, physical health, physical functioning, emotional well-being, and general health). For caregiver life changes (BCOS) [7], the sample size of 132 in each group will provide 80% power to detect a mean difference of 0.9 in the change from baseline, with the TASK III group showing a mean difference of 4.0 and ISR group showing a mean difference of 3.1 and an estimated SD of 2.6 [34]. We will also have sufficient power to address secondary outcomes. A sample size of 132 in each group will achieve 80% power to detect a mean difference of 0.20 in the change from baseline in depressive symptoms at 8 weeks between groups, with a mean difference of –0.80 in the TASK III group and –0.60 in the ISR group and an estimated SD of 0.70 in both groups using a 2-sample *t* test with a significance level of 0.05 [34]. This detectable difference is lower than the difference in depressive symptoms observed in the pilot TASK III R21 study. On the basis of pilot data, it is estimated that there will be 124 (42%) caregivers who screen positive for mild to severe depressive symptoms at baseline (ie, Patient Health Questionnaire-9 [PHQ-9] Depression Scale score >5). Because the randomization will be stratified by baseline depressive symptoms (see the *Sequence Generation* section), we estimate 62 caregivers with mild to severe depression in each group. A sample size of 62 in each group will achieve 80% power to detect a mean difference of 0.60 in the change from baseline in depression symptoms at 8 weeks between groups, with a mean difference of –2.60 in the TASK III group and −2.00 in the ISR group and an estimated SD of 1.20 in both groups, using a 2-sample *t* test with a significance level of 0.05 [34]. This detectable difference is lower than the difference in depression symptoms observed in the pilot TASK III R21 study. For unhealthy physical and mental days, the sample size will provide 80% power to detect a rate ratio of 0.85 (a 15% reduction in unhealthy days) [34]. The planned enrollment is 296 (n=148, 50% in the TASK III group and n=148, 50% in the ISR group) to account for 10.8% (16/148) attrition [34]. Power Analysis & Sample Size (version 12; NCSS LLC) was used to produce all power estimates. Power calculations were not performed for the additional secondary outcomes (ie, other symptoms, self-management steps, exercise self-management, diet self-management, and health care use).

Recruitment

Recruitment methods and retention rates were successful in our previous studies [31,34] and even better in our most recent TASK III R21 feasibility study. On the basis of our recruitment success with our TASK II and TASK III R21 feasibility studies, we plan to screen 3364 caregivers and randomly assign at least 296 caregivers to achieve our goal of 148 (50%) caregivers per

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group (Figure 2). Accounting for 10.8% (16/148) attrition, this should allow us to have at least 132 (89%) caregivers per group at our primary 8-week time point.

Figure 2. Proposed participant flow diagram. The values are provided on the basis of the Telehealth Assessment and Skill-Building Kit (TASK III) R21 (R21NR016992; ClinicalTrials.gov ID: NCT03635151) feasibility study, except for the 24-week and 52-week values, which were based on the Telephone Assessment and Skill-Building Kit (TASK) II R01 (R01NR010388; ClinicalTrials.gov ID: NCT01275495) study. ISR: information, support, and referral.

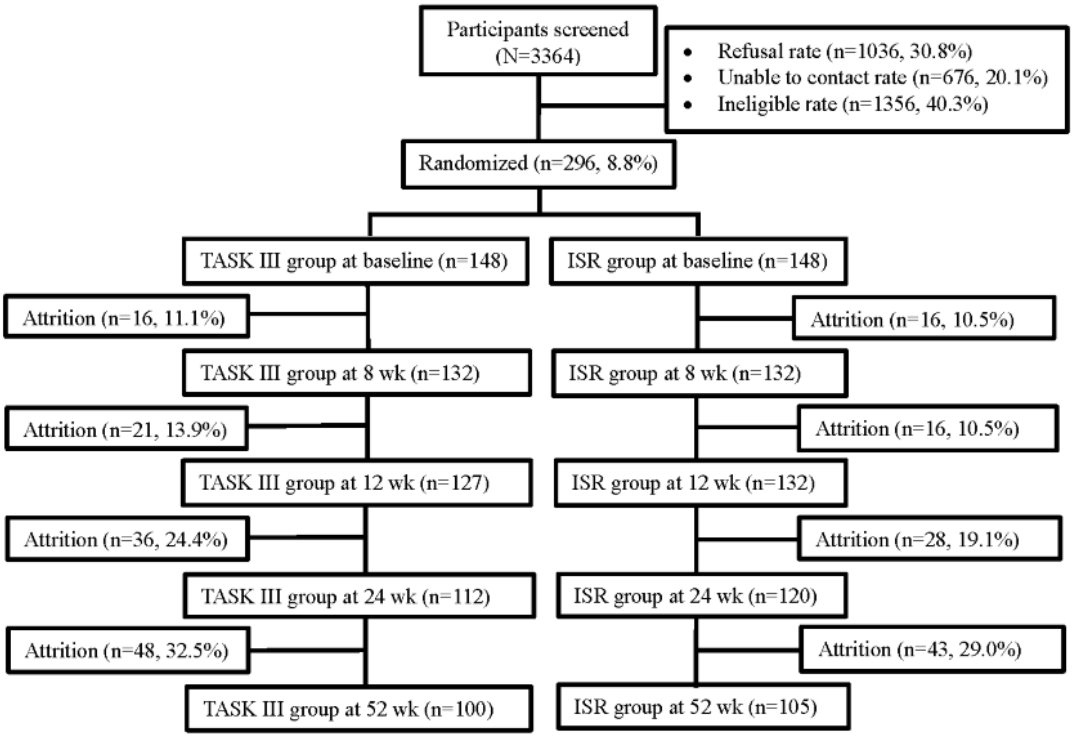

Screening 3364 caregivers over 3 years (1121 per year) is feasible given our strong track record of collaboration and the large number of stroke survivors treated yearly at each recruitment site. As in our previous studies, bioinformaticians, stroke coordinators, or other employees from each recruitment site will provide us with lists of stroke survivors and their next of kin. As approved by our university IRB, study flyers signed by the stroke survivor's physician, nurse, director of the stroke team, along with copies of the informed consent form, will be mailed to caregivers of survivors receiving care from each recruitment site. A telephone number is provided for stroke caregivers to call if they do not wish to be contacted for the study. Approximately 1 week after the study flyers and informed consent forms are mailed, caregivers will be contacted via telephone by research staff to determine their interest and screen for eligibility. Flyers with response cards may also be distributed by staff employed at each recruitment site.

Assignment of Interventions: Allocation

Sequence Generation

Caregivers will be randomly assigned 1:1 to the TASK III or ISR group using a permuted block randomization stratified by type of relationship (spouse vs adult child or other) and baseline depressive symptoms (nondepressed vs depressed, with a PHQ-9 score ≥5) as in the TASK II trial [34]. Random permutations within each block within each stratum will be generated using a random number generator (SAS Proc Plan; SAS Institute).

Concealment Mechanism

The randomization scheme will be concealed in an Excel (Microsoft Corporation) document uploaded to the REDCap project site that will be accessible only to the biostatistician. Randomization will occur by logging into the REDCap project website and entering the type of relationship (spouse vs adult child or other) and baseline depressive symptoms (nondepressed vs depressed, with a PHQ-9 score ≥5) for group assignment (TASK III vs ISR).

Implementation

The biostatistician will generate the allocation sequence and upload it as an Excel file to the REDCap project site as a concealed file. The biostatistician will then program the REDCap project site to generate the group assignment once the PI or the project manager enters the type of relationship and baseline depressive symptoms. After baseline data collection, data collectors will notify the PI or the project manager that the caregiver is ready for randomization. Data collectors will not be involved in the randomization process.

Assignment of Interventions: Blinding

Who Will Be Blinded

Data collectors will be blinded to group assignment to mitigate potential bias during the 8-, 12-, 24-, and 52-week follow-up interviews. Blinding will be maintained by restricting data collector access to group assignments in REDCap. Separate weekly research team meetings will be conducted with the data

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collectors. Caregiver participants will be instructed not to tell the data collectors which group they have been assigned to. Caregiver trial participants, the nurses, the project manager, the PI, and a coinvestigator will be unblinded so that the proper TASK III or ISR materials can be mailed to the participants and the correct TASK III or ISR protocol can be followed. The PI and the coinvestigator will closely monitor treatment fidelity for the TASK III and ISR groups. Separate nurses will be used for the TASK III or ISR groups to avoid treatment diffusion. We have a strong track record of keeping TASK III and ISR groups separate, including strict monitoring of treatment fidelity and adherence to protocol [36]. The lead biostatistician and her master's degree–prepared staff statistician will be unblinded to create reports, assess for missing data, and explore data trends in preparation for Data Safety and Monitoring Plan reports. While analyzing data trends for Data Safety and Monitoring Plan reports, the PI and the research team will be blinded as to which group represents each outcome variable within data tables by labeling each group by a letter rather than using the TASK III or ISR abbreviations.

Procedure for Unblinding if Needed

Only data collectors will be blinded during the trial. Unblinding the data collectors will not be permissible.

Data Collection and Management

Plans for Assessment and Collection of Outcomes

Multimedia Appendix 4 lists the study measures. Most measures were used in our previous studies [7-10,31,32,34]. All measures demonstrated acceptable evidence of reliability and validity, except the Caregiver Evaluation of Technology Scale, which was created specifically for this study. We will assess the reliability and validity of this scale, and if unacceptable, we will analyze it at the item level. Using the measures in Multimedia Appendix 4, the estimated time for telephone interviews for each time point is 60 minutes for baseline, 33 minutes for 8 weeks, 39 minutes for 12 weeks, and 33 minutes for 24 and 52 weeks. Telephone interviews of this length have not been found to be burdensome in our previous studies [7-10,31,32,34].

Plans to Promote Participant Retention and Complete Follow-Up

To promote participant retention and complete follow-up, data collection interviews and TASK III or ISR nurse calls will be made to caregivers at times that are convenient to them. Once a baseline interview is scheduled, REDCap will prepopulate a schedule for all remaining data collection interviews and nurse calls, usually on the same day of the week and time of the day. Using the calendar function in REDCap, the schedule will appear on the calendar while maintaining blinding of data collectors to group assignments. The schedule will be mailed to each caregiver, with assurance that days and times can be rescheduled as needed. A detailed calling protocol will be used by data collectors and nurses, along with call tracking entered within REDCap. To further promote retention and follow-up, caregivers who ask to withdraw from the study will be offered the option to participate in a final data collection interview that contains all the primary, secondary, mediators, and program evaluation outcomes, as specified for the 12-week time point as listed in Multimedia Appendix 4. Consistent with our intention-to-treat design, caregivers who do not complete all 8 weekly calls with the nurse or the ninth booster call with the nurse will still be asked to continue in the trial for the remaining data collection calls.

Data Management

Data management will be overseen by the PI, coinvestigator, project manager, and the lead biostatistician and staff statistician. All data collection interviews and TASK III and ISR nurse calls will be audio recorded for quality assurance. During monthly or bimonthly self-evaluations with nurses and data collectors, audio recordings will be checked for adherence to the protocol and accuracy in data entry. All study data and tracking will be entered into an electronic data system, REDCap [87], which is a secure research electronic data management system with validated data entry, audit trails for tracking data manipulation, and export procedures. It is HIPAA compliant, satisfying all local, state, and federal regulations for the capture and storage of private health information for research purposes. The biostatistician will run quarterly reports assessing for missing data and range checks for data values. Any missing data or suspected errors in data entry will be discussed with the PI and the project manager, who can then access the audio recordings to resolve any issues with data entry.

Statistical Methods

Recruitment, Attrition, and Fidelity Ratings of Data Collection and Intervention Procedures

Using procedures similar to the TASK II study and our TASK III feasibility study, we will monitor screening and recruitment rates, attrition rates, and fidelity ratings of all data collection and intervention procedures [34,36,54,88]. We will compute the number of participants screened and enrolled per month, the proportion of screened eligible participants who enroll, intervention assignment–specific retention rates at each follow-up visit, and the proportion of outcome measures completed. For fidelity ratings, we will use an itemized checklist to monitor adherence to the unique components of the TASK III study [36]. Adherence will be scored with dichotomous responses for the presence or absence of each item. Frequencies and percentages will be calculated for each item by group. Intervention dosage will be calculated for nurse call duration (min) and the time caregivers spend reading study materials (min) for each group. Descriptive statistics for intervention dosage will be computed by group, and between-group mean differences will be evaluated using 2-sample t tests or nonparametric alternatives if the normality assumption is violated.

Assessment of Scales and Descriptive Statistics

After initial data verification, cleaning, and scale scoring, the coefficient alpha will be calculated as a measure of internal consistency reliability on all multiple-item scales. Descriptive statistics (frequencies, measures of central tendency, and variability) will be produced for all variables. Data will be screened for outliers, multicollinearity, and statistical model assumptions.

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Baseline Equivalence and Possible Covariates

Baseline differences in caregiver and survivor characteristics and social determinants of health will be explored to identify potential covariates for our analyses. As in our TASK II trial, stratified random assignment using the type of relationship and baseline depressive symptoms will ensure a balance between the 2 groups for those 2 factors [34]. Baseline differences between the 2 groups will be evaluated using 2-sample *t* tests or Wilcoxon rank sum tests, chi-square tests, or Fisher exact test as appropriate. Baseline variables that are significantly different between the 2 groups at the .05 level will be controlled for in all analyses. In our previous TASK II trial, the ISR calls, on average, were significantly shorter than TASK II calls ($P<.01$) [34]. As in our previous studies [31,34], the number of minutes on TASK III and ISR calls with the nurse may serve as a covariate in our analyses.

Primary Analyses for Specific Aims 1 and 2

Overview

The general modeling strategy for the analyses in aims 1 and 2 will be repeated measures regression modeling using the generalized liner mixed model (GLMM) framework. In GLMM, it is possible to use data from participants when some of the data are missing under the assumption of missing at random. In addition, this modeling strategy allows for time-varying covariates, flexible covariance structures, and participant-specific effects and thus will be able to accommodate the analyses proposed. Our primary goal will be to assess the overall intervention effects on the change from baseline. All primary analyses conducted will be based on the intention-to-treat principle. Analyses will be done using SAS software (version 9.4 or higher).

Specific Aim 1

The *primary outcome* is caregiver life changes as a result of providing care (ie, physical health, physical functioning, emotional well-being, and general health). Life changes are measured using the BCOS total score [7]. The explanatory variables used in the specific aim 1 model will be the intervention group, time, and the intervention group–by–time interaction. Covariates (including social determinants of health) identified using the process described above will be included as appropriate. The number of minutes spent on calls with the nurse in both TASK III and ISR groups will potentially be used as a covariate as well. The model examined will be a 2 (intervention: ISR and TASK III) by 5 (time: baseline and 8, 12, 24, and 52 wk) mixed factorial model, along with covariates. In the GLMM framework, an appropriate link function will be specified depending on the distribution of the dependent variable. Hypotheses related to the immediate postintervention time point at 8 weeks and long-term, sustained efficacy at 12, 24, and 52 weeks will be tested using relevant least square mean contrasts and simple effects constructed within SAS PROC GLIMMIX.

Specific Aim 2

S*econdary caregiver outcomes* are depressive symptoms; other symptoms (stress, fatigue, sleep, pain, and shortness of breath); unhealthy days; self-management of diet and exercise; and self-reported health care use. In the analyses for depressive symptoms, we will look at both overall and subgroup analyses for caregivers who screen positive for depressive symptoms (PHQ-9 score >5) [34]. *Mediators* are task difficulty, threat appraisal, and self-efficacy for exercise and diet. Each of these outcomes will be modeled separately. The models for secondary caregiver outcomes and mediators used in specific aim 2 are similar to those for life changes tested for aim 1 and will include the intervention group, time, and the intervention group–by–time interaction. Covariates (including social determinants of health) identified using the process described above will be included as appropriate, as well as potentially the number of minutes spent on the calls with the nurse in both TASK III and ISR groups. The full model consists of a 2 (intervention: ISR and TASK III) by 5 (time: baseline and 8, 12, 24, and 52 wk) mixed factorial, along with covariates. In the GLMM framework, an appropriate link function will be specified depending on the distribution of the dependent variable. Hypotheses related to immediate postintervention time point at 8 weeks and long-term, sustained efficacy at 12, 24, and 52 weeks will be tested using relevant least squares mean contrasts and simple effects constructed within SAS PROC GLIMMIX. *Program evaluation outcomes* consist of caregiver satisfaction and evaluation of technology ratings. Satisfaction ratings from the Caregiver Satisfaction Scale [32] (usability, ease of use, and acceptability) and evaluation of technology ratings will be summarized at the item and scale levels by intervention group using descriptive statistics, including mean and 95% CI. Caregiver Satisfaction Scale scores, total, and subscales will be compared between groups using 2-sample *t* tests or nonparametric alternatives if the normality assumption appears violated.

Interim Analyses

There are no plans for interim efficacy or futility analysis. There is little chance that we would find harm from the intervention, thus rendering interim efficacy and futility analysis inappropriate.

Methods for Additional Analyses, Including Subgroup Analyses

Age Across the Life Span

We will compare caregiver age between TASK III and ISR groups using 2-sample *t* tests and control for age as a covariate in our analyses if significant age differences are noted.

Sex as a Biological Factor

We will explore sex differences by careful description of subgroup effects.

Minority Group Representation

We will also explore racial differences (ie, Black or African American vs White individuals) by careful description of subgroup effects.

Methods to Handle Protocol Nonadherence and Statistical Methods to Handle Missing Data

We will make every effort to avoid missing data. If missing data are identified, the PI or the project manager will access the corresponding audio recording to determine whether missing

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data were due to an error in data entry. We will assess the reasons, patterns, and distribution of missing data, allowing us to assess whether an assumption of missing completely at random is reasonable or whether missingness is conditional on another variable in the dataset (ie, missing at random). Descriptive statistics will compare the characteristics of patients with and without missing data. If missing at random, we will incorporate variables that are identified to be related to the missingness in the analysis using multiple imputations if the amount of missing data affects the study results. Missing data have been minimal for our original TASK study [31], TASK II randomized controlled clinical trial [34], and TASK III feasibility study; we will use the same procedures to avoid missing data in this study. As mentioned previously, we will use an intention-to-treat design and rigorous treatment fidelity procedures [36] to monitor all research staff for adherence to protocol.

Plans to Give Access to the Full Protocol, Participant-Level Data, and Statistical Code

We will make the full protocol, participant-level data, and statistical code available to others. Data will be shared with undergraduate honors students, graduate students, postdoctoral students, and interested faculty members at our university and other institutions. Special measures will be taken to ensure that family caregivers and stroke survivors are not identified by any data that are shared. Close collaboration with the PI and her research team will be necessary for the use of shared data. Project-generated resources will include our finalized REDCap database, intervention materials, and training manuals for the project manager, TASK III study nurses, ISR study nurses, data collectors, and screening and recruitment staff. Close collaboration with the PI and her research team will be necessary for the use of shared resources by other investigators.

Oversight and Monitoring

General Composition of the Research and Intervention Delivery Team

Overview

The study team will consist of TB (PI and nurse), who will lead the interdisciplinary team of coinvestigators, consultants, TASK III and ISR nurse interveners, project coordinators, and data collectors to successfully achieve the aims of the study. EM (coinvestigator and nurse) will help to guide and train the TASK III and ISR nurses, especially with respect to tracking and maintaining treatment fidelity throughout the intervention period. NK (coinvestigator and physician) will provide valuable expertise on stroke, facilitate recruitment of participants, and provide guidance on future implementation of TASK III intervention into stroke systems of care. BH (coinvestigator and biomedical informatics specialist) will facilitate accessing Epic medical records to obtain lists of stroke survivors and their next of kin for recruitment. HS (coinvestigator and biostatistician) will work with investigators and a staff statistician to develop and implement the statistical analysis plan and dissemination of results. MR (coinvestigator and IT and instructional designer specialist) will oversee the TASK III telehealth technologies and work with an information technologist and website or digital designer for ongoing support and hosting of the TASK III website. KD (coinvestigator and physical therapist) will help promote physical activity in caregivers, provide oversight and interpretation, and assist with the dissemination of physical activity–related data. BB (consultant and dietician) will provide ongoing expertise for study methods and materials related to the caregivers' dietary habits, as well as oversight of the interpretation and dissemination of nutrition-related data. MM (consultant and social worker) will consult on updating and maintaining equitable and accessible community resources and support for both TASK III and ISR. HJ (consultant and nurse) will provide consultation on culturally sensitive approaches for recruiting and interacting with diverse family caregivers. JKA and PHM (consultants and nurses) will be available for consultation as needed for the overall study design and methods.

In addition to the PI, coinvestigators, and consultants, the team will consist of the following staff.

Project Manager

The person selected for this role has a master's degree in public health and will coordinate all aspects of the study including all day-to-day project operations, first-line supervision of research staff, coordination of communication with all study personnel, research team meetings, preparation of agendas and minutes, assistance in the preparation of the training manuals and protocols, maintenance of study files, budget management, scheduling and coordination of all family caregiver calls and mailings, and study coordination with recruitment sites. Furthermore, they will conduct caregiver and stroke survivor screenings and informed consent procedures. Under the direction of the biostatistician and the PI, they will also assist in the development, testing, and maintenance of the REDCap database; conduct the query management process; provide data management documentation, such as the data management plan; and ensure that data are being entered and cleaned in a timely and appropriate manner.

Nurse Interveners

A total of 3 hourly nurse interveners will be hired and trained to deliver the 9 TASK III intervention calls to 148 stroke caregivers randomly assigned to the TASK III intervention group. Three additional hourly nurse interveners will be hired and trained to deliver the 9 ISR group calls to 148 stroke caregivers randomly assigned to the ISR group. Nurses will be required to have a current registered nurse license and excellent interpersonal skills. In addition to making caregiver calls, the nurses will be responsible for self-evaluation of their own audiotapes, further retraining procedures, and documentation of TASK III intervention or ISR content delivered to caregivers. They will also attend weekly research team meetings.

Research Assistants

A total of 4 hourly research assistants will be hired and trained to conduct participant screening and collect data via telephone for 296 stroke caregivers at the 5 time points specified for the project (baseline and 8, 12, 24, and 52 wk). The hourly research assistants will provide coverage for each other in the event of illness or time off, cover a wide range of availability times for caregiver data collection calls, and attend weekly research team

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meetings while remaining blinded to group assignment of caregivers throughout the study.

Informatics Support Person

The informatics support person for this study is a data analyst from the Center for Health Informatics at the University of Cincinnati Department of Biomedical Informatics. The data analyst will be supervised by BH to extract lists of stroke survivors and their next of kin from Epic electronic medical records from the University of Cincinnati Health and University of Cincinnati Health West Chester Hospitals for recruitment.

IT Support and Website or Digital Designer

This person will be supervised by MR and will work closely with TB and her interdisciplinary team to refine and maintain the TASK III telehealth technologies for the TASK III resource guide (ie, mailed hard copy, USB drive, Amazon Fire Tablets, e-book, and TASK III website) and the technologies for nurse calls (ie, telephone, Zoom videoconferencing, and FaceTime on iOS devices). The IT support and website or digital designer will work with Kotobee [50] on the TASK III e-book and Oohology [51] for ongoing support and hosting of the TASK III website. He will also help to train TASK III and ISR nurses on the use of the TASK III telehealth technologies and provide ongoing IT support throughout the project.

Staff Biostatistician

The staff biostatistician will work with HS to carry out the statistical analysis plan to address the study aims.

Composition of the Data Monitoring Committee, Its Role, and Reporting Structure

This study was approved by the university IRB as “no greater than minimal risk.” According to the funder’s policy (ie, National Institute of Nursing Research; NINR), “Monitoring by the PI or designee may be appropriate for protocols involving minimal risk or no more than a minor increase over minimal risk which are conducted at a single site.” For this study, the IRB- and NINR-approved data and safety monitoring plan will be the responsibility of TB (the PI). Members of the research team will provide input, particularly HS, the statistician coinvestigator; EM, the nurse coinvestigator; and NK, the physician coinvestigator. The PI (TB) and research team members (HS, EM, and NK) are well-qualified and will meet quarterly (and more frequently as needed) to review data and the safety of the study procedures and involvement of participants. TB (the PI) will consult with the research team members (HS, EM, and NK), but she will be the monitoring entity for this study. She will collaborate closely with our local IRB throughout the study and will submit the approved IRB-continuing review, including the dates and summarized reports generated from data and safety monitoring meetings with the research team to the National Institutes of Health (NIH) along with the yearly NIH progress report. There are no conflicts of interest with or financial stakes in the research outcome with the PI (TB) or any members of the research team.

Adverse Event Reporting and Harms

The PI (TB) will be seeking input from members of the research team (HS, EM, and NK), and will meet quarterly (and more frequently as needed) with them to (1) review any deviations in the study protocol; (2) review any adverse events; (3) track any negative trends in data that may indicate harmful effects of the study procedures; (4) review study recruitment and retention; and (5) review data management procedures, particularly those designed to protect the privacy of participants. All protocol deviations, adverse events, and unanticipated problems will be reported by the PI (TB) to the local IRB and NINR yearly or more frequently as needed. At the time of the yearly IRB-continuing review, a summary of the frequency and dates of the data and safety monitoring meetings with the PI (TB) and the research team (HS, EM, and NK) will be provided, along with reviews and reports generated from each meeting. The approved IRB-continuing review, including the dates and summarized reports generated from the data and safety monitoring meetings with the PI and the research team, will be submitted to the NINR along with the yearly NINR progress report. The PI (TB) will provide a report of the following to IRB and NINR within 48 hours: (1) unanticipated problems or unexpected serious adverse events that may be related to study protocol; (2) IRB-approved revisions to the study protocol that indicate a change in risk for participants; (3) a summary of recommendations made by the PI and the research team as appropriate and, if applicable, the action plan for response; and (4) notice of any actions taken by the IRB or regulatory bodies regarding the research and any responses to those actions. All personal identifiers will be removed from any documents sent to the NINR. Identifiable data will be stored in locked file cabinets and within our secure, password-protected, HIPAA-compliant REDCap database.

Frequency and Plans for Auditing Trial Conduct

The PI (TB), with inputs from the research team (HS, EM, and NK), will provide auditing of at least 50% of all cases for compliance with IRB requirements, conformance with informed consent requirements, verification of source documents, and investigator compliance. Recommendations concerning the continuation or conclusion of the trial will be made during each quarterly meeting, based on the results of monitoring. The process will involve both the investigators and the sponsor (NINR).

Plans for Communicating Important Protocol Amendments to Relevant Parties

The PI will communicate important protocol modifications with the coinvestigators, consultants, project manager, and research staff as appropriate. All modifications will be approved by the local IRB before implementation and reported to the NINR on the yearly NIH progress report.

Dissemination Plans

This clinical trial is registered (ClinicalTrials.gov ID: NCT05304078), and information about the results will be submitted to ClinicalTrials.gov, which is available to the public. The IRB-approved informed consent form will include the following statement: “A description of this clinical trial will be available on ClinicalTrials.gov, as required by the US Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You

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can search this website at any time." Participants will be encouraged to check back with the ClinicalTrials.gov site for a lay summary of the results after completion of the study. Participants contacting the PI for results will be referred to the ClinicalTrials.gov website. We anticipate that there will be manuscripts, not only from the findings addressing specific aims 1 and 2 but also from secondary analyses of data generated from this study. We will disseminate results from specific aims 1 and 2, as well as results from secondary analyses, in peer-reviewed journals. We will make the data available to others as detailed in the Plans to Provide Access to the *Full Protocol, Participant-Level Data, and Statistical Code* section.

Results

Enrollment and random assignment of the first participant was on November 30, 2022, with an anticipated completion of recruitment by November 30, 2025. The primary end point data analysis is anticipated to be completed by August 31, 2026, with reporting of results in ClinicalTrials.gov anticipated to be by April 1, 2027. As of October 9, 2024, a total of 198 (66.9% of the proposed total sample of N=296) family caregivers have been enrolled and randomly assigned to the TASK III group (n=98, 49.5%) or the ISR group (n=100, 50.5%). On the basis of reviewer comments during the funding process, the exclusion criteria were changed from caregivers or survivors aged <21 years to those aged <18 years. An IRB modification was added to remove the word "unpaid" from the inclusion criteria for family caregivers because some states provide financial resources to family caregivers. Additional IRB-approved recruitment sites have been added, including the use of social media (eg, Facebook; Meta Platforms, Inc) for recruitment [89]. The protocol reported in this paper is protocol version 5, as approved by the IRB on May 9, 2024.

Discussion

Anticipated Results and Interpretation

This study protocol builds upon our findings from our previous studies with both the TASK [31,32] and TASK II R01 programs [34-36], as well as our most recent refinement and feasibility testing of the TASK III R21 program [37,38]. In caregivers with mild to severe depressive symptoms, the TASK II (in comparison with ISR) intervention was found to reduce depressive symptoms up to a year after baseline; however, improvement in caregiver life changes (ie, physical health, physical functioning, emotional well-being, and general health) occurred only from baseline to 12 weeks in this subsample [34]. Furthermore, TASK II caregivers typically waited until nurse calls 5 through 9 to address their own physical and emotional health needs [36]. To strengthen our findings regarding caregiver life changes, we refined the TASK III intervention to include an assessment of life changes using the BCOS [7], starting with nurse call 2, and added a goal-setting tip sheet to improve caregiver health [37]. Promising data trends indicating stronger caregiver life changes in the TASK III R21 intervention compared to the ISR intervention were reported on the ClinicalTrials.gov website. In this proposed trial, relative to the ISR group, we anticipate that caregivers randomly assigned to the TASK III group will show greater improvements in our primary outcome of caregiver life changes from baseline to 8 weeks (immediately after the intervention) in the total sample, which is sustained for a long term from baseline to 12, 24, and 52 weeks. This study will enable us to (1) successfully conduct a large efficacy trial of the TASK III intervention and (2) further refine the TASK III intervention via program evaluation data (satisfaction and technology ratings) for future implementation. Findings will provide evidence of efficacy for the TASK III program, which is a necessary step toward implementing the TASK III program into stroke systems of care.

Potential Pitfalls, Alternative Approaches, and Future Directions

We have a strong track record of recruitment and retention in our previous TASK, TASK II, and TASK III studies [31,34]. Nevertheless, we will closely monitor recruitment and retention and will secure additional recruitment sites if needed. Our study does not require face-to-face interactions with caregivers; therefore, we are not limited by geographic boundaries for recruitment. Some caregivers might be reluctant to try the new technologically enhanced TASK III resource guide (TASK III USB drive, e-book, and interactive TASK III website) or use videoconferencing (FaceTime and Zoom) for calls with the nurse. During the first TASK III session, we will instruct and demonstrate how to use the new Amazon Fire Tablet; how to connect with the nurse via FaceTime (if they have an iOS device); how to connect with the nurse via Zoom; and how to use each TASK III resource guide delivery mode (TASK III USB drive, e-book, and interactive TASK III website) and the American Heart Association website. We will encourage caregivers to explore these newer technologies during each call from the nurse but respect their preferences [38] and suggest that they call us if they have difficulties. We will have IT support available for caregivers. For the ISR group, during the first call, we will instruct and demonstrate how to use the new Amazon Fire Tablet, how to connect with the nurse via FaceTime (if they have an iOS device), how to connect with the nurse via Zoom, and how to access the American Heart Association website.

Our future directions include procedures detailed in the *Dissemination Plans* section that include reporting our findings in ClinicalTrials.gov (ID NCT05304078) and peer-reviewed journals and making our data available to others. Once we are able to demonstrate that TASK III intervention is efficacious, our next goal is to translate the optimized TASK III intervention into stroke systems of care to meet recommendations and guidelines for follow-up care for survivors and caregivers.

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Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist based on the SPIRIT guidelines [89-91] and the CONSORT-EHEALTH (Consolidated Standards of Reporting Trials of Electronic and Mobile Health Applications and Online Telehealth) checklist [92] based on the CONSORT (Consolidated Standards of Reporting Trials) guidelines [88] are available upon request.

Authors' Contributions

All authors have contributed to the planning and designing of the trial and writing, reading, and editing of the manuscript. All authors have read and approved the submitted version and agree to be personally accountable for their own contributions, as well as those in which they were not personally involved.

TB, JKA, and PHM contributed to the conception of the study. All authors contributed to the design of the work. TB, NK, JI, and BH were involved in the acquisition of data. TB, HS, and KD analyzed the data, and TB, EM, HS, NK, and KD were involved in the interpretation of data. All authors drafted and substantially revised the work.

Conflicts of Interest

NK was associated with the Astra Zeneca Speaker Bureau (this conflict has ended) and is a National Football League unaffiliated neurotrauma consultant. All other authors declare no other conflicts of interest.

Multimedia Appendix 1
List of recruitment sites.
[PDF File (Adobe PDF File), 93 KB - resprot_v14i1e67219_app1.pdf]

Multimedia Appendix 2
The study informed consent statement.
[PDF File (Adobe PDF File), 206 KB - resprot_v14i1e67219_app2.pdf]

Multimedia Appendix 3
Screenshots of the Telehealth Assessment and Skill-Building Kit III website.
[PDF File (Adobe PDF File), 479 KB - resprot_v14i1e67219_app3.pdf]

Multimedia Appendix 4
Measures for primary and secondary outcomes, mediators, program evaluation outcomes, and sample characteristics.
[PDF File (Adobe PDF File), 104 KB - resprot_v14i1e67219_app4.pdf]

Multimedia Appendix 5
Peer review report from the CMGC - Clinical Management in General Care Settings Study Section (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 87 KB - resprot_v14i1e67219_app5.pdf]

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Abbreviations

BCOS: Bakas Caregiving Outcomes Scale
CNCC: Caregiver Needs and Concerns Checklist
GLMM: generalized liner mixed model
HIPAA: Health Insurance Portability and Accountability Act
IRB: institutional review board
ISR: information, support, and referral
NIH: National Institutes of Health
NINR: National Institute of Nursing Research
PHQ-9: Patient Health Questionnaire-9
PI: principal investigator
R01: R01NR010388; ClinicalTrials.gov ID: NCT01275495
R21: R21NR016992; ClinicalTrials.gov ID: NCT03635151
REDCap: Research Electronic Data Capture
TASK III: Telehealth Assessment and Skill-Building Kit
TASK: Telephone Assessment and Skill-Building Kit

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Protocol

Evaluation of the Tu'Washindi Na PrEP Intervention to Reduce Gender-Based Violence and Increase Preexposure Prophylaxis Uptake and Adherence Among Kenyan Adolescent Girls and Young Women: Protocol for a Cluster Randomized Controlled Trial

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Abstract

Background: Adolescent girls and young women constitute a priority population disproportionately affected by HIV, accounting for 25% of annual HIV incidence among people older than 15 years in Kenya. Although oral preexposure prophylaxis (PrEP) is effective in reducing HIV acquisition, its protective benefit has been limited among adolescent girls and young women in sub-Saharan Africa because of low uptake, adherence, and persistence. Intimate partner violence (IPV) and relationship power inequities are widespread among adolescent girls and young women and contribute to higher HIV incidence and lower PrEP use. Interventions are needed to support sustained PrEP use among adolescent girls and young women by addressing IPV and relationship dynamics.

Objective: This study aims to test the effectiveness of Tu'Washindi na PrEP ("We are Winners with PrEP"), a multilevel community-based intervention, to increase uptake and adherence to PrEP and reduce IPV among adolescent girls and young women in Siaya County, Kenya.

Methods: The Tu'Washindi na PrEP intervention was co-designed by our team and adolescent girls and young women using participatory methods and includes 3 components delivered over 6 months: an 8-session, empowerment-based support club for adolescent girls and young women, community sensitization targeted toward male partners, and PrEP education events for couples. The intervention will be evaluated using a cluster randomized controlled trial across 22 administrative wards in Siaya County, Kenya, enrolling 72 adolescent girls and young women per ward (total N=1584). The primary objectives are to test the effectiveness of the intervention on PrEP uptake and adherence immediately after delivery (month 6 after enrollment) and 6 months later (month 12). As secondary objectives, we will test the intervention effect on IPV. A rigorous process evaluation will explore mechanisms of change, contextual factors, and implementation considerations to inform future refinement and scale-up, using programmatic data, participant questionnaires, and qualitative interviews with participants and intervention providers.

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Results: Data collection started in September 2022. As of December 2024, enrollment has been completed in 16 of the 22 study wards, with 72.6% (1150/1584) of participants enrolled. We anticipate that data collection will be completed in May 2026 and results will be available by mid-2027.

Conclusions: The study builds directly on our promising formative and pilot research to develop the evidence base for this youth-designed, multilevel HIV prevention intervention. If effective, Tu'Washindi will be ideally positioned for sustainable integration into existing youth-focused programming to expand and support PrEP use in this priority population.

Trial Registration: ClinicalTrials.gov NCT05599581; https://www.clinicaltrials.gov/study/NCT05599581

International Registered Report Identifier (IRRID): DERR1-10.2196/55931

(JMIR Res Protoc 2025;14:e55931) doi:10.2196/55931

KEYWORDS

adolescent girls and young women; HIV prevention; preexposure prophylaxis; PrEP; adherence; Kenya; intimate partner violence

Introduction

Background

Optimizing the effectiveness of proven biomedical prevention interventions is critical to decreasing the high incidence of HIV among adolescent girls and young women aged 15 to 24 in sub-Saharan Africa, a priority population for HIV prevention. More than 1 in 4 new HIV infections in this region are among adolescent girls and young women [1], who are over twice as likely to acquire HIV as their male counterparts [2]. Oral preexposure prophylaxis (PrEP) is an effective, female-initiated biomedical HIV prevention intervention, but its protective benefit has been limited among adolescent girls and young women across sub-Saharan Africa by challenges to uptake, adherence, and persistence [3-17]. In western Kenya, a study of adolescent girls and young women attending family planning clinics found that 76% met PrEP eligibility criteria, but only 4% initiated PrEP [16], and the proportion of adolescent girls and young women persisting with PrEP for 3 months postinitiation ranged from 5% to 37% across studies [7,10,11,15,17]. In samples of PrEP users at an average of 6 months postinitiation, only 4% to 8% had tenofovir diphosphate (TFVdp) levels suggesting high adherence [4-6]. The public health impact of PrEP will be determined by concurrent interventions that address critical barriers to uptake and adherence.

Adolescent girls and young women who live in a context of heightened gender inequality and risk of intimate partner violence (IPV) represent a large subpopulation who are uniquely vulnerable to HIV infection. IPV is widespread among adolescent girls and young women in western Kenya: 19% reported experience of sexual IPV in the past year, 25% reported physical IPV, and 34% reported emotional IPV [18-20]. Experience or fear of IPV in sexual relationships is associated with having limited relationship power [20,21] and with 28% to 55% higher HIV incidence in adolescent girls, young women, and adult women [21-23]. Studies have found that IPV and other partner-related social harms are associated with 1.5- to 2.5-fold higher risk of poor adherence to oral PrEP and the dapivirine ring for HIV prevention. Similar to HIV treatment and contraception [19,20,24-29], IPV and relationship inequality introduce barriers to uptake of and adherence to PrEP at multiple levels. At the individual-level, restricted access to information and health services, poor negotiation skills, low self-efficacy, and fear of violence or relationship dissolution hinder adoption of health-promoting behaviors [30-32]. Dynamics at the partner level, such as poor communication and low decision-making power, limit disclosure about PrEP use and reduce partner support, which can impact adherence [33-35]. These challenges are further compounded at the community level by a lack of PrEP awareness, inequitable gender norms, and stigma associated with taking PrEP, which contribute to partner and community opposition to female PrEP use [36-39]. A multilevel context-specific intervention to address barriers to PrEP use is needed to ensure that adolescent girls and young women experiencing relationship inequality and IPV benefit from this effective biomedical prevention strategy.

In response, our intervention, Tu'Washindi na PrEP (We are winners with PrEP), was designed in close partnership with local adolescent girls and young women and incorporates strategies targeted to address relationship dynamics and IPV at multiple levels [40,41]. This intervention has 3 components: an empowerment-based support club for adolescent girls and young women, PrEP education events for couples offered in the context of a health fair (Buddy Days), and community sensitization about PrEP targeted toward adolescent girls and young women's partners [40]. The pilot cluster randomized controlled trial (cRCT) of Tu'Washindi at 6 Determined, Resilient, Empowered, AIDS-free, Mentored and Safe (DREAMS) spaces demonstrated feasibility, high acceptability, implementation with fidelity, and promising effects on PrEP and IPV outcomes [42]. PrEP uptake and adherence were both approximately twice as high in the intervention arm as in the control arm ($P<.05$) [43]. Although the adherence was still lower than desired in the intervention arm, with Wisepill openings on 25% of days on PrEP, they still represented substantial improvement over programmatic outcomes [6,17]. We also observed less frequent or severe IPV among intervention arm participants [43].

Because our pilot findings suggested that Tu'Washindi shows promise as an acceptable intervention that can be implemented with fidelity to promote PrEP uptake and adherence among adolescent girls and young women without concomitant increases in IPV, we designed a fully powered effectiveness trial to determine whether these gains translate to increases in biomarker measures of PrEP adherence and whether the intervention can reduce IPV risk.

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Study Objectives

The objective of this study is to test the effectiveness of the multilevel Tu'Washindi intervention to increase effective PrEP use and reduce IPV among Kenyan adolescent girls and young women by addressing relationship dynamics and partner opposition to PrEP. A process evaluation will assess the implementation processes and theorized mechanisms of change influencing intervention effectiveness and identify implementation challenges and strategies to facilitate future scale-up in programmatic settings to maximize public health impact. Study findings will contribute to the limited evidence base for effective PrEP adherence interventions to reduce HIV acquisition in this priority population.

Methods

Design

This study has a 2-arm parallel cRCT design (Figure 1). We have randomized 22 administrative wards in a 1:1 ratio and aim to enroll about 72 adolescent girls and young women from each (total N=about 1584) to receive either the Tu'Washindi intervention plus usual HIV prevention services, or usual HIV prevention services alone. Because of the urgent need for interventions to support PrEP use among adolescent girls and young women in a real-world context, the intervention is delivered outside of DREAMS to evaluate its impact on adolescent girls and young women accessing PrEP from Ministry of Health (MoH) facilities. This pragmatic study design enables us to determine effectiveness of the intervention when layered onto ongoing county-wide HIV prevention programming [44]. After informed consent and baseline data collection, the Tu'Washindi intervention is implemented in each intervention cluster while the control cluster continues with usual HIV prevention services. The duration of study participation is 12 months, with data collection visits at intervention midline (study month 3), intervention endline (study month 6), and at 6 months postintervention (study month 12). A prospective process evaluation is being conducted to characterize intervention implementation, explore theorized mechanisms of change, and capture contextual factors influencing study outcomes. The protocol was written following the 2013 SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (Multimedia Appendix 1).

Figure 1. An overview of the study design. AGYW: adolescent girls and young women; FTCtp: emtricitabine triphosphate; IDI: in-depth interview; IPV: intimate partner violence; PrEP: preexposure prophylaxis; TFVdp: tenofovir diphosphate.

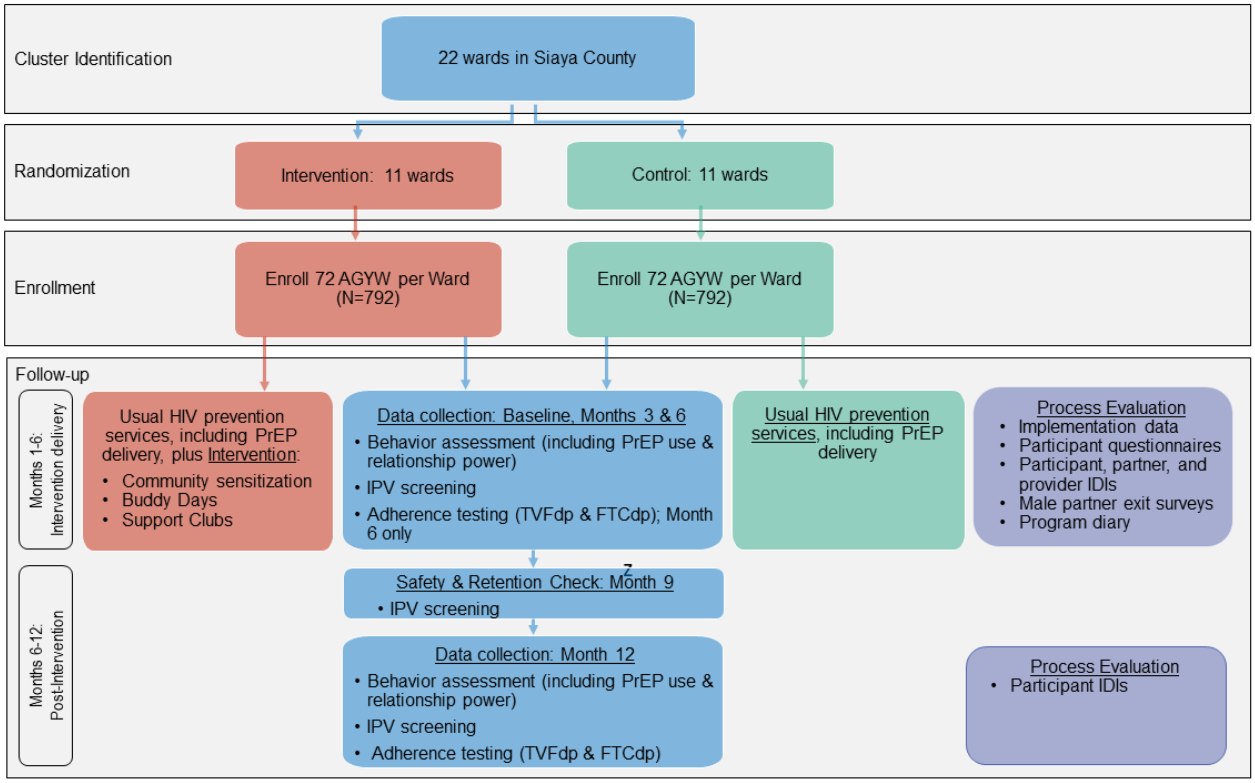

Study Setting

Siaya County is located in the former Nyanza Province in western Kenya, along the shores of Lake Victoria. The county is primarily periurban and rural, and agriculture and fishing are the main economic activities [45]. Siaya County has the second highest HIV incidence in Kenya (2.5% per year); it is the site of 12% of new HIV infections but comprises just 2% of the national population [46]. In addition, the former Nyanza Province has the highest prevalence of gender-based violence in Kenya: 22% of women aged 15 to 49 have reported sexual violence and 56% have reported physical violence at least once since the age of 15 [18].

Study Organization

The Tu'Washindi study leadership is comprised of investigators from RTI International and Impact Research and Development Organization (IRDO) and meets monthly. This group is

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ultimately responsible for the design and conduct of the trial, including intervention updates, protocol preparations and revisions, and protocol and safety monitoring. The trial management committee meets weekly, and it is responsible for the day-to-day conduct of the trial. It includes the principal investigator (PI) and site PI, project director and project coordinator, intervention leads, and quantitative and qualitative data management teams. The University of North Carolina Center for AIDS Research Clinical Pharmacology and Analytical Chemistry Core is responsible for analysis of the dried blood spot (DBS) samples. The study is further supported by a 5-member national-level technical advisory committee who meet annually and advise on design considerations to ensure a smooth transition from research to implementation if the intervention is effective; a 15-member youth advisory board that meets quarterly and provides feedback on study design and methods, data collection tools, and recruitment and retention of study participants; and a 12-member stakeholder advisory board made up of PrEP technical staff from MoH and other delivery partners, IPV referral agency representatives, and other community leaders that meets twice yearly to advise on effective integration of the study into existing structures and on linkage to PrEP and other referral services.

cRCT Component

Site Selection and Randomization

The study clusters comprise 22 of the 30 administrative wards in the county. The 30 wards were categorized into 5 strata based on community type (ie, periurban, rural fishing, or rural nonfishing) and whether the proportion of girls on PrEP is above or below the median, using MoH programmatic data. (Although the geography and PrEP use criteria define 6 strata, only 1 ward in the county fell within the urban, low PrEP use stratum. Because it was not possible to create a pair of intervention and control wards in this stratum, it was excluded.) The 22 study wards were purposively selected to ensure an even number of wards within each stratum and a balanced distribution of wards across strata. Randomization was completed by RTI statisticians once the 22 study wards are selected and placed into strata. Within each stratum, wards were randomly allocated to the intervention or control arms in a 1:1 ratio. After randomization, we created pairs of intervention and control wards within each stratum and determined the order in which they would be enrolled in the study based on the location of each ward, to minimize the risk of contamination while ensuring the feasibility of implementation. Subsequently, one intervention and control site pair were randomly selected from each stratum for inclusion in the qualitative component. Allocation was revealed to the investigators before community mapping (see the Recruitment and Screening section) and to the participants after their enrollment into the study.

Eligibility Criteria

To be eligible, potential participants must be females aged 15 to 24, currently in a sexual relationship with a male partner for at least 1 month, and vulnerable to HIV per a modified version of the DREAMS eligibility screening tool. To reflect the population most likely to participate in this intervention in a programmatic setting, they must be either taking PrEP or interested in taking PrEP (ie, she thinks that she would benefit from PrEP but is not currently taking it). In addition, they must be residents of the applicable study ward; willing and able to attend support clubs; willing and able to provide adequate contact information; fluent in English, Dholuo, or Kiswahili; and able and willing to provide informed consent (or assent and parental consent for nonmature minor participants aged 15 to 17). Potential participants are excluded if they are living with HIV (by self-report); planning any long-term travel or relocation in the next 12 months; or have any condition that the site PI or designee determines would preclude participation.

Individuals who do not meet the criteria for participation in this trial (ie, screen failure) because of criteria that are likely to change over time may be rescreened. Examples include not being resident of the ward or not being interested in taking PrEP.

Recruitment and Screening

Recruitment occurs simultaneously in each pair of wards before moving on to the next pair and focuses on the catchment areas of 2 to 4 health facilities in each ward. Before recruitment, community mapping is conducted to identify key stakeholders, referral resources, locations where adolescent girls and young women gather, and locations where men gather. Recruitment takes place at venues identified through community mapping, including health facilities, schools, churches, DREAMS Safe Spaces, youth groups, and community markets. To ensure that the study findings are generalizable to adolescent girls and young women across the 15- to 24-year age range, we aim to enroll at least 25% of the study participants from the 15- to 19-year age group who have lower rates of PrEP use but have similar HIV incidence to the 20- to 24-year age group [47,48]. Attendees interested in the study are invited to meet with the research assistant after the recruitment meeting to discuss questions, obtain additional information, and schedule an appointment for informed consent, eligibility screening, and, if eligible, for enrollment.

Retention

Once a participant is enrolled in the study, the study team makes every reasonable effort to retain her to minimize bias associated with loss to follow-up. To ensure high retention, IRDO tracks retention rates and follows standard study operating procedures detailing strategies, such as clear explanation of the visit schedule at all visits, collection of detailed locator information with multiple means to contact participants, appropriate and timely visit reminders, offering weekend hours for study visits, and conducting immediate follow-up on missed visits through phone, home or other off-site visits.

Intervention and Control Conditions

Intervention Design

Tu'Washindi was developed by our team using a participatory process with adolescent girls and young women and service providers in Siaya County to ensure that it was responsive to adolescent girls and young women's stated needs for PrEP support in the context of their relationships [40]. The intervention components are informed by social cognitive theory [49] in combination with a socioecologic framework for PrEP

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introduction [50] to address factors at the individual, partnership, and community levels that influence adolescent girls and young women's response to IPV and their PrEP use (Figure 2 [50,51]).

Social cognitive theory informs support club activities to enhance individual-level behavioral capability (eg, knowledge and skills to use PrEP and IPV safety planning), improve outcomes expectations (eg, that PrEP use will prevent HIV without threats to safety or relationship security), and increase self-efficacy to use PrEP safely and consistently. At the partnership level, support clubs also aim to develop skills for healthy communication and PrEP disclosure. Drama activities are integrated into each session to allow participants to practice these skills and build self-efficacy. Adolescent girls and young women follow suggested storylines from the intervention manual, developed by youth in the formative phase [40], to create and enact plays about overcoming partner-related barriers to PrEP use, including one to be performed at the Buddy Days. Buddy Days also work at this level to facilitate disclosure and build male partner support for PrEP use by engaging couples in discussions about PrEP, healthy relationships, and promoting HIV prevention as part of family well-being. To increase men's receptiveness to information provided at the Buddy Days or from their female partners, community sensitization events deliver accurate information about PrEP (eg, safety, effectiveness, and eligibility), discuss common myths and misperceptions, and encourage men to support their partners' PrEP use [53]. At the community level, the community sensitization activities aim to increase PrEP knowledge, reduce PrEP stigma, and reduce the acceptability or normalization of IPV as a response to adolescent girls and young women's PrEP use. Support clubs aim to increase social assets, including peer support for PrEP use and access to IPV resources in the community. Table 1 illustrates the intervention's alignment with the conceptual framework.

Figure 2. The conceptual framework; adapted from Pettifor et al [51] and Mathur et al [50]. IPV: intimate partner violence; PrEP: preexposure prophylaxis.

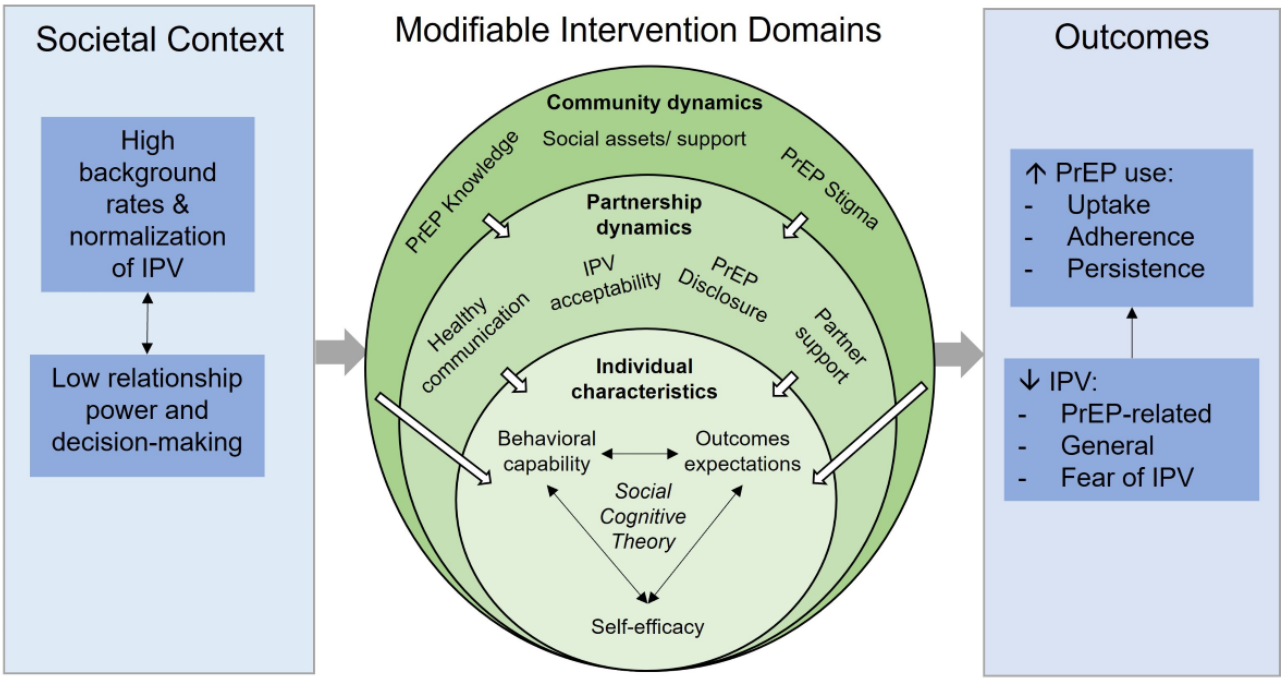

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Table 1. Mapping of intervention components to conceptual framework.

Level and domain	Community sensitization	Buddy Days	Support clubs
Individual			
Behavioral capability			✓
Outcomes expectations		✓	✓
Self-efficacy			✓
Partnership			
Healthy communication		✓	✓
Reduce intimate partner violence acceptability	✓	✓	✓
Disclosure of preexposure prophylaxis use		✓	✓
Partner support or acceptance	✓	✓	
Community			
Preexposure prophylaxis knowledge	✓	✓	
Stigma	✓		
Social assets			✓

Intervention Delivery

Before delivery, the intervention manual and training tools were updated to reflect lessons learned during the pilot and the change to implementation outside of DREAMS. Because age restrictions on PrEP in DREAMS did not permit us to pilot the intervention with adolescent girls aged 15 to 17 years, we pretested the activities with 12 to 15 adolescent girls in this age range over a 1-month period to obtain feedback on comprehension and relevance of the content and how best to support participation.

Delivery takes place in 4 phases, with activities occurring concurrently in 2 wards during phase 1 and in 3 wards during phases 2 to 4. In each ward, the intervention is conducted over a 6-month period with intervention implementation beginning about 1 week after enrollment concludes. Each new phase of the intervention commences immediately after the activities in the previous phase are concluded. This phased approach minimizes staff burden and allows for close monitoring of implementation to identify and correct problems early on.

The intervention activities include sensitization of MoH clinics, intervention staffing and training, community sensitization sessions, Buddy Days, support clubs, and monitoring and quality assurance.

For sensitization of MoH clinics, before study initiation in each intervention ward, we collaborate with the facility in-charges from each of the 2 to 4 health facilities selected for study recruitment to identify PrEP delivery staff and schedule a half to one day training to introduce the study and discuss relationship-related challenges to PrEP use, with the goal of ensuring that the counseling support offered at the clinics complements the messages provided through the intervention. We also review PrEP adherence and couples' counseling and disclosure approaches to more comprehensively address adherence challenges commonly experienced by adolescent girls and young women.

Intervention staffing and training within each ward is delivered by a set of 2 to 4 mentors (ie, women slightly older than the participants who have completed at least some secondary education and are rooted in their communities), an experienced male community organizer, and clinicians and counselors with experience in PrEP provision to adolescent girls and young women (hereafter "intervention providers"). Staff supervisors train each cadre over 1 to 3 days to review the intervention manual and to practice the required activities.

Community sensitization sessions are conducted by the community organizer approximately weekly over the first 3 months of the intervention period, lasting about 60 minutes to 90 minutes each. Sessions occur in places where adolescent girls and young women's male partners are known to gather [54]. Content focuses on PrEP information and dispelling myths and rumors. When time allows, additional content on healthy relationship communication is also included. Clinicians may attend larger sessions to support the organizer.

Buddy Days take place around month 3 of the intervention period, with about 2 to 3 events per ward to maximize participation. The sessions are cofacilitated by the community organizer and clinician and include provision of information about PrEP; facilitated discussion of reasons to support adolescent girls and young women's PrEP use, healthy relationship communication, and acceptability of IPV; and an interactive drama, designed and performed by volunteer Tu'Washindi participants based on story guides in the intervention manual, to illustrate real-world partner-related challenges to PrEP use. The cofacilitators foster audience engagement both during and after the performance by soliciting reflections on the drama, discussions of alternate storylines, and experiences from audience members [55]. To encourage and destigmatize participation, Buddy Days are open to all community members and offer health services, such as HIV testing services and screening for hypertension and diabetes. In addition, all adolescent girls and young women and their

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partners who attend the Buddy Days together as a couple receive a small basket of foodstuffs worth about US $5 as an incentive.

Support clubs meet for approximately eight 2-hour sessions over the 6-month intervention period, facilitated by the mentor or by 1 or more participants with mentor support. About 3 to 4 support clubs are offered at varying times and locations to maximize convenience and maintain a small enough number of attendees (18-24) to build community and trust. The support clubs aim to be youth-friendly and nonjudgmental, with an emphasis on ground rules and confidentiality, and support for PrEP uptake and adherence are integrated throughout. Each interactive, participatory session follows the same basic format: a check-in and activity to build community; recap of the previous session; a new topic related to PrEP and relationships, led by the mentor, clinician, or counselor (Table 2); drama activities; and a closing activity to reflect on lessons learned and build confidence and support.

Table 2. Sample support club topics and coleaders.

Session and topic	Leaders
Session 1: PrEP[a] information	Mentor and clinician
Session 2: disclosure	Mentor and counselor
Session 3: undisclosed PrEP use	Mentor and clinician
Session 4: healthy relationships	Mentor and counselor
Session 5: IPV[b] and PrEP use	Mentor and counselor
Session 6: open session[c]	Mentor
Session 7: open session[c]	Mentor
Session 8: future goals and closing ceremony	Mentor

[a]PrEP: preexposure prophylaxis.

[b]IPV: intimate partner violence.

[c]Participants' choice of topics.

Monitoring and quality assurance involves closely monitoring intervention delivery for quality and fidelity. Staff supervisors will observe at least 15% of community sensitization activities, 100% of Buddy Days, and at least 20% of support clubs using activity-specific observation forms to document assessments of fidelity (ie, adherence to the intervention manual), quality of facilitation (eg, facilitator maintains focus and nonjudgmental delivery), participant engagement, and any factors that may have affected implementation. Intervention staff receive feedback and coaching after each observed session. Findings will inform staff retraining and implementation refinement for subsequent phases. For example, training of intervention providers may be bolstered if gaps are identified.

Usual Care Services

Participants in the intervention and control clusters will have access to a range of evidence-based HIV prevention services offered in the county, including Global Fund–supported services, such as HIV testing services, syndromic management of sexually transmitted infections, family planning and postviolence care services; ongoing DREAMS programming; and PrEP [56]. Participants in both arms receive information about available services and are referred to these services upon request. PrEP is available to adolescent girls and young women aged ≥15 at >100 MoH facilities throughout the county [57], and all the participants who choose to use PrEP in the study can access it through these MoH facilities. In keeping with our study design, this choice of usual services as the comparator condition is realistic, ethical, and relevant [58] because it represents a wide range of evidence-based services to reduce HIV risk. However, PrEP uptake and persistence have been suboptimal in this context, indicating that the intervention is warranted, and that the comparator condition is not sufficiently robust to preclude our ability to detect an effect [59].

Data Collection

Data collection visits occur simultaneously in each pair of wards at enrollment, and months 3, 6, and 12 (Table 3). At enrollment, interviewer-administered questionnaires are used to assess sociodemographics, relationship characteristics, IPV, behavioral HIV risk factors, and history of PrEP use. Measures are repeated in follow-up questionnaires to document changes in relevant characteristics, attitudes, and behaviors.

DBS samples are collected via fingerprick at months 6 and 12 from all participants who report initiation or continuation of PrEP since the last visit. For participants who report discontinuation of PrEP, reasons for discontinuation are recorded, but DBSs are not collected. Due to storage and transport challenges, DBS samples are also not collected for participants who have relocated outside the county and have follow-up visits conducted by phone or at a remote location. DBS samples are stored in freezers at the IRDO laboratory and then shipped to the laboratory at the University of North Carolina Center for AIDS Research Clinical Pharmacology and Analytical Chemistry Core for quantification of drug concentrations by liquid chromatography-tandem mass spectrometry technology [60].

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Table 3. Participant timeline.

Procedures	Month 0 (BL[a])	Month 1	Month 2	Month 3 (3 MFU[b])	Month 4	Month 5	Month 6 (6 MFU)	Month 7	Month 8	Month 9	Month 10	Month 11	Month 12 (12 MFU)
Assess and confirm eligibility	✓												
Informed consent	✓												
Enrollment	✓												
Locator information and update	✓			✓			✓			✓			✓
Quantitative data collection													
Sociodemographic and behavioral characteristics	✓			✓			✓						✓
PrEP[c] use history	✓			✓			✓						✓
IPV[d] history	✓			✓			✓						✓
Hypothesized mechanisms of action[e]	✓			✓			✓						✓
Laboratory assessment (dried blood spots)							✓						✓
Tu'Washindi intervention													
Community sensitization session (weekly)		✓	✓	✓									
Buddy Days				✓									
Support clubs (once or twice per month)		✓✓[f]	✓✓[f]	✓	✓	✓	✓						
Qualitative data collection													
In-depth interviews (subset of participants)							✓						✓
Safety monitoring													
Standardized assessments				✓			✓						✓
Short in-person or telephone contact visit										✓			
Reporting of IPV, injuries, social harms, or other relevant concerns		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

[a]BL: baseline appointment.

[b]MFU: month follow-up appointment.

[c]PrEP: preexposure prophylaxis.

[d]IPV: intimate partner violence.

[e]Also part of process evaluation.

[f]Two support clubs per month.

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Process Evaluation Component

Overview

The mixed methods process evaluation uses implementation data; quantitative adolescent girls and young women participant questionnaires; exit surveys with men who attend intervention activities; qualitative in-depth interviews (IDIs) with adolescent girls and young women participants, their male partners, and intervention providers; and a project diary. Our process evaluation framework (Figure 3 [61]) highlights the key evaluation components, relationships between them, and key measures and data sources [62-65].

Figure 3. Process evaluation framework and key measures. Adapted from the Medical Research Council guidelines for process evaluation of complex interventions [60]. IPV: intimate partner violence; MoH: Ministry of Health; PrEP: preexposure prophylaxis; SAB: Stakeholder Advisory Board; TAC: Technical Advisory Committee; YAB: Youth Advisory Board.

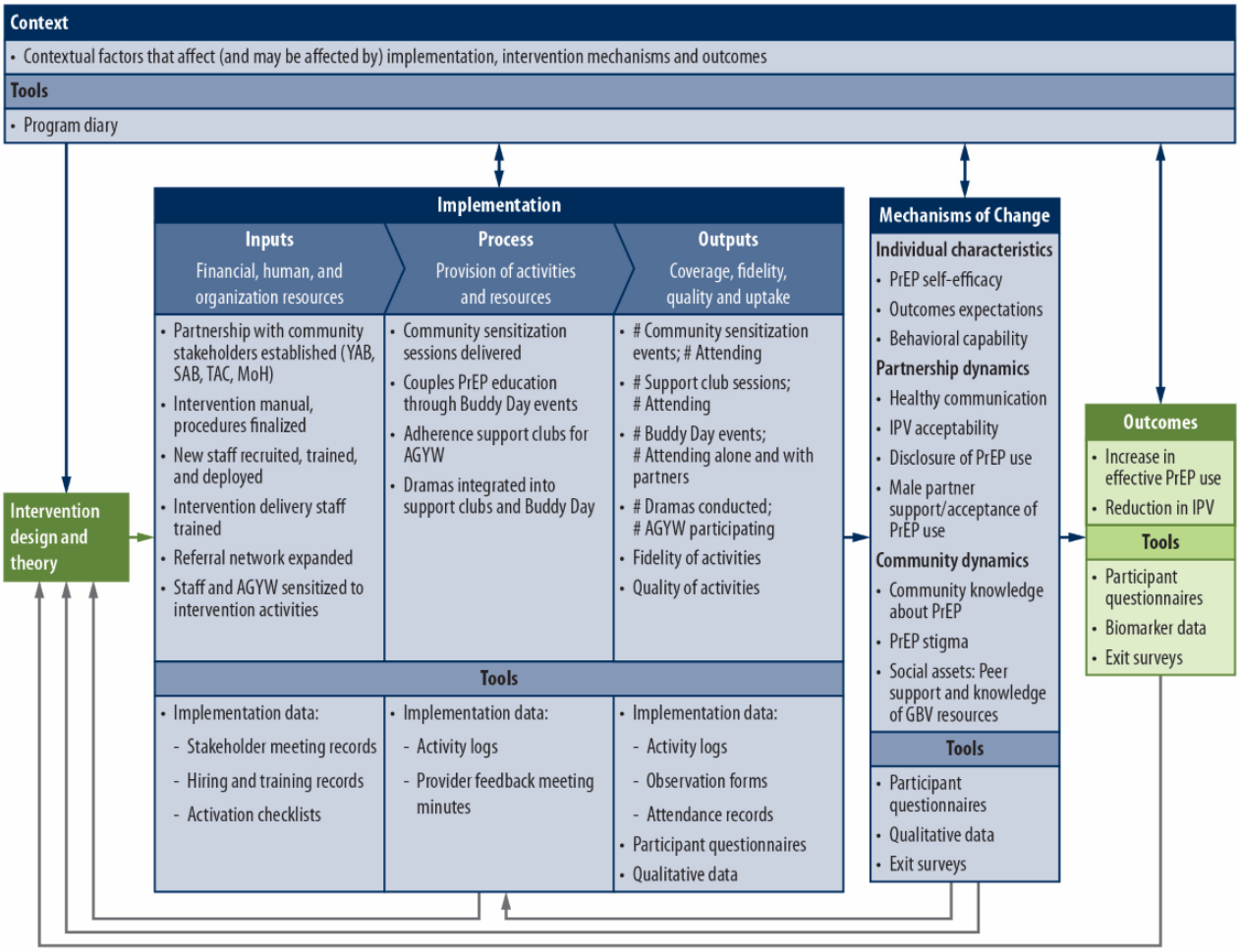

Participants and Eligibility

Eligibility criteria for adolescent girls and young women participants are described in the Eligibility Criteria section. Participants in exit surveys or male partner IDIs must be males aged ≥15 years. In addition, the exit survey participants must have attended a study Buddy Days or community sensitization event and have been present for at least half of the event, while IDI participants must be a sexual partner of the adolescent girls and young women clinical trial participant and that adolescent girls and young women participant must have provided permission for the study staff to contact the male partner. Intervention providers must be aged ≥18 years and have been involved in delivering Tu'Washindi intervention activities. In addition, all participants must be fluent in English, Dholuo, or Kiswahili; willing and able to provide informed consent; and not have any condition that the site PI or designee determines would preclude participation.

Participant Selection and Recruitment

Exit Surveys

At all intervention sites, all men who attend a Buddy Days event as a couple are approached while waiting for incentive distribution and asked to complete a survey. A research assistant approaches about 20% of men who attend community sensitization events and asks them to complete survey after the event.

In-Depth Interviews

For each of the 5 intervention and control ward pairs randomly selected for qualitative research, we use data captured at month 3 to purposively select a subset of adolescent girls and young women participants (n=30; 4 per intervention ward and 2 per control ward) who are behaviorally eligible for PrEP, per self-report, and have attended at least one support club meeting (intervention wards only). We aim to ensure representation of

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PrEP users and nonusers and those with and without a history of IPV. Participants who are selected for IDIs are contacted by a research assistant before their month 6 visit, informed that they have been selected, and invited to participate in the IDI.

On the basis of the information provided by the adolescent girls and young women at the month 6 visit, we purposively select male partners (n=20; 4 per intervention ward) for IDIs to represent a range of exposure to the Buddy Days and community sensitization activities.

Male partners are only contacted with the permission of the adolescent girls and young women participants, who provide contact information. A research assistant then contacts the male partner and invites him to participate in the IDI. Study staff do not disclose the PrEP use status of adolescent girls and young women participants to any partner whom they recruit for the IDIs.

Intervention providers are purposively selected for IDIs by the study coordinator to represent a variety of job functions, including mentors, community organizers, counselors, and clinicians (n=20, 4 per intervention ward).

Data Collection

Implementation data includes staff hiring and training records; minutes from youth advisory board, stakeholder advisory board, and technical advisory committee meetings; and study activation checklists to track activities, materials, and systems required for successful implementation, such as community introductions, final intervention manuals, and vetted lists of referral agencies. Providers maintain activity logs and attendance records for each meeting or event, and supervisors record minutes from feedback and coaching meetings. Quality and fidelity of intervention activities is documented on observation forms as described above.

Participant questionnaires are administered to adolescent girls and young women participants at each visit to assess mechanisms of change (for all participants) and perceived intervention quality (intervention arm) or potential contamination (control arm). The hypothesized mechanisms of change include PrEP self-efficacy and outcome expectations, PrEP knowledge, healthy communication, disclosure of PrEP use to male partner and partner reaction, community knowledge of PrEP, PrEP stigma, and social assets.

Exit surveys are brief, anonymous, quantitative, interviewer-administered questionnaires that gather information on men's views of PrEP, their willingness to support their partner's PrEP use, and feedback on intervention activities.

IDIs are conducted in a private location and facilitated by trained female interviewers following a semistructured guide as follows:

- Serial IDIs with adolescent girls and young women participants are conducted at 2 time points (months 6 and 12). Key topics include relationship quality and experiences of IPV, patterns of PrEP use and barriers and facilitators to PrEP access and use, experiences with the intervention, and perceptions of how the intervention has affected the hypothesized mechanisms of change and study outcomes.
- Male partner IDIs take place at the end of the intervention period and explore men's experiences with the intervention. Interviews also aim to identify mechanisms through which their attitudes toward PrEP were shifted, or reasons why they were not.
- Intervention provider IDIs are conducted at the end of intervention delivery to elicit their perceptions of the adequacy of inputs (eg, training and resources), fidelity and quality of delivery, and challenges and perceived benefits to delivering each intervention component.

A program diary is maintained by the study coordinator to record external events (eg, elections, police activity, festivities, and health campaigns) and internal events (eg, increased funding or supply shortages) that may affect intervention delivery or study outcomes. Before intervention implementation in each ward, the study coordinator identifies a set of sources, including study staff, health facility personnel, community members or others who are well-positioned to provide this contextual information, and contacts them at regular intervals to record any updates.

Data Management

Most questionnaire data are collected on tablets using REDCap (Research Electronic Data Capture; Vanderbilt University) or collected on paper forms and entered into REDCap at the study offices, with hard copies securely stored at the field site [66,67]. RTI implements a quality assurance plan, including routine generation of quality control reports by the data manager and communication of findings for resolution. IDIs are audio-recorded, with debriefing reports completed immediately after each interview and quickly shared with the study team to highlight preliminary findings. Interviews are translated and transcribed at the study site. Electronic copies of forms are securely transmitted to RTI and reviewed for quality control, with weekly query resolutions.

Sample Size Considerations

The study is powered to identify an absolute difference of 15% between intervention and control arms for the primary outcomes: the proportion with effective PrEP use at month 6 and month 12. Power calculations are conducted using simulations based on the logistic model with normally distributed ward (cluster) effects and assuming 11 wards per treatment arm with type 1 error of 0.025 to account for separate analyses at each of 2 time points. With 60 participants per ward, we will have ≥80% power to detect a 15% difference in the outcome as long as the SD for ward variation is ≤10% and the level of effective PrEP use in control wards remains <50% (far higher than observed in recent trials and demonstration projects). To allow for up to 20% loss to follow-up, our total sample size will be 1584 participants: 72 adolescent girls and young women in each of the 22 wards (11 wards per arm).

Data Analysis: Clinical Trial

Outcomes and Hypotheses

The primary outcomes of the study will be the proportion of study participants with effective PrEP use, defined in Table 4, evaluated immediately postintervention, at month 6, and at

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month 12 to gauge the persistence of intervention effect. TFVdp levels will be dichotomized by Clinical Pharmacology and Analytical Chemistry Core laboratory specialists to delineate between consistent (≥4 doses per week) versus inconsistent (<4 doses per week) adherence [68]. The aim 1 hypothesis is that the proportion of participants with effective PrEP use at (a) month 6 and (b) month 12 will be *higher* in the intervention versus control arm.

Table 4. An overview of key measures for the cluster randomized controlled trial, collected at enrollment and months 3, 6, and 12, unless otherwise noted.

Measure	Method
Primary outcomes	
Effective PrEP[a] use (biomarker assessment)	Percentage of all study participants with biomarker TFVdp[b] levels indicating consistent PrEP use (≥4 doses per week) for the past 2 months. [68,69]. Represents a composite outcome of PrEP initiation and high execution to capture these key steps in the HIV prevention continuum. Collected at months 6 and 12 only.
Secondary outcomes	
IPV[c] prevalence	Percentage of participants reporting IPV since the last study visit, measured with the WHO VAWI[d] [70] and classified by the STRIVE consortium definition [71]: any act of severe physical or sexual violence or ≥2 acts of moderate physical violence.
IPV severity	Percentage of participants reporting any sexual or severe physical IPV since the last study visit, measured with WHO VAWI [70].
IPV intensity	Continuous score calculated from the number of specific violent acts reported and the reported frequency of each act (0=never; 1=once; 2=a few times; and 3=often) since the last study visit, measured with WHO VAWI [70].
Exploratory outcomes (subcomponents or alternate measures of primary and secondary outcomes)	
PrEP uptake	Percentage of participants initiating PrEP *among those not on PrEP at baseline*, self-reported and validated by Ministry of Health records.
PrEP execution	Percentage of participants with TFVdp levels indicating consistent use *among those reporting current PrEP use.*
PrEP persistence	Percentage of participants with any detectable TFVdp *among those who ever initiated PrEP.* Participants who self-report discontinuation will be categorized as having undetectable TFVdp levels.
Recent PrEP use (biomarker)	Percentage of all study participants with biomarker FTCtp[e] levels indicating consistent PrEP use (≥4 doses per week) for the past 2 wk. Collected at months 6 and 12 only.
IPV type	Percentage of participants reporting each IPV type (physical, sexual, emotional, and economic) since the last visit, per WHO VAWI [70].

[a]PrEP; preexposure prophylaxis.

[b]TFVdp: tenofovir diphosphate.

[c]IPV: intimate partner violence.

[d]WHO VAWI: World Health Organization's Violence Against Women instrument.

[e]FTCtp: emtricitabine triphosphate.

The secondary outcomes of the study will be the proportion of participants reporting any IPV and severe IPV (Table 4) between enrollment and month 6, and between month 6 and month 12, and the difference in IPV intensity scores at months 6 and 12. The aim 2 hypothesis is that the proportion of participants reporting any IPV and severe IPV and IPV severity scores will all be *lower* at both time points in the intervention arm versus control arm.

In exploratory analyses, we will first explore effect modification by age (15-19 vs 20-24) and DREAMS participation (current, former, or never) for the primary and secondary outcomes. Second, we will break down the primary outcome into steps along the continuum (PrEP uptake, execution, and persistence) and IPV outcomes by type—physical, sexual, emotional, and economic—to understand where the intervention had its strongest effects. Third, we will compare the proportion of participants per arm with emtricitabine triphosphate (FTCtp) levels indicating consistent PrEP adherence over the past 2 weeks. Comparing TFVdp and FTCtp levels will yield insights on adherence patterns over both a long and short window of time before collection. We will also analyze the alignment of adherence measures with HIV risk perception and behavior to better understand adherence patterns.

Analysis Approach

Descriptive and bivariate statistics will be used to compare participant characteristics in the intervention and control arms and those who completed the study versus those lost to follow-up. Outcomes will be modeled using an intent-to-treat approach with mixed effect logistic and linear regression models. Model predictors will include treatment assignments, randomization strata, and a random effect for ward (cluster) within stratum that is assumed to be independent and normally distributed with mean 0. If the cluster randomization does not adequately balance baseline characteristics across arms, we will conduct exploratory analyses controlling for those characteristics. We will analyze the data from each of the 2 time

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points separately and the primary outcomes analyses will use a type I error rate of 0.025 at each time point.

Missing Data

In any situation with missing data, we will perform appropriate secondary analyses adjusting for variables that may be related to the missingness mechanism. If missing data rates are higher than anticipated (>10%), we will include covariates that are related to missingness in regression models. We will also perform sensitivity analyses to assess the potential impact of the missing data.

Data Analysis: Process Evaluation

Quantitative Data

Implementation inputs, processes, and outputs will be analyzed descriptively, and we will draw comparisons across intervention wards. Intervention effects on each mechanism of change will be modeled individually following the approach described for the cRCT. We will regress each mechanism on the exposure (intervention arm assignment), controlling for baseline levels of the mechanism. If the primary analyses show no effect of the intervention on PrEP or IPV outcomes, the results will inform our interpretation of whether the intervention failed to affect the intended mechanism or whether the change in mechanism did not lead to the hypothesized outcome. If the primary analyses suggest a positive intervention effect on PrEP or IPV outcomes, we will conduct causal mediation analysis [72,73]. Coverage, uptake, and exit survey data on perceived impact will also be evaluated as moderators of intervention effectiveness at the site level in exploratory analyses of mechanisms of change.

Qualitative Data

The coding process will involve a core group of about 2 to 5 analysts from IRDO and RTI who will develop one or more codebooks and establish qualitative coding procedures. Data will be coded using a qualitative software package, such as Dedoose (SocioCultural Research Consultants, LLC). A set of preliminary codes will be developed based on key themes or topics identified a priori and the findings highlighted in the debriefing reports for each of the 3 datasets (eg, adolescent girls and young women, male partners, and providers). Each group member will apply the initial set of thematic codes to a common transcript, discuss their coding experiences, and agree on expanding and modifying code names and definitions when necessary. We will continue with an iterative process of revising the codebooks as we continue to read and code the data. Once finalized, the codebooks will be used for a final recoding of all transcripts.

A preselected number of transcripts will be double-coded by 2 coders to establish intracoder and intercoder reliability. Following this process, the coding team will discuss discrepancies, which will ultimately be resolved through consensus. This process will continue until the intercoder reliability is at least 80%. Thereafter the remaining texts will primarily be coded by 1 analyst only, with one or more rounds of consistency checks and regular discussions among the coding team to ensure that coding remains standardized and reliable.

Comprehensive listings of all coded quotations for every code or code "family" will be generated in the qualitative analysis software. Coding memos will be used to summarize and explore the relationship between the constructs of the evaluation framework (eg, the relationship between implementation processes and hypothesized mechanisms of change, or between mechanisms of change and outcomes). Analysts will also review and analyze coded serial IDI content within each participant's dataset to look specifically for patterns over time. The findings and interpretations of the data will be critically discussed until there is group consensus on the dominant themes and meanings contained in the data [74].

Integrated Synthesis of Quantitative and Qualitative Data

For each construct of the evaluation framework, findings from the qualitative and quantitative analyses will be integrated to build a more comprehensive picture of whether the target intervention inputs, processes, and outputs were achieved, whether these resulted in the hypothesized changes in mechanisms of action, whether these changes resulted in the intended outcomes, and how external contextual factors influenced implementation, thereby both evaluating the success of study implementation and testing the theory of change.

Study Monitoring

Protocol Oversight

The study team continuously reviews recruitment and follow-up data to ensure compliance with the protocol and ethical standards. The IRDO study coordinator regularly monitors protocol compliance at study sites. The IRDO internal research monitor conducts quarterly spot checks of 100% of informed consent forms and 10% of data files. Any issues are documented in quality control logs and reviewed with the study staff. Protocol deviations or violations are reported to the study leadership and institutional review board (IRB) within 5 business days.

Data and Safety Monitoring Board

The trial is monitored by a data and safety monitoring board (DSMB) composed of 4 members: a statistician, a medical physician, a researcher with content expertise in IPV, and a researcher with expertise in PrEP use among adolescent girls and young women. All DSMB members are independent from any professional or financial conflict of interest with the research project, study investigators, and study institutions. The DSMB established a charter that outlines their responsibilities and meets approximately semiannually to review data quality and integrity, protocol adherence, participant safety, study conduct, and progress. On the basis of their review, they make recommendations on study continuation and modifications.

Safety Monitoring

This study adheres to the World Health Organization Ethical and Safety Recommendations for Intervention Research on Violence Against Women [75]. All data collection staff receive training on IPV assessment, recognizing warning signs of immediate danger, discussing sensitive topics with participants, managing distressed participants, legal reporting requirements,

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and referral protocols. We aim to ensure that all communication with participants protects against unintentional disclosure of PrEP use, study participation, or reported IPV and does not place participants at additional risk of harm. To increase confidentiality, the study is presented to the community and to the participants as a study on HIV prevention methods in young women, and the focus on IPV is not advertised.

The MoH clinics conduct clinical safety monitoring for PrEP according to Kenyan guidelines. This study focuses on monitoring for adverse events that could be associated with the intervention, including IPV, social harms, serious adverse events, and unanticipated problems. All instances of these events are recorded on case report forms and followed up until resolution or 30 days after the participant exits from the study. These adverse events are reviewed monthly by the protocol team and reported to the IRB and DSMB according to their established protocols.

All staff have been trained to respond to any reports on IPV and social harms using the World Health Organization's Listen, Inquire, Validate, Enhance Safety, and Support (LIVES) approach through referrals [76]. Staff follow up by phone or during subsequent visits to check on referral uptake and provide additional assistance if needed. Participants who report being in immediate danger or feeling unsafe returning home are offered an immediate escorted referral to vetted rescue or shelter services, and study staff follow up with the participant weekly until their situation is resolved or stabilized, or until 30 days after their exit from the study. If staff have concerns about the safety of a participant's enrollment, they alert the site PI or designee to make a final determination about eligibility.

Ethical Considerations

The trial is being carried out in accordance with International Council on Harmonization Good Clinical Practice and the United States Code of Federal Regulations applicable to clinical studies (45 CFR part 46).

Ethics Approval

The study protocol and associated documents have been reviewed and approved by the Maseno University Ethical Review Committee (MUERC; MSU/DRPI/MUERC/00991/21). The RTI International Committee for Human Subjects Research established a reliance on MUERC for the study under a signed IRB authorization agreement. No amendment to the protocol or informed consent forms is implemented without prior ethics committee approval. Protocol violations are reported in writing to MUERC in accordance with their policy.

Informed Consent Process

IRDO study staff obtain informed consent or assent from all participants taking part in the cRCT or IDIs. Study staff explain the study purpose and procedures, risks and benefits to the eligible participants, and compensation for their participation. They emphasize that their participation is voluntary and that there is no penalty if the individual decides not to participate. Participants aged ≥18 years provide written consent in English, Kiswahili, or Dholuo. The IRB has granted a waiver of parental consent for adolescent girls and young women participants who meet the criteria for "mature minors" outlined in MoH guidelines for Conducting Adolescent HIV Sexual and Reproductive Health Research in Kenya [77], and for male partners aged 15 to 17 years to take part in IDIs, because they constitute a minimal-risk research activity. All minor participants may choose to involve their parent in the consent process. For minor participants not meeting the above criteria, or who involve their parents, we obtain parental consent and child assent. The IRB has also granted a waiver of written consent for the brief and anonymous exit interviews focused on program acceptability.

Confidentiality

All study procedures occur in private settings. Each participant receives a unique study identification number, and personally identifiable information does not appear on study data. All electronic data and study records are stored on secure, password-protected devices and uploaded to a secure RTI project server. Access to the system is restricted to trained study staff. Hard-copy data, consent and contact information forms with personally identifiable information are kept in separate double-locked files at the site and not transmitted to RTI.

To minimize confidentiality risks during the follow-up visits, we use contact methods agreed to by the participants, including aliases for study staff. To protect confidentiality during group activities, participants are asked to follow ground rules and pledge not to disclose others' personal details outside the group. At each session's start and end, participants are reminded to respect confidentiality and that there is a risk that others may disclose what they say.

Participants' study information will not be released without their written permission, except as required by law or as necessary for review, monitoring, and auditing by the following:

1. Representatives of the US federal government, including the United States Office of Human Research Protections, the National Institutes of Health (NIH) and contractors of the NIH, and other local, United States, and international regulatory entities
2. Representatives of RTI
3. Study staff
4. Site IRBs

Criteria for Early Termination of Study Participation

Participants can withdraw from the study at any time for any reason. The PI, site PI, or designee may also withdraw participants for safety or noncompliance reasons, with the DSMB notified of such terminations. Efforts are made to complete a final evaluation for participants who withdraw. Staff document withdrawal reasons in study records. Participants who withdraw may rejoin and resume intervention or follow-up visits up to their original exit date, with PI and DSMB consultation.

Study Discontinuation

The study may be suspended or terminated at any time by the NIH, RTI, site IRBs, or other authorities due to funding issues or substantial concerns, such as DSMB recommendations. If this occurs, the PI will be notified in writing with the reasons, and will inform participants, the IRB, and the sponsor. The

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study may resume if safety, protocol compliance, and data quality issues are resolved and approved by the relevant parties.

Dissemination and Use of Findings

Study findings will be disseminated to the study communities, the scientific community, and HIV service and advocacy organizations via peer review publications, professional meetings, research briefs, and stakeholder meetings. All media, presentations, and publications resulting from data collected during this study will be collaborative in nature but require approval from the study leadership. All publications will be submitted to PubMed Central, in accordance with NIH Public Access Policy.

Results

The study was funded in August 2021, and data collection started in September 2022. As of December 2024, enrollment has been completed in 16 of the 22 study wards, with 72.6% (1150/1584) participants enrolled. We anticipate that data collection will be completed in May 2026 and results will be available by mid-2027.

Discussion

Innovations and Future Application

This study offers 4 key innovations. First, it offers the opportunity to address the lack of evidence-based interventions that explicitly confront the role of IPV and relationship dynamics in supporting PrEP use among adolescent girls and young women. Current interventions have focused largely on instrumental adherence support (eg, pill-taking reminders and strategies), motivational interviewing, and peer support, with limited evidence of success [4,5,78-83]. If found effective, the Tu'Washindi intervention will be one of the first to successfully address critical partner-related barriers to uptake and adherence and to directly involve male partners to build their support for PrEP use among adolescent girls and young women. Second, our intervention approach is youth-designed and tailored to meet the specific needs of adolescent girls and young women, qualities that have been specifically called for in recent literature to address shortcomings in existing interventions [84,85]. The intervention components of male engagement and couples' education were added to the design in direct response to the formative research findings, and our participatory design methods resulted in high intervention acceptability and uptake among adolescent girls and young women and high ratings for relevance and perceived effectiveness. Third, our multilevel approach recognizes that IPV and relationship power create barriers to HIV prevention at the individual, partnership, and community levels. Tu'Washindi supports adolescent girls and young women to respond to experienced or anticipated IPV at each level by fostering self-efficacy, improving relationship communication, developing support systems, and encouraging action to maintain safety and HIV prevention adherence [86-88]. Fourth, we assess short- and long-term adherence with biomarker measurements of 2 active PrEP metabolites, TFVdp and FTCtp to gain a more thorough understanding of adolescent girls and young women adherence behavior. Although the field has focused on TFVdp levels to classify long-term (ie, previous 1-3 months) PrEP adherence [89], FTCtp concentrations can delineate between consistent (≥4 doses/week) versus inconsistent (<4 doses/week) PrEP adherence over 2 weeks before sample collection with ≥89% accuracy [90]. Thus, we will have the ability to classify adolescent girls and young women by short-term (2 weeks) adherence in addition to the long-term (2 months) adherence measured by TFVdp levels.

Our intervention and evaluation have been designed from the start to facilitate scalability, sustainability, and rapid adoption. Tu'Washindi was designed to be delivered by trained community members with support from clinicians and counselors, and to integrate into ongoing national or donor-funded youth-focused programs prioritizing HIV prevention. The proposed study uses a pragmatic, rather than exploratory, design to maximize generalizability and ensure results are applicable to real-world settings [44,91]. In addition, our design includes a rigorous process evaluation to document implementation process, quality and fidelity of delivery, resource requirements, and contextual factors to provide valuable guidance to program and policy stakeholders who wish to replicate or adapt the intervention outside of the research setting. In combination, the intervention design and process evaluation approach will reduce the "know-do gap" [92] and accelerate Tu'Washindi's translation from research to practice.

Limitations

Several limitations to this study should be noted. First, there is a risk of PrEP and HIV test kit shortages in MoH clinics, which could interfere with adherence and complicate interpretation of results. We will carefully document shortages as part of the program diary, and study staff will help link participants to other sources of PrEP provision if necessary. Second, cluster randomized studies carry a risk that individual participant characteristics may differ at baseline in important ways. Our design stratifies on 2 important community characteristics (ie, geographic type and baseline PrEP use) to reduce this risk, and our analysis plan incorporates exploratory analyses to control for baseline differences between randomization arms.

Conclusions

Tu'Washindi has demonstrated feasibility and acceptability in pilot research and shows promise to promote PrEP use and reduce IPV among adolescent girls and young women. The proposed study builds directly on our intervention development work to conduct a rigorous effectiveness trial, a critical step in developing the evidence base for this youth-designed, multilevel HIV prevention intervention. Our rigorous process evaluation will clarify mechanisms of change, and implementation considerations to inform policy and practice. If effective, Tu'Washindi will be ideally positioned for sustainable integration into existing youth-focused HIV prevention programming to expand and support PrEP uptake and adherence in this priority population.

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Data Availability

The research tools, protocols, standard operating procedures, analytic code, codebooks, and deidentified data generated in this study will be available from the corresponding author upon reasonable request. Before access to deidentified participant data is granted, a data sharing agreement will be implemented to ensure that the data will be used for the proposed purpose and that no attempts will be made to identify participants.

Authors' Contributions

STR was involved in conceptualization, methodology, writing original draft, supervision, project administration, and funding acquisition. AMM was involved in conceptualization, methodology, writing original draft, and supervision; ENB was involved in methodology, software, formal analysis, data curation, and writing original draft. SN was involved in conceptualization, methodology, investigation, supervision, and writing original draft. ETM was involved in conceptualization, methodology, supervision, and writing original draft; LD was involved in methodology, writing review, and editing. MLC was involved in methodology, resources, investigation, writing review, and editing. JN was involved in methodology, supervision, project administration, writing review, and editing, JB was involved in investigation, supervision, writing, reviewing, and editing. KA was involved in conceptualization, methodology, supervision, resources, writing original draft, and project administration.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 checklist: recommended items to address in a clinical trial protocol and related documents.
[PDF File (Adobe PDF File), 124 KB - resprot_v14i1e55931_app1.pdf]

Multimedia Appendix 2
Peer-review report by the Center for Scientific Review HIV/AIDS Intra- and Inter-personal Determinants and Behavioral Interventions Study Section (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 99 KB - resprot_v14i1e55931_app2.pdf]

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Abbreviations

cRCT: cluster randomized controlled trial
DBS: dried blood spot
DREAMS: Determined, Resilient, Empowered, AIDS-free, Mentored and Safe
DSMB: data and safety monitoring board
FTCtp: emtricitabine triphosphate
IDI: in-depth interview
IPV: intimate partner violence
IRB: institutional review board
IRDO: Impact Research and Development Organization
LIVES: Listen, Inquire, Validate, Enhance Safety, and Support
MoH: Ministry of Health
MUERC: Maseno University Ethical Review Committee
NIH: National Institutes of Health
PI: principal investigator
PrEP: preexposure prophylaxis
REDCap: Research Electronic Data Capture
TFVdp: tenofovir diphosphate

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Protocol

Racial Disparities in Parkinson Disease Clinical Phenotype, Management, and Genetics: Protocol for a Prospective Observational Study

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Abstract

Background: Parkinson disease (PD) has been described and studied extensively in White populations, with little known about how the disease manifests and progresses in patients from the Black community. Studies investigating disease features in Black populations are uncommon, with some suggesting that the Black population with PD is more disabled and has greater disease severity and different clinical features compared with the White population with PD. These health disparities are likely to influence the quality of care for Black patients with PD.

Objective: This study aimed to investigate the motor and nonmotor symptoms and quality of life in Black and White participants with PD in a case-case design.

Methods: This is an observational, prospective, multicenter, case-case design study. Other aims will investigate the management of PD in Black individuals and the presence of shared or unique genetic risk factors among the Black PD population. A total of 400 Black and 200 White participants with PD will be recruited. Data will be collected at 7 US sites and entered into a Research Electronic Data Capture database. Linear multivariate regression analysis will be used, except for comparing PD management, which will be analyzed using the chi-square test or Fisher exact test. Bonferroni correction will be applied. This protocol also describes plans for educational programming for clinicians and patients at the end of the study in partnership with national PD organizations.

Results: The Rush Institutional Review Board approved the project as the single-site institutional review board in February 2022, and it was funded by the National Institute of Neurological Disorders and Stroke in April 2022. Recruitment began in July 2022. At the time of submission of this manuscript, 131 participants had been recruited.

Conclusions: To our knowledge, this is the largest study of PD phenotype and management in Black patients in the United States. The planned collaboration with the Global Parkinson's Genetics Program and PD GENEration will enhance our understanding of genetic risk factors for PD in this understudied population.

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KEYWORDS

Parkinson disease; racial disparities; clinical protocol; health disparities; genetic risk factors; quality of life; quality of care

Introduction

Background

Parkinson disease (PD) is a progressive and incurable neurodegenerative disorder affecting 1 million people in the United States [1]. Health care resource usage costs for patients with PD in the United States are high and rise 2 to 3-fold in individuals with advanced disease [2]. Our current understanding of PD is disproportionately based on studying populations of European ancestry, leading to a significant gap in our knowledge about the clinical characteristics, life experiences, functional outcomes, and pathophysiology in individuals of African descent. The cumulative incidence of PD in African Americans has been estimated at 23/100,000, compared with 54/100,000 in European Americans [3]. Direct comparison of Black and White patients suggests greater disability and disease severity in Black individuals [4], and our data suggest that quantitative measures may be more sensitive in detecting these differences [5]. Factors proposed to account for phenotypic differences include barriers to access to care and methodological confounds due to inconsistent diagnostic criteria or ascertainment bias [6-8]. It is also possible that population-specific genetic variation modifies PD risk and clinical manifestations of PD in Black individuals. Approximately 90 common susceptibility loci for PD and a growing number of rare gene variants are now well-established in White populations [9]. Still, the impact of these factors on the Black population is largely unknown.

In our pilot work, Black and White patients with PD participated in a clinical phenotyping study, and the results showed no significant differences between the groups in sex, education, disease duration, Hoehn and Yahr stage, or Movement Disorder Society-Unified PD Rating Scale (MDS-UPDRS) part III Motor scores [10]. However, quantitative NIH Toolbox performance measures detected differences in gait and balance between Black and White participants with PD: gait speed (0.8±0.3 vs 1.1±0.2, $P<.001$), pegboard (41.4±15.6 vs 33.2±10.9, $P=.04$, and standing balance (32.7±13.1 vs 47±12, $P<.01$) [5]. In the nonmotor assessments, the Montreal Cognitive Assessment (23.4±3.1 vs 27±2.1, $P<.005$) and Symbol Digits Modalities Test (39.4±14.1 vs 49.6±9.1, $P=.01$) scores were worse in Black participants after correcting for education level. Hamilton Depression scale scores were worse in Black participants with PD compared with White participants (7±5.6 vs 4±3.5, $P=.04$), but other neuropsychiatric scales were similar between groups. The PD Quality of Life (PDQ-39) scores were higher (worse) in Black participants with worse ratings in participation in social roles and activities.

In summary, this pilot data showed differences in the motor examination, nonmotor features, and quality of life of Black patients with PD that warranted the current larger study. In our previous work and this protocol, race is self-identified by the patient as Black or White. Traditionally in the Chicago metropolitan area, this includes Black patients who are African, Afro-Caribbean, African American, or who report a mixture of races.

Racial disparities in the clinical management of PD include inequitable access to care and disparities in therapeutic interventions. Previous studies show that Black individuals with parkinsonism are less likely to see a neurologist, have less access to telemedicine, and are less likely to receive treatment, including antiparkinsonian medication, surgical procedures, and rehabilitation therapy. Black patients are 30% less likely to see an outpatient neurologist for neurologic conditions [11], and both Black persons and those with lower socioeconomic status are less likely to receive specialized care for PD [4]. Compared with White persons with PD, Black patients with PD were 40% less likely to receive any rehabilitation therapy (physical therapy, occupational therapy, and speech therapy). Black persons with parkinsonism were less likely to be receiving any antiparkinsonian medication on their initial visit to a movement disorders center [12]. They were half as likely to receive newer antiparkinsonian medications but twice as likely to be on antipsychotic medication. African Americans were 4 times less likely to receive any treatment for PD (medication or physical therapy) in a cohort with the same health care insurance (Medicaid) [13], and White persons were nearly twice as likely to be prescribed medications for PD in a study of racial disparities in stroke (National Institute of Neurological Disorders and Stroke [NINDS] Reasons for Geographic and Racial Differences in Stroke study) [14]. African Americans were also found to be 5 to 8 times less likely to undergo deep brain stimulation surgery for PD than White patients [15,16]. Notably, racial disparities in access to care and clinical management are likely to be associated with adverse outcomes, including greater severity of Parkinsonian symptoms and greater disability [4].

Genetic susceptibility loci and genetic variants causing monogenic PD have been explored in populations of European, Latino, and Asian ancestry [17]. Based on preliminary work, it appears that the cumulative genetic risk for Black and African American patients with PD shows significantly different distributions compared with European populations when applying the genetic risk score composed of the 90 risk loci previously linked to European populations [17].

More recent work from the Global Parkinson's Genetics Program confirms this differential risk, identifying a novel genetic risk factor in *GBA1* in patients with PD of African ancestry [18]. This supports the need for additional work in this area.

Objective

The overall objectives of this study are to perform comprehensive phenotyping, compare Black and White persons with PD, and investigate causes of racial disparities, including differences in clinical management and responsible genetic risk factors. The study is partnering with the ongoing Global PD Genetics Program (GP2) [19], which contributes samples and granular phenotypic data from the enrolled participants to enhance our understanding of the genetic architecture of PD in

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the Black population. The long-term goal of this application is to address the critical gap in knowledge of PD in this underserved population to improve diagnosis, optimize treatment, and plan for clinical trials. The central hypothesis is: PD is phenotypically and genetically different in Black versus White populations, and Black patients receive different and suboptimal clinical management. The research questions this study hopes to answer are as follows: (1) whether Black participants with PD have worse quantitative motor function and cognition, higher levels of depression and disability, and reduced quality of life compared with White participants with PD; (2) whether pharmacological, surgical, rehabilitation, mental health, and telehealth interventions differ by race with underuse of newer or more costly interventions in Black participants with PD; and (3) whether the contribution of genetic factors to PD risk and heterogeneity differs by race.

Methods

Overview

The overall strategy is to describe clinical phenotypes, genetic risk profiles, and treatment disparities in the American Black PD population and use the results to develop guidance for educating Black patients and their treating clinicians on how to prevent racial disparities in PD and foster future research opportunities in racial disparities and improve management (Figure 1). This is a multicenter, cross-sectional, case-case, nonrandomized, observational study.

Figure 1. Conceptual model. GP2: Global Parkinson's Genetic Program; PD: Parkinson disease.

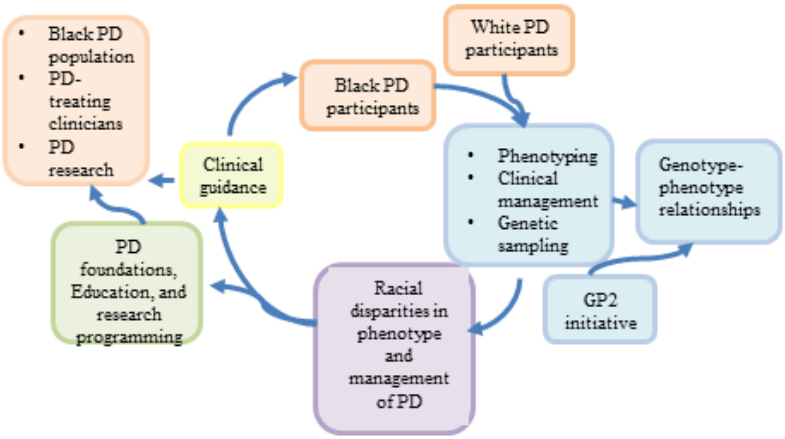

Study Setting and Design

The 7 study sites are Rush University, University of Maryland, University of Cincinnati, University of Pennsylvania, University of Chicago, Emory University, and Morehouse University (Figure 2). The sites were chosen based on US census data showing higher populations of Black persons in these geographic regions. A total of 400 Black patients with PD and 200 White patients with PD will be recruited. Patients who consent to enroll will have a single study visit encompassing data and sample collection for all 3 aims. A virtual option can also be used to complete questionnaires, followed by an in-person visit for the remaining measures.

Figure 2. Overview of the organizational structure. GP2: Global Parkinson's Genetic Program; PD: Parkinson disease.

Eligibility Criteria

The eligibility criteria are intentionally broad to facilitate the inclusion of diverse samples and ensure the achievement of enrollment targets. Inclusion criteria include age >18 years and fulfilling the Movement Disorder Society Clinical Diagnostic Criteria for Parkinson's Disease [20]. Patients must self-identify as being Black or White race. Patients must also be able to sign an evaluation to sign consent [21] or have a legally authorized representative (LAR) sign on their behalf. Exclusion criteria include insufficient English to complete study activities or inability to meet idiopathic PD criteria. Eligibility criteria are broad to include representative samples and ensure meeting enrollment targets.

Recruitment and Screening Strategies

Recruitment will occur in the outpatient movement disorder clinics at the 7 study sites. Treatment clinicians or study coordinators will approach potential participants to discuss participation. Potential participants will be identified by prescreening medical records or by referral to the treating provider. Each White participant was initially matched to be within 5 years of age of the mean age of every 2 Black participants enrolled at the same site. Each time 2 Black

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participants were enrolled at a site, the study statistician would contact the site with the age range of the next White participant. Part-way through the study, propensity matching replaced this manual process. Potential participants will be interviewed to determine if they meet the eligibility criteria for enrollment.

Black patients with PD have been underrepresented in clinical research [22]. Therefore, study planning includes targeted strategies to facilitate recruitment and foster participant satisfaction with research participation. An advisory board of 6 individuals comprised of Black individuals with PD and family members of affected individuals assists in developing outreach strategies and providing feedback on their study visit experience, with protocol modifications as needed. The patient advisory board members will have participated in the study at 1 of the study sites. Educational strategies include initiatives for both study participants and study staff. A brief video and flip charts with culturally appropriate information are used to improve understanding of participation in research, including the informed consent process [23]. Participation of Black study coordinators is encouraged to foster rapport and cultural sensitivity. Teaching cross-cultural sensitivity is part of the prestudy and annual activities for all site investigators and coordinators [24]. Barriers to recruitment and enrollment will be explored, with each enrolled participant completing a Participations in Clinical Trials Questionnaire that includes a question on barriers to research participation [25]. During quarterly Steering Committee meetings with all site investigators, recent publications on minority recruitment and research are reviewed with the study author.

Study Assessments and Outcome Measures

Study participants will have a single visit with the site investigator and coordinator after obtaining consent or a hybrid combination of in-person and virtual visits. Recommendations of the NINDS PD CDE Working Group informed the choice of measures, scales, and questionnaires. Data will be collected and entered into a REDCap (Research Electronic Data Capture) system that uses electronic data entry forms. General assessments include demographic data (age, sex, education, and income), medical history, and a confirmatory neurological examination. The remaining assessments fall into 3 categories, namely motor and nonmotor symptoms (Table 1), quality of life and social determinants of health (Table 2), and management of PD (Table 3, Multimedia Appendix 1).

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Table 1. Motor and nonmotor measures for phenotyping.

Data type or domain and measure or instrument	Description
Parkinson disease severity	
MDS-UPDRS[a] parts I to IV[b]	Revised, improved version of the MDS-UPDRS for use in PD[c] studies [26]
Hoehn and Yahr stages	Common system for staging PD [27]
Physical function	
2-minute walk, 4-meter gait speed, 9-hole pegboard, grip strength, and balance test[b]	To quantitate physical performance relative to available age and gender norms [28]
Functional reach	A single-item assessment of balance [29]
Schwab and England Activities of Daily Living Scale	A single-item rating of independent function [30]
PROMIS Profile-29 Physical Function version 2.0 4a[b]	Measure of disability [31,32]
Cognitive function	
Montreal Cognitive Assessment version 8.3[b]	Detects mild cognitive impairment in PD [33,34]
Benton Judgment of Line Orientation 15-items	Measure of spatial perception and orientation [35,36]
Hopkins Verbal Learning Test	Test of verbal short-term memory requiring rapid encoding of information [37]
Digit span	Measure of verbal working memory [38]
Semantic fluency	Measures semantic fluency using animal categories [39]
Symbol Digit Modalities Test[b]	Screens for cognitive impairment [40]
Mental health	
PROMIS Profile-29 depression, anxiety	Measures depression and anxiety
Pain	
PROMIS Profile-29 Pain Interference version 1.1	Measures pain interference with daily life [41]
PROMIS Profile-29 Pain Intensity version 1.0	Measures severity of pain
Sleep	
Epworth Sleepiness Scale	Measures daytime sleepiness in adults [42]
PROMIS Profile-29 version 1.0 Sleep Disturbance 4a, PROMIS Profile-29 version 1.0 Fatigue 4a	Measures sleep disturbance and fatigue [43,44]
Autonomic	
Scales for Outcomes-PD Autonomic[b]	Measures autonomic function [45]

[a]MDS-UPDRS: Movement Disorder Society Unified Parkinson's Disease Rating Scale.

[b]Minimum dataset.

[c]PD: Parkinson disease.

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Table 2. Quality of life and patient health expectations measures.

Data type or domain and measure or instrument	Description
Health-related quality of life	
The Parkinson's Disease Questionnaire-8[a]	PD[b]-specific quality of life scale [46]
Patient health expectations	
Expectations Regarding Movement Scale	Expectations regarding movement with aging [6]
Participation in medical research	
Trust in Medical Researchers Scale	Likelihood of participation in medical research [47]
Social determinants	
PROMIS Informational Support version 2.0 4a	Measures access to information and resources [48]
Health Stressors Rush Survey	Covers food security, utilities, insurance, transportation, and housing instability
PROMIS Profile-29 Ability to Participate in Social Roles and Activities version 2.0 4a	Measures satisfaction with social roles and activities [48]

[a]Minimum dataset.

[b]PD: Parkinson disease.

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Table 3. Study assessments for management of Parkinson disease.

Data type or domain and measure or instrument	Description
Pharmacological management	
Parkinson's Disease Medications Questionnaire[a]	Antiparkinsonian drugs[a]
Prescribed Non-Parkinson's Medications Questionnaire[a]	Non-Parkinson drugs
Unprescribed Drugs Questionnaire	Vitamins, dietary supplements, alternative therapies, recreational drugs, drugs of abuse
Surgical management	
Surgical Questionnaire[a]	DBS[b], FUS[c]
Rehabilitation therapy	
Rehabilitation Referral Questionnaire[a]	Physical, occupational, speech therapy
Godin Leisure-Time Exercise Questionnaire, Activity Questionnaire	Exercise and activity [49]
Mental health and social services	
Mental Health and Social Services Referral Questionnaires[a]	Psychiatrist, psychologist, social worker
Telehealth use and acceptance	
Telehealth Use and Acceptance Questionnaire[a]	Perceived usefulness and ease of use [50]
Participation in clinical trials	
Participation in Clinical Trials Questionnaire	Clinical trial participation and barriers to participation
History of treating clinicians for PD	
History of treating clinicians for Parkinson's disease[a]	Number and types of clinicians, medical visit frequency
Medical comorbidities	
Cumulative Illness Rating Scale-Geriatrics (CIRS-G)[a]	Medical comorbidities [51]
Self-efficacy	
PROMIS Self-Efficacy for Management of Chronic Conditions	Self-efficacy for managing daily activities, symptoms, medications, and emotions [52]
Health literacy	
Rapid Estimate of Adult Literacy in Medicine	Health literacy [53]
eHealth Literacy Scale	eHealth literacy [54]

[a]Minimum dataset.

[b]DBS: deep brain stimulation.

[c]FUS: focused ultrasound.

Participants who used a LAR for consent can complete assessments with assistance from a research assistant or proxy (care partner). All scales and questionnaires include a check box to document proxy assistance. The scales are administered by the neurologist (site investigator), study coordinator, or other staff as appropriate. The investigator completes the following assessments: MDS-UPDRS [26], Hoehn and Yahr Staging [27], Schwab and England Activities of Daily Living Scale [55], and the Cumulative Illness Rating Scale [51]. The investigator will also complete a questionnaire for the GP2 study that includes demographic and disease-specific information, such as disease duration. The study coordinator administers the rest of the study assessments.

Participants have blood samples drawn and sent to the National Institutes of Health for genetic studies. All participants are also offered enrollment into the Parkinson's Foundation PD GENEration study in which seven PD genes are examined and results are disclosed to the participant. If the participant consents, an additional blood sample is shipped to the PD GENEration sequencing vendor (Fulgent Genetics). For these participants, genetic counseling, including results disclosure, is performed by either a PD GENEration genetic counselor from Indiana University or the genetic counselor at the Rush University site (either live or through telemedicine).

To optimize recruitment, all Black patients with PD are eligible for enrollment regardless of physical or cognitive impairment level. Therefore, not all patients can complete all study assessments. A minimum dataset, including the primary outcome measures, must be completed, as well as the sample collected for all study participants. The recommended order of study assessments prioritizes outcome measures such that primary outcome measures are completed first, cognitive measures are

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completed early, and the minimum dataset for all study aims is collected. When a participant cannot complete all study assessments, the site investigator must be contacted. The investigator and coordinator should arrive at a consensus about what assessments will be omitted, and coordinators should record the omitted assessments. The patient can only complete selected study assessments (no proxy assistance permitted), including the cognitive assessments and the "Rapid Estimate of Adult Literacy in Medicine" [25].

Outcome Measures

The primary outcome measures to characterize PD phenotypes include the NIH Toolbox Motor assessments (2-minute walk, 4-meter walk, balance test, pegboard test, and grip strength) [28]; the Montreal Cognitive Assessment (MoCA), Symbol Digit Modalities Test (SDMT), PROMIS Profile-29 Physical Function, Parkinson's Disease Questionnaire-8 (PDQ-8), and the MDS-UPDRS. The primary outcome measures to assess PD clinical management include the proportion of participants with antiparkinsonian medications prescribed at the initial visit to the neurologist, the proportion of participants with initial treatment of depression, and the proportion of participants with PD surgical interventions. To characterize genetic risk variants in our sample, the frequencies of the 90 established common PD genetic risk variants based on published genome-wide association studies in a predominantly White population will initially be examined. The study team will also aggregate and summarize sequencing results from PD GENEration, including potential rare variants among 7 established PD genes. The proportion of LRRK2- and GBA-PD will be summarized based on either PD GENEration, which permits comprehensive detection of potential pathogenic alleles, or GP2 genotyping, which can detect many of the most common, recurrent pathogenic variants. Finally, exploratory genotype–phenotype analyses will determine whether established PD risk variants modify clinical manifestations in Black individuals.

Sample Size

The sample size was calculated for each primary outcome measure described above with 80% power and a 2-sided test to detect a similar effect size observed from our pilot data (Table 4). Bonferroni correction was applied to control the overall significance level at .05. The minimal sample size for these analyses requires 365 Black and 183 White participants to complete this aim. The data observed in 3 studies guided the sample size calculation for PD clinical management (White vs non-White or Black: 78% vs 62% for measure 1 [4], 92% vs 80% for measure 2 [56], and 10% vs 0.4% for measure 3 [57]). The sample size was calculated using 90% power and a 2-sided test for each primary measure. Bonferroni correction was applied to control the overall significance level at .05. With a 1:2 ratio, the largest sample size required among all 3 measures is 173 White patients with PD and 346 Black patients with PD. For the genetic studies, our sample size will permit exploratory analyses, and all data will be contributed to GP2 for fully-powered meta-analysis.

Table 4. Pilot data effect sizes for sample size calculation.

Primary measures	White patients with PD[a] (n=25), mean (SD)	Black patients with PD (n=25), mean (SD)
4-meter walk computed score	1.1 (0.2)	0.8 (0.3)
Balance *t* test score	47 (12)	32.7 (13.1)
Pegboard dominant score	33.2 (10.9)	41.4 (15.6)
MoCA[b]	27 (2)	23.3 (3.1)
SDMT[c]	49.6 (9.1)	39.4 (14.1)
PDQ-39[d]	12.8 (7.9)	22.5 (12.3)

[a]PD: Parkinson disease.

[b]MoCA: Montreal Cognitive Assessment.

[c]SDMT: Symbol Digit Modalities Test.

[d]PDQ-39: Parkinson's Disease Questionnaire.

Data Collection and Monitoring

The co-principal investigators (DH and LS), core administrative, and coordinating personnel meet weekly to identify potential issues with consent or assessment procedures, manage any reported adverse events, and monitor the sites' progress. The REDCap database created to house the data is audited weekly to ensure fidelity. All study data are directly entered into the REDCap database in real time unless internet connectivity is an issue at the site.

Statistical Analysis

Each primary outcome measure will be compared between Black and White patients with PD. Bonferroni correction will be applied. The primary outcome measures are a 4-meter walk computed score, Balance test *t* score, Pegboard dominant *t* score, MDS-UPDRS motor score [26], MoCA [33], SDMT [58], PROMIS Profile-29 Physical Function, and PDQ-8 [46]. For significant measures, linear regression analysis will be performed to examine further the difference between the 2 groups with adjustment for age, sex, and disease duration. The interaction effects of race with these 3 variables will be explored. Regression analysis for cognitive measures will adjust for depression and anxiety scales in addition to these demographics. Regression will also be adjusted for comorbidities using the Cumulative Illness Rating Scale-Geriatrics score. The study site effect will be controlled as a random effect in the model. All analyses will be done using SAS (version 9.4).

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For the PD management analysis, each primary outcome measure will be compared between Black PD and White PD groups using the chi-square test or Fisher exact test. Bonferroni correction will be applied. A hierarchical logistic regression analysis will assess the determinants of racial disparities in management. Besides race, age, sex, and education, income, symptom severity, and comorbidities will be included in the model. The interaction effect of race with those variables will be explored. The study site effect will be controlled as a random effect in the model. Secondary analyses will investigate differences between White PD and Black PD groups in other clinical management measures, including telehealth, participation in clinical trials, and rehabilitation therapy.

Genetic Analysis

This study will leverage a quality control and analysis pipeline established for the GP2 program. After standard quality control of raw genotyped data, data will be imputed to the most recent build of the multiethnic 1000 genomes reference panel using the default settings of miniMac2. This will yield ~15 million variants to test after additional quality control. These data will be contributed to GP2 for genome-wide association meta-analysis and admixture mapping. Within the RaDPD sample, ~90 currently established common PD risk variants to examine frequencies will be extracted. For analyses of PD genetic modifiers, linear regression—with an initial focus on outcome phenotypes with established evidence from the published literature, including age of onset, motor progression, and cognition—will be performed [59-65]. These outcomes will be supplemented with the most promising outcomes based on the results from aim 1 analyses identifying clinical features that differentiate PD in Black versus White patients. Sequencing results will be available for participants in PD GENEneration for 7 genes associated with PD: *GBA*, *LRRK2*, *PRKN*, *SNCA*, *PINK1*,*PARK7*, and *VPS35*. Comprehensive genome sequencing of all samples is planned for a future project.

Ethical Considerations

This study was approved by the Rush Institutional Review Board (IRB; ORA 20121005), which serves as the single-site IRB for this study. Each participant will sign a consent form, which includes blood and genetic analysis, before participation. Each participant also signs permission for the DNA results from sequencing to be housed in the PDGeneration database and the National Institutes of Health (deidentified) through GP2. If the participant requests genetic results, they are identifiable to PDGeneration, facilitating the return of results. Potentially vulnerable study populations are patients with cognitive impairment and socioeconomic disadvantages. Given the study aims to investigate racial disparities in the phenotype–genotype differences between Black and White patients with PD, it is necessary to include these populations. Study participants must be able to provide informed consent as determined by the Evaluation to Sign Consent to confirm they understand the risks and benefits and can provide their informed consent. This low-risk study does not present a greater risk to potentially vulnerable populations. Given the short duration of this study (1 study visit), it is not expected that significant cognitive decline will occur throughout the study to impact a participant's ability to provide ongoing consent. Participants unable to achieve a passing score on the Evaluation to Sign Consent will be excluded unless a LAR is present to provide consent.

A human subjects research ethics review will occur at the time of IRB approval. The informed consent process occurs with the study team live during the study visit. Data are entered directly into a password-protected, Health Insurance Portability and Accountability Act–compliant REDCaP database, with the participant having an assigned site-specific study ID. Participants are compensated US $100 for the study visit plus US $25 for travel expenses, and some sites arrange transportation with established institutional programs.

Results

The Rush IRB approved the project as the single-site IRB in February 2022 and funded by NINDS in April 2022. Recruitment began in July 2022. At the time of submission of this manuscript, 131 participants had been enrolled. One of the original study sites has been replaced by a new site due to issues with regulatory approval. Other activities have included quarterly steering committee and monthly coordinator meetings. Steering committee meetings include discussing recent publications and speakers focused on racial disparities.

Discussion

Study Rationale

The study rationale is that the knowledge gained will improve clinical diagnosis and management for Black persons with PD, drive programming to improve access to care and management, and inform research strategies in PD in the Black community. It is anticipated that the main findings of this study will be that Black patients with PD will have more gait abnormalities and higher rates of genetic variants for PD specifically seen in the Black population. It is also anticipated that Black individuals with PD will be less likely to have been referred or have access to specialized care for PD, including surgical treatments and nonmedication therapies. This protocol was structured as a one-time visit to encourage participation and to optimize the likelihood of full data collection. Aim 3 is a collaborative effort with the Global Parkinson's Genetics Program (GP2), a worldwide consortium funded by the Aligning Science Across Parkinson's initiative to understand the genetic architecture of PD. This collaboration enables samples collected in this study to be part of a larger gene discovery effort with investigators from African and Afro-Caribbean patients with PD to foster a greater understanding of genetic variation specific to the Black population [17]. This study fills a unique niche by performing deep phenotyping to study racial disparities and analyze genotype–phenotype relationships in PD.

The recruitment of Black patients into research studies is historically much lower than White patients [22]. Contributory factors include distrust owing to historical research abuse and institutional racism, lack of information and understanding of research studies and informed consent, insufficient recruitment efforts by researchers, social stigma, and financial considerations [66]. In 1993, the National Institutes of Health established the

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Revitalization Act, which mandated minority inclusion in randomized clinical trials. An important strategy to promote study recruitment in both Black and White patients with PD is raising awareness of previous studies showing evidence of racial disparities in access to care, disease features, and clinical management.

A potential barrier to participation in PD research is motor and cognitive impairments, present in patients with PD of all racial and ethnic backgrounds. To accommodate the needs of patients with more severe motor and cognitive impairment, the protocol was designed to allow for the collection of a "minimum dataset." The goal is to complete as many study assessments as possible. However, implementing more limited data collection will enable the successful completion of enrollment targets and ensure the inclusion of a representative range of disease severity. The typical time of the study visit is between 3 to 6 hours, and more limited data collection, focused on the primary outcome measures for each of the study aims, reduces the visit time to 1 to 2 hours.

Conclusions

Many unique challenges arise in clinical research in the Black PD community, but the importance of understanding racial disparities warrants focus on this population. Given what little is known about how PD manifests in Black patients, this will be the most comprehensive study of the phenotype and management of PD in the US Black population, with the potential to improve clinical diagnosis and management and to foster future research directions. It is not clear what the true implications of the study will be, but improvement of study recruitment in this population, education of patients, caregivers, and clinicians on disparities, and ultimately, changes in practice will drive the final impact of the study and drive health policy recommendations at a national level.

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Data Availability

The datasets generated and analyzed during this study will be available upon reasonable request. These will be distributed to individual investigators on approval of the principal investigators (distribution costs covered by the requesting investigator). The study teams will use common data elements and a REDCap system to maximize the ability to share these data. Other products of the blood samples (serum, etc) may be shared if there are remaining samples. Research results will be disseminated publicly through publication in scientific journals and in the context of scientific meetings at which project findings will be reported. Such data publication will occur during the term of the project or after its conclusion, as appropriate and in keeping with normal scientific practices for reporting results.

Authors' Contributions

DH and LS conceived the program and wrote the protocol with JH's help. JS, SBC, AS, and RaDPD study group members provided ongoing critical review. BO aided in sample size calculation and analyses. DH and MHST drafted the manuscript, and all authors reviewed and approved the final version.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Instruments, measures, and scale information.
[DOCX File , 22 KB - resprot_v14i1e60587_app1.docx]

Multimedia Appendix 2
Peer-review report from the Clinical Neuroscience and Neurodegeneration Study Section (CNN) - Brain Disorders and Clinical Neuroscience Integrated Review Group - Center for Scientific Review (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 78 KB - resprot_v14i1e60587_app2.pdf]

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Abbreviations

GP2: Global Parkinson’s Genetic Program
IRB: Institutional Review Board

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LAR: legally authorized representative
MOCA: Montreal Cognitive Assessment
NINDS: National Institute of Neurological Disorders and Stroke
PD: Parkinson disease
PDQ-39: Parkinson's Disease Quality of Life
REDCap: Research Electronic Data Capture
SDMT: Symbol Digit Modalities Test

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Protocol

Methadone Patient Access to Collaborative Treatment: Protocol for a Pilot and a Randomized Controlled Trial to Establish Feasibility of Adoption and Impact on Methadone Treatment Delivery and Patient Outcomes

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Abstract

Background: Access to methadone treatment can reduce opioid overdose death by up to 60%, but US patient outcomes are suboptimal. Federally allowed methadone treatment accommodations during the COVID-19 public health emergency were not widely adopted. It is likely that staff-level characteristics such as trauma symptoms influence the adoption of treatment innovation.

Objective: Methadone Patient Access to Collaborative Treatment (MPACT) is a 2-phased project (pilot and field trial) to develop and test a staff-level, multimodal intervention to increase staff adoption of low-barrier, patient-centered methadone treatment practices and ultimately improve treatment retention and patient outcomes.

Methods: A pilot and national trial will measure implementation feasibility, acceptability, and effects of the MPACT intervention on treatment practice change, clinic culture, patient retention, and patient posttraumatic stress symptoms (PTSS). The pilot will be a single-arm 5.5-month pilot study of MPACT conducted in 2 Arizona methadone treatment clinics (rural and urban) among 100 patients and 22 staff. The national trial will be a 20-month cluster randomized trial conducted among 30 clinics, 600 patients (20 per clinic), and 480 staff (18 per clinic). Data will be gathered by staff and patient surveys and patient chart review. The primary study outcome is increased patient methadone treatment retention measured as (1) time to first treatment interruption from study enrollment; (2) active in treatment at enrollment, day 30, 60, 90, and 120; and (3) continuous days in treatment during

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the study period. Secondary study outcomes include reductions in vicarious trauma and PTSS among enrolled opioid treatment program staff and PTSS among enrolled patients.

Results: The pilot study was funded by the National Institute on Drug Abuse (award R61DA059889, funded September 2023), and the field trial will be funded under the associated R33 mechanism in September 2025. The pilot study was completed in March 2025. The randomized controlled trial will begin in December 2025. Both the pilot and trial have been approved by the University of Arizona Human Subjects Protection Program and have been registered with the clinical trials network.

Conclusions: The MPACT study will provide a foundation for an evidence-based, staff-level intervention aimed at improving patient retention in methadone treatment. Future studies should examine the individual components of MPACT to determine their differential contributions to the primary outcome of patient methadone treatment retention and to secondary outcomes of staff and patient reduction in stress symptoms.

Trial Registration: ClinicalTrials.gov NCT06513728; https://clinicaltrials.gov/study/NCT06513728 and ClinicalTrials.gov NCT06556602; https://clinicaltrials.gov/study/NCT06556602

International Registered Report Identifier (IRRID): DERR1-10.2196/69829

(JMIR Res Protoc 2025;14:e69829) doi:10.2196/69829

KEYWORDS

methadone; implementation; patient-centered treatment; opioid use disorder; posttraumatic stress symptoms; vicarious trauma

Introduction

Background

Methadone is one of the most essential tools available to reduce opioid overdose deaths because it is safe, effective, and patient-preferred for the treatment of opioid use disorder (OUD) [1-3]. Access to methadone, one of 2 safe and effective OUD treatments, can reduce overdose mortality by up to 60% [4,5]. However, the promise of methadone is significantly diminished by geographic maldistribution of clinics and variations in the delivery of methadone maintenance treatment (MMT) across the country [6-8]. Treatment variations likely produce the observed wide-ranging MMT retention rates (30%-84%) [9,10].

MMT in the United States is delivered only by opioid treatment programs (OTPs; “methadone clinics”) certified and accredited by the federal government [11]. Variation in treatment quality and access maldistribution means that the impact of poor MMT outcomes is felt most acutely in rural communities as well as among populations who are Black, Hispanic, or Indigenous [12]. Unlike other health care environments, OTPs serve a daily average of more than 100 people in a narrow time window [13] and have been described as feeling “like bus stations” [14] rather than medical clinics. OTPs have been criticized as being unresponsive to patient need for treatment flexibility [15] and are not equipped to address what we know to be higher rates of patient trauma exposure and posttraumatic stress symptoms (PTSS) compared to the general population [16,17]. While MMT outcomes can be impeded by patient trauma [18], it is also possible that poor MMT outcomes and patient trauma are exacerbated by OTP practice and culture [19,20]. Patients report disenfranchisement from treatment decision-making through language referring to dosing as “privileges,” staff behavior described as “carceral” [21], and being tied to the OTP by “liquid handcuffs” due to daily required in-clinic supervised dosing [22].

Policy and systems evolution is occurring to improve the way MMT is delivered in the United States. Unprecedented US regulatory change during the COVID-19 public health emergency [23] and again in February 2024 [11] permitted and then further clarified methadone dosing and delivery flexibility so that treatment was more individualized and patient-centered. However, as has been observed, policy changes during the COVID-19 public health emergency were insufficient to ensure sustained changes [24-26]. This is likely the result of multiple factors hindering the implementation of MMT innovation. Implementation science suggests that in addition to the outer setting factor of federal policy, there are inner setting factors that likely influence the adoption of MMT treatment innovation [27]. These include clinic organizational characteristics and culture as well as staff characteristics and staff beliefs. Figure 1 displays our current thinking about hypothesized relationships between and among inner setting factors, adoption of innovation, and patient outcomes.

Staff trauma is one particular inner setting factor that is linked to the adoption of innovation and quality of treatment delivery. A preliminary study by several authors here suggests that OTP staff trauma may play a central role in shaping clinic culture and methadone treatment practice changes [14]. Evidence from studies among other types of health professionals demonstrates that vicarious trauma (VT), or work-related trauma (ie, coexperiencing patient distress and change in worldviews because of ongoing distress), is associated with reduced staff empathy and increased PTSS [28]. VT outcomes include burnout, reduced patient empathy and compassion satisfaction, low morale, impaired clinical decision-making, and compromised patient care [29-31]. The only extant study of OTP staff trauma histories and symptoms found that 63% of staff exhibited PTSS at clinical levels, indicating a need for treatment [32]. Therefore, a potential strategy to facilitate the adoption of MMT innovation is to implement staff-level interventions aimed at reducing PTSS and VT while providing training about low-barrier, patient-centered methadone treatment.

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Figure 1. Potential inner setting factors impacting methadone treatment outcomes.

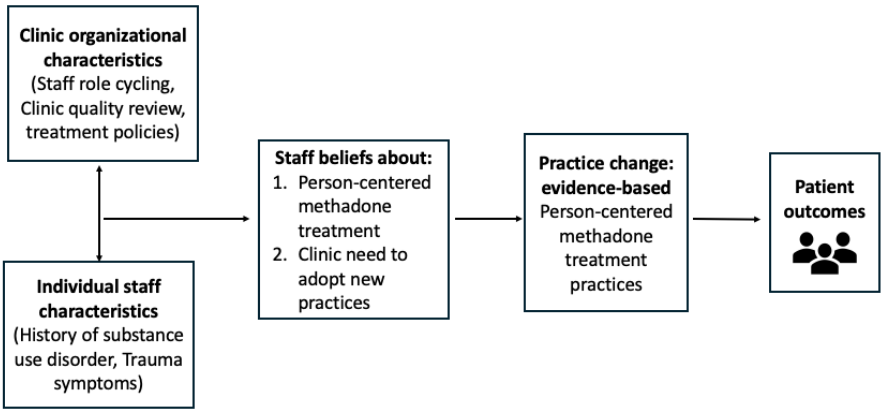

To this end, we developed Methadone Patient Access to Collaborative Treatment (MPACT): a multimodal intervention to increase staff awareness of and readiness to adopt MMT treatment innovation. MPACT promotes treatment flexibilities allowed by federal regulators and patient-centered, trauma-informed MMT and seeks to empower OTP staff and clinic groups to adopt these treatment flexibilities by addressing staff VT and PTSS, which will improve treatment quality and ultimately MMT retention. The objective of this study is to test the adoption, feasibility, and impact of MPACT on methadone treatment delivery and patient outcomes. There are 6 specific aims for the MPACT study over the 6-year project period. The specific aims are listed here and will be described in the following subsections.

Phase 1, Years 1-2: MPACT Intervention Development and Pilot Testing

Phase 1 aims (1) to develop MPACT through multilevel, iterative planning with methadone clinic staff and people with recent methadone treatment experience; (2) to determine MPACT implementation feasibility, acceptability, and preliminary effect on methadone treatment practice change and clinic culture; and (3) to determine the preliminary effect of MPACT on methadone treatment retention and patient PTSS.

Phase 2, Years 3-6: Hybrid, Cluster Randomized Controlled Trial

Phase 2 aims (4) to quantify the effects of MPACT on methadone treatment practice change and clinic culture, (5) to determine the efficacy of MPACT on methadone treatment retention and patient and staff PTSS outcomes, and (6) to evaluate the effect of patient and staff trauma on primary outcomes and staff MPACT implementation.

Methods

Ethical Considerations

The MPACT study protocol and related documents were reviewed and approved by the University of Arizona Human Subjects Protection Program (pilot: #STUDY00003631 and trial: #STUDY00005677), the single institutional review board overseeing all sites participating in the study: University of Arizona, Indiana University, Western Michigan University, and Columbia University. All participants will engage in a web-based informed consent process prior to study enrollment. The consent will be downloaded and retained by the study as documentation. Patient participants will consent to both survey participation and the release of specified elements of their clinic medical record for the purpose of the study. Confidentiality of staff and patient participants in the enrolled MPACT clinics will be preserved by making every effort to prevent the clinic leadership and staff from knowing which patients are enrolled as study participants and keeping clinic leadership and patients from knowing which staff are enrolled as study participants. Unique identifiers will be created at the time of enrollment and used throughout the study period. All study personnel (staff and investigators) have been trained in human participant protection through the completion of Social Behavioral Research and Biomedical Research modules with the Collaborative Institutional Training Initiative program and the completion of conflict of interest training and have annually declared conflicts of interest for review by the University of Arizona Human Subjects Protection Program. All reported data will be aggregated and deidentified. All information will be stored in a secure and encrypted drive and accessible only by the principal investigator (BEM) and the study coordinator (SY). The study was registered under ClinicalTrials.gov (NCT06513728 for the phase 1 pilot and NCT06556602 for the phase 2 trial). Participants will be offered financial remuneration totaling US $100 for the completion of all 5 surveys on time and during the pilot study period and US $160 for the completion of surveys on time and during the trial study period.

Phase 1, Years 1-2: MPACT Intervention Development and Pilot Testing

Overview

- Aim 1: Develop MPACT through multilevel, iterative planning with methadone clinic staff and people with recent methadone treatment experience.

MPACT is an experimental intervention comprised of 4 evidence-based components adapted by a group of people who have been in methadone treatment within the past 5 years in Arizona, a group of OTP staff in all clinic roles (front desk, peer support staff, case management, counseling, clinical supervision, medical, and administrative) from 3 Arizona OTPs (2 urban and 1 rural), and a group of subject matter experts focused on clinical supervision, human resources, and employee education.

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The adaptation of MPACT components was accomplished through an iterative codevelopment process involving OTP staff and methadone community (patient) groups. The creation of a trauma-informed codevelopment space was crucial to facilitate safer and more open discussions. To accomplish this, we established a parallel, intervention refinement process using a helical structure developed by this team and based on our prior research with structural indicators for community-based participatory action research [33]. As shown in Figure 2, the "hand off" of work drives an iterative (helical) thinking process. This structure provides distinct spaces for thoughtful dialogue within and between each group.

The outcome of the codevelopment process was a robust multimodal intervention (MPACT) comprised of the following 4 elements.

Figure 2. Trauma-informed, collaborative development structure to refine MPACT components. MPACT: Methadone Patient Access to Collaborative Treatment; OTP: opioid treatment program.

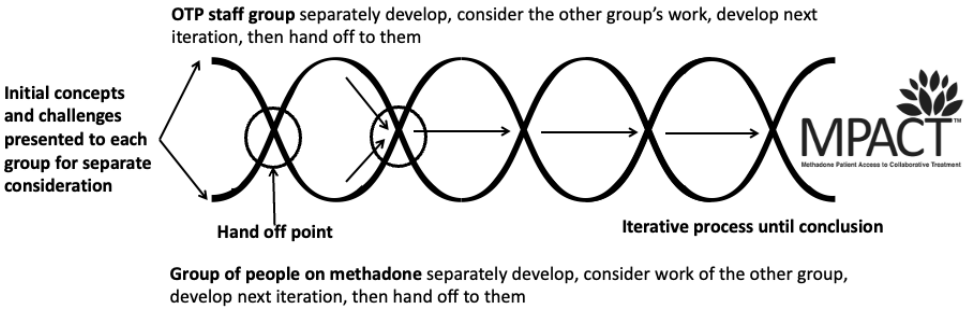

Accredited Psychoeducational Training

A jointly accredited, self-paced, 3-module psychoeducational training focused on (1) the definition and application of low-barrier, patient-centered, trauma-informed methadone treatment; (2) public and clinic policy (federal and state); and (3) clinic staff opportunities to increase patient-centered, trauma-informed methadone treatment. The training seeks to empower staff to initiate any positive change at the individual and staff group levels. Joint accreditation offers continuing medical education for physicians and nurses as well as continuing education credits for social workers, psychologists, peer support specialists, case managers, and administrators. Training completion is incentivized by the award of 3 free continuing education credits according to professional discipline. While training is voluntary, to receive the continuing education credits, staff of MPACT-enrolled clinics must complete the training within 2 weeks of the MPACT launch within the clinic. New staff can complete the training as they are hired during the MPACT intervention period. This modular training approach was adapted from a prior successful project focused on increasing pharmacy syringe sales to people who use drugs [34].

Staff Wellness Education and Assessment

All staff in MPACT-enrolled clinics will receive training about trauma exposure and reactions, trauma-informed methadone treatment, availability and modalities of trauma treatment, and VT through curated presentation materials. These materials will be accessible to all staff through an MPACT web portal and through training or communications as determined by the enrolled clinics. The training materials include video and visual content designed for easy integration into clinic employee training, onboarding, or as refresher training. As part of the training, staff will be introduced to an anonymous web-based "wellness" screener, which includes an 8-item posttraumatic stress disorder symptoms screener (Posttraumatic Stress Disorder Checklist [PCL-5]) [35,36] and an 8-item Vicarious Trauma Scale [37]. Individual screening outcomes (results) trigger a curated and immediately presented message regarding self-care, referral to the VA PTSD Coach [38,39] (a downloadable, free application) and referral to the employee assistance program offered as a behavioral health benefit to employees where indicated. Employees will have access to wellness training throughout the MPACT intervention period and can use the self-screener repeatedly if desired. The screener will also be "advertised" in staff-only areas with a curated poster on stress, including a link or QR for easy access.

Trauma-Informed Clinic Self-Assessment

A trauma-informed clinic self-assessment (TICA) will be conducted quarterly during the study period. TICA assessment outcomes are generated by data from aggregated responses to a 16-item anonymous survey of staff measuring staff development, available resources, support, safe physical environments, trauma-informed policies, and patient-centered practices specific to methadone clinics. Items were selected and modified by the study team using an organizational trauma-informed practice tool as a reference instrument [40]. Summarized results are discussed with clinic leadership who will decide how and when to share them with clinic staff.

Reflective Supervision Consultation

Reflective supervision is an evidence-based professional development intervention focusing on the relationship and process of collaborative case consultation and reflection for clinicians providing psychosocial support [41,42]. Reflective supervision provides strategic guidance to increase self-reflectiveness and self-awareness and encourages participants to independently process clinical encounters and solve challenges. These skills have been shown to improve patient care [43,44]. To our knowledge, there are no existing reflective supervision consultation models tailored to OTP staff. Therefore, we adapted the standard reflective supervision practices to apply and be accessible to all OTP staff who have intensive and consultative interactions with patients. These staff roles include case managers, counselors, and peer support. Reflective supervision will begin in month 1 of the intervention period and will continue on a biweekly basis throughout the

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intervention period for each MPACT-enrolled clinic. Sessions are facilitated by a trained reflective supervisor who will also be trained by the MPACT study clinician.

- Aim 2: Determine MPACT implementation feasibility, acceptability, and preliminary effect on methadone treatment practice change and clinic culture.
- Aim 3: Determine the preliminary effect of MPACT on methadone treatment retention and patient PTSS.

A single-arm 5.5-month pilot study of MPACT will address aims 2 and 3 and involves 2 Arizona-based OTPs (1 rural and 1 urban), 100 patients, and 22 staff (25 patients and 6 staff of the rural clinic and 75 patients and 16 staff of the urban clinic). Data collection will be accomplished through a web-based survey of staff and patient participants monthly during the pilot study period, which began in October 2024 and ended in March 2025. The 4 elements of MPACT intervention were delivered during the 4-month period following study recruitment. Eligibility criteria for study inclusion included being 18 years of age or older, being a staff member or a patient at 1 of the 2 pilot clinics, being willing to participate in monthly surveys during the pilot study period, and (for patients) agreeing to share selected components of their medical charts with the study team.

Measures

The primary study outcome is increased patient methadone treatment retention. This outcome is measured in three ways: (1) time to first treatment interruption, calculated as the number of days to first missed dose from day 0 (MPACT enrollment); (2) evidence of being active in treatment, a binary (yes or no) if receiving dose at points in time on day 0, 30, 60, 90, and 120; and (3) continuous days in treatment during the study period, calculated as time (days) to discharge. Data measuring this outcome are gathered by patient surveys and chart reviews.

Secondary study outcomes include reductions in VT and PTSS among enrolled clinic staff and PTSS among enrolled patients. Data measuring secondary outcomes are gathered by a survey of staff and patients enrolled in the study. For staff and patients, PTSS are measured using the 8-item posttraumatic stress disorder symptoms screener otherwise known as the PCL-5 [35]. Staff VT is measured by the Vicarious Trauma Scale [37], burnout is measured by a 3-item scale [45], and compassion satisfaction and compassion fatigue are measured by the shortened, 9-item Professional Quality of Life Scale for staff [46].

The degree to which methadone treatment is patient-centered is also a secondary outcome measured through staff surveys (assessing whether they believe they are providing it) and patient surveys (assessing whether they feel they are experiencing it). Patient-centered care competency is measured by a 19-item scale [47] including the following subscales: respecting patient perspectives, promoting patient involvement in the care process, providing patient support, and advocating for patients. Patient-centered care, as defined by the study team, is measured using a 5-item instrument that reflects the concepts of patient-centered care introduced during the accredited training modules. This scale is administered to staff, with an adapted version used for patients.

Other individual-level variables of interest for the staff participants include (1) personal characteristics—demographics, personal substance use disorder and treatment experience, and trauma exposure history (measured by the Life Events Checklist-5) [48]; (2) work characteristics—training, education, and licensure related to their clinic role; (3) empowerment using a 5-item empowerment scale [49]; (4) stigma—toward people with OUD with a 9-item scale [50], self-stigma with a 9-item scale [51], and fear of enacted stigma through a 9-item scale [52]; (5) beliefs—about trauma-informed care measured by the attitudes toward trauma-informed care [53] and about abstinence measured by the Abstinence Orientation Scale [54]; (6) comfort with targeted practices related to the most recent federal changes to methadone treatment delivery measured by items adapted from prior studies measuring comfort with practices [34,55,56]; and (7) fidelity to MPACT—the degree to which the clinic implements the MPACT intervention.

Other individual-level variables of interest for the patient participants include (1) personal characteristics—demographics, housing, trauma history (Life Events Checklist-5), and trauma symptoms (PCL-5); (2) methadone treatment—time in treatment and dose sufficiency; (3) empowerment—as measured by a 15-item scale [57] and through an adapted 16-item Kim Alliance Scale [58]; and (4) fidelity to MPACT—the degree to which the clinic implements the MPACT intervention.

As this is a hybrid (implementation and effectiveness) pilot and trial, we are specifically focused on reach, implementation, adoption, and (in the trial) maintenance using the RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) framework [59]. Measures collected for the pilot will also be collected for the trial.

Data Collection

Primary and secondary study outcomes will be measured by surveys and patient chart reviews. Surveys will be administered monthly for the pilot study: assessment 1 (baseline at enrollment) and assessment 2-5 in 30-day sequences through the study period, with a contact reminder at day 27 and a completion forgiveness period of 5 days (day 35). Table 1 displays the sequencing of measures across the 5 pilot surveys.

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Table 1. Sequencing of Methadone Patient Access to Collaborative Treatment (MPACT) primary and secondary measures (assessment 1-5).

Construct	Assessment 1 (enrollment)		Assessment 2	Assessment 3	Assessment 4	Assessment 5 (study conclusion)
	Staff items, n	Patient items, n				
Personal characteristics						
Demographics	5	6	—[a]	—	—	—
Personal SUD[b] experience	10	—	—	—	—	—
Methadone treatment						
Time in MMT[c] and clinic, reasons for choosing methadone as treatment	—	13	—	—	—	—
Methadone interruption	—	2	✓	✓	✓	✓
Dose, sufficiency, OD[d]	—	13	✓	✓	✓	✓
Trauma history and symptoms						
Trauma history (LEC[e])	17	17	—	—	—	—
Vicarious Trauma Scale	8	—		✓		✓
PCL-5[f] (trauma symptoms)	8	8	✓[g]	✓	✓[g]	✓
Burnout, compassion fatigue						
Burnout scale	9	—	✓	✓	✓	✓
ProQoL[h] (compassion fatigue, Compass Sat, burnout)	9	—	✓	✓	✓	✓
Work characteristics						
Years working (SUD and this clinic) and role	5	—	—	—	—	—
Training and education for role	2	—	—	—	—	—
Baseline exposure to MPACT-related practices						
Reflect Sup (some staff)	1	—	✓	✓	✓	✓
Self-care	9	—	—	✓	—	✓
MPACT-specific practices	9	—	✓	✓	✓	✓
Empowerment						
Staff empowerment scale	5	—	—	✓	—	✓
Patient empowerment (Bann scale)	—	15	✓	✓	✓	✓
Beliefs						
Abstinence Orientation Scale	11	—	—	✓	—	✓
Comfort with MMT innovations	10	—	—	✓	—	✓
ARTIC[i]	10	—	—	✓	—	✓
Person-centered climate (PCQ-S[j])	5	—	—	✓	—	✓
Stigma						
Stigma toward people with OUD[k]	8	—	—	✓	—	✓
Self-stigma	9	—	—	✓	—	✓
Fear of enacted stigma	9	—	—	✓	—	✓
Patient-centered care practices						
PCC[l]	19	—	—	✓	—	✓
Team-derived PCC scale	6	6	✓	✓	✓	✓

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Construct	Assessment 1 (enrollment)		Assessment 2	Assessment 3	Assessment 4	Assessment 5 (study conclusion)
	Staff items, n	Patient items, n				
Kim Alliance Scale	—	16	✓	✓	✓	✓
Implementation						
MPACT feasibility, accept and fit; likelihood of continuing practices	5	—	—	—	—	✓

[a]Not applicable.
[b]SUD: substance use disorder.
[c]MMT: methadone maintenance treatment.
[d]OD: opioid overdose.
[e]LEC: Life Events Checklist.
[f]PCL-5: Posttraumatic Stress Disorder Checklist.
[g]Patients only.
[h]ProQoL: Professional Quality of Life Scale.
[i]ARTIC: attitudes toward trauma-informed care.
[j]PCQ-S: Patient-Centered Climate Scale for staff.
[k]OUD: opioid use disorder.
[l]PCC: person-centered competence.

For the 20-month trial, there will be 8 surveys from baseline assessment at enrollment through the remaining 7 assessments conducted every 77 days. Survey responses will be collected using the Qualtrics platform, accessible directly by participants.

For all enrolled patients, a review of their methadone clinic medical chart will include the duration of their treatment at the clinic, from treatment initiation to discharge or study end, whichever occurs first. This review will take place at the conclusion of the study period in accordance with the data sharing agreement (DSA) established between the clinic organization and the University of Arizona. A feasibility test with a sample of 50 charts with deidentified data was conducted in June 2024 and confirmed timely data transfer, data completeness, and utility for outcome measurement for the pilot clinics. Our national survey of OTP clinic directors found that 22.2% of clinics allowed DSAs with researchers, but the vast majority (77.3%) indicated that such agreements were not allowed or that they were not aware of the clinic organization's position on them [60]. For the purposes of the trial, then, only clinics allowing DSAs will be eligible for study enrollment. The following medical chart segments will be requested for each patient participant: (1) the digest of the patient history of starting and leaving treatment at that clinic (dates), (2) case notes, (3) discharge summary, (4) treatment plans, (5) milligram dosing, and (6) take-home medication status over time. Case notes include qualitative data on patient stability, challenges reported by the patient (eg, housing, transportation, safety, and dosing sufficiency), and instances of missed doses. For the trial, the data will be transferred using unique identifiers that will correspond with the study unique identifiers. No personally identifying information (name and street address) will be transferred.

Study Recruitment

Recruitment is stepwise for both the pilot and the trial. For the national trial, clinics will first be recruited through email from a national list of methadone clinics responding to a prior survey by this team during 2024 [60]. A second strategy will involve an email to the state opioid treatment authority with a request to forward study information and the recruitment flyer to methadone clinic directors in their state. State opioid treatment authorities are the single opioid regulator in each state. Clinics that allow study recruitment among staff and patients, establish a DSA for the transfer of patient participant methadone treatment chart data at the conclusion of the 20-month trial, and identify a clinic "champion" to assist with study enrollment and study contact will be eligible for randomization as described below.

Following clinic enrollment, each clinic champion will post recruitment flyers in staff-only areas (for staff participants) and in patient-only areas (for patient participants). Recruitment flyers for staff lead to a study portal (web-based) presenting information about the study and requesting agreement to participate. If agreement is made, staff participants will immediately complete the enrollment survey (baseline assessment 1). The same process will occur for patients. Payment for timely completion of each survey is US $20 for patients and staff. This cost was determined by a group of staff and patients who completed the work associated with aim 1.

Patient and staff confidentiality will be maintained by centralizing the enrollment process. Recruitment flyers will be displayed in staff-only and patient-only areas with a QR code or URL leading to information for potential participants to learn more about the study and to voluntarily enroll. This process ensures the anonymity of study participants within the clinic, meaning that patients and staff participants will not be known to the study clinic. Further, at the time of enrollment, a unique identifier will be established by the participant and will be used

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henceforth. At no time will the clinic leadership or clinic champion know the identity of the study participants. The only exception to this is at the conclusion of the study when patient chart data transfer will occur, and at that time, only 1 person handling data transfer will have the name and dates of birth of the participants whose charts will be transferred for study purposes.

Fidelity Tracking and Application of RE-AIM

MPACT fidelity tracking will assess the degree to which clinics assigned to the intervention arm implement MPACT components. This will be evaluated by a fidelity tracking instrument and video conversations with the clinic champions—biweekly during the pilot study and monthly during the trial period. A fidelity tracker will first be populated with data from study databases, including accredited training completion, TICA survey participation (number and ratio of staff completing surveys), number of anonymous wellness self-screenings, and reflective supervision participation (number of staff by role per biweekly session). During fidelity conversations, the clinic champion will indicate the number of wellness trainings offered to staff (current or new staff) in the past 2 weeks, whether posters for the wellness screener were shared in the staff-only areas, and whether there were other issues raised by staff about MPACT participation that may require troubleshooting.

MPACT feasibility will be measured through fidelity tracking (what the clinic does and does not implement and the feedback about issues related to that) and through items measured in the staff survey. The RE-AIM framework will guide the assessment of reach, adoption, implementation, effectiveness, and maintenance. Reach is focused on staff and patient participants in the MPACT study. Measures of reach include the number and proportion of clinics participating in the study (number participating/number in recruitment sample) and the number and proportion of staff and patients participating by the study clinic. Adoption is focused on the participation in MPACT intervention overall and by the MPACT component. This is measured by reported staff participation through the surveys and through completion data gathered through the intervention components. Examples include accredited training completion or progress toward completion, reflective supervision participant reports, and wellness assessment completion reported through study surveys and through wellness screening data output (duplicated unless noted by the participant by selecting “I have taken this assessment before,” and if selected, the participant can select the number of times the assessment has been completed prior). Implementation is measured through the fidelity check meetings with champions and reported MPACT activity (such as posting flyers about particular intervention components). Effectiveness is measured by primary and secondary outcomes related to the aims of this study. Maintenance will not be measured in the pilot study (4-month period) but will be measured through a survey conducted 6 months after the conclusion of the trial period.

Phase 2, Years 3-6: Hybrid, Cluster Randomized Controlled Trial

Overview

- Aim 4: Quantify the effects of MPACT on methadone treatment practice change and clinic culture.
- Aim 5: Determine the efficacy of MPACT on methadone treatment retention and patient and staff PTSS outcomes.
- Aim 6: Evaluate the effect of patient and staff trauma on primary outcomes and staff MPACT implementation.

Findings from the pilot study will determine the preliminary effect size to confirm power analyses and final sampling for a hybrid type 1, 20-month cluster randomized controlled trial among 30 clinics, 600 patients (20 per clinic), and 480 staff (18 per clinic). This hybrid type 1 trial will focus primarily on MPACT’s effect outcomes while examining the association of MPACT implementation fidelity and acceptability and identifying the multilevel factors influencing implementation.

For the trial, the clinic is the unit of randomization. The intervention condition will be the MPACT intervention, and the control condition will involve accredited training about methadone that does not overlap aspects of the MPACT intervention. As shown in Table 2, we will allow a 20-month study period to accommodate staggered trial initiation through month 12 of year 2. Given the 20-month trial period, we will allow for new staff members to enroll through the end of the 7th month of their site’s trial period.

Table 2. Cluster randomized controlled trial of Methadone Patient Access to Collaborative Treatment.

	Year 1		Year 2		Year 3		Year 4	
	Half 1	Half 2	Half 1	Half 2	Half 1	Half 2	Half 1	Half 2
Intervention arm clinics (n=15)	Start-up	Intervention	Intervention	Intervention	Intervention	Intervention	Intervention	Closeout
Control arm clinics (n=15)	Start-up	Usual care	Usual care	Usual care	Usual care	Usual care	Usual care	Closeout
Key processes	Randomization process finalized	Trial allows for staggered starts based on recruitment	Trial allows for staggered starts based on recruitment	Trial allows for staggered starts based on recruitment	Trial follow-up	Trial follow-up	Trial follow-up	Trial outcome analyses and dissemination

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Clinic Stratification Factors

By the time of trial planning finalization, we anticipate that the state regulatory environment in each trial location will be a likely outer setting impact. Given the importance of state policy for regulating OTPs and methadone treatment, we will measure state regulatory favorability toward OTPs using a 2-level coding structure used in prior studies by this team [60]. We will code state laws based on the Pew state regulatory review [8] as "expanding methadone access" or "not expanding or limiting access." Randomization to trial condition will be stratified based on outcomes of this state regulatory coding.

Statistical Analysis

Our primary outcome is patient time to first treatment interruption (confirmed in the pilot). Secondary outcomes include treatment retention (yes or no) at selected time points (1, 3, 6, and 12 months) and time to treatment discontinuation. To accommodate the clustering induced by nesting patients within clinics, we will use a mixed effects Cox proportional hazards model (shared frailty model) [61,62] to accommodate differential survival probability among clusters. The mixed model will include a random intercept for the clinic and a fixed treatment effect for MPACT or control assignment. We will also include patient-level covariates for age, sex, and time in MMT.

Our initial sample size calculation uses asymptotic normal results for log hazard ratio as well as sample size inflation factors (eg, Donner) [62] for cluster randomized trials. In designing the future R33 trial, we will make use of specific sample size methods for cluster randomized trials with time-to-event outcomes [63,64]. The relative frequency of first treatment interruption [65] is estimated as 66% at 12 months of MMT until we have confirmation from the pilot. We evaluate the number of clinics and number of patients, assuming that MPACT intervention reduces this frequency to 45% (n=240), 50% (n=300), and 55% (n=330). The power curves based on independent observations (no cluster effect) are shown in Figure 3. The graph shows that the recruitment of 30 clinics, with 20 patients per clinic, provides greater than 80% power to detect a difference in treatment interruption rates of 66% (control) and 55% (MPACT) with α=.05. Consistent with the cluster randomization trial design, we also consider the average number of patients per clinic as 10, 20, and 40 and different degrees of intraclinic clustering using intraclass correlation coefficients of 0.05 and 0.10.

Figure 3. Number of clinics and patients for 80% power (vs 66% treatment interruption rate), MPACT trial. ICC: intraclass correlation coefficient; MPACT: Methadone Patient Access to Collaborative Treatment.

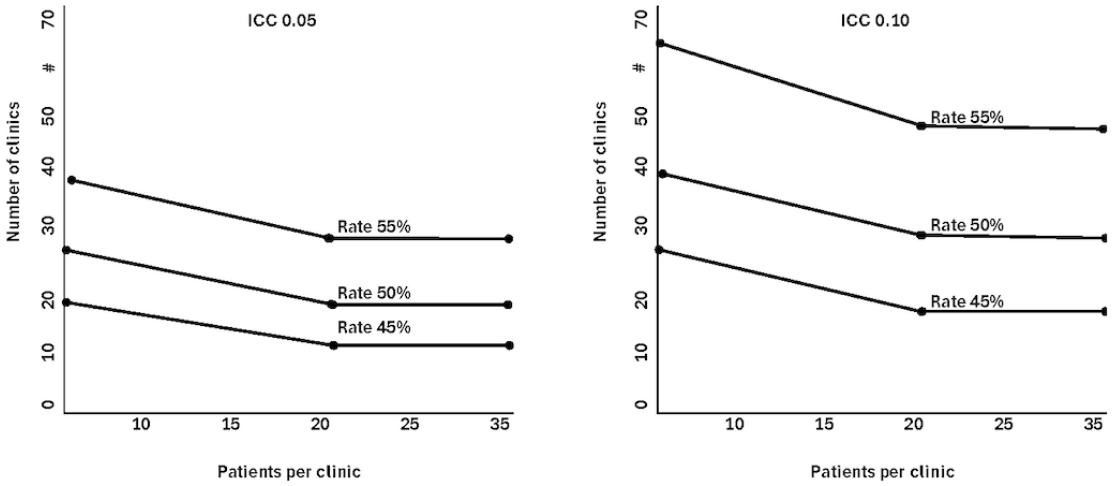

Results

The pilot study is funded by the National Institute on Drug Abuse (award R61DA059889, funded September 2023), and the field trial will be funded under the associated R33 mechanism in September 2025. The pilot study was completed on March 17, 2025. We are currently analyzing the pilot study findings. The randomized controlled trial will begin in December 2025.

Discussion

The MPACT study will provide a foundation for an evidence-based, staff-level intervention aimed at improving patient retention in MMT. We anticipate a decrease in reported levels of VT and PTSS among staff and an increase in methadone treatment retention among patients. The pilot outcomes are focused primarily on implementation with a preliminary indication of impact or effectiveness. The preliminary outcomes from the pilot will inform the final sampling to properly power the study. The trial outcomes are focused both on the implementation and effectiveness of the MPACT intervention. Future studies should examine the individual components of MPACT to determine their differential contributions to the primary outcome of patient MMT retention and to secondary outcomes of staff and patient reduction in stress symptoms.

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Acknowledgments

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Data Availability

The datasets generated and analyzed during this study will be made available in the HEAL data ecosystem through the Inter-University Consortium for Political and Social Research within 1 year of the pilot and of the trial conclusion, or at the time of first publication from the pilot (or trial), whichever occurs first.

Authors' Contributions

BEM led the study conceptualization, data curation, funding acquisition, investigation, and methodology and provided project administration and supervision of study staff and investigators. BEM also led the visualization and original writing and editing of the manuscript. AD supervised data curation and conducted formal analysis. AD also advised the methodology and conducted data validation. AD participated in the editing of the manuscript. RAC advised study conceptualization, data curation, funding acquisition, investigation, and methodology. RAC also participated in the editing of the manuscript. LBLK assisted study conceptualization, funding acquisition, investigation, and methodology and participated in the editing of the manuscript. BRB and ANM assisted study conceptualization, funding acquisition, and methodology and participated in the editing of the manuscript. GAC assisted study conceptualization, funding acquisition, investigation, and methodology and participated in the editing of the manuscript. DF, JR, ED, JE, MFJ, MJ, BL, HML, MDP, and KT assisted study methodology and participated in the editing of the manuscript. SY assisted data curation and investigation, managed software, and participated in the editing of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from ZDA1 SKP-E (O2) - National Institute on Drug Abuse Special Emphasis Panel HEAL Initiative: Translating Research to Practice to end the Overdose Crisis (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 89 KB - resprot_v14i1e69829_app1.pdf]

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Abbreviations

DSA: data sharing agreement
MMT: methadone maintenance treatment
MPACT: Methadone Patient Access to Collaborative Treatment
OTP: opioid treatment program
OUD: opioid use disorder
PCL-5: Posttraumatic Stress Disorder Checklist
PTSS: posttraumatic stress symptoms
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
TICA: trauma-informed clinic self-assessment
VT: vicarious trauma

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Protocol

Calibration and Validation of Machine Learning Models for Physical Behavior Characterization: Protocol and Methods for the Free-Living Physical Activity in Youth (FLPAY) Study

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Abstract

Background: Wearable activity monitors are increasingly used to characterize physical behavior. The development and validation of these characterization methods require criterion-labeled data typically collected in a laboratory or simulated free-living environment, which does not generally translate well to free-living due to limited behavior engagement in development that is not representative of free living.

Objective: The Free-Living Physical Activity in Youth (FLPAY) study was designed in 2 parts to establish a criterion dataset for novel method development for identifying periods of transition between activities in youth.

Methods: The FLPAY study used criterion measures of behavior (direct observation) and energy expenditure (indirect calorimetry) to label data from research-grade accelerometer-based devices for the purpose of developing and cross-validating models to identify transitions, classify activity type, and estimate energy expenditure in youth aged 6-18 years. The first part of this study was a simulated free-living protocol in the laboratory, comprising short (roughly 60-90 s) and long (roughly 4-5 min) bouts of 16 activities that were completed in various orders over the span of 2 visits. The second part of this study involved an independent sample of participants who agreed to be measured twice (2 hours each time) in free-living environments such as the home and community.

Results: The FLPAY study was funded from 2016 to 2020. A no-cost extension was granted for 2021. A few secondary outcomes have been published, but extensive analysis of primary data is ongoing.

Conclusions: The 2-part design of the FLPAY study emphasized the collection of naturalistic behaviors and periods of transition between activities in both structured and unstructured environments. This filled an important gap, considering the traditional focus on scripted activity routines in structured laboratory environments. This protocol paper details the FLPAY procedures and participants, along with details about criterion datasets, which will be useful in future studies analyzing the wealth of device-based data in diverse ways.

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KEYWORDS

physical behavior assessment; youth activity; wearable devices; activity monitoring; digital health; physical behavior characterization; criterion dataset

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Introduction

Device-based assessment of physical behavior has become common in health research [1-6]. Despite significant advancements in this field, a major challenge remains: the translation and generalization of device outputs, which are crucial for accurate interpretation and use [1,7]. This challenge arises partly from the methodological approaches used, as well as from the way data are collected to calibrate and validate these methods. Traditional static regression models for physical behavior assessment, such as those used in the 2003-2006 National Health and Nutrition Examination Survey [8], rely on population-, attachment site-, and device-specific cut points or regression equations to estimate energy expenditure (EE) and physical activity intensity [9]. However, these models tend to perform poorly when applied to the dynamic and complex nature of real-world behavior, as well as when tested on out-of-sample datasets [10,11]. For example, legacy models such as the Freedson equation for children [12] have been shown to underestimate moderate-to-vigorous physical activity by up to 51% during free-living conditions [11], highlighting a key limitation in the field. This discrepancy arises because these models were developed using structured laboratory data, which fail to capture the sporadic and irregular movement patterns typical of free-living environments. Furthermore, traditional methods often segment accelerometer data into fixed time intervals (eg, 1-min epochs), assuming that each data point is independent and represents a continuous bout of activity—an assumption that is rarely valid in real-world settings [13-15].

Advancements in sensor technology, including the use of wrist-worn accelerometer-based devices and the integration of additional sensor types (ie, gyroscopes and magnetometers), have improved the potential ability to capture a broader range of movement behaviors with different characteristics, such as the discrimination of sedentary behavior [16-18]. These innovations offer promising solutions for improving physical behavior assessment, particularly in youth populations. However, challenges remain in using raw data from these devices to accurately predict EE and categorize activity types [1,19,20]. The use of machine learning algorithms has been an interesting development in this space, showing potential for improving activity classification and EE estimation [21-24]. However, as with traditional methods, these machine learning algorithms have been primarily trained on structured laboratory activities, leading to poor performance when applied in free-living conditions and to new datasets [21,25]. The key issue lies in the segmentation of activity bouts and the identification of transitions between activities, which are much more subtle and irregular in free-living environments compared to the abrupt transitions typical of laboratory-based protocols [26-28].

The Free-Living Physical Activity in Youth (FLPAY) study was an effort to address these gaps by collecting transition-rich data in free-living conditions for calibration and validation of device-based models of physical behavior. The purpose of this paper is to describe the methods and data associated with the FLPAY study, thereby encouraging procedural replication in future studies and providing a comprehensive background for future analyses of data from this study. By addressing the complexities of free-living data, particularly the segmentation of activity bouts and transitions, this study aims to improve the accuracy, precision, and applicability of device-based physical behavior assessments and contribute to the development of more effective methods for characterizing physical behavior in youth.

Methods

Study Design

The FLPAY study was a 2-part investigation to develop and validate sensor-based methods for detecting transitions between activities as a precursor to predicting EE. The first part of this study took place in a simulated free-living laboratory environment conducive to method development (calibration), while the second took place in unstructured free-living environments conducive to method validation. Both studies were for youth participants aged 6-18 years who were recruited through word of mouth and flyers. The overall study design was conceived to address common limitations of prior method development studies, which have focused on the collection of steady-state laboratory data and structured ambulatory activities, rather than allowing naturalistic transitions and data collection in free-living.

Below, we present protocol and data summaries for each component of this present study in separate subsections. Portions of the information have been reported previously [26,29-31]. This present study was not a clinical trial. Due to the overlap in the methods for each part of this study (eg, similar equipment), the following sections are focused primarily on unique elements of each part, while recurring elements are presented in Multimedia Appendix 1.

Ethical Considerations

Both parts of this study were approved by the University of Tennessee Knoxville Institutional Review Board (UTK IRB-15-02487-FB). For all participants, written informed consent was obtained from a parent. Participants also provided written informed assent. Both parts of this study involved video recording on an opt-in basis, and thus, there were separate consent and assent signatures for general enrollment and video recording. However, for both parts of this study, the consent and assent documents did not include language for public data sharing, and thus, only deidentified data will become available from the FLPAY study. For screening, parents filled in a health history questionnaire, with participants being excluded if they had medical conditions or musculoskeletal injuries that prevented engagement in physical activities. Additional exclusion criteria included conditions or medications affecting metabolism. Participants were compensated for their participation in this study. Details on compensation are included within the subsections for each study component.

Part 1: Laboratory-Based Component

Participants—Laboratory-Based Component

A total of 100 participants were recruited. Approximately even distributions were recruited across sex and age groups (6-9, 10-12, 13-15, and 16-18 years). Participant characteristics are shown in Table 1.

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Table 1. Physical characteristics of participants from the laboratory study.

	Full sample (N=100)	Male (n=48)	Female (n=52)
Age (years)			
Mean (SD)	12.1 (3.53)	12.3 (3.32)	11.9 (3.74)
Median (IQR)	12.1 (9.3-15.2)	12.4 (9.9-15)	11.7 (9-15.2)
Age group (years), n (%)			
6-9	33 (33)	13 (27.1)	20 (38.5)
10-12	25 (25)	15 (31.3)	10 (19.2)
13-15	23 (23)	12 (25)	11 (21.2)
16-18	19 (19)	8 (16.7)	11 (21.2)
Height (cm)			
Mean (SD)	150 (19.2)	152 (20.5)	148 (17.9)
Median (IQR)	151 (134-166)	156 (140-167)	150 (133-162)
Sitting height (cm)			
Mean (SD)	74.9 (9.5)	75.4 (9.7)	74.3 (9.5)
Median (IQR)	74.5 (66.5-83.1)	74.5 (68.6-84)	74.4 (65.9-82.6)
Leg length (cm)			
Mean (SD)	75 (11.4)	77 (11.8)	73.2 (10.8)
Median (IQR)	76 (66-82.8)	77.5 (69.6-85.8)	74.3 (63.8-80)
Weight (kg)			
Mean (SD)	44.7 (18.7)	46.5 (20.3)	43 (17.2)
Median (IQR)	40.5 (29.6-55.7)	41 (34.1-56.3)	38.3 (29.3-55.7)
Fat mass (kg)			
Mean (SD)	10.4 (7.5)	9.2 (6.8)	11.4 (7.9)
Median (IQR)	7.5 (5.7-12.1)	7 (5.6-10)	9.5 (6.5-13.7)
Body fat (%)			
Mean (SD)	21.9 (6.4)	18.7 (4.8)	24.9 (6.3)
Median (IQR)	20.8 (17.5-24.5)	17.5 (15.6-19.7)	23.7 (21.1-27.5)
Fat-free mass (kg)			
Mean (SD)	34.3 (12.9)	37.2 (14.6)	31.6 (10.6)
Median (IQR)	32.7 (23.3-42.8)	33.8 (27.3-48.1)	30.3 (22-41.6)
BMI (kg/m^2)			
Mean (SD)	19 (4.4)	19.1 (4.4)	19 (4.5)
Median (IQR)	18 (16.2-20.5)	18 (16.3-19.9)	17.9 (16.2-20.6)
BMI percentile (%)			
Mean (SD)	51.6 (27.4)	50.9 (26.8)	52.3 (28.2)
Median (IQR)	49.4 (33.6-73.3)	48.8 (34.2-72.2)	49.6 (33.6-74.6)
BMI classification			
Underweight	5 (5)	2 (4.2)	3 (5.8)
Healthy weight	80 (80)	40 (83.3)	40 (76.9)
Overweight	9 (9)	2 (4.2)	7 (13.5)
Obese	3 (3)	3 (6.3)	0 (0)
Severe obese	3 (3)	1 (2.1)	2 (3.8)
Race or ethnicity			

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	Full sample (N=100)	Male (n=48)	Female (n=52)
Hispanic White	4 (4)	1 (2.1)	3 (5.8)
Non-Hispanic African American	9 (9)	3 (6.3)	6 (11.5)
Non-Hispanic White	87 (87)	44 (91.7)	43 (82.7)
Handedness			
Right	94 (94)	45 (93.8)	49 (94.2)
Left	6 (6)	3 (6.3)	3 (5.8)

Laboratory-Based Component Procedures

All research visits were conducted in the Applied Physiology Laboratory and the surrounding area at the University of Tennessee Knoxville. The protocol entailed 2 visits on separate days, each lasting approximately 2-2.5 hours. The main feature of the protocol was the completion of 16 activities (Table S3 in Multimedia Appendix 1) that were divided across the 2 visits. A key goal of this study's design was to simulate realistic transitions between activities. Therefore, each activity was performed twice, with 1 instance lasting approximately 60-90 s and the other lasting approximately 4-5 min. Within those ranges, participants self-selected when they transitioned to the next activity unless guidance was needed from the research team (eg, if the upper limit of 90 s or 5 min was reached or if the walking circuit reached a specific stopping point to facilitate speed calculations). They also self-selected the order of the 8 activities they were prescribed each day, except that the same activity could not be performed twice in a row, and the activities were grouped by location (ie, in an upstairs laboratory or a separate recreation area) to minimize total transition time. The order of short and long bouts for each activity was randomized.

Throughout each research visit, participants wore a portable indirect calorimeter and a variety of activity monitors. Participant behavior and posture were coded by direct observation, using a focal sampling approach that allowed continuous logging of behaviors, transitions, and posture. Video recording was also performed for most participants. The video recordings served as a backup in case the live coded observation records needed to be reviewed and revised for any reason (eg, adjusting timestamps if an error was noted during the live coding process).

Laboratory-Based Component Detailed Timeline

For the first visit, participants were asked to refrain from eating or drinking (except water) for 2 hours before the visit and to wear lightweight athletic clothing and closed-toed shoes. After completing the enrollment and consent processes, they removed their shoes and socks and had anthropometric measurements taken. Standing and sitting height (cm) were measured using a wall-mounted stadiometer. Body mass (kg) and body fat (%) were measured using a Tanita BC-418 bioelectrical impedance analyzer (Tanita Co. of America, Inc).

Following the anthropometric measurements, participants were fitted with this study's equipment and completed a 30-minute assessment of resting metabolic rate (RMR). The remainder of the visit involved completing the 8 activities assigned for that day. Participants received a US $30 gift card at the end of the visit.

For the second visit, participants were given the same previsit instructions. Upon returning to the laboratory, they were fitted with the same study equipment as visit 1 before performing the remaining 8 activities, such that all participants completed the full set of 16 activities under normal circumstances (ie, assuming there is no withdrawal, refusal, or space unavailability due to scheduling). Participants received a US $45 gift card at the end of the visit.

Laboratory-Based Component Equipment

All participants wore 5 ActiGraph GT9X devices (GT9X; ActiGraph LLC), which were the primary activity monitors of interest for this study. One was placed on the right hip, 1 on each wrist, and 1 on each ankle. The hip-worn device was worn on an elastic belt and positioned over the right iliac crest along the anterior axillary line and secured using a manufacturer-specific belt clip. The wrist-worn devices were worn in manufacturer-specific watch bands that the devices clipped into. The watch bands were positioned proximal to the styloid processes with the devices oriented where the LCD could be read naturally by the participant, as a standard watch face would be. The ankle-worn devices were clipped into manufacturer-specific clips worn on slip-through Velcro bands. The clips were positioned so that the devices were on the lateral aspect of the ankle proximal to the lateral malleolus. Additional detail is given in Section S1.1 in Multimedia Appendix 1.

Secondary activity monitors, both research- and consumer-grade, were also worn in various locations on the body as detailed in Sections S1.2 and S1.3 in Multimedia Appendix 1.

Criterion Measures

Participants were observed using the Noldus Observer XT and Pocket Observer software platforms (Noldus Information Technology), which served as a criterion measure of behavior and posture. Participants also wore a Cosmed K*4b*^{2} (COSMED s.r.l.), which was the criterion measure of EE. General details of these tools can be found in Sections S1.4 and S1.5 in Multimedia Appendix 1. Specific details applicable to part 1 of this study are discussed below.

The Observer XT desktop platform (version 12.5) was used to create a 2-class focal sampling coding scheme, which was then exported for use in the Noldus Pocket Observer application (version 3.2). The latter application was run on Samsung Galaxy Tab 4 tablets (Samsung) and used for real-time coding of participant behavior and posture. Several activity monitoring

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studies have taken a similar approach to direct observation using Noldus products [22,28,32-34].

The coding scheme included a 19-item list of activity behaviors (ie, for the 16 activities listed in Table S3 [Multimedia Appendix 1], plus labels for the start time of the observation period, transitions between activities, and unknown activities) and a 6-item list of postures (lying, reclining, sitting, standing, stepping, or unknown). The label for unknown activities was used whenever an unlisted activity occurred, such as a water break or bathroom break, and was accompanied with a posture label of unknown.

Whenever a new activity was initiated, users tapped the corresponding label in Pocket Observer, which issued a timestamp for the new activity and then prompted the user to indicate the participant's posture. This created a continuous and timestamped record of activities and postures. After finishing the protocol, live-coded observations were imported back into the Noldus Observer XT software program for conversion to Excel format. The resulting files were then processed in R (R Foundation).

Section S1.5 in Multimedia Appendix 1 describes the procedures that were used when syncing data from the various sources.

Processing of Criterion Data for Laboratory-Based Component

While the activity monitor data were collected for flexible use (eg, to be processed and tested in different ways across future studies), the criterion data from direct observation and indirect calorimetry were designed for consistent usage across future studies. Therefore, we describe the processing and aggregation of criterion data in the sections that follow, while monitor data processing is left for future studies to describe according to the unique needs of the study.

Direct Observation Data

Each participant was observed by a single trained observer in real time during each study visit. The observation files were inspected for comments and anomalies that indicated errors (eg, the user entered a comment indicating a button was pressed at the wrong time or that the activity duration was outside the expected range). Corrections were made by a senior reviewer cross-referencing the video recordings and adjusting labels or timing accordingly. For participants without video recordings, observations were used as they were created from the live coded direct observation (n=3). Each row of the observation files indicated a start time and duration for the corresponding activity and posture, and by definition, there were no gaps between activities. Thus, every second of the data collection period could be mapped to a specific activity and posture label that was active at that time, allowing a second-by-second record to be constructed from the information in the observation files.

Portable Indirect Calorimeter Data

EE was calculated based on oxygen consumption (VO_2) and RMR, both measured by the K4b^2. The values were expressed in youth metabolic equivalents (MET_y), where

As described in the Sections S2.1 to S2.3 in Multimedia Appendix 1, calculations for RMR and continuous VO_2 were the same for parts 1 and 2 of the FLPAY study. Below, we provide additional detail about calculating steady state EE as this was unique to part 1 of this study.

Steady state periods were defined for the longer activity bouts. All bouts longer than 3 minutes, 40 seconds were included in the analysis. The steady state period was defined as the last 60 seconds of each activity, after discarding the final 10 seconds. For each of these periods, the corresponding K4b^2 data were extracted in breath-by-breath format. An average VO_2 was then calculated using manufacturer-specified procedures (Section S2.1 in Multimedia Appendix 1). This value was divided by RMR to obtain MET_y for the steady state period. Posture was determined by cross-referencing the direct observation data from the steady state period.

Activity intensity was derived from EE (MET_y) and posture, using the following accepted definitions [35]: for sedentary behavior, ≤1.50 MET_y and seated, lying, or reclining posture; for light physical activity, 1.51-2.99 MET_y regardless of posture (or ≤1.50 MET_y if posture was upright); and for moderate-to-vigorous physical activity, ≥3.00 MET_y regardless of posture. For each activity and age group (ie, those aged ≤12 versus >12 years), data were cleaned by removing values <0.2 MET_y, or >2 SD above or below the mean.

Part 2: Unstructured Free-Living Study

Unstructured Free-Living Study Participants

A total of 84 participants were recruited to this study, of whom one was excluded (final N=83). Participant characteristics are shown in Table 2.

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Table 2. Physical characteristics of participants from the free-living study.

	Full sample (N=83)	Male (n=39)	Female (n=44)
Age (years)			
Mean (SD)	11.2 (3.4)	11.1 (3)	11.3 (3.7)
Median (IQR)	10.6 (8.5-13)	10.5 (8.9-12.7)	11.2 (8.4-13.6)
Age group (year), n (%)			
6-9	35 (42.2)	17 (43.6)	18 (40.9)
10-12	26 (31.3)	13 (33.3)	13 (29.5)
13-15	14 (16.9)	6 (15.4)	8 (18.2)
16-18	8 (9.6)	3 (7.7)	5 (11.4)
Height (cm)			
Mean (SD)	146 (19.4)	145 (16.1)	147 (22.2)
Median (IQR)	144 (132-162)	143 (135-159)	145 (130-164)
Sitting height (cm)			
Mean (SD)	73.5 (9.2)	73.3 (8.4)	73.7 (10)
Median (IQR)	73 (67-80)	73 (67-79.5)	73 (66-80.3)
Leg length (cm)			
Mean (SD)	72.5 (10.9)	72 (8.3)	72.9 (12.8)
Median (IQR)	71 (66-81)	70.5 (67.3-78.9)	71.8 (63.4-84.9)
Weight (kg)			
Mean (SD)	42 (18.6)	39.9 (13.9)	43.9 (22)
Median (IQR)	36.1 (28.4-53.9)	36.1 (30.7-50)	37.6 (26.5-55.2)
Fat mass (kg)			
Mean (SD)	8.9 (7.8)	9.7 (6.6)	8.2 (8.8)
Median (IQR)	6.2 (3.9-11.8)	8.6 (4.3-13.4)	4.8 (3.7-7.5)
Body fat (%)			
Mean (SD)	19.3 (9.3)	21.9 (9.1)	17.1 (9)
Median (IQR)	17.9 (13.6-24)	22.2 (15.4-27.1)	15.3 (12.6-18.3)
Fat-free mass (kg)			
Mean (SD)	33.1 (13.5)	30.2 (8.2)	35.7 (16.5)
Median (IQR)	30.2 (23.3-39.7)	27.6 (23.7-37.5)	31.7 (21.9-42.8)
BMI (kg/m^2)			
Mean (SD)	18.7 (4.3)	18.3 (3.5)	19.1 (4.9)
Median (IQR)	17.7 (15.8-19.7)	17.8 (15.9-19.6)	17.6 (15.7-20)
BMI percentile (%)			
Mean (SD)	53.3 (26.2)	51.5 (24)	55 (28.2)
Median (IQR)	52.8 (33.4-72.4)	47.6 (33.7-72.3)	54.5 (33.9-72.5)
BMI classification, n (%)			
Underweight	3 (3.6)	1 (2.6)	2 (4.5)
Healthy weight	67 (80.7)	34 (87.2)	33 (75)
Overweight	6 (7.2)	2 (5.1)	4 (9.1)
Obese	4 (4.8)	1 (2.6)	3 (6.8)
Severe obese	3 (3.6)	1 (2.6)	2 (4.5)
Race or ethnicity, n (%)			

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	Full sample (N=83)	Male (n=39)	Female (n=44)
Hispanic Hawaiian or Pacific Islander	1 (1.2)	0 (0)	1 (2.3)
Hispanic White	2 (2.4)	2 (5.1)	0 (0)
Latino White	1 (1.2)	0 (0)	1 (2.3)
Non-Hispanic African American	2 (2.4)	0 (0)	2 (4.5)
Non-Hispanic Asian	6 (7.2)	1 (2.6)	5 (11.4)
Non-Hispanic Native American or Alaskan	1 (1.2)	0 (0)	1 (2.3)
Non-Hispanic White	70 (84.3)	36 (92.3)	34 (77.3)
Handedness, n (%)			
Left	3 (3.6)	0 (0)	3 (6.8)
Right	80 (96.4)	39 (100)	41 (93.2)

Unstructured Free-Living Study Procedures

The overall goal of this part of this study was to collect free-living data with diverse activities and transitions between them. Therefore, research visits were conducted in varied settings, such as in the community, participants' homes, local parks, and approved facilities of community partners. Data were collected across 2 separate days, with the goal to have one in the participant's home and the other somewhere else.

The first study visit was generally conducted in the participant's home environment and began with the informed consent and assent process and participant screening. Once enrolled, participants had anthropometric measurements taken, including standing and sitting height (cm) using a portable stadiometer and body mass (kg) and body fat percentage measured using a Tanita BF-350 bioelectrical impedance analyzer. Anthropometric measurements were taken with shoes and socks removed. Following the completion of the anthropometric measurements, a 30-min RMR assessment was conducted using a Cosmed K4b^2 or K5 (used in breath-by-breath mode to align with the K4b^2) portable indirect calorimeter before participants engaged in activities of their choice for up to 2 hours. In some cases, the RMR assessment was conducted on a separate visit (for a total of 3). Participants were compensated US $25 for the RMR assessment and US $25 for the free-living data collection period.

For the second study visit, an alternative environment was sought for each participant. When this was not possible, participants were asked to engage in different activities than what they chose during their initial visit, which helped to mimic different environments and promote engagement in a wide range of activity behaviors. Similar to the first visit, the participants engaged in behaviors of their choice for up to 2 hours. An additional US $25 of compensation was given for completing the second study visit.

Throughout this study's visits, participants were given free rein to select activities, so long as they had parental permission, did not put the equipment at risk (eg, from water damage), and did not risk harming themselves or others.

All participants wore the same research-grade devices as described in the equipment portion of part 1 including the primary devices of interest (ActiGraph GT9X on the hip, both wrists, and both ankles; see also Section S1.1 in Multimedia Appendix 1) and the secondary research- and consumer-grade monitors (see Sections S1.2 and S1.3 in Multimedia Appendix 1, respectively). Participants wore a Cosmed K4b^2 or K5 portable indirect calorimeter, both of which collected breath-by-breath data as a criterion measure of EE (see Section S1.5 in Multimedia Appendix 1 for more detail). During the consent process, participants were able to opt-in to be video recorded throughout each research visit, and only 3 participants did not do so. Live coding was performed for those who did not opt into the video recordings. For the others, the video recordings were later used for direct observation to obtain a record of the behaviors and postures they engaged in, along with relevant contextual factors (eg, indoors versus outdoors and alone versus with others). These video-based observations were performed using the Noldus Observer XT software program for Windows desktop computers.

Unstructured Free-Living Study Equipment

Most equipment matched what was used for part 1 of the FLPAY study, with the addition of the Cosmed K5 alongside the K*4b*^{2}. The main difference in part 2 was the coding scheme used for direct observation and the reliance on video recordings for direct observation rather than live-coded observations. For participants who did not opt into video recording, real-time observations were performed using similar procedures to those described in part 1 above, except that a new coding scheme was used (Table S2 in Multimedia Appendix 1). Otherwise, the video recordings were coded using the Noldus Observer XT Direct Observation software program (version 12.5) for Windows desktop machines.

The coding scheme for part 2 included a longer list of potential activities and postures, as discussed below. It also included prompts about the activity context (eg, indoor or outdoor and alone or with others). Otherwise, the general structure of the coding scheme matched with part 1, such that every second of the data collection period could be mapped to a single entry in the observation record.

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Table S4 in Multimedia Appendix 1 lists the main activities that were included in the coding scheme. As before, extra labels were included for coding the start of the observation period, transition behaviors, and unknown activities (ie, activities not previously defined), and events where the participant was off-camera (ie, in a private space, bathroom, etc). After the primary activity behavior was coded, posture was coded as lying, sitting, standing, standing or stepping, squatting or kneeling, reclining, mixed posture, or unknown (used only when the activity behavior was "off camera"). Section S1.5 in Multimedia Appendix 1 describes the procedures that were used when syncing data from the various sources.

Unstructured Free-Living Study Processing of Criterion Data

The data processing procedures for part 2 broadly mirrored what has already been discussed in part 1 resulting in a second-by-second dataset with information about EE, behavior, posture, and context. The direct observation procedures differed from part 1 due to the open-ended nature of this study and the reliance on video recordings. Specifically, at least 2 trained reviewers coded each video, and a third senior reviewer then compared their observations side-by-side. Additional detail is available in S1.4.3 in Multimedia Appendix 1.

Results

The FLPAY study was funded in June 2016, and recruitment and data collection for part 1 began in January 2017. Funding ended in March 2019, and the project and data collection concluded in March 2020. Some preliminary and auxiliary findings have been reported previously [26,29-31], whereas the protocol described herein will serve as the authoritative guide for ongoing research with the finalized dataset. Part 1 of this study enrolled 100 individuals, and part 2 enrolled 84 individuals. Data loss is described in Section S3 in Multimedia Appendix 1. The overall sample characteristics are shown in Table 1 and Table 2, whereas sample sizes for individual analyses may differ depending on overlap with additional missing data for different activity monitors. Table 3 provides an overview of prior completed analyses and current and ongoing analyses.

Table 3. Summary of research activities related to the FLPAY[a] study.

Component	Notes
Completed analyses	• Please see references [26,29-31].
Ongoing analyses	
ActiGraph, GENEActiv, and Axivity	• Please see references [36-38]. • Ongoing analyses include the development and testing of models to predict energy expenditure [36,37] and classify activity type [38]. • Additionally, we are preparing the dataset such that it can be used for out-of-sample validation of models developed by other research groups.
activPAL	• Please see reference [39].

[a]FLPAY: Free-Living Physical Activity in Youth.

Discussion

Contributions

The design of the 2-part FLPAY study emphasized naturalistic behaviors and periods of transition between activities. This filled an important gap in prior development studies focused on physical behavior characterization. In this paper, we summarized the FLPAY procedures and participants, along with details about criterion datasets that will be useful in future studies that look at various aspects of the data from the activity monitors. Future studies can proceed with novel method development and testing for a variety of research-grade and consumer-grade wearable devices. These data may be especially useful for ongoing work to refine methods involving transition detection for data segmentation [27,30].

It is worth noting that the main device from this study (ActiGraph GT9X) has been replaced by a newer model (ActiGraph LEAP). Although the manufacturer remains committed to backward compatibility, testing will be necessary to compare outputs from the GT9X and LEAP. Such comparisons should include not only direct factors such as agreement of the accelerometer and gyroscope outputs but also indirect factors such as battery life, memory consumption, and participant acceptability. Unpublished data from our laboratory showed that the GT9X battery life was <36 hours when collecting data from both the accelerometer and gyroscope. The LEAP includes a different gyroscope sensor that may be longer-lived, and it also includes additional sensors for richer monitoring (eg, barometer and microphone). These factors may affect usability in lengthy protocols (eg, >1 week) and vary from study to study depending on what sensor configuration is selected. It will also be important to consider the volume of data collected by LEAP, as our unpublished data showed that the GT9X was able to generate >1 GB of data before depleting its battery. As future studies begin to draw on the wearable data from the FLPAY study (especially, but not exclusively, the ActiGraph GT9X data), the implications of these decisions will be important to consider.

Strengths and Limitations

The FLPAY study had notable strengths, including its collection of data from both laboratory and free-living contexts, with realistic transition periods and behavioral patterns. Another

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strength was the inclusion of criterion measures for EE, behavior, and posture. These will substantially benefit future work toward the development and validation of novel methodological approaches for the variety of research-grade devices that were used in this study.

Despite its strengths, the FLPAY study also had limitations. A key limitation was the limited diversity of the samples along the lines of racial and ethnic background. While the recruitment strategy was designed to mirror the census makeup in the surrounding area, results may not be fully generalizable for youth who come from underrepresented backgrounds. The open-ended nature of the free-living component could also be viewed as both a strength and a limitation, as the heterogeneity of the data may create a high level of variability that is difficult to address or interpret in future analyses. Lastly, we emphasized detailing the criterion data measurements of RMR, EE, and direct observation in the FLAY study as these will be foundational for a wealth of secondary research that is possible when paired with the monitor data collected in this study.

Acknowledgments

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Data Availability

Deidentified data from the FLPAY study may be available upon reasonable request from the corresponding author. Video data cannot be deidentified and cannot be shared under any circumstances.

Conflicts of Interest

PRH has received funding from ActiGraph LLC. This study predates said funding, representing no conflict of interest. The authors have no conflicts of interest to report.

Multimedia Appendix 1
Additional digital content.
[DOCX File , 63 KB - resprot_v14i1e65968_app1.docx]

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Abbreviations

EE: energy expenditure
FLPAY: Free-Living Physical Activity in Youth
METy: youth metabolic equivalent
RMR: resting metabolic rate
VO2: oxygen consumption

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Protocol

Interactive Computer-Adaptive Chronic Kidney Disease (I-C-CKD) Education for Hospitalized African American Patients: Protocol for a Randomized Controlled Trial

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Abstract

Background: End-stage kidney disease (ESKD) or kidney failure is a condition where the kidneys lose the ability to function. African American individuals are 4 times as likely to develop ESKD compared to White American individuals. In addition, African American patients are less likely to have an optimal dialysis start and to choose renal replacement therapy modalities that align with their goals and values. Our prior work shows that culturally tailored, in-person education improves patient outcomes. This is the foundation for our innovative intervention using an African American virtual patient educator as an option for hospitalized patients with chronic kidney disease (CKD).

Objective: The Interactive Computer-Adaptive Chronic Kidney Disease (I-C-CKD) study will determine whether the computerized adaptive education and usual hospital care impact the health literacy of African American patients with kidney disease. It will also assess how patients' lifestyle and commitment to health goals are impacted by the method of health literacy education.

Methods: We will screen, recruit, and enroll hospitalized patients who self-identify as African American and have advanced CKD based on their estimated glomerular filtration rate. Eligible patients who verbally consented will be randomly assigned into either the computerized adaptive education intervention group or the control group (usual hospital care). Patients in the intervention group will receive a culturally tailored, adaptive education module. To analyze pretest, posttest, and follow-up survey results on patient CKD knowledge, ESKD treatment options, and health goals, we will use a paired, 2-tailed *t* test with a Bonferroni adjustment for multiple comparisons.

Results: Recruitment for the I-C-CKD study began on May 2, 2023. We are currently recruiting and have enrolled 96 patients who completed both pretest and posttest surveys as of December 2024. This includes 50 patients in the control group and 46 patients in the intervention group. Data analysis has not occurred.

Conclusions: African American individuals often receive less patient education about self-care and treatment options for CKD. We hope this study provides a solution to increase hospitalized African American patients' knowledge of CKD and motivation for CKD self-care through computerized adaptive education, reduce disparities, and improve patient outcomes.

Trial Registration: ClinicalTrials.gov NCT06364358; https://clinicaltrials.gov/study/NCT06364358

International Registered Report Identifier (IRRID): DERR1-10.2196/66846

(JMIR Res Protoc 2025;14:e66846) doi:10.2196/66846

KEYWORDS

chronic kidney disease; computerized adaptive education; end-stage kidney disease; end-stage renal disease; glomerular filtration rate; kidney failure; usual hospital care; inpatient

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Introduction

Background

End-stage kidney disease (ESKD) or kidney failure is a condition where the kidneys lose the ability to function. African American individuals are 4 times as likely to have ESKD compared to White American individuals [1]. African American patients are more likely to have comorbidities such as diabetes, obesity, high blood pressure (hypertension), and heart failure, which all increase the risk of developing kidney disease [1].

Hemodialysis can help patients with ESKD feel better and live longer. However, dialysis is not a cure for ESKD, and patients on hemodialysis have high morbidity and mortality rates [1]. Patients on hemodialysis can also experience side effects such as low blood pressure (hypotension), muscle cramps, sleep problems, anemia, bone disease, high blood pressure (hypertension), and access-site complications [2]. In-center hemodialysis (IHD) with thrice weekly sessions in a dialysis unit is the most common treatment for ESKD. Patients who use IHD experience greater inconvenience, worse waste clearance, and more issues with transportation in comparison to other ESKD options. Alternatives to IHD include home hemodialysis, peritoneal dialysis, and kidney transplantation. These methods are associated reduced morbidity and mortality, or improved quality of life, compared to IHD [3].

There are racial disparities in the use of these renal replacement therapy (RRT) modalities. African American patients are less likely to be informed about better RRT options. African American patients are 47% less likely to use peritoneal dialysis and 3.5 times less likely to have a kidney transplant [4]. Often, African American patients are less likely to receive information from their provider about their CKD stage, treatment options, and self-care to prevent and treat CKD [3]. The hospital can be an important intervention site because hospitalization rate rises sharply in the 3 months before dialysis initiation. In addition, even patients who are not connected to primary or specialty care can present to the hospital.

Our previous work to was to develop and test a hospital-based CKD intervention, PREP RRT (Patient Referral and Education Program Prior to Renal Replacement Therapy). To develop the intervention, we interviewed African American patients about CKD knowledge and barriers to RRT preparation [4,5]. The intervention in that study includes an in-person African American health educator and written materials [2]. Our results showed an increase in knowledge in the intervention group compared to control group. We also found that culturally tailored interventions improved patient outcomes [6]. Drawing from insights gained in our prior work, our research team developed and implemented the Interactive Computer-Adaptive Chronic Kidney Disease (I-C-CKD) education as a patient education intervention to inform hospitalized African American patients with advanced CKD about their CKD and RRT options. This computer-based education is predicted be more accessible for hospitalized patients through videos that are culturally tailored with a virtual African American narrator, as in-person educators have some limitations.

Primary Hypothesis

Our primary hypothesis is that the computerized adaptive education will be more effective than usual hospital care in improving knowledge about CKD, CKD self-care, and RRT options (primary outcome).

Secondary Hypothesis

Our secondary hypothesis is that the computerized adaptive education will increase patients' intent to participate in CKD self-care compared to usual hospital care. We also believe that the computerized adaptive education will increase patients' action and commitment to CKD health-seeking behavior, access planning prior to dialysis initiation, initiate home dialysis modalities, and/or have a transplant evaluation after discharge and beyond 30-day follow-up.

Methods

Trial Design

The I-C-CKD study is a hospital-based, randomized controlled trial of a computerized patient education intervention compared to usual hospital care. After obtaining verbal consent (Multimedia Appendix 1), each patient will be randomly assigned into two groups: usual hospital care (control group) and the computerized adaptive education (intervention group), which is assisted by a research assistant (RA).

The usual hospital care control group will feature a baseline General Health Knowledge and Intent survey. Participants in the usual hospital care control group will receive the pretest survey and education materials but will not receive specific knowledge about CKD or their CKD condition. Participants in the control group will receive printed patient education materials informing them of the importance of a general healthy lifestyle, including diet, physical activity, and medication adherence. The printed materials for the usual hospital care control group are meant for patients with cardiovascular conditions and do not have any information about CKD. Participants who receive the control condition will also be able to speak with the patient educator if they want to.

The computerized adaptive education intervention group will receive the advanced CKD education module with information on the risk factors, stages, treatment options, and lifestyle of patients with CKD (see Figures 1 and 2). The RAs will assist with the program but not offer any information or knowledge about CKD. Following the patient's review of the advanced CKD education module, the RAs will administer the posttest General Health Knowledge and Intent survey.

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Figure 1. Screenshot of the computerized adaptive education intervention featuring a personal story.

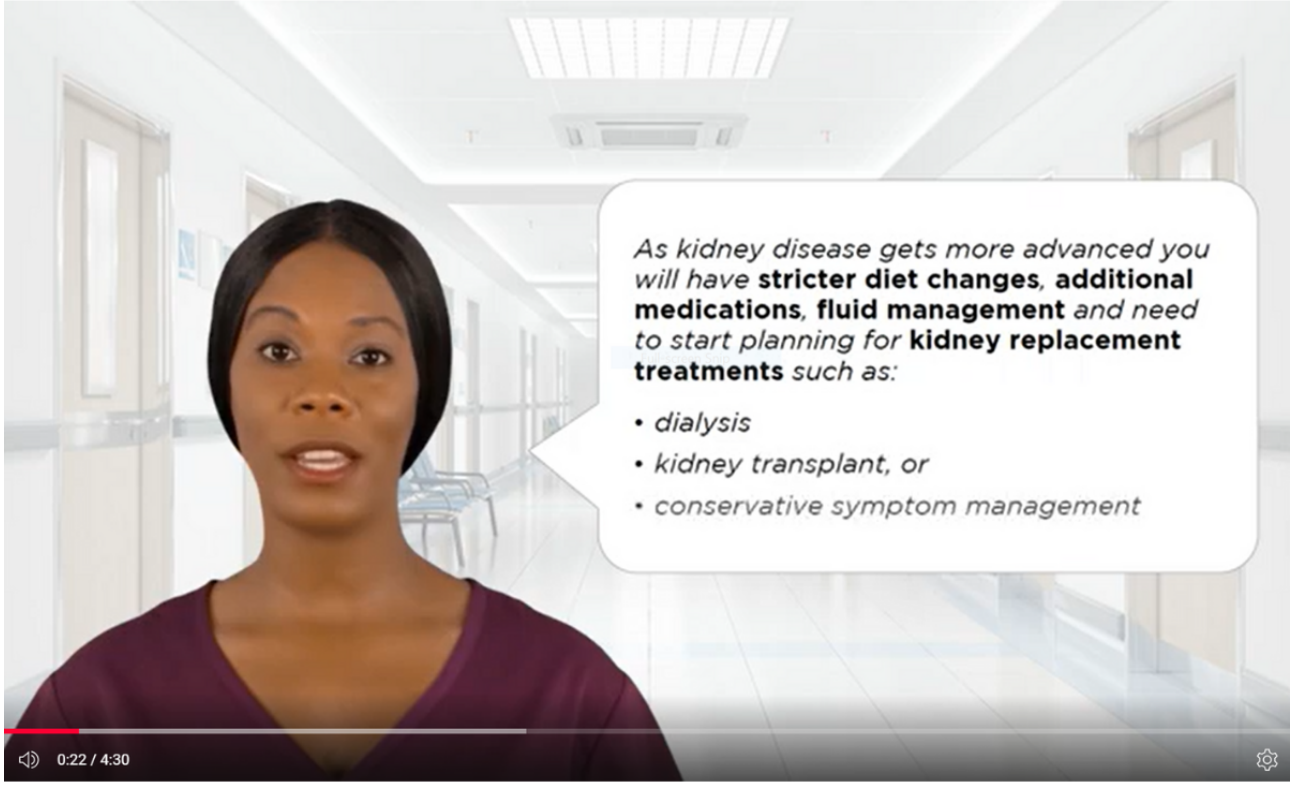

Figure 2. Screenshot of the computerized adaptive education intervention regarding treatment options. CKD: chronic kidney disease.

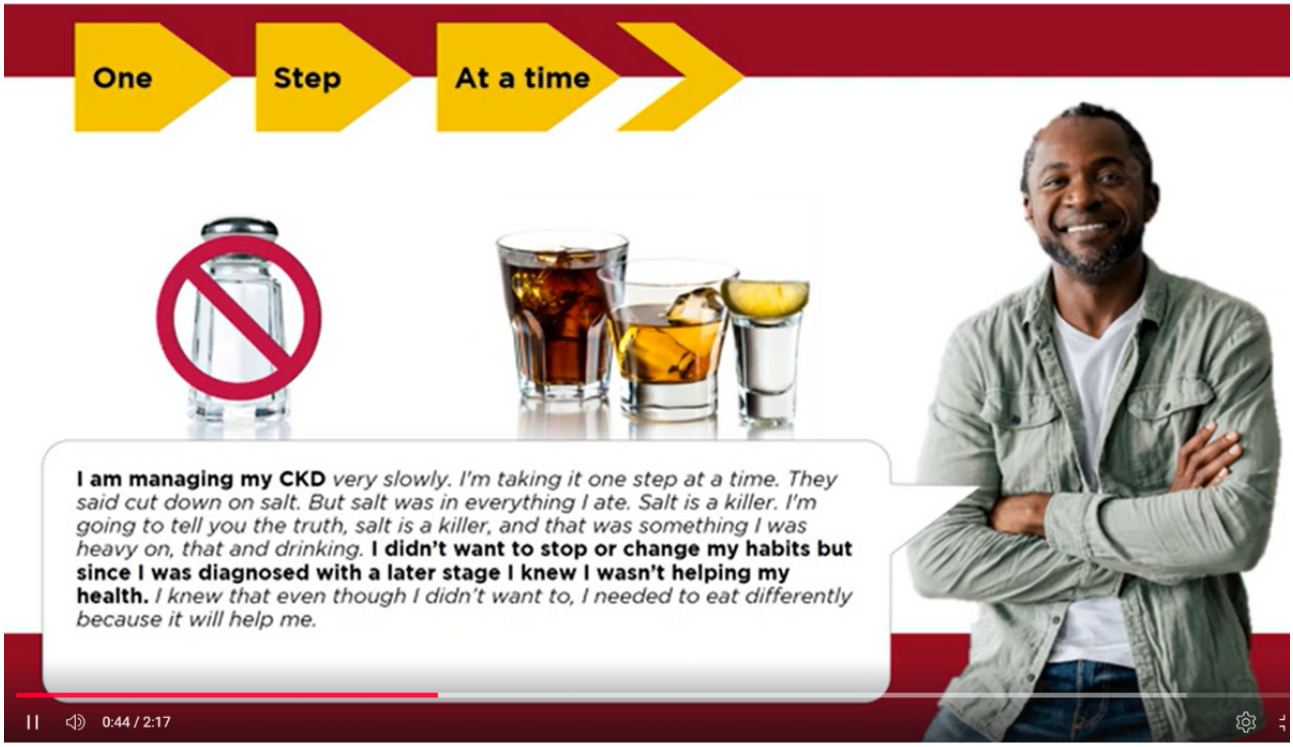

Both the usual hospital care control group and the computerized adaptive education intervention group will complete the "What's Next" form, to assess the patient's commitment to specific self-care activities. Patients will select their top-3 health goals, rate how confident they are about each goal, and identify how important each goal is to them. Patients will also report on their health resources. All the forms will be sent to the patient educator, a trained nephrology social worker.

Each patient will be contacted 30 days after discharge to ask about their commitment to health goals, barriers to self-care, and treatment plans.

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The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist is provided in Multimedia Appendix 2.

Participants and Eligibility

The study will take place at the University of Chicago Medical Center (UCMC). We will approach hospitalized, English-speaking, African American patients at UCMC, aged 18-70 years, who meet the criteria for advanced CKD (Stage 3b or greater) with an estimated glomerular filtration rate (eGFR) <45 mL/min/1.73 m^2; they must not be on dialysis yet or have a history of kidney transplant. In order to be eligible, patients must have an eGFR <45 mL/min/1.73 m^2 during the current hospitalization in addition to prior hospitalizations and/or outpatient visits. We will have access to prior UCMC inpatient and outpatient laboratory values. We will also have access to some inpatient and outpatient laboratory values from other medical centers through Epic Care Everywhere. The exclusion criteria include patients who are hospitalized in the intensive care unit, meet the Montreal Cognitive Assessment criterion for cognitive impairment, or require a proxy for study consent. We will enroll 170 participants and randomly assign 85 to the computerized adaptive education and 85 to usual hospital care.

Recruitment

This study will be a substudy of the Hospitalist Project, an ongoing clinical study that examines a variety of outcomes of patients hospitalized in our general internal medicine services, and includes the analysis of administrative data, inpatient interviews, and 30-day follow-up by phone [7]. Hospitalist Project staff will obtain basic demographic information and medical history. Per the Hospitalist Project protocol, staff will also obtain permission to contact patients after discharge and to access their medical records (ie, at UCMC, from other medical systems, and through Medicare linkage). All inpatients recruited to the Hospitalist Project will be screened daily by the RA to identify patient eligibility for the study.

We will approach all Hospitalist Project–enrolled patients who meet study criteria and obtain informed verbal consent.

Randomization

Participants will be randomly assigned using a computerized spreadsheet, assigning each participant a random number. Participants who are assigned an odd number will be assigned to the intervention group. Participants who are assigned an even number will be assigned to the control group. The RA will begin by identifying an eligible participant who consented to the Hospitalist Project. Then, they will use the randomization spreadsheet to determine if the participant will be part of the intervention group or the control group. They will then approach the patient with the appropriate form and study packet.

The RA will complete the randomization, assignment, and enrollment process.

Blinding

Trial participants will be blinded after group assignment. Participants will view the survey as a Google Form and will not be informed whether they are part of the intervention or control group. They will also receive a study packet, which will not identify if they are part of the intervention or control group. The research team will not be blinded.

Intervention Group

The RA will meet each participant and conduct the pretest survey in the participant's private hospital room. The computerized adaptive education intervention group will receive an advanced CKD education module with information about CKD risk factors, stages, treatment options, and lifestyle modifications. The RA will assist in advancing program modules but not offer any information or knowledge about CKD. The avatar will be an African American woman who will present statistics about African American individuals and CKD. The interactive component will allow participants to personalize the information received based on prior CKD knowledge, diabetes status, and the level of motivation. The interactive CKD video can be completed in 30-45 minutes. Following the patient's completion of the advanced CKD education module, the RA will then readminister the General Health Knowledge and Intent survey.

The computerized adaptive education intervention group (and the usual health care control group) will complete the "What's Next" form, to assess the patient's commitment to specific self-care activities. Patients will select 3 health goals from a list of 10 options, rate their level of confidence in the ability to make change, and identify an action plan to accomplish each goal. Moreover, patients will be asked to report their needs from the medical care team and for community assistance, and they will be provided a resource list. The study will also ask if patients would like a primary care doctor and/or a nephrologist. This information will be relayed to the primary inpatient team. All the forms will be sent to the patient educator, a trained nephrology social worker.

We will encourage participants to complete the voluntary study in one visit. At 30 days after discharge, both groups will complete a follow-up call with the project RA. Participants will be queried about progress on goals set on the health commitment form, knowledge, and health intent.

Control Group

The RA will meet each patient and conduct the pretest survey in the participant's private hospital room. The usual hospital care control group will receive the General Health Knowledge and Intent pretest survey and printed education materials without explicit CKD information or knowledge about their CKD condition. The distributed education materials were intended for patients with cardiovascular conditions and focus on the importance of a general healthy lifestyle, including diet, physical activity, and medication adherence, and does not include CKD specific information. Following the patient's completion of the general health education video module, the RA will then readminister the General Health Knowledge and Intent survey.

The usual hospital care control group (and the computerized adaptive education intervention group) will complete the "What's Next" form, to assess the patient's commitment to 3 participant-selected self-care activities. Participants also will

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be contacted 30 days after discharge to complete the follow-up survey.

Outcomes

Primary Outcome

The primary outcome of this study is the changes in patient knowledge, attitudes, and behavior about CKD and RRT. To evaluate CKD and CKD self-care knowledge, we will use a modified Kidney Knowledge Survey; the CKD Self-Management Knowledge Toolkit, which is a validated instrument [8,9]; and an investigator-developed ESKD knowledge survey. We will measure the change from the baseline observed via the pretest, posttest, and follow-up surveys. The pretest and posttest surveys comprise 20 mixed format multiple-choice and Likert-scale questions (ranging from strongly agree to strongly disagree; from no knowledge to a great deal of knowledge; and from extremely unlikely to extremely likely) to examine the patient's basic understanding of their health, general CKD knowledge, and health management.

Secondary Outcomes

The secondary outcomes are patient motivation and intent. We will administer the CKD Self-Efficacy Scale [10], the Patient Activation Measure [11], and the Kidney Failure Treatment Preferences [12] before the intervention, immediately after the intervention, and at 30 days after discharge. We will administer the General Health Knowledge and Intent survey, an investigator-developed instrument, to assess RRT preferences and commitment to CKD self-care activities, including intent to seek a nephrologist, noncatheter dialysis access initiation, and completion of a transplant evaluation. Each patient will be contacted 30 days after discharge to discuss their commitment to each selected health goals, barriers, and treatment plan.

Data Collection and Management

We will retrieve baseline survey information from the Hospitalist Project, which includes patient demographics and comorbidities. The initial trial data will be collected, stored, and saved in Google Forms with linked Google Sheets for the pretest and posttest surveys on the computer. The RA will photograph and save participants' written packet responses digitally. The RA will deidentify the packet responses and save them according to their initials, study visit date, and enrollment number. We will ensure participant responses remain confidential. Information about the patient's medical status, enrollment, and participation will be maintained through a password-encrypted file.

The RA will use password-encrypted laptops to conduct the study. The participant's responses on the study packet will be photographed, deidentified, and saved in a password-encrypted digital folder. The analysis file will not be attached to protected health information to protect patient privacy. We will conduct analysis in a locked office with a password-protected computer. All transcripts and surveys will be deidentified.

Statistical Methods

The planned total sample size is 170 (85 per group), which accounts for participant dropout due to unexpected discharges, changes in clinical status, or study disenrollment. The primary outcome will be measured by the change in baseline observed via the pretest, posttest, and follow-up surveys. Using a 2-sample, 2-tailed *t* test, a total of 154 (77 per group) participants is required to obtain >90% power to detect at least a 10% difference with the most conservative SD of 21% with a 1-sided type-1 error of 5%.

Our team will use the paired, 2-tailed *t* test with a Bonferroni adjustment for multiple comparisons with the usual hospital care and computerized adaptive education groups. We will use one-way ANOVA and chi-square tests to examine the significance between the usual hospital care and computerized adaptive education groups. This will determine whether there is a statistically significant difference between the two groups. We will also determine if the difference between observed and expected data is because of chance or a relationship between the usual health care and computerized adaptive education groups.

Data analysis will take place in an UCMC office. We will continue to monitor patient medical records after the study to determine whether they may be later included or excluded from the study.

Data Tracking

Data will be tracked in Google Sheets, linked to each survey. This will also help identify participant's responses with the date, time, and enrollment number. Study packet responses will be saved in a password-protected box. Retrospective review will also be done to ensure each enrollment number matches the correct medical record number. Our research team will have access to the final trial dataset, and we will keep the data for 5 years after the study is completed.

Ethical Considerations

We obtained institutional review board (IRB) approval for this protocol (IRB 23-0385), and the parent study (the Hospitalist Project) is also IRB approved (IBR 16-1131). Written, informed consent to participate in the Hospitalist Project will be obtained from all participants. Participants will also verbally consent and be enrolled in the I-C-CKD study.

Patients will be informed that the study is completely voluntary and may withdraw at any time. Discontinuation will also occur if patients are in acute distress or experience declining health conditions during hospitalization. For example, if the patient is transferred to intensive care unit, is intubated, or has an altered mental status and can no longer participate, then we will withdraw them from the study. Patients will also be able to meet with patient educator who is a licensed clinical social worker if they are interested in additional information, are under distress, or want posttrial care.

Patients will receive US $25 gift cards upon completion of the pretest and posttest surveys and US $10 for partially completed surveys. All participants will be compensated. This study is minimal risk, as an education intervention is the only experimental procedure involved. Additionally, reports will be made to the IRB in the case of an adverse event, along with any

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protocol modifications to the investigators, IRB, trial participants, journals, and regulators.

Results

Recruitment for the I-C-CKD study began May 2, 2023. We are currently recruiting and have enrolled 96 patients who completed both pretest and posttest surveys as of December 2024. This includes 50 patients in the control group and 46 patients in the intervention group. Data analysis has not occurred. We will communicate trial results to trial participants, health care professionals, and the public via a journal publication.

Discussion

We believe our study will result in the computerized adaptive education intervention group experiencing a greater improvement in CKD knowledge, CKD health-seeking behavior, and self-care in comparison to the control group. The goal of this study is to increase hospitalized African American patients' knowledge of CKD and motivation for CKD self-care. We have created and will assess a culturally tailored, computerized adaptive education intervention that expands on the information gathered from in-person interventions. Computerized adaptive education can evaluate patients' concerns and provide personalized education. Customized patient education information is more likely to be recalled and significantly influence a patient's motivation and behavior modification.

African American patients diagnosed with CKD experience inequities in the quality of health education, self-care, and medical treatment for ESKD [13]. Patient education can encourage African American patients with advanced-stage CKD to make informed decisions and take control of self-care and health decisions to delay progression to ESKD. Providing CKD education during hospitalization can address gaps in care to help patients initiate preventative care, plan for future RRT, and build a treatment team that aligns with their health and lifestyle preferences.

This intervention focuses on hospitalized African American patients who represent more than 80% of the general medicine population at our medical center. The intervention is culturally tailored to African American patients. The hospital also serves patients who are not followed by routine medical providers and have trouble accessing outpatient care due to limited transportation, limited or no insurance, mobility issues, and socioeconomic constraints [14]. Hospitalized patients may be more open and responsive to CKD education efforts when they are focused on their health during a hospital stay. The intervention can also link these patients to outpatient care. We will also ask if patients would like a primary care doctor and/or a nephrologist. This information will be relayed to the primary inpatient team.

Limitations of this study include the single-hospital study design, which reduces the generalizability of the results. In addition, we are testing the intervention only among hospitalized African American patients who are generally admitted with urgent or acute health concerns, which may reduce their ability to fully participate or complete this study. An additional barrier for inpatient kidney education to be disseminated on a large scale is that the results may differ among a different group or in a different health care setting.

In conclusion, African American individuals often receive less patient education about self-care and medical treatments for CKD. We hope our study provides one way to reduce this disparity. However, to improve CKD outcomes, African American patients—and all patients with CKD—require frequent, understandable education about CKD across all sites of care.

Acknowledgments

The authors appreciate the faculty and staff of the Hospitalist Project, particularly Ms Neha Khadka, who made this study possible. The study was funded by the National Institutes of Health's National Institute of Diabetes and Digestive and Kidney (R21DK121262). The project is sponsored by the University of Chicago Medical Center's General Internal Medicine department. This research did not receive any specific grant from funding agencies in the commercial or not-for-profit sectors.

Data Availability

The datasets generated or analyzed during this study are not publicly available as data analysis has not occurred at this time but are available from the corresponding author on reasonable request.

Authors' Contributions

MS is the primary investigator. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Institutional review board–approved consent form.
[PDF File (Adobe PDF File), 81 KB - resprot_v14i1e66846_app1.pdf]

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Multimedia Appendix 2
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 122 KB - resprot_v14i1e66846_app2.pdf]

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Abbreviations

CKD: chronic kidney disease
eGFR: estimated glomerular filtration rate
ESKD: end-stage kidney disease
I-C-CKD: Interactive Computer-Adaptive Chronic Kidney Disease
IHD: in-center hemodialysis
IRB: institutional review board
PREP RRT: Patient Referral and Education Program Prior to Renal Replacement Therapy
RA: research assistant
RRT: renal replacement therapy
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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UCMC: University of Chicago Medical Center

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Protocol

The Comprehensive Adaptive Multisite Prevention of University Student Suicide Trial: Protocol for a Randomized Controlled Trial

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Abstract

Background: Suicidal ideation is increasing among university students. Despite growing demand for services, university counseling centers (UCCs) face limited resources to meet the complex needs of students who are suicidal.

Objective: The Comprehensive Adaptive Multisite Prevention of University Student Suicide (CAMPUS) Trial evaluates 4 treatment sequences within UCCs to develop evidence-based treatment guidelines.

Methods: The CAMPUS Trial consists of a feasibility study followed by a sequential multiple-assignment randomized trial (SMART). The original CAMPUS protocol was modified during the COVID-19 pandemic to accommodate new UCC tele–mental health services, including remote treatment, assessments, and monitoring. A smaller-scale feasibility study was conducted to (1) evaluate implementation of hybrid telehealth and in-person interventions and (2) fine-tune online procedures. Following the feasibility study, university students (aged 18-25 years) seeking UCC services with moderate to severe suicidal ideation will enroll in the CAMPUS Trial. Student participants are randomly assigned to 1 of 4 treatment sequences with 2 stages of intervention. In stage 1, students receive 4 to 6 weeks of either (1) a suicide-focused treatment—Collaborative Assessment and Management of Suicidality—or (2) enhanced treatment as usual. Treatment responders enter the maintenance phase. In stage 2, nonresponders are rerandomized for an additional 1 to 8 weeks of (1) Collaborative Assessment and Management of Suicidality or (2) an intensive skills-based treatment—dialectical behavior therapy for UCC settings. UCC counselors will enroll in the CAMPUS Trial to complete measures about their experience working with students who are suicidal. CAMPUS Trial administration includes representation from all sites to facilitate cross-site coordination and an advisory board of stakeholders from all UCCs to facilitate treatment implementation.

Results: Student participant recruitment began on October 25, 2022, and ended on May 16, 2024. As of November 2024, data collection for the SMART was ongoing with active study participants. Data collection was completed in November 2024, and as of April 2025, data analysis is underway. Full results will be available in 2025.

Conclusions: The CAMPUS Trial offers a model for future SMARTs for the treatment of suicidal thoughts or behaviors (or both) across various settings. The results will inform treatment guidelines for students presenting with suicidality at UCCs.

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Trial Registration: ClinicalTrials.gov NCT04707066; http://clinicaltrials.gov/ct2/show/NCT04707066
International Registered Report Identifier (IRRID): DERR1-10.2196/68441

(JMIR Res Protoc 2025;14:e68441) doi:10.2196/68441

KEYWORDS
suicide; adaptive treatment strategies; Collaborative Assessment and Management of Suicidality; CAMS; dialectical behavior therapy; DBT; university students

Introduction

Background

Among university students, suicide is the second leading cause of death [1]; 6% of university students report suicide attempts (SAs) in their lifetime, and 2.4% report attempting suicide in the last year alone [2,3]. Suicidal ideation (SI) is even more frequent. Approximately 1 in 4 students report a history of SI, including 14% in the last year [4,5]. These numbers are climbing among university students—paralleling an increase in suicide rates among individuals aged 10 to 24 years from 2007 to 2021 [6]. University counseling centers (UCCs) are the front line for mental health services for a growing number of students experiencing SI [7,8]. However, UCCs face limited resources, higher demand for services, and increasingly complex cases [9,10], with more than half reporting that waitlists develop within a few weeks of a new academic year and last throughout the term [11].

Managing students presenting with SI in UCCs can be challenging due to heterogeneity in presentations. Some university students struggling with SI respond rapidly to treatment, whereas others require considerably more time and resources [12]. Despite aspiring to provide brief therapy (5-6 sessions) [7], UCCs often provide ≥20 sessions to a segment of their student population [13]. In fact, 20% of students have been shown to use 50% of counseling resources [13], with highly distressed students needing more resources [12]. Suicidal thoughts or behaviors (STB; or both) are likely a key driver of this pattern of use as SI has become a primary presentation at UCCs [14], with over one-third of treatment-seeking students reporting serious SI in the last year [13]. Students with persistent SI place a significant strain on UCC resources and use 20% to 30% more services than other students [15]. Use of UCC resources devoted to *rapid access* services, which guarantee an appointment within 1 to 5 days for students in crisis, has increased by 28% [16]. Despite this need, there is currently no *gold standard* approach for treating students with SI in UCCs. Due to the varying levels of severity and treatment needs among university students struggling with STB, UCCs would benefit from evidence-based guidelines to inform clinical decision-making.

The Comprehensive Adaptive Multisite Prevention of University Student Suicide (CAMPUS) Trial is a National Institute of Mental Health (NIMH)–funded multisite sequential multiple-assignment randomized trial (SMART). The aim of this study is to evaluate the relative effectiveness of 4 adaptive treatment strategies (ATSs) for university students who report SI when seeking services for a new course of care at a UCC. The CAMPUS Trial ATSs follow a stepped-care model of treatment delivery, with those not responding to an initial course of brief therapeutic care being offered additional treatment of longer duration or greater intensity. The implementation of these ATSs will be monitored to better understand the acceptability, appropriateness, feasibility, fidelity, and costs related to suicide-focused treatment within UCCs. This hybrid effectiveness-implementation approach combines components of clinical effectiveness and implementation research, facilitating the future translation of empirically validated treatments within the UCC context.

Rationale for Study Design

What Is a SMART?

A SMART is a type of factorial design used to develop and optimize adaptive interventions by studying treatments in a sequential manner [17-19]. In a SMART, participants can receive multiple interventions over time depending on their response to previous treatments and may be randomized more than once. For example, if a participant does not sufficiently respond to an initial course of care that they were initially randomized to receive, they might be rerandomized to one of several second-line treatments. The number of stages and the specific treatments received by a participant depend on their response at each stage, guided by one or more tailoring variables that informs clinical decision-making. The ultimate goal of SMARTs is to develop empirically supported clinical guidelines for providing treatment and modifying the course of care based on an individual's baseline characteristics and other time-varying outcomes, such as treatment response and compliance [17-19]. ATSs are vital for personalizing the provision of care to improve outcomes and ensure that interventions are responsive to the changing needs of individuals.

Rationale for the Use of a SMART Design to Treat STB Within UCCs

ATSs are recommended in situations in which (1) patients vary in their response to treatment, (2) the effectiveness of an intervention changes over time due to fluctuating symptoms, (3) comorbidities make treatment more complex, or (4) there is a high probability of relapse [18]. All of these conditions apply when treating suicidal university students. UCCs will likely benefit from data on how to tailor treatments to individual students to better manage their finite resources and optimize outcomes. A similar pilot SMART was previously conducted and served as the foundation for this study [20]. However, that pilot study had several limitations: it had a small sample size; was conducted at a single UCC; relied solely on in-person assessments and treatments; and evaluated ATSs of considerably longer duration (up to 24 weeks), which was not conducive to

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wide dissemination and adoption across various UCC contexts. The CAMPUS Trial design addressed these shortcomings.

Overview of the ATSs Evaluated in the CAMPUS Trial

The goal of the CAMPUS Trial is to evaluate sequences of treatments for use in UCCs to treat a wide range of university students presenting with STB. It follows a stepped-care model that begins with shorter and less resource-intensive treatments [21,22] and continues with more intensive treatments for students who do not respond sufficiently to the initial course of care. To improve dissemination of the ATSs, the duration of each treatment stage is kept brief to match the practices of UCCs (5-6 sessions on average) [13]. The schedule of enrollment, interventions, and assessments can be found in Table 1.

The CAMPUS Trial aims to identify sequences of care across 2 stages of treatment, with clear decision points for optimal outcomes. Stage 1 evaluates whether starting with a suicide-focused treatment (ie, Collaborative Assessment and Management of Suicidality [CAMS]) is superior to traditional, non–suicide-focused psychotherapies commonly provided in UCCs (ie, enhanced treatment as usual [E-TAU]). Stage 2 assesses whether switching to a more intensive skills-based treatment (ie, counseling center dialectical behavior therapy [CC-DBT]) is superior to continuing CAMS among insufficient responders to stage 1 CAMS and whether CC-DBT is superior to CAMS among insufficient responders to stage 1 E-TAU. Both CAMS and dialectical behavior therapy (DBT) have been shown to reduce SI, suicidal behavior, or both in university students [20,23] and have already been adopted in some UCCs [14,24]. The ATSs evaluated in the CAMPUS Trial align closely with the Zero Suicide policy initiative [25,26] recommendations to (1) target STB instead of mental disorders; (2) train counselors to deal directly with STB; and (3) base clinical care on risk stratification and evidence-based, suicide-specific interventions.

The four ATSs to be evaluated in the CAMPUS Trial are as follows:

1. ATS 1: start with 4 to 6 sessions of CAMS. If responding, enter maintenance phase; if not, continue with 1 to 8 sessions of CAMS.
2. ATS 2: start with 4 to 6 sessions of CAMS. If responding, enter maintenance phase; if not, switch to 1 to 8 sessions of CC-DBT.
3. ATS 3: start with 4 to 6 sessions of E-TAU. If responding, enter maintenance phase; if not, switch to 1 to 8 sessions of CAMS.
4. ATS 4: start with 4 to 6 sessions of E-TAU. If responding, enter maintenance phase; if not, switch to 1 to 8 sessions of CC-DBT.

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Table 1. Assessment battery and schedule of activities for the Comprehensive Adaptive Multisite Prevention of University Student Suicide Trial.

	Screening: week −1	Baseline: week 0	Stage 1						Stage 2								Follow-up: week 26
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	
UCC[a] intake counselor																	
Screening data form[b]	✓																
Student participants																	
Demographic information		✓															
Sexual orientation and gender identity		✓															
CCAPS[c]	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
CGI-S[d]		✓			✓			✓				✓				✓	✓
CGI-I[e]					✓			✓				✓				✓	✓
AEs[f] and SAEs[g]		✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
DERS[h]		✓						✓				✓				✓	✓
DBT-WCCL[i]		✓						✓				✓				✓	✓
AAQ[j]		✓						✓				✓				✓	✓
SCS[k]		✓			✓			✓				✓				✓	✓
Self-efficacy for managing emotions		✓			✓			✓				✓				✓	✓
OHS[l]		✓			✓			✓				✓				✓	✓
PAI-BOR[m]		✓															
LSC-R[n]		✓															✓
DAST[o]		✓														✓	✓
AUDIT[p]		✓														✓	✓
STCQ[q]			✓						✓								
STEQ[r]			✓						✓								
CSQ[s]								✓								✓	
Academic functioning		✓														✓	✓
Independent evaluators[t]																	
UWRAP[u]		✓			✓			✓				✓				✓	✓
CGI-S[v]		✓	✓		✓			✓				✓				✓	✓
CGI-I[v]					✓			✓				✓				✓	✓
SSI[w]		✓			✓			✓				✓				✓	✓
SITBI[x]		✓						✓				✓				✓	✓
GAS[y]		✓			✓			✓				✓				✓	✓
THI[z]		✓														✓	✓
Research staff																	
Informed consent		✓															
Inclusion and exclusion checklist		✓															

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	Screening: week −1	Baseline: week 0	Stage 1						Stage 2								Follow-up: week 26
			1	2	3	4	5	6	7	8	9	10	11	12	13	14	
CAMS[aa] rating scale–3[ab]																	
DBT[ac] adherence rating scale[ab]																	
Counselor participants																	
Reveal randomization			✓						✓								
DIF[ad,ae]		✓															
Treatment compliance item[b]			✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	
ZSWS[af,ag]	✓																
Exit interview[ah]																	

[a]UCC: university counseling center.

[b]These measures are exclusively collected in the Titanium electronic medical record and exported at regular intervals throughout the study period.

[c]CCAPS: Counseling Center Assessment of Psychological Symptoms.

[d]CGI-S: Clinical Global Impressions–Severity.

[e]CGI-I: Clinical Global Impressions–Improvement.

[f]AE: adverse event.

[g]SAE: serious adverse event.

[h]DERS: Difficulties in Emotion Regulation Scale.

[i]DBT-WCCL: Dialectical Behavior Therapy Ways of Coping Checklist.

[j]AAQ: Acceptance and Action Questionnaire.

[k]SCS: Suicide Cognitions Scale.

[l]OHS: Optimism Hope Scale.

[m]PAI-BOR: Personality Assessment Inventory–Borderline Features Scale.

[n]LSC-R: Life Stressor Checklist–Revised.

[o]DAST: Drug Abuse Screening Test.

[p]AUDIT: Alcohol Use Disorders Identification Test.

[q]STCQ: Student Treatment Credibility Questionnaire.

[r]STEQ: Student Treatment Expectations Questionnaire.

[s]CSQ: Client Satisfaction Questionnaire.

[t]For all assessments collected as part of an independent evaluator (IE) visit (ie, those assessments not collected specifically at treatment visits), there will be a window of −1 week to +1 week around the scheduled assessment date for the purposes of data collection. IE assessments conducted outside this window will still be collected, and values will be imputed based on when the assessment should have occurred.

[u]UWRAP: University of Washington Risk Assessment Protocol.

[v]These assessments were completed following the students' last treatment session, which may be earlier than week 6 (for stage 1) or week 14 (for stage 2). The CGI-I and CGI-S were collected at the last treatment sessions at both stage 1 and 2 and at weeks 6 and 14.

[w]SSI: Scale for Suicidal Ideation.

[x]SITBI: Self-Injurious Thoughts and Behaviors Interview.

[y]GAS: Global Assessment Scale.

[z]THI: Treatment History Interview.

[aa]CAMS: Collaborative Assessment and Management of Suicidality.

[ab]Research staff will complete this measure on a random sample of therapy sessions.

[ac]DBT: dialectical behavior therapy.

[ad]DIF: demographic information form.

[ae]Counselor participants will complete this measure once when they enter the study.

[af]ZSWS: Zero Suicide Workforce Survey.

[ag]This measure was also collected at the 6-, 12-, 18-, and 24-month counselor follow-up assessments.

[ah]Counselor participants will complete this interview at the end of their participation in the study.

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Timeline, Adaptations, and Changes in Design Due to the COVID-19 Pandemic

The CAMPUS Trial was originally scheduled to begin enrollment in May 2020, with all procedures developed for in-person implementation. However, the COVID-19 pandemic necessitated significant changes to the way UCCs provided mental health treatment. Consequently, the CAMPUS Trial procedures and protocols were modified to fit a hybrid tele–mental health (TMH) and in-person format. Training of counselors and assessors occurs online via live Zoom (Zoom Video Communications) sessions. Study treatments and safety monitoring of students are offered both in person and via TMH. Decisions about the type of sessions to hold are made by the counselor based on several factors, including university and UCC policies and location or preference of the student and counselor. Data on treatment modality are collected via electronic medical records.

The results of the CAMPUS feasibility trial showed that a hybrid model, with most sessions being TMH, is feasible, acceptable, and safe when treating college students for suicide risk [27]. Overall, a hybrid model has the greatest future dissemination and implementation potential across UCCs, where the expectation is that treatment delivery will continue to vary within and across settings and will likely retain some combination of in-person and TMH options. After the completion of the feasibility trial, the originally proposed SMART was launched.

Overview of Study Aims

The Primary Aims of the CAMPUS Trial

Aim 1 is to compare the relative effectiveness of the 4 ATSs in reducing university student STB (or both; primary outcomes) and includes the following secondary outcomes: changes in overall distress, depression, anxiety, substance use, eating concerns, academic functioning, health care use, and self-reported ratings of STB.

Aim 2 is to determine whether ATSs beginning with an explicitly suicide-focused intervention (ie, CAMS) produce greater reductions in STB than those beginning with traditional, non–suicide-focused psychotherapies often provided in UCCs (ie, E-TAU).

Aim 3 is to determine whether ATSs providing a comprehensive skills-based, suicide-focused intervention (ie, CC-DBT) to insufficient responders to stage 1 treatments are more effective in reducing STB than a less intensive suicide-focused approach (ie, CAMS).

The Secondary Aims of the CAMPUS Trial

Aim 4 is to evaluate treatment-specific mediators of change, including changes in suicide-focused processes, emotion regulation, and self-efficacy.

Aim 5 is to evaluate nonspecific predictors and moderators of treatment response, including number of lifetime SAs [28], features of borderline personality disorder (BPD) [29], baseline distress [30], sexual orientation and gender minority self-identification [31,32], and comorbid substance use [33].

The Exploratory Aims of the CAMPUS Trial

Aim 6 is to assess the implementation outcomes outlined by Proctor et al [34] using the Quality Implementation Framework [35].

Aim 7 is to explore counselor experiences working with university students presenting with SI.

Aim 8 is to determine whether CAMS is associated with greater reductions in STB than E-TAU within stage 1 and whether CC-DBT is associated with greater reductions in STB than continued CAMS within stage 2.

Methods

Participants

In total, 2 study populations will participate in the CAMPUS Trial: university students and UCC counselors. A target sample size of 480 university students seeking treatment at their counseling center will participate in the CAMPUS Trial from 4 universities: Duke University; Rutgers University–Newark; University of Nevada, Reno; and University of Oregon. To participate in the study, students must (1) be officially enrolled at the university; (2) be eligible to receive counseling services; (3) be seeking treatment services at their counseling center; (4) have not received treatment services at their counseling center within the previous 3 months; (5) be aged between 18 and 25 years; (6) endorse moderate to severe SI on the Counseling Center Assessment of Psychological Symptoms [36], other similar standard questionnaires, or via self-report to the clinician during intake; (7) present with SI considered severe enough to be a focus of treatment as determined by the intake counselor; and (8) agree to video or audio recording of all therapy and assessment sessions. A target sample size of 20 counselors will be recruited for participation across sites. Inclusion criteria for counselor participants are (1) current employment as a counselor or trainee at the counseling center; (2) agreement to participate for at least 1 year; (3) endorsement of a willingness to work with suicidal college students, attend all CAMS and CC-DBT trainings, and participate in weekly consultation groups; and (4) completion of measures about themselves and the students they treat as part of the study.

Student participants will be recruited through standard intake procedures at each UCC site from August and September 2022 to April and May 2024. As part of these procedures, all students seeking services are assessed for SI. Students who meet study eligibility criteria are offered the opportunity to meet with a member of the research team to learn more about the study and complete the informed consent process.

Counselor participants are initially identified by the UCC directors or hired as trainees to work at the UCC and be part of the study. All interested counselors are referred to the site investigators for possible study participation and to complete the informed consent process.

Ethical Considerations

To streamline and expedite the institutional review board (IRB) review process across the multiple participating institutions and to ensure consistency in ethical review, this study uses a single

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IRB, specifically, the Duke University Health System IRB. Written informed consent is obtained for all participants and captured via the REDCap (Research Electronic Data Capture; Vanderbilt University) eConsent framework. Each site IRB and the Duke single IRB approved the consent forms and protocol before study initiation (approval: Pro00104815).

All research data will be kept in the REDCap database, which is managed by the Duke data center. REDCap data are encrypted both at rest and in transit. The Duke University Medical Center database-hosting infrastructure was audited by the Duke Information Security Office for compliance with HIPAA (Health Insurance Portability and Accountability Act) and Duke Health data security policies. With the participants' approval, deidentified data from this study will also be submitted to the NIMH Data Archive (NDA) at the National Institutes of Health (NIH) and stored indefinitely. Digital-based data will not be submitted to the NDA at the NIH. During the course of the study, an individual participant can choose to withdraw consent to have their data stored at the NIH. Student participants are reimbursed for completing each assessment based on the following rates: US $40 at baseline, US $20 at week 3, US $40 at week 6, US $20 at week 10, US $50 at week 14, and US $50 at week 26. The total reimbursement for any student who completes all assessments is US $220.

Design Overview

As illustrated in Figure 1, the CAMPUS Trial used a 2-stage SMART design. In stage 1, all student participants who consent and meet study inclusion criteria are randomized to 4 to 6 weeks of either CAMS or E-TAU. Sessions are individual and scheduled weekly. Starting at the end of session 4 (noting that all students are offered at least 4 therapy sessions), and after each subsequent session, counselors use their ratings of student improvement in STB since baseline to inform treatment decisions. Between sessions 4 and 6, students whose suicidal risk improves above a specified threshold (refer to the Tailoring Variable section) are defined as treatment responders and move into the maintenance phase of the study, which involves monthly contacts via email by research staff. Students whose suicide risk has not improved sufficiently by session 6 are classified as treatment nonresponders and rerandomized to an additional 1 to 8 weeks of 1 of 2 stage 2 treatments: CAMS or CC-DBT.

Assessments are administered by independent evaluators (IEs) blind to treatment condition at week 0 (baseline), week 3 (mid–stage 1), week 6 (end of stage 1), week 10 (mid–stage 2), week 14 (end of stage 2), and week 26 (3-month follow-up).

Figure 1. Comprehensive Adaptive Multisite Prevention of University Student Suicide Trial study design. CAMS: Collaborative Assessment and Management of Suicide; CC-DBT: counseling center dialectic behavior therapy; E-TAU: enhanced treatment as usual; NR: nonresponder to treatment; R (black): responder to treatment; R (red): randomization point.

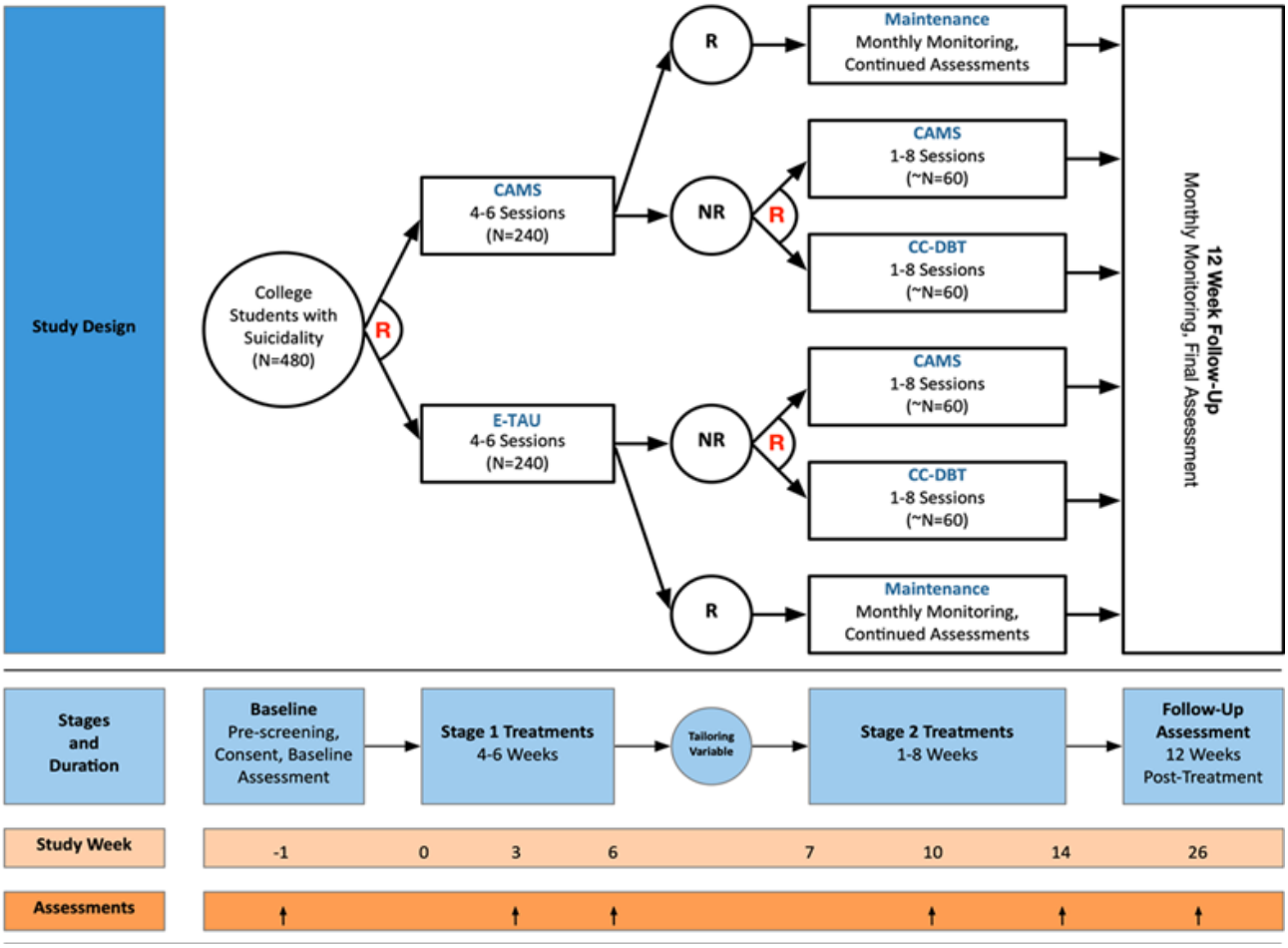

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Randomization

To maintain reasonably good balance among the 4 ATSs, student participants are randomized using a stratified block randomization procedure implemented via the REDCap randomization module [37,38]. Stratification variables used in this procedure are treatment site (Duke, Rutgers, University of Nevada, and University of Oregon), self-identified student sex at birth (male or female), history of previous SAs (yes or no), and current use of psychotropic medications (yes or no). The site principal investigator (PI) or delegate signs off on each randomization.

Sample Size and Power Estimates

Statistical power was calculated for aims 1 to 5 using a continuous outcome. Estimated effect sizes for moderation and mediation aims based on the sample size required for aim 1 are also reported. Statistical power for exploratory aims was not calculated. Power is dependent on the respective treatment comparisons of interest as well as attrition and response rates per stage. To represent the respective contrasts of interest, the ATSs embedded by design are listed in Table 2. All sample size and power estimates were calculated based on the target sample size of 480.

The primary goal of aim 1 is to identify the most effective ATS among the 4 embedded strategies (A+B, A+C, D+E, or D+F, as shown in Table 2) that leads to the greatest reduction in STB. This aim focuses on finding the best-performing ATS rather than testing a hypothesis. The sample size of 480 was found to ensure an 80% probability of correctly identifying the ATS with the lowest mean outcome, assuming that such a strategy exists. This calculation is based on the method outlined by Scott et al [39] and Oetting and Levy [40] and assumes equal marginal variance of outcomes across the ATSs, a normally distributed mean outcome, a type-I error rate of 2.5% where we adjust the standard 0.05 level by a factor of 2 for the 2 primary outcomes of STB, a standardized effect size of 0.50, and no more than 50% attrition by stage 2.

The objective of aim 2 is to examine the main effect of the stage 1 treatments—whether it is more effective to begin an ATS with a suicide-focused intervention (CAMS) or with traditional counseling (E-TAU). This comparison allows for the evaluation of the main effect of the 2 initial treatments averaged across the second-stage treatments among stage 1 nonresponders (A+B+C vs D+E+F). The test statistic for this comparison is the standard test for a 2-group comparison in large samples and is not specific to the SMART design. A 2-sided, independent-sample *t* test with a type-I error rate of 2.5% will provide 85% power to detect a small effect size (d=0.30) on the primary outcome, with a target sample of 480 participants randomized to the 2 stage 1 treatments. Assuming an SD of 7.0 on the Scale for Suicidal Ideation (SSI) [41] (based on previous studies, including pilot data), this effect size corresponds to a clinically meaningful difference of 2 points on the SSI.

The purpose of aim 3 is to evaluate the main effects of stage 2 treatments—specifically, whether CC-DBT is more effective than CAMS among those who do not respond to stage 1 treatments (B+E vs C+F). Assuming a 50% response rate to stage 1 treatments (n=240) and a 20% attrition rate, approximately 48 participants will be eligible to be randomized to each of the 4 stage 2 treatment conditions (B, C, E, and F). On the basis of the method outlined by Oetting and Levy [40], and assuming a within-person correlation of 0.60 with a type-I error rate of 2.5%, we will have 80% power to detect a small to moderate effect size (d=0.34) on the primary outcome between the CC-DBT (n=96) and CAMS (n=96) stage 2 treatments.

Best practices for power calculations in mediation and moderation models within SMART designs are still a topic of debate. For mediation, we will follow the work by Fritz and MacKinnon [42], who report sample size requirements to ensure 80% power under the sequential regression framework, and the formulas by Vittinghoff et al [43]. Assuming a medium effect size for the intervention on the mediator and the outcome (covarying the mediator) and a type-I error rate of 2.5%, a total sample size of at least 166 is required. Therefore, our design, with a total sample size of 96 in each of the 2 stage 2 treatments (or n=192), is sufficiently powered to detect medium-sized mediation effects within stage 2. For moderation, based on the power tables by Cohen, our sample size of 480 at the start of stage 1 and at least 96 participants per treatment in stage 2 are more than sufficient to detect a medium to large effect size for a moderator.

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Table 2. The 4 adaptive treatment strategies embedded in the implemented sequential multiple-assignment randomized trial.

Adaptive treatment strategy, stage 1 treatment, and status at the end of stage 1	Stage 2 treatment	Strategy denomination[a]	Cells involved in comparisons
1—CAMS[b]			A+B
Responder	Maintenance and monitoring	A	
Insufficient responder	Continue CAMS	B	
2—CAMS			A+C
Responder	Maintenance and monitoring	A	
Insufficient responder	Switch to CC-DBT[c]	C	
3—E-TAU[d]			D+E
Responder	Maintenance and monitoring	D	
Insufficient responder	Switch to CAMS	E	
4—E-TAU			D+F
Responder	Maintenance and monitoring	D	
Insufficient responder	Switch to CC-DBT	F	

[a]For simplicity, the letters A to F are used in this column to denote the corresponding stage 2 treatment listed in the previous column.

[b]CAMS: Collaborative Assessment and Management of Suicidality.

[c]CC-DBT: counseling center dialectical behavior therapy.

[d]E-TAU: enhanced treatment as usual.

CAMPUS Trial Treatments

Overview

In developing ATSs for university students struggling with thoughts of suicide, we were interested in addressing 2 specific questions that often arise when managing this population. First, should STB be the focus of care ahead of other concerns raised by the students, or should the counselor monitor STB but provide more general supportive care? This question is addressed by comparing outcomes between students who started treatment with E-TAU versus those who started with CAMS. Second, for those students who are insufficient responders to their initial course of care, should the counselor stay the course by offering more sessions, or should the counselor switch to a new treatment approach? This question is addressed by our treatment sequences, where nonresponders either continue the same treatment across stages or switch treatments. The treatment sequences also allow us to address whether it is best to use a more intensive skills-based, suicide-focused approach (CC-DBT) or a more streamlined weekly approach (CAMS) for the second line of treatment.

E-TAU Intervention

Students randomly assigned to E-TAU receive the customary individual therapy that they would receive at that UCC, which can also be supplemented with group participation or medication referral at the counselor's discretion. In E-TAU, counselors are allowed to determine the level of care and therapeutic modality depending on the needs of the participant. For clinical consultation, counselors follow their clinic's procedures (eg, consulting with the clinical director and attending case management meetings). The only stipulations provided to counselors offering E-TAU is that sessions should be weekly even if this is not the norm at their UCC, and they are required to monitor student participants' STB to rate their response to treatment. Accordingly, this treatment is designed as *enhanced* treatment as usual (TAU). Counselors conducting E-TAU treatment are asked to provide counseling as usual for a period of 4 to 6 weeks but are asked not to use CAMS (eg, suicide status forms and sitting next to the client) or CC-DBT (eg, diary card and DBT skills)–specific strategies. Counselors are informed that all their sessions are recorded and some sessions will be randomly rated on adherence to ensure that no CAMS and CC-DBT strategies are used.

CAMS Intervention

CAMS is an evidence-based, suicide-focused framework that was first developed and studied in a UCC [44]. CAMS is a problem-focused treatment that targets client-defined suicidal *drivers* or issues that lead to SI [21]. To date, 11 open clinical trials of CAMS have reliably shown significant reductions in SI and overall distress [45,46], 3 of these with university students [47-49]. Furthermore, 7 randomized controlled trials (RCTs) have found that CAMS reduced SI compared to control care as usual [50], led to reductions in overall distress while increasing hope and patient satisfaction in comparison to control care [51], performed similarly to DBT in terms of reductions in nonsuicidal self-injury (NSSI) and SAs [52], lowered risk of SA following discharge from an inpatient setting compared to TAU [53], and reduced SI and depression more than TAU in a university student population [49]. A 9-study meta-analysis showed that CAMS significantly reduced SI and overall symptom distress, increased hope and decreased hopelessness, and increased retention to care (when compared to control care) [54]. Finally, CAMS can be used effectively via telehealth [55] and has been shown to be cost-effective [56].

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UCCs need an efficient and effective stepped-care approach to treating students with STB, delivering more intensive treatments only to those who need them. CAMS is an ideal first-line intervention because it is flexible and easy to train for, and several UCCs report already using CAMS [14]. While there are other empirically based suicide-focused approaches [57,58], they either have not been tested within a UCC or require more extensive training than CAMS.

CC-DBT Intervention

DBT is an empirically validated treatment for complex clinical presentations, including BPD, SI, and NSSI. Comprehensive DBT (which includes individual therapy, skills group, between-session skills coaching, and peer consultation for counselors) has been noted to result in gains for clients across a variety of domains, including SI, BPD, SAs, NSSI, hospitalizations, and social functioning [59,60]. DBT is based on a skills deficit model that suggests that BPD is a disorder of emotion dysregulation stemming from deficits in interpersonal, emotion regulation, and distress tolerance skills. STB are viewed as maladaptive problem-solving behaviors reinforced by an immediate reduction in emotional arousal or by the environment's response [61]. Thus, DBT focuses on teaching skills from 4 domains (mindfulness, interpersonal effectiveness, emotion regulation, and distress tolerance) and facilitating the replacement of maladaptive behaviors with skillful behaviors.

Members of the CAMPUS Trial research team previously conducted the only RCT to date using comprehensive DBT for university students with STB [23]. Compared to an optimized control condition, 7 to 12 months of DBT led to significantly greater decreases in SI, depression, NSSI events, and BPD symptoms and greater improvements in social adjustment. DBT was particularly effective for students who were suicidal and were lower functioning at baseline. However, some students dropped out before the end of treatment due to improvement, suggesting that a less intensive and shorter approach might be adequate for certain students. Although there has only been 1 RCT with DBT at UCCs, open trials have also been conducted with DBT at UCCs [62,63], and more than a dozen studies have investigated the use of DBT skills groups in UCCs [24]. A recent survey concluded that approximately one-third of UCCs already use some elements of DBT [24], and a significant body of research indicates that DBT is effective for the types of clinical presentations at UCCs [64].

The CAMPUS Trial evaluates an adaptation of comprehensive DBT for UCCs (CC-DBT) as a second-stage treatment for students who were insufficient responders to CAMS or E-TAU in stage 1. Our adapted form of DBT (CC-DBT) was designed for dissemination within UCCs, with adaptations based on feedback and data on treatment adherence from the CAMPUS feasibility trial [27]. The modifications prioritized key elements of DBT (diary card self-monitoring, chain analyses, skills teaching, and generalization) to facilitate ease of use and fit a timeline more consistent with UCC practices and client preference. The skills training portion was reduced to 6 sessions teaching a core subset of the DBT skills package. CC-DBT also included weekly peer consultation meetings for the counselors that took place remotely and across sites, and depending on site policies, phone skills coaching was offered during business hours.

Maintenance Phase

Student participants who are classified as responders during either stage 1 or stage 2 enter the maintenance phase. Students are able to continue receiving UCC services during this phase but do not receive any additional CAMPUS Trial treatment. Students continue to complete regularly scheduled IE assessments and remain in the maintenance phase until the end of their study participation at 26 weeks. During this phase, the study team contacts students every 4 weeks via email to provide mental health and crisis resources. The 4-week contact schedule continues until their final assessment point. Relapses in STB during the maintenance phase can be reported during the scheduled IE assessments, in response to a 4-week contact, or by the student spontaneously contacting a member of the CAMPUS Trial clinical or research team. In these instances, students are referred to their UCC for standard care. Treatments received outside of the study are documented via the Treatment History Interview [65] and a review of the electronic medical record at the UCCs.

Assessments

Overview

The CAMPUS Trial assessment battery (summarized in Table 1) uses multiple informants to capture comprehensive information about aspects of student functioning, treatment experiences, and program implementation. The informants include (1) student participants; (2) IEs who conduct semistructured student assessments; and (3) counselor participants who provide study treatment, assess student response to treatment, and provide information about their own study experiences. Measures were adopted if they (1) had adequate psychometric characteristics, (2) were used in previous suicide treatment studies, (3) were shown to be sensitive to change, (4) had been used in previous studies with university students, (5) mapped onto the NIMH's Research Domain Criteria categories (Negative Valence Systems, Positive Valence Systems, Cognitive Systems, Social Processes, and Arousal and Regulatory Systems) [66,67], (6) were directly relevant to the application of CAMS or DBT, and (7) allowed for reduced burden to student participants. Assessment manuals for IEs and counselor participants fully specified the rationale and procedures for each of the assessment measures. All self- and IE-reported assessments are collected from student participants regardless of treatment status.

The Primary Outcome Measures

The primary outcome is reduction in STB as measured by the IEs at each assessment using 2 standardized interviews: the SSI [41] and the Self-Injurious Thoughts and Behaviors Interview (SITBI) [68]. Changes in SI are assessed using SSI total scores. Suicidal behaviors, including NSSI and SAs, are captured via the SITBI. The SSI interview is presented in a semistructured format and consists of 19 items that include 3 subscales of SI: passive suicidal desire, active suicidal desire, and specific plans for suicide. Each item is rated on a 3-point Likert-type scale from 0 to 2 and then summed, with higher total and subscale

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scores indicating greater severity of SI. The SITBI is also presented in a semistructured format and comprises modules that assess SI, suicide plans, suicide gestures, SAs, and NSSI. The IEs are trained and certified on both interview measures as described in the following sections. Recognizing that measurement of suicide-related behaviors is fraught with challenges [69], a separate study will also explore defining suicide risk as a composite measure of SI, SAs, and NSSI.

Tailoring Variable

In the context of SMART designs, tailoring variables are characteristics of participants that trigger adaptations to the ATSs. The tailoring variable used in this study is a modified version of the Rating of Clinical Improvement–Suicidality (RCI-S) scale, an adapted version of the Clinical Global Impressions scale [70] designed to assess overall improvement in suicide risk. Beginning in session 4, and following each subsequent session, counselors use the 4-point Likert-type RCI-S to rate the students' treatment response trajectory with respect to their suicidal symptoms since baseline from *Responder* (1) to *Significant Worsening* (4). Students who are rated as responders move into the maintenance phase of the trial. Insufficient responders (those with RCI-S ratings of ≥2) at the end of stage 1 are eligible to be rerandomized into 1 of the 2 stage 2 treatments.

Secondary Measures

Secondary measures (also listed in Table 1) were designed to capture overall distress, depression, social and generalized anxiety, substance use, eating concerns, academic functioning, and clinical global impressions by both participants and assessors of severity and improvement in suicidal risk. These measures are included to allow for the examination of mediators, predictors, and moderators of treatment response, which could be incorporated as secondary tailoring variables in later studies or during dissemination. Quantitative and qualitative assessments to monitor implementation activities and address barriers that arose during the study are also collected. The implementation monitoring plan was guided by three components: (1) critical steps of the Quality Implementation Framework [35], (2) process evaluation and implementation monitoring outlined by Saunders [71], and (3) implementation outcomes specified by Proctor et al [34]. These measures include student and counselor views on treatment experiences and satisfaction as well as comparisons between in-person counseling and TMH formats.

Student Safety Procedures

Overview

Given the inherent risks of the population under study, particular care was taken to develop and implement strategies to ensure participant safety. These include procedures for adverse event (AE) monitoring, detailed manual-based protocols to minimize risk of worsening symptoms and manage emergent crises, and procedures to quickly detect and alert research staff when an AE occurs. The study protocol allows for an increase in session frequency if needed, and student participants who worsen significantly might be removed from the study and referred to a higher level of care if needed. The CAMPUS Trial is also monitored by a blinded NIMH Data Safety and Monitoring Board (NIMH-DSMB). The NIMH-DSMB meets 3 times per year to review and approve all protocol changes, enrollment data, safety data, and data integrity.

AEs and serious AEs (SAEs) are monitored at each treatment and assessment visit. For the purposes of this study, the following events are considered AEs: (1) breach of confidentiality, (2) evidence of coercion to participate, (3) evidence of distress during assessments (using data from the University of Washington Risk Assessment Protocol) [72], and (4) significant increase in SI (relative to baseline) as rated by counselor participants (at each treatment visit) and IEs (at each assessment visit). SAEs include (1) suicide death, (2) nonsuicide death, (3) SA (not death) with nonzero intent to die, (4) inpatient hospitalization, and (5) emergency department visit.

During treatment visits, counselor participants document any new AEs or SAEs spontaneously reported during therapy sessions. Unsolicited events that meet the definition for AEs or SAEs prompt further inquiry by the research team to ascertain onset; severity; relatedness to treatment; outcome; and measures taken to address the event, if any. During each assessment visit, AEs and SAEs are also assessed and monitored through general inquiry by the IEs. IEs also implement the University of Washington Risk Assessment Protocol [72] at each assessment to monitor suicide risk more closely.

Special Considerations for Risk Management During Remote Assessments and Treatment Visits

Because of the remote nature of TMH care, each student's current location, as well as emergency contact numbers for third-party involvement (eg, parents or roommates approved by the student), are obtained should there be a worsening of symptoms. IEs are also trained to gather information for secondary backup methods, even tertiary when possible, for reconnecting with students in case of technological issues or an unstable internet connection. Before initiating any remote assessments with student participants, IEs receive basic training in TMH by viewing the first 3 segments of the American Psychological Association Telepsychology Best Practices 101 series webinars [73].

Quality Assurance

Overview

UCC counselors wishing to be study counselors undergo a rigorous certification process for CAMS and CC-DBT. For CAMS, certification requirements occur in stages. Before treating a student participant, counselors must (1) read all CAMS treatment-related materials, including the study protocol; (2) watch a 3-hour CAMS online training course; and (3) attend a full-day CAMS role-play workshop. Following these trainings, counselors must (1) attend weekly cross-site consultation calls and (2) receive a minimum of *good* on CAMS adherence ratings for 3 sessions or until the student completed treatment (ie, if suicide risk resolved in <6 sessions), with individual feedback to clinicians provided via email. Once counselors are certified as study adherent to CAMS, 2 CAMS sessions from each student participant will be randomly selected and rated for adherence to the CAMS model.

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Before treating a student participant using CC-DBT, counselors must (1) read all CC-DBT treatment-related materials, (2) attend a 4-day online DBT training workshop and a 1-day online skills training workshop, and (3) attend weekly cross-site consultation team meetings following the trainings. Recordings of each session of a counselor's first CC-DBT student are reviewed for adherence by DBT expert clinicians, and feedback is provided via email. CC-DBT sessions are rated for adherence until each counselor demonstrates that they can meet the threshold for adherence on the DBT Adherence Checklist for Individual Therapy (a score of ≥22) [74] on at least 2 sessions, with at least one of these sessions being a later session of treatment (ie, sessions 3-8). Once counselors are certified as study adherent to DBT, 2 CC-DBT sessions from each student participant will be randomly selected and rated for adherence to the DBT model.

IEs also undergo a rigorous certification process. IEs must (1) read all study-related materials, including the study protocol; (2) attend a 2-day online training covering each of the IE-administered outcomes; (3) complete *on your own* practice administering study interviews and outcomes; (4) watch and score a standardized video of an assessment; (5) practice administering an assessment with a standardized practice participant; and (6) attend twice monthly cross-site assessment supervision meetings where scoring questions and concerns are discussed (note: SSI and SITBI consultant Dr Julia Harris will also be present to facilitate challenging classification of questions and concerns).

Data Management

All research data are kept in an encrypted REDCap database managed by the Duke data center at the Duke University Medical Center. With participants' approval, deidentified data will also be submitted to the NDA. Study procedures include detailed instructions for data acquisition, processing, and upload to the REDCap platform. Any data collected on paper forms are double entered by site study staff and directly uploaded into the REDCap database using specific electronic case report forms. Many data validation rules (eg, out-of-range values and skip patterns) are enforced by the electronic data capture system during data entry. The Duke data center continually monitors data quality throughout the study, conducting daily checks using the REDCap auditing system to annotate and document any inconsistencies or possible errors to be resolved by site study staff.

Design Challenges and Alternatives Considered

In the process of refining the CAMPUS Trial design, we considered the following design alternatives but ultimately did not use them for ethical, pragmatic, and clinical reasons.

Using Different Counselors for Different Treatments

The CAMPUS Trial team carefully considered the option of using different counselors to implement the different treatments. Although this is desirable from an efficacy-based perspective, we discarded this design option due to compelling ethical and clinical, pragmatic, and methodological reasons and decided to have the same counselors deliver all interventions. Requiring student participants with unresolved STB (or both; who might struggle with fears of abandonment) to switch counselors at the end of stage 1 could lead to an escalation in STB [29] or increased likelihood of treatment dropout. Previous research has demonstrated that keeping the same counselor across treatment transitions in a UCC is associated with half as many treatment dropouts and fewer sessions overall [75]. Furthermore, this design better reflects what would happen in the *real world* in that counselors often evolve or change their treatment plans if a client is not responding rather than refer them to another counselor. Quality assurance procedures were developed to assess for contamination of CAMS or CC-DBT into E-TAU.

Mandating a Full Course of Treatment

A priority of the CAMPUS Trial is to develop evidence-based ATSs that are feasible to implement in UCCs, which must operate with limited resources and in the context of an academic calendar. Mandating a full course of treatment for all students is impractical in the UCC setting. Provided that students receive a *minimum dose* of 4 treatment sessions, they are not required to continue study treatment once they are classified as treatment responders. In other words, students only receive as much treatment as they need to improve. We also allow for flexibility in the delivery of treatments to accommodate the academic calendar. All treatment sessions are conducted either in person or remotely via a HIPAA-compliant TMH platform. Thus, continuity of treatment during short breaks is facilitated by the use of a telehealth option. For longer academic breaks (eg, winter break), students are permitted to take a *break* from CAMPUS Trial treatment while they are on a scheduled break (and often unable or ineligible to receive UCC services due to residing out of state) and then continue where they left off upon their return to campus. This is an essential adaptation to the UCC setting and was considered in terms of recruitment rates. Breaks will also be considered in the analyses (eg, dosage defined as number of sessions and not time since randomization per stage and number of additional treatment sessions received).

Deviations From the Original Protocol

The protocol presented in this publication differs from the initial design that was peer reviewed by the funding agency. These modifications were necessary due to the unforeseen impact of the COVID-19 pandemic, which posed challenges that could not have been anticipated at the time of initial planning. To ensure participant safety and adapt to logistical constraints, we implemented substantial changes in the trial design and methodology. These modifications were carefully considered and implemented in consultation with the scientific advisory board, UCC implementation advisory board, and program officer from the funding agency. Each of these stakeholders provided invaluable guidance to ensure that the changes maintained the scientific integrity of the study while allowing for adaptation to the evolving situation. Any adjustments to the initial design were transparently documented, reviewed, and approved by the funding agency, each site's IRB, and the assigned NIMH-DSMB. This approach aimed to ensure that the study findings remain as unbiased as possible despite the external constraints encountered.

Most of the deviations from the original protocol were necessitated by the COVID-19 pandemic and included procedures to accommodate UCC TMH services, including

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remote treatment, assessments, and safety monitoring. Counselor trainings were also modified to accommodate remote delivery. However, additional modifications arose from lessons learned during the subsequent feasibility study required by the NIMH and NIMH-DSMB. These included changes to the assessment battery to reduce participant burden and improve remote data collection procedures and adaptations to comprehensive DBT to better fit the UCC setting and academic calendar.

Organization and Study Management

To ensure scientific integration of research procedures, overall managerial and administrative responsibilities rest with the CAMPUS Trial steering committee (SC), which comprises the PIs and coinvestigators from each site, principal statistician, and NIMH-DSMB liaison. As relevant, additional team members, including project coordinators, participate in SC meetings. The SC is responsible for all decisions concerning the overall research program, including plans for data analysis and publications. The SC holds weekly videoconference calls to monitor the overall course of the study, including recruitment, retention, and any out-of-protocol deviations. In case of disagreements, each site has 1 vote, and the statistician will break a tie. Various subcommittees (eg, quality assurance, treatment, and assessment) will be formed across investigators and consultants, and these subcommittees present potential challenges and solutions to the SC (these actions are documented via minutes).

There are also two advisory boards: (1) a scientific advisory board composed of a suicide researcher with expertise in multisite trials, a psychiatrist, a research scientist with expertise in SMART methodology, and a UCC expert; and (2) a UCC implementation advisory board composed of the 4 site UCC directors or clinical directors. The PIs, coinvestigators, and project coordinators attend an annual in-person study meeting and also meet at professional conferences throughout the study period.

Results

Student participant recruitment began on October 25, 2022, and ended on May 16, 2024. Data collection was complete in November 2024, and as of April 2025, data analysis is underway. Full results will be available in 2025.

Discussion

Expected Findings

The CAMPUS Trial offers a model for future SMART designs in UCCs and similar settings. Primary and secondary results of the CAMPUS Trial will offer important clinical decision-making guidelines for informing the treatment of university students presenting with STB in UCCs. A previous pilot SMART [20] laid the groundwork for the CAMPUS Trial, which was designed to improve upon previous limitations by increasing the sample size, incorporating multiple UCCs, integrating remote assessments and treatments, and evaluating ATSs with shorter durations to enhance feasibility and broader adoption across diverse UCC settings. We hypothesized that starting with CAMS and then (1) ending treatment and entering maintenance if student participants improve (stage 1) or (2) switching to a more intensive treatment if there is insufficient improvement (stage 2) would be the most effective treatment sequence for students who are suicidal seeking services at UCCs.

The hybrid intervention format of the CAMPUS Trial represents an important contribution to efforts to improve treatment of suicidality via telehealth. Before the COVID-19 pandemic, the prevailing belief was that clients with STB posed too great a risk for treatment via TMH. The CAMPUS Trial feasibility pilot study demonstrated that TMH is a feasible and acceptable modality for delivering suicide-focused treatments [27]. Results from the trial may provide additional insights into whether treatment modality impacts response rates and provide guidance to UCCs and other organizations on how to deliver suicide-focused treatments.

Limitations

First, a key concern is the heterogeneity of E-TAU. Because E-TAU was not standardized across sites, variations in the type and theoretical orientation of care received by student participants have the potential to influence outcomes. While this variability reflects real-world clinical practice, it can present challenges for interpretation. To address this, we implemented systematic monitoring of E-TAU, including quality control ratings to assess for contamination of CAMS and CC-DBT principles into E-TAU, and gathered information on clinicians' theoretical orientations and treatment choices when delivering E-TAU. However, another important limitation is that E-TAU may not fully reflect true TAU at UCCs. The CAMPUS Trial counselors were trained in suicide-focused treatments and served as their own controls, which may have influenced the way in which they delivered TAU even in the absence of direct contamination from CAMS and CC-DBT. Although quality control measures were implemented to prevent cross-treatment contamination, the fact that all counselors had formal training in structured suicide-focused approaches means that the TAU they provided may be different from what is typically offered in UCCs. This could limit the generalizability of findings regarding the effectiveness of standard TAU provided outside the trial. Although this design introduces some challenges, treatment provision at UCCs varies considerably, and this reflects the reality of the setting. Furthermore, future secondary studies offer the potential to make a significant contribution to the field of suicide prevention by characterizing TAU in the context of suicidal risk and further examining how clinician training influences TAU delivery.

Because the CAMPUS Trial participants are university students, there can be concern about the lack of generalizability of the results to broader populations. However, the findings of this study should have relevance beyond university settings. Young adults in higher education represent a diverse group with varying backgrounds, mental health histories, and treatment needs, making them an important population for studying suicide-focused interventions. In addition, many of the challenges addressed in the CAMPUS Trial—such as accessibility of care, personalizing the provision of care to improve outcomes, and the integration of TMH—are applicable across different clinical settings. The CAMPUS Trial results

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can inform best practices for delivering suicide-focused treatments in community mental health centers, primary care settings, and other outpatient environments. Furthermore, the use of ATSs to tailor interventions based on individual response patterns provides a flexible framework that can be adapted for different populations, including those in nonuniversity settings.

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Data Availability

The datasets generated or analyzed during this study are available in the National Institute of Mental Health Data Archive.

Conflicts of Interest

The following conflicts of interest are reported: (1) DAJ receives book royalties from Guilford Press, and he is the founder and co-owner of CAMS-care, LLC (a professional training and consultation company); (2) SLR receives royalties from Guilford Press and advertisement revenue from YouTube; (3) SNC receives royalties from Elsevier; and (4) JP receives royalties from New Harbinger Publications and is co-owner of Contextual Change LLC.

Multimedia Appendix 1
Peer review reports from the ZMH1 ERB-K (04) - National Institute of Mental Health Special Emphasis Panel (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 6132 KB - resprot_v14i1e68441_app1.pdf]

Multimedia Appendix 2
Authors' response to peer reviews from the ZMH1 ERB-K (04) - National Institute of Mental Health Special Emphasis Panel (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 434 KB - resprot_v14i1e68441_app2.pdf]

Multimedia Appendix 3
Author commentary on original peer reviews.
[DOCX File , 13 KB - resprot_v14i1e68441_app3.docx]

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Abbreviations

AE: adverse event
ATS: adaptive treatment strategy

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BPD: borderline personality disorder
CAMPUS: Comprehensive Adaptive Multisite Prevention of University Student Suicide
CAMS: Collaborative Assessment and Management of Suicidality
CC-DBT: counseling center dialectical behavior therapy
DBT: dialectical behavior therapy
E-TAU: enhanced treatment as usual
HIPAA: Health Insurance Portability and Accountability Act
IE: independent evaluator
IRB: institutional review board
NDA: National Institute of Mental Health Data Archive
NIH: National Institutes of Health
NIMH: National Institute of Mental Health
NIMH-DSMB: National Institute of Mental Health Data Safety and Monitoring Board
NSSI: nonsuicidal self-injury
PI: principal investigator
RCI-S: Rating of Clinical Improvement–Suicidality
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SA: suicide attempt
SAE: serious adverse event
SC: steering committee
SI: suicidal ideation
SITBI: Self-Injurious Thoughts and Behaviors Interview
SMART: sequential multiple-assignment randomized trial
SSI: Scale for Suicidal Ideation
STB: suicidal thoughts or behaviors
TAU: treatment as usual
TMH: tele–mental health
UCC: university counseling center

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Protocol

Physical Activity Measurement Reactivity Among Midlife Adults With Elevated Risk for Cardiovascular Disease: Protocol for Coordinated Analyses Across Six Studies

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Abstract

Background: Cardiovascular disease (CVD) remains the leading cause of death in the United States, and adults aged 40-60 years with specific health conditions are at particularly elevated risk for developing CVD. Physical activity (PA) is a key cardioprotective behavior and many interventions exist to promote PA in this group. Effective promotion requires accurate assessment of PA behavior; as PA is often estimated by averaging across multiple days, a threat to accurate assessment is *measurement reactivity*, or an atypical increase in PA behavior at the start of measurement periods that may bias conclusions. Evidence for PA measurement reactivity is equivocal, though concern has resulted in recommendations to add or drop PA measurement days from inclusion, which may introduce undue burden on participants. At present, the extent of PA measurement reactivity and the behaviors most likely to be affected (eg, steps vs minutes of exercise) among those at risk for CVD are unclear, as are participant characteristics such as gender and study expectations (eg, intervention vs observation only) that may contribute to differences in these patterns.

Objective: The goal of this study is to improve on the current understanding of the extent of PA measurement reactivity and potential moderators among US adults aged 40-60 years with CVD risk factors.

Methods: To achieve this goal, we will conduct coordinated multilevel analyses across 6 studies. Data are from nationally representative, publicly available datasets (observation only: 2 studies) and baseline weeks of observation from behavioral weight loss clinical trials (4 studies), all collected in the United States. The publicly available datasets National Health and Nutrition Examination Survey (NHANES; 2013-2014) and the Midlife in the United States (MIDUS) Study (2004-2009; total n=1385) were used, which are available from the Inter-university Consortium for Political and Social Research website. Behavioral weight loss trials were conducted by the Drexel University Weight Eating and Lifestyle (WELL) Center (2011-2023; total n=444), in person or remotely via Zoom. Relevant data from each study were extracted for adults aged 40-60 years who have ≥1 risk factor for CVD (total n=1832; 11,707 total days of PA measurement with 6-7 days per person). Changes in PA behavior across the measurement period will be examined at the day level, using 2-level multilevel models (days nested within persons) and cross-level interactions (for moderation effects).

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Results: This project was funded in August 2022 and received supplementary funding in September 2023. Dataset acquisition and data cleaning were completed in October 2024. Analyses are expected to be completed in April 2025, and findings are anticipated to be shared in July 2025.

Conclusions: Results from this coordinated analysis project will provide the first large-scale estimation of the extent of PA measurement reactivity in an at-risk group. Findings will inform best practices for mitigating potential measurement reactivity in multiday assessments of PA behavior.

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KEYWORDS

physical activity; measurement reactivity; gender difference; cardiovascular risk; intensive assessment; midlife; research participation effects

Introduction

Cardiovascular disease (CVD) remains the leading cause of death in the United States, and risk for CVD meaningfully increases during midlife (ages 40-60 years) [1,2]. Increased risk for CVD during midlife is due to universal aging processes and associated conditions such as obesity and hypertension, as well as to sex-specific metabolic and hormonal changes (eg, the onset of menopause), which result in distinct risk patterns for women and men [2-6]. Engaging in regular physical activity (PA) during midlife can significantly reduce the risk of CVD for both women and men [7,8]. Unfortunately, low PA engagement among midlife adults is common, which exacerbates their CVD risk and contributes to their substantial health care costs [4,9]. This problem persists despite decades of efforts to promote PA that include high participation rates among midlife adults [10,11], and when PA promotion is effective, the benefits of participation are short-lived [12]. This applies to the many PA interventions that are specifically tailored for midlife adults, including those that are gender-specific (ie, enroll only men or women or focus on sex- or gender-specific content, such as PA in the context of gender roles, effects of PA on menopause symptoms, or risk for prostate cancer) [13-18]. Evidence consistently shows that very few midlife adults—particularly those with CVD risk conditions such as obesity, hypertension, or type 2 diabetes—achieve PA levels that would confer significant protection against CVD [19-21]. Thus, additional work is needed to effectively promote PA to reduce CVD risk among midlife adults.

Critically, however, our understanding of current PA engagement and the benefits of PA for reducing CVD risk among midlife adults relies on accurate PA measurements in this at-risk population. Assessment of PA using research-grade or commercially available devices (eg, Fitbit) provides more accurate estimates of PA engagement than methods such as self-report [22]. To ensure accurate estimates by accounting for normal daily variability in PA engagement [23], monitoring periods typically last 7 days, and observed PA behavior (eg, steps per day, minutes of moderate-to-vigorous-intensity activity) is averaged across these days to generate an overall estimate of PA engagement [24]. Evidence across the multidisciplinary field of PA promotion highlights the potential for bias in the assessment of PA using monitoring technology; one source of this bias is *measurement reactivity*, or change in PA behavior due to the introduction of its measurement [17,21,25,26]. Introducing PA monitoring via an external device during participation in a research study is thought to increase the salience of both immediate PA engagement and the notion that someone else is watching [27,28]. This increased awareness can lead to significantly more PA engagement early in the monitoring period than is typical or sustainable. Specifically, PA measurement reactivity typically manifests as greater PA at the start of observation periods, relative to subsequent days (eg, negative linear slope across days, or higher on day 1 or days 1-2) [25]. When estimates are calculated as averages across days, initial elevation could skew these estimates to show greater engagement than is typical or sustainable [25]. The resulting inflation of PA estimates could mask the effects of PA interventions, as preintervention starting points could be overestimated [17] (among other confounds), leading to incorrect conclusions about PA engagement among at-risk groups such as adults in midlife.

To fully understand the value of promoting PA to reduce CVD risk among adults in midlife with existing risk factors, it is critical to ensure the accuracy of PA measurements in this population. As noted, if measurement reactivity effects are substantial, the resulting biased estimates of PA in at-risk groups such as midlife adults could lead to incorrect conclusions and next steps for PA promotion. PA measurement reactivity has been observed in a subset of studies to date [25,29-31], and some PA researchers consider reactivity a critical source of bias that warrants increased attention and mitigating actions, such as requiring extra days of observation to get used to the PA monitor or removing the first 1-2 days of PA observation from analyses [30]. The evidence is equivocal, however, with some studies showing no reactivity patterns or patterns that are not clinically significant (and thus, would not meaningfully affect overall PA estimates) [25,28]. As a result, there is considerable debate about the need for such drastic measures, or even the need for ongoing attention to this phenomenon. PA recordings on these days represent actual PA engagement, even if the level of engagement is not “typical,” and adding assessment days increases participant burden [32]. Consequently, the extent of PA measurement reactivity and best practices for handling PA data to address the potential for it to affect estimates have yet to be identified.

Existing evidence is also limited in three key ways. First, studies of PA measurement reactivity have often focused on children

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or healthy, younger adults. Because these populations generally are more active than midlife adults with elevated risk for CVD (or similar at-risk groups) [19,33], they may respond differently to the introduction of PA monitoring. Second, there is little consistency between existing studies with respect to definitions of reactivity or which PA outcomes are affected; outcomes of interest have included steps per day, light PA, moderate-to-vigorous PA (MVPA), and sedentary time [29,30,33], which have distinct implications for CVD risk that differ by gender [34,35]. In addition, some work has defined reactivity as an overall linear decrease in PA across days of observation [25,36], whereas others have examined direct comparisons between day 1 and subsequent days (days 2, 3, 4, or combinations) [29,37]. Third, there has been little attention to the contexts where PA measurement reactivity is a meaningful problem, leading to inconsistent and often drastic recommendations for addressing it. As noted, these include adding observation days, which increases participant burden, and removing the first 1-2 days of observation, which reduces the precision of estimates (or both of these steps) [25,27,30,38]. Although there is some convergence in PA estimates between commercially available wearable devices and research-grade monitors [39], differences in the location of wear (eg, wrist vs hip) and the extent to which a device offers PA feedback (eg, via a digital display of accumulated steps per day in real time) could influence reactivity by differentially increasing the salience of PA [31]. Assessment of PA prior to the start of an intervention (vs in studies that use observation alone) may also affect reactivity via differences in participants' anticipation of future increases in their PA [30].

In addition, individual differences in mental health symptoms, physical health characteristics, and psychosocial processes are known determinants of PA engagement and thus may influence reactivity patterns [39]. For example, depressive symptoms, number of cardiovascular risk factors, and BMI are negatively associated with PA engagement [40,41] and, as a result, may limit reactivity. In contrast, tendencies toward self-evaluation relative to others and increased motivation for health behaviors may have the opposite effects [40,42]. Specifically, women and those who have stronger tendencies to make and value social comparisons (ie, self-evaluations of one's traits or behaviors compared to others [43]) may show greater measurement reactivity responses, as these individuals may be particularly interested in managing others' perceptions of them (such as researchers) [43-46]. Higher (vs lower) levels of PA motivation and more (vs fewer) past attempts at PA behavior change may also be associated with stronger reactivity responses, as these may indicate greater focus on PA overall [47]. Greater attention to individual differences and contexts, rather than treating PA measurement reactivity as universally problematic versus not (as it is currently), could identify optimal and tailored targets for mitigating reactivity in future studies.

Thus, the role of PA measurement reactivity in PA promotion for at-risk groups remains unclear, and no existing study has examined the extent of reactivity based on research design, study procedures, and individual participant characteristics. For this study, we will capitalize on the availability of existing data resources with a multilevel coordinated analysis across 6 studies (including 2 nationally representative observational studies and 4 intervention trials) to achieve the following aims:

1. To characterize midlife adults' PA measurement reactivity in each dataset. We will determine whether daily PA engagement meaningfully changes over 6-7 days of observation, across available PA outcomes. Available data include monitor-independent measurement summary (MIMS) units, activity counts, and steps per day.
2. To determine whether the presence or extent of measurement reactivity differs based on demographic, medical, or psychological characteristics. We hypothesize that reactivity will be weaker among adults with higher (vs lower) BMIs, numbers of CVD risk factors, and depressive symptoms. Conversely, we hypothesize that reactivity effects will be stronger among women, adults with higher (vs lower) PA motivation and social comparison tendencies, and those with more previous attempts to increase PA or lose weight. We will further examine whether gender moderates the effects of other individual difference characteristics on PA engagement over 6-7 days by including the interaction effect between gender and other predictors.
3. To determine whether the presence or extent of measurement reactivity differs based on study characteristics. We hypothesize that reactivity effects will be stronger in studies that use observation only (as there is no expectation of later improvement), commercially available devices (which tend to be visible throughout the day), wrist wear (based on both visibility and sensitivity to movement [31,48]), and devices that offer feedback in real time (as they provide additional information that can prompt a behavioral response [49]). We will further examine whether gender moderates the effects of study characteristics on PA engagement over 6-7 days by including the interaction effect between gender and other predictors.

Methods

Overview

Using a coordinated analysis approach [50], we will model differences in PA engagement across days of observation using data from each of the 6 studies. These include 2 observational studies that have publicly available datasets and 4 clinical trial datasets. All data were collected between January 2005 and January 2023. Procedures included 6-7 days of intensive PA assessment using a research-grade or commercially available device. Analysis of available datasets leverages existing resources to address questions beyond those originally intended; this limits cost and eliminates additional participant burden while offering insights into important phenomena [51]. This approach is uniquely suited for the present study, as the concern about PA measurement reactivity is that it appears any time PA monitoring devices are introduced. If this concern is warranted, evidence of measurement reactivity should be observed in studies that were not specifically designed to test this phenomenon (eg, studies for which PA was assessed for other purposes and data are already available). The datasets used for

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this set of secondary analyses were selected for their accessibility to the research team, representation of a large number and range of individuals in the target population, and heterogeneity in study designs and monitoring PA devices used. Together, these datasets will enable examination of reactivity patterns following the introduction of PA measurement devices in multiple people and contexts.

Observational Studies

These include samples from the National Health and Nutrition Examination Survey (NHANES) [52] and the Midlife in the United States (MIDUS) [1] Study (combined n=1385). NHANES is a national, longitudinal program of research focused on understanding various aspects of health among adults and children in the United States, and data are publicly available. We will use data from the most recent wave of collection that included PA monitoring (2013-2014; 7 days of assessment with the ActiGraph GT3X). MIDUS is a longitudinal investigation of life circumstances and health outcomes among adults aged 25-75 years. The present analyses use data from the MIDUS Biomarker Project (2004-2009), which included PA monitoring (6 days of assessment with the Actiwatch-64).

Randomized Clinical Trials

These studies were tests of improvements to standard behavioral weight loss treatment (4 studies, combined n=444). Each study used a 7-day pretreatment observation window, which will be used to examine PA measurement reactivity. Project ENACT (NCT01858714) tested the effects of an enhanced focus on the food environment and the use of acceptance and commitment skills to support behavior change on long-term weight loss [53]. The collection of the data to be used in the planned analyses began in 2011 and finished in 2013. Project IMPACT (NCT02363 010) tested an increased emphasis on PA and acceptance and commitment skills to support behavior change on long-term weight loss [54]. Collection of the data to be used in the planned analyses began in 2014 and finished in 2016. The last 2 studies examined the added benefits of sharing PA self-monitoring data, either with coaches (Project FitLink Pilot, 2018-2019; NCT03337139 [55]) or with coaches, a designated member of the participant's existing social network (friend or family member), and other participants (Project FitLink Full, 2021-2023; NCT05180448 [56]). ENACT and IMPACT used the same research-grade accelerometer (Actigraph GT3X), worn on the hip. FitLink Full used a commercially available wearable PA monitor (Fitbit Inspire 2), worn on the wrist, and FitLink Pilot used both the research-grade hip-worn accelerometer and a commercially available wrist-worn monitor (Fitbit Flex; Table 1). The commercial device was worn from the baseline period through treatment; the research-grade device was added at a 3-month assessment (ie, at randomization to condition after a uniform treatment period). ENACT, IMPACT, and FitLink Pilot were conducted in person in a large city in the northeastern United States, whereas FitLink Full was conducted remotely using national recruitment and enrollment.

Table 1. Physical activity measurement by study.

Study	Device	Duration	Outcomes
Observational studies			
NHANES[a] (n=1208)	ActiGraph GT3X (wrist-worn)	7 days	Monitor-independent movement summary units
MIDUS[b] (n=177)	Actiwatch-64 (wrist-worn)	6 days	Total activity count units
Randomized clinical trials (intervention programs)			
ENACT (n=143)	ActiGraph GT3X+ (hip-worn)	7 days	Steps per day
IMPACT (n=140)	ActiGraph GT3X+ (hip-worn)	7 days	Steps per day
FitLink Pilot (n=31)	Fitbit and ActiGraph GT3X (hip-worn; week 13)	7 days	Steps per day
FitLink Full (n=130)	Fitbit	7 days	Steps per day

[a]NHANES: National Health and Nutrition Examination Survey.

[b]MIDUS: Midlife in the United States.

Participants

Eligible participants are adults in midlife (aged 40-60 years) with ≥1 risk factors for CVD who completed the relevant PA assessment period (see below for additional details about inclusion in data analyses). CVD risk factors include prediabetes, type 2 diabetes, hypertension, high cholesterol, obesity, and current smoking. As noted, observational studies (n=1385) recruited nationally in the United States; clinical trials (n=444) were behavioral weight loss studies completed in the northeastern United States, one of which was conducted remotely. Participant demographics are listed in Table 2.

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Table 2. Participant demographics across 6 studies.

	NHANES[a] (n=1208)	MIDUS[b] (n=177)	ENACT (n=143)	IMPACT (n=140)	FitLink Pilot (n=31)	FitLink Full (n=130)
Age (years), mean (SD)	49.9 (6.0)	50.9 (5.8)	52.3 (5.6)	52.9 (5.0)	50.9 (6.1)	51.5 (5.7)
Gender, n (%)						
Women	628 (52.0)	105 (59.3)	117 (81.8)	116 (82.9)	28 (90.3)	109 (83.8)
Men	580 (48.0)	72 (40.7)	26 (18.2)	24 (17.1)	3 (9.7)	21 (16.2)
BMI (kg/m^2), mean (SD)	31.2 (7.4)	32.0 (7.2)	36.3 (4.5)	35.5 (4.4)	36.3 (4.5)	36.5 (4.8)
BMI category, n (%)						
<18.5 kg/m^2	9 (0.8)	1 (0.6)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
18.5-25 kg/m^2	224 (18.6)	26 (14.7)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
25-30 kg/m^2	321 (26.6)	43 (24.3)	7 (4.9)	6 (4.4)	0 (0.0)	4 (3.1)
>30 kg/m^2	653 (54.1)	107 (60.4)	136 (95.1)	131 (95.6)	31 (100.0)	126 (96.9)
Race[c], n (%)						
American Indian or Native Alaskan	__[d]	0 (0.0)	1 (0.7)	0 (0.0)	1 (3.2)	0 (0.0)
Asian	115 (9.8)	2 (1.1)	1 (0.7)	1 (0.7)	0 (0.0)	3 (2.3)
Native Hawaiian or Other Pacific Islander	—	0 (0.0)	1 (0.7)	0 (0.0)	0 (0.0)	0 (0.0)
Black or African American	273 (23.4)	50 (28.4)	51 (35.7)	35 (25.0)	12 (38.7)	17 (13.1)
White	486 (41.6)	103 (58.5)	84 (58.7)	98 (70.0)	14 (45.2)	107 (82.3)
Other or mixed race	32 (2.7)	21 (11.9)	5 (3.5)	6 (4.3)	4 (12.9)	3 (2.3)
Ethnicity[c], n (%)						
Hispanic or Latino	262 (22.4)	0 (0.0)	8 (5.6)	5 (3.6)	2 (6.4)	10 (7.7)
Not Hispanic or Latino/a	906 (77.6)	177 (100.0)	134 (94.4)	135 (96.4)	29 (93.6)	120 (92.3)
Marital status, n (%)						
Married	685 (58.6)	100 (56.5)	84 (59.2)	91 (65.0)	15 (48.4)	90 (69.2)
Widowed	28 (2.4)	4 (2.3)	2 (1.4)	2 (1.4)	1 (3.2)	1 (0.8)
Divorced	198 (17.0)	32 (18.1)	22 (15.5)	21 (15.0)	4 (12.9)	8 (6.2)
Separated	52 (4.4)	9 (5.1)	3 (2.1)	5 (3.6)	3 (9.7)	—
Never married	143 (12.2)	32 (18.1)	31 (21.8)	21 (15.0)	8 (25.8)	—
Single	—	—	—	—	—	20 (15.4)
Cohabitating	61 (5.2)	—	—	—	—	9 (6.9)
Not cohabitating	—	13 (16.9)	—	—	—	2 (1.5)
Income[e] (US $), n (%)						
$0-$25,000	294 (25.5)	63 (36.6)	9 (6.4)	4 (2.9)	1 (3.2)	—
$25,000-$50,000	210 (18.2)	53 (30.8)	21 (14.9)	13 (9.5)	4 (12.9)	—
$45,000-$55,000	94 (8.2)	—	—	—	—	—
$50,000-$75,000	126 (10.9)	27 (15.7)	31 (22.0)	15 (11.0)	7 (22.6)	—
$75,000-$100,000	113 (9.8)	14 (8.1)	24 (17.0)	23 (16.8)	6 (19.4)	—
>$100,000	251 (21.8)	8 (4.6)	13 (9.2)	20 (14.6)	2 (6.4)	—
$125,000-$150,000	—	2 (1.2)	18 (12.8)	17 (12.4)	6 (19.4)	—
$150,000-$175,000	—	2 (1.2)	8 (5.7)	18 (13.1)	0 (0.0)	—
$175,000-$200,000	—	0 (0.0)	5 (3.6)	13 (9.5)	2 (6.4)	—

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	NHANES[a] (n=1208)	MIDUS[b] (n=177)	ENACT (n=143)	IMPACT (n=140)	FitLink Pilot (n=31)	FitLink Full (n=130)
>$200,000	—	3 (1.7)	12 (8.5)	14 (10.2)	3 (9.7)	—
Education, n (%)						
Less than 9th grade	80 (6.8)	2 (1.1)	0 (0.0)	0 (0.0)	0 (0.0)	—
Partial high school	156 (13.4)	10 (5.6)	1 (0.7)	0 (0.0)	0 (0.0)	—
High school or GED[f]	280 (24.0)	35 (19.8)	13 (9.1)	5 (4.3)	1 (3.2)	—
Associate's degree, technical, or partial college	373 (31.9)	52 (43.5)	22 (15.4)	19 (16.4)	4 (12.9)	—
Bachelor's degree	279 (23.9)	44 (24.9)	52 (36.4)	41 (35.3)	11 (35.5)	—
Graduate or professional degree	—	34 (19.2)	55 (38.5)	51 (44.0)	15 (48.4)	—

[a]NHANES: National Health and Nutrition Examination Survey.

[b]MIDUS: Midlife in the United States.

[c]Race and ethnicity questions were combined for NHANES.

[d]Not available.

[e]Income was based on household, not individual, and had different cutoff values.

[f]GED: General Education Development.

Procedures

Datasets were chosen for the availability of consecutive days of PA measurement captured immediately following the introduction of commercial and research-grade accelerometers. PA data were recorded using research-grade or commercially available devices (see Table 1). Participant demographics and individual difference characteristics were collected using questionnaires or structured interviews. Specific details about these measures are described in detail below.

Measures

Demographics

Participants' basic demographics were collected via self-report. These data included age, gender, racial and ethnic identity, marital status, income, and education (see Table 2). NHANES collected these data during structured, in-person interviews with participants. The remaining studies captured these data using electronic or paper questionnaires.

Physical Activity

Included studies captured 6-7 days of PA data using different PA monitoring devices and will enable examination of device-specific effects. ActiGraph devices were used for observational studies and 3 (of 4) clinical trials. These devices were wrist-worn and hip-worn ActiGraph models for observational studies and clinical trials, respectively; remaining clinical trials used commercially available Fitbit devices (see Table 1). PA outcomes were daily PA summary metrics or steps per day. Observational studies used MIMS units [57] and total activity counts; clinical trial datasets provided steps per day (also detailed in Table 1). Steps per day captured using Fitbit at baseline and both a Fitbit and ActiGraph at 3 months into treatment during the FitLink Pilot will allow for comparison of potential recurrence of reactivity patterns after the onset of behavioral weight loss treatment.

Individual Difference Measures

Measures of individual differences are shown in Table 3.

CVD risk conditions include prediabetes or type 2 diabetes, hypertension, high cholesterol, obesity, or current smoking. Participants were prompted to report whether they had a physician diagnosis of prediabetes, type 2 diabetes, hypertension, and high cholesterol. BMI ≥30 kg/m2 will be used to indicate obesity and will be calculated based on measured height and weight. Table 4 summarizes the risk factors assessed in each study. Participants with pre-existing CVD will be excluded from analyses, including those who self-report a history of heart disease, heart failure, stroke, or heart attack. We will calculate the proportion of CVD risk factors endorsed out of the risk factors assessed to determine an overall risk percentage.

Depressive symptoms were measured in each study using validated self-report measures, including the Patient Health Questionnaire (PHQ-9) [58], the Center for Epidemiologic Studies Depression Scale (CES-D) [59], and the Beck Depression Inventory [60]. Total scores for these measures range from 0 to 27, 0 to 60, and 0 to 63, respectively, with higher scores indicating more severe depressive symptoms. Depressive symptoms were captured for the FitLink Pilot using the Weight and Lifestyle Inventory (WALI [61]), which prompts participants to report experience of depressed mood or anhedonia during the past month.

Social comparison will be examined for 3 datasets (ie, MIDUS, ENACT, and FitLink Full). MIDUS captured health-related social comparison experiences; participants were prompted to indicate their perception of their level of risk for a heart attack compared to others (ie, higher, lower, or the same) and the degree of this difference (eg, a lot higher, somewhat higher, or only a little higher). Social comparison experiences for clinical trial participants were measured using the Iowa-Netherlands Comparison Orientation Measure (INCOM) [43]. This measure

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assesses respondents' perceptions of their own tendency to make social comparisons, generally and tendencies toward upward (ie, better off) and downward (ie, worse off) comparison targets. Higher total scores indicate stronger tendencies toward social comparison.

Motivation to be physically active was assessed for 3 datasets (clinical trials; ie, ENACT, IMPACT, FitLink Pilot) using an adapted version of the Treatment Self-Regulation Questionnaire (TSRQ [62]). This measure assesses different types of motivation for changing health behaviors by capturing the extent to which respondents endorse particular reasons for changing their health behavior on a scale (from 1=not at all true to 7=very true). Specific TSRQ item scores are summed to calculate summary scores for autonomous motivation, introjected regulation, external regulation, and amotivation, with higher scores indicating greater endorsement of motivation subtypes.

History of weight loss attempts was collected in 5 studies. All 4 clinical trials used the WALI [61], which asks respondents to report their age at the time of these efforts, weight loss method, and pounds lost. These occurrences will be summed to indicate participants' history of weight loss attempts. NHANES collected these data by prompting participants to indicate if they attempted weight loss during the past year, and if so, asking whether they used specific weight loss methods. Participants' responses to these prompts will be summed to indicate the total number of weight loss methods used during the past year.

Table 3. Measures of individual difference characteristics by study.

Characteristic	NHANES[a]	MIDUS[b]	ENACT	IMPACT	FitLink Pilot	FitLink Full
BMI	Measured	Measured	Measured	Measured	Measured	Measured
CVD[c] risk	Individual questions (diagnosis)	Individual questions (diagnosis)	WALI[d] and BMI	WALI and BMI	WALI and BMI	WALI and BMI
Depressive symptoms	PHQ-9[e]	CES-D[f]	BDI-II[g]	BDI-II	WALI	BDI-II
PA motivation	—[h]	—	TSRQ[i]	TSRQ	TSRQ	—
Weight loss attempts	Self-reported (past year)	—	WALI	WALI	WALI	WALI
Social comparison	—	Comparison of CVD risk	INCOM[j]	—	—	INCOM

[a]NHANES: National Health and Nutrition Examination Survey.
[b]MIDUS: Midlife in the United States.
[c]CVD: cardiovascular disease.
[d]WALI: Weight and Lifestyle Inventory.
[e]PHQ: Patient Health Questionnaire.
[f]CES-D: Center for Epidemiologic Studies Depression Scale.
[g]BDI: Beck Depression Inventory.
[h]Not applicable.
[i]TSRQ: Treatment Self-Regulation Questionnaire.
[j]INCOM: Iowa-Netherlands Comparison Orientation Measure.

Table 4. Cardiovascular disease (CVD) risk conditions assessed by the study.

CVD risk condition	NHANES[a]	MIDUS[b]	ENACT	IMPACT	FitLink Pilot	FitLink Full
Hypertension	✓	✓	✓	✓	✓	✓
High cholesterol	✓					
Prediabetes	✓					
Type 2 diabetes	✓	✓	✓	✓	✓	✓
Obesity (BMI ≥30 kg/m^2)	✓	✓	✓	✓	✓	✓
Smoker	✓	✓	✓	✓	✓	

[a]NHANES: National Health and Nutrition Examination Survey.
[b]MIDUS: Midlife in the United States.

Ethical Considerations

The coordinated, secondary analysis plan outlined here is approved as exempt (no human subjects enrollment) by the Institutional Review Board at Rowan University and Rowan-Virtua School of Osteopathic Medicine (protocol number PRO-2021-550). Original data collection for public datasets and clinical trials was approved by the organizations' home

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institutional review boards, and participants received monetary compensation for their time and effort [1,52-56]. All consent processes involved authorization for secondary analyses. Datasets were anonymized or deidentified prior to analyses.

General Analysis Plan

Our primary analyses will examine how device-assessed PA behavior varies within persons across days of participation, using multilevel models. Each dataset includes summary indicators of PA on a given day, and days are nested within persons, creating dependence best accounted for by 2-level multilevel models. Primary outcomes of interest will be MIMS units, activity counts, and steps per day, as available in each dataset. As noted, data from participants who met demographic and medical criteria were included in the present analyses. We also set minimum PA monitoring device wear time to 10 hours of wake time per day, and days with <10 hours of valid wear time were excluded from analyses. The original, reduced, and analytical sample sizes for each study based on these criteria are provided in Figure 1.

Figure 1. Anticipated analytical sample sizes for included studies. MIDUS: Midlife in the United States; NHANES: National Health and Nutrition Examination Survey.

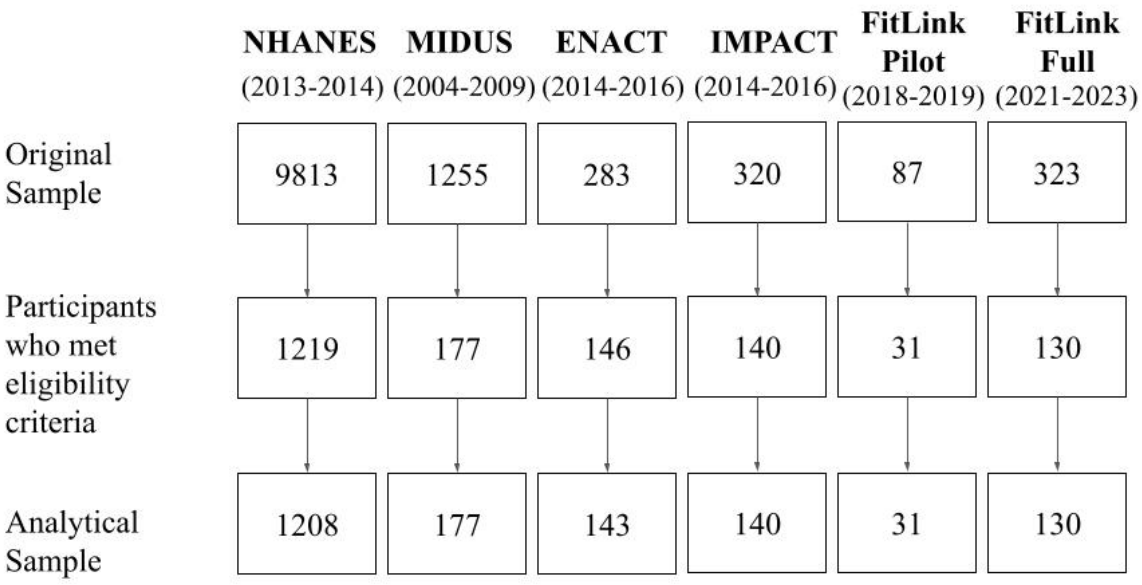

Coordinated Analysis Approach

As we have multiple datasets that share subsets of our outcomes and moderators of interest, we will use coordinated analysis to arrive at conclusions [50]. In coordinated analysis, models are parameterized and fit to datasets, and statistical results from specific datasets are compared and contrasted to efficiently replicate substantive conclusions [63,64]. Given the differences in study design, we will fit equivalent models separately across datasets, and standardized estimates can be generated to determine the consistency of effects with respect to direction and relative size. As in our previous work, we will use semipartial correlation coefficients as standardized effect size estimates [65-68]. Fitting separate models also allows for exploration of dataset-specific covariates and associations to address substantive questions relevant to individual datasets.

Aim 1

To address our first aim, we will fit models that examine whether daily parameters of PA behavior at level 1 change within a person as a function of day of measurement to describe the pattern of measurement reactivity. For these models, we will examine day of measurement as a continuous predictor of PA using both linear and quadratic trends. Further, we have the opportunity to consider the day of measurement as a categorical predictor to identify whether a particular day of measurement shows greater or lower activity counts relative to adjacent days. As in previous work, we will document patterns where day 1 and days 1-2 meaningfully differ from other days of observation as measurement reactivity [29,37,65,69].

Aim 2

We will then add moderators of change across days to address our second aim: to understand whether patterns of measurement reactivity differ based on BMI, percentage of CVD risk factors assessed, depressive symptoms, and gender. We will also examine whether patterns of measurement reactivity depend on motivation to engage in PA, social comparison responses, and previous attempts to lose weight. All moderators will be entered at level 2 as between-person predictors, and the cross-level interaction with the day of measurement will be included to assess for differences in patterns of measurement reactivity. We will also examine whether any reactivity that does emerge differs between genders. To do this, we will incorporate the 3-way interaction among gender, day of measurement, and the above moderators. Significant interactions will be probed with specific contrasts and visualizations separately for each group for categorical moderators or at 1 SD above and below the mean for continuous moderators.

Aim 3

To address our third aim, we will use standardized estimates to compare the effect of the day of measurement on PA summary scores across study designs and device characteristics. Consistent with our follow-up analyses for our second aim, we will incorporate a cross-level interaction with gender and day

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of measurement to determine whether any effects of study design and device type depend on the gender of the individual being measured.

Results

The datasets described provide 11,707 valid PA observations across 1832 adults in midlife with ≥1 risk factor for CVD. As indicated, participant characteristics for each study can be found in Table 2. Dataset acquisition is complete, and data cleaning in preparation for analysis is underway. We expect to complete analyses by April 2025 and to make full results available by July 2025.

Discussion

This study will be the first to systematically investigate PA measurement reactivity in a population with elevated CVD risk using a coordinated multilevel analysis. Analyses will be executed on a large, diverse sample of midlife adults with elevated risk for CVD, who are frequent targets of PA promotion and who make up substantial subgroups in broader PA programs [2-7]. A critical advantage of the proposed analytic approach is that days will be treated separately and nested within individuals to determine the extent of potential effects of reactivity on estimates of averages [22]. This approach will also be applied across multiple research designs, PA monitoring devices, and individual difference characteristics, allowing for the identification of potential moderators of PA measurement reactivity responses.

A noteworthy limitation of our approach is that there is no opportunity to compare the same PA outcome across all studies. Only certain variables are publicly available for NHANES and MIDUS (ie, total activity counts and MIMS units, respectively), and these cannot be converted to estimates of steps or minutes of activity per day [70]. Conversely, only the latter are available for clinical trials, and these cannot be converted to corresponding units. To address this, we will report and compare standardized effect sizes across outcomes and studies [24]. In addition, a subset of participants in each study did not contribute enough valid PA data to be included, and participants who were included occasionally had days where valid data were missing due to insufficient wear time on that day (<20% of expected days) [25]. An additional advantage of a multilevel modeling approach is that these models are robust to missing data [71,72]. Thus, estimates and conclusions are unlikely to be affected by the observed level of missingness at the day level [25,28]. At the person level, we will also compare participants who were included in analyses to those who were excluded for having too few days of valid PA data. This will allow us to determine whether these groups differ with respect to demographic or medical characteristics and to what extent this level of missingness might impact the generalizability of our findings.

As noted, there is considerable debate about the need for substantial steps to address PA measurement reactivity, such as adding and removing days of observation or blinding participants to PA feedback from their measurement devices [25,29-31,73]. Limitations notwithstanding, findings from this study will indicate whether such steps are warranted among adults in midlife with elevated CVD risk and under what circumstances (eg, across participants or study designs vs for certain subgroups or study designs). Adults in this population are primary targets and recipients of PA assessment research and intervention, as evidence consistently shows low PA in this group despite considerable PA promotion efforts. However, very little PA measurement reactivity work has focused on this group. Drastic measures to minimize reactivity responses may improve PA estimates if reactivity is substantial; if not, such measures are likely to limit the benefits of self-monitoring in an intervention [74], as well as waste resources and increase participant burden for those who are most in need of support. Alternatively, there may be subgroups for whom or research contexts in which PA measurement reactivity is particularly problematic. Focusing attention on low-burden ways to minimize reactivity responses in situations where it is most likely to bias PA estimates would be more cost-effective than universal measures. For example, introducing participants to the concept and the possibility of reactivity, encouraging participants to be aware of it, and emphasizing engagement in normal PA behavior despite research participation or the presence of a monitor may effectively mitigate effects on PA estimates [65,75]. Such an approach, rather than adding days of assessment, would also increase the accessibility of research and intervention for midlife adults, who often have busy, unpredictable schedules [76] and who may find additional days of assessment overwhelming (and therefore, decline to participate or withdraw after enrollment [77,78]). Findings from this study will provide high-quality evidence to determine the effect of measurement reactivity on PA estimates in a key population of interest, and thereby contribute to best practice recommendations for measuring PA in daily life [31,38].

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Data Availability

Data from the National Health and Nutrition Examination Survey (NHANES) and the Midlife in the United States Study (MIDUS) are publicly available from the Inter-university Consortium for Political and Social Research. Data analyzed from the clinical trials described earlier are available from the corresponding author upon reasonable request.

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Authors' Contributions

KB was involved in data curation, project administration, writing – original draft, writing – review and editing. GMS was involved in writing – original draft and writing – review and editing. IB was involved in writing – original draft and writing – review and editing. ALF was involved in data curation, formal analysis, writing – original draft, and writing – review and editing. RS was involved in writing – original draft and writing – review and editing. LMK was involved in writing – review and editing. MLB was involved in conceptualization, investigation, supervision, and writing – review and editing. JAM was involved in conceptualization, data curation, methodology, formal analysis, writing – original draft, and writing – review and editing. DA was involved in conceptualization, funding acquisition, methodology, supervision, writing – original draft, and writing – review and editing.

Conflicts of Interest

None declared.

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Abbreviations

CES-D: Center for Epidemiologic Studies Depression Scale
CVD: cardiovascular disease
INCOM: Iowa–Netherlands Comparison Orientation Measure
MIDUS: Midlife in the United States Study
MIMS: monitor-independent measurement summary
MVPA: moderate-to-vigorous physical activity
NHANES: National Health and Nutrition Examination Survey
PA: physical activity
PHQ-9: Patient Health Questionnaire
TSRQ: Treatment Self-Regulation Questionnaire
WALI: Weight and Lifestyle Inventory
WELL: Weight Eating and Lifestyle

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Protocol

Validating a Patient-Reported Outcome Measure to Improve Emergency Department Asthma Care: Protocol for an Observational Study

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Abstract

Background: Asthma affects 1 in every 12 persons in the United States, resulting in 1.9 million emergency department (ED) visits annually. However, the lack of patient-reported outcome measures (PROMs) validated for use in the ED limits the evaluation of interventions to improve ED asthma care.

Objective: To address this knowledge gap, this study protocol will (1) develop and test the validity and reliability of the Patient Reported Outcomes for Acute Asthma Care and Treatment instrument (PROAACT), (2) test whether receiving more guideline-concordant ED care is associated with improved PROAACT responses, and (3) evaluate the association between PROAACT score and subsequent ED revisits and hospitalizations.

Methods: This is a prospective cohort study of adult patients visiting the ED for acute asthma exacerbation across 3 EDs at an urban, tertiary care health system. Eligible patients are 18 years or older, have a prior diagnosis of asthma (self-reported or documented in the electronic health record), are English-speaking, and experiencing an ED visit for asthma exacerbation as determined by the treating clinician. Enrolled participants complete an initial PROM survey during their ED visit assessing their symptoms in the preceding 7 days, then complete a follow-up survey 7 days after ED discharge assessing changes in the symptoms in the subsequent 7 days. To test whether guideline-concordant care is associated with improved PROAACT scores, we will conduct a retrospective chart review of medications ordered during the ED visit, and then compare guideline adherence to changes in PROAACT scores. To test whether improved PROAACT scores are associated with fewer return ED visits and hospitalizations, we will extract all-cause ED visits and hospitalizations within 30 days from a regional health information exchange, and then compare usage to changes in PROAACT scores. We will use item response theory to develop scale responses based on summed item responses, which will allow us to test associations with clinical outcomes, including adherence to guideline-recommended care and return ED visits and hospitalizations.

Results: Recruitment is ongoing and has experienced numerous challenges related to the COVID-19 pandemic. To date, we have enrolled over 250 participants and have completed over 200 follow-ups. Recruitment is expected to conclude in spring 2025.

Conclusions: Our study is intended to validate the use of PROMs during ED visits for acute asthma exacerbation among adult patients. Completion of the proposed aims will result in one of the first PROMs intended for use among adult ED patients and support the feasibility of collecting PROMs in the ED setting.

Trial Registration: Clinical Trials.gov NCT04349020; https://clinicaltrials.gov/study/NCT04349020

International Registered Report Identifier (IRRID): DERR1-10.2196/67195

(JMIR Res Protoc 2025;14:e67195) doi:10.2196/67195

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KEYWORDS

asthma; patient-reported outcomes; emergency care

Introduction

Asthma affects 1 in every 12 persons in the United States [1], resulting in 1.9 million emergency department (ED) [2] visits annually; however, the impact of ED care on patient-reported outcomes after acute exacerbations is unknown. Racial and ethnic minorities and individuals with low socioeconomic status are more likely to have asthma and experience worse health outcomes, including asthma-related ED visits and hospitalizations [3]. According to the Centers for Disease Control and Prevention (CDC), female, Black and Hispanic patients with asthma are more likely to seek care in the ED, be hospitalized, and die of asthma-related complications [4,5]. Thus, patients who seek asthma care in the ED represent a population in critical need of interventions to improve clinical and patient-reported outcomes.

Patient-reported outcome measures (PROMs) are surveys that have been developed to ensure valid and reliable measurement of these patient-reported outcomes [6]. The National Institutes of Health and National Quality Forum have endorsed the use of PROMs to assess health outcomes and quality of care [6-8]. However, the adoption of PROMs in clinical settings remains limited, in part due to the lack of PROMs validated for use in ED settings [9]. Existing PROMs assess disease control and outpatient disease management [10-15]; however, they have not yet been validated or used among patients seeking ED care for acute asthma exacerbations. Existing PROMs such as the Asthma Control Test (ACT) [12] and Asthma Quality of Life Questionnaire (AQLQ) [10] primarily assess disease control, or specific constructs such as quality of life, and were intended for—and thus developed exclusively in—clinical trials and outpatient disease management.

To assess this knowledge gap, we developed the Patient Reported Outcomes for Acute Asthma Care and Treatment (PROAACT) survey to evaluate PROMs among patients seeking care for acute asthma exacerbations in the ED. This study builds on our preliminary work of assessing the feasibility of administering a PROM in the ED and the ability to engage ED patients in PROM development [9].

Our study has three aims: (1) we will first assess the psychometric validity and reliability of the PROAACT survey to assess outcomes prioritized by adult ED patients with asthma; (2) then, we will test whether receiving more guideline-concordant ED care is associated with improved PROAACT responses 7 days after ED discharge; (3) and finally, we will evaluate the predictive validity by testing the association between PROAACT responses and 30-day ED revisits and hospitalizations (Figure 1).

Figure 1. Data collection, outcomes, and predictors of interest. ED: emergency department; PROAACT: Patient Reported Outcomes for Acute Asthma Care and Treatment instrument.

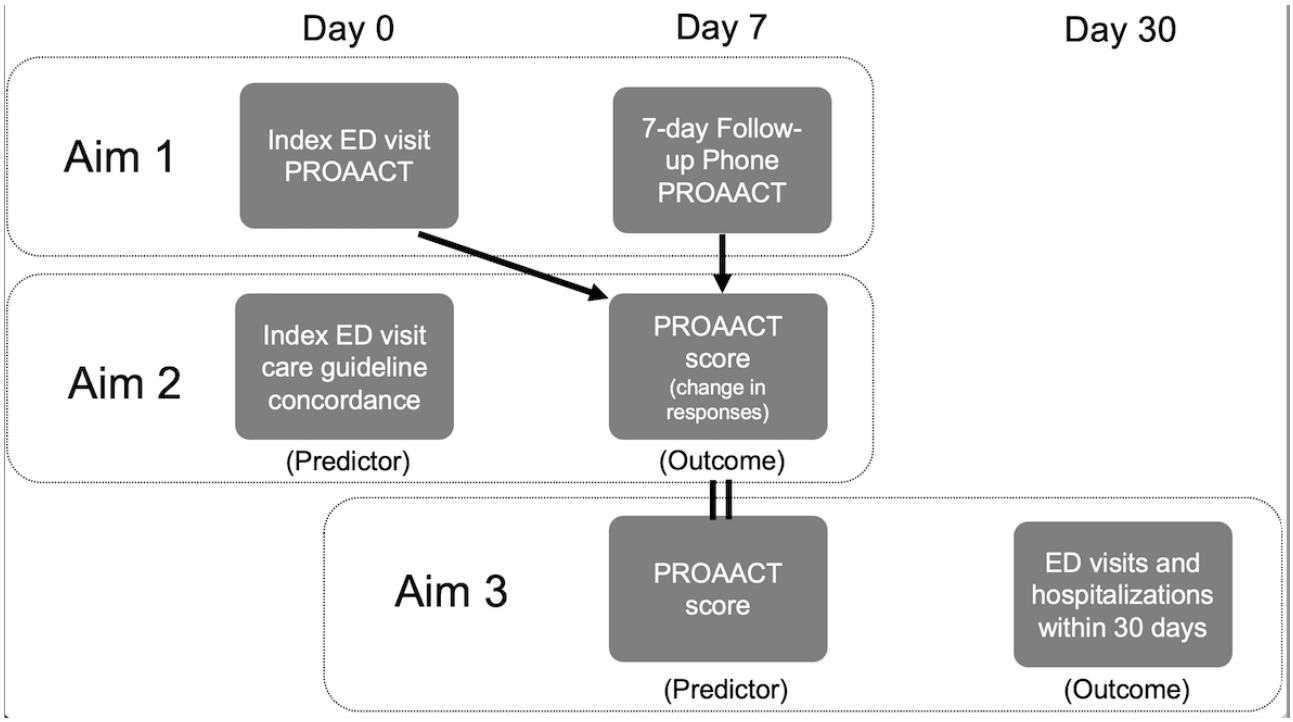

Methods

Study Design

This is a prospective cohort study enrolling a convenience sample of adult patients experiencing an ED visit for acute asthma exacerbation. This study is funded by the National Heart, Lung, and Blood Institute, and the grant review summary statement is included in the Multimedia Appendix 1. We registered the trial at ClinicalTrials.gov (NCT 04349020). We developed questions to be used in the PROAACT questionnaire based on prior published work [16] identifying outcomes of key

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importance to ED patients experiencing asthma exacerbation (Figure 2). After reviewing PROMs assessed in asthma studies and related constructs, we updated the item set by mapping ranked constructs to previously validated Patient Reported Outcome Measurement Information System (PROMIS) [17] item banks and Consumer Assessment of Healthcare Providers and Systems (CAHPS) [18] Survey (Table 1). The complete baseline and follow-up PROAACT surveys are included in the Multimedia Appendix 2.

Figure 2. Study workflow and timeline [16]. PROAACT: Patient Reported Outcomes for Acute Asthma Care and Treatment instrument.

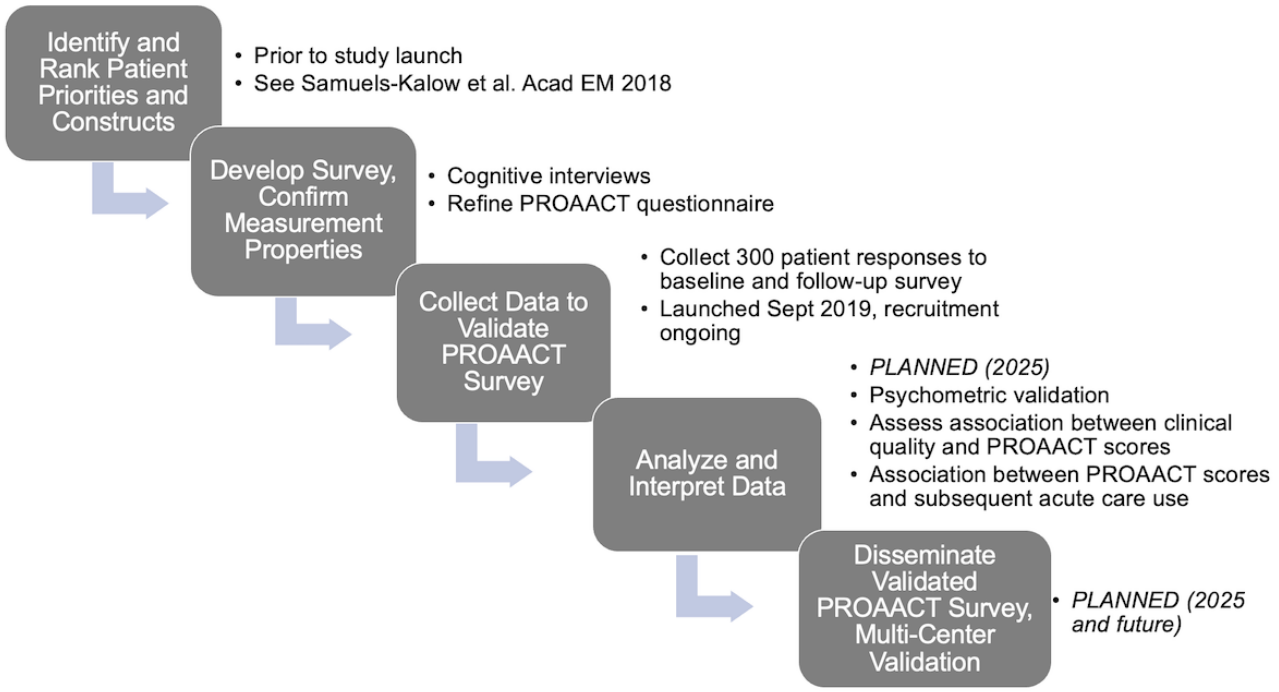

Table 1. Key patient-reported outcome measurement constructs, patient priority ranking, and validated question source.

Domain and ranking	Construct	PROMIS[a] short form
Access to care		Consumer Assessment of Health Care Provider and Systems (CAHPS)[b]
1	Able to get medication supplies	
6	Follow-up with primary care doctor	
Dyspnea and symptoms		
2	Breathing better, less wheezing or coughing	Dyspnea severity
Self-efficacy		
3 (tie)	Taking medications right	Self-efficacy for managing medications
5	Knowing enough about asthma and your plan	Self-efficacy for managing symptoms
Ability to participate in activities		
3 (tie)	Return to normal activities/Sleeping well	Ability to participate in social roles and activities
7	Return to work or school	Satisfaction with participation in social roles
Anxiety and stress		
8	Not needing to go back to the ER	CAHPS
	Feeling less worried or stressed	Dyspnea emotional response

[a]PROMIS: Patient Reported Outcome Measurement Information System.

[b]Not PROMIS Short Forms.

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Study Population and Setting

Participants are eligible to be approached for the study if they are 18 years or older, English Speaking, with a respiratory complaint (eg, “shortness of breath” or “wheezing”), and a self-reported or documented past medical history of asthma, and experiencing an ED visit for asthma as per the treating ED clinician. Because this project is intended to focus specifically on outcomes after ED care, eligible patients include those intended to be discharged to home after the current ED visit for asthma. Patients who are admitted to the hospital after ED evaluation and treatment receive further treatment from inpatient providers and specialists; thus, PROMs in these conditions reflect the entire acute care episode, not solely care provided in the ED.

Exclusion Criteria

Participants who speak a language other than English are not included in the study due to the lack of validation of the study survey in other languages. Participants admitted to the hospital were also excluded from the study. Other exclusions are inability to consent (eg, due to dementia, psychosis, altered mental status, intoxication, hemodynamic instability), serious diagnosis identified in the ED (eg, clinically significant dysrhythmia, structural heart disease, gastrointestinal hemorrhage, myocardial infarction, pulmonary embolism, aortic dissection, ectopic pregnancy, subarachnoid hemorrhage, or stroke), pregnancy, acute COVID-19 infection (probable or confirmed), either symptomatic within 10 days of onset or asymptomatic within 5 days of a positive test and prior diagnosis of chronic obstructive pulmonary disease, inability to read in English (if a friend or family member can read follow-up survey questions, they may still be eligible; however, if they cannot complete the follow-up survey, they are ineligible for the study). Additional exclusions included lack of phone number or mailing address including zip code, email addresses, visually or hearing impaired, and persons in law enforcement custody due to inability to collect 7-day postdischarge surveys.

Setting

Participants are identified and enrolled at 3 urban academic EDs. Site 1 is a 1171-bed tertiary- and quaternary-care teaching facility with approximately 110,000 annual ED visits. Site 2 is an 856-bed teaching hospital with approximately 100,000 annual ED visits. Site 3 is a 495-bed hospital serving 130,000 annual ED visits. The racial and ethnic distribution of the patient population served by these EDs is 35% Hispanic, 29% African-American, 19% White, 1% Asian, and 16% other. With respect to insurance, 13% of adult patients had no insurance, 42% had Medicaid, 24% had private insurance, and 21% had Medicare.

Aim 1: Prospective Recruitment

Study data are collected and managed using REDCap (Research Electronic Data Capture; Vanderbilt University) [19,20] electronic data capture tools. REDCap is a secure, web-based software platform designed to support data capture for research studies, providing (1) an intuitive interface for validated data capture, (2) audit trails for tracking data manipulation and export procedures, (3) automated export procedures for seamless data downloads to common statistical packages, and (4) procedures for data integration and interoperability with external sources.

A trained research coordinator screens participants for eligibility using the electronic health record (EHR). Participants are recruited in the ED from 8 AM to 8 PM, Monday through Friday, during their ED visit for asthma and prior to discharge from the ED. After screening for eligibility criteria (age and presenting problem), the research coordinator approaches an ED clinician (physician, midlevel, or nurse) to confirm if the participant is proficient in English, being treated for asthma, and is appropriate to participate in a survey study.

After confirming eligibility with the clinician, the research staff approaches patients in person to explain the study purpose and what study enrollment entails, including the benefits and risks of participation. Written informed consent is then obtained by the research coordinator to participate in the survey. We use the electronic study database REDCap to capture electronic consent. The e-consent function in REDCap allows us to create a template of the institutional review board (IRB)–approved consent forms, which participants can review and sign electronically, as well as receive a completed copy of the signed copy via email. e-Consent [21] may improve recruitment and retention in clinical research studies by addressing cultural and literacy barriers by including optional explanatory material (eg, defining terms by hovering over them with the cursor). After documenting informed consent, a paper document outlining the purpose of the study, the requirements, risks, and benefits are given to all potentially interested participants to review. Patients are reminded that their clinical care is in no way affected by their acceptance or refusal to participate in the study.

Data Collection

Data are collected and stored in REDCap. After obtaining consent, participants are encouraged to complete the initial PROAACT survey questions by entering responses into the REDCap questionnaire via iPad. Research coordinators are available to assist those with limited literacy and are available to clarify survey items or read survey questions verbatim as needed by participants. Research coordinators then enter name, phone number, email, medical record number, and demographic information as per participant self-report (gender, race, ethnicity, educational attainment, and employment status). Research coordinators also document the extent to which they assisted participants with the completion of the survey.

Follow-Up Procedures

Overview

A total of 7 days after enrollment and completion of the PROAACT survey at the index ED encounter, participants are asked to self-administer a post–ED discharge follow-up survey using an individualized REDCap survey linked to each participant. Research coordinators contact participants via email, phone, and text message using the contact information they provided at the time of enrollment. Emails and text messages are sent once daily for up to 3 consecutive days starting on day 6 to remind participants of their 7-day follow-up survey. Text messages are sent through Twilio (Twilio Inc) [22] for automated SMS survey distribution and response collection, a

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third-party web service that is integrated with REDCap, allowing users to send survey invitations and alerts to participants as SMS text messages. Research staff also attempted to call subjects a maximum of 3 times using on-site telephones in the ED research office. Upon establishing contact, subjects are reminded of the study and asked if they are able to complete the telephone survey.

Upon completion of the telephone survey, subjects receive a US $20 electronic or mailed gift card as an incentive. Subject names and mailing addresses are written directly onto envelopes to be mailed and are not stored. Participants may decline or withdraw from the study by written or verbal request; however, they do not receive the incentive if they elect to withdraw.

Aims 2 and 3: Assessing Concordance

To assess the association between PROAACT responses and adherence to guideline-recommended ED care, we will perform a structured extraction of EHR data at the conclusion of enrollment using the institutional data warehouse. We will collect patient-level factors, including age, sex, past medical history, medication history (to assess asthma severity), insurance status, smoking history, vital signs at triage, medications administered in the ED, and medications prescribed upon ED discharge.

We will obtain data on repeat ED visits and hospitalizations from a regional health information exchange. Prior studies have demonstrated that over 1 in 3 patients who have a repeat ED visit after discharge visit a different facility [23]. Among patients who frequently visit the ED (≥4 ED visits in 30 days), HIE (health information exchange) data from the Healthix Regional Health Information Organization (RHIO) data identified 16% more ED visits than single-site data [24]. Healthix data will be linked to PROAACT responses and patient-level variables collected from the EHR using the patient name and date of birth.

Analysis

Overview

We plan to administer the baseline and follow-up PROAACT survey to 300 adult ED patients with asthma. Based on historical data on annual ED visits by adult patients for asthma across all sites, we estimate a total population size of approximately 4500 over 3.5 years. Thus, a sample of 300 subjects will allow us to approximate a 5% margin of error within a 95% CI. In order to obtain 300 completed follow-up surveys, we anticipate needing to enroll 350 patients in the initial survey phase. Although a baseline sample of 300 is too small for evaluating measurement equivalence, it is adequate for selected latent variable models used in factor analyses [25].

Aim 1 Analysis

Preliminary analyses with item response theory are conducted to examine information functions and derive item parameters for comparison with other sociodemographic groups from data collected in future studies. We evaluate candidate items for item reduction to generate the item set that provides maximum test information at the mean responses, which serve as the final, short-form survey for subsequent external validation, dissemination, and implementation. As part of the psychometric analysis, we develop scale responses based on summed item responses. This enables us to examine construct, convergent, criterion, and predictive validity by examining associations with clinical outcome variables, including adherence to guideline-recommended care and return ED visits and hospitalizations.

Aim 2 Analysis

Next, we will test the hypothesis that improved PROAACT responses are associated with guideline-adherent ED care. We will assess concordance with Level A GINA (Global Initiative for Asthma) recommendations [26]: (1) treatment with inhaled β-agonists in the ED, (2) treatment with systemic corticosteroids in the ED for patients who do not respond completely to initial short-acting β-agonist therapy, (3) treatment with inhaled corticosteroids in the ED for those not receiving systemic corticosteroids, and (4) not treating with intravenous β-agonists in the ED. Given prior research suggesting high adherence to some guidelines (eg, inhaled β-agonists), we will examine concordance as a composite binary predictor (adherence to all 4 guidelines vs not) and separately, evaluate each recommendation as an independent predictor. We exclude the level A recommendation to administer magnesium for severe asthma exacerbations because patients with severe asthma are likely to be admitted and likely unstable to participate in a survey.

We will assess the PROAACT responses (primary outcome) using a distribution-based approach such as the paired t statistic to evaluate the change in responses in relation to the probability that the change occurred at random. We will calculate baseline descriptive statistics for patient characteristics (sex, age, race, insurance, and burden of comorbid illness). We will analyze guideline concordance of ED care both for all patients and stratified by patient characteristics (sex, age category, race, insurance, and burden of comorbid illness), ED provider, and enrollment site in order to identify potential baseline disparities by patient characteristics, provider or institutional adherence to guidelines. We will analyze the relationship between guideline concordance of ED care and PROAACT responses in a multivariable regression applying generalized hierarchical mixed-effects models to account for repeated measures of the same patient, as well as within-provider and within-hospital correlation of observed outcomes. We anticipate a sample size of 300 with an α level of .05 and 80% power will detect a 12% difference in PROAACT responses between groups receiving guideline-concordant care versus not.

Aim 3 Analysis

To test our hypothesis that patients who report greater improvement in patient-reported outcomes after ED discharge will have fewer ED visits and hospitalizations during the ensuing 30 days. The primary outcome is the rate of acute care encounters (all-cause ED revisit or hospitalization) within 30 days after the index ED discharge. We anticipate an overall event rate of 30%-40% based on the observed statewide rate of 26% in our preliminary data and the higher prevalence of risk factors for increased asthma usage in our patient population (Black and Hispanic race, exposure to urban pollution including indoor pests and allergens, limited health care access, lower

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income). ED revisits resulting in admission will count as one event. Secondary outcomes include all-cause ED revisits and hospitalizations within 180 days. We use all-cause ED revisits or hospitalizations given our preliminary data showing a substantial majority of repeat ED revisits and admissions were asthma-related in New York State in 2013 and because the reliability of Healthix diagnosis codes varies by institution. While a sample size of 300 and 35% event rate may not be sufficient to quantify the magnitude of the relationship between PROAACT responses and subsequent health care usage, our test for association and directionality will support the predictive and longitudinal validity of PROAACT as a stand-alone measure of asthma quality.

We will calculate 30-day event rates (for ED revisits and hospitalizations) using each patient's index ED visit as the unit of analysis. We will first perform univariate analyses using chi-square tests to compare groups with and without improved PROAACT responses. To test the adjusted association between PROAACT responses and acute care use, we will conduct multivariable regression, using rate-based outcome distribution such as negative binomial or Poisson with zero inflation in a hierarchical model to account for patient- and hospital-level confounders, such as age, sex, race, ethnicity, burden of chronic conditions, and site of index ED visit.

Ethical Considerations

This study was approved by the Mount Sinai IRB (Mount Sinai IRB protocol number 19-00364 and Stanford IRB protocol number 66322). The IRB has determined that this research involves no greater than minimal risk. Minimal risk means that the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests (45CFR.46.102; 21CFR50.3k). The IRB approved this research under expedited review procedure categories 5 and 7. Study participants provided written informed consent. Participant data are secure and confidential in an encrypted and password-protected REDCap database. Data include identifiers to link PROAACT survey responses to usage data regarding subsequent ED revisits. Participants were paid US $20 via gift card upon completion of the follow-up survey.

Results

Funding was received on August 15, 2019, and recruitment was launched in September 2019. As of December 2024, we have enrolled over 200 participants toward our goal of 300. Recruitment is expected to conclude in spring of 2025 and we anticipate peer-reviewed publication of our findings in early 2026.

Discussion

Overview

Although PROMs are necessary to evaluate the impact of ED Asthma care, no PROMs have been developed or validated in adult ED patients with asthma to date. To our knowledge, this study will be among the first PROMs validated specifically with ED patients for use in ED settings. The diverse population of patients presenting to the ED for asthma at our study sites has the potential to increase the generalizability of our findings.

We anticipate the successful completion of the PROAACT scale's psychometric and predictive validity will enable its use to assess and improve the quality of ED care. The multidimensional nature of the PROAACT scale, which assesses not just physical symptoms such as dyspnea, but also perceptions of access to care, will enable targeted improvements to ED asthma care. Further, if we find patients who do not report improvement on the PROAACT scale have received care that is not concordant with GINA guidelines, we could develop interventions to improve provider adherence to guidelines, for example, clinical decision support and audit-and-feedback. Similarly, if patients without improvement in PROAACT responses are shown to have a higher risk of subsequent ED visits, care management programs may target these individuals for more closely coordinated follow-up care after ED discharge.

Despite their importance and patient-centeredness, PROMs are difficult to collect in the ED. The ED is a fast-paced clinical environment that imposes time and workflow constraints. Many patients are acutely ill and suffer from impaired cognition, which limits their ability to provide reliable responses. Health conditions are often multifactorial and undifferentiated in the ED, which is less problematic for patients with a history of asthma who present with clinical symptoms of acute asthma exacerbation, but may result in the exclusion of patients with new-onset asthma who present with dyspnea and other respiratory symptoms. Many EDs are safety-net institutions with limited technology, poor integration of PROMs with technology systems such as EHRs, and lack of resources to act on PROM data. Our study is intended as a validation study; however, overcoming these logistic barriers is important to enable routine PROM collection in acute care settings.

This study specifically focuses on ED patients who are discharged so that PROMs reflect the care that was provided in the ED setting. Over 80% of adult patients with asthma are discharged nationally [24], thus, these patients represent the majority of patients presenting to the ED with asthma. While the inclusion of admitted patients may allow for higher clinical severity, patients who are admitted to the hospital receive interventions such as specialist consultation, respiratory therapy treatments, and other types of care that do not reflect the quality of care provided in the ED.

We also considered alternative time periods for the follow-up survey in 7 days; however, we sought to adapt the PROAACT items from previously validated sources whenever possible. Thus, because 7 days [27] as previously been used as a time period for assessing post–ED discharge outcomes and the PROMIS scales assessing key domains prioritized by patients (dyspnea, ability to participate in daily activities, etc) had previously been validated for use on a 7-day time scale, we proceeded with a 7-day interval to assess changes in responses.

Limitations

Our study has several limitations. First, this study will be conducted in 3 urban, academic EDs in the Northeast, and the

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study results may not be generalizable to other EDs. However, we are enrolling a racially, ethnically, and socioeconomically diverse population that will provide useful insights for many clinical ED settings. Second, the PROAACT survey is not yet translated or validated in non–English-speaking populations; due to this, we have excluded non-English speakers. We anticipate including non-English speakers in a future study, which will require additional qualitative interviews and validation. Finally, recruitment was launched in late 2019 and impacted by the COVID-19 pandemic shortly thereafter, which has resulted in the following key modifications:

First, the recruitment period, initially intended to be 3.5 years in duration, has been extended to 5 years due to the COVID emergency pandemic occurring in March 2020. Recruitment for the study was paused from April through June 2020 coinciding with the initial surge of the COVID-19 pandemic in New York City. Active recruitment resumed in July 2020 and has been actively screening and enrolling patients since then; however, total ED visit volumes continued to be lower than pre–COVID-19 levels, consistent with national trends showing reductions of up to 42% compared to 2019 [28]. While ED visit volumes have since increased in each subsequent year, they have not yet returned [29,30] to pre–COVID-19 levels. Thus, recruitment is still ongoing. We also experienced substantial turnover in staff, which delayed our ability to recruit eligible patients. These workforce changes are consistent with national trends showing double the historical rate of job resignations in 2021 [29,31]. To fill this gap, we used medical students and undergraduate students to supplement recruitment needs.

Conclusion

Our study is among the first PROMs developed specifically with ED patients for use in ED settings and has the potential to be used in future interventions to improve ED asthma care. We anticipate study results will inform a future study in which there will be a multicenter validation and implementation study of PROAACT. The validation of a PROM for ED asthma will enable the evaluation of interventions to improve ED asthma care and accelerate improvements in asthma care quality.

Acknowledgments

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Conflicts of Interest

During the conduct of this study, MPL received funding from the Agency for Healthcare Research and Quality (AHRQ) and National Institute on Aging (NIA) unrelated to this work; LG received funding from the National Institute of Minority Health and Health Disparities (NIMHD), National Institute of Drug Abuse (NIDA), Department of Defense, and University of California at Davis unrelated to this work; and LDR received funding from the National Heart, Lung, and Blood Institute, National Cancer Institute, NIMHD, NIDA, and Leidos Biomedical Research, Inc unrelated to this work.

Multimedia Appendix 1
Peer review report from MPOR (MA) - NHLBI Mentored Patient-Oriented Research Review Committee (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 144 KB - resprot_v14i1e67195_app1.pdf]

Multimedia Appendix 2
PROAACT (Patient Reported Outcomes for Acute Asthma Care and Treatment instrument) survey.
[PDF File (Adobe PDF File), 103 KB - resprot_v14i1e67195_app2.pdf]

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Abbreviations

ACT: Asthma Control Test
AQLQ: Asthma Quality of Life Questionnaire
CAHPS: Consumer Assessment of Healthcare Providers and Systems
CDC: Centers for Disease Control and Prevention
ED: emergency department
EHR: electronic health record
GINA: Global Initiative for Asthma
HIE: health information exchange
IRB: Institutional Review Board
PROAACT: Patient Reported Outcomes for Acute Asthma Care and Treatment instrument
PROMIS: Patient Reported Outcome Measurement Information System
PROM: patient-reported outcome measure
REDCap: Research Electronic Data Capture
RHIO: Regional Health Information Organization

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Proposal

A Brief Engagement Intervention Adapted for Racial and Ethnic Minority Young Adults in Mental Health Services: Protocol for a Pilot Optimization Trial

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Abstract

Background: Young adults from racial and ethnic minority (REM) groups are at greater risk of disengaging from vital mental health services than their majority group peers. Emerging research suggests developmentally tailored interventions that enable personalized exploration of cultural and structural contexts; encourage trust in relationships with service providers; enhance hope for recovery; and increase self-efficacy to adhere to treatment can improve engagement among underserved REM young adults with mental health disorders.

Objective: Just Do You is a brief young adult treatment engagement intervention. Although Just Do You showed evidence of efficacy with medium effect sizes in a previous clinical trial, not all participants benefited, and some of the proposed mediators were not changed. Grounded in the multiphase optimization strategy (MOST), we propose to improve the provision and effects of Just Do You by testing a set of new candidate intervention components that complement the original Just Do You program. This can potentially enhance its effects on engagement and mental health service use for REM young adults.

Methods: A total of 3 new candidate behavioral intervention components and their putative mediators were designed in collaboration with REM young adults and other key informants. The new candidate components and their mechanisms of action are (1) cultural identity (perceived cultural competency), (2) future self (hope), and (3) understanding environments (self-efficacy). A pilot optimization randomized controlled trial will be conducted in an outpatient mental health setting with REM participants aged 18-34 years (N=80). The candidate components will be tested in a 2^3-factorial design where all participants will receive Just Do You and be randomly assigned to one of 8 experimental conditions, each composed of a unique combination of candidate components. We will assess the new components' acceptability and feasibility, and explore preliminary evidence of their effects on the primary outcome (engagement in mental health care) and mediators at a 3-month follow-up assessment.

Results: The study began recruitment in December 2024 and is planned to continue through December 2026. Final study completion is planned for March 2027. The results will be disseminated via professional and scientific publications, presentations, and social media, as well as to members of the participant community.

Conclusions: Findings from this study will supply critical deployment-focused evidence to inform a future randomized controlled trial as the next step in this program of research. We ultimately aim to create an effective, efficient, and scalable intervention to improve engagement and mental health outcomes among REM young adults.

Trial Registration: ClinicalTrials.gov NCT06508450; https://clinicaltrials.gov/study/NCT06508450

International Registered Report Identifier (IRRID): DERR1-10.2196/68885

(JMIR Res Protoc 2025;14:e68885) doi:10.2196/68885

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KEYWORDS

racial and ethnic minorities; mental health; young adult; engagement; optimization; adaptation, multiphase optimization strategy; factorial design

Introduction

Background

In the United States, young adults (aged 18-34 years) with mental health disorders who are from racial and ethnic minority (REM) groups are at high risk for withdrawing from mental health treatment prematurely [1], particularly those with lower socioeconomic statuses [2]. Younger adults in general have lower rates of treatment for their mental health concerns than any other age group [3]. Among young adults with serious mental illness (SMI; eg, schizophrenia-spectrum and mood disorders), poor adherence to mental health care is associated with significant health and social disadvantages (eg, poverty, incarceration, and early mortality) [4,5]. On the whole, staying engaged in mental health treatment leads to improvements in health outcomes and mental health recovery [6]. However, there is very little evidence-based interventions designed for increasing the participation of young adults with mental health disorders in treatment [7], and studies show disparities in outcomes for REM groups [8,9].

Engagement Interventions Tailored for the Transition to Adulthood

Adult mental health services are not generally equipped to address the developmental complexities of young adulthood, and typically lack services and interventions adapted specifically for young adults [10,11]. Young adulthood is an exploratory period marked by transitions and instability in various areas of life (eg, residential status, work, school, and social relationships) [12]. Treatment adherence can be a challenge under these circumstances, especially considering that young adults gain greater responsibility and autonomy over their mental health care during this developmental period [13,14]. Stopping and starting treatment is common. Because symptom onset often occurs around this age [15], deciding to drop out of treatment is risky for young adults with SMI. Without treatment, SMI symptoms can place significant constraints on developmentally appropriate exploration [16] and successful life transitions [4,17]. Recent approaches to maintaining engagement in mental health care during the transition to adulthood target individuals ranging from 15 to 35 years old [18], and have primarily focused on expanding adolescent and family service models [19-21]. However, research suggests that young people with mental disorders become less engaged with treatment once they enter adult systems of care [4,22], and that marginalized young adults may not have access to family members who can provide support [16,23].

Developmentally tailored approaches that focus on improving mental health care literacy and self-efficacy have the potential to improve engagement in treatment among REM young adults with mental health disorders [21]. Studies show REM young adults report apprehension and uncertainty about the nature of treatment and the processes for accessing it [24,25]. Research on mental health help-seeking among young adults indicates that negative perceptions about treatment play a significant role in their reluctance to initiate care [14,26]. Young adults with mental health conditions report that treatment services can seem irrelevant and unhelpful [27], and they experience stigma [28,29] and hopelessness about the future [30] that can present barriers to engagement in services [31].

Person-Centered, Culturally Responsive Interventions

Interventions that target cultural and intersectional factors along with developmental stage are essential for engaging REM young adults living with mental health disorders [20,21,32]. The most intensive exploration of racial, ethnic, and other key social identities often happens during young adulthood [33], and informs an individual's sense of self and direction in life [34]. REM young adults have expressed hesitancy about mental health treatment due to historical and current racism in health care [35], differences in perceived need for mental health care [36], and cultural beliefs and preferences around how to address mental health problems [37]. Studies show that REM young adults experience structural vulnerabilities (eg, living in high poverty areas, more coercive rather than voluntary treatments) [38], report low cultural competency among mental health care providers [39], along with high levels of mistrust of providers [24], which serve as key barriers to participating in treatment. Research on REM young adults in mental health care indicates that they desire greater knowledge and understanding of their identities and social positions by mental health professionals [25].

Culturally responsive interventions can improve treatment engagement by facilitating communication about the cultural and structural context from the young adult's perspective [40]. This allows treatment providers to be responsive to young adults' experiences and identify barriers that can arise and strengths that can be drawn upon in treatment [41-43]. Mental health interventions adapted for REM youth have incorporated culturally relevant elements (eg, language, metaphors, values, and traditions) for specific racial-ethnic groups [44]. But, adapting intervention protocols for each cultural group is not feasible for public and community mental health services that will likely provide care for youth from a wide range of backgrounds [42,45]. Also, interventions adapted for a specific racial-ethnic group may not be able to address an individual young person's intersectional social positions (eg, gender, sexuality, wealth, immigration, and multiracial-ethnic statuses) that influence their mental health and experiences of mental health care [42]. Recent research on cultural adaptation favors person-centered approaches that invite discussion of cultural and structural factors, and allow individuals to articulate what matters most about their identities, without the need to adapt intervention protocols for prespecified aspects of cultural identity [46,47].

Just Do You Intervention

This study tests 3 new candidate behavioral intervention components focused on cultural and structural content that can

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potentially be added to the Just Do You intervention in order to improve its effects for REM young adults with SMI. Just Do You [48] is an evidence-informed treatment engagement intervention that uses narrative health communication, role models, and expressive arts in a brief curriculum aimed at orienting young adults to treatment in adult mental health care settings. As young people become familiar with the staff at a clinic and the services that are available, they form impressions about treatment that allow them to make informed decisions about whether to continue. The overall goal of Just Do You is to provide an orientation to mental health treatment that will support both initial and ongoing service engagement [49]. Just Do You is delivered by a clinician and a professional peer who is further along in their mental health recovery and life experiences (a Recovery Role Model) who facilitates conversations and expressive activities based on the orientation content. This cofacilitator approach models for young adults how to collaborate with professionals in their treatment. The developmentally tailored curriculum conveys information about mental health treatment and clinic services to young adults through credible sources (eg, peer and celebrity testimonials) and multisensory activities (eg, art therapy directives) designed to hold their attention and positively shape their perceptions about treatment, stigma, and service providers [49]. In a recent randomized controlled trial (RCT) conducted at 4 sites associated with 2 large urban mental health organizations in the eastern United States (ClinicalTrials.gov, NCT03423212), Just Do You demonstrated feasibility, acceptability, and efficacy for improving treatment engagement and personal mental health recovery at 3 months after baseline, with a medium effect size, among a sample of 121 young adults with SMI, 95% of whom were from Black, Latinx, and multiracial minoritized groups [50,51].

Just Do You is based on the young adult framework of mental health service use [24]. The young adult framework was developed through studying young adults with mental health disorders and applying theories of behavior change [52,53] and mental health service use [54] to describe the phenomenon of disengagement from treatment during the transition to adulthood. Just Do You was designed to target mechanisms of engagement in services identified by the young adult framework through developmentally tailored behavior change techniques [55]. In the most recent clinical trial described above, Just Do You demonstrated statistically significant effects on four proximal mediators from the young adult framework: (1) perceived advantages of treatment, (2) trustworthiness and (3) credibility of treatment providers, and (4) stigma surrounding service use. The young adult framework was validated by trial results, but Just Do You did not impact all targeted mediators [50], including hope and self-efficacy, suggesting the need for further culturally tailored adaptations to strengthen the intervention's influence on theoretical mechanisms of engagement and service use, as well as mental health outcomes.

Conceptual Model

Results from the original Just Do You trial, along with findings from previous research discussed above, suggest that adding select behavioral intervention components may boost the effects of Just Do You on key mediators for REM young adults. Participant data in the original Just Do You trial across both treatment and control conditions showed that REM young adults had strong racial-ethnic identities (ie, sense of belonging and connectedness to their racial-ethnic groups) [35,56], and that strong racial-ethnic identity was associated with treatment engagement through increased hope, self-efficacy, and provider credibility ratings [57]. Building upon the conceptual model for the previous trial of Just Do You, we have designed 3 new candidate behavioral intervention components to address important mediators for REM young adults (Figure 1). The new candidate components expand upon these findings regarding the importance of racial-ethnic identities and the salience of structural barriers, and they add content to improve cultural and structural competency practices in mental health [46,58]. The new candidate behavioral intervention components seek to (1) enhance perceived cultural competency of providers, (2) improve hope (ie, self-belief and outcome expectancy that recovery is possible), and (3) improve self-efficacy for treatment engagement (ie, decrease perceived difficulty or increase control of engagement behaviors). Hope and self-efficacy were targeted as mediators in the previous trial of Just Do You but did not change [50].

Figure 1. Conceptual model.

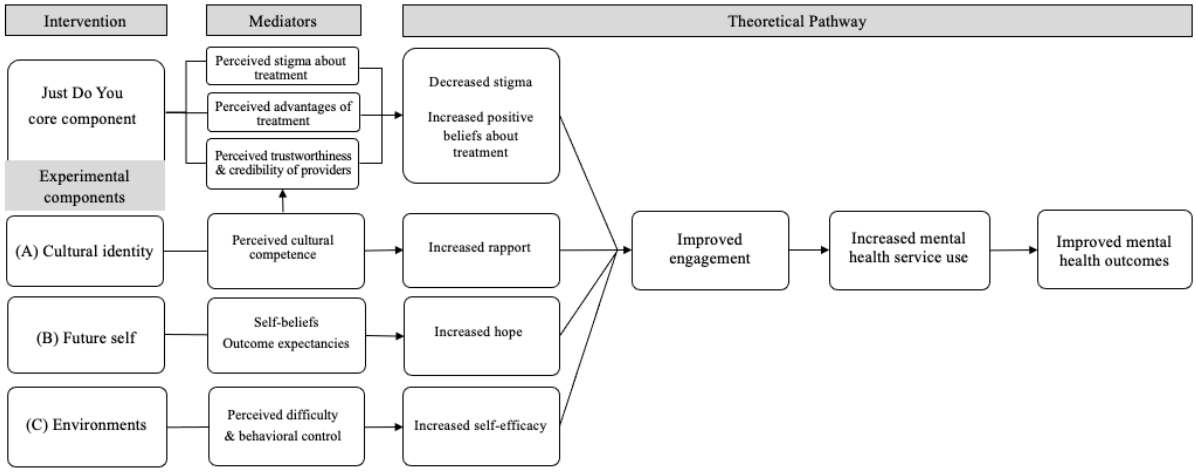

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Candidate Behavioral Intervention Components

Overview

The new candidate components are designed to explicitly address person-centered cultural and structural content while targeting the proposed mediators of engagement specified in the conceptual model. The candidate components were selected by the first author in consultation with the research team, which included a creative arts therapist and the creator of Just Do You. All candidate components maintain the theoretical framework and delivery approach of the original intervention. The components use narratives, role models, and creative arts to preserve fidelity to the original Just Do You curriculum's evidence-informed health communication strategies. Each candidate component was selected to meet these criteria based on preliminary research, and they were collaboratively designed using the ADAPT-ITT (Assessment, Decision, Adaptation, Production, Topical experts-integration, Training, and Testing) model [59]. ADAPT-ITT is a well-established participatory approach for modifying interventions to be effective with a specific target population. Through this process, new components were designed with REM young adults and mental health professionals, including peer service providers, in community-based adult psychiatric services. Our year-long collaborative design project produced versions of the candidate components that are more likely to be acceptable, feasible, and effective in adult community mental health settings. The 3 new candidate components, and their respective training and fidelity protocols, were manualized and formatted to complement the Just Do You core intervention as additional sessions.

Component A

Cultural identity is based on recent advances in cultural identity-affirming psychosocial interventions for youth [60,61] and the Cultural Formulation Interview (CFI) for *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) [46]. Research suggests rapport-building strategies that prompt positive cognitions about culture in REM young adults can communicate, both implicitly and explicitly, that their cultural identities are important and will be respected within the therapeutic relationship [62]. The CFI guides mental health service providers to initiate conversations about the cultural context of individual patients at the start of treatment, in order to better address barriers that can arise and identify cultural strengths that can be drawn upon in clinical care. The CFI has been shown to enhance initial health communication and therapeutic rapport [63], and improve ongoing treatment attendance among adults and youth from minoritized racial-ethnic groups in outpatient mental health treatment [42,43].

Component B

Future self draws upon concepts from solution-focused brief therapy [64] and identity-based motivation in health [65] to help young adults generate positive, culturally relevant imagery of their future selves and connect those images to sustained engagement in mental health services. Solution-focused brief therapy techniques explicitly focus on generating hope and receptivity to new thoughts and actions [66]. Identity-based motivation techniques involve framing the actions needed to attain a desired future as congruent with social identities that are most salient to a young person [67]. Component B also uses elements of Photovoice [68], in which young adults take photos or videos to express a narrative storyline about their future self in recovery. Photovoice has been used as a mental health recovery intervention for people living with SMI [69,70], and previous studies highlight the utility of this approach and its alignment with the narrative and creative arts strategies in Just Do You [69,71].

Component C

Understanding environments draws from the structural competency framework [72] to address social and environmental factors that shape REM young adults' engagement in mental health services (eg, unstable housing, poverty, community violence, and community protective factors). Using elements from neighborhood mapping [73,74], the professional peer facilitator (Recovery Role Model) initiates planning with young adults to manage barriers and increase their self-efficacy to sustain engagement. This approach makes use of the peer support strategy already employed in Just Do You, and previous research indicates that working with peers who relate to their social challenges is associated with greater outpatient engagement [75] and reduced disparities in service use among REM young adults with mental health disorders [76].

Multiphase Optimization Strategy

This study will examine the new candidate intervention components using the multiphase optimization strategy (MOST) [77]. MOST is a principled method for identifying the optimal combination of intervention components before testing an intervention in a resource-intensive RCT [78]. The MOST framework consists of 3 stages: preparation, optimization, and evaluation of the intervention in a standard 2-arm RCT. This pilot trial comprises the preparation stage of MOST, in which we will pilot the study protocols to enroll and assess participants and deliver the components in a community mental health setting using a factorial design. The pilot optimization trial will establish the feasibility and acceptability of the approach and the candidate components in the intervention setting, and explore preliminary evidence of components' effects on study outcomes and mediating variables, in preparation for a future fully powered optimization RCT.

Study Objectives

The overall goals of our pilot research are (1) evaluate the acceptability and feasibility of the new candidate intervention components, (2) explore preliminary indications of components' impact on engagement and service use (ie, active involvement and attendance to treatment) and on hypothesized mediators at 3-month follow-up, and (3) refine aspects of the approach for a future optimization RCT (eg, implementation, recruitment, and assessment strategies). We will test the new candidate components with REM young adult participants in an outpatient community mental health setting, using mixed methods to collect and integrate data from quantitative measures and qualitative interviews.

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Methods

Pilot Trial Design

This study uses a balanced 2^3 factorial experiment. Each factor will have 2 factor levels, included (yes) or excluded (no), resulting in 8 experimental conditions that represent all possible combinations of the new candidate components (see Table 1). All participants will receive the Just Do You core component, followed by the candidate components they were assigned to receive, if any. Thus, participants will be randomly assigned to one of 8 experimental conditions and receive Just Do You and 0-3 new components. We will explore preliminary evidence of component effects on the primary outcomes by comparing the mean outcomes across included conditions versus the mean outcomes across excluded conditions. For example, Component A conditions 5-8 will be compared to conditions 1-4. The factorial design does not directly compare each condition or use a traditional control group. Instead, each factor level serves as its own control. Consistent with a convergent parallel mixed methods design [79], semistructured qualitative interviews will be conducted postintervention with participants to provide context and improve our interpretation of quantitative results. A total of 80 participants will be enrolled.

Table 1. Experimental conditions in the 23-factorial design.

Experimental condition	Just Do You	Component A	Component B	Component C	Sample size, n
1	Yes[a]	No[b]	No	No	10
2	Yes	No	No	Yes	10
3	Yes	No	Yes	No	10
4	Yes	No	Yes	Yes	10
5	Yes	Yes	No	No	10
6	Yes	Yes	No	Yes	10
7	Yes	Yes	Yes	No	10
8	Yes	Yes	Yes	Yes	10

[a]Yes: component is included.

[b]No: component is excluded.

Study Setting

Young adult participants will be recruited from an outpatient psychiatric rehabilitation program (the study site) in the eastern United States that serves a community of primarily adult Black and Hispanic or Latine individuals. Mental health services offered by the study site include therapeutic and skills-based group treatment, individual counseling, medication support, and resource coordination for transportation, housing, employment, and other recovery supports.

Eligibility Criteria

Young adult participants will be eligible if they are between the ages of 18 and 34 years, identify as REM (ie, from racial and ethnic groups other than non-Hispanic, White), and are enrolled in mental health services at the study site. The eligible age range is consistent with definitions of young adulthood by the United States Census Bureau [80] and the age range most commonly targeted in early intervention services for SMI [18]. Participants will be excluded if they cannot comprehend and speak English or if they cannot understand the consent process.

Recruitment

Participants will be recruited through flyers distributed by the research team that briefly describe the study and how to contact research staff for more information. Research staff will be present at the study site on a weekly basis to provide information in person. Interested participants who make contact with the research staff will be offered a brief eligibility screening. Participants who are eligible will be asked to provide their informed consent for enrollment.

Recruitment activities are planned to take place over 24 months. Administrative staff at the study site reported that there are about 30 young adults meeting eligibility criteria enrolled in the clinic services at any given time, with about 4 new enrollments per month. We estimate a 10% refusal rate based on the low rates of refusal in the previous Just Do You trial, which will allow us to recruit the sample over 24 months. To enhance tracking and retention for follow-up assessments, we will collect extensive contact information for all participants, which includes contact information for up to 3 individuals who will be able to locate them, and use reminder calls or texts for assessment appointments.

Randomization

Upon enrollment in the study, participants will be assigned to an experimental condition using a randomization plan programmed into a database on the REDCap (Research Electronic Data Capture) platform [81]. The program will assign participants using block randomization to maximize balance across conditions (ie, random assignment to 1 of 8 conditions per block). Condition assignments will be unblinded.

Intervention

The intervention period for each participant will last from 1 to 5 weeks, depending on the experimental condition. The conditions have a maximum of 5 sessions, delivered once per week, and sessions last for up to 1.5 hours (refer to content in

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Table 2). Following a baseline assessment, the core intervention will be delivered for all participants, and additional components will be delivered subsequently in the following weeks. In addition, participants are expected to attend all appointments for mental health treatment at the study site. All intervention components will be delivered by a mental health clinician and a professional peer specialist employed by the study site. The principal investigator will provide initial and ongoing training to the interventionists on the manualized intervention components and reporting procedures for adverse events throughout the study.

Table 2. Content and duration of components.

Component	Number and duration of sessions	Topics and activities
Just Do You	1 Session 60 minutes	• Guiding principles of recovery • Recovery Role Model personal narrative • Videos of celebrity service users • Personal goals related to recovery • Characteristics of a trustworthy professional • Introduction to clinic services
A: Cultural identity	1 Session 60 minutes	• Feeling seen and heard • Introduction to creative arts therapy techniques • Cultural identity art activity • Recovery Role Model personal narrative
B: Future self	2 Sessions 60 & 30 minutes	Session 1 • Overcoming challenges and finding hope • Introduction to creative arts therapy techniques • Mental health resilience in music and videos • Strengths and inspiration of art activity • Recovery Role Model personal narrative • Introduce guidelines for photo activity Session 2 • Brief check-in after completing the photo activity
C: Understanding environments	1 Session 60 minutes	• Overcoming barriers in the environment • Introduction to creative arts therapy techniques • Map of your environment art activity • Recovery Role Model introduces services/strategies for addressing barriers to engagement

Assessment Procedures

Assessments of engagement will occur at baseline, posttest (after intervention completion), and 3-month follow-up. At each assessment, participants will report on involvement in their treatment, and their perceptions of stigma, benefits, trust and rapport with providers, hopefulness, and the difficulty associated with treatment engagement. In-depth acceptability interviews will be conducted at posttest with 40 participants purposively sampled from each experimental condition. Acceptability interviews will be focused on experiences with intervention components, aspects of implementation, and any factors that promoted or impeded intervention adherence. Each assessment is expected to last for 1 hour.

Screening, consent, and assessment interviews with participants will be administered by the principal investigator or another trained member of the research team and will take place in person at the study site or via encrypted videoconferencing. All staff involved in data collection will be trained on the assessments by the principal investigator, and all research staff will complete training on informed consent, good clinical practices, and all safety and reporting protocols as certified by New York University's institutional review board (IRB).

Process Evaluation

To determine the extent to which the program is delivered as intended, treatment fidelity will be monitored by research staff who observe selected sessions and rate the content delivered using checklists. Interventionists will use session checklists to record the content delivered and attendance in each session, and report on issues that arise regarding participants and study activities. The principal investigator will hold weekly supervisory meetings with interventionists to review the study process, receive feedback, and see that concerns are addressed in a timely manner.

Measures

Acceptability will be measured by a self-report questionnaire based on the theoretical framework of acceptability [82]. The scale has 9 items (eg, how much effort did it take you to participate in the intervention sessions?), with total scores ranging from 9 to 45, and higher scores indicating greater acceptability. Can be found in Multimedia Appendix 1 for interview guide. We will also record rates of intervention

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adherence as the number of assigned components completed by participants. To assess feasibility, we will record rates of recruitment, enrollment, retention, and assessment, and attempt to learn reasons for any dropouts through follow-up contacts. We will document interventionists' feedback throughout the study to determine component challenges and facilitators, and any key aspects they believe are of particular importance to the intervention. We will also regularly meet with administrative staff from the study site to assess their perceptions of the study's impact (challenges/benefits) on the clinic and document their ideas for overcoming any challenges to implementation. These meetings will clarify the elements involved in the feasible implementation of the intervention and the overall study, such as the integration of the study into the clinic workflow.

Engagement in treatment will be measured using 8 items from the Client Engagement in Child Protective Services Scale involvement or buy-in subscale [83]. Responses are on a 5-point Likert scale. An example item is "I am not just going through the motions. I'm really involved in working with providers." The range for the scale is 8 to 40, with higher scores indicating higher levels of engagement. This scale has demonstrated acceptable reliability with the study target population (=.82) [51,83]. Service usage will be measured at a 3-month follow-up by participant medical records. The total number of contacts each participant makes with the treatment program, and the dates for all contacts, starting 1 month before baseline through 3-month follow-up, will be collected to assess change in service use over the study period. Demographic information will be collected at baseline, and targeted mediators and mental health symptoms will be collected by self-report measures at all timepoints. Study measures have been extensively tested by the research team [84] and previous studies with REM populations, young adults, and individuals living with SMI. All have been found to have good psychometric properties. Can be found in Multimedia Appendix 2: Baseline assessment measures for a full list of the study measures collected during the baseline assessment.

Study Timeline

The study will take place over 4-5 months for each participant, and the total study duration is expected to last 2.5 years. Consenting participants will be enrolled, randomized, and administered a baseline assessment on the first day. They will be scheduled to receive the Just Do You core component within 1 week of completing the baseline. They will receive each subsequent component within 1 week of the previous component based on their experimental condition (Figure 2). After completing the intervention, participants will be administered the posttest assessment, which includes the study outcomes and acceptability measures. Participants will be administered the final assessment 3 months after the baseline, and the research staff will receive a report from the study site documenting each date a treatment service was received by the participant over the study period.

Figure 2. Pilot optimization trial of an engagement intervention for racial and ethnic minority young adults.

Study Period					
	Enrollment	Allocation	Post allocation		
Timepoint	$-t_1$	0	t_1	t_2 *Posttest*	t_3 *3-month*
Enrollment:					
Eligibility screen	✓				
Informed consent	✓				
Allocation		✓			
Interventions:					
[Just Do You Core]			✓		
[Just Do You + A]			✓		
[Just Do You + B]			✓		
[Just Do You + C]			✓		
[Just Do You + AB]			✓		
[Just Do You + AC]			✓		
[Just Do You + CB]			✓		
[Just Do You + ABC]			✓		
Assessments:					
[Demographics, Baseline measures]	✓	✓		✓	✓
[Medical record]					✓
[Acceptability interviews]				✓	

Data Management

A secure REDCap database will be used to enter and manage recruitment, consent, enrollment, and assessment data. Research data will be assigned an identification code and stored separately from participant names and contact information. Only trained members of the research team will have access to the data throughout the study.

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Data Analysis

Acceptability will be based on an average rating above the mid-point of the scale and overall positive thematic qualities in the interview data. Feasibility estimates will be based on recruitment rates and retention rates for assessments and components, component adherence rates, and component fidelity rates. Benchmark criteria for feasibility will be recruitment of 3 participants per month, completed assessment rates of 75%, and components completed by 85% of participants. Quantitative data on feasibility will be summarized with descriptive statistics. Confidence intervals will convey the direction, magnitude, and precision of estimates. Infeasible study elements or elements with low acceptability will be identified and then modified or removed from the protocol before subsequent stages of intervention testing.

For qualitative data, interviews will be transcribed and analyzed to describe and assess the acceptability of the intervention components using procedures for thematic analysis [85] and coding techniques from content analysis [86]. First, analysts will code independently using a priori codes (eg, constructs assessed in quantitative measures) and determine emergent codes based on participants' responses. Next, analysts will meet regularly to reach consensus on coding and jointly construct common, divergent, and subthemes. These processes will assist analysts to consider and manage how their own perspectives influence or guide the analytic process. Then, verbatim text will be ordered within thematic categories. Finally, data on outcomes that are assessed both qualitatively and quantitatively (eg, acceptability, feasibility, and adherence) will be integrated for side-by-side comparison using matrices and joint displays [87]. We will ensure methodological integrity by using audit trails and transparently documenting all analytic procedures and decisions [88]. Integrated results will be used to inform any future modifications to protocols and procedures for later phases of the intervention adaptation and evaluation process.

To assess treatment engagement outcomes, exploratory analyses will examine the distributions of all variables, identify outliers, and calculate descriptive statistics for each assessment timepoint, and with respect to the 3 components. We will use an intent-to-treat approach for the analysis. Factorial ANOVA using effect coding will be used to estimate the main effects and interactions between factors (ie, components) on the mean change in number of contacts with treatment services and the level of engagement at 3-month follow-up. Each intervention component will be assigned a value of +1 or –1 depending on whether it was included or excluded from the experimental condition (ie, yes or no). In addition, we will explore evidence of effects on mediators at posttest and 3-month outcomes. Analyses will rely on an examination of the overall pattern of changes (eg, strength and change in the intended direction) instead of hypothesis testing. The sample size of 80 is sufficient for the planned analyses and provides 79% power to detect main effects, corresponding to a correlation of 0.6 and a medium effect size (d=0.50), given α=.05.

Ethical Considerations

The trial protocol was approved by New York University's IRB Human Research Protection Program on December 4, 2024 (IRB-FY2024-9043). Any future protocol amendments will be reviewed by the IRB and reported on ClinicalTrials.gov. Before giving consent to enroll in the study, eligible individuals will receive a detailed description of the study and be informed that they may choose not to participate or to stop participating at any time. They will be informed of the limits to confidentiality, including that research staff will report any indications of harming themselves or others to clinical staff at the study site, and that researchers may withdraw them from the study if their health or well-being worsens.

To minimize the risk of loss of confidentiality, all informed consents and assessments will take place in a private space that assures confidential communication. Reminders of assessments made by phone or text will communicate only about the upcoming assessment appointment and not about any study or participant details. No participant information will be shared outside of the research team, with the exception of a situation where it is legally required or if the participant reports they are at risk of harm to themselves or someone else. We will follow protocols within the clinic study site and provide a "warm hand-off" to clinic staff if such a report of risk is made, or if participants require medical assistance during any research activities. While we do not foresee any event in which a participant would need to leave the study, adverse events that occur will be brought to the attention of the principal investigator and reported immediately to the IRB. Any adverse events will be reviewed and the researchers will determine whether to withdraw a participant from the study. Participants are paid US $30 in cash immediately, or by debit card in a timely manner, for each completed assessment.

Dissemination

We will disseminate study findings in a timely fashion through presentations at scientific meetings, publications, press releases, social media, and share findings with the study site administration and participant population. Final study status will be available on ClinicalTrials.gov within one year after the study's primary completion date.

Results

All hiring and training of study staff for the pilot optimization trial were completed in October 2024. Participant recruitment and randomization began in December 2024 and are planned to continue through December 2026. Follow-up assessments will continue through March 2027, with final study completion (ie, data analysis and interpretation of results) planned for May 2027.

Discussion

Principal Findings

This study will generate the preliminary data needed for a large-scale optimization RCT of the Just Do You intervention. First, we will establish the acceptability of the new candidate intervention components when added to the existing Just Do You intervention. We anticipate that findings will show preliminary evidence of the new components' positive impact on engagement and service use outcomes at 3-month follow-up.

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Second, we will ascertain the feasibility of implementing the study protocol and achieving robust recruitment, retention, adherence, and fidelity rates. These data will allow for making any necessary improvements to the components' design or the study procedures before moving on to later stages of testing. Finally, this pilot optimization trial represents the initial stage in the MOST framework [78], which we plan to apply to improving the Just Do You intervention iteratively over time. The ultimate goal is to develop an efficient, evidence-based engagement program, tailored to be developmentally and culturally responsive to REM young adults with mental health disorders. Previous young adult mental health service engagement interventions have used RCTs to test multiple-element interventions as a treatment package [19,21], which lacks precision for determining the relative contribution of intervention components. The results of this pilot would allow us to address this gap through systematically assessing the candidate components individually in a future well-powered optimization RCT. Understanding the relative value of the candidate components is likely to inform improvements to Just Do You and lead to an optimized intervention.

Importantly, this study demonstrates a deployment-focused approach to intervention design and testing that can expedite the translation of our research into practice. The candidate intervention components were intentionally designed through incorporating the perspectives of young adults and service providers, and they are being tested in a typical community-based clinical setting. We have chosen this approach, based on previous research [48,89], to support the development of an intervention that can improve mental health service engagement and be delivered in nonacademic, real-world community treatment settings in the United States, MOST has also been used to optimize interventions, enhance their scalability, and increase the probability of successful implementation in resource-constrained settings [77]. By combining these methods, this pilot trial will allow us to collect several indicators of acceptability and fit of the approach, and determine the main constraints on implementation (eg, costs, workforce capacity, and clinic workflows). The latter will guide us in selecting an optimization objective for testing the candidate components in the future optimization RCT. We anticipate this will help to ensure that we can develop a future Just Do You intervention that is feasible, scalable, and can be disseminated widely into US community mental health services.

Limitations

This study faces some potential challenges. First, testing an intervention with a "hard-to-engage" population often requires a considerable amount of resources. Another potential challenge is implementing a complex study with 8 experimental conditions in a clinical setting. Building on pri previous or research experience, the study team have taken several measures to ensure the success of the trial. To minimize attrition, we will use well-established methods for tracking difficult to engage populations such as on-going reminder contacts and messaging, and collecting contact information for other people we can reach respondents through. We are also allowing 2 years to recruit participants in order to have a sufficient amount of time, and to avoid overtaxing our recruitment site. In addition, we have designed the 3 new candidate intervention components to require very few additional resources to implement. Finally, the study team includes both researchers who have extensive experience with implementing MOST trials, and researchers who are skilled in conducting trials in psychiatric care settings. Our combined expertise will improve our ability to identify and address challenges in the pilot stage and determine how to enhance feasibility for future stages of the research.

Conclusion

This research will yield critical, deployment-focused findings essential for informing a subsequent randomized controlled trial, representing the next proposed stage in this research agenda. The overarching objective is to establish an effective, efficient, and scalable intervention designed to enhance engagement and mental health outcomes within the REM young adult population.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are available from the National Institute of Mental Health Data Archive on reasonable request.

Authors' Contributions

The methodology was developed collaboratively by KLM, LMC, MG, and MRM. For the investigation, KLM, MRM, and AHR conducted data collection and related activities. Funding acquisition was secured by KLM, MRM, MG, LMC, and DFC. KLM and AHR were responsible for writing the original draft. All authors contributed to reviewing and editing multiple versions of the manuscript.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
Interview guide.
[DOCX File , 18 KB - resprot_v14i1e68885_app1.docx]

Multimedia Appendix 2
Baseline assessment measures.
[DOCX File , 47 KB - resprot_v14i1e68885_app2.docx]

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Abbreviations

ADAPT-ITT: Assessment, Decision, Adaptation, Production, Topical experts-integration, Training, and Testing
CFI: Cultural Formulation Interview
***DSM-5*:** *Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)*
IRB: institutional review board
MOST: multiphase optimization strategy
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
REM: racial and ethnic minority
SMI: serious mental illness

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Protocol

Resilience Coaching for Adolescent Chronic Musculoskeletal Pain: Protocol for a Pilot Randomized Controlled Trial of Promoting Resilience in Stress Management (PRISM)

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Abstract

Background: Levels of self-perceived psychological resilience are low to moderate among youth with chronic musculoskeletal pain (CMP). Furthermore, resilience has been associated with symptom severity in CMP. Resilience coaching programs may therefore be of benefit in the nonpharmacologic management of adolescent CMP and may serve as an adjunctive way to access mental health services in an approachable and affordable way.

Objective: The main goal of the study is to assess the feasibility, acceptability, and preliminary efficacy of the resilience coaching program called Promoting Resilience in Stress Management (PRISM) and to obtain the data needed to plan a larger trial.

Methods: The Resilience Coaching for Adolescents with Chronic Musculoskeletal Pain pilot study is an investigator initiated, 2-arm, randomized controlled trial (RCT) of PRISM in the interdisciplinary management of CMP among adolescents. The study will compare usual care versus PRISM+usual care among adolescents newly diagnosed with CMP in the outpatient setting. One caregiver per patient will also be enrolled. The control group will receive usual care with no specific intervention. The treatment arm will receive PRISM, which is a remotely delivered, 1-on-1resilience coaching program, consisting of 4 required skill-based sessions and an optional final session. Sessions will be delivered every 1-2 weeks, lasting about 3 months in total. The primary outcome is the Functional Disability Inventory (FDI) score at 3 months postrandomization. The secondary objectives are to evaluate potential patient- and caregiver-level moderators of PRISM and identify facilitators of and barriers to engagement in PRISM. The estimated sample size is 65 patient-caregiver dyads per group, for a total of 130 dyads.

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Results: The trial is currently open. Initial Institutional Review Board approval was obtained on April 4, 2023, and protocol version 4 was amended on January 14, 2025. Recruitment began on May 8, 2023, and recruitment is anticipated to be completed on August 1, 2025.

Conclusions: Resilience coaching has demonstrated excellent feasibility, acceptability, and efficacy in teenagers with chronic illness; however, evidence to support its use in adolescent CMP is lacking. Resilience coaching has the potential to improve patient outcomes in this population. This pilot RCT will demonstrate acceptability, feasibility, and preliminary efficacy and reveal critical barriers to and facilitators of engagement. This will inform a larger multisite trial to evaluate the definitive efficacy of the intervention.

Trial Registration: ClinicalTrials.gov NCT05834725; https://clinicaltrials.gov/study/NCT05834725.

International Registered Report Identifier (IRRID): DERR1-10.2196/73385

(JMIR Res Protoc 2025;14:e73385) doi:10.2196/73385

KEYWORDS

resilience; chronic pain; chronic musculoskeletal pain; pediatric rheumatology; pilot study

Introduction

Chronic musculoskeletal pain (CMP), or pain in the bones, joints, and tissues lasting longer than 3 months [1], is a common condition affecting up to 25% of children and adolescents [2]. Many adolescents with CMP experience significant psychological distress [3], exhibiting higher levels of depression and anxiety than youth without CMP [4]. Further elucidating the relationship between stress and pain, higher pain intensity in adolescents with CMP is associated with greater emotional and behavioral challenges [5]. Along with these mental health challenges, CMP is also associated with functional disability in various domains, including school attendance, reduced social contact, sleep problems, and family functioning [6].

The current standard of care treatment for adolescent CMP consists of nonpharmacological, interdisciplinary care combining physical, occupational, and psychological therapies [7-10]. These treatments require intensive physical activity, which can be both physically and emotionally taxing. Mental health interventions are a key element of this multimodal treatment approach, with cognitive behavioral therapy (CBT) being the most common [10]. However, many patients encounter months-long waitlists to access specialized interdisciplinary pain care.[11]

Considering that experiencing chronic pain and adhering to CMP treatment recommendations can be significant life stressors, researchers have proposed psychological resilience as a method of coping with chronic pain [12,13]. Adolescents with CMP have been demonstrated to have low-to-moderate self-perceived psychological resilience [14], which is defined as “a dynamic process of positive adaptation or continued development in the context of significant adversity” [15,16]. Higher levels of resilience in youth with CMP have been found to correlate with lower symptom severity, increased function [14], and reduced odds of suicidality [17]. Thus, further research is needed to establish whether interventions targeted at increasing resilience can improve pain coping, ultimately leading to improvements in pain-related clinical outcomes, such as functional disability and psychological distress. Brief resilience coaching programs also have the potential to alleviate difficulties in accessing specialized pain care, as coaching can be readily initiated in the time between initial diagnosis and a patient’s first specialized pain clinic appointment.

Promoting Resilience in Stress Management (PRISM) is a 1-on-1 resilience coaching program consisting of 5 skill-based sessions offered in person or remotely via videoconferencing or telephone for adolescents with chronic illness. PRISM’s efficacy has been shown via improved resilience, health-related quality of life, and mental health outcomes for adolescents and young adults with serious illnesses, including cancer, type I diabetes, and cystic fibrosis [18-21]. Although CBT and other evidence-based psychological strategies have strong evidence supporting their use in the treatment of pediatric chronic pain [22], the use of a resilience framework and resilience coaching has not been formally examined among youth with CMP.

Our prior single-arm pilot study to assess PRISM’s feasibility and acceptability among youth with CMP was the first effort to investigate resilience coaching in this patient population. In this study, participants completed patient-reported outcome measures (PROMs), pre- and postintervention, and both patients and caregivers provided qualitative feedback. The feedback was highly positive, reinforcing our hypothesis that PRISM offers an acceptable alternative psychosocial intervention for youth who either struggle to access mental health services or face stigma associated with them. The study also confirmed that PRISM is feasible and acceptable among youth with CMP, while exploratory analyses suggested improvements in resilience, functional disability, and psychological distress [23]. Significant changes were not observed in pain intensity, pain catastrophizing, and global health; however, we did not have a control group for comparison, nor were we powered to examine efficacy. Based on the findings of this pilot study, we determined that PRISM holds promise for the treatment of adolescent CMP and that additional work is needed to evaluate the efficacy of PRISM compared to usual care and explore factors informing its implementation.

One challenge observed during the single-arm pilot study was that 55% of participants were already engaging in psychological treatment, limiting our ability to attribute changes in PROMs solely to the effects of PRISM. Qualitative interview findings also suggested that the intervention could be of more value to those who were naive to psychological counseling. We

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determined that future research is needed to separate the effects of PRISM from those of CBT by excluding patients who are actively receiving CBT at the time of screening. We also intended to limit future studies to patients with mild or greater impairment due to pain in order to direct the intervention toward adolescents most in need, while increasing the possibility of demonstrating an improvement in functional disability scores. Lastly, to further assess the durability of PRISM, we planned to extend data collection beyond 3 months to include a 9-month follow-up survey. We also aimed to incorporate participant feedback from our single-arm pilot trial regarding overall helpfulness and benefits, reasons for deciding to participate, session logistics, accessibility, mental health perceptions, and caregiver interest in resilience into future protocols to better meet the needs of patients.

In this paper, we present the protocol for an ongoing pilot phase 2 randomized controlled trial (RCT) of PRISM for adolescents with CMP. The goal of this study is to determine whether the addition of PRISM to usual care demonstrates greater improvements in functional disability than usual care alone. Usual care was chosen as the comparator group to best mimic the clinical real-world setting and because denial of these services would not be ethically sound. Secondary aims include (1) determining the impact of PRISM on pain intensity and psychological distress, (2) exploring moderators of intervention effects, and (3) examining implementation outcomes of, facilitators of, and barriers to intervention engagement. This work provides the basis for a future definitive multicenter RCT to evaluate the efficacy of the intervention and feasibility of delivering resilience coaching across sites, as this will facilitate and support implementation of resilience coaching within usual care for CMP.

Methods

Study Design and Setting

The study was registered at ClinicalTrials.gov (NCT05834725) on April 28, 2023. This study is a single-center pilot, 2-arm, RCT using a mixed methods approach (quantitative patient outcome measures combined with qualitative interview data). Participants are recruited from an outpatient pediatric rheumatology clinic and an interdisciplinary pain clinic at the Children's Hospital of Philadelphia (CHOP) in Philadelphia, PA, USA. See Multimedia Appendix 1 for the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.

The PRISM Intervention

PRISM consists of 4 required skill-based sessions that focus on stress management, goal setting, cognitive restructuring, and benefit finding (see Figure 1). The optional fifth "coming together" session focuses on discussing with a family member, with the participant's permission, the skills that the participant found beneficial, the ones they did not, and how they can continue to implement the skills learned in the future once the program finishes. Each session is around 30-50 minutes, with sessions scheduled 1-2 weeks apart. Participants are given access to "cheat sheets" and worksheets for each session and a mobile app that can be used to practice the skills learned.

Figure 1. Overview of sessions in the PRISM program. PRISM: Promoting Resilience in Stress Management.

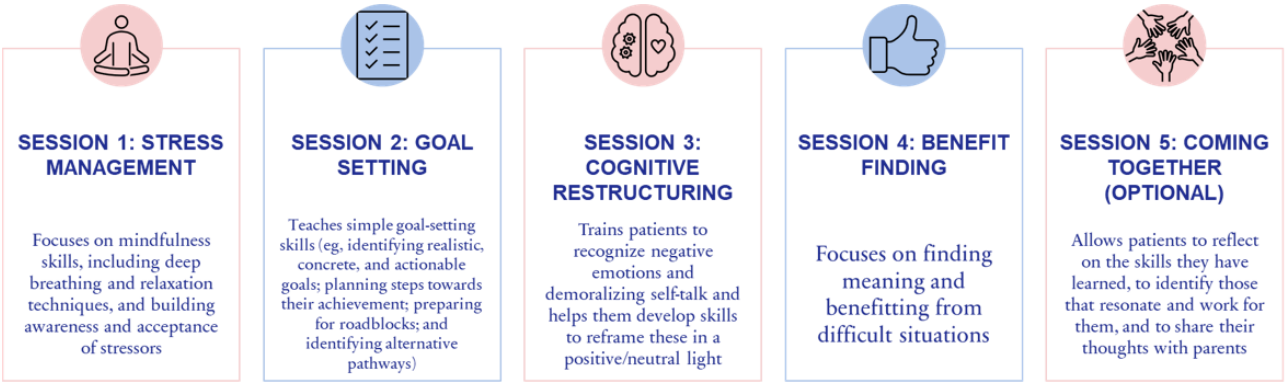

PRISM coaches have a bachelor's degree (at minimum), have gone through an 8-hour training and certification process for the administration of PRISM, and have practiced delivering the intervention with 2 peers to demonstrate competency. A standardized manual is used to guide PRISM coaches through each session and includes guided discussion prompts to facilitate rapport building and patient participation. Sessions are audio-recorded, and fidelity checks are conducted regularly by a supervisor. There is a standardized fidelity checklist used for scoring purposes and a safety plan to address psychological distress, as needed.

Participants

This study includes males and females aged ≥12 and <17 years who have a new diagnosis of CMP and are coming in person for a clinic visit, and one of their parents or legal guardians. Exclusion criteria include patients (1) with isolated and localized head pain or abdominal pain, (2) with a diagnosis of complex regional pain syndrome (CRPS), (3) currently receiving CBT, and (4) not capable of understanding the study or providing assent/consent.

Recruitment and Randomization

Eligible participants are identified by study personnel through screening of the pediatric rheumatology and subspecialty pain clinic schedule via electronic medical records (EMRs). An EMR review is conducted to confirm eligibility, and if further information is needed, an in-person or telephone query is conducted to ensure eligibility. Study personnel approach the eligible patient and a parent or legal guardian at the time of their

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clinic visit or retroactively via telephone. The study is introduced using the Institutional Review Board (IRB)-approved informed consent form as guidance, and all questions are answered in accordance with IRB regulations. If the patient and their parent express interest but need more time to think about it, they fill out a contact information sheet, are provided with a consent form to take home, and are contacted after the clinic visit via telephone. If eligible and interested, they can provide electronic consent (e-consent) at the time of the clinic visit (Figure 2).

Figure 2. PRISM RCT recruitment, screening, and consent process. CHOP: Children's Hospital of Philadelphia; CMP: chronic musculoskeletal pain; e-consent: electronic consent; EMR: electronic medical record; PRISM: Promoting Resilience in Stress Management; PROMIS: Patient-Reported Outcomes Measurement Information System; RCT: randomized controlled trial.

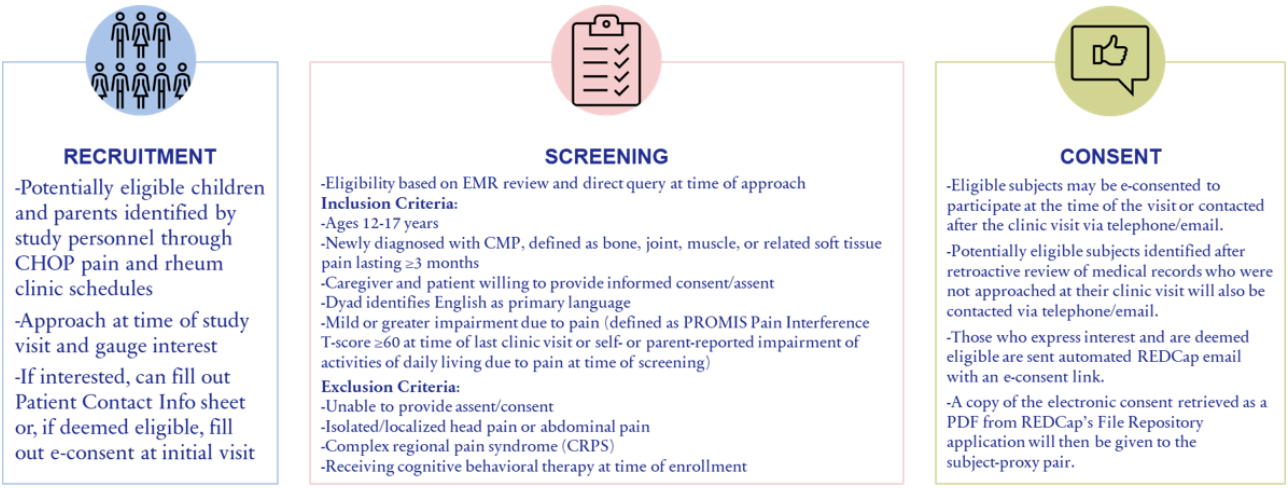

Those who are not approached at their clinic visit can be contacted retroactively via telephone and, if interested and eligible, can be e-consented via REDCap (Research Electronic Data Capture), a secure, web-based software platform designed to support data capture for research studies [24,25]. For anyone who declines participation, their reasoning is recorded in the study's master log. Study personnel attempt to contact patient-caregiver dyads a maximum of 3 times before discontinuing recruitment efforts. Once baseline surveys are complete, the dyads will be randomly assigned to a study arm using a 1:1 allocation ratio: PRISM+usual care versus usual care.

Stratified randomization will be implemented by the study statistician in REDCap to ensure a balance in sex (male vs female) and clinic (rheumatology clinic vs interdisciplinary pain [amplified musculoskeletal pain] clinic) between the 2 study arms. The final randomization scheme will be prepared by a statistician independent of the study team to prevent bias. Study staff will not get access to randomization algorithms. Tracking of dyads and randomization will be recorded in the study's master log.

Medical Record Review and Questionnaires

Each enrolled participant's medical chart will be reviewed by a study team member for information relevant to the study, including demographics, previous diagnoses, family medical history, previous surgeries, pain-related symptoms, and past treatment. Both members of each dyad will complete questionnaires at 0 months/time of enrollment; 3 months postenrollment or, if in the treatment group, immediately after intervention completion; and 9 months postenrollment. Questionnaires will be completed using an online REDCap survey. Participants will get 45 days to complete each set of questionnaires. Reminder emails or text messages (depending on participant preference) will be sent once a week to ensure completion, and reminder calls will be made a maximum of 3 times. Participants will be compensated for their time and completion of surveys. Caregivers will be paid US $20 for completion of survey 1, US $40 for completion of survey 2, and US $20 for completion of survey 3. Patient participants will be paid US $25 for completion of survey 1, US $50 for completion of survey 2, and US $25 for completion of survey 3. Should subjects request early termination, we will enumerate the next study survey as the final study survey and compensate participants with US $10 for completion of the final surveys. Next, we describe the study measures included in the questionnaires.

The patient measures are as follows:

- Demographics and medical history survey. For the first set of surveys, adolescent participants will be asked whether they have or are currently receiving counseling services and physical therapy, as well as about their exercise routine and whether they perform desensitization exercises.
- The 10-item Connor-Davidson Resilience Scale (CD-RISC-10) [26] measures the overall sense of resilience, or ability to cope with stressors/challenges, and assesses treatment response. Higher scores (0-40) indicate greater resilience. The CD-RISC-10 has good internal consistency and test-retest reliability.
- The Benefit Finding Scale for Children (BFSC) [27] is a 10-item measure of benefit finding designed for children. It is a unidimensional measure and has excellent internal consistency reliability. In a sample of children with cancer, small but significant correlations were found with measures of optimism and self-esteem and a negative correlation with trait anxiety [27].
- The Pain Catastrophizing Scale, Child report (PCS-C) [28] is a validated self-report measure used to assess negative

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thinking associated with pain. Higher scores reflect higher levels of catastrophic thinking [29].

- The Children's Hope Scale [30] measures hopeful thought patterns, or the perception that one's goals can be achieved. Higher scores indicate greater hopeful thought patterns.
- The Children and Adolescent Mindfulness Measure (CAMM) [31-33] is a unidimensional measure of mindfulness. Higher scores indicate higher levels of mindfulness. CAMM has good psychometric properties overall.
- The 8-item Chronic Pain Acceptance Questionnaire Adolescent Short Form (CPAQ-A8) [34] measures pain acceptance using 4 items for each established factor (pain willingness and activity engagement) and is sensitive to treatment. It is correlated with clinically important variables, as its full-length version. Items are scored on a 5-point Likert scale (0=never true to 4=always true). Higher scores indicate more positive perceptions of pain.
- The Pain Self-Efficacy Scale Child (PSES-C) [35] is a 7-item measure assessing child self-efficacy for functioning normally when in pain. Items are scored on a 5-point Likert scale, with lower scores indicating higher self-efficacy. Initial validation has provided support for the PSES-C's validity and reliability.
- The PROMIS (Patient-Reported Outcomes Measurement Information System) Pediatric Global Health 7 (PGH-7) [36,37] is a brief and reliable 7-item summary assessment of a child's self-reported health. It represents an individual's overall assessment of their health, focusing on physical, mental, and social health components. The PGH-7 is well understood by children as young as 8 years of age. The measure has test-retest reliability estimates above 0.80, indicating excellent stability. The measure is unidimensional and factor invariant by the age of the child. Raw scores are converted to T-score (SD) values. The mean score is 50 (SD 10).
- The Functional Disability Inventory (FDI) [38] is a measure of pain-related disability. It is a 15-item measure assessing the degree to which pain interferes with children's physical functioning over a 2-week period. The FDI has demonstrated adequate psychometric properties in youth with CMP aged 8-18 years [38,39]. The FDI has high internal consistency, moderate-to-high test-retest reliability, and good predictive validity [38-40].
- The PROMIS Pediatric Numeric Rating Scale v1.0 – Pain Intensity [41] provides a numerical value for self-reported pain intensity experienced by the child in the past 7 days.
- The PROMIS Pediatric Bank v2.0 – Pain Interference Short Form 8a [41] measures self-reported consequences of pain.
- The 8-item Patient Health Questionnaire (PHQ-8) [42-46] is a reliable and valid measure of depression severity and a good screening measure in adolescents [43].
- The 7-item Generalized Anxiety Disorder scale (GAD-7) [47,48] has been demonstrated to be a useful screening measure for anxiety severity in adolescents (11-17 years).
- The Kessler-6 Psychological Distress Scale (K6) [49,50] is a 6-item scale that measures the level of psychological distress experienced in the past month. It was developed for the US National Health Interview Survey and is currently being used in Canada, Australia, and the rest of the world as part of the World Health Organization's (WHO) world mental health initiative. The instrument strongly discriminates between community cases and noncases of *Diagnostic and Statistical Manual of Mental Disorders* (DSM)-IV psychiatric disorders, such as serious emotional distress or serious mental illness (area under the curve [AUC]=0.74-0.88) [51]. The K6 has been extensively cross-validated, including among adolescents and parents. Responses are scored on a 5-point Likert scale (total score ranging from 0 to 24). Previous studies have shown that scores≥7 are consistent with high distress, and scores≥13 meet the criteria for serious or debilitating psychological distress [49].
- The Pain and Symptom Assessment Tool (PSAT) [52] is a modified version of the 2010 American College of Rheumatology (ACR) criteria for fibromyalgia (FM) syndrome, which has demonstrated good specificity and sensitivity for the diagnosis of juvenile FM in adolescents [53]. The PSAT consists of 2 components: the Widespread Pain Index (WPI) and the Symptom Severity (SS) checklist. The WPI is a questionnaire that identifies pain in the past week in 19 body locations (score 0-19). The SS checklist comprises 2 components that identify the severity of cardinal symptoms on a scale from 0 (no problem) to 3 (severe problem) and the presence or absence of associated somatic symptoms. A score is assigned based on the overall number of symptoms (0-3: 0=none to 3=a great deal of symptoms). A final SS score is calculated by adding the cardinal symptoms' scores to the somatic symptoms' checklist scores (maximum score=12). According to the adult ACR FM criteria, a score of ≥5 and a WPI of ≥7 or an SS score of ≥9 and a WPI of 3-6 indicates a positive diagnosis for juvenile FM.
- The Acceptability of Intervention Measure (AIM), the Intervention Appropriateness Measure (IAM), and the Feasibility of Intervention Measure (FIM) [54,55] are 4-item measures of implementation outcomes that are often considered leading indicators of implementation success. With readability at the fifth-grade level, these measures can be administered to a wide range of stakeholders to determine the extent to which they believe an intervention or an implementation strategy is acceptable, appropriate, and feasible. The IAM items can be modified to specify a referent organization, situation, or population. Cutoff scores for interpretation are not yet available; however, higher scores indicate greater acceptability, appropriateness, and feasibility. The AIM, IAM, and FIM have demonstrated strong psychometric properties. Specifically, the measures have demonstrated content validity, discriminant content validity, reliability, structural validity, structural invariance, known-groups validity, and responsiveness to change. The predictive validity of the measures is currently being evaluated.
- Satisfaction with PRISM. Session-specific and overall intervention satisfaction will be measured via a 5-point Likert scale (1=very dissatisfied to 5=very satisfied). The intervention will be defined as acceptable if the mean level

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of satisfaction (including session-specific and overall intervention satisfaction) is ≥3.

The caregiver measures are as follows:

- CD-RISC-10
- K6
- The Pain Catastrophizing Scale – Parent report (PCS-P) [56] measures parental catastrophizing about their adolescent child's pain. The PCS-P includes 13 items concerning different catastrophic thoughts and feelings parents may have when their child experiences pain. The items are scored using a 5-point Likert-scale (0=not at all to 4=extremely). The PCS-P yields 3 subscale scores for rumination, magnification, and helplessness, as well as a total score ranging from 0 to 52.
- The Adult Hope Scale (AHS) [57] measures Snyder's cognitive model of hope, which defines hope as a "positive motivational state that is based on an interactivity derived sense of a) agency (goal-directed energy), and b) pathways (planning to meet goals)." The AHS consists of 12 items. Four items measure pathways thinking, four items measure agency thinking, and four items are fillers. Participants respond to each item using an 8-point scale ranging from definitely true to definitely false. When administering the scale, it is called the Future Scale. The agency subscale score is derived by summing items 2, 9, 10, and 12. The pathways subscale score is derived by adding items 1, 4, 6, and 8. The total AHS score is derived by summing the 4 agency and the 4 pathway items.
- The PROMIS Global Health (GH-10) measure version 1.2 [58] is a brief and reliable 10-item summary of an adult's self-reported physical and mental health. It was developed as part of the US National Institutes of Health's (NIH) PROMIS initiative using item response theory and rigorously validated in a sample of >20,000 people, primarily from the community. It is freely available and can be used across diseases with T-scores normalized to the US general population. It takes adults no more than 1-2 minutes to complete. Raw scores are converted to T-score (SD) values. The mean score is 50 (SD 10). Higher T-scores reflect more of the trait being measured.

Ethical Considerations

The study was approved by the CHOP IRB (IRB 22-020664; approval date April 21, 2023; most recent amendment #21 approved on May 8, 2025). The protocol was also reviewed by the National Institute of Arthritis and Musculoskeletal and Skin Diseases (NIAMS) at the NIH. Any further amendments to the study protocol will be communicated to the CHOP IRB and NIAMS at the NIH for formal approval.

Written informed consent will be obtained from all participants, as described in this protocol. All participants will provide informed consent by acknowledging that they have read and understood the consent form before randomization. Information about the study's significance, purpose, procedures, risks, and benefits will be provided to all eligible patients during the consent process. Identifiable information will be collected from subjects and parent participants only to link the questionnaires and qualitative data from the interviews to the EMR data. Identifiable information linking individual subjects to their PHI (i.e., the master list) will be stored electronically in a Microsoft Excel file located on a secure research SAN drive for the duration of the study and will be maintained in keeping with CHOP policy. Research documents located on the SAN drive will be accessible only to members of the study team. Upon study completion, the database will be maintained in locked mode for a minimum of 3 years, as per regulatory guidelines. Data management procedures are included in our manual of operating procedures, which can be made available upon request.

Since the survey measures ask questions about mood, stressors, psychological symptoms, and feelings, this might put participants at risk for having negative thoughts and emotions. It is not likely that answering these survey measures will create additional distress beyond that which is already present, but research staff will offer referral for clinical services (for child or parent) for any reported distress warranting clinical attention. In addition, if during study participation, the study team discovers abuse or neglect or if threat to harm self or others occurs, they will follow established institutional procedures for mandatory reporting of this information and will provide referrals for appropriate clinical follow-up. We also have a data safety monitoring plan (DSMP) and a data safety monitoring board (DSMB). The DSMB consists of 4 members, who meet once a year to review study progress and safety or confidentiality concerns. In the unlikely event of an adverse outcome associated with this study protocol (eg, disclosure of patient information), it will be documented and discussed with the research team and promptly reported to the local IRB and study sponsor, if appropriate. Any serious adverse events will be reported to the local IRB and the DSMB within 48 hours and to the study sponsor.

Treatment Group

Patients randomized to the treatment (PRISM+usual care) group will complete the first PRISM session within ~45 days of enrollment. Patients will complete the PRISM sessions remotely using a HIPAA (Health Insurance Portability and Accountability Act)-complaint videoconferencing platform. Each session will be scheduled approximately 1-2 weeks apart but must be completed within 45 days of the previous session. We will invite each patient-parent dyad to participate in an optional 30-minute semistructured interview (see Multimedia Appendix 2 for the interview guide) that will ask about their thoughts regarding PRISM, including background, timing, duration, attendance, content, sessions, and overall satisfaction. Participants will be purposively selected to enrich the cohort for those with early dropout and ensure representation of a variety of ages, races, and ethnicities. These interviews will be conducted by a study staff member other than the PRISM coach, and they will be audio-recorded and transcribed verbatim for qualitative assessment. Participants will be paid US $25 each for their time and completion of semistructured interviews.

Control Group

This is the usual care group. This group will be assigned online questionnaires, as described earlier. Control group participants will not receive the PRISM intervention but will receive usual care. Although adolescent participants cannot be actively

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engaged in CBT at the time of enrollment, they will be allowed to start any type of mental health treatment recommended as part of their treatment plan for their CMP at any point during the study. Additionally recommended as part of usual care will be cardiovascular exercise and desensitization, which may include formal physical and occupational therapy. See Figure 3 for a comprehensive description of study visit activities and the timeline for both study arms.

Figure 3. Schedule of study enrollment, interventions, and assessments. EMR: electronic medical record; FDI: Functional Disability Inventory; K6: Kessler-6 Psychological Distress Scale; PRISM: Promoting Resilience in Stress Management; PROMIS: Patient-Reported Outcomes Measurement Information System.

		Study period							
	Enrollment	Baseline assessment and allocation	Postallocation					Follow-up	Close-out
Timepoint (days)	**–45**	**0**	**14**	**28**	**42**	**56**	**70**	**90**	**270**
Enrollment									
Eligibility screen	X								
Informed consent	X								
Allocation		X							
Intervention									
PRISM+usual care			◆	—	—	—	◆		
Usual care alone			◆	—	—	—	◆		
Assessment									
EMR abstraction		X							X
Primary outcome: FDI		X						X	X
Secondary outcome: PROMIS Pediatric Numeric Rating Scale v1.0 – Pain Intensity		X						X	X
Secondary outcome: K6		X						X	X
Patient survey		X						X	X
Caregiver survey		X						X	X
Feasibility and acceptability measures								X	X
Semistructured interviews							X	X	

Statistical Analysis

The primary objective of this study is to determine whether PRISM, along with usual care, reduces functional disability more than usual care alone. The primary outcome or measure of efficacy is the FDI score at 3 months postrandomization (control group) or postintervention. The secondary efficacy outcomes are patient psychological distress (as measured with the K6), as well as the patient-reported pain intensity (as measured with the PROMIS Pediatric Numeric Rating Scale v1.0 – Pain Intensity). The secondary objectives are to determine a reduction in pain intensity and psychological distress with PRISM at intervention completion; determine reductions in functional disability, pain intensity, and psychological distress with PRISM at 6 months postintervention; evaluate potential patient- and caregiver-level moderators of PRISM; examine implementation outcomes (feasibility, acceptability, appropriateness); and identify facilitators of and barriers to engagement in PRISM.

The study team plans to publish the study findings in a peer-reviewed pediatrics, psychology, or rheumatology journal to disseminate the findings. No individually identifiable protected health information will be published. Summary results will be available on ClinicalTrials.gov.

Quantitative Data

Quantitative measures will be used to assess the primary and secondary efficacy outcomes, moderators of PRISM, and implementation outcomes. Demographics and baseline clinical characteristics will be summarized by standard descriptive summaries (eg, means and SDs for continuous variables, such as age, and percentages for categorical variables, such as gender). The primary analysis will use an intention-to-treat (ITT) approach to mitigate confounding from nonrandom participant attrition. We anticipate a total of 100 evaluable subjects. To ensure valid randomization, we will assess demographic and clinical features, along with baseline measures of outcomes, such as physical function, pain intensity, and psychological distress, and compare the intervention to the control arm. The primary outcome will be functional disability (FDI score) assessed at the end of the intervention (month 3). The key predictor is PRISM. Secondary outcomes will include the FDI score at the conclusion of the observation period (month 9, 6 months postintervention) and psychological distress (K6 total) and pain intensity (PROMIS Pediatric Numeric Rating Scale v1.0 – Pain Intensity) at both 3 and 9 months.

Assuming balanced arms postrandomization, we will evaluate the differences in clinical outcomes between the 2 arms at months 3 and 9 using 2-sample Student *t* tests. Longitudinal changes from month 3 to month 9 will be assessed using MANOVA (multivariate analysis of variance) and linear mixed effects models to account for within-subject correlation due to repeated measures. The linear mixed effects model can additionally adjust for a few known prognostic covariates, such as fulfillment of criteria for juvenile FM. Similar analyses will

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examine outcomes of psychological distress and pain intensity separately.

Linear regression will be conducted to assess the association between the change in FDI scores and changes in the intervention targets, adjusted for baseline covariates of interest. These analyses will be repeated to examine correlations between changes in secondary outcomes (pain intensity and psychological distress) and hypothesized intervention targets at month 3, and we will conduct multivariable linear regression models, adjusting for covariates of interest.

Furthermore, we will explore adolescent- and caregiver-level moderators of intervention effects, guided by an intersectionality framework [59]. For instance, we will investigate whether age moderates the intervention's impact on functional disability by including the age × intervention interaction in the linear mixed effects regression model. If the interaction is significant, we will interpret it by plotting simple regression lines for younger (12-14 years) and older (15-16 years) adolescents. If PRISM proves more beneficial for younger participants, future studies may focus on this age group to maximize intervention effects. Additionally, we will evaluate whether biological sex moderates the intervention's impact, ensuring adequate inclusion of male participants, given the predominance of females in the population with CMP [60].

Analyses will include calculation of eligibility, recruitment and attrition rates, and power considerations for the future full-scale RCT and evaluation of treatment fidelity. We will report the number of eligible subjects approached, the proportion of those subjects enrolled in the study, and the mean percentage of required sessions (PRISM 1-4 sessions + "coming together" session) attended among enrolled subjects. The study will be defined as feasible (binary) if the recruitment rate is ≥60%, the completion rate of all sessions among enrolled subjects is ≥70%, and the mean FIM score is ≥4. The intervention will be acceptable and appropriate if the mean AIM and IAM scores are ≥4 each. Intervention satisfaction (including session-specific and overall intervention satisfaction) will be reported as mean scores from the 5-point Likert scale (1=very dissatisfied to 5=very satisfied).

With a sample of 130 patient participants and an assumed ~20% attrition rate, we have more than 80% statistical power to detect a difference down to 5 points in the FDI between the intervention and control arms, given a prespecified mean FDI score of 26.9 (SD 11.8) and a significance level of .05 for the Student *t*-test. Table 1 lists the detectable differences (DDs) for the outcomes of interest, as well as the minimal clinically important difference (MCID) for each measure. The effect sizes of CBT on the FDI in similar patient populations have been strong to moderate (0.8-0.9), with between-group differences in the FDI score of 5.39 (95% CI 1.57-9.22). Therefore, we will be adequately powered for the primary outcome [61,62].

Table 1. DDs[a] in mean instrument scores between groups, given 80% power and a 5% type I error rate (N=100[b]).

Outcome (instrument)	Sample mean (SD)[c]	MCID[d]	DD
Physical function (FDI[e])	26.9 (11.8)	8.0	5.0
Pain (PROMIS[f] Pediatric Numeric Rating Scale v1.0 – Pain Intensity)	6.2 (2.3)	2.0	0.9
Psychological distress (K6[g])	9.1 (6.0)	3.0[h]	2.4

[a]DD: detectable difference.

[b]Anticipated dropout rate of ~20% (total=130), resulting in 100 evaluable subjects.

[c]Sample means from preliminary data.

[d]MCID: minimal clinically important difference.

[e]FDI: Functional Disability Inventory.

[f]PROMIS: Patient-Reported Outcomes Measurement Information System.

[g]K6: Kessler-6 Psychological Distress Scale.

[h]Half the SD of mean baseline scores.

Qualitative Data

Semistructured interview findings will be used to understand barriers and facilitators to support future implementation of PRISM. Three team members will conduct the interviews after completing training on interview facilitation best practices. Research team members have a diverse experience spanning the domains of chronic pain, rheumatology, patient-centered care, and qualitative research methods and have varied levels of preknowledge of CMP. The principal investigator's interpretation of interview findings will be informed by their expertise in treating adolescents with CMP, while several other team members have prior knowledge of CMP through their research work. To maximize reflexivity, the research team members will discuss their assumptions about the research topics and how these might influence their interpretation of findings both before and during data analysis.

Interviews with patients and caregivers will be transcribed verbatim. Two members of the study team will code transcripts independently and meet to identify emergent themes arising from a line-by-line review of narrative content, as well as a priori codes derived from the Consolidated Framework for Implementation Research (CFIR) and the Assessment, Decision, Adaptation, Production, Topical experts, Integration, Training and Testing (ADAPT-ITT) framework [63]. Next, 20% of interviews will be double-coded to insure intercoder reliability of the developed coding schema and enhance credibility of

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findings. Discrepancies will be resolved through consensus. Quantitative findings on efficacy and implementation outcomes will be synthesized with qualitative findings on facilitators of and barriers to engagement to support wide-based dissemination of PRISM in a multicenter RCT.

Results

The trial is currently open. Initial IRB approval was obtained on April 21, 2023, and protocol version 4 was amended on January 14, 2025. Recruitment began on May 8, 2023, and we anticipate recruitment completion on August 1, 2025.

Discussion

Summary

This pilot RCT protocol is designed to assess whether the addition of PRISM to usual care is associated with greater improvements in functional disability compared to usual care alone. This intervention has the potential to enhance pain management and overall well-being for youth with CMP, who have been shown to have lower resilience than unaffected adolescents. The results of this study will heighten our understanding of the role of resilience over time and shed light on strategies that promote psychological resilience for patients with CMP and their caregivers. These insights will lay the groundwork for multicenter studies on the efficacy of PRISM in CMP and inform future treatment strategies for this population.

Limitations

In terms of limitations of this protocol, it may be lacking in generalizability, as the population with CMP at our institution has been limited in racial and ethnic diversity. However, we do expect that our study sample will reflect the demographic makeup of patients with CMP within our clinic population. It is unclear based on the current literature whether our patient population aligns demographically with the population with CMP nationally. Our protocol is also limited to English-speaking participants. Offering PRISM in other languages would further increase the generalizability of future studies. Additionally, although pilot trial participants have approved of our flexibility in scheduling PRISM sessions outside of normal business hours, this may not be feasible in real-world clinical settings. Similarly, the 1-on-1 format of the intervention may be too time and resource intensive for routine clinical practice. This emphasizes the importance of future research to address these limitations and guide future implementation efforts.

Conclusion

Findings from this work will further enhance our understanding of psychosocial factors that play an important role in adolescent CMP, with the goal of reducing the disease burden and improving long-term outcomes. A future multicenter RCT of PRISM for adolescents with CMP will provide further evidence of the efficacy of this program and inform clinical implementation. For some adolescents, the addition of PRISM to routine clinical care could offer sufficient pain-coping skills to reduce their need for individual counseling. For others, these learned skills may serve as a critical interim until formal CBT becomes available. Although PRISM would not fully solve issues such as clinic wait times, the integration of PRISM into clinical care could help prioritize the limited appointments in pediatric chronic pain clinics for those with the greatest need for interdisciplinary care.

Acknowledgments

We are grateful to our study participants and advisory panel of patients and caregivers for their ongoing contributions to our research. This publication was funded by the National Institute of Arthritis and Musculoskeletal Skin Diseases (award number K23AR081409, totaling US $804,060, 100%), with 0% financed from nonfederal sources. PFW is funded by mentor award number K24AR078950. The contents of this publication are solely the responsibility of the authors and do not necessarily represent the official views of the National Institutes of Health. The funding sources played no role in the study design and will not play any role during its execution, analyses, interpretation of the data, or decision to submit the results.

Data Availability

Data sharing is not applicable to this paper as no datasets will be generated or analyzed during the study.

Authors' Contributions

SG, MM, NB, RX, PFC, JFY, TMP, PFW, and ARR all contributed to the application of the PRISM (Promoting Resilience in Stress Management) intervention to this specific patient population, conceptualized this study, and helped obtain funding. NB and MM were responsible for trial registration, continue to lead recruitment of participants, and are responsible for the administration of PRISM and data management. NB, SG, and MM drafted the manuscript. All authors have critically reviewed the manuscript and approved the final version.

Conflicts of Interest

PFW serves as a consultant to Lilly, Pfizer, and Novartis. JFY receives royalties from Oxford University Press for a book on an unrelated topic. The remaining authors have no conflicts of interest to disclose.

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Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[PDF File (Adobe PDF File), 117 KB - resprot_v14i1e73385_app1.pdf]

Multimedia Appendix 2
Semistructured interview guide.
[DOCX File , 24 KB - resprot_v14i1e73385_app2.docx]

Multimedia Appendix 3
Peer-review report from AMS - Arthritis and Musculoskeletal and Skin Diseases Special Grants Study Section, National Institute of Arthritis and Musculoskeletal and Skin Diseases (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 117 KB - resprot_v14i1e73385_app3.pdf]

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Abbreviations

ACR: American College of Rheumatology
AHS: Adult Hope Scale
AIM: Acceptability of Intervention Measure
CAMM: Children and Adolescent Mindfulness Measure
CBT: cognitive behavioral therapy
CD-RISC-10: 10-item Connor-Davidson Resilience Scale
CHOP: Children's Hospital of Philadelphia
CMP: chronic musculoskeletal pain
DSMB: data safety monitoring board
e-consent: electronic consent
EMR: electronic medical record
FDI: Functional Disability Inventory
FIM: Feasibility of Intervention Measure
FM: fibromyalgia
IAM: Intervention Appropriateness Measure
IRB: Institutional Review Board
K6: Kessler-6 Psychological Distress Scale
MCID: minimal clinically important difference
NIAMS: National Institute of Arthritis and Musculoskeletal and Skin Diseases
NIH: National Institutes of Health
PCS-C: Pain Catastrophizing Scale, Child report
PCS-P: Pain Catastrophizing Scale, Parent report
PGH-7: Pediatric Global Health 7
PRISM: Promoting Resilience in Stress Management
PROM: patient-reported outcome measure
PROMIS: Patient-Reported Outcomes Measurement Information System
PSAT: Pain and Symptom Assessment Tool
PSES-C: Pain Self-Efficacy Scale Child
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SS: Symptom Severity
WPI: Widespread Pain Index

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Protocol

Evaluating the Effectiveness of a Mobile HIV Prevention App to Increase HIV and Sexually Transmitted Infection Testing and Pre-Exposure Prophylaxis Initiation Among Rural Men Who Have Sex With Men in the Southern United States: Protocol for a Randomized Controlled Trial

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Abstract

Background: Gay and bisexual men who have sex with men (MSM) in the rural United States are less likely to test for HIV and sexually transmitted infections (STIs) and use pre-exposure prophylaxis (PrEP) compared to urban MSM. Given the challenges in building brick-and-mortar facilities serving the sexual health needs of MSM in rural communities, there is a need to evaluate digital engagement strategies. Combine is a smartphone app designed to provide HIV prevention information and resources to MSM that may be particularly well suited to support rural MSM. HealthMindr, an app from which Combine is adapted, has previously been shown to increase HIV testing and PrEP uptake among urban MSM. Because rural MSM face additional barriers to accessing HIV prevention services, a motivational interview (MI) focused on HIV prevention strategies might enhance the effectiveness of Combine to increase uptake of HIV testing, STI testing, and PrEP.

Objective: This study aims to determine the effectiveness of the Combine app to increase HIV testing, STI testing, and PrEP initiation among rural cisgender MSM. We will also assess the effectiveness of 2 adjunctive interventions: the availability of free HIV and STI self-test kits and the offering of an MI.

Methods: In this type 2 hybrid effectiveness-implementation randomized controlled trial, we will assess the effectiveness of Combine to increase HIV testing, STI testing, and PrEP initiation among rural MSM across the Southern United States. A total of 464 men will be recruited and randomized to 1 of the 4 arms. Participants in all 4 arms will have access to most app features (eg, health resources, quizzes, health care provider locators, and ordering free condoms and lubricants). Using a 2×2 factorial design, half (232/464, 50%) of the participants will be randomized to receive access to free at-home HIV and STI self-test kits and half (232/464, 50%) will be randomized to receive an MI. Participants will complete surveys every 6 months to allow for assessment of self-reported outcomes: app use, HIV testing, STI testing, and PrEP initiation over the 24-month follow-up period. Self-reported PrEP uptake will be verified by dried blood spot testing or uploading a photograph of a PrEP prescription.

Results: Participant recruitment began in March 2024. As of July 2025, 395 participants have been enrolled and randomized. Recruitment is expected to be completed by December 2025.

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Conclusions: This trial will determine whether the Combine app increases HIV testing, STI testing, and PrEP uptake among rural MSM in the Southern United States. It will also provide critical information about the most effective strategies for implementing digital health interventions for rural MSM.

Trial Registration: ClinicalTrials.gov NCT06205368; https://clinicaltrials.gov/study/NCT06205368

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KEYWORDS

HIV; rural; men who have sex with men; testing; pre-exposure prophylaxis

Introduction

Background

Gay, bisexual, and other men who have sex with men (MSM) are disproportionately affected by HIV and other sexually transmitted infections (STIs), including in the rural Southern United States. The Southern United States represents just 37% of the US population [1], but in 2022, 47% of all new HIV infections attributable to male-to-male sexual contact occurred there [2]. The Southern United States is also home to 6 of 7 states identified as priority jurisdictions for the Ending the HIV Epidemic campaign due to the number of new diagnoses in these states occurring in rural areas [3]. The seventh state, Missouri, is geographically contiguous with the Southern United States. Many of the rural counties in Alabama, Georgia, Mississippi, and South Carolina are in the top decile of HIV prevalence in the United States [4].

The HIV epidemic in rural areas resembles the epidemic in urban areas in that the unmet HIV prevention and treatment needs among MSM account for most new diagnoses. In 2018, 77% of new HIV diagnoses in rural areas were among men, and among those, 77% were attributable to male-to-male sexual contact, similar to the proportions attributable to male-to-male sexual contact in urban (83%) and suburban (79%) areas [5]. Moreover, Black people in the Southern United States bear a disproportionate burden of new HIV diagnoses, accounting for 53% of all new diagnoses in 2017; 60% of these diagnoses were among Black MSM [6]. New HIV diagnoses have been increasing steadily among Hispanic MSM and decreasing among non-Hispanic White MSM [6]. Overall, in the United States, 80% of rural residents are non-Hispanic White [7], whereas the overall US population is 60% non-Hispanic White [1]. However, southern states have much larger populations of rural residents of color [8]. Of the 17 states that comprise the Southern United States, 13 have >20% rural populations of color; 3 states (South Carolina, Mississippi, and Texas) have rural populations comprising >40% people of color [8]. Rural MSM, particularly rural MSM of color, represent a key group to prioritize in order to improve HIV and STI health equity across multiple dimensions.

Uptake of HIV testing, STI testing, and pre-exposure prophylaxis (PrEP) among MSM in rural areas is low. MSM in rural areas face a number of challenges in accessing these services, including limited access to culturally competent care, increased experiences of stigma, and lower self-perceived risk of HIV and STI infections compared to MSM in suburban and urban areas [9,10]. HIV testing is the foundation of the National HIV/AIDS Strategy [11] because it serves as the entry point to prevention programs, such as HIV PrEP, among those who test negative and HIV treatment initiation among those who test positive. The Centers for Disease Control and Prevention recommends that sexually active MSM be tested for HIV, *Neisseria gonorrhoeae*, *Chlamydia trachomatis*, and syphilis at least annually [12,13]; more frequent STI screening is recommended for MSM at elevated risk [13]. However, only 40% of rural MSM have been tested for HIV in the past 12 months [14]. STI testing uptake is even lower, particularly for rectal and pharyngeal STIs; <25% of rural MSM have had an STI test in the past 12 months, and <10% have been tested at any extragenital sites. Sexual behavior is remarkably consistent across levels of rurality; in a recent study, approximately 71% of MSM had indications for PrEP, irrespective of rurality [14]. Despite similar levels of awareness and willingness to use PrEP, PrEP use is drastically lower in rural compared to nonrural MSM [15].

Mobile health (mHealth) interventions are effective tools for increasing HIV and STI testing uptake among urban MSM [16-18], and using technologies to support HIV prevention is acceptable to rural MSM [19,20]. Evidence is needed to demonstrate that the acceptability of mHealth interventions among rural MSM translates to intervention effectiveness. Rural MSM have been found to have a strong interest in accessing health care remotely, including at-home HIV and STI testing and tele-PrEP, to assuage concerns about confidentiality and stigma [21,22]. Smartphones are widely accessible to MSM who are most at risk. Overall, among Americans, 96% of people aged 18 to 29 years, 80% of African American people, and 80% of rural residents own smartphones [23]. The internet has also been proven effective in reaching MSM in rural areas to promote HIV prevention [24].

In this type 2 hybrid effectiveness-implementation randomized controlled trial (RCT), we will test an adaptation of HealthMindr, a mobile HIV prevention platform for MSM [25]. HealthMindr is grounded in social cognitive theory [26]. Its development has been described elsewhere [25,27,28], and multiple adaptations of the HealthMindr platform have been tested among different priority populations [17,29,30]. M-Cubed, an adaptation of HealthMindr that provides pop-up HIV prevention messaging, demonstrated efficacy to increase HIV testing and PrEP uptake among urban MSM [17].

There is a need to understand which *components* of app-based HIV prevention are necessary to promote prevention to inform

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future implementation. A standard feature of most app-based HIV prevention interventions is access to free HIV and STI self-test kits [30-32]. These may be particularly attractive to MSM in rural areas for whom options for HIV testing and extragenital STI screening are limited. Because mail-out test kits have been universally available in previous studies, it is not clear if they are a necessary component of these interventions, as an app-only control condition without self-test kits is not available for comparison. Future implementation will be logistically more complicated if test kits need to be provided to ensure the effectiveness of the app, and some public health officials are hesitant to implement at-home testing programs. We need to know whether self-test kits are necessary to promote testing uptake and whether the kits are necessary for the success of other aspects of the interventions (eg, PrEP uptake). For example, HealthMindr has been found to increase PrEP uptake [17], but it is not clear if this effect would persist in the absence of free self-testing.

Brief behavioral motivational interviewing–based interventions are effective in preventing HIV and STI transmission [33], and motivational interviews (MIs) might be an effective adjunctive intervention to increase engagement with an app-based intervention and improve outcomes. Engagement with app content and maintenance of use is another challenge for technology-delivered HIV prevention interventions [16]. In the pilot study of the HealthMindr app, only 25% of the participants continued to use the app throughout the full 4 months of follow-up [25]. Other studies of app-based interventions have encountered similar drop-offs in use over similar follow-up periods [16]. Sustained use over longer follow-up periods will almost certainly be lower. Although alterations to app design and aesthetics might improve user engagement, adjunctive interventions, such as motivational interviewing, might increase user motivation to use app-based interventions on a sustained basis while also providing an opportunity to increase users' ability to overcome barriers related to privacy, confidentiality, and stigma. Motivational interviewing is an effective tool for reducing HIV risk behavior [33]; however, additional data are needed to understand the effectiveness of motivational interviewing among rural MSM, particularly in the context of mHealth interventions.

Apps are an effective method to increase HIV and STI prevention service uptake among MSM in urban areas. Rural MSM face additional barriers that might mitigate the effectiveness of app-based interventions, and there are outstanding questions about the most effective implementation strategies for these interventions. To address these knowledge gaps, we adapted an existing evidence-based app, HealthMindr, into a new app, Combine, specifically focused on rural MSM. We conducted online focus group discussions with rural MSM about their health care experiences and obtained feedback on Combine. Participants had a wide range of backgrounds with respect to accessing HIV prevention services, and an overwhelming majority expressed interest in using Combine to access information and services related to HIV prevention and expected that others in their peer group felt the same [19]. On the basis of participant reports of limited formal knowledge about sex and sexual health, we have expanded the frequently asked questions to provide more detailed information about sex, HIV, and STIs, including options for reducing risks, common symptoms of HIV and different STIs, and treatment options, and tips for negotiating prevention options with a sex partner. We also added enhanced service navigation support, including the option to connect with study staff directly through the app via in-app messaging to receive personalized support.

We conducted an online survey of rural MSM and asked participants about the availability and reliability of cellular service where they lived and their willingness to participate in a research study of a mobile HIV prevention app [34]. Cellular coverage and data access were widely available. A total of 80.3% (147/183) of the participants reported reliable coverage, indicating they could obtain a cellular signal whenever they needed one. Only 3.8% (7/183) of the respondents classified their coverage as unreliable. Large proportions of respondents reported conducting data-intensive activities (unrelated to HIV prevention activities) on their phones, including watching videos (159/183, 86.9%), and 89.1% (163/183) of the participants reported never experiencing difficulties downloading apps due to bandwidth issues. Overall, 89% (162/182) of the participants were willing to download a mobile app as part of an HIV prevention research study.

This Study

Using a 2×2 factorial RCT, we will assess the effectiveness of the Combine app to increase HIV testing, STI testing, and PrEP use among rural MSM and evaluate the effect of 2 specific implementation approaches on testing uptake and app engagement: the availability of HIV and STI self-test kits and an MI intervention to enhance the existing app features. We hypothesize that HIV testing, STI testing, and PrEP uptake will be higher in conditions that include HIV and STI self-test kits or the MI and that uptake of all 3 will be highest in the condition that includes both test kits and the MI.

Methods

Overview

We will conduct a type 2 hybrid implementation-effectiveness, 2×2 factorial RCT to evaluate the effectiveness of the Combine app to increase HIV testing, STI testing, and PrEP initiation among rural cisgender MSM and to assess the effectiveness of 2 adjunctive interventions: an MI and the availability of HIV and STI self-test kits. A detailed description of the components included in the Combine app is provided subsequently. After randomization, participants in intervention arms have access to additional features. Those in intervention arms 1 and 3 have the option to participate in an MI (described subsequently) with a trained study staff member. Those who are in intervention arms 2 and 3 have access to order free at-home STI and HIV testing kits. Participants in the control arm (ie, arm 0) will have access to the app but not to the MI or the HIV and STI test kits. We chose to provide participants in this arm with the app because this app platform has been previously demonstrated to increase HIV prevention service uptake among nonrural MSM [17]; therefore, we did not deem it ethical to withhold the app from participants in the control arm.

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Participants will be followed for 24 months as shown in Figure 1. Primary and secondary outcome measurements will be conducted via online self-administered surveys every 6 months using a Health Insurance Portability and Accountability Act (HIPAA)–compliant survey platform. Surveys will take approximately 30 to 45 minutes to complete. To limit survey duration, some nonlabile survey elements (eg, race, age) will not be assessed at every time point. There will be minimal differences in follow-up surveys depending on intervention assignment; otherwise, surveys will be identical for all those enrolled. All surveys will be optimized for mobile devices.

Figure 1. Flow of recruitment, enrollment, and follow-up in a randomized controlled trial of a mobile health intervention among rural, gay, bisexual, and other men who have sex with men in the Southern United States. STI: sexually transmitted infection.

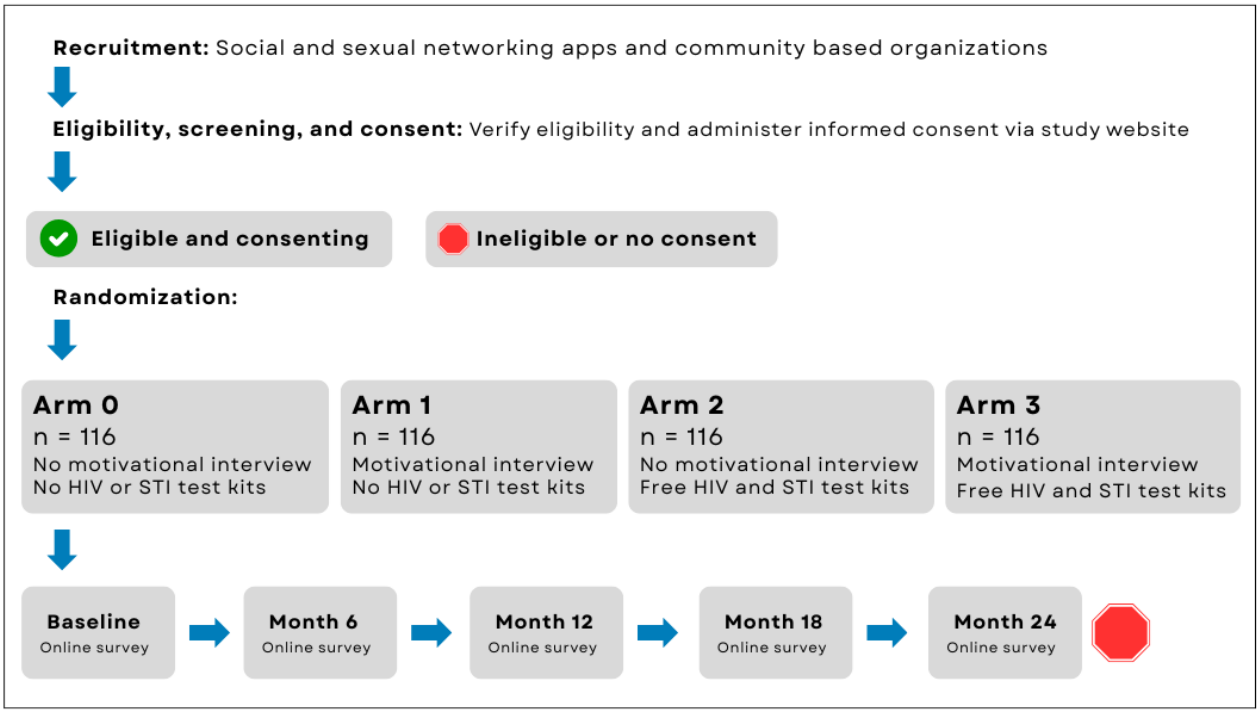

Study App

Overview

The Combine app is embedded within the Study Management and Retention Toolkit (SMaRT) web participant application. SMaRT has been used to promote participant retention and management in multiple previous studies [29,30,35,36]. The SMaRT web application automates regularly scheduled participant contacts (eg, prompts to complete follow-up surveys); allows staff and study participants to exchange secure messages, including return of HIV and STI test results upon request through a HIPAA-compliant file exchange; and allows participants to see their personalized study timeline. The SMaRT app also contains all the Combine intervention content.

Example screenshots are provided in Figure 2. Once logged in, participants will select the Combine study and will be brought to their unique timeline. From here, they will navigate through the app using the bar across the bottom of the screen to get to other documents, their profile, and more resources. This is where all the intervention content is located. We developed videos and infographics to demonstrate app functionality for participants. Each app section is subsequently described briefly.

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Figure 2. Example screenshots of the Study Management and Retention Tool (SMaRT) web application, including the different Combine intervention content sections: (A) log in screen, (B) study timeline, (C) intervention content home screen, (D), health resources section, (E) frequently asked questions about pre-exposure prophylaxis.

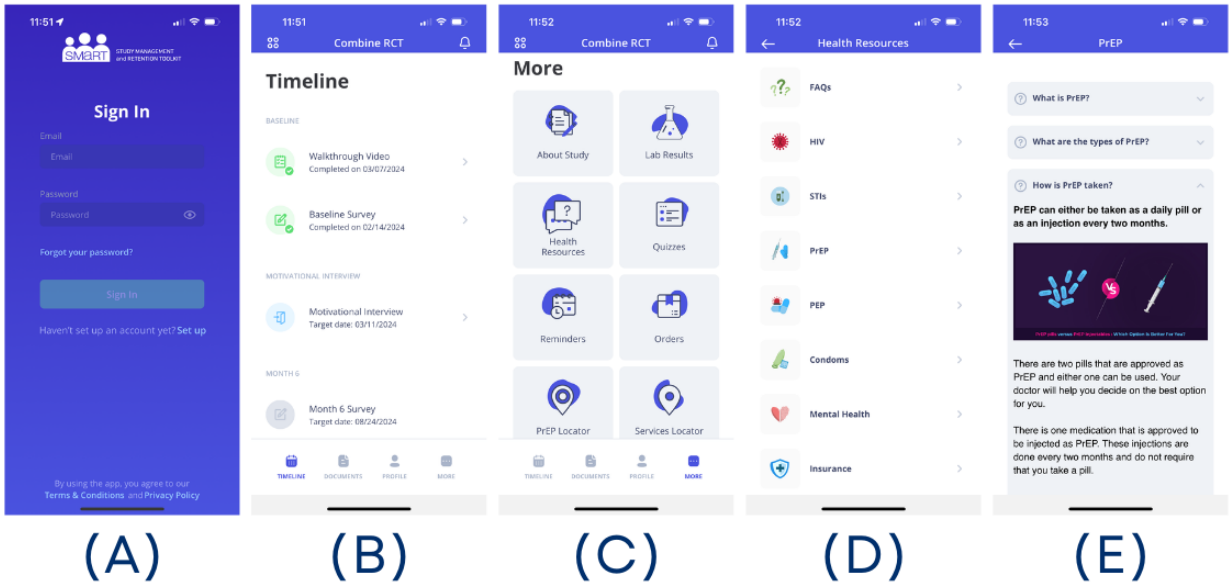

Timeline

This section includes the major time points of the study (baseline, month 6, month 12, month 18, and month 24). It allows participants to see upcoming and previously completed surveys. A walk-through video of the app is pinned at the top of the timeline so that it can be revisited at any point during the study period.

About Study

This section provides participants with a summary of the study's purpose and scope. Contact information for study staff is provided in this section.

Health Resources

This section details app-specific and study-specific information as well as sexual, mental, and medical health information. To engage participants, information is presented as text, graphics, videos, and links to other resources. Resources are broken down into 8 categories and include the following sections:

- Frequently asked questions—general information about the study and app
- HIV—information about HIV transmission, risk factors, testing, symptoms of infection, and treatment options
- STIs—information about STIs, including transmission, risk factors, symptoms, testing, and treatment options
- PrEP—information about PrEP modalities, effectiveness, side effects, cost, payment assistance, and how to find a PrEP provider
- Postexposure prophylaxis—information about postexposure prophylaxis, including indications for use, cost, and how to find a PrEP provider
- Condoms—information about how to use condoms, condom-compatible lubricants, how to make condoms more comfortable, condom use and PrEP, and how to get condoms, including through the Combine app
- Mental health—information about mental health, including definitions of mental health, prevalence of mental health conditions, and how to seek mental health services
- Insurance—information about how to obtain health insurance coverage

Reminders

Participants can set custom reminders to prompt them to complete HIV and STI testing on a regular schedule.

Locators

Participants have access to 4 service locators within the app:

- PrEPLocator [37]
- HIV and STI testing provider locator
- Substance Abuse and Mental Health Services Administration's mental health and substance use service provider locator
- US Department of Health and Human Services and Minority HIV/AIDS Fund HIV services locator

Orders

Participants can order sexual health resources for free through the app. All participants can order condoms and condom-compatible lubricants. Participants in arms 2 and 3 are also able to order HIV and STI self-test kits.

Quizzes

Brief self-assessments are provided to allow participants to monitor their sexual behaviors associated with HIV and STI acquisition and transmission, mental health, and substance use and help determine which testing options are best for them.

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Laboratory Results

This section provides a secure portal for study staff to deliver STI test results or for participants to upload test results obtained outside of the study.

Access to App Content

Most app content is the same for all participants. However, participants in arms 1 and 3 can schedule an MI through the app, and participants in arms 2 and 3 can order free HIV and STI self-test kits through the app.

Participants and Recruitment

We plan to enroll 464 participants (n=116, 25% per arm). The inclusion criteria are as follows: participants should be cisgender male (ie, assigned male sex at birth and currently identify as male), be aged ≥18 to 45 years, reside in the Southern United States as defined by the US Census Bureau or in Missouri (an Ending the HIV Epidemic rural priority state not in the Southern United States), live in a county classified as rural per the Index of Relative Rurality (IRR [38]; refer to subsequent sections for details), own an Android or iOS phone with active service, be willing to download a study app to their phone, be able to read and understand English, report anal sex with a man in the past 12 months, be of unknown serostatus or tested negative for HIV, and not be currently using PrEP.

Participants who are not able to provide informed consent will be ineligible. We plan to enroll a diverse sample comprising at least 50% (232/464) men of color, with an emphasis on enrolling non-Hispanic Black and Hispanic MSM.

The IRR is a continuous metric used to assign a level of rurality to counties in the United States [38]. The IRR is bounded from 0.0 to 1.0 (inclusive), with higher scores indicating greater rurality. IRR scores for counties in the southern US and the state of Missouri from the year 2020 [39] were used to determine participant rurality. Counties with an IRR score of >0.4 are typically considered to be rural [38]; we used a cutoff of 0.35. We have previously shown that an IRR score of >0.4 is a meaningful threshold with respect to access to and uptake of HIV prevention services [14]. To determine a threshold for enrollment into this study, we also explored disparities in HIV prevention service uptake using an IRR threshold of 0.35 to increase the population of potential participants. We observed similar disparities in HIV testing, STI testing, and PrEP uptake using an IRR threshold of 0.35, so we opted to use this threshold to define rurality. We assessed participant geography using self-reported zip code. IRR is determined at the county level, so we use a validated method [40] to crosswalk self-reported participant ZIP code to county to determine participant rurality for eligibility.

Recruitment will occur primarily online and include various approaches given the constantly evolving nature of online venues and platforms. Common approaches include social networking (eg, Instagram [Meta Platforms, Inc] and Snapchat [Snap Inc]), sexual networking and dating apps (eg, Jack'd [Perry Street Software], Scruff [Perry Street Software], and Grindr), or other websites frequented by MSM (eg, Queerty). These online methods have had previous success in recruiting tens of thousands of MSM into HIV prevention research studies [41-43].

In-person recruitment will occur in collaboration with community-based organizations (CBOs) throughout the recruitment period and include the distribution of recruitment materials (eg, palm cards and flyers) during events or in clinic settings.

Unique tracking links will be used so that we will be able to identify the recruitment source for each participant.

Screening and Consent

The online screening process begins once a potential participant has clicked on an advertisement and is redirected to our screener, hosted on a HIPAA-compliant platform, Alchemer. This screener landing page includes a brief overview of the study and a screening consent (Multimedia Appendix 1). Potential participants are also able to leave contact information if they do not have time to take the screener or wish to take the screener at another time. Study staff sends each of these individuals a link to the screener so they can complete it at their convenience. The brief screening consent covers points, such as protected health information, what types of questions will be on the screener, and whom to contact regarding questions about the study. Potential participants must agree to the screening consent to move on to the screening survey, which will determine their eligibility status. The screener should not take more than 5 minutes to complete.

After completing the screener, eligible participants are prompted to complete the enrollment consent form (Multimedia Appendix 2). Included in this enrollment consent is a video consent that highlights key aspects of the consent form in an audio and visual format. Once eligible participants have completed the enrollment consent and provided their contact information, they are able to immediately take their baseline survey. If eligible participants prefer to take their baseline survey later, they will be emailed a link instead. Those who are ineligible are provided with links to HIV prevention information and locators to identify testing providers. They are also able to provide their contact information to be contacted about future opportunities to participate in research conducted by Emory University.

Baseline Survey

The baseline survey is the first of 5 surveys that participants will complete. Because it is the most comprehensive of the surveys, the estimated time to complete the survey is approximately 30 to 45 minutes. Participants receive a US $50 electronic gift card to their preference of Amazon, Target, or Walmart for completing the baseline survey and fraud check (described subsequently). Domains in the baseline survey include demographics, health care access and use, HIV and STI testing history, sexual behavior, PrEP awareness and use, substance use, stigma, and mental health. Select questions are repeated across the screener and baseline surveys for comparison. Any discrepancies in participants' answers across the 2 surveys are resolved during the fraud check (described in the Fraud Prevention, Enrollment, and Randomization section). The entire instrument is included as Multimedia Appendix 3.

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Fraud Prevention, Enrollment, and Randomization

To avert fraudulent registrations, details of eligibility criteria will not be reported before screening, and screening surveys will not have a back button to discourage users from manipulating the screener for eligibility purposes. The screener survey also includes reCAPTCHA to filter out fraudulent responses. Once an eligible participant has completed their baseline survey, a fraud check is initiated that requires potential participants to complete a fraud check phone call with study staff. During the fraud check call, study staff review any discrepancies between the screener and baseline surveys, verify that participants have downloaded the mySMaRTmobile app, and assist in any troubleshooting for the participants upon logging into the app or creating their account. If participants are unable to adequately explain any discrepancies in their responses across the screener and baseline survey, they are determined to be ineligible. After successfully passing the fraud check, the study staff randomizes and enrolls the participant. Any participants identified as fraudulent after enrollment will be removed from the study and excluded from analyses; enrollment totals will be increased to account for the fraudulently enrolled participants.

Arm assignments were generated using random permuted block randomization. Assignments were unmasked. Those who are randomized to a study arm with one or both of the adjunctive interventions are able to see that content following randomization.

Follow-Up Surveys

Follow-up surveys are conducted at months 6, 12, 18, and 24, and each survey is expected to take approximately 25 minutes for participants to complete. Participants are compensated US $50 upon completion of each survey with their choice of an Amazon, Target, or Walmart electronic gift card. Domains in follow-up surveys are similar to the baseline survey, with the addition of questions assessing use of HIV tests, STI tests, and PrEP in the previous 6 months and arm-specific questions regarding the acceptability and use of adjunctive interventions. The complete instrument can be found in Multimedia Appendix 4.

Retention

A preplanned schedule of contact attempts that consists of a variety of follow-up methods will be used to increase retention. Survey reminders are sent 14, 7, and 2 days before the closing of the follow-up surveys. Study staff can record in SMaRT when each activity is completed. Reminders are also sent to participants in the MI arms (arms 1 and 3) if they have not scheduled their interview yet, with instructions on how to do so. Regular messages will also be automatically sent to participants to remind them about different features in the app (eg, locators and product ordering).

Video walk-throughs are available to orient participants to the app and are customized based on individual arm assignment. These videos are easily accessible at the top of the participant's timeline, beginning the day the participant is enrolled in the study, and will stay there for the entirety of the study period. These brief walk-through videos contain important information about how to access follow-up surveys and the different sections available in the SMaRT web application, including the different Combine intervention content sections.

Primary Outcomes

The primary effectiveness outcomes are HIV testing, STI testing, and PrEP initiation. All primary outcomes will be measured via self-report on each follow-up survey. The first time a participant reports PrEP use on a follow-up survey, they will be asked to provide a photo upload of their prescription for a US $15 incentive or submit a self-collected dried blood spot sample for a US $40 incentive to verify PrEP use.

The primary implementation outcome is maintenance. App-based interventions provide the opportunity to obtain detailed metrics on participant engagement [44,45]. Even over relatively short time periods, there tends to be a substantial decrease in the use of HIV prevention apps [44]. However, it is difficult to know whether the reduced app use reflects intervention failure [46]. If a user initiates and sustains a regular HIV testing regimen following app use, the testing intervention would be maintained over time despite a lack of engagement with the app. Thus, to fully understand and describe maintenance of the intervention, both app use and effectiveness data are needed over a prolonged time frame. The Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework defines maintenance at the individual level as sustained intervention use 6 months after initiation [47]. However, this time frame was arbitrary [48] and is too short for an outcome of HIV and STI testing, which are recommended at least annually for most MSM [49,50]. This need for prolonged follow-up motivated the 2-year follow-up time frame for our study. Thus, maintenance of HIV testing will be defined as at least 1 HIV test in the first 12 months and at least 1 test in the final 12 months of follow-up. Similar definitions will be used for maintenance of STI testing and PrEP.

Statistical Analysis

We will examine the main effects of the motivational interviewing intervention and availability of test kits on the clinical outcomes of HIV and STI testing uptake and PrEP initiation in each year of study follow-up. We will use a multivariable generalized linear mixed model with a log link and binomial outcome distribution to estimate the relative probability of HIV testing uptake comparing those who had the ability to order HIV test kits compared to those who did not and among those who received an MI compared to those who did not. An analogous method will be used for the outcomes of STI testing and PrEP initiation. We hypothesize that there will be main effects of both the MI and access to free test kits. Participants will be analyzed based on their arm assignment (ie, intention-to-treat analysis). Although we will not have the statistical power to assess the interaction between the 2 intervention components, we will conduct exploratory analyses to assess evidence of any synergistic effects.

The final, deidentified dataset will be shared through the Inter-university Consortium for Political and Social Research [51].

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Power Analyses

Power calculations are based on simulations using a binomial model of the form as follows:

$$\log(P(\text{uptake}|\text{kit},\text{mi})) = \alpha + \beta 1\text{kit} + \beta 2\text{mi}$$

where kit and mi are binomial variables representing the availability of self-test kits and an MI, respectively. We simulated 10,000 trials representing the following underlying assumptions of HIV testing uptake in each arm: 44.8% (52/116) in arm 1 (a slight increase over the baseline estimate of 38% from the American Men's Internet Survey) and 76.7% (89/116) uptake in arms 2 to 4 (ie, similar effect of kits and MI without interaction). The 76.7% (89/116) uptake (a relative increase of 71% over control) is based on the results of a 4-month pilot of HealthMindr [25], so it is likely an underestimate of expected uptake over 24 months. Assuming α of .05 and a sample size of 376 (n=94, 25% per arm), we will have 93% power to detect an effect of each of the intervention components (ie, self-test kits and MI). The smallest detectable difference (ie, 80% power) will be an uptake of 72.4% (84/116) in the intervention arms. Assuming the aforementioned sample size of 94 per arm, and control uptake of 25% (29/116; a slight increase in the baseline estimate of 22% from the American Men's Internet Survey), we will have 80% power to detect a relative increase of 112% in STI testing (uptake: 61/116, 52.6% in arms 2-4). The uptake of STI testing in the HealthMindr pilot was 47% without STI self-testing [25], so this is also likely an underestimate. Less reliable data are available for the prevalence of PrEP use among rural MSM; however, only 11% of rural MSM in the Southern United States have ever used PrEP [15]. Assuming the current prevalence of PrEP use is 5% (ie, half of those who have ever used PrEP are currently using PrEP), we will have 80% power to detect an absolute difference in PrEP use of 29% (assumptions: 6/116, 5.2% in arm 1 and 34/116, 29.3% in arms 2-4; risk ratio: 5.1). With respect to maintenance of the intervention, in the HealthMindr pilot study, 22.9% (25/109) of the participants used the app in the fourth (and final) month of follow-up [25]. We used the simulation-based method described earlier to determine power to detect a similar absolute increase in intervention maintenance as we proposed for the effectiveness outcome (ie, 28 percentage point increase; 127% relative increase). We will have 80% power to detect continued engagement with the app (ie, maintenance) of ≥50%. We anticipate that the hypothesized referent maintenance level of 22% is high because it is based on only 4 months of follow-up, so this is a conservative estimate of power. These power calculations assume a single observation per participant; however, our longitudinal design will result in increased power to detect a difference between treatment arms [52]; therefore, our estimates of power are conservative. To allow for 10% attrition per year, we will enroll a total sample of 464 (n=116, 25% per arm) participants.

Cost and Cost-Effectiveness Analyses

We will conduct comprehensive analyses to assess the cost of developing and implementing the interventions using a microcosting approach. We will use standard economic evaluation methods as recommended by the US Panel on Cost-effectiveness in Health and Medicine [53-55] and adapted for HIV and AIDS programs by Jain et al [56]. These methods have been used for economic analyses for a variety of recruitment, HIV testing, and linkage to care interventions, including for MSM in the United States [57-59]. The economic analysis will be conducted from the societal perspective (the cost to the party implementing the program plus the cost to the men participating in the program) to estimate the cost and cost-effectiveness of the innovative strategies to promote repeat HIV testing among MSM using the Combine app relative to the comparison strategy. The societal perspective accounts for costs to all parties, acknowledges the value of competing uses for society's resources, and maximizes comparability with other cost-effectiveness analyses. Data will be entered into a standardized Microsoft Excel spreadsheet with embedded formulas to calculate costs similar to publicly available data collection and costing spreadsheets used in similar studies [57-59]. The implementation strategy costs will not be discounted to aid in budget impact analyses. Cost information will be abstracted from accounting records, study surveys, published literature reports, and electronic time stamps.

Cost-effectiveness analyses will include calculating the incremental cost-effectiveness ratio (ICER) for each arm compared to standard of care as follows:

$$[(\text{Cost_Intervention} - \text{Cost_StandardofCare})] \;/\; [(\text{Outcome_Intervention} - \text{Outcome_StandardofCare})]$$

ICERs will be calculated for each primary outcome (ie, HIV testing, STI testing, and PrEP initiation). These comparisons will help implementers weigh the relative costs and benefits of each strategy. Costs and effects will be discounted at 3% per year [53,54]. One-way sensitivity analyses for all input variables will determine which inputs the ICERs are most sensitive to. We will also conduct a sensitivity analysis excluding development costs under the assumption that the implementation strategies could be rolled out without significant investment in development. Intervention cost-effectiveness will be estimated over the 2-year time horizon of the trial.

MI Session

Overview

Participants in arms 1 and 3 will have the opportunity to participate in an MI. The MI session, delivered via HIPAA-compliant Zoom (Zoom Communications, Inc), is designed to promote engagement with HIV and STI testing and other prevention behaviors using the Combine app. A systematic review identified 8 behavioral change techniques that have demonstrated impact on HIV and STI behavioral change, including problem solving, feedback on behavior, social support, instructions on how to perform the behavior, information about health consequences, information about social and environmental consequences, demonstration of the behavior, and a credible source. These 8 behavioral change techniques form the foundation of the MI session. Specifically, the MI aims to achieve the following: (1) increase insight into the Combine app utility and personal HIV risk and prevention behaviors, (2) enhance motivation and empowerment to make sexual health behavior decisions, (3) align participants' values and behavior goals to increase commitment for potential change, and (4)

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operationalize an HIV and STI prevention plan based in individual values and goals and leveraging the study app. A comprehensive MI procedure and quality assurance manual was prepared by a licensed clinical health psychologist and study team member with expertise in MI and HIV (TRG).

The Combine MI manual is used to guide each interview to ensure that the developed curriculum is provided to each participant according to protocol. The MI comprises 4 stages, outlined in Textbox 1.

Textbox 1. The 4 stages of the motivational interview (MI).

Phase 0: consent and agenda setting

- The purpose of this stage is to mitigate any anticipatory distress by presenting what the discussion will cover. Verbal consent for recording is documented at this stage, as consent for the MI itself has already been discussed.

Phase 1: overview and demonstration of the Combine app

- The purpose of this stage is to orient the user to the app, highlight key HIV prevention functions, and provide a foundation for the discussion of HIV prevention planning.
- Behavioral change techniques include instructions on how to perform the behavior and demonstration of health behavior.

Phase 2: HIV prevention counseling with MI-based problem-solving

- The purpose of this stage is to help the participant identify recent HIV risk behaviors, identify potential HIV prevention strategies, reinforce recent HIV prevention efforts, solve problems concerning barriers to HIV prevention, and point out which app features can be used to help their HIV prevention efforts. Grounding the discussion in the app both encourages app use and makes it clear to the participant that they have a resource in their hand that they can use to enact the prevention plan they are building with the interventionist.
- Behavioral change techniques include feedback on behavior, information about health consequences, information about social and environmental consequences, credible source, problem-solving, and social support.

Phase 3: action plan

- The purpose of this stage is to build an individualized plan for engagement in HIV prevention (by picking 2 specific behaviors aligned with personal values and goals) within the context of the app to increase the likelihood of follow-through with their action plan.
- Behavioral change techniques include feedback on behavior and instructions on how to perform the behavior.

Participants who complete the MI will earn a US $25 electronic gift card incentive upon completion of the interview. The interview should occur within the first 60 days of participant enrollment, with reminders sent to participants via text and email. If the participant fails to schedule their interview, staff will continue to send monthly reminders for 12 months. Participants can schedule their interview at any point during their enrollment. The calendar function within the timeline of the Combine app will allow participants to self-select times for their MI, which are updated monthly and monitored daily by study staff based on their availability. Once a participant selects an available time slot, the SMaRT system will notify staff of the appointment selection, and staff can then approve or deny the appointment and send a confirmation message, which includes the Zoom link to the meeting.

Interviewers complete a training program, including readings, a multiday seminar, mock interviews with feedback, and, once assessed to be competent, individual supervision with feedback on 2 initial MI sessions. Quality assurance shall be performed on 19.8% (46/232) of all sessions by trained staff by completing data collection forms and listening to audio recordings for any issues, concerns, or questions. Sessions that will undergo review will be randomly selected on an ongoing basis from batches of approximately 10 visits. Quality assurance documents include a “session fidelity checklist,” which ensures that topics from the Combine MI manual are discussed, and global scales from the *Motivational Interviewing Treatment Integrity Coding Manual 4.2.1* [60], which cover themes of cultivating change talk, softening sustain talk, and fostering partnership and empathy. Forms must score an interrater reliability of >80%. If agreement is <80%, remediation (eg, rerate under supervision, conduct group discussion, and retrain the rater) will occur.

In-Depth Interviews

At the end of the follow-up period, study staff will conduct in-depth interviews (IDIs) with some participants. IDI participants will be randomly selected from a sampling frame of all participants that is stratified by app engagement. In this way, we will purposefully sample from participants who used the app at least once in each 6-month follow-up period and those who used the app less frequently. These IDIs will focus on the features of the app that participants found most and least useful and the factors that might influence them to use an HIV prevention app outside the context of a research study. The IDI will begin by asking the participant to walk the interviewer through a “typical use session” of the app during which the interviewer will probe into key decisions (eg, why one function was used over other functions). The interview will examine the participant’s views on the positive and negative elements of the app. Specifically focusing on the RE-AIM domain of maintenance, the interviewer will probe reasons for continued use among those with high engagement, reasons for not using the app among those with low engagement, and strategies for improving maintenance. The goal of these interviews will be to develop actionable items that we can incorporate with quantitative data from follow-up surveys, app paradata, and

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qualitative data from stakeholders to further refine implementation strategies specifically tailored for rural MSM.

During IDIs with key stakeholders at health departments and CBOs, we will explore considerations around implementation within the domains of RE-AIM and strategies from the Expert Recommendations for Implementing Change project [61]. The goal of these discussions will be to identify common themes and actionable items to support future implementation of app-based HIV prevention interventions in community settings. Interviewees will first be asked to describe current programs to support HIV testing among rural MSM and their experience with mHealth interventions in general and rural MSM specifically. Depending on their previous experience, interviewees will be asked to describe actual or hypothetical barriers to implementing mHealth interventions for rural MSM. Interviewees will also be probed for strategies they have successfully used to reach rural MSM in the past and ideas for adapting those strategies in mHealth interventions. Other key aspects of implementation and maintenance that will be probed include technological capabilities of the implementers, additional capacity building that might be necessary to support an mHealth intervention, and strategies for supporting sustained use. Example IDI questions for stakeholders are included in Table 1.

Table 1. Sample in-depth interview questions for stakeholders.

Domain	Questions
Reach	• How do you engage clients in HIV and STI[a] testing interventions? • What proportion of your target population are you able to engage in HIV and STI testing? • How could an app-based intervention affect your ability to reach MSM[b] for HIV and STI testing?
Effectiveness	• What type of effectiveness data would convince your organization to adopt a new intervention?
Adoption	• What strategies have you used in the past to encourage adoption of interventions among your health care providers and staff? • Would cost data be useful for justifying allocating resources to an app-based intervention? • What type of cost data are used to make decisions in your organization?
Implementation	• What types of changes might be needed in your infrastructure to support the implementation of an app-based intervention? • What type of support might you need to increase capacity to support app-based interventions?
Maintenance	• What is your capacity to support the prolonged use of app-based interventions among your clients? • What type of support would you need to build on this capacity?

[a]STI: sexually transmitted infection.

[b]MSM: men who have sex with men.

Qualitative Analysis

All IDIs will be digitally recorded, transcribed verbatim, and deidentified. Transcripts will be entered into MAXQDA (VERBI Software), which facilitates the processes of coding, annotating, and retrieving text such that analysts may note patterns in the textual data across themes. Data analyses will be conducted using a phenomenological inquiry framework [62,63]. Phenomenology is focused on describing what people within a group have in common as they experience a phenomenon and is an inductive analytic approach that allows the patterns, themes, and categories of analysis to emerge from data [62,63]. After close readings of the text, the lead analysts will create a preliminary codebook to capture emergent themes. We anticipate developing a codebook consisting of 12 to 15 codes representing key themes, including explicit domains from the interview guides and the RE-AIM domains (deductive themes) and pervasive, unanticipated themes that were emergent across various transcripts (inductive themes). Provisional definitions will be given to each code. The preliminary codebook will be presented to other analysts (per the phenomenological approach), and a group discussion will occur. After edits are made to the codebook, all analysts will apply the preliminary codebook to a single transcript. The coded transcripts will be merged for comparison, and code definitions will be revised based on an examination of coding disagreements. This process will be repeated until consistent agreement is attained among all coders. A finalized codebook will be created, and the trained analysts will start coding (from scratch) all the textual data for the project. The goal of this analysis will be to describe the key factors anticipated to affect future implementation of the Combine app in real-world settings and inform the development of implementation strategies to support optimal implementation of the Combine app for rural MSM.

Dissemination Plan

Trial results will be disseminated through publications in scholarly journals and direct communications with research participants and community partners. The study team has developed an authorship agreement that outlines expected roles on primary and secondary result papers.

Ethical Considerations

This study has been reviewed and approved by the institutional review board at Emory University (STUDY00006280) and has been registered at ClinicalTrials.gov (NCT06205368). This is a low-risk trial, and adverse events are not expected; however, any adverse events that arise will be reported to the sponsor and

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funding agency as required. All protocol modifications will be approved by the institutional review board before implementation and will be reported to the funding agency and updated on ClinicalTrials.gov.

All participants will provide informed consent to complete the eligibility screener and enroll in the study. Data are not deidentified or anonymized. All data are maintained on secure servers that require password access. All participants are compensated for completing study activities. Participants are compensated US $50 for each of the baseline and follow-up surveys. Participants who report PrEP initiation are invited to submit a photo of their prescription (US $15 incentive) or a self-collected dried blood spot sample (US $40 incentive) as verification. Those who participate in MIs will receive US $25 and those who participate in IDIs will receive US $60. All compensation is provided in the form of an electronic gift card.

Results

Participant enrollment began in March 2024. As of July 2025, 395 participants have been enrolled and randomized (arm 0: n=100, 25.3%; arm 1: n=97, 24.6%; arm 2: n=98, 24.8%; arm 3: n=100, 25.3%). Of those who have been eligible to complete a 6-month follow-up survey so far, 81.3% (122/150) have done so. Recruitment is projected to be completed by December 2025; participant follow-up will be completed 2 years later. Study results are expected to be available in 2028.

Discussion

Anticipated Findings

MSM in the rural Southern United States face numerous obstacles to accessing HIV prevention services, including limited to no access to culturally competent care, enhanced experiences of stigma, and concerns of sexual identity disclosure [22,64-66]. Although rural MSM have expressed interest in and willingness to use mobile technology to access HIV testing, STI testing, and PrEP [19,20], large-scale studies have not yet demonstrated the effectiveness of mHealth interventions to increase access to these services among rural MSM. Thus, the goal of this study is to assess the effectiveness of the Combine intervention, based on the HealthMindr platform, to increase uptake of these services while also assessing the modifying effects of 2 adjunctive interventions—free, at-home self-test kits and an MI. Using a 2×2 factorial randomized design, we will be able to answer questions not only about intervention effectiveness but also the necessary components of the intervention to achieve optimal HIV prevention outcomes.

Specifically, the factorial design will allow us to assess the independent effects of including free HIV and STI test kits and an MI to increase HIV prevention service uptake. Although financial constraints prohibit enrolling a study population large enough to facilitate assessing the interaction between test kit availability and the MI, we will assess the interaction effects in secondary analyses. This knowledge will not only inform future intervention implementation for HIV prevention among rural MSM but also will likely generalize to nonrural settings.

Limitations

This study has limitations. Due to cost constraints, the app is only available in English. Although a Spanish-language version of the app would be ideal, it is currently cost prohibitive. There is a substantial Latino and Hispanic population in the rural Southern United States. However, we expect most Hispanic and Latino MSM will be eligible because, as of 2014, 76% of Latino people in the United States in the proposed age range for this study were proficient in English [67]. The primary outcomes are measured via self-report and are therefore subject to recall and reporting bias. To mitigate social desirability bias, participants complete surveys online and are encouraged to complete the survey in a private place. The study is also limited to cisgender men. Although there are other priority populations who could benefit from a similar intervention, the language in the app is tailored to cisgender MSM. Engaging other communities in this study without properly adapting and modifying the app would lead to potentially stigmatizing experiences. We have previously found an adapted version of HealthMindr to be acceptable among transmasculine people [68], and future research should continue to explore adaptations among other priority groups. Participants will be followed for 2 years to allow for multiple opportunities to test under current recommendations from the Centers for Disease Control and Prevention [49], which presents challenges with respect to participant retention. We have incorporated multiple touchpoints along the way to keep participants engaged and believe that the incentive structure for surveys will encourage retention. In addition, the same barriers that prevent HIV prevention service uptake among rural MSM might also limit willingness to participate in an HIV prevention study. We have successfully recruited rural MSM in the past [34], and we will work diligently with CBOs to successfully meet recruitment goals. Finally, mHealth interventions pose unique challenges with respect to the ever-evolving technology landscape. We have an ongoing relationship with our software developer and have budgeted for anticipated modifications to ensure that the app continues to work with future releases of the Android and iOS operating systems.

This study will provide critical data on the effectiveness of and key implementation factors necessary to support mHealth interventions to increase HIV testing, STI testing, and PrEP use among rural MSM in the Southern United States.

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does not necessarily represent the official views of the National Institutes of Health. The funding agency did not have a role in study design; data collection, management, analysis, or interpretation; or preparation of this protocol and the decision to submit it for publication.

Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Screening informed consent form.
[DOCX File , 283 KB - resprot_v14i1e69540_app1.docx]

Multimedia Appendix 2
Enrollment informed consent form.
[DOCX File , 147 KB - resprot_v14i1e69540_app2.docx]

Multimedia Appendix 3
Baseline survey.
[DOCX File , 99 KB - resprot_v14i1e69540_app3.docx]

Multimedia Appendix 4
The 6-month follow-up survey.
[DOCX File , 88 KB - resprot_v14i1e69540_app4.docx]

Multimedia Appendix 5
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOCX File , 54 KB - resprot_v14i1e69540_app5.docx]

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Abbreviations

CBO: community-based organization
HIPAA: Health Insurance Portability and Accountability Act
ICER: incremental cost-effectiveness ratio
IDI: in-depth interview
IRR: Index of Relative Rurality
mHealth: mobile health
MI: motivational interview
MSM: men who have sex with men
PrEP: pre-exposure prophylaxis
RCT: randomized controlled trial
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
SMaRT: Study Management and Retention Tool
STI: sexually transmitted infection

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Protocol

Improving Prediction of Falls and Cognitive Impairment in Parkinson Disease: Protocol for a Decentralized Observational Study

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Abstract

Background: Falls and cognitive impairment are major sources of disability in Parkinson disease (PD). The ability to accurately identify individuals with PD at high risk for falls and cognitive impairment would provide an opportunity for intervention and potentially improve long-term outcomes. In a previous study, Assessing Telehealth Outcomes in Multiyear Extensions of Parkinson Disease Trials (AT-HOME PD), we remotely characterized participants with early PD who had participated in 1 of 2 PD clinical trials over 2 years of follow-up. These participants with advancing disease provide a unique opportunity to examine whether the capture of objective in-home measures via digital tools and bothersome symptoms via direct participant report improves the prediction of disease milestones.

Objective: Assessing Telehealth Outcomes in Multiyear Extensions of Parkinson Disease Trials–2 (AT-HOME PD2) aims to examine whether digital tools and remote participant reporting can improve the prediction of falls and cognitive impairment, quantify changes in physical activity over time, and explore the relationship between physical activity and clinical progression over time.

Methods: This is a decentralized observational study of up to 200 individuals with PD, with clinical and digital phenotyping for up to 3 years of follow-up. Participants are those who took part in the STEADY-PD III (NCT02168842), Study of Urate Elevation in Parkinson's Disease, Phase 3 (SURE-PD3; NCT02642393), AT-HOME PD (NCT03538262), or PD GENEration (NCT04057794) studies. All participants complete 2 video visits per year, wear 2 wrist-worn sensors (Fitbit Charge 5 and ActiGraph CentrePoint Insight Watch) for 1 week each month, complete smartphone-based motor tasks (using the mPower 2.0 app) for 10 days each quarter, and complete online surveys (within the companion Fox Insight study) each quarter. Falls are

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assessed via a weekly automated telephone call. A cognitive diagnosis is determined by a consensus committee that considers scores on a global cognitive measure, detailed neuropsychological tests, a cognitive-related disability measure, and clinical information. Prediction models will be constructed, and prediction accuracy will be compared across the models.

Results: Recruitment for the study was initiated in September 2023. Enrollment is ongoing, with 142 participants enrolled as of January 2025. Within the cohort, the average age is 69.2 (SD 8.7) years; 85 (59.9%) participants are male, 137 (96.5%) are White, and 2 (1.4%) are Hispanic or Latino; and the average disease duration is 8.9 (SD 1.3) years.

Conclusions: AT-HOME PD2 is remotely clinically and digitally phenotyping participants with midstage PD to predict falls and cognitive impairment and to provide insights into long-term progression.

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KEYWORDS

Parkinson disease; falls; decentralized; digital health technologies

Introduction

Parkinson disease (PD) is a progressive, neurodegenerative disorder that is increasing in prevalence [1]. Falls and cognitive impairment are major sources of disability in PD, associated with loss of independence, hospitalization, long-term care facility placement, and mortality [2-7], contributing to the estimated US $52 billion annual cost for PD care in the United States [8]. The early identification of individuals at risk for falls and cognitive decline is critical to enable appropriate intervention, which may take the form of home modifications, medication changes, or other adjustments, and to improve long-term outcomes. While many PD-specific and nonspecific risk factors for falls have been identified, the single best predictor for falls remains a prior history of falls, and new, more accurate models for fall prediction are needed [9-11]. Similarly, while many PD-specific and nonspecific risk factors for dementia have been identified [12-17], few studies have examined predictors of the new onset of PD-related mild cognitive impairment [18-20].

Digital tools, which enable frequent and objective in-home assessment of motor [21-24] and nonmotor function [25-29], stand to improve the management of PD and may improve the prediction of falls and cognitive impairment. However, they are not routinely used in clinical practice to aid in the prediction of falls or cognitive impairment. Many fall prediction models incorporate performance-based tests, which are typically conducted in a traditional clinic setting. However, relevant metrics, such as gait speed, cadence, and stride time variability, can be measured with digital tools in the home [11,30,31]. Studies have demonstrated the potential to use digital tools to predict falls and time to a first fall [32,33]. Digital tools have also been used to demonstrate that slower gait speed, lower levels of physical activity, less time spent outside of the home, and fewer trips outside the home are associated with cognitive impairment in older adults [34,35]. Novel methods of capturing the most bothersome symptoms and their functional impact [36] can generate a participant-reported natural history of PD [37] that may contextualize and inform understanding of data obtained from objective in-home assessment. Studies are needed to determine whether in-home digital metrics and remote participant reporting can improve the prediction of important PD-related clinical milestones.

In a previous study, AT-HOME PD (Assessing Telehealth Outcomes in Multiyear Extensions of Parkinson Disease Trials), we remotely characterized motor and nonmotor progression of participants with early PD using annual video visits, quarterly smartphone-based motor assessments, and quarterly online surveys over 2 years of follow-up [38]. AT-HOME PD was designed to assess a novel framework for the remote follow-up of clinical trial participants, to compare digital and traditional outcomes, and to identify novel digital disease measures. AT-HOME PD enrolled 226 participants (mean age 64.7, SD 8.8 y; 40% female; mean time since diagnosis 3.8, SD 1.2 y) from 42 US states and 1 Canadian province, who participated in either STEADY-PD III (NCT02168842) or Study of Urate Elevation in Parkinson's Disease, Phase 3 (SURE-PD3; NCT02642393)—both multicenter, randomized, controlled, phase III studies of potential disease-slowing agents [38-40].

In this study, we will leverage this well-characterized cohort and describe the protocol for AT-HOME PD2 (Assessing Telehealth Outcomes in Multiyear Extensions of Parkinson Disease Trials–2), a decentralized observational study with clinical and digital phenotyping that will: (1) evaluate the extent to which digital tools and remote participant reporting can improve the prediction of falls and cognitive impairment compared with traditional models; (2) quantify change in physical activity and gait over time; and (3) explore the relationship between physical activity, development of falls or cognitive impairment, and symptom progression over time. We hypothesize that digital assessment of gait, sleep, and physical activity in the real world will improve the prediction of falls and cognitive impairment compared with a model composed of traditional measures.

Methods

AT-HOME PD2 is a decentralized, observational PD study with up to 3 years of follow-up. All visits and assessments are conducted remotely in the participant's natural environment. Participants complete 2 video visits per year, wear 2 sensors (Fitbit Charge 5 and ActiGraph CentrePoint Insight Watch) for 1 week each month, complete smartphone-based motor tasks (using the mPower 2.0 app) each quarter, and complete online surveys (via Fox Insight) each quarter (Figure 1).

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Figure 1. Overview of AT-HOME PD2 (Assessing Telehealth Outcomes in Multiyear Extensions of Parkinson Disease Trials–2) study design.

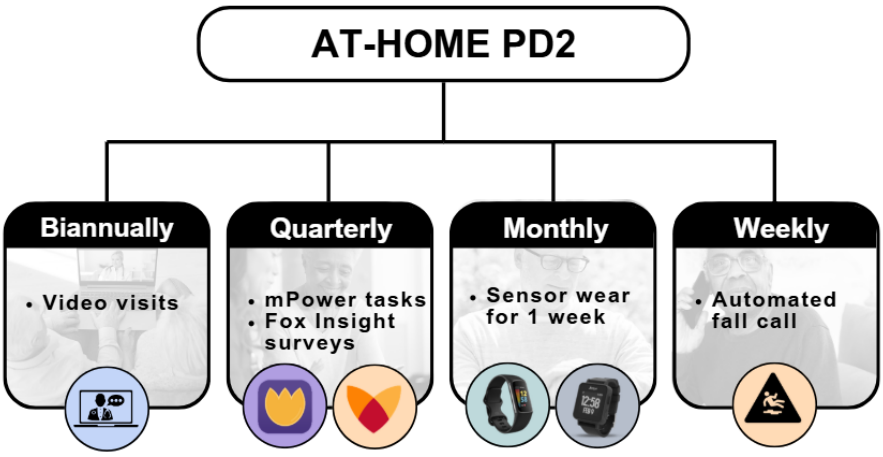

Study Setting

Visits are conducted by video at the University of Rochester using a cloud-based, HIPAA (Health Insurance Portability and Accountability Act)–compliant platform.

Ethical Considerations

This study was approved by the University of Rochester Institutional Review Board (STUDY00008433). All participants provide informed consent and may choose to opt out of the study. Participants receive US $50 for each video visit, for up to a total of US $350, and keep the Fitbit upon completion of the study. The study team makes every effort to maintain data confidentiality and protect participants' personal information. This includes assigning each participant a globally unique identifier, which is used to label collected information; restricting access to the study databases; transferring study data securely; and deidentifying study data before sharing it with qualified external researchers.

Study Participants

Eligible participants were originally defined to be those who participated in AT-HOME PD and those who participated in STEADY-PD III (NCT02168842) or SURE-PD3 (NCT02642393) and provided consent to future research contact but did not participate in AT-HOME PD. Participants must have access to an internet-enabled device that supports video visits. Participants are provided with a webcam, Bluetooth adapter, smartphone stand, tablet stand, or an Android study phone with a data plan, when needed, to enable participation. There are no other technological requirements. A history of prior falls or cognitive impairment does not exclude individuals from participating.

In December 2024, because of concerns regarding our ability to meet the enrollment target, recruitment was opened to individuals who participated in PD GENEration (NCT04057794), a PD genetic testing study led by the Parkinson's Foundation [41,42]. Specifically, AT-HOME PD2 participation was opened to individuals who participated in the first 2 phases of PD GENEration, which included clinical assessments [42]. The eligibility criteria are the same, with 2 exceptions. Participants from PD GENEration must have been diagnosed with PD 6 to 12 years ago and possess an iPhone. The disease duration requirement was added to ensure that newly recruited PD GENEration participants had a similar disease duration to those already participating in AT-HOME PD2. The iPhone stipulation was added, given the plans to incorporate the use of a smartphone app that is available only on iOS systems.

Study Procedures

Enrollment of the STEADY-PD III, SURE-PD3, and AT-HOME PD Participants

Outreach to potential participants is conducted via telephone, email, and mail. Interested potential participants are sent a link to the electronic informed consent (eConsent) and scheduled for a screening visit, which may be performed by telephone or video. During the screening visit, informed consent is obtained, eligibility is confirmed, demographics are collected, and the need for equipment is assessed. The Fitbit Charge 5, ActiGraph CentrePoint Insight Watch, and any other needed equipment are shipped to the participant after the screening visit. Enrollment occurs on a rolling basis, with the enrollment visit scheduled within 60 days of the screening visit, and participants from the original AT-HOME PD study joining between month 48 and month 72, relative to their baseline AT-HOME PD visit. During the enrollment visit, participants receive instructions on mPower 2.0, Fitbit Charge 5, and ActiGraph CentrePoint Insight Watch use and, if required, assistance in enrolling in Fox Insight. All other assessments are as described subsequently and listed in Table 1.

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Table 1. The assessments conducted during annual video visits.

Assessment domain	Instrument or measure
Motor assessments	• Movement Disorder Society–Unified Parkinson's Disease Rating Scale parts II, III, and IV • Clinician falls and freezing assessment • Patient falls assessment • mPower 2.0 motor tasks
Cognitive assessments	• Montreal Cognitive Assessment • CANTAB[a] connect: Rapid Visual Information Processing • CANTAB connect: Paired Associates Learning • CANTAB connect: Pattern Recognition Memory • CANTAB connect: Spatial Working Memory • CANTAB connect: One Touch Stockings of Cambridge
Other nonmotor assessments	• Movement Disorder Society–Non-Motor Scale • Movement Disorder Society–Unified Parkinson's Disease Rating Scale part I
Global assessments	• Schwab and England Activities of Daily Living • Clinical Global Impression (Severity and Change)[b] • Patient Global Impression (Severity and Change)[b]
Study assessments	• System Usability Scale • Perceived Research Burden Assessment

[a]CANTAB: Cambridge Neuropsychological Test Automated Battery.

[b]Clinical Global Impression–Change and Patient Global Impression–Change are only completed during the follow-up visits.

Enrollment of PD GENEration Participants

The Parkinson's Foundation sends PD GENEration participants an email invitation to participate in AT-HOME PD2. Interested potential participants who provide their consent to be contacted by the AT-HOME PD2 study team will then complete a screening form. Outreach to potential participants is conducted via telephone, email, or mail. The remainder of the procedures is as described earlier.

Video Visits

Participants are followed for up to 3 years and complete annual video visits with a comprehensive clinical assessment and interim video visits to support adherence to study activities. Patient-reported outcomes are completed within Research Electronic Data Capture (REDCap) outside of the scheduled clinical assessment visit. Some outcomes—falls assessment, Movement Disorder Society–Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part Ib and II [43], and Patient Global Impression-Severity and Change [44]—are completed before the video visit, while others—System Usability Scale [45] and Perceived Research Burden Assessment [46]—are completed after the video visit. The remainder of the assessments (Table 1) and any incomplete pre–video visit patient-reported outcomes are completed during the video visit. Participants also complete up to 3 interim research coordinator–led video visits. These are brief visits during which the mPower 2.0 active tasks are completed and adherence with the digital health technologies is reviewed.

Remote Monitoring With Digital Health Technologies

Within the mPower 2.0 smartphone app, participants complete 3 active motor tasks (ie, resting tremor, gait and balance, and finger tapping) each day for 10 days every 3 months. To minimize variability in performance, participants are instructed to perform the tasks during their self-identified PD medication ON state and to complete them at approximately the same time each day. Participants are also asked to complete 3 cognitive tasks (ie, dimensional card sort, digit symbol substitution test, and spatial working memory) once every 3 months. Participants may optionally consent to passive monitoring of movement and motor activity patterns.

Participants wear 2 sensors, the Fitbit Charge 5 and the ActiGraph CentrePoint Insight Watch, on their nondominant wrist for 7 days each month. Specifically, participants are instructed to wear the sensors during waking hours for 6 days and one complete 24-hour period on the seventh day. Participants are randomly assigned to wear either the Fitbit Charge 5 or the ActiGraph CentrePoint Insight Watch in the most distal position. Participants use the Fitbit app and the CentrePoint Connect app to sync their data to the Fitabase and CentrePoint platforms, respectively, throughout their wear week. The Fitbit Charge 5 is equipped with an accelerometer and photoplethysmography sensor. It captures wear time, motor parameters (eg, steps taken, distance, active zone min), and nonmotor parameters (eg, heart rate, heart rate variability, breathing rate, skin temperature, oxygen saturation, sleep stages, and sleep interruptions). The ActiGraph CentrePoint Insight Watch is equipped with an accelerometer and a near-body temperature sensor. It captures wear time, motor parameters (eg, steps taken, nonsedentary time, and physical activity), and nonmotor parameters (eg, sleep time, sleep onset latency, and sleep efficiency).

Adherence to digital health technologies is assessed during each visit. Participants receive a monthly calendar that indicates expected sensor wear and mPower 2.0 use. During the review

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of the calendar with the participant at the enrollment visit, the coordinator encourages them to inform the team if they need to adjust or reschedule a month's sensor wear week to accommodate their personal schedule. Outside of the scheduled visits, the study team sends a reminder to the participant shortly before their next sensor wear week. The study team conducts monthly monitoring of the CentrePoint and Fitabase dashboards to monitor sensor battery levels, ensure consistent data uploads are completed by the participant, and identify any errors that require troubleshooting. If the battery level of a sensor falls below 20% or a data upload error occurs for a participant, the study team contacts the participant to assist with troubleshooting.

Fox Insight

Fox Insight is an online, observational research study sponsored by the Michael J Fox Foundation for Parkinson's Research [47]. Every 3 months, participants complete a set of questionnaires, including the Patient Global Impression–Change, PD Patient Report of Problems [36], PD questionnaire-8 [48], and the Non-Motor Symptoms Questionnaire [49]. The Penn Parkinson's Daily Activities Questionnaire [50], EQ-5D [51], and MDS-UPDRS part II are completed on a biannual basis. The Geriatric Depression Scale-15 [52], REM Sleep Behavior Disorder Single-Question Screen [53], and Physical Activity Scale for the Elderly [54] are completed annually.

Outcomes: Falls Assessment

Participants are provided with the following definition of a fall, based on an established expert consensus definition [55]: "a fall is an unexpected event in which you come to rest on the ground, floor, or a lower level." To limit the possibility of recall bias, participants receive a weekly automated telephone call during which they are asked to enter the number of falls they have had (if any) in the past week [56]. Participants who are unable to answer the automated telephone calls (eg, those on Canadian phone plans who cannot receive calls from the United States) receive a weekly email from the study team instead. Participants who report a fall receive follow-up from a study coordinator to gather additional details on the fall circumstances and outcomes.

Outcomes: Cognitive Assessment

A consensus committee comprised of movement disorder and cognitive experts will use cognitive, functional, and clinical data to assign a cognitive diagnosis (ie, normal cognition, mild cognitive impairment, or dementia) for each participant at each annual visit. The committee will consider scores—including change from baseline—on a global cognitive measure (Montreal Cognitive Assessment) [57,58]; on specific neuropsychological tests (ie, Paired Associates Learning, Pattern Recognition Memory, Spatial Working Memory, One Touch Stockings of Cambridge; and Rapid Visual Information Processing from the Cambridge Neuropsychological Test Automated Battery) [59], and on the 15-item Penn Daily Activities Questionnaire, a measure of cognition-related functional abilities. The committee will also consider clinical information, such as the use of cholinesterase inhibitors.

Safety Monitoring

We capture information on events of interest (eg, hospitalization, participation in a clinical trial, and neurological events) as spontaneously reported by the participant or observed by a member of the study team. To reduce the risk of falls during study assessments, participants who typically use an assistive device or have the assistance of another person to walk are instructed to complete walking tasks under their usual conditions. Participants and/or any member of the study team may opt not to complete walking tasks because of a perceived safety concern. We have a medical safety escalation plan that guides the response of the study team to medical or safety issues that may arise during a video visit. For example, in the event of an urgent medical concern that requires immediate attention, the participant or care partner is instructed to contact emergency services. If they are unable to do so, a member of the study team will contact emergency services on their behalf and remain in contact with the participant until emergency services arrive.

Data Sharing

All study data from the video visits, mPower 2.0, Fitbit, ActiGraph, Fox Insight, and falls assessments will converge in Synapse (Sage Bionetworks), a cloud-based data management platform. Within Synapse, deidentified clinical and digital data will be available to qualified researchers. Clinical data will be transferred to the Parkinson's Disease Biomarkers Program Data Management Resource, merged with data from the STEADY-PD III, SURE-PD3, AT-HOME PD, and PD GENEration parent studies, and made available to qualified researchers.

Statistical Analysis

Statistical analysis will focus on (1) determining the extent to which digital tools and remote participant reporting improve the prediction of falls and cognitive impairment; (2) quantifying change in physical activity and gait metrics over time; and (3) exploring the relationship between physical activity, falls, cognitive impairment, and progression.

Prediction accuracy for time to first fall after baseline (AT-HOME PD2 enrollment), time to a recurrent fall (2 falls within 1 year), time to first-ever fall, and development of mild cognitive impairment and dementia at 1, 2, and 3 years after baseline will be compared among (1) a model using traditional measures; (2) an augmented model that also includes measures captured by remote assessment of motor and cognitive function; and (3) an augmented model that further includes participant-reported bothersome symptoms. Predictors included in the traditional model will comprise age; sex; disease duration (ie, years since diagnosis); measures of disease disability (Schwab and England Activities of Daily Living and Hoehn and Yahr); prior history of falls; prior history of freezing of gait; cognitive performance (Montreal Cognitive Assessment); medication use; measures of disease severity (MDS-UPDRS, MDS-Non-Motor Scale); and, for prediction of cognitive impairment, markers of socioeconomic status (ie, education and income level). The augmented digital model will also include digital measures of gait, physical activity, steps taken, heart rate, sleep parameters, motor function, and cognition. The augmented participant report model will also include curated descriptions of postural instability and cognition. Prediction models will be constructed using both traditional Cox proportional hazards regression and logistic regression, as well

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as survival or random forest classification methods. Prediction accuracy will be compared using the relative concordance index (for falls) or the area under the receiver operating characteristic curve (AUC; for mild cognitive impairment and dementia). We will evaluate the incremental value of the augmented models based on an improvement in the concordance index or AUC that is significantly greater than 0.05 at a 2-tailed significance level of $P<.05$.

We will calculate the mean steps per day and the mean time spent in moderate-to-vigorous physical activity for the Fitbit (using proprietary algorithms) and for the ActiGraph (using PD-specific cut points [60]) for each 7-day monitoring period. Gait dynamics (eg, step regularity and freezing of gait) will be extracted from active motor task performance and passively collected data within the mPower 2.0 app. We will visualize the interdevice reliability between the Fitbit and ActiGraph for step count and moderate-to-vigorous physical activity using Bland-Altman plots and quantify it using intraclass correlation coefficients.

Linear mixed effects models will be used to analyze the trajectories over time in physical activity, steps taken, and gait measures collected passively with the Fitbit, ActiGraph, and mPower 2.0 app over the 3-year follow-up period. Pearson or Spearman correlations will be used to assess the relationships between changes in these passively collected measures and changes in patient-reported outcome measures at specific follow-up time points.

Cox proportional hazards regression models will be used to examine the association between physical activity (ie, moderate-to-vigorous physical activity during the initial 7-day monitoring period) and the development of clinically relevant milestones (ie, the time to a first-ever fall and a fall after baseline, the time to a recurrent fall, the time to mild cognitive impairment, and the time to dementia). Associations between the trajectories over time in physical activity and traditionally assessed motor and cognitive progression will be examined by jointly modeling physical activity and symptom responses using mixed models that account for the correlation between these responses [61].

Sample Size

In 2 midstage PD cohorts, 30% to 32% of participants experienced at least 1 fall over a year [62,63]. Assuming a sample size of 160 participants, a fall rate of 30%, and an AUC of 0.70 using traditional predictors, the study will have 80% power to declare that prediction using remote assessment measures is significantly better than an AUC of 0.75 if the true AUC for this model is at least 0.85. The study will have 80% power to declare that prediction using these measures in combination with reports of participant experience is significantly better than an AUC of 0.85 if the true AUC for this model is at least 0.94. A sample size of 200 participants will account for a 20% dropout rate.

Study Oversight

The steering committee is composed of the principal investigator (RS), the study biostatistician (PA), and individuals with wide-ranging expertise (AA, JB, SB, KB, RD, AE, EM, DN, DO, SS, MS, TS, CT, and DW). The steering committee meets quarterly and provides oversight of the study, including the review of safety data and study progress, as well as oversight of analysis and publication plans.

Results

A notice of award from the National Institutes of Health was received on April 3, 2023 (Multimedia Appendix 1). The study was approved by the University of Rochester Institutional Review Board in August 2023. Study recruitment was initiated on September 15, 2023, and is ongoing. The original pool of potential participants included 215 individuals from the AT-HOME PD study and 256 individuals from the STEADY-PD III or SURE-PD3 studies who had provided consent for future contact but did not participate in the AT-HOME PD study. Participation was opened to individuals from the PD GENEration study on November 18, 2024. As of January 15, 2025, 142 participants have enrolled. Of these, the average age is 69.2 (SD 8.7) years, 85 (59.9%) are male, 137 (96.5%) are Caucasian, 2 (1.4%) are Hispanic or Latino, and participants have a mean disease duration of 8.9 (SD 1.3) years. Among enrolled participants, 110 (77%) participated in the AT-HOME PD study, 9 (6%) in STEADY-PD III only, 8 (6%) in SURE-PD3 only, and 15 (11%) were recruited from the PD GENEration study. Among enrolled participants, 135 reside in 34 US states and the District of Columbia, and 7 reside in 1 Canadian province. Enrollment is anticipated to be completed by April 2025.

Discussion

AT-HOME PD2 has enrolled 71% of the target number of participants from 3 research cohorts and is expected to generate new insights into the prediction of falls and cognitive impairment, inform the understanding of the role of physical activity in the management of midstage PD, and extend the longitudinal characterization of early PD clinical trial participants to up to 10 years through a participant-friendly, decentralized framework. Remote clinical and digital phenotyping in AT-HOME PD2 will complement in-person observational cohort studies, such as the Parkinson's Progression Markers Initiative [64] and the Oxford Parkinson's Disease Centre Discovery cohort [65], and long-term follow-up studies of other clinical trial cohorts, such as Levodopa in Early PD [66], and will provide insights into PD progression in the current treatment era. The inclusion of participants from PD GENEration will enable comparison of progression between clinical trial and observational research cohorts.

In AT-HOME PD2, traditional clinical assessments are complemented by digital tools, including a smartphone-based app, a commercial wrist-worn sensor, and a research-grade wrist-worn sensor. Many larger-scale digital phenotyping efforts have focused on populations with early-stage, untreated PD [67-69]; however, digital tools also have the potential to support the development of new treatments for and the care of individuals with later-stage PD. In AT-HOME PD2, we focus on a population with later-stage disease and use a combination of active motor assessments and passive data collection to

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generate insights into PD motor impairment, gait, physical activity, steps taken, and sleep. Our primary aim is centered on improving the prediction of falls and cognitive impairment—2 patient-centered disease milestones that are highly relevant to individuals with later-stage disease. To this end, we will use rigorous methods to capture the occurrence of falls and cognitive impairment. Falls are captured via a weekly automated telephone call, which will limit the potential for recall bias. Cognitive diagnosis is determined by a consensus cognitive committee comprised of experienced physicians who will use cognitive, functional, and clinical data to determine cognitive status [70].

Nonetheless, we recognize that this approach has limitations; for example, we anticipate that adherence to weekly fall reporting will decline over the study period. In addition, we recognize that some participants will have already experienced a fall or developed cognitive impairment at the time of study entry. While we will primarily focus on the prediction of time to first fall and development of mild cognitive impairment and dementia after study entry, secondary analyses will evaluate the prediction of fall frequency, time to first fall requiring hospitalization, time to first fall resulting in injury, time to first-ever fall, time to a recurrent fall, time to development of mild cognitive impairment, and time to development of dementia. In addition, we acknowledge that we do not capture every potential risk factor—for example, objective assessment of autonomic function is limited to the capture of heart rate, and neither of the wrist-worn sensors captures blood pressure. We also acknowledge the potential for differential attrition, with participants with greater physical or cognitive impairment more likely to be lost to follow-up. To partially address this, we collect contact information for a secondary informant at baseline.

Beyond the prediction of clinically meaningful events, this study will yield 3-year longitudinal data on change in motor and nonmotor digital measures, which will inform understanding of progression in this understudied stage of PD. Increased physical activity in PD is likely associated with slower decline [71,72] and a lower risk of mortality [73]; yet, studies to date on longitudinal change in physical activity have largely been limited to early PD or relied on self-report [68,74]. We will use active motor tasks and passive monitoring to objectively measure physical activity, steps taken, and gait parameters in a midstage PD sample. In turn, we will identify measures that capture progression over up to 3 years and examine the relationship with change in traditional clinical measures (eg, the MDS-UPDRS), and with the occurrence of clinically meaningful events. An improved understanding of the impact of physical activity on clinical outcomes will inform the counseling of individuals with midstage PD.

In addition, we will compare the performance of the consumer-oriented Fitbit with that of the research-grade ActiGraph device. Digital devices and algorithms must be validated in the appropriate context of use, which in this case is the monitoring of midstage PD in the home environment. While commercial devices are widely available, easily accessible, and may be acceptable for at-home assessment of physical activity in PD, they require validation before integration into clinical care or clinical trials. In this study, participants will wear the Fitbit and ActiGraph simultaneously on the same wrist, which will enable comparisons between devices. We will compare the feasibility of remote wrist-worn sensor assessment through an evaluation of wear-time adherence. We will also examine interdevice reliability through a comparison of physical activity, step count, and sleep parameters. The identification of a consumer device that accurately and reliably captures activity and sleep in PD would provide a potentially scalable method for monitoring these variables as part of clinical care.

In conclusion, in AT-HOME PD2, we will remotely clinically and digitally phenotype 200 participants with midstage PD, with the goal of improving the prediction of falls and cognitive impairment, characterizing long-term changes in physical activity, and examining the relationship between physical activity and clinical progression.

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Data Availability

The datasets generated or analyzed during this study will be available to qualified researchers in the Sage Bionetworks Synapse repository [75]. The clinical dataset generated or analyzed during this study will be available to qualified researchers in the Parkinson's Disease Biomarkers Program Data Management Resource [76].

Authors' Contributions

AH contributed to data collection, data analysis, and drafting of the manuscript. CD was responsible for data collection and critical review of the manuscript. PA contributed to study design, data analysis, and critical review of the manuscript. KM, MP, KS, and RW were responsible for data collection and critical review of the manuscript. AA, JB, SB, KB, ERD, AE, EAM, MHGM, DN, DO, LO, MS, SS, TS, CT, and DW contributed to study design and critical review of the manuscript. RBS was responsible for study conception, study design, and drafting of the manuscript.

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Conflicts of Interest

AH, CD, PA, KM, MP, KS, RW, DN, DO, LO, and MAS report no financial conflicts. AJE has received grant support from the National Institutes of Health and the Michael J Fox Foundation; personal compensation as a consultant or scientific advisory board member for Mitsubishi Tanabe Pharma America (formerly Neuroderm); Amneal; Acadia; Avion; Acorda; Bial; Kyowa Kirin; Supernus (formerly USWorldMeds); NeuroDiagnostics, Inc (SYNAPS Dx); Intrance Medical Systems, Inc; Merz; Praxis Precision Medicines; Citrus Health; and Herantis Pharma. AJE serves as chair of the Data Safety Monitoring Board of AskBio and has received publishing royalties from Lippincott Williams & Wilkins, Cambridge University Press, and Springer. He cofounded REGAIN Therapeutics and is a coinventor of the patent "Compositions and Methods for Treatment and/or Prophylaxis of Proteinopathies." MHMG has received speaker honoraria from Bial. In the last 12 months, TS has served as a consultant for AskBio; BlueRock Therapeutics; Critical Path for Parkinson's Consortium; Denali; General Electric, Inc; Kyowa; the Michael J Fox Foundation; Neuroderm/MTPA; Prevail/Lilly; Roche/Genentech; Sanofi; Sinopia; Takeda; TrueBinding; and Vanqua Bio. TS has served on advisory boards for AskBio; Biohaven; Denali; GAIN; General Electric, Inc; Kyowa; Neuron23; the Parkinson Study Group; Prevail/Lilly; and Roche/Genentech. TS has also served as a member of the scientific advisory boards for Koneksa, Neuroderm/MTPA, Sanofi, and UCB, and received research funding from Neuroderm, the National Institute of Neurological Disorders and Stroke, the Michael J Fox Foundation, the Parkinson's Foundation, Prevail, Roche, and UCB. In the past 12 months, CMT has served as a consultant for Neurocrine, Praxis (advisory board via the International Parkinson's and Movement Disorder Society), Jazz/Cavion, Roche/Genentech, and Bial. CMT also reports grant support to her institution from the Michael J Fox Foundation, the National Institutes of Health, Gateway LLC, the Department of Defense, Roche Genentech, and the Parkinson's Foundation. In the past year, DN has received research funding or support from the Michael J Fox Foundation for Parkinson's Research, the International Parkinson and Movement Disorder Society, the National Institutes of Health, the Parkinson's Foundation, and the US Department of Veterans Affairs; honoraria for consultancy from AbbVie, Boehringer Ingelheim, Cerevel Therapeutics, CHDI Foundation, Citrus Health Group, Medscape, Modality.AI, the Parkinson Study Group, Roche, Sage Therapeutics, Scion NeuroStim, Signant Health, and Vanqua Bio; and license fee payments from the University of Pennsylvania for the Questionnaire for Impulsive-Compulsive Disorder in Parkinson's Disease and the Questionnaire for Impulsive-Compulsive Disorder in Parkinson's Disease Rating Scale. KB is a full-time employee and minor stockholder of Eli Lilly. ERD has received honoraria from Adivo Associates France, the American Neurological Association, Dartmouth, Elsevier, HMP Education, International Parkinson and Movement Disorder Society, Massachusetts Medical Society, the Michael J Fox Foundation, the National Institutes of Health, the National Multiple Sclerosis Society, Northwestern University, the Patient-Centered Outcomes Research Institute, the Philadelphia Neurological Society, Stanford University, Stony Brook, Sutter Health, the Texas Neurological Society, and the University of Toronto. ERD has served as a consultant for Abbott; AbbVie; Acadia; Acorda Therapeutics; Advarra; Aspen Neuroscience, Inc; Biogen; Biohaven Pharmaceuticals; BioSensics; Boehringer Ingelheim; Caraway Therapeutics; Cerevance; CuraSen; DConsult2; Denali Therapeutics; Eli Lilly; Genentech; HanAll BioPharma; Health & Wellness Partners; HMP Education; Kairos Cinema, LLC (PBS); Karger; KOL groups; Life Sciences Consultant; Mediflix; MedRhythms; Merck; Mitsubishi Tanabe Pharma America, Inc; MJH Holdings; NACCME; Novartis; Otsuka; Praxis Medicine; Sanofi; Seelos Therapeutics; Spark Therapeutics; Springer Healthcare; Theravance Biopharmaceuticals; VivoSense; and WebMD. ERD has received grant support from Averitas Pharma, Biogen, the Burroughs Wellcome Fund, the Michael J Fox Foundation, the National Institutes of Health, Pfizer, Photopharmics, Roche, and the Safra Foundation, and holds ownership interests in Included Health, Mediflix, SemCap, and Synapticure. SS is an employee of Sage Bionetworks. RBS receives research funding from the National Institutes of Health, the Michael J Fox Foundation for Parkinson's Research, Biohaven Pharmaceuticals, Acadia Pharmaceuticals, and Bial, and receives monetary support from Clintrex Corporation for participation on a Data and Safety Monitoring Board.

Multimedia Appendix 1
Peer review report from CIDH - Clinical Informatics and Digital Health Study Section, Healthcare Delivery and Methodologies Integrated Review Group (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 88 KB - resprot_v14i1e71955_app1.pdf]

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Abbreviations

AT-HOME PD: Assessing Telehealth Outcomes in Multiyear Extensions of Parkinson Disease Trials
AT-HOME PD2: Assessing Telehealth Outcomes in Multiyear Extensions of Parkinson Disease Trials–2
AUC: area under the receiver operating characteristic curve
HIPAA: Health Insurance Portability and Accountability Act
MDS-UPDRS: Movement Disorder Society–Unified Parkinson’s Disease Rating Scale
PD: Parkinson disease
REDCap: Research Electronic Data Capture
SURE-PD3: Study of Urate Elevation in Parkinson’s Disease, Phase 3

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Protocol

Promoting Equity in Parent Presence and Participation in Neonatal Intensive Care: Protocol for a Prospective Cohort Study

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Abstract

Background: Parents of infants born preterm experience many barriers to their presence in the neonatal intensive care unit (NICU) and participation in infant caregiving. Parents from historically marginalized backgrounds or with limited social or economic resources may experience even more profound barriers, creating a significant source of health inequity for these parents and their infants. While the specific barriers and facilitators of parent presence and participation (PPP) in caregiving are unknown, PPP may be critical for improving clinical outcomes and neurodevelopment for infants born preterm.

Objective: This study aims to (1) longitudinally determine the barriers and facilitators affecting PPP specific to parents with diverse sociodemographic characteristics, (2) determine the effect of PPP on infant clinical outcomes and neurodevelopment and the potential mediating effect of parent-infant responsiveness, and (3) determine the moderation effect of PPP on the relationship between infant stress exposure and infant clinical outcomes and neurodevelopment. We hypothesize that barriers and facilitators of PPP will vary based on sociodemographic characteristics and will change over the duration of a NICU hospitalization. We expect that higher levels of PPP will be associated with better infant outcomes.

Methods: Parents (N=375) of infants born preterm, at <32 weeks' gestational age, will be enrolled in a prospective cohort study. The parents will complete a daily survey documenting the amount of time spent in the NICU and the caregiving activities performed. The parents will also complete surveys at regular intervals during their infant's admission to report barriers and facilitators of PPP, NICU-related stress, depressive symptoms, experiences of discrimination, and engagement with NICU staff. Additional data will be collected throughout each infant's hospitalization, including invasive procedures, infant clinical data, and nursing documentation of PPP. The parents will complete the maternal-infant responsiveness instrument at the time of NICU discharge and at 3 months' corrected age (CA). Infant clinical outcomes include the achievement of feeding milestones and the length of NICU stay. The infants will be assessed at 3 months' CA using the test of infant motor performance and at 12 months' CA using the Bayley scales of infant and toddler development, fourth edition.

Results: Funding was awarded in August 2024. Data collection and analysis are expected to be completed by July 2029.

Conclusions: By identifying the important barriers and facilitators of PPP over the duration of hospitalizations of infants born preterm and differences in these factors based on sociodemographic characteristics, time- and population-targeted interventions can be developed to remove system-level barriers and enhance facilitators. These efforts may increase PPP and promote health equity for diverse families.

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KEYWORDS

premature infant; neonatal intensive care units; parents; health promotion; health inequities

Introduction

Background

Sociodemographic disparities exist in the outcomes of infants born very preterm (ie, infants born before 32 weeks' gestational age [GA]) [1-4] and in the protective factors that promote more typical neurodevelopment. Parent presence in the neonatal intensive care unit (NICU) and participation in caregiving—protective factors associated with better clinical outcomes (eg, decreased length of stay) [5-8] and neurodevelopment [9]—are threatened by racial and socioeconomic disparities [10-13]. Although a few studies have reported lower parent presence and participation (PPP) for Black parents than for White parents [10-13] and for unmarried parents compared with married parents [11,12], the reasons underlying these disparities are unknown, and prior study findings are inconsistent, with some studies reporting associations between such factors and others reporting none [14]. Importantly, studies of PPP have been primarily conducted in the United States, followed by countries in Europe, with relatively few studies outside of these regions [14]. While factors associated with PPP have not been studied systematically, a combination of barriers and facilitators, many of which originate in the health care system, likely contribute to differences in PPP and the observed relationship with race and economic status. Our preliminary work, conducted as a survey study of NICU parents across the United States, revealed differences in the NICU experiences of diverse parents. Specifically, the most highly educated parents reported the highest levels of engagement with NICU staff; Black parents and Asian parents reported higher levels of discrimination compared with White parents [15]. However, whether these experiences affected PPP could not be determined from this cross-sectional study. A better understanding of barriers and facilitators and their relative influence on PPP will support the development of interventions to remove barriers and promote system-level changes that advance health equity for all infants born preterm and their parents.

PPP in infant caregiving (eg, feeding, diapering, bathing, holding, and skin-to-skin contact [SSC]) are necessary to ensure a timely, safe NICU discharge [16] and may also be important for improving infant outcomes [17,18]. PPP reduces the physical separation between parents and their hospitalized infants [19] and facilitates the development of responsive parent-infant relationships. Parent-infant responsiveness, defined as the prompt, contingent, and appropriate reactions that parents display in everyday parent-child interactions [20], develops through participation in early caregiving and is particularly important for the development of infant stress regulation [21] and positive cognitive outcomes [22,23]. PPP may also buffer the effects of unmodifiable influences on infant neurodevelopment, such as NICU stress exposure [24,25], which is associated with abnormal brain growth and neurodevelopmental impairment [26-28]. In the short term, there is some evidence that PPP buffers infant stress responses to painful procedures, resulting in lower pain scores and fewer behavioral distress signs compared with other nonpharmacological pain management interventions [29,30]. However, maternal skin-to-skin contact (SSC), the most commonly measured form of parent participation [17], while associated with lower mortality [31], better pain control [31], lower rates of hospital readmission [31], and more mature neurobehavior at NICU discharge [17], has unclear effects on length of stay [17] and longer-term neurodevelopment [31].

Despite the potential benefits of parent participation in caregiving, parent presence, a necessary precursor to participation in caregiving, is often unpredictable and infrequent [9,32], accounting for as little as 5% of the infant's cumulative NICU hospitalization [9]. Moreover, although PPP may improve neurodevelopment and clinical outcomes for infants born preterm, infrequent parent presence is associated with more parent-reported emotional and behavioral problems during early childhood [33]. To develop interventions to promote PPP and potentially improve infant outcomes, the important barriers and facilitators and the specific factors affecting historically marginalized populations must be identified.

Guiding Theoretical Model

The *behavioral model of health services use* identifies the important constructs influencing engagement with the health care system, namely attributes of the health care system, the external environment (ie, social determinants), perceived need, health status, and demographic characteristics (Figure 1) [34]. The model has been previously used to guide qualitative research to determine the barriers and facilitators of parent SSC in the NICU [35]. Similar to SSC, PPP is likely influenced by factors within the health care system [10,32,35], social determinants that affect many health outcomes [12,13,36], the perceived need of parents to be close to their infant [35,37-39], the health status of parents (ie, parent well-being) [10,32,39], and demographic characteristics [10,36,37,39]. Aligned with these constructs from the model developed by Andersen, we have identified specific variables to be measured in this study based on a literature review and our prior research.

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Figure 1. Barriers and facilitators of parent presence and participation. BW: birthweight; GA: gestational age; NICU: neonatal intensive care unit.

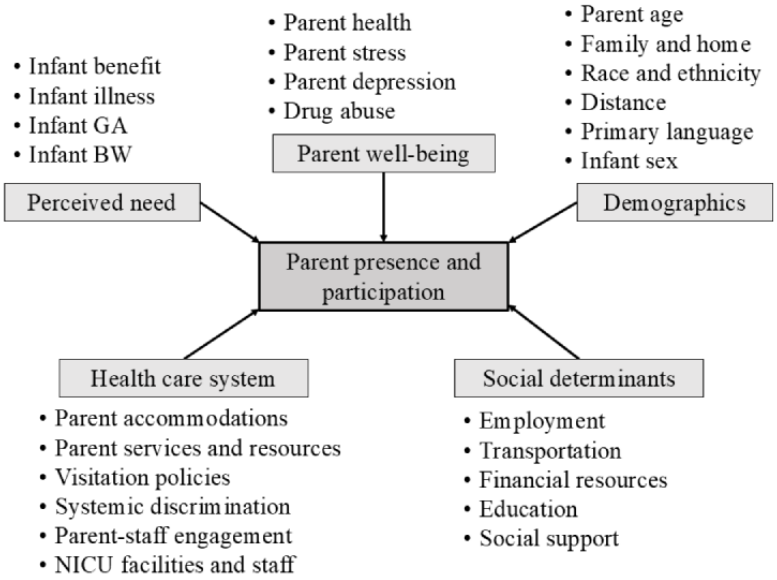

Objectives

Interventions are needed to eliminate barriers to PPP and reduce health inequities. However, foundational to this work is a better understanding of the barriers and facilitators of PPP and the effects on infant outcomes. This study aims to (1) longitudinally determine the barriers and facilitators affecting PPP specific to parents with diverse sociodemographic characteristics, (2) determine the effect of PPP on infant clinical outcomes and neurodevelopment and the potential mediating effect of parent-infant responsiveness, and (3) determine the moderation effect of PPP on the relationship between infant stress exposure and infant clinical outcomes and neurodevelopment (Figure 2). We hypothesize that the barriers and facilitators of PPP will be different for parents with different sociodemographic characteristics; parents with more influential barriers and fewer facilitators will have lower levels of PPP. We also expect that some of the barriers and facilitators—especially those related to the well-being of parents and the perceived need of parents—will change over time. Importantly, we expect that higher levels of PPP will be associated with more responsive relationships between infants and parents and, ultimately, better infant outcomes. Finally, we expect that PPP will attenuate the effect of NICU stress exposure on infant outcomes.

Figure 2. Conceptual model and aims.

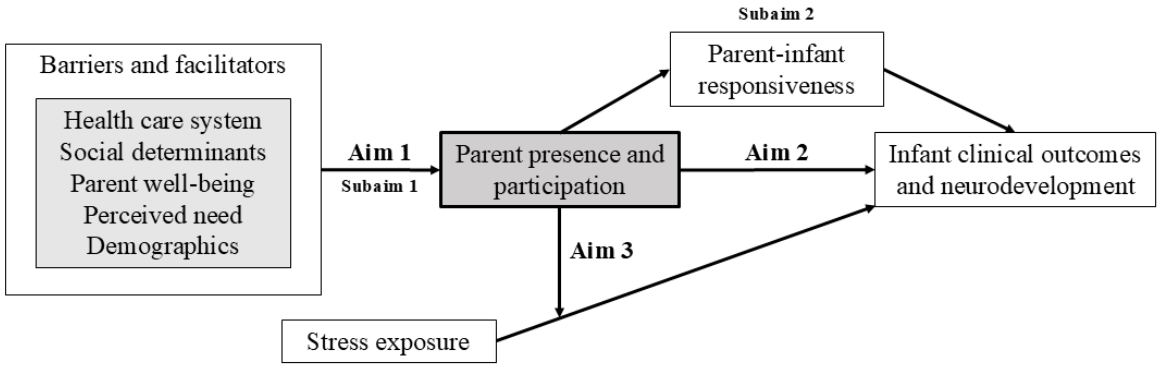

Methods

Study Design

We will use a nonexperimental, prospective observational design to address the aims. Study participation will begin within the first week of life for each infant and will continue until 12 months' corrected age (CA; chronological age adjusted for degree of prematurity). Data will be used to build predictive models that include the most important barriers and facilitators of PPP for parents from different sociodemographic backgrounds.

Participants and Setting

The primary participants in this study will be parents or primary caregivers with an infant born at <32 weeks GA and admitted to 1 of 3 NICUs in a large midwestern US metropolitan area. The NICUs include a level III 38-bed unit with primarily open bays and a few single-patient rooms; a level III 48-bed unit with single-patient rooms and a few double-occupancy rooms, which are typically reserved for multiple-birth siblings; and a level IV, all-referral, 48-bed unit with primarily single-patient rooms and a few beds in open bays (large room units typically with bedspaces separated only by curtains). Eligible parent participants will meet the following inclusion criteria: (1) be

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English- or Spanish-speaking, (2) be aged ≥18 years, and (3) have an infant born at <32 weeks' GA who is expected to survive, based on assessment by the attending physician. Because approximately 20% of twin pregnancies and 65% of triplet pregnancies result in preterm birth before 34 weeks' GA [40], parents of twins or higher-order multiples will be included. However, we will randomly select only 1 infant from a set of multiples to participate in the study.

The target sample size is 300 parents, which will ensure an adequate sample size to address the primary aim—barriers and facilitators of PPP. With 300 parents, we will be able to include up to 30 variables in multivariable models (assuming 5-10 observations per variable [41]), allowing for substantial flexibility in model selection. To account for attrition, we plan to enroll 375 parents. Assuming 2 parents enroll for 50% of infants and 1 parent enrolls for the remaining 50%, we expect to enroll 250 infants born preterm. To address disparities in PPP, we will enroll at least 150 Black or African American parents (40% of the sample). With an analytic sample of 120 Black or African American parents (after allowing for 20% attrition), we will be able to build an additional predictive model for PPP among Black or African American parents that could include 12 to 24 predictive and control variables.

Measures

Data collection will begin at enrollment, within the first week of life for the infants, and will end when the infants reach 12 months' CA. Data will be collected by parent report, the electronic health record (EHR), and NICU documentation.

Barriers and Facilitators

To systematically identify barriers and facilitators related to the health care system, social determinants, perceived need, the well-being of parents, and demographics—and to examine the influence of these factors over time—we will collect data by parent report and from the EHR at regular intervals.

The parent-report of barriers and facilitators questionnaire (PRBFQ) is a 21-item, investigator-developed questionnaire that quantifies how often 11 potential barriers and 10 potential facilitators affect the ability of parents to be present in the NICU and participate in caregiving. The PRBFQ includes barriers, such as uncomfortable NICU facilities and lack of transportation, and facilitators, such as social support and employer-provided leave. It was pilot-tested and revised following a national survey study of NICU parents [15]. Parents will rate how often each barrier or facilitator affected their ability to be present and participate in caregiving using a 5-point Likert scale.

The discrimination in health care measure (DHCM) is a 7-item, self-report questionnaire that assesses the frequency of discrimination in interactions with health care providers and staff [42]. Across multiple studies of discrimination based on race, religion, sexual orientation and gender, and socioeconomic status, the DHCM demonstrated good internal consistency reliability [43]. The DHCM has been used to study perceived discrimination among White, Black, Hispanic, Asian, and Native American populations in various health care settings [43]. Perceived discrimination based on race, ethnicity, and socioeconomic status, as measured by the DHCM, is associated with poor patient-provider communication, health care mistrust, and lower satisfaction with the quality of health care [43]. Items are rated on a 5-point Likert scale. Summary scores are calculated as the mean of item ratings, ranging from 1 (no discrimination) to 5 (persistent discrimination) [43].

We will use the parent participation subscale of the empowerment of parents in the intensive care questionnaire to quantify parent-staff engagement in the NICU. In a sample of racially and socioeconomically diverse parents in the United States, the parent participation subscale demonstrated good internal consistency reliability (0.82) and was moderately correlated with measures of NICU satisfaction (ρ=0.39-0.46) [44]. The 8 items comprising this subscale are scored on a 5-point Likert scale. Summary scores are derived as the mean of item scores and range from 1 (no engagement) to 5 (high engagement).

The neonatal intervention score (NIS) will be used to measure infant illness severity, which may be related to the perceived need of parents to be close to their infant. Data to complete the 48-item NIS will be extracted from the EHR. The NIS has been validated in infants born preterm for use as a repeated measure to account for change based on normal physiological maturation or medical complications [45]. Psychometric testing in a sample of 99 infants born preterm revealed good internal consistency reliability (0.80) and validity [45]. The NIS scores in the first 24 hours of life were moderately correlated with other measures of illness severity. Furthermore, infants born preterm who did not survive to discharge had persistently higher median NIS scores over the course of hospitalization and higher peak NIS scores compared with survivors. Summary scores are calculated as a sum of weighted interventions, including the highest score for mutually exclusive items (eg, enteral tube feedings <75% and enteral tube feedings <100%); item weights range from 0 to 7. Infants receiving full oral feedings and no supplemental interventions receive the minimum summary score of 0. Because of the additive nature of the scale, there is no maximum summary score; summary scores in the validation study ranged from 0 to 32.5 [45].

The Patient-Reported Outcome Measurement Information System Short Form version 1.0–Depression 8b (PROMIS-D-8b) will be used to measure symptoms of depression in parents. The PROMIS-D short forms have demonstrated high internal consistency reliability across samples [46,47] and validity in males and females, as well as in racially, ethnically, and socioeconomically diverse populations [47]. The PROMIS-D short forms are also highly correlated with other measures of depression (ie, Edinburgh Postnatal Depression Scale, Center for Epidemiologic Studies Depression Scale, and Beck Depression Inventory); they are responsive to change over time and can be compared easily with these other measures [48,49]. The PROMIS-D-8b includes 8 items, rated on a 5-point Likert scale, with higher scores indicating more depressive symptoms. Summary scores are reported as standardized *t* scores with a mean of 50 and an SD of 10, based on the general US population [50].

In addition to depression, we will also measure NICU-related stress in parents using the parental stressor scale: NICU (PSS:

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NICU), a 20-item instrument with 3 subscales assessing parental perceived stress related to the NICU environment [51]. The internal consistency reliability coefficients of the overall PSS:NICU and its subscales are good [51]. Construct validity has been established, and the subscales are generally correlated [51]. Items are rated on a 5-point Likert scale. Summary scores are calculated for each subscale as a sum of item scores.

Measurement of PPP

The parents will report their PPP using the parent participation diary. The parents will complete the diary daily, recording the duration of their presence in the NICU. If present on a given day, the parents will also report the number of minutes of SSC or holding and the number of diaper changes, bathing episodes, or feedings in which they participated; these will be converted to minutes of participation (ie, 5 min for a diaper change, 20 min for bathing, and 30 min for a feeding) based on previous research [52]. The parent-reported data will be verified using NICU sign-in logs and the nursing documentation in the EHR. The PPP will be operationalized as a duration (ie, time in min) and a frequency. For frequency, presence will be defined as the percentage of days during the infant's hospitalization that the parents were present. Participation frequency will be defined as the percentage of days present that were spent providing infant care.

Infant Outcomes

We will measure infant clinical outcomes, including the length of stay and the achievement of oral feeding competence, using data extracted from the EHR. The achievement of oral feeding competence is typically a criterion for NICU discharge [16]. Oral feeding skill is also an early indicator of neurobehavioral development and an important predictor for future neurodevelopmental outcomes [53]. We will measure the achievement of 3 indicators of feeding competence: time from the first oral feeding to full oral feedings, time from the first oral feeding to hospital discharge, and time from full oral feedings to hospital discharge. Each indicator will be measured in days, following published protocols [54,55]. Full oral feedings are achieved when the infant is consuming all nutrients orally (formula or breast milk) without intravenous or enteral tube supplementation, for 24 hours.

In addition to the clinical outcomes, we will measure infant neurodevelopment at 3 and 12 months' CA, using the test of infant motor performance (TIMP) and the fourth edition of the Bayley scales of infant and toddler development, fourth edition (BSID-IV), respectively. The TIMP, a norm-referenced assessment of early motor performance, evaluates spontaneous movements and postural control in infants born preterm up to 4 months' CA [56]. The TIMP has demonstrated excellent reliability [57,58] and validity [57] and is responsive to change over time [56,57]. In infants born very preterm, TIMP scores at 3 months' CA are significantly associated with cognitive, language, and motor performance on the BSID at 2 years' CA [59]. The test begins with an observation for 13 spontaneous movements, scored as present or not present, followed by 29 elicited items that measure head and trunk control and are scored from 4 to 7 points. The TIMP raw scores are converted to *z* scores, based on age-equivalent standards for CA at the time of assessment [56]. At 12 months' CA, we will use the BSID-IV, a measure consisting of 5 scales of development: cognitive (81 items); language—receptive (42 items) and expressive (37 items); motor—fine (46 items) and gross (58 items); social-emotional (35 items); and adaptive behavior (10 skill areas). The number of items administered is based on the child's age at the time of testing. Raw scores can be converted to scaled scores, which can then be converted to composite score equivalents. The internal consistency reliability of the scales ranges from 0.85 to 0.98 [60].

Parent-Infant Responsiveness

We will use the maternal-infant responsiveness instrument (MIRI), a 22-item self-report scale that measures parent responsiveness to their infant, recognition of infant responsiveness to the parent, and difficulties in responsiveness [61]. Participants will respond using a 5-point Likert scale, with higher scores indicating higher responsiveness. A recent integrative review of 15 interdisciplinary studies found good internal consistency reliability in samples including both mothers and fathers [54,55] and both White and Black or African American parents [62]. The MIRI is highly inversely correlated with measures of stress, anxiety, and depression, and highly directly correlated with measures of self-efficacy and parental competence [62]. The MIRI is most commonly used when infants reach term-equivalent age (similar to the age at NICU discharge) and during the first 6 months' CA [62]. Parents will complete the MIRI at discharge or 40 weeks' postmenstrual age, whichever comes first, and at the time of the infant's outpatient follow-up appointment at 3 months' CA.

Stress Exposure

We will use a count of invasive procedures to quantify stress exposure in the NICU. Researchers commonly quantify stress exposure as a count of skin-breaking procedures [26], which may include other noxious procedures, such as nasogastric tube insertion [63], endotracheal intubation [63,64], or tracheal suctioning [63], and have found associations with brain maturation and neurodevelopment [63,65]. Because procedures, such as nasal, oral, or tracheal suctioning [66], intubation [67], and enteral feeding tube insertion [68] are associated with stress responses in infants, we will measure stress exposure as a count of invasive procedures, defined as procedures or procedural attempts that break the skin or involve the insertion of a foreign object into the body.

Procedure

Data collection will begin after written informed consent is obtained. The parents will complete surveys at regular intervals by either directly entering data into REDCap (Research Electronic Data Capture; Vanderbilt University) [69,70] hosted at The Ohio State University and accessed through a personalized, emailed link or using paper-and-pencil surveys, based on their preference (Table 1). Parent-reported NICU data collection will begin at the time of enrollment and will conclude when the infants reach 40 weeks' postmenstrual age or are discharged from the NICU, whichever comes first. The number of surveys and their frequency will depend on the infant's GA at birth and chronological age, respectively, with parents of the

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youngest infants, born at 22 weeks GA, completing surveys for up to 18 weeks, and parents of infants born at later GAs completing fewer. We will collect EHR data throughout each enrolled infant's hospitalization to obtain clinical data needed to complete the NIS, feeding competence, and stress exposure measures. At discharge, infants born preterm at <32 weeks GA are scheduled for routine follow-up appointments in the developmental follow-up clinic. The parents will complete their final survey when their infant returns for the first developmental follow-up appointment at 3 months' CA. We will extract data from the EHR for the TIMP and the BSID-IV after each enrolled infant's follow-up appointments in the developmental clinic at 3 and 12 months' CA, respectively.

Table 1. Parent-report survey data collection time points.

Measure	At enrollment	Collection intervals during the NICU[a] stay	At discharge[b]	At 3 months' CA[c]
Demographic form	✓	Once	—[d]	—
Participation diary	✓	Daily	—	—
PRBFQ[e]	✓	Every 2 weeks	—	—
DHCM[f]	✓	6 and 12 weeks of life[g]	—	—
EMPATHIC-PP[h]	✓	6 and 12 weeks of life[g]	—	—
PROMIS-D-8b[i]	✓	6 and 12 weeks of life[g]	—	—
PSS[j]: NICU	✓	6 and 12 weeks of life[g]	—	—
MIRI[k]	—	—	✓	✓

[a]NICU: neonatal intensive care unit.

[b]Data collected at discharge or 40 weeks' postmenstrual age, whichever comes first.

[c]CA: corrected age.

[d]Not applicable.

[e]PRBFQ: parent-report of barriers and facilitators questionnaire.

[f]DHCM: discrimination in health care measure.

[g]Data collected at 6 weeks of life or discharge, whichever comes first; and at 12 weeks of life, 40 weeks' postmenstrual age, or discharge, whichever comes first.

[h]EMPATHIC-PP: empowerment of parents in the intensive care–parent participation.

[i]PROMIS-D-8b: Patient-Reported Outcome Measurement Information System Short Form version 1.0–Depression 8b.

[j]PSS: parental stressor scale.

[k]MIRI: maternal-infant responsiveness instrument.

Statistical Analysis Plan

To determine the barriers and facilitators affecting PPP and examine changes in these factors over time, we will use generalized estimating equations (GEEs) to estimate the effects of predictors on PPP as both a frequency and a duration. The GEE approach allows for clustering of observations from the same individual. We will conduct this analysis for the entire sample and for subgroups of participants, focusing on parent race and socioeconomic status (ie, low, moderate, and high), to address reported disparities in PPP. The predictors will be operationalized as summary scores from the DHCM, parent participation subscale of the empowerment of parents in the intensive care, PROMIS-D-8b, and PSS:NICU (as described earlier for each measure); each barrier or facilitator from the PRBFQ, categorized as not present (Likert=1), somewhat influential (Likert=2-3), or highly influential (Likert=4-5); and demographic characteristics. We will estimate the relative increase or decrease in PPP based on differences in levels of these factors in 2-week intervals [71] using a variable selection approach tailored for GEE [72] to identify the most important predictors of PPP. The resulting statistical models will include the most important predictors associated with PPP.

To determine the effect of PPP on infant clinical outcomes and neurodevelopment, we will use linear regression models, with each outcome (clinical or neurodevelopmental) measure modeled as a function of parent presence, total time providing SSC, and total time providing other care. We will estimate the effects of parent presence and all forms of parent participation, including the potentially unique effects of SSC. To determine the mediation effect of parent-infant responsiveness on the relationship between PPP and infant clinical outcomes and neurodevelopment, we will conduct standard mediation analyses using bias-corrected bootstrapped CIs. These analyses will be conducted using PROCESS (Andrew Hayes), a macro compatible with multiple statistical software programs, for inferential testing [73].

To determine the moderation effect of PPP on the relationship between infant stress exposure and infant clinical outcomes and neurodevelopment, we will use linear regression and model each infant's outcome as a function of stress exposure (defined as a count of invasive procedures), parent participation (defined as total time in minutes providing care), and the interaction between stress exposure and parent participation.

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Ethical Considerations

The study was approved by the institutional review board at Nationwide Children's Hospital (STUDY00004110) in April 2024. Parents will provide written informed consent for themselves; 1 parent is required to provide written informed consent for the infant's inclusion. Participation is completely voluntary and will not affect clinical care. Parents may withdraw consent for themselves and their child at any time. Data confidentiality will be maintained throughout the study using standard best practices, including coding of data, secured storage spaces for data collected on paper forms, and password-protected, encrypted servers for data stored in electronic forms. The data repository that will be made available when the study is completed will be deidentified. Parents will receive compensation for completing all data surveys, including the daily diary. Compensation will be provided weekly, and the amount will depend on the number of surveys completed, with a maximum compensation of US $325 for parents of infants born at 22 weeks' GA, the youngest possible GA for the study.

Results

Grant funding from the National Institutes of Health was awarded on August 15, 2024. As of January 2025, all surveys and data forms have been created and tested in REDCap. Participant recruitment began in February 2025; 66 parent participants and 43 infant participants have been enrolled as of June 30, 2025. Data collection began in March 2025 and is expected to be complete in February 2029 when all infants are >12 months' CA. Data analysis will be performed after all data have been collected with expected results in the spring and summer of 2029.

Discussion

Anticipated Findings

The overarching objective of this study is to determine the barriers and facilitators associated with PPP and identify differences among racial and socioeconomic groups. This information is needed to develop interventions that promote health equity for parents and infants. Unfortunately, robust data on PPP are lacking. This may be because PPP is difficult to quantify, resulting in measures across studies that cannot be compared. Systematic reviews of PPP reporting data sources and measures used to quantify PPP have shown that nursing documentation is the most common method for collecting data on parent presence, followed by parent report and unit visitor logs; few studies use >1 data source [14]. Furthermore, the frequency of presence—measured as the proportion of days visited during hospitalization—is the most common measure of parent presence, followed by duration of presence. Few studies incorporate both measures [14]. Data on parent participation in NICU caregiving are lacking. Parent participation is most commonly conceptualized as SSC, with little inclusion of other critical caregiving activities (eg, feeding and bathing) [17]. This study will address these limitations by quantifying the frequency and duration of parent presence as well as the caregiving activities in which parents participate.

While many researchers have investigated the demographic predictors of PPP, such as the age of the parent, socioeconomic status, and race, or infant characteristics, such as the GA at birth, the length of the NICU stay, and the sex [14], this study focuses on the modifiable factors, with an emphasis on those originating from the health care system, that may disproportionately affect parents from racially underrepresented groups or those lacking financial and social resources. This is an important aspect of the study—the recognition that individual parents cannot be held responsible for the barriers originating within systems. Rather, it is the system that must respond to the needs of the parent and the infant and create environments and processes that encourage presence and participation. We are including demographic and clinical variables so that we can develop population-targeted interventions that may differ across groups of parents. To date, researchers have not prospectively determined the relative importance of specific barriers and facilitators of PPP or the changes in these factors over the period of hospitalization, thus limiting the ability to develop time- and population-targeted interventions. This will be the first study to systematically measure PPP, the barriers and facilitators of PPP, and the specific effects of PPP on infant outcomes. By using a theory-guided approach to understanding the barriers and facilitators of PPP, we will be prepared to develop interventions that equitably promote PPP and improve outcomes for infants born preterm and their families.

Strengths and Limitations

The proposed study has several strengths. First, it centers on parent equity by seeking to identify the barriers to PPP in the NICU. Furthermore, the large sample size, longitudinal analysis, and comprehensive data collection will allow us to demonstrate the effect of PPP on both the child and the parent.

There are also limitations. We may need to extend recruitment beyond the initially identified sites. Fortunately, there are additional local NICUs within the identified hospital system that we can include without further institutional review board review. We may still encounter challenges in recruiting a diverse group of parent participants, which could also necessitate adding another NICU with greater diversity, even if it has fewer admissions. Although we intend to recruit a diverse sample of parents, our efforts may be constrained by the demographic characteristics of the accessible population. We expect to enroll 150 Black or African American parents, but we may be unable to recruit a sufficient number of parents from other races or ethnicities to facilitate meaningful analysis. Similarly, although all surveys have been professionally translated into Spanish, historical admissions data from the hospital system suggest that only a limited number of Spanish-speaking participants will be eligible. Thus, our analysis will be limited to including language as a possible predictor of PPP; we will not be able to build predictive models specifically for Spanish-speaking parents. We will also need to minimize missing data; therefore, we will maintain daily contact with parent participants. This will include daily "rounds" by a research team member in each NICU, during which we will greet parents if they are present or leave a short note for them at their infant's bedside. We will also use SMS text message reminders for parents who choose this option, sending reminder SMS text messages and follow-up texts if

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surveys are not submitted. To reduce missing data for neurodevelopmental outcomes assessed during routine neonatal follow-up appointments, we will contact parents before their scheduled appointments at 3 and 12 months' CA and will send birthday cards for infants on their 1-year birthday, which will fall between these appointments.

Conclusions

Data from this study will be used to develop time- and population-specific interventions to remove the barriers and enhance the facilitators that affect PPP in the NICU. In doing so, we aim to improve infant outcomes and reduce disparities in PPP and infant outcomes, thereby promoting health equity for all infants born preterm and their parents.

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed.

Authors' Contributions

MDN and RHP contributed equally to the article and were responsible for conceptualization, funding acquisition, developing the methodology, supervising the project, and drafting and revising the article. ABS participated in conceptualization, developing the methodology, and writing and revising the article. LDN participated in conceptualization, supervising the project, and reviewing and revising the article. LSS participated in conceptualization and reviewing and revising the article.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from ICSc - Interdisciplinary Clinical Care in Specialty Care Settings Study Section (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 187 KB - resprot_v14i1e71930_app1.pdf]

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Abbreviations

BSID-IV: Bayley scales of infant and toddler development, fourth edition
CA: corrected age
DHCM: discrimination in health care measure

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EHR: electronic health record
GA: gestational age
GEE: generalized estimating equation
MIRI: maternal-infant responsiveness instrument
NICU: neonatal intensive care unit
NIS: neonatal intervention score
PPP: parent presence and participation
PRBFQ: parent-report of barriers and facilitators questionnaire
PROMIS-D-8b: Patient-Reported Outcome Measurement Information System Short Form version 1.0–Depression 8b
PSS: parental stressor scale
REDCap: Research Electronic Data Capture
SSC: skin-to-skin contact
TIMP: test of infant motor performance

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Protocol

Using American Sign Language–Fluent Community Health Navigators to Advance Cancer Screening Adherence through Videoconferencing With Deaf, Deafblind, and Hard of Hearing Adults: Protocol for a Randomized Controlled Trial

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Abstract

Background: Cancer screening nonadherence persists among adults who are deaf, deafblind, and hard of hearing (DDBHH). These barriers span individual, clinician, and health care system levels, contributing to difficulties understanding cancer information, accessing screening services, and following treatment directives. Critical communication barriers include ineffective patient-physician communication, limited access to American Sign Language (ASL) cancer information, misconceptions about medical procedures, insurance navigation difficulties, and intersectional barriers for multiply marginalized individuals.

Objective: This randomized controlled trial addresses these barriers by implementing the first videoconference-based study of ASL-fluent community health navigators (ASL-CHNs) to improve cancer screening adherence among adults who are DDBHH. The study tests whether ASL-CHN intervention results in greater adherence to cancer screening guidelines, improved patient-physician communication ratings, and increased cancer knowledge compared to standard care.

Methods: The study uses a videoconference-delivered, block-randomized design stratifying 200 participants who are DDBHH by age and sex, with 100 participants assigned to the ASL-CHN intervention and 100 to standard care. All participants are confirmed as nonadherent to at least 1 of 5 age-appropriate cancer screening guidelines recommended by the United States Preventive Services Task Force for breast, cervical, colorectal, lung, and prostate cancers. Recruitment occurred nationwide through multiple strategies including prior study participants, community partners, and major community events. The intervention arm receives support from specially trained ASL-CHNs over several months, accommodating lengthy scheduling processes for cancer screenings. Primary outcomes measure completion of age- and risk-appropriate cancer screening, with prostate cancer focusing on shared decision-making participation. Secondary outcomes assess patient-physician communication using the validated National Cancer Institute's Health Information National Trends Survey (NCI-HINTS) Patient Centered Communication questionnaire in ASL. Tertiary outcomes examine cancer knowledge through validated measures. The analysis uses intent-to-treat methodology using multivariable logistic regression, accounting for potential clustering effects and anticipated 25% attrition.

Results: As of August 2025, more than 75% of the target enrollment has been achieved. Preliminary data indicate that the intervention group is consistently outperforming the standard care group in cancer screening adherence, supporting the study hypothesis that ASL-CHNs are effective in promoting cancer screening adherence among previously nonadherent participants who are DDBHH.

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Conclusions: The ASL-CHN intervention represents an accessible, scalable solution for reducing cancer screening disparities. By combining personalized navigation with ASL-fluent community health support through videoconferencing, this intervention addresses limitations of previous screening programs that lacked accessible support. If successful, the ASL-CHN model could provide health care providers with a practical, recommendable option for patients who are DDBHH requiring navigator support that can be done remotely through videoconferencing, potentially improving early detection rates and reducing cancer mortality in this underserved population while advancing accessible care delivery.

Trial Registration: ClinicalTrials.gov NCT06492993; https://clinicaltrials.gov/study/NCT06492993

International Registered Report Identifier (IRRID): DERR1-10.2196/65078

(JMIR Res Protoc 2025;14:e65078) doi:10.2196/65078

KEYWORDS

deaf; sign language; cancer screening; adherence; hearing loss

Introduction

Background

Cancer health disparities are common issues across underserved populations that are driven by social determinants of health. As detailed in *Community Health Navigators for Cancer Screening among Deaf, Deafblind, and Hard of Hearing (DDBHH) Adults Who Use American Sign Language* [1], the barriers to health screening and treatment are multilevel, persisting at the individual, clinician, and health care system levels, and can affect patients who are deaf, deafblind, and hard of hearing (DDBHH) across their lifespan. There are documented reports of difficulties in understanding cancer health information in print [1-3], accessing clinical services for screenings [1,4-7], and understanding and following treatment-related directives if the screening results in a cancer diagnosis [8]. Communication difficulties contribute to delayed diagnoses, exclusion from clinical trials, and differential treatment that result in poorer cancer outcomes for deaf and hard of hearing patients.[9]. The complexity of the field of oncology and rapidly expanding associated vocabulary further exacerbates these health inequities. Despite the availability of basic cancer information in American Sign Language (ASL) that helps improve cancer literacy for people who use ASL, the complex nature of cancer prevention, detection, and treatment creates barriers to care for individuals who are DDBHH that even exceed the challenges of hearing non-English speaking populations. The current standard of care for individuals who are DDBHH may include visiting doctors alone, with a sign language interpreter who may or may not be capable of interpreting at the level needed in the complex oncology environment, or with a family member.

Community health workers (CHW) and navigators (CHN) are becoming more common in health care systems, based on research that confirms their ability to help patients more successfully navigate through their health care system [10]. For example, the Baltimore HEARS project demonstrated the success of a CHW-delivered intervention program for older adults who already had considerable spoken and written language proficiency because their hearing loss occurred later in life [10]. The CHW hearing loss program relied upon materials that are not easily accessible to people who rely upon ASL as their preferred form of communication. Thus, the focus of this research project was to create and evaluate a training program to prepare CHNs to work with individuals who are DDBHH, the majority of whom use ASL as their primary means of communication and have limited English language skills.

For the vulnerable group of people who are DDBHH in need of cancer screening and preventive care, an intervention delivered by CHNs who use ASL and ASL-based teaching materials offers an excellent source of relief and support in the face of barriers to health care. This paper describes the development and evaluation of a CHN intervention that is accessible in ASL as a logical strategy for reducing barriers to improved health care access for people who are DDBHH.

Trial Aim

The aim of this trial is to implement the first randomized controlled trial of a DDBHH CHN intervention that is (1) accessible in ASL and English, (2) easy to understand, (3) relevant to the experiences of people who are DDBHH, (4) inclusive of videoconferencing for face-to-face ASL communication, and (5) easy to use. The intervention will be evaluated using multiple criteria to assess the effectiveness of the navigator in guiding patients who are DDBHH through the cancer screening process.

Hypothesis

This study tested the hypothesis that the use of ASL-fluent CHNs (ASL-CHNs) will result in:

1. Patients who are DDBHH demonstrating greater adherence to cancer screening guidelines compared to those assigned to the standard of care group (without access to this program's trained CHNs).
2. Higher patient-physician communication ratings by patients who are DDBHH compared to those assigned to the standard of care group.
3. A direct relationship between increased cancer knowledge and cancer screening adherence compared to the standard of care group.

Methods

Ethical Considerations

The protocol (IRB-FY21-120) was reviewed and approved by Gallaudet University's Institutional Review Board (IRB) prior to recruitment.

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Eligible participants undergo a consenting process with an ASL-fluent clinical research coordinator who explains the study purpose and expectations in both English (fourth grade reading level) and ASL (using common sign vocabulary while minimizing fingerspelling). Participants understand they must share that the cancer screening appointment has been completed and its results with researchers for evaluation purposes, since the evaluation of the experimental arm's intervention ended at the point of completed screening.

All participants receive tokens of appreciation. Two equal-sized financial gifts were originally approved by the IRB. However, as long-term retention in the study proved to be a concern, an alternate gifting strategy was requested and approved by the IRB: a smaller gift after baseline data collection ($25) and a larger one after completing the final assessment ($75) to recognize the greater value of their persistence in the study.

Study Design

This study uses a parallel group, block-randomized design with 1:1 allocation stratifying 200 participants who are DDBHH by age and sex, with 100 participants assigned to the ASL-CHN intervention and 100 to standard of care.

All participants were confirmed as being nonadherent to at least 1 of 5 age-appropriate cancer screening guidelines recommended by the United States Preventive Services Task Force (USPSTF [11]). Nonadherence to the guidelines was confirmed during the recruitment process and again during the gathering of baseline data postrandomization. If a randomized participant either realized that they had indeed already been screened for all recommendations or were screened during the interval between recruitment and baseline data collection, they were removed from the study. In these instances of removal, those participants were moved to a separate database for future studies that they may be eligible for.

No significant protocol modifications have been implemented since trial commencement.

Sample Recruitment

Multiple recruitment strategies were used to attract a diverse sample of individuals who are DDBHH nationwide. One strategy was to contact individuals who are DDBHH who had participated in prior studies conducted by this paper's senior Gallaudet University researcher. The prior study participants were reminded of their past study participation and asked if they would be willing to learn about a new research study that also had the potential to benefit the DDBHH community.

Another recruitment strategy was to work with community leaders across the nation to set up local recruitment events. A third was to attend major community events that attracted large groups from the community where study recruitment could be efficiently conducted. The recruitment and consenting process used for all of these strategies were comparable.

Those who indicated their interest in participating were asked a set of questions to determine their eligibility for the new study. Once their eligibility was confirmed, they were told a follow-up contact would be made to formally enroll them in the study. During the follow-up enrollment conversation, the participants' eligibility was reconfirmed and then they were enrolled in the study and randomly assigned to a study arm based on their sex and age as previously decided by the randomization scheme.

Study Arms

Intervention Arm

In the intervention arm with videoconferencing, specially trained ASL-CHNs meet with participants over a period of up to 11 months. This extended timeframe is deliberately designed to accommodate the often-lengthy scheduling process for certain cancer screenings, which can take several months from initial referral to completion due to limited availability of specialists, preparation requirements, and health care system delays.

The intervention begins with an initial meeting to complete the consenting and randomization processes, gather baseline data, work with the participant to select the screening they would like to accomplish first, and provide directions on how to proceed with that screening. During the second meeting, about 2 weeks later, the ASL-CHN determines whether the screening has occurred or is scheduled and identifies any barriers encountered in making appointments or accomplishing the screening. If problems were encountered, the ASL-CHN engages in role-playing related to both the specific problem and commonly encountered problems during health care interactions.

All participants receive at least 4 months of intervention support. For those who have not completed screening by this 4-month assessment point, the study provides up to 7 additional months of support (for a total of up to 11 months). Throughout this period, the ASL-CHN continues to meet with participants to address emerging barriers, provide coaching through role-playing exercises, and offer support until screening is accomplished or until the maximum 11-month timeframe is reached.

Standard of Care Arm

The standard of care arm receives basic information about age-appropriate cancer screenings that have not been completed according to the recommended guidelines. The staff meet with standard of care participants through video calls. They help the participants select which screening the participant would like to accomplish, but without the navigation support offered to the experimental arm participants. They are asked to report back when they accomplish their screening.

If after 4 months in the standard of care arm they still have not scheduled their screening, they are recorded as "failed to be screened." Participants remain blinded to their original group assignment, with measures in place to prevent cross-contamination despite the small DDBHH community. They are then told that they can be admitted to the other study arm (without any specific details about the difference between the 2 study arms), if they would like to again try to accomplish their screening.

A CONSORT (Consolidated Standards of Reporting Trials) diagram of trial enrollment is provided in Figure 1.

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Figure 1. CONSORT (Consolidated Standards of Reporting Trials) diagram of the randomization process.

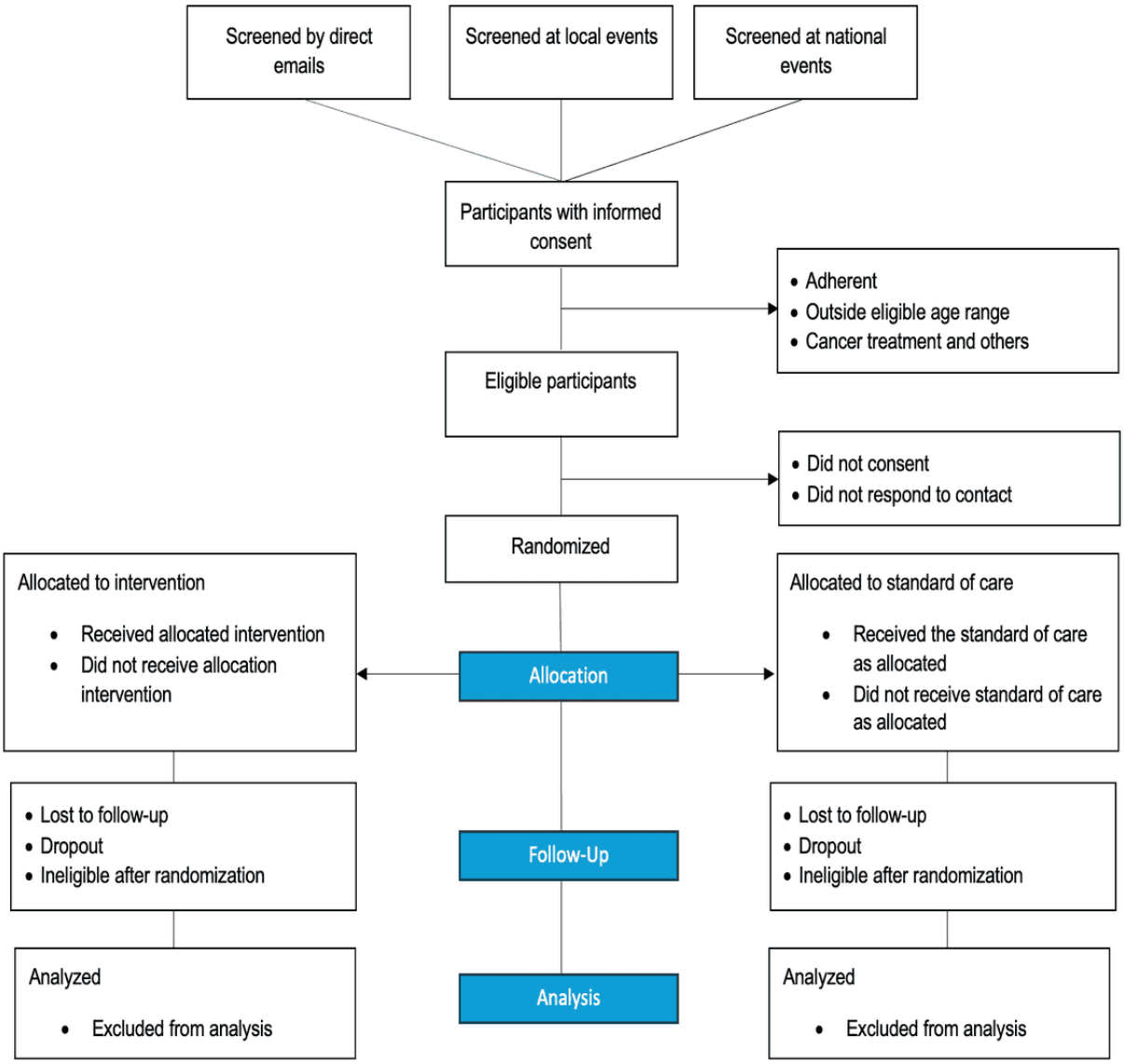

Study Integrity

The protocol implements several mechanisms to ensure study integrity and participant engagement. CHNs conduct comprehensive needs assessments with intervention participants, creating customized documentation of health care goals and questions. Both groups receive reminder messages before scheduled study visits, though only intervention participants receive screening appointment reminders. Follow-up data collection occurs at 2 weeks, 2 months, and 4 months, with standardized measures of cancer knowledge and patient-physician communication compared to baseline.

The study designates participants as "successful" if they complete recommended screenings during the trial period, with documentation required as evidence. To manage potential community interactions among this low-incidence population, CHNs and participants are instructed not to discuss their participation outside the study team, with provisions for reassignment if working relationships prove unsuccessful or conflicted.

To streamline the study's focus, participants with multiple screening recommendations initially choose just 1 screening guideline, though they are encouraged to pursue additional screenings if the first is completed. Upon conclusion, a clinical research coordinator conducts videophone exit interviews and debriefing sessions with all participants to gather final insights about their experience.

Setting and Participants

The study is conducted at Gallaudet University, with participants recruited across the nation. We will enroll a minimum of 200 study participants who have been defined as not having had 1 or more recommended screenings during the past year in the clinical trial. Each participant who is DDBHH must meet all of

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the following eligibility criteria: (1) be age-eligible for cancer screening, (2) have been born deaf or experienced loss of hearing by age 13 years (defined as "early deafness"), (3) be unaligned with their age- and risk-appropriate cancer screening during the past year, (4) have no contraindications to cancer screening, and (5) be available to participate during the study period. We will use USPSTF guidelines for breast, lung, prostate, colon, and cervical cancers to evaluate for possible contraindications and determine eligibility [11].

Outcome Measures

Bilingual ASL-English measures (eg, sociodemographics, cancer screening knowledge, and patient-physician communication) will be administered at screening and again after the fourth month or by 11 months for comparison.

The primary outcome is completion of age- and risk-appropriate recommended cancer screening, which is a binary variable measured at the closeout follow-up for breast, cervical, colon, and lung cancer. For prostate cancer screening, the primary endpoint is participation in shared decision-making with the clinician.

The secondary outcome is patient-physician communication measured by the National Cancer Institute's Health Information National Trends Survey (NCI-HINTS) Patient Centered Communication questionnaire that was validated in ASL [12]. The set of items for the Patient Centered Communication score are outlined in Textbox 1.

Textbox 1. Items for the Patient Centered Communication score.

How often did the doctors, nurses, or other health care professionals you saw during the past 12 months do each of the following:

a) Give you the chance to ask all the health-related questions you had?

b) Give the attention you needed to your feelings and emotions?

c) Explain things in a way you could understand?

d) Spend enough time with you?

c) Involve you in decisions about your health care as much as you wanted?

d) Make sure you understood the things you needed to do to take care of your health?

e) Help you deal with feelings of uncertainty about your health or health care?

The tertiary exploratory outcome is cancer knowledge and includes two questions:

1. It seems like everything causes cancer.
2. How much do you think that gaining weight in adult life can influence whether or not a person will develop cancer?

Analysis Plan

All analyses will be conducted using SAS 9.4, with a 2-sided *P* value <.05 considered statistically significant. The DDBHH sample size sufficiently powers the detection of differences in the primary study outcomes. Based on a 2-sided Z-test with unpooled variance and a significance level (α) of .05, our study sample of 200 participants with 100 in each group will achieve at least 80% power to detect a difference in proportions of 14%-17% in the group proportions of adherence (ie, almost 82%-92% adherence in the intervention group, assuming 65%-78% of the eligible participants in the standard of care group have obtained age- and risk-appropriate cancer screening at follow-up) based on previous studies. Univariate statistics for baseline characteristics will be computed with stratification by group, as will patient-physician communication and cancer knowledge at baseline and follow-up. Bivariate analyses will examine group differences in patient characteristics. We will primarily use an "intent-to-treat" approach, using multivariable logistic regression to evaluate whether the recommended cancer screening rates are higher in the intervention group than in the standard of care group. Though we do not expect strong clustering effects with CHNs, we will account for potential clustering using generalized estimating equations, with regression models including group assignment and adjusting for relevant covariates.

If a sufficient number of participants cross over from the standard of care arm to the intervention group, we will conduct sensitivity analyses to assess whether they performed better than the standard of care group. Despite efforts to maximize retention, we anticipate approximately 25% attrition, which may introduce bias. To address this, we will determine if dropouts differ between randomized groups, adjust for any resulting imbalances in baseline covariate distributions, and perform sensitivity analyses under different assumptions (missing completely at random, participants who dropped out would have been responders, or participants who dropped out would have been nonresponders).

If more than 10% are missing endpoint or covariate data, we will consider multiple imputation under the missing at random assumption and conduct sensitivity analysis with the imputed data. This comprehensive approach will help ensure robust evaluation of intervention effects while accounting for potential sources of bias in our study design. Our analytical strategy balances methodological rigor with practical considerations related to participant retention and data completeness, allowing for reliable conclusions about the effectiveness of our intervention for improving cancer screening rates.

Results

Participant recruitment commenced in July 2023 and continued until August 2025. Follow-up data collection has commenced

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and will be completed by February 2026, with results expected in March 2026.

While the clinical trial study is ongoing, more than 75% of the target enrollment has been achieved. Preliminary data indicate that the intervention group is consistently outperforming the standard of care group in cancer screening adherence, supporting the study hypothesis that ASL-CHNs are effective in promoting cancer screening adherence among previously nonadherent participants who are DDBHH.

Discussion

Anticipated Findings

The need to promote cancer screening adherence among adults who are DDBHH is significant. Our ASL-CHN intervention responds to the findings that individuals who are DDBHH face complex systemic, attitudinal, communication, and personal-level barriers when seeking cancer screening [1]. By using CHNs who are ASL-proficient and share lived experiences with the DDBHH community, the intervention addresses specific challenges identified in our needs assessment, including ineffective patient-physician communication, limited access to cancer information in ASL, misconceptions about medical procedures, difficulties navigating insurance systems, and intersectional barriers for individuals with multiple marginalized identities. The intervention focuses on training CHNs to provide appropriate support, clear explanations of cancer screening terminology using ASL, assistance with health care system navigation for cancer screenings, and emotional support—ultimately working to reduce cancer screening gaps documented among individuals who are DDBHH.

By engaging patients who are DDBHH via ASL-fluent navigators, the ASL-CHN intervention offers a scalable, participant-centered, and highly accessible solution. The language concordant communication included in ASL-CHN programming is intentionally designed to help participants focus on getting screened for cancer without feeling marginalized by the health care system. This careful approach is intended to mitigate health care mistrust, which is a major impediment to long-term engagement with preventive care in this population [13,14].

Preliminary evidence suggests that the ASL-CHN intervention is promising in promoting cancer screening and adherence among adults who are DDBHH [1]. The integration of personalized navigation with ASL-CHNs addresses key limitations of previous cancer screening interventions, which often lacked the accessible support necessary to sustain long-term health care engagement. Our approach in this randomized controlled trial aligns with recent studies that have highlighted the importance of combining Zoom and videophone technology with accessible human interaction to promote engagement and adherence in preventive health programs.

Understanding the mechanisms of action underlying the efficacy of ASL-CHN is highly significant. In this study, we are examining how our intervention improves cancer screening adherence through enhanced patient-centered care and strengthened shared decision-making between patients who are DDBHH and their physicians. By addressing communication barriers and empowering patients with accessible health information, ASL-CHN creates opportunities for meaningful dialogue about screening options, personal preferences, and concerns. These data will inform further refinement and optimization of the ASL-CHN program to maximize patient engagement in cancer prevention decisions.

This study has a few limitations worth acknowledging. We face retention challenges due to participants' limited understanding of clinical trial processes and procedures. Additionally, our requirement for ASL fluency restricts our ability to include the broader DDBHH population who may use different communication methods. Our focus on only 5 major cancer screening types (breast, cervical, colorectal, lung, and prostate) may not address other important cancer prevention needs.

However, if successful in promoting cancer screening adherence for the 5 major cancer screening types, the ASL-CHN intervention could provide a practical, scalable option that health care providers can recommend to patients who are DDBHH who are not screening-adherent and may benefit from navigator support. Because early detection has been shown to reduce cancer mortality, the ASL-CHN intervention has the potential to play a critical role in improving health outcomes in this underserved population.

Conclusions

The availability of an effective, accessible ASL-CHN service has the potential to shift future research that improves health outcomes, which helps lower the cost of associated health care and promote longer lives among people who are DDBHH who use ASL. We envision an ASL-CHN functioning as a patient navigator who is able to promote cancer screening adherence among people who are DDBHH. Patients who are DDBHH may experience even greater benefit from CHNs who are fluent in ASL, since so few clinicians are available and competent when caring for patients who are DDBHH. This should help support improvements in health care with regards to availability, affordability, adequacy, and administrative simplicity. It should also increase engagement with and adherence to cancer screenings, thereby improving health outcomes for people who are DDBHH who use ASL. To achieve this vision, cancer screening guidelines as well as navigation tools accessible in ASL are needed as resources for ASL-CHNs who encounter patients who are DDBHH in their care.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report by ZRG1 MOSS-*t* (54) Center for Scientific Review Special Emphasis Panel UNITE Transformative Research to Address Health Disparities and Advance Health Equity at Minority Serving Institutions (U01) (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 148 KB - resprot_v14i1e65078_app1.pdf]

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Abbreviations

ASL: American Sign Language
ASL-CHN: ASL-fluent community health navigator
CHN: community health navigator
CHW: community health worker
CONSORT: Consolidated Standards of Reporting Trials

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DDBHH: deaf, deafblind, and hard of hearing
IRB: institutional review board
USPSTF: United States Preventive Services Task Force

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Protocol

Engineering Resilient Community Pharmacies for Chronic Care Management: Protocol for the Development of a Medication Safety Map

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Abstract

Background: The increase in people with complex chronic health conditions is stressing the US health care delivery system. Community pharmacies play a role in ensuring patients' safe medication use for chronic care management (CCM), but their efforts are undermined by volatile work demands and other system barriers. Medication safety in community pharmacies is a multidimensional issue shaped by the work system and interactions among pharmacists, primary care providers, and patients.

Objective: The objective is to create and evaluate a system of CCM that supports safe medication use. The CCM system design will focus on creating and evaluating a Medication Safety Map (MedSafeMap) for patients with complex chronic health conditions. This study has three aims: (1) identify and define community pharmacy work system design requirements for safe medication practices, enabling resilient performance; (2) design and develop MedSafeMap, a feasible and sustainable solution, to facilitate safe medication practices through resilient performance; and (3) implement MedSafeMap in community pharmacies and pilot-test its impact on pharmacy staff attitudes, behaviors, and performance.

Methods: This study will leverage participatory design and human factors engineering methods throughout the 3 aims. For aim 1, four rounds of qualitative observations within 6 pharmacy sites will be conducted to parse areas MedSafeMap could address. Two rounds of interviews with pharmacists and technicians from each of the sites will be used to expand upon areas of interest identified during the observations. Observational and interview data will be used to construct functional resonance analysis method models and resilience narratives to map both risks and best practices within the system based on daily workplace factors. For aim 2, focus groups with pharmacist and technician stakeholders will be guided by participatory stakeholder engagement to inform prototyping for MedSafeMap. Simulation-based research involving standardized patients in CCM scenarios will be used to test and refine MedSafeMap components. Finally, for aim 3, MedSafeMap will be implemented in pharmacies. Observations using the work observation method by activity timing (WOMBAT) for the time and motion study will aid in understanding how MedSafeMap impacts pharmacy staff workflow. We will assess adoption challenges and resilience-focused attitudes, behaviors, and performance to support CCM.

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Results: As of August 2025, all 6 pharmacy sites have been recruited. Three of the 4 rounds of observations, 2 rounds of interviews with 12 pharmacists and 12 technicians from the study sites, and the 6 focus groups have been conducted. Preparations for the simulations are ongoing.

Conclusions: MedSafeMap is an innovative approach that will guide pharmacists and technicians in safely providing care to patients with complex chronic health conditions. It will help them navigate the complex tasks and communications between the pharmacy, patient, and primary care provider arising with this type of complex care.

International Registered Report Identifier (IRRID): DERR1-10.2196/69011

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KEYWORDS

medication safety; community pharmacies; provider status; pharmacy intervention; participatory design; stakeholder groups; resilience; safety-I and safety-II

Introduction

Background

More than 100 million Americans have multiple chronic conditions [1] that contribute to more than 1 million adverse drug events (ADEs) annually, prompting 4 million people to seek medical care, costing the US health care system >US $8 billion per year [2,3]. Health care spending for patients with multiple chronic conditions is up to 20 times higher than for patients with no chronic conditions; that is, Americans with 5 or more chronic conditions comprise 12% of the population but contribute to 41% of the total health care spending, averaging 20 physician visits per year and using up to 50 times more prescription medications [1]. Challenges with managing multiple chronic conditions have a direct impact on health care use, with such patients representing a quarter of all hospital admissions annually, with one-third of all patients having at least 1 emergency department visit every year [1]. Despite these health consequences, efforts to improve medication safety for patients with complex chronic health conditions in outpatient settings have not been allocated appropriate resources to be effective.

Community pharmacists are recognized as the champions of medication safety not only for performing dispensing tasks but also for their expanding role in chronic care management (CCM) [4]. CCM can include managing health problems and goals, medications, other health care providers, and community services that patients have and need. In many states, CCM also encompasses ordering and interpreting tests for chronic conditions, such as diabetes [4], through collaborative practice agreements with health care providers and ensuring patients receive appropriate screenings and immunizations. Such expanded practice was facilitated by the COVID-19 pandemic due to pharmacists being one of the few health care professionals providing face-to-face care and assuming clinical responsibilities when primary care physicians and nurses were managing COVID-19 emergencies [5].

Furthermore, community pharmacists play a vital role in medically underserved communities [6], such as in locations with too few primary care providers, high poverty, or a high older adult population. Patients in these areas face difficulties or delays in getting basic health care because of long travel distances to health care providers, long wait times for appointments, or a lack of health care providers who can serve uninsured or underinsured patients. Therefore, pharmacists are considered accessible primary care practitioners, seeing patients 5 to 8 times more frequently than primary care physicians [7]. Numerous studies have demonstrated the ability of pharmacists to address medication nonadherence [8], support naloxone provision and opioid safety counseling [9], provide pain management and palliative care [10], improve diabetes and cardiovascular outcomes [11], and improve vaccination rates in medically underserved communities [12,13].

However, the abilities of community pharmacists to fill this gap are constrained by a work system that is unsustainable and essentially broken [14]. Pharmacies adhere to product-based reimbursement contracts with pharmacy benefit managers, incentivizing pharmacy staff to fill more prescriptions. Therefore, for more than a decade, pharmacists have reported high workload and burnout, with opaque corporate performance metrics based on prescription volume and customer service [14] rather than on safety or clinical outcomes. The COVID-19 pandemic exacerbated pharmacists' workload strain by adding testing and vaccinations to a system that is chronically understaffed and stretched beyond capacity. With pharmacist burnout rates at an all-time high, a call for action to improve pharmacist work systems is critical to prevent a complete collapse in the US pharmacy system. Pharmacists across the United States have been executing a series of walkouts since September 2023 to improve harsh working conditions and preventable errors in care [15]. In Walgreens alone, 600 employees across 20 stores have participated in walkouts, resulting in multiday disruptions in workflow and patient care [15]. The purpose of these walkouts is to shed light on the need for a solution to improve the working conditions of pharmacy staff.

In light of pharmacists' unmanaged workload, there is a push for them to do more. This is evidenced by the introduction and recognition that pharmacists are health care providers (eg "provider status") [16]. This status will allow pharmacists who provide services such as CCM, comprehensive medication management, and immunizations to receive reimbursement for such clinical services in addition to product-based dispensing services [17]. This provides a timely opportunity for pharmacists to envision innovative designs to improve medication safety for their patients. To reimagine community pharmacies as an accessible destination for CCM, we must recognize the increased complexity of the community pharmacy work system. Similar

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to the increase in pharmacy staff responsibility related to the COVID-19 pandemic response, adding more clinical services with the addition of reimbursement has potential implications for the quality of pharmacist education, business practices, and safe medication dispensing. Opening up avenues for reimbursement that are not product based allows stronger sustainability of expanded services and greater impact in their patient care practices, which can potentially fill a critical gap in Wisconsin, where two-thirds of its counties are medically underserved [12,13].

This opportunity to adopt new services and create coordinated care models can present a significant medication safety challenge. Community pharmacists' heroic response to the COVID-19 pandemic demands created work systems that increased stress and negatively impacted their ability to ensure safe use of medications they dispense [18]. Pharmacist provider status can lead to sustainable and collaborative programs that holistically address chronic care conditions of patients with complex chronic health conditions. However, doing so without prospectively considering and testing unintended consequences may negatively transform the community pharmacy work system, threatening the very medication safety strategies on which pharmacists have come to rely. The consequence of this reality is synergistic; high workload demands contribute to medication errors and ADEs, leading to pharmacists experiencing "learned helplessness" and a lack of resiliency (or the ability to adapt to unpredictable work situations) in the face of these ADEs [19-22].

Approaches to Medication Safety

Many medication safety studies strive for "zero harm" [23-25] by focusing on "what went wrong" in the face of undesired outcomes, referred to as a "safety-I" approach [26]. The traditional harm-reduction approach has been to conduct root cause analyses of errors and understand the contributing factors that led to the error to reduce their incidence or mitigate their harm. A number of strategies have been encouraged based on this approach, including those developed and tested in our previous studies [27,28], but in the end, these frequently result in more constraints in a complex system that limit workers' ability to adapt. Such strategies end up limiting the capacity to adapt to practice demands and make the system more brittle, which can unintentionally lead to other medication safety hazards. Furthermore, stacking isolated interventions does not lead to fundamental changes to the approach to medication safety. It is not surprising that little progress on substantive improvement has been made in medication safety in the outpatient community pharmacy setting [29].

Medication safety must be considered in a new way that encompasses safety-II, the "what went right approach." Safety-II [30] is based on resilience engineering, which focuses on understanding how resilient performance is achieved, creating a work system that will address unexpected threats while also responding to opportunities [31]. Instead of framing safety as a linear, failure-based model, we need to broaden the scope of inquiry to recognize the complexity and inherent variability in modern systems, such as community pharmacies. Furthermore, we need to shift beyond an exclusive consideration of ADEs and failures to understand and strengthen a work system's abilities to continuously create safety in everyday practice [32]. This goal is achieved by focusing on the abilities of a work system to absorb significant stress before a disruption impacts safety, return to normal operations as quickly as possible, and, importantly, adapt to undesirable situations. A system with adaptive capacity can anticipate disruptions and reorganize workflows using alternative paths to maintain successful work and minimize disruptions [33]. An example of safety-I and safety-II approaches can be found in Textbox 1.

Textbox 1. Examples of safety-I and safety-II approaches.

Safety-I example

- Checklists can decrease risk by imposing a structured process but may be counterproductive
- A checklist can be completed by rote rather than thoughtfully
- A checklist may instill a false sense of security when there is an assumption that all important items are contained in the checklist
- Current conditions may be different from the conditions under which the checklist was conceived
- The ability for workers to adapt to new conditions is lost

Safety-II example

- A checklist restricts an unexpected situation
- Workers double-check facts against each other
- Workers are open and honest about explaining why they wish to deviate from the checklist
- There is a healthy skepticism about deviating from the checklist
- Workers ask for constructive criticism, ensuring that they are taking the best possible novel approach
- Workers embrace team members from other work systems for their outside the box thinking

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The Patient Safety Learning Laboratory: Engineering Resilient Community Pharmacies

Despite numerous calls, there has not been a systematic engineering approach toward outpatient medication safety within community pharmacies.

Previous patient safety learning laboratories (PSLLs) have evaluated the physical environment, sociotechnological factors, and clinical workflow within inpatient and clinical settings but not within the outpatient community pharmacy settings [34]. This project, informed by resilience engineering, will address the challenges common in community pharmacies to achieve safe medication use in community-dwelling patients with multiple complex chronic conditions. The goal is to evolve from the safety-I approach to a combined safety-I and safety-II approach. The resulting outcome, the Engineering Resilient Community Pharmacies (ENRICH) PSLL, is expected to gain knowledge of strategies for building resilience capacity in community pharmacy work systems in conducting CCM. PSLLs encompass a systematic engineering approach to allow cross-disciplinary professionals to evaluate clinical processes and approaches toward improvements in patient safety [34].

Our long-term goal is to position the ENRICH PSLL as the premier center for medication and patient safety and CCM in community pharmacies. Despite our previous work, a current gap exists in the systematic application and evaluation of human factors and health systems engineering approaches to improve medication safety and staff work life in community pharmacies. Our PSLL, which is led by experts in human factors and health systems engineering, represents a foundational step toward the creation of a center to promote and normalize a safety-I and safety-II approach in pharmacy systems research. Our PSLL will include a focus on the use of the principles of dissemination and implementation research to enhance the potential for sustainability of improvements resulting from patient safety innovations. In addition, this PSLL is designed to generate ideas for future research projects and examine the implications and outcomes related to pharmacists' provider status, which can serve to expand CCM to support patients with complex chronic health conditions living in medically underserved areas. The PSLL resulting from this study represents the beginning of a new paradigm, unprecedented in the pharmacy setting, for improving medication safety for community-dwelling patients with complex chronic diseases.

Methods

Design Overview

The methods used in this project have demonstrated success with other health care practitioners and in other patient safety studies [27,28]. The concepts for applying resilience engineering (CARE) model guides our data collection, analysis, and interpretation (Figure 1). Resilience is the ability of the community pharmacy work system to adjust its functioning before, during, and following sentinel or unexpected events and thereby sustain operations under both expected and unexpected conditions [35]. It assumes that variability in the environment creates the need for adjustment. Work as imagined (WAI) is conceptualized as the intended or imagined alignment between demands of the system (prescription volume and patient acuity) and the capacity to meet those demands. Demand and capacity can never completely align because of the complex nature of the system; there will always be unforeseen demands that require workers to adjust in situ. In addition, workers do not simply comply with protocol but naturally adapt and innovate as part of taking control over their environment. In the CARE model, work as done (WAD) refers to the adjustments and natural variability in how tasks are conducted. Predicting acceptable (what goes right) and unacceptable (what goes wrong) outcomes depends on an understanding of WAD in different demand and capacity circumstances. In this project, we will be using the concepts of WAI and WAD to identify the gap in how pharmacy staff plan their approaches to patient care and how they are able to actually fulfill their responsibilities (Figure 1).

Figure 1. Concepts for Applying Resilience Engineering model.

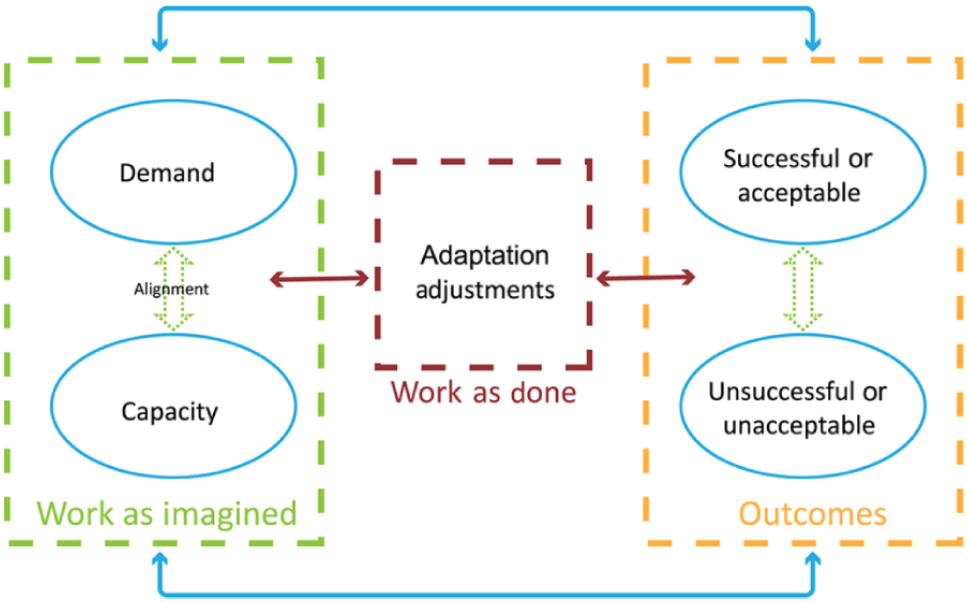

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Because resilience also applies to the organizational level and adaptations in complex systems, it is essential to ensure that characteristics and adaptations of the entire work system are captured. To operationalize the discrete facets of the work system, we have used systems engineering initiative for patient safety (SEIPS) 2.0, a human-factors engineering model to improve patient outcomes (Figure 2 [36]). The SEIPS model has framed the design and analysis of many safety studies, including the research we conducted in community pharmacies [28,37-39]. The CARE and SEIPS models work well in tandem because both models contain feedback loops and account for the interconnectedness of work system components. In Figure 2, *professional work* references both pharmacists and technicians. Patient work includes the work of the patient and their caregiver, which is essential to CCM (Figure 2).

Figure 2. Systems Engineering Initiative for Patient Safety 2.0 model adapted for the community pharmacy work system.

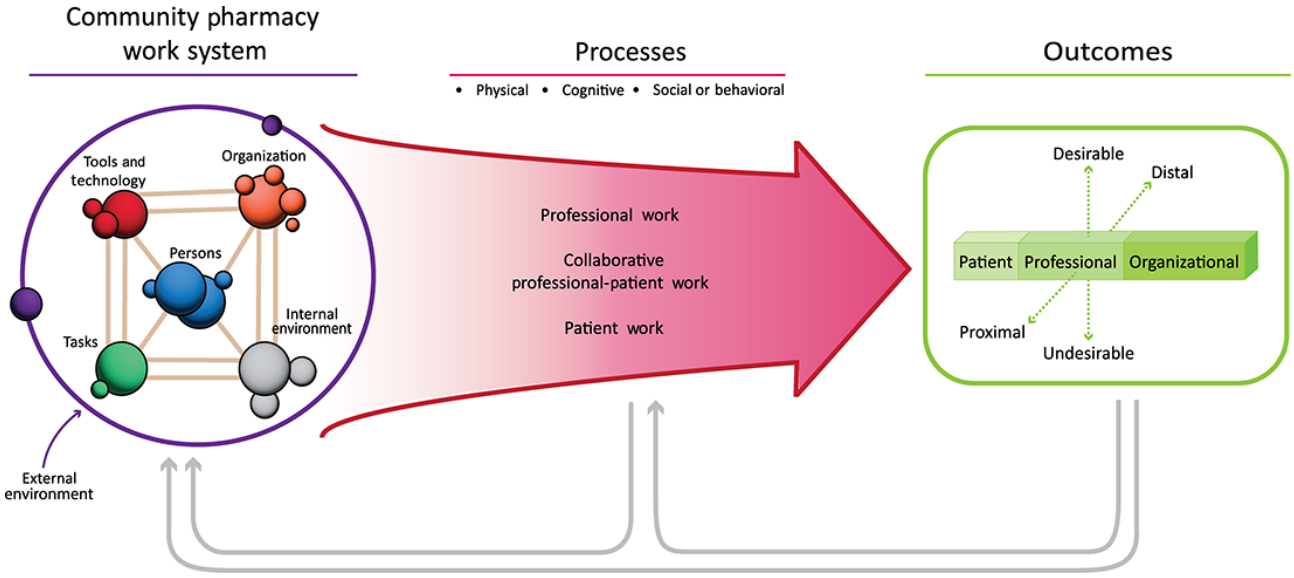

Ethical Considerations

Ethics approval for human participant research will be obtained from the University of Wisconsin–Madison Institutional Review Board (S-2023-1100, S-2024-1747). Each aim of this study will be individually submitted to the institutional review board (IRB) for review and approval before initiating the research activities concerning each aim.

Human Participant Ethics Review Approvals

Aim 1: Observations in the Community Pharmacies, Pharmacist and Pharmacy Technician Interviews, and Pharmacy Staff Demographic Sheets

Aim 1 received ethics approval from the University of Wisconsin–Madison Institutional Review Board (S-2023-1100) on August 7, 2023. Research activities for this aim were conducted in accordance with the University of Wisconsin–Madison ethical regulations. Several days before observation, the study's primary contact at each community pharmacy was provided with a sample email script for notifying pharmacy staff about the purpose of the observations and when they would be taking place. Upon arrival at the pharmacy, researchers introduced themselves to the staff, explained the purpose of the observation, and clarified observation duration and how staff anonymity is preserved. Pharmacist and pharmacy technician interviews were conducted via Zoom (Zoom Communications, Inc) at a time most convenient for the participant. Participants were provided with an IRB-approved information sheet and waiver of signed consent detailing the study's purpose, tasks required for participation, and information regarding confidentiality protection. They were also informed that their participation was entirely voluntary, and they all had the right to withdraw from the project at any time without any negative consequences. Before the interview, they were also provided with an interview guide for either the first (Multimedia Appendix 1) or second (Multimedia Appendix 2) round of interviews.

Aim 2: Pharmacist and Pharmacy Technician Participation in Stakeholder Focus Groups, Pharmacy Staff Demographic Sheets, and Simulations

Aim 2 received ethics approval from the University of Wisconsin–Madison Institutional Review Board (S-2024-1747) on January 2, 2025. Research activities for this aim are being conducted in accordance with the University of Wisconsin–Madison ethical regulations. Participants are being provided with an IRB-approved information sheet and waiver of signed consent detailing the study purpose, tasks required for participation, and information regarding confidentiality protection. In addition, participants are being informed that their participation is entirely voluntary, and they all have the right to withdraw from the project at any time without any negative consequences.

Materials for Aim 3

Materials for aim 3—Medication Safety Map (MedSafeMap)'s implementation into pharmacies and pre- and postimplementation observations using work observation method by activity timing (WOMBAT) for time and motion study and postimplementation evaluations—are still in development and will be submitted for ethics approval from the University of Wisconsin–Madison Institutional Review Board before the start of research activities concerning aim 3. The anticipated timeline

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for submission of aim 3 study materials to the IRB is December 2025 and will include a script for observers to read to pharmacy staff, detailing a brief introduction, the purpose of the observation, the duration of the observation, and how staff anonymity will be preserved.

Privacy and Confidentiality

Throughout all project research activities, all participant information will be anonymized with the use of participant numbers and in accordance with the university's policies. Additional protection measures include secure storage of data per the university's policies, limiting data access to only approved study personnel and ensuring there is no participant-identifiable information included in publications.

We will adhere to the National Institutes of Health Grants Policy Statement on *Availability of Research Results: Publications, Intellectual Property Rights, and Sharing Resources*. We will take into account any additional policies and rules including but not limited to institutional policies; local IRB rules; and local, state, and federal laws and regulations. We acknowledge that the rights and privacy of people who participate in National Institutes of Health–sponsored research must always be protected. Thus, data intended for broader use will be free of identifiers that would permit linkages to individual research participants and variables that could lead to deductive disclosure of the identity of individual participants.

Participant Compensation

Each pharmacist and pharmacy technician who participated in an interview was paid US $50 via an electronic gift card. For the focus groups, pharmacists and pharmacy technicians were or will be paid US $80 in cash for the first, second, third, and fourth meetings. They will each be paid US $120 in cash for the fifth meeting and US $160 each for the final meeting. For the simulations, each pharmacist and pharmacy technician will have the opportunity to participate in up to 3 simulation sessions, earning US $150 each for their participation in each session. For the post implementation interviews during aim 3, pharmacists and pharmacy technicians will each be paid US $50 via an electronic gift card. Details on compensation are included in both recruitment communications with the participation and the information sheet that is provided to the participant upon requesting more information on the study.

Study Sites

To ensure a complete understanding of the problems and implementation strategies of varied community pharmacy work systems, we will partner with 3 pharmacy organizations. First, Advocate Health is the 10th largest not-for-profit, integrated health system in the United States, with 70 community pharmacies that are geographically dispersed throughout urban and rural Wisconsin and Illinois. Second, UW Health is the integrated health system of the University of Wisconsin–Madison, with 12 outpatient pharmacies. Third, Boscobel Pharmacy and Center Pharmacy are located in rural southwest Wisconsin and are independently owned.

Within each of these organizations, 2 pharmacies will participate that serve ethnically diverse populations and people in medically underserved areas that have high area deprivation indices based on income, education, employment, and housing quality for 6 pharmacy sites. In addition, all pharmacies will have at least read-only access to the electronic health records of their patients, which may serve as a tool to facilitate CCM.

We will also partner with Fitchburg Family Pharmacy to conduct in situ simulations, in which we will use simulated scenarios of patients with complex chronic health conditions in a pharmacy itself rather than in training facilities for the design and development phases (aim 2) of the project. Fitchburg Family Pharmacy is a medium-sized urban independent pharmacy that provides CCM to a diverse patient population.

Project Aims

Table 1 describes our project structure, starting with problem analysis (aim 1) and continuing with design and development (aim 2), which will lead to implementation and evaluation (aim 3). An expert advisory board, comprising transdisciplinary stakeholders, will be formed to provide us with high-level consultation and content expertise for each of the 3 project aims. This board includes patients, caregivers, a pharmacy technician researcher, a pharmacy owner, primary care physicians, managers of independent, local, and chain pharmacies, and leaders of pharmacy and medical societies in Wisconsin.

Table 1. Project structure guided by the Agency for Healthcare Research and Quality Request for Application 5-step methodology.

	Problem analysis (step 1)	Design (step 2) and development (step 3)	Implementation (step 4) and evaluation (step 5)
Aims	• Identify and prioritize (aim 1)	• Prototype and simulate (aim 2)	• Pilot and evaluate (aim 3)
Methods	• Observations and interviews • Information flow diagraming • Artifact analysis	• Participatory design • Simulation	• Time motion • Before and after evaluation • Expert evaluation • Surveys and interviews
Outputs	• Resilience narratives • Functional resilience analysis method diagrams	• Prototypes • Ideal interactions • Detailed design specifications	• Impact of prototypes on process and outcomes • Tools to assess capacity for resilience • Implementation guide

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Aim 1: Identify and Define Design Requirements

Overview

To develop effective and sustainable interventions, an in-depth problem analysis of the work system must be conducted. Thus, aim 1 seeks to understand and map work system resilience, including how WAI differs from WAD, how adjustments are created, and how outcomes are generated. Iterative data collection and analysis will allow continual refinement and clarification of the work system.

Observations

In-depth ethnographic observations will be conducted over 4 visits to each of the 6 pharmacy observation sites (Textbox 2). Study team members will debrief after each observation as well as in situ as needed to adjust observation approaches or focus on specific aspects of the workflow. We will complete 24 hours of observations over 4 days. Observed artifacts that reflect WAI, such as policies and procedures, memory aids, and cognitive tools, will also be collected and recorded. Full descriptive field notes will be produced immediately after each observational session. Data will be collected concurrently at each setting, and researchers will work across all settings so that comparisons between the settings can inform ongoing data collection strategies.

Textbox 2. Observations at the pharmacy sites.

High-level observation questions

- What contributes to variability in demand and capacity?
- What misalignment occurs between demand and capacity and why?
- What pressures, problems, or goals are pharmacists and technicians responding to when they create new ways to achieve outcomes?
- How and under what circumstances do adjustments or adaptations lead to successful and unsuccessful outcomes?

Visit 1: exploratory evaluation

- Observe the pharmacy environment holistically
- Identify staff roles and responsibilities, processes, procedures, flows of information and communication, coordinating mechanisms, and supporting tools and technology
- Identify interest areas for more precise and targeted observations in subsequent stages

Visits 2 to 4: observations

1. Observe the pharmacy staff
2. In-depth observations of important processes, such as shift-change handoffs and medication reconciliation for patients during hospital discharge, as processes critical to providing chronic care management
3. Short, structured discussions and facilitated reflection from staff on aspects of the concepts for applying resilience engineering model and using the systems engineering initiative for patient safety model components

Interviews

Semistructured interviews will be separately conducted with 2 pharmacists and 2 technicians from each of the 6 pharmacy locations to explore and follow up on issues from the previous observation stages to identify processes or areas for additional observation. Questions for the first round of interviews will focus on how people do their work and how they manage tricky situations, with probes about variability, adaptations, problems, and challenges (Multimedia Appendix 1). Questions for the second round will focus on staff experiences with, understanding of, and expectations for specific nondispensing services within community pharmacies (Multimedia Appendix 2). Interviews will be audio recorded and transcribed for analysis with participants' consent.

Data Analysis

Data analysis will proceed in 3 stages. First, a combined deductive-inductive approach will be used to thematically analyze the observation and interview data. A coding scheme will be developed based on elements of the SEIPS model as well as important themes in the data not captured by the model (Table 2). Categories will be developed by constantly refining the coding scheme, and comparisons will be made between different respondents, different pharmacies, and different processes.

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Table 2. Aim 1 observation and interview coding scheme.

Levels	Comparison of WAD[a] and WAI[b]
Teams of pharmacists and technicians	• Interpersonal communication, including verbal and nonverbal • Teamwork skills, including leadership and situation awareness
Technology	• Usability, flexibility, adjustability, and adaptability
Internal environment	• Interruptions and distractions • Lighting • Physical ergonomics of the workspace • Crowding and disorganization
Tasks	• Task demands and workload • Contextual changes, including situation deviations from normal or expected • Production pressure
Organization	• Complexity, uncertainty, and risk • Information flow, including quantity and pacing • Culture and climate • Policies and procedures • Incentives and disincentives

[a]WAD: work as done.

[b]WAI: work as imagined.

Second, guided by the CARE model, we will expand on the SEIPS coding scheme to construct functional resilience analysis method (FRAM) models [36,40] to visualize WAD and articulate the discrepancies between WAI and WAD. FRAM models allow all activities within selected processes to be visualized to show how they relate to each other and how they interact, based on six aspects, namely (1) input, (2) output, (3) precondition, (4) resources, (5) time, and (6) control, demonstrating the system's complexity [41]. Each process within the community pharmacy is linked, which allows the study of the variability of each process. That variability can produce amplified and unpredictable outcomes (either acceptable or unacceptable) [36,40].

Third, the themes generated by the deductive-inductive approach and the FRAM models will be used to create resilience narratives describing trajectories of activity linking misalignments of demand and capacity, adjustments, adaptations, and outcomes. The narratives will focus on how adjustments and adaptations (WAD) mediate between pressures caused by misalignments of demand and capacity and outcomes.

Aim 2: Design and Develop MedSafeMap

Overview

Stakeholder-engaged participatory design and simulation-based research will be used in an iterative fashion to design and develop MedSafeMap, a package of components to optimize pharmacy staff interactions within their work system and with patients, and detailed pharmacy design recommendations. Standardized scenarios of patients with complex chronic health conditions will be developed to have both internal validity and fidelity to the real-world pharmacy environment. The goal is to create MedSafeMap components that will ultimately lead to pharmacy staff resilience and optimized patient interactions around CCM.

Participatory Design

Participatory design is an approach to system design that actively involves all stakeholders at several stages of the innovation process to help ensure that the result meets their needs and is usable [28]. Two stakeholder groups will be used: one group consisting of 5 community pharmacists and another group consisting of 5 technicians.

Stakeholder group meetings will be held 6 times, approximately every 6 to 8 weeks. The first 4 meetings will be held with the pharmacists and technicians separately because they have different work responsibilities, tasks, and concerns. We also want technicians to fully engage in MedSafeMap development without a pharmacist's presence imposing a power differential. The resilience narratives and FRAM diagrams developed in aim 1, which demonstrate variability and resilience potential, will inform the design and development of the MedSafeMap. We will focus on the processes required to conduct CCM for patients with complex chronic health conditions, including the possibility of a communication tool to support a discussion of alternatives, enhanced instructions for patients, and cognitive aids to support memory. The final 2 meetings will involve MedSafeMap refinement. To do so, we will bring the pharmacist and technician groups together to work collaboratively. Textbox 3 provides a list of anticipated or possible MedSafeMap components. Completed MedSafeMap components will be peer reviewed by our advisory board to confirm that they will reproduce the experience in a real-world pharmacy. Scenarios will be piloted in the in situ simulated setting and refined before implementation in aim 3.

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Textbox 3. Current interactions and potential Medication Safety Map (MedSafeMap) components to encourage ideal interactions.

Current interactions

- Chronic care management seen as important but has an impact on workload, which is a barrier to sustained services.
- Fragmented information across health care providers
- Medication information gap (eg, multiple pharmacies, no diagnoses, or laboratory values)
- Busy retail pharmacies lead to reduced interactions with patients
- Coordination gap between pharmacists and caregivers, patients, and health care providers
- Technicians limited by traditional roles
- Medication concerns not adequately addressed
- Limited support and space for shared decision-making

Potential MedSafeMap components

- Modeling behaviors: tactics to overcome communication barriers in pharmacies and engage health care providers; patient and family support to bridge the information gap
- Information support: use technology or low-technology strategies to push eligible patients into the pharmacy workflow; create mechanisms that provide caregivers the opportunity to be involved before, during, and after an appointment
- Cognitive aids: physical structures to improve pharmacists' and technicians' situation awareness; supports in addressing high-priority medication needs
- Collaborative work support: facilitate a huddle between pharmacist and technician to create an appointment agenda, anticipate patient challenges, and review monitoring needs
- Role clarity and cross-training: empowering technicians as equal partners and leaders in the community pharmacy

Simulation-Based Research

In situ simulation [42], or simulation in an actual community pharmacy, will then be conducted to study the ergonomics and physicality of the work setting on performance. In situ simulations will also promote process and MedSafeMap refinement before deployment in actual pharmacies.

The final 2 stakeholder meetings will involve 3 rapid adaptive simulation cycles for MedSafeMap refinement (Figure 3). Each simulation cycle will include 5 different standardized patients (hired for the study). Each patient will represent 1 of the 5 different complex CCM scenarios that will include at least 2 chronic conditions and at least 1 social determinant of health (eg, a low health literacy patient with diabetes and congestive heart failure who is nonadherent to medications). Staffing and equipment, level of complexity, and other critical indicators identified in the participatory design will vary and allow for comparisons across the 5 patient scenarios. Creating robust and standard scenarios is important to mitigate threats to internal validity. Thus, we will devote considerable time to ensuring that MedSafeMap may be used in different patient cases and different community pharmacy settings (ie, is pharmacy agnostic; Figure 3).

Figure 3. Simulation cycles.

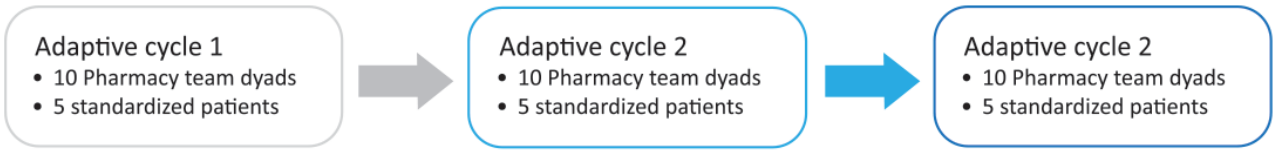

In total, 10 pharmacist and technician dyads will be recruited to participate in each adaptive simulation cycle. In each adaptive cycle, the pharmacy and technician dyad will complete the simulation 5 times, once for each standardized patient. The process will be replicated for each of the 10 pharmacy dyads, resulting in 50 simulations per adaptive cycle. At the completion of each cycle, the study team will use the data collected, combined with significant reflection and formative evaluation, to refine MedSafeMap that facilitates resilience and encourages adaptation by pharmacy staff.

Data Collection

Four wide-angle video cameras will be used to record the simulation from locations that best capture how pharmacy staff interact with the physical space, communicate, share information, and use artifacts within the work system. In addition, 2 sets of eye-tracking glasses (Tobii Pro Glasses) [43-45], one each for the pharmacist and the technician, will be deployed to track eye movement in the natural world, which will inform the development of prototypes. Specifically, as pharmacy staff navigate the physical pharmacy space, the glasses collect data that will provide an understanding about which artifacts are most instrumental to performing CCM, factors that

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influence pharmacy staff and patient decision-making, and workflow. Gaze data will be recorded as pharmacy staff read and review information on prescriptions and prescription profiles in the pharmacy electronic health record and interact with and educate patients. Aim 2 will be accomplished in 3 steps, conceptualized in Table 3.

Table 3. Aim 2 data collection procedures.

	Step 1	Step 2	Step 3
Tasks	Record simulations and document individual and collective behavior	Introduce MedSafeMap[a] and record simulations: simulate with 10 pharmacist and technician dyads for each of 5 different standardized patients	Conduct individual debrief interviews with the pharmacists and technicians following completion of each simulated scenario
Goal	Identify patterns of interactions and thought processes	Reproduce situations identically to increase confidence in the MedSafeMap's ability	Gain insights into the thoughts and cognitive processes of pharmacists and technicians
Output	Descriptive account of how community pharmacy staff make decisions or share information; understand rare events, such as sentinel medication errors	Explain variation in the outcome of interest	Understand participants' perceptions of (1) understanding the problem, (2) assessing prototype feasibility, (3) evaluating the effect of the prototype, and (4) optimizing the design and implementation of the prototype

[a]MedSafeMap: Medication Safety Map.

Data Analysis

Observational checklists will be used to code participant behavior recorded on the videos, thereby assessing MedSafeMap's feasibility and effectiveness. The recordings from the wide-angle video cameras and eye-tracking glasses will be analyzed for themes among participants and across sites by assessing which areas of interest participants fixate on for extended periods. Using gaze duration as a proxy for the wearer's attention provides insights into which elements of MedSafeMap are influential in shaping pharmacy staff's behavior. For example, if one of the components of MedSafeMap includes a technician training to speak up when they are concerned that the pharmacist missed a medication-related problem, we can respectively code the reactions of the pharmacist and technician based on the videos [46,47].

Qualitative data from pharmacist and technician stakeholder meetings will be subjected to a rigorous analytic approach [37,48-51]. We will use deductive content analysis, inductive patterns, themes, and categories in our data, guided by our theory-based approach [52]. A conceptual coding structure will be created, and as each interview transcript is added to the analysis, passages will be classified according to existing codes, and codes will be added as needed. Inductive content analysis will also be conducted to determine unanticipated work system characteristics that may facilitate or inhibit resilience.

Aim 3: Implement and Pilot-Test MedSafeMap

Overview

Although simulation-based research can have high internal validity by controlling the highly standardized scenarios that will be developed in aim 2, it is critical to implement and evaluate MedSafeMap in real life, where WAD diverges from WAI, and address external validity concerning pharmacy work systems relevant to CCM. With this approach, we can determine whether changes in performance can be attributed to MedSafeMap rather than other external (eg, regulatory changes) or internal elements (eg, updates to electronic health records) and how such elements can affect MedSafeMap's performance or impact. The 6 community pharmacies that participated in aim 1 observations and interviews will implement MedSafeMap for optimal interactions designed in aim 2.

Implementation and Adaptation

A stepped wedge design [39] will be used, where the MedSafeMap will be sequentially implemented in 2 clusters, each cluster comprising 3 pharmacies (1 pharmacy from each organization; Figure 4). The 2 pharmacies from each organization will be randomized into the 2 clusters. Each cluster will commence with baseline pretest data collection and then cross over from the control condition (before implementation) to the intervention condition, where a formative evaluation of MedSafeMap and the strategies from the implementation guide will be conducted. This evaluation will be performed for each cluster 4 months into its implementation period to consider "what might be missing, what sociotechnical factors had not been considered, and to identify 'bugs and glitches' that still need to be addressed" [53]. The evaluation will include one day of observations by shadowing pharmacy staff and may involve short discussions and facilitated reflection from staff at each of the 3 pharmacies in cluster 1. Those observations will be reported to the research team and advisory board to identify opportunities to improve MedSafeMap. Following the formative evaluation in cluster 1, we will refine and improve MedSafeMap and implementation strategies to mitigate vulnerabilities or unintended consequences that may expose patients to new harms or further burden the pharmacists and technicians with more work. The adapted MedSafeMap and implementation strategies will be deployed for cluster 2, which will also undergo a similar evaluation. It is possible that minor adaptations will be made, if necessary, before subjecting the cluster to a posttest evaluation [54] (Figure 4).

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Figure 4. Stepped-wedge design and data collection methods.

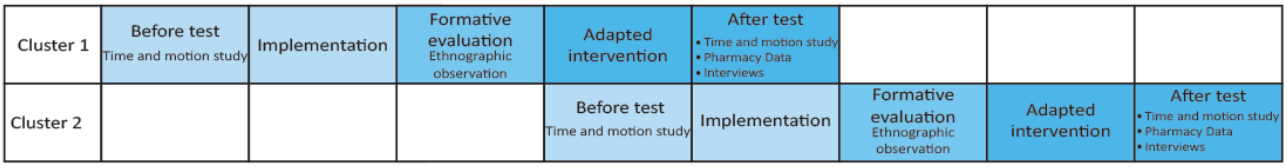

Evaluation

We will use a sequential explanatory design in which the initial data are quantitative (time and motion study and work volume) and complemented by qualitative data (interviews and medication error reporting). This mixed methods approach will allow the research team to understand variables individually and determine which ones will require further analysis. In line with the CARE and SEIPS 2.0 models, we will collect and analyze data that reflect workflow and care processes and the perspectives of pharmacists and technicians.

Time and Motion Study

Our evaluation goal is to examine the impact of MedSafeMap on pharmacists' and technicians' ability to be resilient, that is, to successfully attend to unexpected threats while also responding to opportunities [31], such as CCM. To do so, we must understand clinical work processes and the way that care is delivered to patients. We anticipate that MedSafeMap will impact the way pharmacists and technicians perform their work and how they engage each other and their patients. Time and motion studies have been used to measure clinical workflow–related factors, including time and task distributions, frequency of multitasking and interruptions, and who completes tasks, with a goal of improving efficiency [55,56].

We will conduct observations before and after the implementation of the adapted MedSafeMap. Using the observational data collected in aim 1, we will develop a pharmacy work task classification (Table 4). The classifications will be incorporated in the WOMBAT program to allow for the consistent recording of observational data [57,58]. WOMBAT allows observers to time the start and end of tasks and record multiple simultaneous tasks using the multitasking function. If an external factor appears to cause a pharmacist or technician to stop performing one task and start another task, an interruption can be recorded.

Table 4. Pharmacy work task classifications.

Work task classification	Examples
What: the task being performed	Counseling and communication with the prescriber
Where: the physical location where the task is undertaken	Behind the desk, in the office, and over the counter
With whom: whom the pharmacy staff was with when performing the task	Alone, patient, technician, and student
How: any tools used to complete the task	Phone, face-to-face, and computer

Observer Training

Before MedSafeMap's implementation and baseline data collection, 2 observers will be trained to use the WOMBAT program. Data collection will begin when simultaneous but independent observations of the same events, such as those seen in Table 4, yield an interrater reliability score of at least 85% [59].

Data Collection

Observations will be purposely scheduled across a variety of weekday shifts to maximize data variability and capture the full pharmacy workday. One observer will shadow a pharmacist equipped with a tablet with the WOMBAT software installed on it, while, at the same time, a similarly equipped second observer will shadow a technician. In total, 2 pharmacists and 2 technicians will be observed at each pharmacy. Observations will be limited to three 2-hour sessions per day, each separated by a brief break to reduce participant or observer fatigue. During each break, observers will note down any thoughts regarding future questions or more in-depth observation. The pharmacists and technicians will be observed for 36 hours both before and after implementation, over a 72-hour period. We estimate observing tasks across 72 hours in each pharmacy [55], yielding 432 hours across the 6 participating pharmacies [57,60].

Data Analysis

To assess changes in pharmacists' and technicians' task and time distribution after implementation, we will calculate the proportion of total observed time in each task category by study period (before vs after implementation) for each pharmacy. The proportions of total observed time where pharmacists complete tasks with technicians or alone and use different information tools will also be calculated for each pharmacy. To assess the extent to which the introduction of MedSafeMap increased opportunities for pharmacists and technicians to engage with patients in CCM, we will examine changes in the time pharmacists and technicians spent in (1) having discussions with each other on responding to opportunities (ie, identifying patients with complex chronic health conditions who would benefit from CCM) and attending to unexpected threats (ie, personnel absences) and (2) having discussions with patients about medications [60]. Z tests for proportions will be used to compare the extent of before and after implementation change in the proportion of total observed time for each task category in each pharmacy site. A significance level of $P<.05$ will be used as well as the Holm approach to account for multiple comparisons, with 95% CIs based on the large sample normal approximation.

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Pharmacy-Reported Data

We anticipate that MedSafeMap will support pharmacists' and technicians' ability to embed CCM and other clinical services into their workflow, which will improve the quality of patient care, ideally, without increasing workload. To assess perceived changes in service provision, pharmacists and technicians will be administered a validated subjective workload survey [61]. Moreover, the number and type of documented medication-related problems during CCM services [62] that are identified and resolved for 6 months before and 12 months following MedSafeMap implementation will be collected. Pre-post comparisons of services provided and medication-related problems that they averted will be conducted.

Pharmacist and Technician Evaluation

We also want to gain a more in-depth understanding of how MedSafeMap changed attitudes, behaviors, and performance. It is expected that pharmacists and technicians will feel more resilient after the implementation of MedSafeMap, that is, they will feel more "capable, facilitated, and supported by the organization to utilize resources to continually adapt and flourish at work, even if/when faced with challenging circumstances" [63]. This construct will be represented through the Employee Resilience Scale [63], a measure of behavioral elements, such as learning orientation, proactive posture, positive outlook, network leveraging, and adaptive capacity.

Pharmacists and technicians also are likely to eventually feel a greater sense of shared responsibility and teamwork, which would create an environment that enhances the medication safety of their patients. This construct will be represented through the National Aeronautics and Space Administration (NASA)–developed Cockpit Management Attitudes Questionnaire [64,65], comprising 3 scales, namely communication and coordination, command responsibility, and recognition of stressor effects, which have application for the pharmacy work system.

Because we are working with a small number of pharmacists and technicians and we want to conduct an in-depth exploration of pharmacy staff attitudes and behaviors, we will adapt the Employee Resilience and Cockpit Management Attitudes Questionnaire items into an interview guide that will include semistructured probes. In addition, 8 months following MedSafeMap's implementation, interviews will be conducted using a retrospective pre- and posttest design approach [66,67] by asking, "Compared to before MedSafeMap was implemented..." This approach is appropriate because it is pragmatic and less time consuming, eliminates the impact of response-shift bias [66], and has been used successfully in pharmacy studies [68,69]. Questions will prompt insights into the impact of MedSafeMap on pharmacist and technician resilience, teamwork, and shared responsibility. Interview data will be subjected to the same rigorous qualitative data analysis techniques described in aim 1.

Outcomes

Study outcomes are targeted to help populations of medication safety researchers and organizational leaders responsible for implementing proven practices. A summary of the anticipated outcomes can be found in Textbox 4.

Textbox 4. Anticipated outcomes.

Aim 1

- Resilience narratives and functional resilience analysis method models that are context rich and context dependent
- Potential to uncover anticipated relationships between variables that can be tested in the subsequent aims to inform the development of the Medication Safety Map (MedSafeMap)

Aim 2

- Components of MedSafeMap that support chronic care management in community pharmacies
- MedSafeMap components that may include designs that realign currently existing tasks, coordinate tasks with different pharmacy staff members, or incorporate new practices
- MedSafeMap components that may include tools to facilitate pharmacist and patient and pharmacist and prescriber collaboration or to provide cognitive support for pharmacists and technicians to anticipate crises or other problems

Aim 3

- Quantitative and qualitative evaluation of the impact of MedSafeMap on community pharmacy processes and outcomes
- Toolkit to assess capacity and resilience
- Implementation guide

Project Duration

The anticipated duration of the project is from September 30, 2023, to August 31, 2027. Activities concerning aim 1 were anticipated to end by August 31, 2024, but data collection has extended beyond that date. Activities concerning aim 2 were planned to commence on September 1, 2024, but began in February 2025 and will conclude in December 2025. Activities concerning aim 3 will begin on January 1, 2026, and last till August 31, 2027. Participant recruitment is expected to be completed by the conclusion of aim 3, alongside data collection. Results from varying analyses within the project are anticipated to be disseminated during the project's duration and following its completion. Aims 1 and 2 have received IRB approval, and

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aim 3 will be reviewed by the University of Wisconsin-Madison IRB before recruitment begins.

Results

As of August 2025, all 6 pharmacy sites have been recruited. In total, 3 of the 4 rounds of observations, 2 rounds of interviews with 12 pharmacists and 12 technicians from the study sites, and he 6 focus groups have been conducted. Preparations for the simulations are ongoing. Preparations for aim 3 will begin closer to November or December of 2025. Recruitment for aim 3 will begin once it has received approval from the IRB.

Discussion

Anticipated Findings

The prevailing safety-I approach for improving medication safety has emphasized retrospective incident analysis, reactive measures targeted at past problems, human error as an explanation, and control of work through procedural compliance and outcome monitoring [70]. This approach has proven to be insufficient and frustratingly slow at achieving zero harm in outpatient settings and specifically the community pharmacy [71]. Such a lack of success stems from investigating medication errors through root cause analysis, which assumes a shortsighted linear cause-and-effect model rather than a complex model [72]. Finally, importantly, these approaches create a negative psychological impact on staff by creating a culture of blame [31,73,74].

Strengths

This study will be the first to operationalize resilience engineering to include a safety-II approach to medication safety in community pharmacies. Most of the safety studies involving community pharmacies assume a linear work process, which limits understanding of community pharmacies as complex work systems. Our research demonstrates that work is not conducted linearly but rather is composed of interdependent processes [75]. The use of the innovative FRAM model will provide a robust model to map multiple processes and their variability, which can inform co-design of potential solutions [36,76,77].

This project will prioritize and emphasize the role of pharmacy technicians as critical members of the community pharmacy work system. Technicians are increasingly being recognized for their willingness to assume new roles and adapt to changing environments [78] which was expedited during the COVID-19 pandemic. Technicians have proven themselves effective in collecting patient medication histories [79], performing administrative functions associated with vaccinations, and even providing immunizations to patients [80].

Pharmacist provider status, a new legal designation authorizing Medicaid reimbursement for pharmacists' services, presents a timely opportunity to evaluate how increased or broadened responsibilities can be adopted while improving quality of care and medication safety. Legal endorsement to stretch professional boundaries and envision innovative designs [53] is the perfect circumstance to move the needle on outpatient medication safety through the design of the next generation of community pharmacies. Pharmacists and technicians, depleted by the unrelenting workload and additional responsibilities since the COVID-19 pandemic, find the safety-II approach to be attractive [71]. Safety-II also better represents and supports a culture of safety because it accurately portrays the constant variability of pharmacy work, the need for adjustment, and the importance of flexible adaptation in producing outcomes.

Introducing and using a safety-II approach will provide the test bed, tools, metrics, and frameworks to build the ENRICH PSLL. This new paradigm of approaching CCM with resilience engineering methodologies to improve quality in community pharmacies could then be disseminated to and adopted by medication safety researchers around the country.

Limitations

Participant bias caused by sensitivity to the researcher's presence is a recognized risk in qualitative observational studies, but it can be minimized by ensuring that observers have frequent presence in the research setting, which can lead to habituation to their presence and improvement in the researcher's sensitivity to and respect for pharmacy staff's concerns, and their ability to build relationships and trust. The risk of measurement bias will be reduced by having 2 researchers collect data only after achieving a satisfactory interrater reliability rate, ensuring that differences in interpretation can be identified, discussed, and resolved before full data collection is accomplished.

We will use 1 simulation site, despite being aware that community pharmacies have very different work systems. We also know that using multiple simulation sites would increase the generalizability of findings and enable comparison between sites. However, using simulations to evaluate prototypes that focus on workflow changes related to CCM is unprecedented in community pharmacies, so we want to begin with a single setting to ensure a robust infrastructure to evaluate such simulations. To expand our understanding beyond the single work system exemplified by the simulation site, we will seek input from advisory board members who will provide feedback on the feasibility of implementing MedSafeMap in their diverse community pharmacy settings.

Conclusions

Community pharmacies have experienced a great deal of change in the last decade alone. With an increase in responsibilities due to the COVID-19 pandemic as well as changes to the health care structure that increase their workload, pharmacy staff are becoming increasingly burnt out. Coupled with high turnover rates and understaffing concerns, there is an unprecedented risk of safety errors and resulting patient harm. To allow the pharmacy staff to take on these responsibilities as CCM health care providers, we must find a way to manage the workload and optimize resources. We are in a unique position to provide support directly to the pharmacies and give them a voice to influence change in the pharmacy work system. Through this PSLL, we can rethink the current safety approaches and develop an improved work system for medication safety, resulting in improved work conditions for pharmacy staff and increased patient care.

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Acknowledgments

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Data Availability

The datasets generated or analyzed during this study will be made available through the Interuniversity Consortium for Political and Social Research, a CoreTrustSeal certified repository, in adherence with the National Institutes of Health Data Management and Sharing policy.

Authors' Contributions

MAC and JHF II initiated the project as coprincipal investigators of the study and jointly supervised the writing of this protocol. AMG, JAS, and ELH contributed to the conceptualization of this study. JAS managed and coordinated research activity. MAC, MEB, AMG, JAS, KGM, ELH, and JHF II drafted the initial manuscript. MEB collected and organized the relevant data for publication. MEB and ELH updated the proposed models and created new graphics. All authors contributed to the revision process. All authors read and approved the final version of the manuscript.

Conflicts of Interest

MAC is a co-owner of Fitchburg Family Pharmacy, which serves as the simulation site for this project. MAC will not receive any payment for the use of the pharmacy for this project. The other authors declare no conflicts of interest.

Multimedia Appendix 1
Aim 1: pharmacy staff interview guide round 1.
[PDF File (Adobe PDF File), 223 KB - resprot_v14i1e69011_app1.pdf]

Multimedia Appendix 2
Aim 1: pharmacy staff interview guide round 2.
[PDF File (Adobe PDF File), 144 KB - resprot_v14i1e69011_app2.pdf]

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Abbreviations

ADE: adverse drug event
CARE: concepts for applying resilience engineering
CCM: chronic care management
ENRICH: Engineering Resilient Community Pharmacies
FRAM: functional resilience analysis method
IRB: institutional review board
MedSafeMap: Medication Safety Map
NASA: National Aeronautics and Space Administration
PSLL: patient safety learning laboratory
SEIPS: systems engineering initiative for patient safety
WAD: work as done
WAI: work as imagined
WOMBAT: work observation method by activity timing

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Protocol

Optimizing Self-Monitoring in a Digital Weight Loss Intervention (Spark): Protocol for a Factorial Randomized Trial

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Abstract

Background: Self-monitoring is a vital component of behavioral obesity treatment. It often involves tracking dietary intake, physical activity, and body weight. However, the optimal combination of self-monitoring strategies that maximizes weight loss is unknown. To address this gap, we leverage a framework called the multiphase optimization strategy, which facilitates the identification of an intervention's "active ingredients" that promote weight loss and its "inactive ingredients" that have little impact, thus adding unnecessary patient effort and time demands.

Objective: This study aims to examine the unique and combined weight loss effects of 3 popular self-monitoring strategies (tracking dietary intake, steps, and body weight).

Methods: Spark was an optimization-randomized clinical trial that used a 2 × 2 × 2 full factorial design with 8 experimental conditions. Participants, US adults with overweight or obesity (N=176), were randomized to receive 0-3 self-monitoring strategies in a 6-month fully digital weight loss intervention. For each assigned strategy, participants were instructed to self-monitor daily via commercially available digital tools (a mobile app, wearable activity tracker, and smart scale) and received a corresponding goal (eg, a daily calorie goal) and weekly automated feedback. All participants received core intervention components, including weekly lessons and action plans informed by Social Cognitive Theory, to promote healthy eating and physical activity. Assessments occurred at baseline and at 1, 3, and 6 months. Weight was assessed objectively via a smart scale. The primary aim is to test the main effects of the 3 self-monitoring components and their interactions on weight change from baseline to 6 months. Secondary outcomes include change in BMI, caloric intake, diet quality, physical activity, and health-related quality of life, as well as 1- and 3-month weight change and the relation between self-monitoring engagement and weight change. Patterns of engagement will be operationalized as the percentage of days of self-monitoring during the 6-month intervention. Moderators of weight loss success will be explored to understand whether certain subgroups of individuals benefit more from specific self-monitoring strategies. We also conducted a separate embedded experiment to test the impact of a self-directed web-based orientation session on 6-month trial retention. After the intervention, semistructured qualitative interviews were conducted with a subset of participants to elucidate factors that impact engagement and its link to weight loss.

Results: Recruitment occurred from September 2023 to November 2024. Data collection was completed in June 2025. Data analysis is ongoing.

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Conclusions: This trial will provide evidence as to which self-monitoring strategies are the "active ingredients" in a fully digital weight loss intervention and begin to explore which subgroups may do best with which strategies. These results have potential for public health impact by maximizing weight loss while minimizing patient burden.

Trial Registration: ClinicalTrials.gov NCT05249465, https://clinicaltrials.gov/study/NCT05249465

International Registered Report Identifier (IRRID): DERR1-10.2196/75629

(JMIR Res Protoc 2025;14:e75629) doi:10.2196/75629

KEYWORDS

weight loss; obesity; intervention; self-monitoring; tracking; digital health; multiphase optimization strategy; behavior change; behavioral obesity treatment; RCT; randomized controlled trial

Introduction

Background

With the prevalence of overweight and obesity at approximately 71% among US adults [1,2], there is a critical need for weight loss interventions that are both effective and scalable. Gold standard behavioral obesity treatments are effective in producing weight loss of 5%-8%. These 6-12 month treatments pair frequent counseling with evidence-based behavioral strategies to promote healthy dietary change and physical activity [3,4]. Despite their efficacy, these treatments are not easily scalable or accessible due to their high intensity, personnel costs, and time demands.

Digital health interventions can overcome these barriers by delivering weight loss programs remotely and in a standalone format (ie, without a human counseling component). They also have the potential to target broad segments of the population with overweight or obesity, including geographically, racially, and ethnically heterogeneous populations who are underrepresented in traditional obesity treatment research [5-8] despite being disproportionately burdened by obesity [9,10]. However, fully digital weight loss interventions produce only modest weight loss, ranging from 2% to 4% [11-19]. Thus, to fully capitalize on these highly scalable digital interventions, more work is needed to enhance their potency.

Self-monitoring is a well-established behavioral strategy for facilitating weight loss among adults with overweight or obesity [20-22]. It involves tracking a behavior (eg, dietary intake [23] and physical activity [24,25]) or a health-related outcome (eg, body weight [26]). Self-regulation theories, including the Social Cognitive Theory and the Control Theory, posit that behavior change occurs through a cyclical process of goal setting, paying attention to behaviors via self-monitoring, receiving feedback on how one's current performance compares to one's goal or past performance, creating an action plan to adjust behavior, and repeating the process to get closer to attaining one's goal [27,28]. These behavioral strategies work in tandem to promote greater behavior change [29-32]. Self-monitoring is one of the strongest predictors of behavior change [29] and weight loss [31,33]. Numerous systematic reviews and meta-analyses have demonstrated that greater engagement in self-monitoring is consistently linked to greater weight loss [21-23,26,34,35]. Further, this relation holds across many intervention contexts, including human counseling–based and fully digital interventions [22]. However, self-monitoring engagement often declines over time [36-39]. Common barriers include time demands, perceived burden, accessibility challenges, waning novelty, lack of clarity on how to use such data to change behavior, and constraints related to literacy and numeracy [40-42].

One way to promote self-monitoring engagement is by using digital rather than paper-based methods of self-monitoring [22]. Advantages of using digital platforms for self-monitoring include immediate personalized feedback, time savings when using devices such as wireless activity trackers and smart scales, and high portability of mobile health tools, which increases the likelihood of engagement while reducing retrospective errors. In our systematic review of self-monitoring in digital weight loss interventions among adults with overweight or obesity, we found that 81% of interventions included self-monitoring of dietary intake, 82% included self-monitoring of physical activity, and 72% included self-monitoring of weight. In total, over half (54%) of the interventions included all 3 of these self-monitoring strategies [22]. In summary, self-monitoring is a theory-informed and evidence-based approach for weight loss that can be delivered via digital tools.

Gap in the Field

To the best of our knowledge, no study has systematically examined the optimal combination of self-monitoring strategies included in behavioral obesity treatment. Specifically, weight loss studies often combine multiple self-monitoring domains—tracking dietary intake, physical activity, and body weight—into 1 bundled "treatment package," which is then compared to a suitable control in an evaluation-randomized controlled trial (RCT) [21-23,34,35]. In this classical treatment package paradigm, these trials can determine the overall efficacy of a weight loss intervention but cannot disentangle the effects of individual self-monitoring components. Thus, in trials using the classical paradigm, if an intervention demonstrates superiority, it would be unclear whether all self-monitoring strategies were needed to produce clinical impact. In addition, if an intervention shows a null effect, it would be unclear whether any of the self-monitoring strategies were beneficial, or whether their effects were dampened by other burdensome intervention components. In summary, trials using the classical treatment package approach are not able to discern whether all or none of the self-monitoring strategies are valuable.

Similarly, in comparative effectiveness trial designs, the unique effects of individual self-monitoring components can be established but not their combined effects. Past studies have

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used these designs to isolate the effects of 1 self-monitoring domain, including self-monitoring weight (vs not) [43,44] or self-monitoring diet (vs not) [36,45,46]. Other studies have varied the content or frequency of what is being self-monitored within 1 domain (eg, comparing simplified to detailed versions of dietary self-monitoring) [47-53]. Taken together, it is unknown whether some or all 3 of these popular self-monitoring strategies are effective.

Examining whether any interaction effects exist among the 3 most common self-monitoring strategies has the potential for enhancing the efficacy of digital interventions while limiting patient burden. Interactions can be synergistic (ie, when combined, the components result in better outcomes than expected based on the main effects alone) or antagonistic (ie, worse outcomes than expected based on the main effects alone). For instance, a synergistic interaction could occur if combining self-monitoring components provided individuals with clearer insights into changing health behaviors, leading to greater weight loss than expected. In contrast, an antagonistic interaction could occur if a burdensome self-monitoring component increased the risk of disengagement from one or more other self-monitoring components, undermining the effect of those components. This antagonistic interaction results in the combined effect being smaller than what would be expected based on the main effects of the self-monitoring components.

Leveraging the Multiphase Optimization Strategy

Intervention optimization can be used to guide the selection of self-monitoring strategies for use in weight loss interventions. To do this, the multiphase optimization strategy (MOST), an engineering-inspired framework, enables researchers to build effective multicomponent behavioral interventions through a 3-phase process of preparation, optimization of the intervention, and evaluation of the newly optimized intervention [54,55]. First, the preparation phase consists of understanding gaps in the field, selecting intervention components to test, and developing a conceptual model. Second, the optimization phase consists of conducting a fully powered optimization-RCT to rigorously test the intervention components' unique and combined effects on the outcome of interest. Third, a subsequent evaluation phase involves testing the newly optimized intervention versus a comparator in a traditional 2-arm evaluation-RCT.

Objective

The Spark trial, focused on the optimization phase of MOST, seeks to optimize self-monitoring in a 6-month fully digital weight loss intervention for adults with overweight or obesity. Specifically, we are examining the unique and combined effects of 3 popular self-monitoring strategies (tracking dietary intake, steps, and body weight) on 6-month weight change. In doing so, we will be able to isolate their individual effects and examine whether any synergistic or antagonistic interactions exist among them. Results will inform the development of a newly optimized intervention that retains only the self-monitoring strategies that have a clinically meaningful effect in order to maximize weight loss while minimizing patient burden. We will also assess the self-monitoring strategies' unique and combined effects on secondary outcomes, including caloric intake, diet quality, physical activity, and health-related quality of life, as well as on 1- and 3- month weight change and the relation between self-monitoring engagement and weight change. Moderators of weight loss success will be explored to understand whether certain subgroups of individuals benefit more from specific self-monitoring strategies. Using an embedded experimental design, we will test whether a self-directed web-based orientation session—completed prior to enrollment—promotes greater 6-month retention in the Spark trial. Finally, we will conduct semistructured qualitative interviews with trial participants to explore factors that impact engagement and its link to weight loss. This paper describes the study protocol, following the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2025 Checklist (see Multimedia Appendix 1), which are standardized guidelines for reporting clinical trial protocols [56].

Methods

Study Design and Overview

The Spark trial was an optimization RCT that tests the unique and combined effects of 3 self-monitoring strategies (tracking dietary intake, steps, and body weight) in a 6-month fully digital weight loss intervention for adults with overweight or obesity. The study used a 2^3 full factorial design (ie, 2 × 2 × 2), whereby each participant was randomized to 1 of 8 experimental conditions that represent all possible combinations of these self-monitoring strategies. For each strategy, half of the participants were assigned to receive it ("Yes") while the other half did not receive it ("No"; see Table 1). All participants received a core intervention that included weekly lessons and action plans for promoting healthy eating and physical activity. We recruited 176 participants (22 per condition). The trial was preregistered in February 2022 at ClinicalTrials.gov: NCT05249465. The trial registry includes the study protocol [57]. No patient involvement occurred, though study procedures and intervention content were adapted from the principal investigator's (PI's) prior digital weight loss trials (ie, GoalTracker [36], Spark Pilot [47], and Ignite Pilot [58]) that gathered qualitative participant feedback on perceived satisfaction and difficulty of intervention components, feasibility of study procedures, and suggestions for improvement.

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Table 1. Factorial design (2 × 2 × 2) testing three self-monitoring strategies in the Spark trial.

Experimental condition	Core	Track diet	Track steps	Track weight
1	Yes	No	No	No
2	Yes	No	No	Yes
3	Yes	No	Yes	No
4	Yes	No	Yes	Yes
5	Yes	Yes	No	No
6	Yes	Yes	No	Yes
7	Yes	Yes	Yes	No
8	Yes	Yes	Yes	Yes

Participants

The inclusion and exclusion criteria are listed in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Adults aged ≥18 years.
- BMI of 25.0-45.0 kg/m^2, which corresponds to having overweight or obesity [59].
- Smartphone ownership and access to a personal email account.
- Willing to install the Fitbit mobile app (Google) on one's personal phone.
- Proficiency in the English language.
- Living in the United States.
- Interested in losing weight through behavioral strategies.

Exclusion criteria

- Concurrent enrollment in another weight management intervention.
- Loss of ≥10 lbs (ie, 4.5 kg) in the past 6 months.
- Current use of a weight loss or antiobesity medication.
- Prior or planned bariatric surgery.
- Current, recent, or planned pregnancy during the study period.
- Currently breastfeeding or lactating.
- Living with someone else participating in the study.
- Inability to engage in moderate forms of physical activity akin to brisk walking (assessed via the Physical Activity Readiness Questionnaire for Everyone [PAR-Q+] [60])
- Potential contraindications to losing weight due to a serious medical condition (eg, cancer or dementia) or medication (eg, steroids).
- A history of an eating disorder or cardiovascular event or uncontrolled diabetes mellitus or uncontrolled hypertension that could predispose an individual to be better suited for a more intensive or different type of intervention.
- Investigator discretion for safety reasons.

Study Procedures

The study procedures are depicted in Figure 1.

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Figure 1. Study procedures diagram in the Spark trial. SWAT: study within a trial.

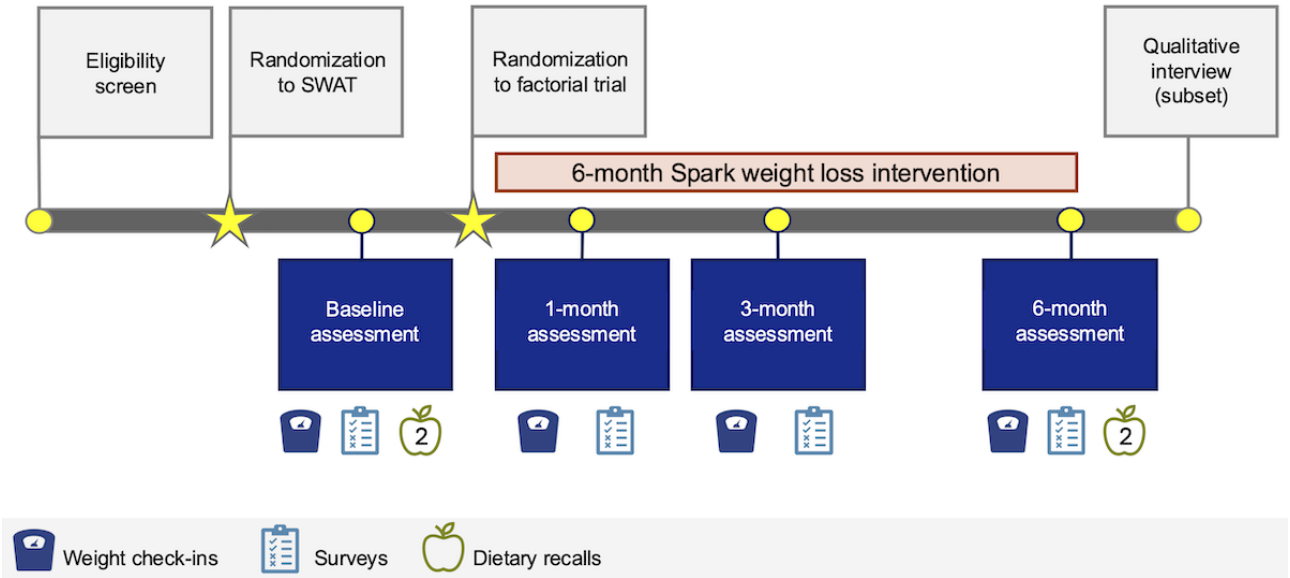

Recruitment

The study was fully remote and was delivered across the United States. Enrollment occurred on a rolling basis until our target sample size was met. We aimed for at least 50% recruitment of US racial or ethnic minority group members, given their underrepresentation in behavioral weight loss trials [6,7] and the disproportionate burden of obesity among Black and Hispanic adults in the United States [61]. We recruited participants via remote channels, including ResearchMatch (a web-based US national registry of volunteers interested in participating in health-related studies), an institute-specific diabetes registry, and ClinicalTrials.gov (a globally recognized registry of clinical trials). Recruitment materials included a brief description of the study and eligibility criteria, along with a link to a web-based eligibility screen on REDCap (Research Electronic Data Capture; Vanderbilt University), a secure, web-based software platform hosted at Stanford University. [62] Those who were eligible were prompted to provide contact information at the end of the screen.

Self-Directed Orientation Session

Eligible individuals were randomized 1:1 to either receive a self-directed orientation session or not receive it as part of an embedded experiment that began prior to the Spark weight loss trial (see preregistration repository: protocol SWAT (Study Within A Trial) 211 [63]). Participants in the SWAT control arm were sent an automated email prompting them to sign up for a baseline visit using a scheduling website (Calendly). Those in the SWAT intervention arm were sent an automated email prompting them to complete the self-directed orientation session, lasting approximately 20-25 minutes. This web-based orientation session consisted of video content and interactive activities (using Articulate [Articulate Global LLC] e-learning software) geared at explaining the rationale for the study and for randomization, setting clear expectations of study activities, visualizing the time commitment via a graphic timeline, and ensuring the trial was a good fit for their interests by self-generating pros and cons for joining the trial. The orientation session was modeled after the innovative Methods—Motivational Interviewing Approach [64,65], which was developed to increase retention in clinical trials by empowering potential participants in making an informed decision about trial participation prior to enrollment. At the end of the orientation, individuals had the option to sign up for a baseline visit using the scheduling website. Thus, it was possible for some participants to enroll in the embedded experiment without enrolling in the weight loss trial. These types of embedded experiments are often referred to as a Study-Within-A-Trial (ie, “SWAT”) and facilitate empirically testing strategies to promote recruitment or retention in clinical trials [66,67].

Baseline Tasks

All participants attended a remote baseline visit with trained study staff held via Zoom (Zoom Communications, Inc) videoconference. This visit lasted approximately 1.5 hours in length and focused on reviewing the purpose and procedures of the study, confirming eligibility, obtaining informed consent using REDCap’s electronic signature feature, installing the free, commercially available Fitbit mobile app, completing a dietary recall assessment, and administering a health literacy assessment. The study staff created a unique Fitbit account for each participant and ensured that participants could log into it. At the end of the baseline visit, the participants received a link to the baseline survey. Once completed, study staff mailed an smart scale (Fitbit Aria Air) to the participant’s home. Once the scale was delivered, participants received an email that provided information on syncing their device with the Fitbit app and prompted them to weigh themselves the following morning using a standardized protocol (see “Data collection and measures” section, below). Study staff were available for troubleshooting via phone or email to assist in syncing devices.

Randomization to Factorial Trial

Following recommendations for factorial designs [68], we randomized participants to the 8 conditions using restricted randomization stratified by sex assigned at birth and using

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permuted block randomization with a block size of 8. The allocation sequence was generated using SAS (SAS Institute Inc) by the study's statistician (JAG) and stored in REDCap [69]. Study staff used REDCap to implement the random allocation sequence (ie, randomize a participant) once both the baseline weight and web-based surveys were submitted. If a participant was randomized to a condition that tracks steps (ie, conditions 3, 4, 7, and 8), then study staff mailed them a Fitbit activity tracker (Inspire 3) within 2 business days. Once delivered, instructions on syncing the tracker with the Fitbit app were emailed. The first day of the weight loss intervention occurred approximately 1 day after the tracker arrived (if in conditions 3, 4, 7, or 8) or 4 days after randomization (if in conditions 1, 2, 5, or 6). We chose 4 days based on the mean number of days for the tracker to be delivered once ordered. This period enabled standardization of the number of days between randomization and the start date across all conditions. On the first day of the weight loss program, participants received an automated email describing their treatment assignment (see "Intervention" section, below).

Masking

Participants were not masked to treatment assignment, by design, as they were informed before enrollment about the 3 types of self-monitoring to which they could be assigned. Study staff were not masked to treatment assignment due to logistical limitations and the need for quality assurance. However, all surveys were sent via REDCap and were completed without study staff involvement. In addition, study staff did not have access to the allocation sequence. The study statistician (JAG) will analyze the primary outcome in a masked fashion such that treatment assignment will not be revealed.

Quality Assurance

During their baseline visit, participants were asked to refrain from self-monitoring behaviors that were not assigned to them. The study's research question and expectations were explained prior to enrollment to provide an opportunity for potential participants to decide whether the study would be a good fit. We have found high adherence to these requests in our prior trial [36]. In the first couple of weeks of the intervention, study staff verified whether participants were self-monitoring correctly (ie, tracking what they were asked to track and not tracking what they were asked not to track) through review of objective self-monitoring data. If a deviation occurred, the staff member flagged it, and the participant was sent a one-time email via REDCap reminding them of their self-monitoring assignments.

Intervention

Overview

All participants received a 6-month behavioral weight loss intervention, which was empirically based [29-31,33,70-75]. This intervention was fully digital, meaning that no human counseling was provided, which was designed to promote scalability and broader reach. All participants received core components of an overall 10% weight loss goal and weekly behavioral lessons and action plans. Our conceptual model (Figure 2) outlines how we envision the self-monitoring strategies promoting weight loss. Each strategy being tested has an expected mechanism of action (ie, increased engagement in self-monitoring), which, in turn, is expected to enhance self-efficacy and self-regulatory skills, as posited by the Social Cognitive Theory and the Control Theory [27,28]. Together, these psychosocial and engagement mechanisms are expected to promote behavior change (ie, improvement in diet and physical activity), which is anticipated to create a caloric deficit, leading to weight loss. A summary of intervention components is provided in Table 2.

Figure 2. Conceptual model of the weight loss intervention in the Spark trial.

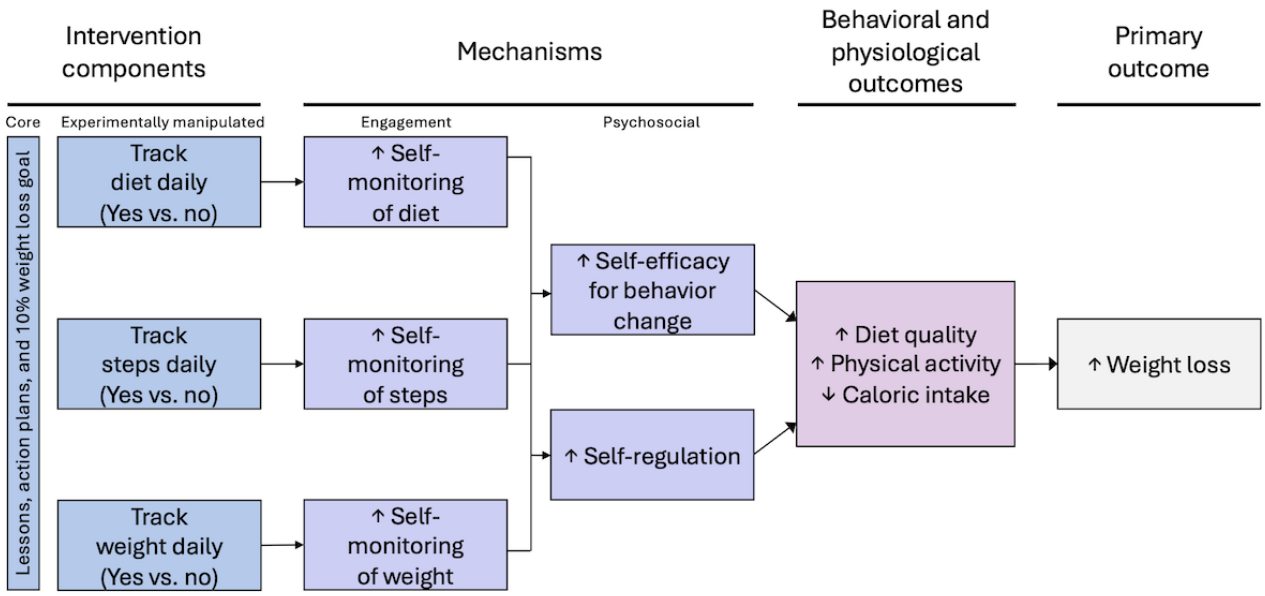

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Table 2. Intervention components and digital modalities in the Spark trial.

Intervention component	Digital modality	Experimental components			
		Core	Track diet	Track steps	Track weight
Daily self-monitoring					
Dietary intake	Fitbit app		✓[a]		
Steps	Activity tracker (Fitbit Inspire 3)			✓	
Body weight	Smart scale (Fitbit Aria Air)				✓
Goals[b] and weekly tailored feedback[c]					
Calories	Emailed progress report		✓		
Steps	Emailed progress report			✓	
Weight loss, weekly	Emailed progress report				✓
Weight loss, overall	Emailed progress report	✓			
Weekly skills training					
Lessons	Emailed PDF handout	✓			
Action plans	Emailed link to Qualtrics survey	✓			

[a]Check mark indicates that the component was received by participants receiving the experimental condition.

[b]On the first day of the intervention, participants were emailed a Goal Sheet.

[c]Every day, participants could also view their progress via the Fitbit app.

Core Components

All participants received a goal of 10% weight loss by 6 months. This goal is consistent with obesity treatment guidelines [3]. Each week, participants received evidence-based skills training materials, including lessons and action plans. These were sent via email and were adapted from gold standard weight loss curriculum [70]. The lessons ere electronic handouts focused on nutrition, physical activity, and behavior change topics (see Table 3). Each lesson had a corresponding action plan (administered via a Qualtrics [Qualtrics, LLC] survey) that incorporated motivational interviewing [76,77] and problem-solving strategies [78]. Specifically, participants were guided through a series of questions to reflect on their current behaviors and areas for change, generate actionable steps related to the week's lesson, reflect on their confidence level in doing so, and brainstorm potential barriers and solutions. Reminders were sent 4 days after the initial email to participants who had not yet completed that week's action plan.

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Table 3. Topics of 19 lessons in the Spark trial.

Lesson number	Week	Topic
1	1	Overview of the Spark weight loss program
2	2	Physical activity: the basics
3	3	Increasing Green Zone Foods
4	4	Navigating the grocery store
5	5	Reading food labels
6	6	Decreasing Red Zone Foods
7	7	Paying attention to portion control
8	8	Reducing added sugar
9	9	Understanding obesity
10	10	Preparing meals at home
11	11	Stepping up to physical activity
12	12	Managing emotional eating
13	14	Planning ahead for eating out
14	16	Staying motivated
15	18	Being aware of environmental cues
16	20	Identifying social cues and social support
17	22	Planning for special occasions
18	24	Taking charge of thoughts
19	26	Maintaining progress

Intervention Components Being Experimentally Manipulated

Overview

Participants received 0-3 possible self-monitoring strategies (dietary intake, steps, and body weight; see Table 1). Each strategy involved daily self-monitoring instructions, a personalized goal [29,30], and tailored feedback [32,79-81]. These 3 self-regulation strategies work in tandem to promote behavior change [29-31]. Feedback was provided each week via a "progress report" in the format of an electronic handout sent via email. It captured progress on goals (described below) as well as on the number of days of self-monitoring each week. A reminder of goals was provided in each progress report. Participants could also view real-time, graphical feedback in the Fitbit app. The app was available on both iPhone and Android platforms and was set up by study staff after randomization (prior to the first day of the intervention) to reflect the participant's self-monitoring domains (dietary intake, steps, body weight) and corresponding goals (calories, steps, weight loss).

Component 1: Self-Monitoring of Dietary Intake

Participants randomized to receive this component were instructed to self-monitor their dietary intake daily via the Fitbit app. The app allowed users to track all foods and beverages consumed using a built-in nutritional database, barcode scanner, or manual entry. To aid in ease of use, recently and frequently eaten items were quickly accessible. The app automatically summed daily caloric intake and allowed users to view graphs of caloric intake over time. Participants assigned to dietary self-monitoring received a daily calorie goal based on their anticipated weekly rate of weight loss [82], calculated using data reported at baseline, including age, sex, weight, and height. For safety, the minimum daily calorie goals that could be assigned were 1200 kcal for women and 1500 kcal for men, based on national guidelines [59].

Component 2: Self-Monitoring of Steps

Participants randomized to receive this component were instructed to self-monitor their step count daily via a wrist-worn activity tracker (the Fitbit Inspire 3). In conjunction with the self-monitoring goal, a daily step count goal was provided that adapted based on weekly progress. The initial week's step goal was based on the participant's baseline scores on the Godin Leisure-Time Exercise Questionnaire (GLTEQ) leisure score index [83,84], with scores ranging from 0 to 13 (interpreted as "insufficiently active") assigned to a goal of 5000 steps per day, scores of 14-23 ("moderately active") assigned to 7000 steps per day, and scores ≥ 24 ("active") assigned to 10,000 steps per day. Starting in the second week of the intervention, an adaptive step goal was given using an empirically tested algorithm [85,86] that was previously adapted and tested in our team's prior pilot study [47]. The algorithm calculated the 60th percentile of the past week's daily step counts, rounded up to the nearest multiple of 50, and assigned that as the subsequent week's daily step goal. For example, a week with daily steps of 5000, 5100, 6000, 6500, 7000, 8200, and 8500 (ranked from lowest to highest) would result in a daily step goal of 6800 for the subsequent week. The new step goal appeared in each week's

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progress report. The Fitbit activity tracker was synced with the Fitbit app to allow participants to view their progress toward the step goal.

Component 3: Self-Monitoring of Weight

Participants randomized to receive this component were instructed to self-monitor their body weight daily via a Bluetooth-enabled smart scale (the Fitbit Aria Air scale). The smart scale was synced with the Fitbit app, providing graphical feedback on weight change. These participants received a weekly weight loss goal of 0.5-2.0 lbs (0.23-0.91 kg) per week, depending on how much weight loss was required at baseline to achieve 10% weight loss at 6 months based on their baseline weight. This goal remained the same throughout the 6-month intervention. It appeared in their Fitbit app as well as in each week's progress report.

Data Collection and Measures

Study assessments were conducted remotely at all 4 time points: baseline, 1 month, 3 months, and 6 months (see Figure 3 [83,84,87-109]). At each assessment, participants received an automated email instructing them to weigh themselves on the smart scale, input values into a web-based weight check-in form, and complete a web-based survey. REDCap was used for survey administration and data management. Reminders to complete these tasks were automatically sent via REDCap. If the surveys were not completed after several days, study staff reached out to participants via text message, email, or phone call. Confidentiality of participant data was maintained by storing data in secure electronic files accessible only to trained study team members, prioritizing using participant ID numbers instead of names, and presenting study data in aggregate.

Figure 3. Assessment schedule in the Spark trial.

Construct		Measure or assessment tool	Time point (months)			
			0	1	3	6
Anthropometric, behavioral, and demographic measures						
	Weight (primary outcome)	Smart scale (Fitbit Aria Air; Ross and Wing, and Pebley et al)	✓	✓	✓	✓
	Height	Self-reported (Cui et al)	✓			
	Caloric intake	ASA24 (Automated Self-Administered 24-hour) dietary recall (Subar et al)	✓			✓
	Diet quality	Healthy Eating Index, (Shams-White et al) measured by ASA24				
	Physical activity	GLTEQ (Godin Leisure-Time Exercise Questionnaire) (Godin, and Godin and Shepard)	✓	✓	✓	✓
	Physical activity guideline adherence	Stanford Leisure-Time Activity Categorical Item (L-Cat; Kiernan et al)	✓		✓	✓
	Step count	Activity tracker (Fitbit Inspire 3)	→	→	→	→
	History of self-monitoring	Self-reported use of self-monitoring of diet, steps, and weight in the month prior to study enrollment (Linde et al)	✓			
	Sociodemographic and clinical characteristics	Self-reported age, race and ethnicity, sex, gender, sexual identity, birth country, marital status, education, employment, income, household size, number children in home, prediabetes, type 2 diabetes, hypertension, and smoking	✓			
Engagement metrics						
	Percentage of days of self-monitoring (diet, steps, and weight)	Digital tools (Fitbit app, Fitbit Inspire 3 activity tracker, Fitbit Aria Air Smart Scale, respectively)	→	→	→	→
	Percentage of action plans completed	Study-designed action plans in Qualtrics	→	→	→	→
Psychosocial measures						
	Health-related quality of life	SF-36 (36-item Short Form Health Survey; Ware)	✓			✓
	Self-efficacy for dietary change	Weight Efficacy Lifestyle Questionnaire Short-Form (WEL-SF; Clark et al)	✓		✓	✓
	Self-efficacy for exercise	Exercise Self-Efficacy Scale (Sallis et al)	✓		✓	✓
	Self-regulation for eating	Three-Factor Eating Questionnaire (TFEQ-R18; Karlsson et al)	✓		✓	✓
	Sleep	Pittsburgh Sleep Quality Index (PSQI; Buysse et al)	✓		✓	✓
	Motivation	Treatment Self-Regulation Questionnaire (TSRQ; Levesque et al)	✓		✓	
	Mastery for self-monitoring	Self-Report Habit Index (SRHI) Automaticity subscale (Verplanken and Orbell, and Gardner et al)		✓		
	Self-efficacy for self-monitoring	Adapted from Bandura's self-efficacy measure (Bandura) to assess self-efficacy for self-monitoring diet, steps, and weight	✓	✓		
	Outcome expectations or realizations	Outcome Expectations (Neff and King)	✓			✓
	Confidence in participating fully	Investigator-designed 1-item measure to capture confidence in participating in weight loss intervention over next 6 months	✓			
	Health literacy	Newest Vital Sign (NVS; Weiss et al, and Weiss) via interview	✓			
	Weight bias internalization	Weight Bias Internalization Scale (WBIS; Durso and Latner)	✓			
	Stress	Perceived Stress Scale (PSS-10; Cohen et al)	✓			
	Negative life events	Occurrence of negative life events over the past 12 months	✓			
	Stages of change	Stages of change questionnaire in weight management (S-Weight; Andrés et al)	✓			
	Social support	Social Support for Diet and Exercise (Sallis et al)	✓			

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Primary Outcome Measure

Consistent with our trial preregistration (NCT05249465), our primary outcome was weight change from baseline to 6 months. Negative values indicate weight loss, whereas positive values indicate weight gain. Weight was obtained using a commercially available smart scale (Fitbit Aria Air).

Participants were asked to follow standardized procedures [110]:

1. Place the scale on a hard, flat surface.
2. Remove all articles of clothing and accessories.
3. Weigh on the scale in the morning before eating or drinking and after emptying their bladder.
4. Step on the scale and record the value.
5. Repeat it 2 more times for a total of 3 weight measurements per time point.

Weights synced from the smart scale to the Fitbit app via Bluetooth. As a preventive measure in case of syncing errors, participants were also asked to input their weight values on a web-based weight check-in form. There is high concordance between weights measured from commercial smart scales and those from scales used in a clinical setting [87,88].

Secondary Outcome Measures

Weight was also assessed at 1 and 3 months via the same protocol described above. BMI will be computed as the weight in kilograms divided by the height in meters squared, and the change in BMI from baseline at 1, 3, and 6 months will be reported.

Caloric intake was assessed via the Automated Self-Administered 24-hour (ASA24) Dietary Assessment Tool (versions 2022 and 2024), which is a free web-based tool developed by the National Cancer Institute [90]. Participants were asked to complete a total of 4 24-hour dietary recalls, including 2 at baseline and 2 at 6 months. At both time points, we requested 1 weekday recall and 1 weekend day recall. We sent up to 4 reminders via email or SMS text message per time point. We will exclude from our analyses any recalls with outliers of daily caloric intake reported as <600 kcal or >4400 kcal for women and <650 kcal or >5700 kcal for men, in accordance with ASA24 recommended procedures based on NHANES (National Health and Nutrition Examination Survey) data [111]. To compute caloric intake at each time point, we will calculate the mean of the weekday recall and the weekend-day recall. If only one recall is available at a given time point, we will use that value. Diet quality will be assessed using the Healthy-Eating Index-2020 [91], calculated from ASA24 data.

Physical activity was assessed via the GLTEQ, a self-report measure that assesses the past week's frequency of different types of exercise (strenuous, moderate, and mild or light) that were engaged in for more than 15 minutes during one's free time [83,84]. Strenuous activities were described as those where one's "heart beats rapidly" (eg, running, jogging, or swimming), moderate activities were described as "not exhausting" (eg, fast walking or tennis), and mild activities were described as requiring "minimal effort" (eg, yoga or easy walking). A leisure score index will be created using the following formula: (strenuous × 9) + (moderate × 5) + (light × 3), with higher scores indicating more frequent exercise. To assess weekly moderate-to-vigorous physical activity, a composite score will be created using the same procedures but excluding the light activities. From this moderate-to-vigorous physical activity score index, scores of ≥24 units will be interpreted as "active," and scores <24 will be considered "insufficiently active" [112].

We also objectively assessed step count using the Fitbit Inspire 3 activity tracker for those participants assigned to track steps (conditions 3, 4, 7, and 8). In our analyses, we will operationalize the week 1 step count as the average of the first 7 days of the intervention and the 6-month step count as the average of the last 7 days (week 26), so long as ≥3 valid days per week are reported [113]. Fitbit activity trackers have shown acceptable to excellent validity for step measurements [114].

Health-related quality of life was assessed using the 36-item Short Form Health Survey (SF-36) [94], with scores provided for both the physical and mental components. It captures 8 domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health.

Self-monitoring engagement was assessed objectively for all 182 days (6 months) of the intervention using data collected from the Fitbit digital tools. Data were pulled from the Fitbit app and retrieved via Fitabase (Small Steps Lab, LLC), a software data management platform. In our analyses, engagement will be operationalized as the percentage of days in the intervention that participants self-monitored dietary intake, steps, and weight (reported separately for each domain). For self-monitoring of diet, we will count days as valid if they have ≥800 kcal recorded, which is a threshold that best predicted weight loss [37] and is commonly used for determining minimum adherence [36,115,116]. For self-monitoring of steps, we will count days as valid only if ≥1000 steps are recorded. This minimum threshold is used to minimize the possibility of inaccurately counting days with high amounts of nonwear time [117]. We also assessed engagement in other intervention components, including the percentage of action plans completed, which was objectively assessed via Qualtrics, with 100% indicating completion of all 19 action plans. Using self-report at 6 months, we assessed which of the 19 lessons were read and the frequency with which progress reports were reviewed, with options of "weekly," "less than 1 time per week," "less than 1 time per month," and "never."

Putative moderators were assessed via self-report survey measures administered at baseline, including demographic (eg, sex, age, and education), psychosocial (eg, stress and self-efficacy), behavioral (eg, pretreatment caloric intake and physical activity), and clinical (eg, diabetes diagnosis) characteristics. A health literacy questionnaire, the Newest Vital Sign, was administered orally by study staff at the baseline visit [104]. In exploratory aims, change in psychosocial outcomes were assessed via self-report survey measures over time. At the 1-month assessment, 2 measures (self-efficacy for self-monitoring and mastery for self-monitoring) specifically asked about only the domains that a given participant was instructed to self-monitor (ie, diet, steps, and weight).

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Adverse events were documented via a REDCap report and reviewed by our Independent Safety Officer. If serious adverse events occurred, they were reported promptly to the Institutional Review Board and the National Institutes of Health.

Acceptability data were collected via survey to assess perceived helpfulness and perceived difficulty of intervention components.

Outcomes of the Embedded Experiment

Our embedded experiment tests whether implementing a self-directed web-based orientation session improves the Spark trial's 6-month retention rate (the primary outcome of embedded experiment). Retention is operationalized as the percentage of participants who report weight at 6 months out of total participants in the Spark trial (N=176). We will also examine the orientation session's impact on the secondary outcomes listed in Textbox 2.

Textbox 2. Secondary outcomes in the embedded experiment

- 1- and 3-month retention in the Spark trial.
- Weight change from baseline to 6 months.
- Proportion of participants achieving ≥5% weight loss at 6 months from baseline.
- Engagement in self-monitoring over the 6-month intervention.
- Proportion of the 391 participants in the embedded experiment who enrolled in the Spark trial.
- Whether orientation sessions affect characteristics of the sample who enroll in Spark.
- Perceived value of retention.
- Knowledge of the importance of retention.
- Completion rates of the orientation session.

Qualitative Interviews

After the end of the intervention, a subset of participants were invited to participate in a one-to-one semistructured qualitative interview, held via Zoom videoconference. Interviews lasted 30-45 minutes. Using an interview guide, trained research team members asked participants about factors that impacted self-monitoring engagement, perceived helpfulness, and satisfaction of the intervention components (eg, goals, self-monitoring, lessons, action plans, and progress reports), contributors and barriers to weight loss, perceived changes in self-efficacy, and to what extent self-monitoring contributed to weight loss. To contextualize and tailor their questions, interviewers integrated each participant's engagement and weight loss outcomes as well as their 6-month acceptability data. Example questions included "You tracked your food [*x%*] of days over the 6-month Spark program. What factors contributed to tracking that amount?" and "You rated tracking your food as ["not at all" up to "very"] helpful. What contributed to feeling this way?"

Interviews were recorded and then transcribed verbatim using a professional transcription service. Memos were used by interviewers to reflect and record emerging themes. Data saturation was achieved once no new themes emerged from the interviews, at which point we stopped recruitment for the interviews. Transcripts will be coded using an iterative team-based approach to reduce potential bias. A cloud-based software platform (Dedoose; SocioCultural Research Consultants, LLC) will be used to facilitate the coding process. A codebook was created both deductively (derived from the PI's experience and from the research questions) and inductively (derived from an initial set of transcripts). Data will be analyzed using thematic analysis. A mixed methods approach will be used to integrate the data [118,119]. providing insight into how self-monitoring engagement and weight loss are or are not related, and if so, why (ie, mechanisms). Joint display tables will be used to depict how the qualitative data provide context to the quantitative outcomes from the trial [120]. The design and reporting of the qualitative study will adhere to the COREQ (Consolidated Criteria for Reporting Qualitative Research) checklist [121].

Statistical Analysis

Unlike an RCT that compares the means of each arm to one another (1 vs 2 vs 3, and so on), in a factorial trial, the means across combinations of conditions are used to test main effects of components and their interactions [122]. In our 2^3 full factorial trial (ie, a 2 × 2 × 2 with 8 conditions), we are testing whether 3 self-monitoring strategies, alone or in combination, improve weight loss at 6 months (our primary time point). To estimate the main effect of each self-monitoring component on weight change, we will examine the difference between the mean of conditions where the target component is present and the mean of conditions where the target component is absent [54]. For example, for "Tracking Diet," the mean of experimental conditions 5, 6, 7, and 8 (ie, the component is present) will be compared to the mean of conditions 1, 2, 3, and 4 (ie, the component is absent; see Table 1). We will use effect coding (ie, –1 when a component is absent and 1 when a component is present) for analyzing the main effects and interactions of the components, as recommended for factorial designs [54]. Thus, a main effect is interpreted as the effect of a factor averaged across all other factors. Since each main effect and interaction is based on the entire sample, the factorial design is considered efficient and economical [123].

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Sample Size and Statistical Power

Using a power calculation, we determined that a sample size of 176 participants would be required in our factorial trial to detect a minimum clinically important difference of 2.4 kg at 6 months, which is associated with improvements in cardiometabolic risk factors [59]. We assumed an SD of 4.5 kg, based on prior 6-month weight loss outcomes in digital interventions [49,124,125]. Thus, we sought to detect a main effect or interaction effect of Cohen d=0.53. Specifically, assuming 80% power, an α of 5% in a 2-sided test, and 35% attrition at 6 months (a conservative estimate based on prior trials of fully digital weight loss interventions [22,36,50,126]), a sample size of 172 is needed. To obtain an equal number of participants in each treatment condition, we increased the sample size to 176 total participants (22 per condition). Allowing for an equal number of participants per condition permits the tests of the main effects and interactions to be uncorrelated. Even if unequal sample size across conditions occurs due to differential dropout resulting in minor imbalance, the correlations between effects should be small [122]. This power analysis was computed using the FactorialPowerPlan SAS Macro (version 1.0) [127].

Our trial uses a 2^3 factorial design since it has 3 factors, each with 2 levels (Yes and No). In these types of 2^k factorial trial—those with k number of factors—all else being equal, the power for detecting a β-weight corresponding to an interaction effect is the same as that for detecting a β-weight corresponding to a main effect when using effect coding to represent the levels of the factors [54]. Thus, no additional participants are needed to detect interactions in 2^k factorial trials.

Analytic Plan for Primary Outcome

Our primary outcome is weight change, in kilograms, from baseline to 6 months. Using intent-to-treat principles, we will use linear mixed models to examine the main effects of the 3 self-monitoring components and all of their interactions on mean weight change at each follow-up time point. This model will include fixed effects for the following: time point (1, 3, or 6 months), sex assigned at birth (ie, the stratification variable), self-monitoring component, pairwise interactions of each component, and the time-by-component and time-by-pairwise interactions. We will fit an unstructured covariance matrix to take into account the correlation of weight measures within a person across time. We will use maximum likelihood to estimate the model parameters, allowing for missingness at random. Data will also be disaggregated by sex in exploratory analyses.

Analytic Plan for Other Outcomes

Secondary Outcomes

Similar linear mixed models will be used to assess the main effects and interactions on the secondary outcomes, including BMI, caloric intake, diet quality, physical activity, and health-related quality of life (see Figure 3). To assess differences in achieving clinically significant weight loss (≥5% from baseline) [59] between the “present” versus “absent” levels of each factor, we will fit a log-Poisson GEE (generalized estimating equations) model [128] with robust SEs [129,130] and an unstructured working correlation matrix to take into account repeated measures across time. From these models, we will report risk ratios comparing levels of intervention components and their interactions. As recommended by the CONSORT (Consolidated Standards Of Reporting Trials) statement for randomized trials [131], we will report both absolute and relative effects of these models.

Moderators

We will use signal detection analysis [132] to assess whether there are any moderators or predictors of ≥5% weight loss at 6 months and whether this varies by self-monitoring strategy. Signal detection analysis is a nonparametric recursive partitioning technique that can identify patient subgroups that demonstrate a better or worse response to an intervention. In this analysis, we will examine demographic, psychosocial, behavioral, and clinical characteristics, all assessed at baseline. These exploratory analyses help generate hypotheses that can inform which interventions are most suitable for which individuals [133]. We will use publicly available ROC5 program software (Stanford University) to conduct this analysis [134].

Engagement and Its Association with Weight Loss

We will first assess patterns of self-monitoring engagement over 6 months using descriptive statistics (medians and IQR if non-normally distributed, as is expected [36]) and via graphical presentation. Then, we will use Spearman rank correlation coefficients (if engagement data are non-normally distributed) and linear regression models to examine the relation between self-monitoring engagement and weight change at 6 months. Using descriptive statistics, we will also assess completion of the other intervention components (action plans completed, lessons read, and progress reports reviewed) and follow similar procedures to examine the relation between engagement in each of these components and weight change at 6 months.

Characterizing the Sample

Descriptive statistics will be used to describe baseline characteristics. To determine whether any baseline variables differ by retention status (completers vs noncompleters), we will use Pearson chi-square tests for categorical variables, ANOVA for continuous variables, and Fisher exact tests for small cell counts.

Analytic Plan for the Embedded Experiment

We will assess differences in 6-month trial retention between participants who were randomized to receive versus not receive the self-directed orientation. We will fit a log-Poisson GEE model with robust SEs [129,130] and an unstructured working correlation matrix to take into account repeated measures across time. As is common in embedded experiments, sample size is constrained by the number of participants in the parent trial (the Spark weight loss trial) [66]. A power calculation was run to determine the effect size that could be detected assuming a sample size of 176, 80% power, an α of 5% in a 2-sided test, and retention of 65% in the arm not receiving the orientation (assuming 35% dropout). We would have 80% power to detect a retention rate of 83% in the arm receiving the orientation.

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Data Monitoring

The PI was responsible for regular monitoring of the data, in accordance with the Data Safety and Monitoring Plan. Issues of safety were reviewed with the independent safety monitor, who was not involved in the study's design or conduct. If they occurred, major protocol deviations were reviewed by all investigators. The PI and study statistician will have access to the final dataset.

Decision Criteria for Selecting Components for an Optimized Intervention

Using the MOST framework for intervention optimization, this study seeks to balance intervention effectiveness (ie, weight loss) against efficiency (ie, minimizing participant burden). Thus, our "Optimization Objective" is to create an intervention made up of all active components without any inactive components. To decide which self-monitoring strategies should comprise our newly optimized intervention, we will use the component screening approach described by Collins [54], which iteratively sorts through the results of the factorial trial. A minimum mean weight loss threshold of 2.1 (SD 4.5) kg at 6 months will be used to decide whether to consider including any self-monitoring components alone or in combination. This magnitude equates to an α of .10. We selected a higher alpha level during this decision-making phase when constructing the newly optimized intervention because we want to lower the chance of mistakenly discarding an intervention component that is actually beneficial (ie, reduce the type 2 error rate). This rationale reflects the "decision-priority perspective" of MOST. In contrast, the "conclusion-priority perspective" is focused on drawing scientific conclusions from a trial using well-established conventions of α level $\leq$.05 [54,55].

Using the component screening approach, first, the main effects of each self-monitoring component on 6-month weight change will be determined. The self-monitoring strategies that meet or exceed this threshold will be tentatively included in the "screened-in" set while those not meeting this threshold will be included in the "screened-out" set. Then, lower-level interactions will be examined, first among any components in the screened-in set, followed by those in the screened-out set. Next, we will examine the interaction among all 3 self-monitoring components. For interactions meeting or exceeding the 2.1 kg threshold of weight loss, their components will be considered for inclusion in the screened-in set (even if the components, by themselves, did not demonstrate main effects). To aid in interpretation of interactions, we will plot the predicted marginal means. This visualization will provide information on whether synergistic or antagonistic interactions exist. Results of this trial will inform development of a newly optimized intervention that can be tested in a subsequent evaluation-RCT. If no self-monitoring strategies, alone or in combination, exceed our 2.1 kg weight loss threshold, then we will return to the preparation phase of the MOST framework to refine the conceptual model, brainstorm and pilot test new candidate components, adapt existing components, or strengthen the core digital health intervention.

Ethical Considerations

All study procedures and human subjects research ethics were approved by the Stanford University Institutional Review Board (protocol number 64716; approval date: March 28, 2022). The participants provided written informed consent via electronic signature before enrollment. They were informed that participation is voluntary, and they could withdraw or opt out at any time. The consent form is available on the trial registry [57]. Participants were compensated a maximum of US $60 (via electronic gift cards) for their completion of assessments, as follows: US $20 at 3 months, US $30 at 6 months, and an additional US $10 for completion of all 4 dietary recalls (2 each at baseline and 6 months). Those who participated in the qualitative interviews received an additional US $25. Deidentified data will be used in study analyses and in disseminated materials.

Results

The study received funding in April 2022 (see Multimedia Appendix 2). The first participant was enrolled (ie, consented) in the Spark trial on September 22, 2023. Randomization to the factorial trial occurred between October 6, 2023 and November 26, 2024. We recruited 176 participants. Data collection was completed June 23, 2025. Upon analysis of trial data, results will be disseminated to study participants via an optional webinar. They will also be shared through presentations at national conferences, via publication in peer-reviewed journals, and posted on ClinicalTrials.gov. Data analysis is ongoing and results are expected to be published in early 2026.

Discussion

Scientific Contribution

The Spark trial will provide the first set of evidence on optimizing self-monitoring in a weight loss intervention for adults with overweight or obesity. It is common for behavioral obesity treatment to include self-monitoring of diet, physical activity, and body weight, yet it is not actually known whether all 3 of these components are necessary for weight loss or whether any are ineffective, or even detrimental. Removing any inactive components would help to minimize patient burden and effort. Using an intervention optimization framework (MOST) enables our team to build an effective and efficient fully digital weight loss intervention, which is much needed given the high prevalence of obesity, its detrimental health consequences, and the limited scalability of existing weight loss interventions. Further, to our knowledge, our trial will be the first to empirically test the impact of a self-directed web-based orientation session on trial retention. If deemed effective, this orientation session may be an affordable, brief, and scalable strategy that could be easily adapted and embedded in behavioral intervention research to enhance the validity of trial outcomes.

Limitations

Several limitations exist. First, while our trial's primary outcome is weight loss, it is possible that a component may have limited impact on weight but still improve diet quality, physical activity, or health-related quality of life. The MOST framework provides

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flexibility in interpreting the data in different ways depending on the Optimization Objective of interest. Thus, the intervention could be optimized for a different outcome, which would involve simply reinterpreting the trial's existing data in light of that outcome. Second, due to funding constraints, we are unable to collect data beyond the 6-month time point, thus precluding the examination of long-term weight loss maintenance, which could be a focus of future research. Third, it is unknown whether results would generalize to digital weight loss interventions that include direct human counseling. However, by design, our trial focused on fully digital interventions (without such counseling) since they offer an opportunity to reach broad populations, including those with limited access to high-quality obesity treatment, and to deliver a weight loss program in a more scalable manner. Fourth, due to the behavioral focus on the intervention, participants are not masked to factorial condition, which could introduce bias. We aimed to establish clinical equipoise during our discussion of the various self-monitoring components at the baseline visit. Fifth, due to technical limitations, the Fitbit app is not able to reflect participants' adaptive step goal each week. Therefore, the step goal feedback provided by the app likely differed than the feedback provided via our weekly progress reports. Sixth, our embedded experiment that is testing the effect of a self-directed orientation session may be underpowered to detect small differences in retention due to sample size constraints of the Spark trial. This is an inherent limitation of embedded experiments [67], yet given their simpler and less resource-intensive nature, they are designed to be replicated across multiple clinical trials to build up the evidence base on potential retention-promoting strategies. These data can then be evaluated together in meta-analyses.

Implications for Research and Clinical Care

From a research standpoint, we hope that our findings will shed light on which self-monitoring strategies should be included in behavioral obesity treatments. Considering MOST's continual optimization principle, interventions should be continuously improved upon in an iterative fashion to enhance outcomes. Future research could seek to optimize other components of fully digital interventions, such as type of feedback, skills training materials, and gamification approaches, and could test artificial intelligence–driven strategies for tailoring intervention content based on participant preferences, needs, and treatment response. From a clinical standpoint, we hope this work will inform clinicians who provide obesity counseling as to which self-monitoring strategies they should be recommending to their patients who are seeking to lose weight in a standalone manner.

Conclusions

The Spark trial leverages an intervention optimization framework to understand whether self-monitoring diet, steps, or body weight maximizes weight loss, alone or in combination, which addresses a critical research gap. Ultimately, building a fully digital intervention comprised of only clinically meaningful self-monitoring strategies has potential for broad public health impact in providing scalable, potent, low burden, and far-reaching weight loss interventions. If the optimized intervention is effective, it could serve as a first-line weight loss treatment for adults with overweight or obesity.

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Data Availability

Data sharing is not applicable to this article as no datasets were analyzed yet during this study.

Authors' Contributions

Conceptualization: MLP (lead), ACK (supporting), LGR (supporting), GGB (supporting)
Data curation: MLP
Funding acquisition: MLP, ACK, LGR, GGB
Investigation: MLP, ABZ, PST, PCC, KAC, AWL, TSK
Methodology: MLP, ACK, LGR, GGB, LMC, JAG

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Project administration: MLP, ABZ, PST
Writing–original draft: MLP
Writing–review & editing: MLP (lead), ACK (supporting), LGR (supporting), GGB (supporting), LMC (supporting), JAG (supporting), ABZ (supporting), PST (supporting), PCC (supporting), KAC (supporting), AWL (supporting), TSK (supporting)

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT 2025 checklist for the Spark trial.
[PDF File (Adobe PDF File), 132 KB - resprot_v14i1e75629_app1.pdf]

Multimedia Appendix 2
Peer review report from the Digestive Diseases and Nutrition C Study Section Digestive Diseases and Nutrition DDK-C Subcommittee (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 121 KB - resprot_v14i1e75629_app2.pdf]

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Abbreviations

ASA24: Automated Self-Administered 24-hour
CONSORT: Consolidated Standards Of Reporting Trials
COREQ: Consolidated Criteria for Reporting Qualitative Research
GEE: generalized estimating equation
GLTEQ: Godin Leisure-Time Exercise Questionnaire
MOST: Multiphase Optimization Strategy
NHANES: National Health and Nutrition Examination Survey
PAR-Q+: Physical Activity Readiness Questionnaire for Everyone
PI: principal investigator
RCT: randomized clinical trial
REDCap: Research Electronic Data Capture
SF-36: 36-item Short Form Health Survey
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SWAT: Study Within a Trial

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Protocol

Identifying and Reducing Stigmatizing Language in Home Health Care With a Natural Language Processing–Based System (ENGAGE): Protocol for a Mixed Methods Study

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Abstract

Background: Stigmatizing language is common in clinical notes and can adversely affect the quality of patient care. Natural language processing (NLP) is a promising technology for identifying such language across large volumes of clinical notes in electronic health records.

Objective: This study proposes an NLP-driven reduce stigmatizing language (ENGAGE) system to automatically identify and replace stigmatizing language.

Methods: Using a mixed methods study, we will extract electronic health record data for patients admitted to 2 large, diverse home health care (HHC) organizations between January 2019 and December 2021. We propose the following 4 aims: aim 1 is to refine the ontology of stigmatizing language in HHC by (1) interviewing a diverse sample of HHC nurses and patients to identify terms to avoid and (2) analyzing clinical notes from various regions in the United States to categorize stigmatizing language. Aim 2 is to determine the best NLP approach for accurately identifying stigmatizing language by training algorithms and comparing their performance to human annotations. Aim 3 is to analyze the prevalence of stigmatizing language based on patients' race and ethnicity using adjusted statistical analyses of a sample of approximately half a million HHC patients (34% racial and ethnic minority groups). Aim 4 is to develop the NLP-driven ENGAGE system by (1) testing NLP methods (rule based; "delete, retrieve, and generate"; and transformers) for suggesting alternative wording and (2) designing and refining the user interface for clinical trial preparation.

Results: We received funding from the National Institute on Minority Health and Health Disparities in September 2023. Recruitment began in May 2024, and as of March 2025, interviews have been completed for 9 enrolled participants. We anticipate completing all study aims by April 2027.

Conclusions: This study will leverage extensive data sources to examine stigmatizing language in HHC settings and contribute to the development of systems aimed at effectively reducing the use of such language among HHC nurses.

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KEYWORDS

natural language processing; racial bias; stigmatizing language; home health care; artificial intelligence; AI

Introduction

Home health care (HHC) is one of the fastest-growing outpatient settings in the United States, where 200,000 nurses provide care for more than 5 million patients annually [1,2]. Although the quality of nursing care is affected by numerous factors (eg, structural resources, levels of education, and patient-per-nurse ratios) [3-5], nurses' biases toward their patients influence the delivery of high-quality care [6]. Implicit bias is the negative inclination of one group and its members relative to others unconsciously or unintentionally [6]. Recent literature reviews [7,8] found widespread, implicit biases among nurses toward their patients. Specifically, a recent review of 215 studies [9] found that nurses frequently display biases based on patients' race or ethnicity, influencing treatment decisions and impacting patient adherence and outcomes [10,11].

Racial biases can be propagated via the language used in electronic health record (EHR) documentation [12-15]. Research has shown that stigmatizing language used in clinical notes can harm patient care [12-15]. Patients for whom stigmatizing language was used had HHC visits that were 24 minutes shorter than those whose records were without such language (average visit length 46 vs 70 minutes, respectively) [16,17]. This is concerning because shorter HHC visits are associated with poor outcomes (eg, higher risk of hospitalizations) [10-12,16-22]. A recent study found that 10% of 22,959 patients who reviewed their clinical notes felt judged or offended by stigmatizing language [23]. This is crucial because, as of April 2021, health care organizations, including HHC, must share EHR data with patients under the 21st Century Cures Act's "Information Blocking" Rule [24]. More than 80% of HHC agencies have EHRs, and reducing stigmatizing language use can decrease racial biases and improve the quality of care and patient outcomes [25].

When applied appropriately, technology can help identify and reduce biases in health care [26]. One promising technology is natural language processing (NLP), a branch of artificial intelligence that analyzes free-text data, such as clinical notes in EHRs, to extract meaningful insights [27]. NLP has been used to detect health care provider biases by identifying stigmatizing language in clinical notes [28]. Common NLP techniques include rule-based methods such as NimbleMiner [29], which identify specific stigmatizing terms [30,31], as well as machine learning and deep learning models such as the clinical bidirectional encoder representations from transformers (BERT) model, which can detect more subtle, context-dependent patterns in the language [32]. In our previous research, we applied NimbleMiner to identify stigmatizing language in clinical notes and found that 38% of notes contained such language. In addition, notes about Black patients had up to 50% higher odds of containing stigmatizing language than those about White patients [30].

Given the high prevalence of stigmatizing language, what it represents in relation to bias, and its negative impact on patient care, this study proposes an NLP-driven reduce stigmatizing language (ENGAGE) system to automatically identify and address bias and replace stigmatizing language in clinical notes.

Methods

Ethical Considerations

This research was approved by Columbia University's institutional review board (AAAU7957). Eligible and willing participants will provide informed consent via Qualtrics (Qualtrics International Inc) or verbal consent (patient only). Participants can choose to opt out at any point throughout the study. All data will be deidentified to protect participant privacy. The participants will be compensated US $50 in the form of an Amazon electronic gift card for a one-time interview. Nurses serving as content experts will return for a second interview and will receive a US $100 Amazon electronic gift card. Compensation transparency is ensured through recruitment flyers and consent forms, both of which contain the compensation type and amount.

Study Design

We proposed 4 corresponding study aims that followed a mixed methods study design to achieve study goals (Figure 1). This protocol is reported in accordance with the Standards for Reporting Implementation Studies statement [33], except for the Results section, which is reported according to *JMIR*'s requirements for protocols. In aim 1, we will adapt the ontology of stigmatizing language for HHC via interviews with patients and nurses and qualitative analysis of clinical notes. In aim 2, we will develop and compare several NLP approaches to automatically identify stigmatizing language in clinical notes. In aim 3, we will compare the prevalence of stigmatizing language by patients' race and ethnicity. In aim 4, we will develop an NLP-driven ENGAGE system to reduce the use of stigmatizing language in clinical notes. This 4-aim study design is informed by the data, information, knowledge, and wisdom conceptual framework [34,35]. This framework suggests that discrete data points generate meaningful information that can be turned into knowledge. Wisdom is the appropriate use of knowledge to manage and solve problems. We will identify stigmatizing language from interviews and clinical notes (data: aims 1 and 2), categorize it (information: aims 1 and 2), analyze its associations (knowledge: aim 3), and apply the findings to develop the intervention (wisdom: aim 4; Figure 1). This study aligns with the National Institute on Minority Health and Health Disparities' framework, focusing on health care and interpersonal and individual levels in HHC nursing [36].

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Figure 1. Reduce stigmatizing language (ENGAGE) study design. HHC: home health care; NLP: natural language processing.

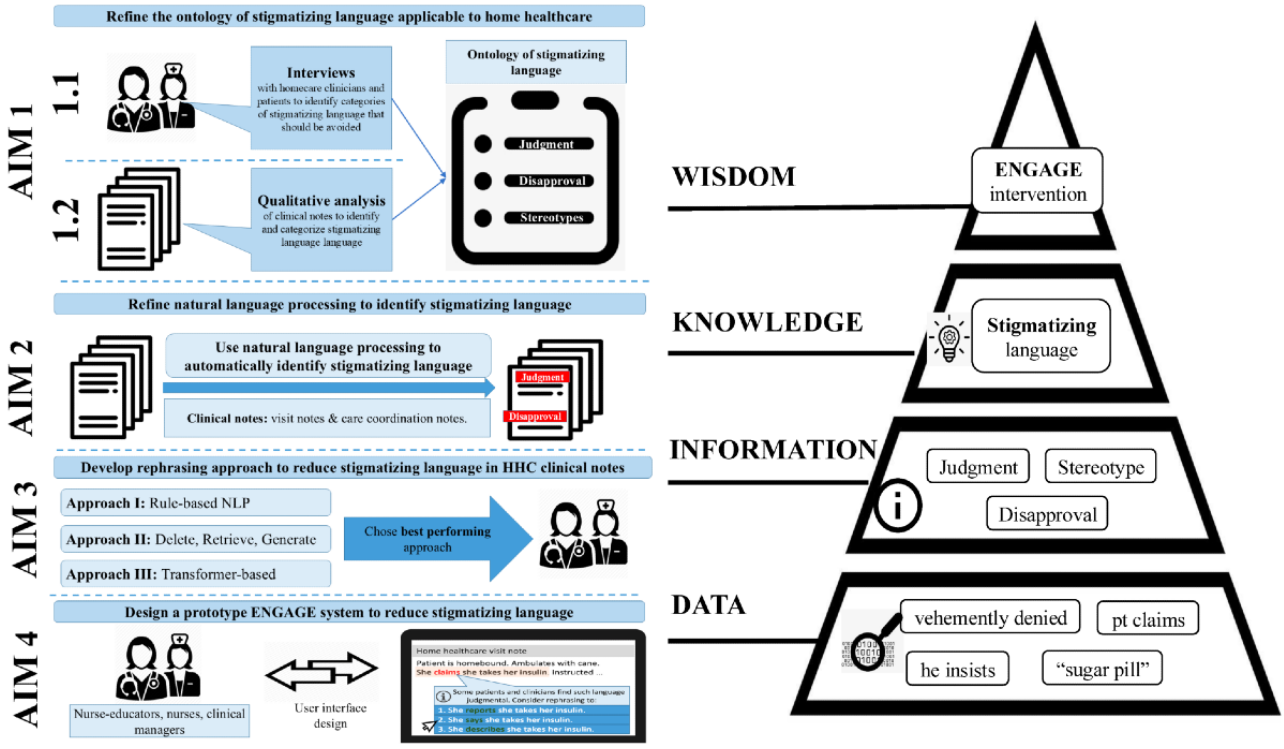

Study Setting and Data Sources

This study will be conducted within 2 diverse, large HHC organizations: one is a large not-for-profit HHC agency serving patients in New York City and its surrounding suburbs. The other is a national HHC provider network with more than 300 HHC agencies in more than 30 states in the United States. EHR data will be extracted for patients admitted to HHC between January 1, 2019, and December 31, 2021 (3 years). We expect to include approximately half a million unique patients. The expected patient demographics will be 67% White (non-Hispanic), 15% Black (non-Hispanic), 11% Hispanic, 2.5% Asian, and 4.5% other (including American Indian, Alaska Native, Native Hawaiian, and Pacific Islander). This should yield over 16 million clinical notes, accounting for the involvement of over 10,000 HHC nurses.

The following study variables will be extracted from the EHR (Table 1): (1) the Outcome and Assessment Information Set (OASIS)—OASIS is a comprehensive, Centers for Medicare & Medicaid Services–mandated standardized assessment tool designed to collect nearly 100 items related to a recipient's functional status, clinical status, and service needs during an HHC episode [37]—(2) administrative data: human resources data will be used to extract HHC nurse characteristics; and (3) clinical notes: the stigmatizing languages and their classifications will be identified at the clinical notes level in aim 2.

Table 1. Study variables and sources.

Variable categories	Variables	Data source
Sociodemographics	Age at start of care, race, ethnicity, sex, and geographic location	OASIS[a]
Physiological measures	Height, weight, and BMI	OASIS
Functional status	Activities of daily living and disability	OASIS
Cognitive status	Cognitive impairment	OASIS
Clinical information	Diagnosis and comorbid conditions	OASIS
Presence of stigmatizing language	Categories of stigmatizing language extracted via NLP[b]	Clinical notes

[a]OASIS: Outcome and Assessment Information Set.

[b]NLP: natural language processing.

Participant Interviews and Recruitment

We will conduct interviews with a sufficient maximum variation sample of 35 HHC nurses and 35 patients in aim 1 [38]. For nurses, we aim to create a diverse sample stratified by race and ethnicity, years of experience (<5 years vs ≥5 years), and geographic location [39-41]. HHC nurses will be enrolled if they are currently being employed by the participating HHC organizations. About 15 (43%) of those nurses will serve as content experts and partake in an additional interview in aim 4.

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For patients, we will get a sufficient maximum variation sample stratified by race and ethnicity, sex, and geographic location. Patients will be included if they are aged ≥18 years and recently admitted to or discharged from HHC within the last 3 years.

Nurses will be recruited through email advertisements and presentations at nursing team meetings. Patients will be recruited through direct outreach (ie, phone calls) based on records of recently treated and discharged patients.

Study Procedures

Aim 1: Identify the Ontology of Stigmatizing Language

On the basis of our previous work [29,42-44], the ontology of stigmatizing language will be refined and expanded from the interviews with HHC patients and nurses and a review of clinical notes.

Participant Interview

To generate a sufficient maximum variation sample, we plan on conducting about 30 to 35 interviews for HHC nurses and patients separately. Interviews will continue until data saturation is reached, lasting up to 2 hours and conducted by phone, Zoom (Zoom Video Communications, Inc), or in person (for patients only). An interview guide with semistructured and open-ended questions will be used. These guides were developed to facilitate discussions with nurses (Multimedia Appendix 1) and patients (Multimedia Appendix 2), aiming to refine the categories of stigmatizing language to avoid. Example questions include the following: "Have you noticed negative, discriminatory, or stigmatizing language used by HHC clinicians? Please explain." "We found expressions like 'claims smoking cessation, but ashtray still noted on nightstand' in the HHC clinical notes. Would you consider this judgmental or offensive? Should this language be changed or eliminated?" All interviews will be audio-recorded for analysis.

Clinical Notes

A subset of clinical note samples will be selected to identify stigma language in clinical notes. We will aim for a maximum variation sample of clinical notes. This sample will be stratified by (1) geographically diverse HHC agencies (Northeastern, Midwestern, and Southern United States and the New York City boroughs); (2) urban, suburban, and rural areas; (3) diverse patient populations; and (4) HHC nurses of varying sex, race, and ethnicity, years of experience, educational levels, and geographic locations. On the basis of our pilot work [29,42-44], we estimate that 10% to 20% of clinical notes will contain stigmatizing language. To capture linguistic patterns fully, we will initially analyze 10,000 clinical notes, with additional batches of 2500 notes if necessary to reach knowledge saturation [45]. We will annotate each clinical note for stigmatizing language and its categories (eg, "Stereotyping by race or social class" or "Portraying the patient as difficult") [13]. Using a hybrid, qualitative approach of inductive and deductive coding [46], we will begin with the 5 categories from our previous study and refine or add categories as needed through discussions with annotators, the study team, and the Stakeholders Engagement Board (SEB; an interdisciplinary team of experts). Four annotators will review each note: 2 experienced HHC nurses (1 White and 1 from a minority group), a social worker with racial bias detection expertise, and a minority patient who received HHC services. Annotations will be done using Amazon Web Services SageMaker Ground Truth [47], with each annotator independently marking instances of stigmatizing language. Results will be merged and reviewed. Interrater reliability will be tracked using κ statistics, aiming for strong agreement (>0.8) [48].

Aim 2: Determine the Optimal NLP Approach for Stigmatizing Language Identification

We will evaluate and compare 3 NLP approaches using SageMaker Ground Truth. The first approach, key-term discovery with NimbleMiner [29,43,49,50], will build on previous work by creating vocabularies of synonyms and excluding irrelevant terms, followed by machine learning classification using models such as XGBoost, random forest, support vector machines, and long short-term memory neural networks, with predictions reviewed until saturation. The second approach involves fine-tuning a publicly available clinical BERT model [51,52] trained on a large set of clinical notes [53] using our HHC notes to improve language representation. The third NLP approach includes 2 aims: feature generation and model training. Feature generation will use techniques such as one-hot encoding; term frequency–inverse document frequency; word embedding techniques (ie, Skip-Gram [54], Glove [55], and FastText [56]); and dynamic (conceptualized) word embedding techniques (ie, ELMO [57] and clinical BERT [52]). During model training, machine learning classifiers will be trained and validated in the model training to identify stigmatizing language in clinical notes. To enable this comparison, the annotated sample of approximately 10,000 clinical notes from aim 1 will be split into training (60%), validation (10%), and testing (30%) sets, stratified by stigmatizing language categories.

Aim 3: Compare the Prevalence of Stigmatizing Language by Patients' Race and Ethnicity

On the basis of our pilot work in hospital and ambulatory settings and HHC, we hypothesize that 2 or more stigmatizing language categories (eg, questioning patient credibility [ie, judgment]; stereotyping by race or social class) will be associated with the patient's race and ethnicity. We define race and ethnicity based on the categories available in the federally mandated HHC assessment data (OASIS) [36] that we will use in the study, as follows: non-Hispanic Black, Hispanic, Asian or Pacific Islander, American Indian or Alaska Native, and non-Hispanic White. The data available in federally mandated OASIS are 99% complete (ie, no missing data) based on our 2 decades of experience working with these data. Potential covariates will be identified from the data resources of OASIS and administrative data.

Aim 4: Develop an NLP-Driven ENGAGE System

To enable the development of an NLP-driven ENGAGE system, we will first identify the best method for rephrasing stigmatizing language without altering meaning. Three approaches will be compared: a rule-based method using synonym lists reviewed by annotators; a "delete, retrieve, and generate" method that modifies stigmatizing attributes [58]; and transformer-based

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models (eg, BERT [51], generative pretrained transformers 3 [59], and text-to-text transfer transformer [60]). Two datasets will be created and used for this comparison, including a training set of 2500 clinical notes with stigmatizing language (500 examples per category) and a test set of 4000 sentences. In total, 5 reviewers will rewrite the sentences and reach a consensus through Delphi rounds, generating sentence pairs for training and testing. For this task, we define NLP performance as (1) the system's ability to replace stigmatizing language with nonstigmatizing neutral language and (2) the system's ability not to alter the meaning of the source sentence significantly. The identified NLP approach with the best performance will help paraphrase stigmatizing language without significantly changing the original text's meaning in the NLP-driven ENGAGE system.

Next, the best NLP approach will be incorporated into the NLP-driven ENGAGE system. Iterative user-centered design methodologies will be used (Figure 2) to develop the NLP-driven ENGAGE system based on agile software development approaches [61,62] that were implemented by our research team in numerous previous studies [63-67]. We will start with an initial storyboard prototype (prototype 1) and refine it through team discussions, leading to several low-fidelity prototypes (prototype 2). These will be reviewed with a subset of HHC nurses from aim 1 and SEB, resulting in a high-fidelity web-based prototype (prototype 3) built with the Shiny visualization package in R (R Foundation for Statistical Computing). This iterative process will continue until a final user interface (Figure 3) is developed, addressing key questions about screen layout; visualization of recommendations; delivery methods (pop-up, dashboard icon, and message); and timing within clinician workflows.

Figure 2. Iterative development process of the reduce stigmatizing language (ENGAGE) system. HHC: home health care; NLP: natural language processing.

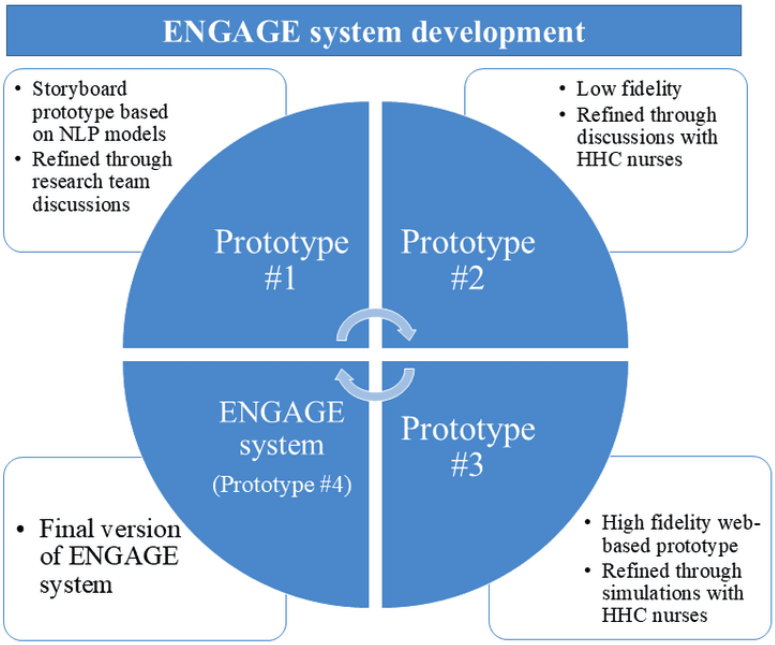

Figure 3. User interface of a potential stigmatizing language reduction system.

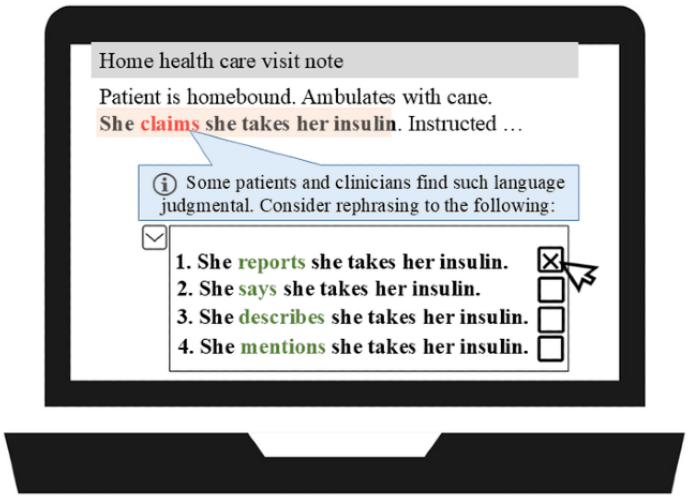

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Data Analysis Plan

In aim 1, interview audio data will be transcribed by the research assistant, with 20% to 30% validated by another study team member. Data will be analyzed using thematic analysis—a qualitative descriptive approach for identifying, analyzing, and reporting themes within the data [68-74]. Qualitative analysis software (NVivo [75]; Lumivero) will be used to implement the analysis. The analysis includes six aims: (1) familiarization with data by listening to recordings and reading transcripts; (2) generating initial codes based on interview questions; (3) data coding by 2 researchers with dual coding to ensure >90% agreement; (4) collating codes into themes; (5) defining and naming themes; and (6) producing a final report with quotes, linking themes to the research question and the literature.

In aim 2, the performance of 3 NLP approaches will be compared on the testing set to identify the best one for identifying stigmatizing language. For each stigmatizing language category, we will calculate the area under the receiver operating characteristic curve (AUC-ROC), area under the curve of precision recall (AUC-RP), and the *F* score (a harmonic mean between precision and recall). AUC-ROC is the tradeoff between a true positive rate (sensitivity) and a false positive rate (1–specificity). It has the advantage of being invariant to the class distribution but does not provide sufficient information about the model's precision [76]. On the other hand, AUC-RP is the tradeoff between recall (true positive rate) and precision [76]. Because our goal is to maximize the sensitivity and precision of the NLP systems in identifying clinical notes with stigmatizing language, we will rank the performance of NLP systems using AUC-RP. We aim to achieve an *F* score and AUC-ROC >0.80, which indicates a well-balanced and functioning system. If NLP approaches fail to achieve this performance level, we will conduct another cycle or cycles of data annotation (with increments of 2500 clinical notes) and NLP system fine-tuning until the desired performance is achieved.

In aim 3, we will compare the prevalence of stigmatizing language by patients' race and ethnicity. The dependent variable will be the presence of stigmatizing language in the clinical note (yes and no). Analyses will be conducted at the clinical note level, starting with bivariate assessments of potential confounders (eg, sex, age, disease diagnosis, and comorbidities). Significant variables ($P<.05$) will be included in mixed-effects regression models to examine associations between race and ethnicity and stigmatizing language, accounting for clustering within patients and nurses. If stigmatizing language is infrequent, mixed-effects Poisson or negative binomial regression will be used. We will control the false discovery rate at 0.05 for multiple comparisons.

In aim 4, we will evaluate the best approach for rephrasing stigmatizing language. Each NLP method will generate 4 paraphrased options from the test set. Five human reviewers will independently select options that replace stigmatizing language without altering the sentence's meaning. The research group will then conduct Delphi rounds to reach a consensus on the best versions. A new group of 5 reviewers, including diverse HHC nurses, a minority patient, and an SEB chair, will rate each rephrased sentence on a 5-point Likert scale for effectively replacing stigmatizing language and preserving meaning. This group will first independently review each rephrased sentence and, on a 5-point Likert scale (range—1=almost completely, 2=to some extent, 3=unsure, 4=to a small extent, and 5=did not change), indicate (1) to what extent stigmatizing language was replaced with a neutral, nonstigmatizing language and (2) to what extent the meaning of the source sentence was altered. We will generate mean and median scores for each NLP approach and examine whether any of the NLP approaches achieved statistically significantly better performance on questions 1 (replace stigmatizing language) and 2 (not changing the meaning of the sentence) using ANOVA [77].

Results

We received funding from the National Institute on Minority Health and Health Disparities on September 24, 2023, with a project end date of April 30, 2027. Recruitment and enrollment began in May 2024. As of August 2025, we enrolled 13 participants. Table 2 presents the planned timeline and current progress for each study phase.

Table 2. Timeline and study progress.

Phase	Planned timeline	Current progress
Aim 1	May 2024-December 2025	Interviews completed for 9 participants
Aim 2	January 2025-December 2025	Data processed for analysis
Aim 3	January 2026-April 2026	Not yet initiated
Aim 4	May 2026-April 2027	Not yet initiated

Discussion

Anticipated Findings

Reducing racial biases in health care is a national priority. This innovative study will leverage extensive data sources to explore stigmatizing language in clinical notes, addressing critical gaps in detecting racial bias in EHRs and improving system design to minimize such language used by HHC nurses. The research team includes qualified researchers who will ensure the study's implementation and timely completion.

One expected outcome of this study is the identification of an expanded ontology of stigmatizing language categories. In a previous study, 5 categories were identified: questioning patient credibility, expressing disapproval of patient reasoning or self-care, stereotyping by race or social class, portraying the patient as "difficult," and emphasizing clinician authority over the patient [13]. However, these categories were derived from

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600 encounter notes written by 138 physicians. This study will expand the data to a larger sample of clinical notes and interviews with patients and nurses. With this larger dataset and diverse perspectives, the expectation is to identify additional categories of stigmatizing language. These expanded and refined categories will allow for a more comprehensive analysis of stigmatizing language in clinical notes.

The prevalence of stigmatizing language is expected to vary across different racial and ethnic groups. Using data from one of the largest not-for-profit HHC agencies in the United States, a pilot NLP study was conducted to examine stigmatizing language use among HHC nurses. The study found that stigmatizing language was least prevalent in the Asian group of patients. Compared to this group, the prevalence increased by 22%, 37%, and 39% in the White, Black, and Hispanic groups, respectively [12]. In this study, using a similar population, it is expected that these racial and ethnic differences will persist. Therefore, it is crucial to develop interventions to reduce racial bias and stigmatizing language in clinical notes.

Several NLP approaches, such as rule-based methods and BERT-based models, have been evaluated for identifying stigmatizing language in clinical notes [15,28,31,78,79]. These approaches have their limitations. For example, rule-based approaches, which rely on predefined vocabularies, are rigid and often miss context-dependent nuances, while transformer-based models such as clinical BERT capture context better but are limited by the training data. Recent advancements in large language models, such as Mistral and Large Language Model Meta AI 3 [80,81], have improved the performance across various NLP benchmarks. Therefore, future research can explore and compare these newer models in addressing stigmatizing language in clinical notes.

Strengths and Limitations

This study has several strengths. First, this is an original study that will examine the ontology of stigmatizing language and explore the NLP approach to automatically identify and reduce stigmatizing language use in HHC. Second, the strengths of our study include the rich data resource of approximately 16.7 million clinical notes for about 667,000 unique HHC patients. This rich dataset enables a comprehensive understanding of racial bias in the language used in clinical notes. Third, an interdisciplinary team of experts in linguistics, health disparities, HHC nursing, qualitative analysis, and NLP has been assembled to design a nurse-centered, NLP-based system. With strong expertise in both content and methodology, the team has carefully considered potential biases and limitations, developing a plan to address them and enhance scientific rigor.

Limitations have also been identified. First, stigmatizing language can be ambiguous and difficult to identify. To mitigate this, the interdisciplinary team of experts includes experts in racial health disparities. In addition, data annotators will represent diverse racial perspectives. Various “interrater reliability” steps will be included within the protocol to reduce the potential for such ambiguities and others that may be overlooked. Second, developing an effective ENGAGE system will pose challenges. To address this, a comprehensive, iterative development plan will be created with input from diverse HHC clinicians.

Conclusions

The ENGAGE study protocol addresses the critical issue of stigmatizing language in HHC through developing an NLP-driven system. This innovative mixed methods study, conducted within 2 large and diverse HHC organizations, aims to refine the ontology of stigmatizing language, develop and test various NLP methods for identifying and replacing such language, and examine the prevalence and impact of stigmatizing language across different racial and ethnic groups. The project will comprehensively analyze the patterns and consequences of stigmatizing language in clinical notes by leveraging extensive EHR data and using robust statistical and machine learning techniques. With the successful development and iterative refinement of the NLP-driven ENGAGE system, which integrates the most effective NLP approach for rephrasing stigmatizing language without altering the original meaning, the final system will be ready for testing in a clinical trial.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author upon reasonable request.

Authors' Contributions

SS, JYT, and MT were responsible for conceptualization, acquisition, investigation methodology, project administration resources, supervision, validation, and visualization. ZZ, PG, SS, MVM, JYT, and MT were responsible for data curation. ZZ, PG, and MT were responsible for formal analysis. SS, JYT, and MT were responsible for arriving at the investigation methodology. MT was responsible for software. ZZ, PG, SP-T, LP, MM, SS, MVM, CWR, JYT, and MT were responsible for writing, reviewing, and editing the original draft.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
Interview guide for nurses.
[DOCX File , 17 KB - resprot_v14i1e69753_app1.docx]

Multimedia Appendix 2
Interview guides for patients.
[DOCX File , 16 KB - resprot_v14i1e69753_app2.docx]

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Abbreviations

AUC-ROC: area under the receiver operating characteristic curve
AUC-RP: area under the curve of precision recall
BERT: bidirectional encoder representations from transformers
EHR: electronic health record
ENGAGE: reduce stigmatizing language
HHC: home health care
NLP: natural language processing
OASIS: Outcome and Assessment Information Set
SEB: Stakeholders Engagement Board

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Protocol

Promoting Healthier Meal Selection and Intake Among Children in Restaurants: Protocol for a Cluster-Randomized Trial

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Abstract

Background: US children's diets are high in calories and are of poor nutritional quality, and a likely contributing factor is the consumption of food from restaurants. While children readily accept the sweet and salty foods that characterize restaurant children's menus, research shows that their taste preferences are malleable, and regular exposure to healthier foods can promote their acceptance.

Objective: We describe a cluster-randomized controlled trial testing the effects of behavioral intervention strategies (choice architecture and repeated exposure) on ordering and dietary intake among children in restaurants and present baseline demographic data for the study cohort.

Methods: Six locations of a regional quick-service restaurant chain were randomized to the intervention or control group in pairs based on income in surrounding census tracts. Families with children aged 4 to 8 years were recruited and asked to complete 8 visits to the study restaurant, including a baseline assessment completed at the time of enrollment, followed by 6 visits during a designated 2-month exposure period and a final posttest assessment. Intervention content provided to intervention group families after baseline assessments includes placemats promoting 2 healthier kids' meals and the opportunity to redeem their kids' meal "cone token" for a toy instead of a dessert (choice architecture strategies). In addition, participating families receive frequent diner cards, which can be used to earn a free kids' meal after purchasing a promoted kids' meal 6 times (repeated exposure strategy). Families in control restaurants receive generic versions of these materials (eg, frequent diner cards that can be redeemed for a free kids' meal after purchasing any 6 kids' meals). The primary outcome is the meal ordered for the child at a posttest restaurant visit following the exposure period (ie, whether or not a promoted meal was ordered). Additional order data will include calories, saturated fat, sodium, and sugar content of children's orders at posttest. Other outcomes include children's in-restaurant and daily consumption of calories, saturated fat, sodium, and sugar.

Results: This study was funded in 2019, with preregistration completed in 2020, data collection occurring from June 2021 to November 2024, and data processing, analysis, and primary outcome manuscript preparation in 2025-2026. A total of 236 families provided baseline data on children's orders and comprise the study cohort; 234 of these families provided demographic data (n=184, 78.3% female parents; n=133, 56.8% female children; child mean age 6.5, SD 1.3 years).

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Conclusions: Given that restaurants are normative eating contexts for many children, this intervention has the potential to impact children's dietary intake and health. If found to be successful, future directions could include scaling the current intervention approach and conducting further effectiveness, implementation, and dissemination research to understand its applicability and impact across different types of restaurants and sociodemographic contexts.

Trial Registration: ClinicalTrials.gov NCT04334525; https://clinicaltrials.gov/study/NCT04334525

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KEYWORDS

restaurant; choice architecture; repeated exposure; menu; child; diet; health

Introduction

US children's diets are generally of poor nutritional quality [1]. A likely contributing factor is frequent consumption of food from restaurants, where meals tend to be higher in energy content and lower in nutritional quality than those prepared at home [2]. While young children readily accept the sweet and salty foods that tend to characterize typical restaurant meals [3-5], research shows that their taste preferences are malleable, and regular exposure to healthier foods can promote acceptance of these foods beginning early in life [6,7]. In this paper, we describe a 2-arm cluster-randomized controlled trial testing the effectiveness of an intervention using evidence-based approaches from the behavioral sciences to promote healthier eating among children in quick-service (ie, fast food) restaurants.

Studies have shown that the minority of children's meals offered at quick-service and full-service restaurant chains meet nutritional recommendations [3-5]. In turn, consumption of restaurant food has been linked with increased daily energy intake and poor diet quality among children, including higher saturated fat and sugar intake [8]. Furthermore, restaurants have become normative eating contexts for many families, with more than one-third of children eating fast food on a given day [9]. Given the frequency at which children eat from restaurants and typical consumption patterns while there, targeting children's food selection in restaurants has the potential to improve diet quality and shape healthy eating habits.

A nationally representative study showed that more than half of children would accept fruits or vegetables with children's meals, but an even higher percentage of children reported being likely to order meals that came with French fries [10], suggesting that the promotion of healthier options may be most successful when these options are not in direct competition with less-healthy, familiar offerings. In other words, if children have a choice between a fruit or vegetable side versus French fries, many may choose French fries, but if fruits and vegetables are made the default option, many children would be satisfied with these options.

Choice architecture approaches that increase the prominence of healthier choices can facilitate the selection of these options. Choice architecture approaches modify the environment in which decisions are made and have demonstrated success in nudging consumers toward a particular option without overt health messages or the removal of choice. For example, making healthier side dishes the default offering with children's meals has been linked with healthier meal selection in quick-service [11] and full-service restaurants [12,13]. The power of defaults is also supported by extensive behavioral economics research in other domains outside the realm of food choice (eg, [14,15]). There is also evidence that modifying the prominence of target items by using engaging names [16] or serving target items before the main meal [17] can increase children's consumption of those foods, with this research conducted in a childcare center and in a university campus-based, full-service restaurant, respectively. Although these strategies show promise, there is limited research examining interventions intended to nudge children toward healthier meals in restaurants, including in quick-service restaurant chains that are frequented regularly by families. Our team conducted a pilot study to begin filling this gap. In this study, families were recruited from a single location of a regional quick-service restaurant chain and randomly assigned to return during a 2-week intervention or control period. During the intervention period, families received placemats that featured 2 healthier kids' meals, positioning these options as special ("Kids' Meals of the Day"), prominent (listing only the featured meals on the placemats), fun (using names like The Nutty Monkey meal), and automatic (bundling healthy sides and beverages with featured main dishes). Children who received these placemats ordered a greater number of healthier foods than controls, and children who ordered promoted healthier main dishes consumed less saturated fat than those who did not [18]. The relatively small effect sizes observed, along with a trend where controls rated their meals as more palatable compared to intervention group children, highlighted opportunities to bolster this pilot study. This trial was designed to build upon this work through an in-restaurant intervention that (1) takes place along a longer timeline, (2) promotes healthier meals previously rated by children as palatable, and (3) combines the choice architecture strategies used in the pilot study with repeated exposure.

A robust evidence base supports simple repeated exposure to tastes of target foods as one of the most effective ways to promote healthier food preferences and intake among children [6,7], with recent research suggesting that 6 exposures or less can be enough to increase acceptance of target foods [19-22]. To our knowledge, this approach has not been studied systematically in restaurants; however, it fits well with the goal of promoting healthier eating in restaurants as taste is a leading factor influencing the meals children select in these settings [23]. For this trial, our intervention combined choice architecture—that is, an evidence-based behavioral economics

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approach designed to nudge participants' attention toward 2 healthier children's meals—with a repeated exposure intervention in the form of a frequent diner card designed to incentivize continued ordering of the promoted healthy meals and build preferences for these meals through these exposures over time.

For this cluster-randomized trial, our team is working with the same restaurant chain as in our pilot study, this time randomizing all 6 of its locations to intervention or control. The same kids' meals are available in the intervention and control restaurants, but in intervention restaurants, choice architecture and repeated exposure strategies are used to promote 2 healthier children's meals. Order and intake data of participating children aged 4 to 8 years are collected in the restaurant at baseline and again at a posttest visit following a 2-month exposure period. During the exposure period, it is recommended that families visit the restaurant at least 6 times, and weekly internet-based surveys are administered to parents. The recommended 6 restaurant visits during the exposure period correspond to the frequency that participants typically dine out, as only families who dine out at least 2-3 times per month were eligible for the study. The primary outcome is whether or not the child orders one of the promoted healthier kids' meals at the posttest assessment following exposure to the intervention strategies. It is hypothesized that children in intervention restaurants will be more likely to order the healthier kids' meals, which were promoted in their restaurant location, and will demonstrate healthier orders (lower calories, saturated fat, sugar, and sodium) and intake (lower calories, saturated fat, sugar, and sodium) in the restaurant.

Taken together, research to date suggests that repeated exposure and choice architecture have the potential to make healthier options more appealing and easier to choose. Given how frequently children eat food from restaurants, the typical unhealthy consumption patterns while there, and the evidence supporting the potential of repeated exposure to impact eating behaviors broadly, this intervention has the potential for meaningful impacts on children's diets and health.

Methods

Overview

In this 2-arm cluster-randomized controlled trial, all 6 locations of Anderson's Frozen Custard, a quick-service restaurant chain in the Western New York region of the United States, were paired based on poverty levels in the surrounding census tracts before participant enrollment (ie, 0% and 4%, 10.2% and 10.3%, and 29% and 38.1% living below the federal poverty level), and a location from each pair was randomized to either the intervention or control group by a study statistician (RP). The locations were paired before randomization to avoid an imbalance in socioeconomic status across the study groups. While participants could see the specific intervention materials described herein after their baseline assessments, they were not told that they were in an intervention versus control group specifically; it was not possible to mask data collectors from study group assignment.

Data collection was planned to take place over 3 years, with each pair of restaurants assigned a priori to 1 of 3 cohorts (see Adaptations Due to COVID-19 section for details on slight modifications made due to the emergence of the COVID-19 pandemic at the start of the planned study timeline). Families with children aged 4 to 8 years were recruited at each location, with a focus on the age range expected to order from the children's menu. Eligible, enrolled families were asked to complete 8 visits to the restaurant location where they were recruited. Visits include a baseline visit (with data collected following recruitment), followed by 6 visits within a specified 2-month exposure period, and finally, a posttest visit, with in-person assessments at the initial and posttest time points. Data collection methods are consistent with our pilot study [18]. Detailed procedures are described herein.

Recruitment

During the baseline period, study staff were present in the restaurant during designated days and times (generally from Wednesday to Saturday between 4:30 PM and 8 PM), and families with children who entered participating restaurant locations during those times were screened for interest and eligibility. One adult and one child were recruited from each interested, eligible family. Inclusion criteria were: participating child aged 4 to 8 years, with the parent or guardian reporting that the child normally eats food from restaurants at least 2-3 times per month. The participating adult also had to be 18 years of age or older, and the child's parent or legal guardian, and both the parent and child had to be English speaking and planning to order a meal for the child in the restaurant that day. Parent-child dyads were excluded if the above criteria were not met, if the child had allergies that would preclude safe participation, or if the child participated in a pilot study involving taste tests of the study's featured healthier kids' meals in 2019 [24]. If multiple children within a family met eligibility criteria, only a single child was enrolled, with the study team recommending the child with the most recent birthday. Baseline data collection procedures described herein were administered after the family finished their meals on the recruitment day, with intervention materials to be provided thereafter.

Ethical Considerations

All study procedures were approved by the University at Buffalo Institutional Review Board (STUDY00003356) and registered at clinicaltrials.gov (NCT04334525) before participant enrollment. Participants could receive up to US $265 for successful participation or up to US $300 if they were selected to and decided to participate in an additional, optional observational substudy [25]. All adult participants provided informed consent and permission for their children's participation, and children provided assent before commencement of study procedures. Given the minimal risk of the study, there are no stopping criteria. Participants are informed that their participation is voluntary and that they can discontinue their participation at any time. After each data collection day, a daily debrief is sent to the principal investigator to allow monitoring for any adverse events. Data collected to assess study aims are stored separately from identifiers. Identifiable information (eg, names and contact information) is

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stored securely and separately and will be destroyed within 10 years of the study's conclusion.

Sample Size Calculation

The primary outcome for this trial is whether or not the child ordered one of the promoted healthier children's meals at posttest. We estimated that about 27.8% of participants exposed to intervention content would order promoted healthier meals versus 6.7% of the control group [18]. Using these values, an alpha of .05, power of 80%, 6 clusters, and an intraclass correlation of .01 based on previous restaurant research [12], it was estimated that 124 families would be needed to detect intervention effects on meal selection. Considering return rates from previous restaurant research [26], as well as the plan to explore additional outcomes, we increased this estimate by 35% in estimating the sample size for primary outcome analysis, resulting in a target sample size of at least 168 families (84 per group), with our enrolled study cohort exceeding this target.

Intervention

Overview

After baseline assessments, families are asked to return and dine at the restaurant location where they were recruited 6 times over a 2-month period during which intervention components are in place. Those recruited in restaurant locations that had been randomized to the intervention group experience an in-restaurant intervention that combines choice architecture and repeated exposure strategies to promote 2 healthier kids' meals.

Choice Architecture

Families in intervention restaurants receive crayons and placemats promoting 2 healthier kids' meals during the exposure period (see Figure 1). Placemats are mailed to enrolled families after their baseline assessments and are also available to all families dining in the intervention locations, whether or not they are participating in the study, throughout the exposure and post periods. The placemats are available to take from a child-friendly display; restaurant staff are also trained to include a placemat and a set of crayons with every kids' meal order. Promoted meals were selected based on formative research conducted before the main study. In this formative work, 10 possible main and side dishes were taste-tested by 37 children aged 4 to 8 years across two locations of the study restaurant [24]. Children rated their liking and rank-ordered preference for each food option. Highly-rated meal components included grilled chicken strips with ranch dip, a peanut butter and banana sandwich, steamed broccoli, and strawberry yogurt. We bundled these preferred items into 2 featured kids' meals, along with preferred beverages (100% apple juice and water), with each bundled meal meeting nutritional criteria corresponding to the National Restaurant Association's Kids' Live Well program and the Dietary Guidelines for Americans [27,28].

Figure 1. Sample placemat for the intervention group.

As in our pilot study [18], intervention placemats position the 2 promoted meals as special ("Kids' Meals of the Day"), prominent (ie, featuring only them on the placemats), fun (ie, with fun names like The Nutty Monkey and Grillin' Chicken), and automatic (ie, bundling healthier sides and beverages with featured main dishes). Placemats also aim to shift the default nature of desserts by promoting the opportunity for children to redeem the "cone token" that comes with all kids' meals at this restaurant for a small toy (eg, dinosaur building block set or squishy toy animal) instead of a dessert. Final toy options were selected after brief focus groups conducted with a separate, small group of children in the same age range. Like the

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placemats, the toy promotion is available to all customers in the restaurant during the exposure and posttest periods. Signage that reinforces the messages from the placemats (ie, promoting the featured meals and toys) is also displayed in the intervention restaurant locations during the exposure and posttest periods, including a large sign posted next to the kids' menu board above the cash register and smaller signs displayed throughout the restaurant. The placemats and signs used were the same throughout each year's exposure and posttest period, with minimal adjustments from year to year to reflect minor details such as the current year and current kids' meal prices.

Repeated Exposure

After baseline data collection, participating families also receive frequent diner cards for use during the study's exposure period. In intervention restaurants, participating families can earn a free kids' meal at posttest if the child orders one of the promoted healthier meals 6 times during the designated 2-month exposure period. These cards are provided electronically, with a link to an image (see Figure 2) sent to each participating family, which features a code that can be scanned in the restaurant. When providing the cards to families, study staff clarify which 2 specific meals can be used to earn a scan of the digital frequent diner card, and that either one of these meals may be purchased. When a promoted meal is purchased, restaurant staff scan the card, and the child gets to choose a sticker. After using the card for an eligible meal 6 times, a free kids' meal automatically populates in the participant's account. The frequent diner card can be used once per visit and only by the participating child. Unlike the placemats, signage, and toys, this component of the study is available to study participants only.

Figure 2. Sample frequent diner card for the intervention group.

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Control Group

Control-group families receive crayons and generic placemats featuring the restaurant's full kids' menu, with these materials and corresponding signage displayed in control restaurants during the exposure and posttest periods. The components of the 2 meals that are promoted as part of the study are available in control restaurants as part of the kids' menu, but are not bundled together or promoted in any way. In contrast to intervention group materials, the generic placemats and signs do not advertise the promoted meals over and above any other kids' meals, nor do they note the opportunity to redeem the kids' meal token for a toy instead of a dessert. Control families also receive a frequent diner card, which can be scanned when purchasing any kids' meal during the exposure period. Children in this group earn a free kids' meal at posttest if any 6 kids' meals are purchased during the 2-month exposure period. There was no toy promotion in the control group. Both groups receive study payments for study activities that they complete, including attending the posttest session, whether or not the free kids' meal is earned.

Measures

Overview

At both the baseline and posttest assessments, study staff collect order and intake data in person, after the family has finished their meal. Table 1 shows detailed study outcomes by time point and measure. The final paragraph of the measures section describes slight modifications to procedures and measures that were necessary during the first (2021) cohort only, due to the COVID-19 pandemic.

Table 1. Planned study outcomes by time point and measure.

Study outcomes	Baseline	Exposure period	Posttest
Children's restaurant meal orders			
Items ordered for children in the study sample[a]	P[b]	P	P[c]
Total calories, saturated fat, sodium, and sugar in child meal orders[a]	P, N[d]	P, N	P, N
Children's meal orders in study restaurants overall during study	S[e]	S	S
Children's intake: in the restaurant and total daily			
Total calories, saturated fat, sodium, and sugar consumed in a restaurant[a]	W[f], N	—[g]	W, N
Total daily calories, saturated fat, sodium, and sugar consumed.[a]	—	—	P (ASA24[h])
Other variables of interest			
Demographics[a]	P	—	—
Parent restaurant meal orders[a]	P, N	P, N	P, N
Process measures (parent and child perspectives, tracking intervention materials, and restaurant staff perspectives) [a]	P, C[i]	P, I[j], O[k]	P, C, O
Observations of parent-child interactions in the restaurant[a]	—	O[l]	—

[a]Depicts individual-level measures.
[b]P: parent report.
[c]Primary outcome.
[d]N: nutrition information from the restaurant.
[e]S: sales data.
[f]W: weighed plate waste.
[g]Not collected at this time point.
[h]ASA24: Automated Self-administered 24-hour Dietary Assessment Tool.
[i]C: child report.
[j]I: restaurant staff interview.
[k]O: observation.
[l]Observed in a random subsample once during the 2-month exposure period.

Order Content and Liking

To assess the impact of the intervention on the meal ordered for the child (primary outcome), study staff first ask the participating parent to identify all items ordered for and eaten by the participating child in the restaurant that day and record the specific main dish(es), side dish(es), beverage(s), and dessert(s) ordered for and eaten by the child, noting whether each item was shared, will be taken to go, or was finished in the restaurant, as well as whether the child used the token that comes with all kids' meals to select a dessert, toy, or neither. Total calories, saturated fat, sugar, and sodium ordered for the child are calculated using nutrition information from the restaurant. Parents also report what they ordered for themselves

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as part of the self-administered survey described below. In addition to the main, in-person assessments of orders, links to brief internet-based surveys are sent to participating parents electronically (typically via text message, with email communication also available when preferred) each week of the exposure period. Surveys include questions about the family's visit(s) to the study restaurant during the past week, including the parent's and the child's meal selections and liking of the meals. Calories, saturated fat, sugar, and sodium ordered are calculated from this information as described above.

Dietary Intake in the Restaurant

To assess the intervention effect on children's intake during their meal, plate waste methodology is used during the in-person visits at baseline and posttest [18,29]. Participating families are instructed to avoid throwing away any leftover food or trash until our team has collected information from them after their meal. After asking the parent which items were ordered for and consumed by the participating child, study staff collect, package, and label all corresponding uneaten food and containers from the child's meal. Items are postweighed in the laboratory following data collection, with pre-to-post weight differences indicating grams consumed. For any items the child wishes to take home with them, the postweight is instead taken in the restaurant. Preweights are estimated by purchasing 3 replicates of each food/beverage item ordered for children during the study and averaging their weights to arrive at a standard preweight. Grams consumed are converted to percentages consumed using total grams from preweights, and these percentages are multiplied by the total calories, saturated fat, sodium, and sugar found in the full item to calculate calories and nutrients consumed.

Total Daily Dietary Intake

Following the posttest assessment, parents report children's daily dietary intake using the Automated Self-administered 24-hour Dietary Assessment Tool (ASA24). Parents are asked to report their children's dietary intake on the day immediately after the posttest restaurant visit. A previous validation study of the ASA24 with 40 parents of children aged 2 to 5 years showed that parent report of child intake matched that of observed dietary intake with nearly 80% accuracy [30]. These data will be used to examine potential intervention effects on children's daily intake of energy, sugar, saturated fat, and sodium, to shed light on potential broader impacts of the intervention, as well as the potential for any compensation.

Demographics and Restaurant Experiences

After the parent is interviewed about the child's order at baseline and posttest, parents are provided with an electronic tablet to self-report on other aspects of the child's restaurant meal that day, and at baseline only, demographics within a brief self-administered internet-based survey.

Demographics

At baseline, parents report their age, sex, race, ethnicity, education level, and income, and their child's age, sex, race, ethnicity, height, and weight.

Restaurant Experiences

When completing the internet-based survey on site at both the baseline and posttest assessments, parents also indicate who selected the child's meal, the reason for the meal choice, how often the child eats at restaurants, and how often the child eats at the study restaurant, using questions adapted from our previous research [10]. At posttest, parents also report on their child's visits to the study restaurant since the last study contact and their perspectives on the study materials.

Child Perspectives

While parents are self-administering surveys at baseline and posttest, a study staff member asks the child: whether they knew what they would be having before arriving at the restaurant, whether they had been to this restaurant before, whether this was the meal they typically ordered, who selected the meal, and how they liked their meal [10]. In addition, at posttest, children answer questions about study materials (see Multimedia Appendix 1). Visual aids are used to assist children with answering the questions (eg, smiley face scale for indicating how much they liked their meal). Children's responses are entered into an electronic tablet by the study staff member asking the questions.

Other Measures

In addition to the main measures collected at baseline, the assessments during the exposure period, and posttest, several other sources of data are collected as part of the study. These include sales data, intervention implementation tracking, restaurant staff interviews, and parent-child observations, each of which is described briefly below. Components that are considered to be process measures include the implementation tracking and restaurant staff interviews, as well as parents' and children's perspectives on the intervention collected via the aforementioned surveys (see Table 1).

Sales Data

Aggregated sales data from each participating restaurant location are collected to monitor the sales of healthier and all kids' meals across all customers during the baseline, exposure, and posttest periods within each of the cohorts and parallel time points 1 and 2 years before. These data will allow an examination of overarching trends in the purchases of the healthier kids' meals in intervention versus control restaurants over the course of the study, which can provide insights into the impacts of the choice architecture intervention components on a larger scale, with less direct researcher involvement.

Intervention Implementation Tracking

During each week that intervention materials are on display at study locations, a study coordinator visits each restaurant location and records whether study materials are displayed as intended. Quantities of study materials used are also recorded (eg, number of placemats distributed by restaurant locations; number of toys requested at the intervention locations). This information, as well as data on the use of the frequent diner cards, will be aggregated and summarized at the end of the study.

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Restaurant Staff Interviews

During each study year, at least 1 month into the exposure period, restaurant staff are invited to participate in semistructured interviews to share their perspectives on the study. Question development was guided by the Consolidated Framework for Implementation Research (CFIR) [31]; questions include how familiar the respondent is with the study objectives, how easy or hard it is to implement different aspects of the study interventions, and whether these are a good fit for the restaurant. The restaurant owner, managers, and other employees are invited to participate in interviews, with a slightly different set of interview questions depending on their role (see Multimedia Appendices 2 and 3). In each study year, recruitment for the interviews continues into early November or until our sample size quota for that year is satisfied. We planned to complete up to n=12 interviews per year, aiming for representation of each restaurant location, as well as representation across the different roles (eg, managers and other employees) each year.

Observations of Family Interactions

Finally, parent-child interactions are observed as an ancillary measure to provide descriptive information to contextualize this study's results and also generate hypotheses for future research, given the current lack of observational data on parent-child eating occasions in restaurants. These observations allow examination of parent-child interactions in this setting generally (eg, parenting behaviors), as well as families' engagement with study materials.

Parent-child interactions during meals are observed during the exposure period. The original goal was to conduct observations on about 10% of the total sample. We randomly selected one year (2023/Cohort 3) during which these optional observations would take place. Interested families are recruited into the optional observation component of the study on a first-come first-served basis. Participating families are scheduled for an observation during one of their regular visits to the study restaurant during the exposure period. Unobtrusive observations take place during the first 5 minutes after families are seated at their table and the first 5 minutes they are eating, following procedures adapted from previous research [32,33]. The 5-minute intervals are a standard time frame used in the behavioral coding system from which the study procedures were adapted. Trained, reliable observers collect data on key variables of interest [25].

Adaptations Due to COVID-19

The study procedures and measures described herein correspond to procedures used between 2022 and 2024. During 2021, the first year of data collection, modifications were necessary due to the COVID-19 pandemic, impacting 11% of the study cohort (n=26). The main change was that the research team collected data remotely, rather than being in the restaurant with participants, primarily affecting recruitment methods and the collection of baseline and posttest data. The restaurant was open, and customers could visit as usual. Given that it was not appropriate for us to approach customers in person during this time, we relied on passive recruitment methods, posting opportunities to sign up for the study throughout the restaurant, which included avenues for learning more about the study and for contacting our team. Our team was working off-site Monday through Sunday evenings, fielding inquiries, screening and enrolling individuals into the study, and administering baseline assessments using a text messaging system and internet-based surveys. The questions about children's meal orders were the same as those of the other cohorts, but were administered via internet-based survey rather than starting with an interview. Weighed plate waste measurements were not possible under these circumstances, so we used food photography methods to approximate child intake at posttest. Details of those procedures and a subsequent study of their validity will be presented separately. Children were not interviewed during this first cohort. All other study components were as originally intended and thus consistent across cohorts (eg, provision and display of intervention materials, administration and completion of internet-based surveys during the exposure period). Given these changes to the first cohort, we added a fourth cohort, so we would still be able to conduct in-person data collection with each restaurant location and reach sample size goals.

Statistical Analyses

To examine preregistered aims, mixed models will be used to examine the effects of the intervention on meals ordered for children and children's intake. Key questions will be whether children's restaurant meal orders differ between the intervention and control group at the posttest assessment, with specific outcomes of interest including whether or not a promoted healthier meal was ordered for the child, whether a dessert was ordered, and calories, saturated fat, sodium, and sugar ordered. We will also examine group differences in calories, saturated fat, sodium, and sugar consumed by the child at posttest and changes in the order and intake outcomes over the course of the study by group.

Before implementing the mixed models, we will conduct an assessment of the randomized unit of our cluster-randomized trial, restaurant location, examining the variance component estimates in each model. When cluster variance is either estimated as effectively 0 or negative, we will report the cluster intraclass correlation and omit the random effect of restaurant location from our model. With only 6 unique locations being randomized in our trial, small cluster size adjustments will be applied to any models with the random effect of restaurant location retained, to improve type I error rates [34]. More specific details about the analyses that will be used to address each study aim follow.

For dichotomous outcomes (eg, whether or not one of the promoted healthier meals was ordered), we plan to use logistic regression with generalized linear mixed models, which have the flexibility to handle dichotomous outcome distributions. Models will include fixed effects of group, time point, and the group*time point interaction, with an adjustment for baseline status on the outcome variable and a random effect of participant (ie, repeated time points within persons). Restaurant location will be included as a random effect pending tests of clustering. Logistic generalized linear mixed models will use a binomial distribution and a logit link function. The percentage of participants in each study group who ordered the healthy

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promoted meal items will be described over time, with a corresponding figure illustrating the percentage ordering the healthy meal at each time point. Analyses predicting ordering of healthier promoted meals will be conducted once with the promoted meals strictly defined: that is, must include a promoted main dish, side dish, and beverage, and again with two less restrictive definitions: (1) considering the meal to be healthier if it included at least the promoted main dish and (2) considering the meal to be healthier if it included at least one of the promoted items. We will use the same analytic approach for the analysis of whether or not a dessert was ordered for the child in the restaurant.

For continuous outcomes (eg, total calories, saturated fat, sodium, and sugar ordered for the child in the restaurant), we will use mixed models to examine intervention effects across baseline, all exposures, and posttest. Models will include fixed effects of group, time point, the group*time point interaction, and baseline outcome, with a random effect of individual participant. Restaurant location will also be included as a random effect pending tests of clustering. Parallel models will be conducted to examine intervention effects on children's consumption, including calories, saturated fat, sodium, and sugar consumed during the restaurant meal. For the dietary intake models, only baseline and posttest data points will be used, given that intake data were not measured during the exposure period.

We will also examine: (1) associations between selection of healthy promoted meal items and nutritional characteristics of children's meal orders and intake, (2) potential covariates and effect moderators (eg, child sex, age, weight status, and who selected the child's meal order), (3) intervention effects on children's 24-hour intake, and (4) intervention impacts on ordering of healthier items in aggregate sales data. Data from implementation tracking will be summarized. Restaurant staff interviews are recorded, transcribed, and checked for accuracy. A codebook will be developed using a combination of inductive and deductive approaches guided by CFIR [31] in collaboration with the study principal investigator (SAF) and a co-investigator with expertise in qualitative methods (LAL). The transcripts will be independently coded by 2 trained coders using Atlas.ti (Lumivero) qualitative analysis software. Codes will be reviewed and summarized into themes represented by illustrative quotes. Analysis of data from the parent-child observation substudy, which concluded before the main study, has been published previously [25].

We will conduct sensitivity analyses to examine the robustness of the primary results, including conducting our primary data analyses with and without the first cohort included, to see whether the modified mode of data collection during the COVID-19 pandemic impacts study results. The main analysis plan is to include all participants who provided baseline child order data, but supplemental analyses will be presented as appropriate if sensitivity analyses demonstrate impacts on study results.

Results

This study was funded in 2019, with preregistration completed in 2020, data collection occurring from June 2021 to November 2024, and data processing, analysis, and primary outcome paper preparation in 2025-2026. Participants in restaurant locations A and B were recruited in the Summer of 2021, those in C and D were recruited in the Summer of 2022, and those in E and F were recruited in the Summer of 2023. Modifications to procedures were needed in 2021 due to the COVID-19 pandemic, as described above. Given these modifications, as well as the fact that fewer families than anticipated participated during this initial, pandemic-impacted year, we recruited an additional, fourth group of participants: in 2024, we recruited (different) families from restaurant locations A and B, allowing us to reach our target sample size and to collect data from families in each restaurant location using the originally planned study procedures. In total, 1094 families were approached, 268 were eligible, 240 enrolled in the study, and 236 provided baseline data on children's meal orders and are considered the study cohort (see Figure 3 for the CONSORT [Consolidated Standards of Reporting Trials] diagram). Among the 234 study cohort families providing demographic data, 184 (78.3%) of parents were female, 133 (56.8%) of children were female, and the average child age was 6.5 years (SD 1.3 y). Most children were white (196; 83.8%); 24 (10.3%) were multiracial, 11 (4.7%) Hispanic or Latino, 10 (4.3%) Black, and 1 (0.4%) Asian. Complete baseline demographic characteristics of the study cohort are shown in Table 2.

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Figure 3. CONSORT (Consolidated Standards of Reporting Trials) study flow diagram through randomization.

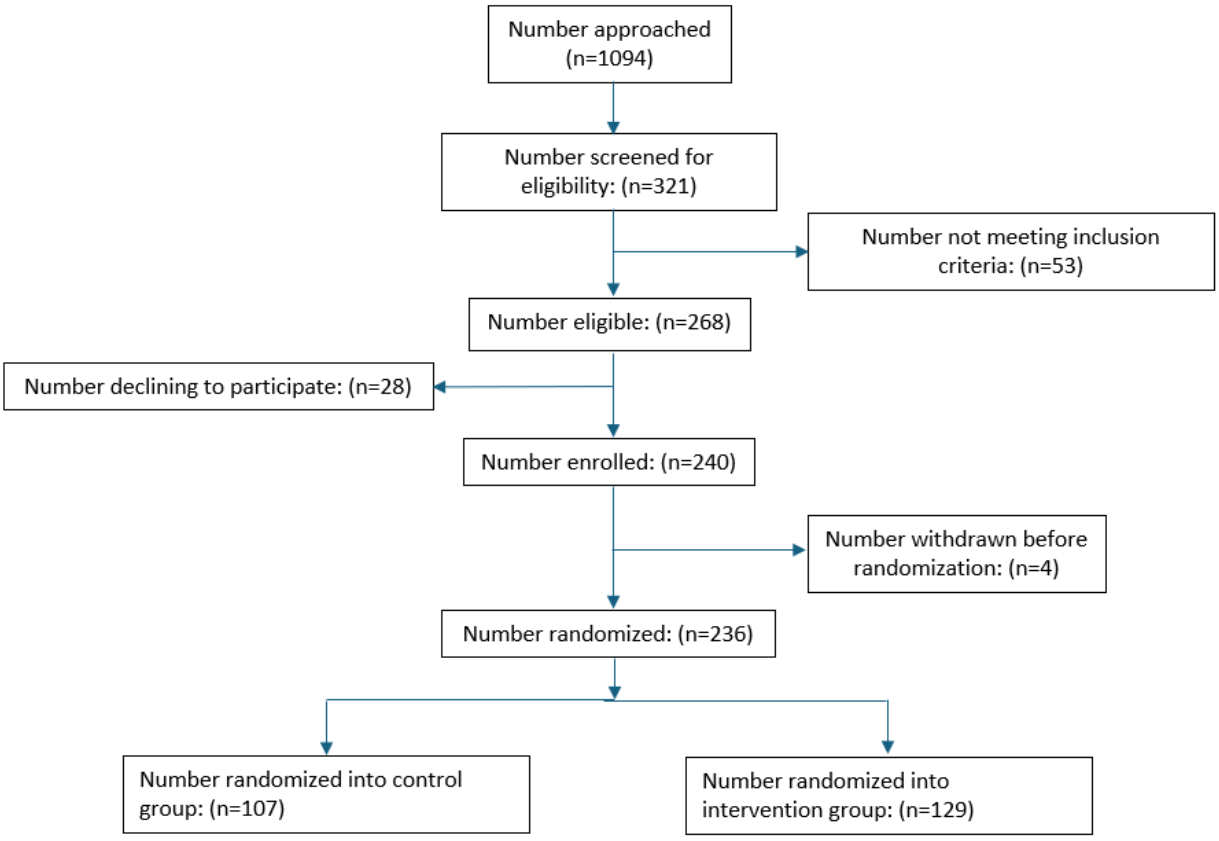

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Table 2. Demographic characteristics of the study cohort at baseline (N=234).

Characteristic	Results[a]
Parent sex, n (%)	
Female	184 (78.3)
Male	50 (21.3)
Parent age (years), mean (SD)	39.4 (7.5)
Parent race and ethnicity, n (%)	
White	212 (90.6)
Black	12 (5.1)
Asian	3 (1.3)
Multiracial	5 (2.1)
Hispanic or Latino	8 (3.4)
Parent education, n (%)	
<High school graduate or equivalent	16 (6.8)
Some college or associate's degree	39 (16.7)
Bachelor's degree	73 (31.2)
Graduate degree	103 (44)
Marital status, n (%)	
Married or living with partner	194 (82.9)
Divorced, widowed, or separated	18 (7.7)
Never married	19 (8.1)
Household annual household income (US $), n (%)	
<24,999	4 (1.7)
25,000-34,999	3 (1.3)
35,000-49,999	14 (6)
50,000-74,999	24 (10.2)
75,000-999,999	36 (15.3)
>100,000	142 (61.4)
Prefer not to answer	11 (4.7)
Children's ages (years), mean (SD)	6.5 (1.3)
Children's sex, n (%)	
Female	133 (56.8)
Male	101 (43.2)
Children's race and ethnicity, n (%)	
White	196 (83.8)
Black	10 (4.3)
Asian	1 (0.4)
Multiracial	24 (10.3)
Hispanic or Latino	11 (4.7)

[a]Two participants from the analytic sample (N=236) did not complete the demographic survey, resulting in N=234 for analysis of participant demographics.

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Discussion

Principal Findings

Findings hypothesized to result from this study include a greater selection of promoted healthy meal items in the intervention group versus controls and corresponding improvements in the nutritional characteristics of children's meal orders and dietary intake. The planned research will build upon the existing evidence highlighting choice architecture and repeated exposure as potentially promising intervention approaches in restaurants, including emerging evidence demonstrating potential small effects of approaches that increase the prominence of healthier children's menu items [18,35,36] and evidence suggesting that these impacts may be magnified if incorporating optimal defaults [12] and repeated exposure [6]. If the intervention significantly impacts the meal selected for the child, findings would support the idea that these intervention approaches can facilitate the selection of healthier meals for children in restaurants. Such findings could support restaurant usage of existing loyalty programs, placemats, and signage, not just to encourage purchasing but also to promote healthy choices.

If intervention effects within the sales data have an equal or greater magnitude compared to individual-level results, findings would support choice architecture as a promising intervention approach, given that the repeated exposure component of the intervention (the frequent diner card) was only provided to those enrolled in the study. If, by contrast, the results are of the greatest magnitude during the exposure period in the study participant sample, these findings would support the frequent diner card as a meaningful addition. If hypotheses are not confirmed, and the intervention does not impact orders or intake, these findings would suggest alternative approaches are needed. This could imply the need for an approach centered on reworking children's menus so the majority of available options are nutritious, and all meals come with healthy sides by default [12,13,37], although it is unclear whether previous successful implementation of these strategies would generalize to a broader population of restaurants.

Strengths of this study include the cluster-randomized design and data collection within naturalistic restaurant settings that includes measurement not only of children's orders but also gold standard measurements of dietary intake via weighed plate waste. Limitations include the possibility of demand characteristics, with participants' or restaurant staff behaviors influenced by perceptions of the researchers' goals, and the results may not generalize beyond regional quick-service restaurant chains similar to this partner restaurant chain or to populations beyond the demographics of those studied here. Demographics reflect that the sample is comprised of children aged 4 to 8 years (by design), with representation of both male and female children, but less racial and ethnic diversity, as most of the children were white. Future directions could include scaling the current approach, if successful, and testing its effects in different types of restaurants and among participants of different sociodemographic backgrounds. Additional possible extensions include further implementation and dissemination research, and consideration of other modalities of food purchasing, such as drive-throughs and delivery.

Conclusions

As restaurants are normative eating contexts for many families, in-restaurant interventions that make selecting healthier options easier and more normative have the potential to have a meaningful public health impact. This study's intervention brings together the limited extant research on promoting healthy choices for children in restaurants with approaches from the behavioral sciences —choice architecture and repeated exposure—which have been successful in other environments, such as laboratories and childcare centers. The present approach differs from existing restaurant interventions that are information-based, such as providing nutrition information via calorie labeling (eg, [38]), and has the potential to elicit change while minimizing concerted effort required from customers, a characteristic that may be important in the context of busy, quick-service restaurants. Results from this trial can inform future health promotion efforts in restaurants by shedding light on the feasibility and effectiveness of choice architecture and repeated exposure strategies in this setting.

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Data Availability

Data are available upon reasonable request to the corresponding author after planned analyses are completed by the study team.

Authors' Contributions

Conceptualization: SA-F, LE, JH, AG, LAL
Methodology: SA-F, LE, JH, AG, LAL
Investigation: ST, MJF, JG

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Data curation: MJF
Formal analysis: RP
Writing – original draft: SA-F, ST
Writing – review & editing: All authors
Supervision: SA-F
Project administration: SA-F, ST, MJF, JG

Conflicts of Interest

None declared.

Multimedia Appendix 1
Sample child interview (posttest time point, intervention group, aged 4 to 5 years).
[DOCX File , 322 KB - resprot_v14i1e73618_app1.docx]

Multimedia Appendix 2
Sample interview guide: restaurant manager.
[DOCX File , 28 KB - resprot_v14i1e73618_app2.docx]

Multimedia Appendix 3
Sample interview guide: other restaurant employees (not owner or manager).
[DOCX File , 27 KB - resprot_v14i1e73618_app3.docx]

Multimedia Appendix 4
Peer-review report by PRDP - Psychosocial Risk and Disease Prevention Study Section, Risk, Prevention and Health Behavior Integrated Review Group (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 469 KB - resprot_v14i1e73618_app4.pdf]

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Abbreviations

ASA24: Automated Self-administered 24-hour Dietary Assessment Tool

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Protocol

At-Home Morning Bright Light Treatment for Chronic Nociplastic Pain: Protocol for a Randomized Clinical Trial

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Abstract

Background: Fibromyalgia, the quintessential nociplastic pain condition, affects more than 20 million Americans and results in significant disability, lost productivity, and poor quality of life, with profound individual and societal cost. As pharmacological treatment approaches offer only modest benefits and result in a high rate of discontinuation due to adverse effects, nonpharmacological interventions such as physical therapy, exercise, and cognitive behavioral therapy are recommended. However, cost and access to these treatments can create barriers to care, and engagement can be problematic. Morning bright light treatment is a promising option for improving fibromyalgia symptoms, with early studies indicating clinically meaningful improvements in fibromyalgia symptoms.

Objective: This study aims to prospectively examine the potential benefits and active elements of morning bright light treatment and sleep timing stabilization for individuals with fibromyalgia in the largest randomized controlled trial to date.

Methods: We will recruit 390 adults who meet diagnostic criteria for fibromyalgia and report at least mild symptoms. Participants will be randomized to one of three groups: 4 weeks of morning bright light treatment (1 hour per day, using a commercially available Re-timer device), 4 weeks of sleep timing stabilization alone (a component of morning bright light treatment, some benefit anticipated), or 4 weeks of treatment as usual, with equivalent study contact. Patient-reported outcomes of function and pain will be assessed before and after treatment, with mood, sleep quality, and morningness-eveningness examined as potential mediators of treatment effects. Social determinants of health risk will be examined as a potential moderator influencing baseline symptoms, treatment engagement, and treatment response.

Results: Data collection began in September 2024 and is projected to end in March 2029.

Conclusions: Morning bright light treatment is well-positioned to be an effective nonpharmacological treatment for fibromyalgia with minimal side effects. The study findings will provide important insights relevant to the development of morning bright light treatment as an accessible treatment for chronic nociplastic pain.

Trial Registration: ClinicalTrials.gov NCT06567886; https://clinicaltrials.gov/study/NCT06567886

International Registered Report Identifier (IRRID): DERR1-10.2196/75060

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(JMIR Res Protoc 2025;14:e75060) doi:10.2196/75060

KEYWORDS

fibromyalgia; light; mood; nociplastic; pain; sleep

Introduction

Chronic nociplastic pain includes conditions such as irritable bowel syndrome, interstitial cystitis, and the quintessential nociplastic pain condition, fibromyalgia, which alone affects more than 20 million Americans [1]. While the mechanisms underlying nociplastic pain are not completely understood, central nervous system–mediated amplification of pain and other sensory input, along with altered pain modulation, play a major role [2]. In addition to pain, mood and sleep disturbances, fatigue, and cognitive symptoms are common [3,4]. Resultant disability, lost productivity, and poor quality of life have profound costs at the individual and societal level [5]. Underserved individuals experience these impacts more profoundly [6] as symptom burden is heavily influenced by demographic risk factors, including social determinants of health (SDOH: eg, education, income, medical insurance, and community resources) [7-10].

While a pharmacological approach has traditionally been the first line of treatment for fibromyalgia, drug therapies offer only small benefits [11-14] and result in a high rate of discontinuation due to adverse effects [11]. Newer national guidelines suggest that the initial approach to the treatment of fibromyalgia consists of non-pharmacological interventions [15-17]. Physical therapy, exercise, and psychological therapies such as cognitive behavioral therapy (CBT) have demonstrated efficacy but can be difficult to access in terms of cost and availability [18-20], and engagement can be problematic [21]. Indeed, individuals with chronic pain are most adversely impacted by SDOH, have the least access and ability to consistently engage in nonpharmacological therapies [7]. Thus, a need exists to develop novel adjunctive approaches to manage fibromyalgia symptoms that have optimal treatment effects, minimal side effects, and are easy to implement and readily accessible for all.

Morning bright light treatment is a promising option for improving fibromyalgia symptoms. Meta-analyses have confirmed that morning light treatment improves mood (reduces nonseasonal depression) with medium effect sizes similar to those observed with pharmacological antidepressants [22,23]. Similarly, a meta-analysis indicated that morning light treatment improves sleep with medium effect sizes [24]. Improvements in mood and sleep are well-recognized as contributing to improvements in chronic pain [25,26]. Morning bright light treatment also advances circadian timing (shifts circadian timing earlier toward “morningness” [27]). As later circadian timing (“eveningness”) is associated with worse fibromyalgia pain [28,29], circadian phase advances associated with morning bright light treatment may help reduce symptoms (see Figure 1). In addition, emerging research in rodent models suggests green light exposure to be antinociceptive [30,31]. Importantly, while light treatment is associated with some side effects (headache, eyestrain, nausea, and agitation [32]), these symptoms often spontaneously remit [32,33], and patients rarely discontinue treatment due to these side effects [33]. Furthermore, light devices with a UV filter are considered safe with no changes in ophthalmologic examinations observed after 6 years of daily use (in fall and winter months) [34].

Figure 1. A conceptual model illustrating that morning bright light treatment, which is known to improve mood and sleep and to shift circadian timing earlier, has the potential to improve fibromyalgia. The measure used to assess each domain is shown in italics: Patient Health Questionnaire (PHQ-9), Morningness-Eveningness Questionnaire (MEQ), PROMIS Sleep Disturbance 8b, Fibromyalgia Impact Questionnaire–Revised (FIQR), and Brief Pain Inventory (BPI).

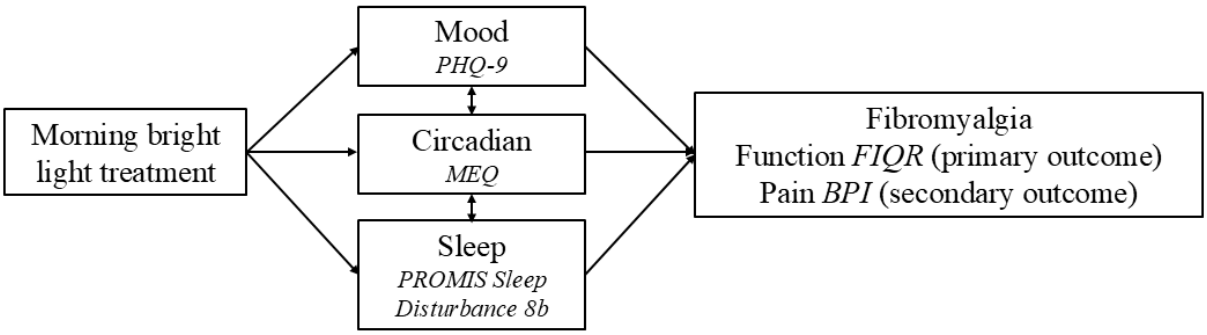

To date, only 3 studies have tested light treatment in people with fibromyalgia. In our first study, we tested 6 days of either a 1-hour evening or 1-hour morning bright light treatment in 10 participants with fibromyalgia [35]. Only the morning bright light treatment led to clinically meaningful improvements in function (>14% reduction in baseline Fibromyalgia Impact Questionnaire—Revised [FIQR] score [36]). In this study, we travelled to participants’ homes to set up white light boxes, which was burdensome for participants and staff. This experience led us to switch to a novel commercially wearable light device (Re-timer), which permits ambulation while receiving light from green LEDs positioned below the eyes. Our second study was a randomized clinical trial that tested 4 weeks of a 1-hour daily morning light treatment (bright or dim) using the Re-timer in 60 people with fibromyalgia [37]. We found that both groups responded to the morning light treatment, with clinically meaningful improvements in the FIQR (mean decrease of 11.2, P=.003). The findings were similar to those

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seen after exercise and were double those seen with CBT or analgesics (meta-analysis [38]). A third study by Martin et al [39] tested 7-9 weeks of a 1-2 hour daily white versus green light treatment in 21 people with fibromyalgia. The light was generated from LED strips, and the time of day of light exposure was not reported. They found that only the green LED light led to significant reductions in pain intensity, and quality of life and self-reported function also improved. Overall, morning bright light treatment is well-positioned to be a potentially accessible and scalable nonpharmacological treatment for fibromyalgia with minimal side effects. Furthermore, light treatment devices are commercially available, and light treatment can be self-administered at home, allowing easy access and dissemination once efficacy is established.

To further examine the potential benefits and active elements of morning bright light treatment for people with fibromyalgia, we will conduct a larger parallel groups randomized controlled trial with 3 conditions: 4 weeks of 1 hour/day green morning bright light treatment (Re-timer), a sleep timing stabilization alone treatment (a component of morning bright light treatment, some benefit anticipated [40-42]) and treatment as usual (treatment as usual [TAU], a control group to control for attention and time in study effects). We hypothesize that (1) participants who receive morning bright light treatment will show greater improvements in function and pain; (2) that SDOH risk will influence baseline symptom burden, treatment adherence (engagement), and treatment response; and (3) that treatment response may be partially mediated by improvements in depressive symptoms and sleep, and a shift toward morningness. The study findings will provide important insights relevant to the development of morning bright light treatment as an accessible treatment for chronic nociplastic pain.

Methods

Study Design

The FM Sleep A to ZZZ Study is a prospective single-center randomized clinical trial with a 3-arm parallel groups design comparing 4 weeks of morning light treatment, sleep stabilization, and TAU in patients with fibromyalgia. The TAU group will be presented to participants as a study of sleep monitoring to minimize group differences in treatment expectations. A sample diagram of the study protocol is shown in Figure 2. There are weekly study visits during the 5-week protocol, with outcome variables assessed after a week of sleep monitoring at pre-treatment (visit 3), 4 weeks later at posttreatment (visit 7), and then a follow-up 3 months after posttreatment (visit 8). All study visits will occur remotely via Zoom (Zoom Video Communications).

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Figure 2. A diagram of the 5-week study protocol with a 3-month follow-up for a participant with an average sleep schedule of 11 PM to 7 AM who is assigned to the morning light treatment. At visit 2 (V2), participants are instructed on how to wear a wrist actigraphy monitor and complete daily logs while sleeping ad lib at home. A week later, at visit 3 (pretreatment, V3), outcome measures are collected and participants are informed of their randomization to morning light treatment, sleep stabilization, or treatment as usual (TAU). During weekly visits (V4, V5, V6, and V7) participants' adherence to the light treatment and/or sleep schedule are checked (if assigned to morning light treatment or sleep stabilization), and daily logs and side effects are reviewed (all groups). Outcome measures are collected again during visit 7 (post-treatment, V7) and 3 months later during visit 8 (V8). The sleep stabilization study protocol looks similar to the morning light treatment protocol except there is no morning light treatment. The TAU study protocol looks similar to the morning light treatment protocol except the ad lib sleep during the first week of the study continues throughout the 5-week study protocol. The anticipated duration of each study visit is shown.

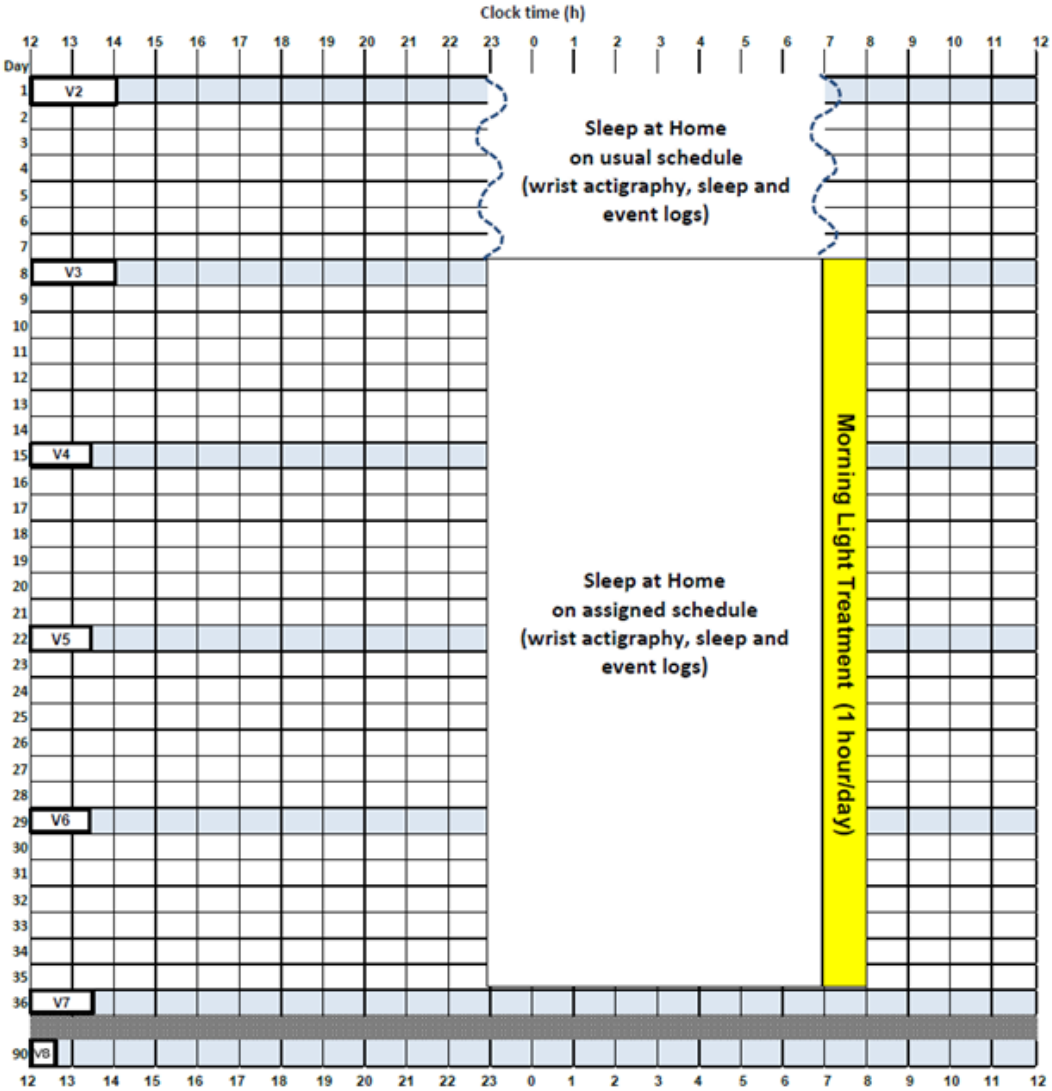

Ethical Considerations

The University of Michigan Medical School Institutional Review Board approved the research study before launch (HUM00240590), and all participants are required to provide a written informed consent document before study participation. The informed consent document outlines that the participants can withdraw from the study at any time. All research staff are required to maintain training in human participants' research, including how to maintain privacy and confidentiality. As part of the study, personal identifying information is only collected on an as-needed basis and stored in a secure REDCap (Research Electronic Data Capture; Vanderbilt University) database, or in written progress notes that are stored under lock and key in the Sleep and Circadian Research Laboratory. The clinical trial has been registered on ClinicalTrials.gov (NCT06567886). Once participants are accepted into the study, they are compensated after they complete each study visit: US $50 after Visit 2 and 8, US $100 after Visit 3, 4, 5, 6, and 7. Participants also receive a US $50 study completion bonus, as well as US $50 when the study supplies are returned, for a total payment of up to US $700.

Setting

Study participants will be recruited by the University of Michigan's Back & Pain Center using various resources of the University of Michigan's health system. The University of Michigan's Back & Pain Center is a large tertiary pain clinic that assesses around 5000 patients every year. A clinical pain research team is embedded with the clinic and has established the APOLO registry [43]. This large registry provides an ample means for recruitment of fibromyalgia patients, as most of the

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patients in the registry have agreed to be contacted for research studies. In addition, with Institutional Review Board approval, potentially eligible participants will be identified through a review of electronic medical records when available, and the study will be advertised on the University of Michigan Research Participant Registry [44]. Finally, the services provided by the Publicly Engaged Research Core within the Chronic Pain and Fatigue Research Center at the University of Michigan will also be used to prioritize the recruitment and enrollment of high SDOH risk participants. All study visits will occur with staff located at the Sleep and Circadian Research Laboratory in the Department of Psychiatry at the University of Michigan.

Study Population

We aim to enroll 390 individuals, aged 18 years or older, who meet the 2016 revised diagnostic criteria for fibromyalgia [45] (see Textbox 1). We anticipate ~70% of the sample will be female based on our previous work [46,47]. To ensure participants have at least mild symptoms, a FIQR score of ≥31 will also be required [48]. We have chosen inclusion and exclusion criteria to permit as many people with fibromyalgia as possible to participate safely, while maximizing the generalizability of findings. For example, prescribed hypnotics, over-the-counter sleep aids, antiepileptics, antidepressants, opioid analgesics, and muscle relaxants will be permitted as their use is common in fibromyalgia, but these permitted medications will need to be stable for 30 days before and during the study. Participants will be able to continue psychological therapy, physical therapy, and exercise if the treatment was started 30 days before enrollment and continues during the study period. Participants must have internet access (a cell phone can be provided for the study if required) and a private space for the remote study visits. Participation will be scheduled ≥1 month from night work, travel outside the local time zone, and other research participation, and will be scheduled during a period with minimal special events (eg, weddings, concerts, examinations).

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria:

1. Age ≥18 years old
2. Meets 2016 revised diagnostic criteria for fibromyalgia:
   - Symptoms present ≥3 months.
   - Widespread Pain Index (WPI) ≥7 & Symptom Severity (SS) ≥5 or WPI 4-6 and SS ≥9.
   - Pain reported in at least 4 of 5 body regions.
3. Fibromyalgia Impact Questionnaire–Revised (FIQR) score ≥31.
4. Fluent in English.
5. Access to the internet (study cell phone provided if required).
6. Private space for remote study visits.

Exclusion criteria:

1. Health:
   - Other significant chronic physical disease (eg, autoimmune disorders, uncontrolled diabetes, advanced liver disease, cancer, kidney failure, uncontrolled cardiovascular disease, seizures, light-triggered migraines).
   - Has a pacemaker or defibrillator (potential interference from Fitbit device).
   - Retinal pathology, cataracts, glaucoma, and colorblindness.
   - Lifetime history of psychotic or bipolar disorders.
   - Suicidality in the past 6 months
   - Alcohol or substance use disorder in the past 3 months (cannabis use ≤1/week ok).
   - High risk for or diagnosed with narcolepsy.
   - Severe hearing problem or significant cognitive impairment.
   - Pregnant, trying to get pregnant, or breastfeeding.
   - Has a child or pet at home that disturbs sleep often.
   - Pending medical leave application at work, pending legal case or litigation.
   - Working shiftwork that affects sleep.
   - Recent (<1 month) travel outside the local time zone.
   - Participating in another research study.
2. Medications:
   - Taking photosensitizing medications to blue-green light.
   - Unstable medication use 30 days before or during the study.
3. Light treatment:
   - Average wake time is before 5 AM.
   - Unable to fit 1 hour of light treatment into morning routine.
   - Previous use of light treatment in the past 6 months.

Procedures and Assessments

Potential participants will be prescreened for major inclusion and exclusion criteria using a telephone interview conducted by staff in the Back & Pain Center in the Department of Anesthesiology at the University of Michigan. If eligible, participants will then complete visit 1 (eligibility visit), which includes obtaining written informed consent and collection of self-report measures related to clinical history, demographics, and health information to determine further eligibility. Medications will be reviewed with available medical records and confirmed with each participant for accuracy. Height, weight, and visual impairment, including colorblindness, will also be collected via self-report due to the remote nature of the study (see schedule of assessments in Table 1).

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Table 1. Schedule of measure administration.

Measures	Screening		Study visits						3-month follow-up
	Phone interview	Visit 1	Visit 2	Visit 3	Visit 4	Visit 5	Visit 6	Visit 7	Visit 8
Screening and baseline measures									
Informed consent, eligibility confirmation		✓							
Demographics	✓	✓							
Height and weight (self-report)		✓							
Medical history, medications	✓	✓							
Social determinants of health (SDOH) risk score		✓							
Experiences of discrimination (EOD)			✓						
Multidimensional Scale of Perceived Social Support (MSPSS)			✓						
CDC Social Vulnerability Index (SVI)			✓						
Restless legs (CHQ[a] and sIRLS[b])			✓						
Sleep apnea (STOP-BANG)			✓						
Positive and Negative Affect Schedule (PANAS)			✓						
Self-report measures									
FIQR[c] (primary outcome)	✓			✓				✓	✓
BPI[d] (secondary outcome)				✓				✓	✓
PHQ-9[e]				✓				✓	
PROMIS[f] Sleep Disturbance 8b				✓				✓	
Morningness-Eveningness Questionnaire (MEQ)				✓				✓	
Daily logs (sleep and events)			✓	✓	✓	✓	✓	✓	
Treatment expectation				✓					
Treatment satisfaction								✓	
Objective measures									
Wrist actigraphy			✓	✓	✓	✓	✓	✓	
Safety Measures									
C-SSRS[g] (past 6 months)		✓							
C-SSRS (since last visit)			✓	✓	✓	✓	✓	✓	✓
BDI[h]			✓	✓	✓	✓	✓	✓	
SAFTEE[i]					✓	✓	✓	✓	

[a]CHQ: Cambridge Hopkins Questionnaire.
[b]sIRLS: self-administered International Restless Legs Syndrome Severity Rating Scale.
[c]FIQR: Fibromyalgia Impact Questionnaire—Revised.
[d]BPI: Brief Pain Inventory.
[e]PHQ-9: Patient Health Questionnaire—9.
[f]PROMIS: Patient-Reported Outcomes Measurement Information System.
[g]C-SSRS: Columbia Suicide Severity Rating Scale.
[h]BDI: Beck Depression Inventory.
[i]SAFTEE: systematic assessment for treatment emergent events.

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Eligible participants will be enrolled in the study at visit 2, during which questionnaires to characterize the sample will be completed (Table 1). Before visit 2, participants will be randomized to the morning light treatment, sleep stabilization treatment, or TAU group, and will be mailed the appropriate study supplies (see below for more details). All participants will receive a Fitbit Charge 5 or 6 to wear on their nondominant wrist to track their sleep and activity throughout the 5-week study protocol, along with daily logs to report their subjective experience of sleep and caffeine, alcohol, and medication use. A week later, at visit 3, pre-treatment outcome assessments will be administered, and treatment expectations will be assessed. The randomly assigned treatment condition will then begin the morning after visit 3. Thereafter, there will be weekly visits (visits 4, 5, and 6) to review each participant's adherence to instructions (sleep timing alone or paired with the use of the Re-timer, depending on treatment group) and to systematically assess side effects (all groups). At visit 7, posttreatment outcome measures will be administered, and study satisfaction will be assessed. Participants will be required to abstain from alcohol and cannabis use within 24 hours of visits, with reminders the day before each visit.

Randomization and Blinding

Participants will be randomized to either 4 weeks of morning light treatment (1 hour per day), 4 weeks of sleep timing stabilization alone, or 4 weeks of TAU in a 1:1:1 ratio. Randomization will use a minimization approach to reduce imbalances in important variables, including FIQR score (31-65 vs 66-100 to reflect the divide between mild to moderate symptoms vs severe symptoms), age (18-44 vs ≥45 years to reflect that more circadian disruption is observed in younger participants and the prevalence of FM is higher ≥45 years), biological sex (male or female), and SDOH risk index (0-2 vs 3-6, explained below). Study research assistants assessing outcomes at study visits 3 and 7 will be blinded to treatment assignment and instructed not to discuss any aspect of the treatment with participants. The participants will also be instructed not to discuss the study treatment with the blinded research staff. Otherwise, unblinded study staff will meet with participants weekly to download data from the wrist monitor and Re-timer device (in the morning light treatment group), provide feedback on adherence, and assess treatment side effects.

Intervention: Morning Light Treatment

The morning light treatment will be self-administered at home using the commercially available wearable Re-timer light therapy glasses, which emit a green light and are designed to optimize therapeutic wavelength (~500 nm, 230 $\mu W/m^2$, and 500 lux) by being close to the peak sensitivity of the circadian photoreceptors (~480 nm) [49,50]. The Re-timer device can be worn over glasses and does not interfere with ambulation, vision, reading, or computer work. Participants will be instructed to start the light treatment the morning after visit 3, immediately following their assigned wake time. Their assigned wake time will be their average final wake time as determined during the baseline week, or up to an hour earlier than their average wake time, to allow time for light treatment [37,51,52]. If the participant's assigned wake time is advanced from their average wake time, then their bedtime will also be shifted earlier to avoid sleep deprivation. The earliest start time for light treatment is 6 AM. The Re-timer device automatically turns off after 1 hour. Participants will complete the 1-hour light treatment sessions for 28 consecutive days at the same time each day. Participants will also be instructed not to sleep or meditate (closing eyes) within five hours after their assigned light treatment start time, to avoid creating a dark pulse that can counteract the effect of the light.

Adherence will be assessed via light and actigraphy data measured by a monitor (1-minute epochs, Actlumus, Condor Instruments) attached to the Re-timer, which will be reviewed with participants at the weekly study visits by unblinded staff. Research staff will contact all participants via phone call or text 10 minutes after their assigned light treatment start time each morning to ensure that they have started the light treatment. Participants will also be provided an alarm clock set to their assigned wake time to promote adherence.

Intervention: Sleep Stabilization

Participants will be instructed to start following an assigned sleep schedule the morning after visit 3. Similar to the light treatment intervention, the assigned wake time will be their average final wake time as determined during the baseline week, or up to 1 hour earlier than their average wake time. If the participant's assigned wake time is advanced from their average wake time, then their bedtime will also be shifted earlier to avoid sleep deprivation. Participants will also be instructed not to sleep or meditate (closing eyes) within 5 hours after their assigned wake time, to avoid creating a morning dark pulse that may shift circadian timing.

Adherence will be assessed via actigraphy data measured by the Fitbit Charge 5 or 6, which will be reviewed with participants at the weekly study visits by unblinded staff. Research staff will contact all participants via phone call or text 10 minutes after their assigned wake time each morning to ensure that they are awake and out of bed. Participants will also be provided an alarm clock set to their assigned wake time to promote adherence.

Comparator: Treatment as Usual

Participants assigned to TAU will be instructed at visit 3 to follow their usual ad lib sleep schedule, as they did during the baseline week. Research staff will contact these participants via phone call or text each day to encourage them to complete their daily logs. This contact, together with the weekly study visits, will ensure equivalent study contact and attention between the morning light treatment group and the TAU group. The TAU participants' wrist actigraphy data will also be reviewed weekly during the Zoom visits, with feedback on following the study procedures.

Outcome Measures

Study outcomes will be assessed in each group at pretreatment (visit 3), posttreatment (visit 7), and then at a follow-up 3 months after posttreatment (visit 8) to evaluate the duration of

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any changes in each treatment condition. The study assessment schedule is shown in Table 1.

Self-Reported Outcomes

The primary outcome measure is the FIQR [48]. The FIQR consists of 21 items that assess function, overall impact, and symptoms. Total scores range from 0 to 100, with higher scores representing worse functional status. The secondary outcome measure is the Brief Pain Inventory (BPI), which assesses for the presence of pain, pain intensity, and functional interference from pain [53]. The BPI consists of 2 scores (pain severity and pain interference) with higher scores indicating more pain or greater pain interference. The BPI has been validated for fibromyalgia specifically [54,55].

Three additional outcome measures will be explored as potential mediators. The Patient Health Questionnaire-9 (PHQ-9) is a reliable measure of the severity of depressive symptoms [56]. The PHQ-9 consists of 9 items, and higher scores reflect higher levels of depressive symptoms. The Patient-Reported Outcomes Measurement Information System (PROMIS) Sleep Disturbance Short-Form 8b is a reliable measure of sleep quality [57]. Higher scores on the PROMIS Sleep Disturbance Short-Form 8b reflect worse sleep quality. The Morningness-Eveningness Questionnaire (MEQ) [58] will be used as a proxy marker of circadian timing. The MEQ score correlates well with the gold standard circadian phase marker, the dim light melatonin onset [59], and significantly increases towards more “morningness” after 13-28 days of a morning light treatment [60]. This will allow us to confirm an expected phase advance or earlier shift in circadian timing in response to morning light treatment.

Social Determinants of Health Measures

At visit 1, an SDOH index score will be derived from individual and community-level data consistent with previous publications [61,62]. Individual-level data collected will include education, household income (and number of individuals in household to assess poverty level), marital or partner status, employment, and medical insurance status. Community-level data will also be assessed with the national Area Deprivation Index (ADI) percentile, derived from each participant’s full address. Each SDOH factor will be scored 0 for protective or 1 for risk, determined by evidence-based ranges and then summed to calculate an SDOH Risk Index score (0 indicating no risk to 6 indicating high risk). This approach accounts for the additive burden of numerous SDOH variables [63]. The following SDOH factors will be coded as 1 for high risk: (1) education up to and including high school (beyond high school is protective [64]); (2) household income below US Federal Poverty guidelines (above is protective [65]); (3) no marital or partner is a risk (presence of a partner is protective [66]); (4) being unemployed, disabled, a student or homemaker is a risk (being employed or retired is protective [67]); (5) no medical insurance is a risk (having medical insurance is protective [68]); (6) ADI percentile >80% is a risk (≤80% is protective [69]).

We will also collect three measures at study start (visit 2) to explore their utility when examining symptom burden, adherence, and treatment outcomes. These measures include the Experiences of Discrimination (EOD) questionnaire, which is a self-report measure that assesses how often people feel they have experienced unfairness on the basis of race, ethnicity, gender, age, religion, physical appearance, sexual orientation, or other characteristics [70]. Scores range from 10-60, with higher scores indicating greater lifetime discrimination. Participants will also be asked to complete the Multidimensional Scale of Perceived Social Support questionnaire, which is a self-report measure that assesses an individual’s perceived level of social support with family, friends, and significant others [71]. Scores range from 0-72, with higher scores indicating a greater perceived level of social support. The third measure will be the Centers for Disease Control’s Social Vulnerability Index (SVI) derived from each participant’s full address. The SVI is a more recently available community-level variable and incorporates census variables to identify vulnerable communities within counties based on 15 factors organized within 4 themes: SES, household composition, ethnicity/race/language, and housing transportation [72]. Higher values indicate greater vulnerability.

Additional Measures

At study start (visit 2), after eligibility is determined, participants will complete several questionnaires to characterize the sample. The Cambridge-Hopkins questionnaire [73] will assess for restless leg syndrome (RLS). For those who screen positive, the severity of RLS will be determined with the validated patient-report International Restless Leg Syndrome study group severity rating scale [74]. This scale assesses symptoms over the past 7 days, and the total score ranges from 0 (no symptoms) to 40 (very severe symptoms). Patients who do not screen positive will be assigned a severity score of 0. The severity score will be used as a moderator in the statistical analysis (see below). Participants will also be assessed for obstructive sleep apnea (OSA) with the STOP-BANG questionnaire [75]. This questionnaire assigns a point for each symptom or risk factor, and this score will also be used as a moderator in the statistical analysis. The Positive and Negative Affect Schedule (PANAS) questionnaire [76] will assess for trait positive and negative affect, and will be used to derive predisposing dispositional traits (protective or vulnerable) [77]. These traits will also be examined as a potential moderator in the statistical analyses. Finally, participants will also complete two brief questionnaires about their study expectations at visit 3, after they are informed of the condition they have been randomized to, and a study satisfaction questionnaire at visit 7.

Participants will wear the Fitbit Charge 5 or 6 on their non-dominant wrist to monitor activity and sleep. The Fitbit Charge uses accelerometry and cardiac autonomic signals to estimate sleep and has been compared to gold-standard polysomnography, demonstrating differentiation of sleep and wake states superior to US Food and Drug Administration cleared actigraphy [78]. We will export data from the Fitbit Charge in 30-second intervals using the Fitabase software. To augment the sleep data collected by the Fitbit device, sleep diaries will be completed, and participants will text a research email account to identify when they are trying to fall asleep (bedtime) and at their final wake time. Bedtime and rise time data through the time-stamped text messages will allow for confirmation of correct sleep onset and offset and calculation

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of total sleep time, wake after sleep onset, and sleep efficiency [79]. These objective sleep parameters will be primarily used to verify participant adherence to the morning light treatment and sleep timing stabilization schedule, but will also be examined for group differences. Participants will also track their daily use of caffeine, alcohol, medications, exercise, and psychotherapy on a daily event log.

Safety Measures

At each weekly visit after the start of treatment (visits 4-7), participants will complete a self-reported measure of physical and emotional symptoms they have experienced in the past week using the Systematic Assessment for Treatment Emergent Events (SAFTEE) as we and others have used in previous light treatment trials [37,52,80]. Unblinded research staff will assess the severity of symptoms and their relevance to the study and assigned group, to ensure no significant negative effects are associated with the study participation. If severity meets a pre-determined threshold based on SAFTEE, the unblinded research staff will alert an unblinded study physician to further assess the participant's safety and risk for an adverse event. In addition, at each weekly visit and 3-month follow-up, suicide risk will be assessed using the Columbia Suicide Severity Rating Scale (C-SSRS) [81], and during weekly visits, mood worsening will be examined with the Beck Depression Inventory (BDI) [82]. At least annually, an independent safety monitor will review the reported side effects and confirm it is safe to continue the study.

Statistical Power and Analysis

We plan to enroll 390 individuals, aged 18 years or older, who meet the 2016 revised diagnostic criteria for fibromyalgia [45] and have at least mild fibromyalgia symptoms (FIQR score of ≥31) [48] (see Textbox 1). We aim for 309 participants with complete data (103 per each of the 3 groups), assuming 20% attrition during the 5-week study period. The sample size will provide 80% power to detect a difference in the standardized effect sizes (changes from baseline to post-treatment) of 0.47, 0.16, and 0.05 in FIQR in morning bright light treatment, sleep timing stabilization, and TAU groups, respectively, with a two-tailed 0.05 level 1-way ANOVA test. The effect size in the morning bright light treatment group is clinically meaningful and detectable based on our previous study [37]. The effect size in the sleep timing stabilization arm is 1/3 of that in the morning bright light group, and we conservatively estimated an effect size of 0.05 in the TAU group due to study participation. The study should also have adequate power to detect a binary outcome of clinically meaningful improvement (≥30% from baseline) or achieving a treatment response (≥16.8 decrease in FIQR) [83].

We will conduct an intention-to-treat analysis. We will report descriptive statistics of the data and visually explore the summary statistics by group at each visit. We will analyze both primary and secondary outcomes using a mixed-effects longitudinal data model with participants as random intercepts to account for between-participant variability. Predictors will include post-randomization time, two intervention group indicators with TAU as the referent group, and the interactions of time by group indicators. We will examine the extent and pattern of key missing outcomes data, and if missingness is greater than 15%, we will use logistic regression to assess baseline characteristics predictive of missingness postrandomization and will include those baseline characteristics as covariates in the final model. While FIQR scores will be examined as a continuous variable, we will also examine the proportion of participants who show clinical response (a binary outcome of clinically meaningful improvement (≥30% from baseline) or achieving a treatment response (≥16.8 decrease in FIQR [83]) and analyze the binary outcome variable using a generalized linear mixed model with logit link. We will also explore the severity of restless leg syndrome, obstructive sleep apnea, dispositional trait, and biological sex as potential moderators of any treatment effects.

Results

The study was funded in July 2024. Data collection began in September 2024 and is projected to end in March 2029, with final analysis complete by June 2029. As of mid-July 2025, we have enrolled 55 participants.

Discussion

This protocol paper describes a single-center 3-arm randomized controlled trial of morning bright light treatment versus sleep stabilization alone versus TAU in people with fibromyalgia. We hypothesize that (1) participants who receive morning bright light treatment will show greater improvements in function and pain, (2) that SDOH risk will influence baseline symptom burden, treatment adherence (engagement), and treatment response, and (3) that treatment response may be partially mediated by improvements in depressive symptoms and sleep, and a shift toward morningness. This study will provide further insight into the effect of morning bright light treatment on function, pain, depression, circadian timing, and sleep in people with fibromyalgia, and inform on its role as an adjunctive therapy for patients with active symptoms. In addition, the results will help reveal SDOH barriers to assist the future dissemination and implementation of morning bright light treatment in a variety of communities.

As pharmacological therapies for fibromyalgia offer only modest benefits [11-14] and result in a high rate of discontinuation due to adverse effects [11], newer national guidelines suggest that the initial approach to the treatment of fibromyalgia consists of nonpharmacological interventions [15-17]. Physical therapy/exercise and behavioral therapies such as CBT have demonstrated efficacy but can be difficult to access in terms of cost and availability [18-20], and engagement can be problematic [21]. In our earlier study [37], we found a reduction in the FIQR similar to reductions observed after weeks of exercise, and double that seen with weeks of CBT or the use of analgesics, as reported in a recent meta-analysis [38]. Furthermore, there is a good rationale for morning bright light treatment improving fibromyalgia symptoms, due to its recognized effects on mood [22,23], sleep [24], and circadian timing [27] (see Figure 1). Thus, morning bright light treatment has good potential as a readily accessible adjunctive approach

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to manage fibromyalgia symptoms, which can be self-administered with minimal side effects.

The strength of this study includes the randomized trial design with a control group, blinding of study staff directly involved in assessing study outcomes, and a well-described conceptual model of the potential mechanistic relationship between morning bright light treatment and study outcomes. In addition, we plan for a large sample size of 390 eligible participants for good statistical power, and the study will be entirely remote, which will assist the participation of eligible participants from a wide range of sociodemographic backgrounds across the United States. The feasibility of the planned approach is high given our team's previous experience in conducting large remote clinical trials [84,85] and obtaining good treatment adherence and good-quality outcome data in our earlier pilot study (n=60) [37]. While the primary outcome measure, FIQR, is a self-report questionnaire, it is widely used in clinical trials for assessing changes in functional status and the global impact of symptoms in fibromyalgia [55]. The BPI has also been validated for fibromyalgia specifically [54,55]. We are using the Re-timer light therapy glasses because of the added convenience of enabling participants to be ambulatory during the morning light treatment, but given our earlier pilot work [35], we anticipate that our study results will also generalize to the use of bright light boxes. The anticipated study limitations include that the interventions are only 4 weeks long, although a study follow-up assessment 3 months after active treatment ends will help inform on longer-term treatment benefits of morning bright light treatment in people with fibromyalgia. We also note that, as a fully remote study, some degree of technological literacy is required of participants, such as knowing how to join an online Zoom call, and participants need to have internet access (Textbox 1).

This is the first National Institute of Health (NIH)–funded large randomized controlled trial of morning bright light treatment in fibromyalgia and has the potential to improve our understanding of the impact of morning bright light treatment on patients with nociplastic pain and fill a gap in adjunctive nonpharmacological fibromyalgia treatment. This study will also increase our understanding of the mechanistic relationships between mood, circadian timing, sleep, and fibromyalgia symptoms. If this large trial continues to support morning bright light treatment as efficacious for fibromyalgia, future research protocols can test the implementation and dissemination of morning bright light treatment for fibromyalgia and, potentially, other nociplastic pain conditions. At the conclusion of the trial, results will be disseminated via presentations, scientific publications, and self-help materials provided by the Chronic Pain and Fatigue Research Center at the University of Michigan. Summary data will be available on clinicaltrials.gov, and deidentified individual participant data will be available from the National Sleep Research Resource (see Data Availability statement).

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Data Availability

The datasets generated during this study will be available in the National Sleep Research Registry repository [86].

Authors' Contributions

Conceptualization: HJB, KTS, ALH
Data curation: HJB, AAR, KAN, JM, AF, MR
Funding acquisition: HJB, ALH
Investigation: HJB, AAR, KAN, JM, TD, MR
Methodology: HJB, AAR, KAN, JM, AF, MR, ALH
Project administration: HJB, AAR, KAN, JM, TD, MR, SS
Supervision: HJB, ALH
Writing – original draft: HJB, AAR, KAN, JM, HMK
Writing – review & editing: HJB, AF, TD, MR, KTS, CC, JWB, SS, ALF

Conflicts of Interest

HJB is a consultant for Natrol, LLC. None declared by the other authors.

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Abbreviations

ADI: Area Deprivation Index
BDI: Beck Depression Inventory
BPI: Brief Pain Inventory
CBT: cognitive behavioral therapy
C-SSRS: Columbia Suicide Severity Rating Scale
EOD: experiences of discrimination

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FIQR: Fibromyalgia Impact Questionnaire–Revised
MEQ: Morningness-Eveningness Questionnaire
NIH: National Institutes of Health
OSA: obstructive sleep apnea
PANAS: positive and negative affect schedule
PHQ-9: Patient Health Questionnaire—9
PROMIS: Patient-Reported Outcomes Measurement Information System
REDCap: Research Electronic Data Capture
RLS: restless leg syndrome
SAFTEE: systematic assessment for treatment emergent events
SDOH: social determinants of health
SVI: Social Vulnerability Index
TAU: treatment as usual

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Protocol

Testing the Efficacy of 2 Interventions to Improve Health Outcomes and Quality of Life Among Rural Older Adults Living With HIV: Protocol for a Randomized Controlled Trial

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Abstract

Background: Rural people living with HIV in the United States have higher mortality rates and lower rates of HIV suppression compared to nonrural people living with HIV. In addition, compared to younger people living with HIV, older people living with HIV face numerous challenges to maintaining health and well-being. However, few interventions have targeted health or quality-of-life outcomes in rural older people living with HIV.

Objective: This randomized controlled trial will evaluate the efficacy of 2 remotely delivered interventions—supportive-expressive peer social support groups and strengths-based case management—to improve viral suppression, medication adherence, quality of life, and depressive symptoms in people living with HIV aged >50 years in rural counties in the southern United States.

Methods: We will enroll 352 rural older (aged >50 y) people living with HIV and test the interventions using a 2 (social support groups: yes or no) × 2 (strengths-based case management: yes or no) factorial design. Supportive-expressive peer social support groups aim to increase social support and lower HIV stigma, thereby improving HIV health outcomes and quality of life. Trained facilitators will deliver the 8 weekly sessions with a set curriculum to groups of 8 to 12 participants via videoconference. Strengths-based case management is an individual-level, individually tailored intervention delivered by trained staff. Over 5 sessions, the participant-staff duo selects a barrier impacting HIV care or quality of life and identifies short-term goals to overcome the barrier, focusing on the process of incremental problem-solving while recognizing accomplishments. We will assess HIV viral load—using participant-collected dried blood spot samples—at baseline and 8 and 12 months after the intervention. Using surveys, we will assess adherence, quality of life, depressive symptoms, and secondary outcomes at baseline and 4, 8, and 12 months after the intervention. We hypothesize that participants randomly assigned to each intervention will be more likely to be virally suppressed and adherent to antiretroviral therapy and have higher quality of life and fewer depressive symptoms at follow-up than those not assigned to each intervention. Secondary hypotheses are that, compared to those not receiving each intervention, participants in each intervention will report greater social support, self-efficacy, and likelihood of accessing needed services; less loneliness and internalized HIV stigma; and fewer structural barriers. Data will be analyzed using generalized linear mixed models.

Results: Funded in April 2023, the study began enrollment in April 2024, with 177 participants having given consent by July 2025. Data collection will run through 2027 followed by analysis and publication by 2028.

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Conclusions: This study will evaluate 2 remotely delivered interventions for rural older people living with HIV for their effects on HIV health outcomes, quality of life, and depressive symptoms. If effective, these scalable interventions could improve outcomes for this growing population.

Trial Registration: ClinicalTrials.gov NCT06269081; https://www.clinicaltrials.gov/study/NCT06269081

International Registered Report Identifier (IRRID): DERR1-10.2196/71429

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KEYWORDS

HIV; older adults; rural; health outcomes; remotely delivered intervention

Introduction

Background

In the United States, more than 59,000 people living with HIV reside in rural areas, and approximately 2000 rural residents are newly diagnosed with HIV each year [1]. Rural people living with HIV have higher mortality rates than nonrural people living with HIV [2,3] and are more likely to have mental illness, substance dependence, and social isolation [4-8]. Despite having greater health care needs, rural people living with HIV are challenged by having health care providers with less experience in HIV care [4,9-11] and longer travel to medical specialists and other services [4,11-13]. Rural people living with HIV also fare worse on HIV-specific outcomes: they are less likely to be engaged in HIV care and to be virally suppressed than people living with HIV in urban areas [14].

Older adults living with HIV in rural areas face even greater challenges than their younger counterparts in overcoming barriers to care engagement and achieving viral suppression. Many older people living with HIV lack sufficient practical assistance and social support, and changes in physical and cognitive abilities may also impede care engagement and medication adherence [6,8,15,16]. To date, few interventions have been developed to improve health outcomes or quality of life among rural older people living with HIV. A 2021 systematic review of psychosocial interventions for older people living with HIV found only 9 such studies published since 2001, with the majority having fewer than 25 participants [17]. While most of these studies leveraged remotely delivered interventions, none were specifically focused on the challenges faced by rural older people living with HIV.

To address this research gap, our team has conducted a series of studies to understand challenges faced by rural older people living with HIV and develop intervention programs to improve their HIV health outcomes and quality of life. We first conducted qualitative interviews with 29 older people living with HIV in rural areas, finding that worries about HIV status disclosure, ageism, homonegativity, physical and psychological loneliness, and depression were commonly mentioned barriers to mental well-being and health care engagement [6].

We subsequently conducted a cross-sectional study of 446 rural older people living with HIV from throughout the United States and found that more than 25% had markers of low engagement in HIV care [18]. We identified a number of factors associated with low care engagement, including lower income, lack of internet access, higher stress, and longer travel distance to an HIV provider [18]. In addition, rural older people living with HIV with lower social support, greater experienced HIV stigma, lower quality of health care, experiences of discrimination in medical settings, and more structural barriers to care reported lower quality of life and poorer mental health [19]. Subsequent interviews with 27 personnel from organizations that provide medical or social services to rural older people living with HIV in the southern United States identified poverty, social isolation, stigma, and the lack of comprehensive case management services as barriers to care [20].

On the basis of this foundational research, we identified potential intervention targets to improve HIV health outcomes and quality of life, including social support, HIV stigma, structural barriers, and technology access. We then worked to adapt existing interventions and develop new interventions for remote delivery to this population. Four potential interventions were piloted with older rural people living with HIV to evaluate their feasibility, acceptability, and preliminary impact [21]. Two interventions—supportive-expressive peer social support groups and individual strengths-based case management (SBCM)—showed high levels of acceptability and positive preliminary impact [21].

Supportive-Expressive Peer Social Support Group Intervention

Supportive-expressive peer social support groups are an evidence-based intervention with the objectives of increasing social support, reducing loneliness, and reducing internalized HIV stigma and in turn improving antiretroviral therapy (ART) adherence, viral suppression, depressive symptoms, and quality of life.

Social isolation is a prominent issue faced by many older people living with HIV, particularly those living in rural areas [12]. Low levels of perceived social support have been shown to negatively impact adherence to medication among older people living with HIV [22], and increasing social support can lead to improved health outcomes and reduced internalized HIV-related stigma [23]. A review of support groups for people living with HIV found that support group interventions were associated with reductions in morbidity and mortality and improvements in retention in care and quality of life [24]. However, the benefits of in-person support groups may be unavailable to rural-dwelling older people living with HIV due to their geographic isolation. Older rural people living with HIV may be unable to access these groups due to limited transportation options, long travel distances, and limited group availability in their areas.

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On this evidence base, we lightly adapted the supportive-expressive peer group therapy intervention from Project Linkage [25] for remote delivery to older rural people living with HIV. When delivered by telephone, this intervention was shown to reduce depressive symptoms among older people living with HIV [25]. However, its efficacy for improving viral suppression, medication adherence, and quality of life for older people living with HIV has not been tested, nor has it been delivered by videoconference.

SBCM Intervention

The SBCM model is derived from social action theory [26], which situates behavior as the consequence of individual-level factors (eg, attitudes and beliefs), environmental affordances, and structural barriers (eg, access to transportation or the lack thereof). SBCM is a protocol-driven, individually directed model of social support that focuses on identifying and leveraging individual strengths to address life stressors that function as obstacles to sustained behavior change (eg, HIV medication adherence). Core elements of the SBCM intervention include establishing rapport, strengths assessment, personal planning, resource acquisition, and interpersonal collaboration between the counselor and the participant. The SBCM model [27] has been successful in linking recently diagnosed or out-of-care people living with HIV to care and reducing HIV transmission risk among people living with HIV [28-31].

Given this evidence base, we selected and adapted an individually tailored SBCM intervention [21] for delivery by telephone or video to older people living with HIV with the goal of helping address the multiple structural barriers faced by rural older people living with HIV identified in our formative research [5,6]. SBCM is hypothesized to impact health outcomes through several pathways: first, by increasing levels of self-efficacy; second, by increasing the use of available services (eg, Supplemental Nutrition Assistance Program benefits, Medicare, transportation, or medication delivery services) through referrals and warm hand-offs to service agencies; third, by reducing structural barriers; and fourth, by increasing levels of perceived social support.

Objectives and Aims

This 4-year study, supported by the National Institute of Nursing Research, will evaluate the efficacy of 2 interventions—supportive-expressive peer social support groups and SBCM—to improve viral suppression, medication adherence, quality of life, and depressive symptoms in a large sample of older (aged >50 y) people living with HIV who live in rural counties in the southern United States. Given the promise of these 2 distinct interventions, we opted to test both interventions simultaneously using an efficient 2×2 factorial design [32], which allows us to evaluate the main effect of each intervention as well as any interaction between the interventions. Group or individual interventions may better match the needs and capacity of community organizations wishing to implement interventions for rural older people living with HIV; therefore, demonstrating the efficacy of both interventions may maximize the potential for scale-up. We also chose to focus on multiple outcomes, including HIV health outcomes (viral suppression and ART adherence), broader quality of life, and mental health (depressive symptoms).

Here, we describe the protocol for the randomized controlled trial (RCT) evaluating these 2 interventions. We hypothesize that participants randomly assigned to each intervention will be more likely to be virally suppressed and adherent to HIV ART and will report higher quality of life and fewer depressive symptoms at follow-up than those not randomly assigned to each intervention. Secondary hypotheses are that, compared to those not randomly assigned to each intervention, participants randomly assigned to each intervention will report greater social support, self-efficacy, and likelihood of accessing needed services; less loneliness and internalized HIV stigma; and fewer structural barriers.

Methods

Overview of Study Design

This RCT will assess the efficacy of 2 remotely delivered interventions—supportive-expressive peer social support groups and individual SBCM—for increasing viral suppression, ART adherence, and health-related quality of life, as well as decreasing depressive symptoms, among 352 rural older people living with HIV in the southern United States. We will assess these 2 interventions using a 2×2 factorial design. Interventions will be delivered over a 5- to 8-week period, and participants will complete surveys at baseline and 4-, 8-, and 12-month follow-ups and viral load assessments at baseline and 4 and 12 months. Participant flow through the study is shown in Figure 1. The study is being conducted by researchers at the Medical College of Wisconsin's Center for AIDS Intervention Research and community partners at the Southern AIDS Coalition.

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Figure 1. Participant flow through the study. DBS: dried blood spot; SBCM: strengths-based case management.

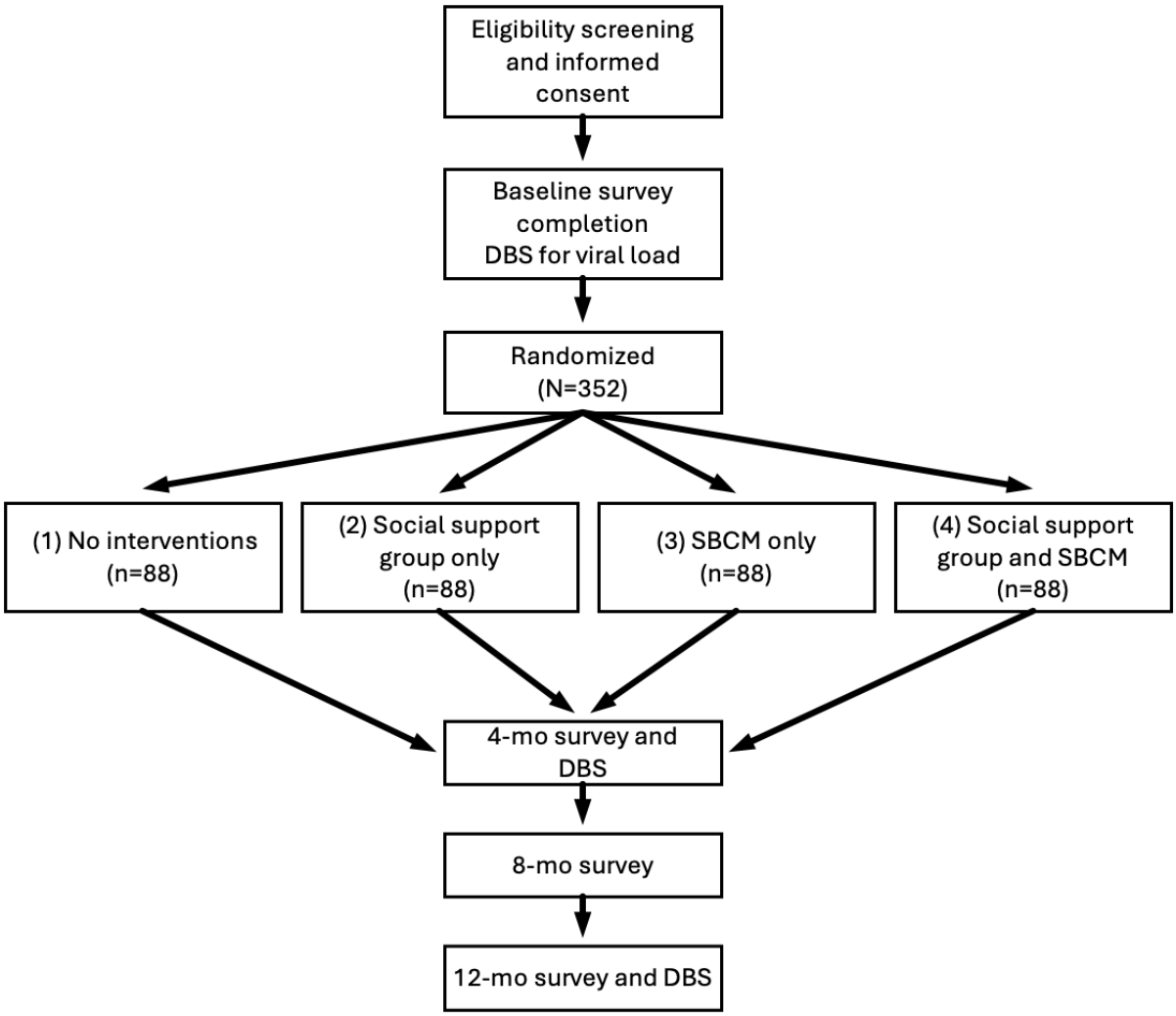

The study is registered on ClinicalTrials.gov (NCT06269081).

Ethical Considerations

This study was reviewed and approved by the Medical College of Wisconsin Institutional Review Board (00044668). A waiver of documentation of written consent was obtained to reduce the risk of loss of confidentiality, particularly for participants completing the survey on paper by mail. Per the Code of Federal Regulations (45 CFR §46.117(c)) [33], written consent may be waived for research that involves minimal risk to participants and involves no procedures for which written consent is normally required outside of the research context. Participants enrolled in this study will still undergo an informed consent process with an informed consent document. All participants will speak with study staff, who will fully describe all elements of the study and answer participant questions. Participants completing the survey via the web will check a box indicating that they have read the informed consent document and agree to participate in the study; they will be emailed a copy of the informed consent document for their reference. Participants completing the study on paper will receive a copy of the informed consent document to read and keep for their reference; returning their surveys by mail will indicate consent to participate.

Participants will receive US $50 compensation for each survey completed and US $50 compensation for each dried blood spot (DBS) specimen returned. In addition, we will provide US $5 compensation for each core intervention session attended. Furthermore, participants can earn US $20 each for referring up to 2 additional participants to the study.

Interventions

Both interventions tested in this RCT were previously shown to be feasible for remote delivery and acceptable to rural older people living with HIV during our pilot study [21].

Supportive-Expressive Peer Social Support Groups Intervention

This program, adapted from Project Linkage [25], is delivered to groups of approximately 8 to 12 participants by trained facilitators from the Southern AIDS Coalition. The groups meet weekly for 90-minute sessions over 8 weeks. Participants may choose to join each session by videoconference with or without video, or they may join by telephone for an audio-only experience. Each session has a unique focus: (1) introductions,

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program overview, and establishing group rules and expectations; (2) feelings around HIV diagnosis, stigma, and questions of "why did HIV happen to me?"; (3) values and priorities in life and thoughts about mortality; (4) uncertainty, challenges, and lack of control; (5) physician-patient relationship; (6) friend and family relationships; (7) body image and sense of self; and (8) reflection, summary, and closure. On the basis of participant feedback during our pilot, we incorporated the topic of HIV-related stigma into this intervention and also recruited group facilitators who had more shared lived experiences with participants. After the 8 group meetings, participants in groups are offered the opportunity to share their contact information with other participants if they are interested and sent instructions on how to host their own videoconference meetings should they wish to continue meeting to provide mutual social support.

SBCM Intervention

This adapted individually tailored SBCM intervention [21] is delivered by telephone or video by trained research staff over 5 sessions. The first session lasts 45 to 60 minutes and is focused on the following: (1) developing facilitator-participant rapport; (2) discussing participants' background, current needs, and life challenges (eg, transportation, food insecurity, insurance, mental health, or technology); (3) identifying and ranking life challenges that participants experience as stressors and barriers to HIV care or quality of life; (4) identifying 1 stressor to focus on for the remaining sessions; (5) discussing past strategies to deal with the stressor; and (6) setting a short-term goal related to the stressor. After the first session, the facilitator compiles and sends the participant relevant, individually tailored resources (local and online) to aid in addressing contextual factors related to the stressor of focus. During the second session of similar length, the facilitator and participant will (1) review the resource list; (2) assess progress toward the short-term goal; (3) talk about accomplishments, strengths, and skills the participant has identified in their own life; and (4) revise the strategy to achieve the participant's goals, incorporating identified strengths and skills to support progress. The final 3 sessions are optional, brief (15-30 min) check-ins, occurring at 1- to 2-week intervals, as determined by the participant and facilitator. These sessions focus on the achievement of an intermediate or long-term goal via the same collaborative process carried out in the first 2 sessions.

Control Condition: Information About Successfully Aging With HIV

All enrolled participants will be sent by US mail a printed packet of information on HIV treatment and health challenges, aging with HIV, and social support. The printed packet also includes an extensive list of resources available nationally and online for help with HIV information and support, mental health, violence, substance abuse, housing, transportation, finance, nutrition, health, and aging. Resources have been compiled from publicly available websites and brochures from the Centers for Disease Control and Prevention, National Institutes of Health, and HIV advocacy organizations [34,35]. This information will be the only intervention received by the 25% of participants not assigned to either active intervention.

Participants

The target enrollment is 352 participants who meet the following eligibility criteria: (1) living with HIV, (2) aged more than 50 years, (3) living in 1 of the 17 target states (Textbox 1; target states include rural states prioritized by the "Ending the HIV Epidemic" initiative [36] as well as other states in the US Census southern region [37] that contain rural counties), (4) living in a county with an index of relative rurality of ≥0.4 [38], (5) having a telephone at home, (6) conversant in English, and (7) able to provide informed consent. We aim to recruit a sample that represents the population of rural people living with HIV in the southern United States with respect to sex, race, and ethnicity. Accordingly, we aim to have a sample that is comprised of at least 25% female participants and 50% racial and ethnic minority participants.

Textbox 1. Eligible states.

Alabama, Arkansas, Delaware, Florida, Georgia, Kentucky, Louisiana, Maryland, Mississippi, Missouri, North Carolina, Oklahoma, South Carolina, Tennessee, Texas, Virginia, West Virginia

Recruitment

Participants will be recruited in several ways. First, study information will be distributed to AIDS service organizations and other relevant community agencies serving people living with HIV in the 17 target states. Southern AIDS Coalition staff will assist by encouraging recruitment by agencies with whom they have ongoing relationships. These agencies will be asked to distribute study flyers to their clients or patients by US Postal Service, by email, or on social media. Second, we will recruit via social media, particularly Facebook (Meta). A Facebook page has been created for the study, and paid ads targeted to older people in the target counties will be posted. Posts on the study Facebook page may also be shared by AIDS service organizations, other community organizations, or individuals. In addition, other web- and mobile app–based recruitment methods may be used to reach potential participants, such as advertisements on dating apps used by sexual minority men in rural areas (eg, Growlr, Grindr, and SilverDaddies). Third, we will contact potential participants interested in research opportunities from research registries. Finally, we will invite participants to recruit friends or acquaintances who are people living with HIV to enroll. These approaches were used to successfully reach and enroll older rural people living with HIV in our previous studies [18,19,21].

Procedures

Participants will be screened for eligibility using a web-based screener or by telephone. Study flyers contain the study web page, QR code, and our study telephone number. Online advertisements and postings contain a direct link to the screener. Study staff will contact eligible participants by telephone to

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describe the study, review the main components of the consent, and answer questions. Participants interested in enrolling will be sent either (1) a link to the web-based informed consent document and baseline survey by email or SMS text message or (2) a packet containing the informed consent document, baseline survey, and a stamped and addressed envelope for survey return via US mail. All participants interested in enrolling will also be sent a DBS study kit via US mail (refer to the HIV Viral Load Testing subsection). To guard against duplicate and fraudulent enrollments, we will require a unique and valid telephone number and postal address for each participant and speak with each participant before enrollment.

Only eligible participants who enroll in the study, complete a baseline survey, and return the baseline DBS study kit to the laboratory will be randomly assigned (refer to the Randomization subsection). After assignment, participants will be offered 0, 1, or 2 remote interventions depending on group (refer to the Interventions subsection). These interventions will be delivered over 5 to 8 weeks. Participants will complete follow-up assessments at 4, 8, and 12 months after assignment and provide DBS specimens at 4 and 12 months after assignment.

We will maximize retention by collecting multiple types of contact information (eg, telephone numbers, email address, and postal address) from participants upon enrollment. We will maximize participation in intervention sessions by providing reminders before each session using each participant's preferred method of communication and by providing a modest compensation for each core intervention session attended.

Quality Control and Fidelity Monitoring

Both interventions are manualized, and staff who deliver the interventions will be trained on using the manuals. Those delivering interventions will be equipped with checklists to further assist in obtaining fidelity. Sessions will be audio recorded (with participant agreement) to allow fidelity checks. Approximately 10% of the sessions will be randomly selected for formal review. These fidelity methods have been used successfully in our pilot [21].

Randomization

Participants will be randomly assigned to 1 of 4 conditions in a 2 (social support groups: yes or no) × 2 (SBCM: yes or no) between-participants factorial design. Randomization will occur on an individual basis using the REDCap (Research Electronic Data Capture; Vanderbilt University) randomization module. An equal number of participants will be randomly assigned to each condition. Randomization will occur in blocks of 8 and be stratified based on sex. Neither participants nor study staff will be blinded to condition assignment.

Measures

Primary and secondary outcome measures along with covariates are described in Table 1. Primary outcomes include DBS-assessed viral suppression, ART adherence, health-related quality of life, and depressive symptoms. The secondary outcomes are potential mediators of intervention effects, including social support, loneliness, internalized HIV stigma, general self-efficacy, treatment adherence self-efficacy, social and medical service use, and structural barriers (such as transportation as a barrier to care and housing instability). All primary and secondary outcomes are assessed in each survey (at baseline and 4, 8, and 12 mo) except for viral suppression, which is assessed via DBS at baseline and 4 and 12 months. Covariates are variables that will be controlled for in outcome analyses should they differ across randomized conditions or be associated with retention. We also include measures of feasibility and acceptability in the 4-month survey.

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Table 1. Study measures.

Domains and subdomains	Description or scale
Primary outcomes (baseline and 4, 8, and 12 mo)	
Viral suppression	Measured viral load <839 copies/mL in HemaSpot (Spot On Sciences) DBS[a] sample (baseline and 4 and 12 mo only)
ART[b] adherence	Wilson adherence scale [39] scores recoded to indicate imperfect vs perfect adherence, as suggested in the literature [40]
Quality of life	Scale score (0-100) on the WHOQOL-HIV BREF[c] [41], calculated as in the study by Walsh et al [21]
Depressive symptoms	Scale score (0-27) on the PHQ-9[d] depression module [42]
Secondary outcomes (baseline and 4, 8, and 12 mo)	
Social support	Scale score (1-5) on the MOS[e] social support survey [43]
Loneliness	Scale score (1-5) on the loneliness survey from the NIH[f] Toolbox [44]
Internalized HIV stigma	Scale score (1-5) on the internalized stigma subscale of the HIV Stigma Mechanisms Scale [45]
General self-efficacy	Scale score (1-5) on the New General Self-Efficacy Scale [46]
Treatment adherence self-efficacy	Scale score (0-4) on the HIV-ASES[g] [47]
Service use	Participants will report which of 12 HIV-related social and medical services they have needed during the previous 3 mo and which of these needed services they were able to obtain [48]; a composite variable will indicate whether participants successfully accessed at least 1 needed service (0=no, 1=yes)
Structural barriers	Participants will report barriers faced in the past 3 mo, with items assessing the following: not having current health insurance, transportation as a barrier to health care, finances as a barrier to health care, not having enough food to eat, not having stable housing, and lacking eHealth literacy; the number of barriers will be summed (scores 0-6)
Covariates (baseline)	
Demographics, socioeconomic position, and health	Age, sex, gender identity, sexual orientation, race and ethnicity, education, income, employment, insurance status, years living with HIV, number of comorbid health conditions, and mode of survey completion (web-based vs paper)
Geography	State of residence and Index of Relative Rurality [38,49]
Use of other services	Use of HIV case management and participation in other social support groups
Acceptability and feasibility (4 mo)	
Acceptability of interventions	Satisfaction with interventions [50,51]
Acceptability of DBS testing	HemaSpot usability and acceptability questions [52]
Session attendance	Tracked by study staff

[a]DBS: dried blood spot.

[b]ART: antiretroviral therapy.

[c]WHOQOL-HIV BREF: World Health Organization Quality of Life–HIV questionnaire short version.

[d]PHQ-9: Patient Health Questionnaire-9.

[e]MOS: Medical Outcomes Study.

[f]NIH: National Institutes of Health.

[g]HIV-ASES: HIV Treatment Adherence Self-Efficacy Scale.

HIV Viral Load Testing

At enrollment, 4 months, and 12 months, participants will be sent a DBS kit by US Postal Service to self-collect a blood sample for HIV viral load testing. The DBS kits contain a HemaSpot collection device (volume capacity 80 µL); alcohol pads; 2 single-use retractable safety lancets; gauze pads; bandages; a biohazard bag labeled with participant ID; a postage-paid envelope for specimen return; and an instruwction card, written at an eighth-grade reading level, that describes how to collect the specimen. Participants are instructed to call study staff if they need additional assistance while collecting their samples. Participants will return specimens directly to the clinical laboratory for testing using a preaddressed shipping envelope. Shipping will be tracked by the study team, and specimen arrival will be logged by the laboratory.

HemaSpot devices with sufficient blood volume will be tested using the automated Abbott m2000 platform and the RealTime HIV-1 DBS reverse transcription polymerase chain reaction

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assay [53]. The assay has a limit of detection (LOD) of 2.92 log copies/mL (839 copies/mL) and can quantify up to 7.0 log copies/mL [54]. When no HIV-1 RNA is detected, the laboratory will report a result of "not detected" or "undetectable." Detectable specimens will be binarized into qualitative and quantitative results based on the LOD. Qualitative viral load results will include those detectable but not quantifiable, as they fall below the LOD of 839 copies/mL. The laboratory will report quantitative viral load results when HIV-1 RNA is both detectable and quantifiable (≥839 copies/mL). The primary outcome of viral suppression will be defined as a viral load of <839 copies/mL.

Self-collection of DBS specimens for viral load monitoring was shown to be highly feasible and acceptable in our pilot work with older rural people living with HIV [21].

Sample Size

With the recruitment of a sample size of 352 participants and anticipated 80% retention over time, tests for effects of the interventions will have a power of 0.80 or greater for a type I error of 0.05 to detect a difference of 0.35 SDs in the mean quality of life and depressive symptoms and of 35% in ART adherence and viral suppression between participants receiving versus not receiving each intervention at each follow-up assessment. A higher retention rate will increase power to detect smaller effects.

Statistical Analysis

We will describe demographic characteristics for the sample and baseline levels of all primary and secondary outcomes. We will use ANOVA and chi-square tests to assess baseline differences in demographics and outcomes for those assigned to the 4 conditions. If significant differences between conditions exist, these will be accounted for in the primary analyses. Finally, we will assess possible sample attrition bias by examining demographic characteristics associated with loss to follow-up and by comparing retention across the 4 conditions.

We will use an intent-to-treat approach when analyzing outcomes [55]. The focus will be on the main effects of each intervention. We will use generalized linear mixed models (GLMMs) to test the impact of each intervention on the primary outcomes of viral suppression, ART adherence, quality of life, and depressive symptoms over time. This approach will test hypotheses within a repeated measures framework, with an individual identifier included in the models as a random effect to account for the correlation between participants' outcomes over time. We will test hypotheses that the social support intervention and the SBCM intervention increase the likelihood of viral suppression and ART adherence, improve quality of life, and reduce depressive symptoms at 4-, 8-, and 12-month follow-ups, compared to not receiving each intervention, by examining the main effect of each intervention. The impact on viral suppression will be evaluated at 4 and 12 months only. GLMMs will also test the 2-way interaction between the interventions to understand whether the interventions are enhanced or offset by one another. If any differences between the randomized conditions emerge in preliminary analyses, covariates will be included in the models to account for these differences; similarly, if any covariates are associated with retention in the study, these covariates will be included in the models to improve the handling of missing data. Separate GLMMs will evaluate each hypothesis, with appropriate link functions used for binary outcomes (viral suppression and adherence) and continuous outcomes (quality of life and depressive symptoms). Hypotheses will be tested at the $P<.05$ level.

The same approach will be used to test the impact of each intervention on the secondary outcomes of social support, loneliness, stigma, self-efficacy, service use, and structural barriers. We will test hypotheses that the social support intervention and the SBCM intervention increase social support, self-efficacy, and uptake of needed services as well as decrease loneliness, stigma, and structural barriers at 4-, 8-, and 12-month follow-ups, compared to not receiving each intervention, by examining the main effect of each intervention.

Exploratory analyses will assess whether intervention effects differ based on demographic characteristics—including sex, race, and age (age 50-64 y vs age >65 y)—and baseline engagement in care (low vs high). Moderation analyses will shed light on who most benefits from the intervention programs, which can help guide better targeting of the programs or future efforts to refine and tailor interventions to meet the needs of any who do not benefit. We will test moderation by introducing interaction terms into the GLMM models assessing primary and secondary outcomes. In separate models for each moderator and outcome, we will include interactions between the moderator and assignment to each intervention as predictors of outcomes. Significant interaction terms will indicate differing intervention effects across subgroups. Significant interaction terms will be "plotted and probed" to examine intervention effects within different subgroups of participants [56].

Additional exploratory analyses will test whether the amount of each intervention received (ie, the number of sessions attended) or the mode of intervention delivery (ie, Zoom [Zoom Video Communications, Inc] vs telephone) relate to outcomes. These analyses will include only those participants randomly assigned to receive each intervention. GLMM models will examine associations between the number of intervention sessions attended or mode of intervention delivery (predictors) and outcomes (viral suppression, ART adherence, quality of life, and depressive symptoms), controlling for demographic covariates as needed. Separate models will estimate dose-response and mode-response relationships for each intervention-outcome combination.

Finally, analyses will explore the mediators of intervention effects on outcomes to shed light on the potential mechanisms of intervention effects. Understanding mediating mechanisms can help guide future efforts to optimize programs by capitalizing on the key processes involved in generating health outcomes. Mediation will be tested in a structural equation model, which will be fit in Mplus (Muthén & Muthén) [57] using a full-information maximum likelihood estimator robust to nonnormality. The model will include effect-coded interventions as predictors; social support, loneliness, self-efficacy, service use, and structural barriers as mediators;

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and viral suppression, adherence, quality of life, and depressive symptoms as outcomes. For a longitudinal test of mediation, models will include mediators assessed at 4 months and outcomes assessed at 8 and 12 months. Paths will lead from interventions to all mediators and from all mediators to all outcomes. Residual correlations between different mediators and different outcomes will be allowed, and covariates will be included as needed. Although we anticipate specific mechanisms for each intervention, this method will allow for a complete understanding of the mechanisms. We will use bootstrapped CIs to assess the indirect effects of the interventions on outcomes via mediators.

To inform future intervention implementation, we will also summarize information related to the acceptability and feasibility of each intervention and of the HemaSpot DBS testing for viral load. Acceptability will be assessed by survey items (Table 1). In terms of feasibility, we will summarize participation in each intervention (eg, number of sessions attended).

Results

Recruitment and enrollment began in April 2024, with 177 participants consented as of July 2025. Recruitment is planned to conclude by April 2026. Final participant follow-ups will end by April 2027, followed by data analysis. RCT results will be disseminated by 2028 via peer-reviewed publications, presentations at scientific meetings, and ClinicalTrials.gov. Results will also be disseminated to AIDS service organizations and other community organizations via a written report and webinars. If the interventions are shown to be efficacious, full manuals will be made available to the public on our website.

Discussion

Contributions to the Field

This manuscript describes the protocol for an RCT testing the efficacy of 2 remotely delivered interventions that aim to improve viral suppression, medication adherence, health-related quality of life, and depressive symptoms among rural older people living with HIV in the southern United States. These interventions are designed to reach and engage rural older people living with HIV, a growing yet underserved population in need of health-related services. Innovations of this research include the focus on rural older people living with HIV; remote delivery of interventions to participants at home, overcoming transportation and distance barriers often faced by rural older people living with HIV; and objective assessment of viral suppression via self-collected DBS specimens.

Limitations

Our study protocol has several limitations. First, although our multiple recruitment methods are designed to reach people living with HIV with varying levels of care engagement, including those with low engagement in care who are not virally suppressed, our partial reliance on AIDS service organizations for recruitment may lead to underrepresentation of those with the lowest care engagement. However, we have reached participants with suboptimal engagement in care and medication adherence and detectable viral loads in our previous studies with this population [18,19,21]. Similarly, because there may be lower barriers to screening online (vs placing a call to study staff) and because some recruitment activities will take place online, we may be more likely to reach participants who use the internet. To avoid excluding participants without internet access, we have ensured that there are offline pathways to recruitment (study flyers mailed to potential participants and displayed in community agencies), enrollment (via telephone), survey completion (on paper via mail), and intervention participation (via telephone). Finally, although our study uses an objective measure of viral suppression that has been successfully used in our pilot work, other outcome measures are self-reported.

Conclusions

If successful, these manualized interventions, delivered to older rural people living with HIV at home, can be scaled up for rural settings across the United States, improving health equity. We hope that the results from this study will provide us with tools to improve health outcomes for a vastly understudied population and therefore advance the US “Ending the HIV Epidemic” initiative.

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Data Availability

Upon study completion, the datasets generated or analyzed during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization: AEP (lead), JLW (lead), SH (supporting), KGQ (supporting), SAJ (supporting), OHA (supporting), LR (supporting), TM (supporting)
Data curation: JLW (lead), OHA (supporting), LR (supporting)
Formal analysis: JLW (lead), TM (supporting)
Funding acquisition: AEP (lead), JLW (lead)

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Investigation: AEP (lead), JLW (lead), OHA (supporting), LR (supporting), DWL (supporting)
Methodology: JLW (lead), AEP (lead), OHA (supporting), LR (supporting)
Project administration: OHA (lead), LR (lead)
Supervision: JLW (lead), AEP (lead)
Visualization: JLW
Writing – original draft: AEP (lead), JLW (lead), OHA (supporting), LR (supporting)
Writing – review and editing: AEP (lead), JLW (lead), SH (supporting), KGQ (supporting), SAJ (supporting), OHA (supporting), LR (supporting), DWL (supporting), TM (supporting)

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report by PPAH - Population and Public Health Approaches to HIV/AIDS Study Section, Healthcare Delivery and Methodologies Integrated Review Group (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 147 KB - resprot_v14i1e71429_app1.pdf]

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Abbreviations

ART: antiretroviral therapy
DBS: dried blood spot
GLMM: generalized linear mixed model
LOD: limit of detection

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RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SBCM: strengths-based case management

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Protocol

Home-Based Digital Technologies to Support Aging-in-Place for Rural African American People With Alzheimer Disease and Their Care Partners: Protocol for a Mixed Methods Feasibility Study

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Abstract

Background: Rural, low-income African American people have the highest Alzheimer disease and related dementia (ADRD) incidence and prevalence rates but have the least access to formal dementia care. To support individuals living with ADRD, growing evidence suggests that remote monitoring technologies can augment existing care by facilitating the completion of activities of daily living (ADLs) and maintaining communication between individuals living with ADRD and their care partners. Despite the success of remote technologies, no studies have investigated the usability, acceptability, and feasibility of these technologies among rural, lower-income African American people living with ADRD and their care partners. Understanding the potential impact of remote monitoring technology on this population can guide the development of tailored aging-in-place interventions.

Objective: Among rural, low-income African American people living with ADRD and their care partners, our study, "Revolutionizing Empowerment of African Americans' Cognitive Health Through Innovative Technology," aims (1) to identify barriers to aging-in-place, current technology use behaviors, and attitudes toward remote monitoring technologies and (2) to examine the usability, acceptability, and feasibility of deploying a remote monitoring system in the homes of this population for supporting ADLs.

Methods: In total, 10 low-income African American people living with ADRD and their care partners will be recruited from rural cities in South Carolina. Participants will complete a short web-based survey to collect demographics and their knowledge, experience, and comfort with using internet-connected devices, followed by 45- to 60-minute in-depth interviews (objective 1). In phase 2 (ie, objective 2), 10 additional pairs of participants will be recruited to use a remote monitoring system for 18 months. "Weekly Health Update" surveys will measure changes in health and time spent at home. In-depth interviews will be used at 18 months to examine the usability and acceptability of the system. Feasibility will be determined by the percentage of days data are collected across all sensors.

Results: This study was approved by the institutional review board in June 2024. Recruitment for objective 1 began in January 2025. To date, 5 persons living with ADRD and their care partners have been recruited, surveyed, and interviewed about their

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challenges to aging with ADRD or caring for someone with the disease, technology use, and openness to remote monitoring technology. Recruitment for objective 2 is anticipated to begin in fall 2025, and data collection will conclude by May 2027. Results for objectives 1 and 2 are expected to be published in fall 2026 and winter 2027, respectively.

Conclusions: Findings from the Revolutionizing Empowerment of African Americans' Cognitive Health Through Innovative Technology study will contribute to the refinement of the Collaborative Aging Research Using Technology platform, a multisensor remote monitoring system to support the ADLs for low-income, rural-dwelling African American people living with ADRD.

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KEYWORDS

dementia; Alzheimer disease; remote patient monitoring; Black or African American; aging-in-place; digital technology; wearable electronic devices; internet of things; culturally appropriate technology; rural health; caregivers

Introduction

African American People and ADRD Prevalence

African American people are more than twice as likely to develop Alzheimer disease and related dementias (ADRD) than their White counterparts [1-3]. The proportion of African American people with ADRD is expected to increase by almost 25% over the next 4 decades [4]. Racial disparities in ADRD prevalence and incidence can be partially attributed to the higher burden of ADRD risk factors (ie, chronic diseases) and the long-term racial marginalization of African American people via structural racism. For example, African American people of any racial or ethnic group have the highest rates of hypertension, a risk factor for ADRD, than other racial groups [5]. Chronic disease occurrence and management are correlated with socioeconomic indicators such as income [6,7]. Evidence also demonstrates that rurality is associated with worse health outcomes [8,9], especially among southern, rural-dwelling African American people [10]. Therefore, African American people who reside in rural areas may be at higher risk for ADRD than those living in urban areas.

Aging-in-Place for Rural-Dwelling Low-Income African American People With ADRD

Rural low-income African American people with ADRD are more likely to age at home. Data from the National Alzheimer's Association show that 65% of individuals with ADRD reside in the community as opposed to living in a long-term care facility [11]. Gaugler et al [12] report that African American people are 70% more likely than White people to delay entry into a long-term care facility. These differences can be somewhat explained by factors such as African American care partners' cultural avoidance or mistrust of medical institutions [13]. A care partner is defined as "a person who undertakes, in shared partnership with another person, an active role in the provision of health, welfare, maintenance, and protection of a person" [14]. African American people with ADRD also have a higher probability than White people with ADRD of being admitted to lower quality, mostly Medicaid-funded facilities that often lack specialized ADRD care units [15]. In rural areas, these disparities are compounded by the absence of physical access to long-term care facilities, precipitated by staffing or bed shortages, lower incomes, lack of transportation, and further distance to the nearest facility compared to urban-dwelling residents [16,17]. Thus, rural low-income African American people with ADRD could greatly benefit from interventions that can support their ability to age in place.

Remote Monitoring for Supporting Individuals Living With ADRD

Remote monitoring can be useful for supporting aging-in-place for individuals living with ADRD. Considerable technological advances over the past 2 decades have enabled remote monitoring devices to assess an individual's health status, movement, or other metrics and automatically transmit this information back to care providers [18]. A remote monitoring platform can be comprised of multiple wearable, mobile or wireless, or implantable technologies [18]. For persons with ADRD, these systems frequently include passive infrared or wearable sensors for detecting or monitoring activities such as mobility (eg, walking speed), wandering, sleep quality, social isolation, disease symptoms, and completion of basic activities of daily living (ADLs; eg, eating and dressing) as well as instrumental activities of daily living (IADLs; eg, taking medication and shopping) [19,20]. Conjunctively, the data from these sensors can be analyzed in real time to identify patterns indicative of cognitive decline [21] or a threat to the individual's safety [22]. Wu et al [23] found that individuals with mild cognitive impairment (MCI) have a higher frequency of trips to the restroom and kitchen when compared to those without cognitive impairment. Similarly, findings from Alberdi et al's [24] analysis of continuous remote monitoring data show that sleep, mobility, daily routine, and outings are positively correlated with cognition and can therefore be used for tracking cognitive decline among individuals with ADRD [25,26] and also lead to a reduction in care partner distress [27,28] (identified as a key determinant of institutionalization among those with ADRD [29-31]) by enabling them to identify threats to the safety or health of the person with ADRD. Overall, these technologies may be feasible for use among individuals with early-stage ADRD and their care partners, but the routine use of remote monitoring may vary based on several factors, including the feasibility and perceived usefulness [32] of the technology and the extent to which it affects privacy [33,34].

Study Rationale

No studies, to the best of our knowledge, have explored the feasibility of using remote monitoring among rural-dwelling low-income African American people with ADRD. A growing,

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but small number of studies have investigated the feasibility and acceptability of remote monitoring for urban-dwelling African American people with MCI. Specifically, 4 recent systematic reviews on the use of remote monitoring for individuals with MCI included no African American people [31,35-37]. Five other studies [38-42] included African American people, but each comprised less than 15% of African American people with total study sample sizes averaging 70. These 5 studies examined the feasibility of using remote monitoring technology for (1) assessing the validity of using walking speed as an indicator of MCI [38,39]; (2) determining if time out-of-home is a reliable assessment of a person's cognitive, physical, and emotional state [40]; (3) discriminating between individuals with MCI and healthy individuals via a web-based questionnaire [41]; and (4) assessing the efficacy of using computer use patterns as an indicator of MCI [42]. Each study concluded that unobtrusive remote monitoring technologies could be feasibly and effectively used in homes to identify changes in cognition. More recent studies included larger samples of African American people (range 39-68), but African American people in these studies served as healthy (ie, no cognitive decline) urban comparison groups [23,43,44]. The largest of these studies was conducted to develop and test the feasibility of the remote monitoring Collaborative Aging Research Using Technology (CART) remote monitoring platform (proposed for use in this study and described in detail in the Methods section) to capture data from a variety of sensors over an extended period [44]. Their 301-participant sample included 4 diverse cohorts: rural White veterans from Oregon and Washington, low-income White people from Portland, Oregon; African American people (n=68) from Chicago; and Latinx and Hispanic residents from Miami [44]. The findings show that the CART platform was feasible for capturing scalable, real-time data from persons with and without MCI [44]. Analyses were not conducted on racial or ethnic or rural versus urban differences in feasibility. Based on these studies, remote monitoring may be feasibly used among urban-dwelling, African American people who are healthy or have cognitive impairments, but little is known about feasibility in the homes of rural-dwelling, low-income African American people. Therefore, additional research is warranted to determine if remote monitoring is appropriate for empowering this population to manage their health. The study objectives below attempt to fill this research gap. To enhance participants' ability to remember the study name and emphasize the mission of this research, the research team created the following name and acronym: Revolutionizing Empowerment of African Americans' Cognitive Health Through Innovative Technology, which will be referred to by its acronym "REAACH-IT" throughout the remainder of this narrative.

REAACH-IT Study Objectives

To ascertain the readiness of rural-dwelling African American people with ADRD and their care partners to accept CART remote monitoring technologies and the challenges to implementing such technologies in rural areas, our research aims (1) to identify barriers to aging-in-place, current technology use, and attitudes toward remote monitoring technologies among low-income African American people with ADRD and their care partners and (2) to examine the usefulness, usability, acceptability, and feasibility of deploying an existing remote monitoring system in the homes of rural low-income African American people with ADRD for supporting ADLs. Related to objective 2, we will examine whether the usefulness, usability, and acceptability of the individual CART remote monitoring technologies (eg, smartwatch) are correlated with participants' characteristics (ie, demographics), digital readiness, and feasibility. Further, we would like to determine if outcomes differ between persons with ADRD and care partners.

Conceptual Framework

The research will be guided by the unified theory of acceptance and use of technology [45] and the dynamic tension model of aging-in-place [46]. The former suggests four key constructs: (1) performance expectancy (ie, usefulness or the degree to which a person believes that using a technology will contribute to personal gains), (2) effort expectancy (ie, usability or the degree of ease with technology use), (3) social influence (ie, the degree of importance that one perceives their social network will place on the use of the technology), and (4) facilitating conditions (ie, feasibility or the degree to which one believes that an organizational and technical infrastructure exists to support system use), along with other personal factors (eg, age and experience) contribute to an individual's adoption of a technology for routine use [45]. The latter postulates that aging-in-place experiences are comprised of 3 interconnected constructs: identity as an older adult (ie, independence and feeling purposeful), connectedness with others (ie, socialization), and sense of place (ie, comfort or familiarity in home and community) [46]. Older adults experience threats to each of these facets of their aging-in-place experience and must negotiate a balance between them and the agency of the older adult or care partner [46]. According to Lawton and Nahemow [47], how well a person can manage their day-to-day activities (ie, adaptive functioning) depends on personal factors such as their physical and cognitive health (ie, competence) and the challenges or opportunities presented by the environment (ie, environmental press). Therefore, adaptations to the environment or the strategies used to strengthen the older adult's ability to complete tasks could enhance the fit between the older adult and their home environment. For example, cognitive decline may compromise a person's ability to remember to take medications (IADL), but they might negotiate this threat by adopting a pillbox with alerting capabilities. Based on these theoretical concepts, remote monitoring technologies that are feasible and perceived as useful for facilitating the completion of ADLs or IADLs may be considered acceptable for long-term use by care partners and persons with ADRD.

Methods

Study Reporting

This study adheres to the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) and [48] the MMR-RHS (Mixed Methods Reporting in Rehabilitation and Health Sciences) [49] guidelines to improve the quality and transparency of our study reporting.

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Description of the CART Remote Monitoring Platform

The CART platform [44,50] is a nonproprietary remote monitoring system iteratively developed since 2001 by researchers, statisticians, and software developers at the Oregon Center for Aging and Technology. Leading-edge discrete sensors, communication technologies, and data algorithms comprise the platform that enables the continuous measurement of daily activities and behaviors in the homes of older adults. It can integrate data from several commercial sensor technologies (Figure 1). Data are securely transmitted to secure servers by a hub computer using a virtual private network or via application programming interface calls to third-party vendor servers (eg, Fitbit for smartwatch data). Advanced algorithms translate the data into useful information, such as sleep and waking cycles and medication adherence. For the proposed study, the following CART technologies will be deployed and tested for feasibility: (1) smartwatch: tracks step counts and sleep metrics; (2) electronic pillbox: records timestamps when the pill compartment lids are opened and closed; (3) computer or phone activity tracker: collects the number or duration of computer sessions, phone calls, or texts and types of apps used; (4) door sensors: tracks door opening or closing; (5) motion sensors: measures walking speed and rooms visited; (6) undermattress sleep sensors: measures waking or sleeping times, sleep quality, and heart rate; and (7) scale: measures weight and body composition.

Figure 1. Example of a home outfitted with CART technologies. CART: Collaborative Aging Research Using Technology.

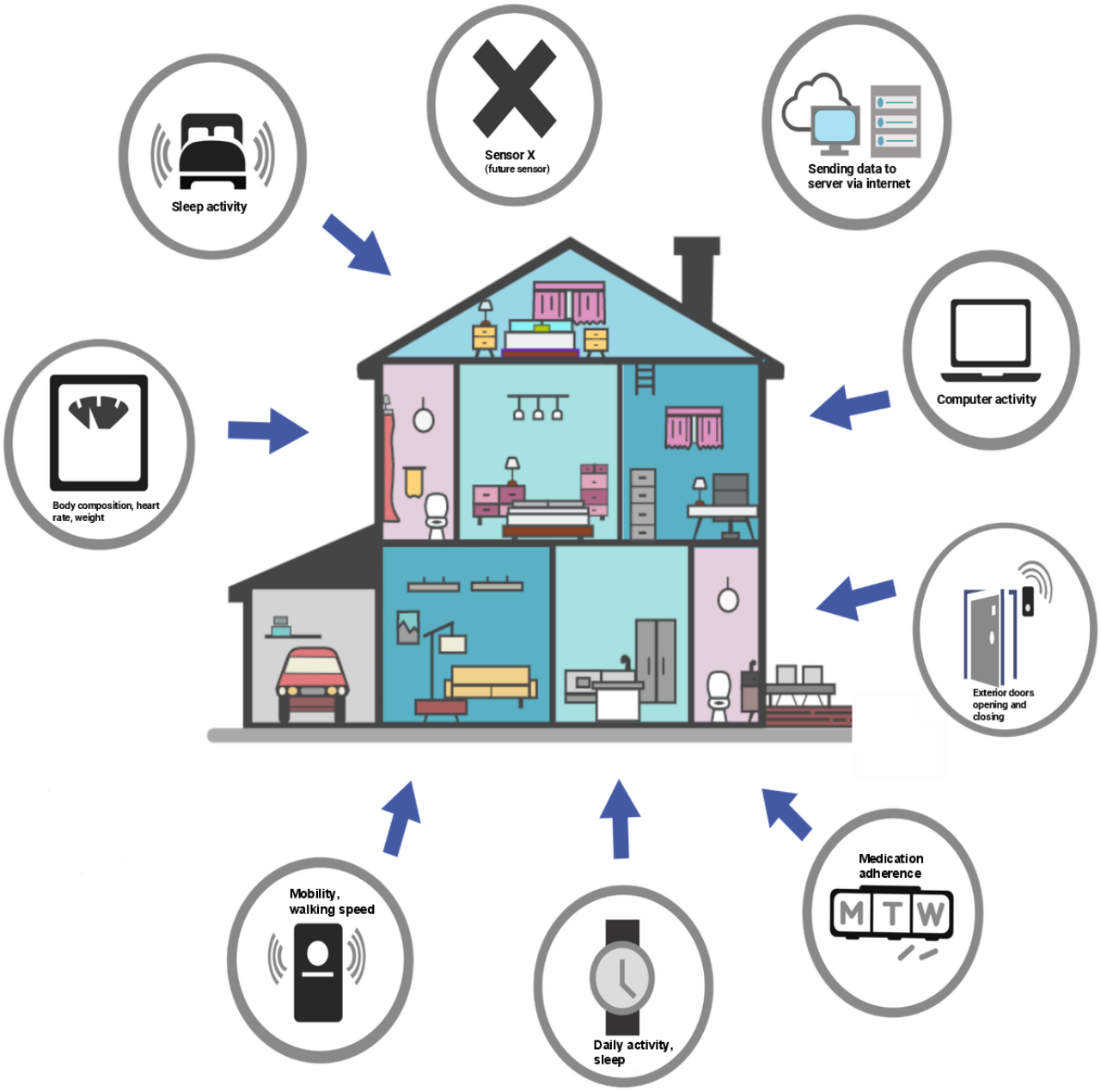

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Study Design

The study used a mixed methods, parallel convergent study design to independently gather qualitative and quantitative data, which will be merged to compare and interpret the findings in the context of our study questions.

Setting

All research activities will be conducted in the homes of study participants in rural South Carolina.

Participant Recruitment and Eligibility

For study objective 1, a sample of 10 pairs, that is, 10 African American people with early-stage ADRD and 10 care partners will be recruited to complete surveys and in-depth semistructured interviews. Care partners can live with or separately from the person with ADRD. However, the care partner should have an active role in supporting the person with ADRD with a strong knowledge about the challenges they are experiencing with aging in place. An additional 10 pairs of participants will be recruited for study objective 2 to test the CART platform, complete a web-based Weekly Health Update survey, and complete in-depth semistructured interviews. See Multimedia Appendices 1 and 2 for copies of the similar, but separate, interview guides for care partners and persons living with ADRD. Participants must meet the criteria outlined in Textbox 1 or will otherwise be excluded. Initial study eligibility will be determined by telephone, where participants will be asked about their race, income, and zip code. Cognition status will be determined using the 11-item Telephone Interview for Cognitive Status (total score of 40, where lower scores can denote cognitive decline) [51] and the 10-item Quick Dementia Rating System (total score of 30, where higher scores can denote cognitive decline) [52]. The Telephone Interview for Cognitive Status measures a person's memory, orientation, attention, and language and has been validated for use in multiethnic populations [53]. Similarly, the Quick Dementia Rating System is a short, validated self-reported scale that assesses functioning in different domains of day-to-day life and has also been used in multiethnic studies [52,54-58]. Persons with ADRD who score between 23 and 33 (MCI or early-stage ADRD) [59] on the Telephone Interview for Cognitive Status and ≧1.5 on the Quick Dementia Rating System (mild or greater cognitive impairment) [54] will be eligible to participate. Care partners' cognition will also be assessed using the Patient-Reported Outcomes Measurement Information System Short Form version 2.0—Cognitive Function Abilities Subset 8a, an 8-question survey with Likert scale responses [60]. Care partners must have a *T* score equal to or above 50 on the Patient-Reported Outcomes Measurement Information System (in addition to other criteria in Textbox 1) to be considered eligible. Any person not meeting all eligibility requirements will be excluded from the study.

Textbox 1. Participant inclusion criteria.

Person living with Alzheimer disease and related dementia (ADRD)

- Have a self-reported memory impairment
- Telephone Interview for Cognitive Status score between 23 and 33
- Quick Dementia Rating System score ≧1.5
- Identify as African American
- Be English-speaking
- Can consent or assent to study participation
- Live in a rural area as defined by the US Census Bureau
- Have a household income below 200% of the federal poverty level
- Has a caregiver who is willing to participate in the study
- Must have home internet access (criteria for objective 2 only)
- Be comfortable with being remotely monitored for 1 month (β test) or 18 months (feasibility test; criteria for objective 2 only)

Care partner

- Be at least 18 years of age
- Have no self-reported memory impairment
- Patient-Reported Outcomes Measurement Information System *T* score ≧50
- Be comfortable using remote monitoring technology for 1 month (study objective 1, β test) or 18 months (study objective 2, feasibility test; criteria for objective 2 only)
- Be English-speaking
- Can legally provide consent to study participation for a person living with ADRD if they assent
- Must have internet access (criteria for objective 2 only)

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Recruitment strategies used in this study will be based on the framework proposed by Dennis and Neese [61], which was designed for recruitment and retention in minority communities. The framework emphasizes community-based participatory research methods, including conceptualization, planning, and development of the recruitment plan and promotional materials in collaboration with community or institutional partners. In this ongoing study, participants will continue to be recruited in partnership with multiple local academic organizations, community-based organizations, and rural clinics. These organizations will display, distribute, mail, or email flyers to potential participants. Flyers contain contact information for the principal investigator (OO) and a QR code that links to a study interest form.

Sample Size

The sample size for this study was selected based on project resources and the number of participants needed to conduct an exploratory study that can be used to generate hypotheses about which factors might have the greatest influence on the successful acceptance and use of the CART platform and also estimate effect sizes for a larger study in the future [62,63].

Data Collection for REAACH-IT Study Objective 1: Formative Research

The care partner and person with ADRD will each complete separate short demographic surveys along with their questionnaires to assess "digital readiness," a concept described by Leese et al [64] as "a participant's knowledge, experience, and comfort level with using Internet devices." This questionnaire contains 16 items with Likert-scale response items that range from 1=strongly disagree to 5=strongly agree. Both surveys will be administered via Qualtrics XM (Qualtrics), a web-based survey dissemination tool that can be accessed via email or administered by the principal investigator (OO). Care partners and persons with ADRD will then be engaged in separate 60-minute in-depth interviews to assess their key challenges to aging-in-place or being a care partner, current technology use behaviors, and attitudes toward remote monitoring technologies. In-depth interviews are ideal for this study because they provide a similar breadth of content as focus groups but require significantly fewer people to reach saturation [65,66].

Saturation will be determined by the point at which there is no new salient information [67]. If saturation is not reached within the 10 dyads, additional dyads will be recruited. Including care partners and persons with ADRD in separate interviews will solicit authentic individual perspectives uninfluenced by acquiescence bias or conversation domination that can occur when there is a power differential within a dyad [68]. We acknowledge that persons with ADRD may have varying challenges with word finding, abstract reasoning, concentration, and other skills necessary to follow a complex conversation [69], but there are several evidence-based strategies (eg, allowing ample time to respond, using participant wording, redirecting conversations, monitoring for signs of fatigue, making visual and sensory adaptations to interviews, and participatory techniques that prioritize the hands-on involvement of people with dementia) that can be used to effectively involve individuals with early stage ADRD in interviews [69-71]. The interview guide for this study will be based partly on a worksheet created by Tiersen et al [72] that assists care partners and those with ADRD to identify and prioritize ADL or IADL challenges that can be addressed by remote monitoring technology. The worksheet contains pictures of each daily activity (eg, taking medication) with space to indicate the level of priority for needing support for each task on a 0=not important to 10=very important scale. Based on the selected items, the interviewer will pose questions about how participants with ADRD and their care partners co-manage these tasks. Participants will also be asked about the strategies or types of technologies they use to overcome the identified challenges. To explore their openness to using remote technology, the facilitator will present pictures or physical examples of 7 remote monitoring technologies and explain how they might overcome ADL or IADL challenges. After each explanation, participants will be asked about their perceived usefulness, usability, acceptability, feasibility, and barriers to using the technology. All participants will be shown the types of data that can be derived from each of the 7 technologies, along with ways these data could potentially be visualized in a weekly, "at a glance" report. The goal is to determine the most useful data for all participants. For persons with ADRD, their comfort with having remote monitoring devices installed in their homes and the specific types of monitoring devices they deem appropriate will be ascertained. These open-ended questions will be based on both validated measures (ie, barriers to aging-in-place [72], perceived usefulness [45], usability [64], and acceptability [64]) and the expertise of the research team (ie, barriers to technology use). See Table 1 for all measures and outcomes for both study objectives.

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Table 1. Theoretical constructs, outcomes, measures, and data collection methods.

Research objective	Theoretical constructs	Indicators or outcomes of interest	Measures	Data collection methods
1	Threats to aging-in-place[a]	Challenges with ADLs[b] or IADLs[c]	• Needs map ranking worksheet of ADLs or IADLs that can be addressed via technology • Open-ended questions about challenges to ADLs or IADLs	• Survey • In-depth interviews
1 and 2	Performance expectancy[d]	Usefulness of technology	• Open-ended questions about the usefulness of technology • Perceived Usefulness Scale [45]	• In-depth interviews • Surveye
1 and 2	Effort expectancy[d]	Barriers to technology use	• Open-ended questions about barriers to technology use • Technology Usability Scale [64]	• In-depth interviews • Surveye
1 and 2	Social acceptance[d]	Acceptability	• Open-ended questions about acceptability • Technology Acceptability Scale [64]	• In-depth interviews • Surveye
2	Facilitating conditions[d]	Feasibility	• Percentage of days of continuous data collected	• Automated data tracking
1 and 2	Individual characteristics	N/A[f]	• Demographics • Digital readiness measure [64] • Weekly Health Update	• Surveys

[a]Construct from the dynamic tension model of aging-in-place.

[b]ADL: activity of daily living.

[c]IADL: instrumental activity of daily living.

[d]Construct from the unified theory on technology use and acceptance.

[e]Surveys will only be administered during feasibility testing (research objective 2).

[f]N/A: not applicable.

Statistical Analysis for REAACH-IT Study Objective 1

Descriptive and inferential survey data statistics will be generated using SPSS (version 26.0; IBM Corp). Qualitative analysis will follow a 6-step thematic analysis approach [73] guided by our theoretical framework. The principal investigator (OO) and a coder will (1) read all transcripts for accuracy and become familiar with the data and (2) independently open-code transcripts by hand to develop a set of initial codes, which will be thoroughly discussed. The most salient codes will be used to create a codebook and to recode (ie, axially code) transcripts using NVivo (version 17.0; Lumivero). The coding team will meet to engage in an analytic process, whereby emergent themes relevant to barriers to aging-in-place for African American people with ADRD, strategies used to address these barriers, and attitudes on remote monitoring will be compared and contrasted within and between interviews. The process will include (3) discussing emergent themes, (4) reviewing and deciding on the most prominent themes, and (5) defining a final set of themes. The thematic discussion will occur only after intercoder agreement is met. If not met, the coding team will meet to discuss areas of disagreement to improve study reliability and bring in a third coder to develop consensus as needed. The final step will be (6) using the results to determine if specific CART remote monitoring technologies are appropriate for use in this population.

Data Collection for REAACH-IT Study Objective 2: Feasibility

β *Testing Experiment*

All β testing activities will be in the homes of 2 dyads (n=4) who participated in objective 1 interviews. Persons living with ADRD must have home internet to participate in β testing, and care partners must have general internet access. β Testing will identify any unforeseen issues before full technology deployment and will take place over 1.5 months. During week 1, the principal investigator and a technology installer will deploy the 7 aforementioned CART technologies (ie, smartwatch, pillbox, computer or phone activity tracker, door sensors, motion sensors, sleep sensors, and scale). To complete the Weekly Health Update surveys and receive weekly data reports, all participants will need access to email. Participants without access to a mobile device or computer will be provided with a tablet to be used specifically for the study. The principal investigator will assist participants without a current email address in setting up an email address. Other than an explanation of the installed technologies and ensuring each participant's access to email, no additional training is required because of the passive nature of the system. Over the next month, the research team will monitor the system to ensure that it is

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working properly. The care partner and person with ADRD will receive an automated weekly email with an "at a glance" report that will relay plain-language information from all sensors (eg, times medication taken each day). Persons with ADRD will complete an emailed Weekly Health Update survey (13 items) that solicits information about health events and other behaviors in the prior week, such as emergency room visits or travel [64]. The survey will be distributed via a Qualtrics survey. Qualtrics-generated reminders will be sent daily for up to 3 days before the principal investigator contacts the person with ADRD or their care partner to complete the survey. In an instance where the person with ADRD is unable to complete the survey, the care partner will be forwarded the link and asked to complete it. At the end of the month, the principal investigator will schedule separate 30-minute in-person interviews with care partners and persons with ADRD to ask about the usefulness, usability, acceptability, and barriers to using each of the installed remote monitoring technologies [64]. The principal investigator will then collect all CART technologies and compensate each participant US $100 for their participation. Qualitative data will be analyzed using a similar process to research objective 1. Saturation will not be necessary for β testing, as the goal is to assess critical barriers to implementation prior to the feasibility study. Feasibility will be calculated based on the data coverage (ie, percentage of days the technology successfully collected and transmitted data, with 80% as the measure of success). Descriptive statistics will be calculated for the Weekly Health Update survey.

Feasibility Study

The CART platform will be deployed as described in the β testing experiment to collect data remotely over 18 months in the homes of 10 persons living with ADRD who were not involved in objective 1 or β testing activities. Following consent, care partners and persons with ADRD will receive short surveys on a tablet computer, with assistance from the principal investigator, that solicits demographic information (10 items) and measures digital readiness (16 items) [64]. Qualtrics will send the Weekly Health Update questionnaire to persons with ADRD and reminders once per day for 3 days before the care partner and the person with ADRD are contacted by the principal investigator. Care partners and persons with ADRD will be emailed "at a glance" reports each week that provide meaningful data from all sensors (eg, quality of sleep). After 18 months, all participants will be interviewed separately about the usefulness, usability, acceptability, and barriers to using each of the remote monitoring technologies. They will also each be provided with a survey administered via a tablet that measures usefulness [45] (4 items), usability [64] (5 items), acceptability [64] (4 items), and barriers to use [64] (6 items) for each of the sensors and devices individually. This survey will be pretested with a sample of 5 volunteers prior to deployment. Feasibility will be determined by the percentage of days data are continuously collected across all remote monitoring sensors [64]. Each participant will receive US $55 per month compensation for their time and effort.

Statistical Analysis for REAACH-IT Study Objective 2

Quantitative Analysis

Descriptive and inferential statistics of survey data will be generated using SPSS. To examine the relationships between dependent (usefulness, usability or barriers to use, and acceptability) and independent variables (digital readiness and demographics) across all participants, we will run Pearson correlation analyses for each of the sensors and devices. Independent 2-tailed *t* tests will be used to compare differences in independent and dependent outcomes of the care partner and the person living with ADRD. Technical feasibility success will be benchmarked to 80% of days with sensor or device activity captured and 80% with watch wear-time, pillbox lid openings, and weight taken.

Qualitative Analysis

Data analysis will follow a 6-step thematic analysis approach as described in objective 1. Quantitative and qualitative results will be integrated consistently with a mixed methods (convergent parallel) design to give a comprehensive picture of whether and under what circumstances remote monitoring technology is useful, usable, acceptable, and feasible among the target population. More specifically, to integrate quantitative and qualitative data, a matrix will be used to merge data by mapping survey items for usefulness, usability or barriers to use, and acceptability to qualitative data [74,75]. The matrix will enable co-coders to systematically identify areas where the qualitative and quantitative data converge and diverge. For example, if quantitative data indicate that a specific system component (eg, smartwatch) is easy to use, the team can not only investigate whether the qualitative results mirror the quantitative results but also what features of the smartwatch make it easy to use. In the instance where qualitative and quantitative data diverge across multiple participants, the team will engage in member checking to explore possible contextual explanations for these differences in quantitative and qualitative reporting. Member checking will also enhance the credibility and confirmability of the data.

Ethical Considerations

Ethics approval was granted by the University of South Carolina's Institutional Review Board (Study ID: Pro00137669, June 19, 2024). The study was conducted according to the principles expressed in the Declaration of Helsinki [76]. The principal investigator will first review the consent form with the care partner before requesting their signature. Once the care partner has consented and indicated their willingness for the person with ADRD to participate, persons with ADRD will undergo a brief interview to determine their capacity to give consent. The principal investigator will review a printed copy of the consent with persons who have ADRD. The person with ADRD will then be asked 5 questions from the "Evaluation to Consent" instrument (α=.81) [77], which will determine whether he or she understand factors such as "two things they will be asked to do as a part of the study" and "what to do if they no longer want to participate in the study" [77]. All answers must be correct to be deemed eligible to provide consent. If the person

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with ADRD can consent, they will be asked to sign a consent form after the principal investigator responds to any questions. Persons unable to consent, based on the "Evaluation to Consent" instrument, will be asked to provide assent with the care partner's permission. Those unable to consent or assent will be excluded. The same consent process will be used for all participants (ie, study objectives 1 and 2). Rigorous measures will be implemented to ensure the confidentiality of participants' personal information. All data will be stored on highly secure computer servers, which will be restricted to authorized study personnel. To maintain confidentiality, these encrypted data will not be directly linked to the participant's name, phone number, or other key identifying information. Audio data will be quickly transcribed and destroyed immediately following transcription. Transcripts will also be stored on secure computer servers. Physical data storage areas will also be locked and monitored to deter unauthorized physical access. Participants who complete objective 1 will receive a one-time US $100 gift card. Participants who complete the β or feasibility study in objective 2 will receive a US $55 gift card at the end of each month for the duration of the study.

Results

To date, we have recruited half of the participants needed for our formative study (objective 1), which is expected to be completed by September 2026. Recruitment for objective 2 is anticipated to begin in fall 2025, and data collection will conclude by May 2027. Results for objectives 1 and 2 are expected to be published in fall 2026 and winter 2027, respectively.

Discussion

Principal Findings

This protocol outlines a mixed methods effort to assess the feasibility of a remote monitoring platform, CART, among low-income rural-dwelling African American people living with ADRD and their care partners. We anticipate, based on our theoretical framework and prior literature, that CART technologies will be reported as useful, easy to use, and acceptable for persons living with ADRD and their care partners, but these outcomes will be highly dependent on participant's characteristics (eg, education), digital readiness (eg, prior experience using similar technologies), and perceived performance of the technology to manage aspects of their daily lives. Study findings will contribute to a comprehensive understanding of the unique needs of low-income rural-dwelling African American people living with ADRD and their care partners. Results will elucidate under what circumstances and to what extent individual CART technologies and the platform can address the needs of persons with ADRD and their care partners. Further, findings will be valuable for the co-refinement of CART in partnership with input from community end users and stakeholders. Future dissemination of a culturally appropriate version of CART among diverse socioeconomic and racial or ethnic groups with ADRD can empower them to remain safely in their homes.

Comparison With Prior Work

Several studies have highlighted the benefits of remote monitoring technology for persons with ADRD, such as the successful monitoring of the mobility and daily activities of persons with ADRD [31,35-37]. The CART platform, which will be tested in this study, has been feasibly and efficaciously used for continuous monitoring of multiple wellness indicators (eg, sleep, cognition, physical mobility, and social engagement) in ethnically, racially, and socioeconomically diverse cohorts in urban and rural settings [44,50]. However, the African American participants in these evaluations were cognitively sound and lived in urban areas. To our knowledge, CART nor any other comprehensive multisensor remote monitoring platforms have been evaluated among low-income, rural-dwelling African American people with ADRD. The proposed study will fill this research gap by determining the usefulness, usability, acceptability, and feasibility of deployment in the homes of rural low-income African American people with early-stage ADRD and their care partners.

Strengths and Limitations

One key strength of this study is the use of a mixed methods study design, which will provide a methodologically rigorous means to corroborate research findings and gain a contextual understanding of factors influencing the usefulness, usability, acceptability, and feasibility of the CART platform among an understudied population. Limitations include this exploratory study's small sample size, which limits the generalizability of study findings and also inhibits more complex statistical analyses. However, this study will still be useful in the generation of hypotheses and the estimation of effect sizes for a larger study in the future. For example, a strong positive correlation between digital readiness and usability scores, even if not statistically significant, would suggest that digital readiness is a key factor to consider in recruitment and training for a subsequent study. Likewise, observing a medium to large effect size in a small sample could indicate a practically meaningful difference between the care partner and the person living with ADRD that warrants further investigation. Guided by findings from this study, future research should evaluate the CART platform among a larger participant sample and explore the system's capacity for providing clinically meaningful health outcomes or diagnostic data.

Conclusions

The CART remote monitoring platform represents a promising innovation for enabling aging-in-place among rural, low-income, African American people with early-stage ADRD or their care partners. Our proposed research is critical for assessing CART's usability, acceptability, and feasibility among a highly vulnerable population. This protocol outlines a mixed methods approach to gain a thorough understanding of participants' lived experiences and daily needs that can be reliably supported by the CART platform. Findings will contribute to further customization of the CART platform that may lead to a greater likelihood that low-income, African American people with early-stage ADRD can safely age in place in the future. Having access to additional technological support to augment

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home-based and clinical care may also improve the quality of life for both persons with ADRD and their care partners.

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Conflicts of Interest

Oregon Health & Science University authors (JK, ZB, TR, and NS) have a financial interest in Life Analytics, Inc (CEO: LF), a company that may have a commercial interest in the results of this research and technology. This potential conflict of interest has been reviewed and managed by Oregon Health & Science University.

Multimedia Appendix 1
Alzheimer disease and related dementia interview guide.
[DOCX File , 36 KB - resprot_v14i1e78623_app1.docx]

Multimedia Appendix 2
Care partner interview guide.
[DOCX File , 37 KB - resprot_v14i1e78623_app2.docx]

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Abbreviations

ADL: activity of daily living
ADRD: Alzheimer disease and related dementia
CART: Collaborative Aging Research Using Technology
IADL: instrumental activity of daily living
MCI: mild cognitive impairment
MMR-RHS: Mixed Methods Reporting in Rehabilitation and Health Sciences
REAACH-IT: Revolutionizing Empowerment of African Americans' Cognitive Health Through Innovative Technology

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SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

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Protocol

Artificial Intelligence–Assisted Image Extraction in Neonatal Echocardiography for Congenital Heart Disease Diagnosis in Sub-Saharan Africa: Protocol for Model Development

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Abstract

Background: Sub-Saharan Africa (SSA) bears the highest global burden of under-5 mortality, with congenital heart disease (CHD) as a major contributor. Despite advancements in high-income countries, CHD-related mortality in SSA remains largely unchanged due to limited diagnostic capacity and centralized health care. While pulse oximetry aids early detection, confirmation typically relies on echocardiography, a procedure constrained by a shortage of specialized personnel. Artificial intelligence (AI) offers a promising solution to bridge this diagnostic gap.

Objective: This study aims to develop an AI-assisted echocardiography system that enables nonexpert operators, such as nurses, midwives, and medical doctors, to perform basic cardiac ultrasound sweeps on neonates suspected of CHD and extract accurate cardiac images for remote interpretation by a pediatric cardiologist.

Methods: The study will use a 2-phase approach to develop a deep learning model for real-time cardiac view detection in neonatal echocardiography, utilizing data from St. Padre Pio Hospital in Cameroon and the Red Cross War Memorial Children's Hospital in South Africa to ensure demographic diversity. In phase 1, the model will be pretrained on retrospective data from nearly 500 neonates (0-28 days old). Phase 2 will fine-tune the model using prospective data from 1000 neonates, which include background elements absent in the retrospective dataset, enabling adaptation to local clinical environments. The datasets will consist of short and continuous echocardiographic video clips covering 10 standard cardiac views, as defined by the American Society of Echocardiography. The model architecture will leverage convolutional neural networks and convolutional long short-term memory layers, inspired by the interleaved visual memory framework, which integrates fast and slow feature extractors via a shared temporal memory mechanism. Video preprocessing, annotation with predefined cardiac view codes using Labelbox, and training with TensorFlow and PyTorch will be performed. Reinforcement learning will guide the dynamic use of feature extractors during training. Iterative refinement, informed by clinical input, will ensure that the model effectively distinguishes correct from incorrect views in real time, enhancing its usability in resource-limited settings.

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Results: Retrospective data collection for the project began in September 2024, and to date, data from 308 babies have been collected and labeled. In parallel, the initial model framework has been developed and training initiated using a subset of the labeled data. The project is currently in the intensive execution phase, with all objectives progressing in parallel and final results expected within 10 months.

Conclusions: The AI-assisted echocardiography model developed in this project holds promise for improving early CHD diagnosis and care in SSA and other low-resource settings.

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KEYWORDS

AI-assisted echocardiography; congenital heart disease (CHD) screening; neonatal cardiac imaging; Sub-Saharan Africa health care; telemedicine and AI integration

Introduction

Sub-Saharan Africa (SSA) is the region of the world with the highest burden of under-5 mortality: 56.7% of the 4.9 million global under-5 deaths in 2022 occurred in SSA [1], despite the region accounting for only one-quarter of births. As progress has been made in tackling infectious diseases in children, the relative burden of other causes of death, including congenital anomalies (CAs), has increased, such that CAs are now the sixth leading cause of under-5 deaths in SSA [1]. The largest contributor to CA, in terms of both prevalence at birth and mortality, is congenital heart disease (CHD). While child mortality associated with CHD has declined—often dramatically—in most high-income countries (HICs), there has been no improvement in most SSA countries [2]. This lack of progress is impeding achievement of Sustainable Development Goal 3.2, a reduction in child mortality, as well as Sustainable Development Goal 3.8, equity of access to quality essential health care services. The challenges of CHD care in SSA are multifactorial. A recent analysis of African pediatric and CHD services showed that only 18 (40%) countries in Africa were able to provide a full CHD service, including cardiac surgery and interventional cardiac catheterization [3]. Moreover, the capacity of these services is low, with inadequate infrastructure and severe shortages of specialized personnel. Indeed, there are only a median of 0.17 (IQR 0.02-0.35) pediatric cardiologists per million population, far below the internationally recommended ratio of 2 per million [3].

This lack of capacity results in late or missed diagnoses, leading to delayed interventions and poorer outcomes [4,5]. The problem is compounded by the centralization of pediatric cardiac facilities in major urban areas, often located hundreds of kilometers from most birthing centers [4]. To address these challenges, interventions that strengthen the capacity for early CHD detection and decentralize care are critical.

Postnatal screening for CHD involves a combination of clinical examination, pulse oximetry screening, and echocardiography. Pulse oximetry screening is a simple, noninvasive test that measures oxygen saturation in a newborn's blood [6]. Low oxygen levels, or a significant difference between readings in the hand and foot, may indicate critical CHD and prompt further investigation with echocardiography. Despite recent concerns about the suboptimal performance of the device in dark-skinned infants [7,8], pulse oximetry screening is highly recommended and is increasingly being adopted by many low- and middle-income countries (LMICs), including those in SSA [6,9]. However, pulse oximetry results are not specific to CHD, as low oxygen saturation may also indicate other conditions, such as pneumonia—the leading cause of neonatal mortality in SSA. Therefore, all suspected CHD cases identified by pulse oximetry must be referred to an expert pediatric cardiologist for confirmation through echocardiography. Consequently, the growing uptake of pulse oximetry in SSA is increasing the number of suspected CHD referrals and adding to the workload of the already strained workforce of echocardiographers and pediatric cardiologists. This burden is further compounded by the costs involved and the arduous, often long journeys required for particularly fragile neonates—some of whom may ultimately turn out to be false-positive cases.

The introduction of low-cost, compact mobile ultrasound devices has dramatically increased the availability of ultrasound services in LMICs and has helped to address, to some extent, the centralization of diagnostic services [10]. However, the lack of diagnostic expertise continues to limit their use for highly specialized procedures such as echocardiography. Obtaining optimal echocardiographic images presents significant challenges [10]. The probe must be correctly positioned, and parameters such as gain, contrast, resolution, depth, and magnification must be individually adjusted for each specific view [11]. When combined with patient-related factors such as uncooperative pediatric behavior and complex CHD anatomy, these challenges result in longer scan times, increased workloads, and a greater need for highly trained sonographers or echocardiographers.

Training programs have been shown to improve both image capture and anomaly detection [11]. However, these programs are often labor-intensive and time-consuming, and require repetition due to staff turnover [11]. Therefore, a complementary approach is needed to sustain and build upon the improvements achieved through training.

In recent years, there has been a growing number of projects using artificial intelligence (AI) models to facilitate CHD diagnosis [11-15]. However, most of these projects originate from HICs, potentially limiting their applicability in LMICs due to domain shifts related to equipment, operator expertise, ethnicity, disease profiles, and differences in clinical workflows

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or infrastructure. Moreover, existing research disproportionately focuses on adult echocardiography, with limited attention to prenatal CHD and little consideration of neonatal applications. Critically, current AI efforts concentrate on image interpretation rather than supporting nonexperts with real-time image acquisition.

This paper outlines an ongoing project leveraging AI to enable nonexpert echocardiographers—such as sonographers, nurses, midwives, and doctors with minimal specialized training—to perform basic cardiac ultrasound "sweeps" on neonates (aged 0-28 days). The AI system will be designed to automatically extract predefined cardiac views, which can then be transmitted to remote pediatric cardiologists for interpretation. The AI model will be limited to image extraction and will not extend to diagnosing or identifying potential CHD. This approach aims to streamline the initial screening process for CHD. AI-assisted echocardiography will be selectively used for babies with positive pulse oximetry screening results or other clinical indications suggestive of cardiac issues, helping to identify cases requiring further evaluation by specialized pediatric cardiologists (Figure 1).

Figure 1. Artificial intelligence (AI)–assisted echocardiography congenital heart disease (CHD) screening process. Echo: echocardiography.

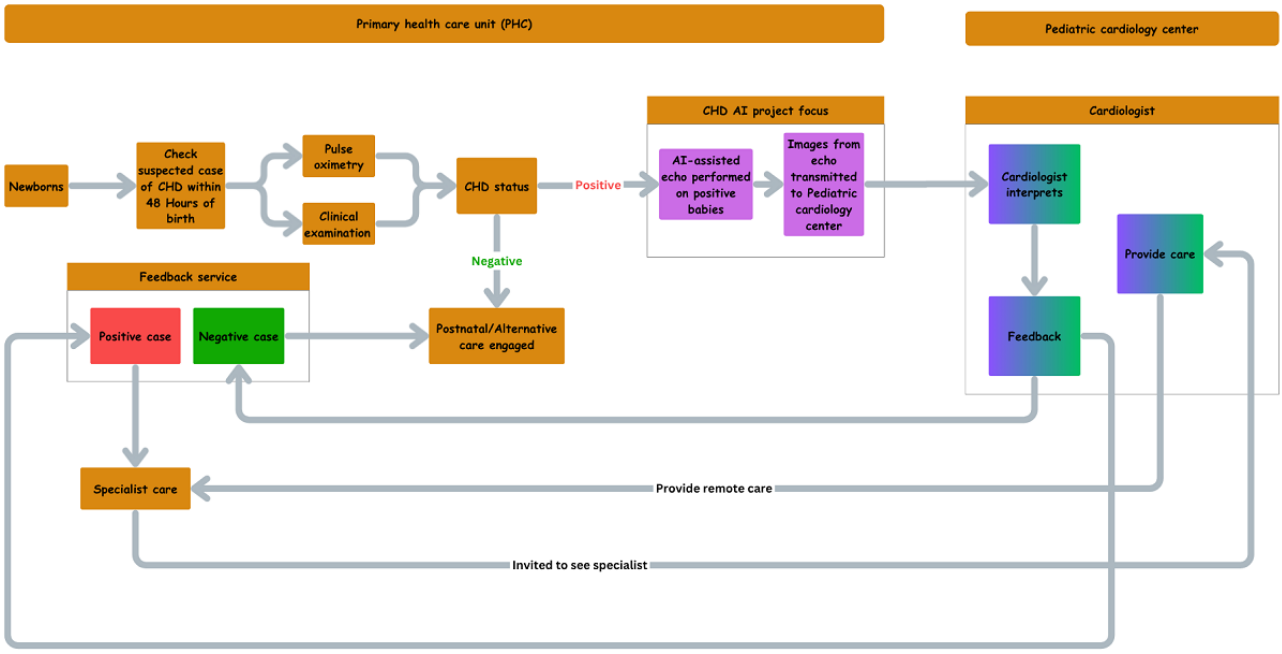

Methods

Study Population and Cardiac Views

This study focuses on extracting accurate cardiac views in neonates aged 0-28 days suspected of CHD. To guide the selection of relevant views, 2 critical questions were considered: (1) can nonexperts reliably maneuver the probe to allow the AI system to capture the desired views, and (2) which views would provide the most valuable insights for cardiologists in determining the need for further investigation. Based on these considerations, and in accordance with the 2024 American Society of Echocardiography guidelines [16], our panel of expert cardiologists identified 10 essential cardiac views (Table 1).

Table 1. Selected cardiac views of interest and label codes.

Cardiac view	Label code
1. Subcostal long axis	SCLA
2. Apical 4 chamber	A4C
3. Apical 5 chamber	A5C
4. Parasternal long axis	PLAX
5. Parasternal short axis—aortic valve	PSAX_AV
6. Parasternal short axis—mitral valve	PSAX_MV
7. Parasternal short axis—papillary muscle	PSAX_PM
8. Suprasternal long axis	SSLAX
9. Other diagnostic	OTHER_DIAG
10. Background	BKG

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Data Requirements

To train AI models that guide nonexpert operators in acquiring specific cardiac views, a dataset of real patient ultrasound videos is essential. This dataset must include not only the desired (positive) views but also a substantial amount of background (negative) data representing nonessential or incorrect views. Such data are crucial for enabling the model to effectively distinguish target views from the more common, nonideal images that nonexpert operators are likely to produce in real-world settings.

Existing data saved by expert cardiologists during routine clinical scans provide a readily available source with minimal ethical concerns. However, cardiologists typically save only the most relevant cardiac views, meaning that existing hospital datasets contain these specific views without the necessary background elements. Additionally, a significant domain shift exists between existing datasets—primarily collected in HICs—and newly acquired data from LMICs, where variations in clinical protocols, imaging equipment, and patient demographics may affect model generalizability. Furthermore, the scarcity of publicly available neonatal echocardiography datasets makes data acquisition a critical challenge. To obtain data containing both target views and background elements, new data must be collected prospectively. This approach also allows for modifications to facilitate frame extraction and labeling, as described in the "Data Labeling" section. However, prospective data collection is time-consuming and resource-intensive. Ethical considerations must also be addressed, including obtaining informed consent from parents and ensuring that data collection does not disrupt routine clinical workflows. A practical approach to mitigate these limitations while maximizing the benefits of both dataset types is to develop the model in 2 phases: initially leveraging existing hospital datasets for pretraining, followed by fine-tuning with prospectively collected data to ensure adaptability to LMIC settings.

In the first phase, existing data will be used to build an initial model framework, while prospective data are collected simultaneously. Once the new prospective data become available, they will be used in the second phase to refine and enhance the initial model developed from the existing data (see the "Model Building" section). This hybrid approach enables the project to leverage readily available existing data to initiate model development, while ensuring that the final model is trained on a comprehensive dataset containing both the target cardiac views and the necessary background elements. Both types of datasets will include all scanned cases, regardless of whether the neonate's heart was abnormal.

The proposed AI model is intended for use in neonates aged 0-28 days. However, to expedite data collection and increase the sample size, the project will also include data from infants aged 0-2 years, based on the observation that the cardiac structure of older infants is similar to that of neonates [17].

In the first phase of model development, the project will aim to gather short anonymized echocardiographic video clips from 500 babies. Each dataset will consist of 1-7 clips per baby, depending on scan availability and quality. These clips are expected to include 1 or more of the 10 cardiac views utilized in the project. The retrospective dataset of 500 babies will be selected to provide a minimum of 1500-3500 labeled echocardiographic clips, ensuring at least 73 examples per cardiac view to statistically support a 95% accuracy target with a 5% margin of error at 95% confidence. Each video clip is expected to be approximately 3-5 seconds long, with an average file size of up to 4 MB. Based on these parameters, the total number of clips is estimated to range from 1500 to 3500, resulting in an expected storage requirement of approximately 14 GB for the raw video data. Additional space for data preprocessing, model training, and backups will increase the total storage needed for this phase to around 200 GB, including 50 GB allocated for backups.

In the second phase of model development, the project will collect prospective echocardiographic video data from 1000 babies. Each baby will have 1 continuous video clip representing a complete echocardiographic scan, recorded at a higher frame rate of 60 frames/second, with an average duration of 20 minutes. Shorter video clips corresponding to individual cardiac views will subsequently be extracted from these long recordings for analysis. The sample of 1000 babies has been chosen to ensure sufficient diversity in anatomical presentations, imaging conditions, and potential CHDs, enabling the development of a robust and generalizable model applicable across varied clinical contexts. In addition to this contextual rationale, the sample size will provide sufficient statistical power to support model development. Assuming a minimum of 203 labeled examples per cardiac view is required to achieve 95% classification accuracy with a 3% margin of error at 95% confidence, the sample of 1000 babies is expected to yield the necessary number of view-specific clips to meet this threshold, accounting for natural variation in view representation. Each 20-minute video is anticipated to have an average file size of 1 GB, resulting in a total raw data size of approximately 1 TB. Accounting for data preprocessing, extraction of shorter clips, model training, and storage redundancy, the total storage requirement for this phase is projected to reach around 15 TB, including 5 TB allocated for backups.

By focusing on video clips directly, the project will simplify data collection while preserving the variability and dynamic features necessary for robust model training. The shorter clips extracted in the second phase will ensure compatibility with the analysis framework established in the first phase.

Study Sites and Data Collection

The project will collect data from 2 hospitals: St. Padre Pio Hospital in Douala, Cameroon, and the Red Cross War Memorial Children's Hospital in Cape Town, South Africa. Approximately 80% of the data will come from South Africa, with Cameroon contributing 20%. These sites were carefully selected to ensure representation of diverse patient demographics, which will be critical for the performance and external validity of the developed model. Data from both sites will be pooled and randomly split for training, validation, and testing. While the model does not use a dedicated external dataset, the inclusion of diverse populations and imaging conditions is expected to enhance its generalizability across

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clinical contexts in SSA. This approach allows the inclusion of data from multiple facilities using different ultrasound machines. Consequently, metadata on equipment type, settings, and resolution will be collected to assess potential heterogeneity. Where possible, domain adaptation techniques will be explored to further improve model robustness.

Cameroon is a bilingual (French and English) country in central Africa, often referred to as "Africa in Miniature." The country reflects the vast diversity of SSA, encompassing multiple cultural, linguistic, and geographical variations. St. Padre Pio Hospital in Douala is one of the few referral centers for pediatric cardiology in Cameroon and receives patients from across the country. The Children's Heart Disease Research Unit at the Red Cross War Memorial Children's Hospital in Cape Town serves a racially and ethnically diverse population, with considerable variability in socioeconomic factors and access to health care. Together, data from Cameroon and South Africa will provide the representativeness needed to ensure that the model performs effectively across different clinical conditions and patient demographics in SSA.

Existing data (short video clips) will be extracted from locally saved sources at the participating hospitals. Prospective data will be collected during routine echocardiography scans performed by expert cardiologists or sonographers. Before data collection, the experts will obtain informed consent from the parents or legal guardians of each participating infant. The informed consent form and study information sheet are provided in Multimedia Appendix 1. Parents may refuse participation without any impact on the care their child receives. The project team is committed to conducting data collection ethically, respecting the rights and well-being of participating families. It is essential that the process does not interfere with routine clinical care. The expert is expected to perform the scan as usual, with 2 simple modifications:

- Before starting the scan, the expert shall connect a screen-capture device to record the entire echocardiography session from start to finish.
- For the cardiac views of interest, in addition to the usual routine pause to save the frame, the expert is expected to label the frame at a defined position (top-right corner of the screen).

At the end of the scan, the recorded video will be saved on a separate screen-capture device. A standard operating procedure (SOP) has been developed to guide all cardiologists involved in the prospective data collection, minimizing operator variability (Multimedia Appendix 2). Our expert cardiologists believe that labeling the frames during the scan will not affect the typical scan duration.

Data Deidentification, Metadata Generation, and Data Transmission and Storage

Overview

This project is part of the broader Data Science for Health Discovery and Innovation in Africa (DS-I Africa) Network. As one of the network's research initiatives, it will leverage the on-premises cloud storage and computing infrastructure provided by DS-I Africa through its eLwazi Open Data Science Platform. This infrastructure, specifically the **Illifu system**, forms the backbone of the data transmission and storage processes described in the "**Data Transmission and Storage"** section, enabling secure and efficient data management.

All existing and prospective data will be transmitted to a central, secure on-premises cloud storage solution, where model building and data analysis will be conducted. Before transmission, the data will undergo several processes, including deidentification (covering both anonymization and pseudonymization), metadata generation, and secure transfer. These processes will ensure that data privacy, integrity, and security are maintained, adhering to the highest standards of data protection.

The thematic diagram (Figure 2) illustrates the overall process flow, including data collection, deidentification, metadata generation, and secure transmission and storage. It provides a visual overview of how data progresses through each stage of the workflow.

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Figure 2. Thematic data flow diagram for the CHD-AI project. AI: artificial intelligence; CHD: congenital heart disease.

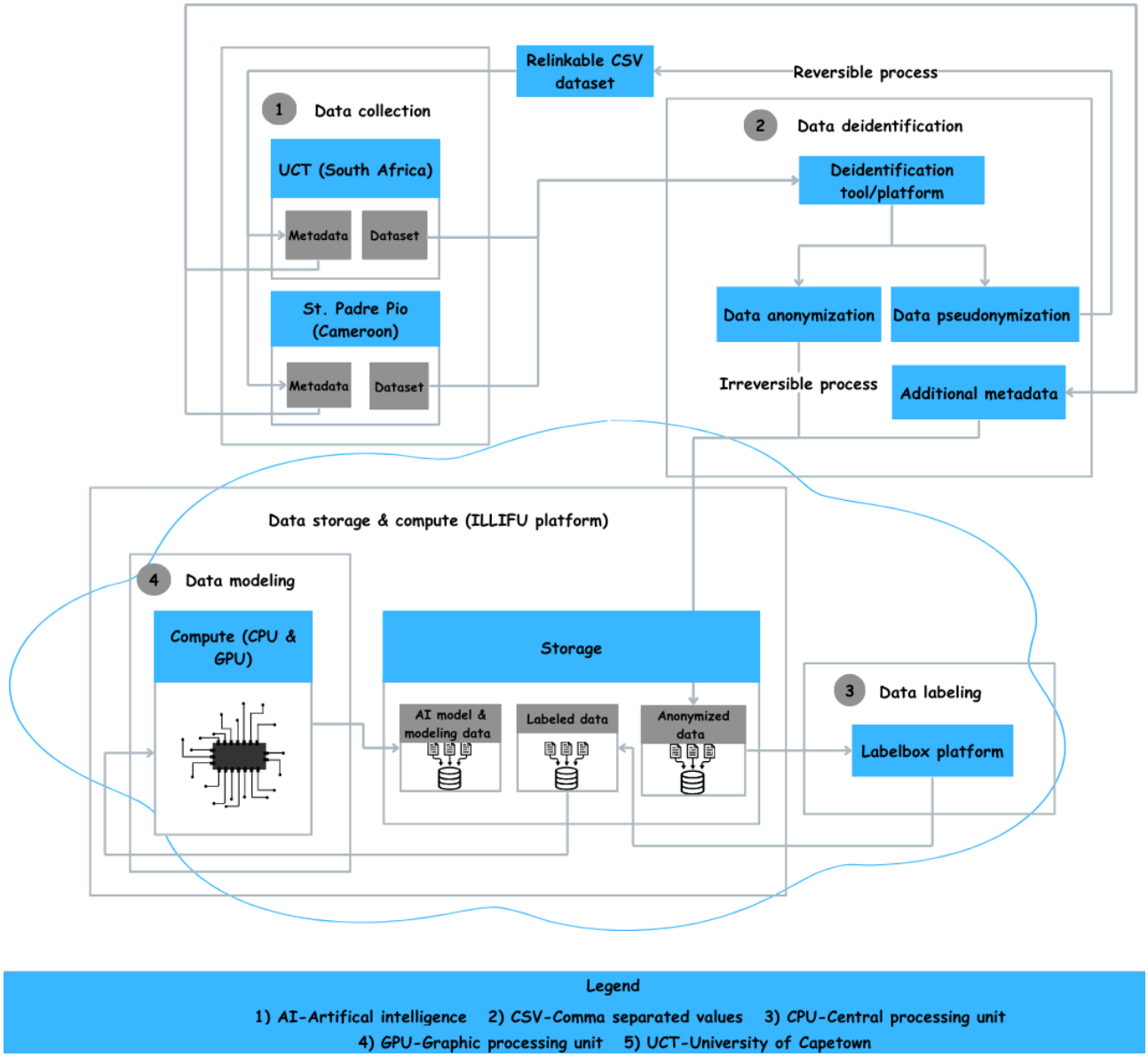

Data Deidentification

To ensure patient privacy and compliance with ethical guidelines, all data will undergo a deidentification process to remove personally identifiable information before use. This will be implemented using a custom anonymization script developed by the project engineering team, which automates the removal of sensitive details while preserving data integrity. Additionally, unique project identification codes will be assigned to facilitate internal traceability without revealing personal information. When controlled data access is required for specific research purposes, a secure pseudonymization approach will be used, allowing authorized personnel to reference anonymized data without compromising privacy.

Metadata Generation

After deidentification, metadata are generated to provide contextual information about the data, as shown in Figure 2. These metadata will support subsequent data management and analysis.

- Types of metadata: Includes patient age, sex, and diagnosis to support analysis and traceability.
- Automated metadata extraction: Ensures consistency and minimizes human error by generating metadata automatically using a script developed by the engineering team.
- Use of metadata: Metadata will accompany anonymized and pseudonymized data as needed, maintaining transparency and traceability while adhering to privacy requirements.

Data Transmission and Storage

For this study, data will be securely transmitted to the Illifu on-premises cloud storage solution provided by the eLwazi Open Data Science Platform, a key infrastructure component of the DS-I Africa Network. This stage, as illustrated in Figure 2, ensures secure and compliant storage accessible only to authorized personnel. The platform will also serve as the computing environment for model development, providing the necessary resources for data processing and analysis.

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The decision to utilize the Illifu infrastructure reflects its strong alignment with DS-I Africa's goals of advancing data science capabilities across its projects. While Illifu serves as the primary infrastructure, similar objectives could be achieved using other cloud storage solutions—such as Google Cloud Platform, Amazon Web Services, or Microsoft Azure—provided they are configured to meet required privacy and compliance standards.

Data Labeling

Existing Data Labeling

Labeling of the existing echocardiographic data will be conducted by expert cardiologists using the Labelbox platform, integrated with Google Cloud. This process will ensure consistent, high-quality annotations essential for model training (Textbox 1).

Textbox 1. Labeling procedure.

1. Labeling parameters

The labeling will involve the following parameters:

- Cardiac views: Each video clip will be assigned 1 of the 10 predefined cardiac views, as determined by the expert cardiologists in the project and for each view, a subparameter will indicate the presence of color Doppler, labeled as "Color" or "No Color" depending on whether color Doppler imaging is visible in the clip.
- Frame quality: Each frame will be rated for quality on a 3-tier scale: poor, normal, or good. This rating will help filter and prioritize frames for model training.
- Metadata integration: Labels will be linked to metadata, including patient-specific information (age, sex, and diagnosis) and labeling-specific attributes (labeling cardiologist ID and time stamp).

2. Labeling workload and quality assurance

As the labeling process is demanding, each video clip will be labeled by a single cardiologist. To ensure interrater reliability, 5% of each cardiologist's labeled data will be randomly assigned to a second cardiologist for cross-validation and assessment of variability.

We anticipate the participation of 10 cardiologists, with each assigned approximately 500 video clips to label over a 3-month period.

Prospective Data Labeling: Automated Label Derivation

Prospective data collected during routine echocardiography scans already include labels of the cardiac views assigned by the cardiologist or sonographer. However, these labels cannot be directly used to train the AI model, as the model would merely learn to recognize the labels rather than understanding the actual cardiac views. This would limit its ability to generalize and identify unlabeled cardiac views in real-world applications.

To address this challenge, the team will develop an automated script to extract unlabeled cardiac views from the labeled prospective data. The script will analyze the ultrasound video clips, identifying pauses that indicate when the expert saved specific views. It will then assign the names of these saved views based on the expert-assigned labels. Finally, the script will extract unlabeled video segments from between these pauses, representing the same cardiac views labeled by the expert but without visible labels.

The unlabeled clips, along with their associated labels stored separately, will then be uploaded into Labelbox for further annotation of video quality and any additional view-specific parameters. The aim is to provide diverse examples of the same cardiac view for model training while keeping the labels hidden during the training phase.

To ensure consistency in labeling, a subset of the labeled data will be independently reviewed by multiple annotators, and interrater reliability will be assessed using the Cohen κ statistic. Any discrepancies will be resolved by consensus or by a senior clinical reviewer.

Metadata Extraction and Format

After labeling, the data will be exported in JSON format from the Labelbox platform and processed for model training in the Python (Python Foundation) environment provided by the Illifu platform. The metadata will follow a predefined structure to ensure consistency and usability across the dataset. This structure will include the following key details: Video ID, Cardiac View, Doppler Color, Frame Quality, Labeling Cardiologist ID, Labeling Timestamp, Is Labeled, and Label-Associated Field. Figure 3 illustrates the standardized format for labeled video metadata, ensuring consistency and usability for model training. This structured format allows labeled and unlabeled data to be handled separately while maintaining consistent metadata attributes. It also facilitates tracking and integration of the data into the model training pipeline.

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Figure 3. Sample of labeled video clip metadata structure in JSON format.


```
{
  "VideoID": "CHDAIP0000101",
  "CardiacView": "Apical Four-Chamber",
  "DopplerColor": "Color",
  "FrameQuality": "Good",
  "LabelingCardiologistID": "CARD001",
  "LabelingTimestamp": "2025-01-02T14:35:00Z",
  "IsLabelled": true,
  "LabelAssociatedField": "Normal Function"
}
```


Every labeled video exported from Labelbox will follow this predefined format, ensuring uniformity and ease of integration. Each video will be uniquely identified by a "Video ID," such as CHDAIP0000101. The labels of interest extracted from the labeled dataset are Cardiac View, Frame Quality, and Doppler Color. The "Cardiac View" parameter specifies the view represented in the video, with the available options detailed in Table 1. The "Doppler Color" parameter indicates whether color Doppler imaging is present, labeled as either "Color" or "No Color." The overall quality of the video frames is assessed under the "Frame Quality" parameter, categorized as "good," "medium," or "poor" based on clarity and diagnostic usability. Each video is also associated with a "Labeling Cardiologist ID," serving as a unique identifier for the cardiologist responsible for labeling, along with a "Labeling Timestamp" recording the exact date and time of labeling. The "Is Labelled" parameter distinguishes between frames that are prospectively labeled and those extracted by the automated script. For unlabeled clips, the "Label Associated Field" will contain labels derived from the automated script, ensuring that these clips can still be used in analysis.

This structured format will not only ensure consistency in metadata attributes but also enable efficient tracking of labeled and unlabeled data. It will streamline the integration of these data points into the model training pipeline, enhancing the overall accuracy and reliability of the process. The flowchart in Figure 4 illustrates the entire workflow.

Figure 4. Metadata processing steps.

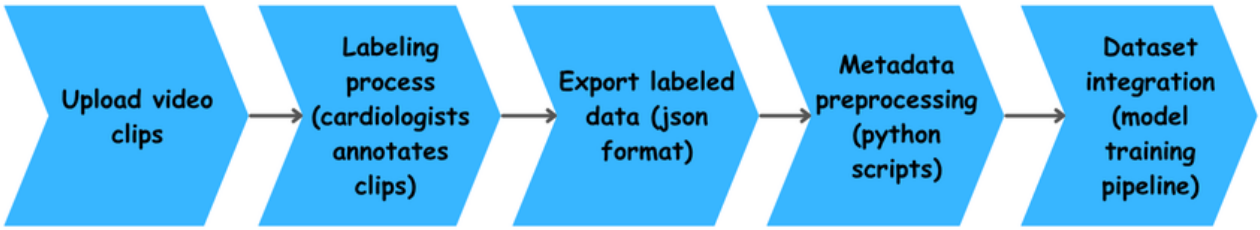

Development of the AI Model

Methodology and Deployment Considerations

The proposed AI model will build upon the successful and validated work of Gearhart et al [18] and Mason et al [19]. Its development will involve 4 key steps: data collection and preparation, data preprocessing, data exploration and visualization, and model building and evaluation.

Although transformer-based architectures represent a promising area of research in computer vision, our focus will be on solutions that can be feasibly deployed in remote, resource-constrained environments. Therefore, we will prioritize lightweight and computationally efficient convolutional neural network models, such as MobileNet and EfficientNet, which are better suited for real-time inference on low-power devices.

Data Preprocessing

Data processing will involve 2 major tasks: (1) enhancement of pictorial information for human interpretation and (2) processing of image data for storage, transmission, and representation for autonomous machine perception. The data preprocessing steps can be categorized into low-, mid-, and high-level processes (Textbox 2).

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Textbox 2. Data preprocessing steps.

1. Low-level processes

Images and frames extracted from videos will undergo basic image processing operations, such as Gaussian filtering for noise reduction, histogram equalization for contrast enhancement, and unsharp masking for image sharpening. These steps improve the clarity and quality of input images before further processing.

2. Mid-level processes

Following the procedure described in Gearhart et al [18], images from the low-level processing step will undergo further processing, including removing Doppler and split views (segmentation) and sampling random background frames.

3. High-level processes

Images from the mid-level processing step will undergo further processing, including cropping the field of view and rescaling, inpainting labels and annotations on the images, and splitting the data into training and test sets.

Data Exploration and Visualization

This step will involve identifying common data issues that may arise during model training, some of which relate to object detection, as we will be detecting the cardiac plane and heart structures. We anticipate issues related to the following:

- Image dimensions and aspect ratios: Images may have different sizes (eg, one image could be 32×32, while another could be 123×47).
- Label composition: Imbalances in labels, including variations in bounding box sizes and aspect ratios, may occur (eg, some cardiac views may have more images than others).

To address these issues, we will use dedicated tools such as Google Facets (Google LLC/Alphabet Inc), a data visualization platform, to explore the image data and make informed decisions accordingly.

Model Building

Phase 1: Model Development

To detect cardiac views and localize heart structures in newborns using real-time echocardiography videos, we will adopt a novel approach inspired by Gearhart et al [18]. Their work demonstrated an efficient pipeline for video object detection, achieving state-of-the-art performance.

To adapt their architecture for our dataset, we propose an interleaved framework with 2 feature extractors of distinct speeds and recognition capabilities. These extractors will process different frames, with the extracted features maintained in a shared visual memory through a convolutional long short-term memory layer. The convolutional long short-term memory fuses contextual information from previous frames with features from the current frame to generate accurate detections.

Following Gearhart et al [18]'s approach, the interleaving policy, which determines when to run each feature extractor, will be learned through reinforcement learning. The convolutional long short-term memory is particularly well-suited for sequential image data, making it ideal for analyzing short echocardiography video clips. The training specifics are presented in Textbox 3.

Textbox 3. Training specifics.

Dataset composition

The dataset consists of short echocardiography video clips in AVI format (St. Padre Pio Clinic, Cameroon) and DICOM format (University of Cape Town, South Africa), along with metadata files in Excel (Microsoft Corp) format containing patient age, sex, and diagnosis.

Metadata utilization

Metadata will be incorporated into model training to enhance feature representation, enabling the model to leverage diagnostic context alongside visual data.

Labeling annotations

Video clips will be annotated on the Labelbox platform with the following:

- Cardiac view: 10 predefined categories, with subparameters indicating Doppler presence.
- Video quality: categorized as poor, normal, or good.

As illustrated in Figure 5, given a video stream, a visual memory model fuses features from fast and slow feature extractors across frames to generate live detections. The layers and weights of this pretrained model will be fine-tuned on our dataset, focusing specifically on the cardiac views of newborns.

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Figure 5. An illustration of a memory-guided interleaved model.

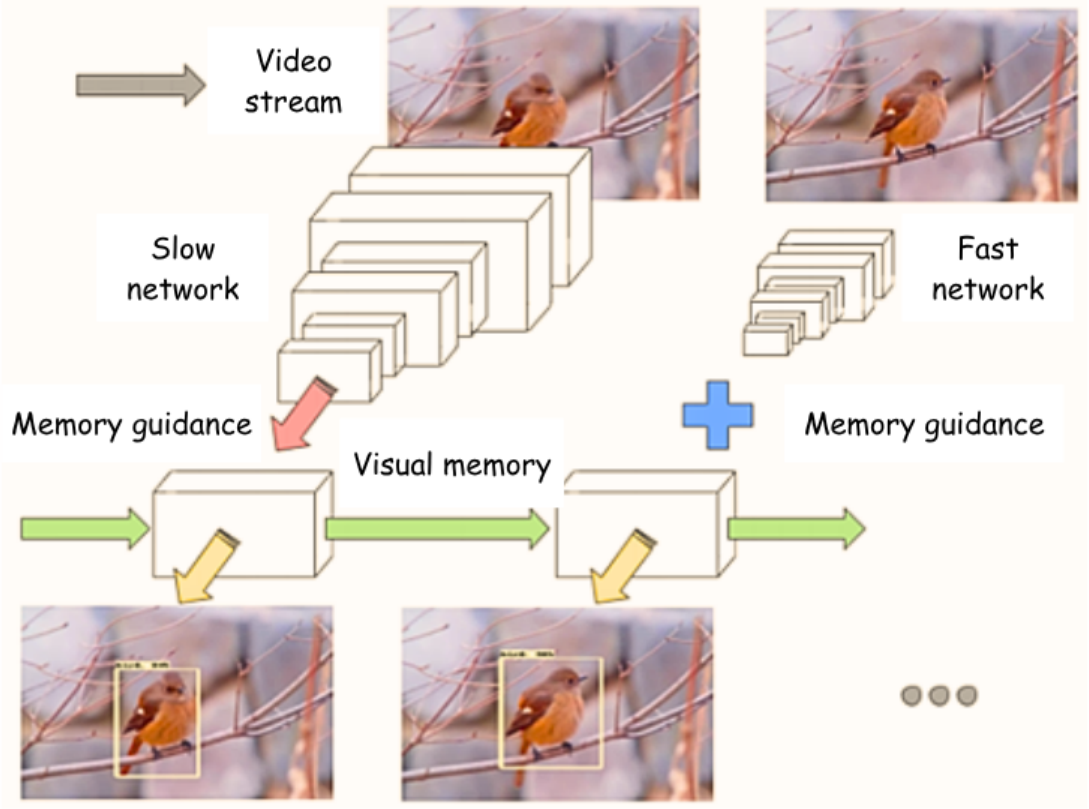

It is important to emphasize that, to mitigate overfitting, training will incorporate early stopping, dropout regularization, and k-fold cross-validation. If signs of overfitting are observed during training (eg, a large divergence between training and validation loss), the model complexity will be adjusted accordingly. In addition to convolutional neural networks, we will explore transformer-based architectures, which have shown promise in video and sequential image interpretation tasks. Comparative performance evaluations will be conducted to determine their suitability in this clinical context.

Training Process

Training will follow an iterative approach, with checkpoints saved at regular intervals to allow seamless resumption in case of interruptions. The model will initially be trained from scratch using the collected and constructed dataset. As additional data become available from various sources, a fine-tuning strategy will be employed to gradually enhance performance and adapt the model to new variations. Training will be conducted using libraries such as TensorFlow and PyTorch, leveraging high-performance graphical processing units on the computing cluster to optimize efficiency and scalability.

Phase 2: Model Refinement

In phase 2, prospective data will be used to refine the initial model, ensuring improved accuracy and adaptability. The model will leverage prediction confidence (PC) to optimize video clip extraction and assess quality (Textbox 4).

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Textbox 4. Model refinement.

1. Dynamic prediction confidence

Given an ultrasound video stream, the model will compute the probability (prediction confidence [PC]) that an extracted image frame or video clip corresponds to a specific cardiac view:

- Video clip extraction will begin once a defined PC threshold is met for an image frame.
- Subsequent frames meeting the PC threshold will be compiled into a 5-second video clip for the identified view.
- If multiple video clips of the same view are generated, the clip with the highest average PC across frames will be retained as the final clip.

2. Video quality optimization

As image quality can vary depending on the ultrasound device, the model will allow users to set a PC threshold during first use to ensure optimal image quality:

- High PC: If the initial PC setting exceeds the device's capabilities, the model will prompt the user to lower the threshold.
- Low PC: Conversely, if the initial PC setting is too low, the model will suggest increasing the threshold to maximize quality.

These mechanisms will ensure that the highest-quality images are extracted, regardless of device variability. An accompanying manual will guide users to start with higher PC settings during initial model use.

3. Integration with training pipeline

- During model refinement, metadata (eg, age, sex, diagnosis) will be used alongside visual data to enhance feature representation and improve diagnostic accuracy.
- Labels generated during the annotation phase (eg, cardiac view, Doppler presence, and video quality) will also be incorporated into the refinement process.

Figures 6 and 7 illustrate the sequence and flow of the video clip extraction and PC adjustment mechanisms during real-time ultrasound scans.

4. Refinement goals

- To integrate metadata-driven learning by leveraging age, sex, and diagnosis to fine-tune the model.
- To enhance adaptability across different ultrasound devices while ensuring robust performance.

5. Expected outcomes

The proposed protocol combines state-of-the-art video object detection with metadata integration, enabling robust detection of cardiac views and localization of heart structures in echocardiography video streams. The model's reinforcement learning–based interleaving policies, dynamic PC adjustments, and quality control mechanisms ensure adaptability across different devices and datasets.

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Figure 6. Sequence diagram of our artificial intelligence model system.

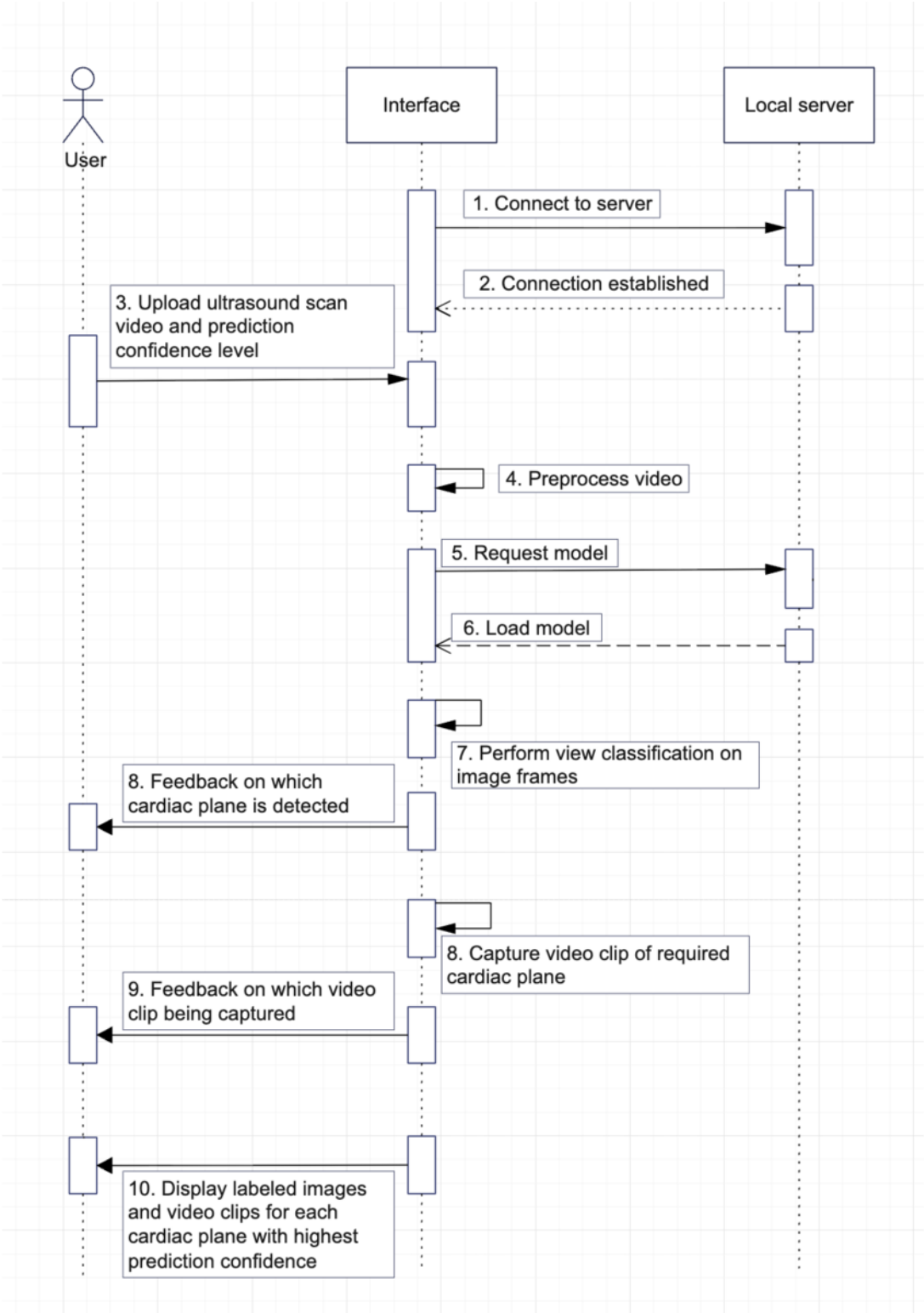

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Figure 7. Extractions of sequence diagram.

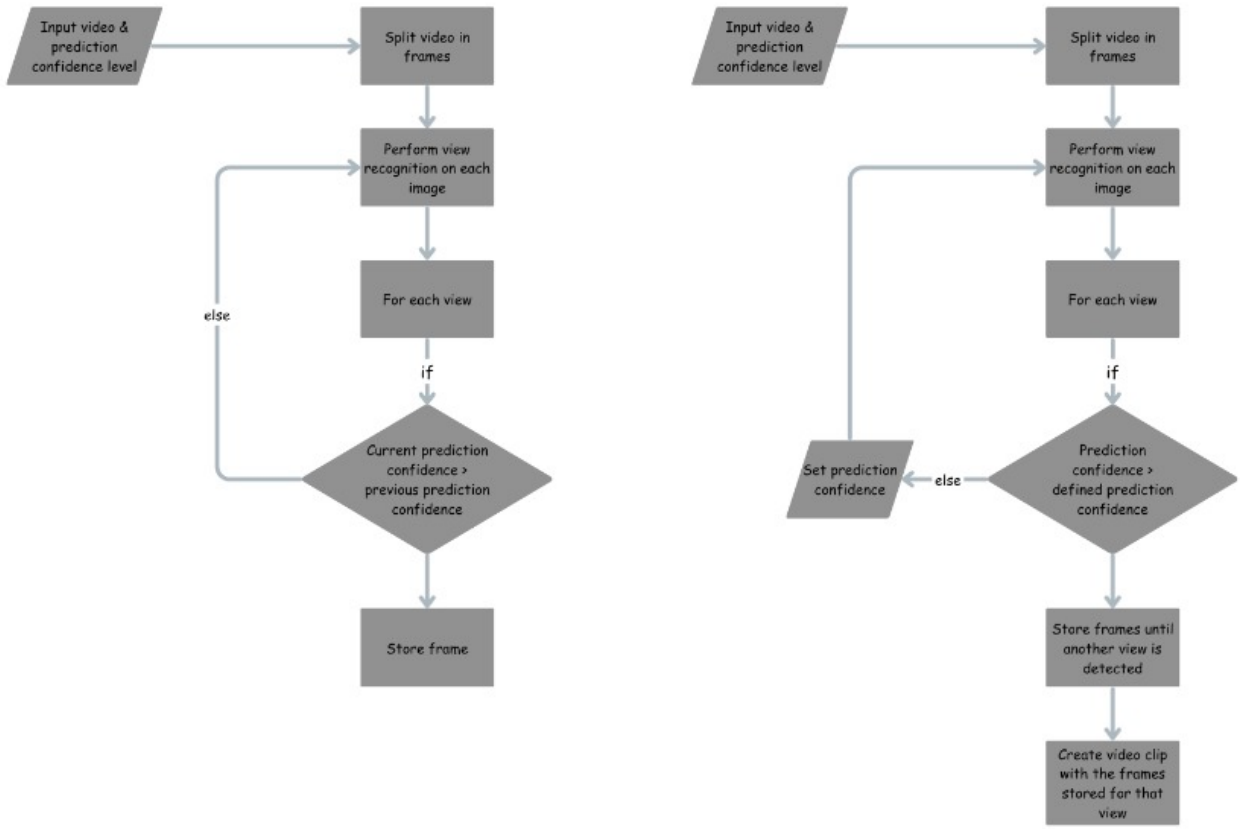

Model Evaluation

To comprehensively assess the model's performance in detecting cardiac views and localizing heart structures in neonates, a robust evaluation framework will be implemented. The evaluation will use an 80/20 training-testing split to ensure a representative data distribution. Additionally, k-fold cross-validation (eg, 10-fold) will be applied to improve the reliability of performance metrics by averaging results across multiple splits. The model will be trained, validated, and tested on a combined dataset from Cameroon and South Africa using stratified random splits. Although no site is reserved exclusively for external validation, this approach is designed to capture variability across regions and equipment, supporting real-world generalizability. The evaluation metrics are listed in Textbox 5.

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Textbox 5. Evaluation metrics.

1. Overall accuracy

The percentage of correctly classified instances across all classes in the test dataset.

2. Per-class accuracy

The accuracy for each individual cardiac view, providing insights into the model's performance across different heart structures.

3. Average accuracy

The mean accuracy across all classes, offering a balanced assessment of class-specific predictions.

4. Confusion matrix analysis

Confusion matrices will be generated to visualize true positives, false positives, true negatives, and false negatives for each class. These matrices will help identify systematic misclassifications and underperforming classes.

5. F1-score

The harmonic mean of precision and recall, calculated for each class, to measure the balance between false positives and false negatives. The macro F_1-score will summarize overall classification performance.

6. Receiver operating characteristic curve and area under the curve

For binary classification tasks (eg, Doppler vs non-Doppler views), receiver operating characteristic curves will be plotted to illustrate the trade-off between sensitivity and specificity. The area under the curve will quantify the model's discriminatory ability.

7. C-statistics

Calculated to measure the concordance between predicted and actual classes, serving as an overall indicator of the model's diagnostic performance.

8. Saliency maps

- Visualization techniques will be applied to highlight regions in input images that strongly influence the model's predictions, enhancing interpretability and ensuring alignment with domain knowledge, such as focusing on heart structures in echocardiography images.
- To support explainable artificial intelligence, methods such as Grad-CAM, Grad-CAM++, and other class activation mapping techniques will be utilized.
- These approaches will help visualize the model's decision-making process, providing deeper insights into how specific features contribute to classification outcomes.

9. Class-specific evaluation metrics

- Precision (positive predictive value): The fraction of correctly predicted positive observations.
- Recall (sensitivity): The ability of the model to identify all relevant instances in a class.
- Specificity: The ability of the model to exclude irrelevant instances.

10. Video-based metrics

For evaluating performance on the short video clips, the following will be evaluated:

- Clip prediction accuracy: The percentage of correctly classified video clips, where the assigned view corresponds to the majority or highest-confidence prediction across frames.
- Temporal consistency: The consistency of predictions within a video clip, measured as the proportion of consecutive frames with matching predictions.

11. Metadata-driven analysis

Using age, sex, and diagnosis from the metadata, model performance will be evaluated for specific subpopulations (eg, neonates with congenital heart disease vs those without). This ensures that the model performs robustly across diverse patient demographics and clinical conditions.

By combining these quantitative and qualitative evaluation metrics, the model's accuracy, reliability, and interpretability will be rigorously assessed. The evaluation will follow the approach of Mason et al [19] but will be extended to include video-based and metadata-specific metrics, accounting for the unique characteristics of the dataset.

Model Interpretability and Explainability

In recognition of the importance of trust and transparency in clinical decision-making, the model will incorporate interpretability techniques to support clinician acceptance and regulatory readiness. Specifically, saliency map methods such as Grad-CAM will be applied to highlight image regions that most influence model outputs. These visualizations will be used during internal review and validation phases to confirm alignment with clinically relevant anatomical features. During pilot implementation, these explainability outputs will be presented to end users—pediatric cardiologists and trained frontline clinicians—for interpretability assessment. This process will help ensure that model behavior is understandable, clinically

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grounded, and suitable for integration into human-in-the-loop diagnostic workflows.

Workflow

A GitHub repository for the project will be created, and members of the engineering team will have access to clone it to their local machines and contribute code. A branch protection rule will be implemented so that all contributions are reviewed by the administrator (senior engineer) before merging. The repository will also include the work of Gearhart et al [18], which is freely available on GitHub.

SOP and Instructional Video on Echocardiography Sweep for Nonexperts

Using relevant materials from the literature, our expert cardiologist on the research team will develop a step-by-step procedure for performing an echocardiography sweep, enabling the AI model to capture the defined frames/cardiac views of interest. This procedure is designed to support nonexpert operators in acquiring the correct cardiac views and capturing usable echocardiographic video (see Multimedia Appendix 2). This SOP will be complemented by an instructional video included in the project toolkit. The video will detail preparatory steps before initiating an echo scan, tips on probe handling and maneuvering, and the sequence of moving the probe across the baby's chest, including start and end positions. Once the SOP is finalized, it will serve as the basis for developing the instructional video to facilitate training of nonexpert operators.

Investigating the Diagnostic Utility of the Video Clips Produced From the AI Model in Relation to Their Use in Clinical Practice

Overview

We will evaluate the clinical utility of the AI-extracted video clips through the following steps.

Develop a Platform to Operate the Model

The platform will run on a local computer or server and serve as an interface for the AI model to process uploaded live video streams.

Obtain Live-Stream Echocardiography Videos From Clinical Practice

We will recruit 4 nonexperts—a general practitioner, a nurse, a midwife, and a sonographer—who will receive basic training and guidance on postnatal echocardiography and probe sweeps using the SOP and instructional videos developed. Practice sessions will take place at St. Padre Pio Hospital in Douala, Cameroon. After training, the nonexperts will perform test echocardiography scans (basic sweeps) on neonates referred to the hospital to obtain video streams. Each test scan will be conducted after the baby's routine clinical scan, with each session expected to last approximately 3 minutes, yielding a 3-minute video clip. The entire exercise is planned over 4 months, during which at least 16 neonates are expected to be scanned, producing 16 video clips. It is important to emphasize that scans performed by nonexperts are for study purposes only and will not replace the baby's routine specialist scan. However, if deemed relevant after evaluation, the images or video clips produced by the AI model could be used by the expert to support diagnosis. For each baby, the expert's scan will be retained alongside the test videos from the nonexperts. All videos will be deidentified using our anonymization script. Parents will receive orientation about the exercise and provide signed informed consent, with the option to decline participation (see Multimedia Appendix 3 for the information sheet and consent form).

Extraction and Labeling of Images/Video Clips From the Ultrasound Videos

Videos from both expert and nonexpert ultrasound sessions will be loaded into the AI model platform on the computer, allowing cardiac views (short video clips) to be extracted and sent for expert review.

Evaluate Extracted Images/Video Clips

The video clips will be randomly distributed to our panel of specialist pediatric cardiologists for independent evaluation. They will assess the quality of the extracted clips/frames, the correctness of the AI-assigned frame labels, and the usability of the video clips in real clinical practice, using a 5-point Likert scale. Additionally, the experts will examine the images for any CHD diagnosis as they would in routine clinical practice. At the end of the exercise, the results will be tallied, and the panel will reconvene—chaired by a designated member—to deliberate on cases with disagreements. A comparison will also be made between video clips obtained by the experts and those obtained by the nonexperts. The review process is expected to last approximately 3 months.

Ethical Considerations and Data Security

Human Participant Ethics Review Approvals

Ethical approval for this study has been obtained in both Cameroon and South Africa. In Cameroon, approval was granted by the Health Research Foundation Institutional Review Board (HIRB02643525), with subsequent administrative approval obtained from the Regional Delegation of Public Health (approval number 0616/AP/MINSANTE/DRSPL/BCASS). In South Africa, ethical approval was obtained from the Human Research Ethics Committee of the University of Cape Town (UCT HREC: 697_2024). A waiver of informed consent was granted, as this study is registered as a substudy of the UCT HREC–approved PROTEA CHD registry and biorepository (UCT HREC: R017-2014). The PROTEA registry involves the collection and storage of echocardiograms, for which all participants have already provided informed consent.

In developing this methodology, we have placed particular emphasis on ethical considerations to ensure that the AI model is not only effective and efficient but also equitable, transparent, and respectful of patient rights and cultural contexts. Our approach seeks to balance technological innovation with patient safety, data privacy, and equitable distribution of benefits. Accordingly, key ethical aspects have been addressed to ensure compliance with both international standards and local regulations.

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Informed Consent

Given the focus on neonatal research, informed consent has been made a cornerstone of the study. Parents or legal guardians of participating neonates will be fully informed about the study's objectives, procedures, and potential benefits and risks. This ensures that participation is entirely voluntary and that parents understand how their child's data will be used. Consent forms will be provided in appropriate local languages, and researchers will be available to answer any questions, addressing potential literacy barriers and fostering trust.

Privacy and Confidentiality

Neonatal echocardiography involves sensitive medical data, making confidentiality essential. All imaging data and associated patient information will be anonymized before storage or analysis. Encryption protocols and secure data transfer methods will be employed to prevent unauthorized access. These measures comply with international guidelines, including the General Data Protection Regulation, as well as the national data protection laws of the study countries.

Equity and Bias Mitigation

We recognize that equitable access to the benefits of the AI model is a critical ethical priority. SSA faces significant disparities in health care access, and introducing this model could inadvertently exacerbate existing inequalities if not implemented thoughtfully. By design, this study will prioritize deployment of the AI tool in low-resource settings where access to expert cardiologists is limited, ensuring that the intervention aligns with its goal of addressing health care inequities.

Another major ethical concern is the potential for bias in AI algorithms. The model's training data must represent the diverse populations it aims to serve to ensure diagnostic accuracy across different demographic groups. Inadequate representation could lead to disparities in model performance, undermining trust, and fairness. To mitigate this, the study will incorporate data from diverse neonatal populations in Cameroon and South Africa, with plans to expand the dataset to include additional low-resource settings.

Transparency and Accountability

We are committed to transparency and accountability, which are integral to the ethical deployment of AI tools. Health care providers using the AI tool must understand its capabilities and limitations. The AI tool is intended to support, not replace, clinical judgment, serving as an aid for nonexperts. We will provide clear communication regarding the tool's accuracy, error rates, and scope of applicability to prevent over-reliance and promote responsible use. Additionally, the study will establish mechanisms for continuous monitoring and reporting of any adverse events or unexpected outcomes during the implementation phase.

Equity, Sustainability, and Local Capacity Building

Lastly, we recognize that the long-term sustainability and scalability of the AI model may raise ethical questions regarding resource allocation and stakeholder involvement. To address this, we aim to engage local health care professionals, policy makers, and community leaders early in the process, ensuring that the model is culturally appropriate and responsive to the specific needs of the target population. Measures have been incorporated to build local capacity, training nonexperts in the use and maintenance of the AI tool. This approach reduces dependency on external entities and fosters self-reliance within the health care system.

Compensation Details

No financial compensation will be provided to participants. Participation is entirely voluntary, and all procedures are noninvasive and part of standard care, ensuring that families are not subjected to any additional burden beyond routine clinical interactions.

Image Use and Identifiability

All images used in the study will be fully anonymized, with no identifiable patient features included. If any image inadvertently poses a risk of identifiability, explicit written consent will be obtained from the parent or legal guardian, and the corresponding documentation will be submitted in accordance with ethical policies.

Results

Retrospective data collection for the project began in September 2024. Since then, data from 308 babies have been collected, of which 145 babies' data from Cameroon have already been labeled, while data from 163 babies in South Africa are still being transmitted. In parallel, the project model is under development, with the labeled data from Cameroon being used to initiate training. Although the initial test results are not optimal, these preliminary tests serve as a calibration step, given that all project data must be labeled and consolidated into a single dataset. Overall, the data collection process remains ongoing, and we anticipate that full data collection will be completed by October 2025. Model completion, validation, and publication of the full results will follow thereafter.

Discussion

Anticipated Findings

Modern advancements in data science and digital health technologies present unique opportunities to transform health care delivery in low-resource settings. This protocol outlines a structured approach for developing an AI-assisted echocardiography model designed to empower nonexperts to perform neonatal cardiac scans and capture accurate images for expert review. By addressing critical gaps in CHD diagnosis, the project represents an important step toward improving early detection and referral pathways, ultimately enhancing survival rates for neonates in SSA.

A key next step involves integrating the AI model with existing pulse oximetry and clinical ultrasound systems, alongside establishing a telemedicine platform to enable the transmission of images to remote pediatric cardiologists. One potential platform for such integration is the Commonwealth Award-winning Global Birth Defects app [20], which is designed to support accurate diagnosis of CAs for research and surveillance programs operating in low-resource settings. The

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app already supports the collection of data on CAs, including images and videos, which can be sent to an expert panel for evaluation. Currently, it is primarily designed for externally visible CAs. Integrating assistance with pulse oximetry and echocardiography via the CHD AI model would make the app more comprehensive, potentially transforming it from a surveillance and research tool into a clinical decision-support platform. This expansion also aligns with the mission of our new sub-Saharan African Congenital Anomaly Network [21], which could lead efforts for large-scale adoption across SSA and other LMICs.

Comparison With Prior Work

The adoption of AI in clinical practice is not without challenges, including skepticism, ethical concerns, and regulatory requirements. To address these, the protocol incorporates processes for rigorous clinical validation and stakeholder engagement. This includes piloting the AI model with target users, assessing the quality of AI-extracted images by expert pediatric cardiologists, and collecting feedback from health care providers on the feasibility of integrating AI into routine clinical workflows. These steps ensure alignment with ethical standards and enhance the model's clinical relevance and acceptance. As the current AI model is limited to image capture and does not provide CHD diagnoses, it is expected to foster greater acceptance among health care providers and the public.

Strengths and Limitations

The inclusion of diverse patient populations from Cameroon and South Africa further strengthens the external validity of the proposed model. This diversity better captures regional differences in health care infrastructure and patient demographics, improving its broader applicability across SSA. Nevertheless, generalizing AI models to varied contexts remains a significant challenge [22]. Expanding the dataset to include additional SSA countries and other low-resource settings will enhance model robustness and support wider adoption.

The protocol's imaging sequences and cardiac views adhere to the 2024 American Society of Echocardiography guidelines [16], ensuring a standardized approach to data collection. Additionally, the dual-phase model development strategy, leveraging both retrospective and prospective datasets, addresses limitations in data availability while maintaining compliance with ethical guidelines. The incorporation of metadata-driven insights and quality assurance protocols further strengthens the model's diagnostic accuracy and clinical utility.

Future Directions

Future updates to the current model could provide real-time feedback to guide users in probe maneuvers, enhancing both image accuracy and user expertise. As the model evolves, its scope could expand to include older pediatric populations, prenatal echocardiography, automated CHD subtype detection, and predictive analytics for treatment planning and survival outcomes. These advancements have the potential to increase the robustness and utility of the AI tool, broadening its impact on CHD management in resource-limited settings.

Sustainability and Capacity Building

To promote long-term sustainability, the project incorporates mechanisms for real-world performance monitoring, periodic model retraining with new data, and local capacity-building through partnerships with clinical and academic stakeholders. Open-source training materials and documentation will support local ownership and reduce reliance on external experts. Recognizing the infrastructural and human factors that influence the success of mobile health (mHealth) tools in SSA—such as connectivity limitations, digital literacy gaps, and trust in digital systems [23-25]—the project emphasizes human-centered design, transparent AI behavior, and integration into existing health care structures to facilitate scalable and equitable deployment.

Dissemination Plan

Study findings and tools will be disseminated through integration with established platforms such as the Global Birth Defects app and the sub-Saharan African Congenital Anomaly Network, promoting adoption across LMICs. Engagement with Ministries of Health, research communities, and global health bodies will support regional uptake, feedback loops, and sustainable scale-up.

Conclusions

This protocol exemplifies a rigorous, ethical, and scalable approach to leveraging AI for neonatal echocardiography in low-resource settings. By integrating the AI model with established clinical and research standards, this unique approach will set the stage for broader development and adoption of AI technologies to improve neonatal health outcomes in SSA and other low-resource settings.

Acknowledgments

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Data Availability

This manuscript describes a research protocol. As the study is ongoing, no datasets have yet been generated or analyzed. Upon completion of data collection and model development, anonymized echocardiographic video data and associated metadata may be made available to qualified researchers upon reasonable request, subject to ethical approvals and data-sharing agreements, in compliance with national regulations and institutional policies governing human participants' data. Because of the sensitive nature of neonatal health data and the inclusion of video imaging, data will not be deposited in a public repository. Interested researchers may contact the corresponding author (AZL) to initiate a data access request, which will be reviewed in collaboration with the relevant ethics committees and partner institutions in Cameroon and South Africa. In the future, derived outputs such as pretrained model weights and code for preprocessing and model training will be shared via a public GitHub repository or similar open-access platform, contingent upon successful validation and compliance with institutional guidelines.

Authors' Contributions

Conceptualization: AZL (equal), HD (equal)
Data curation: LLSD (equal), YSW (equal), TD (equal), APK (equal), PM (equal), BK (equal), RB (equal), FD (equal), NKT (equal), OA (equal), FNM (equal)
Formal analysis: AZ (equal) L, MNM (equal), CT (equal), HD (equal)
Funding acquisition: AZL (lead)
Investigation: AZL (equal), TA (equal), TD (equal), JL (equal), CT (equal), FC (equal), LZ (equal)
Methodology: AZL (equal), LLSD (equal), YSW (equal), HD (equal)
Project administration: AZL (lead)
Resources: AZL (equal), TA (equal), TD (equal), MNM (equal), JL (equal), CT (equal), FC (equal), LZ (equal), HD (equal)
Software: LLSD (equal), YSW (equal), TD (equal), APK (equal), PM (equal), BK (equal), RB (equal), FD (equal), NKT (equal), OA (equal), FNM (equal)
Supervision: AZL (equal), MNM (equal), HD (equal)
Validation: AZL (equal), TA (equal), TD (equal), MNM (equal), JL (equal), CT (equal), FC (equal), LZ (equal), HD (equal)
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Conflicts of Interest

None declared.

Multimedia Appendix 1
Study information sheet and consent form (data collection).
[DOCX File , 15 KB - resprot_v14i1e75270_app1.docx]

Multimedia Appendix 2
Statement of purpose for acquiring targeted cardiac views and video capture during echocardiographic examinations.
[DOCX File , 19 KB - resprot_v14i1e75270_app2.docx]

Multimedia Appendix 3
Study information sheet and consent form (artificial intelligence model pilot test).
[DOCX File , 16 KB - resprot_v14i1e75270_app3.docx]

Multimedia Appendix 4
Peer review report from the ZRG1 BTC-L (70) - Center for Scientific Review Special Emphasis Panel, RFA RM 22-022: DS-I Africa RFAs (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 137 KB - resprot_v14i1e75270_app4.pdf]

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Abbreviations

AI: artificial intelligence
CA: congenital anomaly
CHD: congenital heart disease
DS-I Africa: Data Science for Health Discovery and Innovation in Africa
HIC: high-income country
LMIC: low- and middle-income country
mHealth: mobile health
PC: prediction confidence
SOP: standard operating procedure
SSA: sub-Saharan Africa
UCT: University of Cape Town

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Protocol

Maximizing Engagement, Trust, and Clinical Benefit of AI-Generated Recovery Support Messages for Alcohol Use Disorder: Protocol for an Optimization Study

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Abstract

Background: Successful recovery from alcohol use disorder requires long-term lapse risk monitoring. Self-monitoring is difficult, given the dynamic, complex interplay of the many risk factors over time. An automated recovery monitoring support system embedded with a machine learning lapse prediction model could improve sustained, adaptive, and personalized self-monitoring by delivering daily support messages.

Objective: We propose to optimize the components included in daily support messages to increase engagement with a recovery monitoring support system.

Methods: The participants will include 304 US adults with moderate to severe alcohol use disorder. Participants will complete daily surveys and provide geolocation data for 17 weeks. Participants will receive daily support messages, starting in week 2, that convey a combination of individualized information from a lapse prediction model. Manipulated message components include (1) lapse probability and lapse probability change, (2) an important model feature, (3) a risk-relevant recommendation, and (4) message personalization on tone preference.

Results: The National Institute on Alcohol Abuse and Alcoholism funded this project (R01AA031762) on August 9, 2024, with a funding period from August 20, 2024, to July 31, 2029. The institutional research board of the University of Wisconsin-Madison Health Sciences approved this project (IRB #2024-0869). Enrollment will begin in December 2025.

Conclusions: Message components that either increase engagement or improve clinical outcomes will be recommended for use in future recovery monitoring support systems and digital therapeutics.

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KEYWORDS

substance use disorders; precision mental health; continuing care; relapse prevention; MOST; Multiphase Optimization Strategy

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Introduction

Alcohol Use Disorder

Alcohol use disorder is highly prevalent and costly. Over 30 million adults in the United States had an active alcohol use disorder in 2021, and 23.3% reported engaging in past-month binge drinking [1]. Alcohol ranks as the third leading preventable cause of death in the United States, accounting for approximately 140,000 fatalities [2,3] and economic costs that exceed US $249 billion annually [4].

Relapse Prevention

Alcohol use disorder is a chronic condition. Relapse rates following initial treatment are high [5,6]. Lapses (ie, single instances of goal-inconsistent alcohol use) are a necessary precursor for relapse (ie, full return to harmful levels of alcohol use). As a result, preventing lapses and guiding behavior change immediately following a lapse are key goals in both acute and continuing care alcohol use disorder treatment.

Marlatt and Gordon's seminal relapse prevention model [7,8] provides the backbone for contemporary, clinician-delivered interventions for alcohol use disorder (eg, cognitive behavioral therapy [9,10] and mindfulness-based relapse prevention [11]) that have the highest level of empirical support [12-14]. The relapse prevention model provides a detailed framework to understand how emotions, events, and situations can lead to lapses and relapse back to alcohol use. This framework includes both distal and proximal precipitants of lapse such as lifestyle imbalances, craving, high-risk situations, stressors, negative affect, self-efficacy or confidence, and abstinence violation effects. The model's influence is clearly seen in numerous, efficacious intervention modules and supports that are included in cognitive behavioral and mindfulness-based interventions (eg, coping skills training, lapse management, urge surfing, stimulus control techniques, and positive lifestyle changes).

The relapse prevention model highlights that relapse is a complex, nonlinear function of many risk and protective factors that combine and interact to affect relapse timing and severity [15-19]. Many of these factors are transient, leading to fluctuating relapse risk. Urges, mood, lifestyle imbalances, self-efficacy, and motivation all vary over time. Social networks evolve to be more protective or risky. High-risk situations can occur at any time.

Much like other chronic conditions, clinical observation and research suggest that successful recovery from alcohol use disorder requires lifelong monitoring [15,17,19-21]. However, individual (eg, clinician bandwidth) and systemic (eg, overburdened health care system) resources are insufficient for long-term clinician-guided care. Additionally, self-monitoring is difficult, given the dynamic, complex interplay of many risk factors over time.

Recovery Monitoring Support System

An automated recovery monitoring support system that includes embedded machine learning lapse prediction models powered by personal sensing could enable sustained, adaptive, and personalized monitoring. For example, it could help an individual track their risk of lapsing, alert an individual to important drivers of their lapse risk, and potentially recommend personalized recovery activities and other supports.

Moment-by-moment personal sensing of intra- and interpersonal risk factors for alcohol use disorder is already feasible [22-33]. Self-report sensing methods, like ecological momentary assessment (EMA), offer privileged access into subjective factors, such as craving, affect, valence, and self-efficacy, that may be difficult to quantify reliably through other sensing methods. More novel sensing methods, such as tracking geolocation and cellular communications, could provide a window into risk-relevant information difficult to obtain with self-report. For example, individuals may not have the insight to report on subtle changes in routine or changes to one's social circle. Other information, such as time spent in risky locations, could not possibly be collected solely by self-report without drastically increasing the burden of EMA (eg, by increasing the number of questions or frequency of prompts). Irrespective of the method used, sensing lapse risk factors can provide ongoing monitoring that cannot be accomplished in real time by clinicians and is difficult for patients to implement consistently on their own.

Machine learning models can predict future alcohol use [28,33,34] and lapses [32,35] using these sensed features. Our group has developed a model that uses EMA, collected 4 times daily, to predict future lapses back to drinking in the next day [35]. Critically, the model's performance exceeded general benchmarks for excellent performance [36], with an area under the receiver operating characteristic curve of 0.91, when rigorously assessed on new data from new individuals.

Methods from interpretable machine learning [37] can be used to identify patient-specific predictors of lapse risk at any moment in time [35]. These outputs can be anchored within the relapse prevention model to identify specific interventions and supports that are risk-relevant for each patient—much like a clinician would do if they were available in the moment. For example, during sensed periods of high stress, guided mindfulness and body scans could be recommended. Moreover, these systems can harness valuable information that a clinician could not realistically capture, like real-time changes in activity patterns. If increased time with risky people or locations is driving lapse risk, the recovery monitoring support system could provide information on local Alcoholics Anonymous or other support meetings.

Beyond exceptional performance and interpretable inputs, it is imperative that feedback from these machine learning models is intentionally tailored such that patients use the information and follow its recommendations. Communication research has begun to explore how humans communicate with artificial intelligence and other embedded algorithms [38,39] and how qualities of these communications influence trust, acceptance, and the use of "advice" [39-44].

The degree of transparency of the model's outputs (ie, the system's reasoning) is one potential area for tailoring. Research has demonstrated that making predictions or recommendations from "black-box" machine learning models more transparent can improve perceptions, acceptance, and trust of these

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embedded machine learning models [45-51]. In the context of a recovery monitoring support system, some transparency, such as revealing key factors driving an individual's lapse risk, may also promote patient learning and insight to yield additional clinical benefits [46,52-54]. However, in some instances, overly complex or otherwise detailed explanations of how a system works may erode confidence in that system because incremental feedback provides more information than necessary, reveals errors, or leads users to question the system even when it was correct [45,48,51,52,55-57].

Research also suggests that people are more likely to trust, prefer, and engage with automated systems that portray human-like traits, emotions, and intentions [58-60]. Tailoring the linguistic style and tone may be one way to deliver feedback in a manner that more closely resembles an authentic supportive interaction.

Automated communications written with an informal linguistic style have been shown to be related to higher perceptions of human-likeness and trust compared to formal styles. However, this relationship between style and trust is likely context-dependent. In studies where interactions with automated agents are more task- and goal-oriented (eg, during a customer service interaction), informal style was associated with perceived human-likeness, but not trust or overall satisfaction [61,62].

Substantial research exists on human-written (rather than automated) supportive messages and advice. Messages written in tones that acknowledge the recipient's feelings, help the recipient feel accepted, validate experiences of distress, and emphasize the feasibility of following the advice or recommendation have all been shown to be important [63-65]. Given that people tend to anthropomorphize automated messaging systems, these tones are likely important when extending to a supportive messaging system. It is less clear, however, which tones are most appropriate and would be best received in the context of a recovery monitoring support system that delivers important information about lapse risk.

Additionally, important individual differences in linguistic style and tone preferences exist. Research shows that people tend to rate automated messages and agents more favorably when they reflect traits similar to their own (ie, the similarity-attraction effect [66]). These findings have been demonstrated to exist broadly at the group level (eg, culture [67], gender [68,69], and age [70]) and narrowly at the individual level (eg, cognitive and personality style [71,72]).

In the context of digital mental health applications, more broadly, promoting trust is important for eventual therapeutic benefit [73], and mistrust is a key factor in abandonment of mobile health apps [74]. Moreover, declines in user engagement are a known issue in the context of digital mental health supports and may not be exclusively related to trust in the system [75]. Therefore, for a recovery monitoring support system to succeed, we must first explicitly evaluate and optimize the feedback from these embedded machine learning models to maximize patient engagement, trust, and clinical benefit.

Objectives

Our broad goal is to develop a recovery monitoring support system with personalized daily support messages for people with alcohol use disorder. In this project, we propose to optimize the components included in these daily support messages to increase engagement with the support system.

Our approach is guided by the Multiphase Optimization Strategy (MOST) framework [76-78]. MOST has become highly influential for the optimization and evaluation of adaptive and multicomponent interventions in digital health. Its core assertions are that (1) interventions should be explicitly optimized to meet specific criteria; (2) intervention optimization and intervention evaluation are different phases of research, pursue different specific aims, and require different methodological approaches; and (3) the optimization of an intervention should precede its evaluation. The research in this project focuses on the MOST optimization phase. Completion of study objectives sets the stage for future, programmatic MOST research to evaluate optimized smart digital therapeutics using appropriate designs (eg, randomized controlled trial) for subsequent phases of development.

We will manipulate 4 candidate components of daily support messages that convey transparent, individualized, risk-relevant information from our machine learning lapse prediction model to participants. These message components include (1) the user's current lapse probability for that day and trends in that daily lapse probability over the past 2 weeks, (2) an important lapse feature contributing to their current lapse probability, (3) a risk-relevant recommendation for a recovery activity to complete that day, and (4) linguistic style and tone personalization for the support message. These components use output that would be available from any machine learning lapse prediction model such that conclusions about the impact of these components on engagement can generalize beyond our system.

Models will be optimized on a measure of engagement (days of engagement with the daily support messages). We will use a MOST factorial experiment to determine which of the 4 message components encourages individuals to continue engaging with the support system. We will also look at secondary optimizing outcomes of trust in the support system, perceived usefulness of the support messages, and digital working alliance with the support system, as these are likely to drive long-term engagement.

In addition to the engagement outcome, we will test message component effects on clinical outcomes because the risk-relevant information from our machine learning model may provide direct benefits to participants through mechanisms other than engagement (eg, information about relapse processes highlighted by important model features may promote gradual adaptive lifestyle and behavioral adjustments that are difficult to quantify). Message components that either increase engagement or improve clinical outcomes will be recommended for use in future recovery monitoring support systems and digital therapeutics.

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Methods

Overview

The primary goal of this study is to optimize daily support messages from our Smart Technology for Addiction Recovery (STAR) recovery monitoring support system to increase participant engagement with the system. To this end, participants will receive daily support messages from the STAR system for 16 weeks. We will manipulate 4 separate components of these support messages independently in a fully crossed, 4-way factorial, between-subjects design. Each component is operationalized to be binary (eg, include or exclude) so that each is either included or excluded in the support message delivered to the participant. This yields 16 between-subjects conditions, with each participant assigned to receive support messages defined by one of these conditions for the entire study period.

The first 3 components of the support messages involve personalized information based on output from the lapse risk prediction model embedded within the STAR system. The three prediction model-based components are (1) the user's current lapse probability for that day and trends in that daily lapse probability over the past 2 weeks, (2) an important lapse feature contributing to their current lapse probability, and (3) a risk-relevant recommendation for a recovery activity to complete that day.

The fourth component of the support message is linguistic style and tone personalization. The support messages are created using a large language model (LLM) that takes the relevant prediction model-based components as inputs along with a prompt that dictates the linguistic tone and style of the message. Participants either receive support messages using a linguistic tone and style that matches their prespecified preferences or is yoked to another participant's preferences.

The primary analyses for this study evaluate the main effects and 2-way interactions among these 4 message components on days of engagement with the STAR system daily support messages. The secondary analyses examine the effects of the components on other perceptions of the STAR system (message usefulness, system trust, and system digital working alliance) and clinical outcomes (eg, days of drinking and heavy drinking and flourishing).

Participants

Participants must be 18 years of age or older and meet criteria for alcohol use disorder with at least moderate severity (≥4 *Diagnostic and Statistical Manual of Mental Disorders [Fifth Edition;DSM-5*] symptoms). All participants will report a goal of abstinence from alcohol, with their most recent use of alcohol between 1 week and 3 months in the past at study intake [79]. Participants with medical and psychiatric comorbidities will not be excluded. However, participants must be able to read in English and will be excluded if they have disabilities that prevent the use of a smartphone (eg, uncorrected vision, hearing problems, or profound cognitive impairment). Participants must have a smartphone and cellular plan.

We will recruit 304 individuals to participate for up to 17 weeks. This includes a 1-week burn-in period to collect input features prior to using the lapse risk prediction model for personalized support messages followed by 16 weeks of daily support messages from the STAR system combined with data collection of study outcomes. Participants will be recruited using social media and through laboratory-affiliated treatment centers. A diverse sample with respect to age, sex, race or ethnicity, and population density (eg, urban, suburban, and rural regions) will be recruited. We will track recruitment success and make ongoing adjustments to meet our target sample characteristics throughout the recruitment period.

Participants will be paid US $40 for the intake visit and US $20 for phone visits at 8 and 16 weeks into the data collection period. Participants will also be paid up to US $105 each month on study for completing daily EMAs (up to US $50 per month depending on adherence), for sharing geolocation data (US $5 per month), and to offset costs of cell phone service (US $50 per month).

Procedure

Participants will first complete an intake session by phone or videoconference according to their preference. During this session, study staff will describe study procedures, requirements, and participant compensation. Study staff will also confirm the participant's alcohol use disorder diagnosis (via module E of the Structured Clinical Interview for *DSM-5*) and assess other inclusion or exclusion criteria to determine study eligibility (eg, abstinence goal and duration). Eligible participants will be randomly assigned to 1 of 16 possible message conditions (a crossed factorial design of 4 message components included or not included in the messages).

Following the intake session, participants will start to complete daily EMAs and provide geolocation data. After a 1-week burn-in period, participants will begin receiving personalized daily support messages based on output from the lapse risk prediction model embedded in the STAR system (see Daily Support Messages section). Participants will continue to complete EMAs, share geolocation, and receive daily support messages for 16 weeks following the burn-in period. Participants will complete 2 phone follow-up visits at 8 and 16 weeks into this data collection period to measure other study outcomes. Figure 1 presents a flow diagram of study participation.

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Figure 1. Participant flow diagram. During enrollment, participants are assessed for eligibility and complete baseline measures. Eligible participants are subsequently randomized to 1 of 16 possible messaging conditions. Each of the 4 message components, lapse probability and trend, important lapse feature, recovery activity recommendation, and style and tone personalization, can be turned on or off (ie, 2×2×2×2 factorial design). Participants then immediately begin providing ecological momentary assessment and geolocation data. After a 1-week burn-in period, participants begin receiving daily support messages. Participants complete 2 follow-up visits at 8 and 16 weeks after messaging begins. Each follow-up visit consists of an interview and a battery of self-report measures.

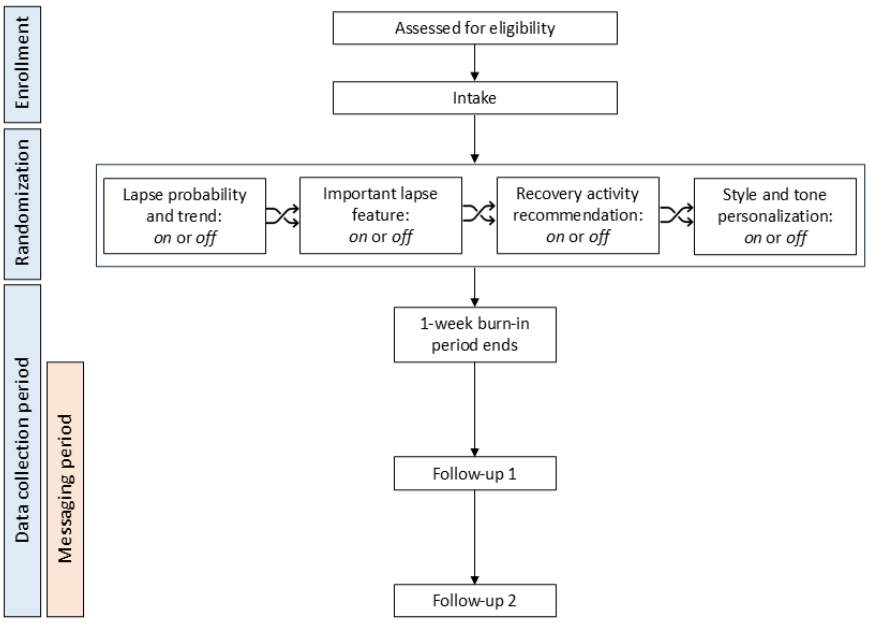

Lapse Risk Prediction Machine Learning Model

Following the methods and analysis workflow used in Wyant et al [35], we have developed a machine learning model that uses both geolocation and daily EMAs to predict the probability of a lapse back to alcohol use in the next day. This elastic net model was trained using approximately 300,000 labeled observations from 146 participants with moderate to severe alcohol use disorder [31,35]. Critically, the model has high combined sensitivity and specificity as indicated by its area under the receiver operating characteristic curve that exceeds 0.90 for held-out observations (using grouped k-fold cross-validation). This model can be used to provide both the probability of a lapse back to alcohol use in the next 24 hours and the change in that lapse probability over the past 2 weeks (eg, increasing, decreasing, or stable). A complete description of the model, including model coefficients and feature engineering details, is available on the Open Science Framework (OSF) repository for this project [80].

Local feature importance [37] for risk categories (eg, craving, stress, and risky situations) is quantified in log-odds using model coefficients and scores for features within each risk category that are associated with each model prediction (ie, a predicted lapse probability for a specific participant on a specific day). Locally important features are features that substantially increase or decrease the predicted probability of a lapse for that participant at that time from the aggregate lapse probability (ie, average probability across all participants and times in the original training data). We consider features that increase or decrease the log-odds of a lapse by >|0.1|, clinically important for binary classification models [37]. By extracting local (ie, for a specific, single prediction) feature importance, we can use the model to determine not only the probability of a lapse and its change over time but also information about why that lapse is likely or unlikely to happen.

Our model features tap into key constructs from the relapse prevention model such as craving, affect, stressors, lifestyle imbalances, high-risk situations, self-efficacy or confidence, and abstinence violation effects. This allows us to use the relapse prevention model to identify interventions and other supports that are personally relevant to that participant at that moment in time to address their risk. Following methods implemented by Fisher et al [81] and Fernandez et al [82] (also see [83-86]), combinations of lapse probability (categorized into low, moderate, or high risk) and important feature categories are mapped to specific recommendations using a mapping matrix based on clinical expertise guided by the relapse prevention model. Combinations of lapse probability and important features (ie, cells of the mapping matrix) often map to more than 1 appropriate module. For example, if craving is important and lapse probability is low, multiple useful urge management recommendations exist (eg, guided urge surfing and distracting games and activities). Thus, this procedure allows us to use the lapse prediction model to identify the set of interventions and supports that are most personally relevant to the participant at that moment in time, given their recent experiences, current lapse probability, and important risk features.

Daily Support Messages

Overview

All participants will receive daily support messages beginning after the 1-week burn-in period. Each day, participants are sent an SMS text message that will contain a Qualtrics (Qualtrics XM) link. The daily support message is accessed and viewed or read in Qualtrics by clicking on that link. The use of Qualtrics

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to display the support message allows us to have a time-stamped confirmation that the support message has been accessed that day. Text messages with this Qualtrics link will be sent out at 5 AM each morning in the participant's own time zone so that the support message is available at the start of the new day upon waking. A reminder is also sent by text message at 11 AM and 4 PM if the participant has not yet accessed the support message in Qualtrics by those times.

The support messages are generated for each participant each night using an LLM (GPT-4o) that is accessed by the STAR system through the Microsoft 365 Copilot application programming interface. LLM prompts and example messages are provided on the OSF repository for this project [80]. The core of each support message is a simple statement that encourages the participant to engage with their recovery that day. In addition to the core statement, the message may include up to 4 additional components of personalized information derived from their linguistic tone or style preferences and the lapse risk prediction model to guide their recovery efforts that day. These components are (1) their current lapse probability for that day and trends in that daily lapse probability over the past 2 weeks, (2) an important lapse feature contributing to their current lapse probability, (3) a risk-relevant recommendation for a recovery activity to complete that day, and (4) linguistic style and tone personalization. These 4 message components are operationalized as follows.

Current Lapse Probability and Trends in Daily Lapse Probability Over the Past 2 Weeks

If included, the support message will contain categorical information about the participant's lapse probability in the next 24 hours based on output from the lapse risk prediction model. Lapse probability will be provided using a 3-level categorization of "low risk" ($P \leq .05$), "moderate risk" ($.05 < P \leq .20$), or "high risk" ($P > .20$). These probability cut points were determined both from clinician input and distributional information in the sample of 151 participants with alcohol use disorder where we developed our model [35]. The cut points represent approximately the 10th and 60th percentiles in the overall distribution of the ~300,000 observed probabilities. The decision to convey lapse probability categorically (rather than numerically) follows current best practice recommendations to avoid complex numerical probability statements, especially for those with low numeracy, and provide the minimal information needed for individuals to assess the magnitude of risk, weigh options, and act [87-91]. It also follows the format from an existing app that characterizes the risk associated with various blood alcohol concentration levels [92].

If included, the support message will also contain categorical information about the trend in the predicted probabilities of a lapse over the past 2 weeks. Lapse probability change will be reported using a 3-level categorization of "decreasing risk" (lapse probability decreases by ≥.05 over 2 weeks), "increasing risk" (probability increases by ≥.05 over 2 weeks), or "stable risk" (probability changes by <.05 over 2 weeks). Lapse probability change is quantified as the difference in mean weekly predicted lapse probability over the 2 previous weeks (ie, week 2 mean–week 1 mean). We use a simple weekly mean difference to capture both linear and more complex (eg, increasing monotonic) trends across these 2 weeks. The 2-week lapse probability trend is provided because trajectory information may make subtle changes in risk level more apparent, can relieve cognitive load associated with monitoring over time, and can provide incremental value beyond absolute risk levels alone [93]. The decision to convey this information categorically follows the same best practice recommendations as for lapse probability [87-92].

Important Lapse Feature

If included, the support message will contain a description of 1 important model feature category that contributes to the participant's predicted lapse probability that day. The feature category will be selected from among the set of important feature categories that day as defined based on the categories' log-odds values (ie, feature categories that increase or decrease the log-odds of a lapse by $>|0.1|$). Among this set of important features, features will be ranked or sorted by how often they have been included in recent support messages and then the magnitude of their importance score. This will prioritize providing the participant with information about new but also important risk features. We include this message component because providing risk feature information may help participants both identify which issues to target for change and select appropriate support tools matched to these issues [94]. Emerging best practices from interpretable machine learning suggest that this information may make the machine learning model less of a "black box," which may build trust, or allow individuals to engage more thoughtfully (eg, questioning false positives and scrutinizing model behavior) and gain insight [95-97].

Risk-Relevant Recommendation for a Recovery Activity

If included, the support message will contain a suggestion to consider completing a specific recovery activity that has been identified by the lapse risk prediction model as personally risk-relevant, given their lapse probability and important model features. All recovery activities are drawn from existing empirically based treatment protocols for relapse prevention, including matrix [98], cognitive-behavioral coping skills therapy [99], and motivational enhancement therapy [100]. As with the feature information mentioned earlier, when multiple risk-relevant recovery activities are available and appropriate, given the lapse risk prediction model output, activities that have not been recommended recently will be selected. We include this message component following best practice suggestions to pair risk information with specific action recommendations to address the risk [101]. This component follows directly from the guiding thesis of our research that improved clinical outcomes will result from increases in adaptive, personally relevant engagement rather than simply more engagement. This component also follows recent examples of digital therapeutics that used machine learning prediction models to generate intervention recommendations for medical or health issues other than alcohol use disorder [102,103].

Linguistic Style and Tone Personalization

In addition to the relevant lapse risk prediction model–based message components for that participant, the LLM prompt for

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support message creation also includes details about the linguistic style (formal or informal) and tone (legitimizing, caring and supportive, self-efficacy support, acknowledging, value affirming, and normalizing) for the support message. These styles and tones were selected based on research on linguistic factors that can affect the acceptance and use of advice during algorithmic or computer-mediated communications [44,104], medical decision-making [105-107], and communications more generally [108-111].

At intake, participants rate how much they would like to receive messages written in each of the available tones and styles independently on a 7-point Likert scale with 1=strongly disagree and 7=strongly agree as anchors. Participants are assigned to either receive support messages matched to their preferences (ie, across days, support messages will be written using any of the tones or styles that were rated higher than the neutral midpoint of the scale) or yoked to receive messages that match the preferences of another participant.

Measures

Overview

Detailed descriptions of the measure items, sources, and administration are available on the project's OSF repository [80]. Our description of study measures is organized into 5 categories: demographic and other stable characteristics, lapse prediction model inputs, primary or optimization outcome, secondary system outcomes, and secondary clinical outcomes. A summary of these measures is also presented in Table 1.

Table 1. Measure constructs, sources, frequency, and use.

Constructs	Source	Measurement frequency	Measure use
Geolocation	FollowMee app	Continuous	Model input
Daily experiences and events (eg, craving, affect, stressors, and risky situations)	EMA[a]	Daily	Model input
System engagement	Confirmation support message accessed	Daily	Primary or optimization outcome
Demographics	Laboratory-created	Intake visit	Baseline characterization or covariate
Alcohol use disorder symptoms	*Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)*	Intake visit	Baseline characterization or covariate
Alcohol use history	Laboratory-created	Intake visit	Baseline characterization or covariate
Lifetime substance use	World Health Organization's Alcohol, Smoking, and Substance Involvement Screening Test	Intake visit	Baseline characterization or covariate
Trust in automated systems	Adapted from Propensity to Trust Questionnaire and Trust in Automation Scale	Intake visit	Baseline characterization or covariate
Message usefulness	Laboratory-created	8- and 16-week follow-up visits	Secondary system outcome
System trust	Adapted from Trust of Automated Systems Test and Trust in Automation Scale	8- and 16-week follow-up visits	Secondary system outcome
System digital working alliance	Digital Working Alliance Inventory	8- and 16-week follow-up visits	Secondary system outcome
Number of drinking days (past 30 days)	Alcohol Timeline Follow-Back and EMA	8- and 16-week follow-up visits	Secondary clinical outcome
Number of heavy drinking days (past 30 days)	Alcohol Timeline Follow-Back and EMA	8- and 16-week follow-up visits	Secondary clinical outcome
Anxiety	Generalized Anxiety Disorder-7	Intake and 8- and 16-week follow-up visits	Secondary clinical outcome
Depression	Patient Health Questionnaire-9	Intake and 8- and 16-week follow-up visits	Secondary clinical outcome
Human flourishing	Flourishing Measure	Intake and 8- and 16-week follow-up visits	Secondary clinical outcome
Recovery capital	Multidimensional Inventory of Recovery Capital	Intake and 8- and 16-week follow-up visits	Secondary clinical outcome

[a]EMA: ecological momentary assessment.

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Demographic and Other Baseline Characteristics

At the intake visit, we will collect self-report information about demographics (age, sex at birth, gender identity, sexual orientation, race, ethnicity, household income, education level, marital status, and number of individuals living in the household), *DSM-5* alcohol use disorder symptoms, general alcohol use history characteristics (eg, age of first use, years of regular use, number of quit attempts, and previous treatment received), and lifetime substance use (World Health Organization's Alcohol, Smoking and Substance Involvement Screening Test [112]). We also measure individual differences in generic trust in automated systems using a subset of items from the Propensity to Trust Questionnaire (6 items [113]) and the Trust in Automation scale (7 items [114]).

Lapse Prediction Model Inputs

Input features for the lapse risk prediction model are engineered from two sources: (1) 1 time daily EMA and (2) passively sensed geolocation. Participants will complete 1 brief (less than 1 minute to complete) EMA each day. EMAs will be sent to the participant by SMS text message at 5 PM each night in the participant's own time zone. These SMS text messages will include a link to a Qualtrics survey optimized for completion on their smartphone. A reminder to complete the survey is sent by text message at 7 PM if a participant has not yet completed it.

On each EMA, participants will report their current mood (ie, affective valence and arousal), their peak alcohol craving since their last EMA, and the occurrence and intensity of any positive events and any stressors or hassles since their last EMA. They also report how likely they are to encounter risky situations (people, places, or things) and pleasant and stressful events in the next week and how confident they are about abstaining from alcohol use in the next week. They conclude each EMA by reporting any alcohol use that they have not yet reported, the time of the start of that use, the duration of the drinking episode, and the number of drinks consumed.

Participants' location will be continuously sensed passively using the FollowMee (FollowMee LLC) geolocation tracking app. We will increase the predictive signal from geolocation by gathering contextual information about the locations that participants visit frequently (≥2 times per month). For frequent locations, participants will report the location type (eg, home of friend, bar, restaurant, workplace, and Alcoholics Anonymous meeting location), if alcohol is typically present at that location, if they drank there previously, their typical emotional experience at that location (pleasant, unpleasant, mixed, or neutral), and the perceived risk to their recovery associated with that location. This contextual information can be gathered quickly by appending these additional questions about a newly detected frequent location to their next daily EMA.

Primary or Optimization Outcome

Our primary outcome for this study is STAR system engagement. System engagement is measured by counting the days that participants access the daily support message by following the link to the support message provided to them by text message. We will calculate message engagement scores that count the number of days the support message is accessed across the full 16 weeks of data collection. Support message engagement serves as the optimization outcome for this study.

Secondary System Outcomes

We measure 3 secondary STAR system outcomes at 8 and 16 weeks into the data collection period: daily support message usefulness, system trust, and system digital working alliance. Daily support message usefulness is measured with 7 items scored on a 7-point Likert scale. These items ask participants to rate the perceived helpfulness, general liking, and personal relevance of the messages [115-118]. Trust in the overall STAR recovery monitoring support system is measured with 10 items scored on a 7-point Likert scale. These items come from the Trust of Automated Systems Test (9 items [119]) and the Trust in Automation scale (1 item [114]). The system digital working alliance between the participant and the STAR system is measured with the Digital Working Alliance Inventory [120]. This measure consists of 6 items measured on a 7-point Likert scale.

Secondary Clinical Outcomes

We will measure 2 primary clinical outcomes recommended by the Food and Drug Administration [121] for the evaluation of interventions for alcohol use disorder: number of drinking days and number of heavy drinking days in the past 30 days. These 2 outcomes are quantified at 8 and 16 weeks into the data collection period. Information about participant alcohol use is obtained from 2 sources. First, participants report episodes of alcohol use in the daily EMAs as described earlier. Second, study staff conduct a 30-day alcohol Timeline Follow-Back (TLFB) procedure [122] at the study phone visits at 8 and 16 weeks in the data collection period. The TLFB procedure is a calendar-assisted retrospective reconstruction of how many standard alcoholic drinks were consumed by the participant each day in the assessment period. This procedure is further enhanced by adding previously reported drinking episodes (dates, times, and number of drinks) from the daily EMAs to the calendar used with the participant. This provides an opportunity to validate those previous reports and collect any additional drinking episodes that may have been missed by the EMAs. The number of drinking days is defined as the number of days that any alcohol is consumed during the relevant 30-day period. The number of heavy drinking days is defined as the number of days that more than 3 or 4 standard drinks are consumed for women and men, respectively, during the relevant 30-day period. The TLFB will also be administered by study staff during the intake visit to determine inclusion or exclusion criteria (ie, time since last drink).

We will also collect secondary measures of anxiety (General Anxiety Disorder-7 [123]), depression (Patient Health Questionnaire-9 [124]), human flourishing (total score and subscales from the Flourish Measure [125]), and recovery capital (Multidimensional Inventory of Recovery Capital [126]). Each of these measures will be collected at intake and at 8 and 16 weeks into the data collection period.

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Data Analytic Plan

Overview

All data preprocessing, visualization, and exploratory analyses will be done using the tidyverse ecosystem [127] in R (R Foundation for Statistical Computing). General or generalized mixed effects models will be fit using the *lme4* package [128] in R. Multiple imputation will be performed using the *mice* package [129].

Primary Analyses

MOST [77] highlights the importance of optimizing any intervention prior to evaluating it with a formal randomized controlled trial. The goal of this project is to optimize support message components in the STAR system by identifying which of the several message components increase engagement with the daily support messages. Such information will be crucial to develop future digital therapeutics for alcohol and other substance use disorders that use personalized supportive messages based on machine learning lapse risk prediction models.

Collins [130] advocates for the use of the factorial experiment as a highly efficient and powerful design to optimize intervention components generally. We use this design to evaluate the effects of our 4 message components (current lapse probability and trends in daily lapse probability over the past 2 weeks, important feature contributing to current lapse probability, risk-relevant recommendation for a recovery activity, and linguistic style and tone personalization) on the primary or optimization outcome (count of days of support message engagement) measured at the end of the data collection period (week 16). The goal of these analyses is to determine the effect of each support message component and whether the effect of one component varies depending on the level or setting of another component (eg, Is the effect of a recovery activity recommendation greater if given in combination with lapse probability or an important feature?).

We will analyze support message engagement in a generalized linear model (with Poisson or negative binomial distribution dependent on the distribution diagnostics for the count data). We will use unit-weighted orthogonal contrasts to code for main effects and 2-way interactions among the 4 message components. Support message engagement will be indexed as the count of days on which the support message was accessed by the participant across the full 16 weeks in the data collection period. Baseline covariates will be included in the model, as described in the Covariates section. This analysis will include all participants who were randomized into the study, following intention-to-treat principles. If participants discontinue use of the STAR system during the data collection period, they will get a 0 for each subsequent day they do not engage with the message.

Secondary Analyses

Analyses for secondary outcomes will follow the same analytic plan as for the primary analyses but will use the secondary outcomes (eg, daily support message usefulness, system trust, system digital working alliance, and clinical outcomes) as the outcome variable. These analyses will allow us to determine whether the effects of message components on engagement also extend to other perceptions of the STAR system and clinical outcomes. The error distribution (Gaussian, Poisson, and negative binomial) for these generalized linear models will be selected based on the distribution of the outcome variable. These secondary analyses will use mean scores for each outcome across the 16 weeks (ie, average of scores at 8 and 16 weeks) as the dependent measure because the effects of time are not a primary focus, given the relatively short duration of the study. These analyses will only include participants who provided at least 1 measurement for the secondary outcomes during the data collection period (ie, at 8 or 16 weeks). For participants missing 1 measurement, scores will be imputed using multiple imputation (see Missing Data section).

Covariates

The use of covariates has been demonstrated to improve estimation efficiency and increase power to test parameter estimates in linear models [131-135]. Given this, the inclusion of baseline characteristics measured prior to assignment to levels for message components will be considered as covariates in the primary and secondary analyses. When available, the baseline scores associated with the study outcome for each model (eg, baseline flourishing for the model examining flourishing) will be included in the model to control for baseline differences on that measure. In addition, following well-established practices in our laboratory [136-138], other baseline characteristics (eg, demographics and alcohol use or history measures and baseline scores on other outcomes) will be included in the model if they demonstrate a significant relationship with the outcome variable for that model, independent of (ie, controlling for) message component effects. This allows for the selection of covariates that will increase statistical power but not bias the parameter estimates for the message component effects.

Sample Size Planning

The primary optimization outcome (count of days of support message engagement) will be analyzed in a generalized linear model (with Poisson or negative binomial distribution) and contrast coding for the main effects and 2-way interactions of the 4 message components. We planned the sample size for this study by simulating the power to detect main effects or interactions of the message components across varying effect sizes and baseline (all message components off) support message engagement rates. We simulated count data using the Poisson distribution for support message engagement across 112 days (16 weeks), with λ (mean count for distribution) calculated as the number of days of observation multiplied by the baseline engagement rate. We added a message component effect to these data by increasing the count to reflect an increased rate of support message engagement across days (eg, on 5% more days) when the component was included in the support message. These simulations indicated that 304 participants would provide 85% power to detect a message component main effect or interaction that increased support message engagement rates by 3% of days when the baseline engagement rate was 85% of days. Power was higher still when message effects were larger (ie, >3%) or the baseline engagement rate was lower (eg, <85%

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of days). We believe that message components that increase engagement rates by less than 3% would not be sufficiently large to warrant including that component in future versions of the STAR system. Furthermore, if baseline engagement exceeds 85%, there would not be much need for support messages to increase engagement further. Therefore, we believed these bounds to be appropriate to represent the minimal clinically meaningful contribution from message components. It should also be noted that this power estimate is likely conservative because it does not include potential covariates that will be included in the analysis model.

Missing Data

We pursue a variety of methods to minimize biases that can occur when participants are dropped from analyses because of discontinued participation or missing data. First, we follow guidelines and procedures that have been recommended for clinical trials [139,140].

Second, our primary optimization outcome (support message engagement) will use all participants who were randomized to the study because days of support message engagement can be measured for all participants who were randomized, even if they do not complete the full 16 weeks of data collection.

Third, our Food and Drug Administration–recommended clinical outcomes (days of drinking and heavy drinking) are somewhat robust to missing data because they can be scored independently from 2 separate methods (daily EMA and TLFB at 8- and 16-week visits). Ideally, both measurement methods will contribute to the most reliable measurement of these outcomes. However, either is sufficient to score these clinical outcomes and can be used in isolation if the other method is missing (due to missing periods for daily EMA or missing study visits).

Finally, our secondary analyses use outcomes that are averaged across 2 measurement periods. This will provide a more reliable measurement for the outcomes. In instances where participants are missing a measurement, we will use multiple imputation to estimate the missing score. Multiple imputation does not attempt to estimate each missing value with a single imputed value but instead uses a random sample of imputed values. This allows for valid statistical inferences that properly reflect the uncertainty that results from missing values, such as valid SEs and CIs for parameters [141]. In brief, we will use *mice* to impute missing values in the dataset using predictive mean matching. Five distinct imputed datasets will be generated. Relevant statistical models for each secondary analysis will be fit to these imputed datasets, and parameter estimates will be averaged.

Ethical Considerations

The institutional research board of the University of Wisconsin-Madison Health Sciences approved this project (IRB #2024-0869). All participants will provide written informed consent and will be told they can discontinue at any time without penalty. Participants will share location data through the use of a third-party app (FollowMee). Their location data will only be identified by a randomly generated Device ID created when the app is installed. Location data are encrypted and sent to the FollowMee servers, where it will be automatically deleted after 14 days. The University of Wisconsin Cybersecurity Office has reviewed the FollowMee software, its security practices, data loss history, and encryption system for transmitting data and judged the risk of a data breach to be low. All raw data (including geolocation) will be stored on Health Insurance Portability and Accountability Act (HIPAA)–compliant servers protected behind a firewall. Raw data will be labeled with an anonymous study identification number. We also have obtained a certificate of confidentiality, which prevents the disclosure of identifiable, sensitive research information to anyone not connected to the study except with explicit consent by the participant. While we use an LLM to generate personalized support messages, no identifiable participant data will be passed into the LLM. It will only be given up to 4 pieces of information about the participant: lapse probability (high, moderate, or low), trend in lapse probability (increasing, decreasing, or stable), one important lapse feature category selected from several categories, and preferences for style and tone.

Results

The National Institute on Alcohol Abuse and Alcoholism funded this project (R01AA031762) on August 9, 2024, with a funding period from August 20, 2024, to July 31, 2029. Enrollment will begin in December 2025. We plan to recruit participants for approximately 3 years.

Discussion

Clinical observation and research suggest that successful recovery from alcohol use disorder requires long-term and perhaps lifelong self-monitoring of lapse risk. Self-monitoring, however, is difficult given the dynamic and complex interplay of numerous risk factors over time.

Machine learning lapse prediction models are now emerging. Recovery monitoring support systems that synthesize these developments can potentially guide patients toward personally risk-relevant engagement that is adaptive, efficient, and more effective. Research is needed to determine the optimal feedback from embedded machine learning prediction models such that patients make the best use of these automated capabilities.

The optimization study in this project is guided by the MOST framework. The research in this project focuses on the MOST optimization phase. We propose to optimize feedback from a lapse prediction model (via daily engagement messages) both to increase engagement with a recovery monitoring support system and to improve clinical outcomes. We will evaluate the effects of 4 message components (lapse probability or lapse probability change, an important feature, a risk-relevant module recommendation, and tone personalization) that comprise the daily engagement messages and can make the output from our machine learning model more transparent to participants. Completion of our specific aims sets the stage for future, programmatic MOST research to evaluate optimized recovery monitoring support systems using appropriate designs (eg, randomized controlled trial) for that subsequent phase of development.

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Additionally, the optimization components use output that would be available from any machine learning lapse prediction model such that conclusions about the impact of these components on engagement can generalize beyond our specific machine learning model. Similarly, engagement messages including these message components could be used in any recovery monitoring system or digital therapeutic for alcohol use disorder, allowing conclusions to generalize to current and future system variants. At the conclusion of the grant period, we will also deliver this optimized recovery monitoring support system as a tangible product and model for how to embed sensing and machine learning into other existing systems.

Acknowledgments

This protocol is funded by the National Institute on Alcohol Abuse and Alcoholism (R01AA031762). The project has been funded for a 5-year period starting in August 2024.

Data Availability

The datasets generated or analyzed during this study will be available in the Open Science Framework repository upon completion of the study [80].

Authors' Contributions

JJC contributed to funding acquisition, methodology, writing the original draft, supervision, and software. KW contributed to the methodology and writing of the original draft. SJS contributed to the methodology. CMM and CJ contributed to the software. SEW contributed to project administration. All authors contributed to the conceptualization and reviewing and editing the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report by the National Institute on Alcohol Abuse and Alcoholism (R01AA031762).
[PDF File (Adobe PDF File), 154 KB - resprot_v14i1e81697_app1.pdf]

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Abbreviations

DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)
EMA: ecological momentary assessment
HIPAA: Health Insurance Portability and Accountability Act
LLM: large language model
MOST: Multiphase Optimization Strategy
OSF: Open Science Framework
STAR: Smart Technology for Addiction Recovery
TLFB: Timeline Follow-Back

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Protocol

Supporting Oral and Long-Acting HIV Preexposure Prophylaxis Decision-Making Among Pregnant Women (MyChoice Intervention): Protocol for 2 Pilot Randomized Controlled Trials

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Abstract

Background: HIV preexposure prophylaxis (PrEP) has potential for preventing HIV during the perinatal period, but few strategies promote person-centered shared decision-making (SDM) about PrEP use in these contexts. The MyChoice study aims to evaluate the feasibility, acceptability, and appropriateness of an SDM approach to support pregnant and breastfeeding women in Lilongwe, Malawi, integrating PrEP into antenatal care to encourage consistent use.

Objective: Two pilot studies will assess the feasibility, acceptability, and appropriateness of an SDM intervention to support pregnant and breastfeeding women in making informed HIV prevention choices. The intervention will also explore the perspectives of participants, their male partners, and implementers. Each study compares the MyChoice intervention to standard-of-care PrEP counseling, with different HIV prevention method choices available.

Methods: We will conduct 2 pilot randomized trials to evaluate the MyChoice intervention, designed to support PrEP decision-making among pregnant women in Lilongwe. Both studies will compare the MyChoice intervention to standard-of-care PrEP counseling. Study 1 will include 100 participants who will be offered oral PrEP and condoms for 3 months. Study 2 will include 50 participants who will be offered oral PrEP or injectable long-acting cabotegravir and condoms for 2 months. The primary end points for MyChoice study 1 are intervention acceptability, intervention appropriateness, and intervention feasibility, whereas for MyChoice study 2 they are intervention acceptability and intervention appropriateness. The secondary end point for MyChoice study 1 is decisional conflict, and for MyChoice study 2, it is the feasibility of study procedures. Exploratory end points include PrEP uptake assessment and dried blood spot measurement of PrEP adherence for MyChoice study 1 and PrEP uptake assessment for MyChoice study 2.

Results: Data collection started on July 30, 2024, for study 1 and on February 10, 2025, for study 2. A total of 100 participants were enrolled in MyChoice study 1, and 50 participants were enrolled in MyChoice study 2. Study follow-up has been completed. Data analysis is expected to be completed by November 2025.

Conclusions: The MyChoice pilot studies will provide critical evidence on a novel intervention for PrEP decision-making during pregnancy and breastfeeding. If feasible and acceptable, these results will form the basis for larger efficacy trials to promote PrEP uptake during pregnancy.

Trial Registration: ClinicalTrials.gov NCT06394323; https://clinicaltrials.gov/study/NCT06394323 and ClinicalTrials.gov NCT06397690; https://www.clinicaltrials.gov/study/NCT06397690

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KEYWORDS

pre-exposure prophylaxis; shared decision-making; pregnancy; prevention; choice; HIV

Introduction

Background

HIV preexposure prophylaxis (PrEP) is a proven yet underused tool to eliminate mother-to-child HIV transmission. With high adherence, daily oral PrEP with tenofovir-emtricitabine is highly efficacious in preventing HIV infection [1-3], including among expectant mothers, and it is safe to use during pregnancy and breastfeeding [4]. However, despite its promise, significant implementation challenges exist [5]. There is evidence suggesting that PrEP may be highly acceptable among PrEP-naive women without HIV, yet attrition and nonadherence are significant challenges for women using PrEP [6-10]. Women in PrEP trials have had consistently poor adherence despite adherence support [11]. Promoting user fit may be critical to achieve prevention-effective PrEP use among pregnant and breastfeeding women [12]. Recent advancements in biomedical HIV prevention have introduced the injectable PrEP option of long-acting cabotegravir (CAB-LA). Injectable formulations offer the benefits of a lower adherence burden and discreet use, particularly well suited for pregnant and breastfeeding women with complex health care needs [13,14]. However, use of injectable PrEP methods still requires user effort to return for repeat injections. Thus, engaging patients in the choice between different PrEP methods will still be critical to ensure patient engagement for persistence and adherence.

Objectives

To ensure that medical decisions such as the choice between PrEP formulations and competing HIV prevention options align with a patient's values and preferences, patient-centered counseling approaches such as shared decision-making (SDM) are recommended. SDM is a collaborative process in which patients and clinicians work together to make informed health care choices [12]. Few SDM or other patient-centered approaches for PrEP decision counseling exist; those developed to date have focused on male and nonpregnant US-based populations [15,16]. To address this gap, we developed the MyChoice intervention to support PrEP decision-making among pregnant women in the context of antenatal care in Malawi. MyChoice is a counselor-delivered SDM intervention facilitated by a paper-based patient decision aid. We developed this intervention through formative work to understand women's values and preferences for PrEP decision-making in the context of pregnancy [17,18] and user testing. Through this process, we developed 2 versions of the intervention: one that only addresses oral PrEP as an option and another that addresses both daily oral PrEP and injectable CAB-LA as options. In parallel feasibility studies, we aim to evaluate the feasibility, acceptability, and appropriateness of each version of the MyChoice SDM intervention to support informed decisions about different PrEP modalities during pregnancy in Lilongwe, Malawi.

Methods

Study Context

The MyChoice intervention was developed with input from women receiving antenatal care at Bwaila District Hospital in Lilongwe, Malawi. We conducted extensive formative research with pregnant women, male partners, and clinicians from the study site to develop the intervention for these pilot studies. The findings of this research (regarding women's values for PrEP decision-making, the implications of these values for feelings regarding PrEP use, and preferences for partner involvement [17]), as well as key guidelines (the Ottawa Decision Support Framework [19] and International Patient Decision Aid Standards Collaboration [12]) informed the development of the PrEP SDM intervention, known as MyChoice for HIV Prevention (MyChoice). The intervention was further refined ahead of these pilot studies through an iterative process of clinician and stakeholder feedback followed by feedback from 15 patient participants.

Study Location

This study will take place at a government health facility, Bwaila District Hospital, a high-volume district facility run by the Malawi Ministry of Health. Approximately 1500 babies are delivered each month at Bwaila District Hospital, and approximately 500 women present each month for immunization visits for their babies at 9 months after delivery. Bwaila District Hospital has provided prevention of mother-to-child transmission services since April 2002 and has promoted male participation since 2007.

Target Population

HIV-negative pregnant women are the primary population to be recruited for this study and will need to meet the following inclusion criteria: age of ≥18 years, a documented pregnancy confirmed via a urine pregnancy test or physical examination, and a documented HIV-negative status within the previous 3 months (Textbox 1). Participants should have factors indicating elevated risk of HIV acquisition per the Malawi national PrEP eligibility guidelines. These include a current or recent sexually transmitted infection within the previous 6 months (self-reported or clinically diagnosed), engagement in transactional condomless sex (including sex workers and clients), condomless sex with an HIV-infected partner not on antiretroviral therapy (ART), or with "Unknown viral load", condomless sex with a partner of unknown HIV status who has other high-risk partners, anal intercourse with a nonregular partner without a condom, or injecting drug use with needle sharing [20]. Participants must demonstrate a willingness to remain within the study site

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catchment area, comply with the visit schedule, and provide informed consent. Exclusion criteria include a positive HIV test at the time of screening, absence of HIV risk factors per Malawi national PrEP eligibility guidelines, and any risk of intimate partner violence or social harm from participating in the study as judged by study staff.

Textbox 1. Eligibility criteria.

Pregnant women inclusion criteria

- Age ≥18 years
- Documented pregnancy via urine pregnancy test or physical examination
- Documented negative HIV status within the previous 3 months
- Identified factors for elevated risk of HIV acquisition per national preexposure prophylaxis (PrEP) eligibility guidelines
- Willingness to remain in the study site's catchment area over the course of the study follow-up and to comply with the visit schedule
- Ability and willingness to provide informed consent

Pregnant women exclusion criteria

- Positive HIV test at the time of screening
- No identified HIV risk factors per national PrEP eligibility guidelines
- Risk of intimate partner violence or social harms as a result of participation per the judgment of the study personnel

Male partner inclusion criteria (in-depth interviews only)

- Referred by a study participant as her partner
- Age ≥18 years
- Ability and willingness to provide informed consent

Study staff inclusion criteria (in-depth interviews only)

- All study staff
- Ability and willingness to provide informed consent

Study Design

We will evaluate each version of the intervention in 1 of 2 separate pilot feasibility studies. In study 1, a total of 100 pregnant women will be randomized 1:1 to receive either the SDM intervention addressing daily oral PrEP and alternative HIV prevention methods (condoms) or standard-of-care (SOC) counseling addressing the same prevention methods. In study 2, a total of 50 pregnant women will be randomized 1:1 to receive either the SDM intervention addressing daily oral PrEP, CAB-LA, and alternative HIV prevention methods (internal and external condoms) or SOC counseling addressing the same prevention methods. In both studies, we will evaluate the acceptability and appropriateness of the intervention. Pregnant women who express interest in either PrEP method will be referred to government PrEP services. Table 1 summarizes the study design. Study 1 was conceived before the CAB-LA rollout, with the sample size powered to detect an intervention effect on the secondary end point of decisional conflict. As CAB-LA became a viable option, we expanded the intervention to include it and secured funding to evaluate this expanded version. Study 2 focuses solely on evaluating intervention acceptability and appropriateness and feasibility of study procedures (no evaluation of intervention effect). Therefore, we selected a sample size appropriate for feasibility studies, aligning with similar research.

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Table 1. Study design summary.

	Study 1	Study 2
Sample size	100 women	50 women
Intervention	MyChoice SDM[a] counseling with choice of oral PrEP[b] or condoms	MyChoice SDM counseling with choice of oral PrEP, CAB-LA[c], or condoms
Follow-up duration	3 months	2 months
Primary end points	Intervention acceptability, appropriateness, and feasibility	Intervention acceptability and appropriateness
Secondary end points	Decisional conflict	Feasibility of study procedures
Exploratory end points	PrEP uptake assessment and dried blood spot assessment of PrEP adherence	PrEP uptake assessment

[a]SDM: shared decision-making.
[b]PrEP: preexposure prophylaxis.
[c]CAB-LA: long-acting cabotegravir.

Study Intervention

The study intervention, MyChoice, is a counselor-delivered SDM tool for pregnant women considering PrEP (Table 2). The counseling sessions last approximately 45 minutes. Three counselors will deliver the intervention after undergoing training spanning 3 days and including a mix of content review and practical exercises to deliver counseling.

Table 2. Shared decision-making intervention content.

Counseling component	Content
Precounseling	• Overview of counseling content • Discussion of the participant's desire to include their partner in counseling
MyChoice counseling	
HIV information and risk assessment	• HIV risk in pregnancy and breastfeeding • Evaluation of HIV risk criteria according to Malawian national guidelines
HIV prevention options	• Present oral PrEP[a] and condoms • Feature attributes and potential advantages and disadvantages of each
Value clarification	• Identify and discuss participant-valued features of available options (attributes and personal and interpersonal implications of each method)
Structured deliberation	• Assess and address unmet decision-making needs • Collaboratively determine whether the participant is ready to decide and identify preferred methods
Postdecision counseling	• Persistence or adherence counseling • Disclosure coaching if desired
PrEP referral	• If oral PrEP is selected, referral to SOC[b] services or to an ongoing cohort study • If CAB-LA[c] is selected, referral to an ongoing cohort study
Postcounseling	• Adherence counseling for selected HIV prevention method • Disclosure support • Partner ART[d] adherence counseling (if applicable)

[a]PrEP: preexposure prophylaxis.
[b]SOC: standard of care.
[c]CAB-LA: long-acting cabotegravir.
[d]ART: antiretroviral therapy.

Before the counseling visit, women will receive information about the content of MyChoice counseling and discuss whether they wish to have their partner or another person (eg, another family member) participate in counseling alongside them. MyChoice counseling may be conducted with any accompanying supporters depending on the participant's preference. MyChoice counseling begins with a review of HIV risk in pregnancy and breastfeeding and includes discussion of the population-specific risk factors that may apply to the participant. After the participant understands her HIV risk, the counselor will present

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various HIV prevention options, including relevant PrEP methods and internal and external condoms, discussing their attributes, advantages, and disadvantages. Following the discussion of the HIV prevention options, a value clarification exercise will be implemented to help the participant identify which features of the prevention options offered matter most to her (product attributes and personal and interpersonal implications of each method). The counselor will then review the responses to the exercise and valued features for each method offered with the participant. The value clarification exercise will be used to understand and address any unmet participant decision support needs and will serve as the basis for structured deliberation to collaboratively identify the participant-preferred HIV prevention methods. The participant may defer or decline to make an HIV prevention method decision and may request a follow-up counseling visit, which will allow the participant to take more time to consider her preference or return with a partner or other supporter. When a decision is made, the counselor will provide postdecision counseling, including adherence counseling and disclosure counseling if desired.

Participants who choose PrEP will be asked whether they hope to disclose their decision to anyone. If yes, the participant will be offered additional coaching to support disclosure. Participants who have a partner living with HIV presently will receive brief counseling on the continued importance of ART adherence and mutual support for ART and PrEP adherence (if applicable). While counseling is intended to take place on 1 day, if the participant requests follow-up counseling (eg, wants more time to decide or wishes to come back with a partner for a future session), reasonable accommodations will be made for the MyChoice counselor to meet with the participant a second time. Women who choose PrEP during the intervention counseling session will be referred to government services to initiate PrEP (daily oral tenofovir disoproxil fumarate/emtricitabine) or to an ongoing observational cohort study that is evaluating the impact of PrEP on pregnancy, infant, and maternal health outcomes (CAB-LA or daily oral tenofovir disoproxil fumarate/emtricitabine) [21].

SOC (Control Arm)

Participants randomized to the control arm will receive PrEP counseling delivered by a trained study nurse following the current SOC per Malawi national guidelines. SOC counseling includes the following elements: HIV risk assessment according to PrEP eligibility criteria, discussion of a combination prevention approach (PrEP and condoms), and risk reduction strategies that are not discussed in SDM. Participants will receive comprehensive education on both the advantages and limitations of PrEP, including guidance on managing potential side effects. Subsequently, the counselor will assess the woman's eligibility, willingness, and readiness to start using PrEP. Women who choose oral PrEP during the SOC counseling session will be referred accordingly. No SDM counseling is provided in the SOC arm.

Recruitment and Enrollment

We will recruit 100 eligible women for study 1 and 50 eligible women for study 2. Study staff will provide interested participants with study information and a referral to the study. Potential participants will be identified at any point in their pregnancy. All women attending the study site who meet the eligibility criteria will be invited to participate in the study. All male partners of invited female participants will be identified and invited to participate. Study staff will also be eligible for recruitment. Prospective pregnant women who choose to complete enrollment on the same day as screening or require additional time to return for the enrollment visit will be accommodated. Enrollment will be finalized upon completion of the informed consent process.

In addition to the primary sample, for qualitative data collection, we will enroll male partners and health care providers (including counselors) for in-depth interviews (IDIs) to assess their perception of feasibility and acceptability. The intended qualitative sample size is summarized in Table 3, although the final sample size will depend on theme saturation. Male partners are eligible for interviews if they are referred by a study participant as her partner, are aged ≥18 years, and provide informed consent. Study staff are also eligible to participate in interviews.

Table 3. Study sample size summary by participant type.

Type of participant	Study 1	Study 2
Pregnant women	100 (up to 30 complete IDIs[a])	50 (up to 20 complete IDIs)
Male partners of pregnant PrEP[b] users (IDIs only)	Up to 20	Up to 10
PrEP counselors or health care workers (IDIs only)	Up to 15	Up to 15

[a]IDI: in-depth interview.

[b]PrEP: preexposure prophylaxis.

Randomization

In each study, pregnant women will be randomly assigned to either the intervention or SOC comparison arm. Health care providers and male partners will not be randomized but will participate only in the qualitative component. Randomization will be conducted using statistical software to generate a 1:1 allocation ratio. The assignments will be placed in opaque, sealed envelopes and sequentially numbered with participant identification numbers.

Study Follow-Up

Participating pregnant women will receive their selected PrEP method (if applicable) through existing services or studies outside the scope of this study. Initiation of either PrEP method (ie, receipt of prescription) will be confirmed through clinic or

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pharmacy records, and information on reasons for noninitiation, if applicable, will also be collected. In study 1, we will conduct follow-up visits at months 1, 2, and 3 after enrollment (Table 4). Study 2 will have follow-up visits at months 1 and 2 after enrollment (Table 5). Study visits will be scheduled to align with antenatal care or pharmacy visits whenever possible to minimize the number of trips needed to the clinic.

Table 4. Schedule of evaluations for study 1.

	Screening	Enrollment	Month 1	Month 2	Month 3
Eligibility assessment					
Pregnancy status	✓				
HIV status	✓				
Additional eligibility criteria	✓				
Participant-reported assessments					
Questionnaires					
Demographic information		✓			
Intervention assessment		✓		✓	
Decisional conflict		✓			
Partner information		✓	✓	✓	✓
Social harms		✓	✓	✓	✓
Qualitative interviews			✓		✓
Oral PrEP[a] adherence assessment					
PrEP uptake assessment			✓		
Pill count			✓	✓	✓
Self-report			✓	✓	✓
Dried blood spot assessment				✓	

[a]PrEP: preexposure prophylaxis.

Table 5. Schedule of evaluations for study 2.

	Screening	Enrollment	Month 1	Month 2
Eligibility assessment				
Pregnancy status	✓			
HIV status	✓			
Additional eligibility criteria	✓			
Participant-reported assessments				
Questionnaires				
Demographic information		✓		
Intervention assessment		✓		✓
Decisional conflict		✓		
Partner information		✓	✓	✓
Social harms		✓	✓	✓
Qualitative interviews			✓	

Data Collection

Interviewer-administered questionnaires will be completed at the month 1 and final follow-up visits (month 3 for study 1 and month 2 for study 2). Questionnaires will assess study outcomes and associated social and behavioral measures to contextualize understanding of primary study outcomes, as summarized in Tables 4 and 5.

At each follow-up visit, pregnant women who have chosen oral PrEP will undergo adherence assessment through self-report and pill counts. In study 1, we will also collect dried blood spots at month 2 to assess adherence among all oral PrEP users.

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Qualitative IDIs will be conducted at designated visits to assess women's satisfaction with study counseling, session quality, and decision-making experience. Follow-up interviews will explore their experiences using the selected HIV prevention method and the perceived impact of study counseling. Additional feedback on the intervention and study procedures will be gathered.

IDIs with male partners and study staff will provide information on their experiences, perceptions of integrating SDM into routine care, and suggestions for improvements. A trained research assistant fluent in Chichewa and English will conduct the interviews using semistructured guides (Multimedia Appendix 1). Interviews will be audio recorded, transcribed, and translated into English for analysis.

Retention

Once participants are enrolled, the study team will implement strategies to ensure high retention and minimize bias from loss to follow-up. Retention rates will be closely monitored, and challenges will be addressed proactively. Key strategies include providing a thorough explanation of visit schedules and procedures during informed consent, collecting detailed locator information at enrollment, and using timely reminders such as phone calls or SMS text messages (with participant consent). The study team will also follow up on missed visits through home or alternative off-site visits when feasible. Trained outreach workers will also conduct in-person follow-ups at participants' homes or other agreed upon locations to enhance retention. If participants choose to discontinue their involvement in the study, we will document their stated reasons.

Safety Monitoring

At each study visit, study staff will evaluate participants for social harms and adverse events. A social harm will be defined as a nonmedical untoward consequence of study participation, including difficulties in personal relationships, stigma, or discrimination from family or the community. An adverse event will be defined as any untoward medical occurrence in a study participant, including any unusual clinical features (eg, non–within-reference findings on physical examination or laboratory tests), symptom, or disease temporally associated with the individual's participation in the study regardless of whether it is considered related to participation in the study.

General Statistical Approach

Initial analyses will include descriptive statistics of the randomized study populations' general characteristics (eg, sociodemographics) and each outcome. Any key characteristics that differ significantly by study arm will be treated as covariates in sensitivity analyses; otherwise, primary and secondary analyses will be unadjusted. The analysis will focus on estimation rather than hypothesis testing, with an α of .05 used throughout to compute 95% CIs. Exact statistical methods to estimate 95% CIs will be used in cases of small cell counts or analysis of continuous measures where $n<30$. Given potential for precision loss with exact CI methods and the pilot nature of these studies, we will use large-sample methods (eg, Wald CIs) when the nominal CI coverage level is tenable. Missing data are expected to be uncommon (≤10%), and a complete case analysis including only evaluable measures will be conducted by default. If missing data exceed 10%, multiple imputation methods may be used where relevant.

Primary End Points

Overview

Primary study end points evaluated in both studies include intervention acceptability and appropriateness assessed via survey measures. The additional primary end point of intervention feasibility will be evaluated in study 1. Descriptive statistics will be calculated for primary outcomes among intervention arm participants. For each 4-item scale, item scores will be averaged to produce a composite score for each participant (range 1-5). Higher scores will indicate a greater level of acceptability, appropriateness, or feasibility. We will estimate the mean differences between arms for each primary outcome with a corresponding 95% CI and *P* value.

Intervention Acceptability (Studies 1 and 2)

We will evaluate intervention acceptability, defined as the extent to which participants perceive the intervention to be agreeable, palatable, or satisfactory. Acceptability will be assessed through participant self-report using a validated 4-item scale. This scale measures how agreeable and satisfactory women find the intervention (responses rated on a 5-point Likert scale ranging from "completely disagree" to "completely agree"). This assessment will be conducted at both month 0 and month 2 using the Acceptability of Intervention Measure scale [22].

Intervention Appropriateness (Studies 1 and 2)

We will also evaluate participant perceptions of intervention appropriateness, defined as the perceived relevance and usefulness of the intervention to support decision-making about HIV prevention methods. Appropriateness will be assessed through self-report using a validated 4-item scale to measure women's perceptions of intervention relevance and usefulness (responses rated on a 5-point Likert scale ranging from "completely disagree" to "completely agree") [22].

Intervention Feasibility (Study 1)

We will also evaluate participant perceptions of intervention feasibility, defined as the extent to which the intervention is deemed feasible or practical from their perspective. This feasibility of intervention measure will be administered at both month 0 and month 2. The items on the scale will be measured using a 5-point Likert scale, and individual responses will be averaged to obtain a score for each measure. Higher scores will indicate a greater level of feasibility [22].

Secondary End Points

Decisional Conflict (Study 1)

The Decisional Conflict Scale (DCS) will be used to gauge women's perceptions of decision uncertainty, satisfaction, clarity of personal values, and support for decision-making. This 16-item measure assesses these aspects on a 5-point scale, with scores totaling 100 points (mean rating multiplied by 25) [19,22-24]. A low DCS score will be identified using a cutoff of 25 out of 100, which has been linked to reduced decisional regret and enhanced choice retention. DCS scores will be

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computed based on women's responses to statements, where higher scores indicate greater decisional conflict whereas lower scores indicate diminished conflict and heightened certainty in decision-making. The scale will be administered at the enrollment visit following completion of study counseling. Summary scores will be presented descriptively (mean and SD across participants in each arm by study) using an intention-to-treat approach. We will first compare group means of DCS scores by study arm and then examine the intervention's effect on this outcome using a 2-sample Welch *t* test. If demographic variables related to decisional conflict differ substantively by study arm, we will instead use augmented inverse probability weights to conduct doubly robust estimation of the average intervention effect.

Study Procedure Feasibility (Study 2)

The feasibility of the study procedures refers to how effectively these procedures can be implemented in the study setting. To assess this feasibility, we will analyze study records and focus on several specific outcomes. These outcomes include the mean number of women screened weekly; the proportion of eligible women who enroll in the study; and retention rates, which encompass the proportion of women returning for each scheduled follow-up visit. In addition, we will measure the number of days required to meet both enrollment and retention targets, starting from initiation of enrollment and from the first scheduled follow-up visit, respectively. Descriptive statistics such as mean, SD, or percentages will be used to evaluate each of these feasibility outcomes.

Exploratory End Points

PrEP Uptake (Studies 1 and 2)

We will assess PrEP uptake (ie, receipt of PrEP prescription) among participants who choose PrEP during the counseling session in both arms. This will be assessed through clinic or pharmacy records.

Retention With Functional Adherence (Study 1)

The clinical exploratory end point to be measured among participants using oral PrEP is retention in care with functional adherence to PrEP at 2 months. We will assess adherence to oral PrEP among participants taking it through tenofovir diphosphate (TFVdp) concentrations in participant dried blood spot samples. TFVdp will be measured using established liquid chromatography tandem mass spectrometry methods [25]. Using published thresholds [26], TFVdp concentrations will be categorized as shown in Table 6. Emtricitabine triphosphate concentrations will also be quantified and may be interpreted in an exploratory manner (eg, in the event that TFVdp is below the level of quantification). Participants will be considered for this composite outcome if they have any record of oral PrEP initiation following study-assisted referral. Participants retained at 2 months who meet the relevant definition of functional adherence (Table 6) will be categorized as retained with functional adherence.

Table 6. Adherence interpretation of tenofovir diphosphate (TFVdp) concentration levels.

Interpretation	Dried blood spot TFVdp concentration per punch (fmol)	
	Pregnant participants	Postpartum participants[a]
Approximately 7 doses per week	≥650	≥1050
2-6 doses per week	200-649	300-1049
<2 doses per week	<200	<300

[a]Participants will be enrolled during pregnancy but may deliver before the month 2 visit, when this outcome is assessed.

A treatment effect on PrEP adherence among participants who adopt PrEP will be explored as sample size and rates of adoption permit. We will compare the proportion of the sample retained in care with functional PrEP adherence at the 2-month follow-up between the 2 randomization arms using a linear binomial model. Women who are not retained at the 2-month follow-up will be counted as failures and will contribute to the analysis denominator. From the linear binomial model, the site-adjusted risk difference of being retained and in care with functional PrEP adherence for the intervention arm versus the control arm will be calculated, along with the corresponding 95% CI. In addition to the primary analysis, assessing functional PrEP adherence as a binary outcome, secondary analyses will compare the adherence categories between the study arms using a Wilcoxon rank sum test. This analysis will be restricted to women with an evaluable adherence score.

Intervention Fidelity (Studies 1 and 2)

With participant consent, intervention sessions will be digitally audio recorded. A randomly selected subset of sessions (approximately 20%) will be reviewed by a study team member using a structured fidelity assessment tool to evaluate intervention fidelity. Study staff will use recordings to evaluate whether counseling was delivered as expected (adherence to intended components and quality of counseling delivered) using the structured tool. Raters will score each counseling section as well as providing an overall score, with elements rated on a 5-point scale (0="no effort"; 4="exemplary effort").

Qualitative Assessment of Intervention and Study Procedure Perceptions (Studies 1 and 2)

Thematic analysis will be used for the qualitative data [27]. The interviews will be transcribed and translated into English. Analysis will follow several steps. The first step is reading for content. We will read the data until content becomes intimately familiar. As the data are reviewed, emergent themes will be noted. The second step is coding. A list of codes will be created and documented in a codebook based on identified themes in addition to structural codes corresponding to initial interview questions. Two coders will independently code each transcript.

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To ensure intercoder reliability, 10% of the data will be double coded. The third step is data reduction. We will review the data related to each code to identify principal subthemes that reflect finer distinctions in the data. This entails taking an inventory of what is related to a given code, observing the variation or richness of each theme, and noting differences between individuals or among subgroups. The fourth step is data display and comparison. Matrices that categorize and display data will be used to help facilitate comparisons across the sampling groups. Throughout the analysis, the research team will engage in ongoing reflexivity through memos, considering how our positionalities, assumptions, and disciplinary backgrounds shape data interpretation. We will address key criteria for trustworthiness in qualitative research. Credibility will be promoted through iterative coding and team discussions to refine data summary and interpretation. Dependability will be established by documenting coding and other analytic decisions. Confirmability will be supported through cross-checking of interpretations within the research team. Finally, transferability will be communicated through detailed narrative description of both the research context and participants, allowing readers to assess the applicability of the findings to other settings and populations.

Ethical Considerations

The study protocol and participant consent forms were approved by the Malawi National Health Science Research Committee (23/10/4210 and 23/10/4211) and the University of North Carolina at Chapel Hill Institutional Review Board (23-3102 and 24-0511). The 2 studies were prospectively registered in ClinicalTrials.gov (NCT06394323 and NCT06397690). Written informed consent was obtained from all study participants before taking part. Consent forms are available in Chichewa and English. Participants receive transport reimbursement equivalent to US $10 in Malawi kwacha at the prevailing exchange rate in accordance with the local ethics committee's recommendation. Trial NCT06394323 was registered on April 26, 2024. Trial NCT06397690 was registered on April 19, 2024.

All data are deidentified and stored securely on locked cabinets or encrypted servers, with transcripts anonymized. To ensure the security of the data and maintain participant confidentiality, all interviews and data collection will take place in private areas at the health facility. Any audio recordings made during qualitative interviews will be promptly transferred to a secure computer, and the original recordings will be erased. The transcripts of these recordings will not include any identifying information. Similarly, paper clinic charts and other documents will be deidentified to remove any personal details. Electronic files will be stored on encrypted devices with password protection to further ensure data security. These measures are in place to safeguard the privacy of the participants and maintain the integrity of the research data.

Results

Data collection commenced on July 30, 2024, for study 1 and on February 10, 2025, for study 2. MyChoice study 1 has enrolled 100 participants, and MyChoice study 2 has enrolled 50 participants, with all participants completing the study follow-up. Data analysis is expected to be completed by November 2025.

Discussion

Our feasibility pilot study seeks to assess the acceptability and appropriateness of the MyChoice intervention to facilitate informed choices about PrEP use during pregnancy. The results of this study will provide novel evidence on the feasibility of delivering PrEP SDM in an antenatal care context and the potential utility of this approach to help women make personally appropriate choices regarding HIV prevention methods during pregnancy and breastfeeding. Currently, there is limited understanding of effective strategies to engage pregnant women in PrEP and identify appropriate candidates within this population. While many pregnant women in sub-Saharan Africa meet the HIV risk criteria for PrEP, such as having a partner with known HIV status or a history of sexually transmitted infections [28,29], studies have shown that women meeting these criteria often exhibit low adherence to PrEP [6-8]. This low adherence may indicate that assessed HIV risk alone is not an adequate motivator for sustained PrEP use.

Fit and motivation for PrEP use are crucial for promoting adherence, and an SDM process may play a key role in achieving both [12]. Unlike ART, the choice to use PrEP is highly sensitive to individual preferences. While PrEP offers the advantage of being a woman-controlled HIV prevention method, it may not be the right choice for every woman during her pregnancy and while breastfeeding. Evidence of variation in women's preferences for HIV prevention methods based on personal values indicates the need for decision support [30-33]. SDM can support user fit by promoting value-aligned decisions and reducing decisional conflict—defined as uncertainty about the best choice among competing options or discomfort with the decision made [34]. Our study provides an opportunity to assess SDM in the context of choosing between oral PrEP and CAB-LA for HIV prevention during the perinatal period. SDM helps reduce decisional conflict by improving individuals' understanding of available options and their benefits and risks and clarifying personal values. Both theoretical frameworks and empirical evidence show that SDM promotes value-congruent decisions and supports adherence to treatments such as ART, as well as therapies for conditions such as depression [35,36]. In HIV care, SDM is highly accepted; strongly desired by patients; and linked to better ART adherence by promoting patient engagement, adherence self-efficacy, confidence in the treatment plan, and satisfaction with the patient-health care provider relationship [37-39]. We need to help women decide which HIV prevention method best fits their needs and preferences as this method will be the most likely to be used effectively [40].

Few studies have evaluated PrEP decision support interventions in women's health settings. A pilot study of women in addiction treatment receiving a PrEP decision aid observed increased interest in PrEP from 25% to 89% and increased likelihood of a scheduling a health care provider visit [41]. A trial of a digital PrEP decision support tool developed for adolescent girls and young women in South Africa demonstrated higher PrEP

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persistence among young women receiving the tool [42]. With the MyChoice intervention, we aim to provide in-clinic PrEP decision support tailored to pregnant women, and we will evaluate the potential effect of the intervention on PrEP persistence and adherence in a future trial. To our knowledge, MyChoice is the first empirically evaluated PrEP decision support intervention for perinatal populations.

Limitations to the design of these pilot trials should be noted. As pilot studies, these trials are not designed to detect an intervention effect on the ultimate outcome of PrEP use but are rather designed to assess the appropriateness, acceptability, and feasibility of the study intervention. If the study intervention and design prove feasible, we will evaluate the effect of the intervention on PrEP use in a larger randomized controlled trial in the future. The self-reported primary and secondary end points in these studies are subject to social desirability bias. To mitigate this potential bias, we ensured that the study staff delivering the intervention were separate from those conducting study questionnaires and interviews with participants and also made clear to participants that there were no right or wrong answers to any questions and that we welcomed all feedback, both positive and negative.

PrEP presents an opportunity to dramatically reduce the elevated risk of HIV acquisition in pregnant and breastfeeding women in sub-Saharan Africa, and SDM may complement the potential impact of PrEP by identifying the appropriate users and promoting adherent use. No evidence-based approaches for PrEP SDM in pregnancy exist. Thus, we aim to fill this gap with these pilot studies to determine the feasibility, acceptability, and appropriateness of a novel SDM intervention and associated study procedures to inform a future efficacy trial.

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Authors' Contributions

LMH is the principal investigator, and in Malawi, FS is the investigator of record and TP is the study coordinator. FS, TP, IK, HC, MT, GN, MC, LN, AB, LP, NM, WK, and PW are involved in data collection. LMH, FS, BHC, CG, LP, and SM contributed to the study protocol development. All authors have contributed to the development of this manuscript and have read and approved the final version for publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview guide.
[DOCX File , 36 KB - resprot_v14i1e76442_app1.docx]

Multimedia Appendix 2
Peer review report from HIBI - HIV/AIDS Intra- and Inter-personal Determinants and Behavioral Interventions Study Section, AIDS and Related Research Integrated Review Group (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 43 KB - resprot_v14i1e76442_app2.pdf]

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Abbreviations

CAB-LA: long-acting cabotegravir
DCS: Decisional Conflict Scale
IDI: in-depth interview
PrEP: preexposure prophylaxis
SDM: shared decision-making

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SOC: standard of care
TFVdp: tenofovir diphosphate

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Protocol

An Open-Road Driving Performance Task to Examine Long-Term Medical Marijuana Use and Prescription Opioid Positivity Among Adults Aged 50 Years and Older: Protocol for an Observational Trial

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Abstract

Background: Driving performance involves multiple underlying components of psychomotor functioning, such as attention, executive functions, and vehicle control. While the effects of acute medical marijuana and prescription opioid intoxication are known, how long-term use of medical marijuana under real-world conditions affects driving performance is unknown. Additionally, there are numerous ongoing physical and cognitive changes that affect driving performance with age. Given the proliferation of medical marijuana and prescription opioid use in adults aged 50 years and older, the prevalence of polypharmacy, and declining functional abilities, it is imperative to understand the long-term effects of daily medical marijuana use. Further, we need to understand how co-occurring use of medical marijuana and prescription opioids, in the presence of comorbidities such as chronic pain, affects real-world driving outcomes.

Objective: This study aims to document the observational trial protocol. The primary goal of this study is to identify the effects of daily long-term (ie, use for >12 months daily or most days of the week) medical marijuana use on driving performance outcomes using an open-road driving performance task under real-world conditions in adults aged 50 years and older who endorse chronic or severe nonmalignant pain and to examine the combined effect of daily long-term medical marijuana use and prescription opioid use on driving outcomes. A secondary goal is to qualitatively explore self-regulation of medical marijuana and prescription opioid use in this population.

Methods: We plan to test medical marijuana use as the exposure variable in adults aged 50 years and older on an open-road driving task performance as the primary outcome. The study will detail tetrahydrocannabinol exposure through ecological momentary assessment and urinalysis and will compare performance with a race-sex–matched group of non–marijuana users.

Results: This study is funded by a grant from the National Institute on Drug Abuse (5R01DA057965). Recruitment began on May 19, 2025. As of November 2025, a total of 30 participants had been enrolled. Recruitment is anticipated to be completed by 2029. Publication of the complete results and data from this study is expected by 2030.

Conclusions: Data from this study will identify the effects of long-term medical marijuana use and the combined effect of that use with prescription opioids to develop risk screening protocols and intervention targets for this population. The development and dissemination of screening and intervention guidelines will be the next step in this work.

Trial Registration: ClinicalTrials.gov NCT06995937; https://www.clinicaltrials.gov/study/NCT06995937

International Registered Report Identifier (IRRID): DERR1-10.2196/77944

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(JMIR Res Protoc 2025;14:e77944) doi:10.2196/77944

KEYWORDS

chronic pain; driving; medical marijuana; older adults; opioids

Introduction

With increasing marijuana use, cannabinoids have become one of the most frequently encountered psychoactive substances in the blood or oral fluids of drivers who are drug-impaired or involved in motor vehicle accidents [1]. The 2015 US National Roadside Survey showed that the rate of tetrahydrocannabinol (THC)–positive drivers increased 48% among all drivers [2]. Further, THC is associated with a 50% increased risk for traffic crashes [3,4], and the risk of motor vehicle collision while driving under the influence of marijuana is twice as high as when driving unimpaired [1,5]. Opioid use is associated with a 47% increased risk of crash involvement [6,7]. Further, motor vehicle collisions are among the leading causes of unintentional morbidity and mortality in North America [8,9]. While the cause of motor vehicle collisions is multifaceted, a potential contributor is the use of psychoactive medications such as prescription opioids [6,10,11]. Due to developmental life stage, older adults have a higher risk for multiple drug use, including polypharmacy [12], which puts them at a higher risk for drug-drug interactions [13]. Driving performance involves multiple underlying components of psychomotor functioning, such as attention, executive functions, and vehicle control [14]. While the effects of acute medical marijuana and prescription opioid intoxication are known [13,15-17], how long-term use of medical marijuana affects driving performance—a complex skill needed for continued independence with age—is unknown. Additionally, there are numerous ongoing physical and cognitive changes that affect driving performance with age [18,19]. Given the proliferation of medical marijuana use and prescription opioid use in adults aged 50 years and older [20-23], the prevalence of polypharmacy, and declining functional abilities, it is imperative that we understand the long-term effects of daily medical marijuana use. Further, we need to understand how co-occurring use of medical marijuana and prescription opioids, in the presence of comorbidities such as chronic pain, affects real-world driving outcomes.

Findings regarding the effects of long-term marijuana use are mixed. Some evidence indicates that long-term, heavy cannabis use (ie, daily or almost daily use) may cause impairment in cognitive and motor functions [24]. Long-term heavy use is associated with decreased motor control, decreased attentional control in both sustained and divided attention, greater cognitive impairment, and greater short-term memory deficits [24,25]. Current heavy use is also associated with decreased vehicle control [1]. However, some studies suggest that impairment due to long-term heavy use does not persist after extended abstinence periods and that mild to moderate use is not associated with impairment [26].

For mid- to late-life adults, participation in driving activities allows them to meet their social roles and stay independent [14,27,28]. Factors such as age-related functional impairments due to chronic pain and side effects of medications such as medical marijuana and prescription opioids can compromise participation in driving and lead to heightened crash risk [28-30]. In the United States in 2015, more than 85% of adults aged 65 to 84 years and nearly 70% of adults aged 85 years and older were licensed to drive [31]. By 2030, the number of older adults is projected to account for 21% of the US population, and most older adults will retain their driver's licenses [32,33].

To date, no studies have systematically assessed driving performance in a rigorous and ecologically valid manner accounting for long-term medical marijuana use and the combined effect of prescription opioid use in adults aged 50 years and older, who endorse chronic or severe nonmalignant pain. Further, studies examining how older adults self-regulate prescription medication use and driving behavior are limited, with none rigorously examining medical marijuana.

Thus, the overall objective of this study is to address the research questions: Does daily long-term medical marijuana use affect performance on an open-road driving task in adults aged 50 years and older who endorse chronic or severe nonmalignant pain, and what is the combined effect of long-term medical marijuana and prescription opioid use on driving performance outcomes in this population?

Methods

Ethical Considerations

This research was approved by the Florida State University Institutional Review Board (STUDY00005560) in December 2024. Informed consent is obtained prior to beginning any study procedures. Participation is completely voluntary. Participant privacy and data confidentiality are protected through multiple measures, including a private interview setting for all study procedures, a Health Insurance Portability and Accountability Act (HIPAA)–compliant data storage platform (Research Electronic Data Capture [REDCap; Vanderbilt University]) and text message delivery application (Mosio), and coding of all data so that it cannot be associated with any individual. Participants will receive up to US $245 if all assessments are completed as directed in the study protocol.

Study Design

We are using a two-group observational study design with a group with medical marijuana use for more than 12 months daily or most days of the week (medical marijuana group [MMG]) versus a race-sex–matched group with no marijuana exposure in the past 10 years and no history of daily use (no marijuana group [NMG]). We chose 10 years as the no–marijuana-exposure window to ensure that recreational use was not a confounder. We will test the difference between long-term medical marijuana exposure and no marijuana exposure on driving performance outcomes in adults aged 50 years and older who endorse chronic or severe nonmalignant pain through an open-road driving assessment. There will be

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up to 3 in-person assessment sessions over approximately 10 days. Assessment session 1 (AS1; the first assessment session) is the onboarding session, which will include informed consent, sociodemographics, a battery of psychosocial measures, and urinalysis to test for the presence of marijuana, opioids, and other commonly misused substances. After AS1, we will use ecological momentary assessment to capture medical marijuana use (MMG) or mood and medication use (NMG). MMG participants will complete twice-daily assessments of medical marijuana use for 7 days. To attention match, the NMG will complete twice-daily assessments of mood and any medication use daily for 7 days. Assessment session 2 (AS2; the second assessment session), the open-road driving performance task, will occur approximately 8 days after AS1 and, for MMG participants, 8-12 hours after the last medical marijuana use. At AS2, vision screening to ensure appropriate visual acuity and urinalysis will be completed before the drive. Additionally, we will request permission from MMG participants only to extract Office of Medical Marijuana Use (OMMU) purchase history data, which include the dispensary name, date of purchase, quantity of medical marijuana purchased, and route of administration. Assessment session 3 (AS3; the third and final assessment session) will be a qualitative interview with a subset of participants (n=60) regarding self-regulation of medical marijuana and prescription medication use, to be completed no later than 3 days after the drive (Figure 1).

Figure 1. Study flowchart. LC/MS-MS: liquid chromatography–tandem mass spectrometry; MMTC: Medical Marijuana Treatment Clinics of Florida.

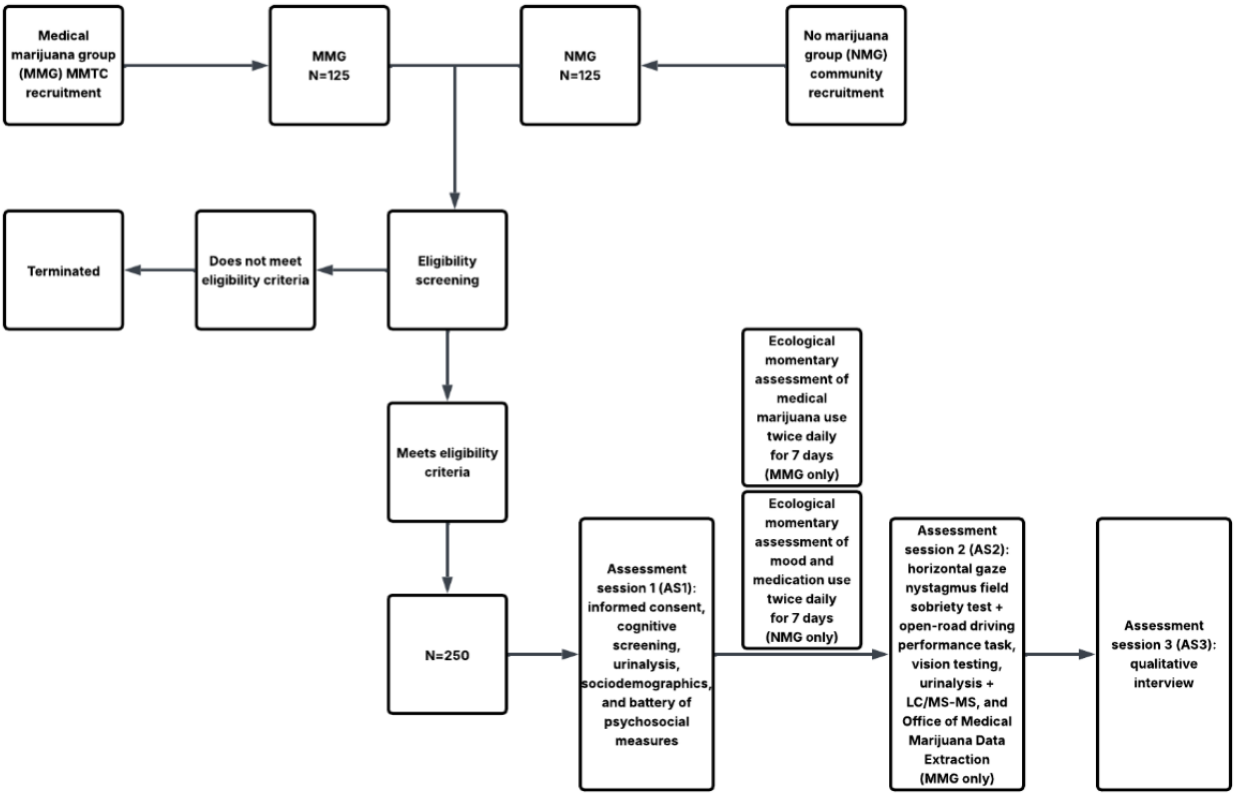

This study is designed to address an urgent public health issue: “What are the effects of chronic, habitual marijuana use on adults aged 50 years and older?” Mid- to late life is a sensitive time period that involves significant changes that can impact quality of life, and understanding how chronic habitual marijuana use affects cognitive and psychomotor function is a significant and vital public health question. This study is designed to obtain data needed for the development of guidelines and best practices for use among adults aged 50 years and older who use marijuana daily or most days. The primary outcome, driving performance, is a vital measure of continued independence with aging and represents a real-world activity that captures cognitive, motor, memory, and executive functions in a single task. Therefore, the estimand of this study is to understand the difference in driving performance errors (ie, lane maintenance errors, speed regulation errors, adjustment-to-stimuli errors, yielding errors, signaling errors, vehicle positioning errors, visual scanning errors, and gap acceptance errors) among adults aged 50 years and older who have used medical marijuana daily or most days for at least the past year (MMG), as compared race-sex–matched adults who do not consume any marijuana (NMG). Further, we are intentionally using an 8- to 12-hour timeframe, as that is consistent with how adults in this population report marijuana consumption behavior in relationship to driving. This study design maximizes both ecological and external validity by estimating group differences in performance that reflect long-term neuroadaptation and real-world use patterns rather than acute intoxication. In addition, urine metabolites are collected before each drive so chronicity of marijuana use will be on a continuous spectrum as measured by 11-nor-9-carboxy-tetrahydrocannabinol (THC-COOH) output. The focus of our study design is to better understand chronic

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habitual use and whether there are any impacts on driving performance under real-world conditions.

Primary Outcome

Open-Road Course Driving Performance Test

Our standardized road course is a fixed route in Gainesville, Florida, with a gradual progression of driving difficulty. The scoring mechanism is based on errors, which are used to evaluate driving maneuvers. A standardized scoring sheet with a total of 49 driving maneuvers and 8 types of possible driving errors is used by the certified driver rehabilitation specialist (CDRS) or driver rehabilitation therapist (DRT) while the participant is driving. The driving errors are defined in the subsequent subsections.

Lane Maintenance Errors

These refer to the lateral positioning of the vehicle during driving maneuvers such as turns, straight driving, lane changes, and while stopped, reflecting the ability to maintain steering control.

Speed Regulation Errors

These reflect the ability to follow and maintain speed limits and adequately control acceleration and braking features of the vehicle; examples include not coming to a complete stop at a stop sign, traveling too slowly or too fast, inadequate merging speed, and abrupt or inappropriate braking or acceleration.

Adjustment-to-Stimuli Errors

These capture the ability to adjust appropriately to changing road sign information, other vehicle movements, and pedestrian movements, and to recognize potential hazards; examples include not adjusting speed for posted limits, not following proper directions given by the evaluator, choosing an improper lane from posted signage, and improper responses to traffic, pedestrian, or cyclist movement.

Yielding Errors

These refer to the ability to recognize common rules of road safety and to give the right-of-way when appropriate; these are assessed at 4-way or 2-way stop intersections when other vehicles are present, during right turns on red, and during merges.

Signaling Errors

These reflect the proper use of turn signals; examples include leaving the turn signal on, not using the turn signal when turning, using the turn signal inappropriately (eg, using the wrong signal for a given turn), or signaling for too short a duration before a maneuver.

Vehicle Positioning Errors

These refer to the anterior-posterior position in relation to other vehicles, objects, and pavement markings; they capture following distance during forward movement and vehicle spacing during lane changes and merges. Examples include traveling too closely or tailgating, having an inadequate space cushion during a merge or lane change, and stopping across a crosswalk or too far back from either pavement markings or other vehicles.

Visual Scanning Errors

These refer to demonstration of visual scanning of the driving environment; examples include not checking blind spots or mirrors during turns and lane changes and not looking left or right before proceeding through an intersection.

Gap Acceptance Errors

These refer to choosing an appropriately safe time and spacing distance to cross in front of oncoming traffic in the context of an unprotected left turn; these are based on evaluator judgment given the speed of oncoming traffic and the number of lanes to be crossed.

Scoring Criteria

Scoring in this study is based on assessing driving errors to discern how participants perform on the road and to identify driving performance deficits. The 8 driving errors are being measured on a scale from 0 (physical intervention indicating very poor driving performance) to 3 (no driving errors indicating good driving performance). For each maneuver, a maximum score of 3 is given if no errors are committed. Specifically, the scoring is as follows: 3 indicates no errors, 2 indicates any error in any driving behavior for the given maneuver, 1 indicates that the evaluator must use verbal cues or repeat instructions (not hearing-related) to modify or change driving behavior, and 0 indicates that physical intervention (such as grabbing the steering wheel or using the auxiliary brake) is required. At the end of the driving course, the sum of the points attained is computed as the sum of maneuvers score (SMS), ranging from 0 to 147, with 147 indicating a perfect driving score (zero errors) [34,35], which provides detailed information to identify deficits in the participants' driving performance.

Study Setting and Recruitment

Participants will be recruited from Medical Marijuana Treatment Clinics of Florida (MMTC) in Gainesville, Ocala, and The Villages. To date, at the 3 locations from which we will recruit, medical marijuana physician services are provided to 4653 adults aged 50 years and older, with 3119 having at least 1 recertification appointment or more. Recertification in the state of Florida occurs every 210 days; therefore, we have an adequate number of potential participants to meet the sample size demands for the MMG. NMG participants will be race-sex–matched adults aged 50 years and older who endorse chronic or severe pain, recruited from the community using flyers and handouts, newspaper advertisements, internet advertisements, social media, in-person lectures and events, and contact by mail, email, and through the infrastructure and support of Oak Hammock at the University of Florida (UF), a residential retirement community.

Retention

First, we will develop a strong collaborative relationship between participants and members of the research team. Second, participants welcome participation when they know that they are contributing and that their efforts have the potential to improve other people's experiences. Therefore, we will send

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information on pain management, other related resources, and local events that highlight the benefits of research. Finally, to enhance retention for this proposal, we will obtain additional contact information, communication preferences, and use dedicated research staff time for connecting, tracking, and follow-up.

Sample Size and Power

Power estimates for this study are based on the number needed for the subanalysis to ensure we have sufficient power to answer aim 2. Using G*Power for the *F* test, we calculated the sample size for a small effect size (f=0.20) based on the expectation of a smaller effect size for subgroup analyses than for the main analyses [36]. Therefore, with an α of 0.5 and power set at 80%, a total sample size of 198 is needed to detect a small effect between subgroups of medical marijuana only, medical marijuana and prescription opioids, prescription opioids only, and no use at all. However, to ensure we have the full sample needed, we are planning for a potential early termination rate (eg, drive not completed due to intoxication or other reasons) of 5%, which indicates we need a sample size of 250—as 198 + 10 (5%) = 250 (125 per group). We anticipate a medium effect size for aim 1 based on the first ROAD ACE (Reactions of Older Adults Driving After Cannabis Exposure) project (1R21DA048067) that examined driving errors and medical marijuana 7-day pattern of use in a driving simulator. We found a Pearson r=0.459, which is equal to a medium effect size (see preliminary data above). Therefore, we will have sufficient power to test the effects in aims 1 and 2.

Participants

Participants will include 250 adults aged 50 years and older who have been registered with the state of Florida for at least 12 months to obtain medical marijuana and report use daily or most days of the week (n=125), as well as race-sex–matched participants with no marijuana use in the past 10 years and no history of daily use (n=125). Textbox 1 provides the inclusion and exclusion criteria. To examine age as an independent factor, we will ensure that age variability is balanced between the two groups. We selected a 10-year no marijuana exposure window to ensure that recreational use does not confound our findings. We chose to match participants by sex to ensure that sex differences do not account for driving performance outcomes. We also chose to match participants by race to ensure that differences in psychomotor functioning by race among older adults do not account for the findings. Groups will be balanced by age (±1 year) to allow for observation of group differences by age.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Aged 50 years and older who endorse chronic or severe nonmalignant pain
- Resident of Florida with an active and valid Florida driver's license
- Active medical marijuana card for >12 months issued by the state of Florida
- Can communicate in English
- Willing and able to complete study procedures
- Race-sex match who has not used marijuana in the past 10 years with no history of daily use

Exclusion criteria

- Active psychosis
- Lost or revoked driving privileges
- Score below 24 (out of 30) on the Montreal Cognitive Assessment (MoCA)
- Control participant who tests positive for marijuana use by urine test or reports any marijuana use in the past 10 years

Study Procedures

Screening

Participants referred to the study by MMTC, community-dwelling adults who self-nominate for participation, or those identified by our recruitment specialist will undergo preliminary screening for eligibility, including questions related to chronic or severe pain, frequency of medical marijuana use, date of last marijuana use, Florida medical marijuana card status, and Florida driver's license status, as well as basic sociodemographic information. Once eligibility has been verified, participants will be scheduled for their first assessment session. They will be instructed to bring a valid Florida driver's license, a valid Florida medical marijuana card (MMG only), and a list of all current prescription medications, over-the-counter medications, vitamins, and supplements with the names, doses, and frequency of administration for each. Screening IDs will be separate from participant IDs, which will be assigned after study enrollment and informed consent. Screening data will be used for the Consolidated Standards of Reporting Trials (CONSORT). Figure 1 provides the study flow.

Assessment Session 1 (Onboarding, Informed Consent, and Questionnaires)

At the AS1 study appointment, participants will be greeted by a study research assistant who will introduce the study and provide informed consent. Following informed consent, participants will be screened for cognitive fitness to proceed using the Mini-Mental State Examination–Second Edition Brief Version (MMSE-2:BV), a 16-item screener used to efficiently

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assess cognitive function [37], to ensure that participants are eligible for the study. If a participant scores fewer than 14 points on the MMSE-2:BV, the study team will administer the Montreal Cognitive Assessment (MoCA), a 30-item screener emphasizing attention and executive function that is used to detect cognitive impairment [38]. Participants must score at least 24 points on the MoCA to proceed. Participants will then complete an assessment battery that includes sociodemographic data and psychosocial measures, including detailed assessments of medical marijuana and other substance use, pain levels, and overall current health status. We will obtain the past 3-year driving record from the Division of Motor Vehicles using the current ROAD ACE protocol. Participants will be compensated US $50 for this assessment.

Assessment of Daily Use

After the AS1 study visit, participants will be instructed to track their medical marijuana or mood and medication use for 7 days at home. Participants will be prompted by Mosio, a HIPAA-compliant text messaging service supported by REDCap, to respond to use surveys twice per day by entering all medical marijuana use (MMG) and mood and medication use (NMG) for 7 days. The surveys will begin 7 days before AS2, with the final survey administered the evening before AS2. All data gathered by the Mosio platform (protected health information or non-protected health information) will be subject to the same security, privacy, and breach notification measures that apply to all entities subject to HIPAA standards, and the Mosio platform is bound by the business agreement established with Florida State University. Mosio may also be used to communicate other study-related messages to participants and within the research team. NMG participants will be compensated in the same manner as MMG participants for completing daily assessments of their mood and medication. Participants will be compensated US $10 per day, with a US $5 bonus for providing data for all 7 days.

Assessment Session 2 (Driving Performance Task)

Participants will arrive at the UF Smart House either by Uber or by a driver of their choice. For MMG participants only, AS2 will take place 8-12 hours after the last medical marijuana use. Upon arrival at the Smart House, a study team member will complete vision screening with the UFOV (Posit Science) and Optec 5000 (Stereo Optical) visual analyzer machine and collect a urine sample for urinalysis. A portion of the urine provided by MMG participants will be reserved for analysis using liquid chromatography–tandem mass spectrometry, which provides a more precise measurement of the level of THC-COOH, a metabolite of THC, present in urine. We will request permission from MMG participants only to extract OMMU purchase history data, which includes the dispensary name, date of purchase, quantity of medical marijuana purchased, and route of administration.

The CDRS or DRT will begin the open-road driving performance task evaluation, which begins with a standardized field sobriety test to detect the presence or absence of horizontal gaze nystagmus, the involuntary jerking or sudden eye movement that naturally occurs when the eyes gaze to the side [39]. The evaluator will instruct participants to focus on and follow the trajectory of a slow-moving horizontal object, typically a pen, presented directly in front of their face. The evaluator will observe both the right and left eye for 3 distinct signs: lack of smooth pursuit, distinct nystagmus at the maximum eye deviation (N_{max}), and onset of nystagmus prior 45° deviation (N45) [40]. These signs will be recorded as “present” or “absent,” and participants will be classified as “failed” if all factors are noted as “present.” Participants who fail the sobriety test will be informed that they cannot complete the drive and will be compensated US $20 for a partial AS2 visit.

After sobriety is ascertained, the task continues with a “warm-up” period using a dual-brake program vehicle (a 2019 Toyota Camry or 2020 Toyota Corolla) in a parking lot. The evaluator will review the general controls for mirrors, seats, and automatic transmission shift. Drivers will perform simple maneuvers and practice perpendicular or angled parking for approximately 3 minutes. The course is designed to progress from simple to moderate and then high-complexity environments. The parking lot or “off-road” area transitions directly into a residential or simple driving environment. To ensure adequate exposure within each level of difficulty, the course is designed to include at least 3 examples of each type of maneuver within each level of difficulty. Multimedia Appendix 1 contains road course documentation and scoring details. The assessments will take place during daylight hours from mid-morning through late afternoon—approximately 9 AM to 4 PM. Assessments will be cancelled if the clinical evaluator deems the conditions unsafe due to inclement weather or unsafe road conditions. The complete course consists of 49 maneuvers through Gainesville, Florida. The driving performance form is designed so a single evaluator can document observed driving errors adequately and remain attentive to the driver and surrounding conditions. The fixed route ensures all participants are given the same maneuvers. The evaluator will check observed errors from a list of behaviors under each maneuver. The SMS is the total number of points accumulated over the set number of maneuvers divided by the total possible number of points (49 maneuvers × 3 = 147 possible points, indicating perfect driving). Participants will be compensated US $50 for this assessment and an additional US $20 as a transportation supplement for expenses such as gas or rideshare fees spent traveling to the Smart House.

Assessment Session 3 (Qualitative interview)

Participants will be a convenience sample recruited from the MMG and NMG after AS2. We anticipate that 60 participants (30 per group) will be adequate to reach qualitative saturation [41], and interviews will continue until saturation is reached. We will ensure that groups are balanced by age, race, and sex to ensure the breadth of perspectives from both sides. Interviews will be one-on-one, semistructured, and conducted using an interview guide; sessions will be audio recorded and transcribed using a HIPAA-compliant research transcription company. The goal of this aim is to understand self-regulation of use, including types of products used, THC/cannabidiol percentages, and quantity of use, by integrating qualitative findings and quantitative data to identify markers for risk screening, use guidelines, and intervention targets for this population.

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Participants will be compensated US $50 for completing the qualitative interview. Participants may receive up to US $245 if all assessments are completed as directed in the study protocol.

Study Conditions

Exposure: Medical Marijuana Group

Any patient who has been certified for medical marijuana use and has held an active medical marijuana card in the state of Florida for at least 12 months, is aged 50 years or older, endorses chronic or severe pain, and reports using medical marijuana purchased through the state of Florida dispensation system daily or most days of the week for the past year, as documented by purchases over the course of the year in the OMMU database, has an active Florida driver's license and the visual acuity to perform the task with or without vision corrective apparatus (glasses or contacts). Medical marijuana was legalized in Florida in January 2017. Per Florida state statute 381.986, residents of Florida have access to marijuana for medical use if authorized by a qualified medical marijuana physician. All medical marijuana patients must register with the state for access to medical marijuana, which includes the certification process identifying a qualifying condition, the reason the patient is authorized to use medical marijuana, and tracking all purchases through the OMMU. Qualified medical marijuana patients are allowed to purchase up to 2.5 ounces of smokable flower every 35 days, and limits on the milligrams of all other routes of administration are set by the physician. Patients must be recertified to use medical marijuana every 210 days (7 months). We will track dosage, frequency, type of product used (high vs low cannabidiol/THC), and route of administration. All medical marijuana participants will be recruited from the MMTC, our medical marijuana recruitment partner. Participants will be allowed to complete the drive regardless of a negative or positive urine screen for opioid use. Our current data suggests that approximately 40% of medical marijuana patients will also test positive for opioid use.

No Marijuana Use Group (Past 10 Years)

NMG participants will be race-sex–matched adults aged 50 years and older who endorse chronic or severe pain, recruited from the community using flyers and handouts, newspaper advertisements, internet advertisements, social media, in-person lectures and events, and contact by mail, email, and the infrastructure and support of Oak Hammock at the UF—a residential retirement community. We will also phone individuals enrolled in the UF Clinical and Translational Science Institute's Integrated Data Repository, a database organizing clinical information across UF Health's clinical and research programs [42]. Individuals enrolled in UF Health services or taking part in UF research studies can provide consent to be contacted within this system, and data can be queried using National Institutes of Health's Informatics for Integrating Biology and the Bedside tool, which provides researchers with a HIPAA-compliant and UF Institutional Review Board–approved limited dataset [43]. In querying this dataset for adults aged 55-84 years (adults aged 45-54 years were grouped together and thus excluded from the query) with who endorse chronic or severe nonmalignant pain, the tool reported 7463 potential participants who have consented to be contacted for research participation. Participants will be allowed to complete the drive regardless of a negative or positive urine screen for opioid use. Our current data suggests that approximately 25% of control participants will also test positive for opioid use, with literature estimating of up to 50% of patients with chronic or severe nonmalignant pain using opioids.

Data Blinding

Due to the extent of participant engagement with the CDRS and DRT, we will ensure that the CDRS and CDRT, who are responsible for the primary outcome, are blinded to participant condition to minimize any potential bias.

Participant Data Protection

Any computers or tablets containing identifying data, such as participant logs, will be protected by multiple security codes using standards set by Florida State University. During data analysis, all identifying information, except the participant identification number, will be removed. The Intervention Research Advancing Care Excellence laboratory (director: NE) and Institute for Driving, Activity, Participation, and Technology (director: SC) benefit from outstanding security, backup, and technical support provided by the University of Florida Clinical and Translational Research Institute and the College of Public Health and Health Professions. Data are collected at the UF Smart House and are managed by our central data management team. All electronic medical records marijuana data will only be accessed by core study staff with the appropriate training and prior institutional review board approval.

Safety Monitoring

Primary Outcome

The safety of all participants will be ensured through: (1) sobriety testing, (2) vision screening, (3) no drives conducted in rainy conditions, (4) all drives completed during daylight hours during and periods of lower traffic congestion, and (5) use of a dual-brake controlled vehicle equipped with an eye check mirror for the CDRS or DRT. In addition, a closed-road driving observation period will be conducted by the CDRS or DRT, during which any safety concerns will result in termination before entering the open road. The CDRS or DRT will provide verbal cues as needed and take over steering if necessary to prevent harm, as trained and in accordance with best practices.

Mitigation of Risk

Our on-road course is highly regulated. The CDRS or DRT will observe for safety, provide instructions to the driver, and implement interventions such as braking the vehicle or taking over steering if necessary. No drives will be conducted in moderate to heavy rainy conditions (as determined by the CDRS or DRT), and all drives will be completed during daylight hours and midday during periods of lower traffic congestion. During the AS2 drive study visit, we will check participants' visual acuity and motor skills. After those steps, we will teach participants about the vehicle they will drive—a 2019 Toyota Camry or a 2020 Toyota Corolla dual-brake vehicle with in-vehicle information systems (eg, a back-up camera) and advanced driver assistance (eg, emergency braking control) features—and make sure they know how to operate the vehicle's

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controls (eg, steering, brake, gas). None of the other smart features (eg, adaptive cruise control or lane centering system) will be activated during the drive.

Data Analysis Plan

We will initially compute descriptive statistics to provide demographic and clinical characterization of the study sample. We will examine whether the MMG and NMG participants differ at study entry on potential confounding variables before testing study hypotheses and we will test medical and demographic variables as predictors of study outcomes. Medical and demographic variables that are significant predictors will be used as covariates and controlled for in subsequent analyses. Highly skewed covariates will be analyzed using spline, log transformation, or other acceptable normalization (eg, square root transformation). Finite mixture modeling and generalized linear modeling, accounting for individual- and group-level outcomes, will be used to test the study hypotheses. Primary study hypotheses will be tested using analysis of covariance (ANCOVA), given that the primary outcome SMS is a continuous variable (range 0-147) and inclusion of covariates will reduce error variation and increase statistical power, particularly as this study lacks random assignment.

Hypotheses Testing

Hypothesis 1a and 1b (Driving Performance—Between-Group Analyses)

To answer the question of whether long-term medical marijuana use affects behavioral driving outcomes, we will compare the SMS between MMG and NMG using an independent 2-sample *t* test. ANCOVA will then be used to determine whether the two groups differ on SMS by adjusting for significant sociodemographic, driving, behavioral, and clinical variables. A model-building approach, which will include age, will be used, and analyses will be performed with and without covariate adjustment, since sample-dependent variables may explain some outcome variance. Tukey's honestly significant difference test or Tukey-Kramer test will be used to estimate the clinical significance of the findings.

Hypothesis 2a (Prescription Opioids—Combined Effect)

To test the hypothesis that prescription opioid use will be associated with worse outcomes on driving performance (SMS), we will conduct a 2-sample *t* test to see if SMS differs in prescription opioid users versus nonprescription opioid users, regardless of medical marijuana use status. Then, similar to aim 1, we will use ANCOVA to test the relationship between SMS and prescription opioid use; the variable selection process will be based on the significance of variables and the adjusted R^2, while the medical marijuana use status will not be included in the list of variables for the selection. This will tell us if prescription opioid use affects driving performance regardless of medical marijuana use status. Additionally, if the best-fitted model contains different covariates from the best model for medical marijuana use seen in aim 1, we will also perform a model to adjust the same covariates as in aim 1 to compare the results for prescription opioid use and for medical marijuana use. This will allow us to see which one alone has a bigger effect on driving performance when adjusting for the corresponding and the same covariates.

Hypothesis 2b

Then we will check the combined effect of medical marijuana and prescription opioid on driving performance (SMS) using ANCOVA. The best fitted model we find in aim 1 will be performed in the subgroup of medical marijuana users and non–marijuana users, respectively. Thus, we will have a clear picture of the driving performance in the 4 groups: medical marijuana and prescription opioid, medical marijuana without prescription opioid, prescription opioid without medical marijuana, and no medical marijuana no prescription opioid. Thus, the combined effect can be determined.

Alternative Design Plan

Limitations may be related to the distribution of the dependent variable, as ANCOVA has strict assumptions. An alternative plan would be to use generalized linear mixed models, which can handle non-Gaussian data, correlated data, unbalanced data, and address missing data while still maintaining power. Possible mitigation approaches include creating a dichotomous variable of high versus low for outcomes and using logistic generalized linear mixed model regression or other functional form as dictated by the distribution of the dependent and independent variables.

Missing Data

Regarding missing data, we will also perform sensitivity analyses to assess the impact of missing data. Further, we will perform appropriate secondary analyses to adjust for variables that may be related to systematic missingness.

Qualitative Aim Analysis

We will use content analysis, an analytic approach that allows qualitative data to be systematically gathered, described, and analyzed, with an emphasis on identifying patterned meaning across the data to identify key concepts, themes, subthemes [44]. A deductive approach to coding will be used, guided by the 3 theoretical frameworks described above. Both theoretical and investigator triangulation will be used to ensure the qualitative trustworthiness of the data. Using a mixed methods approach we will integrate both qualitative and quantitative data. We will use a quantitative plus qualitative structure, which is the simultaneous collection and analysis of quantitative and qualitative data, giving equal weight to both types of data. The function of the mixed methods approach is for development, with the long-term goal of developing effective intervention procedures to optimize risk screening, guidelines, and driver safety for adults aged 50 years and older regarding long-term medical marijuana and prescription opioid use. We will use a merge process to converge the two datasets, integrating quantitative and qualitative data by connecting the datasets to build on each other using NVivo (QSR International Pty Ltd).

Results

Recruitment for the study began in May 2025, with the first participant enrolled the same month. As of the time of manuscript submission, a total of 30 participants have been

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enrolled. Recruitment is anticipated to be completed by 2029. The complete results and data from the study are expected to be published by 2030. Informed consent is obtained prior to beginning any study procedures. Participation is completely voluntary. Participant privacy and data confidentiality are protected with a number of measures, including a private interview setting for all study procedures, a HIPAA-compliant data storage platform (REDCap) and text message delivery application (Mosio), and coding of all data such that it cannot be associated with any individual. Participants will receive up to $245 if all assessments are completed as directed in the study protocol.

Discussion

Expected Findings

Our work will (1) focus on medical marijuana use with a sample who has used daily or most days for 12 months or longer, (2) confirm medical marijuana use based on date of card qualification and purchase history—all products used in the previous year will be downloaded from the OMMU to quantify use patterns over the course of the past year, (3) quantify medical marijuana use for 7 days before the on-road driving performance task using twice-daily ecological momentary assessment for all MMG participants, (4) measure prescription opioid using urinalysis on the day of the drive, and (5) measure driving performance using an open-road course under the observation of a CDRS or DRT trained to evaluate impaired driving in a test vehicle with the needed evaluator controls (eg, eye check mirrors and auxiliary brake) to maneuver the car and prevent any adverse occurrences, including near misses or crashes, if any dangerous situations arise. Older adults are more likely to be involved in crashes at intersections or during merges, and these crashes are inherently more fatal [45,46]. The challenging, fast-paced environment presented by intersections and merges puts extra demand on cognitive, sensory, and motor domains critical for driving, and slower response time, inattention, and difficulty with executive functions may lead to more driving errors, potential crashes, or fatal crashes [44]. Therefore, measurement using a standardized open-road course with a clinical CDRS or DRT in the passenger seat of the vehicle will ensure optimal safety of the driver and other road users. Specifically, we will provide state-of-the-art technology (a 2019 Toyota Corolla and a 2020 Toyota Camry, both equipped with instrumentation) for high-impact, low-risk, rigorous measurement of driving to assess users under the influence of medical marijuana and the combined effect of prescription opioid use. As medical marijuana use grows, prescription opioid use continues, and the US population ages, this study provides needed data to develop risk screening, recommendation guidelines, and relevant interventions for this population.

Strengths and Limitations

As with any trial, our proposed study faces design and feasibility challenges. First, recruiting and retaining 250 older adults within the scope of our eligibility criteria may be challenging due to the complexity of the study, given that older adults are less inclined to engage with technology such as ecological momentary assessments or may feel uncomfortable performing an activity such as driving while being evaluated. However, we have experience with this population and an excellent recruitment infrastructure, which increases confidence in the study and provides the needed guidance with technology. Further, we have built in support for a dedicated research assistant to allow for the time and resources to onboard, train, and problem-solve throughout the assessment period. With guidance from our bioethicist, we have a predetermined protocol for anomalous findings suggesting impairment, which will be provided to participants upfront to ease concerns regarding potential loss of driving privileges. The goal of this study is to assess effects, not make clinical judgments; therefore, our on-road outcome is the SMS, and not the global rating scale of pass or fail outcomes. If we have concern about the on-road performance of a participant, we will report back to the referring physician, who may choose to counsel their patient accordingly. Given our experience with this population, we do not anticipate any difficulties that cannot be managed. Second, is the issue of generalizability. Since we will be using convenience sampling at our partner sites with stringent eligibility criteria, our sample may not be representative of all adults aged 50 years and older. However, since our goal is to determine the effect of an exposure (medical marijuana) on an outcome, representativeness is not necessary. Finally, it is possible that we will need to consider alternative factors that may influence our outcome, such as sex as a moderator due to dosage or titration schedules. We have considered this and are confident that we have the statistical expertise to address this issue as needed.

Conclusions and Future Directions

We know a large percentage of adults aged 50 years and older who are using medical marijuana report use daily or most days of the week. A substantial percentage of adults aged 50 years and older are also using medical marijuana combined with prescription opioids. Previous data indicate that medical marijuana use patterns are associated with driving performance outcomes, particularly in the domains of divided attention and executive functioning. However, lack of vehicle feedback and kinesthetic-only (paper-and-pen) assessment of divided attention and executive function are insufficient. Due to the complexity of driving, evaluation by a CDRS or DRT is needed in order to assess the effectiveness of driving performance under real-world conditions. Data from the first ROAD ACE (1R21DA048067) indicate that our prospective study design and follow-up time period of 3 months is insufficient to identify the full extent of the role medical marijuana use plays in driving performance outcomes. Further, prescription opioid use needs assessment. This current proposal's rigorous measurement of medical marijuana use combined with an open-road driving evaluation based on a valid and reliable measure, combined with our team's expertise, will provide high-impact data that transforms the field by identifying risks that could be screened for and identifying needed intervention targets for self-regulation of use to support driving performance in this population.

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Acknowledgments

The authors did not use generative artificial intelligence for any portion of the generation of this manuscript.

Data Availability

The datasets generated or analyzed during this study are not publicly available due the timing of data submission to our identified repository, but are available from the corresponding author on reasonable request.

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Authors' Contributions

All authors made substantive contributions to the development, design, and writing of this manuscript. NE and SC co-led the development, conceptualization, and writing of this manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Road Course and Scoring Documentation.
[PDF File (Adobe PDF File), 352 KB - resprot_v14i1e77944_app1.pdf]

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Abbreviations

ANCOVA: analysis of covariance
AS1: assessment session 1
AS2: assessment session 2
AS3: assessment session 3
CDRS: certified driver rehabilitation specialist
CONSORT: Consolidated Standards of Reporting Trials
DRT: driver rehabilitation therapist
HIPAA: Health Insurance Portability and Accountability Act
MMG: medical marijuana group
MMSE-2: BV: Mini-Mental State Examination–Second Edition Brief Version
MMTC: Medical Marijuana Treatment Clinics of Florida
MoCA: Montreal Cognitive Assessment
NMG: no marijuana group
OMMU: Office of Medical Marijuana Use
REDCap: Research Electronic Data Capture
ROAD ACE: Reactions of Older Adults Driving After Cannabis Exposure
SMS: sum of maneuvers score
THC: tetrahydrocannabinol
THC-COOH: 11-nor-9-carboxy-tetrahydrocannabinol
UF: University of Florida

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Protocol

Improving Access to HIV Prevention Services in Community Pharmacies in the US Southeast: Protocol for a Hybrid Type 1 Effectiveness-Implementation Study

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Abstract

Background: Despite advancements in HIV prevention, many Americans, particularly those from historically underserved communities (eg, racially and sexually minoritized individuals and people who use drugs), continue to face significant barriers to accessing crucial HIV prevention services such as HIV testing and pre-exposure prophylaxis. Integrating these services into community pharmacies is a viable yet underused solution to overcoming access-related challenges. However, few studies have used an implementation science approach to assess the implementation and effectiveness of such services in pharmacy settings.

Objective: The Pharmacy-Based Access to HIV Prevention Services study aims to develop and evaluate a sustainable pharmacy-based model for increasing access to HIV testing and prevention services (eg, pre-exposure prophylaxis dispensing) in community pharmacy settings.

Methods: We are using a hybrid type 1 effectiveness-implementation study design to evaluate the implementation and effectiveness of HIV testing and prevention services within community pharmacies, particularly among those that offer non–HIV-related screenings (eg, COVID-19, blood pressure, and cholesterol screening) and those that do not. We apply 3 well-established implementation science frameworks—the Exploration, Preparation, Implementation, Sustainment framework, the Consolidated Framework for Implementation Research, and the Systems Engineering Initiative for Patient Safety—to assess multilevel factors influencing the adoption of HIV prevention services in community pharmacy settings. This study consists of three phases: (1) a mixed methods exploration phase to identify barriers and facilitators of implementing HIV prevention services in community pharmacies, (2) a preparation phase to assess the effectiveness of two HIV training programs designed for pharmacy staff, and (3) an implementation and sustainment phase to evaluate the effectiveness and implementation of HIV prevention services in these settings.

Results: The Pharmacy-Based Access to HIV Prevention Services study was funded in June 2023 by the National Institute of Mental Health (R01MH123470) and launched in September 2023. Recruitment and enrollment for the first phase, including data

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collection, are currently underway. We have exceeded our Phase 1 pharmacy staff survey target, with 310 participant surveys completed (goal: 300). Completion is anticipated by early 2026.

Conclusions: Expanding access to HIV prevention services through community pharmacies is a promising and accessible approach to addressing social and health inequities in HIV, supporting the goal of Ending the HIV Epidemic in the United States. Implementation science, with its systematic frameworks, is essential to advancing this goal. Our study is among the first to use an implementation science approach to integrate HIV prevention services within community pharmacies in high-prevalence HIV areas.

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KEYWORDS

HIV prevention; PrEP; HIV; implementation science; protocol; HIV testing; PrEP screening; prophylaxis; access; pharmacy; pre-exposure prophylaxis

Introduction

Background

Regular HIV testing and uptake of pre-exposure prophylaxis (PrEP) are the 2 most effective, yet underused HIV prevention strategies. In the United States, at least 1 in 2 Americans diagnosed with HIV is estimated to have been infected for at least 3 years [1,2], leaving a substantial window for disease progression and transmission in the community. The US Centers for Disease Control and Prevention recommends that people aged 13-64 years get tested for HIV at least once in their lifetime, and yearly for individuals at increased risk of infection (eg, people who use drugs and sexual and gender minoritized individuals) [3]. Despite this, 54% of the US population has never been tested for HIV, and only 8% have tested in the past year [4]. Similarly problematic, daily oral PrEP can prevent up to 99% of HIV infections [5], yet only 25% of those who need PrEP are currently prescribed [6,7]. Inequities in PrEP use by race are dire: in 2019, just 8% of Black people in need of PrEP received a prescription, compared to 60% of White people [8]. Just 3 years later, in 2022, PrEP uptake only increased 5% for Black people compared to a 34% increase for White people, totaling to 94% of White people who need PrEP being provided a prescription compared to 13% of Black people [8,9]. Barriers to HIV testing and PrEP uptake include limited access due to geography, medical mistrust, HIV testing stigma, and fear of a positive HIV test result [10-13].

Community Pharmacies Are Strategic Sites for HIV Prevention

In this study, we use the term community pharmacy to refer to nonhospital, retail-based pharmacies that provide direct access to medications and basic health care services to the general public [14,15]. These include chain pharmacies, independently owned pharmacies, and those located within grocery stores or mass retailers. Beyond dispensing medications, many provide preventive and clinical services such as immunizations, health screenings, Clinical Laboratory Improvement Amendments waived testing, medication therapy management, and counseling, positioning them as important sites for public health interventions [16]. Community pharmacies are increasingly recognized as a strategic and viable solution to address documented barriers to HIV prevention services. In fact, the Centers for Disease Control and Prevention, National Institutes of Health, and other public health agencies recently declared engaging pharmacies as an integral component to Ending the HIV Epidemic (EHE) [7,14,15]. Indeed, integrating HIV prevention services in pharmacies, specifically in community pharmacy settings, could drastically expand the availability of HIV prevention services and reduce inequities in HIV for several reasons (Multimedia Appendix 1). First, about 95% of Americans live within 5 miles of a pharmacy, and most pharmacies are open beyond typical working hours (eg, 9 AM-5 PM) and on weekends [11]. Second, pharmacy staff (eg, pharmacists and pharmacy technicians) have a documented history of engaging and counseling groups at increased risk for HIV to provide HIV testing and risk reduction assessments [17-20]—even when HIV testing stigma is high [17]. Recent studies also demonstrate that pharmacy staff are especially willing to provide HIV prevention screenings [17,18,21], and that populations placed at increased risk for HIV, such as sexually minoritized men, are willing to use these services in pharmacy settings [19,20,22]. Third, data show that if pharmacies were integrated into the provision of HIV prevention services, they could increase access by over 80-fold in the US Southeast alone [23]. Lastly, integrating HIV- and non-HIV-related services can reduce stigma and increase uptake of HIV testing and prevention strategies [17]. Specifically, data show that integrating HIV testing with non-HIV services that are perceived as less stigmatizing increases pharmacy client HIV testing uptake by 42% among people who report high HIV stigma [17]. This suggests that when HIV testing is offered in a neutral, nonstigmatized setting, with other screening services that are less stigmatized (eg, cholesterol screening), it can be normalized and the fear of accepting the HIV test reduced. Recently, COVID-19 testing and vaccination have been integrated into the menu of services for many pharmacies, which opens an opportunity to integrate other infectious disease screenings [24]. Pharmacies with existing non–HIV-related screening services may be able to integrate HIV prevention services more easily than pharmacies that do not, and this may facilitate HIV testing uptake by reducing HIV exceptionalism, the fear that an HIV diagnosis is different than any other health diagnosis [17,25].

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Dissemination and Uptake of Pharmacy-Based HIV Prevention Interventions

Despite strong evidence, the dissemination and implementation of pharmacy-based HIV prevention services are extremely scarce. As of November 2024, only 14 states in the United States have passed legislation permitting pharmacists to independently provide HIV prevention services, such as prescribing PrEP [26,27]. Notably, only 1 state (ie, Arkansas) in the US South, the region most heavily impacted by HIV, has enacted such legislation [28]. The reasons for the limited adoption of similar legislation in other Southern states remain unclear. Pharmacies in the Southern region could be an accessible source for HIV prevention where other HIV prevention resources are sorely lacking [23]. Gathering evidence to explain this policy gap from local pharmacy boards that develop the protocols and regulations for pharmacy-based services is critical to implementing and scaling HIV prevention in pharmacies. On the pharmacy staff level, while many chain pharmacy staff have been able to access training to provide HIV prevention services [27], community pharmacy staff consistently report inadequate training and referral systems for positive HIV screenings as barriers to integrating HIV testing into the pharmacy work system [18,27]. Community pharmacies generally have fewer employees and may lack staff support to obtain existing training that is at least a day long [27]. Moreover, these trainings fall short of teaching pharmacy staff about oral HIV testing sample collection [27], which many community pharmacy staff want to be aware of in case their clients are unable or unwilling to perform self-HIV testing—the now standard test in many nonclinical settings [18,29].

Implementation Science Frameworks Are Essential to Advancing Pharmacy-Based HIV Prevention Dissemination

The pharmacy work system is influenced by multiple components across various levels (eg, individual, organizational, and policy levels) [30]. In order to advance the dissemination and uptake of pharmacy-based HIV prevention services, implementation science frameworks can aid in better understanding these components and assessing how integrating HIV prevention services might drive changes within them [5]. The Exploration, Preparation, Implementation, Sustainment (EPIS) framework [18] is a widely used implementation science framework that consists of 4 well-defined phases, wherein each phase systematically addresses specific factors that can facilitate or hinder the adoption and integration of HIV prevention services within pharmacy systems. Applied to pharmacy-based HIV prevention services, EPIS is an anchoring implementation science framework that guides what is needed to advance the overall research question, rather than guide specific measures. For example, the Exploration phase would examine potential barriers and facilitators of pharmacy-based HIV prevention service integration across pharmacies, pharmacists, and pharmacy technicians. The Preparation phase would include training of pharmacy staff, increasing self-efficacy, and reducing barriers to pharmacy HIV prevention service provision. Additionally, this phase offers an opportunity to evaluate existing programs to inform and optimize implementation strategies. The Implementation phase would then test the integration of HIV prevention services in pharmacies, and the Sustainment phase would examine the multilevel influences of offering HIV prevention services.

Within EPIS, the Consolidated Framework for Implementation Research (CFIR), could guide the specific constructs and measures across each study stage [19]. CFIR posits that 5 domains influence effective implementation: intervention characteristics, outer setting, inner setting, characteristics of the individual, and process [31]. Given that community pharmacies have a unique work system, implementation science frameworks specific to the pharmacy setting are also needed to enhance our understanding of all of the pharmacy work system components [32]. Systems Engineering Initiative for Patient Safety (SEIPS) is a multilevel model previously used to guide evaluation of interrelated work systems, processes, and outcomes within the community pharmacy as implementation occurs. A number of community interventions that seek to improve client services (ie, medication therapy management and cognitive pharmaceutical services) have leveraged SEIPS, as it focuses on the design of sociotechnical systems to improve patient care [32].

The combined use of the CFIR and SEIPS models will allow both evaluation and integration of each component from a social and technical standpoint. For example, improving pharmacy-based HIV prevention access relies on implementable HIV prevention activities. In turn, these activities are completed by the pharmacists and technicians who need training and self-efficacy to implement HIV prevention screening services. This work is then supported by the pharmacy environment, which includes distal organizational structures that enable or prohibit tasks such as workflow, space, time constraints, or unrealistic compensation models [26]. Finally, pharmacy organizational factors may also underpin stigma toward HIV and HIV prevention services if these services or specific clients are singled out. Therefore, focusing on the process between work system and client factors, including acceptability and satisfaction among the pharmacy staff and clients, will be critical. Taken together, the simultaneous use of these frameworks (ie, EPIS, CFIR, and SEIPS) can shape how we understand these services and create systems that can be implemented and scaled.

Objective

The primary goal of the Pharmacy-Based Access to HIV Prevention Services (PATH) study is to evaluate the implementation and effectiveness of HIV testing and prevention services within community pharmacies, particularly in the US Southeast. Drawing on implementation science frameworks and mixed method approaches, we aim to (1) examine policy and pharmacy staff-level barriers and facilitators of adopting HIV prevention services in community pharmacies, (2) assess existing pharmacy staff HIV prevention service trainings, and (3) test the integration of HIV prevention services in community pharmacies on effectiveness and implementation outcomes. This study uses a hybrid type 1 effectiveness-implementation design [6] that simultaneously allows us to collect data that will provide critical insight into factors that may impact PATH's

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real-world implementation. In the following section, we describe the protocol for all 3 aims of PATH.

Methods

Study Design

The PATH study uses a mixed methods, hybrid type 1 design to test the effectiveness and evaluate the implementation of HIV prevention services in pharmacies. Two types of pharmacies will be examined (those that offer non-HIV-related screenings [eg, COVID-19, blood pressure, glucose, and cholesterol screening] and those that do not), given that integration of HIV prevention services may be different depending on the existing services offered in pharmacies. To enhance the organizational framework of the implementation and evaluation of PATH, we draw on the EPIS framework, progressing through the study in three main phases: (1) an ongoing Exploration phase with quantitative web-based surveys from community pharmacy staff and qualitative interviews with key stakeholders, including board of pharmacy members and pharmacy staff; (2) a Preparation phase to assess the effectiveness of two existing pharmacy staff centered HIV prevention training programs; and (3) a planned Implementation and Sustainment phase to test pharmacy-delivered HIV prevention services and evaluate implementation factors in 10 community pharmacies. Below, we describe the recruitment, data collection, and planned analyses for each phase.

Conceptual Framework

Drawing on the CFIR and SEIPS implementation science frameworks, we developed a multilevel conceptual framework for integrating HIV prevention services into pharmacies (Figure 1). The initial step to improving access relies on implementing HIV prevention activities that can be seamlessly integrated into the pharmacy setting. These activities are carried out by the pharmacists and technicians, who require proper training and self-efficacy to effectively implement HIV prevention screening services. The successful implementation of these activities is supported by the pharmacy environment, which includes organizational structures that enable or prohibit tasks such as workflow, space, time constraints, or unrealistic compensation models [11]. Finally, organizational factors within the pharmacy may contribute to stigma toward HIV and HIV prevention services, particularly if these services or specific clients are singled out. Therefore, it is critical to focus on the processes that link the work system with client factors, including acceptability and satisfaction among both pharmacy staff and clients. By addressing these elements, we aim to create a supportive environment that facilitates the successful integration of HIV prevention services into community pharmacies.

Figure 1. Conceptual framework for integrating HIV prevention services into pharmacies guided by the CFIR and SEIPS. CFIR: Consolidated Framework for Implementation Research; PrEP: pre-exposure prophylaxis; SEIPS: Systems Engineering Initiative for Patient Safety.

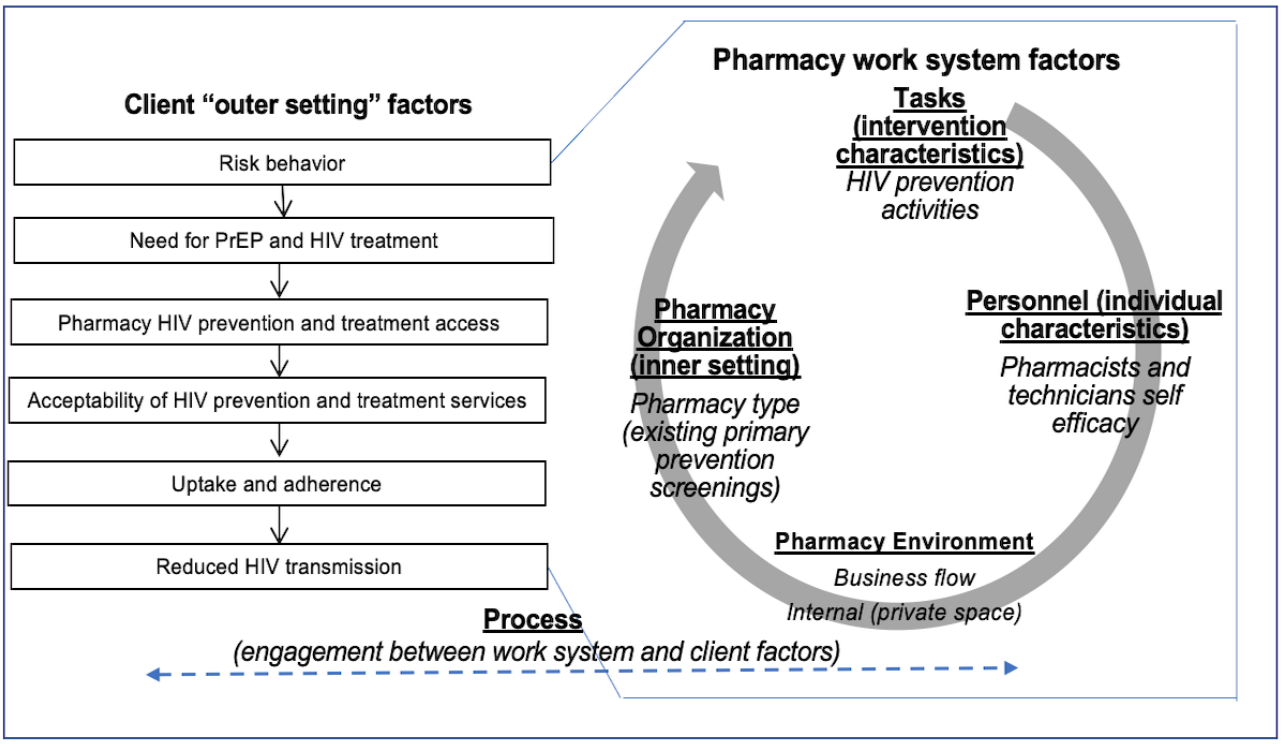

Ethical Considerations

Ethics approval was obtained from the Emory University Institutional Review Board (STUDY00005878). All procedures involving human subjects will follow ethical principles and comply with federal regulations for the protection of human subjects. Informed consent will be obtained from all participants before participation. For the web-based survey, participants will be required to read and electronically agree to a consent form before proceeding. For qualitative interviews, verbal consent will be obtained and documented at the start of each session. All data will be deidentified before analysis. Survey data will be collected using a secure, password-protected platform. Interview transcripts will be stripped of personal identifiers

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during transcription. All study data will be stored on encrypted servers accessible only to research staff. Survey participants will receive a US $20 electronic gift card upon completing the survey. Stakeholders participating in interviews will receive a US $50 electronic gift card as compensation. No identifiable images of participants will be included in this paper, future study materials, or publications.

Phase 1: Exploration Phase

The primary purpose of the Exploration phase is to establish an understanding of the policy-, pharmacy staff-, and client-level barriers and facilitators of integrating HIV prevention services into community pharmacies.

Recruitment

Pharmacy Staff

To recruit pharmacy staff (pharmacists and technicians) who complete web-based surveys (n=300), we will obtain a complete list of pharmacies located in each state across EHE areas in the US Southeast from each state's Board of Pharmacy. Pharmacy lists include the name, addresses, phone numbers, and type of pharmacy (eg, independent, chain, compounding, etc) registered to practice in each state. For states that do not make these data available (eg, AL and MS, United States), we obtained data from the Google Business application programming interface based on their location. We geocoded pharmacies to determine their locations in EHE priority jurisdictions in the Southeast [7]. We also sample from chain pharmacies within these regions. We will purposively sample participants who completed the web-based survey for 40 in-depth interviews (IDIs) with pharmacy staff. We will recontact pharmacy staff, based on pharmacy location and the presence of existing non–HIV-related screening services, to determine their willingness to participate in the IDIs.

Pharmacy Board Members

To recruit pharmacy board members, we will obtain a list of current board members for each state in the Southeast from their respective state Board of Pharmacy websites. We will then contact the president or chair of each board to introduce this study. Subsequently, we will request an interview with the president or chair and ask them to share introductory letters about our study with other board members to garner interest in participating. We will recruit 2 pharmacy board members from each state.

Data Collection

Pharmacy Staff Survey

The 15-minute web-based survey among pharmacy staff, including pharmacists, technicians, and other pharmacy personnel, will determine the landscape of readiness for pharmacies to integrate HIV prevention services. Survey measures, informed by the CFIR and SEIPS implementation science frameworks, will include both individual and organizational-level measures of readiness such as HIV testing self-efficacy (eg, "I feel confident I can offer HIV testing to my clients"), HIV training level (eg, ever trained and training type), presence of HIV information in pharmacy, availability of a private space, time availability, HIV knowledge, attitudes and beliefs, HIV stigma (adapted from validated instruments [33]), and a checklist of health screenings provided in the pharmacy (eg, COVID-19 testing blood pressure, blood glucose and hemoglobin A_{1c} levels, and cholesterol levels). Demographic and professional characteristics such as gender, race or ethnicity, position within the pharmacy, and years of experience will also be captured to explore subgroup differences in readiness. Survey measures are described in Table 1.

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Table 1. Assessment strategy guided by the CFIR[a] and SEIPS[b].

CFIR construct or SEIPS component	Description	Assessment	Specific scales from which survey items were derived or qualitative domains
Intervention characteristics			
Relative advantage	Perceptions of the advantage of implementation	IDIs[c]	Open-ended questions about whether HIV testing and referral are perceived as beneficial
Complexity	Perceived difficulty of implementation	IDIs	Open-ended questions about the perceived difficulty of implementing HIV testing and referral
Tasks	HIV and non-HIV service offerings	Online surveys	Items on HIV and non-HIV related service provision from existing studies
Outer setting			
Client needs and resources	Perceived client needs; barriers and facilitators for meeting them	IDIs	Open-ended questions about HIV in the population and barriers and facilitators to pharmacy HIV testing
Client needs and resources	Perceived client needs; barriers and facilitators for meeting them	Surveys	Pharmacy staff HIV training level, HIV information presence in pharmacy, willingness to provide HIV testing
Cosmopolitanism	Knowledge of HIV organizations	IDIs	Open-ended questions on the knowledge of HIV service organizations, presence, and quality of relationships with HIV service organizations
External policy and incentives	Policies that could help or hinder implementation	IDIs	Open-ended questions about perceived barriers and facilitators to pharmacy HIV testing and referral implementation
Inner setting			
Structural characteristics or organization	Descriptive characteristics of pharmacy, staff, and their relation to HIV	Surveys	Checklist on non-HIV-related service provision, HIV stigma
Structural characteristics or organization	Descriptive characteristics of pharmacy, staff, and their relation to HIV	IDIs	Open-ended questions soliciting detailed descriptions of referral and communication processes
Culture	Norms, values of the specific clinic setting	IDIs	Open-ended questions about attitudes and beliefs about HIV and populations affected
Available resources or pharmacy environment	Descriptive characteristics of pharmacy environment	Surveys	Availability of a private space for HIV testing, time availability, and staff training
Individual characteristics			
Knowledge and beliefs	Familiarity with HIV	Surveys	Items on HIV knowledge from existing studies
Self-efficacy	Individual belief in their own capability to implement HIV testing in the pharmacy	Surveys	The study team will modify items from the general self-efficacy scale to measure efficacy for implementing HIV testing in pharmacies
Process			
Relative advantage	Perceptions of the advantage of implementation	IDIs	Open-ended questions about whether HIV testing and referral are perceived as beneficial

[a]CFIR: Consolidated Framework for Implementation Research.

[b]SEIPS: Systems Engineering Initiative for Patient Safety.

[c]IDI: in-depth interview.

Key Stakeholder Qualitative Interviews

Interview guide measures are described in Table 1 and will cover a range of topics within 4 domains: general public health and HIV/AIDS policy, pharmacy use of health services, pharmacy-based HIV prevention services, and pharmacy-HIV organization partnerships. Informed by CFIR and SEIPS, specific IDI questions will address support for HIV prevention services, policies influencing HIV prevention service delivery, referral and monitoring in pharmacies, potential barriers to the delivery of an intervention in a pharmacy, knowledge of epidemiological data on HIV, sexual behavior, and drug use, and sustainability.

Key Stakeholder Compensation

Pharmacy staff who complete the 15-minute web-based survey will be sent a US $20 electronic gift card via email. Key stakeholders will be compensated with a US $50 electronic gift card for each IDI.

Planned Analyses

Online Survey Data Cleaning and Analysis

Exploratory data analysis (EDA) for web-based survey data will be conducted through data editing using SAS (SAS Institute Inc) or R (R Foundation for Statistical Computing) programming. EDA will include calculations of means, medians,

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percentages, proportions, SDs, and skewness or kurtosis as appropriate. We will create new variables by collapsing response options when necessary. Differences in group means on continuous variables will be tested using 2-tailed *t* tests or rank tests, after interpretable normality transformations if necessary. Distributions of categorical variables will be compared between groups using chi-square tests, exact tests, or 95% CIs to guide interpretation. Group comparisons will be determined based on the outcomes of interest (eg, willingness, readiness, etc). Correlates of pharmacy HIV prevention service readiness will be examined, and relevant mediators or confounders, such as years in pharmacy practice, will be accounted for via regression modeling. The influence of outliers will be assessed, with nonparametric tests used as available and warranted. We plan to separately examine the relationship between each confounder and the outcome of interest using *t* tests or rank tests on continuous measures and exact tests of categorical values. Initial unadjusted comparisons will be made using exact tests if categorizations are used. If significant bivariate associations are found, we will incorporate these exposures as covariates using linear regression for continuous variables and logistic regression for binary variables.

Key Stakeholder Data Cleaning and Analysis

IDIs will be digitally recorded for verbatim transcription by a professional agency. A reflexive thematic analysis approach will be applied to all IDI data to ultimately develop a codebook that will be applied to all transcripts [8]. Analyses will integrate deductive coding using the CFIR and SEIPS frameworks as guides, along with inductive coding or analysis of emergent themes. All interviews will be coded, and all analyses will be performed by research assistants with master's-level training in public health and qualitative methods. At each phase of data analysis, research assistants will reflexively identify any biases, values, personal factors, cultural, or other characteristics that may influence their interpretation of data. The research team will use MAXQDA Analytics Pro (VERBI Software) for data analysis.

Data Integration

IDIs from key stakeholders and web-based survey data will be aggregated to inform the preparation, implementation, and sustainment phases of this study. A joint display approach will be used to align quantitative findings with qualitative results. This side-by-side comparison will help determine which implementation barriers are commonly reported by both pharmacy staff and key stakeholders, and which differ between groups. Key barriers that are identified across CFIR constructs and SEIPS organizational levels will inform which aspects of the training programs require modifications to better address gaps identified during the preparation phase.

Phase 2: Preparation Phase

The primary goal of the preparation phase is to evaluate the effectiveness of 2 existing pharmacy staff-centered HIV prevention training programs through a prepost assessment and comparative analysis. Participants from each program will complete prepost assessments to measure changes in key outcomes, including self-efficacy, HIV prevention knowledge, and readiness to prescribe PrEP. Comparative analysis will explore differences in training outcomes across the 2 programs and assess which approach more effectively addresses gaps in knowledge and practice. The anticipated components of HIV prevention training programs are detailed in Table 2.

Table 2. Anticipated components of HIV training modules for pharmacy staff.

Components	Description of content
Component 1	Overview of local HIV-related needs and epidemiology
Component 2	Strategies to discreetly engage customers in conversations about HIV testing
Component 3	Post-HIV testing counseling, including interpretation of HIV test results, HIV care, and discussion on risk reduction strategies
Component 4	Linkage to HIV care services, including a PrEP[a]-prescribing physician (for customers who have a nonreactive HIV test) and HIV treatment physician (for customers who have a reactive HIV test)

[a]PrEP: pre-exposure prophylaxis.

Pharmacy Staff Training

Recruitment

Pharmacy staff (n=100) who completed the web-based survey in the Exploration phase will be recruited to participate in the existing pharmacy staff-centered HIV prevention training programs. If additional participants are needed, recruitment efforts will be expanded to include advertisements through local pharmacy boards, direct phone calls to pharmacies, and distribution of advertisements via mail or email. Participants will be evenly distributed between the 2 programs, with 50 individuals assigned to each HIV prevention training. Enrollment will be based on participants' interest in enhancing their HIV prevention service delivery skills and their willingness to complete both the training and the pre- and postassessments.

Data Collection

To evaluate the effectiveness of 2 pharmacy-based HIV prevention training programs as a part of the preparation phase, we will administer pre- and posttraining surveys. These surveys are designed to assess changes in key outcomes, including HIV and PrEP knowledge, self-efficacy in providing HIV prevention services, and readiness to conduct HIV testing, counseling, and referral. The surveys will collect both individual-level and pharmacy-level characteristics. Individual-level variables will include gender, race, or ethnicity, position in the pharmacy, and years of experience in pharmacy practice. Pharmacy-level characteristics will include pharmacy type (eg, chain

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independent), geographic setting, availability of private space, and typical patient volume.

Planned Analyses

We will conduct both within-group and between-group analyses. Analysis of pre- and posttraining levels and comparative analyses between the 2 training programs will be conducted using variables capturing pharmacy staff self-efficacy for HIV testing, counseling, and referral, as well as HIV and PrEP knowledge. Appropriate methods for paired data, including McNemar test for binary outcomes and paired *t* or Wilcoxon signed rank tests for continuous outcomes, will be used to make inferences for each training type. For Likert scale measures, we will also consider the use of available indices for capturing change in ordinal variables based on paired data [34,35]. To comparatively assess different measures, we will report 95% CIs and use 2-group tests comparing proportions achieving positive change for binary outcomes and 2-sample *t* or rank sum tests for continuous outcomes. Univariate associations will be assessed between potential confounders and the difference between each outcome of interest pre- and posttraining, as well as the difference in differences between the training groups. When significant bivariate associations are found, we will incorporate those as covariates using linear regression for continuous outcomes and logistic regression for binary outcomes. In the comparative analysis, we will also control for pretraining differences in the outcomes across groups.

Phase 3: Implementation and Sustainment Phase

The primary purpose of the implementation and sustainment phase is to test the efficacy of pharmacy-delivered HIV prevention services and evaluate implementation factors.

Recruitment

Pharmacy Sampling, Recruitment, and Enrollment

Ten community pharmacies in Georgia will be selected to test and evaluate the pharmacy HIV prevention service implementation model. The selection will focus on community pharmacies, based on their location and client flow. Initially, we will target pharmacies identified in Phase 1 as being in the EHE priority jurisdictions in Georgia. To reach populations at the greatest risk of HIV transmission, we will choose neighborhoods with census tracts that are over 70% Black. Additionally, to ensure adequate pharmacy client recruitment in the pharmacy, we will screen pharmacies with at least 100 client visits per month. In order to achieve the target client sample, we expect 13 clients will need to be informed about this study in each pharmacy per month.

All participating pharmacies will have a private space where clients can self-administer HIV tests with complete privacy. If the pharmacy does not already have a space, additional measures will be taken to ensure participants' privacy as needed, such as providing additional wall partitions or screens, noise machines, and noise-cancelling curtains. We will obtain consent from at least 1 pharmacist and 2 to 3 pharmacy technicians at each site to participate in this study (n=3-4 staff per pharmacy). However, we will allow participation from as many pharmacists and technicians as are willing. Given that we are recruiting from community pharmacies, which often staff fewer people, we do not expect more than 3-4 staff at each pharmacy.

Pharmacy Client Recruitment, Eligibility, and Enrollment

Pharmacy staff will discreetly inform pharmacy clients about this study through brochures placed in their prescription bags and posters displayed throughout the pharmacy (refer to Figure 2 for the study flyer). Interested clients can scan a QR code to access a 10-question electronic screener survey to determine their eligibility. Participants will be eligible if they are (1) 18 years or older, (2) English-speaking, (3) have engaged in sex or drug use in the past 12 months, or (4) have never had an HIV test. Clients who complete the screener survey will receive a US $1.00 e-credit or coupon for their next pharmacy purchase. Eligible clients interested in participating will be prompted to inform a pharmacy staff member via their phone. The staff member will then offer the client free health screenings (ie, HIV self-testing as well as any other health screening already offered at the pharmacy) and inform them about the research study, which includes compensation for completing a more in-depth survey. Clients can choose to receive the health screenings or complete the survey. If they are unable to participate immediately, they will be given the option to schedule an appointment at a later date.

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Figure 2. Example of a pharmacy brochure given to pharmacy clients. PrEP: pre-exposure prophylaxis. Reproduced from Crawford et al [21], which is published under a Creative Commons Attribution 4.0 International License [36].

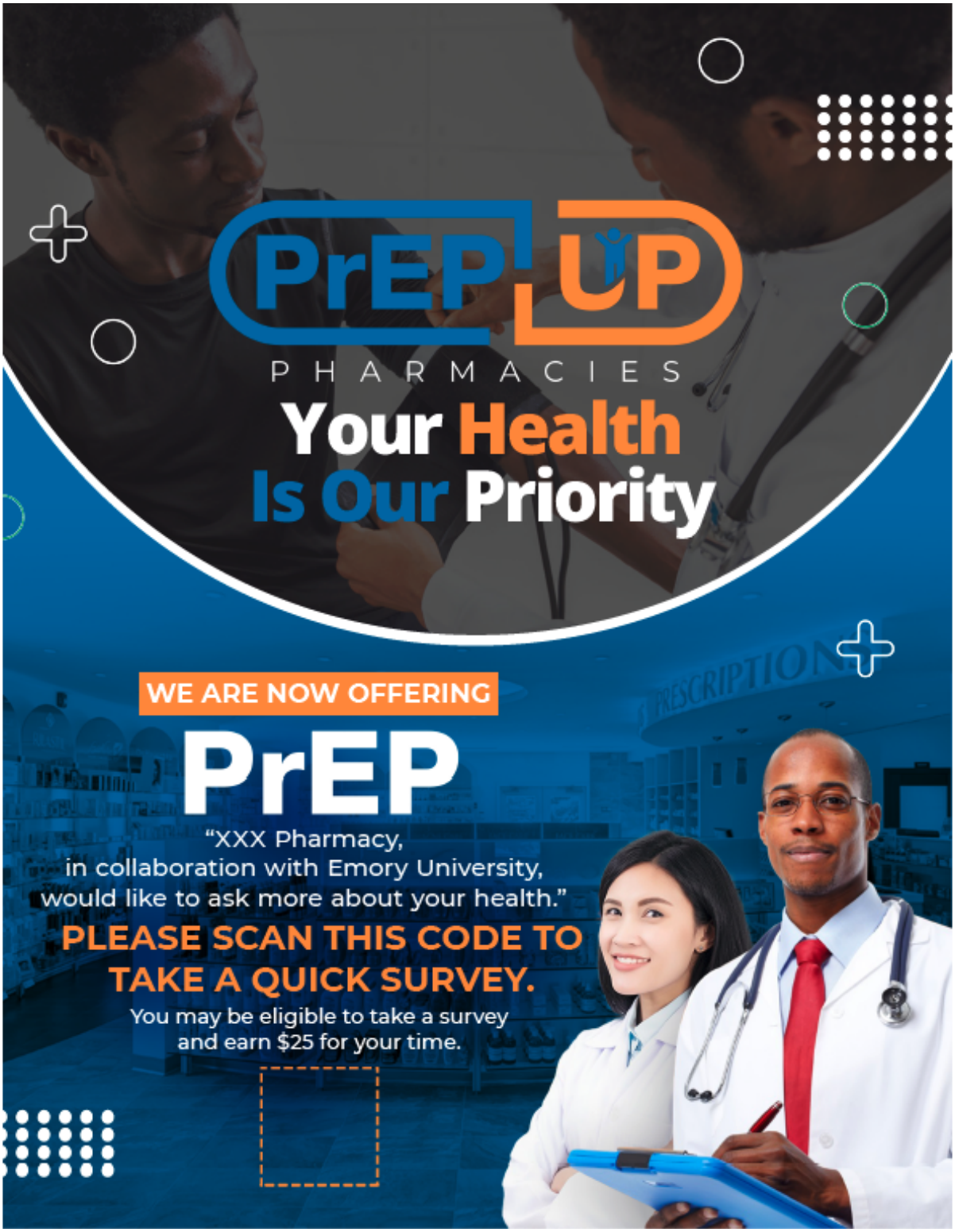

HIV Prevention Service Training Evaluation

As described earlier, during the Preparation phase, pharmacy staff will participate in existing virtual training programs on HIV prevention. Following the training, research staff will schedule a 1-hour, in-person session with each pharmacy to support the integration of HIV self-testing into their services. For pharmacies without existing primary prevention screenings, the session will cover stocking self-HIV tests and configuring workflows to ensure a private area for screening. For pharmacies already offering such screenings, the session will focus on colocating HIV self-tests and advertisements alongside other primary prevention services. In all pharmacies, advertisements, including posters and brochures, will be placed strategically throughout each pharmacy to promote the availability of HIV testing (Figure 2). Designed to appeal to a broad customer base,

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these materials will use inclusive, nonstigmatizing language and imagery. We have tested and used similar fliers to recruit participants in other pharmacy-based studies [21]. Fliers will be positioned with other health-related literature and resources inside and outside of the pharmacy to ensure accessibility and reduce the potential for stigma by avoiding a sole focus on HIV services.

Data Collection

Fidelity Assessments

To ensure consistency in the delivery of HIV testing and referral protocols by pharmacy staff, the research team will conduct periodic "mystery shopper" assessments at least once every 6 months throughout this study's period. Pharmacy staff will be informed at enrollment and during the consent process that their services may be evaluated at various times during data collection, and that research team members will not identify themselves as part of the Emory study team during these assessments. If inconsistencies or deviations from the protocol are observed, we will inquire about these discrepancies and conduct follow-up one-on-one training sessions with pharmacy staff to address specific protocol-related concerns.

Pharmacy Staff Survey

Survey measures will capture implementation outcomes across the four components of SEIPS: (1) personnel, (2) the pharmacy organization, (3) the pharmacy environment, and (4) the tasks required for this study (Table 3). We will include CFIR constructs that assess barriers and facilitators to providing HIV testing and referrals across each SEIP component. To gauge the burden on pharmacy staff, we will also examine the resources required for this study. We will estimate this based on the number of clients who initiated HIV testing, HIV testing costs, time required for HIV testing counseling, PrEP, or HIV treatment referral, based on pharmacists' time providing medication therapy management (about US $2-$3 per minute) [37,38]. These preliminary estimates will inform a formal cost-benefit analysis in the scale-up of this proposal.

Table 3. Variables to be collected among pharmacy staff by the SEIPS[a] model.

Work system component	Pharmacist and technician description of variables
Personnel	Age, race or ethnicity, sex, attitudes, willingness, and perceptions of HIV prevention, PrEP[b], and ART[c] services, and HIV stigma
Organization	Years in practice, pharmacy workflow, average number of customers, average number of customers who fill prescriptions for STIs[d], estimated number of customers, experience providing point of care testing, experience working with physicians, and pharmacist-physician collaborative index [39]
Pharmacy environment	Business flow, availability of internal private space for testing, and neighborhood characteristics (safety, physician access, and demographic characteristics)
Tasks	Ability to and perceptions of engaging clients about HIV testing, PrEP, and treatment, ability to set up a behavioral survey, ability to provide a biological screening kit, ability to link with a PrEP or treatment physician, ability to provide culturally appropriate information about PrEP and treatment

[a]SEIPS: Systems Engineering Initiative for Patient Safety.

[b]PrEP: pre-exposure prophylaxis.

[c]ART: antiretroviral therapy.

[d]STI: sexually transmitted infection.

Pharmacy Staff Retention

Participating community pharmacies will receive US $2000 per year because the activities will require more of their time and the use of a designated area of space for an unknown period each week. Each pharmacy technician (we estimate 3 technicians per pharmacy) will receive US $40 for the training session plus US $40 for each quarter of participation in this study.

Pharmacy Client HIV Testing

Clients in pharmacies without existing primary prevention screenings will be offered HIV testing only. Clients in pharmacies with existing primary prevention screenings will be presented with the option of doing a primary prevention health screening that includes the available primary prevention screenings as well as HIV testing. In this case, HIV testing will be highlighted as knowing your HIV status as a general health issue that also encompasses being aware of COVID-19, hypertensive, diabetic, and hypercholesterolemic status. Clients who agree to obtain an HIV test will be provided with a prepackaged kit of self-administered tests for HIV, with illustrated instructions to facilitate the oral swab. According to the processing time of the tests, the results will be apparent in no longer than 15 minutes. Clients will be asked to wait in a private area, and if they are willing, complete the 20-minute sociobehavioral survey during this time. Regardless of survey completion, they will be asked to provide their follow-up information (ie, phone number, email, address, and contact for someone who can reach them) for tracking following their HIV result. Clients who are unwilling to obtain an HIV test will be (1) counseled on the importance of HIV prevention, (2) provided with information about our community partner for future consideration, and (3) told that there is a survey that they can participate in regardless of their willingness to test.

The pharmacist or technician will interpret the results of the rapid HIV OraQuick (OraSure Technologies, Inc) test. Pharmacy staff will be trained to deliver results to the client. The pharmacy will be provided with a documentation system for maintaining the participants' results in a locked file cabinet. Individuals who

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have an inconclusive HIV test will be told that their test is inconclusive and will be referred to our community partner for a confirmatory HIV test. All clients who test for HIV (regardless of reactivity) will be provided HIV posttest counseling. If a client tests positive for HIV, they will be immediately referred to our community partner for confirmatory testing and linkage to treatment services. Clients will be informed that during the PrEP referral process (counseling about the need for PrEP and identification of a nearby provider), their contact information will also be given to the PrEP-prescribing physician's office, so the physician may also reach out to them to establish an appointment. Pharmacy clients may refuse to participate at any time, or if they have time constraints, they can schedule the HIV (and other health) screening at a later date. If they are uncomfortable completing HIV (or other health) screening in the pharmacy, but are interested in being screened, we will also provide them with a referral. We will complete a 3-month follow-up phone call with clients who obtained an HIV test to determine whether they were linked to HIV care or PrEP.

Pharmacy Client Survey

Clients who are eligible (based on the screener) and willing to complete the sociobehavioral survey will provide electronic informed consent via an electronic tablet. The 20-minute client surveys will collect data on demographics, sex, and drug use risk behaviors, chronic and mental health, social exposures, and feasibility, acceptability, and safety of HIV testing (Table 4).

Table 4. Social and behavioral survey measures.

Characteristics	Description
Demographics	Age, education level, employment, race or ethnicity, homelessness, nativity, incarceration history, health care access, health insurance coverage, housing stability, transportation access, and pharmacy practices
Sex and drug use behaviors	Sexual preferences, unprotected anal or vaginal sex, number of partners, HIV testing history, STI[a] screening history, PrEP[b] screening history, PrEP use, willingness to use PrEP, HIV status, partner HIV status, prescription and nonprescription drug use battery
Chronic health	History of high blood pressure, hypercholesterolemia, and diabetes
Mental health	Depression and anxiety
Social exposures	Social support, HIV stigma, and discrimination
Pharmacy service use history	Willingness and history of obtaining primary prevention screenings in pharmacies (COVID-19 testing, blood pressure, cholesterol, and glucose screening)
Feasibility	Ability to complete HIV self-screening
Acceptability	Satisfaction with where or how they were informed about HIV testing, receipt of a brochure, survey, self-screening, counseling from pharmacy staff, and PrEP or treatment referral
Safety	Perception of HIV and PrEP stigma, comfort performing self-HIV testing in the pharmacy, privacy, and confidentiality perceptions

[a]STI: sexually transmitted infection.

[b]PrEP: pre-exposure prophylaxis.

Pharmacy Client Compensation

Individuals who agree to complete the baseline and follow-up survey will be compensated via a US $25 electronic gift card for each complete survey.

Planned Analyses

Upon compilation of data, new variables will be created, and variables may be collapsed as needed to explore the proportions and correlates of outcomes. EDA and data management will be conducted using SAS or R programming, as will data editing, along with calculations of descriptive statistics (eg, means, medians, percentages, proportions, SDs, and skewness or kurtosis, as appropriate). If outliers or nonstandard distributions are identified, variable transformations or standardized cut points will guide the recoding of continuous variables, following externally validated standards where available. The influence of outliers will be assessed, and medians (or rank tests) will be used if required. Primary outcomes for pharmacy staff (implementation and sustainability outcomes) and pharmacy clients (self-HIV testing uptake) will initially be compared between pharmacies offering non–HIV-related services and those that do not, using chi-square tests, exact tests, or with 95% CIs. We will examine correlates of interest for pharmacy staff (eg, years in practice and position) and clients (eg, health insurance, sexual and drug use behavior, mental health, and social exposures). Each potential confounder's relationship to the outcome of interest will be evaluated separately using t tests or rank tests for continuous measures and exact tests for categorical measures. Those found to be univariately associated with outcomes will be included in appropriate regression models to assess the adjusted association relationship between each outcome and the presence of non–HIV-related services (yes or no). The primary analyses will account for potential clustering of individuals within pharmacies through mixed linear or nonlinear regression models. Additionally, variables with potential to modify or confound associations between outcomes and pharmacy categorization (ie, the presence or absence of HIV-related services) will be accounted for in the final model-based analyses, with appropriate interpretations.

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Results

PATH funded in June 2023. Participant recruitment and data collection began in November 2023. As of September 15, 2025, we have exceeded our Phase 1 pharmacy staff survey target, with 310 participant surveys completed (goal: 300). Data analysis for this phase is currently underway. Recruitment and data collection for Phase 1 IDI are ongoing; four IDIs have been completed at the time of this manuscript submission, with completion anticipated by early 2026.

Discussion

Principal Findings

PATH is a hybrid type 1 effectiveness-implementation study that focuses on integrating HIV prevention services into community pharmacies. We expect that this intervention will improve access to HIV prevention, reduce stigma around HIV in pharmacy settings, and identify the key operational challenges and systemic factors that affect the long-term success of these services. The expected findings will highlight improvements in pharmacy staff confidence, patient engagement, and the feasibility of integrating HIV prevention into everyday pharmacy practice. This study represents an important contribution to the field by integrating geospatial methods and implementation science frameworks such as CFIR and SEIPS—a model that is well-established in the industrial engineering subspecialty of human factors, but new to public health and behavioral sciences.

Comparison to Prior Work

PATH is a promising pharmacy-based HIV prevention intervention and represents an important contribution to the field of HIV prevention service delivery for several reasons. While prior studies have shown that pharmacy-based interventions can be effective in promoting HIV prevention, they often fail to address the organizational and workflow challenges that hinder long-term sustainability. Thus, real-world effectiveness remains elusive as existing HIV prevention programs have not survived beyond the study time frame [12,13,16,38,40-43]. Many of these studies focus on the efficacy or the intervention itself but overlook the operational barriers within pharmacies, such as workflow inefficiencies, staffing challenges, and a lack of integration with other health care services. PATH aims to address these gaps by integrating theoretical frameworks used in the pharmacy discipline and integrating geospatial methods, ensuring that HIV prevention services are implemented in high-burden areas, thereby having the greatest impact. The inclusion of SEIPS provides a novel approach to examining the community pharmacy work system, focusing on human factors and organizational processes, an aspect missing from prior research. Hence, findings from this study will provide a much-needed understanding of how to incorporate and sustain HIV prevention services by characterizing specific breaks within the community pharmacy work system that promote or weaken pharmacy HIV prevention service delivery. The proposed research is expected to contribute a sustainable, pharmacy-based HIV prevention model that can be implemented in community pharmacies and serve as a foundation for expanding access to HIV prevention services, particularly among populations with limited access to existing resources. The successful development of PATH could provide evidence for the expansion to large chain pharmacies and also establish pharmacies as a venue for additional HIV prevention services, such as oral and long-acting injectable PrEP screening and dissemination, as well as PrEP checkups. By integrating HIV prevention services into pharmacies, this model has the potential to reduce strain on existing HIV health service providers, decompressing their current work systems. This outcome will be mutually beneficial for HIV public health practitioners and for community pharmacists, as provision of HIV prevention services has the potential to increase pharmacy business and revenue.

Strengths and Limitations

PATH uses geospatial targeting to optimize service delivery and focuses on real-world implementation. The integration of both CFIR and SEIPS offers a comprehensive evaluation of the system factors influencing service delivery and sustainability. PATH is subject to 2 main limitations in its current form while we actively enroll participants. First, although we aim to recruit a sufficient sample of pharmacy staff from each state, these data will not be generalizable to all pharmacies in the US Southeast. These data will represent the context of community pharmacies in high HIV prevalence areas rather than all pharmacies. Moreover, selection bias may arise if a pharmacy or pharmacy client refuses to enter this study, potentially limiting the generalizability of the sample. Given that this study's purpose is to develop evidence for integrating HIV prevention services into pharmacies, we are less concerned about the impact of this potential bias. Nonetheless, PATH is a necessary first step in building the evidence for integrating HIV testing into pharmacies. Second, self-report bias may arise due to surveys querying pharmacy staff's HIV-related stigma beliefs and pharmacy clients' sex and drug use behaviors. To mitigate this bias, we use electronic surveys, which have been shown to improve validity by minimizing invalid reports such as socially desirable answers [38], as well as ordering questions in a way to enhance recall. Lastly, logic checks in the survey will be used to prevent invalid reporting by a respondent, preventing participants from proceeding in the survey if they report inconsistent responses. Participants who consistently contradict themselves in survey responses will be excluded from these analyses.

Although this study is conducted within the context of community pharmacies in the United States, considerations around international relevance and applicability are warranted. The structure, scope, and function of community pharmacy practice vary across countries. In the United States, community pharmacies often serve as accessible sites for preventative care, where pharmacists may provide immunizations, health screenings, and counseling in addition to dispensing medications. In contrast, in many international settings, pharmacists may have limited authority to deliver clinical or preventive services due to differences in professional scope, regulatory frameworks, or reimbursement policies [15]. These differences should be considered when interpreting the generalizability of our findings. Adaptation to local policy and

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practice environments will be necessary for effective implementation beyond the US context.

Conclusions

Despite these limitations, early evidence of PATH currently shows that pharmacy-based HIV prevention services in community pharmacies are implementable in the US Southeast. The PATH intervention integrated into community pharmacies provides a unique opportunity to increase access to critically needed evidence-based HIV prevention innovations, such as HIV prevention and PrEP, especially for those who are members of communities or live in neighborhoods that might be disproportionately exposed to factors that increase their HIV risk.

Acknowledgments

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Data Availability

The data that support the findings of this study are available upon reasonable request from the corresponding author.

Authors' Contributions

NDC, DIA, AH, CC, SZ, HNY, AQ, SAH, RHL, JMS, CES, and MES conceptualized this study. SZ and CH curated the data. NDC handled the funding acquisition. AH, CH, and RR conducted the investigation, and NDC provided the methodology. NDC and AH administered the project, with NDC overseeing supervision. DIA and CH visualized this study. DIA led the writing on the original draft, with NDC, AH, and CH contributing to it. DIA, CH, AH, NDC, CC, SZ, HNY, AQ, SAH, RHL, JMS, CES, and MES reviewed and edited this paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review summary from PPAH - Population and Public Health Approaches to HIV/AIDS Study Section, Healthcare Delivery and Methodologies Integrated Review Group (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 141 KB - resprot_v14i1e72283_app1.pdf]

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Abbreviations

CFIR: Consolidated Framework for Implementation Research
EDA: exploratory data analysis
EHE: Ending the HIV Epidemic
EPIS: Exploration, Preparation, Implementation, Sustainment
IDI: in-depth interview
PATH: Pharmacy-Based Access to HIV Prevention Services
PrEP: pre-exposure prophylaxis
SEIPS: Systems Engineering Initiative for Patient Safety

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Protocol

A Mobile Game Intervention for Young Persons Living With HIV and Depression in Nigeria: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Young people living with HIV bear a disproportionate burden of depression, which is associated with poor HIV outcomes. Problem-solving therapy (PST) has been shown to be effective for depression management and can be delivered with fidelity by nonspecialists, especially in resource-limited settings. PST is designed to equip individuals to manage the impact of stressful life events on their mental health. Change My Story is a narrative digital game designed to improve PST engagement among young people living with HIV in Nigeria.

Objective: This trial will evaluate the impact of PST alone or PST with Change My Story on mental health outcomes among young people living with HIV in Nigeria.

Methods: We will conduct a pilot hybrid implementation-effectiveness randomized controlled trial with 80 young people living with HIV (aged 16-24 years) in Nigeria with depression (9-item Patient Health Questionnaire [PHQ-9] ≥9) over 3 months. Participants will be randomized to receive PST with or without Change My Story. All participants will engage in weekly PST sessions for 6 weeks delivered by trained nonspecialists (clinic HIV adherence counselors). At 6 and 10-12 weeks, scores on PHQ-9 will determine the frequency of PST sessions during the remaining intervention period. Primary implementation outcomes, including engagement, satisfaction, feasibility, acceptability, and appropriateness from the participant perspective, will be assessed using validated scales, programmatic data, and focus group discussions at 3 months. Secondary clinical outcomes will assess changes in depressive symptoms, psychological distress, functional disability, antiretroviral therapy adherence, and HIV viral suppression at 3 and 6 months. Implementation outcomes (all but engagement and satisfaction) will be assessed through validated scales and focus group discussions from the implementer perspective at baseline and 6 months.

Results: This study is funded by the US National Institutes of Health (funding commenced on March 8, 2024), institutional review board approval was received on April 15, 2024, and recruitment and data collection began in June 2025. Thus far, we have screened 103 youths and enrolled 23 participants. Among enrolled participants, 15 (65%) were male; 1 (4%) had a PHQ-9

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score ≥17, and 6 (26%) had suicidal thoughts. We anticipate recruitment will be completed by January 2026 and follow-up by June 2026. We will assess our hypotheses that PST with Change My Story is feasible, acceptable, and appropriate and that individuals receiving PST integrated with Change My Story will have greater engagement, satisfaction, and depression remission compared to those receiving PST alone.

Conclusions: This pilot randomized controlled trial attempts to establish preliminary data on the feasibility, acceptability, appropriateness, and efficacy of task-shifted PST and supplementary mobile health technology on improving HIV and mental health outcomes among young people living with HIV in Nigeria. These findings may serve as a basis for future large-scale interventions.

Trial Registration: ClinicalTrials.gov NCT06389565; https://clinicaltrials.gov/study/NCT06389565

International Registered Report Identifier (IRRID): PRR1-10.2196/74199

(JMIR Res Protoc 2025;14:e74199) doi:10.2196/74199

KEYWORDS

HIV comorbidities; young people living with HIV; cognitive behavioral therapy; problem-solving therapy; HIV; mental health; depression; low- and middle-income countries; LMICs; sub-Saharan Africa

Introduction

Background

Approximately 10% of the world's 4 million young people, aged 15-24 years, living with HIV reside in Nigeria—an African nation with the fourth largest global population of people living with HIV [1-3]. Young people living with HIV also bear a disproportionate burden of depression compared to the general population, which is a key driver of poor HIV outcomes such as higher rates of interruptions in care, medication nonadherence, virologic failure, and progression of HIV [4-7].

Cognitive behavioral therapy (CBT)–based interventions are highly effective in treating depression and have been successfully used across the age spectrum from adolescents to older people [8-10]. Problem-solving therapy (PST) is a CBT-based intervention that is typically administered face-to-face with a trained counselor in 6 to 15 sessions; session duration is typically 30 to 60 minutes. PST uses 7 basic steps to teach problem-solving orientation and skills to equip individuals to manage the impact of stressful life events on their mental health [11,12]. PST interventions are highly effective for the treatment of depression both among adults as well as among women during the perinatal period in Nigeria [13-16]. PST also offers advantages over pharmacologic treatment for mild to moderate depression for people living with HIV, as PST avoids concerns about increasing pill burden and potential drug-drug interactions. Further, PST can be delivered by nonspecialist health workers, which may serve to overcome the critical gap in providing mental health care in Nigeria and other settings with a limited mental health care workforce [17-21].

Completion of PST sessions is required for optimal mental health outcomes; therefore, strategies that maximize adherence to PST may lead to the greatest benefit [11,12,22-24]. Digital games deployed through mobile health (mHealth) technologies present a unique and innovative opportunity to support psychosocial interventions like PST in a youth-friendly manner. Youth-friendly health care is an important care strategy recommended by the World Health Organization (WHO) to address the specialized needs of young people and to promote their engagement in critical health services [23,25-27].

Digital games are played by youths worldwide, and an estimated 71% of adolescents and young adults are connected online [28]. Coupled with the rapid increase in ownership of mobile phones in low- and middle-income countries (LMICs; 90% in Nigeria), digital games provide a compelling format for intervention delivery [29]. A genre of games called serious games is developed specifically for a reason other than pure entertainment (ie, promotion of health behaviors or health outcomes) [30]. One subgenre, narrative digital games, tells stories in an immersive environment, and this appealing format has been leveraged to promote observational learning, cognitive and behavioral rehearsal, and problem-solving for HIV prevention among adolescents and young adults [31,32]. Emerging evidence suggests that interactive games are both feasible and potentially effective tools for supporting chronic disease management and mental health treatment among youths [33-35].

In this paper, we outline a pilot hybrid implementation-effectiveness randomized controlled trial (RCT; ClinicalTrials.gov NCT06389565) to compare Change My Story combined with PST to PST alone among 80 young people living with HIV with depression. We will use the Consolidated Framework for Implementation Research (CFIR) to explore factors influencing engagement, feasibility, acceptability, and satisfaction among young people living with HIV and facilitators and barriers to intervention delivery [36].

Study Objectives

This 2-arm parallel hybrid implementation-effectiveness study will compare outcomes of PST alone to PST integrated with a novel digital game, Change My Story, for young people living with HIV. Implementation outcomes (primary outcomes) from the perspective of young people living with HIV (feasibility, acceptability, appropriateness, satisfaction, and engagement) will be compared across the 2 study groups. This study will also assess the effectiveness (secondary outcomes) of Change My Story in improving depression, psychological distress, and HIV viral suppression. In addition, we will assess the feasibility, acceptability, and appropriateness of the intervention from the perspective of implementers.

This trial is designed to assess 2 hypotheses. First, we hypothesize that pairing PST with Change My Story will provide

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a more comfortable entry point into mental health care and thus improve implementation outcomes including engagement, satisfaction, feasibility, acceptability, and appropriateness. It is through this mechanism that we believe PST integrated with Change My Story will have improved preliminary effectiveness on mental health and HIV outcomes compared to PST alone. Second, we hypothesize that integrating PST with Change My Story will be feasible, acceptable, and appropriate from the perspective of implementers.

Methods

Study Site

Participants will be recruited in Nigeria from the HIV Clinic, Infectious Disease Institute, College of Medicine, University of Ibadan. The clinic has approximately 6600 patients active in care, with about 400 of these being young people living with HIV. The Infectious Disease Institute also runs a monthly youth clinic, whose activities include a support group and other youth-friendly activities in addition to clinical care for 15- to 24-year-old people. Participants for this study will be recruited from young people living with HIV attending the Infectious Disease Institute by direct outreach to the adolescent clinic with the guidance of our team's peer champions.

Intervention Package

We developed Change My Story, a theory-grounded, narrative-based serious game designed to enhance engagement with PST for young people living with HIV in Nigeria. Players of Change My Story navigate emotionally difficult experiences vicariously through the characters and choose a narrative path toward the story's conclusion. Guided by the social cognitive theory, the game promotes observational learning and self-efficacy by allowing players to explore the consequences of player choice and build problem-solving skills [37,38]. The development process was guided by the Integrate, Design, Assess, and Share framework, a user-centered design approach for digital behavioral health tools [39]. We conducted formative research with young people living with HIV to identify core mental health stressors [40]. This early work highlighted high mobile phone use, frequent gameplay, and a strong preference for story-driven games. We used a user-centered design process that included youth cocreation through an interactive activity where participants developed compelling storylines informed by their lived experiences. Thematic analysis of these narratives informed the development of 3 choose-your-own-adventure style digital storylines focused on HIV disclosure, stigma, and health literacy created in collaboration with a professional game studio. The intervention package additionally includes the provision of PST (Table 1), task-shifted from clinical psychiatrists to HIV adherence counselors who are an integral part of the existing infrastructure of the study site's HIV clinic (and many other HIV clinics in this environment). This component of the intervention is further described in the Provider Training section.

Table 1. Problem-solving therapy (PST) session outline.

Session	Patients receive PST alone	Patients receive PST and Change My Story
Session 1	Psychoeducation and introduction to PST.	Psychoeducation and introduction to PST and Change My Story game. Selection of narrative for game play based on participants' life experience or current problem.
Session 2	Administer PST steps and agree on homework tasks.	Administer PST steps supported with experience from game play: discuss similarities, differences, and outcome expectations. Agree on homework tasks and narrative for gameplay.
Sessions 3-5	Administer PST steps and review homework tasks.	Administer PST steps supported with experience from gameplay. Review homework tasks and reflect on experience with gameplay.
Session 6	Summarize and reinforce lessons learnt. Assess with PHQ-9[a] to determine further treatment plan.	Summarize and reinforce lessons learnt and parallels from the game narrative. Assess with PHQ-9 to determine further treatment plan.

[a]PHQ-9: 9-item Patient Health Questionnaire.

Choice of Comparators

Arm 1 will receive the outlined PST intervention delivered by adherence counselors based in the HIV clinic. Arm 2 will receive the outlined PST intervention integrated with the Change My Story game. Both arms will offer phone-based PST for selected sessions to improve accessibility. We anticipate that both arms will show improvement in mental health outcomes assessed using the 9-item Patient Health Questionnaire (PHQ-9; secondary outcome). However, we hypothesize that integrating PST with Change My Story will improve implementation outcomes (primary outcomes) including satisfaction, feasibility, acceptability, and appropriateness (from the perspective of study participants). It is through these mechanisms that we believe individuals in arm 2 will have greater engagement (primary outcome) in the intervention and improved preliminary effectiveness on both participants' PHQ-9 score and HIV viral load compared to those in arm 1.

Provider Training

Prior to recruitment, HIV adherence counselors and physicians will be trained in depression identification, documentation, and management, including support and referral protocols for patients with suicidal ideation or severe depression. HIV counselors will additionally receive training on the delivery of the manualized PST intervention package developed by Gureje et al [15]. Study physicians will receive further training on the appropriate risk assessment, treatment, and referral requirements for high-risk patients using a format that has been successfully used to train nonspecialists and to improve knowledge, attitudes

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toward mental illness, and competency in diagnosing and treating depression [15,41,42]. To effectively integrate Change My Story with PST delivery, the counselors in this arm will participate in a workshop where they have an opportunity to play the game, review key narratives and themes, identify how narrative themes may relate to important PST principles that can be highlighted in treatment sessions, and role-play PST sessions with and without Change My Story.

Eligibility Criteria

Trained study staff will approach consecutive attendees at the Infectious Disease Institute while they are waiting to see their health care providers or during youth club sessions. These staff will screen interested participants for eligibility by administering validated screening tools for depression (PHQ-9) as well as for bipolar and psychotic disorder (adapted from the World Mental Health Composite International Diagnostic Interview [WMH CIDI]) in a private area of the waiting room [43-46]. Patients will meet the inclusion criteria if they (1) are HIV seropositive, (2) are 16 to 24 years of age, (3) possess a self-reported proficiency in reading and understanding English, and (4) have depressive symptoms (defined as PHQ-9≥9) [45]. Patients will be excluded if they are pregnant or nursing, have been on antiretroviral therapy (ART) for 6 months, have been out of care for ≥6 months, or have a history of or positive assessment for bipolar or psychotic disorder (based on adapted WMH CIDI) [46]. Individuals who meet eligibility criteria will be invited to provide written informed consent. Consenting individuals with a PHQ-9 score between 9 and 17 will be randomized. Further, individuals with a score of 12-17 will be referred to a clinic physician to ensure that no further specialized psychological assessment is indicated. Those with a PHQ-9 score ≥18 or who are assessed to have serious suicidal risk (ie, indicate thoughts of suicidality) will be immediately referred to a psychiatrist to be evaluated for safety and treatment needs; in these 2 scenarios, if individuals are cleared by the clinic physician or psychiatrist, they may be reconsidered for study eligibility and randomized.

Randomization

Participants with a PHQ-9 score ≥9 will be randomized 1:1 in a parallel group design by the study statistician to study arm 1, PST alone, or study arm 2, PST with Change My Story. Randomization will be stratified on 2 key baseline variables: age category (16-19 vs 20-24 years) and HIV mode of transmission (perinatal vs nonperinatal). Younger people living with HIV in LMICs may have more limited access to technology, which may impact the feasibility of the mHealth platform [47]. Perinatally and nonperinatally infected young people living with HIV often differ in psychosocial contexts and stigma experiences, which may influence both their engagement with the intervention and mental health outcomes [48]. The random allocation sequence will be generated centrally by the study statistician and implemented using sequentially numbered, opaque, sealed envelopes to ensure allocation concealment until the point of assignment.

Blinding

Due to the nature of the intervention, it will not be possible to blind participants or implementers.

Procedures (Both Study Arms)

PST (Study Arms 1 and 2)

All participants will receive PST delivered using a stepped-care approach. Figure 1 outlines this study schema. PST appointments will be prescheduled and last approximately 30 to 45 minutes. The first, second, and sixth intervention sessions will be delivered face-to-face in the clinic to facilitate introductions and familiarity with the PST steps. The other sessions will be administered via mobile phone or in person (based on participant preference). The first PST session will include a discussion that will facilitate the generation of a problem list, which will be the focus of subsequent sessions. The first 6 weeks, referred to as “step 1,” involve weekly PST sessions (Table 1).

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Figure 1. Study schema. MD: medical doctor; PHQ-9: 9-item Patient Health Questionnaire; PST: problem-solving therapy; SRQ-20: Self-Reporting Questionnaire-20.

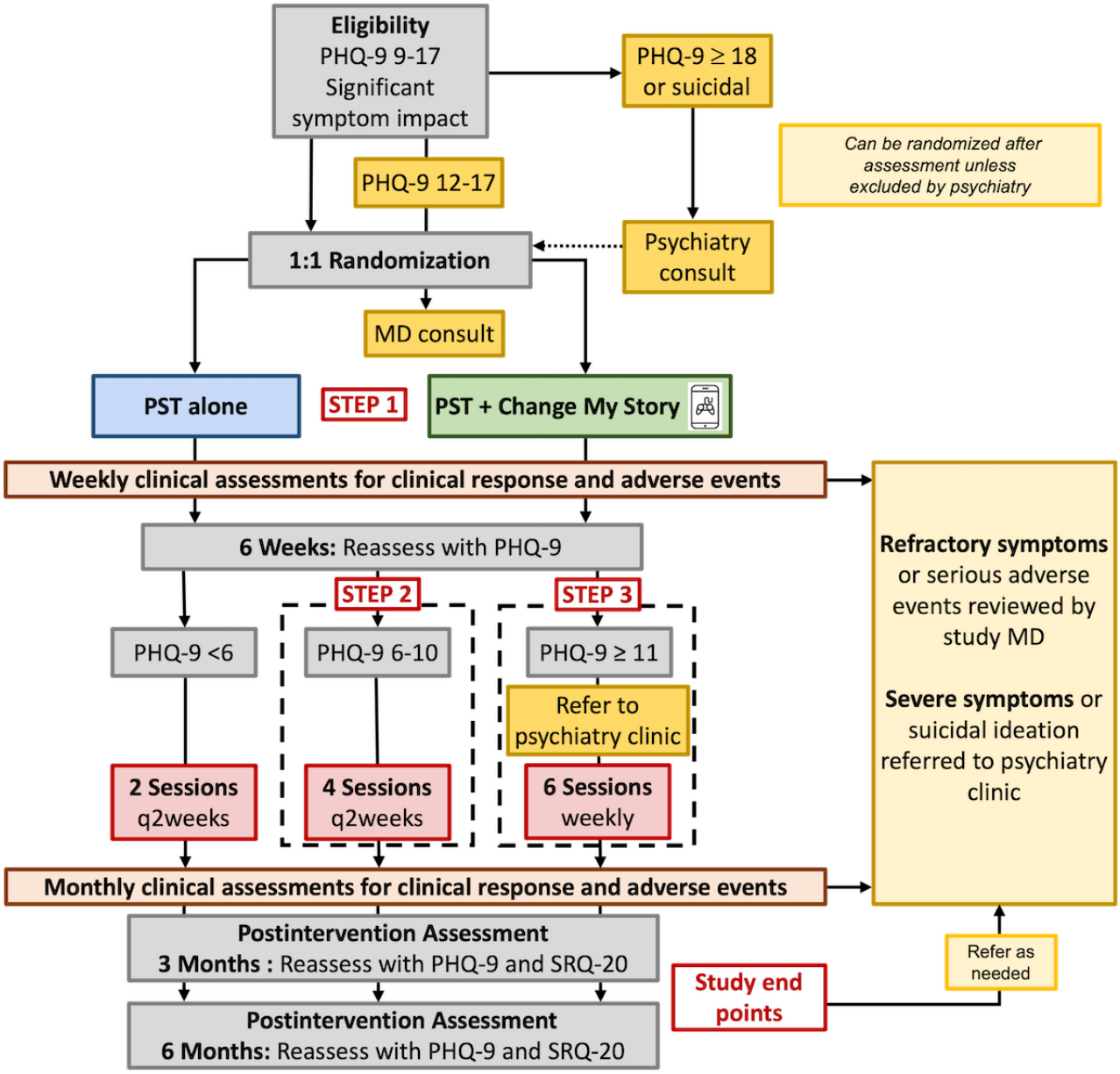

Subsequent care will be determined based on the participant's PHQ-9 score at the week 6 evaluation. Participants with a PHQ-9 score <6 will be considered to be in remission and will receive 2 additional PST sessions delivered every 2 weeks. Participants with a PHQ-9 score of 6-10 will be considered to have mild to moderate depressive symptoms and will receive 4 additional sessions delivered every 2 weeks; this is titled "step 2." Participants with a PHQ-9 score ≥11 will be considered to have moderate to severe depressive symptoms and will receive an additional 6 sessions of weekly PST; this is titled "step 3." Participants whose PHQ-9 score is >17 or who express suicidality will be referred for evaluation at the psychiatry clinic. All participants who do not achieve remission (PHQ-9 score <6) after completion of the additional 6 weekly therapy sessions will be required to have a referral to either the general medical doctor or psychiatrist at the Infectious Disease Institute to determine the need for pharmacologic treatment or additional intervention based on local clinical guidelines (Figure 1) [14,41,49].

PST With Change My Story (Study Arm 2)

At enrollment, participants randomized to study arm 2 will download the game onto their phones, receive information about the game structure or layout, and receive recommendations on how to play the game. Participants will be asked to play through at least 1 of the 3 narratives each week, within 48 hours of the PST session. Participants will be encouraged to set a weekly reminder alarm for their gameplay session. Participants will receive the PST intervention as described in the PST (Study Arms 1 and 2) Section. Counselors will be encouraged to use the participant's game experience as a tool to help introduce and guide the patient through difficult discussions to facilitate the PST sessions. As such, during the first PST session, the counselor and client together will choose a narrative story that might resonate with the participant's background and concerns.

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In subsequent sessions, the patient and counselor may reflect on the patient's experience with the game, discuss the patient's thoughts and feelings about the character's narrative path, and use this discussion to help identify similarities or differences between the character's and participant's life challenges. As they identify and work through the participant's problem list and different problem-solving strategies, the counselor may encourage the participant to play a particular character again and explore a different narrative path to illustrate key features of problem orientation; this may allow the patient to see how characters achieve desired outcomes, reframe their own outcome expectations, and promote self-efficacy in problem-solving. We believe that patients in this study arm will be more engaged in the therapeutic process, have a more satisfying intervention experience, and thus be more likely to complete the recommended PST sessions.

Ongoing Evaluation for Suicidality or Serious Adverse Events

During each PST session, the counselor will ask the participant structured questions to identify those at risk of suicide. Participants who indicate suicidality or ongoing refractory disease at reassessment points will require immediate consultation by the Infectious Disease Institute psychiatry clinic. The psychiatry team will determine whether the patient requires initiation or escalation of pharmacotherapy or other intervention [41,50].

Outcome Assessment

The study will use a type II hybrid design to assess both implementation and effectiveness outcomes across study arms. Outcome assessors will receive training on administering data collection instruments.

The primary outcomes for this study are implementation outcomes (engagement, satisfaction, feasibility, acceptability, and fidelity) and will be compared across participants in PST alone to PST with Change My Story arms. Engagement in the intervention is defined as the percentage of recommended PST sessions attended. Satisfaction with the intervention is based on an adapted version of the Client Satisfaction Questionnaire (CSQ-8) [51]. Feasibility and acceptability as well as facilitators and barriers to achieving implementation and clinical outcomes—from the patient's perspective—will be assessed via focus group discussion (FGD) as well as via Weiner's Feasibility of Intervention Measure (FIM) and Acceptability of Intervention Measure (AIM) [52]. For feasibility, programmatic data, including the proportion of consented patients enrolled, proportion of game play sessions interrupted by technical problems, proportion of users requiring a mobile phone (at baseline), a replacement phone (due to loss or theft), or data needs, will also be assessed. For acceptability, the number of minutes and number of days of total game play per month, the percentage of recommended game play minutes completed, and the proportion of narratives completed will also be assessed from aggregated game play metrics. We will assess fidelity by determining whether core components of the PST intervention are implemented as planned and as detailed in the intervention manual via direct observation of a random subset of 15% of PST sessions (2 and 5) rated on several dimensions according to a scale that has successfully been used by the study team in Nigeria [53].

Secondary outcomes are clinical outcomes (remission of depression or psychological distress, ART adherence, and viral suppression). Specifically, remission will be defined by a reduction in PHQ-9 from baseline to follow-up (PHQ-9 score <6) [43,44]. Functioning across 6 domains will be measured via the WHO Disability Assessment Schedule [54]. HIV outcomes, including ART adherence and viral suppression, will be, respectively, measured via pharmacy refills and laboratory values (HIV RNA <200 copies per milliliter) at baseline and 3 to 6 months after intervention completion. Laboratories will be drawn for this assessment if participants do not have a routine clinical viral load obtained within this window.

Quantitative Data Collection

Participant Quantitative Data Collection

Trained study staff will administer a battery of widely validated instruments to participants at baseline, 3 months, and 6 months. The battery includes tools to assess depression (PHQ-9 and WMH CIDI), psychological distress (WHO Self-Reporting Questionnaire-20), HIV stigma (Berger's HIV Stigma Scale), social support (Social Provisions Scale-24), food insecurity (Household Food Insecurity Access Scale), functioning in individuals with psychiatric disorder (WHO Disability Assessment Schedule), and substance-related risks in adolescents (Car, Relax, Alone, Forget, Family/Friends, and Trouble Questionnaire screening test; Table 2) [43,44,46,54-58].

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Table 2. Participant data collection.

Outcome and measure	Baseline	3 months	6 months
Baseline covariates			
Demographics			
Questionnaire	✓		
Psychological distress			
SRQ-20[a] [44]	✓	✓	✓
Depression			
PHQ-9[b] [43]	✓	✓	✓
WMH CIDI[c] [46]	✓		
HIV stigma			
Berger Stigma Scale [55]	✓		
Social support			
Social Provision Scale [56]	✓		
Food insecurity			
Household Food Insecurity Access Scale [57]	✓		
Disability			
WHO[d] Disability Assessment Schedule [54]	✓	✓	✓
Substance abuse			
CRAFFT[e] Scale [58]	✓		
Clinical data			
CD4+[f] count, HIV viral load, ART[g] adherence	✓	✓	✓
Primary outcomes			
Engagement			
Percentage of sessions attended		✓	
Satisfaction			
CSQ-8[h] [51], FGD[i]		✓	
Feasibility, acceptability, appropriateness			
Weiner's FIM[j], AIM[k], IAM[l] surveys [52]; enrollment rate; mobile phone or data needs; game play metrics; FGD		✓	
Secondary outcomes			
ART adherence			
Percentage of pharmacy refill	✓	✓	✓
HIV viral load		✓	✓

[a]SRQ-20: Self-Reporting Questionnaire-20.
[b]PHQ-9: 9-item Patient Health Questionnaire.
[c]WMH CIDI: World Mental Health Composite International Diagnostic Interview.
[d]WHO: World Health Organization.
[e]CRAFFT: Car, Relax, Alone, Forget, Family/Friends, and Trouble Questionnaire.
[f]CD4+: cluster of differentiation 4+ T-lymphocyte cell.
[g]ART: antiretroviral therapy.
[h]CSQ-8: Client Satisfaction Questionnaire.
[i]FGD: focus group discussion.
[j]FIM: Feasibility of Intervention Measure.
[k]AIM: Acceptability of Intervention Measure.

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[l]IAM: Intervention Appropriateness Measure.

Implementor Quantitative Data Collection

We will administer pre- and posttest knowledge assessments after initial training (focusing on screening, identification, and treatment for depression and components of PST). We will also conduct a baseline readiness assessment, including Rohrbach's readiness tool and the Organizational Readiness for Implementing Change tool, and assess pre-implementation feasibility, acceptability, and appropriateness from health facility leaders (n=2), the HIV clinic providers (n=4), and HIV counselors (n=4-5) [59,60]. At 3 months, we will administer an assessment of implementation outcomes to this group, which will include Weiner's Intervention Appropriateness Measure, FIM, and AIM [52]. In addition, the scalability of the intervention will be assessed using the Intervention Scalability Assessment Tool (Table 3) [61].

Table 3. Implementer data collection.

Implementation outcome	Measure	Baseline	3 months	6 months
Workshop training assessments	Pre- or posttest, evaluation form	✓		
Readiness	Rohrbach and ORIC[a] tools [58,59], FGD[b]	✓	✓	
Patient engagement	FGD		✓	
Feasibility	Weiner's FIM[c] [51], FGD	✓	✓	
Acceptability	Weiner's AIM[d] [51], FGD	✓	✓	
Appropriateness	Weiner's IAM[e] [51], FGD	✓	✓	
Fidelity	Direct observation	Ongoing	Ongoing	Ongoing
Scalability	Intervention Scalability Assessment Tool [60]		✓	

[a]ORIC: Organizational Readiness for Implementing Change.

[b]FGD: focus group discussion.

[c]FIM: Feasibility of Intervention Measure.

[d]AIM: Acceptability of Intervention Measure.

[e]IAM: Intervention Appropriateness Measure.

Qualitative Data Collection

Participant Qualitative Data Collection

FGDs will be conducted with study participants (n=20) at the study end. Our FGD guide was developed using the CFIR framework and focused on determinants of key implementation outcomes (feasibility, acceptability, satisfaction, and engagement) of our patient-facing strategies and environment [36,62]. We will examine outer setting factors, such as IT infrastructure, to enable digital game use, community-level stigma, and sociocultural norms influencing mental health and HIV care. Inner setting constructs will explore participants' perceptions of the clinic environment and its support for mental health services. Characteristics of individuals will include participants' knowledge, beliefs, and self-efficacy related to using the digital game and engaging in PST. Intervention characteristics will be examined through perceptions of the game's relevance, quality, and usability and the coherence between the game content and PST sessions. Finally, implementation process factors, such as clarity of instructions, support received, and game-clinic integration, will be assessed to understand what facilitated or hindered engagement. The full guide can be found in Multimedia Appendix 1. These qualitative insights will inform the contextual appropriateness and potential scalability of the intervention.

Implementer Qualitative Data Collection

We will conduct 2 FGDs with health facility leaders (n=2), HIV clinic providers (n=4), and HIV counselors (n=4-5), once during pre-implementation to assess knowledge and attitudes about mental health, PST, and readiness for the intervention, and again at the study end to assess implementation outcomes and their determinants. As with the participants, the CFIR will guide our assessment of implementation outcome determinants, appropriateness and feasibility of implementing this strategy in Nigeria (outer setting), the clinic's culture and attitudes toward mental health screening and treatment, internal capacity to support mHealth-based interventions, impacts of the intervention on other services (inner setting), knowledge and beliefs about the intervention, confidence in implementor's abilities to administer the intervention and integrate the game-based strategy into the intervention (provider characteristics), effectiveness of provider training, effectiveness of integration of the strategy into clinic workflow, facilitators and barriers to intervention fidelity (process of implementation), and complexity and quality of the intervention and implementation strategies (intervention characteristics), challenges, as well as contextual factors influencing acceptability and satisfaction with the intervention [36,62]. The full guide can be found in Multimedia Appendix 2.

Sample Size and Power Considerations

With a total sample size of 80 participants (40 per study arm), the study will have approximately 80% power to detect a

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difference between the intervention and control groups equivalent to 0.635 SDs in the outcome measure using a 2-sided *t* test with a significance level of .05.

Engagement in the Intervention

Using prior data from a study on PST for depression and common mental disorders among adults in Zimbabwe in which the SD for the number of sessions attended was 18.5%, we anticipate having 80% power to detect a difference of 11.7% in the mean proportion of sessions attended between the study arms [24]. If the SD in our study population is as low as 10% or as high as 25%, then we will have approximately 80% power to detect mean differences in the proportion of sessions attended of 6.3% and 15.8%, respectively. If up to 20% (16/80) of participants are lost to follow-up (LTFU), then we anticipate having 80% power to detect a difference of 13.2% in the mean proportion of sessions attended between the study arms.

Satisfaction With the Intervention

While there are no preliminary data in similar populations, in diverse populations receiving PST, the SD of the CSQ-8 (scores range from 8 to 32) was 4.78-4.95 [63,64]. Assuming SDs of 4.5, 4.75, and 5.0 in the CSQ-8 scores and no LTFU, we anticipate having 80% power to detect differences of 2.9, 3.0, and 3.2, respectively, in the mean scores between study arms. With 20% (16/80) LTFU, these estimated detectable differences are 3.2, 3.4, and 3.6, respectively. While we will not be powered to detect differences in our secondary clinical outcomes in this pilot RCT, we believe the value of this intervention approach may not necessarily come from changing PST efficacy but from improving adoption and engagement for young people living with HIV with the intervention, thus improving its overall effectiveness or so-called mosaic effectiveness [65].

Retention

To promote retention and minimize LTFU, we will use established clinic strategies including phone reminders for appointments and targeted outreach by clinic or study staff for missed visits. To reduce participation burden, only 3 PST sessions will be required to be in person, others can be delivered via mobile phone (per participant preference), and participants will receive travel reimbursement and refreshments for the face-to-face sessions and outcome assessments. Participants who elect to discontinue from the study will be asked to complete an exit visit, which will include the assessments outlined in Table 2.

Data Analysis

Overview

Primary outcomes include (1) engagement in the intervention defined as the percentage of recommended PST sessions attended, (2) satisfaction with the intervention using the CSQ-8, (3) feasibility, and (4) acceptability (from the patient perspective; Table 2). These outcomes will be collected throughout the course of the study through engagement with the app and participation in PST sessions. Exceptions include the CSQ-8, FIM, and AIM, which will be administered at 3 months, and the fidelity checklist, which will be applied to 2 separate sessions during the study.

Our secondary outcomes include remission of depression, level of mental distress, disability, ART adherence, and HIV viral suppression (Table 2). These outcomes will be assessed at 3 and 6 months (viral suppression will be assessed once between 3 and 6 months).

Quantitative Data Analysis

Engagement and satisfaction scores (primary outcomes) and ART adherence (secondary outcome) will be compared between study arms using a Wilcoxon rank sum test to avoid making distributional assumptions. Additional secondary outcomes (remission of depression and psychological distress and viral suppression) will also be compared using chi-square tests. We will compare primary and secondary outcomes between study arms using semiparametric cumulative probability models. Because of the relatively small sample size, baseline covariates will be included using a propensity score to account for any covariate imbalance between the treatment arms. Missing covariate data, if any, will be multiply imputed with 20 imputation replications using chained equations. Primary analyses will be intention-to-treat analyses; we will also perform secondary, as-treated analyses. Persons who are out of care will be assumed to have been nonadherent over the period for which they were out of care, and intervention engagement over these gaps will be assigned the value 0. Secondary analyses will exclude person-time when individuals are not in care. Descriptive statistics will be used to summarize the ordinal responses obtained from FIM and AIM surveys in addition to programmatic and game log data measuring other features of feasibility and acceptability. We will assess other factors associated with the study primary and secondary outcomes, in addition to potential confounders and mediators of the relationship between the intervention and outcome including baseline sex, cluster of differentiation 4+ T-lymphocyte cell count, age, marital status, psychological distress, HIV stigma, social support, food insecurity, quality of life, and substance abuse [43,44,55,57,66-70].

Qualitative Data Analysis

After gaining consent, we will record and transcribe all interviews. Transcripts will be read by 2 individuals to ensure that they are complete and adequately address the research questions as well as to develop an initial codebook. The first 5 interviews will be pulled to assess the identification of expected deductive codes identified from the CFIR framework and relevant literature [36]. Unexpected codes will be generated and defined for future coding. Coding will be conducted, as interviews are completed to ensure we reach data saturation. We will assess intercoder agreement. Coding and analysis will be done using MAXQDA (version 12; VERBI), with a directed content analysis approach informed by the 5 CFIR domains [36].

Data Integration

We will use a convergent parallel mixed methods design to integrate qualitative and quantitative data [71]. After initial independent analysis of both patient and implementer datasets as described earlier, the multidisciplinary team will examine the quantitative and qualitative data analyses concurrently to

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identify areas where the findings converged, diverged, or added insight to one another to inform assessments of our hypothesis that participants who receive PST integrated with Change My Story will have improved implementation and effectiveness outcomes compared to those receiving PST alone. We will additionally assess emergent themes that can further inform determinants of study outcomes. Data integration discussions, particularly addressing any concerns with divergent results, will include both the broader study team and youth advisors to ensure contextual validity and the creation of additional data collection plans if deemed necessary.

Quality Control Mechanisms

The quality of the study outputs will be ensured by using validated data collection tools. In addition to the creation and implementation of operations manuals, data collectors and supervisors will be trained on all data collection tools and procedures. In total, 1 research assistant will manage the mobile app technology to ensure proper functioning, 2 Nigerian-based research assistants will coordinate the overall research, and 1 US-based research assistant and US-based program manager will provide continuous supervision throughout the entire follow-up. All case report form data will be stored on the University of Ibadan secure network drives and captured onto a secure, password-protected REDCap (Research Electronic Data Capture; Vanderbilt University) database. The encrypted REDCap data servers will be hosted by the University of Ibadan. Electronic mobile technology use data will be stored on a back-end storage system at the University of Ibadan that meets Health Normative Standards Framework guidelines, which call for restricted access and the separation of patient demographics and health data.

Recognizing that loss of privacy is a serious issue, especially for an mHealth-grounded intervention for youths, measures will be put in place to protect identifiable data. First, all investigators and research personnel will receive training on the protection of human participants. Second, identifiable information will only be made available to a few specific research personnel who will need access to the data purely for study purposes. All paper records will be stored in secure, locked cabinets only accessible to study personnel. Third, the mHealth app was developed with security as the top priority. The security features include early deidentification of data through the assignment of participant ID numbers, storage of data in an encrypted format, secure HTTPS-based data transmission between the mHealth app and a password-protected, Health Insurance Portability and Accountability Act (HIPAA)–compliant cloud-based storage system, robust user-level authentication to access the app, and automatic log-out after a period of inactivity. To minimize risk to confidentiality and privacy, the app will not include any explicit indications to its purpose as an HIV intervention. From an outside perspective, Change My Story will appear like other general apps, without obvious associations to mental health or HIV-related services. Fourth, participants will be counseled on the low risk of data breach with these safeguards, but also on how to further minimize data breach when phones are shared. Participants will additionally be taught to use the app and participate in remote PST sessions in ways that protect their privacy. These safeguards will be present in the demonstration session, introducing the participants to the app. Nonetheless, these risks will be explicitly discussed with participants at the time of enrollment and consent for study participation. Given the limited scale of the study, the research team will maintain direct oversight of all procedures and data collection; no additional monitoring processes are anticipated.

Ethical Considerations

This study involves human participants and was reviewed and approved by the Mass General Brigham Institutional Review Board (IRB) in the United States (Protocol #: 2024P000857) and the University of Ibadan IRB in Nigeria (Protocol #: UI/EC/24/0484). Written informed consent will be obtained from all participants prior to enrollment. Individuals aged 16 years and older as well as emancipated youths can consent for research in compliance with Nigerian regulations and IRB requirements. The consent process will include a clear explanation of the study's purpose, procedures, potential risks and benefits, voluntary nature of participation, and the right to withdraw at any time without penalty. All participants will receive due incentives and refreshments for in-person study visits (including outcome assessments) to account for their time and transportation needs. Participants randomized to the integrated PST and Change My Story arm will receive monthly mobile carrier bundles during the intervention period to ensure data access required for study activities. These reimbursements are intended solely to offset costs incurred as a result of participation and are not considered coercive. No performance-based or outcome-dependent incentives will be provided. All participant data will be deidentified through assignment of unique study identification numbers prior to storage or analysis. The Change My Story mobile app was developed with security as a priority, using encrypted data storage, secure HTTPS-based data transmission, robust user authentication, and automatic log-out.

Dissemination

The findings from this proposal will be shared as abstracts at international HIV conferences and submitted for publication in peer-reviewed journals. At the conclusion of the trial, we will consolidate findings and prepare a presentation oriented to an audience of trial participants and other young people living with HIV at the Infectious Disease Institute.

Data Monitoring Committee

A Data Safety and Monitoring Board has been formed to safeguard the interests of participants. The Data Safety and Monitoring Board is an independent advisory group that will provide recommendations. The members have expertise in clinical psychiatry, HIV clinical trials, adolescent medicine, and biostatistics.

Patient and Public Involvement Plan

End users and key clinical and public health partners in the field of HIV have been integrally involved in the development of the Change My Story game. Throughout the data collection and follow-up period, the end users along with clinical and public health partners will provide key perspectives on outlined implementation outcomes in addition to how they can be overcome to maximize patient benefit.

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Results

This study is funded by the US National Institutes of Health (funding commenced on March 8, 2024), and IRB approval was received on April 15, 2024. Participant recruitment and data collection began in June 2025. Through this study, we will assess our hypothesis that participants who receive PST integrated with Change My Story will have improved implementation and effectiveness outcomes compared to those receiving PST alone. Thus far, we have screened 103 youths and enrolled 23 of a planned 80 trial participants. Among enrolled participants, 15 (65%) were male, 1 (4%) had a PHQ-9 score ≥17, and 6 (26%) had suicidal thoughts underscoring the need for routine mental health screening and intervention in this population. We anticipate recruitment to be completed by January 2026 and follow-up to be completed by June 2026.

Discussion

Nigeria and other LMICs are facing overlapping epidemics of HIV and mental disorders that have gone largely unaddressed despite their well-documented interrelationship [72,73]. Depression is common among young people living with HIV, a finding underscored by our early enrollment data, and is strongly associated with ART nonadherence, LTFU, and virologic failure [4-7]. Although CBT interventions such as PST are effective for depression in both high-income and LMIC settings [11-16,22,24], their scalability is limited by a shortage of mental health specialists [17-19]. Task-shifting PST to trained lay providers can improve access, but sustained engagement in multisession therapy remains challenging for young people living with HIV due to mobility constraints, stigma, and discomfort discussing mental health in clinic settings [5,6,23].

This pilot trial addresses these challenges by integrating PST with Change My Story, a culturally tailored, narrative-based serious game designed with youth input to provide a low-stigma, youth-friendly entry point to care [25-27]. Serious games have demonstrated promise for health behavior change [30-35], and narrative formats can enhance identification, observational learning, and self-efficacy [31,32,37,38]. However, prior HIV-related gaming interventions have largely focused on prevention rather than mental health, and few have been embedded within evidence-based psychotherapy for young people living with HIV in LMICs. By combining a stepped-care, task-shifted PST model with a behaviorally grounded digital game [37-39], this study targets 2 major implementation gaps: limited scalability of specialist-delivered care and poor retention in psychotherapy among youths [22,24].

While our approach addresses important barriers to engagement, it does not directly address social determinants of health (such as poverty, housing instability, food insecurity, gender-based violence, and structural stigma) that also shape adherence and mental health outcomes [5,6,55,57,66]. mHealth platforms offer a low-friction strategy to deliver psychosocial support, which may reduce some care access barriers (when delivered remotely) and equip young people living with HIV with coping skills to better manage and navigate these persistent stressors [11,12,33]. Our mixed methods design, guided by the CFIR, will allow us to identify unaddressed barriers, including those reflecting social and structural determinants, and inform adaptations for future iterations of the intervention [36].

The primary limitation of this study is its modest sample size as a pilot trial, which will limit statistical power to detect changes in secondary clinical outcomes and may reduce generalizability. Recruitment from a single, well-resourced HIV clinic with established youth-friendly services may also limit applicability to other settings with fewer resources. To address this, we plan to conduct supplementary FGDs with young people living with HIV and stakeholders from other regions in Nigeria to assess transferability. Despite these limitations, this trial will yield critical early evidence on the feasibility, acceptability, and preliminary effectiveness of an mHealth-enhanced, task-shifted psychological intervention for young people living with HIV, filling a major evidence gap in the literature. Findings from the trial will advance the literature on integrating digital innovations into mental health care for HIV and—if effective—may inform scalable strategies to close the persistent gap between innovation and impact in global HIV and mental health care.

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Data Availability

The datasets that will be generated during this trial are available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization: AAA (lead), BO, OG, CMA, DG, OA (contributors)
Funding acquisition: AAA (lead), BO, OG, KMK, LJP, CMA (contributors)
Investigation: TO (lead), BO, KMK, OA (contributors)
Methodology: AAA (lead), CE, AAA, LJP, KMK, DG, CMA, OG, BO (contributors)
Project Administration: LJP, TO (lead)
Software: DG

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Supervision: AAA, BO, KMK
Visualization: AAA, CE (equal)
Writing—original draft: CE (lead), AAA
Writing—reviewing and editing: CE, TO, KMK, LJP, DG, CMA, OA, OG, BO, AAA

Conflicts of Interest

None declared.

Multimedia Appendix 1
Participant focus group discussion guide.
[DOCX File , 17 KB - resprot_v14i1e74199_app1.docx]

Multimedia Appendix 2
Implementer focus group discussion guide.
[DOCX File , 17 KB - resprot_v14i1e74199_app2.docx]

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Abbreviations

AIM: Acceptability of Intervention Measure
ART: antiretroviral therapy
CBT: cognitive behavioral therapy
CFIR: Consolidated Framework for Implementation Research
CSQ-8: Client Satisfaction Questionnaire
FGD: focus group discussion
FIM: Feasibility of Intervention Measure
HIPAA: Health Insurance Portability and Accountability Act
IRB: institutional review board
LMIC: low- and middle-income country
LTFU: lost to follow-up
mHealth: mobile health
PHQ-9: 9-item Patient Health Questionnaire
PST: problem-solving therapy
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
WHO: World Health Organization
WMH CIDI: World Mental Health Composite International Diagnostic Interview

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Protocol

Doula-Delivered Cognitive Behavioral Training and Cardiovascular Health Intervention for Birthing Individuals in a Low-Income New York City Population: Protocol for a Living Healthy for Moms Randomized Type I Hybrid Effectiveness-Implementation Trial

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Abstract

Background: In the United States, mental health complications and cardiovascular events are the 2 leading causes of death for birthing parents in the year following delivery. Most of these deaths are preventable, with Black and Latinx individuals experiencing higher rates of these postpartum complications. Current postpartum care has not reduced these disparities.

Objective: This randomized controlled trial aims to train nonmedical professionals in a novel intervention to prevent postpartum depressive symptoms and improve cardiovascular health following childbirth in a low-income New York City (NYC) birthing population.

Methods: We aim to recruit 600 birthing individuals over 3 sites across NYC. After screening and consent, participants will be randomized to the Living Healthy for Moms intervention (doula-delivered cognitive behavioral therapy and cardiovascular behavioral health intervention) or attention control (a variation of standard postpartum doula care). Daily telephone contacts for the first 7 days immediately after hospital discharge are followed by 12 doula-led video sessions conducted over 6 months. The primary outcomes are postpartum depressive symptoms and cardiovascular health, with secondary outcomes of psychosocial status, health behaviors, health care use, and patient satisfaction. All outcomes are measured via REDCap (Research Electronic Data Capture; Vanderbilt University) surveys administered at baseline, 2 weeks, 6 weeks, 3 months, and 6 months post discharge. Physiological measurements of glycated hemoglobin (hemoglobin A_{1c}), lipids, and blood pressure will be collected at baseline, 3 months, and 6 months. Doulas, hospital staff, and birthing individuals will be recruited to evaluate the implementation of the intervention following the conclusion of recruitment at each site. A mixed methods triangulated approach will be used, including electronic health record data extraction, web-based surveys, key informant interviews, and focus groups.

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Results: Recruitment and data collection began at the first site in Brooklyn on January 23, 2025. Data collection for participants from each of the 3 recruitment sites will be concluded by November 30, 2027, February 29, 2028, and August 31, 2029, respectively, for Brooklyn, Queens, and upper Manhattan. Thus, all data for the total expected 600 participants will be collected by the end of the grant year 6, August 31, 2029. Trial results will not be analyzed until grant year 7, beginning September 1, 2029. Data will be analyzed on an intention-to-treat basis by study team members blinded to participant conditions.

Conclusions: This hybrid type 1 effectiveness-implementation randomized controlled trial will test a novel nonspecialist intervention to prevent mental health and cardiovascular health complications of childbirth, culturally adapted to our local population in NYC. We expect that our findings will contribute to knowledge on the effectiveness and implementation of nonspecialist postpartum interventions in low-resourced settings and the expansion of doula care in the post partum.

Trial Registration: ClinicalTrials.gov NCT06666400; https://clinicaltrials.gov/study/NCT06666400

International Registered Report Identifier (IRRID): DERR1-10.2196/76871

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KEYWORDS

postpartum; mental health; cardiovascular disease; doula; cognitive behavioral therapy

Introduction

Maternal Mortality

In the United States, mental health (MH) and cardiovascular events are the 2 leading causes of death for birthing parents in the year following delivery. It is estimated that over 84% of these maternal deaths are preventable, stressing the importance of enforcing both physical and mental hygiene during the postpartum period [1]. Over one-fourth of eclampsia cases and pregnancy-related strokes happen within the first 7-10 days post partum, and approximately 5% of individuals develop hypertension only after hospital discharge [2,3]. Overall, 40% of maternal mortality occurs within the first 6 weeks post partum, making this a high-risk period [2,3].

Some populations are at higher risk of postpartum complications. In New York state, MH conditions are 1 of the top 3 causes of postpartum deaths for Black and Latinx individuals [4]. It has been estimated that over 75% of these deaths are preventable [4]. Similarly, Black birthing individuals are at the highest risk of cardiovascular deaths in the postpartum period [5,6]. Black and Latinx individuals bear a higher cumulative burden of stress and stressful life events, which can lead to a greater likelihood of both MH and cardiovascular events developing during the perinatal period [7]. This can also lead to a greater risk of complications in subsequent pregnancies [8,9].

Lifelong Impacts

Postpartum depression (PPD) is highly detrimental to health and overall well-being. Individuals with PPD can remain depressed for up to 11 years after delivery [10]. PPD is associated with significant medical and functional impairment, higher medical costs, obesity, a sedentary lifestyle, and smoking [11]. PPD is also linked to decreased adherence to medical and self-care procedures, as well as overall poor health behaviors [11]. For individuals with depression, there is a higher risk of death due to suicide and substance misuse [1]. PPD is also adversely related to decreased maternal care, reduced responsiveness, bonding issues, and breastfeeding challenges. These stressors can impact infants' emotional, cognitive, and social development [12].

Individuals who experience adverse outcomes during pregnancy or delivery are at a greater risk of developing similar health conditions during future pregnancies and are at a greater risk of developing life-threatening cardiovascular conditions. Women who experience a hypertensive disorder during pregnancy have a fourfold higher risk of being diagnosed with hypertension within 6-12 months post partum [13,14]. Similarly, gestational diabetes mellitus (GDM) is the most common complication of pregnancy and confers risk for later development of type 2 diabetes mellitus (T2DM); racial and ethnic minorities are at both greater risk of developing GDM and T2DM if they have GDM. T2DM is a powerful risk factor for cardiovascular disease (CVD) [15]. These poor health outcomes can arise as early as hospitalization for delivery and can persist for more than 5 years post partum. The risk for these poor health complications is more significant for vulnerable communities, who bear a greater cumulative stress burden and have a higher lifetime risk of CVD [4].

Therefore, pregnancy is seen as a "stress" test for future CVD [8,16,17]. The steps needed to reduce the likelihood of developing CVD are reflected in the American Heart Association's (AHA) metric of cardiovascular health, Life's Essential 8 (LE8). LE8 has 2 categories, behavioral and physiological, with 4 components in each category. The 4 behavioral components include diet, physical activity, cigarette smoking, and sleep. The 4 physiological components include blood pressure (BP), cholesterol, blood glucose, diabetes, and body mass index [18,19]. Ideal levels on the LE8 score (defined as 80-100 on a 100-point scale) are associated with lower risk of CVD (including heart failure), cancer, mortality, adverse pregnancy outcomes, cognitive decline, and dementia, as well as high health care costs [18]. For vulnerable communities, achieving ideal levels of LE8 is extremely beneficial. For Black individuals, achieving an ideal score on one of the 8 components is associated with lower risk of cardiovascular complications (in 1 study, 40.4% vs 25.3%), and reaching 2 ideal LE8 component scores is associated with even lower risk (16.8%) [19]. To date, LE8 has not been tested in the postpartum context.

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Shortfalls in Existing Postpartum Care

Postpartum care is often underused and tends to inadequately address the mental and physical health needs of individuals post partum. Despite aggressive screening and treatment recommendations from the American College of Obstetricians and Gynecologists (ACOG) [20], limited time for visits, access barriers, and lack of provider knowledge in addressing both mental and cardiovascular health mean that fewer than one-third of people living with PPD are formally diagnosed. Of those, only 16% receive any treatment, with only 6% getting adequate care and 3% achieving remission [21]. These numbers are stark and highlight a growing need for comprehensive PPD screening and treatment. Similarly, a systematic review revealed that among birthing parents with GDM, rates of postpartum follow-up were lowest for minorities, those with limited education, and comorbid MH conditions [22]. Implementing screening for PPD can increase attendance and the effectiveness of comprehensive care visits, including monitoring for hypertension and T2DM [23]. However, marginalized communities are often not screened for PPD and have less access to comprehensive care and medical providers. Up to 25% of those in marginalized communities cannot identify their postpartum provider, and over 50% of marginalized individuals do not go to postpartum obstetric visits [23,24]. These statistics reveal a prominent inequity within current medical treatment for postpartum individuals.

Structural racism, social racism, and unconscious bias both in and out of the health care system leave many vulnerable communities unable to receive adequate and necessary postpartum care [25]. In a 2022 Community Health Needs Assessment conducted by NewYork-Presbyterian (NYP) Hospital (the health system covering 2 of the 3 sites in our trial), postpartum individuals and community organizations identified 3 shortcomings in the health care system for vulnerable populations [25]. The first was hesitancy to seek care due to past negative interactions with health care providers and the health care system. The second was the lack of accessible, affordable, convenient, and high-quality health care services, which are severely lacking in vulnerable communities. The third was a need for more doulas and community health workers to bridge the gap between the current health care system and vulnerable communities in the postpartum period; this includes (but is not limited to) more community health workers in education, screening, preventive services, and secondary and tertiary care.

The ACOG recommends that postpartum care must be treated as a continuous process tailored to each individual's physical and MH needs [26-28]. All women should have contact with their obstetric care provider within 3 weeks post partum, with a comprehensive postpartum visit within 12 weeks post partum [29]. The postpartum visit should be considered a full assessment, covering mood and emotional well-being, infant care and feeding, sexual health, sleep and fatigue check-ups, physical recovery, chronic disease screening and management, and general health maintenance [29]. During these postpartum visits, clinical and social resources must be available, and providers should refer patients for long-term care, especially for those with conditions such as hypertension, diabetes, thyroid disorders, and mood disorders [29]. ACOG recommends follow-up within 7-10 days for women with hypertensive disorders of pregnancy, and 72 hours for those with severe hypertension [30]. However, few health care providers have implemented these recommendations. There is still no clear roadmap for managing MH and cardiovascular conditions post partum [29]. Members of these vulnerable populations often experience complex emotional and physical stressors, some of which are time-sensitive [31,32]—for example, postpartum preeclampsia, deep vein thromboses, and postpartum endometritis commonly occur during the first 7-10 days of post partum [2,3].

New York City (NYC) has increased community-based doula care to address the shortcomings of postpartum care for vulnerable communities. Doulas provide affordable nonmedical care during pregnancy, birth, and post partum. Doulas can extend physical, emotional, and informational support to people and their families [33]. They effectively increase satisfaction and lower the risk of severe maternal morbidity [34]. While doula care shows promise as a valuable resource for individuals in the postpartum period, most doula care in NYC is focused on intrapartum care, and evidence to support postpartum doula care is still evolving [35]. We propose to address these gaps by implementing and evaluating a doula-delivered intervention, Living Healthy for Moms (LHMoms), in 3 geographically distinct settings and populations (Brooklyn, Queens, and Northern Manhattan). We set out to culturally adapt an existing cognitive behavioral therapy (CBT) intervention delivered by nonspecialists for our NYC population, integrating cardiovascular health. We expected that doulas would be willing and able to receive training to deliver this intervention. The overall trial hypothesizes that participants completing the intervention will have lower prevalence of postpartum depressive symptoms (PPDS), better cardiovascular health, and greater engagement with postpartum health care than those receiving a variant of usual doula postpartum care [34,36].

Methods

Study Overview

LHMoms is a hybrid type 1 effectiveness-implementation trial developed to build new knowledge on alternative models of postpartum care that may better meet the needs of high-risk birthing parents. LHMoms will use a phase 1 randomized controlled trial (RCT) to test a novel, evidence-based, doula-delivered intervention that integrates CBT and LE8, compared to a variant of standard postpartum doula care. LHMoms partners with doulas from 2 community organizations: the Caribbean Women's Health Association (CWHA) and the Northern Manhattan Perinatal Partnership (NMPP). LHMoms is based on the Thinking Healthy Programme (THP), a widely used intervention endorsed by the World Health Organization that uses nonspecialists to deliver CBT-based care in underresourced settings around the globe. THP has shown high efficacy for both treatment and prevention of PPD in numerous settings [37-39] and has also been adapted for populations enduring physical health disorders such as diabetes and knee osteoarthritis [40-42]. We began our work to adapt THP with

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a series of focus groups with doulas, health care providers, and birthing individuals from the communities served by our hospital sites. This study's team (which includes community partners and doulas) then created and refined an intervention designed to address both physical health and behavioral conditions that arise post partum. The initial draft was created over several months using feedback from the focus groups.

Participants in LHMoms are randomized to the intervention arm, where participants receive the doula-delivered CBT+cardiovascular health intervention, or the attention control arm, where participants receive a variation of standard doula-delivered postpartum care (based on a community-informed and provider-informed standardized checklist for doula care routinely used by one of our community partners, CWHA). Individuals are enrolled during delivery hospitalization and are consented and connected to their doulas in the hospital, predischarge. The intervention begins within the first week post hospital discharge and continues up to 6 months post hospital discharge. Throughout the 6 months, the intervention arm receives a total of 12 doula-led sessions. The attention control arm also receives a total of 12 doula-led sessions. Sessions for all participants are delivered via Zoom (Zoom Communications, Inc) or phone, based on the participants' preference. All participants are fitted for and receive a home BP monitoring device and are trained on the correct way to use it before discharge. The LHMoms intervention arm begins with a 7-day emergency detection period, during which doulas contact participants daily within the first week at home to monitor MH and cardiovascular health, as the highest risk of severe maternal morbidity exists during this time period. The LHMoms study design is outlined below in Figure 1. The primary outcomes will be prevention of PPDS and cardiovascular health, measured at 6 months post partum. Doulas are supervised by this study's psychiatrist or psychologist throughout this study, and all study data is entered into a REDCap (Research Electronic Data Capture) database maintained at the primary study site.

Figure 1. The LHMoms intervention study design includes recruitment of 600 birthing individuals and 6 months of follow-up for each participant. BP: blood pressure; CBT: cognitive behavioral therapy; CV: cardiovascular; DBP: diastolic blood pressure; LE8: Life's Essential 8; LHMoms: Living Healthy for Moms; MH: mental health; PALS: Patient-Activated Learning System; PD: post discharge; PP: postpartum; PPD: postpartum depression; SBP: systolic blood pressure; SI: suicidal ideation; w/: with.

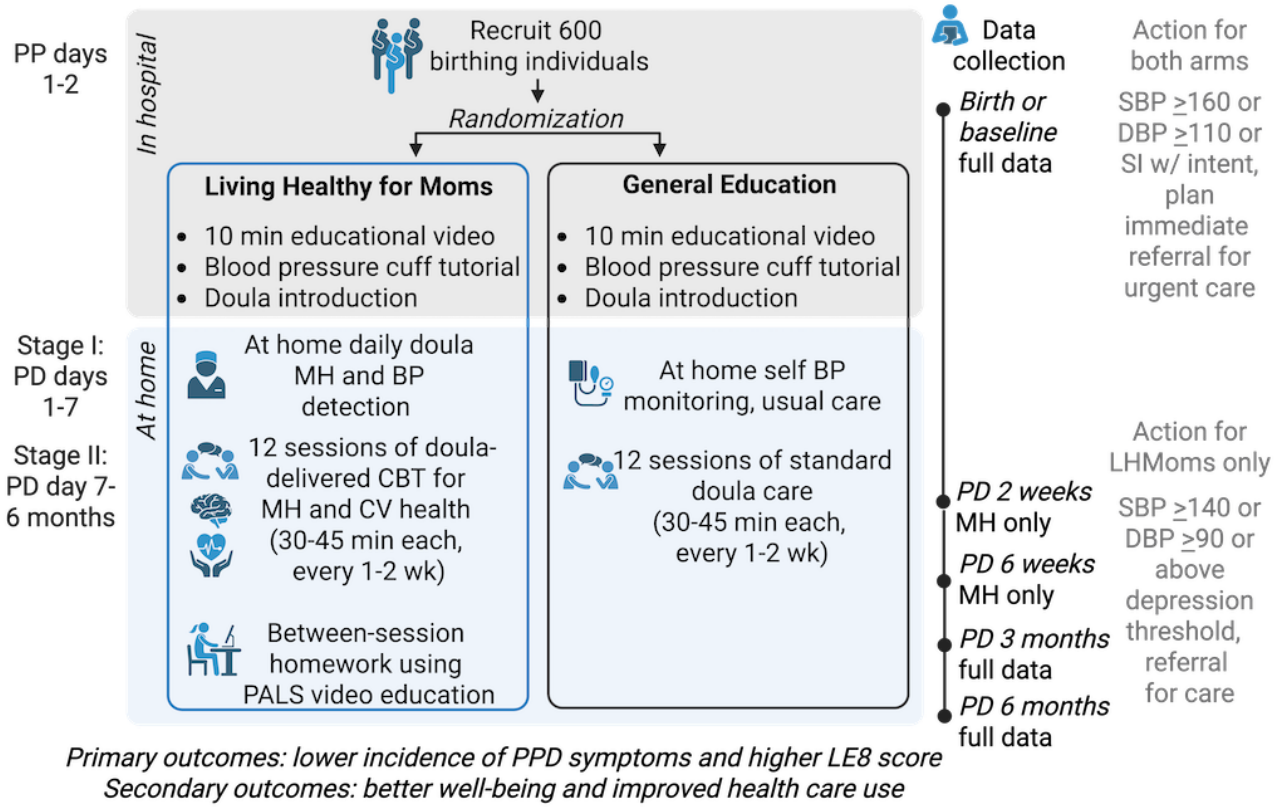

Implementation Evaluation

In addition to the effectiveness trial, LHMoms aims to evaluate the success of the implementation and explore how the findings can be used to strengthen future interventions. LHMoms will use a landscape analysis, which will collect information on the implementation process and evaluate the outcomes and factors (eg, community, people, organizations, etc) that affect implementation. Doulas, hospital staff (including clinical providers and hospital administrators), and participants who have participated in the RCT will be recruited to collect data on the effectiveness of the implementation of LHMoms. To collect data, we will use a mixed methods triangulated approach, which includes electronic health record (EHR) data extraction, web-based surveys, key informant interviews, and focus groups.

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These data will be gathered from representative participants, including doulas, health care providers, and birthing individuals, allowing us to incorporate feedback from participants overall and specific to each site to help us further refine the intervention. Data collection and analysis will be guided by the Consolidated Framework for Implementation Research (CFIR) and RE-AIM, a framework based on 5 key components: Reach, Effectiveness, Adoption, Implementation, and Maintenance.

Study Population, Setting, and Recruitment

This study aims to enroll 3 types of participants for the RCT and implementation process analysis. The first is doulas, who will be trained to deliver either the LHMoms intervention or the attention control variation of standard doula care to RCT participants. The second is birthing individuals participating in the RCT. The third comprises hospital staff, including clinical providers and hospital administrators, for the implementation process analysis phase. Three hospitals in NYC that serve low-income communities will be included: the NYP Brooklyn Methodist Hospital in Brooklyn, New York; the NYP Allen Hospital in upper Manhattan, New York; and the NYC Health + Hospitals Queens Hospital in Queens, New York. These sites were chosen because they serve underresourced individuals, including high numbers of Black, Latinx, low-income, and immigrant individuals.

The selection of doulas occurred before finalization of the intervention manual, approximately 8 months before RCT participant recruitment began at our first hospital site. Doulas will be selected and trained at the other 2 sites, approximately 8 months before participant recruitment, to allow time for training and certification. There will be 8 doulas per site, with 4 being assigned to the intervention arm and 4 being assigned to the control arm, for a total of 24 doulas across all sites. Purposive sampling is used in selecting doulas, who will be recommended by our community groups based on their interests and skills.

The recruitment period for the RCT will be staggered across years 2 to 6 of this study.

There will be an 18-month recruitment period at each hospital site, and we aim to recruit 200 participants per site for a total of 600 participants. At each hospital location, a community-based recruiter will be on-site. Research staff prescreen the EHR for eligible subjects and then discuss potential recruits with onsite principal investigators and hospital staff. The care team first approaches potentially eligible patients, inquires about their interest in LHMoms, and informs research staff about their willingness to be contacted. Research staff then approach eligible individuals within 48 hours after their delivery and before their hospital discharge.

A purposive sample of doulas, hospital staff, including clinical providers and hospital administrators, and participants will be recruited to assess the efficacy of LHMoms implementation, guided by the CFIR and RE-AIM frameworks. Ten doulas or members of health care staff at each site will either complete a web-based survey or participate in a focus group, and 7 of these will be recruited to participate in key informant interviews. Seven participants from each site will also be recruited to complete either web-based surveys or key informant interviews.

Doula Training and Creation of Intervention

Intervention development started with this study's team (which includes doulas and staff from our community partners) meeting with doulas to obtain advice about cultural adaptations and realistic expectations. The team then prepared a first draft of the intervention manual, based on the THP, cardiovascular health interventions previously undertaken by this study's team, and the recommended cultural adaptations and realistic expectations. An important component of making the intervention realistic is time constraints and the realities of living with an infant, leaving little time for intervention delivery. To accommodate the need for education, the intervention relies on the theory-driven, evidence-based Patient-Activated Learning System web-based education platform, designed by team members to provide information about medical conditions for people with low health literacy and racially marginalized individuals. The education component is designed to be self-driven, with specific assignments demanding no more than 15 minutes for completion before intervention sessions. Education components deliver knowledge on education on postpartum health, cognitive behavioral strategies, cardiovascular health, and overall health and are designed to support the intervention sessions, which are more behaviorally oriented [43].

In semiweekly training sessions (1.5 hours each) across 4 months, the initial cohort of LHMoms doulas was trained in CBT and motivational interviewing (MI) principles and role-played delivery of each intervention session. Doulas also received an overview of the Patient-Activated Learning System. Simultaneously, doulas provided feedback for this study's team, who refined and adapted the intervention iteratively, following an approach previously developed by our team [44]. Sessions were recorded, and any doula who missed a session was required to watch the recording. Following refinement of each session, doulas were paired to continue practicing the intervention with each other and with members of this study's team. For doulas at our subsequent hospital sites, or any doulas recruited as replacements, training will begin with watching recordings of the initial training sessions, followed by a reduced number of sessions with this study's team emphasizing CBT and MI principles, role play, and practice.

Doulas assigned to the attention control arm were trained over a total of 6 sessions, focusing on session-specific content and role-playing with no education on CBT or MI principles. They reviewed typical postpartum care topics, avoiding any discussion of topics specific to the LHMoms intervention.

Once doulas expressed confidence in their ability to deliver a session, they were certified on each session by a study clinician (psychiatrist or psychologist with expertise in cognitive behavioral interventions), assuring that a minimum level of competence had been achieved. Certification used a Doula Fidelity Checklist, shown below in Figure 2, which is a rating assessment to evaluate doula competency and adherence to protocol in delivering each session. A "minimum performance" checklist was developed within the Doula Fidelity Checklist,

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and doulas had to deliver each session to this study's psychiatrist or psychologist to meet the Doula Fidelity Checklist minimum performance standards before becoming certified. Doulas who did not meet the minimum performance standards on their initial certification attempt were asked to engage in additional practice until they met the minimum performance standards.

Figure 2. The Doula Fidelity Checklist assesses adherence and competence of doulas in delivering the LHMoms sessions. LHMoms: Living Healthy for Moms; PALS: Patient-Activated Learning System.

Adherence		
	Yes	**No**
Did the doula deliver the intervention session as intended (did not skip any parts)?		
Did doula review the participant's blood pressure reading with them?		
Did doula review the PALS homework and assignment questions?		
Did doula practice ThinkingHealthy with the participant on the session topic?		
Did doula review next session's homework with the participant?		
Did doula schedule the next session with the participant?		

Competence: Please rate the doula on the following scale.			
	Almost always-always=skill consistently demonstrated (skill demonstrated >75% of the time)	**Sometimes=skill sometime or occasionally demonstrated (skill demonstrated 25-75% of the time)**	**Not or rarely observed=skill rarely or never demonstrated (skill demonstrated <25% of the time)**
Communicates in a respectful, positive, nonjudgmental manner.			
Engages in rapport building and self-disclosure.			
Demonstrates empathy, warmth, and genuineness.			
Uses open ended questions.			
Uses affirmative statements.			
Uses reflective listening.			
Summarizes.			
Avoids directive statements.			
Asks permission to offer advice.			
Appropriately reinforces participants' ideas and opinions.			
Correctly conveys and communicates LHMoms principles.			

Screening Procedures and Eligibility Criteria

The inclusion criteria for doulas include affiliation with our community partners (CWHA or NMPP) and experience working with 10 or more clients in the catchment areas of our hospital sites. Doulas planning to move out of the area in the next year are not invited to participate.

Inclusion criteria for the RCT include birthing individuals aged 18 or older, having delivered a singleton live birth, having

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self-identified Black race or Latinx ethnicity, or being a Medicaid beneficiary. Exclusion criteria are birthing individuals younger than 18 years; unable to communicate in English, Spanish, or Haitian Creole; using other nonhospital doula services already; having a multifetal pregnancy, known major fetal anomaly, or stillbirth; being an active user of intravenous drugs; having known suicidal ideation with intent and plan or a known primary psychotic disorder; being on hemodialysis; having gestational age <24 weeks at delivery; and having plans to move out of the area within the next 6 months.

For the implementation evaluation cohort, doula and birthing individual criteria will be as above. For hospital staff, the only inclusion criteria will be employment at the hospital site, working on obstetrical wards, being aged 18 years or older, and being able to communicate in English, Spanish, or Haitian Creole. Staff who have no interaction with birthing parents are not invited to participate.

Randomization and Informed Consent

At each of the 3 hospital sites, 200 participants will be enrolled and randomized, 100 per arm. The blinded study statistician creates the randomization design to randomize doulas and participants on an equal (1-to-1) basis. This study's statistician, recruiters at each hospital, and study principal investigators remain blinded to randomization until the participant's completion of the last study assessment, which is 6 months post hospital discharge. The randomization of participants occurs after the recruiter has obtained informed consent and completed in-hospital enrollment, before hospital discharge. The research program coordinator in the Weill Cornell Medicine Obstetrics and Gynecology Department is unblinded and executes the randomization of all RCT participants.

Doulas in both the intervention arm and attention control arm are assigned to the participants randomized to the respective arm, with no crossover, using block randomization, also designed by the blinded study statistician and executed by the unblinded research program coordinator. RCT participants are made aware of the arm to which they are randomized. Doulas and RCT participants are not blinded throughout this study, as both parties are inevitably aware of the program in which they are participating due to preparatory doula training and from session content.

After enrollment, while still hospitalized, all participants are given a home BP monitor and are taught how to take their BP using the device. All participants are asked to record BP values in a logbook provided by this study.

Participant Groups

Intervention Arm

The LHMoms intervention arm receives the doula-delivered intervention focusing on MH and cardiovascular health. The intervention promptly begins within the first day post discharge, when the doula calls each participant to introduce herself. In the 1-7 days post discharge, LHMoms intervention participants receive daily calls and texts from their doulas. Doulas monitor participants' BP readings, collected in a daily log, and scan for postpartum complications: infection, bleeding, stroke, hypertension, cardiomyopathy, and depression. After the first 7 days, participants begin the 12-session CBT-based intervention, delivered via phone or Zoom every 1-2 weeks (Table 1).

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Table 1. After the initial 7-day emergency detection period, the LHMoms[a] intervention is delivered via 12 Zoom sessions[b-e].

Session	Topic[b-d]
1	Overview, introduction to healthy thinking, and heart health
2	Sleep for mom
3	Stress
4	Bonding with baby
5	Physical activity[e]
6	Life's Essential 8: cholesterol, BP[f], and smoking
7	Life's Essential 8: diabetes
8	Healthy eating
9	Relationships, community, health buddies, and asking for help
10	Planning for the future, pregnancy as a window to future health, and health passport
11	Review past session topics as desired
12	Final session and send-off

[a]LHMoms: Living Healthy for Moms.

[b]Each session includes cognitive behavioral therapy and cardiovascular health content tailored to the topic.

[c]Patient-Activated Learning System readings and videos for the next session topic are assigned for each session. Participants are also instructed to monitor their blood pressure, practice replacing negative thoughts with positive thoughts, and work on their individualized goals.

[d]Doula care is provided at each session with wellness check-ins, connections to resources, and screenings for suicidal ideation and intimate partner violence as needed.

[e]Doula care for session 5 includes a discussion of the participant's changing body and body image.

[f]BP: blood pressure.

Attention Control Arm

Participants in the attention control arm receive a variation of standard doula postpartum care. Participants are instructed in the hospital on how to measure and record their BP at home daily. They do not have daily contact with their doulas in the first 7 days post discharge. Following that, they begin the 12-session attention control sessions, delivered via phone or Zoom every 1-2 weeks (Table 2).

Table 2. Attention control sessions are delivered via 12 Zoom sessions.

Session	Topic
1	Birth experience and your body
2	Supporting mom or infant feeding support
3	Infant feeding support
4	Baby sleep
5	Human papillomavirus
6	Newborn care
7	Reproductive life cycle
8	Sudden infant death syndrome and smoking
9	Well-child care and immunizations
10	Maternal health
11	Review past session topics as desired
12	Final visit and long-term support plan

Doula Supervision and Assessment

Intervention doulas have weekly supervision sessions with a study psychologist and the LHMoms research coordinator. These supervision sessions happen throughout the 24 months of the doulas' participation at their respective RCT sites. These sessions help ensure that each doula is delivering the LHMoms intervention as intended. Doulas can ask this study's psychologist or psychiatrist questions about specific participant cases, LHMoms intervention delivery, or other issues that may

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arise. Additionally, each month, 2 randomly sampled LHMoms sessions are audio-recorded for each doula, with the consent of the doula and participant. These sessions are evaluated using the Doula Fidelity Checklist and are evaluated by this study's psychologist for additional factors: nonverbal and verbal communication, rapport, problem-solving, and more.

Attention control doulas also engage in weekly supervision sessions with the LHMoms study coordinator as well as leadership from the respective community organization, CWHA or NMPP, offering opportunities to ask questions about specific participant cases and other issues that may arise.

Data Collection

Data are collected from doulas as well as participants. Doulas complete a pretrial implementation survey collecting information on their background and demographics, doula training, and their views on the NYC postpartum care landscape, as well as the feasibility and acceptability of the intervention.

For all trial participants, data are collected at baseline in the hospital predischarge, 2 weeks post discharge, 6 weeks post discharge, 3 months post discharge, and 6 months post discharge. The LHMoms study team collects data via web-based surveys on the primary outcomes of PPDS, using the Edinburgh Postnatal Depression Scale (EPDS) as a proxy for the incidence of symptoms of PPD (with scores >9 indicating the presence of PPDSs), and the "heart score," an evaluation of LE8 provided by the AHA. Figure 3 below illustrates the key areas of LE8.

Figure 3. Life's Essential 8 includes key areas for improving and maintaining cardiovascular health as defined by the American Heart Association.

Quality of life is measured via short (15-minute) and long (30-minute) web-based surveys. Long web-based surveys, administered at baseline, 6 weeks, and 6 months, take 30 minutes to complete and assess psychosocial status and other health behaviors using the EPDS, General Anxiety Disorder Assessment, Pittsburgh Sleep Quality Index, Perceived Stress Scale, Brief Resilience Scale, Scale of Perceived Social Support, Posttraumatic Stress Disorder Checklist for *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]), and smoking status. Short web-based surveys, administered at 2 weeks and 3 months post discharge, take 15 minutes to complete and assess psychosocial status using EPDS, General Anxiety Disorder Assessment, and Pittsburgh Sleep Quality Index (Table 3).

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Table 3. Data are collected via short and long REDCap[a] surveys, and in-person measurements are taken by this study's team[b-e].

Data collection instruments and measures	Long web-based survey, 30-min[b]	Short web-based survey, 15-min[c]	In-person measurements[d]
EPDS[e]	✓	✓	
GAD-7[f]	✓	✓	
AHA[g] My Life Check (Heart Score)[h]	✓		
PCL-5[i]	✓		
PSS-10[j]	✓		
PSQI[k]	✓	✓	
BRS[l]	✓		
Perceived social support	✓		
Hemoglobin A_{1c}[m]			✓
Cholesterol			✓
Weight and height			✓
Blood pressure			✓
Smoking status	✓		

[a]REDCap: Research Electronic Data Capture.
[b]Baseline, 6 weeks, and 6 months.
[c]2 weeks and 3 months.
[d]Baseline, 3 months, and 6 months.
[e]EPDS: Edinburgh Postnatal Depression Scale.
[f]GAD-7: General Anxiety Disorder Assessment.
[g]AHA: American Heart Association.
[h]My Life Check is only completed in baseline and 6–month-long surveys.
[i]PCL-5: Posttraumatic Stress Disorder Checklist for DSM-5 (Diagnostic and Statistical Manual of Mental Disorders [Fifth Edition]).
[j]PSS-10: Perceived Stress Scale.
[k]PSQI: Pittsburgh Sleep Quality Index.
[l]BRS: Brief Resilience Scale.
[m]Hemoglobin A_{1c}: glycated hemoglobin.

In addition to web-based survey administration, study staff collect physiological data at in-person study visits. Staff perform point-of-care testing for total and high-density lipoprotein cholesterol and hemoglobin A_{1c}, and measure BP, height, and weight at baseline, 3 months, and 6 months. Point-of-care testing occurs in the hospital shortly after enrollment and at a community location at 3 and 6 months for the convenience of participants.

Health care use is assessed via questions presented to all participants at 3- and 6-month post discharge regarding attendance of obstetric and primary care provider visits. This study's team also performs an EHR review of clinical visits and encounters to understand contact with the individual health systems. A Client Satisfaction Questionnaire-8 (CSQ-8) is administered at 6 months. All data are collected in a secure REDCap database housed at the main study site. The RCT schema is shown below in Figure 4.

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Figure 4. The RCT schema is shown below, beginning with participant enrollment in the hospital, postdelivery, and before discharge, and continuing until 6 months post discharge. BP: blood pressure; CBT: cognitive behavioral therapy; CSQ-8: Client Satisfaction Questionnaire-8; CV: cardiovascular; FG: focus group ; HBPM: home blood pressure monitoring; KII: key informant interview; LHMoms: Living Healthy for Moms; PALS: Patient-Activated Learning System; PD: post discharge; PP: postpartum; RCT: randomized controlled trial; REDCap: Research Electronic Data Capture.

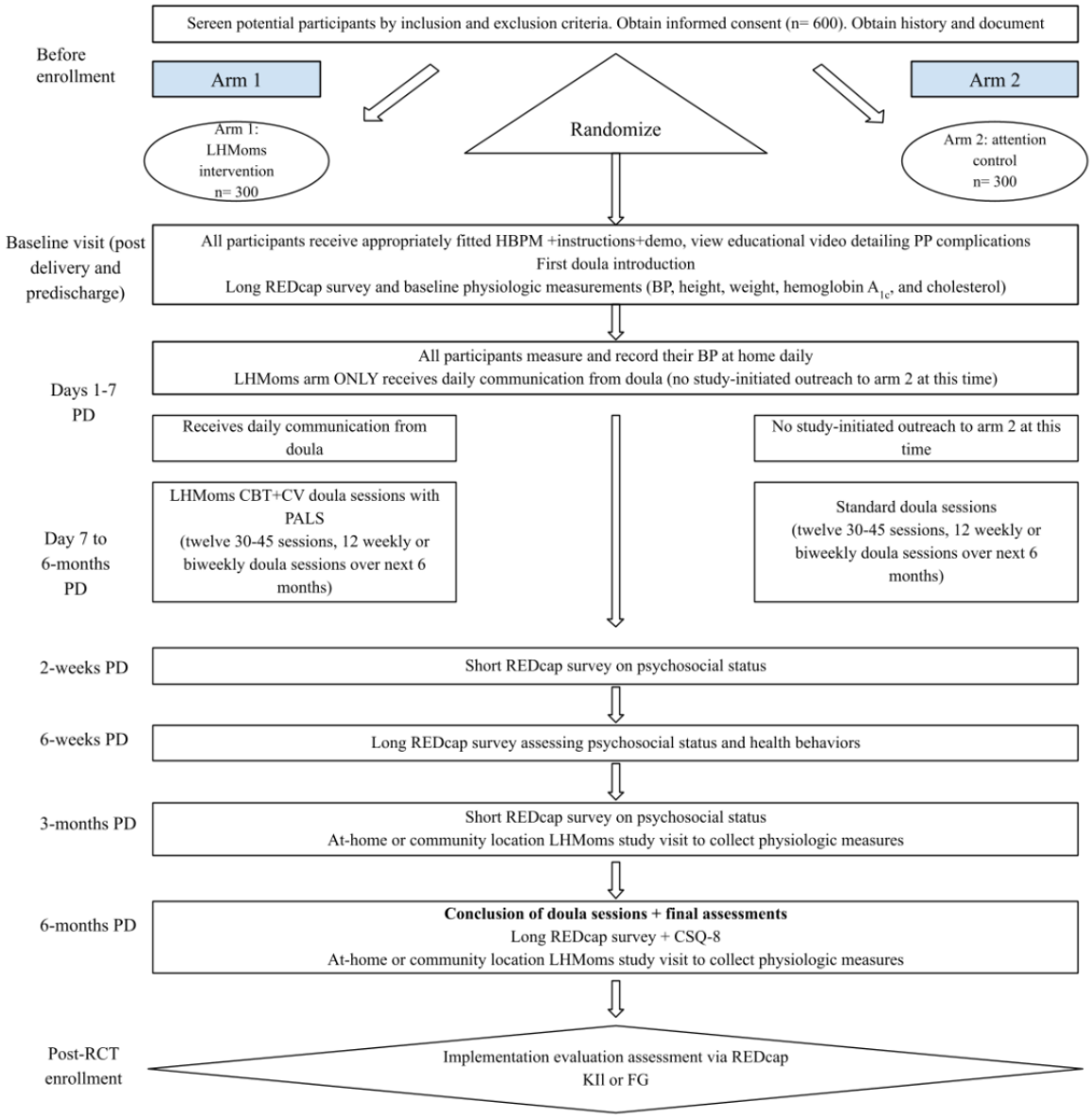

Statistical Analysis: Analysis of the Dual Primary End Points

Preliminary statistical analysis examines baseline characteristics between study arms (LHMoms intervention vs attention control) to verify that the randomization generated comparable groups. Categorical variables are summarized as frequencies and proportions. Statistical significance is set at $P<.05$ and tested using chi-square or Fisher Exact tests for variables with low expected frequencies (eg, <5). Continuous variables are described as mean, SD, median, and IQR. Statistical significance is tested using a 2-tailed Student *t* test or Wilcoxon Rank Sum for variables with unequal variance or skewed distributions.

The primary outcome of PPDS is operationalized as the presence or absence of PPD symptoms as indexed by an EPDS score greater than or equal to 9 (EPDS >9) at 6 months post partum (Table 4). Linear mixed models, designed to account for the nonindependence of observations within the same person that is inherent to repeated measures designs, are used to estimate the mean EDPS score with 95% CIs and make group comparisons between the LHMoms intervention and attention control at baseline and 6 months post partum. This approach enables an intention-to-treat analysis whereby all participants randomized into the trial are included in the primary analysis regardless of the number of sessions completed due to the flexibility of linear mixed models to handle the presence of missing data. Baseline characteristics associated with PPDS in univariate regression models (eg, parity) or group imbalance detected at baseline are included in linear mixed models as relevant covariates.

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Table 4. Primary and secondary outcomes measured in REDCap[a] surveys assess psychosocial status and other health behaviors, as well as health care use and patient satisfaction.

Primary or secondary	Name of outcome	Specific measure to be used
Primary	PPDS[b]	EPDS[c]≥9
Primary	Cardiovascular health	LE8[d] (continuous measure)
Secondary	Anxiety	GAD-7[e]
Secondary	Posttraumatic stress disorder	PCL-5[f]
Secondary	Perceived stress	PSS-10[g]
Secondary	Sleep	PSQI[h]
Secondary	Resilience	BRS[i]
Secondary	Social support	Perceived Social Support Scale
Secondary	Health care use	Contact at 7 days; 6 weeks postpartum visit attendance
Secondary	Satisfaction with postpartum care	CSQ-8[j]
Secondary	Implementation process	Focus groups, surveys, and interviews

[a]REDCap: Research Electronic Data Capture.
[b]PPDS: postpartum depressive symptom.
[c]EPDS: Edinburgh Postnatal Depression Scale.
[d]LE8: Life's Essential 8.
[e]GAD-7: General Anxiety Disorder Assessment.
[f]PCL-5: Posttraumatic Stress Disorder Checklist for DSM-5 (Diagnostic and Statistical Manual of Mental Disorders [Fifth Edition]).
[g]PSS-10: Perceived Stress Scale.
[h]PSQI: Pittsburgh Sleep Quality Index.
[i]BRS: Brief Resilience Scale.
[j]CSQ-8: Client Satisfaction Questionnaire-8.

To determine changes in the second primary outcome of cardiovascular health, we similarly compare LE8 scores from baseline to 6 months with a linear mixed model approach as previously described. Following published guidelines, the LE8 metric is summed into a 1-100 score [17,45]. In addition to comparisons of mean scores at baseline and 6 months post partum, changes in group mean scores across this period are compared (ie, the interaction between treatment and time, eg, heart health score from baseline to 6 months post partum in the intervention vs attention control participants). Components of the LE8 score include diet, physical activity, tobacco use, sleep, weight, cholesterol, blood glucose, and BP—each of the 8 elements is scored separately, and a summary score is created. An 80 or higher on the LE8 metric is considered ideal, with 50-79 being intermediate, less than 50 meaning poor, with a range of 0 (poor) to 100 (ideal). Prior work shows a 10-point change is considered clinically meaningful [46].

For both primary end points, given the longitudinal nature of the intervention, dose is an important effect for exploration. Additionally, we model a site (ie, hospital) effect as a fixed main effect and explore a site by treatment interaction (eg, given the potential for personnel [ie, doula] differences across sites, there is potential for a site-level difference in treatment response).

Sample Size Determination for Primary End Points

The EPDS scores from baseline to 6 months are used to analyze PPDS in LHMoms and control arms. While we considered PPDS and LE8 as dual primary end points, we chose 1 outcome to base our sample size on, which was PPDSs as defined by an EPDS score >9. This score was specifically chosen because it is used as the screening cutoff to refer for clinical evaluation in our hospital system, as it represents the possible presence of depressive or anxiety symptoms. The rate of EPDS >9 ranges from about 30% to 40% depending on other characteristics of the clinics (we selected 33.5% as the lower tertile of this observed range for our nonintervention group in the power calculation). We project we will observe a reduction in the PPDS proportion from 33.5% in the control arm to 23% in the intervention arm. This yields a minimum detectable difference of 31.5% lower incidence of PPDS in the LHMoms intervention arm compared to the attention control arm at 6 months. Our minimum detectable difference is calculated with a sample size of approximately 450 individuals (225 per study arm), assuming a 1:1 randomization, a design effect of 1.5 to account for variance among sites and doulas, a power of .90, a 2-sided significance level of 0.05, and a 20%-25% attrition. Our recruitment projection is for a sample of 600, 300 per arm; however, we have conservatively built in a 25% attrition rate for the longitudinal study (thus powering from a 450 analytic sample), although in past studies we have achieved 80%-85%

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retention in studies with a longer 1-year observation period [47-50].

Analysis of Secondary End Points

The secondary end points include attendance at obstetric postpartum visits, linkage to primary care, and patient satisfaction (Table 4). The secondary end points are assessed through questionnaires at 3- and 6-month post discharge. The questions assess attendance of obstetric or primary care visits and an EHR review of clinical visits by this study's team.

Participant satisfaction scores are measured using the CSQ-8 survey administered at 6 months post discharge as part of the long REDCap survey. The CSQ-8 survey consists of 8 questions, each weighing 4 points respectively; the survey consists of a range of responses, with 1 being "this does not apply to me" and 4 being "applies to me" [51]. Scores for the CSQ-8 survey can fall between 8 and 32, with higher scores reflecting greater satisfaction experienced by the participant with the care provided. For the CSQ-8 survey, scores 8-13 indicate poor satisfaction, 14-19 represent fair satisfaction, 20-25 mean good satisfaction, and 26-32 indicate excellent satisfaction. For our study, a 4-point difference on the CSQ-8 survey is defined as "clinically meaningful," assuming an SD of 6 points [51]. No existing literature or research has a consensus on what point difference on the CSQ-8 survey can be considered "meaningful." This is likely due to the CSQ-8 survey not being uniform and being applied in various settings. The estimated average for the CSQ-8 score for the control group is 13. This is due to the low satisfaction with care in the population that LHMoms is serving.

Analysis of Tertiary End Points

The tertiary end points for this study evaluate the implementation outcomes and the process of implementing the LHMoms intervention. Tertiary end points evaluate the type 1 hybrid effectiveness-implementation trial using triangulated mixed methods data from interviews and surveys. Tertiary end points investigate the barriers to adopting the LHMoms program, doula competence and training, and strategies for implementation. Implementation strategies include RE-AIM and CFIR via EHR review and interviews or focus groups with doulas, clinical providers, hospital providers, and birthing individuals. CFIR consists of 5 domains—innovation, outer setting, inner setting, individuals, and implementation process (Table 5). CFIR is the "why," as it helps guide the assessment of barriers and facilitators in the LHMoms implementation [52]. RE-AIM encompasses the "who, what, where, how, and when" as it examines implementing evidence-based interventions in real-world settings and how that implementation can be approved or adopted better (Table 6) [53].

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Table 5. CFIR[a] measures are applied to the LHMoms[b] implementation evaluation.

CFIR construct	Example interview item	Example survey scale or item
Innovation		
Relative advantage	What are the advantages of using LHMoms versus usual care? Versus other doula-based programs?	How essential is LHMoms to high-quality postpartum care? (Likert scale)
Adaptability	How hard will it be to adapt LHMoms to your setting?	Adapted from previously used and validated scale items regarding relative advantage, complexity, cost, evidence, and trialability (Likert scale)
Complexity	How hard will it be to implement LHMoms in your setting?	Adapted from previously used and validated scale items regarding relative advantage, complexity, cost, evidence, and trialability (Likert scale)
Outer setting		
Local attitudes	How likely is this hospital to use LHMoms?	Level of enthusiasm at this hospital for this program (Likert scale)
Partnership and connections	Do you have sufficient partnerships and connections to conduct LHMoms?	Level of existing partnerships (5-point Likert scale from “none” to “a lot”)
Financing	Is there hospital-level funding for community programs?	Funding is a barrier for community programs (yes or no); ORC[c] 4-item resources subscale
Inner setting		
Relational connections	Are relationships with community partners well established enough to implement LHMoms?	I work with community doula organizations (5-point Likert scale from “none” to “a lot”)
Communications	How hard will it be to implement communication between care providers or a hospital system and LHMoms?	Level of communication with organizations outside the hospital (5-point Likert scale from “easy” to “extremely difficult”)
Tension for change	Do you think the current postpartum care system works well?	Current postpartum care is: 5-point Likert scale from “extremely inadequate” to “extremely high quality, no need for change”; ORC
Relative priority	How important is fixing postpartum care compared to other needs?	Compared to other priorities, the importance of fixing postpartum care is: 5-point Likert scale from “not very important” to “the highest priority”
Individuals		
High-level leaders	Is hospital leadership likely to be enthusiastic about the new program?	How likely are hospital leaders to embrace this program? 5-point Likert ORC 4-item leadership culture subscale
Innovation deliverers	Will doulas embrace the new roles embedded within LHMoms?	How likely is it that doulas will embrace the enhanced roles required by LHMoms? 5-point Likert; ORC 4-item staff culture subscale
Innovation recipients	Will patients such as LHMoms?	How likely is it that patients will find LHMoms acceptable? 5-point Likert scale
Implementation process		
Teaming	Will it be challenging to form a team with community partners and hospital players?	How challenging will it be to form a team with community partners and hospital players? 5-point Likert scale from “not very” to “very”
Tailoring	Will it be hard to find strategies to fit our context?	How difficult will it be to choose strategies to fit our context? 5-point Likert scale
Adapting	Will it be hard to adapt LHMoms for your setting?	How difficult will it be to adapt LHMoms for this setting? 5-point Likert scale

[a]CFIR: Consolidated Framework for Implementation Research.

[b]LHMoms: Living Healthy for Moms.

[c]ORC: Organizational Readiness to Change.

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Table 6. LHMoms[a] implementation measures are guided by RE-AIM[b].

RE-AIM construct	Description of construct	Outcomes	Phase
Reach	Who: what patients are intended to benefit, and who actually participates or is exposed to LHMoms?	• Percent of patients approached who agree to participate • Percent of participants who finish the program	Implementation

Effectiveness	What are the most important benefits you were trying to achieve, and what is the likelihood of negative outcomes?	• Immediate postpartum outcomes: percentage of participants with indicated health care visit post partum
		• Longer-term outcomes:
		  • Percentage of participants in each arm with PPDS[c]
		  • Percentage of change in the number of LE8[d] scores for participants in each arm
		  • Difference between arms in stress, resilience, and social support
			Implementation and sustainment

Adoption	Where was LHMoms applied and by whom?	• Number of doulas trained in LHMoms	Implementation
Implementation	How consistently was the program delivered, how was it adapted, how much did it cost, and why did the results come about?	• Competency in LHMoms: number of trial sessions to be competent • Treatment fidelity: mean observation score from a representative sample of audio-recorded sessions • Barriers or facilitators: CFIR[e] constructs	Preparation or implementation
Maintenance	When did LHMoms become operational; how long was it sustained; how long were individual results sustained?	• Continued use of LHMoms: percentage of doulas who indicate they will continue to use LHMoms; percentage of intervention doulas who train other doulas • Barriers or facilitators: CFIR constructs	Sustainment and ecologically valid sustainment

[a]LHMoms: Living Healthy for Moms.

[b]RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance.

[c]PPDS: postpartum depressive symptom.

[d]LE8: Life's Essential 8.

[e]CFIR: Consolidated Framework for Implementation Research.

Ethical Considerations

Institutional Approval

This study was approved and reviewed by the Institutional Review Board (IRB) of Columbia University as the single IRB #AAAV1436. Weill Cornell Medicine and the individual hospital sites will rely on Columbia. This trial is registered on ClinicalTrials.gov (ID NCT06666400).

Consent Procedures

LHMoms study team members obtain written informed consent according to the International Council for Harmonisation, Good Clinical Practice, and local regulations. Oral explanations and written consent forms are available in English and will be available in Spanish and Haitian Creole. These consent procedures are IRB-approved and in compliance with the HIPAA (Health Insurance Portability and Accountability Act). Consent is documented via electronic signature on the IRB-approved REDCap consent form. Consent complies with Department of Health and Human Services regulations and describes the following principles of this study: purpose of this study, research procedures, foreseeable risks, benefits, alternative procedures, record and data storage details, compensation, information about who to contact with questions, and participation is always voluntary. Study staff obtaining informed consent acknowledge the possibility of a loss of confidentiality or privacy as a risk of study participation. Staff will assure participants that every effort will be made to maintain the confidentiality of their identity and data, as consent highlights deidentification of data and secure storage of deidentified data within a password-protected database or locked file cabinet only accessible to authorized staff. Compensation is explicitly outlined within the consent form, stating "all participants will receive compensation (in the form of *ClinCards*, a maximum of $200 compensation: $50 for the baseline visit, $35 for the first full data survey at 6 weeks, $20 for the shorter surveys completed at 2 weeks and 3 months, and $75 for the final survey at 6 months)." The currency is in US dollars.

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Care and Referrals

Participants are referred to appropriate treatment if they exhibit any symptoms of extreme psychological distress. For reference, if participants show signs of active suicidal ideation (including intent and plan), they are instructed to go to the emergency department and obtain immediate medical evaluation. If the participant cannot go to the emergency department, the doulas and study team members assist in calling 911. There are also protocols in place for participants reporting intimate partner violence and abuse, as well as urgent mental and physical issues. Participants are given contact numbers for clinical emergencies; these numbers are accessible 24/7. Participants are also referred to clinical and counseling resources and emergency care, as well as community-based resources (such as housing, food, and resources for intimate partner violence), as needed. Participants can access these resources through a link in the online surveys, and once accessed, principal investigators and coinvestigators follow up to ensure care is received correctly.

BP is monitored closely throughout RCT participation by the LHMoms study team and doulas. Specifically, the LHMoms BP safety protocol follows ACOG guidelines throughout the critical 7-day period and within the first 12 weeks postdelivery, and AHA guidelines thereafter. Participants are instructed to contact their obstetric provider, if within the first 12 weeks postdelivery, or their primary care provider, if more than 12 weeks postdelivery, for any mild or elevated range BP readings. Participants with severe or hypertensive crisis range BP readings with or without hypertensive symptoms are instructed to present to the emergency department immediately or call 911.

The LHMoms study team also monitors hemoglobin A_{1c} and lipids point-of-care testing results collected for research. In the event of an abnormal result, this study's team instructs the participant to contact their primary care and obstetric providers. If baseline results are abnormal while the participant is still in the hospital, this study's team also immediately alerts their hospital postpartum care team of their results.

The LHMoms study team and doulas provide any further assistance needed to connect participants to their care providers.

Results

Data collection for participants from each of the 3 recruitment sites will be concluded by November 30, 2027, February 29, 2028, and August 31, 2029, respectively, for Brooklyn, Queens, and upper Manhattan. Thus, after completion of follow-up study activities for upper Manhattan participants, all data for the total expected 600 participants will be collected by the end of the grant year 6, August 31, 2029. The final grant year 7, from September 1, 2029, to August 31, 2030, will be designated for completion of data analysis. Data will be analyzed on an intention-to-treat basis by study team members blinded to participant conditions.

Discussion

Summary and Conclusions

This hybrid type 1 effectiveness- implementation RCT tests a novel nonspecialist intervention to prevent MH and cardiovascular health complications of childbirth. Our design is rigorous—we test the intervention against an attention control and measure numerous secondary outcomes having to do with health care use.

We hypothesize that, compared to attention control participants at 6 months post discharge, intervention arm participants will have at least 31.5% lower incidence of PPDS (score >9 on EPDS), and at least 1-point greater improvement in cardiovascular health using the LE8 score. We also expect that participants randomized to the intervention arm will experience better quality of life, reporting lower perceived stress and substance use and higher rates of resilience and perceived social support. Regarding health care use and satisfaction, we anticipate that more intervention than control individuals will have an indicated health care provider contact within the first 7 days post discharge or attend 6-week postpartum visits. We also hypothesize that intervention participants will report greater patient satisfaction with postpartum care, with higher scores on the CSQ-8 survey than control participants. We have culturally adapted an existing intervention to our local population in NYC, and will also be tracking specifics of implementation that will allow us to adapt the intervention further for other contexts. We will obtain important data from participants and key players in the implementation that will support and inform on the long-term sustainability and scalability of the LHMoms program.

Dissemination

The LHMoms intervention is designed to reduce PPDS and cardiovascular complications during the postpartum period in pregnancy. Additional findings from the LHMoms intervention will help us understand how the LHMoms intervention may improve satisfaction with care within vulnerable populations. We expect that our findings will contribute to the literature on the use of nonspecialist interventions in low-resourced settings, as well as to the literature on doula care in the postpartum period.

Acknowledgments

Educational materials were created by MedExplain Health. We plan to resume recruitment at our Brooklyn site by December 2025 and complete the RCT and analysis by August 31, 2030.

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Obstetrics and Gynecology at Weill Cornell Medicine to complete the enrollment of participants, and all new recruitment ceased at that time. Funding from the National Institutes of Health was subsequently reinstated, effective July 29, 2025.

Data Availability

As part of the National Institutes of Health Maternal Health Research Centers of Excellence Initiative, data will be shared with existing data repositories such as the National Institute of Child Health and Human Development Data and Specimen Hub. Before sharing, data science expertise will be used to maximize data comparability and facilitate data harmonization. The Innovation Hub will manage a secure, cloud-based data infrastructure and role-based access control for Research Center investigators in the Maternal Health Research Centers of Excellence initiative to access sensitive or deidentified data and develop documentation to ensure all datasets can be appropriately used by all Research Centers and the Implementation Science Hub. A data structure will be developed that will make the datasets accessible for controlled public use at the end of the program.

Authors' Contributions

LMO, HL, KSH, MD-M, MS, UR, and VSC conceptualized, visualized, and handled the resources of this study. They also acquired funding for this project. KV curated the data, formally analyzed it, and worked on its software. LMO and VSC investigated, with the help of JMF, KK, and LRR. LMO, HL, KSH, KV, MD-M, MS, UR, and VSC worked on the methodology. JMF and LRR administrated this project with KK as support. LMO and VSC led the supervision with assistance from JMF, KSH, LRR, MD-M, MS, VSC, and UR. LMO, IB, and JMF wrote the original draft, with input from HL, KSH, KV, LRR, MD-M, MS, UR, and VSC. LMO, IB, and JMF reviewed and edited the writing with the aid of LRR, HL, KK, KSH, KV, MD-M, MS, UR, and VSC.

Conflicts of Interest

MedExplain Health, the nonprofit organization creating the educational content for the intervention of this study, was founded by Ariel Barasch, a family member of MS. MS receives no financial compensation from and holds no executive or managerial role with MedExplain Health. The other authors have no conflicts to report.

Multimedia Appendix 1
Peer review report by the ZRG1 CTH-F (71) - Center for Scientific Review Special Emphasis Panel - Maternal Health Research Centers of Excellence (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 255 KB - resprot_v14i1e76871_app1.pdf]

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Abbreviations

ACOG: American College of Obstetricians and Gynecologists
AHA: American Heart Association
BP: blood pressure
CBT: cognitive behavioral therapy
CFIR: Consolidated Framework for Implementation Research
CSQ-8: Client Satisfaction Questionnaire-8
CVD: cardiovascular disease
CWHA: Caribbean Women's Health Association
DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)
EHR: electronic health record
EPDS: Edinburgh Postnatal Depression Scale
GDM: gestational diabetes mellitus
hemoglobin A1c: glycated hemoglobin
HIPAA: Health Insurance Portability and Accountability Act
IRB: Institutional Review Board
LE8: Life's Essential 8
LHMoms: Living Healthy for Moms
MH: mental health
MI: motivational interviewing
NMPP: Northern Manhattan Perinatal Partnership
NYC: New York City
NYP: NewYork-Presbyterian
PPD: postpartum depression
PPDS: postpartum depressive symptom
RCT: randomized controlled trial
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
REDCap: Research Electronic Data Capture
T2DM: type 2 diabetes mellitus
THP: Thinking Healthy Programme

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Protocol

Knowledge and Recommendations of Stakeholders Regarding Ethical Oversight of Data Science Health Research: Protocol for a Qualitative Study

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Abstract

Background: Data science health research (DSHR) uses novel computational methods and high-performance computing to analyze big data from conventional and nonconventional health and related sources to generate novel insights and communications. DSHR creates assets but generates ethical, legal, and social challenges. Key gaps in current ethical oversight of DSHR include blurred boundaries between research and nonresearch data use, inadequate protection of data donors, power imbalances that risk extractive research practices, algorithmic biases, and regulatory inadequacies. Nigeria, a typical low- and middle-income country with rapidly expanding DSHR, exemplifies this environment and concerns.

Objective: This study will elicit answers from Nigerian DSHR stakeholders and contribute to understanding the ethical, legal, and social implications (ELSI) of DSHR and developing novel ethical oversight frameworks.

Methods: Between October 2024 and January 2025, we conducted Key Informant Interviews with 65 stakeholders of 87 individuals. The Key Informant Interview guide comprised 11 construct-based question domains addressing awareness of policies and laws, ethical oversight processes, ELSI considerations in policy development, experiences addressing DSHR challenges, organizational and procedural frameworks, ideal oversight components, stakeholder roles, research impact on ethics and policy, regulatory influences on research practices, equity-enhancing policies, and balanced regulations. The interviews lasted 60-90 minutes and were transcribed. We analyzed the transcripts using a hybrid deductive-inductive approach. A priori codes derived from research objectives provided the analytical framework while allowing for the identification of emergent concepts. The iterative 3-level coding process involved initial code generation, evaluation, and refinement, with codes grouped into thematic families and semantic networks representing hierarchical concept relationships. Query tools and Boolean operators were used to interrogate the codes to extract findings.

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Results: Of 87 invited individuals, 22 (25%) were unable to participate. The 65 participants (age: mean 47.9, SD 7.9 years; 50/65, 77% male) included data science health researchers (25/65, 39%), biomedical researchers (17/65, 26%), Health Research Ethics Committee members (12/65, 19%), and policymakers (11/65, 17%). Most held doctoral degrees (38/65, 57%) and were affiliated with academic institutions (45/65, 69%) and government organizations (26/65, 40%), and had received general research ethics training (50/65, 77%). However, only 12% (8/65) had received predominantly short-duration ethics-specific DSHR training, while 92% (60/65) acknowledged the need for specialized DSHR ethics education. As of January 2025, the interview transcripts have been generated, with checking completed, with qualitative analysis scheduled for completion by March 2025 and completion of primary manuscripts by the end of 2025.

Conclusions: This study will generate stakeholder-informed recommendations for ethical oversight of DSHR that address issues relating to broad consent, ELSI, data ownership, benefit-sharing, and donor protection in resource-limited settings. Our findings will inform global DSHR and research ethics communities on the development of contextually appropriate oversight mechanisms that promote equitable partnerships, co-ownership, and tiered data governance.

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KEYWORDS

data science; health research; ethics; ethical oversight; Nigeria; low- and middle-income countries (LMICs); qualitative research; stakeholder engagement

Introduction

Data science health research (DSHR) is a novel and rapidly growing field derived from several disciplines that coalesced around the use of novel computational methods and high-performance computing to collect, store, manipulate, and analyze huge amounts of health and related data to generate results or reports and novel insights [1]. The sources and types of data used in data science research come from the full spectrum of human activities [2]. They include conventional data from national and institutional health records, various surveillance data, regular systematic and opportunistic surveys, and data from research projects [2-4]. The nonconventional sources of data for data science research include social media, geospatial data, and wearables [5-7]. Linkage of these data sources results in deeper and richer datasets, which, when combined with advanced computational methods such as advanced deep learning, machine learning, and artificial intelligence (AI), create highly valuable assets for data science research, innovation, and discovery [8,9]. The generation, collection, and analyses of these conventional and nonconventional data for health research and discovery poses considerable ethical, legal, and social implications (ELSIs) challenges that require urgent response by research ethicists, regulatory agencies, and policymakers, particularly in low- and middle-income countries (LMICs) such as Nigeria.

Research generating enormous amounts of data that uses data science methods is increasing in LMICs, including Nigeria. In Africa, programs such as the Human Heredity and Health in Africa, Health Education Partnership Initiative, and President's Emergency Plan for AIDS Relief laid the foundation for DSHR by generating data and developing guidance for research ethics and data sharing based on the classical principles of research ethics. However, DSHR poses unique challenges to these classical ethical principles [10].

DSHR occurs in a pervasive data environment where digital footprints from nonresearch activities (eg, social media and wearables) are often repurposed for health research, sometimes without the awareness or consent of the data participants [11,12]. This blurs the boundaries between traditional health research data and other data types, complicating ethical oversight, particularly when consent modalities for primary data collection are unclear or inadequate [13,14]. Secondary data use and analysis are pervasive in DSHR, and some of these data may have been collected in nonresearch contexts or under outdated consent frameworks. This raises critical questions about confidentiality, data ownership, representational veracity, and privacy. While anonymization and deidentification are standard safeguards in regular research projects, advanced data science methods can reidentify participants through linkage of disparate datasets, thereby undermining assumptions of confidentiality [15-17]. Furthermore, DSHR's reliance on heterogeneous datasets—collected across diverse contexts, jurisdictions, and timelines—risks accumulating biases and ambiguities, which may distort interpretations and harm communities if results lack contextual fidelity [18,19].

Another issue of concern, particularly in LMICs, is the power imbalance on account of the "inverse care law" and digital data poverty arising from the limited availability of data. There are also challenges with extractive data practices where international researchers or entities leverage infrastructural disparities to conduct "helicopter research" without equitable and empowered inclusion or with token inclusion of local researchers or communities [20,21]. This "predatory inclusion" practice perpetuates data colonization, where international researchers or entities exploit LMICs' data for profit without fair benefit-sharing, thereby eroding public trust in research in those countries [22,23]. Furthermore, new biases such as algorithmic bias due to a lack of diversity in the data used to build models and among data science researchers further compound these challenges [24,25]. These kinds of biases perpetuate health inequities when the outcome of DSHR is deployed for clinical or public health use without rigorous scientific, methodological, and ethical scrutiny.

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In Nigeria, a typical LMIC, the National Code for Health Research Ethics mandates ethics committee review of all research projects, including DSHR, even when secondary data is used [26]. However, there are regulatory gaps with cross-border DSHR projects because the mechanisms for harmonizing ethics reviews across jurisdictions remain underdeveloped [27]. Additionally, pressures from the involvement of commercial entities create new challenges for the traditional ethics review processes, which lack the resources and ability to enforce ethical oversight of research conducted by international, multinational, extra-territorial individuals or corporations and prevent profit-driven data exploitation [22].

Several characteristics of the LMICs environment—poor democratic governance, weak legal infrastructure, high rates of poverty, low levels of education, and poor information technology penetration—lead to limited ability to protect the interests and guarantee of benefits of research to local researchers, research participants, and local communities. This raises significant concerns about the validity and thoroughness of ethical oversight of DSHR in these environments [28,29]. Lack of global rules and enforcement mechanisms remains a major concern that is particularly relevant in DSHR, given the transnational nature of the generation, collection, storage, and manipulation of data across national borders. Most LMICs cannot afford local data centers, given their high cost; hence, their data must be "exported" if they are to contribute to the "big data" used in some DSHR projects.

The ethical challenges caused by DSHR, therefore, demand novel ethical frameworks to address the blurred consent boundaries, reidentification risks, algorithmic biases, and the risk of commercial exploitation, while ensuring equitable representation and benefit-sharing for all populations [30,31]. To ensure this, we are conducting a qualitative study that engages all stakeholders in DSHR with the intention of answering these research questions:

1. What is the current level of awareness and knowledge among stakeholders regarding policies, laws, and ethical frameworks governing DSHR in Nigeria?
2. How effectively do existing ethical oversight mechanisms address the unique ELSI of DSHR in the Nigerian context?
3. What are stakeholders' experiences with addressing ELSI challenges in DSHR, including issues of consent, privacy, data ownership, and algorithmic bias?
4. What components should constitute an ideal ethical oversight framework for DSHR in Nigeria, considering both international standards and local contexts?
5. How can Nigeria implement adequate ethical regulations while facilitating DSHR, international collaborations, and partnerships that prioritize health research goals and innovations?
6. What roles should various stakeholders, including researchers, patients, participants, communities, policymakers, and ethics committees, play in developing and implementing ethical oversight of DSHR?

The primary outcomes of interest in this study are:

1. Perspectives on broad consent mechanisms appropriate for DSHR contexts, particularly regarding secondary data use, future research applications, and the complexities of obtaining informed consent in pervasive digital data environments.
2. Comprehensive recommendations addressing the ELSIs of DSHR, including strategies for preventing algorithmic bias, protecting data privacy despite reidentification risks, ensuring equitable benefit-sharing, and addressing power imbalances in international research collaborations.
3. Guidance on data ownership structures, benefit-sharing arrangements with data donors and their communities, and protections for primary data donors from potential harms arising from big data analytics and algorithmic biases.

Historically, the development of ethical oversight lags novel research methodologies and technologies; nevertheless, we plan to implement a plan for the codevelopment of a novel ethical oversight framework for DSHR in Nigeria, a typical LMIC African country, that is built on the insights generated from this research [32-34]. The current study's outcome will also inform global ethical discourse on DSHR and the development of ethical oversight for DSHR in different parts of the world.

Methods

Theoretical Framework

We engage multiple theoretical frameworks for this study (Figure 1). This includes classical research ethics principles, ELSI framework, decolonial and postcolonial theory, and stakeholder engagement theory. The classical ethical theory rests on principles articulated in the Belmont report and expanded in subsequent writings [35-37]. This includes respect for persons, beneficence and nonmaleficence, and justice. The ELSI framework, which was originally developed for genomics, provides a systematic approach to identifying the broader societal implications of emerging technologies in research [38,39]. It encompasses ethical, legal, and social (ELS) dimensions. Our analyses embrace decolonial and postcolonial perspectives, which illuminate data colonialism, extractive research, epistemic justice, and structural power imbalances in research relationships [40,41]. Lastly, we use stakeholder engagement theory, which posits that meaningful participation of all parties with interests in or affected by research leads to more legitimate, acceptable, and effective outcomes. In this study, we integrate these theoretical frameworks into a mutually reinforcing approach that honors universal ethical principles while remaining contextually appropriate; addressing novel technological challenges while learning from established ethical precedents; confronting historical and ongoing power imbalances; and engaging all relevant stakeholders in cocreating solutions.

These theoretical frameworks directly informed our study design and implementation in (1) stakeholders' selection wherein we included distinct groups of stakeholders who contribute unique experiences and expertise, (2) the constructs that were used to organize the research questions, (3) analysis approach which uses deductive and inductive coding and allows for theory driven analyses, and (4) expected outcomes. The frameworks support the exploration of our study's questions, including knowledge and awareness of existing ethical frameworks and legal

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instruments, current ethical oversight, a novel ethical framework for DSHR, equity, and justice. The strengths of our frameworks include their comprehensive coverage of the ethics of DSHR, contextual sensitivity, practical applicability, and flexibility.

Figure 1. Study design and conceptual flow. DSHR: data science health research; ELSI: ethical, legal, and social implications; HREC: Health Research Ethics Committee; KOL: key opinion leader.

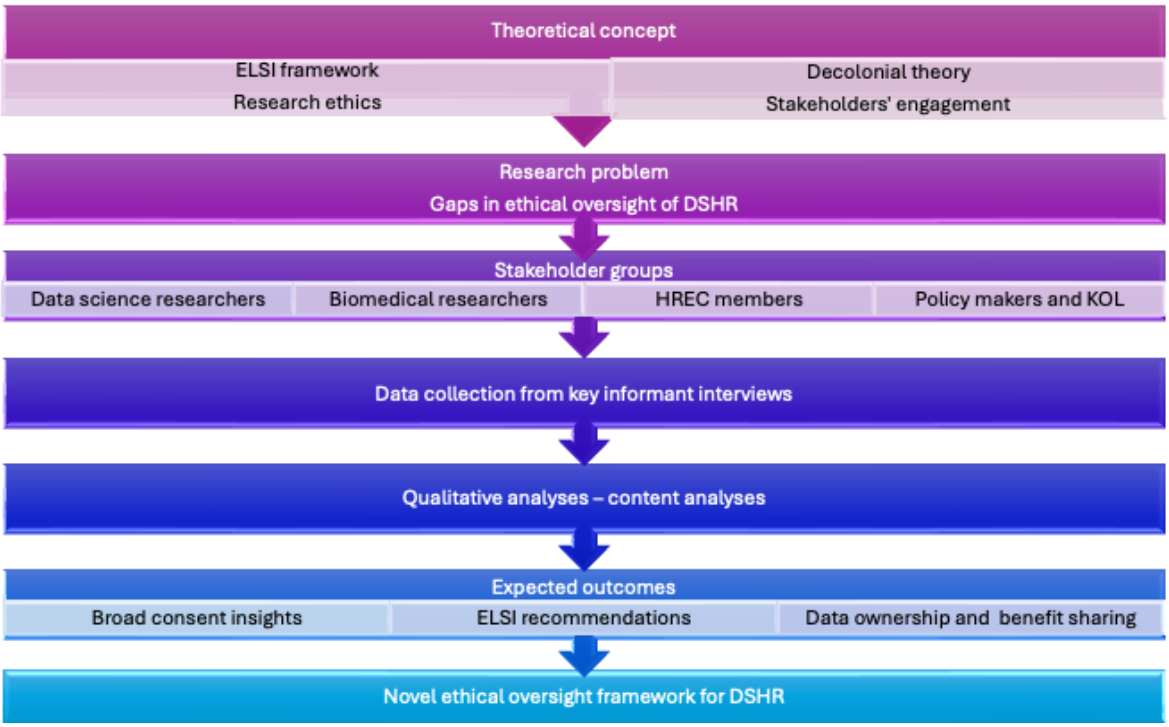

Study Design

We will use the Key Informant Interview (KII) qualitative research method for this study.

Setting

This study will be conducted in Nigeria, the most populous (237 million) and one of the largest economies in Africa, with a purchasing power parity gross domestic product of US $2.6 trillion in 2025 [42].

Participants

In this study, we will recruit individuals from 4 major stakeholder groups across Nigeria to participate in KII. These groups are:

1. Health researchers who are using data science research methods for their projects in Nigeria.
2. Members of Health Research Ethics Committees (HREC) that have reviewed DSHR proposals.
3. Data scientists who are conducting DSHR.
4. Policymakers, funders, and key opinion leaders (KOL) in DSHR in Nigeria.

We used lists of prime or subcontract awardees in the National Institutes of Health's Harnessing Data Science for Health Discovery and Innovation in Africa (DS-I Africa) program in Nigeria, obtained from the DS-I Africa Program Officers, to identify researchers involved in data science projects and members of the ethics committees in the institutions hosting DS-I Africa projects in Nigeria. Further, we searched databases such as PubMed, Scopus, Web of Science, etc, for researchers who have published papers on DSHR in Nigeria. We contacted officials of the Nigerian Ministries of Health, Justice, Communication, Science and Technology, and Education to identify policymakers responsible for health research and data science in the public sector in Nigeria. Given the active and successful private data science sector in Nigeria, we also contacted relevant trade organizations and invited their members to participate in this study. We identified other KOLs on data science, health, and research in Nigeria through publicly available information and invited them to participate in this study [38]. We used multiple strategies to invite participants, including phone calls, personal contacts, and emails.

Design of KII Guide

We developed a semistructured KII guide organized by constructs based on common perceptions and published literature on data science, health research, ethics, and protection of individuals whose data may be used in DSHR (Multimedia Appendix 1). The KII guides included the following questions:

1. Awareness and knowledge of policies and laws related to data science in Nigeria.
2. The ethical oversight of the design and implementation of research projects in Nigeria.
3. What and how the ELS issues associated with data science are considered in the development of institutional and national policies for ethical research in Nigeria.
4. Awareness and knowledge of the ELS issues related to DSHR in Nigeria.
5. Experience with addressing the ELS issues associated with data science research in Nigeria.

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6. Description of the processes and organizations relevant to the oversight of DSHR in Nigeria. What are the benefits, limits, and gaps in the policies and organizations?
7. The components of an ideal oversight framework and policies for DSHR.
8. The roles of researchers, patients, research participants, groups, and communities in the development of ethical oversight of DSHR.
9. The impact of DSHR on research ethics and policy in Nigeria and vice versa.
10. The roles of Nigerian laws in researchers' decisions about the processes and practices of data science research.
11. The policies that enhance equity and justice in the deployment of data science tools for health research across different socioeconomic groups in Nigeria.
12. How Nigeria can implement adequate regulations while facilitating collaborations and partnerships that prioritize health research goals and innovations in Nigeria.

We also collected demographic data and information on past training in research ethics and data science from the participants.

Sample Size, Data Collection, Management, and Analyses

We will interview 65 participants. Based on the principles for computing sample size for qualitative studies, data saturation is typically reached with 5 to 10 participants. So, we plan to recruit 5 to 10 participants in each stakeholders' category [28,29]. Though some participants may represent multiple categories of stakeholders, we will ensure a minimum of 5 interviewees per category, as shown in Table 1.

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Table 1. Categories and number of participants in each stakeholder group, Nigeria 2024.

Participants' categories	Participants, n
Age (years)	
<40	5
40-60	5
>60	5
Sex	
Male	5
Female	5
Others	5
Discipline	
Data science	5
Health	5
Biology	5
Computer science	5
GISs[a]	5
Research ethics	5
Policymaker	5
Others	5
Domain	
Commercial	5
NIH[b] and other agencies	5
Foundation-sponsored groups	5
Local government-funded groups	5
Private sector-funded groups	5
Consortia	5
Collaborations	5
Researchers involved in data science projects in Nigeria	5
Members of the ethics committees of institutions hosting DS-I Africa[c] projects in Nigeria	5
Officials of Ministries of Health, Justice, Communication, Science and Technology, and Education in Nigeria	5
Key stakeholders in the Nigerian data science private sector	5

[a]GIS: geographic information system.

[b]NIH: United States National Institutes of Health.

[c]DS-I Africa: Harnessing Data Science for Health Discovery and Innovation in Africa.

Data Collection

The KIIs would be conducted by a research associate assisted by a notetaker who would take notes and record participants' nonverbal cues, which would be used to supplement the audio recordings. Interviews would be conducted in person and virtually using zoom (Zoom Communications, Inc). Each interview would last 60 to 90 minutes, and we would use the KII guide to guide the interviews. All interviews will be recorded, and we will transcribe the recordings to generate transcripts. We will work with KII participants to clarify their comments and correct the information they provide as required. Before conducting the KIIs, participants would be provided with an information sheet outlining this study's objectives, confidentiality measures, and their rights as participants.

Qualitative Data Analyses

We will conduct content analysis using a combination of deductive and inductive processes with manual and computer-assisted data analyses using ATLAS.ti (version 7.5.2; ATLAS.ti Scientific Software Development GmbH) software. We will create a priori codes based on our research objective, as a general framework, while allowing for emergent concepts from the discussions. For each code, we will write a description

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in the code manager to provide contextual information. The coding would be an iterative process, with the first level of coding generating initial codes that would be evaluated before a second and third level of coding. We will group codes into families according to shared themes and create semantic networks representing hierarchical relationships between concepts after a review of the codes. We will analyze each code to identify emerging opinions and themes for the research objective. The reflective and thematic memos that we keep during the coding process would be used to provide contextual information. We will use query tools and Boolean operators to interrogate the codes and obtain the results that will be published using the COREQ-32 (Consolidated Criteria for Reporting Qualitative Research) [42]. We will use simple descriptive statistical analyses for the quantitative data associated with these qualitative data.

Ethical Considerations

This study was approved by the National Health Research Ethics Committee of Nigeria (NHREC/01/01/2007-24/12/2024D) and the Institutional Review Board of the University of Maryland, Baltimore (HP-00102012). It was conducted according to the guidelines in the Nigerian National Code for Health Research. Informed consent was obtained from all the participants whom we interviewed. Participants were compensated with US $2 for attending the interviews. All audio recordings and transcripts were deidentified and stored in password-protected computers.

Results

Reasons for Nonresponse Among Participants Invited for the KII

Some 25% (n=22) of the individuals who were invited were unable to participate in the KIIs. Table 2 shows the main reasons for the inability to participate. Most (13/22, 59%) did not respond to our invitation, 27% (6/22) declined to participate, while the remaining 14% (3/22) were unable to participate due to logistical or scheduling constraints, and bureaucratic delays. Among those who did not respond to our invitation to participate in this study, data science researchers were the largest group (5/13, 39%), followed by policymakers (3/13, 23%), HREC members (3/13, 23%), and biomedical researchers (2/13, 15%). Of the 6 participants who declined to take part in the KII, most (5/6, 83%) were data science health researchers, while the remaining 1 (1/6, 17%) person was a biomedical researcher. The 3 participants who were unable to participate due to scheduling difficulties and bureaucratic delays were 1 policymaker, 1 data science health researcher, and 1 biomedical researcher.

Table 2. Response rate of participants invited for study, Nigeria 2024.

Reasons	Values, n (%)
Nonresponse	13 (100)
Policymaker	3 (23)
Data science health researcher	5 (39)
Health Research Ethics Committee	3 (23)
Health data scientist	2 (15)
Declined	6 (100)
Data science health researcher	5 (83)
Health data scientist	1 (17)
Others	3 (100)
Policymaker	1 (33)
Data science health researcher	1 (33)
Health data scientist	1 (33)

Analysis of Quantitative Data

Table 3 shows the baseline characteristics of the 65 stakeholders who participated in this study. Their mean age was 47.9 (SD 7.9) years. Most (50/65, 77%) were male, while 23% (15/65) were female. More than half (38/65, 57%) of the participants had doctoral degrees, 25% (16/65) had master's degrees, and 19% (11/65) had only a first degree. Some 39% (25/65) of the participants identified as data science health researchers, 26% (17/65) were biomedical researchers, 19% (12/65) were members of HREC, and 17% (11/65) were policymakers. Their affiliations were mainly with academia (45/65, 69%), government organizations (26/65, 40%), nongovernmental organizations (7/65, 11%), commercial entities (2/65, 3%), and teaching hospitals (18/65, 28%). Most (50/65, 77%) reported having received training in research ethics. Of these, 59% (38/65) had completed short-term training, 12% (8/65) long-term training, and 6% (4/65) medium-duration training. Most of the participants (57/65, 88%) had not received any training in the ethics of DSHR, while 12% (8/65) had received such training. Among those who had received ethics of DSHR training, 88% (7/8) completed short-duration training, while 13% (1/8) had medium-duration training. Most (60/65, 92%) of the participants agreed that there is a need for specific training in the ethics of DSHR.

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Table 3. Baseline characteristics of study participants, Nigeria 2024.

Variables	Participants, n (%)
Sex	
Male	50 (77)
Female	15 (23)
Education	
First degree	11 (17)
Masters	16 (25)
PhD	38 (59)
Category	
Policymakers	11 (17)
Data science health researchers	25 (39)
Health Research Ethics Committee	12 (19)
Health data scientist	17 (26)
Role within the HREC[a]	
Chairperson	5 (42)
Member	7 (58)
Group within HREC	
Scientist	11 (92)
Nonscientist	1 (8)
Data science health researcher	
Directly use DSM[b]	15 (60)
Work with others who use DSM	19 (76)
Do not use DSM	0 (0)
Others	1 (4)
Current data science role	
Administrative or managerial	2 (12)
Project lead or principal investigator	7 (41)
Data or ML[c] engineering	8 (47)
Data scientist	14 (82)
Statistician or bioinformatician	1 (6)
Data architect	2 (12)
Data analyst	7 (41)
No direct data science role	0 (0)
Other	3 (18)
Affiliation	
Academia	45 (69)
Government	26 (40)
NGO[d]	7 (11)
Commercial	2 (3)
Teaching hospital	18 (28)
Level of training received in research ethics	
Short (<2 months)	38 (59)

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Variables	Participants, n (%)
Medium (at least 2 months)	4 (6)
Long (>2 months)	8 (12)
None	15 (23)
Level of training received in the ethics of DSHR[e]	
Short (<2 months)	7 (11)
Medium (at least 2 months)	1 (2)
Long (>2 months)	0 (0)
None	57 (88)
Do you think there should be specific training in the ethics of DSHR?	
Yes	60 (92)
No	5 (8)

[a]HREC: Health Research Ethics Committee.
[b]DSM: data science methods.
[c]ML: machine learning.
[d]NGO: nongovernmental organization.
[e]DSHR: data science health research.

Study Timeline

As of January 2025, the interview transcripts have been generated and checking completed, with qualitative analysis scheduled for completion by March 2025 and completion of primary manuscripts by the end of 2025.

Discussion

Principal Findings

This is the first comprehensive, qualitative investigation of the perspectives of multiple stakeholders on the ethical oversight for DSHR in Nigeria, a typical African LMIC. Of the 87 individuals invited, 22 (25.3%) were unable to participate, with 59% (13/22) not responding to invitations. Data science researchers comprised the largest group among nonresponders (5/13, 39%), which may reflect time constraints, research fatigue, or discomfort with ethics-focused discussions. This pattern warrants attention in future engagement efforts and suggests the need for sustained iterative approaches to stakeholder consultation in DSHR ethics development. The demographic profile of our participants reflects the current landscape of DSHR engagement in Nigeria, with most participants (50/65, 77%) being male, over half holding doctoral degrees (38/65, 57%), and the majority affiliated with academic institutions (45/65, 69%) and government organizations (26/65, 40%).

A striking finding was the substantial lack of specialized training in DSHR ethics, with only 12% (8/65) having received any training specific to the ethics of DSHR, and this was predominantly short-duration training. This deficit is particularly concerning given that 92% (60/65) of participants acknowledged the urgent need for specialized DSHR ethics training. This finding aligns with recent observations about the lag between technological advancement, such as DSHR, and the development of appropriate ethical oversight mechanisms [30,43]. The high proportion of participants who recognize the need for training of stakeholders in the ethical aspects of DSHR suggests receptiveness to capacity-building initiatives and readiness for meaningful engagement in developing contextually appropriate ethical frameworks.

Comparison to Prior Work

Our study contributes to the growing body of literature examining ethical governance of DSHR in Africa. Recent work emphasized that DSHR in Africa poses unique challenges, including blurred consent boundaries, reidentification risks, algorithmic biases, and transnational commercial exploitation [30]. Our multistakeholder approach directly addresses previous recommendations for engaging diverse perspectives in developing novel ethical frameworks suitable for resource-limited settings. The methodology we used in this study aligns with established best practices in research ethics policy development, similar to the 7Ps Framework for stakeholder identification in Patient-Centered Outcomes Research, emphasizing the importance of including patients, providers, purchasers, payers, policymakers, product makers, and principal investigators [44]. Our study adapted the 7Ps framework to the DSHR context in Nigeria, ensuring representation from researchers (both data science and biomedical), ethics committee members, research sponsors, and policymakers. Recent work has demonstrated that effective stakeholder engagement requires clarifying objectives, embedding engagement in research frameworks, and fostering collaborative relationships, which are the principles that we operationalized through our semistructured interview approach [45]. The training deficit we identified resonates with broader assessments of research ethics capacity in Africa. While substantial progress in building general research ethics capacity has been made, most of these assessments of ethics capacity occurred before the rapid expansion of DSHR and did not address the specialized competencies required for DSHR

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oversight [46]. Our finding that only 12.3% (8/65) of participants had received DSHR-specific ethics training highlights a critical gap that has emerged recently and requires focused intervention.

On broad consent, which we anticipate would emerge as a major theme when we complete our qualitative analysis, a recent comprehensive review highlighted that while broad consent enables data sharing for secondary research, concerns remain about whether it adequately protects participants' autonomy and community interests in LMICs [47]. Stakeholders' preferences have also been found to be highly varied [48]. Our study's inclusion of multiple stakeholders, including policymakers who shape consent frameworks, positions us to contribute nuanced insights about the applications of broad consent to DSHR in Nigerian contexts. Algorithmic bias emerged as a critical ELSI concern in our literature review and is likely to feature prominently in our analysis. Recent work in this area demonstrated that algorithmic bias poses substantial challenges in Africa, particularly regarding fairness and integrity of AI applications, with the potential to perpetuate data colonization if large multinational corporations impose solutions without local innovation [49]. It may constitute a "silent threat to equity" because equity must be engineered as a foundational design principle in DSHR rather than retrofitted into algorithms, data, or analyses [50]. These observations underscore the urgency of developing ethical frameworks that explicitly address algorithmic bias before DSHR tools are widely deployed in Nigerian health care contexts.

The challenge of data sharing and ownership in African health research has been well-documented. Data sharing between African and international health researchers is influenced by ethical, legal, social, institutional, and governmental factors, and freighted with concerns about predatory inclusion and inadequate benefit sharing [51]. While Open Science principles are increasingly applied by African researchers, the "inverse care law" and digital data poverty risks amplification of extractive data practices [51]. By focusing on stakeholder perspectives regarding data ownership and benefits sharing directly, we will be able to address these concerns within the specific context of DSHR in Nigeria. Recent work on data protection legislation across Africa identified considerable variation in requirements for cross-border data transfers and secondary data use, with enumeration of several proposals to improve data sharing, including standardized modules for safe data flows, trusted data environments, dynamic consent mechanisms, and codes of conduct for secondary data use [52]. We anticipate that similar themes would emerge from our stakeholder consultations. By including policymakers and KOLs in our stakeholders' group, we recognize that ethical oversight of DSHR requires engagement beyond traditional research participant communities to include those shaping broader societal understanding and governance of data science.

LMICs must develop appropriate guidelines for the ethical oversight of DSHR. This is particularly urgent in countries such as Nigeria because of the need to protect data donors, donor communities, and local researchers. At the same time, LMICs need to promote DSHR to take advantage of this powerful new resource and use it to solve many hitherto intractable health problems. LMICs need to contribute data to global databases to alleviate data poverty, which contributes to algorithmic and other biases, and the limited effectiveness of data science tools in their environment. LMICs need to develop the right infrastructure, manpower, training, and oversight mechanisms for meaningful participation of their researchers and communities in global DSHR [53].

Strength and Future Directions

Our study has several conceptual and methodological strengths that enhance its validity and potential impacts. The multistakeholder approach ensures that we capture diverse perspectives, and this responds to prevalent power asymmetry in policy development. We also operationalize the principle of epistemic humility and equitable participation [54]. This inclusive design increases the likelihood that recommendations arising from our study will be contextually appropriate, broadly acceptable, and implementable within Nigeria's research ecosystem. The hybrid deductive-inductive content analysis approach provides methodological rigor while remaining open to emergent themes not captured in existing literature. We will use an iterative 3-level coding process with thematic families and semantic networks that enable identification of complex relationships between concepts crucial for understanding how multiple ELSIs intersect in DSHR contexts. The commitment to reporting findings according to COREQ-32 criteria enhances the transparency and reproducibility of our study, aligning with international standards for qualitative health research reporting. Our focus on Nigeria, a large and populous country with a rapidly expanding data science use environment and well-established research ethics infrastructure, yet with gaps reminiscent of other LMICs, ensures that our findings would be generalizable to other LMICs.

Our findings would serve as resource materials for training in the ethics of DSHR and creation of standard operating procedures for ethics committees addressing DSHR proposals, particularly in helping to focus on consent frameworks for secondary data use, algorithmic bias assessment, and cross-border data sharing governance. Future studies should examine the implementation and effectiveness of our recommendations and conduct longitudinal assessments during the evolution of the ethical oversight of DSHR in Nigerian institutions. Comparative studies examining stakeholder perspectives across multiple African countries would test the generalizability of findings and potentially inform regional harmonization efforts for DSHR governance. Additionally, future work should explore mechanisms for dynamic and ongoing stakeholder engagement in DSHR ethics as the field continues to evolve. The rapid pace of technological change in data science means that static ethical frameworks quickly become outdated. Establishing communities of practice that bring together researchers, ethicists, policymakers, and community representatives for regular deliberation about emerging DSHR ethics challenges would create adaptive governance capacity.

Our study has several limitations. The 25% nonparticipation rate, consisting mainly of data scientists, introduces potential selection bias. This limitation is partially mitigated by our large sample size, which still included a lot of data scientists.

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Nevertheless, our findings should be interpreted with awareness that the most reluctant or time-constrained data scientists may hold perspectives different from those who participated. Second, our study's cross-sectional design captures stakeholder perspectives at a single time point at an early stage in the implementation of DSHR in Africa. Perspectives may evolve as stakeholders gain more experience with DSHR, with changes in DSHR technologies and methods, and as the ethical challenges of DSHR become more apparent through real-world applications. Our study partially addresses this limitation through its planned dissemination and engagement activities, which will enable longitudinal tracking of the evolution of perspective on ethical oversight of DSHR in future research. The documentation of substantial variation in participants' training and experience levels provides some insight into how perspectives might evolve with increased engagement. Third, our interview-based methodology, while providing rich qualitative data, does not capture quantitative measures of stakeholder agreement or priorities. Future phases of framework development would benefit from mixed methods approaches, perhaps using Delphi techniques to achieve consensus on key principles and priorities. Such approaches would complement the qualitative insights from this study with quantitative data on stakeholder priorities.

Finally, our study occurs within a specific regulatory and technological context that is rapidly evolving. Nigeria's data protection legislation, the Nigeria Data Protection Act 2023, was recently enacted and is still being implemented, meaning stakeholders' understanding of its implications may be incomplete. Similarly, rapid advances in AI and machine learning mean that the DSHR landscape stakeholders described may quickly change. These temporal limitations necessitate ongoing monitoring and periodic reassessment of ethical frameworks developed from our study findings. More research and community consultations to validate our findings would be required.

Dissemination of Findings

We are committed to the widespread dissemination of our findings. We will disseminate our findings to all stakeholders in the research ecosystem through submission of a report to members of national and institutional HRECs, presentations at research conferences and meetings, and in peer-reviewed publications. We will communicate our results directly to the volunteers who participated in our study, DS-I Africa principal investigators, and project sponsors. We will work with the sponsors to advocate for our findings using personal contacts, webinars, conferences, and workshops so they can influence DSHR stakeholders in Nigeria and other African countries.

Conclusions

This is the first study that we are aware of that will generate stakeholder-informed recommendations for ethical oversight of DSHR within resource-limited settings. Participants will contribute insights on how to address the applications and scope of broad consent for data use, the ELS challenges, data ownership and data sovereignty, benefit-sharing, and donor protection in DSHR. The findings will inform the global DSHR and research ethics communities and guide them on the implementation of contextually appropriate oversight mechanisms that promote equitable partnerships, co-ownership, and tiered data governance while protecting the rights of data donors and advancing global health research innovation.

Acknowledgments

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Data Availability

Data from this study will be available in a publicly accessible data repository according to the National Institutes of Health Data Sharing Guidelines and will be provided by the corresponding author upon receipt of reasonable requests.

Authors' Contributions

Conceptualization– CA.
Data curation– AA (lead), PI (equal), CA (supporting).
Formal analysis– CA (lead), PI (equal).
Funding acquisition– TO (lead), CA (equal).
Investigation– CA (lead), AA (supporting), PI (supporting), SNA (supporting), SC (supporting), OCM (supporting), The BridgELSI Project as part of the DS-I Africa Consortium (supporting).
Methodology– CA
Project administration– CA (lead), TO (supporting), SNA (supporting).

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Resources– CA (lead), TO (supporting), The BridgELSI Project as part of the DS-I Africa Consortium (supporting).
Software– PI (lead), CA (equal).
Supervision– CA (lead), TO (supporting), SA (supporting), AJ (supporting).
Validation– CA (lead), SNA (supporting).
Visualization– CA (lead), AA (supporting), PI (supporting).
Writing – original draft– PI (lead) AA (equal), CA (supporting).
Writing – review and editing– CA (lead) PI (supporting), AJ (supporting), SC (supporting), SA (supporting), TO (supporting), OA (supporting), SNA (supporting).

Conflicts of Interest

None declared.

Multimedia Appendix 1
Key Informant Interview Guides.
[DOCX File , 1409 KB - resprot_v14i1e78557_app1.docx]

Multimedia Appendix 2
Peer review report from the Center for Scientific Review Special Emphasis Panel RFA-RM-20-017: Harnessing Data Science for Health Discovery and Innovation in Africa – Ethical, Legal and Social Implications Research (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 56 KB - resprot_v14i1e78557_app2.pdf]

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Abbreviations

AI: artificial intelligence
COREQ-32: Consolidated Criteria for Reporting Qualitative Research
DSHR: data science health research
DS-I Africa: Harnessing Data Science for Health Discovery and Innovation in Africa
ELS: ethical, legal, and social
ELSI: ethical, legal, and social implication
HREC: Health Research Ethics Committee
KOL: key opinion leader
KII: Key Informant Interview
LMIC: low- and middle-income country

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Protocol

Community-Based Adaptation and Evaluation of a Peer-Led Intervention to Address Alcohol Use and HIV in Pregnant and Breastfeeding Women in South Africa: Protocol for the “Mentor Mothers Plus” Randomized Control Trial

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Abstract

Background: In South Africa, pregnant and lactating women (PLW) face a dual burden of high alcohol use and HIV prevalence, both of which adversely affect maternal and infant health. However, few interventions address alcohol use and HIV risk concurrently in this population.

Objective: This study seeks to adapt and pilot-test in a randomized controlled trial (RCT) the peer-led multisession intervention Mentor Mothers Plus (MM+) to integrate alcohol reduction strategies with HIV prevention and care support (in a seroneutral intervention) among PLW in Saldanha Bay, Western Cape, South Africa.

Methods: Using the ADAPT-ITT (assessment, decision, adaptation, production, topical experts, integration, training, testing) framework, we adapted the evidence-based Mentor Mother (MM) model, originally aimed at reducing vertical HIV transmission among mothers with HIV. Our mixed methods design includes (1) qualitative research, including in-depth interviews (IDIs) and focus group discussions (FGDs), to assess drivers of perinatal alcohol use and HIV risk; (2) intervention adaptation through community-based participatory workshops with stakeholders to refine the MM+ intervention in order to include culturally and contextually strategies; and (3) a pilot RCT with 100 pregnant women (≥16 years old, reporting recent alcohol use) randomized in a 1:1 ratio to the MM+ intervention (motivational interviewing [MI], including HIV and alcohol reduction messaging) or enhanced standard of care (SOC). Primary RCT outcomes include reduced alcohol use, via phosphatidylethanol (PEth) blood levels at 6-month follow-up. Secondary outcomes include uptake and adherence to pre-exposure prophylaxis (PrEP) and antiretroviral therapy (ART) among women with HIV, as well as intervention fidelity, feasibility, and acceptability.

Results: Community research included 2 FGDs with health workers (n=6) and community leaders (n=7) and 31 interviews with partners and peers of PLW. Data showed that women are motivated to reduce alcohol use for child health but face barriers (eg, misconceptions about safety of alcohol use, poverty, trauma, and intimate partner violence [IPV]). Alcohol use is with friends/family

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members/partners and tied to financial stress, unplanned pregnancy, and poor mental health. MM+ support preferences emphasize nonjudgmental, peer-based mentorship, family involvement, and faith/community engagement. Gaps include stigma around HIV and contraceptive services. Communities recommend mentor mothers with lived experience, providing culturally relevant, empathetic support, and linking to social and clinical services. In August 2025, a community workshop refined the intervention, emphasizing the need for trustworthy mentor mothers with lived experience. Priorities included culturally relevant information on alcohol use, HIV prevention, family planning, trauma and interpersonal violence support, and flexible delivery. Next steps involve finalizing materials, training mentor mothers, and launching the RCT.

Conclusions: Our community-based, participatory study, MM+, offers a promising approach to address co-occurring alcohol use and HIV among PLW. Stakeholder engagement enhances contextual relevance and supports future scalability. The RCT will evaluate efficacy of the model in reducing alcohol and improving HIV outcomes.

Trial Registration: Clinicaltrials.gov NCT06962592; https://clinicaltrials.gov/study/NCT06962592

International Registered Report Identifier (IRRID): DERR1-10.2196/78856

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KEYWORDS

alcohol; HIV; peer-led intervention; pregnant and lactating women; community-based approach

Introduction

Background

South Africa bears the highest global burden of both alcohol use during pregnancy and HIV prevalence. [1-3]. These interlinked public health crises are particularly concerning for pregnant and lactating women (PLW) due to their compounded impact on maternal, fetal, and child health. In the Western Cape province in South Africa, alcohol use during pregnancy is prevalent, contributing to some of the world's highest rates of fetal alcohol spectrum disorder (FASD), with estimates ranging from 64 to 310 per 1000 live births [4,5]. Further, breastfeeding while consuming alcohol can impair child neurodevelopment, emphasizing the need for intervention throughout the perinatal period [6].

Pregnancy and postpartum are also periods of heightened risk for HIV, with the likelihood risk of acquisition more than doubling during this time [7]. Recent formative work among pregnant women at risk of HIV in Cape Town found that pregnant women who engage in alcohol use are more likely to report having recent condomless sex and multiple sex partners [8]. Qualitative work contextualized these findings, suggesting that alcohol use, HIV risk behaviors, nonadherence to HIV treatment, and experiences of intimate partner violence (IPV) are all inextricably linked health issues [9,10]. Despite the Joint United Nations Programme on HIV/AIDS (UNAIDS) and the World Health Organization's (WHO) 2025 targets to eliminate vertical HIV transmission (defined as <2% HIV transmission or <50 cases per 100,000 live births) [11], South Africa's pediatric HIV incidence still exceeds 750 per 100,000 live births. This is largely driven by a 30% antenatal HIV prevalence [11]. Considering the high HIV incidence in pregnancy, access to oral and other forms of pre-exposure prophylaxis (PrEP) are essential for PLW who do not have HIV [12,13], while women with HIV must be on and adhere to antiretroviral therapy (ART) to mitigate vertical HIV transmission [14-16]. However, alcohol use interferes with HIV care engagement, delaying ART initiation, reducing adherence, and ultimately increasing the risk of vertical HIV transmission [14-17]. Given the evidence that alcohol use disrupts biomedical HIV prevention and treatment, adherence-targeted interventions are critical.

Despite these risks, community-informed interventions targeting both HIV and alcohol use among PLW are lacking. The few existing brief interventions targeting alcohol use during pregnancy have shown limited effectiveness, in part due to short follow-up periods and the absence of biomarker validation [18,19]. Integrating peer mentor mothers into existing care structures is one promising evidence-based approach that has improved maternal health outcomes and reduced vertical HIV transmission in South Africa [20,21]. The existing Mentor Mother (MM) intervention, implemented by peer mothers to mothers, leverages task shifting, where positive deviant peer mothers provide counseling and support, typically through home-based delivery. The prior models have focused mostly on prevention of vertical HIV transmission but do not include any messaging on alcohol or substance use reduction. The previous interventions have been successfully adapted to address broader maternal-child health outcomes in Africa and have shown promise in reducing alcohol use [22]. However, alcohol has never been the primary focus of MM intervention content. Guided by ADAPT-ITT (assessment, decision, adaptation, production, topical experts, integration, training, testing), a framework developed to systematically adapt evidence-based HIV interventions, our study seeks to adapt the MM approach to reduce alcohol use and improve HIV prevention and treatment outcomes among PLW in South Africa [23].

Brief interventions for alcohol use in pregnancy have shown limited effectiveness. Although interventions such as the Philani Program Plus (an MM model) have shown reduction in alcohol use over extended periods, achieving early abstinence remains challenging [24]. Our study aims to bridge these gaps by integrating motivational interviewing (MI) techniques to assist with reduction in alcohol or other substance use through peers with lived experience of being pregnant and reducing or stopping alcohol use during pregnancy and breastfeeding.

The MM approach is well suited for this context, offering a cost-effective, accessible, and scalable approach through leveraging existing community health worker structures [25-27].

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The model is highly adaptable, having been successfully implemented to address diverse health challenges across Africa, including HIV, nutrition, and child development [28,29]. The approach has also demonstrated effectiveness, producing significant reductions in vertical HIV transmission and improved ART adherence [27,30]. In addition to this approach, to further enhance the intervention impact, we will integrate MI—another evidence-based strategy shown to reduce alcohol use among PLW—into our adapted MM model [19,31].

Theoretical Approach: Theory-of-Change Framework

Given the sociocultural complexities of alcohol use and HIV risk among PLW in South Africa, identifying a theory of change is critical to understanding the causal pathways that drive these behaviors and designing a responsive intervention [32]. The theory of change is an outcomes-based approach to understanding health behavior that maps how and why change occurs, articulating causal linkages between activities, outcomes, assumptions, and contextual factors [33].

The theory-of-change model identifies the multilevel determinants influencing alcohol use and HIV risk among PLW, including individual (eg, stress, depression), interpersonal (eg, intimate partner violence [IPV], peer influence), and community (eg, social norms, poverty) factors [34-36]. Key components of this framework include long-term (reduced maternal alcohol use, improved HIV prevention behaviors, and decreased vertical HIV transmission), intermediate (improved alcohol use disclosure, increased uptake and adherence to PrEP/ART, and reduced stigma in accessing care), and immediate (increased knowledge and motivation to reduce alcohol use, improved access to health services, and strengthened peer and community support systems) outcomes.

Methods

Study Design

This study was registered at ClinicalTrials.gov (NCT06962592, v1.0). The study is being implemented in Saldanha Bay, located in Western Cape, South Africa, which has a high burden of HIV and PLW who use alcohol. This periurban/rural fishing community has a population of over 150,000 people. The prevalence of FASD in the area was 64 children per 1000 affected (6.4%) in 2014—one of the highest rates worldwide [11].

The study location (Figure 1) presents unique context where Black and mixed-race women in South African communities face a confluence of social and structural challenges that exacerbate the risk of perinatal alcohol use and HIV [37]. A legacy of the apartheid era, the *dop* system—where laborers were paid with alcohol—contributed to a culture of heavy alcohol use, further reinforced by informal local bars, called *Shebeens*. Given the significant contextual and cultural drivers of alcohol use in PLW in this setting, we will prioritize community input and coadaptation of the intervention to optimize intervention fit and relevance.

Figure 1. Map of the West Coast region, South Africa.

This work is being carried out in partnership with the Foundation for Alcohol-Related Research (FARR), which has a longstanding community service presence in Saldanha Bay since 2012. We are leveraging this strong community presence to facilitate reaching this hard-to-reach population, build trust, and deliver

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services in a way that is responsive to their needs and grounded in longstanding local relationships.

Study Aims and Approach

The study aims (Figure 2) are as follows:

Figure 2. Study research aims and activities mapped on the ADAPT-ITT and theory-of-change frameworks. FGD: focus group discussion; IDI: in-depth interview.

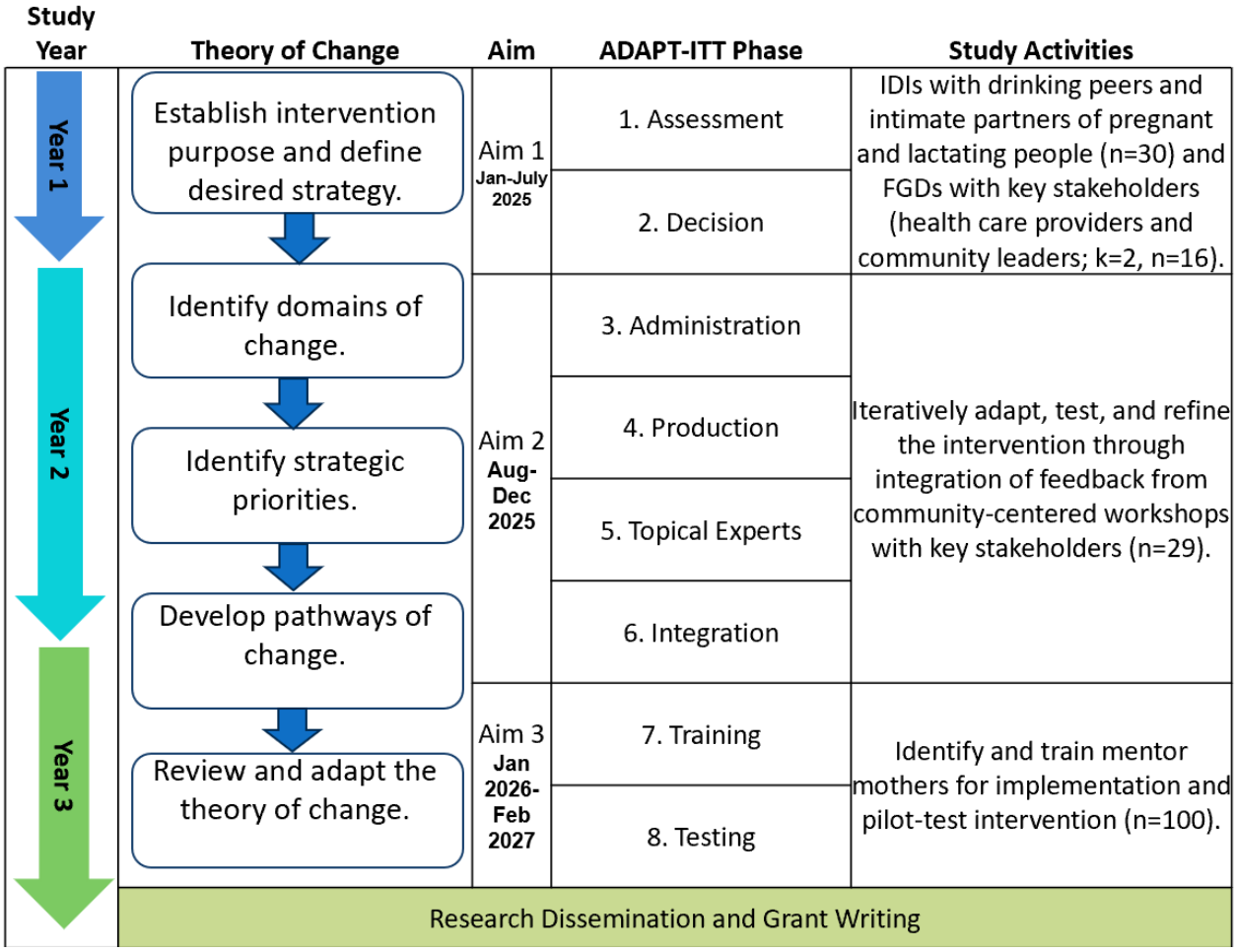

- Assess the drivers of perinatal alcohol use from the perspective of key individuals who influence behaviors (drinking peers, intimate partners, community leaders, health care providers) through a mixed methods assessment to identify barriers to and facilitators of alcohol use reduction.
- Adapt the MM model by collaborating with stakeholders and refining the "Mentor Mothers Plus" (MM+) intervention, integrating culturally and contextually appropriate alcohol reduction strategies.
- Evaluate the intervention's feasibility and acceptability by conducting a pilot randomized controlled trial (RCT) with 100 PLW using alcohol and determine the intervention's preliminary impact on alcohol use and HIV prevention and treatment behaviors.

Qualitative Research

We conducted in-depth interviews (IDIs) with partners, as well as peers and family members of pregnant women who drink alcohol. We also conducted focus group discussions (FGDs) with health care and community stakeholders to assess the drivers of perinatal alcohol use from the perspective of key individuals who influence behaviors. We have completed IDIs and FGDs with PLW previously [9,10]. We conducted concurrent mixed methods research with key stakeholders of PLW who use alcohol to explore facilitators of continued alcohol use in pregnancy at the interpersonal, community, and health care facility levels, with the aim of identifying and assessing intervention needs and opportunities (step 1 of ADAPT-ITT).

Inclusion Criteria (Formative Stage)

We identified intimate partners and drinking peers (drinking partners, who include friends and family members) of PLW to examine interpersonal and social facilitators of alcohol use while pregnant. In addition, we engaged health care providers working with PLW (nurses, midwives, and HIV counselors) and local leadership (influential community and religious figures) in FGDs to identify facility-, provider-, and community-level barriers to addressing alcohol use in this population (Table 1).

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Table 1. Description of the purpose, sample, and content of data collection in aim 1 of the MM+[a] study.

Study methods	Population: intimate partners and peers	Health care population: health care providers and community leaders
Purpose	• Understand interpersonal factors contributing to alcohol use among PLW[b] • Understand how alcohol use and HIV risk intersect among PLW • Identify support from partners or peers • Identify points of intervention	• Assess how maternal health care providers address alcohol use in pregnancy as well as access to HIV prevention and care services • Identify points of intervention
Sample	• Drinking partners (n=15) • Intimate partners (n=15)	• Health care workers (k=1, n=8) • Community and religious leaders (k=1, n=8)
IDIs[c]/FGDs[d]	• Firsthand experience of using alcohol with PLW or peers • Perceptions of alcohol use in pregnancy • Perceived facilitators and barriers to reducing alcohol use in pregnancy • Other HIV risk behaviors	• Perspectives on alcohol use among PLW • Current interventions to address alcohol use among PLW (for providers) • Facilitators and barriers to reducing alcohol use in pregnancy and HIV intervention uptake in PLW
Survey measures	• Sociodemographic data	__[e]

[a]MM+: Mentor Mothers Plus.

[b]PLW: pregnant and lactating women.

[c]IDI: in-depth interview.

[d]FGD: focus group discussion.

[e]Not applicable.

Trained researchers conducted semistructured IDIs and FGDs using interview guides in Afrikaans and English. All materials were drafted in English and translated into Afrikaans by experienced team members. Data collection for this aim includes (1) semistructured IDIs with drinking and intimate partners of PLW who use alcohol, (2) FGDs with health care providers and community leaders, and (3) concurrently collected brief surveys administered to IDI participants to gather sociodemographic and behavioral data, including perceptions and practices regarding alcohol use during pregnancy (eg, proportion of providers assessing alcohol use at visits, proportion of partners supportive of alcohol use during pregnancy). For qualitative analysis, we will focus on salience-based saturation [38], identifying key themes mentioned by two or more participants.

FARR community-based staff used purposive sampling and snowball sampling for recruitment of drinking partners and intimate partners of PLW who use alcohol. Data collectors received training on sensitive interviewing dealing with distressed participants and referrals.

Eligibility Criteria and Key Informant Recruitment

Health care providers were purposively selected from Saldanha Bay municipality clinics and the Vredenburg Provincial Hospital. Community leaders were recruited with help from our Community Advisory Board (CAB), clinic staff, government leaders, social workers, and FARR. An IDI participant must identify as an intimate partner, friend, or family member of a PLW who used alcohol during pregnancy. Participants include adults (≥18 years old) in professional or community roles related to HIV care, maternal health, or alcohol use or in community roles, such as elders, members of faith-based organizations, or civil society representatives, able to provide informed consent. For IDIs with partners, friends, and family members, participants included adults (≥18 years old) living in the study community who reported drinking with a pregnant woman now or in the past. Recruitment was facilitated by the community-based partner through local networks and snowball referrals.

IDIs and FGDs were held in private community spaces or at FARR offices to ensure confidentiality. Participants were reimbursed for their time, inconvenience, and expenses they may have incurred due to being interviewed, with a grocery voucher for a local store. For the FGDs and IDIs, we used rapid qualitative analytic methods. Audio recordings, detailed notes, and transcripts were reviewed by researchers trained in qualitative methods (authors DD and ZP) and fluent in Afrikaans. Data review followed a structured extraction template organized around key domains relevant to intervention adaptation (eg, experiences of people living with HIV [PLWH], provider perspectives, and contextual barriers and facilitators). Data were then transcribed and translated, and two additional analysts (authors ZE and AM) independently populated the template as second reviewers, after which findings were reconciled to resolve discrepancies. The reconciled data were then summarized and cross-checked by the broader study team, including study leadership, to ensure analytic rigor and validity. Extracted data were examined for consistency, key themes, and areas requiring clarification, with opportunities for member checking with community participants to enhance credibility. The resulting thematic findings informed the content presented in the consensus-building workshop and guided adaptation of the intervention.

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Community Workshop

We applied the community-based participatory action research (CBPAR) principles through three sequential activities to refine and adapt the MM model:

- Adaptation of the MM model through collaborative consensus-building workshop. In August 2025, we conducted a collaborative consensus-building workshop with 29 stakeholders in Saldanha Bay to adapt the MM model (step 3 of ADAPT-ITT). Formative findings from aim 1 and the essential components of the existing MM model (content and literature) were reviewed in a participatory 1-day workshop with health care providers, social workers, civil society, women with lived experience, and community leaders recruited by FARR. The workshop was cofacilitated by the study team with FARR, in both English and Afrikaans, depending on participants' preferences. Feedback and comments were used to collaboratively adapt key components of the intervention. The study staff obtained consent from participants using English or Afrikaans consent forms. Participants were reimbursed for the time, travel, and expenses. Following the workshop, the adapted MM+ intervention will be iteratively pilot-tested (steps 4-6 of ADAPT-ITT).
- Development of draft MM+ model (August-December, 2025). The research team will use the updated draft intervention and qualitative findings from the workshop to produce a draft ready for pilot-testing among pregnant women and develop study materials, including consent materials, standard operating procedures (SOPs), monitoring and evaluation indicators and tools, and research related instruments (survey and SOPs for blood tests) in preparation for piloting of the MM+ intervention in aim 3.

Analytic Approach

We applied rapid qualitative analysis methods for the consensus-building workshop. Notes were reviewed by trained researchers to capture key points from group discussions. Participants focused on core intervention components: who should be included, what content to address, where sessions should take place, and how/when delivery should occur. Each group presented its recommendations to the larger workshop, where ideas were compared and discussed to identify approaches most appropriate for the community context [39,40]. We used findings to inform adaptation of the MM model and development of finalized manuals for the pilot study.

Study Design for the Pilot RCT (January 2026-February 2027)

We will identify and train 3-5 mentor mothers from the community. Inclusion criteria for mentor mothers include women (≥25 years old) in the community with lived experience who are either on PrEP or have HIV and are on ART and who reported reducing or stopping using alcohol during pregnancy. Mentor mothers will be trained on the adapted MM+ curriculum and MI techniques (step 7 of ADAPT-ITT). We will include 10-15 providers (midwives, nurses, and counselors) to be part of the MM+ training and support the integration of MM+ in three antenatal care (ANC) clinics. Concomitant ante- and postnatal care, including HIV testing and ART and PrEP provision, will be provided to all women regardless of study allocation.

Following training, trained study staff in three local clinics and surrounding communities will recruit and enroll 100 pregnant women who report recent (past 2 months) alcohol use to evaluate the effectiveness and feasibility of the MM+ intervention in reducing alcohol use in PLW, PrEP use in PLW without HIV, and ART adherence in PLW with HIV (step 8 of ADAPT-ITT). Participants will be randomized in a 1:1 ratio to the MM+ study arm or enhanced standard of care (SOC). SOC is focused on HIV counseling by peers, without alcohol messaging. If we are unable to identify 100 women in the three select clinics and communities, we will expand to additional communities and clinics.

Description of the MM+ Intervention

MM+ will involve mentor mother delivery of brief MI sessions individually over a series of clinic-based visits over a 6-month period during pregnancy and postpartum. Although the exact number of mentor mother sessions, the finalized intervention content, and the full menu of HIV prevention services offered will be finalized during the community workshop, based on the dose from previous MI RCTs in South Africa [41,42], we anticipate no fewer than five to six 15-20–minute MI sessions focused on the benefits of reducing alcohol use during pregnancy and managing HIV risk among women without HIV and the importance of ART use and viral suppression for reducing the risk of vertical HIV transmission. Participants in both study arms will receive enhanced HIV prevention counseling integrated into routine ANC visits, including PrEP and ART biofeedback adherence using urine tenofovir (TFV) tests that are point-of-care inexpensive tests that provide feedback on the recent use of PrEP or ART in the past 72-hours [43-45]. In the intervention arm, these services will be provided by a trained study nurse. See Figure 3 for a breakdown of the anticipated intervention structure.

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Figure 3. Randomization and allocation of intervention and enhanced standard of care in Mentor Moms+ Study, South Africa.

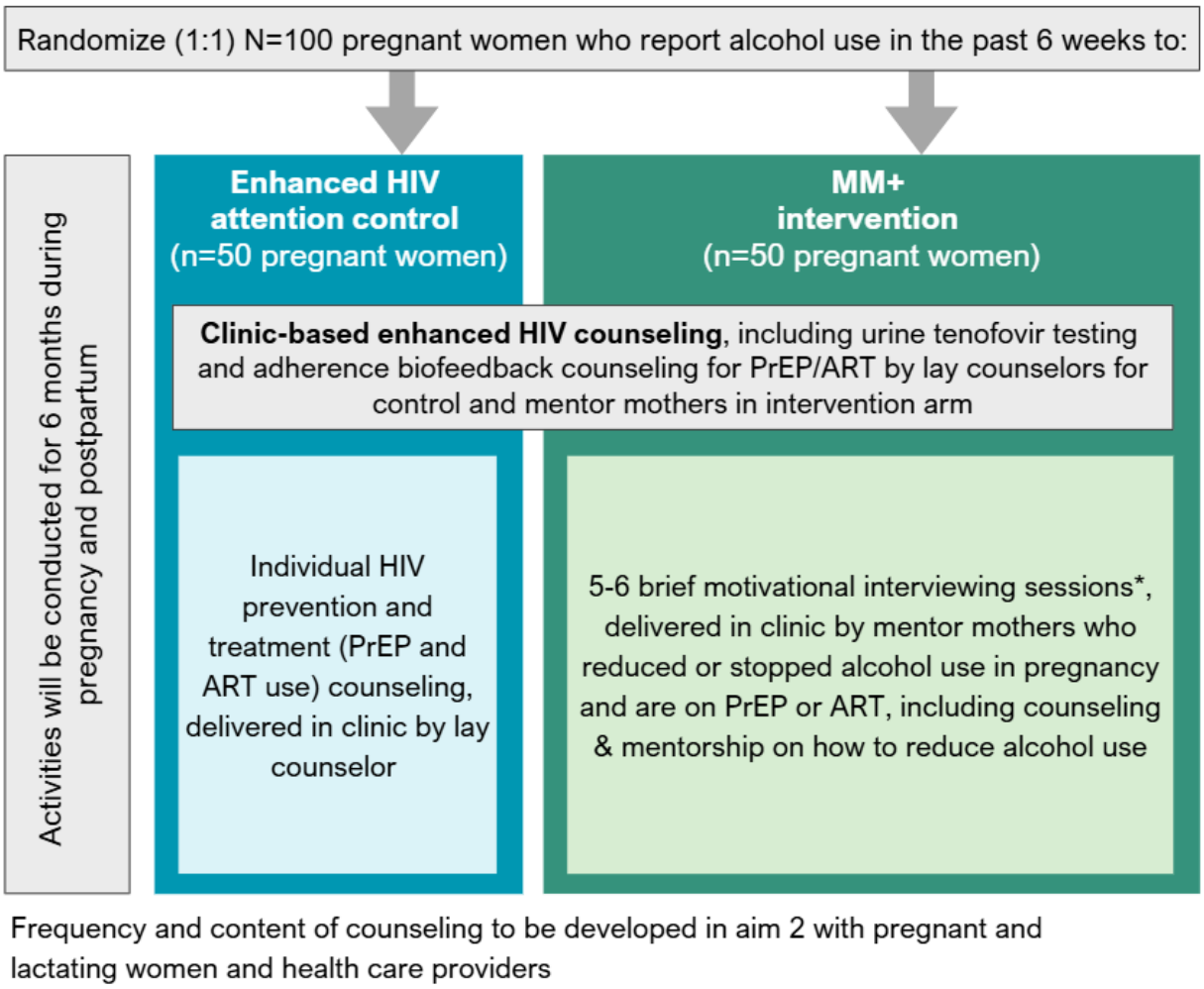

RCT Outcomes

The RCT primary outcome is the preliminary effectiveness (comparing the MM+ arm to the enhanced HIV attention control arm using intention-to-treat analysis) defined as a reduction in alcohol use via biomarker-confirmed self-reported and biological samples (comparing baseline to 6 months in phosphatidylethanol [PEth] blood samples).

Secondary outcomes include (1) PrEP initiation and adherence (via patient records and urine TFV testing at 6 months) and (2) ART adherence (via urine TFV testing and self-report). In addition, we will evaluate three of the eight implementation outcomes, as defined by Proctor et al [46]: feasibility, acceptability (including participant satisfaction with the intervention), and fidelity. We will also track any social or health harms in the study and relatedness to the study intervention through study surveys and review of medical records. Table 2 describes how these outcomes will be measured. We will track session attendance, as well as ART and PrEP adherence, at each study visit.

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Table 2. Description of aim 3 implementation outcomes.

Evaluation parameter	Description	Methods	Frequency
Theoretical model	Evaluate changes in alcohol use and HIV prevention or treatment (eg, PrEP[a] and ART[b] use) using the theory-of-change model measuring change and which sociodemographic and behavioral characteristics are associated with change in order to understand any subpopulations receptive toward the strategic priorities and pathways of change identified by our model.	Quantitative surveys at each visit and biomarker data	Baseline and 6-month follow-up
Participants' self-reported fidelity	Evaluate completeness of the intervention through a checklist assessing whether specific topics were covered during intervention sessions, including an assessment of the quality of intervention interactions, where participants will rate implementer engagement during intervention sessions.	Quantitative surveys at each visit and biomarker data	Baseline and 6-month follow-up
Acceptability and uptake of and satisfaction with the intervention	Evaluate the organizational, provider, and PLW[c] acceptability of the intervention, including the number and percentage of sessions attended and IDI[d] feedback following the sessions. Success would be >80% of sessions attended with very good/good feedback postsessions.	Mixed methods	Postimplementation mixed methods: 6-month survey (all participants), followed by IDIs with 20 providers and 20 participants
Fidelity to training assessment	Evaluate sessions (20% recorded and reviewed by the principal investigator) and fidelity to training using a checklist of key parameters. Success would be >80% of sessions supervised following training SOPs[e].	Monitoring forms: comparison of SOPs and audio-recorded MM+[f] sessions	Postimplementation mixed methods: 6-month survey (all participants), followed by IDIs in 20 providers and 20 participants
Feasibility of the intervention	Evaluate organizational, provider, and PLW views on the feasibility and scalability of the implementation of the intervention.	Mixed methods	Postimplementation mixed methods: 6-month survey (all participants), followed by IDIs in 20 providers and 20 participants

[a]PrEP: pre-exposure prophylaxis.

[b]ART: antiretroviral therapy.

[c]PLW: pregnant and lactating women.

[d]IDI: in-depth interview.

[e]SOP: standard operating procedure.

[f]MM+: Mentor Mothers Plus.

Outcome Data Ascertainment

Participants will be followed for 6 months. During this time, they will have three study visits, in which they will self-report alcohol use and PrEP or ART initiation or continuation to study staff. At each study visit, we will ascertain dried blood spots for assessment of recent alcohol use, via PEth testing (PEth<20 ng/mL represents light or no consumption [47]) and AUDIT-C, a validated survey of alcohol use (0=abstinence, >0=recent alcohol use). Participant medical files will be reviewed at the end of the study to ascertain birth outcomes (including any pregnancy loss or stillbirth), reported harms, and PrEP and ART prescription. At each study visit, participants will provide a urine sample to the study staff for analysis of recent PrEP or ART use using urine TFV testing (of recent adherence in the past 72 hours). Urine TFV results will show recent adherence and will be evaluated in conjunction with viral loads (VLs). For those on ART, we will review their files for VLs to evaluate VL suppression at baseline and end of the trial (VL<200 copies/mL). If VLs are unavailable, we will track them online with the national health laboratory service.

Enhanced Standard of Care

Given that existing MM models focus on vertical HIV transmission and HIV prevention and treatment, and our primary aim is to understand how inclusion of alcohol reduction strategies reduces alcohol use and improves adoption of ART/PrEP use, we will use enhanced SOC with the same time frame for the intervention (eg, two to three sessions during antenatal and two to three sessions during postpartum periods). This will consist of educational counseling delivered by peers (mentor mothers) on HIV risk, partner testing modalities, and PrEP/ART urine assay testing, followed by real-time in-clinic adherence counseling delivered privately (one on one) by mentor mothers (separate from intervention mentor mothers to avoid contamination), all coinciding with routine ANC visits when possible.

Benefits of the study include counseling and support from lay counselors (in SOC) and mentor mothers (in the intervention) to address alcohol use and HIV prevention and care. Risks include unintended disclosure of alcohol use or HIV status by providers or staff and potential breaches of confidentiality that

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could cause social harms, including IPV. We will train staff and providers to ensure they are aware of these risks and do not share details of participants' status outside of the study. We will monitor all social and other study harms throughout the study through regular surveys and review of medical records.

RCT Inclusion Criteria

Women who are ≥16 years old, with a confirmed pregnancy; who report alcohol use during pregnancy (in the past 2 months); who live within 20 km of the study facility; and who are able and willing to consent to study participation are eligible to participate.

One trained research assistant based at the ANC clinic will screen and obtain informed consent from PLW during their routine ANC visits using a set script for screening participants. We have received a waiver of parental consent for adolescents aged 16 and 17 years.

We will randomize the enrolled participants who have provided informed consent to the MM+ intervention or to enhanced HIV attention control in a 1:1 ratio. Randomization will be performed immediately following enrollment using dynamic permuted blocks with REDCap randomization sequentially. Trained researchers will not have access to the random allocation sequence. The intervention is nonblinded.

All study procedures will be in a private space in the Saldanha Bay municipality clinics, including screening, review, and signing of consent forms, surveys, and other procedures. This space will be dedicated research space given to the Human Science Research Council (HSRC) and FARR teams. We will ask pregnant women who may be interested in the study to see the study staff (in the study room) at the end of their visits or to get an appointment for another day to return to the clinic for study enrollment (if eligible).

Analysis Plan

Outcomes

The implementation outcomes include feasibility (provider, organizational, and participant feedback), acceptability (number of sessions attended, feedback on content), and fidelity to study SOPs on MM+. The safety outcomes include IPV and pregnancy and birth outcomes (including preterm birth, birth weight, and miscarriage or stillbirth and infant survival) [48,49].

Power Calculations

We calculated power based on a 20% or more reduction in alcohol use in the intervention arm compared to no reduction (or minimal <5% reduction) in the control group. By enrolling 100 pregnant women (n=50, 50%, per arm), our study will be adequately powered at >80% for all primary effectiveness outcomes of feasibility and reduction in alcohol use. In qualitative work, the sample size is determined by the number of interviews expected with a specific population to reach thematic saturation [50,51].

Qualitative Data Analysis

We will transcribe, translate, and import postintervention qualitative data into a software package, and a team of three researchers with expertise in qualitative research methods will code the data using a hybrid inductive-deductive approach. We will measure interrater reliability to ensure consistent code application between interviewers; this process will be iterative, and code definitions will be refined until application is consistent across coders. We will develop code summaries and memos for emerging themes using an experienced trained team of qualitative researchers from the HSRC and the San Diego State University (SDSU), who will use open coding to analyze segments of the data, create focused codes, and highlight quotable text. We will use a deductive approach from our theoretical framework on individual-, facility-, and HIV-level facilitators of alcohol reduction or abstinence and PrEP or ART continuation and adherence, allowing inductive codes to emerge. We will use a thematic analysis allowing key issues to emerge from the data. Multiple data sources (participants, providers) will be triangulated to provide a holistic understanding of the intervention acceptability [52]. We will use the COREQ (Consolidated Criteria for Reporting Qualitative Research) checklist to ensure positionality, reflexivity, etc, are covered to ensure rigor [53].

Descriptive Analysis and Effectiveness Outcomes

We will use basic measures (proportions, means and SDs, medians and IQRs, as appropriate) and graphical displays to describe distributions of key variables. Bivariable analyses will use Student's *t* tests (replaced by Mann-Whitney U tests for nonnormal distributions) or chi-square tests (replaced by exact tests for sparse data), as appropriate. We will compare study arms' descriptive statistics without tests of statistical significance. Comparisons of randomized groups' primary analyses will be by intention to treat, with secondary analyses based on intervention uptake. Specifically, we will evaluate reductions in alcohol use from baseline to 6-month follow-up in PEth levels, with confirmation of self-reported AUDIT-C scores compared by study arm. For secondary HIV outcomes, we will evaluate ART and PrEP adherence by study arm using urine TFV levels for recent adherence and VLs at 6 months for women on ART.

All statistical tests will be two-sided at α=.05; all effect estimates will be reported with 95% CIs. For both aims, we propose a priori subgroup analyses by age and HIV status. For subgroup analyses, effect modification will be assessed from the fully adjusted model on the additive scale by calculating the relative excess risk due to interaction [54] and on the multiplicative scale by examining the interaction term in regression models. Data will be analyzed in Stata version 15.

We will track missing variables in our monthly quality control and follow-up on all missing exposures and outcomes at each visit. We will conduct sensitivity analyses, including multiple imputation, to include evaluation outcomes and exposures from missing data and incomplete retention. Our retention efforts will focus on retention in both groups to ensure that there is no differential loss to follow-up. Analysis of implementation outcomes will entail descriptive summarization of acceptability, feasibility, and fidelity of MM+, including for women of different socioeconomic statuses or education levels.

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Data management procedures will be developed with the statistical analysis plan and available upon demand to study investigators.

Mixed Methods Analyses

We will conduct an explanatory sequential mixed methods design [55], collecting and analyzing quantitative data first (surveys, monitoring forms), followed by qualitative interviews with a purposively selected subsample of health care providers and participants to expand on findings from the quantitative phase.

Ethical Considerations

We have obtained approval from relevant institutional review boards (University of California, Los Angeles [UCLA] IRB#24-0130, HSRC REC #2/31/01/24). Prior notice will be given, and informed consent will be sought and obtained from all study participants. All participants will go through an informed consent process. The study staff will provide information for those who are interested in being tested but not interested in study participation. All study participation is strictly voluntary, and participants can refuse specific procedures or further study participation at any time.

Study staff members who will have contact with participants will receive training on the protection of human subject research before engaging in study-related activities. Additionally, the staff will undergo Good Clinical Practices (GCP) training, as required. Evidence of ethics training will be submitted with every ethics approval application and maintained throughout the study.

All potential participants will read the informed consent form (ICF) or have the ICF read to them. The ICF will be available in relevant local languages (eg, Afrikaans, isiXhosa) and English, and participants will complete the informed consent process in their preferred language. Each participant will be given an opportunity to ask questions about study participation. If a participant agrees to participate in the study, the study staff will obtain written consent. After consenting to participate, the participant may voluntarily withdraw from the study at any time and can choose not to have their responses submitted to the study team. Study participation is voluntary, and we will ensure ongoing respect of participants throughout the research process through ensuring confidentiality and privacy principles.

To ensure confidentiality, all data will be coded by participant number. Data recorded on paper will be kept in locked cabinets with access only to members of the research team. There will be strict limited access to electronically stored data, using password protection. Research records will be kept confidential following national regulations. Every participant's name or other personal identifiers will not be included with specimens sent to the laboratory, which will be identified only by a code number. Interviewers and support staff will be trained on procedures for maintaining confidentiality.

We will use phone calls and text messages for follow-up to improve retention. Text messages will be neutral and not contain personal information about the participants (eg, appointment reminders will say, "Your appointment is on Tuesday at 3:00 p.m."). At each visit, staff will ask about social harms, complete a detailed report, link the participants to community resources for support, and report social harms to the ethics review board. If multiple social harms are observed, the study procedures and text message content will be reviewed by the study team and CABs and recommended changes submitted to regulatory bodies for review.

All data collection procedures, regardless of the source, will follow standardized procedures outlined in the *Manual of Operating Procedures*, with individual activities guided by SOPs. RCT data (aim 3) will be collected by trained study interviewers using REDCap electronic software, which is Health Insurance Portability and Accountability Act (HIPAA)– and Protection of Personal Information Act (POPIA)–compliant for research studies. The interviewers will ask questions and complete the responses using a handheld tablet with internet connectivity for rapid data access and quality control.

The Data Safety and Monitoring Board (DSMB), which will comprise experts in the field of HIV and substance use in pregnancy, will be formed in the first year of the study and will meet quarterly to evaluate safety outcomes and data monitoring. A CAB was formed in 2025 that includes pregnant individuals, health care providers, and community leaders from Saldanha Bay and has held two meetings to date. CAB members are supporting the study by providing input, guidance, and feedback on the study's methodology and implementation throughout the study period, ensuring community perspectives are considered.

Results

We launched our formative work in January 2025 with community research in Saldanha Bay. We conducted 2 FGDs with health workers (n=6) and community leaders (n=7), as well as 31 IDIs with partners and peers of PLW who reported alcohol use during pregnancy. We have conducted the initial rapid analysis of the results. Participants reported that PLW have strong motivations to reduce alcohol use for their child's health but face multiple barriers, including misconceptions about the safety of alcohol in pregnancy, poverty, trauma, IPV, social pressure to drink to connect with peers, and stigma. Alcohol use was frequently linked to financial stress (particularly around the need to support a child), an unplanned pregnancy, and poor mental health. Preferred support strategies emphasized nonjudgmental, peer-based mentorship, family and partner engagement, and involvement of faith and community networks and leaders. Additional gaps included stigma surrounding HIV prevention (PrEP awareness, access, and use were limited) and contraceptive services. Communities recommended that mentor mothers be women with lived experience who are empathetic, discreet, and culturally relatable, with structured training, supervision, and referral linkages.

Following rapid analysis, a community workshop was convened in August 2025 with 29 stakeholders, including community leaders, health professionals, social workers, and people with lived experience, to refine the MM+ intervention. Participants reinforced the importance of mentor mothers as trusted, trained women with lived experience, and highlighted priorities, such as clear, culturally relevant education on alcohol use, HIV

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prevention, and family planning; trauma and IPV support; and flexible delivery across home, community, and group settings.

The next steps include identification and training of mentor mothers, finalization of intervention materials, and preparation for implementation of the RCT.

Discussion

Summary

Our study addresses the overlapping challenges of alcohol use and HIV among PLW in a high-burden setting by developing and piloting MM+, an adapted, community-informed version of the MM model. Through a phased, participatory approach grounded in the ADAPT-ITT framework and community-based research principles, MM+ integrates alcohol reduction with HIV prevention and treatment using a HIV seroneutral approach. The intervention is designed to reflect the real-world needs of PLW, their partners, health care providers, and communities.

Although PLW face increased risks related to both HIV and alcohol use, few community-informed interventions have directly addressed these intersecting vulnerabilities. Existing brief interventions to reduce alcohol use during pregnancy have shown limited and short-lived impact, partly due to minimal follow-up and lack of biomarker validation. Evidence from South Africa demonstrates that integrating peer mentor mothers into care structures can improve maternal health outcomes and reduce vertical HIV transmission through task shifting, whereby trained peer mothers deliver counseling and support within routine and community-based care. These MM models, pioneered by mothers to mothers, have primarily focused on preventing mother-to-child HIV transmission and improving maternal-child health, with only limited adaptation to address alcohol or substance use. Although alcohol has not been a central component of MM interventions, prior adaptations illustrate the flexibility and effectiveness of this platform for addressing broader maternal-child health priorities.

Building on this foundation, our study applies the ADAPT-ITT framework to systematically tailor the MM model to explicitly incorporate alcohol use reduction alongside HIV prevention and treatment. By leveraging an established, trusted, and evidence-based delivery platform, we aim to ensure that the adapted intervention is both responsive to community needs and feasible for integration into existing health systems. Through a structured participatory process using rapid qualitative methods, we demonstrated the feasibility of adapting the MM model for the South African context. Findings from formative interviews and a consensus-building workshop highlighted strong stakeholder support for tailoring content, delivery modalities, and session structures to local realities. Participants emphasized the value of integrating women with lived experience as peer mentors, delivering sessions in accessible community-based venues, and addressing both health-related and psychosocial challenges faced by PLW.

Strengths

This study has several notable strengths. First, it builds on an established, evidence-based MM platform that has been successfully implemented to reduce vertical HIV transmission, increasing the feasibility and sustainability of our adaptation. Second, the intervention is community informed and peer delivered, which enhances cultural relevance, trust, and the likelihood of uptake among PPW. Third, the use of the ADAPT-ITT framework ensures a systematic and theory-driven approach to intervention modification, increasing the rigor of the adaptation process. In addition, incorporating biological markers of alcohol use alongside self-reported measures strengthens the validity of outcome assessment and addresses limitations of prior studies. Finally, the focus on integrating HIV prevention and alcohol reduction within maternal and child health platforms reflects a holistic approach that aligns with existing health system priorities.

Limitations

Several limitations should be acknowledged. As an adaptation and implementation study, findings will be context specific, and generalizability beyond the study setting may be limited without additional testing. The reliance on peer-delivered counseling may pose scalability challenges in regions with limited MM program coverage or constrained human resources in the current South African context. Although biomarkers improve accuracy, they may not fully capture patterns of alcohol consumption, and social desirability bias in self-reports could remain. Finally, the intervention's impact on longer-term outcomes, such as sustained alcohol reduction and HIV incidence, will require extended follow-up beyond the study period.

Conclusion

This pilot trial will assess the feasibility, acceptability, and preliminary impact of MM+, while also generating insights into personal and structural barriers to care. We hypothesize that the intervention will be acceptable among pregnant women and providers and will reduce alcohol use during pregnancy, while also improving access to HIV prevention and care. Findings will inform future scale-up efforts, with the goal of improving maternal and child health through a practical, scalable strategy in high-burden and low- and middle-income settings.

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Data Availability

Data will be available for review upon request to study investigators. The trial protocol and statistical analysis plan can be accessed via the study principal investigators. All data will be disseminated during the study period to the community, participants, and stakeholders through regular meetings. Primary and secondary outcomes, including formative research results, will be communicated through conferences and peer-reviewed manuscripts during and following the trial period.

Authors' Contributions

ZE was responsible for conceptualization and funding acquisition and wrote the first draft of the protocol paper; ZP was responsible for conceptualization and investigation, including qualitative interviews; AM was responsible for conceptualization, funding acquisition, and methodology development; SSD was responsible for editing and project administration; DD and HH were responsible for editing, project administration, and data collection; TB was responsible for conceptualization and statistical methodology review; JL was responsible for conceptualization, editing, and project administration; and DJD was responsible for conceptualization, funding acquisition, methodology, and administration.

Conflicts of Interest

DJD has received funding for research from ViiV, Gilead, and Merck. APM has received two investigator studies awards from Merck/Sanofi Pasteur (MSP). All other coauthors have no conflicts to report.

Multimedia Appendix 1
Focus group topic guide.
[PDF File (Adobe PDF File), 169 KB - resprot_v14i1e78856_app1.pdf]

Multimedia Appendix 2
Interview guide.
[DOCX File , 44 KB - resprot_v14i1e78856_app2.docx]

Multimedia Appendix 3
Peer-review report by PPAH-Population and Public Health Approaches to HIV/AIDS Study Section (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 213 KB - resprot_v14i1e78856_app3.pdf]

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Abbreviations

ANC: antenatal care
ART: antiretroviral therapy
CAB: Community Advisory Board
FARR: Foundation for Alcohol-Related Research
FASD: fetal alcohol spectrum disorder
FGD: focus group discussion
HSRC: Human Science Research Council
ICF: informed consent form
IDI: in-depth interview
IPV: intimate partner violence
MI: notivational interviewing
MM: Mentor Mother
MM+: Mentor Mother Plus
PEth: phosphatidylethanol
PLW: pregnant and lactating women
PrEP: pre-exposure prophylaxis
RCT: randomized controlled trial
SOC: standard of care
SOP: standard operating procedure
TFV: tenofovir
VL: viral load

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Improving Digital Mental Health Services With and for National Minority, Indigenous, and Refugee Youth in Norway: The InvolveMENT Multiphase Mixed Methods Research Project Protocol

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Abstract

Background: Worldwide, minority youth receive culturally sensitive mental health services less often than the majority peer population. In Norway, limited research exists on the mental health and service use among youth from national minority (Forrest Finns, Kven or Norwegian Finns, Jews, Roma, and Romani), Indigenous (Sámi), and refugee backgrounds. Although the Norwegian government provides a public communication channel for youth, including mental health information and support, digital services have not been adapted to meet the needs of these groups. There is currently no research to determine the use, acceptability, effectiveness, cost-effectiveness, and safety of these services for these youth.

Objective: The main aim of the *InvolveMENT* project is to improve the mental health of national minority, Indigenous, and refugee youth. The project's objectives are, for these groups of youth, to (1) determine the mental health and digital support needs and possible barriers to and facilitators of service use; (2) assess the use of and satisfaction with digital services to meet their mental health needs; (3) explore their perspectives on digital mental health services; (4) develop recommendations that can be used to adapt digital services to meet their needs and rights; and (5) assess the use, acceptability, satisfaction, effectiveness, cost-effectiveness, and safety of adapted services.

Methods: The 4-year *InvolveMENT* project consists of four phases: (1) establishing a longitudinal cohort consisting of national minority, Indigenous, and refugee youth, using surveys to assess their mental health, well-being, digital support needs, use and satisfaction with digital services, and possible barriers to and facilitators of service use; (2) conducting qualitative interviews with minority youth to explore their perspectives and synthesizing data from phases 1 and 2 for a mixed methods analysis; (3) involving youth and health care and other professionals to develop proposals to adapt and improve the existing digital services; and (4) a randomized controlled trial and a qualitative study to evaluate the adapted services.

Results: Cohort and qualitative study designs have been completed. Ethics applications have been approved, and recruitment to the cohort and qualitative studies has started.

Conclusions: The *InvolveMENT* project has the potential to enhance the accessibility and quality of health care services and early interventions, reduce inequality in service provision for minority groups, and strengthen collaboration between youth, public, and research organizations. Through this, it has the potential to improve the mental health of youth from these groups. The findings might be transferable to other minority groups, both nationally and internationally.

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KEYWORDS

digital services; Indigenous; mental health; national minority; Norway; refugees; youth

Introduction

Background

Approximately 10% of youth worldwide are diagnosed with mental disorders [1]. There are mental health disparities among minority youth internationally, and these are affected by social determinants of health that are influenced by factors such as socioeconomic status, access to education and health care, and experiences of discrimination [2]. Youth from Indigenous and national minority groups have poorer mental health than the general population. For example, a systematic review found that Indigenous populations had suicide rates 20 times higher than non-Indigenous populations, with the highest rates in youth aged 15 to 24 years [3].

The Indigenous population in Norway is the Sámi. There is limited knowledge about the mental health of Sámi youth. During the period from 1970 to 1998, suicide rates among Sámi youth were twice those of the majority youth population in Norway [4]. Internationally, asylum-seeking and refugee youth have high rates of mental disorders, such as posttraumatic stress disorder, anxiety, and depression [5-8]. In Norway, up to 42% of asylum-seeking and refugee youth have been found to fulfill the criteria for psychiatric disorders [9]. A recent review reporting on the mental health of the Roma population in Europe found a higher proportion of mental disorders among children compared to the majority population and limited access to mental health care [10]. There is, however, no knowledge about the mental health among youth who belong to the following five national minority groups: Forrest Finns, Jews, Kven or Norwegian Finns, Roma, and Romani [11].

Mental Health Care Service Use Among National Minorities, Indigenous, and Refugee Youth

The mental health care needs of national minority, Indigenous, and refugee youth in Norway have only been assessed to a limited extent [9,11,12]. Service use may be low, and dropout rates may be high. There are cultural and language barriers, difficulties in developing trust, marginalization of minority groups, a lack of immigrant staff and interpreters, and ineffective care coordination [13,14]. Limited effort has been made to adapt services to meet their needs, despite the right to health pursuant to the International Covenant on Economic, Social and Cultural Rights (Article 12), which was made into Norwegian law in 1999. Although the Sámi Norwegian National Advisory Unit—Mental Health and Substance Use offers services to support the Sámi population, youth more often seek help from friends, partners, or family members [12,15], and scientific knowledge about their digital service needs is lacking. Apart from a single hospital-based mental health clinic, the Transcultural Centre at Stavanger University Hospital [16,17], no clinics in Norway specialize in or have adapted services to meet the mental health needs of asylum-seeking and refugee youth. Studies that focus on the different cultural backgrounds of youth (ie, culturally sensitive studies) are needed to determine how to develop services that are culturally relevant and appropriate to support minority youth [18-20].

Digital Mental Health Care Services for National Minority, Indigenous, and Refugee Youth

Young people often use the internet to access information about mental health [21]. According to the technology acceptance model, youth are more likely to use digital services if they perceive them as both useful and easy to use. Moreover, trust in technology plays a central role in youths' engagement with digital services [22]. Digital mental health interventions may facilitate service access for national minority, Indigenous, and refugee youth by addressing geographic, economic, and social disparities [23,24]. However, there is an evidence gap, and culturally sensitive, effective, and safe modes of digital health care delivery must be further developed and tested [24,25].

DigiUng is a Norwegian public cross-sectoral collaboration, run by the *Directorate for Children, Youth and Family Affairs* and the *Directorate of Health*. It has developed the public communication channel *ung.no* to provide information, health care, and support services for youth. However, these services have not been adapted to meet the mental health needs of national minority, Indigenous, and refugee youth, and there is no research evidence regarding their acceptability, effectiveness, cost-effectiveness, and safety for these groups.

Aim and Objectives

The overall aim of the *InvolveMENT* project is to improve the mental health of national minority, Indigenous, and refugee youth. This will be done by adapting digital mental health services to meet their personalized information and support needs.

The objectives of the *InvolveMENT* project are to (1) determine mental health and digital support needs and the barriers to and facilitators of service use for national minority, Indigenous, and refugee youth; (2) assess the use of and satisfaction with digital services to meet the mental health needs of national minority, Indigenous, and refugee youth; (3) explore the perspectives of national minority, Indigenous, and refugee youth on digital mental health services; (4) develop recommendations that can be used to adapt digital services to meet the needs and rights of national minority, Indigenous, and refugee youth; and (5) assess the use, acceptability, satisfaction, effectiveness, cost-effectiveness, and safety of the adapted digital services to meet the support needs of national minority, Indigenous, and refugee youth.

Methods

Study Design

The *InvolveMENT* project uses a participatory, multidisciplinary, multiphase, mixed methods research design [26] to adapt digital

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mental health services to meet the mental health needs of national minority, Indigenous, and refugee youth in Norway. The four stages of the research include a cohort study (work packages [WP1]) to assess the needs, barriers, and facilitators of service use; qualitative studies (WP2) to explore the perspectives of youth from these groups on digital mental health services; co-design activities (WP3) to develop recommendations for adapting digital services; and an evaluation study (WP4) to assess the adapted digital mental health services through a randomized controlled trial (RCT) and a qualitative study.

The project will use the Trials within Cohorts (TwiCs) design to test the acceptability, effectiveness, cost-effectiveness, and safety of the adapted digital services in WP4. This design offers several advantages over conventional RCTs and quasi-experimental approaches, particularly in studies involving hard-to-reach populations. TwiCs design enables fast and efficient recruitment to the RCT, as participants are already enrolled in the broader cohort from which trial participants are selected. It helps to reduce attrition rates because individuals in the control group are not informed about interventions they are not offered, thereby minimizing disappointment bias. Moreover, by avoiding disclosure of unavailable treatments, the design enhances the generalizability of results, as participants' expectations and behaviors are less likely to be influenced by knowledge of the intervention [27]. One-year rolling recruitment is used to compensate for natural attrition.

A participatory, multidisciplinary, multiphase, mixed methods design is particularly suited to complex health interventions, as it allows for the integration of diverse perspectives and methodological approaches. The participatory component ensures that youth voices are actively included throughout the research process, enhancing cultural relevance, acceptability, and ethical rigor. The multidisciplinary and multiphase structure enables the project to move iteratively from needs assessment to service adaptation and evaluation, ensuring that findings from each stage inform subsequent phases. Finally, the mixed methods approach provides both the breadth of quantitative data and the depth of qualitative insights, offering a more comprehensive understanding than any single method alone.

A participatory design approach is used to adapt digital services [23], involving national minority, Indigenous, and refugee youth and professionals working in health services, social services, and related sectors (eg, education). Close collaboration, cultural sensitivity, and empowerment of participants are used to develop strong partnerships and to ensure co-ownership. The project encourages and facilitates multisectoral collaboration between the services and support and interest organizations for national minority, Indigenous, and refugee youth; health care and service providers; and university-based research centers. The collaborative component with active involvement of youth strengthens the relevance of the research to meet the needs of these groups of youth. Youth representatives, representatives of health and service providers, health care workers, and co-researchers from minority groups are involved in all phases of the project, including planning, interpretation, and dissemination of results [28].

Study Setting or Location

This national project involves youth and professionals in all 4 health regions in Norway. Online questionnaire surveys are carried out in the cohort study (WP1) and the RCT (WP4), facilitating participation of youth from different parts of the country. The locations for the qualitative studies (WP2) and co-design workshops (WP3) vary for the different minority groups but are spread throughout the country.

Study Population

Throughout all phases of the project, participants will be recruited among youth who identify as belonging to at least one of the following groups: national minorities (Forest Finns, Jews, Kven or Norwegian Finns, Roma, and Romani), Indigenous Sámi youth, and refugees. In addition, in the first 2 of 3 cohort surveys (WP1), youth not belonging to the mentioned minority groups will be included. The inclusion of the broader group of youth will enable comparisons between minority and nonminority youth. During the co-design phase (WP3), professionals working in health and social services who engage directly with these youth groups will also be recruited.

In WP1, up to 1500 youth with minority backgrounds will be recruited for each of the 3 cohort surveys. Additionally, the first 2 cohort surveys will include up to 1500 youth who do not identify as belonging to the described minority groups. WP2 will include 50 to 100 youth from the different minority groups, ensuring representation across all groups. WP3 will involve a minimum of 50 youth and professionals. WP4 will recruit approximately 300 youth from the WP1 cohort for an RCT and 25 to 45 youth for a qualitative study based on their exposure to the adapted digital services, regardless of RCT participation.

Inclusion and Exclusion Criteria

In WP1, WP2, and WP3, the inclusion criteria are youth aged 16 to 25 years who identify as belonging to at least one of the following groups: national minorities (Forest Finns, Jews, Kven or Norwegian Finns, Roma, and Romani), Indigenous Sámi youth, and refugees. The term "refugees" is used inclusively to refer to all youth who consider themselves to be refugees, regardless of their official status as defined by the national government. Moreover, the first 2 cohort surveys in WP1 also include youth aged 16 to 25 years who do not define themselves as belonging to any of these minority groups. WP3 also includes professionals working in health services, social services, and related sectors (eg, education) who engage directly with youth from minority backgrounds, as well as youth representatives aged 16 to 35 years who belong to any of the mentioned minority groups. Additional inclusion criteria for youth participating in the RCT in WP4 include a Patient Health Questionnaire (PHQ-9) score indicating mild to moderately severe depressive symptoms (scores from 5 to 19). Youth included in the qualitative study in WP4 are those who have been exposed to the adapted digital services. Youth aged <16 or >25 years are excluded from participation. Participants across all groups must provide written informed consent to take part in the research.

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Study Outcomes

Given the nature of the *InvolveMENT* project, specific primary and secondary outcomes are defined for the RCT (WP4), which is the only component designed to evaluate the effectiveness of adapted digital mental health services quantitatively.WP2 and WP3 are exploratory and developmental in nature and therefore do not include predefined outcome measures. The primary outcome is the PHQ-9 score at 12 months of the trial. The secondary outcomes include scores for Generalized Anxiety Disorder [29,30], the Flourishing Scale [31], and the Children's Somatic Symptoms Inventory 8 [32]. These outcomes are based on self-report and may be influenced by factors such as cultural, language, and social differences in diverse minority populations. While no single outcome measure has been validated, and culturally adapted tools are lacking across the included minority ethnic groups, these commonly used instruments have been selected as a choice to support knowledge generation in the absence of more inclusive and adapted alternatives. Service acceptability will be assessed by calculating the proportion of participants who use the adapted services.

Study Procedures

Participant Recruitment

Participant recruitment in WP1, WP2, and WP3 is conducted through a broad range of channels tailored to reach minority ethnic youth from diverse backgrounds. These include secondary schools nationwide—particularly those with introduction classes for refugee youth and those with higher proportions of Indigenous and national minority youth—as well as higher education institutions (including one for students with Indigenous backgrounds), health care services, and language learning centers. Recruitment also involves collaborating with the national minority youth organizations, which are partners in the project, using their networks and social media platforms. In addition, outreach is conducted via social media channels commonly used by these groups of youth populations, such as TikTok (ByteDance), Instagram (Meta Platforms), and Snapchat (Snap Inc.). Recruitment takes place nationwide to ensure a diverse representation of perspectives. Participants who wish to contribute further may contact the research team to express interest in taking part in qualitative interviews and co-design workshops. A rolling recruitment method will be used over a period of 1 year for WP1 and WP4.

In the evaluation phase (WP4), participants for the RCT are selected from among those who scored between 5 and 19 on the PHQ-9 at baseline, indicating mild to moderately severe symptoms of depression. Participants for qualitative interviews in this phase are recruited based on their experience with the adapted digital mental health services.

Randomization

In WP4, participants who meet the inclusion criteria will be randomly allocated in a 1:1 ratio using Microsoft Excel, either to receive the intervention (the adapted digital services) or to continue with usual care as part of the control group. Those assigned to the control group will not be informed that they are part of a trial or that other participants are receiving an intervention. This approach is consistent with the TwiCs design [27,33], which stages and tailors the consent process to reflect real-world clinical practice. The design ensures that individuals receiving usual care are not informed about treatments they will not be offered, thereby minimizing potential for disappointment bias.

Data Collection, Interventions, and Follow-Up Procedures

As part of the cohort study (WP1), the project aims to recruit up to 1500 youth aged 16 to 25 years from national minority, Indigenous, and refugee backgrounds. On the basis of currently available data, it is reasonable to estimate that the population includes between 50,000 and 65,000 youth with minority ethnic backgrounds [34-40]. Data will be collected at 3 time points (ie, at baseline, 6 months, and 18 months) using online surveys developed in collaboration with youth minority representatives and partner organizations. The surveys are available in 14 languages: Arabic, Dari, English, Farsi, French, Kven, Lule Sami, Northern Sami, Southern Sami, Norwegian, Russian, Swahili, Tigrinya, and Ukrainian. Draft versions were piloted in English, Norwegian, Arabic, and Dari with a separate sample of 1500 participants, including youth from the majority Norwegian population and those with immigrant backgrounds [41,42]. The baseline survey will serve both as a primary data collection point and as a pilot phase to evaluate and refine recruitment strategies.

The qualitative studies (WP2) aim to explore the perspectives of minority youth on digital mental health services through individual and focus group interviews depending on participants' preferences. These interviews will examine youths' understanding of mental health; their needs for digital services, including those related to culture, language, and gender; and their pathways to support. They will also explore experiences with service availability, approachability, acceptability, and appropriateness, including trust in services and professionals. Participant numbers will be guided by the concept of information power [43]. Interviews will be conducted, whenever possible, in participants' preferred languages, with professional interpreters used when necessary. Interview guides have been developed in collaboration with youth representatives and project partners. All interviews will be audio recorded and transcribed verbatim.

The co-design study (WP3), which will develop recommendations for adapting digital services to better meet the needs and rights of youth from national minority, Indigenous, and refugee backgrounds, will include youth recruited through the WP1 cohort and WP2 interviews, youth representatives, co-researchers, and professionals from health and social services (eg, school nurses, psychologists, general practitioners, child welfare workers, and employment office staff). A series of 6 to 8 workshops involving youth (approximately 4‐7), professionals (approximately 4‐7), or both will be conducted. However, the number and composition of workshops may vary, as they can be conducted with a single minority group or a mix of youth from different backgrounds, depending on participant preferences and the type of input needed to inform the recommendations. Data will be collected through observations and field notes and will be enriched by findings from WP1 and

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WP2, youth input from a dedicated seminar, and contributions from project meetings and events. Youth will be actively involved throughout the co-design process, from planning and recruitment to facilitation, ensuring their right to be heard at the systems level, in accordance with Article 12 of the UN Convention on the Rights of the Child [44]. The resulting recommendations will be presented to service providers to support informed decisions on implementation.

The evaluation study (WP4) will assess the implementation of recommendations developed in WP3 through two complementary procedures: an RCT and a qualitative study. The RCT will use the same survey instruments as WP1, with baseline data collected at the 6-month survey (before service adaptations) and follow-up data at the 18-month survey. The qualitative study will explore youth experiences with the adapted digital services, focusing on perceived support, safety, and satisfaction. Data will be collected through individual and focus group interviews depending on participants' preferences. They will be conducted in participants' preferred languages with professional interpreters as needed. Participants may include both RCT participants and others exposed to the adapted services. The number of participants will be guided by the concept of information power [43], with an estimated 25 to 45 participants. Interviews will be analyzed using qualitative content analysis [45], and findings will be integrated with RCT data through mixed methods analysis, applying triangulation to assess convergence, complementarity, and discrepancies [46].

Measurement Tools

Measurement tools in the cohort study (WP1) and the RCT (WP4) include self-report questionnaires, PHQ-9, the Generalized Anxiety Disorder scale [30], the Flourishing Scale [31], the Children's Somatic Symptoms Inventory 8 [32], and single variables to determine participants' familiarity with, use of, and satisfaction with digital services, as well as their perspectives on service providers' cultural and linguistic competence and youths' preferences regarding continuity and confidentiality in care.

Safety Considerations

The project includes several measures to ensure participant safety and well-being. Participants who may need support during the study are encouraged to contact established health care services, including school health professionals, general practitioners, and mental health helplines, with emergency services available for urgent situations. The project also includes culturally sensitive communication and interview procedures to reduce the risk of misunderstanding or harm.

Data Safety

All personal data collected are handled in accordance with strict privacy regulations. Data are used solely for the purposes outlined in the study, and participants' confidentiality is safeguarded throughout. Participants also retain the right to access, correct, or delete their personal information and to file complaints with the Data Protection Authority if they have concerns about data processing. All sensitive data are securely stored on a dedicated server. These measures ensure that the research is responsive to participants' needs and conducted with appropriate protections.

Statistical Considerations and Data Analysis

Sample Size Calculation

Approximately 25% of youth are expected to experience mild to moderately severe symptoms of depression (PHQ-9 scores of 5 - 19) [9,12,47]. To ensure a sufficient number of eligible participants for the RCT (WP4), a population cohort of 1500 youth will be recruited. This cohort size is designed to provide an adequate number of individuals who meet the inclusion criteria, which are scores of mild to moderately severe range on the PHQ-9, and to account for potential exclusions due to eligibility, nonconsent, or attrition. On the basis of an anticipated 20% dropout rate, 80% statistical power, a significance level of 0.05, and a moderate effect size of 0.35 (Cohen *d*), with equal allocation between intervention and control groups, the required sample size for the RCT is estimated to be 294. This has been rounded up to 300 to maintain sufficient power and accommodate potential variability.

Participant Numbers in the Qualitative Phases

In the qualitative phases of the project (WP2 and the qualitative component of WP4), participant recruitment will be guided by the principle of *information power*, which posits that the number of participants should be determined by the richness, relevance, and sufficiency of the data in relation to the study objectives [43]. For planning purposes, the estimated number is 50 to 100 youth participants for WP2 and 25 to 45 participants for WP4. However, these estimates remain flexible and will be adjusted based on ongoing assessments of data adequacy in addressing the research questions. Recruitment will also be shaped by practical constraints, particularly the limited availability of participants from certain minority youth populations, which may impact the final participant numbers.

Data Analysis

Quantitative data analyses will be carried out for WP1 and WP4. In WP1, data analysis will include univariate analyses for descriptive statistics, whereas factors associated with service use will be assessed using correlation analyses, regression models, and multiple regression models to explore multiple predictors and adjust for confounders, for example, generalized linear models and linear and generalized additive models for nonlinear associations between predictor and outcome. Temporal changes will be assessed using mixed models to assess factors affecting service use.

To assess the use and acceptability of the intervention, that is, the adapted digital mental health services for youth, we will use data from the RCT to determine the proportion of participants who report using it. An intention-to-treat analysis will be used to test the effectiveness of the intervention offer, whereas an instrumental variables analysis will be applied to determine the effectiveness of the received intervention [48]. The primary outcome will be the PHQ-9 at 12 months of the trial. Subgroup analyses will be carried out for different minority groups. Results will provide data on variability in depression outcomes in the different groups. Safety will be assessed by determining

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the proportion of participants with deteriorated mental health status through higher PHQ-9 scores. Service satisfaction will be assessed using single-item questions, each targeting participants' satisfaction with 1 of 8 different types of digital services. A cost-effectiveness analysis of the intervention for youth will be carried out by undertaking a cost-consequences analysis [49]. It will compare individuals taking advantage of the adapted services with those who do not. The analysis will take a societal perspective, relating costs associated with introducing the new interventions and attributable to youths' mental health, school absence, and work productivity (if they are in work), as well as their quality of life.

Qualitative data analyses will be carried out in WP2 and the qualitative part of WP4. The data will be analyzed using qualitative content analysis [45] or similar types of analyses. Moreover, 2 mixed methods analyses will be conducted: the first will integrate qualitative data from WP2 with quantitative data from the cohort surveys in WP1, using triangulation to assess convergence, complementarity, and discrepancies [46]; the second will be carried out within WP4, combining data from the RCT and qualitative interviews to evaluate the implementation and impact of adapted digital services. The specific analytic approaches for both mixed methods analyses will be determined based on the nature and quality of the data collected, allowing for flexibility to ensure methodological rigor and relevance.

Data collected in WP3 will be analyzed using a thematic approach, drawing on principles of participatory and design-based research. Field notes and observations from the co-design workshops will be reviewed to identify recurring themes, patterns, and insights related to youth and professional perspectives on digital service adaptation. These qualitative data will be triangulated with findings from WP1 and WP2, as well as input gathered during youth seminars and project meetings, to ensure a comprehensive and contextually grounded analysis. The analysis will be iterative and collaborative, involving youth coresearchers throughout the process to ensure that interpretations reflect their lived experiences and priorities. This participatory approach supports the development of actionable recommendations that are both evidence-informed and aligned with the rights of youth, particularly those from minority backgrounds. The final recommendations will be synthesized and presented to service providers for consideration and potential implementation.

Ethical Considerations

According to the World Medical Association's Declaration of Helsinki, vulnerable groups may participate in research when it is responsive to their health needs and priorities and when appropriate protections are in place. This project is supported by strong legal and ethical arguments, particularly because the voices of youth from minority backgrounds are seldom heard and they remain underrepresented in health research, despite existing public policies and legislation advocating for inclusion.

Participants are aged ≥16 years, granting them the legal right to independently decide on their participation. To ensure informed consent, participants receive both written and verbal information. Safeguarding procedures have been developed in collaboration with youth minority representatives and professionals working with these groups. These procedures include mechanisms for recommending additional health care support when needed, thereby protecting the well-being and integrity of participants.

While the researchers maintain overall responsibility for the project, it is designed as a collaborative effort involving multiple stakeholder groups. These include youth representatives from minority backgrounds, health care professionals, and service providers. Their involvement spans all phases of the project, from planning and design to data analysis and dissemination, to ensure cultural sensitivity and relevance. This includes co-development of research materials, such as information sheets, consent forms, interview guides, survey instruments, and promotional content. Such collaboration helps minimize the risk of misrepresentation or harm to minority youth participants. Stakeholders also contribute perspectives during data analysis and are invited to co-author scientific and popular publications, as well as participate in media and social media outreach. Written and signed collaboration agreements have been established to clarify the rights and responsibilities of all parties involved.

The project uses the TwiCs design, which asks potential participants to consent to the use of their identifiable data, to be recontacted, and to allow their data to be used in evaluating interventions [27]. Only those offered an experimental intervention are informed about the developed intervention, aligning the consent process more closely with real-world clinical practice. This approach is considered more ethical than traditional models that require full disclosure of all potential interventions upfront [33,50]. TwiCs studies have received ethical approval in 10 countries [33], including youth mental health research [51]. Youth participants were offered gift cards for their involvement in each activity, in appreciation of their time and contributions: NOK 100 (US $10) for surveys (WP1/WP4), NOK 250 (US $25) for qualitative interviews (WP2), and NOK 600 (US $59) for workshops (WP3).

The University of Stavanger, through SHARE—Centre for Resilience in Healthcare, holds overall responsibility for data management, with the project lead serving as data steward. The project adheres to General Data Protection Regulation (GDPR) [52] and Norwegian ethical standards [53], ensuring informed consent and secure handling of personal and sensitive data. Consent procedures include options for recontact and data sharing, with safeguards for anonymity and participant rights. All data handling, including classification, storage, and processing, follows strict protocols to ensure privacy, integrity, and ethical compliance throughout the project lifecycle. Sensitive data are stored on a Sensitive Data Services server.

Ethical approval for this project has been granted by the Regional Committees for Medical and Health Research Ethics (ID 780840). Additionally, collective consent for Sámi youth participants has been approved by the Expert Ethics Committee for Sámi Health Research (ID 1133459). Moreover, Sikt, the Norwegian Agency for Shared Services in Education and Research, has considered the processing of personal data to be lawful based on consent (GDPR Article 6(1)(a)) and explicit

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consent (GDPR Article 9(2)(a), applicable to special categories of data) [52] (reference number 374832).

Results

We have completed recruitment to the project of youth representatives from all national minority, Indigenous, and refugee youth groups, which are the end users of the research. The panel now consists of 32 youth representatives. Ethics approval has been granted. A recruitment plan has been developed, and recruitment is estimated to start in December 2024. Draft versions of the cohort survey have been piloted in English, Norwegian, Arabic, and Dari, with a separate sample of 1500 participants [41]. This pilot study was conducted before the main data collection and included youth from both the majority population in Norway and those with immigrant and refugee backgrounds. On the basis of feedback from the pilot, the survey was subsequently adapted in collaboration with youth minority representatives and other project partners. This cohort study has been translated into 14 languages and will include up to 1500 youth who identify as belonging to national minority, Indigenous, or refugee backgrounds. In addition, another 1500 youth who do not belong to these groups will be included to enable meaningful comparisons between minority and nonminority populations. Youth minority representatives have also contributed input to the planning of qualitative studies. Funding was obtained from the Research Council of Norway for the time period from July 1, 2023, to June 30, 2027. Data collection started in January 2025, after submission of the manuscript (November 18, 2024).

Discussion

Anticipated Findings

The *InvolveMENT* project will offer an understanding of the mental health status of youth with national minority, Indigenous, and refugee backgrounds, together with their familiarity with and use of digital mental health services. This will supplement the existing research evidence, which only to a limited extent reports on perceptions of the impact of digital services on mental health among groups of minority youth [54]. While existing platforms provide general access to support, they often fall short in addressing the culturally specific requirements of these populations. Together with language needs, this can undermine youths' trust in service providers and ultimately serve as a barrier to the use of services [24].

Adapting digital mental health services also holds the potential to address challenges resulting from refugee youths' limited knowledge about the national health system and to reduce the harmful effects of mental illness–related stigma [55]. Through both survey data and qualitative interviews, the project will explore how youth from diverse backgrounds understand mental health, their experiences with digital services, and their preferences for culturally relevant support. These insights will inform the co-design process involving minority youth and professionals working closely with them, resulting in concrete proposals for culturally adapted, equitable, and sustainable digital mental health services.

The final phase will bring new knowledge about the acceptability, effectiveness, cost-effectiveness, and safety of digital services aimed at meeting the needs of minority ethnic youth in Norway. Others have stressed the importance of integrating user experiences to assess acceptability, self-reported effectiveness, and satisfaction with services [24]. This phase will lay the groundwork for future trials by identifying variability in mental health and service needs across different groups.

An expected impact of the project is to increase the proportion of minority youth who seek and receive appropriate digital support at an early stage, thereby contributing to timely diagnosis, intervention, and prevention of prolonged mental health complaints. As found by others, digital mental health interventions have the potential to support youth with refugee backgrounds who may be reluctant to consult mental health professionals due to fear or shame [24].

Moreover, by establishing a cohort using the TwiCs design, the project also creates opportunities for testing additional interventions during and beyond the 4-year study period. The project will also expand international research networks and explore the development of future collaborative studies focused on minority youth in diverse global contexts.

The Involvement of Youth Throughout the Research

The *InvolveMENT* project marks the first time national minority, Indigenous, and refugee youth—whose voices have rarely been heard—are actively involved in assessing and developing digital mental health services. Research using participatory approaches, which actively engage youth and integrate cultural elements into interventions, has been found to facilitate the development of programs that meet the needs of minority youth, such as those from Indigenous backgrounds [56]. It is our hope that the extensive involvement of youth in the project may also contribute to reducing concerns about privacy and confidentiality, which are common among these groups of youth [57]. Together with the involvement of professionals providing services for these groups of youth, the extensive and active involvement of youth in co-design processes ensures that their needs remain at the center of the research aimed at the development of adapted, equitable, and sustainable health care support services.

Strengths and Limitations

The strengths of the *InvolveMENT* project include the novelty of the project, which aims to improve mental health outcomes for national minority, Indigenous, and refugee youth in Norway by addressing the lack of culturally sensitive digital services tailored to their needs. The broad range of methodologies used will contribute to a better understanding of youth from minority ethnic groups, in particular with regard to the development of culturally adapted services that are suited to meet their mental health needs. A key strength lies in the youth-centered approach, ensuring that services are equitable, relevant, and sustainable, and marking the first time these populations are directly engaged in shaping mental health support in Norway. The main risk of this project is the recruitment of national minority, Indigenous, and refugee youth for the cohort (at least 1500 youth) and for

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the qualitative study. There are no exact population figures for the included minority groups, but estimates suggest 50,000 to 65,000 (age group 16 - 25), and recruitment will take place through multiple channels. A recruitment rate of 2% to 3% is a conservative estimate as participation rates in youth surveys were 73% to 87% in the Norwegian *Ungdata* survey [58] and 77% in our pilot [42]; and minority youth will be informed that the project aims to hear their views and that they will influence service development, which will encourage participation. The substantial involvement of youth representatives and coresearchers from minority groups in the project will be a great advantage for the recruitment process. Another limitation is the reliance on self-reported measures, which may introduce bias due to cultural differences in language and response styles. This concern may be particularly relevant in culturally diverse populations, where language, response styles, and social desirability norms can influence how questions are understood and answered [59]. However, the randomized design enhances internal validity, and the integration of qualitative interviews with survey data allows for triangulation that may help mitigate these limitations. By assessing the acceptability, effectiveness, cost-effectiveness, and safety of adapted services, the project not only enhances early intervention and reduces long-term mental health issues but also lays the foundation for future trials and international collaboration. Its findings will generate vital knowledge, expand research networks, and offer scalable models for culturally adapted digital mental health services worldwide.

Dissemination Plan

The project's dissemination strategy includes a variety of communication and publication activities. It encompasses a diverse range of dissemination activities tailored to various audiences. These include publishing scientific articles in journals and popular science outlets to engage the scientific community, professionals, youth, and interest organizations; and producing project reports and academic theses aimed at public decision-makers. Additional outreach efforts involve media interviews and articles for youth, parents, schools, and the general public; oral and poster presentations at conferences and seminars; contributions to organizational publications; and dynamic content on social media platforms such as TikTok, Snapchat, LinkedIn, Instagram, and Facebook, designed to reach youth, parents, interest organizations, and the broader public.

Conclusions

The *InvolveMENT* collaborative research project will contribute to improving the quality, equity, and efficiency of digital mental health services for groups of minority youth in Norway. The project will assess their use of and experiences with digital mental health services. Services can be adapted so they are culturally sensitive and meet the needs of national minority, Indigenous, and refugee youth.

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Data Availability

The data supporting the findings of this study are subject to controlled access. In accordance with the project's Data Management Plan, full access to the data is restricted to members of the research team at the University of Stavanger. Indirectly identifiable information is removed from any data shared with nonacademic partners involved in the analysis process (eg, youth from minority groups). Data will only be made available in line with the consent provided by participants. As a result, not all data generated in the study can be shared. Data that require less stringent security measures may be deposited in the UiS Open Research Data repository [60], where they will be accessible if permitted by participant consent and ethical approvals. Researchers interested in accessing data that cannot be publicly archived may submit a request to the corresponding author. Requests will be evaluated on a case-by-case basis and can only be granted when consistent with participant consent, ethical requirements, and data protection regulations.

Authors' Contributions

Conceptualization: PV
Funding acquisition: PV
Writing – original draft: PV, ER
Recruitment – partner organizations: AS, KLH, and PV

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Perspectives – youth coresearchers: LM and LKP
All authors read and approved the final manuscript.
All authors contributed to the project funding application, including their knowledge of the field of research (groups of youth and research design), and in writing parts of the funding text, as well as input to the manuscript.

Conflicts of Interest

None declared.

Checklist 1
NALHN Research Governance Office - Research Protocol Template
[PDF File, 343 KB - resprot_v14i1e64531_app1.pdf]

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Abbreviations

CCA: cost-consequences analysis
CEA: cost-effectiveness analysis
CSSI-8: Children's Somatic Symptoms Inventory
GDPR: General Data Protection Regulation
ITT: Intention-To-Treat
IV: instrumental variables
PHQ-9: 9-item Patient Health Questionnaire
RCT: randomized controlled trial
TwiCs: Trials within Cohorts
WP: work packages

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Patient Living With Chronic Illness Perception of Interprofessional Collaboration in a Telehealth Context in Primary Care: Protocol for a Qualitative Descriptive Study

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Abstract

Background: The enhancement of primary care and the prevalence of chronic diseases are key issues worldwide, especially in Canada. The rising incidence of chronic illnesses, now the leading cause of mortality worldwide, creates complex challenges that can compromise the quality of care provided to patients. A lack of communication directly affects relational continuity. These challenges highlight the importance of establishing clear patient pathways within interprofessional teams, ensuring that information is shared efficiently and the continuity of care is coordinated effectively, especially in a telehealth context. Since 2019, telehealth has become an essential tool for patients with chronic disease, although often implemented with no specific infrastructure. Interprofessional collaboration (IPC) plays a critical role in the use of telehealth in managing chronic diseases.

Objective: This study aims to understand the IPC process as experienced by patients in a telehealth context within primary care, with a focus on patient engagement. More specifically, the study's objectives are (1) to describe the IPC process in telehealth within primary care from the perspective of patients living with chronic conditions; (2) to identify, in collaboration with patients living with chronic disease, the barriers and facilitating factors in this process; and (3) to understand the engagement of these patients in relation to the IPC process in a telehealth context.

Methods: This qualitative research study is based on constructivist research methodology to describe the process of IPC in the telehealth context in primary care from the perspective of patients living with chronic disease. The research team will construct knowledge derived from the interpretation of information that was obtained during the interviews with participants. To meet the study's objectives, we carried out qualitative journey mapping for data collection. Individual interviews were analyzed iteratively. This method is useful for this research as it visually and collaboratively captures patients' lived experiences.

Results: Data collection was completed in November 2024. A total of 22 interviews were conducted. The project was funded in March 2022. As of December 2025, all participants had been recruited, and the qualitative data analysis was currently underway. Multiple manuscripts are in development, and the first set of findings was submitted for publication in fall 2025.

Conclusions: The results of this study will support and improve the IPC process in the telehealth context by providing concrete insights into patients' experiences, identifying gaps and strengths in current collaborative practices, and offering evidence-based recommendations. Journey mapping will help identify potential facilitating factors for improving primary care in the telehealth context according to the patient's journey. The results will be used to build a practical guide (in phase 2) supporting IPC in the primary care telehealth context.

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KEYWORDS

primary care; interprofessional collaboration; chronic disease; telehealth; patient engagement; qualitative method

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Introduction

Chronic disease is recognized as a long-term, persistent, and mostly noncommunicable condition requiring ongoing management [1]. In Canada, 44% of adults aged 20 years and older live with chronic diseases [2]. This percentage increases significantly with age [2]. Over 4.9 million (73%) Canadians aged older than 65 years live with at least one chronic disease. For patients living with these diseases, access to primary care is an essential element contributing to their continuity of care and patient engagement [1,3,4]. However, the lack of access to primary care does not promote efficient chronic disease management or active engagement of patients living with chronic disease [5,6] and ultimately affects their health [7,8]. The COVID-19 pandemic has amplified the delay in accessing primary care [9,10].

Various publications describe patients living with chronic disease as those who consult primary care most frequently [1,11]. These patients receive regular interprofessional follow-up by the primary care team, including nurses, family doctors, pharmacists, social workers, and others [12,13]. This interprofessional necessity of chronic disease management and the need to provide optimal interprofessional care implies that each professional involved must apply the recommended interprofessional practice standards [14,15]. Interprofessional collaboration (IPC) is defined as the process by which professionals from different disciplines develop modalities of practice that provide a coherent, integrated response to the needs of the individual, their loved ones, and the community [14]. To ensure continuity of care, it is essential that all professionals contribute to a shared, coordinated approach that supports seamless transitions and consistent communication throughout the patient's care trajectory [16-18].

During a well-established IPC process, a way to improve the quality of care is to offer care with the support of telehealth to increase access [19-21]. Telehealth is defined as "any interaction between a patient and a health care professional that takes place at a distance and uses some form of information or communication technology (ie, telephone, email, SMS, videoconferencing platform, electronic medical record [EMR])" [22]. In several Canadian provinces, telehealth is being used to better meet patient needs, such as improving accessibility to care [6,23]. Telehealth experienced significant growth during the SARS-CoV-2 pandemic but has since lost momentum. However, some studies point out that Canadians want to maintain access to telehealth consultations in the postpandemic context, mainly because of the time saved on travel and improved access to an appointment [24]. Telehealth consultations not only increase accessibility but also reduce the costs associated with care for the health care system when used optimally and appropriately [25,26]. For health care professionals and the health care system, proper use of telehealth facilitates communication between health care professionals, which ultimately supports IPC [4,20,27]. Despite the benefits of offering care through telehealth, it can have negative effects on patient health if used suboptimally or inappropriately [19,20], affecting IPC and the quality of patient engagement [24,28]. This acceleration was not only because of the pandemic [29,30] but also to support access to care in certain more remote regions [31]. Telehealth is supported in the literature for improving access to care and helping the health system adapt to demographic changes [6,20,32,33]. Although telehealth offers many advantages and is appreciated by patients and professionals alike [34,35], some studies point to the importance of further adapting this service modality to the needs of patients living with chronic diseases (eg, video-assisted telehealth for older patients due to digital literacy or patients with technological challenges). Other studies emphasize that to achieve positive effects for patients, it is essential to support professionals and patients in their appropriation of this intervention modality and to promote the maintenance of IPC despite the remote work or care context [36]. This might be explained in part because telehealth is often used without a defined framework and left to the discretion of each care setting [6,17,36]. Telehealth implemented without a clear framework (tools, work procedures, etc) for primary care increases work overload and stress for professionals [13,27,30]. Including the perspective of patients living with chronic diseases remains crucial and essential to guide professionals in keeping telehealth and IPC responsive to their needs [15,20].

The patient perspective helps improve health outcomes for individuals and increases patient satisfaction, confidence, and engagement in their health [37]. However, to date, the patient perspective of the IPC process, including patient engagement among patients living with chronic disease in a telehealth context, is still underresearched [38,39]. The Montreal model (Multimedia Appendix 1), the Canadian Institutes of Health Research, and the Strategy for Patient-Oriented Research also support this approach to integrating patient partners into the research team [40-42].

This study will aim to understand patients' engagement experience in the process of IPC in a primary care telehealth setting, considering the patient perspective. To achieve this aim, this research project has three specific objectives:

1. To describe the telehealth IPC process in primary care from the perspective of patients living with chronic disease
2. To identify, in collaboration with patients living with chronic disease, the barriers and facilitators in this process
3. To understand how these patients are engaged in the IPC process in a telehealth context.

Methods

Overview

The focus of the study is to better understand patient perspective on telehealth. This study therefore includes one patient partner in the research team. Meetings were held with the patient partner and the research team to develop the study protocol, interview guide, and mapping template, laying the groundwork for future data analysis and ensuring that findings can be effectively translated into practice through knowledge transfer strategies. This approach is based on the recommendations of Pomey et al [40] and their conceptual framework for patient engagement in research.

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This qualitative research is based on a constructivist research methodology, where the research team constructs knowledge from the analysis of information obtained during dialogues with participants [43,44]. To meet the study's objectives, we carried out a qualitative journey mapping data collection, following the approach of Trebble et al [45]. This method enables users (in this case, patients living with chronic diseases) to be involved early and throughout the mapping development process. Pathway mapping in telehealth (Multimedia Appendix 2) allows us to delineate the patient journey, detailing their engagement and experiences with telehealth services at the primary care level. This approach helps identify areas for enhancing the quality of patient care. Journey mapping also places the patient at the center of analysis to better understand and improve the process of IPC [46]. It also allows us to identify the points of contact between patients and professionals during the telehealth consultation process (ie, method of communication, pathway to an appointment, and other processes) based on patients' expressed or unexpressed needs [45]. This type of approach provides a better understanding of elements starting from service entry, navigation, and ongoing experience right through to patient discharge from the health care system [46].

Two conceptual frameworks will be used to structure this study. To enrich the understanding of patient engagement regarding the IPC process, the IPC-related domains of the Interprofessional Education for Collaborative Patient-Centred Practice (IECPCP) model (Multimedia Appendix 3) will be used for this project [14]. This model of IPC is patient centered and intends to improve patient outcomes. In this model, the process is divided into four dimensions: (1) governance; (2) rules to structure the team; (3) shared goals and vision; and (4) sense of belonging [14].

To adequately integrate the dimension of patient-centered care and to focus specifically on patient engagement within care processes, the Montreal model [40] can be used as a conceptual reference. Although this model primarily emphasizes the concept of partnership rather than engagement per se, it nonetheless offers a useful framework for conceptualizing varying levels of patient engagement. For the purposes of this project, only the dimension related to patient engagement within care processes will be retained, allowing for a targeted application of the model in the context of IPC and chronic disease management.

The patient's voice is considered on an equal footing with other stakeholders in the primary health care team. Moreover, the patient can also be supported by a caregiver to better express their experience [40]. Ultimately, this model relies on patients' experiential knowledge, enabling them to make informed decisions and exercise leadership at the same level as health care professionals [40]. The direct care delivery section is a logical level of the model that refers to interactions between professionals, as individuals and as a team, and patients [40]. It provides an understanding of the level of engagement of professionals and patients at the clinical level. In addition, the telehealth context will be highlighted in the consultation section of the Montreal model, where the patient must have had a telehealth consultation [40]. Finally, the components present in this model will support our understanding of the phenomenon of patient engagement living with chronic diseases in a telehealth context.

Study Population

The target population is all adult patients living with chronic diseases who have consulted virtually through telehealth in a primary care clinic in which different health care professionals practice collaboratively (ie, the presence of communication channels or an alternating care plan that is already established).

The settings studied for this research will be university primary care clinics called "university family medicine groups" (U-FMGs) in Quebec. U-FMGs (groupings of family physicians who work together and in close collaboration with other health and social services professionals) [47] are the main model of primary care service in Quebec [13,48]. Some family medicine groups are affiliated with universities and integrate the training of family medicine residents and externs. This study will focus on U-FMGs that practice telehealth.

Sampling and Recruitment Strategy

We will use purposive sampling to provide a diverse description of telehealth IPC experiences in primary care [49,50]. This type of sampling allows the research team to recruit participants who meet specific inclusion criteria and are representative of the phenomenon under study [50]. We will strategically select research sites and sampling methods based on their perceived richness and utility in providing comprehensive insights into the phenomenon under investigation [51]. The literature also points to other important strengths, such as lower cost, convenience, and reduced data-collection time [52]. A 2-tiered recruitment will be used, namely the development of a partnership with U-FMGs and subsequently the direct recruitment of patients from partner U-FMGs. This partnership will enable the team to recruit 2 U-FMGs. These U-FMGs will be recruited face-to-face to enable us to develop a relationship of trust between the research team and the U-FMGs administration from the outset. From the first meeting, the team will ensure the existence of an IPC process (eg, presence of communication channels or alternating care plans already established), as well as a French- or English-speaking clientele and the presence of telehealth consultations for patients. Once the U-FMGs have been selected, the research team and U-FMG managers will work together to ensure adequate patient recruitment. Posters will be placed in waiting rooms with information relevant to the study to solicit participation from the target population. Data collection was concluded after 22 interviews once thematic saturation was achieved, that is, when no new themes or insights emerged from successive interviews, consistent with qualitative methodological guidance [53-55]. This decision was discussed and validated among the research team. Data analysis will be carried out on an ongoing basis throughout the data collection process to check for redundant information, for example, when the research team begins to hear the same comments repeatedly, using a saturation grid [54,55] as a method of keeping track of this redundancy. This will allow them to stop data collection and finalize the analysis.

As inclusion criteria, adult participants have to declare that they live with at least 2 chronic diseases that are recognized by the

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Public Health Agency of Canada [2], have consulted at least 3 times in the last year in the participating clinic, and have had at least one of the 3 appointments in a telehealth context. Selected patients must have consulted the primary care clinic in connection with their chronic diseases. Recruitment from this population is justified by a higher likelihood of having had IPC experiences in a telehealth setting due to the need to maintain follow-ups in primary care [23,51].

Data Collection

We will be collecting data in the format of a journey mapping through a maximum of 90-minute semistructured interviews describing patient engagement within care processes in IPC from the perspective of patients living with chronic diseases [50,56]. These interviews will be conducted in either French or English, depending on patient preference. This type of interview allows the researcher to ask a question or several questions from a predetermined list, depending on the direction of the dialogue. This type of interview allows the patient's experience to emerge. Due to the geographical distance between the researcher or interviewer researcher and the potential U-FMGs and for the advantage and flexibility of the patient, the interviews will be conducted using the Microsoft Teams platform [57] to maintain consistency of format between each participant.

The semistructured interview guide will be oriented toward the IPC's experience in the engagement within care processes in the primary care clinic in the last 12 months in a telehealth context and was developed considering both conceptual frameworks [14,40]. We will begin the interview with an initial question: "Tell me about your experience with your clinic's team of health care professionals during telehealth consultations in the last 12 months." The purpose of this initial question is to activate memories of the past to enable the start of a conversation that will map the journey of these patients living with chronic disease and their experiences using telehealth [58,59]. The interview guide includes subquestions to gather information on the patient's journey, as well as facilitators and barriers. The interview questionnaire will be customized as needed to capture the IPC experience of each patient living with chronic diseases in a telehealth context.

As soon as consent to this study has been obtained, all recruited participants will be asked to complete a sociodemographic form covering their clinical and professional sociodemographic characteristics as supported by the conceptual frameworks. A logbook will also be used by the first author to record her field notes.

Data Analysis

We will analyze the individual interviews qualitatively and iteratively using the method reported by Gale et al [60]. This method is useful for analysis by different people from interprofessional teams, including those with little experience in qualitative analysis [60]. This method of analysis comprises seven steps: (1) transcription; (2) familiarization with the data; (3) coding; (4) development of the analytic framework; (5) application of the analytic framework; (6) graphical representation of the data; and (7) interpretation of the data. Analysis in this project will take the form of journey mapping, a method used to visually and thematically structure the experiences shared by patients. This approach captures the sequence of events, emotions, interactions, and decision points encountered throughout their care journey, allowing for a comprehensive understanding of how they navigate the health care system and how IPC and telehealth shape their experiences. In accordance with the principles of patient-oriented research, the analytical process is designed to balance meaningful patient engagement with methodological rigor. The patient partner's involvement is concentrated in steps 4 and 7, where experiential knowledge is most valuable for shaping the analytic framework and interpreting findings, while earlier phases are completed by the research team to maintain consistency in data coding and ensure analytic reliability [61]. Coding will be both inductive (based on respondents' subjective experience) and semideductive (guided by the IPC theme domains of the IECPCP model and the Montreal model) [14,40,62]. The domains of the IECPCP model are not used to generate a codebook but to guide the structure of the journey-mapping framework. Each of the 4 domains, governance, team structure, shared goals and vision, and sense of belonging, served as an organizing lens to segment the mapped data and visually represent how IPC and patient engagement unfolded across the patient's care experience. This allowed the mapping process to remain theoretically grounded while still reflecting the participants' lived experiences derived through inductive analysis.

The first author will do field noting during the interview process and may validate certain information with the patient during the interview [15,60]. Next, the first author will ensure that the information is fully transcribed in cartographic format by listening to the interviews (step 1). She will be responsible for familiarizing herself with the transcribed data, auditory data, and interview notes (step 2) while entering the information directly into the journey mapping. Mapping is a practical and visual method that supports reflection on continuity of care, reduction of wait times, and enhancement of patient safety, aligning with the principles of the Montreal model by fostering meaningful patient engagement and with the IECPCP model through its emphasis on interprofessional, patient-centered collaboration [45,63]. At this stage, the first author will invite a subset of participants to review the coded information for accuracy (member checking). Participants will have the opportunity to clarify or elaborate on their responses before data analysis proceeds.

The first author will then begin coding the data collected (step 3), thus initiating the mapping condensation. As the process moves forward, the analysis will be iteratively refined through journey mapping, which serves as a core analytic and visual tool to trace patient experiences across various stages of care. This method enables the research team to revisit and revise codes, frameworks, and interpretations as new insights emerge from ongoing data collection. By mapping the care trajectories of patients living with chronic disease in a telehealth context, the research maintains continuous alignment with the principles of patient engagement and IPC, thereby enhancing both the accuracy and the contextual relevance of the findings [45,60,63]. Once the data have been coded, the research team, together with the patient partner, will meet to verify (co-code) the data (step

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4). The research team will then apply the analysis frameworks to the collected and coded data (step 5). Following the data condensation process, the first author will produce graphic representations in the form of journey maps (step 6), visually illustrating the key themes and pathways that emerged from the analysis. These maps will reflect the condensed data and highlight patients' experiences, interactions, and critical moments across their care trajectories. She will be supported by one patient partner, and they will meet to finalize the analysis and interpretation of the data. At this stage, the team and patient partner will verify the data collected with the condensed mapping. Throughout the analysis, the research team will use the two conceptual frameworks to guide them. In addition, particular attention will be given to equity criteria when analyzing according to the PROGRESS+ (place of residence, race/ethnicity/culture/language, occupation, gender/sex, religion, education, socioeconomic status, and social capital plus) model [64] but not limited to this model, since these factors can influence IPC, the use of technological tools and their functions, and the delivery of telehealth [65]. PROGRESS+ is associated with diverse characteristics of the target population, ensuring their representation [64]. These criteria will be considered during the recruitment and at every stage of the project.

All barriers and facilitators related to IPC will be retained as information to be analyzed and interpreted to describe the IPC process. The team will ensure that the interview and the information retained focus directly on the experiences related to the IPC process and the patient engagement in the telehealth context. The research team will maintain reflexive journals to document assumptions, decisions, and potential biases throughout the data collection and analysis process. Reflexivity will be discussed regularly in team meetings to ensure that interpretations remain grounded in participants' perspectives.

Ethical Considerations

Before the study, the ethics committee at the Centre intégré Universitaire de santé et de services sociaux of Saguenay-Lac-Saint-Jean acted as the reviewer and granted ethics approval on May 9, 2024 (2023‑047). The project was also approved by the Ethics Committee of the Université de Sherbrooke's Faculty of Education and Social Sciences on December 15, 2023 (2023‑4057) and by the Vitalité Health Network on January 23, 2024 (101931). Written consent will be obtained from all study participants. At the beginning of each interview, the researcher will explain the project, the expected participation, and the associated risks. The interview process and data collection will be explained. There will also be a question period. Following this introduction, written consent will be obtained. All research data (eg interview recordings and transcripts) will be anonymized and stored on a secured server; files will be stored in a password-protected folder on a computer from the Centre de recherche médicale de l'Université de Sherbrooke research chair. All files will be retained for 7 years in accordance with institutional policies. It is also important to note that our study will comply with ethical considerations according to the Tri-Council Policy Statement: Research Ethics (2022) [66].

Results

The project was funded in March 2022. Data collection activities were completed in November 2024 following the recruitment and interview of participants living with chronic illness who received primary care services via telehealth. The recruitment process met the predefined sampling targets, ensuring adequate representation for qualitative analysis. Data collection was concluded after 22 interviews once thematic saturation was achieved, that is, no new themes or insights emerged from successive interviews, consistent with qualitative methodological guidance [67]. This decision was discussed and validated among the research team. As of December 2025, all participants had been recruited, and the qualitative data analysis was underway. Multiple manuscripts are in development, and the first set of findings was submitted for publication in fall 2025.

Discussion

Anticipated Findings

This study will better support and improve IPC in the context of telehealth using a patient-centered approach. Journey mapping will identify potential facilitating factors for improving primary care in telehealth settings, based on the patient's pathway. Recommendations will be made to build a practical guide supporting IPC in the primary care telehealth context. Various strategies will be implemented by the research team to promote knowledge transfer and knowledge integration.

This research possesses several notable strengths. First, it adopts a patient-centered research approach [40] and strongly collaborates with a patient partner, thereby ensuring the inclusion of perspectives and experiences of individuals directly affected by the health condition under investigation. Second, the use of journey mapping offers a comprehensive understanding of the patient journey, particularly emphasizing patient engagement within care processes of the IPC process, including its facilitators and barriers. This approach will enhance the knowledge transfer process and has the potential to positively influence primary care practice. Furthermore, this study contributes to addressing a gap in the current literature concerning the patient perspective on IPC in the context of telehealth.

Memory bias represents a significant limitation, as the intervention requires participants to recall information that may span 12 months [66]. However, the implementation of the pathway mapping approach serves as a method [46,66] to reengage memories, thereby mitigating this bias [58,59]. Another limitation of this study is that it was carried out only in 2 U-FMGs. This choice was deliberate to ensure consistency in organizational context and access to comparable interprofessional team structures, which supported the study's analytic depth rather than statistical generalization. We acknowledge that this may limit the generalizability. These teaching institutions are more supervised at the IPC level and better equipped for telehealth [15]. However, the team's research expertise, having already conducted several qualitative studies with U-FMGs, as well as the approach used, allows us to reduce

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this bias and truly understand how the U-FMG context may influence the results and transferability.

Conclusions

This research protocol presents a qualitative study designed to explore the experiences and perspectives of patients living with chronic illness regarding IPC in a telehealth context within primary care. Given the increasing reliance on telehealth modalities to deliver care, particularly for patients with complex and ongoing needs, this study addresses a critical gap in current knowledge. By focusing on the patient perspective, the findings are expected to inform best practices for IPC, guide improvements in telehealth service delivery, and support the development of patient-centered, coordinated care pathways. The results will contribute to optimizing the integration of telehealth in chronic disease management, ultimately enhancing the quality and continuity of care in primary care settings.

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Data Availability

Data sharing is not applicable to this paper as no datasets were generated or analyzed during this study.

Authors' Contributions

Conceptualization: MM, MEP, YC, IG, MDP
Methodology: MM, MEP, YC, IG, MDP
Patient or public involvement: MDP (patient coleader), involved in all stages of the study
Supervision: MEP, YC, IG
Writing—original draft: MM
Writing—review and editing: MEP, YC, IG, MDP, MM

Conflicts of Interest

None declared.

Multimedia Appendix 1
Montreal model.
[DOCX File, 141 KB - resprot_v14i1e79019_app1.docx]

Multimedia Appendix 2
Example of pathway mapping.
[DOCX File, 120 KB - resprot_v14i1e79019_app2.docx]

Multimedia Appendix 3
Interprofessional Education for Collaborative Patient-Centred Practice model.
[DOCX File, 251 KB - resprot_v14i1e79019_app3.docx]

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Abbreviations

IECPCP: Interprofessional Education for Collaborative Patient-Centred Practice
IPC: interprofessional collaboration
U-FMG: university family medicine group

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Development of an Intervention for Managing Adolescent Anxiety Using Community-Based Participatory Methods: Protocol

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Abstract

Background: Youth of color who live in urban communities face disproportionate anxiety levels due to systemic inequities, including exposure to violence, economic instability, and neighborhood disadvantage. Despite increased need, these communities often lack accessible mental health interventions.

Objective: This study presents a protocol for an anxiety prevention intervention developed through a community-based participatory approach that is tailored to urban youth of color using community-based participatory research methods.

Methods: The intervention, co-developed with a community partner and guided by a youth advisory board, includes 5 structured weekly sessions on psychoeducation, coping skills, and role-playing exercises. Facilitators trained in social work or psychology will deliver the intervention, with at least 1 facilitator from the target community ensuring cultural relevance. Recruitment will occur through collaboration with a local high school, with counselors identifying high-risk youth. We will enroll a sample of 30 high school–aged youth at minimum (maximum 50 youth) into the study. Two cohorts of youth will participate in the study. The groups will be separated by sex (male and female). The primary outcome is reduction in anxiety, measured by the Generalized Anxiety Disorder-7 scale. Data will be collected at baseline, after the intervention, and during follow-up assessments (3 months after). Statistical analyses will include parametric tests (eg, repeated measures ANOVA and 1-tailed *t* tests) to compare anxiety reduction across groups.

Results: This pilot intervention is a part of a larger study that began in September 2020 and ended in August 2025. Enrollment for the pilot intervention began in May 2025. The anxiety intervention is expected to reduce anxiety among a high-risk group of youth. Methods to improve facilitator fidelity to the intervention model are expected to support high fidelity to the curriculum.

Conclusions: This study highlights the development of a new anxiety intervention using a community-based participatory approach. Findings will be reported and used to scale up the pilot intervention into a larger clinical trial to serve a larger population of youth in the targeted community. In addition, the results will contribute to knowledge on improving mental health accessibility for marginalized youth. If effective, this model could be expanded to support youth in other underresourced communities.

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KEYWORDS

adolescent mental health; mental health; urban; prevention; community; community-based participatory research; co-development; co-design

Introduction

Background

In the United States, the prevalence of anxiety among youth has continued to steadily rise over the past few years [1]. Findings from the National Survey of Children's Health showed a 27% increase in anxiety from 2016 to 2019 and, by 2020, 5.6 million children had been diagnosed with anxiety problems [1]. Increased anxiety among youth of color has also been observed over the past few years [2,3]. Addition, the rate of increase in anxiety disorders among Black people overall exceeded the rate seen for White people over the same period (17.1% for Black people vs 4.5% for White people) [2]. Moreover, data from the

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National Comorbidity Survey, which assessed for lifetime prevalence of mood and anxiety disorders among English-speaking households, revealed that Hispanic or Latinx youth were at the highest risk for mood and anxiety disorders compared to non-Hispanic White adolescents [3]. Besides disparities across racial and ethnic groups, adolescents from low-income households, especially those in urban communities, are at higher risk for anxiety compared to their peers from high-income households [4,5].

While there may be many factors that play a role in the development of anxiety symptoms among youth, research has shown that increased rates of mental health issues, specifically among urban youth, are significantly related to the environment in which they live and if they are at a neighborhood disadvantage [6]. Characteristics of the urban environment, such as community violence, gang activity, substance use, and poverty, disproportionately affect urban youth and increase their exposure to potentially traumatic events such as incidents related to community-level violence [7]. This type of trauma exposure has been linked to the development of depression, anxiety, and early-age substance use. Similarly, neighborhood disadvantage consisting of limited resources, lack of safety, subpar housing, and unemployment has also been associated with anxiety among urban youth [5,7]. As evidenced, due to the amount of stressors youth are exposed to in urban communities, anxiety among this population is a significant public health problem, and the lack of resources in these communities exacerbates these issues. Underresourced urban communities are in dire need of services and programs that can improve the climates of spaces youth spend the majority of their time in, which can improve the overall mental health of the youth living in these communities.

As youth spend approximately one-third of their early developmental years within an academic setting, schools have been identified as effective sites for the implementation of mental health programming [8,9]. Due to schools being such key places for youth, school-based interventions have the opportunity of reaching youth who may have been previously unidentified or untreated [10]. Compared to community-based mental health clinics and primary care settings, delivering interventions in urban school settings, as an example, can address some of the many barriers faced by urban youth in underresourced communities such as removing the need for travel, unfamiliarity, cost, and time [11].

Importance of Community-Based Participatory Research

Community-based participatory research (CBPR) can be used as a critical approach in the development and implementation of mental health interventions, particularly in urban communities, as it is essential that these programs and interventions incorporate the voices of those living in these communities [12]. Researchers agree that the insights gained from receiving direct feedback from community members enhance the researchers' understanding of the problems affecting the community while also building on the strengths of the community. CBPR engages community members as equal partners and cogenerators of knowledge throughout the research process, ensuring that interventions are culturally relevant, contextually appropriate, and responsive to the specific needs of the population [12]. This collaborative methodology has proven effective in addressing systemic issues that contribute to mental health disparities, such as poverty, exposure to violence, and inadequate access to health care services [13]. Furthermore, CBPR fosters trust between academic researchers and historically marginalized communities, promoting the sustainability of mental health programs and enhancing their real-world impact [14].

Youth advisory boards (YABs) within CBPR projects, composed of young individuals from the very communities being studied, with diverse perspectives, play a pivotal role in ensuring that interventions are youth centered, engaging, and accessible. In recent years, research has shown the importance of including youth feedback in the development of mental health interventions for them [15]. It has been shown that the use of YABs helps to ensure that youth voices are heard within systems and helps to identify youth priorities related to mental health needs and issues [16]. Research also demonstrates that the use of youth participatory methods is helpful in obtaining meaningful insight from youth, engages them in the research process, and therefore empowers youth to be coparticipators in problem solving [17]. On a larger scale, including youth participation in research can also lead to more effective community-level policies that directly improve health outcomes and quality of life of this population [18]. By having youth actively participating in the co-design process, YAB members provide valuable insights into the language, delivery methods, and intervention components that resonate with their peers. Their involvement fosters a sense of ownership and empowerment, increasing the likelihood of program uptake and success.

Pertaining to youth mental health outcomes, engaging community members and YABs is crucial in developing effective interventions for young people, particularly in addressing mental health challenges such as anxiety. Community members offer invaluable insights into local needs, cultural dynamics, and systemic barriers that can influence the implementation and sustainability of interventions [18]. Their lived experiences help shape programs that are contextually relevant and responsive to the specific challenges faced by youth in their communities.

Purpose of This Study

The purpose of this protocol is to outline steps that were taken for the development of a pilot feasibility trial of a community-based psychoeducational intervention for anxiety designed to alleviate anxiety symptoms among youth living in an urban environment. This curriculum was developed through a collaborative partnership with a licensed clinical social worker who was born and raised in the study setting, ensuring that the intervention is both culturally relevant and grounded in the lived experiences of the community. Recognizing the unique stressors faced by youth in urban settings, including exposure to community violence, economic instability, and limited access to mental health resources, this program integrates evidence-based anxiety prevention strategies with community knowledge. The curriculum is designed to be interactive,

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incorporating cognitive behavioral techniques, mindfulness practices, and resilience-building exercises tailored to the realities of youth living in this community. By centering local expertise and youth voices, this intervention seeks to empower participants with the tools needed to manage stress, build emotional resilience, and improve overall mental well-being, while fostering a sense of community support and engagement. The primary aims of this intervention are to (1) increase participants' knowledge and understanding of anxiety, including its causes, symptoms, and physiological effects; (2) reduce stigma by normalizing conversations around anxiety and seeking different levels of help (eg, peer support, spiritual support, talking to a trusted adult, and therapy); and (3) increase participants' confidence in managing anxiety by equipping them with practical coping skills to navigate stressors in their daily lives.

Methods

Study Setting

The study will be conducted in Paterson, New Jersey, a northeastern urban community with a population of approximately 157,864 residents, with children and youth aged <18 years comprising about 27% of the population [19]. The city faces significant socioeconomic challenges, including a poverty rate of 23.5%, more than double the state average of 9.7%. These economic hardships contribute to increased mental health concerns among residents, particularly youth, highlighting the urgent need for targeted mental health interventions. The study's principal investigator (PI) has worked with the city as a community-based participatory researcher for almost a decade and leads multiple National Institutes of Health (NIH)–funded studies centered in this community, including a 5-year NIH-funded grant, the Paterson Prevention Project, which examines the impact of neighborhoods on youth substance use and mental health in the city [20]. Using previously published research from work conducted in the target community, and using a community-based participatory approach, the study has identified anxiety as a critical concern among Paterson youth. Addressing anxiety through targeted interventions has emerged as a crucial step in improving mental health access and outcomes in this underserved community.

Participatory Co-Design Process: Initial Development

The development of the intervention was a collaborative and community-engaged process that underscores the importance of co-designing with trusted community partners to enhance feasibility, cultural relevance, and sustainability. The initial intervention idea came from CP, a licensed clinical social worker and a longstanding, trusted community partner of the Paterson Prevention Project. Through her active participation in research activities in the project, including data collection and engagement with youth, CP identified a critical need for anxiety prevention resources and independently initiated an informal intervention at a local high school. Confirmed with evidence from qualitative and quantitative findings from the study, the PI decided to co-develop a pilot intervention with the community partner. This collaboration ensured that the intervention was not only informed by community insights but also grounded in evidence-based strategies. First, CP provided an outline of the sessions, such as topics that were important to address. CP met with the study's PI and the study team several times to decide on a specific framework to use and activities that would be included in each session. By integrating evidence-based practices with the lived experiences and firsthand observations of a community-based mental health practitioner, the intervention was strengthened in its feasibility, acceptability, and potential for scalability.

Co-designing interventions with community partners such as CP facilitates the integration of scientific rigor with practical, real-world application, increasing the likelihood of successful implementation and long-term sustainability. This approach aligns with participatory research principles, which emphasize the value of local expertise in shaping interventions that are responsive to community needs. Through this iterative process, the intervention was refined to balance evidence-based strategies with culturally and contextually relevant components, ensuring it could be effectively scaled and sustained within the community.

Theoretical Framework

The intervention is guided using cognitive behavioral therapy (CBT) principles, a well-established evidence-based approach that targets maladaptive thoughts and behaviors to improve mental health outcomes [21]. In addition to psychoeducation around symptoms of anxiety, CBT also emphasizes skill development and implementation such as breathing techniques, visualization, and graded exposure and role-playing. Given the unique needs of urban youth, adaptations of how CBT will be delivered have been developed to enhance its cultural relevance and effectiveness. Research has demonstrated that culturally tailored CBT interventions for urban youth populations incorporate contextual stressors such as systemic inequities, racial discrimination, and community violence, making the approach more applicable and impactful for these communities [22]. AdditionAdditionally, our intervention integrates principles from trauma-focused CBT, which has been shown to be effective in addressing trauma-related symptoms among youth who have experienced adversity [23]. By incorporating both frameworks alongside trauma-informed strategies, our approach aims to provide a comprehensive and culturally responsive intervention for urban youth facing multiple forms of psychosocial stressors.

Development of the Intervention Facilitator Guide

Overview

The initial intervention materials for the curriculum were developed by CP, BD-B (project manager at the time of study), and the PI (IO) in collaboration with YAB members of the Paterson Prevention Project. The research staff was instrumental in the development of graphics and curriculum structure (SJ, CM, and HV); the accuracy of session topics and strategies was reviewed for accuracy by a licensed child psychiatrist on the team (KA) and postdoctora research fellow and psychologist (RER).

In addition, the Paterson Prevention Project YAB, which consists of 8 teenagers and young adults who live in Paterson, was instrumental in reviewing materials with research staff

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during biweekly meetings over the course of 2 years. All research activities including the development of sessions and evaluation materials were supervised and approved by the PI (IO). One of the advisory board members is a recent Master of Social Work graduate and has been trained as a cofacilitator of the intervention.

Theater Testing

Theater testing is a critical step in the development and refinement of an intervention, allowing facilitators to practice the delivery of the curriculum with a small group before full-scale implementation. This process helps identify strengths, areas for improvement, and any logistical or content-related challenges that may arise. By running the intervention in a controlled environment with a representative sample, facilitators can assess whether the activities, discussions, and pacing are engaging and effective for participants. Research supports the use of pilot or feasibility testing in intervention development, as it provides essential feedback to refine content, delivery style, and overall structure, ensuring that the program is both evidence based and practical for real-world application [24]. Additionally, theater testing allows facilitators to become more comfortable with the material, enhancing their ability to deliver sessions with confidence and consistency [25].

In February 2025, the study team conducted a theater test of the intervention with 5 members of our YAB during an 8-hour session in person in Paterson, New Jersey. The facilitators led participants through the full intervention while a designated study team member took notes on participant engagement, clarity of instructions, and areas needing improvement. After completing the session, the study team convened to discuss feedback and make necessary revisions to the curriculum. Additionally, a follow-up meeting was held with the PI to review the final adjustments before moving forward with pilot testing. This iterative process ensures that the intervention is responsive to the needs of the target population, aligns with best practices in youth mental health programming, and is optimized for successful implementation.

Finalization of Intervention

While there are no control conditions, as the intervention will run over multiple iterations, a staggered start design will be used to account for potential differences in groups. A staggered start design is a phased implementation approach that allows for iterative assessment and refinement of an intervention before full-scale delivery. In this study, this design involves initiating the intervention with 2 initial cohorts, each consisting of 8 to 10 youth stratified by sex (male and female). This first cohort will complete sessions 1 to 5 while facilitators document process implementation using fidelity assessment tools. This approach enables real-time evaluation of intervention delivery, facilitator adherence, and participant engagement, allowing for any necessary refinements before subsequent cohorts are enrolled. Following the completion of the initial cohorts, an additional 2 cohorts will be recruited, with this process continuing until we reach our target enrollment of 30 to 50 youth. We anticipate recruiting 2 cohorts.

Supervision will be provided by a licensed clinical social worker (CP) who is deeply familiar with the community and was instrumental in the development of the intervention and a project manager on the team. External reviews of fidelity and intervention outcomes will be reviewed by the study PI and a licensed child psychiatrist who is on the study team.

Pilot Study Procedures: Recruitment, Selection, and Consent Process

This study is approved by the institutional review board of Yale University and has been registered on Clinical Trials.gov (NCT07044752). The recruitment plan for the pilot study intervention will involve a collaborative partnership with a local high school, working closely with the principal and lead school counselors to identify youth who may benefit from participation. School counselors and teachers will play a key role in identifying students who exhibit signs of heightened anxiety or have been classified as high risk based on behavioral observations, academic performance, and self-reported concerns. To ensure a targeted and effective approach, recruitment will prioritize students who have been flagged by school guidance counselors for increased anxiety symptoms, difficulty managing stress, or other related mental health challenges. Once identified, eligible students will be invited to participate, with parental consent waived as per institutional review board approval. The intervention cohorts will be divided by sex (self-identified by the youth) to foster a comfortable and supportive group dynamic, allowing for tailored discussions and activities that align with the unique experiences and stressors faced by male and female students. This structured recruitment approach ensures that the intervention reaches those in greatest need while maintaining a supportive and inclusive environment for all participants. After referral to the intervention, the relevant information of the study will be provided to all participants in detail, and they will be given sufficient time to consider whether to participate in the study. If the participants agree to participate in the intervention, they will sign an informed assent form. Parental consent will be waived; however, all parents of youth participants will receive an information sheet indicating that their child is participating in an intervention. No blinding or randomization will occur in this phase of pilot testing. Due to participants being classed as a vulnerable population, they will also be notified of mandated reporter requirements. Each intervention group will consist of 5 to 10 participants, with a preferred group size of 8 with a total sample of 50 participants.

Intervention Facilitators

The intervention will be facilitated by a license-eligible social worker who is on the study's YAB and is from the community and a license-eligible clinical psychologist on the study team. Having facilitators from the community is crucial, as research indicates that community-based mentors and professionals foster stronger connections with participants, enhance engagement, and improve intervention outcomes [25,26]. These facilitators bring an intrinsic understanding of local stressors, social dynamics, and cultural nuances that external professionals may not fully grasp. Their presence helps to build trust and relatability, making the youth feel more comfortable discussing their experiences and applying coping strategies. Additionally,

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incorporating local facilitators into the program fosters sustainability, as they can continue to serve as mental health advocates within their community beyond the duration of the intervention [25,26]. This approach ensures that the program is not only evidence based but also deeply rooted in the strengths and needs of the community it serves.

Study Measures: Baseline and Posttreatment Tests

The study will be conducted over 5 weeks with multiple assessment points depending on the measure. Outcome measures will be collected at the first session, which will be considered at baseline (T1) and after treatment (T2; 4 weeks from the baseline assessment or after the last intervention session has been completed).

Primary Outcomes

The primary outcome is the mean change in anxiety scores on the Generalized Anxiety Disorder-7 (GAD-7) questionnaire for adolescents between the baseline, after the intervention, and at the 3-month follow-up (T2). The questionnaire has 7 items, each with a 4-point scale, with scores between 0 and 21 points. Scores are considered as follows: 0 to 4 symptoms (minimal), 5 to 9 symptoms (mild), 10 to 14 symptoms (moderate), and 15 to 21 symptoms (severe). The GAD-7 has demonstrated excellent psychometric properties [27-30]. The items inquire about the degree to which the patient has been bothered by feeling nervous, anxious, or on edge; not being able to stop or control worrying; worrying too much about different things; having trouble relaxing; being so restless that it is hard to sit still; becoming easily annoyed or irritable; and feeling afraid as if something might happen.

Secondary Outcomes

Secondary outcomes will include the Coping Self-Efficacy Scale, a validated instrument assessing individuals' confidence in using adaptive coping strategies to manage stressors [31]. Depression symptoms will be assessed using a validated measure such as the Patient Health Questionnaire-9 [32], which will allow us to explore whether reductions in depressive symptoms contribute to improvements in other targeted outcomes. By integrating these measures, we aim to comprehensively evaluate the intervention's impact and identify key mechanisms driving behavior change.

Sample Size and Power Justification

This study was powered based on the primary aim of assessing the feasibility of the newly developed intervention. Sample sizes ranging from 24 to 50 have been recommended for feasibility studies [31,32]. With a sample size of 50, we expect to retain at least 80% of the participants at 3 months after the intervention. For primary and secondary aims, we will estimate effect sizes from means and SDs, which will be used to determine the power needed for a future randomized controlled trial.

The planned analyses will include both descriptive and inferential statistics to assess the intervention's effectiveness. The main outcome of interest will be anxiety. We expect that mean GAD-7 scores in the posttest assessments will be significantly lower than baseline scores. Baseline demographic characteristics, including age, sex, race, and socioeconomic status, will be reported. A repeated measures ANOVA within a within-subjects design will be used to test this hypothesis, with Shapiro-Wilk tests assessing normality assumptions. Based on previous literature that has used these measures, the distribution of difference scores will likely be normal. The study team will also explore whether changes in GAD-7 scores differ by sex. In addition, the study team will conduct statistical analyses to assess the reliability and construct validity of the GAD-7 questionnaire within the sample. Specifically, confirmatory factor analysis and Cronbach α will be used to evaluate the scale's factor structure and internal consistency. Given previous use of the GAD-7 questionnaire in similar samples of youth of color [27,28], we anticipate that the scale will demonstrate strong psychometric properties in this population [29,30].

Additionally, logistic regression models will estimate the likelihood of clinically significant improvements in mental health and behavioral outcomes based on key predictors, including baseline symptom severity, intervention dosage, and demographic factors. Given the longitudinal nature of our data, we will use linear mixed-effects models to account for within-subject correlations and evaluate changes over multiple follow-up points. These models will help determine whether intervention effects are sustained and whether specific subgroups (eg, sex-based cohorts) exhibit differential responses.

Fidelity to Intervention

A fidelity form created by the study team will be used to monitor fidelity to the intervention. Each facilitator will complete the fidelity form after each session. The form will track the main activities engaged in, skills covered, deviations from protocol, and adverse events that emerge during each session. Open-ended responses will be reviewed by the study team to identify any themes.

Qualitative Analysis

Focus groups will be conducted after the final session with youth participants and after the baseline and posttreatment surveys have been completed. A study team member who was not involved in delivering the intervention will facilitate the groups to reduce bias and enhance transparency. Findings will offer deeper insight into the intervention's effectiveness and acceptability, as well as how participants describe anxiety and its environmental influences in their lives.

Ethical Considerations

To safeguard the confidentiality of the participants and to ensure proper handling of all data, processing of all data reporting complies with Collaborative Institutional Training Initiative recommendations and is in accordance with the established guidelines on ethical conduct in human research. Participants will provide written informed assent. All participant data will be allocated a deidentified code so that confidentiality is maintained during the study and when the data are stored. Deidentified data will be stored in password-protected secure online data storage repositories at Yale University. Only PIs, interventionists, the statistician, the project manager, and research assistants will have access to these deidentified data

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for the following purposes: (1) assessment of participants' acute mental health, (2) quality improvement of the intervention, and (3) publication of findings. Any adverse events or clinical complications that arise as a result of the intervention will be reported by the interventions to the supervisor and PI after the session and during regular project supervision. All adverse events will be documented.

Due to participants being classed as a vulnerable population, they will also be notified of mandated reporter requirements during the assent process and at the beginning of each session. Considering that youth may share vulnerable personal information, students will be reminded of the importance of confidentiality at the beginning of each session. As participation will take place on school grounds, measures will also be taken to not reveal students' participation in the group to nonparticipating peers. While students will be provided with resources at the end of each session, should a participant express high, acute mental health needs outside of the scope of the intervention, they will be referred to the school's psychologist or social worker.

Results

This pilot intervention is a part of a larger community-based study funded by the NIH. The study began in September 2020 and ended in August 2025 [21]. Recruitment for the pilot intervention trial began in April 2025, with the first session beginning in May 2025. In collaboration with a local high school in the city of Paterson. School counselors referred youths who were considered to display moderate to high levels of anxiety. The intervention was completed at the end of June 2025. The intervention took place during school hours, in a local classroom that was provided by the high school.

Discussion

Anticipated Findings

The study teams hypothesize that there will be a reduction of anxiety symptoms in youth who participate in the intervention. In addition, there may be notable differences by sex and how messages around anxiety are received. The significant psychosocial burden of anxiety and persistent resource accessibility gaps necessitates continued efforts to blend best practices in CBT with the unique needs faced by underresourced urban youth. This study will be testing out hypotheses around the application of CBT skills in addressing the underlying mechanisms that create and maintain anxiety for urban youth; that is, participants will be encouraged to actively identify and challenge unhelpful or unrealistic cognitions related to salient experiences (examinations and class presentations) and difficult interpersonal interactions. This process is complemented by behavioral activation to encourage broader engagement in coping skills and support seeking. Participants will also be encouraged to practice graded exposure to reduce the avoidance of participant-identified stressful situations, as well as problem-solving barriers to effectively engage in helpful coping (eg, seeking support when current coping skills are no longer effective). One major strength of the pilot intervention design is that the conceptualization of this intervention has had significant input from the population it aims to support: urban youth. It also tackles some of the frequent situations and target maladaptive cognitions the youth identified. While individual and group CBT-based anxiety interventions have been considered very useful in preventing and treating childhood anxiety [33], there is less research on using such interventions within a community-level participatory framework. We acknowledge the potential bias introduced by conducting theater testing with an existing YAB. However, we believe that the invaluable feedback provided by their participation mitigates this confounder. Findings from this community-based pilot study will be disseminated widely, including the local school where the intervention was implemented. Results will also be shared with community stakeholders through infographics, an end-of-year report to city officials, and on social media platforms (eg, Instagram) to ensure accessibility and transparency.

While a lack of randomization of this pilot study is a limitation, the decision to offer the intervention to eligible youth reflects our commitment to addressing an urgent community-identified need—particularly in a city where no formal anxiety-focused interventions currently exist. Future directions include scaling the intervention through a larger waitlist-controlled or randomized controlled trial and adapting it for implementation in other cities facing similar mental health disparities.

Conclusions

This pilot study will provide a basis for the efficacy of a CBPR-guided, CBT-informed intervention for anxiety in school-aged urban adolescents. Outcomes from this study will provide evidence for the feasibility of incorporating this framework within urban communities and highlight the importance of researchers collaborating and cocreating solutions with youth and community members.

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Authors' Contributions

IO was responsible for conceptualization, data curation, investigation, methodology, resources, funding acquisition, and supervision. CP was responsible for investigation and conceptualization. IO, RER, CM, SJ, HV, and KA were responsible for writing—original draft and review and editing. BD-B was responsible for project administration, data curation, visualization, and writing—review and editing. CM was responsible for project administration. SJ and HV were responsible for visualization. KA was responsible for the supervision.

Conflicts of Interest

None declared.

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Abbreviations

CBPR: community-based participatory research
CBT: cognitive behavioral therapy
GAD-7: Generalized Anxiety Disorder-7
NIH: National Institutes of Health
PI: principal investigator
YAB: youth advisory board

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Protocol

Evaluating the Impacts of Community-Campus Engagement on Population Health in Ottawa and Thunder Bay, Canada: Protocol for a Mixed Methods Contribution Analysis

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Abstract

Background: Municipalities play a crucial role in population health due to their community connections and influence on health determinants. Community-campus engagement (CCE), that is, collaboration between academic institutions and communities, is a promising approach to addressing community health priorities. However, evidence of CCE's impact on population health remains limited. Measuring the impacts of CCE is inherently complex due to factors such as diverse stakeholders, context-specific variables, and dynamic interactions within a community.

Objective: This study aims to develop robust evidence on the impacts of CCE on population health outcomes in Ottawa and Thunder Bay, Ontario, Canada, focusing on 5 shared health priorities: housing, discrimination, poverty, violence, and mental health.

Methods: We will use a proven CCE model called CityStudio, which has been implemented in both cities. We will use Mayne's mixed methods contribution analysis in three stages: (1) formulating a theory of change that outlines the expected contributions of CCE to population health outcomes; (2) gathering qualitative and quantitative data in line with the established Theory of Change; the data will be collected from various sources, including case studies of existing CityStudio projects, a web-based CCE stakeholder survey, a literature review, and population and community health data; and (3) reviewing the gathered evidence to determine the extent of CCE impacts on population health.

Results: Ethical approval for this project was granted in May 2023. We have since initiated stage 1 by reviewing the literature to inform the development of the theory of change. We expect to complete this study by May 2026.

Conclusions: This study will address two critical gaps about how improving health outcomes depends on CCE: (1) how academic institutions can best engage with their communities to improve population health outcomes, and (2) how municipalities can engage with academic institutions to address their community health priorities. Conducting our work in differing contexts will allow us to consider a broader range of other influences on outcomes, thus making our work applicable to various settings and outcomes.

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KEYWORDS

community-campus engagement; population health; contribution analysis; mixed methods; health determinants; community health; CityStudio; theory of change; impact evaluation

Introduction

Background

Achieving improved population health outcomes requires a comprehensive, multisectoral approach beyond healthcare [1-3]. With their robust community ties and influence over various health determinants, municipalities are well-positioned to drive progress [1-3]. In Canada, local governments and community partners often identify their communities' priority health needs through established safety plans or social policy frameworks [3]. These needs are expressed in Ontario, the country's most populous province, through provincially mandated Community Safety and Well-Being Plans (CSWBPs) [4]. Updated every 4 years, these plans serve as strategic roadmaps, guiding municipalities' efforts to improve population health outcomes [4,5].

Collaborations between municipalities and their local academic institutions have the potential to contribute positively to the health of the local community [6-9]. Through collaborative efforts, community-campus engagement (CCE) fosters mutually beneficial relationships between local stakeholders (eg, community organizations, city representatives, and residents) and academic institutions (eg, universities and research centers) [6-8]. Municipalities can contribute their deep understanding of local needs and priorities to such engagement, while academic institutions provide research expertise and resources [6,8,10]. This collaborative framework facilitates shared decision-making, efficient resource allocation, and the development of tailored strategies to directly address specific health concerns within the community, ultimately leading to improved health outcomes [6,10].

CCE can take various forms, such as community-based research and service learning [6,10]. Community-based research involves collaboration between faculty members, students, and local communities to address critical issues [6,10]. On the other hand, service-learning integrates classroom learning with community service, equipping students with the skills to tackle real-world challenges while also improving their communities [6,10]. Each form can potentially contribute to the community's health in different ways. For instance, community-based research can identify emerging health disparities in specific neighborhoods, while service-learning programs can equip future health care professionals with the skills to address these issues.

While CCE shows promise in supporting municipalities' health agenda goals, there remains significant uncertainty about the specific mechanisms and pathways through which it influences population health outcomes, underscoring the need for further research to understand its impact at the municipal level [11]. Existing literature in this area is mainly reflective [12,13] or qualitative [14,15], primarily focusing on health outcomes resulting from individual partnerships [16-19] and the perspectives of faculty and students involved in CCE [10,14,20,21]. Although these studies provide valuable insights, they offer only a partial understanding of CCE's broader impact on population health because they do not fully investigate the pathways, conditions, and contextual factors that influence outcomes.

Some studies have reported positive health outcomes, such as reduced substance misuse [16] and increased physical activity [17]. However, these studies often fail to clearly outline the change processes that explain these positive outcomes, focusing mainly on end results. This emphasis on outcomes, with insufficient attention to the processes, limits our understanding of how specific actions, stakeholder interactions, and contextual factors contribute to health improvements. Consequently, the complexity of the mechanisms driving these changes remains underexplored, making it difficult to pinpoint the pathways through which CCE initiatives achieve their impact. This knowledge gap highlights the need for more robust research to evaluate the impact of CCE on population health at the municipal level that specifically focuses on the contexts and mechanisms that result in change.

Contribution Analysis: a Promising Approach for Evaluating the CCE Impacts

As with community engagement in general, the complexity of measuring CCE impacts on population health makes experimental approaches to measuring CCE impacts neither practical nor feasible, as many factors cannot be controlled for [22], such as the involvement of diverse stakeholders with diverging interests (eg, local governments, faculty and students, community groups) [15,23,24], the evolving dynamics of operations [25], and the influence of external factors like governmental policies and local socioeconomic conditions [15,26,27]. Experimental approaches may thus overlook the underlying causes of an intervention's success or failure, providing limited insights into the causal mechanisms at play [28,29].

Contribution analysis is a theory-based impact evaluation approach that is particularly suited to contexts of high uncertainty, where the goal is not to prove causation definitively but to reduce uncertainty by establishing a plausible association between interventions and outcomes [28-32]. This emphasis on reducing uncertainty makes CA particularly suitable for evaluating the CCE impact on population health [11].

An integral component of contribution analysis is the theory of change, which outlines the causal mechanisms in a results chain running from inputs to impact and illustrates how the intervention being examined is expected to bring about change [31]. However, the theory of change goes beyond a standard results chain or logic model by elucidating assumptions, risks, unintended effects, and other vital factors underpinning the relationships [30,31].

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Narrative statements, known as contribution claims, are generated once the theory of change has been developed [32]. These claims are presented as hypotheses, proposing how the intervention's activities and outputs contribute to the observed outcomes while considering influencing factors and context [30]. The theory of change and contribution claims are refined and validated iteratively using qualitative and quantitative data and stakeholder participation [22,32]. This process alternates between theory development and empirical testing, resulting in a robust, evidence-based theory of change [30]. The ensuing theory is the foundation for the contribution story, which offers a detailed account of the intervention's impact and the stakeholders' perspectives [33].

Contribution analysis may be carried out at 3 levels: minimalist, direct influence, and indirect influence, each tailored to the complexity of the intervention and the depth of the assessment [22]. Minimalist contribution analysis is ideal for interventions with clear, measurable outcomes. It formulates a theory of change, confirms output delivery, and validates contribution claims using existing data and evidence [22,32]. Direct influence contribution analysis is suitable for complex interventions with diverse outcomes, as it builds on minimalist analysis by using empirical data to confirm the intervention's contribution to the impact [22]. Indirect influence contribution analysis, suitable for complex interventions with uncertain, emergent outcomes, builds on direct influence analysis by further testing contribution claims against alternative explanations, offering a more comprehensive understanding of what caused an observed impact [31,32].

Objective

This research project uses contribution analysis to rigorously assess and reduce uncertainty about whether, how, and to what extent CCE has contributed to improving population health in Ottawa and Thunder Bay, Ontario, Canada. The study will focus on 5 specific shared population health priorities for both municipalities: housing, discrimination, poverty, violence, and mental health. Our specific objectives are as follows.

- Identify and outline the key mechanisms and processes through which CCE is anticipated to impact population health outcomes in Ottawa and Thunder Bay.
- Assess the extent to which CCE has contributed to the targeted population health outcomes, evaluating their impact against the mapped mechanisms and processes.

Methods

Study Setting

Our study will be conducted in Thunder Bay and Ottawa, 2 Ontario municipalities with medical schools and health education institutions. These cities have developed CSWBPs by reviewing local data comprehensively and holding community consultation sessions to identify their population's unique needs and characteristics [34,35]. Despite differences between the Ottawa and Thunder Bay CSWBPs, both cities have identified 5 similar priorities related to population health, as outlined in Table 1.

Table 1. Shared priorities in the Thunder Bay and Ottawa Community Safety and Well-Being Plans.

Priority areas	Description
Housing	Ensuring all residents have access to safe, affordable, and suitable housing.
Discrimination	Addressing systemic issues perpetuating discrimination, marginalization, and racism within the community.
Poverty	Achieving financial security and reducing poverty for community members.
Violence	Preventing and reducing gender-based violence and violence against women in the community.
Mental health	Promoting positive mental health and well-being for all community members.

To help address these priorities, both municipalities have adopted CityStudio, a transferable, nonprofit, project-oriented, evidence-based model of CCE [36,37]. This model aims to innovate how cities are co-created to become healthier communities and assist community stakeholders in improving their neighborhoods [38]. The model is demand-driven, leveraging expertise and resources from educational institutions to meet the priority needs identified by the city. The CityStudio project cycle encompasses 5 stages, from initial collaboration for project development and confirmation through work on a real site to final project design for scalability [36].

The cities of Ottawa and Thunder Bay have formally launched CityStudio and initiated and completed various projects. To date, 63 projects have been carried out involving community groups, city staff, and faculty and students from 6 academic institutions in these regions. CityStudio Ottawa and CityStudio Thunder Bay are engaged in this research study, providing full access to a list of stakeholders involved in their projects and data on an inventory of CCE projects.

Study Design

We will apply Mayne's contribution analysis within a convergent parallel mixed methods design to assess the contribution of CCE to population health in Ottawa and Thunder Bay [39]. A convergent parallel design allows for the simultaneous collection and independent analysis of both qualitative and quantitative data, with results from each strand analyzed for congruence and integration during the interpretation phase [40]. Mayne's approach is particularly suited for complex interventions such as CCE and has been effectively used in assessing the impacts of interventions and policies in fields such as international development [41] and public administration [42]. However, our recent scoping review suggests that this approach is infrequently applied in health-related interventions [43]. Therefore, our research aims to both generate rigorous

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evidence of CCE's impact on health and provide valuable insights for using contribution analysis in health research and evaluation.

The following preliminary evaluative questions will direct our analysis. These questions will be refined further upon the completion of stage 1.

- What are the specific mechanisms and pathways by which CCE influences population health outcomes in Ottawa and Thunder Bay?
- To what extent does CCE contribute to changes in population health outcomes relative to other factors in both cities?

We will specifically use the cause-to-effect strategy, which begins with CCE and works forward to understand how it contributes to health outcomes. The cause-to-effect strategy focuses on identifying "causal packages"—combinations of CCE activities and other contributing factors that collectively explain the observed changes [44]. We will adopt a streamlined version of Mayne's 6-step approach to contribution analysis, condensing it into the 3 crucial stages described by Delahais [30]. The 3 stages are as follows.

- Stage 1—theory of change development: This stage involves using a 3-phase approach to developing a robust theory of change that accurately represents the potential pathways and external factors describing how CCE is expected to contribute to improved population health outcomes in Ottawa and Thunder Bay. This stage is expected to last 7 months.
- Stage 2—evidence gathering: Both qualitative and quantitative methods are used to generate evidence in line with the established theory of change. The collected evidence forms the basis for empirical examination. This stage is expected to last 11 months.
- Stage 3—theory of change assessment and refinement: This stage involves reviewing the gathered evidence to determine the extent of CCE impacts on population health. Any identified limitations lead to a return to stage 2 for additional data collection until satisfactory evidence is gathered. This stage is expected to last 5 months.

Figure 1 provides a visual overview of the research process, illustrating the dynamic relationship between data collection (stage 2) and theory testing (stage 3) [30].

Figure 1. Overview of the research process. CCE: community-campus engagement.

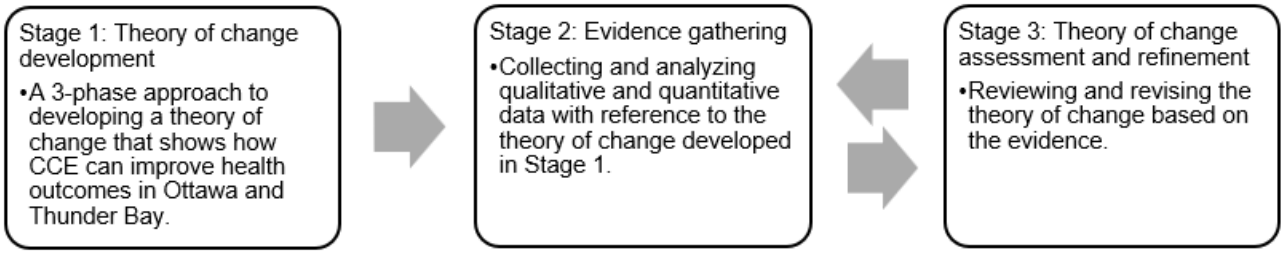

This study adheres to the Good Reporting of A Mixed Methods Study (GRAMMS) guidelines [45] to ensure comprehensive and transparent reporting of the mixed methods design, including the justification for the approach, the integration of qualitative and quantitative data, and the insights gained from their convergence (Multimedia Appendix 1).

Stage 1: Theory of Change Development

Overview

Stage 1 will use a 3-phase approach to construct a credible theory of change. Each phase corresponds to one of the approaches proposed by Funnell and Rogers [46] for purposeful theory development: (1) deductive, (2) articulation of mental models, and (3) inductive, which will be implemented sequentially in the theory of change development process, with the potential for iteration to accommodate evolving requirements. An overview of each phase and corresponding methods is presented in Table 2. While our approach follows a structured sequence, we acknowledge that the evolving nature of developing a theory of change requires flexibility, allowing for iteration as needed. Each step of the theory of change development will be carefully documented to maintain transparency in this iterative process. This includes tracking the initial assumptions, the evolution of claims based on stakeholder input and empirical evidence, and the methodological adjustments made throughout the process. The documentation will highlight how and why specific claims were refined, discarded, or validated, ensuring that the process remains transparent and aligned with best practices in contribution analysis.

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Table 2. Overview of the study's 3-phase approach to developing the theory of change.

Phases	Description	Proposed methods
Phase 1: Deductive	Draft an initial theory of change based on existing theories and knowledge.	Conduct a narrative literature review on the health impacts of CCE[a], focusing on the 5 shared Ottawa and Thunder Bay priorities.
Phase 2: Mental model articulation	Express the implicit assumptions or mental models of stakeholders.	Hold stakeholder workshops to provide feedback on the drafted theory of change and identify context-specific factors influencing outcomes.
Phase 3: Inductive	Validate and refine the theory of change using practical insights and external expertise.	Conduct semistructured interviews with experts in CCE and program evaluation for validation and refinement.

[a]CCE: community-campus engagement.

Phase 1: Deductive

Phase 1 uses Funnell and Rogers' deductive approach [46] to formulate an initial theory of change based on existing theories and knowledge, ensuring a solid theoretical foundation. To accomplish this, we will conduct a narrative literature review chosen for its flexibility and capacity to identify critical theories, concepts, and findings related to CCE and its impact on population health concerning the five identified areas of population health [47]. The results of this review will lay the groundwork for the development of the theory of change, as detailed in the subsequent sections.

Narrative Literature Review Procedures

In collaboration with a librarian, we will design and execute a comprehensive search strategy that encompasses relevant health databases and sources. The selected literature will be imported into Covidence (Veritas Health Innovation Ltd), a web-based literature review tool, for screening by independent reviewers [48]. At least 3 research team members will review various sources, including academic papers, reports, and policy documents, to inform the initial development of the theory of change. Screening criteria will include relevance to the 5 key population health priorities and use for the theory of change.

Team members will create an annotated bibliography for each paper using a standardized template based on Bennett's hierarchy [49], a framework that categorizes program outcomes (inputs, activities, outputs, and impacts) [50]. The template will be divided into three sections: (1) CCE implementation, focusing on inputs, activities, participation, and reactions; (2) knowledge and practice change, focusing on knowledge, awareness, skills, attitude, and practice change; (3) results and impact, focusing on final health impacts or changes for individuals, communities, systems, or organizations. Team members will hold weekly meetings to share insights from the literature and discuss potential pathways.

Development of the Initial Theory of Change

Following the literature review, team members will convene to create the initial theory of change using Vogel's team-based approach, which is specifically designed to develop theories of change for research projects. This approach includes guiding questions on 5 key areas: context analysis, long-term change, sequence of events, assumptions, and diagram and narrative summary [51]. To document decisions and track modifications, the team will use Theory of Change Online 3.0 (ActKnowledge), a web-based software designed explicitly for the collaborative theory of change building [52]. This initial theory of change will remain adaptable, allowing for iterative revisions based on feedback and new data. Once the initial draft of the theory of change is completed and agreed upon, the team will proceed to the mental model articulation phase.

Phase 2: Mental Model Articulation

In phase 2 of the theory of change development, we will use Funnell and Rogers's mental model articulation approach [46]. This approach will help us integrate stakeholder insights, ensuring they are context-specific, comprehensive, and account for relevant influencing factors. To achieve this, we will conduct participatory workshops with stakeholders involved in CCE through CityStudio Ottawa and Thunder Bay [53,54].

Recruitment of Stakeholders

We will use a purposeful sampling strategy to invite stakeholders based on specific criteria such as their location (Ottawa and Thunder Bay), experience with CCE, stakeholder roles (academics, community partners, and city staff), and knowledge related to the 5 shared population health priorities. This approach will ensure a diverse representation of stakeholders, balancing their professional backgrounds, geography, and CCE experience. [55].

Our initial outreach will target CityStudio Ottawa and CityStudio Thunder Bay stakeholders who expressed interest in our workshops during 2 information sessions held in May 2023, which aimed to gather feedback on the proposed protocol and identify potential workshop participants. The participants will include academics, community partners, and city representatives involved in CCE who expressed interest and shared their contact details through a web-based survey during their participation in the information session.

We will engage CityStudio coordinators in Ottawa and Thunder Bay if additional participants are needed. They will circulate an invitation email to their contact lists, which include a broader network of individuals involved in CCE. The email will provide information about the project, the purpose of the workshops, and the importance of their participation. All participants will be asked to sign a consent form before their involvement.

Stakeholder Workshops Procedures

We plan to conduct 2 separate workshops conducted via Zoom. The first workshop will assemble 10-12 stakeholders from Ottawa, and the second will gather a similar group from Thunder

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Bay. Each workshop, lasting 3 hours, will be divided into 2 parts.

- Introduction and overview: We will provide essential details about contribution analysis and the theory of change. We will then present an overview of our draft theory of change and explain the process used to develop it.
- Feedback and identification of context-specific factors: We will use Kranias' participatory facilitation techniques [56] to collect feedback on the plausibility of our initial theory of change and, for each city, identify the roles of other influencing factors and alternative explanations that could affect the theory of change's impact pathways. To identify specific contextual factors with participants, we will use the classification of Pawson et al [57], which divides these factors into 4 categories: individual, interpersonal, institutional, and infrastructure. This classification has proven helpful for identifying contextual factors in a workshop setting in previous applications of contribution analysis [50,58]. This classification and stakeholder input will be revisited iteratively as needed, ensuring the theory of change remains aligned with emerging contextual insights.

At least 2 research team members will facilitate each workshop, following a facilitation guide based on Vogel's approach [50]. With participant consent, workshops will be recorded for review purposes. Workshop participants will receive CAD $100 compensation (approximately US $71 at the exchange rate at the time of the study: CAD $1=US $0.71) for their time and contribution and a summary of the key outcomes and changes made to the theory of change for validation.

Phase 3: Inductive

Phase 3 involves assessing the theory of change's coherence, logic, and theoretical foundations and identifying potential gaps or areas for enhancement. Following Funnell and Rogers [46], we will conduct semistructured interviews with experts. This method is particularly effective for gathering in-depth, expert-based insights, which will be instrumental in refining our theory of change and ensuring its robustness and relevance.

Recruitment of Experts

We will use a snowball sampling strategy to identify 5-6 experts in population health, CCE, and theory-based evaluation. Our research partners will provide us with a list of potential interviewees. These individuals will receive an invitation via email, including a detailed description of the study and their expected participation. Before participating, they must sign a consent form and declare no conflict of interest. Each expert will be compensated CAD $150 (US $105.87) for their time.

Data Collection and Analysis

We will send a documentation package to the experts for review 3 weeks before the interview. This package will include the drafted theory of change and its narrative, the development process used, and an assessment grid based on Mayne's validated criteria for an in-depth theory of change analysis [31]. The assessment grid will contain questions to assess the overall logic and structure of the theory of change, the clarity of its expected outcomes, the validity of its assumptions, and the independence of assumptions for each causal link [31]. A research team member will contact the experts to ensure they understand the documentation and answer any questions.

The semistructured interviews will combine structured questions from the assessment grid with open-ended questions for comprehensive feedback [53]. To avoid potential bias, the interviews will be conducted by research team members who were not involved in the theory of change development process. During the interview, we will collect their comments and suggestions. All interviews will be recorded for accuracy.

Formulation of Contribution Claims

Upon completion of the interviews, we will collate and discuss the differences and similarities between the reviewers' assessments and the feedback received. Based on their suggestions, we will adjust the theory of change and formulate initial contribution claims. As mentioned, these claims are narrative statements derived from the theory of change that articulates the anticipated pathways through which CCE is expected to improve population health outcomes in the specific contexts of Ottawa and Thunder Bay [30]. The initial theory of change and contribution claims developed during this phase are considered provisional. As new evidence is gathered and stakeholder insights are integrated, these claims will be iteratively refined. This flexibility is essential to capturing the complex and context-specific pathways through which CCE impacts population health. We will proceed to the second stage of the study once we reach a consensus that the theory of change and the generated contribution claims are sufficiently articulated, credible, plausible, and logical.

Stage 2: Evidence Gathering

Overview

In this stage, we will use a mixed methods approach to gather substantial evidence that will be used to examine the theory of change and the associated contribution claims developed in stage 1 [30]. The evidence-gathering process is designed to be adaptive. If emerging data suggest new pathways or causal mechanisms, earlier stages may be revisited, and claims adjusted accordingly. This iterative approach ensures that the contribution claims remain aligned with the evolving evidence base. We will create a data collection plan to identify specific indicators, data sources, and methods for examining each contribution claim and its assumptions. The plan will identify at least three evidence sources for each claim, using Delahais' triangulation approach [30] for validation, to allow examination from multiple perspectives.

Data Collection

We will collect qualitative and quantitative data from various sources: (1) case studies, (2) a web-based stakeholder survey, (3) pathway-specific literature review, and (4) population and community health data. Flexibility in data collection will be maintained by revisiting or expanding data sources as necessary, based on initial analyses or gaps identified during triangulation. Table 3 provides an overview of the data sources and their respective aims.

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Table 3. Overview of data collection and sources for stage 2.

Data collection	Aim	Data sources
Case studies	Examine the impact of existing CCE[a] projects with high potential for positive health outcomes in Ottawa and Thunder Bay on the 5 population health outcome areas.	Interviews and document reviews from appropriately 30 CityStudio projects.
CCE Health Impact Survey	Identify the perceived health impacts of CCE projects not selected for case studies.	A web-based survey for stakeholders involved in or impacted by CCE projects through CityStudio Ottawa and CityStudio Thunder Bay.
Pathway-specific literature review	Assess the evidence for CCE's impact on population health outcomes.	Peer-reviewed research and evaluation literature related to health outcomes in CCE.
Population and community health data	Identify trends in disparities to understand CCE's impact on health outcomes.	Data from Community Safety and Well-Being Plans of Ottawa and Thunder Bay and other health indicators.

[a]CCE: community-campus engagement.

Case Studies

Aim

Case studies involve a detailed examination of a selection of CCE projects with the most significant potential to positively influence Ottawa and Thunder Bay health outcomes. They can provide evidence on the theory of change and have often been used in contribution analysis to understand the factors contributing to intervention success or failure in different contexts [46,50].

Case Selection

We will collaborate with CityStudio Ottawa and Thunder Bay coordinators to identify and rank approximately 15 CCE projects from each city with the most promise for positively impacting at least one of the shared population health priorities. We aim to have at least 1 case study for the 5 health priorities. We will create a checklist based on a review of existing tools and measurement instruments to evaluate projects on successful engagement, possible health impact, and data reliability and accessibility. The final selection of projects will be determined through group consensus using the checklist. The rationale for each selection will be documented in a report for transparency and accountability. The case study pool may be expanded or adjusted accordingly if new CCE projects emerge during data collection that shows high potential for positive outcomes.

Data Collection Tools for Case Studies

As suggested by Yin [59], we will use 2 sources to enhance the rigor of case studies: semistructured interviews and organizational documents.

Semistructured Interviews

We will conduct semistructured 1-hour interviews with key stakeholders in each selected case using an interview guide based on the components of our theory of change. Each interview will focus on uncovering the initiative's perceived impacts, foundational mechanisms, and broader outcomes. We will record each interview and take notes during the interviews. Participants will be asked to sign a consent form before the interview and receive CAD $25 (US $17.64) compensation for their contribution. The interviews will be transcribed, with copies uploaded to a secure database in PDF format.

Project Document Review

Our study team will review documents related to selected CityStudio projects, such as project descriptions, monitoring and evaluation reports, output reports, progress reports, and annual reports. We will obtain project documentation from our research collaborators, CityStudio Ottawa and CityStudio Thunder Bay. This review will help us identify expected activities, outputs, and outcomes and provide insights into the strategies used, challenges encountered, and the overall progress and impact of the projects. The total number of documents we will review will depend on the number of projects and their complexity. However, we aim to review as many relevant documents as possible to understand the projects comprehensively. All project documentation will be securely stored for future reference and analysis.

CCE Health Impact Survey

Aim

The CCE Health Impact Survey is designed to collect insights from diverse stakeholders involved in or impacted by CCE projects in Ottawa and Thunder Bay. The survey aims to understand potential health outcomes related to housing, discrimination, poverty, violence, and mental health.

Sampling Strategy

We plan to gather data from individuals who have actively participated in or been affected by projects from CityStudio Ottawa or CityStudio Thunder Bay. Individuals must not be case study participants to be eligible for the survey. They must also belong to one of the following stakeholder groups: students, faculty or researchers, city representatives, or community members. If survey participation is lower than expected or new stakeholder groups are identified, the sampling strategy may be adjusted to ensure comprehensive data collection.

Potential participants will be selected for our survey through convenience sampling. The CityStudio coordinators from Ottawa and Thunder Bay will email these individuals, outlining the project's objective and emphasizing the importance of their participation. Before participating in the survey, individuals must complete a consent form.

The recruitment for the survey will conclude once we have received a sufficient number of completed surveys to ensure

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robust statistical analysis. The exact number will be determined using the Cochran formula [60], which accounts for a 95% CI and a 5% margin of error. Additionally, we will aim to ensure a diverse and representative sample by including participation from each stakeholder group and maintaining balanced representation from both cities.

Measures

The survey will consist of 3 sections. The first section will collect details about the respondents' involvement in the CCE project, such as their role, duration of participation, and affiliation with the organization. The second section will delve into the specifics of the CCE project, including its objectives, the strategies used for its implementation, the deliverables, and the stakeholders involved. The final section will focus on the perceived health impacts of the CCE project. Respondents will be asked to share their observations and experiences and to report any noticeable changes they have observed in 5 key areas: housing, discrimination, poverty, violence, and mental health.

Before launching the survey, we will conduct a pretest with potential participants from all targeted groups to ensure its clarity and relevance. The survey will include Likert scales and open-ended questions, and we anticipate it will take approximately 15 minutes to complete. Participants will receive a CAD $25 (US $17.64) compensation upon completion.

Pathway-Specific Literature Review

Aim

We will synthesize peer-reviewed literature to evaluate the significance and evidence level for each pathway in the theory of change. This will help us understand how these pathways influence the impact of CCE on population health outcomes. Our process will include an analysis of studies that have investigated similar pathways. We will scrutinize their methodologies, findings, and conclusions and assess the overall robustness and limitations of the existing literature. The literature review process will be iterative, allowing for additional rounds of review if new gaps or needs are identified during data collection or analysis. The review procedure for pathway-specific literature will adhere to the guidelines for the narrative literature review outlined in stage 1.

Population and Community Health Data

Aim

We will collect health data to evaluate the impact of CCE on health outcomes in Ottawa and Thunder Bay. This will include information on health behaviors, outcomes, access to health care services, and social determinants of health. By examining population characteristics, health measures, and factors influencing health outcomes, we aim to understand how CCE affects immediate and downstream health outcomes. We will also draw on indicators, results, and performance measures developed and tracked by the municipal CSWBP teams. Domains of eligible indicators include (1) socioeconomic environment (income, social support, education, and employment); (2) physical environment (green space, air quality, housing, and transportation); (3) healthy child development (birth weight, immunization, and early development indicators); (4) health behaviors (smoking, substance use, diet, and physical activity); (5) individual capacity and coping skills; (6) biology and genetic endowment; (7) health services; and (8) sociodemographic environment (culture, race or ethnicity, and sex or gender).

Data Analysis Approach

Our data analysis approach involves qualitative and quantitative analysis, followed by aggregation.

Qualitative Data Analysis

At least 2 research team members will perform a thematic analysis of project documents and semistructured interviews. We will adhere to the 6-step thematic analysis coding framework proposed by Braun and Clarke [61], which includes (1) familiarization of data, (2) generation of codes, (3) combining codes into themes, (4) reviewing themes, (5) determining the significance of themes, and (6) reporting of findings [57]. The thematic analysis will be conducted iteratively, allowing for additional rounds of coding and theme development if new insights or patterns emerge. For example, if initial analysis reveals unexpected causal pathways or unanticipated factors, further in-depth analysis will be conducted to explore these themes. We will focus on identifying linguistic indicators of change or cause-effect relationships in interviews using Nour et al's argumentative discourse analysis [62]. This process entails a detailed examination of specific linguistic markers such as "it is obvious/clear that" and "compared to." These markers serve as indicators of patterns or relationships in the data. We will use NVivo software (Lumivero) [63] for data organization and analysis.

Quantitative Data Analysis

We will collect quantitative data from CityStudio projects, the CCE Health Impact Survey, and existing, deidentified publicly available population and community health indicators. We will use descriptive and appropriate inferential statistical analysis using statistical software (STATA version 14.2, StataCorp LLC) [64] to describe and analyze patterns, relationships, and impacts pertinent to the contribution pathway.

Aggregation of Evidence

We will use Delahais and Toulemonde's Evidence Analysis Database [32] to combine, examine, and summarize the evidence gathered for our theory of change and the contribution claims and related assumptions or risks associated with it. Triangulation will be conducted iteratively, allowing for the inclusion of new evidence sources or reexamination of previously collected data if discrepancies are identified during the analysis. The database will be structured as a digital spreadsheet, with each row corresponding to a piece of evidence linked to a specific contribution claim from our theory of change. For each piece of evidence, we will record the following details: label (an identifier for the evidence), statement (a brief description of the evidence), data source (case studies, CCE Health Impact Survey, pathway-specific literature review, and population and community health data), type of evidence (primary or secondary), interpretation (confirming or refuting the claim), strength of evidence (rating of the evidence's strength and

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justification), and comments (additional notes or observations about the evidence or implications based on the city).

Stage 3: Theory of Change Assessment and Refinement

Overview

In this stage, our objective is to assess and refine the contribution claims formulated from our theory of change based on the evidence gathered and analyzed in the preceding stage. To ensure a rigorous assessment, we will adopt Downe's approach [65] of using an independent review panel, consisting of experts recruited in the inductive phase of the theory of change development (stage 1). If those experts are unavailable, we will use a snowballing strategy to find other relevant experts.

Review Panel Procedures

We will send a review package to the experts 3 weeks before the panel meeting. This package will include the draft theory of change and its narrative, the development process used, and an assessment grid for the contribution claims. The number of claims will be determined based on the theory of change. The assessment grid will contain questions to assess the plausibility and strengths of these claims, along with the overall logic and structure of the theory of change. A research team member will contact the experts to ensure they understand the documentation and answer any questions they may have. Workshop participants will be asked to sign a consent form and will receive compensation of CAD $200 (US $141.15) for their time.

The panel meeting will last 4 hours and will be facilitated by 2 research team members who were not involved in data collection and analysis. It will be divided into 2 parts.

- Introduction and question-and-answer: Panel members will receive presentations from the research team on the methods and contribution claims, followed by a question-and-answer session where they can ask for clarifications or additional information about the presented materials.
- Assessment: Panel members will be invited to share their feedback on the contribution claims and rate them by consensus according to their plausibility and rigor on a scale from 1=very weak to 4=very strong. They will use the aggregated data in Delahais and Toulemonde's Evidence Analysis Database [32] to verify the coherence of the contribution claims by contrasting both qualitative and quantitative data collected on them. Contribution claims with low scores will be used to prompt panel members for additional information sources. This feedback leads to another round of targeted data collection using data sources described in phase 2, ensuring our findings are reliable, accurate, and context specific.

Refinement and Reporting

After the panel meeting, the research team will compile a detailed report that includes the theory of change, the supporting evidence, and the panel's ratings and feedback. By documenting the evidence and the narrative of how it substantiates the theory of change, along with the expert panel's evaluations, this report aims to present a comprehensive and credible account of the contribution story. The report will also highlight the iterative nature of the process, documenting how contribution claims were progressively refined, validated, or adjusted based on new evidence. This transparency in the evolution of claims is crucial for demonstrating the credibility and robustness of the evaluation findings.

Ethical Considerations

This study adheres to the ethical guidelines and principles relevant to human research. It has been granted ethical approval by the Bruyère Research Ethics Board (M16-23-009) on May 4, 2023. Ethical approval for our site in Thunder Bay is currently pending, and as such, no data will be collected at the site until we receive the necessary approval. This research is supported by the Canadian Institutes of Health Research (PJT-180529). All participants will provide written informed consent after being fully informed of the study's purpose, procedures, potential risks, and their right to withdraw at any time without consequence. Identifiable information will not be disclosed in study publications or presentations. Our approach to compensation is described in the Method section.

Results

Our study is in the second stage, focusing on evidence gathering. We anticipate study results will be available by the end of May 2026. The findings will provide insights into the impact of CCE initiatives on population health in Ottawa and Thunder Bay, contributing to the broader understanding of these complex relationships.

Discussion

Expected Findings

CCE is increasingly recognized for its potential to address local health needs. However, a more rigorous and precise understanding of its impact on population health is needed. This research uses a 3-stage, convergent parallel mixed method design combined with contribution analysis to provide robust evidence on how CCE has improved population health in Ottawa and Thunder Bay, 2 distinct settings in Ontario, Canada. The study will provide evidence for CCE's impact on 5 shared population health priorities for both municipalities: housing, discrimination, poverty, violence, and mental health. By focusing on reducing uncertainty and disentangling the complex interactions among contributing factors, our study will provide a clearer and more nuanced understanding of how and under what conditions CCE contributes to these health outcomes. This approach goes beyond simply assessing whether CCE has an impact and delves into the mechanisms, contexts, and pathways through which these contributions occur.

While Mayne's approach has been effectively used in assessing the impacts of interventions and policies in fields such as international development [32] and public administration [39], its application in health research is less explored. Our study aims to generate rigorous evidence of CCE's impact on health and provide valuable insights for applying contribution analysis in health research and evaluation. Our protocol ensures robust findings using 3 triangulation types: data triangulation using a mixed methods approach, analyst triangulation by involving various members of the research team and stakeholders in all 3

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stages of the study, and external validation for an objective evaluation of our theory of change and contribution story. This ensures reliable and context-specific results.

The implications of these findings are substantial. Policy makers will be equipped with evidence-based insights that can be used to refine community engagement strategies and optimize resource allocation for improved population health outcomes. Health education institutions can leverage these insights to strengthen their community engagement endeavors, enrich curricula, and demonstrate their commitment to social accountability. Furthermore, communities will gain invaluable evidence for a scalable CCE model that can be applied across diverse settings.

While this study focuses on CCE initiatives in Ottawa and Thunder Bay, the findings are intended to be transferable to other contexts. By identifying common configurations, mechanisms, and contextual factors that contribute to health outcomes, this study offers insights that can be adapted and tested in different settings. For instance, understanding the conditions under which CCE initiatives are most effective can inform similar efforts in municipalities with comparable socioeconomic conditions or health challenges. The transferability of findings will be discussed in detail, emphasizing the specific aspects of the intervention that may be generalizable across contexts.

Limitations

The precision of our analyses may be constrained by the challenge of obtaining high-quality data for CCE projects. Contribution analysis is relatively novel, adding complexity to our study. Stakeholder participation in participatory research presents challenges such as ensuring effective communication, equitable authorship access, and fair compensation mechanisms. The potential for participant bias exists, which could affect data objectivity but will be mitigated by maintaining neutrality during data collection and analysis and providing clear study guidelines to participants. Another limitation is the dependence on perceived outcomes and correlational relationships, which will be addressed through triangulation methods involving multiple data sources to cross-verify findings and provide a comprehensive understanding of impacts.

Conclusions

This protocol outlines a novel approach to assessing the impact of CCE on Ottawa and Thunder Bay population health. The study aims to provide robust evidence on how CCE contributes to population health improvements by using a convergent parallel mixed methods design and contribution analysis. The study's findings are expected to fill critical knowledge gaps regarding the specific pathways, configurations, and contextual factors that influence CCEs. These insights will be valuable for policy makers, health education institutions, and communities seeking to optimize their engagement strategies. Despite the limitations, such as geographical scope and potential participant bias, the iterative, flexible, and rigorous design enhances the reliability and applicability of the findings. The research team anticipates that the findings will validate and refine the contribution claims derived from the theory of change and guide future research and interventions in community engagement and health. This study represents a significant step forward in understanding and harnessing the potential of CCE in improving population health.

Acknowledgments

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Authors' Contributions

All authors contributed to drafting and revising the manuscript and approved the final version for publication. Each author is accountable for the content and will address any inquiries about its accuracy and integrity.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Good Reporting of a Mixed Methods Study (GRAMMS) checklist.
[DOCX File , 17 KB - resprot_v14i1e58546_app1.docx]

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Abbreviations

CCE: community-campus engagement
CSWBP: Community Safety and Well-Being Plans
GRAMMS: Good Reporting of A Mixed Methods Study

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Protocol

Decentralized Management of Home Care Services for Seniors: Protocol for a Participatory Action Research

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Abstract

Background: The centralization of decision-making power in the public health care system has a negative impact on the practice of professionals and the quality of home care services (HCS) for seniors. To improve HCS, decentralized management could be a particularly promising approach. To be effective, strategies designed to incorporate this management approach require attention to 3 elements: autonomy of local stakeholders, individual and organizational capacities, and accountability for actions and decisions. Not many studies have focused on strategies for integrating decentralized and collaborative management at the local level in HCS.

Objective: The overall aim of this study is to coconstruct HCS management strategies and explore decentralized practices in the day-to-day work of low-level managers and professionals. The specific objectives, in collaboration with local HCS stakeholders, are to (1) identify concrete and achievable strategies for decentralized management, and (2) describe factors (facilitators and obstacles) that could potentially influence their integration.

Methods: This participatory action research involves a cyclical process. Before initiating the cycles, a preliminary stage consists of forming a steering committee composed of managers (n=3), professionals (n=3), seniors (n=3), informal caregivers (n=3), and the research team (n=3). This committee will facilitate multistakeholder consultation to coconstruct local management strategies based on a real-life problem identified by the committee. The steering committee will also guide the research process. The first cycle will consist of establishing an initial plan of decentralized management strategies. During the observation phase, meetings of 4 homogeneous focus groups, including managers, professionals, seniors, and informal caregivers, will be held. During the reflection phase, a thematic analysis will be carried out, and data will be interpreted and validated by the steering committee. Then, in the action phase, results will be presented to managers and professionals so that they can coconstruct a plan of decentralized management strategies to prioritize. The second cycle will explore the factors involved. The observation, reflection, and action phases will be repeated. Ultimately, the results of the 2 cycles will be integrated in a model coconstructed by the steering committee.

Results: Data collection is in progress; the partnership officially began on February 1, 2024, and the plan is to continue data collection through 2025. The steering committee will validate the data to ensure that they are accurate and that the results reflect the reality of local stakeholders.

Conclusions: By identifying decentralized and collaborative management strategies at the local level as well as factors to facilitate their integration in HCS, this approach can be used for other decentralized management projects in different areas of the health care system. This study will give decision makers insight into strategies aimed at improving the management of their institution, which will enhance seniors' well-being and the quality of their health care services.

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KEYWORDS

health system; decentralization; management; home care services; seniors; collaboration

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Introduction

Background

Over the past 4 decades, health care systems in most countries have been reshaped by reforms based on new public management (NPM) [1]. NPM aims to improve the effectiveness, efficiency, and quality of services by focusing on results-based management and cost control [2]. Inspired by NPM [3,4], the last 2 health and social service reforms in the Canadian province of Québec made a shift toward the centralization of management practices [5,6]. With the aim of improving health system performance, the 2003 [7] and 2015 reforms [8,9] gradually concentrated decision-making power, responsibilities, and control, and moved them from lower management to the senior management level of the health system [3,6]. The trend toward centralized management seems to be continuing with the new 2024 reform [10-12], which will concentrate decision-making power in the hands of a new agency called *Santé Québec* [13]. Such centralization of decision-making power necessarily relies on management by results, accountability, and partial privatization of services [9,14]. Consequently, departmental priorities focus on effectiveness and efficiency [14]. The changes resulting from centralized management can have an impact on the conditions of practice of local stakeholders [14], including low-level managers, professionals, seniors, and informal caregivers. These changes also influence the quality of home care services (HCS) for seniors [14], a sector where demand is increasing as the population ages [15,16]. Centralization reduces the latitude of managers and professionals [5], which in turn is associated with a reduction in how meaningful they find their work [14,17]. Their ability to offer services that are accessible and adapted to the needs of the population diminishes [18-20]. Professionals and seniors agree that the continuity and quality of HCS must be improved [18].

To address the present challenges faced by HCS, decentralization could be a particularly promising approach [5,21]. Decentralization implies the delegation of decision-making, power, and responsibilities [21]. The decentralization process involves reconfiguring relations among the national, regional, and local levels to work toward collaborative vertical and horizontal management [22]. A decentralization process involves decentralized management strategies, which are management practices that promote the delegation of decision-making, power, and responsibilities from a higher to a lower level [23]. To be effective, local decentralized management involves three elements: (1) delegating authority to lower-level managers and professionals, (2) strengthening their individual and organizational capacities, and (3) sharing accountability for decisions to be made [23]. Decentralization has the potential to improve the performance of the health system [21,24], the efficient allocation of material and human resources, and responsiveness to the needs of seniors [22].

Moving toward decentralized management is particularly relevant when we consider the main effects of the current centralized management on the health system in Québec. First, administrative reforms and a centralized management approach can reduce the autonomy of professionals [4,14], whose decisions must be approved by senior management, which delays the taking of concrete action in the field [5,19]. The centralization of decision-making power and formalized communication mechanisms limit direct relationships between different local stakeholders [19]. Second, the standardization of practices and use of statistics have increased the focus on performance optimization (eg, cost-effectiveness) [19]. On the one hand, the management and organizational techniques put in place to optimize the work of professionals (eg, standardized clinical tools) [14] require them to invest a great deal of time in their daily tasks [15,19], which decreases the time they devote to direct care for seniors [14,19]. On the other hand, this standardization leads to a tightening of HCS allocation criteria, which impacts the accessibility of services [19]. Some seniors are being denied services, although they were eligible before the 2015 reform [19]. Third, there is a wide gap between the expectations of professionals and managers [15]. Professionals are mainly concerned with improving the quality of care and services for seniors [15]. Managers are more focused on the performance of HCS. For example, HCS must contribute to reducing hospitalization times and increasing the number of seniors who received services [15]. Fourth, services are developed in silos, without any overall coordination [25,26]. This leads to the duplication of services, blurred roles for each HCS provider, a lack of coordination, and competition between service providers [27]. As a result, overly centralized management has negative effects on the practice of professionals and the quality of services for seniors.

Now that the Québec government has made decentralization a priority [28-30], documenting decentralized management in its HCS becomes relevant. Some studies have examined the integration of decentralization in a health care system but generally only from the viewpoint of evaluating this in a specific context. However, each health system has its own management context and structure [31]. Thus, in today's hypercentralized system, bringing decision-making closer to Québec managers, professionals, seniors, and informal caregivers requires finding a way to integrate decentralized management strategies at the local level of HCS. This study aims to answer the following question: To integrate decentralized management in HCS effectively, what potential strategies should be used and what factors should be considered? The overall aim of this study is to coconstruct HCS decentralized management strategies in the day-to-day work of low-level managers and professionals. The specific objectives, in collaboration with local HCS stakeholders, are to (1) identify concrete and achievable strategies for decentralized management, and (2) describe factors (facilitators and obstacles) that could potentially influence their integration.

Theoretical Model

According to the theoretical model of Ohrling and colleagues [24], decentralization is a dynamic process that evolves over time and in which three elements interact: (1) delegation of authority to local stakeholders, (2) strengthening of individual and organizational capacities, and (3) accountability for actions and decisions. *Authority* refers to the different degrees of decision-making power and autonomy delegated to lower levels

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of managers and professionals [24]. To achieve a balanced distribution of authority at different levels of management, managers need to identify tasks and decisions that can be delegated. To ensure that the selection of priorities is in line with the needs of seniors, managers must have a certain amount of latitude in their decision-making [32]. Thus, strategies that support effective decentralized management involve low-level managers having sufficient authority to select those priorities, identify tasks and decisions that can be delegated, and allocate resources [24]. *Capacities* involve the possibility of strengthening individual and organizational abilities to assume delegated decision-making power and responsibilities [24]. The individual ability of managers and professionals to take the initiative is based on their personal aptitudes [33]. As for organizational capabilities, certain norms and culture help encourage the initiatives of managers and professionals [24]. Finally, managers and professionals need to be *accountable* for their decisions and their impacts on HCS [24]. This element involves specifying how responsibilities will be integrated and distributed between managers at all levels and professionals [24]. Also, to facilitate the delegation of authority and sharing of responsibility, managers and professionals should coordinate services, ensure quality, and meet institutional standards [24]. To be effective, strategies must include a sufficient degree of delegation, combined with the capacity on the part of local stakeholders and institutions to make choices in line with optimized performance and to be accountable for these choices aligned with local needs and priorities [34].

Literature Review

This study addresses the question: What potential strategies should be used and what factors should be considered to effectively integrate decentralized management into HCS? Based on the 3 elements of the model of effective decentralization (authority, capacity, and accountability) [24], the literature review presents these strategies and factors.

Decentralizing Management: Strategies to Be Explored at the Local Level

The main strategy of *authority* involves establishing clear policies that contain guidelines regarding the changes to be made to the degree of autonomy and decision-making power at each management level (provincial, regional, and local) [35-37]. When local stakeholders are involved in developing them, these policies are closer to local needs and improve the quality of services [38]. However, these policies often have gray areas that make them difficult to integrate at the local level [37], such as poor communication between provincial, regional, and local levels regarding policy applications [35,39]. Furthermore, it is important to consider the financial dimension of HCS with respect to managers' decision-making power over budget allocation [23]. This strategy involves increasing local control and autonomy over budget management, including the choice of how to allocate funds [40,41]. This control enables choices to be made in line with local needs, which leads to more responsive services [41].

Capacity strategies comprise ways to increase managers' individual capabilities. For example, training programs should focus on managerial leadership skills, health management organization, and organizational changes to come with decentralized management strategies [33,35]. To increase organization capacity and sustain local control and autonomy with respect to budget management requires a system for allocating financial resources [37]. Under such a system, the provincial level retains the power to divide tax revenues equitably between various local institutions [40,42].

Accountability calls for a variety of strategies that are easier to integrate at the local level and have more lasting positive effects [40]. The most promising of these strategies is, first, the creation of clinical networks or committees that give local stakeholders a voice with HCS senior management [38,43]. Second, one of the most common strategies is to reorganize responsibilities between the central government and the local institutions to increase the latters' autonomy [24,36,37,41,44,45]. Third, the reorganization of human resources management responsibilities includes increasing the decision-making power of local organizations in recruiting and training professionals [36,37,46]. A fourth strategy is to have provincial and regional levels use a bottom-up approach to plan health priorities that involve local managers and communities in identifying initiatives and projects for strategic planning of HCS [47,48]. A fifth strategy involves local managers using clear report cards that include objectives, concrete strategies, and performance indicators for decentralization-related changes in the institution [24].

Factors Influencing the Integration of Decentralized Management Strategies

Factors facilitating (n=8) the integration of decentralized management strategies are presented first, followed by factors representing obstacles (n=7). Regarding *authority*, 2 facilitators encourage the delegation of decision-making power to lower-level managers and professionals [24]. The willingness of managers at different levels to delegate certain tasks and responsibilities encourages their participation in the integration of decentralized management strategies [32]. Coaching senior managers through monthly meetings can help build a relationship of trust between the provincial and local levels [49]. Senior management's commitment helps motivate lower-level managers to take on accountability [39]. Two facilitators can help strengthen organizational *capacities*, leading to enhanced integration of decentralized management strategies [24]. First, the institution must have the material, human, and financial resources needed to put the strategies into practice [35,46,48,50]. For example, quality equipment (such as a high-performance IT system) [39], the right infrastructure, a qualified workforce, and budget planning facilitate the integration of changes linked to decentralization [35]. Creating a culture of mutual trust within the institution encourages managers and professionals to take the initiative and make decisions [33]. In terms of individual capacities, 2 facilitators reflect the personal skills of managers at different levels and professionals [33]. The first concerns coping strategies for managers and professionals, which are methods they can put in place to help them reorganize their work routines [51]. These methods enable them to spend more time on their new tasks and responsibilities, for instance, by reducing the number of meetings they need to attend [41,51]. Senior managers can help by limiting the amount of bureaucracy they have to deal with [33,52]. The second facilitator is the

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leadership skills of managers at different levels. These skills can facilitate the integration of decentralization to define new relationships with provincial and regional levels, plan resource allocation, build a new shared vision, and lead change [43,53]. Two facilitators are associated with *accountability*. Clarity of roles and responsibilities between provincial and local levels regarding resource allocation and accountability for action enables proactive integration of decentralized management strategies [33,47]. Collaboration between provincial and local levels facilitates the integration of a budget that respects local needs, strategic direction, and government priorities [46].

Several factors stand in the way of integrating decentralized management strategies. Regarding *authority*, 2 factors make it more difficult for the provincial level to delegate to lower levels [24]. Difficulties communicating between the provincial level and local institutions regarding the execution of a policy or reform can lead to confusion [37,41,51]. As a result, a gap may be created between policy and its implementation [39]. Good communication means that information about the new policy to be implemented is clear, accurate, and transmitted to the right individuals [39]. Moreover, when the provincial level decides to retain a high degree of control over local institutions, it is more difficult to integrate decentralized management strategies [41,47]. Local managers then lack autonomy [41] and decision-making power [36], which makes it difficult to lead change. As for organizational *capacity*, lack of resources and funds can limit the changes to be integrated [46,49,51,52]. Concerning individual capacity, limited managerial skills [49,54], and lack of preparation [48,51] can affect managers' ability to make decisions in their new role and demotivate them [48]. In addition, 2 obstacles are associated with *accountability* for coordinating quality services aligned with local needs [24]. A lack of clarity in roles and responsibilities is a source of confusion when new responsibilities linked to decentralized management strategies are added [37,38]. Managers and professionals then find it difficult to assume their new responsibilities, for which they may be accountable. The second obstacle concerns budget allocation based on the central government's political motivations. This factor can create a gap between government funding and actual budgetary needs at the local level [46].

The studies discussed in the aforementioned literature review are useful as they focus on decentralized management strategies and factors likely to influence their integration. However, some of them were carried out in countries where the political, organizational, and legal structures of the health care system differ from those in Canada and Québec [24,29,55]. Furthermore, some studies did not involve the participation of all local stakeholders in developing decentralized management strategies. As a result, none of them fully captures the complexity of the dynamic and evolving process of decentralization and the factors that can influence it in the Québec context.

Methods

Design

To meet our objectives, a participatory action research (PAR) design was chosen [56]. The PAR design gives HCS stakeholders the power and the tools to explore and coconstruct management strategies adapted to their context and to solve a specific problem that they have identified [56]. The study will start with a preliminary stage, followed by 2 cycles, each composed of 3 phases (observation, reflection, and action), and end with a modeling stage (Figure 1 [57]). The preliminary stage consists of selecting the research site and forming a steering committee. The first cycle will establish a plan of decentralized management strategies (objective 1). The second cycle will consolidate the decentralized management strategy plan and anticipate its integration in HCS by describing factors that could potentially influence the integration of these strategies (objective 2). Finally, the modeling stage will combine the results of the 2 cycles and consolidate the decentralized management strategy plan. A cyclical reflective process is necessary for PAR to ensure constant 2-way feedback between theory and practice [58,59].

Figure 1. Cyclical process of participatory action research based on the participatory action research model developed by Roy and Prévost [57]. HCS: home care services.

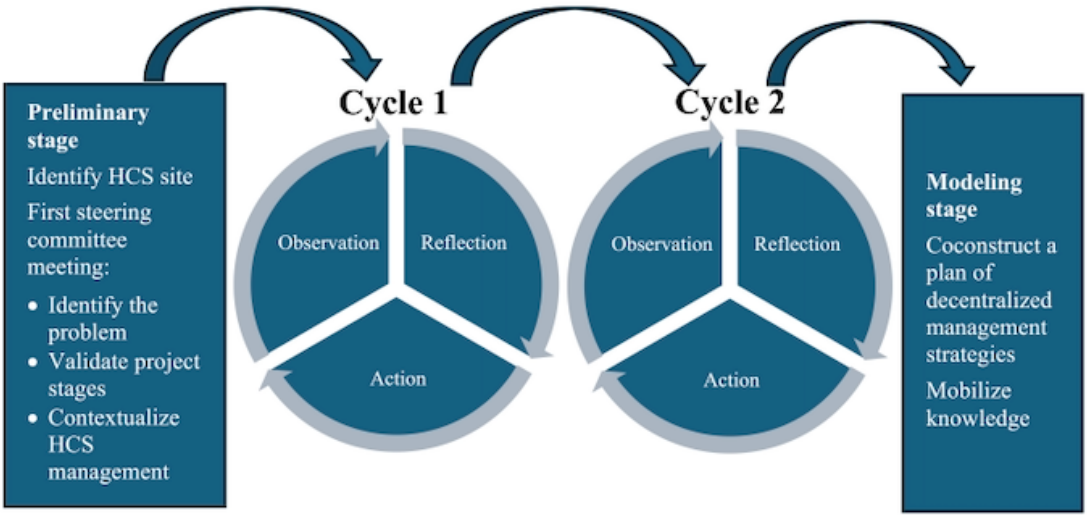

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Study Components (Preliminary Stage)

To define the problem and initiate the PAR process, a steering committee will be set up, composed of 3 managers, 3 professionals, 3 seniors, and 3 informal caregivers identified at the site as well as 3 members of the research team (VS, JQ, and AC). Each type of stakeholder will be equally represented to encourage constructive exchanges and ensure that all steering committee participants feel free to express themselves [56]. The committee will enable a concerted stakeholder approach to the study, aimed at coconstructing [56] decentralized management strategies based on a real-life problem identified by the committee. Before starting the PAR cycles, an initial meeting of the steering committee will be held to discuss everyone's role and involvement [56]. In addition, this meeting will provide an opportunity to contextualize current HCS management and identify a target problem to be addressed in this study. Committee members will be invited to comment on the proposed research process [56]. Members of the research team on the steering committee will play a facilitating role and support the other members in the effective search for solutions [56].

Cycle 1: Identify Decentralized Management Strategies (Objective 1)

Observation Phase: Data Collection

A convenience sample of 24 participants will be recruited to form 4 focus groups of 6 participants each (managers, professionals, seniors, and informal caregivers) to collect data [60]. Each group will be homogeneous to encourage participants to express themselves freely [61]. The qualitative research literature recommends having 6-8 participants in each focus group to ensure interesting exchanges and the opportunity for each participant to answer questions and share their point of view and experience [60]. These focus groups will be used to gather views on decentralized management strategies and the factors influencing their integration as identified in the literature, according to their different status (manager, professional, senior, or informal caregiver) [62]. A member of the steering committee will be present during the discussions to assist the research team. Focus group meetings will last 90 minutes [62]. The aim will be to identify decentralization strategies to solve the target problem. Focus group interviews will be recorded and conducted with the help of a guide [60]. In addition, the student researcher (VS) will document her reflections and the different stages of the study in a research journal [63].

Reflection Phase: Data Analysis

First, an initial list of potential codes will be drawn up from the literature review on decentralized management strategies (objective 1), for example, establishing clear policies [64]. Second, initial deductive codes will be generated by identifying the units of meaning linked to a list of codes based on the literature review. The emergent initial codes will be generated by identifying the units of meaning in the data relating to decentralized management strategies that are not included in the list of codes (objective 1). Third, to search for themes, codes will be selected to create potential themes. Relevant coded data extracts will be collected for the created themes [64]. To ensure that the themes and subthemes are meaning-based interpretative stories [65], each will have a definition based on the extracted codes. Fourth, the themes will be examined in relation to the coded data extracts and the data as a whole [64]. Themes and subthemes will be organized in a chart to think creatively and reflexively the data and facilitate communication with steering committee members [56,65]. Fifth, the themes, subthemes, and overall chart will be revised and defined [61]. Sixth, relevant and illustrative data extracts will be selected to represent the themes [64]. The 6 steps of the Braun and Clarke's [65] analysis will be carried out by the student researcher (VS) and validated by 2 members of the research team (AC and JQ). Seventh, a meeting will be held with steering committee members to validate and enrich these analyses. The validation will enable us to make sure that the themes that have been created represent the perspective of field stakeholders [65]. The chart resulting from the data analysis will be presented to the steering committee and will help members reflect on the solutions and decentralized management strategies to be integrated.

Action Phase: Identify and Coconstruct Decentralized Management Strategies

During this phase, the results of the reflection phase will be shared with all HCS stakeholders involved in the strategies identified (ie, professionals on the HCS team). These stakeholders will be identified by the steering committee. A meeting will be held with these stakeholders led by the student researcher (VS) and a member of the steering committee. First, the student researcher will present the decentralized management strategies. Then she will invite the stakeholders to prioritize the strategies according to 3 criteria: strategy's relevance to the problem identified, strategy's feasibility in terms of accessibility of the necessary resources, and strategy's acceptability to all stakeholders (managers, professionals, seniors, and informal caregivers) [66]. Finally, a plan of decentralized management strategies will be drawn up with the stakeholders [56,67]. This will identify the decentralized management strategies to be prioritized, the associated tasks, the resources needed, and the time required [56].

Cycle 2: Identify Factors Influencing the Integration of Decentralized Management Strategies (Objective 2)

Observation Phase: Data Collection

With the same 24 participants, meetings of 4 homogeneous focus groups of 6 participants each (managers, professionals, seniors, and informal caregivers), lasting 90 minutes [62], will be conducted. In the second cycle, the focus groups will be used to anticipate and coconstruct factors that could potentially influence the integration of decentralized management strategies in HCS.

Reflection Phase: Data Analysis

A thematic analysis using Braun and Clarke's 6 steps [64] will be conducted to interpret the data collected and will be carried out in the same way as in the first cycle. Both deductive and inductive approaches will be used to define an initial list of potential factor codes based on the literature and to allow new themes to emerge [64]. The analysis will generate a chart of factors linked to the decentralized management strategies

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identified in the first cycle. A steering committee meeting will then be held to present the chart and validate the factors involved in integrating decentralized management strategies [56].

Action Phase: Describe the Factors Influencing Integration of the Strategies

In the second cycle, the action phase will consist of a meeting with the same stakeholders as in the first cycle. This meeting will provide an opportunity to share the factors (facilitators and obstacles) identified and to reflect on those most likely to influence the integration of the decentralized management strategies identified in the first cycle. This discussion will lead stakeholders to consolidate the plan of decentralized management strategies and anticipate their integration [56,67]. Thus, at the end of the 2 cycles, the data collected should enable empirical saturation to be reached, with further collection no longer providing sufficiently new or different information to justify another PAR cycle [68].

Modeling Stage

The PAR process will end with a fourth meeting of the steering committee. At this meeting, the results (decentralized management strategy plan and factor figures) will be integrated into a model coconstructed by the steering committee [56,67]. Based on this model, the decentralized management strategy plan will be converted into recommendations regarding which strategies to prioritize to resolve the management issues identified.

Recruitment and Sampling

The participants will be main HCS stakeholders: managers, professionals, seniors, and informal caregivers. They will be recruited with the help of steering committee members, who will explain the research project to them and verify their interest in participating. Convenience sampling will then be used to target a total of 6 managers, 6 professionals, 6 seniors, and 6 informal caregivers (n=24) [64]. Participants will be recruited according to the following inclusion criteria: (1) they must have received services or worked in HCS for a continuous period of at least 6 months; (2) they must have an interest in HCS management; (3) they must be able to express themselves in French; and (4) they must be able to consent to participate in the study. They will participate in the observation phase in both cycles.

Ethical Considerations

This study was approved by the research ethics board of the integrated university health and social services center (#2024-5221/Carrier). All participants will be required to provide free and informed written consent for each cycle. Participants will be able to withdraw from the study at any time without any repercussions. They will also be informed of the confidential nature of the data collected and the procedures followed to ensure confidentiality and anonymity. The data collected will be secured (on a password-protected computer or in a locked fireproof filing cabinet at the Research Centre on Aging) and only the research team will have access to them. Members of the steering committee will fill out a collaboration protocol, based on the one developed by Fortier et al [69]. As a PAR, the impact of change on participants must be considered. The study, which is conducted in partnership with the participants [61], who are treated with respect throughout the research process, cannot be used to evaluate their work [61]. Seniors and informal caregivers will receive financial compensation of CAD $25 (US $17.67) for their transportation to a point of service offering HCS.

Results

The study started in February 2024 and will be carried out according to an optimal schedule over a 1½ period (Table 1). In the preliminary stage, we obtained ethical approval and developed the interview guides. We also developed a research partnership with an HCS site. Initially, one meeting of the steering committee was planned. However, 2 additional meetings were necessary to contextualize the management and organization of the HCS site. The first cycle began in July, with the first focus group in July 2024. We had recruited 12 managers and 7 home care workers. We are currently at the stage of conducting focus groups with seniors and caregivers. Each cycle will last approximately 4 months. To ensure knowledge mobilization, the research team will prepare scientific papers and make presentations. Members of the steering committee will be invited to participate. This study received financial support (June 2023) from a major Canadian funding body, the Social Sciences and Humanities Research Council of Canada (#430-2023-00783/Carrier).

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Table 1. Tasks and timeline for each cycle of the participatory action research.

Task	Time
Preliminary stage	
Ethics approval	December 2023[a]
Development of interview guides	December 2023[a]
Development of research partnership	February 2024[a]
First meeting of steering committee	March 2024[a]
Second and third meetings to contextualized HCS[b]	June-July 2024[a]
First cycle	
Focus group	July-October 2024[a]
Thematic analyses	November-December 2024[a]
Fourth (initially second) meeting of steering committee	December 2024[a]
Meeting with local stakeholders	January 2025
Second cycle	
Focus group	January 2025
Thematic analyses	February-March 2025
Fifth (initially third) meeting of steering committee	March 2024
Meeting with local stakeholders	April 2025
Modeling stage	
Sixth (initially fourth) meeting of steering committee	April 2025
Dissemination and mobilization strategies	June-October 2025

[a]Tasks completed at the time of publication of this paper.

[b]HCS: home care services.

Discussion

Strengths and Limitations

This study is designed to explore decentralized management strategies that are concrete and adapted to the realities of local stakeholders as well as to anticipate factors involved in integrating the strategies. The methodological choices are scientifically rigorous and will be validated in each phase of the study by members of the steering committee [68,70]. To encourage greater reflexivity on the part of the student researcher (VS), the focus group interviews will be cocoded with at least 1 member of the research team, and the analyses will be validated by the steering committee. The research team's experience in the health care system is an asset as they are familiar with the management context [61,68,70]. However, decentralized management strategies will be developed in a centralized management context, which could present an obstacle to the integration of some strategies. In addition, given the power relationship between managers and professionals, social desirability is a potential bias. Nonetheless, the views of various local stakeholders will enrich the steering committee's discussions [56]. In addition, the research team members will play a facilitating role and support other members in effectively identifying decentralized management strategies and the factors involved [56]. The research team will pay attention to power issues during discussions to ensure that all members can express themselves freely [56].

Broad Implications

The research project will address a gap in the literature by identifying concrete decentralized management strategies adapted to the local reality of an HCS site and anticipating factors involved in integrating these strategies. The results will advance practical knowledge regarding decentralized management, which can serve as a basis for further studies designed to advance knowledge in this field.

This study will provide recommendations for innovative solutions to a management issue identified by an HCS site. It considers the main stakeholders in HCS in the search for innovative solutions and helps identify decentralized management strategies that meet the needs of the institution. The strategies identified can also be adapted to other environments with similar characteristics [71]. Knowledge of decentralized management will be transferred between participants and members of the steering committee [58]. In addition, this project will increase the self-determination of steering committee members through the PAR process, which will encourage them to get involved in the search for strategies [58]. By involving seniors and informal caregivers in the steering committee and focus groups, this study encourages

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community participation in the search for management strategies. As a result, the decentralized management strategies identified will undoubtedly meet seniors' needs [72].

Acknowledgments

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Conflicts of Interest

None declared.

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Abbreviations

HCS: home care services
NPM: new public management
PAR: participatory action research

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Protocol

User-Oriented Requirements for Artificial Intelligence–Based Clinical Decision Support Systems in Sepsis: Protocol for a Multimethod Research Project

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Abstract

Background: Artificial intelligence (AI)–based clinical decision support systems (CDSS) have been developed for several diseases. However, despite the potential to improve the quality of care and thereby positively impact patient-relevant outcomes, the majority of AI-based CDSS have not been adopted in standard care. Possible reasons for this include barriers in the implementation and a nonuser-oriented development approach, resulting in reduced user acceptance.

Objective: This research project has 2 objectives. First, problems and corresponding solutions that hinder or support the development and implementation of AI-based CDSS are identified. Second, the research project aims to increase user acceptance by creating a user-oriented requirement profile, using the example of sepsis.

Methods: The research project is based on a multimethod approach combining (1) a scoping review, (2) focus groups with physicians and professional caregivers, and (3) semistructured interviews with relevant stakeholders. The research modules mentioned provide the basis for the development of a (4) survey, including a discrete choice experiment (DCE) with physicians. A minimum of 6667 physicians with expertise in the clinical picture of sepsis are contacted for this purpose. The survey is followed by the development of a requirement profile for AI-based CDSS and the derivation of policy recommendations for action, which are evaluated in a (5) expert roundtable discussion.

Results: The multimethod research project started in November 2022. It provides an overview of the barriers and corresponding solutions related to the development and implementation of AI-based CDSS. Using sepsis as an example, a user-oriented requirement profile for AI-based CDSS is developed. The scoping review has been concluded and the qualitative modules have been subjected to analysis. The start of the survey, including the DCE, was at the end of July 2024.

Conclusions: The results of the research project represent the first attempt to create a comprehensive user-oriented requirement profile for the development of sepsis-specific AI-based CDSS. In addition, general recommendations are derived, in order to reduce barriers in the development and implementation of AI-based CDSS. The findings of this research project have the potential to facilitate the integration of AI-based CDSS into standard care in the long term.

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KEYWORDS

medical informatics; artificial intelligence; machine learning; computational intelligence; clinical decision support systems; CDSS; decision support; sepsis; bloodstream infection

Introduction

The first clinical decision support systems (CDSS) date back to the 1970s. Early systems, such as MYCIN, a program designed to advise on the choice of therapy selection for patients with infections [1], were rule-based expert systems. Nowadays, a wide variety of CDSS exist. These can be categorized as either knowledge-based or non–knowledge-based systems.

Knowledge-based systems operate on logical decision rules (IF <condition> THEN <action>). The system retrieves data and transforms it into an output following distinct rules. Further segmentation can be made into Bayesian networks, causal-probabilistic networks, and rule-based systems: The latter are usually based on medical guidelines [2].

Non–knowledge-based CDSS require a clinical data source and generate recommendations using artificial intelligence (AI) including machine learning or statistical pattern recognition [3,4]. The potential of AI models to sustainably improve patient care is estimated to be enormous for almost all aspects of the clinical decision-making process (prevention, diagnostics, and therapy) [5]. Based on big data analytics, AI-based CDSS offer the ability to pool, link, and combine data, that would be impossible for humans to interpret due to its complexity. In this way, these models can improve medical outcomes by optimizing care [6].

While AI is established in some disciplines, such as radiology (eg, automated image recognition), the transfer of AI-based CDSS into clinical use is lagging behind. Due to the inhomogeneity of different disease patterns, AI-based CDSS are often developed specifically for a target disease or a selected group of disease patterns, such as sepsis [7,8].

Sepsis is a life-threatening organ dysfunction caused by a dysregulated immune response to infection. It is a leading cause of mortality, with 49 million cases and 11 million deaths each year [9]. So far, only symptomatic therapies are available, that attempt to replace the function of the failed organ systems. Treatment of the dysregulated immune response as a cause of sepsis has not been successful in large trials and subsequently has therefore not found its way into clinical practice or sepsis guidelines.

AI-based CDSS could be particularly useful in sepsis care due to the high heterogeneity and complexity of the disease [10]. Non–knowledge-based respectively data-based CDSS are subject to a trade-off between model complexity and interpretability. As sepsis is an extremely complex condition, a majority of machine learning–based CDSS for this disease can be considered “black box” systems. Their treatment recommendations cannot or can only be interpreted by health care providers, with relatively high effort [11,12]. Health care providers may have to rely on these systems without understanding how the algorithms reach their conclusions, due to their black box nature. This lack of transparency can negatively impact the acceptability of such systems [13-15].

In addition to the black box nature of AI-based CDSS, there may be other possible reasons why such systems do not manage the transition into standard care, such as a nonuser-oriented development approach without or at least without sufficient consideration of the needs and preferences of future users [16-18], resulting in reduced user acceptance and implementation barriers (eg, computer literacy of the future users, data availability or legal issues) [4].

These may be possible reasons why there is still no AI-based CDSS for sepsis in Germany that is included in the standard care of the statutory health insurance (SHI) system and is used nationwide. Currently, only a few prototypes in the form of individual solutions are in use or under development (eg, [19,20]).

The reluctance to adopt AI-based CDSS does not appear to stem from the performance of such systems. The sepsis prediction algorithm InSight, developed by AI start-up Dascena, has been demonstrated in several articles to outperform traditional rule-based scores such as the Systemic Inflammatory Response Syndrome, the Sequential Organ Failure Assessment or the quick Sequential Organ Failure Assessment [21,22]. This and other developed algorithms have the potential to improve patient-relevant outcomes. In particular, this encompasses a reduction of sepsis-related mortality, a reduced average length of hospitalization, or an earlier treatment, for example, in the form of the timely administration of antibiotics [21,23,24]. Instead, the reluctance to implement AI-based CDSS can be attributed to a number of factors that are independent of their performance. These include a paucity of evidence, particularly prospective studies [22], a lack of capacity in health care systems to integrate AI into current workflows [25], and ethical concerns, such as the risk of discrimination against certain populations [25-27]. Also in other indications, despite a high frequency of development, only a marginal proportion of such systems successfully transition from the development phase into standard care.

Therefore, the multimethod research project “User-Oriented Requirement Profile for AI-Based Clinical Decision Support Systems Using the Medical Example of Sepsis – KI@work,” seeks to investigate AI-based CDSS in the above-mentioned disease context. In the framework of this research project, it is assumed that there are 2 reasons for the lack of implementation. First, there are administrative and organizational barriers (data availability, data collection, knowledge gaps among potential users) as well as legal and institutional hurdles (implementation of European and national legal requirements, [medical] liability law, competent bodies) within the German health care system that make it difficult to transfer and integrate AI-based CDSS

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into the SHI system. Second, to ensure (sustainable) use and acceptance of AI-based CDSS, the system must have a high perceived usefulness according to the Technology Acceptance Model [28]. In addition, future users should be involved in the development phase, as suggested by the Recursive Innovation Management Model [18]. Due to the strongly technology-driven development of AI-based CDSS, this is currently only done in a fragmentary manner, so that the requirements and preferences of users are only insufficiently taken into account within the framework of such systems.

The multimethod research project addresses both aspects, resulting in two equally important research objectives, that are (1) to identify and remove or overcome barriers by developing health policy recommendations for action to facilitate the transfer of AI-based CDSS across all indications in the German health care system in the future and (2) to develop a clinical requirement profile that can be incorporated into the initial development of CDSS or can be considered in the further development of existing systems. This should enable an increase in usability and thus the acceptance of AI-based CDSS. The requirement profile is developed using the example of sepsis and is, therefore, indication-specific.

In order to achieve the objectives, 3 research questions and 3 sub-questions were determined (Textbox 1).

Textbox 1. Research questions of the multimethod research project.

- What insights can be gained from AI-based clinical decision support systems (CDSS) that are already established in health care and which best practices can be derived?
  - What is the data basis of these CDSS (input)?
  - How are the decisions and recommendations of the CDSS presented to the health care providers (output)?
  - How does the interaction between health care providers and CDSS take place (setting)?
- What specific problems exist or are seen in the establishment of AI-based CDSS in patient care, with a particular focus on clinical sepsis care as well as on the German health care system?
- What are the preferences of health care providers regarding the use and design of CDSS in the prevention, diagnosis, and treatment of patients with sepsis?

The research project is conducted by the Institute for Health Care Management and Research at the University of Duisburg-Essen. Consortium partners are the Department of Anesthesiology, Intensive Care Medicine and Pain Therapy at the University Hospital Knappschaftskrankenhaus Bochum, the Knappschaft Kliniken GmbH, the Department of Medical Informatics, Biometry and Epidemiology at the Ruhr University Bochum and the German Sepsis Society. The research project is funded by the Innovation Fund of the German Joint National Committee (funding code: 01VSF22050).

Methods

Overview

The research project is conducted over a period of 36 months (cf Multimedia Appendix 1) and uses a multimethod approach. It is separated into 3 work packages. Work package 1 combines a scoping review, focus groups with physicians and professional caregivers, and semistructured interviews with relevant stakeholders of the German health care system. At the end of this work package, the interim results (problems, barriers, and corresponding solutions) of the research project are summarized and a set of criteria for AI-based CDSS is derived. Based on the results of the preceding work package, work package 2 includes the central element of the research project: a survey of physicians, including a discrete choice experiment (DCE). Work package 3 involves the development of a requirement profile for AI-based CDSS and the derivation of health policy recommendations for action, which are discussed in an expert roundtable discussion. The research project concludes with a summary of the results in a white paper (cf Figure 1).

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Figure 1. Overview of the multimethod research project. The results of work packages 1 and 2 are indirectly incorporated into module 3.3, as indicated by the dashed lines. AI: artificial intelligence; CDSS: clinical decision support system.

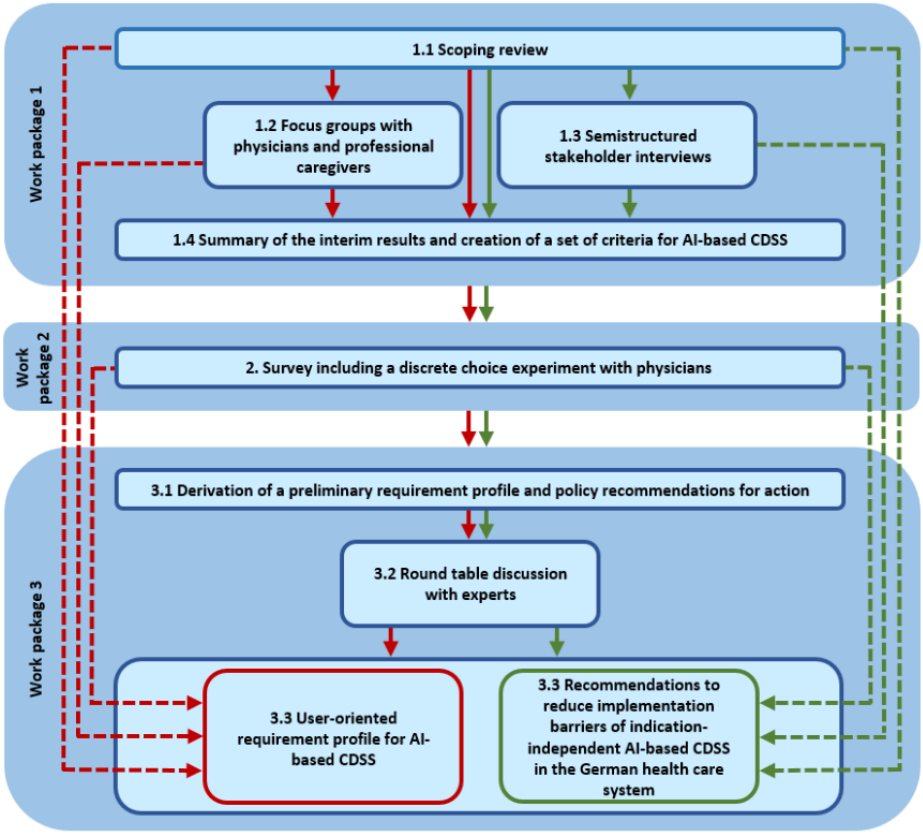

Work Package 1

Work package 1 addresses both research objectives. It serves to identify problems and barriers regarding the transfer of AI-based CDSS into the SHI system (first research objective) and to create a preliminary set of criteria for AI-based CDSS in sepsis care (second research objective). Work package 1 is divided into 4 modules.

Scoping Review (Module 1.1)

The scoping review combines systematic and structured research. The focus of the scoping review lies on research questions 1 and 2, thus addressing both research objectives.

Scoping Review

The actual scoping review examines the currently available evidence on the patient-relevant benefit of AI-based CDSS in the field of sepsis. Furthermore, it aims to identify factors that pose barriers to the transition of CDSS into the health care system and to identify solutions that reduce or overcome these barriers. Methodically it is based on the Joanna Briggs Manual for Evidence Synthesis [29]. Further development of the foundational work of Arksey and O'Malley [30] and Levac et al [31]. The documentation of the scoping review is based on the PRISMA Extension for Scoping Reviews [32]. The search strategy is designed using the PCC (Population, Concept, and Context) framework. The population encompasses individuals with or at risk of sepsis, the concept used is AI and the context are CDSS. Relevant search terms according to the predefined PCC framework are identified and linked with “OR” operators in order to form search blocks. The search blocks are linked with “AND” operators to generate search strings. All search terms are restricted to their occurrence in the abstract, the title, or as a keyword, and in the case of existing index terms (eg MeSH and Emtree), the corresponding terms are added. The databases examined are Medline and Embase as well as ACM Digital Library and IEEE Xplore. This proceeding is to ensure that the interdisciplinary character of the research project can be adequately investigated from both the medical and the informatics perspectives. Following the identification and removal of duplicates, 2 reviewers (GDG and PR) independently screen the titles and abstracts against predefined inclusion and exclusion criteria (cf Textbox 2) to determine whether an article is eligible for full-text screening. Subsequently, the same 2 reviewers conduct a full-text screening of the included articles against the same criteria.

The reviewer PR then uses the program MAXQDA (VERBI Software GmbH) to identify and tag relevant content in the included articles. The final categories are then discussed and systematized in a workshop (NB, GDG, and PR). The results of the workshop are recorded in Microsoft Excel.

In order to add further evidence, the reference lists of the articles identified in the scientific databases are screened. In addition, a structured search is conducted for gray literature (eg, working papers and guidelines) from various governmental and nongovernmental stakeholders, such as associations or public institutions, and their websites.

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Textbox 2. Inclusion and exclusion criteria for the scoping review.

Inclusion criteria

- Articles focusing on sepsis and
- involving AI-based clinical decision support systems, that
  - describe patient-related benefits
  - describe problems with development, implementation, or application, or
  - describe approaches to overcome identified problems

Exclusion criteria

- Exclusively technical description of systems.
- Focus on the description of the evaluation of binary classifiers.
- Articles describing AI-based clinical decision support systems for neonates and children or animals.
- Not addressing any of the research questions in more detail.
- Research protocols, conference abstracts, letters to the editor, or expression of opinions.
- Article published before 2008.
- Language other than English or German.

Additional Structured Medical Device Database Search

The additional structured search aims to provide an overview of authorized AI-based CDSS already in use (irrespective of the indication area of sepsis). In order to identify such systems, the European Database on Medical Devices is analyzed. The filters “system,” “software,” and “risk class (IIa, IIb, III)” are used. The structured search examines the data on which the decisions of the systems are based (input), how the results are presented (output), and how the CDSS are integrated into the clinical context (setting). Particular focus is placed on the search for best practice examples and the identification of clinical areas where the use of AI is already established. These examples are used to recognize aspects that increase the likelihood of such systems being implemented.

Focus Groups With Physicians and Professional Caregivers (Module 1.2)

The focus groups with physicians and professional caregivers build on the interim findings of the scoping review (module 1.1). The findings of the focus groups contribute to the preparation of a standardized questionnaire for the survey in work package 2. Relevant aspects of input, output, and setting in the context of AI-based CDSS in the field of sepsis diagnosis and therapy are collected and derived, thus addressing the second research objective.

Five web-based focus groups are held using the conferencing tool integrated in Microsoft Teams. The participants include physicians and professional caregivers familiar with the care and treatment of adult patients with sepsis, as well as those who contribute to the prevention and diagnosis of sepsis. During the process of participant recruitment, attention is paid to ensure the inclusion of a heterogeneous group of hospitals, representing various levels of care (from primary to quaternary care). In addition, a balanced composition of focus groups in terms of gender is prioritized. Furthermore, participants with differing levels of experience are integrated into the individual focus groups. Three focus groups are conducted with physicians and 2 with professional caregivers. The discussions are based on semistructured guidelines. The focus groups are led by a moderator team according to Krueger and Casey [33], recorded and transcribed. They are then subjected to thematic qualitative content analysis based on Kuckartz and Rädiker [34] using the program MAXQDA (VERBI Software GmbH). The aspects of input, output, and setting represent deductive codes and are defined before data analysis. Inductive codes are supplemented during the process of analysis. A final categorization is conducted in a workshop (NB, GDG, and PR). The findings of the workshop are recorded in Microsoft Excel.

Recruitment of participants is supported by the Department of Anesthesiology, Intensive Care Medicine, and Pain Therapy of the University Hospital Knappschaftskrankenhaus Bochum and the Knappschaft Kliniken GmbH. In addition, participants from other hospital providers are also invited in order to represent a broad and provider-independent perspective of physicians and professional caregivers.

Semistructured Stakeholder Interviews (Module 1.3)

Semistructured interviews with stakeholders from different domains of the German health care system are conducted to complement the results of the scoping review (module 1.1) with the perspectives of various stakeholders. The expert interviews are undertaken to identify problems and barriers related to the implementation of AI-based CDSS in standard care (first research objective). Experts in the field of medical device law, representatives of the SHI system, patient representatives, physicians, and professional caregivers, representatives of quality management, data protection, and ethics, and various research institutions as well as private developers are interviewed. Similar to the focus groups, the interviews are recorded, transcribed, and subjected to qualitative content analysis according to Kuckartz and Rädiker [34].

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Summary of the Interim Results (Problems, Barriers, and Corresponding Solutions) and Creation of a Set of Criteria for AI-Based CDSS (Module 1.4)

Based on the results of the first work package, a set of criteria for AI-based CDSS in sepsis care is developed in module 1.4 (second research objective), which is based on national and international evidence and qualitative survey methods. Furthermore, the identified problems and barriers as well as corresponding solutions are systematized and summarized (first research objective).

Work Package 2

The central element of work package 2 is a cross-sectional survey to identify perceived problems and barriers to the integration and usage of AI-based CDSS (first research objective) and to ascertain physicians' preferences regarding the design of AI-based CDSS in sepsis care (second research objective). The results of work package 1 serve as a basis for the development of the survey, including the DCE.

The questionnaire is divided into 3 sections. First, sociodemographic data and general attitudes toward AI applications are collected; the second section aims to identify potential barriers to the integration of AI-based CDSS into care; and third, a DCE is conducted to determine preferences for the criteria in the preliminary AI requirement profile. In particular, preferences are sought regarding the preferred information content and the appropriate integration into the care process.

The sociodemographic section comprises personal details, such as age groups or gender of the respondents, in addition to occupational data. This includes, for instance, professional experience in intensive care medicine (in 5 groups from none to >10 years), the medical specialty in which the participants are active as well as an evaluation of the degree of digitalization within the hospital where the respondents work. This procedure ensures the anonymity of the participants. The section concludes with an evaluation of general attitudes toward AI.

The second section of the questionnaire focuses on the potential barriers and problems associated with the integration of AI-based CDSS into standard care. It begins with questions concerning non–AI-based CDSS and then progresses to questions related to the use of AI in health care in general. The section concludes with questions on AI-based CDSS. In this part of the questionnaire, problems are primarily assessed using the Likert scale.

The last section of the questionnaire is intended to ascertain the requirements and preferences of physicians with regard to AI-based CDSS. For this purpose, a DCE is conducted to determine preferences regarding the design of such systems. Participants are presented with 2 fictitious systems and asked to indicate their preference.

The sample size of the survey could not be defined before the development of the questionnaire as it depends on the attributes queried in the DCE in the third section. The attributes are derived from the results of work package 1 and were thus not available at the time of the preparation of the grand proposal. Moreover, no comparable research projects could be identified from which recommendations for the required sample size and estimates of the utility of the items could have been derived [35]. Nevertheless, for orientation, initial sample size planning was done according to the heuristics developed by Johnson and Orme [36]. Therefore, 12 choice decisions, 2 selection sets per task, and a maximum of 3 levels were assumed, for which 125 evaluable questionnaires must be available. Since an additional evaluation according to subgroups such as gender (male, female, or diverse), age, or occupational group is to be conducted, the necessary number increases to 125×8=1000 completed questionnaires. Once the exact number of choice decisions, tasks, and levels is known, a statistical assessment is made to ensure statistical power for the given sample size.

In accordance with Pöge et al [37] gender identity is used as a binary variable, so transgender and cisgender people are evaluated together. Gender-diverse people are not reported separately in order to avoid identifiability due to the expected low number of cases but are included in the overall category of all respondents.

A total of 6667 physicians must be contacted, assuming an average response rate of 15% (1000/6667). Therefore, approximately 400 members of the German Sepsis Society and 250 physicians from the Knappschaft Kliniken GmbH who fulfill the inclusion criteria—(1) familiarity with adult medical care and (2) experience in intensive care medicine—are included. The sample is supplemented by randomly selected records of an address register. Based on the inclusion criteria, only addresses of physicians from the medical specialties of intensive care medicine, anesthesiology, orthopedics and trauma surgery, general surgery, visceral surgery, and internal medicine are selected. The Knappschaft Kliniken GmbH hospitals are excluded during the address data extraction process of the address register, as the hospital addresses are known and can be defined as an exclusion criterion to prevent duplicates. Furthermore, a duplicate check is conducted between the address register and the German Sepsis Society to avoid duplicates and to ensure that all physicians are not contacted twice.

In order to reach "offliners," it is possible to take part in the survey both online (LimeSurvey) and on paper. A pretest is conducted before the distribution of the survey in order to identify potential deficiencies and implement necessary modifications. A think-aloud protocol is used to ascertain the comprehensibility, manageability, completeness, and time required to complete the questionnaire [38]. In addition, the online version undergoes several functional tests for layout and usability.

Univariate or bivariate descriptive analyses are carried out as part of the evaluation of the second part of the questionnaire. Depending on the type of variable, frequency distributions, mean values, or medians are compared with simultaneous testing of statistical significance. Subgroup analyses are also conducted, for example, in relation to age or gender. The DCE (third section of the questionnaire) is expected to be analyzed using logit or mixed logit models. As both the absolute influence of the attributes and the relative influence of the levels are of interest, dummy coding is used.

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Work Package 3

In work package 3, a white paper is developed. It includes (1) the final requirement profile for AI-based CDSS and (2) the determined health policy recommendations for action to reduce implementation barriers. Therefore, a preliminary requirement profile and health policy recommendations for action are developed (module 3.1), discussed with experts (module 3.2), and finally summarized in a white paper (module 3.3).

Derivation of a Preliminary Requirement Profile and Health Policy Recommendations for Action (Module 3.1)

The preliminary requirement profile for AI-based CDSS in the treatment of sepsis is developed based on the results of module 1.4 (summary of interim results and creation of a set of criteria for AI-based CDSS) as well as the results of the survey from work package 2 (second research objective). Furthermore, the identified barriers to the implementation and integration of AI-based CDSS in the German SHI system are used to develop targeted strategies for the removal and reduction of implementation barriers and translated into health policy recommendations for action (first research objective).

Expert Roundtable Discussion on the Requirement Profile and Corresponding Health Policy Recommendations for Action (Module 3.2)

In module 3.2 an expert roundtable is held. The aim of the discussion is to evaluate and optimize the preliminary requirement profile for AI-based CDSS as well as the corresponding health policy recommendations for action. In order to gain a comprehensive perspective, different stakeholders involved in the development and provision of AI-based CDSS are invited. In the context of the requirement profile for AI-based CDSS for sepsis care, the expert roundtable discussion focuses on input (data basis), output (presentation of decisions or recommendations), and setting (context of interaction between AI-based CDSS and user). Besides technical requirements, the results can include further requirements such as organizational, procedural, legal, or medical content.

The discussion is divided into four parts, after (1) introductory presentations, the (2) preliminary requirement profile for AI-based CDSS and (3) the health policy recommendations for action for the use of these systems in the German SHI system are presented. The workshop then provides an opportunity for (4) open discussion of the partial results of the requirement profile and the health policy recommendations. In addition, selected topics can be discussed in small groups with relevant experts, and the results of the discussions are presented in a plenum to reach a consensus among the stakeholders on the main issues.

A maximum of 30 stakeholders are invited to the workshop. In addition, there are at least 2 moderators and a technical and organizational staff member from the Institute for Health Care Management and Research from the University of Duisburg-Essen, as well as representatives from the University Hospital Knappschaftskrankenhaus Bochum and the German Sepsis Society. Discussions are led by a team of facilitators using prepared guidelines. The results of the workshop are recorded, transcribed, and subsequently analyzed.

Finalization of the Requirement Profile as Well as the Health Policy Recommendations for Action and Preparation of a White Paper (Module 3.3)

Based on the results of the expert roundtable discussion (module 3.2), the requirement profile for AI-based CDSS is finalized using the example of sepsis care. This enables a user-oriented development of AI-based CDSS in this context. Wherever possible, generic aspects are elaborated and presented in order to include indication-independent and therefore generalizable information in the requirement profile.

In addition, the health policy recommendations for action are concretized. It is discussed how to reduce or overcome barriers to the implementation and establishment of AI-based CDSS in clinical care and finally, proposals for legal adaptations are derived.

The results of both research project objectives, the requirement profile for an AI-based CDSS, and the health policy recommendations for action, are published in a white paper.

Ethical Considerations

In agreement with the ethical review committee of the Medical Faculty of the University of Duisburg-Essen, an ethics vote is not required as only physicians and experts are surveyed or interviewed within the project and no patient data is collected or used.

Results

The research project started in November 2022. The scoping review has been completed and the qualitative modules have been subjected to analysis.

As part of the scoping review, factors that pose barriers to the transition of CDSS into the health care system as well as solutions that reduce or overcome these barriers are analyzed. The review also sought to investigate the potential patient-relevant benefits of AI-based CDSS. The scoping review thus serves both to develop the guidelines for the qualitative modules and to derive potential problems for the survey (section 2 of the questionnaire).

The expert interviews, conducted between June and August 2023, aim to identify further problems and possible solutions for AI-based CDSS in the context of the German SHI system. The findings derived from the expert interviews are subsequently employed in the development of the survey (section 2 of the questionnaire).

The objective of the focus groups, conducted in June 2023, is to ascertain the preferences and requirements of health care providers with regard to the input, output, and setting of AI-based CDSS. The findings of the focus groups are used in the development of the DCE (section 3 of the questionnaire).

The conception of the survey, including the DCE, is finalized. It focuses on the preferences and requirements of physicians regarding the design of AI-based CDSS and the potential

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problems associated with their implementation. The questionnaire is subjected to a series of comprehensive pretests. Furthermore, it is implemented on the web-based survey platform LimeSurvey (LimeSurvey GmbH) to facilitate digital participation.

Recruitment of the 6667 survey participants was initiated at the end of July 2024 and the results of the scoping review, and the qualitative modules are expected to be published at the end of 2024.

Discussion

Principal Findings

AI-based CDSS are developed for various diseases. These systems possess the potential to enhance the quality of care and thereby positively impact patient-relevant outcomes (such as a reduction of sepsis-related mortality, a reduced average hospital length of stay, or an earlier administration of antibiotics) [21,23,24]. Nonetheless, despite extensive development efforts, the majority of CDSS developed have not been adopted in standard care and do not make a significant contribution to improving care in their current form.

There may be 2 primary reasons for this. First, it is assumed that a technology push development is currently taking place, wherein AI-based CDSS are being developed without or only insufficiently considering the requirements and preferences of users [16]. Such requirements may relate to the complexity of the algorithm, with simpler algorithms potentially being preferred to more complex approaches that are incomprehensible and may be perceived as black boxes by users. Requirements related to the design and layout of AI-based CDSS may vary depending on professional experience or age. An analysis of current evidence reveals that other authors have identified various requirements for AI-based CDSS among health care providers in qualitative studies. These criteria include ease of implementation, predictive capability, and costs [39]. In addition, workload requirements [40] and the need for training programs [41] have also been highlighted.

Second, the implementation of such systems may face various barriers during the transition from the developmental phase to standard care, for instance, operational problems or regulatory uncertainties [4]. These and other hindrances may have a negative effect on the successful integration of AI-based CDSS and need to be identified and addressed before AI-based CDSS can be sustainably integrated into care.

Based on these 2 hypotheses it is necessary to analyze potential barriers, as well as the requirements and preferences of health care providers for AI-based CDSS. The results are summarized in health policy recommendations for action to reduce barriers and a requirement profile for AI-based CDSS in order to develop user-oriented systems and thereby optimize user acceptance.

Since the requirements for AI-based CDSS vary depending on the indication, the requirement profile is developed using the specific example of sepsis. Sepsis is a suitable subject for investigation due to its heterogeneity and complex pathophysiological processes, which pose challenges for health care providers in terms of diagnosis and treatment [10]. In addition, the intensive medical treatment and the continuous monitoring of patients with sepsis in the intensive care unit generate a large amount of data suitable for use in AI-based analysis.

The requirement profile for sepsis-specific AI-based CDSS, which is developed based on the requirements and preferences of health care providers, can help to ensure that future CDSS development is aligned with medical practice needs. Involving future users of such systems may counteract the current technology-push development and contribute to greater user acceptance. Following completion, the requirement profile is evaluated in terms of generalizability, and transferability to other indications. In addition, indication-independent health policy recommendations for action are developed based on the identified inhibiting factors for the implementation of AI-based CDSS.

Strengths and Limitations

The results of this multimethod research project, combining qualitative and quantitative research methods, represent the first attempt to create a comprehensive user-oriented requirement profile for the development of sepsis-specific AI-based CDSS. In addition, general recommendations are derived to reduce barriers to the development and implementation of such systems. Thus, this research project has the potential to promote future technology and facilitate the transfer of AI-based CDSS into standard care.

Despite the comprehensive design of the research project, it is not free of limitations. International literature is analyzed in the scoping review to provide an international perspective. However, all subsequent modules are limited to the perspective of health care providers and stakeholders in the German health care system, which may limit international comparability.

Qualitative and quantitative methods each have inherent limitations. Combining both is expected to leverage their strengths and mitigate their weaknesses. For instance, the predominantly qualitative findings from work package 1, which tend to be subjective and nongeneralizable, are tested for generalizability through the quantitative survey conducted in work package 2. However, not all nuances obtained through the qualitative approaches can be fully reflected in the quantitative survey. The combination of various research approaches—scoping review, expert interviews, focus groups, quantitative survey, and expert workshop—ensures that the project delivers comprehensive and well-founded results.

Furthermore, recruitment for the survey and the DCE may lead to selection bias. Although the majority of respondents are randomly selected from an address register, there is a risk of overrepresentation of physicians from the German Sepsis Society and Knappschaft Kliniken GmbH.

Dissemination Plan

The dissemination plan for this research project includes publishing the findings of the scoping review, the qualitative modules, the survey including the DCE, and the white paper in peer-reviewed open access journals dedicated to health

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informatics, digital health, data science, and emerging health technologies. The results will also be presented at national and international conferences focusing on digitalization, sepsis, and health services research.

Conclusion

Based on the results of this research project, developers are provided with guidelines for the development of new AI-based CDSS or the revision of existing systems in order to make their products more user-oriented. In addition, the research project culminates in the development of health policy recommendations for action to reduce barriers to the implementation of AI-based CDSS. Ultimately, this enables AI-based CDSS to become a future standard in health care practice, providing benefits to patients.

Acknowledgments

This research is part of a wider research project (Multimethod Research Project on Requirements for Artificial Intelligence-Based Clinical Decision Support Systems Using the Medical Example of Sepsis (="KI@work")) funded by the German Federal Joint Committee (funding code: 01VSF22050 –KI@work). We acknowledge support by the Open Access Publication Fund of the University of Duisburg-Essen and Mr Björn Koos for his support in preparing the grant proposal.

The large language models ChatGPT (GPT-3.5) and DeepL (classic language model) were used exclusively to support the translation of the manuscript from German to English.

Data Availability

The datasets generated during and/or analyzed during this study are not publicly available for privacy reasons but are available from the corresponding author on reasonable request.

Authors' Contributions

Authors CA, GDG, JW, MA, HN, SM, NT, MT, FMB, and NB obtained the necessary funding and developed the design of the research project. All authors contributed to the organization of the research project. NB is responsible for project administration and supervision. PR drafted the study protocol. All authors reviewed, read, and approved the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Timeline of the multimethod research project.
[PNG File , 58 KB - resprot_v14i1e62704_app1.png]

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Abbreviations

AI: artificial intelligence
CDSS: clinical decision support system
DCE: discrete choice experiment
PCC: Population, Concept, and Context
SHI: statutory health insurance

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Protocol

Prehabilitation Program for Lung and Esophageal Cancers (Boosting Recovery and Activity Through Early Wellness): Protocol for a Nonrandomized Trial

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Abstract

Background: Cancer is the leading cause of death in Canada, responsible for 28.2% of all deaths. Based on surgical candidacy and disease status, both lung and esophageal cancer are treated through surgical resection by a thoracic surgeon. Although surgery contributes to improved outcomes, the 30-day postoperative mortality risks are as high as 10% and 2.8%, respectively. Evidence has shown that prehabilitation is a way in which patients can have improved postoperative outcomes. Prehabilitation is multimodal, often including some form of movement, nutrition, stress management, and smoking cessation. Given the complexity of the health care system, pragmatic trials are important methodological tools to assess internal validity and improve current practice under real-world conditions. Concurrently, using community resources is imperative to keep people active in their community and create sustainable programming.

Objective: The Boosting Recovery and Activity Through Early Wellness (BREATHE WELL) study aims to explore the feasibility, implementation, and preliminary effectiveness of a clinically integrated, community-based, prehabilitation health coaching program. This includes nutrition, smoking cessation, sleep hygiene, and movement for individuals scheduled to undergo surgery for lung or esophageal cancer.

Methods: This is a pilot, nonrandomized, pragmatic, repeated measures, mixed methods trial. We will recruit 32 participants diagnosed with lung or esophageal cancer and are scheduled to undergo surgical resection into the prehabilitation program, with 32 additional participants who decline participation to act as a control group. Participants who agree will then go through an 8-week tailored prehabilitation program (in person or virtual), covering movement, nutrition, stress management, nutrition, goal setting, and smoking cessation. They will complete 6 sessions prior to surgery and then have 4 sessions, 1×/week following surgery. Following the completion of the program, they will have 3 booster sessions via phone or Zoom (Zoom Video Communications). The primary outcome is feasibility: (1) recruitment feasibility—recruitment rate (the number of participants referred per month), enrollment rate (the number of enrolled participants divided by the number of referred participants), reasons for declining, and prehabilitation window (time between consent and surgery); and (2) intervention feasibility—adherence to the movement intervention, attrition, safety, study completion rate, and adverse events. Secondary outcomes include measures of

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preliminary effectiveness including patient-reported outcomes, such as well-being, fatigue, and functional measures. All measures will be assessed before, during, and after the prehabilitation program.

Results: Enrollment has begun in January 2025, with 2 participants enrolled in the health coaching program. The full study is expected to be completed in approximately 3 years and be published in winter 2027.

Conclusions: This study will inform the feasibility, implementation, and preliminary effectiveness of a clinically integrated, community-based, prehabilitation program in Nova Scotia, Canada, for people scheduled to undergo curative intent surgery for lung and esophageal cancer.

Trial Registration: ClinicalTrials.gov NCT06354959; https://clinicaltrials.gov/study/NCT06354959

International Registered Report Identifier (IRRID): PRR1-10.2196/60791

(JMIR Res Protoc 2025;14:e60791) doi:10.2196/60791

KEYWORDS

cancer; prehabilitation; physical activity; lung; esophageal; wellness; surgical; candidacy; feasibility; implementation; community-based; coaching program; Canada; lung cancer; esophageal cancer; surgery; nonrandomized trial; mixed method

Introduction

Cancer is the leading cause of death in Canada, responsible for 28.2% of all deaths [1]. Among these cancers, lung cancer is the most frequently diagnosed in the country, resulting in 25% of cancer-related deaths [2]. Esophageal cancer, while less common, presents unique challenges due to its effect on patients' nutritional status, its tendency to metastasize rapidly, and, consequently, its poorer prognosis [3]. Based on surgical candidacy and disease stage, surgical resection by a thoracic surgeon is a mainstay of treatment for lung and esophageal cancers. Although surgery contributes to improved outcomes, the 30-day postoperative mortality risk are as high as 10% and 2.8% for lung and esophageal cancers, respectively [4,5]. Postoperative complications (eg, pneumonia and pain) pose a significant risk to patients undergoing curative-intent, lung and esophageal cancer surgeries [6]. These events not only increase the length of hospital stay but also negatively impact the patient experience, decrease quality of life, and result in substantial financial burdens for health care [7-10]. Therefore, it has been proposed that completing a prehabilitation program prior to undergoing surgery may lead to improved postoperative outcomes for patients. Prehabilitation refers to assessments and interventions initiated prior to treatment to create a physiological and psychosocial buffer against anticipated deconditioning, complications, and other comorbidities that typically occur as a result of treatment [11,12]. Prehabilitation is multimodal, often including some form of movement, nutrition, stress management, and smoking cessation.

Previous research has found that older adults (aged 70 years and older; American Society of Anesthesiologist score III/IV) who participated in prehabilitation experienced 50% less postoperative complications relative to the control group; this type of intervention was safe and feasible and showed cost-savings of up to €800 (~US $833.62) per patient [13]. Although prehabilitation interventions have generally shown benefit [14], there is still little uptake into the standard of care. This could be due to a wide variety of factors, including the complexity of implementing programs in a health care setting. Therefore, there needs to be more consideration for clinical care pathways, delivery strategies, and infrastructure and personnel for the local uptake of these programs.

Given the complexity of the health care system, pragmatic trials are important methodological tools to assess internal validity and improve current practice under real-world conditions [15]. Concurrently, using community resources is imperative to keep people active in their community and create sustainable programming. Practice-based evidence is an emerging field that strives to ensure research is applicable to real-world settings [16,17]. Practice-based evidence is derived from implementation science research methods, which assess effective intervention in real-world settings and provide insights into the system's capacity and preparatory needs for dissemination and scalability [18]. The purpose of Boosting Recovery and Activity Through Early Wellness (BREATHE WELL) is to explore the feasibility, implementation, and preliminary effectiveness of a clinically integrated, community-based prehabilitation health coaching program, including nutrition, smoking cessation, sleep hygiene, and movement for individuals scheduled to undergo surgery for lung or esophageal cancer. Central to our research endeavor is the driving question: "How can a clinically integrated, community-based prehabilitation program be successfully implemented in the community, and can it lead to improved functional outcomes in patients undergoing surgery for lung or esophageal cancer?" This overarching question provides the study with its core focus and serves as a guiding force throughout the research process. The aim of this study is to investigate the implementation, feasibility, and effectiveness of BREATHE WELL, a community-based prehabilitation health coaching program specially designed for individuals scheduled to undergo surgery to address lung or esophageal cancer.

Methods

Design

This is a pilot, nonrandomized, pragmatic, repeated measures, mixed methods trial to assess the feasibility, implementation, and effectiveness of a clinically integrated, community-based, multimodal prehabilitation program for patients with lung and esophageal cancers in an urban academic health center in Halifax, Nova Scotia, Canada. Participant flow throughout the study is presented in Figure 1. This study aligns with the

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TREND (Transparent Reporting of Evaluations of Nonrandomized Design) checklist (Multimedia Appendix 1) for nonrandomized trials [19].

Figure 1. Participant flow.

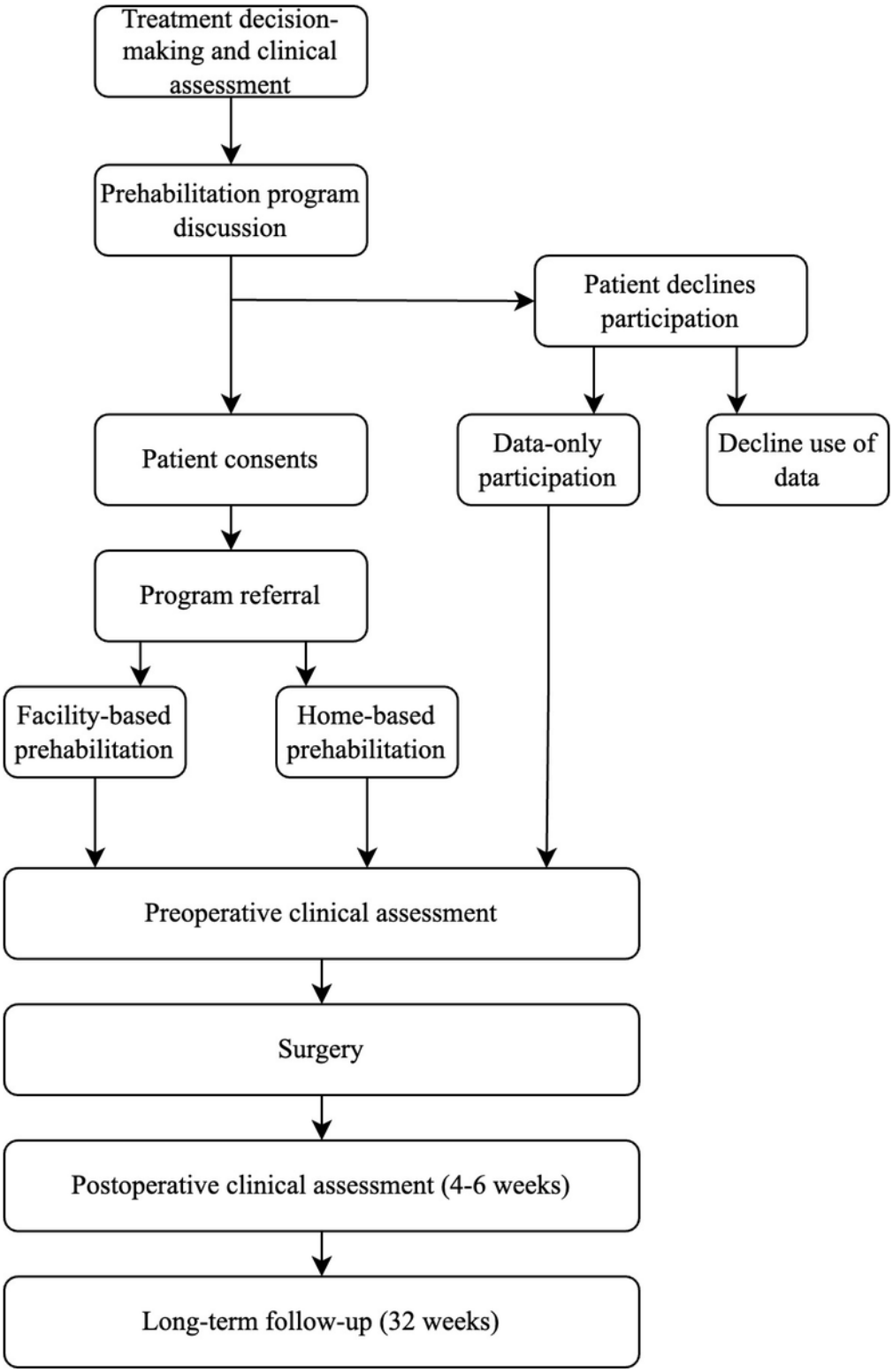

Participants

Based on a monthly surgical volume of 10 patients per month to the referring surgeon, assuming an enrollment rate of 25% while accounting for 20% attrition within a 16-month recruitment window, we will seek to recruit 64 participants (aged 18 years and older) diagnosed with lung or esophageal cancer (32 in the program and 32 who decline). This is based on the number of surgical candidates that the current surgeon sees in a 2-year period. Participants will be identified based on the following inclusion criteria: (1) confirmed diagnosis of lung or esophageal cancer; (2) treatment plan includes surgery (at least 2 weeks from the time of consent) [20]; (3) fluent in English; and (4) surgical oncologist approval. Exclusion criteria

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include (1) unstable or symptomatic cardiac disease, musculoskeletal injury, or comorbid disease that precludes the ability to safely engage in physical activity or (2) significant cognitive limitations.

Enrollment and Assessment

Each potential participant will go through an assessment with the surgeon, including height, weight, blood pressure, heart rate, pulmonary function tests, grip strength, and a stair climb test as part of their clinical assessment. The thoracic surgeon will then raise the subject of prehabilitation with patients. At this point, patients will have the choice to participate in the prehabilitation program or not. If the participants do not agree to the study, they will continue with a standard of care. If a participant agrees to participate and provides written informed consent in accordance with the Nova Scotia Health Research Ethics Board, they will be referred to the research team and YMCA for immediate start of a prehabilitation program. Those who do not participate in prehabilitation will be used as a comparison group, through a waiver of consent; only those as part of the circle of care will pull these deidentified data for the research team.

Intervention

Participants will first have an appointment with a community-based, qualified exercise professional to discuss a tailored prehabilitation program. This will be dependent on a current functional fitness assessment (completed by the surgeon), goals of care, and surgery date. Participants will receive a handbook that will guide them through this process. The handbook will include a calendar of events, a guide to prehabilitation modalities (eg, movement, nutrition, sleep hygiene, stress management, and smoking cessation), publicly available resources (eg, Canada's Food Guide, CSEP 24-Hour Movement Guidelines, and Smoking Cessation guidelines), and helpful worksheets and other resources (Tobacco Free Nova Scotia Quit Line and mindfulness webinars). Participants will have the choice of delivery modality: either at home, virtual via Zoom (Zoom Video Communications), or at the nearest community-based YMCA. Both in-person and virtual programs will run in the same fashion. All participants will be given 2 resistance bands to assist with their at-home exercises. The intervention will last a total of approximately 8 weeks (Figure 2), depending on the time of surgery and postoperative follow-up. The intervention follows a tailored design, whereby the first 2-3 weeks provide more support, followed by weekly support and then biweekly support. This approach will help contribute to the autonomy of each patient. Following each counseling session, participants will engage in tailored movement sessions.

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Figure 2. Timeline of prehabilitation intervention. Note that the "Prehab" phase may be longer than 1-2 weeks depending on the time from diagnosis to surgery. Prehab: prehabilitation.

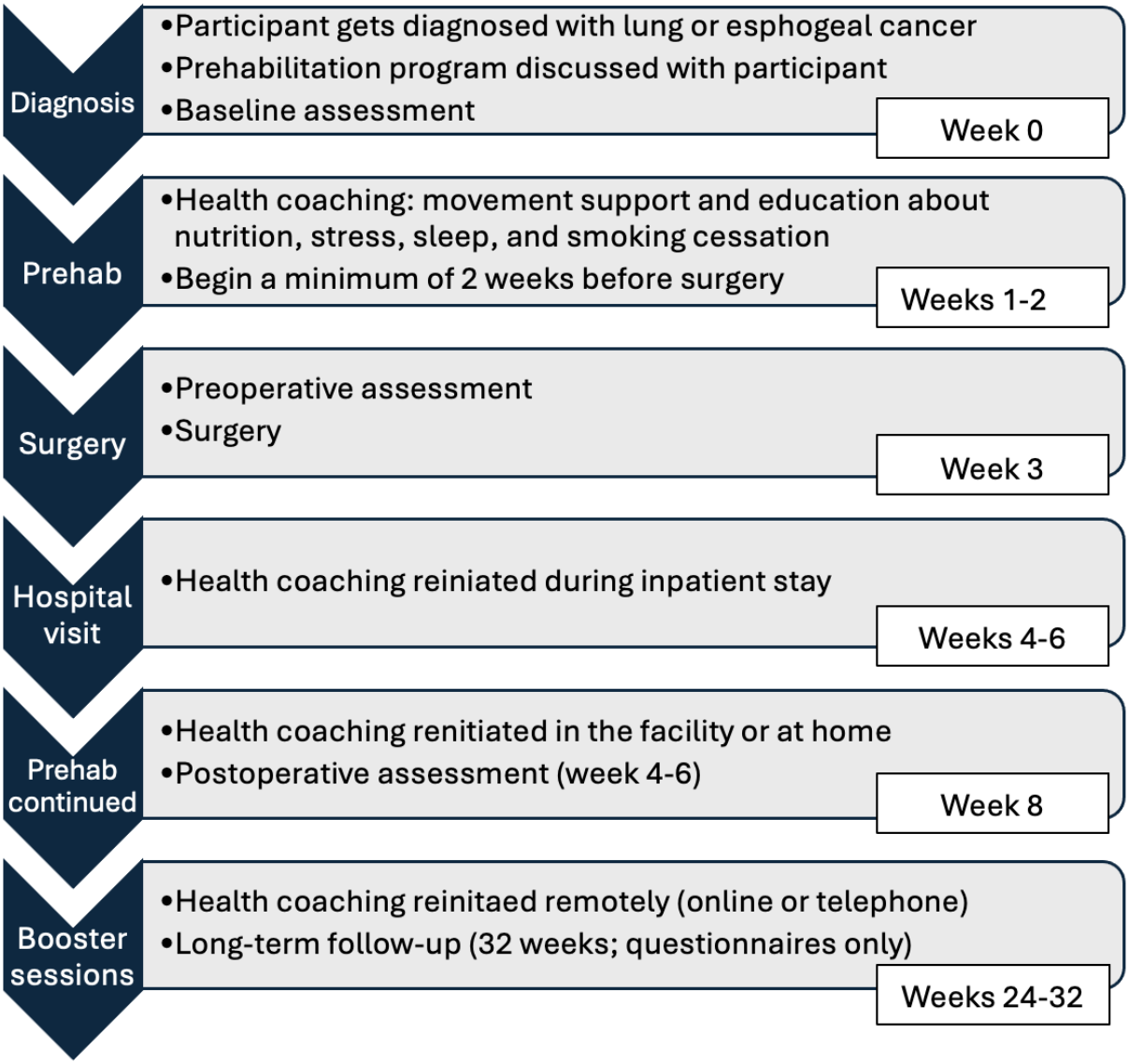

Health Coaching

Participants will work with a qualified exercise professional who is trained in motivational interviewing (MI) to promote positive lifestyle habits. Participants will meet virtually or in person for counseling and movement sessions. Participants will receive 6 health coaching sessions prior to surgery (approximately 3×/week), with 5 additional wellness sessions after surgery (1×/weekly in the first month), and a follow-up (approximately 4-6 weeks after surgery). Health coaching will last 10-15 minutes, and the aim of these MI-informed behavioral counseling sessions is to develop personalized goals. Through MI techniques, qualified exercise professionals will use a shared decision-making approach with participants to promote evidence-based lifestyle modification, while using publicly available, evidence-informed resources to educate the participant on healthy and positive lifestyle behaviors. Following health coaching, the coach will lead the participant through a 15-45-minute movement routine. The booster sessions will provide health coaching over the phone or via Zoom only (Table 1).

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Table 1. Overview of health coaching sessions.

Session	Week	Topic	Goal of session
Before surgery			
1	1	What to expect?	The goal is to have a clear understanding of what to expect from the diagnosis, surgery, and health coaching program. The qualified exercise professional will work with the participant to create a list of questions to discuss with their surgeon prior to their next visit. The qualified exercise professional will also start the process of what resources participants might need during their treatment, including Cancer Patient Pharmacare (which covers prescription cessation aids for example), Canadian Cancer Society patient supports (transportation supports), and other potential supportive services.
2	1	Understanding your body	The qualified exercise professional will go through how participants know their body the best, and things to look for when doing more movement. Key concepts of this session will be a rating of perceived exertion, use of our environment, and history of physical activity.
3	1	Movement + me	Participants will work with qualified exercise professionals to better understand what movement looks like for them and what type of movement they enjoy. Finding movement enjoyable is key to successful long-term movement.
4	2	Smoking cessation or sleep hygiene	If a participant reports current tobacco use, the qualified exercise professional will help the participant to understand the importance of smoking cessation as they prepare for surgery. This will include providing information about Tobacco Free NS and assisting with steps to access appropriate cessation resources. As well, participants will discuss sleep quality and the importance of sleep in preparation for and recovery from thoracic surgery.
5	2	Mindfulness	The qualified exercise professional will go through basic mindfulness attitudes, including patience, acceptance, and trust. The qualified exercise professional will review techniques for stress reduction and breathing.
6	2	Prepping for surgery	The qualified exercise professional will go through a reminder about things to bring with them to the hospital and talk about what to expect in the next few days. Participants will be reminded of the work they have done this far and be given a hospital date for their meet-up.
Surgery			
7	3	How are you feeling now?	The qualified exercise professional and participant will discuss how they are feeling and what supports the qualified exercise professional can offer to facilitate the transition from hospital to home setting.
8	4	Movement at home	The qualified exercise professional will assist the participant in better understanding movement at home and how they can make small movements as part of their everyday life. The focus of this session will be on doing small movement “snacks” and listening to their body.
9	5	Goal setting	Qualified exercise professionals will go through SMART[a] goals with the participants. This will include long- and short-term goals with an understanding of upcoming treatment and how that will affect goals.
10	6	Nutrition	The qualified exercise professional will assist the participant in the understanding of food as a whole and how important nutrition is when undergoing treatments for cancer, this will include tips from Canada’s Food Guide. If needed, the qualified exercise professional will also have resources for the food bank and how to access these types of services in their community.
11	8	Long-term planning: what is next?	The qualified exercise professional will discuss a long-term plan for the participant to sustain healthy lifestyle habits. They will go through their movement notes together and find a movement plan that will work for this participant, whether that be at home, at a local gym, or a more structured program.
Follow-up appointment with surgeon			
12	16	Booster session: where we are now?	The qualified exercise professional will discuss how the participant is feeling now and revisit goals. If participants require further support, the qualified exercise professional will also do anything within their scope and also refer to the Community Health Team resources, which offer support on many wellness topics and are free to all Nova Scotia residents.
13	24	Booster session: where we are now?	The qualified exercise professional will discuss how the participant is feeling now and revisit goals.
14	32	Booster session: where we are now?	The qualified exercise professional will discuss how the participant is feeling now and revisit goals.

[a]SMART: Specific, measurable, attainable, realistic, time orientated.

Movement Programming

All movement programming will be tailored to each individual participant’s current health status, goals, interests, and abilities. Each one-on-one movement session is expected to last 15-45 minutes and will include time for both warmup and cooldown. Participants will be instructed to begin at a light-to-moderate intensity (ie, 3-6 on a 10-point Borg Scale); systematically

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progress (ie, periodized); and combine aerobic and resistance training programs for 15-45 minutes, 3 days/week. Should a participant feel that any movement is beyond their comfort level or ability, they will be instructed to inform the qualified exercise professional so that the movement can be modified to better suit their needs (Table 2).

Table 2. Outline of a movement programming[a].

	Description	Frequency	Intensity	Type	Time
Warmup	All sessions begin with a 5-minute warmup to gently increase heart rate and mobilize major muscle groups (RPE[b] 1-3/10).	—[c]	—	—	—
Aerobic	—	3-7× per week (3 supervised and 0-4 unsupervised)	MICT[d] (3-6 RPE) or HIIT[e] (7-9/10 RPE)	Rhythmic repetitive movements (eg, walking, marching, cycling)	10-15 minutes
Resistance	—	3× per week	4-7/10 RPE	Targeting major muscle groups including: • Legs (eg, sit to stand) • Back (eg, horizontal row) • Chest (eg, wall pushups) • Core (eg, dead bug) • Shoulders or arms (eg, shoulder press or bicep curl)	2 sets of 6-15 reps; 10-15 minutes
Balance	—	3-7× per week (3 supervised and 0-4 unsupervised)	4-7/10 RPE	Examples include single leg balance and tandem stance	2 × 30 seconds; 5 minutes
Flexibility	—	3-7× per week (3 supervised and 0-4 unsupervised)	4-7/10 RPE	Examples include hip flexor or quad stretch, hamstring stretch, and chest openers	2 × 20 seconds; 5 minutes
Locoregional	—	3-7× per week (3 supervised and 0-4 unsupervised)	4-7/10 RPE	Surgery-specific resistance and flexibility exercises (eg, swallowing exercises for esophageal participants)	2 × 20 seconds; 3-5 minutes
Cooldown	All sessions will conclude with a 5-minute cooldown to gently return heart rate to resting values (RPE 1-3/10).	—	—	—	—
Progression—aerobic	Sessions will begin at the lower limit of the desired range (eg, 3 sessions at 40% HRR[f]) and progress to the upper limit of the desired range (eg, 7 sessions at 70% HRR) as tolerated.	—	—	—	—
Progression—resistance, balance, and locoregional	Sessions will begin at the lower limit of the desired range (eg, 4/10 RPE) and progress to the upper limit of the desired range (eg, 7/10 RPE) by modifying repetitions, sets, or difficulty of exercises as tolerated.	—	—	—	—

[a]All programs will be tailored to each individual based on their functional level and environment.

[b]RPE: rating of perceived exertion.

[c]Not applicable.

[d]MICT: moderate intensity continuous training.

[e]HIIT; high intensity interval training.

[f]HRR: heart rate reserve.

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Qualified Exercise Professional Training

Multiple YMCA-qualified exercise professionals will be trained in health coaching and MI to complete this study. This training will include (1) Thrive health services exercise oncology training [21], an exercise oncology-specific asynchronistic training module; (2) Health Coaching Certification [21], an evidence-based training that focuses on empowering health behavior change; and (3) completion of a full-day workshop on study protocol and MI techniques, including talks from experts in the field, individuals with lived experience of lung or esophageal cancer, and other health care professionals. Each counseling session will have a checklist and protocol for qualified exercise professionals to use outlining the targets and goals for each session. All qualified exercise professionals will be overseen by the YMCA clinical exercise physiologist who will offer advice and guidance on movement programming and health coaching sessions.

Outcome Measures

Feasibility (primary outcome) will include (1) recruitment feasibility—recruitment rate (the number of participants referred per month), enrollment rate (the number of enrolled participants divided by the number of referred participants), reasons for declining, and prehabilitation window (time between consent and surgery); and (2) intervention feasibility (adherence to the movement intervention, attrition, safety, study completion rate, and adverse events). The feasibility target for recruitment is a 25% enrollment rate. The feasibility target for adherence is 70% or more, measured by attendance to movement sessions with the qualified exercise professional. The feasibility target for attrition is 20% or less [22]. A timeline of feasibility measures is available in Table 3.

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Table 3. Timeline of program measures[a].

	T0 (baseline)	T1 (before operation)	Surgery	T2 (after operation; weeks 4-6)	T3 (long-term follow-up; week 32)
Feasibility and acceptability					
Referral rate	✓				
Referring provider enrollment	✓				
Referred patient	✓				
Enrollment rate	✓				
Adherence		✓		✓	✓
Prehabilitation window		✓			
Safety	✓	✓		✓	✓
Reasons for decline	✓				
Attrition	✓	✓		✓	✓
Patient characteristics					
Demographic information	✓				
Cancer (type and stage)	✓				
Treatment Status	✓				
Surgery type	✓				
Resting, physical fitness, and patient-reported outcomes					
Height	✓	✓		✓	
Weight	✓	✓		✓	
Vitals	✓	✓		✓	
Pulmonary function	✓	✓		✓	
5TST[b]	✓	✓		✓	
Stair-climb test	✓	✓		✓	
Grip strength	✓	✓		✓	
FACT-L[c] or FACT-E[d]	✓	✓		✓	✓
FACIT-F[e]	✓	✓		✓	✓
Clinical outcomes					
Clavien-Dindo Surgical Complication (grade)			✓	✓	
Postoperative hospital LOS[f]			✓	✓	
Readmission and ED[g] visits			✓	✓	
Mortality			✓	✓	

[a]Pulmonary function test consists of tidal volume, forced vital capacity, vital capacity, and functional residual capacity. Vitals consist of blood pressure and pulse rate.

[b]5TSTS: 5 times sit to stand.

[c]FACT-L: Functional Assessment of Cancer Therapy—Lung.

[d]FACT-E: Functional Assessment of Cancer Therapy—Esophageal.

[e]FACIT-F: Functional Assessment of Chronic Illness Therapy—Fatigue.

[f]LOS: length of stay.

[g]ER: emergency department.

Participant outcome measures will include demographic information (age, sex, gender, socioeconomic status, race, marital status, educational level, and health knowledge), anthropometric measurements (height, weight, and BMI), medical information (surgery type, diagnosis, date of diagnosis, treatment status, and other chronic conditions), and patient-reported outcomes (PROs) that include quality of life (Functional Assessment of Cancer Therapy–Lung or Functional

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Assessment of Cancer Therapy–Esophageal) [23,24] and fatigue (Functional Assessment of Chronic Illness Therapy–Fatigue) [25]. Both the Functional Assessment of Cancer Therapy–Lung or Functional Assessment of Cancer Therapy–Esophageal and Functional Assessment of Chronic Illness Therapy–Fatigue have been extensively validated and are reliable and widely used tools in the oncology setting [23]. Participants will have the option of completing surveys using the web-based (REDCap [Research Electronic Data Capture]; Vanderbilt University) database or using a pen and paper–based survey. A comprehensive assessment of functionality will be conducted in person in the clinic by the surgeon. Functional assessments are based on the Canadian Society of Exercise Physiology's Physical Activity Training for Health Protocol and include height, weight, resting heart rate and blood pressure, 5× chair sit-stand, stair climbing test, and grip strength. As part of standard of care, participants will undergo pulmonary function tests; these measures include tidal volume, forced vital capacity, vital capacity, and functional residual capacity.

The participants will be interviewed prior to the commencement of the program to better understand their perception of prehabilitation health coaching and to better understand their history with movement and healthy lifestyle behaviors. This will include questions that are based on past behaviors and future goals. This interview will be audio recorded and transcribed verbatim. A content analysis will be done using the Behavior Change Wheel and Theoretical Domains Frameworks [26,27]. This will aid in better understanding the behavior and barriers or facilitators to engage in the behavior. For sustained behavior change, participants need to have the Capability, Opportunity, and Motivation to perform the behavior [27]. Participants will also be interviewed at the end of the program to better understand their satisfaction with the program. This will also aid in understanding participants' perceptions of where they are regarding long-term behavior change. Postprogram interviews will be conducted to better understand their perspective on the program and how or if they found the program beneficial; these interviews will probe the understanding of sustained health behavior change and program satisfaction.

Postoperative outcomes include length of hospital stay and postoperative complications. The severity of complications will be graded according to the Clavien-Dindo classification [28,29]. Return to the emergency department within 90 days after the operation and 90-day mortality will also be assessed.

Statistical Analyses

The statistical analysis for this trial will be conducted with R (R Foundation for Statistical Computing). Participant characteristics will be summarized using descriptive statistics (mean, SD, frequency, and percentage). We will report on reasons for exclusion, attrition, and adverse events with frequency and percentages for each group. Safety will be determined by examining the total number of adverse events that occur over the duration of the program. Adherence to movement sessions will be summarized as a percentage (the number of movement sessions attended divided by the number of available movement sessions).

Baseline demographic and disease-related variables will be compared between prehabilitation and data-only participants using 1-way ANOVA for continuous variables and a chi-square test for categorical variables. The effectiveness analysis will include a linear mixed model to assess the difference in physical fitness and PROs from baseline (T0) to the preoperative (T1), postoperative (T2), 4-6 weeks postoperative (T3), and 32-week long-term follow-up (PROs only) time points, where the time point is the fixed effect and the individual participant is the random effect. A sensitivity analysis will be performed adjusting for sex, surgical type, and age. Linear mixed effect models will also be used to determine between-group differences. An α of .05 will be considered statistically significant. Point estimates and 95% CIs will be calculated for changes in the physical function and PROs at each timepoint and will also be used to provide important information for future sample size calculations. A Poisson regression will be used to estimate differences between groups for postoperative outcomes (ie, length of hospital stays, postoperative complications, return to emergency department, and mortality). Missing outcome data will be imputed using multiple imputation effects. Conclusions will be drawn using comparisons of each time point relative to the baseline.

Qualitative description is used to describe rather than interpret phenomena. Content analysis, the process of making sense of the meaning in the data will also be used during our thematic analysis. The research assistant will work with an experienced qualitative researcher to conduct multiple reviews of the transcripts and tapes (step 1) to familiarize themselves with the data. The analysis will be initiated as soon as the first interview is completed and continued concurrently with data collection. The analysis will examine what individual, structural, cultural, and institutional contexts are hypothesized to affect success. Additional codes will emerge to develop a thematic framework (step 2) that reflects the language and experiences of participants. An audit trial will be used to document the decision-making process. Sections of the transcripts will be charted into themes (step 3). Codes will be combined into themes during a series of research team meetings in which the relationships between behavior and the patient's capability, opportunity, and motivation to do said behavior will be explored and summarized. Analysts will review the codes and associate themes multiple times to check for potential biases, to ensure they reflect participants' words, and to improve and validate the interpretation (step 4) of the interviews. Additional interviews may be added when new themes emerge. Initial findings will be shared with a group of participants to help with interpretation and generate meaning from the data.

Ethical Considerations

This prehabilitation study includes human participants and was ethically approved by the Nova Scotia Health Research Ethics Board (REB# 1030020) in April 2024. All participants will go through a written informed consent procedure and will be aware that this study is completely confidential and voluntary. Participants will be given a small amount of money to offset the price of gas and parking when participating in an in-person program.

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Author Reflexivity

This study brings together a multidisciplinary team with extensive expertise in research and clinical practice within the field of exercise oncology (JEL, DS, JC, and MRK); exercise measurement, evaluation, and prescription (JEL, DS, JC, and MRK); medical oncology (SS and AW); thoracic surgery (AW); policy implementation (LH and JP); and care experience (SS). The study team has a history of collaboration and has brought in key knowledge users to assist with the implementation of this project after the completion of research funding.

Results

Enrollment has begun in January 2025, with 2 participants enrolled in the health coaching program. It is estimated that it will take approximately 24 months to recruit all participants and collect all measures; analyses will take approximately 6 months; and writing the final manuscript will take approximately 6 months to complete. The full study is expected to be completed in approximately 3 years and be published in winter 2027.

Discussion

Principal Findings

The current standard of care for patients undergoing surgery does not include prehabilitation, although multiple randomized controlled trials have shown the efficacy of these programs [9,10,20,30]. Evidence is growing for the use of prehabilitation in standard of care, yet its implementation in clinical settings is still limited. BREATHE WELL will inform clinicians and knowledge users how structured prehabilitation programming using community settings and resources can bridge the gap between health care and the community. To maximize care pathways, it is imperative that those suited for community programs are triaged accordingly. Further, it is important to ensure that community-based resources are well equipped and trained to work with patients in prehabilitation to allow for sustained health behavior change and safe movement programming. Individuals living with and beyond cancer during and after treatment benefit from engaging in movement; however, they often lack the knowledge, resources, and guidance on how to do so safely and effectively [31-35]. By using an “exercise and educate” model focused on MI and health coaching, the emphasis will be on empowering participants to see the long-term benefits of behavior change and increase overall well-being for individuals. Also, previous community-based physical activity interventions with individuals living with and beyond cancer do see a longer-term increase in physical activity [11]. This could be due to familiarity with the environment and having increased support upfront, which can lead to better physical activity adherence. This study builds on previous evidence that prehabilitation is efficacious, yet its uptake into the standard of care is still lacking [14].

As part of this study, the intentional engagement of knowledge users including key health system partners, clinical care programs, and patients as team members will ensure high-quality evidence. It also provides an excellent infrastructure for rapid dissemination of findings into policy, practice, and clinical care. Knowledge translation initiatives will be ongoing throughout this research, including integrated and end-of-grant knowledge translation. We will regularly engage with all research team members, which includes key knowledge users (JP and LH) and patient partners (SS). The preliminary findings will be shared, when necessary, at team meetings, and interim research summary reports will be circulated via email and existing webinars and continuing education infrastructure established through our team members and collaborators. To support the further development of this project, we will generate an end-of-study summary report of key findings to policy and clinical partners. Findings will be disseminated to lung and esophageal cancer–specific audiences in Canada and internationally through conferences (eg, Canadian Association of Thoracic Surgeons Annual Meeting, American Association of Thoracic Surgeons Annual Meeting, Canada Cancer Research Alliance Annual Meeting, Canadian Society for Exercise Physiology Annual Meeting, and American Society of Clinical Oncology) and will be published in open access journals (eg, *BMC Health Services Research*) to enhance accessibility and potential for global reach and impact. This research will also be disseminated to patients and lay audiences through infographics to increase accessibility to a wider nonacademic audience.

There are several strengths to this study: (1) a pragmatic design allows for a deeper understanding of implementation and feasibility, which will aid in further understanding of prehabilitation in real-world settings; (2) the use of community-based facilities allows for a strong likelihood of not only system-level sustainability but also greater confidence for individuals to adhere to physical activity upon completion of the prehabilitation program; and (3) the use of a standard-of-care comparator group allows for preliminary effect estimates to understand if prehabilitation improves quality of care. However, this study is not without limitations. First, we have limited our sample to patients who have undergone thoracic surgery, which may not be generalizable to other populations with cancer. Second, the prehabilitation window is short (2-3 weeks), which precludes physiological changes. This is due to constraints from the diagnosis to the surgery date; if participants do have a longer window, they will be offered a longer presurgical program. However, with continued support after the surgery, participants will be supported to create long-term positive lifestyle changes and habits. Finally, this is a nonrandomized trial, which may decrease internal validity. However, the focus of this study is pragmatic in nature and the primary outcome is feasibility.

Conclusions

Prehabilitation is a key health intervention for those undergoing cancer surgery, with growing efficacy in the literature, yet the implementation of prehabilitation in real-world settings is lacking. BREATHE WELL will contribute to implementation science regarding approaches to support prehabilitation for surgical patients in a sustainable way that leverages the strengths of the health care and community setting.

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Acknowledgments

The research team would like to acknowledge the continued support from the many administrative staff, Nova Scotia Health, and Dalhousie University, for their assistance in getting this research study off the ground. The study was funded by the Department of Surgery, Dalhousie University. The funder was not involved with the study design. The research team is focused on integrated knowledge translation and has used key support from patient partners (SS) and knowledge users (JC, JP, and LH) in the design, implementation, and dissemination of the study.

Data Availability

The original contributions presented in the study are included in the paper. Any further inquiries can be directed to the corresponding author. There are no data in the protocol paper.

Authors' Contributions

JEL, DS, JC, MRK, SS, JP, SS, and AW participated in conceptualization and funding acquisition. JEL, DS, JC, and AW collaborated on methodology. JEL wrote the first draft of the manuscript with assistance from DS and AW. All authors reviewed the final manuscript. AW supervised the full project.

Conflicts of Interest

None declared.

Multimedia Appendix 1
TREND (Transparent Reporting of Evaluations of Nonrandomized Design) checklist.
[PDF File (Adobe PDF File), 1832 KB - resprot_v14i1e60791_app1.pdf]

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Abbreviations

BREATHE WELL: Boosting Recovery and Activity Through Early Wellness
MI: motivational interviewing
PRO: patient-reported outcome
REDCap: Research Electronic Data Capture
TREND: Transparent Reporting of Evaluations of Nonrandomized Design

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Protocol

Sustainable Implementation of Digital Assistive Technologies in Health Care Through a Simplified Interaction and Control Platform: Protocol for a Cocreative Feasibility Study

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Abstract

Background: With the expected increase in the number of people needing care and the increasing shortage of skilled care workers, new care concepts are required. Therefore, digital assistive technologies (DATs), especially robotics, can improve the situation of people with different needs and create opportunities for participation. For a human-technology interaction to have a high level of usability, DAT's meaningfulness and effectiveness must be accessible to end users. Significant barriers to the use of DATs in health care are the lack of controllability and adaptivity, as well as control functions that are too complex.

Objective: The objective of this paper is to develop an interaction and control platform that is understandable to a layperson and has a programming interface for DAT interactions. The innovation consists of the expansion of usage and interaction options for carers of existing DAT in a more individual manner. This is to be achieved by combining modern interactive media, a modular software architecture, and already available DAT.

Methods: The project is planned as a mixed methods study with a longitudinal design, with multiple user involvements and measurement times in collaboration with 3 care facilities in Germany. When assessing technologies, the satisfaction of the basic human needs of competence, connection, and autonomy plays an important role in the actual use of the technology. These needs can be measured in the form of usability (System Usability Scale), intention to use (Technology Usage Inventory), and satisfaction with the carers' needs (Technology-Based Experience of Need Satisfaction). In the qualitative assessment, user experience is recorded using the think-aloud method and focus groups in order to obtain information about potential improvements of the platform.

Results: The EduXBot (Educational Exploration Robot Application Platform) project was initiated in January 2023 and is scheduled to conclude in December 2025, at which point the project's final results are expected to be available. The initial results were attained in the summer of 2024 when the final concept for the platform prototype was developed. In November 2024, an initial prototype of a functional platform for the simplified interaction and control of DAT was evaluated.

Conclusions: It is expected that the open DAT system architecture enables caregivers without any previous technical knowledge to assemble their individual DAT functional portfolio. The results of the project will provide low-threshold access to interaction options for existing DAT as well as expand the usage of such technologies in an individual and patient-centered way.

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KEYWORDS

digital assistive technologies; human-technology interaction; mixed methods; cocreation; user-centered design; health care; intention to use; feasibility study; long-term care

Introduction

Digital assistive technologies (DATs) have long been discussed as a way to address pressing health care challenges. On the one hand, these challenges are related to the aging of society and the associated increasing need for care services. On the other hand, the acute and future shortage of nurses makes it difficult to provide care for older adults and those who are sick [1-3]. The digital transformation of health care and the use of DAT could be an opportunity to address these challenges [4]. As the health care system in Germany is under pressure to respond to increasing care needs, one measure is to promote the digital transformation of the health care system [5-7]. However, preliminary work shows that DAT, such as mobile apps, telemedicine systems, and robotics, have not yet been implemented in care processes as sustainably as expected [8,9]. However, when used correctly, DAT can provide opportunities to reduce the burden on caregivers [10-13].

The term assistive technology is a generic term for assistive, adaptive, and rehabilitative devices, which, according to the World Health Organization [14], includes all assistive devices, such as crutches, bedpans, or wheelchairs. For the purposes of this study, the term is expanded to include digital technologies such as augmented or virtual reality technologies or robotic systems. A generally valid definition of DAT is difficult to formulate, however, because DAT can develop potential in different areas [15-17], the effects of which would then have to be demonstrated in a specific application.

Nursing can be described as a complex situation in which the patient must be approached individually and according to the situation. The advent of DAT presents a challenge to health care professionals, who must adapt these technologies to the diverse and individual needs of the patients they care for and integrate them into care processes that must be planned individually. Thanks to their training and professional experience, professional nurses are able to quickly understand these complex situations and make appropriate decisions. It is difficult for nurses to imagine that an algorithm-based system can learn their rules and principles and have the flexibility to know when to modify those rules or not apply them at all. Apart from this, nurses recognize that DAT could reduce the error rate for routine tasks that require high concentration, such as medication preparation or documentation [18].

In addition, ethical concerns play an important role in nurses' reluctance to use DAT. An aspect of the discussion is the change in the workflow that occurs with the integration of DAT. Nurses fear that the logic of the devices, which is different from their own, will cause additional stress or even make them feel influenced by others. Nurses also fear losing their jobs as technology takes over their activities. Last but not least, there is a fear of losing interpersonal contacts. A change in the psychosocial component of nursing work goes hand in hand with a reduction in the attractiveness of the profession for nurses and should, therefore, be avoided [18,19].

Previous work shows that technology development research has been approached from a technology-centered perspective. Reference to user interests is often only made in the context of raising awareness among target groups, identifying needs in the testing phase, or for a finished technology [20-22]. Participatory design approaches such as cocreation are a solution to foster usability and user acceptance. Cocreation is defined as a collaborative approach that involves end users and relevant stakeholders in all phases of a project [23]. Early involvement of end users can increase acceptance and have a positive impact on patient satisfaction and quality of care [24,25]. In addition, cocreation can increase the successful implementation of evidence-based interventions and policies through equal and deep involvement of end users [26,27].

In order for DAT to unfold its potential, it is necessary, on the one hand, to provide services that are tailored to the respective functional limitations of those in need of care so that the use of DAT can be planned and problem oriented [28,29]. This means that nurses also play a crucial role in the widespread use of DAT. According to a study by the Bertelsmann Foundation, the acquisition of knowledge about existing technical systems is a prerequisite for the use of DAT in care settings, as is the development of application skills on the part of nursing staff [30]. Preliminary work also shows that application knowledge and skills, as well as the opportunity to use DAT in relation to care problems, are beneficial for nurses' willingness to use DAT [31-34].

To fill this research gap, the EduXBot (Educational Exploration Robot Application Platform) project aims to develop and evaluate a technology-based interaction platform with a reduced complexity control interface as part of a cocreative, exploratory approach to facilitate the control of existing DAT by caregivers. The goal is to provide formal caregivers with a simplified way to use DAT to support caregiving. The aim of this feasibility study is to investigate to what extent a prototype for simplified control of already available DAT changes the willingness of nurses to use them in the nursing process. The collaborative project brings together developers from the field of technology research, nursing scientists, and business partners from the fields of project management for digital work environments and the development of digital formats for knowledge transfer. The cocreative nature of the project means that in addition to the scientific project staff, nurses will be involved as end users in every phase of the project. This ensures that the project goals are better achieved in terms of user needs and technical feasibility.

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Methods

Conceptual Framework

The project aims at the participatory development and evaluation of a platform to promote the applicability of DAT in care settings. A feasibility study with a longitudinal design will be conducted based on a mixed methods approach. The main goal of the platform is a simplified application of DAT to support care processes. The development will be carried out in a participatory manner as a user-centered design (UCD) based on the suggestions of the "Motivation, Engagement, Thriving in User Experience" (METUX) model [35], which takes into account the expectations and experiences of the end users and promotes the intention to use (ITU) and thus the usability, relevance, and creativity of the platform, thus concretizing the overall implementation concept.

In practical implementation, the project is based on the theoretical model of UCD and follows the suggestions of the cocreative design cycle [36]. The UCD approach is used to cocreatively develop a more needs-based and more tailored end product based on the nurses' expert knowledge and to take possible consequences of implementation into account [36-38]. Positive effects are promised in terms of improving the identified outcomes as well as greater usability and user acceptance of technical products [39,40]. The cocreative design cycle is the process by which all relevant stakeholders are involved in the design and development of technologies. End users are actively involved in the design and development of solutions that meet their challenges. The result of the process is innovative and creative solutions that are useful, effective, and user centered, thereby promoting their actual use [41].

The user-centered and cocreative approach used in this study integrates 3 cycles (Figure 1) that incorporate the realities of end users (relevance cycle) and the scientific knowledge base (rigor cycle) into the development of technical products (design cycle) [42-45]. With this chosen approach, it is better possible to theorize, collect, and ultimately practically map the requirements for the technologies used in the study in the sense of determining needs. At the same time, collaboration between scientists and end users is more possible. Furthermore, end users can be more actively involved in product evaluation over the course of the test cycle. This ensures the functionality and, ultimately, the success in terms of improved applicability of a platform.

In the first step (relevance cycle), needs, functionalities, and application scenarios of and with nurses as end users are identified through focus groups. The selection of the DAT used in the project is based on the conditions of the cooperating institutions and the needs of the nursing staff. In order to clearly define nursing problems in the context of the learning scenarios, the concept of nursing need (see §14 Sozialgesetzbuch XI [Social Codebook XI]) is used. Based on this concept, DATs are selected that are already available and ready for use. These should cover a wide range and variety of technologies (from a mobile telepresence system to a complex humanoid robot).

Based on the results of this procedure, concrete scenarios will be outlined that are necessary for the implementation of a first demonstration model of the platform. In the next steps, the prototypes will be developed in 4 iterations with respect to usability, user acceptance, and satisfaction of basic psychological needs of the end users until the first prototype can be tested under simulated and real conditions in the facilities. The development of the prototype takes place schematically in 4 steps (Figure 2).

Figure 1. User-centered and cocreative design of the platform development (according to Farao et al [36]). DAT: digital assistive technology.

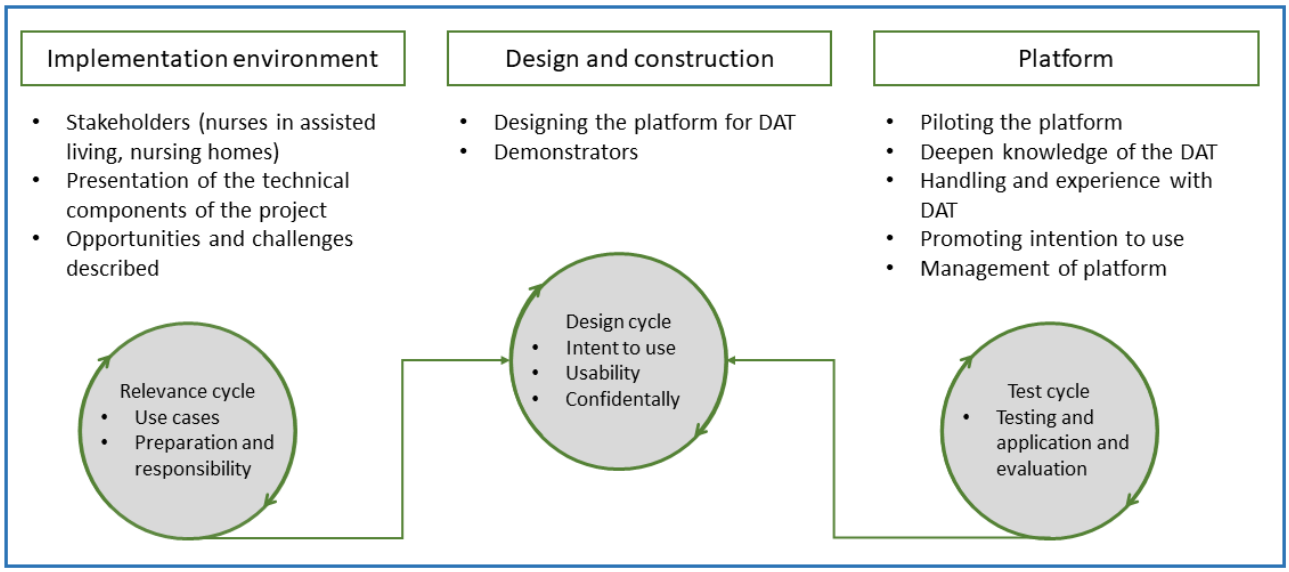

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Figure 2. The development of the platform takes place in 4 steps. DAT: digital assistive technology.

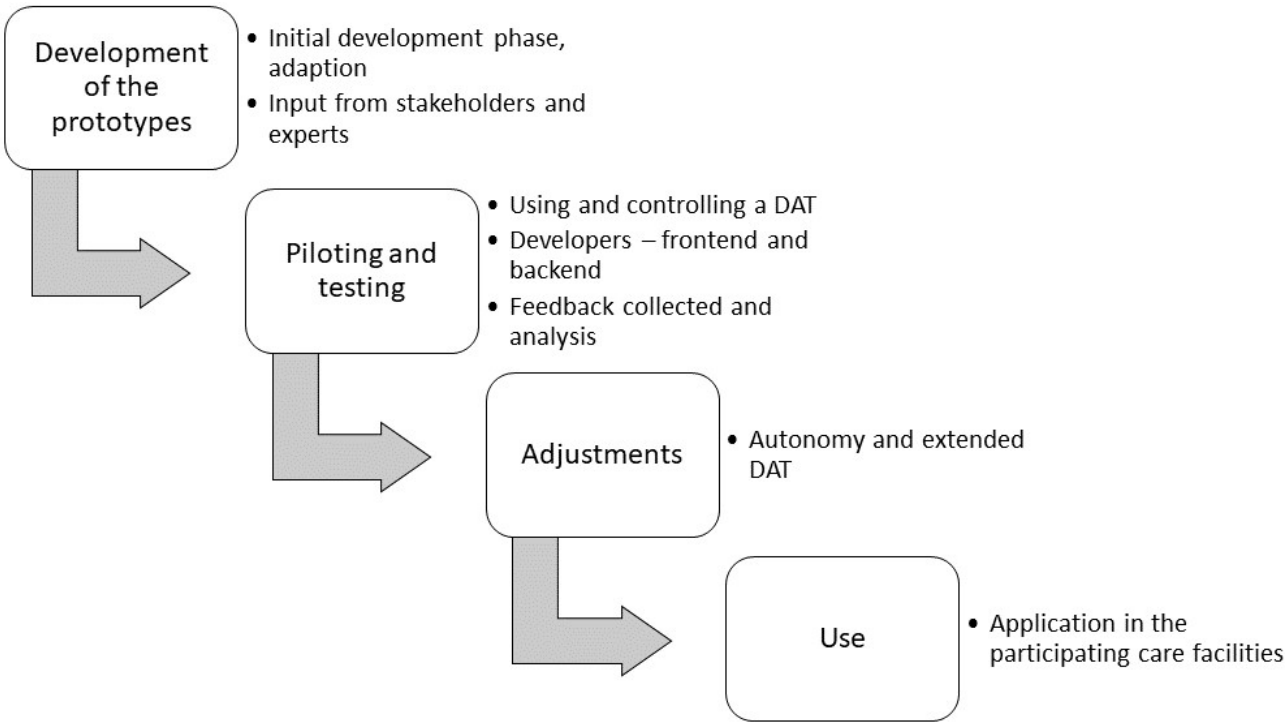

Technical Description

The innovation of the project does not lie in the development of new DAT per se but in the creation of extended usage and interaction possibilities for already available DAT. By combining modern interactive media and a modular software architecture, EduXBot aims to achieve the next level of DAT use in the care of people with disabilities, forced isolation, or restricted movement. The DAT should also promote an individual, programmable user interface for caregivers in an easier way to better meet the needs of those in need of care. EduXBot represents an experience and learning platform with 4 main functions (Figure 3): (1) programming (simplest type of programming), (2) community platform ("widget platform," users can share their apps), (3) using and controlling (easy way to interact, control, and use the DAT), and (4) augmented reality (AR) experience (experience and learn through AR content).

The multipart concept for using the platform then allows people with diverse previous technological knowledge to use DAT. That means EduXBot leads to the development of a layperson's iteration with the intention of human-technology interactions, which is developed in the form of a cocreative process together with the end users. EduXBot does not focus on the development of new care technologies that replace caregivers per se but rather on creating supportive interaction options that could relieve the burden on caregivers. The flexible and open system architecture of the platform supports this by keeping different DAT, sensors, and interaction systems available for different usage options. With the help of the development of low-threshold digital access options through an intuitive user interface with community and operator connections, informal support and supply networks are also strengthened as they enable participation in social networks.

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Figure 3. The 4 main functions of the EduXBot platform. AR: augmented reality.

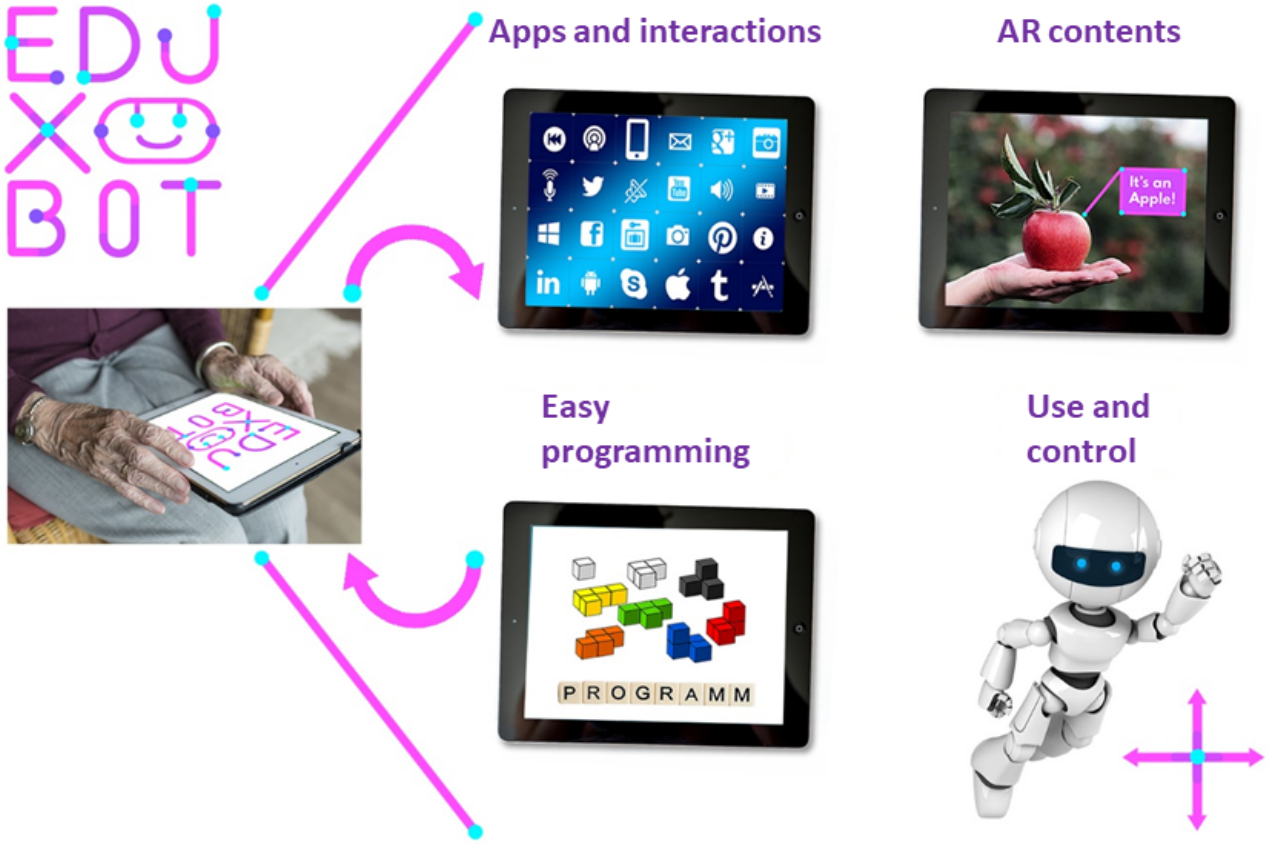

Study Design

Overview

EduXBot is a longitudinal feasibility study based on a mixed methods approach. The mixed methods approach combines aspects of quantitative and qualitative research in order to examine the research topic from different perspectives and to answer questions that could not be answered by a purely quantitative or purely qualitative study [46]. The researchers initiated the study with a quantitative phase, which was followed by a second qualitative phase that provided a more in-depth explanation of the initial results [47].

A total of 3 care institutions (1 inpatient, 1 outpatient, and 1 life-sustaining) that support people in their health care and daily life were recruited to participate in the project. The institutions were contacted as partner institutions in previous DAT research projects and agreed to participate in this project. Therefore, it can be assumed that the participating nurses are generally aware of the topic of DAT in nursing. The facility managers will be informed in detail about the project and will be asked to act as gatekeepers to motivate the nurses and relatives in their facility to participate in the research project.

Participants are invited to take part in the study as test subjects by the facilities with which they are affiliated. The participants are as varied as possible in terms of age, gender, length of professional experience, and so forth [48]. The inclusion of nurses from diverse backgrounds within the facilities serves to enhance the heterogeneity of the study sample, thereby contributing to the study's overall value. It should be noted that some participants may be unable to commit to the study due to scheduling conflicts or other commitments, while others may choose to withdraw (Textbox 1). It is essential to emphasize that no financial compensation is provided for participation in the study. However, those who elect to take part receive certain benefits, including complimentary refreshments during the workshop sessions and, upon request, recognition of their institution and name in the project acknowledgments.

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Textbox 1. Description of the inclusion and exclusion criteria of the participants.

Inclusion criteria:

- The participants could be nurses
- The participants could be the support staff
- Currently in a facility that belongs to the project's practice partner
- Sufficient in written and spoken German

Exclusion criteria:

- Those who do not want to participate at the beginning or withdraw later

In the context of research involving human participants, it is imperative to consider pragmatic factors such as financial resources and the maximum feasible number of participants in accordance with the guidelines for designing and evaluating feasibility pilot studies [49]. According to the guideline, achieving saturation in a study occurs at 30 participants. Statistical principles suggest that 30 individuals are sufficient to ensure the normality of the sample size [50,51]. Therefore, the objective is to recruit a minimum of 30 caregivers. It is important to acknowledge that the implementation of blinding is not a viable option in this context, as the participants are required to actively engage with the technologies under study.

The primary objective of this study is to design the human-technology interaction between the platform and users in a manner that ensures a high level of usability for all users. The objective is to assess whether the accessible platform alters the intended use of DAT by offering a simplified application option for caregivers. This inquiry seeks to ascertain the potential for DAT to be integrated as a supplementary resource in the planning of individual care processes. The central question guiding this study is whether the EduXBot platform offers an interface that enhances the autonomy of caregivers' DAT use. The objective is to enhance usability by a minimum of one level over the course of the study. The primary objective is to ascertain the extent to which the platform affects the usability of DAT (System Usability Scale [SUS]), the intention to use it (Technology Usage Inventory [TUI]), and the satisfaction of caregivers' needs through technology (Technology-Based Experience of Need Satisfaction [TENS]).

The secondary objective is to develop a multilevel benefit concept for EduXBot. This will provide caregivers with different affinities for electronic media, as well as different levels of technical expertise, and will offer them windows of opportunity to use and experience the platform. The objective is to conduct a direct assessment of the EduXBot platform by the participating nurses and to evaluate the platform with the aim of continuously improving the content and application options of the platform. A secondary objective is to record user satisfaction in order to obtain information on potential improvements to the platform through the analysis of structured feedback. The collection of qualitative data will be facilitated through the implementation of think-aloud (TA) and focus group methods. The aim is to empower caregivers to articulate their subjective experiences and perceptions regarding the utilization of EduXBot in an unstructured manner.

The third objective is the long-term evaluation of the EduXBot platform, encompassing not only its readiness for implementation but also its potential for long-term integration, utilization, and management of DAT. A further objective is to examine the interrelationship between the perceived ITU, usability, and user acceptance of the platform, which is currently being developed for the application. The tertiary target variable is the long-term willingness to use DAT in a sustainable manner and to integrate the digital assistive support offering into the existing care provision framework.

The measurement times are based on the development process shown in Figure 2. This allows changes in improving ITU to be measured. Since there are different versions with different application scenarios, especially at TUI, Table 1 is intended to provide an overview of the measurement times and evaluation methods used.

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Table 1. Different questionnaires are used at different measurement times.

Measurement time	Evaluation method
T0: Identification of functionalities and application scenarios	• TUI[a] original questionnaire (pre-post version) • Focus group
T1: Development of the prototypes	• TUI II parallel questionnaire (complete version) • Focus group
T2: Piloting and testing	• TUI II parallel questionnaire (complete version) • SUS[b] • TENS-Interface[c] • Focus group
T3: Adjustments	• TUI II parallel questionnaire (complete version) • SUS • TENS-Interface • Focus group
T4: Use	• TUI II parallel questionnaire (complete version) • SUS • TENS-Interface • Focus group

[a]TUI: Technology Usage Inventory.

[b]SUS: System Usability Scale.

[c]TENS-Interface: Technology-Based Experience of Need Satisfaction–Interface.

Quantitative Evaluation

The TUI is a valid measuring instrument that is based on the established Technology Acceptance Model [52] and its further developments [53]. It comprises 9 subscales, encompassing a total of 33 questions. These questions facilitate the estimation of technology use based on technology-specific and psychological factors. Each scale comprises 3-4 items, which are answered using a 7-point Likert scale. The intention to use scale uses a visual analog scale with a length of 10 cm. The subsequent Table 2 offers a comprehensive overview of the TUI scales.

Table 2. Description of the Technology Usage Inventory (TUI) scales according to Kothgassner et al [53].

Scale	Description
Curiosity	Curiosity and inquisitiveness of a person regarding a specific technology.
Technology anxiety	Independent of specific technology. Overwhelm, fear of using technology.
Interest	Independent of specific technology. Interest in technology and willingness to obtain information independently.
Usability	Perceived user-friendliness of a specific technology.
Usefulness	Perceived usefulness of a specific technology. Refers to support in everyday life.
Skepticism	Mistrust of a person regarding the use of a specific technology. Assessment of risk, danger, and disadvantages.
Accessibility	Perceived accessibility (in the sense of availability, procurability) of a specific technology.
Immersion	Can only be specified in connection with the corresponding technologies.
Intention to use	Intention to actually use a specific technology.

The internal consistencies of the scales can be rated as good overall (Cronbach α=0.70 to α=0.89). Furthermore, the TUI scales (with the exception of accessibility) have been found to be valid indicators of stress and relaxation based on heart rate and heart rate variability [53]. The wording of the individual questions can be adapted to the specific technology being evaluated, with the exception of the technology anxiety and interest scales. The TUI's modular design allows for the exclusion of individual scales contingent upon the investigative objective. For this study, for instance, the immersion scale was excluded, as no technology aimed at immersion was used.

This study uses the questionnaire at each measurement time (Table 1). Before the development of the platform, the original TUI questionnaire pre-post version was used to assess the caregivers' needs, functionalities, and DAT application scenarios. The "pre" version is administered before the introduction of the DAT, with the objective of collecting data on technology usage tendencies. The "post" version is administered after the introduction of the DAT, with the objective of establishing a baseline for measurement. Subsequent to these measurements, the TUI II parallel questionnaire (complete version) will be administered in its entirety. The

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measurement enables the formulation of statements regarding changes in the ITU.

For the purpose of evaluation, a cumulative value was formulated for each scale. The cumulative value commences at 3 or 4, representing the lowest level of the construct, and, contingent on the number of items, ranges from 21 (3 items) to 28 (4 items) at the highest level. The ITU scale constitutes an exception in this regard. The scale is evaluated by measuring the distance from the right endpoint (full rejection) to the answer at the intersection of the line. The distance in millimeters was ascertained and added to all 3 items. The maximum scale value that can be attained is 300. The interpretation of test values is facilitated by the scale description. A high test value is indicative of a high level of the respective construct. In instances where the data does not conform to a normal distribution, it is advised to use stanines (standardized calibration scale with a minimum of 1 and a maximum of 9) and percentile ranks (relativizing the test characteristic value in relation to the reference population) [53]. Standard tables have been developed for this purpose (Table 3). Consequently, a statement regarding the proportion of participants who attained the same or lower values is attainable.

Table 3. Percentage ranks and stanines.

Percentile rank	Stanine	Percentage (%)
0-4	1	4
>4-11	2	7
>11-23	3	12
>23-40	4	17
>40-60	5	20
>60-77	6	17
>77-89	7	12
>89-96	8	7
>96-100	9	4

The SUS assesses the usability of a system as perceived subjectively by the user and is proven to be technology-independent; that is, it can be used for a wide range of systems and technologies [54,55]. The 10 items are divided into 5 positive and 5 negative statements and are each represented on a Likert scale from 0 to 5. The participants' answers result in the SUS item score, which must then be converted into the SUS overall score (from 0 to 100) [56].

The calculation of the overall SUS score entails the subtraction of 1 from the raw value of all odd items in the initial step, whereas the raw value of 5 is to be subtracted from the raw value of all even items. To illustrate this calculation, consider the following example. If item 1 had a raw score of 4, the calculated score would be 3 (obtained as 4 minus 1). For item 2, if the raw score was 2, the score was 3 (derived as 5 minus 2). Subsequently, the sum of these scores was calculated and multiplied by 2.5 to derive the overall SUS score [56].

The average overall score of all studies (68) can be used to interpret your overall score [55,56]. Bangor et al [57,58] also introduced a rating scale using adjectives and letters analogous to the American school grading system as an aid to interpretation (Table 4).

Table 4. Adjective scale of the System Usability Scale (SUS) overall score [54,55].

SUS[a] overall score	Area of acceptance	Adjective scale
90-100	Acceptable	Best imaginable
80-89	Acceptable	Excellent
68-79	Acceptable	Good
50-67	Marginal	Ok
35-49	Not acceptable	Poor
0-34	Not acceptable	Worst imaginable

[a]SUS: System Usability Scale.

Deci and Ryan's [59] assertion posits that the use of the platform is contingent upon the satisfaction of specific fundamental human needs, including autonomy, competence, and connectedness [35]. Psychology posits that the more fundamental psychological needs are met through interaction with the system, the more end users engage with technology [60]. The objective of the TENS-Interface questionnaire is to ascertain the extent to which direct interaction with a technology fulfills the fundamental psychological needs for autonomy, competence, and connectedness [35]. The questionnaires, initially developed in English, underwent translation into German under the guidance of a professional linguist for their

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usage within the project. The translation process was guided by the "Translation Guidelines and Translation Documentation of the European Social Survey (ESS, 2020)" [61] with a focus on maintaining the validity and comprehensibility of the translation.

In the TENS-Interface, the items are each assigned to the basic needs of competence, autonomy, and relatedness. However, they are presented randomly in the questionnaire. The objective is to ascertain the extent to which direct interaction with a technology fulfills the fundamental psychological needs for autonomy, competence, and relatedness [35]. The application is designed to be universally accessible, ensuring autonomy of action, competence in handling, and a connection with the technology facilitated through the EduXBot platform interface. The collected data are then subjected to evaluation according to these objectives.

The descriptive statistics of the quantitative data are presented depending on the distribution, such as mean or median. Categorical data describing the sample are presented as absolute and relative frequencies. In order to answer the main question about the change in ITU, the difference between the measurement times of the individual test subjects, the facilities, and the overall sample is described as an absolute and relative mean difference. Possible further group differences are examined using the parameters "qualification" and "work experience." IBM SPSS is used as a tool for data management and data analysis.

Qualitative Evaluation

The TA methodology is used to qualitatively evaluate the platform. The idea is to ask subjects to express their thoughts and emotions out loud while testing the prototype in order to document them [62,63]. The advantage of this method is that it collects problems with the technology that has been tried by the end users, as retrospective surveys can lead to incomplete information about the problems with a technology. This means that TA protocols are helpful in understanding the thinking strategies of end users [64].

Testing sessions can be conducted on participants' own equipment or in a controlled environment. In protocols, participants think out loud as they complete a series of predetermined tasks. Participants are asked to say anything that comes to mind as they complete the task. This may include what they see, think, do, and feel. Sessions are often audio and video recorded so that developers can review what participants did and how they responded. Raw data comprise the verbalization of the thoughts, perceptions, and feelings that participants articulate as they complete a defined task. In a formal research protocol, all verbalizations are transcribed and then analyzed. In the context of usability testing, observers are asked to take notes on what participants say and do without trying to interpret their actions and words, and in particular, to note where they encounter difficulties [65].

The focus groups conducted during the iteration loops are partially structured with the help of guidelines Multimedia Appendix 1. The overall goal is to generate specific knowledge to answer the research question during the development process. The main factors that play a role are the adaptation of the selected application scenarios to the respective facilities as well as aspects of control and usability.

The composition of the focus groups is specifically based on theoretically based preselection in the sense of theoretical sampling according to the indicator caregiver [66]. In addition to these criteria, the most important thing is the willingness to talk about the respective needs and needs in the context of the platform development. No further criteria are defined in advance, but after the sample pool has been generated, the composition is determined exactly with regard to the contrasting of the groups. The number of participants in the focus groups is limited to 6 to a maximum of 10 people [67,68]. The selection of queries takes place according to the principle of theoretical sampling; achieving statistical representativeness is not intended [69].

All qualitative data were subjected to Kuckartz and Rädiker's [70] qualitative content analysis, which provides a structured framework for the content (Figure 4). Given the project's position within an emerging field of research, the material was coded inductively. This entailed the creation of categories based on the TA protocols and focus groups, thereby facilitating an exploratory evaluation of the material. This methodological approach enabled the systematic organization of the data material according to its content-related characteristics.

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Figure 4. Steps of qualitative content analysis according to Kuckartz and Rädiker [70].

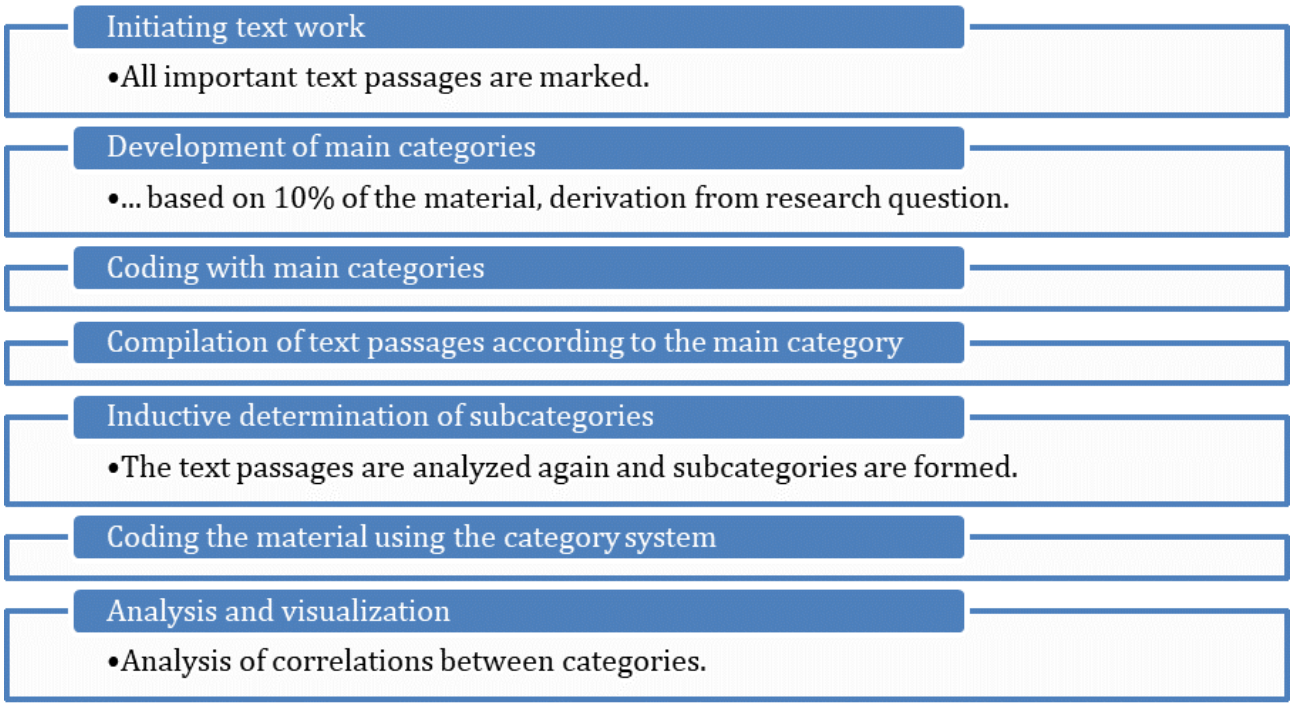

Ethical Considerations

All procedures involving human participants or human tissue will be performed in accordance with the ethical standards and principles of the institutional and national research committee of the 1975 Helsinki Declaration [71] and its later amendments or comparable ethical standards. Informed consent will be obtained from all participants. This study was approved by the Ethics Committee of the Medical Faculty of the Martin Luther University Halle-Wittenberg (approval 2023-190 of August 31, 2023). The study was registered in the German Register of Clinical Studies (DRKS00034195).

Results

The EduXBot project is funded by the Federal Ministry of Education and Research for a period from January 2023 to December 2025. During the summer of 2023, the practice partners were introduced to the project, and the application scenarios for a prototype design of the platform were cocreatively defined. The initial results were attained in the summer of 2024 when the final concept for the platform prototype was developed in collaboration with the target group. A total of 2 workshops were held in February and July 2024. An initial prototype of a functioning platform for the simplified interaction and control of DAT was evaluated in November 2024. The project is scheduled to conclude in December 2025, at which point the final results will be available. To ensure methodological quality, the Transparent Reporting of Evaluations with Nonrandomized Designs (TREND) statement [72] will be used for reporting the results.

Discussion

Principal Findings

The objective of this study is to design the human-technology interaction between an interaction and control platform and nurses in such a way that a process is created that ensures the high usability of DAT in nursing care. The central question guiding this study is whether the low-threshold platform changes the intended use of DAT through the simplified application options for nurses in order to integrate DAT as possible supplementary resources into individual nursing process planning. The objective is to assess whether the platform offers an interface that enhances the autonomy of nurses in using DAT. The evaluation will yield both quantitative and qualitative data, providing insights into the requirements of nurses as end users of DAT. The objective is to enhance the usability of the platform by at least one level over the course of the study.

Strengths and Limitations

The strengths of this study include the triangulation of quantitative and qualitative data. The potential for DAT to streamline individualized interventions in nursing care has implications for its intended use, which, in turn, affects its actual use in everyday work. The findings of this study will encompass practical, scientific, and societal ramifications, thereby paving the way for subsequent studies and interventions aimed at reducing nurses' workload. However, the study is not without limitations.

First, the number of participants is limited. For feasibility studies, the Guidelines for Designing and Evaluating Feasibility Pilot Studies [49] recommend basing the number of participants on practical factors such as availability and financial resources. In the event that the targeted number of 30 participants is not

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attained, the evaluation will be conducted by combining quantitative and qualitative data in accordance with the methods outlined by Creswell and Plano Clark [47].

Second, the participating practice partners have previously engaged in other research projects, have been informed about the digital transformation, and have had experience with DAT. Conversely, participation in this study is voluntary, suggesting that nurses who are generally open to the topic are more likely to participate. The number of participating care facilities is limited to 3, which may limit the generalizability of the findings. While the inclusion of other professional groups, such as support staff, could be considered a valuable addition to the study, future research would benefit from the involvement of a more extensive range of care facilities and health care professionals to enhance the generalizability of the findings.

Conclusion

A scoping review of the state of the art of robotic interaction and control platforms in health care [73] reveals that only a limited number of feasibility or user studies have addressed the interaction and control of DAT by end users in a cocreative manner. The studies emphasize the necessity of end-user engagement to mitigate ethical concerns and ensure the relevance of the developed technologies to their intended beneficiaries [74-76]. A notable limitation of the existing studies is their exclusive focus on home care settings, resulting in a paucity of empirical findings for the domain of long-term inpatient care. In this context, the EduXBot project has been initiated to address this knowledge gap.

The implementation of technologies in nursing care practice is predicated on nurses' perception of their meaningful use. The generalization of the care process into standardized procedures is a challenging and complex scenario. The integration of individualized interactions further complicates the scenario, making it challenging for technical developers to meet the requirements and needs of the target group without the involvement of nursing professionals in the development process [77,78]. Caregivers play a pivotal role in research endeavors. Their expertise in the field, stemming from their in-depth understanding of diseases and their impact on patients, positions them as pivotal potential end users. By incorporating their insights, nurses can influence the development of technologies to align with their needs and requirements for interaction and control [79].

The dearth of development expertise among caregivers precludes them from programming the technologies independently. A potential solution to the usability issues of DAT is the development of a platform that provides an interface for nonprogrammers to create individual interventions using everyday controls and a few intuitive steps. This approach has the potential to ensure the sustainable implementation of DAT. EduXBot signifies an inaugural endeavor in this direction.

Acknowledgments

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Data Availability

The datasets generated during and/or analyzed during this study will be made publicly available upon completion of the study and can be obtained from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Focus group guideline (draft).
[DOCX File , 15 KB - resprot_v14i1e63089_app1.docx]

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Abbreviations

AR: augmented reality
DAT: digital and assistive technology
EduXBot: Educational Exploration Robot Application Platform
ITU: intention to use
METUX: Motivation, Engagement, Thriving in User Experience
SUS: System Usability Scale
TA: think-aloud
TENS: Technology-Based Experience of Need Satisfaction
TREND: Transparent Reporting of Evaluations with Nonrandomized Designs
TUI: Technology Usage Inventory
UCD: user-centered design

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Protocol

Assessment of Community Stakeholders' and Health Educators and Professionals' Needs for the Continuous Enhancement of Sexual and Reproductive Health and Rights in Mali (Project CLEFS): Protocol for a Convergent Mixed Methods Study

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Abstract

Background: In Mali, a lack of qualified human resources in primary health care and sexual and reproductive health and rights (SRHR) is one of the greatest barriers to the population's access to standard health services. Frontline professional training must be strengthened to respond to the needs of the population, particularly those of women and girls. Training must be conducted using an interdisciplinary and adapted approach to promote gender equality.

Objective: This study aims to identify the SRHR training needs among the community, educational actors, and primary health care providers.

Methods: A concurrent mixed methods design was adopted, using 2 methods. A quantitative method, through a cross-sectional analytical survey, will be conducted at the community level with university community health centers (CSCom-U) users and adolescents in CSCom-U health areas, as well as at the health education institution and community health centers levels with teachers, students, and interdisciplinary professional groups within the CSCom-U and district hospital maternity. Descriptive and inferential analyses will be conducted to process quantitative data. This research is at the stage of data analysis and interpretation. A qualitative method, based on 3 sources of data (focus groups, individual semistructured interviews, and document analysis), which involved the same targets as the quantitative component, with additional community actors such as Community Health Associations (Associations de santé communautaire) and Women's Service User Communities. A thematic analysis of the qualitative data using a mixed deductive and inductive method will be performed.

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Results: *:* Field data collection took place from March to April 2022. Quantitative data from 3153 participants are being analyzed using SPSS. Qualitative data from 11 interviews and 27 focus groups were processed with Qualitative Data Analysis Miner. Data analysis is still ongoing.

Conclusions: This study will provide a better understanding of adolescents and SRHR user's service needs in terms of health services availability and quality and SRHR knowledge, issues related to student training quality, the level of adequacy between the training offered and the actual needs of the service recipients, and the level of preparation and ability of teachers to provide quality teaching taking gender equity into account. The recommendations drawn from this assessment will propose concrete actions to improve women and girls' health services provided by professionals, and to better adapt the future health professionals' profiles to the needs of communities, particularly those of women and girls.

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KEYWORDS

mixed methods study; protocol; sexual and reproductive health and rights; Mali; primary health care providers; women and girls' health needs

Introduction

In Mali, the health system does not yet have sufficient capacity to meet the health needs of the population, especially those of women and girls. Primary health care (PHC), considered to be the foundation of sexual and reproductive health and rights (SRHR) service delivery, remains poor [1]. Each year, 33% of pregnant women give birth outside of a health facility, and the maternal death ratio is 440 out of 100,000 births [2]. Although 24% of Malian women aged between 15 and 49 years report having unmet family planning (FP) needs, only 15% of them use modern contraceptive methods [3]. Among women with unmet FP needs, 17% are oriented toward pregnancy spacing [3].

In rural areas, where approximately 75% of the Malian population live, access to PHC services is more difficult, thus creating substantial inequities [4]. There is a significantly higher fertility rate (6.8 vs 4.9 in urban areas), a lower proportion of prenatal care visits (37% vs 67% in urban areas), a higher proportion of deliveries outside a health facility (39% vs 7% in urban areas), as well as more limited access to FP (contraceptive prevalence rate for sexually active women not in a union is of 27% vs 44% in urban areas) [3]. This highlights that women and girls have poor access to nonstigmatizing SRHR services and information as well as insufficient bargaining power regarding their sexual and reproductive health [5,6]. In addition, gender-based violence (GBV), including domestic violence, is also widely common as 45% of women aged 15-49 years are survivors of physical or sexual violence [3]. However, this violence remains poorly documented due to several barriers such as low institutional commitment to integrating this issue, particularly in health reporting. There is also a lack of health professionals training and clinical screening tools for mental health problems, particularly for postpartum depression, GBV survivors, and people affected by armed conflict [7].

Health education institutions in Mali lack the human, material, and financial resources to fulfill their role in teaching PHC and SRHR care [8]. The gaps in undergraduate and continuing education contribute to the lack of skilled human resources in PHC and SRHR, particularly in rural areas [9]. Skills of frontline professionals need to be strengthened at the level of both institutional management and training, to respond to the population's needs using an interdisciplinary approach, to promote gender equality (GE), and, ultimately, to offer training tailored to the needs of the labor market.

To address these concerns, the Canadian consortium—which is composed of Santé Monde, the Cégep de Saint Jérôme and the Centre interdisciplinaire de développement international en santé from University of Sherbrooke and funded by Global Affairs Canada—has implemented the Local Teaching Communities for Healthy Women and Girls (Communautés locales d'enseignement pour les femmes et les filles en santé [CLEFS; French]) project. This project will operate for a 5-year period (2020-2025) in 5 different regions of Mali (Kayes, Koulikoro, Ségou, Sikasso, and the district of Bamako). The CLEFS project was developed in partnership with the Malian Ministries of Health, Higher Education, and Women's Promotion and with health training institutions in Mali (Faculty of Medicine and Odontostomatology [FMOS], National Institute for Training in Health Sciences [Institut National de Formation en Science de la Santé [INFSS]], and private schools), women's user committees, persons in charge at Community health associations (Associations de santé communautaire [ASACO]) for university community health centers (CSCom-U), as well as the Malian district hospitals to which the CSCom-U are attached. CSCom-U is a first-level health center in community settings offering a minimum package of health care. As community health centers with a university orientation, they also offer delocalized internships for medical students.

This project is based on the principle that health education institutions in Mali must fully integrate PHC and SRHR concepts into their curricula and pedagogical approaches to fulfill their social responsibility toward women's and girls' needs. This process involves collecting and analyzing data on the unmet needs of the beneficiaries, as well as those related to training and frontline health care system actors. In this context, the CLEFS project supported the Malian health training institutions (INFSS and FMOS) in conducting a participatory evaluation.

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Methods

Research for the Continuous Improvement of PHC and SRH Training Programs

Improving care in SRHR requires going through all the steps of the training engineering process to ensure continuous improvement of health care services and related training. A key step is conducting a participatory evaluative study to identify the SRHR needs of the communities served by the CSCom-Us, with a focus on women and girls, as well as those of the various actors involved in training and in the provision of PHC services [10,11] to assess the adequacy between the real needs of the communities and the targeted output profiles in SRHR.

SRHR training needs for front-line care providers are those focusing on essential services such as comprehensive sexual health education, FP, antenatal, intrapartum, and postnatal care including emergency obstetric and newborn care, prevention and treatment of HIV and other sexually transmitted infections (STIs), postabortion care, and prevention, immediate services and referrals for cases of GBV, and finally prevention, detection, and management of reproductive cancers [12]. Training needs encompass a patient-centered approach that respects individual gender considerations and human rights.

This participatory approach will allow a better involvement and ownership of the needs assessment methodology by Malian professionals, as well as a better acceptance and use of the resulting findings. The results will reflect a concerted and consensual identification of SRHR needs and therefore an appropriate definition of the expected output profiles at the level of both undergraduate and continuing education.

Study Objectives

Overview

The main objective of this study is to depict the real and differentiated needs of Malian actors and primary care users related to SRHR to improve the training programs and services offered in this area.

This translated into the following specific objectives as follows: (1) to identify the SRHR needs of community actors and beneficiaries (adolescents and CSCom-U users); (2) to identify the SRHR training needs of students, trainers, and health professionals involved in training in terms of SRHR capacity building; and (3) to improve the curricula of nursing and obstetric practitioners in accordance with the needs of the health care professionals and specific needs of the populations served, in particular those of women and girls.

Overall Study Design

Using a participatory approach, this needs assessment adopts a concurrent mixed methods research design combining quantitative and qualitative methods [13]. It is based on the convergence of the analytical results performed for each method with all the actors concerned [14,15].

Method 1: Quantitative

Quantitative Study Design

Cross-sectional surveys were conducted in the 5 project intervention zones, namely the cercles of Sikasso, Kolokani, Baraouéli, Kayes, and Bamako in the regions of Sikasso, Koulikoro, Segou, Kayes, and Bamako. Note that a cercle is the second administrative division of Mali. Mali is composed of 8 regions and 1 capital district (Bamako), with each region divided into 49 cercles.

Three levels were considered as follows: (1) community level: targeting CSCom-U users and adolescents in the CSCom-U health areas; (2) health education institutions level (FMOS and the main INFSS and its regional branch schools [called Annex]) and CSCom-U targeting teachers, students/trainees as well as; and (3) groups of interdisciplinary professionals from CSCom-U and the maternity ward of district hospitals supported by the CLEFS project.

Participant Inclusion Criteria

The study participant inclusion criteria are as follows.

1. Female users: women of childbearing age between 15 and 49 years old who have resided in the household during the last 6 months before the survey.
2. Male users: male heads of household aged 20 years and older or their legal representative aged 20 years and older who have stayed in the household during the last 6 months.
3. Adolescents: unmarried girls and boys aged 15-19 years.
4. Interdisciplinary professional groups: consist of physicians, clinical supervisors, midwives, and obstetric nurses practicing in CSCom-U and district hospitals maternity units for at least 6 months prior to the survey.
5. Teachers: lecturers and supervisors on a temporary or contractual basis in the nursing care and obstetrical care programs at the INFSS or Annex schools and in the family/community medicine programs at the FMOS, who have been teaching for at least 1 year before the survey.
6. Students: students in the nursing care/obstetrical care streams of the INFSS and its Annex schools, as well as those of the Specialized Studies Diploma in Family/Community Medicine programs, from the 2nd year of teaching onwards—including trainees—with a proportional distribution between men and women and between the different years of study.

Sample Size and Techniques

Sample sizes of the different community targets and intervention zone were calculated separately based on the total number of households in the health areas and the size of the population targeted by the survey. Sample size was, considering the proportion of the phenomenon studied, at 50% and the CI at 95% [16]. The choice of 50% value allows us to have a sufficiently large sample to make inferences, regardless of the true value of the phenomenon studied in the real population. It was calculated using Epi Info7 software (Centers for Disease Control and Prevention) and was distributed proportionally to the size of the households in the selected villages.

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Student and teacher sample size was calculated separately based on the total number of students in the nurse and obstetrical care stream at INFSS and its Annex schools and the number of family/community medicine and teachers involved in these streams at the 2 institutions. The calculation was done using the same method and the same software as the community-level actors in a separate way for the INFSS, the INFSS Annexes, and the FMOS. Thus, the calculated sample size (teachers and students) at the Annex schools' level was proportionally distributed based on the number of teachers and students in the different Annexes.

At the Community Level

A multistage sampling technique was used for selecting study participants (stratified random, clusters, and simple random).

Stratified random sampling was performed in the villages or sectors of the CSCom-U health catchment areas considered as natural strata (4 per CSCom-U). The lists of villages in the health catchment areas were established by CSCom-U. Strata were randomly drawn considering proportionality in this population by applying the systematic random method with a sampling step calculation. Once these strata were randomly drawn, the households within these villages or sectors were grouped into clusters (composed of a maximum of 40 households) using the segmentation method for each one. Thus, clusters were randomly selected, and the survey was conducted among the households in these clusters.

Another simple random draw was then conducted within households to select one woman of reproductive age in each household (if there are several) to answer the user survey questions. The head of the household or his/her representative who is 20 years or older was surveyed to answer questions about users. Adolescents (male/female [M/F]) meeting the criteria in the selected households, were also surveyed after a random draw if numerous. If the number of households expected to be surveyed was greater than the number of households in the selected cluster, another cluster was randomly selected to complete the total number of samples required for the survey.

At the Educational Institutions and CSCom-U Levels

A simple random draw without replacement was made from a list of all teachers of the Specialized Diploma of Family Medicine/Community Medicine and the INFSS and Annex schools to obtain the required sample size. Another simple random draw without replacement was also carried out based on the list of the students of the cycles and the level of teaching concerned to obtain the required sample size. The sample size was segregated by gender/level/profession. Randomly selected students were contacted to participate in the survey after obtaining their consent. If a student refused to participate in the survey, another number was randomly drawn to replace him/her until the total sample size was reached.

For the interdisciplinary focus groups in the CSCom-U and district hospitals, as the number of staff is not large, all physicians, midwives, and nurses with a role in SRHR who were available at the time of the team's visit and who gave their consent to participate were surveyed.

There is a low number of professionals in CSCom-U and maternity care. Therefore, all available and willing physicians, midwives, and nurses were solicited for the CSCom-U and district hospitals interdisciplinary professional focus groups.

Quantitative Data Collection and Management

To carry out the data collection, teams of external interviewers and trained supervisors were deployed on site. The interviewers were external individuals with expertise in conducting surveys and were recruited by the project team for the period of the data collection. They were responsible for carrying out the surveys among users, adolescents, and students. Due to the sensitivity of sexual and reproductive health issues, female interviewers conducted the surveys among female respondents and male interviewers among male ones.

Supervisors made up of members of the State's Technical Services and members of the FMOS, INFSS, and Association of Private Health Schools were responsible for verifying the conformity of investigators' work and supporting them when necessary. Their involvement strengthened the process of ownership of the continuous quality improvement approach from data collection to the presentation of evaluation results. This approach ensured the transfer of acquired skills to other stakeholders and replicated the continuous quality improvement process in their respective regions, with little or no outside technical assistance. Supervisors were also responsible for conducting the qualitative component.

The FMOS experts (Mali), in collaboration with the INFSS (Mali) and supported by the CLEFS project team (Canada), developed and customized questionnaires tailored to the various survey targets. These questionnaires were subsequently distributed to all stakeholders involved in the training needs assessment process for review, appropriation, and validation of the tools. Once validated, the tools were created on the Kobocollect platform (KoboToolbox software) and then deployed on tablets or smartphones to collect data. This method offers several advantages such as quickness, error avoidance, the obligation to answer all questions (better completeness of data), and reduction of outliers. All data collected on-site were sent daily to the Kobocollect account and extracted in an Excel file to be reviewed during the data collection.

Prior to data collection, a 3-day training was conducted for the entire evaluation team. This was followed by a 1-day pretest in an area outside of the project's intervention regions to assess its clarity and comprehensibility and to enable the methodology to be adjusted if needed.

Quantitative Data Analysis

Since the data were collected with tablets or smartphones, data entry was instantaneous. Data were extracted from the KoboCollect platform in Excel format, then processed, cleaned, and finally analyzed using Excel (Microsoft Corp) and SPSS software (version 27; IBM Corp).

Data analysis and interpretation are still ongoing. According to our research protocol, we will conduct descriptive analyses, such as examining proportions, averages, and SDs, to gain insights into sociodemographic characteristics. This includes

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examining levels of knowledge, attitudes, practices, and perceptions regarding various aspects of SRHR, specifically FP, sexuality, STIs, HIV, prenatal care, childbirth, and GBV. The level of satisfaction and challenges related to the use of CSCom-U will also be analyzed. Access to information for CSCom-U users and adolescents regarding SRHR will also be measured.

The evaluation will also include an assessment of the satisfaction levels of students with the SRHR programs attended, the training environment and internships including safety aspects; students' sense of preparedness to face professional life; level of preparedness of teachers and health professionals to respond to the needs of students and interns and to train students able to respond to community needs.

Several inferential statistics will be used. For example, chi-square tests will be used to compare the proportions of the variables of interest and the student *t* test will be used to compare mean scores. Gender analyses will also be performed to understand gender specificities. The statistical significance level will be set at 5%. Multivariable regression analysis will be conducted afterwards if significant associations are found in bivariate analyses.

Method 2: Qualitative

Qualitative Study Design

Three groups (ie, multidisciplinary teams, community stakeholders, teaching teams, and students) were targeted for the qualitative component, which was conducted using 3 sources of data: focus groups, semistructured individual interviews, and a literature review.

Participant Selection and Method

Community Actors

Community actors mainly included the project's implementation partners, that is, ASACO members, women's user communities, youth groups, and community relays. This phase also reached users, adolescents, traditional birth attendants, traditional therapists, and community leaders. Targets were chosen according to a purposive sampling and snowball strategy until data saturation was reached according to the inclusion criteria previously identified in the sample of the quantitative component. To ensure a better representation of this population, we aim to select a variety of profiles in terms of age, gender, number of years in office, and as members of different associations.

At the community level, 6 focus groups were conducted as well as semistructured interviews per health area as follows: a mixed focus group (M/F) with members of each ASACO (8 to 12 people); a women's focus group with communities of women users (8 to 12 people); a mixed (M/F) focus group with youth groups, provided that heterogeneous youth groups exist in the localities. If not, or depending on cultural realities, homogeneous groups were conducted; a mixed focus group (M/F) with community relays of 8 to 12 people; a homogeneous focus group with women users of the SRHR services of the CSCom-U; a mixed focus group (M/F) with adolescents; and individual interviews with a traditional birth attendant or rural maternity officer and a traditional therapist per village/area, if available.

CScom-U and District Hospital Maternity Units' Multidisciplinary Teams

These multidisciplinary teams were composed of medical doctors, midwives, and obstetric nurses involved in the SRHR services. CSCom-U and maternity technical staff were not numerous and therefore all of them were involved.

Concerning the data, a mixed (M/F) focus group was organized at each CSCom-U and district hospital maternity unit to explore the following elements: the clinical skills of health professionals, the challenges, and issues they face in providing quality SRHR services to women and girls, their level of ability (training, tools, and equipment) to provide quality SRHR services as well as mental and environmental health issues. Discussions also focused on their ability to provide support and respond to the needs of trainees, including safety issues, and harassment.

Educational Institutions Actors

Overview

Two groups of actors were targeted at this level: teachers and students. They were chosen according to a purposive sample strategy and until data saturation was reached, according to the inclusion criteria already identified in the sample of the quantitative component. To ensure a better representativeness of this population, we selected a variety of profiles in terms of gender, seniority, level of study, teaching field, and type of teacher (lecturer and supervisors).

For the Teachers

Three mixed (M/F) focus groups (1/nursing, 1/obstetrical, and 1 family or community medicine specialty diploma) of 8 to 12 teachers were organized. Our objective was to better understand the level of preparation of the teachers in terms of pedagogy, teaching SRHR, their expectations, and the difficulties they face in teaching in the continuous improvement of programs.

For Students

A heterogeneous focus group for the nursing stream, a homogeneous focus group for the obstetrical stream, and a heterogeneous focus group for the family or community medicine specialty diploma of 8-12 students was organized. Our objective was the following: to identify the main challenges and issues related to the quality of training, the adequacy between training and the needs of the populations, the training environment, GBV, security aspects, and the consideration of their specific needs by teachers. To obtain quality information, students were selected from the 2nd year of training.

Document Analysis

In addition to the literature review, a documentary analysis was conducted and covered: the CSCom-U supervision reports, maternal death audits, CSCom-U and district hospitals activity reports, previous evaluation reports, etc. These reports helped to determine the needs already identified by the national or regional level at the CSCom-U and to understand the underlying problems related to SRHR.

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Qualitative Data Collection and Management

Overview

Focus groups and individual interviews were conducted using interview guides tailored for each target group. They were developed by the project team in collaboration with key partners from FMOS and INFSS and validated by all stakeholders in the needs assessment process. The guides were inspired and adapted to the context and needs of the project based on existing guides such as the Demographic and Health Survey and covered the main themes explored (eg, SRHR knowledge and services offered) according to the actors of each target. The various individual interviews and focus groups were conducted by the survey supervisors, who are the project's supporting partners, that is, agents of the government's technical services, but also key partners. For the focus groups, a minimum of 2 people conducted them. One was responsible for facilitating the discussion and the other for managing the recording, taking notes, and making observations of the participants. For individual interviews, 1 or 2 people conducted them depending on the number of supervisors, one of them was responsible for asking the questions, and the other for taking notes and managing the recording.

At the Community Level

For the recruitment and data collection, our evaluation team informed ASACOs leaders as well as the Technical Directors of the Center of the evaluation process, the date, and the participants to be met. They then informed the other members of the ASACOs, the communities of women users, the youth groups, and the community relays and set up a schedule of visits and meetings with the different participants. The different discussion groups were conducted in the ASACO offices. ASACOs, with the support of the evaluation team, made the necessary arrangements to ensure the involvement of the participants and to respect data confidentiality.

Guidebooks were written in French, but were administered in Bambara, the most widely spoken national language of Mali. The observer took notes directly in French. Each focus group lasted a maximum of 120 minutes and was recorded after obtaining verbal or written consent from the participants. Discussions were fully transcribed as they occur in verbatim form and translated by interpreters when needed.

Individual interviews were conducted with traditherapists, traditional birth attendants, and community leaders and occurred in the villages or areas selected for the quantitative survey. Interviews were held after the ASACO leaders had informed the customary authorities and obtained the free and informed consent of the participants. Interviews lasted 45 to 60 minutes at most. The interviews were conducted in Bambara and verbatims were translated into French.

At CScom-U and District Hospital Maternity Units' Levels

The evaluation team informed the technical directors of the center and the district medical officer, who in turn informed the technical staff of the objectives of the evaluation, the people to be involved in the process, and the schedule for the evaluation team's visit. In collaboration with their ASACO, they made the necessary arrangements to encourage the participation of the people concerned as well as confidentiality during the data collection.

At the Health Education Institution Level

Under the guidance of the evaluation team, the administration of these institutions informed faculty and students of the evaluation process, objectives, and schedule. Together they organized the recruitment of faculty and students who wished to participate in the interviews. They provided a room for the team to ensure the confidentiality of the interviews. At the school level, interviews were conducted directly in French and notes were taken in French. They were also recorded after obtaining participants' consent.

Qualitative Data Analysis Methods

Data analysis and interpretation are still ongoing. Qualitative data analysis will be conducted using an iterative process and will include the listening of audio recordings, successive readings of French transcriptions, team coding, team analysis, and participant validation. The project team will code the interviews using QDA (Qualitative Data Analysis; Provalis research) Miner software using a mixed deductive and inductive approach. This iterative method simultaneously makes sense of the data collected based on the state of knowledge, while potentially identifying new meanings. A brief list of initial codes based on the interview guides will serve as a coding grid a priori. It will be modified and enriched as the analysis proceeds. Coding will be controlled by a double coding technique performed by a member of the project team and the expert researchers. Parallel and independent coding will be done for the first few 4 interviews, followed by a comparison of the results. This process will be repeated until a consensus list of initial codes is obtained as well as intercoder fidelity greater than 90% [17].

Mixed Methods Integration

We will adopt a strategy using the matrix technique to summarize and present the QUAN and QUAL results [18]. First, the main statistical results (QUANT component) of the surveys will be presented by the participant group. Second, the themes emerging from the QUALI component (interviews and group discussions) will also be presented in a matrix by the participant group. This will enable us to look for similarities and divergences within and across participant groups, as well as patterns between different participant groups in each component of the study. Third, our integration strategy will focus on concordance as well as divergence between the main qualitative and quantitative findings [18,19]. Thus, we will develop a mixed methods matrix combining the main QUAN and QUAL results, organizing the data according to key themes and corresponding variables to enable comprehensive analysis and interpretation. This matrix will contain a row for each key qualitative theme (ie, needs related to GBV, FP, pregnancy and neonatal care, STI prevention and treatment, postabortion care, sexual health education, clinical support for GBV survivors, and SRHR capacity building needs for trainers), which will be compared or contrasted with the corresponding quantitative results for each theme (eg, knowledge and practice related to FP, STI prevention, and needs for trainers' pedagogical reinforcement; Figure 1).

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Figure 1. Overview of the main stages of the research study. ASACO: Associations de santé communautaire; CSCom-U: university community health centers; SRHR: sexual and reproductive health and rights.

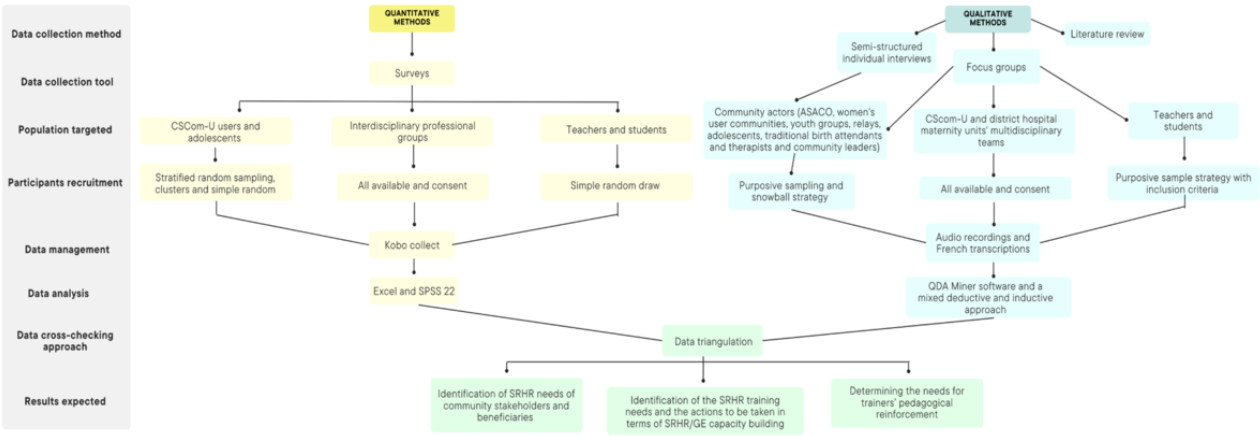

This approach is consistent with guidance on methods that advocate complementing quantitative analyses with in-depth data obtained from focus groups and individual interviews [20,21].

Evaluation Team Training and Formative Research

Overview

Prior to the data collection start-up, a 5-day training session on the use of the QDA Miner qualitative analysis software was organized for the evaluation team in Mali to strengthen their capacity to analyze qualitative data. This training was facilitated by a consultant supported by the University of Sherbrooke who was also in charge of making the software available.

A further 3 days' training on the KoboCollect software was provided to the evaluation team by the project's monitoring and evaluation technical advisor as required.

Prior to the teams' field deployment, a 4-day training session was held for all individuals involved in the needs assessment process. The training was provided by FMOS, INFSS, and the CLEFS project team and focused on the following.

Understanding the Roles and Responsibilities of Team Members

Following are the roles and responsibilities of the team members:

- The interviewer's responsibilities in terms of listening, paying attention, etc.
- The pitfalls to be avoided (nonjudgmental and noninterrupting)
- Setting up conditions to ensure data confidentiality
- Seeking free and informed consent to participation
- Respecting societal and cultural values.

Understanding and Translating the Different Tools to Be Used

The following will be ensured in understanding and translating the tools to be used:

- A detailed explanation of the tools to be administered
- An exchange to validate the translation of these tools into the national language so that any questions asked are understood and worded correctly.

Survey Methodology, Including On-Site Data Collection

The survey methodology involves the following:

- The process of identifying households and survey targets
- The process of obtaining participant consent and discussing the ethical aspects of the research process
- Data collection procedures, including digital data collection (eg, downloading, filling in and saving forms, and sending final versions).

Managing Sensitive Cases and Difficult Situations

Sensitive cases and difficult situations will be managed as follows:

- Training on how the evaluation team should act if respondents confide to us or seek our advice or support
- Following this 3-day theoretical training, a pretest was organized on the fourth day in a Bamako commune with a dozen people to identify and rectify any errors of understanding and phrasing before the team's deployment in the field.

Ethical Considerations

This study adheres to the ethical guidelines and principles relevant to human research. The ethical approval was granted by the Research Ethics Committees of the Malian FMOS (reference number: 20231 132 ICE/USTTB) and the University of Sherbrooke (reference number 2022-3261).

Prior to the teams' deployment, the ASACO's offices informed the local authorities in all villages or neighborhoods of the survey teams' presence. Once on site, the teams visited these authorities to obtain their approval to conduct survey activities in their villages or neighborhoods.

Informed consent to participate from all respondents was obtained at the beginning of the survey and all individuals were fully informed of the study's purpose, potential risks, and their right to refuse to participate, to withdraw at any time, or to not answer certain questions without any justification or prejudice.

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If a participant wished to withdraw during or after the research, he or she had to contact the research team responsible whose contact details were provided on the consent form.

Confidentiality and anonymity of data were explained to the respondents. For minors, consent was also requested from parents or guardians. An informed consent form was developed outlining the objectives of the research, the voluntary and nonprofit nature of participation, data confidentiality and anonymity, and the approximate duration of participation. This form was shared by the collectors and its reading (in Bambara or French, as preferred) was mandatory and they were asked to devote time to explain it to the participants. The supervisors ensured that interviewers complied strictly with these instructions. All data are confidential and will be only used to achieve the project's results.

Identifiable information will not be disclosed in written publications and oral or poster presentations.

Results

Field data collection took place from March to April 2022. Quantitative data were collected using the KoboCollect application, and descriptive and bivariate analyses were carried out using SPSS software on a sample of 3153 participants. For qualitative data, 11 individual interviews and 27 focus groups were conducted and analyzed using QDA Miner software. Data analysis and interpretation are currently being finalized, and the first results should be submitted for publication in 2025.

Discussion

Overview

This research is one of the first to provide a holistic assessment and understanding of SRHR care needs across a continuum of services (from training, and provision to receiving care) covering the perspectives of various stakeholders at different levels (community, educational, and interdisciplinary health care professionals). It is also one of the first SRHR studies to be deployed in 5 regions (Bamako, Kayes, Koulikoro, Ségou, and Sikasso) across Mali.

Expected Findings and Outcomes

The results of the needs assessment will help us to better understand the needs of adolescents and users of SRHR services, not only in terms of availability, quality of services, and responsiveness of health care providers to their specific needs, but also in terms of SRHR information and knowledge.

Results will also help us gain a better understanding of the issues related to the quality of student training and supervision, and the adequacy between the training offered and the health care needs expressed by service users. They will also enable us to assess the readiness and skills of educators to provide quality SRHR teaching while considering GE.

Studies have demonstrated the effectiveness of training interventions in improving the attitudes and practices of health professionals regarding SRHR in low- and middle-income countries [11,22]. Therefore, recommendations resulting from this needs assessment will enable us to suggest concrete interventions for health care professionals and educators, allowing them to meet the community's needs—particularly those of women and girls.

Based on the results, we will design and implement a multifaceted strategy targeting the 3 levels (community, education, and health care providers).

In terms of training programs, the INFSS and FMOS will revise their curricula in line with the prioritized SRHR needs to fill the gaps in the existing modules. The plan is to integrate these needs into existing modules such as those concerning adolescent sexual and reproductive health, as well as care for GBV survivors and postabortion care, and to adopt interactive pedagogical methods to better prepare the future workforce in SRHR. In sum, the content of the existing curriculum modules will be repackaged to incorporate the priority needs and suggestions made by Malian participants and partners at the national, educational, and community levels.

Regarding the training needs, a package of interventions (training workshops and problem-solving exercises such as training on the management of GBV) will be developed, drawing directly on the results and recommendations of the study to enhance the teachers' and health care professionals' knowledge, skills and attitudes in providing SRHR services.

For community members, numerous interventions (eg, image kits, conferences, and training with peer educators on specific topics) will be codeveloped, prioritizing community involvement and ensuring that content will be oriented according to community acceptability and reflective of their needs.

Moreover, to bridge the gap between the study results and tangible impact in the field, the research findings will be disseminated through a variety of strategies and with numerous CLEFS project partners such as the relevant government actors, ASACO, community health centers, health professionals, and other community actors. This will enable key stakeholders to engage with the insights and facilitate the integration of the recommendations within their daily activities (practice and teaching).

This multifaceted strategy aims to ensure that the study results are effectively tailored to the Malian context and that they reach a wide range of stakeholders involved in PHC and in the provision of SRHR services. Having access to and using quality SRHR services are well linked to health care professionals' competencies, GE, and moreover to the well-being, community stability, and development [11,23].

Strengths and Limitations

Several strategies were used to ensure the credibility of this research as follows: triangulation of data sources (participants from 3 community levels, educational institutions, CSCom-U, and district hospital maternity wards), methods (document, focus groups, and interviews with different actors) and researchers (ie, triangulation of several analytical perspectives) to ensure consistency of the data and analysis; double coding for qualitative analysis; double member checking by sending preliminary results to participants belonging to the 3 target

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groups to validate and rectify them if necessary; skeptical peer review by members of the research team who will question methods interpretations, and meanings throughout the process [24]; detailed, rich, and concrete description [25] of the study context to enable readers or research users to judge potential transferability to other contexts, as well as a detailed description of the methodological approach, including the research site and data collection methods; and sample diversification to promote a wider application.

The resulting recommendations will address multiple stakeholders' perceptions and needs, promoting alignment across various actors.

Finally, this research was developed through a collaborative and participatory approach, fostering an equitable partnership between research teams in Mali and the Canadian Consortium. Local researchers and partners led the selection of priority research questions and study design, ensuring that the research project reflected community priorities. Field researchers collected data while minimizing cultural bias, through an ongoing collaborative approach to interpretation between Malian and Canadian research teams. This approach involves local community representatives in several stages of the research process, including validation of tools, recruitment of participants and investigators, and validation of results analysis. To maximize the impact and accessibility of the research, results will be disseminated through many strategies. By focusing on local expertise and perspectives, this approach will promote greater ownership of the results by stakeholders.

However, some limitations were encountered during the data collection process. First, the inclusion criteria (15-19 years old and single) made access to adolescents in rural areas difficult. Most girls are already married by this age, and single girls often move to the city to work as domestic servants. Moreover, adolescents are rarely found at home, choosing instead to go to meeting places or sports activities. This required interviewers to seek them out in schools or conduct interviews in the evening. On the other hand, the availability of service users also posed a problem, requiring late-evening or late-day appointments. Finally, the complexity of the SRHR subject made the questionnaire lengthy, leading to a few complaints, although everyone completed the survey.

Conclusion

In summary, using a concurrent mixed methods study, this needs assessment will help provide essential knowledge on how to align the nursing and medical curriculum with the needs of different levels of stakeholders (community, education, and health care providers), increase the capacity of future and current health care providers to deliver appropriate SRH services, and ultimately address the needs of the Malian community, reduce inequities and promote social justice.

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Data Availability

The datasets generated and analyzed during this study are not publicly available due to ethical and privacy considerations but are available from the corresponding author on reasonable request, if approval is obtained from the relevant ethics committee and data sharing complies with institutional and legal guidelines.

Conflicts of Interest

None declared.

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Abbreviations

ASACO: Associations de santé communautaire
CLEFS: Communautés locales d'enseignement pour les femmes et les filles en santé
CSCom-U: university community health centers
FMOS: Faculty of Medicine and Odontostomatology
FP: family planning
GBV: gender-based violence
GE: gender equality
INFSS: Institut National de Formation en Science de la Santé

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M/F: male/female
PHC: primary health care
QDA: Qualitative Data Analysis
SRHR: sexual and reproductive health and rights
STI: sexually transmitted infection

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Protocol

Development of a Mobile-Based Personal Health Record for Pediatric Attention-Deficit/Hyperactivity Disorder Management: Protocol for a Study Based on Action Research Design

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Abstract

Background: Attention-deficit/hyperactivity disorder (ADHD) is one of the most widespread neurobehavioral problems during childhood. A child's personal health record (PHR) plays an important role in the controlled routine monitoring of ADHD symptom improvement. Along with the advantages, the convenience offered by mobile technology, and the ubiquity of smartphones in contemporary society, there is a compelling need for PHR to be available in the form of a mobile app.

Objective: This study aims to identify stakeholder needs, followed by designing, developing, testing, and evaluating a mobile-based PHR in the context of pediatric ADHD management.

Methods: This study will adopt an action research design structured into 4 stages: diagnosing, planning, taking, and evaluating action. Stakeholders, including parents, pediatricians, occupational therapists, clinical psychologists, and teachers, will participate actively. In stage 1, stakeholder requirements for the mobile-based PHR will be explored through in-depth interviews, focus group discussions (FGDs), and document reviews. Thematic analysis will be used to identify key needs and challenges. In stage 2, a systematic literature review will be conducted to enhance user requirements analysis by synthesizing insights from existing mobile apps for pediatric ADHD management. A mobile-based PHR prototype will be designed and developed based on user requirements enhanced with systematic review results. In stage 3, the prototype will undergo a 6-week trial with participants to evaluate its functionality and address any identified issues. In stage 4, both quantitative and qualitative methods will be used to assess the app's usability and quality. The System Usability Scale (SUS) and the User Version of the Mobile App Rating Scale (uMARS) will be used for quantitative evaluation, while interviews and FGDs will be conducted for qualitative evaluation.

Results: This study commenced in October 2024. As of December 2024, 13 participants (n=5, 38.5%, parents; n=2, 15.4%, pediatricians; n=2, 15.4%, occupational therapists; n=2, 15.4%, clinical psychologists; and n=2, 15.4%, teachers) have been enrolled, meeting the minimum participant requirements for stage 1. Stage 1 was completed at the end of 2024, with stage 2 expected to be completed by September 2025, stage 3 by December 2025, and stage 4 by February 2026. The findings from each stage will inform iterative refinements to the mobile-based PHR. The final results, including usability and quality assessments, are anticipated for publication by the middle of 2026.

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Conclusions: This study protocol outlines a pivotal initiative to enhance the management of pediatric ADHD. By using an action research methodology and actively engaging stakeholders, the study aims to contribute significantly to the field. The iterative cycles of the research seek to develop a mobile-based PHR that is not only user friendly but also effective and uniquely attuned to the diverse needs of those involved in pediatric ADHD care.

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KEYWORDS

ADHD; attention deficit and hyperactivity; mobile app; personal health records; action research; pediatric

Introduction

Background

Attention-deficit/hyperactivity disorder (ADHD) is one of the most widespread neurobehavioral problems during childhood, with a worldwide prevalence of 5.29% [1,2]. The manifestation of ADHD occurs in 5.9% of youth and 2.5% of adults [3]. In the United States, an estimated 11%, equivalent to approximately 6.4 million children and adolescents aged 4-17 years, have received a diagnosis of ADHD [4]. Characterized by persistent patterns of inattention, hyperactivity, and impulsivity, ADHD manifests in various ways, affecting all aspects of a child's life [5,6]. The impact of ADHD extends beyond the immediate challenges of managing symptoms; it often disrupts academic performance, hinders peer relationships, and can contribute to emotional and behavioral difficulties [7-9]. Children with ADHD may face an increased risk of academic underachievement, low self-esteem, and a higher likelihood of engaging in risky behaviors [10-12]. Moreover, the condition places considerable stress on families and educators as they navigate the complexities of providing optimal support [13,14]. Recognizing the widespread prevalence and multifaceted impact of ADHD is crucial for developing targeted interventions and support systems that address the unique needs of affected children and related stakeholders.

Addressing the diverse needs of stakeholders in managing ADHD takes on added significance when considering the integration of personal health records (PHRs) into the care framework [15]. The PHR can serve as a central repository for health-related information, offering a comprehensive view of a child's medical history, treatment plans, symptoms improvement, and daily challenges associated with ADHD [16]. Within the context of pediatric ADHD management, routine and controlled monitoring of symptom improvement plays a pivotal role, and the PHR become instrumental in this process [17]. The PHR provides a structured platform for caregivers and related stakeholders to systematically monitor and analyze the child's response to therapeutic interventions [18]. By documenting the symptoms' progression, medication adherence, and the impact of various strategies, the PHR offers valuable insights that facilitate evidence-based decision-making [19]. Moreover, the ability to monitor symptoms in a controlled and consistent manner allows for a more nuanced and tailored approach to therapy adjustments, ensuring that interventions align closely with the child's unique needs [20]. The incorporation of the PHR into pediatric ADHD management not only enhances the accessibility of critical health information but also empowers stakeholders with a comprehensive tool for informed decision-making and the continual refinement of therapeutic strategies.

Although the idea of a PHR has historical roots in paper-based systems, health information technology now enables individuals to electronically store and manage their health information, granting them convenient access, whenever necessary [21]. In addition, with the ubiquity of smartphones in contemporary society, there is a compelling need for the PHR to be available in the form of a mobile app [22,23]. Furthermore, technological interventions for the assessment, monitoring, and treatment of neurodevelopmental disorders, including ADHD, are increasingly focused on mobile apps [24]. However, few apps related to ADHD provide information about their development processes, and none include evidence supporting their effectiveness [25].

The urgency to develop a mobile-based PHR specifically tailored for pediatric ADHD management stems from the growing demand for facilitating information sharing between stakeholders to promote the adoption of evidence-based practices in the management of children with ADHD [26]. The fragmentation of health care services, coupled with the dynamic nature of ADHD symptoms, necessitates a technological solution that can bridge communication gaps and empower those involved in the child's care [26,27].

Recognizing the imperative for a user-centric approach, the adoption of an action research methodology becomes paramount in the development of a mobile-based app [28-30]. Action research, designed to enhance the engagement of potential mobile app users in the entire research process, can foster awareness within the pediatric ADHD management stakeholders' context of how they experience and interact with technology [31,32]. This inclusive approach ensures that the resulting mobile app is not only technologically sound but also rooted in the practical experiences, preferences, and needs of those directly engaged in the daily challenges of pediatric ADHD management. Through iterative cycles, the action research methodology contributes to the development of an effective, user-friendly, and contextually relevant mobile-based PHR, ultimately advancing the landscape of pediatric ADHD management via the active participation of the stakeholders.

Objectives

The objectives of this study are to first identify the needs of stakeholders concerning the development of a mobile-based PHR for pediatric ADHD management. Based on the identified needs, a customized mobile app will be developed

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collaboratively, with continuous input from the stakeholders to ensure the app addresses those needs effectively. Finally, the usability and quality of the mobile app will be rigorously tested and assessed, ensuring it aligns with the preferences and expectations of the stakeholders and functions as an effective tool for managing pediatric ADHD.

Methods

Study Design

This study will use an action research methodology in the form of a cycle with 4 stages (diagnosing action, planning action, taking action, and evaluating action), integrating both qualitative and quantitative designs [33,34]. The term "action research" in this paper refers to the same definition as "participatory action research," "participatory research," "interactive research," "collaborative inquiry/research," and "engaged scholarship" [35]. The action research design centers on doing "with" rather than doing "for" relevant stakeholders [36]. In this context, the participation of the relevant stakeholders becomes key to the implementation of action research.

Each stage in action research consists of an iterative process (plan, act, observe, reflect), involving the stakeholders at each step [37]. The stages of action research in this study can be succinctly observed in Figure 1.

Table 1 outlines the specific steps in each stage of action research, the measures used to track progress, and the timeline for each activity. Activities at each stage will be carried out, and their progress will be systematically monitored based on the table.

Figure 1. Stages of action research.

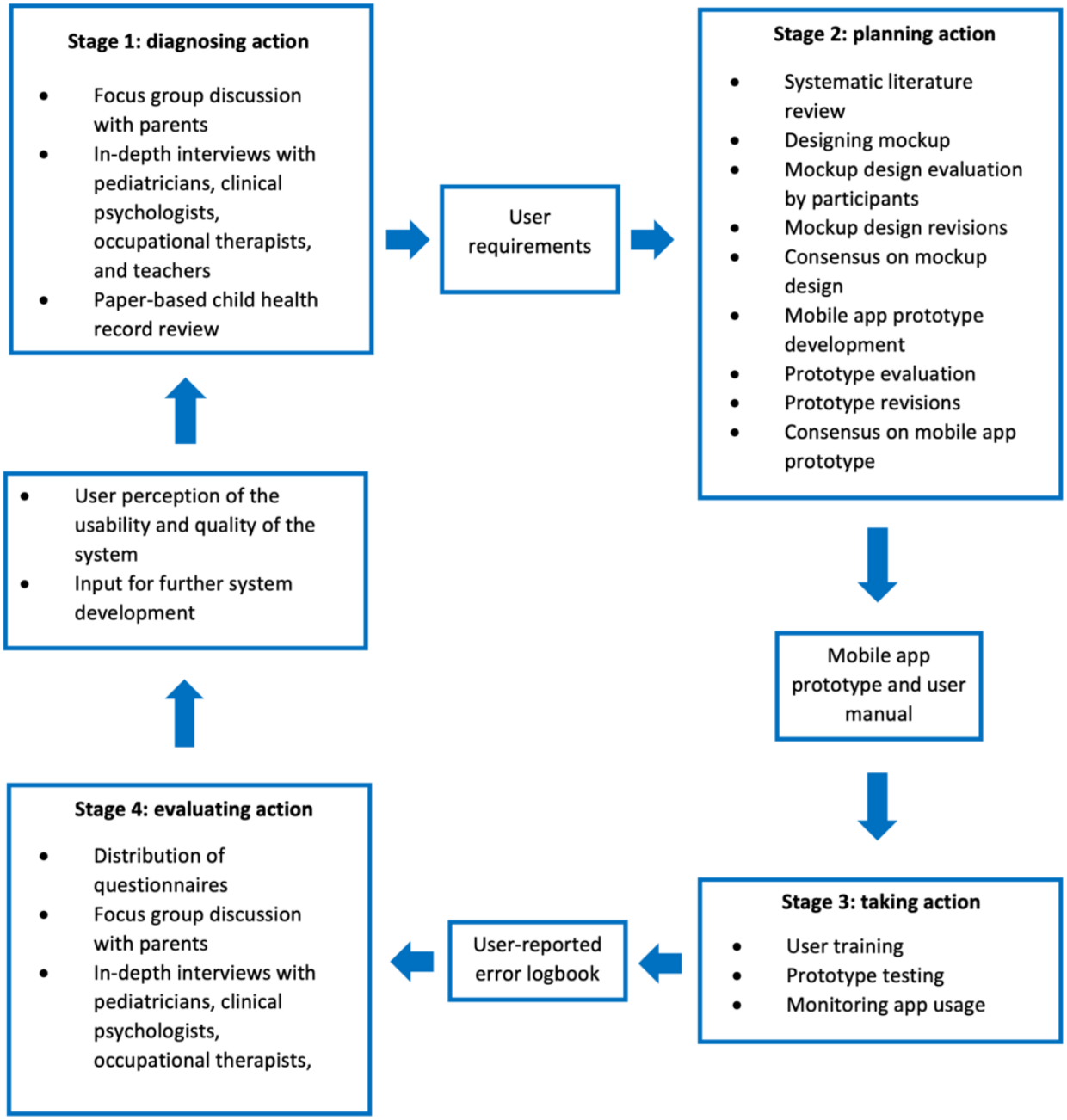

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Table 1. Detailed steps and measures in each stage of the study.

Stage and steps	Measure(s)	Timeline
Stage 1: diagnosing action		
Conduct user requirement analysis through FGDs[a] with parents and interviews with pediatricians, occupational therapists, clinical psychologists, and teachers.	Number of participants, identified user needs	Months 1 and 2
Review paper-based documents managed by parents and related stakeholders.	Completeness of documentation analysis	Months 1 and 2
Stage 2: planning action		
Conduct a systematic literature review on the mobile-based app used for pediatric ADHD[b] management.	Number of reviewed studies, extracted key findings	Months 3-5
Design a mobile-based PHR[c] mockup.	Initial mockup completion	Month 6
Review and revise the mockup design based on participant feedback until consensus is reached.	Number of revisions, participant consensus	Month 7
Develop a prototype based on the final mockup design.	Initial prototype completion	Months 7-10
Review and revise the prototype based on participant feedback until consensus is reached.	Number of revisions, participant consensus	Months 11 and 12
Stage 3: taking action		
Conduct training and mentoring for participants on using the mobile-based PHR.	Participant attendance, knowledge gained	Month 13
Facilitate prototype trial usage among participants.	Number of users engaged	Months 14 and 15
Monitor app usage to identify challenges or technical issues.	Number of reported issues	Months 14 and 15
Stage 4: evaluating action		
Assess system usability using the SUS[d] questionnaire.	SUS score (range 0-100)	Month 15
Evaluate app quality using the uMARS[e] questionnaire.	Mean (SD) of uMARS scores	Month 15
Collect qualitative feedback via FGDs and interviews.	Identified feedback	Months 15 and 16
Summarize findings and provide recommendations for future development.	Final report completion	Months 17 and 18

[a]FGD: focus group discussion.

[b]ADHD: attention-deficit/hyperactivity disorder.

[c]PHR: personal health record.

[d]SUS: System Usability Scale.

[e]uMARS: User Version of the Mobile App Rating Scale.

Study Setting

This research will be conducted at Dr Sardjito Hospital, Special Region of Yogyakarta, Indonesia. This hospital was chosen as the research location because it is an educational and referral hospital with a pediatric health clinic specializing in social pediatrics and neurology, which is commonly referred to by patients with ADHD. As a tertiary hospital, it receives a significant number of pediatric patients with ADHD referred there each year. The hospital's comprehensive health care facilities and expertise in pediatric care, particularly in social pediatrics and neurology, make it an optimal environment for conducting this research.

This research will also be conducted in schools where children with ADHD receive formal education in Indonesia. These children are aged between 4 and 12 years [38]. Teachers who work with children with ADHD, including preschool and elementary school teachers, will be actively involved in the study. It is widely recognized that communication and active involvement of parents, health care providers, and teachers are essential for managing pediatric ADHD [39].

Stage 1: Diagnosing Action

Objective

The objective of stage 1 (diagnosing action) is to systematically identify and understand the diverse needs of stakeholders in relation to the development of a mobile-based PHR. This initial phase will be dedicated to diagnosing and comprehending the requirements of key stakeholders involved, including parents, pediatricians, occupational therapists, clinical psychologists, and teachers of children with ADHD. To develop high-quality apps, it is imperative to build the development process upon a comprehensive understanding of user requirements, derived from a methodology that actively involves users in the process [40]. Through a meticulous process involving document review,

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focus group discussions (FGDs), and in-depth interviews, the stage will seek to uncover issues related to the recording of ADHD symptom development by parents and the PHR's role as a communication medium among parents, teachers, and health care professionals. The outcomes of this stage will include a comprehensive analysis of stakeholder needs, outlining specific requirements for the development of a mobile-based PHR.

Output

The output of this stage will be a document containing specific requirements for the development of a mobile-based PHR. These requirements include data needs, user groups and permissions, app features, functionalities, and expected technology specifications.

Participants

Stakeholders involved in the management of children with ADHD, including parents, pediatricians, occupational therapists, clinical psychologists, and teachers, will participate in this study [41,42]. Selection criteria for research participants are detailed in Table 2.

Involvement of parents or caregivers and teachers is related to the assessment of ADHD that requires evidence directly obtained from them regarding the core symptoms of ADHD, the duration of symptoms, the degree of functional impairment, and associated conditions [43].

We estimate that our study will need around 5 parents, 2 pediatricians, 2 occupational therapists, 2 clinical psychologists, and 2 teachers. This is the minimum number of participants; additional participants may be included during data collection until data saturation is achieved [44].

Table 2. Participant selection criteria.

Participants	Criteria
Parents	• Parents of children diagnosed with ADHD[a] (aged 4-12 years) who have received behavioral therapy and medication, with at least 1 year of experience in taking care of children with ADHD • Experienced in using mobile health apps • Own and actively use an Android- or iOS-based mobile phone with an internet connection
Pediatricians	• Pediatricians managing patients with ADHD whose parents are participating in the research, with a minimum of 2 years of experience in managing children with ADHD • Currently pursuing or have completed subspecialization in developmental pediatrics–social pediatrics or child neurology • Experienced in using electronic medical record systems or telemedicine or both
Occupational therapists and clinical psychologists	• Occupational therapists and clinical psychologists managing patients with ADHD whose parents are participating in the research, with a minimum of 2 years of experience in managing children with ADHD • Experienced in using electronic medical record systems or telemedicine or both
Teachers	• School teachers teaching children with ADHD whose parents are participating in the research, with a minimum of 2 years of experience in teaching children with ADHD • Own and actively use an Android- or iOS-based mobile phone with an internet connection

[a]ADHD: attention-deficit/hyperactivity disorder.

Data Collection

Data will be collected through a systematic approach, including FGDs with parents and in-depth interviews with pediatricians, occupational therapists, clinical psychologists, and teachers. The total number of interviews will be adjusted based on the number of participants involved. Participants will be selected using a purposive sampling method based on predetermined inclusion criteria to ensure representation of key stakeholders actively involved in managing pediatric ADHD. Comprehensive FGD and interview guides have been developed in Indonesian to facilitate semistructured sessions. The inquiry framework acknowledges the dynamic nature of discussions and interviews, allowing flexibility in question sequencing, particularly regarding follow-up inquiries, which may undergo alterations during the research [45]. The guides are designed to explore specific aspects described in Table 3.

The data collection process will follow a systematic procedure. Participants will be recruited through referrals from pediatricians specializing in ADHD to ensure a diverse and representative sample. In-depth interviews and FGDs will be conducted in a private and comfortable environment to encourage open and honest responses. Each session will begin with an introduction explaining the purpose of the study and obtaining consent for audio recording.

All interviews and FGDs will be audio-recorded with the participants' consent, and field notes will be taken to capture contextual details, nonverbal cues, and relevant observations during the sessions. Each in-depth interview session will be conducted for approximately 30-60 minutes, while each FGD session is expected to last from 60 to 120 minutes [46,47]. The semistructured nature of the interviews and FGDs will allow flexibility for follow-up questions and enable a deeper exploration of emerging themes during the discussions.

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Table 3. Key aspects explored in stakeholder interviews and FGDs[a].

Aspect	Focus of exploration
Stakeholder needs	• Essential features required for a mobile-based PHR[b] • Information that needs to be recorded, monitored, and accessed (eg, symptom tracking, medication schedules, therapy progress)
Usability preferences	• Design expectations (eg, user-friendliness, interface layout) • Accessibility concerns, including navigation simplicity for parents and professionals
Data accessibility and security	• Preferences for access control (eg, who can input and view data) • Concerns about privacy and confidentiality of ADHD[c]-related information
Roles of stakeholders	• How each stakeholder envisions contributing to and using the PHR • Collaboration needs between parents, pediatricians, occupational therapists, clinical psychologists, and teachers in managing pediatric ADHD

[a]FGD: focus group discussion.

[b]PHR: personal health record.

[c]ADHD: attention-deficit/hyperactivity disorder.

As a methodological triangulation measure, paper-based child health records managed by parents will be reviewed to validate the essential data needs in the PHR [48]. Parents will be encouraged to present their manually recorded data, which reflects their needs in managing the care of children with ADHD. This will facilitate researchers in scrutinizing and documenting the various data types encapsulated within these records.

Data Analysis

Qualitative data from FGDs and in-depth interviews will be analyzed using thematic analysis following the 6-phase approach [49,50]: (1) familiarization with the data, where researchers immerse themselves in the data by reading and re-reading transcripts; (2) generating initial codes, involving systematic coding of significant features of the data across the entire dataset; (3) searching for themes, where codes are organized into potential themes; (4) reviewing themes to refine and ensure coherence and distinction between them; (5) defining and naming themes, focusing on capturing the essence of each theme; and (6) producing a report that involves a narrative that integrates the themes with supporting evidence from the data [51]. To address methodological rigor, aspects of reflexivity, confirmability, dependability, credibility, and transferability will be considered throughout the analysis process. Reflexivity will be addressed by creating fieldnote reflections, where researchers will document critical interpersonal dynamics affecting participants and their data, record and reflect on decisions made, and highlight moments of analytic insight to enhance transparency and self-awareness throughout the research process [52,53]. Confirmability will be ensured through detailed documentation of the analytic process, and peer debriefing dependability will be supported by maintaining a clear audit trail of the analysis process [54]. To enhance credibility, member checking with selected participants will be conducted, and investigator triangulation will be implemented with 2 researchers collaboratively reviewing and comparing the codes and resolving any differences through discussion for the same text unit [55]. Transferability will be facilitated by providing detailed descriptions of the study context and participant characteristics in this protocol [54]. The qualitative data will be organized using Open Code software version 4.03, ensuring systematic handling and transparency of the coding process [56,57].

Stage 2: Planning Action

Objective

Stage 2 (planning action) aims to design and develop a prototype of a mobile-based PHR that is agreed upon by all research participants. This stage will involve several key steps. First, a systematic literature review will be conducted on mobile apps used in pediatric ADHD management to enhance the user requirement analysis from stage 1 by thoroughly examining and synthesizing the existing literature. In the mobile app development process, understanding the efficient assessment of mobile apps, academic challenges, and other important aspects available in the existing literature is crucial [58]. The review will focus on identifying app features, purposes, target users, reported outcomes, and the measuring instruments used in previous studies. It will also address important considerations, such as the efficient assessment of mobile apps and academic challenges in the field. Next, a mockup design of the mobile-based PHR will be created based on the results of both the user requirement analysis and the systematic literature review. This mockup will be used to validate the user interface's usability [59].

Finally, a mobile app prototype will be developed based on the collective agreement of research participants on the finalized mockup design. The prototype will be developed in collaboration with a team of developers who will be recruited as part of the technical team for this study. The prototype will be built using Flutter, a framework that allows for the development of apps on both Android and iOS platforms, which together dominate the mobile app market [60-62].

Output

The outcome of this stage will be a mobile-based PHR prototype for both Android and iOS platforms, which has gained consensus

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among all research participants and is ready for testing in the next stage. Furthermore, a user manual for the mobile app will be produced during this stage.

Participants

Participants in this stage will be stakeholders related to pediatric ADHD who have previously participated in stage 1. Participants in this stage will actively engage in the design and development process [63].

Data Collection

Data collection will involve several key steps. First, a systematic literature review will be conducted and documented following the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) 2020 guidelines [64]. To comprehensively explore the available literature on mobile apps for pediatric ADHD, a systematic search will be conducted across multiple databases, including PubMed, Scopus, Cochrane Library, and Google Scholar. The search strategy will involve a combination of MeSH (Medical Subject Headings) terms as controlled vocabulary terms and their relevant synonyms related to pediatric ADHD, mobile apps, and pediatric ADHD management stakeholders. MeSH terms used as keywords will include “parents,” “child,” “adolescent,” “family,” “caregivers,” “physicians,” “school teachers,” “pediatrics,” “mobile applications,” “smartphone,” “digital health” and “attention deficit disorder with hyperactivity.” The search strings will be tailored to the specific syntax and requirements of each database. The study/source selection process will follow a systematic and transparent approach. The process consists of 3 main steps. First, titles and abstracts of identified papers will be screened by 2 independent reviewers using predefined inclusion criteria. Any discrepancies will be resolved through discussion, and if necessary, a third reviewer will be consulted to facilitate consensus. Second, a full-text review of selected studies will assess their eligibility, with reasons for exclusion recorded and reported. Finally, relevant data will be extracted from the included studies. Subsequently, the data analysis will explore the apps’ features, purposes, reported outcomes, as well as variations in apps usage across different contexts and participant groups.

Information derived from the systematic literature review will be gathered and used to complement the results of the user requirement analysis, forming the foundation for the design and development of the mobile-based PHR. Next, the designed mockup will be presented to each participant for comprehensive feedback. Every discussion will be recorded, transcribed, and analyzed, with refinements made to the mockup design based on participant input. This iterative process will continue until a unanimous consensus is reached among all participants [65]. Finally, the approved mockup design will be transformed into a mobile-based app prototype. Similar to the mockup phase, the prototype will be discussed with each participant to gather further feedback The discussions will be recorded, transcribed, and analyzed, with subsequent revisions made to the prototype until a unanimous agreement is achieved among all participants.

Data Analysis

Data from the systematic literature review will be analyzed descriptively to map the user groups, as well as the apps’ features, purposes, and outcomes related to the implementation of mobile apps for pediatric ADHD. Additionally, participant feedback on the mockup design and prototype of the mobile-based PHR will be qualitatively analyzed, serving as a foundation for the continuous improvement and refinement of both the mockup design and the prototype.

Stage 3: Taking Action

Objective

Stage 3 (taking action) will involve the trial of the mobile-based PHR. The objective of this stage is for participants to actively use the mobile app in their daily activities while monitoring children with ADHD. Throughout this stage, technical challenges faced by users during the trial period will be identified to facilitate app improvements and refinements.

Output

The output of this stage will be a logbook document detailing the errors or technical challenges reported by users during the trial period. This logbook will serve as a comprehensive record of user feedback, documenting encountered issues and discrepancies. It will function as a crucial control document for the debugging process and for implementing necessary system refinements [66]. By systematically logging user-reported errors, the logbook will become a valuable resource for the iterative improvement process, ensuring that the mobile app prototype is continually enhanced and optimized based on real-world user experiences.

Participants

Participants in this stage will include individuals who have previously participated in stages 1 and 2, along with newly recruited parents of children diagnosed with ADHD. The number of newly recruited parent participants is anticipated to range between 20 and 80 individuals [67]. Eligibility criteria for participation require owning a smartphone compatible with either the Android or the iOS platform and having reliable internet access.

Data Collection

In this stage, participants will be asked to use the mobile-based PHR for 6 weeks before proceeding to the next stage [68]. During the trial period, app usage will be monitored, and users will be asked to report any system errors or technical issues encountered through the reporting form available in the mobile-based PHR. The reported data will be recorded and compiled into an error logbook. This monitoring will allow user issues to be addressed promptly, enabling the technical team to provide targeted support, as needed. To ensure participants use the mobile-based PHR consistently during the 6-week period and can test its entirety, they will be provided with detailed instructions during user training, as well as regular reminders and support throughout the period.

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Data Analysis

The collected data will be descriptively analyzed by grouping similar types of errors or technical issues. Subsequently, app improvements and refinements will be implemented based on the analysis. Users will be informed of the implemented improvements and refinements through notifications in the mobile-based PHR.

Stage 4: Evaluating Action

Objective

Stage 4 (evaluating action) will focus on assessing the overall quality and usefulness of the mobile-based PHR from the user perspective. Unlike earlier stages, which focus on design, development, and refinement, this stage will primarily serve as a comprehensive evaluation of the outcomes of the previous stages. It will involve gathering feedback from participants on the effectiveness of the mobile-based PHR and identifying expectations for its further development.

Output

The output of stage 4 will be a comprehensive evaluation report that summarizes participants' assessments regarding the usefulness and quality of the mobile-based PHR. Additionally, this stage aims to generate valuable feedback for future development.

Participants

The evaluation in stage 4 will involve both quantitative and qualitative assessments of the mobile-based PHR. Participants in stage 4 will consist of those who have participated from stage 1 to stage 3, as well as additional participants newly recruited in stage 3. Qualitative evaluations will be conducted exclusively with participants who have been involved from stage 1 to stage 3, as they can provide comprehensive and holistic feedback based on their entire experience. Meanwhile, quantitative evaluations in stage 4 will focus solely on parent participants, including both parents who participated from stage 1 to stage 3 and newly recruited parents in stage 3. The primary reason for focusing the quantitative assessment on parents is that they will be the main users of the mobile-based PHR, which is being designed to support the management and care of their children with ADHD. Figure 2 illustrates the sequential involvement of participants, starting from the initial recruitment in stage 1 through their continued engagement up to stage 4.

Figure 2. Participant flow diagram for the action research stages.

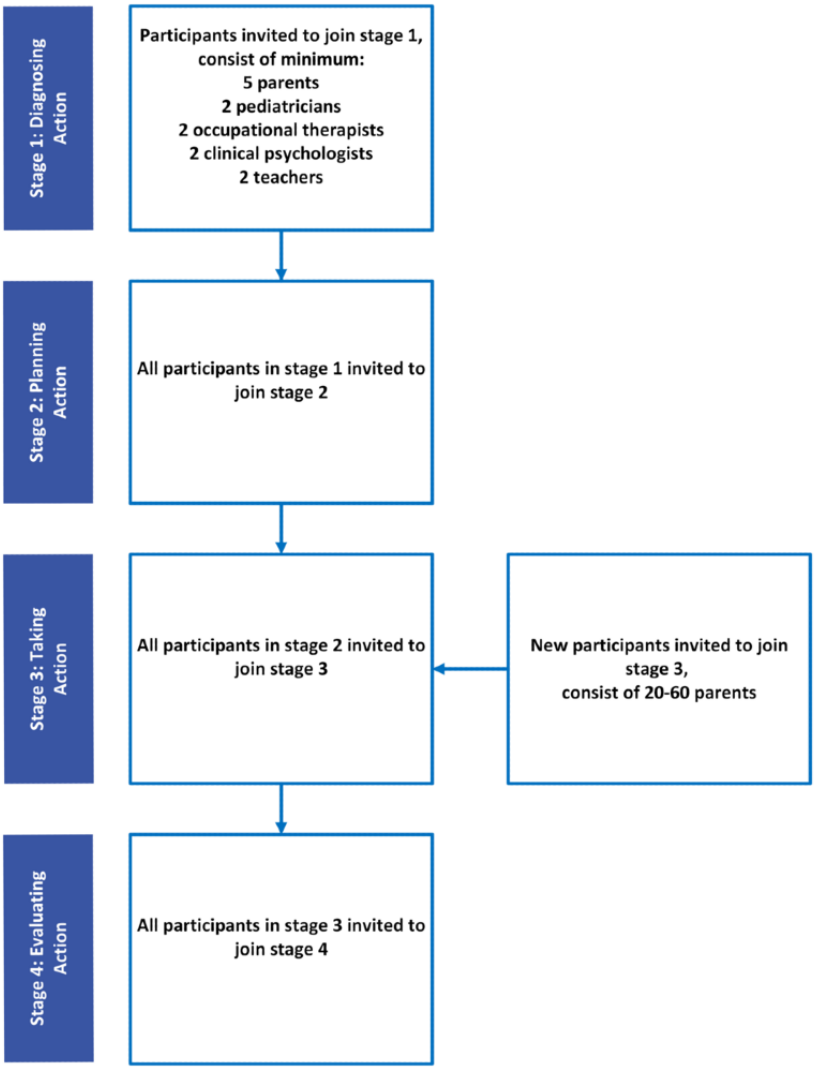

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Data Collection

Quantitative data to assess the usefulness of the mobile-based PHR will be collected using the Indonesian version of the System Usability Scale (SUS) questionnaire [69]. The SUS consists of 10 statements, each scored on a Likert scale of 1-5, where a higher score indicates stronger agreement with the statement [70]. Additionally, quantitative data will be gathered to assess the quality of the mobile-based PHR using the User Version of the Mobile App Rating Scale (uMARS) questionnaire. The uMARS includes 20 items divided into 5 dimensions: engagement, functionality, aesthetics, information, and subjective quality. Each statement is scored on a 5-point Likert scale [71]. Qualitative data will also be collected through in-depth interviews and FGDs to gather comprehensive insights from participants' experiences during stage 3 (taking action). This approach will aim to uncover rich, contextual information regarding usability, satisfaction, challenges encountered, and participants' input and expectations for further development of the mobile-based PHR.

Data Analysis

Quantitative data obtained from the SUS questionnaire will be analyzed descriptively. The results will be summarized, totaled, and then multiplied by a coefficient of 2.5, yielding a final score within a range of 0-100 [70]. This score will be used to determine the percentile ranking. Data from the uMARS questionnaire will be analyzed through descriptive statistical analysis, calculating the mean (SD) to assess the quality of the mobile app. Scores ranging from 1 to 2 indicate "not acceptable," 2 to 3 indicate "poor," 3 to 4 indicate "acceptable," 4 to 5 indicate "good," and 5 indicate "excellent" quality [72]. Qualitative data from in-depth interviews and FGDs will be analyzed using thematic analysis [49].

Trustworthiness

The data in this research will be validated using the action research validation technique, which comprises coherence validation, discursive validation, and practical validation [35]. Coherence validation focuses on how various empirical, interpretative, and conceptual elements are integrated to mutually reinforce each other. The coherence validation technique that will be used in this research is triangulation, a method that will involve cross-referencing the results from FGDs and in-depth interviews regarding user requirements with the findings from the reviews of paper-based PHRs, particularly related to data that must be recorded in the PHR.

Discursive validation emphasizes dialogical and democratic validation in a forum. The discursive validation technique that will be used in this research is member checking, a method that involves returning the research findings to the participants for their review and validation. This iterative process will allow participants to confirm the accuracy and relevance of the data collected during in-depth interviews, FGDs, document reviews, and other research activities. By incorporating member checking, the study aims to ensure the credibility and trustworthiness of the research outcomes, as participants can provide feedback and insights, contributing to the overall validation and refinement of the research findings.

Practical validation focuses on testing in a real environment so that specific knowledge claims can gain sufficient trustworthiness. The practical validation method that will be used in this research is participant engagement, providing participants with an opportunity to actively use the mobile app prototype. Unlike a passive observation approach, participants will be directly involved in navigating and interacting with the prototype, offering insights into the user experience from a firsthand perspective. This hands-on engagement will ensure a more practical and realistic assessment of the mobile app's functionality and usability. By allowing participants to explore the prototype independently, the study aims to gather authentic feedback on the user interface, features, and overall performance, contributing to the refinement and enhancement of the mobile app based on the practical experiences of the end users.

The summary of the action research activities in each stage including output, activities, instrument, variable, participants, and validation methods are presented in Multimedia Appendix 1.

Ethical Considerations

The study has been approved by the Ethics Committee of the Faculty of Medicine, Public Health, and Nursing, Universitas Gadjah Mada (approval no: KE-FK-1257-EC-2023). To maintain ethical standards, we will provide comprehensive information regarding the study protocol to all potential participants. We will outline the purpose, procedure, and potential risks and benefits of their participation, especially in the context of action research [73]. Once they agree to participate, they will be required to provide signed informed consent. Confidentiality and privacy will be rigorously conducted throughout the research process, with measures in place to anonymize and secure sensitive information [74].

Results

This study was initiated in October 2024, with the research process divided into 4 distinct stages:

- Stage 1 (diagnosing action) will focus on identifying user requirements and challenges in managing ADHD care through stakeholder interviews, FGDs, and document reviews. As of December 2024, 13 participants were enrolled, comprising 5 (38.5%) parents, 2 (15.4%) pediatricians, 2 (15.4%) occupational therapists, 2 (15.4%) clinical psychologists, and 2 (15.4%) teachers, meeting the minimum target for participant numbers. This stage was completed at the end of 2024, providing key insights to guide subsequent stages.
- Stage 2 (planning action) will include a systematic literature review, user requirement validation, mockup design validation, and prototype development. The prototype development will be conducted in collaboration with a technical development team. This stage is projected to conclude by September 2025, delivering a finalized prototype for usability testing.
- Stage 3 (taking action) will focus on implementing and testing the prototype with participants during a 6-week trial

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period. During this phase, system usage data, user feedback, and error reports will be collected and analyzed to refine the prototype. This stage is anticipated to be completed by the end of 2025.

- Stage 4 (evaluation action) will involve both qualitative and quantitative assessments of the mobile-based PHR. Qualitative evaluations will gather in-depth feedback from participants who have engaged in all stages, providing comprehensive insights into the user experience. Quantitative evaluations, targeting all parent participants, will assess the usability and quality of the mobile app through embedded questionnaires. This stage is expected to conclude in February 2026. The results of this study will be reported according to reporting guidelines provided for action research [75]. The final results are anticipated for publication by the middle of 2026.

Discussion

Summary

The landscape of future research in pediatric ADHD stands to evolve significantly, particularly in the development of effective electronic systems tailored for gathering crucial information to diagnose and monitor children and adolescents with ADHD [76]. As an innovative response to this research avenue, this study will contribute to this domain by using an action research approach that engages the stakeholders in pediatric ADHD management in all stages, including diagnosing, planning, taking, and evaluating action [77]. To the best of our knowledge, this is the first study that involves active participation and engagement with stakeholders, including parents, medical providers, and nonmedical providers, in the development of a mobile app related to pediatric ADHD management. This dynamic methodology will ensure that the mobile app developed is technologically effective, user-friendly, and contextually relevant.

The insights gleaned from this research will underscore the intricate challenges associated with managing pediatric ADHD and emphasize the critical role of collaborative and patient-centric interventions. These principal findings will pave the way for more targeted and contextually relevant interventions, fostering a deeper understanding of the intricacies involved in pediatric ADHD management.

Limitations

The scope of the study is confined to addressing the needs of stakeholders directly involved in the routine care of children with ADHD within tertiary hospital settings. Although this focus provides valuable insights into the specific challenges faced in such contexts, the findings may not be fully representative of the broader spectrum of ADHD management, especially in community or primary care settings. Additionally, the study's outcomes may be influenced by the regional or institutional characteristics of the selected tertiary hospitals, potentially limiting the generalizability of the results to a more diverse health care landscape. Despite these limitations, the study remains dedicated to refining and optimizing the care of children with ADHD within tertiary hospital environments, with the anticipation that the insights gained can contribute meaningfully to the broader discourse on pediatric ADHD management.

Conclusion

This study protocol outlines a pivotal initiative to enhance the management of ADHD in pediatric populations. By using an action research methodology and actively engaging stakeholders, including parents, medical providers, and nonmedical providers, the study aims to contribute significantly to the field. The iterative cycles of the research seek to develop a mobile-based PHR that is not only user-friendly but also effective and uniquely attuned to the diverse needs of those involved in pediatric ADHD care.

Acknowledgments

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Data Availability

The datasets used and analyzed during this study will be made available from the corresponding author upon reasonable request after the completion of the study.

Authors' Contributions

DBS drafted the initial manuscript and finalized the manuscript. RS, DKN, and MSK provided feedback and contributed to revising the manuscript. All authors have read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Summary of action research activities.
[PDF File (Adobe PDF File), 67 KB - resprot_v14i1e60216_app1.pdf]

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Abbreviations

ADHD: attention-deficit/hyperactivity disorder
FGD: focus group discussion
MeSH: Medical Subject Headings
PHR: personal health record
SUS: System Usability Scale
uMARS: User Version of the Mobile App Rating Scale

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Protocol

Adaptation of the Stakeholders' Walkability/Wheelability Audit in Neighborhoods (SWAN) Tool for Individuals With Diverse Disabilities: Protocol for a Mixed Methods Study

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Abstract

Background: The prevalence of sensory, cognitive, and mobility disabilities in Canada underscores the need to address environmental barriers. This study adapts and validates the Stakeholders' Walkability/Wheelability Audit in Neighborhoods (SWAN) tool to assess the challenges the built environment poses for individuals with disabilities, aiming to inform policy changes for accessibility and inclusivity.

Objective: This study aims to (1) adapt the SWAN tool for those with hearing, vision, or cognitive disabilities; (2) validate SWAN tool for researching environmental barriers for people with disabilities, including older adults; and (3) offer insights for policy changes in the built environment, contributing to literature and guiding future research.

Methods: The study uses a community-based research approach, carried out over 4 phases within an 18-month period in British Columbia. Phase 1 includes adapting and pilot-testing of the SWAN tool. In Phase 2, street intersections are identified for data collection using Geographic Information System tools and consultations with municipal officials. Phase 3 involves recruiting participants across four disability categories. The final phase includes analyzing the data and disseminating findings.

Results: Data collection concluded in September 2024, involving 80 eligible participants across four streams in preidentified hotspots. The results are expected to be published in March 2025. To date, data collection is ongoing, and we are currently in the process of data analysis.

Conclusions: This study will contribute to the growing body of research on built environment accessibility by adapting the SWAN tool for individuals with diverse disabilities. By identifying key barriers in urban spaces, the study aims to inform policy changes that will lead to more inclusive, accessible, and safe urban environments for all individuals.

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KEYWORDS

age and accessibility; disability experiences; community engaged research; inclusive urban design; user-led built environment audits

Introduction

Overview

The number of people living with sensory (hearing and vision), cognitive, and mobility disabilities is increasing in Canada. In 2019, approximately 5% of people aged 15 years and older had a hearing disability, and in 2020, a total of 567,000 people were living with a cognitive disability [1]. About a quarter (24.1%) of the population living with disabilities are aged 65 years and older [2].

Mobility restrictions are not typically the result of a single cause but arise from an interaction of risk factors in various domains, both individual and environmental [3]. Historically, disability research primarily relied on the medical model, emphasizing the individual and their specific impairments or conditions [4]. However, in more recent times, disability models have shifted their focus toward understanding the dynamic interplay between individuals and their surrounding environment [5]. Environmental characteristics are hypothesized to limit or promote an individual's ability to complete purposeful actions and fulfill role expectations, affecting physical functioning and disability [3]. Lawton [6] proposed several dimensions of environment that are important for older adults: personal environment (family and friends), suprapersonal environment (ie, neighborhood racial or age composition), social environment (norms or values related to society or culture), and physical environment (eg, built environment). The physical environment is defined as the human-made or human-altered space in which individuals live out their daily lives [7] and is the focus of this paper. The built environment has a profound impact on the mobility of older adults and people living with disabilities, which can affect their health and quality of life [3,8-11]. This aligns with the International Classification of Functioning, Disability, and Health, which posits disability and functioning as outcomes that result from the interplay between health conditions (such as diseases, disorders, and injuries) and contextual factors, including the built environment.

For instance, individuals who are deaf or hard of hearing (DHH) feel less safe when navigating the pedestrian environment as they struggle to hear traffic on the road [12,13]. Persons living with mild cognitive impairment (MCI) often experience challenges with navigation of their own environment, which is heightened when communities do not integrate sufficient green spaces and landmarks (such as large shops, libraries, community centers, and senior centers) to help reduce the stress of wayfinding [14]. Moreover, people using mobility assistive technologies (MAT) may find it challenging to navigate the built environment, especially during rain and snow because of inadequate drainage or snow removal [10]. People with vision impairment (VI) also face difficulties due to the lack of accessibility in public spaces and transportation systems [11].

Limited research exists on the role of environmental factors on mobility and social participation of individuals with disabilities, creating a gap in the literature [3,8-11]. Environmental variables that can affect the experience of being mobile in a place, fall into 2 broad categories: macroscale, consisting of structural features such as street interconnectivity and land use mix [15,16]; and microscale, or details, such as aesthetics and sidewalk design, and maintenance [17]. While much research has concentrated on macroscale variables that define walkability [18], investigating microscale features is also valuable for understanding the mobility experience [19-22]. Microscale characteristics of the built environment can often be modified at a lower cost and within a shorter timeframe compared with restructuring macroscale designs [23].

Various audit tools have been developed and tested to evaluate the microscale qualities of the built environment, particularly at the street level, through on-site visits [24]. The Stakeholders' Walkability/Wheelability Audit in Neighborhoods (SWAN) is a microscale, user-led audit tool designed to evaluate both objective and subjective aspects of the built environment that affect the lives of older adults and individuals using mobility assistive devices, persons who are DHH, and persons living with MCI including dementia [25,26].

The SWAN tool is an adaptation of the SWEAT-R tool that captures the perspective of persons with disabilities [25]. Moreover, the development of the SWAN tool included a comprehensive literature review and incorporated aspects of other user-led tools, such as the Microscale Audit of Pedestrian Streetscapes [23,27], the Built Environment and Active Transport Neighborhood Assessment [28], and Jane's Walk: Walkability Checklist [29].

Previous research using the SWAN tool was primarily done with individuals with mobility disabilities using MAT [30]. To incorporate a wider variety of disability experiences, the SWAN tool has been adapted to accommodate individuals' living sensory disability (hearing and vision) as well as those with cognitive disabilities, including early stages of dementia and MCI. This adaptation enables these populations to systematically evaluate their neighborhoods.

Using a community-based participatory research approach, the SWAN tool was developed in collaboration with a committee of individuals with lived and professional experience, ensuring that diverse perspectives and needs are integrated into the research process. This approach promotes self-advocacy among participants and facilitates policy changes that are reflective of community needs [31].

Objectives

This study aims to (1) adapt the mobility tool for individuals living with hearing or vision as well as cognitive disability; (2) validate the tool for researching barriers in the built and social environment for persons with disabilities, including those with vision, hearing, cognitive, and mobility disabilities (including older adults); and (3) provide insights for decision-making and policy changes in modifying the built environment.

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This protocol paper aims to contribute to existing literature and guide future studies on how individuals with cognitive, sensory, or mobility disabilities navigate the built environment. The goal is to fill knowledge gaps and provide evidence-based results for municipalities and communities to implement necessary policy changes for a safe and accessible living environment.

Methods

Overview

The research will be conducted over 4 phases within an 18-month period in British Columbia. Advisory committees including individuals with a variety of disabilities have been created to ensure the consideration of inputs or concerns of these individuals in the research project through a participatory research approach. These committees include individuals with mobility, visual, and hearing disabilities and early-stage dementia. The committees meet 2 to 3 times a year to provide feedback on the ongoing phases of the research project, which are presented below.

The first phase involves conducting a literature review, tool consolidation, and pilot-testing. Phase 2 entails identifying street intersections for data collection using Geographic Information System layers and discussions with municipal officials. Phase 3 involves collecting data across various streams of disabilities. The fourth phase includes data analysis and knowledge mobilization efforts.

Ethical Considerations

This study has been reviewed and approved by the ethics boards of Simon Fraser University and the University of British Columbia (H21-01234). To protect identities, names and any other information that might identify a participant will be removed from transcriptions and field notes. Any photos taken as part of data collection that could potentially identify individuals will be blurred. All data will be collected, managed, and stored in accordance with university research ethics procedures, and all data will be anonymized. We perceive that the risks for physical or emotional harm to the participants associated with the proposed research are minimal. The time and effort required by participants is minimal, and there is no deception or other manipulation of participants. Given that participants might share difficult experiences, which may lead to emotional and/or psychological distress, the researcher will make clear at the beginning and throughout the interview that participation is voluntary, and participants can withdraw their consent at any time without harm. Participation in this study is voluntary, and participants can decide to opt out. An honorarium of CAD $75 (approximately US $53) will be provided to participants.

Phase 1: SWAN Tool Development Process

Overview

To conduct the walking/wheeling audits with DHH individuals and those living with cognitive and vision disabilities, the original SWAN tool (that is, SWAN for MAT users) was adapted through reviewing the literature and consultations with persons with disabilities or persons with professional experience. Involving persons with disabilities and professionals with relevant experience fosters a more inclusive approach, ensuring that the tool reflects the diverse perspectives within the community. The incorporation of findings from both academic and gray literature allows for evidence-based adaptations, increasing the tool's validity and reliability for the target populations.

Literature Review

Relevant concepts pertaining to DHH individuals and those living with cognitive and vision disabilities, focusing on their experiences and interactions with the safety and accessibility of the outdoor built environment, were taken from reviews done by our study team [10,25,32,33]. This allowed for collating similar concepts to pinpoint areas where the tool may need expansion or clarification to better support these specific populations.

Content Comparison and Tool Consolidation

After developing the newly adapted tools, they were charted in Microsoft Excel alongside the original SWAN tool for content comparison, sequencing of questions, and language simplicity and consistency. Upon review of all tools, they were finalized as the Hearing and Mobility Tool, the Dementia Tool, and the Vision Tool.

Pilots

To test the functionality of the tools in the field, 4 pilots were conducted with persons with disabilities from the 4 populations of interest. These pilots served as an opportunity to try the tools with participants and gather feedback on the questions, content, process, and flow of data collection. Since data collection involves a walking/wheeling method, both the research team and participants experience this process in the field, allowing for adjustments to be made accordingly. During the pilot sessions, particular attention was given to ensuring the clarity and comprehensibility of the terminology used in the tools. This was done to ensure individuals with different levels of abilities could easily understand the features being inquired about.

Following the pilot session with individuals with vision disabilities, substantial adjustments were implemented to improve the tool's readability. These changes encompassed modifications to align the tool with the Canadian National Institute for the Blind standards, ensuring adherence to best practices for accessibility in both design and functionality. These adjustments, informed by participant feedback and collaboration with the Canadian National Institute for the Blind standards, are aimed at fostering a more user-friendly and inclusive experience for individuals with vision disabilities during data collection.

Phase 2: Identification of Data Collection Locations Through Community and Research Project Partnerships

Overview

To identify areas for data collection, the research team undertook a stepwise approach, namely (1) generating prioritized sites and (2) hosting an interactive community forum to finalize locations.

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Intersections for Data Collection

The research team identified data collection areas in 6 partner municipalities across Metro Vancouver using open-source data and ArcGIS. They focused on pedestrian-involved collisions data, integrating additional layers such as transportation hubs (eg, sky train stations) and city center locations to create maps and identify "hotspots" for data collection. The outcome was maps highlighting 7 to 10 intersections in each municipality. Subsequently, the team met with municipal officials to discuss and prioritize 3 to 4 intersections for the data collection per municipality based on their feedback and guidance.

SWAN Community Forum

The second step involved hosting an interactive forum with persons with disabilities, community partners from senior centers, and municipal officials. The goal was to understand challenges at intersections and surrounding areas, examining barriers and facilitators to mobility. The forum also explored designing interventions based on evaluating these areas in relation to municipal priorities and funding.

Phase 3: Participant Recruitment, Coordination, and Data Collection

Overview

Finalizing the tool and confirming selected intersections enables the research team to proceed with participant recruitment for the 4 populations: individuals with cognitive, mobility, hearing, and vision disabilities, starting with those living with cognitive disabilities. In this study, we aim to collect data from 80 participants across various disability categories. The minimum sample sizes for each category are as follows: 30 participants using MAT, 15 individuals with MCI, 15 individuals who are DHH, and 20 individuals with VI. These numbers are selected to ensure sufficient data for validity and reliability tests. The larger sample size for participants using MAT reflects their greater prevalence compared with the other groups, allowing for a more comprehensive analysis of the effects of MAT in our study. All data collection will be concluded by September 2024. While our recruitment methods are committed to diversity and inclusion, we recognize the importance of providing specific details on participant demographics. By including a diverse range of participants in terms of age, gender, ethnicity, and disability type, we aim to gain a comprehensive understanding of the barriers and facilitators present within the built environment.

Recruitment

The research team will recruit participants from community centers, relevant organizations serving persons with disabilities, and health care connections. This ongoing process targets DHH individuals, those with hearing and vision disabilities, those with early stages of dementia or MCI, and MAT users. To streamline participant onboarding, a researcher will act as the central administrator. This individual will verify eligibility, review study details, consent, web-based online tool training, and COVID-19 protocols with participants before scheduling data collection sessions. Sessions will be scheduled based on participant and research team availability. The lead research assistant (RA) for each session will maintain communication with participants and ensure all necessary documents (SWAN tools, consent forms, and equipment) are ready for the efficient completion of the audits.

On-Site Preparation Research Team

On the day of data collection, the lead and accompanying RAs will arrive in advance to assess the presence and accessibility of public washrooms. Additionally, they will identify either an indoor or covered location for the completion of the SWAN Secondary Observation Form (SOF). This form will be filled out in the format of a 15- to 20-minute qualitative interview.

On-Site Preparation Participant

Before starting the audit with the participant, the lead RA will review the consent form to ensure the participant understands the study objectives, the use of collected data, and their right to withdraw. Next, a demographic form will be completed to contextualize the participant's answers. The participant will be oriented on the path of travel using a map of the intersections to be covered. The lead RA will accompany the participant throughout the walking/wheeling audit, providing assistance as needed or taking a more active role by reading questions aloud, based on the participant's preference.

SOF Content

The SOF includes open-ended questions similar to those in the SWAN tool, encouraging discussion and reflection from the participant. Responses will be either audio recorded or handwritten based on the participant's consent choice. By incorporating the secondary observation interview guide, the SWAN tool gains a more comprehensive understanding of participants' interactions with their neighborhoods.

Home and Community Environment Survey

During the data collection phase, 2 complementary tools will be used: the Home and Community Environment (HACE) tool and the SWAN tool. Participants can either complete these tools themselves or have assistance from a secondary RA. This dual approach enhances the validation process, providing a more thorough assessment of the research variables.

The HACE tool, designed as a self-report measure, will be directly administered by the participants. It aims to evaluate various factors within an individual's HACE that might influence their level of community participation. In this study, the HACE tool serves as an additional validation measure for the effectiveness of the SWAN tool [34].

The initial HACE prototype consisted of 44 items assessing the physical, attitudinal, and political aspects of HACEs. Specifically, questions related to the community mobility domain will be included in the SWAN project's data collection process.

Sidewalk Accessibility Index

The Sidewalk Accessibility Index (SI) serves as an indicator to assess the performance of sidewalks and public spaces, focusing on the needs and expectations of wheelchair users to define accessible routes within urban road networks. It considers

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various variables that contribute to the comfort and safety of wheelchair users, weighted according to their perceptions [35].

In the SWAN project, the SI will be used as a complementary tool for validation purposes. During data collection, a secondary RA completes the SI, which gathers data on 4 key aspects related to sidewalks: evenness, maintenance, width, and surface quality. However, the SWAN project focuses solely on these sidewalk-specific factors and does not inquire about the suitability of pedestrian crossings.

Sidewalks and public spaces should provide an environment that meets the needs of all users, ensuring comfort and safety regardless of physical limitations, whether temporary or permanent. The SI variables are designed to describe aspects of comfort and safety related to pedestrian movement along the block and crossing street intersections.

Finalization of Data Collection

The participant will then be provided with an honorarium for their time spent, and if required, a discussion of a second data collection will take place to complete any outstanding segments. The lead RA is responsible for ensuring the completion of all documents along with uploading and storing data collected appropriately. Finally, a reflection form will be completed by the researchers to reflect on the data collection.

Phase 4: Data Analysis

Overview

The analysis will focus on validating the SWAN tool, which collects both quantitative and qualitative data. Objective and subjective scores will be calculated for its 5 domains. In order to verify the validity of the SWAN tool, 2 additional audit tools will be used to collect data, including HACE [34] and SI [35]. Walk score results for the audited area will also be compared with the SWAN result for further validation. Details on tool validation methods can be found in the section on tool validity. Additionally, the interrater reliability (IRR) of the SWAN tool will be assessed. More information is provided in the IRR section.

Quantitative data from SWAN and other tools will be entered and organized in Microsoft Excel. This includes coding and scoring based on the codebook and calculating domain scores within Excel. For further analysis, the R programming language in RStudio (Posit, PBC) will be used for IRR and tool validity assessments. Qualitative responses from the SOF will be entered and analyzed in NVivo software (Lumivero). More details on SOF analysis can be found in the *Qualitative Data Analysis* section. The specific steps of data analysis are outlined in the following sections.

Data Cleaning and Reorganization

After data are entered and prior to moving forward with the analysis, certain questions will be moved to their original domains. The questions were moved to a different domain for efficient data collection. Although they were physically sequential on site, they are better organized in a separate domain for analysis. For example, questions about street safety features were placed in the function of the street crossing domain during data collection but belong to the safety domain.

Weighting of Scores

The primary step in calculating scores for street segments involves assigning weights to both the domains and subdomains, ensuring a total cumulative score of 100 for all domains. These weights are determined through a comprehensive literature review and expert recommendations.

For individuals who are DHH, use medical assistance technology, and have cognitive disabilities, the domain weights remain consistent. However, there is a slight variation in the vision stream weighting, reflecting the unique needs of individuals with visual impairments. Specifically, the “appearance and maintenance” domain is considered less critical. Therefore, the vision stream receives a weight 5 points lower than other streams, which is then added to the “sidewalk functionality” subdomain.

“Functionality” and “safety” are deemed the most crucial domains for neighborhood accessibility for individuals with disabilities. Consequently, each of these domains will be assigned the highest weight. As shown in Table 1, functionality is divided into crossing functionality (20 points) and sidewalk functionality (15 points in vision stream, 10 points in other streams). The same weights will apply to safety subdomains, traffic safety at 20 (covering pedestrian and vehicle interaction safety), and personal safety at 10 (focusing on subjective safety perceptions).

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Table 1. Domain and subdomain weights.

Domains and subdomains	Vision stream	Other streams
Functionality	30	35
Crossing functionality	20	20
Sidewalk functionality	10	15
Safety	30	30
Traffic safety	20	20
Personal safety	10	10
Land use and supportive features	20	20
Appearance and maintenance	15	10
Social aspect	5	5
Total	100	100

The "land use and supportive features" domain, recognized as the second most critical, will receive a weight of 20. "Appearance and maintenance" will be weighted at 10 for vision and 15 for all other streams, due to overlapping questions within the land use and supportive features domain. In contrast, the "social aspects" domain, with a limited set of 5 questions focusing on subjective assessments, will have the lowest weight.

Subsequently, a detailed review of questions within each domain and subdomain will extract essential concepts and elements. The assigned weight will then be evenly distributed among these identified concepts and elements to avoid undue emphasis on specific concepts. For instance, the 20 points allocated to the subdomain of crossing functionality will be evenly divided among concepts (eg, curb ramp, crosswalk, and pedestrian signal) within that subdomain. Finally, the weight assigned to each category of questions will be equally distributed among all questions within that category to ensure a balanced weighting process.

Objective Scores

There will be 3 steps to calculate the objective score for each domain. First, responses to questions will be converted into numeric codes based on the code book. Second, these codes will be multiplied by the question's weight to calculate the question's score. Third, the scores for all questions within a domain will be summed and divided by the maximum possible score for that domain. To make the aggregated objective score easier to understand, it will be multiplied by 100% for each domain.

Some questions in the SWAN tool are reverse-coded to avoid confusion. For instance, a positive response to the presence of a certain physical feature indicating a barrier (eg, "transition from the curb ramps into the crosswalk causes problems") would be scored as "1," though it is not a facilitator in this context. These questions were reverse-scored as needed to ensure the total score includes only true "Yes" scores.

In addition to the final objective score for each domain, a total score for the SWAN tool will be calculated by averaging the scores for each domain. This total score will facilitate comparisons between different audited segments.

Codebook

In the SWAN tool, response options typically include "Yes," "No," "Don't Know," and "Not Applicable," as shown in Table 2. However, for individuals with vision disabilities, an additional option, "Cannot detect," is provided for cases where the participant cannot clearly see the object but is aware of its existence. When participants with vision disabilities choose this option, it is treated as equivalent to selecting "No," as the object is not detectable or functioning properly for the user. During the coding process, a value of "1" will be assigned for the presence of an assessed environmental feature that enhances walkability/wheelability, and "0" for its absence. Reverse-coded questions, such as "The outdoor patio(s) is/are an obstacle to walking/wheeling," will use "0" to represent the presence of this barrier and "1" to denote its absence.

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Table 2. Different types of questions and scoring rationale (missing data: n=99).

Type of question and possible responses	Code
General questions	
Yes	1 (0 in case of reverse coding)
No (cannot detect, specifically in the tool designed for vision impairment)	0 (1 in case of reverse coding)
Not applicable	98
Don't know	97
Both sides questions	
Both sides	2 (0 in case of reverse coding)
One side	1
Neither side	0 (2 in case of reverse coding)
Not applicable	98
Don't know	97
Directional questions	
One-way	1
Two-way	0
Not applicable	0
Don't know	0

For items referring to "one side or both sides" of a street segment, they will be grouped together as a scale. For example, "Are there curb ramps/cuts present?" will be coded as "2" if they are present on both sides, "1" if present on only one side, and "0" if not present at all. The same approach applies to items with a positive or negative impact on walkability/wheelability.

In addition to general and 2-sided questions, the SWAN tool includes questions about the direction of traffic, with responses like "one-way" and "two-way". Through a disability lens, "one-way" responses will be coded as "1" and "two-way" as "0" since crossing one-way streets is less complex.

Responses like "not applicable" and "don't know," based on the data collection area and participants' familiarity, will be excluded from the scoring system to ensure it accurately reflects walkability/wheelability factors.

Subjective Ratings

Participants in the SWAN tool provide subjective ratings using a 5-point Likert scale at the end of each domain. This scale ranges from "poor" (scored as "1") to "excellent" (scored as "5"), reflecting their subjective experience of the assessed domain. These ratings are averaged and converted into percentages to indicate participants' subjective perceptions of the audited segment. Comparing these subjective scores with the objective scores may reveal interesting findings.

Qualitative Data Analysis

As indicated, the qualitative data will be collected using the SOF which contains open-ended questions based on the 5 primary domains, and 4 subdomains in the SWAN tool. Qualitative data gathered using the SOF is intended to capture detailed insights from the participants regarding the built environment and their lived experiences. For instance, within the personal safety subdomain, participants will be asked the following "Are there things that make you feel safe or unsafe when walking/wheeling during the daytime?" Collectively, the SOF data and the photo commentary build the qualitative dataset connected to the SWAN tool.

The qualitative data will be analyzed by using both Braun and Clark's [36] seminal multistep thematic analysis process and by drawing on later advances in their methodological framework [37]. Their original analytical process consists of six integrated phases including (1) data familiarization and review, (2) code development and comparison, (3) code consolidation and early theme exploration, (4) theme confirmation and mapping, (5) theme refinement and name creation, and (6) research findings write-up (Braun and Clark [36]). While the open-ended questions contained in the SOF are grounded in the conceptual domains of the SWAN tool, the qualitative analysis process will be both inductive and reflexive [36,37]. Therefore, the analysis will be guided by the data itself [36] and will aim to identify insights and interpretations of the data beyond known built environment barriers and facilitators while also embracing the subjectivity of the research team members [37]. The research team will also independently and collectively engage in reflexive journaling practices and group discussions throughout the qualitative analysis process [38]. These practices will help the research team examine their subjectivity and understand its connection to their analysis [39]. Last, this will also contribute to the quality of the analysis; specifically, the adoption of these reflexive methods will contribute to the equitable and fair representation of all participant perspectives [38].

Step 1: Data Familiarization and Review

The raw qualitative data will undergo initial transcription and cleaning using Otter.ai. Subsequently, the transcriptions will also be verified by several RAs. This process will not only

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ensure a clear and reliable dataset for analysis but will also help the research team familiarize themselves with the data.

Step 2: Code Development and Comparison

After the data have been transcribed and cleaned the coding process will begin. This will include the development of early/open codes and exploration of the codes across transcripts [36]. Coding will be undertaken by individual research team members, however, will be complemented by group discussions to allow for exploration of the research team's subjectivity and interpretation of the data.

Step 3: Code Consolidation and Early Theme Exploration

Following the coding of the transcripts, the research team will work to consolidate the existing codes and explore relevant themes identified within the data [36]. This process will be collaborative as all research team members will aid in collating existing codes, and in the development of a preliminary thematic map/diagram.

Step 4: Theme Confirmation and Mapping

After the potential themes have been identified, the research team will work to solidify the themes. This will involve examining if the preliminary themes fully represent and reflect the data [36]. This process will be iterative and will potentially involve revisiting the coding process. This stage will not conclude until all team members agree that the analysis fully captures the data, and a cohesive thematic map has been developed.

Step 5: Theme Refinement and Name Creation

The research team will then work to ensure each theme is well-defined and succinct [36]. This process will also be iterative and will work to identify the relevance of each theme in relation to the broader goals of the SWAN tool.

Step 6: Write-Up of Research Findings

In the final step, the team will elaborate on each theme, discussing their significance with evidence from the data, including quotes. This comprehensive write-up will aim to convey theme frequency, and importance, within the research context.

IRR Analysis

The reliability of the SWAN will be determined by calculating IRR using the paired observer method. The IRR will compare the objective scores of older adults or persons with disability and the secondary RA. This will be calculated both in percentage agreement and Cohen κ to compare the results [40]. Percentage agreement is a straightforward measure that calculates the proportion of agreement between 2 observers as a percentage of the total observations; however, in 1960, Cohen [41] critiqued the use of percent agreement due to its inability to account for chance agreement. He introduced the Cohen κ, developed to account for the possibility that raters actually guess on at least some variables due to uncertainty [40]. Cohen suggested the κ result be interpreted as follows: values ≤0 as indicating no agreement, 0.01-0.20 as none to slight, 0.21-0.40 as fair, 0.41-0.60 as moderate, 0.61-0.80 as substantial, and 0.81-1.00 as almost perfect agreement [41].

Tool Validity

To validate the SWAN tool, correlation analyses will be conducted between its domains and other environmental audit tools used in data collection: HACE, SI, and Walkscore. HACE and SI scores will be normalized using formulas outlined in their respective papers [34,35], while Walkscores for the audited area will be obtained via web. After examining data distribution, the appropriate correlation analysis method, Pearson correlation, will be applied to assess associations between scores from different tools. Pearson correlation lies between –1 and 1. Values near 0 mean no (linear) correlation and values near SD 1 mean very strong correlation. The negative sign means that the 2 variables are inversely related, that is, as one variable increases the other variable decreases. The following table gives a guideline on the strength of the linear relationship corresponding to the correlation coefficient value [42].

As no comprehensive audit tool similar to SWAN was identified in existing literature, each additional audit tool was purposefully selected to assess the validity of specific SWAN domains. Therefore, SI will be compared with functionality, HACE with safety, and Walkscore with land use and supportive features. The matrix in Table 3 illustrates which SWAN domains or subdomains will be compared with measures from HACE, SI, and Walkscore tools.

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Table 3. Similarity between the Stakeholders' Walkability/Wheelability Audit in Neighborhoods (SWAN) domains and subdomains and other tools.

Extra tools and measures used for tool validation	Domains and subdomains of the SWAN tool						
	Functionality		Safety		Land use and supportive features	Appearance and maintenance	Social aspect
	Street crossing	Sidewalk	Traffic safety	Pedestrian safety			
SI[a] (sidewalks)							
Even		✓		✓			
Well-maintained		✓		✓		✓	
Surface condition		✓		✓		✓	
Width		✓					
Intersection	✓		✓	✓			
HACE[b]							
Uneven sidewalks		✓		✓			
Easy to use sidewalks		✓		✓			
Safe	✓	✓	✓	✓			
Places to rest							✓
Curb ramps	✓		✓				
Walkscore							
Access to amenities					✓		

[a]SI: Sidewalk Accessibility Index.

[b]HACE: Home and Community Environment.

Results

Data collection concluded in September 2024, involving 80 eligible participants across 4 streams in preidentified hotspots. The results are expected to be published in March 2025. To date, data collection is ongoing, and we are currently in the process of data analysis.

Discussion

Expected Findings

By focusing on a diverse group of participants, including those using MAT, those living with MCI and VI, and those who are DHH, the study aims to provide a comprehensive understanding of the barriers and facilitators present within the built environment using the SWAN tool. As there are no validated tools to capture this population perspective while navigating the built environment, the anticipated findings are expected to contribute to the existing literature by validating the SWAN tool in diverse disability categories. We hypothesize that similar to prior research, functionality and safety will emerge as key factors influencing accessibility across all disability groups. Past studies have consistently shown that features like sidewalk width, smoothness, and the presence of safe crossings are fundamental to pedestrian mobility [3,8-11]. However, our approach considers physical features, by integrating subjective participant ratings and qualitative data collected through the SOF to capture subjective experiences. This dataset should provide a more comprehensive view of how the built environment influences community participation and social participation for individuals with disabilities.

A key strength of this study is its comprehensive inclusion of multiple disability types. This research adopts a holistic perspective, capturing the full spectrum of disability-related accessibility challenges.

One important aspect that was not fully addressed in this study was the inclusion of individuals who are deaf-blind. This population, which experiences both vision and hearing impairments simultaneously, faces unique challenges that were not directly captured in this phase of the research. Due to the complexity of their needs, the lack of comprehensive accessibility tools for this group, and the potential for logistical difficulties in coordinating data collection with deaf-blind individuals, this population was excluded from this study. However, their experiences are equally critical to understanding how the built environment affects individuals with multiple disabilities.

To ensure that the findings from this study reach a wide audience and have a meaningful impact, we have developed a comprehensive knowledge mobilization strategy. A central element of this plan is the community forum, which will provide an interactive space for people with disabilities, urban planners, local government officials, and other key stakeholders to engage

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directly with the research findings. This forum will facilitate the exchange of experiences and insights from individuals with disabilities, offering a platform to share their lived experiences navigating urban spaces. Through this collaborative dialogue, we aim to raise awareness and generate actionable recommendations for improving the accessibility of urban environments.

Additionally, as part of the knowledge mobilization strategy, we will develop multimedia resources including games and videos to engage both the disability community and the general public in the study's outcomes. The games will simulate the various mobility challenges faced by individuals with disabilities, offering an immersive experience for users to understand and empathize with the barriers these individuals encounter. These interactive tools will be used as educational resources in community centers, schools, and public awareness campaigns to foster greater understanding and empathy.

Conclusion

This study introduces a new approach to assessing urban accessibility for individuals with various disabilities using the SWAN tool; by adopting a community-based methodology, the research emphasizes the importance of including diverse disability perspectives in evaluating the built environment. The anticipated findings will provide valuable insights into the barriers and facilitators that impact mobility, safety, and overall accessibility in urban spaces.

While the study's limitations include the exclusion of individuals who are deaf-blind and the focus on specific urban areas, these gaps present opportunities for future research. Expanding the participant pool and environments will strengthen the generalizability of the findings.

This work contributes new knowledge to the field by offering a comprehensive framework for urban accessibility that integrates both subjective and objective measures. It underscores the importance of inclusive design and offers practical implications for urban planners and policymakers striving to create more accessible, inclusive communities.

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Data Availability

The datasets generated or analyzed during this study will be available from the corresponding author upon reasonable request.

Authors' Contributions

RN collected and analyzed data, contributed to the interpretation of results, and wrote the manuscript. AM contributed to the study design and critically revised the manuscript for important intellectual content. BM contributed to the interpretation of results and critically revised the manuscript. All authors agree to be accountable for all aspects of the work, ensuring the accuracy and integrity of the research presented. All authors have read and agreed to the published version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

DHH: deaf or hard of hearing
HACE: Home and Community Environment
IRR: interrater reliability
MAT: mobility assistive technologies
MCI: mild cognitive impairment
RA: research assistant
SI: Sidewalk Accessibility Index
SOF: Secondary Observation Form
SWAN: Stakeholders' Walkability/Wheelability Audit in Neighborhoods
VI: vision impairment

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Protocol

The Fire Fighter Cancer Cohort Study: Protocol for a Longitudinal Occupational Cohort Study

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Abstract

Background: Firefighters are at an increased risk of cancer and other health conditions compared with the general population. However, the specific exposures and mechanisms contributing to these risks are not fully understood. This information is critical to formulate and test protective interventions.

Objective: The purpose of the Fire Fighter Cancer Cohort Study (FFCCS) is to conduct community-engaged research with the fire service to advance the evaluation and reduction of firefighter exposures, along with understanding and mitigating effects leading to an increased risk of cancer and other health conditions. This involves establishing a long-term (>30 years) firefighter multicenter prospective cohort study.

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Methods: The structure of the FFCCS includes a fire service oversight and planning board to provide guidance and foster communication between researchers and fire organizations; a data coordinating center overseeing survey data collection and data management; an exposure assessment center working with quantitative exposure data to construct a firefighter job exposure matrix; and a biomarker analysis center, including a biorepository. Together, the centers evaluate the association between firefighter exposures and toxic health effects. Firefighter research liaisons are involved in all phases of the research. The FFCCS research design primarily uses a set of core and project-specific survey questions accompanied by a collection of biological samples (blood and urine) for the analysis of biomarkers of exposure and effect. Data and samples are collected upon entry into the study, with subsequent collection after eligible exposures, and at intervals (eg, 1-2 years) after enrollment. FFCCS data collection and analysis have been developed to evaluate unique exposures for specific firefighter groups; cancer risks; and end points in addition to cancer, such as reproductive outcomes. Recruitment is carried out with coordination from partnering fire departments and eligible participants, including active career and volunteer firefighters in the United States.

Results: The FFCCS protocol development was first funded by the US Federal Emergency Management Agency in 2016, with enrollment beginning in February 2018. As of September 2024, >6200 participants from >275 departments across 31 states have enrolled, including recruit and incumbent firefighters. Biological samples have been analyzed for measures of exposure and effect. Specific groups enrolled in the FFCCS include career and volunteer structural firefighters, women firefighters, trainers, fire investigators, wildland firefighters, firefighters responding to wildland-urban interface fires, and airport firefighters. Peer-reviewed published results include measurement of exposures and the toxic effects of firefighting exposure. Whenever possible, research results are provided back to individual participants.

Conclusions: The FFCCS is a unique, community-engaged, multicenter prospective cohort study focused on the fire service. Study results contribute to the evaluation of exposures, effects, and preventive interventions across multiple sectors of the US fire service, with broad implications nationally.

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KEYWORDS

firefighter; cancer; prospective cohort study; biomonitoring; protocol

Introduction

Background

There are >1 million active career and volunteer firefighters in the United States [1]. Elevated cancer rates have been reported in US firefighters, including all cancer incidence and mortality; individual cancer sites, including but not limited to bladder, brain, colon and rectum, kidneys, lung and pleura, prostate, skin, and testis; as well as some hemopoietic cancers [2-4]. Occupational exposure as a firefighter is carcinogenic to humans, as determined by the International Agency for Research on Cancer (IARC) of the World Health Organization, based on sufficient evidence in humans for mesothelioma and bladder cancer [5]. While the IARC determination applies to all types of firefighters, most research supporting this determination has focused on career male municipal or structural firefighters. Far less information is available on other firefighter groups, including but not limited to volunteers, women as well as ethnic and racial groups underrepresented in the fire service, aircraft rescue and firefighting members, wildland firefighters, those responding to wildland-urban interface (WUI) fires, trainers, and fire cause investigators. Firefighting has also been associated with adverse reproductive effects. Specifically, male firefighters have been reported to have an increased risk of infertility [6], as well as an increased risk for birth defects in their children [7] and sperm abnormalities [8]. Female firefighters are at an increased risk of miscarriage [9], preterm birth [10], and reduced reproductive reserve [11].

Firefighters are exposed to numerous known, probable, and possible human carcinogens, including combustion products from fires (eg, benzene, polycyclic aromatic hydrocarbons [PAHs], and formaldehyde), asbestos, diesel exhaust, per- and polyfluoroalkyl substances (PFAS), flame retardants, and other hazards [12]. Exposure to some contaminants, such as PAHs, can occur both through inhalation and dermal exposure [13]. Night shift work, which is common among firefighters, has been determined as a probable human carcinogen [12]. However, we currently do not understand which individual exposures are responsible for cancer in firefighters, the mechanisms by which these exposures cause cancer, or the effective means of reducing exposures. As cancer has a long latency period, biomarkers that can measure the effects of carcinogen exposure are also needed well before the development of cancer, when interventions to prevent the disease could be effective. Furthermore, the IARC evaluation determined that there is strong evidence for 5 toxic mechanisms, also termed key characteristics of carcinogens, resulting from occupational exposure as a firefighter, including genotoxicity, epigenetic changes, oxidative stress, chronic inflammation, and modulation of receptor-mediated effects [12].

Because most published studies on firefighter exposures and effects have been based on predominantly male career firefighters, the cancer risk for other firefighter groups has not been adequately studied. Of the 1,041,200 estimated firefighters in the United States, 676,900 (65.01%) are volunteers [14], but information on the specific cancer risk of US volunteer firefighters is limited. The extent of cancer risk for wildland firefighters is also not known, despite the presence of known carcinogens in wood smoke [15], and exposure to wood smoke

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and combustion of biomass is associated with an increased cancer incidence in animal and human studies [16,17]. The limited available studies of US women firefighters suggest that career women firefighters are at an increased risk of cancer compared with the general population. A study of women career firefighters in Florida reported a 63% increase in overall cancer incidence as well as increases in cervical and thyroid cancers and Hodgkin disease compared to the general population [18]. Daniels et al [2] reported significant increases in bladder cancer incidence and mortality in women firefighters based on a few cases, as well as nonsignificant increases in breast cancer and overall cancer incidence. Published information on cancer rates for understudied racial and ethnic groups is also limited. In a study of California firefighters, cancers of the tongue, testis, and bladder; non-Hodgkin lymphoma; chronic lymphocytic leukemia; and chronic myelogenous leukemia were significantly elevated among understudied firefighter groups, predominantly Hispanic or Black (but not non-Hispanic White) firefighters compared to the general population [3].

Objectives

The Fire Fighter Cancer Cohort Study (FFCCS) is designed to address the distinctive challenges of conducting research in the fire service because it is a community-engaged partnership of academic and governmental research centers with the fire service. In community-engaged research, community representatives and researchers share all aspects of the research process, including co‐learning and reciprocal transfer of expertise, shared decision-making, and mutual ownership of the processes and products of the research [19]. Community-engaged research with firefighters is critical to not only answer their research questions but also to effectively share this information with the broader fire service community and inform actions to protect their health. Furthermore, the prospective nature of the FFCCS allows for the collection of survey data and biological samples before the development of disease. The goal of the FFCCS is to work with the fire service to advance firefighter cancer control and prevention, as well as evaluation and prevention of other health conditions. The primary and secondary objectives of the FFCCS are listed in Textbox 1.

Textbox 1. Primary and secondary objectives of the Fire Fighter Cancer Cohort Study.

Primary objectives

- Measure acute and chronic exposures experienced by firefighters
- Create a firefighter job exposure matrix
- Measure biomarkers of effect, including but not limited to epigenetic changes (eg, DNA methylation and microRNA expression)
- Compare exposures and effects across firefighter groups, including women; men; understudied ethnic and racial groups; volunteer, career, structural, wildland, and wildland-urban interface firefighters; trainers; investigators; and airport firefighters
- Communicate information regarding individual and aggregate study results to firefighter participants and the fire service community
- Identify characteristics of firefighters at increased risk for cancer
- Evaluate the effectiveness of exposure reduction and disease prevention interventions and communicate effective exposure mitigation approaches

Secondary objectives

- Evaluate the risk for reproductive health, mental health conditions, and other health conditions prioritized by the fire service
- Characterize noncarcinogenic exposures

Methods

Study Design

The FFCCS is a community-engaged prospective multicenter occupational cohort, enrolling incumbent firefighters at various points throughout their careers, as well as recruiting firefighters during their fire academy training, generally before their live-fire training. Most volunteer firefighters in the FFCCS were enrolled as part of the Firefighter Cancer Assessment and Prevention Study (CAPS), in collaboration with the FFCCS, with some differences in study procedures. CAPS enrolled participants from 41 US volunteer or combination (both volunteer and career) fire departments in Connecticut, Illinois, Kansas, Maryland, Maine, Missouri, New Jersey, Tennessee, and Washington. Participants enrolled through CAPS have been incorporated into the FFCCS for follow-up surveys and biological sample collection.

Ethical Considerations

The FFCCS protocol was initially reviewed and approved by the University of Miami Institutional Review Board in 2017 (ethics approval number STUDY00002192). In October 2023, the reviewing institutional review board (IRB) was transferred to the University of Arizona. Academic and government partners have established reliance agreements with the reviewing IRB of record. The US Department of Homeland Security Compliance Assurance Program Office also reviewed and approved the projects funded by the US Federal Emergency Management Agency. Participants provided informed consent electronically through a REDCap (Research Electronic Data Capture; Vanderbilt University) study database system, with some using hard copy consent forms in situations where no internet access was available. FFCCS research personnel ensure that participants understand key study activities, data confidentiality, and risks before providing consent. FFCCS research personnel then countersign to confirm the consent.

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CAPS uses slightly modified consent procedures to allow researchers to obtain informed consent electronically without countersigning before the initial data collection event. Depending on the research project, participants are provided personalized results from analysis of their collected specimens.

FFCCS Organizational Structure

The FFCCS is organized with administrative and operational units (Figure 1). The oversight and planning board (OPB) is composed of representatives from national fire service organizations and individual firefighters with expertise in active research projects who review current and new research projects under consideration, FFCCS policies, and FFCCS committee appointments. An OPB steering committee composed of a limited number of OPB members takes a more active role in FFCCS operations, including participation in the FFCCS leadership team. The FFCCS leadership team, called coleads, is composed of FFCCS center directors, individual research program principal investigators (PIs), and select OPB steering committee members. The coleads are responsible for making research operational decisions, with guidance from the OPB and OPB steering committee members. The daily operation of the overall FFCCS is run by the director. Individual FFCCS projects are run by their PIs and program coordinators. FFCCS committees (eg, publication committee) are established on an as-needed basis and can include coleads, other research faculty staff, and OPB members. The REDCap data manager and regulatory and compliance manager assist all PIs and report to the FFCCS director.

Figure 1. The Fire Fighter Cancer Cohort Study's (FFCCS) organizational structure. IRB: institutional review board; REDCap: Research Electronic Data Capture.

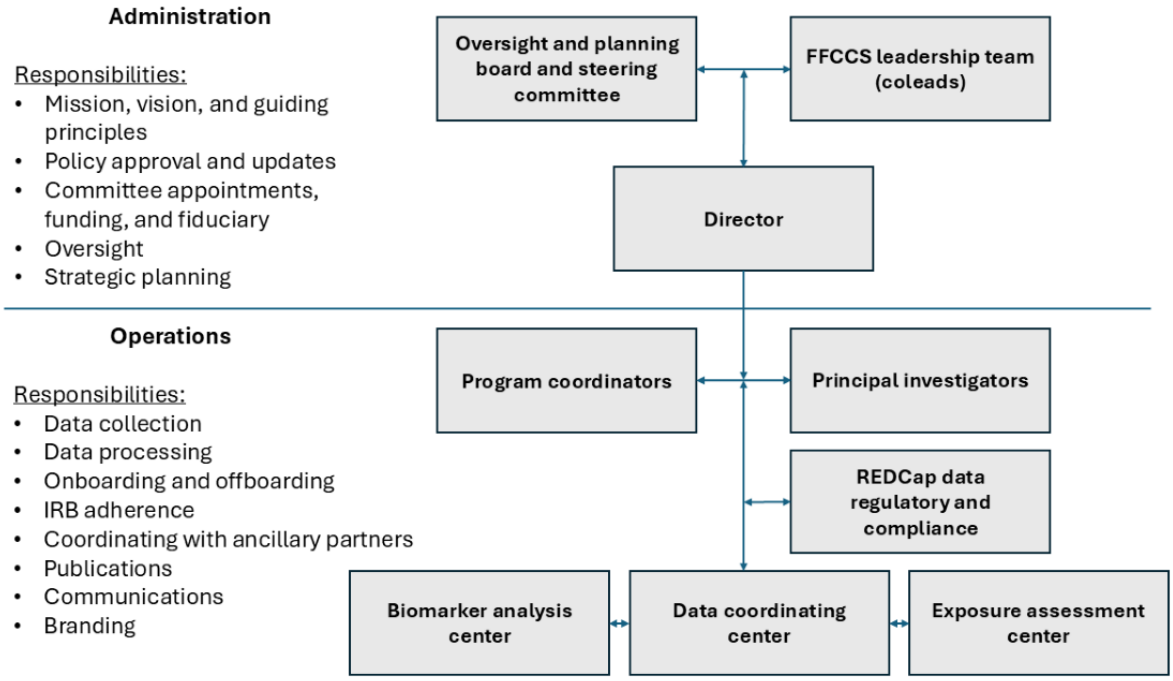

There are 3 FFCCS centers. The data coordination center designs and updates standardized participant survey data collection tools and analysis protocols to address the short- and long-term study objectives, as well as to facilitate any future linkages with long-term outcome data, including cancer development and mortality. The data coordination center also manages the survey data and oversees the process of internal and external data requests. The exposure assessment center collects and combines quantitative biomarkers of exposure measurements with information gleaned from self-reported characteristics of exposure (eg, job history, job task, and personal protective equipment) for the development of a job exposure matrix (JEM). These data will provide improved occupational exposure data for comparison with biomarkers of effect and eventual cancer outcomes. The biomarker analysis center provides a biorepository for blood and urine samples and carries out studies of biomarkers of exposure and effect, including epigenetic markers, comparing firefighters with a range of acute and cumulative exposures.

Community Engagement and Policy

For many career and a few volunteer partner fire departments, ≥1 firefighter research liaison selected by the department coordinates FFCCS participant enrollment and follow-up. Firefighter liaisons serve a critical role in community collaboration and are vital to the success of the study. At least 1 liaison is onboarded to the IRB-approved protocol following the completion of a shortened human participants training course and receipt of a signed permission form from the department. Only IRB-approved liaisons have access to information on who has enrolled in their departments for which they are liaising and can assist with contacting participants to coordinate follow-up collections and complete study materials as needed. Study personnel, primarily study coordinators at academic institutions, provide frequent updates to department liaisons with information on study goals, progress, and next steps. Department liaisons

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are encouraged to engage with the academic team to provide feedback on study design and implementation. Department liaisons are often asked to review study materials, such as surveys and results reporting formats, to provide feedback and ensure that study materials are relevant to the fire service. To help ensure community engagement, fire department liaisons are notified before study materials (ie, participant results and newsletters) are sent to participants.

In addition, fire department liaisons are provided with information on study results before academic publication and dissemination. Study liaisons may be involved in manuscript development and study presentations. Furthermore, department liaisons provide firsthand knowledge of the fire service and are vital for identifying relevant research questions and ensuring that the research is aligned with the fire service. For some departments, such as volunteer departments participating in CAPS, research liaisons primarily support general communications and organizing study sessions rather than participant-specific activities. In these cases, research liaisons are not required to complete human participants research training. Working with firefighter liaisons through these avenues ensures consistent input from community partners and reinforces collaboration within the fire service.

Individual Research Projects

The FFCCS is composed of individual, separately funded research projects with overlapping periods of performance (Table 1). These projects are based on research needs within the fire service, with fire departments requesting specific research studies from academic partners or vice versa. Academic institutions participating in the FFCCS have included Colorado State University; Duke University; National Development & Research Institutes (Kansas City); Rutgers, the State University of New Jersey; Tennessee Technological University; the University of Arizona; University of California at Los Angeles; University of Miami; University of Michigan; University of Washington; and Wildfire Conservancy. Government institutions directly involved in the FFCCS or providing analytical support have included the National Institute for Occupational Safety and Health (NIOSH) within the Centers for Disease Control and Prevention (CDC), the National Center for Environmental Health (NCEH) within the CDC, and the New Jersey Department of Health Public Health and Environmental Laboratories.

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Table 1. Individual Fire Fighter Cancer Cohort Study (FFCCS) projects. Additional funding has been provided by individual fire departments, the International Association of Fire Fighters, and the National Institute of Environmental Health Sciences (NIEHS).

Project	Initial funding	Funding agency	Objectives
Pre-FFCCS	2015	FEMA[a]	Developed the community-engaged protocols for the FFCCS in partnership with the Tucson Fire Department, evaluated exposure reduction interventions, and established the association of epigenetic markers with cumulative firefighter exposures
Framework	2016	FEMA	Established the multicenter IRB[b]-approved protocol; baseline survey; partnership of academic, government, and fire service partners; as well as the OPB[c], DCC[d], BAC[e], and EAC[f]
Expansion	2018	FEMA	Added more fire departments and focused on evaluating exposures and epigenetic markers of toxicity and cancer risk in firefighter trainers, fire investigators, and volunteer firefighters
PFAS[g]	2019	FEMA	Evaluated PFAS exposure in aircraft rescue and firefighting members as well as PFAS exposure from wearing new gear and responding to fires
NIOSH[h] WUI[i]	2019	NIOSH within CDC[j]	Evaluated exposures and epigenetic effects of these exposures in firefighters from 2 California County fire departments during the campaign WUI fires
Women project (2 projects)	2020 and 2022	FEMA	Addressing priority research areas requested by women firefighters, including cancer risk, reproductive health, and stress
Volunteers and CAPS[k] (2 projects)	2020 and 2022	FEMA	Added volunteer and combination fire departments and focused on evaluating environmental exposures (PFAS) and cancer risk factors and behaviors, as well as cancer risk reduction
Wildland (2 projects)	2021 and 2023	FEMA	Added both wildland and WUI exposure monitoring, evaluation of carcinogenic effects, and testing of exposure reduction interventions
Arizona PFAS	2023	Arizona Board of Regents	Evaluating serum levels of PFAS in firefighters and opportunities for linked randomized controlled trials designed to reduce serum levels of PFAS and improve epigenetic age
High risk	2023	FEMA	Focused on evaluating the effects of firefighter exposure to high-risk, low-frequency incidents, such as the train derailment and fire in East Palestine, Ohio, and the wildfires in Maui, Hawaii
North Carolina PFAS	2024	State of North Carolina	Enrolling additional North Carolina firefighters into the FFCCS and evaluating their PFAS exposure and health effects
NIEHS WUI	2024	NIEHS	Enrolling Los Angeles County Fire Department and Orange County Fire Authority firefighters likely to respond to WUI fires, evaluating exposures and exposure reduction interventions

[a]FEMA: Federal Emergency Management Agency.
[b]IRB: institutional review board.
[c]OPB: oversight and planning board.
[d]DCC: data coordinating center.
[e]BAC: biomarker analysis center.
[f]EAC: exposure assessment center.
[g]PFAS: per- and polyfluoroalkyl substances.
[h]NIOSH: National Institute for Occupational Safety and Health.
[i]WUI: wildland-urban interface.
[j]CDC: Centers for Disease Control and Prevention.
[k]CAPS: Firefighter Cancer Assessment and Prevention Study.

Study Population

Overview

The enrollment goal for the FFCCS is 10,000 firefighters, with the representation of major firefighter employment types (eg, career and volunteer), response activities (eg, structural and wildland firefighters, those responding to WUI fires, aircraft rescue and firefighting members, trainers, and fire investigators), and geographic (urban, suburban, rural, and state) and demographic (sex, race, and ethnicity) groups across the United States. The study duration is planned for a minimum of 30 years, given the rolling cohort entry and latency period between the first cancer-related mutation and diagnosis of cancer, which can exceed 25 years for some forms of cancer [20].

The sample size of 10,000 firefighters will permit the evaluation of the potential for biomarkers to predict cancer outcomes and provide adequate power to evaluate the incidence of more common cancers, such as breast and prostate cancers. With a

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proposed sample size of 2000 female firefighters and a new case rate of breast cancer in the general population of 129.4 per 100,000 women each year [21], we estimate that we will have 80% statistical power to detect a 30% increase in breast cancer among female firefighters followed for >30 years compared with age-, race-, and calendar period–standardized rates in the US general population. For context, breast cancer in female individuals occurred at a (nonstatistically significant) 45% increased rate in a previous retrospective study of career female firefighters, with the US population referent [2]. For prostate cancer, with a proposed sample size of 2000 firefighters from understudied (predominantly Hispanic and Black) ethnic and racial groups, compared with >3700 non-Hispanic White career firefighters, and assuming a 5.2% cumulative 30-year incidence in all firefighters [2], we anticipate having 80% power to detect a 32% difference in prostate cancer rates between the 2 groups. A previous study found a 2.42-fold increase in prostate cancer odds ratio in understudied ethnic and racial group firefighters and a 1.4-fold increase in non-Hispanic White firefighters compared to the general population [3].

Recruitment and Enrollment

Our recruitment strategy generally works through individual fire departments; for specific populations (eg, volunteer women firefighters), we may enroll individual firefighters without prior department contact. Department contact begins with discussions with fire department representatives, followed by discussions with department administration and, for career departments, union representatives. Signed letters of support are obtained before the start of enrollment. Recruitment materials, such as study flyers, may be shared by email through the department, and informational webinars may be provided if the department or union requests. For some studies, fire department liaisons may visit each fire station and shift to provide additional information, and a scheduler platform may be used for interested participants to sign up for enrollment days and times. The voluntary nature of participation in the FFCCS is emphasized repeatedly. All active-duty firefighters aged ≥18 years with potential for fireground exposure are eligible for participation. Enrollment typically occurs at central locations or stations identified by our fire service partners. At these events, study researchers and firefighter liaisons explain the study to participants before they provide informed consent using an electronic consent form or a paper consent form if needed as backup. Following consent procedures, participants complete the enrollment questionnaire and provide biological samples. For CAPS, participants complete the consent form and enrollment questionnaire before meeting with the study team for sample collection.

Data Collection Methods

The FFCCS study design is based on the collection of 3 primary sources of data: information provided through surveys; measures of exposure and effect in biological samples; and departmental fire run data, when available. Additional data are collected for specific populations or projects as needed. Examples include exposures measured in air or passive silicone sampling devices.

Survey Data Collection

All FFCCS participants complete an enrollment survey. Subgroup-specific surveys may be used for enrollment and as needed subsequently, such as after biological sample collection, to capture information about firefighter subgroups. Annual follow-up surveys were rolled out to all CAPS participants starting in 2023 and are being sent to all FFCCS participants starting in 2024. The enrollment survey collects fire service and other occupational history and exposures, sociodemographic information, and cancer history and cancer-related risk factors. These risk factors include questions about health care access and cancer screening, mental health, behavioral factors (eg, physical activity, tobacco, and alcohol use), as well as height and weight to calculate BMI. The annual follow-up survey builds upon the enrollment survey, asking participants for changes in the aforementioned categories since enrollment, and provides an opportunity to recapture any missing data.

Biological Samples

Urine and blood are collected at enrollment and, when possible, approximately every 2 years (18-24 months) thereafter; through retirement from the fire service; or conclusion of the study (whichever comes first). They may also be collected for individual research projects at additional specified intervals. Additional biological samples collected differ based on the project.

Blood is collected using a butterfly needle by a trained phlebotomist. The blood tubes collected include 2 glass red-top Vacutainer tubes (supplier number: 366430, Beckton, Dickinson and Company); 1 plastic blue-top sodium citrate Vacuette tube (supplier number: 454332, Greiner Bio-01e); 1 or 2 plastic purple-top ethylenediaminetetraacetic acid (EDTA) Vacuette tubes (supplier number: 456002, Greiner Bio-01e), depending on the project; and 1 Tempus Blood RNA tube (supplier number: 4342792, Applied Biosystems). After collection, the serum tube is left for 1 hour at room temperature to allow clotting, and the other tubes are immediately stored at 4 °C. All blood tubes are shipped at 4 °C to the processing facility at the University of Arizona. Samples are stored at 4 °C until they are processed within 24 to 48 hours of collection. The Tempus blood is divided into two 4.5 ml aliquots, and 2.5 ml of whole blood is removed from the EDTA tube for storage. The remaining blood is centrifuged at 1300 revolutions per minute and 4 °C for 15 minutes. Two 0.5 ml aliquots of plasma are extracted from the separated EDTA blood, and the remaining packed cells are stored. Three 0.5 ml aliquots of plasma are extracted from the sodium citrate tubes. A total of 7 aliquots of serum are extracted from the glass Vacutainer tubes, ranging from 0.5 to 2.5 ml. All samples are documented and stored in the study biorepository at –80 °C.

Urine is collected by participants in polypropylene collection cups (supplier number: 01 0100, Thermo Scientific) and stored and transported on dry ice to the processing facility at the University of Arizona, NIOSH, or another research laboratory. Upon receipt at the laboratory, urine is stored at –80 °C until it is processed. All urine undergoes 1 freeze-thaw cycle before processing to maintain consistency. Urine is thawed in a shaking incubator at 25 °C and 100 revolutions per minute for 2 hours

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and then divided into six 1.8 ml aliquots and one 12 ml aliquot. The samples are documented and stored in the study biorepository at –80 °C.

Exposure Assessment

Overall Approach

In a subset of many firefighter subgroups, we have collected quantitative exposure measurements using biological samples (eg, blood and urine), self-reported exposure data from exposure tracking applications (eg, type of response, use of personal protective equipment, and presence of smoke), characteristics of exposure (eg, job history and job title) from the enrollment survey, and incident records from participating fire departments. Over time, these data will be used to develop and validate a JEM to better understand the potential exposures for firefighters by job title (eg, captain, firefighter, or paramedic), employment type (eg, volunteer and career), and subgroup (eg, wildland firefighters, fire cause investigators, and trainers).

Exposure Assessment Biomonitoring

For JEM development, blood samples collected at enrollment into the study and approximately 1 year to 2 years later (when feasible) may be analyzed for brominated flame retardants and PFAS. In addition, firefighters' self-collected urine samples at enrollment into the study and 3, 6, and 24 hours after up to 10 fire responses over a period of 2 years may be analyzed for urinary metabolites of PAHs. In some substudies, spot urine samples are collected at the beginning and end of a shift (eg, after training fires or after WUI fire responses). For some substudies (ie, WUI study), urine samples may also be analyzed for other compounds (eg, volatile organic compounds [VOCs], heavy metals, organophosphate esters, and PFAS).

Exposure Tracking Application Data and Fire Department Records

If fire department records are not available, self-exposure tracking applications used include the National Fire Operations Reporting System (NFORS) developed by the International Public Safety Data Institute and the Personal Exposure Reporter (PER) developed by the University of Miami. For all FFCCS structural fire department participants, when possible, we request a minimum records-based exposure dataset (Textbox 2) from their fire departments between baseline and follow-up collections. A similar minimum exposure dataset is being developed for wildland firefighters, adapted for their operations. For individual projects where departmental data are not easily obtained (eg, volunteer fire departments) or additional exposure information is needed (eg, fire cause investigators), the participating firefighters have also been asked to complete either the NFORS or PER exposure tracking application.

Textbox 2. Minimum dataset for structural fire department.

- Participant identification number
- Date range (participant's enrollment to specified follow-up date)
- For each type of fire within the date range
  - Run number (if future information on a fire is needed)
  - Date and time of call
  - Type of fire (eg, structural and vehicle)
  - Elapsed time on scene
  - Rank
  - If available, job assignment on the fire (eg, rapid intervention crew)
- Total number of emergency medical service calls during the date range

Industrial Hygiene Evaluation

For some substudies (eg, trainers in the expansion study), industrial hygienists are present during fire responses and conduct environmental monitoring, such as area and personal air sampling. Exhaled breath samples are also collected before and immediately after fire responses. Air samples are analyzed for compounds that are also measured in urine (eg, PAHs and VOCs) and exhaled breath (ie, VOCs) to allow for comparisons between airborne exposures and internal dose [22].

Furthermore, passive silicone samplers (eg, wristbands) may be worn during some substudy activities, such as wildland fire response, and analyzed for exposures that are measured in the air or biological samples (eg, PAHs and brominated flame retardants) [23-25].

JEM Creation

Incident records from fire departments and self-reported NFORS or PER records will be modeled against quantitative exposure data (ie, urinary and blood concentrations) to identify the primary determinants of the systemic exposures. This allows for an evaluation of the association of fireground and emergency medical service exposures with measured exposure biomarkers (eg, serum PFAS or brominated flame-retardant measurements) and outcomes (ie, epigenetic markers) [26-28] and can also be used to estimate exposures using the exposure tracking application data. Within the JEM, exposures among the different firefighter subgroups and job titles will be compared to identify how exposure varies for specific roles within the fire service, culminating in the creation of a JEM.

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Effects Assessment

Overall Approach

Effects assessment by the FFCCS includes measurement of biomarkers of effect related to disease pathways and evaluation of cancer and other priority disease outcomes. Biomarkers of effect have included epigenetic markers, such as peripheral blood DNA methylation; microRNA expression; serum anti-müllerian hormone (AMH); urine metabolome; and, in more limited settings, DNA mutations. The use of additional markers is anticipated in the future. Cancer and other priority disease outcomes are evaluated through self-reporting on annual follow-up surveys, which may be supplemented by FFCCS participants' voluntary participation in the National Firefighter Registry (NFR) for cancer [29] and plans for medical records requests to document cancer diagnosis.

Biomarkers of Effect

Cancer is a multistage process with a latency period between exposure and the onset of disease from as short as 5 to >30 years [20]. Molecular biomarkers, including epigenetic alterations, reflect subtle biological changes that occur following exposures that can contribute to subsequent disease development. The epigenome consists of alterations to the genome that do not change the underlying DNA sequence but can be inherited across cell divisions and influence gene regulation. Epigenetic modifications include noncoding RNA expressions, such as microRNAs and DNA methylation. The epigenome controls normal cellular function by regulating gene expression, but aberrant epigenetic modifications contribute to nearly all known disease processes, including cancers [30-33]. While the epigenome differs by cell and tissue type, blood is commonly used as a surrogate tissue in epidemiological studies. Analyzing epigenetics in firefighters' blood samples and linking these markers to acute or cumulative exposures can reveal subclinical changes that may increase cancer risk.

AMH is a marker of functional ovarian reserve routinely tested during fertility treatments and a proxy for reproductive health, given its association with oocyte yield, infertility diagnosis, time of menopause, miscarriage, and preterm birth. AMH levels steadily decline with age to mirror the decline in the number of oocytes [34]. AMH is, therefore, used for clinically monitoring natural and iatrogenic declines in ovarian function [34,35]. Adverse mental health conditions, including posttraumatic stress disorder and anxiety, have been shown to influence fertility [36] and AMH levels [37]. In addition, AMH levels are susceptible to alterations by inhaled exposures, including smoking and burning fuel for heating or cooking [38]. This supports previous research showing that smoking increases the risk of infertility [39] and earlier age at menopause [40]. Smoking and biomass fuel burning result in similar combustion products, including PAHs, and PAH exposure has been shown to decrease AMH levels [41].

The metabolome can serve as a surrogate composite measure of response to stressor and environmental exposure profiles and may elucidate mechanisms linking exposures to disease. Metabolomic profiling systematically measures thousands of exogenous and endogenous metabolites and can provide key insight into subtle signatures of cancer and other diseases, often before they become clinically apparent [42]. In addition to serving as early biomarkers of risk, prospective studies of metabolites may offer further advantages by identifying biological pathways and metabolites that may themselves be modifiable, either through dietary or other behavioral changes or enhancements to occupational protections. Differential urinary metabolites have been identified when comparing patients with and without breast cancer [43], prostate cancer [44,45], and bladder cancer [46], the latter including those associated with phenylacetate, propanoate, fatty acid, pyruvate, arginine, glycine, and serine metabolism, as well as bile acid biosynthesis. An untargeted metabolomics study of patients with prediagnostic breast cancer found that syringol (a biomarker of wood smoke) was predictive of future breast cancer incidence [47]. In our previous study of metabolomic changes in municipal firefighters after responding to structural fires, we identified changes in endogenous and exogenous metabolites (including the abovementioned metabolites and syringol) that overlap with cancer risk factors, cancer pathways, and specific cancers [48]. Repeated acute stress from fireground exposures on the biological systems that produce these metabolites may contribute to long-term cancer risk. Evaluation of the specific perturbed metabolites for their ability to predict future cancer is needed and may offer a compelling starting point for interventions. As an example, aryl hydrocarbon receptor activation has been associated with cancer risk [49], and we previously identified that aryl hydrocarbon receptor activity increased in firefighter urine extracts after fighting a fire [50].

Cancer and Other Disease Outcomes

Disease outcomes (eg, cancer diagnoses) are evaluated through self-report on the annual follow-up survey, with the potential to add other diseases in the future as requested by the fire service. To validate these self-reported cancer outcomes and capture outcomes that are unable to be obtained through FFCCS survey mechanisms, the FFCCS is in the process of promoting participant cross-enrollment and establishing a linkage with the NFR for cancer. The NFR is a congressionally mandated voluntary registry of firefighters established by NIOSH. NFR participants, including those cross-enrolled in FFCCS, will be followed prospectively for any cancer diagnoses by periodically linking with all state cancer registries across the United States. Enrollment in the NFR is being offered during new FFCCS enrollments, and a consent addendum will be offered to existing FFCCS participants during study follow-up visits. Separately, FFCCS processes are being implemented to request medical records that document cancer diagnosis reported on annual follow-up surveys.

Reporting Results

The FFCCS measures and reports back to participating firefighters a broad range of hazardous exposures and their effects, including urinary levels of PAH metabolites reflecting combined inhalation, dermal, and ingestion exposures, as well as serum levels of PFAS and AMH. Individual report-back templates are also being developed for DNA methylation epigenetic clocks and silicone wristband exposure monitoring results. These personalized results enable firefighters to better

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understand their exposures and are critical to reporting information back in a timely manner. In addition, a summarized report without personal identifying information is provided back to the fire department. Newsletters are used to share findings from individual FFCCS substudies and are distributed to all FFCCS participants. Furthermore, the study website [51], contains contact information, information on overall organizational structure, substudies, and publications.

External Data Requests

Data security is at the forefront of all stages of FFCCS data collection and use. FFCCS study participants have expressed concern about the potential use of data outside uses approved by the FFCCS research team and OPB. Specifically, they worry that the FFCCS data could be used against them by their department, municipality, or other administrative entity should they have a workers' compensation cancer claim or other adverse event. Therefore, in addition to protections in place by the IRB, the FFCCS has obtained a Certificate of Confidentiality from the National Institutes of Health. The informed consent document explains to participants how their data will only be shared with approved research team members and provides information about the Certificate of Confidentiality. To comply with data-sharing requirements associated with specific federal funds (eg, National Institutes of Health), the FFCCS website contains contact information that can be used for requesting deidentified study information. Requests will be reviewed by the FFCCS OPB for their alignment with the overall FFCCS mission and best fit of current datasets to answer requesters' research questions. For data limited to specific departments, the external request will also be reviewed through a process determined by the fire service research liaisons of the participating fire departments. The process for requesting biological samples from the biobank for research is currently under development.

Results

Enrollment to Date

The FFCCS has enrolled 6200 firefighters from >275 fire departments across 31 states as of September 2024. The demographic and firefighter subgroup characteristics of the participating firefighters are shown in Table 2.

Table 2. The Fire Fighter Cancer Cohort Study participants' demographics and department type (N=6200).

Demographics and department type	Recruits (n=1448, 23.4%), n (%)	Incumbents (n=4752, 76.6%), n (%)	Total, n (%)
Race or ethnicity			
American Indian, Alaska Native, Native Hawaiian, or other Pacific Islander	11 (0.7)	51 (1.1)	62 (1)
Asian	52 (3.6)	85 (1.8)	137 (2.2)
Black	80 (5.5)	116 (2.4)	196 (3.2)
Hispanic	368 (25.4)	769 (16.2)	1137 (18.3)
White, non-Hispanic	715 (49.4)	3234 (68.1)	3949 (63.7)
Other or multiple	71 (4.9)	227 (4.7)	298 (4.8)
Missing	151 (10.4)	270 (5.7)	421 (6.8)
Sex			
Male	1050 (72.5)	3927 (82.6)	4977 (80.3)
Female	346 (23.9)	756 (15.9)	1102 (17.8)
Missing	52 (3.6)	69 (1.5)	121 (2)
Department			
Career structural	1302 (89.9)	3106 (65.4)	4408 (71.1)
Volunteer	11 (0.8)	775 (16.3)	786 (12.7)
Wildland[a]	126 (8.7)	568 (12)	694 (11.2)
Airport[a]	18 (1.2)	322 (6.8)	340 (5.5)

[a]Some firefighters (n=28) are both wildland and airport firefighters.

The average age of participating firefighters is 37.8 (SD 11) years, including the age of recruits at enrollment (mean 29.3, SD 5 years) and the age of incumbents at enrollment (mean 40.3, SD 11 years). Of 6200 participants, the top 5 states by current enrollment include California (n=1843, 29.72%), Arizona (n=1278, 20.61%), Massachusetts (n=597, 9.63%), Florida (n=277, 4.48%), and Washington (n=273, 4.4%).

In addition to career municipal firefighters, separate grants have supported the enrollment of firefighter subgroups, including volunteers; trainers; fire investigators; and women, wildland, WUI, and airport firefighters. Of 6200 participants, 1102 (17.8%) are women firefighters, 196 (3.2%) are Black, 1137 (18.3%) are Hispanic, 3949 (63.7%) are White and non-Hispanic, and 298 (4.8%) are multiple or of another race.

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Career firefighters constitute 71.1% (n=4408) of our study participants, volunteer firefighters 12.7% (n=786), wildland firefighters 11.2% (n=694), and airport firefighters 5.5% (n=340), with some participants (n=28, 0.5%) categorized as both wildland and airport firefighters.

Biological Sample Collection, Analysis, and Repository

As of September 2024, a total of 11,738 blood samples have been analyzed for serum PFAS concentration by either the New Jersey Department of Health Public Health and Environmental Laboratories, Eurofins, or NCEH within the CDC. Furthermore, 1248 blood samples from women firefighters have been analyzed for AMH by Motive Biosciences (Webster), and 638 urine samples have been analyzed for hydroxylated metabolites of PAHs by the New Jersey Department of Health, NCEH, or the Human Health Exposure Analysis Resource Laboratory.

Early Study Results

The FFCCS has already expanded our knowledge of firefighter exposures to everyone on the fireground [52], increases in serum levels of PFAS in firefighters compared with the general population and the effects of workplace exposures [27,28,53], the effectiveness of exposure reduction protocols established by the fire service [54], differences in cancer prevention practices in the volunteer fire service [55,56], and cancer risk perceptions among women firefighters [57]. Furthermore, we have found marked reductions in serum AMH levels in female firefighters associated with self-reported clinical diagnoses of anxiety and posttraumatic stress disorder, as well as characterizations of stress and posttraumatic stress disorder [58-60]. Epigenetic findings in the FFCCS to date include the identification of DNA methylation loci and microRNA that differ in incumbent and recruit municipal firefighters [61,62]. When following up recruits over time (approximately 2 years of employment), microRNA and DNA methylation change, including in cancer-related genes [26,63]. We have also reported differences in epigenetic age, a biomarker of biological aging, by serum levels of PFAS and when comparing recruits with incumbents [64,65], as well as differential methylation of prostate cancer genes in association with years of firefighting and serum levels of PFAS [66].

In addition, we have compared metabolites in the urine of firefighters at baseline and after a fire and observed broad changes, including altered excretion of indole compounds, uremic toxins, several amino acids, and hormones and alteration of the vitamin B3 (nicotinate and nicotinamide) pathway [48]. We hypothesized that if disruption of uremic pathways and increased excretion of uremic toxins are experienced regularly, then multiple acute hits to this pathway may mediate firefighter's increased risk for urinary tract cancers. Moreover, we used the untargeted metabolomics results for hypothesis generation; for instance, we observed some overlap among elevated metabolites after fires with metabolites that have been implicated in Alzheimer disease and related dementias.

Discussion

Overview

The FFCCS provides a framework for community-engaged prospective evaluation of firefighter exposures, mechanisms of toxicity, and cancer outcomes through the integration of survey, biological, and exposure data. This work adds to the existing growing body of literature from firefighter cohorts around the world, including additional cohorts within the United States and other global cohorts in Korea, Australia, and other regions of the world [67,68]. These cohorts have examined markers of cardiovascular health, environmental exposures, the impact of disasters such as 9/11, and cancer incidence [69-71]. The FFCCS has contributed to scientific knowledge within the fire service and beyond, and with continued expansion and participant follow-up, the potential to identify important exposures, toxic mechanisms, effective exposure reduction, and chronic disease preventive activities will increase markedly. Additional health outcomes prioritized by the fire service and researchers, such as adverse reproductive effects, are also being evaluated.

Strengths

The strengths of the FFCCS include its ongoing engagement of the firefighter community in research, the multicenter prospective approach permitting evaluation of different firefighter subgroups, regional exposures and fire service practices, the inclusion of recruit and incumbent firefighters, and the establishment of a biobank. Participation of firefighters in all phases of the research helps ensure that the research questions address fire service concerns and that the research results can be used to inform fire service policies. Differences in cancer rates by geographic region have been noted in previous US studies of firefighters [2,3], and very little is known about cancer rates in US firefighters outside of male career structural firefighters, emphasizing the need for the multicenter approach to establishing a firefighter cancer cohort. This study has effectively prioritized the inclusion of women, with female firefighters making up >17% (1102/6200) of the participants despite women comprising only 9% of the overall US firefighting population [14]. The inclusion of recruit firefighters before live-fire exposure provides a comparison group to help identify changes specific to firefighting, adjusting for age differences between the 2 groups. Furthermore, the prospective nature of the study and collection of biomarkers of exposure and effect samples before the establishment of cancer is an essential strength of the study, along with the establishment of a biobank enabling future analyses on stored samples.

Limitations

The limitations of the FFCCS include the potential for self-selection bias; the lack of a defined nonfirefighter longitudinal comparison group; some types of self-reported survey information, such as occupational exposure history; and the lack of long-term funding. As participation rates vary among groups offered enrollment in the study, with enrollment among recruits generally >80% and incumbent enrollment generally <50%, there may be differences in exposures and biomarkers of effect when comparing firefighters choosing and not choosing to participate in the FFCCS. Although we adjusted for age, some

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longitudinal changes in measured biomarkers of effect may be due to age alone rather than occupational exposure. In addition, although firefighters generally tend to remain in the same department, only participants continuing to serve as active firefighters will be kept in the biomarker collection part of the study. Results from this study may also be impacted by the healthy worker effect [69,72]. The study includes self-reported survey information, which may be subject to recall bias. The lack of long-term funding may limit our ability to conduct regular follow-up evaluations, including blood and urine collection from all study participants outside of currently funded projects.

Future Directions

The FFCCS will continue to expand as we work toward reaching our target enrollment of 10,000 firefighters, focusing on the goal of advancing firefighter cancer control and prevention while evaluating other health conditions. Specifically, we will continue to enroll and categorize exposures among subgroups, such as women firefighters, understudied racial and ethnic groups, wildland firefighters, WUI firefighters, and firefighters responding to high-risk events. Expansion within these subgroups is critical to accomplishing the mission of the FFCCS. In addition, study findings will continue to be regularly communicated to participants and our fire service partners as the study progresses.

Conclusions

The establishment of the FFCCS, in collaboration with the fire service community, has provided a unique research platform to advance the understanding of firefighter exposures, help identify biomarkers of carcinogenic effect and cancer risk, and provide a setting for the observational evaluation of the effects of exposure reduction and wellness activities carried out by the fire service.

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Conflicts of Interest

None declared.

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Abbreviations

AMH: anti-müllerian hormone
CAPS: Firefighter Cancer Assessment and Prevention Study
CDC: Centers for Disease Control and Prevention

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EDTA: ethylenediaminetetraacetic acid
FFCCS: Fire Fighter Cancer Cohort Study
IARC: International Agency for Research on Cancer
IRB: institutional review board
JEM: job exposure matrix
NCEH: National Center for Environmental Health
NFORS: National Fire Operations Reporting System
NFR: National Firefighter Registry
NIOSH: National Institute for Occupational Safety and Health
OPB: oversight and planning board
PAH: polycyclic aromatic hydrocarbon
PER: Personal Exposure Reporter
PFAS: per- and polyfluoroalkyl substances
PI: principal investigator
REDCap: Research Electronic Data Capture
VOC: volatile organic compound
WUI: wildland-urban interface

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Protocol

Co-Designing an Antiracist Dental Health System: Protocol for an Aboriginal and Torres Strait Islander–Led Mixed Methods Study

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Abstract

Background: Racism arrived in Australia with colonization and its intentionally oppressive policies and actions toward Aboriginal and Torres Strait Islander Peoples. To a large extent, colonial and biomedical agendas are maintained by Australia's health system that underlies much of the racialized health inequities in the country. Dentistry significantly lags behind medicine and other health care areas in the uptake of antiracism, with the dental accreditation body only acknowledging racism as a determinant of oral health in 2022.

Objective: This project will comprehensively co-design strategies for an antiracist dental health system in Australia through the following objectives: (1) development of an antiracist curriculum for dental students; (2) workforce strategies that support the attraction, retention, and well-being of the Aboriginal and Torres Strait Islander dental workforce; and (3) oral health promotion training for Aboriginal Health Workers/Practitioners.

Methods: This project is grounded in decolonizing and Indigenous methodologies, which guide our ways of working at the knowledge interface. Co-design Yarning sessions will inform the development and implementation associated with each of the objectives through tabulation and narrative synthesis of sessions. Objectives will be evaluated with both quantitative and qualitative measures and analyzed accordingly with inverse probability of treatment weighting, content analysis, or reflexive thematic analysis.

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Results: The study received ethical review approval in February 2024 and received funding in June 2024. The co-design phase for each objective will run from July 2024 to February 2025. The dental curriculum will be developed in 2025 and delivered to the 2026 student cohort. Evaluation data will be collected from the comparator student cohort in 2025 and the implementation cohort in 2026. Data collection for the development of workforce strategies will be collected from October 2024 to July 2025; the framework will be developed from August to December 2025 and disseminated in 2026. Oral health promotion training will be developed from August to February 2024, implemented from March to June 2025, and qualitative evaluation data will be collected between July and September 2025.

Conclusions: The proposed research will develop an antiracism curriculum for dental students, a tailored Aboriginal and Torres Strait Islander dental workforce framework, and an oral health promotion training program for Aboriginal Health Workers/Practitioners. The processes and final outcomes of this research will be scalable and able to be tailored to different contexts. Together, these strategies will build oral health knowledge at the Community level, in turn supporting Aboriginal and Torres Strait Islander self-determination of oral health.

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KEYWORDS

racism; anti-racism; dentistry; Aboriginal and Torres Strait Islander; dental workforce; dental curriculum; oral health promotion; Aboriginal Community Controlled Health Organizations; Aboriginal Health Workers/Practitioners

Introduction

It is widely accepted that social determinants of health [1,2], and for some, commercial determinants of health [3], directly impact one's oral health outcomes. There remains a disconnect between the role structural factors play in shaping oral health among clinicians, public servants, and researchers [4]. Beyond debating the use of race as an indicator for certain dental procedures [5] or to assess racial disparities in oral health outcomes [6], limited action has been taken to address the role structural racism plays in creating oral health inequities [7,8]. Both cultural and structural racism emerge within dentistry, impacting oral health outcomes in several ways. At a cultural level, racism is perpetuated through interpersonal racism and implicit bias, whereby clinicians discriminate against patients on the basis of race and ethnicity [9]. At a structural level, racism manifests as institutional practices, policies, and ideologies that inherently afford advantages to some racial groups over others [10,11]. Racism is, in fact, a dental public health threat due to its intentional deprivation of access to health equity and sovereignty (the rights and abilities for Communities to make their own decisions about all aspects of their lives), further entrenching cycles of disease burden within racially oppressed communities [9].

Racism arrived on the shores of Australia in 1788 with colonization and the intentional dehumanization of Aboriginal and Torres Strait Islander Peoples by settler colonists [12,13]. Colonization violently established whiteness as the societal and human ideal in Australia, and indeed in other settler colonial nations, based on the rights of "white possession" and individual sovereignty [14]. Aboriginal and Torres Strait Islander Peoples had better oral health outcomes than non-Indigenous people up until the 1970s, which demonstrates that the oral health inequities are grounded in persistent racialized ideologies of colonial care [15]. The institutionalization of care within Australia via state welfare maintains "White ignorance" [16] and colonial ideologies within the reality of ongoing and systemic racial violence [17]. While medicine and other areas of health care have been slow in the uptake of an antiracist agenda into their conduct of practice, dentistry significantly lags behind [7,9]. Internationally, only a few antiracism initiatives have been undertaken within dentistry, including 1 training program for dental students [18] and 1 regulatory framework [19]; there have been no Australian-based initiatives. The accreditation process for all dental practitioners, as established by the Australian Dental Council, failed to name racism as a determinant of oral health until 2022 [20]. This exemplifies the racialized foundations of the Australian dental health system and provides rationale for why dental decay remains the most prevalent chronic condition experienced by Aboriginal and Torres Strait Islander Peoples across all age groups [21]. Racism embedded in Australia's infrastructure is not restricted to the dental health system but manifests across mutually reinforcing structures, from child removal and incarceration [22] to missing and murdered women and children [23]. Widespread and ongoing stereotyping across all aspects of Australian society perpetuates racialized discourses about Aboriginal and Torres Strait Islander Peoples and leads to embedded discrimination in systems experienced when accessing care, which negatively affects access to health care and culminates in negative health outcomes [24]. There remains a relational and moral obligation to counter racism in its various forms, particularly in the dental context where moral ignorance has fed the normalization of racism as the status quo since dentistry's inception [25].

Structural racism in Australia's dental health system creates differentials in professional leadership, workforce representation, advocacy, and access to services. For example, while Aboriginal and Torres Strait Islander Peoples represent 3.8% of the Australian population, as of 2020, only 0.4% of all practicing dentists were Aboriginal and/or Torres Strait Islander. Across Australia's 9 dental schools and peak national dental bodies, none of these institutions are led by an Aboriginal and/or Torres Strait Islander person. Such a degree of underrepresentation is one of the largest among all health professions [26], positioning dentistry significantly behind the targets of the National

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Aboriginal and Torres Strait Islander Health Workforce Strategic Framework and Implementation Plan [27]. These imbalances created and perpetuated by structural and cultural forms of racism also normalize expressions of interpersonal racism in dental clinical settings. Research indicates that patients' race affects providers' clinical decisions [28], which affects quality of care. Due to power imbalances between students and educators or patients and clinicians, oral health practitioners in Australia are rarely accountable for discriminating against Aboriginal and Torres Strait Islander patients, reflecting the inability of the dental health system to provide culturally safe care. This intensifies oral disease inequities, as evidenced by lower dental attendance for Aboriginal and Torres Strait Islander patients [29]. Subsequently, oral health practitioners' assumptions that racially minoritized patients do not give importance to oral health are reinforced by the racial ideologies that initially influenced oral health inequities. The impact of oral diseases spans across the life course, affecting outcomes such as identity, chronic diseases, lost economic productivity, social and emotional well-being, as well as difficulty finding a job [2]. The Australian dental system's inability to properly address the oral health needs of Aboriginal and Torres Strait Islander Communities demonstrates how oral health inequities are rooted in racialized systems that continue to perpetuate a cycle of trauma and intergenerational disadvantage for Aboriginal and Torres Strait Islander Peoples.

It is critical to apply collaborative solutions that tackle racism within Australia's dental health system and promote the delivery of culturally safe and quality dental care for Aboriginal and Torres Strait Islander Communities [7]. Grounded in decolonial methodologies, we will comprehensively co-design strategies that mitigate the impacts of racism across different contexts within Australia's dental health system.

Study Aims

This project aims to implement evidence through co-designed strategies that apply best practices for dental health system changes and foster the provision of antiracist dental care in Australia through the following objectives (Textbox 1).

Textbox 1. Co-designed objectives.

- Develop and implement an antiracist curriculum for dental students that can be robustly evaluated. The benefits include an evidence-based model and pedagogical framework for a curriculum that will provide the necessary foundation for antiracist practice across Australia's dental health system.
- Generate a framework of strategies to be implemented across a number of professional settings (ie, dental organizations, dental schools, and dental clinics) to support the attraction, retention, and well-being of the Aboriginal and Torres Strait Islander dental workforce. The benefits include fostering support and growth of the Aboriginal and Torres Strait Islander dental workforce in Australia.
- Create and evaluate an oral health promotion training module for Aboriginal Health Workers/Practitioners (AHW/P). The benefits include supporting Aboriginal and Torres Strait Islander well-being by sharing oral health promotion information in a manner that equips AHW/P with knowledge to have everyday yarns about oral health with Community members.

Methods

Positionality Statement

Our appreciation of the importance of positionality and relationality has largely been influenced by decolonizing frameworks and Indigenous methodologies [30,31]. As a collective coming to this work, we intentionally position ourselves within these processes to acknowledge our connections, relationships, and responsibilities [32-34]. As a team comprised of Aboriginal and Torres Strait Islander researchers, dental professionals, Community leaders and non-Indigenous researchers, we are grateful for the opportunity we share to work alongside Aboriginal and Torres Strait Islander Communities. We are led by a proud Yamatji woman and a Project Governance Committee (PGC) consisting of 25 Aboriginal and Torres Strait Islander leaders from across so-called Australia. The supporting team consists of Indigenous and non-Indigenous members from Turtle Island, Australia, Brazil, India, and Aotearoa. The strength of this team is in our diverse perspectives and experiences related to racism, our shared values, and our commitments to antiracist health care, equity, social justice, and self-determination. The intentional development of this team facilitates Aboriginal and Torres Strait Islander guidance in decision-making, leadership in data collection and analysis, and ensures robust interpretation of findings. We remain grateful for our relational foundations of this work and committed to (un)learning throughout our individual and collective life-long journeys of antiracism.

Methodology

Decolonizing Methodologies

This study will be informed by decolonizing methodologies, and therefore, grounded in an understanding of settler colonialism in Australia and resistance to colonial marginalization from dominant culture through assertions of individual and collective sovereignty [35-37]. Whereby, dominant culture is understood as aligning with colonial and biomedical values and health systems. In decentring colonial values, this project will follow processes that center Aboriginal and Torres Strait Islander identity, cultural and collective action, as well as self-determination [38,39]. Decolonizing methodologies counteract colonial research processes that are embedded in a history of appropriation, exploitation, misrepresentation, and unethical practices [31,39-42]. The generation, validation, and dissemination of knowledge through colonial research practices enable control of dominant ideologies that subordinate Indigenous knowledge systems [40,43]. The failure of colonial research practices to adequately address Aboriginal and Torres Strait Islander experiences of inequitable health is fundamentally related to the power held by those who determine the value of knowledge and research processes [38]. Therefore, decolonizing methodologies will be used in this

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project to explicitly acknowledge the impacts of colonization and settler colonialism, resist dominant deficit discourses of Aboriginal and Torres Strait Islander ill health [44], and advance Aboriginal and Torres Strait Islander health sovereignty. In the context of dentistry, this requires our team and our project challenge statements and beliefs rooted in colonial and racial ideologies, demand truth-telling, and collectively commit to (un)learning. As Aboriginal and Torres Strait Islander research leadership and governance is critical in ensuring respectful, reciprocal, and culturally safe practices, this project will be governed by a PGC. In undertaking this work from a decolonial standpoint, we acknowledge our continued reliance on colonial processes for findings to have translatable impacts, particularly with regard to advocacy for health system reform. Therefore, we will equally value and weave together 3 types of evidence: lived experiences, professional experience, and academic evidence. We recognize that research will never be entirely "decolonized," as research itself is rooted in colonial foundations; however, we contend that there remains an ethical compulsion to create and maintain spaces that drive Aboriginal and Torres Strait Islander–led programs (Figure 1).

Figure 1. Ways of working conceptual model that weaves together lived experiences, academic evidence, and professional experiences throughout iterative processes that center around shared values.

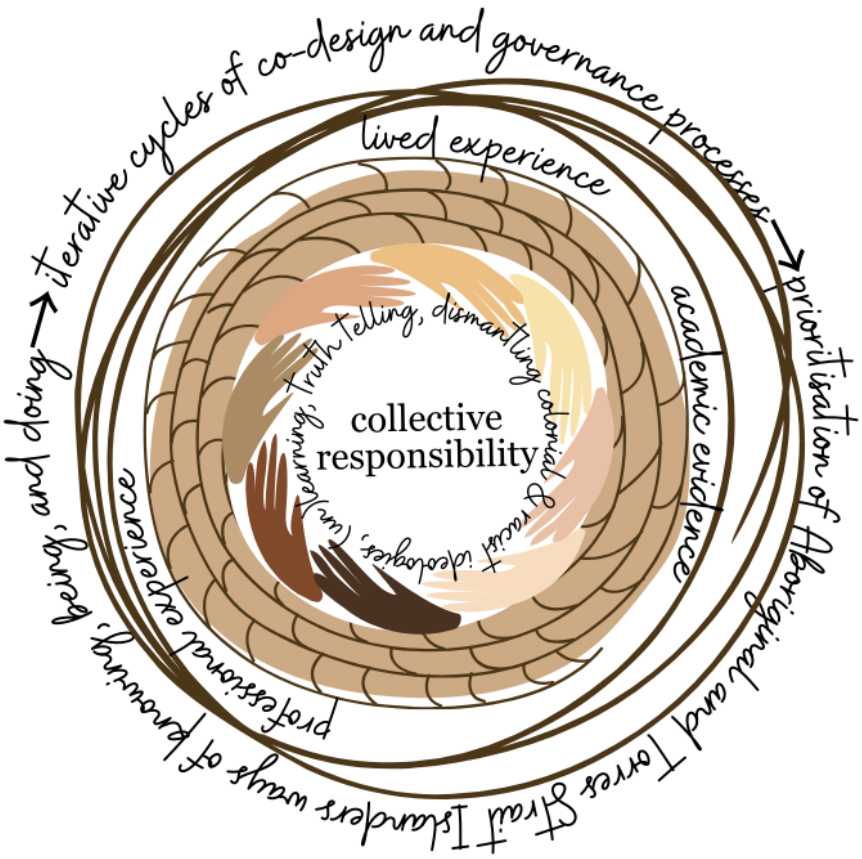

Indigenous Research Methodologies

Employing Indigenous research methodologies and methods supports decolonial values and processes by shifting paradigms and power from colonial academic institutions to Aboriginal and Torres Strait Islander ways of knowing, being, and doing [45]. Indigenous research methodologies necessitate embedded relationality from project inception through to sharing of findings [30,37]; the notion of relationality is represented by the hands sharing our collective responsibilities in Figure 1. The iterative process of co-design Yarning with external stakeholders and internal team members underpins the entire project. Yarning sessions among the research team, throughout the co-design phase, and beyond will dynamically move through the Yarning Process developed by Bessarab, from Social Yarns to Research, Work, and Topic Yarns, as well as Collaborative and Therapeutic Yarns, and back again [46]. This commitment to continuous and relational Yarning [47,48] is critical when exploring (anti)racism due to the need for ongoing individual and collective reflexivity [49] and the creation of a spaces that foster agency for individuals to share information and opinions at their discretion [37]. Our approach to this research is guided by our relationships, prioritizes Indigenous research methods, is accountable to and informed by Aboriginal and Torres Strait Islander Communities, and is led by our Aboriginal and Torres Strait Islander PGC [50].

The PGC is comprised of leaders from partnering organizations, with whom we have established relationships, to ensure that all aspects of the project are conducted in a culturally safe manner that prioritizes self-determination, demonstrates respect, and privileges Aboriginal and Torres Strait Islander ways of knowing, being, and doing [37,45]. Membership includes Aboriginal Community Controlled Health Organizations

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(ACCHOs) representatives, Elders, Aboriginal and Torres Strait Islander dentists, current Aboriginal and Torres Strait Islander dental students, Community leaders, representatives from regulatory and organizational dental bodies, and members of the research team. Aboriginal and Torres Strait Islander members of the PGC are honored not only in their roles as academics, health practitioners, or Community leaders but also for their roles as mothers, fathers, aunties, uncles, and grandparents with lived experiences and vested interest in the oral health of their families and Communities. The PGC will provide governance and input into curriculum development, training development for Aboriginal Health Workers/Practitioners (AHW/P), data interpretation, and dissemination of findings. PGC meetings will be held quarterly throughout the duration of the project, with feedback sought outside of meetings on an ongoing basis. The PGC will be comprised of more than 75% Aboriginal and Torres Strait Islander leaders and will ensure that project processes and outcomes remain relevant and in alignment with Community values, needs, and experiences (Multimedia Appendix 1).

Knowledge Interface

Working at the knowledge interface [51] within colonial research spaces using decolonial and Indigenous research methodologies allows different knowledge systems to be brought together with the aim of generating contextual evidence and novel insights. This requires reciprocal and trusting partnerships that center, rather than marginalize, Aboriginal and Torres Strait Islander ways of knowing, being, and doing [45]. We will prioritize a collaborative approach to knowledge creation through iterative co-design processes across all project objectives whereby lived experiences, professional experiences, and academic evidence are valued equally, which is visually represented by the hands supporting our collective responsibility in Figure 1. To navigate the epistemological tensions that exist when working in decolonial ways at the knowledge interface, as a team we will continuously engage in individual and collective reflexivity through weekly team meetings, independent journaling, and supporting (un)learning processes. Reflexivity requires each member of the team, individually and as a collective, to examine, interrogate, and reflect on our beliefs, feelings, and actions and how they are influencing decision-making. This process of engaging in decolonial knowing has previously been termed “dialoguing with the tensions,” and is a critical step in moving from individual immersion in resources and knowledges to collective and transformative discussions and action [52]. Positioning our project at the knowledge interface is a significant strength of our approach, as this enables the prioritization of decolonial ideologies and Aboriginal and Torres Strait Islander ways of knowing, being, and doing within colonial academic institutions and biomedical health systems.

Study Design

As a result of relationships and experiences, this project brings together Aboriginal and Torres Strait Islander leadership, lived experiences, Community engagement, and research experience across Australia. The project is grounded in collaborations between the University of Adelaide’s Indigenous Oral health unit, 3 ACCHOs (Yadu Health Aboriginal Corporation in Ceduna, Moorundi Aboriginal Community Controlled Health Service in Murray Bridge, and Umoona Tjutagku Health Service in Coober Pedy), the South Australian Dental Service, the Indigenous Dental Association of Australia (IDAA), the Australian Dental Association, and the Australian Health Practitioner Regulation Agency. The 3 objectives of this study described earlier occur over 3 phases: co-design, implementation, and evaluation and dissemination (Figure 2).

Co-design Yarning sessions will provide the foundation of enquiry for each of our 3 objectives [46]. Multiple cycles of Yarning sessions, as a qualitative research method for data capture, will be required for the iterative co-design process. Yarning sessions will be guided by Aboriginal and Torres Strait Islander team members [48], ensuring the prioritization of Aboriginal and Torres Strait Islander research leadership and engagement, respect, Community benefits, culturally grounded approaches, inclusive partnerships, and robust evidence-based decision-making [53]. In accordance with co-design principles, each Yarning session will be centered around a collective goal, and those engaging in sessions will share the responsibility to prioritize equity, partnership, inclusivity, respect, and trust throughout the sessions [48,53]. Co-design Yarning sessions will be driven by 3 types of evidence: lived experience, professional experience, and academic evidence. Existing evidence pertaining to the collective goal of sessions will be collated by our team and disseminated to co-design participants prior to Yarning sessions. Using the knowledge interface as our guiding methodology, we will bring together lived experiences, Community-driven evidence, academic evidence, and professional experiences to determine appropriate next steps as per the respective objective (Figure 1).

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Figure 2. Study design illustrating the interaction between methodologies, methods, and analysis across the objectives and phases of the project. AHW/P: Aboriginal Health Workers/Practitioners; IPTW: inverse probability of treatment weighting.

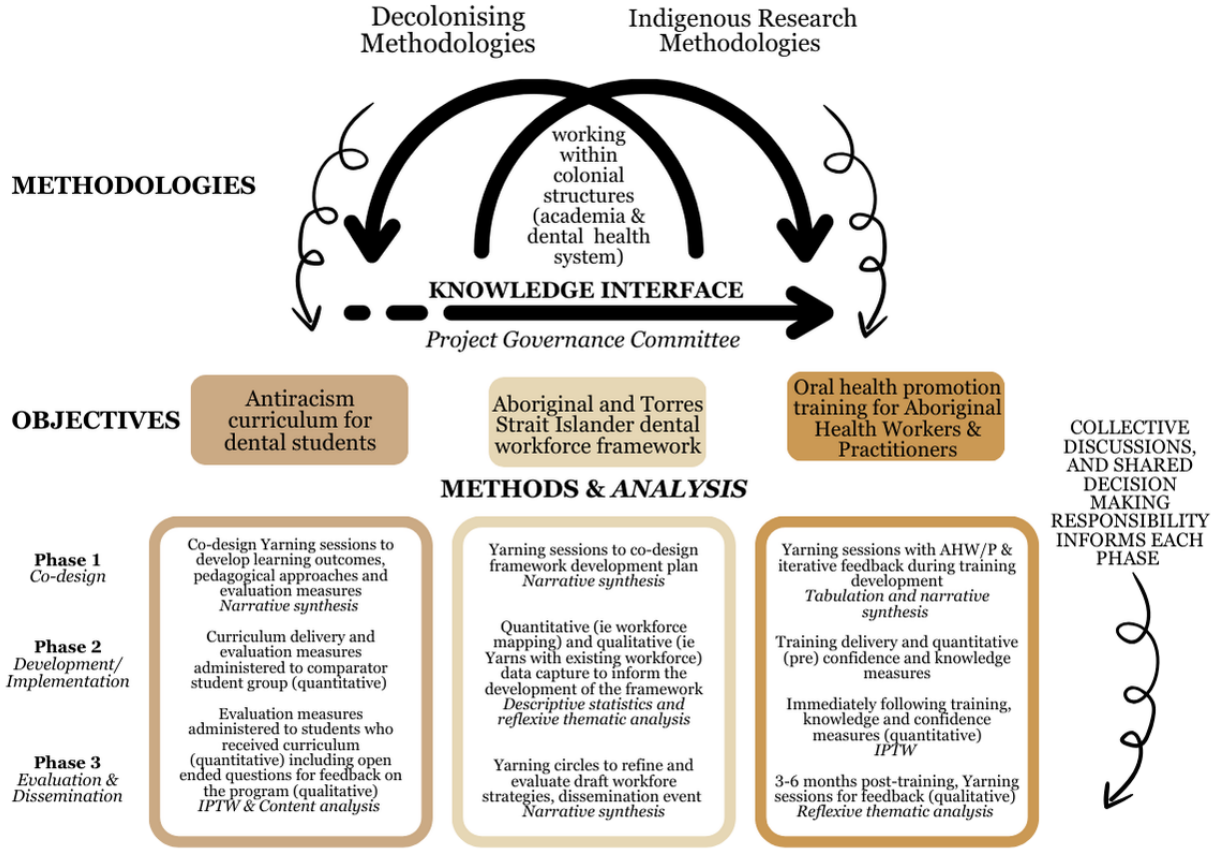

Objective 1: Development of an Antiracism Curriculum

Phase 1: Co-Design Yarning

The co-design Yarning sessions for objective 1 will be an iterative process that actively engages various stakeholders to design and co-construct the curriculum. The collective goal of Yarning sessions will be to develop an antiracism curriculum that equips students to identify racism within the dental care system as well as develop knowledge, skills, and attitudes needed to mitigate racism and its associated consequences. The sessions will be informed by a scoping review of existing antiracism training programs for health trainees (ie, medical and nursing students) and a critical review of evaluation measures of antiracism trainings in health contexts. Overall, the co-design process will be guided by the domains of the Aboriginal and Torres Strait Islander Health Curriculum Framework: respect, communication, safety and quality, reflection, and advocacy; these domains comprise key descriptors such as racism, cultural knowledge, history, strengths-based approaches, equity, and human rights [54]. Working at the knowledge interface, academic evidence from the 2 reviews will be woven together with professional experiences and lived experiences to identify the relevant, theoretically sound, and feasible learning outcomes, pedagogical approaches, and evaluation measures to be included in the curriculum structure.

Phase 2: Implementation

Students enrolled in year 4 of the bachelor of dental surgery at the Adelaide Dental School (approximately 70 students) will receive the antiracism curriculum as a core component of the programs. We will pilot the curriculum with students enrolled in 2026, allowing approximately 1 year for curriculum development. The comparator group will be students enrolled in the same year in 2025. The comparator students, all things being equal, will have access to no educational offerings that are discernibly different from the study cohort, apart from receiving the antiracist curriculum. Multiple pedagogical techniques will be used as determined by co-design sessions; this may include cultural immersion, expert-facilitated small group workshops, and clinical simulation activities. Small group tutorials (flipped classroom, with digital short lectures and video or text resources) and simulation exercises will take place in standard tutorial rooms and workshop areas. The curriculum will be delivered by the research team and invited guests who have a combination of lived experiences, expertise in empirical research on racism in health care settings, and extensive training in population health teaching. Those delivering the curriculum will undergo multiple antiracism training programs and will create space for ongoing collective discussions that allow all team members to continue “dialoguing with the tensions” and ensuring decentering of colonial and racialized ideologies [52].

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Phase 3: Evaluation and Dissemination

Both student groups (2025 and 2026) will complete a set of evaluation measures related to curriculum competencies at the end of their respective years. The evaluation items will be directly informed by the co-design process and related to antiracist behaviors and knowledges, such as the Harvard Implicit Association Test [55] and the Anti-Racism Behavioral Inventory [56]. For students who receive the antiracism curriculum, evaluation will also include open-ended questions that provide an opportunity for feedback on the curriculum [57]. It is important to note that while we will assess knowledge development among students, we are not interested solely in direct comparisons but also in the suitability and sustainability of including antiracism in the curriculum across all dental programs moving forward.

Objective 2: Supporting the Attraction, Retention, and Well-Being of the Aboriginal and Torres Strait Islander Dental Workforce

Phase 1: Co-Design Yarning

Working in partnership with the IDAA, objective 2 will develop meaningful and effective strategies to recruit, support, graduate, and sustain Aboriginal and Torres Strait Islander dental practitioners. Currently, there is minimal infrastructure supporting the Aboriginal and Torres Strait Islander dental workforce within Australia; therefore, co-design Yarning sessions will aim to (1) identify quantitative metrics to be captured with regard to current workforce that can inform strategies (ie, number of Aboriginal and Torres Strait Islander staff within dental schools); (2) identify qualitative data to be collected to inform workforce strategies (ie, directed yarns with existing dental practitioners); and (3) identify key stakeholders important for the dissemination of workforce strategies at the end of the project, so that engagement and relationship building can co-occur throughout development. Prioritizing relationality is key to our collective approach to research and the iterative processes of co-design in this project [30]; hence, the importance of identifying workforce stakeholders at the beginning of the project to ensure relevance of workforce strategies and uptake of recommended strategies among stakeholders. The feedback from these co-design Yarning sessions will directly inform our "development plan" for the workforce strategies.

Phase 2: Development

Based on collective discussions during co-design Yarning sessions, we will seek to collect data that align with the development plan. We anticipate both qualitative and quantitative data will be collected during the development phase. This will likely include mapping of current Aboriginal and Torres Strait Islander leadership and employment in Australian dental schools and peak dental bodies (quantitative) and Yarning about experiences of Aboriginal and Torres Strait Islander dental practitioners and students with existing support pathways available (qualitative). In an iterative fashion, we will share this data back with IDAA, our PGC, and other stakeholders involved in the initial co-design Yarning sessions. We will organically begin to collate data as related to the 6 strategic directions outlined in the National Aboriginal and Torres Strait Islander Health Workforce Strategic Framework and Implementation Plan [27] (Figure 3). The final step, once all data outlined in the development plan is collected, will be to develop a draft of the workforce strategies, with leadership from IDAA and our PGC.

Figure 3. Adapted strategic directions of the National Aboriginal and Torres Strait Islander Health Workforce Strategic Framework and Implementation Plan [27].

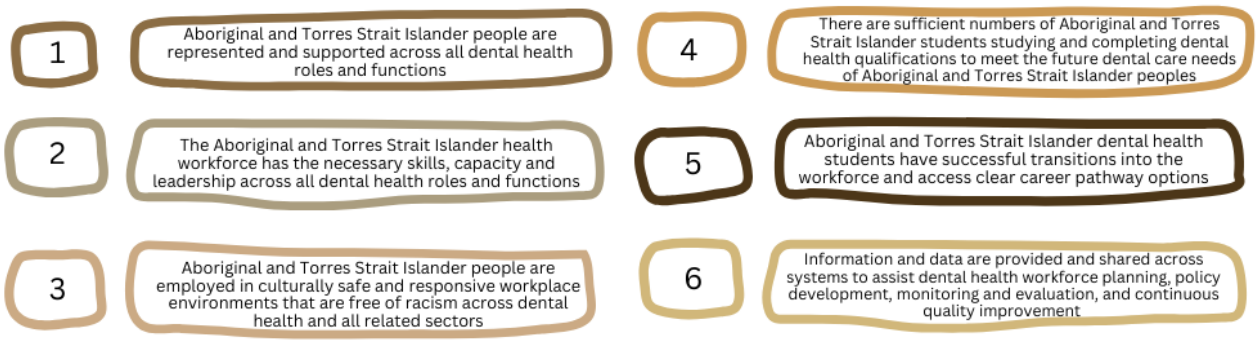

Phase 3: Evaluation and Dissemination

The draft workforce strategies will be shared widely with stakeholders involved throughout development, as well as others with vested interests in the dental workforce. Feedback on the workforce strategies will be garnered in a collective workshop format where everyone comes together to review and share any remaining considerations for the final draft of the workforce strategies. Also at this time, stakeholders will review dissemination plans from the initial co-design Yarning sessions and discuss any other pathways for advocacy and knowledge sharing to support the implementation of the workforce strategies.

Objective 3: Oral Health Promotion Training

Phase 1: Co-Design Yarning

Oral health promotion training for AHW/P is a previously identified Community need [58,59]. We will conduct a scoping review to identify existing oral health promotion materials and previous training programs for Indigenous Health Workers globally. This academic evidence will provide information for co-designing Yarning sessions with AHW/P, whereby both lived experiences and professional experiences will be shared by staff at each of the 3 ACCHO sites. To ensure that this program is relevant and easily integrated by AHW/P, the co-design Yarning sessions will discuss (1) what information

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is most important to be included in the training; (2) the format of the training sessions; and (3) the evaluation of the training. Support provided for different oral health topics from AHW/P will be tabulated, and qualitative data (audio recordings, text feedback, and field notes) will be narratively synthesized. Data will then be used to develop a training outline, and in alignment with the iterative nature of our co-design approach, we will hold further Yarning sessions with our PGC, ACCHO management, and AHW/P prior to final training development. Information will then be expanded upon as based on the shared outline, and any queries raised during this process will be resolved by the PGC or ACCHO representatives. This iterative process is essential to ensure Aboriginal and Torres Strait Islander leadership drives community-based actions to address oral diseases, in alignment with the National Aboriginal Community Controlled Health Organization (NACCHO) strategic directions [60].

Phase 2: Implementation

The pilot of the AHW/P oral health promotion training program will be implemented at 3 partnering ACCHOs in South Australia who have identified the lack of oral health promotion training for their AHW/P staff as a priority area (Yadu Health Aboriginal Corporation in Ceduna, Moorundi Aboriginal Community Controlled Health Service in Murray Bridge, and Umoona Tjutagku Health Service in Coober Pedy). Training will be delivered by team members who have established relationships with AHW/P at each site.

Phase 3: Evaluation and Dissemination

Prior to the delivery of the training program, AHW/P knowledge and confidence on promoting oral health will be discussed and recorded via a short questionnaire. Immediately following the delivery of the training program, the same questionnaire will be provided to AHW/P to understand the impacts of the training program. In total, 3-6 months following delivery of the training, Yarning sessions with AHW/P at all sites will be conducted to debrief on the impact of training and specifically understand any enablers and challenges of transferring knowledge gained during the training program into everyday practice. The findings of the training evaluation will be disseminated to peak bodies, including the Aboriginal Health Council of South Australia, the Victorian Aboriginal Community Controlled Health Organization, and NACCHO, to strengthen capacity for advocacy of state-wide and nation-wide implementation of oral health promotion training for AHW/P.

Ethical Considerations

Ethical approval for this project has been obtained from the Aboriginal Health Research Ethics Committee (#04-23-1085), and the University of Adelaide's Human Research Ethics Committee (#38988). All study participants will be required to provide written informed consent. Data resulting from the project will be de-identified to protect participant privacy and confidentially. Reimbursement for time will be provided to participants who provide their expertise during co-design Yarning sessions to recognize their valuable contributions (Aus $50 [US $31.02] gift voucher suitable for each region will be provided per engagement in sessions).

Recruitment

This research will be conducted in partnership with Aboriginal and Torres Strait Islander Peoples, organizations, and stakeholders who have experience and knowledge related to each objective of the project. This will include ACCHO staff, research institutes, universities, training organizations, and national regulatory bodies. Participants for all objectives will be recruited using relational processes across our existing partnerships and networks [48,61]. We will seek to exhaust all relational mechanisms for recruitment and engagement, in alignment with decolonizing methodologies. Participants will be identified and mapped in our stakeholder database with information relating to their cultural and professional backgrounds, including lived experience to clinical and research perspectives, as well as geographic location. As members of the team are introduced to more people working in this space, we will collectively add stakeholders to our database to invite to participate in relevant aspects of the project. Participants for co-design and implementation of objective 3 will be primarily recruited directly through the ACCHO sites (Table 1). Participants who have English as a second or third language will also be invited; interpretation services will be offered to those who want to participate. Participants eligible for participation will be provided with information on participating in this project via email or hard copy depending on context. These documents will outline the purpose of the study, the rights of participants, and details regarding how data will be collected, analyzed, and disseminated.

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Table 1. Participant eligibility criteria for each project objective.

	Sample size	Participant eligibility criteria
Objective 1	n=50-60 (based on network mapping)	• Be aged 18 years and older. • Co-design phase: Have expertise and knowledge related to antiracism training or racism within Australia's health care system, including lived experience, clinical experience, and research experience in this area.
	n=140 (based on 2× typical enrollment)	• Implementation phase: Be enrolled in the bachelor of dental science program receiving the pilot antiracist curriculum.
Objective 2	n=70-80 (based on IDAA[a] data)	• Be aged 18 years and older. • Identify as an Aboriginal and/or Torres Strait Islander dental stakeholder or occupy a position related to the Aboriginal and/or Torres Strait Islander dental workforce (ie, University dental school dean).
Objective 3	n=40-50 (based on ACCHO[b] staff)	• Be aged 18 years and older. • Identify as an Aboriginal and/or Torres Strait Islander AHW/P or hold a management position at an ACCHO.

[a]IDAA: Indigenous Dental Association of Australia.

[b]ACCHO: Aboriginal Community Controlled Health Organization.

Data Analysis Plan

Objective 1

Data from a scoping review of previous antiracism training programs and a critical review of evaluation measures will inform a draft curriculum outline. During the co-design phase, this outline will be reviewed and discussed among key stakeholders for alignment with our 3 types of evidence: lived experiences, professional experiences, and academic evidence. Co-design will be an iterative process whereby feedback is included in the outline following each session for consideration in the following session. Feedback may include consensus from individual sessions to add topics, remove topics, or further explore new or related topics; this feedback will be visually and narratively incorporated into subsequent versions of the outline. Co-design data will either be audio recorded or documented via note-taking during sessions. Once the curriculum outline is established through collective decision-making among those engaged in this process and our PGC, we will revisit co-design Yarning sessions to expand the outline to a full curriculum. This will include discussions about pedagogical approaches and evaluation measures that align with the outline. All data collected throughout this iterative process will then be collated and narratively synthesized [62] to document the co-design process of the curriculum development.

Data captured during the implementation and evaluation phase will be quantitative (both student groups) and qualitative (only the 2026 group that receives training). Both groups will be administered the evaluation measures at the end of the semester of their respective year levels. We anticipate there will be approximately 70 students in each group. Student scores from both years will be adjusted using inverse probability of treatment weighting to account for potential differences in classroom composition, such as average student age, proportion of international students, and gender distribution [63]. Any textual data provided by students who receive the antiracism curriculum will be analyzed using content analysis [64].

Objective 2

Data gathered during the co-design phase will be narratively synthesized [62] and will inform the development plan for a framework of workforce strategies. Quantitative data related to mapping of Aboriginal and Torres Strait Islander leadership and employment in the dental health system will be analyzed with descriptive statistics. Directed yarns with Aboriginal and Torres Strait Islander dental practitioners [46] and students will be collectively analyzed by both an Aboriginal and/or Torres Strait Islander researcher and a non-Indigenous researcher using reflexive thematic analysis. Processes of analysis will include data familiarity, extensive discussion with the PGC regarding understandings and assumptions developed during the familiarity process, as well as initial identification of themes during inductive and non-structured coding [65]. These data will then be compared to the 6 strategic directions of the National Aboriginal and Torres Strait Islander Health Workforce Strategic Framework and Implementation Plan [27], and recommendations will initially be co-developed with IDAA and our PGC. Through an iterative process of co-design, stakeholders will be invited to provide feedback on the strategies prior to and during a collective workshop.

Objective 3

Data garnered through the co-design phase, including audio recordings, text feedback, and field notes, will be tabulated and narratively synthesized into a training outline. The development will be continuously informed and adjusted through iterative cycles of collective discussions as questions arise during development.

Prior to training delivery, AHW/P knowledge and confidence will be discussed and recorded via a short questionnaire. This same questionnaire will be completed immediately following the training program. Data will be analyzed using inverse probability of treatment weighting, similar to objective 1 [63], to understand any immediate changes among AHW/P as a result of the training. In total, 3-6 months following delivery of the training, yarns with AHW/P [46] will be conducted and audio

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recorded to understand the usability of the training program in everyday circumstances. Qualitative data from these directed yarns [46] will be analyzed using reflexive thematic analysis, as described earlier [65]. The analysis of the yarns will aim to identify patterns across the data that provide insights into improvements that can strengthen the usefulness of training for AHW/P.

Results

The study received ethical review approval in February 2024 and received funding in June 2024. The co-design phase for each objective will run from July 2024 to February 2025. The dental curriculum will be developed in 2025 and delivered to the 2026 student cohort. Evaluation data will be collected from the comparator student cohort in 2025 and the implementation cohort in 2026. Data collection for the development of workforce strategies will be collected from October 2024 to July 2025; the framework will be developed from August to December 2025 and disseminated in 2026. Oral health promotion training will be developed from August to February 2024, implemented from March to June 2025, and qualitative evaluation data will be collected between July and September 2025.

Discussion

Anticipated Findings

If dental inequities are to be eliminated, comprehensive understanding of the complex factors leading to inequitable oral health outcomes needs to be established. The structural racism embedded in Australia's dental health system plays a key role in these inequities. The proposed initiative is a novel and innovative project that builds upon over a decade of relationships, collaborations, and engagement with Aboriginal and Torres Strait Islander Community organizations and leaders. The outcomes will directly contribute to fostering an antiracist dental health system that prioritizes cultural safety, quality dental care, and Aboriginal and Torres Strait Islander leadership. This proposed research will generate evidence and outcomes amenable to translation into policy and practice change, including an antiracist dental curriculum, Aboriginal and Torres Strait Islander dental workforce strategies, and an oral health promotion training for AHW/P. These outcomes will directly enhance the training of non-Indigenous dental health practitioners and support the attraction, retention, and well-being of the Aboriginal and Torres Strait Islander dental workforce and the embedding of oral health within ACCHOs. These strategies will contribute to oral health knowledge at the Community level, in turn supporting Aboriginal and Torres Strait Islander self-determination of oral health. Translation of strategies and learnings will be achieved through dissemination of the research findings to health organizations, services, peak bodies, and universities involved in the research, and subsequent collective advocacy for adoption of evidence into practice guidelines at a practitioner, university, ACCHO, and regulatory level. The collective responsibility and relational nature of this work enhance the feasibility of this work to have tangible impacts across the dental health system in Australia.

Conclusions

This protocol outlines an antiracist health services and system research project that seeks to intervene at 3 levels of Australia's dental health system to address structural racism. The findings and materials generated will directly inform policy regarding the development of an antiracist dental health workforce, including antiracist dental practitioners, supportive environments that increase the number of Aboriginal and Torres Strait Islander dental practitioners, and AHW/P equipped with oral health knowledge. The approach used in this project is vital as dental health systems research has predominantly occurred using biomedical, colonial, deficit, and Western perspectives of oral health and healing [66], therefore missing opportunities to address structural racism and resolve oral health inequities effectively, particularly as they pertain to Aboriginal and Torres Strait Islander Peoples [38].

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Project governance committee terms of reference.
[PDF File (Adobe PDF File), 883 KB - resprot_v14i1e69012_app1.pdf]

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Abbreviations

ACCHO: Aboriginal Community Controlled Health Organization
AHW/P: Aboriginal Health Workers/Practitioners
IDAA: Indigenous Dental Association of Australia
NACCHO: National Aboriginal Community Controlled Health Organization
PGC: Project Governance Committee

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Protocol

Treating Lower Phantom Limb Pain in the Postoperative Acute Care Setting Using Virtual Reality: Protocol for a 4-Phase Development and Feasibility Trial

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Abstract

Background: Phantom limb pain (PLP) affects most people living with lower limb amputations (LLAs). Nonpharmacological interventions, such as graded motor imagery (GMI), have demonstrated promise as PLP treatments. However, GMI access is limited by low patient buy-in and long public outpatient wait times. Considering PLP has been shown to be more prevalent and severe immediately following LLA, there is an urgent need to bypass barriers to allow for prompt access to PLP interventions. In response to this need, the multidisciplinary research team in this study developed a virtual reality (VR) program that administers GMI treatment. This novel intervention may be completed independently and promptly within the postoperative acute care setting. Before conducting a randomized controlled trial, the VR-GMI program must be developed and refined through a rigorous and multistage feasibility assessment.

Objective: This protocol aims to outline the development and feasibility of the VR-GMI prototype for treating people with LLAs in the postoperative acute care setting (ie, inpatient and home settings) through an iterative, patient-centered, and descriptive approach.

Methods: Four phases of prototype development and assessment were conducted. In phase 1 (completed), the VR-GMI prototype was developed in collaboration with engineers at the National Research Council and in consultation with patient partners. In phase 2 (completed), people with lived experience with amputations were recruited from local physiotherapy and prosthetic clinics to trial the VR-GMI program and provide feedback through semistructured interviews and self-report measures. Phase 3 (completed) consisted of a descriptive case series of individuals who trialed the VR-GMI prototype immediately following their LLAs in the hospital. Results from phase 3 informed the development of a primary quantitative feasibility study. Phase 4 (underway) aims to evaluate the acceptability and pilot outcomes of the VR-GMI program in hospital and home settings as well as improve

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study procedures for a future randomized controlled trial (phase 4A). Iterative developments were made to the VR-GMI program between each phase to improve prototype fidelity. These iterative developments will also be reviewed in a series of focus groups to finalize the VR-GMI prototype (phase 4B).

Results: Recruitment for phases 1 and 2 was completed in September 2023. Phase 3 was completed in July 2024, and phase 4A is currently underway with 15 participants recruited as of March 2025.

Conclusions: The intervention developed is the first VR PLP treatment implementing GMI and prioritizing an in-depth, patient-centered approach before assessing its efficacy. Doing so will improve the likelihood of successful clinical implementation. Moreover, very few PLP interventions have been assessed in the acute postoperative period when they may prevent PLP before its onset.

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International Registered Report Identifier (IRRID): DERR1-10.2196/68008

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KEYWORDS

phantom limb pain; virtual reality; lower limb amputation; graded motor imagery; feasibility; postoperative; acute; patient-centered; preventive; pre-emptive

Introduction

Literature Review

More than 7000 lower limb amputations (LLAs) are performed in Canada each year due to (in order of decreasing prevalence) diabetic, vascular, traumatic, cancerous, and congenital indications [1]. Approximately 70% of these individuals will develop phantom limb pain (PLP) [2,3], a type of neuropathic pain where one experiences uncomfortable kinesthetic or somatosensory sensations in their missing limb following amputation [4]. PLP can be experienced for the first time within days following amputation (if not, within 1 year) and persists to variable degrees of intensity over a lifetime depending on the individual [5]. Research suggests that PLP is more likely to occur in people with more recent amputations compared to those who underwent amputations further in the past [2,3]. In addition, those who have an amputation due to chronic conditions (eg, vascular disease or diabetes mellitus) may have worse outcomes than those who undergo traumatic amputations because of preoperative factors (eg, preamputation pain) [2]. While PLP may improve over time if untreated, the lack of PLP treatment most often can significantly reduce quality of life, both psychologically and physically [6,7]. For example, research suggests PLP reduces mobility, which has adverse effects on independence (such as maintaining employment) and social role fulfillment [6,7]. PLP has also been implicated in a variety of other negative sequelae, including poorer sleep quality and increased depressive or anxious symptomatology [8-10]. The high prevalence of PLP among the growing number of LLAs, coupled with a lack of outpatient support, reflects an urgent need to develop effective treatments tailored to address the gap in care between the inpatient and outpatient settings to mitigate these negative sequelae.

In response to this need, researchers have developed many pharmacological and nonpharmacological PLP treatments. Currently, pharmacological interventions are among the most prevalent in clinical practice in treating PLP [11,12]. However, recent studies suggest that pharmacological interventions are both ineffective compared to placebo and considered unsatisfactory by patients with PLP [10-14]. Accordingly, researchers have turned their attention to nonpharmacological PLP treatments. One such treatment, graded motor imagery (GMI) [15], directly targets the central mechanisms implicated in PLP [16] and consists of 3 stages. The first stage of GMI is left and right discrimination (also known as implicit motor imagery), which entails quickly sorting images of left and right limbs. The patient then moves to the second stage, explicit motor imagery, which involves deliberate focus on phantom limb visualization. In the third stage, the patient undergoes mirror therapy, which involves visual feedback of the reflected intact limb (in a mirror box) to create the illusion of phantom limb movement. Despite the efficacy of GMI for PLP [15,17], it is often not clinically feasible due to its heavy reliance on physiotherapists with specialized training [18]. In Manitoba (where this research is being conducted), it can take up to 2 years to visit a pain specialist from a public treatment center [19], let alone a physiotherapist who specializes in GMI. To successfully implement GMI as a PLP treatment, barriers to its access need to be mitigated.

By eliminating GMI barriers, it may be possible to prevent or mitigate PLP onset through early intervention. While most treatments are administered well after PLP first occurs (ie, >3 months following amputation) [20], researchers have successfully prevented PLP by administering both pharmacological and nonpharmacological interventions during the perioperative period of amputation [20-23]. For example, both epidural and systemic analgesia (ie, morphine and ketamine) administered before, during, and after major limb amputation have been shown to reduce PLP incidence compared to a control group up to 1 year and 6 months following the procedure, respectively [21]. Similarly, surgical intervention geared toward neuroma prevention (such as targeted muscle reinnervation) used at the same time as major limb amputation has demonstrated significant PLP reduction compared to a control group at 3-month follow-up [22]. More recently, researchers have even begun to investigate the prophylactic effects of nonpharmacological PLP interventions, which have been shown to reduce PLP incidence and intensity with mirror therapy if administered <2 months following LLA [20,23].

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Administering PLP treatment early may not only bypass barriers to access, but it may also be more efficacious, including preventing the onset of PLP, which could have significant implications for negative downstream health and social sequelae.

Purpose and Rationale

To address current barriers to PLP care, our multidisciplinary research team (consisting of clinical psychologists, physiotherapists, physiatrists, anesthesiologists, surgeons, and engineers) developed a novel virtual reality (VR) program that allows people with LLAs to self-administer GMI treatment. VR is a computer-generated 3D simulated environment in which a user may be immersed with the use of a mounted headset. In recent years, it has been used to treat PLP by simulating mirror therapy or other gamified interventions [24]. The potential advantages of integration between VR and GMI are threefold. First, research suggests VR is more motivating and usable than 2D treatment administration modalities [25,26]. The novelty offered by VR will be invaluable to administer GMI psychoeducation and tasks in a gamified manner to increase patient buy-in, knowledge, and adherence [27]. Second, all GMI psychoeducation and treatment tasks are embedded on the device, removing the need to wait for and travel to a physiotherapist. In recent studies, VR PLP (without embedded GMI) treatment has already been self-administered by participants in their homes and produced promising pilot and feasibility outcomes [28,29]. Finally, virtual visual feedback may be of particular benefit to people with LLAs. Research suggests lower limb movements are more natural when performed asymmetrically (such as pedaling or walking); therefore, VR (through its capacity for asymmetrical movement) may produce more favorable outcomes for people with LLA compared to traditional mirror therapy (which can only be used symmetrically) by generating a higher sense of agency and ownership (defined as perceived control over and possession of the virtual limb, respectively) [30-32]. By bypassing barriers to care through a novel VR-GMI program, PLP can be targeted in the perioperative setting before its onset, when PLP is suggested to be the most intense and receptive to intervention [3,20].

Study Aims

This research aims to develop and assess the feasibility of a novel VR-GMI program for the treatment and prevention of PLP in persons with LLAs through 4 developmental and evaluative phases. The aim of phase 1 (completed) was to develop the initial prototype of the VR program through a multidisciplinary and patient-oriented approach, in accordance with GMI literature and feedback from people with LLAs. In phase 2 (completed), the perceptions of the VR prototype from people with LLAs living in the community were evaluated using a multimethod design. In phase 3 (completed), the preliminary feasibility of the VR prototype was assessed in the acute postoperative setting using a case series design. In phase 4A (in progress), a larger quantitative feasibility study is being conducted to evaluate the VR program in the acute postoperative period (including the hospital and transition to home) immediately following LLA. Phase 4B will conclude with a series of focus groups in which a subset of feasibility trial participants will discuss their experiences in the VR-GMI program and how it might be improved.

Each of the 4 phases was designed according to the Virtual Reality Clinical Outcomes Research Experts (VR-CORE) model [33], which outlines expert recommendations on how to validate a medical VR program. VR1 studies are patient-centered and involve collecting feedback from the population the VR program is designed for (including both clinicians and patients) to ascertain attitudes and expectations regarding treatment. To ensure the VR-GMI program reflects the needs of people with LLA, phases 1, 2, and 3 all meet the criteria for a VR1 study. Meanwhile, phase 4A meets the criteria of a VR2 study, which focuses on establishing the acceptability, feasibility, tolerability, and preliminary efficacy of the VR program. Birckhead et al [33] also describe VR3 studies, which entail using a randomized controlled trial (RCT) to assess the efficacy of a VR program. The VR3 study of the VR-GMI program will be outlined in a separate future protocol. The VR-GMI program will be finalized through a focus group (a VR1 study) to ensure the prototype is of the highest fidelity before proceeding to VR3. Figure 1 presents an overview of the 4 studies that will evaluate the feasibility of the initial VR-GMI prototype.

Figure 1. Visual overview of the 4 phases through which the feasibility of the virtual reality–graded motor imagery program will be assessed.

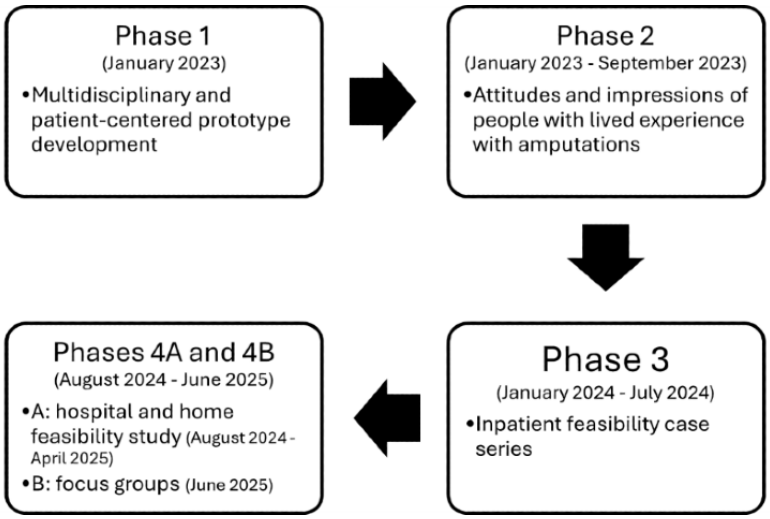

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Methods

Ethical Considerations

Phase 1 did not involve participants; therefore, ethics approval was not required. Consent forms relevant for each phase were reviewed by a research assistant with participants to ensure informed consent. Any ethical amendments were immediately addressed, updated, and communicated to participants. Data are deidentified using a random computer-generated 5-item alphanumeric code. All data are stored in a locked cabinet in a locked office in a secure facility. All investigator communications were completed via password-protected files, and any paper notes (with no identifiers) were destroyed immediately after use. Any photos taken during this study received additional consent from the participants. Ethics approvals for each phase were received. Phase 2 received ethics approval from the research ethics board (Fort Garry) at the University of Manitoba (HE20220374); phase 3 received ethics approval from the research ethics board (Bannatyne) at the University of Manitoba. Phase 4 received ethics approval from the research ethics board (Bannatyne) of the University of Manitoba (B2022107). Honorariums of CAD $50 (US $38.45) were provided to study partners in phase 1, and CAD $25 (US $19.23) gift cards will be provided to participants in all other phases.

Phase 1: Multidisciplinary and Patient-Centered Prototype Development (Completed)

Overview and Objective

In phase 1, the initial VR prototype was developed collaboratively within a multidisciplinary team, including engineers (MS and DS) affiliated with the National Research Council (NRC) of Canada and led by a clinical psychologist (REG) from the University of Manitoba. In addition, study partners (including people with LLAs and physiotherapists) and collaborators (anesthetists and physiatrists) were consulted to iteratively incorporate their feedback and lived experience with amputations during initial prototype development. The objective of phase 1 was to develop a virtual GMI prototype through multidisciplinary and patient-centered feedback.

Study Partners

The study partners consisted of 5 people with lived experience with amputations, including 2 (40%) physiotherapists (EH and PG) and 3 (60%) people with LLA. Both physiotherapists had experience working with people with LLA, using GMI (EH) or other forms of physiotherapy (PG). All 3 of the study partners (male participants: n=2, 67% and female participants: n=1, 33%) with LLAs had experienced disruptive PLP at some point following their surgeries, with the pain being reported to be the worst at its onset. Study partners who were people with LLA were given a CAD $50 (US$38.45) honorarium for their participation.

Procedures

An initial multidisciplinary team meeting was held in January 2021 to formulate a plan for prototype development. Team members then aimed to recruit 5 people with lived LLA experience. Study partners who were people with lived experience with LLAs were approached by team members in their respective clinics to ask about their interest in participation in this program of research. If they expressed interest, the potential study partners were directly contacted by study personnel to receive further information. Interested partners (n=3, 60%) participated in an initial semistructured interview in August 2021 with the principal investigator (REG), research personnel, and lead engineer via Zoom (Zoom Communications, Inc; due to the COVID-19 pandemic). Interview questions inquired about amputation history (including current and past interventions accessed for PLP), initial thoughts relating to the proposed VR prototype, and continued interest in involvement throughout development. Interviews were 1 hour in length. Partners were continually engaged in initial development via Zoom and email to provide feedback on prototype development. Once a prototype was in place, multidisciplinary team members and study partners both viewed videos of the prototype and trialed it at the NRC to provide feedback. It should be noted that, due to delays in development (due to COVID-19), the explicit motor imagery task was not evaluated by study partners over video or in person; however, the written scripts were reviewed and revised by partnered physiotherapists. In addition, one of the study partners with an LLA stopped responding to research correspondence midway through development for unknown reasons. Figure 2 shows an image of our research team and one of our partners (with respective consents provided) trialing the VR-GMI program.

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Figure 2. (A) Research team member trialing the hand control trackers attached to the legs via 3D-printed adapters. (B) Study partner trialing the virtual reality prototype. (C) Larger image of limb simulation stage in program.

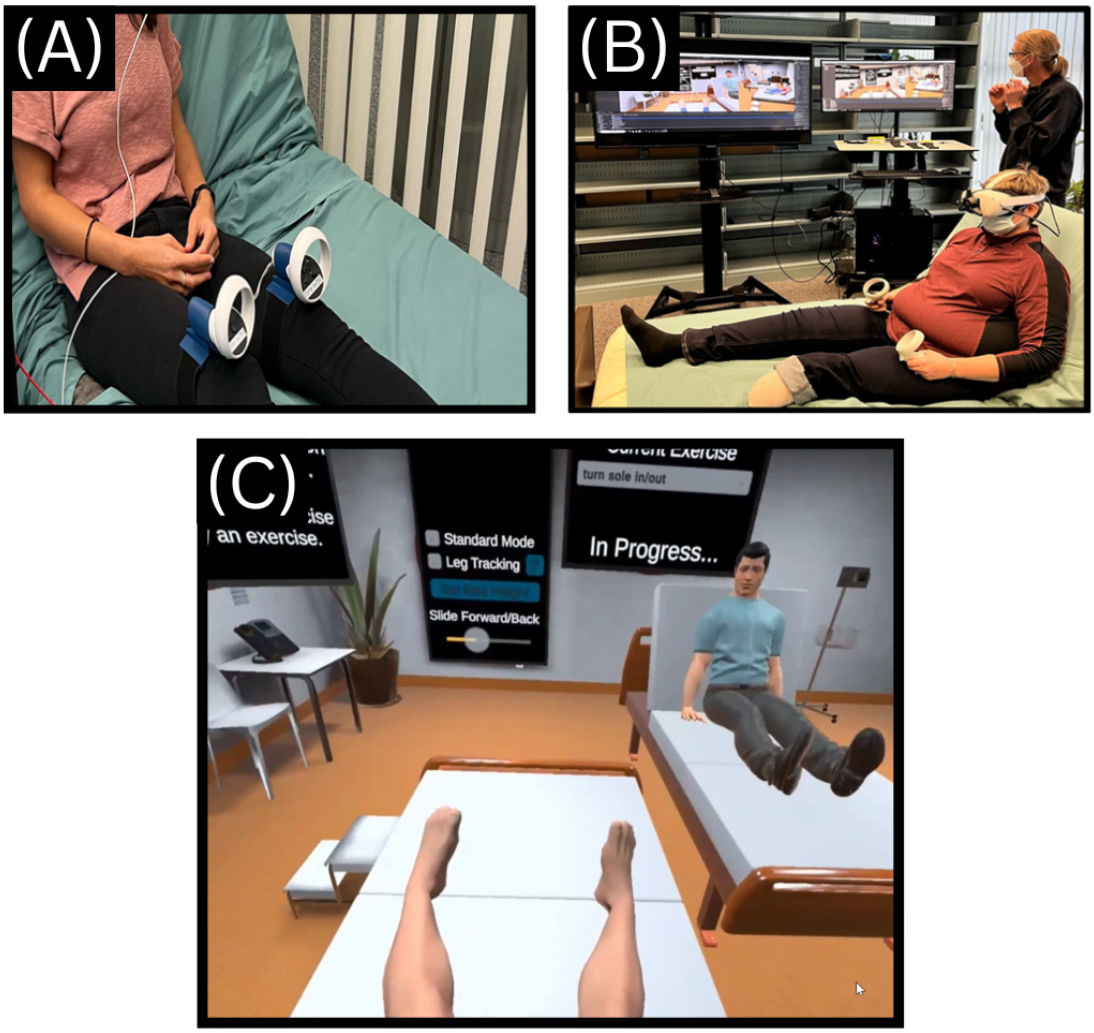

The Initial VR-GMI Prototype

The VR-GMI program was developed using the Unity game engine (Unity Technologies) and operates on the Oculus Quest 2 (Meta Platforms, Inc), a commercially available VR hardware system with a head-mounted display and hand controllers. This stand-alone system is advantageous as it is not encumbered by wires connecting it to an external computer, allowing for ease of setup and use. It also includes functionality for the clinician and research personnel to follow along with the participant by casting over Wi-Fi through the Oculus app (or by attaching a Link cable if Wi-Fi is unavailable) a mirror image of the virtual environment as experienced by the participant to a separate display device, such as a smartphone or tablet. To increase feelings of embodiment for the participant by having their virtual leg movements follow their real-world leg movements, leg tracking was also incorporated into the system. Initial experimentation with third-party tracking devices using ultrasound and inertial measurement units was promising, but performance was inconsistent when tested in different environments. Prioritizing consistency to avoid breaking presence in VR, an alternate approach was adopted using the Oculus Quest 2 hand controllers to track the participant's legs. Custom adapters for attaching the controllers to the user's legs were designed and 3D printed. When leg tracking is enabled in the program, the hand controllers are strapped to the participant's legs above the knee using custom adapters (Figure 2).

Following initial development of the base prototype, GMI elements were included with guidance from physiotherapist partners. The GMI stages, including left and right discrimination, explicit motor imagery, and mirror therapy, formed the basis of the VR program. Implementation was designed to take advantage of the unique affordances of VR. For example, the left and right discrimination task was implemented in a whimsical environment in which the user interacted with the images of feet using their controllers to increase engagement. The explicit motor imagery phase incorporated recorded audio of a body scan to enhance relaxation and focus on the phantom limb [34-36]. Meanwhile, the mirror therapy stage included asymmetrical exercises in the virtual visual feedback, a feature that is not feasible during traditional mirror therapy. Due to the capacity of VR to provide asymmetrical visual feedback, the mirror therapy stage was dubbed "limb simulation."

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Priorities for Future Development

Across both virtual and in-person meetings with study partners, common recommendations emerged that informed the optimization of the VR prototype. These developmental priorities included addressing technological barriers and improving leg tracking. The details of these recommendations can be reviewed in Multimedia Appendix 1.

Phase 2: Attitudes and Impressions of People With Lived Experience With Amputations (Completed)

Overview

In phase 2, developmental priorities for the finalized VR-GMI prototype were assessed by collecting feedback from people with LLAs to ascertain preliminary treatment attitudes and expectations. To accomplish this, 12 people with LLAs were recruited from community settings to trial the VR-GMI program and detail their experience through a combination of observations, self-report measures, and semistructured interviews.

Study Design and Objectives

This study used a multimethod design to elucidate participant perspectives on the VR-GMI prototype in a single, intensive VR session. The first and primary objective was to assess anticipated barriers to and facilitators of using the VR-GMI program in the intended administration settings (including home and hospital settings immediately following LLA) through semistructured interviews. A second objective was to evaluate how engaging and immersive the VR-GMI prototype was using self-report measures. Observations and informal discussions throughout the VR sessions provided context for the triangulated data to inform program development.

Recruitment and Inclusion Criteria

The research team planned to recruit 10 to 15 participants via purposive sampling through community partners, including physiotherapists, surgeons, and prosthetists. Such a sample size is akin to similar user-centered studies evaluating the development of novel interventions [37,38]. Recruitment posters were disseminated in person as well as through email and institutional social media accounts. Interested individuals were contacted by the researchers directly or over the phone if the participant provided verbal consent to a community partner. Potential participants were screened over the phone for the following eligibility criteria: must have a unilateral LLA proximal to the ankle, must be aged ≥18 years, must not be experiencing any hearing or vision loss that would affect interaction with a VR headset, must have experienced PLP or sensation either in the past or present, and must agree to be audio recorded. Participants were also informed that they would be given a CAD $25 gift card (US $19.23) to Tim Hortons to thank them for participating. The research team aimed to recruit 10 to 15 participants between March 2023 and September 2023. By the end of this recruitment period, 12 participants were recruited.

VR Intervention Procedure

Each participant tested the VR program in an intensive session (approximately 2.5 h in duration) at the NRC building in Winnipeg, Canada. Appointments were booked via phone following eligibility screening. Gift cards were given promptly following completion of the informed consent form. Before using the VR program, each participant completed a semistructured interview to collect baseline characteristics, including amputation etiology and pain history. The research assistant (MC) then verbally administered GMI psychoeducation and technical instructions regarding the VR hardware. Afterward, the participant was instructed to vocalize all thoughts they had about each of the 3 VR GMI stages as they navigated them, including operational or instructional confusion, stylistic choices, etc. During program use, the research assistant recorded observations of the participant's behavior on a laptop as well as any vocalizations from the participant. Approximately half of the sessions included at least 2 research personnel, with an engineer at most of the sessions.

Following each of the 3 VR stages, the participants doffed the headset to discuss their experience in that particular task. The research assistant also clarified any observations made during that stage. Once the participants completed the entire VR program, they filled out a series of self-report measures to gauge the quality of their experience in the VR program, in the following order:

- The User Engagement Scale [39] is a 31-item questionnaire that measures how rewarding a given user experience was. It was rated on a 5-point Likert scale and validated in the head-mounted VR context [40].
- The Presence Questionnaire [41] is a validated 20-item questionnaire that measures how immersive a virtual experience was. Each item was rated on a 7-point Likert scale.

Participation concluded with an exit interview discussing anticipated barriers to and facilitators of using the VR program. The final exit interviews were audio recorded via Trint for later transcription and analysis.

Statistical Analysis

Given the small sample size and nature of this study, scores across various measures were descriptively analyzed using R software (version 4.3.1; R Foundation for Statistical Computing). Meanwhile, exit interview transcripts were coded line by line and examined using reflexive thematic analysis [42,43]. Following separate qualitative and quantitative analyses, the results were integrated, along with observations, for interpretation and extrapolation of developmental priorities for the VR-GMI program.

Phase 3: Inpatient Feasibility Case Series (Completed)

Overview

In phase 3, the VR-GMI prototype was implemented in the acute postoperative hospital setting immediately following LLA. Given the novelty of this methodological approach, the research aimed to understand participant experience and feedback on the intervention as well as identify barriers encountered during recruitment and administration before the initiation of a larger feasibility trial. The information gathered directly impacted modifications to the phase 4 protocol to optimize feasibility.

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Study Design and Objectives

Phase 3 was a prospective descriptive case series. Participants were recruited and administered the VR-GMI program at the Health Sciences Centre (HSC) in Winnipeg, Canada, a large academic tertiary hospital and level 1 trauma center. The VR-GMI program was administered daily immediately following LLA for a maximum of 10 sessions or until hospital discharge. Quantitative and qualitative self-reported data were gathered pertaining to patient experience, and details about recruitment and retention were documented.

Phase 3 included 2 objectives. The primary objective was to evaluate preliminary recruitment and retention trends as well as identify potential recruitment barriers for phase 4. The secondary objective was to describe participants' experience with the VR-GMI program in 3 domains, including immersion, tolerability, and overall helpfulness.

Recruitment

The research team aimed to recruit 5 to 10 participants by the end of the recruitment period (January 2024 to July 2024), resulting in a sample size of 6 participants. Participants were required to meet the following inclusion criteria: underwent (postoperative) or were about to undergo (preoperative) a unilateral LLA (hip, below knee, above knee, or foot) of either elective or traumatic mechanisms within the last 5 days; currently receiving inpatient treatment at the HSC in Winnipeg, Canada; and fluent in English (speaking and reading). Potential participants were not eligible if they met the following exclusion criteria: any visual, hearing, or motor impairment that would affect engaging with a head-mounted VR headset or hand controls; anyone with or about to undergo a bilateral leg amputation; and anyone aged <18 years. Potential participants were screened from the following avenues: the preanesthetic clinic (which hosts presurgical visits between anesthesiologists and patients before LLA) and elective and emergency operating room slates (which contain the information of every patient about to undergo an LLA). Any LLAs that appeared eligible were recorded. Once potential participants were identified, health care professionals in their circle of care approached them to ascertain their interest in hearing more about the study from research personnel. If interested, research personnel approached the participant at the HSC to ensure they met eligibility criteria and administered the informed consent form. If a patient was ineligible or declined participation, the reason was recorded.

VR Intervention Procedure

Participants engaged in 1 VR session per day for approximately 20 minutes from their respective ward (orthopedic, vascular, or rehabilitation). At the beginning of the first VR session, after informed consent was obtained and the honorarium was given to the participant, the research assistant administered the sociodemographic and patient characteristic questionnaire (including age, amputation etiology, place of residence, etc). The research assistant then gave a brief verbal introduction to the VR-GMI system and instructed the participant on how to use the VR headset and handheld controls. Following VR instruction and at the beginning of each subsequent VR session, the research assistant verbally administered the Numerical Rating Scales (NRSs; 11-point Likert scales) for PLP, residual limb pain (RLP; ie, physical pain at the amputation site), and nausea before asking if they wanted to engage with the VR program that day. If they declined participation, their reason was recorded.

Participants were only permitted to engage in 1 stage per day. They could only move onto the next VR stage if their RLP, PLP, or nausea NRS scores did not increase by >2 points during or before their next session (given that treatment may exacerbate pain or nausea, and 3 points is considered a clinically significant increase) [44-47]. The participants were permitted to spend as much time as they preferred in each VR stage. If the participant chose to stop the session before the 20-minute goal (a session length used in previous studies) [23,48], the research assistant asked for and recorded their reason for discontinuation. Afterward, the research assistant verbally readministered the NRSs for PLP, RLP, and nausea. Any impromptu feedback or observations made by research personnel were recorded as field notes.

Participants were asked to engage in up to 10 VR-GMI sessions or until hospital discharge, whichever came first. After the last VR-GMI session, before discharge, the Igroup Presence Questionnaire (measuring VR immersion) [49] and VR Impressions Scale (developed by the laboratory for the purposes of descriptive evaluation of a VR intervention; Figure 3) [50] were administered.

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Figure 3. The Virtual Reality Impressions Scale.

Virtual Reality Impressions Scale

Please rate the extent to which you agree with each statement related to your experience with the virtual reality (VR) intervention, ranging from 0% (completely disagree) to 100% (completely agree).

The way information was presented was clear and understandable _____%

I enjoyed my session with the VR system _____%

I could understand and act on the information provided by the system _____%

The system had a very attractive presentation _____%

I had to look for assistance when I used this system _____%

The program froze or stopped unexpectedly _____%

I found the VR system was helpful _____%

Did you experience any motion sickness during the VR system>

☐ 0 None ☐ 1 Slight ☐ 2 Moderate ☐ 3 Severe

What did you like about the VR system? _____

What did you dislike about the VR system? _____

If you found it helpful: In what ways was the intervention helpful? _____

Was participating in the intervention worthwhile, considering the time commitment (for attending the VR session and completing measures)?

☐ Yes

☐ No

Version 1.0 28/11/2022

Data Analysis

For the first objective, eligibility and consent rates were calculated according to the number of patients screened. Reasons for refusals or ineligibility were recorded in pie charts. The secondary objective analyzed patient experience with the VR-GMI program by describing the qualitative and quantitative data of each participant individually to capture unique perspectives. Specifically, participant ratings on tolerability (measured by NRS for PLP, RLP, and nausea), immersion (measured by the Igroup Presence Questionnaire), and overall helpfulness (measured by the VR Impressions Scale) were described individually in conjunction with sociodemographic characteristics (such as age, length of hospital stay, etc) to provide context for interpretation. The qualitative data, including participants' quotes and observations made by research personnel, were integrated to triangulate and increase the strength of the findings.

Phase 4A: Hospital and Home Feasibility Study (Underway)

Overview

In phase 4A, the research team will assess the feasibility and pilot outcomes of the VR-GMI program in the acute postoperative period immediately following LLA (including the hospital and home). The research team aims to recruit 30 participants who recently underwent an LLA through the HSC. A research assistant will visit participants daily to administer the VR-GMI program for approximately 17 days. Participants will then be contacted again 1 month following their final VR session via phone call to assess postoperative PLP. Quantitative data will be collected to assess whether the VR-GMI program and study procedures are sufficient for an RCT.

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Study Design and Objectives

Overview

Phase 4A will consist of a quantitative feasibility study using a 1-group post–test-only design in line with methodological recommendations [33,51]. The feasibility of the program will be evaluated through self-report and administrative quantitative data. The objectives and affiliated hypotheses are mentioned subsequently.

Intervention Feasibility

Participants will consider the VR-GMI program to be acceptable, tolerable, and engaging across administration settings (inpatient, outpatient, and home settings) and VR stages.

Procedural Feasibility

The used recruitment strategies and study procedures will be appropriate for a RCT, as indicated by comparing sample characteristics to administrative data (reflecting all people undergoing LLAs during the recruitment period) in addition to predetermined recruitment, retention, and attrition rate criteria [52].

Pilot Outcomes

Participants who spend an extended amount of time in the VR-GMI program will report lower PLP incidence as well as (for individuals who have already experienced PLP onset) lower intensity and interference. These predictions are in line with previous research investigating prophylactic PLP treatment through mirror therapy in the postoperative period [23].

Exploratory Outcomes

The research team will explore reasons for rejecting participation as well as session or study withdrawal. The research team will also investigate whether acceptability, engagement, or PLP incidence and intensity vary according to baseline, sociodemographic, and exploratory variables (such as anxiety, depression, amputation indication, etc).

Recruitment

The research team aims to recruit 30 participants, 5 (17%) of whom we expect to drop out and 25 (83%) to complete the program. This sample size is in line with previous pilot studies for PLP treatments that precede RCTs [38] and suits the descriptive and exploratory aims of the study. This sample size also has 80% power to detect the desired recruitment criterion [53].

Potential participants will be approached according to the recruitment strategies and eligibility criteria outlined and recommended in phase 3, with 3 exceptions to help mitigate recruitment barriers faced in the previous phase. First, clinical resource nurses on units where LLAs are treated at the HSC will be called each week to ascertain where eligible patients are to increase the recruitment rate. Second, individuals with bilateral amputations will also be eligible for recruitment, given preliminary data from phase 3 suggesting this may be feasible. Third, patients will be eligible to participate for up to 2 months following their LLA, in line with the literature that suggests such a time frame is suitable for the administration of acute PLP intervention [20].

VR Intervention Procedures

Similar procedures to phase 3 will be used in phase 4A, with 3 exceptions made in accordance with preliminary phase 3 data. First, following baseline measure administration, the research assistant will administer a brief video via laptop that introduces the participant to the VR-GMI program, including how to operate the controls and put on the headset. The video (rather than verbal instruction) serves to standardize study expectations and technical knowledge across participants. Second, new measures have been introduced in addition to the measures used in phase 3. The first time a participant completes a stage, they will be administered the Theoretical Framework of Acceptability Questionnaire, which consists of 7 items rated on a 7-point Likert scale inquiring about the acceptability of a behavioral intervention [54] (Figure 4). In addition, following the limb simulation stage (both with and without leg tracking), each participant will be administered the Virtual Embodiment Questionnaire, a validated measure for agency and ownership in a virtual experience involving avatar embodiment [55]. Finally, the Brief Pain Inventory and Patient Reported Outcomes Measurement Information System will be verbally administered over the phone 1 month following each participant's final VR session to measure PLP intensity and interference, respectively, through validated self-report measures [56-58].

The last and most significant amendment made between phases 3 and 4A is the administration of the VR-GMI program in the home setting following hospital discharge. Data from phase 3 suggested that participants were discharged from the hospital before 2 weeks had passed, which prevented them from receiving the VR dose necessary to see a treatment effect [23]. Therefore, a research assistant will contact participants over the phone following their discharge to inquire about their interest in continuing participation for the remaining sessions in their home. If they wish to continue (and they live in Winnipeg), their participation will proceed with home visits. If they do not reside in Winnipeg, their participation will be discontinued by the researcher; however, their willingness to continue the program will be recorded. Participants will be allowed to continue the VR-GMI program for up to 17 days to analyze long-term acceptability and dosage effects. Immediately following the completion of the feasibility trial, relevant modifications will be made to the prototype based on results.

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Figure 4. Adapted Theoretical Framework of Acceptability Questionnaire.

Each TFAQ administration will be preceded with: "When you answer the following questions, think about your experience with this stage specifically in [the hospital/this clinic/your home]."

1. Did you like or dislike the [educational video/insert stage]?

Strongly dislike	Dislike	No opinion	Like	Strongly like
1	2	3	4	5

2. How much effort did it take to [access/engage with] the [educational video/stage]?

No effort at all	A little effort	No opinion	A lot of effort	Huge effort
1	2	3	4	5

3. How fair is it to expect people who recently had a leg amputation to [watch/engage with] the [educational video/stage]?

Very unfair	Unfair	No opinion	Fair	Very fair
1	2	3	4	5

4. It is clear to me how using the [VR program/stage] early on in my recovery will prevent/improve my phantom pain.

Strongly disagree	Disagree	No opinion	Agree	Strongly agree
1	2	3	4	5

5. How confident did you feel about [accessing/engaging with] the [educational video/stage]?

Very unconfident	Unconfident	No opinion	Confident	Very confident
1	2	3	4	5

6. [Watching/engaging with] the [educational video/stage] so soon after my amputation interfered with my other priorities.

Strongly disagree	Disagree	No opinion	Agree	Strongly agree
1	2	3	4	5

7. How acceptable was the [educational video/stage] to you?

Completely unacceptable	Unacceptable	No opinion	Acceptable	Completely acceptable
1	2	3	4	5

Data Analysis

Objectives 1, 2, and 4 will be evaluated descriptively via bar graphs, means, and SDs to compare each objective across administration settings and VR stage according to preset feasibility criteria. Preset feasibility criteria must be met to determine if the VR program is acceptable (mean Theoretical Framework of Acceptability Questionnaire score >3, which indicates a more favorable acceptability rating than no opinion; Sekhon et al [54]), tolerable (at least 70% of the participants do not report any pre- or post-NRS score increases of ≥3 for PLP, RLP, or nausea), and engaging (mean session duration ≥20 min). Similar progression criteria [52] must be met to determine whether procedural feasibility is appropriate for an RCT, including recruitment (at least 50% of the patients at the HSC who appear to meet the eligibility criteria will be screened through the established pathways), retention (at least 70% of the participants who live in Winnipeg will continue to participate in the study for as long as they are able to), and attrition (at least 80% of the participants will respond at the 1-month follow-up period following their final session) rate criteria. The sample will also be compared to the population of all people who underwent an LLA at the HSC during the recruitment period (from June 2024 to March 2025) via administrative chart review to evaluate whether the characteristics are relatively proportional to one another.

For objective 3, scatterplots will be generated to explore the association between the length of program engagement and the

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Brief Pain Inventory or Patient Reported Outcomes Measurement Information System pain interference. Mean or median difference in length of program engagement between participants who have and have not yet experienced PLP onset will also be calculated. If appropriate, exploratory regression models will be used to examine the effect of VR dosage on PLP outcomes.

Phase 4B: Focus Groups

Phase 4B will conclude with a series of focus groups (n=2) consisting of a subset of 5-10 interested participants from phase 4A following completion. Participants will meet in person to discuss their experiences with the VR GMI program in the hospital and home (if applicable), facilitated by members of the research team using a semistructured interview. Immediately following the initial discussion, participants will be invited to trial the updated prototype (headsets will be circulated, and snacks will be provided to those waiting for their turns). Following the trial, another group discussion will occur to provide feedback on the new developments, also using a semistructured interview format. The focus group transcripts will then be analyzed through reflexive thematic analysis [42,43] and interpreted to inform the final development of the VR GMI program.

Results

Initial funding for prototype development and phase 1 was obtained through the NRC New Beginnings Fund, awarded to REG and MSDS as co–principal investigators in December 2020 (US $25,000 + 20% of full-time employment [or 390 h] of engineering time for development). Delays occurred in the initial development of the program due to the COVID-19 pandemic and parental leave (REG). Phase 1 of this study was completed in January 2023, at which point recruitment for phase 2 was conducted until September 2023 and is now published [59]. Additional funding was obtained through the Winnipeg Foundation Innovation Fund (CAD $100,000 [US $74,088] to principal investigator REG) in December 2023. Recruitment for phase 3 began in January 2024 and was completed in July 2024. As indicated earlier, several methodological modifications were conducted to the study protocol before initiation of the final phase. Phase 4A commenced in August 2024 and is expected to be completed in June 2025. As of March 2025, we have screened 101 patients for eligibility and successfully recruited 15 participants. Regardless of ethics approval to initiate intervention before surgery, hospital logistics and communications have created challenges around recruiting participants preoperatively. Phase 4B will be conducted in June 2025, followed by the final refinements of the VR-GMI program. Should significant adjustments need to be made to the program, an additional feasibility trial will be conducted before the larger clinical trial. It is anticipated that results from phase 4 will be published by January 2026.

Meanwhile, the research team will use preliminary data to inform iterative development of the VR-GMI program; between studies, these developments are deployed so that each phase evaluates a higher fidelity prototype than the last. For example, information from phase 2 suggested that a video was embedded into the VR-GMI program to educate patients on the potential benefits of using this treatment. Moreover, VR controls have continuously been simplified to promote treatment use by individuals with lower technological self-efficacy (eg, allowing them to use only 1 control to operate the VR GMI program). Most notably, results from phase 2 indicated that better immersion may be experienced in the VR-GMI program via the use of hand controls as leg trackers. Leg trackers were then 3D printed to allow trial in phase 3. Detailed results from all phases will be available in a future paper to be published. Figure 5 gives an overview of the VR-GMI prototype in its current state, given preliminary data collection and analysis.

Figure 5. The 5 stages of the virtual reality–graded motor imagery program (before entering phase 4A). GMI: graded motor imagery; PLP: phantom limb pain.

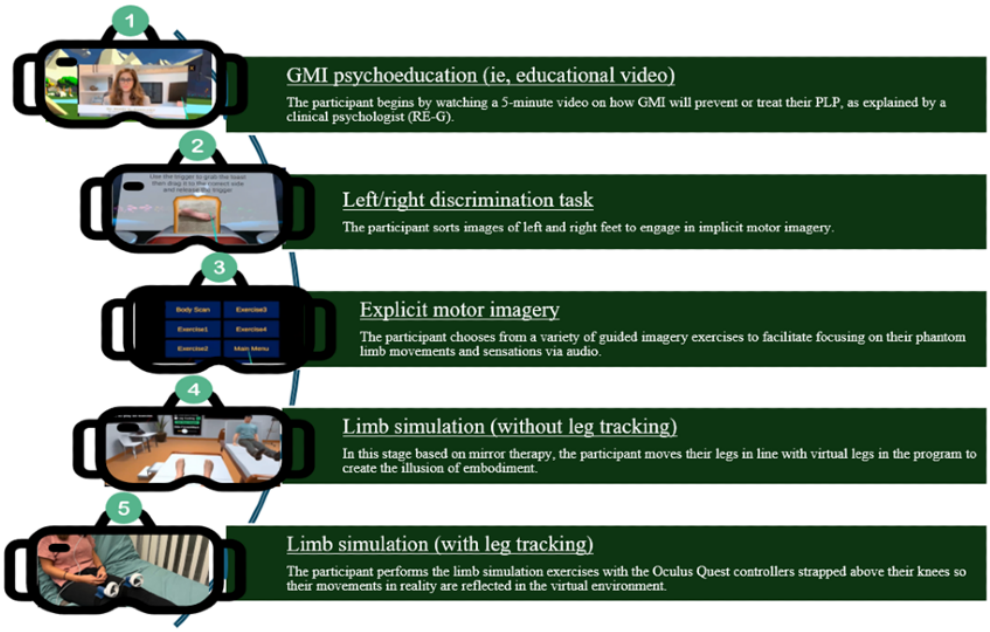

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Discussion

Comparison With Prior Work

This protocol represents both a novel methodological approach and an intervention through which PLP in people with LLAs can be treated. Despite the success VR and GMI have each demonstrated as independent PLP treatments [17,24], they have never been combined. Beyond its potential to increase GMI efficacy, VR can be used to streamline all the GMI components into a convenient, commercially available VR program, improving patient access both economically and logistically. Previous interventions have also leveraged this unique advantage of VR to administer PLP treatment in the home, often using gamification [28,29,60]. However, this is the first protocol to deliberately tailor a VR PLP program to the postoperative acute care setting. Moreover, while previous studies have demonstrated the prophylactic capacity of mirror therapy [20,23], no research has focused on how VR might enhance patient engagement and improve administration efficiency to reduce or prevent PLP onset. These novel contributions are noteworthy strengths that could create a conceptual foundation for further inquiry.

Strengths and Limitations

The most significant strength of this protocol is its prioritization of feasibility through a user-centered approach before empirically assessing the efficacy of the VR-GMI intervention in a clinical trial design. According to the VR-CORE framework [33], using patient-centered design is essential to the iterative development of an effective VR health care intervention. Recently, there has been a movement to design VR interventions with explicit consideration of implementation outcomes (such as acceptability) from the beginning of development [61]. Despite this recommendation, very few studies have examined the feasibility of VR PLP interventions in ecologically valid settings. Many researchers instead develop VR PLP interventions solely to assess their capacity for short-term PLP reduction [62,63]. Such inadequate focus on the feasibility of VR PLP interventions in target settings may contribute to low treatment adherence, limiting and confounding their effectiveness [64]. This 4-phase protocol attempts to address this common issue in VR literature with a thorough consideration of feasibility before conducting an RCT, serving as an example for the application of the VR-CORE framework.

However, each phase of the protocol also presents limitations. The feedback collected in phase 1 was collected informally through open-ended questions; therefore, the resulting recommendations were the result of simple compilation rather than systematic analysis. Furthermore, due to the COVID-19 pandemic, only 2 study partners with lived PLP experience were available to trial the VR prototype in person (all were able to observe video developments). Furthermore, although the initial goal was to recruit 5 diverse partners with lived PLP experience, only 3 were consulted. Meanwhile, phase 2 recruitment was completed via convenience sampling and was limited to interested individuals able to attend at the NRC building. Thus, the results of phase 2 likely do not capture the barriers encountered by the diverse population undergoing LLAs in Canada. Phases 3 and 4 have and will encounter similar bias. While a more representative sample may be recruited at the outset, data from phase 3 suggest participants are discharged from the hospital before completing the VR program for the recommended treatment period. Because only individuals who live in Winnipeg may logistically continue the program after discharge, people who live in rural or Northern communities are unlikely to receive the VR dosage necessary to demonstrate a treatment effect. This exclusion limits generalizability to Indigenous peoples living in Northern communities, who are disproportionately affected by diabetic LLA [65]. These limitations highlight that, while we can use the data of this protocol to inform VR development, more representative recruitment will be necessary before the clinical feasibility of the program for the general population can be ascertained.

Future Directions

Beyond this protocol, further development of the VR-GMI program will prioritize clarifying its feasibility and evaluating its efficacy in the postoperative acute period. Depending on the results of phase 4A, additional feasibility studies on the VR-GMI program may be necessary. This may include a longitudinal study conducted in the homes of participants beyond the city limits of Winnipeg to capture a more representative sample. Furthermore, an RCT will be conducted to assess the efficacy of the program. The first RCT will compare virtual GMI to a distractor control (ie, a natural VR environment), while another RCT may compare the program to traditional GMI. The studies enhance the development of an effective VR program to prepare for clinical implementation. Dates for these studies have not yet been determined as initiation depends upon the results of phases 4A and 4B.

The research team also aims to promote visibility of the proposed intervention through brand awareness to spark interest in its use by health care professionals. In line with this aim, the VR-GMI program will henceforth be coined PIVOT (Phantom Pain Graded Motor Imagery Through Virtual Reality Orthopedic Training). PIVOT will be referenced in upcoming publications, which will detail the results of phases 2, 3, and 4. While a name is ultimately a very small change, it is a step toward connecting with health care professionals that may assist with the clinical implementation of PIVOT following prototype development.

Conclusions

This protocol represents a novel methodological approach to iteratively develop a patient-centered VR intervention. Moreover, it outlines the development of the PIVOT program, which could increase the effectiveness and accessibility of PLP treatment through engaging and prompt self-administration of GMI. Following rigorous feasibility and efficacy evaluation, the clinical implementation of the PIVOT program could improve the quality of life of millions of people with LLAs by reducing their PLP and its downstream negative sequelae.

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Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are not publicly available due to small sample sizes and the collection of qualitative data but may be available from the corresponding author on reasonable request.

Authors' Contributions

REG, MC, EH, KR, DP, and LG contributed to study conception and design. MSDS, REG, DW, MC, EH, PG, and LP contributed to prototype development. REG, MC, MR, GL, MSDS, LP, HJ, and DW contributed to data collection. REG, MC, MR, HJ, and LP contributed to manuscript preparation. REG, MSDS, PG, EH, T Mutter, J March, DP, KR, GL, MC, MR, DW, LP, and HJ contributed to revisions. REG contributed as a guarantor. All authors reviewed the results and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Development recommendations from study partners with lived experience with amputations.
[DOCX File , 16 KB - resprot_v14i1e68008_app1.docx]

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Abbreviations

GMI: graded motor imagery
HSC: Health Sciences Centre
LLA: lower limb amputation
NRC: National Research Council
NRS: Numerical Rating Scale
PIVOT: Phantom Pain Graded Motor Imagery Through Virtual Reality Orthopedic Training
PLP: phantom limb pain
RCT: randomized controlled trial
RLP: residual limb pain
VR: virtual reality
VR-CORE: Virtual Reality Clinical Outcomes Research Experts

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Protocol

Program for Psychosocial Assessment During Pregnancy: Protocol for a Multimethod Study

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Abstract

Background: Onset of depression and anxiety can occur before, during, or after pregnancy, and ongoing conditions can either improve or deteriorate at all stages. National and international guidelines recommend that maternal health care should contribute to improving pregnant women's mental health by consistently asking pertinent questions during pregnancy and offering necessary support and care. The implementation of a program for psychosocial assessment has been carried out in a region in Sweden. The program includes the identification of risk factors and ongoing mental ill-health, consultation with psychologists within maternal and child health care, and care pathways to other health care providers.

Objective: The general aim of this research project is to investigate the effects of a program for psychosocial assessment during pregnancy on patients, as well as to evaluate the experiences of midwives and psychologists when working with the program.

Methods: A multimethod study design will be used to evaluate possible effects of a program for psychosocial assessment during pregnancy, including a pre- and postimplementation comparison, alongside a qualitative study of the professionals' perspectives. Data sources for the research project include patient data from the Swedish Pregnancy Register, medical records, questionnaire responses, and interviews with midwives and psychologists.

Results: The recruitment process is completed, and data collection and analysis are ongoing. The dissemination plan includes several publications of original research and two doctoral theses.

Conclusions: This study's results are expected to be relevant for maternal health care, both nationally and internationally, as scientific evaluations of the effects of implementing a program for psychosocial assessment during pregnancy are scarce. The implementation and evaluation of the program may hopefully, in the future, serve as a model for more standardized and effective care. It may influence national policies and attract attention as a model for improving perinatal mental health and maternity care.

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KEYWORDS

pregnant women; psychosocial intervention; obstetrics; perinatal mental health; midwifery; psychosocial; pregnant; pregnancy; maternal health care; maternal; Sweden; Europe; study protocol; mental health; mental illness; mental disorder; depression; questionnaire; interview; maternity; midwives

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Introduction

Background

This paper describes the study protocol, implementation, and planned evaluation of a program for psychosocial assessment during pregnancy in the Västmanland Region of Sweden.

In this protocol, mental ill-health is defined, according to the Public Health Authority of Sweden, as everything ranging from temporary anxiety, depression, or insomnia to severe mental illness. In order to be designated as mental ill-health, the symptoms must affect well-being and functionality in everyday life. Bipolar disorder, psychosis, severe depression, severe anxiety, and eating disorders are examples of severe mental illness [1].

The words "woman/women" will be used in this protocol to refer to pregnant people, in line with previous literature in the field. Although pregnancy is a physiological condition, rather than an illness, the word "patient" will also be used, since the subject relates to ill-health and illness.

During pregnancy, psychological symptoms are often normal and transient reactions to a stressful life situation. Mental ill-health during this life stage includes a spectrum of different conditions of varying severity [2]. A systematic review conducted in 2017 showed an overall prevalence of perinatal depression of 11.9% [3]. A study from Sweden found that 7% of women had major depression and 11% had an anxiety disorder during pregnancy [4], while a study from Iceland showed that anxiety and combined depression and anxiety were more common than depression alone during pregnancy [5]. In a meta-analysis, approximately 7% to 9% of pregnant women were estimated to meet the criteria for both depression and some form of anxiety [6]. Statistics from 2023 in the Swedish Pregnancy Register (SPR) showed that 11% of pregnant women in Sweden had been treated for mental ill-health [7].

Assessment of mental health in pregnancy is vital [8] and may, if undetected or unaddressed, affect the health of the woman, baby, and family [2]. Ongoing moderate to severe mental illness during pregnancy increase the risk for preterm birth, neonatal complications, and small-for-gestational-age babies [9]. Children of women with untreated or incompletely treated mental illness during pregnancy are at increased risk of emotional and behavioral problems while growing up [10].

Although many depression and anxiety conditions diagnosed in the postpartum period emerge during or before pregnancy [11], fewer women receive support and treatment for mental ill-health during pregnancy than in the postpartum period [12]. Women with prepregnancy moderate-to-severe mental illness are at increased risk of relapse during pregnancy and the initial postpartum period [12,13]. Therefore, it is important to identify these women early in pregnancy, particularly those with bipolar disorder and previous psychosis, because of the related increased risk of postpartum affective psychosis and other serious conditions. Early identification can be achieved by routinely asking all pregnant women structured questions, which enables the creation of a care plan for the pregnancy and postpartum period [11]. Early identification of depression and anxiety and timely treatment during pregnancy are essential and can reduce the rate of postpartum depression [11,14-17] as well as increase the possibility that the woman's health will improve, enabling her to prepare for childbirth and motherhood [18].

A meta-analysis concluded that early identification, followed by thorough psychosocial and clinical assessment, is beneficial, even though evidence supporting a specific method remains limited [19]. At present, assessment with any tool can supplement a broader professional interview, to identify those requiring further clinical assessment and intervention. It is thus important that professionals have appropriate training and enough time to engage in a broad and meaningful conversation with the patient. Referral pathways must be created to ensure quick and accurate diagnostic assessment and effective interventions [17,19]. In Sweden, it has been recommended that a structured program to identify and treat mental health problems during pregnancy be created and that multidisciplinary perinatal mental health teams should be established in Sweden [20].

Sweden's Maternal Health Care System

The health care system in Sweden is primarily funded by regional governments through tax revenue. Residents have general access to publicly funded hospital care and primary health care, as well as maternal health care, child health care, and other publicly funded outpatient services.

There is regional autonomy, and organization varies; maternal health care can be run as part of primary care, as part of hospital obstetrics and gynecology departments, or within other organizations. However, regardless of region and organization, maternal health care coverage in Sweden is essentially 100%. Child health clinics in Sweden are responsible for child health surveillance from infancy to age 6 years. Similar to Swedish maternity clinics, they have essentially 100% coverage and are free of charge.

In Sweden, midwives, working in maternity clinics, are responsible for antenatal care, postpartum care, and sexual and reproductive health, collectively referred to as "maternal health care" in this paper. The maternal health care programs in Sweden are similar in terms of medical, obstetric, psychological, and social content, with some adaptations based on specific regional conditions. These programs usually comprise 9 to 10 visits during pregnancy and 2 visits after childbirth. In cases of comorbidity or complications, more visits can be offered. The midwife may consult, collaborate with, or refer to other professionals or agencies, such as a psychologist in maternal and child health care, general practitioner, obstetrician, psychiatrist, or social services. The midwife retains the main responsibility for care during collaborations of this type [21].

Psychologists within maternal and child health care in Sweden are employed at, or affiliated with, maternity clinics and child health clinics and will be referred to as "psychologists" in this paper. The psychologists have several professional functions, including consultation with midwives, most often in small groups, to obtain guidance for managing pregnant and postpartum women with manifest or suspected mental ill-health. The psychologists also assess and provide psychological

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treatment to individual women, co-parents and partners, and children for development assessment.

Guidelines and Recommendations for Maternal Health Care in Sweden

Since 2015, the Swedish government has made major investments in improving perinatal health care and women's health throughout life. All regions in Sweden are currently working to improve health care in various areas during the perinatal period [17,22].

Guidelines in Sweden from 2016 recommend that each woman be asked about her mental health in early pregnancy, but structured identification is not stipulated [21]. Furthermore, guidance concerning several aspects of maternity care (maternal health care, delivery, and postnatal care) has been subsequently published in 2022 and 2025 by the National Board of Health and Welfare [17,23]. Regarding perinatal mental health, the guidelines recommend that a structured and systematic approach with anamnesis of previous or ongoing moderate-to-severe mental illness in early pregnancy, including identification of depression and anxiety symptoms, should be used in maternal health care. The purpose is to enable preventive measures and early interventions, as well as in-depth assessment and diagnosis by a psychologist or physician, in order to address risks that may negatively affect parenting and thus the child.

According to the different guidelines, various implementations concerning antenatal and perinatal mental health have been established in different regions of Sweden. In Västmanland Region, a program for psychosocial assessment during pregnancy was implemented in spring 2020, according to national and international recommendations [16,21,24,25]. The purpose of the implementation was to provide women with appropriate interventions as early as possible during pregnancy, achieve equity in health care, decrease the postpartum depression rate, facilitate the midwives' work, and develop collaborations between midwives and psychologists. The model used during the implementation process is closely aligned with the Quality Implementation Framework [26,27], and its phases correspond well to those applied in our implementation. The Quality Implementation Framework offers a comprehensive, structured approach for guiding the implementation process, with a focus on facilitating the translation of evidence-based practices into real-world settings [26]. In addition, our implementation process and associated strategies draw upon elements from other established process models and frameworks; however, the effectiveness or outcomes of the implementation itself will not be evaluated in this study.

Although guidelines have been published and various working methods have been implemented across Swedish regions, there is still a lack of evidence supporting a specific method, and no national consensus has been established regarding the most appropriate approach. Moreover, no scientific evaluation has yet been conducted to assess the effects of implementing a program to identify mental ill-health during the perinatal period in Sweden, despite its presumed importance for informing clinical practice. Although several countries have developed clinical guidelines for addressing perinatal mental health, their implementation and evaluation in practice remain insufficiently unexplored, both in Sweden and internationally. This limits our understanding of how to translate these guidelines into routine care and optimize outcomes for mothers, families, and health care systems. To address this knowledge gap, this project was initiated alongside the program's implementation, to evaluate its effectiveness from both patient and professional perspectives.

Aim

The general aim of this research project is to investigate the effects of a program in maternal health care for psychosocial assessment during pregnancy.

Primary Objectives

Objective 1

The first objective aims to answer: Does a program for psychosocial assessment during pregnancy influence the prevalence of pregnant women receiving psychological or medical treatment for mental ill-health?

Objective 2

The second objective aims to answer: Does a program for psychosocial assessment during pregnancy influence the time point for identification of mental ill-health in pregnant women?

Secondary Objectives

Objective 3

The third objective aims to answer: Does a program for psychosocial assessment during pregnancy influence the measures taken within the health care system and collaboration between the maternity clinic, perinatal psychologists, and other health care providers and agencies when mental ill-health is identified?

Objective 4

The fourth objective aims to answer: Does a program for psychosocial assessment during pregnancy influence women's experiences with receiving help and support for identified mental ill-health?

Objective 5

The fifth objective aims to answer: What is the experience of midwives and psychologists when working with the program for psychosocial assessment during pregnancy?

Methods

Objectives

This study protocol outlines the full structure of an ongoing research program composed of multiple objectives, each at different stages of progress. Although certain elements—particularly parts of the data collection—have already been completed, others remain in the planning stage. The current status of each objective is as follows:

- Objectives 2-5: Participant recruitment has been completed.
- Objectives 1-3: Data collection is planned for 2025-2026, with results expected to be compiled in 2026.
- Objective 4: Data collection was completed in 2022; data analysis and results compilation are scheduled for 2025.

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- Objective 5: Data collection was completed in 2024; analysis and results compilation are scheduled for 2025.

Settings

The population of Sweden is approximately 10.5 million [28]. Västmanland Region, one of Sweden's 21 regions, is of medium size with approximately 280,000 inhabitants and is located 108 km from Stockholm, the capital of Sweden. It is reasonably representative of Sweden in terms of the distribution of urban and rural areas, employment, income, education, and immigration levels. In 2023, there were 100,050 births in Sweden, of which 2568 occurred in the Västmanland Region [29].

In Västmanland Region, there are 26 maternity clinics spread out over the region. Approximately 55 midwives are employed; most clinics have 1 to 3 midwives, while 3 are staffed by 4 midwives. Since the implementation began, 3 clinics have closed, and 2 clinics have been added.

Development and Implementation of a Program for Psychosocial Assessment During Pregnancy

The first author (YLL), a coordinating midwife and health care developer, and second author (HN), a psychologist specializing in perinatal mental health and health care developer, are both employed in the regional central maternal health care team and led the implementation and practical training for midwives. The implementation was conducted in collaboration with an associate professor and psychologist specializing in perinatal mental health.

Implementation Strategies

We involved 15 midwives and several psychologists in the design and adaptation of the program, as well as a pilot project to facilitate implementation in clinical practice. The program for psychosocial assessment was created concurring in content with, but actually preceding, the aforementioned national recommendations. The midwives' experiences and opinions were recorded during meetings, and additional adjustments were made based on their suggestions for improvement. The adjustments were as follows: In addition to being asked in early pregnancy, all pregnant women are asked the questions about mental health (including the Whooley questions [30] and Generalized Anxiety Disorder 2-item [GAD-2] [31], see the following sections) again at gestational week 33. Those identified with mental ill-health and illness during pregnancy are asked again postpartum; in-depth questions concerning thoughts and feelings about childbirth, aimed at identifying fear of childbirth, are included; and the timing of questions concerning exposure to violence (already part of the health care program prior to the introduction of the program) was altered.

To carry out the implementation, the clinics' funding was increased according to experiences in the pilot project. During the implementation, the need for contact with the psychologists also increased, and additional funding for psychological treatment was thus provided.

The program was developed, and supporting material was created to facilitate the midwives' work. Collaborations between psychiatrists, obstetricians, general practitioners, and psychologists were established to clarify the referral pathways for women with identified mental illness or ill-health. Establishment of a multidisciplinary consulting team was reinforced with the aforementioned professionals, to provide guidance for the midwives regarding the management of the women identified with severe mental illness, as well as to strengthen the collaboration with other health care providers.

A central part of the implementation was to facilitate the midwives' work and to ensure fidelity to the program. It was conducted with continual briefings in connection with their routine group consultations with the psychologists, and additional education and support were offered both individually and in small groups. To develop the consultation education, a consultation methodology took place at different levels for psychologists and midwives. Education concerning the program for psychosocial assessment was subsequently included in the mandatory introduction program for newly employed midwives.

Challenges in the Implementation

The maternity clinics in Västmanland Region are scattered throughout the county, and many clinics are quite small. As elsewhere in Sweden, there has also been a shortage of midwives in the region for several years. Combined with a vulnerable organization, this initially led to some difficulties in ensuring adherence and fidelity to the program, and implementation took longer than expected. A plan was conducted to facilitate the implementation process, with continuous information and education, support, and follow-up. The implementation process also took place during the COVID-19 pandemic, another aggravating circumstance.

Description of the Program for Psychosocial Assessment

The program for psychosocial assessment comprises several components and is integrated into the overall maternity health care program for pregnancy monitoring in the Västmanland Region. It also includes consultation with psychologists and referral pathways to other health care providers. An overview of the program for psychosocial assessment is presented in Figure 1. The maternal health care program as a whole comprises 9 to 10 antenatal visits, ensuring comprehensive monitoring and support throughout pregnancy. The postpartum assessments (shown after the dashed line in Figure 1) will not be included in this evaluation.

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Figure 1. Overview of the program for psychosocial assessment (Västmanland Region), including maternity clinic visits and questions about mental health and social factors at various gestational weeks (+days); the visits after the dashed line (postpartum) will not be included in this evaluation. EPDS: Edinburgh Postnatal Depression Scale; GAD-2: Generalized Anxiety Disorder 2-item.

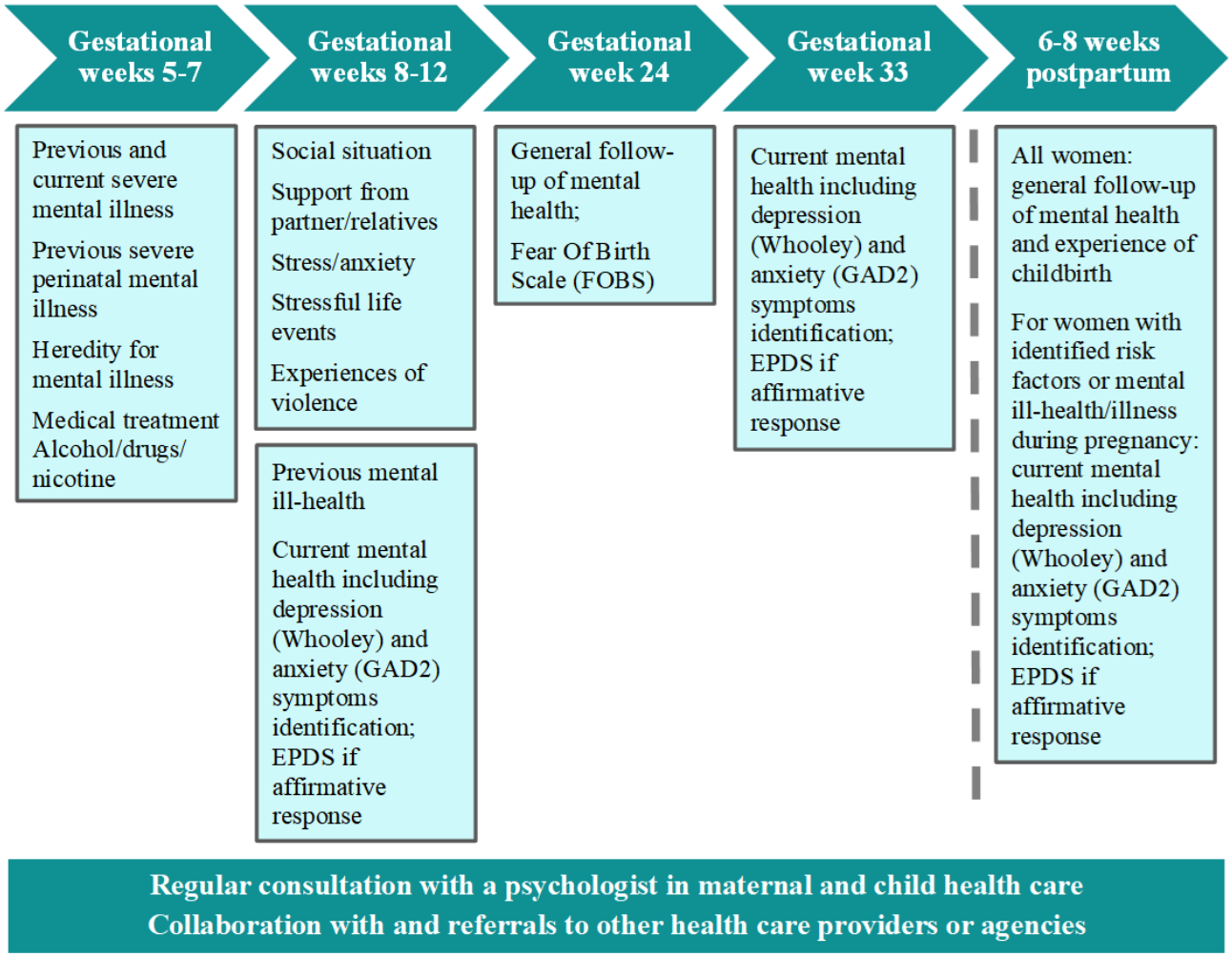

At the first visit (gestational weeks 5-7), the midwife asks all women questions about prior and ongoing serious mental illness or perinatal mental illness and treatment, as well as family history of serious mental illness or perinatal mental illness. At the second visit, which takes place a few weeks later (gestational weeks 8-12), questions are asked concerning prior and ongoing less serious mental ill-health, symptoms of stress and anxiety, social situation, support from relatives and network, and experiences with domestic violence.

Moreover, to specifically identify symptoms of depression and anxiety during the conversation about mental ill-health, the midwife asks all women the Whooley questions [30] and GAD-2 questions [31].

The Whooley questions are designed to identify symptoms that may be present in depression. The questions are as follows:

- During the past month, have you often been bothered by feeling down, depressed, or hopeless?
- During the past month, have you often been bothered by little interest or pleasure in doing things?

The GAD-2 is a brief initial screening tool aimed at identifying symptoms of anxiety. The questions are as follows:

- Over the last two weeks, how often have you been bothered by feeling nervous, anxious, or on edge?
- Over the last two weeks, how often have you been bothered by not being able to stop or control worrying?

If the woman responds in the affirmative to any of these 4 questions, the Edinburgh Postnatal Depression Scale (EPDS) [32] is administered to aid further assessment [2,21,24]. The EPDS is a comprehensive 10-item self-rated scale for identifying symptoms of depression [32]. It has been validated in Sweden for use during pregnancy [33].

The Fear of Birth Scale [34,35] is a self-rated scale administered at gestational week 24 to identify fear of birth. If needed, additional visits are offered for childbirth preparation. There is also the possibility of referral to the Obstetrics Department's specialist unit for assessment and care planning with a midwife, obstetrician, and perinatal psychologist.

The program for psychosocial assessment also includes an action plan for those identified as having a mental illness, including collaboration with other relevant providers and agencies. Routine consultations with psychologists provide midwives support in their assessments and in clinical decisions around referral for further assessment and treatment.

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As aforementioned, women for whom risk factors or manifest mental illness have been identified during pregnancy are asked the Whooley and GAD-2 questions again at the postpartum visit, 6 weeks to 8 weeks after birth. This somewhat overlaps with the program at Swedish child health clinics, according to which the nurses administer the EPDS as a general screening method for all women at approximately 8 weeks postpartum [36].

Study Design

The study will use a multimethod design incorporating both quantitative and qualitative research approaches. The quantitative part includes pre- and postimplementation assessments through the extraction of register-based data on all pregnant women in Västmanland Region during the defined pre- and postimplementation periods (objective 1). Furthermore, questionnaires and medical record data will be collected from study participants (objectives 2-4). The qualitative part will comprise focus group interviews with midwives and psychologists in maternal health care to explore their experiences with and perceptions of the implementation (objective 5). Detailed descriptions of the study design are provided in the corresponding sections for each objective. An overview of the study design is presented in Figure 2.

Figure 2. An overview of the research project, including study designs, data sources, included participants, and time periods.

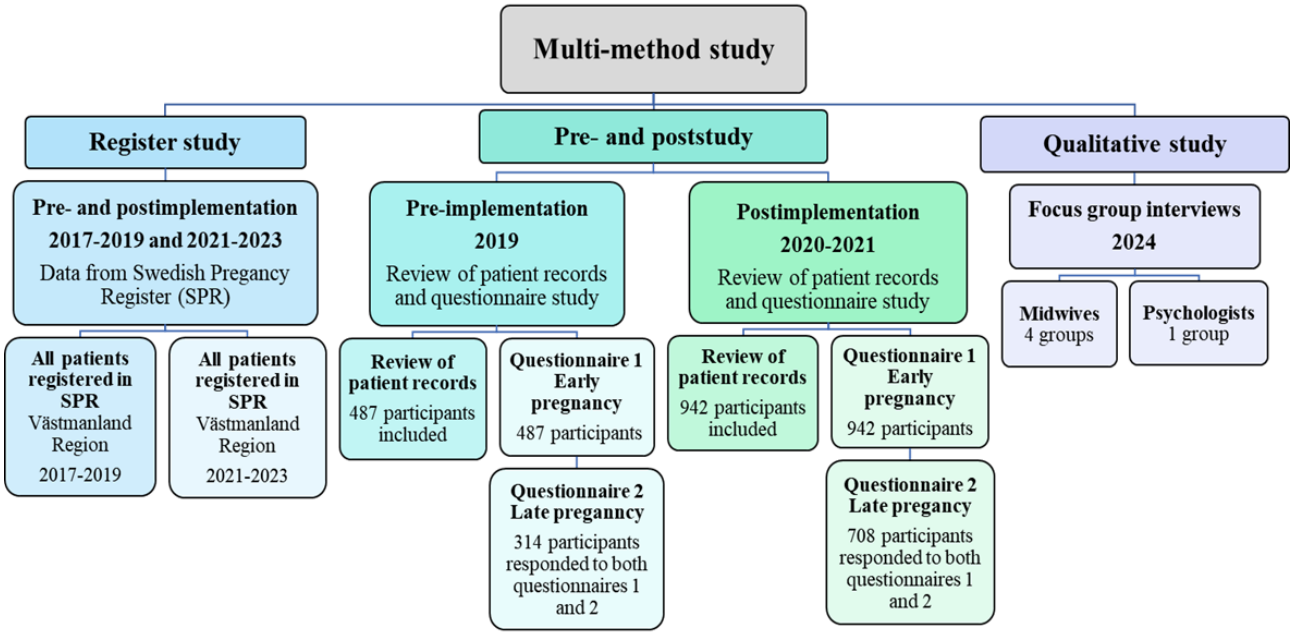

Estimated Sample Size and Power

Sample Size Calculation

Calculation of the sample size was initially based on objective 1, using Minitab 16. The calculation was based on data from the SPR 2017 with a 7% initial prevalence of mental ill-health among pregnant women in the Västmanland Region [37], with an expected increase to 10% due to the rise in detection attributable to the program's implementation. In order to detect an increase by 3 percentage points in identified mental ill-health, with 80% power and a significance level of 5% (2-sided test), at least 534 pregnant women had to be included in each group. The inclusion of several different maternity clinics in the project was also taken into consideration, and we estimated a dropout rate of approximately 20%. This meant that 640 pregnant women had to be included in each group for both pre- and postimplementation measurements.

However, the emergence of the COVID-19 pandemic introduced unforeseen challenges, particularly with regard to participant recruitment and data representativeness. It was hypothesized that the pandemic may have influenced the prevalence of mental ill-health in the target population, potentially confounding the original pre-post comparisons.

In response, a revised strategy for objective 1 was implemented. A new ethical approval was obtained to extend data inclusion and allow for the anonymous use of aggregated register data from the SPR, covering all pregnant women in the Västmanland Region during 2017-2019 (preimplementation) and 2021-2023 (postimplementation). This adjustment enabled a substantial increase in sample size and improved the generalizability of findings for objective 1 while minimizing selection bias and increasing statistical power.

Importantly, although the revised strategy for objective 1 now relies on registry-based data with a broader population base, the original sample size calculations remain valid for objectives 2-4, which continue to use the survey-based data set from pre- and postimplementation phases. The sample size for these objectives was not altered, and the statistical power for each is described in general terms in the following paragraphs.

Furthermore, addressing the recruitment challenges faced for objectives 2-4, it is crucial to note the difficulties encountered in achieving the initial target sample size. Specifically, we aimed to recruit 640 participants in the pre-implementation phase but were only able to enroll 487. This shortfall contrasted with the implementation phase, during which we successfully recruited 942 participants.

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Given the research design outlined in the preceding paragraphs, together with the collected data, this will provide the opportunity to test a wide array of hypotheses in the current research area. Specifically, it is suitable for testing hypotheses involving both dichotomous outcomes, with lower or higher pre-implementation prevalence, and a wide range of continuous outcomes, including when testing for small, standardized differences.

Dichotomous Outcomes

The minimum detectable difference (MDD) with this design varies inversely with the pre-implementation prevalence. For instance, it can reliably, with 80% power, discern an 8% change in a 50% pre-implementation prevalence and more refined changes—such as 5% at a 10% prevalence or 4% at a 5% prevalence, with the same power at a higher prevalence (90% and 95%). This makes the design ideal for testing hypotheses expected to result in either a marked increase or decrease in prevalence rates, ensuring accurate detection of both common and rare conditions, as well as self-rated dichotomous factors according to the questionnaire data.

Continuous Outcomes

The study has the capacity to detect minimal standardized differences as small as 0.15 with 80% power. This level of sensitivity is particularly beneficial for hypotheses investigating subtle changes in continuous measures, such as gradual improvements or declines in health measures, psychological scores, continuous variables according to the questionnaire data, or any other continuous outcomes that fall well within the scope of this design. Given these conditions, the study design is suitable for a broad spectrum of hypotheses and can be used effectively to advance our knowledge in this field.

Handling of Missing Data

The proportion of missing data is expected to be low. Based on register quality and the data collection design, fewer than 5% of individuals are anticipated to have missing values for any variable included in the planned analyses. To assess whether the assumption of missing completely at random (MCAR) is valid, an MCAR test will be performed. This test examines whether the probability of missingness is independent of both observed and unobserved variables. If the assumption of MCAR is supported, complete-case analysis will be deemed appropriate. Should the test indicate that data are not MCAR, we will explore the pattern and mechanism of missingness further, applying multiple imputation or models to assess the robustness of results under plausible missing data scenarios. The final manuscripts will report the MCAR test results, the chosen method, and any observed differences in findings.

Objective 1

Study Design

The study design incorporates pre- and poststudy measurements with comparison of pre- and postimplementation of a program for psychosocial assessment.

Participants and Data Collection

Data will be extracted from the SPR for all registered pregnant individuals in the Västmanland Region, preimplementation (2017-2019) and postimplementation (2021-2023) of the program. We chose 3-year periods for data extraction in order to obtain more representative data concerning any changes, as well as to counteract the effects of the COVID-19 pandemic.

The SPR is a national quality register with certification level 1 (the highest level). This accessibility is a prerequisite for the development of health care and consequently, for improving the health of pregnant women and their children, as well as promoting equitable care and high quality in the chain of care. Improvement work is facilitated by rapid feedback of SPR data and results. The SPR is a rich source for research in the field of pregnancy and childbirth. Of the 99,011 births registered in Sweden in 2023, 97,964 were registered in the SPR, a coverage rate of 98.9% [7].

Measurements

Objective 1 includes data from the SPR, which will be compared pre- and postimplementation of the program for psychosocial assessment, and captures the prevalence of patients who have received (1) medical treatment prepregnancy or during pregnancy, (2) psychological treatment for mental ill-health prepregnancy or during pregnancy, and (3) both medical and psychological treatment prepregnancy or during pregnancy.

Statistical Analysis

Logistic regression analysis, including an indicator variable for pre- and postimplementation, will be performed. The model will also include variables to adjust for potential confounding variables (eg, age, primiparous women, civil status, employment status, maternity clinic), selected according to the disjunctive cause criterion [38].

The effect measure will be the odds ratio (OR) with 95% CIs.

Statistical Power

Based on data from the SPR, which recorded 8246 births between 2017 and 2019 and 7611 births between 2021 and 2023, and an initial prevalence of identified cases of mental ill-health of 7%, the MDD for this register-based study was calculated. Using a 2-sided 2-sample z test for proportions with a 5% significance level (α=.05) and 80% power, the MDD was estimated at 0.8%. This indicates that the study will be capable of detecting changes of 0.8 percentage points or greater, thereby ensuring sufficient sensitivity to identify any clinically meaningful differences.

Objective 2

Study Design

Pre- and poststudy assessments were conducted, with comparison of pre- and postimplementation of a program for psychosocial assessment.

Participants and Data Collection

Pregnant women who could communicate in Swedish and who were enrolled in early pregnancy at maternity clinics in the Västmanland Region were invited to participate in the study. In the poststudy, patients from all 25 maternity clinics in the region were invited to participate. The women were sent an envelope by post with an invitation to participate, a consent

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form, and a questionnaire. Consent covered the review of medical records (objectives 2 and 3) and questionnaire data (objective 4).

Participant inclusion was completed in 2022. Pre-implementation (2019), a request for participation was sent to 887 patients, and 487 were included. Questionnaire 2 was sent to 512 patients, and 314 responded to both questionnaires 1 and 2. Postimplementation (2020-2021), a request for participation was sent to 2368 patients, and 942 were included. Questionnaire 2 was sent to 837 patients, and 708 responded to both questionnaires 1 and 2.

A review of medical records will be conducted in the specific data system for antenatal and perinatal health care used in the region, to extract data for objective 2.

Measures

Objective 2 includes data extraction from medical records for the following variables: gestational age at identification of symptoms of mental ill-health and gestational age at diagnosis of mental ill-health.

Statistical Analysis

For objective 2, survival analysis will be used to assess differences in the timing of mental ill-health identification during pregnancy. Group comparisons will be performed using Cox proportional hazards regression analysis, including an indicator variable for pre- versus postimplementation. The model will be adjusted for potential confounders (eg, age, primiparous women, civil status, employment status, maternity clinic), selected according to the disjunctive cause criterion [38].

The effect measure will be the hazard ratio with 95% CIs.

Statistical Power

To evaluate the statistical power of this component of the study, we estimated the MDD based on the expected number of events. Drawing on the prevalence estimates and sample sizes outlined in the section “Estimated Sample Size and Power,” we approximated a total of 142 events across both study groups. Assuming a 2-sided significance level of 5% and 80% statistical power, the study is capable of detecting a hazard ratio of approximately 1.65, based on the method by Schoenfeld [39]. This suggests that the study is sufficiently powered to detect a 65% or greater difference in the rate of identification of mental ill-health between the pre- and postimplementation groups.

Objective 3

Study Design

This pre- and poststudy design will compare the pre- and postimplementation of a program for psychosocial assessment.

Participants and Data Collection

Participant inclusion and data collection will be performed according to the description in objective 2.

Measures

Objective 3 includes data extraction from medical records for the following variables: whether the patient received psychological or medical treatment for mental ill-health that was initiated prepregnancy, whether the patient received psychological or medical treatment for mental ill-health that was initiated during pregnancy, and referral pathways to other health care providers when mental ill-health is identified.

Statistical Analysis

The proportion of patients referred to specific treatments before and after the intervention will be compared using logistic regression analysis. The primary focus will be on changes in referrals to psychological treatment. The regression model will include covariates selected based on the disjunctive cause criterion to adjust for potential confounding factors (eg, age, primiparous women, civil status, employment status, maternity clinic).

The effect measure will be the OR with 95% CIs.

Statistical Power

As described in the “Dichotomous Outcomes” subsection of the “Estimated Sample Size and Power” section, the study is powered to detect a change of approximately 4% to 5%, using a 2-sided test with an α level of 5% and 80% statistical power.

Objective 4

Study Design

This pre- and poststudy design will compare pre- and postimplementation of a program for psychosocial assessment.

Participants and Data Collection

Regarding objective 4, participant inclusion and data collection have been completed, and data management and analysis are ongoing. Participant inclusion was performed according to the description in objective 2. In the 2 different patient groups, pre- and postimplementation questionnaires were sent twice during pregnancy. The first questionnaire was administered in early pregnancy after the first 2 visits to the midwife, and the second questionnaire was administered after gestational week 33.

Measures

The questionnaires covered the following areas: whether the midwife had asked questions about the participants’ mental health, their experience with the maternity clinic visits, whether they had been given support and help, previous psychiatric diagnoses, current mental health, treatment for mental ill-health during pregnancy, fear of childbirth, and self-assessed mental health.

Objective 4 will include questionnaire data for the following questionnaire items:

- How is your current mental health? (scale 1-10; 1=very poor, 10=very good)
- Have you had any psychological or psychiatric disorder diagnosed by a health care professional? (dichotomous response: Yes or No)
- To what extent do you feel that you received help for your mental health from your midwife? (scale 1-10; 1=not at all, 10=to a high degree)
- If you had extra visits with the midwife, to what extent do you feel they helped you? (scale 1-10: 1=not at all, 10=to a high degree)

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- Did the midwife refer you to another health care provider? (dichotomous response: Yes or No)
- How long did it take to get in contact with another health care provider? (number of gestational weeks)

Statistical Analysis

Dichotomous outcomes will be analyzed using logistic regression models, while continuous outcomes will be analyzed using linear regression models. The regression model will include covariates selected based on the disjunctive cause criterion, to adjust for potential confounding factors (eg, age, primiparous women, employment status, maternity clinic).

For dichotomous outcomes, effects will be expressed as ORs with 95% CIs. For continuous outcomes, effects will be reported as mean differences, also with corresponding 95% CIs.

Statistical Power

As described in the "Estimated Sample Size and Power" section, the study is powered to detect a change of approximately 4% to 5% for dichotomous outcomes using a 2-sided test, with an α level of 5% and 80% statistical power. For continuous outcomes, the study is designed to detect standardized mean differences of approximately 0.15.

Objective 5

Study Design

Focus group interviews will be conducted with an exploratory qualitative design and content analysis.

Participants and Data Collection

Regarding objective 5, participant inclusion and data collection have been completed, and analysis will be conducted in the next phase of the study. Participants are midwives who were working in the Västmanland region before, during, and after implementation of the program, as well as those who were employed after the implementation. We have conducted 4 focus group interviews with 3 to 5 midwives in each group, and we also included 1 group with 4 psychologists within maternal and child health care. The participants received verbal and written information and provided written consent.

Measures

Data were collected during semistructured focus group interviews based on an interview guide. Questions explore experiences with working with the program and whether the content of the consultation with psychologists and collaboration with other health care providers and agencies changed following the implementation of the program. The interviews were recorded and transcribed verbatim.

Data Analysis

Qualitative content analysis with an inductive approach, according to that by Graneheim and Lundman [40], will be undertaken [41,42]. The interviews will be analyzed by the authors. To obtain an overall impression of the data, the transcripts will be read repeatedly. Meaning units will be extracted, condensed, and coded according to relevance to the study aim. The codes will be sorted into subcategories with similar manifest content. The subcategories will be sorted into categories, followed by abstraction and interpretation of both manifest and latent content. The analysis process will be repeated several times and subsequently reviewed by one researcher with extensive experience in qualitative methods in order to ensure trustworthiness.

Ethical Considerations

This project is carried out in accordance with the latest version of the Declaration of Helsinki and has been approved by the Swedish Ethical Review Authority (permit numbers 2018-331, 2018-332, 2019-02380, 2020-03479, 2020-06902, 2023-01892-02). All data will be managed and securely stored according to the General Data Protection Regulation (GDPR).

All collected materials, including interviews, questionnaires, and medical records will be treated with strict confidentiality and de-identified to protect participant privacy. Data management and storage at the Centre for Clinical Research in the Västmanland Region will strictly adhere to GDPR to ensure security.

Participants were provided information about the study, a consent form, and a questionnaire. Consent was requested to access data from the questionnaire and from medical records. Participants were informed that they had the right to withdraw from the study at any time. The completed questionnaires were sent directly to the Centre for Clinical Research in the Västmanland Region to ensure confidentiality. The review of medical records will be limited to the patient record system for pregnancy and delivery care, which is separate from the general medical records stored in the general system. All participants were informed that their responses would only be reported at a group level, ensuring individual confidentiality.

The participants received a gift card of Sk200 (US $20.91) following completion of the second questionnaire.

Results

Study Status

The recruitment of participants for objectives 2-5 is complete. Data collection for objectives 1-3 is planned for 2025-2026, with compilation of the results during 2026. Data collection for objective 4 was completed in 2022, and data analysis and compilation of the results are planned to be conducted in autumn 2025. Data collection for objective 5 was completed in 2024, and analysis and compilation of the results are also planned for autumn 2025.

The data collection for objectives 2-4 was extended in scope and time, as implementation took longer than estimated due, among other factors, to the COVID-19 pandemic outbreak in the first quarter of 2020 [43]. The pandemic was expected to create temporarily elevated levels of mental ill-health and illness, especially during pregnancy. Health care services in Sweden introduced restrictions for pregnant women's partners accompanying them during and after pregnancy, which might have affected both expectant parents.

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Impact of Confounders and Contextual Factors

Several potential confounding factors must be acknowledged when interpreting the results of these future studies. The implementation was conducted within a fragmented organizational context, where variations between units in staffing, resources, and clinical priorities may have influenced both the fidelity of the program and its outcomes. In addition, the implementation coincided with the COVID-19 pandemic, which introduced significant and unpredictable changes in clinical practice, patient flow, and staff availability. Importantly, the pandemic itself is likely to have influenced the measured outcomes, as it contributed to increased levels of anxiety, stress, and other forms of mental ill-health among pregnant women. These factors may impact the effectiveness and the evaluation of the program, and the analysis of results must therefore be interpreted with these limitations in mind.

Discussion

In this research project, we are in the process of investigating the effect of a program for psychosocial assessment during pregnancy.

Principal Findings

This research project underscores the importance of early identification and treatment of mental health issues during pregnancy. Timely intervention can improve maternal mental health outcomes, including reducing the occurrence of postpartum depression [14,24]. This is crucial for the overall well-being of both the mother and the newborn. Furthermore, this research project explores midwives' and psychologists' experiences of working with the program, including consultation and collaboration with other health care providers and agencies following the implementation of the program. Improved collaboration and consultation can lead to a more comprehensive and coordinated approach, ensuring that pregnant women receive holistic care and support [17]. Another important aspect is the midwives' and psychologists' involvement in the evaluation process, allowing for insights into their experiences with the program and related training.

Research in the field of perinatal mental health can contribute to the ongoing development of maternal health care. The results of this research project are expected to be highly relevant for maternal health care, both in the national and international context and from several perspectives. The implementation of this program during pregnancy, as subsequently stipulated in the Swedish national recommendations, can serve as a model contributing to a more standardized and effective approach to maternal health care. If successful, the method might influence national guidelines and policies, setting a precedent for other regions and potentially attracting international attention as a model for improving maternity care. Our findings can further inform enhanced training and professional development programs, ensuring that health care professionals are well-equipped to implement programs for psychosocial assessment and provide high-quality and equitable maternal health care.

Comparison With Prior Work

Evidence on the effectiveness of screening and identification methods remains unclear, with variations across health care systems. In the United Kingdom [24] and Canada [44], a stepped approach is recommended, combining verbal questions with self-report scales. In the United States [45] and Australia [46], universal depression screening using the EPDS [30] is advocated, contingent on availability of diagnostic assessment, treatment, and follow-up. In Australia, psychosocial assessment is also recommended [47]. However, a recent Canadian review questioned the effectiveness of screening during pregnancy and postpartum when relying solely on an instrument [48].

Strengths and Limitations

The research project includes comparison of the periods pre- and postimplementation. This is challenging, as the COVID-19 pandemic occurred in the early 2020s, in close proximity to the introduction of the program for psychosocial assessment. Our analytic strategy will need to include ways to account for the pandemic's effects.

On the other hand, this project has many strengths, including the population-based design, uniformly designed educational programs for all midwives, and use of both quantitative and qualitative methods. Data sources include patient questionnaires, review of medical records, quality register data, and focus group interviews with midwives and psychologists. This multimethod design, combining pre- and poststudy assessment comparisons for patients and including the professionals' perspective, is likely to enhance validity, depth, and interpretability. The findings will allow for both statistical evaluation of changes over time and a deeper understanding. This design is comprehensive and holistic, contributing to both theoretical and practical applications in the field.

No previous study has been conducted in Sweden to investigate the effect of a program of this type, and the results will thus be highly relevant for maternal health care in Sweden.

Clinical Implications

Research in the field of perinatal mental health can contribute to the ongoing development of maternal health care. The results of this research project are expected to be highly relevant for maternal health care, both in the national and international context, and from several perspectives. The implementation of this program during pregnancy, as subsequently stipulated in the Swedish national recommendations, can serve as a model, contributing to a more standardized and effective approach to maternal health care. If successful, the method might influence national guidelines and policies, setting a precedent for other regions and potentially attracting international attention as a model for improving maternity care. Our findings can further inform enhanced training and professional development programs, ensuring that health care professionals are well-equipped to implement programs for psychosocial assessment and provide high-quality and equitable maternal health care.

In summary, this research project is expected to contribute with a positive impact on the care chain in maternal health care by

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promoting early identification, improving support and treatment, implementing a structured approach, and fostering collaboration, to promote professional development and equitable health care. These outcomes collectively contribute to a more effective and patient-centered approach to maternal health care.

Dissemination Plan

The dissemination plan encompasses continuous efforts toward the publication of several original research papers and the completion of two doctoral theses. It is hoped that this work will inspire further research, implementation, and evaluation of structured approaches addressing perinatal mental health.

Future Directions

This research project has the potential to contribute to further studies within perinatal mental health and the application of interventions in clinical practice. However, there are several important questions that we will not be able to explore in depth and which we hope future research will address. An important knowledge gap is the investigation of the long-term effects of interventions in this area. Another important aspect is considering patients who do not speak Swedish—a group we excluded in this research project but one that is essential to evaluate in order to tailor methods and programs to their needs, particularly in relation to how cultural and contextual factors affect the implementation and outcomes of interventions. An additional area of interest is the development of theoretical models to better understand the mechanisms underlying observed effects, which could contribute to more effective interventions. Finally, it would be valuable to evaluate the implementation process itself and examine the effects of interventions under conditions without the presence of an ongoing COVID-19 pandemic, in order to understand how external factors influence the implementation process.

Acknowledgments

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The authors used ChatGPT (GPT-4-turbo, Open AI) for language editing and proofreading during the final phase of this manuscript. We confirm that ChatGPT or any other artificial intelligence (AI)–generated tools were not used to develop this research project or the content in this manuscript. The authors take full responsibility for the content and interpretation of the manuscript.

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Data Availability

The data sets generated or analyzed during this study cannot be publicly shared due to ethical or legal reasons but are available from the corresponding author on reasonable request.

Authors' Contributions

YLL, HN, AS, and CÅ were involved in the conception and design of the study. The first draft of this manuscript was written by the first author (YLL). YLL, HN, AS, and CÅ revised the draft critically for intellectual content, approved the final manuscript, and contributed to the continuation of the project.

Conflicts of Interest

None declared.

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Abbreviations

EPDS: Edinburgh Postnatal Depression Scale
GAD-2: Generalized Anxiety Disorder 2-item
GDPR: General Data Protection Regulation
MCAR: missing completely at random
MDD: minimum detectable difference
OR: odds ratio
SPR: Swedish Pregnancy Register

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Protocol

Patient Experience of Virtual Hospital Care Provided by a Multidisciplinary Team: Protocol for a Mixed Methods Study

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Abstract

Background: Virtual hospitals are defined as the delivery of hospital-level health care via digital services such as videoconferencing technologies, digital platforms, and remote monitoring. The purpose is to leverage virtual technologies to deliver accessible patient-centered care, improve the overall health of communities, and implement improvements driven by real-time access to patient data. Patients and their caregivers have increasingly favored these alternative and complementary service delivery models alongside traditional in-person care. However, this is still a complex issue, and the current literature points to a variety of challenges that need to be overcome to provide optimal models of care.

Objective: This study aims to identify unique challenges to virtual hospitals providing multidisciplinary care for patients at home, and co-design recommendations to improve the patient experience.

Methods: This research is a mixed methods exploratory case study of a virtual hospital in Sydney, New South Wales, Australia. The methods include (1) document analysis: this will be used to identify the current formal processes that govern the virtual hospital; (2) secondary analysis of data: a detailed investigation of existing data collected by the virtual hospital, for example, patient-reported experience measures, patient-reported outcome measures, and other available data; (3) observations of current practices; (4) semistructured interviews; (5) co-designed focus groups; (6) economic analysis; (7) comparative case study; and finally, (8) a triangulation analysis. To synthesize these findings within a unified analytical framework, all data will be subjected to open or axial coding following the Strauss framework, allowing the convergence of themes across codes and methods.

Results: As of April 2025, observations and initial documentation analysis have begun. Multidisciplinary team meetings and clinician shadowing have commenced, along with analysis of Standards of Practice documents.

Conclusions: This protocol outlines a mixed methods case study on a new virtual hospital located in Sydney, New South Wales, Australia. We anticipate our results to provide a comprehensive understanding of patient experience through a range of quantitative and qualitative research activities. We will achieve this by identifying challenges for patients, carers, and health care workers, and documenting informal solutions discovered through our research activities.

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KEYWORDS

co-design; health economics; multidisciplinary teams; recommendations; remote monitoring; virtual care; virtual hospitals

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Introduction

Overview

Virtual hospitals are complex, emerging health care initiatives that remotely provide health care to patients. They achieve this via digital services such as videoconferencing technologies, digital platforms, and remote monitoring [1,2]. The purpose is to leverage digital technologies to deliver hospital-level care to patients at home [3]. Increasingly, patients and their caregivers have favored these new virtual care alternatives and complementary service delivery models alongside traditional in-person care [4]. However, virtual hospitals are still in their infancy, and the current literature points to a variety of challenges that need to be overcome to provide optimal models of care [5-13]. The goal of this research is to identify the challenges of an emerging Australian virtual hospital and develop novel recommendations to improve the patient experience.

Of the variety of challenges patients of virtual hospitals face, one example is the difficulty in building clinician-patient rapport through virtual communication [14]. This was highlighted in a study of a virtual rural service in New South Wales (NSW), where there was a desire for continuity of care and how it was difficult to accommodate patients' preference for "a doctor who knows me" [15]. Another study, a review of telehealth in emergency medicine in Australasia, investigated the difficulties of ensuring the safety of virtual hospital patients [16]. Specifically, when and how to escalate for help, or ways to conduct safe and accurate physical examinations [8]. This challenge is concerning considering the technological barriers patients might encounter when accessing virtual care [5-7]. However, virtual care driven by mobile conferencing technologies can be highly supportive to assist low-staffed emergency departments (EDs). These "virtual care carts" provide an effective communication tool for health care workers, but their use raises questions about appropriateness and lack of privacy when using such technologies in crowded rural emergency rooms [15]. In addition, there has been an increase in additional responsibilities shifted to patients when using virtual care [9-11] (such as setting up remote monitoring technologies at home), calling for further research into the impact of unintended burdens on carers and family support systems [11,12].

The literature also highlights challenges from the perspective of virtual hospital health care workers. One study on a virtual rehabilitation service found that the medical complexity of patients, such as patients with heart failure and cognitive impairments, can impact a health care worker's confidence in virtual care delivery [17]. This can be exacerbated with virtual care's disruption to the clinical culture of a health care team. For example, an interview study of health care workers from 3 NSW virtual hospitals found that the shift to virtual care required a time-consuming and extensive adoption process [18]. This is in addition to the shift in responsibilities for health care workers, requiring further staff training to increase the efficiency, reach, and utility of available virtual hospitals [9-11,17]. Finally, there is a lack of studies and tools available to health care workers to help assess whether patients (and their carers) are appropriately referred to and supported during virtual care [6,11,13].

Virtual hospital solutions, such as the Virtual Care Services (VCS) in the Northern Sydney Local Health District (NSLHD), have made great strides in providing remote health care. In particular, NSLHD VCS uses digital technologies to empower a multidisciplinary approach (eg, collaborative care from nurses, doctors, allied health, social workers, etc) to provide hospital-level care to patients at home. This protocol analyzes and improves the benefits of NSLHD VCS by identifying challenges patients, carers, and health care workers encounter and co-designing practical solutions to improve the patient experience. These perspectives will be analyzed according to the process, clinical, and economic stances, and compared between (1) different timepoints (eg, before and after introduction of VCS), (2) virtual and in-person services, (3) Work-As-Imagined (WAI) and Work-As-Done (WAD), and (4) different stakeholder viewpoints. In addition, the research will conduct a comprehensive economic analysis to assess the economic impact of virtual care on patients, carers, health care workers, and NSW Health. This includes identifying financial implications and the economic impact of implementing and operating VCS from NSLHD's perspective. This study also answers the call for a more rigorous analysis of virtual care solutions using a multimethod approach [19], aiming to co-design practical recommendations to enhance patient safety, improve quality of care, and optimize health care service provision [20].

Study Setting

This study examines the launch of NSLHD's VCS. The goal of the service is to support virtual health care in the NSLHD, which was created in response to the growing demand for health care services in NSW [21]. Physically located in Royal North Shore Hospital, this new service is part of the NSW Health Digital strategy and is a key initiative to facilitate and support the delivery of virtual care to patients and the community across the NSLHD [22]. The services include several health condition–specific models of care, including but not limited to the following:

1. AvoidED: This is an integrated formalized pathway in which NSW Ambulance clinicians can safely access a centralized point of contact for clinical discussion and referral of clinically appropriate patients to NSLHD VCS to reduce preventable presentations to NSLHD EDs.
2. Hyperemesis gravidarum model of care: This is an assessment and care model to provide referral of care between hospital- and community-based services for women impacted by hyperemesis gravidarum.
3. Frailty model of care: An evidence-based 2-week program for older patients who have been assessed as "Frail" at hospital discharge provides follow-up care to reduce the possibility of ED representation within 4 weeks of hospital discharge. This program provides patients with (1) a follow-up on the hospital discharge plan, (2) safety netting and escalation of care as appropriate, (3) virtual physiotherapy services at home, and (4) referral and linkage

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to community-based services for long-term frailty management.

The NSLHD VCS was created to support existing health care services and facilitate access to hospital-level care in a patient's home. Figure 1 depicts a summary overview of the process of how a patient might interact with NSLHD VCS. The alternate pathway choices are by referral from clinicians.

Figure 1. Virtual hospital summary diagram. ED: emergency department; NSLHD: Northern Sydney Local Health District.

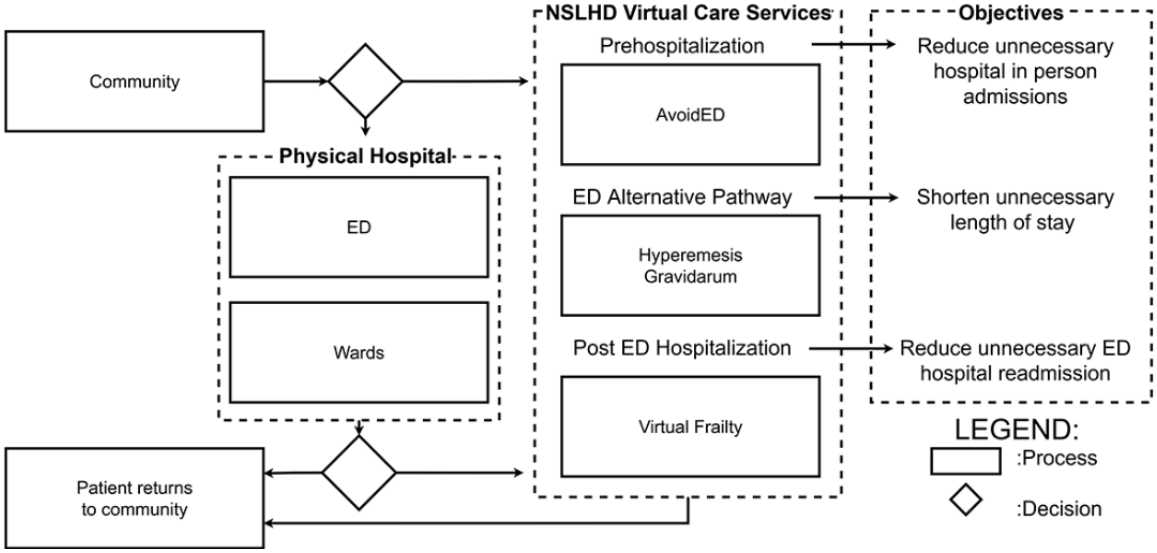

Aim

The primary aim of this study is to evaluate models of care within the NSLHD VCS from the patient's perspective. We will investigate challenges encountered by patients and carers via exploring their experience, identifying existing informal solutions, and collaboratively co-designing recommendations to improve the service. Our secondary aim is to identify these services' clinical outcomes and economic impact. By understanding the financial implications of this service, NSW Health can be better equipped in its decision-making process to provide the best possible care for the patient.

Methods

Research Activities

Considering the novel approach of NSLHD VCS [23,24] and its complex structure [25], this study will use an exploratory mixed methods case study. The purpose of using this approach is to use established mixed methodologies to construct a quality [26], rigorous [27], and credible study [28].

The study was built on a series of stages: (1) document analysis, (2) secondary analysis of data, (3) observations, (4) semistructured interviews, (5) co-designed focus groups, (6) economic analysis, (7) comparative case study, and (8) a triangulation analysis. The expected outcome of this study is a comprehensive understanding of how NSLHD VCS operates [29] and the production of a practical list of recommendations for its improvement [30].

This research protocol and methodology have been presented to a 10-member consumer panel, where it was received positively. Their feedback has been incorporated in shaping our research questions, research activities, and data analysis strategies.

Stage 1: Document Analysis

This initial stage of research aims to identify any documentation that will allow the research team to better understand how these models of care function at the NSLHD VCS (eg, WAI). This includes a review of documents such as (but not limited to): referral and assessment forms, care escalation protocols, internal documents (eg, Standards of Practice [SOP], resources involved, system use, and time spent on various activities), working group documents, official escalation processes, and other publicly accessible documents. The analysis will be guided by Altheide and Schneider's 12-step and 5-stage process (eg, document sampling, protocol development and data collection, data coding and organization, data analysis, and reporting) [31]. Depending on the focus of our investigation, we may consider conducting content or thematic analysis, where an inductive approach will be applied to identify WAI aspects (eg, patient safety and care escalation) contained in the documents.

These data will also be used to inform the study design of prospective data collection approaches (observations, interviews, and focus groups), and as a secondary method in future triangulation of data analysis with the other research activities to contextualize and understand WAI.

Stage 2: Secondary Analysis of Data

The secondary analysis refers to data previously collected by the NSLHD VCS as part of routine procedures and processes. This can include (but is not limited to): (1) patient-reported experience measures; (2) patient-reported outcome measures; (3) administrative data, such as the number of referrals, admission rates, number of separations, and discharge summary reports; (4) process-specific data, such as a model of care workflows and admission summaries; (5) electronic medical record data, such as admission rates, length of stay, demographics, condition type, severity level, and tool scores;

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and (6) Incident reporting, such as the number of escalations and adverse event reports.

Descriptive analysis will be conducted on this routinely collected deidentified data. These data will also be used to inform the study design of prospective data collection approaches (eg, observations, interviews, and focus groups).

Stage 3: Observations

To assist in the development of a detailed understanding of the function of NSLHD VCS (ie, WAD), the research team will conduct a series of observations of the processes involved in models of care and virtual consultations [32]. Through direct observation, we hope to identify elements of care that interviewees might have omitted due to familiarity with the context [33]. Observations shall also assist in understanding the complex relationships between health care staff and recipients of services (eg, patients and their carers), along with the detailed scenarios that occur within clinical environments [34]. This is also referred to as the sociomaterial perspective, which is used to help understand interactions between systems, materials, places, humans, and nonhuman actors that do not easily respond to methods such as surveys and interviews [35]. Observation methodology is chosen considering that real-world behavior is difficult to capture in a research setting [36], where observational data not only minimize self-reporting bias [37] but also provide greater insight into the patient experience at different stages of their virtual hospitalization journey [38].

Observational data collection tools are considered but are not limited to the following:

- Descriptive fieldnotes: the observational data created will include (but are not limited to) descriptive fieldnotes from multiple observers [32] and analytical notes to capture the context of consultations [36].
- Semistructured templates: we have adapted a semistructured template from the work of Fix et al [36]. Here we use a mix of structured and open-ended inputs to capture detailed and consistent observational data. Observations related to constructs informed earlier by Stage 1 WAI document analysis will be recorded. Other observations that have not been previously identified will be recorded in the open-ended free-text section of the semistructured form. For example, to structure the observations of how health care workers interact with the technologies of the virtual hospital, the semistructured template will be based on the IS success model [39]. Here, the constructs will include system quality, information quality, system use, user satisfaction, individual impact, and organizational impact (Multimedia Appendix 1).

The objective of this research activity is to observe multidisciplinary team (MDT) meetings (ie, group meetings), clinician-patient consultations, clinician-IT human-computer interactions, and clinician-clinician interactions. A total of 2 graduate students have been trained to use the semistructured templates and have weekly debriefs to discuss the implications of the observations. These observations are also overseen by 2 senior academics to help interrater reliability.

Observers will have a passive role, meaning they shall not have any clinical intervention or impact on the clinical workflow of the VCS. The goal is to reduce bias through unobtrusive strategies to limit the impact of the researcher on the research environment [40] and provide context-rich information that is difficult to discern through other research activities [32].

The data collected in this stage will be analyzed using conventional data analysis approaches [41], such as narrative, content, or thematic analysis [32,40,42]. Each of these analysis techniques will be triangulated with data from the experience of the observer. This will aid in the interpretation of the data to yield a richer, more representative analysis [43].

Stage 4: Semistructured Interviews

Semistructured interviews will be conducted with patients, carers, and health care workers (ie, clinical and nonclinical staff members of NSLHD VCS). To reach saturation of knowledge [44,45] and the heterogeneity of the sample size [46], we aim to recruit 20 participants from each stakeholder group. This is based on recommendations from the literature that each participant group of a case study should number from 5 to 25 participants [47] or at least 6 [48]. Once the interviews are completed, 2 investigators will review and analyze each of the transcripts created to begin to identify emergent themes [42,49]. Interview transcripts will then be analyzed through thematic and content analysis [42].

Stage 5: Co-Designed Focus Groups

Focus groups will be organized with patients, carers, and health care workers (ie, clinical and nonclinical staff members of NSLHD VCS) using an experience-based co-design approach [50]. The goal here is to unify the data collected and analyzed in the previous stages of this research. Here, different stakeholder groups can be presented with significant interactions identified within NSLHD VCS [51] and collaboratively create recommendations for the improvement of health care services [52]. The health care co-design framework of Boyd et al [50] will be used to guide the focus groups and the evaluation process.

Stage 6: Economic Analysis

A comprehensive analysis will be conducted on the economic effects of VCS from different stakeholder perspectives. Past economic research has assessed VCS within existing health care systems using well-established health economic methods, including cost-effectiveness, cost-consequence, and cost-utility analyses [53,54]. Much of the existing health economic research relies on quantitative data [53], mainly direct costs to the health system [54], but overlooks patient and carer cost impacts (especially from a qualitative perspective) [55]. Depending on study feasibility, time constraints, access to resources, as well as data availability, we aim to collect perspectives from 3 different types of stakeholders, namely:

- The health system perspective: this perspective considers costs incurred by the health care system, including government health care funding, hospitals, and insurers. It includes direct medical costs such as hospital stays, medical procedures, medications, and health care professional fees.

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- The patient and carer perspective: this is the broadest approach, capturing both direct and indirect costs. It includes patient and caregiver expenses, such as out-of-pocket costs, travel, accommodation costs, lost wages due to illness, quality-of-life changes, and informal caregiving.
- The health care worker perspective: this focuses on costs experienced directly by health care workers when working in a virtual hospital environment. It includes out-of-pocket expenses, technology investments (eg, computer costs, internet bills, and electricity costs), and quality-of-life changes.

The goal of the economic analysis would allow the exploration of direct costs, indirect costs, and outcomes without aggregating them into a single measure, providing a detailed view of the effects of VCS models of care. Building on insights from both patients and providers, we will explore different dimensions that outline the diverse value of virtual health care economic assessment. Here, we will determine the impact of VCS using metrics of use, costs, productivity, and health outcomes (where data are available) [56].

Stage 7: Comparative Case Study

This stage aims to evaluate the impact of the NSLHD VCS through examination of clinical, process, and economic outcomes. This stage will help inform future VCS implementation using qualitative and quantitative methods. The comparison will include (but is not limited to):

- Different timepoints: evaluate changes in patient experience, clinical outcomes, and economic impacts before and after the introduction of VCS.
- Virtual and in-person service: understand the variations in patient journeys, clinical effectiveness, and economic implications (such as direct and indirect costs) by comparing the 2 modes of care delivery.
- WAI and WAD: examine how planned processes in NSLHD VCS align with actual implementation and practice to understand operational challenges and the implementation of virtual models of care.
- Different stakeholder viewpoints: understand the perspectives of patients, carers, and health care workers regarding VCS to identify areas for improvement and the value of VCS.

Stage 8: Triangulation Analysis

The final stage is a triangulation analysis of each of the previous stages' data (ie, method triangulation) [57]. The purpose is to synthesize all research activities to develop a comprehensive understanding of the patient experience [26] and increase the level of scientific rigor [58]. Here, we can build a "more detailed and balanced picture of the situation…" where "The contradictions which are often hidden in situations become visible, enabling a more profound interpretation." (p. 117) [59]. The triangulation analysis is represented in a series of phases (Figure 2):

Figure 2. Phases of the research project. EMR: electronic medical record; PREM: patient-reported experience measure; PROM: patient-reported outcome measure; WAD: Work-as-Done; WAI: Work-As-Imagined.

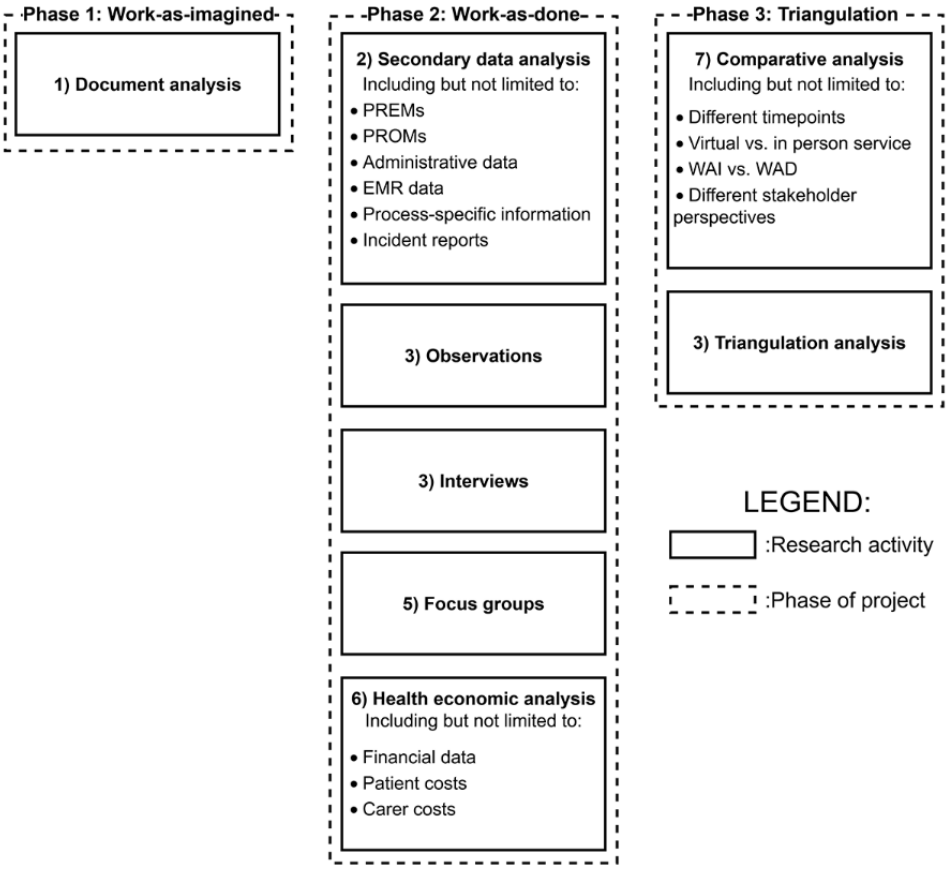

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- Phase 1: WAI. This is the exploration of internal documents to understand the formal structure of VCS and the intentions of use.
- Phase 2: WAD. This is the realistic process of the VCS and how it currently operates. This phase will combine observational, interview, and focus group data.
- Phase 3: Triangulation. This is the complete exploration and comparison of all the research activities. The triangulation method begins with an analysis of each of the different categories of data separately. As Flick [60] outlines, the commonalities and differences are identified (eg, between the WAI and WAD), as well as recognizing broader patterns and the validation of results. To synthesize these findings within a unified analytical framework, all data will be subjected to open or axial coding following the study by Strauss et al [61], allowing for the convergence of themes across codes and methods. This consistent approach to coding allows for the integration of themes and insights across datasets, for a more robust and holistic presentation of results.

Explorative and iterative analysis methods will be used to create comparisons between interactions, perspectives, and timepoints in patients' experiences with VCS. This shall build a comprehensive picture of patient experience and identify where additional support may be provided to patients, health care workers, or their carers.

Participant Recruitment

Primarily, we are seeking to recruit patients, carers, and health care workers at NSLHD VCS. Health care workers (clinicians and nonclinicians) used at NSLHD VCS, as well as patients and carers who have used these virtual hospital services, will be approached to participate in the study. Participants will be included in this study if they meet the following inclusion criteria: (1) they have interacted with the NSLHD VCS; this can include employment, receiving health care, or assisting another receiving health care at the NSLHD VCS; (2) they are older than 18 years; and (3) they have consented to be part of the study.

Health care workers will be recruited through email and education sessions. The goal of the education sessions is to explain the research aims and methodologies, how patient and carer recruitment works, and how health care workers can help and participate.

Patients and carers will be recruited prospectively as well as retrospectively. NSLHD will advertise our study to currently admitted and discharged patients and carers. We will apply inclusion and exclusion criteria for any individuals who contact us or who have provided permission for researchers to contact them. Patients and carers completing a 40-minute interview or a 60-minute focus group will be compensated for their time (a US $26.01 gift voucher for the interview and a US $39.01 gift voucher for the focus group). Any patient or carer participant who is interviewed and participates in a focus group will be given both compensation amounts (ie, a single US $65.02 gift voucher).

Researchers will send emails and SMS reminders to all potential participants (up to 3 times over 2-4 weeks). If there is no response after following up, researchers will assume the individual does not wish to participate and cease follow-up contact.

Prospective Patient and Carer Recruitment

Prospective patients are those who are currently admitted to the NSLHD VCS. They can be recruited via these two approaches: (1) NSLHD health care workers can inform patients and their carers about the study during their routine consultation, seeking permission for researchers to contact them about the research; or (2) A NSLHD VCS team can also send an email and SMS to currently admitted patients.

The email and SMS will contain links to the study Participant Information Sheet (PIS), Participant eConsent form, and research team contact details. Patients and carers can then make an informed decision by reading the PIS and contacting the research team. They can also directly enrol in the study via an eConsent form.

Retrospective Patient and Carer Recruitment

Retrospective patients are those who have been discharged from NSLHD VCS before the start of the study. The NSLHD VCS team will send an email and SMS to retrospective patients, containing a link to the PIS, Participant eConsent form, and the research team contact details. Patients can then make an informed decision by reading the PIS and contacting the Macquarie University research team. They can also directly enroll in the study via an eConsent form via email and SMS. Refer to Figure 3 for a summary of the patient and carer recruitment and consent process.

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Figure 3. Patient and carer recruitment and consent process. EMR: electronic medical record; MQ: Macquarie University; NSLHD: Northern Sydney Local Health District; REDCap: Research Electronic Data Capture.

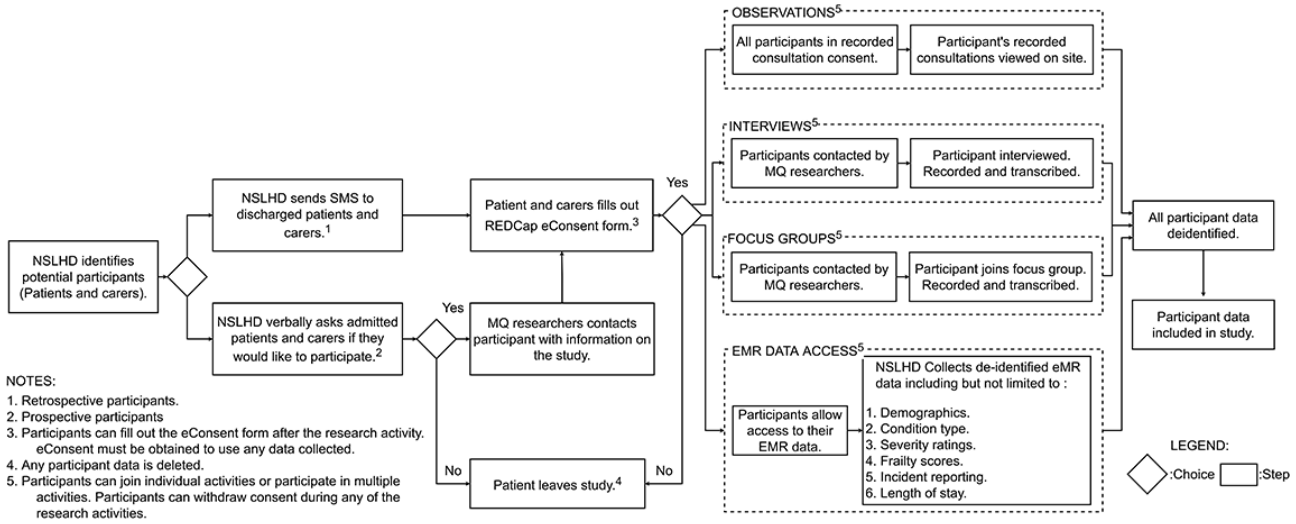

Ethical Considerations

Ethical approval was granted by the Macquarie University Human Research Ethics Committee for Medical Sciences (reference 520241860460310) and the Northern Sydney Local Health District Ethics Review Committee (2024/ETH01430).

Results

As of February 2025, all required ethics applications from NSLHD have been approved and site-specific permission has been granted. Observations and initial documentation analysis have begun. Observations of MDT meetings, clinician shadowing, and analysis of the SOP documents have commenced. We have also begun education sessions for health care workers, commenced recruiting health care workers, and advertised the study to a range of patients and their carers at NSLHD VCS.

Discussion

Principal Findings

This protocol outlines an exploratory mixed methods case study on a new virtual hospital located in Sydney, NSW, Australia. We anticipate our results will provide a comprehensive understanding of patient experience and virtual hospitalization, specifically for those receiving hospital-level care at home, facilitated by a multidisciplinary health care team and supported by digital technologies. Through a range of quantitative and qualitative research activities, we will identify challenges encountered by patients, carers, and health care workers, and co-design a list of practical and evidence-based recommendations to improve the patient experience.

Strengths and Limitations

The strengths of this study stem from the diverse research group and extensive research activities used to study the VCS. However, this study will be limited by the extent of access to patient data. The decision not to access the entirety of patient medical records was first based on the risk to the patient's confidentiality, and second, that deidentified records currently requested will provide ample empirical data of the patient's experience.

Comparison With Prior Work

The significant demand for VCS like NSLHD VCS has seen a rise in mixed methods protocols in Australia and abroad. For example, new protocols have been published on the evaluation of a virtual triage service in Victoria [62] and another on the analysis of an acute respiratory model of care in NSW [3]. Internationally, a recent protocol was published for a pilot breast cancer support application in Copenhagen [63] and another for the launch of a new Diabetes-focused hospital information system in India [64].

However, to the best of our knowledge, few published works and protocols endeavor to explore a multidisciplinary virtual service like NSLHD VCS. The literature referred to above generally has a limited focus and lacks the comprehensive research activities of this protocol. In addition, few include an economic evaluation [3] or a direct comparison of patient experience and the financial costs of virtual services.

Conclusions

This protocol outlines a new collaborative research project to study the NSLHD's VCS. This virtual hospital is an MDT that leverages digital technologies to provide hospital-level care for patients at home. Through a combination of methodologies, our study will provide a comprehensive understanding of the patient experience of virtual hospitals, identify challenges, and co-design a list of practical and evidence-based recommendations to improve the service.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Observation template.
[DOCX File , 18 KB - resprot_v14i1e72729_app1.docx]

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Abbreviations

ED: emergency department
MDT: multidisciplinary team
NSLHD: Northern Sydney Local Health District
NSW: New South Wales
PIS: Participant Information Sheet
SOP: Standards of Practice
VCS: Virtual Care Services
WAD: Work-As-Done
WAI: Work-As-Imagined

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Protocol

Addressing Tobacco-Related Disparities Among Youth Experiencing Homelessness by Engaging Youth Collaborators in Intervention Research: Protocol for a Multimethod, Community-Based Participatory Research Study

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Abstract

Background: Youth experiencing homelessness and housing instability exhibit disparities in tobacco use and co-use of tobacco and cannabis products compared to their stably housed peers. Interventions to address these disparities have had limited success to date. This may be related to a lack of fit between intervention approaches and the unique needs and preferences of this marginalized population. Leveraging strategies to facilitate authentic engagement of youth in intervention research, including collaborating with youth in the cocreation of intervention goals and strategies, presents an opportunity to overcome challenges of previous research to mitigate tobacco-related disparities among youth experiencing homelessness and housing instability.

Objective: This protocol aims to engage youth collaborators in intervention research to address tobacco-related disparities among youth experiencing homelessness and housing instability. It outlines strategies to recruit and partner with youth to cocreate a strengths-based, expressive arts intervention to reduce harms associated with tobacco use and tobacco/cannabis co-use and evaluate our youth engagement strategies.

Methods: The community and academic partners leading this intervention study developed a structure that allows for two levels of youth collaboration. This structure, developed through consultation with a youth action board, facilitates youth (aged between 14 and 26 years) involvement in intervention design, implementation, and pilot testing. At the higher collaboration level, youth will join the intervention research team as “co-researchers,” engaging weekly with study-related tasks and contributing equitably to the research processes (eg, selecting intervention strategies and supporting data analysis) in alignment with their personal and professional goals. At the lower collaboration level, youth will engage with the research team as “advisors,” providing targeted feedback at key points during intervention development. Brief surveys, field notes, ethnographic memos, focus group discussions, and semistructured interviews will be used to evaluate our process and impact among the engaged youth.

Results: To date, we have engaged 7 co-researchers who have participated in several capacity-building and professional development activities, including research ethics training and tobacco prevention advocacy training. Co-researchers have contributed

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to intervention development brainstorming sessions, evaluated available interventions to address youth tobacco use, and developed materials to expand the group of co-researchers and advisors. Preliminary data suggest sufficient youth engagement (study goal of engaging 10 co-researchers in a 2-year study period) and that engagement processes are highly acceptable to youth collaborators. Lessons learned to date have helped us to improve and refine our engagement processes (eg, technological barriers).

Conclusions: This protocol describes a holistic approach to equitably and authentically engaging youth as collaborators in intervention research to address tobacco-related disparities among youth experiencing homelessness and housing instability. The approach may serve as a useful model that can be adapted for other youth-focused intervention research.

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(JMIR Res Protoc 2025;14:e69441) doi:10.2196/69441

KEYWORDS

youth engagement; intervention research; tobacco disparities; homelessness; runaway and homeless youth; youth advisory board; youth action board

Introduction

Background

Cigarette smoking and secondhand smoke remain the leading causes of preventable death and illness worldwide and in the United States [1-4], where nearly 1 in 5 deaths is caused by smoking or exposure to secondhand smoke [4]. Despite significant decreases in smoking over time, particularly in the last 2 decades [5], more than one-fifth of adults and one-tenth of adolescents in the United States report past-month tobacco use in various forms (including cigarettes, e-cigarettes, and other combustible and smokeless tobacco products) [6,7].

Tobacco and Cannabis Prevalence and Health Impacts Among Youth

Smoking and other tobacco use have negative health implications for people of all ages; however, tobacco use in adolescence and young adulthood can negatively impact health across the life course. For example, most adults who smoke tried their first cigarette by the age of 18 years, with a mean age of smoking initiation of approximately 15 years for those who smoke daily [3]. Early initiation of tobacco use is associated with the development of substance use disorders and respiratory, cardiovascular, and other physical health problems in both youth and adults [8]. Tobacco use in adolescence and young adulthood can also have harmful effects on brain development related to learning, mood, impulse control, and academic achievement [8-10]. While cigarette smoking has decreased dramatically for youth over time, rates of e-cigarette use (ie, “vaping”) have largely increased in recent years [11]. Though there is some indication that vaping among adolescents is beginning to decline for the first time in a decade [6], vaping among young adults has continued to increase [12]. As vaping increases, so does vaping dependence. For example, research has found that current levels of vaping dependence among individuals aged between 16 and 19 years in the United States, Canada, and England are comparable to or higher than rates of cigarette dependence, with between 45% and 50% of youth who vape reporting experiences and behaviors consistent with vaping dependence [13].

Similar to tobacco use, cannabis use is associated with negative health impacts among youth, including increased risk for other substance use and disorders [14,15]; impairments to cognitive functioning [16,17]; and mental health problems, such as depression, anxiety, and other psychiatric disorders [15,18]. Among adolescents, cannabis use has remained relatively stable or even decreased over time, with approximately 17% of the adolescents reporting past 30-day use in 2023 compared to 23% in 2013 [19], with some of the largest 1-year decreases ever recorded occurring from 2020 to 2021 (during the COVID-19 pandemic) [20]. These trends are reversed among young adults, however, with significant increases over the last several decades in the number of young adults who report regular cannabis use [21]. For example, among young adults aged 19 to 30 years, participating in the 2023 Monitoring the Future panel study, 29% reported past-month cannabis use, with the highest prevalence of 32% among young adults aged between 23 and 24 years [21]. These rates are among the highest levels of cannabis use ever recorded, which is a 10% increase since 2013.

Tobacco/cannabis co-use (ie, simultaneous use or use of both products within the same time period) is increasingly common among adolescents and young adults, and in some studies, has been found to be more common than using 1 substance only [22,23]. Co-use has also been found to be associated with more frequent and higher quantities of use of both products [24] and increased risk for mental health problems, respiratory symptoms, and lower academic achievement [22,25-27]. Tobacco and cannabis use among young adults share many common determinants, including the use of substances to cope with emotional or psychological distress, peer influence, and the availability of substances [28,29]. However, some distinct drivers of cannabis use include beliefs that cannabis is less harmful to health than tobacco and that it may help to tune out of or escape from one’s environment [29,30]. Importantly, emerging evidence points to frequent cannabis use as a barrier to tobacco cessation [31]. This highlights the need to account for dual use of tobacco and cannabis in efforts to reduce use of either substance, as a failure to do so may limit the effectiveness of these efforts [28,30,32].

Tobacco-Related Health Disparities: A Focus on Youth Experiencing Homelessness and Housing Instability

While smoking and other tobacco use has decreased for some groups over time, the US surgeon general’s recent report on tobacco-related morbidity and mortality highlights persistent tobacco-related disparities along axes of identity and social position, including race or ethnicity, income, education, sexual

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orientation, gender identity, occupation, geography, and behavioral health status [4]. The report refers to these disparities as a "social injustice, in addition to an economic and health burden" [4]. Among the populations identified by the report as evidencing persistent tobacco-related disparities are people experiencing homelessness who have been specifically targeted by the tobacco industry through marketing and efforts to thwart laws that would promote smoke-free policies in housing programs.

A group of particular concern with respect to addressing tobacco-related health disparities across the life course is youth experiencing homelessness and housing instability. Indeed, youth experiencing homelessness and housing instability exhibit rates of tobacco use that are markedly higher than their stably housed peers. Previous research has found that as many as 70% of the youth experiencing homelessness and housing instability smoke and use other tobacco products (eg, e-cigarettes), which is significantly higher than the general population of adolescents and young adults nationally [33-36]. Rates of cannabis use among youth experiencing homelessness and housing instability are similarly high, with estimates that nearly 60% use cannabis [37], which is nearly 2 to 3 times the rate of their stably housed peers [38,39]. Youth experiencing homelessness and housing instability who smoke cigarettes also tend to engage in harmful smoking-related behaviors, such as smoking discarded cigarettes, blocking filter vents, and rolling cigarettes with tobacco from discarded cigarette butts [40,41]. Emerging evidence has begun to find high rates of coconsumption of tobacco and cannabis among youth experiencing homelessness and housing instability as well [42,43]. Importantly, coconsumption may result in more negative impacts on youth development and opportunities for financial stability and social mobility than tobacco use alone. These tobacco- and cannabis-related disparities are a significant health concern for a group particularly susceptible to concomitant negative health and social outcomes [33,44,45].

The Need for Youth-Engaged Intervention Research

Despite documented tobacco-related disparities among youth experiencing homelessness and housing instability, there is evidence that many are interested in quitting or reducing their tobacco use [46-48], and service providers working with this population are committed to supporting their desired behavior changes and goals [49,50]. There have been relatively few intervention studies that aim to address tobacco-related disparities among youth; however, there have been several studies focused on adults experiencing homelessness. To date, these interventions, for both youth and adults, have demonstrated limited to moderate success. For example, a 2020 systematic review of 10 randomized controlled trials of tobacco cessation interventions for adults experiencing homelessness (aged >18 y) found mostly inconclusive evidence to assess intervention effects [51]. A tobacco cessation intervention for youth experiencing homelessness and housing instability using mobile health approaches (text messages) found small to moderate effect sizes [32,52]. A 2013 systematic review of 8 peer-support programs for smoking cessation in "disadvantaged groups," including people experiencing homelessness, found limited evidence of efficacy [53]. Several potential mechanisms of change [54] have been identified and examined across these intervention studies, including increasing access to peer support [32,52,53], enhancing motivation to reduce tobacco use [55,56], and reducing emotional distress [57,58]. Among these, peer support has emerged as a particularly promising approach [53], although overall intervention effects have been variable. This points to a need for a deeper examination of the barriers limiting intervention efficacy in this population.

Several factors contributing to the limited efficacy of previously tested interventions have been identified, including limited statistical power, limited intervention follow-up, and a lack of fit between available interventions and the needs of people experiencing homelessness. Another potential factor includes a lack of intervention fit with the community-based contexts where people experiencing homelessness access resources and build community [51,53]. This lack of fit may be related to a lack of meaningful engagement of people with lived experience of homelessness (as well as the individuals working within service provision contexts) in the intervention development process. Although several published intervention studies indicate gathering insights from relevant stakeholders to inform interventions (eg, 1-time interviews or focus groups), few, if any, explicitly note the inclusion of people with lived experience of homelessness as research collaborators throughout the development and implementation of interventions.

For intervention research focused on addressing tobacco-related health disparities among youth, leveraging strategies to facilitate authentic engagement of youth in the research process, including in the cocreation of intervention goals and strategies, presents an opportunity to overcome challenges of previous research in this area. Indeed, a recent review of behavioral health interventions for youth experiencing homelessness and housing instability found that of 33 unique interventions, fewer than half involved youth or community stakeholders in the design of the intervention, and among those, even fewer involved youth as sustained collaborators in the intervention research process [59].

Objectives

The objective of this protocol is to provide an overview of our youth engagement process and outline strategies to promote equitable collaboration with youth in the context of an intervention pilot study to address tobacco-related disparities among youth experiencing homelessness and housing instability. In addition, we aim to delineate our strategy to evaluate our approach to youth engagement in terms of process and outcomes among youth collaborators.

Methods

Overview

Tobacco and Cannabis Harm Reduction through Expressive Arts (TobExA) is a community-based participatory research pilot study involving the development, implementation, and pilot testing of an intervention to address tobacco-related disparities among youth experiencing homelessness and housing instability. The study is guided by harm-reduction and strengths-based frameworks.

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Aligned with the principles of community-based participatory research, TobExA is equitably coled by investigators at a community-based organization serving youth experiencing homelessness and housing instability ("community partner") in San Diego County, California, and a local public state university ("academic partner"). Previous research has documented the utility of community-academic collaborations in the creation of interventions to mitigate health disparities [60,61], with greater and more sustained impacts than researcher-driven interventions that are not cocreated with community partners [62,63].

The initial idea for TobExA was based on the community partner organization's priority of addressing health disparities and mitigating health risk behaviors among their youth clients accessing emergency shelter and drop-in spaces. Particularly, administrators and staff indicated an interest in understanding the influence of substance use, including tobacco and cannabis product use, on the health and stability of the youth they serve, and addressing tobacco-related disparities through harm reduction and strengths-based approaches. Harm reduction and strengths-based approaches are aligned with the community partner organization's mission and priorities and have been identified as evidence-based strategies for addressing substance use and other health disparities affecting people experiencing homelessness [44]. In addition, several members of the community partner organization's staff have expertise in expressive arts therapy and regularly use expressive arts techniques to engage their youth clients.

The TobExA intervention development process is guided by intervention mapping (IM), a standardized, yet flexible 6-step framework for building theory- and evidence-based health promotion interventions [64]. IM is inherently community engaged, emphasizing the need for feedback from diverse partners at each point in the intervention research process. TobExA partners include the community and academic partner organizations coleading the study, service providers and administrators serving youth experiencing homelessness and housing instability across the San Diego region, and youth with lived experience of homelessness or housing instability.

We assert that authentic youth engagement is central to effectively developing an intervention that will center the needs, experiences, and preferences of youth. This paper outlines our protocol for the engagement of youth collaborators in the TobExA study, including in the development of the intervention. Of note, a protocol detailing the TobExA intervention will be forthcoming (intervention development is in progress). Briefly, the TobExA intervention will be a multilevel group-based intervention grounded in harm reduction and strengths-based frameworks, with expressive arts as a key modality of participant engagement and reflection. The intervention will prioritize goal setting and social support as theory-based strategies for promoting reductions in tobacco and cannabis use among youth experiencing homelessness. The intervention will be co-designed with youth collaborators (as discussed herein).

Guiding Theoretical Framework: Youth Participatory Action Research

The TobExA youth engagement procedures outlined in this protocol are guided by a youth participatory action research framework. Informed by emancipatory education and research [65], youth participatory action research situates young people as "legitimate and essential collaborators" in research and action on issues affecting their lives [66]. Youth participatory action research projects are typically situated within educational or community-based program settings and focus on the needs of marginalized or minoritized communities of youth [67]. Because youth understand their lives in ways that adults cannot, engaging youth as equitable collaborators in the intervention research process will support the development and implementation of an intervention with improved fit and impact than an intervention developed by adult researchers alone [68]. Indeed, youth involved in the cocreation of interventions experience benefits from their participation (eg, personal and professional skills), and youth who participate in interventions that are cocreated by youth experience positive intervention impacts. Thus, there is an individual and community benefit to youth engagement and collaboration in intervention research [69,70].

Youth engagement as a construct captures a broad range of youth participation in the research process. For example, "engagement" in some intervention research may be characterized by relatively low levels of sustained youth involvement or leadership, such as youth providing one-time feedback to inform an intervention during development. In other research, "engagement" may involve youth as collaborators and decision makers throughout the research process, with youth serving as members of the research team whose perspectives are given equal weight to other collaborators, such as investigators, consultants, etc [71]. Although youth engagement has been identified as an "ethical imperative" [72] and "principle in care" [73] in the development of interventions to address youth substance use, there are many challenges to authentic and ethical youth engagement in research. These challenges often relate to power differentials between youth collaborators and adult researchers and limited opportunities for youth to be involved in shared and equitable decision-making [72,74,75].

Youth Engagement Overview

In the spirit of youth participatory action research and to overcome the challenges of previous youth-engaged research, our youth engagement approach and specific processes have been developed through multiple consultations with youth with lived experience of homelessness or housing instability as well as staff serving youth experiencing homelessness and housing instability. Specifically, members of the TobExA research team engaged members of the community partner's youth action board (YAB) at the beginning of the study to gather feedback on in-development plans for youth engagement (eg, compensation, expectations, style of engagement, and recruitment strategies). Although we discussed collaborating with the existing YAB as the primary youth engagement strategy for the TobExA study rather than initiating a study-specific youth engagement protocol, YAB members indicated that

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study-specific engagement was necessary so as not to compete with the YAB's current priorities.

TobExA's youth engagement processes will involve members of the research team, including investigators, research assistants, and other support staff, collaborating with youth as "co-researchers" or "advisors" throughout the intervention research process. They will be invited to commit 5 to 10 hours to collaboration activities (ie, research tasks) per week for a minimum of 3 months (with the opportunity to extend collaboration for the duration of the study). Co-researchers will be recruited on a rolling basis to ensure approximately 2 to 5 active co-researchers throughout the project timeline. Co-researchers will participate in 1 or more stages of intervention design, pilot testing, and dissemination of findings, depending on project timing at recruitment and length of co-researcher engagement. Advisors will provide targeted feedback during the intervention development process via synchronous and asynchronous modalities on 1 or more occasions.

Eligibility and Recruitment

We will recruit approximately 10 co-researchers and 10 advisors across the 2-year study period (August 2023 to July 2025). To be eligible, prospective co-researchers and advisors must be aged between 14 and 26 years, have lived experience with homelessness or housing instability, and be fluent in English or Spanish. They must also be willing to commit to abstaining from using substances (including tobacco, cannabis, alcohol, and other drugs) during their *active* hours contributing to the TobExA study; there are no requirements or expectations regarding abstaining from substance use outside of these active contribution periods. The decision to require abstinence during active hours is aligned with the harm reduction focus of TobExA (as opposed to abstinence or complete cessation of substance use) and our goal of developing the professional capacity of youth to support their success in other professional settings.

Co-researchers and advisors will be recruited via direct referrals, word of mouth, and in-person presentations. Recruitment efforts will focus on the following groups of youth: (1) members of the community partner's YAB, (2) youth receiving services from the community partner organization who are not members of the YAB, and (3) youth receiving services at other local organizations serving youth experiencing homelessness and housing instability. Interested youth will communicate their desire to join the study as collaborators via a study-specific GroupMe channel (Microsoft Corporation), Google Form, email, or a community partner organization staff member's direct referral. Recruitment will be ongoing throughout the study period, as needed. We anticipate focused recruitment "pushes" will occur at key time points in the IM process to support phase-specific youth engagement (eg, during program development and implementation planning).

Youth Engagement Procedures

Overview

TobExA's youth engagement processes will be led by "youth engagement liaisons" (including the lead coauthors of this protocol, who are current doctoral students [ARL and ACL]) with supervision from the academic co–principal investigator (JKF) and a community partner coinvestigator (RE).

Co-Researchers

After expressing their interest in collaborating with the TobExA team, prospective co-researchers will participate in a preliminary onboarding interview (approximately 1 hour) to assess their personal and professional development goals, research interests, current skills and strengths, and availability. Those who are able to commit approximately 5 to 10 hours per week for 3 months (with flexibility as needed) and whose interests are aligned with the study or research generally will be invited to join the study as co-researchers. Before being assigned research tasks, co-researchers will participate in a group training on human research protections and receive an in-depth introduction to the TobExA study. Co-researchers will then be assigned weekly tasks based on study needs and their individual interests and goals. They may also begin to attend TobExA study team meetings at this time.

Co-researchers will participate in 30-minute biweekly individual check-in meetings with the youth engagement liaisons to discuss tasks and troubleshoot any issues or concerns. Every 2 weeks, all co-researchers will participate in a 1.5-hour group meeting led by the youth engagement liaisons where co-researchers will share updates on their tasks; build community with fellow co-researchers and youth engagement liaisons; and collaborate on research tasks, such as analyzing interview data to inform the TobExA intervention (with guidance from the youth engagement liaisons). Co-researchers may complete most of their assigned tasks remotely (with many tasks designed to be completed on a smartphone if a computer is not easily accessible), with group meetings predominantly held in person. They will have access to workspaces with computers and internet at the community and academic partners' offices.

We acknowledge that substantial attrition among co-researchers may occur during the expected 3-month engagement period, partly due to their developmental and life stage (characterized by educational, familial, and personal transitions and changes) and the many stressors and competing priorities for youth with current or previous experiences of homelessness or housing instability [76-78]. To support the retention of co-researchers, we will monitor attendance at weekly group and individual meetings. If waning engagement is noted, youth engagement liaisons will work collaboratively with youth and community partners to assess the individual needs of co-researchers and determine the most appropriate support strategies. These may include additional development opportunities or, if necessary, a compassionate offboarding process. Exit interviews and periodic focus group discussions (detailed subsequently) will provide additional insights into reasons for disengagement and co-researcher retention strategies and will be used to drive changes to strategies as needed. This structured process, along with the co-researcher role's co-designed nature between youth, academic, and community partners, is anticipated to promote engagement in the long term. Several of the authors have experience collaborating with youth in other youth participatory action research studies in which study goals were achieved with as few as 2 to 4 highly involved youth collaborators [79,80].

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Thus, even if we experience high rates of attrition among co-researchers, we expect to engage a sufficient number of youth collaborators throughout the study period to meet our goals.

Advisors

As noted earlier, advisors will participate in specific opportunities to provide feedback on the TobExA intervention. These opportunities will be synchronous, such as group or individual meetings with study staff (in person or over Zoom), or asynchronous, such as providing feedback via email or a secure messaging app. Synchronous opportunities (eg, group meetings) will be coled by co-researchers who will develop the agenda, cofacilitate discussions, and take the meeting minutes. Advisors may participate in 1 or more feedback opportunities (we expect to hold a minimum of 2 feedback opportunities during the study period) and will receive US $19 per hour for their participation, with additional stipends to cover transportation and childcare as needed. Advisors will be given (in person) or mailed a check after participating in a feedback opportunity.

Youth Engagement by Research Stage

Multimedia Appendix 1 provides a visual representation of the TobExA intervention research process (including the 6 steps of IM [64]), crosswalked with youth collaborator participation time points and activities. The first phase of IM (step 1) is the *needs and assets assessment*, which involves developing a *logic model of the problem*. During this phase, we will conduct formative interviews with stakeholders and youth to assess reasons for tobacco and cannabis use among youth experiencing homelessness as well as needs to prevent and reduce use in this population (ie, needs-assessment phase). We will also focus on assessing the context in which the intervention will be implemented to identify strategies to support intervention fit and sustainability. Although co-researchers will not be involved in data collection for this initial phase of the research process, they will provide feedback on and contribute to the development of the *logic model of the problem* during group meetings led by the youth engagement liaisons. These early contributions will be essential to ground the IM process in the local context as informed by the lived experiences and community knowledge of co-researchers and other stakeholders who are familiar with the local context (through lived experience, work roles, etc).

Co-researcher and advisor engagement will be especially critical during the subsequent stages of the research process, including development of the intervention (IM steps 2-4), planning for implementation and evaluation (IM steps 5-6), and piloting the intervention. Throughout these stages, co-researchers and advisors will provide synchronous and asynchronous input that will be directly incorporated into the intervention research process. Specifically, co-researchers will participate in several structured activities to ensure their equitable contributions to the intervention development process. This includes participating in analysis of qualitative data gathered during IM step 1, reviewing and providing feedback on materials to consider for inclusion in the intervention (eg, existing tobacco intervention materials and resources), and attending intervention development meetings with the full TobExA team. Co-researchers will also be invited to lead presentations for the TobExA team to share their ideas and recommendations for the intervention. Co-researchers will be involved in piloting the intervention (eg, supporting recruitment, data collection, and cofacilitation) and supporting dissemination of findings (eg, via scientific conferences, community-based presentations and events, and fact sheets).

Co-researchers will lead discussion sessions or asynchronous communication with advisors to gather their feedback during 2 key phases of the IM process (steps 3-4 and 5-6). Advisors will be asked to respond to specific open-ended prompts or discussion questions that will shape decisions regarding the intervention content and implementation strategies. For example, we may gather feedback from advisors to identify the best approach to hosting intervention group sessions based on age, with questions such as, “The intervention will include group sessions. If you were attending a group about reducing tobacco and/or cannabis use, what age range would you feel most comfortable with? Why?” Advisors will also be invited to provide feedback on recruitment strategies and other related considerations for piloting the intervention, such as appropriate incentives for participation, strategies for data collection, and strategies for gathering detailed participant feedback. Co-researchers will summarize and share feedback from the advisors with the full TobExA team to ensure advisors’ contributions are meaningfully integrated into the intervention research process (at TobExA team meetings or via asynchronous communication). Although we do not currently have plans to engage advisors in findings dissemination, we may schedule feedback opportunities as part of findings dissemination to “member check” our interpretations and gather recommendations for next steps in the TobExA intervention research process (eg, how to improve the intervention for a future efficacy trial).

Measures and Tracking

Overview

Multiple strategies will be implemented to evaluate and document youth engagement strategies and processes throughout the study. To document the process of engagement and identify opportunities for quality improvement, youth engagement liaisons and other TobExA team members working directly with youth collaborators will write field notes and ethnographic memos based on their experiences and learnings (yielding qualitative data).

We will collect data from youth collaborators to document sociodemographic characteristics of youth engaged (co-researchers and advisors—age, education, race, ethnicity, sex assigned at birth, gender identity, transgender status, sexual orientation, and recent housing experiences), evaluate the impact of collaboration on the personal and professional development of youth (co-researchers only), and identify opportunities for quality improvement in our engagement processes (co-researcher and advisors).

Co-researchers will complete surveys at multiple time points, participate in periodic focus group discussions, and complete a semistructured exit interview (approximately 45 min long) when they officially end their time as a co-researcher. Survey

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measures were pilot-tested with a subsample of co-researchers via "think-aloud" cognitive interviews (mean 105, SD 15 min), which allow youth to verbally discuss the survey questions and explain the factors contributing to their answers [81]. Advisors will complete short surveys after participating in a feedback opportunity. Surveys were piloted with members of the community partner YAB. Figure 1 presents a visual overview of evaluation methods. We further detail these evaluation strategies in the subsequent sections.

Figure 1. Youth engagement evaluation methods.

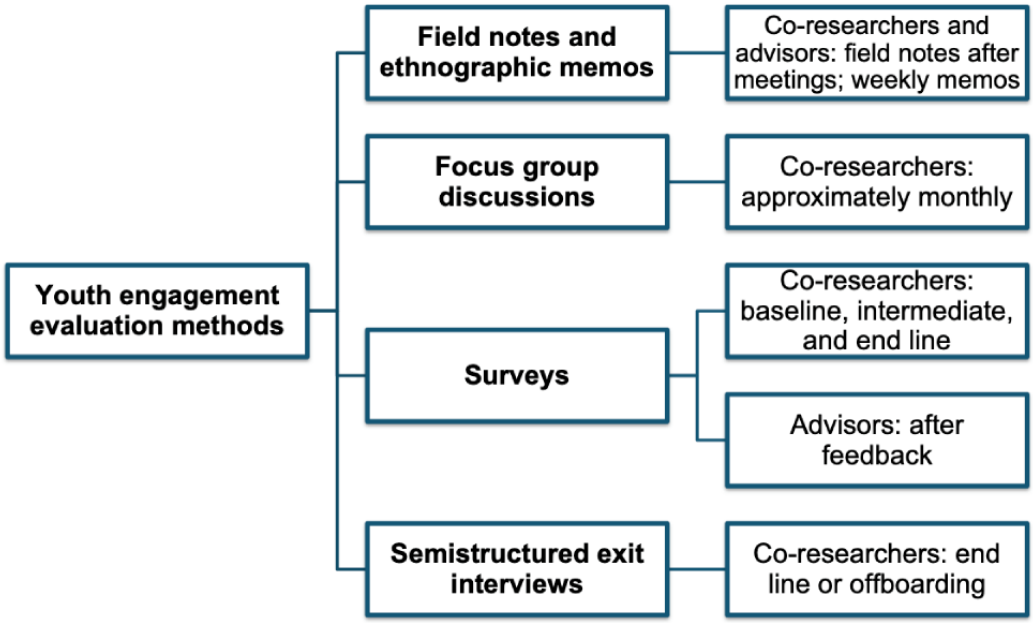

Field Notes and Ethnographic Memos

Youth engagement liaisons and other TobExA team members working directly with youth collaborators will write semistructured field notes after each biweekly meeting with the co-researchers and advisors and weekly unstructured ethnographic memos on the overall youth engagement and collaboration process [82]. Field notes will include prompts to narratively describe the following: (1) barriers to and facilitators of equitable and sustainable youth engagement and collaboration, (2) the application of key youth participatory action research and community-based participatory research principles to our youth engagement processes, and (3) how youth engagement and collaboration activities are connected to and facilitating the completion of TobExA study aims. Field notes will also capture noteworthy milestones and activities in co-researcher development, such as participation in major training and professional development opportunities.

Ethnographic memos will be in the form of unstructured narrative reflections regarding co-researcher–related activities and progress. Memos will document key challenges or needs in the youth engagement process and identify opportunities to refine youth engagement and collaboration strategies. Memos will be regularly reviewed by the academic co–principal investigator and other supporting coinvestigators, allowing for real-time or near real-time communication regarding emergent challenges to be addressed (ethical, logistical, and process related).

Youth Co-Researcher Surveys

We will administer surveys to co-researchers at multiple time points during their involvement in the study (baseline, intermediate, and end line). Baseline surveys will be administered upon the onboarding of youth into the project. Intermediate surveys will be completed iteratively between the defined steps of IM. End line surveys will be administered when youth begin offboarding from their co-researcher roles. The surveys will include items from validated scales and specific measures from the following surveys, scales, and subscales:

- Adult support, empowered skill-building, and positive values subscales from the Youth Program Quality Survey (α=.71, .77, and .79, respectively) [83]
- Supportive adult relationships subscale from the Youth-Adult Partnership Scale [84]
- Participatory behavior subscale from the Research and Action Self-Efficacy Scale (α=.83) [85]
- Self-efficacy or belief-in-self subscale from the Social Emotional Health Survey (α=.76) [86]
- Youth empowerment and leadership skill subscale from the Sociopolitical Control Scale for Youth [87]
- Youth voice in decision-making subscale from the Youth-Adult Partnership Scale [84]
- Perceived Control Scale—organizational and community levels (α=.61 and .63) [88]
- Flourishing individuals subscale from the Community Well-Being Assessment [89]

As noted earlier, we pilot-tested an initial version of the surveys via "think-aloud" cognitive interviews with a subgroup of co-researchers. This resulted in various adaptations to specific

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items and scales, including changes in phrasing for clarity and removal of questions deemed unrelated to the co-researcher role. For example, co-researchers noted that the use of the word "kids" in one item on the Youth Program Quality Survey was not appropriate, given that co-researchers are teenagers or young adults. Therefore, we rephrased this item to better reflect the age of co-researchers. Table 1 presents an overview of the scales, subscales, specific constructs of interest, adaptations to measures, and measurement time points.

Table 1. Youth co-researcher survey measures and data collection time points.

Original scale	Construct and domain (subscale)	Adaptations	Baseline	Intermediate	End line
Social Emotional Health Survey	Self-efficacy and belief in self	• Used in full	✓		✓
Sociopolitical Control Scale for Youth	Leadership competence	• Used in full	✓		✓
Perceived Control Scale	Perceived control (organization level and community level)	• Rephrased to define "community" and "organization" • Removed 3 items to align with study scope[a]	✓		✓
Measures of community well-being	Flourishing individuals	• Six items removed; 1 rephrased to align with study goals	✓		✓
Youth Program Quality Survey	Adult support, empowered skill-building, and positive values	• Used in full; rephrased to specify "adults" • One item adapted to be appropriate for use with adolescents and young adults[a]		✓	✓
Youth-Adult Partnership Scale	Supportive adult relationships and youth voice in decision-making	• Rephrased to specify staff and organizations		✓	✓
Research and Action Self-Efficacy Scale	Participatory behavior	• Removed 2 items specific to youth in schools		✓	✓

[a]Adaptations are based on pilot testing and other youth collaborators' feedback.

Youth Co-Researcher Periodic Focus Group Discussions

Approximately each month, focus group discussions will be held with co-researchers. These group discussions will ask co-researchers to reflect on their overall experience and participation with the collaborative IM and implementation processes. These focus groups serve as a touchpoint with co-researchers to gather insights into their experience of the collaboration process, offering them a space to reflect, share feedback, and even propose potential adjustments to improve our approach. Some examples of focus group discussion questions are as follows: What has it been like to be part of this process? What made you feel included and valued in this process? What, if anything, made collaboration or working together challenging? Detailed notes will be taken during each focus group discussion.

Youth Co-Researcher Semistructured Exit Interviews

To document co-researchers' experiences and solicit feedback on our engagement processes, semistructured exit interviews will be conducted with co-researchers when they offboard from their role. Key constructs of interest include general experiences as a co-researcher, perceptions of personal and professional development over time, contributions to the study, team dynamics and communication, key challenges, and opportunities for improvements to youth engagement processes.

Youth Advisor Measure: Advisor Survey

To evaluate the advisor engagement process, we will gather feedback from advisors at the end of each feedback opportunity via a brief survey of multiple-choice and open-ended questions. The survey items are based on the Youth Program Quality Survey [83]. The surveys and selected measures will be customized based on the format of the feedback session (group, individual, asynchronous, live, in person, and virtual) and session activities.

Planned Analysis

Qualitative data (field notes, ethnographic memos, and semistructured exit interviews) will be analyzed using applied thematic analysis procedures, including cycles of memoing, coding, data reduction, and theme development [90,91]. Qualitative data will be managed and coded using Dedoose qualitative analysis software (SocioCultural Research Consultants). A team of coders will begin by memoing the data to develop a codebook and then participate in consensus meetings to refine the codebook, resolve coding discrepancies, and ensure consistent code application. Once the data are coded, coders will develop "code summaries" to reduce the data for

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theme development. Themes will be initially developed by reviewing code summaries, code frequency and repetition, code co-occurrence, and salience of key concepts. TobExA team members from the academic partner organization will lead analysis and engage members from the community partner organization in key analytic processes, including finalizing themes and interpreting results to inform practice and research [91]. To ensure transparency of our qualitative analysis processes, we will maintain an audit trail to document all coding decisions, including modifications to the codebook, and theme development and interpretation procedures.

Quantitative (survey) data will be summarized using descriptive and inferential statistics as appropriate or possible. At a minimum, we will use descriptive statistics to summarize outcomes for co-researchers at each data point (baseline, intermediate, and end line) and examine individual and group changes over time. Individual scales will be scored in accordance with scoring guidelines. Sociodemographic data will be used to characterize the overall sample of co-researchers and advisors to allow for stratified analyses of data as appropriate (eg, comparing engagement experiences for youth collaborators aged <18 y and >18 y).

Results from quantitative and qualitative data analyses will be periodically (at least quarterly) reviewed by TobExA team members from the community and academic partner organizations. The partners will work together to identify data-driven quality improvement changes to enhance our youth engagement strategies throughout the TobExA project. As appropriate, co-researchers will be provided with summaries of results (aggregated to protect co-researchers' and advisors' privacy and confidentiality) and will also be involved in identifying quality improvement strategies to address any needs or concerns based on the data. Results will also be used to generate recommendations to promote equitable youth engagement and collaboration practices in intervention research, which will be shared via academic and nonacademic dissemination channels (eg, scientific manuscripts, practice reports, and briefs).

Ethical Considerations

Ethics approval for this research was obtained from San Diego State University Institutional Review Board (HS-2023-0248 and HS-2024-0177). We received a waiver of parental consent and written consent and assent for the study. Therefore, all co-researchers provided verbal assent (those under 18) or consent to participate in the evaluation component of the project. The study team has procedures in place to maintain participant privacy and confidentiality.

Co-researchers will receive US $20 per hour of work, with additional stipends to cover transportation and childcare as needed. Hours worked and travel for study-related tasks will be reported weekly, with checks issued by the community partner organization biweekly. Payment for work is not contingent upon completing evaluation activities (eg surveys, interviews).

Results

Youth Co-Researchers

As of December 2024, we have onboarded 7 co-researchers (aged <18 y: n=2, 29%; aged >18 y: n=5, 71%). Initial co-researcher–identified interests include gaining experience in administrative tasks, social media and in-person outreach, research (eg, data collection), disseminating research to diverse audiences, and advocacy. Co-researchers have participated in professional development, capacity building, and study-specific activities to date, as shown in Textbox 1 [64,92,93].

In Table 2, we summarize sociodemographic characteristics of 4 co-researchers who have provided data to date. Co-researchers have worked an average of 5.9 (SD 2.7; range 1.5-10) hours per week and have received compensation for their contributions in the form of checks approximately every 2 weeks (and gift cards for transportation, ie, Uber or Lyft, as needed). Data collection for engagement-related outcomes is ongoing and will be reported in future publications as appropriate.

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Textbox 1. Professional development, capacity building, and study-specific activities completed by the co-researchers.

- Co-researchers completed a 3-hour "CIRTification" human research protections training program. CIRTification is an established curriculum developed for community members engaging in research that can be used as an alternative to the Collaborative Institutional Training Initiative human participants research training courses required by most institutional review boards [92].
- Co-researchers completed a now defunct self-paced virtual advocacy trainings through Take Down Tobacco offered through the Campaign for Tobacco-Free Kids.
- Co-researchers completed a Google Workspace training.
- Co-researchers reviewed adapted study overview documents (eg, a youth-friendly version of the funded grant application) and engaged in group discussion regarding the goals and processes of the Tobacco and Cannabis Harm Reduction through Expressive Arts (TobExA) study and ideas for intervention approaches.
- Co-researchers developed advisor recruitment materials (flyers and interest surveys in English and Spanish).
- Co-researchers provided oral feedback and guidance during the initial stages of the intervention mapping process. For example, 57% (4/7) of the co-researchers attended a virtual group meeting with TobExA team members from the community and academic partner organizations to provide feedback on the in-development "logic model of the problem," one of the first tasks in intervention mapping [64,93].
- Co-researchers reviewed and provided written and oral reflections in response to brief prompts regarding the appropriateness and overall utility of available youth substance use prevention and intervention programs. Initially, we asked the co-researchers to locate these programs themselves through web searches; however, based on feedback from co-researchers, we amended this task so that the youth engagement liaisons first located and condensed information about existing programs into a 1- to 2-page document that could then be reviewed by the co-researchers.
- Co-researchers selected and piloted "take-home" expressive arts activities to consider for inclusion in the TobExA intervention.

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Table 2. Youth co-researcher sociodemographic characteristics (n=4).

Sociodemographic characteristics	Values
Age (y), mean (SD)	19.3 (2.3)
Gender identity, n (%)	
Woman	3 (75)
Gender fluid	1 (25)
Sexual orientation, n (%)	
Heterosexual	1 (25)
Fluid	1 (25)
Bisexual	1 (25)
Queer	1 (25)
Education, n (%)	
Less than high school	2 (50)
High school graduate or GED[a]	1 (25)
Some college	1 (25)
Race or ethnicity, n (%)	
Black or African American	1 (25)
Hispanic or Latino	1 (25)
Other race or ethnicity	2 (50)
Transgender identity, n (%)	
No	4 (100)
Homelessness or housing instability (past 6 months; not mutually exclusive), n (%)	
Shared the housing of other persons	2 (50)
Lived or stayed in cars, parks, public spaces, abandoned buildings, substandard housing, or bus or train stations	1 (25)
Other living situation not listed	1 (25)
Prefer not to answer	1 (25)

[a]GED: General Educational Development.

Youth Advisors

As previously noted, we engaged members of the community partner YAB at the beginning of the study to guide the development of our youth engagement and collaboration approach. During the initial engagement with the YAB to develop our youth collaborator engagement processes, we piloted the advisor survey to refine the survey measure and evaluate the strategies we used to interact with members of the YAB (such that we could adjust strategies for future youth engagement). Of the 5 YAB members who completed the survey, 4 (80%) “strongly agreed” and 1 (20%) “strongly disagreed” with the statement “the TobExA team listened to what I had to say.” All “agreed” or “strongly agreed” that they “felt comfortable giving [their] opinion out loud,” “enjoyed this activity,” and that “there is a good balance of power between YAB members and [academic and community partners] in these meetings.” These results suggest that using similar collaboration strategies with advisors will allow them to feel heard and comfortable sharing opinions and feedback regarding the TobExA intervention. Piloting these measures allowed us to identify 1 question that should be removed before implementing the survey with the advisors, as it was deemed unclear and repetitive.

Additional TobExA advisors were engaged from May to July 2025 (n=5). Some advisors provided asynchronous written feedback via email over multiple instances (n=2, 40%). Topics addressed through this approach included feedback on recruitment strategies, facilitation techniques, general program content, and appropriate participant remuneration. Other advisors attended a one time in person meeting to provide feedback on potential program activities (n=4, 80%).

Discussion

Anticipated Findings

The use and effectiveness of youth engagement strategies in the context of intervention research (eg, co-design) have been underreported and underevaluated in the existing literature. To fill this gap, we have developed youth engagement strategies to promote authentic, equitable, and sustained youth

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collaboration throughout the TobExA intervention research process. These strategies include flexible options for engagement based on youth interests, availability, and personal and professional goals; fair compensation for contributions; tangible support for transportation and childcare needs; access to technology and a physical work space; leadership and professional development opportunities; and guidance and support from community and academic partner organizations' staff.

On the basis of our preliminary findings, we have identified several potential barriers to and facilitators of effective engagement of youth collaborators in the TobExA study. As we complete our study aims, we will leverage these insights to continuously improve and sustain effective youth engagement approaches. We believe these learnings may be useful to other researchers who aim to incorporate similar youth collaboration goals into their studies.

Challenges

Financial Compensation

Concerns regarding equitable compensation for TobExA youth collaborators were a significant focus in initial meetings with the community partner YAB, with YAB members raising concerns about the amount, frequency, and form of compensation (ie, concerns regarding compensation in the form of gift cards vs cash or check stipends). We were pleased to develop a plan that addressed the concerns raised by the YAB members; however, we did not sufficiently outline and create a detailed protocol of the process for compensation and specific roles of each partner organization in ensuring that co-researchers received payment for their contributions. This lack of a formal process led to confusion and, in turn, delays in payment early in the study. In addition, although both the community and academic partner organizations have existing payment structures to compensate collaborators and research participants, co-researchers were not initially onboarded as "employees" or "participants" at either organization, given their unique role on TobExA. This further complicated payment processes, causing some delays in co-researchers receiving payments for their contributions. These challenges led to the community and academic partners working together to delineate a specific protocol for tracking and communicating co-researchers' hourly contributions to the study, thereby decreasing confusion or frustrations among co-researchers and other TobExA team members and improving the timeliness of payment. This experience is aligned with many challenges regarding compensation for youth involved in community-engaged research [94] and emphasizes the importance of establishing clear processes for compensation before engaging youth collaborators.

Navigating Professional Boundaries

Another challenge relates to navigating and maintaining professional boundaries between co-researchers, youth engagement liaisons, and other members of the TobExA team who work with the co-researchers outside of the TobExA study, that is, as service providers at the community partner organization. For example, there have been some occasions in which a co-researcher contacted a specific TobExA team member from the academic partner organization with a request. If the co-researcher was unsatisfied with the response, they would then contact a TobExA team member from the community partner organization with the same request in an attempt to get a different response. Alternatively, a co-researcher would contact one TobExA team member from each of the partner organizations (community and academic) with the same request. If or when responses differed or partners deferred to the other, the co-researcher would become understandably frustrated. This led to duplicative staff efforts (2 individuals attempting to respond to the same request) and the need for lengthy discussion among TobExA team members regarding relatively minor requests.

TobExA team members from the community partner organization have likened this to "staff splitting," a phenomenon that occurs in health and social services when clients with multiple staff or clinicians responsible for their care engage in actions that create division or polarization among staff in order to influence decisions around their care [95]. While a frequent example of staff splitting in the literature relates to clients seeking more leniency in their treatment plans [96], our experiences have been related to co-researcher expectations regarding responsibilities and processes related to remuneration. Although "staff splitting" has been a new experience to TobExA team members from the academic partner organization, those from the community partner organization (ie, service providers and administrators) have explained that this is a relatively common experience in the provision of social services to youth (and may be aligned with the youth's developmental stage). They have provided guidance to the TobExA youth engagement liaisons on how to mitigate similar issues in the future.

Relatedly, there have been challenges regarding communication (eg, timely responses to messages), meeting attendance, and completing assigned activities on the part of the co-researchers. This is expected given that for many co-researchers, this is the first time working in a professional work setting. Our ability to overcome these challenges has been somewhat complicated by team members from the community and academic partner organizations having different ideas for resolution. TobExA team members from the academic partner organization were initially very cautious about enforcing specific expectations regarding communication, attendance, and transparency, fearing such an approach would alienate co-researchers and lead to disengagement. In contrast, several TobExA team members from the community partner organization and even some of the co-researchers have stressed the need to foster and uphold basic professional standards for the co-researcher role, such as responses to communications and requests within an agreed-upon period. Indeed, TobExA team members from the community partner organization encouraged those from the academic partner organization to view the co-researcher role as an important opportunity for youth with limited resources and access to professional development opportunities to develop professional skills in a supportive environment that could benefit them in future jobs and in navigating their transition into a stable adulthood.

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Competing Priorities of Youth Collaborators

We have experienced challenges gathering all co-researchers for collaborative working sessions, given their many competing priorities, as all co-researchers are in school or have other work commitments, and many have specific family commitments, such as parenting. This is a challenge we are accustomed to navigating in community-academic research efforts in which team members have many competing priorities and limited availability. Much of the co-researchers' tasks on TobExA are designed to be conducted remotely; however, there is a need for at least some collaborative working sessions and these competing priorities and busy schedules have made it challenging for all co-researchers and key members of the TobExA youth engagement team to meet. We have addressed this challenge through a flexible meeting schedule and increasing support for co-researchers to attend meetings in person (eg, additional transportation support).

Legitimization of the Co-Researcher Role

Other challenges regarding the organizational legitimization of the co-researcher role have occurred to date. For example, co-researchers are required to complete administrative forms to officially "volunteer" (ie, work) with the academic partner organization and to obtain an institution-specific email address. These forms request information that may be challenging for some co-researchers to provide, such as a permanent address or government ID verification. This was further complicated when our study staff learned that the academic partner organization requires volunteers to be aged ≥18 years. To address these barriers, youth engagement liaisons worked with co-researchers to complete necessary forms. For those aged <18 years, the community partner organization issued an email address. While obtaining "official" status with an academic partner organization may be beneficial to youth collaborators, it is important to critically examine how institutional barriers (particularly at academic institutions) may act as a form of gatekeeping, restricting youth' ability to engage in research [97].

Technological Barriers

Many of the co-researchers have experienced technological barriers to participation. For example, a lack of reliable access to computers has made it difficult for some co-researchers to complete self-paced training, as they had to complete the training on their mobile phones or come in-person to a provided workspace to complete it. In addition, at least 1 co-researcher lost access to their mobile phone during their time collaborating on the study, delaying their communication with the youth engagement liaisons and other TobExA team members. Although both the community and academic partners provide access to computers with internet at their respective organizations, co-researchers have experienced challenges coming to these locations during operational hours. To address this issue, we have worked with co-researchers to identify ideal in-person working times and ensured TobExA team members are available to be on-site and provide oversight and guidance for assigned tasks during these times.

Researchers who aim to collaborate with youth, including youth experiencing homelessness and housing instability, should anticipate and prepare to address technological barriers to participation, which may include the provision of computer devices for temporary use, free software programs [98], and nondigital approaches [99]. Researchers should develop clear protocols to address broken or lost devices and be mindful of related organizational requirements.

Facilitators of Youth Engagement

We have identified several facilitators of youth engagement to date. For example, we have found that engaging multiple direct-service providers from the community partner organization in the youth engagement process has strengthened and facilitated co-researcher recruitment. Specifically, staff with established rapport with individual youth have helped us to recruit highly engaged co-researchers. Relatedly, cocreating the co-researcher and advisor roles with the community partner YAB helped us ensure that each position was appropriate and appealing to potential youth collaborators and resulted in us recruiting multiple YAB members to become co-researchers for the TobExA study.

Another facilitator of youth engagement and collaboration has been tailoring each co-researcher's research and training tasks to their individual goals and interests. On the basis of interviews with prospective co-researchers and initial onboarding meetings, we have identified customized training opportunities and tasks for each co-researcher. For example, some co-researchers indicated an interest in learning more about the use of social media in research and were subsequently assigned tasks related to reviewing and evaluating existing social media accounts related to substance use prevention to inform the TobExA intervention.

Strengths and Limitations

The quality of our protocol must be considered in the context of its strengths and limitations. A key strength is that our youth engagement approach is embedded within a larger community-based participatory research study that builds upon a multiyear community-academic partnership. This infrastructure allows for our learnings to be implemented and sustained within the partnership moving forward. Another strength is our approach to evaluation, including adaptation of validated quantitative measures to assess how youth collaborators may benefit from participation in the study and qualitative measures to document the process and identify opportunities for real-time quality improvement. We are particularly pleased to be able to fairly compensate youth collaborators for their contributions, which aligns with recommendations from the community partner's YAB and with established best practices of youth engagement. Furthermore, our payment structure provides hourly compensation for the youth's contributions to the study, with more involved, sustained roles earning greater compensation for their contributions compared to those who engage as advisors. Finally, our adaptable and flexible youth engagement process is a strength, as it allows us to respond in real time to necessary changes or challenges related to engaging youth collaborators.

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A key limitation relates to engaging youth who do not primarily speak English or have limited English proficiency. Indeed, TobExA team members from the community partner organization have consistently expressed concerns that youth engagement would not be inclusive of youth who prefer Spanish and seek housing-related services at their organization. While we have developed some materials in Spanish and have plans for increasing engagement of youth who prefer Spanish as co-researchers and advisors, we have yet to engage youth who prefer Spanish specifically (we do have bilingual [English and Spanish] co-researchers on the team). A related limitation is the sociodemographic characteristics of our current co-researchers who are aged 19 years, on average, have completed some college, and are predominantly cisgender young women. Those whom we have yet to sufficiently engage, including youth aged <18 years, young men, and transgender youth, may require different approaches to collaboration due to developmental, social, or gender-specific differences.

In addition, we did not include quantitative measures that explicitly assess the co-researchers' or advisors' colearning or codevelopment regarding tobacco- and cannabis-specific prevention or advocacy. We instead selected measures that capture these community-based participatory research principles broadly, including the following: (1) the Research and Action Self-Efficacy Scale, which captures participatory behaviors (eg, "I have spoken with other youth about issues that I want to improve in the community.") [85]; (2) the Youth-Adult Partnership Scale, which assesses collaborative youth-adult relationships (eg, "There is a good balance of power between co-researchers and SDYS/SDSU staff on the TobExA team.") [84]; and (3) the Youth Program Quality Survey, which evaluates perceived skill-building opportunities (eg, "I was challenged to think and build new skills.") [83]. In addition, our qualitative data (semistructured exit interviews and process-related field notes) may reveal whether more specific, tobacco- and cannabis-related learning has occurred. While this approach may limit our understanding of outcome-specific knowledge gains, our measurement plan may be more applicable across content areas. We plan to include more targeted measures of tobacco- and cannabis-related colearning and codevelopment when we pilot the intervention.

Finally, several of the co-researchers engaged to date have served as members of the community partner's YAB, which has a strong youth engagement and leadership structure. Thus, current and former YAB members who join the TobExA team may be accustomed to collaborating with adult partners and contributing to the development of programs or interventions without the need for extensive capacity building. Youth who have not served on a YAB or in a similar professional capacity may require more support. To foster trust and teamwork among these youth, we plan on implementing strategies to encourage relationship building, including structuring meetings with both co-researchers and advisors to include time for socializing and ice breakers, creating mentor-mentee pairs when appropriate between more senior youth collaborators and those who are newly onboarded and conscientiously creating collaborative groups so that youth have ample opportunity to work with different team members.

Conclusions

This protocol describes a holistic approach to engaging youth as collaborators (as "co-researchers" and "advisors") throughout the intervention research process to address tobacco-related disparities among youth experiencing homelessness and housing instability. Our approach may serve as a useful model that can be adapted for other intervention research studies addressing health disparities among young people and research focused on youth and young adults more broadly.

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Authors' Contributions

ARL contributed to conceptualization, data curation, funding acquisition, methodology, and writing the original draft. ACL contributed to conceptualization, data curation, methodology, and writing the original draft. RE contributed to conceptualization, project administration, and reviewing and editing the manuscript. NC contributed to reviewing and editing the manuscript. LC contributed to reviewing and editing the manuscript. JPC contributed to conceptualization and reviewing and editing the manuscript. LU contributed to reviewing and editing the manuscript. BA contributed to reviewing and editing the manuscript. SJ contributed to conceptualization, project administration, and reviewing and editing the manuscript. SS contributed to reviewing and editing the manuscript. JKF contributed to conceptualization, data curation, funding acquisition, methodology, project administration, and writing the original draft.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
Youth co-researcher and advisor participation during key intervention research stages.
[PNG File , 179 KB - resprot_v14i1e69441_app1.png]

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Abbreviations

IM: intervention mapping
TobExA: Tobacco and Cannabis Harm Reduction through Expressive Arts
YAB: youth action board

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Protocol

Platform Technology for Extended Reality Biofeedback Training Under Operant Conditioning for Functional Limb Weakness: Protocol for the Coproduction of an at-Home Solution (React2Home)

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Abstract

Background: Functional neurological disorder (FND), including functional movement disorders (FMDs), arises from disruptions in the perception-action cycle, where maladaptive cognitive learning processes reduce the sense of agency and motor control. FND significantly impacts quality of life, with patients often experiencing physical disability and psychological distress. Extended reality (XR) technologies present a novel therapeutic opportunity by leveraging biofeedback training to target sensory attenuation and amplification mechanisms, aiming to restore motor function and the sense of agency.

Objective: This study aims to coproduce and evaluate the usability of an XR technology platform for FND rehabilitation, focusing on functional limb weakness. The platform integrates biofeedback training with haptic and visual feedback to support motor relearning and control.

Methods: We propose to use an experience-based co-design framework to engage patients with FND, caregivers, and health care professionals in collaboratively designing the XR platform. Stakeholders can share their experiences through narrative interviews and co-design workshops, which can identify emotional touchpoints and prioritized patient-centered needs. Insights will be synthesized through qualitative analysis and used to guide the development of system requirements via quality function deployment, ensuring that the platform aligns with user needs. XR training tasks—virtual reality relaxation, XR position feedback, and XR force feedback—will be integrated as needed into a unified therapeutic game experience through 4-week Agile sprints. Usability will be assessed using the System Usability Scale and qualitative feedback, with themes analyzed in NVivo to identify key areas for subsequent improvement.

Results: High usability scores (>85) were recorded for the XR position feedback tasks in the predesign study, reflecting excellent usability and participant satisfaction. However, the virtual reality relaxation and XR force feedback tasks exhibited interindividual variability, underscoring the need for personalization. Key themes included customization, comfort, accessibility, and XR technological quality, ensuring that the XR platform effectively addressed diverse patient needs. The predesign study highlighted the potential of XR technology for FMD rehabilitation by integrating biofeedback training into a patient-centered game design framework. Approaches such as experience-based co-design and quality function deployment can support coproduction by systematically addressing usability and accessibility challenges. Brain-based metrics may further strengthen this evaluation. Accordingly, this study will use portable brain imaging to capture dynamic functional connectivity in key brain regions, enabling personalized interventions.

Conclusions: Through coproduction and iterative refinement, this study aims to demonstrate the promise of personalized XR gaming technology as a scalable, at-home solution for FMD rehabilitation. In this context, personalization and accessibility are

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critical for optimizing usability and long-term clinical outcomes, paving the way for at-home implementation within the FND stepped care model.

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KEYWORDS

functional neurological disorder; functional movement disorder; extended reality; biofeedback training; experience-based co-design; EBCD; quality function deployment; QFD; rehabilitation; coproduction; artificial intelligence; AI

Introduction

Background

Functional neurological disorder (FND), a condition in which individuals experience neurological symptoms (eg, weakness and tremor) without a structural brain lesion, is a complex disorder at the intersection of neurology and psychiatry, involving a dynamic interplay between brain-body processes and the mind [1]. A key explanation concerns a neurobiologically informed model of hierarchical Bayesian inference [2], which describes perception as a process of combining prior expectations and sensory input to minimize prediction errors [3]. FND symptoms arise when these prediction errors are not properly updated over time, leading to dysfunction in Bayesian perception and action [3]. Maladaptive, highly weighted prior expectations, influenced by bodily attention, are central to this process [2]. Empirical evidence supports this model, such as studies on altered predictive mechanisms in functional gait disorder [4]. In this context, functional movement disorders (FMDs), a subtype of FND [5], are atypical movement patterns (eg, tremor, dystonia, and weakness) not explained by organic disease, altered by distraction or nonphysiologic maneuvers and distinct from neurologic disease–related movement disorders. FMDs are common in neurology, accounting for 15% of new referrals, second only to headaches. FMDs have a poor prognosis, with 39% of patients remaining the same or worsening over time, often experiencing high physical disability and psychological issues [6]. These disorders present a clinical paradox: while the movements appear voluntary, patients experience them as involuntary and uncontrollable. The prevalence of FMDs among neurology patients in neurology clinics underscores the need for effective therapeutic interventions to address the significant disability associated with these disorders.

Recent research has highlighted the role of sensory attenuation and the sense of agency in the pathophysiology of FMDs [6]. Sensory attenuation refers to the brain's ability to predict the sensory consequences of voluntary movement that suppress the actual sensory feedback, that is, reafference, a process that is crucial for distinguishing self-produced sensations from external stimuli [7]. In this predictive mechanism, a duplicate of the motor command, known as an efference copy, is postulated to be sent to a forward model that integrates the efference copy with an estimate of the body's state to predict the sensory consequences of the movement. This predictive mechanism is postulated to be impaired in patients with FMD [8], reducing their ability to accurately predict the sensory consequences, thereby leading to the development of a reduced sense of agency over their self-generated movement [3]. This reduced sense of agency could explain why these patients perceive their movements as involuntary despite their voluntary appearance [9].

The sensory attenuation process is primarily mediated by forward models within the motor control system [7] that predict the sensory consequences of a planned action and modulate the reafference accordingly [10]. When an action is self-generated, the forward model predicts the resulting sensory input and attenuates the sensory experience to prevent self-caused sensations from interfering with the processing of external stimuli. Sensory attenuation can be measured using the force-matching task, where participants match a force applied to their finger either directly using their opposite hand (direct condition) or indirectly using a potentiometer and a torque motor (slider condition) [11]. Healthy individuals typically overestimate the force in the direct condition, producing greater matched force due to sensory attenuation. This phenomenon is reduced in individuals with FMD, potentially due to altered predictive mechanisms affecting their sensory attenuation process [8].

The force-matching task needs a well-designed haptic device, developed using robust methodological considerations [11], that can be combined with wearable brain imaging targeting key brain regions [3] for brain-behavior analysis. The primary motor cortex (M1) is involved in the execution of voluntary movements and plays a critical role in the sensory attenuation process [12]. Using the theta burst stimulation (TBS) approach, Voss et al [12] applied continuous TBS and intermittent TBS over the M1 to alter its excitability. The authors found that continuous TBS, which decreases cortical excitability, reduced sensory attenuation and improved performance in a force-matching task, suggesting a disruption in the predictive process. By contrast, intermittent TBS had no effect on sensory attenuation. The cerebellum also plays a crucial role in fine-tuning motor actions and predicting their sensory consequences [13]. The study by Blakemore et al [13] demonstrated that the cerebellum predicts the sensory outcomes of motor actions and signal discrepancies between expected and actual (afferent) sensory feedback. Positron emission tomography scans of participants performing a delayed tactile task showed increased cerebellar activity with longer delays, confirming its role in fine-tuning motor actions and motor learning by comparing intended and achieved movements. Within the cerebello-thalamo-cortical network, the thalamus acts as a subcortical relay station. Most afferents to the thalamus, whether ascending or cortical, are collateral branches of axons targeting lower motor centers, suggesting that thalamocortical

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pathways primarily monitor ongoing motor commands, with modulatory inputs adjusting information flow based on attentional demands [14]. The thalamus exhibits reduced activity during self-generated sensations, indicating its (relay) attenuation [15]. Hua et al [15] applied dynamic causal modeling analysis that indicated top-down modulation from the right inferior parietal lobe during sensory attenuation of an auditory stimulus. In this context, sensory attenuation is evident not only in somatosensory domains but also in auditory and visual modalities; for instance, self-generated sounds and visual stimuli are perceived as less intense than those generated externally, highlighting the broad applicability of sensory attenuation mechanisms across different sensory modalities. In FMDs, impaired sensory attenuation during movement may disrupt the cortico-cerebello-thalamo-cortical loop (a disruption referred to as dysrhythmia) [16], resulting in exaggerated or reduced movements, with both reflecting a reduced sense of agency over one's own actions [17]. On the basis of a literature review of predictive coding and adaptive control in human-machine interfaces (HMIs; the systems or devices that enable interactions between users [patients] and robotic platforms or rehabilitation devices), Dutta [3] proposed the somato-cognitive action network (SCAN; a proposed brain network of intereffector regions within M1 that integrates motor planning with cognitive, physiological, and whole-body action control) as a key M1-based system linking effector and intereffector regions to support action intention, sensorimotor integration, and self-agency (or "awareness of being the agent of one's own actions" [18]) by closing the cortico-cerebello-thalamo-cortical loop [16].

The 2 key theories of the sense of agency are the comparator model and the theory of apparent mental causation [19]. The right temporoparietal junction (rTPJ; a brain region implicated in the sense of agency and self-other distinction in movement control) is postulated to be a key node in the agency network for neuromodulation in FND [20]. However, the coordinates of the mean peak of activity in the temporoparietal junction (TPJ) have varied across studies [21], showing activation in the angular gyrus, middle temporal gyrus, parietal operculum, and supramarginal gyrus. This variation reflects the multidimensional processes at the TPJ contributing to the sense of agency, such as mismatch detection, action awareness, and sensory-motor conflicts. The angular gyrus is involved in intersensory mismatch detection, action awareness, and multisensory integration, while the supramarginal gyrus processes sensory-motor conflicts. Changes in perspective, mentalizing, and deception specifically activate the TPJ and posterior superior temporal sulcus, highlighting the role of perspective [22] in assigning motor actions to oneself or others. Overall, different neural mechanisms and specific brain areas within the TPJ contribute to the formation of agency when motor control is disrupted [3]. Functional neuroimaging has shown reduced activity and impaired connectivity of the rTPJ during functional tremor, indicating that altered rTPJ connectivity may play a contributing role. An impaired self-agency can be tested using intentional binding (motor intention is temporally matched with sensory feedback [23]) and sensory attenuation paradigms presented by Maurer et al [17]. The authors found decreased functional connectivity in patients with FMD between the rTPJ—crucial for self-agency—and bilateral sensorimotor regions, including the right sensorimotor cortex, bilateral cerebellum, bilateral supplementary motor area (SMA) [24], and right insula.

In contrast to sensory attenuation, sensory amplification occurs when the perceived intensity of a sensory stimulus is enhanced due to the influence of selective attention [25], for example, after error commission [26]. This effect is particularly noticeable when an individual directs their visual attention to a specific touch event, thereby increasing the perceived intensity of the touch. This phenomenon is related to the visual enhancement of the touch effect, where simply viewing (or even mentally imagining [27]) a body part can change tactile acuity for that part. Frontal and parietal cortices are involved in the modulation of sensory precision by attention that involves neural hierarchies [25]. Increased activity in the posterior parietal cortex is associated with enhanced sensory perception when visual attention is directed toward a stimulus, supporting the idea of optimizing sensory precision through attention. Empirical studies have shown that visual attention to a touch event, whether active or passive, amplifies the perceived intensity of the touch. This sensory amplification effect is significantly larger than the sensory attenuation effect, underscoring the powerful influence of attention on sensory perception. Overall, the interplay between sensory attenuation and amplification highlights the complex nature of sensory processing, where the brain dynamically adjusts the perceived intensity of stimuli based on predictive models and attentional focus [10,25]. Understanding these sensory mechanisms provides valuable insight into how sensory experiences are modulated in various contexts, including during the observation of others' actions and in conditions involving altered sensory processing, such as FMD [8]. In understanding sensory mechanisms, it is important to distinguish between interoception, the sense of internal bodily states, and exteroception, which relates to the perception of the external environment through senses. Pain, for instance, can be interoceptive when it arises from within the body; and, in some cases, dysfunctional sensory amplification due to the overweighting of nociceptive input can lead to exaggerated prediction errors, reinforcing and intensifying the perception of pain [28], a common feature in FND-related pain symptoms and diagnoses [29].

We aim to leverage the interplay between sensory attenuation and amplification in exteroception, which is crucial for action in the external environment, by applying an operant conditioning–based implicit learning approach [30]. While this method can also be applied to interoception, this study focuses specifically on external action. This approach has shown therapeutic potential in addressing learned nonuse, a condition thought to arise from a maladapted forward model, in individuals with chronic stroke [31]. Our operant conditioning technique reinforces desired motor behaviors using visual feedback by dynamically adjusting gain and noise, with the goal of reweighting sensory attenuation and amplification [30]. This multilevel stimulation process adjusts prediction errors by aligning predicted and actual sensory input within the brain's predictive coding framework [30]. Kumar et al [31] showed the feasibility of the virtual reality (VR)–based balance training

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system that used the operant conditioning approach proposed by Dutta et al [30], where higher weighting of the center of pressure from the paretic limb for visuomotor control implicitly encouraged patients with hemiplegic stroke to engage the affected limb during weight-shifting gaming tasks. Intermediate catch trials provided unbiased measures of standing balance capability. This implicit learning approach incorporated individualized weight distribution for VR tasks as well as subtle reinforcement (including suggestions) during VR gaming as an operant factor [32] that improved paretic limb behavior.

Hypothesis for Operant Conditioning Sense of Agency

Figure 1 shows the neurocomputational framework of agency and motor control [3] illustrated for fundamentals of laparoscopic surgery (FLS) training with a camera-equipped FLS trainer box [33]. It depicts how voluntary movement and the sense of agency are generated through a brain-body loop involving a prospective sense of agency leading to intention, prediction, and feedback. The prefrontal cortex (PFC) sets goals based on a prospective sense of agency, which are evaluated by the basal ganglia for cost and reward before being translated into motor commands via inverse and forward models. The cerebellum predicts the sensory consequences of action, and delayed reafferent signals from the body (eg, touch and position) are compared against these predictions. Discrepancies (prediction errors) update the internal state of the parietal cortex and feed into the SCAN for retrospective agency judgment. We found that portable brain imaging can capture error-related brain-behavior relationships during complex motor tasks [33], as demonstrated in Figure 2, by revealing distinct microstate transitions between expert and novice groups within the Bayesian predictive coding framework. Together, the prospective and retrospective senses of agency support metacognition and are crucial for rehabilitation using extended reality (XR; an umbrella term encompassing VR, augmented reality, and mixed reality technologies), where reestablishing predictive control and agency is key, particularly in disorders such as FMD.

Figure 1. Neurocomputational framework of the sense of agency (SoA) and motor control during the action-perception cycle from perception of error (observation model) to the corrective action (correction step). (A) Schematic of neural mechanisms underlying SoA and motor control, illustrating cortical and subcortical interactions across prefrontal cortex, basal ganglia, premotor cortex, motor cortex, cerebellum, and parietal cortex. The supplementary motor area (SMA), involved in internally generated motor planning, is functionally integrated within the somato-cognitive action network (SCAN). The proposed framework integrates intention and goal setting, cost-reward evaluation, internal forward and inverse models, sensory prediction, and reafference processing. Multisensory deviance contributes to SoA judgments via the SCAN. (B) Illustration of action correction step during laparoscopic simulation training using a fundamental of laparoscopic surgery (FLS) trainer box, highlighting the correction loop in response to perceptual error observed using camera feedback on a video monitor. (C) Action-perception loop during active tool manipulation in the FLS trainer box environment, emphasizing real-time integration of motor commands and perceptual feedback. (D) Camera close-up of task performance using laparoscopic tools for perception-action cycle, illustrating the observation model and its role in modulating corrective actions.

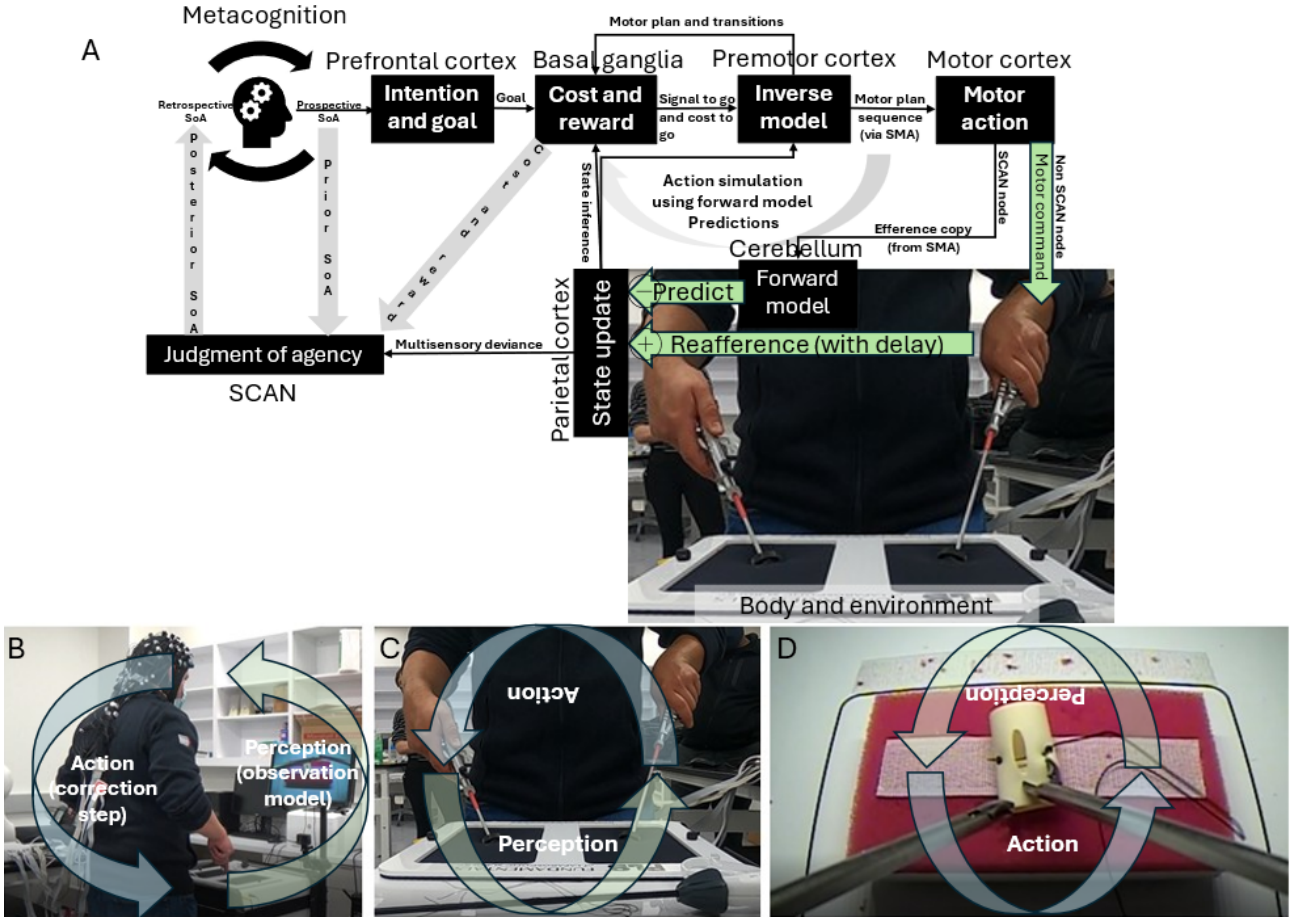

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Figure 2. Interpretation of microstate transitions in expert and novice groups within the Bayesian predictive coding framework (adapted from Walia et al [33], which is published under Creative Commons Attribution 4.0 International License [33]). During learning, the brain alternates between acting as an observer and as a controller: the "brain as controller" model (correction step) depends on predictions generated by the "brain as observer" (observation model), and vice versa. This dynamic is particularly relevant to switching state-space models in neuroimaging.

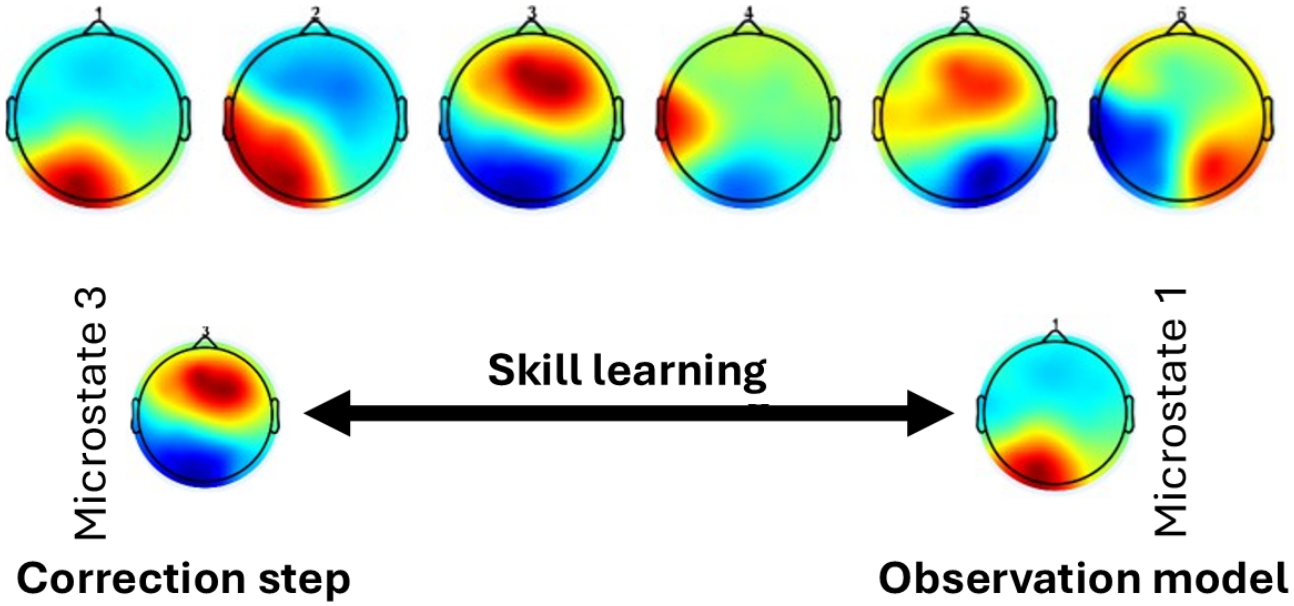

The central hypothesis is that a prospective sense of agency, which enables self-initiated movement intentions, can be generated in a top-down manner through "suggestion and imagery" within an XR environment. This process can be monitored using slow movement-related cortical potentials (MRCPs) [34], such as the early readiness potential originating from the SMA complex (Bereitschaftspotential I) to the SCAN regions of the M1 (Bereitschaftspotential II). At the intereffector SCAN regions, MRCP is postulated to begin with a slow negative shift around 1.5-2 seconds before movement onset, peaking negatively at movement onset, which coincides with a sharp increase in event-related desynchronization in the mu and beta bands. While event-related desynchronization is reflected in non-SCAN regions of M1, the intereffector SCAN regions are postulated to support body integrated action planning. Within the XR context, exafferent sensory input will be modulated following self-initiated motor execution to integrate with reafferent feedback through postulated Bayesian fusion [3], thereby influencing prediction error dynamics that arise from a disrupted forward model, as observed in FMD [35]. Following movement execution (postmovement positivity in MRCP), beta event-related synchronization signals the return to a baseline state. In this context, through operant conditioning embedded in XR-based gaming rewards, implicit learning is postulated to drive the recalibration of the forward model, progressively reducing reliance on exafferent input and supporting the restoration of normal motor function (Figure 3).

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Figure 3. The modular HRX-1 is a haptic robotic device that integrates functional near-infrared spectroscopy (fNIRS), electroencephalography (EEG), and machine learning to support both top-down and bottom-up exafferent modulation within an extended reality (XR) environment. Its aim is to reduce abnormal regulation of EEG beta-frequency activity with EEG-fNIRS joint-imaging facilitating its localization in the supplementary motor area, which is commonly observed in Functional Movement Disorder (FMD). In FMD, patients often lack the typical beta desynchronization that occurs before and during movement. This suggests their brains may struggle to effectively "release the brake," transitioning from motor planning to execution, which contributes to symptoms such as tremor, weakness, and abnormal movements.

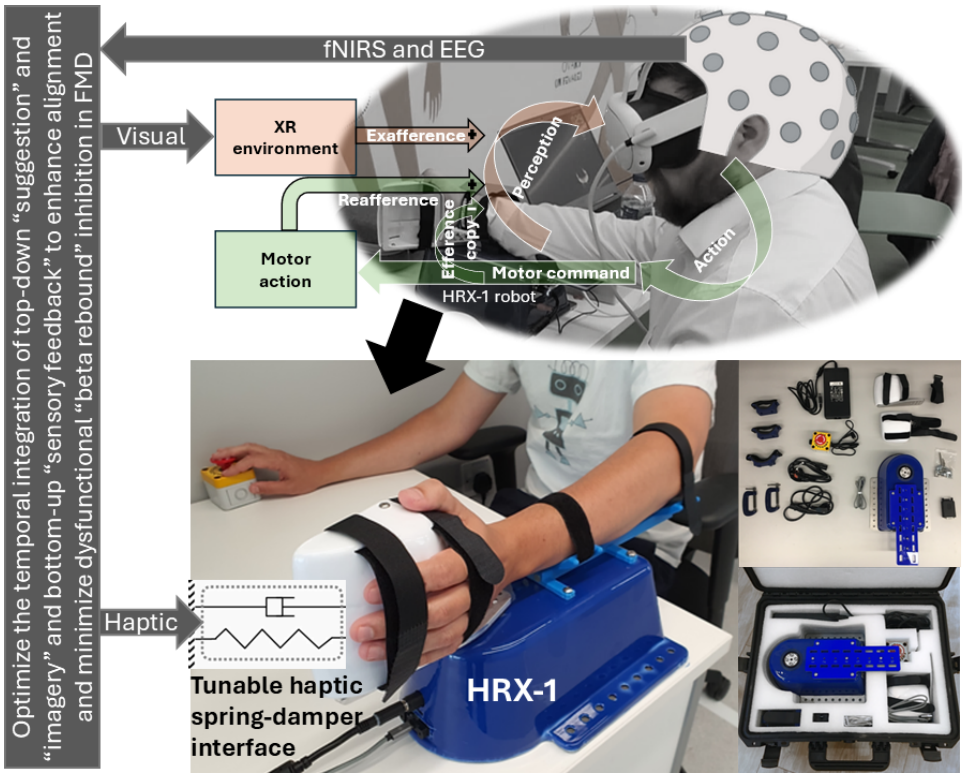

Voluntary movement is initiated by neural activity that first appears in the rostral cingulate zone within the dorsal anterior cingulate cortex, followed by activation in the pre-SMA and SMA regions and then in the M1 [36]. All these regions send projections to the spinal cord, with the M1 serving as the primary conduit for transmitting motor commands via the corticospinal tract. Concurrently, an efference copy of the motor commands is sent to the primary somatosensory cortex, cerebellum, and striatum, where it supports real-time correction, motor learning, and the inhibition of competing movements. We propose that during the preparatory stage of a voluntary motor task, efferent signaling from the SMA complex [24] sets the initial conditions by modulating the SCAN node within the M1 [3], thereby priming the non-SCAN effector regions for context-appropriate action. We suggest that this contextual modulation of the SCAN node by the SMA is impaired in FMD [24,37], which can lead to persistent fatigue [38]. Moreover, stress-related mechanisms in FMD may arise from overlapping adrenal connectivity and medial motor regions (the SMA and dorsal anterior cingulate cortex) disrupting the integration of motor intention and bodily arousal [36].

Building on the findings of Maurer et al [17] that link impaired self-agency to disrupted connectivity between the rTPJ and sensorimotor regions, we propose using simultaneous mobile brain and body imaging (brain-behavior joint monitoring [33,39]) to monitor intentional binding and efferent signaling. In this context, action-perception coupling monitoring [39] will leverage task-specific dynamic functional connectivity (dFC; a method for assessing time-varying brain network interactions during tasks) [40] between the rTPJ and sensorimotor cortex to assess abnormalities in sensory feedback processing in FMD, specifically, dFC between the rTPJ and the SMA complex [24], which contributes to efferent signaling and intentional binding [41-43] from the pretask to posttask phases, respectively, in the action-perception cycle.

In FMD, increased (localized to the left SMA [37]) and persistent beta synchronization [44] disrupts motor preparation, diverging from the typical role of brief beta bursts in facilitating cognitive control and goal-directed behavior [45], that is, "brain as controller." We propose that within the sensorimotor cortex, mu rhythms support the brain's role as an "observer" [22] engaged in action observation, salience detection [46], and contextual gain setting [47], while beta rhythms reflect the brain's role as a "controller," governing motor execution and precision [48]. In this context, it is further postulated that mu rhythms are linked to SCAN-like intereffector zones and the cingulo-opercular (salience) network [36], whereas beta rhythms are more specifically tied to non-SCAN effector-centric motor control in the M1. These sensorimotor rhythms alternate in bursts to modulate corticospinal excitability in healthy individuals, that is, motor-evoked potential amplitudes measuring corticospinal excitability peak during the beta rhythm's peak-to-falling phase and the mu rhythm's trough-to-rising phase in the sensorimotor cortex [49]. The beta rhythms extend to broader motor-related regions, including the basal ganglia, and play a role in motor control and movement stabilization crucial in "brain as controller." The dynamic interplay of mu and beta event-related desynchronization and

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event-related synchronization, which is essential for normal motor function, is disrupted in FMD and may be restored through electroencephalography (EEG; a technique for recording electrical activity of the brain, used here for assessing cognitive and motor states) via biofeedback-driven training, which sequences the execution of an observation model through to the correction step [35,50] in XR-based motor tasks (Figure 1).

The amygdala has functional and anatomical connections to cingulo-opercular network nodes such as the anterior insula and anterior cingulate cortex [51]. FMD is postulated to involve maladaptive cognitive learning from aversive stimuli, leading to overactivity in the amygdala [52]. A heightened fronto-amygdala connectivity can disrupt the left PFC's role in flexible, top-down cognitive control [53]. Therefore, our operant conditioning approach in XR begins with a relaxation and deep-breathing activity [35] combined with vagus nerve stimulation [54]. This is followed by a motor relearning task using a haptic device, rooted in the behaviorist framework formulated by Skinner [55] and formalized through reinforcement learning [30], designed to deliver implicit rewards and promote the adaptation of the internal forward model through gaming behavior [35]. This process relies heavily on the cerebellum for prediction error coding to facilitate effective motor adaptation to exafferent signaling for reinforcement learning [56]. In this context, portable neuroimaging also enables the investigation of individual activity in the brain regions such as the ventrolateral PFC, superior parietal lobule, supramarginal gyrus, angular gyrus, dorsolateral PFC, frontal eye field, and premotor cortex, and M1 [33,39]. Within the frontoparietal network, a distinction is postulated between attention driven by unexpected stimuli (bottom up) and attention that is controlled and goal directed (top down) [33]. The ventral frontoparietal network, including regions such as the temporoparietal cortex and inferior frontal cortex, is specialized for detecting behaviorally relevant stimuli, particularly when they are salient or unexpected (bottom up). This network acts as a "circuit breaker" for the dorsal system, directing attention to salient events. By contrast, the dorsal frontoparietal network, comprising areas such as the intraparietal sulcus and frontal eye fields, is primarily involved in goal-directed, top-down attentional control. This system is engaged during focused attention on specific targets or tasks. Understanding the interplay between these brain networks using switching state-space models for neuroimaging [57] is crucial during operant conditioning in FMD. In this context, the information flow model for developing the sense of agency [58] involves a leading network for mismatch detection, including the right supramarginal gyrus, left anterior inferior parietal lobule, anterior insula, and rTPJ. Mismatch information is relayed through intermediate areas before reaching the lagging network, which includes the bilateral PFC, cingulate cortex, and bilateral posterior inferior parietal lobule. The role of the PFC in the lagging network suggests its later involvement in retrospective sense of agency processing.

Related Prior Works

Expertise in the FLS "suturing and intracorporeal knot-tying" task was assessed through error-related brain states using portable, multimodal brain imaging [33]. The study by Walia et al [33] revealed significant differences in EEG microstate dynamics between experts and novices during complex surgical task training, aligning with the microstate taxonomy formulated by Bréchet et al [59]. Microstate 1 (comparable to microstate C [ventral visuospatial attention] in the taxonomy formulated by Bréchet et al [59]) and microstate 3 (comparable to microstate D [focus switching and reorientation]) were dominant across conditions. Experts lacked microstate 2 (comparable to microstate A [exploration processes]) during error epochs, indicating reduced exploratory motor responses and a more efficient exploitative strategy. Experts transitioned frequently to microstate 3 for error correction, while novices relied heavily on microstate 1 and transitioned back and forth between microstates 1 and 3, reflecting ongoing attempts at skill learning (Figure 2). In addition, experts exhibited prefrontal activity (microstates 5 and 6) preceding transitions to microstate 3, while novices showed left-right transitions (microstate 4) to microstate 1. Thus, microstate analysis highlighted that experts use refined attentional dynamics and reduced exploratory activity during errors, consistent with the neurophysiological underpinning described by Bréchet et al [59]. Recently, we used wearable functional near-infrared spectroscopy (fNIRS; a noninvasive brain imaging method using light to measure changes in cerebral blood oxygenation) [60] to assess brain activation during simulated operative dictation in an ecologized enactive framework. The operative dictation of a surgical task with "brain as controller" relies on first-person mental imagery—"brain as observer" [22]—to consciously recreate and manipulate past action experiences as mental representations without physical stimuli (refer to the "action simulation" loop in Figure 1). Simultaneous expert feedback and cues (exafferent external suggestions) can enhance enactment imagination, facilitating beneficial updates to the internal models.

The cerebellum plays a crucial role in reshaping the relationship between motor intention, action, and outcome through its connectivity with the medial PFC, as well as its interactions within the thalamocortical circuitry, including the cerebellum-thalamus-SMA pathway, for sensory gating mechanisms in the correction step (Figure 2) [61]. This dynamic interaction in the "action simulation" loop (Figure 1) likely provides a foundation for hypnosis to modulate the sense of agency [62]. Evidence suggests that the cerebellum contributes to the prediction and coordination of motor actions, integrating sensory feedback to refine the alignment between motor intentions and perceived outcomes [13]. Hypnosis, through its effects on attention and sensory modulation, may influence these cerebellar processes, which can be facilitated with noninvasive brain stimulation [63,64], enhancing the precision of prediction errors [56,65]. The study by Polito et al [66] highlights how hypnotic suggestions can disrupt habitual motor-sensory loops, potentially recalibrating the perception of control over actions. In addition, Blakemore et al [62] demonstrated that hypnosis can modify the temporal binding of intentional actions and their outcomes, further supporting its capacity to reshape the sense of agency through altered cerebellar and SMA connectivity. These insights suggest that hypnosis, by interacting with the neural substrates involved in sensory gating and motor planning, has the potential to refine

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the brain's representation of agency, particularly in conditions where the sense of agency is disrupted.

A recent study by Bréchet et al [67] examined how intense meditation training modulates EEG microstates, revealing significant postmeditation topographical changes. Two novel microstate topographies emerged after meditation, explaining nearly 50% of the data variance, and were localized to brain areas involved in self-related multisensory experiences, including the insula, supramarginal gyrus, and superior frontal gyrus. Unlike prior studies that observed stability in microstate topographies [68], meditation induced notable deviations from the premeditation and placebo conditions, including the absence of microstate C (postulated in "observation model" in Figure 2) dominance after meditation. These findings align with meditation-induced changes in consciousness, such as enhanced self-observation activity, which may increase during meditation-primed self-hypnosis [22]. The study by Katayama et al [69] explored EEG microstates during different stages of hypnosis, ranging from resting, light hypnosis, deep hypnosis, and recovery, to understand changes in brain activity associated with altered states of consciousness. The "classic" 4 classes (A, B, C, and D) were identified, with microstates A and C increasing in duration, occurrence, and time coverage during deep hypnosis, while microstates B and D decreased. Resting and recovery conditions exhibited intermediate microstate characteristics between light and deep hypnosis, indicating distinct trajectories in the transition to hypnotic states. The findings suggest that deep hypnosis prioritizes specific cognitive processes related to the postulated "brain as observer," enhancing insight [22] while reducing executive processes related to the postulated "brain as controller." Comparisons with other states revealed similarities between deep hypnosis and schizophrenia (eg, reduced executive control) and between light hypnosis and meditation (eg, relaxation and heightened awareness). Overall, the study by Katayama et al [69] demonstrates that EEG microstates systematically evolve with hypnotic depth, reflecting shifts in the brain's cognitive and functional dynamics. In this context, the postulated "brain as observer" approach [22] highlights the functional contributions of the anterior and posterior subsystems of the default mode network (DMN) and their connectivity during future-oriented thought; for example, combining insight meditation (with self-hypnotic induction) to support "brain as observer" and enactment imagination (with suggestions) to enhance "brain as controller" may help modulate FMD symptoms. In the related study by Xu et al [70], participants reported higher levels of vividness and self-projection when reflecting on their future self, highlighting the dominant cognitive function of future-self imagery. A functional dissociation was observed within the DMN: the anterior DMN was more active during present-self reflection, associated with self-referential processing ("brain as observer"), while the posterior DMN was preferentially activated during future-self reflection, linked to mental scene construction ("brain as controller"). These findings highlight the distinct roles of DMN subsystems in future-self oriented thinking to escape the present brain-body FND state, offering insight into the neural basis of the "brain as observer" versus the "brain as controller" functions [22].

Goal of This Study

"Suggestion" and "imagery" are key tools in psychotherapy. For operant conditioning in XR [35], mental imagery can help patients reimagine movement scenarios with positive outcomes. Suggestions (with or without hypnotic induction [71]) can be used to challenge distorted beliefs about limb weakness with evidence [72] and promote adaptive perspectives. Priming new perspectives [73] can be strengthened with positive sensory feedback using an adaptive XR-based HMI to simulate "normal" movement state transitions [74]. This study introduces an innovative HMI approach by combining top-down and bottom-up attention facilitation to develop a sense of agency in an engaging XR gaming environment; for example, participants may lack task-error perception in the lagging network [58], showing low medial frontal cortex activity. In this context, portable brain imaging of medial frontal cortex activity can guide participant-specific motor control interventions to improve action-perception coupling via intentional binding using a haptic robotic device (HRX-1; a modular haptic robotic device developed by HumanRobotiX Ltd, used in this study for force feedback and biofeedback-based motor training; Figure 3). Our approach also aims to uncover—using brain-behavior monitoring—how the sense of agency develops through action-effect contingencies using tunable haptic feedback and XR force-matching tasks [3,11] under the action-effect binding paradigm [75].

In this study, we examine perception-action binding in FMD within the predictive coding framework [3], focusing on dFC across key brain regions, including the sensorimotor cortex, the pre-SMA and SMA regions (SMA complex [24]), and the rTPJ, all of which are essential for motor preparation, control, and the sense of agency [43,76]. In stimulus-cued movement, postmovement beta synchronization both predicts behavioral stimulus–response binding and is significantly elevated in patients with FMD compared to healthy controls [37]. Midcentral beta rebound reflects the electrophysiological "resetting" of overlapping networks in the motor area and SMA [24], also linked to visual cued motor imagery [77]. Persistent beta synchronization during motor preparation, not just after movement, may reflect abnormal explicit control of movement in FMD [44]. This likely results from excessive attentional focus on the act of moving itself, with attention misdirected away from the movement's goal and instead fixated on the mechanics of movement. This suggests active monitoring of the state [3] (Figure 1), which is likely driven by the perceived risk and uncertainty within the intermittent control framework [78].

In FMD, the normal intermittency of active feedback control characterized by on-off switching seems to be replaced with active monitoring of the state [3], potentially due to perceived risk and uncertainty reflected in persistent beta synchronization [78]. While directly correlating on-off switching with beta desynchronization-synchronization is complex in real-world settings, this study aims to explore this relationship in a controlled XR environment where stochastic movements may reveal meaningful patterns. In addition, perceived risk and uncertainty can be modulated in an XR environment while probing intermittent control in individuals with FMD versus healthy controls. In this context, we suggest that "action

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simulation" as active observer originating from SCAN nodes within the M1 (Figure 1) operates in parallel with the motor execution loop, which arises from non-SCAN effector-specific regions in the M1 responsible for motor commands (postmovement beta rebound is generated in the motor cortex [79]). During motor imagery, this execution pathway is inhibited, allowing "action simulation" to dominate. Predictions generated by the "action simulation" active observer are integrated with reafference from body sensors via Bayesian fusion that may not always be optimal [3]; for example, in individuals with FMD, impaired beta synchronization may reflect dysfunction in this fusion process, potentially resulting in the disproportionate weighting of internally generated active observer predictions from the action simulation loop over actual sensory evidence from body sensors. We propose to normalize this fusion process through the integration of top-down motor imagery ("action simulation") and bottom-up sensory feedback from body sensors modulated with exafferent inputs in the XR gaming environment. Our co-designed XR-based HMI aims to offer an artificial intelligence (AI)—and machine learning (ML)—enabled personalized platform for delivering a game-based intervention for home rehabilitation [35].

Prior studies on intentional binding [76,80,81] suggest that repeated operant experience can strengthen associations, linking it to lower-level, implicit aspects of the sense of agency through automatic associative learning. Prior studies also highlight a distinction between implicit and explicit aspects of the sense of agency. In this context, the conscious expectancy in conscious, reflective judgment of the sense of agency can be developed by showing patients with functional motor symptoms their physical signs, such as the Hoover sign or tremor entrainment [82]. Automatic link formation with associative learning for a prereflective, automatic experience of the sense of agency can be developed via repeated operant experiences as shown in our learned nonuse cases [31]. While the implicit and explicit aspects of the sense of agency are separable, they interact through the same top-down and bottom-up mechanisms [81] that can be artificially modulated in the XR through exafference (Figure 3). Therefore, XR with exafference holds significant potential for advancing the understanding, diagnosis, and treatment of FMD. The recent review by Brouwer et al [74] highlighted how VR can be used to explore neurocognitive mechanisms, such as the sense of agency, attention, and suggestibility, and proposed VR-based interventions that could offer novel therapeutic avenues. The premise is that VR can manipulate and study predictive coding abnormalities to uncover the mechanisms of FMD where the key concepts include attention, the sense of agency, and suggestibility.

A compelling recent study [83] showed that multidisciplinary treatment comprising physiotherapy and psychotherapy can significantly improve the physical component of quality-of-life outcomes in patients with FMD. However, a lack of specialists means that access to these treatments is sparse. Even when available, the cost for patients to attend regular hospital sessions can be financially prohibitive. Lord Darzi's 2024 report further highlighted the need to bring care closer to home by aligning financial incentives and prioritizing technology [84]. Our proposal is therefore ideally timed [85], aiming to bring cost-effective and accessible VR rehabilitation [74] into the homes of people with FMD. We aim to create a scalable, home-based rehabilitation solution that shifts care from clinic to home with a stepped care model [86,87]. Home care reduces the need for travel; promotes sustainable health care; and offers accessible, personalized rehabilitation. Our approach addresses the growing demand for remote health care and will provide equitable and cost-effective therapies. The proposal also includes a product delivery road map with technoeconomic analyses applied to the stepped care model. This stepped care model proposed for Neurorehabilitation Online [88] can lower health care costs, encourage adoption, and expand the solution's use to other rehabilitation needs.

Methods

Ethical Considerations

The predesign study, part of patient engagement and technology coproduction, was classified as service development and quality improvement, not requiring full National Health Service (NHS) ethics review. All participants gave written informed consent, and the study followed the Declaration of Helsinki principles. For this study, ethics approval will be obtained from the relevant institutional review boards and the health research ethics committee at Lancashire Teaching Hospitals NHS Foundation Trust before commencing each research stage. All participants will provide written informed consent before participation. They will receive accessible materials explaining the project's goals, methods, and potential risks, emphasizing their right to withdraw at any time. All personal and biometric data will be anonymized and encrypted. Data management protocols adhering to ISO (International Organization for Standardization) 27001 standards will be implemented to ensure confidentiality and secure storage, in compliance with the General Data Protection Regulation. Participants involved in narrative interviews will review and approve video content intended for research dissemination. They retain the right to withdraw their consent for the use of their video at any stage.

Participant Population

This study will recruit adults aged ≥18 years with a confirmed diagnosis of functional limb weakness, a well-characterized subtype of FMD. Functional limb weakness is among the most common presentations of FMD and is particularly suited for XR-based motor retraining due to the clarity of its diagnostic criteria (eg, the Hoover sign [72]), the reproducibility of motor tasks in VR environments [35], and alignment with clear rehabilitative goals [89]. This focus aligns with emerging evidence supporting the feasibility, usability, and potential of hypnotherapy in this subgroup [90]. All participants will be assessed by a consultant neurologist using positive diagnostic signs consistent with *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) criteria and established clinical features (eg, the Hoover sign and variability with distraction). This study will emphasize safety, usability, and the personalization of XR-based interventions in the home setting.

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Inclusion and Exclusion Criteria

The inclusion and exclusion criteria are presented in Textbox 1.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Adults (aged ≥18 y)
- Confirmed diagnosis of functional limb weakness by a neurologist using positive clinical signs
- Able to understand and provide informed consent
- Willing and able to participate in home-based extended reality (XR) interventions
- Access to a home environment suitable for safe XR device use

Exclusion criteria

- Presence of co-occurring neurological disorders with structural pathology (eg, stroke and multiple sclerosis)
- Other subtypes of functional movement disorder (eg, tremor and dystonia)
- Severe cognitive impairment or psychiatric comorbidity interfering with participation
- Inability to safely use XR equipment at home

Recruitment Strategy

Participants will be recruited through neurology outpatient clinics and the specialized FND service affiliated with the Royal Preston Hospital in Preston, Lancashire, England. Treating clinicians will identify eligible individuals during routine care, and interested participants will be referred to the study team for consent and screening. Partnerships with FND charities and patient advocacy groups will support broader outreach and ensure inclusive recruitment.

Experience-Based Co-Design

The research domain criteria (RDoC) framework [91], developed by the National Institute of Mental Health, offers a dimensional approach to understanding shared pathways, which can guide the development of targeted neurotechnological innovations. Unlike traditional diagnostic methods that focus on symptom-based categories, the RDoC framework seeks to understand disorders by integrating multiple levels of information, including neuroscience and behavioral science. The adoption of a dimensional, neuroscience-based framework is proposed to facilitate better phenotyping of heterogeneity and the identification of biomarkers, potentially leading to more precise and effective rehabilitation technologies [92].

While the RDoC framework offers a comprehensive approach to explaining the diagnosis and developing more personalized rehabilitation technologies, Spagnolo et al [92] acknowledge practical challenges, particularly the complexity of integrating multiple levels of analysis into the clinical care pathways. To address this, we propose using experience-based co-design (EBCD; a participatory method involving patients, caregivers, and clinicians in designing health care solutions based on lived experience) [93] adapted for technology integration with the proposed optimum clinical pathway for adults with FND [94]. Rehabilitation technologies encompassing HMIs that access, monitor, investigate, assess, manipulate, and emulate neural systems present significant ethical concerns due to their profound impact on human identity, autonomy, privacy, and well-being. In this context, engaging patients and stakeholders is essential for conducting health care economic analyses and addressing ethical issues in implementing rehabilitation technologies for FND.

This study aims to coproduce an at-home rehabilitation solution using XR biofeedback training under operant conditioning for functional limb weakness, integrated into the FND stepped care framework [86] for multidisciplinary treatment and rehabilitation. The goal also ensures that at-home rehabilitation solutions are not only precise and effective but also sustainable, economically viable, and ethically sound. Our predesign study [35], funded by Engineering and Physical Sciences Research Council (EPSRC) Network+ funding, led to the development of this study, beginning with activity 1 (engagement with and preferences of people with lived experience and broader stakeholders). Activity 1 will focus on understanding and innovating at-home rehabilitation XR solutions for integration into the adult clinical pathway, starting with recruitment and consent once ethics approval is obtained. While *invention* refers to the act of creating something entirely original, *innovation* involves enhancing existing technologies in new ways to use them. Our innovation effort will ensure that the co-design is informed by people with lived experience and broader stakeholder engagement and preferences, leading to more effective and meaningful implementation. The EBCD process involves 3 phases (Figure 4): capture the experience, understand the experience, and improve the experience (with the final phase being addressed in activity 2). Activity 2 will translate at-home rehabilitation XR technology requirements from activity 1 into actionable items using the predesign framework [35], considering broader stakeholder input and health care economics. We anticipate diverse views on AI regulations and the cost-effectiveness of XR technologies in FND, with concerns about equity and economic viability, particularly in resource-limited settings [94]. Cost-effectiveness analyses (CEAs) often overlook ethical considerations, potentially perpetuating disparities, especially in conditions such as FND [95]. To address the predisposing, precipitating, and perpetuating

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factors in FND [96], we will integrate rehabilitation technologies into a disease severity–based stepped care framework for FND management [86]. This activity, focused on activity 2 (requirement translation of XR technologies in FMD), will deliver actionable items and prioritized steps to close the loop, incorporating equity weights for CEAs based on patient disease severity [97] within the stepped care framework [86].

Figure 4. Flow diagram representing the experience-based co-design (EBCD) process. XR: extended reality.

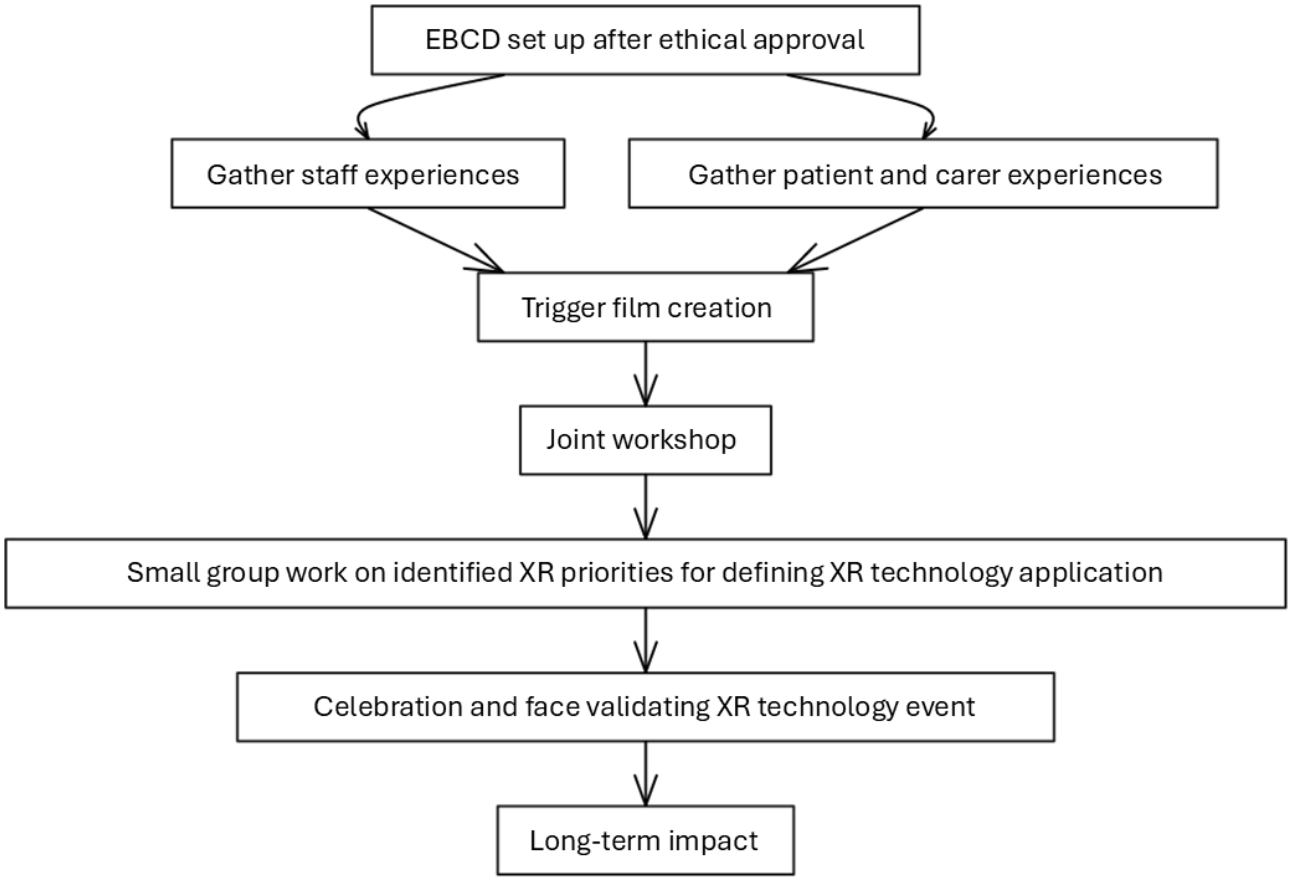

Activity 1, Phase 1 (Mo 1-12): Recruit Stakeholders and Capture the Experience

Overview

Building on the predesign framework from our EPSRC Network+ seed-funded project [35] (Multimedia Appendix 1), we aim to ensure that the XR platform is accessible, impactful, and tailored to patient needs. Figure 4 illustrates the EBCD process, adapted for FMD care with XR technology integration across the clinic-to-home continuum. This multistage approach, partly based on prior research work [98], focuses on improving the transition of FMD rehabilitation from clinic to home through collaboration among staff, patients, and caregivers. Each component of the EBCD process is described in detail in the following subsections.

Components of the EBCD Process

EBCD Set Up After Ethics Approval

In this initial phase, ethics approval is secured, and preparations begin to gather experiences from health care staff and patients with FMD and their carers.

Gather Staff Experiences

This stage involves in-depth interviews and observations with health care staff to identify emotional touchpoints and challenges in the FMD care process after diagnosis.

Gather Patient and Carer Experiences

The focus shifts to patients with FMD and their caregivers, who share their experiences through 12 to 15 filmed narrative interviews. These narratives capture their journey and key emotional moments after the FMD diagnosis.

Trigger Film Creation

A 30-minute “trigger film” is edited from the narrative interviews, allowing staff to connect more deeply with the experience of patients with FMD by seeing and hearing their perspectives directly.

Joint Workshop

This workshop brings together staff, patients with FMD, and carers to review the film and share insights. It is a collaborative session essential for identifying specific constructs for applying XR technology in the FMD care process, spanning from clinic to home.

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Small-Group Work on Identified XR Priorities for Defining XR Technology Application

Small groups are formed to address specific XR constructs, such as a virtual cognitive behavioral therapy coach, XR force feedback games, and XR position feedback games. They operate in 4-week Agile sprints to define and refine XR technology applications that align with the needs identified in the joint workshop.

Celebration and Face-Validating XR Technology Event

After specific prototype developments and design verification, a face-validation and celebration event takes place. This event celebrates progress and fosters a sense of achievement among participants.

Long-Term Impact

While each 4-week sprint provides incremental improvements, the co-design process over a maximum of 3 years, culminating in construct validation, is expected to lead to a patient-centered XR technology platform tailored to enhance FMD care from clinic to home settings for clinical usability and ecological validity testing.

Addressing Accessibility, Inclusivity, and Equity

The XR platform will include personalization and accessibility features, such as adjustable haptic controls, audio guidance, and customizable displays, tailored to patients' needs as identified in the EBCD process. We aim for a diverse participant base, ensuring that the technology is suitable for patients across various ages, cultural backgrounds, and socioeconomic statuses. By actively recruiting underrepresented groups, especially female individuals, in whom FND is more prevalent [99], through patient advocates and charities, we prioritize inclusivity in development. Continuous feedback for prototyping and design verification, with parallel face validation, will allow iterative refinement based on user requirements.

Partnership and Stakeholder Involvement Strategy

Industry partners Nudge Reality Ltd and HumanRobotiX Ltd as well as robotic rehabilitation and haptic technology experts will enhance the platform with design-for-manufacture principles. Collaboration with FND charities and clinical networks will ensure that patient perspectives remain central. Patient advocates Katerina Hatjipanagioti and Matthew Newsham, from the EPSRC Network+ seed-funded project [35], will support outreach and participant recruitment.

Ensuring Responsible Innovation

The EBCD process will ensure transparency, inclusivity, and accountability by documenting development and integrating feedback, resulting in an accessible, ethical XR platform for FMD rehabilitation from clinic to home settings, aimed at enhancing both quality of life and health equity.

Activity 2, Phase 2 (Mo 1-48): Requirement Translation of XR Technologies in FMD

Overview

To develop the XR platform for FMD rehabilitation from technology readiness level (TRL; a scale [ranging from 1 to 9] used to assess the maturity of a technology from concept [TRL 1] to full deployment [TRL 9]) 2.0 [35] to 3.5, we adopt a work cycle approach in work package 1, focusing on meeting user and stakeholder needs for translation and impact. Using coproduction, we ensure patient-centered quality by design (ISO 16355-1:2021) through patient and public involvement and engagement, iterative critical function validation (4-wk sprints), and testing (ISO 9241-220:2019) in an engineering laboratory with healthy participants. NVIDIA provides guardrails for physical AI through its Isaac platform and Jetson hardware, ensuring safe, reliable, and tested deployment of the XR platform. The work packages are illustrated in Figure 5 and are detailed in the Work Packages subsection, showing how quality function deployment (QFD; a structured method for translating user needs into engineering specifications during system development) will be operationalized alongside EBCD and 4-week Agile sprints during XR platform development.

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Figure 5. Overview of the work packages highlighting their structure, interactions, and key objectives within the project. TRL: technology readiness level.

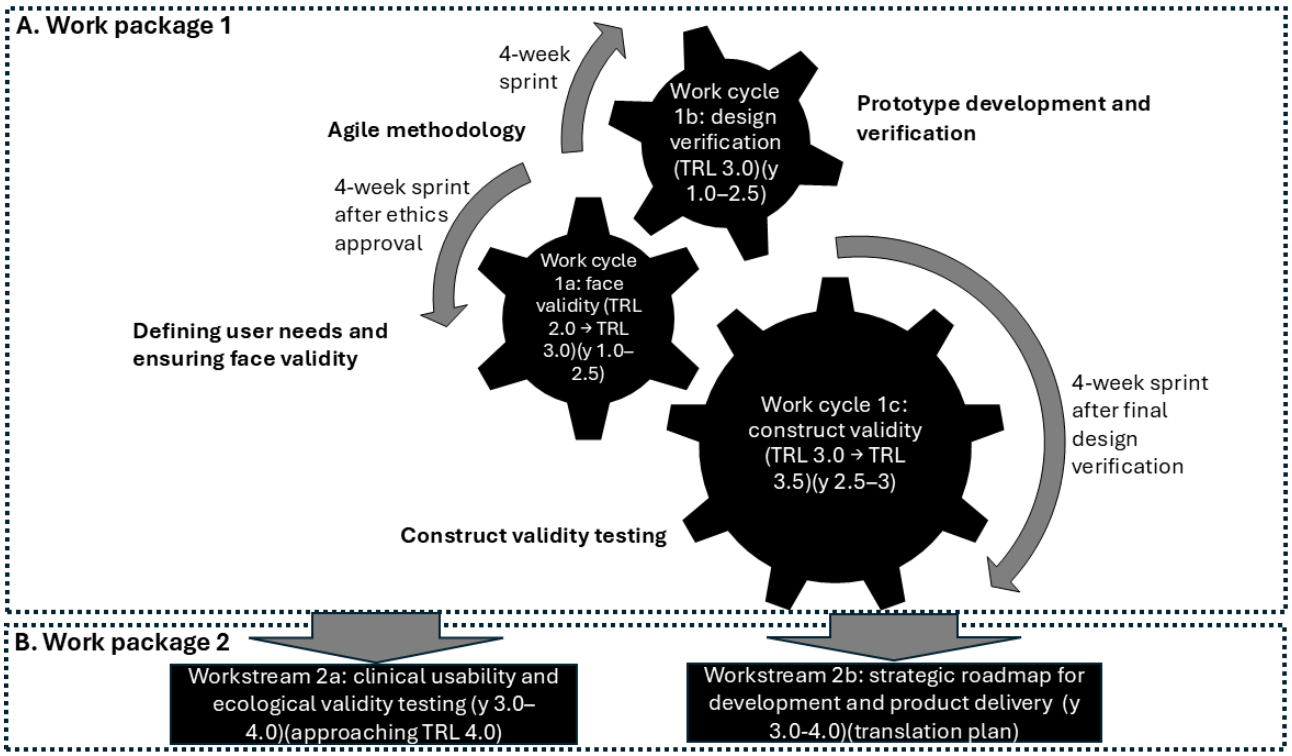

EBCD Workshops: Capture of User Needs

EBCD workshops with patients, caregivers, and clinical staff will generate narrative data and structured feedback identifying key emotional touchpoints and rehabilitation needs. These are synthesized into user stories and functional requirements using thematic analysis in NVivo (Lumivero).

QFD Application: Translation Into Engineering Specifications

These user requirements are then mapped into a QFD matrix (house of quality) to prioritize technical features based on the frequency and criticality of patient and staff feedback. Relationships between user needs (eg, “easy-to-use interface” and “low visual discomfort”) and design components (eg, haptic resistance levels and XR visual rendering) are identified. Qualitative insights into quantifiable system parameters and performance metrics (eg, range of motion thresholds and feedback latency <100 ms) are translated. Each QFD matrix is reviewed by the cross-functional team (engineers, clinicians, and patient advocates) at the start of every sprint cycle, ensuring alignment between stakeholder input and design focus.

Agile Sprints: Implementation and Feedback Loops

Each 4-week Agile sprint consists of the following components:

- Week 1: sprint planning meeting, informed by QFD-derived priorities and usability issues identified in prior sprint testing
- Weeks 2 and 3: iterative prototype refinement, integrating hardware (HRX-1, brain imaging, and neurostimulation if necessary) and software (XR environment)
- Week 4: sprint review and testing session with 3 to 5 participants (patients or controls), using the System Usability Scale (SUS; a standardized 10-item questionnaire used to evaluate the usability of a product or system) and open-ended feedback

Validation and Loop Closure

Usability feedback is again categorized thematically and translated back into the next iteration’s QFD matrix, closing the loop between user experience and technical refinement. This process ensures that the prototype evolves in a traceable, patient-centered, and evidence-driven manner.

Work Packages

Work Package 1: Advancing Prototype and Construct Validity Through TRL 2.0 to 3.5

Work Cycle 1a: Defining User Needs and Ensuring Face Validity

This cycle engages patients with FMD, carers, health care staff, and FND charities through surveys, focus groups, and workshops following the EBCD approach (Figure 4). Insights inform critical function analysis and QFD to align XR technology with stakeholder needs, achieving face validity through iterative 4-week sprints.

Work Cycle 1b: Prototype Development and Verification

The HRX-1 device is reengineered and integrated with the Meta Quest 3 headset and wearable brain imaging capabilities, guided by QFD. A prototype characteristics matrix informs iterative development and verification through 4-week sprints to ensure compliance with design requirements (Figure 6). Expectation maximization (EM) is used in conjunction with the Kalman filter [3] when model parameters (eg, transition probabilities and noise covariances) are unknown and must be estimated from data. While the Kalman filter excels at real-time state

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estimation, assuming fixed parameters, EM is ideal for parameter estimation in probabilistic models, especially when working with incomplete or noisy data, such as neural signals. In brain state transitions (Figure 1), EM is used in switching state-space models to learn hidden brain state dynamics (eg, attention states) from fNIRS and EEG recordings, while the Kalman filter performs the real-time estimation of latent states once the model is trained [3]. These methods will be combined with EM performing offline learning, with the Kalman filter embedded in its expectation step for state inference [3]. This approach is well documented in neuroscience and signal processing literature [100,101].

Figure 6. Verification and validation (V&V) of the artificial intelligence– and machine learning–enabled extended reality platform. System-level verification will be conducted to identify design flaws and resolve requirements. ISO/IEC 5927:2024 provides safety and well-being guidelines for immersive technologies such as virtual reality and augmented reality, covering risks such as motion sickness, eyestrain, and safe setup practices. The ISO 9241 series focus on ergonomics and usability in human-system interaction, with portions such as 9241-920 and 9241-940 specifically addressing the design and evaluation of haptic and tactile feedback. Together, these standards support the development of user-friendly, safe, and effective extended reality (XR) systems. IEC: International Electrotechnical Commission; ISO: International Organization for Standardization.

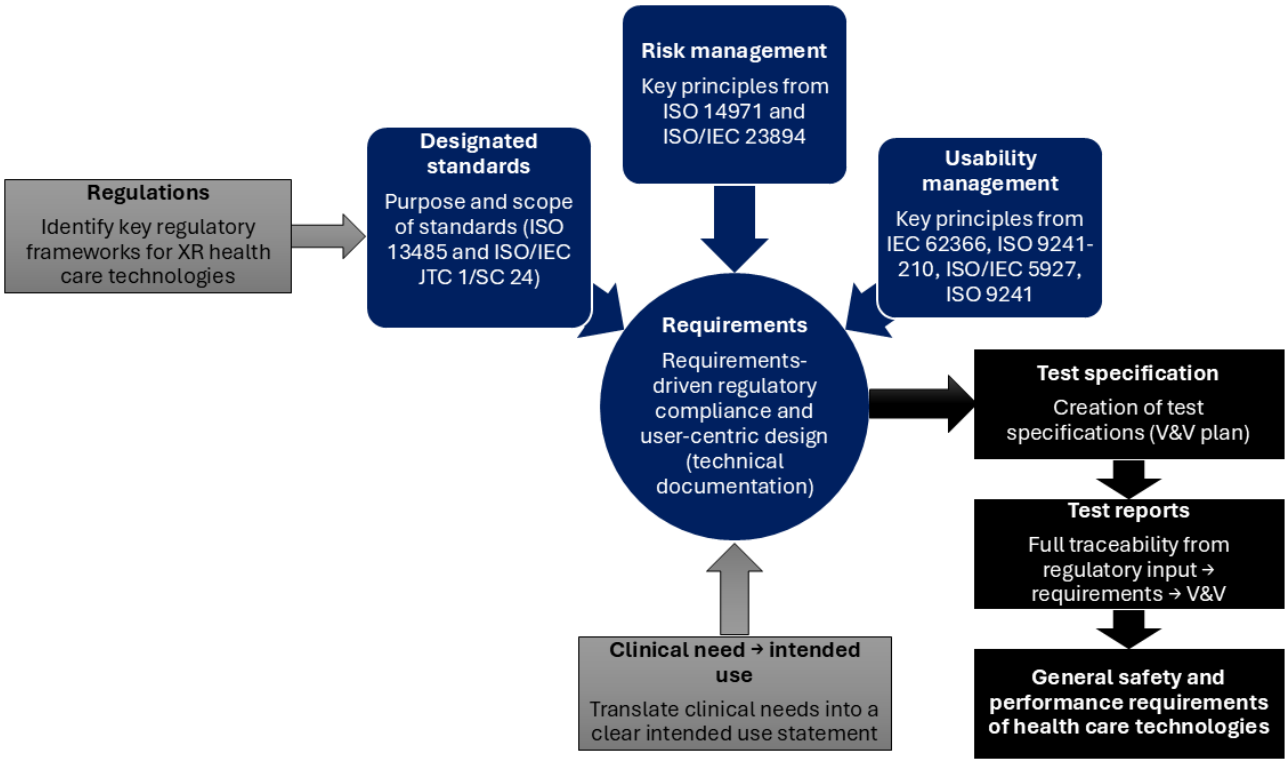

For personalization, the XR platform will incorporate haptic device control algorithms that adapt both the difficulty of training tasks and the parameters of haptic feedback in real time [3]. Specifically, data streams from haptic device sensors (eg, motion and force input) and neuroimaging modalities (eg, fNIRS and EEG) will be used to infer user brain-behavior engagement, motor effort, and cognitive workload. A reinforcement learning framework will then adjust task parameters such as target accuracy thresholds, movement speed, or visual feedback gain based on performance trends and error profiles; for example, if a user demonstrates consistent overshooting or hesitation during reaching tasks, the system will gradually adjust the virtual target zones and reduce haptic resistance to facilitate motor learning while maintaining an appropriate level of challenge. Similarly, attention-aware modeling using switching state-space models will classify brain states associated with fatigue or disengagement, prompting breaks or switching to lower-load tasks. These adaptive control strategies will be trained offline using EM to learn individual response patterns and updated in deployment using embedded Kalman filtering for real-time state estimation [3]. This integration of AI and ML enables dynamic personalization of the rehabilitation experience, ensuring that the XR environment responds to each patient's evolving abilities, optimizing both usability and therapeutic efficacy. At this stage, design-time guardrails must be established through trustworthy development pipelines that integrate third-party safety assessments (eg, MATLAB, Simulink, System Composer, and Requirements Toolbox) and follow robust processes focused on reliability and security in the AI- and ML-enabled model-based systems engineering of the XR platform.

Work Cycle 1c: Construct Validity Testing

SUS assessments and open-ended interviews will be conducted with healthy controls to refine sensor, effector, and AI and ML usability (Figure 6). Validation-time guardrails are enforced through hardware-in-the-loop high-fidelity simulation environments (eg, MATLAB, Simulink, System Composer, and Requirements Toolbox), enabling the testing of the AI- and ML-enabled XR platform across many real-world scenarios (eg, sensor fault [102], security, and authenticity [103]). Pilot studies will then assess convergent and divergent validity of brain responses (eg, beta oscillations and SMA efferent network activity from dFC) using the XR platform in an engineering laboratory environment.

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Work Package 2: Advancing Usability, Validity, and Strategic Delivery

Workstream 2a: Clinical Usability and Ecological Validity Testing

Usability studies will be conducted with 50 patients with FMD for 3 alternate-day clinic visits, evaluating SUS scores and the platform's clinical validity in a safe, controlled setting. Deployment-time guardrails will be responsible for executing real-time performance monitoring and error detection, as well as initiating fallback procedures during the XR platform operation under controlled clinical conditions.

Workstream 2b: Strategic Road Map for Development and Product Delivery

A translation and impact plan using the results from workstream 2a will be developed for future validation in a stepped care clinic-to-home framework (TRL ≥4.0). Guardrails for surveillance will ensure continuous monitoring, issue detection, regulatory compliance, and safe updates to maintain safety and performance. To support the scalability and real-world adoption of XR-based rehabilitation for functional limb weakness in FMD, this study will conduct a rigorous economic evaluation using the generalized risk-adjusted cost-effectiveness (GRACE; a method to adjust willingness-to-pay [WTP] thresholds by considering risk, severity, and outcome distributions) framework [97]. This approach improves upon traditional CEA by integrating patient-level risk preferences and variability in health outcomes, which are especially important in heterogeneous conditions such as FMD. A discrete choice experiment will be conducted with 50 patients diagnosed with functional limb weakness to estimate their WTP thresholds for home-based XR therapy and to quantify the quality-of-life impact of untreated symptoms. We will quantify the perceived impact of untreated FMD symptoms (functional limb weakness) on quality of life; estimate patients' WTP thresholds for home-based XR rehabilitation; and identify trade-offs that patients are willing to make between convenience, effectiveness, risk, and cost. This will allow us to elicit patient-centered utility values and incorporate preference heterogeneity into the economic model. The results will inform a patient-centered utility model that accounts for preference heterogeneity. Unlike traditional CEA that relies on average quality-adjusted life years (QALYs), the GRACE framework computes generalized risk-adjusted QALYs, incorporating outcome variance (uncertainty in outcomes), skewness (asymmetric benefits), and kurtosis (extreme outcome tails) to better reflect patient-specific risk profiles and treatment uncertainty. This allows us to reflect not only the mean effectiveness of the XR intervention but also its distributional effects, including benefits for those at higher risk or with more severe impairment. This enables the calculation of a risk-adjusted WTP threshold (K_{GRACE}) using the following formula:

$$K_{GRACE} \geq \Delta Cost \,/\, \Delta(GRAQALYs)$$

where $\Delta Cost$ is the incremental cost of the XR intervention compared to standard care, *GRAQALYs* stands for generalized risk-adjusted (for baseline severity, disability, and risk preferences) QALYs, and $\Delta(GRAQALYs)$ is the gain in risk-adjusted health benefits (QALYs). By integrating clinical outcomes, cost, and patient risk tolerance, this approach provides a robust basis for determining value for money, guiding pricing, reimbursement, and the equitable implementation of XR rehabilitation in FND care pathways. Ultimately, this integrated approach ensures that home-based XR rehabilitation is not only clinically promising but also economically justifiable and aligned with real-world patient values.

Work Package 3: Team Management - Workstream 3: Maintain Strong Team Coordination

We will use weekly meetings, 4-week sprints, and cross-team synchronization meetings held every 2 weeks to align development and clinical goals. Centralized tools, shared repositories, and cross-team workshops will enable transparent communication and knowledge sharing for risk management. Progress tracking through key performance indicators and Agile feedback loops will ensure seamless integration, address stakeholder feedback, and align priorities for timely XR platform delivery.

Participants: Number and Diversity

Patients With FMD

We plan to recruit up to 50 patients with FMD to account for variability in symptoms such as functional weakness and dystonia, enabling subgroup analyses. This sample size is based on statistical power analysis using SUS scores from pilot testing across 3 XR tasks (hypnotic relaxation, position feedback, and force feedback) [35]. An effect size (Cohen *d*) of 0.81 was calculated, indicating a large difference between usability scores for position feedback and force feedback tasks. With a significance level of .05 and 80% power, approximately 15 participants per group are needed for usability testing. Recruiting 50 patients ensures that the study is adequately powered to detect meaningful differences and supports robust platform refinement and clinical translation.

Healthy Participants

Approximately 15 healthy participants will be included in the pilot studies in work package 1 to validate usability, construct validity, and core platform functions through a test-retest study over 6 repeats. Participants will be drawn from diverse backgrounds, focusing on inclusivity across socioeconomic groups, ages, and underrepresented populations. Given the higher prevalence of FMD in female individuals, recruitment efforts will emphasize female participation.

Recruitment and Engagement

Collaboration with FND charities (eg, FND North and FND Action) and patient advocates will support recruitment, ensuring diverse participation through purposive sampling. EBCD processes will be used to coproduce the XR platform with participants, aligning the development with stakeholder needs.

Procedures

Initial studies will take place in controlled laboratory settings at the Lancashire Clinical Research Facility to prioritize safety. Studies involving patients with FMD will be conducted under clinical supervision.

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Areas of Substantial or Moderate Impact

Minimal physical risks are anticipated with XR use. Co-design efforts will address known discomforts such as eyestrain, and iterative feedback will ensure participant safety and well-being during XR tasks. Recognizing the vulnerability of patients with FMD, therapeutic environments within the XR platform will be carefully co-designed to prevent distress, guided by feedback from the EBCD process. Transparent consent processes, stringent deidentification protocols, and active stakeholder collaboration will mitigate ethical risks associated with the research.

Results

Predesign Study

The predesign study, supported by EPSRC Network+ funding, investigated the usability of an XR neurotechnology platform for FND rehabilitation, focusing on biofeedback training for functional limb weakness [35] (Multimedia Appendix 1). In the first round of a Delphi survey (a structured expert consensus method involving multiple rounds of questionnaires to refine opinions or priorities) involving 20 participants with lived experience of FND, there was strong consensus on the potential of VR with haptics for biofeedback-based motor rehabilitation. Participants highlighted the immersive experience, real-time feedback, and customizable environments as key advantages for improving motor control in functional limb weakness. However, several barriers to adoption were identified including high equipment costs, limited accessibility through public health care systems, concerns around usability (eg, motion sickness, technical learning curve), and sensory overstimulation. These findings informed subsequent predesign study of a home-based rehabilitation system integrating operant conditioning within mixed-reality environments. Limited accessibility through public health care systems prompted the need for the integration of patient-centered cost-effectiveness analysis in coproduction that accounts for disease severity, disability, and individual preferences thereby addressing limitations in traditional QALY models.

The predesign study evaluated an XR-based biofeedback platform for upper limb rehabilitation in individuals with FND, developed through co-design with patients and clinicians. Among the 3 tested XR tasks, high usability scores (>85) were recorded for XR position feedback task, indicating excellent user satisfaction. By contrast, the VR relaxation task produced mixed reactions due to motion discomfort, and the XR force feedback task showed varied results depending on individual motor impairments, such as functional dystonia, emphasizing the need for personalized approaches. Qualitative feedback highlighted the importance of comfort, immersive content, personalization, and accessibility. Therefore, predesign study findings emphasized the potential of XR in FND rehabilitation but highlighted the need for personalized approaches to meet diverse patient needs in FND. The predesign study further demonstrated the promise of XR technology for functional motor disorder rehabilitation by embedding biofeedback training into a patient-centered game design framework. EBCD and QFD emerged as valuable methods for coproduction and to systematically address usability barriers. To deepen personalization, this study will incorporate portable brain imaging to assess dFC in key regions during XR intervention, enabling individually responsive dosing. Moreover, the themes for improvement identified from the predesign study included customization, comfort, accessibility, and technological quality.

This Study

This coproduction study is projected to be completed within 4 years, with results anticipated for publication in 2029.

Discussion

Summary

The REACT2HOME proposal lays the groundwork for a personalized, home-based XR rehabilitation approach tailored to individuals with functional limb weakness [89]. This subtype of FMD has a clearly defined semiology and lends itself well to structured motor retraining in XR. Our approach leverages operant conditioning and dynamic feedback loops to recalibrate predictive motor models, targeting the neural circuits implicated in agency and sensory attenuation. While full-scale clinical efficacy remains to be demonstrated, early indicators from usability testing and prior XR and VR studies suggest that targeted digital biofeedback could serve as a promising adjunct to multidisciplinary FND treatment [35,74,104]. Given the variability in FMD presentation, we expect recovery trajectories to be most significant in patients with functional weakness who retain volitional motor capacity but show impairment in motor planning, agency, or learned nonuse patterns [90].

The predesign study demonstrated the potential of XR technology as a transformative tool for FND rehabilitation [35]. The perception-action cycle, which is central to human adaptation, is disrupted in FND due to maladaptive learning processes that diminish agency and disrupt motor control. By integrating biofeedback training with immersive XR environments, this approach addresses both motor and sensory dysfunctions, presenting a novel therapeutic avenue. The findings align with the results of our Delphi survey (a structured expert consensus method involving multiple rounds of questionnaires to refine opinions or priorities) on VR haptic biofeedback [105], which highlighted the relevance of XR technology in improving motor control for patients with FMD. Participants in both the predesign and Delphi studies emphasized the immersive and customizable nature of XR environments as a critical factor for engagement and recovery. However, barriers such as cost, accessibility, and motion sickness need to be addressed to enable widespread adoption, as reflected in both studies.

The usability testing revealed higher satisfaction with VR relaxation and XR position feedback tasks, aligning with the Delphi findings that underscored the importance of comfort and accessibility [35]. However, the variability in XR force feedback usability, particularly among participants with conditions such as functional dystonia, emphasizes the need for personalized approaches. These results support the Delphi survey recommendation for task-specific customizations and accessibility enhancements to ensure broader usability across

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diverse patient needs. The predesign study also underscored the importance of coproduction in designing rehabilitation technologies, as demonstrated by the mixed methods approach and Delphi framework. Engaging patients with FND and clinicians in the design process ensures that the technology addresses real-world challenges, such as motion sickness and sensory overload, highlighted in both the predesign and Delphi studies.

This study builds on prior predesign work in FND rehabilitation [35] and integrates key pathophysiological insights specific to functional limb weakness, namely deficits in sensory attenuation, motor intention encoding, and agency disruption, to refine the XR platform for this targeted clinical application. By aligning the XR interventions with these mechanistic targets, such as prediction error recalibration and intention-action coupling, the platform aims to deliver therapeutically relevant biofeedback experiences. Patient-specific adjustments, including calibration for individual motor impairments and optimization of sensory inputs, are incorporated to enhance comfort, usability, and therapeutic responsiveness. Using a structured EBCD process, our approach supports meaningful engagement with patients and caregivers, ensuring that the technology remains responsive to their evolving needs. The platform's modular design, guided by insights from both iterative usability testing and Delphi surveys, positions it for broader integration into a stepped care FND model, facilitating sustained improvements in functional outcomes and patient experience from clinic to home.

While several VR interventions have been explored for FND [74], most existing tools are based on cognitive behavioral therapy principles, exposure-based paradigms, or distraction techniques aimed at symptom habituation or anxiety reduction; for example, VR protocols often focus on mirror visual feedback and exposure therapy to reduce symptom expression during tasks [104]. By contrast, our XR platform introduces a mechanistically grounded operant conditioning framework designed to recalibrate sensorimotor prediction errors and restore the sense of agency. This is achieved through the real-time, implicit reinforcement of volitional motor behaviors using personalized visual and haptic feedback. Rather than focusing solely on cognitive reframing, the platform targets disrupted forward models and sensory attenuation mechanisms, engaging dynamic brain-behavior loops through closed-loop feedback for implicit learning [3]. In addition, our use of wearable neuroimaging and dFC analysis to guide task adaptation and monitor agency-related brain networks (eg, SMA-rTPJ connectivity) represents a significant technical and conceptual advancement over prior VR applications in FND rehabilitation. This biologically informed, adaptive XR approach fills a critical gap between top-down cognitive interventions and bottom-up motor retraining strategies. However, we recognize that FMD encompasses a broad spectrum of presentations, including functional tremors and dystonia, which may respond differently to XR-based interventions. Therefore, while the current design is optimized for patients with functional limb weakness, future iterations of the platform could include additional modules tailored to other FMD subtypes; for example, tremor-specific VR scenarios could be introduced using wearable sensors and visual feedback techniques.

As AI- and ML-enabled XR technologies continue to evolve, their adaptability offers significant promise for addressing the heterogeneity of FMD, for example, by using physical AI to address real-time force feedback in functional dystonia [35]. Advances in wearable brain imaging, AI- and ML-enabled personalization, and modular haptic feedback design will facilitate expansion beyond single subtypes. By grounding these tools in robust clinical frameworks and coproduction with patients, AI- and ML-enabled XR platforms can support both therapeutic engagement and mechanistic understanding of symptom recovery in FND. In this context, our long-term vision is to incorporate this technology within a stepped care model [86], enabling equitable, scalable, and home-based rehabilitation for a broader population with FMD. Ongoing stakeholder engagement and iterative validation will be key to achieving this translational pathway. To ensure long-term sustainability beyond the 4-year study timeline, we are developing an implementation road map that aligns with the priorities of the NHS long-term plan for digital health and community-based care. Upon the successful demonstration of clinical efficacy and usability, we aim to transition the XR platform into validated digital therapeutics that can be adopted within existing care pathways for FND. We plan to partner with integrated care systems, NHS Trusts, and neurorehabilitation clinics to pilot deployment within stepped care service models. In parallel, we will engage early with commissioners, health economists, and digital health assessment frameworks (eg, the National Institute for Health and Care Excellence evidence standards framework for digital health technologies [106]) to ensure readiness for regulatory approval and health technology assessment. Reimbursement strategies will include positioning the platform under NHS tariff codes for remote rehabilitation and pursuing designation as an "innovation technology payment" candidate [107]. In addition, we will explore partnerships with insurers and digital health platforms to extend reach into community and private care settings. Open-source models for modular hardware components and software algorithms will also be evaluated to support broader dissemination and integration. These combined strategies will help embed this XR platform into routine FND care, making it a scalable and sustainable solution beyond the initial funding period.

Conclusions

The REACT2HOME study presents a novel, interdisciplinary approach to at-home neurorehabilitation for functional limb weakness. Grounded in predictive coding and agency-related neuroscience, the XR platform combines operant conditioning with adaptive feedback to restore volitional motor control and recalibrate disrupted sensorimotor processes. The methodology integrates EBCD, QFD, and Agile engineering sprints to ensure that the technology is user centered, technically robust, and clinically meaningful. Personalization is achieved through ML algorithms that dynamically adjust task difficulty and haptic feedback based on individual behavioral and neurophysiological responses. A rigorous risk management strategy aligned with ISO 14971 and ISO/IEC (International Electrotechnical Commission) 5927:2024 ensures safety and usability, while economic evaluation under the GRACE framework addresses long-term value, equity, and risk-adjusted cost-effectiveness.

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Importantly, the study establishes a road map for sustainable adoption through partnerships with health care providers, regulators, and payers, positioning XR-based rehabilitation as a scalable solution within stepped care models for FND. Through this protocol, we aim to transform how functional motor symptoms are managed, delivering evidence-based, accessible, and adaptive therapy directly into patients' homes.

Acknowledgments

The authors thank all research participants for their time and valuable feedback to develop this study protocol. This study protocol development was supported by the N-CODE Engineering and Physical Sciences Research Council Network+ (hot-topic workshop held in October 2023 at the University of Central Lancashire) and the Engineering and Physical Sciences Research Council Rehabilitation Technologies Network+. Preliminary findings were presented at the National Rehabilitation Technologies Conference 2024 and the Royal Society's discussion meeting on digital health care for the management of functional neurological disorders, with feedback informing this study. The authors also thank Nudge Reality Ltd and HumanRobotiX Ltd for technical input and Jacqueline Twamley for coordinating patient engagement. Special thanks to patient advocates Katerina Hatjipanagioti and Matthew Newsham for their key contributions to outreach and study design. Portions of this article were prepared with the assistance of Microsoft 365 Copilot [108], an artificial intelligence tool provided by the University of Birmingham. The authors have reviewed the content and take full responsibility for it.

Data Availability

The datasets generated or analyzed during this study are available in the GitHub repository [109].

Authors' Contributions

A Dutta was responsible for conceptualization, methodology, formal analysis, investigation, data curation, writing the original draft, reviewing and editing the manuscript, visualization, project administration, and funding acquisition. A Das was responsible for validation and reviewing and editing the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
National Rehabilitation Centre Rehabilitation Technologies Conference 2024 presentation.
[MP4 File (MP4 Video), 27955 KB - resprot_v14i1e70620_app1.mp4]

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Abbreviations

AI: artificial intelligence
CEA: cost-effectiveness analysis
dFC: dynamic functional connectivity
DMN: default mode network
DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)
EBCD: experience-based co-design
EEG: electroencephalography
EM: expectation maximization
EPSRC: Engineering and Physical Sciences Research Council
FLS: fundamentals of laparoscopic surgery
FMD: functional movement disorder
FND: functional neurological disorder
fNIRS: functional near-infrared spectroscopy
GRACE: generalized risk-adjusted cost-effectiveness
HMI: human-machine interface
ISO: International Organization for Standardization
M1: primary motor cortex
ML: machine learning
MRCP: movement-related cortical potential
NHS: National Health Service
PFC: prefrontal cortex
QALY: quality-adjusted life year
QFD: quality function deployment
RDoC: research domain criteria
rTPJ: right temporoparietal junction
SCAN: somato-cognitive action network
SMA: supplementary motor area
SUS: System Usability Scale
TBS: theta burst stimulation
TPJ: temporoparietal junction
TRL: technology readiness level
VR: virtual reality
WTP: willingness-to-pay
XR: extended reality

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Protocol

Introducing Public Health Vending Machines in Rural Communities: Protocol for a Study Using a Community-Based Participatory Approach

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Abstract

Background: Drug-related overdoses impact communities all over the United States. In the past 2 decades, over 28,000 people have died of a drug overdose in North Carolina (NC). Research has shown that there has been an increase in overdose deaths throughout NC, particularly in rural areas. To reduce overdose rates, health care interventions should be expanded. Naloxone distribution is one intervention to combat overdose rates. Naloxone is a medication designed to reverse an opioid overdose rapidly. Public health vending machines (PHVMs) are a strategy recently implemented in some US communities to expand access to harm reduction supplies. Examples of locations where PHVMs have been installed include public health departments, libraries, county detention centers, and law enforcement offices.

Objective: This protocol aims to develop a community-engaged approach to implementing PHVMs as a health care delivery option for harm reduction supplies in 5 rural counties in NC.

Methods: This study will use a community-based participatory approach in which we partnered with the NC Harm Reduction Coalition and Community Impact NC to engage with substance use prevention providers and community members in 5 rural counties in NC to improve naloxone access. We will collect qualitative interview data from people with lived experience of substance use to identify the optimal placement of PHVMs and items to be stocked in PHVMs. To do this, we will hire 1 local community member with lived experience of substance use from each county to be an interviewer who will recruit, conduct interviews, and collect data from other community members with lived experience of substance use. Interviewers will be trained to recruit participants, conduct interviews, and collect and analyze data. Developing a protocol for training interviewers includes an interview training presentation with an adapted collaborative institutional training initiative portion.

Results: Data will be collected from 2024 to 2025. The findings will inform the implementation of PHVMs to improve harm reduction access and assist in decreasing overdose deaths.

Conclusions: This study will use in a community-based participatory approach to improve naloxone access in rural communities. Community partners will assist the academic team in developing a sustainability plan for each county and an implementation toolkit for other communities to use.

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KEYWORDS

public health vending machine; naloxone; community-based participatory approach; rural; protocol; North Carolina; community-based participatory research; CBPR

Introduction

Overdose Epidemic in the United States

In the United States, there is a growing epidemic of drug-related overdoses. Since 1999, there has been a continuous increase in the number of drug-involved overdose deaths in the country [1]. In 2022, there were 105,452 drug overdose deaths [2]. This epidemic affects all genders, ages, and racial and ethnic groups. The number of deaths from drug overdoses has increased drastically, particularly among individuals living in rural areas throughout the country [3]. In studies examining where overdose deaths occurred, it was found that rural areas had the highest rates of drug overdose deaths [1].

Recently, the United States has experienced a notable decline in drug overdose deaths, marking a significant shift in the trajectory of the overdose crisis. Provisional data from the Centers for Disease Control and Prevention indicate a 3% decrease in deaths in 2023, which was the first annual decline since 2018 [4]. This downward trend has continued into 2024, with preliminary figures showing nearly a 24% decline from the previous year and the lowest total since June 2020 [5]. Despite these encouraging developments, the overdose crisis remains complex. While deaths involving opioids, particularly synthetic opioids such as fentanyl, have decreased, fatalities associated with stimulants such as cocaine and methamphetamine have risen [6]. In 2023, overdose deaths involving cocaine increased by 4.9%, and those involving psychostimulants rose by 1.9% [7]. Moreover, polysubstance use—especially combinations of opioids with stimulants—continues to drive a significant portion of overdose deaths (nearly 50% in 2021), underscoring the evolving nature of the epidemic [8].

The North Carolina (NC) age-adjusted drug overdose mortality rate almost doubles the national average according to the most recent data published by the Centers for Disease Control and Prevention [9]. The combined cost of opioid use disorder and fatal opioid overdose in NC was US $39.37 million; NC ranked eighth in the United States based on the high economic toll of the opioid crisis [9]. In total, 40% of NC residents live in a rural county according to the NC Department of Commerce [10]. The NC Department of Commerce identifies that 80 out of the 100 counties that make up NC are rural based on a population density of 250 people per square mile or less [10].

Over the past decade, in NC, rural populations have experienced higher overdose mortality rates than residents of metropolitan areas [11]. Rural areas comprise open country and settlements with under 5000 residents and under 2000 housing units [12]. Rural communities in NC have higher rates of drug and alcohol use, suicide, years of productive life lost, injury, uninsured patients, and preventable hospitalizations. Residents of rural areas in NC face a shortage of all types of medical providers [13]. The higher rates and shortages associated with rural areas affect the communities' overall health outcomes. These disparities are shaped by longstanding social and structural factors that limit access to health care and infrastructure development and foster economic disinvestment and historical marginalization [14].

The expansion of naloxone access has been a priority intervention to combat the overdose epidemic. Naloxone is a fast-acting opioid antagonist medication that, when administered promptly, can reverse an overdose from opioids—including heroin, fentanyl, and prescription opioid medications [15]. Naloxone is easy to use, and there are 2 forms that anyone can use without medical training: prefilled nasal spray and injectable [15]. For naloxone to be effective, it must be made available and used within the correct time frame.

Increasing Availability of Naloxone

To reduce opioid overdose deaths, organizations have worked to make naloxone more readily available and easily accessible to lay individuals to assist with combating the rising rates of overdoses; as of 2023, naloxone has become available to the public in all 50 states as an over-the-counter medication [16]. Lay individuals can access naloxone through their local pharmacy, community-based naloxone programs, most syringe services programs (SSPs), and local health departments [17]. The availability of naloxone has been shown to have an impact on decreasing rates of drug overdose deaths [17]. Studies have shown that, in locations where there was more accessible naloxone, the rates of drug overdose were lower than in locations with less availability [18].

In recent years, public health vending machines (PHVMs) have been installed in various locations to help increase access to naloxone and other wellness supplies. Supplies offered in machines can change over time and include various items such as over-the-counter medications (paracetamol, antihistamines, and antacids), sunscreen, insect repellent, socks, water, syringes, clean smoking supplies, testing strips, hand warmers, dental kits, hygiene items, and diapers. PHVMs allow access to life-saving supplies that might otherwise have been difficult for one to access [19]. The Trac-B Exchange program in Nevada installed PHVMs in a family medical clinic, behavior health offices, gay and lesbian community centers, substance use treatment centers, a health district office, and a detention center to examine the extent to which naloxone dispensation in PHVMs was associated with changes in overdose fatalities [20]. They found that, within a year following the installation of the PHVMs, naloxone dispensation in PHVMs was associated with immediate reductions in overdose fatalities [20]. In New York, the Medication for Addiction Treatment and Electronic Referrals network deployed 15 harm reduction vending machines stocked with Narcan and fentanyl and xylazine test strips across the state [21]. All supplies from the vending machines are accessible at no cost [22]. The new service was implemented to allow individuals and organizations across the state to request harm reduction supplies free of charge [22]. In Cincinnati, Ohio, the implementation of an automated harm reduction dispensing

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machine led to increased accessibility of harm reduction products and services [23]. It was associated with a lower countywide incidence of unintentional overdose death and HIV [3]. In Los Angeles County, California, naloxone vending machines were introduced in public spaces at detention centers [8]. After the first 9 months, the machines reported distributing >20,000 doses of naloxone. Several other jurisdictions nationwide have followed this example and expanded naloxone access in detention centers [24]. In NC, naloxone vending machines have been implemented in detention centers in the Buncombe, Cumberland, Forsyth, Guilford, Orange, Pitt, and Wilkes counties at no cost through a program sponsored by the National Center for State Courts [25]. The NC Harm Reduction Coalition (NCHRC) assisted in identifying sheriffs and officials to help distribute naloxone, find optimal placement for the machines in facilities, and assign responsibility for filling the machines [26]. Some research suggests that younger people and female individuals tend to use PHVMs more frequently to avoid stigma from other facilities where one could obtain harm reduction supplies, such as an SSP [27]. There are barriers to PHVM implementation, for example, some communities' attitudes (stigma) and fear of vandalism or the fact that all the supplies will be depleted by 1 person [28,29]. Other factors that contribute to barriers are that people who use drugs choose not to use PHVMs due to police intervention located near them [26]. Additional barriers are related to the lack of planning for the placement of the machines or the need to register for the machine to use it [30].

Lack of PHVMs in Rural Areas

PHVMs have been associated with decreasing rates of drug overdoses [31]. Most PHVMs have been implemented in urban or suburban areas, and there has been very little evidence of implementation in rural areas [32]. Participants in these studies have demonstrated a desire to have naloxone PHVMs available in rural areas to reach underserved communities [33]. There is a clear gap in current research concerning expanding PHVMs to hard-to-reach locations with limited substance use resources. Future work should be conducted to better understand how to scale up overdose prevention interventions, including PHVMs, in rural areas. Each community has unique needs and cultures, which would benefit from a tailored approach to implementing PHVMs. Thus, there is a need for a protocol to help communities identify their unique needs for overdose prevention to establish PHVMs in those locations. Furthermore, studies on the sustainability of PHVMs have been limited. Due to the novelty of PHVMs, there are limited data on their long-term impact and sustainability.

Objectives

This study's purpose is to use a community-based participatory approach to improve naloxone access in rural communities in NC. The results will be used to improve operational procedures for PHVMs.

Methods

Community-Based Participatory Approach

This study uses a community-based participatory research (CBPR) approach. A CBPR approach is a collaborative research approach that will involve community members, researchers, and other stakeholders in the research process, combining knowledge and recognizing the strengths that each entity can bring [34]. CBPR will provide a framework to equitably involve all stakeholders of the research, identifying and maximizing the importance of their diverse contributions [35]. CBPR has been used to help understand health disparities and promote health equity across diverse populations and issues that matter to communities of concern [36]. CBPR will be a vital strategy for engaging communities in research directly affecting their lives. Our study team will use the Structural Indicators for Community-Based Participatory Action Research to guide their work [37]. It is essential to our study team to establish meaningful engagement and partnerships with people who use drugs in our selected communities. These relationships will be essential to conducting research that will be impactful in supporting the desired implementation outcomes and reducing drug-related harms [38].

Our partnership consists of academic partners (East Carolina University and Wake Forest University School of Medicine), the NCHRC, Community Impact NC (CINC), and community members and community organizations (Figures 1 and 2) located in 5 rural counties in NC. The academic partners have an established working relationship and a shared history of engaging in community outreach and research focused on substance use. Their collaboration is strengthened by mutual experience and a commitment to addressing substance use challenges in meaningful, community-driven ways. The community partners, the NCHRC and CINC, are key collaborators in this work and currently oversee an overdose prevention grant. As part of this grant, they provide support and oversight to awardees across the state. Notably, the 5 counties where we propose to implement the PHVM initiative are all recipients of this grant funding, positioning them well for successful implementation and ongoing partnership.

Through collaborative efforts with our community partners (CINC and the NCHRC) and individuals with lived experience with substance use from the NCHRC, the team cocreated all training and study materials. This will involve an iterative process in which materials will be reviewed, feedback will be given, and revisions will be made. This process will be repeated until the partnership agrees that the materials meet the standards of all members. By applying insights and expertise from our partners, we will tailor the materials to resonate most effectively with our target communities and participants.

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Figure 1. Community partnership consisting of North Carolina Harm Reduction Coalition, Community Impact North Carolina, community members, and community organizations.

Figure 2. Academic partners: East Carolina University and Wake Forest University.

Ethical Considerations

The expedited application for this study (University and Medical Center Institutional Review Board 23-001800) was approved on September 11, 2023, by the corresponding authors' institution.

Setting

Five counties in NC (Figure 3; Carteret, Jackson, Surry, Stanly, and Swain) were selected based on the following criteria: (1) being a Health Resources and Services Administration–designated rural county, (2) high rates of drug overdose deaths, (3) high rates of illicit opioid–involved overdose deaths, (4) high rates of drug overdose emergency department visits, (5) high rates of residents receiving an opioid prescription, and (6) having an established relationship with CINC. The 5 counties are modest in size, represent different regions of NC, and have structural inequities. Furthermore, all 5 counties have documented drug overdose disparities based on the race and ethnicity of the residents, with higher rates than the state of overdoses among American Indian, Alaska Native, or Black non-Hispanic residents [13]. In NC, naloxone is primarily distributed to laypersons by SSPs and medical providers such as pharmacies. There are currently 71 registered SSPs that serve residents of NC [26]. However, only 2 of the 5 participating counties are currently served by an SSP, and the SSPs that serve the 2 counties are not physically located in the counties. There is a demonstrated need to expand naloxone distribution within these 5 counties by establishing a fixed-care delivery site.

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Figure 3. Map of partner counties and research hubs.

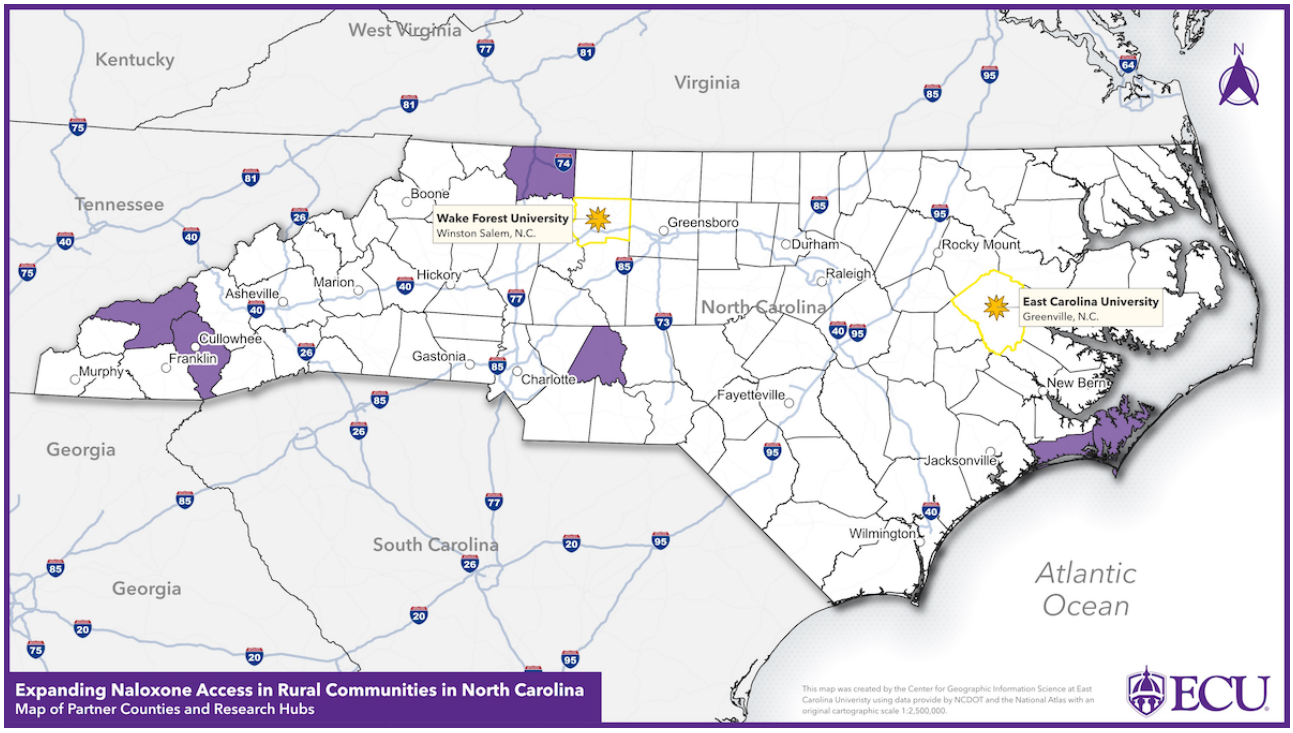

Interview Guide

The interview guide (Multimedia Appendices 1-3) was developed in direct collaboration with our community partner, who brings valuable lived experience with substance use. The questions in the guide were shaped by the stakeholders' priorities and insights, the literature, and grant deliverables (establishing a care delivery site [PHVM or other mechanism], improving access to naloxone, determining the preferred placement of PHVMs, publicizing the PHVMs, and assisting with developing a county-specific sustainability plan).

Identifying and Hiring Community Members to Serve as Interviewers

Interviews with local community members (n=10 per county) will be conducted to identify optimal placement for implementing a PHVM stocked with naloxone. The academic team, in collaboration with local community partner organizations, the NCHRC and CINC, will take the lead in identifying and recruiting community members to serve as interviewers. As a first step, the academic team will participate in video conference town hall meetings that will be hosted by CINC and the NCHRC where they will engage with substance use prevention providers from each community. Following these town hall meetings, the academic team will meet individually with each prevention provider or their designated community representative to further discuss and recruit potential interviewers. CINC and the NCHRC will coordinate these meetings and be present to support the process.

To facilitate outreach, the academic team will request names and contact information for local organizations that work with individuals with lived experience. These organizations may include peer recovery groups, faith-based health initiatives, local health departments, re-entry programs, and postoverdose response teams. To support this effort, academic partners will ask local community partners to provide a "warm handoff" by introducing them to these organizations through email. This personal introduction will help establish trust and assist with effective interviewer recruitment.

Individuals eligible to participate as interviewers must be aged ≥18 years and live in 1 of the 5 selected counties: Carteret, Jackson, Surry, Swain, and Stanly. They will have lived experience of using substances such as opioids, fentanyl, cocaine, or psychostimulants; work within the harm reduction agency (paid or volunteer); and be able to provide references of their experience and qualifications.

After the meeting, the academic team will connect with community partners to discuss potential candidates for interviewer roles. To ensure that selected individuals meet the necessary criteria, the academic team will ask those recommended to complete an application. This application will provide details about their experience conducting interviews; any involvement in research, whether as a participant, a researcher, or both; the recency of their lived experience; their level of community involvement; their current work with harm reduction agencies; and any other relevant experience. Before making final hiring decisions, the academic team will meet individually with each candidate. Throughout this process, the partnership will collaborate closely with local community partners to identify and select individuals best suited for the interviewer positions.

Once interviewers are recruited and hired, they will be trained through a video conference presentation conducted by the academic team. The interviewers will be classified as consultants and paid US $1000 for their work. The payment will occur upon completion of the 10 interviews.

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Training Community Members to Serve as Interviewers

The training protocol for interviewers will include a virtual interview training presentation (Table 1) with an adapted collaborative institutional training initiative portion. The training presentation includes how to conduct interviews, analyze the data, and share the findings from the interviews. Interviewers will be encouraged to recruit participants through personal contacts and given tools to help recruit. These tools include a recruitment script (Multimedia Appendix 4), flyers (Figure 4), and pass-along cards (Figures 5 and 6). The tools will be mailed to interviewers before the training so they can be reviewed during the training.

Table 1. Interview training presentation outline.

Section	Description of section
Introduction to the study and purpose of training	Introduction to the study team, objectives of the study, overview of agenda, and review of materials
CITI[a] training	Introduction to the key principles and ethical considerations involved in human subject research as covered by the CITI program; a simplified—user-friendly—CITI training was developed by the partnership and approved by the IRB[b]
Conducting interviews	Steps to conduct the interview, how to schedule and recruit people to interview, how to obtain participant consent, learning how to probe and use an interview script, note taking and documenting the interview, and distribution of reimbursement to participants
Safety	How to end an interview if they are feeling unsafe and determining a safe location for the interview to take place
After the interview	How to contact and follow up with the study team
Team data analysis	Data collection and how to analyze qualitative data
Share findings	Data reporting and poststudy involvement

[a]CITI: Collaborative Institutional Training Initiative.

[b]IRB: institutional review board.

Figure 4. Recruitment flyer seeking volunteers to participate in the interviews.

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Figure 5. Recruitment pass-along card surveyors share to recruit individuals to participate in the interviews (front).

Figure 6. Recruitment pass-along card surveyors share to recruit individuals to participate in the interviews (back).

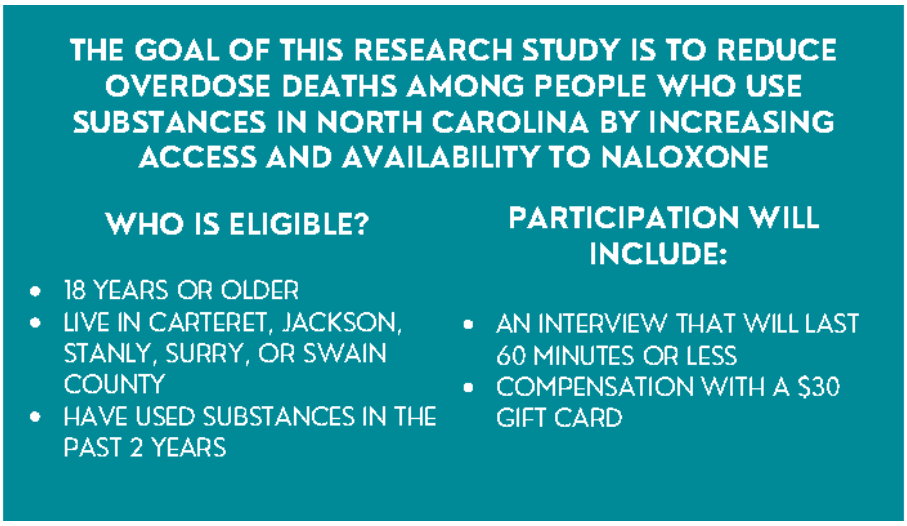

Interview Participants

To be interviewed for this project, participants must reside in 1 of the 5 preidentified high-need rural counties in NC. Participants must be aged >18 years and have lived experience of using substances such as opioids, fentanyl, cocaine, or psychostimulants in the past 2 years. No one is excluded from this study based on race, ethnicity, or biological sex. A total of 10 interviews will be conducted in each county, totaling 50 interviews, which aligns with commonly accepted thresholds for achieving data saturation in qualitative research [39]. This sample size is sufficient to capture a range of perspectives and identify recurring themes without the emergence of substantially new information in later interviews.

Interview Recruitment

Interviewers will be provided with a list of names of interested community members by the study team. Interviewers will recruit participants using word of mouth, a recruitment script, recruitment flyers, and pass-along cards provided by the academic team. Interviewers will be encouraged to share information with personal contacts to help recruit participants. Interviewers will notify the academic team of participants before conducting the interviews. Interviewers will schedule the interviews by contacting the participants based on the information given by the study team. Each interviewer will conduct 10 interviews per county. Interviewers will be encouraged to engage a diverse range of participants, including individuals of different sexes, races, and ethnicities. They will also be guided to conduct interviews across various areas of their county rather than focusing solely on 1 neighborhood or the county seat to ensure broader geographic representation.

Interview Data Collection

The location of the interview will be determined through a reference interview location list that will be established with the assistance of the partnership. The location will be comfortable and safe for both the participant and the interviewer. The principal investigator or coinvestigator of the study team will conduct a follow-up meeting with the interviewer 72 hours following the completion of an interview. During this follow-up, the interviewer can ask questions, seek clarification, and receive additional training as needed. In addition, this time will be used to discuss the thoughts or notes taken during the interview. This step is very important in case the interview questions or procedure need to be adjusted.

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All participants' personal information will remain confidential. During the interviewer training, interviewers will be trained on how to protect participants' privacy and obtain consent. Before starting the interviews, interviewers will provide participants with an alias.

During the training, before the interviews, interviewers will be provided with interview kits containing a recorder, notebook, batteries, frequently asked question answer sheet, acknowledgment form, and interview script (Figure 7). The interview script (Multimedia Appendix 4) will provide interviewers with questions to ask and follow during the interview.

First, interviewers will provide the participant with a copy of the consent form and will read the consent form to the participant. The interviewer will inform the participant that they may take notes if they ask any questions that were not on the interview guide or if they have a thought that they want to write down to share with the academic team. The interviewer will tell the interviewee that they have the right to look at the notes. After the participant has agreed to take part, the interview will start. At the start of the interview, interviewers will turn on the recorder and state the participant's alias and the date and county. The interviewer will have the participant state the following: "I consent to this interview."

After the interviewer has completed the interview, they will encourage the participant to recruit other participants and provide them with 5 pass-along cards (Figures 5 and 6). The interviewer will then distribute a gift card for US $35 to the participant. The interviewer will record the participant saying that they received the gift card, have the participant sign the acknowledgment form with their alias, and document in their notebook that they provided the gift card with the date and alias name. To conclude the interview, the interviewer will thank the participant and turn off the recorder. Upon completing the 10 interviews, the interviewer will return the recorder and acknowledgment sheet to the study team via a prepaid envelope.

Figure 7. Surveyor interview toolkit. These items are provided to surveyors before training and recruitment of participants.

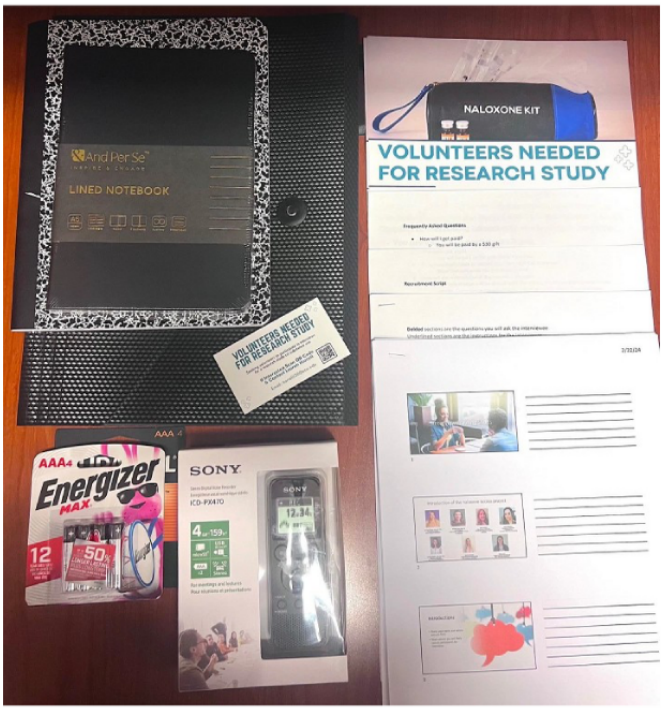

Interview Data Analysis

After concluding the interviews, the interviewer will provide their data to the academic team. They will also provide their notes from the interviews, all documents that the participants signed, and the recordings. The academic partners will be responsible for data management, analyses, and dissemination. The academic partners will transcribe the recordings of the interviews and organize the data using NVivo (QSR International). The interviewers will be asked to join the academic team meetings to assist in interpreting the data together.

The qualitative data will be coded using a priori codes and emergent themes. The a priori codes will be that rural communities face significant barriers in obtaining naloxone, including stigma and limited availability [31]. Two people from the academic partnership will independently code the sample to achieve a uniform understanding of the codes. A coding conference will be held to identify and manage any code discrepancies. Upon agreement on the final coding scheme, a conference will be held with all interviewers (n=5) and the partnership to review the codes and confirm observations and findings. If any discrepancies arise, they will be discussed and addressed during this meeting. The final coding scheme will then be used by a primary coder from the academic partners to code all interviews. A final data conference will be held with the entire partnership to confirm observations and determine priority findings related to the operational procedures for PHVMs, location, and items to be stocked [39-41].

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Review of Interview Findings With Community Decision-Makers

The academic partners will work hand in hand with the community partners to identify key individuals within the county who are decision-makers as well as early adopters of the PHVMs. Rogers [42] states that early adopters are people or organizations willing to implement the "new practice" before the public. Decision-makers may include law enforcement, emergency management services, faith-based leaders, prevention and treatment providers, public health departments, hospital personnel, and other advocates. Early adopters will be vital in assisting the partnership in creating opportunities for relationships within each rural community. In addition, early adopters can advocate for the PHVM among the county residents and other key decision-makers. They act as a conduit to provide vital information about the community to the partnership and vice versa. Such information includes details about the county's unique region, including its history, institutions, traditions, and demographics. Understanding these characteristics within rural communities has been suggested as a way to create capacity and enable implementation projects that will be sustained over time [38]. The partnership, along with early adopters and the interviewer, will collaboratively identify individuals and organizations in each community to disseminate the findings. In addition, they will identify how and where to share the findings with the community. Securing support from influential community members (elected officials) is necessary [38]. Thus, the partnership will collaborate closely with early adopters to identify decision-makers and elected officials. Studies indicate that rural implementation success is strengthened with relationships; thus, having an advocate such as the early adopter attend in-person meetings is important [43]. Community engagement strategies in rural settings are different from those in urban settings, and it has been shown that increasing participation, especially of all community members, within rural communities leads to improved sustainability [43]. Therefore, an intentional selection of key individuals is necessary.

Upon completion of the identification of key community members, an email will be sent by the partnership introducing the team and the project and inviting them to attend an informational meeting. The early adopter may also send an email or call individuals and provide a personal invitation to the meeting. This step may be vital in communities where there are critics who could prevent the successful implementation or sustainability of the PHVM. Studies have found that credibility in rural communities is developed from the connection to the community rather than from an institution, degree, or title [38].

The structure of the informational meeting will be determined by the partnership in combination with the early adopter. Who will welcome and introduce the partnership will be determined. Ideally, the early adopter will welcome and introduce one member of the academic or community partnership, at which time that member will introduce the rest of the team. During the informational meeting, an overview of how and why the partnership was developed and who the members of the partnership are, as well as of the funding, deliverables, and how each county was selected, will be provided. National and regional overdose and PHVM data will be shared. An explanation of what community-based participatory approaches are and why they will be used in this project will be provided, as well as a description of how interviewers will be hired and trained. The findings from each county's interviews will be shared after interviews have been completed and analyzed. This information will assist in determining the optimal placement of the PHVMs within each community.

In addition, the findings will guide the next steps within each community. The partnership will collaboratively identify additional individuals or organizations to include in the implementation or sustainability of the PHVMs. The partnership and community decision-makers will develop a sustainability plan for the PHVMs based on the findings and each community's unique needs. The sustainability plan will vary depending on the county's resources and support and the items to be placed in the PHVMs. For example, if the interview results reveal that people with lived experience report that they would like to have syringes in the vending machine but the decision-makers are not in support of such an item, then a decision will be made based on the communities' feedback and alignment with current legal and health policies. This determination will be made based on the community members, not the partnership; this promotes buy-in and ownership over the PHVMs, both of which are important for a successful implementation and sustainable project. The community will be informed that naloxone is the only item required in the PHVM due to being a deliverable in the grant. The brand of naloxone (eg, Narcan or RiVive) and how it is administered (eg, nasal or intramuscular) is negotiable. The development of the sustainability plan may include the identification of grants, local or state funding, grassroots and faith-based organizations, and other social and health agencies.

Results

Data will be collected from 2024 to 2025. Five PHVMs will be implemented in 5 rural NC counties. The location and supplies of the PHVMs will be determined based on stakeholder interviews and community collaborations (eg, public health director; members of the emergency medical services, sheriff, and fire departments; hospital administrators; faith-based organizations; county commissioners; town managers; and prevention and harm reduction advocates).

The results of this study protocol will be the development of a PHVM implementation toolkit designed to offer practical materials such as email templates, guides, and resources to support other communities in implementing a PHVM (Figure 8). An implementation framework will be used to develop an implementation plan with the community. The exact factors related to the implementation and placement of the PHVMs will be shared in future manuscripts.

Funding for this project was provided by the Health Resources and Services Administration of the US Department of Health and Human Services, from August 2023 to August 2025. Institutional review board approval for this project was received from September 11, 2023, to May 31, 2026. Interview data collection occurred from June to December, 2024. Data analysis for the interview data has been completed, with one publication

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under review in August 2025. The sustainability data for the PHVM is currently being collected with the anticipation of one publication being produced in 2026.

Figure 8. Public health vending machine logo.

Discussion

Anticipated Findings

This study will be designed to engage a community-based participatory approach to improve naloxone access in rural communities. Interviews with local community members with lived experience, county leadership, and other community decision-makers will be used to examine the optimal placement for implementing a PHVM stocked with naloxone. In addition, community partners will assist the academic team in the development of a sustainability plan for each county.

A key innovation of this study design will be the training of individuals with lived experience from each rural community to serve as recruiters and interviewers. This approach will not only foster trust and rapport with participants but also ensure that the voices of individuals who are often marginalized or unheard are meaningfully included. By empowering community members to lead data collection, we will facilitate the authentic representation of local perspectives and will create a direct line of communication between these voices and community decision-makers.

Limitations

The proposed study will use a CBPR approach focused on 5 rural counties in NC, which imposes some limitations on the types of data and the nature of the information that can be collected. We expect that additional limitations may be identified during study conduct. The results-oriented manuscript will identify and describe new limitations to follow the PHVM intervention.

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Data Availability

Data will be available upon reasonable request with the corresponding author. Interview data will be published upon completion. The public health vending machine implementation toolkit will be published upon completion.

Authors' Contributions

Conceptualization: LAE (lead) and KLE contributed to conceptualization equally.
Funding acquisition: LAE (lead) and KLE contributed to funding acquisition equally.
Investigation: LAE (lead); KLE (equal); and MG, LH, and RH (supporting). LAE and KLE contributed equally to the investigation and MG, LH, and RH provided support to the investigation.
Methodology: LAE (lead) and KLE (equal) LAE and KLE contributed to the methodology equally.
Project administration: LAE (lead) and KLE (equal) LAE and KLE contributed to the project administration.
Resources: LAE (lead); KLE (equal); and MG, RH, and LH (supporting). LAE and KLE contributed equally to the resources, and MG, LH, and RH provided support to the resources.
Supervision: LAE (lead) and KLE (equal) LAE and KLE contributed to the supervision.
Writing—original draft: MG (lead) and LAE (equal) LAE and MG contributed to the writing of the original draft
Writing—review and editing: LAE (lead); KLE (equal); and MG, RH, and LH (supporting). LAE and KLE contributed equally to the review and editing of the writing and MG, LH, and RH provided support to the investigation.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
Interview guide—page 1.
[PDF File (Adobe PDF File), 171 KB - resprot_v14i1e64913_app1.pdf]

Multimedia Appendix 2
Interview guide—page 2.
[PDF File (Adobe PDF File), 25 KB - resprot_v14i1e64913_app2.pdf]

Multimedia Appendix 3
Interview guide—page 3.
[PDF File (Adobe PDF File), 15 KB - resprot_v14i1e64913_app3.pdf]

Multimedia Appendix 4
Recruitment script.
[PDF File (Adobe PDF File), 86 KB - resprot_v14i1e64913_app4.pdf]

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Abbreviations

CBPR: community-based participatory research
CINC: Community Impact North Carolina
NC: North Carolina
NCHRC: North Carolina Harm Reduction Coalition
PHVM: public health vending machine
SSP: syringe services program

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Protocol

Interventions to Prevent Sexual Harassment Against Nurses—StopSH: Protocol for an Intervention Development Study

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Abstract

Background: Patients' sexual harassment against nurses is a worldwide phenomenon. Some forms occur on a daily to weekly basis. Despite the known high prevalence and its negative consequences, there is still a lack of evidence-based measures to prevent patients' sexual harassment against nurses. Given the complexity of the problem, multidimensional interventions are required.

Objective: The main objective of the StopSH project is to develop an evidence-based, complex intervention package to prevent patients' sexual harassment against nurses and minimize its negative consequences for the acute care sector in the German-speaking part of Switzerland.

Methods: This project is an intervention development study with a multimethod design. It involves the participative development and testing of a complex intervention package in one to two Swiss hospitals as practice partners. The project is carried out in four project phases. First, a systematic scoping review will be conducted to identify and map existing interventions aimed at preventing sexual harassment of nurses or minimizing its consequences. The review will include interventions at the individual, organizational, and network levels of nurses. The problem and needs analysis form the second phase, where a cross-sectional web-based survey will be carried out among nurses in one to two partner hospitals. The aim is to assess the prevalence, forms, and perceived consequences of sexual harassment, as well as existing and desired strategies or support structures. The results will inform the development of the intervention package. As a third phase, a complex intervention package will be codeveloped using a participatory action research approach, based on the findings from the first two phases. This process will involve nurses, hospital management, human resources, and other relevant stakeholders to ensure contextual relevance and feasibility. Finally, during a feasibility assessment, the developed intervention package will be implemented and tested on two to three test wards within the partner hospitals. The mixed methods feasibility study will assess the acceptability, practicality, and preliminary effects of the intervention. Survey data, as well as contextual and observational data, will be collected.

Results: The project was launched in February 2024 and is scheduled to last for 5 years. As of August 2025, this project is in phase 2. Data collection is ongoing. The StopSH project is expected to develop and test a complex intervention package for the prevention of patients' sexual harassment against nurses. This intervention package is predicted to reduce the prevalence and negative effects of sexual harassment against nurses.

Conclusions: The results of this project will provide important guidance for nurses, but also for their employers, and as such can contribute to the long-term reduction of sexual harassment against nurses. It lays the foundation for the development and adaptation of interventions in further nursing settings and other health care professions.

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KEYWORDS

acute care; hospitals; intervention development; nurses; sexual harassment; prevention

Introduction

Background

Sexual harassment toward nurses constitutes a significant issue both internationally and in Switzerland [1-3]. Sexual harassment is defined as any behavior of a sexual or gender-specific nature that is unwelcome on one side and that violates a person's dignity [4]. It can take place through words (verbal), gestures (nonverbal), or acts (physical) [4,5]. While workplace sexual harassment can occur in many different fields [6,7], health care professionals often report significantly higher rates [8-10], with nurses being among the most frequently affected [11-14].

One reason for nurses being most frequently affected by workplace sexual harassment is [11-14] that patients are among the main perpetrators of sexual harassment in health care [9,11,15,16], and nurses are the professionals who spend the most time directly at the patient's bedside, performing tasks with close physical contact [17-20]. Further, sexual harassment is often facilitated by power imbalances, and nurses typically work within hierarchical health care systems where they may hold less institutional power compared to other professional groups [14,15,21].

In health care, sexual harassment against nurses can originate from various groups, including patients, patients' family members, nurse-colleagues, supervisors, and physicians. The primary perpetrators vary across studies, depending on the setting and the cultural context [3,16,22-24]. In studies from the Global North, such as Switzerland, patients are most often identified as the main perpetrators [16,17,23,25]. In contrast, studies from the Global South often report higher rates of harassment by physicians, nurse-colleagues, or patients' family members [22,24,26-28].

The prevalence of sexual harassment against nurses varies greatly across countries (5%-70%) [23,24,26,27,29,30]. This large range is mainly due to the different measurement methods used in the studies, but also to differences depending on culture, country, and setting [2,3]. Furthermore, the issue of sexual harassment is still often associated with shame, which can lead to incidents not being reported and therefore being undetected [3,17,22,31,32]. A recent study conducted in the German-speaking part of Switzerland, using a newly developed sensitive instrument by Vincent-Höper et al [5] and adapted by Adler et al [29], revealed an alarming prevalence: 95.6% of nurses reported experiencing at least one form of sexual harassment from patients in the past 12 months. Some forms were encountered on a weekly or even daily basis [1].

Sexual harassment against nurses has various negative effects on those affected, but also on the institution and the quality of care provided to patients. Almost 70% of nurses affected report negative psychological and physical consequences [26,33], such as anxiety, humiliation, frustration, gastrointestinal complaints, headaches, insomnia, and exhaustion. In addition, several studies have confirmed negative consequences on the work performance, work motivation, and quality of care of nursing staff [15,17,22,23,26,34].

Poor working conditions, emotional stress, and workplace violence have been shown to affect nurses' retention in the profession [35,36]. As seen globally, the shortage of nursing staff is also a prevailing issue in Switzerland, which can be exacerbated by workplace sexual harassment [37,38]. Studies have shown that sexual harassment can increase the pressure on nurses to such an extent that they go on sick leave, resign, or even change jobs. This is particularly the case if this occurs on a recurring basis [17,22,25,26,39].

The prevalence of sexual harassment against nurses, the groups of perpetrators, influencing factors, and forms, as well as the behavioral patterns of nurses and the negative consequences, have been extensively researched worldwide [2,3,15,34]. However, there are currently no universally applicable recommendations for strategies regarding this issue [40], and the development of evidence-based, tailored interventions and guidelines for health care facilities is deemed necessary [15,41-43]. Given the complexity of the problem, it is clear that there is no one-size-fits-all solution and that multidimensional interventions are required, including the individual, organizational, and network level [40,44-46].

Research results on specific measures to prevent patients' sexual harassment against nurses and minimize its negative effects are lacking. The StopSH project aims to fill this research gap. The project will focus on the acute care sector in the German-speaking part of Switzerland and the perpetrator group of patients. The focus on patients and acute care is partly due to the fact that in countries of the Global North, including Switzerland, patients are the main perpetrator group [9,16,23,25], and about half of the nursing staff in Switzerland work in hospitals [47]. Furthermore, studies report that acute care nurses experience sexual harassment more frequently than nurses in other sectors [1,3].

Objectives

The main objective of the StopSH project is to codevelop an evidence-based, complex intervention package to prevent patients' sexual harassment against nurses and minimize its negative consequences for the acute care sector in the German-speaking part of Switzerland. The aim is to enable health care organizations, nurses, and their network to take action against sexual harassment.

The main research question of this project is, which individual, organizational, and network interventions to prevent patients' sexual harassment of nurses and minimize its negative consequences are considered feasible and applicable in Swiss hospitals by key stakeholders involved in the participatory development process?

In addition to the overarching question, three subquestions were formulated to achieve the objective: (1) What evidence-based interventions to prevent workplace sexual harassment against nurses and minimize its negative consequences at the individual,

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organizational, and network levels of nurses are described in the literature? (2) What problems and needs do stakeholders from Swiss hospitals state regarding the prevention of patients' sexual harassment of nurses and the minimization of its negative consequences? (3) Which interventions at individual, organizational, and network levels are suitable, feasible, and acceptable for the prevention of patients' sexual harassment of nurses and the minimization of its negative consequences in Swiss hospitals, based on stakeholder input and feasibility testing?

Each subquestion is addressed in a dedicated study phase and outlined in the Methods section.

Methods

Project Design and Phases

The StopSH project is an intervention development study with a multimethod design. It involves the development and testing of a complex intervention package to prevent patients' sexual harassment of nurses in hospitals located in the German-speaking part of Switzerland. This intervention development process will be carried out participatively with one to two Swiss hospitals in the German-speaking part of Switzerland as practice partners. The hospitals will be selected based on availability and willingness to participate. Inclusion criteria comprise a high level of motivation to address the issue of sexual harassment, a commitment to long-term collaboration with the research team, and an interest in sustainably implementing the intervention package.

Conducting the project in collaboration with one to two practice partners allows for a focused and resource-efficient development process, enabling close collaboration with stakeholders and iterative refinement of the intervention package. In follow-up projects, the intervention package can be adapted and implemented in additional hospitals and care settings to increase its reach and applicability.

The development and testing of a complex intervention package to prevent and minimize the negative consequences of patients' sexual harassment against nurses is carried out in four project phases (Figure 1):

- Phase 1: literature review
- Phase 2: problem and needs analysis
- Phase 3: development of the intervention package
- Phase 4: feasibility assessment

Figure 1. Overview of the StopSH project phases with reference to the MRC framework. MRC: Medical Research Council.

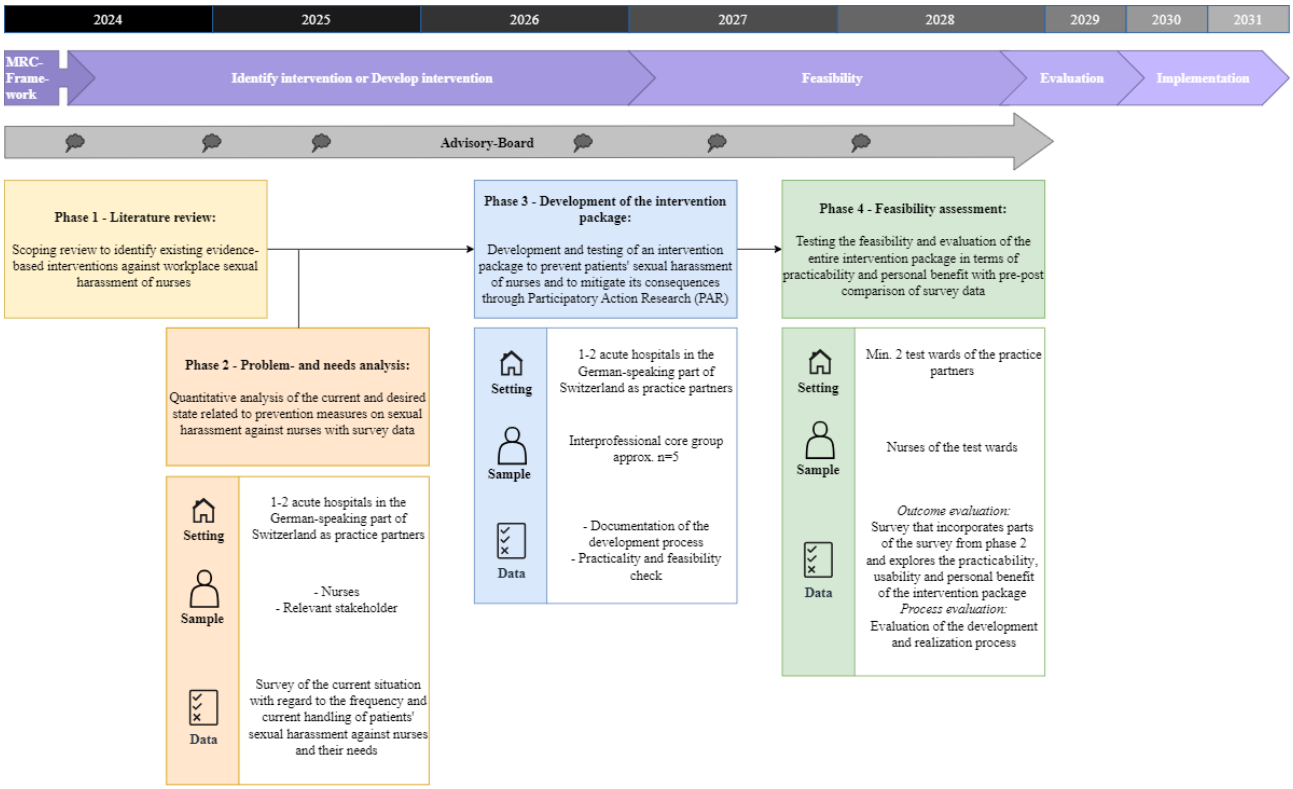

To support the participatory development process, an interprofessional core group of approximately five key stakeholders of the practice partners will be formed. This core group may include nursing staff, vocational trainers, people from the field of quality development and psychology, nursing managers, and human resources representatives. Furthermore, the inclusion of an advisory board ensures the participation of key stakeholders from the Swiss health care system and field experts throughout the development process. This structure ensures that the intervention package is both contextually relevant and feasible for the practice partners and facilitates later broader implementation in the Swiss acute care sector. The interprofessional core group will be actively involved in phases 3 and 4 of the project, contributing to the participatory development and feasibility testing of the intervention package. The advisory board advises the project throughout all four phases and meets twice a year. It provides strategic input, supports scientific and contextual alignment, and ensures that

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the intervention package remains relevant beyond the immediate hospital setting.

The Medical Research Council (MRC) framework [48-51] forms the methodological framework for project implementation and the overall structure of the project. StopSH covers the MRC phases "identify or develop intervention" and "feasibility," while the phases "evaluation" and "implementation" are beyond its scope and will be addressed in follow-up projects. The "Conceptual Framework for Systematic Capacity Strengthening for Health Policy and Systems Research (HPSR)" [46] forms the conceptual framework for realization. In this project, the Conceptual Framework for Systematic Capacity Strengthening for HPSR [46] provides the conceptual foundation for the participatory research approach and the development of appropriate interventions to prevent patients' sexual harassment of nurses in Swiss hospitals. It emphasizes the importance of working with shared goals, values, and principles, while addressing all three capacity levels: individual, organizational, and network. The key components of the Conceptual Framework for Systematic Capacity Strengthening for HPSR [46] are reflected in the objectives and design of each phase. Both frameworks are suitable for the development of complex interventions and emphasize the importance of addressing all relevant levels (individual, organizational, and network) to ensure effectiveness and sustainability. Complexity is addressed through several strategies: first, the intervention is designed as a multicomponent package, incorporating measures at the individual level (eg, training for nurses), organizational level (eg, reporting structures), and network level (eg, collaboration with external stakeholders). Second, the participatory approach ensures that the intervention package is tailored to the specific needs and contextual conditions of the practice partners, allowing for iterative refinement based on stakeholder feedback.

Phase 1: Literature Review

In the context of the Conceptual Framework for Systematic Capacity Strengthening for HPSR [46], the evidence-based literature is an important basis for informed decision-making [46,52]. Accordingly, phase 1 forms the basis of the StopSH project, providing the evidence base that will inform both the survey in phase 2 and the codevelopment of the intervention package in phase 3. This phase aims to identify existing, evidence-based intervention measures against workplace sexual harassment of nurses, without restrictions regarding the type of perpetrator or care setting. Using a scoping review design, the state of the literature will be determined (subquestion 1).

All types of evidence published in English or German will be included, provided they focus on interventions addressing workplace sexual harassment of nurses in any setting. No restrictions will be applied regarding the publication date. The literature search will be conducted in medical databases such as MEDLINE, CINAHL, and PsycInfo. In addition, supplementary searches will be performed using Google Scholar and trial and guideline registries, as well as forward and backward citation tracking. Included studies will undergo a thematic analysis and a numerical summary to identify existing interventions and highlight potential research gaps. In line with scoping review methodology [53], no critical appraisal of included studies will be conducted, as the aim is to map the existing evidence rather than evaluate their quality. Further information on the scoping review can be found in the published protocol on the Open Science Framework by Bruschini et al [54]. The reporting of the scoping review will follow the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guideline as outlined by Tricco et al [55].

Phase 2: Problem and Needs Analysis

Overview

According to the Conceptual Framework for Systematic Capacity Strengthening for HPSR [46], the process of improvement starts with an assessment of the current situation and needs. It is important to involve different people in this process in order to obtain a collective picture of the situation and current capacities. Therefore, project phase 2 aims to carry out a problem and needs analysis with nurses and other relevant stakeholders of the practice partners (subquestion 2).

Design and Setting

The problem and needs analysis will be carried out using a cross-sectional design. A quantitative web-based survey will be conducted in one to two hospitals as practice partners in the German-speaking part of Switzerland. The results from phase 1 will contribute to the development of the survey, with a particular focus on identifying existing interventions and those that nurses would like to see in the future.

Participants and Sampling

Nurses of the participating practice partners, who are working in direct patient care, will be invited to participate in the survey. There will be no restrictions regarding nurses' age, gender, years of professional experience, or level of education. For each participating hospital, the aim is to conduct a full census of all eligible nurses. Depending on the size and structure of the participating hospitals, the inclusion of all departments may not be feasible. In such cases, a convenience sampling strategy will be applied in collaboration with the practice partners to ensure the inclusion of relevant departments.

In addition to nurses, other relevant stakeholders, such as nurse managers, vocational trainers, psychologists, and human resources personnel employed by the practice partners who have prior experience in dealing with sexual harassment of nurses and are involved in safeguarding employee integrity or managing crisis situations, will also be invited to participate in the survey. As the study aims to conduct descriptive analyses only and follows a full census approach, no a priori sample size calculation is performed. The research team aims to recruit a minimum of 100 nurses and 10 other relevant stakeholders for the survey.

Data Collection and Analysis

Overview

Data collection will be conducted via REDCap (Research Electronic Data Capture; Vanderbilt University) [56,57] in a cross-sectional manner over a period of 1 to 2 months per practice partner. Recruitment and data collection will follow a

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stepwise approach. Participants will receive a survey link via the internal email system of the practice partners. The survey will consist of approximately 80 items and include the following components.

Section A (Current State)

Items assessing the prevalence, impact, and influencing factors of sexual harassment. This includes the full, reliable and validated (Cronbach α 0.80 to 0.92) "Sexually Harassing Behavior Questionnaire from an Extraorganizational Perspective" (SHBQ-X) [5,29], as well as selected items from a Swiss national survey on workplace sexual harassment developed by the Federal Office for Gender Equality (FOGE) and the State Secretariat for Economic Affairs (SECO) [10].

Section B (Desired State)

This section includes adapted items from the FOGE/SECO survey and newly developed items based on findings from phase 1. It focuses on intervention needs, desired preventive interventions, and perceived barriers and facilitators for implementation.

Section C (Demographics)

These items will collect information about the participants' age, gender, education, and professional experience. They will be used for the description of the participants.

All instruments used in the survey are available in German, which is the language of the study. Permissions to use the SHBQ-X and the FOGE/SECO items were obtained from the original authors [5,10,29].

To ensure content validity, the created survey for phase 2 will undergo a content validation process following Yusoff [58], involving 6-10 experts (including advisory board members, representatives, and nurses of the practice partners). Content Validity Index values will be calculated for each item [58]. The data will be analyzed descriptively using the programming language and environment R (R Core Team) and RStudio (Posit Software, PBC).

Phase 3: Development of the Intervention Package

Overview

The "Strengthening and unleashing" process of the Conceptual Framework for Systematic Capacity Strengthening for HPSR [46] aims to strengthen capacities at all three levels (individual, organizational, and network), taking into account identified resources and needs, as well as values and principles. The third phase will develop an intervention package to prevent sexual harassment against nurses and minimize its negative consequences. This will be accomplished in a participatory manner together with nurses and other relevant stakeholders in the selected one to two hospitals (interprofessional core group). In this phase, single interventions for the intervention package will be developed, tested, and adapted for everyday use (subquestion 3).

Design and Setting

Phase 3 is based on the participatory action research approach. Specifically, the plan-do-study-act (PDSA) process by Deming [59] and adapted by Magnuson et al [60] will be used to develop, test, and adapt the prototype of the intervention package. The intervention package will be developed and tested in a participatory manner with the practice partners and the research team. Further, the process will be supported by the advisory board. The results from phases 1 and 2 will inform the development process by identifying interventions that are both evidence-informed, contextually appropriate, and preferred by nurses in the partner hospitals. The previously gained knowledge will serve as the foundation for codeveloping an intervention package tailored to the specific needs and realities of the practice partners.

Participants and Sampling

The practice partners' interprofessional core group will participate in the PDSA process and collect data while developing and testing the single interventions. Depending on the specific focus of each intervention within the package, key stakeholders from the practice partners and advisory board will be identified, and the core group will be assembled accordingly. The composition of the core group will remain flexible to ensure that the expertise required for each single intervention is adequately represented.

Data Collection and Analysis

Each intervention undergoes the PDSA process individually. The process is repeated until a customized intervention package is available. During the development process, documentation and observation data are collected. This is done using documentation forms, meeting and discussion minutes, implementation logs, and reflection diaries. This data is used to document the development process, support decision-making, and contribute to the process evaluation in the subsequent project phase 4.

To determine the success of each PDSA cycle, predefined criteria will be established for each intervention component. These will include formative process indicators (eg, feasibility, acceptability, and initial fidelity) and outcome-oriented perceptions (eg, perceived relevance, usability, and practicability). Progression to the next cycle or finalization of an intervention will be based on whether these criteria are met, as assessed through documentation and feedback from the core group and advisory board.

The final intervention package is expected to comprise approximately three to five single interventions. This range is based on practical considerations, including available resources and the intention to ensure a manageable scope of change within the clinical setting.

Phase 4: Feasibility Assessment

Overview

Although the Conceptual Framework for Systematic Capacity Strengthening for HPSR [46] does not explicitly refer to the step of intervention testing and evaluation, this phase can be understood as part of the "unleashing" process. The MRC framework [48-51] emphasizes the importance of testing interventions within the given context and evaluating both the process and the outcome. Therefore, in this phase, the feasibility,

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benefit, and acceptance of the entire intervention package developed will be tested and evaluated. Project phase 4, together with phase 3, serves to answer subquestion 3.

Design and Setting

This feasibility study serves to evaluate the entire intervention package (outcome and process evaluation). The outcome evaluation does not yet test the effectiveness of the intervention package regarding the prevention of patients' sexual harassment and minimization of its negative consequences, but serves to evaluate the feasibility, practicability, and personal benefit of the developed intervention package. The application of the intervention package prototype and the feasibility assessment are carried out on at least two test wards of the practice partners.

Participants and Sampling

For the evaluation process, all nurses with direct patient contact working on the test wards are invited to participate in a second survey. Some of the participants may be the same as in the first survey conducted in phase 2. This overlap is likely, as phase 2 may involve a full census of all nursing staff employed at that time. While prior participation can lead to increased sensitization regarding the topic of sexual harassment, this cannot be fully controlled due to the anonymous nature of the survey and the possibility of informal exchange among nurses. Consequently, even those who did not participate in phase 2 may have gained knowledge about the topic. Since phase 4 focuses on assessing feasibility, usability, and perceived benefit rather than effectiveness, differences in prior exposure to the survey or study topic are not considered problematic.

Data Collection and Analysis

To explore early indications of the intervention package's performance and to describe possible changes (outcome evaluation), a before-and-after comparison will be carried out using a quantitative web-based survey. The second survey includes items from Section A of the phase 2 survey, aiming to reassess the prevalence, impact, and influencing factors of sexual harassment. Section A comprises the validated SHBQ-X questionnaire [5,29] and selected items from the Swiss national survey on workplace sexual harassment [10].

The quantitative baseline data from project phase 2 will be compared with data collected 3 to 6 months after the application of the intervention package on the test wards. To account for potential differences in prior exposure to the study topic, participants will be asked whether they have already taken part in the initial survey conducted in phase 2. This information will be used to explore possible variations in responses between returning and new participants.

The before-and-after comparison is exploratory in nature and aims to identify early indications of change. Descriptive subgroup analyses will be conducted to explore potential variations in responses between returning and new participants. In addition, the second survey includes items specifically designed to assess the intervention package's perceived benefits for nurses, as well as its practicability and usability.

For the process evaluation, contextual and observational data on the implementation setting will be collected by the research team. This documentation and observation data from phases 3 and 4 will be analyzed to assess the fidelity of implementation in relation to the planned intervention package.

Quantitative data will be analyzed descriptively using the programming language and environment R and RStudio (Posit Software, PBC). Textual and documentation data for process evaluation are analyzed using MAXQDA (VERBI Software) based on inductive content analysis according to Kyngäs [61] and Elo and Kyngäs [62].

Ethical Considerations

The planned project was submitted to the Cantonal Ethics Committee of Zurich (BASEC—Nr. Req-2024-01085). In accordance with Article 2, the research project does not fall within the scope of the Swiss Human Research Act [63], as it does not investigate questions related to human diseases or the structure and function of the human body, nor does it involve the analysis of health-related data or biological material. The research project complies with Swiss law and the ethical principles of the Declaration of Helsinki [64]. Participation in the study is voluntary and does not involve any risk for the participants. No financial compensation is provided for participation. Nurses who do not take part in the study do not experience any disadvantage. All study participants must give their consent to participate in the study. In the web-based survey, consent is indicated by placing a cross in the checkbox provided. For core group participants, written informed consent will be obtained using a consent form prior to their participation. Due to the sensitive nature of the topic, participants are provided with contact details for counseling centers regarding workplace sexual harassment and have the option of withdrawing their consent to participate in the study at any time. The study is designed to minimize emotional burden by avoiding open-ended questions or detailed descriptions of personal experiences. Participants are asked to respond to predefined categories (eg, types of sexual harassment encountered and perceived consequences). The main focus lies on the development of prevention measures. Further, during data collection, particular attention is paid to the voluntariness of responses. With the exception of the consent form and eligibility criteria at the beginning of the survey, none of the questions are mandatory, and participants may skip any items they do not wish to answer. Data collection in phases 2 and 4 is done anonymously via the electronic web app REDCap [56,57].

Confidentiality and Availability of Data and Materials

The protection of sensitive data is guaranteed throughout the entire research process. Personal information is stored separately from the research results. All data are stored in a secure, password-protected folder at the study site, with the server located in Switzerland and archived for 10 years. All study and participant data will be treated with the utmost discretion and will only be accessible to members of the research team. In the planned scientific publications, the data will be presented in such a way that no conclusions can be drawn about individuals or single institutions. Data will either be collected anonymously or be pseudonymized during data collection, by assigning participant codes (with the key stored separately) and removing directly identifying information.

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The collected data will not be passed on to third parties. However, metadata that support the findings of this project will be made publicly available via a public repository.

Dissemination Policy

The StopSH project aims to produce three scientific publications. For this purpose, the authorship eligibility guidelines of each journal will be followed. The results will be published with open access. Furthermore, study results will be communicated at public lectures and congresses for health care professionals. Study results are also made available to the public in easy language.

Results

Current Status of the Project

This 5-year project was initiated in February 2024. As of August 2025, this project is in phase 2. In this regard, the data collection of phase 2 via web-based survey is ongoing, with approximately 50 participants recruited so far from one practice partner. Furthermore, preparations are underway for the publication of phase 1 (scoping review).

The project was originally planned to run for 3 years. However, in August 2025, due to the current recruitment status and the absence of secured third-party funding, the research team decided to extend the duration to 5 years to ensure sufficient time for completion of all phases.

Expected Results

The StopSH project will develop and test an evidence-based, complex intervention package for the prevention of patients' sexual harassment against nurses. This will be achieved through close collaboration with the practice partners and the advisory board. The intervention package can empower health care organizations, nurses, and their network to take action against sexual harassment, thereby improving the workplace safety of nurses in Switzerland. In the long term, the intervention package is expected to reduce the prevalence and negative effects of sexual harassment against nurses. Improved working conditions can enhance work satisfaction and reduce the number of nurses leaving the workforce early.

Discussion

Principal Findings

This study protocol refers to a project that aims to make a significant contribution to the prevention of patients' sexual harassment of nurses. The StopSH project provides an overview of potential preventive interventions and offers insights into the current and desired future state regarding prevalence and prevention of workplace sexual harassment in the acute care setting of the German-speaking part of Switzerland. It also transparently documents the development process of evidence-based interventions and evaluates their feasibility. As such, the StopSH project lays an important foundation for addressing patients' sexual harassment in health care settings and can serve as a model for similar initiatives in other health care sectors.

The #MeToo and #EndNurseAbuse movements have drawn national and international attention to the issue of workplace sexual harassment in nursing [32,65-67]. Increased media coverage in recent years has raised public and political awareness of this issue in Switzerland. This heightened awareness forms the basis for the realization of this project. Despite this increased awareness, the sensitive nature of the topic may still pose challenges during implementation. Discussing experiences of sexual harassment can evoke discomfort or fear of stigmatization among participants [15,25,29]. The research team is therefore prepared to address potential resistance or hesitancy by fostering a safe and respectful environment, ensuring anonymity, and providing access to support services. These considerations are essential to promote trust and engagement, and to ensure the feasibility of the intervention package in real-world health care settings.

Given the high prevalence of sexual harassment against nurses [23,24,26,27,29,30] and the lack of effective prevention [15,41-43], there is an urgent need for targeted interventions. Ensuring the safety of nursing staff is essential for the sustainable development of the profession. Research has shown that improving working conditions and protecting the health of nurses positively influences retention in the profession [68]. By codeveloping an intervention package, this project addresses a critical research gap and responds to an urgent need identified in clinical practice.

StopSH contributes to improving working conditions in nursing and further promotes awareness of the issue. The involvement of the practice partners, experts, and nurses from the outset ensures that interventions are aligned with practical needs and are feasible. According to Cook et al [20], a participatory approach is essential for developing effective interventions against patients' sexual harassment of nurses, as it enables an understanding of the complexity, dilemmas, and relationship values held by nurses.

Strengths

This project, which aims to develop evidence-based prevention measures for sexual harassment in the nursing profession, is the first of its kind in Switzerland. It can contribute to achieving the goals of the Swiss nursing initiative, a program aimed at nationally improving working conditions, enhancing nursing education, and increasing the attractiveness of nursing professions [69].

The project's added value is highlighted by the cocreation of a specific intervention package designed to prevent sexual harassment against nurses in the acute care sector and mitigate its negative consequences, considering all three capacity levels as outlined by Mirzoev et al [46].

Limitations

The implementation of the participatory action research design is dependent on the active participation of the practice partners and stakeholders. This makes the success of the project reliant on the commitment, resources, and motivation of the practice partners. Shortages of health care staff and resources are also ubiquitous in Switzerland, which poses obstacles for the project. For this reason, the development of the intervention package

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must be adapted to the resources of the respective practice partners. To mitigate these resource-related limitations, the research team is seeking third-party funding to compensate the practice partners. In addition, the research team will be preparing all study materials and communication templates to reduce the administrative burden of the practice partners.

This project focuses on nursing staff working in one to two hospitals in the German-speaking part of Switzerland. This specific focus and small sample do not allow the generalization of the results to other health care settings. Furthermore, as the study is designed for descriptive and developmental purposes only, no causal inferences can be drawn from the findings. Nevertheless, the close collaboration with one to two practice partners enables a context-sensitive and resource-efficient development process. The findings and intervention package will serve as a foundation for future projects aiming to adapt and evaluate the intervention package in broader health care contexts.

The voluntary nature of participation and recruitment in the project may introduce selection bias. Individuals who are particularly affected by workplace sexual harassment might be more inclined to participate due to personal relevance, or alternatively, they might choose not to participate due to emotional burden. Despite the possibility of either underrepresentation or overrepresentation of those affected, voluntary participation is considered ethically appropriate given the sensitive nature of the topic.

Furthermore, demonstrating the long-term effects of the intervention package regarding the prevention of patients' sexual harassment and minimization of its negative consequences, as well as the implementation process, is beyond the scope of the StopSH project and will be addressed in a follow-up project (longitudinal intervention study).

Conclusions

Maintaining a respectful, nonviolent work environment is key to keeping nurses in the profession. The results of this project will provide important guidance for nurses, but also for their employers. It may contribute to the long-term reduction of sexual harassment against nurses and therefore sustainably improve workplace safety.

Acknowledgments

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Authors' Contributions

This study protocol was prepared by the first author together with the last author (Principal Investigator).

Conflicts of Interest

None declared.

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Abbreviations

FOGE: Federal Office for Gender Equality
HPSR: Health Policy and Systems Research
MRC: Medical Research Council
PDSA: Plan-do-study-act
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
REDCap: Research Electronic Data Capture

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SECO: State Secretariat for Economic Affairs
SHBQ-X: Sexually Harassing Behavior Questionnaire from an Extraorganizational Perspective

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Protocol

Strengthening the Capacity of Service Providers to Reduce the Impact of the COVID-19 Pandemic on African, Caribbean, and Black Communities: Protocol for the COVID-19 African, Caribbean, and Black Providers Project 2.0 Implementation and Evaluation

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Abstract

Background: The COVID-19 pandemic emerged as an unprecedented challenge for health care systems across the world, disproportionately impacting immigrant and racialized populations. Canadian African, Caribbean, and Black (ACB) communities represent some of the populations considered most vulnerable in terms of their susceptibility to health-related risks, receipt of adequate care, and chances of recovery.

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Objective: The COVID-19 ACB Providers Project 2.0 aims to strengthen the ability of health care providers to address this community's COVID-19–related health care needs. Informed by the COVID-19 ACB Providers Project 1.0, a mixed methods study that examined the COVID-19 pandemic's impact on African, Caribbean, and Black communities in Ontario (Ottawa and Toronto), this second study seeks to develop and implement educational programs in 5 key areas (modules) to strengthen the capacity of service providers (SPs) working with African, Caribbean, and Black populations. These modules (topics) include (1) the COVID-19 pandemic and its impacts on health, (2) social determinants of health and health inequities, (3) critical health literacy, (4) critical racial literacy, and (5) cultural competence and safety.

Methods: An implementation science approach is used to guide the development, implementation, and evaluation of the evidence-informed interventions. The intersectionality lens, socioecological model, and community-based participatory research frameworks are informing the research process. To ensure active stakeholder engagement, the project advisory committee includes 16 African, Caribbean, and Black community members, health providers, and partner agency representatives. Five modules have been developed: 2 web-based simulation games in collaboration with leading simulation experts and 3 nonsimulation modules. The analysis, design, development, implementation, evaluation instructional design method was used as a framework to design and develop the educational modules.

Results: The module development was completed in early 2024, and the training program was officially launched in April 2024 at the University of Ottawa. The synchronous format was delivered until November 2024, and the asynchronous format remained available until the end of May 2025. By January 2025, a total of 322 SPs from 33 organizations had completed training. The focus groups were held in November and December 2024 and surveys were administered between June 2024 and May 2025. Data cleaning will continue until September 2025, analysis is scheduled for September and October 2025, and findings are expected to be submitted for publication in November 2025.

Conclusions: This protocol outlines a scalable, community-informed intervention to build SP capacity in delivering equitable care to African, Caribbean, and Black communities. The findings will inform future health equity training and policy development across Canada and beyond. The results of this study will be disseminated in community workshops, web-based learning platforms, at academic conferences, and in peer-reviewed publications.

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KEYWORDS

COVID-19; education; health and social service providers; health equity; critical health literacy; critical racial literacy

Introduction

Background

The COVID-19 pandemic emerged as an unprecedented challenge for health care systems and has disproportionately affected immigrant and racialized populations globally [1-5]. Canadian African, Caribbean, and Black communities represent some of the populations considered most vulnerable, due to a combination of heightened susceptibility to infection, inadequate receipt of care, poorer recovery outcomes, and death [6,7]. Existing data show that the neighborhoods with the highest proportions (≥25%) of racialized groups (or visible minority) groups experienced a COVID-19 pandemic mortality rate twice as high as neighborhoods with the lowest proportions (<1%) of racialized populations [8].

Social determinants, including racism, income and employment insecurity, housing insecurity, and limited access to health care, are known to account for the disproportionate health risks and differential health outcomes experienced in African, Caribbean, and Black populations [9-13]. In the case of the COVID-19 pandemic, African, Caribbean, and Black individuals are overrepresented in risky frontline and essential jobs with a greater risk of exposure and less access to protections. Excess cases and deaths have been attributed to disproportionately high rates of comorbid conditions (eg, diabetes and hypertension) in African, Caribbean, and Black communities [14]. National surveys indicate that economic impacts have compounded these risks. Black Canadians reported economic vulnerability arising from the COVID-19 pandemic crisis, with 33.2% living in a household reporting difficulty to meet its basic financial commitments in the last 4 weeks [15]. This was almost twice as likely as non–visible minority Canadians (16.6%). The unemployment rate rose more sharply among Black Canadians, by 5.3 percentage points, compared to a 3.7 percentage-point increase among non–visible minority Canadians, which contributed to difficulties in fulfilling housing-related financial obligations [15]. These intersecting inequities reinforce the need for targeted and equity-oriented public health responses.

From a health systems perspective, the consequences of these inequities are far-reaching. The increased burden of the COVID-19 pandemic morbidity and mortality among African, Caribbean, and Black populations contributed not only to individual health harms but has also translated into greater challenges for health systems and for governments through loss of social capital, productive labor force, and erosion of cultural equity [16,17]. Evidence consistently suggests that "one size does not fit all" in terms of the response to public health disasters in populations considered vulnerable [18,19].

It is well documented that African, Caribbean, and Black communities experience multiple and intersecting barriers to accessing appropriate and responsive health services, from institutional discrimination, inadequate training of service

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providers (SPs), and lack of culturally responsive services in relevant languages to poor representation in health care leadership, research, and decision-making structures [20,21]. Services often fail to reflect the linguistic, cultural, and lived realities of the communities they aim to serve, and consequently, access is limited, distrust grows, and inequities deepen over time.

Numerous scholars have identified the urgent need to build capacity (eg, culturally responsive training) and reduce stigma and paternalism among health providers working with African, Caribbean, and Black communities [22-24]. Central to these recommendations is the widespread acknowledgment that African, Caribbean, and Black communities and scholars must not only be recipients of care but also be actively involved in all aspects of health system responses (eg, prevention, treatment, and outreach-related policy and practices) [24-26].

From 2020 to 2021, the COVID-19 African, Caribbean, and Black Providers Project (CAPP) 1.0 engaged African, Caribbean, and Black community members, health care providers, and system leaders to identify barriers to equitable health care during the pandemic [27]. CAPP 1.0 identified considerable knowledge and capacity gaps among health providers in terms of understanding of African, Caribbean, and Black -specific barriers, antiracism training, cultural responsiveness and safety, and sufficiency of tools to support equitable care. It further generated four priority areas for SPs to meet the needs of African, Caribbean, and Black communities: (1) transform the health system's capacity to deliver anti-racist care; (2) strengthen the African, Caribbean, and Black community's capacity for authentic participation in health policy, practice research, education, and leadership; (3) create programs and policies that foster disaggregated race-based data collection, governance, and develop strategic partnerships; and (4) create accountability measures for anti-racist healthcare for African, Caribbean and Black people within all levels of the healthcare system.

In response to the urgency of capacity building, the current phase, CAPP 2.0, directly builds on those findings and targets these priority areas by creating and evaluating web-based capacity-building interventions to address the key gaps from CAPP 1.0. The education sector has adopted and used webinars more extensively in the 21st century to create engaging learning resources, particularly with the onset of the COVID-19 pandemic [28]. The term "webinar" refers to communication over the internet between 2 or more participants using audio, video, and activities, such as polls and quizzes, with the possibility to allocate participants into breakout rooms to work together on a topic or solve a problem [29]. Webinars have been used both synchronously and asynchronously as engaging learning formats. In synchronous formats, learners participate together at a predefined time, while in asynchronous formats, they may engage in a webinar independently at any time. In a recent systematic review, Gegenfurtner and Ebner [30] found that synchronous webinars were slightly more effective than control conditions (web-based asynchronous learning management systems and offline face-to-face classroom instruction), but these differences were trivial in size. Moreover, little research to date has examined the implementation and impact of innovative web-based strategies to address professional capacity-building needs to serve African, Caribbean, and Black communities.

Objectives

The overarching aim of the CAPP 2.0 project is to accelerate the use of high-quality, real-time evidence (collected on the contextual vulnerability and challenges experienced by African, Caribbean, and Black communities) to codevelop, implement, and evaluate community-driven solutions that confront structural and systemic inequities in health care. To achieve this aim, the project is guided by two core goals: (1) to develop and implement tailored webinar-based training modules to strengthen provider capacity and responsiveness to African, Caribbean, and Black health needs and deliver culturally responsive and antiracist care and (2) to evaluate the uptake, engagement, and effectiveness of these interventions for improving provider capacity. For the purpose of this study, we use "service providers" as an umbrella term throughout the manuscript to refer collectively to health care professionals (including physicians, nurses, and allied health staff), students in training to become health professionals, public health professionals. professors, social workers, and staff members (eg, managers) from community-based organizations. To guide the design, delivery, and evaluation of the training modules, the CAPP 2.0 project draws on community-based participatory research (CBPR) principles [31] and established implementation science frameworks. It adopts an intersectionality lens [32] to account for the overlapping structural barriers that affect African, Caribbean, and Black health outcomes and is informed by the socioecological model (SEM) [33] which highlights the interplay between individual, interpersonal, community, organizational, and systemic factors that influence health access. The Consolidated Framework for Implementation Research (CFIR) provides further structure to assess how the intervention design, setting characteristics, and external policies influence implementation [34]. To support the overarching aim and project goals, the CAPP 2.0 project has four specific objectives: (1) engage African, Caribbean, and Black communities and key stakeholder groups in the codevelopment of community-driven strategies to reduce the burden in these communities during and after the pandemic; (2) develop and implement innovative evidence-based modular health educational interventions (ie, critical health and racial literacy modules) to address the gaps identified in CAPP 1.0; (3) assess the reach, uptake and effectiveness of the synchronous and asynchronous webinar formats to enhance health care SPs' ability to provide effective health care for African, Caribbean, and Black people; and (4) improve evidence-based communication among health stakeholder groups (ie, health planners, health providers, and African, Caribbean, and Black communities) to reduce COVID-19–related health inequities.

The flexible formats, context-specific and community-rooted training content are expected to promote SP engagement. Participating providers are expected to demonstrate increased knowledge of critical racial and health literacy principles, improved confidence in delivering culturally safe care, and a greater alignment between service delivery and the needs of African, Caribbean, and Black communities. Ultimately,

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effective webinar-based education that is codeveloped and grounded in the lived experiences of their communities has the potential to mitigate systemic barriers and push for health equity reforms.

Methods

Conceptual Frameworks

CBPR frameworks and an implementation science approach are being used to guide the development, implementation, and evaluation of the evidence-informed interventions to transform the health system's capacity to address structural inequities and anti-Black racism in health care. CBPR [31] is being used to involve African, Caribbean, and Black communities in the co-design and implementation of interventions, practices, and policy tools. Community members are to participate and take ownership of the process and cocreate innovative solutions that reflect the lived experiences of African, Caribbean, and Black communities, in partnership with other stakeholders and decision makers.

In addition, the intersectionality lens and SEM frameworks are informing the design and research process. Intersectionality is an analytical tool used in equity work to understand and interpret the complexity of the world around us [32]. It emphasizes that health issues are influenced by broader social factors and do not occur in isolation, but rather these factors intersect and mutually enhance their negative impacts on health outcomes [35]. In this project, it provides a critical lens to understand how overlapping social identities and systems of oppression contribute to the health inequities that the African, Caribbean, and Black population experiences. This lens informs all project stages and promotes reflexivity and equity-centered interpretation throughout the research process. SEM identifies a vast array of layered macro-, meso-, and microlevel factors [33] to consider when addressing health inequities, including COVID-19 infection and its impact among racialized populations. In this project, SEM is being operationalized to contextualize the multiple layers of influence (individual, interpersonal, community, organizational, and policy) and inform a more holistic intervention. The Analysis, Design, Development, Implementation, Evaluation instructional design model [36] helped translate these complex insights into actionable educational interventions and provides a practical and systematic model for testing and refining webinar modules responsive to community-identified needs.

Finally, the CFIR provides a comprehensive structure to assess multidimensional domains associated with effective implementation (ie, intervention characteristics, outer setting, inner setting, characteristics of individuals, and process) [34]. The focus of this project is on constructs of the outer setting, such as external policy and incentives, and constructs of the inner setting, such as climate and leadership. The CFIR framework is a good fit for CAPP 2.0 specifically given its extensive use in community-based programs and interventions as well as its capacity to tailor interventions according to the research objectives. A variety of tools are being developed for the evaluation, including website analytics, preintervention and postintervention surveys, and follow-up interviews with providers and agencies.

Together, these conceptual frameworks are being used synergistically to garner community involvement and participatory development, frame a more nuanced understanding of overlapping identities and structural inequities, develop and implement a multilevel and holistic intervention, and guide a rigorous evaluation with an explicit equity focus. In addition, this triangulation ensures that the intervention is more culturally relevant, contextually sensitive, practically feasible, and evaluable within complex health systems.

The Research Process

Overview

This 3-year research project is integrative and organized in phases. Phase 1 focuses on preplanning and module development—stakeholder engagement and knowledge mobilization tools development (year 1) to raise awareness among African, Caribbean, and Black people about the social determinants of COVID-19 pandemic vulnerabilities and to set the stage for the learning modules implementation and uptake; phase 2 involves innovative module development and implementation (year 2) for SPs' collective empowerment and capacity building to build requisite skills, abilities and critical perspectives for effective COVID-19 pandemic and health equity responses among African, Caribbean, and Black communities; and phase 3 features module implementation and evaluation as well as other knowledge mobilization activities (year 3) to mobilize providers, African, Caribbean, and Black people and other stakeholders in the collaborative development and implementation of evidence-informed programming, research and policy to address COVID-19–related health inequities in African, Caribbean, and Black communities.

Phase 1

To ensure active stakeholder engagement, a project advisory committee (PAC) has been formed, comprising 16 African, Caribbean, and Black community members, health providers, partner agency representatives, and other stakeholder groups. The PAC meets quarterly. The development of the web-based learning intervention was led by JE and assisted by the PAC and high-impact field-based interventions laboratory. The intervention consists of a series of five web-based educational modules for SPs aimed at (1) social determinants of health and health inequities, (2) the COVID-19 pandemic and its impacts on health, (3) critical health literacy, (4) critical racial literacy, and (5) cultural competency and safety. These themes were rigorously reviewed and prioritized through iterative consultations with the PAC and a stakeholder engagement event facilitated by the CO-CREATH Lab. The 5 themes were selected based on a comprehensive analysis of findings from the CAPP 1.0 project, which identified critical knowledge and practice gaps among SPs working with African, Caribbean, and Black communities. Specifically, quantitative and qualitative data from CAPP 1.0 revealed a lack of awareness and understanding of the barriers faced by African, Caribbean, and Black clients in relation to health equity, culturally responsive care, and the impacts of the COVID-19 pandemic. These themes were further

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validated and refined through consultations with the PAC and through a stakeholder engagement event involving African, Caribbean, and Black community members, researchers, SPs, and decision makers facilitated by the CO-CREATH Lab. Each theme is operationalized into individual modules with clearly defined learning objectives that directly target the identified provider competency gaps.

These modules are also grounded in current behavioral science principles and insights, such as formatting messages in clear and easy-to-understand language, using social media platforms commonly used by African, Caribbean, and Black communities, using compelling stories from the community, making educational events social, and using evidenced-informed messages delivered by trusted messengers, such as African, Caribbean, and Black community health professionals. The instructional design process was guided by the analysis, design, development, implementation, evaluation model [36] to systematically plan, test, and refine the modular context based on stakeholder feedback and implementation feasibility.

Each theme has been integrated into the educational modules using a combination of instructional strategies, including narrative-based learning, community-informed scenarios, and virtual simulation (VS) pedagogy. These instructional strategies were selected to support the intended learning outcomes in a manner that maximizes engagement, cultural relevance, and opportunities for critical reflection. For example, the Canadian Alliance of Nurse Educators using Simulation virtual experience templates developed for CAPP 2.0 include character sketches and real-life scenarios drawn from CAPP 1.0 participant quotations. This enabled each module to reflect the lived experiences and contextual realities of African, Caribbean, and Black communities. An e-learning expert and instructional design consultants were contracted to guide the development of the nonsimulation modules for themes 1 and 2.

The other 3 modules for themes 3, 4, and 5 are VS educational modules. VS educational modules are innovative and accessible resources that provide effective instruction and critical thinking in health care education, comparable with or exceeding outcomes associated with other simulation modalities or teaching methods [37-39]. The benefits of VS pedagogy were especially highlighted during the COVID-19 pandemic when most health care education had to shift to virtual formats. Learners report that VS is an engaging and enjoyable educational strategy that is easy to use and contributes to their applied learning [40]. Additional benefits include the ability to place all learners in decision-making roles, to increase accessibility to larger groups of learners, to provide instant and evidence-based feedback, to increase flexibility in self-pacing, and to have the potential to create a more psychologically safe learning environment [41]. Authors ML-F and JT are VS experts who supported the creation of these simulation modules using the Canadian Alliance of Nurse Educators using Simulation VS design process [42]. The contracted e-learning specialist oversaw the development of an accessible website to host the 5 learning modules.

Phase 2

Two different (synchronous and asynchronous) formats have been used and are being tested for the implementation of capacity-building activities among SPs. The first format (synchronous) primarily targets health providers such as physicians and nurses in 5 prespecified practice settings (ie, Ottawa Public Health, Somerset West community health center, Southeast Ottawa community health center, AIDS Committee of Ottawa, and the African Caribbean Council on HIV in Ontario). In each setting, the research team is working with local health partners to engage and deliver training to at least 75% of agency staff through internal communications, staff meetings, and direct outreach by organizational leaders.

SPs more broadly are also targeted to engage in the asynchronous web-based modules housed in a website developed for this project. Recruitment has been initiated through professional networks, health care institutions, and partner organizations across Ontario. Promotional materials, such as flyers, email invitations, and social media posts were distributed to reach a wide range of SPs, including physicians, nurses, allied health professionals, and students. The website and web-based modules have been primarily promoted to health care facilities (eg, primary care, hospitals, long-term care, and community organizations) and provider groups (eg, physicians, nurses, and allied health staff). The aim was to reach a minimum of 100 individual SPs with our broader outreach activities. This target sample size was set based on the reach experiences from CAPP 1.0, using similar recruitment pathways. In addition, it reflects a balance of recruitment feasibility (limitations of provider time and capacity), diversity, and representation from organizations across primary care, public health, and community-based services in Ontario. This minimum target would enable us to compare implementation experiences, engagement patterns (synchronous vs asynchronous), and learning outcomes across sectors and learning formats, while also supporting adequate variation for subgroup analysis (eg, by profession, delivery format, or organizational setting). Figure 1 illustrates the logic model which is being used to track project indicators throughout.

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Figure 1. COVID-19 African, Caribbean, and Black Providers Project 2 logic model. ACB: African, Caribbean, and Black.

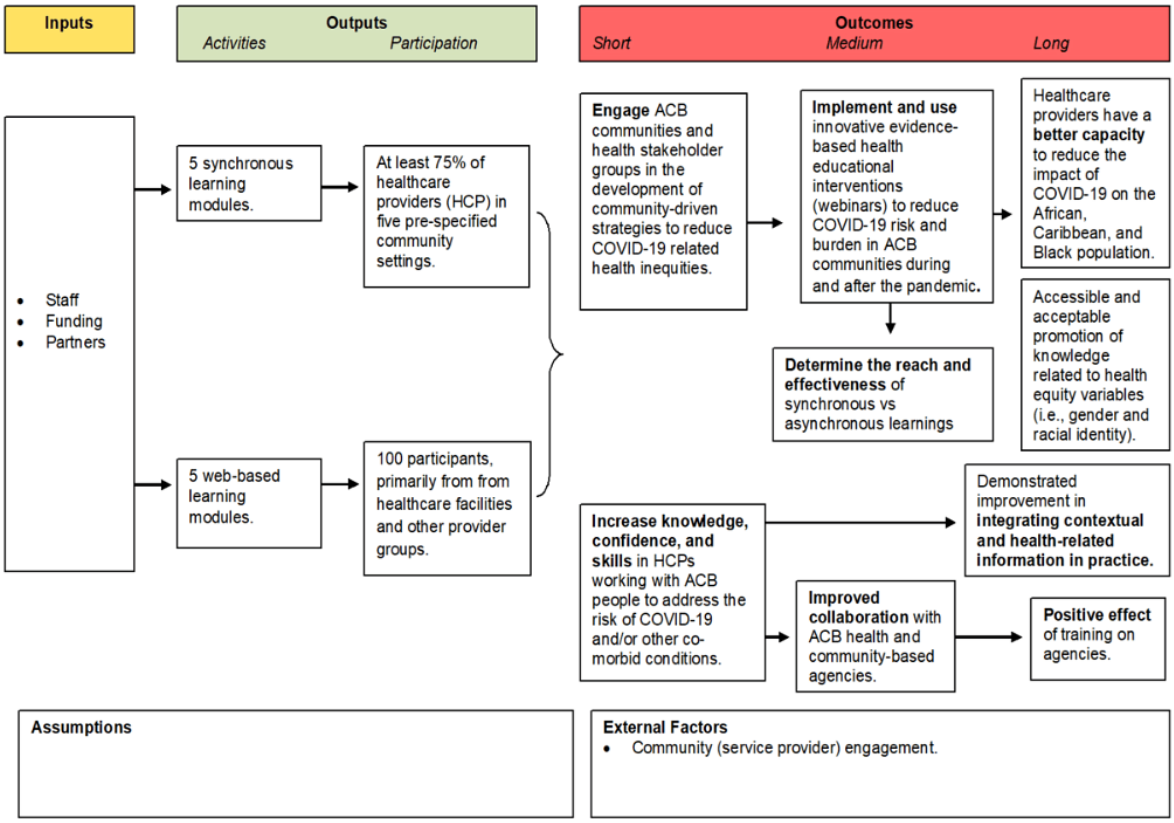

Phase 3

A comprehensive mixed methods evaluation is being continuously conducted to assess the project's activities and impacts, including implementation outputs, short-term and long-term outcomes (as seen in the logic model in Figure 1). The preprogram and postprogram module surveys are linked to each module's learning objectives and must be completed by all participants to track changes in knowledge, confidence, and the perceived ability to deliver culturally responsive and equity-focused care to African, Caribbean, and Black people. All recruited participants have to complete the pretraining survey before participating in the program. After completing the program, they are directed to the posttraining survey (on Survey Monkey).

Participants recruited for the postprogram focus group discussions (FGDs) are purposively sampled from among those who complete the training modules. Invitations are sent out by email for representations across roles, including primarily health care professionals. Participation is voluntary, and informed consent is obtained before participation. The focus groups are being used to evaluate the reach, implementation challenges or successes, and effectiveness of the training modules. Survey data will be analyzed using descriptive statistics, including measures of central tendency (eg, mean) and variability (eg, range), to assess program reach, participant satisfaction, and self-reported changes in knowledge and capacity. Website analytics will also be examined using descriptive statistics to examine metrics, such as the number of users, time spent per module, and completion rates. All quantitative analyses will be conducted using statistical software, such as SPSS (IBM Corp) or Microsoft Excel. FGD recordings will be transcribed and coded inductively using Microsoft Excel or NVivo (Lumivero). Thematic analysis will be conducted on the FGD data. Multiple members of the research team will be involved in the generation, review, and validation of codes and themes. The final themes will be refined collaboratively for better alignment with the study's theoretical frameworks and objectives, and to provide a comprehensive understanding of participants' training experiences and feedback.

The implementation research and evaluation is being informed by CFIR, with consideration of its 5 domains: intervention characteristics, outer setting, inner setting, characteristics of the individuals involved, and the process of implementation [34]. Furthermore, this project focuses on the characteristics of the inner and outer settings that influence implementation (eg, structural characteristics, policies, and implementation climate). Specifically, this project is interested in learning whether SPs who participate in setting-specific training using the web-based modules are more likely to benefit from the training and engage in quality improvement and system transformation initiatives in their agencies than SPs who complete the web-based modules independently.

Together, the preintervention and postintervention survey items, focus group topics, completion metrics, and the CFIR-guided evaluation comprise an integrated evaluation framework to assess both instructional effectiveness and implementation fidelity in relation to each module's objectives. This integrated evaluation approach assesses not only learning outcomes but also the utility and sustainability of the intervention within real-world health care settings. The expected short-term outcome for SPs includes increased knowledge, confidence, and skills

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in working with African, Caribbean, and Black people to address the risk of COVID-19 infection and other comorbid conditions. Long-term outcomes include a demonstrated improvement in integrating contextual and health-related information in practice, a positive effect of training on agencies, and improved collaboration with African, Caribbean, and Black health and community-based agencies.

Rigor and Dissemination

To establish the trustworthiness and scientific rigor of this research, the research process will be guided by the framework for assessing the quality of qualitative research postulated by Lincoln and Guba [42]; that is, credibility, transferability, confirmability, and dependability. Credibility refers to the confidence readers have in the analytical and interpretive processes and findings. In this research, transparent analytical steps are identified and informed by established qualitative research principles. Transcripts will be carefully verified and checked. In the analysis process, attention will be paid to misrepresentation of the evaluation component, FGD data. We will interrogate the data until data saturation is reached. Furthermore, the research team is trained in the conduct of ethical and sensitive research with this study populations. Transferability is the extent to which the study results might be relevant to similar populations that have similar characteristics. Transferability is dependent on "thick description," which in this work will be the detailed and precise narrative that will be constructed following the comprehensive analysis of the evaluation data. The narrative description will provide sufficient detail for others to make a judgment on the quality of the results. Confirmability will be achieved by reflexive team and PAC meetings. Dependability will be achieved by the establishment of a clear audit trail and accurate documentation of the research processes and procedures, including the analytical process, field notes, digital recordings, and transcripts.

Ethical Considerations

The ethics approval was obtained (July 2023) from the Research Ethics Boards of the University of Ottawa (H-01-23-8069), and operational site permission will be obtained where necessary before commencing research.

Voluntary written informed consent will be obtained from all participants. As part of the consenting process, participants will be assured that they do not have to answer every demographic or FGD question, they can choose to be recorded on audio (or not), and they can withdraw at any time. They will especially be informed that their nonconsent will not affect their employment conditions.

The principles of confidentiality and anonymity will be observed at all times, including during data collection, analysis, and in the storage of research materials. Research materials will be securely stored on password-protected digital platforms or in locked physical locations. If instances of distress are encountered, participants will be offered information about counseling support services. Participants will receive a gift card (CAD $25 or $30 [US $18 or $22]) compensation for their time and contributions. The posttraining survey and FGD will be performed on a secured digital platform (SurveyMonkey) or in-person location at the University of Ottawa or a partner agency.

No identifiable images or personal data will be included in the manuscript or supplementary materials. If any such materials are used in future dissemination, explicit written consent will be obtained and documented.

Results

The CAPP 2.0 training initiative was developed by the CO-CREATH Lab between 2023 and early 2024 as part of the CAPP 2.0 project. The training program officially launched in April 2024 at the University of Ottawa. The asynchronous sessions were delivered until November 2024, while the asynchronous training was available until the end of May 2025. So far, 322 SPs from 33 organizations have participated in the training program. Mixed methods evaluations involving surveys and FGDs are underway to explore participants' feedback, experiences, perceptions, and self-reported changes in knowledge and capacity of critical areas. Specifically, four focus groups were conducted in November and December 2024, while the surveys were administered between June 2024 and May 2025. Cleaning of the data collected since January 2025 will continue in September 2025, and analysis of our mixed-method data will be completed in September and October 2025. The findings from the program evaluation are expected to be submitted for publication in November 2025.

Discussion

Anticipated Findings

This protocol outlines the plans to develop, implement, and evaluate CAPP 2.0, designed to strengthen the capacity of SPs to deliver equitable care to African, Caribbean, and Black communities in Ontario during and beyond the COVID-19 pandemic. The anticipated outcomes include an increase in SP knowledge, confidence, and skills to address barriers to health care access, particularly through the use of culturally responsive, community-informed web-based learning modules. Accessible resources and practice and policy tools will be developed to enable health policy makers and planners throughout the province to meet the health care needs of African, Caribbean, and Black communities currently and after the pandemic. The widespread impact of the COVID-19 pandemic demands that previously considered local concerns now become global concerns. Provincial collaboration, such as the one in this project, will bring different research perspectives to bear on the issue of the COVID-19 pandemic and health service provision from the perspective of African, Caribbean, and Black people in Ontario. Specifically, this project will promote and strengthen knowledge exchange and links to providers, knowledge users, and researchers across Ontario, with the potential for national scale-up. It will facilitate exposure to innovative ideas and approaches. It will provide opportunities for redesigning and identifying promising models for SP capacity building, informed by critical and diverse perspectives. While there are no quick solutions, sustained gains in providers' COVID-19–related health equity capacity, such as the one that would be provided

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by this project, will successfully harness health care providers who can address critical postpandemic health priorities.

Moreover, the co-designed, community-involved, and evidence-based model developed through this initiative will provide a scalable and adaptable model or framework to help address health inequities. The model crucially centers the lived experiences of African, Caribbean, and Black communities and integrates VS pedagogy, and in turn informs future interventions across Canada and globally, especially in contexts where racialized populations face systemic and structural barriers to equitable health care. The findings and tools generated through this project can potentially influence broader health policy, inform culturally responsive training initiatives and standards, and contribute to public health efforts to promote health equity.

Strengths and Limitations

Strengths of this protocol include its grounding in CBPR, intersectionality, its use of implementation science frameworks, VS pedagogy, and its emphasis on cultural competency and safety. The co-designed model centers the lived experiences of African, Caribbean, and Black communities and produces provider training tools and potential practice and policy-informing resources that can support training and health equity reform across sectors. A limitation is that the evolving nature of the pandemic and health system priorities may affect module uptake or relevance over time. While the uptake may be affected by the pandemic priorities, the modular design and flexible delivery formats increase its potential for relevance, scalability, and sustainability.

Conclusions

The tools, approaches, and findings from CAPP 2.0 may inform culturally responsive training policies and contribute to broader public health and systems change efforts that intend to combat structural and systemic inequities. Consequently, the CAPP 2.0 initiative offers a scalable and adaptable model that could be implemented across Canada and potentially adapted globally in settings where racialized populations face systemic and structural barriers to care. In terms of future directions, there is a need to adapt the model for other marginalized populations, as well as longitudinal assessments of impacts on provider behavior and patient outcomes. The dissemination plan includes community workshops, academic presentations, peer-reviewed publications, and an open-access web-based learning platform for broad accessibility and impact.

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Authors' Contributions

All authors contributed to the study and drafted the manuscript. JE conceived the study and drafted the proposal. HL, LB, SY, CD, EBE, BG, WA, JT, ML-F, JR, and RT assisted with refining the research design. ON, BK, WT, HI, RE, J Kiirya, SA, KK, and J Kemei reviewed the proposal and assisted with the strategic assembly of team composition and community partnerships. JE and AWF led the revisions to the manuscript. Graduate students and other trainees assisted with proposal review, organization, editing and referencing, and overall formatting. All team members are authors, and they all critically reviewed and revised the manuscript. All authors read and approved the final manuscript.

Conflicts of Interest

JT and ML-F are copresidents of the Canadian Alliance of Nurse Educators using Simulation (CAN-Sim). No other conflicts of interest are declared.

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Abbreviations

CAPP: COVID-19 African, Caribbean, and Black Providers Project
CBPR: community-based participatory research
CFIR: Consolidated Framework for Implementation Research
FGD: focus group discussion
PAC: project advisory committee
SEM: socioecological model
SP: service provider
VS: virtual simulation

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Protocol

Use of Indigenous-Based Methodologies to Enhance the Understanding of Local Context in Ugandan Communities: Protocol for a Mixed Methods Study

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Abstract

Background: With many socially disadvantaged populations experiencing a higher level of illness than the general population, health research has begun to recognize the impact of social determinants on health outcomes. Community-based research has increasingly been used to understand the complexities of the local context. However, given the number of interdependent factors influencing individual well-being, no single methodology can explore this level of complexity alone. To put context into perspective, research processes need to shift from the sole use of Western methodologies and, instead, incorporate collaborative methods from nontraditional research. Specifically, Indigenous methodologies have been developed to better understand the complexity of context within multiple worldviews, but current studies have failed to apply these approaches within other cultural settings.

Objective: This mixed methods study will use Western and Indigenous methodologies to adapt a digital health program for remote communities in Uganda.

Methods: Using the principles of community-based research and user-centered design, a 4-phase mixed methods study will be conducted. The Indigenous method of 2-eyed seeing will be used to promote a reflexive engagement strategy throughout all study phases. Phase 1 will focus on partnership building to codevelop the project priorities and study design. Phase 2 will involve a needs assessment to elicit a context-focused understanding of the local clinic and community environment. Phase 3 will involve a series of system adaptations to co-design the program. Phase 4 will consist of a community-based field study to evaluate the usability and cultural relevance of the adapted program.

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Results: This study was approved by the Makerere University School of Medicine Research and Ethics Committee (Mak-SOMREC-2021-63) and the University Health Network Research Ethics Board (20-6022). This protocol provides a novel strategy leveraging a range of community-based methods to ensure that the contextual significance of each community's challenges is reflected in the design of the Medly Uganda program. Partnership building was initiated in June 2019, and the first stage of data collection in phase 2 began in January 2021. At the time of manuscript submission, phases 1 to 3 have been completed. Phase 4 data analysis is ongoing and expected to be completed in October 2025.

Conclusions: Integrating the community's local knowledge into the design of the Medly Uganda program will lead to the development of meaningful interventions that improve health outcomes.

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KEYWORDS

community-based research; digital health; heart failure; participatory research; user-centered design

Introduction

Over the past few decades, health research has begun to recognize the influential impact of various social determinants on individual health and well-being [1,2]. Specific contextual environments have been associated with poorer population health outcomes simply due to the conditions individuals are born into [1,3]. With a variance in social, political, and environmental settings, a community's well-being is often shaped through its accessibility to basic human necessities such as housing, food, water, education, safety, and employment [2-4]. Thus, many underserved, low-income, and socially disadvantaged populations face a significantly higher level of illness due to complex factors related to poverty, social stratification, and overall disparities in their social determinants of health [1,2,4]. To better support the unique needs of these communities, understanding the state of their contextual environment and the underlying contributors influencing their health outcomes is pivotal.

With several evolving and interdependent factors contributing to the disparities in a population's social determinants of health, many studies recognize that no single methodology can explore or understand this level of complexity alone [3,5]. Instead, to improve a health service or develop a care program in reflection of these contextual factors, using a combination of collaborative approaches will lead to the development of a more effective research strategy. Community-based participatory research (CBPR) is being increasingly used to support the production of knowledge in a manner that places local voices at the center of a partnership to promote meaningful change [5-7]. The lived experiences and unique perspectives provided by community members allow for a deeper sense of context to be explored, but it is important to recognize that, as each individual comes from certain positionalities, they express different worldviews [3,5,8]. The definition of health and healing can vary within different cultural settings, whereby the reality of specific circumstances can even be experienced and shared by individuals in different ways [5]. Thus, to allow for multiple perspectives to be better recognized for their own value, there is a need for research processes to shift from the predominant focus on Western biomedicine and, instead, recognize the value and strengths of different cultural worldviews.

Compared to Western notions of dichotomous thinking and individualism, many Indigenous knowledge frameworks embrace the process of reflexivity, collaboration, and interconnectedness to better understand multiple worldviews [9,10]. These frameworks recognize the importance of reflecting on one's positionality and personal motivations to conduct research, to the extent that the intention and process of data collection are held at equal importance to that of the knowledge acquired [9,11]. Through this paradigm, CBPR is able to set the foundation for understanding community context, but Indigenous methodologies are able to serve as the vehicle to translate the principles of partnership and self-reflection into practice [5,9]. Given that the term *Indigenous* refers to any population or group of people originating from a specific region before colonization and modern geographical borders were defined, we recognize that different Indigenous methodologies have been developed in reflection of a community's cultural values [10]. Notably, across Canada and Australia, Indigenous researchers or knowledge keepers have conducted decades of extensive evaluative research to develop frameworks that uphold the strengths of cultural knowledge within the process of traditional research practice [5,10,11]. While Indigenous and non-Indigenous communities outside Canada and Australia may face varying challenges within their local environment, the integrative nature of these methods allows for the exploration of a deeper understanding of community context [9,11]. Other participatory methods may involve community members in data collection, but Indigenous knowledge frameworks provide a deeper outlook on the knowledge gathered and how it relates to different dimensions of well-being beyond just one's physical health. Despite these benefits, current studies have failed to apply these methods within other cultural settings, and the course of pilot projects failing to meet local community needs continues [9,11]. To address this gap and better understand the contextual challenges faced by underserved communities, this protocol paper outlines a mixed methods study using both Western and Indigenous methodologies to adapt a digital health program for remote communities in Uganda. We anticipate that the use of community knowledge and clinical expertise will lead to the development of a more impactful and culturally relevant digital health program that will improve care outcomes.

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Methods

Medly Uganda: A Digital Health Program for Remote Heart Failure Care

In Uganda, a substantial level of health disparities has been reported as many communities currently live below the poverty line [4]. With the burden of noncommunicable diseases continuing to grow, the interplay between poverty and health care access has been found to be one of the largest contributors to poorer health outcomes [4,12]. Specifically, community risk factors related to food insecurity, unemployment, and poorly resourced health care systems have led many patients living with cardiovascular diseases such as heart failure (HF) to present advanced stages of the disease early in their diagnosis [12-14]. Despite the severity of the disease, HF is largely treatable or controllable if patients are given the tools to support their ability to self-care [15-17]. However, with the lack of health resources available in Uganda, there is a need for affordable strategies to be introduced for the benefits of self-care to be realized [14,18].

Given the widespread penetration of mobile phones, digital health has emerged as a unique opportunity to assist populations with limited resources [19,20]. By leveraging the use of ubiquitous technologies such as mobile phones, digital health interventions are able to provide evidence-based, individualized care support (ie, education, lifestyle reminders, and decision support) directly to patients [19-21]. The Uganda National Panel Survey of 2019 to 2020 estimated that approximately 74% of all households owned a mobile phone; thus, digital health can serve as a low-cost option to provide clinical expertise and remote care support [22-24]. Recognizing the benefits of digital health, in 2016, the Uganda Heart Institute (UHI), the University Health Network (UHN), and Yale University collaborated to adapt a mobile phone–based app for HF self-care developed and tested in Canada for the Ugandan setting [25]. To guide the adaptation of the mobile phone–based program, known as Medly Uganda, a mixed methods study including 101 patient surveys and a series of in-depth patient, caregiver, and clinician interviews was conducted [25]. Building on this work, a prospective cohort study was recently conducted at the UHI in Kampala, Uganda, to evaluate the effectiveness of the Medly Uganda program on patient outcomes (ClinicalTrials.gov identifier NCT04426630) [26]. By generating tailored self-care advice based on patient-centered symptoms and providing remote nursing support, the Medly Uganda program was able to demonstrate improvements in patient self-care and health-related quality of life with respect to HF [26].

Research Aim

Despite the positive findings of the aforementioned Medly Uganda pilot study, it is important to recognize that patients in this study had the financial resources to travel to the UHI or the benefit of residing in the capital city, where specialized expertise and clinical resources are more readily available [12,13]. With approximately 84% of Ugandans residing in rural communities, rural access to health care remains a challenge. Urban bias has led many of the poorest communities with the highest health care needs to receive the least care support [12,13]. Given these conditions, the Medly Uganda program has the potential to provide greater benefits for communities residing in rural areas with limited access to care, but the unique needs of each community would need to be reflected in the program's design. To facilitate this aim, this mixed methods study will work in partnership with remote clinics in Uganda to identify the cultural and service-level requirements to adapt the Medly Uganda program.

Study Design

The principles of CBPR and user-centered design (UCD) will be used to conduct a 4-phase mixed methods study for the remote clinic adaptation of the Medly Uganda program [22,27]. In many digital health–focused studies, researchers have often arrived in communities with pre-established research agendas without understanding the drivers or barriers leading to their health inequities [24,27]. To better understand the local context and empower the local Ugandan voice, a series of Indigenous-based methodologies originating in Canada and Australia will also be used to promote a reflexive community engagement strategy throughout all stages of the study. Specifically, the "Nothing about us without us" tenet, focused on partnership, mutual learning, and informed co-design, will be used as the theoretical paradigm for this study [28].

To initiate the community-based adaptation of the Medly Uganda program, phase 1 of this study will be centered on partnership building to codevelop the project priorities, study design, and methods for data collection and analysis. Phase 2 involves the conduct of a needs assessment with patients and health care providers to elicit a context-focused understanding of the local clinic and community environment, as well as the cultural and service-level needs to adapt the program. On the basis of the feedback from phases 1 and 2, phase 3 will involve an iterative series of system adaptations to co-design the Medly Uganda program to meet the local needs highlighted in phase 1. Finally, to evaluate the changes to the adapted system, phase 4 will consist of a community-based field study to evaluate the usability and cultural relevance of the adapted tool.

Phase 1: Partnership Building

Overview

As part of the Rheumatic Heart Disease Research Collaborative, the UHI currently works with 4 clinics in the central, western, and northern regions of Uganda (ie, Lubowa, Mbarara, Gulu, and Lira) [29]. On the basis of guidance from UHI stakeholders in Kampala, community outreach to the northern clinics in Lira and Gulu will first be initiated as a greater need for care support was expressed by their local teams. To ensure that respectful engagement strategies are used throughout the partnership-building process, the Intervention and Research Readiness Engagement and Assessment of Community Health Care (I-RREACH) tool will be used [22]. The I-RREACH tool, developed with Indigenous communities in Canada, is a community-based engagement and assessment resource comprising (1) Indigenous participatory consensus cycles, (2) a community profile tool, (3) a key informant interview guide, (4) a focus group guide, and (5) a participant evaluation survey to support the implementation of interventions in low-resource environments [22]. Various components of the I-RREACH tool

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will be used throughout this study to ensure that the cultural and lived experiences of the community are guiding the adaptation of the Medly Uganda program.

To initiate the partnership-building phase, a series of engagement sessions with each clinic's (ie, in Gulu and Lira) key clinical (ie, nurses, administrators, and clinicians) and community (ie, village health teams [VHTs], parish coordinators, and community leaders) stakeholders will be conducted using the I-RREACH tool's participatory consensus cycles [22]. Each stakeholder will be asked to participate in a minimum of 3 engagement sessions to help codevelop the project priorities and overall study approach. This process will consist of a negotiation built on trust, honesty, and reciprocity between stakeholders. To identify the participants for the consensus cycles, this study will work collaboratively with the lead research nurse from each clinic to leverage their guidance on the appropriate clinical and community representatives.

Cycle 1: Initiation

The first engagement session will serve as an introductory discussion to explore each community's current care priorities, as well as the local perspective regarding the proposed research approach. The study team will begin the engagement session by presenting their skills and interests regarding collaboration. The stakeholders will be informed that, despite the study team's given skills and interests, the study objectives and program adaptations will be determined by what the clinic and community set as a priority. A guided discussion with the clinic and community stakeholders will then commence to broadly explore and identify the scope of the challenges present. To elicit a rich dialogue based on previous research evidence, we have previously completed two scoping reviews investigating (1) the use of digital interventions in low-resource settings and (2) the various community engagement strategies to co-design health interventions [10,24]. The findings of these reviews will be discussed in relation to the stakeholders' lived experience to ensure that the topics are explored in a manner reflecting the local community conditions. At the end of the engagement session, participants will complete the adapted I-RREACH clinic profile community demographic survey. The study team will also summarize the dialogue exchanged for the stakeholders to further review, discuss, and modify.

Cycle 2: Validation

The second engagement session will use the process of member checking, also known as respondent validation, to confirm each stakeholder's perspective regarding the proposed research approach. To facilitate this aim, a summary of the program objectives based on the feedback from cycle 1 will be provided to all stakeholders during an in-person community site visit. This will allow the study team to formally collect each stakeholder's views regarding whether the program objectives reflect their own beliefs and priorities. If a mutual agreement regarding the study objectives is not achieved by the end of cycle 2, additional engagement sessions will be held for further collaborative discussion.

Cycle 3: Finalization

The third engagement session will serve as the final member checking to validate the study's objectives and overall research approach. A summarized report of the previous engagement sessions will be provided to each stakeholder, where they will subsequently be asked to provide written feedback on their agreement with the outlined study objectives. Stakeholders will also be asked to complete a questionnaire to confirm their level of involvement within the study (ie, data collection, data analysis, knowledge translation, and advisory), as well as to provide their suggestions for some of the practical aspects of the study regarding the recruitment strategy, interview location, study start date, and community outreach.

Phase 2: Engagement and Needs Assessment

Study Procedures

Following the approval of the study approach and project objectives by the clinic and community stakeholders, the study team will conduct an iterative needs assessment with a convenience sample of patients with HF, clinicians, and VHTs at each clinic. On the basis of community partner guidance regarding patient availability and staff workflows, we aim to recruit a total of 15 patients, 10 clinicians, and 5 VHTs to participate from each of the clinics in Lira and Gulu. At the beginning of the session, participants will be given an overview of the study objectives, as well as the opportunity to ask questions before providing written informed consent. With the support of each clinic's lead nurse, we will provide participants with the option to conduct the session in English or their local language (ie, Acholi, Luo, Runyankole, and Langi). Once written informed consent is obtained, a series of yarning-style semistructured interviews will be conducted to discuss each participant's perceptions of the contextual influencers affecting HF outcomes and the cultural and service-level needs to adapt the Medly Uganda program. The process of yarning allows interview discussion guides to move away from directed questions and more toward relationship building through the exchange of real stories. By using the Indigenous method of yarning, participants will be able to share their stories and lived experiences in a more conversational approach that embraces different cultural values [30,31]. This study will work with clinic partners to codevelop the interview guide and integrate the yarning style based on relationship-building strategies used within Ugandan culture. For example, the use of the radio for information gathering is often adopted, as well as strong family ties for caregiver support. Participants will also be asked to complete a postinterview evaluation survey and a demographic survey consisting of questions regarding their lifestyle, access to care, community support, medication availability, cell phone access, and disease conditions. Using the I-RREACH tool's interview guide, participant evaluation survey, and community profile sheet, all data collection instruments will be codeveloped with the community's core stakeholders to ensure that the questions are both relevant and appropriate.

Recruitment

The study team will work in partnership with the local clinic and community stakeholders to initiate a recruitment strategy

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at each site. This may include the use of posters, community outreach initiatives, clinic referral, or self-referral. With support and leadership from the local clinic team, we will invite clinicians and VHTs for participation through both verbal and written (ie, email and posters) invitations. Individuals who express interest in joining the study will be connected with a member of the study team through a phone call. The study team will then provide the clinician or VHT with information regarding the study procedures and will offer them the opportunity to schedule a time for an in-person interview. To optimize inclusivity and the diversity of the participants, we will aim to recruit individuals of varying genders, ages, and socioeconomic statuses.

Patient recruitment will follow a similar procedure, where the local clinic and community leadership will help spearhead the recruitment of eligible patients from each site. Eligible patients interested in the study will be connected with a member of the study team to review the various study procedures, and they will then be asked whether they would like to participate in the interview or survey. Once written informed consent is obtained from each patient, interviews will be conducted in a private room at each clinic. All participants who complete phase 1 will be asked to participate in the next study phases, but this will not be a requirement.

The participant inclusion criteria are presented in Textbox 1.

Textbox 1. Inclusion criteria.

Health care providers

- Physicians or nurses working at a Lira or Gulu clinic

Village health teams (VHTs)

- VHTs or community health workers providing care support within Lira or Gulu communities

Patients

- Aged ≥18 years
- Receipt of care at a Lira or Gulu clinic
- Confirmed heart failure diagnosis (ie, medical report or other supporting information)
- Ability to provide informed consent

Data Analysis

All interviews will be audio recorded, deidentified, and transcribed verbatim. Interviews conducted in local languages will be translated into English, and the resultant translation will be reviewed by a local staff member from each site to confirm its accuracy. Interview transcripts will be analyzed using conventional content analysis and the Indigenous method of *2-eyed seeing* developed by Mi'kmaq Elder Albert Marshall [32]. The process of *2-eyed seeing* is defined as a metaphor for negotiating between 2 cultures, where one eye is grounded in Indigenous (in this case, Ugandan) knowledge, whereas the other eye is grounded in Westernized knowledge to allow multiple perspectives to be better recognized for their own value [32]. To support the application of this method, all transcripts will be analyzed by 1 member of the UHN team and 1 member of the local clinic team, where each researcher will also use the memoing technique to document their reflective notes [33]. Reflective notes will then be shared between the UHN and local clinic team member during each analytic discussion meeting to optimize the sharing of diverse worldviews. Each team member will be given the opportunity to reflect on their agreement with or disapproval of the interpreted findings. Discrepancies regarding data interpretation will be shared with the local clinic team lead for further contextual analysis. Following this, both researchers will use the "value-adding" approach by Eakin and Gladstone [34] to further explore the analytic interpretation of the thematic findings in relation to the survey data [30].

Phase 3: Design and System Adaptation

Using both the qualitative and quantitative data from phase 2, a set of system design requirements will be codeveloped with each site to guide the community-specific adaptation of the Medly Uganda program. In accordance with the principles of UCD and community-based research, system adaptations will take place over a series of iterations to allow for feedback on and refinement to the prototype [22,35]. The study team will set weekly co-design meetings via Zoom (Zoom Video Communications) with each site to review the summarized data from phase 2, as well as to discuss the findings in relation to the proposed system adaptations. This study recognizes that stakeholders may prefer to provide feedback through other modes of engagement, such as focus groups, community-based workshops, or individual interviews. Thus, using the stakeholder guidance from phase 1, the study team will work collaboratively with the lead nurses at each site to establish the appropriate mode to conduct the co-design meetings and incorporate community feedback. At the end of each meeting, stakeholders will be asked to complete the I-RREACH tool's participant evaluation survey to ensure that their feedback has been suitably obtained.

This phase will also integrate the method of *2-eyed seeing* for the development of the system design requirements [32]. Specifically, during the first co-design meeting, all stakeholders will be given the opportunity to engage in a leadership role to summarize the core research findings into a series of program features. These design features will be reviewed at the subsequent stakeholder co-design meetings for discussion. This

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study aims to have at least one representative from the community be involved in reviewing each iteration alongside the UHN team member. Co-design meetings will be held until a mutual agreement regarding the program design requirements is reached between stakeholders.

Phase 4: System Validation and Evaluation

Study Procedures

Following the approval of the program adaptations, a convenience sample of patients, clinicians, and VHTs will be invited to participate in a community-based field study to evaluate the system changes. Similar to phase 2, we aim to recruit a total of 15 patients, 10 clinicians, and 5 VHTs to participate from each of the clinics in Lira and Gulu. Using the principles from systems design and community-based research, a combined cognitive walk-through and human-technology ladder–informed interview will be conducted to evaluate both the usability and cultural relevance of the adapted program [3,36,37]. The human-technology ladder provides a framework to allow for a better understanding of how individuals engage with technology across physical, psychological, team, organizational, and political dimensions. This can include hand-eye coordination, memory, team interactions, workflows, or societal implications. Through the cognitive walk-through, participants will be asked to complete a series of task scenarios (ie, symptom reporting, medication use, nurse support, and community outreach) on a provided mobile phone. The actions and responses to the system tasks will be reviewed by the study team to allow for a goal-focused evaluation of the Medly Uganda system. All task scenarios will be codeveloped with the community and clinic stakeholders. Following the cognitive walk-through, a semistructured interview will be conducted to allow for a multilayered evaluation of the program's utility, usability, and applicability. The 5 levels of the human-technology ladder will be used within the interview guide as this framework recognizes the importance of understanding how various human factors influence individual health behaviors [38-40]. At the end of the interview, participants will be asked to complete the System Usability Scale and the I-RREACH participant evaluation survey to evaluate the usability of the system and the appropriateness of the session.

Recruitment

All participants from the previous phases will be invited for the system validation and evaluation. Similar to phase 2, the study team will work in partnership with each community's stakeholders to initiate the recruitment strategy (eg, posters, community outreach, and clinic or self-referral). Clinicians and VHTs will be invited for participation through both verbal and written (ie, email and posters) invitations. Individuals who express interest in joining the study will be connected with a member of the study team through a phone call. A member of the study team will then provide the clinician or VHT with an overview regarding the study procedures and will seek to schedule a time for an in-person session. Using the guidance from the clinic and community stakeholders, we will recruit patients through clinician and VHT referrals and community outreach (ie, posters and a radio talk show). Eligible patients interested in the study will be connected with a member of the study team to review the study procedures and subsequently schedule a session date. Once written informed consent is obtained from the participants, each session will be held in a private room at the clinic. This study phase will use the same eligibility criteria as those for phase 2 regarding participant recruitment.

Data Analysis

All deidentified audio recordings will be transcribed verbatim for thematic analysis. Interviews conducted in the local languages will be translated into English, and the resultant translation will be reviewed by a local staff member from each site to confirm its accuracy. Similar to phase 2, each transcript will be analyzed by 1 member of the UHN team and 1 member of the local clinic team using conventional content analysis and the Indigenous method of *2-eyed seeing*. Both reviewers will also use the memoing technique to document their notes in reflection of the research aim and the guiding principles from the human-technology ladder. Quantitative analysis of the completed surveys will be conducted concurrently with the qualitative analysis to evaluate the system's usability. All clinic and community stakeholders will also be invited to participate in the data analysis stage to provide feedback regarding whether any further system adaptations are needed. Participants interested in analyzing or receiving the core study findings were provided with a separate form to outline their contact information for the distribution of the study findings. Given the importance of equitable and transparent principles of knowledge ownership, the control and possession of all study records will be determined by the guidance from the local team. The UHN team aims to continue their collaborative engagement with the local team to appropriately distribute the study findings beyond academic platforms. This may include avenues such as radio shows, posters, or community events.

Ethical Considerations

This study was approved by the Makerere University School of Medicine Research and Ethics Committee (Mak-SOMREC-2021-63) and the UHN Research Ethics Board (20-6022). Written informed consent will be obtained from all participants. All information obtained during the study will be held in strict confidence. To safeguard the confidentiality and security of the identifiable study data, all participants will be identified with a unique study number, and audio recordings will be erased after transcription. At the conclusion of data analysis, all unique identifiers will be destroyed. Patient participants will receive time compensation of UGX 10,000-15,000 (US $3-$4) as well as a transport refund (if applicable) for approximately UGX 10,000-15,000 (US $3-$4). Clinician participants will receive a transport refund (if applicable) and time compensation of UGX 30,000-40,000 (US $9-$12). This research complies with all the relevant national regulations and institutional policies within the study region.

Results

The process of partnership building was initiated in June 2019, and the first stage of data collection (phase 2) began in January 2021. At the time of manuscript submission, phases 1 to 3 have

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been completed. Phase 4 data analysis is ongoing and expected to be completed in July 2025.

Discussion

Principal Findings

Many low-income populations are often labeled as vulnerable or marginalized without recognizing the system and societal constructs that have limited their ability for growth and well-being. In Uganda, the disparities between rural and urban communities represent a clear example of how the inequitable delivery of health services has impacted population health outcomes [11,12]. To effectively facilitate meaningful change, there is a need for health services to recognize the unique circumstances, challenges, and experienced barriers that affect an individual's well-being. Many studies have begun to implement community-based research strategies to better understand the complexities of different population contexts, but they have failed to recognize the importance of putting context into perspective [1,3,12]. Despite obtaining community input, the implication of solely using traditional Western research methods involves the assumption that each individual is willing to tell their story in the same manner with the same worldview [4,32]. Unlike Western research approaches, Indigenous methodologies integrate diverse ideologies, such as "your truth is not my truth," to emphasize the importance of learning through lived experiences and understanding the existence of different realities [41]. As part of this framework, researchers are encouraged to engage in a continuous process of self-reflection to better recognize their individual preconceptions regarding different contexts [9,11]. These approaches to research can be integrated within any population group to better understand the dynamics of different worldviews and the importance of community or family relationships; however, current research has yet to apply these methods within non-Indigenous settings.

With the burden of HF continuing to grow in Uganda and the need to understand the contextual challenges faced by remote communities, this study aims to use both Western and Indigenous methods to adapt a digital health program for the northern communities in Uganda. To our knowledge, this is one of the few studies applying Indigenous ideologies for the collaborative co-design of a digital health program in a non-Indigenous setting [5,22]. Given the number of digital health studies that have failed to progress beyond the pilot stage in Uganda, we believe that using a diverse range of community-based methods will help ensure that the contextual significance of each community's challenges is reflected in the program's design [12]. Specifically, by placing local voices at the center of the research and using collaborative methods to better understand the underlying contributors to various health inequities, a more comprehensive assessment of community heart health and well-being can be conducted.

Limitations

Despite this project's focus on community outreach in remote settings, the participants recruited were already patients of either the Gulu Regional Referral Hospital or the Lira Regional Referral Hospital. Due to the restrictions associated with the COVID-19 pandemic, limited outreach to the surrounding lower regional health centers and community groups was available. The UHN lead (SW) was unable to travel to Uganda for phases 1 and 2 due to the pandemic, leading to the bulk of the data collection being conducted by the nurse leads at each site (JA and JK), with SW attending through internet-based Zoom platform. SW was unable to fully explore the contextual insights described in phase 2 but was able to travel to facilitate the sessions in person for phases 3 and 4.

Conclusions and Future Work

This study recognizes that, within the field of digital health, advancements in technology move at rapid speed, whereas factors related to the digital divide continue to grow [19]. With the current mismatch between technological innovation and human social structures, by integrating a community-based approach within the UCD process, it is anticipated that various cultural and clinical factors will be identified for the adaptation of the program. As the incidence of rural poverty continues to grow in Uganda, this research believes that integrating the community's local knowledge and lived experience into the design of the Medly Uganda program will lead to the development of a meaningful intervention to improve HF outcomes. This study recognizes that the core program adaptations will be informed by feedback from Lira and Gulu that may not reflect the contextual challenges of other communities across the country. Thus, future work will seek to collaborate with other regional referral hospitals to explore the synergies and changes needed to adapt and integrate the program within existing health system workflows. By combining the intentional use of CBPR and Indigenous methods, this study will offer a replicable blueprint for the development of more meaningful global health interventions.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request. A results paper will also be published in follow-up to this protocol.

Authors' Contributions

SW, JS, AM-P, JA, JK, HR, and JC contributed to the design of this study. SW drafted the manuscript for all the authors to comment on and revise. All authors approved the final version of the manuscript.

Conflicts of Interest

None declared.

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Abbreviations

CBPR: community-based participatory research
HF: heart failure
I-RREACH: Intervention and Research Readiness Engagement and Assessment of Community Health Care
UCD: user-centered design
UHI: Uganda Heart Institute
UHN: University Health Network
VHT: village health team

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Protocol

Codevelopment of a Shared Decision-Making Resource Platform for Women and Girls in 3 Low- and Middle-Income Countries (ENGAGEEs): Protocol for a Participatory Research Project

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Abstract

Background: Women and girls around the world face significant barriers in participating in health care decisions, particularly in low- and middle-income countries. Despite growing interest in shared decision-making (SDM), little is known about its implementation in these countries, and no rigorous assessment of the decision-making needs of women and girls in these contexts has been conducted. There is little SDM training and there are few decision-support tools (DSTs) specifically designed for health care decision-making by women and girls in these countries. DSTs (paper or digital) present options and probabilities and help users articulate their values and preferences.

Objective: We aim to codevelop an SDM resource platform, including locally relevant DSTs and instructional materials, to support SDM with women and girls in Brazil, Cameroon, and Senegal.

Methods: We will conduct a 4-phase participatory research project. We will use the Gender-Based Analysis Plus tool to support inclusive participatory research throughout the study. First, we will follow the Integrated Knowledge Translation framework to form a local steering committee in each country, including patients and community representatives, health and social service professionals, and decision-makers. Second, we will follow the Ottawa Decision Support Framework to conduct individual interviews and focus groups to identify the decision-making needs of women and girls. We will include 20 women and girls, along with their family members, 15 health and social service professionals, and 15 representatives of community-based

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organizations in each country (n=150). The Double Diamond human-centered design framework will be used to codevelop a digital SDM resource platform where DSTs and instructional materials for SDM training can be made accessible. Finally, we will assess the scalability of the platform by using the Innovation Scalability Self-Administered Questionnaire. We will report our study by using the Standards for Reporting Qualitative Research guideline and the Guidance for Reporting Involvement of Patients and the Public.

Results: Financial support for this project was received on February 1, 2023. This protocol was submitted during data collection but before analysis. Data collection began in January 2025. By July 2025, 92 of the 150 participants had been recruited. We expect to publish our results in December 2026.

Conclusions: Ultimately, more women and girls from low- and middle-income countries will be involved in health care decisions, and more clinical teams will be able to integrate SDM into their care practices. The local steering committees will ensure equitable partnerships and the SDM resource platform will promote more inclusive approaches to SDM worldwide. The scalability assessment will help us plan to expand the impact of the platform to other regions.

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KEYWORDS

shared decision-making; health decision-making; women's health; low- and middle-income countries; decision support; decision aid; global health

Introduction

Health care decisions have traditionally been unilaterally made by health care providers or clinical teams [1]. Shared decision-making (SDM) has proved to be an effective practice for changing this power dynamic [2]. SDM is a collaborative process in which clinical teams and patients engage together in choices related to health decisions, considering the best available evidence and the values and preferences of the person receiving care [3]. It has a beneficial effect on reducing health inequalities, as underserved populations have been shown to benefit the most [4]. Decision-support tools (DSTs) (eg, decision aids, personal decision guides, conversations aids) and the training of health professionals can facilitate SDM [5,6].

DSTs enable patients and professionals to adopt the behaviors essential to SDM. They can be used before, during, or after a consultation, and their use has proven effective in reducing decisional regret [5,7]. However, DSTs are mostly implemented in high-income countries, particularly in the United States, Canada, and Europe, and little is known about how they could support SDM in low- and middle-income countries (LMICs) [5]. Moreover, existing DSTs and instructional materials for SDM training are not tailored to LMICs and are rarely developed with health care stakeholders from these countries.

The research priorities set out in the United Nations Research Roadmap for the COVID-19 Recovery include helping eliminate discrimination (eg, racism, gender, poverty-based exclusion) in service delivery by engaging diverse stakeholders so that health systems become drivers of equity in society [8]. The document emphasizes the importance of engaging women and girls from LMICs in health care, since they are disproportionately excluded from decisions about their own health [9]. For example, a recent survey on maternal health decision-making in Nigeria showed that health care decisions were made by the husbands of 90% of the participants [10]. Women's and girls' unequal access to and engagement in health care services is based in part on unequal power relations shaped by sex and gender norms, including the division of labor between men and women (Figure 1) [11]. There is therefore an urgent need to develop interdisciplinary research for scaling SDM interventions so that more women and girls can benefit from them, especially in the context of LMICs.

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Figure 1. Power dynamics in society and participation in decision-making.

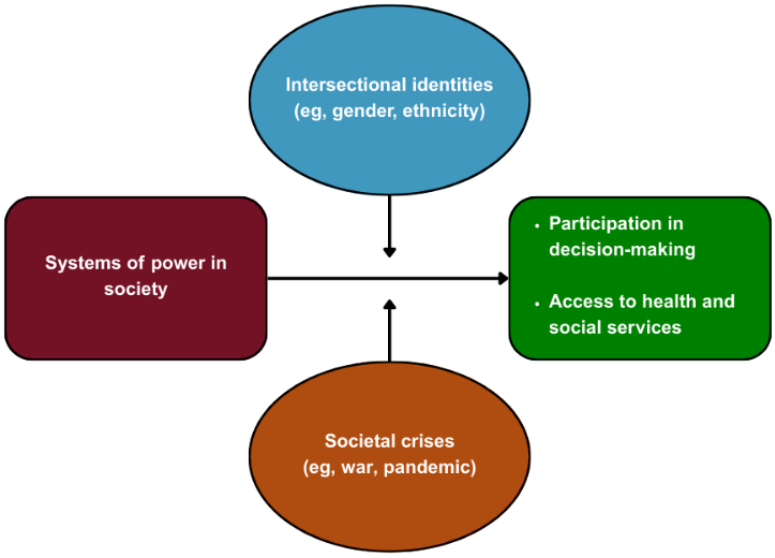

As gender power dynamics and societal expectations put women and girls at the greatest risk of vulnerability, consideration of sex and gender is recommended as an entry point to a better understanding of the complex and converging factors that influence access to health services and affect involvement in health care decisions among systematically underserved groups [11]. For example, gender norms embedded in families and cultures can affect women's involvement in decisions about their health, as well as the advice given, options offered, and quality of care provided [12]. However, to fully capture the complexity of the experience of women and girls, an intersectional analysis is essential—one that accounts for the interrelated social determinants of their involvement in decision-making, such as age, geography, ethnicity, socioeconomic status, marital status, and cultural beliefs [13]. Taking a human rights perspective acknowledges that all these intersecting factors may contribute to impeding the ability of women and girls to freely make informed decisions about their own health, essential for their human dignity as well as for their health and well-being [14]. Therefore, there is a need to create initiatives and partnerships that can enable this group to make informed decisions about their health and well-being.

In general, the development of DSTs and SDM training programs is guided by the decision-making needs of a targeted group [15]. Decision-making needs may be defined as factors that prevent people from making informed health care decisions. They are usually identified in relation to a specific decision point (eg, a choice faced in the context of a specific health condition, treatment, screening) and may include inadequate knowledge, uncertainty, unclear values, or a lack of support and resources to make an informed decision [15]. To the best of our knowledge, no systematic assessment of the decision-making needs of women and girls in LMICs has been undertaken.

In line with the priorities of the United Nations Research Roadmap for the COVID-19 Recovery (Figure 2) and in collaboration with partners in Francophone Africa and Latin America, the ENGAGEEs (*ENGAger les femmes et les filles du Sud Global dans les décisions concernant leur santé et leur bien-être pour la mise en œuvre de la décision partaGÉE*, or Involving women and girls in decisions about their health and well-being through SDM) project aims to codevelop a digital resource platform for supporting SDM among women and girls in Brazil, Cameroon, and Senegal. The specific objectives of the project are to (1) establish an equitable and sustainable partnership with partners in the 3 countries, (2) identify decision-making needs in terms of the health and well-being of women and girls in these countries, (3) codevelop an SDM resource platform that meets these needs, (4) explore strategies for scaling SDM in the 3 countries through a scalability assessment of the codeveloped SDM resource platform, and (5) build SDM capacity in the 3 countries.

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Figure 2. Social innovation based on key areas of the United Nations (UN) Research Roadmap for the COVID-19 Recovery blueprint. SDM: shared decision-making.

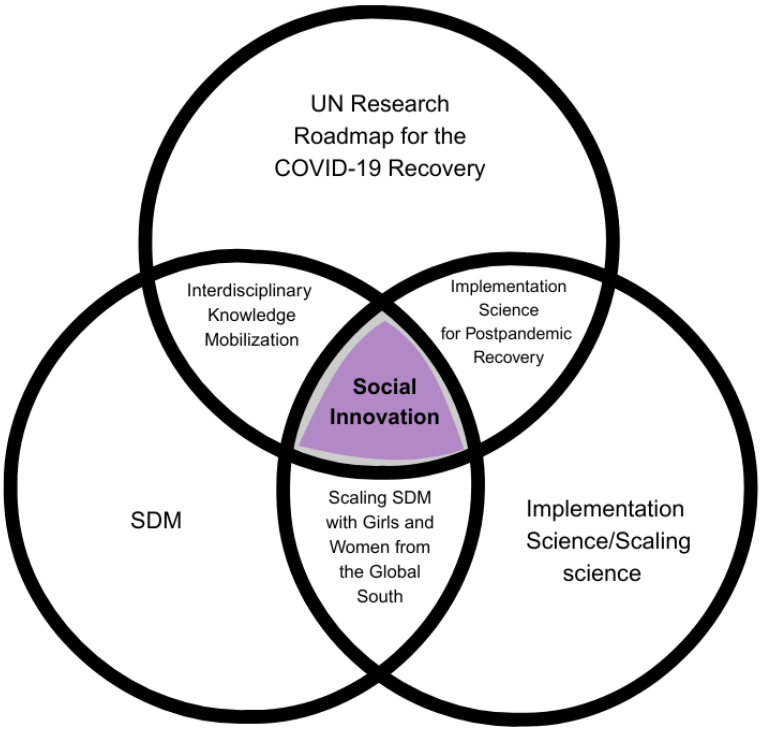

Methods

Context of the Study

The project coordination committee is based in the province of Quebec in Canada. It is led by 2 early-career researchers from Togo and Brazil, with mentorship from a Canadian senior researcher with 20 years of expertise in SDM. The research team based in Canada also includes one research professional and one student, both from Burkina Faso. The decision to perform the project in 2 African countries (Cameroon and Senegal) and 1 Latin American country (Brazil) was based on the knowledge, experience, and networks of the team members, who identified local research teams interested in SDM and who had access to the resources necessary for the development of the study. It is worth noting that Rwanda was originally included in the project. However, it was withdrawn because the researcher associated with the grant application and designated as the local project leader had been promoted to a position within the Rwandan government and was no longer available to continue implementing the project. The research team informed the funding agency, which approved the withdrawal.

Overall Methodology

The ENGAGEEs project will take place in 4 phases: (1) forming local steering committees to establish equitable and sustainable partnerships in the 3 countries, (2) conducting individual interviews and focus groups to identify the decision-making needs related to the health and well-being of women and girls in the 3 countries, (3) codeveloping the SDM resource platform by using a human-centered design approach, and (4) assessing the scalability of the codeveloped platform by using an evidence-based scalability assessment tool. Each phase corresponds to a specific objective and methodology. Building SDM capacity is a cross-cutting objective throughout the project.

Gender-Based Analysis Plus

Our team is experienced in integrating sex and gender considerations into implementation research on SDM [16,17]. We will apply the Gender-Based Analysis Plus (GBA Plus) tool at all phases of the project [18]. To mitigate the risk of reproducing inequalities in the project and to ensure the inclusion of groups that are systematically disadvantaged, such as women and girls in LMICs, we will mobilize additional efforts and targeted strategies. These include, for example, engaging community representatives to support recruitment, using plain language in communications and questionnaires, assembling interdisciplinary teams, and allocating extra resources to respond to situations involving gender-based violence. Thus, when designing project activities, we will apply the GBA Plus tool to the composition of the governance structures and the selection of participants, helping us to (1) reflect on and make informed methodological and analytical decisions in light of the expected impacts of the project on women and girls, as well as on health care stakeholders in the 3 countries; (2) identify which activities should be tailored to meet their diverse needs; and (3) discover, anticipate, and mitigate any barriers preventing women and girls from accessing, participating in, or benefiting from the project. In data collection and analysis, in each country, we will operationalize GBA Plus and the intersectional approach through the collection and disaggregation of data according to the PROGRESS Plus variables: gender, place of residence, race, ethnicity, language, occupation, religion, education, socioeconomic status, and social capital [13,19,20]. We will use the Sex and Gender Equity in Research guidelines to ensure

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appropriate reporting of gender-related information in study design, data analysis, results, and interpretation of findings [21].

Phase 1: Partnership Development and Establishment of Steering Committees

Study Design

We took 5 months to implement this phase. We followed the Integrated Knowledge Translation model to design the project's governance structures [22]. The model recommends that knowledge users be involved in project development as equal partners from the beginning, ensuring the relevance and the usability of the knowledge products of the research. Our Integrated Knowledge Translation strategies included (1) an assembly made up of members of the international project team, including collaborators who participated in securing the funding; (2) an executive committee formed of the heads of each country team; and (3) local steering committees and local research teams in each country (Canada, Brazil, Cameroon, and Senegal). The local steering committees ensure that health care stakeholders, including women and girls who will be impacted by the project, are involved at all stages of the ENGAGEEs research project. The project governance is presented in Figure 3.

Figure 3. Project management structure.

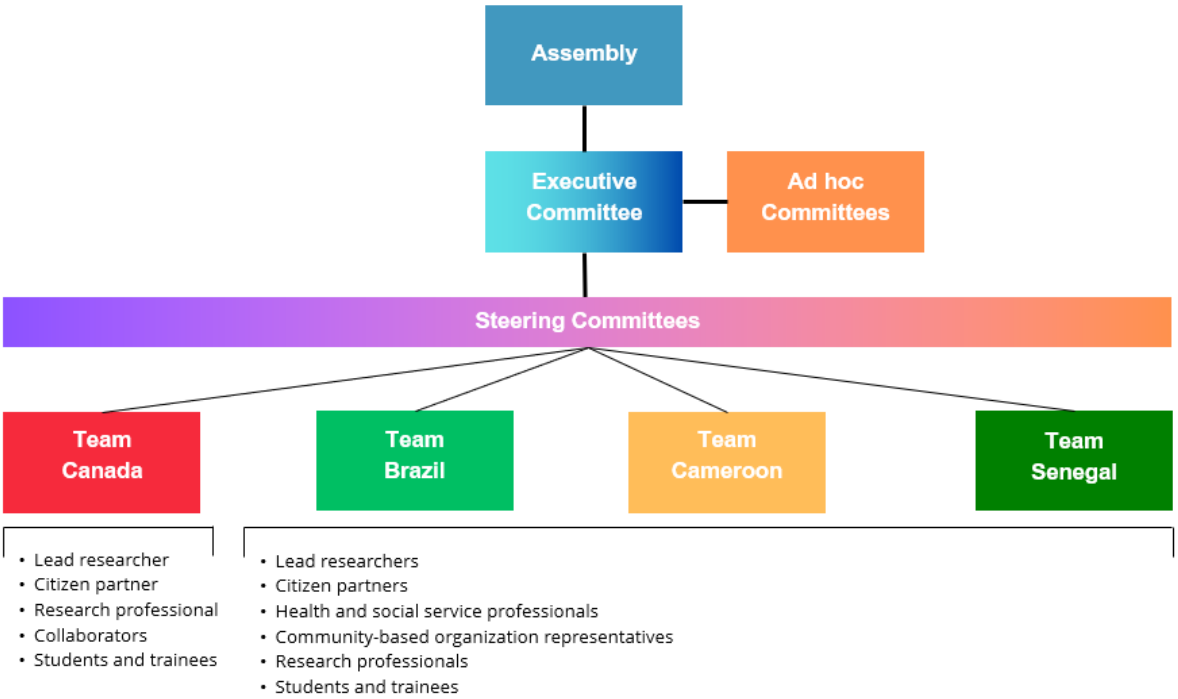

Participants

The assembly is composed of researchers, citizen partners, and collaborators (eg, policy decision-makers and health and social professionals) who participated in designing the project and securing the funding. It is an interdisciplinary team (eg, philosophy, medicine, psychology) with diverse expertise (eg, social justice, women's health, scaling of innovations) (See ENGAGEEs group in the Acknowledgments section). The executive committee is composed of the researchers leading the project in each country and the research officers supporting the development of project activities.

For the local steering committees, we included health care stakeholders involved in the project and in the health and well-being of women and girls, including themselves and their family members. We targeted health and social service professionals, community representatives, researchers, and decision-makers, ensuring that at least one person from each of these groups was present on the local steering committees. Local research teams were also formed of project researchers, research officers, and students. For interviewing, we only engage local partners who are trained in qualitative research techniques such as how to ensure participants' psychological safety during interviews and how to mitigate interview bias. If they are unqualified in these techniques, we offer training. We used the Guidance for Reporting Involvement of Patients and the Public guideline to report on the involvement of these stakeholders in the project.

Ensuring an Equitable Partnership

The project's governance is structured around strategies to facilitate shared learning and action. To ensure an equitable partnership, we adopted the following strategies.

First, each research team was provided with the financial resources necessary for the development of project activities and is responsible for managing them, making their own decisions according to their local context. This strategy aimed to ensure that research teams have a sense of ownership over the project and autonomy in conducting the research with reference to the particularities of their own contexts. Second, each local research team built on existing networks and strategies in their own country to involve health care stakeholders and women and girls in the project. For example, local research teams relied on community health agents who

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are essential staff in primary health care in the countries of the project to identify and invite a woman or girl to take part in the steering committee. Third, we conduct monthly meetings of the executive committee, including the local research teams, to share decisions on the project's direction, follow up on activities, and present preliminary data.

We use communication platforms that are most suitable in the local contexts (eg, mobile phones, social media) and will contribute to upgrading communication equipment in country teams where necessary. To accommodate different time zones, we adapt schedules to the various geographical areas. All project documents are provided in both French and Portuguese. We combine human assistance with online translation tools for translating documents and meetings. In rural areas where populations speak local languages, members of the local research team provide simultaneous interpretation if necessary. If not, they engage local interpreters who speak both the local and the official languages. During the meetings, dedicated time is set aside for each country's team to speak, and every contribution is documented. In addition, the Canadian team will visit each country to engage with local stakeholders and discuss research needs in SDM. A visit to Canada by researchers from all countries is also planned to share the project's initial results, challenges, and proposed solutions. The training modules offered by the Quebec Support for People and Patient-Oriented Research and Trials Unit will be presented to all project stakeholders, with the option of translation into other languages (eg, Portuguese) [23].

Phase 2: Identification of the Decision-Making Needs of Women and Girls in Brazil, Cameroon, and Senegal

Design

Phase 2 is scheduled to last 6 months. To identify the decision-making needs of women and girls, we will conduct a qualitative descriptive study [24] guided by a pragmatic vision of the world and adopting a pluralist position consisting of collecting more than one type of data in order to best answer the research question [25]. In the SDM literature, decision-making needs are generally associated with a specific decision point (eg, about a health condition such as diabetes or about a screening procedure such as a breast cancer diagnostic test). However, in the context of the ENGAGEEs project, these needs may not be limited to a single decision point. Instead, they may reflect foundational needs required to support the practice of SDM, such as women's and girls' awareness of their right to participate in health care decisions or clinical teams' knowledge of the steps and benefits of SDM. The Standards for Reporting Qualitative Research guideline will be used to report the qualitative research [26].

Study Population

We will include 20 women and girls along with their family members, 15 health and social service professionals, and 15 representatives of community-based organizations in each country (n=150) [25].

Eligibility Criteria

The eligibility criteria will be as follows.

1. Eligible women and girls will be 18 years of age or older, will have encountered difficulties in accessing health services or are interested in the subject, and will be available to participate in a 1-hour interview or a focus group session.
2. Eligible health and social service professionals are those willing to work in an interprofessional team.
3. Eligible representatives of community-based organizations are those willing to work in an organization that develops actions with women and girls aimed at improving their health and well-being.

Recruitment

Local teams will recruit participants in health and social service facilities (eg, family planning services, community organizations and associations working for the health and well-being of women, networks of associations working to promote women's rights, hospitals). The local research teams and steering committees will use their networks to identify representatives of community organizations that include women and girls who may not have access to health and social services. Recruitment strategies will include placing posters advertising information sessions and actively recruiting through word of mouth, networking, and the snowball method. Local research teams will monitor recruitment using the PROGRESS Plus variables to ensure inclusivity and to verify that underserved groups are adequately represented in the participant samples [25].

Data Collection

Following the Ottawa Decision Support Framework, we will conduct semistructured individual interviews and focus groups to identify the decision-making needs of women and girls [27]. Based on existing literature in the field and principles of data saturation [28], we determined that a minimum of 50 participants per country—at least 20 women, girls, and their family members, 15 health and social service professionals, and 15 representatives of organizations—will be sufficient. The steering committee's expertise will be mobilized to ensure a variety of participant profiles.

Prior to the interviews and focus groups, participants will watch a short video on SDM to allow them to better express their experiences in decision-making concerning their health. We will primarily use existing publicly available SDM videos, and local adaptations will be made by local teams as needed [29]. The viewing will be preceded by a brief introduction, followed by a time of sharing and discussion. Note-taking and/or recordings of these sessions will be performed by a research team member, and the analysis of this data will enrich project documentation and the development of SDM resources and tools for disseminating the project's results. Interviews and focus groups will last approximately 1 hour and will be held either in person or online and recorded with the consent of the participants. The consent form must be completed before starting the data collection. Because of the vulnerability of this population and the sensitivity of some of the topics discussed, such as domestic violence, particular attention will be paid to managing the risks of interviewer bias, social desirability bias, and ensuring data reliability.

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To minimize interviewer bias, interviewers will be trained to approach subjects with empathy, respect, and good humor, and to receive responses neutrally. To minimize social desirability bias, we will collect more than one source of information, triangulate the data, and identify socially desirable responses. The researchers will conduct interviews and focus groups only after gathering information from document analysis. We will include time to develop a relationship of trust with the interviewee to develop confidence and encourage unbiased answers. Data collection will take place in a comfortable and private location, and interviewees will be reassured about the anonymity and confidentiality of their personal information. However, in some political contexts, social desirability bias is inevitable due to social and political repression. In these cases, the researchers will not avoid it but will include it in their analysis and discussion [30].

We will incorporate standardized data collection tools, adapted as necessary for cultural appropriateness. Supervision and regular debriefing sessions, including steering committee meetings, will be conducted. Based on the elements of PROGRESS Plus, information on the sociodemographic and professional profile of the participants will be collected using a questionnaire at the beginning of each meeting. Interviews will be conducted in the official languages of each country, and if necessary, in participants' mother tongues, by members of the project team in each country.

Data Analysis

Descriptive analyses will be conducted for sociodemographic data, which will be disaggregated according to the PROGRESS Plus variables. For qualitative data, interviews will be transcribed verbatim and, if necessary, translated into French. The anonymized transcripts will be uploaded to NVivo software (QSR International) for analysis. To categorize the decision-making needs and available services, information, and support opportunities, we will conduct a thematic analysis. We will perform a mixed analysis by using both an inductive and deductive approach. We will create themes based on the Ottawa Decision Support Framework (deductive approach) and explore the decision-making needs in relation with elements of intersectional and contextual factors to identify emerging themes (inductive approach) [27,31]. A preliminary list of the themes is provided in Table 1.

The decision-making needs identified will be classified based on their frequency in interviews and focus groups. Results will be presented in tables for each country separately as well as in aggregate form. To support the dissemination of findings to lay audiences, we will use concept maps and figures. The data will be written in plain language and summarized in a report format.

Table 1. Decision-making themes from the Ottawa Decision Support Framework [27].

Categories	Themes
Needs assessment (determinants of the decision)	
Perception of the decision	• Knowledge • Decision-making conflict • Decision-making steps • Predisposition
Perception of others	• Roles in decision-making
Resources needed for decision-making	• Personal: previous experience, self-confidence, motivation, decision-making skills • External: support (information, advice, moral, material, financial, professional aid) from social assistance networks and organizations
Characteristics	• Client: age, sex, marital status, education, occupation, culture, residence, medical diagnosis and prognosis, health status • Practitioner: age, gender, education, specialization, culture, practice situation, experience, counselling style
Provision of decision support	
Providing access to information	• Health status • Options
Provision of advice and support	• Communicating with others • Access to support and resources

Phase 3: Codevelopment of the ENGAGEEs SDM Platform

Design

We anticipate 9 months to implement this phase. The Double Diamond human-centered design framework will guide the codevelopment of the ENGAGEEs SDM platform [32,33]. We will use an iterative process that includes exploring the decision-making needs of women and girls (discover phase); identifying their decision-making priorities (define phase); co-designing DSTs, SDM instructional materials, and the layout of the ENGAGEEs SDM platform (codevelopment phase); and testing and evaluating the ENGAGEEs SDM platform with local stakeholders (deliver phase) [32,33]. The whole process

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will be conducted through online workshops and local working groups composed of members of the research teams, steering committees, and collaborators in each country.

Exploring the Decision-Making Needs of Women and Girls

The results of phase 2 will be discussed by the project stakeholders (assembly, committees, and research teams) in a 1-day online workshop. The aim of this workshop is to understand the decision-making needs of women and girls in the 3 study countries and to discuss common findings as well as contextual differences. First, as a preparatory activity, the report produced in phase 2, including tables, concept maps, and figures, will be sent to participants 2 weeks before the meeting. Second, during the workshop, each local research team will present the health care context in their country, the data collection context, project development activities, and the results of phase 2. Third, an open discussion session will be held to exchange impressions and insights. A report of this workshop will be prepared by the research team based in Canada and sent to all participants within 2 weeks.

Identifying Decision-Making Priorities

Upon receiving the report from the first workshop, local research teams and steering committees will be asked to meet and form working groups to classify and prioritize the decision-making needs of women and girls in their country. The results of the local working group discussions will then be presented in a second 1-day online workshop, during which project stakeholders will discuss the decision-making needs and priorities to be addressed by the ENGAGEEs SDM platform. Prioritization will be based not only on the importance of each decision-making need but also on the feasibility of codeveloping DSTs and instructional materials that address them for inclusion on the platform. These priorities may be specific to one country or reflect the common needs identified across all 3 countries. A report of this workshop will be prepared by the research team based in Canada and sent to all participants within 2 weeks as well.

Co-Designing DSTs

This step includes identifying the evidence-based data, writing the draft version of the DSTs, and evaluations of the draft by the local steering committees. At least one DST (eg, option grids, videos, decision aids) will be drafted for each country by local working groups with support from the team in Canada. First, the Canadian research team will search scientific databases and the Ottawa Decision Support Framework Decision Aids Library Inventory to identify potential DSTs that can be adapted and improved to address the decision-making needs prioritized by the ENGAGEEs project [34]. The local working groups may also contribute to this process by complementing the search and developing their own resources if none of the existing DSTs match their needs. Second, working groups will be requested to write a draft version of their proposed DSTs. Third, the Canadian team will meet with each local working group to review the strengths and weaknesses of proposed DSTs, consider relevant contextual factors, and determine appropriate formats for the resources. Finally, women and girls, along with health and social service professionals from the local steering committees, will evaluate the codeveloped DSTs and propose modifications if needed. The final versions of the DSTs will be provided in French, English, and Portuguese, and will be reviewed for comprehensibility by a literacy service.

Co-Designing Instructional Materials

This step will be led by the Canadian research team. The Canada Research Chair in Shared Decision Making and Knowledge Mobilization developed and keeps a directory of evidence-based SDM training courses [6,35]. Several of these courses for health and social service professionals have been evaluated [36]. In addition, the team itself has many years of experience with SDM training, including SDM workshops for the public. We will select instructional materials from existing training programs and enrich them with the contextual findings from phase 2. The aim is to inform both clinical teams and women and girls in Brazil, Cameroon, and Senegal about the essential elements and necessary skills for SDM. The instructional materials will include information on SDM and related tools presented through short texts, illustrations, and/or video links. The Canadian research team will use an iterative process to review and approve the instructional materials in collaboration with the local steering committees. The instructional materials will be made available in French, English, and Portuguese.

Co-Designing the ENGAGEEs SDM Platform

We will co-design the layout of the ENGAGEEs SDM platform through an ideation and cocreation process involving local research teams and local steering committees in collaboration with technical experts. The goal is to integrate the developed resources and ensure their usability for end users, including layouts for smartphones and tablets. The Canadian research team will work with digital development experts at Université Laval to present the goals of the ENGAGEEs SDM platform, define user profiles, and share the materials to be included (DSTs and instructional materials). Based on this input, the experts will develop the first prototype of the platform. This prototype will be presented to project stakeholders for feedback and suggestions for improvement. This process will continue until a satisfactory and usable version is achieved. The platform will be developed in French and Portuguese, the official languages of the participating countries, and will contain all the developed project resources. The translation of the project deliverables will be performed by bilingual researchers and professional translators on the project team to ensure the accuracy and quality of the content.

Testing and Evaluating the ENGAGEEs SDM Platform

We will adopt a mixed methods approach that combines validated quantitative instruments with participatory qualitative techniques to test and evaluate the ENGAGEEs SDM platform. We will use the System Usability Scale, a widely recognized 10-item questionnaire that provides a global measure of perceived usability for digital platforms [37]. In addition, the Health Information Technology Usability Evaluation Scale will be applied, as it is specifically designed to assess usability in health technology contexts, including perceived usefulness, ease of use, and user control [38]. The evaluation will involve

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women and girls as well as health and social service professionals who are members of the local steering committees. To complement the quantitative data, guided discussions will be conducted by the local research teams to gather feedback on platform content, accessibility, and contextual relevance. Notes will be taken during these sessions to capture participants' reflections, perceived barriers, and suggestions for improvement. Both types of data will be triangulated to enhance comprehensiveness and to ensure that the platform is user-centered, contextually appropriate, and responsive to the needs of key stakeholders.

Phase 4: Assessing the Scalability of the ENGAGEEs SDM Platform

Six months have been allocated for the implementation of this phase. We will use the Innovation Scalability Self-Administered Questionnaire (ISSaQ 4.0) to assess the scalability of the ENGAGEEs SDM platform, including its resources (DSTs and instructional materials). ISSaQ 4.0 is a scalability assessment tool that integrates considerations of sex, gender, equity, diversity, and inclusion. It consists of 37 items divided into 12 components deemed essential for scaling health and social innovations [39]. The questionnaire will be completed by the local steering committees who will reflect on the potential and strategies for scaling the ENGAGEEs SDM platform in their respective countries, with the goal of increasing its impact and supporting SDM among a broader and more diverse group of women and girls. We will assure long-term sustainability of the platform with the following strategies.

1. The initial version of the platform will be built using a free web-based collaborative tool, thereby minimizing initial capital expenditure and recurring licensing costs. This choice enhances affordability, flexibility, and ease of customization for future needs.
2. A sustainability plan will be developed to explore local resources for long-term ownership through integration into existing institutional systems.

Ethical Considerations

Ethics approval was obtained from the ethical boards of each country: Comitê de Ética em Pesquisa da Escola Nacional de Saúde Pública and Comissão Nacional de Ética em Pesquisa of Brazil (76227523.6.0000.5240), Comité Régional d'Ethique de la Recherche pour la Santé Humaine du Centre of Cameroon (0120/CRERSHC/2024/), and Comité National d'Ethique pour la Recherche en Santé of Senegal (2024/0430MSAS/CNERS/SP). In accordance with ethical requirements and local data protection regulations, all data collected, including recordings, will be stored securely on access-controlled media in each country and on Université Laval's secure platform, Valeria, which includes the REDCap (Research Electronic Data Capture) web-based software [40] REDCap provides audit trails for tracking data manipulation, and export procedure issues related to data sharing and sovereignty will be addressed through interinstitutional collaboration agreements that involve administrative, legal, and financial services from all partner institutions. These agreements will be grounded in the principles of equitable partnership, ensuring mutual recognition of data ownership, transparent decision-making processes, and fair access to research outputs across all participating countries. Informed consent will be obtained from each participant before data collection (sociodemographic questionnaire, focus groups, and interviews) begins. Participants will also be informed that they may refuse to answer any question or withdraw from the interview at any time without any negative consequences. The data collected will be anonymized to respect confidentiality and protect participants' information. The various research documents will be coded, and only the researchers in charge of the project will have access to the list of names and codes. The information obtained as part of our study will be published in an anonymous, aggregated form so that individual responses cannot be identified and will not be passed on to third parties. To compensate for expenses incurred and constraints experienced, such as time and travel (1 hour per participant), participants will receive a lump sum according to the group to which they belong and the local context of the target countries, whether it is a woman/girl, a health care professional, or a representative of a community organization.

Capacity Building

Our focus on capacity building throughout the project will be demonstrated by involving master's students and other trainees from each country in developing project activities. This also includes monthly scientific discussions to share lessons learned from each country and to enhance global knowledge and practices in SDM. Additionally, we will prioritize publications and research dissemination on the topic, focusing on sharing experiences and assisting other teams working on SDM in partnerships between LMICs and high-income countries.

Results

Funding for this project was obtained in February 2023. Interinstitutional collaboration agreements have been signed with partner institutions to formalize roles, responsibilities, and shared commitments. The steering committee has been formed in each country. The ethics boards, namely the Comité Régional d'Ethique de la Recherche pour la Santé Humaine du Centre of Cameroon, the Comitê de Ética em Pesquisa da Escola Nacional de Saúde Pública and the Comissão Nacional de Ética em Pesquisa of Brazil, and the Comité National d'Ethique pour la Recherche en Santé of Senegal gave their approval on March 13, 2024, July 15, 2024, and December 2, 2024, respectively. Data collection began in January 2025 in Cameroon. In September 2025, data collection was complete in Cameroon, 47 of the 50 participants were enrolled in Senegal, and the funds transfer was finalized in Brazil. Consequently, data collection will begin in Brazil in October 2025. All project results are expected be published in national and/or international journals by December 2026.

Discussion

Principal Findings

Our study aims to codevelop a digital SDM resource platform adapted to the contexts of Brazil, Cameroon, and Senegal, providing locally relevant DSTs and instructional materials to

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support SDM with women and girls in these 3 countries. The ENGAGEEs project is in line with the research priorities of the United Nations Research Roadmap for the COVID-19 Recovery, including helping to eliminate gender discrimination in health and social service delivery and facilitating the engagement of women and girls from LMICs in health care decisions [8]. Our research proposal combines key areas recognized as fundamental to postpandemic recovery with our expertise in SDM and knowledge mobilization to create a social innovation that improves the engagement of women and girls in LMICs in decisions about their health and well-being. This project will be enriched by the cross-cutting objective of capacity building in SDM, particularly from the perspective of increasing equitable partnerships in health research.

First, we will integrate GBA Plus into the codevelopment of a health innovation to facilitate SDM among women and girls in LMICs. This project will contribute to addressing power relations based on gender, which, intersecting with other systems of oppression such as racism and poverty, place women in an unequal position in society, thereby undermining their ability to participate in decisions about their own health [11].

Second, the codevelopment of the ENGAGEEs SDM platform will equip women and girls in 3 LMICs and health and social service professionals to share health care decisions and improve health outcomes. The project will fill a gap related to the lack of rigorous assessment of the health decision-making needs of this population of women and girls in LMICs [7]. Some studies have examined women's autonomy in the context of reproductive health in LMICs, but few have explored women's autonomy in other types of health care decisions [41,42]. In addition, most studies on decision aids have been developed in high-income settings [43]. The codevelopment of suitable DSTs and instructional materials will address immediate needs, while their testing and scalability assessment will provide insights for expanding their use and developing additional long-term resources [39].

Third, all our knowledge mobilization activities will be inclusive, participatory, nonhierarchical, multistakeholder, and interdisciplinary. This means that research findings will be contextualized and formulated in a way that increases their value, reliability, and relevance for policymakers and their priorities as well as for diverse groups of people. Our knowledge mobilization activities will not perpetuate or exacerbate existing inequalities and will align with a broader social change agenda. The scaling of the ENGAGEEs SDM platform will be contingent on its potential to reduce health inequities rather than exacerbate them. This will be ensured using the ISSaQ 4.0 scalability assessment tool, which considers equity a key condition for scaling.

Fourth, one of the distinguishing features of this project is the establishment of equitable partnerships for bidirectional capacity building in SDM, as provided by its governance structure. The governance is based on the principles of fair and equitable research collaboration focusing the project on the needs, priorities, and experiences of the partner countries [44]. The project activities will consider local realities, valuing different types of knowledge and evidence, being flexible and responsive to changing contexts and needs. In addition, we will integrate diverse perspectives and expertise, ensuring open and transparent communication between partners with a view to building partnerships based on trust, mutual learning, and long-term cooperation [11].

Potential Challenges and Mitigation Strategies

We recognize that structural inequalities may lead to significant differences in the ability of women and girls to participate in the project based on their geographic location (urban vs rural), socioeconomic status, access to resources, social norms, and decision-making power. To mitigate these inequalities, we will implement several strategies. First, we will be attentive to the timing and location of data collection and project activities, understanding that women may be available at different times of the day due to caregiving responsibilities or work obligations and may face barriers such as limited access to transportation. When necessary, we will provide financial support for community workers and participants, including transportation and other participation-related expenses. Second, we will ensure accessibility by offering assistive devices and accommodation to support women with disabilities, including those with invisible or episodic conditions and mental health challenges, not only those with visible or permanent impairments. Third, we will address digital inequalities by exploring the use of offline access options for the ENGAGEEs SDM platform. Downstream, we will adopt a lightweight content design approach, thereby avoiding large images and videos and leveraging high-performance platforms (eg, Vimeo) for video storage when necessary. We will ensure that key documents, tools, or training materials are available in formats that can be downloaded for offline use. Where feasible, we will provide devices, print versions of key materials, or work through local community organizations to facilitate access for participants with limited digital literacy or internet connectivity. One facilitating factor in our participant countries is the widespread use of mobile money transaction solutions. These measures will help ensure equitable and sustained access to project resources, even in low-connectivity environments.

We are aware of the power imbalance between research teams in high-income countries and in LMICs, including differences in access to funding, language fluency, and recognition in academic spaces. We will address these power imbalances by ensuring that local research teams have full decision-making authority over activities in their context, are equitably resourced, and are recognized as co-leads in all project outputs.

Finally, in addition to the challenges of power inequalities, we acknowledge that a multiphase, multicountry project, especially in LMICs, is likely to encounter logistical challenges. We experienced this in the loss of the research lead in Rwanda, who was recruited by his government just as we were beginning the implementation of the project. Our funding application addresses the resource constraints with mitigating strategies such as providing financial support for local research leads in African countries. This is complemented by the 25% indirect costs provided by the grant and disbursed along with the transfer of funds for project implementation in each country. The team is flexible and experienced in adapting to changing circumstances.

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Moreover, members of the principal research team in Canada have close connections with the research networks in the target countries. Team members have already collaborated with these research teams and share their culture and languages.

Conclusion

This project exemplifies a deep commitment to equity, diversity, and social inclusion in collaborative research. It aims to establish research partnerships that are not only equitable but also effective and sustainable, creating a positive impact on reducing social inequalities. The governance structure, based on the principles of transparency and mutual respect, ensures collective and inclusive decision-making. Local research teams and deliberative workshops will reinforce the relevance and impact of the project. By planning to identify and prioritize needs and develop suitable SDM resources, we aim to create sustainable and contextually relevant solutions. The knowledge users in this project will come from diverse groups: women and girls and their family members, health professionals, community organizers, health policymakers, researchers from LMICs, and funders. We will ensure that the results are returned to knowledge users and have a real impact in their respective organizations. These strategies have proven to be keys to success in building strong and lasting partnerships.

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Data Availability

The datasets generated and analyzed during this study will be available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

DST: decision-support tool
ENGAGEEs: ENGAger les femmes et les filles du Sud Global dans les décisions concernant leur santé et leur bien-être pour la mise en œuvre de la décision partaGÉE
GBA Plus: Gender-Based Analysis Plus
ISSaQ: Innovation Scalability Self-Administered Questionnaire
LMICs: low- and middle-income countries
REDCap: Research Electronic Data Capture
SDM: shared decision-making

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Protocol

Developing a Core Outcome Set and a Core Outcome Measurement Set for Studies Evaluating Interventions to Minimize Physical Restraint Use in Adult Intensive Care Units: Protocol for a Modified Delphi Study

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This is a corrected version. See correction statement: https://www.researchprotocols.org/2025/1/e88851

Abstract

Background: Heterogeneity in outcome selection and measurement methods has been noted in studies examining the minimization of physical restraint use in adult intensive care units (ICUs). This variability undermines evidence synthesis, limiting the development of evidence-based approaches to minimize restraint use and improve patient outcomes.

Objective: This protocol outlines the methods for developing international consensus on core outcomes and standardized measurement approaches for studies focused on physical restraint minimization in adult ICUs.

Methods: We will follow the Core Outcome Measures in Effectiveness Trials Handbook. Drawing on our previous work, including a scoping review of studies on physical restraint minimization and interviews with family members, we will compile a list of potential outcomes for a 2-round Delphi survey. In round 1, stakeholders will rank outcomes using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) scale. In round 2, they will review the aggregated results for rescoring and refinement. A consensus meeting using the modified nominal group technique will finalize the core outcome set, followed by another meeting to agree on standardized measurement methods.

Results: Research ethics board approval is in progress. Recruitment has not yet begun. Project initiation is anticipated in January 2026, with completion planned for April 2027 and publication of findings is expected by June 2027.

Conclusions: This study will be the first to establish a core outcome set and a core outcome measurement set for minimizing restraint use in adult ICUs. Standardization will enhance comparability across future studies and support evidence synthesis. The resulting outcome and measurement sets will provide a foundation for high-quality research and guide evidence-based strategies to improve patient safety and care in ICU settings.

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KEYWORDS
core outcome set; core outcome measurement set; Delphi process; physical restraint minimization; intensive care unit; ICU

Introduction

Background

Physical restraints are frequently used in intensive care units (ICUs) to prevent agitated patients from interfering with life-saving devices such as endotracheal tubes [1,2]. However, emerging evidence indicates that restraints may not prevent device removal in patients who are critically ill and could lead to a range of adverse psychological consequences for patients [3]. These include an increased risk of developing or worsening preexisting delirium or agitation and long-term effects such as a higher risk of posttraumatic stress disorder after ICU discharge [4,5]. The adverse impact of physical restraints extends beyond the patients themselves; family members frequently report feelings of helplessness and profound emotional responses such as sadness and anxiety [6,7]. ICU clinicians also experience emotional uncertainty and moral conflict when making decisions about restraint use as they navigate the complex balance between perceived risks and benefits [8,9]. Considering these adverse outcomes and the limited evidence supporting the effectiveness of physical restraints in preventing device removal, many international guidelines recommend minimizing their use in the ICU and applying restraints only as a last resort after exhausting all potential alternatives [10-12].

With the growing recognition of the importance of restraint minimization in adult ICUs, studies evaluating interventions to reduce physical restraint use continue to proliferate. A critical gap in the current body of evidence on physical restraint use and minimization is the absence of a systematic approach to selecting, measuring, and reporting outcomes [13]. This lack of standardization prevents the pooling of studies in systematic reviews and meta-analyses, which is critical for determining true effect sizes and generating robust guidance to inform practice guidelines [14]. In the absence of such evidence-based guidance, restraint practices may become inconsistent, potentially leading to negative patient outcomes such as unplanned extubations, physical harm, and psychological distress [15]. Furthermore, outcome selection in existing literature on physical restraint use and minimization is often driven by researchers' perspectives, potentially overlooking outcomes that hold greater significance for patients and their families [13].

To address these gaps in the variability of outcome selection and measurement, the development of a core outcome set (COS) and a core outcome measurement set (COMS) is crucial. A COS is a standardized list of outcomes that are reached through consensus as essential to report across all trials within a specific health condition or intervention area [16]. A COMS is a set of standardized and agreed-upon measurement tools for assessing the outcomes identified in the COS [17]. Currently, the absence of standardization limits the ability to compare results across studies, contributes to research waste, and undermines the translation of evidence into practice. Guided by the principle that standardized outcomes and measurements enhance comparability and ensure alignment with stakeholder priorities, a COS and a COMS promote consistency, improve the quality of systematic reviews and meta-analyses, and facilitate clearer guidance for practice and policy [18]. Importantly, by involving patients, families, and clinicians in determining which outcomes matter most, a COS ensures that the research agenda is aligned with the priorities of those directly affected by restraint practices [19,20]. This protocol outlines the methods we will use to establish an international consensus on the core outcomes to be prioritized and reported as well as the standardized methods for measuring these outcomes in studies aimed at minimizing physical restraint use in adult ICUs.

Scope

Health Condition and Target Population

The focus of this COS and COMS is on adult patients who are subjected to physical restraint use during their ICU stay. In addition, this COS focuses on individuals at risk of physical restraint use, specifically those with an endotracheal tube. This population includes patients with various medical conditions for whom physical restraints may be used to promote safety or prevent device removal.

Intervention

This COS and COMS include any nonpharmacological intervention aimed at minimizing physical restraint use in adult ICU patients.

Context of Use

This COS and COMS are intended for use in adult ICUs across diverse health care settings, including academic medical centers and community hospitals. Although the COS and COMS to be developed are intended for use in research, they can also be applied in clinical audits and quality improvement initiatives aimed at evaluating interventions to minimize physical restraint use in adult ICUs; for instance, hospitals may use the COS to standardize outcome reporting during audit cycles evaluating physical restraint minimization interventions, allowing for benchmarking across units or regions. The COS and COMS are applicable regardless of regional practices or institutional protocols, promoting consistency and comparability in outcome reporting.

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Methods

Overview

We have developed this protocol in alignment with the Core Outcome Set–Standardized Protocol statement (Multimedia Appendix 1) and have adhered to the guidelines outlined in the Core Outcome Measures in Effectiveness Trials (COMET) Handbook (version 1.0) [21,22]. This protocol has been registered in the COMET database (3368). Key stakeholders, including family members, clinicians, and researchers, provided feedback in separate informal conversations during the development of this protocol, helping refine data collection methods to ensure that they were appropriate, feasible, and respectful.

Building on this foundation and to ensure broad representation, methodological rigor, and feasibility, the study will proceed in three structured stages: (1) preparatory stage and ethics approval, (2) establishing the COS, and (3) development of the COMS. Each stage is described in detail in the following subsections. A comprehensive project timeline, including stages, key activities, and anticipated timeline for completion, is provided in Multimedia Appendix 2.

Stage 1: Preparatory Stage

Our steering committee will include 3 experts with clinical and research expertise in physical restraint use in the ICU, along with a patient or family representative. As the study progresses, we will expand our steering committee to include representatives from key stakeholders across all participating countries. To guide and optimize our engagement with ICU survivors and families throughout the development and execution of the COS study, we will use the patient and public involvement toolkit and COMET checklist for public research partners and COS study developers involved in designing a COS study [23].

Stage 2: Establishing the COS

Information Sources

Outcome List Generation

We will use the following data sources to generate a list of potential outcomes.

Scoping Review

We will use our previously conducted scoping review of studies on interventions to minimize physical restraint use in adult ICUs to generate a list of outcomes reported in the included studies [13]. The scoping review followed established methodology, with a search strategy developed iteratively and informed by an experienced information specialist. A combination of controlled vocabulary terms (eg, “restraint, physical,” “intensive care unit,” and “critical care”) and keywords (eg, “restrain*,” “intensive,” “critical,” and “acute”) was used. Seven databases, along with gray literature, were searched from inception to 2019. Two researchers independently screened and extracted data on study characteristics, outcomes, and outcome measurement instruments and definitions. Studies included were those in which the primary goal was to minimize physical restraint use in adult ICUs. Studies published in languages other than English were excluded. We will update our search strategy and execute a search to capture both published studies and ongoing trials from 2019 to 2025, using the same databases and gray literature sources. A table of outcomes, their definitions, and corresponding measurement tools will be created using studies included from the updated search, along with those already included in the previously conducted scoping review. We will calculate the proportion of studies reporting each outcome and rank them by frequency. Measurement tools will be evaluated for their psychometric properties using the COSMIN (Consensus-Based Standards for the Selection of Health Measurement Instruments) checklist [24].

Family Member Interviews

We will review the transcripts from our previously conducted interviews with family members regarding their perspectives on physical restraint practices and minimization in adult ICUs [6]. This was a qualitative descriptive study that involved one-on-one semistructured interviews with 15 family members in a medical-surgical trauma ICU in Toronto, Ontario, Canada. The study inclusion criteria were as follows: (1) self-identification as a family member aged 18 years or older who had observed the use of physical restraint on their loved one for at least 6 hours in the ICU, (2) a history of visiting the patient in the ICU during the period when they were physically restrained, and (3) the ability to speak English. The theoretical domains framework was used to guide both data collection and analysis, using a deductive content analysis approach. Three themes emerged: (1) barriers and facilitators to physical restraint minimization; (2) unilateral decision-making regarding physical restraint use, where clinicians made decisions without adequate communication with families or obtaining consent; and (3) the emotional impact of physical restraint use, with families experiencing sadness and shock and believing that patients would have similar emotional responses. We will thoroughly review the interview transcripts and create a comprehensive list of outcomes reported by family members.

Outcome List Reduction

Two researchers from the research team will independently review the outcome list derived from the family interviews and merge it with the outcome list obtained from the scoping review, consolidating similar outcomes and eliminating redundancies. The 2 researchers will then independently group outcomes with similar definitions under the same outcome name; for example, “Duration of physical restraint use (hours)” and “Average number of hours per day a patient is restrained” will both be grouped under the outcome name “Duration of restraint use.” The outcomes will then be classified into broader outcome domains in accordance with the COMET taxonomy [25]; for instance, “Duration of restraint use” and “Type of restraint used” will be grouped under the “Clinical outcomes” domain within the COMET taxonomy. Outcomes that do not duplicate those identified in the scoping review will be categorized according to the COMET taxonomy and marked as being identified exclusively by patients and family members. Any disagreements in the process of outcome reduction and categorization will be resolved through discussion or, if necessary, by consulting a third researcher serving as an independent arbiter.

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The final outcome list will undergo a thorough review by the steering committee to ensure accurate categorization of outcomes, clarity, and the use of simple language that can be easily understood by all stakeholder groups. Before the Delphi process begins, the Delphi survey will undergo pilot testing with at least 4 researchers or clinicians external to the core research team and 4 patients or family members to assess face validity and ensure that the wording is clear and easily understood. As part of this pilot test, participants will be asked to report the time taken to complete the survey and to provide feedback on any difficulties in maintaining attention or engagement. On the basis of this feedback, we will make all necessary refinements to optimize clarity, usability, and feasibility for all stakeholder groups.

Stakeholder Recruitment and Sample Monitoring

Overview

We will seek a purposive and maximum variation sample from 3 key stakeholder groups—ICU survivors and their family members, researchers, and clinicians—drawn from an international population [26,27]. ICU survivors and family members will be included to capture patient-centered perspectives that may differ from those of clinicians and researchers. Clinicians and researchers will be recruited for their specialized expertise, ensuring that the selected outcomes are clinically meaningful, measurable, and aligned with current evidence and best practices. Multimedia Appendix 3 outlines the key sampling characteristics for stakeholders. To ensure that our participants represent a diverse mix of these characteristics, we will continuously monitor participant demographics during recruitment and adjust recruitment strategies as needed to allow for maximum variation and address any gaps in representation.

Recruitment Methods

To recruit ICU survivors and family members, we will use a multimethod strategy that includes the use of a dedicated study X (formerly Twitter) account, engagement with relevant patient and family support and advocacy groups (eg, the Canadian Critical Care Trials Group Patient & Family Partners Community), outreach through personal contacts, and snowball sampling. Participants will be included if they, or someone they consider a family member, have experienced physical restraint in an ICU setting. In addition, they must be able to read and speak English.

Researchers will include individuals who have published at least one clinical study related to any area of adult critical care. Clinicians will encompass physicians, registered nurses, respiratory therapists, and allied health care professionals (eg, physical therapists) with varying levels of experience in adult ICUs. All participants must be able to read and speak English. Recruitment of both researchers and clinicians will be conducted through personal contacts, snowball sampling, and emails to corresponding authors of the studies included in our scoping review. While practical, this approach may result in over- or underrepresentation of stakeholder groups, potentially influencing which outcomes are prioritized in the Delphi survey. To monitor and mitigate this, we will track participant demographics, professional backgrounds, and geographic distribution across rounds. Broad outreach strategies, including social media campaigns and dissemination through professional networks, will be implemented alongside targeted engagement with patient and family advocacy groups serving diverse communities to enhance representativeness. Recruiting participants who can speak and read only English may exclude non-English-speaking stakeholders, potentially underrepresenting certain cultural or patient perspectives. Although resource constraints preclude translation of study materials, we will actively engage organizations that serve multilingual populations to facilitate participation and ensure diverse perspectives.

Sample Size

There are no strict guidelines or formal power calculations for determining the sample size in a COS consensus process, as it is influenced by practical considerations and the scope of the COS [22]. However, it is emphasized that broad representation across all key stakeholder groups is crucial. To ensure comprehensive and inclusive input, we will aim to recruit 60 to 80 participants, with 20 to 30 participants per individual stakeholder group selected deliberately to represent all characteristics outlined in Multimedia Appendix 3. For the consensus meetings, we will aim to recruit 15 to 20 participants, including representatives from each key stakeholder group. This sample size was selected based on published COS studies and the recommendation in the COMET Handbook [22,28,29]. Participants will be purposively selected to ensure diverse perspectives across disciplines, geographic locations, and experience with physical restraint use in ICUs.

Consensus Process for the COS

The consensus process will include 2 web-based modified Delphi survey rounds, followed by a modified nominal group meeting.

Delphi Survey Round 1

Overview

The Delphi survey will be administered using REDCap (Research Electronic Data Capture; Vanderbilt University), a secure platform that allows customized survey design and automated email distribution, making it well suited for multiround Delphi studies. The first part of the survey will collect baseline data to characterize the stakeholder sample and assign each participant a unique identifier. This identifier will allow for personalized follow-ups and reminders in subsequent rounds. Participants will be asked to self-select their stakeholder group (eg, ICU survivors, family members, clinicians, or researchers).

The second part will present the list of outcomes described in lay terms, with any medical terms provided in parentheses, for participants to rate based on importance, without consideration of measurability or feasibility. The importance of each outcome will be rated using the GRADE (Grading of Recommendations, Assessment, Development, and Evaluations) approach on a 9-point Likert scale: 1 to 3 (not important for inclusion), 4 to 6 (important but not critical), and 7 to 9 (critical for inclusion) [30]. The GRADE scale was selected because it is recommended

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by COMET to facilitate maximum discrimination between survey items [22]. To reduce incomplete responses, the survey will include an "unable to score" option. Participants will also have the opportunity to provide free-text comments and suggest additional outcomes. To minimize presentation bias, the order of outcome domains will be randomized. Participants will have 3 weeks to complete the survey, with 2 reminder emails sent: one at the start of the second week and another at the beginning of the third week.

Round 1 Analysis

For each outcome, we will calculate the proportion of participants rating it as 7 to 9 (critical for inclusion), 4 to 6 (important but not critical), or 1 to 3 (not important for inclusion) for the entire stakeholder panel and each stakeholder group separately. All survey responses will be analyzed on an item-by-item basis. Partial completions will be retained, as responses to individual items may still offer valuable insights and contribute meaningfully to the consensus process.

If new outcomes emerge in round 1, the steering committee will carefully review them to ensure that they represent distinct concepts (meaning that they are not overlapping in definition or intent with existing outcomes), are clearly articulated, and are free from duplication before being included in round 2. If needed, a third Delphi survey round may be conducted specifically for these new outcomes, allowing for 2 rounds of scoring for each outcome before the final consensus meeting.

Delphi Survey Round 2

Overview

Participants who complete round 1 will be invited to take part in round 2. All outcomes from round 1 will be carried forward to round 2. Any newly identified outcomes from round 1 will also be introduced in round 2 for scoring on the 9-point GRADE Likert scale. Participants will receive a summary of responses from round 1, including aggregated feedback from all stakeholder groups, a summary of responses for each stakeholder group, and their own individual responses. Participants will be asked to rescore each outcome using the GRADE scale. If a participant adjusts their rating, moving it into a new category (eg, from "important but not critical" to "critical for inclusion"), they will be prompted to provide a free-text rationale for the change. The same 3-week response window and 2 email reminders at the beginning of weeks 2 and 3 will be sent to all participants.

Round 2 Analysis

For round 2, we will calculate the proportion of participants rating each outcome as either "critical for inclusion" or "not important for inclusion." As recommended by the COMET Handbook, outcomes will be brought forward to the consensus meeting only if at least 70% of the respondents rate them as "critical for inclusion" and less than 15% rate them as "not important for inclusion" across all stakeholder groups combined [22]. We will also calculate the proportion of participants rating each outcome separately within each stakeholder group. Outcomes with mixed ratings—for example, those that reach consensus in the patient or family group but with clinicians on the fence—will be brought forward to the consensus meeting for in-depth discussion and potential rerating.

Attrition Bias Between Rounds

Attrition bias may arise if a subset of participants drops out or fails to respond between rounds, resulting in a nonrepresentative final group [22]. Differential attrition across stakeholder groups (eg, clinicians, researchers, or patient representatives) may disproportionately influence which outcomes are prioritized, potentially skewing the Delphi survey results toward the perspectives of participants who remain engaged. To mitigate this risk, participants will receive personalized invitations, multiple reminders, and direct access to the research team for support [31]. The survey will be scheduled outside holiday periods, and its length will be optimized to reduce participant burden. A 3-week response window will be provided, and participants will be acknowledged for their contributions through a personalized thank-you email. Regular updates on study progress and findings will also be shared to maintain engagement.

Attrition rates will be monitored and reported in accordance with Core Outcome Set–Standards for Reporting guidance, including the number and characteristics of participants who drop out. Characteristics of completers and noncompleters will be compared to assess whether systematic differences exist. Although there is no strict threshold for an acceptable response rate, an attrition rate of up to 20% is generally considered acceptable [22]. If attrition exceeds this threshold between rounds 1 and 2, we will extend the survey period and invite additional eligible participants to ensure sufficient representation.

Consensus Meetings for the COS

To finalize the outcomes for inclusion in the COS, we will conduct 1 online consensus meeting, offered in 2 separate time slots to accommodate different international time zones and maximize stakeholder participation. If selection of the final outcomes for the COS cannot be decided, an additional meeting will be scheduled. All meetings will be conducted via Zoom (Zoom Video Communications, Inc) and will include broad representation from all key stakeholder groups. The research team will facilitate the meetings, using Zoom features such as breakout rooms for small-group discussions, virtual whiteboards, and chat functions to enhance engagement and streamline the consensus process. The consensus meeting will follow a structured process: (1) project leads provide an overview of Delphi survey round 2 results and the purpose of the meeting; (2) participants engage in small-group discussions to begin ranking outcomes that reached the consensus threshold in Delphi survey round 2; (3) small groups present their rankings in a large-group discussion; (4) participants are reshuffled into new small groups to refine rankings with facilitator guidance; and (5) small groups share revised rankings in a final large-group discussion, followed by formal anonymous voting to confirm consensus on the final COS. This approach ensures balanced input from all stakeholders, minimizes the influence of dominant voices, and allows participants to prioritize outcomes from most to least important.

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Stage 3: Development of the COMS

Information Source

For each outcome that achieves consensus in our COS consensus meeting, we will identify the most relevant outcome measurement instruments and their corresponding measurement time horizons from the studies included in our scoping review. If an outcome identified during the consensus meeting was not captured in the scoping review, we will consult existing critical care–specific COSs to determine appropriate measurement instruments and time horizons [29,32,33]. Each identified instrument will be appraised using the COSMIN risk-of-bias checklist to assess measurement properties such as reliability and validity. Our research team includes a member with methodological expertise in outcome measurement, including the application of the COSMIN framework and evaluation of psychometric properties in critical care contexts. We will also assess feasibility through consultations with our research team, relevant stakeholders experienced in using these instruments in ICU settings, and representatives from our patient and family member group. In preparation for the COMS consensus meeting, we will develop and distribute comprehensive "measure cards" to all participating stakeholders, using plain language to ensure that they are understandable to all stakeholder groups. Each card will outline the scope of the COMS, provide a clear description of each proposed measurement instrument, and summarize its psychometric properties and feasibility of use in clinical practice.

Consensus Meetings for the COMS

We will send an invitation via email to stakeholders involved in the COS consensus meetings, inviting them to participate in online COMS consensus meetings on Zoom. To accommodate participants from different time zones and encourage maximum involvement, we will provide several scheduling options. We will ensure that attendees represent our key stakeholder groups.

Before the consensus meetings, stakeholders who have agreed to participate will be invited to propose additional measurement instruments for consideration. Any newly suggested instruments will undergo a rigorous evaluation by the research team to determine their validity, reliability, and feasibility before inclusion in the consensus discussions.

Members from the research team will facilitate the COMS consensus meetings. At the outset of these meetings, participants will be provided with a clear overview of the COMS scope, inclusion criteria for measures (ie, reliability, validity, and feasibility), and the voting process. For each outcome, measurement instruments outlined in the briefing documents will be presented, followed by structured small- and large-group discussions. Voting will be conducted using Zoom's polling function, with response options of yes, no, or uncertain for inclusion in the COMS. Each participant will vote for a single option per poll and will be encouraged to select "uncertain" rather than abstain if undecided. Consensus will be defined as at least 70% of participants voting "yes" for inclusion. If consensus is not reached in the first vote, additional discussion will follow before a second round of voting. If consensus remains unresolved, the reasons will be documented. After finalizing the selection of measurement instruments, participants will discuss and vote on appropriate measurement time horizons for those measures that reached consensus.

Ethical Considerations

Before study commencement, we will obtain centralized ethics approval through our home institution and secure research ethics board or equivalent approval from any institution or country that requires it. Informed consent will be obtained from stakeholders before the COS and COMS consensus meetings and will be documented via signed forms. Clear information sheets outlining the study purpose, procedures, voluntary participation, and withdrawal rights will be provided. Participation in the Delphi survey rounds will be considered implied consent. All data will be handled with strict confidentiality, encrypted, stored on a password-protected computer, and accessible only to the research team. Data retention and destruction will follow institutional and regulatory requirements, ensuring compliance with applicable privacy regulations. Participants will be offered compensation for their time in the form of a US $20 gift voucher, subject to availability of funding. This will be clearly explained during the consent and recruitment process.

Results

The outlined methods will support the development of a COS and a COMS for studies on physical restraint minimization in adult ICUs. Establishing these standardized sets could strengthen evidence synthesis, drive meaningful practice change, and ultimately improve patient outcomes. Research ethics board approval is in progress. Recruitment has not yet begun. The project is scheduled to begin in January 2026 and conclude by April 2027, with results expected to be published by June 2027.

Discussion

This study is expected to produce a consensus-based COS and COMS to guide outcome selection and measurement in research focused on physical restraint minimization in adult ICUs. Previous studies on physical restraint use and minimization have used a variety of outcomes and measurement tools, leading to significant heterogeneity that limits the ability to effectively synthesize evidence and inform clinical practice. The development of a COS and a COMS aims to standardize outcome selection and measurement, incorporating input from diverse stakeholders. A key strength of this COS and COMS protocol is its adherence to the recommendations outlined in the COMET Handbook. The protocol has been developed in accordance with relevant guidelines, including the Core Outcome Set–Standardized Protocol, ensuring methodological rigor. In addition, multiple methods will be used to enhance the comprehensiveness of COS and COMS development, including an updated scoping review, a review of previously conducted interviews with family members, a Delphi process, and consensus meetings. Another significant strength is the novelty of this work—no existing COS or COMS currently address this area, making their development both timely and essential. Furthermore, the inclusion of international stakeholders will

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enhance the global applicability and relevance of the final COS and COMS.

Limitations include restricting the inclusion of studies in our scoping review to those published in English, as well as recruiting only participants who can read and speak English. This may limit the ability to capture outcomes and measurements that are deemed significant by non-English speakers. Another limitation is that the qualitative interviews being reviewed were conducted solely with family members and were not originally designed to explore their perspectives on outcomes they believe should be selected and measured in physical restraint minimization studies. As a result, the identified outcomes from these interviews may not be comprehensive and may not fully reflect the patients' perspectives. However, by including both ICU survivors and family members in the steering committee and broader panel, we will ensure that the identified outcomes are not only relevant to their experiences but also capture any additional outcomes they deem significant. The COS and COMS will be shared with all Delphi survey and consensus meeting participants through plain-language summaries and email updates, with optional webinars to explain key findings. Results will be published in peer-reviewed journals and presented at relevant conferences, with deposition in the COMET database to ensure accessibility for researchers. To support translation into practice, the COS and COMS will be disseminated through ICU professional organizations and international networks, including the Canadian Critical Care Society and the Restraint Reduction Network, facilitating integration into practice standards. In conclusion, the outlined methods will facilitate the development of a COS and a COMS for studies on physical restraint minimization in adult ICUs. By standardizing outcome selection and measurement, these sets have the potential to enhance evidence synthesis, inform best practices, and ultimately improve patient care and safety.

Acknowledgments

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Authors' Contributions

ZA was responsible for the study conception, methods development, manuscript writing, and revisions based on reviewer comments. LR contributed to the study conception, methods development, manuscript editing, and revisions based on reviewer comments. CD and SM contributed to the study conception, methods development, and manuscript editing. WE, NA, MA, and RS contributed to methods development and manuscript editing. AO contributed to revisions based on reviewer comments, provided intellectual input, and supported manuscript editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Standardized protocol statement.
[PDF File (Adobe PDF File), 90 KB - resprot_v14i1e76405_app1.pdf]

Multimedia Appendix 2
Study timeline.
[PDF File (Adobe PDF File), 91 KB - resprot_v14i1e76405_app2.pdf]

Multimedia Appendix 3
Key sampling characteristics for stakeholders.
[PDF File (Adobe PDF File), 88 KB - resprot_v14i1e76405_app3.pdf]

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Abbreviations

COMET: Core Outcome Measures in Effectiveness Trials
COSMIN: Consensus-Based Standards for the Selection of Health Measurement Instruments
GRADE: Grading of Recommendations, Assessment, Development, and Evaluations
ICU: intensive care unit
REDCap: Research Electronic Data Capture

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Protocol

Digital Health Tool for Preventing Blindness From Diabetic Retinopathy: Protocol for a Qualitative Study

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Abstract

Background: Diabetic retinopathy (DR), a leading cause of preventable blindness among working-age adults, leads to worse health outcomes among Black, Latine, and individuals with lower income in comparison to other ethnic, racial, and socioeconomic groups in the United States.

Objective: We aim to engage community members directly to identify barriers and facilitators of DR screening and co-design a digital health tool that is accessible, user-friendly, and community-responsive.

Methods: We conducted focus groups with individuals from the Greater New Haven, Connecticut area, aged 18 years or older, and diagnosed with diabetes to (1) conduct a comprehensive disease-management needs assessment and (2) inform the development of a community-responsive digital health tool to optimize DR education and to increase access to DR screening in high-risk populations. We transcribed the focus group interviews, used rapid qualitative analysis to generate themes, and completed affinity mapping to identify content and features for a digital health tool for preventing blindness from DR.

Results: We recruited and interviewed 19 individuals (13/19, 68% female; 9/19, 47% Black; 5/19, 26% Hispanic; 2/19, 11% Native American or Alaska Native) for 4 focus groups. Over 94% (18/19) had access to smart devices other than a computer. Participants self-reported mean hemoglobin A_{1c} of 6.77 (SD 1.93). Approximately 58% (11/19) of the participants completed some college. Frequently occurring themes (>30) obtained from coding contextual interviews were desired app attributes such as options for customization, covering topics such as, the mental impact of living with diabetes, informal support (eg, peer support), diabetes education, barriers to controlling blood sugar and maintenance of health, dietary guidance, and notifications. We created high-fidelity wireframes incorporating key features. Next, we will iteratively design a prototype with community feedback.

Conclusions: We anticipate that this study will characterize the experiences of people living with diabetes. Using a community-led approach,we will continue to analyze the data that will generate insights regarding the key features, content, and benefits that are most important for the creation of a digital health tool for DR prevention.

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KEYWORDS

diabetes mellitus; DM; diabetic retinopathy; mobile apps; digital health tool; community engagement; preventable blindness; user-centered design; mobile health; mHealth; digital tool; blindness; prevention; qualitative study; community-led

Introduction

Diabetic retinopathy (DR), a leading cause of preventable blindness among working-age adults, represents a significant public health challenge, particularly among racial and ethnic minoritized communities in the United States [1,2]. Despite advances in therapeutic interventions, disparities in screening and treatment outcomes persist, disproportionately affecting non-Hispanic Black, Latine, American Indian, Alaska Native, and lower-resourced communities [3-6]. These groups are less likely to be screened for DR and are more likely to present at advanced stages of the disease. They also face significant barriers to follow-up care, which ultimately leads to a higher prevalence and severity of the condition [4-8].

The underutilization of DR screening services in these high-risk populations highlights a critical gap in our current health care delivery models, which fail to account for the nuanced needs of diverse communities. Moreover, existing health technologies, including mobile health tools, often do not reach or effectively serve marginalized groups, further exacerbating health disparities [9-13]. This inequity stems from a variety of complex factors, including socioeconomic conditions, structural racism, historical underrepresentation in health research, and lack of culturally tailored health interventions [14-17].

Addressing these challenges requires innovative approaches that embrace technological solutions while prioritizing community engagement and responsiveness to underserved populations' specific needs and preferences [18]. Utilizing feedback from intended users and understanding their technology usage and behaviors can mitigate the risk of perpetuating further inequalities [19-21]. Thus, the primary objective of this study is to develop and evaluate a novel digital health tool designed to enhance DR screening rates and health education through a community-driven design. By integrating community insights into every stage of the development process, this project aims to bridge the gap between evidence-based screening practices and the actual utilization of these services among those most at risk.

Findings from the 2005 to 2008 National Health and Nutrition Examination Survey showed that 10.6% of their US cohort aged ≥40 years, representing an estimated 9.8 million individuals nationally, were unaware that they had DR [22]. Through a community-led research approach, this project will engage community members directly to identify the barriers and facilitators of DR screening and co-design a digital tool that is accessible, user-friendly, and culturally relevant. The anticipated outcome is a scalable digital health solution that not only increases DR screening rates but also serves as a model for addressing health care disparities in other domains.

Methods

Study Design, Study Setting, and Participants

This protocol has 2 specific aims: (1) to complete a comprehensive needs assessment and (2) to develop a community-responsive digital health tool to increase access to DR screening in high-risk populations and optimize DR education. There will be 4 phases that encompass the 2 aims of the protocol: needs assessment, design, development, and evaluation (Figures 1 and 2). This protocol has been initiated, and we have completed our first aim. We are currently working on our second aim. We recruited individuals with diabetes mellitus from the Greater New Haven, Connecticut area. Results from a study by Guest et al [23] revealed that more than 80% of all themes are discoverable within 2-3 focus groups, and 90% of themes could be discovered within 3-6 focus groups. To ensure rich discussion and engagement, we planned to conduct 4 focus groups with 5-8 participants each session, as smaller groups facilitate deeper participant interaction while still allowing for diverse perspectives.

Figure 1. Overview and steps for aim 1 of digital health tool creation.

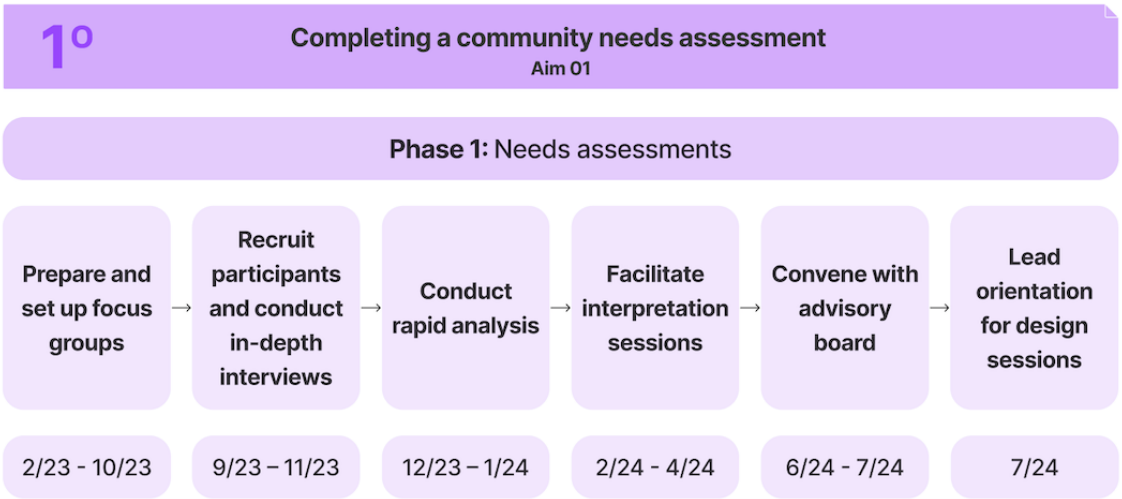

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Figure 2. Overview and steps for aim 2 of digital health tool creation.

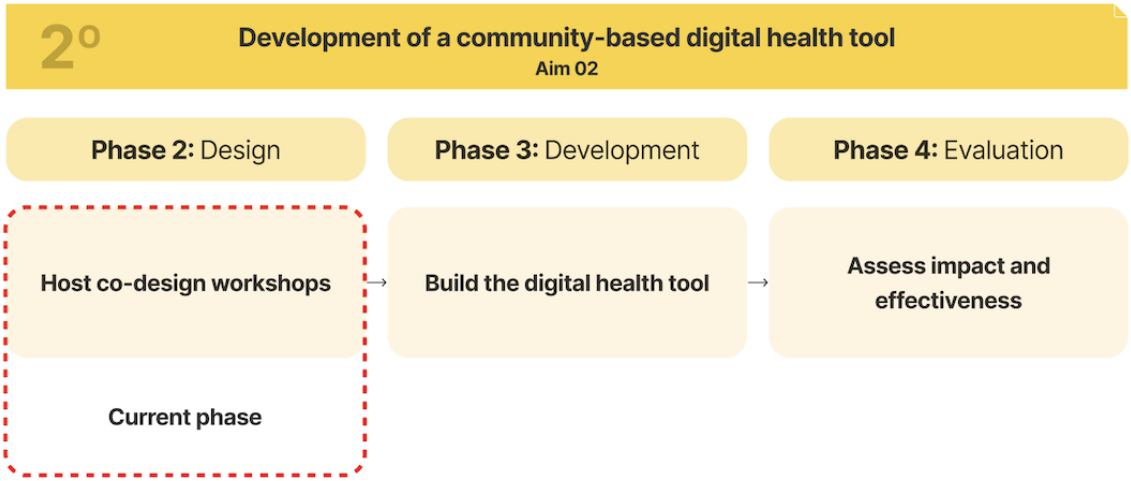

This research was conducted with the Sight-Saving Engagement and Evaluation in New Haven (SEEN) Lab at the Yale School of Medicine and the Consumer Health Informatics Lab (CHIL) at Yale School of Public Health. The SEEN Lab combines quantitative and qualitative research methods to address health disparities in DR by designing sustainable community-engaged solutions toward equity. CHIL engages in cutting-edge research, focusing on inclusive design and usability testing of consumer health products for diverse populations.

We developed this study in collaboration with the community-engaged research steering committee, a longstanding academic-community partnership. Members of this group provided insight into community-level needs and individual capacities. We convened an advisory board that includes local stakeholders, health care providers, and community leaders to provide insights into the community needs and to guide the research process, ensuring the tool's development is grounded in real-world contexts. At every phase of this study, we will convene to disseminate findings to the board and to receive guidance on our design and methods in order to continuously address specific community needs and contexts. Each advisory board member will receive a US $50 gift card per advisory board meeting attended.

Aim 1: Completing a Community Needs Assessment

The first aim of the protocol focuses on conducting a community needs assessment.

Phase 1: Needs Assessment

Research Design and Data

For our digital health tool, we used 4 theoretical frameworks to help formulate a community needs assessment. The Equity-focused Dissemination and Implementation framework, which provides a foundation for the operationalization of widespread health equity research implementation, served as the overarching guidance for our study's development [24]. The Consolidated Framework for Implementation Research informed our study's methodological structure to convene an advisory board, conduct focus groups, and subsequently analyze the focus group transcripts, as this framework gives guidance on organizing implementation [25,26]. The Four Is of Health Equity provide strategies on how to reduce health disparities and promote health equity [27]. We used this framework to steer our study's objective to focus on identifying health disparities and implementing evidence-based interventions to reduce disparities. The COREQ (Consolidated Criteria for Reporting Qualitative Research) checklist provided a guided reflection of the study upon submission of the manuscript. Lastly, the Reach, Effectiveness, Adoption, Implementation, and Maintenance (RE-AIM) framework informed the metrics the research team will use to evaluate the design process of the digital health tool [28].

Recruitment and Interviewing of Individuals Living With Diabetes

Research team members from the SEEN Lab (JF, TC, AF) and CHIL (BA, MK) recruited participants from the Yale Eye Center, primary care offices, and community settings such as restaurants and libraries. We engaged directly with the community through connections and community networks across Greater New Haven community clinics, faith-based organizations, and the Yale New Haven Hospital network [23]. To be eligible for the focus group, participants needed to be at least 18 years old, have a diagnosis of type 1 or type 2 diabetes mellitus, speak English fluently, and be able to attend the interview in person. Although the ability to speak English fluently restricted the inclusivity of our cohort, it was necessary to make this restriction to efficiently design the first prototype of the tool. Future iterations of the tool will account for non-English speakers. Each participant received a US $50 gift card for their participation.

Data Collection

The research team (AF, JF, TC, BA, KHN, TM, MS, QY) developed an interview guide in collaboration with the advisory board (Multimedia Appendix 1). The interview guide includes questions about the participants' experiences with diabetes, their eye health awareness, their technology usage, and their preferences for features in a digital tool to learn about eye health and screening. We collected data from October to November 2023. Semistructured focus group interviews were conducted to gathered qualitative data on participant experiences with diabetes management, awareness of DR, and perceptions of

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existing health technologies. One member from the research team (AF) served as the moderator, and the remainder served as notetakers (BA, MK, JF, TC, KHN, VHK). The focus groups were audio-recorded, professionally transcribed, and analyzed [24,25]. Participants provided informed consent prior to the interview, and identifying information was removed from the transcript to preserve confidentiality.

Data Analysis

The analytic team comprised of members from the SEEN Lab and CHIL (TC, JF, BA, AF, MK, AG, SSA, AL, KHN, TM). Following each focus group interview, the research team conducted the rapid qualitative analysis method to efficiently process data and facilitate interpretation sessions [26,29]. This method allowed the team to systematically collect and analyze participants' thoughts and experiences within a shorter timeframe [30]. Before the first focus group session, the analytical team developed a structured template (Multimedia Appendix 2) to organize key insights, including the research team members' initial impressions, detailed accounts of participants' experiences with diabetes care and the use of technology in health care and eye care, and the team member's' summative thoughts on each interview. The research team made minor adjustments to the template as needed to gather more information about eye care experiences. Next, the research team engaged in a series of interpretation sessions with affinity mapping, which is a collaborative process to thematically analyze qualitative data [31]. To keep the information organized, the information was compiled using Miro [32]—an online visual collaboration tool that uses digital sticky notes to help teams organize and synthesize their thoughts. These sessions were moderated by a facilitator (TM). The objective of these sessions was to analyze all the data, which included the original transcripts, summary documents from the rapid review, and notes from each focus group, to systematically code the interviews, categorize responses into emerging themes, and prioritize features. Over multiple sessions, these sticky notes were reorganized to create thematic categories, which will be used to create draft models for the design of the digital health tool [31].

Aim 2: Development of a Community-Based Digital Health Tool

The second aim consists of 3 phases: design, development, and evaluation of the digital health tool for DR prevention.

Phase 1: Design

The design phase leverages insights from the focus groups in the needs assessment phase to cocreate the digital health tool with community members. Using the list of app features and content generated from focus group analysis, the research team created detailed user journey maps to visualize different user experiences as the participants, advisory board members, and other stakeholders interact with the tool—identifying pain points and opportunities to enhance user engagement. First, the research team will collaborate with the advisory board to develop culturally tailored health education content for the tool, including engaging and informative materials on DR, its risk factors, and the importance of regular screening. Then, the research team will develop low-fidelity wireframes and interactive prototypes. These prototypes will be tested and refined through usability testing sessions with community members to ensure that the tool is intuitive and user-friendly.

Phase 2: Development and Usability Testing

The next phase consists of building the digital health tool, which will involve translating design prototypes into a functional digital health tool. The research team will collaborate with designers and app developers to build the tool, ensuring it is accessible on various devices and integrates seamlessly with existing health care systems. Lastly, the research team will conduct a usability testing phase with a select group of intended users from the target population. The RE-AIM framework will guide the research team in choosing participants who are representative of the target population and the internal discussion among the research team regarding the tool, especially whether the tool has effectively improved health care management through keeping appointments, encouraging discussion about diabetes, and empowering users to make more informed choices in diet and exercise. The adoption criterion of RE-AIM will also encourage reflection on whether the tool is serving its target population directly. The team will summarize usability walk-through sessions qualitatively. Tobii eye-tracking software will be used to produce heat maps that identify the focus of the participants' attention on screens to inform user interface design. We will administer the Questionnaire for User Interface Satisfaction and analyze and summarize the open-ended portion. Areas that require optimization will be discussed with the design team, and well-designed areas will be highlighted. Efficiency will be measured by the time required to complete a series of tasks within the app prototype and the number of taps needed to complete each task. We will obtain information on user satisfaction with the app from the metrics calculated from the Questionnaire for User Interface Satisfaction. Statistical analysis will be conducted using SPSS (version 26; IBM Corp). The results of usability testing will inform the app design and help refine the features of the tool through iterative design. Next, we will evaluate the impact of the tool.

Phase 3: Evaluation

The final phase, evaluation, will focus on assessing the tool's impact and effectiveness in increasing DR screening rates. We will implement a pilot study to evaluate the tool in a real-world setting by using the RE-AIM framework to assess its reach, effectiveness, adoption, implementation, and maintenance. Feedback from our intended users will be gathered during the pilot. The feedback will be used to identify and resolve problems, improve usability, and refine tool features before the full launch. We will collect quantitative and qualitative data from users—tracking screening rates, user engagement metrics, and participant feedback.

Lastly, we will conduct iterative usability testing sessions with a diverse group of end users to continuously improve the tool's interface and functionality. The participants will be adults recruited from local community organizations such as the Dixwell Congregational Church, a historically Black church, with a congregation that spans the ages from children to older adults (65 years and older). Insights from these sessions will

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inform ongoing adjustments to enhance user experience and ensure the tool meets the community's needs.

Ethical Considerations

This study received approval from the Yale School of Medicine Institutional Review Board (IRB # 2000034710). All research procedures were followed in accordance with the Yale School of Medicine institutional review board and the World Medical Association's Declaration of Helsinki. All participants provided informed consent and were given the opportunity to opt out at any time during the study. All data pertaining to the results of focus groups and related subsequent analyses were deidentified to maintain privacy and confidentiality, and participant-protected health information was stored on an encrypted Yale University information technology department–managed SharePoint server with access restricted to authorized research team members. No images in this manuscript contain participant-identifiable information. Participants received a US $50 gift card for their participation, and advisory board members also received a US $50 gift card for their participation.

Results

As of December 2023, we completed 4 focus groups with 19 participants. Data from the interviews were used by the research team to conduct descriptive rapid analysis of each focus group session transcript and categorize common themes: the need for enhanced diabetes knowledge, diet-related guidance, informal support through peer connections, integration with electronic health records, and mental health support needed for individuals living with diabetes. The research team then conducted interpretation sessions from February 2024 to April 2024 to efficiently process data, identify pain points, and share findings with the broader study team to start the design process. The team identified features that address the themes of needs expressed by the participants interviewed. The features included a social media component that allows "following" and "liking" posts to create a supportive community, a curated library of recipes for nutritional guidance for people with diabetes, customizable home screens and health metrics like body mass index calculations, integration of functions and data within the MyChart app, appointment reminders, and a curated library of sources of information that served both as a reference for the user and as the training data for a large language model to answer the user's questions reliably. As of April 2025, the design sprint has been completed, with low and high-fidelity wireframes incorporating the planned features. The next step is to plan for the app's development and implementation.

Discussion

Overview

In the United States, approximately 9.6 million individuals are diagnosed with DR [27]. Unfortunately, many living with DR face barriers to screening and treatment [4,5,7]. DR is a leading cause of blindness, which is preventable and often treatable when patients are empowered to receive timely screening and treatment [1,28,33]. Advancements in technology, such as personal digital health libraries, have helped increase patient engagement and provide the general population with instant access to medical records, including diagnoses and treatment options. Yet, communities of color, Latine, and individuals with lower income are diagnosed and treated less often, experience worse outcomes, and generally engage less with DR care [9-13].

Anticipated Findings

We anticipate that the patient community with DR needs a culturally responsive digital health tool that prioritizes the communities it serves. Valuable insights from the first phase of the study will enable our development of a tool that aligns with the vision held by the communities it serves. Our community-based approach not only lifts the voices of participants from communities, which often go unheard in health care research, but will also empower them through an educational component, including connecting the participants to resources to help them manage DR.

The culturally responsive digital health tool will include 3 components: a risk calculator, educational features, and self-scheduling software. The risk calculator will help assist providers, especially eye care providers, in clinical decision-making to identify if patients are at a high risk of certain ophthalmic diseases [34]. The educational features will include a large library of curated sources and information, which will also serve to train an artificial intelligence chatbot that will be able to answer queries for users. The self-scheduling software tool will be able to assist with health care navigation by providing appointment reminders and suggestions on which medical practitioners are most recommended by patients.

We will co-design the tool with community partners and continue by using coded interview and user experience data as a guide to iteratively design and evaluate the efficacy of our digital health tool as it is developed. We expect the digital health tool to be well received by and engaging for the Black, Latine, and lower-income communities. We will adhere to the RE-AIM framework to guide the dissemination of our tool, starting with local communities.

Study Limitations

This study will provide valuable information to help create a digital health tool, however several anticipated limitations can and have appeared in this study. In using focus groups as a methodological approach, there are some limitations that can arise. Some challenges that can arise include recruitment of participants, group dynamics, group composition, sample size, dynamics, and logistic barriers. When designing focus group sessions, a moderate sample size and number of sessions allow for a diverse range of participant experiences and perspectives, ensuring meaningful insights [35]. Although literature suggests a minimum of 4 focus groups for qualitative research, sometimes there is potential for a limited sample size due to various circumstances such as accessibility due to timing, transportation, and availability [36,37]. Despite the research team's best efforts, participant availability and logistical barriers impacted attendance. Some focus groups had higher attendance than others. The research team recognized this possibility and scheduled multiple sessions in advance, providing convenient weekday and evening sessions, and were flexible to increasing

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the number of focus group sessions, if needed, to ensure data saturation [35]. Although we could not provide virtual participation, that may be a possibility for future focus group sessions that may allow more accessibility for participants. We also acknowledge that during the recruitment period, we were only able to enroll participants fluent in English. As a result, some individuals were excluded, as proficiency in English was necessary for participation. Future studies could address this limitation by incorporating focus groups with non-English speakers (eg, Spanish only) participants to ensure their perspectives are represented, particularly as they are part of the racial and ethnic minoritized populations.

One inherent limitation of focus group research is selection bias, as participants may not fully represent the broader population. Instead, they tend to provide a snapshot of perspectives from those who chose to participate [38]. The research team aimed to recruit participants with relevant experiences to provide meaningful insights [35]. We carefully considered group composition in terms of number, gender, and age distribution [39,40]. Our focus was to provide a diverse range of perspectives within each focus group. Although we aimed to recruit a diverse sample, we recognize that certain demographic groups may have been underrepresented.

Given the study's setting within a smaller urban community, there was a possibility that participants knew or were familiar with one another. During the focus group sessions, we emphasized confidentiality at the beginning of each session and ensured that facilitators guided discussions in a way that maintained privacy and encouraged broad, nonidentifying contributions.

Another potential limitation we anticipated was participants' cultural mistrust, which could influence participants' willingness to share personal experiences [41]. To foster a comfortable and trusting environment, we ensured that the moderators, facilitators, and/or notetakers were members of the same cultural or community group as the participants. This approach aimed to build rapport and encourage open discussion while minimizing reluctance to disclose information.

Despite these limitations, we believe our approach allowed us to gather meaningful insights that contribute to our study objectives.

Conclusion

Despite the existence of effective treatments for DR, historically marginalized populations experience poorer health outcomes, including irreversible vision loss. Personal health information technologies have focused on developing patient portals that facilitate communication between patients and providers and enable control of information by the patients themselves. However, their *one-size-fits-all* approach leaves behind communities of color, Latine, and lower-income communities. Our community-based approach empowers the creation of a culturally responsive digital health tool that will engage more of the patient population with DR.

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Conflicts of Interest

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Multimedia Appendix 1
Focus group topic guide.
[DOCX File , 15 KB - resprot_v14i1e65894_app1.docx]

Multimedia Appendix 2
Diabetic retinopathy digital health tool focus group interview summary template.
[DOCX File , 18 KB - resprot_v14i1e65894_app2.docx]

Multimedia Appendix 3
COREQ checklist.
[DOCX File , 33 KB - resprot_v14i1e65894_app3.docx]

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Abbreviations

CHIL: Consumer Health Informatics Lab
COREQ: Consolidated Criteria for Reporting Qualitative Research
DR: diabetic retinopathy
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
SEEN: Sight-Saving Engagement and Evaluation in New Haven

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Protocol

Understanding Intimate Health in Online Spaces Among Women in Aotearoa New Zealand: Protocol for a Mixed Methods Study

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Abstract

Background: Social media has become an important tool facilitating communication and connection in a postpandemic landscape. This context has prompted an increase in the sharing of information and disinformation about general health. This provides an opportunity to seek information about and support for intimate (ie, sexual and reproductive) health, with the added assurance of maintaining a degree of anonymity in a socially taboo context.

Objective: The aim of this study is to better understand how women in Aotearoa New Zealand use social media to access sexual and reproductive health information and support. Engagement with stakeholders and community groups will be undertaken throughout the study to analyze the findings and present solutions to identified issues.

Methods: This online survey is the first stage in a study which uses a mixed methods approach involving the collection of qualitative and quantitative data through an anonymous survey on the Qualtrics platform. Recruitment occurred through advertising on the University of Auckland | Waipapa Taumata Rau and University of Waikato social media accounts and physical posters in various locations nationwide. These posters prioritized recruitment of groups that are often underrepresented. This study will also present the preliminary results to stakeholders, prioritizing *whakawhanaungatanga* (building relationships) and *manaakitanga* (kindness and respect for others, emphasizing responsibility and reciprocity) in the co-designing of future research aims. Subsequent analysis of all the above data forms will be performed using reflexive thematic coding analysis, using codes derived from both the literature and emergent from the data. Results will be disseminated in academic, participant, and stakeholder circles. The analysis plan involves research assistants and investigators working collaboratively and independently, progressively comparing codebooks and results to reiteratively code for the eventual thematic results.

Results: Ethical approval to conduct this study was granted by the University of Auckland ethical review board on June 28, 2023, and an amendment to change survey questions and expand recruitment was approved on July 1, 2024. Online data collection

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closed in February 2025, and focus groups and interviews are scheduled to begin meeting in August 2025 with stakeholder engagement occurring throughout. Compensation was not provided for completion of the online survey, but will be provided (NZ $50 [US $28.93] vouchers) for focus group and interview participants when stage 3 of the project is undertaken.

Conclusions: From early data analysis, we anticipate survey results will confirm our hypothesis that social media communities can provide increased access to information and support for women who have had or continue to have limited access to intimate health care due to a number of factors, including social (embarrassment), structural (location), or cultural (lack of health care provider training) factors.

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KEYWORDS

sexual and reproductive health; social media; information dissemination; women's health; digital health

Introduction

During the COVID-19 pandemic, social media peaked as a major tool for communicating health information and connecting people to each other during a time of physical distancing; it was widely used by public health professionals and conspiracy theorists alike [1]. Since the beginning of the COVID-19 pandemic, the use of social media for obtaining health information and support on all kinds of health-related topics has increased [2]. The use of social media to convey information and provide support in relation to socially taboo topics, specifically sexual and reproductive health, will be further investigated in this study. We focus on the experiences of women living in Aotearoa New Zealand, and their use of social media for sexual and reproductive health information and support. We define social media as any online environment that builds relationships and facilitates connection as well as the sharing of information and lived experiences of those who use it. Textbox 1 provides definitions of important local terms.

Textbox 1. Local terms of reference

Hui: a meeting, workshop, or gathering.

Kanohi ki te kanohi: face-to-face interaction; a culturally significant approach in Māori contexts that emphasizes the importance of personal connection, presence, and direct engagement.

Koha: a gift or offering used to acknowledge a contribution, grounded in principles of reciprocity and care for others.

Māori: the Indigenous people of Aotearoa New Zealand.

Manaakitanga: the expression of care, hospitality, and kindness toward others, upholding their dignity and well-being.

Marae: a communal and sacred meeting space that serves as the focal point for Māori social, cultural, and spiritual life, typically including a meeting house (wharenui) and other associated buildings.

Takatāpui: a traditional Māori term that has been reclaimed to describe a person who is Māori and identifies with diverse genders and/or sexualities, encompassing both cultural and LGBTQIA+ identities.

Te reo Māori: the Māori language, an official language of Aotearoa New Zealand and a cornerstone of Māori identity, culture, and heritage.

Whakawhanaungatanga: the process of building and maintaining relationships through shared connections, trust, and mutual respect.

Sexual health is a state of complete physical, emotional, spiritual, mental, and social well-being regarding sexuality, sexual orientation, sexual expression, and gender identity [3]. It also encompasses the ability of a person to have safe and pleasurable sexual experiences [3]. Reproductive health extends this definition and focuses on a complete state of well-being in relation to the body's reproductive system and processes [3]. Reproductive autonomy is a core feature of this definition, as people must have autonomy over whether, when, and by what means they have a child [3]. The achievement of optimal sexual and reproductive health is dependent on environments that affirm, promote, and respect health for all individuals regardless of their sex assigned at birth or their gender [3]. This includes environments that allow individuals timely access to comprehensive, high-quality, and unbiased information, where they are free from coercion and discrimination [3].

The COVID-19 pandemic accentuated the crucial role of social media in information dissemination. Social media can be an effective communication tool in times of crisis, as the need to quickly disseminate information is particularly pressing [4]. Equally, the interactive nature of social media allows individuals to seek support from others. Social media provides opportunities for connection, identity formation, and a sense of group belonging [5,6]. Online communities on social media provide resources for individuals in relation to sexual and reproductive health information and support [7]—topics that are often shrouded in embarrassment and shame [8].

Despite appearing on the world stage to be socially progressive in many areas [9], Aotearoa New Zealand has a sexually conservative culture [10,11]. This makes seeking sexual and reproductive health information and support difficult for many. Fear of being judged, feeling shy, embarrassed, or ashamed, not knowing how to access care, and concerns about

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confidentiality are reported as reasons for unmet needs in sexual and reproductive health care service provision in Aotearoa New Zealand [12]. Adolescents and young adults appear to be the demographic most negatively impacted [12,13]. For Māori, stigma and negative societal attitudes toward sexual health intersect with the systemic racism inherent in Aotearoa New Zealand's health system [14,15]. All of these combine to negatively impact the way sexual and reproductive health information and support are accessed, as well as the quality of formal health care services provided [12,16]. This stigma intersects with other access barriers, such as cost, transport, and cultural fluency, limiting access to intimate health care. We posit that social media and online communities expand access to intimate health care by providing people with anonymous spaces to discuss and share information that they may not be able to discuss and share within their own communities, or in spaces where they lack anonymity.

In Aotearoa New Zealand, people who are Māori or Pasifika, have a disability, are overweight, or identify as lesbian, gay, bisexual, transgender, *takatāpui*, queer/questioning, intersex, asexual/aromantic/agender, or another marginalized identity (LGBTTQIA+) are more likely to have negative, hostile, and stigmatizing interactions with health care services [17-20]. Moreover, women from these vulnerable populations are more likely to face disparities and inequalities due to multiple levels of existing social injustice [21].

Women's sexual and reproductive health in Aotearoa New Zealand is of particular relevance due to the high incidence of sexually transmitted infections (STIs) in comparison to other Western countries [10,11]. National STI rates in Australia, the United States, and the United Kingdom are lower than regional STI rates in Aotearoa New Zealand [10]. Women in sexual relationships with male partners older than themselves may be particularly at risk of contracting an STI [11]. Other intimate health concerns include the long-term mental and physical impacts of untreated STIs, such as infertility and ectopic pregnancy [12,22], and the incidence of cervical cancer, which is often not adequately screened for in Aotearoa New Zealand [23].

For this study, we have chosen to define women as those who were assigned female at birth, and/or anyone who has ever self-identified or currently self-identifies as a woman. Upon consultation with extended networks, we acknowledge this inclusive definition will not be favored by everyone [24]. Defining gender and sexuality is an active space, and we recognize that these concepts are ever-evolving and that descriptions can and do change over time. Grounded in the underlying philosophical paradigm of intersectional feminism [25], this study's research question is as follows: In the context of women's experiences of the Aotearoa New Zealand health system, how do women use social media to find information and support around sexual and reproductive health?

Further, we ask what advantages and disadvantages they perceive regarding such social media use. The findings from pilot testing the survey [26] suggest that that individuals may find benefit from social media, as well as encounter feelings of embarrassment, shame, and stigma in their use of social media for sexual and reproductive health information and support.

Methods

Overview

This multistage study aims to (1) better understand the relationship between social media and women's sexual and reproductive health in Aotearoa New Zealand and (2) meaningfully engage with stakeholders and community groups to interpret the findings and propose solutions to identified problems.

This cross-sectional, mixed methods research will be conducted over 24 months in three stages: (1) online data collection, (2) presentation of findings to stakeholders, and (3) pilot focus groups and interviews. This paper addresses the primary stage of data collection (online data collection) and follows the Checklist for Reporting Results of Internet E-Surveys (CHERRIES) checklist [27].

Survey Design

The survey (Multimedia Appendix 1) targets women living in Aotearoa New Zealand who have used or use social media resources or communities to access information about sexual and reproductive health care. The survey draws from a convenience sample and asks for respondents who have ever identified or currently identify as women, and/or who were assigned female at birth. The survey asks for respondents who are aged 18 years or older, fluent in English, and live anywhere in Aotearoa New Zealand. The survey does not incorporate the ability to check for duplicate responses; nor does it have strict access controls. We recognize that this may impact the veracity of the results as a stand-alone dataset, but as this online survey is intended to be part of a 3-pronged approach collecting multimodal data, we believe that the data collected will be relevant and valuable in conjunction with the focus groups and individual interviews with known, recruited participants.

Ethical Considerations

Institutional Review Board Approval

This survey was approved by the Auckland Health Research Ethics Committee on June 28, 2023, for 3 years. The approval was amended on July 1, 2024, to expand the survey (AH25633).

Informed Consent

Participants were provided with a participant information sheet standard to the University of Auckland amended to reflect the specific aims of this research. Participants provided electronic authorization of their consent to participate at the beginning of the survey.

Data Protection

Survey responses are held securely at the University of Auckland. Email addresses provided are decoupled from survey responses prior to access by members of the research team. All storage complies with local data security guidelines, and data will be destroyed after 10 years.

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Compensation

Each focus group and interview participant will receive an NZ $50 (US $28.93) supermarket voucher as *koha* (gift) as a token of acknowledgment for their contribution to the research. Compensation was not provided for completion of the online survey.

Development and Pretesting

Development and testing of the survey occurred in 2020-2021 as part of a bachelor of nursing (honors) project. This is detailed in the thesis of author HP [26].

Stage 1: Online Survey

Recruitment Process and Description of the Sample Having Access to the Questionnaire (Contact Mode and Advertising the Survey)

The online survey was an open survey. Participant recruitment occurred through posts from the social media platforms of the Universities of Auckland and Waikato (Figure 1). Funding was allocated to push recruitment among specific population groups that are often underrepresented in online research; these groups are the focus of this study. Physical advertisements of our research were displayed on or in local community notice boards, coffee shops, gyms, libraries, local *marae* (communal and sacred meeting spaces), beauty salons, toilets, and supermarkets nationwide. The physical advertisement is shown in Figure 2. The researchers identified organizations invested in sexual and reproductive health care for sharing digital or poster recruitment flyers. These organizations were recruited as community partners as part of research outreach conducted by members of the research team.

Figure 1. Social media participant recruitment advertisement. The image does not show participants in this study. Image source: Leinio's Team via Canva.com.

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Figure 2. Physical participant recruitment advertisement. The image does not show participants in this study. Image source: Leinio's Team via Canva.com. Social media logos sourced via images from rawpixel.com on Freepik.

Survey Administration

The study used a web survey hosted on a static webpage by the University of Auckland via the Qualtrics XR platform (Qualtrics LLC). The University of Auckland hosts a number of surveys, and each survey includes a standardized information page regarding the research being conducted, as well as links to contact researchers. This research relied on outreach (detailed above in the *Recruitment Process* section) to bring visitors to the University of Auckland survey page. The survey was voluntary and questions were not randomized. The survey was open from July 1, 2024, to February 15, 2025. No monetary incentives were offered for participation in the online survey, but respondents were offered a 1-page summary report of the survey results.

Adaptive questions were used to determine participant eligibility (via self-reporting) but were not used throughout the remainder of the survey. There were a total of 24 questions (including eligibility and consent questions; 19 if these are excluded) across 14 screens. No single screen had more than 4 questions, and questions that were grouped together were related. There was no completeness check conducted for participants before submitting. Respondents were able to reassess questions via the use of a back button.

Regarding the response rate, approximately 500 responses were recorded, of which approximately 320 were complete and indicated that the eligibility requirements were met. Four responses were identified as chatbot responses based on one or more indicative signals (eg, part of the question was included in the answer, which indicates a chatbot response in the experience of the research team, or text from the chatbot tool identifying itself as a chatbot was included). This survey did not control for multiple entries from the same individual at point of collection.

Analysis

To prepare the results of the survey for preliminary analysis and stage 2 of the research, an inclusive approach will be used with incomplete survey questions. After informed consent is provided, all responses will be included, even if the entire survey

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is not complete. This inclusive approach ensures that all available data contribute to the analysis, enhancing the representativeness of participant experiences and reducing response bias. Given the voluntary nature of participation and the potential for survey fatigue or partial completion, excluding incomplete responses could disproportionately exclude certain groups or perspectives. Including partial data supports equity in research by valuing all contributions and allows for more robust descriptive and exploratory analysis, particularly in early-stage or qualitative-informed research.

As we anticipate that only descriptive statistics will be feasible for the survey data, advanced statistical corrections or inferential analyses are not required at this stage. This is appropriate given the exploratory nature of the study and the likelihood of incomplete responses. The primary objective is to identify patterns and trends in the data to inform stage 2 of the research, rather than to draw generalizable conclusions. Descriptive analysis allows for meaningful insights while respecting the limitations of the dataset.

Questionnaires submitted with an atypical timestamp (eg, unusually fast completion times or submissions outside expected timeframes) will be flagged and reviewed for quality assurance. These cases will not be automatically excluded, but rather assessed contextually to determine if the data appear valid and consistent with other responses. This approach ensures that we do not inadvertently exclude legitimate responses from participants who may complete the survey quickly due to familiarity with the content, while still maintaining data integrity.

Stage 2: Presentation of Findings to Stakeholders

The research team will undertake preliminary data analysis, present these findings to community stakeholders, and engage them for assistance with interpretation and making of meaning. VE, CV, and HP have existing relationships with Māori health care providers, Hāpai Te Hauora, Well Women and Family, Sexual Wellbeing Aotearoa, and the Cancer Society New Zealand, who will all be warmly invited to participate meaningfully. Additional stakeholders may also be invited through the research team and stakeholder networks. It is likely that stage 2 will include a mix of in-person stakeholder *hui* (workshops) and *kanohi ki te kanohi* (face-to-face) meetings individually and in small groups.

Whakawhanaungatanga (building relationships) and *manaakitanga* (kindness and respect for others, emphasizing responsibility and reciprocity) will be prioritized throughout, using a flexible approach to best meet the needs, availability, and preferences of the stakeholders. The aim of the stakeholder engagement activities is to obtain feedback on the findings of stage 1 and to facilitate the co-designing of future research priorities. We anticipate that stakeholders will want to co-design in-depth focus groups and interviews with us; we will use the results of these focus groups and interviews as a foundation for further investigation. The focus groups and interviews are described in stage 3.

Stage 3: Focus Group and Interview Guide and Pilot Focus Groups and Interviews

Based on the results of the survey and the stakeholders' engagement, a research approach and focus group and interview guide will be developed and piloted with approximately 5 to 8 participants. The authors acknowledge this will require an amendment to existing ethics approval. The aim of stage 3 is not to reach qualitative data saturation but to confirm a research approach and focus group and interview guide for an in-depth qualitative study in the future. Focus groups and interviews will be offered in English and te reo Māori and will be audio-recorded and transcribed verbatim. Focus groups and interviews conducted in te reo Māori will undergo forward and backwards translation into English by a certified University of Auckland or University of Waikato translator. Interview participants will be sent copies of their interview transcript, and they will have 2 weeks to edit or add to the written version of the transcript.

Data Analysis

The multiple forms of data obtained in stages 1 to 3, including the qualitative survey results, the interpretations and meaning developed with stakeholders, the focus group and interview guide, and the pilot focus group and interview transcripts, will be analyzed together using a collective, team approach to reflexive thematic analysis [28]. Analysis will use NVivo (version 14; Lumivero, LLC). The quantitative survey results will be analyzed using descriptive statistics generated in SPSS (version 30; IBM Corp).

Results Dissemination

The findings will be disseminated through academic conference presentations, peer-reviewed journal articles, summary reports to participants, detailed reports to stakeholders, and the University of Auckland and University of Waikato social media accounts. As the online portion of the study encompasses 1 of 3 stages, early results will be published with recognition that focus groups and interviews will significantly enhance the understanding of these initial data. Author SM is a medical illustrator and experienced graphic designer who will lead the social media dissemination. We anticipate that this will be completed with significant involvement from stakeholder groups. The results of this survey will be used to prioritize the focus of in-depth qualitative interviews and focus groups in stage 2, detailed above. Additional funding and ethical approval for this future research has been sought.

Results

Ethical approval for the online survey was granted from the Auckland Health Research Ethics Committee on June 28, 2023, for 3 years, with amendments approved on July 1, 2024 (AH25633). The timeline of our research is presented in Table 1.

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Table 1. Timeline of our research.

Activity and outcomes	2023	2024		2025	
	October to December	January to June	July to December	January to June	July to December
Stage 1					
AHREC[a] amendment	✓	✓			
Extend survey recruitment	✓	✓	✓		
Stage 2					
Stakeholder engagement and *whakawhanaungatanga*[b,c]	✓	✓	✓	✓	✓
Analyze preliminary results		✓			
Hui (workshops) with stakeholders		✓	✓		✓[d]
Submit papers 1, 2, and 3 for publication			✓		
Stage 3					
Co-design study protocol and external funding applications			✓	✓	
Apply to the Marsden Fund (NZ $360,000 [US $205,992])			✓	✓	
Apply to the MBIE[e] Endeavour Fund (NZ $1 million [US $572,200])				✓	
Apply for HRC[f] Project (NZ $1.2 million [US $686,640])					✓
Apply for Google Award for Inclusion (NZ $94,000 [US $53,787])				✓	

[a]AHREC: Auckland Health Research Ethics Committee.

[b]*Whakawhanaungatanga*: the process of building and maintaining relationships through shared connections, trust, and mutual respect.

[c]Ongoing throughout.

[d]After submission of funding applications, a celebratory *hui* will be held with all stakeholders and research partners.

[e]MBIE: Ministry of Business, Innovation & Employment.

[f]HRC: Health Research Council of New Zealand.

Discussion

Anticipated Findings

The Understanding Intimate Health in Online Spaces project aims to better understand the relationship between social media and women's sexual and reproductive health in Aotearoa New Zealand. We anticipate (from early results [26]) finding that social media plays a significant role in allowing women to seek out information and care that they would otherwise struggle to access, and that this study can help inform clinical practice in community outreach.

A strength of the approach we have described is the meaningful involvement of stakeholders in the interpretation and meaning-making of the survey findings; in-depth interviews and focus groups provided input into the anticipated next phase of the research. This study takes a multidisciplinary approach bringing together researchers from a variety of disciplines, including public health, biostatistics, nursing, and public policy, as well as anthropology and the social sciences. The aim of doing so is to better understand from diverse perspectives how and if social media impacts some of the most intimate aspects of the health of marginalized groups in Aotearoa New Zealand, namely the sexual and reproductive health of women.

A limitation of our survey is that there were few methods used to assure the validity of participant responses. Responses that were clearly copied and pasted from an artificial intelligence tool were automatically excluded, but no questions were integrated as attention checks.

Conclusions

The data analyzed to date support the multistage research design, which aims to use this internet survey–based research to launch more targeted in-person and in-community research methods to refine the data collected.

This study was conducted in one particular geographical and sociocultural context (that of Aotearoa New Zealand), and

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findings may therefore not always be generalizable to other contexts. However, the findings we expect to encounter align with the current literature on social media use and women's sexual and reproductive health.

The methods used in this study are standard quantitative (survey) and qualitative (survey, focus groups, and interviews) research methods, and can be applied in a variety of contexts. Our study contributes novel insights into the role of social media as a tool for women to access sexual and reproductive health information and support, particularly when these women otherwise have limited access to these resources. Our research also highlights the importance of stakeholder engagement in knowledge production. This protocol provides a framework for investigating this topic in other, international contexts.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Survey.
[PDF File (Adobe PDF File), 199 KB - resprot_v14i1e65288_app1.pdf]

Multimedia Appendix 2
CHERRIES checklist.
[DOCX File , 26 KB - resprot_v14i1e65288_app2.docx]

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Abbreviations

LGBTTQIA+: lesbian, gay, bisexual, transgender, takatāpui, queer/questioning, intersex, asexual/aromantic/agender, or another marginalized identity
STI: sexually transmitted infection

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Protocol

Co-Design of a Digital Health Platform for Chronic Disease Management in Rural Settings Using a Person-Centered, Collaborative-Care Model: Protocol for a 3-Phase Mixed Methods Study

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Abstract

Background: Chronic diseases represent a significant global burden, accounting for 85% of the total disease burden in Australia. This burden is particularly pronounced in rural areas, where chronic disease rates are higher, and access to health care services is more limited. Digital technology has the potential to address these disparities by overcoming challenges such as workforce shortages and geographic isolation.

Objective: Our objective is to develop a digital health platform (DHP) to support the monitoring and management of chronic disease in collaboration with rural and regional stakeholders, including researchers, health care providers, and patients. The platform is being designed to be flexible, enabling applications across a range of chronic health conditions relevant to rural contexts.

Methods: Guided by implementation science methodologies, we are adopting an evidence-based approach to developing a DHP for chronic disease management. Informed by co-design frameworks and best-practice guidelines, our development plan comprises three key phases: (1) stakeholder needs analysis, (2) co-design and platform development, and (3) postdesign evaluation and testing. The Federation University Human Research Ethics Committee (HREC Ref: 2023/169) granted ethics approval for this study.

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Results: Data collection is underway. The phase 1 review has been completed, and we have 84 survey responses. Phase 2 has commenced, with 9 workshops and 2 interviews conducted to date. Phase 3 will not commence until phase 2 has been completed. At this stage, project completion is anticipated by late 2026.

Conclusions: Findings will inform the desirability, feasibility, and acceptability of co-designed DHPs for chronic disease management in rural Australia. Further, the study will contribute to the evidence base on collaborative, context-sensitive digital health innovation for resource-limited populations.

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KEYWORDS

behavior change; digital health; chronic disease; prevention; early intervention; hypertension; type II diabetes; rural health

Introduction

Background

Chronic diseases, also known as "noncommunicable diseases" or "long-term health conditions," are generally characterized by their persistent effects [1] and are a leading global health concern, responsible for serious illness, disability, and premature death [2]. The World Health Organization (WHO) reports that in 2020, noncommunicable diseases accounted for 7 of the world's top 10 causes of death [3]. In Australia, recent figures indicate that chronic diseases account for 85% of the total disease burden [1]. Furthermore, approximately 90% of Australia's nonfatal burden of disease is due to chronic conditions, with the nonfatal burden rising by 64% between 2003 and 2023 [4]. Collectively, these statistics underscore an escalating public health challenge and signal the value of pursuing effective strategies for chronic disease management and mitigation.

The increasing prevalence of chronic conditions highlights the need for innovative management strategies. Digital health solutions, including mobile apps, messaging platforms, telehealth services, wearable monitoring devices, artificial intelligence for risk prediction and precision medicine, and electronic prescribing, have the potential to enhance chronic disease management. They do so by enabling remote monitoring, personalized interventions, and greater patient engagement [5]. This is especially true in rural areas, where chronic disease rates are higher [6], and digital technology has the potential to bridge gaps caused by health care provider (HCP) shortages and geographic barriers [7].

The WHO's Global Strategy on Digital Health 2020-2025 highlights the global momentum toward the integration of digital technologies into health care with the aim of enhancing service delivery and patient outcomes [8]. Digital health platforms (DHPs) that incorporate a range of digital health approaches can serve as a central hub, connecting systems to enable faster, more efficient, and more reliable information exchange [9]. By integrating data across various devices, these platforms enhance accessibility and improve coordination in health care delivery. However, they are often not used to their full potential due to low end-user adoption and engagement [10]. A key reason for this is thought to be the historical lack of, or limited use of, user-centric design processes in the development of digital health products [11,12]. As such, it can be argued that not involving users in the design process has led to "difficult to use" digital products that are not optimally based on end-user preference or need.

Using participatory approaches when designing digital health products provides a clearer understanding of the needs and requirements of the target populations, as well as the barriers and facilitators influencing their continued engagement with digital devices [13,14]. Recent reviews highlight recurring facilitators of digital health adoption, including improved patient-provider communication, enhanced engagement and adherence, the tailoring of tools to user needs, simplicity of use, and intuitive design [15-18]. Common barriers include limited digital literacy [19], concerns about data privacy and security [16], poor interoperability with existing systems [20], and patient preferences for face-to-face care [16]. Structural challenges such as patchy infrastructure [20], workforce issues including training and organizational support [21], and a lack of sustainable funding also constrain long-term uptake [22,23]. While these themes are well established, there is limited translation into actionable, locally grounded design. Our study addresses this gap by using co-design methods to adapt digital health solutions to the specific contexts and constraints of Australian rural populations, with the expectation that insights generated here may inform approaches in other resource-limited populations.

Findings from primary research and systematic reviews of health service co-design [24-27] suggest several key considerations relevant to the management of chronic diseases. These include involving patients, HCPs, and their service organizations from the beginning of the design process; using a variety of co-design activities (eg, workshops and interviews); involving diverse participants (eg, patients and relatives, HCPs and managers, and individuals with varying technological capabilities and application interests); prototyping and conducting iterative usability testing sessions to gather feedback; eliminating critical errors; and ongoing optimization activities.

Co-design means that user characteristics directly inform appropriate and accessible technology development. However, a recent review of the use of co-design approaches in digital health interventions found methodological problems in the conduct and reporting of these approaches and a lack of guidelines for co-design activities [28]. Beyond co-design and critical error testing phases, improvements (optimization) should continue to occur over the lifespan of a DHP (eg, acceptability

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or feasibility testing, efficacy testing, and implementation and beyond) [29]. To produce a needs-based, usable, engaging, and secure DHP ready for the implementation trial, it is desirable to codevelop a DHP specification document (ie, detailing the necessary digital tools, design features, and functionality required), build the digital platform, and test for critical usability errors, as well as test platform security properties (ie, penetration testing).

Rural and regional health care systems are characterized by persistent shortages of general practitioners, allied health professionals, and specialist services, alongside digital infrastructure gaps and geographical barriers to accessing care [6,30]. These constraints contribute to even further fragmented service delivery and reduced continuity of care. It can be argued that a DHP has the potential to alleviate some of these problems, as it enables the integration of multiple functions, including risk assessment, communication, patient education, and monitoring, within a single system that can be tailored to local needs. By enabling service integration across distances and supporting task-sharing among a stretched workforce, digital platforms offer a scalable and sustainable approach for improving chronic disease management in rural settings.

Despite growing recognition of the burden of chronic disease and the promise of DHPs, a notable lack of rigorously co-designed solutions tailored to rural populations remains. This study addresses this gap through a 3-phase process of needs analysis, co-design, and iterative testing, with the aim of producing a usable, acceptable, and secure platform that is grounded in end-user perspectives and optimized for real-world implementation.

Objective

Our primary objective is to develop a specification for a DHP that supports HCPs and their patients in rural and regional settings, with the aim of facilitating the monitoring and management of chronic diseases. The platform is intended to be broadly applicable across chronic health conditions, with particular emphasis on cardiovascular disease and diabetes, reflecting their high burden in rural communities [31-34]. As such, the co-design process will engage a diverse array of participants, including patients with a variety of chronic conditions and different types of HCPs, so as to support broad applicability across chronic disease types and health care settings.

The study will use a mixed method approach, working with both HCPs and patients (1) to identify the barriers and facilitators of digital tools use as well as user preferences and needs regarding DHP features (through a literature review and survey); (2) to guide the design and refinement of the platform by evaluating potential features and overall functionality, drawing on insights gathered through participatory workshops and in-depth interviews; and (3) to detect and resolve errors in the digital platform prototype (through critical error testing).

By following a 3-phase process, comprising a needs analysis, co-design build, and postdesign development and testing, all of which incorporate direct input from community members (HCPs and patients), the co-design of the DHP will enhance the relevance and usability of health care technology. By integrating diverse perspectives, we will create a system that is user-centered and focused on end-user accessibility, efficiency, and health outcomes. This collaborative model fosters trust, improves adoption rates, and helps ensure that the platform effectively addresses real-world health care challenges [28]. Ultimately, we expect the co-design process to pave the way for a more inclusive, equitable, and impactful digital health product.

Methods

This protocol was prepared in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines, and a completed SPIRIT checklist is provided as Multimedia Appendix 1.

Setting

The target research setting is rural and regional Victoria, Australia, where health services face persistent challenges, including shortages of general practitioners, allied health professionals, and specialists [35], as well as significant travel distances and transport barriers for patients [36]. Service delivery is further constrained by variable digital infrastructure [37] and by digital literacy levels, which tend to be lower than those observed in urban areas [38]. This setting provides a critical context for developing a DHP that is responsive to rural realities and likely adaptable to other resource-limited populations.

Design

We will undertake the project's "digital build" engagement in 3 phases using mixed method data collection approaches. Participants will include HCPs and health care consumers (hereafter referred to as patients) who live or work within the service areas supported by our rural and regional industry partners. The build plan includes the following components: (1) stakeholder needs analysis, (2) co-design build, and (3) postdesign development and critical error and IT security testing. A flowchart detailing the development and data collection process is provided in Figure 1, and an outline of each phase is presented in Table 1. To ensure robust theoretical foundations underpinned the project, each phase of the DHP co-design is guided by relevant frameworks and established methods (Table 1). The behavioral intervention technology model [29] is used to map the functional and technological requirements of chronic disease interventions, ensuring that both health behavior change mechanisms and platform architecture are systematically addressed. The nonadoption, abandonment, scale-up, spread, and sustainability framework [39] is applied to anticipate barriers to adoption and to consider long-term sustainability challenges, particularly relevant in rural health care contexts.

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Figure 1. Flowchart outline of the digital cobuild phases and associated activities. DHP: digital health platform.

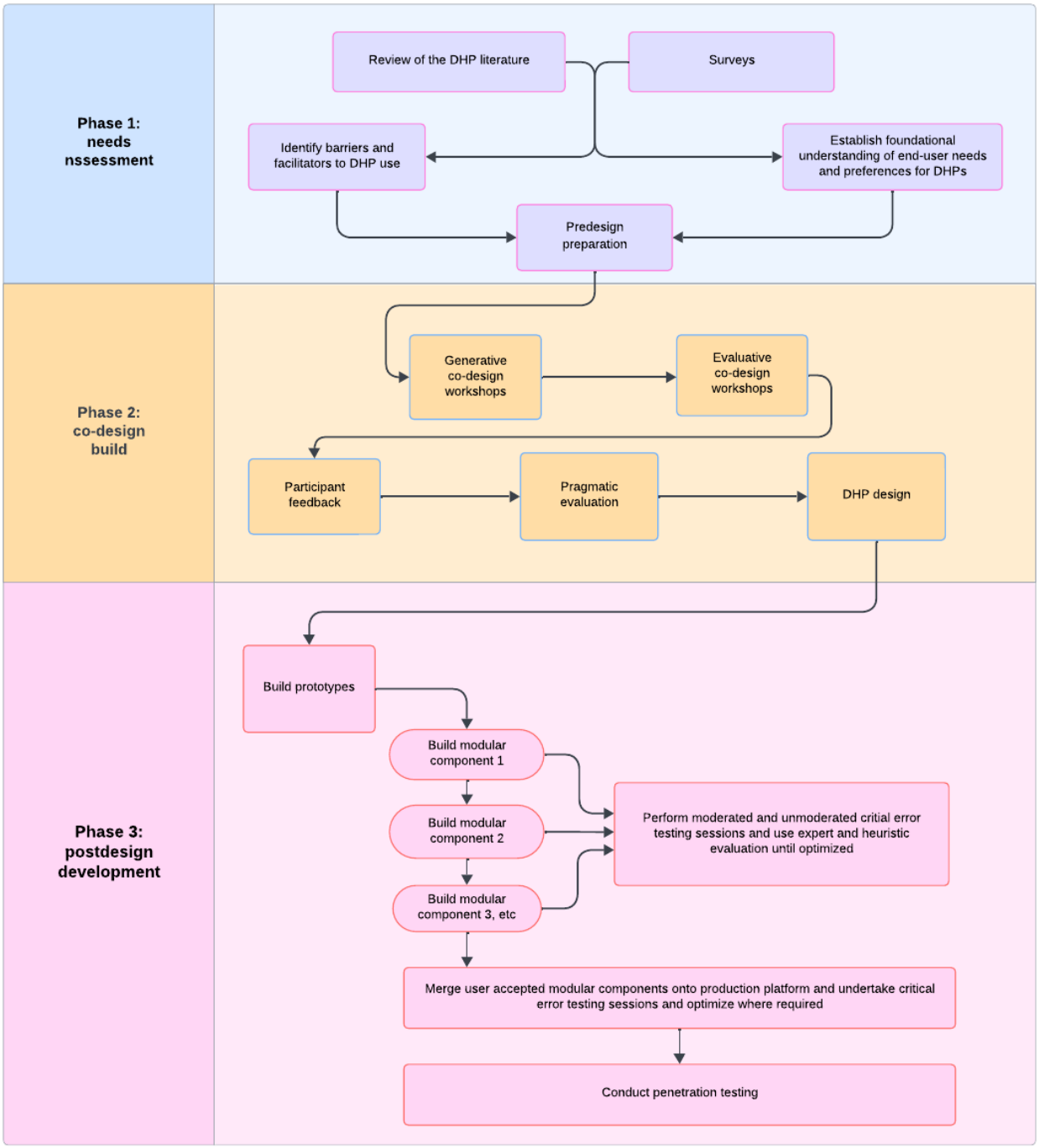

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Table 1. Digital cobuild phases, stages, and data collection methods.

Phase and stage (sample)	Method	Frameworks or guideline and application
1. Stakeholder needs analysis		
Evidence-based needs assessment (from both patient and HCPs[a] perspectives)	A review of existing literature investigating which digital tools are the most preferred or effective when using digital platforms for chronic disease management in service delivery for HCPs and their patients.	• BIT[b] model guides the identification of functional and technological requirements for chronic disease interventions [29]. • NASSS[c] framework used prospectively to anticipate barriers to adoption and sustainability (eg, digital literacy and infrastructure in rural areas) [39].
Surveys (up to n=150, HCPs: n≤50 and patients: n≤100)	Online surveys, which include a series of quantitative and qualitative questions, aimed at identifying general barriers, facilitators, and preferences regarding digital tools and apps.	• BIT model informs survey design by aligning questions with behavior change functions and usability factors [29]. • Co-design literature emphasizes early capture of end-user perspectives to inform subsequent workshops.
2. Co-design		
Generative workshop (2 groups separately: patients+caregivers and HCPs+management)	Workshops to generate ideas regarding platform design and features required, through co-design generative activities such as storyboarding of health journey and use of personas.	• Generative co-design framework for health care innovation supports structured creative exploration and ideation [40]. • Extended co-design framework for mobile health results in diversity of user perspectives (different health conditions, digital literacy, and access) [41].
Evaluative workshop (2 groups separately: patients+caregivers and HCPs+management)	Prototypes tested with participants to confirm understanding and guide final modifications.	• Agile principles and iterative prototyping continuous cycles of build-test-refine [42]. Application of user-centered design principles to validate alignment with end-user needs.
Interviews (HCPs and patients, where required)	Should the workshops fail to provide sufficient information for build specifications, interviews (≤ 30) will be conducted to garner greater detail or information.	• Enables deeper exploration where workshops are insufficient. Guided by experience-based co-design to elicit detailed narratives [24].
3. Postdesign development and testing		
Modularly component builds (HCPs and patients)	Using agile methodologies, commence building in a modular "component" fashion. Before committing to the platform, wireframes and prototypes are developed for each modular component for feedback.	• Agile or strategic modular building methods staged development with feedback loops to enhance adaptability [42].
Critical error testing (HCPs and patients)	Iterative usability testing of the components and the platform as a whole to make sure that all components work together.	• The think-aloud protocol validated usability method capturing cognitive processes during interaction [43]. • System Usability Scale standardized quantitative usability measure [44].
Penetration testing	A full security audit of the platform is to be undertaken by an independent third party.	• Penetration tests by an ethical hacker to ensure platform robustness and compliance with digital health IT security standards [45].

[a]HCP: health care provider.

[b]BIT: behavioral intervention technology.

[c]NASSS: nonadoption, abandonment, scale-up, spread, and sustainability.

During the co-design phases, frameworks including the generative co-design framework for health care innovation [40] and the extended co-design framework for mobile health apps [41] provide structured approaches to engaging participants with diverse perspectives and varying levels of digital literacy. These frameworks inform the design of generative and evaluative workshops, as well as semistructured interviews, ensuring that end-user input directly shapes the design features and functionality of the platform. The use of Agile methodologies [42] further supports iterative prototyping and refinement, promoting responsiveness to user feedback and practical implementation considerations.

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In the postdesign testing phase, we apply well-established usability evaluation methods. The think-aloud protocol, a recognized technique in human-computer interaction research, is used to capture participants' real-time cognitive processes as they navigate the platform, providing rich insights into usability barriers [43]. The System Usability Scale (SUS) [44] provides standardized quantitative measures of platform usability. SUS scores will be interpreted using established benchmarks, where scores above 68 are generally considered above average, and higher scores indicate better usability [46]. Consistent with established procedures [46], a mean score below this threshold will trigger targeted refinements. Scores in the "good to excellent" range (≥80) [47] will be taken as an indication that the platform is ready for larger-scale implementation trials. In this way, SUS results will not only provide a quantitative measure of usability but also function as a decision-making tool, signaling whether further iteration is required before moving to subsequent phases. The integration of these methods means that the platform will not only be functional and secure, but it will also be engaging and intuitive for end users.

Despite growing use of co-design in digital health innovation, prior initiatives are often limited by methodological fragmentation, inadequate stakeholder involvement, and insufficient attention to how rural or resource-limited settings shape feasibility [30,38,48]. Our approach addresses these limitations by embedding rural patients, caregivers, and HCPs across all 3 phases of the research. A needs analysis will reveal context-specific constraints and preferences; generative and evaluative workshops will facilitate the iterative process of feature tailoring; and usability testing will help ensure that the platform is intuitive, feasible, and acceptable in rural contexts. In this way, the study builds on but extends prior co-design literature by translating general design principles into actionable, locally grounded solutions for resource-limited rural populations.

Participants

The study will include HCPs and patients from the specified setting. We will recruit HCPs from various discipline backgrounds, including general practitioners, nurses, mental health workers, physiotherapists, occupational therapists, dietitians, and other allied health workers. Similarly, we will aim to recruit patients with diverse demographics, backgrounds, health statuses, and conditions. All participants will be Australian residents aged 18 years or older, able to read and understand English and provide informed consent independently, and able to attend the nominated location onsite or online (in the case of workshops, interviews, and critical error testing).

To ensure equitable participation and inclusion of individuals with diverse literacy levels and digital access, we provide multiple format options, including printed materials, paper-and-pencil surveys with reply-paid envelopes, and in-person information sessions, to support participants less familiar with digital platforms. Phone-based participation options are also available for interviews and workshops to address technological or accessibility barriers. In addition, critical error testing will be used to capture perspectives across the digital-literacy spectrum, identifying potential barriers and usability issues for vulnerable groups engaging with digital health services. By including participants with limited digital access and lower levels of digital confidence, we aim to ensure that the platform features are responsive to the needs and capabilities of all end users.

Procedure

Phase 1: Needs Analysis

To gain an initial understanding of barriers and facilitators of digital health tools and end-user DHP needs and preferences, we will conduct a brief environmental scan and mapping literature review and survey HCPs and patients. The literature review will focus on investigating which digital tools are the most preferred or effective when using chronic disease management digital platforms in service delivery for HCPs and patients. The survey will focus on gaining an understanding of barriers and facilitators of using digital tools in the provision of health care (eg, Wi-Fi or broadband issues in their catchment areas, digital readiness or literacy, and what health-related software they are using or have access to), perceived benefits and concerns when using digital tools (eg, more efficient but less personal, confidentiality or security), and preferences or needs around digital tools or features (eg, what digital tools or features they would like to have or use). The survey was developed based on the research team's understanding of the domain, which includes experts in digital health, chronic disease, public health, psychology, information and technology, and software developers. Survey questions were informed by the literature and the social context of the study population and include both open- and closed-ended items. HCPs and patients will be invited to complete the survey anonymously online (hosted by SurveyMonkey) or via a paper-and-pencil version.

The survey will identify general barriers, facilitators, and preferences around digital tools and apps. Recruitment material will include the survey URL, where individuals will first read the Plain Language Information Statement (PLIS) and give consent by clicking a checkbox stating that "I understand and agree with the above conditions" before they are presented with survey items. Consent for the paper-and-pencil version will be implied by the return of the survey via a reply-paid envelope. The survey will take approximately 10 minutes to complete.

Phase 2: Co-Design Build

Two types of workshops will be conducted separately with HCPs and patients: (1) generative workshops to ascertain ideas regarding platform design and features and (2) evaluative workshops conducted using a prototype platform to determine whether any modifications, additions, or deletions are required ahead of the final build. The decision was made to separately collect data from HCPs and patients for a number of reasons, including likely differences in the lived experience, role-specific insights, power dynamics, and socially desirable responses.

Our industry technology partner WellAware, who have experience in DHP development and implementation, will lead workshops and interviews. Academic members of the research team will also participate in the workshop data collection and interpretation processes. Workshop discussions will be framed around topic questions relevant to health and the giving and receiving of health care services and support in rural areas. We

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will work to understand barriers to integrating digital health technologies into health care service delivery.

Up to 10 generative workshops will be conducted (5 for each cohort), each involving between 6 and 15 participants and running for up to 3 hours. It is believed that this workshop size supports active participation and balanced discussion, while the overall number is guided by the principles of information power [49,50]. This approach recognizes that sample adequacy depends on the richness of the data, the specificity of the research aim, and participant expertise. Empirical guidance further suggests that 3-6 focus groups per segment are typically sufficient to capture the majority of salient themes [51].

If, after the final workshop, the research team determines that novel perspectives remain to be captured, up to 30 semistructured, one-to-one interviews will be undertaken, each lasting up to 60 minutes. Interviews may also be conducted with individuals who are unable to attend a scheduled workshop. In some cases, workshop participants may be invited to elaborate further on their perspectives in an interview; however, most individuals will contribute through either a single workshop or a single interview.

Following the completion of each workshop or interview, the researchers involved will debrief to discuss the emergence of new insights. Data sufficiency will also be guided by the principles of information power [50], with saturation defined as the point at which additional data yield negligible substantive insights. A stop-rule will be applied: if successive workshops yield negligible insights, recruitment will cease; otherwise, additional workshops will be convened. Once sufficient data have been collected, the study team will convene to review co-design activity data and compile a list of requested design and digital tool features, along with accompanying descriptions. A triangulation procedure will be used to validate the findings. More specifically, the design and tool features list will be shared with selected workshop and interview participants for their review, feedback, and confirmation. Once accuracy is confirmed, a more pragmatic discussion will occur around what is achievable based on platform architecture, project timelines, and budgetary constraints.

People taking part in the generative workshops will be invited back to participate in the evaluative workshops. If rerecruitment from the generative workshop participants is insufficient, additional people will be recruited specifically for the evaluative workshops. For the evaluative usability workshops, we will recruit 6-12 participants per stakeholder group, per round. This target is consistent with human-computer interaction research, which demonstrates that sample sizes of approximately 12 are sufficient for identifying the majority of usability issues [52,53].

The evaluative workshops will focus on refining the functionality, usability, and acceptability of the DHP. Using the prototypes developed after the generative workshops, participant understanding will be checked, modifications made, and additions or deletions will be made to specify the final build. Participants will complete structured tasks that reflect typical use of the platform (eg, logging in, setting a health goal, and accessing educational resources). Facilitators will observe interactions and record usability issues, followed by a short group discussion to capture qualitative feedback on navigation, clarity, and perceived usefulness. The final design will then be discussed with the project chief investigators and finalized.

Once findings have been ratified, the write-up of the IT specification document will commence. This will be developed by WellAware team members, in conjunction with their software engineers, and it will detail all the platform works required. The resulting document will be reviewed by the chief investigators and lead partner representatives for their input and final approval. Development will begin once everyone has agreed to the works described in the IT specification document. This will include a series of sprints and testing sessions over the course of the build. The exact nature of this testing will be determined as part of the research process and outlined in the specification document.

Phase 3: Postdesign Development and Testing

Following the creation of the DHP prototype, critical error testing sessions will be conducted with HCPs and patients. Each session will consist of 1-3 participants and take up to 2 hours, depending on the discussion topics and dynamics. Sessions will involve participants testing the prototype and its components to ensure that any core usability errors are identified and fixed. A think-aloud process will be used, where a participant vocalizes each step of their actions as they use the platform [43]. Heat mapping software may also be used to provide data on where participants click, how far they scroll, and what they look at or ignore on the webpages. Following completion of the session, participants will be asked to complete the SUS [44]. Once the platform has been completed, we will conduct penetration testing, which will involve an independent company simulating cyberattacks on the platform to identify vulnerabilities that attackers could exploit [45]. Results will be fed back to the study team and remedied as needed.

If substantial usability or security issues are identified during late-stage testing, iterative refinement loops will be undertaken to address these issues prior to wider deployment. Final decisions regarding design modifications will be guided by clinical safety, feasibility within rural health care contexts, and alignment with evidence-based practice. Where necessary, adjustments to timelines will be made to ensure that only a functional, secure, and user-acceptable platform progresses to larger-scale trials.

Recruitment

HCPs and patient participants will be recruited through our health care service delivery partner sites as well as through the general promotion of the study within the targeted communities. This will include print and social media, community presentations, and snowball sampling. Each health care partner will be provided with study advertisements (ie, posters and postcards) to display in staff areas and general patient waiting rooms, copies of the PLIS, and paper-and-pencil surveys (with reply-paid envelopes).

Study research fellows will conduct information and recruitment sessions onsite and online as required. In addition, HCPs and patients wanting to take part in a workshop, interview, or critical error testing session can indicate their interest by (1) contacting

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a study research fellow, (2) registering their interest following completion of the online survey where they will be redirected to a separate survey to provide their contact details (this will mean that survey data and contact details cannot be connected), (3) registering their interest by returning a reply slip via a reply-paid envelope available at our health care partner service delivery sites, and (4) registering their interest online by following a URL provided in the PLIS or posters.

To ensure diversity and representativeness, recruitment will be undertaken systematically across multiple rural health services, using purposive sampling to capture variation in professional roles, including general practitioners, nurses, allied health professionals, practice managers, and patient or caregiver demographics, including age, gender, geographic location, and service-use experiences. Participant characteristics will be tracked throughout, with recruitment strategies adjusted as needed to maintain breadth and balance across stakeholder groups. Multiple recruitment pathways will be used, including traditional study advertisements (ie, posters and postcards), plain language information statements, online registration, and reply-paid envelopes, to minimize barriers to participation and reduce exclusion of less technologically informed individuals. Transparent reporting of participant characteristics, response rates, and nonparticipation will further support evaluation of representativeness. Social desirability bias will be minimized through anonymized data collection, separating responses from identifying information and emphasizing confidentiality. During workshops and interviews, research fellows will use reflexivity practices, such as maintaining journals, to acknowledge potential influences on data interpretation and participant interactions. Finally, triangulation methods, including the combination of survey data and workshop findings, will be used to validate results and enhance credibility.

Data Collection

Workshops, interviews, and critical error testing sessions will be conducted either face-to-face, online via Microsoft Teams, or by telephone (for interviews only). Participants will be nominally reimbursed with a US $19.59 gift card per hour of study involvement unless their participation is part of the HCPs' paid work-related activities. All participants will provide written informed consent to participate in this study. For face-to-face study activities, signed consent forms will be obtained on the day. For study activities conducted online or by telephone, consent will be obtained ahead of the activity either online, by email, or regular mail. All workshops and interviews will be audio-, video-, or screen-recorded.

Analyses

Phase 1

We aim to collect up to 150 survey responses (approximately 100 patients and 50 HCPs) across the participating health care service provider sites. This sample size is expected to yield sufficient data to identify key enablers and facilitators of digital tool adoption. Data from online surveys will be analyzed using descriptive statistics. Where relevant, bivariate or multivariable analyses using parametric or nonparametric tests will be conducted to assess group differences across outcomes. Open-ended survey responses will be analyzed using a structured descriptive approach. Coding will be guided by survey domains and informed by relevant theoretical frameworks (eg, digital readiness, usability, and implementation factors). This pragmatic approach will facilitate the identification of salient issues and perspectives to inform subsequent phases of the study, including co-design workshops and digital platform development.

Phase 2

Workshops and interviews will be audio-recorded, transcribed, and deidentified. Qualitative data will be subject to reflexive thematic analysis [54,55], in order to identify major themes relating to the DHP build and implementation. Members of the research team will meet regularly to review summaries, which will be generated after each data collection session. They will work collaboratively to establish consensus on the accuracy of the summaries and determine when saturation has been achieved. When it comes time to formally analyze the qualitative data, transcripts will be reviewed to support familiarization, and then coded inductively to capture meaningful units of text. Codes will be collated into categories and higher-order themes through an iterative process. In line with reflexive thematic analysis, formal interrater reliability statistics will not be calculated, as consensus-building is prioritized over numerical agreement [55]. NVivo (QSR International) will be used to support the coding process and facilitate data management.

Phase 3

We plan to conduct up to 10 critical error testing sessions with 1-3 participants in each session (n=10-30 participants, with 5-15 HCPs and 5-15 patients). Critical error testing is an iterative process in which any errors identified are fixed between sessions and continues until no further errors are found (saturation). Typically, 3-5 sessions are required to reach saturation [52]. Critical error testing session metrics will be used to identify and address usability issues. Quantitative evaluation metrics will include task completion rates, time-on-task measurements, error frequency analysis, success or failure ratios, user satisfaction scores, and the SUS questionnaire [44]. Using the method outlined in the Design section, SUS scores will be interpreted and used to guide iteration or readiness decisions. Researcher notes will support reporting on cobuild activities (eg, workflow mapping and workshop notes) and implementation metrics (eg, cost). In addition, they will be reviewed thematically for contextual or design-related factors that may account for quantitative outcomes.

Governance, Data Storage, and Security

To manage any potential conflicts, we have adopted shared decision-making processes that emphasize collaboration and open communication. All project activities, including funding contributions and intellectual property arrangements, have been detailed in governance agreements, and records of relevant meetings and project updates are openly shared between partners. Roles and responsibilities have been clearly defined, with academic researchers maintaining authority over study design, data collection, analysis, and reporting, while the industry partner contributes technical expertise in platform development and implementation.

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For the duration of the research, all electronic data will be placed into a secure, password-protected environment within the Research Data Store at Federation University. All service audit, research notes, and online survey data will be nonidentifiable, and semistructured interviews and workshop audio files and transcripts will be deidentified. Upon completing this research, all electronic data will be stored on a secure, password-protected virtual machine within the Research Data Store provided by Federation University.

Ethical Considerations

The Federation University Human Research Ethics Committee (HREC Ref: 2023/169) granted ethics approval for this study. Per the approved protocol, all participants will provide written informed consent before participating in the study. Participants will be informed of the study purpose, procedures, potential risks, their right to decline or withdraw at any time, and the voluntary nature of participation. Consent will also be obtained for the recording of interviews and workshops. To protect privacy and confidentiality, identifiable information will be stored separately from research data on secure, password-protected institutional servers accessible only to authorized team members. Transcripts and survey data will be deidentified prior to analysis, and any quotations used in publications will be anonymized to ensure individuals cannot be identified. Participants will receive a small-value gift voucher (US $19.59) for their time, as approved by the ethics committee. They will be informed that this compensation does not depend on completing all study activities, and participants may withdraw without penalty. If there is a need to modify the study protocol for any reason, the change will be documented and sent for approval to the Federation University Human Research Ethics Committee.

Results

The project was approved for funding in November 2022, and data collection is currently underway. Project status, as it relates to the 3 study phases, is as follows:

- Phase 1: At the time of writing, the environmental scan and mapping literature review exercise had been conducted, and we had received survey data from 35 HCPs and 49 patients.
- Phase 2: At the time of writing, we had conducted 9 workshops (5 patient and 4 HCPs). In addition, we had undertaken interviews with 2 HCPs, for which we had been unable to coordinate a convenient time for workshop participation. A preliminary analysis of the workshop and interview data was conducted to assess whether data saturation had been achieved. At the time of writing, the researcher's assessment was that saturation had likely been achieved within the patient group (pending confirmation through more detailed analysis), while additional data were still required to reach saturation for the HCP group.
- Phase 3: This phase had not commenced at the time of writing.

We anticipate completing the project by the end of 2026.

Discussion

Overview

Engaging patients and HCPs throughout the design and development of the DHP helps ensure that the platform is relevant, user-friendly, and effective. Embedding the platform within a person-centered collaborative care model is a transformative strategy for managing chronic health conditions. Evidence supports this approach: digital programs developed with patient involvement have improved glycemic control in type 2 diabetes [56], and digitally supported person-centered models with structured telephone care have enhanced self-efficacy in people with chronic obstructive pulmonary disease and chronic heart failure [57]. This is consistent with systematic reviews highlighting the benefits of co-design in chronic condition management [58] and aligns with the WHO's call for integrated, people-centered health services [59]. Our study demonstrates how these co-design principles can be operationalized in rural contexts to produce a locally grounded, scalable platform.

Strengths and Limitations

To facilitate the successful integration of DHP findings into regional HCP services, we established early partnerships with regional health authorities. We also plan to introduce pilot programs to trial these solutions in real-world health care settings, allowing for adjustments based on local needs and challenges. Doing so will allow adaptation to local contexts, ensuring feasibility and sustainability. Ongoing feedback loops will be established to evaluate the impact of the DHP, allowing for continuous improvement and refinement as we move forward. Several strategies such as diverse recruitment pathways, anonymized data collection, reflexivity, and triangulation will be used to minimize selection and bias. These design features strengthen the validity of our findings, though residual limitations may remain.

The transferability of the study findings beyond rural and regional Victoria will be influenced by several contextual factors. The focus on health care service delivery partners across rural Victoria provides insights that may be generalizable to other rural and regional health care settings with similar demographic profiles, resources, and digital infrastructure (ie, internet access). However, transferability may be limited by factors unique to rural Victoria, such as travel distances, population density, and patient-to-health provider ratios. This means that findings, and the resultant DHP, may not be transferable to metropolitan, other regional, remote, or otherwise incomparably served areas.

We recognize that consensus in co-design activities is not always achievable, particularly where stakeholder priorities or preferences diverge. If substantial disagreement remains, final design decisions will be guided by clinical safety, feasibility within rural health care contexts, and alignment with evidence-based practice. Similarly, if the DHP is not accepted by the participants during testing, findings will be critically examined to understand the barriers to uptake. These insights will be used to adapt or refine the platform or, where appropriate, to modify implementation strategies to better fit

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local contexts. By anticipating these challenges, the study is positioned to generate valuable evidence about both the opportunities and the limits of DHP co-design in rural settings.

Future Directions

Dissemination will be guided by a strategic plan targeting HCP service networks, local communities, and academic audiences. Findings will be shared through peer-reviewed publications, conference presentations, and accessible resources for HCPs and community members. To support integration into practice, partnerships with regional health authorities and pilot programs will enable adaptation to local contexts, ensuring that solutions remain both effective and sustainable. These activities lay the groundwork for the platform's broader implementation and its long-term potential to transform rural chronic disease management.

Conclusions

The co-design of the DHP represents a significant step toward enhancing the management of chronic conditions, particularly in rural and regional health care settings. The co-designed platform will be tailored to the needs of rural patients and HCPs. The strategic dissemination of the platform's findings, combined with partnerships with regional health authorities and pilot testing, will support successful adoption and ongoing refinement in health care services. Ongoing feedback will support continuous improvement, with the potential to enhance outcomes and reduce inequities in rural chronic disease management and mitigation.

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Authors' Contributions

Conceptualization: BK, AEY, CJB, FJC, TH, SAT, CH, MT
Data curation: AEY
Formal analysis: AEY, HVN, BK, PRP, LRB, CH, MT
Funding acquisition: SAT, BK, CJB, FJC
Investigation: AEY, MT, CH, PRP, LRB, BK, LNF, CJB
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Software: MT, CH, BK, AEY, PRP, LRB, HVN, SAT, CJB, FJC, TH
Supervision: BK, CJB, FJC, SAT
Validation: AEY, BK, PRP, LRB, MT, CH
Visualization: AEY
Writing—original draft: BK, AEY
Writing—review and editing: AEY, BK, TED, MD, HVN, QZ, PRP, CJB, LRB, LNF, SAT

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT checklist.
[PDF File (Adobe PDF File), 101 KB - resprot_v14i1e77844_app1.pdf]

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Abbreviations

DHP: digital health platform
HCP: health care provider
PLIS: Plain Language Information Statement
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SUS: System Usability Scale
WHO: World Health Organization

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Corrigenda and Addenda

Correction: Evaluating the Effectiveness of a Multimodal Psychotherapy Training Program for Medical Students in China: Protocol for a Randomized Controlled Trial

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Related Article:

Correction of: https://www.researchprotocols.org/2025/1/e58037

(JMIR Res Protoc 2025;14:e71220) doi:10.2196/71220

In "Evaluating the Effectiveness of a Multimodal Psychotherapy Training Program for Medical Students in China: Protocol for a Randomized Controlled Trial" ([JMIR Res Protoc 2025 Jan 3:14:e58037.]doi:10.2196/58037) the authors noted one error.

In "Table 3," the "Rating" for "Appraisal" appeared as follows:

> *"4=somewhat likely; 3=neutral; 2=unlikely; 1=not at all likely"*

This has been corrected as follows:

> *"5=very likely; 4=somewhat likely; 3=neutral; 2=unlikely; 1=not at all likely"*

The correction will appear in the online version of the paper on the JMIR Publications website on 05 Feburary 2025, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: Auricular Acupressure Versus an Intermittent Low-Carbohydrate Diet in Children With Overweight or Obesity With Gastric-Heat and Dampness-Obstruction Syndrome: Protocol for a Randomized Controlled Trial

Wen Sun[1*], MSc; Jingwei He[1*], MSc; Wenqin Wang[1], MSc; Chen Lu[1], PhD; Yating Lin[1], BSc; Yalan Dou[2], PhD; Weili Yan[2], PhD; Jian Yu[1], PhD

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Related Article:

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In "Auricular Acupressure Versus an Intermittent Low-Carbohydrate Diet in Children With Overweight or Obesity With Gastric-Heat and Dampness-Obstruction Syndrome: Protocol for a Randomized Controlled Trial" the authors noted 3 changes.

The author affiliation information has been changed from:

> *Wen Sun[1], MSc; Jingwei He[1], MSc; Wenqin Wang[1], MSc; Chen Lu[1], PhD; Yating Lin[1], BSc; Yalan Dou[2], PhD; Weili Yan[2], PhD; Jian Yu[1], PhD*
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to:

> *Wen Sun[1*], MSc; Jingwei He[1*], MSc; Wenqin Wang[1], MSc; Chen Lu[1], PhD; Yating Lin[1], BSc; Yalan Dou[2], PhD; Weili Yan[2], PhD; Jian Yu[1], PhD*
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> *[*]these authors contributed equally*

An equal contribution footnote has also been added for authors Wen Sun and Jingwei He.

In addition, under "Participant Timeline in Methods", in Table 1, the entries for Auricular acupressure at t_1 1 month and t_2 3 months, and Intermittent carbohydrate restriction diet at t_1 1 month have been changed from:

> *"N/A"*

to:

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"✓".

We intend to convey that the intervention duration for auricular acupressure is 3 months, while the intervention duration for dietary restriction is 1 month. It appeared incorrectly in the final published version.

The correction will appear in the online version of the paper on the JMIR Publications website, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: Assessment and Intervention for Diabetes Distress in Primary Care Using Clinical and Technological Interventions: Protocol for a Single-Arm Pilot Trial

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Related Article:

Correction of: https://researchprotocols.org/2025/1/e62916

(JMIR Res Protoc 2025;14:e75984) doi:10.2196/75984

In "Assessment and Intervention for Diabetes Distress in Primary Care Using Clinical and Technological Interventions: Protocol for a Single-Arm Pilot Trial" (JMIR Res Protoc 2025; 14:e62916) the authors made one addition.

An Acknowledgements section was added to the paper as follows:

We wish to acknowledge colleagues Sheana Bull and Adam Salyers at Clinic Chat, LLC, who developed the chatbot technology described in the manuscript.

The correction will appear in the online version of the paper on the JMIR Publications website, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

Submitted 14.04.25; this is a non–peer-reviewed article;accepted 15.04.25; published 23.04.25.

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Corrigenda and Addenda

Correction: Using Wearable Devices and Speech Data for Personalized Machine Learning in Early Detection of Mental Disorders: Protocol for a Participatory Research Study

Ramon E Diaz-Ramos[1*], MS; Isabella Noriega[2*], MS; Luis A Trejo[3*], PhD; Eleni Stroulia[1*], PhD; Bo Cao[4*], PhD

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Related Article:

Correction of: https://www.researchprotocols.org/2023/1/e48210

(JMIR Res Protoc 2025;14:e78287) doi:10.2196/78287

In "Using Wearable Devices and Speech Data for Personalized Machine Learning in Early Detection of Mental Disorders: Protocol for a Participatory Research Study" (JMIR Res Protoc 2023;12:e48210), the authors noted an error.

The following references:

> *32. Chen I-M, Lin P-H, Wu V-C, Wu C-S, Shan J-C, Chang S-S, et al. Suicide deaths among patients with end-stage renal disease receiving dialysis: a population-based retrospective cohort study of 64,000 patients in Taiwan. J Affect Disord. Feb 2018;227:7-10. [doi: 10.1016/j.jad.2017.10.020] [Medline: 29045916]*
>
> *33. Wang F, Wang Y, Tian Y, Zhang P, Chen J, Li J. Pattern recognition and prognostic analysis of longitudinal blood pressure records in hemodialysis treatment based on a convolutional neural network. J Biomed Inform. Oct 2019;98:103271. [FREE Full text] [doi: 10.1016/j.jbi.2019.103271] [Medline: 31454648]*

Have been revised to 32 and 33:

> *32. Chen C, Liu C-C, Weng P-Y, Cheng Y. Mismatch Negativity to Threatening Voices Associated with Positive Symptoms in Schizophrenia. Front Hum Neurosci. 2016;10:362. [FREE Full text] [doi: 10.3389/fnhum.2016.00362] [Medline: 27471459]*
>
> *33. Wang D, Ding Y, Zhao Q, Yang P, Tan S, Li Y. ECAPA-TDNN Based Depression Detection from Clinical Speech. In Interspeech. In Interspeech. 2022;10:3333-3337. [doi: 10.21437/Interspeech.2022-10051]*

The correction will appear in the online version of the paper on the JMIR Publications website, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

References

32. Chen C, Liu CC, Weng PY, Cheng Y. Mismatch Negativity to Threatening Voices Associated with Positive Symptoms in Schizophrenia. Front Hum Neurosci 2016;10:362 [FREE Full text] [doi: 10.3389/fnhum.2016.00362] [Medline: 27471459]

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33. Wang D, Ding Y, Zhao Q, Yang P, Tan S, Li Y. ECAPA-TDNN Based Depression Detection from Clinical Speech. In Interspeech. In Interspeech 2022;10:3333-3337. [doi: 10.21437/Interspeech.2022-10051]

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Corrigenda and Addenda

Correction: Rationale for the Use of Acupuncture to Stabilize Blood Pressure Fluctuations During Total Laparoscopic Hysterectomy: Protocol for a Pilot Parallel-Group Randomized Clinical Trial

Jee Young Lee[1*], PhD; Ju-Won Roh[2], MD; Kyung-Hee Han[3], MD; Min-Jeong Kim[2], MD; Young Jeong Na[2], MD; Bo Seong Yun[2], MD; Joohyun Lee[4*], MD

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Related Article:

Correction of: https://www.researchprotocols.org/2025/1/e77009

(JMIR Res Protoc 2025;14:e82570) doi:10.2196/82570

In "Rationale for the Use of Acupuncture to Stabilize Blood Pressure Fluctuations During Total Laparoscopic Hysterectomy: Protocol for a Pilot Parallel-Group Randomized Clinical Trial" ([JMIR Res Protoc 2025;14:e77009]) the authors noted one error.

Under the Acknowledgments section, the phrase:

> *...(grant number: RS-2023-KH139140 [HF23C0097]).*

has been replaced by:

> *...(grant number: RS-2023-KH139468 [HF23C0097]).*

The updated Acknowledgments section now appears as follows:

> *This research is supported by a grant from the Korea Health Technology R&D Project through the Korea Health Industry Development Institute, funded by the Ministry of Health & Welfare, Republic of Korea (grant number: RS-2023-KH139468 [HF23C0097]). The funders had no role in the study design, data collection, analysis, interpretation, manuscript writing, or decision to publish the results.*

The correction will appear in the online version of the paper on the JMIR Publications website, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

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Corrigenda and Addenda

Correction: Gamification of Incentive Spirometry in Trauma Patients: Protocol for a Prospective, Observational Feasibility Study

Areen Al-Dhoon[1], MD; Arthur Grimes[2], MD; Carma Goldstein[3], MD; Peter Spronk[4], MD, PhD, EDIC; R Shayn Martin[3], MD, MBA; Aarti Sarwal[5], MD

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Related Article:

Correction of: https://www.researchprotocols.org/2025/1/e75871

(JMIR Res Protoc 2025;14:e83839) doi:10.2196/83839

In “Gamification of Incentive Spirometry in Trauma Patients: Protocol for a Prospective, Observational Feasibility Study” (JMIR Res Protoc 2025;14(1):e75871) the authors made two clarifications.

The Results section in the Abstract has been changed from:

> *The study was approved by the institutional review board of Atrium Health Wake Forest Baptist Medical Center and was registered at ClinicalTrials.gov. However, no participants were ever enrolled, as the OmniFlow partners did not supply the device for the study. Despite this, it remains a potentially beneficial tool, and future studies may confirm its benefits once the device becomes available.*

to

> *The study was approved by the institutional review board and registered on ClinicalTrials.gov. Due to an unexpected delay in the initiation of the project, no patients were enrolled.*

The Results section in the main body of the paper has been changed from:

> *The study was approved by the institutional review board and registered on ClinicalTrials.gov. However, no participants were enrolled, as the OmniFlow devices were never delivered. Despite initial agreements, the device supplier became unresponsive and failed to fulfill the shipment. Multiple attempts to reestablish contact were unsuccessful. This unexpected barrier highlights the importance of reliable vendor partnerships when implementing novel therapeutic technologies in clinical research.*

to

> *The study was approved by the institutional review board and registered on ClinicalTrials.gov. Due to an unexpected delay in the initiation of the project, no patients were enrolled.*

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Corrigenda and Addenda

Correction: Ethical Principles Pertaining to the Care of People With Dementia: Protocol for a Qualitative Thematic Synthesis of Legal Documents

Daniel Sperling[1], PhD; Frederik Schou-Juul[2], PhD; Sigurd Lauridsen[2], PhD; Muhammad Asaduzzaman[3], MD, MPH, MPhil; Seda Guney[4], PhD; Dominika Kohanová[5], PhD; Vaitsa Giannouli[6], PhD; Corinna Porteri[7], PhD; Rodrigo Serrat[8], PhD; Ana Morais[9], PhD

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Related Article:

Correction of: https://www.researchprotocols.org/2025/1/e71490

(JMIR Res Protoc 2025;14:e87273) doi:10.2196/87273

In “Ethical Principles Pertaining to the Care of People With Dementia: Protocol for a Qualitative Thematic Synthesis of Legal Documents” [1] the authors noticed that the Acknowledgments statement had been inadvertently omitted, and have now added the following:

> *This article is based upon the work from COST Action EDEM (Ethics in Dementia; CA21137), supported by COST (European Cooperation in Science and Technology).*

The correction will appear in the online version of the paper on the JMIR Publications website, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

Reference

1. Sperling D, Schou-Juul F, Lauridsen S, Asaduzzaman M, Guney S, Kohanová D, et al. Ethical Principles Pertaining to the Care of People With Dementia: Protocol for a Qualitative Thematic Synthesis of Legal Documents. JMIR Res Protoc 2025;14; ../../2025/1/e71490 :e71490. [doi: 10.2196/71490]

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Corrigenda and Addenda

Correction: Testing a Machine Learning–Based Adaptive Motivational System for Socioeconomically Disadvantaged Smokers (Adapt2Quit): Protocol for a Randomized Controlled Trial

Ariana Kamberi[1], MBA; Benjamin Weitz[1], BS; Julie Flahive[2], MS; Kavitha Balakrishnan[1], BS; Julianna Eve[3], PhD; Reem Najjar[1], BS; Tara Liaghat[4], MS; Daniel Ford[4], MD; Peter Lindenauer[3], MD; Sharina Person[2], PhD; Thomas K Houston[5], MD, MPH; Megan E Gauvey-Kern[4], MS; Jackie Lobien[4], BSN, CCRP-CP; Rajani S Sadasivam[1], PhD

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Related Article:

Correction of: https://www.researchprotocols.org/2025/1/e63693

(JMIR Res Protoc 2025;14:e79873) doi:10.2196/79873

In "Testing a Machine Learning–Based Adaptive Motivational System for Socioeconomically Disadvantaged Smokers (Adapt2Quit): Protocol for a Randomized Controlled Trial," [1] the authors made one addition:

Kavitha Balakrishnan, BS

was added as an author to the study protocol. Neither the 'Acknowledgments' nor 'Conflicts of Interest' needed to be amended.

The correction will appear in the online version of the paper on the JMIR Publications website, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

Reference

1. Kamberi A, Weitz B, Flahive J, Eve J, Najjar R, Liaghat T, et al. Testing a Machine Learning-Based Adaptive Motivational System for Socioeconomically Disadvantaged Smokers (Adapt2Quit): Protocol for a Randomized Controlled Trial. JMIR Res Protoc 2025 Apr 16;14:e63693 [FREE Full text] [doi: 10.2196/63693] [Medline: 40239194]

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Correction: Testing a Machine Learning–Based Adaptive Motivational System for Socioeconomically Disadvantaged Smokers (Adapt2Quit): Protocol for a Randomized Controlled Trial
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Corrigenda and Addenda

Correction: An Integrated Virtual Reality–Based Telerehabilitation Platform to Support Recovery and Maintenance of Functional Abilities Among Older Adults: Protocol for a Usability and Acceptability Study

Marco Benadduci[1*], BSc; Claudia Franceschetti[1*], MEng; Rachele Alessandra Marziali[1*], MSc; Sebastian Frese[2*], PhD; Peter Stephan Sándor[3*], MD; Valentina Tombolesi[1*], BA; Valentina Bozzi[4*], MSc; Lorena Rossi[1*], MEng

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Related Article:

Correction of: https://www.researchprotocols.org/2025/1/e68358

(JMIR Res Protoc 2025;14:e88023) doi:10.2196/88023

In “An Integrated Virtual Reality–Based Telerehabilitation Platform to Support Recovery and Maintenance of Functional Abilities Among Older Adults: Protocol for a Usability and Acceptability Study” [1] the authors noted two errors.

In the originally published manuscript, affiliation 1 appeared as follows:

> *Centre for Innovative Models for Aging Care and Technology, Istituto Nazionale di Riposo e Cura per Anziani, Ancona, Italy*

In the corrected manuscript, affliation 1 appears as follows:

> *Centre for Innovative Models for Aging Care and Technology, IRCCS INRCA, Ancona, Italy*

In the originally published manuscript, affiliation 4 appeared as follows:

> *Scientific Direction, Istituto Nazionale di Riposo e Cura per Anziani, Ancona, Italy*

In the corrected manuscript, affliation 4 appears as follows:

> *Scientific Direction, IRCCS INRCA, Ancona, Italy*

The corrections will appear in the online version of the paper on the JMIR Publications website, together with the publication of this correction notice. Because these were made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

Reference

1. Benadduci M, Franceschetti C, Marziali RA, Frese S, Sándor PS, Tombolesi V, et al. An Integrated Virtual Reality–Based Telerehabilitation Platform to Support Recovery and Maintenance of Functional Abilities Among Older Adults: Protocol for a Usability and Acceptability Study. JMIR Res Protoc 2025 Jul 29;14:e68358 [FREE Full text] [doi: 10.2196/68358] [Medline: 40729692]

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Corrigenda and Addenda

Correction: Fermented Food Consumption Across European Regions: Protocol for the Development and Validation of the Web-Based Fermented Foods Frequency Questionnaire (3FQ)

Emmanuella Magriplis[1], PhD; Sotiria Kotopoulou[2], PhD; Signe Adamberg[3], PhD; Kathryn Jane Burton-Pimentel[4], PhD; Vaida Kitryte-Syrpa[5], PhD; Marta Laranjo[6], Prof Dr; Victoria Meslier[7], PhD; Theodoros Smiliotopoulos[1], MSc; Guy Vergères[4], Prof Dr; Bojana Vidovic[8], PhD; Christophe Chassard[9], PhD; Michail Syrpas[5], PhD

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Correction of: https://www.researchprotocols.org/2025/1/e69212

(JMIR Res Protoc 2025;14:e86393) doi:10.2196/86393

In Fermented Food Consumption Across European Regions: Protocol for the Development and Validation of an Web-Based Fermented Foods Frequency Questionnaire (3FQ)" [1] the authors noted one error which was an omission to acknowledge the work from COST Action.

A correction of the Acknowledgements section adding the following text:

> *This article/publication is based upon work from COST Action PIMENTO CA20128, supported by COST (European Cooperation in Science and Technology).*"

The Acknowledgments section now reads:

> *This article/publication is based upon work from COST Action PIMENTO CA20128, supported by COST (European Cooperation in Science and Technology).*
>
> *The authors sincerely thank all National Contact Points (NCPs) who helped disseminate the questionnaire (in alphabetical order): K Adamberg, D Ağagündüz, M Beglaryan, D Borch Ibsen, E Brouwer Brolsma, J Burtscher, M Cerjak, K Chandolias, Z Ciesarová, I Ciprovič a, De Filippis, E Delia, M Deschasaux, A Gamero, M Gandia, A Giertlova, MC Grech Perry, L Hoxha, D Jaros, H Jenssen, P Jones, A Kalea, B Kalyoncu, J Karl, L Kennes, G Kostov, A Kusar, M Laranjo, E Mantzari, N Mikulec, E Mudura, NE Nagybakay, L Ove Dragsted, L Ozola, NA Pancevska, P Papademas, D Pipoyan, I Pravst, H Rohm, P Russo, T Sar, M Starowicz, I Talkic, B Trajkovska, A Vukojevic, M Wronkowska, G Nakov, T Pohjanheimo. The authors*

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received financial reimbursement from the Promoting Innovation of Fermented Foods (PIMENTO) Cooperation in Science and Technology (COST) Action (CA20128) for the meetings and workshops conducted during tool preparation. Author MS received a grant to launch the questionnaire to specific populations. Author SK is alone responsible for the content and views expressed in this study, and they do not represent the decisions, policy, or views of the Hellenic Food Authority.

The correction will appear in the online version of the paper on the JMIR Publications website, together with the publication of this correction notice. Because this was made after submission to PubMed, PubMed Central, and other full-text repositories, the corrected article has also been resubmitted to those repositories.

Reference

1. Magriplis E, Kotopoulou S, Adamberg S, Burton-Pimentel KJ, Kitryte-Syrpa V, Laranjo M, et al. Fermented food consumption across European regions: protocol for the development and validation of the web-based Fermented Foods Frequency Questionnaire (3FQ). JMIR Res Protoc 2025 Aug 09;14:e69212 [FREE Full text] [doi: 10.2196/69212]

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Implementation of Virtual Focus Groups as an Effective Strategy in Qualitative Research to Engage With Undersupported Communities: Protocol for Virtual Focus Groups

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Abstract

Background: Qualitative research offers a valuable lens for understanding human experiences, behaviors, and social contexts, drawing upon communication, social interaction, and sociological perspectives. Focus groups are a key method within qualitative research for exploring these complex topics. While traditional focus groups offer valuable insights into group dynamics and shared perspectives, they can be limited by logistical challenges, such as geographic constraints and participant availability. To mitigate these issues, virtual modalities have emerged as a viable alternative, offering greater flexibility and accessibility for diverse populations. However, they also highlight persistent challenges, such as managing group dynamics in online settings and ensuring participant engagement and privacy concerns. Our protocol considers these issues and implements strategies, such as cofacilitators, more engaged research assistants, and the use of important security measures (participant name obfuscation, sharing links only on the day of the session, and password protection) as a way to overcome said issues.

Objective: Expanding the methods for data collection in qualitative research is essential for advancing health differences research in hard-to-reach populations and public health emergencies. In this paper, we aim to describe our experience when implementing an adapted protocol for conducting virtual focus groups, the barriers encountered, and how we obtained a participation rate of 86% (63/73) compared to 55% (40/73) when done in person.

Methods: To achieve this, we adapted and implemented a focus group protocol that approaches undersupported populations (social vulnerability index ≥0.45) who face challenges participating in traditional focus groups and addresses reported barriers in scientific literature using virtual focus groups. Our protocol was implemented in an exploratory qualitative study conducted from 2020 to 2021 to understand the community's health needs in southern Puerto Rico. This protocol ensures participant and research team interactions in circumstances that require it, including pandemics, geographically displaced populations, and patients who are bedridden. After evaluating the practical and ethical considerations, our research team established this new protocol for collecting qualitative data in a virtual focus group environment and promoting the inclusion of groups experiencing health differences.

Results: As a result, we collected quality data and found added benefits. We obtained a participation rate of 86% (63/73) compared to 55% (40/73) when done in person. Our findings also reveal further benefits that could impact groups that generally do not have the chance to participate in focus groups.

Conclusions: This approach to focus groups could aid researchers who wish to study these hard-to-reach participants and support qualitative health differences research.

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KEYWORDS

virtual focus groups; qualitative research; protocols; undersupported communities; community engagement

Introduction

Background

Qualitative research offers a valuable lens for understanding human experiences, behaviors, and social contexts, drawing upon communication, social interaction, and sociological perspectives [1,2] . Focus groups are a key method within qualitative research for exploring these complex topics. One of the best approaches in qualitative research to understanding these specific behaviors and perspectives is the use of focus groups, where a group of participants (generally 6 - 12) are interviewed simultaneously, with a moderator who guides the process and encourages interactions and discussion among participants [3,4]. While traditional focus groups offer valuable insights into group dynamics and shared perspectives, they can be limited by logistical challenges, such as geographic constraints and participant availability [5]. To mitigate these issues, virtual modalities have emerged as a viable alternative, offering greater flexibility and accessibility for diverse populations [6]. However, they also highlight persistent challenges, such as managing group dynamics in online settings and ensuring participant engagement [7,8]. Our protocol takes these issues into consideration and implements strategies, such as cofacilitators and more engaged research assistants to overcome said issues.

According to Creswell and Creswell [2], qualitative methods require a mindful recruitment procedure to appropriately select participants to ensure study questions and objectives are answered and achieved. Relating to individuals who participate in a qualitative study, four main aspects have been identified: (1) the setting in which the study is taking place, (2) the individuals being interviewed, (3) the actions of the participants, and (4) the development of the events that are taking place [2]. These 4 aspects ensure that the focus group can run optimally and that quality data can be obtained to ensure an understanding of the phenomenon being studied.

COVID-19 Pandemic and Virtual Modalities

The COVID-19 pandemic further underscored the need for adaptive research methods, leading to the accelerated adoption of virtual focus groups to continue essential studies while prioritizing participant safety [9]. Similar to studies conducted during this period [10-13], our study used virtual focus groups to examine health needs with a hard-to-reach population. This modality helped protect participants and research teams by preventing any potential health risks related to COVID-19 while also complying with national governmental restrictions. The shift to a virtual modality also raised ethical concerns, such as ensuring informed consent and protecting participant privacy in online settings [14], all of which our team was conscious of and ensured participant protection.

One such study that demonstrates the successful implementation of these strategies was that of Crocker and Stout [10], who studied the feasibility of transitioning an at-home in-person visit asthma program into a virtual format. Through their efforts, they were able to identify benefits, such as convenience for the participants and safety, as virtual visits were considered safer. Challenges included the need for more effective assessment strategies, potential engagement problems, and digital literacy. The researchers recommended strategies, such as rapport building, technical support, and the possibility of hybrid models. Such challenges were relevant to our study as well, and we share our solutions, which included more involved communication with participants before and during the focus groups.

Building on Matos-Castro et al [15] methodology, we created a refined virtual focus guide based on our experiences and identified more benefits that strengthen the validity of the results. We proposed this method not as a substitute for standard focus groups but as an alternative approach. Therefore, researchers can apply this method to different circumstances that could warrant using remote focus groups for emergencies and study populations that could benefit from this modality.

Role of the Internet in Conducting Research

Since the emergence of the internet, its role in research has been recognized as a potential tool for gathering information from users across different locations [16]. Internet usage has continued to grow and become intricately intertwined with people's lives; therefore, it is not surprising that various studies have been conducted to assess how this can be used in focus groups [17-19]. By leveraging technological advancements, there is an opportunity to widen the boundaries of qualitative research, including focus groups [5]. With this technology, it is possible to address many problems presented by traditional focus groups.

Early studies dealing with virtual focus groups predominantly adopted an asynchronous approach using email, chat rooms, and websites [17,19,20]. The qualitative data obtained in these studies were like those of traditional focus groups. On many occasions, participants appreciated the convenience and accessibility of expressing their thoughts at their own pace when they felt ready.

Another benefit was that patients experiencing chronic health conditions and mobility issues could use these platforms as online peer support groups [17].

However, these previous methods had several limitations. As mentioned before, focus groups were used because of the interactions between the participants. Other factors can also serve as valuable data on specific topics, such as tone of voice, body mannerisms, and facial expressions, which can be lost in a text-based focus group. Although this does not necessarily decrease the data quality, it should not be overlooked. One alternative that has been studied and used, with similarities to traditional focus groups and permits convenience and accessibility to participants, is videoconference-style focus groups. With these stated disadvantages in the loss of nonverbal cues, it should be noted that recent advancements in videoconferencing tools have enabled real-time virtual

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"face-to-face" conversations that can closely mimic in-person interactions.

Nonverbal cues offer valuable information that can be used for qualitative data reporting, including facial expressions, gestures, posture, and tone, which allow for clarification of intent and facilitate rapport building [21]. In video-based modalities, some cues remain but are diminished by factors, such as the camera's position, video quality, and participants' choices not to turn on their camera or to turn it off during a session [8]. In audio-only groups (synchronous) or text-based groups (asynchronous or synchronous), such cues are reduced or completely removed. This can pose a problem for interpreting group reactions and interactions. Thus, although videoconferencing serves as a means to maintain some of these cues and represents an improvement over early text-based methods, limitations remain. Researchers should remain attentive to these differences and consider them when implementing this type of protocol, as some research contexts may necessitate the use of these cues.

Videoconference-style focus groups try to recreate the face-to-face focus group experience by using video software in which the moderator and participants have cameras and audio devices. Before the COVID-19 pandemic, literature describing this area was relatively scarce and had not been explored thoroughly, as stated in a comprehensive review of virtual focus groups by Rupert et al [6]. In this review, chat and video focus groups were compared with in-person focus groups, and costs were found to be similar. In virtual focus groups, preparation time was decreased due to less travel and allowed recruitment of harder-to-reach populations. They observed increased miscellaneous costs (participant webcams, services, etc), and a higher participant attrition.

Despite these hurdles, virtual focus groups offer a unique opportunity by reducing logistical constraints. In response to these hurdles, and using our experience, we found that the associated costs were not as high as predicted and proved cost-effective. This could be attributed to the increased use of videoconferencing software due to the pandemic to the point of a reported "abnormal consumer interest," as stated by Tudor [22], while also considering that US citizens have reported an increase in internet use [23]. With better access to the internet, it is more probable that participants will have videoconference-ready devices.

In Puerto Rico, where this study took place, statistics indicate an overall internet penetration of 87.3%, increasing the feasibility of virtual engagement. Due to this high access to the internet, this served as a critical enabler for successful protocol implementation in the context of our study [24]. Furthermore, in our experience with the participants and researchers, the virtual environment ensured cost savings in areas such as travel and preparation of venues for the groups, offsetting other costs associated with virtual modalities.

By implementing strategies, such as providing tailored technical support to undersupported communities, using cofacilitation techniques to enhance participant engagement, and engaging community health workers to promote recruitment, we offer a protocol for enhancing accessibility and rigor in a virtual focus group research context.

Methods

Phase 1: Ethical Approval and COVID-19 Protocol

The study was first approved by the Ponce Health Sciences University (PHSU) Institutional Review Board (IRB) on April 14, 2021, and last approved on August 25, 2023. Due to the COVID-19 pandemic, an addendum was made in which we proposed moving our protocol to a virtual nature to be able to continue research activities. To obtain this approval, the team identified which platform would conform to privacy standards. When implementing the study, Zoom (Zoom Communications Inc) software contained the features necessary for addressing privacy concerns. Among these were (1) the encrypted nature of videoconferencing, (2) the ability to have closed rooms that could only be accessed via passwords provided by the research team, (3) moderation tools that would allow for videoconference control, and the capacity to create breakout rooms in case a participant requires support, aided by one of the facilitators. Only those who had confirmed participation would be given the password to enter. The team made sure that all video and audio recordings were done through the computer to restrict access to the research team. After these modifications, we were able to run the virtual focus groups. The research team handled all identifiable data (eg, contact numbers and names), and participants remained unknown to any other participants. During conversations, participants were assigned numbers and encouraged to use them during discussions to avoid saying their names.

Phase 2: Community Engagement and Team Formation

As part of the PHSU-Research Center for Minority Institutions (RCMI), the Community Engagement Core (CEC) focuses on health differences associated with chronic health conditions among disadvantaged populations in the southern region of Puerto Rico. The project follows a Community-Based Participatory (CBPR) approach as a model to address community health needs and differences [25]. CEC obtains helpful information and opinions from communities in disadvantaged positions, which will be referred to as undersupported populations. In the context of this study, the term undersupported populations refers to communities whose social vulnerability index (SVI) had a score of 0.45 or more. The CDC (Centers for Disease Control and Prevention)/ATSDR (Agency for Toxic Substances and Disease Registry) SVI is a place-based index designed to identify socially vulnerable areas based on factors, such as poverty, unemployment, age, race, and infrastructure, among others [26]. The score of 0.45 was chosen, as it falls within half or more of the most vulnerable population, with SVI typically being separated into quintiles, with 0.4 - 1 falling into the moderate to greatest vulnerability groups [27]. The CEC team is comprised of community members and academic researchers in an active partnership in which all parties weigh in on all processes. Community members are assembled into 2 fully community-led groups, including the Community-Trained Workforce (CTW) and the Community Scientific Advisory Committee (CSAC). Both CTW and CSAC are groups of local community leaders who have worked closely

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with CEC. These members have been recruited in the past and have completed training in core areas, such as research ethics, data collection, and community investigations. These team members serve as liaisons between the research and the community via disseminating study information and ensuring research materials are culturally appropriate and relevant to the communities. All parties had to agree on every phase before any investigation or intervention was completed.

Phase 3: Study Design and Participant Recruitment

An exploratory qualitative design was implemented using focus groups [2]. Online focus group participants were selected from communities in the following southern municipalities of Puerto Rico, including Peñuelas, Juana Díaz, Santa Isabel, Guayanilla, Guánica, and Coamo. Participants were (1) required to be 21 years or older, (2) belonged to the particular communities that were under study, and (3) provided informed consent. Exclusion criteria included participants with impairments that would not permit informed consent, as discussed by Matos-Castro et al [15].

As part of creating the focus group discussion questions, including logistics and locations, the CEC team (academic researchers, CTW, and CSAC) collaboratively developed a relevant, comprehensible, culturally competent, and sensitive process. For this purpose, a series of meetings was held between all groups in which feedback and revisions were made to the process.

A convenience sampling method was used for recruitment. To achieve a broad range of health status experiences within the communities, various strategies were used to disseminate study information, including printed materials, social media posts, and community partners. This approach enabled us to obtain varied perspectives from members of the communities in our exploratory study.

Phase 4: Research Team Composition and Analytical Reflexivity

The research team was composed of academic researchers with expertise in focus group dynamics, psychology, and community engagement, as well as trained community partners from the CTW and CSAC. Team participation was divided by phases in which some members of the research team, in tandem with the CTW and CSAC, oversaw the identification of potential communities and participant recruitment to ensure culturally relevant sites and community trust [28]. Moderators and research assistants participated only in the data collection phase. They ran and supported the virtual focus group sessions, ensuring they occurred effectively. Notably, research assistants were the only ones to have contacted participants before the sessions. Moderators and cofacilitators began the sessions without prior knowledge of which participants were in these groups.

Transcription was handled by research members who had not participated in the groups. Initial coding was conducted by 2 members who participated in the focus groups, and then, to ensure reliability, 3 research members who did not participate in the focus groups coded the material separately at a subsequent time using the same process. Disagreements were discussed and resolved via team discussions and the use of an expanded codebook definition [29]. Additionally, the ensuing results were discussed with CTW and CSAC in follow-up meetings to ensure an adequate and contextualized understanding.

Phase 5: Virtual Focus Groups Procedure and Data Collection

Virtual Focus Group Process

Figure 1 illustrates workflow implemented for the adapted virtual focus group protocol. The research team delegates assistants to participant groups who provide technical instruction and support to ensure comfort with Zoom prior to sessions, while a cofacilitator ensures smooth flow and research assistants address technical difficulties, sustain communications, and provide emotional support.

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Figure 1. Workflow for the adapted virtual focus group protocol showing delegation of participant support to assistants and cofacilitation.

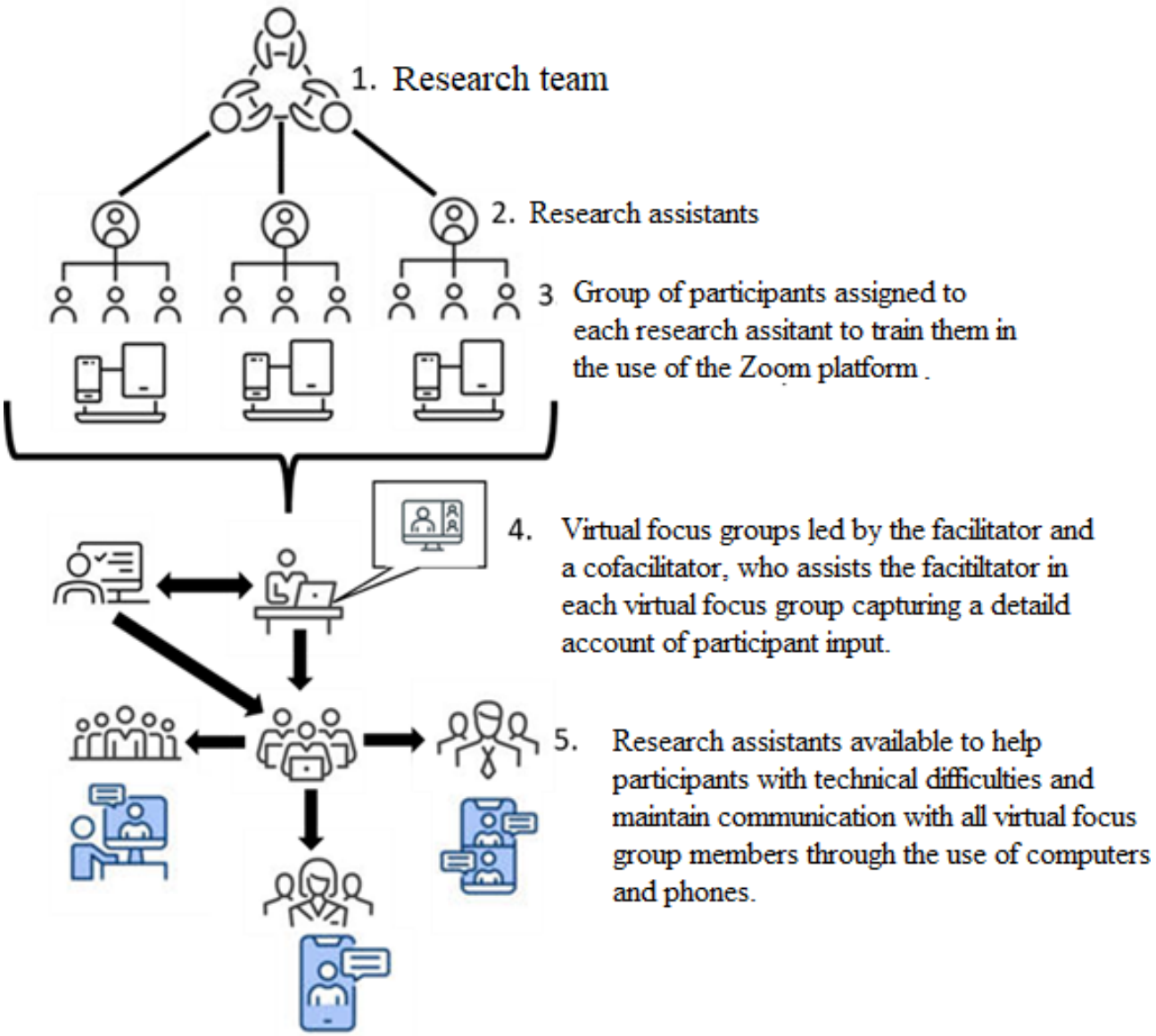

Research Team

Recruitment Strategies

Potential participants were invited to participate in the virtual focus groups using the strategies mentioned below.

Community Partners Networking

Members of the CTW leveraged existing community networks with other community leaders and associations to identify and reach potential areas of recruitment. This included phone calls with leaders, distribution of materials, WhatsApp messages in group chats, and social media sharing, all following COVID-19 safety protocols.

Social Media Platforms

Posts or virtual flyers were used to invite participants. These posts were shared through different platforms and pages (eg, Facebook [Meta Platforms, Inc], WhatsApp [Meta Platforms, Inc], and online community groups) frequently visited by target communities.

Printed Materials

Flyers and brochures were disseminated, following all safety protocols for COVID-19. The disseminated material contained contact information for the research team, which could be used to connect with potential participants and debrief them on the study's essential and relevant information. After participants were debriefed and provided their informed consent, they were given an online form in which they would be able to sign digitally and receive a copy of the informed consent to their emails. If participants had no experience filling out online forms, the research team would guide them. Once all participants had been confirmed, the research team called them to obtain their availability and asked them to inform what time was most convenient for their participation. The research team cross-referenced the desired times and created a schedule accommodating participants.

Research Assistant Training

Members of the research team were trained to fulfill the duties of notetakers in a focus group. Additionally, members were

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trained to be familiarized with the videoconference software and its functionalities while also making sure to understand the layout. In this way, they could monitor participants in both video and chat formats if needed. The members, including moderator and cofacilitator, were all prepared to offer psychological first aid and participant support to ensure both technological and emotional well-being.

Research Assistant Follow-Up and Helping Participants

Participants were equitably assigned to trained researcher assistants, who instructed them to use the videoconferencing software (eg, Zoom) and the platform. Research assistants asked participants if they had questions about accessing or using the platform and provided recommendations for best practices for virtual focus groups, such as maintaining video cameras during the session, being in a private and quiet place, and communicating any troubles regarding connection.

Research assistants asked participants if they had the required hardware (eg, desktop, laptop, tablet, or smartphone) for virtual focus groups and if they had a stable internet connection. If participants answered no to any of these, the research team could loan the equipment necessary for these virtual focus groups for the duration of the groups. This equipment would only be lent out if necessary and returned to the research team after the study.

Before carrying out focus groups, research assistants called participants again to confirm whether they were available for the focus group session. Participants were given a password-protected link to Zoom videoconference. This platform was chosen because it uses encryption for communications and has protocols for the protection of confidential information [30]. Additionally, the research team implemented other strategies to ensure privacy, such as participants being assigned numbers before entering the chat and being recommended to use these numbers instead of names to ensure anonymity. Participants were encouraged to set apart a private physical space for privacy during sessions.

Virtual Focus Group Sessions

During the focus groups, a cofacilitator was present to assist the main facilitator, who was running the virtual focus groups. The cofacilitator was ready to step in in case of technical difficulties for the moderator to keep participation active. If not, they only provided technical support.

Each session began with a moderator-led “ice-breaker” activity designed to commence dialogue and set a relaxed and inclusive tone, always emphasizing that all participation at any level is appreciated and that there were no right or wrong answers, promoting open sharing among participants and helping with any apprehension to participation.

Support From Research Assistants During Focus Groups

Research assistants were on standby for any technical difficulties. If a participant had connection issues, research assistants contacted them through chat or phone to maintain their participation, help with troubleshooting, and transmit any messages typed in the chat.

Support From the Research Team in Cases of Mental Health Distress or Crises

All personnel present in this phase were trained in psychological sciences and in managing potential crises to provide psychosocial support. Although no incidents occurred during these sessions, the team was equipped with a protocol for cases in which a participant was to confront a situation. In such cases, the research team could intervene, and if needed, move participants to a breakout room if they desired. If this were to occur, mental health aid would be provided, and the patient would be referred to a local wellness center associated with the institution for follow-up care. Additionally, all personnel involved in these groups had significant numbers for local services and hotlines. Forms were created to report these situations, detailing the incident and the steps taken.

Considerations

The approach of using numbers as identifiers stems from earlier focus groups done in our research, in which, when given tags with numbers, participants would begin to use these as identifiers without instructions. In practice, participants in the virtual focus groups rarely used these, often using natural conversational references, such as “I agree with what she said.” This pattern of rapport might be due to local context and social norm; therefore, in other settings, pseudonyms or self-selected identifiers might be considered.

It is also important to note that the moderator was responsible for running focus groups and had the same responsibilities as that of a traditional moderator. Co-facilitators and Research Assistants provided technical support and note-taking during sessions, refraining from intervention except to communicate missed text or offer emotional support if needed. Any follow-up to dropouts was done to ensure that this was done willingly and not due to technical problems.

Phase 6: Data Analysis

The focus group sessions were audio- and video-recorded using the Zoom platform. All audio data were transcribed manually via text editor software by members who did not participate in the focus groups and analyzed using the qualitative data analysis software Atlas.ti version 8 (ATLAS.ti Scientific Software Development GmbH). Content analysis was conducted through the lens of the Health Belief Model’s (HBM) theoretical approach to guide the focus groups’ domains and main topics, as described by Matos-Castro et al [15]. This approach has been used for past focus groups [31,32] and was developed using this model. Guided by the HBM, main domains and topics were identified and classified. Also, emergent topics not included in the HBM were included through the use of grounded theory to capture emergent topics in an inductive manner [33]. A thematic framework was developed once all the domains and topics were created [29]. Using this combination of theory and model, we conducted a deductive analysis based on the different components that can be found in the HBM as well as any other subthemes that were identified in coding, as discussed in the analysis in Matos-Castro et al [15].

The codebook was constructed iteratively, with initial categories that were coded openly. After initial coding, broad categories

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and emergent subcategories were identified. Subsequent coding used this codebook to code all transcripts. When no additional new codes or themes were identified, the final codebook can be found in Table S1 in Multimedia Appendix 1. Saturation was achieved after no new codes were identified upon examining transcripts. Two members of the research team who had participated in the focus groups did the initial coding to allow insight and perspectives for informing the first stage. Subsequently, to improve reliability and minimize bias, 3 members performed the analysis independently. Intercoder disagreements were discussed, and consensus-based resolutions were applied through team discussions and expanded codebook definitions. Subsequent interpretations were discussed with CTW and CSAC members to ensure adequate and contextual understanding. An example of the focus group interviews can be displayed in Table 1.

Table . Example of the focus group interviews.

Category	Questions guide for group discussion	Participant's responses
Knowledge	What comes to mind when you hear the phrase "chronic diseases?"	"It is a condition, which has no particular cure, nor is momentary. From there, it begins to affect patients if they do not care for themselves and, and it becomes a long-term disease."
Vulnerability	What can you say about chronic diseases present in members of your community or relatives?	"Depression, anxiety, cancer... The progress of chronic conditions is concerning. In our case, in Puerto Rico, it's alarming to see that previously you would go to offices where people were over sixty, and nowadays, dramatically, from the ages of 20 or 30, you already see patients with chronic diseases."
Barriers	Which difficulties do you consider the community may face regarding the prevention or management of chronic diseases?	"There are people who don't have health insurance because of what they earn they don't qualify for the government plan, they get sick, they have to go to appointments and see the doctor, but they don't do it because they don't have the money to take care of themselves or to have medical insurance."

Ethical Considerations

Ethical Approval

This study was approved by the Ponce Health Sciences University Institutional Review Board (protocol number: 1904011672R002, approval date April 14, 2021; last approval August 25, 2023). In response to the COVID-19 pandemic, an addendum was approved to move the protocol to a virtual format, ensuring research continuity while upholding participant privacy and data security standards.

Informed Consent

All participants provided informed consent prior to joining the study. The research team explained the study's objectives, the voluntary nature of participation, possible risks, and the confidentiality measures.

Privacy and Confidentiality

Zoom was selected as the videoconferencing platform for its compliance with privacy standards, including encrypted communications, secure (password-protected) sessions, and tools for moderating discussions and providing private support as needed. Only preregistered participants were given access, and all recordings were stored securely and accessible exclusively to the research team. Identifiable information (contact details and names) was handled strictly by the research team. During focus group discussions, participants were assigned numbers, which they used instead of names to maintain anonymity and confidentiality. All personally identifiable information was removed during data analysis and reporting.

Compensation

Participants were compensated for their time and contributions in accordance with institutional policies. The compensation provided was US $25, following the completion of each focus group session, at a later date. The amount was set to reimburse any costs that the participant might have had to participate, such as internet use and time.

Results

Participant Characteristics

Ten online focus groups were created and were composed of adults aged 21 years or older (N=73) who were residents of the southern regions of Puerto Rico. Of the participants, 77% (n=56) were cisgender women, and 23% (n=17) were cisgender men, with an average age of 46 (SD 14.46) years (refer to Table 2), showing a skewed representation for women. This result was expected, as past experiences and literature suggest that males are reluctant to participate in health research, which might explain this trend [34]. All focus groups were held between 2020 and 2021. Participants were given a stipend for their time and any costs incurred in the participation of focus groups. To obtain this stipend, participants were required to sign a receipt for compensation, which was completed after the focus group sessions at a location agreed upon by both the participant and the research team. This would follow all IRB and HIPAA (Health Insurance Portability and Accountability Act) compliance requirements, with only research team members handling identifiable information, ensuring that all information was maintained anonymously and securely.

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Table . Sociodemographic data.

Variable and characteristic	Participants, n (%)
Gender	
Cisgender Man	17 (23)
Cisgender Woman	56 (77)
Marital status	
Widower	1 (1)
Single/Never Married	22 (30)
Married	37 (51)
Divorced/Separated	10 (14)
Living with a partner	3 (4)
Highest level of education	
High school or less	15 (21)
Technical degree	5 (7)
Associate degree	8 (11)
Bachelor's degree	27 (37)
Master's degree	15 (21)
Doctorate's degree	3 (4)
City of residence	
Peñuelas	7 (9)
Guanica	14 (19)
Guayanilla	16 (22)
Coamo	16 (22)
Santa Isabel	8 (11)
Juana Diaz	12 (16)

Recruitment, Participation, and Attendance

A participation rate of 86% was achieved in our virtual focus groups, compared to a rate of 55% in previous in-person groups. Minimal dropouts occurred. Various recruitment strategies (community networks, social media, flyers, and CTW/CSAC) contributed to achieving a broad range of health status experiences in the sample.

Technology, Privacy, and Logistical Outcomes

Possible challenges were identified and addressed through different methods, which are detailed in Table 3.

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Table . Identified challenges and proposed solutions.

Identified challenges	Proposed solutions
Lack of knowledge on the part of the participants about the use of technology.	• Research assistants train participants by telephone on the use of technological equipment for the virtual focus group (cell phones, tablets, and computers). This orientation takes place several days before the virtual focus group is held.
Reduce dropout rates	• Research assistants will follow up through bidirectional communication with participants on previous days to minimize difficulties that they might encounter leading up to a dropout. For example, assistants called participants days before to clarify doubts and remind them of the date and time of the virtual focus groups.
Participants were in locations with various physical interruptions and privacy concerns.	• Research assistants guide participants on the importance of being in a private and comfortable place free of distractions in which they can express themselves freely during the virtual focus group (for example, a room at home).
Participants do not have knowledge about the use of the Zoom app.	• Research assistants contacted participants via telephone days before the virtual focus groups with the aim of guiding the participants, step by step, on the use of Zoom and technical support if needed. • Test exercises are carried out several days before the virtual focus group is held.
The internet connection goes down, and the participant involuntarily disconnects from the virtual focus group.	• The research assistant assigned to that participant quickly contacts the participant by phone to identify and resolve potential technical glitches. If the situation is not resolved, the research assistant becomes the interlocutor, "immediately conveying the participant's expressions and comments on the discussion topic to the other members of the virtual focus group."
The participant's internet signal is weak and causes the image to freeze or the audio to not be heard clearly during the virtual focus group.	• The research assistant assigned to that participant communicates quickly via telephone and offers them the possibility of continuing their participation in the focus group via telephone or to withdraw from the study, while consistently emphasizing that participation in the group is entirely voluntary.
In-person delivery of the stipend, which required participant signature for the institutional documents.	• Research team communicated with participants to agree on a safe location following any health guidelines implemented (eg, open spaces), on a date that worked for the participant. • In the case that the participant was not able to arrive at a location, an identified person could serve as a proxy if the participant permitted and provided a written agreement. • Following all IRB[a] and HIPAA[b] compliance, any identifiable information was handled by the research team and receipts were secured.
Privacy challenges	• During meetings with the research team, participants were told in an individual manner about the importance of being in a private and comfortable environment. • Zoom links and passwords were only sent on the day of the focus group, making sure that these were sent to the correct email addresses or phone numbers (depending on the preference of the participant). • Zoom rooms were password-protected.

[a]IRB: Institutional Review Board.

[b]HIPAA: Health Insurance Portability and Accountability Act.

Focus Group Dynamics and Observations

Participants were told and advised about the importance of being in a private and comfortable environment. Participants were assigned numbers before entering the chat and were recommended to use these numbers instead of names to ensure anonymity, as guided by past groups and behaviors. In practice, participants in the virtual focus groups rarely used these, often using natural conversational references such as "I agree with what she said." The research team ensured that privacy guidelines were sufficiently explained before and during the sessions to prevent identity disclosure. If names were said, these were censored and replaced with the participant's number in transcriptions, though this rarely occurred.

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Sessions began with moderator-led "ice-breaker" activities to promote open sharing and participation. Research assistants provided technical and emotional support throughout. No incidents of mental health crises required intervention, but all personnel were prepared, and protocols had been established.

Thematic Analysis Outputs

Key domains and emergent topics were identified through the HBM framework, as detailed in Table 1.

Discussion

Principal Findings

After the COVID-19 pandemic began, owing to different health restrictions, many researchers had to find ways to continue their studies without compromising participants' health. This has led to many studies using videoconferencing software to continue reporting their findings [7,9,35]. As a protocol, our goal is not only to present our findings but also to describe a method that can be built upon and refined in other settings. Several studies discuss how videoconferencing software (in most cases referring to Zoom, the most widely used and available platform for research/educational institutions) allows the continuation of research activities, specifically focus groups. In a study by Halliday et al [7], they emphasized how virtual focus groups reduce logistical barriers, such as travel and costs of hosting physical places while maintaining data quality. Our protocol builds upon these principles and addresses other factors, such as digital exclusion through participant technical support, ensuring balanced access. This emerging field merits investigation, as it could have various advantages that could improve the implementation of qualitative research and, specifically, the focus group experience.

Innovative methods are needed, as qualitative research methods can result in risk factors for transmitting health problems during crises, such as epidemics or pandemics. Thus, creating an environment that allows study individuals to participate without being directly affected by the global COVID-19 pandemic was essential. Using our adaptations can help to promote the participation of groups that experience health differences while assuring the quality of the experience for participants and the integrity of the data collected. However, it is important to acknowledge that this may not be suitable for all research questions or populations. In some cases, such as those that require direct observation of participants, an in-person or hybrid method may be more appropriate. Nevertheless, in contexts that do merit virtual environments, we aim to address the various challenges that are present and demonstrate the virtual method's advantages.

In recent qualitative focus group studies, selection and social desirability biases were identified because they only attracted participants interested in a specific topic in their interviews [36]. Kloppe et al [37] stated that to overcome this challenge, one must ensure that additional stakeholders are included so they can provide a different perspective; thus, our work with the CTW and CSAC members in identifying communities and recruiting participants helped reduce the likelihood of researchers' selective sampling based on implicit preferences. Beyond sampling, other studies have identified that these types of interviews and in-person focus groups can bias participants' responses due to the researcher's presence [2]. Hence, we understand that it is essential for the moderator to set an environment for open discussion without creating bias owing to their own beliefs and preconceptions.

We implemented various practices to help mitigate these challenges. Sections of the protocol were segmented in a way that research members would only be involved in specific parts and minimize potential bias. We minimized overlaps in tasks. For example, transcription and analysis were done so minimally by members who were directly in the focus groups for initial coding, with a completely different team working independently for coding. Finally, moderators and cofacilitators were to follow question guides developed in conjunction with the community members, making changes in areas to be more culturally relevant to participants, which researchers might not have considered, recognizing that due to inherent subjectivity in qualitative work, it cannot be wholly eliminated but can be diminished.

Creating focus groups that effectively engage hard-to-reach populations presents many challenges. Some cited in the literature include members who are geographically far from where the focus group is being held, the lack of transportation, or participants who have physical health limitations, such as chronic conditions or limited mobility. The latter can be due to different factors, such as individuals who are in active treatment for a condition, are ill, or have been recommended bed rest [17-20]. Excluding such individuals can result in the loss of novel and unique data. By implementing our virtual focus group protocol, we obtained valuable perspectives from these hard-to-reach individuals living with physical health conditions that impede mobility or have geographical restrictions. We believe this to be one of the most important benefits of the virtual focus group modalities. This inclusion should be taken into consideration for future focus group discussions. The voices of these participants are generally not present in a focus group setting; however, this modality allows them to provide data on certain phenomena. Unlike one-to-one interviews, they have the opportunity to interact with other participants.

One participant best stated this:

> *Thank you for meeting with us in this manner. I am a cancer patient and can't get out of bed… In this way, I can participate.*

This approach was initially used as an alternative to in-person focus group sessions due to the COVID-19 restrictions in place; thus, for many researchers, this was their first time using this modality, including ourselves. As a result, the data collected during this period, in which participants were living in a different context due to the pandemic, could have influenced group dynamics. Some studies have reported that virtual focus groups do not produce the desired outcomes and have identified specific issues, such as those discussed by Aligato et al [35] and Lobe et al [38]. Issues identified include the need for notetakers to be more involved in their responsibilities, scheduling problems, higher dropout rates, a distraction from the environment, early departure, technical problems, and privacy concerns.

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Maintaining group dynamics in virtual settings can also be difficult due to limits in nonverbal cues and interruptions caused by technical problems. Our use of a cofacilitator and research assistants mitigated these challenges by ensuring active participation and addressing problems in real-time without interrupting the focus group session, thus relieving the moderator of technical problem-solving and reducing session disruptions. In the literature, the group size for virtual focus groups was 4 - 6 participants. In our experience, we were able to have group discussions with 8 - 10 participants, thanks to the more involved team and through the moderator's role of facilitating participation, maintaining focus on maintaining discussions aligned with the question guide, and providing an inclusive environment for better rapport. Technical challenges were handled solely by the cofacilitator and research assistants, not intervening during discussions, while the moderator focused fully on focus group discussions as a traditional moderator.

Other issues in this area include not everyone having access to the internet or technology and some lacking the necessary skills [39]. This study design necessitates internet access; a weak internet connection can lead to audio or vocal distortions, dropped calls, and pauses, resulting in unintelligible interview segments [9]. Furthermore, a restricted connection may cause limited data collection when a participant uses only audio and deactivates the camera. This could lead to digital exclusion, where participants are excluded due to not being technologically literate [40]. Though we tried to mitigate this potential problem via in-depth technical help, we cannot discard this possibility.

Additionally, we must consider the ethical implications beyond the ethical protocols implemented for this study, as this research poses further implications that need to be considered when using virtual tools. First, what other measures can researchers implement to better ensure the anonymity of those participating in these groups? Second, to create honest data, what can be done to facilitate a comfortable setting for virtual focus group participants, where safety and well-being can be ensured?

In our experience, we were able to maintain ethical approaches and participant privacy by using internet-based consent forms and ensuring direct communication with researchers to explain these consent forms. During sessions, persons were given numbers, which were used during focus groups so as to protect anonymity. Additionally, participants were encouraged to be in a private and comfortable environment to make sure that all conversations were as private as possible. However, it should be noted that the location was ultimately the participant's choice, which means that guidance given by the research team has to be comprehensive and should ensure that the participant understands these ethical principles for their own protection.

Even with these identified challenges, we successfully adapted the focus group modality for virtual data collection using videoconferencing software. We implemented several novel aspects that facilitated the process, ensuring a high participation rate and effective data collection. Unlike previous studies that relied solely on participants' existing resources and knowledge (eg, Nobrega et al [8]), our protocol included a comprehensive orientation session, minimizing the risk of nonparticipation due to lack of technological knowledge. Additionally, studies by Lobe et al [38] emphasized the need for virtual focus groups to have a more structured approach due to different factors. Our approach extended this by incorporating cofacilitators and research assistants who provided real-time technical support and helped maintain group engagement. Another recommendation by this same author is conducting presession technical checks, which our protocol was able to apply before and during participation.

After participants agreed to participate, our research team evaluated their means of communication. This included assessing whether the potential participant had access to devices, such as computers, tablets, or smartphones. Participants also consulted with research assistants to gauge their familiarity with Zoom software. The research team provided step-by-step guidance for those unfamiliar, ensuring they understood how to use the platform. This individualized communication was key to ensuring participant engagement and reducing dropouts.

We also emphasized the role of a cofacilitator, whose responsibilities included handling technical details, scheduling meetings, managing participant screening to ensure only scheduled individuals joined, and serving as a backup moderator in case of technical difficulties. Cofacilitators were trained research team members who were proficient with the software and equipped to manage unforeseen circumstances.

Research assistants played a more involved role in this adaptation. In addition to taking notes and observing focus groups, they maintained direct communication with participants. If a participant disconnected for any reason, their assigned research assistant contacted them via phone or messaging (based on participant preference) to resolve the issue and guide them back to the session. Research assistants also facilitated participation by compiling and sharing text chat messages, ensuring contributions from soft-spoken individuals were included in the discussion, thereby enriching the data.

Prior to implementing the virtual focus groups, participation rates in our in-person sessions were 55% (40/73 participants). We identified several barriers that might have led to these dropouts, such as geographic distance, scheduling problems, and availability of venues that were convenient for all participants. When the COVID-19 pandemic required a shift to virtual modalities, we used these experiences to ensure better participation. We introduced flexible scheduling by offering multiple time blocks for participant preference. Additionally, this modality removed the geographic limitations, as participants could participate using their devices in areas they termed appropriate.

The inclusion of a more involved process for participant participation, such as technical assistance, orientations for the focus groups, and follow-up after participants expressed interest in participation, always emphasizing the voluntary nature of participation and the option to withdraw at any time, encourages more follow-through, this leading to an increase in the participation rate of 86% (63/73) in the virtual modality.

Financial costs appeared to remain minimal (although no itemization of costs was made at the time of implementation). We believe this is likely due to the widespread accessibility of

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videoconferencing software. These findings demonstrate that, when carefully implemented, virtual focus groups can overcome challenges and provide a valuable platform for qualitative data collection.

This methodology was effective in our case for health differences research due to its ability to facilitate diverse participation, reduce logistical barriers, and provide comfort for participants. However, the protocol could also be adapted for use in other fields, such as education or social work, by adjusting the data collection instruments and tailoring the technical support to meet the specific needs of those fields.

In Nobrega et al [8], virtual focus groups were used to evaluate the impact of a diversity program. The study highlighted several advantages, including a larger geographical reach, easier access for individuals with limited mobility, and greater comfort for participants. In another example, Turner et al [41] used online focus groups for the evaluation of energy use and investment decisions by personality traits. Participants were shown a marketing video and later convened in a virtual focus group setting. In this case, the virtual manner was found to have limitations in regard to participation, but benefits regarding more comfort in participation due to perceived anonymity and more engagement due to the ease of attendance and less worrying about tasks that could be done while conversing. Finally, we can also mention the use of this modality in a study by Borti et al [42], in which virtual focus groups and communications were used to study teachers' opportunities and knowledge in sub-Saharan Africa using the Ubuntu research paradigm. This used different virtual platforms to establish productive collaborations using virtual groups. Of importance was the need for researchers to support collaborators in accessing the necessary technologies and to take into consideration the platforms that are used.

These examples show that virtual focus group methodologies can be applied in different contexts, such as project evaluations, commercial applications, and social science applications. Key benefits include their ability to overcome geographical barriers, enhance accessibility for diverse participants, and create a comfortable environment conducive to open and honest discussion. These various studies showed that the method was effective for these research goals. With this in mind, we wish to be able to provide a guide that other researchers can use to establish their own virtual focus group, including key elements, such as establishing the necessary members in a research team, addressing technological barriers for participants, and implementing other aspects for a smooth operation. The changes, benefits, and challenges are detailed in Table 4. As seen from these papers, different strategies were applied, but these lacked some of our suggested additions and practices, such as that of comoderators, research assistants, and procedures to facilitate participation. We hope to be able to facilitate these processes with our guide.

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Table . Comparison of traditional focus groups and virtual focus groups, with benefits and possible challenges.

Traditional focus groups	Adaptations in virtual focus groups	Benefits and challenges from adaptation
• Informed consent can be read at the site or venue and signed on paper	• Informed consent should be read to participants before the session, which could be done through phone or private virtual sessions.	• Requires more preparation, but ensures that participants are informed correctly.
• A venue is chosen beforehand, and time is established based on participants' input. • It could prove difficult for some members to arrive due to geographical constraints.	• Due to the virtual nature of the study, participants will be in their home or most comfortable environment. • Participants are advised on best practices to ensure a private environment. • Time can be adjusted based on members' availability. • Members might arrive due to technical difficulties.	• Requires technical support and follow-up, but leads to better accessibility for participants via the reduction of travel barriers
• Led normally by 1 facilitator or moderator who runs the focus group and moderates interactions in a way that there is balanced participation, controlling for dominant participants and encouraging participation through dialogue and nonverbal cues.	• Led by a moderator for running the group and a cofacilitator for backup, technical assistance, emotional support if needed, and ensuring participation. • Moderation is done through dialogue, but text can also be read, though these should only be used to enrich conversations and dialogue. • Fewer nonverbal cues are possible due to limited body vision through webcams.	• Team-based moderation is required, with cofacilitator and research assistants taking active roles in real-time monitoring for technical problems. This requires additional training and preparation for the use of virtual conference software but ensures technical issues are minimal to the sessions, which allows moderators to serve their traditional role. • Nonverbal cues are kept to a minimum or eliminated if participants opt not to turn on the camera.
• Notetakers have a passive role and oversee making important notes of certain interactions, body language, and important topics and writing them down. • Usually, 1 or 2 per session	• Notetakers, or research assistants in this case, take on a more active role, communicating with participants before and during the sessions to ensure optimal conditions for participation. • Serve as support for technical difficulties • Facilitator for communication to assigned participants • Serve as emotional support if needed. In this case, more than 2 are recommended to cover all participants.	• Requires more personnel but ensures participation, follow-ups on losses due to technical issues, and gives a chance for less talkative individuals to communicate via private messages.
• Focus group size is generally 6-12 participants.	• Focus group size can be done with larger groups but should be limited to 6-8 to ensure better control. • More than 10 participants are not recommended.	• Smaller groups can facilitate richer and more in-depth discussion. Additionally, with smaller groups, the technical burden is reduced per session. • Depending on software use, there might be a limit to the number of screens visible to the moderator; thus, a smaller group is preferred in this instance.

Limitations and Recommendations for Future Protocols

Although our sampling approach worked for the purposes of our exploratory study, we acknowledge that in different research contexts, greater comparability and homogeneity might be desired. In these cases, we recommend the addition of a prescreening assessment step added to the protocol, which can be done through the use of survey software to ensure that participants comply with inclusion criteria according to the studies' aims.

Despite the variety of recruitment strategies used (CTW liaisons, printed materials following COVID-19 safety measures, word of mouth, and online outreach), women had a much higher rate of participation (77%). This approach led to a larger reach but did not overcome the gender imbalance, which may also reflect contextual factors and recruitment modalities. Future implementation should consider exploring additional outreach measures that target males, such as using men's groups, work sites, and organizations. Acknowledging that this gender participation trend is reflective of local realities in community engagement in Puerto Rico, it might limit the transferability of our findings in other contexts.

In Puerto Rico, where the study was conducted, internet penetration is approximately 87.3% [24]. Furthermore, the context of the COVID-19 pandemic led many individuals to

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acquire digital skills and familiarity with virtual platforms rapidly, facilitating broad participation in virtual focus groups. During recruitment, all participants were confirmed to have the necessary technology. However, it should be noted that this circumstance may not apply in other regions. In settings with lower internet penetration or limited access to technology, researchers may face significant barriers to participation and should consider this a critical limitation when adapting similar protocols.

Recommendations for a quiet and private environment represent an ideal situation rather than an expected result. While our protocol emphasized the importance of contacting participants before focus groups to provide instruction and offer advice on best practices, this does not guarantee that participants will follow them. Ultimately, this is a decision that lies with the participant; thus, they should not be pressured or expected to have cameras on. This can be considered an inherent limitation to this methodology. Though in our experience with proactive support and attending to the participants' technical needs before the group, very few elected not to show their camera.

Although the research team managed stipend delivery during the COVID-19 emergency, future studies, especially those covering larger geographic areas, may benefit from empowering trained community members to assist with this process. Leveraging community-led teams for stipend distribution could increase efficiency, reduce logistical burden for research staff, and foster deeper community partnership, supporting both scalability and sustainability of qualitative research protocols. Additionally, one could implement electronic signatures and use electronic payment measures to ensure the least amount of contact occurs between the research team and participants.

Several safeguards were established to protect participant privacy. The nature of audio and video recording presents an inherent privacy risk that cannot be fully eliminated. While measures, such as assigning numbers and changing display names, can manage some aspects of anonymity, each participant's face and voice are still tied to their contribution. Thus, transparency must be exercised by researchers, and they must adopt comprehensive privacy protocols as described, while also exploring additional methods that could enhance anonymity in future virtual focus groups.

It should be noted that although participation increased in virtual groups (86%) compared to in-person groups (55%), this comparison occurred in distinct time periods and under changing circumstances, such as the COVID-19 pandemic, which might have given participants more time to participate. Additionally, other factors, such as community outreach, flexible schedules, internet penetration of approximately 87.3% [24], and technical support, may have contributed to these results. These circumstances can vary by location, and in cases where there is lower internet penetration or limited access to technology, researchers may face significant barriers. This represents a limitation that should be considered when adapting this protocol in different areas.

Thus, implementations should be taken cautiously. However, we still believe that if planned according to the participants' time and increased accessibility, this could lead to high participation. Similarly, we perceived the costs for virtual focus groups as minimal due to savings in venues and travel, but no formal itemized cost analysis was carried out. Thus, future studies might wish to use a prospective approach to compare direct costs.

Conclusion

We believe that virtual focus groups are an important and effective tool to facilitate the participation of undersupported populations, especially those who, for health reasons or lack of transportation, find it difficult or cannot reach a physical place to participate in traditional focus groups. Likewise, our virtual focus group protocol can be used anytime and be applied in different scenarios. It is an effective tool for continuing qualitative research and collecting information in real-time and reducing barriers that could impede the process. Following our protocol, past challenges were mitigated, we found an increased participation rate, and an adapted modality was established for future qualitative research.

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Data Curation: ARL, DAVM, DRT, JMC, and JLMP.
Formal Analysis: ARL, JMC, and JLMP.
Funding Acquisition: JJC and MMR.

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Investigation: ARL, DAVM, DRT, JMC, and MMR.
Methodology: ARL, JJC, and MMR.
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Resources: ARL, JMC, JJC, and MMR.
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Conflicts of Interest

None declared.

Multimedia Appendix 1
Codebook of themes and quotations.
[DOCX File, 20 KB - resprot_v14i1e77937_app1.docx]

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Abbreviations

ATSDR: Agency for Toxic Substances and Disease Registry
CBPR: Community-Based Participatory Research
CDC: Centers for Disease Control and Prevention
CEC: Community Engagement Core
CSAC: Community Scientific Advisory Committee
CTW: Community-Trained Workforce
HBM: Health Belief Model
HIPAA: Health Insurance Portability and Accountability Act
IRB: Institutional Review Board
PHSU: Ponce Health Sciences University
RCMI: Research Center for Minority Institutions
SVI: Social Vulnerability Index

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Evaluation of the Effectiveness of Close-Knit Medical Alliances on the Integration of HIV Prevention and Treatment in County-Level Areas in China: Protocol for a Delphi Study

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Abstract

Background: Integrated care for patients living with HIV in rural and economically disadvantaged regions remains a critical challenge. This study aims to develop a 3D evaluation index system to assess the effectiveness of integrated medical care and prevention for patients living with HIV in county-level regions of China. The framework encompasses disease prevention, clinical treatment, and the integration of medical services with public health interventions.

Objective: This study aims to develop a scientifically validated, 3D evaluation index system for assessing the effectiveness of integrated medical care and prevention for patients living with HIV in county-level regions of China.

Methods: A structured Delphi method will be used to establish consensus among experts on key evaluation indicators. The study will begin with focus group discussions guided by the Valentijn Rainbow Model, followed by multiple rounds of Delphi surveys to refine the indicator system. A total of 75 experts will include clinical professionals, public health specialists, health policy researchers, and representatives from nongovernmental organizations. Experts will participate in iterative rounds, ranking and validating indicators using statistical methods such as the analytic hierarchy process and Kendall W coefficient to assess consensus.

Results: The Delphi study was initiated in April 2025, with 3 rounds of questionnaires distributed between May and September 2025. Data analysis is ongoing, and the finalized county-level HIV integration index system is expected to be published by spring 2026. The study is projected to be completed by January 2026.

Conclusions: The developed evaluation system will offer a comprehensive and scientifically validated tool for assessing health care outcomes in resource-constrained settings, contributing to policy improvements for HIV service integration in China and other low-resource settings globally.

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KEYWORDS

HIV; AIDS; integrated health care; Delphi method; public health evaluation; county-level medical services

Introduction

HIV remains a significant global public health challenge, with the integration of medical and preventive services being crucial for effective disease management. By 2021, the global number of people living with HIV had reached 40 million (38 - 42.4 million), an increase from 29.5 million (28.1 - 31 million) in 2010 [1]. By the end of 2022, an estimated 39 million (33.1 - 45.7 million) individuals were living with HIV, two-thirds of whom (25.6 million) resided in the World Health Organization (WHO) African region. Despite ongoing efforts, achieving the global targets of reducing HIV incidence and mortality by 2030 remains highly challenging. Over 40 million people will continue to require lifelong antiretroviral therapy (ART) in the coming decades [2]. Moreover, funding for HIV prevention and control in low- and middle-income countries has declined to US $20.8 billion in 2022—returning to 2013 levels and falling significantly short of the US $29.3 billion needed by 2025 [1]. Since no cure for HIV exists, governments and health care institutions must urgently implement integrated strategies for HIV prevention, diagnosis, treatment, and long-term care. This approach is critical for transforming HIV

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into a manageable chronic condition, allowing people living with HIV to lead long and healthy lives.

China faces considerable challenges in HIV prevention and control, particularly in integrating medical and preventive services in rural and county-level areas. The 2013 WHO Consolidated Guidelines on the Use of Antiretroviral Drugs for Treating and Preventing HIV Infection emphasized not only the importance of HIV testing and ART coverage but also patient satisfaction, service quality, and the continuity of care between prevention and treatment. The United States was one of the first countries to implement integrated HIV medical and preventive services, with the Office of National AIDS Policy leading the nationwide efforts. Various government agencies, including the Centers for Disease Control and Prevention (CDC), the National Institutes of Health (NIH), and the Health Resources and Services Administration (HRSA), have worked collaboratively to integrate HIV prevention and treatment into broader health care systems [3]. Similarly, sub-Saharan Africa has focused on incorporating HIV services into primary health care frameworks, particularly in managing chronic conditions alongside HIV care [4].

However, China continues to face significant gaps in HIV prevention, treatment, and regulatory integration, with complex social determinants driving the epidemic. HIV prevalence remains high among men who have sex with men, while heterosexual transmission is increasing, often in hidden and hard-to-prevent patterns. Rural areas represent a critical weak link in China's HIV response due to persistent poverty, inadequate financial support, limited access to high-quality health care and stable housing, fragmented health systems that hinder comprehensive HIV care, poor transportation infrastructure restricting medical access, and low public awareness of HIV prevention, leading to delayed diagnosis and treatment [5]. In rural Guangxi, a significant loss to follow-up has been observed between HIV diagnosis and ART initiation, while studies in parts of Yunnan Province indicate that people living with HIV aged 50 and older often have low health awareness, contributing to continued high-risk behaviors. Addressing these gaps requires a more integrated and comprehensive approach to HIV prevention and treatment [6].

In recent years, the Chinese government has prioritized the development of integrated HIV medical and preventive services. The Healthy China 2030 blueprint, released in 2016, reinforced measures such as expanded HIV testing, ART access, follow-up management, nucleic acid testing for blood safety, and the prevention of mother-to-child transmission, helping to maintain a low overall epidemic level. The National Action Plan on HIV Prevention and Control (2024 - 2030) further highlights key priorities, including government leadership, multisectoral collaboration, social mobilization, and public participation. It emphasizes a prevention-first approach while integrating treatment and control, with a focus on high-burden regions and vulnerable populations. The plan also calls for the innovation of medical-preventive integration mechanisms to improve the quality and effectiveness of HIV prevention and control. A key step in achieving these goals is the development of an evaluation framework for HIV medical-preventive integration at the county level. This framework would allow for a more precise assessment and monitoring of HIV prevention, treatment, and regulatory measures, particularly in rural areas where health care resources are limited.

The integration of medical and preventive services is essential for improving the long-term quality of life of people living with HIV, especially in resource-limited settings. However, a scientifically robust evaluation framework for this integration has yet to be developed. Current research on HIV policies has primarily focused on HIV testing rates and ART coverage, often neglecting critical aspects such as patient satisfaction, service coordination, and health education. Future studies should aim to construct a comprehensive evaluation system that encompasses not only traditional indicators (eg, HIV testing rates and ART coverage) [7-9] but also broader dimensions such as health care service coordination, patient experience, and long-term health outcomes. Such a framework would provide policymakers with more holistic evidence for decision-making, ultimately leading to more effective HIV control and long-term disease management [10].

One potential approach is the application of the Valentijn Rainbow Model, which offers a multidimensional perspective on integrated care [11]. The primary objective of this study is to develop a 3D evaluation index system through the Delphi method, based on the Rainbow Model, specifically designed to assess the effectiveness of integrated medical care and prevention for patients living with HIV in county-level regions of China. This comprehensive framework encompasses 3 critical dimensions: disease prevention, clinical treatment, and the integration of medical services with public health interventions. The resulting system aims to provide a scientifically validated measurement tool that can be adapted for evaluating HIV health care outcomes in rural and economically disadvantaged areas globally, thereby offering valuable references for strengthening the global HIV response in resource-constrained settings.

Methods

Focus Group Discussions

This study develops a preliminary indicator system framework for the county-level integration of HIV medical and preventive services, guided by the Valentijn Rainbow Model and refined through focus group discussions (FGDs) [12]. The Rainbow Model provides a comprehensive theoretical foundation, emphasizing person-centered and population-centered integration. It comprises 6 dimensions: system integration (macrolevel), organizational and professional integration (mesolevel), clinical integration (microlevel), and normative and functional integration, which facilitate coordination across all levels [13]. This model aligns well with the practical need for seamless medical-preventive service integration in HIV care, ensuring a holistic and patient-centric approach.

The Rainbow Model provides a structured perspective on integrated care, emphasizing that successful service integration requires multilevel coordination. System integration ensures policy alignment and resource allocation at the macro level; organizational and professional integration at the meso level enhances interdisciplinary collaboration and institutional

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efficiency, while clinical integration at the micro level focuses on seamless patient care. Additionally, normative integration (shared values and goals) and functional integration (harmonized workflows and IT systems) serve as critical connecting mechanisms across levels. By adopting this model, the study acknowledges the complexity of health care systems and provides a structured method to evaluate HIV service integration at the county level [14].

Textbox 1 outlines the framework of the indicator system for the county-level integration of HIV medical and preventive services, based on the Valentijn Rainbow Model. This model highlights the coordination across multiple levels—system, organizational, professional, and clinical—and categorizes indicators into primary dimensions such as policy support, health care accessibility, and service coordination. These indicators are crucial for evaluating the effectiveness of integrated HIV services in rural, county-level regions.

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Textbox 1. Framework of the indicator system for county-level integration of HIV medical and preventive services.

System integration

- Policy support
  - Inclusion of HIV prevention and treatment in county development plans in the past 3 years [15]
  - Formulation of HIV prevention and treatment implementation plans in the past 3 years [16]
- Work system
  - Development of an annual work plan for HIV prevention and treatment in the past year [17]
  - Establishment of incentive measures for HIV prevention and treatment in the past year

Organizational integration

- Organizational structure
  - Participation of relevant government departments in HIV prevention and treatment [18]
  - Participation of public health institutions in HIV prevention and treatment
  - Functional complementarity and cooperation among different institutions in HIV prevention and treatment [19]
- Organizational collaboration
  - Signing of agreements between health care institutions for HIV prevention and treatment [17]

Professional integration

- Collaboration forms
  - Involvement of senior public health professionals in grassroots HIV prevention and treatment
  - Regular guidance by senior physicians on grassroots HIV prevention and treatment
  - Reasonable professional composition of family physician teams for HIV services
- Coordination mechanism
  - Establishment of chronic disease joint outpatient clinics within the county-level medical consortium [20]
  - Establishment of a communication mechanism for HIV prevention and treatment services among health care personnel [20]
  - Distribution of condoms and other pre-exposure prevention measures in the county

Clinical integration

- Accessibility
  - Coverage rate of integrated HIV prevention and treatment services in primary health care institutions
  - Number of newly enrolled people living with HIV receiving treatment
  - Baseline viral-load detection rate [21]
  - CD4 T-cell detection rate [22]
  - Proportion of people with CD4 count < 100 cells/μL [23]
  - Antiretroviral therapy coverage rate [24]
  - Sulfamethoxazole usage rate
- Comprehensiveness
  - Timeliness of infectious-disease reporting
  - Screening rate of high-risk populations for HIV [25]
  - Standardized management rate of people living with HIV [25]
  - Incorporation of traditional Chinese medicine services into integrated HIV prevention and treatment
  - Incidence of HIV-related complications [26]
- Continuity

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- Follow-up rate of people living with HIV [27]
- Patient loss rate within the year or month
- Proportion of patients receiving care within 3 months after diagnosis [28]

- Coordination
  - Tracking rate of referred patients [25]
  - Follow-up rate of patients referred back [25]

- Safety
  - Regular viral-load testing [29]
  - Mortality rate within the year or month [29]

- Satisfaction
  - Patient satisfaction [30]
  - Staff satisfaction with integrated HIV services [30]

Normative integration

- Funding support
  - Establishment of dedicated funds for integrated HIV prevention and treatment by county governments
  - Proportion of medical-consortium surplus funds allocated to HIV prevention and treatment performance incentives

- Talent support
  - Number of general practitioners per 10,000 population [27]
  - Number of family physician teams per 10,000 population
  - Number of infectious-disease specialists per 10,000 population in secondary hospitals [27]
  - Annual number of special training sessions on integrated HIV prevention and treatment in the county [27]
  - Establishment of an information-system platform for management of patients living with HIV in the county [31]

- Information system
  - Information sharing among health care institutions within the county
  - Utilization rate of electronic health records [29]
  - Coverage rate of telemedicine services in primary health care institutions

Functional integration

- Service supervision
  - Supervision and management of integrated medical and preventive services by health administrative departments [17]
  - Development of service procedures for integrated medical and preventive care by health care institutions [32]

- Organizational commitment
  - Participation of health care personnel in integrated medical and preventive services [32]

To refine the framework, FGDs were conducted, engaging 3 public health professors, 10 HIV health care professionals, and 7 graduate researchers. Participants engaged in 3 rounds of discussion, with graduate students systematically reviewing PubMed, Web of Science, China National Knowledge Infrastructure (CNKI), and Wanfang to gather evidence on HIV policies and intervention [33]. The discussion process facilitated an evidence-driven and consensus-based refinement of the tertiary indicators, ensuring that the evaluation framework is both empirically grounded and contextually relevant. The resulting tertiary indicator system is detailed in Textbox 1.

The application of FGDs enhances the practical relevance and stakeholder alignment of the indicator system [33,34]. By incorporating experts with diverse backgrounds, this study ensures that the framework reflects real-world health care challenges and policy priorities. The rationality of the theoretical approach lies in its ability to bridge theory and practice, using

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the Rainbow Model structured framework to guide integration while refining the indicators through expert consensus. This approach enhances the validity, feasibility, and applicability of the proposed indicator system, making it a valuable tool for evaluating and improving HIV service integration at the county level.

Delphi Method

The Delphi method, developed by the RAND Corporation [35] in the 1950s, is a structured communication technique that gathers and refines expert opinions through multiple rounds of questionnaires, aiming to achieve consensus on complex issues [36]. In public health, this method is instrumental in areas where empirical evidence is scarce or inconclusive, facilitating the development of guidelines and evaluation frameworks [37,38]. For instance, it has been used to define criteria for selecting peer educators in HIV management in China, ensuring that the chosen individuals are well suited to current practices.

In the context of HIV prevention and treatment in rural China, the Delphi method has been used to develop performance evaluation systems for the CDC at various administrative levels [39]. By engaging experts in iterative consultations, this approach ensures that the resulting evaluation indicators are both contextually relevant and scientifically robust, addressing the unique challenges faced in underdeveloped regions [40].

Patient and Public Involvement Strategy

Participants engaged in 3 rounds of discussion, with graduate students systematically reviewing PubMed, Web of Science, CNKI, and Wanfang to gather evidence on HIV/AIDS policies and intervention strategies, including those related to HIV service delivery during the COVID-19 pandemic, with a focus on key populations in diverse settings. The search results were systematically analyzed, and experts with a high volume of publications in high-impact journals and a research focus aligned with the study objectives were selected as consulting experts. In addition, we included professionals with more than 5 to 10 years of experience from the Health Commission and CDC [41], as well as medical personnel involved in AIDS prevention and treatment (Textbox 1). Two rounds of consultation questionnaires were then distributed via email. Upon receipt of the feedback, comprehensive data analysis and consistency tests were performed to validate the responses.

Designing the Delphi Questionnaire

The Delphi questionnaire is designed to develop a 3-tier indicator system for HIV prevention and treatment in China's counties and rural areas. Its purpose is to achieve consensus on key themes and indicators and to assess the degree of consistency across various focus areas.

Recruitment Strategy

Recruitment for this study will involve sending emails and letters to 100 targeted individuals. Additionally, recruitment efforts will be extended through networks across China, patient-oriented research support groups, and academic institutions via word-of-mouth and strategic email campaigns. The primary participants will include staff from health and wellness committees, disease control centers, university professors and researchers, and medical personnel involved in AIDS prevention and control.

The use of financial incentives (500 RMB [US $30]) in this study is intended to motivate expert participation and compensate for their time and effort, especially given the multiple rounds of feedback required by the Delphi method. This approach helps ensure a high response rate and minimizes participant attrition. However, there is a potential risk of bias, as experts may feel subtly influenced by the incentive. To mitigate this, it is important to emphasize that participation is voluntary, with a clear assurance that responses will remain anonymous and independent.

To mitigate potential respondent loss, the sample size will be expanded to 200 during the first round of recruitment.

Study Participants

The selection criteria for experts in this study were based on the recommendations proposed in 1975 by Delbecq, Van de Ven, and Gustafson regarding the selection of Delphi research participants. These recommendations include (1) senior management decision-makers who will use the outcomes of the Delphi study, (2) professionals and their support teams, and (3) respondents to the Delphi questionnaires whose opinions are being solicited [42].

Accordingly, we selected 3 key categories of experts in the field of HIV prevention and control: government officials, health care professionals, and academic researchers. Among them, government officials from disease prevention and control agencies were required to encompass all administrative levels, including the Chinese Center for Disease Control and Prevention (China CDC), provincial CDCs, municipal CDCs, and county-level CDCs. Health care professionals were drawn from tertiary hospitals, township health centers, and community health service centers, ensuring representation across different tiers of the health care system. Efforts were made to achieve a balanced distribution of experts across these various levels [40].

To enhance the representativeness and authority of the expert panel, we established specific inclusion criteria tailored to each category of experts. Determining the appropriate sample size in Delphi studies is crucial for achieving a reliable consensus. While there is no universally prescribed number, research suggests that a sample size of 10 to 15 participants may be sufficient if the expert panel is homogeneous [43]. However, for multistakeholder Delphi surveys, a minimum of 60 to 80 participants is recommended to ensure high replicability of results. Considering the scope and diversity of our study, we aimed to include 60 to 75 experts, balancing feasibility with the need for diverse and comprehensive input [44].

This structured and deliberate approach to expert selection is designed to ensure that the Delphi process yields robust, credible, and actionable insights for advancing HIV prevention and control efforts (Table 1)

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Table . Expert selection criteria for the Delphi study on HIV prevention and treatment integration.

Source	Inclusion criteria	Participants (range)
Government agencies related to HIV prevention and control	At least 5 years of relevant work experience in health commissions or disease prevention and control centers	20 - 25
HIV prevention and treatment institutions (hospitals, primary health care service institutions)	At least 5 years of relevant work experience in HIV prevention and control; includes staff from tertiary hospitals, secondary hospitals, community health centers, and township health center or village health unit personnel	20 - 25
Research institutes	At least 5 years of experience in HIV-related research and has published related core journal articles as the first author	20 - 25

Subsequent Validation

Subsequent validation of the evaluation framework will include pilot testing in 2 hospitals in Yunnan Province, involving 5 physicians in each hospital. This small-scale, real-world application will test the framework's feasibility and allow for the collection of feedback from health care professionals. Presurveys will also be conducted to assess the initial perceptions and readiness of the health care staff. Based on the pilot results and feedback, adjustments will be made before broader implementation. The framework will then be evaluated through field implementation across additional county-level areas to assess its effectiveness, applicability, and impact on improving health care service integration.

Ethical Considerations

The project was reviewed and approved by the Ethics Committee of Tongji Medical College, Huazhong University of Science and Technology (ID: 21YJA630062). This study strictly adheres to the ethical principles of the Declaration of Helsinki. Full voluntary informed consent was obtained from all participants, with clear disclosure of data collection purposes, scope, and secondary use rights, as well as the right to withdraw without prejudice. Collected data was de-identified and encrypted to protect privacy and the study. Participants were compensated up to 500 RMB (US $30).

Dissemination

The research findings will be presented at international conferences and published in reputable international academic journals. Additionally, a policy report on the "China County AIDS Prevention and Control Evaluation Effect Indicator System" will be submitted to the relevant stakeholders.

Delphi Process

Based on the WHO guidelines for HIV, we identified key research themes during each round of our Delphi expert consultation. As shown in Figure 1, our process involved 3 rounds of letter-based consultations that ensured active expert participation and refined the indicators until a practical, consensus-based index system was achieved.

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Figure 1. Delphi process.

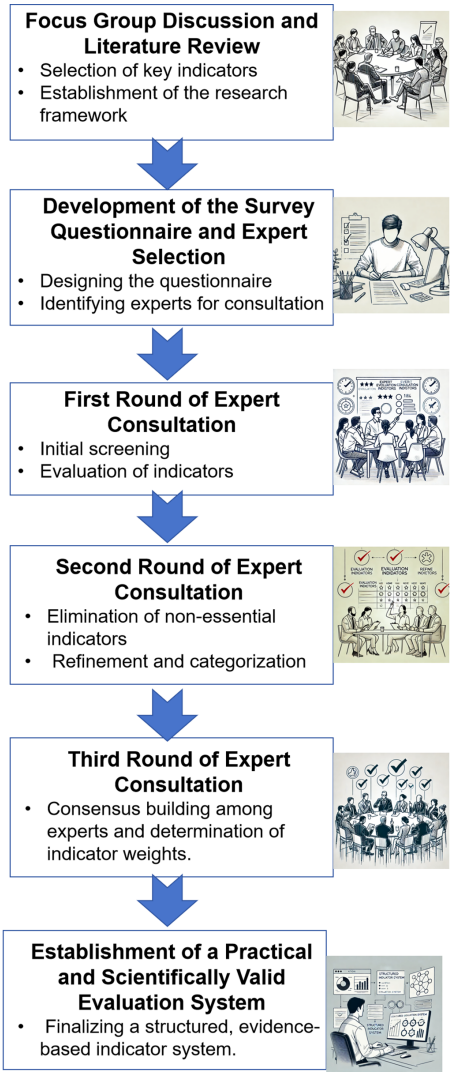

Administration of the Delphi Questionnaire

The study will be conducted from April 1, 2025, to January 31, 2026. The first to third rounds of questionnaires will be distributed using Tencent Documents, from May to September 2025, and qualitative interviews will be conducted using Zoom (Zoom Communications, Inc) and telephone consultation. Respondents who wish to receive a printable version of the questionnaire can choose to receive a PDF version of the questions. The members of the research group will submit a reply through Tencent Documents. Quantitative and qualitative data analysis will be carried out between the 3 rounds of surveys, and the development of the indicator system and the dissemination of the final report will be completed by January 2026.

First Round

The first round of the Delphi study aims to refine the evaluation framework for the county-level integration of HIV medical and preventive services by eliminating nonessential indicators and dimensions. A panel of 60 to 75 experts is invited to assess the preliminary indicator framework, providing suggestions for additions, deletions, and modifications based on practical experience, theoretical analysis, peer knowledge, and intuitive judgment. Experts rate the importance of each indicator on a 1 to 5 scale, with higher scores indicating greater importance. Their feedback is used to calculate engagement, authority, coordination, and consensus levels, guiding the selection of indicators and ensuring iterative refinement.

Statistical analysis is conducted using SAS (SAS Institute Inc) to compute the mean, SD, coefficient of variation, and Kendall W for each indicator, assessing the degree of expert agreement. Nonparametric tests are applied to determine statistical significance ($P<.05$), indicating whether expert opinions are significantly divergent. Additionally, R (R Foundation for Statistical Computing) is used for analytic hierarchy process (AHP) to derive indicator weights. The consistency ratio is calculated to validate expert agreement in the AHP process, with CR<0.1 indicating acceptable consistency.

Findings from this round will be used to refine the evaluation framework, ensuring that the selected indicators are scientifically robust and relevant to assessing the integration of medical and preventive services for HIV. Expert feedback and statistical validation contribute to the systematic development of a comprehensive and evidence-based assessment system.

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Second Round

The second round of the study focused on identifying the key themes and indicators prioritized by the participants in the first round. During this round, participants were tasked with selecting a predetermined number of topics across multiple dimensions, including prevention and health education for potential patients, diagnosis and treatment, health intervention for patients, and the interface between prevention and treatment. The specific number of topics selected for each category was determined based on insights from the first round, and a weighting calculation was applied to determine the final selection of topics and indicators in similar categories. Topics and indicators that received the highest participant selection advanced to the next round.

Cronbach α was used to assess the internal consistency of the responses in each round. Additionally, 2 members of the research team analyzed the free-text comments provided in the questionnaires to identify relevant changes in the survey topics. These findings were reported in detail to the advisory group, which evaluated the need to add or modify topics and indicators accordingly.

Third Round

In the third round of the Delphi expert consultation, efforts were made to ensure that the evaluation index system for regional HIV medical and preventive integration was comprehensive, practical, and refined. The research team conducted a collective review of the primary and secondary topics related to HIV integration at the county level, aiming to minimize bias and capture all key concepts to enhance the scientific rigor and practical applicability of the indicator system.

First, indicators and dimensions that received little attention from experts in the first and second rounds were eliminated. Second, the questions were revised to include clear definitions of medical terms and, where possible, to use simpler language, facilitating the implementation of the indicator system in practical evaluations. Finally, participants were informed that they could complete the round in multiple sessions, save their progress, and would receive a reminder if their questionnaire remained incomplete after 1 week.

The purpose of the third round is to accept suggestions on the modification of the index system already obtained by experts in the first 2 rounds, accept feedback, and resolve the uncertainty of the index system determined by the first 2 rounds of expert review. The research team analyzes the advice provided by 2 master's and PhD experts in order to inform any final adjustments if necessary. These changes will be reviewed and finalized by the research team of 7 master and doctoral students and 2 associate professors. The task force will use these findings to develop a countywide AIDS prevention and control indicator system that best matches actual needs.

Results

The Delphi study was initiated in April 2025, with 3 rounds of questionnaires distributed between May and September 2025. Data analysis is ongoing, and the finalized county-level HIV integration index system is expected to be published by spring 2026. As of the most recent round, the expert panel has refined the core indicators, with high consensus achieved on key dimensions of service integration. Initial data suggest promising trends in both service accessibility and coordination across county-level health institutions, indicating potential for meaningful improvements in HIV care integration.

Discussion

Anticipated Findings

This study aims to systematically develop an evaluation framework for county-level HIV service integration, contributing to both theoretical and methodological advancements in the field. While previous research has explored various metrics for assessing HIV-related health outcomes [45], diagnosis, and treatment effectiveness, no prior study has provided a comprehensive, empirical framework specifically for evaluating the integration of HIV prevention and medical care at the regional level [46]. The key contributions of this study are as follows.

First, this study uses the Rainbow Model as the theoretical foundation to construct an integrated health care service framework, developing a 3D indicator system encompassing medical services, public health interventions, and social support [47]. This model emphasizes a multilayered integration of prevention and treatment, facilitating a more comprehensive assessment of HIV service effectiveness at the country level. Second, the study engages a diverse group of stakeholders, including policymakers, researchers, and health care professionals, ensuring that the evaluation framework incorporates multidisciplinary perspectives and remains relevant to real-world implementation [48]. Finally, this study uses a mixed-methods approach by integrating FGD, the Delphi method, and AHP**,** which helped reduce participant attrition while enhancing the interpretability and practical applicability of the findings.

Limitations

Despite its contributions, this study has several limitations. First, the developed framework is designed to assess the overall effectiveness of integrated HIV service delivery at a regional level rather than evaluating the impact of specific health education or intervention programs. Therefore, its primary utility lies in policy and system-level evaluations rather than in assessing individual interventions. Second, the literature review is conducted primarily using Chinese-language databases, and the recruited experts are predominantly from China, which may limit the generalizability of the framework to other geographical contexts. Future research should incorporate international datasets and expert input to improve the global applicability of the framework. Third, although the Delphi method and AHP enhance consensus-building, expert judgments remain inherently subjective, potentially influencing the selection and weighting of indicators. Selection bias in expert recruitment may also limit the comprehensiveness of the identified indicators, which is a known limitation of the Delphi process.

The effectiveness of the framework will be measured through both qualitative and quantitative assessments. During the pilot

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testing phase, we will gather feedback from health care professionals and administrators regarding the framework's feasibility, ease of use, and impact on service integration. Additionally, key performance indicators such as patient satisfaction, service coordination, and health care outcomes will be tracked during the field implementation phase. We will use statistical methods, including pre- and postimplementation comparisons, to evaluate the framework's effectiveness in improving HIV service delivery at the county level. We have now explicitly included this in the methods section for clarity.

Conclusions

The findings of this study will have significant implications for HIV prevention and treatment policies and implementation science. First, this study refines the conceptual framework of HIV service integration, providing a structured approach to enhancing the continuity of care and comprehensive lifecycle services for people living with HIV [48]. Second, by identifying key indicators, this study develops a robust evaluation framework specifically tailored for resource-limited settings, offering policymakers a practical tool for assessing the effectiveness of integrated HIV interventions. Finally, by engaging 75 leading HIV prevention and treatment experts in China, this study contributes to evidence-informed policymaking and promotes cross-disciplinary collaboration in HIV service delivery.

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Authors' Contributions

SD conceptualized the study and led data analysis; YL contributed to data curation and formal analysis; QL designed the methodology; RD conducted the investigation and visualized the data; JH drafted the manuscript; Yong Yang supervised the research; and Yiqing Yang secured funding and edited the manuscript. The manuscript was reviewed and approved by all authors before submission for publication.

Conflicts of Interest

None declared.

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Abbreviations

AHP: analytic hierarchy process
ART: antiretroviral therapy
CDC: Centers for Disease Control and Prevention
CNKI: China National Knowledge Infrastructure
FGD: focus group discussion
HRSA: Health Resources and Services Administration
NIH: National Institutes of Health
WHO: World Health Organization

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Protocol

Influence of Partnership Relationships on Long-Term Neurological Rehabilitation in Germany: Protocol for a Qualitative Retrospective Study

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Abstract

Background: Acquired neurological diseases entail significant changes and influence the relationship between a patient and their significant other. In the context of long-term rehabilitation, those affected collaborate with health care professionals who are expected to have a positive impact on the lives of the affected individuals.

Objective: This study aims to examine the changes in the relationship between the patient and their loved ones due to acquired neurological disorders and the influence of health care professionals on this relationship.

Methods: Through sociogenetic type building, we will identify different types of patient-caregiver dyads and their effects on health care professionals and vice versa. The results will then be integrated into a model based on the theory of symbolic interactionism and Baxter's Relational Dialectics Theory.

Results: This study is not funded and was approved by the ethics committee of the German Society for Nursing Science, and it complies with the Declaration of Helsinki. The data collection started in June 2024 based on narrative couple interviews and is running. We assume that patients and their relatives will demonstrate heterogeneity as individuals, as well as in their interactions within the dyad, regarding certain orientations such as coping with illness, motivation for therapy, and coping strategies.

Conclusions: Our findings address a biopsychosocial perspective that enhances treatment approaches in neurological long-term care. Understanding the influence of professionals on dyadic couple relationships can improve rehabilitation effectiveness by tailoring therapeutic approaches to various patient types, relatives, and dyadic relationship constellations. This fosters patient- and family-centered therapy in line with holistic care.

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KEYWORDS

neurological rehabilitation; neurological injury; therapeutic alliance; relationship building; caregivers; family; partnership; health professionals; neurological; therapeutic; Germany; retrospective study; narrative interview; biopsychosocial; family-centered

Introduction

Scientific and Practical Relevance of the Project

Rehabilitation is effective for any person with a long-lasting disability at any stage of the illness. A patient-centered biopsychosocial rehabilitation approach involving a multidisciplinary team is particularly essential for individuals with neurological conditions, as they frequently experience lifelong limitations and require comprehensive, individualized support to enhance their quality of life and achieve maximum independence [1].

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Neurological damage is acquired through stroke, traumatic central nerve injury, or traumatic brain injury. The resulting sudden loss of independence often leads to irreversible harm and is one of the main causes of lifelong support and home care needs. Strokes cause a high economic and health burden [2]. For example, the cost of stroke to health care systems in 32 countries totaled US $28.2 billion in 2017 [3]. This is why the Stroke Alliance for Europe emphasizes the need for European countries to invest in cost-effective stroke interventions to improve rehabilitation and the quality of life of stroke survivors [3]. The number of patients with traumatic brain injury in 2016 in Germany was 419,507 [4]. More than 4000 patients become long-term care cases due to severe permanent injuries, resulting in high costs and limited ability to work [5]. The rehabilitation process for neurological diseases is highly complex, depends on numerous influencing factors, and is vague concerning the results. The effectiveness of rehabilitation is highly dependent on its integration within a biopsychosocial framework and requires an individualized, person-centered approach [1]. Functional, cognitive, and psychological challenges directly impact the ability to perform daily tasks independently [6]. Acquired neurological damage leads to a loss of social roles for those affected and requires adaptation to the new living conditions [7]. In the context of illnesses, the individual coping strategies used vary greatly across the different patients [8]. Life orientations, goals, ideas, and expectations about one's own life and future development represent a relevant aspect of rehabilitative cooperation and success. Relatives of those who are directly affected not only experience trauma but also deal with the illness and its lasting personal consequences for themselves [9]. Individual processes take place within partnership dyads and domestic cohabitation. This is particularly relevant for Germany where 63% of people in need of care are cared for exclusively by relatives in a domestic setting. Nursing homes care for only 16% of people in need of long-term care in Germany [10].

Family Change Processes and Relationship Dynamics

In the partnership dyad between the person affected and the caregivers, dual roles arise as a spouse, patient, or caring relative [11]. Changes caused by a sudden loss of independence and the need for assistance due to a family member's illness impact power dynamics, role distributions, tasks, and decision-making between patients and their relatives. On the one hand, relatives provide their resources while on the other hand, they need help themselves. Within the framework of the existing family system, relatives thus have to face new challenges [9,12]. In this context, the rehabilitation process after acquired neurological damage is associated with fears, worries, and adaptations for many patients and their caregivers [13].

The therapeutic relationship significantly influences the rehabilitation process of neurological diseases and is of paramount importance [14,15].

Family caregivers play a central role in providing care, therapy, and social support, particularly in the case of lifelong disability due to acquired neurological damage [16]. According to recent international studies, the psychosocial effects of neurological damage have already been described for patients [12,17] and family caregivers of affected persons [18]. Studies also explore the dynamics between patients and therapists, as well as the relationships formed in patient-therapist interactions [12,19]. However, given the importance of biopsychosocial aspects in therapy and the close interactions affecting the well-being of patients and their relatives, there is a lack of studies on the influence of health care professionals on the dyadic relationship between patients and relatives in different phases of rehabilitation.

Our study addresses the following questions:

1. How does the dyadic relationship between persons with acquired central nervous chronic impairment and their significant others change over time and what does it mean for the therapeutic process?

2. How do relationships and relationship aspects influence the rehabilitation process?

3. What is the influence on the dyadic relationship that affects persons and their life partners which attributes to the health care professionals?

Furthermore, we want to discuss how health care professionals should react to the different situations and dyads in the rehabilitation process to enable the best possible quality of life from the perspective of the affected person and their life partner.

Underpinning Theories and Theoretical Approach

The theory of symbolic interactionism (SI) is based on the fundamental idea that actors influence each other within the framework of interaction processes and the resulting ongoing interpretations [20]. In relation to the object of the study, this means that 2 people enter a relationship with each other based on a "self" resulting from their history of interaction. The "self" is called into question by the sudden injury that leads to a long-term need for help, is no longer connectable in the strongly changed interaction, and needs a challenging adaptation.

Building on the understanding of SI, Leslie Baxter's Relational Dialectics Theory (RDT) focuses on forming a meaningful relationship between partners [21]. The relationship between the patient and the caregiver is established in dialogue and is subject to continuous change. Examples of dialectics within the dyadic relationship are integration-separation, stability-change, or expression-nonexpression. According to the RDT, these dialectics are natural and unavoidable in any relationship, and they play a crucial role in shaping how individuals communicate and interact [22]. This is particularly relevant to understand the changes within the couple relationship of patient and relative over time.

From a theoretical perspective, this study aims to increase the knowledge on the influence of changes in the couple's relationship on the rehabilitation process and vice versa, and consequently on the quality of life of patients and caregivers. Different types of patient-caregiver dyads can be identified and empirically validated based on theoretical approaches. This approach makes it possible to link empirically identified types back to the theory of SI [20], and the RDT [21], to support them empirically or to change, refute, or expand them. A major novelty of the study lies in the theoretical foundation of the

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reciprocal effects of relational changes in acquired central nervous damage in rehabilitative processes and interaction with health care professionals.

From a practical perspective, standardized types of dyads can be recognized, and various rehabilitative approaches can be postulated at the practice level on a sociopsychological basis. This enables the enhancement of individual care for affected individuals, with a focus on improving their quality of life.

Methods

The study follows the Standards for Reporting Qualitative Research [23].

Approach, Sampling, and Recruitment

Approach

We use a qualitative approach, exploring how individuals maintain and shape their relationships in response to changed life situations within a domestic environment.

Sampling

Our sample consists of people with similar neurological conditions. Within the scope of the study, we include adult couples in which one person is chronically affected by an acquired neurological injury. Within these cases, disturbances, social status, age, and duration of affliction should be heterogeneous to ensure a high degree of diversity.

The inclusion criteria are (1) people who had an acquired central nervous system injury at least 6 months before and their partners, (2) the partnership existed before the injury and still exists at the time of the survey, (3) partners live together in a household, (4) participants have the capacity to give consent, (5) participants exhibit sufficient visual and hearing ability in order to understand the questions during the interview, (6) residence in Germany, and (7) sufficient understanding of German language.

Recruitment and Field Access

We recruit participants by displaying notices and flyers in public areas, including doctor's waiting rooms and neurological rehabilitation centers. This approach promotes voluntary participation. The study aims to achieve theoretical saturation without relying on predetermined statistical methods. Participants and their partners may choose the location for the interviews, which can be either through video call or in a place of their preference. The decision regarding the interview setting (face-to-face or online) is made by the concerned family dyads to avoid complicating the caregiving situation. No payment or reimbursement of expenses is provided for participation.

Data Collection Instruments and Data Processing

Narrative episodic joint couple interviews were conducted as part of this study. A deliberate decision was made to engage in dialogue with the spouses collectively, as this approach reflects the shared reality and facilitates negotiation processes between the individuals. Our research will deliberately consider the role of power dynamics within the interview setting, with a particular focus on the use of interruptions, attributions, accusations, and consents in relation to the discussed issues. This will be done in order to explicate the power structures and roles within the relationship and to analyze them in the context of the rehabilitation process. The couple's interviews will be recorded using an audio recording device. To meet the criterion of intersubjective traceability, the researcher will meticulously maintain posttranscripts and research diaries, which will document not only the content of the interview but also the researcher's personal feelings and reflections after each interview. This process will include active reflection on the researcher's role in the field, ensuring a transparent examination of potential biases and interactions.

The project uses the transcription system "Talk in Qualitative Research" for data processing, which was developed within the framework of the documentary method [24,25].

Data Analysis

The analysis of the narrative couple interviews is carried out according to Bohnsack's documentary method (Figure 1) [24]. The main researcher will systematically engage with the material, using a step-by-step immersion process to gradually extract insights and develop comparative horizons through case comparisons. This approach will ensure a thorough exploration of each case before proceeding to the next. The material and interpretations will be discussed with the research team using a 4-eyes principle and in workshops to gain diverse perspectives, validate findings, and enhance analytical rigor.

Figure 1. Methodical approach according to the documentary method.

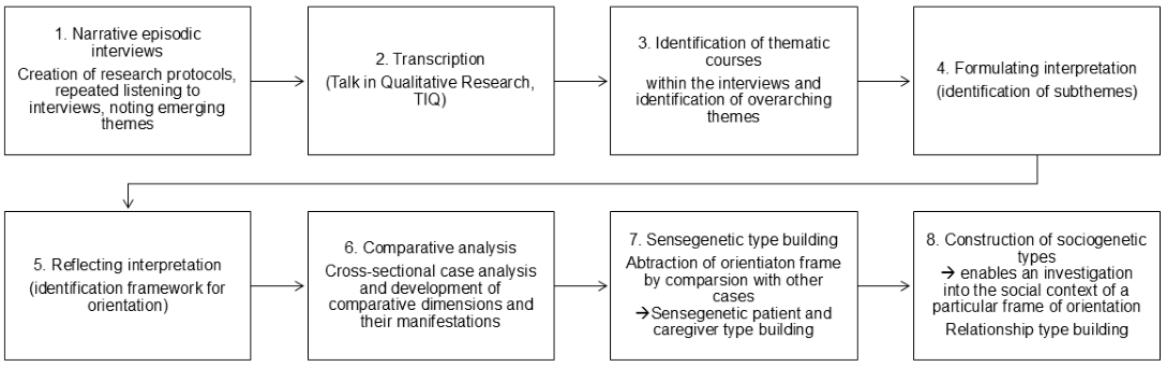

Accordingly, the documentary method does not only remain at the level of an actor's reflexive knowledge but also allows access to practice-relevant action. This is pertinent in relation to the attitudes and behavior of those affected and their

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caregiving relatives. By examining dyadic relationships retrospectively, the research seeks to understand how the meanings and dynamics within these relationships have developed and changed over time. The formulating textual interpretation summarizes what has already been interpreted by the actors in the research field. This forms the basis for the reflexive interpretation, which consists of a formal and a semantic interpretation.

Comparative Analysis and Type Formation

The reconstruction of the habitus based on biographical narratives is conducted with the objective of determining the extent to which the habitus interpretations developed from the initial sequence can be confirmed, differentiated, or expanded through the analysis of subsequent sequences of this case. This is achieved through a comparative contrast with thematically similar sequences from other cases [26]. In a comparative analysis, the horizons of the respective cases within this study (eg, attitudes of patients and caregiving relatives) are compared and related to each other [25]. In sense-genetic type formation, we work out different orientation frameworks for dealing with a problem, for example, coping strategies for illness, and typify them [26]. Building on this, sociogenetic typing includes social contexts within the partnership and the relationship with health care professionals (Figure 1 [24]).

A flowchart of the study procedure and work packages is provided in Figure 2.

Figure 2. Flowchart of study procedures and work packages, own illustration. WP: work packages.

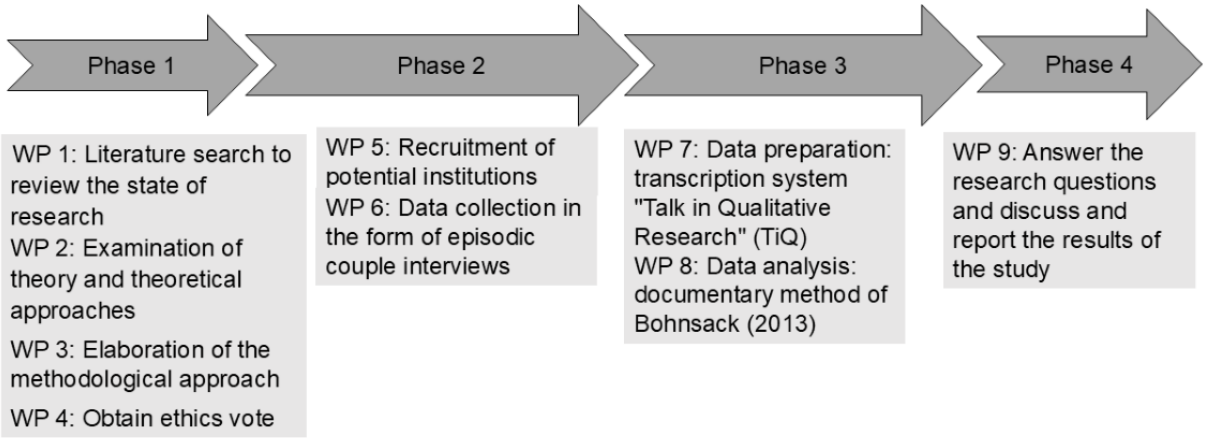

Ethical Considerations

The study was approved by the ethics committee of the German Society for Nursing Science (EK-23-018) and it complies with the Declaration of Helsinki. This study is not funded. Each participant provided both verbal and written informed consent to the first author before data collection commenced. During data collection, an initial review of the material is conducted to identify emerging themes within the interviews, enabling a deeper exploration of contrasts between them. Participants were advised that they could contact the interviewer at any time if they required further information or wished to reflect on the interview's impact. Due to the sensitive nature of discussing intimate relationship dynamics, particularly within the context of illness and rehabilitation, strict confidentiality must be upheld. Considering the emotional sensitivity of patients and their partners, the lead researcher undertook specialized training in sensitive interviewing techniques.

Anonymization and Data Security

We will anonymize all participant names, including their place of residence and treatment facility as well as names of workplaces and contact persons. We will manage and store the raw and analytical data (transcripts) and the code list in separate, password-protected data repositories. The data will be stored for 10 years in accordance with the data protection ordinance. No payment or reimbursement of expenses is provided for participation.

Results

The research question has been little explored and, in accordance with qualitative research principles, remains open to new and unexpected findings. The data collection started in June 2024 based on narrative interviews and is actually running. Currently, 15 dyads have been recruited and 7 have been interviewed. The current stage of the project is in work packages 6 and 7 (Figure 2). Due to the extensive procedures involved and the depth of reconstruction anticipated, we expect a sample size of up to 20 dyads. We anticipate that the study will be completed by June 2025, with data analysis concluding in the first quarter of 2025 and publication expected in the third quarter. We assume that patients and their relatives will demonstrate heterogeneity as individuals, as well as in their interactions within the dyad, regarding certain orientations such as coping with illness, motivation for therapy, and coping strategies. Furthermore, we expect that these orientations will manifest dynamically throughout the rehabilitation process and may therefore change over time.

Discussion

Overview

This study aims to enhance our understanding of how the relationships of affected couples evolve over the long term and how these changes impact the rehabilitation process. We propose that the nature of the relationship dynamics between patients and their partners varies based on the individual characteristics

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of both the patient and the partner, significantly influencing the rehabilitation experience. These dynamics may affect how patients and their partners interact and adapt to the challenges of rehabilitation. Therefore, it is essential that intervention strategies are customized to the specific types of relationships in order to provide effective therapy.

From a biopsychosocial perspective, it is crucial to involve not only the affected persons themselves but also their social environment in therapy and rehabilitation [27]. The impact of a neurological impairment extends far beyond the individual and touches on the family members and friends. Incorporating health care professionals into the everyday lives of individuals with long-term illnesses signifies a significant shift for both the patients and their partners. Frequent interactions with health care providers, whether through medical appointments or therapies, have a direct effect on patients' health, their level of independence, and the dynamics of their shared lives.

A systematic review conducted by Weitkamp et al [28] suggests that couples dealing with chronic illness benefit from effective stress communication, supportive dyadic coping, and shared appraisals of their situation. We hypothesize that similar strategies will be identified in our study, as couples may use comparable communication techniques to manage stress and enhance mutual support. Furthermore, we expect to gain additional insights into coping strategies, including various communication patterns, and how these influence both the couple's relationship and the rehabilitation process. This variability in coping strategies underscores the intricate ways in which couples adapt to chronic illness. We anticipate that these findings will have implications for therapeutic approaches, emphasizing the importance of recognizing and supporting diverse communication styles and options for action.

Strengths and Limitations

The reconstruction method used in this study promises a significant gain in understanding through an in-depth analysis of the unique life worlds of the dyads. This approach aligns with Flick's [29] advocacy for narrative and reconstructive methods, which are instrumental in revealing deeper insights within qualitative data.

Through nationwide recruitment, we aim to minimize one-sided outcomes and regional disparities in care, thereby enhancing the representativeness of our findings. The study's methodological strengths, bolstered by the application of the documentary method, provide a solid framework for analysis. However, we acknowledge certain limitations, such as the challenges in recruiting same-sex couples and the difficulty in reaching individuals from lower socioeconomic backgrounds. Despite these challenges, we will strive to assemble a heterogeneous sample to increase the study's validity and ensure representation across various societal strata.

Theoretical and Practical Implications

The findings of our study are expected to contribute to the theoretical understanding of couple dynamics in the context of chronic illness and rehabilitation. We hypothesize that the variations in coping strategies will not only reflect different communication patterns but will also emerge from the specific characteristics of patients, their relatives, and the types of relationships involved. This differentiation will enhance our understanding of how various relational dynamics influence the rehabilitation process, thereby supporting existing theories while potentially introducing new dimensions to the discussion. By identifying these nuances, we aim to provide a more comprehensive framework for future research and interventions in this field. We assume that our study will support the principles of RDT by indicating that couples oscillate between change and stability, engaging in a dynamic negotiation process as they adapt to evolving relational and emotional landscapes. The theoretical grounding provided by our engagement with these theories (SI and RDT) offers a robust foundation, allowing for connections to be made with established assumptions in the field.

Enabling a deeper understanding of the interactions between professionals, patients, and their family caregivers could ultimately contribute to an increase in the quality of life of patients and their caregivers. This holistic approach has the potential to increase the effectiveness of rehabilitation by making therapy patient- and family-centered. This could create a more positive outcome in life for all those who are involved. Costs for the health care system could be reduced through effective therapy that also takes into account the mental health of relatives. Furthermore, our results could make it easier for health care professionals to provide care and could be used to support the interaction depending on the patient and the relative type as well as the relationship type.

The results will be published in both a scientific journal and a practice-oriented publication in neurological long-term rehabilitation, reaching a broad readership within the health care sector. This includes health care professionals who support affected individuals and their relatives during various phases of rehabilitation, such as doctors, nurses, physiotherapists, occupational therapists, and speech therapists. A brief summary of the results will also be prepared in patient-friendly language, similar to a patient guideline, and sent to participants upon request.

Due to a further increase in chronic diseases in the coming decades, for example, as a result of environmental, climate, and demographic changes, it is necessary to develop interventions on a physical, psychological, and social level to reduce the burden of chronic diseases [30].

Conclusion

The successful completion of the study will provide recommendations for action for practitioners, and, if possible, will facilitate the development of a treatment concept to improve the care of people with neurological disorders and their caring relatives. A deeper understanding of psychosocial processes in connection with chronic illnesses is of great importance for the development of comprehensive, personalized care strategies.

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Data Availability

The datasets generated during this study are not publicly available due to confidentiality and ethical considerations but are available from the corresponding author on reasonable request.

Authors' Contributions

AvB was responsible for the conceptualization and research questions, study design, visualization, and writing of the original draft as well as the ethical approval, and is responsible for the analysis of the data material. EJ supported the selection of the study design (methodology), supervised the research work and the preparation of the ethical approval, and will support the analysis. PK supported the conceptualization of the study design against the background of his nursing science perspective and will support the analysis of data.

Conflicts of Interest

None declared.

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Abbreviations

RDT: Relational Dialectics Theory
SI: symbolic interactionism

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Protocol

Technology-Enabled Workplace Learning Through Rethinking Electronic Health Records to Support Performance Feedback: Protocol for a Mixed Methods Study

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Abstract

Background: The health sector collects a plethora of electronic health data via digital technologies, such as electronic health records (EHRs) and electronic medical records (EMRs). The primary use of EHRs includes supporting service delivery, providing data on patient information, and health care operations. Secondary uses of these systems can include quality improvement activities and research, and possibly inform policy. One underexplored secondary use of data from these systems is to enable health care professionals to understand their performance, reflect on their practice, and potentially support enhanced professional and workplace learning. There is growing interest and an increase in policies to focus on motivating the use of this type of data as part of mandatory Continuing Professional Development. Despite this, the design of EHRs is not conducive to the use of these systems for reflective practice, and there are few best practice guides for how to scaffold the use of these data for secondary use.

Objective: The aim of this project is to determine how EHRs and EMRs can be leveraged to enable formative performance feedback for health care professionals. The primary objective is to explore the use of these systems by health care professionals to further understand the current and possible future use of these records for reflective practice, performance feedback, and workplace learning.

Methods: The project will use a mixed methods design to enable a holistic picture of participant behaviors. Study data are being collected over 3 phases. Phase 1 consists of interviewing health care professionals and clinicians about their experiences with EHRs and EMRs. Phase 2 will involve surveying health care professionals about specific EHR features, and phase 3 will encompass workshopping discussions around EMR functionality and design with key informants. Participants for phases 1 and 2 will be a convenience sample of health care professionals who self-select and volunteer to participate in the study. Participants for phase 3 will consist of policy makers, representatives from peak bodies, technology vendors, health care professionals, and others. Data from phase 1 will be thematically analyzed to identify key features of EMR and EHR design for prioritization in phase 2. Phase 2 survey responses will be descriptively analyzed to understand the most important features in record design to support reflective practice. Phase 3 workshop data will be thematically analyzed to identify design insights for EHRs and EMRs that support professional learning.

Results: The project is currently in its interview phase and is expected to publish results in mid-2025.

Conclusions: The project will generate new knowledge on the extent to which data collected by workplace technologies provide health care professionals with formative performance feedback. It will also develop a conceptual design for EHRs that supports health care professional learning, which could be leveraged by developers of these technologies in future implementations.

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KEYWORDS

digital health; electronic health records; reflective practice; professional learning; technology; digital technology; EHR; mixed methods

Introduction

Background

The modern health sector is highly digitized [1]. As a result, health care professionals, consumers, and other stakeholders interact with a plethora of commonly used digital health technologies [2-4]. One widely used technology in the health sector is electronic health records (EHRs) and electronic medical records (EMRs), which are types of clinical information systems that serve as sources of patient health information. They are designed for use by health care professionals to capture data reflecting specific clinical experiences [5]. The data that clinical information systems including EHRs and EMRs collect have great potential for a range of secondary applications, including research, informing policy, and quality improvement [6,7]. However, these systems are currently underused for secondary applications such as Continuing Professional Development (CPD), practice reflection, personalized workplace learning, and insights about their performance [8,9].

CPD, reflective practice, and lifelong learning are essential activities for health care professionals to stay up to date on the latest evidence and maintain their registration to practice [1]. Health care professionals engage in a variety of learning activities, including attending local or international conferences, participating in mentorship and peer review, joining seminars, journal clubs, and other activities [10]. A large portion of these activities also takes the form of workplace learning [11]. The workplace provides a unique environment and a unique instructional context that is often focused on informal and experiential learning [12] to help overcome workplace problems or improve performance [12]. It can also offer a range of formal and informal pathways for receiving performance feedback. Although much of the learning that health care professionals engage in takes place in the workplace, there is a dearth of research on how to align learning activities with the clinical environment and on the pedagogical value of doing so. One mechanism to support data-driven professional development and enable better-aligned workplace learning is the utilization of data from EHRs and EMRs for the personalization of digital workplace education, data-driven CPD, or supporting reflective practice [8].

EHRs are sources of electronic health data that are increasingly being implemented in health care [13]. Existing enterprise-level systems focus on the use of their data for immediate patient care and billing, with a particular focus on recording patient information, including patient demographics, progress notes, medication, and laboratory results, which is generated by one or more encounters in any health care delivery setting [5]. The primary intent of EHRs is to provide data on patient care and health care operations; however, there is an increasing desire to explore the secondary use of data from clinical information systems in nondirect care operations, such as research, analytics, and measurements of quality and safety. In this context, they have been used for projects, such as research using population-wide data on cancer patient experiences and therapy outcomes [6], and quality improvement activities, such as toxicity monitoring and symptom management of chemotherapy treatments [7].

One underexplored secondary use of EHRs and EMRs is to support health care professional learning, performance review, and reflective practice. Reflective practice is the process by which professionals review and reflect on past experiences to gain understanding and identify opportunities for potential improvement [14]. While modern EHRs increasingly incorporate feedback through clinical decision support systems and dashboards, less work has focused on how EHRs can more effectively use onboard data to support reflective practice and health care professional learning. However, interest in better using clinical information systems is increasing, with a small but growing body of research in an area termed “Practice Analytics” [15-17]. Practice analytics seeks to equip health care professionals, their workplaces, and their associated peak bodies with the data and tools needed to review their own clinical practice [16]. Literature related to the use of electronic health data to date indicates that, when used correctly, it can help health care professionals understand their performance [7]. Further, it indicates that health care professionals themselves would like to access these data for learning purposes [9]. However, it has also been noted that health care professionals currently have varied access to these data for understanding their performance, and there is considerable variation in the ways it is visualized and shared with them [18].

Study Objective

The aim of this project is to determine how EHRs and EMRs can be leveraged to enable formative performance feedback for health care professionals. Over the course of the project, the researchers aim to understand how health care professionals are currently using EMRs and EHRs to support their practice, what the role of these technologies is in performance feedback and reflective practice of medical practitioners, and how the design of these technologies can be rethought to support a “next-generation” EHR that could support reflective practice. This project has been designed to build upon existing literature in the field of practice analytics and beyond, indicating that clinical information systems could better facilitate health care professional learning [19]; however, current solutions are not well-designed to do so [20]. This work is particularly timely, as global work is being undertaken to develop next-generation EHRs and EMRs [21]. This provides a unique opportunity to design new systems that incorporate interface design and scaffolds, ensuring that EHRs not only use data for direct patient care but also provide data back to health care professionals and teams for performance review and to support evidence-based practice. There is not only technological innovation driving change in this space but also an evolution of the policy landscape regarding how health care professionals engage in learning activities. Policies are increasingly encouraging health care

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professionals to better use electronic data collected from repositories, such as EHRs, as a component of mandated CPD and for revalidation [22].

Methods

Study Design

A mixed methodology is being used to undertake the project, as this methodology is the most appropriate for answering the individual aims of the study. Mixed methodologies are particularly beneficial for balancing out the limitations of qualitative and quantitative methodologies and are particularly important for getting a holistic picture of participant behaviors [23]. The methodology is particularly aligned with the project described in this proposal, as it will not only enable the collection of data on what people do but also provide a rich understanding of why these behaviors occur [23].

The project will be undertaken in 3 phases: needs finding (phase 1), prioritization (phase 2), and key informant consultation (phase 3). For an overview of the research flow, refer to Figure 1. The protocol follows recommendations listed in the TIDieR (Template for Intervention Description and Replication) checklist [24] (Multimedia Appendix 1).

Figure 1. Study design. EHR: electronic health record.

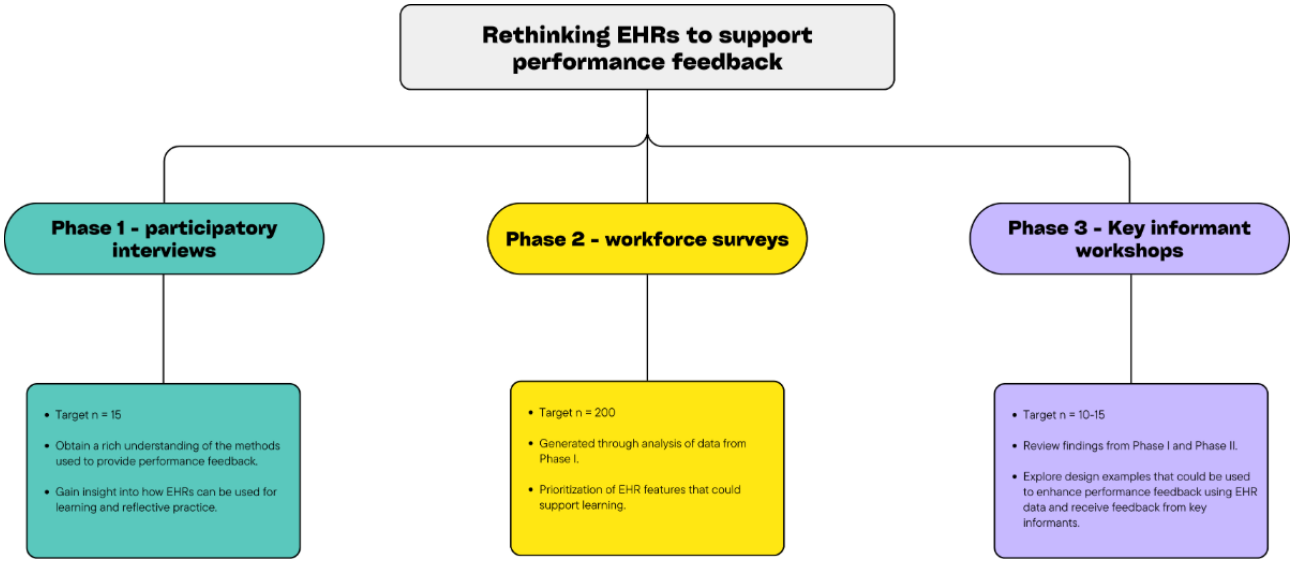

Participant Recruitment and Sample Size

Phases 1 and 2

Potential participants for phases 1 and 2 will be a convenience sample consisting primarily of health care professionals from Australia who self-select and volunteer to participate in the study. Although, health care professionals from other countries who use EMRs and speak English are also eligible to be interviewed. All professions listed as eligible are accredited by the Australian Health Practitioner Regulation Agency [25] and are eligible to participate in interviews. To be eligible to participate in the study, health care professionals do not need to use a specific EMR. However, it is anticipated that many will use Oracle [26] or Epic Systems [27], as these are widely used enterprise solutions. For phase 3, potential participants will consist of a purposeful sample of key informants from Australia who volunteer to participate in workshops discussing EMR functionality and design. Key informants will include policy makers, representatives from peak bodies, technology vendors, health care professionals, and others.

A convenience sample method will be used to recruit participants for phases 1 and 2 of the research. Potential participants will be primarily recruited via email notices sharing information about the study and a link to the digital participant information and consent form, circulated by organizations with links to health care professionals.

The researchers will also distribute a link to the survey through their professional social media profiles (examples include Twitter [subsequently rebranded X] and LinkedIn) and professional networks, which include contacts at numerous health care organizations, and ask them if they can share the link with individuals they may know. Participants who consent to participate in phase 1 will have the option to indicate if they wish to be recruited for subsequent phases of the project. All phase 1 participants will be invited to complete the phase 2 survey if they indicate they are happy to be contacted for this purpose; however, it is anticipated that most survey respondents will be a new cohort of health care professionals.

In addition to the methods listed above, snowballing will be used to recruit potential participants for this study. Interviewees who consent to participate in the study will be asked whether they have any suggestions for other individuals we could speak to about the project. Passive snowballing will be used, where interviewees who suggest others for the interview will be asked to forward information about the study to the relevant person, including instructions on how interested individuals can reach out to the research team to participate.

The sample size for phase 1 will be determined by the point at which saturation is reached during the interviews—that is, when no new insights are emerging from interviews. The size at which saturation occurs in qualitative research is debated [28]; however, in this study, we anticipate that 15 participants will

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be required to achieve saturation of themes for phase 1. At the conclusion of this phase, the researchers aim to have developed a thorough understanding of the methods used to provide performance feedback and to have gained insights into how EHRs can support these approaches.

The target sample size for the survey is 200 complete responses. This sample size has been chosen as it is feasible for recruitment and sufficient to provide enough data for descriptive statistical analysis to identify key insights related to the research questions. At the conclusion of this phase, the researchers aim to have a prioritized list of suggested changes that could be implemented in EHRs to enhance their design to support performance feedback and reflective practice.

Phase 3

A purposeful sample will be used to recruit participants for the final phase of the research. Potential participants will be identified through publicly available sources such as organizational websites, as well as through the researcher's professional networks of individuals who have relevant expertise to participate in the workshops. The names and contact information (email addresses) of key informants who are eligible to participate in the study will be aggregated into an email distribution list.

An initial contact will be made with potential participants on this list by a member of the research team via an email introducing the project and providing information about the co-design workshops. The email will also provide information clarifying how the participants' email contact information was obtained. Potential participants will be given a detailed participant information sheet to provide them with information about the study and will be given time to consider whether they wish to participate before they opt to complete the internet-based consent form. When completing the internet-based consent form, participants will be given the option to find out more about the study from a member of the research team prior to consenting.

The sample size for phase 3 will be determined by the point at which saturation is reached during the interviews, that is, when no new insights are emerging from the interviews. We anticipate that around 10 participants will be required to achieve saturation for phase 3. At the conclusion of this phase, the researchers aim to have worked examples of how EHRs' design could be modified or extended to incorporate the features prioritized in the phase 2 survey.

Data Collection and Procedures

Phase 1

In this initial phase of the project, data are being collected via semistructured interviews. Health care professionals who use EMRs as part of their jobs will be recruited via the methods described in the previous section. Each interview is anticipated to take a maximum of 45 minutes. As part of this process, potential participants will be made aware that their involvement in the study is voluntary. The initial email provides potential participants with a link to a digital participant information statement and consent form. The consent form must be signed prior to participation in the study. Consent will be reconfirmed at the beginning of the interview or technology observation session. Participants will have the option to stop the interview at any time and request to withdraw from the study.

Each semistructured interview will be undertaken by a researcher experienced in qualitative methods and informed by an interview guide to ensure consistency of data collection. For the semistructured interview guide, refer to Multimedia Appendix 2. Interviews will be conducted using an online videoconferencing tool. The interviews will be audio and video recorded. Audio recordings from the interviews will be transcribed and deidentified by a member of the research team prior to analysis. Each participant will be allocated a code that will be used to deidentify their interview transcript.

Phase 2

In the second phase of the project, data will be collected via a secure internet-based survey platform. Health care professionals who use EMRs as part of their jobs will be recruited via the methods described in phase 1. Participants will be provided with a link to access the survey. All responses collected through the survey will be anonymous. It is anticipated that the survey will take approximately 15 minutes to complete. For the prioritization schema that will be used in the survey, refer to Multimedia Appendix 3.

Phase 3

In the final phase of the project, data are being collected via online and face-to-face workshops. Key informants including health care professionals, technologists, and regulators will be recruited to participate in the workshops using the methods described in the phase 2 workshops are expected to take approximately 60 minutes. For the workshop guide, refer to Multimedia Appendix 4.

Each workshop will be undertaken by researchers experienced in qualitative methods and guided by a consistent workshop outline. The workshops will be audio-recorded. Audio recordings from the workshops will be transcribed and deidentified by a member of the research team prior to analysis. A second researcher will also be present to take detailed field notes of key points of discussion during the workshops.

Data Analysis

Phase 1

Semistructured interviews (phase 1) will be transcribed and deidentified. Braun and Clarke's [29] thematic analysis techniques will be broadly applied to inform the coding process. Transcripts will be read by the researchers prior to coding to gain a clear understanding of the material. Line-by-line coding of the transcripts will be conducted by each researcher independently and then discussed and reflected on to identify common points and understand subjective variations. Codes will then be grouped by related themes and subthemes with the end goal of creating a summary list of topics that describe key features of EMR and EHR design that support the reflective practice of health care professionals. Iterative discussion between researchers will be used to establish consensus on

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agreed themes and subthemes and to inform the final list of topics that will be incorporated in the phase 2 survey.

Phase 2

Survey responses will be extracted from the internet-based platform, cleaned to remove incomplete responses, and then analyzed in aggregate form. Descriptive analyses will be used to identify key insights related to the research questions from the survey data. This analysis will include identifying which features of EHR and EMR design health care professionals most highly prioritize for integration into a redesigned feature, as well as a potential description of features in current systems that are prohibitive to reflective practice.

As this is a mixed-methods study, integrative analysis of the survey and interview data will also be undertaken to understand key insights from the results [30]. Data from different sources will be triangulated to build a complete picture of how health care professionals use EHRs and EMRs to engage in reflective practice and identify opportunities to enhance the design of these systems to support learning and reflective practice more effectively.

Phase 3

Workshop recordings will be transcribed and deidentified. Analysis will be undertaken using methods described for phase 1. Transcripts will be read by the researchers prior to coding to get a good overall sense of the material. Line-by-line coding of the transcripts will be conducted until saturation has been reached. Codes will then be grouped by related themes and subthemes. Iterative discussion between researchers will be used to establish consensus on agreed themes and subthemes.

Ethical Considerations

The study received ethics approval from the University of Sydney Human Research Ethics Committee (protocol number 2024/HE000253). All participants will provide written informed consent before participating in the study. All data will be deidentified prior to analysis. Participants do not receive compensation for participation in the study.

Results

As of January 2025, we have interviewed 6 participants. We expect to write up the results by late 2025.

Discussion

Expected Findings

This protocol describes a methodology for undertaking a mixed methods study designed to generate insights on how next-generation EMRs and EHRs could better support health care professional learning. The study is undertaking a triphasic approach consisting of phase 1 (needs finding), phase 2 (prioritization), and phase 3 (key informant consultation). This approach is being used to obtain a rich understanding of the complex challenges of designing clinical information systems that support reflective practice, understanding of health care professional performance, and workplace learning. It has been recognized that there is a notable knowledge gap on the secondary use of clinical information systems like EMRs and EHRs for enabling health care professionals to gain insights into their performance [9,20]. Furthermore, policy changes are increasingly encouraging health care professionals to use data from these types of systems to chart data and set goals; however, there are few evidence-based methods for providing feedback to support professional learning and reflective practice [17].

The findings from this study will expand the understanding of the methodologies that can be used effectively in the relatively new field of practice analytics. There is currently only one protocol published presenting a practice analytics methodology [15], which emphasizes the need to use multidisciplinary approaches for delivery on a large-scale program. The study described in this protocol builds on the existing methodological approaches used in practice analytics, incorporating multidisciplinary methods, such as needs finding interviews and key informant workshops, to gain a deeper understanding of how technology design and human interaction with it could be used to enable workplace-based learning in the area of practice analytics. A triphasic approach is being used to identify health care professionals' needs for EHRs that enable reflective practice and workplace learning, prioritize features that are most conducive to this process, and then aggregate key stakeholder perspectives on how these priorities could be harnessed in a next-generation EHR or EMR design.

Finally, this study aims to generate new insights on how next-generation EHRs and EMRs could be designed to better support performance feedback, workplace learning, and data-driven CPD. The literature to date has identified that health care professionals have an interest in accessing more data about their practice from clinical information systems [9], and there is advocacy for enhancing existing clinical information systems to better facilitate health care professional learning [19]. Despite this interest, there is notable variation in current approaches for visualizing and sharing these data with health care professionals [8], and there are few examples of best-practice approaches for designing clinical information systems that support reflective practice [20]. The study described in this protocol aims to address this gap by generating new knowledge on how one type of clinical information system, EHRs and EMRs, could be better used to support workplace learning, reflective practice, and performance feedback.

Limitations

A limitation of this study is that we are using a convenience sample, largely recruited from Australia, for the first 2 phases of the study, which may limit the generalizability of our findings across health professions and geographic regions. This limitation is being mitigated by undertaking extensive recruitment via a breadth of channels in an attempt to reach participants with a breadth of insights. An additional potential limitation is not focusing on a single EMR or EHR as part of recruitment for this study, as this may also influence the generalizability of findings. The researchers decided not to take this approach because these records have limited use in supporting reflective practice. We aimed to obtain a broad range of insights into how health care professionals are using these systems, and focusing on only the most commonly used enterprise solutions could

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exclude valuable insights from bespoke EMRs, EHRs, or smaller systems. Future researchers should consider undertaking a study looking specifically at larger enterprise systems for supporting reflective practice.

Conclusions

EHRs are increasingly prevalent in the health sector, and their implementation and ongoing support often represent a significant financial investment. They are a unique repository of electronic health data that has a plethora of potential uses in health professions. One underexplored use of EHRs and the data they collect is to enable health care professionals to understand their performance and engage in data-driven learning activities. Increased understanding of the extent to which these workplace technologies provide health care professionals formative performance feedback is important in order to understand opportunities to design and use these technologies more effectively to support reflective practice in the future.

Acknowledgments

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Data Availability

The datasets used or analyzed during the study can be made available from the corresponding author upon reasonable request.

Authors' Contributions

AJ developed the initial methodology and wrote the first draft for publication. MN reviewed drafts, undertook literature reviews to contribute further, and managed submission.

Conflicts of Interest

None declared.

Multimedia Appendix 1
TIDieR (Template for Intervention Description and Replication) checklist.
[PDF File (Adobe PDF File), 232 KB - resprot_v14i1e66824_app1.pdf]

Multimedia Appendix 2
Interview guide.
[PDF File (Adobe PDF File), 123 KB - resprot_v14i1e66824_app2.pdf]

Multimedia Appendix 3
Prioritization schema.
[PDF File (Adobe PDF File), 94 KB - resprot_v14i1e66824_app3.pdf]

Multimedia Appendix 4
Workshop guide.
[PDF File (Adobe PDF File), 85 KB - resprot_v14i1e66824_app4.pdf]

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Abbreviations

CPD: Continuing Professional Development
EHR: electronic health record
EMR: electronic medical record
TIDieR: Template for Intervention Description and Replication

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Protocol

Barriers and Facilitators to HIV and Viral Hepatitis Testing in Primary Health Care Settings in the Kyrgyz Republic (BarTest): Protocol for a Mixed Methods Study

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Abstract

Background: In the Kyrgyz Republic, it is estimated that 18% of people living with HIV are undiagnosed and more than half are diagnosed late (CD4 lymphocyte count of <350 cells/µL). For viral hepatitis, before 2023, free testing was only available to people living with HIV, which led to a low testing uptake. A new national program on the elimination of HIV and viral hepatitis infection for the years 2023-2027 recognizes the need to scale up testing to reduce the gap in undiagnosed people in the country.

Objective: This study aimed to identify and describe the most important barriers and facilitators to HIV and viral hepatitis B, C, and D testing from the perspective of health care workers working in primary health care settings in the Kyrgyz Republic.

Methods: A cross-sectional, mixed methods study was conducted in 2 phases. A purposive sampling approach was applied to recruit health care workers in primary health care settings. In phase I, in-depth, semistructured interviews were conducted with 22 participants to gather detailed information about the key barriers and facilitators for testing. We applied a thematic approach for qualitative analysis. The themes identified informed the development of a questionnaire with the main barriers and facilitators for phase II. The questionnaire was distributed electronically, and the target sample size was 400 participants. We performed descriptive analyses of the questionnaire data, reporting the most frequently mentioned barriers and facilitators for HIV and viral hepatitis testing.

Results: The study received financial support in the framework of the Global Health Protection Programme by the Federal Government of Germany. Data collection took place in June 2024 for phase I and in November 2024 for phase II. Data analyses and writing up of results will be done in early 2025 and results are expected to be published in spring 2025.

Conclusions: The results of the study will improve the understanding of existing barriers and facilitators to HIV and viral hepatitis testing in order to increase testing offers and uptake in primary health care settings in the Kyrgyz Republic. Importantly, the findings will inform steps to improve the implementation of the new testing strategy and, ultimately, increase the number of people diagnosed and treated in the Kyrgyz Republic.

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KEYWORDS

HIV; viral hepatitis; testing; barriers; health care workers; Kyrgyz Republic; primary health care

Introduction

HIV and viral hepatitis remain large public health challenges in the World Health Organization (WHO) European region. An estimated 3 million people are living with HIV, 10.6 million with hepatitis B, and 8.6 million people with hepatitis C [1-3]. In the European region, the public health burden of HIV and hepatitis B and C is particularly high in the Eastern European and Central Asian countries [4].

HIV and viral hepatitis share similar modes of transmission and coinfections are common [5]. For both diseases, a large proportion of those living with the diseases remain undiagnosed due to the often asymptomatic nature of the infections [5,6]. For HIV, around 77% are aware of their HIV status in the WHO European region [7]. For viral hepatitis, an estimated 16% and 29% were diagnosed with hepatitis B and hepatitis C by the end of 2022, respectively [3,5]. There is a large need to scale up testing offers and uptake to reduce the number of people who are undiagnosed and people who are diagnosed late (CD4 lymphocyte count <350 cells/µL), which accounts for 50% in the WHO European Region [8]). This is important not only to facilitate linkage to care and improve individual health but also public health by reducing onward transmission.

WHO has published regional action plans for ending AIDS, viral hepatitis, and sexually transmitted infections for the period 2022-2030 [9] to reach elimination goals by 2030. While some progress has been made, challenges and gaps in reaching elimination remain. One strategic direction in the WHO strategy emphasizes a people-centered approach, and importantly integration and decentralization of services for HIV and viral hepatitis (and other sexually transmitted diseases) in primary health care (PHC) settings where appropriate. A people-centered approach and offering testing for more than one disease has the potential to increase testing uptake, for example, by implementing rapid point-of-care multiplex tests for HIV and viral hepatitis. The strategy also defines testing targets needed to reach elimination by 2030. For HIV, 95% of those living with HIV should know their status and 90% of those living with hepatitis B or hepatitis C should be diagnosed [9].

In the Kyrgyz Republic, it is estimated that 18% of people living with HIV are undiagnosed [10] and more than half are diagnosed late. For viral hepatitis, before 2023, free testing was only available to people living with HIV, which has led to a low testing uptake, further worsened during the COVID-19 pandemic [10]. During a WHO HIV and viral hepatitis program review in the Kyrgyz Republic in April 2022 [10], one priority recommendation was to make use of the experience and structure of the HIV program to optimize synergies, human resources, and the infrastructure for both HIV and viral hepatitis and move away from vertical program structures. It was also recommended to scale up screening for HIV in health care settings by testing patients presenting with conditions that are either AIDS-defining or associated with an undiagnosed HIV prevalence of >0.1% (HIV indicator conditions) [10-12]. HIV and viral hepatitis are political priorities in the Kyrgyz Republic, and a program of the Cabinet of Ministers on the elimination of HIV and viral hepatitis infection for the years 2023-2027 has been adopted [10]. The program recognizes the need to scale up testing and that stigma and discrimination are large barriers, in particular for key populations, for coming forward for testing. The program outlines several steps to improve testing uptake in the Kyrgyz Republic. For HIV, the testing algorithm and clinical treatment guidelines have been revised to be in accordance with WHO guidelines and services have been brought closer to the population in PHC facilities. Moreover, rapid tests have been implemented in hospitals. For viral hepatitis B and C, testing is implemented in hospitals for health care workers (HCWs), pregnant women, patients (before surgery), and people living with HIV whereas testing services were paid out of pocket until 2023. Although rapid testing for viral hepatitis has been partially implemented, available evidence on coverage and uptake is scarce. As part of the national program implementation, awareness-raising of the importance of testing for the general population and key populations is planned, as well as an assessment of current practices. The political commitment is there along with the newly signed-off strategy with targets for improving testing. However, although a strategy and guidelines exist, the offer and uptake of HIV and viral hepatitis testing remain insufficient to reach the elimination targets and reduce the burden of disease in the country. While the opportunities are there, also for integrated HIV and viral hepatitis testing [13], more knowledge and data on barriers and facilitators are needed to foster and improve the implementation of testing.

Barriers are often described on 3 levels; system level, provider level, and patient level [14-16], but can also be analyzed using various frameworks, including the Capability, Opportunity, and Motivation model [17,18]. Our study will focus on the barriers and facilitators perceived by HCWs (provider level) to offer HIV and viral hepatitis testing in health care settings. This will be the first systematically collected overview and analysis of the most important barriers and facilitators to testing from the perspective of primary HCWs in the Kyrgyz Republic.

The overall aim of the study was to identify and describe the most important barriers and facilitators to HIV and viral hepatitis B, C, and D testing in primary health care settings in the Kyrgyz Republic.

This study aimed to answer the following research question following: What are the main barriers and facilitators for HIV and viral hepatitis testing in primary health care settings from the perspective of HCWs in the Kyrgyz Republic?

Methods

Study Team and Cooperation

The study was developed and carried out in collaboration with national public health authorities including the National Institute of Public Health of the Ministry of Health (MoH), the Republican Center for Viral Hepatitis, and HIV or AIDS Control

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at the MoH of the Kyrgyz Republic and professional networks of national study coordinators.

The local study partners were involved in the initial discussions and provided input to the protocol, study documents, and data collection tools. The local partners played a key role in study site selection. Local contextual knowledge and experience were crucial in this important first step of the study.

Study Population

The target study population consisted of a broad range of HCWs including, but not limited to, physicians, nurses, and allied HCWs involved in the provision of HIV and viral hepatitis testing in primary health care settings.

Study Design

A cross-sectional, mixed methods study was conducted to explore the views of HCWs working in primary health care settings in the Kyrgyz Republic on barriers and facilitators to HIV and viral hepatitis testing. We used multiple data collection methods and triangulation which included an overview of the current testing landscape, data collected through in-depth interviews with HCWs, and survey data collected through a questionnaire distributed among HCWs. The study was divided into 2 main phases (Figure 1).

Figure 1. The 2 data collection phases of the study. HCW: health care worker.

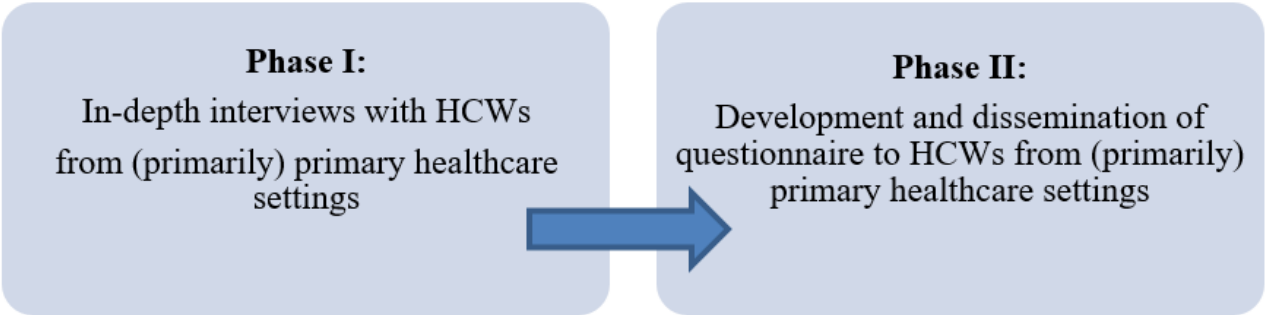

Phase I included qualitative data collection and analysis by exploring the main barriers and facilitators perceived by HCWs in their testing roles. By conducting in-depth, semistructured interviews with a selected group of HCWs, we aimed to gather detailed information and their perspectives on the key barriers and facilitators to HIV and viral hepatitis testing in PHC settings. The method was chosen because it is particularly effective in exploring possibly sensitive topics such as HIV and viral hepatitis infection and service delivery practices, where personal experiences, attitudes, knowledge, and social contexts are crucial. The details obtained can provide insights into personal opinions, attitudes, behaviors, and motivations, information that is often not accessible through quantitative methods. In addition, in-depth interviews allowed us to maintain a degree of flexibility while probing more deeply into important areas that emerge during the interview [19-21]. The strength of phase I lies in its ability to uncover deeper, potentially overlooked insights by engaging directly with HCWs. This enabled a more detailed understanding of the complex dynamics of factors that influence testing practices [19-21].

Following phase I, the study moved to phase II, where a questionnaire was developed and distributed among HCWs in PHC settings. This questionnaire was designed based on the data from phase I and thereby collected more information from a wider range of HCWs. In addition to expanding the geographic coverage, it enabled an increase in the multitude and diversity of perspectives collected. The goal of this phase was to supplement and quantify the findings from phase I and to improve our understanding of the facilitators and barriers to testing among a broader group of HCWs.

Study Sites

The study sites from which HCWs were recruited included PHC and a few large specialized medical centers across the Kyrgyz Republic. There are in total 9 administrative regions (7 oblasts [Batken, Chui, Issyk-Kul, Jalal-Abad, Naryn, Osh oblast, and Talas] and 2 independent cities [Bishkek City and Osh City]) in the Kyrgyz Republic, with 44 districts (Figure 2).

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Figure 2. Overview of the 7 oblasts in the Kyrgyz Republic for data collection (phase 1 marked with blue).

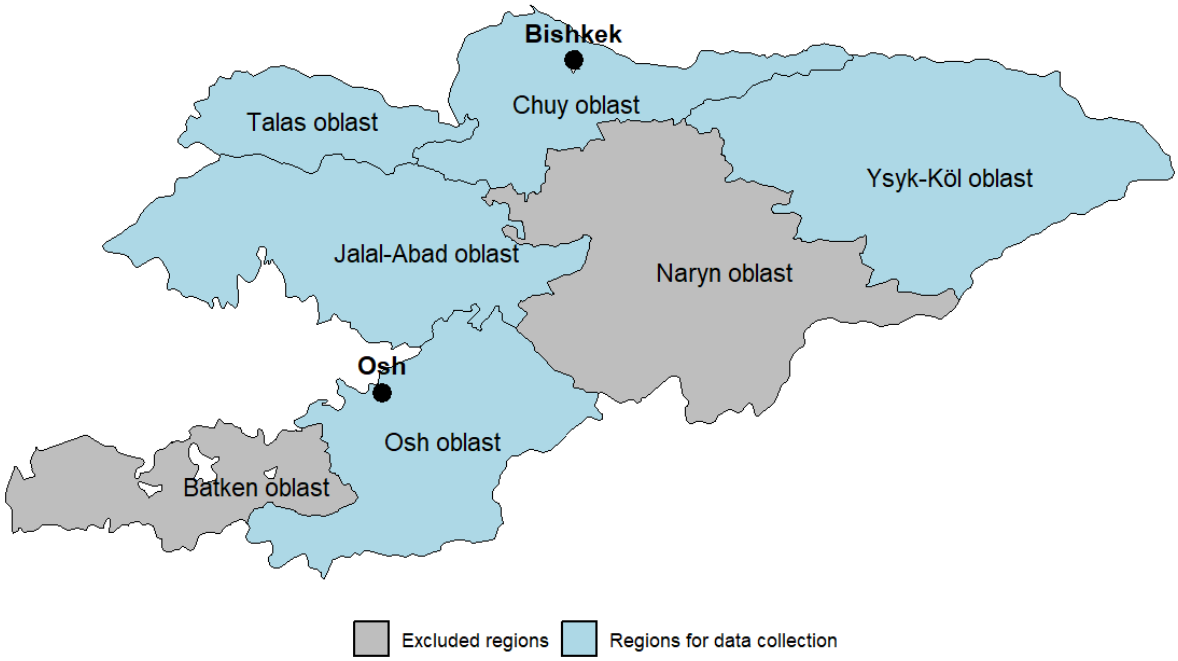

For phase I, up to 15 sites were contacted that are located in different geographic areas, as well as sites located in both urban and rural settings from these 7 regions: Bishkek City, Chui, Issyk-Kul, Jalal-Abad, Osh City, Osh oblast, and Talas. The selection of the 7 regions is described in detail under the Sampling and Recruitment section.

For phase II, HCWs from all primary health care services in all of the 7 oblasts (Figure 2) were invited to take part in the survey. The selection of participants is explained in detail in the *Sampling and Recruitment* section.

Sample Size

Phase I: In-Depth Interviews

The target sample size in phase I was up to 20 respondents. This size was considered a standard sample for qualitative studies of a medium size [19,22]. However, the final number of participants in this study was defined by the data saturation moment, which is the point where no new relevant insights on the research topic are received from our participants [19,22,23]. Data saturation was determined during the team meetings of the research group and data collectors. This approach ensured that the research process remained both efficient and focused by adjusting the scope of the study to match the quality of information collected, up to the point where further interviews would not add to the understanding of the research question [19,23].

Phase II: Questionnaire

By using a 95% confidence level and a 5% margin error, the sample should have been 385. Accounting for potential nonresponse, our target sample size in phase II was 400 participants.

Sampling and Recruitment

Phase I: In-Depth Interviews

We recruited participants through the local study partners (see the *Study Team and Cooperation* section).

We used a multistage approach to select primary health care facilities in the country. Together with the National Institute of Public Health of the MoH, we went through their data including a complete list of primary health care facilities and their HIV and viral hepatitis testing volumes for 2023. This allowed us to conduct a geographical assessment using 3 key parameters: facility location, annual testing volume, and local population density. In order to identify facilities with the greatest need for assessment, we established a testing ratio by comparing each facility's annual number of tests to the population density of its catchment area.

To supplement our facility selection process, we conducted confidential consultations with local civil society organizations that work closely with key populations affected by HIV and viral hepatitis. This allowed us to get information on reported experiences of stigma and discrimination in specific health facilities, which helped to contextualize potential barriers to testing services. Due to the sensitive sociopolitical environment and evolving regulatory framework affecting civil society organizations in the Kyrgyz Republic, we do not report identifying details about these consulting organizations to protect their operational security [24].

We sent the proposed list of facilities to the MoH for review and coordination. The national coordinators communicated with the MoH and selected facilities and provided them with detailed information about the study including contact information for the primary investigators, and confirming their capacity to participate within the proposed time frame. If a facility was unable to take part as a study site, another eligible facility from the same region was selected to ensure that all target regions

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were represented. This iterative selection process continued until we achieved our desired coverage of sites in the regions.

Phase II: Questionnaire

For the questionnaire, all health care services from the list of medical facilities provided by the partners in the Kyrgyz Republic were invited to take part in the internet-based survey and were asked to distribute the link to their HCWs. Probability-based sampling was not possible, as the exact number of HCWs in the different regions was unknown. However, due to the exhaustive content in the list of preselected health care services (N=77) covering all geographic areas, it was anticipated that the included study population would to a large extent be representative of HCWs in primary health care services in the regions. The electronic questionnaire was available through a link and was distributed via email and other preferred social and internet-based communication channels among the target population.

Data Collection

Data collection consisted of a qualitative (phase I) and a quantitative (phase II) part, which is described in more detail below. Before the development of the semistructured interview guide and the following questionnaire, an overview of the testing landscape in the Kyrgyz Republic (in the form of a desk review) was conducted to understand by whom and where testing takes place. Questions and areas to which information was needed were developed by the Robert Koch Institute (RKI) study team and sent to the local partners to be completed. Answers and the final overview were provided and developed by local country partners to illustrate who should be tested according to national guidelines, which tests were available, as well as the current testing uptake and prevalence in the country (Multimedia Appendix 1). This context helped to inform the development of the interview guide and questionnaire.

Phase I: In-Depth Interviews

Data collection for phase I took place in June 2024. The semistructured interviews were conducted in both Russian and Kyrgyz depending on the preference of the participant (Multimedia Appendix 2). A total of 3 interviewers in total were involved in the data collection phase, but only 1 interviewer was present at each interview. The interviews lasted approximately 1 hour, face-to-face at a location chosen by the participant for their convenience and privacy. The interviews were audio recorded if permitted by the participants. A professional transcription service was contracted before data collection and transcribed the recordings using specialized software. To protect the anonymity of the participants, pseudonyms chosen by the participants were used in the transcripts. Finally, a certified translator translated the transcripts from Russian and Kyrgyz into English to ensure that high-quality data were accessible for analysis and reporting. The transcripts and their translation were proofread by the interviewer for data validation and verification.

Phase II: Questionnaire

The questionnaire was developed on the basis of the material and insights collected in phase I. A Likert scale (strongly agree, agree, disagree, and strongly disagree) was produced for the most frequently reported barriers and facilitators asking to what extent these were experienced by HCWs surveyed in phase II (Multimedia Appendix 3). The questionnaire also included a question on hepatitis B vaccination among HCWs (ever vaccinated, when and if partly or fully vaccinated). The questionnaire was available through the internet-based platform Voxco and accessible through a link and answers were saved directly through the survey-server Voxco.

Analyses

Qualitative Analysis

Throughout the qualitative part, we followed the Consolidated Criteria for Reporting Qualitative Research [25]. The analysis of the collected data was conducted in English, taking advantage of the flexibility that problem-centered interviews offer, especially when exploring people's experiences [19]. Given the focus of the study on individual experiences, multiple methods of analysis were considered. Our intention was not to generalize findings, but to look for patterns while remaining open to exploring the nuances, discrepancies, and potential conflicts inherent in the data [19].

Given our interest in identifying patterns of meaning in the data regarding barriers and facilitators to HIV and viral testing services, we used an inductive approach to reflexive thematic analysis [21,23]. This method is characterized by its adaptability and effectiveness in addressing different research questions and analyzing various types of data [21,23]. The inductive approach was chosen because it allowed us to develop codes and themes under the influence of the data, rather than being constrained by a predefined theoretical framework. In doing so, we ensured that all data collected, regardless of their initial perceived value, were included in the final analysis, providing a comprehensive understanding of the topic and allowing us to develop themes that the researchers were not aware of before embarking on data collection.

The data were analyzed using NVivo 14 software (released in 2023). A total of 2 researchers (IS and NL) conducted the analysis following Braun and Clarke's [26] 6-step process for thematic analysis. In the first familiarization step, both researchers independently engaged in multiple readings of the interview transcripts to develop an understanding of the content and prepare the ground for analysis. Following familiarization, IS and NL proceeded with preliminary coding using the first 3 interview transcripts. To ensure analytical rigor, these transcripts were double-coded by both researchers. The coding process adopted an inductive approach. During this phase, both IS and NL identified and labeled segments of text relevant to understanding barriers and facilitators to HIV and viral hepatitis testing. The initial coding was done independently to ensure that both researchers identified a wide range of codes. Once the initial coding was completed, the 2 researchers discussed and refined the initial codes and merged overlapping concepts to develop a consolidated coding framework which was applied to the remaining transcripts, moving from an inductive to a more structured deductive approach. In the third step, the codes were organized into potential themes that involved grouping related codes to form overarching themes that capture the essence of the data. After identifying potential themes, in step 4 IS and NL

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shared evolving codes and themes with the core research team for discussion and refinement to ensure the reliability and validity of the analysis.

Once the final themes were defined, the 2 researchers defined and named subthemes to capture specific nuances of each theme, and then completed the final analytical step involving synthesizing the themes into a narrative story [27] which addressed the research question.

The background and previous experience of the researchers influenced the study from the development of ideas and data collection tools, to the analysis of data. Personal reflexivity shaped the analytical steps and is important to reflect on [27]. The first and second authors who carried out the 6 steps of the thematic analysis have different professional backgrounds and views and thereby a natural step of the analysis process was to use reflexive practices to align and discuss decisions during both developmental and analytical steps of the research.

The first author (IS) has a public health background specializing in infectious disease epidemiology and has experience with viral hepatitis and HIV. Her previous experience mainly with key populations might have influenced a particular focus on and interest for these groups, however knowing that the experience primarily comes from a European context.

The second author (NL) brings a dual perspective to this research as both a medical professional and a community member, with clinical experience in HIV medicine and a background in global health research with active use of the qualitative methodology. As a gay man from Eastern Europe with cultural ties to Central Asia, he has insider knowledge of the needs of Gay, bisexual, and other men who have sex with men communities in the region. This dual role as both health care provider and service user strengthened data collection and analysis.

To achieve trustworthiness in qualitative research, it is important to reflect on credibility which we in this study tried to achieve by extended involvement and discussion within the larger research team as well as triangulation with observations during the interviews. To achieve transferability, the methods will be meticulously described and explained for readers to be able to follow all steps. Dependability and confirmability will be ensured by thorough documentation of steps and through notes and confirmability through discussion with both project partners in the Kyrgyz Republic, but also with the wider project team.

Quantitative Analysis

The analyses from the questionnaire will be conducted in R 4.2.2 (with the packages “dplyr” and “epitools”). The analyses will be descriptive. We will derive frequencies for categorical variables, including the most frequently reported barriers and facilitators for HIV and viral hepatitis testing.

If the number of respondents and available data are sufficient to ensure statistical validity, stratified analyses will be conducted to explore differences in barriers and facilitators across subgroups using chi-square tests. As a start, the data will be stratified according to the following:

1. Geography: urban and rural region
2. Type of HCW: specialty and background
3. Age of participants
4. Sex: male and female

Other variables that may also be of interest include knowledge and training, experience with key populations, and availability of free tests as well as awareness of current testing guidelines.

Quality Assurance

The protocol was reviewed by the entire project team including the project partners in the Kyrgyz Republic. The semistructured interview guide developed for the interviews was checked and evaluated by the project team members and piloted with one HCW from the Kyrgyz Republic in order to also control for a possible translation bias. The interview guide was revised based on the feedback provided.

Ethical Considerations

Ethics approval was obtained from the institutional review board of Scientific and Practical Health Care in Kyrgyzstan in Bishkek, Kyrgyz Republic (01-3/15; May 23, 2024). A study information sheet was provided to potential participants (in phases I and II) and written informed consent was collected before participation. Participants in phase I were also asked to consent to be quoted in publications and had the option to only consent to participation (and no quotes in publications). The informed consent form included information about study objectives, and data protection (procedure and rights), including how long and where data will be stored and who has access. The form also included information on the person responsible for the study and the person responsible for data protection. The participant was informed of their rights to withdraw participation at any time without negative consequences. All participants had to be older than 18 years of age. Privacy and confidentiality were ensured by a review of the acquisition and processing procedures provided by the RKI data protection officer. The in-depth interviews were recorded and transcripts were produced in the Kyrgyz Republic. Only anonymized written text was shared with RKI through the secure server Cryptshare. After the transfer of the interviews to a secure server, they were deleted from the recording devices. All personal data will be deleted after the end of the study.

The informed consent forms will be kept at RKI until the end of the study and it will not be possible to link the data to the personal information (ie, names of participants). All personal data will be deleted after the end of the study.

A list of participants in phase I was needed for the purpose of providing incentives for participation. This list will be deleted 6 years after the end of the study.

Participants in the in-depth interviews were reimbursed with a financial incentive for their time, transport, and participation of 2000 Soms (equivalent to around €22 [US $24.58]).

Results

Data collection took place in June 2024 for phase I and in November 2024 for phase II. Data analyses and writing up of results will be done in early 2025 and results are expected to be published in spring 2025.

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Discussion

The new national program on the elimination of HIV and viral hepatitis (2023-2027) in the Kyrgyz Republic demonstrates a political will to improve the response to these 2 diseases. Important content of the program addresses improving testing and decentralizing care, moving testing from specialist to primary HCWs. While this task shift makes sense in theory, there may be various reasons why the implementation is challenging. It is anticipated there will be more barriers to HIV testing, in particular among key populations, due to lack of experience and training, but also stigma and discrimination against certain population groups. Moreover, this is expected to be more prevalent in rural areas. Viral hepatitis is expected to be less stigmatized as it is more common among the general population and barriers here might be more related to lack of time or competing priorities.

An important strength of this study is that the protocol and data collection instruments were reviewed by a larger study team as well as local partners with contextual knowledge. The involvement of already trusted local partners was important in order to ensure successful implementation and distribution, and approval from partners ensured support from the MoH, and also primary health care settings who took part. The testing landscape was a good foundation for all further methodological steps of the study. Moreover, the triangulation of contextual background information in the form of a testing landscape, as well as our mixed methods approach was valuable in creating both a deep, but also nuanced understanding of testing activities and important barriers and facilitators in the country.

Despite important strengths, our study will also be subject to challenges and limitations. There is a risk of selection bias in case some participants did not have the capacity or time to participate. It may also be that the HCWs will appreciate the opportunity to express their concerns or ideas on the topic. Careful instructions at the beginning of the interviews, securing anonymity and patience throughout the interview hopefully provided a safe space to express their views on barriers and facilitators.

For the questionnaire, a nonrandomized sampling of HCWs might have created bias as some groups may be underrepresented providing a skewed picture of barriers and facilitators for testing. Involving the MoH in recruitment might have ensured a large number of participants, but may also have affected the information provided by the participants, despite anonymity, and they may have been prone to report what they think they are expected to report. The involvement of local partners was a strength, but may also be a weakness as it can influence who takes part and what they report, as the study team at RKI is not independent of local constructs in the country. A lot of testing in the country takes place in specialized settings, such as hospitals, clinics for sexually transmitted infections, and blood centers. Moreover, community testing as well as self-testing has been rolled out in the country. However, due to time, budget, and staff limitations it was necessary to narrow down the scope of the study.

With this study, we will be able to report on important barriers and facilitators, both detailed and in-depth through interviews, but also from a large study population (HCWs) through the questionnaire. The study will hopefully highlight reasons for gaps in testing and be able to provide recommendations for how to improve testing offered in primary health care in the Kyrgyz Republic.

Acknowledgments

The authors acknowledge team members from the National Public Health Institute in Kyrgyz Republic for their help with the study coordination. Further acknowledgments go to colleagues from the WHO (World Health Organization) Regional Office for Europe and the WHO country office in the Kyrgyz Republic for their input and logistical support. This study received financial support in the framework of the Global Health Protection Programme by the Federal Government of Germany.

Data Availability

The datasets generated during and/or analyzed during this study are not publicly available due to data protection, particularly for the qualitative data (phase I), but are available from the corresponding author upon reasonable request.

Authors' Contributions

IS, NL, AS, MB, OK, VB, BG, and SD conceptualized the study. IS wrote the original draft of the overall study protocol and manuscript, and NL the part on qualitative methods. All authors critically reviewed and edited the manuscript, and approved the final version. NL and AS were involved in data curation for the qualitative part as interviewers.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Testing landscape.
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Multimedia Appendix 2
Semistructured interview guide.
[DOCX File , 18 KB - resprot_v14i1e62929_app2.docx]

Multimedia Appendix 3
Online questionnaire.
[DOCX File , 22 KB - resprot_v14i1e62929_app3.docx]

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Abbreviations

HCW: health care worker
MoH: Ministry of Health
PHC: primary health care
RKI: Robert Koch Institute
WHO: World Health Organization

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Protocol

Participatory Strategies to Enhance Resilience and Job Satisfaction and Reduce Stress to Mitigate Early Retirement Intentions Among Nurses: Protocol for a Qualitative Study

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Abstract

Background: As Canada's population ages, so does its workforce. Early retirement among nurses is on the rise and has become the norm within this workforce. It represents a major concern for maintaining an adequate and qualified workforce. On the one hand, the decision to take early retirement can be influenced by various factors, including occupational stress. By contrast, low job satisfaction can exacerbate early retirement intentions, while resilience is positively associated with the intention to remain at work. Little is known about how to mobilize these factors to promote healthy job retention for nurses as they age.

Objective: This study aims to (1) explore the experiences of older nursing staff regarding their intention to take early retirement and the influence of occupational stress, resilience, and job satisfaction; (2) explore interventions used to optimize the influence of resilience and job satisfaction and minimize the influence of occupational stress on early retirement; and (3) generate and validate participatory strategies tailored to the context of older nursing staff to optimize the influence of resilience and job satisfaction and minimize the influence of occupational stress on early retirement.

Methods: A 3-phase qualitative research design will be used. In phase 1, we will use an interpretive descriptive design using semistructured interviews to explore the experience surrounding early retirement intentions and related factors among nurses. In phase 2, we will use a scoping review to explore interventions used to optimize the influence of resilience and job satisfaction and minimize the influence of occupational stress on early retirement. In phase 3, we will use the technique for research of information by animation of a group of experts method with a group of 8 participants. This method will allow us to generate and validate participatory strategies tailored to the context of older nurses.

Results: Initial results are expected in August 2025. The findings of this study will be shared through multiple platforms to maximize their reach and impact. This will include publishing scientific articles, completing a research dissertation, and presenting at conferences. A concise summary document highlighting key findings will be sent to study participants, who will also have the option to receive links to the online publications derived from the research.

Conclusions: This protocol presents detailed information about the entire structure of the 3-phase research project. Studying early retirement issues among older nurses is essential. It promotes their health, retention, and inclusion, and recognizes their contributions to the sector.

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KEYWORDS

occupational stress; resilience; job satisfaction; early retirement; nurses; qualitative research; protocol

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Introduction

Background

The aging of Canada's population has become a predominant demographic feature [1]. In Canada, between 1921 and 2018, the median age increased by approximately 16 years, from 23.9 to 40.8 years, and it will continue to increase steadily until 2034 [1]. By 2043, 24.3% of the Canadian population will be aged >65 years [1]. With the aging of the population comes the aging of its workforce [2]. An older worker is defined as a worker who is aged ≥55 years [3]. In 1996, there were 2.7 Canadian workers aged 25 to 34 years for every worker aged ≥55 years. By 2018, this ratio had decreased to 1 [1]. This ratio is insufficient to offset the declining number of younger workers [4], a situation that could be attributed to declining birth rates as well as the increasing number of young adults pursuing higher education [5,6].

In the same context, workers who provide care to an increasingly older population are aging themselves [2]. Among Canadian nurses, approximately 1 in 5 were aged ≥55 years in 2016, compared to <1 in 10 in 1996 [2]. As nurses age, they retire, and issues such as labor shortages and the loss of the most experienced care staff members arise [7]. Considering the difficult working conditions of nurses, such as long hours and staff shortages, this can increase the tendency to retire relatively early [8]. In 2001, the average retirement age of nurses in Canada was 56 years [9]. With the aging of this workforce, this average has slightly increased to 58.1 years in 2019 [10], but it remains relatively early compared to the average retirement age in the general population in Canada, which is 64.4 years [11]. In addition, the distinct challenges faced by this population may increase the risk of early retirement. Nurses are considered to be a susceptible population as it is composed mostly of older, female individuals from an immigrant background [12-14]. Advancing age is not without health risks, as older workers are more susceptible to both physical and psychosocial issues, which can lead to periods of disability, whether related to occupational injuries or personal health conditions such as chronic illness [15]. Some studies suggest that female nurses are more frequently exposed to verbal violence compared to their male counterparts [16], while others have reported that female health care providers face a higher prevalence of violence, particularly sexual violence [17,18]. Immigrant nurses face unique challenges that place them at a disadvantage in the workplace. Studies have shown that immigrants are more often exposed to social exclusion [19]. Particularly, immigrant nurses must navigate complex cultural and organizational adjustments, which can lead to higher levels of work-related stress and ultimately increase their likelihood of leaving the profession or retiring early [20]. Moreover, the discrimination and marginalization of internationally educated nurses in host countries are well documented, often exacerbated by communication barriers, which can further hinder their ability to thrive in the workplace [21].

Early retirement is usually defined according to age. In the province of Québec in Canada, workers in the public sector are eligible for early retirement when they are aged 55 years [22]. Early retirement is a major concern when it comes to maintaining a sufficient, qualified workforce [23]. According to the World Health Organization, the shortage of health care professionals reached 7.2 million worldwide in 2013 [24], and this number will reach 18 million by 2030 [25]. Nursing staff shortage leads to a low caregiver-to-patient ratio [26]. It is also associated with stress, burnout, and job dissatisfaction among nurses [26,27].

In this context, there are several factors influencing the decision of these nurses to take early retirement. We have grouped the influencing factors in terms of individual, family, and occupational factors [28]. Individual factors can include the health condition of workers and their economic status [29]. Family factors may include the marital status of older nurses, in which studies show that those with spouses retire early [13,30]. Occupational factors can refer to the work environment factors [31], such as occupational stress, workload, decision latitude, and satisfaction with the work environment [13,30,32-35].

In this regard, occupational stress among nurses increases the risk of early retirement [36]. Occupational stress is defined as the harmful physical and emotional responses that occur when work demands do not match the worker's abilities, resources, or needs [37]. Nurses are constantly exposed to occupational stress, which increased during the COVID-19 pandemic, becoming a real occupational hazard [38,39]. In addition, low job satisfaction would exacerbate intentions to take early retirement among older nursing staff [34]. Job satisfaction is defined as a general feeling about the job or a large set of related attitudes about various aspects or facets of the job [40]. Low job satisfaction is one of the most important factors in the increase in early retirement intentions [41,42]. It is influenced by several factors, such as heavy workloads and long working hours [43], and it further increases occupational stress in these workers [44], which further increases the risk of early retirement.

By contrast, there are factors that can decrease the intention of early retirement, namely resilience, which is linked to the intention to stay at work and is a protective factor for personal health [44]. Resilience is defined as the ability to recover from adversity, uncertainty, failure, or even positive changes that seem overwhelming, such as increased responsibility [45]. Resilience in older nursing staff can reduce occupational stress, increase job satisfaction [44], and negatively influence intentions to take early retirement [46].

In view of the increasing number of older nurses and the problem of early retirement and labor shortage among nurses, it is important to study the reality of older nurses and to find strategies in order to counter the problem of early retirement among this population.

Aim

The general aim of this study is to promote the health and job retention of older nurses through the creation of participatory strategies by examining the influence of resilience, job satisfaction, and occupational stress on early retirement.

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Methods

Overview

To reach our aim, a 3-phase qualitative study will be conducted. The first phase will explore the experiences of older nurses, their views on or intentions of retiring early, and the influence of occupational stress, resilience, and job satisfaction. The second phase will explore the interventions used to optimize the influence of resilience and job satisfaction and minimize the influence of occupational stress on early retirement. In the third phase, we will generate and validate participatory strategies tailored to the context of older nurses to optimize the influence of resilience and job satisfaction and minimize the influence of occupational stress on early retirement. Figure 1 shows our research approach.

Figure 1. Research approach. TRIAGE: technique for research of information by animation of a group of experts.

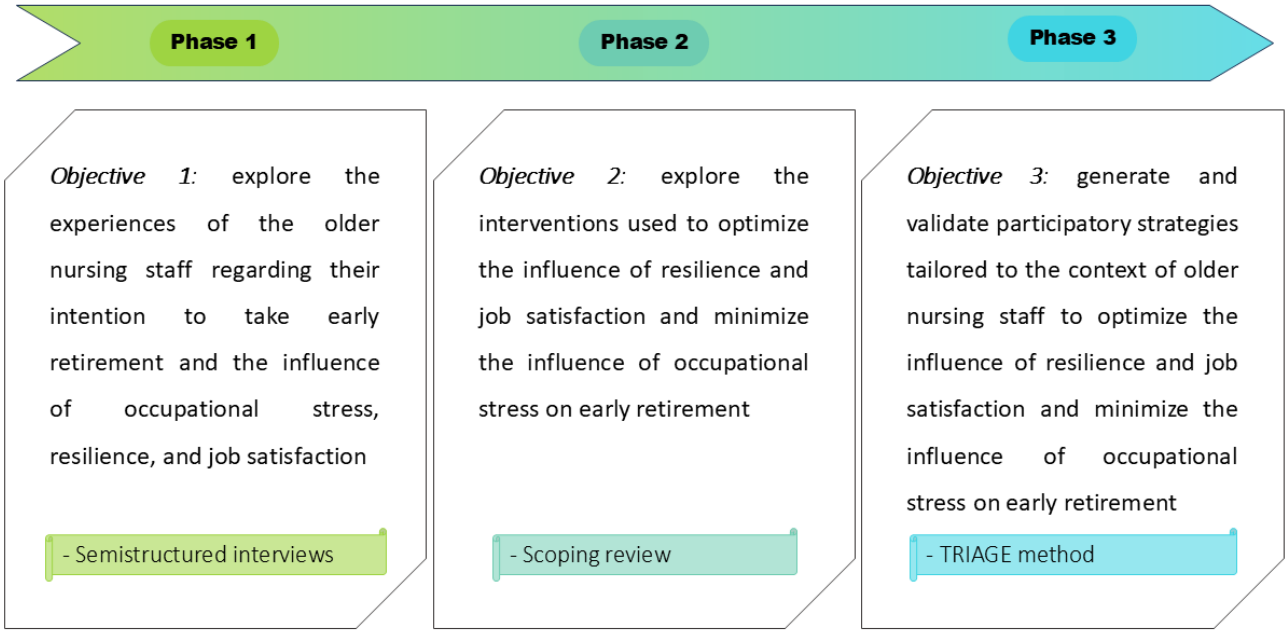

Phase 1

Design

To describe the experiences of older nurses and their intentions to retire early, a descriptive interpretative study will be conducted [47].

Population

This study will focus on nursing personnel working in the public sector (ie, registered nurses, nurse practitioners, clinicians, and licensed practical nurses). To be eligible for participation, individuals would have to be employed as a nurse in the public sector and possess ≥5 years of professional experience. The literature indicates that a minimum of 3 to 5 years of work experience is necessary to effectively examine workers' attitudes toward employment and career decisions [48,49]. Furthermore, participants must fall within the age range of 45 to 55 years. Our chosen age group is deliberate, as individuals in our target population become eligible for early retirement when they are aged 55 years. Consequently, we are focusing on a slightly younger demographic because this study will be centered on examining the intention to retire early. We will strive to target diversity among our participants in terms of gender, cultural and ethnic backgrounds, and practice settings (eg, general and specialist care, mental health, and perinatal care) to ensure our sample reflects various perspectives within the studied population. However, this diversity is framed within a homogeneous sample in terms of profession (nursing staff) and professional context (public sector), which will allow us to deeply explore the shared experiences and perceptions of this older population regarding early retirement.

Sampling and Recruitment

An initial number of 20 participants is estimated for this study. This number is based on findings from previous research [50,51]. For example, some authors report that when participants belong to a relatively homogeneous group, as is the case in our study, where all participants are nursing staff working in the public health care sector, data saturation can generally be achieved with ≤16 interviews [50]. Other authors suggest that 6 to 12 participants may be sufficient to reach saturation when the group shares a similar reality, such as working in the same field [52]. In contrast, samples with greater heterogeneity may require >20 participants to achieve saturation [50,51]. While our sample may present some diversity in terms of practice settings, it remains professionally and contextually homogeneous. Therefore, setting an initial target of 20 participants strikes a balance between ensuring diversity within a focused context and achieving thematic saturation. Saturation will be reached, and recruitment will stop when redundancy is observed in the ideas put forward by participants [52-54]. The final number will be adjusted during the course of the study based on the percentage of new information identified in each interview.

Using the saturation assessment method developed by Guest et al [55], we will agree on the final number of participants to

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recruit in order to achieve data saturation at a threshold of 95%. Thus, based on the initial sample size set at 20 and a new information threshold set at 5%, we will continue conducting interviews until they yield <5% new information. At that point, recruitment will end, as we will have reached 95% saturation.

Participant recruitment will be done using a nonprobabilistic convenience method on a voluntary basis [54,56]. We will use a recruitment poster to invite potential participants. A digital version of the poster will be published on the *Chaire de recherche UQTR (jr) sur la santé des travailleuses et travailleurs vieillissants* (Research Chair on the Health of Aging Workers) website and its LinkedIn page as well as shared via other social media platforms. Members of the research team will also disseminate the poster via their personal networks. In addition, the Université du Québec à Trois-Rivières (UQTR) Partnership Service will be requested to share the poster within its network of collaborators. To further enhance outreach, the poster will be sent to union organizations and nursing associations across the province. We will also contact the various nursing orders in Québec to request access to their email distribution lists. A formal procedure will be established, which includes completing a request form and submitting the information and consent forms to the relevant professional orders for nurses. We will also use snowball sampling by encouraging participants to share the study information with their colleagues who may be eligible and interested in participating.

Participation in this study is entirely voluntary. Participants are completely free to participate or to withdraw at any time without penalty and without having to provide any explanation. If a participant decides to withdraw from the study, all data provided will be deleted and will not be used as part of this research.

Data Collection

We will conduct semistructured interviews based on a guide developed from a comprehensive review of the literature on early retirement, occupational stress, job satisfaction, and resilience among nurses. The guide will then be pretested with 2 people having the same characteristics as our participants [57]. We will document various themes (eg, intention to retire early, influence of occupational stress, satisfaction, and resilience) by asking different questions (eg, “What are your current thoughts on early retirement?” “How has the stress you experience at work influenced your thoughts on early retirement?” “How has your job satisfaction evolved throughout your career?” and “Can you share any key experiences or moments?”) [54]. Interviews will be conducted either in person or online via Microsoft Teams, depending on the participant’s choice. If a participant opts for an in-person interview, it will take place in a familiar and comfortable location of their choice. In both cases, the interview will be audio recorded to allow for an in-depth qualitative analysis. Each interview is expected to last approximately 90 minutes to allow for an in-depth exploration of the research topics [58,59]. However, participants will be informed of the expected duration in advance and will be free to take comfort breaks at any time during the interview. They will also be reminded that they can stop the interview at any moment without providing any justification. The interview process will be flexible and respectful of each participant’s pace and comfort. Should any participant experience emotional distress during or after the interview, appropriate support resources will be made available. Participants will receive information on local social services and community organizations that offer emotional and psychological support. Public sector employees may also benefit from support and representation offered by local unions, such as the *Fédération de la Santé et des Services Sociaux* in cases of work-related concerns. Moreover, participants will have access to the *Employee Assistance Program*, a free and confidential professional support service provided to staff and managers to help address personal or professional challenges. Although these resources will be provided to participants, we cannot guarantee that all participants will be eligible for or able to access every service.

Data Analysis Plan

The first author will transcribe the interviews. When interview recordings have been fully transcribed verbatim, a qualitative data analysis will be conducted using a five-step thematic analysis strategy: (1) repeated reading of the data corpus to allow analysts to develop a sense of immersion, (2) initial coding of identified units of meaning, (3) assigning meaningful labels to the coded units of meaning, (4) synthesizing and assembling codes into a general structure with categories and themes, and (5) “moving back and forth” between the data corpus and the general structure to ensure the interpretation of selected units [60]. Two analysts will independently analyze each interview. Afterward, they will meet after each analysis to discuss, compare, and integrate their coding to generate a common version that ensures interjudge agreement [61,62]. Subsequently, a third person will review the coding of each interview to provide input on the coherence of ideas. We will adopt an inductive approach in this thematic analysis. This approach is well suited for descriptive interpretive research [47]. NVivo software (version 15; Lumivero) will be used to support the analysis.

Phase 2

Design

To explore the interventions used to optimize the influence of resilience and job satisfaction and minimize the influence of occupational stress on early retirement, we will opt for a scoping review design [63]. This choice is motivated by the need to comprehensively examine the amount, range, and nature of existing research related to a specific topic, namely the interventions designed to decrease early retirement intentions [63,64]. To uphold scientific rigor throughout our review process, we will adhere to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines [65]. These guidelines are specifically designed for scoping reviews and will serve as our framework for transparently reporting the insights derived from our scoping review [65].

Procedure and Analysis

The review followed the Joanna Briggs Institute (JBI) methodology for scoping reviews, with further refinements

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made in accordance with the guidelines outlined by Peters et al [66].

Step 1: Review Question

The research question should be broad and exploratory to include the most relevant manuscripts [64]. A clear scoping review question informs the inclusion criteria, supports protocol development, enhances the efficiency of the literature search, and provides a structured foundation for the review [66]. The main research question that will guide the scoping review is as follows: What interventions are used to optimize the influence of resilience and job satisfaction and minimize the influence of occupational stress on early retirement?

Step 2: Inclusion Criteria

Manuscripts will be selected based on the following inclusion criteria: (1) manuscripts addressing interventions regarding resilience, job satisfaction, occupational stress, or any combination of the 3 and (2) manuscripts addressing the context of work. All types of manuscripts are eligible, with the exception of literature review–type studies, which will be considered only to examine the studies they include, as this will avoid duplicate representation of studies and allow us to add any unretrieved articles meeting the selection criteria [67]. The inclusion of all types of manuscripts, with the exception of literature reviews, will allow capturing the full breadth of available evidence on interventions related to resilience, job satisfaction, and occupational stress. It will allow us to comprehensively examine the amount, range, and nature of existing research related to the interventions designed to decrease early retirement intentions, which aligns with best practices recommended for the conduct of scoping reviews [64,68]. While this approach may result in the inclusion of manuscripts that are less rigorous or interventions that are less relevant, selection steps (ie, step 4) will be strict and function as additional filters. The selection will be conducted based on the predefined inclusion and exclusion criteria as well as the relevance of each manuscript to the research objective, ensuring that only pertinent data are included in the study. The inclusion criteria will be tested on a sample of 5 selected manuscripts to ensure clarity, and adjustments will be made if necessary.

To provide a contemporary picture of the situation, only manuscripts published within the last 15 years will be selected. The decision to limit the search to studies published within the last 15 years is made in accordance with the JBI methodology, which emphasizes the importance of using date restrictions in an informed manner, as potentially relevant studies may be missed if the time set is too recent [69]. The JBI methodology also emphasizes that the search strategy for a scoping review should aim to be as comprehensive as possible within the constraints of time and resources [66]. In response to that and while the health care system has undergone changes over time [70], interventions developed in the past 15 years may remain relevant and continue to be used or adapted in present-day practice. For feasibility reasons, only manuscripts written in English and French will be included.

Step 3: Search Strategy

A subject specialist librarian will be consulted to generate the search strategy used for the scoping review [71]. Different combinations of keywords (eg, interventions AND resilience) will be generated. Because the subject covers several areas of interest (ie, health, gerontology, and management), we will conduct systematic searches on different databases selected based on their relevance to the main areas of interest (eg, APA PsycINFO [EBSCO], CINAHL [EBSCO], MEDLINE [EBSCO], AMED [EBSCO], Scopus, and ABI/INFORM Global).

To ensure the most comprehensive search for identifying manuscripts, we will adopt a strategy involving data retrieval from various sources. In doing so, we will also review the reference lists of selected manuscripts to identify other relevant manuscripts.

Furthermore, gray literature documents will be examined by manually searching on Google. Due to the large number of results generated by Google searches, it is important to rely on the relevancy ranking that brings the most relevant results to the first pages. Hence, the titles and short descriptions found in the first 10 pages will be screened [72]. Targeted searches on the websites of relevant health care organizations and public health databases will be conducted (eg, the *Institut de recherche Robert-Sauvé en santé et en sécurité du travail* and the *Institut national de santé publique du Québec*).

Step 4: Source of Evidence Selection

Following the search, all identified manuscripts will be uploaded to EndNote (Clarivate) software.

Then, selection will be performed by 2 reviewers, with a third reviewer intervening in case of disagreement on manuscript eligibility. A 2-step approach will be used for selection. First, reviewers will examine the title and abstract to determine eligible manuscripts. Second, the full texts of selected manuscripts will be examined by the 2 reviewers.

Step 5: Data Extraction

Data extraction will be carried out using an extraction grid based on the TIDieR (Template for Intervention Description and Replication) checklist, with several criteria to be followed (eg, intervention name, who provided the intervention, what materials and procedures were used in the intervention, where did the intervention occur, why is the intervention conducted, and how is the intervention delivered) [73], to ensure the comprehensiveness of information on interventions used to optimize the influence of resilience and job satisfaction and minimize the influence of occupational stress on early retirement. Such a grid has previously been found useful to describe interventions in the field of work [74]. The grid will first be tested by 2 reviewers by independently extracting data from 25% of the manuscripts. Following a meeting between the 2 reviewers, a final version of the grid will be presented and used for extraction without modification.

Step 6: Data Analysis and Presentation

This final step involves presenting the results by providing a general overview of the literature and identifying knowledge

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gaps [66]. This step will include a description of the selected manuscripts and a narrative summary of the results [66]. First, a descriptive analysis using statistics will be used to present a descriptive numerical summary of the extent, nature, and distribution of the studies, such as the distribution of studies geographically, and the range of interventions [66]. Next, a thematic analysis will be conducted to group the interventions extracted from the selected manuscripts into key themes, such as resilience-building strategies, improving job satisfaction, and occupational stress management [66]. The steps of thematic analysis will follow the same steps that will be used in phase 1.

Phase 3

Design

We will use the technique for research of information by animation of a group of experts (TRIAGE) [75] to generate and validate participatory strategies tailored to the context of older nurses. These strategies aim to optimize the influence of resilience and job satisfaction and minimize the influence of occupational stress on early retirement. This method aligns with the participatory approach adopted for phase 3 of this project, as it provides a user-friendly way to engage individuals affected by a common issue [76]. The TRIAGE method is chosen as it allows for consensus building on a specific topic through participant discussions while fostering the emergence of new ideas [77]. This process will help generate and achieve consensus on various participatory strategies adapted to the context of older nurses to optimize the influence of resilience and job satisfaction and minimize the influence of occupational stress on early retirement.

Population

According to Tétreault and Guillez [78], TRIAGE groups with 6 to 8 participants are often the most productive. Our TRIAGE group will consist of 8 participants, including nursing staff. The inclusion criteria are the same as those of phase 1. The recruitment methods for this phase will mirror those used in phase 1, namely a nonprobabilistic convenience sampling approach based on voluntary participation, supplemented by snowball sampling. In addition, participants from phase 1 will be contacted to assess their interest in taking part in this subsequent phase.

Data Collection

Overview

The TRIAGE method will involve four systematic steps: (1) preparation, (2) individual production, (3) compilation, and (4) interactive production. Figure 2 illustrates the steps of the TRIAGE method.

Figure 2. The technique for research of information by animation of a group of experts (TRIAGE) method.

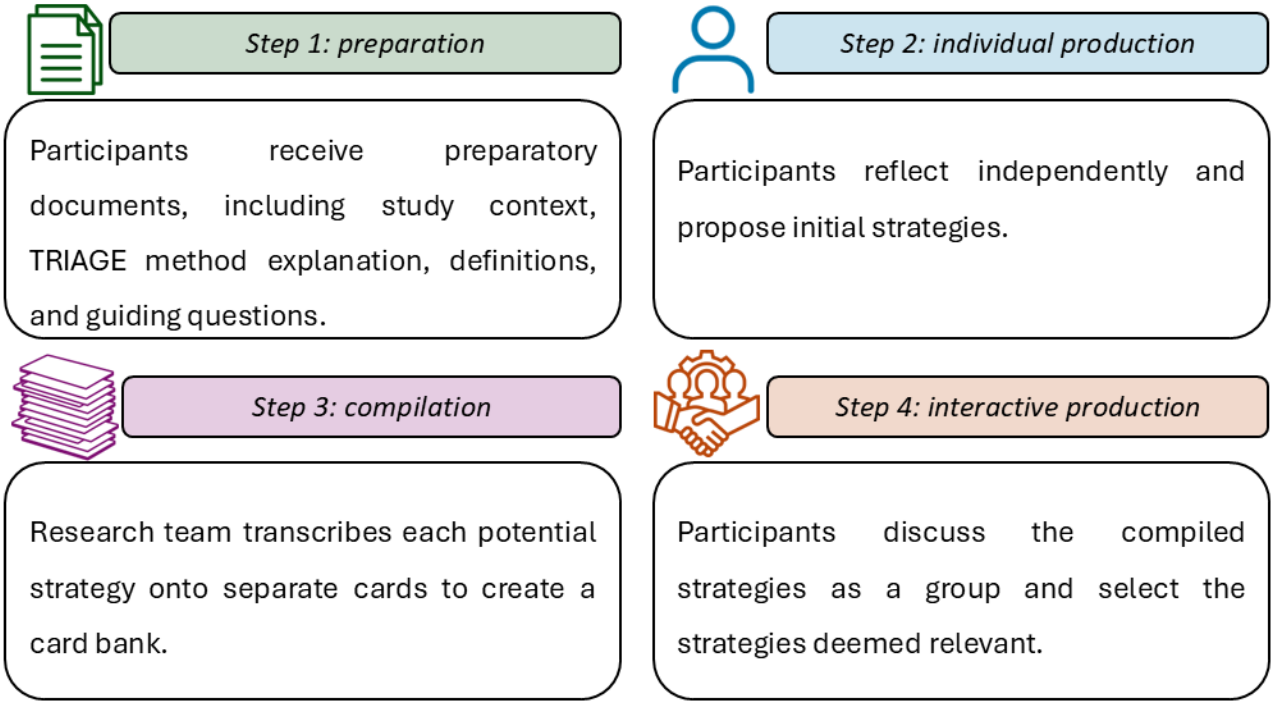

Step 1: Preparation

Before the individual production, we will provide participants with preparatory documents containing information about the study's context and the TRIAGE method. The preparatory documents will be prepared by the research team. This includes the study's objectives, key concept definitions, a brief description of the TRIAGE method, and a summary of the results from phases 1 and 2 [77]. In addition, we will develop questions to guide participants' strategy proposals (eg, How to create a less stressful work environment to encourage older nurses to stay at work?). Questions will concern early retirement and our 3 factors of interest (ie, occupational stress, job satisfaction, and resilience). These documents will be sent electronically and pretested with 2 individuals matching the participants' characteristics to ensure content relevance and clarity [75].

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Step 2: Individual Production

During this individual step, participants (ie, older nurses) will generate participatory strategies tailored to the context of older nurses. To do so, they will be asked to answer the questions developed during step 1 independently and remotely, in a setting of their choice, by suggesting potential strategies [75,76]. This step will start once participants receive the preparatory documents and the questions electronically. Participants will be given 2 weeks to respond to the questions and return them to the research team.

Step 3: Compilation

This step will be conducted by the research team. It will involve transcribing each potential strategy generated in step 2 onto separate cards without modification or analysis [75]. This will create a card bank containing potential strategies for each question (ie, for each of our 3 factors of interest regarding early retirement). Each card bank will be processed separately during the interactive production step [77].

Step 4: Interactive Production

This step will be characterized by the animation of a sorting process with visual support, illustrating six sections: (1) dynamic memory, (2) grouping, (3) selection, (4) garbage bin, (5) refrigerator, and (6) veto [75,76]. This step will be conducted through an online group meeting via Microsoft Teams involving the first author and the participants.

First, all potential strategies will be displayed in the *dynamic memory* section. Once participants understand all the potential strategies, they will transfer the potential strategies they deem relevant to the *grouping* section and those they deem irrelevant to the *garbage bin* section [75]. The latter will be permanently discarded [77]. Next, the potential strategies transferred to the *grouping* section will be discussed. Those with similar meanings will be merged and given more precise titles. Potential strategies containing more than one idea may be split into distinct parts, each with new titles [77]. Discussion in this section may also lead to the emergence of new potential strategies [75].

In case of uncertainty among participants, a potential strategy will be temporarily placed in the *refrigerator* section for later reconsideration to avoid prolonging momentarily unproductive discussions [77]. This will allow the sorting process to continue and promote group harmony [77]. Ideally, if there is still disagreement, a possible strategy will be placed in the *veto* section to be submitted to other experts at a later date [77]. Finally, the potential strategies definitively placed in the *selection* section will constitute the participatory strategies retained in this study [77].

This step will last a maximum of 3 hours to ensure data quality. This time frame will enable the participants to offer pertinent information, while extending beyond this time frame will risk compromising results due to increased participant and animator fatigue [77].

Data Analysis Plan

The participatory strategies collected using the TRIAGE method will be immediately validated through group interactions, eliminating the need for verbatim transcription and content analysis [75]. In other words, rapid data analysis will help validate participatory strategies tailored to the context of older nurses, optimizing the influence of resilience and job satisfaction and minimizing the influence of occupational stress on early retirement.

Ethical Considerations

An information and consent form detailing the objectives of the study, the modalities of participation, the duration of the participation, and the process of the individual interviews will be sent to the participant by email before the interview date in phase 1 and before step 1 (preparation) in phase 3. The participant will have the opportunity to read the form carefully and will provide written consent. Financial compensation will be provided to each participant after the completion of the interview to compensate for any expenses incurred through their participation, such as the time devoted to the interview and any other personal constraints related to their participation.

Each participant will receive financial compensation upon completion of the TRIAGE group discussions, in recognition of any expenses incurred through their participation, including the time devoted to the study and any personal constraints associated with their involvement.

To ensure data confidentiality and participant anonymity, a coding system will be used for the interviews. All data will be kept for a period of 5 years after the conclusion of the study and then securely destroyed to ensure confidentiality and data protection. They will not be used for purposes outside the scope of this research. Finally, all the information written and recorded during the various stages of the study (such as interviews and transcripts) will be kept in a computerized, password-protected file and a secure OneDrive (Microsoft Corporation) file. Ethics approval from the human research ethics committee of the Université du Québec à Trois-Rivières has been obtained (CER-24-313-07.07).

Results

Initial results are expected in August 2025. This study aspires to promote the health and job retention of older nurses through the creation of participatory strategies by examining the influence of resilience, job satisfaction, and occupational stress on early retirement.

On the basis of the results, actionable recommendations for both practice and policy will be formulated.

The findings of this study will be disseminated through various channels to maximize their impact and ensure they reach the intended audience. This will include the publication of scientific articles, the completion of a research dissertation, and participation in conferences through presentations. In addition, a concise summary document highlighting the main research findings will be prepared and emailed to the participants. They will also have the option to receive a link to the online publications resulting from the study.

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Discussion

Anticipated Findings

The aim of this study is to promote the health and job retention of older nurses through the creation of participatory strategies by examining the influence of resilience, job satisfaction, and occupational stress on early retirement. The results of this study could make numerous contributions to the advancement of knowledge and provide input for practice, organization, society, and decision makers.

For practice, the results of this study will support the proposal of concrete strategies to foster a healthier work environment for nurses. These authors recognize the importance of finding systemic strategies dedicated to health care workers, especially after their experiences throughout the COVID-19 pandemic [44]. For instance, studies reveal a positive influence of intervention programs based on optimizing resilience, which results in lower stress and lower burnout symptoms among nurses [78,79]. Consequently, this promotes the health of these workers and promotes a healthy work environment. In fact, having a healthy work environment for older nurses is very important for several reasons. First, it influences the staff's perception of feeling supported and appreciated at work [80]. Second, it has a reducing effect on the shortage of nursing staff members [81]. Finally, it helps nursing staff provide effective, quality patient care and improve the health care system [27,82]. On another note, while conducting the study, the participatory approach in the development of these strategies can help older nurses feel more integrated and part of a community at work. In fact, having a sense of community in which workers consider their place of work as a resource for meeting key social and psychological needs, such as the need for inclusion and affiliation, is found to be a major predictor of job satisfaction [83]. Although the strategies proposed because of this study will have to be assessed for their realism in the light of organizational and societal realities, the fact that they will emerge from the workers themselves will optimize their probability of success. The intention of the study is that the findings will inform not only academic knowledge but also the development of workplace interventions tailored to support older nurses; therefore, the next step will prioritize engagement with health care stakeholders to facilitate the implementation and evaluation of these strategies in future research as well as into organizational policies and support programs.

On a societal and an organizational level, early retirement is a major problem for labor shortages [7]. By addressing this problem, this study would be promoting the job retention of the most experienced workers, thereby mitigating labor shortages. Decision makers, specifically the employers of nurses, are faced with a very worrying problem that is turnover, and one of the top reasons for nurses' turnover is retirement [84]. In the United States, nurses' turnover costs are at an all-time high, as the average cost of turnover for a nurse can be >US $50,000, resulting in the average hospital losing between US $6.6 million and US $10.5 million [85]. With >1 million nurses projected to retire between 2020 and 2030 [86], retaining these older workers is essential to the sustainability of the workforce. Consequently, having tailored strategies for older nurses, which are available to their employers, would be a breakthrough, as it would allow them to effectively benefit from reduced turnover rates due to retirement, which, in turn, lowers recruitment and training costs. In this sense, strategies to support nurses' health and well-being must not merely be short-term and discrete initiatives; employers must embed them systematically into every aspect of nursing, including retirement [87]. However, it is worth mentioning that these strategies must be complemented with a restructuring of organizational processes to ensure their effectiveness [88]. For instance, if the strategy proposed is based on promoting meditation for nurses to minimize occupational stress during their shifts, but the employers discourage nurses from taking breaks, then the effectiveness of this strategy is likely to be considerably diminished. Although this is a process involving many actors and factors, the results of this study will provide some initial information for reflection on such a process.

Strengths and Limitations

In the context of this study, we will generate participatory strategies based on increasing resilience and job satisfaction and decreasing occupational stress to reduce early retirement intentions among nurses. By including this population in the process of developing strategies, we can gain a better understanding of the unique needs, preferences, and challenges faced by this specific population and tailor strategies to address them. Furthermore, the rigor and transparency in the methodological process will allow for adequate reproducibility.

On the other hand, while scoping reviews promote a broad overview of a specific topic, they do not seek to assess the quality of evidence [63]. Consequently, we cannot determine whether the studies selected for the review will provide robust or generalizable findings, and we cannot ensure the effectiveness of all interventions.

For the purpose of this study, only nurses will be invited to participate in the TRIAGE phase of the study, as the objective is to generate strategies directly from their lived experiences and perspectives. This approach will ensure that the strategies will be tailored to their specific needs and realities. Moreover, maintaining a homogenous group of participants (all being nurses) will support group cohesion and encourage more open dialogue during the collective production process, even if they come from diverse practice settings [77]. However, it is important to acknowledge that this approach does not capture the perspectives of other key stakeholders, such as nurse managers or decision makers, whose input could also be relevant in the development and implementation of workplace strategies. Exploring their views could be the focus of a subsequent study to complement and enrich the findings of this study.

Conclusions

Health care services face a number of challenges, including an older workforce, early retirement, and labor shortages. Through this study, we will explore, in depth, the factors pushing older nurses toward early retirement and develop strategies to modify them. These workers are undoubtedly an invaluable source of experience for the health care sector. Therefore, it becomes imperative to not only retain them in the workforce but also

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ensure an environment that will sustain their well-being. The care sector will benefit from the skills and knowledge of older nurses, which will help alleviate the labor shortages.

In conclusion, this study seeks to inform the development of participatory strategies that may support resilience, enhance job satisfaction, and mitigate occupational stress among older nurses. While the effectiveness of these strategies remains to be empirically evaluated, the findings are expected to offer valuable insights that could guide future initiatives addressing similar challenges across the health care sector.

Acknowledgments

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Authors' Contributions

GD conceptualized the study and wrote the manuscript. AL contributed to the writing and editing of the study protocol. All authors read and approved the final study protocol.

Conflicts of Interest

None declared.

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Abbreviations

JBI: Joanna Briggs Institute
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
TIDieR: Template for Intervention Description and Replication
TRIAGE: technique for research of information by animation of a group of experts
UQTR: Université du Québec à Trois-Rivières

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Protocol

Ethical Implications of Artificial Intelligence in Vaccine Equity: Protocol for Exploring Vaccine Distribution Planning and Scheduling in Pandemics in Low- and Middle-Income Countries

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Abstract

Background: The COVID-19 pandemic highlighted significant disparities in vaccine distribution, particularly in low- and middle-income countries (LMICs). Artificial intelligence (AI) has emerged as a potential tool to optimize vaccine distribution planning and scheduling. However, its ethical implications, including equity, transparency, bias, and accessibility, remain underexplored. Ensuring ethical AI implementation in vaccine distribution is crucial to addressing health equity challenges worldwide.

Objective: This study aims to assess the ethical implications of AI-assisted vaccine distribution planning and scheduling in LMICs during pandemics. It seeks to evaluate AI's role in ensuring equitable vaccine access, analyze ethical concerns associated with its deployment, and propose an ethical framework to guide AI-based vaccine distribution strategies.

Methods: Our multiphase qualitative research approach will combine a systematic scoping review, a witness seminar with key stakeholders (health care professionals, AI developers, policymakers, and bioethicists), and a meta-synthesis of findings. The scoping review will follow PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses Extension for Scoping Reviews) guidelines, focusing on studies from 2019 to 2023. The witness seminar will provide firsthand insights into AI's ethical impact on vaccine equity. Thematic content analysis and qualitative coding will be used for data interpretation, with findings integrated into a policy-driven ethical framework.

Results: This study received institutional ethical approval in October 2023. Recruitment commenced in mid-August 2024 through email requests to prospective participants, and recruitment for the witness seminar (focus group discussion) is still ongoing, with 7 expert participants confirmed. Data collection is projected to conclude by August 2025. Preliminary literature analysis from the scoping review is ongoing, and qualitative data analysis from the witness seminar is scheduled for September 2025. The final results and proposed ethical framework are expected to be published in early 2026.

Conclusions: By examining the ethical implications of AI in vaccine distribution, this research will provide actionable recommendations for policymakers, health care organizations, and AI developers. The findings will contribute to the discourse on responsible AI deployment in health care worldwide, ensuring transparency, fairness, and inclusivity in pandemic response strategies.

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KEYWORDS

algorithmic bias; digital inequity; digital inequities; ethical decision-making; vaccine logistics; health equity

Introduction

The COVID-19 pandemic, which emerged in 2019, exposed critical weaknesses in health care systems worldwide, particularly in the distribution and administration of vaccines. This crisis highlighted disparities in health care access, making vaccine equity a principle ensuring fair and just vaccine distribution a central concern [1]. Governments, international organizations, and health care authorities faced significant challenges in designing and implementing effective vaccine allocation strategies to ensure fair distribution across diverse populations [2,3]. Addressing these logistical challenges requires technology to play a pivotal role in supporting vaccine distribution efforts, and artificial intelligence (AI) is emerging as a promising tool for enhancing efficiency and equity. AI is applied in data analysis, pattern recognition, and predictive modelling [4,5]. AI could optimize vaccine distribution during pandemics by predicting outbreak hotspots, streamlining supply chains, and improving resource allocation. Its integration into vaccine planning and scheduling could improve both speed and fairness in distribution, particularly in resource-constrained settings.

However, vaccine equity is not solely a logistical issue; it also involves ethical and social considerations. Equitable vaccine access must account for socioeconomic status, geographic location, race, gender, and other intersectional identities [6]. During a pandemic, structural inequalities often result in marginalized populations experiencing greater barriers to vaccination [7]. Additionally, the increasing reliance on digital technology raises concerns about digital inequity, as disparities in internet access, digital literacy, and technological infrastructure can further limit vaccine access for disadvantaged communities [8,9]. Addressing these challenges requires a system that prioritizes vulnerable populations, responsibly leverages AI, and promotes inclusive vaccine distribution strategies.

The application of AI in vaccine distribution also introduces complex ethical dilemmas [10,11]. Questions regarding prioritization, transparency, accountability, privacy, and fairness arise in AI-driven decision-making. If not carefully designed, AI systems may reinforce biases, compromise trust, and shift critical health care decisions from human oversight to automated algorithms [4,12]. Digital platforms have been used for appointment scheduling, vaccine inventory tracking, cold-chain monitoring, and last-mile delivery coordination [4]. Geographic Information Systems (GISs) help map high-risk zones, while mobile apps assist in public outreach, reminders, and postvaccination surveillance [12]. In high-income settings, predictive analytics and cloud-based dashboards have enabled real-time decision-making. In low- and middle-income countries (LMICs), however, technological integration remains uneven due to infrastructure gaps, limited digital literacy, and resource constraints [8]. Nonetheless, several countries have piloted or adopted AI and machine learning tools for demand forecasting, route optimization, and prioritization models during the COVID-19 pandemic. These examples illustrate the promise and complexity of integrating advanced technologies into vaccine delivery systems. It is crucial to examine the ethical implications that emerge from such innovations, particularly in low-resource settings.

Methods

Study Design

This study will use a multiphase qualitative research design guided by an interpretivism approach [13], which emphasizes understanding the ethical implications of AI in vaccine distribution through the perspectives of key stakeholders. The study will integrate a systematic scoping review, a witness seminar [14,15], and a meta-synthesis [16], ensuring a comprehensive exploration of AI's role in vaccine equity. Heterogeneous maximum variation sampling will be used to select diverse participants, including health care professionals, AI developers, policymakers, bioethicists, and vaccine recipients, to capture a broad spectrum of insights. The research aligns with Sustainable Development Goal 9 (SDG 9: Industry, Innovation, and Infrastructure) and SDG 10 (Reduced Inequalities) by examining how AI-driven vaccine distribution can enhance technological equity, while addressing disparities in health care worldwide. Through thematic content analysis and qualitative coding, the study aims to develop an ethical framework that promotes responsible and equitable AI implementation in pandemic response strategies. Although this study seeks to establish an ethical framework for AI-assisted vaccine distribution across LMICs, it is essential to note that it is intended to be exploratory and adaptable rather than universally prescriptive. The diversity among LMICs in terms of health care infrastructure, digital capacity, and sociopolitical contexts makes a one-size-fits-all model impractical. Instead, this study will produce a context-sensitive foundation (Indian context), informed by cross-sectoral perspectives, which can be refined and localized through future research. The witness seminar and metasynthesis are designed as initial steps in a phased approach, to generate core ethical considerations and actionable principles. Thus, although the scope is broad, the study explicitly recognizes its role as a starting point for iterative framework development, contributing foundational insights to the evolving discourse on ethical AI in public health logistics.

Ethical Considerations

This study complies with ethical guidelines set by the Indian Council of Medical Research (ICMR) in 2017 and the World Medical Association Declaration of Helsinki (WMA DoH, 2013). Approval from the Scientific Review Board (SRB) of Yenepoya Medical College (Mangalore, Karnataka, India) was obtained on September 9, 2023, and ethical approval (YEC-1/2023/269) was granted by the college's Institutional Ethics Committee (IEC) on May 10, 2023. All participants in the witness seminar will provide written informed consent after reviewing the participant information sheet (PIS), with the option to approve the edited transcript before publication. The

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study poses minimal-to-no risk, with no financial incentives, but offers academic contributions to public health ethics. Original recordings will remain confidential, while edited transcripts will be publicly available for research transparency.

Study Plan

Figure 1 shows the study plan including the phases of this research.

Figure 1. Study plan.

Phase 1

The first phase of this study involves a systematic scoping review to analyze existing AI applications in vaccine equity, identifying key ethical considerations, challenges, and potential solutions. Following PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses Extension for Scoping Reviews) guidelines, the review will include full-text, open-access, peer-reviewed papers in English from PubMed, ScienceDirect, and the DOAJ, covering 2019-2023 (COVID-19 pandemic period). The study will focus on LMICs, examining how AI influences vaccine distribution planning and scheduling. Thematic analysis will use data from academic literature, government reports, and international health organizations. Heterogeneous maximum variation sampling will ensure diverse stakeholder perspectives, including policymakers and health care professionals. Papers will be screened based on predefined population, concept, and context (PCC) criteria, excluding gray literature and unpublished sources. The review will use string-based searches with AI-related keywords to ensure comprehensive coverage of AI-driven vaccine allocation and ethical dilemmas.

The inclusion criteria are as follows: studies (wide range of study designs or methods) involving stakeholders or systems related to vaccine distribution, in the English language, and with a time frame of 2019-2023. The exclusion criteria are as follows: papers that do not specify any LMIC-relevant context; do not discuss ethical issues, health equity, or decision-making implications; are published in languages other than English; or are not accessible in full text.

The search string includes the following terms: “AI-powered solutions” AND “Vaccine delivery” AND “Resource-constrained environments”; “AI ethics guidelines” AND “Vaccine logistics” AND “Equity in health care Ethics of AI applications” AND “Vaccine rollout” AND “Social justice”; “AI-driven vaccine allocation” AND “Ethical dilemmas” AND “Global health governance”; “Vaccine allocation ethics” AND “AI-based scheduling” AND “Health care disparities”; “AI-enabled scheduling” AND “Vaccine shortage” AND “Ethical decision-making”; “Artificial Intelligence applications” AND “Equitable vaccine access” AND “Low- and middle-income countries”; “Ethics of AI” AND “Pandemic response” AND “Vaccine scheduling”.

Handling of Duplicates and Data Management

Search results will be imported into the Zotero reference manager to identify and remove duplicates. Extracted data will be charted using a developed data extraction sheet to record study objectives, AI applications, ethical concerns, and outcomes relevant to equity. The extracted data will then be analyzed thematically. A PRISMA-ScR flow diagram will be used to report the screening and selection process (Figure 2).

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Figure 2. Screening process for paper selection based on PRISMA-ScR guidelines. PRISMA-ScR: Preferred Reporting Items for Systematic reviews and Meta-Analyses Extension for Scoping Reviews.

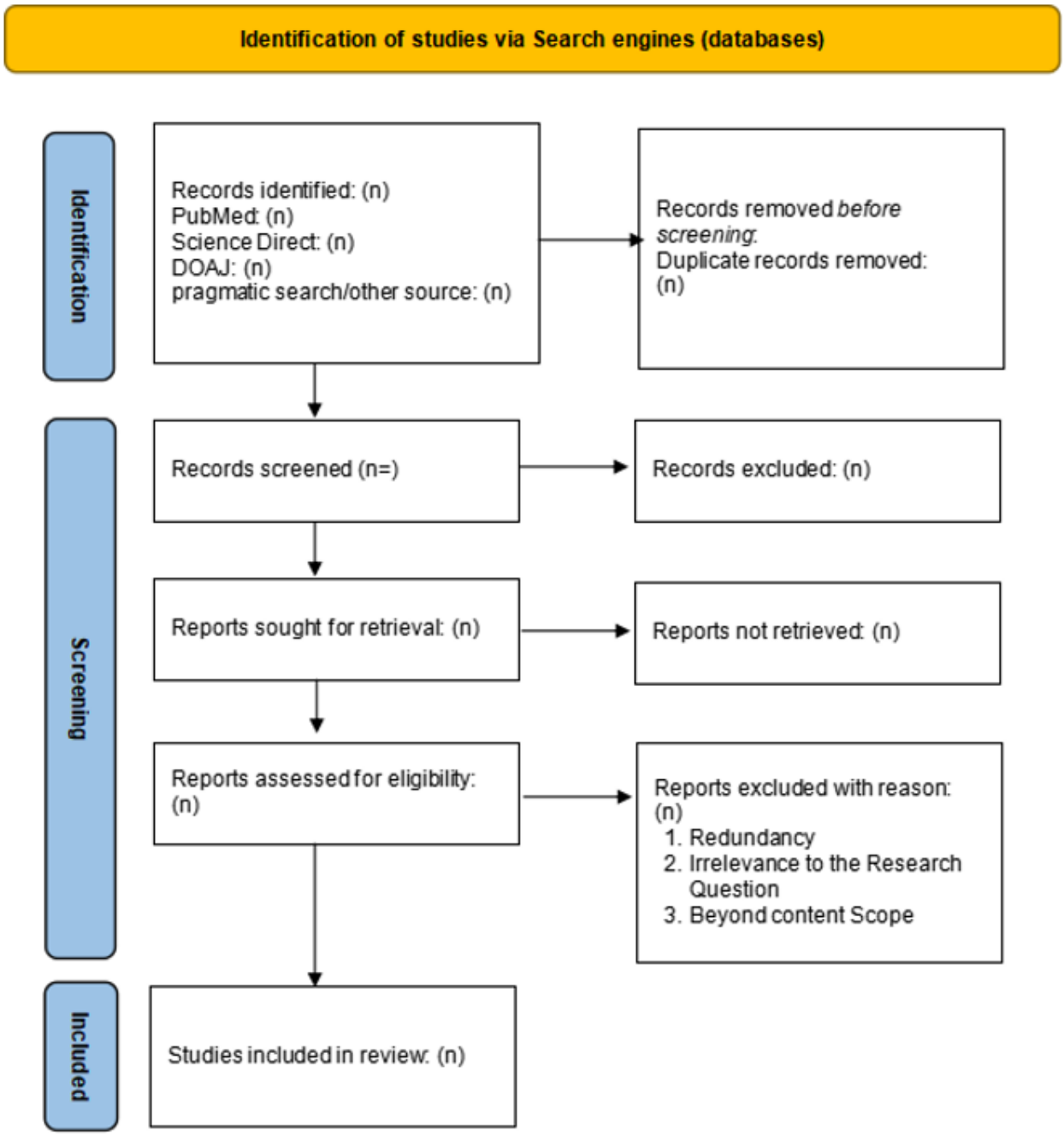

Phase 2

The second phase of this study will involve a witness seminar, bringing together key stakeholders, health care professionals, policymakers, AI developers, bioethicists, and vaccine recipients to share their firsthand experiences of AI's role in vaccine distribution during the COVID-19 pandemic. As a historical event, the pandemic provides an opportunity to document ethical challenges related to privacy, data security, algorithmic bias, and the impact on marginalized communities in LMICs. The seminar will be transcribed and thematically analyzed to extract critical insights.

Phase 3

The third phase will involve developing an ethical framework for AI-supported vaccine distribution, using metasynthesis to integrate findings from the scoping review and witness seminar. Additionally, existing ethical frameworks and relevant case studies will be analyzed to shape a comprehensive model for responsible AI deployment in vaccine logistics. This multiphase qualitative and quantitative (qual/quant) study, conducted at Yenepoya (Deemed to be University) will span 18 months and rely on primary data collected from expert stakeholders.

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Sample Size

A total of 6-15 participants will be divided into 2 smaller groups, with each workshop comprising 5-7 participants at 2 time points. The participants will include prospective witness panelists selected for the seminar, ensuring alignment with the study's research objectives and context. Participants will be chosen based on their expertise and direct relevance to AI-supported vaccine distribution, guaranteeing meaningful and insightful contributions. Although direct experience may be preferred, it is not mandatory. A smaller group size will allow for focused, in-depth discussions, facilitating a comprehensive exploration of diverse viewpoints, while maintaining high data quality. Additionally, resource constraints and feasibility considerations will make a smaller, well-curated panel more manageable within the available time frame and budget. The study will adopt a theoretical saturation approach, meaning data collection will continue until no new themes or ethical insights emerge during the seminar discussions. This will ensure that key patterns and perspectives are adequately captured despite the limited number of participants. Maximum variation sampling will be used to recruit stakeholders, emphasizing diversity in perspectives and fostering an environment of privacy and confidentiality, encouraging candid exchanges on AI's ethical implications in vaccine equity. The emphasis on qualitative depth over breadth is consistent with witness seminar methodology, which prioritizes rich experiential narratives over statistical generalization. If thematic saturation is not achieved within the initial panel, a follow-up mini panel may be convened to address thematic gaps, ensuring rigor and completeness in capturing diverse ethical concerns.

Recruitment

Maximum variation and purposive sampling will be used to recruit key stakeholders, including health care professionals, policymakers, AI developers, bioethicists, and vaccine recipients with relevant experience in AI-driven vaccine distribution, pandemic management, or health policy. Eligible participants must have at least 1 year of relevant experience, while those with less than a year's or no relevant experience in, for example, vaccine distribution, digital health systems, or ethical policy discussions, will be excluded. Witness panelists may withdraw consent at any time, although their insights may still be used in the analysis after data are collected, based on the participants' permission. Participants will be excluded if they decline to participate, fail to respond within 15 days, or face relocation or scheduling conflicts that prevent their involvement.

Semistructured Interview Guide Development

A semistructured interview guide will be used as the primary research tool for the witness seminar (Tables 1 and 2). The guide will contain a list of open-ended questions designed to explore the ethical implications of AI in vaccine distribution. These questions are intended for clarity and flexibility, allowing for probing and in-depth discussions that align with the study's objectives. There will be no fixed number of questions, as the inquiry process will emphasize knowledge and experience sharing among participants, including probes.

The interview schedule covers 5 key domains: AI in vaccine distribution, ethical implications of AI, vaccine distribution planning during pandemics, ethical considerations in vaccine scheduling, and equitable access to vaccines. Panelists will have the freedom to express their thoughts, emotions, and experiences to ensure a rich and nuanced discussion. To ensure validity, the interview schedule was reviewed by 3 experts, including 1 qualitative researcher and 2 bioethicists. Following validation, necessary revisions were made before dissemination via email. Additionally, the questionnaire underwent pretesting with 2 prospective panelists, who will not participate in the final seminar, to assess clarity, coherence, and language accuracy, ensuring the questions are easily understood and effectively elicit relevant responses.

Table 1. AI[a]-based distribution planning and scheduling systems' effectiveness in ensuring equitable vaccine distribution in LMICs[b].

Session	Description
Session 1: opening and introduction (5 minutes)	• Brief overview of the seminar's purpose, objectives, and format. • Introduction of the panelists and their domain.
Session 2: COVID-19 vaccine access and vaccine equity (5-minute presentation to open up the discussion)	• Each panelist presents their perspective on COVID-19 vaccine access and vaccine equity during the COVID-19 pandemic in LMICs (15 minutes).
Session 3: using AI support systems for vaccine scheduling and distribution (5-minute presentation to open up the discussion)	• Each panelist presents their perspective on using AI support systems in vaccine distribution during the COVID-19 pandemic in LMICs (15 minutes).
Session 4: ethical implications of using AI support systems for vaccine scheduling and distribution and how it impacts equity (5-minute presentation to open up the discussion)	• Each panelist presents their perspective on the ethical implications of AI support systems for vaccine scheduling and distribution and how using AI support impacted equity during the COVID-19 pandemic in LMICs (15 minutes).
Break (10 minutes)	• Break to refresh
Session 5: health equity toward responsible AI implementation (5-minute presentation to open up the discussion)	• Panelists share recommendations for responsible AI implementation in vaccine distribution to ensure health equity and ethical considerations (15 minutes).

[a]AI: artificial intelligence.

[b]LMIC: low- and middle-income country.

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Table 2. Interactive discussion questions (based on the sessions) for the focus group interview.

Session	Questions
Session 2: COVID-19 vaccine access and vaccine equity	• How can AI[a] be leveraged to enhance vaccine equity and promote equitable vaccine distribution (eg, registration, appointment scheduling, and outreach)? • How might integrating AI into vaccine scheduling and distribution enhance access and equity? • How will AI-based systems be made to recognize and address specific vulnerabilities of groups or biases in the processes that affect equitable distribution? • How do AI-driven approaches impact the decision-making process for prioritizing vaccine distribution? • How do you think AI can contribute to promoting vaccine equity?
Session 3: using AI support systems for vaccine scheduling and distribution	• What potential challenges or limitations exist in implementing AI-driven approaches to enhance health ethics worldwide in promoting vaccine equity?
Session 4: ethical implications of using AI support systems for vaccine scheduling and distribution and how it impacts equity	• What potential ethical challenges do you foresee in implementing AI-driven approaches for vaccine equity (eg, individual privacy concerns, transparency, accountability, potential biases or inequalities, marginalization, cultural and social integration)? • What steps should be taken to address these limitations or unintended consequences that may arise from AI-driven approaches in vaccine distribution?
Session 5: health equity toward responsible AI implementation	• What are the perceptions and attitudes of individuals toward AI-driven approaches in promoting vaccine equity, and how do these perceptions influence their willingness to participate?

[a]AI: artificial intelligence.

Semistructured Interview Administration

The witness seminar will be conducted in a structured and interactive format to gather insights from expert panelists on the ethical implications of AI in vaccine equity during pandemics. Invitations will be sent to selected stakeholders, including health care professionals, policymakers, AI developers, bioethicists, and vaccine recipients, who have firsthand experience of AI-based vaccine distribution. The seminar will be held in hybrid mode, with the physical venue at Demo Room II, 3rd Floor, Centre for Ethics, Yenepoya (Deemed to be University), and a Zoom link for online participants. To ensure informed discussions, panelists will receive background reading materials before the event, with downloadable links provided during registration. A question schedule will guide discussions, prompting participants to share their experiences, ethical concerns, and recommendations regarding AI-driven vaccine allocation.

The entire session will be recorded with participant consent, and comprehensive notes will be taken to capture key insights, perspectives, and areas of agreement or disagreement. Following the seminar, the recordings will be transcribed, and a thematic analysis will be conducted to identify emerging patterns and ethical concerns. Panelists will get an opportunity to review and verify the accuracy of the findings before dissemination. The final report, including key discussion points and recommendations, will be shared with stakeholders, policymakers, and the broader research community through publications, presentations, or policy briefs. This process will ensure transparency, accuracy, and meaningful contributions to the ongoing discourse on ethical AI implementation in vaccine distribution.

Data Analysis Plan

A holistic approach will be used to analyze the qualitative data, providing a comprehensive understanding of AI's impact on vaccine equity, distribution, planning, and scheduling during pandemics. The witness seminar transcripts will undergo thematic content analysis, identifying key themes, patterns, and ethical concerns related to AI-driven vaccine allocation in LMICs. Thematic insights will be extracted through focused coding, while summative content analysis will be used to map responses against established ethical principles. The principal investigator (PI) will independently conduct the initial analysis, which will then be reviewed and compared with findings from the research guides (coinvestigators) to ensure accuracy and consistency.

Although the study is primarily qualitative, it incorporates a limited quantitative descriptive component in the form of (1) trend analysis from the scoping review (eg, publication frequency by year, geographical distribution of studies, use of AI methods) and (2) a code frequency during the witness seminar. These data will be analyzed descriptively to identify frequency patterns and dominant ethical themes. The quantitative findings will be used to triangulate and support the thematic insights from qualitative coding, aligning with a qual/quant-embedded design, where qualitative data are dominant and quantitative data play a supportive role.

The qualitative data collected through the witness seminar will be analyzed using a thematic analysis approach, specifically following the 6-phase framework by Braun and Clarke [17]: (1) familiarizing with data, (2) generating initial codes, (3) searching for themes, (4) reviewing themes, (5) defining and naming themes, and (6) producing the report. Transcripts will

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be coded both inductively and deductively, with predefined ethical concepts guiding initial coding, while allowing for the emergence of novel themes. To enhance intercoder reliability, 2 researchers will independently code a subset of the data. Discrepancies will be resolved through discussion, and a third reviewer will adjudicate unresolved differences. Cohen κ>0.70 will be considered acceptable for intercoder agreement. A codebook will be maintained throughout, and regular peer debriefing sessions will be held to ensure consistency.

Validation of findings will involve member checking, where participants will review the analyzed summaries to verify the accuracy of their perspectives; triangulation of findings from the scoping review and witness seminar to cross-validate emerging themes; and audit trails documenting decisions made during analysis, ensuring transparency and reproducibility. Biblioshiny and R (R Foundation for Statistical Computing) will be used strictly for the descriptive and bibliometric analysis of the scoping review phase (eg, tracking publication trends, co-occurrence of keywords, and country-wise contributions). These quantitative insights will support, but not replace, the primary qualitative thematic findings.

Trustworthiness of the Study

Ensuring the trustworthiness of this study is critical to establishing the rigor, reliability, and validity of the findings. This will be achieved through credibility, transferability, dependability, and confirmability, supported by multiple verification techniques.

Credibility

The study will incorporate triangulation, member checking, and negative case analysis. Triangulation will be achieved through a multiphase approach, integrating data from the systematic scoping review, witness seminar, and metasynthesis to ensure a comprehensive understanding of AI's ethical implications in vaccine equity. Member checking will allow witness seminar participants to review edited transcripts and verify the accuracy of their statements before finalizing the analysis. Additionally, negative case analysis will be conducted by identifying divergent perspectives on AI implementation in vaccine distribution, ensuring that all viewpoints are represented.

Transferability

The study will provide a reasonable description of the research context, including detailed participant experiences, ethical challenges, and AI's impact on vaccine distribution in LMICs. Through the documentation of specific factors influencing AI-based vaccine allocation, the findings can be applied in similar settings worldwide.

Dependability

The study will ensure dependability through an audit trail, systematically documenting all research steps, from protocol development to data collection, analysis, and reporting. A structured data management approach will be followed, with the PI and research guides independently reviewing findings to ensure consistency and replicability.

Confirmability

The research process will be transparent and objective, minimizing potential researcher bias. The audit trail will maintain records of data collection methods, coding processes, and analysis decisions to allow external validation.

Reflexivity

A reflexive approach will be maintained throughout the study to acknowledge and address potential researcher biases. This will involve continuous self-evaluation and critical reflection on how the researchers' backgrounds, perspectives, and assumptions may shape data interpretation.

Results

This study received ethical approval in October 2023. As of June 2025, recruitment for the witness seminar is actively ongoing, with 7 panelists confirmed, including representatives from public health policy, bioethics, and AI development sectors. The scoping review phase is in progress, and literature analysis is yet to be finalized. Data collection for the witness seminar is projected to be completed by August 2025, with data analysis and synthesis planned for September-October 2025. Final findings, including the proposed ethical framework, are expected to be submitted for publication in early 2026.

Discussion

Summary

This study is expected to reveal that AI-based systems could offer logistical advantages in vaccine distribution, such as predictive modelling, scheduling, and supply chain management. However, these systems also raise significant ethical concerns. Anticipated themes include algorithmic bias, data privacy risks, marginalization due to digital inequities, and a lack of transparency in AI decision-making processes [18-21]. Although previous studies have examined AI applications in health care logistics and ethical issues in digital health, few have explicitly focused on the intersection of blockchain and vaccine distribution. This study fills that gap by triangulating evidence from the literature and lived experiences of diverse stakeholders. Moreover, it distinguishes itself by using a witness seminar method, a novel qualitative approach for capturing real-time policy-relevant ethical narratives.

Strengths and Limitations

A significant strength of this study is its multimethod design, integrating a scoping review, a witness seminar, and a metasynthesis to enhance validity and triangulation. Additionally, including multiple stakeholder types ensures a holistic understanding of the ethical landscape. However, the study is limited by its small sample size and recruitment from India in the witness seminar, which, despite efforts to reach data saturation, may not fully capture the diversity across all LMIC contexts. Furthermore, ethical frameworks developed through qualitative synthesis may require further field validation in specific countries or communities to test relevance and applicability.

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Based on this protocol, follow-up studies will focus on country-specific validation of the ethical framework and development of context-sensitive AI governance tools for public health use in LMICs. Engagement with policymakers, ethicists, and AI developers will be crucial to refine and scale ethical guidelines in future pandemics. The findings will be shared through peer-reviewed publications, academic conferences, and policy briefs targeted at public health authorities, AI developers, and health organizations worldwide. Stakeholder engagement sessions and webinars will also be conducted to translate the ethical framework into actionable guidance. All outputs will be made available via open access platforms to support transparency and uptake in LMIC contexts.

Conclusion

This study will explore the ethical implications of AI in vaccine distribution, particularly in LMICs, where access disparities persist, integrating a systematic scoping review, a witness seminar, and a metasynthesis to provide insights into both potential benefits and ethical challenges of AI-driven vaccine allocation. The findings could inform policymakers and health care professionals, offering practical recommendations for responsible AI deployment in pandemic response efforts. Additionally, the study aims to develop an ethical framework to guide equitable and transparent AI implementation in vaccine distribution. Through stakeholder engagement and policy recommendations, this research will contribute to ethical AI governance in health care worldwide. The generalizability of findings to different LMICs may pose limitations. However, this study can serve as a model for new learnings, offering valuable insights that can be adapted and refined for similar research and policy development.

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Data Availability

The data generated and analyzed during the interviews will be made publicly available upon reasonable request, but as of this protocol publication, no data are available.

Authors' Contributions

AI, VV, and PEE contributed to the conceptualization, methodology, final manuscript draft, and approval for submission of the protocol.

Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
LMIC: low- and middle-income country
PRISMA-ScR: Preferred Reporting Items for Systematic reviews and Meta-Analyses Extension for Scoping Reviews
PI: principal investigator
qual/quant: qualitative and quantitative
SDG: Sustainable Development Goal

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Protocol

Social Participation When Aging With an Early-Onset Neurological Disability: Protocol for Descriptive Qualitative Research

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Abstract

Background: Due to improvements in health care and rehabilitation, as well as better social conditions, individuals living with traumatic brain injury (TBI), multiple sclerosis (MS), or spinal cord injury (SCI) are living longer. It is therefore necessary to ensure the presence of social and health services adapted to the realities and specific needs of these populations aging with disabilities. Social participation is a key determinant of active aging and health. However, there is limited evidence regarding the social participation of these aging populations. To support the development of more inclusive approaches promoting the health of older adults, it is essential to better understand the diversity of social participation experiences among individuals aging with neurological disabilities.

Objective: This study aims to explore how social participation is experienced by individuals aging with TBI, MS, or SCI; document the barriers and facilitators to their social participation; and explore avenues for interventions supporting their social participation.

Methods: This descriptive qualitative research is part of a larger action research project conducted in partnership with individuals aging with disabilities, researchers, and community organizations providing services to these populations. Individuals 50 years or older living with TBI (n=8), MS (n=8), or SCI (n=8) will participate in a semistructured interview. The interviews will be transcribed verbatim, and the accuracy of the transcripts will be ensured through peer validation. Qualitative data will be analyzed using a mixed approach in alignment with the Framework methods. The use of the Human Development Model–Disability Creation Process (HDM-DCP) conceptual model will be used for deductive analysis. The coding tree will combine significant themes arising from the interviews' inductive part and the themes from the HDM-DCP. Also, 12.5% of the analysis will be tested for stringency (ie, double-blind and interrater reliability exercise).

Results: This study will provide insights into the diversity of social participation experiences of these populations as well as the influence of individual characteristics and environmental resources on their social participation.

Conclusions: This project will lay the groundwork for the codevelopment of health promotion programs aimed at supporting the social participation of individuals aging with neurological disabilities. This study will also help to identify the resources and strengths that support social participation for these populations, as well as the systemic barriers that need to be addressed.

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KEYWORDS

social participation; active and healthy aging; gerontology; geriatrics; older adults; elder; elderly; older person; older people; aging; individuals aging with disabilities; neurological disability; traumatic brain injury; TBI; multiple sclerosis; MS; spinal cord injury; SCI; neurological illnesses; neurological diseases; neurological conditions; neuroscience; neuro; neurologists

Introduction

Background

In Canada, one in four individuals has one or more disabilities [1]. Due to medical and rehabilitation advancements, as well as improved social conditions, individuals living with disabilities are experiencing a significant increase in life expectancy [2,3]. Consequently, the number of individuals aging with disabilities is on the rise [3], many of whom are impacted by long-term neurological conditions such as traumatic brain injury (TBI), multiple sclerosis (MS), and spinal cord injuries (SCI). Thus, these populations represent a significant proportion of individuals served in rehabilitation and community organizations, as they constitute a substantial percentage of neurological conditions in Canada [4,5].

Individuals aging with disabilities remain an understudied population [3,6-8], and there is limited evidence on the realities of aging with disabilities and the related needs. While research on aging with a disability is progressing, it remains marginal, particularly concerning the long-term experiences of individuals aging with early-onset neurological disabilities [9]. Available knowledge about the realities and social participation experiences of these populations is especially limited. There is a critical lack of representation of patient perspectives in the current literature. Addressing this gap is crucial for several reasons. First, sharing the perspectives of these individuals allows for a more comprehensive understanding of the challenges and opportunities they face, which can inform more effective and tailored interventions. Second, it empowers these individuals by giving them a voice in shaping policies and services that directly affect their lives. Finally, by highlighting their experiences, we can challenge societal misconceptions about aging with disabilities and promote a more inclusive approach to health care and social services. This hinders the development of appropriate solutions that support access to social and health services for individuals aging with disabilities and thus impedes the active aging of this population [10,11]. One such challenge is ensuring that individuals aging with disabilities have access to social and health services that are tailored to their specific needs and unique realities [12,13]. Continuity of access to social and health services adapted to the reality of individuals aging with disabilities is particularly important since obstacles to accessing social and health services, such as physical, cognitive, informational, and financial barriers, may lead to further restrictions in social participation [14]. To support this access, it is important to develop and improve solutions that enhance the availability, accessibility, acceptability, affordability, and usability of these services [15].

Furthermore, the aging of individuals with disabilities presents significant challenges, which compound the broader issues associated with the aging Canadian population [14,16]. The double stigma associated with ageism and disability can reduce the social participation of individuals aging with disabilities [17-21]. Levasseur et al [22] defined social participation as “a person’s involvement in activities providing interactions with others in community life and in important shared spaces, evolving according to available time and resources, and based on the societal context and what individuals want and is meaningful to them.” Although social participation is a key determinant of the health of aging populations [23], there is little scientific literature on the social participation of individuals aging with a neurological condition such as TBI, MS, or SCI [24].

This study is part of a larger research program aimed at developing health promotion programs to support the social participation of individuals aging with disabilities. In this descriptive exploratory qualitative study, the choice not to develop hypotheses is justified by several reasons. First, the exploratory nature of the research aims to examine a little-studied phenomenon without preconceived ideas, thus allowing an openness to unexpected discoveries. Second, the absence of predefined hypotheses helps to avoid potential biases that could influence the interpretation of the data and limit the open-mindedness necessary for in-depth exploration [25-27]. Finally, this approach aligns with the adopted socioconstructivist epistemological stance [28], which considers that knowledge is socially constructed through interactions, thus favoring the emergence of meaning from the data rather than the verification of pre-established hypotheses [25,26]. This study will contribute to laying the groundwork for the codevelopment of such programs by informing on how individuals aging with TBI, SCI, or MS would like to be supported in terms of social participation.

Interest in Those Populations

Neurological disorders account for a significant number of health conditions in many countries worldwide [29,30]. In Canada, they have a substantial impact (ie, funding allocated to care and services, hospitalization rate) [4]. The choice of these 3 populations is based on the prevalence of MS in Canada, which is one of the highest in the world [31], and a high incidence of TBI in the country (approximately 456 individuals per day) [31,32]. Thus, by 2031, TBI will be among the most common neurological disorders in Canada [32]. The prevalence of SCI will rise to over 120,000 individuals, approximately more than 3600 new cases per year [33,34]. Finally, these populations offer a contrast between aging with a degenerative condition (MS) and nonprogressive conditions (TBI and SCI).

Objectives

This study will pursue 3 objectives aimed at providing insights into the experiences and needs regarding the social participation of individuals aging with neurological disabilities. The objectives are as follows: 1) explore how social participation is experienced by individuals aging with TBI, MS, or SCI; 2) document the obstacles and facilitators to their social

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participation; 3) explore intervention strategies supporting their social participation.

Methods

Overview

This study aims to coconstruct knowledge with individuals who have long-term neurological disabilities. It is part of a larger participatory action research project financed by the Canadian Institutes of Health Research (grant number 202403-TLP495860, 2023-2026). Figure 1 presents the entire procedure of the study.

Figure 1. Application of the seven stages of the Framework method. HDM-DCP: Human Development Model–Disability Creation Process.

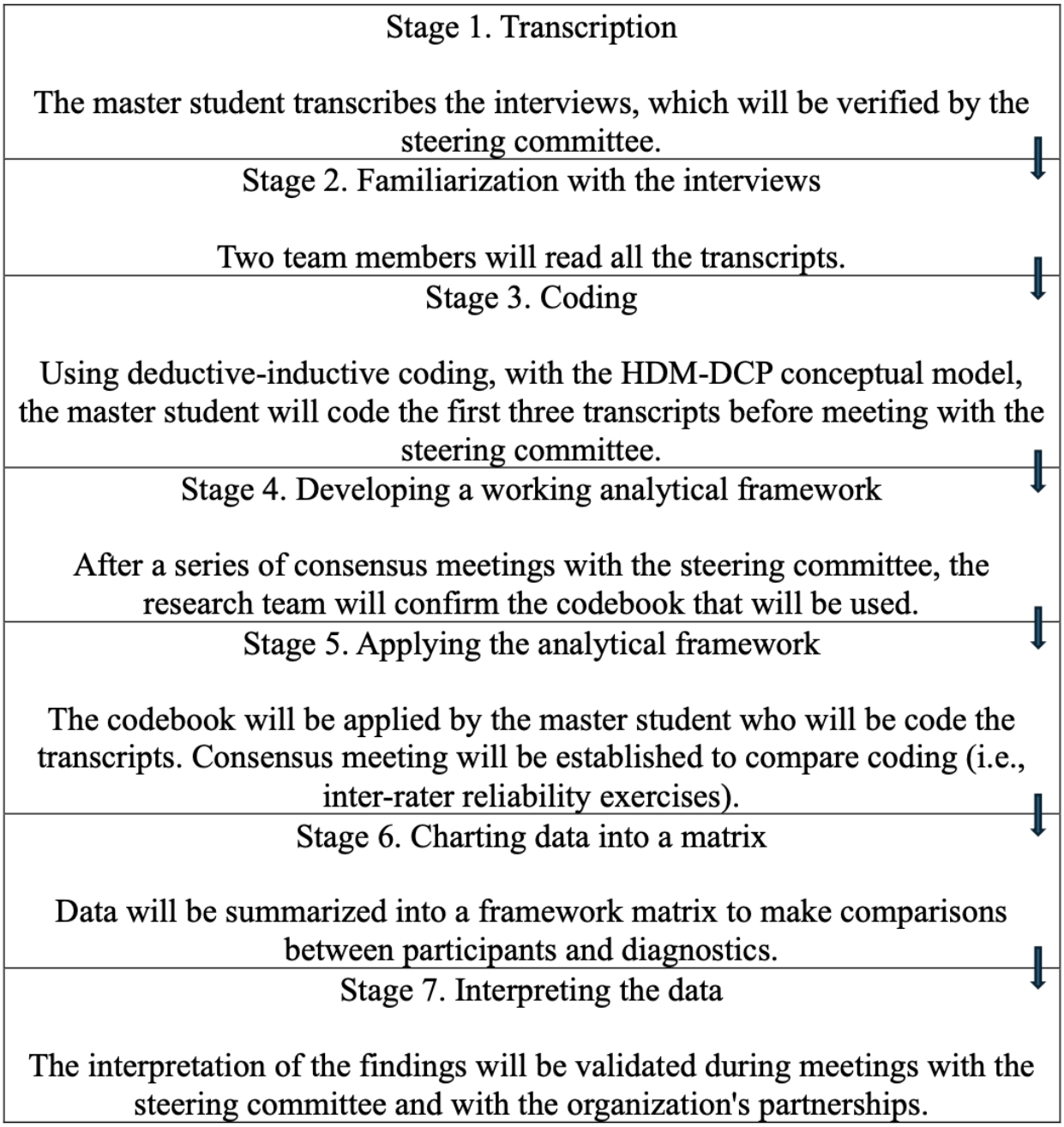

Study Design

Given the lack of prior studies addressing these objectives, this descriptive qualitative research serves as an exploratory study, providing an initial overview of key elements that can inform and guide future research in this area. In alignment with best governance practices in partnership-based research [35-37], a steering committee will be established. It will be composed of individuals aging with disabilities (n=3), representative of the sample size and aged between 50 and 65 years, community workers working with these populations (n=2), a research professional (n=1), the principal investigator (n=1), and a graduate student (n=1). The individuals chosen to compose the

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steering committee will ensure a good representation of the diagnoses of interest and different stakeholders. The partners have been longstanding collaborators with the research committee. This committee upholds and fosters best practices in partnership-based research, both of which are core values for the team [35-37]. The graduate student's role within the committee will be to coordinate research activities throughout the entire process. The relevance of this study will be discussed and validated with the individuals aging with disabilities, and the community workers involved in the steering committee. For this qualitative research, the steering committee will also be involved in the review of data collection tools and the knowledge transfer plan [38].

The results of this project will be reported according to the COREQ (Consolidated Criteria for Reporting Qualitative Research) (see Multimedia Appendix 1) [39]. This qualitative research tool provides a 32-item checklist to ensure that all important aspects are reported. The COREQ checklist includes three domains guiding qualitative research reports (eg, research team and reflexivity, study design, analysis, and findings). The epistemological stance of the research team is based on social constructivism [28]. By adopting a constructivist perspective, the team is able to develop knowledge about aging and the social participation of individuals living with a TBI, MS, or a SCI, acknowledging that this understanding emerges from the lived experiences of those affected [28].

Recruitment

The target population of this project consists of individuals aged 50 years and older, with a long-term neurological disability for more than 10 years. The choice of a duration since diagnosis will allow us to explore the aging experiences of individuals who have been adapting for a significant number of years and are no longer receiving rehabilitation services. Exclusion criteria include cognitive impairment causing an inability to consent freely and enlighten to the participation in the study. Three populations will be initially targeted: individuals aging with a TBI, an MS, or a SCI. The recruitment of 24 participants aged with one of the mentioned conditions (ie, TBI, SCI, or MS) will be divided equally among the three health conditions (n=8 per condition). Participants must meet the inclusion criteria that are presented in Textbox 1. For this exploratory study, data saturation will be assessed throughout data collection [40]. To ensure data saturation, we will use an iterative approach to data collection and analysis, continuously reviewing and refining our themes as new interviews are conducted [40]. In addition, we will use member checking, where preliminary findings will be shared with participants for validation and to identify any gaps in our understanding, thus enhancing the comprehensiveness of our data and ensuring that all relevant themes are captured. More participants could be recruited if data saturation is not reached with this sample size [41,42].

Textbox 1. Criteria for recruitment.

Inclusion criteria

- 50 years old and older
- Diagnosed with traumatic brain injury (TBI), multiple sclerosis, or spinal cord injury for at least 10 years
- Moderate or severe TBI
- Spinal cord injury and multiple sclerosis, regardless of the type of diagnosis
- Ability to communicate in French or English

Exclusion criteria

- Cognitive impairment causing an inability to give consent
- Mild TBI

Recruitment will be done through purposive sampling to promote diversity in the profiles of recruited individuals (ie, sex, gender, diagnosis, time since diagnosis) [43]. Participant recruitment will be carried out in collaboration with research partnerships that have been established with four organizations in the province of Quebec (ie, Adaptavie, Servio, Multiple Sclerosis Canada, and Moelle épinière et motricité Québec). Each of these organizations provides support services and activities for individuals living with neurological disorders. Adaptavie's mission is to provide individuals with functional limitations access to a diverse range of adapted physical, recreational, and social activities that promote inclusion, well-being, and active living. Moelle épinière et motricité Québec, formerly known as the Quebec Paraplegic Association and the Foundation for Spinal Cord Research, is a nonprofit organization dedicated to promoting self-sufficiency, independence, and quality of life for people with disabilities. Servio is also a nonprofit organization dedicated to individuals living with a traumatic brain injury. The eligibility criteria and interview procedures will be shared and discussed with our community partners. This collaboration aims to ensure a mutual understanding of the study objectives and to facilitate the identification of potential participants in an ethical and respectful manner. Our partners, with their expertise and in-depth knowledge of the community, will play a crucial role in the appropriate recruitment of interested individuals for our study. A snowball sampling strategy could be used if needed as a complementary approach [44]. Also, the sample of 24 people aging with a long-standing disability of neurological origin, MS (n=8), TBI (n=8), and SCI (n=8) will allow us to identify the major initial themes common or distinct between the participants in terms of their experiences of social participation and aging with a disability. The research team aims to describe in a rich and detailed manner the representations of the MS, TBI, and

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SCI clientele rather than only superficially reporting the representations of several distinct clienteles. Thus, the selection of participants does not aim to reflect the heterogeneity of the clientele. As a reminder, this is an exploratory project that will lay the foundations for the codevelopment of a health promotion program to address the challenges of social participation of populations aging with a neurological disorder. Furthermore, the choice to focus on these 3 clienteles and the sample size (n=8 per condition) also explains the contrasts which characterize them. It is crucial to emphasize the exploratory nature of this research. Our goal is to document key elements and major themes, both common and distinct, among participants regarding their experiences of social participation and aging with a disability. Rather than drawing stark contrasts, this approach will allow us to identify elements associated with aging with disabilities that transcend the specific nature of the impairment and are thus common across these populations. Our methodology seeks to establish a holistic understanding of the experiences of aging with a disability while acknowledging the particularities of each condition studied. By doing so, we will gain a better understanding of the shared challenges and unique experiences of each group.

Data Collection

Data collection methods included obtaining consent from the participants, the conduct of the semistructured interview, and completing a sociodemographic questionnaire. As part of the development of the interview guide, the steering committee will be invited to comment on the relevance and clarity of the questions (see Multimedia Appendix 2 for the actual version of the guide). The interview guide and the sociodemographic questionnaire will be pretested with individuals representing each target population (n=3). Following the review of data collection tools, feedback will be integrated and validated by the steering committee members. Participants will be asked to complete a sociodemographic questionnaire (ie, sex, gender, age, ethnocultural origin, socioeconomic status, educational level, housing situation, marital status, diagnosis, rehabilitation history, and impacts on daily life). The interview will last between 60 and 90 minutes and will be conducted by the master's student, who is a part-time community worker with individuals living with neurological disabilities for almost 2 years. To safeguard participants' confidentiality and privacy, we have implemented a data management plan. All audio recordings and transcripts will be stored on a secure university server. Following data collection, personal identifiers will be promptly removed and replaced with unique codes, with the linking key accessible only to the principal investigator. Access to the deidentified data will be strictly limited to authorized research team members directly involved in data analysis [45]. Interviews will be audio recorded with a voice recorder and securely stored at The Interdisciplinary Research Center on Rehabilitation and Social Integration (Centre interdisciplinaire de recherche en réadaptation et intégration sociale; Cirris) and confidentially managed [45].

To maximize inclusion for participants with communication, physical, or memory challenges, strategies for full participation, such as flexible interview methods, will be used [46,47]. From the perspective of providing comfort during the interview, the sociodemographic questionnaire and a semistructured interview guide will be provided to each participant before the meeting. The research team is aware of the transportation challenges faced by participants. Thus, the team will demonstrate flexibility in the locations for the interviews, as well as in how they are conducted. And so, the interview will be conducted according to the participants' preferences (eg, at home, in a research center room, or via video conference). The master's student will initiate contact with selected participants via phone, maintaining sensitivity and attentiveness throughout the interaction. For interviews conducted via videoconference, any concerns about technology access will be addressed and resolved in advance [45]. This initial contact will serve as an opportunity to clarify questions about the project or interview process and establish optimal conditions for the interview [45]. The data collection process can be spread over as long a period as necessary to respect their capacity (ie, split the interview into 2 sessions or take a break).

Data Analysis

Before the data analysis, the interviews will be transcribed verbatim. The first transcriptions will be validated by the research professional to ensure fidelity. Preliminary results will undergo consultation to support the utility and clarity of the themes emerging from the analyses. To ensure rigor, various validation steps will be conducted throughout the transcription and data analysis process (eg, double-blind validation and validation with quality assurance). Also, 12.5% of the transcripts will be validated by interrater reliability exercises by a neutral party. Before the qualitative analysis, the team will meet to ensure the unfolding of the Framework method [48]. The interest of this approach is that the Framework Method provides 7 steps to follow and produces highly structured outputs of summarized data [48]. Using this method will help structure the analysis method before beginning the qualitative analysis. The use of NVivo (version 15; Lumivero) software [49] for the analysis of qualitative data will make it possible to organize and structure the data from the interviews. Data analysis will be conducted using the mixed inductive-deductive thematic analysis method. The deductive part will rely on the Human Development Model–Disability Creation Process (HDM-DCP) [50]. This model presents three closely interconnected domains: lifestyle habits, personal factors, and environmental factors. Those domains mutually influence one another and collectively shape social participation. Our coding tree is derived from the detailed descriptors of the various components that constitute these domains, ensuring a comprehensive and theoretically grounded analysis of social participation. The use of this model allows understanding of the interaction between the individual, their environment, and their lifestyle habits [51]. The relevance of this model choice lies in the recognition of environmental factors alongside personal factors and lifestyle habits [51]. The environment plays an active role in the individual's disability [51]. The inductive part of data analysis will allow themes to emerge from the verbatim. A descriptive analysis of sociodemographic data will be reported through summary descriptive statistics (ie, means, ranges, frequencies) to establish sociodemographic profiles of the encountered populations. Comparative analyses will be conducted to systematically

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examine differences (or similarities) based on variables such as sex, gender, or diagnosis. As mentioned, these populations are likely to offer a contrast between aging with a neurological disability. The results will establish sociodemographic profiles of the encountered populations.

Ethical Considerations

This project has been approved by the ethics committee of the Centre intégré universitaire en santé et services sociaux de la Capitale Nationale (CIUSSS-CN; number 2024-2971). A monetary compensation of CAD $40 (US $29) was offered to each participant. Before the interview, each participant will be informed that their confidentiality will be protected and that they could choose not to answer any questions they find uncomfortable. Also, they will be free to withdraw from the research whenever they want. The interviewer will be attentive to signs of discomfort and will adjust as needed based on signs of discomfort. The purpose of the project and the required involvement will be briefly explained during the initial contact, and the informed consent form will be sent to each participant before the interview. Informed consent will be obtained before the interview by reading and signing the consent form. Thereby, every modification of the data tools will be approved by the ethics committee at any stage of modification, if applicable.

Results

The study opened to recruitment and data collection in April 2024. By December 2024, 24 participants have been interviewed. Following the 7 steps of the Framework method, the Application of the Seven Stages of the Framework Method (see Figure 2) demonstrates the process of the research project [48]. Data analysis is anticipated to begin in January 2025 and will provide evidence-based knowledge on the diversity of social participation experiences of these populations. It will determine, if applicable, commonalities in social participation and active aging, and which elements are specific to each population. We expected that there would be similarities between the SCI and MS populations according to their physical disability. This project will also shed light on different ways in which these populations wish to be supported in their participation, and the role of individual characteristics and environmental resources in shaping these experiences. The findings will prioritize the richness of social participation experiences over diagnostic differences, rather than focusing on the severity of impairments or variations within the same population (eg, type of MS, severity of TBI, or level of SCI). Findings and interpretations will be reported in line with guidance from the COREQ checklist [39]. We expected to begin the knowledge transfer plan during the spring and summer of 2025 [38]. Partner organizations will be consulted to determine the knowledge transfer methods to be used. The tools will be developed in alignment with the interests of the partners and their members [52]. Thus, the expected results are to be published in fall 2025.

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Figure 2. Study protocol chart.

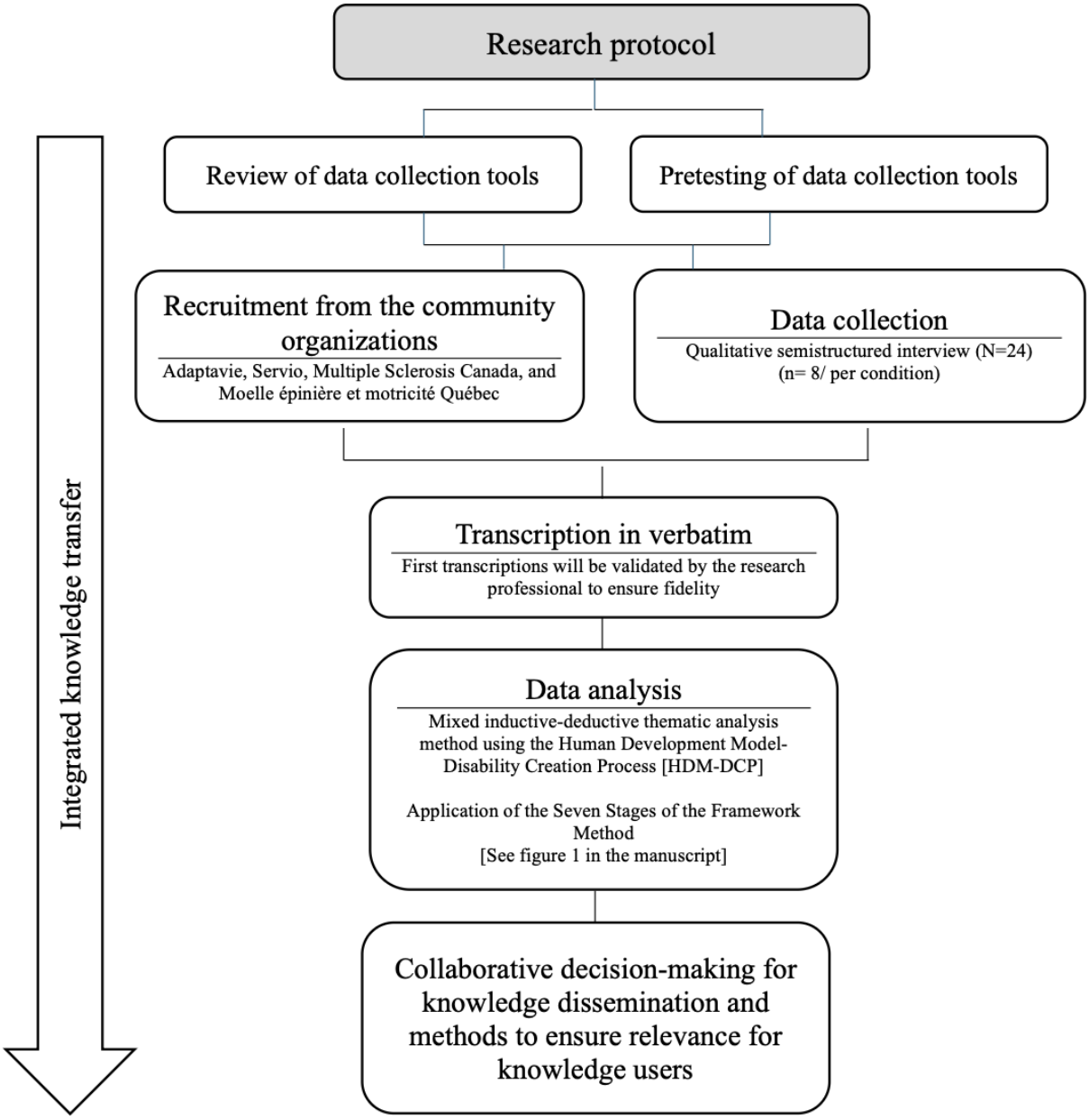

Discussion

Principal Findings

This qualitative study is intended to explore the aging experiences of individuals with a long-term neurological disability and to describe the barriers and facilitators to achieving their social participation. This is the first study to explore the social participation experiences of 3 populations aging with a disability, as a TBI, an SCI, or an MS.

Methodologically, our study aims to adequately address considerations related to the principles of equity, diversity, and inclusion. To achieve this, the approaches will be adapted (eg, data collection strategies). Indeed, in the interest of inclusion, it is necessary to adjust to the participants' abilities and offer flexibility in our approach to enable full participation. This inclusive stance is essential for the study, as it ensures greater scientific rigor by supporting the quality of the data collected.

Internationally, various health organizations, such as the World Health Organization (WHO), recognize disability as a significant factor in situations of inequality [53]. The WHO recognizes the need to develop coordinated actions to ensure that people with disabilities have equitable access to effective health care services [53]. Also, some organizations have developed action plans to improve community health, such as the Quebec Pride in Aging: Government Action Plan 2024-2029 [54] that recognizes the importance of social participation as a key determinant of seniors' health. Social participation is positively associated with the health of individuals aging with disabilities [23], a reduced risk of mortality [24], and greater life satisfaction [23]. This study will undoubtedly establish important guidelines to promote the well-being of individuals aging with disabilities.

Social participation is a modifiable determinant of health. Various studies involving other populations living with a neurological condition addressed the barriers and facilitators to social participation of individuals aging with disabilities [11,55].

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Others have also demonstrated the positive impact of enhancing social participation by modifying environments and providing assistive devices to promote it. An interdisciplinary team worked on the codevelopment of a toolkit that brings together strategies to promote the social participation of individuals aging with spina bifida, their families, and caregivers [56]. Also, some neurological disability (ie, SCI, cerebrovascular accident) can lead to important physical disability. Another research has demonstrated the positive impact of the use of a wheelchair to improve social participation [57]. The results of this study will enable researchers, professionals, and organizations to develop health services and care in alignment with the experiences explored in this research. Thus, by acting on social participation, these studies have shown positive outcomes for seniors living with disabilities.

Limitations and Strengths

A key strength of this study is the large number of members in the organization partnerships who are involved in research and are guiding decision-making processes. Furthermore, the interviewer has clinical expertise with the populations under study in her role as a community worker. These conditions together form a strength in the implementation of this participatory research project.

Some limitations of this study are related to the health conditions regarding the neurological disability of the target populations. For example, some individuals with a TBI may be facing language disorders, such as aphasia or memory disorders. Thus, although some aging experiences with this clientele would be significant for the study, it would not be possible to transcribe the discussion or conduct an interview either.

In addition, while this study is exploratory and not intended to provide comprehensive knowledge, it will play a valuable role in informing future research and practice. The findings will contribute to a deeper understanding of the diverse experiences of aging and social participation within the population of interest, potentially paving the way for the development of best practices and evidence-based approaches in this field.

Conclusion

This project will lay the groundwork for the codevelopment of health promotion programs that support the social participation of individuals aging with a TBI, MS, or SCI. Findings can guide not only health, community, and social service professionals but also disability rights organizations, caregivers, and individuals aging with disabilities themselves in how to move toward a more inclusive vision of aging and to dismantle systematic barriers to social participation in populations facing social and health inequities.

Acknowledgments

We wish to express our sincere gratitude to our community partners, namely *Adaptavie*, *Servio*, Multiple Sclerosis Canada, and *Moelle épinière et motricité Québec*, for their commitment to individuals living and aging with neurological disorders, as well as for their support and implication in this research program.

Conflicts of Interest

None declared.

Multimedia Appendix 1
COREQ (Consolidated Criteria for Reporting Qualitative Research) checklist.
[PDF File (Adobe PDF File), 350 KB - resprot_v14i1e66963_app1.pdf]

Multimedia Appendix 2
Semistructured interview guide.
[DOCX File , 22 KB - resprot_v14i1e66963_app2.docx]

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Abbreviations

Cirris: Centre interdisciplinaire de recherche en réadaptation et intégration sociale
CIUSSS-CN: Centre intégré universitaire en santé et services sociaux de la Capitale Nationale
COREQ: Consolidated Criteria for Reporting Qualitative Research
HDM-DCP: Human Development Model–Disability Creation Process
MS: multiple sclerosis
SCI: spinal cord injury

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Protocol

Extension of the Consolidated Criteria for Reporting Qualitative Research Guideline to Large Language Models (COREQ+LLM): Protocol for a Multiphase Study

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Abstract

Background: Qualitative research provides essential insights into human behaviors, perceptions, and experiences in health sciences. The COREQ (Consolidated Criteria for Reporting Qualitative Research) checklist, published in 2007 and endorsed by the Enhancing the Quality and Transparency of Health Research Network, advanced transparency of qualitative research reporting. However, the recent integration of large language models (LLMs) into qualitative research introduces novel opportunities and methodological challenges that existing guidelines do not address. LLMs are increasingly applied to research design as well as processing, analysis, interpretation, and even direct interaction ("conversing") with qualitative data. However, their probabilistic nature, dependence on underlying training data, and susceptibility to hallucinations necessitate dedicated reporting to ensure transparency, reproducibility, and methodological validity.

Objective: This protocol outlines the methodological development process of COREQ+LLM, an extension to the COREQ checklist, to support transparent reporting of LLM use in qualitative research. The three main objectives are to (1) identify and categorize current applications of LLMs used as qualitative research tools, (2) assess how LLM use in qualitative studies in health care is reported in published studies, and (3) develop and refine reporting items for COREQ+LLM through a structured consensus process among international experts.

Methods: Following the Enhancing the Quality and Transparency of Health Research Network guidance for reporting guideline development, this study comprises 4 main phases. Phase 1 is a systematic scoping review of peer-reviewed literature from January 2020 to April 2025, examining the use and reporting of LLMs in qualitative research. The scoping review protocol was registered with the Open Science Framework on June 6, 2025, and will adhere to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines. Phase 2 will use a Delphi process to reach consensus on candidate items for inclusion in the COREQ+LLM checklist among an interdisciplinary international panel of experts. Phase 3 includes pilot testing, and phase 4 involves publication and dissemination.

Results: As of September 2025, the steering committee has been established, and the initial search strategy for the scoping review has identified 5049 records, with 4201 (83.20%) remaining after duplicate removal. Title and abstract screening is underway

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and will inform the initial draft of candidate checklist items. The COREQ+LLM extension is scheduled for completion by December 2025.

Conclusions: The integration of LLMs in qualitative research requires dedicated reporting guidelines to ensure methodological rigor, transparency, and interpretability. COREQ+LLM will address current reporting gaps by offering specific guidance for documenting LLM integration in qualitative research workflows. The checklist will assist researchers in transparently documenting LLM use, support reviewers and editors in evaluating methodological quality, and foster trust in LLM-supported qualitative research. By December 2025, COREQ+LLM will provide a rigorously developed tool to enhance the transparency, validity, and reproducibility of LLM-supported qualitative studies.

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KEYWORDS

qualitative research; large language models; LLMs; Consolidated Criteria for Reporting Qualitative Research; COREQ; reporting guideline; artificial intelligence; AI

Introduction

Background

Qualitative research serves a foundational role in health sciences by providing deep, contextualized insights into human behaviors, perceptions, and lived experiences [1-3]. Unlike quantitative approaches, qualitative studies use non-numerical methods, enabling detailed exploration and generating novel perspectives within health care [1,4]. Qualitative research encompasses diverse methodologies, predominantly involving interviews, focus groups, participant observation, and analysis of documents or artifacts, supported by analytic techniques, such as coding, thematic analysis, and content analysis [5,6].

Ensuring rigor and transparency in qualitative research requires standardized reporting guidelines. Since its publication in 2007, the COREQ (Consolidated Criteria for Reporting Qualitative Research) checklist has become widely accepted, with endorsements from organizations such as the Enhancing the Quality and Transparency of Health Research (EQUATOR) Network, and has been cited more than 30,000 times [7]. COREQ supports methodological transparency and clarity and, consequently, the interpretability and trustworthiness of qualitative findings.

However, qualitative research methodologies are evolving rapidly due to the accelerated integration of large language models (LLMs), a type of artificial intelligence (AI). These technologies introduce both unprecedented opportunities and novel methodological challenges beyond the scope of the original COREQ guidelines. LLMs, trained on extensive text corpora, generate coherent, contextually relevant text in response to user inputs (prompts) [8]. Their capacity to analyze, interpret, and generate humanlike language underpins their increasing use across qualitative research and practical applications.

The integration of LLMs into qualitative research workflows is expanding rapidly. Researchers use these models at multiple stages, including formulating research questions; designing interview protocols; supporting data processing tasks, such as transcription and translation; aiding analytic processes, such as coding and theme identification; drafting manuscript sections; and facilitating interactive dialogue with qualitative datasets [9-19]. This adoption is largely motivated by the perceived benefits offered by LLMs [20]. Notably, LLMs can enhance the speed and efficiency of data analysis by rapidly processing extensive textual datasets, enabling researchers to undertake more expansive and expedited investigations. Beyond efficiency, LLMs provide novel analytic perspectives by identifying latent semantic patterns, proposing new thematic frameworks, and distilling complex narrative content. These capabilities complement human interpretive efforts and have potential implications for reducing interpretive biases. Consequently, leading qualitative analysis software packages, including ATLAS.ti and MAXQDA, now integrate LLM functionalities [21,22].

Despite these advantages, the integration of LLMs into qualitative research introduces several methodological risks and necessitates rigorous reporting standards. Unlike conventional software tools that often rely on deterministic algorithms, LLMs function probabilistically. While adept at identifying and reproducing language patterns from training data, their semantic comprehension, particularly regarding nuanced contexts and subtexts, remains uncertain and under active scientific investigation [23]. Furthermore, because LLMs are trained on large-scale datasets that reflect statistical regularities within human language, they are susceptible to reinforcing existing biases, perpetuating dominant cultural narratives, and systematically underrepresenting marginalized perspectives [24,25]. The internal mechanisms guiding their outputs are often opaque (“black box” phenomenon), which poses significant challenges for interpretability and explainability. In addition, LLMs are prone to producing outputs that are syntactically plausible yet factually inaccurate, a behavior known as “hallucination” [26]. In the context of qualitative research, such inaccuracies may be especially difficult to detect due to interpretive depth and narrative complexity. These factors collectively introduce critical challenges to reproducibility, validity, and overall trustworthiness of qualitative research facilitated by LLMs.

Reflecting these concerns, the qualitative research community is actively debating the appropriate role and regulation of LLMs. Schroeder et al [27], after interviewing 20 qualitative researchers, highlighted an “urgent lack of norms” governing model use and advocated for tool-supported transparency. Zhang et al [28] further argued that enhancing transparency and

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deepening researchers' understanding of LLM capabilities can improve their effective use. Similarly, in a workshop involving 40 scholars, Quéré et al [29] observed that LLMs have already been integrated into many researchers' workflows; however, they emphasized the need for defined standards to assess validity and rigor that, at present, remain undefined.

The existing COREQ checklist offers insufficient guidance for navigating these complexities. Its only applicable item (item 27: "What software, if applicable, was used to manage the data?") inadequately captures essential methodological details needed to assess the implications of LLM use. Merely naming software or models used is insufficient; understanding precise use contexts, limitations, and verification strategies is crucial for evaluating research quality.

Existing reporting guidelines for AI, such as TRIPOD-LLM (Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis–Large Language Model), CONSORT-AI (Consolidated Standards of Reporting Trials-Artificial Intelligence), and SPIRIT-AI (Standard Protocol Items: Recommendations for Interventional Trials-Artificial Intelligence), primarily address areas that are not specific to qualitative research. Instead, these guidelines focus on topics such as the development or evaluation of LLMs, randomized controlled trials involving AI, and clinical trial protocols evaluating interventions with AI, respectively [30-32].

Recognizing this critical methodological gap, we are developing COREQ+LLM, a rigorous extension of the established COREQ checklist. COREQ+LLM will introduce specific reporting items essential for transparently describing and critically evaluating qualitative research incorporating LLMs. This extension aims to capture detailed methodological information, enabling a thorough appraisal of rigor, trustworthiness, and reproducibility, thereby maintaining the foundational integrity of qualitative research in the era of AI.

Objectives

The overall objective of this study is to extend the existing COREQ checklist to support transparent and responsible reporting of LLMs in qualitative research. To achieve this, we aim to (1) identify and categorize current applications of LLMs used as qualitative research tools (eg, conducting interviews, analyzing focus group discussions, and extracting themes from textual data; refer to Inclusion and Exclusion criteria section for more details), (2) assess how LLM use as a qualitative research tool is reported in peer-reviewed empirical studies, and (3) develop and refine reporting items for COREQ+LLM through a structured consensus process among international experts.

Compared with earlier natural language processing (NLP) approaches, such as statistical n-gram models or task-specific neural networks, LLMs function as general-purpose problem-solvers [33]. Their breadth of capability arises from massively scaling model parameters, training data, and compute used for training [34]. While traditional NLP pipelines were engineered for narrowly defined tasks, such as feature extraction, LLMs can generalize across an extensive array of linguistic tasks, which they were never explicitly trained to perform. Therefore, focusing the COREQ extension on LLMs is warranted on both technical and pragmatic grounds. From a technical perspective, LLMs possess generative capacities that create entirely new epistemic objects (eg, full paragraphs, code blocks, or analytic summaries) rather than merely classifying or extracting text. These capabilities introduce LLM-specific risks that are intrinsic to the model architecture, notably hallucinations and nondeterministic outputs [35]. From a pragmatic standpoint, expanding our checklist to encompass other AI modalities, such as computer vision, reinforcement learning, symbolic AI, or rule-based NLP, would render the resulting framework overly complex and risk impeding consensus among researchers. Given that qualitative research fundamentally engages with linguistic artifacts, such as interviews and documents, maintaining a language-first focus ensures that our guidance remains aligned with the empirical substrate of qualitative inquiry while avoiding an unwieldy, modality-agnostic approach.

At the same time, the integration of LLMs into qualitative research represents part of a broader trend toward the adoption of AI in qualitative research. By focusing on LLMs, COREQ+LLM provides a timely and targeted response to the most prominent and methodologically disruptive form of AI currently impacting qualitative inquiry. This extension can serve as a foundational step toward broader guidance on AI-supported qualitative research while ensuring actionable and consensus-driven reporting standards for the most immediate use cases. For these reasons, we propose the guideline extension to be titled "COREQ+LLM" rather than "COREQ+AI."

Methods

Overview

The development of the COREQ+LLM extension adheres to internationally recognized methodologies for creating health research reporting guidelines, primarily drawing upon the guideline development approach provided by the EQUATOR Network [36]. This approach aligns with precedents set by other AI-focused reporting guideline extensions, such as TRIPOD-LLM, CONSORT-AI, and SPIRIT-AI [30-32]. Recognizing the complexity and rapid evolution of LLM technologies, we use a rigorous, multiphase methodology, comprising a scoping review (phase 1) and a Delphi consensus process (phase 2). Given the rapid evolution of the use of LLMs in qualitative health research and the lack of standardization, a Delphi method allows for structured expert deliberation while integrating emergent, interdisciplinary knowledge [37]. Table 1 summarizes the research process.

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Table 1. Summary of the process for development of the COREQ+LLM (Consolidated Criteria for Reporting Qualitative Research and Large Language Models) extension.

Phase and description	Goals	Timeline
Phase 0: preparation		
Establish a steering committee consisting of clinicians, methodologists, and researchers with vast experience in qualitative data analysis and LLMs to oversee guideline development	Governance and oversight set	April 2025 to May 2025
Register extension with the EQUATOR[a] network as a guideline under development; publish the study protocol	Duplication of efforts prevented	June 2025
Phase 1: scoping review		
Conduct a scoping review in accordance with PRISMA-ScR[b] to identify health care journal articles using LLMs for qualitative research to identify potential candidate items for checklist extension and current best practices	List of potential items created (first set)	March 2025 to June 2025
Phase 2: Delphi rounds		
Conduct an online Delphi survey in accordance with DELPHISTAR[c] among multispecialty experts to assess the first set of extension candidates and collect suggestions for additional items; conduct additional Delphi rounds, as needed; ratings on a 5-point Likert scale, with consensus defined as more than 75% agreement	First set of items assessed and additional items added	July 2025 to September 2025
Hold a consensus meeting to discuss disagreements and reach a final consensus (>75% agreement) on the inclusion or exclusion of items	Consensus achieved and draft of final COREQ+LLM checklist created	September 2025
Phase 3: pilot testing and finalization		
Pilot-test the COREQ+LLM checklist with researchers conducting LLM-supported qualitative health research and revise COREQ+LLM accordingly	COREQ+LLM pilot-tested and finalized	October 2025 to November 2025
Phase 4: dissemination		
Publish COREQ+LLM in a journal and on the EQUATOR website, including an explanation and elaboration document	COREQ+LLM published and disseminated	December 2025

[a]EQUATOR: Enhancing the Quality and Transparency of Health Research.

[b]PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews.

[c]DELPHISTAR: Delphi studies in social and health sciences – recommendations for an interdisciplinary standardized reporting.

Phase 0: Preparation

This study will be overseen by a 6-member steering committee comprising AI researchers, clinicians, ethicists, experts in qualitative research methodology, and representatives for good scientific practice from Witten/Herdecke University. The protocol will be registered with the EQUATOR Network as a reporting guideline under development. The scoping review protocol was registered with the Open Science Framework on June 6, 2025 [38], and adheres to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines [39].

Phase 1: Scoping Review

Review Questions

The scoping review addresses 2 primary questions aligned with our objectives: (1) What are the current applications of LLMs as qualitative research tools? (2) What specific reporting practices are used in studies that use LLMs for conducting qualitative research?

Inclusion and Exclusion Criteria

We include peer-reviewed, discipline-agnostic articles published between January 1, 2020, and May 27, 2025, written in English, which use at least 1 qualitative method supported by an LLM for tasks beyond manuscript writing improvement. Conference presentations and abstracts are excluded.

LLM applications will be defined as instances where an LLM is used as a qualitative research tool, that is, to support or automate tasks traditionally conducted in qualitative research, such as interviewing, transcription, thematic coding, content analysis, or interpretive synthesis. We will exclude studies in which LLMs are only the subject of evaluation (eg, studies assessing model performance or accuracy) or those focused solely on perceptions, attitudes, or acceptance of LLMs. Only studies in which the LLM actively contributes to the qualitative research process will be included.

The restriction to English-language publications is based primarily on the dominance of English as the main language of publication in LLM and qualitative health research, where most of the methodological developments and applications are disseminated. To assess potential bias, we conducted a targeted search using equivalent German-language terms as a model check and found no eligible studies, suggesting that the likelihood of excluding relevant non-English literature is low.

The 5-year time frame is justified by the recent emergence and rapid evolution of LLMs. While ChatGPT (OpenAI), the most widely used generative LLM, was released in November 2022, we aim to capture not only early research involving ChatGPT

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but also earlier applications of generative LLMs, including those based on preceding models. Extending the time frame beyond 5 years is not appropriate, as the use of LLMs to support qualitative research did not exist before this period.

If the initial search strategy yields an insufficient number of peer-reviewed articles (fewer than 5 articles), we will supplement the review with preprints sourced from Scopus Preprint.

Search Strategy and Study Selection

We developed a comprehensive search strategy across the databases APA PsycINFO, PubMed, Business Source Premier, Scopus, and CINAHL, informed by an initial literature snowballing process. Keywords, synonyms, and Medical Subject Headings terms were used (see Multimedia Appendix 1). Duplicates will be automatically removed based on digital object identifiers. Three reviewers will independently screen titles and abstracts to determine eligibility, with inclusion requiring agreement by at least 2 reviewers. Data extraction will be validated by a fourth reviewer.

We will document the full study selection process, including the number of records identified, screened, assessed for eligibility, and included in the final synthesis. Reasons for exclusion at the full-text stage will also be recorded. This process will be transparently presented using a PRISMA-ScR flow diagram.

Data Analysis and Synthesis

The extracted data will include study metadata, study characteristics (eg, study aim, study design, and type of qualitative method used), the details of the LLM application (eg, model configuration, prompting approaches, and validation strategies), and the level of reporting transparency (eg, presence of statements regarding ethical considerations, LLM-specific biases, and role of LLMs' interpretive analysis). Three reviewers will independently and in parallel complete an initial round of data extraction using a specifically developed data charting form. This will be followed by a joint discussion to determine whether the form requires adaptation. In case of persistent disagreements, a fourth reviewer will arbitrate. In the second round, data will be re-extracted using the updated form to ensure consistency. Finally, all reviewers will examine the completed form, resolving any disagreements through consensus to ensure uniformity in the data charting process.

Extracted data will include study type (eg, interview, thematic analysis, and ethnography), publication year, discipline, country of origin, and detailed reporting of LLM use (eg, model version, parameter settings, use case, and prompting). The synthesis will involve frequency mapping of selected variables (eg, study metadata, characteristics, and LLM application types) and narrative summaries for others (eg, reporting transparency). Together, these analyses will provide an integrated synthesis of LLM application and reporting characteristics, informing a preliminary candidate item list for the guideline extension. Stakeholder consultation with the steering committee may be conducted to validate the candidate list before the Delphi consensus process.

Phase 2: Delphi Consensus Process

Overview

The goal of the Delphi consensus process is to systematically elicit expert judgment to validate, refine, and add items and ultimately achieve expert consensus on the content of COREQ+LLM. The Delphi process will evaluate, refine, and finalize candidate reporting items derived from the phase 1 scoping review.

Design

We will conduct a Delphi study to meet the pressing need for timely reporting guidelines in qualitative research involving LLMs. The Delphi study will be guided by the Delphi studies in social and health sciences–recommendations for an interdisciplinary standardized reporting framework recommended by the EQUATOR network for Delphi design and reporting [37,40]. Experts will independently and anonymously evaluate each candidate item and suggest additions or changes until group consensus on the COREQ+LLM reporting items is achieved. These experts are the participants of the Delphi study. Participants will be provided with structured aggregated results to help reconcile individual differences and achieve group consensus. The list of candidate items for COREQ+LLM will be collated by the steering committee based on the results of the scoping review. Items will be pilot-tested for clarity, relevance, and comprehensibility before round 1. This pretest aims to identify ambiguous wording, improve clarity, and ensure the relevance of each candidate item before round 1 [40,41]. The Delphi surveys will be hosted electronically on LimeSurvey. Information sheets and consent forms will be embedded within the platform. Delphi participants can choose to remain anonymous. Contact information is collected to provide results, invite participants to the subsequent rounds and the consensus meeting, and provide the option to be named in the acknowledgments. Contact information will be collected separately and stored independently from survey responses. Data processing will follow the General Data Protection Regulation–compliant procedures, including pseudonymization, voluntary consent, and restricted access to personal data. No identifying information will be linked to Delphi responses, and all data will be used solely for scientific purposes.

The results of the first round will be calculated as described subsequently. The steering committee will determine when to proceed to the online consensus meeting. Divergent views will be retained and analyzed by the steering committee to inform item refinement. This Delphi study adopts a constructivist epistemological stance, recognizing that consensus reflects situated expert perspectives rather than objective truth [41].

Recruitment Process and Expert Panel Selection

Delphi study participants will be identified by the steering committee via publications, professional networks of the steering committee, and snowball sampling from initial recruits. They will be vetted by the steering committee based on criteria such as publication history, methodological experience, and recognized contributions to qualitative health research. The Delphi study participants should represent geographic and disciplinary diversity, including key stakeholder groups, for

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example, researchers (particularly those conducting qualitative research in health care), health care professionals, journal editors, funders, policymakers, health care regulators, and patient advocate groups. Potential participants will receive personalized invitations via email as well as 2 reminders. The email will describe the objectives, process, and timeline of the Delphi consensus process to develop COREQ+LLM. We aim to invite at least 100 participants. In the event of low initial response or substantially attrition between rounds, we will issue additional reminders and consider extending the response window or inviting additional experts from the same stakeholder groups to maintain adequate participation and panel diversity. Participants may be acknowledged by name in project publications, if desired. Each Delphi round will remain open for 3 weeks, with reminders sent after 1 and 2 weeks.

Online Delphi Rounds

Participants will be asked to consider the following guiding principles when assessing the candidate items for exclusion or inclusion in COREQ+LLM: (1) items should be broadly applicable across qualitative health care studies using LLMs while allowing for assessment of contextual relevance; (2) items should promote transparent reporting of how LLMs were integrated into the qualitative research process, enabling understanding and potential reproducibility; (3) items should support appraisal of methodological rigor and potential biases introduced through LLM use; (4) the overall set should reflect the minimum information needed to responsibly report LLM-supported qualitative research; and (5) items should encourage ethical and epistemic accountability, including reflection on the implications of using LLMs in health research.

Participants will rate each candidate reporting item on a 5-point Likert scale as follows: “5—essential for inclusion,” “4—desirable for inclusion,” “3—neutral or unsure,” “2—rather not include,” and “1—definitely exclude” following a similar scale used in the development of TRIPOD+AI [42]. Consensus will be defined as more than 75% of participants rating an item as “desirable for inclusion” or “essential for inclusion” following internationally established consensus thresholds [43,44]. Items with 50% agreement or less will be excluded. Items with more than 75% agreement will be included in COREQ+LLM. Items with majority agreement but no consensus (>50% and ≤75%) will be merged or rephrased to be presented to the expert panel for re-evaluation in the next round. In addition, participants in round 1 can provide free-text suggestions for adding, merging, or altering items. Free-text responses will be thematically analyzed by 2 researchers and carried to round 2. Responses will be aggregated across all participants and summarized using descriptive statistics (eg, frequencies and proportions for each rating category), alongside a qualitative synthesis of the free-text comments. Participants will receive aggregated quantitative results and an anonymized synthesis of free-text responses from the previous round to inform their reassessment. We anticipate conducting at least 2 Delphi rounds. If substantial disagreement persists or many items fall within the intermediate range, a third online Delphi round will be initiated to further refine the list of candidate items.

Consensus Meeting

An online consensus meeting will be conducted to re-evaluate items from the online Delphi rounds that received the most support (>50%) but did not reach the predefined consensus threshold (>75% agreement). The primary goal of this meeting is to finalize the set of reporting items to be included in COREQ+LLM. The meeting will include a subgroup of up to 20 participants from the previous Delphi rounds, selected by the steering committee to ensure broad stakeholder representation. Before the meeting, participants of the consensus meeting will receive a detailed agenda, along with the results of the scoping review and a summary of the previous round’s findings, compiled by the steering committee. During the meeting, steering committee members will facilitate a structured discussion of each outstanding item, and participants will vote on each item using a live polling tool. To minimize bias, the live polling will be anonymous, and steering committee members will remain nonvoting. Items reaching more than 75% agreement for inclusion will be considered as having achieved consensus and included in the final COREQ+LLM checklist. During the consensus meeting, items lacking consensus will be discussed with reference to dissenting viewpoints. If consensus remains unattainable, these items may be documented as contested, along with the rationale, in the final checklist or accompanying elaboration documents. The meeting will conclude with agreement on a draft version of COREQ+LLM.

Phase 3: Pilot Testing

The steering committee will oversee the development of the COREQ+LLM explanation and elaboration document, with draft versions circulated to consensus meeting participants for review and feedback. To enhance clarity and usability, pilot testing will be conducted with 3 to 5 researchers, including PhD students, who are currently conducting qualitative research involving LLMs as a research tool. Feedback will be used to identify any items that are unclear or difficult to interpret. Participants will apply the draft checklist to a relevant study or their own work and provide structured feedback on item clarity, relevance, and ease of use. On the basis of this input, the steering committee may revise the checklist (adding, modifying, or removing items) as necessary to ensure the final version is both comprehensive and practical.

Phase 4: Dissemination

We plan to disseminate COREQ+LLM widely by publishing it in a peer-reviewed journal, presenting it at major academic and clinical conferences, and making it freely accessible to the global research community through the EQUATOR Network website [45].

Ethical Considerations

The ethics committee of Witten/Herdecke University raised no objection regarding ethical concerns (S-165/2025). Each participant will be asked to provide informed consent prior to their participation in the Delphi study. No financial incentives will be offered to participants.

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Results

As of May 2025, the 6-person steering committee to oversee COREQ+LLM development has been established (the authors of this protocol). The search strategy identified 5049 records; after duplicate removal, 4201 (83.20%) studies progressed to title and abstract screening. The title and abstract screening process is currently ongoing and will inform the initial draft of candidate checklist items. We anticipate completing the scoping review and Delphi process, along with publication of COREQ+LLM results, by December 2025.

Discussion

Anticipated Findings

The integration of LLMs into qualitative research signifies a substantial shift in methodologies for data collection, analysis, and interpretation. Without specialized reporting guidance, there is a risk to the quality, transparency, and trustworthiness of research involving LLMs. We anticipate the scoping review will reveal variability and gaps in reporting practices concerning the use of LLMs, reinforcing the need for structured guidelines. Given these challenges, we expect great stakeholder interest in the Delphi process, as the absence of clear reporting standards constitutes a considerable burden. COREQ+LLM aims to bridge this critical gap by offering a comprehensive, consensus-driven framework for transparently reporting the use of LLMs in qualitative research.

Anticipated Impact

The COREQ+LLM guideline is designed to support diverse stakeholders. Researchers will gain structured guidance for transparently documenting LLM use; peer reviewers and journal editors will have a robust tool to evaluate the completeness and methodological rigor of submissions; clinicians, policymakers, patients, and other researchers will benefit from enhanced clarity and confidence when interpreting LLM-assisted qualitative findings. Ultimately, COREQ+LLM seeks to improve the credibility, validity, and practical relevance of qualitative research using advanced LLM-supported methodologies.

Comparison to Prior Work

To the best of our knowledge and based on a review of the "reporting guidelines under development for other study designs" section of the EQUATOR Network, there are no reporting guidelines that specifically address the use of LLMs in qualitative research [46]. AI-focused extensions of reporting guidelines exist (eg, CONSORT-AI, TRIPOD-LLM, and SPIRIT-AI); however, they do not address the specific methodological implications of using LLMs in qualitative inquiry. Existing guidelines, such as COREQ, contain only minimal references to software use and do not account for the probabilistic, generative, and opaque characteristics of LLMs. COREQ+LLM addresses this gap by focusing on the use of LLMs as qualitative research tools rather than their evaluation or perception.

Strengths and Limitations

A major strength of this protocol is its adherence to EQUATOR and DELPHISTAR guidance, ensuring methodological rigor in both the scoping review (registered with the Open Science Framework [38]) and the Delphi consensus process. One potential limitation is that expert participation in Delphi studies can vary; therefore, strategies to mitigate low response rates have been included. Furthermore, the scoping review will be restricted to English-language publications, and although the steering committee will be purposefully composed to reflect diverse geographic regions and disciplines, it may not encompass all perspectives. These factors may influence the generalizability of the final checklist.

Future Directions

Upon completion, COREQ+LLM may serve as a foundation for broader extensions addressing other AI modalities in qualitative research (eg, computer vision). It may also stimulate further methodological research into the integration of LLMs and hybrid human-AI analytic workflows in qualitative research studies.

Dissemination Plan

The results from this study, including the final COREQ+LLM checklist and explanation and elaboration document, will be published in a peer-reviewed journal and submitted to the EQUATOR Network for public use (refer to phase 4: Dissemination section). Moreover, we will plan to present findings at relevant academic and clinical conferences to promote awareness and uptake across the qualitative health research community.

Conclusions

COREQ+LLM responds to the growing use of LLMs as a qualitative research tool by providing structured, consensus-based guidance for transparent reporting. This protocol outlines a rigorous, multiphase development process that combines systematic evidence synthesis with expert consensus through a Delphi process. The resulting guideline aims to enhance trust, reproducibility, and methodological transparency in LLM-assisted qualitative research.

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Authors' Contributions

LF contributed to conceptualization, methodology, reviewing and editing the manuscript, supervision, and project administration. JF contributed to methodology, writing the original draft, reviewing and editing the manuscript, data curation, and resources. CK contributed to data analysis (literature review) and reviewing and editing the manuscript. PAT contributed to methodology, supervision, reviewing and editing the manuscript, and validation. PR contributed to methodology, writing the original draft, reviewing and editing the manuscript, data curation, and resources. SM contributed to methodology, reviewing and editing the manuscript, and validation. All authors read and approved the final manuscript. LF, JF, and PR contributed equally to this work as first authors.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Overview of the search strategy.
[PDF File (Adobe PDF File), 129 KB - resprot_v14i1e78682_app1.pdf]

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Abbreviations

AI: artificial intelligence
CONSORT-AI: Consolidated Standards of Reporting Trials-Artificial Intelligence
COREQ: Consolidated Criteria for Reporting Qualitative Research
EQUATOR: Enhancing the Quality and Transparency of Health Research
LLM: large language model
NLP: natural language processing
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
SPIRIT-AI: Standard Protocol Items: Recommendations for Interventional Trials-Artificial Intelligence
TRIPOD-LLM: Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis-Large Language Model

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Protocol

Intergenerational Cooperation at Work to Promote Inclusion and Healthy Participation of Older Workers in the Foodservice Sector: Protocol for a Qualitative Study

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Abstract

Background: Increasing intergenerational coexistence in the job market may heighten the risk of intergenerational conflicts, which can negatively impact the inclusion and healthy participation of older workers. The foodservice sector is characterized by significant intergenerational coexistence, reinforced by the presence of student workers. According to the literature, practices promoting intergenerational cooperation can reduce the risk of conflict and contribute to a healthier work climate.

Objective: The main objective of this research project is to propose a prioritized list of intergenerational cooperation practices to promote the inclusion and healthy participation of older workers in the foodservice sector.

Methods: This project will be carried out in 2 stages. The first stage will use a descriptive interpretative design based on the photo-elicitation method to identify intergenerational cooperation practices from the perspective of older workers. The second stage will use the Technique for Research of Information by Animation of a Group of Experts method to obtain a group consensus among professionals, managers, and researchers to prioritize the identified practices.

Results: The first stage of this project is underway. The study has been funded by the Quebec Network for Research on Aging since September 2024. Participant recruitment began at the end of January 2025, following ethics committee approval, and ended in May 2025. In total, 12 participants were recruited for stage 1. The data collected are currently being analyzed, and the results are scheduled to be submitted for publication in 2026.

Conclusions: On a theoretical level, this project will propose a list of practices promoting intergenerational cooperation at work in the foodservice sector, giving a voice to older workers to better understand their perspectives. This project will also offer a prioritization of those practices, based on the perspective of different actors (researchers, professionals, and managers of the foodservice sector). On a practical level, this knowledge will help the actors of the foodservice sector to integrate these practices into their organizations to promote the inclusion and healthy participation of older workers.

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KEYWORDS

intergenerational cooperation at work; older workers; healthy participation; inclusion; foodservice sector; photo-elicitation; focus groups; TRIAGE method; Technique for Research of Information by Animation of a Group of Experts

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Introduction

Background

Older workers, aged 55 years and older, are an increasing part of the workforce in Canada [1,2]. For example, in the Canadian province of Quebec, more than 20% of workers are aged 55 years or older [1]. The number of young workers has never been so low compared to older ones [1]. Nearly 75% of workers aged 55 to 59 years were active on the job market in 2021, compared to 55% in 2001 [3]. Given labor shortages, lower birth rates, the rise in life expectancy, and their growing proportion in the current workforce, older workers are in high demand to fill vacancies across all sectors [2,4]. The foodservice sector is one that has been particularly affected by the labor shortage in recent years [5]. Nearly 46.3% of businesses in the hospitality and foodservice sector forecast difficulties in recruiting staff in 2022 in Canada [6]. As a result, many restaurants have had to reduce their opening hours and implement strategies to attract and retain staff, such as increasing salaries [7,8]. These ongoing labor shortages, which have been growing for several years in the sector, have raised concerns about job insecurity [5] and continue to pose challenges today [9]. Hiring or helping older workers stay employed is seen as one of the solutions to address these shortages [2,10]. Although the foodservice sector is predominantly made up of young adults, it also includes 14% of older workers [9]. Those workers often work alongside colleagues aged between 15 and 24 years (44%) [11], illustrating a high degree of intergenerational coexistence at work, which can sometimes be challenging. How could this coexistence be eased in this sector? This is what we aim to explore in this study.

Depending on the legal or national context, up to 6 generations may coexist in today's labor market: the Traditionalists, the Baby Boomers, and Generations X, Y, Z, and Alpha [12]. This intergenerational diversity can be beneficial on several levels, as organizations can benefit from a variety of perspectives [13]. However, this diversity can also increase the risk of intergenerational conflict, which can be defined as disagreement or tension between people of different generations [14,15]. Such conflicts may arise from various factors such as age-related prejudices [16,17], stereotyping or discrimination [18], perceived differences [19], conflicts of values, differences regarding work representation [20], communication and learning style differences [13], or even rivalry between members of different generations [15]. Some authors argue that these conflicts are rooted in real differences in values and perspectives, while others suggest that they may stem more from perceived differences. Despite government policies against discrimination in the workplace, ageism remains a persistent issue [21]. In the foodservice sector, which is predominantly made up of young workers, age discrimination is still observed in recruitment, training, and job retention [22,23].

Intergenerational conflicts can undermine the inclusion and healthy participation of older workers. Ageism and conflicts may lead to reduced job satisfaction, lower engagement, and diminished self-esteem among older employees, who may begin to question their professional competencies [14,24]. Such tensions may reduce collaboration between age groups [14], causing generational fragmentation that limits knowledge transfer, team cohesion, and support between colleagues, an important psychosocial factor. Increased psychosocial risks are associated with adverse outcomes such as absenteeism, injuries, and early retirement among older workers [25]. The foodservice sector is particularly exposed to these stressors, including irregular hours, high service pressure, demanding customer interactions, and cognitive overload [26,27]. Promoting intergenerational cooperation is seen as a promising strategy to mitigate the risk of intergenerational conflict and foster inclusion and healthier work environments [18,20,28].

Some intergenerational cooperation practices have been identified in the literature (eg, reverse mentoring, proactive intergenerational management model, and career legacy circle) [18,29]. However, such practices are not always well-established in workplaces, as organizations may fear not being able to manage significant changes, inadvertently favor one generation over another, or create tensions between generations if these practices are not properly implemented [18].

While there is some evidence on key guidelines for intergenerational cooperation in the workplace, the current literature lacks insights into concrete practices that various actors can implement to reduce intergenerational conflict and promote the inclusion and healthy participation of older workers. Although intergenerational cooperation has been studied across various fields, including nursing [30], education [31], transportation [32], and computer science [33], the foodservice sector remains largely unexplored in this regard. Many studies examine generational trends from the perspective of customers [34,35], but few have addressed the intergenerational experiences of workers themselves [36].

General and Specific Objectives

The general objective of this research project is to propose a prioritized list of intergenerational cooperation practices to promote the inclusion and healthy participation of older workers in the foodservice sector. To achieve this, two specific objectives were set: (1) to identify individual, collective, organizational, and societal practices that foster intergenerational cooperation at work (ICW) and (2) to prioritize these practices for implementation in the foodservice sector.

Conceptual Framework

Intergenerational Cooperation at Work

This project is based on the concept of ICW. Given that the existing literature provides limited concrete definitions to better understand and apply this concept in professional settings, we started by examining its meaning in the context of a previous study that specifically focused on its analysis. In that study, we proposed a definition of the concept [37]:

> *Intergenerational cooperation at work (ICW) can be defined as the achievement of social cohesion within intergenerational teams committed to a common goal, through their interaction, knowledge sharing, mutual support, understanding and acceptance of their differences, in a process of intentional change supported by the organization. ICW thus implies the*

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inclusion of all generations in a healthy work environment that promotes intergenerational equity, trust, and respect. It requires the involvement of all actors, who must be convinced of its importance.

Although introducing ICW in an organization takes time, its potential benefits are significant. ICW can improve the organizational climate, employee motivation, satisfaction, and well-being [18]. For the organization, this translates into improved knowledge transfer, team efficiency, and productivity [38,39]. In addition, this conceptual work highlighted the role played by various actors in the workplace in enabling intergenerational cooperation, showing that the individual worker, the work team, and the organization must all contribute to this collective effort. Society may also have a role to play in implementing measures that support such cooperation and fostering the inclusion of older workers [40].

As part of this project, the definition of ICW will be shared with all participants involved in this project to ensure a common understanding of the concept. A shared understanding minimizes the risk of divergent interpretations that could affect the quality and consistency of the data collected. This definition will also serve as a framework for coding and interpreting the results, ensuring that the analysis is grounded in a consistent and shared interpretation of intergenerational cooperation.

Intergroup Contact Theory

This project is also grounded in Allport's [41] theory of intergroup contact, which posits that bringing individuals from heterogeneous groups together can reduce stereotypes and prejudices by improving attitudes toward one another, provided 4 conditions are met [42]. First, group members must have equal status. Second, they must be able to cooperate, meaning there should be no competition between them. Third, they must work toward common goals. Finally, they must benefit from institutional and societal support that encourages their interaction. Applied to an intergenerational context, this theory suggests that pairing people from different generations at work and encouraging them to collaborate toward shared objectives could improve the work environment by reducing prejudice and stereotypes. In this way, their frequent interactions would help them understand and accept each other's differences [42]. Given the challenges previously identified, such as intergenerational conflict and ageism in the workplace, Allport's theory provides an appropriate framework to address these issues by fostering positive intergenerational contact. Furthermore, a study by Firzly et al [43] applied this theory in their research on ageism at work, knowledge sharing, and job satisfaction, exploring how age-related intergroup relations affect younger workers' perceptions of older colleagues. This theory has also been applied by numerous researchers examining intergenerational relations in workplace settings, demonstrating that high-quality intergenerational contact can positively influence attitudes and help reduce ageism at work [44-46]. This conceptual framework will allow for a more comprehensive and nuanced analysis of the intergenerational cooperation practices identified in the study. In our analysis, we will pay particular attention to the conditions outlined by Allport (eg, presence of hierarchy, competition, shared goals, and organizational support) and how they may influence intergenerational dynamics.

Methods

Study Design

This research project will be carried out in 2 stages, as shown in Figure 1, which presents the process and how its components are interconnected. The first stage involves a photo-elicitation study to identify intergenerational cooperation practices, carried out in 4 steps. The second stage, based on the Technique for Research of Information by Animation of a Group of Experts (TRIAGE) method, aims to prioritize these practices in 4 phases as well.

Figure 1. Stages of the research project. TRIAGE: Technique for Research of Information by Animation of a Group of Experts.

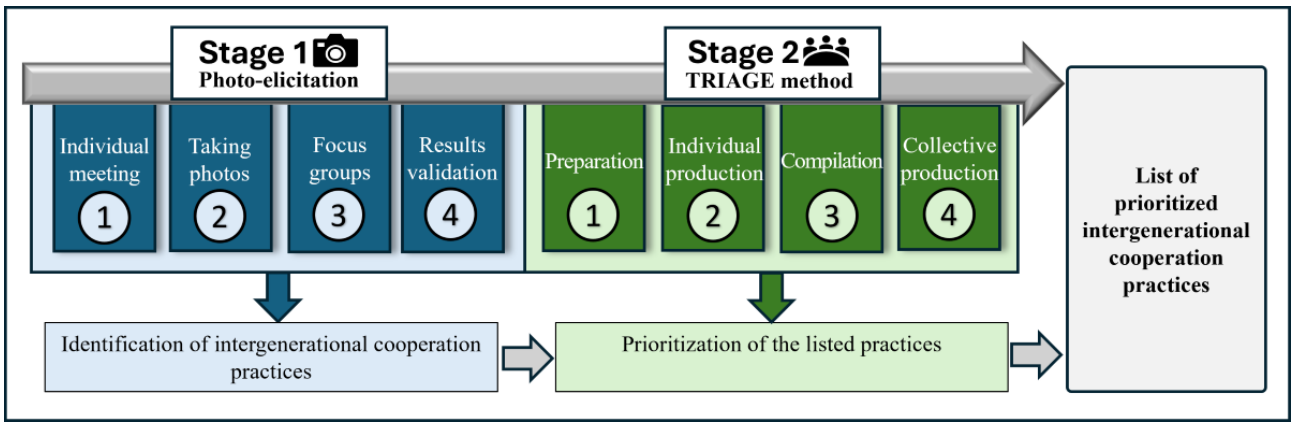

Stage 1: Identification of Practices That Promote or Hinder Intergenerational Cooperation

Design

A qualitative research design of the descriptive-interpretive type will be used to conduct this project, based on the photo-elicitation method. The descriptive-interpretive approach is used to gather participants' perspectives in order to understand the meaning they assign to the phenomenon they experience [47]. The photo-elicitation method involves using photographs to enrich qualitative interviews [48]. First described by Collier [49], this method was originally used in anthropology and sociology before expanding into fields such as public health, education, and health care [48]. This approach will allow us to

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explore older workers' perspectives on practices that promote or hinder ICW, providing access to images that evoke their personal narratives. This, in turn, makes it possible to observe elements that might be difficult to capture using more conventional methods [50,51]. The photo-elicitation method will also enable us to consider each participant's unique perspective by allowing them to share their knowledge and experiential insights, thus fostering the participation and engagement of older workers in the research project [50]. The photo-elicitation method will be combined with focus groups to discuss the corpus of photographs. The project will also adopt an intersectoral approach, combining the experience of researchers from various fields, including health, social sciences, and engineering. Given that the concept of intergenerational cooperation spans various domains and can impact workers' health, social relations at work, management practices, and even the use of technology, it is crucial to embrace this approach.

Participants

In line with evidence-based recommendations, we plan to conduct focus groups consisting of 6 participants each. The recommended number of participants for focus groups typically ranges from 5 to 12, allowing everyone sufficient time to share their views and ensuring diverse perspectives on the topic being explored [52]. The literature also suggests conducting at least 2 focus groups to ensure comprehensive coverage of the topic [52]. According to Guest et al [53], conducting 2 to 3 focus groups typically covers over 80% of the topics under study. Several aspects of our approach support early saturation [53]: the use of a semistructured interview guide, the clear and shared understanding of the research topic among participants, and the triangulation of data through participant-generated photographs. While the foodservice sector is diverse, our sample is relatively homogeneous in key aspects: all participants are older workers operating in the same sector, from the same region, and with similar levels of education. Moreover, the analytical framework is based on predefined categories (individual, collective, organizational, and societal practices), which allows for systematic and focused coding. However, in line with an iterative approach, the final number of participants will be determined by data saturation, which will be reached when the most significant elements related to our research topic have been covered during the focus groups [53].

Recruitment is ongoing. Participants are selected based on their interest in the study and meeting the eligibility criteria. They could come from both the commercial and noncommercial foodservice sectors. The commercial sector refers to establishments where food sales are the primary objective (eg, restaurants), while the noncommercial sector includes organizations where foodservice supports another main mission, such as long-term care facilities. The eligibility criteria are (1) being at least 55 years of age, (2) working in the foodservice sector, and (3) working with colleagues younger than 25 years of age.

This last criterion reflects our desire to ensure a workplace environment where different generations work closely together. While intergenerational coexistence may include generations that are relatively close in age, intergenerational conflicts tend to arise more when age differences are perceived as salient [54]. This generational threshold was chosen to maximize intergenerational contrast and explore salient dynamics or forms of cooperation between age groups while still allowing participants to reflect on their interactions with younger colleagues from a range of age groups. Furthermore, by highlighting the experiences and perspectives of older workers, we sought to better understand the barriers they face as well as the solutions they themselves propose to support their inclusion and healthy participation. There are no exclusion criteria. Since 56% of restaurant workers are women and 44% are men [55], we aim for gender diversity that reflects the industry's reality.

Participants are recruited in collaboration with the Conseil Québécois des Ressources Humaines en Tourisme, a sectoral workforce committee dedicated to the tourism industry, through the dissemination of a recruitment poster on their social media platforms. This poster is also shared via the research team's own social media channels. Interested participants are invited to contact us by email. Word-of-mouth also assists in the recruitment process. Additionally, door-to-door canvassing in both commercial and noncommercial food service establishments in the Montérégie-Ouest region of Quebec further supports recruitment efforts. To ensure representative diversity within the foodservice sector, recruitment takes place in several cities across Montérégie-Ouest, including both urban and rural settings. Special attention is given to the selection of establishments to include various types of foodservice (fast food, full-service restaurants, and noncommercial food services). To reach individuals with varying employment statuses (full-time, part-time, day, or evening shifts), door-to-door visits are scheduled across a range of time slots, including weekdays, weekends, daytime, and evening hours. Cultural diversity is also sought by selecting establishments located in areas known for their ethnocultural plurality. The research team verifies participants' eligibility based on the pre-established inclusion criteria via email or phone.

Procedure

Stage 1 consists of 4 steps (see stage 1 in Figure 1). The first step involves an initial one-on-one meeting with each participant. Once participants who meet the inclusion criteria are recruited, a time slot is scheduled for a face-to-face meeting based on their availability. Each participant is met individually at a location of their choice. During this meeting, the project is presented, and key concepts related to the study are defined. For example, the concept of ICW is explained to ensure a shared understanding. The study's objectives and the photo-elicitation method are also discussed. Participants are provided with a disposable camera, and instructions are given to ensure that they are comfortable using it. A cellphone cannot be used to take the photos for reasons of hygiene and ethics. This meeting also serves as an opportunity to complete the information and consent form, as well as the sociodemographic questionnaire. This questionnaire contains questions about participants' education, cultural or ethnic background, geographic location, and any disabilities. The second step involves photo-elicitation. Each participant is asked to take photos, with the disposable camera, over a 2-week period, of key elements, objects, or moments they believe either promote or hinder ICW. Photos

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may be taken at the workplace or outdoors. The location is secondary to the meaning the participant wishes to convey. For ethical reasons, no identifiable faces may appear in the photographs. This photo-taking process includes a prephotographic reflection, during which participants consider what they wish to capture, followed by a postphotographic reflection, where they contemplate how they want the image to be interpreted. To support the feasibility of the process, participants are encouraged to focus on a limited number of photos, ideally around 5, for the focus group. The photos are then developed and digitized. Since the photographs are taken using disposable cameras, the research team is responsible for developing and securely storing the materials, ensuring both the security and anonymity of the images. The photos are kept on a protected, secure institutional platform. Any photos containing identifiable features are anonymized through blurring. Verbal consent from the employer to the participant is required to allow photographs to be taken in the workplace, as specified in the information and consent form that the participant reads and signs. Participants are advised that they must adhere to their employer's policies and directives related to taking photographs in the workplace.

The third step involves the focus group discussions, which are held remotely and scheduled based on each participant's availability. Each session lasts approximately 120 minutes, as the recommended duration for focus groups is between 90 and 120 minutes, allowing sufficient time to explore the topic while maintaining participant engagement [52]. If the participant is unable to take part, experiences technical difficulties, or does not have access to the necessary technology, an individual interview will be conducted with this person. During the discussion, participants are invited (1) to respond to questions from a semistructured interview guide covering themes related to ICW and (2) to share their thoughts and reactions to the set of photos, reflecting on what these images represent to them. The semistructured interview guide was developed by 2 members (CC and AL) of the research team and validated by the rest of the team to ensure methodological rigor [56] and an intersectoral perspective. In addition, it was pretested with 2 individuals who share similar characteristics to the study participants. The guide includes questions focused on individual, collective, organizational, and societal practices that may promote or hinder intergenerational cooperation. For example: "Tell me about practices that can be implemented by workers, individually, to promote intergenerational cooperation in your workplace." Photos serve as the primary discussion material, with the guide offering questions related to the images (eg, "What do you think this image illustrates?") to help participants express their thoughts and reactions.

The final step involves offering participants the opportunity to provide feedback following the preliminary data analysis. This step is optional. The main preliminary findings will be compiled into a nonpersonal document and sent to participants for their feedback, should they choose to provide it. Their feedback will help enhance the credibility of the results by confirming that they accurately reflect participants' own words [56].

Analysis

First, verbatims will be transcribed from the audio and video recordings of the focus group discussions. A thematic analysis strategy will then be applied to identify and classify emerging themes [57]. The data from both focus groups will be coded based on related ideas. Initially, the data will be categorized based on whether they represent individual, collective, organizational, or societal practices. Further categories will be developed to define emerging concepts and the relationships between them. The raw data will be reviewed multiple times and interpreted using mainly an inductive approach. Theme identification and the development of the thematic tree will follow a continuous thematization approach, ensuring rigor and a rich analysis [57]. The thematization will be supported by NVivo software (Lumivero). Two evaluators will initially analyze the data independently. They will then meet to compare results, resolve discrepancies through discussion, and adjust the categorization based on shared interpretations. This collaborative process will strengthen the analytical rigor and minimize interpretive bias [58]. In case of disagreement between the 2 evaluators during the analysis, a third evaluator (AL) will be consulted to reach a final decision. The Government of Canada's Gender-Based Analysis Plus approach will be used to assess the potential impacts of the identified practices, considering various identity factors [59]. This approach promotes inclusivity through an intersectional lens, considering dimensions such as disability, culture, education, socioeconomic status, sexual orientation, and geographic location [59]. During the thematic analysis, the Gender-Based Analysis Plus approach will be integrated into both coding and interpretation processes. Coding will involve identifying themes that reflect participants' experiences in relation to identity factors. These themes will then be interpreted by linking them to participants' sociodemographic profiles. This process will help reveal how these dimensions may influence participants' perceptions and experiences related to the issue under study.

In summary, stage 1 of this project will generate a concrete list of individual, collective, organizational, and societal practices that promote intergenerational cooperation with a focus on inclusion and the healthy participation of older workers.

To support effective implementation in workplace settings, it is essential to prioritize this list of practices, providing relevant actors with clear guidance on where to begin. Step 2 of the project will therefore focus on enabling the prioritization of the practices identified during the first phase, through a group of researchers and professionals who will validate and rank the list accordingly. The final list will thus be more robust and will have fostered a dialogue between professionals and researchers.

Stage 2: Prioritization of the Identified Practices of Intergenerational Cooperation

Design

The TRIAGE method will be used to complete this stage. The aim of the method is to achieve a group consensus [60,61]. Originally developed in the field of education, the TRIAGE method is now applied in rehabilitation and health care [61,62]. It is particularly well-suited for prioritizing elements among

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multiple choices [60]. For instance, some researchers have used the TRIAGE method to prioritize elements in a research process related to the needs of caregivers of older adults [63]. The method differs from other consensus techniques, such as the nominal group technique, which focuses more on generating new ideas, and the Delphi method, an iterative process involving several rounds to reach consensus on complex issues [61,64].

Participants

In total, 8 individuals with relevant knowledge will be recruited to participate in the TRIAGE process, in accordance with the literature, which recommends 6 to 12 participants [61]. To address potential participant withdrawal, additional potential participants will be identified in advance and may be invited to join if needed, ensuring that group dynamics and diversity are preserved throughout the study. For this study, we will select individuals with specific knowledge in either management or aging. It would be particularly valuable to include those with experience in foodservice management or researchers with knowledge in intergenerational issues. The goal is to gather diverse perspectives while maintaining a sufficiently homogeneous group to support effective group dynamics [61]. Purposive sampling will be used, as participants will be intentionally selected based on their knowledge and skills related to the study subject [61]. The inclusion criteria are as follows: (1) being a researcher, manager, or professional and (2) having relevant knowledge in management or aging.

Efforts will be made to ensure a diverse and complementary representation of individuals, including both those with knowledge of aging and those with experience in management.

Considering the range of target groups in this study, multiple recruitment strategies will be used:

- For the recruitment of researchers: Potential candidates will be identified by reviewing scientific publications related to management and aging. An email, including a recruitment poster, will be sent to individuals with relevant academic knowledge. Word-of-mouth will also help identify researchers through academic networks. Participants may suggest other individuals with similar experience [60].
- For the recruitment of managers and professionals: A recruitment poster will be shared via the research team's social media platforms and in online communities targeting foodservice professionals. Word-of-mouth will further support the recruitment of professionals within the community. Additionally, foodservice managers will be approached directly through an outreach strategy such as door-to-door canvassing.

Procedure

The TRIAGE method consists of 4 phases (see stage 2 in Figure 1) [61]. The first phase, known as "preparation," is the longest for the research team [61]. During this phase, the research question to be explored is defined. In this study, this question could be formulated as follows: "Which intergenerational cooperation practices should be prioritized in the foodservice sector?" This phase also involves participant recruitment. To support this process, 3 key documents will be prepared: a cover letter, a preparatory document, and a questionnaire [61]. The cover letter will provide general information about the study and its procedure. The preparatory document will support participants' reflection by outlining the study's objectives, defining intergenerational cooperation, and presenting an overview of the TRIAGE method [61]. Finally, the questionnaire, designed to be completed by participants, will serve as the basis for the group session. It will be divided into 2 sections. In the first section, participants will review the practices identified in stage 1, organized into 4 categories: individual, collective, organizational, and societal. Participants will be asked to read all practices listed within a category, rate each one on a scale from 1=priority practice to 5=nonrelevant or unrealistic, and justify their choices. Based on this reflection, they will then rank the practices within each category in order of priority. In the second section, participants will identify the 3 most important practices overall, regardless of category, and may also propose additional practices they believe should be considered. These documents will be pretested with 2 individuals who share similar characteristics to the participants [61]. Once finalized, they will be sent out to participants to initiate the second phase [61].

The second phase, known as "individual production" [61], will be conducted remotely. During this phase, participants will receive and review the preparatory documents. After reading the materials, they will be asked to reflect individually on the questions posed and provide answers based on their experience, as outlined earlier [60]. The aim is to collect participants' individual perspectives on the proposed practices and to determine which ones they consider most important for prioritization in the foodservice sector.

The third phase, known as "compilation" [61], will begin once the questionnaires have been completed by the participants. The research team will collect and transcribe the responses onto cards [61]. These answers will be transcribed verbatim to accurately reflect the participants' input, allowing them to recognize their own answers, even though the cards will remain anonymous [61]. To ensure anonymity and improve organization, the cards will be arranged alphabetically [61]. All responses will be included, even those with noticeable repetition [61].

The fourth phase, referred to as "interactive production" [62] or the "group production phase" [60], involves an in-person meeting with all participants. This phase is typically conducted face-to-face; however, in cases of logistical constraints (eg, geographic distance), it may be held virtually using a shared interactive board, as illustrated in the work of Porro et al [65]. The session will last between 2 and 3 hours to allow enough time for discussion while maintaining participants' attention [61]. The goal of this meeting is to reach a consensus on the prioritization of the intergenerational cooperation practices identified earlier [62]. If the session is held in person, participants will sit around a table facing a board that displays all the individual answers collected on cards [61,62]. Figure 2 shows the different sections of the board that will be presented to participants (collective memory, selection, trash, fridge, veto, and grouping), where individual answers will be discussed. The cards will be presented in the "collective memory" section on the board [61]. Participants will decide, by consensus, whether

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to keep a practice ("selection" section) or discard it ("trash" section) if there is agreement [61]. The "grouping" section, for its part, allows them to cluster similar ideas, divide or refine them, or add new ideas that emerge during the discussions. If consensus cannot be reached on a specific practice, it may be set aside temporarily ("fridge" section) to be revisited later or completely discarded ("veto" section) if no agreement is reached [61]. Thus, the objective will be to place all the practices in a priority order in the "selection" section based on the consensus of the participants. To ensure balanced participation during the focus groups, 2 facilitators will be present: one will guide the discussion, while the other will monitor speaking time to promote equitable contributions and actively encourage input from quieter participants, thus mitigating the risk of dominance by any subgroup.

Figure 2. Visual representation of the TRIAGE process. TRIAGE: Technique for Research of Information by Animation of a Group of Experts.

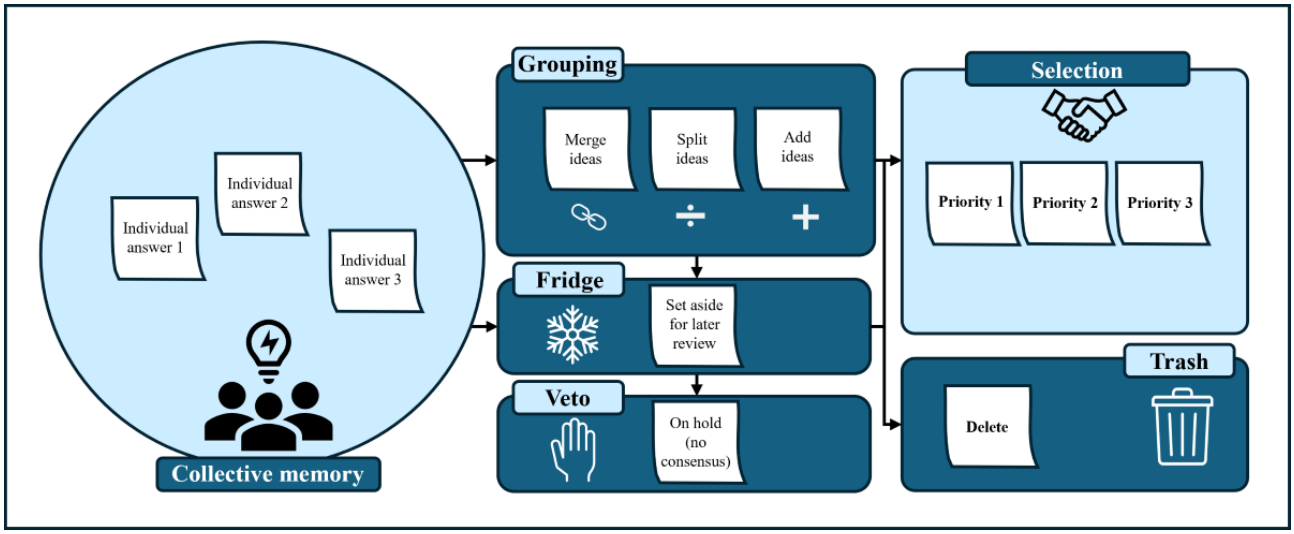

As this study uses the TRIAGE method, no scoring or ranking system is applied. The method relies on group discussions and the consensus reached among participants rather than on numerical evaluation. Practices placed in the "selection" section reflect this consensus, emphasizing collective agreement. This shared agreement thus represents the operational consensus threshold for this process.

Analysis

Conducting an initial content analysis of the responses from the individual production phase will help identify similarities and divergences [60]. In addition, this method allows for relatively quick data analysis, as the prioritization of practices will be validated by the participants through the consensus reached during the discussions [60,61]. Consequently, results can be accessed immediately after the discussion, provided consensus is reached, by transcribing the answers from the "selection" section of the board.

Ethical Considerations

Our study was approved by the research ethics committee on rehabilitation and social integration of the Centre Intégré Universitaire de Santé et de Services Sociaux de la Capitale-Nationale (approval: 2025-32-58) as well as by the research ethics committee for human research of the Université du Québec à Trois-Rivières (approval: CER-25-317-10.02) on January 14, 2025. The information and consent form are presented and explained to participants, who then complete it to provide informed consent. Participants are reminded that they may withdraw from the study at any time. All data collected in this study are coded to ensure the confidentiality of participants' information. They receive compensation of CAN $100 (approximately US $71) for the time they dedicate to the research project.

Results

Our project has been funded by the Quebec Network for Research on Aging since September 1, 2024. Participant recruitment began in late January 2025, following ethics committee approval. Recruitment of the 12 participants for stage 1 of the study was completed in May 2025. Data analysis is currently underway. Results for this stage are expected to be submitted for publication in 2026.

Discussion

Anticipated Impacts of the Research Project

On a theoretical level, this project will provide a prioritized list of practices that promote ICW, with the aim of supporting the inclusion and healthy participation of older workers in the foodservice sector. This list will contribute to advancing knowledge on such practices and will be categorized according to the actors involved. The results may also serve as a foundation for further research, particularly on the impacts of implementing these practices into the foodservice sector, for instance.

On a practical level, this knowledge could support implementation efforts within workplaces, thereby influencing the health and well-being of older workers. Integrating these practices may also promote the retention of older workers by reducing age-related biases and stereotypes, improving the work climate, and minimizing intergenerational conflicts. In turn, enhancing the participation of older workers in the workforce could help address labor shortages, yielding benefits from a

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societal perspective as well. Given the ongoing labor shortage, exploring such solutions is essential, and mobilizing the older workforce is a strategy currently being considered and applied within the foodservice sector [9].

Giving a Voice to Older Workers

On one hand, this study will shed light on the perspectives of older workers, contributing to a deeper understanding of intergenerational dynamics in the foodservice sector. Given that few, if any, studies have specifically explored their point of view on this topic, the first stage of the project will offer these individuals an opportunity to express their experiences. The use of photo-elicitation further supports this aim by engaging participants who might not typically take part in traditional question-based research, thus representing a meaningful form of inclusion. In doing so, this study will expand our understanding of the practices that either facilitate or hinder intergenerational cooperation at different levels (individual, collective, organizational, and societal) based on participants' lived experiences. The photo-elicitation method also promotes active engagement in the research process [51,66] and enhances reflexivity by stimulating more cognitive domains than verbal discussion alone [67]. Additionally, participants' pre- and postphotographic reflections will enrich the dialogue during the focus groups.

Adding the Perspective of Individuals With Relevant Knowledge

The TRIAGE method gathers insights from a diverse group of individuals with substantial experience and knowledge in management or aging. Building on the practices identified by older workers, these participants will engage in group discussions to determine which practices should be prioritized in the foodservice sector, drawing on their knowledge. These discussions will foster rich exchanges and support consensus-building, ensuring that the final list of practices is both practical and aligned with the realities and specific needs of the foodservice environment.

Limitations

The results of the first stage of this study will be based on the photo-elicitation method, which involves participants independently taking photographs over a 2-week period using a provided disposable camera. However, certain limitations may arise if the camera is lost or damaged or if participants forget to take photos during the designated time frame. In such cases, participants will still participate in the focus group, drawing on their own reflections and photographs taken by other participants. In addition, since focus groups require participants to meet at the same time, they will be conducted online to reduce geographical barriers. However, this approach assumes that participants have access to a computer or smartphone and feel comfortable using this format. In addition, door-to-door recruitment may introduce a bias in terms of the representativeness of the diversity within the foodservice sector, as it involves selecting a specific region, which limits the ability to reflect the realities of all regions across Quebec. Furthermore, the absence of younger workers' perspectives represents a limitation, as it restricts the scope of our conclusions to the experiences of older workers. It would be valuable in future research to carry out a similar exploration with younger workers.

The results of the second stage of this study will be based on the TRIAGE method. Like any method, TRIAGE has both strengths and limitations. Its effectiveness depends on the facilitator's ability to guide the group discussion and the participants' perspectives [61]. Additionally, the presence of all participants during the interactive production phase is essential, which can be challenging, particularly due to geographical constraints. In such cases, a virtual format will be used [65]. Moreover, if a participant completes the individual production but is unable to attend the interactive production, this may pose difficulties, as the facilitator and other participants could struggle to fully grasp the nuances of that participant's contributions presented on the cards.

Conclusions

Given the aging population and the ongoing labor shortage, it is essential to explore practices that promote the inclusion and retention of older workers in the labor market. In today's multigenerational workforce, attention must be paid to the impact of intergenerational conflicts on the well-being and health of older workers while also considering the potential benefits of generational diversity, particularly when collaboration is effective. The foodservice sector, which has been especially affected by labor shortages in recent years and is experiencing increased intergenerational coexistence, provides a particularly relevant context for addressing these issues. Therefore, the prioritized list of practices promoting intergenerational cooperation that this project seeks to develop represents an important step in this direction.

Funding

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Authors' Contributions

CC, AL, and MML reflected on this study protocol. CC and AL drafted this study protocol. MML thoroughly reviewed the manuscript and made revisions to enhance its quality. The manuscript was submitted after all authors approved the final version.

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Conflicts of Interest

None declared.

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Abbreviations

ICW: intergenerational cooperation at work
TRIAGE: Technique for Research of Information by Animation of a Group of Experts

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Protocol

The Mental Health of Farmers and Farmworkers Impacted by Flooding and Drought: Protocol for a Mixed Methods Study

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Abstract

Background: Farmers and farmworkers in England are a population group who are particularly vulnerable to the mental health impacts of environmental stressors, including flooding and droughts. While international studies, particularly from Australia, have examined these impacts, there is a critical gap in understanding the mental health consequences of such events for England's farming community. This gap is particularly concerning given the increase in frequency and severity of flooding and drought events due to climate change, which will have significant repercussions for the mental well-being of those whose livelihoods depend on affected land.

Objective: This study aims to investigate the mental health impacts of flooding and drought events on farmers and farmworkers in England. It will examine how these events affect their livelihoods and explore both compounding and mitigating factors associated with mental health challenges.

Methods: A mixed methods approach will be used, beginning with a national online survey distributed via trusted intermediary agricultural organizations from January 2025 to March 2025. The survey will include the Warwick-Edinburgh Mental Wellbeing Scale to assess participants' mental well-being. A subset of respondents will be selected for follow-up semistructured interviews in late 2025 to early 2026 to gather more in-depth data. Data will be thematically analyzed, allowing for the identification of key patterns in mental health impacts, coping mechanisms, and resilience-building strategies.

Results: Survey and interview data will be analyzed during 2025 and 2026 to identify themes and patterns related to the mental health challenges faced by the farming community. This will include exploring coping mechanisms, support networks, and resilience-building strategies, with findings used to inform national interventions. Data obtained from the Warwick-Edinburgh Mental Wellbeing Scale component will be assessed against results from existing studies that have used the scale for other population groups to provide comparative results.

Conclusions: Findings from this study will inform the development of health protection interventions, supporting the farming community in building resilience to future flooding and drought events. This study will also provide valuable insights into the mental health impacts of flooding and droughts in England, contributing to the growing international research on the mental health effects of climate change.

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KEYWORDS

mental health; well-being; flooding; drought; water; resilience; climate change; agriculture; farming

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Introduction

Background

Exposure to flooding and drought events is already an increasing issue for health and well-being in the United Kingdom. This trend is expected to continue because of further climate changes, with warmer and wetter winters and hotter and drier summers projected [1]. Using the Representative Concentration Pathway 8.5 high emissions scenario in which the world continues to create high levels of emissions, UK Climate Projections data show that, by 2070, winters in the United Kingdom are projected to be up to 4.5 °C warmer and 30% wetter than they were in 1990. Summers in the United Kingdom may be up to 6 °C warmer and 60% drier [2].

The agricultural sector in England is highly susceptible to the effects of flooding and droughts. Farmers and farmworkers, whose livelihoods depend directly on the land, are particularly vulnerable to these events, which can disrupt agricultural production, damage infrastructure, and lead to financial loss. The resulting strain on physical and economic resources can also have significant consequences for mental health, contributing to stress, anxiety, depression, and other psychological challenges [3,4].

Flooding Impacts

Coastal, fluvial, and surface water flooding can all lead to "significant" impacts according to the National Risk Register [5], with likelihoods of significant impact currently at approximately 1% to 5% for all 3 flood types over a 5-year period in the United Kingdom. The third UK Climate Change Risk Assessment [6,7] published in 2023 and the National Risk Register [5] have identified flooding as one of the most important climate change adaptation challenges facing the United Kingdom. In all future climate change scenarios, direct and indirect flood risks are projected to rise over the 21st century. Increasingly higher average rainfall and changing rainfall patterns, alongside rising sea levels, will contribute to a projected rise in the frequency and severity of flood events.

While the greatest expected annual damage is likely to remain being caused by river flooding until at least the 2080s, the greatest increase in expected annual damage risk is projected to be from surface water and coastal flooding [7]. The increase in flood frequency and severity will likely lead to a corresponding increase in knock-on health impacts from coinciding threats, such as landslides and critical infrastructure service damage or disruption.

Drought Impacts

As assessed by the 2025 National Risk Register [5], drought events could have wide-ranging impacts between "minor and catastrophic," with likelihood levels between <0.2% and 5% (occurrence over 5 years) in the United Kingdom. However, "the future risk of droughts due to climate change is increasing, and there is a trend towards hotter summers with associated increasing water demand. Simultaneously, changes in consumer habits and population growth are increasing water use in the UK" [5]. Droughts, in contrast to flooding, are often slow-onset, complex phenomena determined by a combination of rainfall, evaporation, water demand, and local ground and environmental conditions.

Multiple definitions of drought exist, commonly split into the 4 categories of hydrological, meteorological, agricultural, and ecological drought depending on whether and how impacts are considered [8]. Although there are many indicators available for each category, particularly for meteorological and hydrological droughts, there is still no consistent approach to characterize agricultural and ecological droughts [9].

Similar to flooding, droughts also have the potential for compounding and coinciding hazards, including heat waves and wildfires [10]. However, there are difficulties in identifying impacts and documenting health effects from droughts due to their slow onset and given the complexities in assigning a defined beginning and end to droughts, where effects tend to accumulate over time [11].

Mental Health of Farmers and Farmworkers

Although some studies suggest lower general rates of depression and anxiety among farmers than among other population groups [12], far more studies and surveys indicate the opposite [13-15]. Lower rates of anxiety and depression in farmers in certain areas on a day-to-day basis may be attributable to the resilience derived from the characteristics of farming families in some communities [14]. In addition to depression and anxiety, other mental health impacts on farmers following flooding and drought may include posttraumatic stress disorder and suicide [16], social isolation [17], stress and worry over loss of income, and penalties for not meeting contractual agreements with supermarkets [9]. Indeed, the mental health impacts of droughts and flooding for farming populations can be particularly intertwined with various socioeconomic circumstances as well as environmental and community factors.

An integrative literature review on the mental health impacts of climate change among vulnerable populations worldwide [18] found that the most impactful and well-documented manifestation of climate change for mental health is drought and lack of water resources. An English national study of flooding and health that surveyed people in neighborhoods affected by flooding in the winters of 2013 to 2014 and 2015 to 2016 revealed that there was an adverse impact on mental health among those whose lives were disrupted by flooding as well as those whose homes were flooded [19]. Farmers and farmworkers are a group who are particularly exposed to health impacts from flood and drought events due to their livelihoods being so closely dependent on the land and agricultural output [20]. A systematic review conducted by Vos et al [21] in 2021 also identified mental health as a major health theme of importance during droughts and farmers as a rural community that is particularly vulnerable to the mental health impacts of drought.

Knowledge Gap and Rationale

Most of the evidence for mental health impacts to farmers has been focused on drought in Australia. In Australia, drought is commonly defined as hot and dry drought usually associated with summer. However, in the United Kingdom, where reservoir and groundwater levels generally rise during the autumn and

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winter, a winter (or multiple winters) with low rainfall can lead to slow-onset drought events that have a significant impact [22]. Flooding also occurs in a variety of types in the United Kingdom, with multiple and complex impacts for farmers. Land flooded by sea water in coastal and estuarine environments, for example, often requires many years to recover due to soil damage from salinization. In addition to direct impacts from floodwater inundation, high-velocity fluvial and surface water flooding can cause riverbank and ground surface erosion and the loss of farmland, topsoil, infrastructure, livestock, and crops. Impacts such as those from soil erosion may be exacerbated by repeated flood events or land use practices occurring in some parts of the country.

While there is evidence worldwide to demonstrate the mental health impacts of droughts on at-risk groups, including farmers and farmworkers, there is currently a gap in knowledge assessing the impacts specifically for the United Kingdom [23,24]. The UK Health Security Agency's Health Effects of Climate Change in the UK report states that "the greatest health impacts of flooding in the UK are on mental health" [25]. However, there remains a particular gap in knowledge when considering the mental health impacts on farmers and farmworkers from flooding in the United Kingdom. While there may be benefits from taking lessons from studies focused overseas and more general studies in the United Kingdom, impacts on health vary between populations and at-risk groups for reasons related to population vulnerability and the types of flooding or drought events [26].

The 2024 farmer confidence survey carried out by the United Kingdom's National Farmers' Union (NFU) shows confidence levels at record lows, with extreme weather the leading concern with 82% of participants citing this as having a "very negative" or "fairly negative" impact on their business in the previous year [27]. Further severe flood events occurred in the United Kingdom after the 2024 NFU survey. With both drought and heavy rainfall predicted to become more common and intense in the United Kingdom due to climate change, the NFU is promoting a holistic water management practice, including the management of both too much and too little water together [28]. Due to the numerous routes through which water management issues could impact mental health and well-being, they recommend that flooding and drought impacts should be monitored and researched together. We adopt the combined approach to flooding and drought mental health impacts in this study.

Aim

This study aims to fill the existing knowledge gap by investigating the mental health impacts of both flooding and drought on farmers and farmworkers in England. Through the exploration of the direct and indirect effects of these events, as well as the factors that contribute to or mitigate mental health challenges, the implementation of the protocol will provide valuable insights for policymakers, health professionals, and agricultural support organizations, as well as farmers and farmworkers themselves.

Objectives

The objectives of our mixed methods study to assess the impact of flooding and drought on the mental health of farmers and farmworkers in England are to (1) investigate how farmers and farmworkers and their lives and livelihoods are impacted by flooding and droughts, (2) explore the perceived impacts of flooding and droughts on the emotional and social well-being of farmers and farmworkers, (3) investigate the factors that directly or indirectly compound the mental health impacts of flooding and droughts (eg, preexisting physical or mental health conditions and external stressors, including socioeconomic circumstances), and (4) examine the factors that may mitigate the root causes of mental health impacts from flooding and droughts.

Methods

This study uses a sequential mixed methods approach. Data collection is broken down into 2 core phases that are shown in Figure 1: an online survey and semistructured interviews.

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Figure 1. Study phases for assessing the impact of flooding and drought on the mental health of farmers and farmworkers in England. WEMWBS: Warwick-Edinburgh Mental Wellbeing Scale.

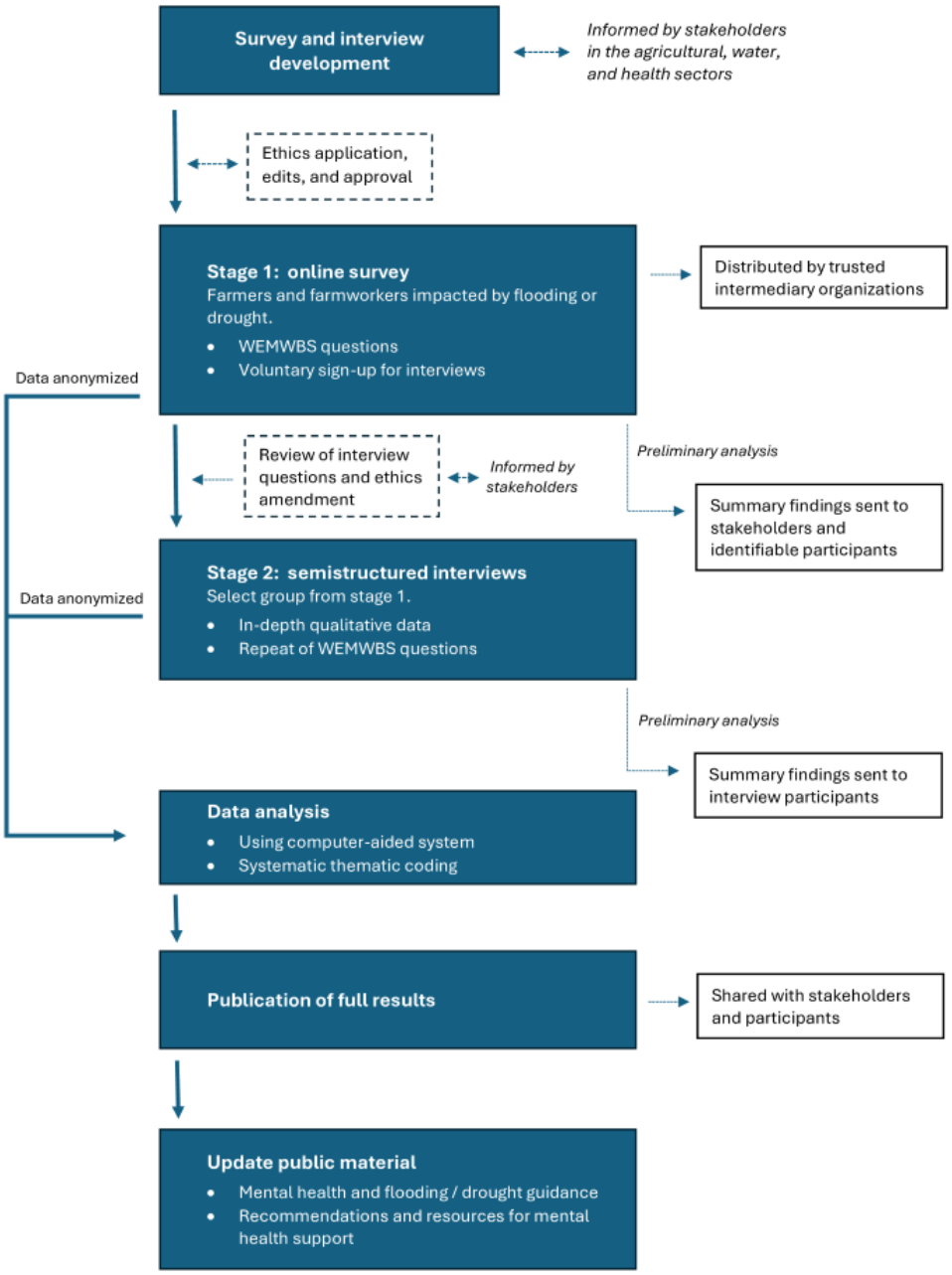

Stage 1: Online Survey

The primary method being used for data collection is an online survey compiled through Microsoft Forms and accessed through a shortened Microsoft Forms URL. This method has been identified to have multiple advantages in the population of interest. Surveys allow for a large amount of data to be collected quickly and allow participants to complete them in their own time, with both open- and closed-ended questions to capture quantitative and qualitative data. Responding to surveys is also one of the quickest ways to collect data, which addresses the engagement barrier of being "too busy" identified by Lyon et al [29] in 2020. A postal survey will not be conducted due to limited resources and capacity and because this was deemed unnecessary for the intended audience following discussions with multiple stakeholders in the agricultural sector. The survey is mobile phone–compatible as this was deemed important to maximize the response rate.

Data will be collected at the household level to allow for exploration of factors affecting other members of the family or household. A dedicated contact will be available for those who may have questions about how to complete the survey or other research processes. Survey data will be collected from a questionnaire on the following themes, with individual questions outlined in Multimedia Appendix 1 and guided by feedback from stakeholders in the agricultural, health, and water sectors:

- Demographics and farm information (including farm details)
- Experience with flooding and drought
- Mental health impacts and coping strategies
- Warwick-Edinburgh Mental Wellbeing Scale (WEMWBS)

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- Open feedback and option for contribution to the interview component
- Mental health resources and support

The survey will enable a broad overview of the mental health implications for farmers and farmworkers across England, with potential trends identified. The survey will also be used to recruit for follow-up semistructured interviews through a voluntary component of the questionnaire that explains this and allows participants to enter contact details. We recognize that caution is required regarding the timing of surveys or other assessments of mental health related to disasters as they may coincide with other circumstances unrelated to the disasters. Additionally, surveys conducted soon after a disaster (or multiple disasters) may coincide with specific psychological phases of the typical disaster recovery cycle [30] and large variations in corresponding emotional highs and lows.

From the reviewed literature, the most used mental health assessment tool was the 10-question Kessler Psychological Distress Scale [31]. However, as most studies reviewed were conducted in Australia, this study will instead use a tool that has been more commonly used in UK studies, including with farming populations [15], to improve the analysis: the validated 14-item WEMWBS[32]. The WEMWBS comprises only positively worded items related to different aspects of mental health [32]. The WEMWBS was developed by an expert panel drawing on academic literature, qualitative research with focus groups, and psychometric testing of an existing scale. It has been validated on different populations, including university students [33], secondary mental health care users aged ≥18 years [34], the general population [32], and the UK farming population [35]. In its original UK validation study, the Cronbach α scores were 0.89 and 0.91 across student and general population samples, respectively, indicating good interitem homogeneity [32]. Test-retest reliability at 1 week was high (0.83), and the WEMWBS correlated positively with established scales such as the World Health Organization–Five Well-Being Index (r=0.77; P<.01) [32]. The WEMWBS has been used in several studies that have included subsequent interventions, and Blodgett et al [36] conducted a review to assess the effectiveness of different intervention types. These may usefully inform the development of resilience-building strategies that follow from this study. The survey will allow for the collection of WEMWBS data on mental health experiences within the farming population that can be compared to those other population types in the United Kingdom. It is recognized that these data will be quite broad given the variety of participants who may complete the survey. Nevertheless, they will provide a valuable opportunity to compare with existing WEMWBS datasets.

Stage 2: Semistructured Interviews

Participants will be invited to a 1-hour semistructured interview via Microsoft Teams, and previous consent will be sought. Interviews will enable the collection of more in-depth qualitative data regarding mental health impacts, coping mechanisms, and other stressors. The WEMWBS will again be used as part of the stage 2 interview questions. This will allow for the collection of WEMWBS data from targeted participants, ensuring a coverage of different farm types and sizes (based on the UK government 2024 farm classification [37]) and further information from respondents about the sources of distress. In addition to comparisons to WEMWBS findings from other published studies, the collection of WEMWBS data from the interviews will allow for comparisons to the initial WEMWBS data collected from the same participants during the stage 1 survey. This will prove useful given the different data collection techniques and the fact that floods or droughts may occur in between stages 1 and 2 of data collection.

Alongside stressors, coping mechanisms will be further explored to better understand what interventions could be most useful. These factors have been informed by previous research, including that by Staniford et al [38] in 2009, Wheeler et al [39] in 2018, and Lyon et al [29] in 2020. The interviews will allow us to use an open framework to engage in guided discussion. Importantly, this format of questions gives space for the interviewee to influence the focus and encourage dialogue with the interviewer [40].

An interview protocol and topic guide based on a schedule of common questions and informed by responses from the stage 1 survey will be piloted and used to ensure consistency and enable comparison across interviews. However, the following are the main criteria, with initial proposed question themes outlined in Multimedia Appendix 2:

- Demographic information—updates following stage 1 and discussion
- Personal mental health impacts and coping mechanisms
- WEMWBS
- Farm impact and resilience measures
- Community (including family) impact and resilience measures
- Resources and assistance
- Policy and advocacy
- Outlook and open discussion

A summary of key findings will be shared with participants after both the survey and interviews.

Participants

The participant group for both stages of this study is farmers and farmworkers working on multiple farm types and sizes across England [37]. England has been chosen due to the remit of the UK Health Security Agency only covering this country of the United Kingdom.

Inclusion criteria are (1) farmers and farmworkers in England, defined as those who own, live on, or are involved in the day-to-day management of the farm (this includes farm owners and operators, farmworkers, and tenant farmers and contractors); (2) farmers with all farm types (ie, cereals, horticulture and potatoes, specialist pigs, specialist poultry, dairy, upland grazing livestock, lowland grazing livestock, and other; adapted from the UK farm classification [37] through stakeholder engagement); and (3) age of ≥18 years.

Farmers or farmworkers with farms that have been impacted by flooding or drought are being actively encouraged to participate.

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Exclusion criteria are (1) casual and seasonal farmworkers (ie, those who do not spend most of their working hours on the farm throughout the year), (2) children under the age of 18 years (data will not be collected directly from children; however, adults of the household may wish to include their views in the survey), (3) those who speak languages other than English due to limitations of the research team and translation capacity, and (4) agriculture types that are not typically classed as a type of farming by the UK government farm classification system [37] (eg, forestry, agroforestry, and aquaculture).

Participant Recruitment

Previous studies have shown that farmers prefer to be approached by and engage with people or organizations whom they already have a connection to and who have knowledge about farming [41]. Therefore, links and information to the stage 1 survey are being distributed through a variety of communication channels by intermediary organizations already engaged with the community in the farming and agricultural sector. This includes existing newsletters, social media, and internal communication methods through office holders and their staff at both regional and national levels. Intermediary organizations will not have knowledge of who has chosen to complete the survey.

Survey respondents will be invited to participate in a follow-up interview (stage 2) to be conducted within the following 12 months, and a subset of up to 10 respondents will be selected for interview. Participants for the interview stage will be selected at random, although the research team will check that the random selection covers a range of demographics, regions, and farm types. If not, another random selection will be generated.

Participant Sample

Convenience sampling with snowballing will be used in this study. This allows for quick and easy access to participants of interest and for additional participants to be identified. This method has been chosen due to the population's expressed preference to work with organizations that they are already involved with and being an underrepresented population for mental health considerations [41].

Recognizing the differences in flooding and drought events experienced across England, a geographical spread of participants from across the country will be sought. Where possible, minimum sample sizes of 300 for the stage 1 survey and 12 for the stage 2 interview will be sought. A sample size of 300 is often considered a "good" sample size for survey research [42,43], and Guest et al [44] found that most (97%) key research themes are captured in 12 interviews.

This survey description and design will naturally target those affected by flooding or drought rather than collecting data that assess mental health more generally within the population. Additionally, the methods used to recruit participants (including through intermediary organizations that focus on providing support to affected individuals and communities in the agricultural sector) will mean that a large proportion of the population surveyed and interviewed will be those already affected by flooding or drought and who have already sought support. This will be acknowledged in the study write-up.

Data Analysis

The statistics functions on Microsoft Forms will be used for preliminary analysis of stage 1 survey data to identify headline themes that are emerging. Stage 1 data will be exported in the Microsoft Excel format for further analysis.

Stage 1 and 2 datasets will be thematically analyzed and coded using the NVivo (Lumivero) software and a coding framework constructed through an iterative process that will be both inductive and deductive and trialed and agreed to by the research team.

Thematic analysis will identify recurring themes, patterns, and key experiences related to the mental health challenges that farmers face during flooding and droughts. Comparisons will be made across different demographic groups, regions, and types of farming to explore any variations in mental health impacts. This approach will provide a deep understanding of the emotional, psychological, and social effects of environmental stressors on farmers, supporting the overall aims of this study.

Ethical Considerations

This study involves humans and the surveying and discussion of potentially sensitive topics. Ensuring that this potentially sensitive research is conducted ethically and avoidance of any harmful impact on participants is of paramount concern to the research team. This study adheres to appropriate ethical review and approval as per institutional guidelines. Ethics approval for this study has been granted by the UK Health Security Agency's Research Ethics and Governance Group (reference R&D601; November 11, 2024).

In recognition that the subject matter and qualitative interview process could be reflective and emotional for interviewees and may elicit sensitive and personal information and "unanticipated themes," this study has been divided into 2 distinct and optional stages. Participants will be provided with information sheets and consent forms in advance of each stage that will outline and ensure understanding of (1) details of the study, (2) the fact that participation in only the second stage will involve taking part in an interview and that this will involve participating to discuss experiences and views on mental health impacts and will last for up to 1 hour, (3) the fact that participation in this study is entirely voluntary and that they can withdraw from the study up until the point that the data are not identifiable by the research team without giving a reason, and (4) the fact that they are welcome to discuss any concerns about the study or participation with any member of the research team.

Information on mental health support and resources available for participants has been drafted by the research team in collaboration with multiple stakeholders, including mental health and farming-focused organizations, and will be provided at the start and end of both study stages (Multimedia Appendix 3).

Data collected from the survey will be stored in a deidentified format. Regarding the collection of secondary personal identifiable information for the purpose of making contact for interviews, these details will be stored in a separate document and not be added to questionnaire response documents.

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Interviews will be recorded and transcribed verbatim for data analysis using the postmeeting transcripts available through Microsoft Teams, with any necessary corrections to wording made by the member of the research team who conducted the interview. All research output materials will be anonymized, and participants will not be identifiable within the research outputs. All data will only be accessible to the members of the research team. Any data published as a part of the analysis in reports or peer-reviewed papers will be anonymized.

Results

Stage 1: Online Survey

This survey was distributed through trusted intermediary organizations from January 2025 to March 2025. As of February 12, 2025, a total of 58 participants had completed the survey. Responses so far cover most regions of England, providing a broad overview of the mental health impacts of flooding and drought across the country's agricultural sector. Data analysis will focus on identifying trends in mental well-being and mental health issues, with particular attention to how different types of flooding and drought events have affected various farming communities. Demographic factors such as age, gender, and farm size will also be considered to explore any potential disparities in mental health outcomes. Results from the WEMWBS questions will be compared to those from other studies that involve both the agricultural sector and other population groups [32,34,35] to compare mental health and well-being outcomes.

Stage 2: Semistructured Interviews

At least 10 participants will be selected for semistructured interviews to be held in late 2025 to early 2026, with the aim of collecting more detailed qualitative data on the mental health impacts of flooding and drought. As of February 12, 2025, a total of 20 survey respondents had volunteered to participate in further research, including interviews. The interviews will explore the emotional and psychological challenges faced by farmers and farmworkers, as well as the coping mechanisms they have used. The thematic analysis of the interview data alongside the stage 1 survey data will provide a deeper understanding of the specific stressors and support systems that influence mental health in the farming community. Results from the WEMWBS questions in this part of the study will also be presented, allowing for a longitudinal comparison with those from the stage 1 survey, the consideration of any cascading or compounding events in between with potential for long-lasting impacts on mental health [45,46], and comparisons with those of previous studies. Results from both stage 1 and stage 2 are expected to be published in mid- to late 2026.

Discussion

Principal Findings

This study will provide critical insights into the mental health impacts of flooding and drought on farmers and farmworkers in England. Through the use of both quantitative and qualitative methods, this study will identify common themes and challenges while also allowing for a nuanced exploration and discussion of individual experiences. The findings are expected to highlight the importance of mental health support services and mechanisms that can be tailored to the needs of farmers and farmworkers in England.

Comparison With Prior Work

Previous research on the mental health impacts of climate change has primarily focused on droughts in Australia, where the agricultural sector faces different challenges compared to the that in United Kingdom. This study will contribute new data specific to the UK context, where farmers face a more diverse range of climate-related stressors, including both flooding and droughts of different types. The study's results will also build on existing findings and survey results, such as the Public Health England [19], Royal Agricultural Benevolent Institution [15], Farm Safety Foundation (Yellow Wellies) [35], and NFU [27] studies, by providing a deeper understanding of how these events affect mental health in the United Kingdom.

Strengths and Limitations

The strength of this study is the novel approach adopted to focus on the mental health of farmers and farmworkers related to flooding or drought together. We also use a mixed methods approach, which adds to this strength. The methodology does not include clinical or medical data from participants as this is not required for the intended outcomes.

A key limitation of this study is the reliance on self-reported data, which may introduce bias. Additionally, the survey is being distributed through intermediary organizations, which may result in a sample that is not fully representative of the wider farming population. However, this is intentional as intermediary organizations (in the agricultural and water sectors in this case) are likely more trusted by the community of interest compared to governmental departments in England. This may reduce bias for certain response topics. This study's focus on farmers and farmworkers already affected by flooding and drought events may also restrict the applicability of the findings to wider agricultural or general populations or those who may be affected in the future.

Conclusions

Findings from this study will contribute to the limited evidence and add new perspectives on mental health impacts to farmers and farmworkers in England from flooding and drought, as well as the coping strategies used. Findings from the mixed methods approach using an online survey and semistructured interviews will inform the development of targeted mental health interventions for farmers and farmworkers in England, helping build resilience for future flooding and drought events. The findings will also contribute to the growing body of research on the mental health impacts of climate change and support the creation of policies that address the unique needs of the agricultural community.

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Acknowledgments

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Data Availability

Data sharing is not applicable to this paper as no datasets were generated or analyzed during this study.

Authors' Contributions

DMB has been involved in every stage of this project following the initial conceptualization and background research. DMB led the writing, review, and editing of all sections of this paper. KB, JI, RC, and AR were involved in the initial conceptualization and investigations, including writing of background information, which informed the Introduction and Methods sections of this paper. KB, SK, and PC provided expert advice and project administration throughout. All authors have reviewed the paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Questionnaire.
[DOCX File , 80 KB - resprot_v14i1e73827_app1.docx]

Multimedia Appendix 2
Interview themes and topics.
[DOCX File , 73 KB - resprot_v14i1e73827_app2.docx]

Multimedia Appendix 3
Mental health support information.
[DOCX File , 68 KB - resprot_v14i1e73827_app3.docx]

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Abbreviations

NFU: National Farmers' Union
WEMWBS: Warwick-Edinburgh Mental Wellbeing Scale

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Maternal Micronutrient Status During Pregnancy and Its Neurodevelopmental Implications for Infants in South Asia: Protocol for a Scoping Review

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Abstract

Background: Pregnancy is a crucial stage characterized by an increased demand for various nutrients. The role of micronutrients becomes especially important during pregnancy and infancy to support neurodevelopment. Micronutrient deficiencies are prevalent in low- and middle-income countries due to socioeconomic disparities, limited dietary diversity, and barriers to quality antenatal care. This results in women of reproductive age and developing offspring being disproportionately affected. Despite extensive research, evidence remains fragmented, leading to a lack of comprehensive synthesis.

Objective: This scoping review aims to explore the existing evidence on the role of maternal micronutrient status during pregnancy influencing neurodevelopmental outcomes in infants. Additionally, it will assess the prevalence and distribution of specific micronutrient deficiencies and identify their sociodemographic determinants within South Asian countries.

Methods: This scoping review uses an iterative, three-step search strategy to identify both published and gray literature. Initially, a targeted search using relevant keywords was developed for PubMed to locate studies investigating maternal micronutrient status or supplementation during pregnancy (women aged 15 - 49 y) and associated neurodevelopmental outcomes in offspring up to two years of age. The search was sequentially narrowed by geographic region (South Asian countries), study design, human studies, English-language publications, and clinical trials. In the second stage, this search strategy will be adapted and implemented across additional electronic databases, including MEDLINE, Embase, Google Scholar, Cochrane Library, OpenGrey, JSTOR, and Wiley, as well as trial registries such as ClinicalTrials.gov and PROSPERO. Further, supplementary hand-searching of relevant journals will be conducted. The third step involves applying a snowballing technique to review the bibliographies of initially identified papers. Two reviewers will independently conduct study selection and data extraction using standardized forms. Quality assessment will use Joanna Briggs Institute critical appraisal checklists. Quantitative findings (study characteristics, exposure definitions, outcome measures) will be summarized with descriptive statistics and visualized in structured tables and charts, and qualitative findings will be coded inductively to develop themes pertinent to the review questions. We will integrate evidence through a convergent narrative synthesis to contextualize how maternal micronutrient deficiencies are influenced by sociodemographic factors and how these relate to infant neurodevelopment. The review will adhere to PRISMA-ScR reporting guidelines.

Results: The initial database search was completed on July 3, 2025. Title and abstract screening is in progress, and final synthesis and reporting are anticipated by January 2026.

Conclusions: This review aims to summarize the available evidence on maternal micronutrients and infant neurodevelopment in South Asia, identify major gaps and inconsistencies in the data, and highlight opportunities for focused research and multisectoral action. The findings will help guide the next phases of the South Asia Collaborative for Maternal Micronutrients and Infant Neurodevelopment (SACMIND) collaborative project, which will include qualitative studies, biomarker assessments, and designing interventions.

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KEYWORDS

pregnancy; micronutrient; infants; neurodevelopment; South Asian countries; maternal nutrition; supplements in pregnancy; child development

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Introduction

Pregnancy is a crucial life stage characterized by increased nutritional requirements, including both macronutrients (calories, proteins, fats) and micronutrients (including vitamins and minerals). Sufficient intake of these nutrients is essential to support the mother's health and the growth and development of the fetus [1]. During pregnancy and early infancy, nutrients and growth factors play a central role in orchestrating development. In particular, brain development during the fetal and early postnatal period is highly sensitive to maternal nutrition, as nutrients regulate processes like cell proliferation and differentiation and neural connectivity. Although all nutrients contribute to fetal growth, some have especially critical impacts on the developing brain during these periods. For example, adequate protein and energy intake support overall fetal growth, and specific micronutrients act as cofactors in brain development pathways.

Several micronutrients are vital for fetal growth during pregnancy, each serving specific functions [2]. Folic acid (vitamin B9) helps prevent neural tube defects and supports early brain and spinal cord development. Vitamin D is important for fetal skeletal development, calcium metabolism, and immune function; a deficiency may impair bone growth and affect neurodevelopment. Iodine is essential for thyroid hormones and brain development, with deficiencies potentially leading to cognitive impairment or cretinism. Iron supports increased maternal blood volume and oxygen delivery to the fetus and is crucial for brain maturation, while deficiency is associated with low birth weight [3-6]. Other nutrients, such as zinc for cellular growth and reduced risk of preterm birth, vitamin B12 for neural development, vitamin A, and essential fatty acids, also contribute to healthy fetal growth and neurological outcomes [7].

Micronutrient deficiencies in pregnant women are a critical public health problem in low- and middle-income countries [1]. Women in low- and middle-income countries often begin pregnancy with pre-existing undernutrition or specific nutrient deficiencies, which can be exacerbated by the increased nutritional demands of gestation. It is also important to recognize that deficiencies often do not occur in isolation. In populations with limited dietary diversity, mothers may be lacking several micronutrients simultaneously. The highest prevalence of such deficiencies is reported in South Asia [8]. Population-based studies in South Asian countries, including India, Bangladesh, and Nepal, have reported deficiencies in zinc (15% - 74%), vitamin B12 (19% - 74%), vitamin E (as α-tocopherol, 50% - 70%), and folate (0% - 26%) among pregnant women [9]. Several investigators have documented the relationship between micronutrient deficiencies and subsequent neurodevelopment in infants [7,10,11], and several others have attempted to study the impact of supplementation [12-14]. The authors of this scoping review have also completed several studies in the field of micronutrient supplementation, including a recently concluded trial on B12 supplementation in pregnant women that resulted in better infant mental development [15-19]. However, a comprehensive overview is required to clarify both the existing evidence and the knowledge gaps regarding how maternal micronutrient status during pregnancy relates to offspring neurodevelopment. Toward this purpose, a preliminary database search found no current or ongoing scoping reviews specifically addressing the relationship between gestational micronutrient status and infant neurodevelopment. Two global scoping reviews were identified: one on maternal nutrition and neurodevelopment [7] and another on the role of zinc in neonatal brain growth [20]. Considering the complex interplay between maternal nutrition and infant neurodevelopment, a scoping review was considered appropriate to map the breadth, characteristics, and gaps of the evidence across diverse study designs and outcome measures. Given the heterogeneity in study designs, exposure definitions, gestational timing, biomarkers, and neurodevelopmental instruments, a meta-analytic approach was deemed premature. However, this review is intended to seed focused systematic reviews in the future—potentially micronutrient-specific and outcome-specific—where methodologically homogeneous subsections would permit quantitative synthesis and meta-analysis. This scoping review is a methodological component of the South Asia Collaborative for Maternal Micronutrients and Infant Neurodevelopment (SACMIND) multicountry collaborative project, which aims to elucidate how maternal micronutrient deficiencies influence infant neurodevelopment and identify effective strategies for tackling maternal micronutrient deficiencies across South Asian contexts.

Methods

Ethical Considerations

The study has been approved by the institutional ethics committee of the Sitaram Bhartia Institute of Science and Research, New Delhi, India (reference number F.1/SBISR-EC/PR 05-24).

Overview

This scoping review will follow the methodological framework originally proposed by Arksey and O'Malley [21], with enhancements from Levac et al [22] and the Joanna Briggs Institute (JBI) methodology for scoping reviews [23]. The review will proceed through the following stages: (1) identifying the research question, (2) identifying relevant studies, (3) selecting studies, (4) charting the data, (5) collating, summarizing, and reporting the findings, and (6) consulting with relevant stakeholders. To maintain methodological rigor and promote reproducibility, the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist will be used as a guiding tool [24].

Stage 1: Identifying the Research Questions

Specifically, our scoping review aims to answer the following questions:

1. Which micronutrient deficiencies during pregnancy are associated with infant neurodevelopment?
2. What is the quality and spectrum of evidence from South Asia on the impact of maternal micronutrient deficiencies on infant neurodevelopment?
3. Which interventions have been attempted in South Asia to address maternal micronutrient deficiencies, and what is

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the evidence of their effectiveness on infant neurodevelopment outcomes?

4. What is the prevalence and geographic distribution of micronutrient deficiencies during pregnancy in South Asian countries, and which sociodemographic factors are associated with these deficiencies?
5. What are the existing gaps and future directions for research on maternal micronutrients during pregnancy and their impact on infant neurodevelopment in South Asia?

The research questions are described using the Population, Concept, and Context (PCC) framework [23] in Textbox 1.

Textbox 1. Population, Concept, and Context framework.

Population (P)

- Pregnant women (15-49 years) and their offspring (up to 2 years of age).

Concept (C)

- To explore the evidence for key maternal micronutrients during pregnancy linked to infant neurodevelopment.
- To study the prevalence of maternal micronutrient deficiencies during pregnancy and contributing factors associated with neurodevelopmental outcomes.

Context (C)

- The exploration of evidence on the association of key maternal micronutrients during pregnancy with infant neurodevelopment will be synthesized globally.
- The prevalence and contributing factors of maternal micronutrient deficiencies during pregnancy will be explored, with particular emphasis on the South Asian region.

Stage 2: Identifying Relevant Studies

Search Strategy

The three-step search strategy as prescribed by JBI will be followed to locate both published and gray literature. In Step 1, an initial search of PubMed has been undertaken. Key concepts for the search were identified; terms based on the concepts were combined using Boolean operators (OR, AND, NOT) to make queries and searched under the All Fields category. As illustrated in Figure 1, the study will be conducted in phases corresponding to the research questions (RQs). To ensure both logistical efficiency and comprehensive coverage throughout each phase, preliminary searches using the selected search terms and Boolean operators were performed on PubMed. These terms were then systematically refined for scope and practicality through an iterative process by the lead authors in consultation with all coauthors prior to finalization (Multimedia Appendix 1).

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Figure 1. Search strategy. RQ: research question.

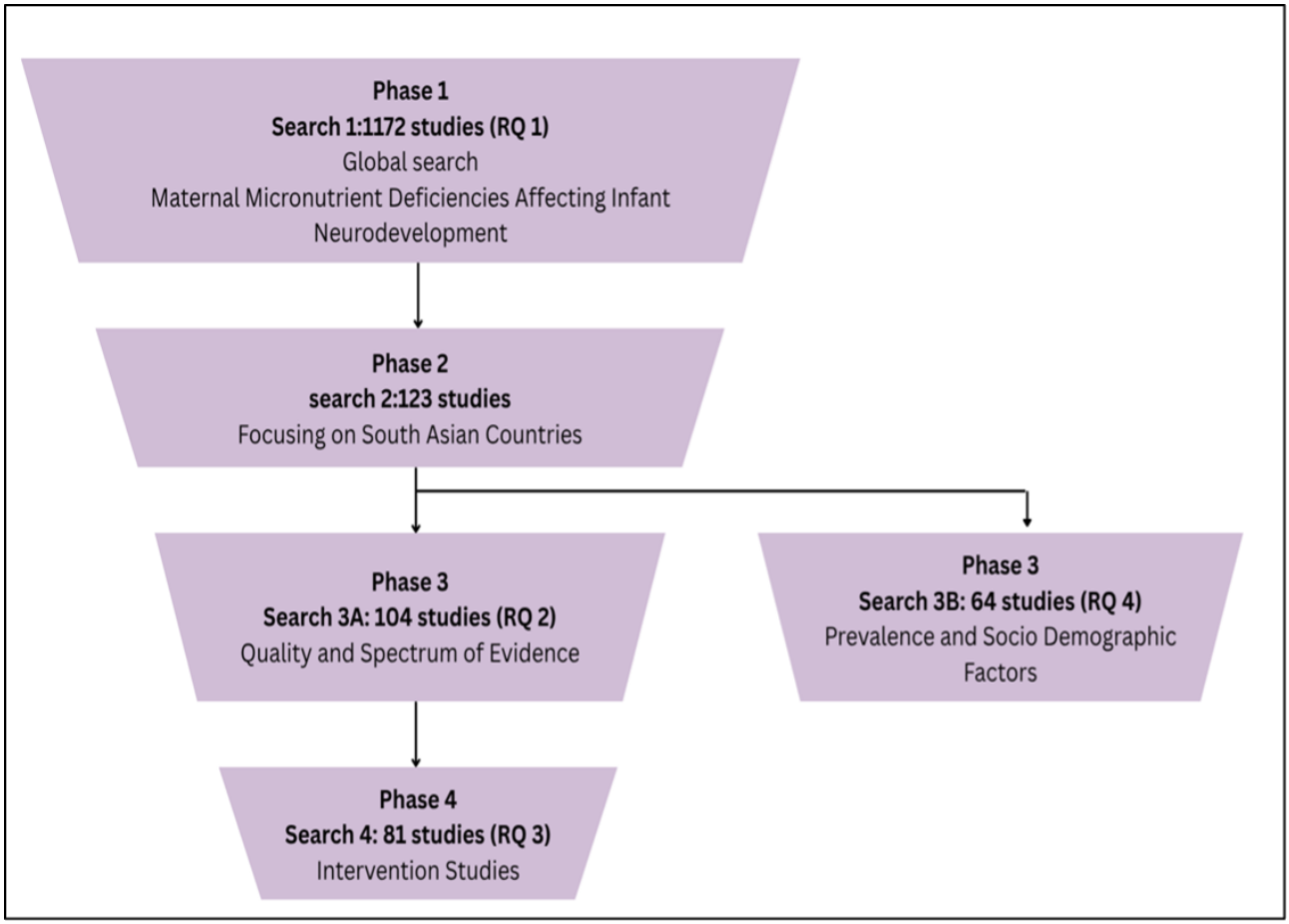

In Phase 1, a global search to identify micronutrient deficiencies during pregnancy that are associated with infant neurodevelopment was conducted. The search strategy (search 1) was developed using the following terms: ((pregnancy) OR (maternal)) AND ((infant) OR (offspring) OR (child)) AND ((micronutrient status) OR (micronutrient deficiency) OR (vitamin A) OR (vitamin B) OR (vitamin C) OR (vitamin D) OR (vitamin E) OR (vitamin K) OR (thiamin) OR (riboflavin) OR (niacin) OR (B5) OR (B6) OR (biotin) OR (folic acid) OR (cobalamin) OR (iron) OR (calcium) OR (sulfur) OR (magnesium) OR (phosphorus) OR (sodium) OR (potassium) OR (zinc) OR (copper) OR (manganese) OR (molybdenum) OR (boron) OR (chlorine) OR (chloride) OR (selenium) OR (cobalt) OR (fluorine) OR (fluoride) OR (iodine) OR (silicon)) AND ((neurodevelopment) OR (“brain development”) OR (“motor development”) OR (“psychomotor development”) OR (“language development”) OR (“cognitive development”) OR (cognition)) NOT (toxic) NOT (gene) NOT (autism) NOT (preterm). This global search yielded 1172 studies.

In Phase 2, the search strategy was narrowed down (search 2) to focus on studies conducted in South Asian countries, aligned with research questions 2, 3, and 4, by adding the terms (“South Asia” OR India OR Bangladesh OR Nepal OR Bhutan OR “Sri Lanka” OR Pakistan OR Maldives) to Phase 1. This phase identified a total of 123 studies.

In Phase 3, search 2 was further narrowed in search 3A by adding the study type filters to answer RQ 2, which yielded 104 results, followed by search 3B, which involved adding the key terms (prevalence OR epidemiology OR incidence OR demography) AND (factors OR determinants OR etiology OR “socio-demographic”) to answer RQ 4; this search identified 64 studies. Finally, in phase 4, search 3A was further refined in search 4 to answer RQ 3 (to extract the evidence on interventions aimed at addressing maternal micronutrient deficiencies and their effectiveness on infant neurodevelopment outcomes) as described in Figure 1, after which a total of 81 studies were obtained.

In Step 2, the PubMed search string will be adapted and applied to the following:

- Electronic databases: PubMed, MEDLINE, Embase, Google Scholar, Cochrane Library, Open Gray, JSTOR, Wiley.
- Trial registers (eg, ClinicalTrials.gov, PROSPERO [International Prospective Register of Systematic Reviews])
- Manual searches of key journals (we will identify common journal titles like *BMC Pregnancy and Childbirth*, *The Journal of Nutrition*, *The American Journal of Clinical Nutrition*, *BMC Public Health*, *Public Health Nutrition*, *BMC Nutrition*, *Maternal and Child Nutrition*, and *Nutrients*)

The history of electronic database searches will be documented in Multimedia Appendix 2.

As a third step, the snowballing method will be used to examine the bibliographies of identified initial articles to find related and potentially relevant papers to again set the starting point. Both backward (reference tracking) and forward (citation

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tracking) snowballing methods will be used. As presented in the selection criteria, only studies published in English will be considered. The search will not be restricted by publication year and all studies published prior to June 2025 will be included. This inclusive time frame is intended to capture all the available evidence on maternal micronutrient status and its association with the neurodevelopment of offspring. Duplicate studies will be removed using the Rayyan software [25].

Information Sources

This review will include both primary and secondary research with the following range of methodologies: experimental studies (randomized controlled trials, nonrandomized controlled trials) on the association of maternal micronutrients and neurodevelopment of offspring; observational studies (prospective and retrospective cohort studies, case-control studies, analytical cross-sectional studies); systematic, scoping, and narrative reviews; qualitative studies; and mixed method studies.

Stage 3: Study Selection

Eligibility Criteria

The eligibility criteria for study selection were also formulated using the PCC framework and are elaborated in Table 1.

Table . Eligibility criteria based on Population, Concept, and Context.

Category	Inclusion criteria	Exclusion criteria
Population	• Studies that measured micronutrient status during pregnancy (15 - 49 y) AND reported neurodevelopment of their infants up to 2 years of age AND/OR • Studies that administered single/multiple micronutrient(s) during pregnancy with or without infant supplementation, by any modality (oral/parenteral), and assessed the neurodevelopment of infants using a standard scale AND • Studies conducted on human subjects AND • Studies published in English AND • All studies published prior to July 2025	• Studies conducted on women with multiple pregnancy OR • Studies conducted on pregnant women with known or prediagnosed chronic medical conditions, mental health disorders, substance abuse, or infertility treatment OR • Studies conducted on infants born extremely preterm, severe small for gestational age, or with neonatal neural disorders OR • Non-English articles
Concept	• Gestation is defined as the period between conception and birth. • Micronutrients will include all vitamins and minerals required by the body in very small amounts. • Neurodevelopmental domains will include motor, language, cognitive/problem-solving using a standardized scale of assessment like the Bayley Scales of Infant and Toddler Development, Standardized Infant NeuroDevelopmental Assessment, or Developmental Assessment Scales for Indian Infants • Infancy will be defined as the period up to 2 years • South Asian countries: specifically, India, Bhutan, Bangladesh, Nepal, and Sri Lanka	—[a]
Context	• Studies conducted to establish the relationship between maternal micronutrient status during pregnancy and neurodevelopment of offspring during infancy	—[a]

[a]Not applicable.

Study selection will be made by two independent reviewers using the study selection form. Separate study selection forms have been developed and standardized for screening at two levels (Multimedia Appendix 3). For standardization, the reviewers' agreement was measured using the Cohen κ statistic of 0.8 or higher for every question (title and abstract screening: 0.96 and full-text screening: 1) [26,27]. For the title and abstract screening form, the first 50 studies from search results after randomization were screened. Ten studies identified for inclusion through title and abstract screening were screened for full text. The forms were modified based on discussions to resolve reviewers' disagreements. Study selection will be made at two levels:

- Level 1: Title and abstract screening. After the removal of duplicates, all the abstracts retrieved from the search will be screened using the title and abstract screening form. Each study will be categorized as "YES," "NO," or "UNCLEAR." Studies marked as "Yes" or "Unclear" will be included for full-text review. Reasons for exclusion will

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be documented for the excluded studies to ensure transparency.

- Level 2: Full-text review. All studies marked as "YES" during level 1 screening will be retrieved in full for this level. Two independent reviewers will screen all the full-text articles using the final eligibility for inclusion in the scoping review. Studies that best fit with the research question will be included, while others will be excluded for documented reasons. Any discordant full-text articles will be reviewed for a second time, and further disagreement about study eligibility at this level will be resolved through discussion with a third reviewer until full consensus is obtained. The unavailability of a full-text article will also be documented. An attempt will be made to contact the authors to request the full text or clarify any concerns.

The references will be downloaded and then imported into a reference library using Zotero (version 7.0.13, 64-bit; Corporation for Digital Scholarship). The PRISMA flow diagram for scoping reviews [28] will be used to graphically depict the movement of sources through the search process to eventual inclusion. A narrative description of the selection process for included sources of evidence will be provided, based on the inclusion and exclusion criteria.

Data Variables

Data will be collected on the following variables:

- Primary outcomes: Direct measures of neurodevelopment in infants up to 2 years of age. These will include development quotients of cognitive development, motor development (both gross and fine), language acquisition, and social-emotional development.
- Secondary outcomes: Maternal micronutrient levels, birth outcomes, infant growth, and biochemical indicators.
- Determinants: Additional factors such as the type, duration, and timing of micronutrient supplementation; the timing of neurodevelopmental assessments; and socioeconomic or demographic correlates that may influence neurodevelopmental outcomes.
- Safety profile: Data related to the safety of maternal micronutrient exposure during pregnancy will also be extracted. This includes maternal adverse effects such as symptoms of toxicity or gastrointestinal disturbances, as well as infant-related adverse outcomes resulting from micronutrient excesses or deficiencies.

Stage 4: Data Collection

The next stage will be "charting" of key information derived from the included studies, which will also be an iterative process. According to Arksey and O'Malley's framework [21], charting is described as a technique for synthesizing and interpreting qualitative data by sifting, charting, and sorting material according to key issues and themes. Two structured data-charting forms have been developed around the PCC framework [29] as per RQ 1 based on a global basis and for subsequent research questions based on South Asian countries. The data-charting forms were developed and refined after pilot-testing by two independent reviewers on the first 5 studies meeting inclusion criteria to enhance clarity and comprehensiveness (Multimedia Appendix 4). Discrepancies or inconsistencies in data extraction were resolved through discussion between the reviewers. If disagreements persisted, a third reviewer was consulted to mediate and finalize the data extraction form. The extracted data will be compiled into a single Microsoft Excel spreadsheet for validation and coding.

JBI's quality appraisal tools will be used [30] for quality appraisal of studies identified after full-text screening for RQ 3.

Stage 5: Data Summary and Synthesis of Results

Data extraction will be conducted independently by two reviewers using standardized forms anchored in the PCC framework, with iterative refinement following pilot-testing. Quantitative variables will include study design, setting and country, sampling frame, gestational timing of micronutrient measurement or supplementation, definition and assay methods for micronutrient status, infant age at assessment (≤24 mo), neurodevelopmental instruments used (eg, Bayley Scales of Infant and Toddler Development, Standardized Infant NeuroDevelopmental Assessment, Developmental Assessment Scales for Indian Infants), and outcome domains (cognitive, language, motor, social-emotional). Descriptive statistics (frequencies, percentages, means, ranges) will summarize study features and outcome distributions. Results will be presented in structured tables and charts to directly address RQs 1 - 4 (RQ 1: which deficiencies are associated with infant neurodevelopment; RQ 2: quality/spectrum of evidence; RQ 3: interventions and effectiveness; RQ 4: prevalence and sociodemographic determinants). Qualitative evidence will be analyzed inductively using ATLAS.ti with open coding to identify concepts related to pathways, measurement heterogeneity, contextual determinants, and implementation barriers and enablers. Codes will be grouped into categories and higher-order themes will be aligned to the review objectives and RQs. Integration will proceed via a convergent narrative synthesis: quantitative summaries will establish the breadth and patterning of exposures and outcomes, while qualitative themes will provide interpretive depth around mechanisms and context. The synthesis will explicitly map findings to each review question. For studies pertinent to RQ 3 (interventions), methodological quality will be assessed using the relevant JBI critical appraisal checklists; quality judgments will be reported in an appraisal table and used to qualify interpretations. All stages of conduct and reporting will adhere to the PRISMA-ScR checklist (Checklist 1) to ensure transparency and reproducibility.

Stage 6: Consultation

Stakeholders, including health care professionals, researchers, and policymakers, will be consulted to provide insights and feedback on the review's findings. The consultation exercise will help refine the review's scope, identify additional relevant studies, and ensure the findings are applicable to real-world settings.

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Results

This scoping review was funded in January 2025 and formally began in February 2025. The final scoping review will be performed and reported according to this protocol and the PRISMA-ScR guidelines. On July 3, 2025, the initial search was conducted on PubMed followed by other databases. Initially, the search returned 12,741 records, and 10,992 records were screened by title and abstract for eligibility after removing duplicate records. A total of 283 studies were identified by abstract screening; as of July 2025, full-text screening is in progress to determine their eligibility. The final synthesis, including a completed PRISMA-ScR flow diagram with study counts at each stage, is anticipated by January 2026.

Discussion

This scoping review is expected to fill an important void by systematically collating and summarizing the available evidence on maternal micronutrient deficiencies and infant neurodevelopment in South Asia. By charting a range of studies—including observational cohorts, trials, and reviews—it will assess the breadth of evidence and highlight patterns or inconsistencies in findings across the region. In doing so, it is expected to highlight research gaps (for example, a lack of long-term neurodevelopmental follow-up studies or an underrepresentation of certain regions or micronutrients or a poor understanding of sociodemographic influences) and suggest priorities for deeper investigation (systematic reviews and meta-analyses). The review will document the prevalence and distribution of key micronutrient deficiencies in South Asian countries and their associated sociodemographic determinants, providing valuable epidemiological context for policymakers. The findings, when integrated with those from a concurrent policy review of South Asian countries, will provide valuable insights into the most prevalent deficiencies and the populations most affected. This understanding can enhance the effectiveness of targeted interventions.

Compared to previous global work [7], this scoping review offers a more focused synthesis of evidence specific to maternal micronutrients, South Asia, and neurodevelopment, addressing a notable gap in the literature. Although earlier global reviews have explored the relationship between maternal nutrition and infant neurodevelopment, few have systematically mapped the prevalence, determinants, and intervention landscape for micronutrient deficiencies in this region. By including a broad range of study designs and emphasizing regional context, this review provides a nuanced understanding that complements and extends prior work.

A key strength of this review is its comprehensive and systematic methodology, which adheres to an established framework (JBI) and aligns with PRISMA-ScR guidelines. The inclusion of multiple study designs and gray literature extends the comprehensiveness of the analysis beyond trials published in indexed journals. By focusing specifically on the South Asian context, the review allows for a more nuanced understanding of regional contexts. Furthermore, integrating findings with concurrent qualitative assessments will enhance interpretability. Nevertheless, several limitations are recognized. The scope of the review is restricted to studies examining maternal micronutrient deficiencies exclusively in relation to neurodevelopment, which may affect the generalizability of the results. The review's limitation to English-language publications introduces the potential for language bias. Variability among study designs, definitions of micronutrient deficiency, and neurodevelopmental assessment tools may hinder comparability and limit the feasibility of quantitative synthesis. Additionally, publication bias may obscure null or negative findings.

Findings will guide subsequent collaborative project activities, including feasibility assessments, biomarker refinement, and intervention design. They will also guide the development of a comprehensive research agenda focusing on underexplored micronutrients, long-term outcomes, and integrated maternal-infant nutrition interventions. This scoping review will also have important implications for both research and policy. For researchers, a synthesized overview of existing studies will illuminate what is known [7] and unknown, thereby informing the design of future studies such as trials of multiple micronutrient interventions or long-term longitudinal studies tracking developmental outcomes or evaluating the dimensions of neurodevelopment impacted by single micronutrient deficiencies. For policymakers and public health authorities in South Asia, the review's findings can guide nutritional strategies to improve early childhood development. If the evidence establishes, for example, that maternal deficiencies in nutrients like vitamin B12 or vitamin D are linked to developmental delays, antenatal care programs could broaden their supplementation schemes beyond iron and folate or implement screening for these deficiencies in high-risk groups. Several South Asian countries are already considering a transition from iron and folic acid supplements to multiple micronutrient supplements in pregnancy, in line with updated global guidelines, to better address the spectrum of deficiencies affecting mothers and infants [4,20]. Evidence from this scoping review could support such policy shifts by providing region-specific data on which micronutrient interventions yield meaningful benefits for child development. Ultimately, by elucidating the relationships between maternal micronutrient status and infant neurodevelopment in South Asia, this work will contribute to shaping more effective nutritional policies and research agendas aimed at ensuring children in this populous region achieve their full developmental potential.

Results will be disseminated through peer-reviewed publications, conference presentations, social media, and stakeholder workshops convened across partner countries. Policy briefs and visual summaries will target public health officials, program managers, nongovernmental organizations, and frontline providers to support translation into antenatal nutrition programs and early childhood development strategies.

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Acknowledgments

The authors declare the use of generative artificial intelligence (GAI) in the research and writing process. According to the GAIDeT taxonomy (2025), the following tasks were delegated to GAI tools under full human supervision: proofreading and editing. The GAI tool used was M365 Copilot. Responsibility for the final manuscript lies entirely with the authors. GAI tools are not listed as authors and do not bear responsibility for the final outcomes. Declaration submitted by JN.

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Data Availability

Data are provided with the manuscript or in supplementary files.

Authors' Contributions

JN, MM, and SR conceptualized the study, contributed to the methodology, and were involved in preparing the original draft. ST and MV were involved in the writing of the original draft. NB, ST, and MV were involved in the statistical analysis. JN, MM, SR, and NB were involved in the reviewing and editing of the protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search queries and details.
[PDF File, 1039 KB - resprot_v14i1e81592_app1.pdf]

Multimedia Appendix 2
Draft table for the electronic database search history.
[DOCX File, 17 KB - resprot_v14i1e81592_app2.docx]

Multimedia Appendix 3
Screening forms.
[DOCX File, 23 KB - resprot_v14i1e81592_app3.docx]

Multimedia Appendix 4
Data extraction form.
[DOCX File, 18 KB - resprot_v14i1e81592_app4.docx]

Checklist 1
PRISMA checklist.
[PDF File, 562 KB - resprot_v14i1e81592_app5.pdf]

Peer Review Report 1
Peer review report by the National Institute for Health Research (NIHR) Global Health Research Development Awards Review Committee, Department of Health and Social Care (United Kingdom).
[PDF File, 130 KB - resprot_v14i1e81592_app6.pdf]

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Abbreviations

JBI: Joanna Briggs Institute
PCC: Population, Concept, Context
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
PROSPERO: International Prospective Register of Systematic Reviews
RQ: research question
SACMIND: South Asia Collaborative for Maternal Micronutrients and Infant Neurodevelopment

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Protocol

Clinical Nurse Educators' Job Satisfaction and Turnover Intentions: Protocol for a Scoping Review

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Abstract

Background: Clinical Nurse Educators (CNEs) play a critical role in supporting the recruitment, retention, and professional development of staff nurses in acute care hospital settings. In the context of the COVID-19 pandemic, which has exacerbated global nursing shortages, CNEs are reporting high levels of burnout associated with unpredictable work expectations and nursing workforce challenges. However, the factors that influence job satisfaction and turnover intentions among CNEs are not well understood.

Objective: The objective of this scoping review is to provide a comprehensive overview of existing literature that focuses on job satisfaction and turnover intentions among CNEs within the acute care setting.

Methods: Joanna Briggs Institute and PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines will be used for this scoping review. Using a predetermined query of keywords, a comprehensive search will be conducted in SCOPUS, CINAHL, MEDLINE, PsycINFO, Web of Science, citation searching, and gray literature sources to identify studies published between January 2013 and August 2024. This review will consider all literature sources that explore the concept of job satisfaction and turnover intentions of CNEs in the context of acute care settings such as hospitals and short-stay units. Two independent reviewers will screen and select studies, and data extraction will be completed using Covidence (Veritas Health Innovation) systematic review software to gather specific data from each literature source. The results will be synthesized to map out themes within existing literature and to identify areas for further research. Supported by tables and graphs, thematic content analysis will be used to provide an extensive overview of what is known about the topic of interest.

Results: The online database literature search was initiated in January 2025, with a total of 4306 records identified during the initial search. After removing duplicates, 2354 unique records will be screened based on title and abstract. As of February 2025, title and abstract screening is currently underway, with a subsequent full-text screening and gray literature search to follow. We expect data analysis to be completed in April 2025 and results published in May 2025.

Conclusions: Rather than evaluating the significance of findings in individual studies, this review will contribute new insights to the existing literature and identify areas for further research.

Trial Registration: OSF Registries osf.io/ectu7; https://osf.io/ectu7

International Registered Report Identifier (IRRID): DERR1-10.2196/66712

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KEYWORDS

clinical nurse educators; job satisfaction; turnover intentions; scoping review; acute care hospitals; nurses; acute care; protocol

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Introduction

The clinical nurse educator (CNE) is an essential bridge between theoretical knowledge and safe clinical practice in acute care environments. Drawing upon advanced knowledge and experience, CNEs are registered nurses who support staff nurses in upholding patient care quality standards through education and professional development initiatives [1,2]. CNEs also respond to the learning needs of undergraduate nursing students, collaborate with other health care professions, and facilitate the adoption of current evidence-based practices [1,3]. The CNE role has been positively associated with higher levels of work engagement, psychological empowerment, and structurally empowering work environments in acute care hospitals [4].

Against the backdrop of a longstanding global nursing shortage, exacerbated further by the COVID-19 pandemic, the need for strategic actions to attract and retain skilled nursing staff is paramount [5]. CNEs play a critical role in recruiting, training, and advocating for new graduate nurses, many of whom experienced serious transition shock and considered leaving the nursing profession entirely during the COVID-19 pandemic [6,7]. Further, new graduate nurses' sense of professional and personal identity, as well as the degree of support received, can influence the quality of patient care delivered in hospitals [8]. CNEs have been studied as a protective factor in promoting retention of new graduate nurses in acute care settings; a mixed methods study of novice nurses in Australia suggests that CNE presence aids in developing confidence and resilience, and contributes to the decision to remain active in the nursing profession [9].

However, recent studies conducted in New Brunswick and Ontario have indicated a shortage of experienced nurses equipped with the knowledge and skills needed to mentor early-career nurses entering the workforce [10,11]. Working independently to balance the needs of frontline staff and managerial expectations, the unique role of the CNE has been described as both isolating and overwhelming [12]. Unlike research involving the general nursing population, proposed reasons for job dissatisfaction within the CNE role include lack of role clarity, insufficient support to balance multiple priorities, lack of orientation or preparation to assume the CNE position, and intrinsic pressure to succeed in demanding environments [12]. Anecdotally, CNEs also cite high levels of job dissatisfaction related to heavy workload expectations and frequent turnover of staff nurses, resulting in frequent cycles of new staff orientation, as factors leading to burnout.

While several review papers focus on the factors associated with nurses' job satisfaction and turnover intention amongst both novice and experienced staff nurses within hospital settings [13-15], there is a paucity of reviews that focus on CNEs in the same regard. Considering the value of the CNE role in supporting positive clinical outcomes for patients and providing transition support for new graduate nurses as well as other newly employed nurses [16,17], it is critical to understand job satisfaction and turnover intentions for this specific population. Findings from this study will provide current insights into clinical practice improvement and human resource management in acute care. This study also establishes a foundation for future research to examine job satisfaction and retention strategies for CNEs in the hospital setting. The research question guiding this review is as follows: What is known in the literature about acute care CNEs' job satisfaction and turnover intentions?

Methods

Inclusion and Exclusion Criteria

This scoping review will follow Joanna Briggs Institute (JBI) recommendations to consider the "PCC" mnemonic, whereby the letters in the acronym stand for Population, Concept, and Context, respectively, to specify which sources will be considered for inclusion [18] and provide a thick description for transferability of study results.

Participants

This review will consider studies about CNEs working in acute care hospitals. Recognizing that there are diverse terms used to describe the role of CNEs in the literature, additional search terms will be used to capture relevant sources, including continuing education nurses, resource nurses, advanced practice nurses, or nurse practitioners.

Concept

This review will consider literature that pertains to the job satisfaction and turnover intentions of acute care CNEs. Relevant search terms will include: job satisfaction, work satisfaction, job turnover, career turnover, intent to leave, intent to stay, and retention.

Context

This review will consider literature specific to the context of acute care settings, including hospitals, short-stay units, ambulatory care facilities, emergency departments, intensive care, coronary care, cardiology, and many general areas where the patient could become acutely unwell and require stabilization. Studies that include the long-term setting and nonclinical areas will be excluded.

Types of Sources

This review will consider all studies, published between January 2013 and August 2024, which use a range of research methodologies, including quantitative, qualitative, and mixed methods study designs. Gray literature, reviews, editorial pieces, and opinion papers will also be evaluated for potential inclusion. Studies written in English and published in the international health care management and nursing literature will be considered.

Methods

Overview

This scoping review protocol was developed following the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) 2015 checklist for systematic review protocols [19] (see Multimedia Appendix 1). The final scoping review will be conducted in accordance with the JBI methodology [20] and the PRISMA-ScR (Preferred Reporting

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Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews). The protocol for this proposed review has been registered with the Open Science Framework. This project is exempt from institutional review board approval requirements.

Search Strategy

The bibliographic search strategy (see Multimedia Appendix 2) uses various terms to capture the key roles of the CNE, acknowledging the diverse terminology used to describe CNEs within the health care field. This ensures that the review is as inclusive as possible of the relevant literature. The completed scoping review will include all modified search queries for other interfaces within the appendices.

The following databases will be searched: SCOPUS (via Elsevier interface); CINAHL (via EBSCOhost interface); MEDLINE and PsycINFO (via OVID interface); and Web of Science. The search will also include gray literature sources, including ProQuest (Dissertations and Theses Global), along with wider platforms such as Google and Google Scholar to counter the impact of publication bias commonly seen in academic journals, as well as to enhance the depth of understanding within the study topic of interest. This strategic selection of databases and information sources will ensure a comprehensive sweep of health care–specific and broader academic literature.

This review will also use a 3-step search validation procedure to ensure credibility, as follows.

Within the first stage, the search strategy will be applied to a preselected group of relevant articles from CINAHL, identified during the initial literature review. These articles are known to meet the inclusion criteria for the present scoping review. If the proposed search strategy fails to retrieve these articles, the search terms or overall search strategy will be further refined to capture these critical literature sources. In the second stage of search validation, the reviewers will conduct a manual search of leading academic journals to ensure no significant articles of interest are overlooked. Reviewers will also manually examine the reference lists of articles selected for review to identify any further studies, which may not have been captured during the initial search. Finally, as the research team progresses through the screening and review stages, the relevance of articles yielded from the search will be evaluated on a continual basis; the search strategy will be revised as necessary.

Procedure to Contact Authors

The reviewers plan to contact authors for additional information or clarification where necessary. If the need arises, the below-streamlined procedures will be followed: (1) criteria for contact; (2) initial email; (3) follow-up process; and (4) author permission for metadata sharing.

Authors will be contacted if essential data in their study is missing, unclear, or if supplementary or updated information is necessary. For the initial email, the reviewers will write a clear and professional email, outlining the purpose of the present review, the specific information needed, and a reasonable response deadline. Any questions or concerns, which may arise from the corresponding author will also be addressed. In the follow-up process, if there is no response from the author within 2 weeks, the reviewers will send a follow-up reminder email. After a third unanswered attempt, we will consider it a nonresponse, ceasing further contact, and recording this information in a detailed log. Finally, for author permission for metadata sharing, our initial emails will seek author consent to share communication metadata in order to ensure transparency and respect privacy. For consistency and professionalism, we will use standard communication templates from OSF Registries.

Results of Contacting Authors

We plan to report the outcomes of our contact for transparency and an enhanced understanding of the comprehensiveness of the present review. The report will detail the number of authors contacted, those who responded, and those who provided extra data or clarification of their study findings (including any relevant data or details not published within their study). This information will be summarized and presented within a table, outlining contact attempts, response types, nonresponses, and any other issues encountered. In addition, this information will be included within the “Methods” and “Discussion” sections of our final report to present any potential biases and a full overview of the review’s scope.

Search Expiration and Repetition

The search cutoff date is purposefully scheduled close to the beginning of our review process to ensure the inclusion of the most current and relevant research. However, the adaptability of this protocol is a key feature in enhancing the relevance and currency of the review; the time frame will be viewed as a guiding principle rather than an inflexible rule. The search strategy will be adapted as necessary in response to the available literature. The present protocol will remain flexible in adjusting the frequency of updates in response to the publication rate in the field, reflecting an understanding of the dynamic nature of nursing education research.

Study Selection

Upon search completion, records will be compiled and uploaded to Covidence software for automatic removal of duplicate citations and article review. Two independent reviewers will screen each title and abstract based on the identified inclusion criteria, with a subsequent full-text review of relevant sources to follow. Any reasons for excluding sources will be recorded and reported. Any disagreements between the two independent reviewers will be attempted to be resolved through discussion; if an agreement cannot be reached, a third, senior reviewer will be consulted.

Data Extraction

Data will be extracted from studies included in the scoping review by two independent reviewers, documenting various aspects including study details, such as title, authors, year of publication, country of origin of the research team, journal name (if applicable), and funding sources (if mentioned; see Multimedia Appendix 3). The data will include specific information regarding study design, type of study, and specifics including the setting and duration of the research, population studied, sample size, demographic and professional characteristics of the participants, as well as any inclusion or

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exclusion criteria applied during the assessment of literature. The concept of the study, focused on job satisfaction and turnover intentions among CNEs, will also be recorded, with specific attention paid to how the acute care context impacts the findings.

Data Analysis and Presentation

To ensure a robust analysis, the research team has collaboratively developed and revised the present review protocol and process, led by an experienced member. The reviewers will systematically organize the extracted data pertaining to key themes, author findings, research methodologies, and the context of acute care practice. Next, a thematic analysis will be performed to uncover key themes, patterns, and trends, involving coding of data, theme development, and further refinement. Braun and Clarke's 6-phase framework [21,22] will be used to conduct thematic analysis, in conjunction with updated guidance from the authors regarding contextual consideration of ideas, flexibility in the development of themes, and documenting ongoing reflection and transparency throughout the process to ensure appropriate reflexivity and confirmability.

Finally, tables and charts (see Multimedia Appendix 4) will be used to create a visual depiction of key findings, including the distribution of literature by publication year, country of origin, research methods, and factors that influence job satisfaction and turnover intention. These visual representations will be complemented with a descriptive summary, which links the results back to the research objectives and questions. In the case that any challenges are encountered during the process (such as data unavailability), the synthesis approach will be adapted, maintaining transparency and providing rationales for any methodological adjustments.

Results

The initial literature search was initiated in January 2025 across the following databases: SCOPUS, CINAHL, MEDLINE, PsycINFO, Web of Science, with additional backward citation searching (reference lists of identified studies were examined to find additional relevant articles for inclusion). A total of 4314 records were identified during the initial search. After removing duplicates, 2360 unique records were screened for inclusion by two independent reviewers based on title and abstract. The PRISMA-*P* 2020 flow diagram [23] was adapted to illustrate the study selection process in Figure 1.

Full-text screening was completed in March 2025. As of May 2025, data analysis is currently underway with results expected to be published in July 2025.

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for the study selection process.

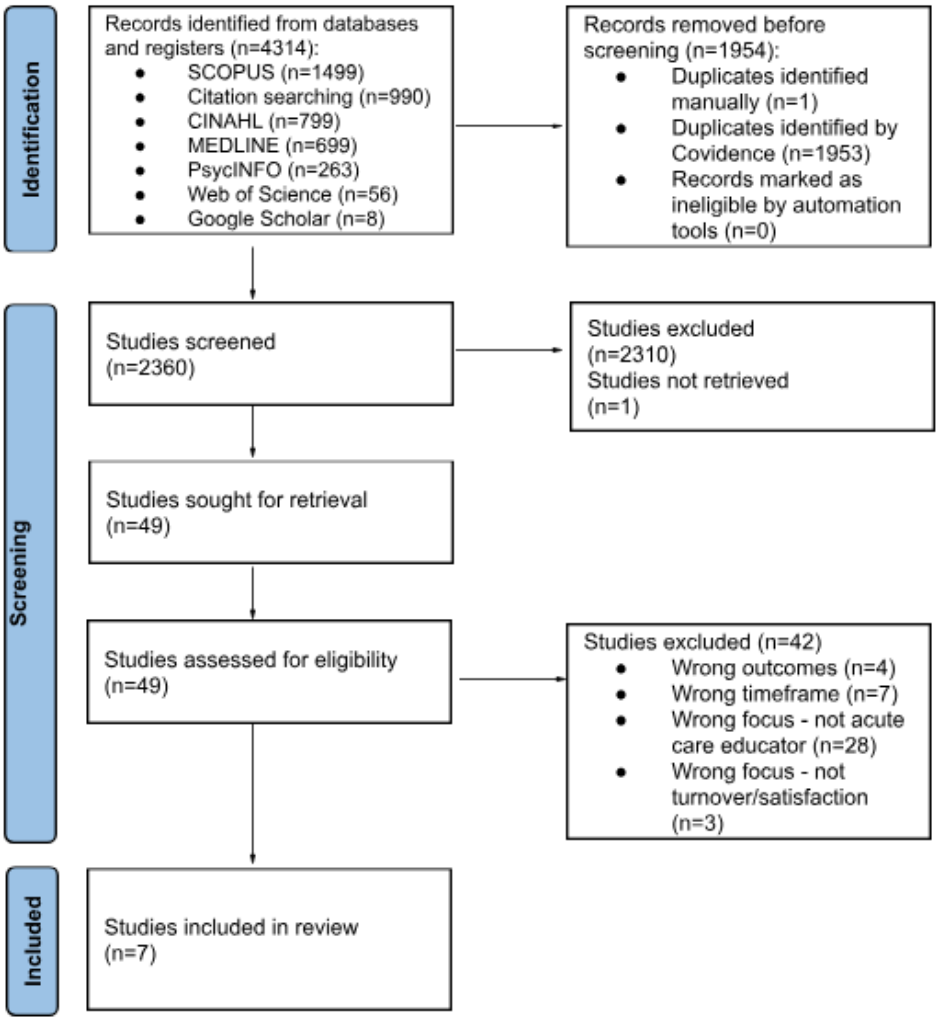

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Discussion

Anticipated Findings

Recent literature on nursing educators in academic settings suggests that manageable workloads and possessing advanced qualifications is positively associated with job satisfaction, while high workloads are associated with high turnover intentions [23]. We anticipate that the main findings of this study will reinforce what is currently known about job satisfaction in CNEs, namely role confusion, lack of support, overwhelming workloads, and intrinsic pressure to sustain high level performance [13]. Due to high turnover rates of new graduate nurses and experienced staff nurses [14-16] in current times, we also expect to find an equivalent correlation in the studied CNE population.

The findings and conclusions from this study will be impactful to current and prospective CNEs, who may be facing similar challenges and feelings of isolation in the workplace. Staff nurses, nursing management, allied health practitioners, and institutional leadership who work with CNEs can benefit from a more fulsome understanding of the factors which influence job satisfaction and turnover intentions in CNEs in order to improve collaborative workplace culture and subsequently, enhance patient care outcomes.

This study has several anticipated limitations. Since the aim of this scoping review is to explore the extent of research related to CNEs' job satisfaction, turnover intentions, and work lives, the quality or validity of individual studies will not be evaluated as this is not a requirement in the scoping review process. This may result in the inclusion of lower-quality research or studies with inherent bias. Another limitation of this study is that the findings may not fully reflect current challenges in acute care settings during, and post–COVID-19 pandemic. We plan to mitigate the impact of these limitations by examining diverse research methods and information sources in order to contribute new insights to the existing literature and identify areas for further research.

Conclusion

This scoping review will explore the extent of research related to CNEs' work life, job satisfaction, and turnover intention, rather than evaluating the significance or magnitude of findings in individual studies. Therefore, the conclusions of this review will reflect the comprehensiveness and scope of the included studies as a whole to identify and highlight gaps in existing research and suggest potential areas for future study.

Acknowledgments

This review received funding from the Social Sciences and Humanities Research Council (SSHRC) Explore Grant. This scoping review protocol manuscript was developed and authored entirely without the use of generative artificial intelligence tools.

Data Availability

Supporting data will be available upon reasonable request from the corresponding author.

Authors' Contributions

KM, ER, AA, and YY contributed to review topic conceptualization. KM contributed to developing the search strategies, while the remaining team members made contributions to outlining the review criteria and methods. All team members were involved in drafting and providing critical editing of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) checklist.
[DOCX File , 22 KB - resprot_v14i1e66712_app1.docx]

Multimedia Appendix 2
Search query string.
[DOCX File , 14 KB - resprot_v14i1e66712_app2.docx]

Multimedia Appendix 3
Data Extraction Tool/Instrument.
[DOCX File , 14 KB - resprot_v14i1e66712_app3.docx]

Multimedia Appendix 4
Table of key findings.
[DOCX File , 14 KB - resprot_v14i1e66712_app4.docx]

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Abbreviations

CNE: Clinical Nurse Educator
JBI: Joanna Briggs Institute
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols

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PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Psychosocial Support Programs for the Mental Well-Being of High School Learners From Low- to Middle-Income Countries: Protocol for a Scoping Review

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Abstract

Background: The World Health Organization reported in 2020 that approximately 50% of all mental health disorders in adolescents manifest before the age of 14 years. However, the literature on mental well-being and programs designed and implemented by nurses for adolescents in low- to middle-income countries (LMICs) is limited. This scoping review explores the development and implementation of psychosocial support programs targeting high school learners in LMICs.

Objective: This prospective scoping review will examine the psychosocial support programs that exist and how they have been implemented for high school learners from LMICs.

Methods: Using the Joanna Briggs Institute scoping review framework, we will identify primary research articles through systematic searches of the ERIC, MEDLINE, ScienceDirect, PubMed, and PsycInfo databases. Gray literature will also be sourced from Google Scholar. Two independent reviewers will apply the predetermined inclusion criteria to select studies. Data will be charted, analyzed narratively, and presented in tables and figures.

Results: This review will analyze the psychosocial support programs for high school learners in LMIC, identifying gaps in the literature and highlighting areas for further investigation, thereby aiding in creating or adjusting such programs. This study is not funded, and data collection was completed in May 2025. Data analysis is currently in progress, and the results are expected to be finalized and submitted for publication in February 2026.

Conclusions: This scoping review will synthesize evidence on psychosocial support programs in LMICs and guide the development of targeted interventions to address the mental health needs of high school learners.

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KEYWORDS

psychosocial support programs; mental well-being; high school; learners; low- to middle-income countries; LMIC

Introduction

The World Health Organization reported in 2020 that approximately 50% of all mental health disorders in adolescents manifest before reaching the age of 14 years globally. For instance, 1 in every 5 adolescents receives a diagnosis of a mental disorder, with three-quarters of them experiencing the onset of initial symptoms before reaching 24 years of age [1]. In China, 41.8% of high school students reported mental health problems, with academic stress being the most common issue [2]. A meta-analysis of Chinese studies found depression (28%) and anxiety (26%) to be the most prevalent problems [3]. Similarly, in Jordan, West Asia, anxiety and depression were associated with higher suicide risk among high school students [4]. Comparatively, in Africa, high school students in Ghana experienced more substantial mental health challenges than university students, including higher levels of academic stress, depression, and suicidal ideation [5]. This highlights the need for more psychosocial support for high school learners.

Academic concerns have been identified as major contributors to mental health deterioration [6,7] among high school learners, with academic stress being reported as the most frequent mental

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health problem [8]. Other notable factors include sleep pattern disruption, the extended use of electronic devices, and social isolation [6,7]. Pre-existing conditions, family dynamics, and the school environment also play crucial roles [8,9]. The interaction of individual, family, school, and social factors markedly shapes adolescent mental health [9].

It has been reported that students with mental health challenges feel they may be unable to pursue their studies [10,11]. Additionally, they may not fully integrate with their peers and social circles, which could negatively affect their interpersonal communication skills. Studies have identified that those who deal with mental health challenges at the adolescent stage are more likely to experience mental health challenges when they enter adulthood [12,13]. The authors add that psychological disorders such as eating disorders, self-harm, and suicide have been reported late in adulthood.

Mental health interventions for adolescents in school settings show promise but require more robust evidence. School-based programs using cognitive behavioral therapy, life skills, and coping skills curricula have demonstrated reductions in depressive symptoms and improvements in problem-solving and overall well-being [12,13]. However, most of these studies have small sample sizes, tend to heavily rely on self-report measures, and are mostly conducted in high-income countries, and as such, their applicability and generalizability in LMICs are questionable.

Although various mental health interventions exist for adolescents in sub-Saharan Africa and LMICs, they are limited in geographic availability and often lack detailed reporting on their development and implementation [14]. Additionally, although some studies examine adolescent mental health in general, there is insufficient research specifically on interventions designed for high school learners in LMICs [15]. High schools are a critical setting for psychosocial support because they provide direct and sustained access to adolescents during a period of heightened vulnerability. Therefore, a scoping review is needed to bring together what is already known about psychosocial support programs in high schools in LMICs, showing what has been tried, what is missing, and what works in specific contexts. The findings will help guide the design of a tailored psychosocial support program that fits the realities of LMIC settings.

Methods

Overview

The Joanna Briggs Institute (JBI) framework proposed by Peters et al [16,17] will be used for this scoping review. The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) flowchart will be included in the final review to illustrate the identification, screening, and inclusion of studies (Checklist 1). The steps are explained in subsequent sections.

Aligning the Objectives and Research Questions

This prospective scoping review will examine how psychosocial support programs have been developed and implemented for high school learners from LMICs.

The research question for the scoping review is “How have psychosocial support programs been developed and implemented for high school learners from LMICs?”

Making the Inclusion Criteria Relevant to the Objectives and Questions at Hand

The inclusion criteria will be based on the population, concept, and context (PCC) format to maintain consistency with the objectives and research topic [17]. Textbox 1 shows a clear relationship between the research question and objectives, which also specifies the PCC. The objectives describe what is expected for the scoping review. Each objective should directly address the research question, which is vital.

Textbox 1. The relationship between the research question and objectives.

Objective

- The objective is to describe psychosocial support programs developed and implemented for learners in high schools in low- to middle-income countries between 2013 and 2023.

Research question

- How have the psychological support programs been developed and implemented for high school learners from low- to middle-income countries?

Population

- High school learners
- Methodological papers that did not include a population but described a tool, its development, and psychometric properties.
- “High school learners” AND/OR “pupils”

Concept

- Psychosocial support programs that promote the mental well-being of high school learners
- “Psychosocial support programmes” AND/OR “strategies”

Context

- Low- to middle-income countries

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Explaining the Intended Strategy for Finding, Identifying, Retrieving, Interpreting, and Presenting Evidence

This scoping review will follow the 3-step technique provided by the JBI framework, since scoping reviews typically take a comprehensive approach using both qualitative and quantitative articles. Peer-reviewed and gray literature will also be included.

Conducting the Search for Evidence

Initial Search

A restricted search of at least 2 databases that apply to the study will be conducted in the initial stage. The objective of this first search is to analyze text terms in the publications that were found, paying particular attention to the abstract and title. The intended strategy for this scoping review includes a primary search that will be conducted using the terms "mental well-being," "psychosocial support programme," "high school," and "learners" on 2 electronic databases, such as PubMed and PsycInfo. The search terms will be connected using Boolean operators like "OR" and "AND."

Secondary Search

Databases to be searched include ERIC, MEDLINE, ScienceDirect, PubMed, and PsycInfo. Keywords such as "psychosocial support programmes," "mental well-being," and "high school learners" and their synonyms will be used with Boolean operators. The search will be supplemented by reviewing references of selected articles.

The researcher and a librarian from the Faculty of Health and Medical Sciences library at the University of Witwatersrand will work together to establish the final search strategy.

Examples of keywords that will be used in the ERIC database search are "psychosocial support programmes" OR "psychosocial intervention" OR "psychoeducation" OR "emotional support" OR "nursing therapy" OR "psychosocial support" OR "mental health programme" AND "mental well-being" OR "mental wellness" OR "psychological well-being" OR "emotional well-being" OR "mental health" AND "high school" OR "secondary education" OR "secondary school" AND "learners" OR "students" OR "pupils" OR "trainees." Multimedia Appendix 1 provides a comprehensive search strategy for all the databases.

Databases vary in how subject headings are indexed. Therefore, keywords may be modified according to each database index term. Table 1 presents essential keywords for constructing the search strategy.

Table . Keywords used in the search strategy and their alternatives.

Keywords	Alternative keywords
"Psychosocial support programmes"	"Psychosocial intervention"; "emotional support"; "nursing therapy"; "psychosocial support"; "mental health program"; "psychoeducation"
"Mental well-being"	"Mental wellness"; "psychological well-being"; "emotional well-being"; "mental health"
"High school"	"Secondary education"; "secondary school"
"Learners"	"Students"; "pupils"; "trainees"

Searching the Reference of Identified Studies and Other Sources

The reference lists of the identified studies will be reviewed to find additional studies. This step is essential to ensure that all potential sources are considered, minimizing the likelihood of excluding relevant studies.

Selecting the Evidence

Overview

Two reviewers will independently screen titles, abstracts, and full texts using EndNote and Covidence. Discrepancies will be resolved through discussion or by a third reviewer.

A Review of the Inclusion Criteria and Eligibility Criteria

Population, Concept, and Context

Studies will be chosen based on the following criteria: (1) population: primary research will be reviewed with high school learners aged 12 to 18 years. In South Africa, any establishment that provides a range of grades from grade 8 to grade 12 is considered a high school [18]; (2) concept: psychosocial support programs that promote the mental well-being of high school learners will be included. Psychosocial programs that do not focus on this will not be included, as not all interventions are tailored to this; and (3) context: this review will only include studies from LMICs to determine what psychosocial support programs are available, as they are scarce compared to high-income countries.

Types of Studies

Quantitative, qualitative, and mixed methods study designs will be considered for inclusion in this scoping review. The context of the current review will not be restricted to opinion papers and other similar material, as the material will not be able to accomplish the goal of the psychosocial support programs, which is to evaluate their impact on high school learners. The data provided by systematic reviews and meta-analyses is based on a pool of interventions and may not be relevant to the scoping review. The purpose of this review is to map and describe primary research evidence on the development and implementation of psychosocial support programs for high school learners' mental health in LMICs. Including systematic reviews or meta-analyses could lead to duplication of evidence, as their findings are already synthesized from primary studies that may also be included in this review. Moreover, scoping

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reviews that aim to explore how interventions are designed and implemented benefit more from analyzing original study data rather than secondary syntheses. Research articles written in languages other than English may need to be translated, which could compromise the accuracy and consistency of data extraction. This may limit the scope of evidence; however, the decision is based on both practical and methodological considerations. In addition, most major databases (eg, PubMed, PsycInfo, and ScienceDirect) predominantly index English-language journals, which means non-English studies are less likely to be captured in standard systematic searches and will deviate the methodology from being consistent. Thus, they will be excluded from this study. An initial search was conducted, and it yielded thousands of articles. Only articles published between 2013 and 2023 will be included to narrow the focus. Articles outside of this time frame will be excluded.

Quality Assessment of Data

Contrary to systematic reviews, scoping reviews do not require a quality data assessment [19]; however, the utility of the review's findings may be compromised if the quality of the scoping review is not assessed. Thus, depending on the review's goal, some authors propose that this may be done at the reviewers' discretion. Two reviewers will ensure the quality of the data is maintained.

Gathering the Evidence

Moola et al [20] state that charting the results, sometimes called extraction of the data, provides a clear and concise summary of the findings. The charting table is updated automatically throughout the iterative process. The data will be extracted using the information highlighted below: author(s), year of publication, origin or country, study population, sample size, methodology, type of intervention, and findings.

Analysis of Data

Data Extraction and Refinement

The researcher will extract data, and the supervisors will review the data; a meeting will be held to determine consensus. If consensus cannot be achieved, a third party will be asked to evaluate the articles and the content analysis approach outlined in Elo and Kyngäs [21] and Sandelowski [22] will be used for data analysis. This process will include data that will be coded independently by 2 reviewers using a predefined coding template, with the possibility to add new codes that may emerge during the analysis. Codes will then be organized into categories and further developed into themes through an iterative process of discussion and comparison both within and between studies. Any disputes will be settled by consensus or with a third party. An audit trail will be maintained to record coding decisions and theme development. The results will be presented as descriptive narratives, with tables and figures to support them.

Expected Results

This review will analyze psychosocial support programs for high school learners in LMICs, identifying gaps in the literature and highlighting areas for further investigation, thereby aiding in creating or adjusting such programs.

Presentation of the Findings

Findings will be presented in tables and graphs, including the components of the PCC, which aligns with the objectives and the research question of this scoping review [19].

Summary of the Findings

Findings will be summarized numerically (eg, study distribution by year and region) and narratively (eg, key themes). Tables and figures will present the detailed PCC.

Ethical Considerations

Ethics approval was not required for this scoping review. The review will synthesize data from existing, publicly available literature and does not involve the collection of primary data or interaction with human participants. According to the *JBI Manual for Evidence Synthesis* [17], scoping reviews that use secondary data do not require a formal ethics approval. In addition, the review will be conducted in accordance with the principles of research integrity and reporting transparency. All sources of data will be referenced, and the review will be conducted according to the reporting framework for the PRISMA-ScR to ensure methodological rigor and transparency. Results will be shared through a peer-reviewed journal and conference presentation to contribute to the research, practice, and policy debates on school-based psychosocial support. Along with results from the study being published in a peer-reviewed journal and presented at conferences, school practitioners, policymakers, and administrators will be provided with research summaries and briefs. These deliverables will provide critical findings, evidence gaps, and potential pathways for action to inform the design and delivery of psychosocial support programs for high school students in LMICs. Other dissemination activities might involve webinars, workshops, or policy briefs to promote the practical use of the results. Patients and the public were not involved in this research's design, reporting, or dissemination plans.

Results

This scoping review is not a funded study, and data collection was completed in May 2025. Data analysis is currently in progress, and the results are expected to be finalized and submitted for publication in February 2026.

Discussion

Anticipated Findings

This scoping review is anticipated to give a general account of the nature of development and delivery of psychosocial support interventions for high school learners from LMICs. Results will inform the understanding of common approaches, key components of successful interventions, and contextual factors affecting their delivery. Although the review may identify useful implications for policy and practice in the future, this review is designed to map the evidence, rather than evaluate effectiveness or provide recommendations for policy. The results are expected to inform further investigation and evaluation studies to enable evidence-based psychosocial interventions to be adapted and

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scaled up and enhance support for mental health in the school environment.

The review will pinpoint the essential components of successful psychological treatments, point out weaknesses in current initiatives, and investigate the external circumstances impacting their execution and efficacy.

The discussion will examine, through an analysis of the research on school-based interventions, how these programs support mental health for high school learners in environments with limited resources, highlighting their capacity to improve coping mechanisms, resilience, and general well-being.

Additionally, the research findings will offer suggestions to legislators, educators, and mental health professionals, assisting them in creating and executing more focused and long-lasting psychosocial treatments. Important knowledge gaps regarding mental health support in LMICs will be filled by identifying areas that need more exploration. Through this review, the study will contribute to the broader discussion about fair access to mental health services in educational settings, ultimately promoting more robust integration of psychosocial support in school systems. The review protocol adheres to the JBI scoping review framework, ensuring systematic methodology, reliability, and validity of the findings.

A thorough search across 5 databases, gray literature, and Google Scholar will be conducted, aligning with defined eligibility criteria. Additionally, the screening process and data extraction involve 2 independent reviewers to enhance transparency, reliability, and minimize bias. It is important to note that the inclusion criteria limit the articles to those written in English and published after 2024. Despite these restrictions, the results from the scoping review will provide insight into the factors that both support and hinder program efficacy, such as institutional support, financial limitations, and cultural considerations.

Strengths and Potential Limitations of This Study

While several scoping review studies have been conducted on the mental health of high school learners, little is known about the development and implementation of psychosocial support programs for this population in LMICs. As a result, this scoping review will provide insight into the program design, implementation procedures, and contextual elements that affect the provision of psychosocial support for the mental health of high school learners in LMIC settings. Two independent reviewers will choose the studies and extract the data to guarantee accuracy and interrater reliability. Only studies published in English will be included in the screening process, which may result in omitting important information in other languages. The evidence will only relate to psychosocial support programs developed and implemented in high schools located in LMICs.

There will be several potential limitations to this scoping review. Limiting the inclusion criteria to English-language studies may result in language bias. There may also be selection bias in the choice of databases and publication bias, as only published sources will be considered. To address these concerns, we will screen gray literature and reference lists of included studies for additional eligible publications.

Conclusion

This review will synthesize evidence on psychosocial support programs in LMICs and guide the development of targeted interventions to address the mental health needs of high school learners.

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Data Availability

Data sharing is not applicable to this paper as no datasets were generated or analyzed during this study.

Authors' Contributions

ECM and NGN initiated and designed the study. ECM and DAA will screen the abstract and full text, with disagreements to be resolved by NGN and ESN. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
Database search strategy.
[DOC File, 53 KB - resprot_v14i1e78035_app1.doc]

Checklist 1
PRISMA checklist.
[PDF File, 107 KB - resprot_v14i1e78035_app2.pdf]

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Abbreviations

JBI: Joanna Briggs Institute
LMIC: low- to middle-income country
PCC: population, concept, and context
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Online Cognitive-Behavioral Programs for Women Living With Endometriosis: Protocol for a Scoping Review

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Abstract

Background: Endometriosis is a chronic inflammatory condition experienced by approximately 10% of women worldwide. Women living with endometriosis experience multidimensional burdens often attributed to pain, fatigue, anxiety, and depression. Treatment patterns frequently focus on acute symptom management, while endometriosis is a lifelong condition. In addition, endometriosis-associated symptoms are complex, requiring multimodal treatment strategies. New complementary approaches for symptom management are needed, where further exploration of current online programs is a necessary next step. Online programs can be noninvasive and convenient, provide a sense of comfort, and are often more cost-effective than traditional in-person medicine. Mapping components within the online programs, using the behavior change ontologies, for women living with endometriosis is necessary for developing effective and long-lasting endometriosis management options.

Objective: The aim of this scoping review is to examine the range and nature of online cognitive-behavioral programs created to manage endometriosis-associated symptoms and to identify key behavior change techniques (BCTs) within the online programs.

Methods: We will conduct the proposed scoping review using the Arksey and O'Malley framework with an interpretive scoping review, consulting stakeholder methodology (6 stages) and referencing the Joanna Briggs Institute Evidence Synthesis Manual. The population-situation framework was used to develop our search strategy, focusing on women living with endometriosis (population) and online programs or online interventions (situation). The study must be a primary source of data, published in 2014 or later, the intervention must take place online and must seek long-term changes for symptom management. Original studies, including peer-reviewed and protocol studies, will be identified from Ovid MEDLINE, Ovid Embase, EBSCOhost CINAHL Complete, ProQuest Nursing and Allied Health Premium, EBSCOhost SPORTDiscus, and ProQuest PsycINFO. Preprints will be identified via the Web of Science Preprint Citation Index. We will also search for active clinical trials from multiple registries. EndNote (Clarivate) will be used for citation management, and Covidence (Veritas Health Innovation Ltd) software will be used for screening and extraction. Up to 5 reviewers will screen studies in Covidence using an inclusion checklist for title and abstract screening and then full-text review. Included studies will be coded to identify BCTs within the online intervention using the BCTs Taxonomy v1. Results will report on the characteristics of the included studies, the BCTs used in the online program or intervention, and the outcomes of the program. Results, including tables and the narrative, have been piloted prior to publication of this protocol using 4 studies that meet our criteria.

Results: Data collection is scheduled to start in October of 2025, with results to be published by the Spring of 2026. This research is not directly funded.

Conclusions: This review will collate information about online symptom management interventions for women living with endometriosis. Findings will identify gaps that can guide future intervention development.

Trial Registration: OSF Registries osf.io/y4dn6; https://osf.io/y4dn6/

International Registered Report Identifier (IRRID): PRR1-10.2196/75981

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KEYWORDS

endometriosis; pain; health-related quality of life; online program; online intervention; behavior change techniques; PRISMA

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Introduction

Endometriosis is a chronic inflammatory and estrogen-dependent disorder in which tissue that mimics the endometrium of the uterus grows outside of the uterus in ectopic sites [1,2]. Endometriosis-associated inflammation can lead to a lower pain threshold via central sensitization and dysregulation of the hypothalamic-pituitary-adrenal axis [3,4]. It commonly affects women of reproductive age, with symptoms ranging widely from pelvic pain and fatigue to gastrointestinal issues, anxiety, and infertility [5,6].

Endometriosis negatively impacts quality of life (QoL), with many women experiencing emotional distress and social isolation, leading to feelings of hopelessness [6]. Endometriosis-associated pain, one of the most common symptoms, can be associated with neuropathic or nociplastic pain, which can vary in intensity [3] and is often exacerbated by stress and psychological factors (eg, anxiety) [7]. Women living with symptomatic endometriosis report worse mental health and day-to-day pain than women living with asymptomatic endometriosis [8]. The endometriosis health profile is a validated health-related QoL self-report measure often used to understand symptom burden on QoL [9]. Due to the wide array of symptoms, multimodal therapy is often required [5,6].

Common treatment options for pain include surgery, hormone therapies, and pain medications (eg, nonsteroidal anti-inflammatory drugs) [10], though more long-term, holistic options are needed. Nonmedical options have also shown promise in helping patients manage their endometriosis-related symptoms. Self-management strategies, such as diet changes [11] or stress reduction [12], have shown short-term benefits, but more research is needed to determine long-term effectiveness. Systematic reviews have concluded that research on physical activity is limited with poor intervention designs and mixed findings regarding improvements in endometriosis-associated symptoms [13,14].

Cognitive behavioral therapies have been shown to decrease pain sensation, improve depression and stress, normalize cortisol levels, and improve aspects of QoL (eg, emotional well-being, control, and supporting autonomy) in women living with endometriosis [15]. Intervention techniques, such as psychoeducation, goal-setting, problem-solving, coping strategies, relaxation training, stress management, and mindfulness approaches, have been used individually or in combination to help women manage their endometriosis [15-17]. Longer duration interventions and randomized controlled trials are needed to understand which cognitive-behavioral techniques are most beneficial and feasible. A scoping review can map the current literature in this area and identify beneficial behavior change techniques (BCTs) used within these interventions.

Since 2020, research involving online programs or interventions has greatly increased due to the worldwide restrictions implemented due to the COVID-19 pandemic [18]. Health care providers, such as nurses and psychologists, have provided digital health care services to their users, such as monitoring and consulting [18]. Online programs can be effective in reducing barriers associated with behavior change and participation. Specifically, for those with endometriosis, online intervention may reduce the stigma associated with seeing a specialist [19]. In the broader pelvic pain population, Seo and Seo [20] conducted a review on the effectiveness of digital health care for managing menstrual-related symptoms among reproductive-age women, reporting that digital and web-based interventions, such as counseling, tele-yoga, and internet-based cognitive behavioral therapies, are accessible and effective tools for managing menstrual symptoms [20].

For women living with symptomatic endometriosis, a single-session digital exercise intervention is effective at providing immediate pain relief [21]. In addition, short-duration online interventions aiming to improve QoL in women living with endometriosis have found improvements in QoL domains of control and powerlessness, emotional well-being, and social support [12,22]. There are active protocol studies involving an online program [19,23], where an in-depth investigation of online programs is necessary for future study designs for improving endometriosis-associated symptoms.

This scoping review aims to examine the range and nature of online cognitive-behavioral programs created to manage endometriosis-associated symptoms. This proposed review will collate identified psychological and behavioral techniques and map the extent of online management options available for women living with endometriosis. The BCT Taxonomy v1 [24] will provide a standardized language for reporting findings, which is a foundational step toward identifying common strategies that can be replicated or used in future intervention development. In addition, the review will summarize the endometriosis-associated symptoms investigated and the outcomes of the online interventions to help identify gaps in online interventions or programs for women living with endometriosis.

Methods

Study Design

This scoping review is guided by the Arksey and O'Malley framework [25], with an interpretive scoping review that consulted stakeholder methodology. The Joanna Briggs Institute Evidence Synthesis Manual will be used synergistically [26]. The data analysis process involves 5 stages, with a sixth describing stakeholder engagement. We will submit the Joanna Briggs Institute scoping review fillable checklist with the completed review (PRISMA-ScR [Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews]; Checklist 1 [27,28]).

Protocol

The protocol document was drafted using the Joanna Briggs Institute scoping review template [29] and PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist [30]. We developed a comprehensive search strategy in collaboration with a Brock University Librarian, Elizabeth Yates. In addition, the Brock Library evidence synthesis review work plan document was completed [31] for the preparation of this protocol. The Consolidated Standards of

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Reporting Trials specific to reporting pain clinical trials [32] were referenced to ensure all criteria for optimizing pain-controlled trials reporting are represented accordingly in this scoping review.

Stage 1: Identifying the Research Questions

We used the population-situation framework [33] to develop our research questions. We originally considered using the population, concept, and context framework but dismissed this because we aim to report on symptoms (context) that the online programs or interventions are targeting. The population-situation framework is used for descriptive and exploratory questions in the health care field. Our "concept one" comprises all women living with endometriosis (population), and our "concept two" comprises online programs or interventions (situation). Identifying concepts within the research question also assisted with developing the search strategy. Our overarching research question is, " What online cognitive-behavioral programs or interventions are available to manage endometriosis-associated symptoms?" We have three subquestions:

1. What are the characteristics of the online intervention or program?
2. What BCTs are used in the study design?
3. What are the outcomes (eg, endometriosis-associated symptoms) of the interventions or programs?

The BCT Taxonomy v1 (93 distinct BCTs) [24] is a method for standardizing language, specifying, and interpreting the active components of an intervention designed to change behavior [34]. There are 16 groupings and 93 hierarchically clustered BCTs. Identifying BCTs in the proposed scoping review provides an agreed-upon language for reporting content and is extremely useful for identifying what components of the intervention themselves may facilitate change or not [35]. In addition, descriptions of behavior change interventions vary widely, making research replicability, evaluation, and implementation in policy and practice difficult, hindering the development of effective interventions [34] in which we aim to address these concerns for online programming interventions for women living with endometriosis. Eligibility will be determined with the following criteria (Textbox 1).

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Must be published in English between 2014 and the present year due to a shift in technology-delivered interventions [18] while accounting for earlier research.
- The intervention or program must seek to improve endometriosis-associated symptoms (eg, health-related QoL, pain, sleep, anxiety, depression, and fatigue) or seek to improve at least 1 psychological outcome (eg, pain acceptance, pain catastrophizing, and illness acceptance) in humans.
- Intervention must be online, with details on the components of the online program.
- Must be a primary source of data.

Exclusion criteria

- If the aim of the program is a stand-alone pain relief intervention or program (eg, only hormonal, drug, and pharmaceutical programs) or is designed for biomedical pain management.
- If the program is for diagnosis or diagnostic techniques.
- If the publication is gray literature (eg, websites and pamphlets), a thesis or conference presentation, or a review, we aim to capture full-text research studies that require detail in the intervention design.

Stage 2: Identifying Relevant Studies

Operational definitions were created to assist in data analysis (refer to Table 1 for operational definitions). The following 6 databases will be searched for peer-reviewed and protocol studies: Ovid MEDLINE, Ovid Embase, EBSCOhost CINAHL Complete, ProQuest Nursing and Allied Health Premium, EBSCOhost SPORTDiscus, and ProQuest PsycINFO. Preprints will be searched using the Web of Science Preprint Citation Index [36]. Active research will also be searched from the ClinicalTrials.gov [37] search engine, World Health Organization International Clinical Trials Registry Platform, European Clinical Trials Register, Australian New Zealand Clinical Trials Registry, and Cochrane Central Register of Controlled Trials. We are including a variety of study designs that meet our criteria, consistent with other scoping reviews [38], including all primary sources of data, experimental studies, observational studies, and qualitative studies (excluding synthesized evidence). We are excluding gray literature (eg, websites), conference presentations, book chapters, and reviews to be able to identify specific components (BCTs) of the online program or interventions through published full-text studies.

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Table . Operational definitions.

Word	Definition
Synchronous program	• Live and real-time with supervision done at a specific time.
Asynchronous program	• Prerecorded and can be done without supervision at any time.
Online program	• Any internet- or technology-delivered (asynchronous, synchronous, or both) program or intervention aimed at improving symptoms related to endometriosis or improving a psychological domain.
Online intervention	• May be an experimental study (eg, randomized controlled trials and controlled trials), an observational study (eg, cohort or longitudinal, case control, cross-sectional, ecological), a qualitative (eg, focus groups, interviews), or a combination that is internet or technology delivered.
Characteristics of the study	• This would include basic information on the publication, for example, author, year, country of publication, stage of research, and publication type.
Characteristic of the online program	• This would include the aim of the program itself, the mode of delivery, the length of the program, the delivery type, the explanation of the program, the cost of the program, the barriers or facilitators of the program, and the referral from a physician who delivers the intervention.
Behavior change techniques (BCTs)	• BCTs are the smallest, observable, and replicable content of a behavior change program or intervention that have the potential to bring about a change [34]. • BCTs will need to be hand-coded for the program or intervention using the BCT Taxonomy v1 as a guide.
Outcomes of the program	• Outcomes of the program will include measures, time points, data analysis, and main findings.

Search Strategy

All women living with endometriosis (concept one) and online programs or online interventions (concept two) were placed into Boolean circles, where the mining of terms began. Ovid MEDLINE was used to develop the search strategy, considering subject headings, keywords, synonyms, related terms, and search syntaxes for both concepts. For example, in concept one, we want to capture all women living with endometriosis, regardless of age, stage, and location. Mining subject headings and keywords in Ovid MEDLINE found terms, such as endometriosis, endo, endometrioma, endometriomas, endometrioses, chronic pelvic pain, fibroids, adhesions, and lesions. Concept two was broken down further into alternative words for online programs and alternative words for online interventions. The refinement of keywords and subject headings was run multiple times via Ovid MEDLINE. This search strategy will be translated from Ovid MEDLINE to incorporate the search syntax used in each database or search engine. The search strategy export will be completed in 1 day by 2 or more members of the research team collaboratively in October 2025. Our final Ovid MEDLINE search strategy is shown in Table 2.

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Table . Search strategy: Ovid MEDLINE example.

Concept[a] and line number	Searches	Results
Population		
1	exp[b] Endometriosis/	26,901
2	endometrio*[c].tw.[d]	39,415
3	exp pelvic pain/	11,805
4	(pelvi* adj[e] pain).tw.	12,054
5	1 or 2 or 3 or 4	57,711
Situation 1		
6	exp Video Recording/ or Telephone/	59,514
7	exp Therapeutics/ or Rehabilitation/ or Patient Education/	54,41,101
8	6 and 7	12,833
9	exp Digital health/	468
10	exp Internet-Based Intervention/	1398
11	exp Internet/	1,02,716
12	exp exercise/	2,61,848
13	11 and 12	1339
14	8 or 9 or 10 or 13	15,926
Situation 2		
15	(online* adj5 (program* or education* or train* or intervention* or treatment* or therap* or platform* or -based* or prevent* or manag* or health* or rehab* or exercise* or physical acitivi*)).tw.	45,762
16	(virtual* adj5 (reality* or program* or education* or train* or intervention* or treatment* or therap* or platform* or -based* or prevent* or manag* or health* or rehab* or exercise* or physical acitivi*)).tw.	43,344
17	(“web” adj5 (reality* or program* or education* or train* or intervention* or treatment* or therap* or platform* or -based* or prevent* or manag* or health* or rehab* or exercise* or physical acitivi*)).tw.	59,086
18	(video* adj5 (program* or education* or train* or intervention* or treatment* or therap* or platform* or -based* or prevent* or manag* or health* or rehab* or exercise* or physical acitivi*)).tw.	30,530
19	(“app” adj5 (program* or education* or train* or intervention* or treatment* or therap* or platform* or -based* or prevent* or manag* or health* or rehab* or exercise* or physical acitivi*)).tw.	10,022
20	(internet* adj5 (program* or education* or train* or intervention* or treatment* or therap* or platform* or -based* or prevent* or manag* or health* or rehab* or exercise* or physical acitivi*)).tw.	24,909

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Concept[a] and line number	Searches	Results
21	(phone* adj5 (program* or education* or train* or intervention* or treatment* or therap* or platform* or -based* or prevent* or manag* or health* or rehab* or exercise* or physical activi*)).tw.	8329
22	(tele* adj5 (program* or education* or train* or intervention* or treatment* or therap* or platform* or -based* or prevent* or manag* or health* or rehab* or exercise* or physical activi*)).tw.	42,534
23	(digital* adj5 (program* or education* or train* or intervention* or treatment* or therap* or platform* or -based* or prevent* or manag* or health* or rehab* or exercise* or physical activi*)).tw.	37,988
24	14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23	2,79,541
25	5 and 24	369

[a]Concept: developed from the overarching research question using the population-situation framework.

[b]expand (subject heading search).

[c]truncation (includes anything after).

[d]search title and abstract (keyword search)

[e]adjacent within the number of words.

Stage 3: Study Selection

Stage 3 describes the process for selecting studies. EndNote (Clarivate) citation management software will be used to organize citations. We will export our search results (from the databases and other sources) into Covidence (Veritas Health Innovation Ltd) software [39] to facilitate the process of removing duplicate items and screening. Merging into Covidence will assist with removing some duplicates. During the screening of titles and abstracts, additional duplicates will be removed by the reviewer by selecting the duplicate study option. Reasons for inclusion or exclusion of studies can be added with notes in Covidence. The data extraction process will be presented in the form of the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart.

Up to 5 reviewers will independently screen titles and abstracts in Covidence. Two reviewers will screen each title and abstract based on our inclusion and exclusion criteria ("yes," "no," or "maybe"). If there is a disagreement, a third reviewer will determine the final result. This process will occur again with the studies labeled "yes," under full-text review, with the inclusion and exclusion criteria. Reasons for inclusion and exclusion will be documented and reported in the PRISMA flowchart. Following screening, all reviewers will perform a full-text review for final inclusion in the scoping review. The primary author, OSP, has prior experience using Covidence and completing the scoping review process [40].

Stage 4: Charting the Data

Three reviewers will independently extract characteristics from the included studies into a Microsoft Excel file. Once completed independently, all extraction characteristics will be discussed together and merged. Row 1 in the Microsoft Excel document includes examples and a definition of each study characteristic to assist all reviewers. The Microsoft Excel file is provided in Multimedia Appendix 1. Extraction characteristics are shown in Textbox 2.

Textbox 2. Extraction characteristics.

- Characteristics of the study: author, year, country of publication, stage of research, publication type, purpose, aims, research questions and hypothesis, sample size, study population, inclusion and exclusion criteria, recruitment methods, comparator condition, support or reject research question or hypothesis, limitations, and implications.
- Characteristics of the online programs: the aim of the program, mode of delivery, length of the program, delivery type, explanation of the program, cost of the program, barriers and facilitators, referral from a physician, who delivers the BCT, grouping of BCT, and BCT used.
- Outcomes of the study: measures, time points, data analysis, and main findings.

BCT Coding

All reviewers will undergo training to code using the BCTs Taxonomy v1 [24,34,41]. This will involve a tutorial consisting of independent readings [24,34], group discussion, and practice coding using the online training course, designed to teach coders how to extract BCT from research studies [41]. The online training provides the opportunity to practice coding BCT excerpts and obtain real-time feedback. During the coding process, all included full-text studies will be downloaded, and

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all coders will independently code BCTs throughout the whole study to avoid unintentionally missing BCTs. Most of the BCTs will be within the "Methods" and if there are appendices. The number corresponding to the BCTs Taxonomy v1 [24] will be directly coded in the document and highlighted, leaving an audit trail, and then reported in the Microsoft Excel file. After independent coding of all studies, BCTs will be discussed together for accuracy checking.

Pilot

The Microsoft Excel document for charting the data has been piloted with 4 target studies [12,19,22,23] that met the inclusion criteria. The file was modified once to include a separate folder strictly for coding BCTs from the BCTs Taxonomy v1 [24]. Tables and the narrative of the results have also been piloted and modified to answer our research questions to provide a comprehensive, logical framework.

Stage 5: Collating, Summarizing, and Reporting the Results

We will have multiple tables that will report on the characteristics of the included studies and the characteristics within the online programs or interventions to address our first subquestion. A table will present frequencies (percentages) of the number of studies using specific BCTs (BCT Taxonomy v1) [24], and a table for the outcomes of the online programs, including target measures related to endometriosis and relevant results.

For the narrative component of the results, a framework will be adopted to prioritize certain aspects of the literature to ensure we answer our research questions [25]. The narrative will have four main sections: (1) an overview of study characteristics, (2) the characteristics of the online programs, (3) the BCTs within the online programs, and (4) the measures and outcomes of the programs. Tables will be used as complementary to the narrative, where new data may be presented in one or the other.

The discussion will be interpretive and reflexive, identifying similarities and differences between studies when necessary [25]. In addition, we will identify the next steps for online interventions or programs for women living with endometriosis. This will be presented in the "Discussion" section. The consulted stakeholder methodology will be used, drawing on expertise from all members of the research team during the interpretation of findings and the write-up [42].

Stage 6: Consultation and Stakeholder Engagement

The proposed scoping review is a foundational step within a larger research program to identify the gaps in developing online symptom management programs for women living with endometriosis. Using the consulted stakeholder methodology by engaging researchers, a librarian, and multiple reviewers combines different perspectives of knowledge and expertise [25,42]. Identifying BCTs involves group engagement and discussion, as the BCTs are interpretations of direct words from the components of the online programs. We aim to minimize interpretation bias by using the BCT Taxonomy v1 and engaging in reflexive discussions [24,34]. The results of this study will be discussed with women living with a diagnosis of endometriosis for additional feedback, as well as with a variety of endometriosis specialists.

Dissemination

All stakeholders will be invited to an online presentation on the findings of this scoping review. Results will be published with open access, and findings will be presented at international conferences. Results will be shared with students in a guest lecture, including how to conduct a scoping review and the importance of research. In addition, research findings will inform and be discussed in the next phase of our research project.

Results

The pilot was conducted in December of 2024. Data collection is scheduled to start in October 2025, with results to be published by the spring of 2026.

Discussion

Principal Findings

This study sought to describe the process for reviewing evidence regarding online interventions or programs aimed at improving endometriosis-associated symptoms. The BCT Taxonomy and newer ontologies [34] were developed to provide a common nomenclature to report interventions, which allows for future synthesis and knowledge accumulation. We anticipate that BCT groupings, such as feedback and monitoring, social support, and shaping knowledge, will be coded in the majority of included studies, as found in other reviews of online programs, which coded BCTs [43,44]. We anticipate that the majority of studies will be early-stage interventions with few randomized controlled trials, given the nascent nature of this research area. Given the ubiquity and continued advancement of digital technologies, the proposed review is positioned to provide an overview of the current state of online interventions for endometriosis symptom management and has the potential to direct future research by illuminating research gaps.

Generally, reviews and meta-analyses have quantified the burden of endometriosis on mental health and examined predictors of mental health. For example, those with endometriosis experience poorer mental health [45], including more symptoms of anxiety and depression [46]. Those with better emotion regulation generally report better mental health functioning [47]. While these reviews paint a clear picture of the poor mental health status often associated with the progression of endometriosis, evidence for the impact of effective and scalable interventions to improve symptom burden is scant.

Past reviews have examined the benefits of clinic-based therapy for pain and QoL [48] among those living with endometriosis. Gandy et al [49] conducted a systematic review and meta-analysis to assess the efficacy of internet-delivered cognitive- and behavioral-based interventions for adults living with chronic pain. Authors concluded that internet-delivered cognitive and behavioral interventions are efficacious and associated with greater clinical gains, including pain management outcomes [49]. Pain is often accompanied by

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endometriosis; however, the experiences and strategies to manage may differ between individuals with endometriosis and those with chronic back pain. Whether online programs can improve endometriosis symptom burden has yet to be explored.

Online delivery improves program reach and may be beneficial for teaching self-management skills that are critical [22]. There are available online programs currently being evaluated and refined that aim to improve symptoms for women living with endometriosis, specifically on health-related QoL and pain [12,19,23]. An endometriosis-specific scoping review will contribute to the broad understanding of strategies currently used to promote symptom management. This review will identify gaps in current intervention design and provide suggestions to guide future online symptom management interventions.

Limitations

There is a risk of misinterpretation of coding BCTs within the studies that outline few methodological details. While this may require researcher interpretation, the structured BCT training increases our confidence in accurate coding. This review includes all types of intervention designs, including early-stage trials. Thus, we will be unable to determine whether online interventions are generally efficacious at improving symptom management for women living with endometriosis.

Conclusions

This scoping review will examine the range and nature of online cognitive-behavioral programs created to manage endometriosis-associated symptoms. By identifying similarities and differences between the intervention designs using the BCT Taxonomy v1 [24], we can guide future research in intervention development to improve endometriosis-associated symptoms. We will seek to publish findings that are open access and create graphics that are shared via social media.

Acknowledgments

We wish to thank librarian Elizabeth Yates as a participating investigator in this project. In particular, Elizabeth provided guidance in creating the search strategy.

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during this study.

Authors' Contributions

Conceptualization: OSP, SRL, KLG, NCG, DRD
Methodology: OSP, SRL, KLG, NCG, DRD
Project administration: OSP
Supervision: SRL
Writing–original draft: OSP, SRL
Writing–review & editing: OSP, SRL, KLG, NCG, DRD

Conflicts of Interest

None declared.

Multimedia Appendix 1
Data extraction file.
[XLSX File, 15 KB - resprot_v14i1e75981_app1.xlsx]

Checklist 1
PRISMA-ScR checklist.
[DOCX File, 86 KB - resprot_v14i1e75981_app2.docx]

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Abbreviations

BCT: behavior change techniques
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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QoL: quality of life

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Medication Management Using Technology-Based Interventions in Older People at Home Care Settings: Protocol for a Scoping Review

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Abstract

Background: Older adults with complex care needs and polypharmacy are at risk of experiencing medication-related problems such as administration errors and adverse drug events. These problems lead to increased use of emergency care and hospital admissions. Technology-based interventions have been introduced to address some of these problems. This review aims to establish key concepts and address the gaps in the evidence base to improve the use of technology-based interventions and reduce medication management-associated problems in home care settings.

Objective: This scoping review aims to understand the extent and type of evidence regarding the management of medications for older people in home care settings using technology-based interventions.

Methods: The review will follow the Joanna Briggs Institute (JBI) methodology. The published studies will be searched through MEDLINE, CINAHL, Scopus, Web of Science, Embase, IEEE Xplore, and ACM digital library, and the unpublished studies through the EBSCO Open Dissertations database. Studies published in all languages will be considered. A broad scope of evidence, including quantitative, qualitative, text, and opinion studies, will be considered. This review will include studies of older adults (aged 60 years or older) living in home care settings and receiving formal or informal social care support for medication management. Studies that focus on the application of the technology for medication management will be included. The titles and abstracts will be reviewed initially for relevance, and then, the full text will be reviewed for in-depth analysis. The results of the search and inclusion process will be presented in a Preferred Reporting Items for Systematic Review and Meta-Analysis extension for Scoping Reviews (PRISMA-ScR) flow diagram. Data will be extracted from the included studies using a data extraction tool developed for this study.

Results: A draft charting table will be developed as a data extraction tool. Results will be presented in a graph, diagram, or table, accompanied by a narrative summary.

Conclusions: This review will identify and synthesize evidence associated with applying technology-based medication management interventions to older people in home care settings and the strategies to overcome those identified challenges. This review will identify knowledge gaps, clarify concepts, and make recommendations for future research on technology-based medication management interventions.

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KEYWORDS

complex social care; effectiveness; medication management; patient safety; digital health intervention; personalized care; decision support system

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Introduction

Overview

Improvement in living conditions and advancement in health sciences have led to people living longer [1]. This has resulted in a rapid increase in the aging population worldwide. With advancing age, people tend to develop problems affecting dexterity, vision, hearing, and cognitive functions, which can significantly affect their ability to take medications or follow instructions, presenting unique challenges that require our understanding and empathy [2]. Furthermore, many older adults are living with multiple health problems (multimorbidity) [1] and are taking multiple medications (polypharmacy) [3]. In addition to health care needs, many older adults have complex social care needs, and they receive care from health care professionals and/or social care support workers in their home settings [4].

The process of medication management involves the identification of a problem, confirmation of a diagnosis, reviewing (starting, stopping, continuing, or changing) medications, and monitoring their effects [5]. Adopting a person-centered and holistic approach is crucial in the process of medication management. This approach not only ensures safe practices but also enhances the health outcomes of older adults [6]. Maidment et al [7] proposed interventions to empower older adults and informal carers to manage the challenges associated with multimorbidity and polypharmacy, which involve identifying older people at risk, maintaining a personalized record of their treatments and health conditions, and sharing it with the individual, informal carer, and practitioners [7].

Managing medicines in home care settings is a complex and challenging task, given the unique home environment and situations that differ from hospital or care home settings [8]. Some older adults self-administer their drugs, whereas others get help from informal caregivers (such as family members, friends, and neighbors) or from social care support workers who may not have the necessary training to manage medications [4]. The roles and responsibilities of individuals involved in providing informal care vary, which may possibly affect communication and increase the risk of medication errors [9].

Problems could potentially occur at any stage of medication use while prescribing, dispensing, storing, administering, or monitoring drugs [10,11]. Some of the challenges associated with medication management in home care settings are non-adherence [12], administration errors, inappropriate storage [13,14], and adverse side effects [15,16]. Additionally, factors including multimorbidity and polypharmacy cause an increased risk of drug-to-drug interactions and drug-to-disease interactions in older adults [3]. These medication-associated problems can affect their health outcomes, causing frailty, falls, frequent hospitalizations, reduced quality of life, and life-threatening events [3]. These challenges lead to increased use of emergency services and hospital beds [17] and can impact health care costs [7].

In recent years, technology-enabled processes such as the use of electronic health records, computerized decision support systems (CDSS), electronic prescriptions, robotic dispensing, electronic medication administration records, and regular telephone follow-up/review have been introduced to overcome problems associated with medication management, offering hope and optimism for the future of geriatric care [11,18]. Additionally, electronic pillboxes, text message reminders, and smartphone applications have been used to enhance medication adherence in older adults [12].

Despite the introduction of these strategies, the problems associated with medication management, such as the incidence of medication error, are high in home care settings compared to primary and secondary care [8,19,20]. Therefore, it is crucial to understand the role of technology-based interventions in managing medications of older adults in home care settings. This will help identify and promote safe medication administration practices. The study will focus on the quality of care, including safety, impact, and accessibility of technology-based medication management interventions [11,21]. The term “impact” refers to “positive or negative, direct or indirect, intended or unintended change produced by an intervention” [22] and the term “accessibility” means availability and ease of use.

A scoping review is an appropriate methodology for this study as they are designed to examine available evidence in the subject area, map key concepts, identify gaps, and develop potential research questions without following strict inclusion criteria [23-25]. Recent reviews on the use of Digital Health Twin (scoping review) [26] and Quality Improvement Intervention (systematic review) [27] in older care settings have demonstrated expected results, that is, improvements in the user implementation of the technologies. A similar review in the setting of older adult care would generate new knowledge for the health and social care system, as well as for older individuals and care providers. The findings of the review, with their broader relevance, have the potential to significantly inform and improve technology-based medication management systems for older adults, thereby meeting current societal challenges.

A preliminary search of the Cochrane Database of Systematic Reviews, Campbell Systematic Reviews, PROSPERO International Prospective Register of Systematic Reviews, and Joanna Briggs Institute (JBI) Evidence Synthesis was conducted. A systematic/scoping review (CRD42023481881-PROSPERO International Prospective Register of Systematic Reviews) is ongoing to explore the impact of nursing roles and responsibilities in optimizing nurse-led digital medication management in older people’s home care. However, this proposed review is different as it will focus on technology-based medication management in older people receiving formal (paid) or informal (family, friends, and neighbors) social care at home and will not include studies involving nursing care. The Cambridge dictionary explains the meaning of social care as “care by public organizations and private companies for people in society who need special help in order to live comfortably, for example, help with washing or eating” [28]. Nursing care in this review refers to care provided by qualified (registered) nurses.

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Aim and Review Questions

The primary objective of this scoping review is to assess and synthesize best available evidence on the use of various technology-based interventions (such as electronic pillboxes, text message reminders, smartphone applications, and electronic medication administration records) in managing medications of older people living in their own home settings with or without the support of formal or informal carers. The quantitative synthesis will identify different types of interventions being used and the qualitative synthesis will focus on understanding the impact of using these interventions on older adults and their carers. The review also aims to explore factors that affect the use of technology-based medication management interventions and the strategies that have been implemented to overcome challenges associated with these interventions. The review questions specifically are: (1) What technology-based interventions are used to support older people living at home and their carers (formal and informal) in managing polypharmacy? (2) What are the impacts of digital health tools (or technology-based interventions) on older people living in home care settings and their carers (formal or informal) in managing medicines? (3) What are the factors (facilitators and barriers) that affect technology-based interventions used for managing medicines for older people living at home? (4) What strategies have been evaluated and implemented in home care settings to address the challenges and improve technology-based medication management interventions?

Methods

The proposed scoping review will be conducted under the JBI methodology for scoping reviews [29].

Search Strategy

A database search will retrieve both published and unpublished studies. A three-step search strategy will be followed to find studies for this review (Table 1). The first step would involve conducting an initial limited search of MEDLINE (via PubMed), the Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Scopus to identify articles on the topic. Thereafter, text words in the titles and abstracts of relevant articles, and the index terms used to describe the articles, will be analyzed to develop a complete search strategy. The second step will involve identifying keywords and index terms in each database and/or information source, including Web of Science, EMBASE, IEEE Xplore, and ACM digital library. Finally, the reference list of all included sources of evidence will be screened for additional studies. The EBSCO Open Dissertations database will be used to retrieve unpublished studies, such as dissertations and theses. Reviews, such as systematic, scoping, and narrative reviews, and letters to editors will be excluded. Studies published in all languages will be included in the review.

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Table . Search strategy on databases.

Participant, concept, and context scheme (#)	Search string	Number of articles retrieved on database search using keywords						
		MEDLINE	CINAHL[a]	Scopus	Web of Science	Embase	IEEE Xplore	ACM Digital Library
Medication (#1)	medication or drug* or medicine*	14,838,278	1,391,268	12,482,052	6,913,972	26,186,006	183,753	97,200
Older adults (#2)	aged or elderly or "old* adult*" or geriatric* or "old* people" or "old* person"	6,598,273	1,226,233	7,217,331	5,207,581	6,965,179	112,529	220,136
Home care settings (#3)	"Home care" or "domiciliary care" or "home based care" or "domestic care" or "informal care" or "home care" or "social care"	142,058	119,349	131,091	95,683	140,035	10,117	1,945
Digital technology (#4)	"Digital technology" or "technolog* interventions" or "technolog* solutions" or telehealth or telemedicine or "digital health" or "digital medicine" or ehealth or mhealth	118,974	55,126	237,816	164,600	155,221	733, 312	23,375
Combine (#5)	# 1, #2, #3 AND #4	713	101	369	212	1,273	231	549

[a]CINAHL: Cumulative Index to Nursing and Allied Health Literature.

Eligibility Criteria

Overview

This scoping review will include the following PCC mnemonics: population, concept, and context. These mnemonics will be used as a guide; therefore, the inclusion criteria of this scoping review will include a detailed description of types of participants, concepts, and context, as well as search strategies, data extraction, charting, analysis, and presentation of the results. The eligibility criteria are listed in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Conference papers.
- Grey literature.
- Studies involving older individuals (60 years or more) associated with technology-based intervention to manage polypharmacy, regardless of gender, age, ethnicity, socioeconomic status, disorders, or disability.
- Studies that include paid or unpaid carers, whether they are family members or friends.
- Studies that include social care providers involved in older care settings and technology-based intervention to manage polypharmacy.
- Studies that evaluate and discuss the process and application of technology-based intervention to manage polypharmacy involving caregivers, older individuals, or family, friends, or relatives.

Exclusion criteria

- Meeting abstracts.
- Review articles.
- Editorial materials.
- Book chapters.
- Studies that do not involve older people living in home care settings.
- Studies that involve older people living in home with support of nursing care
- Studies that do not focus on technology-based interventions in managing polypharmacy or are not directly related to older people living at home with the support of formal or informal social care.
- Studies not in the context of home social care settings.
- Studies where technology-based interventions are not used.

Participants

This review will include studies of older people (aged 60 y or more) living at home and managing polypharmacy by themselves or with the assistance of formal (paid social care) or informal (family, friends, and neighbors) care support, irrespective of diversity, including age, gender, race, ethnicity, socio-economic status, and disability. Studies involving older adults receiving home nursing or medical care will not be included. Receiving home nursing or medical care in this review means receiving care from a qualified (registered) health professional, such as a registered nurse or physician.

Concept

This review will include studies that evaluate technology-based interventions (digital health tools) to support polypharmacy in older people living at home.

Context

Studies that evaluate the effectiveness of medication management in older people in a home care setting will be included. Home care setting in this review means living at own home and receiving social care. Medication management studies involving older people living in nursing homes or care homes or living at home with the support of home nursing care or hospital-at-home care will be excluded from the review.

Types of Sources

This scoping review will consider both experimental and quasi-experimental study designs, including randomized controlled trials, non-randomized controlled trials, before and after studies and interrupted time-series studies. In addition, analytical observational studies, including prospective and retrospective cohort studies, case-control studies and analytical cross-sectional studies, will be considered for inclusion. This review will also consider descriptive observational study designs, including case series, individual case reports and descriptive cross-sectional studies for inclusion.

Qualitative studies will also be considered, including but not limited to, designs such as phenomenology, grounded theory, ethnography, qualitative description, and action research. Text and opinion papers will also be considered.

Source of Evidence Selection

Following the search, all identified citations will be collated and exported to Covidence, and duplicates will be removed using this software. In addition to this, during the screening process, duplicates will be removed by manually checking all the retrieved (published and unpublished) articles. A pilot test of the study selection process will be conducted to ensure the efficacy and reliability of the process. During this phase, team members will independently assess up to 25 randomly selected titles and abstracts for alignment with the eligibility criteria. Any discrepancies in the findings, modifications to the eligibility criteria, and additional clarifications or broadening of the document's scope would be collaboratively reviewed by the entire team. Formal screening would commence on achieving a consensus threshold exceeding 75% as recommended in the JBI scoping review guideline [30].

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Following a pilot test, titles and abstracts will then be screened by two or more independent reviewers for assessment against the inclusion criteria for the review. The quality of unpublished articles will be established by checking if ethical principles have been followed. Potentially relevant sources will be retrieved in full, and their citation details will be imported into the JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI) [30,31]. The full text of selected citations will be assessed in detail against the inclusion criteria by two or more independent reviewers. Reasons for excluding sources of evidence in full text that do not meet the inclusion criteria will be recorded and reported in the scoping review. Any disagreements between the reviewers at each stage of the selection process will be resolved through discussion or with an additional reviewer(s). The results of the search and the study inclusion process will be reported in full in the final scoping review and presented using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) checklist [32] and flow diagram [33]. Consistency and agreement between reviewers will be evaluated by measuring the inter-rater reliability score using Cohen's kappa coefficient statistical method [30].

Data Extraction

Data will be extracted from papers included in the scoping review by two or more independent reviewers using a data extraction tool developed by the reviewers. Translation tools such as Google Translate and Deep L will be used to translate articles published in other (non-English) languages. The data extracted will include specific details about the participants, concept, context, study methods, and key findings relevant to the review question(s).

A draft extraction form will be developed. Some critical information that will be included in the charting table is (but is not limited to): name of the author(s), year of publication, country of origin for the study, aims, study population and sample size, methodology or methods, type of intervention or comparator, duration of the intervention, outcomes measures, and findings. Data on key variables such as technology-based interventions (electronic pillboxes, smartphone applications, text message reminders and electronic medication administration records) used by older adults and their formal/ informal carers, its accessibility (availability of the device, internet connections, and skills to use the device), and its impact including medication adherence, medication errors, and hospitalization will be collected.

Pilot testing of the data extraction form will be conducted on each type of evidence, such as primary research articles, conference papers, and theses. During this stage, each reviewer will complete a data extraction form for a minimum of two to three articles per evidence source type. Thereafter, the reviewers will establish whether it captures the necessary data to answer the review questions. The reviewers will determine if any clarification or modification of the form is required. The draft data extraction tool will be modified and revised as necessary during the process of extracting data from each included evidence source. Modified data extraction forms will be saved using version control and will be shared with all reviewers. Modifications will be detailed in the scoping review. Any disagreements that arise between the reviewers will be resolved through discussion or with an additional reviewer(s). If appropriate, authors of papers will be contacted to request missing or additional data, where required.

Results

The evidence presented would align with the scoping review objective and questions. Data items will be analyzed by quantifying text and counting the frequency of data extraction items using descriptive statistics, such as percentages /proportions. Frequency counting will be used to determine the number of evidence sources that used a particular technology-based intervention to support older people living at home and their carers (formal and informal) in managing polypharmacy, and to determine the country where the study was conducted [34]. Other relevant information will be extracted by mapping interventions to the Template for Intervention Description and Replication (TIDieR) checklist and by answering the items in the checklist using responses such as "fully reported," "partially reported," or "not reported" [35]. Qualitative evidence will be analyzed using a basic qualitative content analysis involving an inductive approach [34].

The data will be presented graphically or in diagrammatic or tabular form. A narrative summary will accompany the tabulated and/or charted results and describe how the results relate to the objective and questions of the review [36].

Discussion

Overview

A rapid increase in the aging population is seen globally [37]. This has led to many people living at home with complex social and/or health care needs. The risk of medication-associated problems is high in older people with chronic illness and polypharmacy [9]. It is estimated that approximately 44% to 76% of people with multiple health conditions do not adhere to prescribed medications [38].

Managing medicines in home care settings presents a unique set of challenges, distinct from hospital or care home settings. The complex and dynamic home environment requires innovative solutions for effective medication management. Technology-based interventions have a vast potential to support the health and well-being of older adults [37]. A systematic review of studies on technology-mediated strategies in maintaining medication adherence in older adults identified 19 studies and concluded that strategies, including the use of electronic pillboxes, smartphone applications, and text message reminders, significantly help older adults adhere to complex medication regimes [12].

These advancements hold promise for the future of geriatric care, instilling hope and optimism in the potential of technology-based interventions. Given the high incidence of medication errors in home care settings compared to primary and secondary care, it is crucial to understand the role of technology-based interventions in managing the polypharmacy of older adults in home care settings. This understanding is vital

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for identifying and promoting safe medication administration practices, underscoring the urgency and importance of this research.

This review will provide information on the availability of different types of technology-based medication management interventions in different countries and the experience of older adults, carers, and health care professionals on their usage. This knowledge will aid in identifying variation in practices and areas for improvement. This study aims to identify the facilitators and barriers to using technology-based medication management interventions in a home care setting by older adults, carers, and health professionals. Understanding the factors that affect its use will help us develop strategies and implement resources to enhance safe practices and promote medication adherence among older adults in home care settings.

Limitations

It is estimated that by 2050, the majority of older adults will live in low- and middle-income countries [39]. Presently, these countries lack health care and social infrastructure to support older adults, which was evident during the coronavirus disease-19 pandemic [40]. There is a possibility of finding a gap in the literature from low- and middle-income countries on the use of technology-based interventions to support medication management of older adults. The findings of this study should be considered with caution, as there is a possibility of the review being limited to high-income countries. A comprehensive search will be conducted using a standard 3-step method, and gray literature will be included to ensure that all relevant articles are considered for review. The quality, transparency and consistency of the scoping review process will be augmented by using the PRISMA-ScR checklist [32]. Additionally, the recommendations proposed by the Agency for Health Care Research and Quality [41] will be followed to minimize the risk of bias in individual studies.

An inclusive approach will be taken to ensure the scoping review generates generalisable findings [27,42]. However, adequate resources for training and research are required for successful implementation of technology-based medication management interventions [37]. Factors such as a lack of resources and digital inequality in low socio-economic populations [43] and lower- and middle-income countries [44] affect the transferability of findings.

The perspectives of health care professionals, patients, and their carers are significant and integral to the review process. However, they were not involved in the process of developing the protocol, which is a limitation of this scoping review. They will be involved in the discussions to support the interpretation of findings and the dissemination of the review.

Conclusions

Presently, there are no ongoing systematic reviews or scoping reviews on this topic. This review will identify and synthesize evidence associated with the application of technology-based medication management interventions in older people in home care settings, including availability, experience and factors affecting the use of these interventions. Additionally, this study will identify the strategies employed to overcome the identified challenges in home care settings for older adults. This review will identify knowledge gaps, clarify concepts, and make recommendations for future research on technology-based medication management interventions.

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Generative AI was not used in any part of the manuscript writing.

Data Availability

All data generated during this study will be included in the original review article (and its supplementary information files).

Authors' Contributions

ST: Conceptualization, Formal Analysis, Investigation (first reviewer), Methodology, Writing– original draft, Writing – review & editing, Data curation.
BF: Conceptualization, Supervision, Writing – review & editing.
JS: Conceptualization, Supervision, Writing – review & editing.
MSRJ: Conceptualization, Supervision, Investigation (second reviewer), Methodology, Data curation, Validation, Writing – review & editing.

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Conflicts of Interest

None declared.

Checklist 1
PRISMA-ScR checklist.
[DOCX File, 110 KB - resprot_v14i1e75200_app1.docx]

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Abbreviations

CDSS: Computerized Decision Support System
CINAHL: Cumulative Index to Nursing and Allied Health Literature
JBI: Joanna Briggs Institute
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
PROSPERO: International Prospective Register of Systematic Reviews

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Protocol

In Silico Evaluation of Algorithm-Based Clinical Decision Support Systems: Protocol for a Scoping Review

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Abstract

Background: Integrating algorithm-based clinical decision support (CDS) systems poses significant challenges in evaluating their actual clinical value. Such CDS systems are traditionally assessed via controlled but resource-intensive clinical trials.

Objective: This paper presents a review protocol for preimplementation in silico evaluation methods to enable broadened impact analysis under simulated environments before clinical trials.

Methods: We propose a scoping review protocol that follows an enhanced Arksey and O'Malley framework and PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines to investigate the scope and research gaps in the in silico evaluation of algorithm-based CDS models—specifically CDS decision-making end points and objectives, evaluation metrics used, and simulation paradigms used to assess potential impacts. The databases searched are PubMed, Embase, CINAHL, PsycINFO, Cochrane, IEEEXplore, Web of Science, and arXiv. A 2-stage screening process identified pertinent articles. The information extracted from articles was iteratively refined. The review will use thematic, trend, and descriptive analyses to meet scoping aims.

Results: We conducted an automated search of the databases above in May 2023, with most title and abstract screenings completed by November 2023 and full-text screening extended from December 2023 to May 2024. Concurrent charting and full-text analysis were carried out, with the final analysis and manuscript preparation set for completion in July 2024. Publication of the review results is targeted from July 2024 to February 2025. As of April 2024, a total of 21 articles have been selected following a 2-stage screening process; these will proceed to data extraction and analysis.

Conclusions: We refined our data extraction strategy through a collaborative, multidisciplinary approach, planning to analyze results using thematic analyses to identify approaches to in silico evaluation. Anticipated findings aim to contribute to developing a unified in silico evaluation framework adaptable to various clinical workflows, detailing clinical decision-making characteristics, impact measures, and reusability of methods. The study's findings will be published and presented in forums combining artificial intelligence and machine learning, clinical decision-making, and health technology impact analysis. Ultimately, we aim to bridge the development-deployment gap through in silico evaluation-based potential impact assessments.

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KEYWORDS

clinical decision support algorithms; in silico evaluation; clinical workflow simulation; health care modeling; digital twin; quadruple aims; clinical decision; decision-making; decision support; workflow; support system; protocol; scoping review; algorithm-based; screening; thematic analysis; descriptive analysis; clinical decision-making

Introduction

The recent advent of artificial intelligence (AI) in clinical decision support (CDS) systems furthers the intended purpose of such systems to enhance medical decision-making by using clinical knowledge and other health information [1]. Traditionally, such systems rely on either standard of care or knowledge-based models [2]. AI models' statistical learning capability—iteratively identifying and learning patterns from large volumes of data—facilitates including more information to arrive at an optimal decision recommendation [3,4]. Despite the prevalence of AI-based CDS development [5], adoption has been limited [6,7]. A significant barrier to adoption is the high trust and safety requirement of health care applications that demand evidence on implications to the broader system and the clinical workflows across the care value stream [5,8,9].

The current state of reporting traditional statistical analysis and CDS development predominantly focuses on accuracy, sensitivity, specificity, goodness-of-fit, and other discrimination-related measures [3] that do not precisely measure patient-, provider-, process-, and cost-related outcomes. These metrics may not capture the actual clinical improvements or the broader consequences that may arise when implementing CDS within the clinical workflows. For example, such metrics may be limited or require calibration when considering context-specific tradeoffs in predictive accuracies. Preference may be higher sensitivity than specificity in different contexts, such as early screening. Conversely, an oversensitive screen may result in more resources needed for confirmatory testing [10]. Hence, the ability to simulate the impact of model calibration and thresholding decisions for downstream workflows and eventual outcomes may be beneficial, especially when provider and process resources could render any CDS-based recommendation impracticable.

Traditional assessments of the implications of health technologies, such as algorithm-based CDS, focus on generating clinical evidence through randomized controlled trials to balance assessment scope and feasibility [11]. However, such assessments are challenged by the following: (1) the need for continuous evaluation of impact both in the development stage [12,13] and when such systems are deployed [14,15], (2) the need for more robust evidence that accounts for variations among real-world care pathways—characterized by heterogeneous settings and patient populations [5,9,16,17], and (3) the cost of an expanded scope of assessment when considering a broader health care pathway or system [18] such as in the evaluation of bundled payments in health care pathways and value-based health care [19,20].

In silico methods that simulate real-world care pathways present an alternative to evaluate CDS at preimplementation while approximating real-world care pathway events, behaviors, disease states, and resource constraints. These methods enable an iterative analysis of different clinical workflow scenarios, addressing the need for continuous impact evaluation without significant resource demands and disruptions to ongoing usual care practice [11,21,22]. In addition, such methods allow for the integral consideration of practical constraints [11,23], such as when at-risk patients are correctly identified by a CDS but cannot receive the appropriate downstream interventions due to resource constraints [24,25]. The value of clinical workflow simulations as an alternative is put forward by the recent inclusion of preclinical evaluation of CDS in guidelines for academic research reporting. Specific to AI-based CDS, the development and exploratory clinical investigations of decision support systems driven by AI reporting guidelines strongly endorse the concept of preclinical or in silico evaluation—that is, via computer simulations before the first clinical trial [18]. Vasey et al [21] cite the development of other guidelines, for example, transparent reporting of a multivariable prediction model for individual prognosis or diagnosis–artificial intelligence [26,27] and standards for reporting of diagnostic accuracy study–artificial intelligence [28], that tackle the reporting of AI-based CDS evaluation at the preclinical stage. In addition, in silico modeling has been previously argued to be beneficial in drug discovery [29], surgical systems innovation [30], and biomedical product regulation [10], as it can address the trade-off between scope and resource demands existing in traditional impact assessments.

Evaluating CDS under uncertainty can leverage mathematical models that consider the inherent stochasticity of clinical workflows and systems, such as simulation models [22]. As decisions are often time-sensitive [31], simulations should also be dynamic. Discrete events simulation (DES) and agent-based models (ABM) are stochastic dynamic models frequently used [32]. These simulation models allow context-specific domain nuances to be captured in the model logic as discrete states, actions, and transitions, thereby capturing the unique characteristics and uncertainties that define clinical workflows across care settings and sites. Queueing, Markov, and other stochastic process models [22,33,34] are closely associated with these models. System-level workflow simulations such as those using DES [22] and ABM [35] can model intricate health care dynamics and are commonly applied to model clinical workflows in health service delivery. These methods facilitate comprehensive analyses encompassing patient journey, resource use, and stakeholder interactions, providing insights into operational efficiencies, bottlenecks, and unintended consequences of implementing automated decision-support

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interventions. It offers a flexible method to capture the dynamic workflows in which the entities (ie, patients and providers) interact and are exposed to important clinical/process events (ie, admission and clinical decision) while consuming and releasing resources (ie, number of nurses in a hospital ward at a given time interval) [36]. By adjusting the decision thresholds, we can evaluate the CDS' impact using a variety of decision-analytic measures, for example, decision curve analysis [37] to determine the most clinically helpful prediction model.

Given the significance of such in silico evaluation via simulation models, a consolidated knowledge base will help to guide their use in evaluating CDS systems. Current research needs to be more cohesive, with disparate methodologies focusing on narrow facets of health care delivery [38,39]. To support the advancement of workflow-sensitive evaluation methodologies for CDS systems, we propose a scoping review protocol that investigates the following components of in silico evaluation: (1) the use of more pragmatic measures of impact that are relevant to the quadruple aims of health care [40,41], and (2) the simulation modeling paradigm used. Specifically, we propose a review protocol that (1) maps out the state-of-art development and application of in silico clinical workflows to evaluate algorithm-based CDS—both traditional statistical analysis- and AI-based—models and (2) identifies relevant research gaps. To our knowledge, this is the first scoping review on in silico evaluation strategies for AI applications in CDS using workflow simulation methods.

Methods

Overview

We followed the stages in a scoping review proposed in the Arksey and O'Malley framework [42] while considering more recent enhancements [43-45] for each stage. Specifically, we followed the steps of (1) identifying the research question, (2) searching and identifying relevant studies, (3) study selection, (4) data extraction, (5) collection, summarizing, and reporting of findings, and (6) consultation with stakeholders. These are detailed in the succeeding sections.

Stage 1: Identifying the Research Question

This scoping review endeavors to synthesize existing knowledge on the in silico evaluation of algorithm-based CDS systems via clinical workflow simulation methods. High-fidelity workflow simulations offer a pragmatic solution by allowing in silico replication of clinical processes, predicting the behavior of systems, and assessing the potential impacts of new models without risking patient safety or disrupting existing services [46]. To identify the scope of the review, we first conducted a rapid scan [45] of existing academic articles that discuss the evaluation of algorithm-based CDS. This review includes those using standards of care, knowledge bases, or AI to support a clinical decision recommendation [2]. In succeeding sections, these are generically referred to as CDS.

Regular team discussions were conducted to summarize findings and shortlist authors who publish peer-reviewed journal articles in our field of interest. Our study team comprises researchers with collective experience in machine learning model development, conducting systematic review studies, systems optimization research, and medical research and practice. The authors of this protocol—a senior clinician (QZ), a senior data scientist (SSWL), a junior data scientist (MD), and a junior pharmacoepidemiology researcher (YLC)—serve as the initial review team. After several initial iterations, we agreed on the research questions in Textbox 1. Further, we identified a list of concepts and accompanying keywords relevant to our main research question. These are presented in Table 1. Our focus lies in the exploration of simulation methods, particularly their application to clinical decision-making tasks. We aim to examine how these simulation models are developed, implemented, and evaluated. Additionally, we seek to identify gaps within the existing body of literature, specifically concerning the design and assessment of simulation-based approaches in health care.

Textbox 1. Main and specific research questions.

Main research question (RQ):

- What are the proposed in silico potential impact evaluation strategies for clinical decision support (CDS) systems?

Specific RQs:

- RQ1: What are the reported clinical decision tasks and domains that report the use of CDS?
- RQ2: What metrics are reportedly used for evaluating potential impact?
- RQ3: What simulation modeling paradigms are used?
- RQ4: What are the intended objectives of the simulation modeling frameworks used?
- RQ5: What are the gaps in existing literature of in silico CDS evaluation?

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Table 1. Concept framework used in searching relevant articles.

Key concepts	Keywords
Clinical decision support models, algorithms, and systems	Machine learning, deep learning, artificial intelligence, reinforcement learning, supervised machine learning, unsupervised machine learning, semisupervised machine learning, self-supervised machine learning, expert system
Objective of the CDS[a] model	Clinical decision support, clinical decision-making, prognosis, diagnosis, screening, triage
Evaluation objective	Validation, potential impact, impact assessment, decision analysis, decision analytics measure, model calibration, model tuning, credibility, cost-benefit analysis
Evaluation strategy	In silico, computer simulation, digital twin, simulation, preimplementation, predeployment, computational simulation

[a]CDS: clinical decision support.

Stage 2: Identifying Relevant Studies

In identifying relevant studies, we first conducted an automated search dated May 2023 of medical (PubMed, Embase, CINAHL, PsycINFO, and Cochrane), open-domain (Web of Science), engineering (IEEEXplore), and preprint (arXiv) academic articles databases using keywords from Table 1 generated during stage 1. Including preprint and engineering databases allows the search to extend to perspectives outside of the medical domain. The arXiv preprint archive was searched to account for more recent articles currently unavailable in peer-reviewed publication databases [47]. Duplicated articles and articles found in the preprint archives that were published will be removed from the pool of potential studies.

We undertook a pilot review on a manageable sample of the more relevant studies to refine the search strategy. The pilot review process allows us to refine our inclusion and exclusion criteria further. The pilot review team comprises at least one senior clinician and a senior data scientist with relevant health care domain experience to guide the construction of search strings—these were refined in a series of team discussions in consultation with a medical librarian. Multimedia Appendix 1 provides details of the source database-specific search strings used for each concept, as shown in Table 1. Differences in search strings are due to discrepancies on what databases can accommodate in a search (eg, wildcard characters may be adapted in some but not in others, and databases may vary in the type of subject heading indexing used). Two junior researchers (MD and YLC) collated the pool of articles identified from these search strings.

Stage 3: Study Selection

A 2-step screening procedure was adopted here—a title-abstract screening followed by a full-text screening was conducted for the articles identified from stage 2. Two reviewers independently screened the articles using the criteria presented in the succeeding paragraphs. The articles' titles and abstracts (ie, step 1 screening) and the full text (ie, step 2) were the basis for screening. The criteria for study selection are continuously revised through regular meetings. The reviewers arrange meetings to resolve any disagreements. The senior reviewers in the study team are consulted to reach a consensus when screening conflicts arise. According to the proposed guidelines for scoping reviews [48,49], we report the article search and screening results in a PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) [50] flow chart shown in the results section.

Our review included the following studies: (1) studies that directly support clinical decision-making specifically for diagnostic, triage, screening, prognostic, and prescriptive purposes; (2) studies that use AI, computer-executed algorithms, machine learning, and traditional statistical multivariate techniques; (3) risk prediction models for a disease condition or a future health outcome; (4) studies that assess CDS models in predeployment stage for its potential impact; (5) studies that propose the use of simulation-based optimization during model development; (6) human studies; (7) experimental or observational studies—including prospective, retrospective, and ambispective studies, clinical trials, pragmatic clinical trials, and validation studies; (8) studies that are published in journal articles, conference proceedings, and preprint archives; (9) studies written in English with no constraints on the year of publication; and (10) risk prediction models for a disease condition or a future health outcome.

We excluded the following studies: (1) studies that do not involve clinical domains as prediction outcomes; (2) studies that focused on the use of AI as therapy (eg, treatment monitoring and glucose control systems); (3) studies that use machine learning, pattern recognition, AI for descriptive analysis; (4) pathological specimen and sensing device signals accuracy-related studies; (5) image segmentation/registration only without classification/prediction with clinical end points; (6) studies that deal with purely system/population level outcomes that are irrelevant to patient-provider interactions; (7) pure qualitative evaluation for clinical usefulness; (8) purely methodological papers on medical data processing (eg, image processing and noise filtering) without specific application domain; (9) studies that use purely ex silico evaluation typically require either a partial or complete deployment of the developed CDS system (eg, randomized controlled trials for actual impact assessment); (10) studies that only use traditional metrics—for example, area under the receiver operating characteristic curve, area under the precision-recall curve, mean squared error, accuracy, sensitivity, specificity, goodness-of-fit, and other discrimination-related measures only—to validate CDS models, systems, and tools, that is, those studies that do not consider broader systems-level usefulness; (11) studies that do not report model development process (eg, proprietary CDS tools or systems) as these do not disclose sufficient information about

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underlying technology and algorithms; and (12) studies which report reviews (eg, scoping reviews, systematic reviews, and rapid reviews).

As our primary aim is to exhaustively review the published potential impact evaluation strategies done in silico for CDS, literature or scoping review studies were excluded. No other articles were excluded based on the year of publication. Deduplication was done using Zotero [51].

Stage 4: Data Charting

Overview

Data charting will collect critical information to answer the research question for the articles extracted from stage 3 after the 2-step screening process. An a priori list of coding variables corresponding to this study's concept framework and research questions has been developed (Table 2). Reporting [52,53] and data extraction [54] guidelines related to the concept framework guided the selection of coding variables to be extracted from the screened article database. As studies may or may not conform to these guidelines, and new categories and subcategories may be derived from the literature, the a priori coding variables may change. The emergent categories and subcategories will be checked for co-occurrences (overlapping concepts) and redundancies. Codes with the same concepts will be aggregated and refined to maximize mutual exclusivity and exhaustiveness. Aside from these structured coding variables, we shall also extract general information about the articles as guided by related published review protocols [55-57].

The data charting form will be developed in a shared collaborative Notion.so [58] database with the structure in Multimedia Appendix 1. The form was designed and maintained by an arbiter who ensures it is comprehensive and flexible. The charting process will be initially blinded. As with the article screening, we conducted a pilot charting trial to validate the encoding items. Each researcher can only see their respective chart to facilitate independent charting. An initial charting form is presented in Table 2. Team discussions were held as the team progressed in the charting process to consider other items to extract. At least 2 reviewers will be assigned to each article for validation. Any discrepancies will be resolved together with the entire team for the final determination of the charted codes. After the pilot trial, all articles included from stage 3 will undergo charting, resulting in an encoding database for this review.

Table 2. Data extraction items.

Data extraction broad concepts	Specific items extracted
Characteristics of the studies included	• Publication year • Research location (ie, country) • Data source • Data collection design • Collection period • Patient cohort description
Decision-making objectives and end points	• Objective of the CDS[a] model (ie, triage, diagnostic, prognostic, and prescriptive) • Specific decision-making tasks assisted by CDS • Clinical domains
In silico[b] evaluation metrics	• Specific evaluation metrics • General themes of the metrics (ie, patient, process, provider, and cost-effectiveness outcomes)
In silico evaluation frameworks	• Simulation modeling paradigm • Simulation modeling objective • Simulation parameters (parameters and parameter groups) • Reported reusability • Access to codes and tools used to conduct the simulation

[a]CDS: clinical decision support.

[b]Evaluations via computer simulations of clinical workflows during preimplementation.

Characteristics of the Studies

We include any study that reports the development of an expert system, a computer-aided clinical decision-making tool, or CDS with an underlying rule base or machine learning—including supervised, self-supervised, and unsupervised methods; deep learning; and reinforcement learning. We also include the more traditional multivariate analysis-based CDS such as linear, logistic, and Cox regression approaches to clinical scoring systems and prediction rules [38]. We encode the type of methods or algorithms used, their reported advantages (ie, aside from empirical performance reported), the disadvantages of the method, and their dependencies on data and the population from which the data was collected, as reported by the study authors. We also collected information about where the research was conducted and the year of publication.

Decision-Making Objectives and End Points

Since CDS model outcomes are directly related to its intended task and use, it is necessary to understand the scope of the desired outcomes from the predictions for an objective potential impact assessment. The development and use of clinical rules predate AI-based CDS. The outcomes of these clinical rules are broadly classified into diagnostic, prognostic, and prescriptive

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outcomes [52,54,59]. We adopt this same classification for AI-based CDS. Diagnostic outcomes generally predict the risk for a particular condition or disease (based on existing health data) to support early intervention or screening decisions. Prognostic outcomes indicate the future course of an illness or disease, including the likelihood of recovery, quality of life, complications, or mortality. Some CDS studies may prescribe treatment beyond diagnosis or prognosis end points [1,59]. Guidelines for reporting [52,53] and appraisal [54] prediction models mention a comparable taxonomy of CDS outcomes. Another reporting checklist for studies that use AI in medical imaging CDS differentiates the intended use (eg, diagnosis, screening, and staging) with the tools' proposed role (eg, triage, replacement, or add-on) [60]. We shall consider these classifications in our analysis.

In Silico Evaluation Metrics

We explore methods to evaluate CDS' potential impact in silico on clinical workflow operations, patient outcomes, and economic outcomes [5]. Our aims take inspiration from the renewed focus of health care towards the Quadruple Aims, which adds the well-being of care providers as a fourth dimension, in addition to the traditional aims of improved patient experience, better health of populations, and cost reduction [41,61]. This underscores the need to devise workflow-sensitive evaluation methods, for example, considering how CDS sustains service providers' productivity (eg, referral rates as a process metric) within a resource-constrained care pathway. Further, we consider how reported studies propose the measurement of potential impact on patient health beyond the traditional accuracy-related measures [38], such as net benefit [62], realized [24] net benefit, and length of stay [63]. Some studies examine how implementing CDS systems impacts hospital budgets, with related metrics including costs and the incremental cost-effectiveness ratio [64]. More broadly, these metrics may be used to validate potential impact across different periods and study sites; this allows the monitoring of CDS performance consistency and the prompt triggering of model updates when necessary [15].

In Silico Evaluation Frameworks

Simulation modeling is a powerful tool for analyzing complex systems by creating representations that mimic the real world. It allows researchers or decision-makers to study how the system will behave over time prior to the actual deployment. Different simulation methods can be characterized by specific attributes, such as discrete or continuous, static or dynamic, and stochastic or deterministic [32]. A discrete simulation models the state of the system at distinct time points. For example, the number of patients in the waiting room only changes when a patient arrives. In contrast, a continuous simulation models the parameter that changes over time regardless of any triggers that change the state of the parameter. A static simulation models the system only at a specific time point, while a dynamic simulation studies the system's evolution over time. Last, a stochastic simulation involves randomness where simulation parameters can be probabilistic. For example, the patient arrival times may follow a specific distribution. However, a deterministic simulation encompasses parameters that have specific values. For instance, if the simulation sets the number of patients per time interval to 10, the value of such a parameter will stay at 10 throughout the simulation.

Our study focuses on existing research that reports using workflow simulation methods to assess the potential impact before embarking on often challenging and costly actual impact assessment. In silico evaluation can provide a more robust basis for successful implementation trials. As such, we consider studies that evaluate AI tools through an in silico approach without the need for actual deployment. Strategies may use reinforcement learning that optimizes a policy for multiple stages of decision-making (ie, such as machine learning–assisted treatment selection) [65]. Another approach may model a clinical care pathway as a discrete set of states and transitions [25], namely, DES, a popular method in health care workflow simulation to study resource allocation as it incorporates how resources change according to triggering events [36]. Another method, ABM, is particularly useful for modeling the interactions between various entities (ie, health care workers) in a clinical workflow [11]. Studies may also use a retrospective evaluation using cross-validation and decision curve analysis [24,62,66] to measure a decision-analytic score. As data extraction proceeds, we shall consider the more precise taxonomy of the simulation modeling [32] while broadly accounting for other in silico approaches, such as the examples. Other paradigms used will be encoded and reported as they arise.

We further consider the intended purpose of simulation, that is, the simulation modeling objective, which may fall under 1 of the three initial categories: (1) to conduct a straightforward measurement of clinical usefulness metrics, (2) to analyze the sensitivity of outcomes to various workflow parameters and scenarios, and (3) to optimize decision-making capability of CDS via a care pathway simulation.

Last, we consider the parameters used to construct the in silico clinical workflow. Specifically, we shall evaluate how patient, provider, process, and cost considerations are represented as simulation parameters. These clinical workflow factors describe the real-world care pathway, including patient condition states, treatment or intervention events, resource availability, duration of events, and many other factors.

Stage 5: Collection, Summarizing, and Reporting of Results

We will collect the data in a table of values corresponding to each variable (ie, column) and each relevant article (ie, row). An analysis of the values extracted will be done to identify sparse- and well-studied themes within and across critical concepts. Frequency and thematic analysis will be used for this analysis [44,67]. Themes combined with the extracted textual information will allow for the study of trends. Univariate and multivariate statistics will be reported as deemed relevant for each type of analysis. Descriptive statistics and charts will be used to describe the characteristics of the included study across the variables listed in Table 2. When appropriate, ANOVA, Kruskal-Wallis, and Pearson chi-square tests will compare trends across different categories. The association of variables based on co-occurrence will also be investigated. Further, the

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reusability of any software artifacts or code repositories associated with included studies will be reported according to the claims of the articles' respective authors. The reporting of results will follow the PRISMA-ScR guidelines [50].

Stage 6: Dissemination and Stakeholder Consultation

Beyond summarizing the results and findings, we will consider the overall implications of the findings for the in silico potential impact assessment of algorithm-based CDS systems, models, and tools. This scoping review will support the development of a draft framework that will guide clinical workflow simulation modeling for impact assessment, with specific considerations on the model purpose, evaluation scope, objectives, and strategy. This framework will further support the in silico evaluation of proposed CDS studies collected through discussion with potential stakeholders—implementation scientists, modelers, and clinicians conducting. This will also allow stakeholders to provide a higher level of interpretation, domain expertise, and perspective to validate the findings further and support effective knowledge transfer and uptake of evidence to ensure the usefulness of the scoping studies for AI developers and clinical researchers [43].

Results

Our review began with an automated search of selected databases in May 2023. The resulting articles were managed using Zotero [51] and Notion.so [58] for automated article metadata collection and note-taking, respectively. Most of the title and abstract screening were finished by November 2023. However, the review team allows for flexibility as the screening criteria are refined throughout the review. Full-text screening proceeded from December 2023 to May 2024, including hand-searching and reference chaining. Charting was concurrently done with the full-text screening. Analysis and writing of the full scoping review results will be finalized in July 2024. The reporting of this scoping review protocol and results as published literature will be from July 2024 to February 2025.

The current stage of our scoping review yielded the results shown in Figure 1. At the first screening stage, most articles were excluded based on titles and abstracts that did not fulfill the inclusion criteria. Moreover, we also excluded at this stage studies that suggest the development of CDS tools but only perform an evaluation using the area under the precision-recall and receiver operating characteristic curves, accuracy, precision, recall, F_1-score, and other traditional confusion matrix-based scores; further, these were studies that do not attempt to evaluate potential impact and usefulness to its intended clinical care pathway placement [38]. Additional studies were also excluded due to the focus on algorithmic developments in processing medical data (ie, image, text, and structured data). On the contrary, articles that mention usefulness and impact evaluation without providing further details in the title and abstracts were included in the full-text screening.

Figure 1. PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) flowchart. Asterisk (*) indicates data as of April 2024.

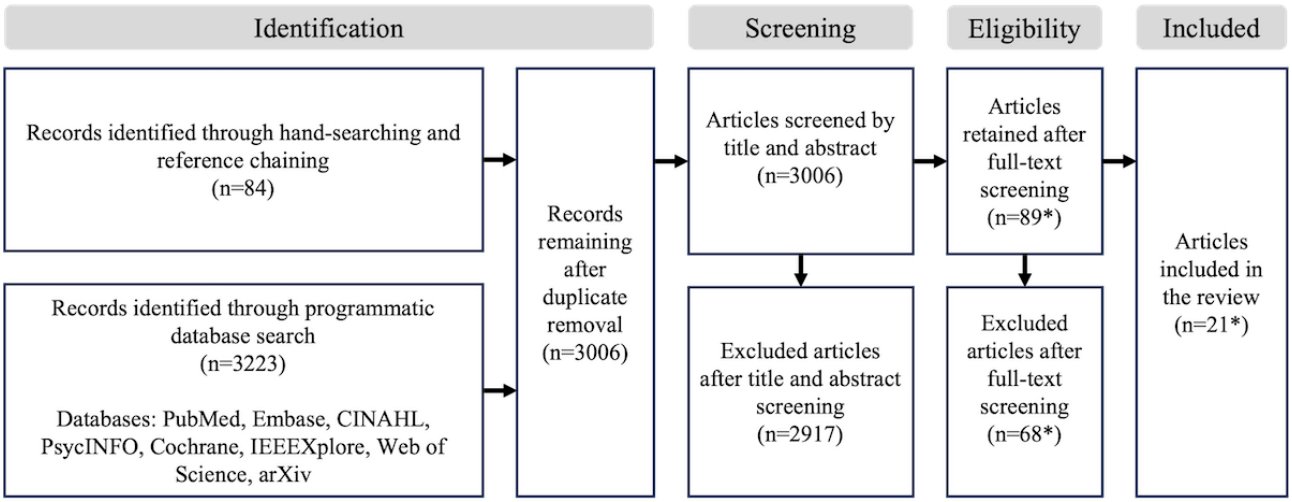

In the second stage of the detailed full-text screening (ie, using the full text as the basis), more articles were excluded due to the lack of potential impact and usefulness evaluation. Other articles were excluded as duplicates not detected in the initial automated deduplication based on article metadata. A few articles were also excluded due to unavailable full text, as only extended abstracts were published. As this stage is ongoing and considering that reference chaining may still be conducted based on the screened articles, the final number of relevant articles will be reported along with the scoping review results. As of April 2024, 21 articles are included in the review.

Discussion

Principal Findings

The proliferation of AI models in health care encourages researchers, patients, and providers to use these technologies to optimize the care delivery processes. Yet, only some models are being translated into clinical practice [6]. The ability of data-driven machine learning methods to generalize to different temporal and geographical patient cohorts is challenged by often changing real-world medical data [17]. This demands more robust and adaptive approaches to encourage user acceptance and trust [12,13,16]. Traditional impact assessments based on

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pilot implementation for health technology assessment can be resource-intensive with the rapid proliferation of new models [68,69]. The in silico evaluation of algorithm-based CDS provides a resource-efficient framework for estimating novel CDS' potential clinical impact to facilitate the seamless integration of a model into the workflow. Moreover, computer simulations require much fewer resources and have less direct implications for ongoing patient care, allowing for regular and repetitive use throughout the CDS development and maintenance lifecycle. Our review aims to analyze and report the scope of using in silico CDS evaluation in published academic literature. We expect that the results will uncover the clinical decision-making domains where such evaluations are used or, otherwise, underused, how clinical workflows are simulated, the potential impact metrics used to illustrate the usefulness of CDS, and areas where more research is necessary.

Several US Food and Drug Administration–accepted patient simulators [70,71] and other approaches [30,68] that simulate patient characteristics enable an in silico evaluation of patient-level impact and have been proposed to be used at a preclinical stage. These simulators allow the assessment of the response to different treatments by the same patient—which is unlikely in real-world treatment scenarios due to dynamic patient conditions. Comparably, clinical workflow enables simultaneous evaluation of various scenarios using the same patient cohort characteristics, sharing the same validation capabilities and objectives [72,73]. However, clinical workflow simulations encompass a broader perspective, considering the efficiency and effectiveness of treatments and interventions, such as CDS, across the entire care pathway.

In a preliminary collection of included articles, the broader perspective was demonstrated by the accounting for process-related factors. For example, time intervals (ie, door-to-doctor time) between workflow events were considered by Alenany and Cadi [63] as an evaluation metric. Misic et al [23] and Rodriguez et al [74] focused on patient volume and referral rates to evaluate workflow throughput. In addition, other studies simultaneously assess patient outcomes with cost-related outcomes, such as length-of-stay and costs per visit [75], early-stage cancer detection rate and cost savings [76], and intensive care unit length-of-stay and corresponding costs [77]. Yin et al [5] highlighted that in the real-life evaluation of AI applications, the outcomes considered can be grouped into patient, cost-effectiveness, and clinician outcomes. We consider this in our review and propose distinguishing between provider, that is, clinician outcomes and process outcomes [22], expanding the outcome themes into 4 categories.

Furthermore, similar themes can also be applied to categorize clinical workflow factors, that is, parameters, used in the design of an in silico care pathway. Lee et al [35] considered time intervals between events as simulation parameters. Other studies [23,25] used provider-related parameters such as provider effectiveness and carrying capacity. Other studies simultaneously consider patient-, cost-, and process-related outcomes—such as in [35,77]. These parameters are typically based on historically observed data distributions, expert judgment, cited from published literature, or determined from prospective time-motion studies. We will report such a basis for parameter initialization accordingly.

The interplay of multiple outcomes and drivers and the expansion of health care also aim to consider provider well-being, which adds to the complexity of impact evaluation. Different simulation modeling paradigms are proposed to handle such complexity—such as in the DES frameworks used by [25], the ABM done by [35], and state-transition models shown in the microsimulation by Rodriguez et al [74], and in the Markov-based transition model used in [78] evaluating wait time–saving effectiveness of an AI-based CDS. Moreover, dynamic treatment regime optimization is proposed to capture staged treatment scenarios and optimize outcomes [65]. Last, considering cost-effectiveness approaches, decision trees can also be used to capture costs and benefits attributed to a hierarchical decision-making scenario; this is demonstrated by Tsai et al [77] to evaluate an extubation failure prediction CDS.

While extensive literature on the usefulness of simulation modeling and knowledge of the simulation of clinical care pathways as avenues for CDS in silico evaluation still lack consolidation [79], possibly due to the significant context dependencies across different health systems. When translated into a quantitative modeling framework for rigorous, objective evaluation, the diversity, human-centricity, and complexity of clinical workflows pose unique challenges [18]. Addressing these challenges requires interdisciplinary groups familiar with hospital management, clinical context, process nuances, and the availability of necessary modeling capabilities. Despite the prevalence in the reported development and advancements of CDS models, accelerated by the surge in AI methods—studies that reported the extent of clinical and workflow impact through in silico evaluation are still relatively sparse [5,6]. A critical need remains to reassess the current model simulation practices to advance this field. We believe this will expedite the integration of novel CDS system development. To the best of our knowledge, this is the first review that aims to understand CDS system in silico evaluation methods beyond traditional accuracy metrics.

Conclusion

This scoping review follows the framework proposed by Arksey and O'Malley [42] and other recent enhancements [43-45]. We searched 8 medical-focused and general academic domain databases to gather articles from an interdisciplinary perspective. An automated search followed by a 2-step screening process was done to implement the scope of the review. Unlike previous reviews, we will specifically include CDS related to traditional multivariate models and machine learning. In addition, we designed a data charting table based on discussions with the multidisciplinary review team and previous reviews on related topics. This table will guide the data extraction phase, and the items will be flexibly revised along with further study of the included articles. Finally, we plan to summarize our results using descriptive and co-occurrence analyses. For example, the distribution of race and ethnicity of collected patient information—as reported by the included articles—will show how fairness is represented in current AI research in health care. Similarly, an analysis of co-occurring themes (ie, in statistical

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analysis methods, CDS decision-making tasks, evaluation metrics, and simulation paradigms) may surface clinical domain-specific and domain-agnostic approaches to in silico potential impact evaluation.

We anticipate our results will be informative about the state-of-the-art in silico evaluation method based on workflow simulation models and the associated outcome metrics and targets. More specifically, our results will describe the characteristics of the clinical decision-making domains being modeled, the relevant measures of impact that are simulated, and how such are captured in clinical workflow simulation. As we also aim to report the reusability of methods cited, our work will serve as a springboard for the reader to find suitable in silico evaluation frameworks, software artifacts, and code repositories. Ultimately, our work is a starting point in developing a unified in silico evaluation framework adaptable to various clinical workflow scenarios.

Limitations

There are several limitations to our approach. First, while some guidelines for reporting may exist, they may need to be revised to cover the variety of studies in our criteria. For example, a transparent reporting of machine learning models developed for diagnosis, prognosis, or prescriptive analytical support is still being developed [27], and conformance to these guidelines may influence the extent and precision of our data charting. Second, a critical appraisal of articles will not be done as we primarily aim to provide an overview of the scope by which in silico evaluation methods have been used. Third, we also included reports from e-Print archives (arXiv), trading off a more exhaustive scope versus the inclusion of non–peer-reviewed articles; an accounting of such articles will be provided in the reporting results. Last, we included only English articles; thus, we cannot extrapolate our findings to publications in different languages. Our findings will add to the knowledge of applications of statistical learning and simulation methods in health care.

Acknowledgments

We want to acknowledge He Yan for her valuable comments on the data charting forms and thank Ginny Chen Zhenzhi for taking on the project management required to move this research forward.

Data Availability

All data generated or analyzed during this study are included in this published article and its Multimedia Appendix files.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Supplementary material showing the keywords used and other details of the literature search, including a sample encoding sheet that uses Notion.so.
[DOCX File , 611 KB - resprot_v14i1e63875_app1.docx]

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Abbreviations

ABM: agent-based models
AI: artificial intelligence
CDS: clinical decision support
DES: discrete events simulation
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Digital Teaching and Learning Media for Nursing and Health Care Courses in Germany: Protocol for a Scoping Review

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Abstract

Background: In Germany, digital transformation and legal regulations are leading to the need to integrate digital technologies into the nursing profession. In addition, to nursing practice, they are also being incorporated into nursing training. Despite comprehensive regulations regarding the use of digital teaching and learning media in nursing education, their specific applicability and implementation vary.

Objective: This study aims to map evidence and identify the main concepts, theories, sources, and knowledge gaps in the use of digital teaching and learning formats in nursing and health care education in Germany.

Methods: The study is planned as a scoping review. The reporting of the study is based on the PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) 2020 guidelines. The sources of information for the review include six bibliographic databases (MEDLINE via PubMed, Cochrane Library, Web of Science Core Collection, ERIC, PROSPERO, and APA PsycInfo). The search results will be presented in accordance with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist. The eligibility of studies is based on the population, concept, and context criteria: (1) learners of nursing and health care professions, (2) digital teaching and learning formats, and (3) forms of implementation in Germany since 2007.

Results: The literature search is planned for January 2025. The selection of titles, the coding of the data, and the data analysis are expected to be completed by March 2025.

Conclusions: In Germany, there is a growing interest in integrating digital teaching and learning formats into nursing and health care education. Our scoping review will map applications of digital teaching and learning media in the education of nursing and health care professions in Germany. In this way, the scoping review provides relevant impulses for fields of application and design aspects of digital teaching or learning media for nursing and health care education.

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KEYWORDS

digital education; digital learning; digital teaching; e-learning; nursing; health care; digital transformation; digital technology; online learning; distance learning; health care education

Introduction

Background

The idea of learning with machines is not new. Back in the 1920s, Sidney L Pressey developed a machine that asked a question and offered four possible answers, like the multiple-choice method [1]. Nowadays, digital technologies are used to create and provide learning materials and to support and control the learning process [2]. In this context, the term “e-learning” describes all forms of learning with electronic or

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digital media [3]. The introduction of the iPhone in 2007 has been an international milestone in the development of e-learning [3,4]. Mobile devices create the conditions for innovative pedagogical approaches such as flipped classrooms or blended learning, by using modern technologies and various teaching methods to make learning more effective and personalized. In corresponding teaching and learning approaches, the time, place, pace, and scope of learning can be freely chosen [2], giving learners more autonomy and control over their individual learning process. A major advantage of mobile devices is that learners often already possess the necessary technical equipment [5]. The digitalization of nursing and health care education is considered to have particular potential due to the complexity of professional requirements and the constant further development of subject-specific knowledge [6,7]. In addition to the relevance of digital teaching and learning formats in nursing and health care education, there is also a need in Germany to incorporate digitalization into health care professional education. This arises from legal regulations such as § 8 Abs. 8 SGB XI or the E-Health Act, which are intended to promote the digitalization of professional practice and require corresponding skills on the part of nursing professionals. The digitalization of health care professional practice is intended to improve the quality of care and effectively prepare professionals for highly complex care situations, which should ultimately lead to better care outcomes for patients [8-10]. In addition, the topic of digitalization can be found in the new legal foundations of the Act on the Nursing Professions (Pflegeberufegesetz, PflBG), the Training and Examination Regulations for the Nursing Professions (Ausbildungs- und Prüfungsverordnung für die Pflegeberufe, PflAPrV) and the framework curricula and framework training plans. These foundations list forms of digital support for various parts of the nursing process.In this regard, there is a need to develop and integrate digital teaching and learning formats for nursing and health care education [6,11].

Objectives

In Germany, there are increasing efforts to integrate digital teaching and learning formats into nursing and health care education. This fact leads to the question, for which educational content and didactic concepts digital teaching and learning formats are used in nursing and health care education in Germany? Furthermore, which scientific findings are present about the use of digital teaching and learning formats in nursing and health care education in Germany? Thus, our main objectives are (1) digital teaching and learning formats and (2) forms of implementation in the context of learners in the nursing and health care professions.

Methods

Study Design

We conduct a scoping review [12,13] in consideration of published primary sources and reviews. All study designs with the exception of opinion studies, commentaries, editorials, letters to the editor, and pure case reports are considered in order to gain a broad overview of the research field. We operationalize the research question by using the population, concept, and context (PCC) scheme [14]. The population includes learners in the nursing and health care professions, the concept focuses on digital teaching and learning formats, and the context refers to forms of implementation in Germany since 2007. Study reporting is based on the PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) [15]. The PRISMA-ScR checklist will be available once the review is complete.

Patient and Public Involvement

Patients and the public are not involved in the design of this protocol. Thus, ethics approval is not required for the scoping review.

Eligibility Criteria

The eligibility of studies is based on the PCC criteria: (1) learners of nursing and health care professions, (2) digital teaching and learning formats, and (3) forms of implementation in Germany since 2007. The scoping review aims to map evidence and identify the main concepts, theories, sources, and knowledge gaps in the use of digital teaching or learning formats in nursing and health care education in Germany. The electronic search is conducted in German and English. Only titles, which are published since 2007 will be included because the iPhone was released for the first time in 2007, which enables new forms of learning and represents an international milestone in the development of e-learning [3,4]. Since this introduction, research into e-learning using mobile devices has increased.

Information Sources

The information sources for the scoping review will include six bibliographic databases (MEDLINE, Cochrane Library, Web of Science Core Collection, Education Resources Information Center [ERIC], PROSPERO, and APA PsycInfo). The starting point will be the search in MEDLINE via PubMed as the central database for scientific studies in the health professions. The PubMed search supports the generation of suitable mesh terms for the research question and is adapted to the databases Cochrane Library, Web of Science Core Collection, ERIC, PROSPERO, and APA PsycInfo [16]. The Cochrane Library provides access to up-to-date and reliable research, which is further complemented by the PROSPERO database as a repository of systematic reviews. ERIC covers the educational discourse on the question and Web of Science Core Collection bundles the vocational education and health care focal points of the question in a database. These focal points are further supplemented and completed by research via APA PsycInfo, which contains peer-reviewed journals, studies, books, and dissertations on learning and teaching methods in health care, including nursing didactics.

Search Strategy

The electronic search strategy will be developed iteratively by the team. The search was based on the PRISMA 2020 statement (Figure 1) [17,18]. The search terms and corresponding MeSH (Medical Subject Headings) terms will be derived to address the two main search topics of the scoping review: (1) digital teaching and learning formats and (2) forms of implementation in the context of learners in the nursing and health care professions.

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Figure 1. PRISMA-ScR 2020 flow diagram (source: own illustration, adapted from Page et al [17], licensed under CC BY 4.0 [18]). EC: exclusion criteria; EC 1: lack of reference to nursing and health care education; EC 2: no reference to digital teaching and learning formats; EC 3: no reference to the research question. ERIC: Education Resources Information Center; PRISMA-ScR: Preferred Reporting Items for Systematic Reviews extension for Scoping Reviews; PROSPERO: International Prospective Register of Systematic Reviews; WoS CC: Web of Science Core Collection.

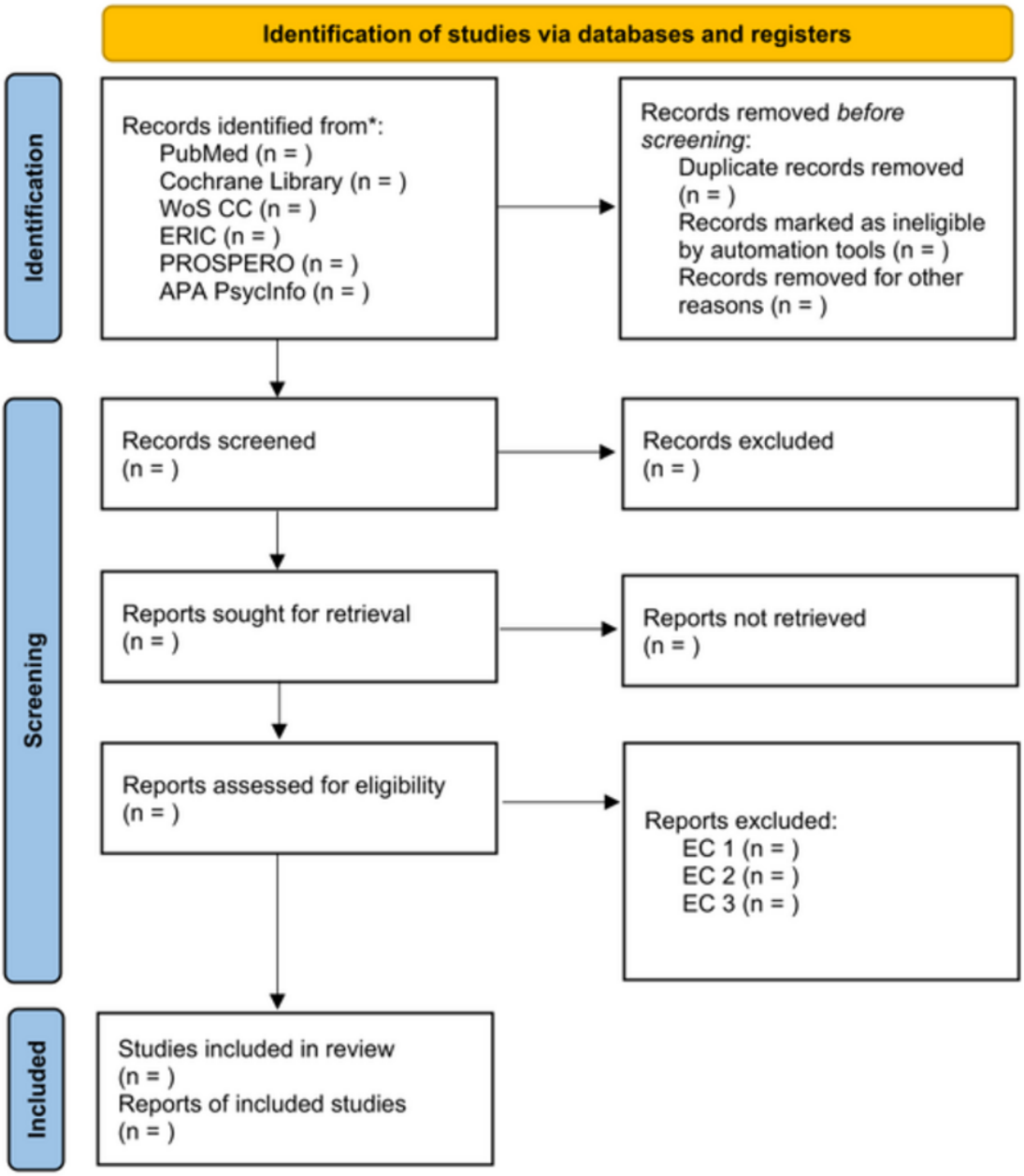

Selection of Sources of Evidence

Two researchers will search in mentioned databases independently of each other using the search strings and will check all studies for relevance and suitability. After screening, two researchers will compare the search results. Any contradictions or inconsistencies in the study assessment will be clarified through discussion. Studies that met the inclusion criteria will be used for the full-text evaluation. This will also be carried out by two researchers. If necessary, we will contact the authors to obtain further information. The study selection will be concluded with a consensus meeting. Afterward, the data for each included study will be extracted by using a self-developed form in Excel (Microsoft Corp). The results of the literature search will be reported in full once the scoping review is complete. A list of included and excluded studies following full-text screening and individual reasons for exclusion will be reported once the review is complete.

Data Charting

We will develop an Excel form for coding and recording all data. Two authors code all data independently of each other. The agreement between the codings is calculated using Cohen κ. If necessary, authors will be contacted to obtain further information. A consensus meeting is supposed to conclude the study selection.

Synthesis of Results

We plan to use qualitative content analysis to form categories in an inductive-deductive alternation [19]. In inductive category

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formation, categories are derived directly from the material [20]. Deductive category formation defines the categories before the data analysis [20] and refers to the used PCC scheme. This is categorized into setting, digital teaching, and learning format, as well as application formats. The coded data will be summarized in a table and then synthesized using descriptive statistics (relative frequencies).

Results

The literature search is scheduled for January 2025. We expect to select the relevant studies, code the data, and appraise the studies until March 2025.

Discussion

Principal Findings

Preliminary literature searches have shown that various digital technologies are used in nursing and health care education in Germany, including learning programs, learning platforms [6], and virtual reality technologies [21]. Our scoping review will include a detailed list of such applications once the studies have been selected. We will assess the outcomes of such digital technologies in the context of nursing and health care education in Germany. The most interesting aspect of our review will be application areas and requirements, as well as trends in digital nursing and health care education in Germany.

Comparison to Prior Work

Various digital learning methods have been widely implemented in nursing and health care education. Kimura et al [22] identified interactive online modules and videos as the most frequently used technology-enhanced tools in nursing education. The application period of digital learning formats in nursing and health care training varies [23,24]. Despite the positive associations, the potential of digital teaching and learning is by no means undisputed or proven. For example, the review by Bajpai et al [25] describes a lack of evidence regarding the effectiveness of digital interventions for the training of health care professions. Furthermore, Arkorful and Abaidoo [26] noted potential drawbacks, including reduced interactivity in e-learning environments. Other studies indicated that the achievement of intended learning outcomes through digital teaching or learning media for nursing and health care professions is influenced by variables such as age, training time, and experience of the participants [27,28]. While these findings are valuable, their direct applicability to the German education system is limited, underscoring the importance of examining country-specific implementations of digital education. In this regard, the literature indicates that there are gaps in the implementation of digital media in nursing education [6,29-31]. Our scoping review contributes to this gap by mapping applications of digital teaching and learning media in the education of nursing and health care professions in Germany.

Strengths and Limitations

This protocol has been rigorously developed and the electronic search syntax was iteratively tested and revised by the authors. Scoping reviews, like this study, contain potential biases in the selection of criteria, the search methodology, and the data analysis. Just German and English-language publications in selected databases will be included. The inclusion of other languages, databases, and additional search terms could lead to an increase in literature sources. Especially regarding the background of the heterogeneous study situation, the methodology of the scoping review is relevant to gain a broad perspective of the use of digital teaching and learning media in nursing and health education in Germany. Nevertheless, the possibility of inaccuracies in a combined interpretation exists.

Implications for Practice and Dissemination Plan

Findings from the scoping review could be of interest to various stakeholders, including educational institutions, researchers, health professionals, policy makers, and companies developing digital teaching and learning media. Therefore, the results of the review should be published in a peer-reviewed journal.

Conclusions

Our scoping review maps areas of application of digital teaching and learning methods in nursing and health education in Germany. In addition to the topic areas, the technical implementation methods and the didactic design should also be shown. The findings could be used to establish and expand digital teaching and learning methods in nursing and health care professional educational institutions, especially in Germany.

Acknowledgments

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Data Availability

This scoping review will be based on previously published data. The datasets generated during or analyzed during this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

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Abbreviations

APA PsycInfo: American Psychological Association PsycInfo
ERIC: Education Resources Information Center
MeSH: Medical Subject Headings
PCC: population, concept, and context
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Applicability of Retrospective and Prospective Gender Scores for Clinical and Health Data: Protocol for a Scoping Review

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Abstract

Background: Gender is known to have a strong influence on human health and disease. Despite its relevance to treatment and outcome, gender is insufficiently considered in current health research. One hindering factor is the poor representation of gender information in clinical and health (meta) data.

Objective: We aim to conduct a scoping review of the literature describing gender scores. The review will provide insights into the current application of gender scores in clinical and health settings. The protocol describes how relevant literature will be identified and how gender scores will be evaluated concerning applicability and usability in scientific investigations.

Methods: Our scoping review follows the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines. A title and abstract screening was conducted on PubMed, followed by a full-text screening. The inclusion and exclusion criteria were discussed by a team of 5 domain experts, and a data-charting form was developed. The charted data will be categorized, summarized, and analyzed based on the research questions during the scoping review.

Results: We will report our research results according to the PRISMA-ScR guidelines. The literature retrieval was carried out on June 13, 2024, and resulted in 1202 matches. As of July 2024, the scoping review is in the data extraction phase and we expect to complete and publish the results in the first quarter of 2025.

Conclusions: The scoping review lays the foundation for a retrospective gender assessment by identifying scores that can be applied to existing large-scale datasets. Moreover, it will help to formulate recommendations for standardized gender scores in future investigations.

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KEYWORDS

gender score; gender medicine; medical informatics; data integration; gender health gap

Introduction

The interaction of sex and gender plays an important role in the symptoms, diagnosis, therapy, outcome, life expectancy, and generally in the health and illness of men and women [1-3]. Gender includes awareness of diverse sexual orientations and identities and their relevance to daily life, including LGBTQ+ (lesbian, gay, bisexual, transgender, queer, and numerous other gender identities and sexual orientations) individuals. Neglecting

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or inadequately considering gender aspects in medical research and practice can have serious consequences for diagnosis, treatment, or risk prediction.

The German Ethics Council defines biological sex by genetic, hormonal, and anatomical conditions or markers, more precisely, by chromosomes, hormones, and internal and external sex organs. Gender, on the other hand, is defined by social attributes, an interaction of biological and psychosocial factors, an individual's social biography, and is shaped by someone's role in society. Psychological attributes determine the individual's self-perception and sexual identity. The sexual identity may differ from someone's physical appearance or biological sex [4]

Despite the known importance of gender in health, such as diagnostic and therapeutic responses, clinical manifestations, and disease progression, gender is currently not sufficiently represented in the health sciences, and sex and gender effects cannot yet be distinguished for most diseases [5]. The work of Vader et al [6], for instance, highlights the importance of gender and shows that gender can be seen as a mediator of sex differences. This particularly concerns chronic diseases with a higher prevalence in women (arthritis, chronic pain, and migraine). The authors even claim, that in these diseases, sex differences would not exist if there was no gender.

To improve the validity and reliability of medical research, it is necessary to encode gender information, in addition to biological sex information. We argue that a systematic gender assessment should be mandatory in future scientific investigations and in particular in clinical and health studies. Adding gender to existing data requires a retrospectively applicable score, ideally suitable for a wide range of applications. Moreover, future health research requires reliable and valid gender scores capable of predicting gender with high accuracy. The scoping review will provide an initial overview of existing gender scores and how they are currently being used in the health sciences. The objectives of this review are (1) to identify and characterize existing gender scores reported in the literature in the health sciences and (2) to systematically assess their applicability to clinical and health research (restricted to selected use cases).

Methods

Design

The scoping review method, as defined by Grant and Booth [7], was selected to provide an overview of the topic and to map the existing literature on the problem. It is well suited because our study deals with heterogeneous methods—covering prospective and retrospective scores, developed using strongly differing approaches—and includes a broad selection of research domains, as all subdomains of health research (eg, psychology and epidemiology) are considered. Furthermore, our review will inform future investigations on the topic [8]. In general, we followed the stepwise approach for scoping reviews described by Mak and Thomas [9] and adapted as many characteristics of the systematic review method as possible [10]. In particular, the review follows the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines [8], and the following steps were carried out: (1) identification of research questions; (2) identification of relevant studies; (3) study selection; (4) data extraction and charting; and (5) collating, summarizing, and reporting the results.

Due to limited resources, the coding of articles was conducted by a single reviewer and based on the database PubMed. It was selected as it is widely used as a standard database for biomedical literature research and is recommended as one of the most important databases for comprehensive systematic reviews [11].

Stage 1: Identification of Research Questions

As outlined in the Introduction section, gender is currently inadequately reflected in most scientific studies. The research questions therefore arose from an initiative to standardize gender encoding in large-scale data collections maintained by the Medical Informatics Initiative Germany (MII; *Medizininformatik-Initiative*) [12] and the Study of Health in Pomerania (SHIP) [13], and to establish recommendations for standardized gender encodings in routine data provided by the Data Integration Center (*Datenintegrationszentrum*) at the University Medicine Greifswald, Germany [14].

The research questions themselves were formulated by 5 domain experts, 3 with a primary background in medicine, 1 with a background in medical informatics, and 1 with a background in medical documentation. The identified and agreed upon research questions for the scoping review are the following: (1) What gender scores exist in medicine? (2) What gender scores are applicable to the SHIP and MII data? (3) How are gender scores currently applied, or are they purely theoretical constructs?

Stage 2: Identification of Relevant Studies

For the first assessment of the topic, a small number of relevant papers [15-17], identified through an initial manual search, were examined to identify keywords and important phrases. Furthermore, literature regarding gender awareness in the medical context [18-20] was examined to identify commonly used scientific terminology regarding gender. While this work defines a gender score as a method for assessing gender, the initial analysis showed that different terminology, such as gender measure or gender index, is used to refer to gender scores in the literature. Therefore, we included these terms in our query and added further terms as synonyms to achieve broad coverage. English language and status as a peer-reviewed article were additional inclusion criteria for our review. Furthermore, we only considered scores applied to adults and excluded scores targeting children.

Based on the extracted keywords, a query was designed to capture the key elements that identify these studies. The query was optimized for recall regarding the initial literature while considering the amount of results. Specifically, the query was designed using Boolean operators, wildcards, proximity search, and a timeline. The time limit was introduced to identify more recent literature and to exclude obsolete research, such as the well-known Bem Sex-Role Inventory [21] which was shown

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to be outdated by Donnelly and Twenge [22]. The timeline was determined based on the distribution of articles, which showed that most research on the topic was published in the last 5 years. Throughout the entire review process, secondary literature relevant to our topic was collected. This particularly concerns older scores, which allows for the identification of earlier published literature that is still applied or cited in more recent publications. Although excluded by our initial time limit, we decided to consider them as secondary literature to evaluate if they are still reasonable to apply or obsolete. The final query was executed on June 13, 2024, and is illustrated in Figure 1.

Figure 1. PubMed query. The query consists of three parts: (1) terminology expressed for gender score, (2) word expressing that the score was developed, (3) timeline restriction (see stage 2 for further explanation); (ot) matches keywords; (tiab) matches title and abstract; (*) wildcards match different word endings; (~1) this proximity search with distance 1 allows another word between the searched terms (different word endings are automatically included).

```
("gender score*"[ot] OR "gender measure*"[ot] OR
 "gender index"[ot]  OR "gender indices"[ot] OR
 "gender model*"[ot] OR "gender classifier*"[ot] OR
 "gender score"[tiab:~1] OR "gender measure"[tiab:~1] OR
 "gender index"[tiab:~1] OR "gender indices"[tiab:~1] OR
 "gender model"[tiab:~1] OR "gender classifier"[tiab:~1])
AND
(create*[tiab] OR establish*[tiab] OR develop*[tiab] OR
 implement*[tiab] OR use[tiab] OR used[tiab])
AND
("2018"[Date - Create] : "3000"[Date - Create])
```

Stage 3: Study Selection

The obtained results were screened by title and abstract to exclude studies that do not relate to gender scores. Articles that could not be clearly excluded based on title or abstract alone were retained for further examination. The final relevance decision for the remaining articles was based on an examination of the full-text document.

Stage 4: Data Extraction and Charting

We developed a data-charting form that was used to determine eligible data extraction points. The form was based on Gierend et al [23] and then adjusted together with the domain experts involved in this study (see stage 2). It was iteratively optimized and continuously updated throughout the process. The charting form is organized into 4 main sections corresponding to an overview and the 3 research questions. The final data-charting form is illustrated and explained in Table 1. Based on the data extraction points, 1 author critically examined the papers and extracted the relevant data. Initially, more than 30% (7/22) of the publications were randomly double-checked by a second domain expert to ensure high data extraction quality. The 2 reviewers were in full agreement on all reviewed articles. Therefore, the remaining articles are reviewed by a single reviewer throughout the remainder of the review process. Irrelevant papers are removed from the charting form.

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Table 1. Summary of data charting.

Section	Description
Section 1: Overview	Summary of the basic publication information
Article metadata	Title, Digital Object Identifier, year of publication (YYYY), keywords
Corresponding author information	Name, research discipline, institute, Research Organization Registry (registry of open persistent identifiers for research organizations)
Publication type	Peer-reviewed or preprint
Study type	Gender score development, use case, or recommendation
Continent	Continents where the study took place or focused on
Funding source	Public, industry, none, or missing
Citation count	Citation count as reported by PubMed and Google Scholar
Objective	Aim or objective of the publication
Methods	The procedures or techniques used to identify, select, process, and analyze information
Summary results	Short description of results
Conclusion	Short description of the conclusion
Section 2: Research questions	Includes the research questions and the required data
What gender scores exist in medicine?	• Necessary variables for the developed gender score • Retrospective or prospective application • Clinical or epidemiological study • Size of cohort • Target variables (feminine, masculine, binary, or continuously) • Model type (statistical model or questionnaire)
What gender scores are applicable to the SHIP[a] and MII[b] data?	• Existence of tool support or executable model • Availability of raw data or code • Reproducibility • Validation • Limitations (eg, restricted scope) • Variable coverage
How are gender scores currently applied, or are they purely theoretical constructs?	• Applicability in other research domains • Practical example of usage • Name and number of used records or databases • Expert evaluation

[a]SHIP: Study of Health in Pomerania.

[b]MII: *Medizininformatik-Initiative* (Medical Informatics Initiative Germany).

Stage 5: Collating, Summarizing, and Reporting the Results

This scoping review aims to summarize recently developed gender scores in health research. The extent of the review is limited to PubMed, the most relevant database for medical research outcomes. We assume that most relevant publications related to health sciences are contained in the resulting dataset. The commonly applied tools for the analytical interpretation of literature such as summary statistics, charts, and figures will be applied to discuss the collected relevant data [24]. We will follow the PRISMA-ScR guidelines [8] and discuss the general interpretation of the results compared to other evidence, the overall aim of the study, effects on practice, and future research, limitations, and recommendations.

Results

In preparation for the scoping review, a search of the database PubMed on June 13, 2024, resulted in 1202 matches. The title-abstract screening step reduced the set to 82 and 30 potentially relevant publications, respectively. It reduced the set of considered papers more than expected. Specifically, our review identified a large number of articles not directly related to the development of gender scores. On the one hand, this is due to the positive trend that gender receives increasing attention in current research. Many articles explicitly consider gender in the form of variables or by applying existing gender scores [25-27]. These articles were matched, as we designed the query to be as inclusive as possible in order not to miss any existing scores or potential extensions of existing scores (including the terms “use” and “used” in our query). On the other hand, in the examined papers the term gender is often used to refer to binary sex categories, for example, girl or boy, female or male, or

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woman or man [28-32]. These papers were excluded from our review.

Full-text screening resulted in a final set of 18 papers identified in the scoping review. An additional 4 articles were identified as secondary literature, which were not covered in the timeline of the query but are still relevant in the current literature, as described earlier. A total of 22 studies were included in the review. The described process is further illustrated by the PRISMA-ScR flow diagram [8] in Figure 2. The results will be included into data charting.

We finalized the data extraction process in the third quarter of 2024 and the review will subsequently be concluded by summarizing and analyzing the results in the first quarter of 2025. The scoping review will provide an overview of recently developed gender scores in the literature. The research questions will allow us to select suited gender scores based on quality criteria and underlying research fields. The charting process will further provide information about their quality and retrospective applicability. This will serve as a basis for selecting eligible gender scores for retrospective application to existing data. Furthermore, the identified prospective scores will allow us to formulate recommendations for the inclusion of gender-dependent variables in future investigations, particularly, to incorporate standardized gender scores in investigations performed in the scope of the MII. The review will also reveal potential gaps and limitations of current gender scores, for example, regarding restrictions in underlying cohorts or research fields.

Figure 2. PRISMA-ScR flow diagram. The diagram illustrates the applied steps for the selection of relevant publications. PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews.

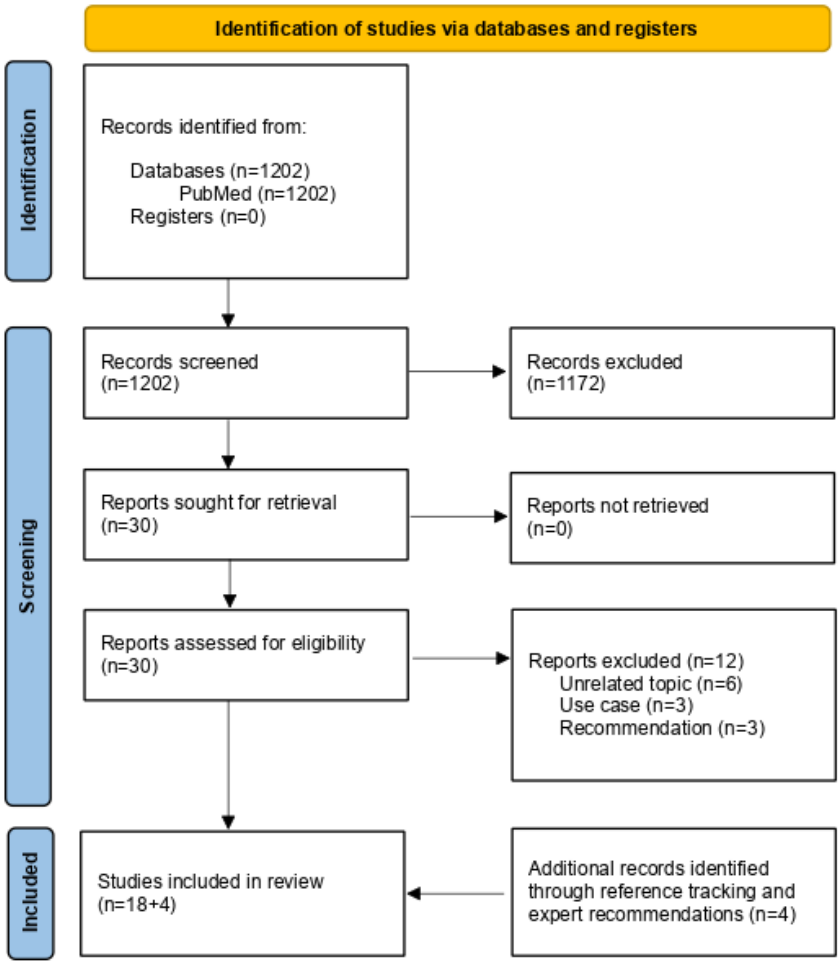

Discussion

Our review investigates the current development and usage of gender scores in health research and aims to assess the applicability of these scores. On the one hand, the insights can help to model gender information in existing data. On the other hand, we anticipate that our data charting will help to identify gender scores that are sufficiently generic and efficient to be implemented on a large scale in future research. Furthermore, our review will provide the basis for future works on the design and development of standardized prospective approaches to gender assessments.

Our review is also a valuable addition to existing scoping reviews that address gender topics. For instance, in 2020 Horstmann et al [33] focused on recently used instruments for the operationalization of sex and gender in health research. Our review identifies gender scores that were recently developed but have not necessarily been implemented yet. We aimed to identify the latest innovations in a very active research field, so we deliberately limited our search to the last 5 years. Indeed,

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13 of the 18 articles in our primary result set were published after 2020. Miani et al [34] published an overview of epidemiological aspects of gender scores. Our work, in contrast, includes gender scores from all areas of health research, such as psychology, cardiology, or neurology. Similarly to Horstmann et al [33] and Miani et al [34], we included publications until 2021.

Limitations of this work are that a single reviewer screened titles and abstracts and that our search was limited to PubMed, as explained in the Design section. However, we believe that a major strength of our review protocol is that it addresses all methods of gender assessment and that our data charting covers a wide range of information.

Appropriate consideration of gender aspects in clinical and health studies remains a fundamental issue, and we believe that further work is required to establish the standardized use of gender scores in medical data recording. While our study will provide an overview of existing gender scores, a general, broader awareness of the topic remains of high importance, and solutions need to be found to systematically apply gender scores to clinical and health studies in the future. Therefore, further effort is required to make this topic more present in the scientific community.

Acknowledgments

This work was funded by the German Federal Ministry of Education and Research as part of the projects InkE (01FP23G10A)—Excellence through Inclusiveness in Medicine—and the Network of Data Integration Centers of the University Medicine (D352210009).

Data Availability

We plan to release the generated data persistently on Zenodo.

Authors' Contributions

LS did the conceptualization, data curation, investigation, methodology, visualization, writing of the original draft, and review and editing of the writing. HB and SR handled the data curation, validation, and review and editing of the writing. EK conducted the conceptualization, validation, methodology, supervision, and review and editing of the writing. SS and DW carried out the conceptualization, funding acquisition, methodology, supervision, writing of the original draft, and review and editing of the writing.

Conflicts of Interest

None declared.

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Abbreviations

MII: Medizininformatik-Initiative (Medical Informatics Initiative Germany)
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
SHIP: Study of Health in Pomerania

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Protocol

Occupational Infections Among Workers in Europe: Protocol for a Scoping Review

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Abstract

Background: Workers may be exposed to different infectious agents, putting them at risk of developing occupational diseases. This can occur in many ways, through deliberate use of specific microorganisms or through potential exposure from close contact with biological material. Infection prevention and control measures against biohazards can reduce the risk of infection among workers. During the last few decades, an increasing proportion of workers in Europe have been exposed to infectious biological agents in their workplace. Knowledge gaps on this topic in Europe have limited our understanding of the overall phenomenon in occupational settings.

Objective: This study aims to understand the extent and type of evidence on the epidemiology of occupational or work-related infections caused by bacterial, viral, fungal, and parasitical agents in European countries, the factors affecting their occurrence among workers, and the burden of disease among workers due to occupational risk.

Methods: The review will be conducted following the Joanna Briggs Institute methodology for scoping reviews and the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines. This review will consider studies that include data on the epidemiology of occupational infections, risk factors and determinants, and burden of disease among workers employed in specific occupational sectors in European countries in the period 2010-2023. The search will include MEDLINE, Web of Science, and Scopus databases. Independent reviewers (including GD, SC, AR, PD, and SM) will screen the titles, abstracts, and full texts of the selected studies. Data extraction will be performed using a tool developed by the researchers. The data will be mapped and analyzed according to the type of extracted data.

Results: The literature search through different scientific databases started in April 2024 and is expected to be completed by December 2024. The findings will be extracted using an ad hoc data extraction tool, and relevant results will be presented in narrative and tabular form.

Conclusions: This scoping review aims to provide rigorous evidence to fill the knowledge gap in the epidemiology of occupational or work-related infections in European countries, the factors affecting their occurrence, and the burden of disease in different professional settings. Such findings could improve the understanding of this complex occupational phenomenon in the European context, enabling more accurate and up-to-date surveillance of infections incurred in the workplace.

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KEYWORDS

infection; work-related; biological hazard; narrative synthesis; Europe; occupational infection; worker; scoping review; infectious; prevention and control; occupational health; epidemiology; burden of disease; phenomenon

Introduction

Biological agents include a variety of microorganisms, toxins, and allergens that may harm human health. In particular, microorganisms capable of causing infections, such as bacteria, viruses, and fungi, can be pathogenic or can produce diseases that can be transmitted to individuals through various modes of transmission, determining acute or chronic health conditions [1].

In the occupational setting at the European level, prevention and management of all hazards and risks present in the workplace are required to safeguard occupational health and safety for all workers [2]. From this perspective, infection prevention and control measures implemented in the workplace against biological hazards can reduce the risk of infection among workers.

Indeed, employees in different professional sectors may be exposed to a variety of infectious agents, putting them at risk of disease. This exposure can occur in many ways, either through "deliberate use" of specific microorganisms (eg, laboratories and biotechnological industries), through "potential exposure" from processes of activities that require close contact with biological material (composting, recycling, and wastewater recycling), through animal contact (agriculture and food processing), or through contact with humans (health care and education). Globally, the overall annual mortality attributable to occupational infections is estimated at approximately 320,000 deaths, 5000 of which occur in the European Union [3]. However, morbidity from work-related infections could be largely underreported in national and international surveillance systems, possibly because of the lack of distinctive characteristics of work-related infectious diseases compared with infections acquired in nonoccupational settings, thereby making it difficult to establish a causal link between work and disease. Nonetheless, work-related infections may result in significant harm to workers' health, potentially resulting in a high disease burden on the working population. Indeed, experiences in tracking occupational diseases from biological agents are rather different [4], facilitating underestimation of the phenomenon. Indeed, there is often vast heterogeneity between countries in the definition of occupational or work-related diseases or injuries caused by biological agents. The case of SARS-CoV-2 infection among workers is paradigmatic: despite the large literature published on the subject, few countries notify this disease as an occupational accident or injury (eg, China and Italy), while the majority of countries have labeled this event as an occupational disease [5]. In fact, according to the Italian legislation on workers' compensation, cases of infectious and parasitic diseases are included in the category of accidents at work "because the virulent cause is equated to the violent one," which is a required characteristic to identify a work-related injury [6,7].

In particular, during the last few decades, increasing proportions of workers in Europe have been reported to be exposed to infectious biological agents in the workplace [8]. This has increased the need to provide more insight into the appropriate study and assessment of biological risks present in European countries, as well as their potential health effects among the workforce, especially in light of the impact of the COVID-19 pandemic on occupational health. Recent reports from the European Agency for Safety and Health at Work have identified several high-risk occupations for occupational infections (eg, animal-related occupations, waste and wastewater management, health care setting, farming, and traveling for work) and have provided recommendations on the implementation of specific preventive and protective measures in these settings. However, due to limited knowledge caused by the lack of up-to-date information on the ecology of pathogens and epidemiology of associated diseases in the European Union, particularly due to data gaps in monitoring systems for occupational diseases in member countries, it has not yet been possible to reach a comprehensive understanding of the overall phenomenon in all occupational settings [9]. Indeed, in many countries, biological agents are often not considered an Occupational Safety and Health priority, resulting in a reactive rather than a proactive approach to recognizing occupational biohazards and managing the risks to the safety and health of workers.

To understand the available knowledge on this topic, a scoping review will be performed to map the existing literature on infectious diseases in the occupational setting, enabling us to gather evidence on both traditional and emerging occupational biological agents and provide useful insights into their determinants and health impact. The scoping review was chosen as the most appropriate type of review as our aim is to achieve breadth rather than depth in our analysis. Therefore, other types of reviews are not deemed methodologically effective [10].

This scoping review is expected to provide the first rigorous analytical and updated synthesis of research data on the epidemiology of injury or disease due to infectious biological hazards, as well as information on the occupational burden. Stratifying infections according to the type of infectious disease and work task involved could add meaningful information and increase our understanding of the risk factors and corresponding determinants. Indeed, filling knowledge gaps and acquiring high-quality evidence concerning the epidemiology of occupational infections in European countries could be used as the scientific basis for developing and implementing effective preventive programs as well as for informing the activities of Occupational Health Services. This would contribute significantly not only to employers, employees, researchers, and occupational health professionals but also to overall public health.

A preliminary search of MEDLINE, the Cochrane Database of Systematic Reviews, and Joanna Briggs Institute (JBI) Evidence Synthesis was conducted, and 2 published systematic reviews

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on the topic were identified [11,12]. However, these 2 systematic reviews did not specifically report data on the prevalence and incidence of occupational infections, definition of risk factors and determinants, as well as direct and indirect burden of disease (eg, economic impact and days absent from work due to ill health). In addition, the most recent systematic review was limited to non–health care workers and covered the period 2009-2020 [12]. Hence, we decided to perform a new review to gather updated evidence on all occupational categories, including health care settings. Furthermore, we decided to restrict the focus of our review to studies performed in European countries, in consideration of sufficiently comparable economic development and diversification, good standards of health care services, including occupational safety and health requirements provisions, as well as similar microorganism ecology, in order to better grasp the updated scientific evidence and possibly reduce confounders and heterogeneity in the subsequent synthesis.

The objectives of this scoping review are (1) to provide a comprehensive and up-to-date synthesis of all studies concerning occupational or work-related infections in European countries; (2) to identify the factors that impact the occurrence of infections among workers; and (3) to quantify the burden of infection among workers in terms of related disabilities, residual working capability, absence from work, and direct and indirect costs generated.

Methods

The proposed scoping review will be conducted in accordance with the JBI methodology for scoping reviews [13] and in line with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines [14].

Review Questions

The review questions of our planned study are as follows:

1. What is the incidence or prevalence rate of infections among workers in European countries?
2. What are the determinants of infection among workers in European countries?
3. What is the burden imposed by infections among European workers in terms of related disabilities, residual working capability, absence from work, and direct and indirect costs?

Eligibility Criteria

Eligibility criteria, defined according to Population, Concept, and Context criteria, are listed in Textbox 1.

Textbox 1. Eligibility criteria defined according to Population, Concept, and Context criteria.

Participants

- Workers employed in specific occupational sectors.

Concept

- Epidemiology of occupational infections, associated risk factors and determinants, burden of impact on health in terms of related disabilities, residual working capability, absence from work, and direct or indirect costs.

Context

- Studies published since 2010, performed in European countries with a common geographical definition of Europe [15].

Types of Sources

- This scoping review will consider all publications that meet the inclusion criteria. This includes, but is not limited to, quantitative, qualitative, and mixed methods studies. Systematic reviews that meet the inclusion criteria will also be considered depending on the research question. If the same data are reported in more than one publication, the primary article or article with the most complete data will be used.
- Analytical observational studies, including prospective and retrospective cohort, case-control, and analytical cross-sectional studies, will be considered for inclusion. Studies not matching the defined Population, Concept, Context criteria, review articles, modeling studies, case series, and individual case reports will be excluded from the review.

Search Strategy

A 3-step search strategy will be followed, as described in the JBI Manual for Evidence Synthesis [13].

An initial limited search of MEDLINE was undertaken to identify articles on the topic of interest. Text words contained in the titles and abstracts of relevant articles and the index terms used to describe the articles were used to develop a full search strategy for MEDLINE (Multimedia Appendix 1). To improve the specificity of the search strategy for injuries and diseases caused by occupational exposure, we adapted the specific filter developed by Mattioli et al [16] to retrieve potentially pertinent citations. The search strategy, including all identified keywords and index terms, will be adapted for each included database and information source. The databases to be searched will include MEDLINE, Web of Science, and Scopus. The reference lists of all included reports will be screened for additional studies. If the full text of a report cannot be accessed, the authors will be contacted. Studies published in English, Italian, French, and Spanish since 2010 will be included.

The second step will consist of a second search of all included databases using the fields, index, and MeSH terms, and all keywords identified during step 1. The databases to be searched will include MEDLINE, Web of Science, and Scopus. An example of the search strategy, including the index and MeSH

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terms and keywords and Boolean logic (AND/OR and truncations), is provided in Multimedia Appendix 1.

The third step will consist of screening the reference lists of all the included articles for additional sources. The search strategy will be adapted for each included database and information source.

Study or Source of Evidence Selection

The source of evidence selection will be completed in the following steps. First, all citations identified through the full search of all included databases will be uploaded into Mendeley Reference Manager 2.91.0, and duplicates removed. Second, titles and abstracts will be screened by 4 independent reviewers to assess the inclusion criteria for the review. Finally, the same 4 independent reviewers will evaluate in detail the full text of the selected articles to verify if inclusion criteria are met. Reasons for exclusion of articles that do not satisfy the inclusion criteria will be reported in the scoping review. Disagreements between the reviewers will be resolved by the fifth reviewer or through discussion to reach a consensus. The complete study inclusion process will be reported in the scoping review and presented in a PRISMA-ScR flow diagram [14].

Data Extraction

Data will be extracted from the included studies by 4 independent reviewers by means of a data extraction tool developed by the Authors (Multimedia Appendix 2). The extracted data will include details on the participants, concept, context, study methodology, as well as key findings.

Data Analysis and Presentation

Data analysis and presentation will depend on the data extraction process and potential modification of the data extraction tool; therefore, it will be subject to changes. All changes will be documented in the review. The data will be manually entered into a Microsoft Excel spreadsheet. The data will also include specific details regarding the participants, study methodology, and most relevant findings. If necessary, the draft data extraction tool will be revised during the extraction process, with details on the modifications presented in the scoping review. Relevant results will be presented in tabular form and with a narrative synthesis. Disagreements between the reviewers will be resolved by an additional reviewer or through discussion. All relevant findings will be assessed and discussed by a national collaborative group of researchers from different Italian Universities, Hospitals, and Local Health Authorities.

Results

The literature search through different scientific databases started in April 2024 and is expected to be completed by December 2024. The review will be submitted for publication in 2025.

Discussion

The findings of this review will demonstrate an up-to-date epidemiological picture of occupational or work-related infections in European countries, the factors affecting their occurrence, as well as the burden of disease among different professional settings. Recently published data have shown several professional groups at risk of infection, such as the military, livestock farm workers, dairy producers, abattoir workers, and forestry workers, with the majority of these occupational groups being exposed to respiratory pathogens [12]. This review will add to the currently available evidence, by involving studies performed on all working categories, including health care workers. Such findings could improve the understanding of this complex occupational phenomenon in the European context, enabling a more accurate and up-to-date surveillance of infections caused by occupational exposure. This study is strengthened by the comprehensive and rigorous methodological approach adopted in the search strategy. Moreover, the composition of a national collaborative group, gathering expertise from researchers from different Italian Universities, practitioners, and professionals from reference Polyclinic Hospitals, and Local Health Authorities from different Regions of Italy, provides the unique possibility for multifaceted discussions of the findings, offering multiple perspectives from the different actors implicated in Occupational Health. However, the scoping review will be limited by a reduced resolution on the specific types of infections and work categories, as well as by the lack of a quantitative synthesis. To improve both limitations, further targeted systematic reviews and meta-analyses will be necessary. Nonetheless, this scoping review may serve as a foundational resource to inform policymakers with updated evidence, which can be used to improve the definition of occupational diseases and injuries caused by infectious agents in Italy, but also in different European countries. Furthermore, this updated evidence could provide useful practical insights for Occupational Health professionals, as well as guide future research goals by highlighting understudied professional categories and pathogens, with the aim of reducing possible knowledge gaps.

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Data Availability

The datasets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

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Authors' Contributions

All the authors were writing original drafts, reviews, and editing. Conceptualization was performed by GD, SC, AR, PD, and SM. Methodology was handled by GD, SC, and AR. Funding acquisition and supervision were conducted by PD and SM.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Tentative search strategy.
[DOCX File , 18 KB - resprot_v14i1e59606_app1.docx]

Multimedia Appendix 2
Data extraction tool.
[DOCX File , 14 KB - resprot_v14i1e59606_app2.docx]

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Abbreviations

JBI: Joanna Briggs Institute
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Exploring the Credibility of Large Language Models for Mental Health Support: Protocol for a Scoping Review

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Abstract

Background: The rapid evolution of large language models (LLMs), such as Bidirectional Encoder Representations from Transformers (BERT; Google) and GPT (OpenAI), has introduced significant advancements in natural language processing. These models are increasingly integrated into various applications, including mental health support. However, the credibility of LLMs in providing reliable and explainable mental health information and support remains underexplored.

Objective: This scoping review systematically maps the factors influencing the credibility of LLMs in mental health support, including reliability, explainability, and ethical considerations. The review is expected to offer critical insights for practitioners, researchers, and policy makers, guiding future research and policy development. These findings will contribute to the responsible integration of LLMs into mental health care, with a focus on maintaining ethical standards and user trust.

Methods: This review follows PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines and the Joanna Briggs Institute (JBI) methodology. Eligibility criteria include studies that apply transformer-based generative language models in mental health support, such as BERT and GPT. Sources include PsycINFO, MEDLINE via PubMed, Web of Science, IEEE Xplore, and ACM Digital Library. A systematic search of studies from 2019 onward will be conducted and updated until October 2024. Data will be synthesized qualitatively. The Population, Concept, and Context framework will guide the inclusion criteria. Two independent reviewers will screen and extract data, resolving discrepancies through discussion. Data will be synthesized and presented descriptively.

Results: As of September 2024, this study is currently in progress, with the systematic search completed and the screening phase ongoing. We expect to complete data extraction by early November 2024 and synthesis by late November 2024.

Conclusions: This scoping review will map the current evidence on the credibility of LLMs in mental health support. It will identify factors influencing the reliability, explainability, and ethical considerations of these models, providing insights for practitioners, researchers, policy makers, and users. These findings will fill a critical gap in the literature and inform future research, practice, and policy development, ensuring the responsible integration of LLMs in mental health services.

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KEYWORDS

large language model; LLM; mental health; explainability; credibility; mobile phone

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Introduction

Background

The emergence of generative artificial intelligence (AI) and the rapid evolution of large language models (LLMs) are introducing new complexities and accelerating technological advancements. Our understanding of the inner workings of these systems remains limited. However, there is a widespread rush across all sectors to adopt these technologies, often overlooking the ethical considerations and potential threats to data privacy and confidentiality [1]. The use of LLMs, such as Bidirectional Encoder Representations from Transformers (BERT; Google) and GPT (OpenAI), in mental health research and health care is growing. However, their ability to provide reliable and empathetic mental health support remains underexplored. LLMs have been shown to excel in tasks such as text generation and summarization, but their application in sensitive fields such as mental health requires careful consideration of factors such as ethical concerns, privacy, and model explainability.

As generative AI becomes increasingly integrated into various tools and applications, its presence in our everyday lives grows. The deployment of AI in smartphones, social media, and platforms such as OpenAI's ChatGPT, Google's Gemini, Anthropic's Claude, and Meta's Llama is a testament to this trend. These technological advancements are becoming a staple in our personal and professional spheres, a presence set to expand further. Their influence on our choices is significant and will only intensify in the coming years, potentially impacting our mental health and overall well-being [2].

A recent research study published on the alignment of outcomes of LLMs to human intentions [3] concluded that, based on publicly available users' opinions about their use of LLMs, in general, users tend to trust those LLMs more that demonstrate higher alignment to human intentions. In *Harvard Business Review* [4], the authors of the review "AI can be both accurate and transparent," which was a study to examine the trade-off between accuracy and explainability, tested a wide array of AI models on nearly 100 representative datasets and found that 70% of the time, a more explainable model could be used without compromising accuracy. This suggests that a reliable LLM can be developed and aligned with transparency and social norms. Another study [5] suggested that ethics-based auditing can be a governance mechanism for building and deploying LLMs and potentially bridge the gap between principles and practice in AI ethics. It argues that ethics-based auditing will improve the quality of decision-making, users' satisfaction with privacy and confidentiality at the center, influence laws and policies that govern these systems and minimize human harm.

Given that this technology is still nascent and research into its effects on society is scarce, evaluating its implications and integration into the medical and health care sectors, particularly in mental health support, is essential. It is imperative to recognize and scrutinize this progression, understand its benefits [6] and associated risks, and identify potential measures to prevent and reduce the adverse effects of these technologies on human lives. The ethical dilemmas surrounding the use of these systems, the safeguarding of user privacy and confidentiality, and the accountability of developers remain largely uncharted territories [7]. It can be said that a lot of the published literature and journals either provide general solutions or look into a specific domain, such as applicability or accuracy.

This exploration seeks to shed light on the current state of LLMs, focusing on their reliability and explainability, especially in providing support for mental health. It will try to add more consistent factors that can account for the credibility of LLMs. There is now a growing body of research on using LLMs for mental health care provision [8]. However, it is worth noting that there are very few to almost no studies on the credibility of LLMs, particularly in medicine [9,10] and mental health support. This review intends to address this gap.

Objectives and Research Questions

The study's overall objective is to explore the current state of evidence on the credibility of LLMs by comprehensively reviewing research on credibility factors such as reliability and explainability. A secondary objective is to derive insights into ethical implications for the responsible use of LLMs in mental health support.

To this end, the following research questions will be pursued in the scoping review:

1. How credible are LLMs in providing mental health information and support?
   - What factors influence the reliability of LLMs for mental health support?
   - How credible are LLMs providing mental health information and support?
2. What are the users' perceptions of using LLMs as reliable and explainable sources of mental health support?
3. What ethical implications should be considered for the responsible use of LLMs in mental health support?
   - How can we ensure privacy and confidentiality when users interact with LLMs for sensitive mental health issues?
   - How can we ensure that the shared sensitive information by the user is secure and private?

Methods

Study Design

The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) [11] will be used as a basic tool, and the Joanna Briggs Institute's (JBI) approach to scoping reviews will be followed [12-14].

Research Strategy and Terms

Information Sources

The selected databases cover a wide range of disciplines relevant to the scope of our review. PsycINFO and MEDLINE focus on psychology and medical research, providing comprehensive coverage of mental health studies. Web of Science ensures multidisciplinary coverage, while IEEE Xplore and ACM Digital Library focus on technological advancements and AI research,

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critical for studies on LLMs. These databases together provide a robust and well-rounded search strategy for this scoping review.

Search Strategy

The search strategy will be continuously updated to capture newly published studies during the review period (Multimedia Appendix 1). Monthly alerts will be set up in key databases, and any relevant new papers will be incorporated into the review until the final synthesis phase. An iterative approach will be followed to develop the search strategy. First, search terms used in previous studies and reviews related to the credibility of LLMs in mental health support will be identified. Second, an initial search in MEDLINE via PubMed and ACM Digital Library will be conducted after analyzing text words (title and abstract) and indexed terms, according to JBI methodology. The initial search strategy for MEDLINE via PubMed is given in Multimedia Appendix 1. This approach will use all received search terms in all databases. Finally, the references for all included contributions will be checked. The terms will be adapted to the essential search particulars such as wildcards (*), truncations, and Boolean operators in each electronic database.

For a more precise explanation of the inclusion criteria, the Population, Concept, and Context (PCC) framework will be followed. Textbox 1 shows the most important criteria based on the PCC framework.

The kinds of literature and papers that provide information on at least one research question from the *Objectives and Research Questions* section will be included. Detailed inclusion and exclusion criteria are mentioned below for each review.

Textbox 1. Population, Concept, and Context scheme.

Population

- Mental health practitioners, researchers, educators, students, and adults (age group: 18-65 years)

Concept

- Nonparticipatory, exploratory, cocreation, and co-design

Context

- Exploration of credibility (reliability and explainability) of large language models for mental health support

Types of sources

- Secondary sources, electronic databases, studies published in the last 5 years (2019-2024), studies published in English or that have an English translation available, and full-text papers

Eligibility Criteria

Papers to be included must meet the criteria mentioned in Textbox 2.

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Textbox 2. Eligibility criteria.

Study design

- The study must be empirical, exploring the application of transformer-based generative language models in mental health support.

Model type

- The study should involve transformer-based models such as Bidirectional Encoder Representations from Transformers (BERT), GPT-2, or later models designed for generative tasks.

Mental health focus

- The study should address mental health support, encompassing therapy, counseling, or other relevant interventions.

Credibility assessment

- The study should evaluate credibility factors, including accuracy, reliability, explainability, or user satisfaction.

Publication date

- Studies published from 2019 onward are included. We chose 2019 as the starting year for including studies because this marks the beginning of a transformative phase in large language model (LLM) development. In late 2018, BERT was introduced, followed by GPT-2 in 2019, setting the stage for subsequent advancements that significantly impacted the field.

Language

- The study must be published in English or have an English translation to maintain data extraction and analysis consistency.

Peer-review or preprint status

- We will prioritize peer-reviewed studies; however, to capture the rapid advancements in this field, we will also include preprint papers from ArXiv and peer-reviewed book chapters. Information from these sources will be presented in a separate table, and interpretations based on these sources will be limited and contextualized regarding the publication status.

Study Selection

The saved papers will be checked for duplicates. The open-source app Zotero (Corporation for Digital Scholarship) [15] will be used as a bibliographic tool. Paper screening will be done using the open-access tool Rayyan.ai (Rayyan Systems Inc) [16]. Two independent reviewers will screen all titles and abstracts separately for inclusion or exclusion. Any discrepancies will be resolved through discussions between the 2 reviewers during the screening and data extraction phases. If consensus cannot be reached, a third reviewer will be consulted. This process will ensure reliability and minimize bias by incorporating multiple perspectives and systematic resolution of disagreements. The search results and the study inclusion or exclusion process will be transparently reported in full in the final scoping review, which will be presented in a PRISMA flowchart (Figure 1).

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Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart. LLM: large language model.

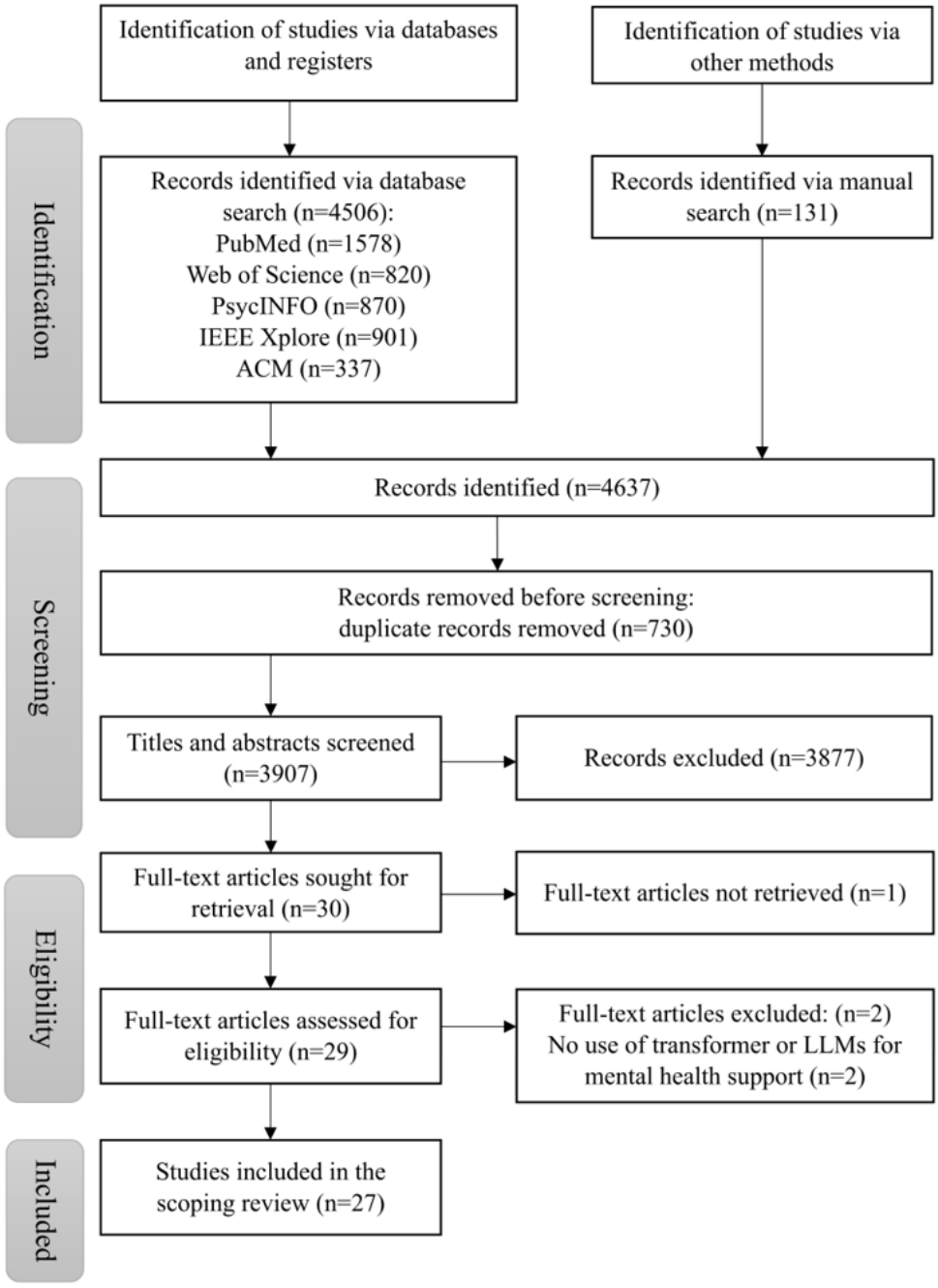

Data Extraction

We will use the literature review matrix method [17] to organize and chart the data extracted from the included research papers. Two reviewers will chart the data independently, continually update the matrix in an iterative process, and discuss the results while all the changes are detailed in the scoping review. After independent extraction, the 2 reviewers will compare their extracted data. Any discrepancies or disagreements will be discussed and resolved through consensus. A third reviewer will be consulted to decide if a consensus cannot be reached. Data extracted will include metrics such as accuracy, reliability, model explainability (eg, explainable AI methods used), user satisfaction scores, and ethical considerations such as privacy and data security measures. Data will be synthesized to address the research questions systematically. The data extraction form will be continually updated in an iterative process as new insights are gained and new studies are reviewed. Reviewers will keep detailed records of any changes to the extraction process and document the rationale. The extracted data will be managed and stored using Zotero for reference management and Rayyan.ai for screening and collaboration. A literature review matrix is given in Multimedia Appendix 2.

Data Analysis and Presentation

To assess the quality of the included studies, we will apply the JBI Critical Appraisal Checklist for Qualitative Research [18]. This tool will evaluate the methodological quality of each study by examining factors such as the clarity of research questions, the appropriateness of the study design, the rigor of data collection, and the credibility of the results. The results of this appraisal will be presented descriptively, helping to

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contextualize the findings of the review and ensuring a nuanced understanding of the evidence base. Given the expected heterogeneity in study designs, methodologies, and outcomes, this scoping review will focus on qualitative synthesis rather than meta-analysis. Descriptive synthesis is more appropriate for mapping the broad and varied landscape of LLM applications in mental health support. This will involve evaluating methodological rigor, reporting clarity, and the findings' relevance to the research questions. The results of this appraisal will be presented descriptively, helping to contextualize the findings of the review. The findings will be presented according to the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist (Multimedia Appendix 3). The extracted data will be presented logically and descriptively, including diagrams and tables based on the objectives and research questions of the scoping review. Data synthesis and presentation will follow an inductive approach. A summary description and discussion of the findings according to the research questions, the flowchart, and the entire research process will be provided in text form and described narratively.

Ethical Considerations

Since the data used in the review are collected from secondary sources and primary data are not collected, formal ethical approval is not required.

Dissemination Plan

The findings of this scoping review will be disseminated through various channels, including a peer-reviewed journal publication and presentations at key conferences in the fields of AI and mental health. We also plan to engage with policy makers and health care stakeholders to help inform the development of guidelines and frameworks that promote the responsible use of LLMs in mental health care. This dissemination strategy aims to ensure that the results reach both academic and clinical audiences, as well as those involved in ethical oversight.

Results

As of September 2024, we have completed the initial search, yielding 1578 studies. Out of these, 244 studies were included for title and abstract screening. Full-text screening is underway for 76 studies. Figure 1 shows the PRISMA flowchart, and the PRISMA-P checklist documenting this process is given in Multimedia Appendix 3. The target date for submitting the scoping review is November 30, 2024.

Discussion

Overview

The anticipated findings of this scoping review will focus on identifying and mapping the factors that influence the credibility of LLMs in mental health support. We expect to find evidence related to the reliability and explainability of these models, particularly in the areas of user trust, data privacy, and ethical considerations. These insights are expected to inform future research, policy development, and clinical practice in integrating LLMs for mental health services.

Principal Findings

This scoping review aims to map factors such as model reliability, explainability, and ethical concerns in the context of LLMs for mental health support. These findings will offer a deeper understanding of how LLMs are evaluated for their potential role in sensitive areas such as mental health. We anticipate uncovering gaps in transparency and user trust as key components influencing the integration of LLMs into clinical settings.

Comparison to Previous Work

This review builds on previous work in AI ethics and health care applications, with a particular focus on LLM credibility. Our findings are expected to align with previous studies that emphasize the need for explainability and user trust, but they will also highlight the specific challenges that arise when these models are applied in mental health contexts. Unlike past research that has focused on broader AI applications, this review narrows its scope to LLMs in therapeutic settings, addressing concerns such as misdiagnosis and misinformation.

Strengths and Limitations

The comprehensive nature of this scoping review, using the PRISMA-ScR framework, allows for a systematic exploration of diverse studies across various domains. However, limitations include the exclusion of non-English studies, which may lead to the omission of important research from non–English-speaking regions. In addition, the rapid development of LLM technologies means some newly published studies may be missed, and publication bias could skew the results toward studies reporting positive findings.

Future Directions

This review will highlight the need for further research, particularly in the user-centered evaluation of LLMs within clinical mental health settings. We expect to identify several gaps in the literature, such as the underrepresentation of studies focusing on the impact of LLMs on vulnerable populations. Future work should explore ways to improve model transparency, explainability, and user trust while addressing ethical concerns surrounding the use of LLMs in mental health.

Conclusions

This scoping review addresses a critical gap in the current literature by systematically evaluating the credibility of LLMs in mental health support. By mapping factors such as reliability, explainability, and ethical considerations, this review will provide a comprehensive understanding of how these models can be responsibly integrated into mental health services. The findings will offer valuable insights for mental health practitioners, researchers, and policy makers, helping to shape future studies and ethical guidelines. In particular, the results will inform decisions about the use of LLMs in clinical practice, guiding the development of policies to safeguard user trust and data privacy. Furthermore, the review will serve as a foundation for further research on improving the reliability and transparency of LLMs in sensitive areas such as mental health.

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Acknowledgments

This scoping review is conducted as part of the master's thesis of author Dipak Gautam under the supervision of Prof Dr med Philipp Kellmeyer. Data and Web Science Group, School of Business Informatics and Mathematics, University of Mannheim, Germany.

Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during this study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 17 KB - resprot_v14i1e62865_app1.docx]

Multimedia Appendix 2
Literature review matrix.
[DOCX File , 18 KB - resprot_v14i1e62865_app2.docx]

Multimedia Appendix 3
PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist.
[DOCX File , 16 KB - resprot_v14i1e62865_app3.docx]

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Abbreviations

AI: artificial intelligence
BERT: Bidirectional Encoder Representations from Transformers
JBI: Joanna Briggs Institute
LLM: large language model
PCC: Population, Concept, and Context
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Migration of Health Workers and Its Impacts on the Nigerian Health Care Sector: Protocol for a Scoping Review

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Abstract

Background: Health worker migration from Nigeria poses significant challenges to the Nigerian health care sector and has far-reaching implications for health care systems globally. Understanding the factors driving migration, its effects on health care delivery, and potential policy interventions is critical for addressing this complex issue.

Objective: This study aims to comprehensively examine the factors encouraging the emigration of Nigerian health workers, map out the effects of health worker migration on the Nigerian health system, document the loss of investment in health training and education resulting from migration, identify relevant policy initiatives addressing migration, determine the effects of Nigerian health worker migration on destination countries, and identify the benefits and demerits to Nigeria of health worker migration.

Methods: This study will follow the Joanna Briggs Institute methodology. A search strategy will retrieve published studies from MEDLINE, CINAHL, Embase, Global Health, Academic Search Premiere, and Web of Science. Unpublished studies will be sourced from dissertations and theses. A comprehensive search will involve keyword scans and citation searches. Exclusion criteria will filter out irrelevant studies, such as studies unrelated to the international migration of health workers and non-English language studies. A total of 2 independent reviewers will screen the titles and abstracts and then review the full text. Data will be extracted from the included studies using a data extraction tool developed for this study. The study selection process will be shown using a PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) flowchart. While the traditional risk of bias assessments is not applied to scoping reviews, the quality of included studies will be evaluated based on methodological transparency.

Results: The process of selecting studies will be shown using a PRISMA ScR flowchart, and information gathering will be done through a charting table that has been prepared in advance. We plan to collect data from January 2025 to March 2025 and present the results to examine publication patterns and study details. The final summary is expected to be released by the summer of 2025. It will provide an in-depth look at how health worker migration impacts the health care sector in Nigeria.

Conclusions: This study holds immense potential to contribute to understanding health worker migration from Nigeria and inform policy and practice interventions to address its challenges. By synthesizing existing evidence, the scoping review will guide future research and policy efforts to mitigate the adverse effects of migration on health care systems and workforce sustainability. Furthermore, the results will aid in recognizing deficiencies in the existing literature; this will offer a defined path for specific policy measures and methods to retain health care workers effectively and thus support the sustainability of health care systems.

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KEYWORDS

training and education; health policy; healthcare workforce; policy interventions; socio-political factors; political instability; workforce capacity

Introduction

Overview

Nigeria is the most populous country in Africa and has one of the largest supplies of health workers on the continent; however, the country has been particularly affected by the migration issue [1]. It is estimated that 20,000 of the 72,000 Nigerian physicians educated in Nigeria were practicing abroad in 2008 [2]. This number represents 28% of the physician workforce trained in Nigeria and is significantly higher than the proportion for any other African country [3]. As a result, Nigeria has a fragile health system that is unable to effectively deliver quality health services to its populace. This includes increased workload for the remaining health workers, decreased access to health care services, and compromised quality of care [4-6]. Furthermore, Nigeria invests substantial resources in training its health workforce, yet many of these trained professionals ultimately migrate to seek better opportunities abroad. Documenting the loss of investment in health training and education due to health worker migration is essential for assessing the economic and human resource implications for Nigeria's health care system [7].

The global crisis in human resources for health has been described as one of the most pressing issues facing the health sector and is now widely acknowledged as a global priority [8]. Addressing the shortage and maldistribution of health workers, including policy dialogue and coordinated action in the area of international migration of health workers, is deemed necessary to avert a long-term global health workforce crisis, which would be detrimental to the attainment of the health-related Sustainable Development Goals and Universal Health Coverage, and ultimately to global health [9]. Policy initiatives have been proposed to address health worker migration in Nigeria, including retention schemes such as offering competitive salaries and benefits, incentive programs like providing opportunities for professional development, and bilateral agreements to regulate the recruitment of Nigerian health workers by foreign countries. Evaluating the effectiveness and impact of these policies is critical for policy makers and stakeholders to develop evidence-based strategies to mitigate the adverse effects of health worker migration [10]. In addition, understanding the effects of Nigerian health worker migration on destination countries is vital for promoting ethical recruitment practices and fostering global health workforce planning. While migration poses challenges for the Nigerian health care system, it also generates remittances, fosters knowledge exchange, and promotes international engagement in health care development initiatives [11].

The migration of highly skilled health workers from developing to developed countries has been cited as contributing to shortages of qualified health workers in many African and Southeast Asian countries. In relation to the Nigerian context, there is evidence that Nigeria has experienced high levels of emigration of health professionals, where the United Kingdom, United States, and Canada are among the leading destination countries [12]. It is important to understand the journeys, distribution, and characteristics of migrant health workers, with the aim of identifying specific policy measures to enhance positive impacts and mitigate negative impacts of migration on health systems in source and destination countries [9,13,14]. In summary, this scoping review protocol seeks to provide a comprehensive overview of health worker migration and its impacts on the Nigerian health care sector. By addressing these issues, the review will inform evidence-based policies and interventions to optimize the management of health worker migration and strengthen the resilience of Nigeria's health care system.

A preliminary search of Campbell's systematic reviews, the Cochrane Database of Systematic Reviews, PROSPERO (International Prospective Register of Systematic Reviews), and Joanna Briggs Institute (JBI) evidence synthesis was conducted. Interestingly, no current or underway systematic reviews or scoping reviews on the topic were identified, highlighting the unique contribution of this study.

Aim and Review Questions

The primary purpose of this study is to establish a better understanding of how migration affects individual developing nations. This understanding will pave the way for new policies that can better manage the recruitment and retention of health professionals, thereby minimizing any negative effects caused by migration. Importantly, this study also holds the potential for positive outcomes, such as increased skill and knowledge within the sector, which can significantly benefit the health care system.

This review will seek to identify the breadth and depth of the available literature, including studies on the causes and consequences of health worker migration, the effectiveness of policy interventions, and the experiences of health workers and their families. This will provide an opportunity to identify research gaps and inform future research and policy decisions. At this preliminary stage in conducting the scoping review, the authors have also found that this type of review is best suited to the resources and time available. Specifically, the review questions are as follows: (1) What factors contribute to the emigration of Nigerian health workers? (2) How does health worker migration impact the Nigerian health system, including its strengths and weaknesses? (3) What effective strategies should be used to promote the retention of skilled health workers within the Nigerian health care system?

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Methods

Overview

Following the JBI methodology [15], the study will conduct a comprehensive search across multiple databases to find relevant studies. Data from these studies will be systematically extracted, organized, and analyzed, ensuring a reliable and comprehensive review, with findings presented in a clear and descriptive format.

Search Strategy

The scoping protocol, a detailed plan outlining the methods and search strategy for the scoping review, will initiate with an initial limited search of databases, focusing on analyzing text words in titles, abstracts, and index terms. This will be followed by a comprehensive 2-way search strategy across multiple databases, including MEDLINE, CINAHL (EBSCO), Embase, Global Health, Academic Search Premiere, and Web of Science (Table 1). Unpublished studies will be sourced from dissertations and theses. The search will involve specified keywords (eg, emigration, immigration, and health workers) and free keywords (eg, brain drain and migration). Additional strategies, such as citation and chain searches, will be used to enhance search completeness. Exclusion criteria will filter out studies unrelated to the international migration of health workers or not centered on the Nigerian health care sector. Only English-language studies from an appropriate date range will be considered, aligning with the review's scope and context. Finally, hand-searching of reference lists from relevant primary studies or review articles will be conducted. To address potential publication bias, the review will include measures such as searching for gray literature, unpublished studies, and reports that may contain negative or nonsignificant findings. This approach will help ensure a more comprehensive and balanced understanding of the topic. The scoping protocol plays a crucial role in ensuring the systematic and rigorous conduct of the scoping review, and its adherence will be reported in the final scoping review.

Table 1. Search strategy on databases.

Participant, context, and concept scheme	Number	Search string	MEDLINE (March 28)	CINAHL	Web of Science	Embase	Global Health	Academic Search Premier
International migration AND its impacts on the Nigerian healthcare sector	1	emigration OR immigration OR health workers OR skilled healthcare workers OR health professionals OR healthcare professionals OR healthcare personnel	339,025	119,968	349,710	22,039	12,876	3789
International migration AND its impacts on the Nigerian healthcare sector	2	brain drain OR migration OR healthcare workers	387,827	43,054	851,446	9098	456	1789
	3	#1 AND #2	19,789	11,006		2004	55	2908
Migration AND its impacts on the Nigerian healthcare sector	4	Nigeria OR Nigerian	41,946	7366	4540	455	34	45
Combined	5	#3 AND #4	292	113		23	12	9
Filters	6	English, from 2001 to date (excluding Magazine and book chapters)	33	112		34	33	54

Eligibility Criteria

This scoping review will incorporate the PCC (Population, Concept, Context) framework as a guide, ensuring a comprehensive and inclusive approach. We will thoroughly describe the characteristics of participants, concepts, and contexts alongside our search strategies, data extraction methods, analysis techniques, and result presentation formats. The eligibility criteria, designed to be comprehensive and inclusive, are detailed in Textbox 1. In addition, this review will involve iterative consultations with experts and stakeholders to refine the research questions and inclusion criteria.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria:

- Health workers migration from Nigeria.
- English.
- Studies from 2001 to 2024.
- Conference papers.
- Quantitative and qualitative evidence.
- Gray literature.
- Studies identifying policy initiatives aimed at addressing health worker migration in Nigeria.
- Research mapping out the impacts of health worker migration on the Nigerian health system.

Exclusion criteria:

- Meeting abstracts.
- Editorial materials.
- Book chapters.
- All other languages.
- Studies from 2001 and earlier.
- Studies not related to health worker migration from Nigeria.
- Literature not focused on the effects of health worker migration on the Nigerian health system.
- Articles lacking information on factors encouraging health worker emigration from Nigeria.
- Publications not discussing policy initiatives addressing health worker migration in Nigeria.

Participants

This scoping review will include studies involving health workers who have migrated from Nigeria to other countries. The focus will be on health care professionals, including but not limited to doctors, nurses, midwives, pharmacists, radiographers, and laboratory scientists. In addition, individuals receiving health care services in Nigeria impacted by the migration of health workers will also be considered participants in this review.

Concept

The primary concept under investigation is the migration of health workers and its impacts on the Nigerian health care sector. This includes examining factors contributing to health worker migration, such as motivating factors, as well as the consequences of migration on health care delivery, workforce dynamics, health care access, quality of care, and health outcomes in Nigeria.

Context

The review will consider studies conducted regarding the Nigerian health care sector, including public and private health care facilities, hospitals, clinics, primary health care centers, and community health centers. Equally important, studies focusing on the health care systems of destination countries where Nigerian health workers have migrated will also be included to provide a comprehensive understanding of the context.

Types of Sources

This scoping review will consider a variety of sources, including empirical research studies, policy documents, reports, and gray literature. Gray literature, which refers to nontraditional sources of information that are not published in commercial publications, can include conference papers, theses, government documents, and unpublished research. Specifically, quantitative studies such as surveys, cohort studies, and quantitative analyses of secondary data will be included. Qualitative research using methods such as interviews, focus groups, and case studies will also be considered. In addition, policy documents, government reports, organizational reports, and academic publications addressing the migration of health workers and its impacts on the Nigerian health care sector will be included in the review. For instance, a government report on the brain drain of health workers from Nigeria would be a relevant source for this review.

Study or Source of Evidence Selection

Following the search, all identified citations will be collated and uploaded into EndNote (version 20; Clarivate Analytics), and duplicates will be removed. Following a pilot test, titles, and abstracts will then be screened by 2 or more independent reviewers for assessment against the inclusion criteria for the review. Potentially relevant sources will be retrieved in full, and their citation details will be imported into the JBI System for the Unified Management, Assessment, and Review of Information [16]. Two or more independent reviewers will thoroughly assess the full text of selected citations against the inclusion criteria. Reasons for the exclusion of sources of evidence in full text that do not meet the inclusion criteria will

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be recorded and reported in the scoping review. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion or with an additional reviewer or reviewers. The results of the search and the study inclusion process will be reported in full in the final scoping review and presented in a PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) flow diagram [17]. This process ensures the transparency and rigor of the study selection process.

Data Extraction

To ensure the reliability and consistency of the data, 2 independent reviewers will meticulously extract data from each included study using a standardized data extraction form. The data extracted will include specific details about the participants, concept, context, study methods, and key findings relevant to the review questions. This thorough process guarantees the accuracy of our findings. A draft charting table will be developed as a data extraction tool. This charting table will also serve as the basis for data synthesis, and it will be modified and revised as necessary during the process of extracting data from each included evidence source. The purpose of this table is to provide a structured format for recording the extracted data, ensuring consistency and facilitating the analysis process. The synthesis will follow a narrative, descriptive approach, with identified patterns, gaps, and emerging themes categorized for further analysis. Modifications to the charting table will be detailed in the scoping review. Any disagreements that arise between the reviewers will be resolved through discussion or with an additional reviewer or reviewers. If appropriate, authors of papers will be contacted to request missing or additional data, where required.

Results

The findings of this scoping review will be shared once we finish extracting the data as planned. Our goal is to finalize the data mapping and synthesis by March 2025. The review results will be organized to showcase a thorough overview of the data based on the main themes recognized during the review process. The table for charting will contain information like the publication year and country of the study as well as its objectives and methodology, along with details on the population studied and sample size considered in the research analysis process, including outcomes assessed and intervention duration when relevant. The final summary of results, which will detail the impact of health worker migration on Nigeria's health care system, is anticipated to be released by the summer of 2025. The analysis will be finalized and submitted for publication in the autumn of 2025.

Discussion

Principal Findings

This scoping study will uncover insights into how health workers from Nigeria migrate and how it affects the country's health care system. The results should highlight patterns in what drives their migration, such as reasons and job prospects along with working conditions, while also pointing out the difficulties caused by this shortage of health care workers in delivering services and ensuring access to health care. Furthermore, the review seeks to pinpoint areas where existing research lacks information, which can serve as a basis for studies and policy making decisions to address the consequences of health worker migration.

Dealing with health worker migration challenges is crucial to improving health care delivery. Like countries facing an aging population, Nigeria is also tackling both an aging populace and a scarcity of health care workers, which is straining the health care system [10]. Projections suggest a severe shortage in the health care workforce by 2038, underscoring the urgent need to address health worker emigration as a top priority [13]. This urgency should resonate with policy makers, health care administrators, researchers, and professionals involved in health care workforce management and policy development in Nigeria.

Recent studies on health worker migration in Nigeria shed light on the factors contributing to the departure of professionals from the country. For instance, some studies pointed out that sociopolitical factors such as political instability and insecurity, as well as professional factors like low wages and poor working conditions, are driving health worker emigration [9,14]. The findings underscore the potential of focused interventions to address issues and motivate health workers to remain in Nigeria, instilling a sense of optimism for the future of Nigeria's health care system.

The consequences of health worker migration go beyond workforce shortages; they also impact the quality and accessibility of health care services in Nigeria. For instance, some research studies emphasized how health care delivery is strained and how health inequalities worsen due to the departure of professionals [12,18]. This should underline the gravity of the situation for policy makers, health care administrators, researchers, and professionals involved in Nigeria's health care workforce management and policy development. Moreover, the issue of health workers leaving the country poses challenges to the health care systems' long-term stability and ability to withstand pressures, highlighting the need for measures to retain and develop capacity [7].

Efforts to address these obstacles and encourage health professionals to stay within Nigeria's health care system have been gaining traction. Research conducted by Ossai et al [19] Falase et al [3] emphasized the significance of overcoming hurdles and offering incentives to retain health workers in the country. Furthermore, the World Health Organization's Global Code of Practice on International Recruitment of Health Personnel serves as a guideline for collaboration in tackling health worker migration and bolstering health care systems [20].

In summary, this review aims to focus on the reasons and effects of health care worker migration from Nigeria and sheds light on the challenges faced by the workforce and health care disparities in the country. Drawing comparisons with research will help put the findings into perspective by highlighting trends and new insights discovered. The study's strengths lie in its methodology and thorough analysis of data; however, it may have limitations due to gaps in less-known sources. Moving

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forward, efforts should be made towards creating targeted policy recommendations and implementing strategies to mitigate the impacts of migration on the health care system. An effective dissemination strategy guarantees that the research outcomes are communicated to policy makers and experts in the field so they can contribute to solutions.

Strengths and Limitations of the Study

The scoping review is designed to identify the gaps in the literature and recommend strategies for further research in this area. The methods used will provide us with an idea of how much research already exists in this domain and examine how research has been conducted on this topic [21]. In addition, the research team, with its extensive experience in different types of systematic reviews, brings a wealth of knowledge and expertise in this specific field, making it well-equipped to tackle the complexities of this research [21-24].

This review has a few limitations that have been considered when considering the findings. A significant limitation of this review is that the studies identified and included provided very little detail on the health worker's experiences abroad and the impact of migration on the health sector (if they were mentioned). It will, therefore, be difficult to provide a comprehensive account of the health worker migration situation and its impacts on the health sector in Nigeria. Given the limited information available in the literature, it may be necessary to consider broadening the scope of the review in the future. This could involve incorporating nonacademic literature and reports, a step that could potentially provide a more comprehensive understanding of the situation. Another potential limitation is the exclusion of any language other than English, such as French language studies. This is due to the reviewers' lack of proficiency in French, making the use of French language studies a time-consuming process. This may have introduced a language bias.

Given the broad scope of the review, it has been a challenge to frame precise research questions and define specific inclusion criteria. This complexity has made it difficult to assess the relevance of the retrieved studies. Moreover, there was significant variation in the concepts and definitions of health professional and "brain drain" among these studies, a factor that will likely influence the findings once the data is extracted and synthesis is carried out.

Conclusion

This analysis sheds light on the studied topic of health care staff migration and the limited data regarding its extent and effects, despite public worry and ample unofficial publications on the matter. The absence of supporting data has resulted in differing opinions; some term it a "crisis" while others raise concerns. Our scoping review approach has mapped the key concepts and sources, provided an understanding of the existing evidence, and paved the way for a comprehensive follow-up review.

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Data Availability

All supporting data will be reported in the manuscript. Any raw data sets supporting the results will be available and presented in the main manuscript or additional supporting files when submitting the systematic review article.

Authors' Contributions

DO contributed to conceptualization, methodology, data curation, writing, original draft, and visualization. EA managed formal analysis, investigation, and visualization. MC handled resources, writing, review, and editing. MSRJ performed supervision, validation, review and editing.

Conflicts of Interest

None declared.

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Abbreviations

JBI: Joanna Briggs Institute
PCC: Population, Concept, Context

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PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
PROSPERO: International prospective register of systematic reviews

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Protocol

Challenges and Strategies Adopted for Remote Teaching of Biochemistry During the COVID-19 Pandemic: Protocol for a Scoping Review

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Abstract

Background: In March 2020, the global landscape witnessed widespread upheavals in both socioeconomic and educational spheres due to the onset of the COVID-19 pandemic. With measures imposed to control the virus's spread, educational institutions around the world embraced digital learning, introducing challenges in the adaptation to virtual education. This shift proved especially daunting in resource-limited nations with limited digital infrastructure.

Objective: This scoping review aims to explore the experiences of biochemistry educators during the COVID-19 pandemic, focusing on successful pedagogical strategies used to overcome challenges in remote teaching. The goal is to compile valuable information applicable to health-related undergraduate and postgraduate courses.

Methods: This review considers studies and experiences related to the transition to remote biochemistry education during the pandemic. It encompasses a variety of pedagogical approaches, including online teaching tools, interactive methods, and alternatives to practical laboratory classes. The search spans databases such as MEDLINE, the Cochrane Database of Systematic Reviews, and Joanna Briggs Institute (JBI) Evidence Synthesis, with a focus on identifying systematic or scoping reviews; however, none were identified in the preliminary search.

Results: Starting in February 2022, the scoping review protocol was scheduled for completion by July 2024. From an initial pool of 1171 results, 85 articles were selected, with duplicate verification pending for the subsequent phase of the project. The findings from this review on biochemistry teaching strategies will be communicated using a combination of descriptive narrative, graphical, and tabular formats, emphasizing diverse pedagogical approaches pertinent to the subject. Dissemination will occur through regional and national scientific conference presentations, alongside publication in a peer-reviewed journal.

Conclusions: This review aims to generate innovative pedagogical approaches and pinpoint learning activities, materials, and tools that support social and collaborative learning across various subjects, including biochemistry. Moreover, it will offer perspectives from students and educators on the implemented activities, with the intention of integrating them as supplementary methods to boost student participation, and thereby, improve learning outcomes and skill development.

Trial Registration: Open Science Framework VZSA7; https://osf.io/VZSA7/

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KEYWORDS

COVID-19; biochemistry; education, distance; teaching; educational technology; review; digital learning; virtual education; teaching tools; remote learning; social support; distance learning; remote teaching

Introduction

The COVID-19 pandemic, declared by the World Health Organization (WHO) in March 2020, caused significant impacts on both socioeconomic and educational fronts, disrupting the routine of in-person education worldwide [1]. Due to restrictions on people's movement to prevent the spread of the coronavirus, schools and universities shifted to digital learning, which helped prevent 2% to 4% of COVID-19 deaths [2]. Consequently, educators and students were compelled to use digital platforms as universities faced the dilemma of either suspending activities indefinitely or restructuring through online education, with the latter prevailing [3,4]. This transition from traditional to virtual education posed challenges, requiring students and educators to adapt to digital platforms and teachers to develop some level of computer proficiency. In resource-limited countries, the limited digital infrastructure hindered online access, rendering online education less effective [3].

While online teaching tools were already used by various institutions, the widespread shift to this mode of education was abrupt for educators across all levels, from basic to postgraduate courses [4,5]. Therefore, pedagogical strategies had to be rapidly developed to achieve desired competencies through virtual learning without significant learning setbacks [4]. In addition, the need to identify optimal communication tools arose early on to facilitate practical aspects, such as ease of use, compatibility with teachers' and students' computer systems, and avoidance of additional costs for students [5]. This led to the adoption of online meeting programs, such as Microsoft Teams, Cisco Webex, GoToMeeting, Jitsi, and Zoom, on all available electronic devices and required changes in the education system to facilitate the development of students' learning habits and critical thinking; this demanded quick adaptability and creativity from teachers in transitioning from a structured teaching method to an innovative one, especially in medical education [5]. Conventional methods of distance learning often involve prerecorded video lectures and theoretical materials, which may be insufficient to engage students and promote learning [6]. Furthermore, the unavailability of teachers to clarify doubts during and after the class may impede communication and content comprehension, a limitation recognized for several years and accentuated by the COVID-19 pandemic [6,7]. As an alternative to maintaining quality education and direct teacher-student contact, interactive pedagogical tools were used to promote active learning through student participation in online classes [8].

The rapid shift to distance learning during the pandemic presented significant global challenges, as evidenced by Lassoued et al [9], which identified pedagogical, technical, and financial obstacles affecting the quality of education in Arab universities, and by Jalali et al [10], who highlighted similar issues in Iran, where prosthetics and orthotics students faced unreliable internet and a lack of digital competence among both students and faculty, severely impacting the quality of online education. Similarly, Anwar et al [11] in Pakistan and Baticulon et al [12] in the Philippines identified several barriers to effective online learning, including low digital literacy, lack of institutional support, financial difficulties, unreliable internet access, the need for students to manage household responsibilities, and mental health challenges exacerbated by the pandemic, all of which hindered students' ability to engage effectively with online education.

In the field of biochemistry education, specific examples of innovative approaches include the work of Botasini et al [13], who assessed the learning objectives of each practical biochemistry class at the University of Montevideo, distinguishing between those developing skills suitable for remote learning and those primarily requiring hands-on laboratory skills. Gasparello et al [14] replaced applied biochemistry practical classes with a remote activity simulating the use of different techniques for diagnosing SARS-CoV-2, the infectious agent responsible for the COVID-19 pandemic. They suggested continuing this strategy in person, with small groups of students to maintain social distancing. Similarly, Vasiliadou [15] proposed adopting virtual laboratories where practical classes were simulated, allowing students to perform them at their own pace, familiarizing them with health and safety regulations, and providing instant feedback. These virtual experiments could be conducted in groups, promoting social interaction and collaboration among students, crucial in a socially distant situation to facilitate communication and reduce feelings of isolation and loneliness.

Singh and Arya [1] reported the development of new approaches tested on various online platforms with a class of 200 biochemistry students. After using 4 different teaching strategies and analyzing student feedback, they combined these approaches with the flipped classroom method. This involved providing slides, quizzes, and support material links at least 24 hours before delivering a video lecture on a carbohydrate metabolism topic. Students' questions were available to tutors before the online class, and the interactive phase of this hybrid strategy was recorded for students with poor connectivity to answer a related questionnaire later.

Challenges continued to emerge as the need to fulfill educational objectives clashed with the physical distance of students [8,16]. Practical laboratory classes, integral to health professionals' training, posed a particular challenge. Teachers in these disciplines had to address how to teach practical content and skills remotely, leading to the implementation of various alternatives based on available digital tools [16].

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As some researchers shared their experiences, such as Thibaut and Schroeder's [17] guide for creating short cases for virtual case-based learning, the value of virtual learning as a complementary tool for the future became evident. In this regard, this scoping review aims to explore different experiences of biochemistry educators during the COVID-19 pandemic, identifying successful pedagogical strategies that engaged students in overcoming challenges posed by this conceptual and abstract discipline. This information can be compiled and used by educators in health-related undergraduate and postgraduate courses. Understanding complex molecular structures, intricate metabolic pathways, and subtle chemical interactions provides profound knowledge of the molecular basis of organism function and, consequently, the development, diagnosis, and treatment of diseases. A preliminary search of MEDLINE, the Cochrane Database of Systematic Reviews, and Joanna Briggs Institute (JBI) Evidence Synthesis did not identify any current or ongoing systematic reviews or scoping reviews on the topic.

Methods

Overview

The research methodology will involve the utilization of the Arksey and O'Malley [18] approach for scoping reviews, comprising the following steps: (1) identify the research question; (2) identify relevant studies; (3) perform study selection; (4) extract and chart the data; and (5) collate, summarize, and report the results. The scoping review methodology will be guided by this framework, and the protocol will follow the relevant PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines [19]. The review protocol was registered in the Open Science Framework [20].

Identify the Research Question

As per Levac et al [21], the research question intended for exploration in this review has been clearly articulated and focused. The question being investigated in this exploratory literature review is "What were the challenges and strategies adopted for remote biochemistry teaching during the COVID-19 pandemic?"

Participants, Concept, and Context Framework for Eligibility Criteria

The inclusion of eligible studies in this scoping review will be guided by the Participants, Concept, and Context framework [22].

Participants

This scoping review will include studies that involve students who participated in biochemistry courses at undergraduate or postgraduate levels, delivered remotely.

Concept

The focus of the study is to analyze the challenges and strategies adopted for remote biochemistry teaching, covering both theoretical and practical approaches, during the COVID-19 pandemic. Studies discussing pedagogical methods, online teaching tools, adaptation of laboratory practices, and other approaches to maintaining the quality of distance education will be considered.

Context

Only studies conducted during the COVID-19 pandemic will be included, as the objective is to explore how biochemistry teaching was adapted and the challenges faced during this specific period. Studies published in any language will be considered.

Exclusion

Duplicate articles, editorials, reviews, conference proceedings, theses, dissertations, and monographs will be excluded.

Identify Relevant Studies

The literature search will be performed from January 2020 to December 2023, during the time period when articles related to tools used for remote teaching during the COVID-19 pandemic were published, in collaboration with a specialized librarian, using an iterative approach. Following the formulation of the question, keywords will be identified ("Teaching"; "Biochemistry"; "Distance Education"; and "COVID-19") that managed to capture articles related to the topic, namely "translational medical research" (Medical Subject Headings terms) and "knowledge translation."

The following databases will be consulted: National Library of Medicine (PubMed), MEDLINE, Scopus, Directory of Open Access Scholarly Resources, Education Resources Information Center, Directory of Open Access Journals, and Google Scholar, through descriptors and their synonyms, according to the Health Sciences Descriptors and Medical Subject Headings, for each item of the strategy (Tables 1 and 2). For the combination of descriptors, the Boolean terms AND, OR, and NOT will be considered.

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Table 1. Search keywords and key terms used for this study.

Subjects	Subject and synonyms in Portuguese (DeCS[a])	Subject and synonyms in English (MeSH[b])
1	"Ensino" OR "Atividade de Treinamento" OR "Atividades Formativas" OR "Atividades de Capacitação" OR "Atividades de Formação" OR "Atividades de Treinamento" OR "Atividades de Treino" OR "Capacitação Acadêmica" OR "Didática" OR "Docência" OR "Formação Acadêmica" OR "Método de Ensino" OR "Métodos Pedagógicos" OR "Métodos de Ensino" OR "Pedagogia" OR "Treinamento Acadêmica" OR "Treino Acadêmico" OR "Técnica de Treinamento" OR "Técnicas Educacionais" OR "Técnicas Educativas" OR "Técnicas de Ensino" OR "Técnicas de Formação" OR "Técnicas de Treinamento" OR "Técnicas de Treino"	"Teaching" OR "Training Technique" OR "Training Technique" OR "Technique, Training" OR "Techniques, Training" OR "Training Technic" OR "Technic, Training" OR "Technics, Training" OR "Training Technic" OR "Pedagogy" "Pedagogies" OR "Teaching Method" OR "Teaching Method" OR "Method, Teaching" OR "Methods, Teaching" OR "Academic Training" OR "Training, Academic" OR "Training Activities" OR "Training Activity" OR "Activities, Training" OR "Activity, Training" OR "Techniques, Educational" OR "Educational Techniques" OR 'Educational Technique" OR "Technique, Educational" OR "Educational Technics" OR "Educational Technic" OR "Technic, Educational" OR "Technics, Educational"
2	"Bioquímica"	"Biochemistry"
3	"Educação a Distancia" OR "Aprendizado Online" OR "Aprendizado a Distância" OR "Aprendizagem Online" OR "Aprendizagem a Distância" OR "Ciberaprendizagem" OR "Cursos por Correspondência" OR "Educação Online" OR "Ensino a Distância" OR "Formação à Distância" OR "Formação à Distância através das TIC" OR "Formação à Distância através das Tecnologias da Informação e das Comunicações" OR "Tele-Educação" OR "Tele-Educação Interativa" OR "Teleducação" OR "Teleducação Interativa" OR "Teleformação" OR "eLearning"	"Education, Distance" OR "Distance Education" OR "Distance Learning" OR "Learning, Distance" OR "Online Learning" OR "Learning, Online" OR "Online Education" OR "Education, Online" OR "Online Educations" OR "Correspondence Courses" OR "Correspondence Course" OR "Course, Correspondence"
4	"Covid-19" OR "COVID19" OR "Doença Viral COVID-19" OR "Doença pelo Novo Coronavírus (2019-nCoV)" OR "Doença por 2019-nCoV" OR "Doença por Coronavírus 2019" OR "Doença por Coronavírus 2019-nCoV" OR "Doença por Coronavírus-19" OR "Doença por Novo Coronavírus (2019-nCoV)" OR "Doença por Novo Coronavírus de 2019" OR" Doença por Vírus COVID-19" OR "Epidemia de Pneumonia por Coronavírus de Wuhan" OR "Epidemia de Pneumonia por Coronavírus de Wuhan de 2019-2020" OR "Epidemia de Pneumonia por Coronavírus em Wuhan" OR "Epidemia de Pneumonia por Coronavírus em Wuhan de 2019-2020" OR "Epidemia de Pneumonia por Novo Coronavírus de 2019-2020" OR "Epidemia pelo Coronavírus de Wuhan" OR "Epidemia pelo Coronavírus em Wuhan" OR "Epidemia pelo Novo Coronavírus (2019-nCoV)" OR "Epidemia pelo Novo Coronavírus 2019" OR "Epidemia por 2019-nCoV" OR "Epidemia por Coronavírus de Wuhan" OR "Epidemia por Coronavírus em Wuhan" OR "Epidemia por Novo Coronavírus (2019-nCoV)" OR "Epidemia por Novo Coronavírus 2019" OR "Febre de Pneumonia por Coronavírus de Wuhan" OR "Infecção Viral COVID-19" OR "Infecção pelo Coronavírus 2019-nCoV" OR "Infecção pelo Coronavírus de Wuhan" OR "Infecção pelo SARS-CoV-2" OR "Infecção por 2019-nCoV" OR "Infecção por Coronavírus 2019-nCoV" OR "Infecção por Coronavírus de Wuhan" OR "Infecção por Novo Coronavírus de 2019" OR "Infecção por SARS Coronavirus 2" OR "Infecção por SARS-CoV-2" OR "Infecção por Vírus COVID-19" OR "Infecções por SARS-CoV-2" OR "Pandemia COVID-19" OR "Pandemia por COVID-19" OR "Pandemias por COVID-19" OR "Pneumonia do Mercado de Frutos do Mar de Wuhan" OR "Pneumonia por Coronavírus de Wuhan" OR "Pneumonia por Novo Coronavírus de 2019-2020" OR "Surto de Coronavírus de Wuhan" OR "Surto de Pneumonia da China 2019-2020" OR "Surto de Pneumonia na China 2019-2020" OR "Surto pelo Coronavírus 2019-nCoV" OR "Surto pelo Coronavírus de Wuhan" OR "Surto pelo Coronavírus de Wuhan de 2019-2020" OR "Surto pelo Novo Coronavírus (2019-nCoV)" OR "Surto pelo Novo Coronavírus 2019" OR "Surto por 2019-nCoV" OR "Surto por Coronavírus 2019-nCoV" OR "Surto por Coronavírus de Wuhan" OR "Surto por Coronavírus de Wuhan de 2019-2020" OR "Surto por Novo Coronavírus (2019-nCoV)" OR "Surto por Novo Coronavírus 2019" OR "Virose COVID-19" OR "covid-19"	"COVID19" OR "COVID 19" OR "SARS-CoV-2 Infection" OR "Infection, SARS-CoV-2" OR "SARS CoV-2 Infection" OR "SARS-CoV-2 Infections" OR "2019 Novel Coronavirus Disease" OR "2019 Novel Coronavirus Infection" OR "2019-nCoV Disease" OR "2019-nCoV Disease" OR "2019-nCoV Diseases" OR "Disease, 2019-nCoV" OR "COVID-19 Virus Infection" OR "COVID 19 Virus Infection" OR "COVID-19 Virus Infections" OR "Infection, COVID-19 Virus" OR "Virus Infection, COVID-19" OR "Coronavirus Disease 2019" OR "Disease 2019, Coronavirus" "Coronavirus Disease-19" OR "Coronavirus Disease 19" OR "Severe Acute Respiratory Syndrome Coronavirus 2 Infection" OR "SARS Coronavirus 2 Infection" OR "COVID-19 Virus Disease" OR "COVID 19 Virus Disease" OR "COVID-19 Virus Diseases" OR "Disease, COVID-19 Virus" OR "Virus Disease, COVID-19" OR "2019-nCoV Infection" OR "2019-nCoV Infection" OR "2019-nCoV Infections" OR "Infection, 2019-nCoV" OR "COVID19" "COVID-19 Pandemic" OR "COVID 19 Pandemic" OR "Pandemic, COVID-19" OR "COVID-19 Pandemics"

[a]DeCS: Health Science Descriptors.

[b]MeSH: Medical Subject Headings.

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Table 2. Search strategy for databases used for this study.

Databases	Search details
National Library of Medicine (PubMed), MEDLINE, Scopus, Directory of Open Access Scholarly Resources, Education Resources Information Center, and Directory of Open Access Journal	(“Teaching” OR “Training Technique” OR “Training Technique” OR “Technique, Training” OR “Techniques, Training” OR “Training Technic” OR “Technic, Training” OR “Technics, Training” OR “Training Technic” OR “Pedagogy” “Pedagogies” OR “Teaching Method” OR “Teaching Method” OR “Method, Teaching” OR “Methods, Teaching” OR “Academic Training” OR “Training, Academic” OR “Training Activities” OR “Training Activity” OR “Activities, Training” OR “Activity, Training” OR “Techniques, Educational” OR “Educational Techniques” OR ‘Educational Technique” OR “Technique, Educational” OR “Educational Technics” OR “Educational Technic” OR “Technic, Educational” OR “Technics, Educational”) AND (“Biochemistry”) AND (“Education, Distance” OR “Distance Education” OR “Distance Learning” OR “Learning, Distance” OR “Online Learning” OR “Learning, Online” OR “Online Education” OR “Education, Online” OR “Online Educations” OR “Correspondence Courses” OR “Correspondence Course” OR “Course, Correspondence”) AND (“COVID19” OR “COVID 19” OR “SARS-CoV-2 Infection” OR “Infection, SARS-CoV-2” OR “SARS CoV-2 Infection” OR “SARS-CoV-2 Infections” OR “2019 Novel Coronavirus Disease” OR “2019 Novel Coronavirus Infection” OR “2019-nCoV Disease” OR “2019-nCoV Disease” OR “2019-nCoV Diseases” OR “Disease, 2019-nCoV” OR “COVID-19 Virus Infection” OR “COVID 19 Virus Infection” OR “COVID-19 Virus Infections” OR “Infection, COVID-19 Virus” OR “Virus Infection, COVID-19” OR “Coronavirus Disease 2019” OR “Disease 2019, Coronavirus” “Coronavirus Disease-19” OR “Coronavirus Disease 19” OR “Severe Acute Respiratory Syndrome Coronavirus 2 Infection” OR “SARS Coronavirus 2 Infection” OR “COVID-19 Virus Disease” OR “COVID 19 Virus Disease” OR “COVID-19 Virus Diseases” OR “Disease, COVID-19 Virus” OR “Virus Disease, COVID-19” OR “2019-nCoV Infection” OR “2019-nCoV Infection” OR “2019-nCoV Infections” OR “Infection, 2019-nCoV” OR “COVID19” OR “COVID-19 Pandemic” OR “COVID 19 Pandemic” OR “Pandemic, COVID-19” OR “COVID-19 Pandemics”
Google Scholar (in Portuguese)	(“Ensino” OR “Atividade de Treinamento” OR “Atividades Formativas” OR “Atividades de Capacitação” OR “Atividades de Formação” OR “Atividades de Treinamento” OR “Atividades de Treino” OR “Capacitação Acadêmica” OR “Didática” OR “Docência” OR “Formação Acadêmica” OR “Método de Ensino” OR “Métodos Pedagógicos” OR “Métodos de Ensino” OR “Pedagogia” OR “Treinamento Acadêmica” OR “Treino Acadêmico” OR “Técnica de Treinamento” OR “Técnicas Educacionais” OR “Técnicas Educativas” OR “Técnicas de Ensino” OR “Técnicas de Formação” OR “Técnicas de Treinamento” OR “Técnicas de Treino”) AND (“Bioquímica”) AND (“Educação a Distancia” OR “Aprendizado Online” OR “Aprendizado a Distância” OR “Aprendizagem Online” OR “Aprendizagem a Distância” OR “Ciberaprendizagem” OR “Cursos por Correspondência” OR “Educação Online” OR “Ensino a Distância” OR “Formação à Distância” OR “Formação à Distância através das TIC” OR “Formação à Distância através das Tecnologias da Informação e das Comunicações” OR “Tele-Educação” OR “Tele-Educação Interativa” OR “Teleducação” OR “Teleducação Interativa” OR “Teleformação” OR “eLearning”) AND (“Covid-19” OR “COVID19” OR “Doença Viral COVID-19” OR “Doença pelo Novo Coronavírus (2019-nCoV)” OR “Doença por 2019-nCoV” OR “Doença por Coronavírus 2019” OR “Doença por Coronavírus 2019-nCoV” OR “Doença por Coronavírus-19” OR “Doença por Novo Coronavírus (2019-nCoV)” OR “Doença por Novo Coronavírus de 2019” OR “Doença por Vírus COVID-19” OR “Epidemia de Pneumonia por Coronavírus de Wuhan” OR “Epidemia de Pneumonia por Coronavírus de Wuhan de 2019-2020” OR “Epidemia de Pneumonia por Coronavírus em Wuhan” OR “Epidemia de Pneumonia por Coronavírus em Wuhan de 2019-2020” OR “Epidemia de Pneumonia por Novo Coronavírus de 2019-2020” OR “Epidemia pelo Coronavírus de Wuhan” OR “Epidemia pelo Coronavírus em Wuhan” OR “Epidemia pelo Novo Coronavírus (2019-nCoV)” OR “Epidemia pelo Novo Coronavírus 2019” OR “Epidemia por 2019-nCoV” OR “Epidemia por Coronavírus de Wuhan” OR “Epidemia por Coronavírus em Wuhan” OR “Epidemia por Novo Coronavírus (2019-nCoV)” OR “Epidemia por Novo Coronavírus 2019” OR “Febre de Pneumonia por Coronavírus de Wuhan” OR “Infecção Viral COVID-19” OR “Infecção pelo Coronavírus 2019-nCoV” OR “Infecção pelo Coronavírus de Wuhan” OR “Infecção pelo SARS-CoV-2” OR “Infecção por 2019-nCoV” OR “Infecção por Coronavírus 2019-nCoV” OR “Infecção por Coronavírus de Wuhan” OR “Infecção por Novo Coronavírus de 2019” OR “Infecção por SARS Coronavirus 2” OR “Infecção por SARS-CoV-2” OR “Infecção por Vírus COVID-19” OR “Infecções por SARS-CoV-2” OR “Pandemia COVID-19” OR “Pandemia por COVID-19” OR “Pandemias por COVID-19” OR “Pneumonia do Mercado de Frutos do Mar de Wuhan” OR “Pneumonia por Coronavírus de Wuhan” OR “Pneumonia por Novo Coronavírus de 2019-2020” OR “Surto de Coronavírus de Wuhan” OR “Surto de Pneumonia da China 2019-2020” OR “Surto de Pneumonia na China 2019-2020” OR “Surto pelo Coronavírus 2019-nCoV” OR “Surto pelo Coronavírus de Wuhan” OR “Surto pelo Coronavírus de Wuhan de 2019-2020” OR “Surto pelo Novo Coronavírus (2019-nCoV)” OR “Surto pelo Novo Coronavírus 2019” OR “Surto por 2019-nCoV” OR “Surto por Coronavírus 2019-nCoV” OR “Surto por Coronavírus de Wuhan” OR “Surto por Coronavírus de Wuhan de 2019-2020” OR “Surto por Novo Coronavírus (2019-nCoV)” OR “Surto por Novo Coronavírus 2019” OR “Virose COVID-19” OR “covid-19”)

After conducting the search, the following will be included: studies conducted in English and Portuguese languages, with quantitative and qualitative approaches; primary studies, systematic reviews, meta-analyses, and meta-syntheses; and books and guidelines published in indexed sources that address the established question.

Duplicate articles, editorials, reviews, conference proceedings, theses, dissertations, monographs, undergraduate final projects, opinion publications, consensuses, retractions, editorials, websites, and advertisements disseminated will be excluded.

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Perform Study Selection

The citations gathered will be transferred to Mendeley Reference Manager for Desktop (version 2.109.0; Elsevier Ltd.) after the search, and the duplicates will be manually removed. Following this, 2 reviewers (TI and JCA) will independently assess titles and abstracts for eligibility using the Participants, Concept, and Context framework. Full texts of potentially relevant articles meeting the eligibility criteria will be retrieved for the 2 reviewers to scrutinize and compare against the inclusion criteria. In case of discrepancies during any phase of article selection between TI and JCA, resolution will be sought through discussion or consultation with ARdAL, the third reviewer. The final scoping review will feature a descriptive account of the search and study selection process alongside a PRISMA-ScR flow diagram [15].

Extract and Chart the Data

The data from all eligible studies will be extracted and processed through data charting. This process involves extracting information from the selected full-text articles. A Microsoft Excel table will be created for this purpose, encompassing sections, such as title, authors, year of publication, geographic area, study objectives, pedagogical approaches, collaborative learning activities, resources adopted, and summary of findings.

Collate, Summarize, and Report the Results

The characteristics of each identified study will be summarized and described (eg, author name, study location, and year of publication), along with the pedagogical approach used in teaching biochemistry; the learning activities, content, and resources used; and any evaluation by students of the strategies used by their professors.

Results

Initiated in February 2022, the protocol for this scoping review was anticipated to wrap up by July 2024. The research process yielded 1171 results, from which 85 articles were selected. Verification of duplicates has not yet been conducted, and this will be carried out in the next stage of the work.

The outcomes of this scoping review on teaching strategies for biochemistry will be conveyed through a blend of descriptive narrative, graphical, and tabular formats. The presentation will be structured to underscore the various pedagogical approaches relevant to the field. These findings will be shared through regional and national scientific conference presentations, as well as publication in a peer-reviewed journal.

Discussion

Expected Findings

During the COVID-19 pandemic, the teaching of undergraduate and graduate courses in the health care field faced significant challenges [9]. The interruption of in-person laboratory activities and the need for quick adaptation to online teaching were some of the main obstacles [11,12]. Furthermore, the lack of access to laboratories and the disruption of clinical practice affected the development of essential practical skills for students [4].

However, some advantages were identified with the strategies adopted by teachers and institutions during the pandemic [8,17]. For instance, the use of online resources such as prerecorded videos and animated slides allowed for greater efficiency in academic work [1,5]. In addition, engaging in vital scientific activities such as reading articles and preparing presentations, coupled with the flexibility provided by remote learning, which enabled greater student participation, contributed to the cognitive development and enhancement of communication and technological skills of the students [1,4,5].

Considering these observations, continuing remote teaching strategies after the pandemic can bring various benefits [8]. The learning flexibility offered by online classes allows students to access content conveniently and effectively, promoting greater inclusion and expanding access to education [5,16]. Moreover, the possibility of continuous material review facilitates understanding and reinforces learning [1].

It should be emphasized that the use of educational technologies helps students develop essential digital skills for the current and future job market [5]. Therefore, blending educational strategies developed during the pandemic with in-person classes could bring additional opportunities for the improvement of teaching and learning not only in biochemistry but also in other disciplines [6,7].

In addition, this scoping review presents limitations. Specifically, there will be no evaluation of the quality of the studies included. There is a possibility of overlooking pertinent data, given that our search is restricted to published studies exclusively. We have chosen multiple sources and formulated meticulous search strategies to enhance the identification of eligible studies.

Conclusions

The results of this review are expected to bring forth ideas for new pedagogical approaches and identify learning activities, content, and resources that facilitate social and collaborative learning processes, both for biochemistry and other disciplines. In addition, insights from students and teachers regarding the activities developed will be provided, aiming to apply them as additional strategies to enhance student engagement, and consequently, learning and the development of various skills.

Acknowledgments

We would like to thank Zélia Cristina Regis at the Faculty of Medicine of São José do Rio Preto (FAMERP) for her contribution to the development of the research process.

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Authors' Contributions

TI, HLGC, ARdAL, and JC conceptualized, designed, and interpreted the data and were the main contributors to writing the manuscript. ABGC, NBGC, VMSB, and DRSS analyzed and interpreted the data. TI, ERdS, NAdASRC, FNFJ, AH, and CM have supervised and revised the final draft.

Conflicts of Interest

None declared.

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Abbreviations

JBI: Joanna Briggs Institute
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
WHO: World Health Organization

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Protocol

Access to Health Care and Use of Health Care Services Among Males in Africa: Protocol for a Scoping Review

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Abstract

Background: There is a scarcity of data on males' health-seeking behavior, as well as their access to and use of health care services, in Africa. According to some studies, men are less likely than women to seek medical help for issues such as communicable and noncommunicable diseases, depression, substance abuse, physical disabilities, and stressful life events. The study of males' health-seeking behaviors is important, because it allows us to learn about male health, how masculinity encourages underuse of health care services, how this affects males' overall health and well-being, and how cultural values and backgrounds may impact older men's health-seeking behaviors.

Objective: The objective of this review is to assess evidence on how males access and use health care services and their health knowledge, attitudes, and perceptions to identify gaps for targeted, context-specific strategies to improve males' health and outcomes, particularly in Africa.

Methods: The scoping review process will be guided by the methodology frameworks of the Joanna Briggs Institute and Arksey and O'Malley and will follow the Preferred Reporting Items for Systematic reviews and Meta-analysis Protocols Extension for Scoping Reviews guidelines. The following electronic databases will be systematically searched for evidence published between January 2010 and 2023: PubMed, Scopus, Web of Science, African Journals Online, and Google Scholar. Two reviewers will independently screen full texts and chart the data; a third reviewer will be engaged in the event of disagreement between the 2 independent reviewers. The results of this scoping review will be summarized quantitatively through numerical counts and qualitatively through a narrative synthesis.

Results: The electronic database search was conducted between March and April 2023 and redone in April 2024 to include the most recent articles. A total of 114,737 articles were retrieved and 4258 removed as duplicates. After title screening, 337 results remained, and after abstract selection, 140 results remained. As of December 2024, the scoping review was in the full-text screening phase. We plan to complete data extraction, synthesis, and writing of the entire manuscript of the review in January 2025, and then submit it to a journal for peer review and publication in February 2025.

Conclusions: The scoping review results will advance the current knowledge about health-seeking behavior and access to and uptake of health care services among African males. To our knowledge, this scoping review is the first on this topic, and it will identify vital information on the barriers to and facilitators of African males' health care access and uptake. It will also provide information on successful health care programs for males that may be tailored and adopted across different African contexts.

Trial Registration: OSF Registries https://osf.io/xz6sr

International Registered Report Identifier (IRRID): DERR1-10.2196/52351

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KEYWORDS

health-seeking behavior; health care; access; uptake; services; men; boys; scoping review; Africa; male; health care services; accessibility; use; noncommunicable disease; depression; substance abuse; overdose; physical disability; stress; older men; men's health; well-being; health literacy; perception; systematic reviews; meta-analysis; electronic database; EHR; electronic health record; narrative synthesis

Introduction

The World Health Organization (WHO) defines health as "a state of complete physical, mental and social well-being and not merely the absence of disease or infirmity" [1]. Sustainable Development Goal 3 complements this definition by pinpointing the need for global commitment to "ensure healthy lives and promote well-being for all at all ages" without exclusion [2]. Admirable and essential as these intentions may be, their success is incumbent upon reaching key populations so that the health care requirements of those populations may be fulfilled. Males the world over are one such key population, and they generally underuse the health care opportunities available to them [3-5]. This is concerning, since it is projected that men's health burden will result in men's lifespans being 7 years less than women by 2030. In South Africa, the male health risk and mortality rates are high due to tuberculosis, as well as noncommunicable diseases like diabetes and cardiovascular diseases, all of which are mostly preventable [6]. There are various reasons for men delaying or avoiding seeking health interventions, with some of the most regularly identified ones being a paucity of male-centered interventions, sociodemographic factors, and attitudes toward health services [7-9]. Nonetheless, there is evidence that a shift in males' attitudes is emerging and that they are becoming increasingly willing to access health care. Consequently, there is a drive to not only provide health care services that cater specifically to men and minimize the barriers to their seeking health care, but also to increase research in this field [8]. Our research will thus add to the body of knowledge that is used to fulfill the aforementioned commitment.

"Men" is a broad term; according to the WHO, there are different terminologies, age ranges, and characteristics used to describe the transition from childhood to adulthood for men. Adolescence has been described as the ages of 10 to 19 years and young adulthood as 10 to 24 years [10]. Guided by these clarifications, the age range in our scoping review included all male-related studies involving individuals aged 13 to 17 years as teenagers and those aged 18 years and older as adults. This age range of minors was included due to the fact that the onset of the teenage years is when young people experience "physiological, psychological, and social changes that lay bare the world of sexual experimentation" [11] and the consequences thereof, which may call for health care. This was deemed significant as it could yield a better understanding of males in this population, specifically with regard to their sexual reproductive health practices. Another population that was deemed significant to our study was transgender males, as their health-seeking behavior is currently underresearched, despite their experience of inordinate health risks and challenges [12].

An examination of health policies of 10 low- and middle-income countries revealed that health care priorities in these countries are largely driven by cost-saving measures and the types of disease that are prevalent. This means that health care priorities can differ significantly across geographical areas. Nonetheless, in most sub-Saharan countries, HIV is prioritized, with lymphatic filariasis, syphilis in pregnant or new mothers, human papilloma virus, tuberculosis, and sexually transmitted diseases being other common conditions [13]. What is striking is that not only are none of these conditions unique to males, but some of them are solely female focused. This is concerning because it conveys the impression that particularly male diseases are not a high priority. For example, the incidence of prostate cancer is escalating in West Africa, and treatment is usually delayed for so long that the health outcomes for men with the condition are dismal. Further, men with prostate cancer symptoms either remain ignorant of the disease or are too poor to seek treatment [14]. Equally dangerous are unhealthy lifestyle choices, like smoking and alcohol abuse, which are more prevalent among men, as well as some chronic diseases like diabetes and cerebrovascular disease, two of the main causes of death in men over the age of 45 years: the South African government has recently acknowledged all of these conditions as worthy of being addressed [4]. It is therefore not unreasonable to conclude that improved health literacy targeted specifically at males could help to mitigate their life-threatening health conditions and choices [15].

Apart from the obvious benefits of disease management, males who are inspired and empowered to take control of their own health can inadvertently improve the lives of their families, as well as society in general. Economically, better health would, in the long run, reduce medical costs that would usually be borne by the family and in some part, the government. Socially, healthy men would more likely be able to lead an active life in which they do not feel compelled to avoid health care to preserve their masculinity, nor fear stigmas associated with, for example, mental health conditions or undergoing antenatal HIV screening with their partners [8,16].

But, within the ambit of our study, we first have to ascertain what strategies have the most reasonable chance of uptake to be able to speculate on the benefits of males engaging in health-seeking practices. What has to be borne in mind is that men's health-seeking behavior, which in Africa is influenced by a particularly patriarchal ethos, limited resources, and faith in traditional medicines and cultural superstitions [8,17], may not necessarily match the behavior of males in countries that do not share similar characteristics.

In essence, this scoping review will seek to describe the variations in health-seeking behaviors among males across the African continent, assess their access to and use of health care services, and identify both challenges and facilitators of health care uptake. Additionally, it will explore males' knowledge, attitudes, perceptions, and beliefs regarding their health care needs and available services. The overall goal is to assess the

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current evidence on these factors to guide the development of strategies that enhance males' health and improve outcomes across the region. To this end, the primary objective of this scoping review is to map evidence on males' access to and use of health care services and identify gaps for targeted, context-specific strategies to improve males' health outcomes, particularly in Africa.

Methods

Study Design

We will use a scoping review approach to map out existing evidence on males' health-seeking behavior and access to and uptake of health care services in Africa. This will enable us to identify aspects for tailored intervention to improve males' health-seeking behavior. In conducting this review, we will apply the methodological approach and review process of the Joanna Briggs Institute (JBI) [18]. The JBI framework enables an extensive and less-biased synthesis of studies by using comprehensive and transparent methods [19]. The JBI framework synthesizes existing knowledge rather than creating new knowledge [20]. This yields decisions that reflect on the feasibility, appropriateness, meaningfulness, and effectiveness of health behavior [19,20] The Preferred Reporting Items for Systematic reviews and Meta-analyses extension for Scoping Reviews (PRISMA-ScR) guidelines [21,22] will be adhered to in reporting this scoping review. The PRISMA-ScR guidelines are congruent with the JBI approach for scoping reviews, which emphasizes the importance of methodological precision for scoping reviews. We believe that the PRISMA-ScR will improve the reporting of our scoping review [22]. According to the 5 main steps [18], we discuss our review process in the following sections.

Step 1—Identifying the Research Question

The scoping review questions will be formulated according to the population, concept, and context (PCC) approach recommended by the JBI. The PCC framework is suitable when developing objectives and eligibility criteria for scoping reviews [23]. In our study, the PCC inclusion criteria will be useful to guide how the data should be extracted. There is no need for outcomes or interventions of interest to be identified for a scoping review [24] (Table 1).

Based on the PCC framework mentioned above, the research questions we will explore are outlined below:

1. What are the varying health-seeking behaviors among males across the African continent?
2. What are health services for males and how do males access and use health care services in Africa?
3. What knowledge, attitudes, perceptions, and beliefs exist among males about their health care needs and health care services in Africa?
4. What are the challenges and facilitators of health care uptake by males in Africa?

Table 1. The population, concept, and context (PCC) elements in this review.

Element	Description
Population	Males only
Concept	Health-seeking behavior; health care service access, use, and uptake
Context	Africa

Step 2—Identifying Relevant Studies

We will systematically search PubMed, African Journals Online, Web of Science, Scopus, and Google Scholar. The search will include papers with publication years from 2010 to 2023 to better reflect more recent information and current health-seeking behavior among males across the African continent. In addition, government reports available on the websites of departments and ministries of health and associations will be reviewed with a focus on males' access to health care services, knowledge, perceptions, and attitudes regarding health care services, as well as barriers and facilitators to uptake of health services by males. This will help us to identify reports related to males' health-seeking behavior in Africa.

The search strategy will include titles, abstracts, and combinations of keywords, as presented in Multimedia Appendix 1 and Multimedia Appendix 2.

Step 3—Study Selection

After collection of study data from the aforementioned bibliographic databases, 3 reviewers will conduct the review; 2 will perform data selection and database searching and the third will perform quality checking and resolve inclusion and exclusion disagreements between the 2 primary reviewers. The 2 primary reviewers will independently use the inclusion and exclusion criteria to search the titles and abstracts, and they will document reasons for inclusion and exclusion as outlined below. Any discrepancies will be discussed and resolved between these 2 reviewers, but if no conclusion can be reached, the third reviewer will be included in the discussion. Furthermore, the reviewers will independently source full-text versions of articles found to be eligible during the title and abstract screening phase. They will exclude articles without full-text versions available after a conclusive discussion regarding the excluded articles is reached. The searched articles will include male-related studies and include qualitative, quantitative, and mixed methods interventions for males' health, knowledge, attitudes, and perceptions regarding health services for males, as well as access and challenges to use of health care services. Overall, this scoping review will include material that fulfill the criteria outlined in Tables 1 and 2. The exclusion criteria entail studies not conducted in Africa; not including males' health care service access and uptake or health-seeking behavior; and those conducted prior to 2010.

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Table 2. The eligibility criteria.

Criteria for study inclusion	Component details
Setting	Only studies from Africa will be considered for the scoping review.
Language	Only English-language studies will be included.
Date	Only studies from the years 2010 to 2023 will be included.
Publication status	All documented studies will be considered and included in the scoping review. This will include only published peer-reviewed articles.
Method	The study will be designed and reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews. Population, concept, and context will be used as the search strategy approach. Qualitative, quantitative, and mixed methods studies will be included.

Step 4—Charting the Data

Data from the identified eligible studies will be collected and charted. Reviewers will record key themes from each eligible article. The themes will include author, journal, publication status, study duration, year, and demographic information (age, ethnicity, marital/relationship status, employment, residential location [rural or urban], income, and education level), geographical information (country and region in which the study was done), research methodology, and findings included in the synthesis (study design, health-seeking behavior, access, uptake, intervention, main results and outcome, limitations, and other important discoveries; Textbox 1). Microsoft Excel, EndNote, and Rayyan will be used in obtaining the data, saving the search, cleaning the data, screening the data, and charting the data for this scoping review.

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Textbox 1. Data chart template (to be expanded during actual review).

Details of elements included in the synthesis

- Author
- Journal
- Publication status
- Study duration
- Year

Demographic information on participants in the synthesis

- Age
- Residential location (rural or urban)
- Ethnicity
- Marital/relationship status
- Income
- Employment
- Education level

Geographic information in the synthesis

- Region where the study was done
- Country

Research methodology and summary findings in the synthesis

- Study design
- Health-seeking behavior
- Access
- Uptake
- Intervention
- Main results and outcome
- Limitation
- Other important discoveries

Other comments, if any

Step 5—Collating, Summarizing, and Reporting the Results

A qualitative and quantitative approach will be used to report and summarize the scoping review. The number and type of eligible studies will be reported numerically, and methods, results, health care services, program, and health-seeking behavior information will be described in a narrative form. Tables and charts will be used to map out the screening process and results. Discussion will be guided by developed themes and study objectives and will include definitions of keywords. The risk of bias will not be assessed, as the scoping review is meant to provide an overview of existing literature about health-seeking behavior of African males and not critically analyze or appraise the selected articles; the limitations of the studies will be noted. Secondary analyses will be performed looking at health-seeking behavior and challenges, knowledge, and stigma regarding access to and uptake of health care services among boys and the transgender population. Analyses will also compare males' health-seeking behavior and service access and use across different regions.

Results

The electronic database search was conducted between March and April 2023 and was redone in April 2024 to include the most recent publications. A total of 114,737 results were retrieved, and 4258 were identified as duplicates. The database was first title screened, and this yielded a total of 337 articles for further abstract screening, which resulted in 140 articles remaining for full article screening. We are currently finalizing full-article screening for the synthesis. We intend to complete the synthesis and initial manuscript write-up in January 2025, for submission for peer review and publication in February 2025.

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Discussion

Expected Findings

We expect to substantiate that the burden of disease in males compared to females is high for a plethora of reasons, such as availability of context-specific health care services for males, access by males to health care, and the socioeconomic position of households. Moreover, available evidence has shown that male health-seeking behavior is often delayed, and the uptake of health care services is poor due to barriers such as cultural beliefs, perceptions of masculinity, stigma, gaps in health knowledge, and social and economic factors [25,26]. Based on the limited number of published articles on males' access to and uptake of health care services, especially in Africa, and observations on trends in the proportions by sex of outpatients (ie, there are more females than males) seeking care in primary health care centers [27-30], there is a need for male health care to be taken into consideration. Facilitators like community-based interventions, male-targeted programs, and peer support have been shown to improve male engagement with health care [26]. To our knowledge, this scoping review is the first on this topic, and it will identify key themes and gaps regarding the barriers to and facilitators of African males' health care access and uptake. The scoping review will summarize and discuss our findings, including challenges and facilitators of health care service access and uptake and health-seeking behavior among African males. The results may form the basis for future qualitative research on exploring the health-seeking behavior of African males, quantitative research on barriers to and facilitators of access to and uptake of health care services, implementation research on intervention programs to influence African males to access and use health care services voluntarily, or systematic reviews of programs for working African males to access health care and support systems and increase their health care–seeking behavior. The results may also help policy makers to develop programs and interventions specifically tailored for the needs of males through males' input. The literature synthesis will support the development of evidence-based practices that will address challenges related to males' access to health care services, enhance their health care knowledge, and promote intervention programs to improve uptake, which may result in a decreased burden of disease and mortality rate among males. We expect our main findings to provide insights into what geography-specific health services are available across the African region, as well as provide the latest evidence on the extent of access and uptake, including contributing factors. The results of this scoping review will be disseminated through scientific conference proceedings and presentations, stakeholder meetings, and by publication in a peer-reviewed journal. During the dissemination of findings, stakeholders will be invited to discuss gaps and challenges affecting males' health-seeking behavior and the uptake of health care services to develop context-specific strategies that can be implemented to address the identified gaps and challenges. The dissemination report will also include recommendations for future research, review limitations, and discuss the risk of bias.

Potential Limitations to the Scoping Review

Through this scoping review, we intend to provide a range of information about the health-seeking behavior of males, including their access to and use of health services. However, as we will limit our search to include only published works written in English and implemented in Africa, we are likely to inadvertently exclude relevant programs, thereby skewing the comprehensiveness of the review. Constraints related to the publication type, language, and geographic region will restrict the diversity of the included sources, limiting its applicability across various contexts. Our search strategy did not use the built-in search functionalities of the relevant electronic databases, such as Medical Subject Headings terms for PubMed. Our search strategy might have increased the risk of missing literature. To mitigate this, we constructed a wide range of search terms to ensure a wider reach.

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Data Availability

The data sets generated during and/or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

All authors contributed equally to conceptualization, methodology, and writing of the manuscript. STL-E contributed to funding acquisition.

Conflicts of Interest

None declared.

Multimedia Appendix 1

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Search permutations.
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Multimedia Appendix 2
Search strategy.
[DOCX File , 14 KB - resprot_v14i1e52351_app2.docx]

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Abbreviations

JBI: Joanna Briggs Institute
PCC: population, concept, and context
PRISMA–ScR: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews
WHO: World Health Organization

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Protocol

Interdisciplinary Strategies to Reduce Surgical Infectious Risk in the Operating Theater: Protocol for Scoping Review

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Abstract

Background: Surgical site infections (SSIs) represent one of the most prevalent and significant complications associated with surgical procedures, often leading to prolonged hospitalization and delayed patient recovery. While recent international consensus guidelines have proposed evidence-based strategies to mitigate SSIs, they fall short in addressing the efficient and interdisciplinary implementation of these measures within the operating theater. Consequently, further research is required to identify and evaluate optimal interdisciplinary organizational approaches for the prevention of SSIs.

Objective: This study aims to map the scope, diversity, and nature of research on interdisciplinary strategies aimed at reducing SSIs and to analyze the impact of interdisciplinary on the effectiveness of preventive interventions.

Methods: Using the Joanna Briggs Institute (JBI) methodology for scoping reviews, a comprehensive search will be conducted across databases including Embase (encompassing MEDLINE and PubMed-not-MEDLINE), CINAHL, and the Cochrane Library, supplemented by manual searches of reference lists from included papers. This review targets studies published between 2016 and 2024, aligning with the World Health Organization's 2016 SSI prevention guidelines, which introduced significant advancements in practice and remain the global benchmark. Only studies published in English or French will be considered. Around 5 reviewers independently distributed the included papers for detailed reading and data extraction, while the lead author concurrently and independently reviewed all papers. Inclusion criteria follow the Participants, Concept, and Context (PCC) framework, specifying that the eligible population comprises surgical teams. The primary concept of interest is interdisciplinary strategies aimed at preventing infection risk. The context focuses on adult surgical procedures within the operating room during turnover periods. Studies using experimental, quasi-experimental, preexperimental, observational, case-control, or cross-sectional designs will be included.

Results: From the 1679 papers initially identified, 45 were selected for detailed analysis by 5 reviewers, with the selection process completed by November 2024.

Conclusions: Emerging interdisciplinary strategies demonstrate significant potential in reducing the incidence of SSIs. This initiative forms part of a broader global project focused on codeveloping standardized protocols for preoperative preparation within the operating room to mitigate SSI risks. The findings of this scoping review will serve as the foundation for a subsequent

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qualitative survey and a pre-post quasi-experimental quantitative study to evaluate the integration and effectiveness of these strategies in clinical practice. The review protocol will be formally registered in the Open Science Framework (OSF) in 2024.

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KEYWORDS

surgical site infection; infection prevention; interdisciplinary strategies; surgical team; operating room; standardized operating procedures

Introduction

Background

The transition to advanced health care technologies is inherently linked to heightened patient safety risks within acute care hospital settings [1]. Operating theaters are environments where multiple risk factors converge, contributing to adverse or severe events. Among these, the risk of infection remains a primary concern and a persistent daily challenge, as infections represent a leading cause of preventable hospital mortality [2]. These infections contribute substantially to morbidity and mortality while also imposing significant additional burdens on health care costs [3]. In Switzerland, surgical site infections (SSIs) are the most prevalent type of health care–associated infection within medical facilities [4].

Adhering to evidence-based practice (EBP) has the potential to significantly reduce infection rates, with the corresponding levels of evidence for SSIs already well-documented in the literature [5]. In the operating theater, the implementation of both standard and procedure-specific precautions is crucial for effective infection prevention [6].

SSIs are nosocomial in nature, occurring after surgical procedures, and primarily influenced by pre-, intra-, and postoperative conditions, host immune response, and surgical cleanliness. Pathogen transmission predominantly occurs through contact, with health care workers' hands serving as a major vector. Effective hand hygiene is paramount in preventing infections, particularly in acute care settings, where it plays a critical role in reducing the incidence of bacteremia, urinary tract infections, SSIs, and ventilator-associated pneumonia [3,7].

Key strategies include maintaining high standards in medical device disinfection, bio cleaning, and surface cleaning to minimize infection risks [8]. Monitoring adherence to disinfection protocols during turnover periods is essential for evaluating interdisciplinary coordination and minimizing contamination risks [9]. Adherence to current guidelines is crucial, given the rapidly evolving nature of EBP, as many practices once deemed acceptable are now considered contraindicated [10,11].

The World Health Organization (WHO) and Society for Healthcare Epidemiology of America (SHEA) recommendations for SSI prevention differ slightly in the level of evidence [2,10]. However, consensus exists regarding key practices, such as appropriate hair removal, surgical hand preparation, the use of alcohol-based skin antiseptics (eg, chlorhexidine gluconate solutions), optimal timing of antibiotic prophylaxis, and effective glycemic control [7,12,13]. Emphasis is also placed on the development of soft skills, the implementation of checklists, adherence to bundled care protocols, SSI monitoring, and providing feedback to operating theater staff members as key strategies for enhancing patient safety [5,12,14,15].

Low compliance with SSI prevention measures persists due to the challenges associated with implementing clinical guidelines effectively. Globally, only 29% of tertiary hospitals across 133 countries have established infection prevention and control (IPC) programs. In Switzerland, according to Swissmedic (2022), 93% of 35 surveyed institutions out of 300 reported deficiencies in critical areas, including procedural adherence, staff training, the presence of hygiene specialists, and cognitive dissonance within operating theater teams.

Operating theaters demand the coordinated efforts of surgeons, anesthetists, technicians, and nurses to deliver high-quality care. Effective IPC depends on robust collaboration, clear communication, cohesive teamwork, and streamlined logistics across various hospital disciplines [16]. The complex and highly technical environment of operating theaters, combined with the diverse professional backgrounds of team members, necessitates effective interprofessional collaboration, particularly in time-sensitive situations [17]. Managing human error in the perioperative period remains a major challenge [18-24].

Interprofessionality emphasizes practical collaboration among skilled professionals, while interdisciplinary focuses on integrating knowledge from diverse academic disciplines to address complex challenges. Both approaches are essential for effective IPC in health care settings.

Although expert guidelines from organizations such as WHO, SHEA, Infectious Diseases Society of America (IDSA), Association for Professionals in Infection Control and Epidemiology (APIC), and American Hospital Association (AHA) provide a strong foundation, they lack sufficient specificity regarding the interdisciplinary applications required for SSI prevention in operating theaters [10]. A preliminary search revealed a lack of recent systematic reviews, underscoring the necessity of investigating and evaluating effective interdisciplinary strategies for reducing SSIs.

Review questions:

1. What are the interdisciplinary strategies to reduce SSIs in the operating theater?

2. What are its characteristics?

3. What improvements have been observed concerning the interventions and their evaluation?

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4. Would it be possible to apply a model considering the culture and the local specificities?

Study Aim

This scoping review seeks to map the scope, diversity, and nature of existing research on interdisciplinary strategies for reducing SSIs. The objective is to identify patterns, gaps, and innovations in the literature while evaluating how the integration of diverse disciplinary approaches enhances outcomes in SSI prevention.

Methods

Overview

The proposed scoping review will be conducted according to the Joanna Briggs Institute (JBI) methodology for scoping reviews [25] and the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) [26].

Search Strategy

A 3-step search strategy will be used for this review. Initially, a preliminary limited search was conducted in MEDLINE (via PubMed) to identify relevant papers on the topic. The text words in the titles and abstracts of these papers, along with the index terms used to describe them, were extracted and cataloged for use as search terms. The second step involves a comprehensive search incorporating all identified keywords and index terms, tailored for each database and information source. Databases to be searched include CINAHL (Multimedia Appendix 1), Embase (Multimedia Appendix 2), MEDLINE (Multimedia Appendix 3), and the Cochrane Library (Multimedia Appendix 4).

The third step comprises a manual search of the reference lists of all included papers to identify additional studies meeting the inclusion criteria. This review focuses on studies published between 2016 and 2024, a period defined by the WHO's designation of SSIs as a global priority and the release of its prevention guidelines. This time frame reflects significant advancements with outdated practices being phased out. Priority was given to studies adhering to these guidelines as no major updates have been introduced since their publication.

Systematic reviews conducted by organizations such as the Centers for Disease Control and Prevention, SHEA, and others broadly align with WHO recommendations, with variations primarily in evidence grading. Additional studies were identified through reference list searches of included papers. Only papers published in English or French were included in the review.

Inclusion Criteria

The Participants, Concept, and Context (PCC) framework was used to guide the identification and selection of studies for inclusion in this review [25].

Participants

The eligible population comprises surgical teams, encompassing all professionals involved in patient preparation within the operating room immediately before surgery. This includes surgeons, anesthetists, anesthetic nurses, registered nurses, scrub nurses, instrument technicians, and nursing assistants. Papers will be included if they address the involvement of at least 3 distinct disciplines [6].

Concept

This review focuses on interdisciplinary strategies for IPC. Interdisciplinary in this context does not merely refer to the diverse characteristics of personnel, such as education or professional roles, but rather to a coordinated framework for joint action, exemplified by standard operating procedures. These interdisciplinary approaches leverage shared mental models and visual triggers to activate synchronization among team members. Such frameworks have been described and validated in other industries, such as task-sharing standard operating procedures used by Airbus in cockpit operations. Papers will be included if they report on at least one interdisciplinary strategy.

Context

The specific context is adult surgical procedures within operating theaters during turnover, defined as the period between the closure of one patient's surgical wound and the incision of the next. This turnover period is critical for infection prevention through measures such as antibiotic prophylaxis and skin preparation. In adult surgeries, turnover often involves high-risk procedures, necessitating robust infection control strategies. Only studies that report interventions during turnover in adult surgical settings will be included; those focusing on pediatric surgery or unrelated contexts will be excluded. A significant body of EBP emphasizes reducing infection risks during this critical transitional phase.

Types of Sources

This scoping review will include experimental and quasi-experimental study designs, such as randomized controlled trials, nonrandomized controlled trials, before-and-after studies, and interrupted time-series studies. In addition, analytical observational studies, including prospective and retrospective cohort studies, case-control studies, and analytical cross-sectional studies, will be considered for inclusion. Publications such as editorials, commentaries, letters, conference proceedings, and gray literature will be excluded as the focus is on identifying effective and validated interdisciplinary models.

Study or Source of Evidence Selection

Following the search, all identified citations will be compiled and uploaded into EndNote 20 (Clarivate), where duplicate entries will be removed. After conducting a pilot test, titles and abstracts will be screened by 2 independent reviewers to determine their alignment with the inclusion criteria. Study selection will involve a dual-review process of titles and abstracts, followed by a thorough analysis of the full text. In cases of discrepancies, a third reviewer will be consulted to reach a consensus. Full-text versions of potentially relevant sources will be retrieved and their citation details will be imported into the JBI System for the Unified Management, Assessment, and Review of Information (JBI) [27]. Around 5 reviewers will independently evaluate the full text of selected citations against the inclusion criteria. Reasons for excluding

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sources that do not meet these criteria will be systematically documented and reported in the scoping review. To ensure thoroughness and consistency, all reviewers will collectively read and analyze a subset of the included papers, while the lead author will independently review all included papers to guarantee a comprehensive and unbiased assessment.

Any disagreements among reviewers at any stage of the selection process will be resolved through discussion or, if necessary, with the involvement of additional reviewers. The search results and study inclusion process will be fully documented in the final scoping review and presented using a PRISMA-ScR flow diagram.

Data Extraction

A total of 5 reviewers divided the included papers among themselves for in-depth reading and data extraction, while the lead author independently reviewed all papers in parallel. In cases of confusion or disagreement, the extraction files were compared and discussed with the relevant reviewer to ensure accuracy and consensus. All reviewers used a custom-designed data extraction tool (Data extraction instrument, Multimedia Appendices 5-8; Textbox S1 in Multimedia Appendix 9) to systematically collect data from the studies included in the scoping review.

The data extracted includes detailed information on participants, the concept under investigation, the context, study methodologies, and key findings pertinent to the review question. In addition, general information about each study, as well as its methods, characteristics, and results, will be documented to provide a comprehensive overview. The draft data extraction tool will be adapted and refined as necessary to ensure the accurate extraction of data from each included evidence source. Any modifications made to the tool will be documented in detail within the scoping review. Disagreements among reviewers regarding data extraction will be resolved through discussion or, if required, with the involvement of an additional reviewer. Where appropriate, the authors of the included papers will be contacted to obtain missing or supplementary data.

Results

From the 1679 papers initially identified, 45 were selected for detailed analysis by 5 reviewers, with the selection process completed by November 2024.

The interprofessional perspectives and interdisciplinary interventional components of various strategies aimed at reducing SSIs in the operating theater will be thoroughly detailed. The review will specify whether these interventions were introduced and developed within the framework of a particular implementation model or care concept. In addition, key elements of the triggers synchronization bundle, which facilitate safe organizational practices, proper procedural sequencing, and the delivery of high-quality care, will be highlighted. At the beginning of the year 2025, the identified preventive strategies will be presented through narrative syntheses and summary tables, supplemented by graphs illustrating the distribution of studies and emerging trends related to the scoping review questions. General extraction information will be summarized in a descriptive table (Textbox S1 in Multimedia Appendix 9) and further detailed (Multimedia Appendix 5) for each category. These categories include years of publication, study locations, study designs, sample sizes, and participant demographics. In addition, for the observed interventions, it will be specified whether they fully or partially align with EBP and international recommendations.

Discussion

Overview

We are conducting a comprehensive review of the literature to identify the most effective multidisciplinary models implemented in operating theaters for reducing SSIs. Our objectives are to characterize the key features of these models, evaluate their impact on organizational outcomes, and explore their association with SSI rates. While it is likely that we will identify efficient models, establishing a definitive hierarchy of their effectiveness may be challenging due to the unique characteristics inherent to each surgical specialty. However, several interdisciplinary practices are expected to exert significant influence—either positively or negatively—on the incidence of SSIs.

Our goal is to propose a generalizable model applicable across the majority of surgical specialties, focusing on improving practices and enhancing communication within the operating room to reduce variability. Furthermore, we aim to identify a replicable model suitable for implementation in Switzerland, emphasizing the importance of a collaborative approach adapted to the specific constraints of health care settings.

Evidence-based interdisciplinary strategies have demonstrated effectiveness in reducing SSIs. Research indicates that the successful implementation of care bundles is frequently associated with improvements in process outcomes rather than direct patient outcomes. Nonetheless, patient outcomes consistently show significant reductions in postoperative infection rates when interdisciplinary interventions are rigorously applied [28]. A significant challenge lies in ensuring the consistent engagement of health care professionals, particularly surgeons, in implementing interdisciplinary strategies. The studies reviewed predominantly offer moderate-quality evidence, highlighting the pressing need for standardized approaches and tools to enhance the effectiveness and reproducibility of interventions [29]. However, the concept of interdisciplinary remains underexplored in the existing literature. While support and training programs are frequently emphasized, no singular pivotal factor emerges as decisively shaping the health care system or fostering interdisciplinary collaboration. Notably, critical principles such as decompartmentalization and care synchronization—core components of the cognitive model bundle developed by the Airbus industry to optimize team efficiency—have yet to be systematically identified or applied within this context.

Limitations

This scoping review is restricted to adult patients and the included papers are limited to those published in English and

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French, which may result in the exclusion of some relevant evidence. In addition, in several selected studies, the outcome measures are not reported, complicating the evaluation of the interventions' impact on SSI rates. Even when SSI rates are provided, the variability in monitoring methods must be taken into account, as it can influence the interpretation and comparability of results.

Conclusions

Emerging interdisciplinary strategies demonstrate promising potential for the prevention of SSIs and could be effectively replicated in Switzerland through a tailored implementation model. The bundles of care analyzed in this review appear to be robust in structure; however, the quality of interdisciplinary and their implementation in the operating theater remains challenging to evaluate, with adherence to recommended practices consistently falling short of optimal levels. The need for standardization of these bundles is frequently emphasized across studies.

Notably, this review did not reveal significant innovations, underscoring a gap in the literature. It forms part of a global initiative to cocreate a standardized approach to preoperative preparation in the operating room to reduce SSIs. While studies often highlight what should be done, they rarely address how to implement these measures effectively, pointing to an urgent need for innovative and actionable strategies. This presents an opportunity to develop a coconstructed model in collaboration with surgical teams, ensuring its feasibility and effectiveness through evaluation in real-world clinical settings.

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Authors' Contributions

DJ and SB contributed to conceptualization. DJ, SB, AR, and CD assisted with methodology. SK, CB, AH, AW, SB, and DJ performed data curation. DJ was involved in writing–original draft. SB and AR were involved in writing–review and editing. CD and AR performed supervision.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CINAHL Search strategy from Dec 2016 to May 2024.
[DOCX File , 15 KB - resprot_v14i1e67660_app1.docx]

Multimedia Appendix 2
Embase Search strategy from Dec 2016 to May 2024.
[DOCX File , 15 KB - resprot_v14i1e67660_app2.docx]

Multimedia Appendix 3
MEDLINE Search strategy from Dec 2016 to May 2024.
[DOCX File , 15 KB - resprot_v14i1e67660_app3.docx]

Multimedia Appendix 4
Cochrane Library Search strategy from Dec 2016 to May 2024.
[DOCX File , 14 KB - resprot_v14i1e67660_app4.docx]

Multimedia Appendix 5
Data extraction instrument.
[DOCX File , 14 KB - resprot_v14i1e67660_app5.docx]

Multimedia Appendix 6
Data extraction instrument Characteristics 1.
[DOCX File , 14 KB - resprot_v14i1e67660_app6.docx]

Multimedia Appendix 7
Data extraction instrument Characteristics 2.

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[DOCX File , 14 KB - resprot_v14i1e67660_app7.docx]

Multimedia Appendix 8
Data extraction instrument Characteristics 3.
[DOCX File , 13 KB - resprot_v14i1e67660_app8.docx]

Multimedia Appendix 9
Data extracted from studies.
[DOCX File , 14 KB - resprot_v14i1e67660_app9.docx]

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Abbreviations

AHA: American Hospital Association
APIC: Association for Professionals in Infection Control and Epidemiology
EBP: evidence-based practice
IDSA: Infectious Diseases Society of America
IPC: infection prevention and control
JBI: Joanna Briggs Institute
OSF: Open Science Framework
PCC: Participants, Concept, and Context
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
SHEA: Society for Healthcare Epidemiology of America
SSI: surgical site infection
WHO: World Health Organization

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Protocol

Understanding the Psychosocial Impact of Assistive Technologies for People With Visual Impairments: Protocol for a Scoping Review

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Abstract

Background: There has been a rapid growth in the literature on the design and evaluation of assistive technologies for people with visual impairments; yet, there is a lack of a comprehensive analysis of the existing literature on the classification of immediate-, short-, medium-, and long-term psychosocial impact of assistive technologies on the quality of life of people with visual impairments.

Objective: This protocol outlines the methodology for a scoping review aimed at identifying and synthesizing the existing literature on the psychosocial impact of assistive technologies on the quality of life of people with visual impairments.

Methods: The review will include primary research studies published in English between 2019 and 2024 that focus on the psychosocial outcomes of assistive technologies for people with visual impairments. Eligible studies will involve participants with visual impairments, of all ages and across various settings, examining psychological (eg, emotional well-being and self-esteem) and social outcomes (eg, social participation and support). Searches will be conducted across 7 electronic research databases: CINAHL (EBSCO), PsycINFO (EBSCO), ACM Digital Library, IEEE Xplore, Scopus, Web of Science, and Google Scholar (first 100 records). Studies will undergo screening and selection based on predefined eligibility criteria, with data extraction focusing on publication details, study design, population characteristics, type of assistive technology, and psychosocial impacts. Results will be summarized using descriptive statistics, charts, and narrative synthesis.

Results: The database search, conducted in July 2024, identified 1145 records, which will be screened and analyzed in subsequent stages of the review process. This protocol outlines the planned approach for identifying, categorizing, and synthesizing evidence. The study findings are anticipated to be finalized and submitted for publication in a peer-reviewed journal by February 2025.

Conclusions: This study will synthesize the recent body of work on the psychosocial impact of assistive technologies for people with visual impairments and recommendations for researchers and designers interested in this research area.

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KEYWORDS

assistive technology; psychosocial impact; quality of life; visual impairment; scoping review protocol; mobile phone

Introduction

Background

Globally, visual impairment affects approximately 1 billion people [1]. Visual impairment significantly impacts people's quality of life, affecting activities of daily living, education, employment, and social interactions [2-4]. The most prominent effects of vision loss are loss of independence and social isolation, leading to anxiety, depression, and other mental health conditions [4]. Due to this, many people with visual impairments

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experience low self-esteem and self-efficacy in their mobility and social interaction [5]. Furthermore, the participation of people with visual impairments in leisure activities is low. Where they do, people with visual impairments participate in passive leisure activities (eg, watching television and listening to the radio) rather than actively participating in physical activities, social interaction, and sports in outdoor places [6]. Research shows that people with visual impairments have low mental health outcomes and overall quality of life compared to sighted people [4,7,8].

The World Health Organization [9] defines assistive technology (AT) as an umbrella term for assistive products, systems, and services designed to maintain or improve one's functioning related to cognition, communication, hearing, mobility, self-care, and vision, therefore promoting health, well-being, inclusion, and participation. The European Parliament research report on AT for people with disabilities [10] distinguishes among five types of ATs for blindness and visual impairment: (1) haptic aids (eg, the white cane, the traditional Braille system, embossed pictures, advanced Braille apps, advanced canes, haptic aids for computer use, and matrices of point stimuli), (2) traveling aids (eg, low-technology haptic aids, obstacle and object location detectors, electronic travel devices, assistive apps in mobile phone technology, embedded technologies, and mixed systems), (3) AT for accessible information and communication, (4) AT for daily living (eg, labeling systems, talking readers, tactile and vibrating clocks and alarms, talking kitchen tools, and talking wallets and purses), and (5) phone and tablet apps (eg, magnification apps, color detection apps, money identification apps, object identification apps, scan and read apps, screen reading apps, voice recognition apps, location and GPS apps, and Braille apps).

Mashiata et al [11] classified ATs for visual impairment into four categories: (1) based on portability (eg, nonwearable devices such as smart canes and assistant robots and wearable travel aids such as head-mounted, ear aids, belt-mounted, blind shoes, glasses, and gloves), (2) based on navigation (eg, audio-tactile maps, indoor, indoor-outdoor, and outdoor such as smart city or urban navigation, vehicle detection, airport accessibility, shopping guide, and pedestrian navigation), (3) based on detection (eg, object recognition and obstacle detection, including vehicle detection, pedestrian detection, staircase, and daily life objects), and (4) based on smartphone assistance (eg, digital assistants, mobile apps, including voice maps, voice search, and mobile games).

Over recent decades, disability has stopped being viewed solely in functional terms. Frameworks such as the International Classification of Functioning, Disability and Health and the World Health Organization Quality of Life [12] now emphasize the importance of psychological and social dimensions in understanding and enhancing the quality of life for individuals with disabilities. However, much of the existing research on the impact of ATs has primarily focused on the functional outcomes associated with their use and attributed the poor uptake of these technologies to functional issues [13,14]. Two key points should be raised in relation to this. First, ATs continue to be designed from a biomedical, deficiency-oriented rather than a psychosocial, person-centered approach, failing to effectively fulfill users' needs [15]. Second, researchers have overlooked the role of psychosocial factors in the perception and use of ATs, which may better explain their acceptance and uptake, prompting the development of instruments such as the Psychosocial Impact of Assistive Devices Scale [13] to address this gap.

As with other disabilities, prior research has mainly focused on the functional outcomes of AT and rehabilitation interventions for people with visual impairments [16-18]; yet, there is a lack of a comprehensive review of the literature to understand the psychological and social impact of AT for this population. This review aims, therefore, to comprehensively examine the research investigating the short-, medium-, and long-term psychosocial impact of AT for people with visual impairments.

Objectives and Review Questions

This scoping review aims to answer the following questions: (1) What psychological and social outcomes are associated with the use of ATs among people with visual impairments? (2) What methods and instruments are used to measure the psychosocial impact and outcomes of ATs for people with visual impairments? (3) What are the key trends in the literature in relation to the population characteristics, countries of study, settings, type of ATs examined, impact period, and research methodologies used to assess the psychosocial impact of ATs for people with visual impairments?

Methods

Ethical Considerations

Ethics approval is not required for this study, as human participants were not involved.

Study Design

This scoping review will be conducted following the framework proposed by Arksey and O'Malley [19], which includes six stages: (1) identifying the research question; (2) identifying relevant studies; (3) study selection; (4) charting the data; (5) collating, summarizing, and reporting the results; and (6) consultation. Methodological recommendations from the Joanna Briggs Institute [20] and the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist [21] will also inform the process.

Stage 1: Identifying the Research Question

The primary research question guiding this scoping review is: What are the psychosocial impacts of ATs on people with visual impairments? This question arose from the recognition that while ATs are often evaluated for their functional efficacy, their broader psychosocial impacts have been less explored, despite these impacts potentially being equally or more important in encouraging the uptake and long-term use of these technologies and improving quality of life among users. This scoping review draws from theoretical frameworks such as the World Health Organization Quality of Life framework [12] and Schalock and Alonso's Quality of Life model [22] to conceptualize psychosocial impacts. That is, psychological outcomes refer to the impact of ATs on the mental and emotional state of the individual, including positive feelings (happiness and life

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satisfaction), negative feelings (anxiety, depression, and stress), and self-esteem. Social outcomes refer to the impact of ATs on the individual's social interactions, support, and participation in community and societal activities.

Stage 2: Identifying Relevant Studies

An initial limited search was conducted by the research team to inform the development and refinement of the search strategy. A university librarian was also consulted at this stage to help identify the databases and refine the search strategy. The search included variations and combinations of the following key concepts:

- AT ("assistive technol*" OR "adaptive technol*" OR "assistive aid*" OR "assistive equipment*" OR "assistive device*" OR "assistive product*" OR "assistive service*" OR "assistive interv*" OR "sensory aid*").
- Visual impairment ("visual impair*" OR "vision impair*" OR "impaired vision" OR "sight impairment" OR "visual loss" OR "vision loss" OR "vision defect" OR "visual handicap" OR "blind" OR "blindness" OR "low vision" OR "partial* sight*" OR "partial vision" OR "visual* disorder*" OR "vision disord*" OR "visual* disab*" OR "vision disab*" OR "eye disord*").

Next, a full literature search of peer-reviewed journal papers and conference proceedings was conducted across 7 electronic databases, including CINAHL (EBSCO) and PsycINFO (EBSCO), as well as ACM Digital Library, IEEE Xplore, Scopus, Web of Science, and Google Scholar (first 100 records). During the initial limited search, PubMed was considered as a potential database but eventually excluded, as its results heavily targeted biomedical and clinical aspects, which did not align with the focus on psychosocial impacts. Instead, CINAHL was selected for its broader coverage of health care topics and more holistic aspects of care, including well-being and quality of life.

To focus on the most up-to-date literature and to capture the latest developments in the field of ATs for visual impairments, the search was limited to studies published in the past 5 years (2019-2024). Furthermore, the search was limited to studies written in English only. A full literature search was conducted in July 2024, which produced 1942 results.

Stage 3: Study Selection

A systematic approach will be used for study selection. Eligibility criteria have been developed to ensure the relevance and quality of included studies. From a *population* perspective, studies will be included if they focus on people with visual impairments, including children and adults, irrespective of the diagnosis and inclusion criteria used by individual studies. At a *concept* level, studies will be included if they (1) refer to the use of AT by people with visual impairments and (2) focus on the psychosocial impact or outcomes associated with the use of ATs. *Context-wise*, studies conducted in any country or setting, including health care, community, education, and work, and across all age groups will be considered. Primary research, including quantitative, qualitative, and mixed method studies reported in peer-reviewed journal papers or conference proceedings, will be included in this review. Conference abstracts only will be excluded. Secondary research (eg, literature reviews and meta-analyses) and nonempirical works (eg, theoretical papers, conceptual frameworks, opinion pieces, and editorials) may be consulted during the review process but will not be included. The review will only include research that includes the design or evaluation of an AT intervention focusing on impact.

Following the literature search, all retrieved studies will be collated and uploaded into a web-based literature review tool, Rayyan (Rayyan Systems Inc) [23], where duplicates will be removed. A random sample of 25 papers from the overall dataset will be first reviewed for pilot-testing of the source selector criteria. Following this, the reviewers will meet to discuss discrepancies and adapt the criteria based on the insights from the pilot test. Independently, 2 reviewers (RS and MB) will then conduct a screening of titles and abstracts to determine their potential eligibility for inclusion. The full texts of potentially eligible studies will be then retrieved and reviewed in detail for final inclusion. Reasons for excluding sources of evidence at the full-text stage that do not meet the eligibility criteria will be documented and reported in the scoping review. Any disagreements between reviewers (RS and MB) at each stage of the study selection process will be resolved through consensus or by consulting a third reviewer (CH). The search results and the study inclusion process will be reported in full in the final scoping review and presented in a PRISMA-ScR flow diagram (Figure 1 and Multimedia Appendix 1).

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Figure 1. PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) flow diagram illustrating the study selection process.

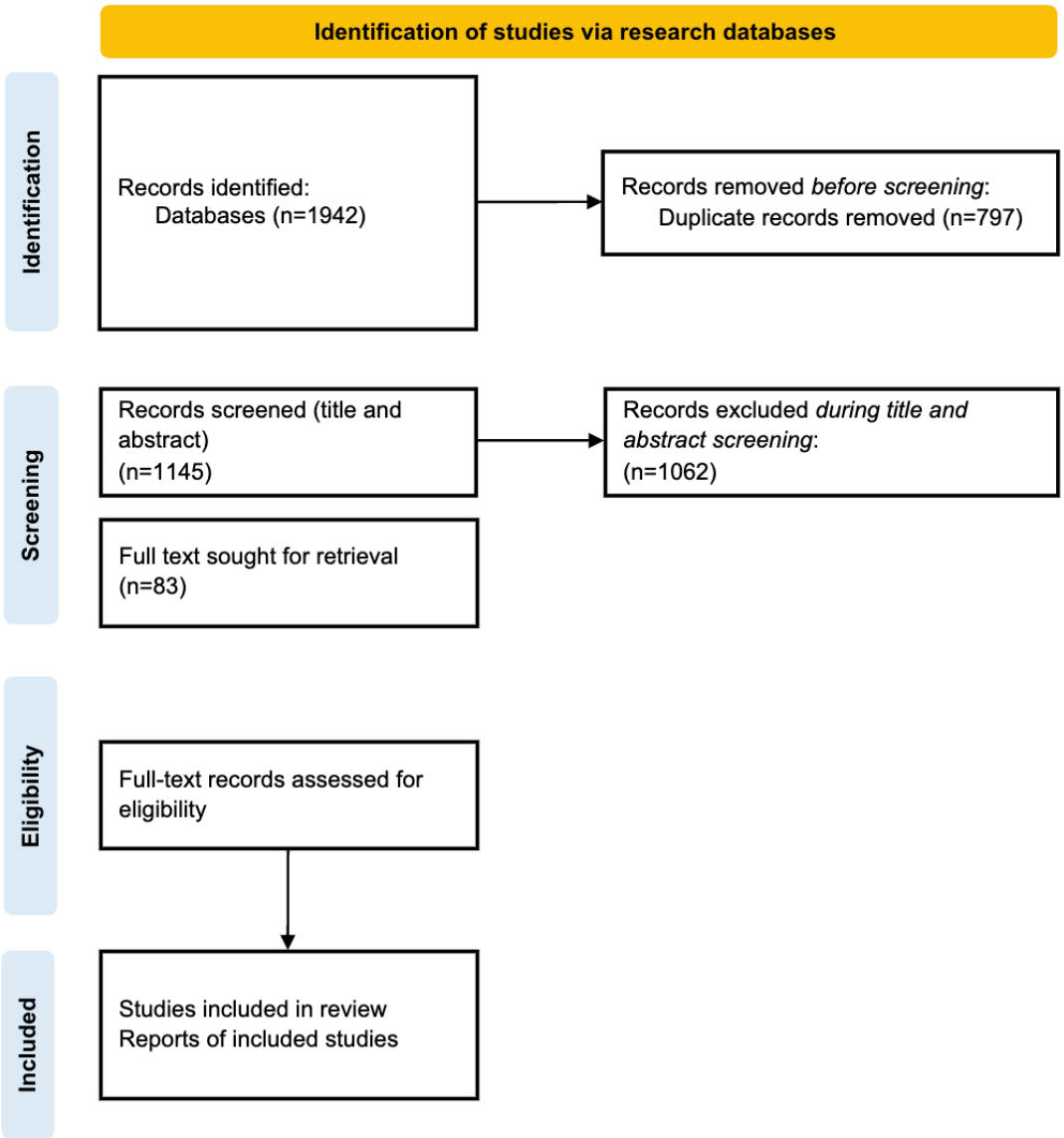

Stage 4: Charting the Data

Data from the studies included in the scoping review will be extracted using a standardized table to ensure consistency and comprehensiveness. The data extraction table will be piloted on a subset of studies and will be revised as necessary. The information to be extracted from each study includes the authors, year of publication, title, source of publication, type of publication, country of study, aim of the study, population and sample characteristics, research design, type of AT or intervention, setting, outcomes, instruments or impact measures, key findings, and the impact period categorized as immediate (less than 1 month), short-term (1 to 6 months), medium-term (6 to 12 months), and long-term (more than 12 months). To ensure the accuracy of the process, a second reviewer (MB) will cross-check the data extracted from at least 25% (n=7) of all included studies. Any discrepancies between reviewers will be resolved through consensus or consultation with a third reviewer (CH).

Stage 5: Collating, Summarizing, and Reporting Results

Descriptive statistics will be used to summarize the overall characteristics of the included studies. These will cover the number of studies, the distribution of studies by publication year, population characteristics, country of origin, study setting, type of ATs examined, impact period, and research methodologies used. Charts and diagrams will also be used to support data presentation. Tables will be constructed to synthesize the psychosocial outcomes reported in the included studies. Tables will detail the methods and instruments used to measure the psychosocial impacts of ATs, including information on specific tools or questionnaires, their reliability and validity, and the context of their app. Additionally, tables will summarize the main findings of the studies included in the review. Furthermore, a narrative summary will accompany the tabular or charted results, providing a description of the literature on the psychosocial impact of ATs on people with visual impairments, including key themes and trends observed. It will also identify gaps in the current body of knowledge, while

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recommendations for future research will be made based on the identified gaps or inconsistencies.

Stage 6: Consultation

To expand the relevance and applicability of the findings arising from this scoping review, consultations will be conducted with stakeholders, including AT researchers, policy makers, and users. In particular, AT users will be provided with a summary of findings and invited to provide feedback through a written commentary. Their insights will inform the interpretation of results and the development of recommendations for practice and policy.

Results

This scoping review protocol was submitted to the Open Science Framework [24] on July 17, 2024. The database search was conducted in July 2024, and 1942 records were identified. During identification, 797 records were identified as duplicates and removed. Next, the title and abstract screening was conducted for 1145, of which 1062 records were excluded. Finally, 83 records were included for full-text screening. Data extraction and synthesis, as well as paper preparation, are currently underway. The paper should be submitted in February 2025.

Discussion

Expected Findings

The findings from this scoping review will shed light on the psychosocial impacts of ATs for people with visual impairments. The review will also explore the methods and instruments used to measure these outcomes and will identify key trends in the literature. These findings are expected to inform the development of a global evidence database mapping the impact of AT for people with visual impairments, with a view to extending it to other disabilities and long-term conditions, including other sensory impairments, mental health conditions, neurodevelopmental conditions, intellectual disabilities, and physical disabilities. The database is also expected to serve as a resource for researchers, clinicians, AT developers, policy makers, and other stakeholders, providing accessible and up-to-date evidence on the impact of AT. It is intended to facilitate evidence-based decision-making, support the development of guidelines, interventions, and policies, as well as identify gaps in the current research landscape. Findings will be presented at relevant conferences and shared with stakeholders (eg, disability and health care organizations, AT developers, and policy makers).

Strengths and Limitations

This scoping review is a comprehensive attempt to map the interdisciplinary literature on the psychosocial impact of AT for people with visual impairments. A full literature search of peer-reviewed journal papers and conference proceedings was conducted across 7 interdisciplinary electronic databases, including CINAHL (EBSCO) and PsycINFO (EBSCO) for literature from health care and psychology, as well as ACM Digital Library, IEEE Xplore for human-computer interaction, computing, and accessibility and AT-related literature, and Scopus, Web of Science, and Google Scholar (first 100 records) to include cross-disciplinary literature. The review will follow the PRISMA-ScR checklist that is specific for scoping reviews [21] to ensure a high level of quality and transparency. To this end, the scoping review protocol has been preregistered with the Open Science Framework [24].

One limitation of this scoping review is the exclusion of previous reviews and non–peer-reviewed publications. Additionally, the review only includes research published in English between 2019 and 2024. Due to the limited scope and time constraints of this review, a comprehensive quality assessment will not be conducted. Finally, this review does not include a full literature search on PubMed due to the clinical focus of search results from initial searches.

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

RS, MB, and CH conceptualized the study as a scoping review. MB and CH provided oversight for scoping review protocol development. RS and MB reviewed and edited the protocol, drafted the search strategy, wrote the manuscript, and designed Figure 1. All authors read, provided feedback, and approved the final manuscript for submission.

Conflicts of Interest

None declared.

Multimedia Appendix 1

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PRISMA-Scr (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist. [DOCX File , 115 KB - resprot_v14i1e65056_app1.docx]

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Abbreviations

AT: assistive technology
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Social Determinants of Health Screening Tools for Adults in Primary Care: Protocol for a Scoping Review

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Abstract

Background: Social determinants of health (SDH) have been shown to be predictors of health outcomes. Integrating SDH screening tools into primary care may help identify individuals or groups with a greater burden of social vulnerability and promote health equity.

Objective: This study aimed (1) to identify the existing screening tools to assess social deprivation in adults in primary care settings; (2) to describe the characteristics of these tools and, where appropriate, their psychometric properties; (3) to describe their validity and reliability in those scales in which validation processes have been conducted; and (4) to identify evidence gaps and provide recommendations for future research.

Methods: This study protocol was structured according to the Joanna Briggs Institute methodology for scoping reviews and reported according to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines. Furthermore, since not all SDH assessment tools are published as scientific papers, we will use a slightly modified form of the scoping review framework to retrieve specific information about specific tools for screening SDH in primary care contexts. The following electronic databases will be searched by 2 reviewers: MEDLINE (via PubMed), CINAHL Plus, Web of Science, and Scopus. In addition, the following sources will also be searched for gray literature: DART-Europe E-thesis Portal, OpenGrey, and Google Scholar. After the revision of inclusion and exclusion criteria, the titles, abstracts, and full text of the included studies will be separately screened by 2 reviewers. A PRISMA-ScR flowchart will be used to depict the sources of evidence screened, and data charting will be used to gain in-depth knowledge. The findings of the scoping review will be presented in both narrative and tabular formats, summarizing the existing literature on tools used for SDH in primary care settings. A critical analysis will be undertaken to address the variability in tool validation, cultural adaptability, and integration into different health care systems. Finally, key gaps in the existing evidence will be explored, and research priorities will be proposed, emphasizing the need for screening tools that are culturally sensitive, scalable, and easily integrated into primary care workflows. This critically appraised information may be useful for implementing SDH screening tools in primary care settings and may contribute to future research addressing feasibility and validation studies in different primary health care systems.

Results: The study began in July 2024. Data collection is expected to be completed in April 2025, with publication expected in October 2025.

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Conclusions: This scoping review will provide a comprehensive and critical description of the available tools aimed at screening SDH in primary care settings. Incorporating these tools into routine care has been recognized as a key strategy for addressing health inequalities, given the growing evidence base on the influence of SDH on health outcomes.

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KEYWORDS

social deprivation; social determinants of health; primary health care; social inequality; screening

Introduction

Background

According to the World Health Organization (WHO), social determinants of health (SDH) are the conditions in which people are born, grow, work, live, and age, along with the broader set of forces and systems that shape the conditions of daily life [1]. These determinants include a wide range of factors, such as income, education, employment, working conditions, housing, neighborhood environments, race, and gender [2]. On the other hand, health inequalities are defined as the systematic, avoidable, and unfair differences in health outcomes that can be observed between different groups of people, which are determined by the SDH [3].

In recent years, there has been a growing awareness of the significant impact of SDH on individual and population health outcomes. This has led to a transformation in health care practices and policies with greater recognition of the role of SDH in perpetuating health inequities and in providing a comprehensive understanding of a patient's health [4].

SDH have been shown to be the predictors of health outcomes, including hospital readmissions [5], emergency department visits [6], multimorbidity burden [7], depression prognosis [8], and lower adherence to preventive measures [9,10]. Identifying individuals or groups with a greater burden of social vulnerability or with the greatest disparities in a particular disease can guide future actions to promote health equity [11], implement tailored social interventions, and direct future research [12]. However, despite the clear evidence of the importance of SDH and the need to address its root causes, there are several issues to be considered. First, without multidisciplinary engagement and workflows, along with the availability of social resources for subsequent referral [13], expectations may be raised without solutions being provided, leading to a loss of patient trust. Second, without intersectoral collaboration, long-term strategies, upstream proposals, and public health policies and workflows, we could fall into perpetuating the "fantasy paradigm" [14]—a parallel fantasy world in which proximal, downstream, and easily tackled exposures are posited as potential solutions to health inequalities [15].

Primary care settings are ideal for addressing SDH because they are often the first, and sometimes only, point of contact for patients within the health care system. They are also the place for multiple consultations with a significant social burden, where longitudinal continuity of care is provided and where clinicians are aware of the community health resources [16]. The importance of SDH screening in primary care is underscored by the fact that social needs are often unrecognized in clinical settings, leading to suboptimal care and poorer health outcomes [17]. Therefore, integrating SDH screening tools into primary care is not only consistent with the principles of holistic and patient-centered care but also represents a crucial step toward addressing the root causes of health disparities [18-20].

There is considerable variability in the implementation of SDH screening tools in primary care settings [21]. The absence of standardized screening tools and protocols, along with varying levels of knowledge and training among providers, hinders the ability to identify SDH-related needs and intervene appropriately [22]. Furthermore, the diverse nature of SDH, which covers a wide range of domains and is influenced by individual-, community-, and policy-level factors, poses a significant challenge to the development of comprehensive screening tools [23]. These tools must be sensitive enough to capture the complexity of social determinants while also being practical for use in time-constrained primary care settings. A number of SDH screening tools have been developed and implemented with varying degrees of success. These tools range from brief questionnaires integrated into electronic health records to more extensive assessments conducted through patient interviews [14,21,24]. The development of these tools is often context specific, taking into account the patient population, health care setting, and available resources for follow-up interventions [25]. However, the variability in the content, format, and application of these tools across different health care systems underscores the need for a comprehensive synthesis of available tools aimed at assessing their effectiveness, validity, and feasibility [14].

Primary care providers face numerous barriers to implementing SDH screening, including time constraints, lack of training, and uncertainty about how to address identified needs [17,26]. There are also concerns that screening may reveal problems that providers are ill-equipped to deal with, leading to increased stress and workload without a clear pathway for patient referral and intervention [14]. Without collaboration between sectors such as social work or community resources in SDH screening and subsequent referral, primary care clinicians alone may not be able to cope [26]. Therefore, an important aspect of evaluating SDH screening tools is to consider not only their ability to identify social determinants but also their integration into care processes, the availability of resources to address identified needs, and their impact on patient outcomes [27].

Rationale for a Scoping Review

To avoid duplication of effort, a preliminary search conducted in July 2024 revealed that although several approaches to

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synthesizing the literature on the use of tools to screen for SDH in clinical settings had been published [17,21,28] or were in progress (Parry et al [29]), many of the known tools had not been published in scientific papers and could only be found on institutional websites or through references to their use in the scientific literature (eg, EPICES score [30]) or book chapters. Therefore, several approaches to synthesizing the existing literature were considered, and scoping was found to be the most appropriate for the needs of this study according to the reasons for deciding to undertake a scoping review proposed by Arksey and O'Malley [31], namely that the use of SDH screening tools in primary care is an emerging issue, and different tools have been proposed because the generalizability across countries and primary care systems may not be possible, so mapping these tools is of scientific interest. In addition, a standard systematic review would leave out numerous tools that have not been published in traditional databases of the scientific literature, such as websites of health institutions, books, and so on. Therefore, suggesting lines of research and methodologies can be of scientific interest.

Study Aims

Our overall aim is to explore the literature describing the usefulness of SDH screening tools for adults in primary care settings. To achieve this, we will address the following specific objectives: (1) to identify existing screening tools for assessing social deprivation in adults in primary care settings; (2) to describe the characteristics of these tools, such as country, year of publication, and items included; (3) to describe their validity and reliability in those scales that have undergone validation processes; and (4) to identify evidence gaps and provide recommendations for future research.

Methods

Overview

In reviewing the existing literature, several approaches were considered, and a scoping review was found to be the most appropriate for the requirements of this study. Therefore, this study protocol was structured according to the 5-stage framework by Arksey and O'Malley [31]. In addition, the scoping review will be conducted according to the Joanna Briggs Institute methodology for scoping reviews [32] and reported following the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines [33]. Furthermore, because not all the SDH assessment tools are published as scientific papers, we will use a slightly modified form of the scoping review framework outlined by Peters et al [34] to retrieve specific information about specific social deprivation screening tools in primary care contexts.

Identifying the Research Question

Some differences can be observed between these two approaches [33,34]. In essence, both approaches can be complementary, as the former is a checklist for reporting a scoping review compatible with the Population, Concept, and Context framework that we have chosen to describe the research question of our review (Multimedia Appendix 1). Our population will consist of adults (aged 18 years or older); our concept of SDH tools is understood as the conditions in which people are born, grow, work, live, and age, and the broader set of forces and systems that shape the conditions of daily life [1]; and as a contextual framework, the tools should be applicable to primary care settings.

Identifying Relevant Studies

The search strategy has been developed in collaboration with the research team and the participant librarians, adapting the PRISMA-ScR guidelines for literature search [35] to a scoping review. Two reviewers (JM-A and VM-V) independently searched the following electronic databases: MEDLINE (via PubMed), CINAHL Plus, Web of Science, and Scopus. The search strategy included terms related to the following descriptors, combined using Boolean operators: (1) SDH, (2) measurement tools, (3) validation studies, and (4) primary health care. All retrieved records will be imported into Mendeley (Elsevier) software, and duplicates will be removed. Textbox 1 provides the search strategy for the MEDLINE database as an example.

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Textbox 1. Search strategy in MEDLINE.

Concept

- (tool [Title/Abstract]) OR (“questionnaire”[Title/Abstract])) OR (“scale”[Title/Abstract])) OR (measurement[Title/Abstract])) OR (“test”[Title/Abstract])) OR (“measure”[Title/Abstract])) OR (“assessment”[Title/Abstract])) OR (“index”[Title/Abstract])) OR (“indexes”[Title/Abstract]) OR (“score”[Title/Abstract]) OR (screening[Title])

AND

Social determinants of health

- (poverty[Title/Abstract]) OR (poverty[MeSH Terms])) OR (socioeconomic status[Title/Abstract])) OR (low socioeconomic status[Title/Abstract])) OR (low socioeconomic status[MeSH Terms])) OR (Social Deprivation[MeSH Terms])) OR (Social Deprivation[Title/Abstract])) OR (Social Vulnerability[Title/Abstract])) OR (Social Vulnerability[MeSH Terms])) OR (Social Determinants of Health[Title/Abstract])) OR (Social Determinants of Health[MeSH Terms])) OR (“social class”[MeSH Terms])) OR (social determinants[Title/Abstract])) OR (socioeconomic factors[MeSH Terms])) OR (socioeconomic factors[Title/Abstract])) OR (deprivation[Title/Abstract]) OR (drivers [Title]) OR (Social Drivers of Health [Title]) OR (social needs[Title])

AND

Validity

- (validity [Title/Abstract]) OR (Feasibility Studies [MeSH Terms] OR (Feasibility[Title/Abstract])) OR (applicability[Title/Abstract])) OR (screening[Title/Abstract])) OR (validation[Title/Abstract])) OR (“validation studies as topic”[MeSH Terms])) OR (health outcome predictor[Title])

AND

Context

- (Primary Health Care [Title/Abstract]) OR (Primary Health Care[MeSH Terms])) OR (primary care[Title/Abstract])) OR (Family Practice[Title/Abstract])) OR (Family Practice[MeSH Terms])) OR (general practice[MeSH Terms])) OR (general practice[Title/Abstract])) OR (clinical setting[Title]) OR (outpatient [Title]) OR (ambulatory [Title]) OR (Internal Medicine[Title])

The search strategy and index terms will be adapted for each electronic database or information source.

In addition, several approaches will be used to search the gray literature, understood as materials and research produced by organizations outside of traditional academic publishing. First, we will search the DART-Europe E-thesis Portal for access to dissertations and OpenGrey, a system for information on gray literature in Europe. We will also search using keywords in Google Scholar, and the first 200 results sorted by relevance will be screened for suitability according to the recommendations of Haddaway et al [36]. Furthermore, a supplementary search of the reference lists of studies selected for inclusion in the review will be conducted to identify additional relevant studies. This will be followed by a systematic citation search using CitationChaser [37] to compile studies citing the papers selected for inclusion. If further information is required regarding the studies of key papers, the authors will be contacted accordingly. Finally, an iterative approach will be used to search the websites of health institutions in the main countries that have implemented health policies related to social inequalities in health. Mendeley will be used as reference manager software.

Study Selection

The identified studies will be transferred to the web-based version of the Rayyan Systematic Review Tool [38] for further processing. Rayyan is a web-based tool designed to facilitate the screening process, which is a critical component of any systematic review. As recommended, two authors (JM-A and VM-V), after agreeing on a framework for screening papers according to the research objectives [33], will independently carry out the title and abstract selection of studies. Full papers will be obtained if the literature meets the inclusion criteria or if a decision cannot be made from the title or abstract alone. The review authors will resolve disagreements by consensus-based decision and, if necessary, by discussion within the group. In addition, we will record the specific reasons for the exclusion of each study.

For our scoping review, the inclusion criteria are given in Table 1. However, we will be aware that a reflexive process of the inclusion and exclusion criteria will be undertaken during the screening process, which will serve to consolidate the criteria [34].

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Table 1. Inclusion and exclusion criteria based on the Population, Concept, and Context framework.

Scope parameters	Inclusion criteria	Exclusion criteria
Population	Adult participants (including older adults)	Pediatric population and adolescents
Concept	Screening tools for SDH[a] that include more than one dimension of SDH and screening tools with social deprivation indexes	Screening tools for only one dimension of SDH (eg, screening tools for only food insecurity)
Context	Primary care settings	Other specialty or emergent care setting
Types of evidence	Full-text papers of empirical research studies (eg, validation studies, randomized controlled trials, and observational studies), study protocols, full-text conference proceedings, papers written in English, documents retrieved from institutional websites, and PhD dissertations	Reviews[b], abstracts, posters, and papers for which we cannot obtain the full text or which are not written in English

[a]SDH: social determinants of health.

[b]Although systematic reviews will not be selected for inclusion, the studies included in these reviews will be reviewed to evaluate their possible inclusion in the scoping review.

Critical Appraisal

As scoping reviews are primarily aimed at identifying and exploring the existing literature on a topic, it has been stated that a quality assessment is not applicable [34]. In our case, as the methods used to develop the SDH screening tool may not always be standardized, conducting a quality assessment is likely to be unsuccessful. However, a critical review assessing their ability to be incorporated into care processes, their relationship to the availability of resources to address identified needs, and their impact on patient outcomes will be included in the *Results* and *Discussion* sections.

Charting the Data

A PRISMA-ScR [33] flowchart will be used to depict the sources of evidence screened, the assessment of documents' eligibility (which may include tools extracted from institutional documents, not just papers), and the tools included in the review, along with reasons for exclusions at each stage.

The data charting is specific to scoping reviews and differs from the data extraction processes commonly used in other types of research synthesis designs, where data extraction is a more structured process often including statistical procedures. In contrast, data charting in scoping reviews is a more comprehensive approach that incorporates narrative information to describe details about how, why, and where the study was conducted [39]. Accordingly, a consensus-based, data-charting form will be used by the 2 reviewers, who will independently extract the data, discuss the results, and iteratively update the data-charting form. This data-charting table will include descriptive variables (year of publication, study design, setting, target population, and data source) and information about the aims and structure (dimensions, items, and procedures for completing the questions) of the tool and setting characteristics.

Ethical Considerations

Ethical approval is not required for this review as it involves the analysis of publicly available empirical studies and the production of secondary data.

Expected Outcomes

Following the publication of this protocol, the search for SDH screening tools, removal of duplicates, and study selection will take place (estimated time: 2 months). The findings of this scoping review will be presented in both narrative and tabular formats, summarizing the existing literature on tools used for SDH in primary care settings. The narrative summary will describe the scope and nature of the identified screening tools including their structure (domains, number of items, and how the information should be obtained [eg, questionnaires and digital platforms]) and the contexts in which they are applied. The integration of these tools into clinical workflows, as well as any evidence of their effectiveness in improving patient outcomes, will also be considered.

Critical Analysis

Overview

The results will include a critical analysis of the strengths, limitations, and usability in primary care settings of the screening tools. This analysis will address the variability in tool validation, cultural adaptability, and integration into diverse health care systems. Potential biases or limitations in the implementation or outcomes of the tools, such as insufficient training of health care providers or limited follow-up on identified needs, will also be concerns to be discussed.

Research Gaps and Priorities

Key gaps in the existing evidence, such as social determinants not included in the tools, concerns about age or gender underrepresentation, and limited follow-up analysis of the usefulness of SDH screening on health outcomes, will also be critically examined. Finally, based on these findings, research priorities will be proposed, emphasizing the need for screening tools that are culturally sensitive, scalable, and easily integrated into primary care workflows (estimated time to complete these tasks: 6 months).

Dissemination of the Results

To ensure that the insights resulting from this review reach a variety of stakeholders, such as health care practitioners, policy makers, and academics, the findings will be disseminated using several dissemination strategies including reporting results in open-access journals and scientific conferences. In addition, stakeholders will be engaged at every stage of the review process to facilitate the adoption and implementation of evidence-based screening tools in clinical settings, thereby increasing their impact on health equity (estimated time: 6 months).

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Results

The study began in July 2024. Data collection is expected to be completed in April 2025, with publication expected in October 2025.

Discussion

Principal Findings

This scoping review will provide a comprehensive and critical description of the available tools aimed at screening SDH in primary care settings. Incorporating these tools into routine care has been recognized as a key strategy for addressing health inequalities, given the growing evidence on the influence of SDH on health outcomes. Nonetheless, the absence of a comprehensive review makes it difficult for health care practitioners to select the most appropriate tools for their context and patient populations.

The importance of identifying and addressing the social needs of the patients attending health care settings has been highlighted by Gottlieb and Fichtenberg [40], and some scientific contributions have previously addressed some issues related to the implementation of SDH screening tools in clinical settings, such as the coverage and economic evaluation of these tools [41], the evaluation of interventions linking social and medical care [42], the barriers to the implementation of SDH in electronic health records [43], and its integration in nonspecific clinical settings [44]. In addition, a report from the US Preventive Services Task Force alerted on the importance of considering SDH in the recommendations of preventive interventions in primary care [19]. However, a catalog of currently available screening tools, their scope, structure, and dimensions is lacking. Furthermore, this review will assess the contextual elements such as resource accessibility and stakeholder involvement (patients, practitioners, and health care providers) that influence the implementation and effectiveness of these technologies in primary care. This review will map the body of literature to identify potential gaps and areas for additional research, including tool validation in varied populations, tool influence on clinical outcomes, and tool integration into larger care systems.

Including SDH screening tools for children in this review might seem to make our review more coherent, but it would greatly increase the complexity of the review. The tools for children and adults are very different. Overall, measuring SDH in children should emphasize developmental needs, relationships with caregivers, and early life conditions, whereas measures for adults tend to focus more on employment, social deprivation, and cumulative social conditions, as well as focus on the individual rather than indirectly asking the caregiver about the child's health [45]. Therefore, a review of SDH in the pediatric population requires a synthesis study, probably with a different methodological approach, focusing exclusively on this topic.

A key strength of this protocol lies in its systematic approach, which adheres to the current methodological frameworks for scoping reviews. This ensures that the review process will be transparent and reproducible, while allowing a broad range of study designs and inclusion settings. However, a limitation of this review is the potential for missing unpublished or non–English-language studies, which may result in an incomplete understanding of the global landscape of SDH screening tools.

Conclusions

This scoping review will provide a valuable synthesis of the available SDH screening tools applicable in primary care and identify critical gaps in the existing literature. This review will provide insights into the implementation of these tools, while identifying areas for further research, including validation in diverse populations. Ultimately, this work aims to support the integration of SDH screening into routine care, contributing to efforts to reduce health inequalities and improve patient outcomes.

Acknowledgments

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Authors' Contributions

JM-A and VM-V contributed to the conceptualization. JM-A and VM-V developed the methodology. JM-A, AEM, HMM, and VM-V performed the investigation. JM-A, VM-V, and AEM managed writing–original draft preparation. NJO, IDLMH, FSV, ACM, HMM, and SC handled writing–review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist.
[DOCX File , 32 KB - resprot_v14i1e68668_app1.docx]

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Abbreviations

PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
SDH: social determinants of health
WHO: World Health Organization

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Protocol

Genetic, Socioecological, and Health Determinants of Extreme Longevity in Semi-Supercentenarians and Supercentenarians: Protocol for a Scoping Review

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Abstract

Background: The study of supercentenarians (individuals aged 110 years or older) offers valuable insights into aging, longevity, and the factors contributing to exceptional lifespans. These individuals often exhibit extraordinary cognitive and physical performance, which can inform strategies to improve the health of the general population. Research on centenarians (individuals aged 100 years or older), semi-supercentenarians (individuals aged 105-109 years), and supercentenarians covers themes like genetic factors, microbiome, inflammation, diet, lifestyle, and psychological aspects. These studies often focus on various aspects of extreme longevity, using varied objectives and methodologies, highlighting the need for a comprehensive synthesis to map the breadth of research and identify gaps in understanding this demographic.

Objective: This scoping review aims to map and synthesize existing evidence on the determinants of extreme longevity, focusing on individuals living beyond 105 years. This review seeks to categorize genetic factors associated with semi-supercentenarians and supercentenarians; explore the range of socioecological factors contributing to their longevity; and identify common themes such as health, functional capacity, cognition, mental health, behaviors, social support, quality of life, personality traits, environmental factors, and religiosity. Additionally, it aims to examine and describe the methodologies and assessment tools used in studies on extreme longevity and provide an overview of global demographic trends and patterns among supercentenarians, including geographic distribution, gender prevalence, and socioeconomic characteristics.

Methods: This scoping review follows the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) 2015 guidelines and the Population, Exposure, and Outcome framework. It includes observational and interventional, quantitative and qualitative studies on supercentenarians and semi-supercentenarians. Data will be sourced from databases like Scopus, PubMed, ProQuest, PsycINFO, and The Cochrane Library. The selection process involves abstract and full-text screening by two independent reviewers, with data extraction focusing on study characteristics, participant demographics, interventions or exposures, and key findings. A thematic analysis will identify patterns across various themes

Results: As of October 2, 2024, five databases were searched, yielding 844 studies. After removing duplicates, 706 studies remained. Following the first and second screening stages, 135 studies were found to be eligible. The study is expected to be completed by the end of February 2025.

Conclusions: By synthesizing evidence, this study will understand the global scope of supercentenarians, describe the main themes of research interest, and identify gaps. The findings are expected to contribute significantly to the body of knowledge on longevity, informing future research and public health policies. This scoping review aims to enhance the understanding of factors promoting healthy aging and extreme longevity, benefiting broader public health initiatives.

Trial Registration: PROSPERO CRD42024512298; https://tinyurl.com/4cmux7h4

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(JMIR Res Protoc 2025;14:e63900) doi:10.2196/63900

KEYWORDS

supercentenarians; semi-supercentenarians; extreme longevity; genetic factors; socioecological factors; health determinants; aging research; scoping review; cognitive performance; data collection methods

Introduction

The study of supercentenarians—individuals who have reached the remarkable age of 110 years or older—holds immense scientific interest. These exceptional individuals provide valuable insights into aging, longevity, and the factors contributing to their remarkable lifespans. Limiting illness—both in duration and the number of individuals affected—becomes more critical as human longevity increases. Studying healthy humans with exceptional lifespans is meaningful in discovering clues to improve the general population's health. Centenarians (individuals aged 100 years or older), semi-supercentenarians (individuals aged 105-109 years), and supercentenarians (individuals aged 110 years or older) are excellent models for the study of healthy longevity. According to research, this aged population surprisingly maintain extraordinary cognitive and physical performance [1].

These studies provide valuable insights into various aspects of supercentenarian aging and use a variety of methodological frameworks for evaluating the determinants of extreme longevity. Currently, there exists a wide range of studies that investigate exceptional lifespans from diverse perspectives. Sebastiani et al [2] discussed genome sequencing in supercentenarians, revealing common and rare genetic variants that may contribute to exceptional longevity. Franzke et al [3] looked into "DNAging" and discovered that supercentenarians exhibit improved DNA repair and antioxidant defense mechanisms compared to younger cohorts. Santos-Lozano et al [4] discovered that both genetic and environmental factors are attributed to exceptional longevity in centenarians and supercentenarians. Some studies discussed morbidity in supercentenarians and found that cognitive and physical function decline is delayed in supercentenarians [5], while other studies investigated other factors contributing to super longevity in supercentenarians such as diet and lifestyle [6,7].

This scoping review aims to comprehensively synthesize the existing evidence to understand the determinants that contribute to extreme longevity in individuals living beyond 105 years, as well as the methodologies used for data collection.

This scoping review's main objectives are as follows:

1. To map and categorize the existing evidence on genetic factors associated with extreme longevity in semi-supercentenarians and supercentenarians;
2. To explore and synthesize the range of socioecological factors, including lifestyle behaviors, environmental exposures, and social support systems, that are associated with achieving extreme longevity;
3. To examine and describe the methodologies and assessment tools used in studies investigating extreme longevity; and
4. To provide an overview of global demographic trends and patterns among supercentenarians, including geographic distribution, gender prevalence, and socioeconomic characteristics.

Methods

Approach

This scoping review follows the Population, Exposure, and Outcome framework [8] and the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines published in 2015 (Multimedia Appendix 1) [9]. The population and outcome are as follows:

- Population: Semi-supercentenarians (aged 105 years or older)
- Exposure: Genetics and socioecological factors
- Outcome: Supercentenarian (aged 110 years or older)

Eligibility Criteria

Study Characteristics

This scoping review will include quantitative and qualitative studies in which supercentenarians and semi-supercentenarians are the focus of the study, including observational research (case-report, case-series, cross-sectional, case-control, and cohort studies) and interventional research (quasi-experimental studies and randomized controlled trials).

Types of Participants

This scoping review will target studies in which groups or subgroups of participants comprise male or female individuals aged 105 years and older.

The exclusion criteria will be studies involving participants younger than 105 years as the primary focus.

Setting and Time Frame

In this scoping review, articles will be screened initially without any time restrictions. Additionally, there will be no limitations on the study settings.

Report Characteristics

Only peer-reviewed studies with full-text availability in English will be included. There will be no restrictions on the date of acceptance or publication. Regarding publication status, only articles that are either published or in press will be considered.

The exclusion criteria will be articles not available in full text, non–English-language studies, and non–peer-reviewed studies (eg, gray literature)

Information Sources

Our sources of information will be limited to electronic databases. An electronic search will be performed through Scopus (including Scopus Secondary literature), PubMed, ProQuest, PsycINFO, and The Cochrane Library (Cochrane Database of Systematic Reviews, Cochrane CENTRAL, and

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Cochrane Methodology Register). Additionally, the reference lists of primary studies included in the review and the reference lists of relevant, previously published reviews will be reviewed.

Search Strategy

The search syntax used in the different databases is shown in Table 1.

Table 1. Search syntax.

Database	Search query	Filters
Scopus Articles	TITLE-ABS-KEY (*supercentenarian* OR semi*supercentenarian) AND (LIMIT-TO (DOCTYPE , “ar”) OR LIMIT-TO (DOCTYPE , “no”) OR LIMIT-TO (DOCTYPE , “cp”) OR LIMIT-TO (DOCTYPE , “sh”) OR LIMIT-TO (DOCTYPE , “le”) OR LIMIT-TO (DOCTYPE , “ed”))	Articles, notes, conference papers, letters, and editorials; excluded reviews and book chapters
PubMed	“supercentenarian”[Title/Abstract] OR “semi*supercentenarian”[Title/Abstract] OR ((“Centenarians”[MeSH[a] Terms] OR “Centenarians”[All Fields] OR “centenarian”[All Fields]) AND “Centenarians”[MeSH Terms])	None
ProQuest	(supercentenarian* OR semi*supercentenarian supercenten*arian OR semi*supercentenarian) NOT (at.exact(“Literature Review” OR “Review”) AND PEER(yes)) Ending truncation: • Search query: supercentenarian* OR semi*supercentenarian Middle truncation: • Search query: supercenten*arian OR semi*supercentenarian Databases: • Coronavirus Research Database • ProQuest Dissertations & Theses Global • Publicly Available Content Database	Peer-reviewed studies; excluded literature reviews and reviews
PsycINFO	*supercentenarian* OR semi*supercentenarian	None
Scopus Secondary Literature (a secondary document is a document extracted from a Scopus reference list, but is not indexed by, or available in, Scopus)	TITLE-ABS-KEY (*supercentenarian* OR semi*supercentenarian)	None
Scopus Patents	TITLE-ABS-KEY (*supercentenarian* OR semi*supercentenarian)	None
Cochrane Database of Systematic Reviews	(centenarian):ti,ab,kw OR (supercentenarian):ti,ab,kw AND (semi-supercentenarian):ti,ab,kw	None

[a]MESH: Medical Subject Headings.

Details of the search records, such as the date of the search, database, keywords, number of studies identified, and the number of eligible studies, will be appropriately documented. The authors will follow the adapted PRISMA-P guidelines to report the screening results.

Study Records: Selection Process

The results from the database search will be entered into Zotero (Corporation for Digital Scholarship), where duplicate records will be removed. Abstract and full-text screenings of the studies will be conducted by two independent reviewers using the eligibility criteria as a guide. Any disagreements among reviewers following abstract screening will be resolved through discussions to reach a consensus. However, a third reviewer will be involved to address discrepancies at the full-text screening stage.

Data Extraction and Coding

Data extraction will be done through systematic categorization of information from the included studies. The information will be categorized into predefined fields to ensure uniformity and consistency. The extracted data will include the following categories:

- Study details: Title, author(s), year of publication, journal, and geographic location
- Study design: Observational (eg, case-report, case-series, cross-sectional, case-control, and cohort studies) or interventional (eg, quasi-experimental studies and randomized controlled trials) studies
- Study population: Demographics (age, gender, and socioeconomic background) and sample size
- Factors analyzed: Genetic determinants, socioecological factors (eg, lifestyle behaviors, environmental influences, and social support), and health outcomes
- Methodological details: Data collection methods, assessment tools, and analytical approaches
- Type of data: Quantitative, qualitative, or mixed methods

The extracted data will then be coded and classified into themes based on the study’s objectives and reported findings. Uniformity will be maintained by using a standardized data extraction template and regular discussions among reviewers

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to resolve ambiguities and discrepancies during the coding process.

Data Synthesis

Thematic analysis will be conducted to synthesize findings from included studies, following the 6-phase framework by Braun et al [10]. This process includes familiarizing with the data, generating codes, identifying and reviewing themes, and producing the final synthesis. Themes will focus on age validation, demographics, health, functional capacity, cognition, behaviors, social support, quality of life, personality traits, environmental and genetic factors, and religiosity. Themes will be identified inductively to allow for novel insights while remaining aligned with the review objectives.

Reflexivity will be ensured through regular team discussions and documentation of assumptions to minimize researcher bias. Confirmability will be achieved by using two independent reviewers for coding, with discrepancies resolved through discussion or a third reviewer. Dependability will be ensured through a standardized coding process and team reviews of the thematic framework.

Credibility will be supported by providing detailed descriptions of themes. Transferability will be addressed by detailing the contexts and characteristics of the included studies and discussing broader implications for aging research.

Results

As of October 2, 2024, five databases were searched, and 844 studies were retrieved. After eliminating duplicates, 706 studies remained. Following the first stage of title and abstract screening, 518 studies were excluded and 188 studies remained. The remaining studies were subjected to full-text screening against the eligibility criteria, which resulted in eliminating 53 studies, leaving 135 studies to be included (Figure 1). The study is expected to be completed by the end of February 2025.

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow chart.

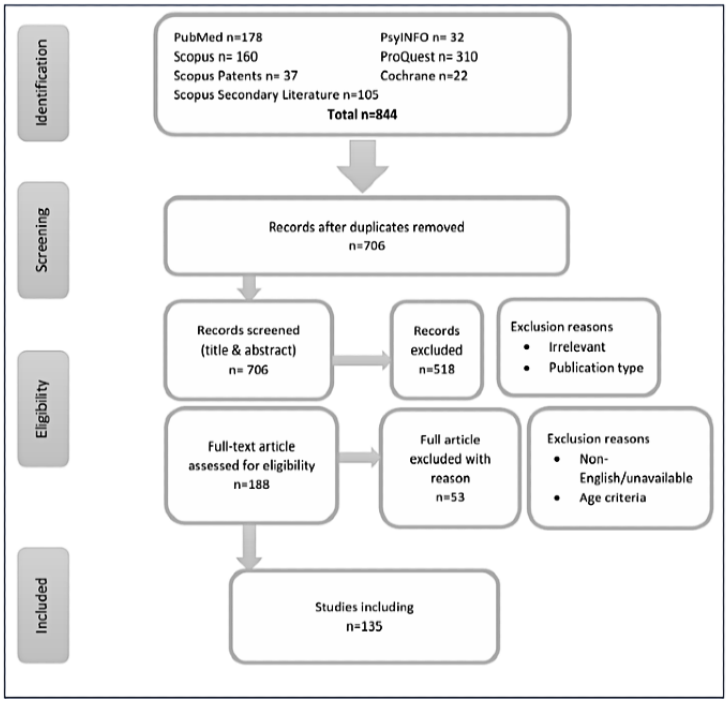

Discussion

Expected Findings

The study of semi-supercentenarians and supercentenarians is extremely valuable in shedding light on healthy aging and longevity [11]. Scholars have studied various areas and numerous factors suspected to contribute to extreme longevity. A study on Italian centenarians and supercentenarians used a multidimensional approach (genetic, demographic, and phenotypic characteristics) to better understand the complex interactions underlying longevity [12]. Other research concentrated on cognition and dementia. Recent research has identified the transcription factor *REST* as an important factor in extreme longevity and cognitive activity [13], while others found that supercentenarians show particularly mild neuropathological findings and thus exhibit remarkable resilience to age-related cognitive decline and dementia [14]. Genetic factors were also studied. A study found strong genetic components to longevity, with siblings of centenarians having significantly higher chances of reaching 90 years [15]. Psychosocial factors, including demographics, personality, and socioeconomic resources, were also found to significantly impact the health and quality of life of centenarians [16]. These are a few studies among many that contribute to the broader discussions on aging theories. On the other hand, more than 25 landmark centenarian and supercentenarian studies have been conducted by specialized organizations across different geographical regions, using diverse methodologies and data collection approaches [17-21]. Given the extensive research on semi-supercentenarians and supercentenarians, this scoping review will serve as a valuable resource for mapping the genetic and socioecological factors associated with individuals aged

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105 and older. It will also identify and summarize the methods and assessment tools used to study the key factors contributing to extreme longevity.

A total of 135 studies has been included, reflecting a diverse body of research. However, the wide range of topics, methodologies, and findings highlights the need for a comprehensive synthesis to consolidate existing evidence and identify gaps for future investigation. This review provides an overview of current research on extreme longevity while pinpointing areas that require further study. This scoping review sets the foundation for future standardized research protocols in longevity studies. Additionally, the findings of this study will have important implications for aging-related health care strategies and interventions. Understanding the genetic and socioecological determinants of extreme longevity can lead to personalized health interventions that aim at promoting healthy aging. Policy makers and health care providers can use this evidence to design lifelong healthy behaviors programs and improve social and community support systems for older adults. The findings of this study will contribute to the body of literature on semi-supercentenarians and supercentenarians, inform future studies and interventions, and guide policy makers in the field of aging and public health.

Study Limitations

This scoping review has limitations that need to be acknowledged. There is a risk of selection bias. This scoping review only includes peer-reviewed, full-text articles in English, which may narrow the findings by excluding relevant studies published in other languages or in gray literature. Moreover, there is difficulty in making direct comparisons due to significant methodological differences, particularly in how longevity determinants are defined and the assessment tools used. Lastly, this scoping review as a study does not establish causal relationships between genetic, socioecological factors, and extreme longevity. Instead, it serves as a foundation by identifying gaps, trends, and inconsistencies in the existing research. It provides insights that can guide future longitudinal studies (which track individuals over time) and experimental research (which tests specific interventions) to better understand the causal mechanisms behind extreme longevity.

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Data Availability

Data are available upon request from the authors.

Authors' Contributions

Conceptualization: WAEKM, OA, SC
Methodology: WAEKM, OA, SC
Investigation: WAEKM, OA, SC
Writing - original draft: WAEKM
Writing - review & editing: WAEKM, OA, SC

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist.
[PDF File (Adobe PDF File), 114 KB - resprot_v14i1e63900_app1.pdf]

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Abbreviations

PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols

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Protocol

Exploring Curriculum Considerations to Prepare Future Radiographers for an AI-Assisted Health Care Environment: Protocol for Scoping Review

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Abstract

Background: The use of artificial intelligence (AI) technologies in radiography practice is increasing. As this advanced technology becomes more embedded in radiography systems and clinical practice, the role of radiographers will evolve. In the context of these anticipated changes, it may be reasonable to expect modifications to the competencies and educational requirements of current and future practitioners to ensure successful AI adoption.

Objective: The aim of this scoping review is to explore and synthesize the literature on the adjustments needed in the radiography curriculum to prepare radiography students for the demands of AI-assisted health care environments.

Methods: Using the Joanna Briggs Institute methodology, an initial search was run in Scopus to determine whether the search strategy that was developed with a library specialist would capture the relevant literature by screening the title and abstract of the first 50 articles. Additional search terms identified in the articles were added to the search strategy. Next, EBSCOhost, PubMed, and Web of Science databases were searched. In total, 2 reviewers will independently review the title, abstract, and full-text articles according to the predefined inclusion and exclusion criteria, with conflicts resolved by a third reviewer.

Results: The search results will be reported using the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist. The final scoping review will present the data analysis as findings in tabular form and through narrative descriptions. The final database searches were completed in October 2024 and yielded 2224 records. Title and abstract screening of 1930 articles is underway after removing 294 duplicates. The scoping review is expected to be finalized by the end of March 2025.

Conclusions: A scoping review aims to systematically map the evidence on the adjustments needed in the radiography curriculum to prepare radiography students for the integration of AI technologies in the health care environment. It is relevant to map the evidence because increased integration of AI-based technologies in clinical practice has been noted and changes in practice must be underpinned by appropriate education and training. The findings in this study will provide a better understanding of how the radiography curriculum should adapt to meet the educational needs of current and future radiographers to ensure competent and safe practice in response to AI technologies.

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KEYWORDS

artificial intelligence; machine learning; radiography; education; scoping review

Introduction

Radiography is arguably one of the most technologically advanced health care disciplines, encompassing various technologies that continuously evolve with advancements in computing power and human knowledge [1,2]. Although the use of technology has always been extensive in the profession, recent technological advancements have focused on incorporating complex machine learning algorithms, which have led to a change in clinical protocols that affect patient outcomes and radiography practice [3-5]. Artificial intelligence (AI) technologies play an increasingly important role in clinical radiography with applications such as scheduling patients, image interpretation and reporting, vetting of examinations, patient positioning, image generation and reconstruction, radiation therapy dosimetry, and image postprocessing [4,6-8]. As the number of AI applications increases in clinical practice [9], it is postulated that the practitioner role may change and expand, and these new roles will require modifications to the competencies and educational requirements of current and future practitioners [4].

The increasing integration of AI technologies in radiography practice raises significant questions about the influences of AI technology on radiography practice and the subsequent ways in which radiography education may be required to change. Recent reviews have explored AI's current and potential applications in radiography practice [5] and examined the AI educational programs available to radiography staff globally [1]. Furthermore, research undertaken in the United Kingdom, Africa, and the Middle East exploring AI topics linked to education in radiography has focused on equipping practitioners for successful AI adoption [10] as well as the perceptions and attitudes of students and practitioners [11-16]. These conversations illustrate that there has been increasing exploration of various facets of AI in radiography, indicating that the emergence of AI technologies will continue to shape the future of radiography and radiography education.

Opinion statements and discussion pieces argue for the inclusion of AI education in undergraduate radiography curricula and appropriate education for current practitioners [3,4,17]. In addition, recommendations were made that higher education institutions must ensure that radiography curricula provide educational opportunities for patient-centered care in relation to AI integration to ensure competent and safe practice [2,3,6]. With increasing automation in clinical tasks, patient-centered care will gain more importance, highlighting the need for academic curricula to prioritize patient-centered care [2,4]. The evolving landscape of radiography, marked by the increasing integration of AI, raises important questions about how to best prepare future radiographers. Therefore, mapping the existing literature on the way that radiography education may need to change because of the integration of AI technologies in clinical practice is needed to grasp the current state of knowledge on the topic for future educational considerations. The aim of this scoping review is to explore and synthesize the literature on the adjustments needed in the radiography curriculum to prepare radiography students for the demands of AI-assisted health care environments.

Methods

Overview

The review will follow the Joanna Briggs Institute methodology for scoping reviews because it uses a rigorous and logical approach to scoping reviews [18,19]. The methodological guideline delineates 6 steps to map the extent of the literature on the research topic. These include (1) defining the research question, (2) developing the inclusion and exclusion criteria, (3) describing the search strategy, (4) searching the literature, (5) data extraction, and (6) analyzing the evidence and presenting the results [19]. The scoping review protocol is registered on the Open Science Framework [20]. The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) reporting guidelines and checklist [21] will be used to report the results (Multimedia Appendix 1).

Step 1: Defining the Review Question

The research question that will guide the scoping review is "How should the radiography curriculum be adapted to prepare radiography students for the integration of AI technologies in the health care environment?"

For this review, radiography refers to the four different radiography categories, including diagnostic radiography, diagnostic ultrasound, nuclear medicine technology, and radiation therapy.

Step 2: Study Selection

Inclusion Criteria

Overview

The types of studies to be considered for this review include quantitative, qualitative, mixed methods studies, scoping, literature, systematic reviews, opinion papers, letters, and conference papers. The selection of study types included in this review is justified based on the need for a comprehensive and nuanced understanding of the topic. The review will consider articles from any country or region, provided that an English translation of the article can be sourced or a translation app is available [22]. The Participants, Concept, and Context (PCC) framework will be used to systematically organize the scope of the review, ensuring it aligns with the objective and the relevant studies are included [18,19].

Population

The population consists of radiography students and educators. In addition, articles that form part of multidisciplinary health

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professions' groups of which radiography forms a portion will also be included.

Concept

The concept focuses on how AI technologies are reshaping the clinical environment and the corresponding adjustments required in the radiography curriculum to prepare radiography students for this evolving landscape.

Context

This review will consider articles from academic and clinical settings in all countries.

Exclusion Criteria

Studies specifically related to other health professions' disciplines will be excluded. Furthermore, technologies discussed in the literature that lack AI will be excluded from consideration. All studies that align with the inclusion criteria, including the PCC, will be included in the review. In addition, articles for which the full text is not available through institutional subscriptions, interlibrary loans, or after contacting the corresponding author will not be included in the review. The authors will attempt to maximize access through the available institutional resources, but limitations may still apply. A full list of the eligibility criteria is provided in Table 1.

Table 1. Eligibility criteria for the scoping review.

PCC[a] Framework	Include	Exclude
Population	• All 4 radiography categories • Radiography educators • Radiography students	All other health professions' disciplines
Concept	• Studies that discuss AI[b] or AI-based tools in the context of radiography	Studies using technology that does not incorporate AI-based tools
Context	• Academic and clinical radiography education • Undergraduate radiography education • Postgraduate radiography education • Continuing professional development	Other health professions' education programs
Study characteristics	• The review will consider all types of study designs. • Sources printed in all languages • Full-text articles	Full-text not available

[a]PCC: Population, Concept, Context.

[b]AI: artificial intelligence.

Step 3: Search Strategy

The search strategy aimed to include published and unpublished literature. A preliminary search was performed on Scopus to identify articles on the topic in collaboration with a library specialist. The Scopus database was chosen because it is the largest indexing and abstract database and hosts a number of widely acknowledged Radiography journals. The search strategy was developed by examining the text found in the titles and abstracts of the relevant literature and the index terms and keywords used to describe the articles. The process entailed screening the titles and abstracts of 50 articles. Thereafter, the search strategy was refined iteratively through consultations with the librarian and between the authors. The detailed final search strategy for all databases, EBSCOhost, PubMed, Scopus, and Web of Science can be found in Multimedia Appendix 2. Gray literature was retrieved from the databases, including book chapters, conference papers, and letters. The total number of sources found was 2224 (Table 2).

Table 2. Electronic databases and gray literature results.

Electronic resources	Sources, n
EBSCO (Academic Search Premier, CINAHL, ERIC)	362
PubMed	1214
Scopus	267
Web of Science	112
Gray literature	269
Results	2224

Step 4: Selection of Evidence

Following the search, all citations were imported and managed using the Covidence online software [23]. All the duplicates were removed after the studies were imported into the software program. The primary investigator (CK) and a research assistant screened the studies during the title and abstract phase based on the inclusion and exclusion criteria to ensure that they are

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relevant to the review [24]. The inclusion and exclusion criteria will be piloted on the first 20 articles to ensure that the criteria are applied consistently and that the relevant studies are included.

After the initial screening, a full-text screening of the selected articles will be performed to determine the literature to be included in the review. The reference list of all selected articles will then be hand-searched for additional studies that may be eligible according to the inclusion criteria. Following the full search, all citations will be captured. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussions, or with an additional reviewer and the changes will be noted and shared in the final scoping review report. Furthermore, reasons for the exclusion of sources of evidence at full-text screening will be recorded and reported in the scoping review.

Step 5: Data Extraction

To meet the aim and research question, the data will be organized according to the Joanna Briggs Institute template source of evidence details, characteristics, and results extraction instrument [22], incorporating key study information such as authors, study population, year of publication, study location, study design, and the key findings (Multimedia Appendix 3). This data extraction instrument was created and will be piloted to minimize potential bias. Piloting of the data extraction instrument will include a selection of 3-5 articles from the scoping review dataset and the two reviewers will perform independent data extraction to ensure that all the necessary data will be captured [21]. The instrument will be used to determine if the inclusion and exclusion criteria have been met during evidence selection. Modifications to the instrument may be made during the course of the literature search and the findings will be detailed in the scoping review report.

Step 6: Data Analysis

Scoping reviews should include a numerical summary outlining the types of literature that were retrieved and a thematic descriptive analysis [19]. The final themes of the scoping review will be developed using an iterative approach. A narrative description will then be used to synthesize the study findings using descriptive content analysis, and the identified themes will be reported.

Results

The final database searches were completed in October 2024 and in total produced 2224 items. Title and abstract screening of 1930 articles is underway after removing the 294 duplicates. The results will be presented in relation to the research question and the objective of the study. Furthermore, the results will be presented in 2 parts as proposed by Peters and colleagues [19]. The first part will consist of the results of the search and the inclusion of the studies will be presented with the PRISMA-ScR flow diagram (Figure 1). The blue arrow indicates the current status. The second part will consist of a narrative description that aligns with the objective of the scoping review. Data analysis and results may be further refined through the review process as the contents of the review are taken into consideration. Finalization of the scoping review is expected by March 2025. The results of the scoping review will be disseminated through publication in an accredited journal.

Figure 1. Flowchart of the PRISMA-ScR for the scoping review process. PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews.

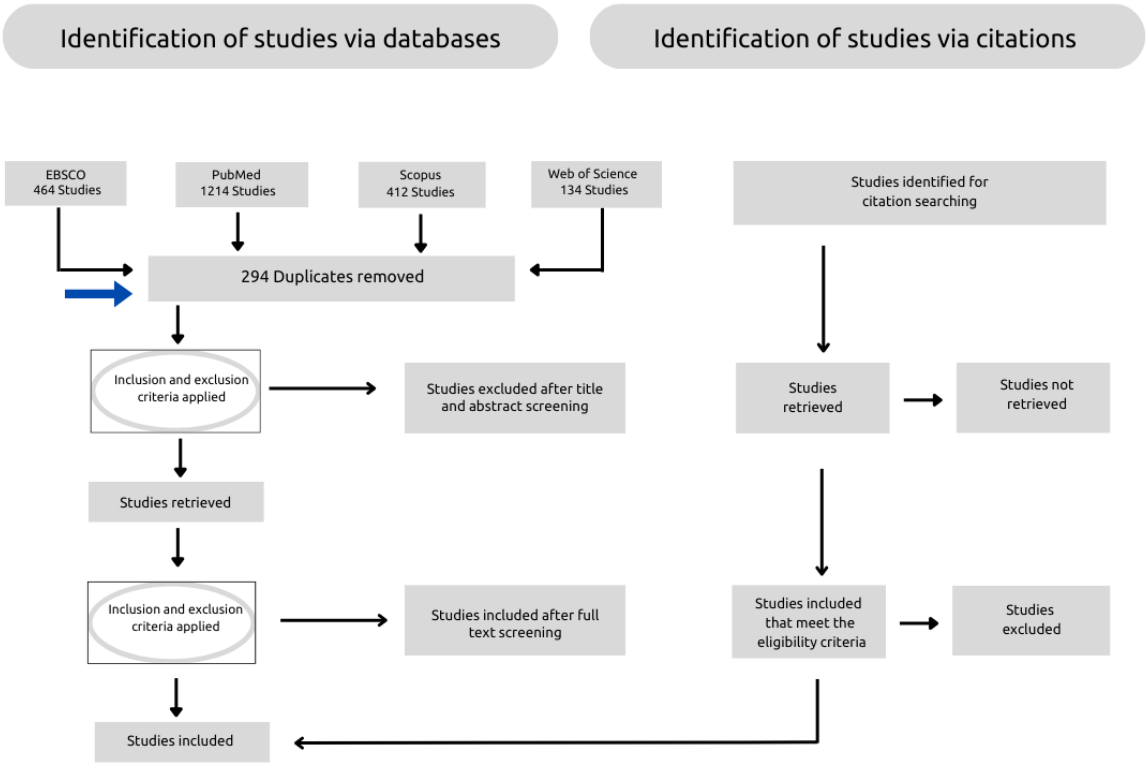

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Discussion

Addressing the call for an update to the radiography curriculum in response to new technological advancements such as AI is critical to prepare and equip current and future professionals for safe practice. This scoping review will map various studies and is anticipated to provide an overview of the adjustments needed in the radiography curriculum to prepare radiography students for the demands of AI-assisted health care environments. In return, the results will help to inform a variety of stakeholders, including radiography educators, radiography regulatory bodies, and radiography professional groups, to plan for needed changes in radiography education in response to the impact of AI-based technologies on clinical processes. To the best of our knowledge, this is the first scoping review to synthesize existing evidence of how the radiography curriculum might best prepare future practitioners for the demands of AI-assisted health care environments.

A strength of the scoping review is that all available studies of published data will be included. Current available literature focusing on how the radiography curriculum might need to change, considering the incorporation of AI technology in clinical practice, focuses on opinion and discussion pieces, and white papers [4,17,24]. In addition, some studies have highlighted the perceptions of educators and students on the incorporation of AI into radiography curricula; however specific methods of integration and a lack of implementation were noted [1]. Therefore, performing this review is warranted to help provide the necessary insights into changes to the curriculum that are aligned with the advances in technology.

A scoping review explores the breadth and not the depth of a topic, and the reviewers cannot comment on the quality of the studies included in the review. In addition, non-English articles may be excluded from this review, which can potentially lead to missing valuable work. However, for the search strategy, all languages are included and the number of studies for all languages will be documented. This process will show how many studies were identified but not included, promoting transparency in the selection process [22]. Furthermore, where possible translations will be sought to limit the omission of information.

This study will provide valuable insights into how the radiography curriculum should adapt to meet the educational needs of current and future practitioners to ensure competent and safe practice in response to AI technologies. Mapping the existing evidence is essential because the growing integration of AI-based technologies in clinical practice must be supported with appropriate education and training [1,4]. After collating and analyzing the findings of the scoping review, a manuscript containing the final analysis will be written and submitted for publication. In addition, this review will contribute toward a PhD in health professions education.

Acknowledgments

We would like to thank the librarian, Mr Yusuf Ras, for his contribution to the scoping review protocol.

Data Availability

All relevant data are available in the study or as multimedia appendices and will be made available upon request.

Authors' Contributions

CK conceptualized the scoping review, wrote the manuscript, and provided data. EA, PEH, and MV provided oversight for the scoping review protocol development.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) checklist.
[DOCX File , 140 KB - resprot_v14i1e60431_app1.docx]

Multimedia Appendix 2
Search strategy.
[DOCX File , 31 KB - resprot_v14i1e60431_app2.docx]

Multimedia Appendix 3
Data extraction tool.
[DOCX File , 19 KB - resprot_v14i1e60431_app3.docx]

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Abbreviations

AI: artificial intelligence
PCC: Population, Concept, and Context
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Indigenous Community Views of Disability in Canada: Protocol for a Scoping Review

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Abstract

Background: Indigenous people do not necessarily view disability in the same way as do other groups. Indigenous concepts of disability are connected to their ancestral history, cultural customs, and environmental context. Some Indigenous languages do not contain a word equivalent to disability. Western approaches to disability seldom reflect the voices of Indigenous people.

Objective: The objective of this scoping review is to collate the perspectives, concepts, and understandings of disability in Indigenous communities in Canada and to map the factors that influence social approaches to disability from an Indigenous perspective.

Methods: Following the methodological framework for scoping reviews of Arksey and O'Malley, we will search electronic databases, including PubMed, Scopus, Web of Science, EBSCOhost ProQuest, Autochtonia, and APA PsycINFO. We will search gray literature through the Google search engine, conference abstracts, dissertation databases, government documents, and Indigenous organization websites. We will include quantitative, qualitative, and mixed methods studies in English and French. The included studies will describe Indigenous approaches to disability, as they are understood based on personal, cultural, and historical contexts. Two reviewers will use Covidence software (Cochrane) to remove duplicates, screen articles, record the step-by-step selection process, and extract data from the included articles. We will follow the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Scoping Reviews) guidelines. We will present the findings in tables, charts, narrative summaries, and through fuzzy cognitive mapping. We will contextualize the literature's findings by comparing them with the stakeholders in Quebec and provide a discussion to explore potential solutions for the identified factors.

Results: An initial limited search was conducted in January 2024. The study will be conducted in 2025. Publication of the results is expected in late 2025.

Conclusions: We anticipate that the findings from the scoping review will be useful for professionals, researchers, policy makers, and Indigenous communities themselves interested in co-designing and implementing evidence-informed disability programs and services, which will prevent mismatches between the programs and the sociocultural context. We will disseminate

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the results of this review through workshops with the participating communities, direct engagement with relevant local stakeholders, and through conference presentations and publications in scientific journals.

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KEYWORDS

Indigenous health; intercultural dialog; cultural safety; traditional medicine; disability

Introduction

The way disability is defined affects the types of disability services offered, who uses the services, and the way they work. The traditional biomedical model, despite frequent criticism, continues to influence Western approaches to disability [1,2]. This model views disability as an individual issue, characterized by abnormalities of the body or mind that medical science treats and social services cater for. In this mindset, experts are seen as the professionals responsible for either treating disabled individuals or coordinating services for them. Also focused on individual abnormalities and perhaps more criticized than the biomedical model for treating differences as medical issues and creating population categories, the moral model depicts disability either as a source of stigma and shame or, alternatively, as a sign of strength [3,4].

Social and inclusion models of disability reflect interactions between people with disabilities and attitudinal or environmental barriers that prevent their full and effective participation in society [5]. These approaches go beyond disability as a personal attribute to frame disability in terms of the conditions created by the social environment that cause people to experience barriers to performance in life situations. In the same way, the International Classification of Functioning, Disability, and Health (ICF) reinforces this view by emphasizing that disability results from the interaction between health conditions and contextual factors both environmental and personal [6,7]. The ICF highlights the importance of addressing not only impairments but also the external barriers that limit activity and participation [3,7,8]. Another approach explores not only physical or mental impairments but also the societal norms that define certain characteristics as disabilities. It's important to examine how social conditions exacerbate these stigmatized characteristics within specific populations [9-11]. A constructive step might be to engage with Indigenous communities to discuss the language and concepts surrounding disability, particularly whether colonialism and its resulting social disadvantages have transformed the social meaning of disability for Indigenous people [12,13].

Literature over the last 2 decades describes Indigenous perspectives and beliefs about disability [12,14-16]. Many Indigenous languages have no word for "disability," suggesting it is a term produced by western constructs [17], rather than anything negative or based on difference [18,19]. Articles about the intersection of indigeneity and disability highlight the importance of family ties, community networks and spirituality [14,16,18,20-24]. Although clearly different from western views, Indigenous worldviews of disability are not monolithic. Views vary between Indigenous cultures and, within any 1 culture, may not be static but responsive to the recovery of traditions and to adaptations [24,25].

With no published systematic review about Indigenous perspectives of disability from Canada, a review from Australia provides a substantial advance in the field [23]. This examined the understanding of disability within Australian Indigenous communities, highlighting that some disability services are shaped by western norms and assumptions that do not reflect their values. The review also notes that scholarly literature on Indigenous conceptualizations, experiences, and practices of disability remains relatively underdeveloped. Our review explores similar themes within the Canadian context. Our aim is to describe the concepts of First Nations, Métis, and Inuit, the 3 constitutionally recognized Indigenous groups in Canada who comprise approximately 5% of the country's population [26] and reflect unique cultural, environmental, and historical influences. Our review will focus on Indigenous points of view, summarizing the diverse narratives and choosing not to reproduce damage-centered approaches that contributed to pain and oppression [27].

We describe here the protocol for a scoping review, a starting point of a larger research program. This will compare and combine different knowledge sources to inform partnerships that address knowledge, policy, and implementation gaps for disability support services in Indigenous communities. The broader research initiative will encompass the following knowledge resources: (1) the scoping review detailed in this protocol; (2) perspectives from personnel of community-based initiatives and Indigenous-led organizations; (3) perspectives of Indigenous elders and knowledge keepers; and (4) perspectives from disability service providers, researchers, policy makers and people encountering disabling situations from the communities and their peers. The Weight of Evidence approach [28] uses fuzzy cognitive mapping [29] and will integrate these diverse sources of knowledge.

Methods

Study Design

We used the PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) [30] checklist (Multimedia Appendix 1) for drafting the protocol. We will conduct the scoping review according to the guidelines proposed by Arksey and O'Malley [31] and the modifications proposed by Levac et al [32]. The 6-stage process includes identifying the research question, identifying relevant studies, developing

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a study selection and data extraction method, charting the data, collating, summarizing, and reporting results, and contextualization with stakeholders. We will adapt the final step to function as a contextualization exercise, guided by the weight of evidence approach [28] that contrasts literature findings with contributions from stakeholders. The final report will follow the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for Scoping Reviews) [33].

Our team consists of 2 Indigenous researchers with expertise in Indigenous perspectives, psychosocial interventions, and inclusion. Other authors bring significant experience working with Indigenous communities in Canada and Mexico, as well as extensive expertise in working with people with disabilities in Nigeria, Zambia, Canada, and Colombia. We will do the first contextualization in the province of Quebec, as we describe below. We will verbally share discussions with our Indigenous researcher partners in Nunavik and Indigenous community members in the Saguenay-Lac-Saint-Jean region (Mashteuiatsh community) and the team leading the Nisidotam Inclusion Initiative in the Greater Montreal area. This ensures that Indigenous worldviews inform the approach, analysis, and findings, including the discovery and description of key knowledge gaps. We may make changes to the protocol, and we will detail and justify any modifications in the final report.

Stage 1: Identifying the Research Question

Our research questions are as follows:

1. What does the literature reveal about Indigenous perspectives, concepts, and understandings of disability in Indigenous communities in Canada?
2. What are the key factors that influence disability among Indigenous communities in Canada?

Inclusion Criteria

The participants, concept, and context (PCC) framework will guide the inclusion of eligible studies in this scoping review [34].

Participants

This review will consider sources that include the First Nations, Inuit, and Métis in Canada as the population of interest. We will include the recognized names of Indigenous peoples as search terms in this review.

Concept

This review will consider studies on Indigenous perspectives, concepts, and understandings of disability in Canada, as well as the factors influencing disability among Indigenous people.

Context

This review will consider studies or reports conducted in any Canadian province or territory, as well as those with a substantial focus on the Canadian context.

Types of Sources

This scoping review will consider peer-reviewed and gray literature. Mixed methods, quantitative, and qualitative studies are eligible for inclusion. The publication date range will be unrestricted.

Stage 2: Identifying Relevant Studies

We will consider sources that describe or reflect Indigenous perspectives on disability, whether they are published in peer-reviewed journals or as gray literature. The study or report must be located within Canada or have a significant component of the Canadian context.

We will design a structured search strategy for the electronic databases PubMed, Scopus, Web of Science, EBSCOhost (Bibliography of Indigenous Peoples in North America), ProQuest (Canadian Business and Current Affairs Database), Autochtonia, and APA PsycINFO to identify relevant published studies. We will develop the strategy using Boolean operators, filters, and truncation for each database. We will search for relevant articles using a mixture of search terms and keywords. We will consider adapting the filter developed by the University of Alberta to retrieve studies related to Indigenous people [35]. The research team will draft and refine a search strategy with the support of a professional librarian. We will pilot the search strategy to check the appropriateness of the keywords and databases. As an example, Multimedia Appendix 2 presents the search strategy for Scopus database.

The search for potentially relevant documents in the gray literature will follow 4 different searching strategies [36]: (1) search gray literature databases such as the Canadian Research Index and the Indigenous Studies Portal at the University of Saskatchewan; (2) use customized Google search engines to examine the first ten pages of results. Combine keywords using simple Boolean operators or hand search relevant subsections of sites; (3) Target Indigenous associations and websites for relevant information; and (4) Consult with experts proficient in research synthesis and aware of relevant documents to gather additional insights. We will contact both Indigenous and non-Indigenous scholars to include multiple sources and ensure our search is as inclusive as possible.

We will hand-search the references for the included articles to identify any additional relevant articles. We will limit the search to articles published in English or French. We will not apply restrictions based on the year of publication or study design.

To stay updated of current work in the field, our scoping analysis methodology will allow us to continually circle back to take newer articles through the screening process and potentially include them in our analysis.

Stage 3: Study Selection

We will export the list of references into Covidence software (Veritas Health Innovation) [37] to conduct title or abstract and full-text screening, first using the software to remove duplicates. Two independent researchers will screen study titles and abstracts against the inclusion and exclusion criteria to identify potentially relevant articles for full-text review. Two reviewers will then conduct a full-text review to confirm the final selection of articles. We will resolve disagreements by consensus or by consulting a third reviewer. A PRISMA (Preferred Reporting

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Items for Systematic Reviews and Meta-analyses) flow chart will show the study selection procedure.

Stage 4: Charting the Data

Two reviewers will use the Covidence data charting framework to extract the relevant data from the included articles. They will pilot the draft data extraction sheet on a random sample of 5 articles. They will use a free use application to chart the data. The first part of the data extracted will include the authors, study title, source or journal, publication type, year of publication, objectives of the study, study design, geographic location, Indigenous group, description of participants, language, findings on perspectives, concepts, understandings, and terminology used about disability. The second part will list all the factors that influence disability from the Indigenous perspective and their relationships. We will present a 3-column edge list, a tabular format to represent relationships in a fuzzy cognitive map. The columns will include causes (originating node), outcomes (landing node), and the sign of the relationship (–1 or +1) [29]. Additional columns will indicate supporting evidence for the relationship and corresponding reference. We will use 1 row for each relationship. If the evidence is quantitative, we will include relationships that are significant at the 95% confidence level. If the evidence is qualitative, we will include quotes, arguments or texts supporting the relationship. We will adjust and refine the data extraction form as needed throughout the data extraction process and document any modifications in the review report. Data extractors will resolve disagreements through discussion.

Stage 5: Collating, Summarizing, and Reporting Results

We will present the results of the review as a qualitative description, incorporating tables, figures, and maps where appropriate. We will present the findings of the scoping review in a fuzzy cognitive map to illustrate the perspectives, concepts and understandings of disability and the factors that influence disability from an Indigenous perspective.

Fuzzy cognitive mapping visually represents knowledge, helping clarify the complex factors that influence outcomes or decisions [38,39]. These maps show assumed causal relationships that can be based on data or unwritten knowledge [40] between concepts or factors (nodes) and the outcomes, connected by arrows or edges [38,39,41]. The source of knowledge assigns different values to the edges, indicating the direction of the causal relationships and quantifying the strength of their influence on the outcome [28,38,39,41,42].

We will create a map for each article included in the review. We will identify whether the influence of a reported factor is positive or negative (+1 or –1) and depict it in a 3-column edge table as described above. If the study shows that an increase in one factor leads to an increase in another factor, we will assign a positive relationship (+1). If it shows a decrease in the second factor, we will assign a negative relationship (–1) [42].

After creating an individual table for each included study, we will calculate the fuzzy transitive closure for each study using the open access software CIETmap (V.2.2) to determine the strength of influence one factor has on others through direct or indirect relationships [43].

We will use Harris' discourse analysis approach to weigh each relationship based on its relative frequency across all the transitive closure maps [44,45]. Factors appearing in multiple maps will be weighted as having a stronger causal influence than those appearing in only 1 or 2 studies [41,45]. By dividing each relationship's occurrence by the highest frequency, we will obtain values between 0 and 1, where values closer to 1 indicate more influence. We will create a composite map of all factors and relationships identified in the scoping review, with relationship weights based on their relative frequency [45]. Multimedia Appendix 3 illustrates an example of a fuzzy cognitive map.

We anticipate refining and expanding the data presentation approach as the nature of the available literature becomes known. We will highlight areas where evidence is lacking and make recommendations for decision-making, practice or further research.

We will report the review methods and findings according to the PRISMA-ScR guidelines. We will disseminate the results of the scoping review in a peer-reviewed publication and present and discuss them in relevant forums, workshops, conferences, and community spaces. Potential limitations of the review include that we may miss studies reported in Indigenous languages and that some local knowledge may not be accessible despite best efforts to search the gray literature.

Stage 6: Contextualization

We will contextualize with stakeholders in the final step of the scoping review [31,32], which is part of a broader participatory research project on disability among Indigenous peoples of Canada. We will adapt the "weight of evidence" approach [28] to contrast and combine the synthesized evidence from the literature with the experiential knowledge of stakeholders, including Indigenous scholars, elders, knowledge keepers, cultural advisors, individuals with disabilities from the communities and their peers, as well as members of community-based and regional organizations representing people with disabilities or First Nations and Inuit in Quebec. We will invite them to share their perspectives, concepts, and understandings of disability in Indigenous communities, and to create maps of the factors that influence disability from an Indigenous perspective.

We will adapt the fuzzy cognitive mapping protocol recommended by Andersson and Silver [39]. A facilitator and a notetaker will support each stakeholder mapping session.

After the stakeholders create their own maps, they will compare them with the composite map from the scoping review. We will combine the scoping review map with the users' maps to update the literature with stakeholder perspectives. The scoping review and the stakeholder maps will serve as the basis for engaging them to explore solutions for the identified issues.

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Results

The preliminary database search was conducted in January 2024. The study is scheduled for 2025, and its results will be published in open-access, peer-reviewed journals by the end of 2025.

Discussion

Principal Findings

The proposed scoping review will identify and map evidence on Indigenous concepts, perspectives, and understandings of disability as well as the key factors that influence disability in Canada. This review offers space for perspectives outside Western paradigms, facilitating a subsequent intercultural dialogue. This dialogue allows stakeholders with different cultural backgrounds to engage in respectful, dynamic communication to address a concern [46], in this case, the conceptualization of disability in Indigenous communities. The review might encourage a more inclusive, comprehensive, and culturally safe understanding of disability. It will contextualize the existing literature in the rich heritage of Indigenous Peoples in Quebec, Canada, including their perspective of disability and the implications of this for disability policy in this province. It will serve as a prototype for contextualizing the literature in the specific belief systems of Indigenous groups in other provinces and beyond Canada.

To our knowledge, no previous literature review has covered this topic in Canada. However, a review published by Australian authors significantly advances the understanding of disability services and disability conceptualization within Indigenous communities.

Strengths and Limitations

This scoping review has several strengths. First, we will include gray literature. By doing so, we will add valuable insights and ensure we don't miss findings and diverse perspectives that may not be found in peer-reviewed academic sources. Second, by contrasting and integrating evidence from the literature with the knowledge of Indigenous communities and people with disabilities through fuzzy cognitive maps, the scoping review will provide a thorough overview. Third, the participatory nature of the exercise will engage all stakeholders in interrogation of the literature and the codevelopment of a uniquely provincial and inclusive perspective. In this important sense, participation in the review process can be a first step in the intercultural dialogue.

The scoping review will have certain limitations. Some studies in Indigenous languages might be missed, and certain local knowledge may remain inaccessible, despite diligent attempts to include gray literature. The review will not include a quality assessment of the studies, which may introduce a risk of bias. We will provide a description of the methodologies and different criteria used to facilitate the contextualization of the findings. Potential limitations could include challenges in language use during fuzzy cognitive mapping for stakeholders, operator bias (influence of facilitators), as well as issues with coding and weighting [29]. To address this, we will train facilitators in protocols to reduce these recognized weaknesses. We are aware that the inclusion of multiple interpretations, factors, and varying levels of methodological rigor across different groups could decrease the precision of results.

Future Directions

By mapping the literature and identifying knowledge gaps, this scoping review will be a first step toward identifying research priorities and developing effective policies and interventions for Indigenous groups with disabilities. Future directions include repetition of the contextualization exercise in other Canadian provinces, generating provincially specific reviews that take account of Indigenous views in that province and the provincial agencies concerned with Indigenous people living with disability.

In addition to scientific publication and conference presentations, we will share the findings through workshops with participating communities and civil society organizations working in disability in Quebec.

Acknowledgments

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Authors' Contributions

All authors contributed to drafting the initial protocol, critically reviewed it for intellectual content, and subsequently revised it for publication. All authors reviewed and approved the submission of the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) 2015 checklist.
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Multimedia Appendix 2

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Search strategy for scopus.
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Multimedia Appendix 3
Example of a fuzzy cognitive map.
[DOCX File , 26 KB - resprot_v14i1e57590_app3.docx]

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Abbreviations

ICF: International Classification of Functioning, Disability, and Health
PCC: participants, concept, and context
PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analysis
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PRISMA-ScR: Preferred Reporting Items for Systematic Review and Meta-Analysis extension for Scoping Reviews

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Protocol

Measuring Adult Health and Well-Being Outcomes Associated With Nature Contact in Parks and Other Forms of Protected Areas: Protocol for a Scoping Review

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Abstract

Background: Growing evidence shows various health and well-being benefits from nature contact in parks and other forms of protected areas. However, the methods to measure these outcomes lack systematic identification, critical appraisal, and synthesis. Researchers working in this area would benefit from a clear framework highlighting key considerations when selecting measurement tools, along with a summary of the measures used, and insights into the limitations of generalizing existing research findings.

Objective: The objectives of this scoping review are 2-fold. First, we aim to identify the instruments used to measure mental health and well-being outcomes of adults associated with direct nature contact in parks and other forms of protected areas. Second, we aim to evaluate the psychometric properties associated with the validity of these instruments to better understand the strengths and weaknesses of current measurement approaches.

Methods: Following PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines, 8 scholarly databases were searched (PubMed, Web of Science, PsycINFO [via ProQuest], ERIC [via EBSCOhost], CINAHL [via EBSCOhost], GreenFILE [via EBSCOhost], OVID, and GEOBASE) on January 4, 2023, for literature measuring the mental health and well-being outcomes associated with nature contact in protected areas. Sources were screened by reviewers based on clear inclusion or exclusion criteria relevant to the research questions: peer-reviewed English language studies measuring mental health and well-being focused on adults (aged 18+ years) with direct, in-person nature contact in parks and protected areas. Data will be extracted, analyzed, and represented according to 3 domains. This includes study details, characteristics of the measurement instruments, and their validity.

Results: The results of the study and submission of a manuscript for peer review are expected in April 2025. The results of the scoping review are expected to contribute to an understanding of the diverse methods used to measure mental health and well-being related to nature contact in protected areas. Expected findings will include an organized summary of existing quantitative and qualitative instruments for measuring mental health and well-being outcomes, including appraisal of the instrument's psychometric properties.

Conclusions: To the authors' knowledge, this will be the first scoping review undertaken on measures used to assess mental health and well-being outcomes related to nature contact in parks and protected areas context, offering a starting point from which to critically examine the validity and consistency of such methods. Findings will aid in identifying the strengths and weaknesses of current measurement approaches to mental health and well-being outcomes of nature contact and may be used to guide future research on this topic, helping researchers choose the best tool to assess outcomes.

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KEYWORDS

nature contact; human health; mental health; well-being; parks; protected areas; outcomes

Introduction

Overview

There is a growing body of research investigating the role of nature in human health and well-being, with numerous studies reporting improvements to physical, psychological, emotional, cognitive, social, and spiritual well-being from time spent in nature [1-4]. Within this context, parks and other forms of protected areas offer unique opportunities to connect with nature, and considerable research has highlighted the increasingly recognized health benefits afforded by these settings [5-8].

Globally, there are more than 295,000 protected areas covering 16.1% of the earth's terrestrial or freshwater area and 8.2% of its marine area [9]. There is also a highly ambitious global initiative to protect 30% of earth's land or freshwater and marine area by 2030, as per the United Nations Convention on Biological Diversity Kunming-Montreal Global Biodiversity Framework [10]. If this goal is achieved, the designation of parks and other forms of protected areas would represent the fastest and largest land or freshwater and ocean allocation in the history of the modern conservation movement. Protected areas differ from most urban green space and local-regional parks in that they have legislated management objectives to conserve nature and provide opportunities for human enjoyment. The International Union for Conservation of Nature (IUCN) defines a protected area as "a clearly defined geographical space, recognized, dedicated and managed, through legal or other effective means, to achieve the long-term conservation of nature with associated ecosystem services and cultural values" [11].

Protected areas can include national and subnational protected area designations, such as national parks, state or provincial parks, and a variety of other designations that fit within the IUCN definition. It is estimated that such areas receive more than 8 billion visits annually [12], underscoring their significance as an essential ecosystem service. It is also estimated that parks and protected areas provide health services valued at US $6 trillion annually worldwide (representing 8% of global gross national product) [13]. Evidence establishing the significance of protected areas to human health and well-being continues to grow at the same time that many nations are committing to significantly expand protected areas networks by 2030. Given these joint trends, this proposed review offers a timely stock take that will help direct the current state of knowledge toward a stronger evidence-informed practice related to the use of parks and protected areas as a nature-based mental health service.

In addition to being timely, the proposed review will provide an important new tool for researchers who face numerous challenges investigating the impact of nature on human health and well-being. Previous research has examined the impact of nature on human health, demonstrating that mental health and well-being outcomes are the most frequently studied [2]. Despite a growing wealth of research, steps to critically evaluate and provide decision support to researchers and practitioners at the level of instrumentation are lacking. The dearth of current decision support presents a critical gap as well-being is a wide-ranging concept, with still wider-ranging options related to measurement. Well-being can capture relatively transitory emotion and mood states, more stable aspects of positive identity such as self-acceptance and self-esteem, broad global evaluations such as subjective life satisfaction, and improvement in clinical conditions such as anxiety and depression.

The need for this review is underscored by a past systematic review conducted by Cooke et al [14]. While not specific to nature-based interventions, Cooke et al [14] identified more than 40 different instruments for measuring well-being that varied widely in length, psychometric properties (ie, validity), and use cases. Linton et al [15] argue that such variability may in part be due to a lack of agreed upon criteria of what an instrument should contain. As noted, despite the current variety, ongoing creation of new instruments, and proliferation of their use in nature-based contexts, there has been no systematic or critical examination of the methods used to measure health and well-being outcomes associated with nature contact in parks and other forms of protected areas. This is a critical knowledge gap that the proposed scoping review will address.

Researchers working in this area would benefit from a clear framework identifying the features to consider in measurement selection as well as a summary of the measures that have been used and their validity. A framework of this type would provide a clearer picture of aspects of well-being that have and have not been investigated or replicated and limits to the generalizability of the research to date. To support further research and decision-making related to outcome-based management in parks and other forms of protected areas, the proposed scoping review seeks to address two objectives: (1) to identify the instruments used to measure mental health and well-being outcomes of adults associated with direct nature contact in parks and other forms of protected areas and (2) to evaluate the psychometric properties associated with validity of the instruments used to measure mental health and well-being outcomes associated with direct nature contact.

Existing Reviews

The current protocol was informed by an initial review of existing peer-reviewed literature to identify potentially comparable knowledge syntheses. To capture the current state of research related to mental health and well-being outcomes from nature contact, we gathered and documented scoping reviews published within the past decade that focused on an adult population. A search was conducted in Google Scholar to locate relevant scoping reviews, using variations of keywords that included "nature contact," "mental health," "well-being," and "scoping reviews." Table 1 outlines details of 7 relevant knowledge syntheses. All identified studies focused on

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constructs related to mental health and well-being. While 6 of the identified studies were specific to health and well-being outcomes related to nature contact, by contrast, none were specific to the unique context of parks and protected areas.

Table 1. Summary of comparable existing knowledge syntheses.

Citation	Title	Objective	Review of measurement instruments	Specific to outcomes from nature contact	Specific to parks and protected areas
Cooke et al (2016) [14]	Measuring Well-Being: A Review of Instruments	Identify and critically evaluate the psychometric properties of instruments measuring well-being and related constructs	Y[a]	N[b]	N
Wendelboe-Nelson et al (2019) [16]	A Scoping Review Mapping Research on Green Space and Associated Mental Health Benefits	Identify the variations across existing literature in the associations between green space and health benefits	Y	Y	N
Christiana et al (2021) [17]	A Scoping Review of the Health Benefits of Nature-Based Physical Activity	Summarize existing literature on the positive association between nature exposure, physical activity, and health outcomes	N	Y	N
Wilkie and Davidson (2021) [18]	Prevalence and Effectiveness of Nature-Based Interventions to Impact Adult Health-Related Behaviors and Outcomes: A Scoping Review	Document the use of nature-based interventions as a strategy to change adult health-related behaviors and outcomes	N	Y	N
Charles-Rodriguez et al (2022) [19]	The Relationship Between Nature and Immigrant's Integration, Wellbeing and Physical Activity: A Scoping Review	Summarize existing research related to nature exposure, immigrant well-being, and physical activity	N	Y	N
Nejade et al (2022) [2]	What is the Impact of Nature on Human Health? A Scoping Review of the Literature	Summarize evidence relating nature-based interventions to health outcomes and examine enablers of nature contact	N	Y	N
Overbury et al (2023) [20]	Swimming in Nature: A Scoping Review of the Mental Health and wellbeing Benefits of Open Water Swimming	Summarize existing evidence relating to mental health and well-being benefits of open water swimming	N	Y	N

[a]Y: yes.

[b]N: no.

Cooke et al [14] reviewed 42 different instruments used to measure aspects of psychological well-being, psychosocial well-being, and psycho-physical well-being. The study categorizes these instruments according to 4 well-being categories (hedonic, eudaimonic, quality of life, and wellness) and a fifth category of composite measures. Evidence of reliability and validity of each instrument is tracked and reported, and authors report a substantial degree of variability in the reporting of evidence related to validity. Results do not report on patterns in the use of instruments according to intervention types or environmental contexts.

In 2 recent reviews, authors documented nature-based interventions and associated health and well-being outcomes. Wilkie and Davidson [18] examined 52 studies including a categorization of environmental settings, exposure times, and theoretical frameworks. They also report on targeted behaviors and outcomes, which includes mental health and well-being in 79% of studies reviewed and physiological health outcomes in 63% of studies. Results track specific outcomes (eg, self-esteem) that were measured but no details around measurement instruments. Nejade et al [2] similarly reviewed 39 papers that provided evidence of mental and physical health outcomes from nature-based health interventions. The forms of natural outdoor environments included green spaces, blue spaces, and mixed green-blue spaces, ranging from urban parks to wetlands, national parks, or reserves (n=2). The study provides a categorization of nature-based health interventions and activities, reports the mental and physical effects of engagement with natural outdoor environments, and discusses barriers and enablers of such engagement. Instruments used to assess health and well-being outcomes are not assessed.

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Despite the proliferation of studies revealing the health and well-being benefits associated with nature contact, there is a clear need to identify and understand the specific instruments being used to assess these benefits. This is especially true in the context of nature contact in parks and other forms of protected areas, where rapid growth in visits to such areas is occurring alongside unprecedented national commitments to protect land or freshwater and marine area the world over. Research is needed to identify the most effective tools for assessing health and well-being outcomes vis-a-vis diverse research contexts (eg, types of environments, activities, and sociodemographic considerations) so that evidence-based policies and guidelines, as well as program outcomes, can be assessed consistently and effectively.

Methods

Research Design and Guiding Frameworks

This scoping review has been registered with the Open Science Framework [21] and developed in accordance with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines [22]. The completed PRISMA-P checklist is available in Multimedia Appendix 1.

Scoping reviews are broader in nature than systematic reviews, allowing researchers to examine the extent, range, and nature of research activity in a chosen area as opposed to finding the best evidence possible to a tightly defined research question [23]. A scoping review was considered the most appropriate method to address the research objectives due to the capacity to answer broad questions and summarize findings to identify gaps in the literature [2,24]. The scoping review applies Arksey and O'Malley's [25] five-stage process by (1) identifying the research questions, (2) identifying relevant studies, (3) selecting for studies in the final review, (4) charting the data, and (5) collating, summarizing, and reporting the results. Levac et al [26] expands on this framework to include a sixth optional consulting stage, which the research team deemed unnecessary for the purpose of this study.

Each stage of the scoping review was guided by the Population, Concept, and Context (PCC) framework to establish cohesion between the research questions, search strategy, and inclusion criteria (Textbox 1). The PCC framework is recommended for scoping reviews as a less restrictive alternative to the Population, Intervention, Comparator, and Outcome framework typically applied to systematic reviews [27]. Throughout this process, the purpose of the scoping review will be referred to, and critically discussed by the research team, to ensure that all decisions align with the research objectives and, ultimately, inform both research and practice.

Textbox 1. Developing a scoping review protocol with Population, Concept, and Context.

- P (Population): adults (aged 18 years or older)
- C (Concept): mental health, subjective well-being, emotional health, psychological health, restoration, coping, attention, mood, and indigenous well-being (including spirituality)
- C (Context): direct contact with parks and protected areas (spatial scope)

Search Strategy

A comprehensive search strategy was developed by a multidisciplinary team of 6 researchers in collaboration with an experienced university librarian. Following the recommendations of the Joanna Briggs Institute [28] for developing a search strategy, a limited preliminary search was conducted in Google Scholar using keywords related to the research objectives that included "mental health," "mental well-being," and "protected areas." This preliminary search produced 22 peer-reviewed papers that were deemed relevant to the review topic. The titles and abstracts of each paper were screened, along with the key terms used to describe the papers. This preliminary review allowed the research team to identify a robust set of key terms for the search strategy. The full literature index used to develop the search terms for this scoping review can be found in Multimedia Appendix 2. The protected areas terminology used in the literature search reflects the internationally recognized IUCN definition of protected areas and protected area categories, including specialized applications (ie, marine-protected areas). In addition, to inform the development of the search strategy, a search in the APA (American Psychological Association) Dictionary of Psychology identified relevant terms related to mental health, well-being, and subjective well-being.

Searches were conducted in 8 scholarly databases (PubMed, Web of Science, PsycINFO [via ProQuest], ERIC [via EBSCOhost], CINAHL [via EBSCOhost], GreenFILE [via EBSCOhost], OVID, and GEOBASE) known to contain journals focusing on human health and the natural environment. The search hedge contained terms related to domains of protected areas, nature engagement or exposure, and human mental health and well-being (Table 2). The search targets the intersection of environmental settings (protected area), with actions or events (nature engagement or exposure), and associated outcomes (mental health and well-being). Protected areas are recognized not only as spaces designated for conservation but also as venues for nature engagement. There is substantial evidence linking nature engagement with improved mental health and well-being, including benefits associated with protected areas [8,29-32]. The search terms were grouped by the Boolean operator "OR" to enhance the accuracy and relevance of results by accounting for as many concepts as possible and then combined using the Boolean operator "AND" to ensure that only relevant literature that contains all listed search concepts would be generated. The proximity operator "NEAR/20" was used to identify terms within 20 words of each other, regardless of their order. To

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promote transparency and replicability in future research, the full search strategy for each of the 8 databases is available in Multimedia Appendix 3.

All database searches were conducted on January 4, 2023. To limit the scope of the searches, the selected databases were filtered to include only peer-reviewed journal papers published in English. No date filters were used to limit results to ensure that all relevant studies were included. By excluding a date limiter, the search strategy is more likely to identify trends over time, for instance, when certain instruments were first used to measure mental health and well-being in a parks and protected areas context.

Table 2. Primary search hedge subsequently adapted by scholarly database.

Concept	Search terms
Protected area classification	"protected area*" OR "national park*" OR "conserv* area*" OR "provincial park*" OR "state park*" OR "wildlife area*" OR "wildlife sanctuar*" OR "tribal park*" OR "nature reserve*" OR "marine reserve*" OR "marine sanctuar*" OR "conserv* territor*" OR "protected landscape*" OR "protected seascape*" OR "habitat management area*" OR "species management area*" OR "natural area*" OR "wilderness" NEAR/20
Nature engagement	exposure OR access* OR time OR engag* OR visit* OR being OR activity OR exercis* OR experience* AND
Mental health and well-being	"well-being*" OR "psychological restoration" OR "psychological health" OR "restorative*" OR "life satisfaction" OR coping OR "stress hormone" OR cortisol OR "mental health" OR "subjective well*" OR cognit* OR stress* OR emotion* OR anxiety* OR anxious* OR depress* OR mood* OR "state of mind" OR "frame of mind" OR brain* OR mind* OR "self-esteem"

Study Selection Process

All studies identified by our search strategy were uploaded into the reference manager software Zotero (Corporation for Digital Scholarship) [33]. Study details were then imported into the scoping review software Covidence (Veritas Health Innovation Ltd) [34] where duplicates were removed. The screening (and data extraction process) was piloted by 2 independent reviewers (JB and RB). These reviewers screened a random sample of 20 sources to ensure relative consistency and understanding of the proposed inclusion or exclusion criteria.

All studies were screened by 2 independent reviewers (CER and RB) at 2 levels. At the first level, the title, keywords, and abstracts of each source were assessed against the following criteria listed in Textbox 2. Where both reviewers agreed based on explicit content that a criterion was not met, the study was removed. Where there was disagreement or a lack of explicit content to make a judgement, the study moved to level 2 for full text review using the same inclusion or exclusion criteria.

Textbox 2. Inclusion and exclusion criteria.

Inclusion criteria

- Relevant to the research questions.
- Measures mental health and well-being.
- Protected area context.
- Focuses on direct contact (being physically present) with protected areas.
- Peer-reviewed papers (accessible for retrieval).
- Focuses on adults (aged 18 years or older).
- Available in English.

Exclusion criteria

- Not relevant to the research questions.
- Measures only other forms of health and well-being (physical, social, etc).
- Nonprotected area context.
- Focuses on nondirect forms of contact with protected areas (virtual reality, photograph viewing, etc).
- Books, book chapters, or reviews: conference proceedings, dissertations, theses, systematic or scoping reviews, gray literature, news articles, social media content, opinion papers, and inaccessible peer-reviewed papers.
- Includes children (younger than 18 years).
- Not available in English.

At the level of full-text screening, the research team attempted to retrieve the full-text files of all potentially relevant studies through available university library services. If unable to retrieve the full text through the library services, a member of the

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research team contacted the corresponding authors to obtain a full-text file. Sources that remained unavailable were removed from the review. Once again, 2 independent reviewers (JB and RB) screened the full-text files applying the same inclusion or exclusion criteria that were used at level 1. Disagreements between reviewers at each stage of the selection process were addressed through discussion, involving a third reviewer to resolve conflicts as necessary.

Data Extraction and Analysis

Data will be extracted using Covidence by 2 independent reviewers (JB and RB) and compared for quality assurance to reduce bias. Any discrepancies that arise will be discussed and conflicts will be resolved by a third reviewer (CER). The proposed data extraction form (Table 3) will be used to identify and extract relevant variables that best address the research objectives. Extracted data from each paper will include descriptive information (eg, author names, title, and year of publication) and study methodology (eg, location, study design, sample, measurement instrument, and timing). Data pertaining to any quantitative or qualitative instruments used to measure mental health and well-being outcomes will also be extracted (eg, dimensions of well-being measured, instrument name, number of items, response scale, and end user engagement). Where a study includes more than 1 instrument of interest, each instrument will be recorded separately.

Table 3. Proposed data extraction template, indicating fields for which researchers will extract data with sample outputs.

Domains	Data extraction fields	Sample outputs
Characteristics of the study	• Reference • Study location • Protected area designation • Study design • Measurement form • Timing of measurement • Time spent in nature	• Full citation of listed study • Canada • National Park • Mixed methods, etc • Questionnaire, interview, etc • While in protected area • Two days, 1 week, etc
Details provided about the quantitative instruments in each study	• Dimensions of well-being • Instrument name • Source • Number of items • Scale size • Substantive validity • Structural validity • External validity	• Affect (eg, feeling, emotion, attachment, or mood) • Positive and Negative Affect Schedule (PANAS) • Author (year) • 20 items • 5-point scale • n=1 (100%) • n=1 (100%) • n=0 (0%)
Details provided about the qualitative instruments in each study	• Dimensions of well-being • Instrument name • Source • “End user” engagement • Multiple researchers involved in theming process • Member checks	• Affect (eg, feeling, emotion, attachment, or mood) • Semistructured interview • Author (year) • n=1 (100%) • n=0 (0%) • n=0 (0%)

Drawing on validity criteria from Simms [35], information that the researchers provide about the quantitative measurement instruments in the “Methods” section of each study will be assessed for 3 aspects of construct validity: substantive validity, structural validity, and external validity. Substantive validity is information about whether a measure is theoretically linked to the construct being studied. Structural validity is information about the degree to which the scores of a scale are an adequate indication of what the items measure, while external validity is information about whether the study findings can be generalized to other contexts [35,36]. Each study will be scored as either yes (1), the validity information was provided, or no (0), the validity information was not provided.

A quality appraisal will also be conducted on qualitative measurement instruments used in reviewed studies. This appraisal indicates whether multiple reviewers were involved in the theming process and checks were performed. Similar to the quantitative instruments, each criterion will be scored as yes (1) or no (0) based on whether studies provide evidence that these activities were incorporated into the methodology.

Results

Preliminary results of the study selection process are reported here using a PRISMA diagram (Figure 1) in accordance with PRISMA-ScR guidelines [28]. Searches in the 8 scholarly databases on January 4, 2023, yielded an initial 4742 studies (1 merged). From these initial studies, 2642 unique studies were identified for title and abstract screening, after the removal of 2100 duplicates. Through title and abstract screening, 180 studies were selected for full-text review, eliminating 2462 studies as they did not meet the previously outlined inclusion criteria. The full-text papers were sought for retrieval (7 were unavailable), resulting in 173 studies assessed for eligibility through the full-text review process. A total of 43 papers were selected for the final analysis. This pool is larger than those in other scoping reviews on adjacent topics [1], which affects the scope and time frame of the analysis. An updated search was conducted on December 11, 2024, yielding an additional 8 papers to be included in the analysis, for a total of 51 papers.

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The results of the final scoping review and submission of a manuscript for peer review are expected in April 2025.

Figure 1. PRISMA flow diagram of the study selection process showing results and exclusions.

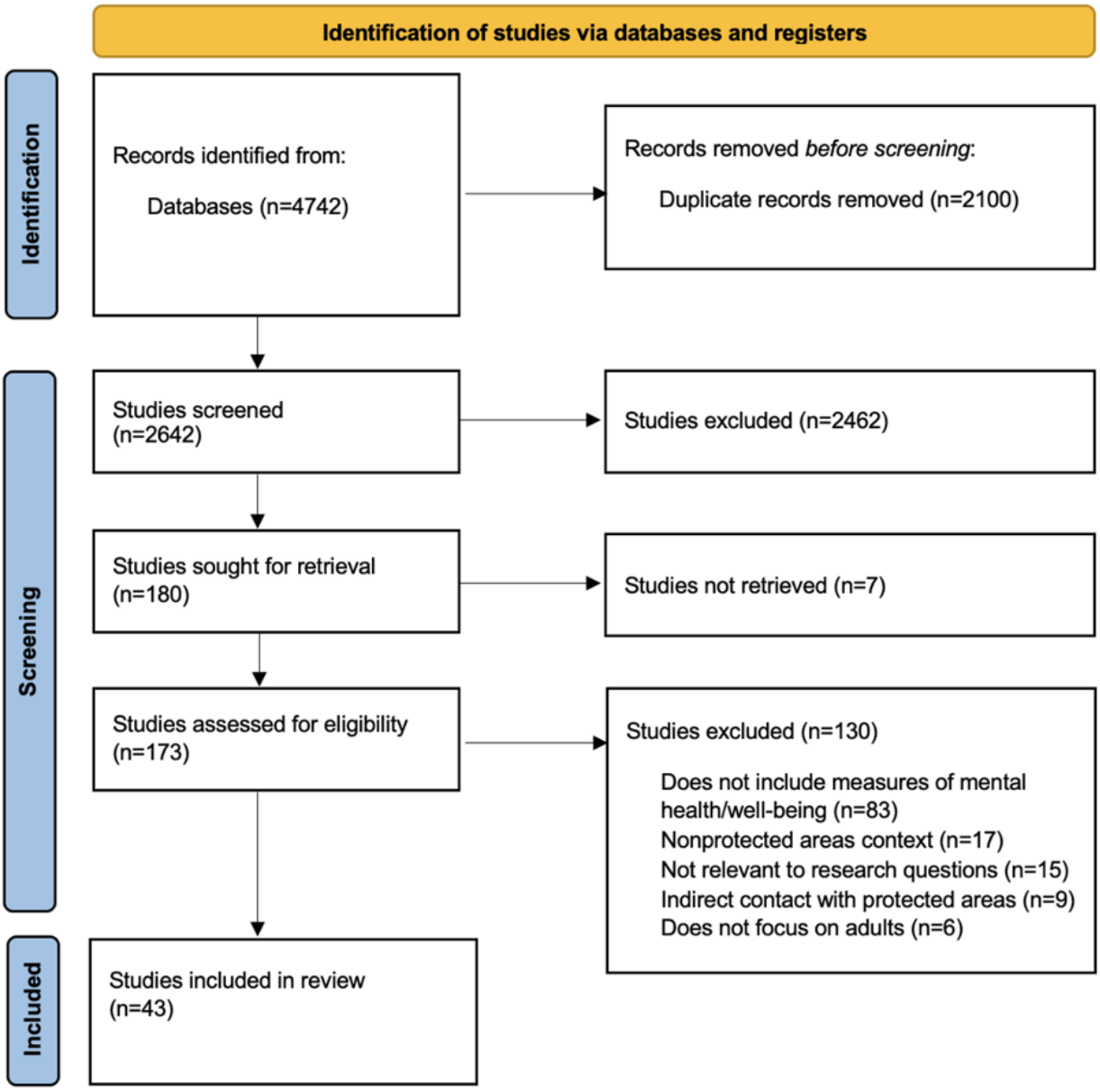

Discussion

Overview

This protocol details the methodology for a scoping review of the instruments that measure health and well-being linked to nature contact in protected areas, including their psychometric properties. Existing reviews have focused primarily on constructs related to mental health and well-being of adult populations associated with nature contact, although none specifically identify parks or protected areas. The volume of studies retrieved through the selection process suggests a robust evidence base regarding the health and well-being benefits of nature contact, with a likely diversity of measurement tools used. The review will identify, evaluate, and compare measures to provide a comprehensive overview of the quantitative and qualitative methodological instruments and tools used in research to date.

Strengths and Limitations

The scoping review is subject to limitations, in that it does not include gray and white literature, as well as studies that are not available in English. Given this, some relevant sources may be missed. Peer-reviewed papers not indexed in the searched databases may also be missed, but this limitation was deemed acceptable, given the need to manage the scope of the project. In addition, the extent to which the psychometric properties of an instrument can be evaluated is limited to the information provided within the included studies, which may be lacking descriptions of scale development. A deeper investigation would require looking elsewhere for additional resources, which is

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beyond the scope of this review. Nevertheless, this review will provide a strong evidence base on which to build future research.

Conclusions

To the authors' knowledge, this will be the first scoping review undertaken on measures used to assess mental health and well-being outcomes related to nature contact in a parks and protected areas context. Findings will aid in identifying the strengths and weaknesses of current measurement approaches to mental health and well-being outcomes of nature contact and may be used to guide future research on this topic. For example, nature prescriptions—a health care program comprising written directives by health professionals for visits to natural settings (either individually or in groups) relying heavily on parks and other forms of protected areas—now exist in at least 6 countries [37]. Canada has more than 12,000 health care professionals prescribing nature in parks, and China's national health strategy includes a commitment to build more than 1000 forest therapy facilities nationwide [38].

Given the unprecedented interest and growth in nature-based health care commitments, it will be necessary to identify and use methods that effectively consider contextual factors. Relevant factors can include demographics (age, gender, and ethnicity) and activities, durations, and environments prescribed. All of these factors must be documented to best ensure reliability and validity when evaluating the outcomes (or benefits) and efficacy of nature prescription programs. This proposed review is also very timely, given the projected growth in the global estate of protected areas as per the United Nations Convention on Biological Diversity Kunming-Montreal Global Biodiversity Framework (detailed in the "Introduction" section).

Adherence to the PRISMA-ScR guidelines will ensure that the findings of this scoping review are of high quality and replicable. Furthermore, by providing insights into the validity of the measurement instruments used, we provide an opportunity to strengthen the methodological quality of future studies. The outlined scoping review will have significant implications for researchers, policy makers, and practitioners working at the nature conservation and human health interface. This review will provide a means to both understand previous research and undertake innovative research initiatives related to mental health and well-being outcomes associated with nature contact in parks and protected areas.

Acknowledgments

Funding to support this work was provided by the Parks Canada Agency (GC1727) and the John McMurry Research Chair in Environmental Geography at Wilfrid Laurier University.

Data Availability

The datasets generated and/or analyzed during this study are available from the corresponding author on reasonable request. The datasets will be reported in the final scoping review manuscript.

Authors' Contributions

JB and RB drafted the first manuscript and contributed to data curation and analysis. CER, LL, MWG, and CJL revised the manuscript. CJL and CER also contributed to study conceptualization, funding acquisition, and supervision of the process. All authors contributed to study design and reviewed and edited the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis Protocols) 2015 checklist: recommended items to address in a systematic review protocol.
[DOC File , 58 KB - resprot_v14i1e63338_app1.doc]

Multimedia Appendix 2
Index of relevant articles that informed the development of the search strategy.
[DOC File , 50 KB - resprot_v14i1e63338_app2.doc]

Multimedia Appendix 3
Search strategy for 8 scholarly databases.
[DOC File , 36 KB - resprot_v14i1e63338_app3.doc]

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Abbreviations

APA: American Psychological Association
IUCN: International Union for Conservation of Nature
PCC: Population, Concept, and Context
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Experiences of Birth Attendants on Upward Obstetric Emergency Referrals in Low- and Middle-Income Countries: Protocol for a Scoping Review

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Abstract

Background: Every day, approximately 800 women die from pregnancy-related causes, alongside 2.6 million stillbirths and 2.8 million neonatal deaths annually. Inadequate referral by skilled birth attendants hinders timely access to necessary emergency obstetric care, challenging progress toward the maternal health Sustainable Development Goal (SDG) 3. The COVID-19 pandemic further disrupted care in low- and middle-income countries, forcing women to rely on traditional birth attendants, thereby affecting the referral system. It is crucial to understand the experiences of both skilled and traditional birth attendants regarding upward referrals in emergency obstetric care to identify barriers and facilitators within these systems in low- and middle-income countries.

Objective: This study aims to map existing evidence on the experiences of skilled and traditional birth attendants regarding upward referral systems in emergency obstetric care within low- and middle-income countries.

Methods: We will conduct a scoping review guided by the Joanna Briggs Institute's methodological framework. Studies will be included if they report on experiences with upward referral in obstetrical emergencies. We will consider studies published in English and French from 2016 to July 2024. The literature search will be conducted in databases including PubMed, EBSCOhost (Academic Search Complete and CINAHL with full text), Scopus, Web of Science, and Google Scholar. Identified citations will be managed using EndNote version 21 (Clarivate Analytics) and Rayyan. Two independent reviewers will screen eligible studies and resolve disagreements through discussion with a third reviewer. Data will be extracted using a validated form and analyzed through content analysis, with findings presented narratively. This protocol aligns with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines. The review will offer a comprehensive narrative of upward referral systems in obstetrical emergencies, focusing on transitions from traditional birth attendants to health care facilities and from lower to higher levels of health care.

Results: The preliminary search was completed in August 2024, and the database search will be conducted within the next 6 months. Findings will be disseminated through medical education conferences and publications.

Conclusions: This review contributes a comprehensive narrative of upward referral systems in obstetrical emergencies, aiming to enhance understanding and improve transitions from traditional birth attendants to health care facilities and between different health care levels. It could significantly impact maternal and neonatal care by identifying the referral experiences of both skilled and traditional birth attendants. The insights may inform interventions that integrate traditional birth attendants into health care

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systems, potentially reducing maternal and neonatal mortality. The results will guide future research aimed at developing a model to improve upward referrals for obstetric emergencies in sub-Saharan Africa.

Trial Registration: Open Science Framework 4HAVZ; https://osf.io/4havz

International Registered Report Identifier (IRRID): PRR1-10.2196/64886

(JMIR Res Protoc 2025;14:e64886) doi:10.2196/64886

KEYWORDS

referral systems; upward referral; obstetric emergencies; traditional birth attendants; skilled birth attendants; low- and middle-income countries; birth attendants; obstetric; middle-income countries; scoping review protocol; pregnancy; neonatal deaths; deaths; obstetric care; health care; medical education; mortality; Africa; pregnant; women's health

Introduction

Pregnancy and childbirth can pose risks to both the mother and fetus [1], sometimes leading to life-threatening situations known as obstetric emergencies [2]. In such cases, specialized care is necessary and provided through a well-established referral system [3], typically an upward referral, which refers to the process by which health care providers at lower levels of the system seek assistance from specialized or better-equipped providers [4]. This system ensures a smooth transfer of patients between different levels of health care facilities, optimizes service delivery, and reduces the risk of complications [5] that can lead to mortality. Skilled birth attendants (SBAs) and traditional birth attendants (TBAs) are crucial in this process [6,7]. Alongside pregnant women, these frontline caregivers navigate the complexities of pregnancy and childbirth, often requiring swift intervention to ensure positive maternal and neonatal outcomes. However, the varying experiences of different stakeholders can negatively impact the obstetric referral process [8].

Every day, approximately 800 maternal deaths occur due to pregnancy-related causes [8], alongside 2.6 million stillbirths and 2.8 million neonatal deaths annually [9]. The global community is committed to improving health care quality to address these alarming statistics [8]. In line with Sustainable Development Goal (SDG) 3, which aims to ensure healthy lives and well-being for all, specific targets highlight the urgency of action. SDG 3, Target 1, aims to reduce the global maternal mortality ratio (MMR) to below 70 maternal deaths per 100,000 live births by 2030. Target 2 seeks to prevent the deaths of newborns and children younger than 5 years to fewer than 25 deaths per 1000 live births and reduce neonatal mortality to 12 deaths per 1000 live births [9]. However, challenges remain, especially in low- and middle-income countries (LMICs) [8], which are defined as countries with a gross national income per capita ranging from US $1086 to US $4255 [10]. Despite the United Nations' recognition of the right to access the highest attainable standard of physical health, including the integration of referral systems [11], obstetric emergencies continue to pose significant threats to the health and lives of mothers and newborns worldwide [8]. TBAs historically played a pivotal role in maternal health care before the formalization of midwifery, but interest in their role has diminished over time [6,12]. Since the 2000s, the focus has shifted toward skilled birth attendance, sidelining TBAs in routine deliveries due to their ineffectiveness in reducing maternal mortality [7]. Nevertheless, a significant proportion of women in LMICs continue to seek TBA services, highlighting their enduring importance [13].

In contrast, SBAs are recognized as a key strategy for reducing high maternal mortality rates and are pivotal indicators of progress in maternal mortality reduction efforts [7]. Addressing high maternal mortality rates through referral systems requires a comprehensive understanding of the experiences of pregnant women, SBAs, and TBAs [7]. However, the current health care system operates in fragmented silos, hindering collaboration between different systems. This lack of integration undermines efforts to combat maternal mortality, despite some pregnant women preferring TBA practices over Western medicine [12].

Research based on the Three Delays Model by Thaddeus and Maine highlights challenges affecting the timeliness of obstetric referrals within health care facilities. These challenges occur at both patient and institutional levels, impacting the referral process [7]. They include difficulties in identifying and reaching health care facilities, often involving TBAs in the referral process, and obstacles in receiving adequate care, often linked to SBAs who are responsible for essential obstetric care during pregnancy [14].

To improve maternal health outcomes, it is crucial to explore and understand the experiences of women, TBAs, and SBAs. Understanding stakeholders' perceptions and navigation of the referral process can help identify gaps in service delivery, such as limited access to emergency obstetric care facilities or communication challenges between health care providers and pregnant women. Addressing these challenges can enhance the efficiency and effectiveness of obstetric referral systems, ensuring timely access to needed care for women.

Although previous studies and reviews have examined referrals in obstetric emergencies [1-3,5,8,14] since the adoption of the SDGs, none have focused on the experiences of upward obstetric emergency referrals in LMICs for both SBAs and TBAs, advocating for integrated referral systems that can save the lives of mothers and babies. Therefore, this review aims to provide a comprehensive overview of the current state of birth attendants' experiences with referral systems in obstetric emergencies in low-income countries.

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Methods

Study Design

Using the steps of the Joanna Briggs Institute (JBI) Scoping Review Methods [14], the researchers will examine and map the available literature related to the experiences of birth attendants with upward obstetric emergency referrals in LMICs. This scoping review protocol has been developed and registered with the Open Science Framework. The protocol will be implemented, and the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines will be used to guide the reporting.

Main Objective and Review Questions

The main objective of this review is to examine available evidence regarding birth attendants' experiences with upward referral systems in emergency obstetric care in sub-Saharan Africa (SSA) since the inception of the SDGs. Based on the objective of this review, the following research questions have been developed:

1. What are the publication characteristics of evidence on upward obstetric referrals?
2. What are the experiences of birth attendants regarding upward obstetric emergency referrals in LMICs?

The objective of this scoping review is part of the PhD study titled "Developing a Model to Enhance Effective Upward Referral of Obstetric Emergencies from Community Health Centres in Oliver Tambo District, Eastern Cape, South Africa: A Grounded Theory Inquiry."

Eligibility Criteria

The eligibility criteria for this review will be based on the JBI mnemonic for formulating systematic review questions, which describe the population, concept, and context of the study [14]. Textbox 1 summarizes the criteria.

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Textbox 1. Eligibility criteria.

Inclusion criterion:

- Population:
  - Skilled birth attendant: a professional health care worker who attends to pregnant women
  - Traditional birth attendant: an unskilled person who attends to pregnant women
- Concept:
  - Upward referral of women during labor and childbirth
  - Referral of women during pregnancy
  - Referral from traditional birth attendants to a health care facility
- Context:
  - Low- and middle-income countries
- Study designs:
  - Qualitative designs
  - Quantitative designs
  - Mixed methods designs
  - Conference proceedings abstracts
  - Gray literature
- Time period:
  - From January 2016 to July 2024

Exclusion criterion:

- Population:
  - Professional health care workers who do not attend to pregnant women
  - Unskilled individuals who do not attend to pregnant women
- Concept:
  - Referral of women outside the pregnancy and childbirth experience
  - Neonatal emergencies
- Context:
  - High-income countries
- Study designs:
  - Letters to the editor
  - Reviews
- Time period:
  - After July 2024

Population

The scoping review will include all relevant peer-reviewed and gray literature focused on upward referral systems in emergency obstetric care in LMICs. The population sample for the review will consist of birth attendants including SBAs and TBAs.

Concept

The concept will be guided by the following: Experiences, perceptions, and upward obstetric emergency referrals**.** According to the World Health Organization (WHO) [15], “referral can be defined as a process in which a health worker at one level of the health care system, having insufficient resources (eg, drugs, equipment, and skills) to manage a clinical

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condition, seeks the assistance of a better or differently resourced facility at the same or higher level to assist in or take over the management of the client's case." Furthermore, an obstetric emergency is defined as a complication or situation of a serious and often dangerous nature, developing suddenly and unexpectedly, and demanding immediate attention in order to save lives [8].

Context

The context of this review will focus on LMICs within emergency obstetric care settings.

Types of Sources

This scoping review will include both experimental and quasi-experimental study designs such as before-and-after studies and interrupted time-series studies. In addition, analytical observational studies, including prospective and retrospective cohort studies, case-control studies, and analytical cross-sectional studies, will be considered for inclusion. Descriptive observational study designs, including case series, individual case reports, and descriptive cross-sectional studies will also be included. Qualitative studies focusing on qualitative data, including, but not limited to, designs such as phenomenology, grounded theory, ethnography, qualitative description, action research, and feminist research, will be considered for inclusion. Furthermore, text and opinion papers will also be considered in this scoping review.

Search Strategy

An initial limited search in PubMed and ScienceDirect was undertaken to identify papers on the topic. The text words from the titles and abstracts of relevant papers, along with the index terms used to describe them, were used to develop a full search strategy (Table 1).

Table 1. Preliminary search strategy.

Date	Database	Search query	Results, n
January 29, 2024	PubMed	((“obstetric labor complications”[MeSH Terms] OR (“obstetric”[All Fields] AND “labor”[All Fields] AND “complications”[All Fields]) OR “obstetric labor complications”[All Fields]) AND (“referral and consultation”[MeSH Terms] OR (“referral”[All Fields] AND “consultation”[All Fields]) OR “referral and consultation”[All Fields] OR (“hospital”[All Fields] AND “referrals”[All Fields]) OR “hospital referrals”[All Fields]) AND (“developing countries”[MeSH Terms] OR (“developing”[All Fields] AND “countries”[All Fields]) OR “developing countries”[All Fields])) AND (2016/1/1:2024/1/31[pdat])	11
July 3, 2024	Science Direct	referral OR referral process OR referral pathway OR care pathway) AND obstetric labour complications AND Developing countries	712

Second, a systematic search will be conducted across 4 remaining electronic databases, namely EBSCOhost (including Academic Search Complete and CINAHL with full text), Scopus, Web of Science, and Google Scholar.

The search strategy, including all identified keywords and index terms, will be adapted for each included database or information source or both. Peer-reviewed journals will be reviewed for primary studies with a clear empirical base, using qualitative, quantitative, and mixed methods addressing the research question. Studies will be identified by searching literature from January 2016 to July 2024. In addition, papers will be searched through the “cited by” search feature as well as through citations included in the reference lists of included papers. The search terms will include referral system, LMICs, obstetric emergency, SBAs, and TBAs. Boolean operators (AND, OR) will be used to separate keywords, and Medical Subject Headings (MeSH) terms will be included during the search. The search syntax will be modified as needed. Reference lists of selected papers will also be searched for additional papers of interest. The services of an experienced subject librarian will be used to ensure that a robust search strategy is followed. The search strategy will be piloted to check the appropriateness of selected electronic databases and keywords. To compile all relevant evidence sources, identify, and remove duplicate records, the EndNote X21 reference manager will be used to import and manage eligible studies.

Source of Evidence Selection

Following the search, all identified citations will be collated and uploaded into EndNote version 21, and then imported into the Ryann systematic review app, where duplicates will be removed. Following a pilot test, titles and abstracts will be screened independently by FZJ and ELMK for assessment against the inclusion criteria for the review. Potentially relevant sources will then be retrieved in full. The full text of selected citations will be assessed independently by FZJ and ELMK to determine whether they meet the inclusion criteria. Reasons for the exclusion of sources of evidence in the full text that do not meet the inclusion criteria will be recorded and reported in the scoping review. Any disagreements between the reviewers at each stage of the selection process will be resolved by OBB. The results of the search and study inclusion process will be fully reported in the final scoping review and presented in a PRISMA-ScR flow diagram [16].

Data Extraction

Data will be extracted from the papers included in the scoping review by FZJ and ELMK independently, using a data extraction tool developed by the reviewers. The data extracted will be informed by the formulated review questions and will include—in addition to paper details such as authors, year of publication, design, and setting—specific details about the participants or population, reasons for referral, challenges experienced, support identified related to the referral, and further recommendations for upward obstetric emergency referrals.

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Before data extraction, the tool will be pilot-tested independently by FZJ and ELMK. The draft data extraction tool will be modified and revised as necessary during the process of extracting data from each included evidence source. Any modifications will be documented in the scoping review. OBB will afterwards check that no relevant information has been omitted. The information to be extracted using this tool is detailed below (Textbox 2).

Textbox 2. Initial data extraction tool.

Criteria:

- Authors or year of publication or both
- Research design
- Study setting
- Nature of population or sample
- Reasons for referral
- Challenges experienced related to the referral
- Support experience related to the referral
- Recommendations related to the referral

Data Analysis

Knowledge and experiences of skilled and traditional BAs regarding referral in obstetric emergencies to combat maternal and child mortality rates will be extracted from this review. The data will be analyzed to develop a comprehensive model for effective referral in resource-constrained settings.

Data summarization and reporting will adopt a fundamental descriptive approach, using content analysis [17]. A narrative approach will present the findings from the included studies, using thematic content analysis to describe the themes that are relevant to experiences with referral systems in obstetric emergencies in low- and middle-income countries. In addition, any other emerging themes will be reported.

Ethical Considerations

This study was approved by the university's ethics committee for BioMedical Research (ethics approval BREC/00006633/2024).

Results

As of August 2024, the preliminary search was completed, and the database search will be conducted within the next 6 months. Findings will be disseminated through medical education conferences and publications.

Discussion

Principal Findings

It is anticipated that this review will map out the different experiences of birth attendants regarding upward referral in obstetric emergencies. It is also anticipated that the experiences of SBAs are different from those of TBAs. These insights will enrich the body of knowledge related to referrals in LMICs. The findings have the potential to aid in improving care for mothers and newborns in several ways. First, the study will synthesize information on referral systems in obstetric emergencies within resource-constrained health care settings. Second, it will identify referrals from both SBAs and TBAs to health care facilities. This information could support the development of interventions that advocate for including TBAs in health care systems to reduce maternal and neonatal deaths. Third, the review's findings will inform a future study aimed at developing a model to enhance effective upward referral of women with obstetric emergencies during labor in an SSA country.

Comparatively, researchers [1,2] have highlighted logistical challenges in emergency referrals, concentrating on gaps in primary care systems and delays in reaching tertiary facilities. This study, on the other hand, provides a more comprehensive understanding of the systemic and interpersonal dynamics influencing emergency referrals in LMICs. The dual focus on both TBAs and SBAs is unique, as it addresses an unexplored area in studies such as [7], which observed that traditional and formal care providers act as fragmented health structures, preventing collaboration. However, in LMICs, a significant proportion of women continue to seek TBA services, highlighting their enduring importance [13]. Therefore, the insights generated could serve as a foundation and guidance for future research aimed at developing a model to improve upward referrals for obstetric emergencies in SSA.

Policy and Practical Implications

The scoping review aims to provide insights into the experiences of both SBAs and TBAs regarding upward referral systems in emergency obstetric care. It will be instrumental in identifying key gaps and challenges in the referral process.

By linking the anticipated results to the SDGs, particularly SDG 3 on good health and well-being, the review highlights the critical role of improving referral systems to reduce maternal and neonatal mortality. The review will inform policy makers about effective strategies to enhance referral processes, ensure timely access to emergency obstetric care, and better integrate TBAs into the health care system.

Health care providers are expected to benefit from the insights this scoping review will provide regarding training needs for

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effective referrals and collaboration between SBAs and TBAs. This will improve referral practices and ensure smoother transitions of care.

Furthermore, the review will emphasize the importance of community involvement in supporting and understanding the referral process. Recommendations for engaging communities through educational campaigns and support systems may strengthen the overall referral network.

Potential Challenges and Limitations

The review includes only studies published in English and French, which may exclude relevant research in other languages and limit the comprehensiveness of the findings. Furthermore, it focuses on studies published and indexed in selected databases, potentially overlooking unpublished research.

Conclusion

This review contributes a comprehensive narrative on upward referral systems in obstetrical emergencies, aiming to enhance understanding and improve transitions from TBAs to health care facilities and between different health care levels. It could significantly impact maternal and neonatal care by describing the referral experiences of skilled TBAs in obstetric emergencies. The insights may inform interventions that integrate TBAs into health care systems, potentially reducing maternal and neonatal mortality. The results will guide future research aimed at developing a model to improve upward referrals for obstetric emergencies in an SSA country.

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Data Availability

All data generated and analyzed will be included in the published scoping review article and will be available upon request.

Conflicts of Interest

None declared.

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Abbreviations

JBI: Joanna Briggs Institute
LMIC: low- and middle-income countries
MeSH: Medical Subject Headings
MMR: maternal mortality ratio
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
SBA: skilled birth attendant
SDG: Sustainable Development Goal
SSA: sub-Saharan Africa
TBA: traditional birth attendant
WHO: World Health Organization

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Protocol

Health Care Social Robots in the Age of Generative AI: Protocol for a Scoping Review

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Abstract

Background: Social robots (SR), sensorimotor machines designed to interact with humans, can help to respond to the increasing demands in the health care sector. To ensure the successful use of this technology, acceptance is paramount. Generative artificial intelligence (AI) is an emerging technology with the potential to enhance the functionality of SR and promote user acceptance by further improving human-robot interaction.

Objective: We present a protocol for a scoping review of the literature on the implementation of generative AI in SR in the health care sector. The aim of this scoping review is to map out the intersection of SR and generative AI in the health care sector; to explore if generative AI is applied in SR in the health care sector; to outline which models of generative AI and SR are used for these implementations; and to explore whether user acceptance is reported as an outcome following these implementations. This scoping review supports future research by providing an overview of the state of connectedness of 2 emerging technologies and by mapping out research gaps.

Methods: We follow the methodological framework developed by Arksey and O'Malley and the recommendations by the Joanna Briggs Institute. Our protocol was drafted using the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for Scoping Reviews). We will conduct a systematic literature search of the online databases MEDLINE, Embase, CINAHL (Cumulative Index to Nursing and Allied Health Literature), Web of Science, and IEEE Xplore, aiming to retrieve relevant data items via tabular data charting from references meeting specific inclusion criteria which are studies published from 2010 onwards, set in the health care sector, focusing on SR with physical bodies and implemented generative AI. There are no restrictions on study types. Results will be categorized, clustered, and summarized using tables, graphs, visual representations, and narratives.

Results: After conducting a preliminary search and deduplication in the second quarter of 2024, we retrieved 3176 preliminary results. This scoping review will be supplemented with the next methodological steps, including retrieving the results in a reference management tool as well as screening titles, abstracts, and full text regarding specific inclusion criteria. The completion of these steps is scheduled for the second quarter of 2025. Limitations based on the heterogeneity of the included studies and the general breadth of a scoping review compared to a systematic review are to be expected. To reduce bias, we adopted a system of dual reviews and thorough documentation of the study selection.

Conclusions: The conducted preliminary search implies that there are a sufficient number of heterogeneous references to complete this scoping review. To our knowledge, this is the first scoping review on generative AI in health care SR.

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KEYWORDS

robotics; social robots; artificial intelligence; generative AI; human-robot interaction; health care sector; PRISMA

Introduction

Background

Social robots (SR) are interactive robots designed to engage with humans in a social or collaborative manner, often mimicking human behaviors, communication, and social cues [1-3]. SR are already being used in geriatric care, rehabilitation, and the care of people with cognitive disabilities [4]. Since much progress has been made regarding the development of SR in recent years [5], it is to be expected that they will find widespread use in the health care sector in the next few years [6]. Between 2005 and 2010, 1300 units of "Paro," an artificial seal for therapy of patients with dementia [7], were sold in Japan [8]; as of 2013, "Paro" was adopted in 80% of local care institutes in Denmark [9]. These examples illustrate that SR could be a way of responding to the needs of people in need of care and of filling the gap between the supply and demand of health care professionals. Other examples for SR that can be applied in the health care sector are "Cruzr" [10], a service robot [7,10]; "NAO" [11], a household robot [7,11]; or "Lio" for older adult care [7,12].

For SR to be effectively integrated and successful, their acceptance is paramount. Simply introducing these innovative robots is not sufficient if individuals are hesitant or unwilling to interact with them [13]. Lum [14] emphasizes that the fundamental challenge for the practical application of SR is the willingness of people to accept them in their everyday lives. In democratically constituted, liberal societies, acceptance is deemed a factor for a successful take-up of a technology by the population [15]. While positive effects such as assistance with everyday tasks [16,17], maintaining of individual autonomy [17-19], or increase of happiness [18] are associated with the use of SR in older adult care, their acceptance is noted to vary [6], with acceptance toward the SR depending on the area of their application [15]. With the ongoing development and practical use of SR, the question of their acceptance as a possible component of people's everyday routines moves further into focus [6,14].

Dialog management is positioned as one of the main goals of human-robot interaction (HRI) [20], increasing user satisfaction and task efficiency [20,21]. In this context, generative artificial intelligence (AI) like OpenAI's ChatGPT [22], being extensively trained on conversational dialog [23,24], could be used to translate instructions given in natural language into actions executable by a SR [25,26], improving multiparty interactions [21]. Since late 2022, there has been a significant growth in the field of generative AI [27], a technology which will have an impact on all industry sectors with the potential to change how people work and to increase productivity [28]. We believe that by implementing generative AI in SR, usability and user acceptance, key elements of HRI, could be vastly increased. Speech, gesture, mimic recognition, robot customizability, intuitive operation, and interaction among others, are aspects we believe to highly benefit from the potential of generative AI. We expect this emerging technology to largely influence the use and functionality of SR, facilitating their widespread use in the health care sector. Health care professionals, patients, and other persons in need of care could benefit from such advanced robots fulfilling a wide array of valuable tasks. With this scoping review, the authors intend to map out if and how these emerging technologies are interconnected.

Definitions and Terms

Social Robots

Sarrica et al [29] point out that there is a wide array of various definitions for SR, which are partially built on existing definitions or introduce new concepts. For example, Bendel [7] refers to SR as sensorimotor machines explicitly designed to be used in the immediate vicinity of and for direct interaction with humans. A machine is defined as an assemblage of parts that transmit forces, motion, and energy to one another in a predetermined manner [30], consequently implying the necessity of a physical body as well as the presence of sensors and motors for interaction with and perception of the environment by a robot in a narrow sense. While Bendel [7] presents the option to broaden the concept of robots and include software robots like chatbots within SR by relativizing the sensorimotor and physical components, scientific definitions overall tend to describe SR as semiautonomous or autonomous physical bodies, with "machines" and "physical" being some of the main dimensions underlying different definitions [29]. As Kuipers et al [31] point out, the creation of robots with a human-like competence of real-world manipulation is a major challenge of research, since the ability to physically change the surrounding world is of utmost relevance to humans [32]. In the context of care, the burden of physical work is high and further increasing [33,34]. Against this background, we consider only SR with a physical body for this review to ensure a high level of comparability of the results.

Generative AI

Generative AI is a type of AI able to generate content [28]. It is based on different kinds of underlying models, for example, generative adversarial networks, encoder-decoder networks, neural networks, or transformers [27]. Subtypes of generative AI are large language models, deep neural networks which are pretrained with millions of parameters on large amounts of unlabeled text [35]. This training enables them to learn the relationship between words or portions of words [28]. Unlike decision tree models, which use algorithms to create predictions or rules based on incoming data, generative AI uses specific algorithms trained on large amounts of data to generate new, previously unseen content [27]. This generated content can be manifold, for example, human-like texts, images, and music [27]. Compared to a conversational AI, which can provide users with human-like responses in a conversation, generative AI can not only generate such responses but generate the content of

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these responses as well [36]. These responses can even surpass the original programming of the generative AI [36]. Since late 2022, the field of generative AI has grown significantly [27,37]; pretrained and then task-specifically modified large language models became the dominant pattern in the field of natural language processing [38-44], with examples being Google's BERT (Bidirectional Encoder Representations from Transformers) [38] and OpenAI's GPT-3 [39]. Generative AI gained increasing public focus since the release of ChatGPT in late 2022, while the concept of generative models of AI began to be recognized since the 2010s [27]. One of the goals in the development of ChatGPT was to facilitate a better reciprocal understanding of the communication between human users and robots [45].

Acceptance

Acceptance, acceptability, adoption as well as other related terms in the context of technology acceptance are often used interchangeably [46], describing the same overall concept. Acceptability is described as the user's willingness toward the use of a system [47]. User acceptance can be defined as "the demonstrable willingness within a user group to employ (information technology) for the tasks it is designed to support" [48]. The aforementioned terms are occasionally used exchangeable with other concepts of human-computer interaction like user satisfaction [49]. User acceptance can be specified as the users' intention to use a future technology, their willingness to integrate it into their daily life [50], and the prospective judgment of this new technology [51]. Beetz et al [15], specify acceptance of assistive robotics as being based on trust. Human-related aspects such as cultural background, living conditions, or expectations toward the functionality of a robot as well as criteria of the robot itself such as design [6,32], language capability, or range of functions are relevant for the acceptance of an SR [6]; specifically, an anthropomorphic approach on the design of SR is deemed to be of high relevance [14]. In the literature, the terms facilitators and barriers are commonly used to describe factors of technology uptake in general, for example, facilitators of the implementation of SR can be mobility aspects [52], being physically accessible [52,53], or offering an economic advantage [54]. Davis [55] developed the Technology Acceptance Model to describe why a person does or does not use a technology. A person's attitude toward using a technology depends on the technology's perceived usefulness and its perceived ease of use, the behavioral intention to use a technology depends on the aforementioned attitude toward using and the perceived usefulness directly [55]. Thus, this model implicates a complex relationship between the user's subjective ability to accept, and the quality of a technology of being acceptable. Based on a revision of this model [56], Heerink et al [57], proposed the Almere Model for technology acceptance of SR by older adult users, examining 12 areas related to HRI: anxiety, attitude toward technology, facilitating conditions, intention to use, perceived adaptiveness, perceived enjoyment, perceived ease of use, perceived sociability, perceived usefulness, social influence, social presence, and trust [57]. The Almere Model integrates the multi-dimensionality of acceptance formation by relating robot-specific factors to their subjective perception by humans.

Literature Gap

To address the intersection of SR and generative AI, we conducted a preliminary search for systematic reviews, scoping reviews, or protocols for reviews in the online databases MEDLINE, Embase, CINAHL, Web of Science, and IEEE Xplore based on our search strategy presented in stage 2. For example, some of these reviews focus on AI in the health care sector in general [58-101]; other reviews focus on social or surgical robots in the health care sector in general [102-118]; a few highlight the use of AI in surgical robots [119,120] or the use of chatbots [80,88,121] in the health care sector; Clabaugh and Matarić [122] conducted a systematic review on enablers of autonomy of SR; Huang et al [123], conducted a systematic review on antecedents and consequences of the application of intelligent SR; Hung et al [124], published a protocol for a systematic review on the facilitators and barriers to the use of robots equipped with AI in older adult care; Lee et al [125] conducted a systematic review and meta-analysis on the effect of AI-equipped SR on cognitive function.

However, none of these reviews focus specifically on the implementation of generative AI in SR in the health care sector and the interconnectedness of these 2 emerging technologies.

Aim

The aim of this scoping review is to map out if and how 2 emerging technologies: generative AI and SR are interconnected. This scoping review is based on an overview of relevant publications that have considered the implementation of generative AI in physical health care SR. We intend to explore whether generative AI is applied in SR in the health care sector, what models of generative AI and SR are used for this implementation, in which setting these implementations take place, and if user acceptance is among the reported outcomes following these implementations.

Methods

Study Design

In this review, we follow the methodological framework developed by Arksey and O'Malley [126] and the recommendations by the Joanna Briggs Institute [127]. We apply the following stages here: (1) identifying the research question, (2) identifying relevant studies, (3) selection of studies, (4) data charting, and (5) collating, summarizing, and reporting the results. To report our results, we use the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews), attached in (Multimedia Appendix 1), and, where applicable, PRISMA-P (Preferred Rpeorting Items for Systematic Reviews and Meta-Analyses Protocols; Multimedia Appendix 2).

Research Team

The research team conducting this review consists of a medical student researcher interested in the fields of medical sociology and medical data science, PL; a researcher with a background in health economics, CG; a professor for digitalization working in the field of digital transformation and applications, DF; the head of information literacy education and systematic review,

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medical library, CD; a professor for medical data science and an expert on human-computer interaction, FB; and a senior researcher working in the field of medical informatics and health care organization and innovation, TS.

Stage 1: Identifying the Research Question

The main research questions of this protocol are as follows: (1) Are generative AI models implemented in SR in the health care sector? The following subquestions are posed: (2) Which models of generative AI and SR are used for these implementations? (3) What are the settings of these implementations? (4) Has the acceptance of SR been reported as an outcome following these implementations?

Answering these questions can support future research by mapping out potential research gaps and providing an overview of the state of connectedness of 2 emerging technologies, SR, and generative AI.

Stage 2: Identifying Relevant Studies

To identify relevant studies, a systematic literature search of the electronic databases MEDLINE (via Ovid; 2010 onwards), Embase (via Ovid; 2010 onwards), CINAHL (via EBSCOhost; 2010 onwards), Web of Science (2010 onwards), and IEEE Xplore (2010 onwards) will be conducted. The selection of these databases follows the recommendation of a member of the research team (CD), an information specialist of the medical library of Charité, covering a broad and interdisciplinary field including computer science, social and behavioral sciences, and medicine. To construct our search queries, we followed the guidelines of the Peer Review of Electronic Search Strategies (PRESS) [128]. Textbox 1 presents the main search terms underlying these search queries. An initial search query was built with Ovid for MEDLINE. The online tool Polyglot Search Translator [129] is used to adapt this search query for the databases Embase, CINAHL, and Web of Science. For IEEE Xplore, the initial search query is adapted manually to account for the different syntax and limit of search terms per search clause. Duplicates will be deleted by using the online tool Systematic Review Accelerator [130] after the corresponding results have been documented and managed using the reference managing software EndNote (Clarivate).

The search terms are based on the expertise of the research team, an internal focus group, and an additional use of the AI chatbot, ChatGPT (OpenAI) to detect further relevant synonyms and terms. These terms are combined using the appropriate Boolean operators AND Specialty OR to generate the search queries. The exact search queries for MEDLINE, Embase, CINAHL, Web of Science, and IEEE Xplore are referenced in (Multimedia Appendix 3).

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Textbox 1. Overview of the main search terms.

Social robot

- Social robot
- Interactive robot
- Companion robot
- Humanoid robot
- Personal robot
- Emotional robot
- Assistive robot
- Service robot
- Communicative robot
- Socially assistive robot
- Socially interactive robot
- Care robot
- Household robot
- Pleasure robot
- Sex robot
- Anthropomorphic robot
- Autonomous robot
- Therapy robot
- Entertainment robot
- Robotics

Generative AI

- Generative AI
- Generative artificial intelligence
- Artificial intelligence
- AI
- Large Language Model
- LLM
- Foundation Model
- Deep Neural Network
- Machine Learning
- ChatGPT
- OpenAI
- YouChat
- Stable Diffusion
- DALL-E
- Runway
- Midjourney
- MusicLM
- VALL-E
- ElevenLabs
- Codex

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- AlphaCode
- GitHub Copilot
- Emotion recognition
- Speech recognition
- Gesture recognition
- Facial expression analysis

Health care sector

- Health care
- Health care Sector
- Health service
- HCS
- Medical Sector
- Hospital
- Clinic
- Nursing home
- Rehabilitation
- Primary care
- Speciality care
- Mental health
- Public health
- Long-term care facility
- Physician
- Nursing
- Allied health professions
- Medical practitioner
- Care
- Medical device
- Health informatics
- Patient
- Person in need of care
- Invalid
- Convalescent
- Sick person
- Elderly
- Elderly person
- Elderly care
- Nursing home
- Nursing personnel
- Aged

Stage 3: Study Selection

The PCC (Population, Concept, and Context) Framework was used as a basis for the inclusion criteria. The population is SR with physical bodies; the concept is the implementation of generative AI in SR; and the context is the health care sector or SR intended for the health care sector. The framework underlying this scoping review is presented in Textbox 2,

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inclusion and exclusion criteria to be used in this scoping review are highlighted in Textboxes 3 and 4.

The screening process is divided into 2 subsequent steps: an initial title and abstract screening, and a secondary full-text screening. At least 2 reviewers (PL and TS) will conduct the primary title and abstract screening independently, using the eligibility criteria. Then, the secondary full-text screening of all references included in the title and abstract screening will be conducted by at least 2 members of the research team (PL and TS) independently, using the same eligibility criteria. In the secondary screening, disagreements will be resolved by discussion and consensus of 3 members of the research team (PL, TS, and CG). Any restrictions regarding study design, time frame, or language are not intended. A PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram will be used to show a graphic representation of the process of study selection.

Textbox 2. Overview of the Population, Concept, and Context framework of this review.

- Population: social robots (SR) with physical bodies.
- Concept: implementation of generative artificial intelligence in SR.
- Context: in the health care sector or SR intended for the health care sector.

Textbox 3. Overview of inclusion criteria.

- Studies focusing on social robots (SR) with physical bodies are considered.
- Generative artificial intelligence must be implemented in these SR.
- Studies set in the health care sector are considered, or studies focusing on SR intended to be used in the health care sector.
- Studies published since 2010 are considered, as the concept of generative models of artificial intelligence began to be recognized in the 2010s [27].
- No restrictions concerning study design (ie, reviews or case studies are included), time frame, or language

Textbox 4. Overview of exclusion criteria.

- Social robots without physical bodies are excluded (ie, chatbots or artificial intelligence avatars).
- Surgical robots are excluded.
- Studies published before 2010 are not considered.
- Studies focusing on social robots outside of or not intended for the health care sector are not considered.

Stage 4: Data Charting

The variables that are to be extracted are based on recommendations by 2 members of the research team (DF and FB). We extract data describing the specifications of the applied SR and model of the implemented generative AI, the characteristics of this Implementation and HRI, as well as general information regarding for example, but not limited to, studies' populations, reported outcomes, or country of origin. Textbox 5 conceptualizes the items we aim to extract from the included studies.

The authors will create preliminary data charting forms in Microsoft Excel, which will undergo independent pilot testing using a sample of publications (for example 10 articles). After achieving consistent results and obtaining approval from at least 2 researchers of the team (DF, FB), data charting will be conducted by one team member (PL) for all included full-text articles. A total of 2 other team members (CG and TS) will verify the charted data to ensure the inclusion of all relevant information. A draft of a data charting form is attached in (Multimedia Appendix 4). A team member (CD) will provide support for this process.

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Textbox 5. Overview of data extraction items.

Items and description

- Author and year: name of first author, year of publication.
- Study type: What type of study was conducted (eg, randomized controlled trial, cohort study, case-control study, qualitative study, etc)?
- Study design: framework, methods, and procedures applied to answer the research question.
- Origin: where the study was conducted.
- Population and sample size: which and how many participants were in the study.
- Aim: purpose of the study.
- Make of social robot (SR): model and developer of SR.
- Shape of SR: traits of the physical body of SR (eg, number of appendices, anthropomorphic or animal-like shape).
- Mobility of SR: ability of SR to move.
- Autonomy of SR: whether the SR is autonomous or controlled remotely.
- Interface of SR: means of communication or interaction with SR (eg, speech, display, touchscreen, gestures, facial expressions, emotion recognition, remote control, haptic, etc).
- Human-robot interaction: specific traits of interaction with SR (eg, duration, tasks, and intention).
- Model of generative artificial intelligence (AI): specific model of implemented generative AI.
- Use of generative AI: what the implemented generative AI is used for.
- Element of health care sector: sub-sector of the health care sector in which SR was applied (eg, inpatient or outpatient sector, nursing home, day care, home care, etc).
- Outcome acceptance: if user acceptance has been reported as a study outcome.
- Acceptance measurement: tools or models used to measure user acceptance.

Stage 5: Collating, Summarizing, and Reporting the Results

The studies will be collated, categorized, summarized, and reported based on the data items extracted in the former step, for example, the type of SR, the context of HRI, the use of generative AI, the country of origin, derived acceptance-promoting aspects, etc. To synthesize the results, we will cluster similar publications by classifying the collected data items. The findings of this synthesis will be presented through a series of adequate tables, graphs, and visual representations, as well as corresponding narrative summaries. While we intend to use the main categories of data items from the former steps, we anticipate and remain open to discovering further categories, as well as expanding or modifying existing ones, as this review progresses. A team member (CD) will provide guidance for this stage.

Results

A preliminary literature search was conducted in the second quarter of 2024 to screen relevant existing literature as well as to verify no other scoping reviews of the same focus have been published. This preliminary search of the electronic databases MEDLINE, Embase, CINAHL, Web of Science, and IEEE Xplore was based on the search strategy presented in Stage 2 of this protocol. In this preliminary search, we retrieved a total of 4112 references, of which 3176 remained after deduplication. Figure 1 presents a flow diagram of our preliminary search for this protocol, and of the subsequent scoping review. Following these preliminary results, we deem the literature sufficient to conduct this scoping review. To our knowledge, this is the first scoping review on the implementation of generative AI in Health care SR. We intend to complete the following methodological steps of the scoping review by the second quarter of 2025.

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Figure 1. Flow diagram of this protocol's preliminary search and subsequent scoping review.

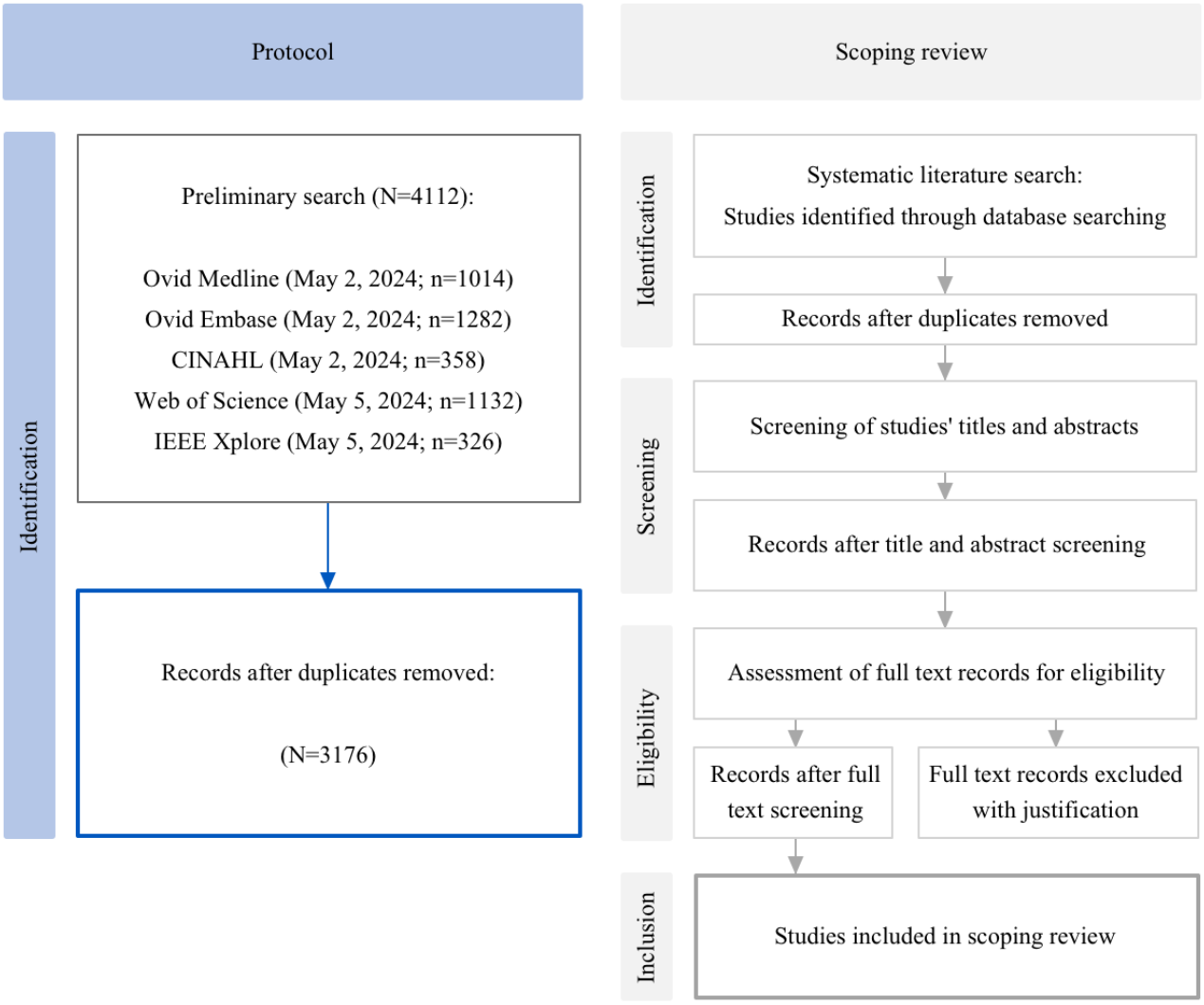

Discussion

Principal Findings

The authors anticipated to retrieve relevant studies, gaining an overview of scientific literature to decide if it is feasible to conduct a scoping review on this topic. We anticipated the results to be sufficient in number, since generative AI and SR are emerging technologies of high relevance. The preliminary search provided 3176 results after deduplication. Based on these preliminary results, we anticipate that there is sufficient literature to conduct this scoping review. To our knowledge, no other reviews of the same scope have been published.

Limitations

Based on the methodology of this protocol, some limitations can be derived. The authors aim to synthesize results from publications that are expected to have widely heterogeneous populations, origins, outcomes, and overall methodologies. For example, different age groups or cultural backgrounds of participants limit our ability to generalize the findings of this review. In general, scoping reviews tend to be inherently limited by focusing on breadth rather than depth [131]. Also, the selection of databases, search terms, inclusion criteria, and studies based on the research team's experience might pose a source of possible bias. To reduce overall bias, we adopted a system of dual reviews, discussing conflicting results with senior researchers of the team, and thoroughly documenting the process of study selection.

Conclusions

This scoping review on the interconnectedness of 2 emerging technologies will outline the implementation of generative AI in health care SR, and to map out and categorize which models of generative AI and SR are used in these implementations. Based on relevant literature and the expertise of the research team, it is the authors' intention to answer the primary and secondary research questions: (1) Are generative AI models implemented in SR in the health care sector? (2) Which models of generative AI and SR are used for these implementations? (3) What are the settings of these implementations? (4) Has the acceptance of SR been reported as an outcome following these implementations? While there are previous reviews on either AI or SR in general in the health care sector, there is merely a scant number of reviews on AI-equipped social or surgical robots, and there are, to our knowledge, no other reviews of the same scope as our review. Conducting this scoping review supports future research by mapping out further research gaps

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and by providing an overview of the state of the connectedness of SR and generative AI, a relatively new technology with vast potential.

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We used the generative AI tool ChatGPT by OpenAI as stated in Stage 2 to detect further search terms, which then have been revised by the research team.

Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-ScR checklist.
[PDF File (Adobe PDF File), 317 KB - resprot_v14i1e63017_app1.pdf]

Multimedia Appendix 2
PRISMA-P checklist.
[DOCX File , 33 KB - resprot_v14i1e63017_app2.docx]

Multimedia Appendix 3
Search queries for MEDLINE, Embase, CINAHL, Web of Science, and IEEE Xplore.
[DOCX File , 22 KB - resprot_v14i1e63017_app3.docx]

Multimedia Appendix 4
Draft of a data charting form.
[XLSX File (Microsoft Excel File), 7 KB - resprot_v14i1e63017_app4.xlsx]

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Abbreviations

AI: artificial intelligence
BERT: Bidirectional Encoder Representations from Transformers
HRI: human-robot interaction
PRESS: Peer Review of Electronic Search Strategies
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
SR: social robot

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Protocol

Patient-Related Metadata Reported in Sequencing Studies of SARS-CoV-2: Protocol for a Scoping Review and Bibliometric Analysis

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Abstract

Background: There has been an unprecedented effort to sequence the SARS-CoV-2 virus and examine its molecular evolution. This has been facilitated by the availability of publicly accessible databases, such as the GISAID (Global Initiative on Sharing All Influenza Data) and GenBank, which collectively hold millions of SARS-CoV-2 sequence records. Genomic epidemiology, however, seeks to go beyond phylogenetic (the study of evolutionary relationships among biological entities) analysis by linking genetic information to patient characteristics and disease outcomes, enabling a comprehensive understanding of transmission dynamics and disease impact. While these repositories include fields reflecting patient-related metadata for a given sequence, the inclusion of these demographic and clinical details is scarce. The current understanding of patient-related metadata in published sequencing studies and its quality remains unexplored.

Objective: Our review aims to quantitatively assess the extent and quality of patient-reported metadata in papers reporting original whole genome sequencing of the SARS-CoV-2 virus and analyze publication patterns using bibliometric analysis. Finally, we will evaluate the efficacy and reliability of a machine learning classifier in accurately identifying relevant papers for inclusion in the scoping review.

Methods: The National Institutes of Health's LitCovid collection will be used for the automated classification of papers reporting having deposited SARS-CoV-2 sequences in public repositories, while an independent search will be conducted in MEDLINE and PubMed Central for validation. Data extraction will be conducted using Covidence (Veritas Health Innovation Ltd). The extracted data will be synthesized and summarized to quantify the availability of patient metadata in the published literature of SARS-CoV-2 sequencing studies. For the bibliometric analysis, relevant data points, such as author affiliations, citation metrics, author keywords, and Medical Subject Headings terms will be extracted.

Results: This study is expected to be completed in early 2025. Our classification model has been developed and we have classified publications in LitCovid published through February 2023. As of September 2024, papers through August 2024 are being prepared for processing. Screening is underway for validated papers from the classifier. Direct literature searches and screening of the results began in October 2024. We will summarize and narratively describe our findings using tables, graphs, and charts where applicable.

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Conclusions: This scoping review will report findings on the extent and types of patient-related metadata reported in genomic viral sequencing studies of SARS-CoV-2, identify gaps in the reporting of patient metadata, and make recommendations for improving the quality and consistency of reporting in this area. The bibliometric analysis will uncover trends and patterns in the reporting of patient-related metadata, including differences in reporting based on study types or geographic regions. The insights gained from this study may help improve the quality and consistency of reporting patient metadata, enhancing the utility of sequence metadata and facilitating future research on infectious diseases.

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KEYWORDS

SARS-CoV-2; COVID-19; genomic epidemiology; GISAID; GenBank; sequence records; patient-related metadata; scoping review; protocol

Introduction

Background

Since the onset of the COVID-19 pandemic, there has been an unprecedented effort in genomic epidemiology (genomic epidemiology links pathogen genomes with associated metadata to understand disease transmission) to sequence the virus, study its transmission, and examine molecular evolution. Public repositories, such as the GISAID (Global Initiative on Sharing Avian Influenza Data) [1] and the National Center for Biotechnology Information (NCBI)'s GenBank [2] host millions of SARS-CoV-2 sequence records. As of September 2024, GISAID contains 16.9 million sequences, while over 8.9 million have been deposited in GenBank.

The availability of this vast amount of genomic data has facilitated significant discoveries, particularly in phylogenetic (the study of evolutionary relationships among biological entities) and phylodynamic (the reconstruction of epidemiological and immunological processes from the shape of phylogenetic tree relating infections) studies [3-5]. Beyond phylogenetic studies, genomic epidemiology aims to understand the transmission dynamics, evolution, and impact of infectious diseases by analyzing the genetic information of pathogens and linking it to patient demographics and disease outcomes [6,7]. This work enables the tracking of the spread of pathogens, identifying high-risk populations, and discovering genetic factors that influence disease transmission, severity, and treatment response [6,8]. This knowledge can, in turn, inform public health strategies, guide the development of targeted interventions, and improve the overall understanding of infectious diseases [9].

Ideally, patient geographic, demographic, and clinical information (such as disease severity and outcome) would be included in the sequence metadata upon its submission to the repository. Both GISAID and GenBank frequently provide the location of the infected host information in their sequence metadata, however, the reported location granularity may vary and often lacks important details such as patient travel history. Similarly, patient demographic and clinical information is rarely complete. A review of available metadata in these 2 large public repositories for SARS-CoV-2 sequences, conducted by the authors in April 2023, found 58.34% (8,943,721/15,329,810) of sequences in GISAID do not include the specific age and 58.58% (8,980,046/15,329,810) do not include the specific gender of the infected host. The information for these may be entered as unknown (eg, "not available," "declined," "not reported"). GenBank lacks standardized fields to include age or gender information with sequence submissions.

Several studies have highlighted the importance and challenges of metadata reporting in SARS-CoV-2 research and identified several shortcomings in the metadata that accompany these sequences [10,11], particularly deficiencies in the completeness and standardization of the reported data. Proposals have been made for the standardization of this data, but they have not been widely adopted [12]. Another review highlighted the importance of patient-related metadata for genomic epidemiology in general but provided no assessment of the availability of these data [13]. These studies collectively emphasize the critical need for improved metadata reporting practices, but they do not provide a comprehensive analysis of patient-related metadata reporting specifically in SARS-CoV-2 sequencing studies across multiple repositories or publications such as what we propose.

Previous research has found that sequence metadata can be enhanced for the location of the infected host using natural language processing and machine learning methods to automatically extract and link this information to the sequence record [14,15]. This patient-related information, or at least a subset of it, may be reported in the published studies of those who obtained and performed the genomic sequencing allowing these methods to be extended and applied to SARS-CoV-2 sequences. However, the extent to which patient-related geographic information, such as their residence or travel history, is reported in SARS-CoV-2 sequencing studies remains largely unexplored. Similarly for patient demographics or other clinical information. Our review aims to bridge this gap in understanding by quantifying the extent and types of patient-related metadata reported in published genomic viral sequencing studies of SARS-CoV-2.

Traditionally, identifying studies for a review requires the development of a detailed search strategy of databases using keywords and index terms, querying the titles and abstracts of published papers. The selection of keywords greatly influences search results, leading to potentially missed studies and the inclusion of potentially irrelevant studies. Moreover, for the particular focus of our study, discussions of sequencing are

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often confined to the methods section of papers, rendering title and abstract screening less informative. While more than 437,000 research papers [16] related to SARS-CoV-2 and the pandemic have been published, there is sparse linkage between the sequence and publication databases. This makes it difficult to identify publications relevant to the sequences, and severely limits meta-analyses and scaling studies by using datasets produced by different investigators. To overcome these limitations, we propose using an automated classifier to identify relevant studies for review. In addition, we will use a traditional database search to validate and compare the approaches.

A bibliometric analysis uses different methods and data points to quantify the trends and assess the impact of publications in a specific field [17]. While several bibliometric analyses have investigated COVID-19–related research trends in general [18-20] and in specific fields such as neurology [21], long COVID [22], and medical imaging [23], or for specific geographic locations such as Africa [24], no bibliometric analysis exists specifically focused on reporting patterns of patient metadata in sequencing studies related to the SARS-CoV-2 genome, nor examined how reporting practices evolved throughout the pandemic. We hypothesize that using bibliometric indicators, differences in metadata reporting will be seen based on study type, institution, and size, with smaller, clinical-based studies reporting more information than larger, surveillance studies.

Our aims with this review and analysis are to address the gaps in the understanding of the extent and quantity of patient-related metadata reporting in genomic sequencing studies by providing a comprehensive assessment of this reporting in the published SARS-CoV-2 sequencing studies. Using bibliometric methods, we will systematically examine factors that may influence metadata reporting in publications associated with SARS-CoV-2 sequence reporting over the course of the pandemic. By combining detailed content analysis of patient metadata with bibliometric analysis, we can identify factors that influence reporting practices, such as journal or institutional policies, international collaborations, or study types as well as highlight the gaps in reporting that may hinder the advancement of genomic epidemiology studies of the COVID-19 pandemic.

Primary Research Objectives

The primary research objectives are the following: (1) To quantitatively assess the extent and quality of patient-reported metadata, including demographic, clinical, and geographic information, in papers reporting original whole genome sequencing of the SARS-CoV-2 virus. (2) To perform a comprehensive bibliometric analysis to ascertain differences and discernible patterns between papers that include patient metadata and those that do not, thereby providing insights into the characteristics and factors associated with the reporting of patient data in the literature. (3) To evaluate the efficacy and reliability of a machine learning classifier in accurately identifying relevant papers for inclusion in the scoping review, enhancing the efficiency and effectiveness of this study's selection process.

Methods

Study Design

Our scoping review will follow the methodological framework identified by Arksey and O'Malley [25] and will be reported in line with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist [26] (Multimedia Appendix 1).

Data Sources

We will use the National Institutes of Health's LitCovid collection [16] for our machine learning classification. LitCovid is a curated collection of scholarly papers related to COVID-19. As of November 2024, the collection contains over 437,000 publications from 8000 journals and is updated daily. LitCovid includes published papers as well as preprints. Additionally, we will independently search Ovid MEDLINE and PubMed Central directly using a 2-faceted search strategy and the NCBI e-utilities program to find publications linked to sequences. This combined approach will help ensure a comprehensive coverage of the literature for our study.

Search Strategy

Classification Model

The details of our classification model have been previously reported [27]. Briefly, our classification model was trained using manually annotated data. A full-text search strategy was developed to filter the LitCovid collection resulting in a corpus of targeted papers for annotation. The papers identified through the pipeline were annotated by 2 experienced annotators using the INCEpTION annotation tool [28] and following methodically created annotation guidelines. The annotators reviewed the full text of 245 randomly selected papers and labeled sentences, which confirmed this study's performance of SAR-CoV-2 sample sequencing from human specimens. The interannotator agreement for the annotation was measured using Cohen κ. The score for agreement on whether the paper reported original viral sequencing was 1, and sentence agreement, which was calculated on papers that reported sequencing (n=74), was moderate [29] (k=0.71). Disagreements were resolved by a third annotator. The final annotated corpus consisted of 50,918 sentences from 245 papers. There were 74 papers that reported SARS-CoV-2 sequencing and, within these papers, 347 sentences were annotated as positive. We split our annotated dataset into 3 random sets: a training set of 147 papers (31,885 sentences), a validation set of 49 papers (9017 sentences), and a test set of 49 papers (10,016 sentences). For our classifier, we pretrained a transformer-based neural network, specifically a bert-base-uncased [30] model from the Hugging Face library. On the held-out test set, the classifier achieved an F_1-score of 0.48 (precision=0.492 and recall=0.469) for identifying sentences that provided evidence of generating new SARS-CoV-2 sequences. While the classifier achieved moderate performance at the sentence level, assessing the performance at the paper level, meaning at least 1 sentence in the paper that indicated sequencing was detected, the classifier achieved a more robust performance of F_1-score of 0.8 (precision=0.667 and recall=1).

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Database Search Strategy

To evaluate our classifier and identify studies that may have been missed due to classification errors or the lack of full text in the LitCovid collection, we will create a search strategy to independently search MEDLINE and PubMed Central. We will develop a 2-faceted search strategy to find "SARS-CoV-2" and "whole genome sequencing" related publications. We will use the search strategy developed for the LitCovid collection with additional keywords added to identify studies that report whole genome sequencing. A sample search strategy is found in Multimedia Appendix 2. Additionally, we will search for publications linked to SARS-CoV-2 sequences using the NCBI's e-utilities eLink programming application programming interface. We will also search gray literature sources, such as Google Scholar and review the reference lists of included studies [31].

A publication date restriction of December 2019 onward will be used in the searches as this review is focused on SARS-CoV-2 sequencing studies. No language restrictions will be placed on the searches, although financial and logistical restraints will not allow translation from all languages.

Inclusion or Exclusion Criteria

Papers positively identified by our classifier and our search results will be reviewed for inclusion in the review based on the criteria outlined in Table 1.

Table 1. Inclusion and exclusion criteria for the scoping review.

Facet	Inclusion criteria	Exclusion criteria
Sample origin	• Individual human subject	• Nonhuman sources (eg, mice, bats, and ferrets) • Wastewater • Microbiome • Cloned or cell culture virus
Sequencing type	• Whole genomic sequencing, including partial or complete sequence results	Studies will be excluded if the following sequencing methods were exclusively performed: • Polymerase chain reaction or loop-mediated isothermal amplification for viral detection • Single-cell sequencing • Gene expression studies • Protocol validation studies on cell culture virus • Exome sequencing
Study design	• Any type of peer-reviewed or preprint study reporting on the original sequencing of SARS-CoV-2 samples. • The study reports the deposit of the sequences into a data repository	• Any other study design • Any study that does not report the depositing of sequences into a data repository
Publication dates	• December 2019 or later	• Before December 2019
Language	• All	• None

Screening and Paper Selection

Two reviewers will perform title and abstract screening using the Covidence systematic review management tool with any disagreements resolved by discussion. We will screen the papers from the different methods in a systematic order (Figure 1). First, we will validate and screen the results from our classifier's predictions on the LitCovid collection. Next, we will screen the papers obtained from our database searches. All results will be uploaded to a Zotero library where duplicate results will be removed. We will then identify if a paper is in the LitCovid collection; those that are not will be moved to screening. For those that are, we will assess whether the paper was screened in the first round, those that were not will be screened in this round. Lastly, for papers identified as having links to GenBank records through NCBI's eLink programming application programming interface, we will identify if any of the resulting papers had been screened in the previous 2 rounds, those that have not will then be screened.

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Figure 1. Flow diagram of proposed screening of identified papers. We will first screen papers from our classifier, then we will screen those identified from database searches to ensure there are no duplicate records screened.

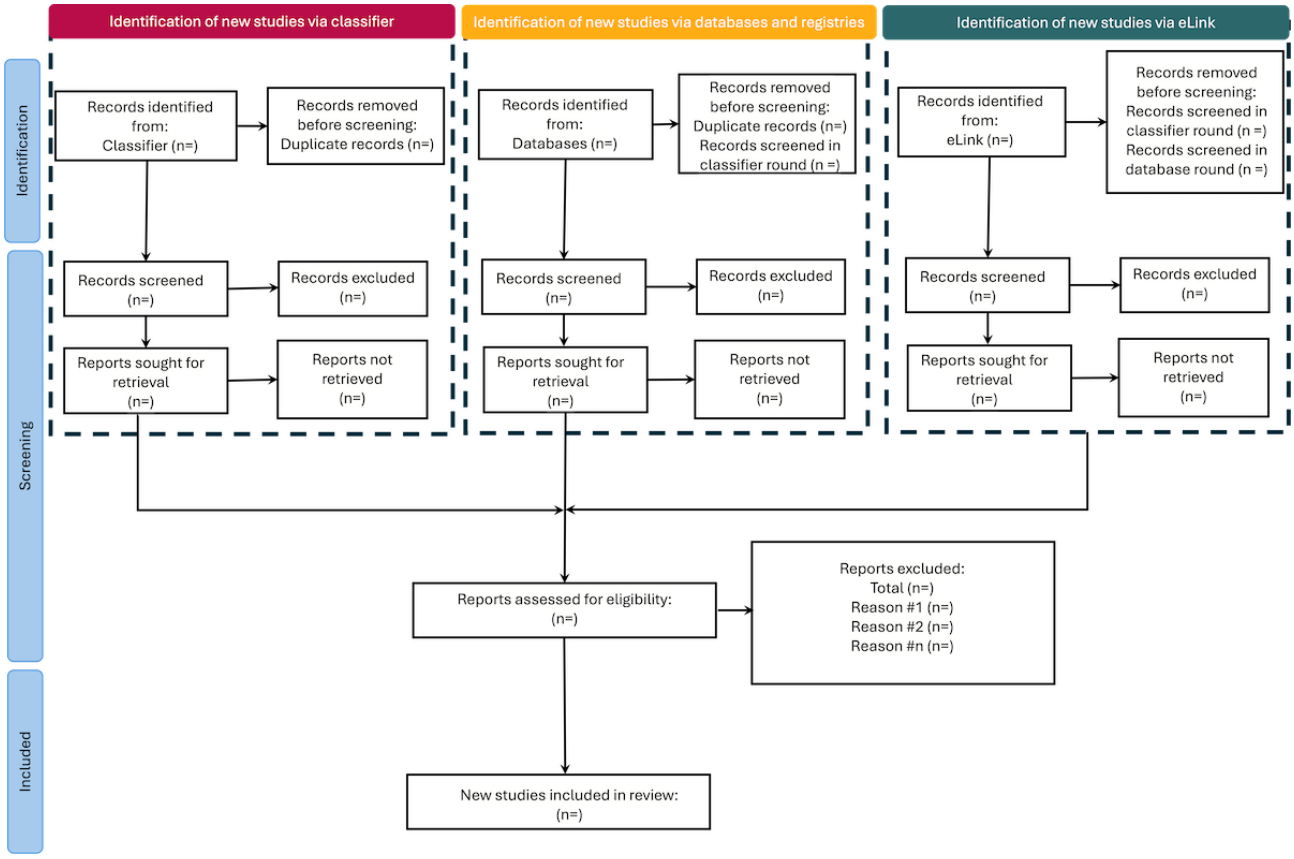

Two independent reviewers will also conduct a full-text review in Covidence. To ensure interrater reliability, a subset of 10% of the screened studies will be independently reviewed by both reviewers. We will assess the level of agreement between reviewers using the Cohen κ coefficient [29]. Any discrepancies will be resolved through discussion. We will report the excluded studies with the reason for exclusion.

Data Extraction

Data extraction will be conducted in Covidence. The reviewers will examine the full text of the papers, including any supplementary files, for data extraction. The customizable interface will be designed to prompt the reviewer to extract various details, such as general publication information, study characteristics, sequencing specifics, and the presence or absence of the patient's demographic, clinical, or geographic information about where the patient resides or had traveled before sample collection, or the location of where the sample was collected. For studies with reported patient metadata, we will note whether information is reported per individual or in aggregate. For missing or incomplete metadata, we will categorize the absence using the following classifications: explicitly withheld for privacy, deidentified before sequencing, partially reported, or not reported. Furthermore, the section where the reported patient metadata within the papers was reported will be noted, for example, text, table, or supplemental materials. An example of the data extraction form can be found in Table 2. As this scoping review aims to report on the current state of published reports of patient-related metadata, we will not contact authors for any missing or additional data not found in the paper.

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Table 2. Example of data that will be extracted from included studies.

Prompt	Response
Publication information	
Study name	Free text
Paper title	Free text
Year of publication	YYYY
Publication type	Journal, conference, and preprint
Study and sequence information	
Study objective	Free text
Location of study (country)	Free text
Number of patients	Free text
Number of samples sequenced	Free text
Short description of how the generated sequences were used in the paper	Free text
Repository sequences deposited to	GISAID[a], GenBank, other, or NR[b]
For studies with >1 patient, are sequences linked to a patient?	Yes or no
Patient demographic information reported	
Age	Yes or no
Gender	Yes or no
Race or ethnicity	Yes or no
If yes to any of the above, where in the paper was the information located	Text, table, or supplemental
Reporting level	Individual or aggregate
If not reported, the reason	Privacy, deidentified, NR, or partial
Patient clinical information reported	
Symptoms	Yes or no
Severity	Yes or no
Inpatient or outpatient	Yes or no
Treatments	Yes or no
Outcomes	Yes or no
If yes to any of the above, where in the paper was the information located	Text, table, and supplemental
Reporting level	Individual or aggregate
If not reported, the reason	Privacy, deidentified, NR, or partial
Patient geographic information reported	
Location of residence	Yes or no
Travel information	Yes or no
If yes to any of the above, where in the paper was the information located	Text, table, or supplemental
Reporting level	Individual or aggregate
If not reported, the reason	Privacy, deidentified, NR, or partial

[a]GISAID: Global Initiative on Sharing All Influenza Data.

[b]Not reported.

We will test the initial extraction form on a subset of papers and revise it as needed.

For bibliometric analysis, all pertinent data points will be extracted for studies included in our review including, author location and institution information, journal, study type, citation metrics, and author keywords or Medical Subject Headings terms when available.

Data Analysis

The extracted data will be synthesized and summarized to quantify the availability of patient metadata in the published

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literature of SARS-CoV-2 sequencing studies using an exported spreadsheet from Covidence. We will summarize and narratively describe our findings, using tables, graphs, and charts when applicable, regarding the number of sequences covered in our included studies, the distribution of the sequences in the respective repositories, and the quantity and type of reported patient metadata in the papers.

For the bibliometric analysis, data will be analyzed and visualized using the VOSviewer software or the *bibliometrix* [32] package for R (R Foundation). These will include publication metrics (eg, annual trends, and distribution by journal and country), author metrics (eg, collaboration networks or productivity), and citation analysis (eg, total and average citations, or highly cited papers). We will present the geographical location of the paper's authors using maps to show the geographic distribution of research output and report our findings, including the most frequent journals and paper types using narrative descriptions or tables. We will use the data extracted from our review to analyze differences between studies that reported patient metadata from those that did not. Co-occurrence networks of author keywords will be presented to highlight the frequency and differences in themes and study type (eg, clinical study, case report, and surveillance study) between these reporting groups. We will analyze coauthorship networks and institutional collaborations to assess if highly collaborative studies are associated with more comprehensive metadata reporting. We will also analyze associations between study location, the potential impact of journal-related policies or characteristics, and the extent of metadata reporting. Specifically, we will examine the proportion of studies reporting different types of metadata (demographic, clinical, and geographic), trends in metadata reporting over time, and potential correlations between metadata reporting and other bibliometric indicators such as citations or journal impact factors. In addition to VOSviewer and *bibliometrix*, we will use the R statistical software to develop scripts for specific analyses related to metadata reporting trends.

As this is a scoping review (and not a systematic review), accepted practice [33] indicates that it need not include an assessment of the methodological quality (risk of bias assessment) of the papers or conduct any evidence synthesis.

Ethical Considerations

This scoping review will consist of collecting and reviewing publicly available data from previously published studies and does not require any ethical approval. Furthermore, quantitative results will be reported in aggregate across the included studies. The results and findings of the completed scoping review will be disseminated through the submission of a paper for peer-reviewed publication and through scientific conferences. This paper will reference this protocol, and any changes or deviations made from this protocol will be acknowledged and justified.

Results

This protocol has been registered at the Open Science Framework registries. This study is expected to be completed in early 2025. Our classification model has been developed and we have classified publications in LitCovid published through February 2023. As of September 2024, papers through August 2024 are being prepared for processing. Screening is underway for validated papers from the classifier. Direct literature searches and screening of the results began in November 2024. We will quantitatively summarize and narratively describe our findings, using tables, graphs, and charts when applicable.

Discussion

Principal Findings

The anticipated findings of this scoping review will provide a comprehensive overview of the current state of patient-related metadata reporting in SARS-CoV-2 sequencing studies. We expect to identify gaps in reporting practices, variations across different types of studies or geographic regions, and potential areas for improvement in metadata reporting standardization. In addition to the findings of our scoping review, the bibliometric analysis will likely identify several other important trends and patterns in the reporting of patient-related metadata. For example, the analysis may find that the reporting of patient-related metadata is more common in certain types of studies, or that it is more likely to be reported in studies from certain geographic regions. The findings of the scoping review and bibliometric analysis will provide valuable insights into the factors that influence the reporting of patient-related metadata and will help to inform future research on this topic.

The COVID-19 pandemic has spurred an unprecedented volume of research, including extensive efforts in genomic sequencing of SARS-CoV-2. However, the utility of these sequences for genomic epidemiology may not be fully realized due to the unavailability of relevant metadata about the patient from whom the specimen was obtained [34]. Shortcomings of this metadata that may accompany these sequences in the data repositories have been extensively noted [10-12]. Methods exist that facilitate the extraction of this data from other resources, such as published literature [14,15,35]. The identification and quantification of the metadata in literature may aid in advancing future research.

Future Directions

Our study may lay the groundwork for determining the feasibility of the development of automated methods to extract patient-related metadata from publications to enrich sequences. These enriched sequences can be made available through a publicly shared repository. The availability of such a comprehensive resource could facilitate studies that compare how the inclusion of additional metadata impacts the conclusions and utility of genomic epidemiology studies. This could help quantify the importance of comprehensive metadata reporting, and potentially provide the impetus for researchers to improve their reporting practice.

Beyond the practices of researchers, there may be other factors that determine whether the patient metadata is published, such as journal data-sharing policies. Based on the findings of this scoping review researchers could develop and propose standardized guidelines for reporting patient-related metadata

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in SARS-CoV-2 sequencing studies. These guidelines could help improve the consistency and completeness of metadata reporting across future studies, enhancing the value of genomic sequences for epidemiological research.

Moreover, our study may reveal insights into the role privacy concerns play in the reporting of relevant patient metadata. This insight could guide targeted interventions to improve reporting practices while also addressing critical patient privacy concerns. Future work could explore the development of privacy-preserving methods for sharing more comprehensive metadata.

By providing a comprehensive overview of current metadata reporting practices, the results of this scoping review may support efforts to enhance both the completeness and ethical handling of patient-related metadata in genomic epidemiology research. These improvements could significantly advance our understanding of SARS-CoV-2 transmission dynamics and inform strategies for managing this and future pandemics.

Strengths and Limitations

We propose a novel approach to identify relevant papers with the development of an automated classifier that will locate within the text of the paper sentences that indicate viral genome sequencing was performed in the paper. This method necessitates openly available, machine-readable texts which could bias our sample from this search to information in open-access papers. This bias should be limited in this study, however, as there was a commitment from publishers early in the COVID-19 pandemic to make content related to the pandemic open and available [36]. Furthermore, we will also conduct an independent search from databases outside of LitCovid to identify any potentially missed papers from our classifier or gaps in the LitCovid collection ensuring a more comprehensive and relevant collection of papers to include in our review. Still, there remains the possibility that some relevant studies may be missed due to search limitations which may lead to an under or overestimation of the extent of metadata reporting. While we aim to follow the best practices in methodology and reporting by adhering to the PRISMA-ScR checklist, we do deviate from standard practice for identifying studies through the use of a classifier. This approach will allow us to identify sequencing studies that may not be apparent from traditional title or abstract screening alone. Other limitations exist, such as potential limitations in reported patient metadata [37,38] and the focus on SARS-CoV-2 sequencing studies, which may limit the applicability of our findings to other pathogens or pandemics. There may also be a gap in publication time between the depositing of sequences and the publication of the paper. Furthermore, reporting patterns may differ from early in the pandemic due to the urgent need to disseminate information, reporting practices and requirements in publications may have changed over the course of the pandemic, and research priorities may have changed as the pandemic continued. Any of these scenarios may affect the ability to draw definitive conclusions about trends in metadata reporting over time.

Conclusion

This protocol outlines the steps that we will take in our scoping review which will be supported by an automated classifier and bibliometric analysis. We will fill the knowledge gap regarding the extent and types of patient-related metadata reported in genomic viral sequencing studies of SARS-CoV-2 and will provide valuable insights by identifying themes and trends in the published literature. The results of this study may encourage improved and standardized reporting practices which will significantly enhance the utility of sequence metadata and aid in advancing our understanding of the SARS-CoV-2 or any future pandemic. Future research can build upon our study to address these gaps and enhance reporting practices in this field.

Acknowledgments

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Data Availability

This study will analyze and synthesize previously published information. Data-sharing does not apply to this paper as no datasets were generated or analyzed during this study. We will submit for publication the completed scoping review and bibliometric analysis. At that time, any extracted data and data generated in our analysis will be made available with the publication.

Authors' Contributions

KO, EL, MS, and GG-H designed this study. KO was a major contributor to the writing of this paper. DW designed the classification methods. KO and AE designed the annotation methods. All authors read, edited, and approved the final paper.

Conflicts of Interest

None declared.

Multimedia Appendix 1

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PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist.
[DOCX File , 84 KB - resprot_v14i1e58567_app1.docx]

Multimedia Appendix 2
Sample search strategy for Ovid MEDLINE.
[DOCX File , 17 KB - resprot_v14i1e58567_app2.docx]

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Abbreviations

GISAID: Global Initiative on Sharing All Influenza Data
NCBI: National Center for Biotechnology Information
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Mapping the Evidence on Compassion Skills in Applied Behavior Analysis: Protocol for Scoping Review

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Abstract

Background: Applied behavior analysis (ABA) is a scientific approach that applies principles of learning and motivation to assess, design, implement, and evaluate social and environmental modifications to produce meaningful changes in human behavior. It has been widely used in various settings, particularly in the treatment of individuals with autism spectrum disorders and other developmental disabilities. Recently, compassion has emerged as a topic of growing scientific interest within ABA. To improve socially relevant behaviors, it is essential to explore how behavior analysts can provide maximum support to clients and promote significant changes through compassionate care. Although compassion skills have been studied by ABA researchers, the literature still presents gaps in understanding how these skills can be effectively integrated into ABA practice.

Objective: This study aimed to map, identify, and provide data available in the existing literature on compassion skills and applied behavior analysis.

Methods: This scoping review will follow the methodological framework of Arksey and O'Malley with previously proposed refinements. The search strategy will use combinations of descriptors and their synonyms according to the Health Sciences Descriptors and MeSH (Medical Subject Headings) terms, using the PCC (population, concept, and context) mnemonic, combined with the Boolean operators AND Mesh OR. The electronic databases to be searched include Embase, Index Psicologia, Lilacs, PubMed, Scopus, and Web of Science. Studies published between 2020 and 2024 in English, Portuguese, and Spanish will be included. Two independent reviewers will screen titles, abstracts, and full texts, with a third reviewer resolving any disagreements.

Results: As this is a protocol, results are pending. The review will synthesize definitions of compassion in ABA, map compassionate skills, analyze existing interventions, and identify outcomes associated with compassionate ABA practice.

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Conclusions: This scoping review is expected to contribute to the evolution of ABA toward a more compassionate and holistic approach, potentially leading to improved outcomes for clients and practitioners. The findings may inform the development of compassion training programs and influence care policies in ABA.

Trial Registration: OSF Registries 10.17605/OSF.IO/F3A6H; https://osf.io/f3a6h

International Registered Report Identifier (IRRID): PRR1-10.2196/66399

(JMIR Res Protoc 2025;14:e66399) doi:10.2196/66399

KEYWORDS

compassion; applied behavior analysis; skills; protocol; scoping reviews; knowledge gaps; training program; client-centered approach; holistic approach

Introduction

Background

Applied behavior analysis (ABA) is an approach widely recognized as effective in improving the quality of life of people with autism spectrum disorder (ASD) [1]. This approach is based on the principles of behaviorism and aims to modify behaviors through systematic and evidence-based interventions [2]. With continuous advancements in this field, recent studies have demonstrated ABA's efficacy not only for individuals with ASD but also for a variety of other neurodevelopmental conditions [3] as the field progresses and scientific interest in humanized interventions grows, the concept of "compassion" has become a topic of discussion, with new skills, such as compassionate care, becoming central to therapeutic process [4]. The incorporation of compassionate practices in ABA has been associated with improved therapeutic outcomes and greater satisfaction among clients and their families [5]. Recent research has further emphasized the importance of concrete compassionate actions in building compassionate experiences within health care settings, including ABA practice [6].

Compassion can be defined as a combination of empathy, care, and willingness to help others, alleviating their suffering [7]. In the context of health care, compassion is considered an essential component for the quality of care and patient satisfaction [8]. To improve the quality of health care, it is essential to focus on a compassionate and client-centered approach, aiming for better outcomes.

However, despite the growing recognition of the importance of compassion, studies have pointed out complaints from those who receive ABA services about the attitudes and behaviors of these professionals, indicating the need to develop strategies that promote more humanized care [3]. These complaints include lack of empathy, inadequate communication, and overly directive approaches by behavior analysts [9].

Although ABA has brought several significant contributions to the treatment of ASD, there is a lack of aspects that encompass the conceptual and operational definition of compassion from a behavioral perspective [10]. Recently, researchers have endeavored to bridge this gap, proposing conceptual models of compassion aligned with the principles of behavior analysis [10]. Most studies on compassion have focused on specific populations, leaving a gap in knowledge about how to develop and apply compassionate skills in different contexts [5]. Furthermore, the integration of compassionate skills in the training and practice of behavior analysts has gained increasing attention in recent literature [9].

These gaps indicate the need for a comprehensive review to map research data on the compassionate skills of the behavior analyst. The importance of such a review is underscored by the growing recognition of compassion as a crucial component in delivering high-quality health care [8]. Unlike other reviews, a scoping review is particularly suitable, as it will allow the identification of critical resources of the ABA professional's compassion skills, analyzing knowledge gaps and providing a comprehensive view of compassion skills in this area of concentration. This type of review has proven effective in mapping evidence in emerging and multidisciplinary fields, such as the integration of compassion in ABA [2]. Furthermore, the scoping review will enable the synthesis of evidence from different types of studies, such as clinical trials, observational studies, and qualitative research [11].

Recent developments in the field have also highlighted the need for standardized measures of compassion in behavioral interventions. Marchese and Weiss [1] have made significant strides in this direction by developing the Parent Partnership Questionnaire, a tool designed to assess compassionate care in ABA settings. This advancement provides a foundation for more rigorous evaluation of compassionate practices and their impact on treatment outcomes.

In addition, the evolving landscape of ABA practice has seen an increased emphasis on cultural responsiveness and empathy as integral components of compassionate care. This shift reflects a growing awareness of the diverse needs of clients and the importance of tailoring interventions to individual and cultural contexts [4]. Such developments underscore the necessity for a comprehensive review that can synthesize these emerging trends and provide direction for future research and practice in the field.

Objective

The primary objective of this scoping review is to map and synthesize the available evidence on the compassionate skills of behavior analysts, identifying knowledge gaps and providing directions for future research and clinical practices.

The specific objectives are:

- To identify the definitions and conceptualizations of compassion in the context of ABA.

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- To map the specific compassionate skills reported in the ABA literature.
- To analyze existing interventions or training programs for developing compassionate skills in behavior analysts.
- To examine the reported outcomes associated with compassionate practice in ABA.
- To identify barriers and facilitators for implementing compassionate practices in ABA.

It is expected that the results of this review will contribute to the improvement of ABA professionals' training and performance, promoting more humanized care focused on clients' needs.

Methods

Study Design

This study is a scoping review protocol. This review model was selected because it is a specific area of interest with little coverage of the topic in the current literature. The review will follow the methodological framework of Arksey and O'Malley [12], with refinements proposed by Levac et al [13] and Peters et al [11]. The results will be presented using the PRISMA-ScR (Preferred Reporting Item for Systematic Review and Meta Analyses extension for Scoping Reviews) guidelines [14] to ensure transparency and quality of the review process.

Research Question

To answer the research question, we considered the target population and the concept to refine the formulation of the PCC (population, concept, and context) acronym. Therefore, the scoping review question was defined as: "What has been widely published in the scientific literature about the compassion skills of the Behavior Analyst?"

The acronym encompasses the components of Population, Concept, and Context as follows: the Population refers to applied behavior analysts, the Concept revolves around compassion, and the Context is related to professional skills and competencies within ABA practice.

In this scoping review, the "context" element of our PCC framework refers to the professional skills and competencies within ABA practice. This encompasses the specific abilities, techniques, and knowledge that behavior analysts use in their professional roles. By focusing on this context, we aim to explore how compassion is integrated into the skillset of ABA practitioners, including their interpersonal skills, therapeutic techniques, and overall approach to client care. This context allows us to examine compassion not as an isolated concept, but as an integral part of the professional competencies required in the field of ABA.

Inclusion and Exclusion Criteria

The inclusion criteria will comprise peer-reviewed studies in Portuguese, English, and Spanish, with any research design that answers the guiding question. The studies will need to present complete abstracts in the databases available accessed via internet web, free of charge, in full, published between 2020 and 2024 (Textbox 1), and referring to research related to the area of concentration of Applied Behavior Analysis. All databases will be consulted through the CAPES Journal Portal.

Textbox 1. Justification for the 2020-2024 time frame.

Rapid evolution of the field: The integration of compassion into applied behavior analysis practices has experienced significant acceleration in recent years. By focusing on the last 5 years, we aim to capture the most current and relevant developments in this rapidly evolving field.

Paradigm shift: The period since 2020 marks a notable shift in applied behavior analysis toward more holistic, person-centered approaches, with increased emphasis on compassionate care. This time frame allows us to concentrate on literature that reflects this important paradigm shift.

COVID-19 impact: The global pandemic has profoundly influenced health care delivery, including applied behavior analysis services, potentially affecting the implementation and perception of compassionate care. Literature from 2020 onwards is more likely to reflect these crucial changes.

Methodological advancements: Recent years have seen significant improvements in research methodologies and measurement tools related to compassion in behavioral interventions. Focusing on this period ensures we capture studies using the most advanced and validated methods.

Policy and guideline updates: Many professional organizations have updated their guidelines and ethical standards in recent years to incorporate compassionate care principles. Literature from 2020-2024 is more likely to reflect these updated standards.

Alignment with current practice: By concentrating on the most recent literature, we ensure that our findings are highly relevant to current clinical practice and ongoing research initiatives.

Manageability of data: Given the comprehensive nature of a scoping review, limiting the time frame to 5 years helps ensure a manageable volume of data while still providing a robust representation of current knowledge.

To ensure comprehensive coverage of relevant research methodologies in ABA, we will explicitly include Single-Case Experimental Designs (SCEDs) in our inclusion criteria. SCEDs are experimental in nature and distinct from descriptive case studies. These designs are widely used in ABA research due to their ability to demonstrate functional relationships between interventions and behavior changes at the individual level. By including SCEDs, we acknowledge their significance in the field and ensure that valuable data from these rigorous experimental designs are captured in our review. Specifically, we will include studies using various SCED methodologies, such as multiple baseline designs, reversal designs, alternating treatments designs, and changing criterion designs. This inclusion will allow for a more comprehensive analysis of compassionate practices in ABA across diverse research methodologies.

While we acknowledge that some seminal works cited in our introduction predate 2020, these are primarily used to provide historical context and theoretical foundations. Our focus on 2020-2024 for the scoping review itself allows us to build upon

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this foundational knowledge with the most up-to-date empirical evidence and practical applications.

We believe this approach strikes an optimal balance between capturing the most current developments in the field and maintaining a manageable scope for our review. However, we remain open to expanding this time frame if our initial search reveals a paucity of relevant literature within the specified period.

Studies will be included only if they are available in full text, either through open access or free availability. Papers that provide only the abstract free of charge will not be included in this review. This decision has been made to ensure a comprehensive and in-depth analysis of the entire content of selected studies, allowing for a more robust and reliable assessment of the evidence. We acknowledge that this choice may limit the scope of the review, potentially excluding some relevant studies that are available only behind paywalls. However, we posit that the benefits of full-text analysis outweigh this potential limitation. To mitigate this constraint, we will conduct a thorough search across multiple databases and, where possible, use institutional access to maximize our coverage of relevant literature. In addition, in cases where a potentially crucial paper is not freely available, we will attempt to contact the authors directly to request access. This approach aims to balance the need for comprehensive analysis with the practical constraints of access to scientific literature.

The exclusion criteria in this study will include research published more than 5 years ago and paper that are not related to the area of concentration of ABA, as well as other items shown in Textbox 2.

Textbox 2. Inclusion and exclusion criteria.

Inclusion criteria

- Quantitative studies.
- Qualitative studies.
- Mixed methods studies.
- Experimental and quasi-experimental design studies.
- Randomized controlled studies.
- Non-randomized controlled studies.
- Systematic reviews.
- Meta-analyses
- Meta-syntheses.
- Books and guidelines published in indexed sources.

Exclusion criteria

- Editorials.
- Expert opinions.
- Narrative reviews.
- Studies that do not contemplate applied behavior analysis.

Search Strategy and Sources of Evidence

The search for published papers will be processed in the following electronic databases: Embase, Index Psicologia, Lilacs, PubMed, Scopus, and Web of Science. These specific databases were selected because they have been used in previous review studies. Based on their comprehensive coverage of behavioral and psychological research, as well as their use in previous systematic reviews in the field of ABA and compassion in health care. Specifically:

- Embase and PubMed were chosen for their extensive coverage of biomedical literature, including behavioral interventions [15].
- Index Psicologia and Lilacs were included to ensure comprehensive coverage of Latin American and Caribbean health science literature, which is particularly relevant given our inclusion of Portuguese and Spanish language studies [16].
- Scopus and Web of Science were selected for their broad, multidisciplinary coverage and their inclusion of high-impact journals in psychology and behavioral sciences [17].

This combination of databases ensures a thorough and diverse search across relevant disciplines and geographical regions.

The search strategy used combinations of descriptors and their synonyms according to the health sciences descriptors and MeSH (Medical Subject Headings) terms, using the PCC mnemonic, combined with the Boolean operators AND and OR.

The research team developed and tested the search strategy on the CAPES Journal Portal with the support of a librarian specializing in the subject. The search strategy is presented in Textbox 3. Once the appropriate papers have been identified

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and duplicates removed, the literature analysis will begin, and if appropriate, the search strategy in the literature list will be refined accordingly. The search strategy is outlined in Table 1.

It is important to note that the term "skills" was listed as a replacement for the descriptor "Abilities" to refine the keywords established for the study and their alternative terms.

The searches were performed using descriptors in Portuguese, Spanish, and English. In Spanish, the descriptors were also used in fields such as "title words" and "abstract word" for greater coverage, but without any results.

The descriptors were inserted into the protocol, along with their respective alternative terms. For greater results, in some databases, only the main descriptor was inserted for the search.

Textbox 3. Selection of keywords for search strategy.

"Habilidades" OR **"Aptidão"** OR "Habilidade Pessoal" OR "Habilidades para a Vida" OR "Talento" OR **"Aptitudes"** OR "Talent" OR "Talents" OR "Ability" OR "Abilities" OR **"Aptitud" AND "Empatia"** OR "Benevolência" OR "Compaixão" OR "Condescendência" OR "Consideração" OR "Deferência" OR "Sentimento de Complacência" OR **"Empathy"** OR "Caring" OR "Compassion" OR **"Empatía"** AND **"Análise do Comportamento** Aplicada" OR **"Applied Behavior Analysis"** OR **"Análisis Aplicado de la Conducta"**

Table 1. Search strategy.

Term	Synonyms in Portuguese (descriptors)	Synonyms in English (MeSH[a])	Synonyms in Spanish (descriptors)
Term 1	"Habilidades" OR "Aptidão" OR "Habilidade Pessoal" OR "Habilidades para a Vida" OR "Talento"	"Aptitudes"* OR "Talent"* OR "Talents"* OR "Ability"* OR "Abilities"*	"Aptitud"
Term 2	"Empatia" OR "Benevolência" OR "Compaixão" OR "Condescedência" OR "Consideração" OR "Deferência" OR "Sentimento de Complacência"	"Empathy" OR "Caring" OR "Compassion"	"Empatia"
Term 3	"Análise do Comportamento Aplicada"	"Applied Behavior Analysis"	"Análisis Aplicado de la Conducta"

[a]MeSH: Medical Subject Headings.

Study Selection

The selected studies will focus on compassion and the area of concentration of applied behavior analysis, with a special focus on the compassion skills of the behavior analyst (Textbox 4).

All reviewers will undergo training on the application of inclusion or exclusion criteria before beginning the screening process to ensure consistency. The entire selection process will be piloted on a subset of 100 papers to refine the procedure before full implementation.

Textbox 4. This study selection process will follow these steps.

Duplicate removal: After retrieving search results from all databases, 2 independent reviewers (DA and DS) will use Rayyan software (Qatar Computing Research Institute) [18] to identify and remove duplicate papers.

Title and abstract screening: The same 2 reviewers will independently screen titles and abstracts of the remaining study against the predefined inclusion and exclusion criteria. They will classify each paper as "include," "exclude," or "uncertain."

Full-text review: For this study classified as "include" or "uncertain," the full-texts will be retrieved and independently reviewed by the same 2 reviewers using the detailed eligibility criteria outlined in the protocol.

Disagreement resolution: Any disagreements at the title or abstract or full-text review stages will be resolved through discussion between the 2 reviewers. If consensus cannot be reached, a third reviewer (JA) will be consulted to make the final decision.

Inter-rater reliability: We will calculate the Cohen kappa coefficient to assess inter-rater reliability for both the title or abstract and full-text screening stages. A κ value of 0.8 or higher will be considered acceptable.

Documentation: Throughout the process, we will maintain a detailed log of all decisions, including reasons for exclusion at the full-text review stage. This information will be used to create the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

Final verification: As a quality control measure, a random sample of 10% of the included studies will be reviewed by a third reviewer (SC) to ensure consistency in application of the inclusion and exclusion criteria.

Eligibility Criteria

In line with established methodological guidelines for scoping reviews, the analysis of study quality will not be considered as an eligibility criterion. This approach is consistent with the primary aim of scoping reviews, which is to map the existing literature on a topic rather than to assess the quality of individual studies [12].

The analysis of study quality will not be considered as an eligibility criterion, as scoping reviews do not include this assessment [13]. The initial reading of the title and abstracts will allow the exclusion of nonrelevant studies. Next, we will examine the full texts of studies that proved relevant or whose nature raised doubts.

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For the calibration of eligibility criteria and to define search strategies among researchers, the title and abstract of 18 papers will be randomly analyzed by 2 researchers. There should be an 80% agreement on the inclusion and exclusion criteria of the papers. If the initial analysis does not achieve the 80% agreement threshold, the 2 researchers will discuss their discrepancies, refine their understanding of the inclusion and exclusion criteria, and repeat the process with a new set of 18 randomly selected papers. This iterative process will continue until the 80% agreement level is reached. Once achieved, this will establish the final set of eligibility criteria to be used for the full review process. This approach ensures a robust and consistent application of the eligibility criteria throughout the study selection phase.

Data Extraction

The Rayyan software [18] will be used in the process of selecting evidence sources, where duplicates between databases and studies that do not address terms of the PCC acronym will be excluded.

Subsequently, the objectives and methods of the studies will be reviewed to verify if they meet the other eligibility criteria (Textbox 5).

These criteria will be applied during the full-text review phase to ensure that all included studies have a robust scientific basis in ABA.

Two reviewers (DA and DS) will independently extract data from each included study using a standardized data extraction form. The form will be piloted on a sample of 5 studies and refined as necessary before full implementation.

A comprehensive data extraction instrument has been developed to systematically collect relevant information from each included study, covering aspects such as study characteristics, ABA-specific information, compassion-related data, outcomes, themes, author conclusions, and quality assessment (Multimedia Appendix 1 for the full data extraction instrument).

Any disagreements in data extraction will be resolved through discussion between the 2 reviewers, with a third reviewer (JA) consulted if necessary. The extracted data will be compiled in a spreadsheet to facilitate thematic analysis and synthesis.

Textbox 5. To ensure that the selected studies have a strong scientific basis in applied behavior analysis, we will establish the following specific criteria.

Theoretical framework: The study must explicitly state that it is grounded in behavioral principles or applied behavior analysis methodology.

Methodology: The study should employ research methods consistent with applied behavior analysis practices, such as single-subject designs, multiple baseline designs, or group designs that focus on behavioral outcomes.

Terminology: The study should use terminology consistent with applied behavior analysis, including but not limited to: operant conditioning, reinforcement, behavior modification, functional analysis, or behavioral intervention.

Outcome measures: The study should include behavioral measures as primary outcomes, such as frequency, duration, or intensity of target behaviors.

Intervention techniques: The study should describe intervention techniques that are consistent with applied behavior analysis principles, such as reinforcement schedules, prompting, shaping, or chaining.

Professional standards: The study should adhere to ethical guidelines and professional standards established by recognized applied behavior analysis organizations (eg, the behavior analyst certification board).

Peer review: The study must be published in a peer-reviewed journal that regularly publishes applied behavior analysis research or in a recognized behavioral science journal.

In addition, the studies should meet the following criteria:

- The studies will need to present in the title, abstract, or descriptors the concepts of applied behavior analysis and terms commonly used by researchers in the area, such as behavioral skills.
- The studies should present in the title, abstract, or descriptors the concepts of compassion or similar terms such as compassionate skills; however, they would need to be linked to applied behavior analysis.

Data Analysis and Synthesis

We will use a thematic analysis approach to synthesize the extracted data (Textbox 6), following the 6-phase framework outlined by Braun and Clarke [19].

We will use both narrative synthesis and visual representations (eg, concept maps) to present our findings. The synthesis will aim to provide a comprehensive overview of the current state of knowledge regarding compassion skills in ABA, identify gaps in the literature, and suggest directions for future research.

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Textbox 6. Data analysis process.

Familiarization with the data: Two reviewers (DA and DS) will independently read and re-read the extracted data, noting initial ideas and potential codes.

Generating initial codes: Using MaxQDA software (VERBI Software), the reviewers will systematically code interesting features across the entire dataset. We will use a combination of deductive coding (based on our research questions) and inductive coding (allowing new themes to emerge from the data).

Searching for themes: Codes will be collated into potential themes, gathering all data relevant to each potential theme.

Reviewing themes: Themes will be checked in relation to the coded extracts (Level 1) and the entire dataset (Level 2), generating a thematic "map" of the analysis.

Defining and naming themes: Ongoing analysis to refine the specifics of each theme and the overall story the analysis tells, generating clear definitions and names for each theme.

Producing the report: Final analysis and selection of compelling extract examples, relating back to the research question and literature.

To ensure rigor and transparency in our analysis, we will:

- Use a codebook to maintain consistency in coding [20].
- Use investigator triangulation, with 2 reviewers independently coding and then comparing their analyses [21].
- Use member checking, where we will share our preliminary findings with a subset of included study authors for feedback [22].
- Maintain an audit trail of analytical decisions [23].

The types of information we will focus on during the analysis include:

- Conceptualizations of compassion within applied behavior analysis (ABA).
- Reported compassionate skills or behaviors in ABA practice.
- Impacts of compassionate approaches on ABA outcomes.
- Barriers and facilitators to implementing compassionate care in ABA.
- Emerging trends or gaps in the literature regarding compassion in ABA.

Ethical Considerations

As this is a scoping review of existing literature and does not involve human participants, ethical approval is not required. However, ethical principles of research integrity will be followed, including accurate and complete reporting of methods and results.

Results

The current status and planned timeline for the study are as follows:

- Protocol development: Completed in December 2024.
- Systematic literature search: Scheduled to commence in January 2025.
- Title and abstract screening: Planned for January-February 2025.
- Full-text review and data extraction: Planned for February-March 2025.
- Data analysis and synthesis: Expected to take place in April-May 2025.
- Final report writing: Scheduled for June-July 2025.
- Submission for peer review: Anticipated in August 2025.

As of this protocol publication, the selection of sources has not yet been initiated. Once the literature search is conducted, we will update this section with the number of papers retrieved and included in the review, using a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram to illustrate the selection process.

Discussion

Principal Findings

This scoping review aims to provide a comprehensive overview of compassion in the context of ABA. We expect to synthesize definitions and conceptualizations of compassion, map specific compassionate skills, analyze existing interventions and training programs, identify outcomes associated with compassionate practice, and highlight barriers and facilitators for implementing compassionate practices in ABA.

Interpretation of Findings

The anticipated findings of this review have the potential to significantly impact ABA practice. By synthesizing existing evidence on compassionate skills in ABA, we expect to highlight the importance of integrating compassion into behavioral interventions. This could lead to a paradigm shift in ABA, promoting a more holistic and client-centered approach that balances behavioral techniques with empathetic care.

Comparison With Existing Literature

While compassion has been extensively studied in other health care fields, its exploration in ABA is relatively new. Our review will build upon existing literature on compassion in health care, such as the work of Sinclair et al [8] on compassion in palliative care, and extend these concepts to the unique context of ABA.

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This review will also complement recent studies on the integration of “soft skills” in ABA practice [4], providing a more focused examination of compassion specifically.

Strengths and Limitations

A significant strength of this study is its comprehensiveness, including a wide range of study types and not being limited to a specific geographical context. This will allow a global view of compassionate practices in ABA. However, a potential limitation is the possibility of missing relevant studies due to differences in terminology or inadequate indexing. To mitigate this, we will conduct a comprehensive search with varied terms and consult with experts in the field.

Implications for Practice and Policy

The results of this scoping review have the potential to inform the development of compassion training programs for behavior analysts, improve clinical practices, and influence care policies in ABA. By identifying specific compassionate skills and existing training programs, we can provide a foundation for developing more comprehensive and effective compassion training in ABA education and professional development.

Future Research Directions

This review is likely to identify gaps in the current understanding of compassion in ABA, providing direction for future empirical studies. Potential areas for future research may include developing and validating measures of compassion specific to ABA practice, conducting intervention studies to assess the impact of compassion training on client outcomes, and exploring the long-term effects of compassionate ABA practice on client well-being and therapeutic relationships.

Conclusions

This scoping review represents a crucial step in understanding and promoting compassionate care within ABA. By synthesizing existing knowledge and identifying areas for future research, we aim to contribute to the evolution of ABA toward a more compassionate and holistic approach to behavioral intervention. This work underscores the importance of balancing technical proficiency with empathetic care in ABA practice, potentially leading to improved outcomes and experiences for clients and practitioners alike.

Dissemination of Results

The results of this scoping review will be disseminated through publication in a peer-reviewed scientific journal. In addition, the findings will be presented at relevant ABA and psychology conferences. A summary of the results will be shared with professional ABA organizations to facilitate knowledge translation into practice.

Acknowledgments

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Data Availability

This protocol has been registered on OSF Registries (osf.io/f3a6h) [24]. The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

All authors handled methodology and writing-review and editing. DA and JA contributed conceptualization. GF, CC, ND, and JA managed validation. DA and JA performed writing-original draft. JA managed supervision. DA conducted project administration. JM, MS, and ES performed visualization. DA, DS, SC, MF, ES, JM, MS, MR, and JA managed formal analysis. SL, NC, HC, JF, VB, AL, PF, DO, and CM conducted resources. GF, CC, ND, and JA software. All authors read and approved the final protocol.

Conflicts of Interest

All authors have completed the International Committee of Medical Journal Editors (ICMJE) uniform disclosure form and declare: no support from any organization for the submitted work; no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work.

Multimedia Appendix 1
Data extraction instrument for a scoping review on compassion in applied behavior analysis.
[DOCX File , 15 KB - resprot_v14i1e66399_app1.docx]

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Abbreviations

ABA: applied behavior analysis
ASD: autism spectrum disorder
MeSH: Medical Subject Headings
PCC: population, concept, and context
PRISMA: Preferred Reporting Items for Systematic Review and Meta-Analyses
PRISMA-ScR: Preferred Reporting Item for Systematic Review and Meta Analyses extension for Scoping Reviews
SCED: Single-Case Experimental Design

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Protocol

Primary Tumors of the Brain and Central Nervous System in Adults and Children in Sub-Saharan Africa: Protocol for a Scoping Review

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Abstract

Background: In Sub-Saharan Africa (SSA), clinical and research investments for oncology screening, diagnosis, and therapy are exceedingly modest, compared to those in higher-income regions. Diseases that are difficult to prevent or treat, such as primary brain and central nervous system (CNS) tumors, are especially challenging in low-resource settings.

Objective: In order to review and synthesize existing evidence to identify research and service gaps, we will conduct a scoping review to assess epidemiological data, clinical series, and health outcomes associated with brain and CNS tumors in SSA.

Methods: This scoping review is guided by the Scoping Review Chapter of the JBI (Joanna Briggs Institute) Manual for Evidence Synthesis. We will search the following databases: Ovid MEDLINE, Embase, Cochrane Library, Scopus, references from salient publications, and the gray literature, the latter focused on the International Agency for Research on Cancer (IARC) and other major global health organizations. We will review titles and abstracts of potentially eligible studies and then full texts by 2 independent reviewers. We will include data from both primary and CNS cancers in persons of all ages. Data will be abstracted independently using piloted data extraction forms, and we will present results according to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) and PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analyses Protocols) guidelines.

Results: A total of 2857 articles were identified through our search strategy. After title and abstract screening, which was completed on February 23, 2025, by 2 independent reviewers, 222 studies met the eligibility criteria, while 2203 were excluded. Full-text screening began on March 3, 2025, and will be followed by data abstraction and analysis from April 15, 2025, until the end of May 2025. The study is expected to be completed by July 2025.

Conclusions: SSA faces substantial challenges in the diagnosis and treatment of CNS tumors due to health care infrastructure limitations, insufficient reporting, and diagnostic supply shortages. The high fatality rates are attributed to underdiagnosis and misdiagnosis as infectious diseases, despite low incidence rates (IRs). The inadequate neurosurgery facilities and pathology resources further complicate the treatment and prognosis. A scoping review will investigate the true burden of underdiagnosis and gaps in outcomes in children and adults in SSA.

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KEYWORDS

tumor; cancer; brain; central nervous system; Africa; adults; children; scoping review; PRISMA

Introduction

A significant proportion of new cancer cases worldwide are estimated to occur in low- and middle-income countries (LMICs), but the true prevalence is underestimated due to limited diagnostic capacities [1,2]. Sub-Saharan Africa (SSA) faces challenges in providing the necessary oncology and neurology services for the management of central nervous system (CNS) tumors. Reported cases in SSA are far lower than the actual disease burden due to insufficient health infrastructure for accurate diagnosis, treatment, prognosis, and reporting of tumors, with limited access to drugs, surgery, and modern immunotherapies. Poverty, poor public health surveillance infrastructures, and a lack of services in the vast rural landscape further hinder accurate monitoring of cancer outcomes in SSA, contributing to an underestimation of the true disease burden [3]. Late detection of cancers is common, with later reporting and higher reported case fatality rates among adults and children [4]. Furthermore, the SSA medical workforce in oncology, neurology, and neurosurgery is severely undercapacitated, further impeding the effective management of brain and CNS tumors.

Although less common than other neoplasms, CNS tumors rank comparatively high as a cause of death due to their high case fatality rates. The exact etiologies of these tumors remain largely unknown, with various risk factors, such as genetics and environmental exposures (chemical, nutrition, and radiation) proposed, but the evidence linking them to brain tumors remains inconclusive [5-7]. With over 150 distinct types of brain tumors [8], diagnosing them is a challenge. The diagnosis of brain and CNS tumors in LMICs is less frequent than that of high-income countries [9,10], but we cannot be sure that lower incidence, prevalence, or mortality result from limited surveillance, poor diagnostic capacities, deaths from brain/CNS tumors that are not confirmed as such, poor health care access, and/or population structures that require age-standardized adjustments. A reported standardized incidence rate (SIR) for primary CNS tumors in LMIC in 2008 was estimated to be 3.2-3.9 per 100,000 population, while high-income countries had a far higher SIR of 20.1 per 100,000 population; the authors of this CNS cancers report suggested limited infrastructure for tumor management teams (eg, oncologists, neurologists, pathologists, radiologists, and neurosurgeons) to be contributing to underdiagnosis [10].

In 2022, the African continent accounted for 5% of all global brain/CNS tumors prevalence and 6.4% of deaths from these causes [11,12]. Since over 18% of the estimated 2022 global population was in Africa [12], this suggests either a truly lower incidence or conspicuous underreporting. Childhood brain/CNS tumors were more commonly reported in Africa, with 14.2% incidence rates (IRs) of new global brain/CNS tumor cases and 16.9% of deaths reported in 2022 for children aged 0-18 years old [11,12]. An additional source of underreporting of brain and CNS tumors in Africa is the scarcity of well-established tumor registries [9,10].

Based on the Surveillance, Epidemiology, and End Results (SEER) Program from the National Cancer Institute, childhood brain and other nervous system cancers account for 15.9% of all new childhood cancer cases in the United States [13]. This is similar to the 14.2% reported IRs in Africa, pointing to the fact that childhood CNS tumors are a noteworthy source of cancer morbidity and mortality in both LMICs and high-income countries. However, the similarity in incidence also emphasizes that underreporting and hence, underdiagnosis, in Africa, possibly obscure the actual burden of CNS tumors in SSA. This highlights the necessity to further investigate the epidemiological and clinical characteristics of childhood brain and CNS tumors in LMICs, considering the existent gaps in diagnosis and treatment.

Neuro-oncologic care in East Africa, with a population of over 440 million people in 2021 relied on only 1 neurosurgeon for every 9 million people, in comparison to 1 per 62,500 people in the United States [1,10], with a 1:144 ratio of neurosurgeons in SSA compared to the United States (population-standardized). This vast neuro-oncologic care gap has been noted for children where only 15%-45% received curative options for brain/CNS tumors in LMICs, in comparison to 80% in high-income countries [1]. In SSA, many primary CNS tumors go undiagnosed, as cases with nonspecific symptoms such as headache, ataxia, vomiting, or seizures are often misdiagnosed for different diseases. Even presentation with a visible cranial mass may not result in a pathology-confirmed diagnosis, particularly in rural areas, as only 35% of the developing countries in Africa have pathology resources in their institutions [14]. Despite efforts to diagnose primary CNS tumors in SSA based on global guidelines, challenges persist due to the low per capita total health expenditure in African countries (US $135 in 2010), in comparison to US $3150 in high-income countries. This discrepancy limits the holistic approach to tumor diagnosis, contributing to underreporting and expected high fatality rates [15].

Given the heterogeneity of existing literature on primary CNS tumors in SSA across both pediatric and adult populations, a scoping review is the most suitable method to map the current evidence and evaluate the knowledge state. Our scoping review will investigate a variety of epidemiological and clinical variables, unlike systematic reviews, which address narrow research questions. This will help pinpoint underexplored topics, present data across different age groups, and compare results across different SSA regions, yielding insights that may be missed in narrower reviews.

There is a noteworthy gap in studies that comprehensively explore both epidemiological and clinical data for children and adults with primary CNS tumors in SSA. Existing scoping and systematic reviews often describe either particular populations or disease aspects [14,16], leaving key interconnections between them unexplored. By investigating data from both groups, as well as focusing on the period from 1999 to 2024 when SSA countries incorporated better usage of imaging modalities like

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computed tomography scans and MRI (magnetic resonance imaging), and World Health Organization (WHO) primary CNS tumors classification was well updated, our review will shed light on the true burden of underdiagnosis and high rates of fatality in SSA.

The aim of our scoping review is to better understand the frequency and outcomes of primary brain/CNS tumors in SSA across both adult and pediatric populations. This includes data interpretation from population-level surveillance registries and clinical health care settings. By considering factors such as age, sex, diagnostic methods, treatment options, and prognostic outcomes, we aim to provide a comprehensive understanding of the epidemiology and distribution of CNS tumors in SSA in the context of regional and sociodemographic differences. We will also investigate the IRs and prevalence to understand the frequency and the burden of tumors. The clinical course of the brain or CNS tumors will be assessed for information on progression, symptoms, complications, and outcomes. We will assess the impact of early diagnosis and treatment, highlighting the benefits and challenges associated with the timely intervention. The insights from this review can facilitate a holistic approach to effective planning and resource allocation, including the establishment of cancer registries in the region.

Methods

Objectives

Our scoping review protocol is designed to provide a comprehensive understanding of the epidemiology and distribution of CNS tumors in SSA, considering regional and sociodemographic variations. Methods for inclusion and analysis of articles will be performed according to the updated JBI (Joanna Briggs Institute) guide to scoping review methodology [17]. The main items in the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) and PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analyses Protocols) [18,19] will guide the reporting of the protocol process, methods, and findings. The protocol is registered with the Open Science Framework since March 21, 2024, and will be updated.

Research Questions

After a preliminary literature review and consultation with experts, we finalized the specific objectives of this scoping review as follows:

1. What is the state of knowledge about brain/CNS tumors in adult and child patients in SSA?
2. What are the best available estimates of SIRs and prevalence of primary CNS tumors, based on SSA population-based surveillance and registries?
3. What are the characterizations of clinical presentations, diagnoses, and outcomes of primary brain/CNS tumors, based on case series from SSA health care settings?

Identifying Relevant Studies—Study Selection and Eligibility Criteria

A few studies have covered similar ground, but we seek to update and expand on the existing research conducted on adults and children in SSA [14,16,20,21]. We will use a comprehensive search strategy without age or language restrictions, searching over a 25+ year period (1999 – 2024). Studies based on secondary/metastatic brain tumors (based on the 2021 WHO classification of Brain/CNS tumors), endocrinological tumors, peripheral nervous system tumors, and metastatic tumors are excluded, such that we only review primary brain/CNS neural tumors in persons of all ages. SSA populations are included from the 48 nations considered to be SSA by the World Bank (Textbox 1) [22]. (There are 46 countries considered by the United Nations Development Programme as SSA and 47 countries are in the Africa Region of the WHO).

Textbox 1. Nations in Sub-Saharan Africa as per the World Bank classification.

Angola; Benin; Botswana; Burkina Faso; Burundi; Cabo Verde; Cameroon; Central African Republic; Chad; Comoros;

Democratic Republic of the Congo; Republic of the Congo; Côte d'Ivoire; Equatorial Guinea; Eritrea; Eswatini; Ethiopia;

Gabon; Gambia; Ghana; Guinea; Guinea-Bissau; Kenya; Lesotho; Liberia; Madagascar; Malawi; Mali; Mauritania; Mauritius;

Mozambique; Namibia; Niger; Nigeria; Rwanda; São Tome and Principe; Senegal; Seychelles; Sierra Leone; Somalia;

South Africa; South Sudan; Sudan; Tanzania; Togo; Uganda; Zambia; Zimbabwe

*Does not include six nations deemed by the World Bank to be in North Africa: Algeria, Djibouti, Egypt, Libya, Morocco, and Tunisia

Data sources include patient series data and population-level data from a 1999-2024 data collection period. Studies published before 1999 are excluded due to limited SSA data availability from that earlier period, the relative local scarcity of diagnostic tools like MRI, and the unavailability of most treatment outcomes in the 20th Century. The inclusion of a given article depends on data contributing to one of the specific objectives of this scoping review, such as clinical presentation, outcome, diagnosis, treatment, prevalence, and/or incidence. Data are eligible from case series, cross-sectional studies, tumor registries, and studies that provide epidemiologic, clinical, and/or outcomes data, Articles that are limited to case studies, systematic reviews, or meta-analyses are excluded in screening but may be relevant to our discussion (as when we compare our findings with previous reviews).

Search Strategy

The review team includes a public health/medical librarian (KDB) for assistance with devising a comprehensive search strategy. The first step of this process was an initial limited search in PubMed conducted by a clinical epidemiologist (SHV). From this initial search, the review team identified relevant validation articles and supplied these to the librarian. By reviewing these papers' title/abstract keywords and index terms (Medical Subject Headings [MeSH]), and by referring to the

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WHO Classification of Brain Tumors, the librarian worked with the team to devise an in-depth search strategy for MEDLINE (Ovid platform) and other data sources.

As the librarian developed the main database search, the research team met frequently to review the search log and address specific questions on nosology to make final decisions on terms that should or should not be used (for example, the decision to exclude chondro-osseous tumors, even though this is listed in the WHO classification, but to include "chondrosarcoma").

This search strategy was peer-reviewed according to the Peer Review of Electronic Search Strategies (PRESS) guidance checklist by the Canadian Agency for Drugs and Technology in Health (CADTH) before it was translated to run in the other databases searched for this in-depth scoping review. The other databases that the team used to search for literature are Embase (Ovid platform), Global Health (Ovid platform), Web of Science (Clarivate Analytics PLC), Africa-Wide Information (EBSCO Information Services), and Africa Index Medicus (WHO). A search across all databases was executed in September 2024 (Multimedia Appendix 1). These databases were chosen because of the breadth of medical literature indexed in all the platforms, the availability of literature pertaining to a wide range of countries (especially SSA nations) in the case of Global Health, Africa-Wide Information, and Africa Index Medicus, and the citation network features and gray literature available in Web of Science. To uncover additional gray literature, the authors will search websites (eg, IARC [International Agency for Research on Cancer], WHO, professional organizations) for policy documents on brain/CNS tumor care, best practices, and additional data. As recommended by the JBI Manual for Evidence Synthesis [23], a 3-step search strategy will be used, including a search of reference lists of the included studies for additional sources.

Selection of Sources/Screening

The search results obtained from the medical librarian will be imported into Covidence (Cochrane Reviews). After removing duplicate articles, we will proceed with a two-stage screening process, which includes evaluating titles/abstracts and full texts against our predefined eligibility criteria. Each stage of screening will be conducted independently by two reviewers from our screening team (AAA-F, MA, CA, and MK). Before the initial screening of titles and abstracts, we will calibrate our citation screening form through pilot testing. This calibration process will involve three reviewers independently assessing a random sample of 25 citations obtained from the literature search. The team will then convene to discuss any discrepancies with the team's senior members (IB, VM, or SHV) and refine the eligibility criteria and screening form. Actual screening of titles and abstracts will commence once we achieve at least 75% agreement among the reviewers.

For full-text screening, all articles marked as "include" by two screeners during the title/abstract screening phase will undergo an independent assessment by a third reviewer (VM or SHV) for disparities in judgments. If we are unable to access the full text of any article through the Yale University database or open-access sources, we will use other libraries and/or initiate contact with the first author via email to request a PDF copy of the article, with a goal of securing all studies deemed eligible for our scoping review.

Throughout the review process, we plan to maintain regular communication and collaboration among the screening team members. We will schedule weekly meetings to discuss any observations or insights related to the review process. If necessary, adjustments to the inclusion criteria will be documented and implemented based on these discussions. In addition, we will diligently document reasons for excluding articles during the full-text review phase in Covidence, and we will adhere to the PRISMA-ScR guidelines to create a flow diagram that visualizes the selection process and documents the exclusion reasons.

Data Charting and Synthesis of Results

A data extraction form using Covidence software and Microsoft Excel file in addition to the PAGER (Patterns, Advances, Gaps, Evidence for practice and Research recommendations) framework [24] to categorize the data will be used to provide a descriptive outline of results that align with our scoping review objectives. Before implementation, the data extraction form will be pilot-tested using the first 25 studies to ensure that all the information was captured accurately. Any deviations or additions to our data extraction table (Multimedia Appendix 2) will be reported in the final scoping review.

The team will extract the following data for each included study:

- Study characteristics, including year of publication, study type, the period of the study, aims of the study, location of patients or participants, and the number of patients with brain or CNS tumors.
- Patient and tumor characteristics including the origin of data (coming from a registry or a health care setting), sex, age or age range, and the types of any diagnosed brain/CNS tumors. Insofar as possible, we will classify tumors as supratentorial and infratentorial and will provide more detailed tumor anatomical distribution information when available.
- Clinical presentation including diagnoses, therapy highlights, outcome highlights per case, age, and sex, will also be identified. In addition, IRs, SIRs, prevalence, survival rates, mortality rates, and case fatality rates (CFR) will all be identified if available from a specific source.

The 2 reviewers will divide the source load and independently extract data from the included articles. Subsequently, each author will review the extracted data of the other [19]. Discrepancies in extracted data will be discussed between reviewers until consensus is reached or by arbitration of a third reviewer (VM or SHV), as required to ensure the dignity and consistency of the scoping review and accurate data collection. To ensure inter-rater reliability, a 20% sample of included articles independently reviewed will then be compared by the 3 members of the research team.

Data Analysis and Presentation

For data analysis and presentation of the results, we will follow the recommendations outlined in the JBI Manual for Evidence Synthesis [23]. In addition, we will use the PAGER framework

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[24] for scoping reviews to identify recurrent themes and patterns through thematic analysis. This approach will facilitate the identification of key themes and patterns, with frequencies used to summarize the extracted qualitative information. Using SAS software (SAS Institute), quantitative data will be analyzed and presented in tables and graphs. After data extraction, which will be conducted using either a standardized Microsoft Excel file or Covidence (to be determined), the data will be imported into SAS for cleaning and analysis. The qualitative data will undergo thematic analysis to identify recurrent themes and gaps in the literature. The PAGER framework will guide this analysis, categorizing the data into five dimensions: Patterns, Advances, Gaps, Evidence for practice, and Research recommendations that align with our objectives [24].

We will apply thematic analysis to identify key patterns across qualitative data using the qualitative software NVivo (Lumivero), organizing the information by country, tumor type, and context. Thematic analysis will be used alongside narrative synthesis to integrate and interpret the findings. Figures related to the qualitative data will address the following points:

- Treatment modalities
- Diagnostic method used
- Location of tumor: infratentorial/supratentorial—pie chart for different tumor types
- Type of health care facility

Quantitative results will be summarized to highlight frequencies and describe notable patterns and findings relevant to our objectives. The results will be presented in tables and graphs to provide an overview of the key findings. Descriptive statistics will be performed for the numerical data (mean, median, range, and frequency distribution), and demographic will be based on geography, age, gender, and ethnicity.

- Summaries of epidemiological data
- Number of patients to doctors, facilities, and frequency diagnostic tools
- Mortality
- Number of studies and type
- Number of countries included in the paper after screening
- Distribution of brain tumors across years/different regions in SSA / ages

Data Visualization

We will summarize IRs, SIRs, prevalence, survival rates, mortality rates, and CFRs using tables. We will also use bar charts to illustrate tumor types, sex, and age distribution for children and adults across different regions. In addition, we will generate heat maps to highlight regional variations in tumor epidemiology.

Ethical Considerations

Our literature review was determined exempt from ethical review by the Yale University institutional review board as it does not involve human subjects; all data reviewed are from published sources. We will disseminate our findings through publication, presentations, and targeted sharing with stakeholders. These include oncology-interested community-based organizations and nongovernmental organizations, medical and cancer centers, Ministries of Health, interested professional organizations including oncologists, neurosurgeons, neurologists, and international organizations.

Results

Initially, we identified 2857 articles relevant to our search strategy. After title and abstract screening, which was completed on February 23, 2025, by 2 independent reviewers using Covidence, we retrieved 222 studies that met our eligibility criteria. A total of 2203 papers were excluded for not meeting the criteria. Full-text screening will commence on March 3, 2025, and is expected to be completed by April 15, 2025. Directly after, data abstraction and charting will begin with 2 independent reviewers to extract the relevant data and key findings, and discrepancies will be resolved by a third reviewer. Data analysis will follow on May 15, 2025, and we aim to complete the final paper by September 2025.

Discussion

Principal Findings

Our scoping review focuses on mapping the evidence on CNS tumors in SSA, comprehensively, across pediatric and adult populations. We anticipate to find noteworthy underreporting of CNS tumors in the SSA region attributed to health care infrastructure limitations, diagnostic constraints, and inadequate cancer registries. Data underreporting likely results in an underestimation of the actual burden of CNS tumors in SSA. We additionally expect the review to reveal a high degree of heterogeneity in the available evidence, with variant tumor types, incidence and prevalence rates, and regional outcomes. This variation is expected to mirror differences in health care accessibility, medical workforce strength, and diagnostic criteria availability, which can identify possible areas that necessitate interventions.

Our review will summarize and present data from a broad range of studies to overcome any limitations or fragmentation of the existing literature [14,16]. Comparing our findings to the current data will suggest how SSA countries can adapt these local contexts to best practices. Our targeted populations and the review span of the last 25 years are essential for age-appropriate strategies for diagnosis and treatment, and the assessment of diagnostic improvements in the detection and management of CNS tumors in SSA. Further, this review can provide beneficial insights for health care providers and policymakers, as we assess regional differences in health care infrastructure and access to neuro-oncological care. Nevertheless, there are expected limitations, such as challenges in producing findings from studies with variations in sample size, methodology, and quality, given the heterogeneous studies. The insufficiency of robust cancer registries in many SSA countries, misdiagnosis, and underdiagnosis of CNS tumors, present a challenge in identifying the true incidence and prevalence rates of CNS tumors in SSA.

Understanding the factors that lead to a high incidence of these tumors, and longitudinal studies to examine patient survival and quality of life, should be an area of focus for future studies

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to improve neuro-oncological care in SSA. Upon the completion of the review, we will seek the dissemination of the findings broadly to ensure that researchers, health care providers, public health organizers, and policymakers have a reach of our review. The aim is to have JMIR as our primary method of dissemination, where our findings can be distributed regionally and globally. We also intend to present the results at international conferences that focus on global health, neuro-oncology, and oncology, which helps in the engagement with many stakeholders.

Patient and Public Involvement

No patients or members of the public were involved in the review protocol. However, many decades of clinical experience and epidemiological study of tumors in Africa are represented by senior members of the research team (CA, IB, VM, SHV) [25-45].

Dissemination

Our scoping review aims to provide valuable insights to various stakeholders involved in cancer care and management in Africa. This includes Ministries of Health, international agencies, cancer centers, patient advocates and policymakers, and health care providers and managers including internists, pediatricians, nurses, neurosurgeons, neurologists, hospital directors, and others caring for oncology patients. By conducting this review, we will address key questions to help set priorities for diagnostic, therapeutic, and research action, clarify brain/CNS cancer trends, and better characterize populations most affected. We hope that the timing is favorable now that HIV and AIDS investments have improved chronic care capacities in many SSA nations [46].

Conclusion

SSA faces a unique set of challenges, including a high burden of infectious diseases and limited health care infrastructure, which increases vulnerability to various health conditions. The lower reported incidence of CNS tumors in this region is likely influenced by underdiagnosis, lack of advanced diagnostic tools, and the absence of comprehensive cancer registries [47]. However, emerging evidence suggests that CNS tumors may be relatively common in this region compared to high-income countries, with certain infections such as Epstein-Barr virus and HIV playing a significant role in their etiology. These infections may complicate the diagnosis and management of CNS tumors, emphasizing the critical need for enhanced diagnostic capacity, targeted research, and effective policymaking to improve health care systems and address this multifaceted challenge.

Acknowledgments

Ms Jan Glover, MLS, Yale University, assisted our literature search with her thorough review. SHV is supported in part by the Yale Cancer Center (P30CA016359).

Data Availability

The data supporting the findings of this scoping review will be open and accessible to everyone in an appendix of the final manuscript. Extracted data will be provided as supplementary materials accompanying this paper. For more specific information, please contact the corresponding authors.

Authors' Contributions

AAA-F, MA, CA, MK, and SHV conducted conceptualization. AAA-F, MA, CA, MK, KDB, and SHV contributed to methodology. CA, IB, VM, and SHV performed validation. MA and AAA-F with the guidance of SV, CA conducted formal analysis. AAA-F, MA, and SHV performed investigation. KDB managed resources. AAA-F, MA, CA, MK, and SHV conducted data curation. SHV, AAA-F, and MA performed supervision. SHV managed project administration and funding acquisition. MA, AAA-F, CA, and SHV conducted visualization. AAA-F, MA, CA, MK, KDB, and SHV wrote the original draft. AAA-F, MA, MK, CA, IB, VM, and SHV handled writing—review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 15 KB - resprot_v14i1e66978_app1.docx]

Multimedia Appendix 2
Data extraction form for each eligible study reviewed.
[DOCX File , 22 KB - resprot_v14i1e66978_app2.docx]

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Abbreviations

CADTH: Canadian Agency for Drugs and Technology in Health
CFR: case fatality rate
CNS: central nervous system
IARC: International Agency for Research on Cancer
IR: incidence rate
JBI: Joanna Briggs Institute
LMIC: low- and middle-income country
MeSH: Medical Subject Headings
MRI: magnetic resonance imaging
PAGER: Patterns, Advances, Gaps, Evidence for practice and Research recommendations
PRESS: Peer Review of Electronic Search Strategies
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analyses Protocols
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
SEER: Surveillance, Epidemiology, and End Results
SIR: standardized incidence rate
SSA: Sub-Saharan Africa
WHO: World Health Organization

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Protocol

Pain Assessment Tools for Infants, Children, and Adolescents With Cancer: Protocol for a Scoping Review

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Abstract

Background: Pain management in children with cancer may be inadequate due to poor pain assessment, and evaluation using suitable tools is necessary. Despite the availability of many pain assessment scales, few studies have summarized the existing assessment tools, making it challenging to select a suitable scale.

Objective: This scoping review aims to map existing pain assessment tools for children with cancer and provide a comprehensive overview of pediatric cancer-related pain screening and assessment tools.

Methods: The scoping review will be conducted according to the guidelines by the Joanna Briggs Institute and reported following the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) framework. Electronic databases, including PubMed, CINAHL, CENTRAL, ICHUSHI (Japan Medical Abstracts Society), and Embase, will be searched to identify eligible studies, without date or language restrictions. We defined the eligibility criteria based on the PCC (Population, Concept, and Context) format. Studies that focused on assessment tools for evaluating pain in children (aged 0-18 years) with cancer in a hospital or at home will be included. Although there are no restrictions on study design, protocols and conference abstracts will be excluded. Two or more reviewers will select studies by reviewing the full text of relevant articles identified by titles and abstracts, and disagreements will be resolved through discussion. Two or more reviewers will extract predefined data items, including characteristics of included studies (eg, author name, title of publication, year of publication, purpose of study, study setting, study population, outline of the assessment tool, study design, and findings) and the characteristics of assessment tools (eg, types of tools, target population, assessor, validity, instructions, precautions, and advantages and disadvantages of the tools). Pain assessment tools will be summarized in tabular format and described in a narrative synthesis.

Results: Through electronic database searches on November 20, 2023, we identified 3748 articles. This review will provide a comprehensive overview of pain assessment tools. The final report is planned for submission to a peer-reviewed journal in 2025.

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Conclusions: This scoping review is the first comprehensive effort to map existing tools on pediatric cancer-related pain assessment tools for infants, children, and adolescents aged <18 years, according to developmental stages. Based on the findings of this study, we will discuss future clinical and research implications for pain assessment and management in children with cancer. The findings are expected to enhance pain management practices in children with cancer and inform health care providers, policy makers, and other stakeholders.

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KEYWORDS

pediatric; infants; children; adolescents; pediatric cancer; developmental stage; pain assessment tool; scoping review

Introduction

Annually, an estimated 400,000 children and adolescents aged 0-19 years are diagnosed with all types of cancer [1,2]. Due to advances in medical care, >80% of these children will become long-term survivors in high-income countries, while <30% will be cured in low- and middle-income countries [1,3]. In Japan, 2000 diagnoses of childhood cancer are issued annually, and the 5-year survival rate is reported to be 80% [4].

Palliative care for children refers to the active total care of the child's body, mind, and spirit, and involves providing support to the family. It begins when the illness is diagnosed and continues regardless of whether a child receives treatment directed at the disease [5]. Children with cancer experience pain resulting from the disease itself, medical treatments (eg, chemotherapy and radiation therapy), and procedures (eg, lumbar punctures and bone marrow punctures), from diagnosis to end of life or post treatment [6]. Pain is one of the most distressing experiences for children during treatment [7]. Studies have shown that 39% of children undergoing cancer treatment and 58% of children who are terminally ill experience severe pain-related distress [8]. Schulte et al [9] suggest that ineffective pain management during treatment, combined with lifestyle factors, late effects, and psychological stress, may lead to long-term chronic pain. Moreover, the child's experience of pain affects family members and is one of the factors that increase family emotional distress during treatment [10]. This distress, in turn, is transmitted to the child, creating a vicious cycle that exacerbates the patient's pain [11].

Underlying the inadequate pediatric cancer pain management is the lack of proper pain assessment, which is key in initiating pharmacologic or nonpharmacologic therapy to assess and modify the effectiveness of treatment and care. Self-report is the gold standard for pain assessment [12], and a 2015 report by Wolfe-Christensen et al [13] found that 99% of children older than 13 years and 96% of children aged 7-12 years can reliably self-report pain. Conversely, children express pain differently depending on their developmental stage and cognitive abilities, requiring the use of differing tools for pain assessment. Therefore, observation of developmental stage-specific expressions, selection of suitable pain assessment tools, and appropriate interventions are necessary. In addition, studies suggest that parents often detect their child's pain more quickly than health care providers do [14]. In a 2019 report, Madden et al [15] indicated that both children and caregivers rated pain and lack of appetite as the most distressing symptoms, with a strong correlation between children's and parents' reports of pain (r_s>0.8). Therefore, parental involvement must also be considered in the assessment of pain in children. Although many tools for pain assessment exist [16], few studies have mapped availability based on children's developmental stages. This study aims to map existing studies on the assessment of cancer-related pain in pediatric patients. Moreover, it summarizes the characteristics of children's expression of cancer pain across developmental stages, as well as tools, instruments, and indicators used for pain assessment and their associated outcomes. This study is also expected to summarize parental involvement and outcomes of cancer-related pain assessment. Based on the findings, the need for future research on pain management in pediatric cancer will be discussed. Thus, our primary goal is to synthesize existing literature on cancer-related pain assessment tools for infants, children, and adolescents aged <18 years, ultimately contributing to more accurate pain assessments essential for effective pain management.

Methods

Study Design

We will conduct a scoping review following the Joanna Briggs Institute (JBI) Manual for Evidence Synthesis [17]. Research team members discussed and revised the drafted protocol. The final report will be presented following the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) [18]. This study will address the question, "What pain assessment tools are available to measure pediatric cancer-related pain according to the child's developmental stages?"

Eligibility Criteria

The eligibility criteria will be decided based on the PCC (Population, Concept, and Context) format and type of study [17].

Population

We will include studies that have targeted infants, children, and adolescents aged between 0 and 18 years [19] with any type (eg, leukemia, tumor, or sarcoma) and any phase (eg, prediagnosis, during treatment, and posttreatment) of cancer. If the studies have focused on a mixed population, including adults and those with other diseases, we will include the studies in which over 80% of the population meets our eligibility criteria.

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Concept

We will include studies that have investigated, described, and validated assessment tools, including scales, instruments, questionnaires, charts, worksheets, and measurements, to assess cancer-related pain. Cancer-related pain was defined as pain caused by the cancer itself and cancer treatments (eg, chemotherapy, stem cell transplantation, immunotherapy, hormone therapy, or radiation). We will include studies that have investigated comprehensive symptom assessment tools if they also include pain assessment as an item. However, we will exclude studies if these tools assess other concepts, such as quality of life. Self-assessment by children with cancer and proxy pain assessment by parents, caregivers, and health care professionals will also be included. While cancer pain is often chronic and multifaceted, procedural and postoperative pain is typically acute and directly related to specific interventions and time limitations [20,21]. Thus, to focus more on cancer-related pain, studies that have focused on procedural or postoperative pain will be excluded. Studies that use measurement tools without providing details about them, such as those evaluating the effectiveness of an intervention, will also be excluded.

Context

We will include studies conducted in any health care (eg, hospitals, hospices, and clinics) and home settings to assess pain in children with cancer.

Types of Studies

We will include both quantitative and qualitative studies, as well as systematic reviews published in English and Japanese. In particular, we will include the following studies: experimental and quasi-experimental (eg, randomized controlled trials, nonrandomized controlled trials, before and after studies), observational (eg, prospective and retrospective cohort, case-control, and cross-sectional studies), descriptive observational (eg, case series, individual case reports, and descriptive cross-sectional), and exploratory (eg, in-depth interviews and focus group) studies. To map detailed information regarding pain assessment tools, we will exclude protocols and abstracts. Moreover, to ensure the quality of the studies, we will exclude gray literature.

Search Strategies and Information Sources

We will search electronic bibliographic databases, including PubMed, CINAHL, CENTRAL, Japan Medical Abstracts Society (ICHUSHI), and Embase to identify relevant studies using text words and index terms at a facility. Search strategies will be developed with a health librarian for each database. We will use keywords based on the PCC format, including “children,” “cancer,” “assessment tool,” and “pain.” Our search strategy for PubMed is shown in Multimedia Appendix 1. Moreover, we will search the identified relevant studies by checking the reference lists of included studies and textbooks. We will not set any limits on the search period and language.

Study Selection

In this study, we will organize a research team. We will screen using Rayyan [22] and report the relevant studies following the PRISMA flow diagram (Figure 1). All search results will be retrieved and imported to a reference management software (EndNote, Clarivate) and duplicate entries will be removed by checking them individually. First, two or more reviewers will independently read the title and abstract and assess the studies that meet our eligibility criteria. Second, two or more reviewers will independently read the full text and assess the eligible studies. Disagreements will be resolved by discussion, and a third author will be included if needed.

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Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

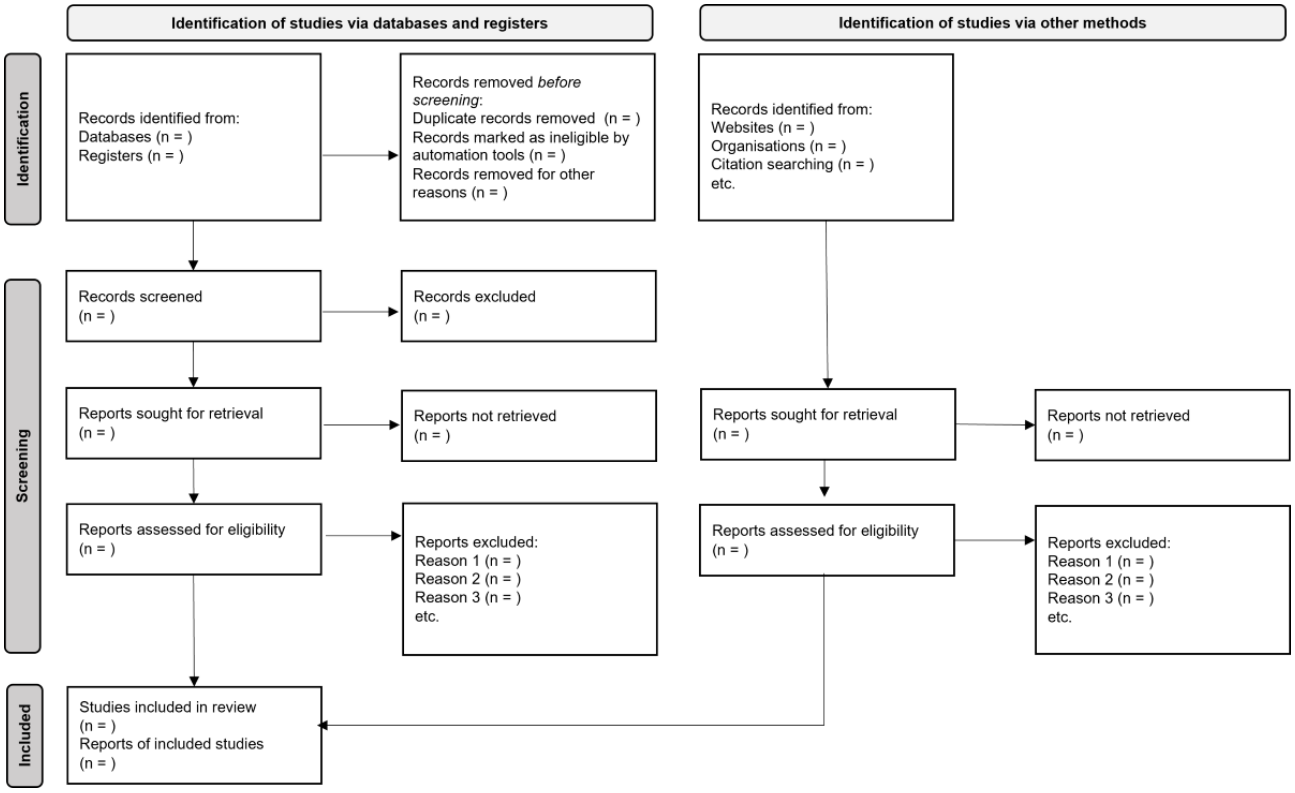

Data Extraction

The research team collaboratively developed a data chart in Microsoft Excel to extract and record data based on the research question. Initially, we intend to use this format for one or two studies and refine it accordingly, if necessary. Two or more reviewers will extract the relevant data from the included studies.

Data Items

We will collect data on the characteristics of the included studies and assessment tools.

The following characteristics will be assessed: author name, title of publication, year of publication, purpose of study, study setting, study population, outline of the assessment tool, study design, and findings (Table S1 in Multimedia Appendix 2).

The characteristics of assessment tools will include types of tools (eg, scale, instrument, or measurement), target population, assessor (eg, self, parents, caregivers, health care professionals), validity (including for Japanese children with cancer), instructions, precautions, and advantages and disadvantages of the tools (Table S2 in Multimedia Appendix 2).

Critical Appraisal of Individual Sources of Evidence

We have no plans to assess the risk of bias in individual studies, as the review aims to map the current evidence rather than synthesize study findings.

Synthesis of Results

The characteristics of the included studies and of assessment tools used to assess cancer-related pain in pediatric patients will be summarized in a tabular format and narratively described. In this synthesis, we will stratify self- and peer-administered assessment tools and present detailed information (eg, appropriate age range, types of pain, and instructions). Subsequently, we will discuss the selection of assessment tools for more accurate pain assessment and the identified research gaps.

Ethics and Dissemination

Formal ethical approval is not required, as primary data will not be collected in this study. The findings will be disseminated through a presentation at a conference and publication in a peer-reviewed journal.

Results

We conducted a database search on November 20, 2023, and identified 3748 articles related to pain assessment tools for children with cancer. This study will map these tools based on the existing evidence, providing a comprehensive overview of pediatric cancer-related pain screening and assessment tools. The final report is planned for submission to a peer-reviewed journal in 2025.

Discussion

To the best of our knowledge, this is the first comprehensive scoping review aimed at investigating pediatric cancer-related pain screening and assessment tools and at providing detailed information, such as target population, assessors, instructions, and validation. Although many pain assessment tools exist [16], few studies have mapped the available pain assessment tools and their instructions according to pediatric developmental stages.

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The findings from this comprehensive scoping review would inform pain management practices in pediatric oncology. Health care professionals can be better equipped to select the most appropriate assessment tools by mapping available tools considering developmental stages, assessors, and instructions for various tools. This tailored approach will lead to more accurate pain assessments, which is crucial for effective pain management. Moreover, a clearer understanding of available tools and their applications could enhance communication among health care professionals, children, and families regarding pain assessment. Respecting children's voices will foster more child- and family-centered care approaches. Ultimately, this may improve pain management outcomes and the quality of life for children with cancer-related pain. These findings may also serve as a valuable resource for health care professionals, policy makers, and other stakeholders in alleviating pain for children with cancer and their families.

The findings of this review will highlight areas where further research is needed, particularly in developing or validating tools for specific age groups. This can guide future research efforts to fill these gaps.

We will conduct a scoping review following the JBI Manual for Evidence Synthesis to rapidly map the existing evidence related to pain assessment tools for children with cancer. By conducting searches and screening based on rigorous methods, it is possible to comprehensively collect and describe existing evidence. The review will be reported according to PRISMA-ScR, ensuring the provision of necessary information. However, potential limitations exist. Although a scoping review depends on the quality of the included studies, this study will not assess the risk of bias as the aim of this study is to map existing evidence. Because we plan to conduct a bibliographic database search, it will be challenging to identify textbooks, books, and other publications not included in the databases. Consequently, some relevant literature on pain assessment tools may be missed.

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Data Availability

All data produced during this study will be included in the comprehensive review article and its supplementary information files.

Authors' Contributions

MH led the conceptualization, and other authors (N Yamaji, SI, AH, MM, TY, DH, EO, and N Yotani) designed this work. MH and N Yamaji drafted the protocol, and SI, AH, MM, TY, DH, EO, and N Yotani each made substantial contributions to critical revisions of the work. All authors approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy for PubMed.
[PDF File (Adobe PDF File), 112 KB - resprot_v14i1e66614_app1.pdf]

Multimedia Appendix 2
Template tables for data collection.
[DOCX File , 16 KB - resprot_v14i1e66614_app2.docx]

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Abbreviations

JBI: Joanna Briggs Institute
PCC: Population, Concept, and Context
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Gamification in mHealth Apps for Rehabilitation: Protocol for a Scoping Review

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Abstract

Background: The use of gamification in physical therapy mobile health interventions has increased rapidly in recent years, particularly with self-management of exercise in a home environment. Prior research has focused broadly on digital exergames, such as virtual reality or video games, or specifically on single concerns, such as stroke or musculoskeletal rehabilitation.

Objective: This scoping review aims to identify studies that have implemented gamification in rehabilitative interventions through mobile apps to treat all conditions addressed by physical therapists. Characteristics related to the rehabilitative process, gamification elements, and patient-related outcomes will be examined.

Methods: A literature search will be conducted on the following databases: MEDLINE (Ovid), Embase, CINAHL, PeDRO, Scopus, and Web of Science. Study inclusion criteria will be based on the PICO (Population, Intervention, Comparison, Outcome) framework, with publications describing the use of a gamified mobile app in a movement-based intervention in any area of physical therapy included. The reporting of results will adhere to PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews). A narrative synthesis of included publications will be performed.

Results: Database searches were completed in May 2024 and yielded 2148 publications, with an additional 49 records identified through manual searching of references. Title and abstract screening, full-text screening, and data extraction are expected to be completed by April 2025. The review is expected to be completed by September 2025.

Conclusions: Findings from this scoping review will provide evidence on gamified mobile apps to assist physical rehabilitation professionals with decision-making on remote interventions. Understanding game elements used in rehabilitative mobile apps may enhance patient engagement and adherence, which may ultimately improve patient-related outcomes.

Trial Registration: Open Science Framework fz9nq; https://osf.io/fz9nq

(JMIR Res Protoc 2025;14:e63600) doi:10.2196/63600

KEYWORDS

telerehabilitation; remote physical therapy; home exercise program; digital health; mHealth; mobile health; rehabilitation; scoping review; gamification; mobile health app

Introduction

Physical rehabilitation interventions following injury or impairment can improve the quality of life through movement-based care [1]. Physical therapists are trained to deliver interventions that treat a multitude of health conditions, including musculoskeletal, neurological, cardiopulmonary, cancer, metabolic, and pain issues. The impact of physical

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therapy can extend beyond the individual to the societal level, especially when the rehabilitation is comprehensive [2]. Thus, physical therapy is not only long-lasting and life-changing but also economically beneficial [3].

Physical rehabilitation is a long-term process that can begin in an inpatient setting and require subsequent services in the outpatient environment. Yet, for therapy to be effective, ongoing exercise in the home environment is often needed [4]. Home exercise programs (HEPs) are forms of supplemental treatment given to individuals to promote progression toward goals and maintain improvements outside of supervised therapy. However, patient adherence, or the extent to which an individual's behavior corresponds to provider recommendations, has been identified as the most significant, yet most unpredictable variable factor in HEP effectiveness [5].

Patient adherence to an HEP is influenced by many factors, from the individuals' beliefs and attitudes toward the treatment to self-efficacy and motivation in performing the activity [5]. Adherence to HEPs may be high in the early stages of treatment but tends to diminish over time, with typical HEP adherence rates estimated to be as low as 30% [4,6]. Given that adherence to HEPs is directly associated with improvement in clinical outcomes [6], strategies to increase adherence are needed to bridge the gap between performance in clinical and home settings. Technological advancements such as mobile health (mHealth) have been proposed to support self-management in home-based rehabilitative programs through low-cost scalable solutions [7]. mHealth is defined as any mobile device, such as smartphones or tablets, or app used to implement medical and public health practice with patients in a home setting through two-way communication [8]. Of the various forms of mHealth, mobile apps targeting health and wellness have seen substantial growth. To date, there are over 350,000 health-related apps available through various app stores worldwide, with nearly 14 million app downloads recorded in 2024 alone [9,10]. While these apps vary widely in terms of functionality, most health-related apps incorporate features such as remote monitoring, exercise instruction, activity tracking, and goal setting [11].

One mobile app characteristic that is important to consider in the context of rehabilitation adherence is gamification, or the use of game design elements to increase patient motivation and engagement [12]. In therapy, gamification has been explored primarily in pediatric neurorehabilitation to focus attention and facilitate repetition through hands-on immersive gameplay [13]. With mobile apps specifically, there has been rapid growth in the use of gamification to track and promote physical activity, such as with the popular augmented reality game, Pokémon GO, which increased daily step counts by 25% in over 32,000 users without directly promoting health outcomes [14]. However, the use of gamelike elements in rehabilitative mHealth apps is still emerging, and evidence supporting its therapeutic benefit is unclear.

Several reviews have examined the use of gamification in rehabilitation [15-20]. However, no review has focused solely on gamification for rehabilitative interventions implemented through mobile apps across all conditions treated by physical therapists. Adlakha et al [15], Alfieri et al [16], and Berton et al [17] considered gamification in rehabilitation without a focus on mobile apps [15-17], while Nussbaum et al [18] examined mobile apps in rehabilitation without a focus on gamification. Other reviews have focused on gamified mobile apps for specific conditions, such as stroke [19] and shoulder [20] rehabilitation, while Ryan et al [11] performed a content analysis of rehabilitation mHealth apps for all conditions and reported the prevalence of features and outcomes.

Given the growing popularity of gamified mobile apps in rehabilitative HEPs and the limited research examining their evidence, a review of gamified mHealth apps across all health conditions treated by physical therapists is warranted. The objective of this scoping review is to summarize the available information from clinical studies that have used game design elements in mobile apps for the exercise-based rehabilitation of patients in physical therapy. We will map and evaluate evidence according to 3 categories [20]: (1) rehabilitative process, (2) gamification elements, and (3) patient-related outcomes.

Methods

Study Design

The scoping review will be conducted using the framework by Arskey and O'Malley [21], which includes the following five stages: (1) study aim identification, (2) relevant study identification, (3) study selection, (4) data extraction, and (5) synthesis and reporting of research results. An optional sixth stage, stakeholder consultation, will be considered. The study inclusion criteria will be based on the PICO (Population, Intervention, Comparison, Outcome) framework [22]. However, the comparison will not be considered in this review. For the reporting of results, we will adhere to PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) [23].

Stage 1: Study Aim Identification

This scoping review aims to synthesize current research on gamified mHealth apps used in physical therapy rehabilitation. Specifically, this review attempts to answer the following questions:

- Rehabilitative process
  - What health conditions treated by physical therapy have used gamified mobile apps?
  - In what phase of the rehabilitation process is the gamified mobile app used?
- Gamification elements
  - How is gamification implemented in the rehabilitative intervention?
  - What game design elements are used?
- Outcomes
  - Which patient-related health, adherence, and safety outcomes are evaluated?
  - Which user experience–related outcomes were evaluated?

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Stage 2: Identification of Relevant Studies

Overview

Researchers used scoping searches to identify keywords and synonyms to include in the search strategy (Table 1). A draft search strategy was developed for MEDLINE (Ovid) with the assistance of a research librarian, who helped translate keywords into controlled subject headings (Multimedia Appendix 1).

Table 1. Keyword and synonym search strategy.

Keyword	Synonyms
Rehabilitation	Telerehabilitation, telehealth, physical therapy, physiotherapy, preoperative care, postoperative care, patient education, disease management
Exercise therapy	Physical therapy modalities, therapeutic exercise, physical training, physical exercise, resistance training, exercise therapy, kinesiology, kinesiotherapy, aerobic exercise
Video games	Exergame, serious game, virtual reality, augmented reality, mobile health, mHealth, eHealth, remote, wearable, web, digital

Researchers adapted the search strategies for the following electronic databases MEDLINE (Ovid), Embase, CINAHL, PeDRO, Scopus, and Web of Science. Searches were conducted from inception to May 2024 and resulted in 2148 studies. For studies that met the inclusion criteria, references were also evaluated for potential inclusion, identifying an additional 49 studies. Only studies written in English with full-text articles were considered. No gray literature was designated for searching.

Inclusion Criteria

Regarding *population*, publications centered on patients in rehabilitative clinical studies with any condition and at any stage of care will be included. Regarding *intervention*, publications will be included that describe the use of a mobile app with gamification elements used in a movement-based intervention in any area of physical therapy. Physical therapy interventions that fit these criteria include therapeutic exercises, functional training, health and wellness promotion, respiratory exercises, motor skill training, or exercise education [1]. Regarding *outcomes*, the following patient-related outcomes will be included: measures of clinical effectiveness (eg, pain intensity, motor function), functional outcomes that enable independence (eg, gait speed, balance), physical or exercise capacity (eg, muscle strength, aerobic fitness), adherence, and adverse events. User experience–related outcomes will also be recorded, including usability (eg, error rate, ease of use) and acceptability (eg, motivation, enjoyment).

Exclusion Criteria

Articles will be excluded if the intervention is not rehabilitation-related or if the intervention is not provided by a physical therapist or under remote supervision by a physical therapist (eg, self-directed physical activity intervention for fitness outcomes). Further, articles will be excluded if movement- or exercise-based therapies are not used, such as manual therapy, respiratory techniques, electrotherapy, or physical agents. Studies will also be excluded if they do not use gamification and a mobile app to deliver the intervention. For example, interventions that solely use other forms of technology such as texting, videoconferencing, computer programs, video game consoles, robotics, exoskeletons, orthoses, or sensors will be cause for exclusion. Lastly, an article will be excluded if it is a review (eg, systematic or nonsystematic review), meta-analysis, case study or series, abstract, thesis, dissertation, commentary, opinion paper, or protocol paper.

Stage 3: Study Selection

Records retrieved from the search will be managed through CADIMA (Julius Kuhn-Institut), where any duplicate records will be removed before screening. Two rounds of screening will be performed: (1) title and abstract screening and (2) full-text review. Reviewers will undergo training and practice screening 5% of the search results before the screening of all search results. Title and abstract screening will be performed by 2 reviewers who will independently conduct screening on the same articles using the inclusion and exclusion criteria. Any discrepancies will be resolved by a third reviewer (JD). Articles included in the title/abstract screening round will advance to a full-text review. Two reviewers will conduct a full-text review independently of each other on the same articles. Any discrepancies in article inclusion will be discussed and, if necessary, resolved by a third reviewer (JD). For an article to be excluded, all reviewers must agree. Reasons for full-text exclusion will be noted and reported in the scoping review.

Stage 4: Data Extraction

Data extraction will be performed in two stages. In the first stage, primary data will be extracted using a standardized form by two researchers working independently and in parallel. Extraction fields will be developed from the preliminary search and designed to address the research questions. The data extraction form (Multimedia Appendix 2) collects bibliographical information, including authors, date of publication, and country of publication; participant characteristics, including condition addressed, intervention setting, and phase of rehabilitation; study design, including study type and blinding; exercise intervention characteristics, including level of supervision, frequency, intensity, duration, and type of exercise; technology characteristics, including type of delivery, intended audience, field of application, and game components; and outcomes reported, including outcome types, measures, and results. In the second stage, the methodological quality of the trials will be assessed using the 11-item PEDro scale [24]. For consistency and error reduction, one reviewer (JD) will oversee the data extraction process. For eligible studies that require clarification of methods or have missing data, the corresponding author will be contacted.

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Stage 5: Collating, Summarizing, and Reporting the Results

The fifth stage will involve data analysis and synthesis of the results in relation to the research question. The research questions will be used to organize the analysis of conditions, interventions, and outcomes from data collected on the extraction form. For conditions, studies will be classified into the following categories as done in a previous review [18]: cancer, cardiac, general rehabilitation, musculoskeletal, other neurologic diseases, pulmonary diseases, spinal cord injury, stroke, and traumatic brain injury. For interventions, a content analysis will be performed to identify themes within the interventions for each condition. In addition, frequency counts will be used to analyze the characteristics of interventions and outcome measures for each condition.

Results will be summarized qualitatively in narrative form, with the use of tables and diagrams where appropriate. Findings will be reported to answer each of the research questions and will therefore describe health conditions and rehabilitation phases addressed with gamified mobile apps; study design, intervention characteristics, and game elements used for each condition; and patient-reported outcomes, adherence, safety, and usability measures.

The discussion of findings will be structured based on identified themes and whether the research questions were answered. In addition, gaps in knowledge and implications for future research will be discussed.

Stage 6: Stakeholder Consultation

The last stage is an optional step intended to inform key stakeholders and validate study findings [21]. We will aim to engage relevant stakeholders, including physical therapists, mobile app developers, and rehabilitative researchers. Consultations will be held to inform data interpretation and results dissemination.

Results

This scoping review was registered with the Open Science Framework on June 4, 2024. Electronic database searches were completed in May 2024 before abstract and title screening, resulting in 2148 studies identified from inception to 2024 (Figure 1). An additional 49 studies were identified from manual searching of references. Of these identified studies, 54 duplicates were removed, 1897 were excluded during title/abstract screening, and 226 were excluded during full-text screening. A total of 20 articles were therefore selected for full-text analysis. Data extraction and analysis are expected to be completed by June 2025. Results will be presented in narrative, graphical, and tabular representations to answer each of the research questions. Findings will therefore be structured to emphasize the use of gamified mobile apps by health condition, rehabilitation phase, intervention, and patient-reported outcomes. Additionally, adherence, safety, and usability measures will be presented.

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram for selection of studies used in the analysis.

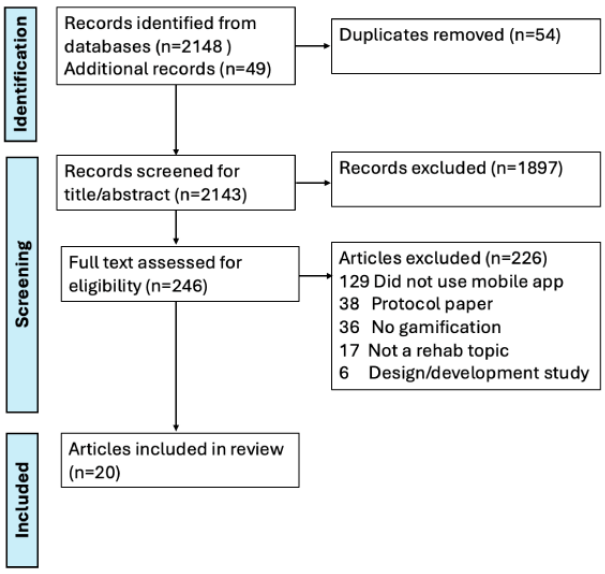

Discussion

This scoping review will map studies related to conditions treated by physical therapists in relation to the use of gamification and intervention delivery through mobile apps. The ubiquity of mobile devices and the capability of current technology make mobile apps an ideal tool for providing scalable low-cost HEPs to bridge care from the clinic to the home environment. Gamified mobile apps can be an attractive option for patients to maintain their rehabilitation routine as they provide high motivation and adherence, which in turn, can influence functional outcomes. However, the sheer number of available apps makes selection challenging for clinicians and patients alike. Although Ryan et al [11] reported on the prevalence of rehabilitative mHealth apps in app stores and their features, and several reviews have examined the use of gamification in rehabilitation in specific conditions [15-20], no review has focused solely on gamification for rehabilitative interventions implemented through mobile apps across all

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conditions treated by physical therapists. Thus, aggregation of the available evidence is needed to identify knowledge gaps and synthesize the usefulness of gamified mobile apps in the treatment and self-management of patients receiving physical rehabilitation. Findings from this scoping review will help inform the design of future studies to improve unmet medical needs and ultimately optimize patient outcomes.

This review has several strengths. It is the first review of gamified mobile apps that is inclusive of all conditions treated by physical therapists and may therefore provide a new perspective. Prior reviews on physical rehabilitation have captured narrower topics, such as focusing on one condition, gamification only, or mobile apps only. Expanding the review across all conditions can give insight into areas that are most frequently addressed, areas that are emerging, and areas of digital practice that are understudied. Another strength of this review is its focus on implications for clinical practice. Prior reviews surrounding mobile apps have described technology features and means by which mHealth is implemented in physical therapy interventions. However, none have focused on patient-reported outcomes and how this may translate to clinical practice. Finally, we will explore the methodological quality of the studies using the PEDRo scale, which was developed for physical therapy interventions. Although interpretation of the PEDRo scale is not to be taken as a measure of validity, it may provide insight into the clinical usefulness of this review and highlight areas where future research is needed.

Limitations

One limitation of this scoping review would be the inability to access the full text of all included studies. To counter this limitation, we will make the best effort to contact authors and report the outcomes of the communication (eg, how many authors respond, send data). A second limitation is the exclusion of gray literature, as unpublished theses, dissertations, conference proceedings, abstracts only, opinion papers, and commentaries will not be considered. Reviewers and extractors will also not be blinded to the journal names or authors during screening or from the research questions during data extraction, both of which would minimize the risk of bias. This decision was made for the pragmatic consideration of completing the screening and extraction of studies promptly. Lastly, we will not conduct a formal evaluation of the risk of bias through a tool such as Cochrane's Risk of Bias. This is in line with the goal of a scoping review to provide an overview of the existing publications rather than critically appraise each source of evidence.

Conclusions

With the use of digital health and telerehabilitation on the rise, the topic of mHealth apps for physical therapy interventions is an emerging and important topic for clinicians. This scoping review seeks to map existing literature on the use of gamified mobile apps in physical rehabilitation in a home environment. Results will summarize research on gamified mobile apps to assist physical rehabilitation professionals with decision-making on remote interventions to enhance patient engagement and adherence. This will help identify knowledge gaps and advance rehabilitative mHealth research, which may ultimately improve patient-related outcomes.

Acknowledgments

The authors wish to acknowledge the librarian at California State University, Long Beach (CSULB), who assisted in defining the search strategy. This work was supported by funding from the College of Health and Human Services of CSULB.

Data Availability

Datasets will be presented in the scoping review and made available from the corresponding author upon reasonable request.

Authors' Contributions

JD conceptualized the project as a scoping review and wrote the scoping review objectives and search strategy. AB aided in the approach for methodological development. All authors contributed to the preparation, review, and revision of the protocol.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 17 KB - resprot_v14i1e63600_app1.docx]

Multimedia Appendix 2
Data collection form.
[XLSX File (Microsoft Excel File), 13 KB - resprot_v14i1e63600_app2.xlsx]

Multimedia Appendix 3

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PRISMA-P checklist.
[DOCX File , 33 KB - resprot_v14i1e63600_app3.docx]

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Abbreviations

HEP: home exercise program
mHealth: mobile health
PICO: Population, Intervention, Comparison, Outcome
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Prognostic Disclosure in Metastatic Breast Cancer: Protocol for a Scoping Review

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Abstract

Background: Prognostic disclosure enables shared decision-making by keeping patients informed about their health and involved in treatment-related choices. In metastatic cancer, patients who understand their prognosis are better placed to evaluate their health situation, have more realistic expectations about treatment, and better end-of-life (EoL) care. However, many oncologists feel uncomfortable discussing prognoses with their patients, as they worry about causing psychological distress and diminishing hope. Other barriers to prognostic disclosure are associated with the inherent uncertainty of prognostication, which is especially prominent in metastatic breast cancer (mBC), as are a lack of timely discussions about EoL care and poor quality of care at EoL. Despite this background, a preliminary literature search has shown that, to date, knowledge about prognostic disclosure in mBC has not been systematically mapped.

Objective: The overall aim of this scoping review will be to comprehensively explore the existing literature pertaining to prognostic disclosure in mBC.

Methods: This scoping review will follow Arksey and O'Malley's expanded framework. We will systematically search electronic databases for peer-reviewed, published journal articles to identify appropriate studies. First, 2 members of the research team will independently review titles and abstracts. Then, they will review full texts to establish whether articles meet inclusion criteria. A data chart for collecting and sorting information will be developed. Results will be reported following the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines and summarized quantitatively and qualitatively.

Results: We expect to present the results in a scoping review in 2025.

Conclusions: To our knowledge, this scoping review will be the first systematic effort aimed at mapping existing literature on prognostic disclosure in mBC, in which rapidly developing therapeutic approaches and changing disease trajectories generate new uncertainties and place new communicative demands on oncologists. The insights gained from this scoping review will inform the development of an interview schedule with oncologists, oncology residents, oncology nurses, and patients with mBC to explore their experiences, views, and perceptions about prognostic disclosure.

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KEYWORDS

scoping review; protocol; metastatic breast cancer; advanced breast cancer; prognostic disclosure; prognosis; communication; truth-telling; ethics; shared decision-making

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Introduction

Background

Metastatic breast cancer (mBC), also termed advanced or secondary breast cancer, occurs when the primary lesion spreads to other sites of the body, most commonly the bones, lungs, brain, or liver. In recent years, new targeted systemic therapies have improved the median overall survival of many patients with mBC, and some patients may be cured by combination therapy or have long-term responses. However, resistance to treatment remains a significant challenge, so most patients will eventually progress and die from their disease [1].

Prognostic disclosure—communicating the likelihood that a certain clinical state or outcome will occur within a certain period—is now a routine part of cancer care in many countries [2]. Grounded in the ethical principles of autonomy and self-determination [3], prognostic disclosure enables shared decision-making by keeping patients informed about their health and involved in treatment-related choices, especially in situations of uncertainty. Patients who understand their prognosis tend to have more realistic expectations about treatment [4]; they are also better able to prepare for the future, have higher quality end-of-life (EoL) care and have better chances of dying in their preferred place [5]. Conversely, concealing a poor prognosis interferes with patients' autonomy and ability to make treatment-related decisions that are aligned with their values, preferences, and goals, often resulting in the pursuit of futile therapies and poor symptom management [3,6].

To promote the value of prognostic disclosure and help clinicians become more familiar with it, consensus guidelines specifically addressing patient-clinician communication have been developed [7]. Yet, many oncologists continue to feel uncomfortable communicating prognostic estimates to their patients, often due to concerns about causing psychological harm and diminishing hope [8-10].

Research on prognostic awareness and its association with anxiety, depression, and quality of life (QoL) among patients with metastatic cancer supports these concerns to some extent, as the evidence is not uniform. Some studies report that prognostic awareness is associated with low anxiety, low depression, and high QoL [11], while others report a varied range of outcomes, including negative psychological impacts [12]. This may reflect the fact that prognostic disclosure that successfully balances hope and realism requires skillful, empathic communication [12-14].

Apart from these possible harms, other barriers to prognostic disclosure have been identified. Prognostication is inherently uncertain, owing to the randomness of future outcomes and the lack of evidence on the probability of outcomes. This lack of evidence is increasingly prominent in oncology because of the rapid pace of advancements in personalized medicine and novel therapies and techniques [15]. In mBC, reducing prognostic uncertainty is especially complex, as the clinical behavior of mBC varies greatly, and the disease trajectory is difficult to predict [16-18]. In addition, studies have found that timely discussions about EoL care, documentation of patient preferences in health records, and quality of care at EoL are particularly lacking for patients with mBC [19]. Thus, it is perhaps not surprising that this patient population has been found to be at increased risk of being overtreated at EoL [20,21], with insufficient access to hospice services and often dying in acute care environments [19].

Despite this landscape, the increasing incidence of mBC, and the large number of patients living with the disease, a preliminary literature search has shown that, to date, knowledge about prognostic disclosure in mBC has not been systematically mapped.

Study Objectives

The overall aim of the proposed scoping review is to identify, summarize, and synthesize knowledge about prognostic disclosure in mBC. We expect that the results of this work will facilitate further research aimed at gathering evidence and gaining insights on the process and outcomes of prognostic disclosure in mBC to help guide medical professionals in challenging yet crucial conversations with patients.

Methods

Study Design

This scoping review will be conducted following the widely known 5-stage framework by Arksey and O'Malley [22] and subsequent recommendations [23,24]. The results will be reported in accordance with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines.

A scoping review is a rigorous, transparent tool that can be used to map or synthesize a range of evidence in order to convey the size and scope of a research field [24]. According to Arksey and O'Malley [22], by conducting a scoping study researchers can survey the extent, range, and nature of research activity in a given field, establish whether a full systematic review is warranted, summarize and disseminate research evidence, or identify gaps in the existing literature.

Compared to systematic reviews, which aim to summarize the best available research related to a given research question, scoping studies generally do not critically evaluate the quality of the studies they cover [25,26]. Compared to narrative or literature reviews, scoping reviews require analytical reinterpretation of the literature. Scoping reviews are helpful when evidence on a topic is emerging or the relevant literature is complex or heterogeneous. In addition, they can cover findings from a range of different study designs and methods [24]. Thus, they are well-suited to synthesizing the literature on a topic that has yet to be comprehensively mapped, such as the one we will endeavor to review.

Stage 1: Identifying the Research Questions

The research questions of this scoping review are the following: What has been reported about prognostic disclosure in mBC? What are the knowledge gaps regarding prognostic disclosure in mBC?

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An exploratory search in PROSPERO—the International Prospective Register of Systematic Reviews of the National Institute for Health Research—and the Cochrane Library revealed no comprehensive systematic reviews addressing similar questions. The research team will revise the protocol as appropriate during the review process.

Stage 2: Identifying Relevant Studies

Eligibility Criteria

To decide the eligibility criteria, the research team followed the PCC (Population/Concept/Context) framework for scoping reviews by the Joanna Briggs Institute [27]. Inclusion criteria are (1) studies wherein the population comprises individuals older than 18 years with mBC and health care professionals (oncologists, oncology residents, and oncology nurses) providing clinical care to patients with mBC, (2) the concept is prognostic disclosure by health care professionals to patients with mBC, and (3) the context is a health care setting.

The following items will comprise further inclusion criteria: articles published in a peer-reviewed outlet, articles in English, articles that include the relevant search terms (see below), articles in which prognostic disclosure to patients with mBC is the main focus or is at least addressed in its own part or section, and articles that were published in 2010 or later, in light of the changes that have since taken place in mBC treatment.

Our exclusion criteria are as follows: articles that focus on prognostic disclosure but only marginally mention mBC and articles that focus on mBC but only marginally mention prognostic disclosure.

Search Strategy and Information Sources

Literature search strategies will be developed using MeSH (Medical Subject Headings) terms and text words related to prognostic disclosure in mBC. Studies will be identified by searching MEDLINE, CINAHL, Embase, and PsycInfo. Targeted internet searching using Google Scholar will also be performed to identify additional studies of interest. A hand search of the reference lists of eligible articles will be carried out to ensure literature saturation. The search strategy will be reviewed by a specialist librarian using the “Peer review of electronic search strategies” guidelines [28].

Stage 3: Selecting the Studies

Results retrieved from all databases will be imported into a reference management software, and duplicate references will be removed. At the first screening stage, 2 researchers will independently review the title and abstract of all references and assess them for eligibility. Disagreements will be discussed until consensus is reached, and if necessary, by consulting a third independent researcher. Articles not related to the topic, theses, articles from the popular press, reports, nonreviewed books and book chapters, presentations, and opinion pieces will be excluded. The 2 researchers will then independently conduct the second eligibility screening, evaluating full-text articles against the inclusion and exclusion criteria. Results will be compared, and any disagreements will again be discussed to reach a consensus on final inclusion, involving the third researcher if needed. A PRISMA-ScR flowchart will be developed to report the process.

Stage 4: Charting the Data

Based on the recommendations by Levac et al [24], we will perform a descriptive quantitative synthesis and a thematic analysis. In line with Arksey and O’Malley [22], our descriptive quantitative summary will begin with the final number of articles included in the scoping review and the essential characteristics of the articles identified, such as first author, year of publication, country, discipline/field of inquiry, study design (ie, qualitative, quantitative, mixed methods, retrospective, prospective, longitudinal, and cohort study), research methods, type of health professional and/or patient involved, number of participants, etc. This information will be presented in the scoping review report to provide an overview of the included literature.

For qualitative data, content analysis will describe the data extracted, highlighting consistencies and differences [29]. The articles will be coded following a multistep process, including open coding, axial coding, and selective coding, using the Dedoose web-based application [30]. In the first phase, units of meaning will be identified and labeled to allow categories to emerge from the data (open coding). Open codes will be categorized, with similar codes grouped, refined, and combined into larger themes (axial coding). The conceptually stable thematic patterns that emerge will then be organized and grouped into higher-order conceptual themes. Selective coding will involve integrating and refining of these concepts [29]. Finally, findings will be integrated and validated through discussion among all members of the research team.

Stage 5: Collating, Summarizing, and Reporting the Results

The essential characteristics of the studies will be tabulated, providing an overall summary of the articles selected. Other results will be presented in diagrams and descriptive summaries, as most appropriate to display and convey the extracted information.

Ethical Considerations

The scoping review methodology consists of reviewing material that is publicly available and does not involve any patient-related data, so this study is not subject to ethical approval.

Results

We expect to present the results of this work in a scoping review in 2025.

Discussion

Patients with a limited life expectancy, such as those with mBC, need information about their prognosis to make sense of their health-related situation, participate in decisions about their treatment, and prepare for the future [31]. However, while information provision is one of the cornerstones of shared decision-making [32], prognostic disclosure can lead to negative effects on patients’ well-being, eliciting anxiety, hopelessness, and demoralization [33,34]. Oncologists thus need to find a

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balance between conveying clear information but not overwhelming patients, being realistic and simultaneously remaining hopeful [12-14], which may leave them feeling torn [35].

To our knowledge, this scoping review will be the first systematic effort aimed at mapping existing literature on prognostic disclosure in mBC. We expect to find that evolving disease trajectories, increasing survivorship, and the need for decision-making about treatment options in the context of rapidly developing therapeutic approaches all place significant new communicative demands on oncologists navigating the challenges and complexities of prognostic discussions [35].

The results of this work will be used to inform the development of an interview schedule with patients with mBC, oncologists, oncology residents, and oncology nurses to explore their experiences, views, and perceptions about prognostic disclosure in mBC. Our findings will be disseminated through presentations at conferences and webinars.

Acknowledgments

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Authors' Contributions

Conceptualization: LB, IG, and CB
Methodology: LB and IG
Writing—original draft: LB
Writing—review and editing: LB, IG, and CB

Conflicts of Interest

None declared.

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Abbreviations

EoL: end of life
mBC: metastatic breast cancer
MeSH: Medical Subject Headings
PCC: Population/Concept/Context
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
QoL: quality of life

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Protocol

Examining Practices Related to Ethical Aspects in eHealth Evaluation Research: Protocol for a Scoping Review

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Abstract

Background: eHealth technologies, including remote patient monitoring (RPM) applications, have the potential to improve care for diseases such as cancer and cardiovascular conditions. However, they also raise ethical aspects that are often inadequately addressed in eHealth evaluation research. This is problematic, as evaluations guide decision-making at multiple levels. To improve evaluation practices, it is essential to understand how ethical aspects are addressed in terms of both content and methodology, enabling the development of tailored recommendations for enhancement.

Objective: This scoping review systematically examines how ethical aspects are addressed in eHealth research, focusing on original studies evaluating RPM applications for cancer and cardiovascular diseases.

Methods: Using Joanna Briggs Institute (JBI) methodology and PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines, this review implemented a comprehensive search strategy with the terms “cancer or cardiovascular diseases,” “eHealth or telemonitoring,” and “evaluation designs.” Searches included MEDLINE, Embase, CINAHL, SocINDEX, Philosopher’s Index, PsycINFO, and Google Scholar. Data extraction will emphasize ethical aspects and methodological approaches to consider them. The analysis will apply inductive-deductive qualitative content analysis.

Results: Initial searches identified 3321 articles published between 2014 and August 2024. Screening and analysis will be completed in the first quarter of 2025, with results anticipated by summer 2025.

Conclusions: Overlooking ethical aspects in evaluation studies can significantly impact eHealth practices. This scoping review will map ethical considerations in original evaluation research, identifying opportunities for more holistic integration of ethics and informing future practical guidance.

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KEYWORDS

cancer; cardiovascular; eHealth; remote patient monitoring; ethics; ethical aspects; applied ethics; evaluation designs; evaluation research; scoping review; protocol

Introduction

Background

Technologies have significantly transformed health care delivery in recent decades. Remote patient monitoring (RPM) pertaining to eHealth exemplifies this transformation by enabling health care services to extend beyond traditional hospital settings. RPM addresses many limitations of clinical environments, such as dependency on physical infrastructure, and reduces geographical barriers, thereby enhancing care accessibility for diverse populations [1]. RPM leverages tools, such as smartphones, web-based platforms, wearable devices, and biomedical sensors, to collect health-related data, including vital signs and symptoms, directly from patients. These data are transmitted to health care providers, enabling them to monitor patients' health progress and promptly intervene in cases of deterioration [2]. RPM shows particular promise in the care of cancer [3,4] and cardiovascular diseases [5], as these conditions often require prompt intervention when health issues arise. Together, they account for more than half of global mortality, with 33% attributed to cancer and 18% to cardiovascular diseases [6]. By enabling early detection of health issues and interventions, such as adjusted medical regimens or prompted medical visits, RPM has the potential to improve the quality of life and even save the lives of patients managing these chronic conditions [7-10].

With the growing adoption of eHealth technologies, such as RPM, the demand for empirical evidence has risen. Evaluation research aims to enhance practical application, generate knowledge, and support informed decision-making regarding an evaluation objective [11]. Ideally, such studies accompany the entire eHealth life cycle, encompassing stages from preprototype and prototype development to pilot testing, demonstration, scaling, and sustained implementation [12,13]. For instance, considering clinicians' preferences at the pre-prototype stage helps tailor eHealth solutions to users' needs, whereas testing prototypes ensures usability and identifies technical issues. Such studies also assess impacts such as improved patient quality of life and uncover factors for successful implementation [14].

There is growing consensus that empirical evaluations alone are insufficient to ensure that eHealth is ethically sound, which is an essential standard in health care [15-17]. This is reflected by recommendations from the World Health Organization (WHO), which emphasize the importance of integrating ethical considerations into eHealth practices, including those related to development, implementation, use, and research [1,18,19]. Despite these recommendations, issues such as unequal access to technologies and risks to data security have been insufficiently addressed in studies [17,20-26]. This is concerning because the findings of evaluation research directly impact the development of technologies, health care delivery, and policy decisions, placing significant responsibility on evaluators and researchers [27-29]. Neglecting ethical considerations in these studies, therefore, risks their insufficient representation in decision-making processes.

To promote ethical practices in eHealth, it is essential to address the limited attention paid to ethical aspects in evaluation research, which may stem from methodological challenges related to the application of ethics [30,31]. Interdisciplinary teams, often lacking ethicists, struggle not only to understand what ethical issues to consider but also how to address them. However, comprehensive guidance, particularly for original evaluation research, remains scarce [31]. To create such guidance, a comprehensive overview of eHealth evaluation research practices is needed to identify challenges and opportunities in addressing ethical aspects in this context [22]. This can inform practice recommendations for researchers that are better aligned with and adaptable to existing evaluation practices. However, the field remains underexplored.

The complexity of ethics, lack of targeted guidance for interdisciplinary teams, and absence of comprehensive reviews of evaluation research practices provide the rationale for this scoping review. These issues are explored in detail in the following sections and further elaborated in the proposed review, using evaluations of RPM in cancer and cardiovascular care as practical case studies.

The Broad Spectrum of Ethical Aspects in eHealth Evaluation Research

The ethical aspects in the literature include questions, concerns, risks, issues, challenges, fallacies, and considerations. Although no universal definition of these aspects exists, there is consensus among proposed definitions regarding their normative nature, as they include implicit or explicit claims about how individuals should behave, act, or how specific circumstances ought to be [32] (eg, the topic "health disparities" implies that access to health care ought to be fair).

In the context of eHealth, ethical aspects concern the impact of technologies on individuals and society. They also relate to the responsibilities and actions of professionals in areas such as software development, health care, and research [33]. Thus, although not exhaustive, 2 key categories—the process domain and the outcome domain—are particularly relevant for classifying ethical aspects in eHealth evaluation research [34,35].

First, the ethical aspects of the process domain: Evaluation research is closely linked to value judgments, which unavoidably connect the process to ethical aspects. Ethical aspects are especially evident when the distribution of power between interest groups is unequal [30]. Kelly et al [36] highlighted several ethical concerns in the eHealth field. Decisions about a study's focus, design, and conclusions are often shaped by the values of individual stakeholders. For instance, stakeholders in influential positions, such as members of the pharmaceutical industry, tend to exert a greater influence on decision-making

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processes. They may determine which health technologies receive funding and are prioritized for research, with choices frequently guided by economic interests. While this profit-driven perspective can foster innovation, it does not always align with actual health care needs, potentially resulting in missed opportunities for improving patient care. The focus on profit can clash with goals such as fairness and justice, which emphasize benefits for society as a whole.

Second, the ethical aspects on the outcome domain: Ethical aspects of eHealth are linked to unintended and dual outcomes arising from the interactions between the intervention components and the environment in which it is applied [37]. An example in this domain is that, while eHealth aims to improve health care access for rural populations, concerns arise about worsening health disparities [38-40]. Disadvantaged groups, such as individuals with lower educational levels or socioeconomic status, may not benefit from eHealth as intended. These patient groups were frequently excluded from the studies, creating a problematic selection bias. If this ethical concern is neglected and eHealth methods are not adapted, health disparities will likely increase [38-41]. In this regard, the underreporting of negative effects associated with eHealth is of particular concern, which impedes a comprehensive understanding of these unintended and dual effects [42].

In summary, the ethical aspects discussed in the literature are diverse and context-specific, emerging from systematic reflections within the broad eHealth field. This makes them less ready to be operationalized and investigated compared with empirical outcomes such as effectiveness. Without proper guidance, this poses a challenge for non-ethicists involved in eHealth evaluations and may contribute to the limited focus on ethical aspects [31].

Integrating Ethical Analysis Into eHealth Evaluation Research

Guidelines for evaluating health technologies, such as those from the WHO [12], lack explicit instructions on how to incorporate ethical considerations into empirical evaluation designs. This reflects the traditional separation between empirical and ethical approaches, which foresees that ethical aspects are considered in systematic ethical analyses as supplementary research [43]. While such systematic analysis can take various forms, it typically includes key components [44]. Simplified, these entail a descriptive assessment of the current situation (the “Is” aspect) and a critical reflection on ethically desirable outcomes guided through ethical approaches (the “Ought” aspect). Among others, these approaches may include the application of overarching moral theories such as consequentialism, deontology, and virtue ethics [45], or context-specific principles from applied ethics [32]. Finally, an ethical analysis entails the formulation of ethically justified recommendations for practice (the “Action” aspect) [44].

The application of ethics in the context of eHealth is an evolving field [37]. The European VALIDATE (VALues In Doing Assessments of health Technologies) project [43] is one initiative focused on developing guidance for the Health Technology Assessment (HTA) context—a process used to evaluate the value of health technologies at various life cycle stages [46]. The findings from the project emphasize that rigid separations between empirical and ethical approaches are problematic. This is because ethical aspects are integral to the empirical evaluation process itself [43], as outlined above, in connection with the ethical aspects of the process and outcome domain. Therefore, it is recommended to systematically integrate ethical considerations into evaluation research practices, rather than treating them in isolation. The VALIDATE handbook offers guidance on integrated approaches for the HTA process, which aims to create reports based on existing data. Thus, it can serve as an initial orientation for the evaluators. However, the handbook does not adequately address the inclusion of ethical considerations in original evaluation research, where the collection of new evaluation data poses specific ethical challenges that require tailored guidance [47].

Integrating ethics into original evaluation research can offer significant benefits, both in terms of addressing ethical aspects during the process and in the outcome domain:

First, the ethical aspects of the process domain: Incorporating ethical approaches into evaluation research encourages reflection on the underlying values and power dynamics. By addressing the ethical challenges identified during this reflection through proposing or applying corrective measures, researchers can enhance the ethical integrity of both the evaluation process and its objective, namely the eHealth technology [36,48].

Ethical aspects in the research process domain are relevant throughout all stages of the eHealth life cycle, regardless of the evaluation design or methods. This is evident in the practice of submitting study protocols to ethics committees, which promotes ethical reflections on methodological choices. However, this approach is limited because it primarily occurs during the study conceptualization phase, varies across countries, and lacks consistent quality standards among ethics committees [47,49].

Beyond the requirement for ethics approval, reporting guidelines and scientific journals encourage authors to address process-related ethical aspects in their final publications. This may involve reflections on participant selection and its impact on result interpretation [27], which is typically discussed in the methods and discussion sections. Another opportunity for including ethical considerations in manuscripts lies in the author’s statements, which can encompass reflections on funding influences and value-based decisions, often reported under conflicts of interest [50].

Second, the ethical aspects on the outcome domain: Integrating ethical considerations into the outcome domain of original evaluation research can improve the focus on unintended and dual effects of eHealth interventions.

For instance, ethical reflections at early stages, such as conceptualization and design, help identify potential ethical issues and proactively address them [51]. Furthermore, integrating ethics throughout the evaluation life cycle ensures continuous assessment from the initial stages to long-term effectiveness studies [52]. Grounding ethical reflections in current evidence leads to practical and relevant recommendations rather than purely theoretical ones [53]. As evaluation research is closely linked to real-world eHealth

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projects, ethical considerations can be applied immediately [54], supporting ethical informed development, implementation, and long-term use. Ultimately, integrating ethics into evaluation research results in well-founded, justified recommendations that are more likely to be accepted by various stakeholders and effectively implemented in practice [32,55].

Qualitative studies are particularly suitable for uncovering unintended or dual effects, owing to their exploratory nature and necessary reflexivity [53,56,57]. Although less detailed, quantitative studies are also intended to address ethical aspects. For instance, the CONSORT (Consolidated Standards of Reporting Trials) eHealth guideline suggests that randomized controlled trials transparently report unintended effects, such as harm or privacy concerns, in final reports [58].

To sum up, existing evaluation research practices already encourage ethical reflections, albeit often unconsciously and in a less systematic manner. Nevertheless, these practices provide a valuable foundation for developing more comprehensive guidance to enhance evaluation research and to move toward fully integrated approaches.

Previous Work

To our knowledge, no review has examined in sufficient depth whether and to what extent ethical aspects are considered in original evaluation research. Some identified reviews relied on the search term "ethics" [22,23,59,60]. Through this, studies that addressed ethical aspects without explicitly labeling them were excluded [22]. Consequently, these reviews lack the necessary evidence to definitively conclude that ethical aspects are overlooked. For instance, a feasibility study by Appleyard et al [61] explored the barriers to eHealth adoption among older patients with cancer. This study highlighted the risk of digital exclusion and recommended tailoring eHealth systems to meet the needs of individuals with limited digital skills. Although the findings were not explicitly framed as ethical considerations, they inherently addressed critical ethical issues such as health disparities, the digital divide, and equity. Misclassifying such studies as neglecting ethical aspects risks reinforcing the misperception of ethics as a detached and isolated concern, rather than an integral part of evaluation research practices [43,62]. Therefore, a more thorough examination of the existing empirical practices related to ethical aspects is required.

Other reviews have focused on HTA reports [26,63,64] without exploring practices within original research studies. Reviews examining original research primarily focused on ethical aspects substantively [23,24,60,65,66], while largely overlooking the methodological domain—specifically, how ethical aspects were addressed (eg, which ethical approaches were used). Without considering these methods, they fail to capture whether ethical issues were considered appropriately. For example, some studies may only reference ethical concerns descriptively, like "eHealth can increase health disparities," without offering a reflective analysis or actionable steps. A more comprehensive approach to eHealth would go beyond merely describing referenced issues; it would involve identifying, reflecting on, and proposing well-justified, practical solutions [44].

Only 1 review by Steerling et al [25] considered referenced ethical approaches in conjunction with reported ethical aspects. Nonetheless, the extent and systematic integration of ethical considerations in the included studies remain unclear. For instance, the review does not discuss the topic in connection with the studies' evaluation design and eHealth life cycle stage, whether ethical aspects were addressed in the process or outcome domain, reported in the introduction or discussion section, and other essential details. These nuances are pivotal in mapping evaluation practices and making tailored suggestions for improvement.

As a consequence, the insights provided in previous reviews are insufficient to provide essential information for the development of guidance regarding integrated ethical approaches in original eHealth evaluation research. Given these limitations, a scoping review is an appropriate method for addressing this research gap. Scoping reviews are specifically designed to explore broad research questions, investigate unknown areas, map research practices, and offer conceptual clarification [67]. These characteristics align with the objectives of this review.

Objective

Original evaluation research has great potential to promote ethical practices in eHealth by informing decision-making in this field. Therefore, addressing the current lack of focus on ethical aspects is crucial. A thorough examination of the existing evaluation research practices, which is the main goal of this scoping review, is an important first step toward improving this area.

The focus will be on studies examining bidirectional RPM technologies—those featuring interfaces for both patients and clinicians—within the context of cardiovascular and cancer care as practical case studies. The insights gained from this review will serve as a foundation for guiding empirical ethical evaluation research in the eHealth context for future studies.

Review Questions

The review questions are as follows:

1. Are ethical aspects of eHealth implicitly or explicitly addressed in original eHealth evaluation research? (Ethical aspects—general overview)
2. Which ethical aspects (eg, process or outcome domain) are addressed? (Ethical aspects—classification)
3. To what extent are ethical aspects addressed in terms of ethical analysis steps and approaches? (Ethical approach—methodology)
4. What are promising starting points for implementing ethical approaches in original eHealth evaluation studies? (Potential for improvement)

Methods

Study Design and Review Team

The proposed scoping review will be conducted according to the Joanna Briggs Institute (JBI) scoping review methodology [68] and will follow the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews; see Multimedia Appendix 1 for the

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PRISMA-ScR checklist) [69]. The review process is supported by Rayyan, an AI-powered web application for the creation of systematic reviews [70].

The interdisciplinary review team consists of nursing scientists (LW, SV, LL, and SDG), ethicists (JK and LK), and a software engineer (AT), bringing together empirical and ethical expertise. Within their respective disciplines, all review team members have a minimum of 3 years of experience with eHealth. To ensure consistency with the JBI Manual, the first author and main reviewer (LW) attended the JBI scoping review workshop in June 2022.

Inclusion Criteria

Participants

This scoping review will consider studies that include clients and providers of eHealth services. The clients will include patients of any age who have cardiovascular disease or cancer. We will also consider studies that include individuals acting on behalf of patients (eg, parents and caregivers) who are involved in the collection of health data and the use of eHealth. Health care providers will be included if they use the collected information, for instance, by retrieving and monitoring it.

Concept

This review will focus on eHealth-enabling RPM. eHealth involves using "information and communications technologies in support of health and health-related fields" [1]. RPM is a health care delivery method that monitors patients' health outside traditional clinical settings, using technology for information transmission between patients and health care providers [2]. RPM devices to be considered include noninvasive disease management applications and web-based platforms. This scoping review will exclude fully automated devices that operate without active patient participation in data entry or transmission, such as fitness trackers, cardiac implants, or medication dispensers. In addition, applications designed solely for patient use, such as those limited to sending notifications about health issues without involving communication with health care providers, will also be excluded.

Context

This review will consider studies investigating the use of eHealth in any clinical context (eg, hospital, outpatient clinic, specialist, or general practice) and in any geographical location. Studies evaluating the use of RPM in inpatient settings, such as intermediate care units or hospice care, will be excluded.

Types of Sources

This scoping review will include qualitative, quantitative, and mixed methods original research. Within the context of eHealth, evaluation studies may have diverse objectives, ranging from explorations of perceptions and experiences in qualitative designs to specific outcomes such as usability, acceptability, and costs in quantitative designs [12,14]. As such, no limitations for inclusion will be predefined in this regard. Studies during the conceptualization and development phases will be included only if testing of an eHealth prototype is reported. Secondary research, abstracts, methods, and opinion papers will be excluded from the proposed scoping review.

Search Strategy

A comprehensive literature search was conducted in August 2024. The full search strategy used the keywords "cancer or cardiovascular diseases," "eHealth or telemonitoring," and "evaluation designs." To create relevant search blocks, we conducted an initial limited search of MEDLINE (PubMed) to identify relevant articles. We used keywords from the titles, abstracts, and index terms of these articles to develop a full search strategy (Multimedia Appendix 2). The development process was supported by an information specialist from the University Library Basel (Switzerland) and involved previously published search blocks from the Biomedical Information study group of the Dutch Library Association as a reference [71].

The search strategy, which included all identified keywords and index terms, was modified for each information source. We accessed MEDLINE (PubMed), Embase (Ovid), PsycINFO (Ovid), CINAHL (EBSCOhost), SocINDEX (EBSCOhost), and Philosopher's Index (EBSCOhost). Gray literature sources were searched through Google Scholar. To limit the influence of previous activities on Google, we searched in private browsing mode [72]. The search strategy focused on original studies published between 2014 and August 2024.

In accordance with the language skills of the main reviewers (LW and JK), articles published in English and German will be considered for screening.

Source of Evidence Selection

After the search, all identified records were imported into the citation management software EndNote 20 (Clarivate Analytics) and subsequently transferred to the Rayyan platform. Duplicate entries were automatically removed using Rayyan when their similarity exceeded 95%. All remaining duplicates were manually reviewed.

To ensure consistency among reviewers, a pilot test of source selection will be conducted. Therefore, the main reviewers will screen 25 titles and abstracts to assess their eligibility based on the inclusion criteria. In line with recommendations, the independently selected articles will be compared, and the process will proceed when a consensus is reached on 75% of the selected articles [67].

Potentially relevant papers will be retrieved in full. The full texts of the selected citations will then be assessed by the main reviewers against the inclusion criteria. Reasons for excluding full-text papers will be recorded and reported in the scoping review. Any disagreements between the main reviewers at each stage of the selection process will be resolved through discussion. If consensus cannot be reached, advice from further reviewers will be sought, according to their field of expertise. The results of the search will be reported in full in the final scoping review and presented in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram [69,73].

Data Extraction

Data will be double-extracted from the papers included by the main reviewers (LW and JK). The reviewers will meet regularly during the process to cross-check each other's extractions and

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discuss their findings. In case of disagreement between the two reviewers, further members of the review team will be consulted to reach consensus through discussion.

Basic study information will be extracted using the JBI data extraction instrument for scoping reviews [68]. In addition, studies will be screened for key findings relevant to the review questions 1-4 in two rounds.

Review questions 1 and 2: In the initial round, we will use the document search function to screen for the term "ethics" to identify aspects that are explicitly labeled. In the next step, we will thoroughly read the evidence sources, focusing on identifying ethical aspects within the full texts that are not labeled as such. Passages implying ethical aspects, such as critical reflections on decision-making in the research process or reported unintended effects, will be extracted. To aid identification, we will use the three moral theories: consequentialism, deontology, and virtue ethics. These theories offer universal guidance, covering a wider range of ethical aspects compared with context-specific principles [45] and have been previously utilized in another review to extract ethical aspects in the context of eHealth [25]. In addition, we will closely examine the authors' use of normative language to express how things ought to be. This will be achieved by screening the text for modal auxiliaries such as "shall, should, ought to, must, need to." Extracted passages indicating ethical aspects will be categorized into 2 domains: the process domain, pertaining to ethical aspects associated with the research process, and the outcome domain, concerning ethical aspects related to unintended effects of eHealth deployment.

Review question 3: In the second round, we will rescreen the studies with identified ethical aspects to extract methodological information. We will focus on text passages that clarify how authors address ethical aspects, including related descriptions ("Is" aspect), reasoning and justifications ("Ought" aspect), and recommendations ("Action" aspect).

Review question 4: In addition, we will take note of emerging ideas for the potential integration of ethical considerations and improved reporting of ethical aspects. Relevant text passages will be extracted for further analysis.

A draft extraction tool (Textbox 1) has been developed with preliminary categories "Ethical aspects" (with subcategories "Yes/No," "Process domain," "Output domain," and "Manuscript section"), "Methodology" (with subcategories "Is," "Ought," and "Action"), and "Potential for improvement." These categories for extracting key information to address the review questions will be further refined inductively during the data extraction and analysis processes. Any modifications to the extraction tool will be deliberated among the primary reviewers and will be documented in the final scoping review.

Textbox 1. Preliminary categories and subcategories of the draft extraction tool.

- Ethical aspects:
  - Yes/No
  - Process domain
  - Output domain
  - Manuscript section
- Methodology:
  - Is
  - Ought
  - Action
- Potential for improvement

Data Analysis

To analyze the study information, we will conduct a descriptive statistical analysis to demonstrate the characteristics of the included studies [74]. The same applies to review question 1, where we will quantify the extent to which ethical aspects are addressed and present the findings in numbers and percentages.

To answer review questions 2-4, we will use a basic qualitative content analysis approach for scoping reviews [74]. We will apply a mixed deductive-inductive approach, following these steps: Data will be extracted deductively using the draft extraction tool. During the reading and initial extraction process, we will conduct open coding and note initial thoughts to further develop our extraction tool, also known as the coding framework. Once the coding framework is finalized, we will extract and organize relevant information within it. Throughout the process, we will review the coding framework and, if necessary, develop new overarching categories. The findings will be presented in a narrative format, accompanied by tables and potentially supplemented with graphs or diagrams.

As it is beyond the scope of a scoping review [75], no formal methodological quality assessment of the included studies will be conducted.

Results

Electronic database searches yielded 3321 results after removing duplicates (Figure 1), encompassing articles published between 2014 and August 2024. As of November 2024, screening of titles and abstracts is in progress. To date, no further analysis

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of the literature has been conducted. The final selection of studies is scheduled to be completed in January 2025, followed by the analysis phase, which is anticipated to conclude in the first quarter of 2025. The results of the study are expected to be published in the second quarter of 2025.

Figure 1. PRISMA 2020 flow diagram for new systematic reviews, which included searches of databases and registers only [73].

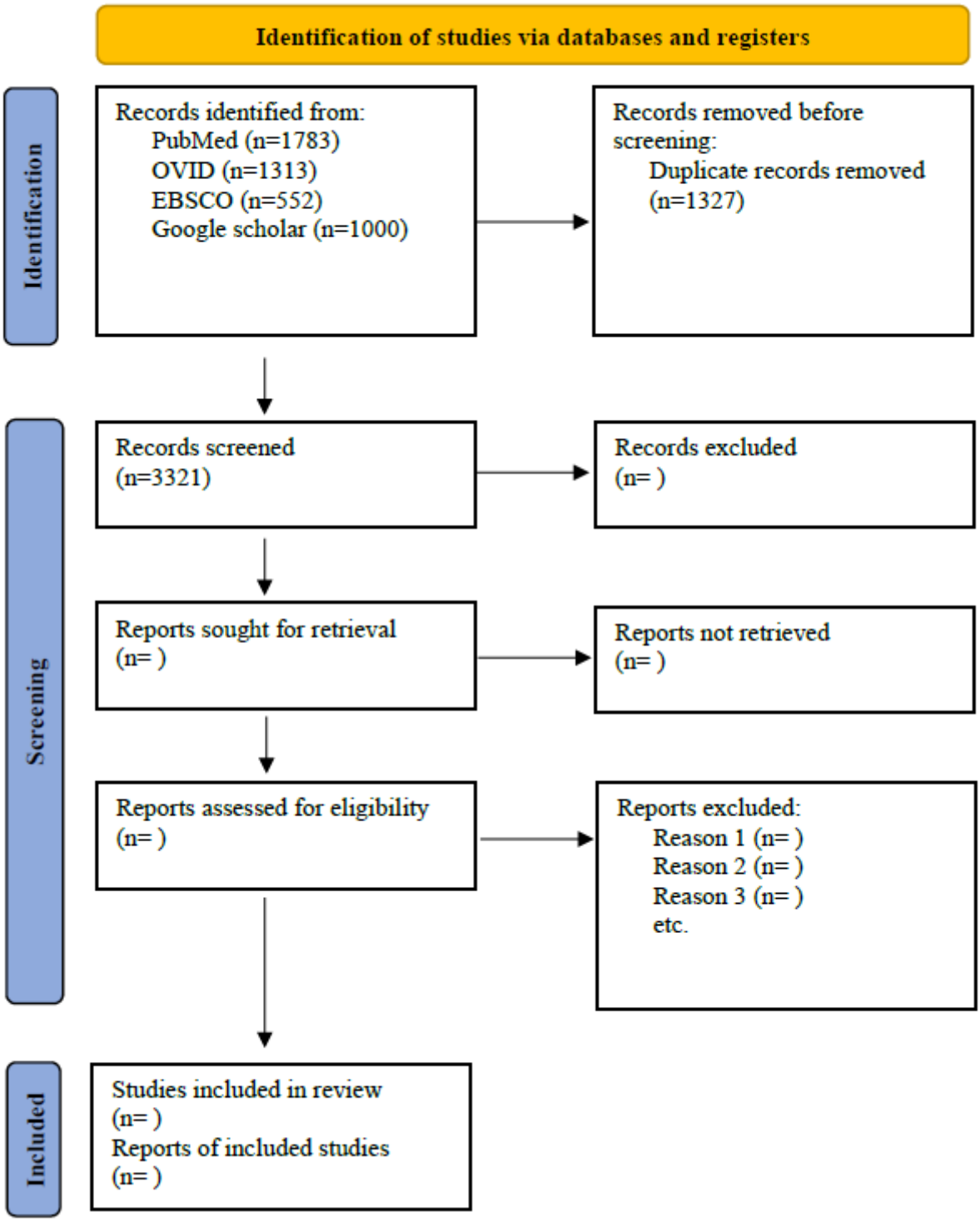

Discussion

Principal Findings

This scoping review protocol emphasizes the importance of integrating ethical considerations into empirical eHealth evaluation research. It underscores the need for practical guidance tailored to interdisciplinary teams and aligned with established evaluation practices, including references to study designs, methodologies, and objectives. However, the limited understanding of how ethical considerations are addressed in eHealth evaluation practices presents a significant challenge to

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achieving this objective. To address this gap, this scoping review will systematically analyze eHealth evaluation studies from the past decade to assess how ethical considerations have been incorporated.

We assume that ethical considerations are addressed more frequently in eHealth evaluation research than previous reviews indicated. This is because the established standards in health care, evaluation, and research mostly reflect ethical norms, as stated by Leiber and Meyer [76] in the context of evaluation practice. These often hidden ethical norms likely play a significant role in promoting the integration of ethical considerations into eHealth evaluation research practices. However, ethical considerations may not always be addressed systematically or clearly presented in the final publications.

Unlike previous reviews that provide a simple yes or no assessment, this scoping review aims to offer a more nuanced understanding of eHealth evaluation practices concerning ethical aspects. Rather than focusing solely on the substantive level, we emphasize the importance of examining the methods used to identify these ethical considerations. Among the existing reviews, the review by Steerling et al [25] stands out as the only one that examines the practices associated with the reported ethical aspects. Their findings revealed a significant methodological shortfall, with 52.9% of the included studies lacking references to ethical frameworks, indicating a gap in systematic ethical approaches in eHealth research.

A common limitation of existing reviews is the focus on explicitly labeled ethical aspects. Articles that addressed ethical concerns only indirectly were excluded. This issue was pointed out by Droste et al [26] in their investigation of HTA reports and by Keenan et al [22] in the discussion of their study's limitations. These exclusions, coupled with the lack of information on ethical approaches, contribute to a distorted representation of the practices concerning ethical aspects in eHealth and hinder efforts to solve the problem of underrepresentation of ethical considerations in the field.

Whether neglected or addressed implicitly, ethical aspects may remain invisible to readers, which can significantly impact eHealth practice. For instance, ethical concerns might be disregarded in individual eHealth projects informed by evaluation research or overlooked in systematic reviews and HTA reports that guide health care practices and policies. This bears the risk that the value of eHealth interventions will mainly be evaluated based on the empirical evidence. This evidence is important, but without systematic critical reflections on broader questions like, "Do we want these profound changes in healthcare? Are they in line with ethical standards?" professionals cannot ensure that eHealth technologies are ethically sound [15].

Both empirical and ethical perspectives are crucial for assessing the overall value of eHealth and for addressing emerging ethical risks, such as growing health disparities, before they become irreversible [52,77,78]. To ensure that ethical considerations are visible in future research, we support the suggestions of van der Wilt et al [43]: We advocate for more holistic integrated approaches to evaluating eHealth interventions within and beyond the context of cancer and cardiovascular care. This will increase the likelihood that ethical concerns will be considered in critical decision-making processes [48], ultimately strengthening the ethical foundation of eHealth practices.

Limitations

Our study will face limitations related to its focus and the complexity of ethics. First, the exclusive focus on cancer and cardiovascular diseases stems from anticipating significant growth in these research areas regarding RPM applications [4,79], considering them as examples for less-studied diseases and eHealth solutions. Our exclusive focus limits the generalizability of our findings to broader eHealth evaluation practices. However, narrowing our scope to specific areas is necessary because of the growing volume of results in eHealth evaluation research and our resource constraints.

Second, limitations arise from the broad concept of ethical aspects, posing challenges to identification and extraction. To tackle this, we will conduct pilot extractions and involve at least two reviewers in the data extraction process, increasing the likelihood of capturing relevant ethical aspects.

Conclusions

Evaluation studies play a crucial role in shaping daily eHealth practices, from software development and health care delivery to public and policy discussions, by providing well-founded insights. This creates a significant responsibility for researchers and evaluators to identify and address (potential) ethical challenges.

However, ethical aspects are often overlooked or only indirectly addressed in eHealth research. This creates a risk that such considerations may not be adequately reflected in critical decision-making about eHealth.

The proposed scoping review is an initial step toward addressing the neglect of ethical aspects in original eHealth evaluation research. It will offer detailed insights into practices related to ethical considerations, highlighting opportunities for their holistic integration. These findings can inform the development of future guidance and recommendations on how to incorporate ethical aspects into original eHealth evaluation research. In this way, this review will support the advancement of more ethical practices in the eHealth context.

Acknowledgments

This scoping review is part of LW's cumulative dissertation, which contributes to the awarding of a PhD. We would like to thank Kathleen Wallace for editing the protocol and Thomas Fürst for valuable advice on our initial search strategy.

In addition to using Rayyan for the scoping review screening and selection process, we used Paperpal (Cactus Communications Services) to facilitate and check the creation of the draft manuscript. This tool was used exclusively for language improvement

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purposes and not for content generation. Multimedia Appendix 3 shows the original Paperpal transcript. The resulting text was subsequently reviewed by the study group and subjected to further refinement by using an editing service.

This study protocol was conducted as part of the binational interdisciplinary project “new DAta new Responsibilities” (DARE), which was funded by the German Federal Ministry of Education and Research (grant 01GP1909B). This study was further supported by the Open Access Publication Fund of the University of Freiburg. The funders were not involved in any aspect of content development or approval.

Data Availability

All data generated during this scoping review will be included in this published article.

Authors' Contributions

LW, JK, SV, and LL contributed to conceptualization. LL, LK, and AT handled funding acquisition. LW, JK, SV, and LL contributed to the methodology. LL, SV, SDG, LK, and AT performed supervision. LW contributed to writing the original draft. SV, LL, LK, SDG, AT, and JK contributed to writing—review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-ScR fillable checklist.
[DOCX File , 107 KB - resprot_v14i1e60849_app1.docx]

Multimedia Appendix 2
Full search strategy.
[DOCX File , 21 KB - resprot_v14i1e60849_app2.docx]

Multimedia Appendix 3
AI - Paperpal edit.
[DOCX File , 202 KB - resprot_v14i1e60849_app3.docx]

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Abbreviations

CONSORT: Consolidated Standards of Reporting Trials
DARE: new DAta new REsponsibilities
HTA: Health Technology Assessment
JBI: Joanna Briggs Institute
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
RPM: remote patient monitoring
VALIDATE: VALues In Doing Assessments of health Technologies
WHO: World Health Organization

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Protocol

Power-Assist Add-Ons for Older Adult Manual Wheelchair Users: Protocol for a Scoping Review

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Abstract

Background: Manual wheelchairs promote independence among older adult users. However, the user's level of disability, strength, and stamina, and the environmental conditions in which the wheelchair is used, may limit the functionality of manual wheelchairs and their impact on independence and active aging. The use of power-assist add-ons may mitigate these limitations and allow an individual to age in place.

Objective: We propose to conduct a scoping review of scientific and gray literature to examine the use of power-assist add-ons by older adults who use manual wheelchairs, as well as their advantages, limitations, and potential benefits in promoting independence and active aging.

Methods: The review will be guided by the Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews checklist, and we will use the Arksey and O'Malley scoping review methodology. The literature search will use a comprehensive approach and will be carried out in two phases: (1) a keyword and Medical Subject Headings search of electronic databases, proceedings, and symposia for relevant titles and abstracts and (2) a search of Google and Google Scholar. Articles will be selected based on predefined inclusion and exclusion criteria. We will include studies of power-assist add-ons for older manual wheelchair users (aged ≥65 years) across any health condition or setting. We will exclude studies not focused on power-assist add-ons or older adults. Data will be synthesized through thematic analysis (attitudes and efficacy) and directed content analysis (limitations and gaps). Results will be summarized narratively and in tables. The findings will be disseminated in peer-reviewed publications and conferences focused on rehabilitation or gerontology.

Results: We will synthesize data on power-assist add-ons by compiling a list of devices, analyzing attitudes toward their use, identifying limitations, and highlighting gaps in the literature. We expect to publish the results in 2025.

Conclusions: The information obtained through this review could inform future research involving wheelchair producers, suppliers, and prescribers.

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KEYWORDS

manual wheelchair; power add-ons; gerontology; aging; mobility; assistive technology; independence

Introduction

Manual wheelchairs support the mobility of older adult users and facilitate activities of daily living, thereby promoting independence, active aging, and aging in place [1]. However, cognitive, physical, and environmental deficiencies may hinder the independence of wheelchair users, jeopardizing their ability to retain their choices to continue to live in their preferred residence and communities [2-4]. Topographic barriers may impede the free movement of wheelchair users [5]; for instance, it can be difficult to self-propel a manual wheelchair uphill or on uneven terrain [6]. There are also a variety of mental and physical limitations that may limit a person's ability to use a manual wheelchair. For example, self-propelling a manual wheelchair requires a minimal level of coordination and upper limb strength, both of which may be absent in the user depending on their diagnosis [7]. The environmental context (eg, wheelchair accessibility, uneven or challenging terrain, and distance) poses additional constraints on manual wheelchairs [1,5,8]. All of these limitations can be exacerbated among older adults, given the normal aging process [9].

One recent development in wheelchair design that addresses these issues is power-assist add-ons for manual wheelchairs, which are gaining popularity among those who need intermittent mobility assistance (eg, for travelling longer distances or overcoming specific environmental features). There are three types of add-ons: powered front-end attachments, powered rear wheels, and powered back-end attachments. The costs of motorized wheelchairs can be prohibitive, and a power add-on for a manual wheelchair may offer a more affordable option for motorized propulsion of a manual wheelchair. A user may also prefer to enhance a manual wheelchair with which they are familiar rather than being forced to obtain and adapt to a new wheelchair, and they may prefer to switch between power and manual as desired.

Despite advances in wheelchair designs, it is not clear how power add-ons for manual wheelchairs can be deployed safely and effectively among older adults. A preliminary search of the literature revealed scoping reviews on the use of manual wheelchairs for older adults [10-12]; however, we were unable to find reviews on power-assist add-on for older adult wheelchair users, nor any registered protocol for a similar scoping review on online protocol registration platforms.

Our aim is to conduct a scoping review of scientific and gray literature in order to explore the use of power-assist add-ons by older adult users of manual wheelchairs. Our specific objectives are to (1) describe the power-assist add-ons used by older adults, if any; (2) review research studies focusing on attitudes, uptake, efficacy, and/or effectiveness of power-assist add-ons; (3) examine the limitations of power-assist add-ons among older wheelchair users; and (4) identify the gaps in existing literature. The findings of this review could inform future research involving wheelchair producers, suppliers, and prescribers.

Our research questions are as follows:

1. What power-assist add-ons exist and are used by older manual wheelchair users?
2. What are the attitudes toward uptake, efficacy, and/or effectiveness of power-assist add-ons used by older adults?
3. What are the limitations of using power-assist add-ons among older adults?
4. What are the gaps in research on the use of power-assist add-ons by older wheelchair users?

Methods

Protocol Registration and Study Design

Our review protocol has been registered on the Open Science Framework [13] and will be guided by the Preferred Reporting Items for Systematic reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA-ScR) checklist extension for Scoping Reviews [14]. We will use the scoping review framework originally developed by Arksey and O'Malley [15] and incorporate additional refinements recommended by Levac et al [16]. This process will include the following five steps: (1) identify the research questions; (2) identify relevant studies; (3) select studies; (4) chart the data; and (5) collate, summarize, and report the results. An optional sixth stage involving consultation with stakeholders may be included, as suggested by Levac et al [16].

The PRISMA-ScR is a guideline that provides a framework for reporting the methodology and results of a scoping review. Using the elements of PRISMA-ScR can help ensure transparency and improve the reporting quality of our scoping review. We will adapt the PRISMA-ScR guidelines to fit the specific objectives and design of the scoping review as this will be helpful in ensuring transparency and completeness in reporting the review process. Some of the elements of the PRISMA-ScR checklist that we will use to provide a clear and structured presentation of the review methodology are as follows:

1. Title—clearly state that it is a scoping review.
2. Abstract—summarize the purpose, methods, and main findings of the scoping review.
3. Introduction—provide background information and rationale for the review.
4. Methods—describe the search strategy, inclusion and exclusion criteria, data sources, and data extraction process.
5. Results—present a summary of the included studies, including key characteristics and themes identified.
6. Discussion—interpret the findings, identify gaps in the literature, and discuss implications for practice and future research.
7. Conclusion—summarize the main findings and implications of the scoping review.

Eligibility Criteria

We will include all articles that describe, assess, or explore the use of power-assist add-ons by older manual wheelchair users. Our definition of a power-assist add-on is a motorized device

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that can be attached to provide external power to a manual wheelchair. Our working definition of older adults will be anyone aged 65 years or older [17-19]. Based on a preliminary search of databases, we anticipate a dearth of literature focused solely on older adult wheelchair users. Hence, we will broaden the inclusion criteria to include studies done with adults and account for this approach in the discussion of our findings.

We will include older adults with all health conditions across any setting (eg, hospital, community, or rehabilitation facility). We will include the academic field of the studies, the general health-promotion programs the studies use, and the health care interventions designed for older adults with disabilities that the studies investigate.

Search Strategy

Our literature search will use a broad approach and will be carried out in two phases.

Phase 1: Search up to December 2024

In phase 1, we will conduct a search of electronic databases (Multimedia Appendix 1), proceedings, and symposia for relevant titles and abstracts using a set of keywords. The keywords are generated from suggestions from team members; mining with Ovid Search Builder, Ovid Citation Analyzer, Medline, PubMed PubReMiner; and through mining within texts.

We have identified the main concepts in this scoping review and generated a list of keywords for each concept. For power-assist add-ons, we will use *power-assisted mobility devices*, *electric wheelchair attachments*, *motorized wheelchair accessories*, and *wheelchair propulsion assistance*. For manual wheelchair users, we will use *wheelchair users*, *individuals with mobility limitations*, and *people who use manual wheelchairs*. For active aging, we will use *healthy aging*, *aging well*, *independent living in older adults*, and *maintaining mobility in older adults*.

We will combine the keywords and synonyms using Boolean operators (AND, OR), as follows: (*power assist add-ons* OR *power assisted mobility devices* OR *electric wheelchair attachments* OR *motorized wheelchair accessories* OR *wheelchair propulsion assistance*) AND (*manual wheelchair users* OR *wheelchair users* OR *individuals with mobility limitations* OR *people who use manual wheelchairs*) AND (*aging* OR *healthy aging* OR *aging wellOR independent living in older adults* OR *maintaining mobility in older adults*).

Truncation or wildcard symbols (*) will be used to capture variations of keywords: (*power assist add-ons* OR *power assist** OR *electric wheelchair attach** OR *motorized wheelchair access** OR *wheelchair propulsion assist**) AND (*manual wheelchair users* OR *wheelchair user** OR *individual** *with mobility limitation** OR *people who use manual wheelchair**) AND (*aging* OR *healthy aging* OR *aging well* OR *independent living in older adult** OR *maintain** *mobility in older adult**).

In addition, Medical Subject Headings (MeSH) and free-text search terms will be applied to each database without limitations for publication period. We will use relevant MeSH terms, such as *wheelchairs* OR *assistive technology* OR *power assisted mobility devices* OR *manual wheelchair users* OR *power add-on* OR *powered rear wheels* OR *back-end attachment* OR *front-end attachment* OR *aged* OR *aging* OR *mobility limitations* OR *rehabilitation* OR *physical therapy* OR *occupational therapy* OR *assistive devices* OR *mobility aids* OR *accessibility* OR *independent living* OR *quality of life* OR *user satisfaction* OR *health outcomes* OR *functionality* OR *ergonomics* OR *safety*.

Phase 2: Search up to First 10 Result Pages

In phase 2, we will search Google and Google Scholar using the same keywords applied in the first phase. Additional relevant articles will be extracted from reference lists of similar reviews and papers. All articles resulting from our search will then be uploaded to the online platform Covidence to eliminate duplicates and for subsequent screening. An example of the search strategy for the Ovid database is presented in Multimedia Appendix 2.

Study Selection

Before we carry out the formal screening, a calibration exercise (pilot testing in 10% of identified studies) will be completed to ensure reliability. Percentage agreement will need to be >80% across reviewers to begin formal screening. Training, screening, and further development of criteria will occur until this interrater agreement threshold is met. The screening will be performed independently by 2 review authors, and discrepancies will be resolved by consensus or with the involvement of a third reviewer. The screening of articles will be completed in two stages. In the first stage, 2 researchers will independently screen the titles and abstracts, and conflicts will be resolved through dialogue or by a third researcher. In the second stage, full-text versions of the resulting articles will be obtained and reviewed by the 2 researchers. Articles will be selected based on the inclusion and exclusion criteria.

Data Charting

Data charting has four objectives: (1) we will enumerate the kinds of power-assist add-ons identified in the review, and we will create a list of names of all add-ons; (2) we will use thematic analysis to explore and identify themes and summarize attitudes toward uptake, efficacy, and/or effectiveness of power-assist add-ons for older adult wheelchair users [20,21]; (3) for any data on the limitations of power-assist add-ons, we will apply directed content analysis to describe the challenges associated with their use, areas for improvement, and strategies to improve quality, application, usability, and acceptance [22]; and (4) in aspects of this review where there is a paucity of data to answer our research question or where some specific methodologies or content are lacking, we will identify these as gaps.

Data Items

For each of the included studies, we will extract the following data: study characteristics, including the study's year and setting (hospital, rehabilitation facility, community, or other); type of add-on; type of health care provider (if applicable); condition studied or age group (as applicable); country or region of origin; funded vs unfunded status; and journal name. We will also record the study's purpose and objectives, including its aim, questions, topic (or concept) addressed, and outcomes (ie,

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identified evidence gaps, future research opportunities, strengths and limitations, and implications for policy or practice), as well as the study's methodology, approach, and scope.

Synthesis of Results

The synthesis of this scoping review will focus on 3 key aspects: the uptake, effectiveness, and limitations of power-assist add-ons for older manual wheelchair users. Thematic analysis will be used to identify and organize key themes from the data, ensuring that the findings reflect a comprehensive understanding of users' attitudes toward these devices.

Themes will emerge through an inductive, iterative process, with data coded and grouped based on similarities and patterns. Each theme will explore factors such as the perceived benefits, challenges, and barriers to adopting power-assist add-ons. The synthesis will also examine how factors like physical, emotional, and social considerations influence users' experiences.

By ensuring methodological rigor and reflexivity, the synthesis will provide a clear, cohesive narrative of older adults' experiences with power-assist add-ons, highlighting critical factors for adoption and their overall effectiveness. The final synthesis will contribute to a deeper understanding of this technology's role in improving mobility for older wheelchair users.

Dissemination

Dissemination of our findings will include (1) producing versions of an executive summary that will be tailored to various groups, including educators, prescribers, and developers, as we expect that our findings will inform further collaboration with clinicians, prescribers, and dealers; (2) publishing in peer-reviewed journals focused on in rehabilitation and/or gerontology and on online platforms; and (3) presenting at relevant conferences (eg, the conference of the Canadian Association on Gerontology).

Results

We expect this scoping review to provide a comprehensive overview of the types of power-assist add-ons used by older adult manual wheelchair users. This could include motorized rear-wheel attachments and other propulsion devices. We anticipate identifying a wide range of power-assist technologies, along with variations in their adoption, usability, and perceived efficacy across different settings and populations.

We expect to discover a wide range of attitudes regarding the adoption and effectiveness of these devices. We expect to find that some users report notable improvements in mobility and independence and a reduction in physical strain. However, challenges such as cost, maintenance difficulties, and concerns related to the device's weight and comfort may also emerge as key factors affecting adoption and use.

Discussion

Anticipated Findings

We foresee identifying several limitations related to the use of power-assist add-ons, including challenges with device integration, safety concerns, and insufficient training or support for users. These limitations are likely to be discussed in the context of how power-assist technologies are implemented in various settings, as well as the potential gaps in existing support systems.

Additionally, we expect this review to reveal mixed perceptions regarding the overall impact of power-assist add-ons on the quality of life and daily functioning of older adults. While some users may experience considerable improvements in these areas, others may face difficulties with the practicality and long-term sustainability of the devices.

We also expect that this scoping review will highlight gaps in the literature, particularly in the areas of long-term outcomes, cost-effectiveness, and the inclusion of older adults with diverse physical abilities and needs. This will help pinpoint areas requiring further research and development. Finally, the findings will inform recommendations for future research aimed at improving the design, usability, and accessibility of power-assist add-ons for older adults, with a focus on addressing identified barriers and enhancing user experience.

Conclusion

It is well known that older adults should be provided the opportunity to maximize independence, social connections, and quality of life. For older manual wheelchair users, these conditions for successful aging could potentially be enhanced by power-assist add-ons. We anticipate that the proposed review will summarize and provide key information to support future research and to enhance the knowledge base needed to further improve the use of power-assist add-ons.

Conflicts of Interest

None declared.

Multimedia Appendix 1
List of databases.
[DOCX File , 15 KB - resprot_v14i1e56375_app1.docx]

Multimedia Appendix 2
Ovid search sample.
[DOCX File , 18 KB - resprot_v14i1e56375_app2.docx]

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Multimedia Appendix 3
Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) Checklist. [DOCX File , 27 KB - resprot_v14i1e56375_app3.docx]

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Abbreviations

MeSH: Medical Subject Headings
PRISMA-ScR: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Strategies and Tools for Electronic Health Records and Physician Workflow Alignment: Protocol for a Scoping Review

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Abstract

Background: Electronic health records (EHRs) have been widely adopted in health care systems globally, offering potential benefits in data accessibility, quality improvement, and enhanced patient outcomes. However, the alignment between EHRs and physician workflows remains a significant challenge, leading to negative impacts on physician well-being and patient care. While health care organizations have attempted various strategies to improve this alignment, critical gaps still persist, highlighting the need for a comprehensive understanding of existing approaches and their effectiveness as a means to chart effective strategies to align physician workflows with EHRs.

Objective: This scoping review aims to identify and synthesize the strategies and tools health care organizations have used to align physician workflows with EHRs. This review will provide a toolkit for health care organizations and researchers, offering insights into effective alignment practices and identifying knowledge gaps for future research.

Methods: This scoping review will follow the Joanna Briggs Institute framework for scoping reviews while incorporating the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist for transparent reporting. We will search multiple databases, including MEDLINE, PubMed, Cochrane, CINAHL, Scopus, Embase, and Web of Science, for relevant literature on tools, strategies, and interventions used to align physician workflows with EHRs. The review will focus on studies involving physicians in direct patient care across primary, secondary, tertiary, and quaternary care settings. Two independent reviewers will screen titles, abstracts, and full texts for inclusion. Data extraction will be performed using a standardized form, and findings will be narratively synthesized and presented in tables and charts.

Results: The study is expected to provide a comprehensive toolkit of strategies, tools, and interventions for EHR-physician workflow alignment. This synthesis will offer health care organizations practical guidance for improving alignment and provide researchers with a foundation for identifying research gaps and future directions. The final report is planned for submission to an indexed journal in August 2025.

Conclusions: This scoping review will offer valuable insights into the strategies and tools implemented by health care organizations to align EHRs with physician workflows. By assessing the effectiveness and limitations of these approaches, the review aims to contribute to improved EHR usability, reduced physician burnout, and enhanced patient care.

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KEYWORDS

electronic health records; electronic medical records; physician workflow; alignment; optimization; scoping review; JBI framework; workflow; implementation; PRISMA

Introduction

The adoption of electronic health records (EHRs) is increasing in national and international health care systems [1]. EHRs are rapidly becoming the preferred method of digitizing health data, making it more accessible to patients and improving quality and analytical opportunities that enhance patient outcomes [2,3]. However, despite the recognized potential of EHRs to improve health care, the claim that they enhance workflow efficiency and productivity appears to be exaggerated [4,5]. The complex and emergent nature of health care, variations in individual physicians' treatment processes, as well as varying needs of patients sometimes conflict with standardized processes in EHRs, leading to workflow challenges [6].

Workflow consists of activities organized in sequential processes, including the necessary resources to complete the task [5]. It is a series of linked steps based on the flow paradigm, distinct from a single task. Workflow is a model that represents the steps involved in a real work environment to move a work description from initiation to completion. For instance, the steps involved in patient-physician interaction, from a patient's arrival at the physician's office to their departure, can be depicted as a workflow [6]. However, while the duties of some health professionals, such as nurses, tend to follow relatively standardized routines, the tasks, task sequences, and priorities of physicians vary greatly by individual style and patient needs [7]. Also, physician workflows, especially in time-bound units such as the emergency and intensive care units, are nonlinear and complex. They depend on a wide variety of data inputs and may involve multitasking and fragmentation [8]. Physician workflows also include a wide range of data management and multilevel communication, such as physician-to-physician, physician-to-nurse, and physician-to-patient [9]. Consequently, it can be challenging to use a standardized EHR workflow specifically designed for clinicians to other interaction groups.

Several issues leading to misalignment between EHR and physician workflow have been documented in the EHR literature [5,10,11]. For instance, some authors have noted that EHR designers who are not health care professionals may not realize the importance of making EHRs adaptable, flexible, and responsive to the unpredictable nature of physicians' workflow [6,12]. These designers, in their pursuit to enhance the value of EHRs, may inadvertently hinder physicians' clinical routines and workflow, resulting in usability issues. Moreover, it can be argued that EHRs are not designed to automate physicians' existing paper-based workflows [6].

The negative impact of workflow interference on physicians is significant and has been identified as a major contributor to burnout [10,11,13]. Furthermore, inadequate physician workflow design in the EHR can impede effective physician-patient interaction, restrict assessment and treatment, and increase the risk of medication errors [5,14]. Suboptimal EHR-mediated workflows often lead to workarounds, which involve using alternative approaches instead of the recommended methods after system implementation [15]. Given that these challenges have a significant impact on physicians, leading to burnout and stress [16], they can result in incomplete and inaccurate patient documentation [5]. Considering that physician workflow is a crucial factor in maximizing the benefits of the EHR [17], it is essential to understand how to navigate the challenges around the alignment between EHR and physician workflow for successful EHR implementation, usage, and value recommendations. It is also important to understand the impact of existing strategies and tools on EHR and physician workflow alignment. An example of such a tool is the integrated software such as Dragon Naturally Speaking app which is a speech recognition software. This software often serves both as a voice-to-text tool and an EHR inbox management system [18,19]. It improves communication and minimizes the time spent on documentation. Another example of a strategy is order-sets optimization within EHRs bundle frequently required tests for specific illnesses or conditions [20,21], which reduces the time spent on orders and improves physician workflow.

Despite the increasing number of studies on how to improve alignment between clinicians and EHR workflows, the existing knowledge is highly diverse and fragmented, creating gaps in our comprehensive understanding. Different studies focus on various aspects of EHR-physician workflow alignment, such as time management, stress levels, and patient outcomes. For example, some studies analyze the amount of time physicians dedicate to EHR tasks compared with patient interaction, while others assess the influence of EHR on physician productivity and job satisfaction [22,23]. The studies in this field lack synthesis, as researchers often work in isolation instead of building upon each other's findings. Consequently, the body of knowledge remains fragmented, without a clear and unified direction for improvement. One of the purposes of a scoping review is to improve understanding of complex issues that affect health care workers and EHRs and to map existing tools to improve this challenge [24,25]. We argue that, to advance understanding of how EHR-physician workflow alignment should be approached, it is necessary to map the intellectual structure of current knowledge through a scoping review. This review will synthesize the concepts and interventions from published articles that focus on EHR-physician workflow alignment, ultimately creating a comprehensive toolkit of knowledge and strategies to achieve maximum alignment and minimize obstacles in EHR implementations. This understanding can assist health care organizations in optimizing alignment, leading to improved usability, increased adoption, reduced medication errors, and decreased physician burnout [20,26]. In addition, it can provide guidance to software developers and vendors on users' and health care organization needs and preferences on how to effectively align EHR and physician workflow. Therefore, a scoping review method was chosen to synthesize diverse evidence from published and gray literature [27].

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Methods

To ensure consistency in the conduct and reporting of scoping reviews, as well as maximize rigor, this study will follow the Joanna Briggs Institute (JBI) guideline for Scoping Reviews [27]. In addition, it will incorporate the recent methodological development on scoping reviews, the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist into the main framework [28] (Multimedia Appendix 1).

Consultation

Consulting stakeholders is a vital aspect of the scoping review method. In this study, a librarian from the Weldon Library at the University of Western Ontario helped develop the search strategy. Once the study is completed, we will seek feedback from physicians who frequently use the EHR in their workflow to ensure an accurate and comprehensive interpretation of the findings. Their objective perspective will help validate the results, identify biases, and enhance the credibility and rigor of the research.

Step 1: Formulate a Research Question

The population, context, and concept (PCC) framework will be used to identify the main concepts of primary review questions and inform the development of search strategies [20] (Textbox 1). Using the PCC framework, our review will focus on the strategies and tools that health care organizations use to align physician workflow with EHR (concept) for physicians that have face-to-face interaction with their patients (population) at any level of care (context).

Textbox 1. Review questions.

- What strategies and tools have health care organizations used to align physician workflows with electronic health records systems?
- How have these strategies and tools impacted the alignment between physician workflows and electronic health records, health care delivery, and patient care?
- What are the strengths and limitations of these strategies and tools?
- What are the gaps that currently exist in literature and what opportunities for future studies exist?

Step 2: Identifying Studies Relevant to the Research Question

To answer the research questions, we will conduct a comprehensive search of several databases, including Embase (OVID), MEDLINE (OVID), PubMed, COCHRANE CINAHL, and interdisciplinary databases such as WEB OF SCIENCE and SCOPUS. To ensure we capture all relevant articles, we will also screen the references of selected articles using the ancestry method. We aim to include scientific peer-reviewed studies and conference proceedings, encompassing all types of scientific study designs and approaches. Furthermore, we will conduct a thorough search for gray literature by identifying pertinent sources such as reports, conference proceedings, theses, and government documents. We will search databases such as ProQuest Dissertations and Theses and OpenGrey to access and hand-pick studies that have not undergone peer review. Also, we will search conference proceedings for abstracts and presentations that may not have been published in journals and take the time to explore the websites of health care organizations and government agencies.

By using this strategy, a preliminary search of the PubMed database in December 2024 returned 516 articles. The sample search strategy is presented in Table 1. This strategy will be repeated for all the identified databases.

Table 1. A sample of the search query.

Search number	Search query	Items found
#1	Search: (((((Electronic Health Records[MeSH Terms]) OR (Electronic Medical records[MeSH Terms])) OR (EHR[Title/Abstract])) OR (EMR[Title/Abstract])) OR (Computerized Provider Order Entry[Title/Abstract])) OR (Electronic health records[Title/Abstract])	56,275
#2	Search: ((Physician workflow[Title/Abstract]) OR (Doctor workflow[Title/Abstract])) OR (Clinician workflow[Title/Abstract]) "physician workflow"[Title/Abstract] OR (("doctor s"[All Fields] OR "doctoral"[All Fields] OR "doctorally"[All Fields] OR "doctorate"[All Fields] OR "doctorates"[All Fields] OR "doctoring"[All Fields] OR "physicians"[MeSH Terms] OR "physicians"[All Fields] OR "doctor"[All Fields] OR "doctors"[All Fields]) AND "workflow"[Title/Abstract]) OR "clinician workflow"[Title/Abstract]	2860
#3	#1 AND #2 Search: (#1) AND (#2) ("physician workflow"[Title/Abstract] OR (("doctor s"[All Fields] OR "doctoral"[All Fields] OR "doctorally"[All Fields] OR "doctorate"[All Fields] OR "doctorates"[All Fields] OR "doctoring"[All Fields] OR "physicians"[MeSH Terms] OR "physicians"[All Fields] OR "doctor"[All Fields] OR "doctors"[All Fields]) AND "workflow"[Title/Abstract]) OR "clinician workflow"[Title/Abstract]) AND ("electronic health records"[MeSH Terms] OR "electronic health records"[MeSH Terms] OR "EHR"[Title/Abstract] OR "EMR"[Title/Abstract] OR "computerized provider order entry"[Title/Abstract] OR "electronic health records"[Title/Abstract])	516

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Step 3: Study Selection

A scoping review protocol should clearly outline the eligibility criteria (inclusion) and sources of information that will be used in the study [28]. The inclusion and exclusion criteria for selecting studies will be achieved based on the scope of the inquiry. Also, the ancestry approach will be adopted to identify relevant studies from the references of selected articles.

Inclusion Criteria (PCC)

The inclusion criteria for the studies will align with the PCC guidelines, which specify the PCC [29].

Population

The study will specifically target physicians who directly interact with patients, excluding non–patient-engaging physicians such as pathologists and radiologists. This inclusion is important because non–patient-engaging physicians interact with the EHR differently than physicians who typically combine documentation and review during patient interactions. Physicians who simultaneously interact with both the EHR and patients have been reported to experience issues such as divided attention and higher cognitive workload leading to burnout and stress [10,11,16]. The study will encompass articles focusing on physicians who use the EHR in primary, secondary, tertiary, and quaternary care (Textbox 2).

Textbox 2. Inclusion and exclusion criteria.

Inclusion criteria

- Studies on electronic health records or electronic medical records
- Studies in the English language
- All publications that seek to optimize the usability of electronic health records for physician's use by improving workflow
- Focuses on physician workflow
- Studies carried out at any level of care, primary, secondary, tertiary, and quaternary care
- Studies that focus on physicians who have direct contact with patients such as primary care physicians, internists, and surgeons
- Studies based on the workflow of a single physician or multiple physicians

Exclusion criteria

- Studies that focus on other health information systems excluding electronic health records and electronic medical records
- Studies not published in the English language
- Studies that do not address the alignment of electronic health records and physician workflow
- Focuses on other health care professionals such as nurses and caregivers
- Studies that focus on the impact of electronic health records on workflow or understanding of physician workflow
- Physician that does not have direct contact with patients
- Studies that target the concept of meaningful use will be excluded

The study will center on physicians, aiming to systematically document and describe the tools and strategies used to optimize their workflow with the EHR. While some studies on clinical workflow will be included in the search using the term "clinical workflow," this is to ensure that studies that explore the combination of physician workflow with other clinician's workflow are not overlooked. Consequently, we will exclude studies that solely concentrate on other clinicians, such as nurses and allied health professionals, during the screening process.

Concept

Our focus is to examine interventions, defined as practical actions or sets of actions intended to facilitate alignment between EHR and physician workflow from all relevant research. This encompasses observational studies, case studies, and any research that addresses related activities. Our primary objective is to understand how organizations have addressed the challenges of aligning physician workflows with EHR systems have been addressed. Also, this review will include studies related to electronic medical records. It does not consider the complexity of the information system's network or interconnectivity, but rather focuses on the suitability of the information system with physician workflow. The studies may be based on the experience of a single physician or multiple physicians. Any additional features or interventions that do not address misalignment in the workflow will be excluded (Textbox 2). Similarly, studies that investigate the impact of EHR design on physician workflow or access physician workflow with a focus on meaningful use will also be excluded. The objectives of meaningful use are not centered around the alignment of EHR and physician workflow but rather on the impact of EHR on the quality of care and adoption.

Context

The study will involve physicians from diverse settings, not limited to hospitals and primary care, to gain insights into the strategies and tools they have adopted to align their workflows with the EHR. Although the workflow of physicians in primary health care, hospital settings, and specialized areas like surgery and pediatrics may vary, the study's objective is to provide an

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understanding of the subject. Therefore, all studies conducted in hospital environments, primary health care, secondary, tertiary, and quaternary settings will be included. This includes studies from both the public and private sectors, as well as all areas of specialization such as emergency medicine, general practice, and surgery. There will be no bias toward specific countries or continents, except for articles not written in English (Textbox 2).

Step 4: Charting and Synthesizing the Data

Data will be input into the Covidence systematic review software, developed by Veritas Health Innovations. This software will be used to remove duplicate articles, select relevant ones, and track the reviewers' activities. Two independent reviewers will assess each article for eligibility during the screening process.

The initial screening phase will involve 2 reviewers independently evaluating the publication's title and abstract. However, if there is a disagreement, the final decision will be made by the third reviewer, who is a more experienced investigator (Figure 1).

Relevant variables will be extracted from selected studies during the full-text review. The articles will be extracted using the data extraction tool in the Covidence software. This tool will create a table using specified variables as its headers, allowing reviewers to complete the tables based on their findings. The extracted variables will cover the scope of the study on physician workflow and EHR alignment. Predetermined variables, such as health care setting, physician specialization, alignment challenges being addressed, and intervention or strategies (Textbox 3), will be extracted.

In the second phase of screening, the articles that pass the title and abstract screening will undergo a full article screening. Full articles will be assessed using the UWO online library. In cases where the article is not available at the UWO library, we will arrange for an interlibrary loan. In addition, if we are unable to access the article through interlibrary loan or if we require methodological details or clarification on missing or unclear data, we will contact the authors.

To ensure broader coverage, we will use the ancestry method, which involves screening the references of selected articles for relevance. Finally, we will use a PRISMA-ScR flow diagram to summarize the screening process, including the inclusion and exclusion criteria, number of included and excluded articles as well as the total number of articles selected for the review. Two reviewers will screen the full text of all articles selected during title and abstract screening to determine if they meet the eligibility criteria for extraction and where conflict arises, eligibility will be determined by the third reviewer who is a more experienced investigator.

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart.

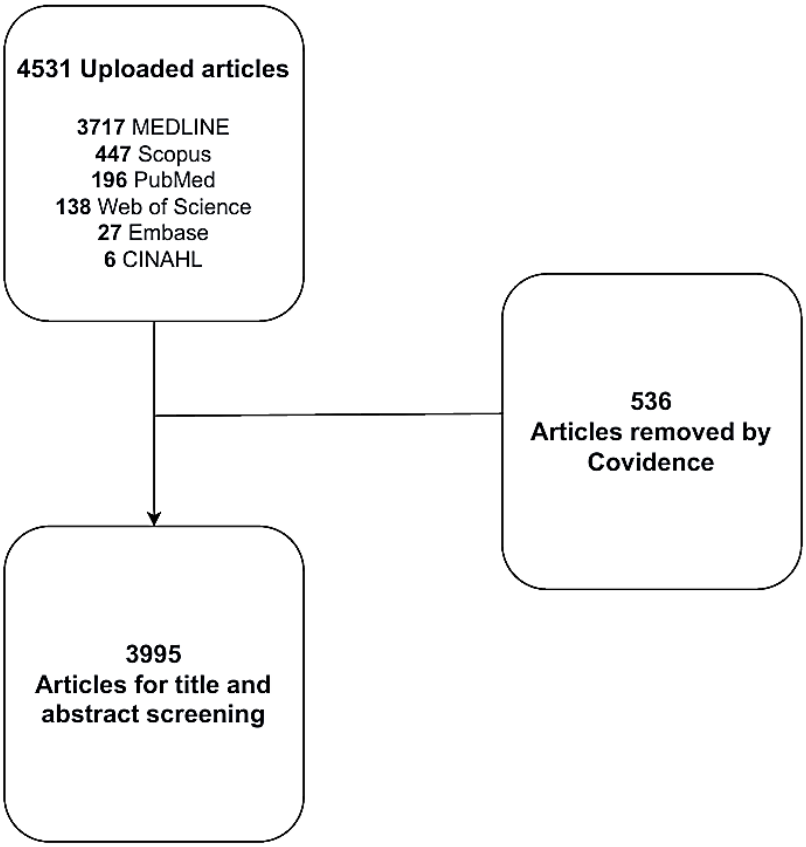

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Textbox 3. Variables that will guide data extraction.

Study design

- Title
- Author
- Year of the study
- Country
- Aim of the study
- Data collection methods
- Setting: hospital, clinic, intensive care unit, internal medicine, and so on
- Physician specialization: primary care, pediatrics, surgery, and so on

Study context and concept

- Addressed challenges
- Intervention, strategy, or tool for alignment
- Impact or outcomes: challenges, advantages, and disadvantages

Step 5: Collating, Summarizing, and Reporting the Results

The PRISMA-ScR extension flow diagram will be used to present the report of the scoping review [28]. The extracted data from the review will be qualitatively analyzed using frequency, common characterization of health care settings (level of care) or physician specialization, study design, and numerical descriptions such as the mean physician time taken to accomplish a task. Thematic analysis technique will be used to analyze the data. The reviewers will aim to identify common conceptual categories from the data, which will then be used to form themes relevant to answering the research questions. The results will be presented in a descriptive format that addresses the research questions by using an interpretive translation of the findings. Therefore, the report will consist of a narrative description of the findings.

Results

We have completed a preliminary search of the identified databases and anticipate finishing the review process by July 2025. The extracted data will be presented in diagrammatic or tabular forms to align with the objective of this review. The report will include a narrative summary that accompanies the tabulated or charted results, in a way that relates to the review's objective. Ultimately, these collated results and findings will be presented for peer-reviewed publication in a reputable journal. The result of this review will be published online and will be shared with relevant stakeholders, especially health care organizations and physicians.

Discussion

Anticipated Findings

The need to align EHR with physician workflow is critical for enhancing health care delivery and reducing physician burnout. Previous studies, such as those by Avendano et al [30] have explored specific EHR-physician alignment strategies, albeit in a limited scope by focusing on only 3 randomly selected strategies. Our scoping review aims to expand on this work by comprehensively identifying all strategies and tools used by organizations to facilitate the alignment of EHR systems with physician workflows.

In conducting preliminary searches in December 2024, we found no existing scoping review protocols or title registrations in the Cochrane and JBI databases that address this specific topic. This gap underscores the necessity of our review to synthesize the diverse strategies and tools used across different health care settings. The scoping review methodology is particularly suited for this endeavor, as it allows for the examination of a wide range of evidence, including diverse research innovations and their impacts. This approach will enable us to map the extent and nature of research activity in this area, identify knowledge gaps, and set the stage for future research agendas. By presenting a comprehensive overview of the strategies and tools used to align EHR with physician workflow, we will provide valuable insights for health care organizations aiming to optimize their EHR system. While utmost effort will be made to follow the guidelines of this protocol, any deviation, uncovered information, and identified limitations will be reported.

Conclusions

This scoping review aims to offer a comprehensive synthesis of the strategies and tools that health care organizations use to align physician workflows with EHRs. By mapping current approaches, identifying gaps in the literature, and highlighting effective practices, this review will assist health care decision makers, inform the development of future interventions, and guide further research focused on improving EHR usability, reducing physician burnout, and enhancing patient care. The findings will be a valuable resource for stakeholders looking to optimize physician-EHR alignment across various clinical settings.

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Authors' Contributions

OOO developed the research questions, method, and designed the protocol. NH, UI, and AH reviewed the methodology and made significant contributions to the drafting and editing of the manuscript. MAI and OT refined the research questions and assisted in the development of the research and study methods.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-ScR checklist.
[DOCX File , 52 KB - resprot_v14i1e60464_app1.docx]

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Abbreviations

EHR: electronic health record
JBI: Joanna Briggs Institute
PCC: population, context, and concept
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Digital Health Interventions Targeting Psychological Health in Parents of Children With Autism Spectrum Disorder: Protocol for a Scoping Review

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Abstract

Background: Autism spectrum disorder (ASD) is a complex, incurable condition requiring lifelong care, often placing significant psychological strain on parents and emerging as a public health concern. While various interventions exist to enhance the psychological health of parents, the role of digital health interventions (DHIs) in this context remains underexplored.

Objective: This scoping review aims to systematically assess the availability of DHIs targeting the psychological health of parents of children with ASD and evaluate the effectiveness of these interventions in improving parental psychological health.

Methods: The review will include English-language studies published from inception to June 25, 2024, focusing on DHIs aimed at improving the psychological health of parents of children with ASD. Eligible studies will involve parents of children with ASD less than the age of 18 years, across various settings, and assess psychological health outcomes. A comprehensive search will be conducted across six databases: (1) CINAHL, (2) Ovid EMBASE, (3) Ovid Global Health, (4) Ovid MEDLINE, (5) Ovid PsycINFO, and (6) Web of Science. Studies will be screened and selected based on predefined eligibility criteria. Data extraction will include publication details, study design, participants' characteristics, intervention specifics, comparisons, psychological outcomes, and key findings. Results will be synthesized using descriptive statistics, charts, and narrative analysis.

Results: The initial keyword-based search, completed in June 2024, identified 5825 records, which were subsequently screened and analyzed. Screening and evidence synthesis were finalized in winter 2024, and the completed scoping review was submitted in December 2024.

Conclusions: This study will provide a comprehensive overview of commonly used DHIs for supporting the psychological health of parents of children with ASD and their effectiveness. The findings will help identify research gaps, inform future studies and funding priorities, and contribute to the development of practice guidelines to enhance parental psychological health.

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KEYWORDS

autism spectrum disorder; digital health intervention; parents; psychological health; scoping review

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Introduction

Background

Autism spectrum disorder (ASD) is a lifelong neurodevelopmental condition characterized by early-onset difficulties in social communication, repetitive and stereotyped behaviors, and narrow interests [1]. According to the Autism and Developmental Disabilities Monitoring (ADDM) Network program, approximately 1 in 36 children are identified with ASD [2]. Despite extensive research, ASD remains a complex neurodevelopmental disorder with an unclear etiology and no definitive cure [3]. While children with ASD generally have a normal life expectancy, they often require lifelong care, particularly from their parents, who typically serve as primary caregivers [4,5]. The demands of caregiving for a child with ASD are significant and can negatively affect the psychological health of parents.

A growing body of evidence indicates that parents of children with ASD are at a higher risk for mental health issues compared to those raising children with other developmental disabilities [6-8]. Studies consistently show that caregiving for a child with ASD is associated with elevated stress levels, negative emotional states, and symptoms of depression and anxiety [8-10]. These psychological difficulties can deplete both parents' and children's coping energies and impair their capacity for problem-solving [11]. The impact of ASD caregiving on parental psychological health has emerged as a critical public health concern, emphasizing the need for targeted interventions.

While considerable emphasis has been placed on providing high-quality treatment and care to children with ASD, less attention has been paid to the psychological health of their parents. Previous research has explored interventions aimed at improving outcomes for children with ASD, as well as for their parents [12,13]. However, many of these studies primarily focus on training parents to promote their child's social skills, communication, and learning [14,15], with relatively few studies directly addressing parental health. Improving the psychological health of parents is critical, not only for their well-being but also for enhancing outcomes for their children. Therefore, there is a need for innovative interventions to support and train parents, especially considering the increasing role of digital technologies in health care delivery.

The rapid advancement of digital health technologies offers significant potential for addressing these gaps. During the COVID-19 pandemic, digital health interventions (DHIs) were widely adopted as a supplement to conventional health services [16,17]. Although the definitions of digital health vary, there is a consensus that DHIs, including computer-based therapies, mobile apps, and wearable devices, can enhance the accessibility, efficiency, and personalization of mental health care [18]. Evidence suggests that digital technologies can empower individuals and families affected by mental health issues, offering convenience, privacy, and opportunities for independent learning [19,20]. These features make DHIs particularly attractive for supporting parents of children with ASD [21,22].

To develop effective DHIs for parents of children with ASD, it is essential to understand which interventions have been developed, tested, and implemented. Several studies have examined the potential benefits of DHIs in reducing parenting stress and enhancing self-efficacy [23,24]. However, most studies have primarily focused on interventions targeting children with ASD, with relatively little attention given to the health of parents [25,26]. A recent review of interventions for parents of older children and adults with ASD highlighted the potential benefits of parent-focused interventions in improving psychological health [27], but it did not address the role of DHI.

This scoping review aims to fill this gap by examining the availability of DHIs designed to support the psychological health of parents and evaluating their effectiveness. It is part of a broader study focused on DHIs aimed at enhancing psychological health among parents of children with ASD. By identifying gaps in the current literature, this review will provide a foundation for the future development of DHIs specifically tailored to the needs of parents. No prior scoping or systematic reviews on this specific topic were identified, making this review an important contribution to the field.

Review Questions

This review will focus on answering 4 key research questions. First, which DHIs have been developed and implemented to support parents of children with ASD? Second, how are these interventions specifically designed to improve the psychological health of these parents? Third, what are the primary psychological health outcomes associated with these interventions? Fourth, what gaps, limitations, and opportunities exist for the future development of DHIs aimed at supporting the psychological health of parents of children with ASD?

Methods

Overview

The scoping review will be conducted in accordance with the methodology established by the Joanna Briggs Institute (JBI). Articles will be screened and selected using the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols), and the results of the review will be presented according to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) [28] (Multimedia Appendix 1). To report the functional classification of the final DHIs selected for review, we will use the Evidence Standards Framework for Digital Health Technologies developed by the UK National Institute for Health and Care Excellence (NICE) [29]. The format of this protocol adheres to the author guidelines of the target publication and is informed by recommendations regarding items to be reported in the scoping review [30,31].

Eligibility Criteria

Researchers use the Population, Intervention, Comparator, and Outcomes (PICO) framework to identify the key concepts of a scoping review, develop appropriate search terms to describe the problem, and determine inclusion and exclusion criteria.

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Population

In our review, we define parents as biological parents, birth parents, or foster parents of children with ASD younger than 18 years. The World Health Organization (WHO) defines children as people younger than 18 years [32]. This age range has been restricted because we are focused on reviewing DHIs that support parents during the early years of their children's development. Studies reporting on DHIs for parents of children older than 18 years will be excluded.

Intervention

This review will include interventions that use communication media for DHI. DHIs, including computer-based therapies, mobile apps, and wearable devices, can enhance the accessibility, efficiency, and personalization of mental health care [18]. This review will include computer-assisted therapy, smartphone apps, and wearable technologies that support parents' psychological health. Studies that do not focus on digital technologies will be excluded.

Comparator

Comparators or comparisons refer to groups that were compared to the intervention group [33]. The comparison can be to another treatment or intervention or no treatment at all. In this scoping review, all articles will be considered for inclusion, regardless of whether they have a control group or the type of control used.

Outcomes

Outcome refers to the measure of interest or the study's target endpoints that are objectively defined, essentially representing the variable being assessed to determine the effect of an intervention or exposure on a population [34]. In this scoping review, the articles must include the outcomes on parental psychological health (stress, anxiety, depression, distress, fatigue, quality of life, positive thinking, happiness, family empowerment, hope, resilience, etc), which will be assessed using validated psychological scales and measures of subjective well-being.

Types of Studies

This scoping review will consider qualitative, randomized controlled trials, cohort studies, case-control studies, cross-sectional surveys, pre- and postintervention studies, mixed methods studies, and observational studies. Studies that are not peer-reviewed, gray literature, nonempirical studies, review articles, conference papers, preprints, or limited to abstracts will be excluded. This review will consider studies conducted or implemented to support parents' psychological health in community settings, school settings, special schools, clinics, hospitals, at home, and child development centers. There will be no exclusion based on region, gender, and sociocultural factors.

Search Strategy

The search strategy was developed in collaboration with an expert medical librarian (JB) and 2 researchers (BJ and ZN). We will conduct our search across 6 bibliographic databases: (1) CINAHL, (2) Ovid EMBASE, (3) Ovid Global Health, (4) Ovid MEDLINE, (5) Ovid PsycINFO, and (6) Web of Science. These databases were selected based on their relevance to the research topic and their comprehensive coverage of the literature in this field. Each database will be searched using both controlled vocabulary and synonymous free-text terms to encompass the concepts of autism and digital health. The search strategy will be tailored to accommodate the syntax specific to each database. Inclusion will be limited to English-language studies, with no restrictions on publication date, from inception to June 25, 2024. Search results will be imported into EndNote (version 20, Clarivate), and duplicate entries will be removed. The final set of included articles will then be uploaded into Covidence systematic review software (Veritas Health Innovation) for screening. Detailed search histories can be found in Multimedia Appendix 2.

Study Selection

Following the search, all identified records will be uploaded into a data screening sheet created in Covidence (Veritas Health Information), where duplicates will be removed. Subsequently, 3 researchers (BJ, IMSB, and XP) will screen the titles and abstracts of all retrieved articles using Covidence, assessing the full texts for eligibility based on predefined inclusion and exclusion criteria. Discrepancies will be resolved through discussion with the senior author (ZN). The reasons for exclusion will be documented for articles eliminated following full-text screening. See Multimedia Appendix 3 for the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of the literature search and selection process.

Data Extraction

A summary of the findings from the included studies will be presented in a table using a data extraction form (Multimedia Appendix 4). This form will capture essential information from the eligible studies, including the authors, publication year, study locations (country), study design, participants, interventions (including name, digital technologies, duration, etc), comparisons, psychological outcomes for parents, and key findings.

Data Analysis and Presentation

We will perform a descriptive analysis to aggregate and synthesize data segments that demonstrate similarities. Deductive coding will be used to categorize and analyze data in line with the identified outcomes from the included studies. Interrater reliability will be assessed to ensure the consistency and accuracy of the coding process. The data extracted from the included studies will be systematically tabulated and summarized narratively. Through narrative synthesis, the analysis organizes findings around recurring themes or clusters, such as types of digital interventions (eg, apps vs wearable devices) and common psychological outcomes (eg, stress reduction and resilience building). The descriptive synthesis also highlights areas with limited research or emerging needs, revealing gaps in interventions targeting specific psychological outcomes or identifying underrepresented study populations and settings.

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Ethical Considerations

There will be no involvement of humans, animals, patients, or the public in this review. This review will synthesize data from peer-reviewed studies that have been published. Thus, ethical approval is not required for this scoping review.

Results

The electronic database search was completed in June 2024, marking the beginning of the research team's familiarization with DHI and the psychological health of parents of children with ASD. During this stage, the team consulted with a medical librarian (JB) at Yale University regarding search strategies and preliminary results. A total of 5825 records were retrieved, and 2296 were identified as duplicates. Full-text screening was conducted in September and October 2024. Data extraction and thematic synthesis were carried out in winter 2024. At the time of submission, the study was in the data analysis phase. The scoping review summarizes findings including population characteristics, study design, participant demographics (number and age), DHI details (name, type, platform/tool, duration), comparisons, psychological outcomes (variables and measurement tools), and key findings (significant changes, group differences, and follow-up effects). The review was submitted for publication in December 2024.

Discussion

This scoping review will explore the existing evidence on the use of DHIs to support the psychological health of parents of children with ASD. Through this review, we aim to identify gaps, limitations, and opportunities in existing knowledge to inform the development of future DHIs. The scoping review protocol presented in this paper is novel. To the best of our knowledge, no previous reviews have specifically focused on DHIs for the psychological health of parents of children with ASD [19,35]. Reviews that examine DHIs in the context of the ASD population have generally concentrated on children with ASD rather than their parents [36,37]. This scoping review will not only identify gaps in the literature but also provide valuable insights to guide future research and the development of practice guidelines aimed at supporting the psychological health of parents of children with ASD.

Psychological health is a complex interplay of mental, emotional, social, and spiritual dimensions of well-being [38]. Like physical health, it is a crucial component of overall wellness. Parenting a child with ASD presents unique challenges that can adversely affect the psychological health of parent carers. Parents of children with ASD are at an elevated risk for negative psychological outcomes, including depression, anxiety, stress, and emotional distress [8,10,39,40]. When a parent's psychological health is compromised, it can hinder their ability to make decisions, regulate emotions, manage behaviors, engage in social interactions, and cope with stress [41]. Moreover, children of parents who experience heightened psychological challenges often experience various negative psychological and developmental outcomes [42,43]. Therefore, supporting parental psychological health is not only crucial for their well-being but also for fostering healthier developmental outcomes in their children.

Parent training and support have long been regarded as important components of early intervention programs for children with ASD. Empirical evidence indicates that parent-focused training and support programs can positively impact children's behavior and functional communication skills, leading to improved parent-child interactions and enhanced psychological health for parents [44,45]. However, traditional in-person interventions for parents of children with ASD face significant limitations due to constraints such as time, location, cost, and accessibility. With the rapid advancements in digital health technologies and the onset of the COVID-19 pandemic, DHIs have become increasingly used in this domain. Nevertheless, most applications of DHIs have occurred in developed countries, and findings regarding their impact on the psychological health of parents of children with ASD have been mixed [19,46-48].

The results of this study will provide a complete picture of the types of DHIs used to improve parental psychological health and their effectiveness. DHIs have been shown to positively influence psychological health [49,50]. Therefore, the integration of digital technologies into interventions may help reduce psychological health problems among parents. The findings of this scoping review will serve as a basis for further research or intervention development.

This scoping review will provide an overview of the existing literature on the use of DHIs to improve the psychological health of parents of children with ASD. One limitation of this review is the exclusion of non-English studies, which may limit the generalizability of findings. In addition, unpublished studies, such as conference abstracts, dissertations, and gray literature, were not included, potentially omitting relevant insights. As a scoping review, this study aims at mapping the available literature rather than assessing the effectiveness of interventions. Future research will build on this work with a quantitative meta-analysis to assess the impact of DHIs on the psychological health of parents of children with ASD. Our dissemination plan includes presentations at conferences and for relevant stakeholders, and publication in a peer-reviewed journal.

Acknowledgments

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Authors' Contributions

BJ wrote the original draft. ZN and JB contributed to the conception of the study and substantively revised the protocol. BJ and JB planned the initial search strategy and conducted a pilot study to test the protocol. BJ and JB developed the data extraction form.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRSIMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist.
[PDF File (Adobe PDF File), 502 KB - resprot_v14i1e68677_app1.pdf]

Multimedia Appendix 2
Search strategy.
[DOCX File , 25 KB - resprot_v14i1e68677_app2.docx]

Multimedia Appendix 3
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.
[DOCX File , 54 KB - resprot_v14i1e68677_app3.docx]

Multimedia Appendix 4
Data extraction instrument.
[DOCX File , 18 KB - resprot_v14i1e68677_app4.docx]

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Abbreviations

ADDM: Autism and Developmental Disabilities Monitoring Network
ASD: autism spectrum disorder
DHI: digital health interventions
JBI: Joanna Briggs Institute
NICE: UK National Institute for Health and Care Excellence
PICO: Population, Intervention, Comparator, Outcomes
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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WHO: World Health Organization

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Protocol

Mapping the Level of Evidence of Prenatal, Childhood, and Adolescent Exposure to Volatile Organic Compounds and Health Outcomes: Protocol for a Scoping Review

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Abstract

Background: Volatile organic compounds (VOCs) are a diverse group of organic chemicals with widespread presence in daily life. VOCs may have detrimental health effects on humans, particularly during critical periods such as pregnancy, childhood, and adolescence. Although the body of evidence is growing, significant gaps remain in the current understanding of the associations of VOCs on health across these developmental stages. Moreover, existing reviews focused on specific VOCs or individual health conditions, highlighting the need for a comprehensive summary of the current literature to stimulate further research.

Objective: This ongoing scoping review aims to map the current evidence concerning exposure to VOCs and their associations with pregnancy outcomes and health during pregnancy, childhood, and adolescence.

Methods: This review will consider studies investigating potential health effects related to exposures to either total VOCs or any of the following 6 specific VOCs: benzene, toluene, ethylbenzene, xylene, trichloroethylene, and tetrachloroethylene or perchloroethylene during critical windows from pregnancy through adolescence. Original articles published in English from January 1, 2000, through the end of the scoping review period, will be included. We will follow the Joanna Briggs Institute methodology for scoping reviews and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines. The literature search will use the Ovid MEDLINE, Embase, and Web of Science databases to identify relevant citations. The following steps of the review will be managed through the Covidence platform. A total of 2 reviewers will independently conduct a rapid screening of paper titles, before evaluating the abstracts and full texts to determine which articles will proceed to the data extraction stage. In case of discrepancies during these steps, the reviewers will discuss to reach a consensus, and a third reviewer may intervene if needed. Reviewers will provide commentaries on their findings from the included studies and suggest areas of interest for future studies.

Results: The literature search yielded a total of 7332 citations published during the period January 1, 2000, to July 25, 2024. After the title screening and reading the abstract and full text, 274 papers were selected for the data extraction phase, which is currently underway. Upon completion of the library's updated literature search, covering July 26, 2024, to the present, we will proceed with data analysis and manuscript writing for submission to a peer-reviewed journal.

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Conclusions: The results are expected to summarize the current state of knowledge on the association of VOCs with health at critical life stages (pregnancy, childhood, and adolescence). We anticipate identifying gaps in the literature as well that could guide future research priorities.

Trial Registration: OSF Registries 10.17605/OSF.IO/EP73G; https://osf.io/ep73g

International Registered Report Identifier (IRRID): DERR1-10.2196/71587

(JMIR Res Protoc 2025;14:e71587) doi:10.2196/71587

KEYWORDS

benzene; BTEX; child health; environmental health; ethylbenzene; human (0 to 18 years); PCE; pregnancy outcomes; toluene; trichloroethylene; tetrachloroethylene; perchloroethylene; VOCs; TVOCs; xylene

Introduction

Volatile organic compounds (VOCs) represent a broad, diverse group of organic chemicals characterized by their ability to vaporize at room temperature [1,2]. While some VOCs occur naturally, most human exposure is through anthropogenic activities and their presence in personal care products. VOCs arise from culinary activities, construction materials, furniture, cleaning products, cosmetics, fuels, and treated wood [3-5]. Humans are exposed through respiratory, dermal, and oral routes [3]. VOCs such as benzene, trichloroethylene, ethylbenzene, toluene, and xylene have been classified as carcinogens or mutagens [1] and are associated with a wide range of health effects, including damage to the neurological, respiratory, and immunological systems [1,4]. Most of the knowledge on the effects of VOCs on human health is from studies focused on occupationally exposed individuals [1,6,7]. The widespread presence of VOCs in daily life has raised concerns about the potential health effects on the general population, particularly during pregnancy and in critical developmental periods [8-10], when rapid growth and development coupled with immature physiological systems may render individuals more susceptible to adverse exposures. This may lead to deleterious consequences even later in adulthood, such as cardiovascular and other chronic diseases (eg, obesity and diabetes) [11].

A rapid preview search of the literature for articles published between 1990 and 2024 (June 5) (via PubMed) on the health effects of VOC exposure on pregnant females and children showed that most research was conducted during the last 3 decades, with only 1 study published in 1995 [12]. There is a need to monitor the current level of evidence on the impact of VOCs on human health during critical life stages to provide accurate information and guide future research. Most available literature reviews on VOCs focused on a few specific VOCs, diseases, or demographic groups [13-18]. We suggest here a scoping review with no restriction on prespecified health effects associated with the following 6 VOCs prioritized by the Center for Leadership in Environmental Awareness and Research (CLEAR) [3] funded by the Superfund Research Program of the National Institute of Environmental Health Sciences (NIEHS): benzene, toluene, ethylbenzene, xylene, trichloroethylene, and tetrachloroethylene/perchloroethylene [19]. Studies with total VOC measurements will be also included. This review will include exposures and health effects that occur to pregnant females or children from conception through adolescence. Searches of the PROSPERO and Cochrane databases showed no ongoing systematic or scoping review registered with similar topics or goals. We aim to (1) describe the current level of evidence regarding the health effects of exposure to benzene, toluene, ethylbenzene, xylene, trichloroethylene, tetrachloroethylene or total VOCs in humans during pregnancy and from conception to adolescence; and (2) identify key knowledge gaps to propose priorities for future research studies on the health effects of VOC exposure during critical developmental periods.

Methods

Overview

This review will follow the Joanna Briggs Institute methodology for scoping reviews and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) guidelines [20,21].

Participants

We will consider studies conducted on associations between exposure to the 6 VOCs of interest (benzene, toluene, ethylbenzene, xylene, trichloroethylene, and tetrachloroethylene) and/or total VOCs and health effects in pregnant females and on the child from conception through 18 years. Table 1 presents the Population, Exposure, and Outcomes (PEO) framework for this review.

Table 1. Population, Exposure, and Outcomes (PEO) framework.

Elements	Definition
Population	Pregnant females, fetuses, and individuals ages 0 to 18 years (ie, infant, child, and adolescent)
Exposures	Benzene, toluene, ethylbenzene, xylene, trichloroethylene, and tetrachloroethylene and derived products and total VOCs
Outcomes	Any health outcome, including birth outcomes

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Concept

Regardless of the assessment method—whether derived from questionnaires, screenings, biomarkers (including epigenetic markers such as DNA methylation changes), laboratory tests, or clinical diagnoses—any health outcome will be considered for this review. Only the relationship of the VOCs with any health effect will be reported. Studies with total VOC measurement will be included, as this method of exposure assessment represents a proxy for the pollutants considered in this review. These will be reported as their own exposure category. Studies using assessment of exposure to VOCs through biological, environmental matrices, or mathematical or geospatial modeling (eg, exposure estimation based on residential address) will be considered. Exposure and health effects occurring during and throughout adulthood (in the nongravid state) will not be considered.

Context

Studies done in any part of the world and published in English will be included. Both occupational and nonoccupational exposures will be examined.

Types of Sources

This scoping review will consider studies that include primary and secondary data, with only peer-reviewed original articles included. All epidemiological research designs such as cross-sectional, retrospective, prospective, bidirectional cohort studies, and case-control studies, and their variations will be explored. Systematic reviews, meta-analyses, and gray literature will not be included in this review (Textbox 1).

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Peer-reviewed original articles.
- Studies conducted in humans at specific life stages described by the Population, Exposure, and Outcomes (PEO) framework (Table 1).
- Studies assessing exposure to volatile organic compounds (VOCs) through biological, environmental matrices or mathematical or geospatial modeling will be considered.
- Papers published from 2000 to the date of the end of the extraction process (likely first quarter of 2025).

Exclusion criteria

- Articles not published in English.
- Papers that are not empirical studies (eg, review articles, conference abstracts, editorials, and commentaries).
- Studies conducted in animals or adult (nonpregnant) humans (>18 years).
- Studies assessing or estimating exposure to VOCs solely through questionnaires; occupation history (ie, no direct estimate of the 6 specific or total VOCs).
- Studies that use risk assessments (for cancer or noncancer outcomes) based on indices such as the target margin of exposure or hazard quotient as their primary measure of health outcomes.

Search Strategy

The literature search will be conducted to find original research articles with primary or secondary data. A previous rapid literature search with the support of the Sladen Library has been conducted through PubMed MEDLINE to identify reviews (systematic, scoping, and meta-analysis) and original papers to define adequate strategies for the scoping review process. The keywords used are presented in Multimedia Appendix 1. The presearch yielded 265 papers from 1990 to 2024 (June 5), from which 103 papers were eligible for full-text reading and data extraction. As only 1 manuscript (published in 1995) was eligible for the period from 1990 to 2000, we will focus on the period from 2000 to the present for this proposed review.

Literature for the proposed review will be identified by searching Ovid MEDLINE, Embase, and Web of Science. Our literature search will follow the strategy described by Liu et al [22] in their systematic review of indoor VOC exposures and health impacts. The Covidence platform (Covidence systematic review software, Veritas Health Innovation, Melbourne, Victoria, Australia) [23] will be used to screen references, extract data, and track the progress of the work.

Study Selection

After the initial search conducted by the Sladen Library, the citations will be uploaded on the Covidence platform. A total of 2 reviewers will independently conduct a rapid screening based first on the paper's titles, removing those that are not relevant or do not meet inclusion criteria. Discrepancies will be determined by a third reviewer. Next, 2 reviewers will evaluate the articles' abstracts and full text for relevance. Each article will be reviewed by 2 reviewers during the full-text review stage. The reviewers will document reasons for the exclusion of any full-text article. Any discrepancies in exclusion or inclusion decisions will be discussed by 2 reviewers and, if necessary, adjudicated by a third reviewer. At the end of this process, the reviewers will examine the bibliographies of the relevant papers (selected for the extraction process) to identify additional articles pertinent to the study objectives. Citations will be managed using EndNote 21 (Clarivate).

Full-text articles must be available to be included in the final analysis of this review. If any publication is unavailable through the Sladen Library resources, we will contact the publication's corresponding author to request the paper's full text. For

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transparency, all details on the results of contacting authors of the unavailable papers will be provided in the methodology section of the final version of the publication resulting from this research. After the data extraction and synthesis, the Sladen Library will conduct a supplementary search to consider any possible new evidence.

Data Extraction

The remaining articles will undergo full-text review for further data extraction and synthesis. To define the level of evidence in this scoping review, the following information will be collected as shown in Textbox 2: metadata (authors, country, and year of publication), aims of the study, list of VOCs investigated, methodology (research design, sample size, measures of association, methods to assess VOC exposure and health outcomes, potential confounders), and main conclusion.

A total of 2 reviewers will extract the information separately. In case of discrepancy, both will discuss to reach a consensus. If needed, a third reviewer may intervene. This data extraction instrument may be modified if required according to its efficiency.

Textbox 2. Draft data extraction instrument.

Information to be extracted

- Authors, country, and year of publication
- Setting (Occupational vs nonoccupational)
- Aims or purpose
- Volatile organic compounds (VOCs) investigated (and VOC mixtures, if applicable)
- Health outcomes investigated
- Participants (age) and sample size
- Study design
- Method of assessment: exposure and outcome
- Covariables or confounders considered
- Main conclusion or findings

Data Analysis and Presentation

This section will address the 2 main review questions. Considering the level of evidence, results will be shown as descriptive data (absolute and relative frequency) of the characteristics of the articles extracted, such as the following:

1. Study design: cohort, case-control, cross-sectional, and others.
2. Techniques used to assess:
3. Exposure: biomarkers (eg, VOC metabolites in blood, urine) or environmental matrices (eg, VOC levels in air, water); ie, direct or estimated exposure.
4. Health outcome: disease presence or absence, severity, overall health or specific function, biomarkers of disease or health.
5. Measures and strength of association: such as relative risk, odds ratios, attributable risk, CIs, and *P* values.

The goal is to describe the current rigor and depth of previous investigations. We will use a table, chart, or figure to highlight our main findings.

To highlight the current gaps and perspectives for future studies, our results will be presented as a conceptual and thematic map considering the 3 components of our PEO framework (Table 1). The overall goal of the map is to highlight aspects of the associations between VOCs and health in critical windows that have been studied in detail as well as those lacking attention.

We will present a narrative review of the literature describing the similarities and differences in studies conducted on the same topic to highlight possible reasons for contradictory or inconsistent findings. Considering the growing interest in studying exposure to pollutant mixtures, we will present data on the number of studies that evaluated exposure mixtures and those that report mixtures that include at least one of the 6 VOCs of interest, and we will summarize both the associations with health outcomes and the methods used to evaluate mixture effects. Finally, we will comment on and suggest possible implications of this scoping review for future research.

Results

To date, a comprehensive literature search, a title screening and a full-text review have been conducted, yielding respectively 7332 citations, 538 full texts, and 274 papers to be extracted. This protocol has been registered on the Open Science Framework [24]. Data extraction is expected to be completed by July 2025. A complementary literature search will be conducted by the library, covering July 26, 2024, to the present, followed by data analysis and preparation of the final report. We anticipate submitting the results for peer review by September 2025 and plan to disseminate the findings through conference presentations and other scholarly platforms.

Discussion

Anticipated Findings

We present the protocol for an ongoing scoping review aimed at evaluating health outcomes associated with 6 VOCs (benzene, toluene, ethylbenzene, xylene, trichloroethylene, and

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tetrachloroethylene) and total VOCs, which are priorities of an NIEHS-funded Superfund Research Center, CLEAR [19]. This review specifically focuses on pregnant females, fetuses, and individuals ages 0 to 18 years and seeks to address key gaps in knowledge.

To our knowledge, no prior review has provided a comprehensive summary focusing on these VOCs during specific critical life stages. While Liu et al (2022) conducted an extensive systematic review of 8 VOCs, their focus was restricted to indoor exposures and health outcomes at all life stages [22]. Other reviews (systematic, meta-analyses, or narrative) have considered VOCs as part of broader air pollution studies [25-28] or focused narrowly on specific aspects such as (1) individual VOC exposures [6,29-31], (2) specific organ systems [18,31], (3) specific health outcomes such as cancer, respiratory diseases, or allergies [13,26,28,32], or (4) specific populations or geographic regions [16]. In contrast, our review will provide a broader and more inclusive analysis of VOC-related health outcomes in critical stages of human development. Emerging paradigms, such as the life-course perspective [33] and the Developmental Origins of Health and Disease (DOHaD) framework [34], underscore the importance of early prevention. These approaches aim to minimize environmental exposures during key developmental periods, reducing the risk of chronic diseases later in life. Focusing this scoping review on exposures and health outcomes from pregnancy through adolescence will guide future research in this area that could lead to primary prevention efforts.

This review will identify gaps in the current literature and facilitate the development of new research questions. For instance, it may reveal a lack of studies addressing the combined effects of VOCs and other environmental stressors, including chemical and nonchemical factors such as social determinants of health. By highlighting the current evidence and knowledge gaps, we aim to contribute to the dissemination of accurate information, address the limitations of current research, and support efforts to reduce health disparities.

This work has several limitations. First, there is a potential risk of bias, as no formal quality assessment will be conducted, given the nature of scoping reviews. In addition, restricting the language criteria to English limits the inclusion of literature predominantly to Western or English-speaking regions. This approach may exclude valuable evidence from non–English-speaking regions, such as countries in West and Central Africa, Southeast and Central Asia, and Latin America.

Conclusion

This scoping review aims to synthesize evidence from studies conducted since the beginning of the 21st century examining associations of VOC exposures with health outcomes in pregnancy through adolescence. This review is expected to inspire additional research, particularly in these population groups, potentially accelerating the development of policies that promote health equity and protect vulnerable populations.

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Authors' Contributions

HAFB, AECB, and JKS conceived the idea. HAFB drafted the manuscript. All authors critically reviewed and edited the manuscript. AECB and JKS acquired funding. All authors approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy for the pre-review process.
[DOCX File , 16 KB - resprot_v14i1e71587_app1.docx]

Multimedia Appendix 2
ChatGPT prompt samples for editing/revising manuscript language.
[DOCX File , 21 KB - resprot_v14i1e71587_app2.docx]

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Abbreviations

CLEAR: Center for Leadership in Environmental Awareness and Research
DOHaD: Developmental Origins of Health and Disease
NIEHS: National Institute of Environmental Health Sciences
PEO: Population, Exposure, and Outcomes
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
VOC: volatile organic compound

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Protocol

Barriers and Facilitators in Diagnostic Pathways That Align Universal Tumor Screening and Mainstream Genetic Testing for Lynch Syndrome in Colorectal Cancer: Protocol for a Scoping Review With a Narrative Synthesis

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Abstract

Background: Approximately 3% of colorectal cancers (CRCs) are due to Lynch syndrome (LS), a hereditary cancer syndrome caused by pathogenic variants (PVs) in the mismatch repair (MMR) genes. Patients with CRC and LS have elevated lifetime risks for a range of cancers and require personalized treatment and targeted surveillance. Relatives of people affected by LS who share the same PV also have elevated cancer risks and can benefit from preventive measures and/or risk-reducing surgeries. Despite this, LS remains vastly underdiagnosed. Universal tumor screening (UTS) for deficient MMR is recommended in diagnosing LS in patients with CRC. This process, when combined with genetic testing (GT) offered within routine cancer care (termed “mainstream GT”), aims to identify individuals at risk efficiently, but integrating UTS and mainstream GT for LS in CRC is a complex endeavor.

Objective: The aim of the proposed scoping review will be to comprehensively explore the literature on diagnostic pathways comprising UTS and mainstream GT for LS among patients with CRC and barriers and facilitators in their implementation.

Methods: The scoping review will follow Arksey and O’Malley’s expanded framework. Results will be reported following the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines and summarized quantitatively. A narrative synthesis will also be performed using the Theoretical Domains Framework.

Results: The results will be presented in a forthcoming scoping review, which we expect to publish in a peer-reviewed journal by early 2026.

Conclusions: Aligning UTS with mainstream GT for LS in CRC may boost early diagnosis and prevention while reducing waiting times and other patient burdens. By addressing barriers to and facilitators in diagnostic pathways, health care systems can improve the identification and management of LS, ultimately leading to better outcomes for patients and their families. The insights gained from this scoping review will inform the development of a mixed methods study about implementing diagnostic pathways for LS in CRC that integrate UTS and mainstream GT in Italy.

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(JMIR Res Protoc 2025;14:e70831) doi:10.2196/70831

KEYWORDS

Scoping review; protocol; colorectal cancer; Lynch syndrome; diagnostic pathway; genetic testing; mainstreaming; barriers; facilitators; implementation; theoretical domains framework

Introduction

Background

Colorectal cancer (CRC) is the third-most prevalent cancer among men and the second-most prevalent cancer among women globally [1]. Approximately 3% of CRCs are due to Lynch syndrome (LS), an autosomal dominant hereditary cancer syndrome caused by pathogenic variants (PVs) in the mismatch repair (MMR) genes *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM*, which are related to the microsatellite instability (MSI) system [2].

Individuals with LS have elevated lifetime risks for CRC and endometrial carcinoma [3]. Risks for other cancers, such as ovarian, stomach, small bowel, urothelial, pancreaticobiliary, and brain cancers, are also greater than for the general population [4,5]. Patients with CRC with LS require personalized treatment and targeted surveillance for metachronous primary CRCs and other LS-associated cancers [6]. Furthermore, as each child of a PV carrier has a 50% chance of inheriting the PV, many of the bloodline relatives of patients with CRC with LS will also have inherited the LS-associated PV and, therefore, the associated cancer risks. Identifying these at-risk relatives can translate into opportunities to prevent CRC, endometrial, and other LS-associated cancers through intensive surveillance and/or risk-reducing surgeries [7].

Challenges in the Diagnosis of LS

Despite these widely demonstrated clinical benefits, most patients with CRC who are affected by LS are never diagnosed with the syndrome, a failure that has long been acknowledged [8].

Previously, access to genetic testing (GT) for LS was granted only through familial and clinical criteria [9]. These criteria have been shown to miss as many as 25% of patients with LS [10], likely because of the complexity of the criteria and the fact that family histories are often unavailable or inaccurate.

To circumvent such limitations, universal screening of all CRC tumors for deficient MMR at the point of diagnosis (universal tumor screening [UTS]) has been endorsed as the standard of care by multiple societies [11-13]. The diagnostic process includes tumor analysis for the loss of MSH2, MSH6, or PMS2 expression, which, if identified, is an indication for genetic counseling and germline GT. Loss of MLH1 expression during immunohistochemistry may be due to promotor methylation with somatic loss (about 80% of cases with loss of MLH14 expression) or less frequently following germline mutation. CRCs with somatic loss of MLH1 (approximately 10%-15%) [14] are excluded by reflex testing for the *BRAF* mutation or *MLH1* promoter methylation prior to patient referral for genetic counseling and testing [13,15].

This screening process involves multiple steps with coordination across multiple departments, which may be logistically complex and costly, and compete with other priorities [10,16,17]. Thus, it is perhaps not surprising that the uptake of UTS-based testing guidelines for LS has been low [18-20].

New Opportunities to Diagnose LS in Patients With CRC

A new impetus for the identification of LS in patients with CRC has arisen from the emergence of immunotherapy based on PD-L1 (programmed cell death ligand 1) blockade, with pembrolizumab being the first site-agnostic agent to be licensed for cancer treatment. This has made the identification of MMR-deficient tumors, whether sporadic or hereditary [21], a growing need in patient care and is generating new opportunities to improve the identification of patients with CRC with LS and their at-risk relatives [22]. More generally, it has promoted the integration of GT for LS into the routine care of patients with CRC [19], an approach termed the mainstreaming of GT [23]. The new algorithm involves performing UTS for deficient MMR protein function analysis alongside reflex testing for *BRAF* and/or *MLH1* promoter methylation to exclude sporadic cases and then directing selected patients to GT through the oncologist (or another specialist health care professional) instead of via referral to genetic services.

The Need to Better Understand Barriers and Facilitators in New Diagnostic Pathways for LS

International studies that reported challenges in implementing UTS [24,25] and mainstream GT in hereditary cancer [26-28] can provide valuable lessons on how to align UTS with mainstream GT. However, diagnostic pathways that integrate UTS and mainstream GT for LS in CRC may vary, as they can, for instance, involve different approaches to pretest counseling and informed consent, with GT being offered by a range of nongenetic health care professionals with different levels of familiarity with genetics and different training needs [27,29]. Variability can also occur in terms of how testing is promoted, staff is educated and trained, appointments are streamlined, and workflows are organized [30] and therefore requires specific attention, with a view to understanding what specific barriers and facilitators can exist in the context of multistakeholder implementation of these novel diagnostic pathways [23,31]. Therefore, we intend to conduct a scoping review that will identify, summarize, and synthesize knowledge about diagnostic pathways that integrate UTS and mainstream GT for LS among patients with CRC and the barriers and facilitators in their implementation.

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Methods

Overview

The proposed scoping review will be based on the well-established framework developed by Arksey and O'Malley [32] and on the recommendations later proposed by Colquhoun et al [33] and Levac et al [34]. The findings will be reported as recommended by the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analysis extension for Scoping Reviews) guidelines.

A scoping review is a thorough, rigorous, transparent tool for knowledge synthesis that maps an existing or emerging body of literature to provide an overview of the size and scope of a research field [34].

Scoping reviews are especially appropriate when evidence on a topic is emerging or when the relevant literature is complex or heterogeneous. Furthermore, they can examine findings from different study designs and methods [34]. Therefore, scoping reviews are ideal for synthesizing literature on topics that still need to be comprehensively explored, such as the one we will endeavor to cover.

Stage 1: Identifying the Research Questions

The research questions of the proposed scoping review are as follows:

1. Which are the diagnostic pathways for LS that align UTS with mainstream GT for LS in CRC described in the literature?
2. What has been reported about the barriers and facilitators in the implementation of these diagnostic pathways?
3. What are the knowledge gaps regarding the barriers and facilitators in the implementation of these diagnostic pathways?

An exploratory search in PROSPERO, the International Prospective Register of Systematic Reviews of the National Institute for Health Research, and the Cochrane Library revealed no comprehensive systematic reviews addressing similar questions. In addition, no previous scoping reviews of the literature on this topic were found.

The research team will revise the protocol as appropriate during the review process. Any changes to the protocol will be detailed and justified in the final report.

Stage 2: Identifying Relevant Studies

Eligibility Criteria

To determine the eligibility criteria of the articles to be included in the review, the research team will follow the PCC (Population, Concept, Context) framework for scoping reviews by the Joanna Briggs Institute [35]. The inclusion criteria will be as follows.

Population

We will include patients with CRC who are older than 18 years and health professionals including pathologists, molecular biologists, gastroenterologists, oncologists, oncology nurses, geneticists, genetic counselors, and surgeons.

Concept

We will examine diagnostic pathways that align UTS with mainstream GT for LS in patients with CRC and barriers and facilitators in the implementation of those diagnostic pathways.

Context

The study will focus on health care settings. There will be no geographic criteria as we aim to provide a comprehensive examination of the literature on this topic.

Other Inclusion Criteria

The following additional inclusion criteria will be considered: articles published in a peer-reviewed outlet, those published in English, those that include the relevant search terms, those in which barriers and facilitators in diagnostic pathways that integrate UTS and mainstream GT for LS in CRC are the main focus or are at least addressed in their own part or section, and those that were published in 2017 or later, after the publication of the relevant NICE (National Institute for Health and Care Excellence) guidelines on molecular testing for LS in people with CRC [13].

Exclusion Criteria

We will exclude articles that do not address the integration of UTS and mainstream GT, those that do not focus on patients with CRC, and those that do not describe barriers and facilitators.

Search Strategy and Information Sources

The literature search strategy will be developed using MeSH (Medical Subject Headings) terms and keywords related to the research questions. Studies will be identified through searches in MEDLINE, Scopus, CINAHL, and PsycINFO. A specialist librarian will review the search strategy using the Peer Review of Electronic Search Strategies (PRESS) guidelines [36].

Backward and forward reference searches for all eligible articles will then be performed to ensure comprehensive literature coverage. Input from expert collaborators will also be sought to supplement the database searches.

Stage 3: Selecting the Studies

All results retrieved from the databases will be imported into the reference management software Rayyan [37], and duplicate entries will be removed. In the first screening stage, 2 researchers will independently review the titles and abstracts to assess eligibility. Any disagreements will be discussed until a consensus is reached, involving other coauthors if necessary. Irrelevant articles, theses, articles from the popular press, reports, nonreviewed books and book chapters, presentations, and opinion pieces will be excluded. The second eligibility screening will be conducted independently by the 2 researchers, who will evaluate the full-text articles against the inclusion and exclusion criteria. Any discordances will be discussed, and a consensus will be reached by consulting other coauthors, as appropriate. A PRISMA-ScR flowchart will be developed to document the process.

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Stage 4: Charting the Data

A descriptive quantitative synthesis and a narrative synthesis will be conducted to chart the data. In accordance with Arksey and O'Malley [32], the descriptive quantitative summary will include the final number of articles and key characteristics such as the first author, publication year, country, discipline, and study design (eg, qualitative, quantitative, and mixed methods). This information will be presented in the scoping review report to provide an overview of the included literature.

In the narrative synthesis, the Theoretical Domains Framework (TDF) will be used to guide the analysis of barriers and facilitators and map them to higher-level behavioral domains and components [38]. The TDF is a validated, comprehensive framework consisting of 14 domains that can influence the behavior of health care professionals (knowledge; skills; social/professional role and identity; beliefs about capabilities; optimism; beliefs about consequences; reinforcement; intentions; goals; memory, attention, and decision processes; environmental context and resources; social influences; emotion; and behavioral regulation) and can be adapted to specific clinical contexts [39].

A data extraction tool will be created, incorporating the specific methodological and design aspects of each publication, the study setting, and factors affecting the implementation of new diagnostic pathways for LS. The tool will first be tested on 2 randomly chosen publications, refined as needed, and finalized for use with the remaining studies. Two researchers will independently conduct data extraction, following a predefined codebook that will be continuously updated throughout the extraction and analysis process. The extracted data items will then be grouped into themes. If the data item cannot be matched to an existing theme, a new theme will be created. Each theme will be mapped to a TDF domain, and the frequency of each domain will be calculated as a percentage of the total number of articles. The differences across health care professionals and clinical disciplines will be described narratively [27].

Stage 5: Collating, Summarizing, and Reporting the Results

The essential characteristics of the studies will be presented in a table format, providing an overall summary of the articles selected. Other results will be presented in diagrams and descriptive summaries as most appropriate to display and convey the extracted information.

Results

The results will be presented in a forthcoming scoping review, which we expect to publish in a peer-reviewed journal by early 2026.

Discussion

Diagnostic pathways standardize diagnostic approaches, enabling equitable access to evidence-based care [40]. In LS, aligning UTS with mainstream GT in patients with CRC may boost early diagnosis and prevention while at the same time reducing waiting times and other patient burdens. Implementing novel practices in real-world health care settings, however, is challenging, and ensuring adequate uptake of complex interventions such as diagnostic pathways requires putting in place targeted approaches to modify clinical practice behaviors [41].

To the best of our knowledge, the proposed scoping review will be the first systematic effort aimed at mapping the literature on different diagnostic pathways that align UTS and mainstream GT for LS among patients with CRC, along with the barriers and facilitators in their implementation. Its results will inform the development of a mixed methods study to be conducted in Italy, involving pathologists, molecular biologists, gastroenterologists, oncologists, geneticists, and surgeons, and focusing on implementing an integrated UTS–mainstream GT algorithm for LS among patients with CRC [31].

The planned scoping review will have some limitations. The search will be restricted to publications in English for feasibility reasons, and only peer-reviewed articles will be included. Furthermore, as is the norm for scoping reviews, a quality assessment for the articles included will not be performed.

The main strength of the proposed scoping review is that it will use the PRISMA-ScR methodology, which is robust, standardized, and reproducible. Another strength is that it will rely on a theoretically underpinned implementation framework, TDF, to identify behavior change determinants (barriers and facilitators) [42], support improved understandings of mechanisms of action, and, ultimately, the development of more effective and sustained interventions [31].

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Authors' Contributions

Conceptualization: L Battistuzzi and MSS
Writing—original draft: L Battistuzzi
Writing—review and editing: L Battistuzzi, EB, AP, L Boni, FG, LT, LV, and MSS

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Conflicts of Interest

AP reports consulting or advisory Role: GlaxoSmithKline, Takeda Pharmaceuticals U.S.A, Takeda Italia S.p.A., Bayer, Daiichi Sankyo Italia, MSD Italia, Amgen, BeiOne, Invited Speaker: Pierre Fabre, Servier, Amgen, Bristol Myers Squibb (BMS), Daiichi Sankyo Research Funding: GlaxoSmithKline (Inst), Amgen (Inst) Travel, Accommodations, Expenses: AstraZeneca, Amgen, Merck Serono. EB reports speaker fees from Eli Lilly and funding (to the institution) from Gilead. All other authors declare no conflict of interest.

Multimedia Appendix 1
PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) Scoping Review Checklist.
[PDF File (Adobe PDF File), 664 KB - resprot_v14i1e70831_app1.pdf]

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Abbreviations

CRC: colorectal cancer
GT: genetic testing
LS: Lynch syndrome
MeSH: Medical Subject Headings
MMR: mismatch repair
MSI: microsatellite instability
NICE: National Institute for Health and Care Excellence
PCC: Population, Concept, Context
PD-L1: programmed cell death ligand 1
PRESS: Peer Review of Electronic Search Strategies
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
PV: pathogenic variant
TDF: Theoretical Domains Framework
UTS: universal tumor screening

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Protocol

How Labeling of Commercial Baby Foods Impacts Parents' Beliefs About Sugar Content and Related Purchasing and Feeding Decisions: Protocol for a Scoping Review

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Abstract

Background: Average sugar consumption among young children in the United Kingdom exceeds the recommended intake. Many parents choose commercial baby foods believing these to be a healthy option. However, surveys show many products contain high levels of added or free sugars, despite labeling suggesting they are "natural" and "healthy." Analysis of labels and studies with parents suggest changes such as removing misleading marketing or adding sugar warning labels may impact parents' beliefs and food choices. However, the literature does not provide a comprehensive understanding of the range of changes to commercial baby food labels that might best support parents in choosing healthier foods for their children.

Objective: This scoping review will explore the published and unpublished evidence base to better understand what is known about how labeling of baby foods impacts parents' beliefs about a product's sugar content and related purchasing and feeding decisions.

Methods: The JBI guidelines for methodology of scoping reviews will be followed, and results will be reported using PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines. The population, concept, and context (PCC) framework will be used to determine eligibility criteria. The search will include various research methodologies, including both quantitative (observational and interventional) and qualitative studies. An initial search of MEDLINE (Ovid) and Embase (Ovid) was conducted to develop a full search strategy for MEDLINE, which is presented here. In addition to MEDLINE and Embase, we will search PsycINFO (Ovid), CINAHL (Ebsco), Web of Science (Core Collection) and the Cochrane Library. Reference lists of included studies will also be searched. Unpublished reports will be identified using Google, Google Scholar, relevant websites, policy statements, and government reports and by contacting relevant government and third-sector organizations. In a 2-stage process, 2 reviewers will independently screen titles and abstracts and then full texts. One reviewer will then extract data and a second will verify accuracy. Findings will be presented in tables and diagrams accompanied by a narrative summary.

Results: The literature searches yielded 2071 records from 6 databases, with 1123 documents remaining after deduplication. The gray literature search used a customized Google search, a targeted search of 34 websites, and contact with 49 experts.

Conclusions: We present a protocol for a scoping review to explore the evidence base to understand what is known about how the labeling of baby foods impacts parents' beliefs about sugar content and related purchasing and feeding decisions. The results of the review will help policymakers better understand regulatory opportunities to improve the labeling of commercial infant foods to help families feed infants and young children lower-sugar diets.

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KEYWORDS

scoping review; sugar; food labels; baby food; commercial infant food; nutrient warning labels; sugar warning labels; weaning

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Introduction

Average sugar consumption among young children in the United Kingdom exceeds the recommended intake, contributing to poor dental health and excess weight gain in the early years [1-3]. Free sugars account for around 10% of calories consumed by children aged 1 to 3 years in the United Kingdom—double the recommendation that free sugar intake should not exceed 5% of total energy [3]. Free sugars include all added sugars; all sugars naturally present in fruit juices, purees, and similar products, in which the structure has been broken down; all sugars in drinks (except dairy-based drinks); and lactose and galactose added as ingredients [3].

Many parents trust that commercial baby foods will contain less sugar than other foods, including home-prepared foods [4]. However, products marketed for infants and young children (aged ≤36 months) often contain high levels of added or free sugars [5-7]. It can be difficult for parents to identify these high-sugar products because of the widespread use of "health halo" statements and imagery that suggest products are healthier than their nutrient profile would indicate, for example, "natural," "organic," and "well-balanced," along with pictures of fruit [8,9]. A survey of labeling on 3427 baby foods across 27 European countries found half included the message "no added sugar," 35% of which contained free sugars [10].

The World Health Organization considers existing regulation of the composition, packaging, and promotion of baby food to be insufficient and has proposed a number of recommendations, including clearer front of pack labeling (FOPL) on products with a high sugar content [11]. The United Kingdom's Childhood Obesity Strategy also highlights this issue and makes a commitment to ensure the sugar content of foods is communicated more clearly on food labels, while pointing out that leaving the European Union will provide greater flexibility for regulatory changes [12].

Adding a high-sugar indicator (ie, a sugar warning label) to products is one way to help consumers recognize high-sugar products while also incentivizing product reformulation [11]. A systematic review and meta-analysis of 156 studies concluded that mandatory FOPL policies for traffic lights, nutrition scores, nutrition warnings, or health warnings encouraged children and adults to purchase healthier products in place of less healthy products [13]. A separate scoping review, focusing specifically on experimental studies of nutrient warning labels on sugar-sweetened beverages and ultraprocessed foods, found that sugar warning labels helped adults and children to identify high-sugar products and discouraged them from purchasing these products [14]. While these reviews bring together evidence regarding adults and children making food choices for themselves, no reviews could be found on the impact of FOPL policies for sugar on parents choosing foods for their infants and young children. A particular consideration when choosing baby food products is the general trust parents have in baby food companies and consequently their products [4]. The widespread use of "health halo" statements on high-sugar baby foods, (eg, "no added sugar" or "contains only natural sugar"), as well as listing fruit or concentrated fruit juice rather than "sugar" in ingredient lists, may also inform beliefs about the sugar content of products [6,11]. However, it is unclear if changing particular label features would support parents in feeding their children diets with a lower sugar content.

The aim of this scoping review is to explore the published and unpublished evidence base to better understand what is known about how labeling of commercial baby foods impacts parents' and other primary caregivers' beliefs about sugar content and their related purchasing or feeding decisions. This will allow policymakers to better understand regulatory opportunities to improve the labeling of commercial baby foods to support families in feeding infants and young children lower-sugar diets.

Methods

Design

The methodology for this scoping review will be underpinned by the JBI methodology [15] and reported using the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guideline [16]. A preliminary search of MEDLINE, PROSPERO, and the Cochrane Database of Systematic Reviews was conducted, and no current or currently underway systematic reviews or scoping reviews on the topic were identified.

The review questions are as follows:

1. What is known about how primary caregivers understand nutritional labeling used on commercial baby food and beverages to describe sugar?
2. What is known about how primary caregivers might use sugar warning labels on commercial baby foods and beverages?

Eligibility Criteria

The population, concept, and context (PCC) framework will be used to determine studies eligible for inclusion (Textbox 1) [17].

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Textbox 1. Eligibility criteria.

Inclusion criteria

- Population: parents or primary caregivers of children aged between 4 and 36 months. The ages of 4 to 36 months were chosen as some products are labeled as appropriate from 4 months [7].
- Concept: the key concepts addressed in the scoping review are baby food (any commercially prepared food or beverage labeled as suitable for consumption by children aged ≤36 months), sugar (mono- and disaccharides, including glucose, fructose, and sucrose found in fruits), food labeling (any information, symbols, or statements on packaging, including, but not limited to, nutrition panels, ingredient lists, traffic light labels, and warning labels), and understanding (how parents interpret, understand, or use labels, including pictures, nutrient or health-related statements, and any other packaging information that may influence perceptions of a product's sugar content).
- Context: studies conducted in northern, western, and southern Europe; North America; Australia; and New Zealand to increase the generalizability of findings to the UK population. These criteria are guided by a previous Public Health England review [18].

Exclusion criteria

- Population: studies including broader age groups without presenting subgroup analysis for the target age group of 4 to 36 months.
- Concept: studies/reports focused exclusively on commercial milk formula, product sales, or parents' perceptions of baby food marketing beyond packaging.
- Context: studies conducted in larger geographical regions without presenting subgroup analysis for target areas.

Types of Evidence

This scoping review will consider both experimental and quasi-experimental study designs, including randomized controlled trials, nonrandomized controlled trials, and before-and-after studies. In addition, we will consider analytical observational studies, including prospective and retrospective cohort studies, case-control studies, and analytical cross-sectional studies, as well as descriptive observational study designs, including case series, individual case reports, and descriptive cross-sectional studies for inclusion.

Qualitative studies will be considered, including, but not limited to, designs such as phenomenology, grounded theory, ethnography, and qualitative descriptive research. In addition to primary research, this review will consider reviews and meta-analyses, opinion papers, non–peer reviewed reports by government departments and agencies, and third sector organizations.

Search Strategy

The search strategy aims to locate both published and unpublished studies. An initial search of MEDLINE (Ovid) and Embase (Ovid) was conducted using terms associated with key concepts, such as "parents," "beliefs," "sugar," and "baby food labels." This initial exploration identified articles investigating the impact of baby food labeling on parental perceptions of sugar content. Words found in titles and abstracts, along with the index terms used to describe the articles, were used to develop a full search strategy for MEDLINE (Table 1). This strategy was collaboratively developed with an academic librarian and will be tailored for each database and information source. Additionally, the reference lists of all included sources of evidence will be screened for additional studies.

To ensure a comprehensive mapping of the literature, a broad range of databases will be searched, including MEDLINE, Embase, PsycINFO (Ovid), CINAHL (Ebsco), Web of Science (Core Collection), and the Cochrane Library. To access unpublished or nonacademic reports, Google and Google Scholar searches will be conducted; relevant websites (eg, the Department of Health and Social Care, the Food Foundation, and Action on Sugar), policy statements, and government reports will be reviewed; and relevant organizations, including those whose websites have been searched, will be contacted.

As this is a scoping review, both process and outcome data will be collected. Potential effect modifiers such as age, gender, ethnicity, and socioeconomic status will also be extracted. Only studies published in English will be considered for inclusion due to time and resource constraints.

In line with Peters et al [17], the search strategy may be modified during the process to include any new terms, concepts, or contexts based on search results and ongoing evidence selection.

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Table 1. Search strategy for MEDLINE (Ovid).

Search	Terms	Records retrieved[a]
1	exp Parents/ or caregivers/ or grandparents/	197,435
2	(parent* or mother* or caregiver* or father* or grandparent* or grandmother* or grandfather* or guardian*).tw,kf	843,311
3	1 or 2	881,170
4	Infant food/	10,285
5	((baby or babies or preschool* or toddler* or infan*) adj3 (food* or snack* or pouch* or jar or jars or meal* or beverag* or drink* or yoghurt* or cereal*)).tw,kf.	5701
6	4 or 5	14,191
7	Beverages/ or Sugars/ or Dietary sugars/ or Sugar-sweetened Beverages/	24,307
8	((Commercial* or packag* or sugar-sweet* or sugar*) adj3 (food* or snack* or pouch* or jar or jars or meal* or beverag* or drink*)).tw,kf.	21,712
9	(NAS[b] or sugar* or sucrose*).tw,kf.	237,077
10	Infant/ or Child, preschool/ or (baby or babies or preschool or pre-school or toddler* or infan* or child or children).tw,kf.	2,533,448
11	(7 or 8 or 9) and 10	15,060
12	6 or 11	28,231
13	product packaging/ or exp food packaging/ or product labeling/	16,302
14	((food* or sugar* or nutri* or health* or promotion* or traffic light* or TLL* or FOP* or front-of-pack* or product) adj3 (label* or warning* or information* or claim* or sign* or marketing or packag* or symbol* or sticker*)).tw,kf.	196,710
15	13 or 14	206,516
16	Consumer Behaviour/ or Choice Behavior/	35,240
17	(consumer* behavio?r* or choice behavio?r*).tw,kf.	4505
18	(knowledge* or understand* or choice* or influence* or perception* or perceive* or purchase* or opinion* or attitude* or view* or preference*).tw,kf.	5,427,916
19	16 or 17 or 18	5,436,263
20	3 and 12 and 15 and 19	371
21	limit 20 to english language	326

[a]The search was conducted on May 9, 2024.

[b]NAS: no added sugar.

Source of Evidence Selection

Following the search, all identified citations will be collated and uploaded to Covidence, an evidence synthesis management tool, where duplicates will be removed. Subsequently, a rigorous 2-step screening process will be undertaken. In stage 1, a pair of independent reviewers will assess the titles and abstracts against the predefined inclusion and exclusion criteria. All studies will be evaluated as “include,” “exclude,” or “unclear.” In stage 2, articles identified as “include” or “unclear” will have their full texts retrieved for assessment against the same inclusion and exclusion criteria. Studies that meet all the predefined criteria will be included in the review.

At both stages, each reviewer will conduct the screening blinded to the other, ensuring unbiased selection. To ensure consistency in our approach, a pilot test will be conducted for both stages of the screening process before completing a review of the literature. Any disagreements between reviewers throughout the process will be resolved though discussion or by consulting an additional reviewer.

A summary of the selection process, with reasons for excluding publications at each stage, will be documented and presented in the final review using the PRISMA-ScR flow diagram [16].

Data Extraction

The data extraction form, adapted from the JBI methodology for scoping review guidelines [15], will include specific details about the participants, concept, context, study methods, and key findings relevant to the review questions:

- Source, year of publication, and reference
- Year of study
- Country and region
- Aims and purpose
- Population and sample size
- Study methods
- Funding sources
- Key findings that relate to parents’ beliefs regarding sugar content in baby foods, related feeding and purchasing decisions, and any additional relevant insights

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This form will be independently piloted by 2 reviewers on 5 included studies and reviewed to determine if any adjustments are required before implementing the form across the remaining studies. Following the pilot phase, one reviewer will independently extract the data from all included studies, while a second reviewer will verify the accuracy of the extracted data. Any disagreements between the reviewers will be resolved through discussion or by consulting an additional reviewer.

Presentation of Results

As recommended by the JBI, the findings will be presented in tables and diagrams accompanied by a narrative summary [15]. Study findings will be grouped according to primary themes that emerge around each of the 2 research questions.

Results

Funding was confirmed prior to commencing the scoping review. The literature searches were conducted from database inception to May 2024. As of June 2025, the academic literature search had yielded 2071 records from 6 databases, with 1123 documents remaining after duplicates were removed. The gray literature search used a customized Google search, a targeted search of 34 websites, and contact with 49 experts.

Discussion

To our knowledge, this will be the first scoping review to explore the evidence base to understand what is known about how the labeling of baby foods impacts parents' beliefs about sugar content and related purchasing and feeding decisions. The search strategy will include a wide range of electronic databases to reduce the risk of missing relevant publications. Sugar intakes exceed recommendations, and commercial infant foods have been identified as making an important contribution to sugar intake [1-3,7]. Additionally, this topic is of interest to public health policy and consumer research; therefore, the search strategy will be supplemented by searching relevant sources in the gray literature. Adhering to the JBI methodology and PRISMA-ScR guidelines will ensure rigor in our review [15].

A limitation of the proposed scoping review is the exclusion of material not published in English, which may limit the generalizability of the results. While we have set out a clear protocol, we recognize that the search strategy or extraction methodology may require modification. Further refinements will be made as necessary during the ongoing data extraction process to better capture content relevant to the scoping review. Any modifications to the protocol will be detailed when the scoping review is reported. A risk of bias assessment is an important element of systematic reviews but will not be undertaken, as the objective of this scoping review is to map the available evidence rather than assess the internal validity of the evidence.

There are increasing calls for policies to curb the rising rates of childhood overweight and obesity [11]. An important element of the package of policy levers currently being discussed is the way food is labeled, as clear and honest labeling is essential to support consumers in making appropriate food choices [7,11,12]. Dietary habits, once established, are difficult to change; therefore, policies focused on improving dietary habits in the early years could be particularly impactful [3]. The results of the proposed scoping review will provide valuable insights into what is already known about the impact of labels on parents' perceptions of the sugar content of baby food. This will help policymakers to better understand regulatory opportunities to improve the labeling of commercial baby foods to help families feed infants and young children lower-sugar diets. Results will also help focus future research investigating how commercial infant food labels can best support healthy food choices.

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Authors' Contributions

Conceptualization: RC (equal), CL (equal)
Investigation: RC (equal), TD (equal)
Methodology: RC (equal), TD (equal)
Writing—original draft: RC (lead), TD
Writing—review and editing: RC (lead), TD, AS, CL

Conflicts of Interest

None declared.

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Abbreviations

FOPL: front of pack labeling
PCC: population, concept, and context
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

Functional Elements of Entrusted Professional Activities for Dental Educators: Protocol for a Scoping Review

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Abstract

Background: Assessing the competencies of health profession educators presents significant challenges, leading to the suggestion of implementing Entrustable Professional Activities (EPAs) as a potential solution. EPAs refer to the authority granted to individuals to perform tasks with a specified level of trust and competence. The concept of EPAs emerged from the complexities of competency-based medical education. This scoping review highlights the emerging yet underdeveloped field of EPAs for dental educators. Despite their established utility in medical education, the concept remains relatively novel for dental educators, with limited literature and inconsistent application across studies.

Objective: This paper presents a scoping review protocol aimed at systematically elucidating the extent, range, and nature of the literature on EPAs for dental educators, as evaluated in the included resources. This review seeks to answer the following research question: what are the key functional elements of EPAs for dental educators as described in the existing literature?

Methods: This scoping review will be conducted in accordance with the framework outlined by Arksey and O'Malley, enhanced by the Joanna Briggs Institute (JBI) guidelines. The literature search will use a 3-step strategy across 5 electronic databases (PubMed, Google Scholar, Scopus, Cochrane Library, and ProQuest), along with additional screening of gray literature. Primary data from relevant studies published from the introduction of EPAs in 2005 through 2024 will be analyzed. This review will include peer-reviewed literature focused on EPAs, specifically those involving dental educators in undergraduate, postgraduate, or continuing education contexts. Studies of any design (qualitative, quantitative, or mixed methods), as well as conceptual papers and reviews, will be considered. Only English-language studies will be included. The literature search process will involve a librarian, while study selection and evidence charting will be conducted by 4 independent reviewers. These reviewers will independently screen titles, abstracts, and full texts against the inclusion criteria. Data will be charted using a standardized extraction form and analyzed thematically.

Results: Findings will be presented in both tabular and narrative formats, highlighting the range, characteristics, and key components of EPAs relevant to dental educators. In addition, these findings will be mapped to the competencies of dental educators. This review is estimated to be completed within 6 months and aims to identify gaps for future research, ultimately supporting the advancement of competency-based dental education. The results of this review will serve as a foundation for a larger study focused on developing a framework of EPAs specifically tailored for dental educators.

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Conclusions: The identification of EPAs and their themes provides an initial framework that can guide the development of more structured, competency-based academic roles for dental educators. A tailored EPA framework holds promise not only for clarifying faculty expectations and enhancing performance assessment but also for supporting faculty development.

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KEYWORDS

dental educators; entrusted professional activities; functional elements; competency-based education; faculty development; assessment; framework

Introduction

Background

Educators in the health professions often bear significant responsibilities as they must fulfill dual roles as both health care providers and educators. Health professions educators are usually trained in their own clinical specialty and receive very little training to be equipped as educators [1]. The educators are the primary instrument for knowledge transfer; however, little emphasis has been placed on the capabilities or competencies of the health professions educators. The question that remains is as follows: how can we assess educators' competency?

EPAs for Health Professions Educators

The competency of educators in Health Professions Education (HPE) has often been undervalued. However, in recent years, an increasing number of medical education professionals have begun to underscore the importance of ensuring educator competency. Concerns have been raised regarding the evidence that supports the assertion that educators are adequately prepared to guarantee the safety and high quality of health care systems, which is essential for maintaining patient trust [2-4]. Despite the foundational work that has been undertaken in this area, assessing the competencies of health professions educators presents significant challenges. This has led to the suggestion of the implementation of Entrustable Professional Activities (EPAs) as a potential solution.

The concept of EPAs emerged from the complexities of competency-based medical education (CBME) [2]. EPAs were introduced with the concept of trust as a central element for effective execution. Initially proposed by Olle Ten Cate in 2005, EPAs are defined as tasks or responsibilities that can be entrusted to a trainee once they have achieved sufficient, specific competence to permit unsupervised practice [5]. The terms "Entrustable" and "Entrusted" are related and have often been used interchangeably in the literature. Therefore, to avoid confusion, the term "Entrustable" will be used exclusively from this point onward.

EPAs represent units of professional practice that are independently executable, observable, and measurable in both their process and outcomes, making them suitable for entrustment decisions [6]. In short, EPAs serve as a means to translate competencies into practical application. EPAs are hoped to link the actual teaching activities and support the development of teaching [1].

EPAs in Dentistry and Dental Educators

Dentistry, as a hands-on clinical program, would significantly benefit from a competency-based approach; thus, EPAs are regarded as a valuable addition to dental training curricula. The concept of EPAs in dentistry has been addressed in numerous publications; however, significant emphasis has largely been placed on students rather than on the capabilities and competencies of educators. It is now imperative to shift the focus of EPAs toward educators, as they play a crucial role as a vital link between the curriculum and the students. This shift is essential to ensure a high-quality educational experience for all learners while maintaining accountability and consistency [7].

There is a growing recognition that for the dental health profession to fulfill its responsibility of training competent practitioners, emphasis must also be placed on the competencies of dental educators. In 1999, the American Association of Dental Schools reported that the quality of dental students' educational experiences is critically dependent on having an adequate number of dedicated faculty with expertise in both content and teaching methodologies [8]. Furthermore, in 2010, the UK Committee of Postgraduate Dental Deans and Directors (COPDEND) established guidelines for dental educators that can be used in their employment, development, and management [9].

There is, however, a notable deficiency in published evidence regarding EPAs for dental educators. Most existing literature on EPAs primarily focuses on student assessments, particularly within postgraduate dental training [10]. A scoping review conducted in 2023 examined EPAs within the broader framework of dental education. The review primarily focused on the development of EPAs for undergraduate and postgraduate dental students, as well as the evaluation of EPAs in general dentistry, without addressing the perspectives of dental educators [11]. This proposed scoping review aims to specifically focus on the literature related to EPAs for dental educators. The findings of this review will establish a foundation for a larger study designed to develop a framework of EPAs tailored specifically for dental educators. While there is a notable gap in the literature on this topic, some evidence does exist. Therefore, a scoping review is essential to systematically search for and report the current findings on EPAs for dental educators. This effort is intended to provide resources for dental educators to incorporate EPAs into training contexts and facilitate faculty development in assessing and enhancing the skills of their educators. This approach also aligns with the skill-based methodologies favored by most universities.

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Objectives and Research Questions

This scoping review aims to explore the breadth and extent of evidence regarding EPAs for dental educators. The review will address this 1 research question: what are the key functional elements of EPAs for dental educators as described in the literature?

Methods

Study Design

This scoping review protocol will follow the methodological framework outlined by Arksey and O'Malley [12] and in accordance with the Joanna Briggs Institute (JBI) guidelines for scoping reviews [13]. Any modifications to the methodological approach will be documented and described in the final scoping review report, according to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines [14]. The adoption of 2 frameworks enhances the credibility and trustworthiness of the review through systematic procedures, while also allowing for adaptability based on emerging insights, thereby meeting high academic standards.

Review Team

The review team consists of 2 qualified medical education experts, each holding a doctorate in medical education and possessing over 5 years of experience in medical education teaching and conducting scoping reviews (MSBY and NSR). Furthermore, the team includes 2 experienced dental educators: one is the lead of the dental education pathway in a renowned medical education center (MAH), while the other currently pursuing a PhD in medical education (NAB). A qualified librarian is also engaged to support the development and refinement of the search strategy to ensure comprehensiveness and systematic retrieval of relevant literature across selected databases (YMB).

Inclusion Criteria

Types of Articles

Given the terms "entrusted" and "entrustable" are related, ensuring no articles are overlooked, this scoping review will examine published primary and secondary research that describes both the Entrusted and Entrustable Professional Activities for dental educators globally, using 5 databases (PubMed, Google Scholar, Scopus, Cochrane Library, and ProQuest). Resources outside of these databases will be excluded from the review.

Concept

This scoping review will encompass resources to capture the evidence, scope, and range of EPAs for dental educators. This review will specifically focus on the EPAs pertinent to dental educators. Dental educators in this context will include individuals involved in teaching at all levels of dental education, including both undergraduate and postgraduate programs, regardless of geographical background. In addition, this review will include articles that explore the various elements related to EPAs, including domains, characteristics, factors, skills, or themes that shape the EPAs essential for effective dental educators. Resources that do not explicitly report on EPAs will be excluded from this review.

Context

The context of this review will encompass the elements, characteristics, domains, or any other related themes that build or describe the EPAs for dental educators irrespective of their teaching level. This includes educators for both undergraduate and postgraduate education including clinical specialty training.

The components of the EPAs for dental educators are grounded in the competencies being assessed, which include educational theories and principles, modes of education, learner issues, educational materials, instructional design, curriculum matters, evaluation, research, management, quality assurance, patient care and health care systems, and professionalism [15]. Resources that do not pertain to the themes of the EPAs and articles unrelated to dental educators will be excluded. The inclusion and exclusion criteria are summarized in Textbox 1 and definitions are provided in Textbox 2.

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Textbox 1. Inclusion and exclusion criteria used during the screening of the population (dental educators), concept (EPAs), and context (element, domain, item, skills, and characteristics) examined in the scoping review.

Inclusion criteria:

- Population
  - Dental educators or dental lecturers.
  - Including either undergraduate- or postgraduate-level educators.
  - Including both private and public education institutions.
- Concept
  - Entrustable professional activities.
- Context
  - Element, standard, domain, item, skills, or characteristics of dental educators.
- Other
  - Published in the English language.
  - Study design: all study types.
  - Study location: from all geographical locations.
  - Published between 2005 and 2024.
  - Full text.

Exclusion criteria:

- Population
  - Nonhealth, nonmedical, and nondental related educators.
- Other
  - Published in a language other than English.
  - Non-full text.

Textbox 2. Definition for the Population, Concept, Context, and characteristics for this scoping review.

- Entrustable professional activities: tasks or responsibilities (to be mastered or certified) that can be entrusted to a trainee, once sufficient, specific competence is reached to allow unsupervised execution [6].
- Dental educator: a professional who teaches dental students and other dental professionals through formal clinical teaching in dental schools including through outreach programs [7].
- Element: one of the parts of something that makes it work, or a quality that makes someone or something effective (Cambridge Dictionary).

Sources

This scoping review will encompass both quantitative and qualitative research and is not limited to primary studies. Since EPAs are relatively new to dentistry, gray literature is considered a crucial source of information [15]. Therefore, to ensure that no significant data are overlooked, both primary research and secondary reviews—including, but not limited to, narrative reviews, scoping reviews, systematic reviews, and meta-analyses—as well as published gray literature limited to conference proceedings, theses and dissertations, working papers, preprints, and protocols relevant to the EPAs of dental educators, will be systematically searched.

As EPAs were first introduced in 2005, the review will only include articles published in English between January 1, 2005, and October 1, 2024. Unpublished literature, websites, and blog posts will not be considered in this review to maintain the authenticity and reliability of the data.

Search Strategy

This review will be conducted using a 3-phase search strategy based on the recommendations of the JBI Scoping Review Guidelines [13]. The initial keywords will be identified and selected from the titles and index terms of relevant reviews. These keywords will be derived from the MeSH (Medical Subject Headings) and Education Resources Information Center (ERIC) databases and will be tested with various search terms using Boolean combinations. The search terms will be refined

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and adapted accordingly after multiple test searches. A qualified librarian (YMB) was consulted to assist in the development of the search strategy, including the identification of relevant databases, refinement of search terms and Boolean operators, and the adaptation of search strings for each database. The librarian also contributed to the peer review of the final search strategy to ensure sensitivity and comprehensiveness. The initial search will be based on the Table 1 below.

Table 1. Table of the key concepts, free text terms, and controlled vocabulary terms.

	Concept 1	Concept 2
Key concepts	• Entrustable professional activities	• Dental educators, dental education, or dentistry
Free-text terms, natural language terms, or author keywords (from papers)	• Entrustable professional activities • Entrusted professional activity • Entrustable professional activity	• Dental educator • Dental educators • Dental education • Dentistry
Controlled vocabulary terms or subject terms	• Not applicable	• Index terms, MeSH[a], or Emtree • MeSH (education, dental, and dentistry)

[a]MeSH: Medical Subject Headings.

The initial keyword search terms will be based on a few key papers and further refined accordingly after a few searches. Keywords identified as (“Entrusted Professional Activities” OR “Entrustable Professional Activities” OR “Entrustable profession* activit*”) AND (“Dental Educator*” OR “Dental Education” OR Dentistry), with a time limit of 2005 to 2024.

A second search using all identified keywords and index terms will be performed across 5 databases, namely Scopus, Google Scholar, PubMed, Cochrane Library, and ProQuest. Reference lists of eligible studies will be back searched as the third phase. The findings will be summarized in tabular form and a narrative synthesis.

Selection Process

The record selection will adhere to the predefined inclusion criteria with the search term monitored by the librarian (YMB). All identified sources will be exported into Microsoft Excel and duplicates will be removed. Once the reviewers are familiar with the selection process, the titles, abstracts, and full-text articles of the included records will be screened according to the inclusion criteria. The selection process will be conducted independently by 2 researchers (NAB and NSR), with any disagreements addressed through the involvement of the other 2 reviewers (MSBY and MAH) and further discussion, if necessary. Records that do not meet the inclusion criteria will be excluded from this study, and the reasons for exclusion will be documented. The search profile of the selection process will be reported using the PRISMA-ScR flow diagram Multimedia Appendix 1 [14].

Data Extraction, Analysis, and Presentation of the Results

A standardized data extraction form is developed based on the JBI guideline as in Multimedia Appendix 2 [13]. The following data will be extracted from each article:

1. Title
2. Authors and year of publication
3. Country or geographical area
4. Study design, tool, or intervention
5. Participant categories (dental educators for undergraduate or postgraduate or both)
6. Elements or characteristics of EPAs
7. Key findings
8. Other relevant information and remarks

This data extraction will be performed independently by 2 reviewers to mitigate the risk of error. To ensure the reliability and consistency of the data extraction process, the reviewers will discuss their extraction strategies and pilot the process by extracting data from 5 records. Transparent reporting will be implemented and duplication of information from primary literature and reviews will be avoided by including a clear list of primary studies to flag duplicates. In addition, the reviewers will collaborate to discuss the outcomes of the data extraction. Any modifications in the data extraction form following the piloting will be reported.

The extracted data will be presented in tabular form and described using descriptive statistics. A thematic approach will be used using NVivo software (Lumivero) for qualitative analysis. The data will be thematically organized according to the elements of the EPAs for dental educators and other related factors. The process will begin with open coding of relevant text (eg, descriptions of EPAs, functional elements, and implementation strategies), followed by a grouping of codes into broader categories and ultimately, into meaningful themes. A narrative summary of each element will be provided, and the elements of the EPAs for dental educators will be mapped to their associated issues or any relevant emerging theme identified during the review. Themes will be refined through team discussions to ensure credibility and consistency. The final thematic map will be used to answer the main research question by identifying key concepts and applications of EPAs for dental educators.

Quality Assessment

A quality assessment of the included articles will be conducted using the tool developed by Kmet and colleagues [16]. While this step is not mandatory in a scoping review, its inclusion will enhance the analysis. This tool provides standardized criteria for evaluating the methodological quality of primary research

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papers across various fields. The quality assessment will help identify potential sources of bias, assess the rigor of study designs, and provide insights into the overall quality of the evidence. A total of 2 reviewers will independently carry out the quality assessment, with any discrepancies resolved through discussion or consultation with the third and fourth reviewers.

Ethical Considerations

This review is classified as a secondary research study, concentrating on the existing literature, therefore, ethical approval is not required.

Results

Overview

Data collection started in October 2024 and is expected to conclude in May 2025 and expected results to be published by the end of 2025.

Expected Outcome

This scoping review aims to offer these outcomes:

1. Provide a comprehensive and structured overview of the literature regarding EPAs for dental educators.
2. Identify the key functional elements of EPAs for dental educators from the available evidence.
3. Contributes to the existing literature on EPAs for dental educators.

Discussion

Principal Findings

This scoping review sought to systematically map the existing literature on EPAs relevant to dental educators. Although a limited number of articles are expected, we anticipate identifying a potential number of EPAs that can be mapped to overarching themes. The limited number of studies reflects a significant gap in scholarly focus on defining and applying EPAs for dental educators.

Comparison to Prior Work

While EPAs have gained considerable traction in medical education, particularly in postgraduate training for physicians and other health professionals, their application in dentistry especially dental educators remains underexplored. Prior studies in medical education have emphasized EPAs as a bridge between broad competencies and day-to-day clinical tasks, facilitating both curriculum design and assessment of workplace readiness. Similar principles could be beneficial for dental educators, particularly in aligning educational tasks with observable and measurable outcomes.

The reviewed articles primarily adapted frameworks from medical education, often with minimal contextualization for the unique scope of dental academic responsibilities. This highlights a critical gap: dental educators' roles-spanning teaching, clinical supervision, research, and administrative duties, demand a tailored EPA framework that reflects the distinct characteristics of dental academia. This review fills this gap by consolidating available evidence and categorizing EPAs into meaningful themes, providing a starting point for further validation and adaptation in dental contexts.

Strengths and Limitations

A key strength of this review lies in its rigorous methodology, guided by the Arksey and O'Malley [12] framework and enhanced through the JBI guidelines. The comprehensive search strategy across multiple databases and inclusion of gray literature ensures a broad capture of relevant materials. The thematic synthesis of the findings offers a structured way to interpret the scattered evidence base. The review also incorporated multiple expert reviewers, including a librarian, to ensure a high-caliber search.

However, several limitations should be acknowledged. First, the small number of included studies and the relatively recent emergence of EPAs in dental education limit the generalizability of the findings. Second, many articles lacked in-depth descriptions of how EPAs were developed, implemented, or assessed, making it difficult to compare methodologies or outcomes across studies. Third, the variation in terminology and conceptual understanding of EPAs may have resulted in relevant studies being excluded despite using different nomenclature.

These limitations suggest that findings should be interpreted with caution. Future research should aim to clarify the operational definition of EPAs for dental educators and develop standardized processes for their design, implementation, and assessment.

Practical Implications

Despite the limited evidence, the review provides several important implications for dental education. The identified EPAs can inform curriculum development for academic training programs, especially for junior faculty members or those undergoing academic leadership development. EPAs also have potential utility in academic performance evaluation, faculty development, and the mentoring of early-career educators by clearly defining what tasks can be entrusted at various levels of competence.

Moreover, the adoption of EPAs in dental education could enhance clarity in role expectations, promote accountability, and facilitate structured feedback—all critical elements for professional development in academic settings.

Future Directions

To build upon this foundation, further research is needed to:

1. Develop and validate a standardized set of EPAs specifically tailored for dental educators.
2. Engage stakeholders including faculty, administrators, and students in cocreating and refining EPA frameworks to ensure contextual relevance.
3. Explore the feasibility of implementing EPAs in academic promotion, continuing professional development, and interprofessional education.
4. Investigate how EPAs can support transitions in faculty roles, such as from clinician to educator or from junior to senior academic positions.

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Longitudinal studies and implementation research could further clarify the impact of EPAs on educational quality, faculty satisfaction, and institutional outcomes.

Dissemination Plan

The findings of this review will be disseminated through publication in peer-reviewed journals and presentations at conferences related to health professions education and dental education. In addition, summaries will be shared with academic leadership and faculty development units to inform ongoing and future initiatives related to academic competency frameworks.

Conclusion

The identification of EPAs and their themes provides an initial framework that can guide the development of more structured, competency-based academic roles for dental educators.

The findings underscore the need for further empirical research to refine and validate EPAs specific to the dental education context. A tailored EPA framework holds promise not only for clarifying faculty expectations and enhancing performance assessment but also for supporting faculty development and succession planning. By advancing the understanding and application of EPAs in dental education, this study lays a foundational step toward more systematic, accountable, and outcome-based academic practice.

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Data Availability

The datasets and/or any supplementary material used in this scoping review will be available from the corresponding author upon request.

Authors' Contributions

NAB conceived the idea, curated the data, analyzed, and wrote the original draft. YMB helped with article resources and the search term. MAH participated as a reviewer. NSR and MSBY were involved in the review, constructed, read, and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-ScR checklist.
[PDF File (Adobe PDF File), 693 KB - resprot_v14i1e74225_app1.pdf]

Multimedia Appendix 2
Data extraction form.
[DOCX File , 15 KB - resprot_v14i1e74225_app2.docx]

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Abbreviations

CBME: competency-based medical education
COPDEND: Committee of Postgraduate Dental Deans and Directors
EPA: Entrustable Professional Activity
ERIC: Education Resources Information Center
HPE: Health Professions Education
JBI: Joanna Briggs Institute
MeSH: Medical Subject Headings
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Home Health Care Providers' Readiness to Care for Children and Youth With Complex Medical Conditions: Protocol for a Scoping Review

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Abstract

Background: Children and youth with medical complexities have chronic conditions, functional limitations, and extensive care needs requiring significant family involvement and frequent health service use. Pediatric medicine has improved their life expectancy, shifting care from acute to home settings. In Ontario, home care is publicly funded and includes nursing, therapy, personal support, and allied health services. However, families continue providing the bulk of care, often at great personal costs. As care complexity increases, so does the reliance on home care providers. Yet, many providers report feeling unprepared due to insufficient pediatric training, lack of supervision, and system-level gaps. Here we applied Weiner's theory of organizational readiness for change, framing readiness as a shared psychological state involving commitment to and confidence in delivering change, thus helping conceptualize provider readiness as encompassing individual competence, contextual supports, and motivational factors. Despite its importance, provider readiness in pediatric home care remains poorly understood.

Objective: We examine how home care providers perceive their readiness to care for children and youth with medical complexities, factors influencing readiness, and strategies proposed to enhance their capacity to deliver safe, coordinated, developmentally appropriate home care.

Methods: This scoping review follows the updated Joanna Briggs Institute scoping review methodology and PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines. Articles focusing on (1) children and youth with medical complexities aged 0-18 years receiving home care and (2) with at least one chronic medical condition, and (3) paid home care providers will be searched on MEDLINE, CINAHL, Scopus, ProQuest Nursing & Allied Health, PsycINFO, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews. Gray literature will be searched on Google Scholar and ProQuest (Dissertations & Theses). A 2-stage screening process will be conducted in Covidence, involving title and abstract screening and full-text review by 2 independent reviewers. Data will be extracted using predefined charting categories and analyzed using both qualitative and quantitative approaches.

Results: As of May 2025, screening is underway. The review will map key themes across provider types, care settings, and training contexts and identify factors influencing provider readiness including access to training, system navigation supports, and workplace role clarity and chart recommendations or strategies to enhance readiness. Gaps in pediatric-specific competencies and workforce preparation may also emerge.

Conclusions: This review will synthesize current evidence on provider readiness in pediatric home care, identifying strengths, challenges, and development areas. Findings will inform provider training, workforce development, and policy strategies to ensure children and youth with medical complexities receive safe, coordinated, effective home care. A deeper understanding of provider readiness will support more sustainable home care systems and improve outcomes for children and youth with medical complexities and their families.

Trial Registration: OSF Registries 10.17605/OSF.IO/N4FAJ; https://osf.io/n4faj

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International Registered Report Identifier (IRRID): PRR1-10.2196/76796

(JMIR Res Protoc 2025;14:e76796) doi:10.2196/76796

KEYWORDS

children; home care; practice readiness; protocol; scoping review

Introduction

Children and youth with medical complexities are a diverse group of individuals who share the following characteristics: (1) they have chronic and severe conditions, (2) they have functional limitations, (3) they have extensive family-identified needs, and (4) they require substantial use of health care services [1,2]. Diagnoses common to them are numerous and include preterm birth, as well as congenital genetic, metabolic, and neurological conditions that require constant and close monitoring of their physical, emotional, behavioral, and developmental well-being [3]. While many children and youth with medical complexities are at risk of premature mortality, advances in medical care and technology have extended life expectancy for others [4,5].

Care for children and youth with medical complexities was previously delivered almost exclusively in acute care settings by specialized health care providers such as pediatricians and pediatric nurses. However, shifts in family preferences to receive care closer to home and rising health care costs have moved much of this care to home and community care settings [6-8]. In regions such as Ontario, Canada, home care services are funded and organized through the provincial government, specifically Ontario Health atHome [9]. Home care services frequently accessed by children and youth with medical complexities include but are not limited to nursing, physiotherapy, occupational therapy, dietetics, speech therapy, social work, and personal support worker care, each playing an essential role in supporting children and youth with medical complexities and relieving the caregiving burden on their families. However, families continue to spend 15.7 million hours per year in caring for children with acute, chronic, or complex health issues [10].

As the medical complexity of the child increases, the required caregiving hours also rise. For example, it takes approximately 130 hours to care for a child with attention-deficit issues and 629 hours to care for a child with complex medical conditions [10]. Many parents willingly take on these responsibilities but report significant impacts on self-care, couple time with their partners, and parenting time and opportunity with their other children [11]. While this review focuses on provider readiness, these caregiver experiences highlight the consequences of inadequate or inconsistent home care support and reinforce the importance of a well-prepared provider workforce. Without timely and adequate support from home care services, prolonged caregiving puts parents at heightened risk of burnout and other mental health conditions, such as anxiety and depression [12,13].

Despite its growing importance, Ontario's pediatric home health care services are notably fragmented and complicated to navigate [14,15]. A 2020 Canadian Institute of Health Information report identified 97,561 children and youth with medical complexities across Canada; only 43% of this population received home care [16]. Families frequently describe the system as slow, reactive, and challenging to access, requiring them to repeatedly "fight" for supplies or services [11,17,18]. Maynard et al [8] found that 7 in 10 children experienced an additional 53.9 hospitalization days due to the lack of home care nursing services. Parents report that home care services are not always guaranteed, necessitating private nursing care while waiting for publicly funded home care services [19]. The consequences of inadequate home care are significant: limited availability of home health care nursing and insufficient support are linked to extended hospital stays and avoidable readmissions [8,20].

Caring for children and youth with medical complexities at home requires home care providers who are both competent in pediatric care and confident in managing the child's specific clinical needs [21,22]. Their needs may include the use of medical devices, be on multiple medications, and require other supports at home and in school due to their functional limitation [16]. Given the complexity of care, McCann [18] reported that parents "do not trust respite care providers to provide a suitable standard of care for their child." Research has highlighted that many home health care providers feel unprepared to provide specialized pediatric care due to a lack of specialized training opportunities to gain the necessary experience and skills, a lack of professional practice support from home care organizations, and limited guidance from supervisors [6]. This review, therefore, draws conceptually on Weiner's theory of organizational readiness for change, which frames readiness as a shared psychological state encompassing commitment to and confidence in implementing a change [23]. In our context, readiness is understood as a multidimensional construct comprising individual competence (eg, knowledge, skills, and confidence), contextual supports (eg, training, supervision, and resources), and motivational factors (eg, perceived role clarity and value alignment). This framework supports a nuanced examination of both system-level and individual factors that shape provider preparedness to care for children and youth with medical complexities at home [23]. While individual studies have examined provider experiences and training needs, there is limited synthesis on the overall readiness of the home care workforce to deliver safe, developmentally appropriate care to children and youth with medical complexities [16,24,25]. In particular, few studies have explored readiness across provider types or contextual factors influencing preparedness, especially within the Canadian health care system [19,26].

This gap in providers' readiness leaves many children and youth with medical complexities with substantially unmet needs that parents/caregivers often have to manage independently [27]. Although studies suggest that home is the preferred setting for

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the long-term care of children and youth with medical complexities, the reported lack of provider preparedness presents a serious safety concern. It also affects families' confidence and decision to entrust their children and youth with medical complexities to home health care professionals [3,28,29]. The continued lack of timely and adequate home health care places parents and/or caregivers at risk of burnout, emotional and psychological distress, financial demands, and social isolation [12]. These outcomes, while not the primary focus of this review, underscore how provider readiness directly influences the sustainability of family caregiving. In this context, understanding the factors influencing provider readiness and identifying strategies to support and strengthen it are critical for improving outcomes for children and youth with medical complexities and their caregivers. This review does not aim to examine caregiver burden directly, but rather to explore provider-related factors that may impact quality and indirectly shape family caregiving experiences.

Therefore, it is necessary to examine the extent and nature of the literature on home and community care health care providers' readiness to care for children and youth with medical complexities. Although this review focuses primarily on provider-related factors, it also considers the characteristics of children and youth with medical complexities receiving home care to better contextualize provider readiness and the types of support required in different care contexts. Findings from this review will help inform policy, workforce development, and future research aimed at strengthening the capacity of home care providers to meet the needs of children and youth with medical complexities and their families.

The research team, including 2 nursing faculty members (JT and EC), 1 nursing librarian (AM), and 1 clinical scientist (MS), developed the overarching review question, "What is known about home health care providers' readiness to care for children and youth with medical complexities at home?" The specific questions are as follows:

- What are the characteristics of children receiving home health care, and how might these shape provider readiness?
- How do home health care nurses, including registered nurses, practical nurses, and other professionals such as therapists and personal support workers, perceive their readiness to care for children and youth with medical complexities at home?
- What factors influence the readiness of home health care providers to care for children and youth with medical complexities?
- What recommendations or strategies have been proposed to enhance providers' readiness in pediatric home care?

Methods

The proposed scoping review will be conducted in accordance with the JBI (Joanna Briggs Institute) methodology for scoping reviews, and in line with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) framework [28,29]. This protocol has been registered in the OSF Registries (osf.io/m58zj/). As per the JBIs' recommendation, a critical appraisal will not be assessed because the purpose of a scoping review is to describe the extent of available evidence in the field [28].

We will include studies that examine the readiness of home care providers (eg, registered nurses, registered/licensed practical nurses, physicians, therapists, and personal support workers) who deliver care to children and youth with medical complexities aged 0 to 18 years with at least one complex medical condition (eg, epilepsy, global developmental delay, cardiopulmonary disease, neurological impairment, genetic and metabolic conditions, etc). For this review, studies must specify provider roles and focus on paid home care services to role-specific relevance. The search strategy for the full range of provider terms considered is outlined in Table 1. Readiness is defined as a combination of clinical knowledge, technical skills, critical thinking, communication, professionalism, and management of responsibilities [26,27]. Complex medical conditions are defined as individuals who (1) have chronic conditions that limit their functional ability, (2) require round-the-clock care, and (3) require substantial use of health care services. The context includes home care settings in which paid health care providers support children and youth with medical complexities through daily living assistance or more specialized interventions such as home-based antibiotic administration. Articles will be included if they report on the level of readiness among home care providers. Studies focused exclusively on non–home care settings, such as acute care, children's emergency rooms, children's treatment centers, schools, and respite care facilities, will be excluded unless they specifically report and discuss findings relevant to home care.

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Table 1. Search strategy draft for MEDLINE (Ovid).

Number	Search queries
1	(nurs* or RN* or RPN* or LPN* or NP* or APN* or APRN* or CNS* or physician* or doctor* or MD* or physiotherapist* or “speech language therapist*” or “speech-language therapist*” or “speech language pathologist*” or “speech-language pathologist*” or dietitian* or dietician* or “occupational therapist*” or OCT* or “social worker*” or “care coordinator*” or “healthcare provider*” or “health care provider*” or HCW* or “healthcare worker*” or “health care worker*” or “interdisciplinary team*” or “multidisciplinary team*”).ti,ab,kw.
2	exp Health Personnel/ or exp patient care management/
3	1 or 2
4	(pediatric* or paediatric* or peds or paeds or teen* or child* or adolescen* or youth* or infant* or newborn* or neonat* or kid* or “young* adult*” or ((one or two or three or four or five or six or seven or eight or nine or ten or eleven or twelve or thirteen or fourteen or fifteen or sixteen or seventeen or eighteen or “1” or “2” or “3” or “4” or “5” or “6” or “7” or “8” or “9” or “10” or “11” or “12” or “13” or “14” or “15” or “16” or “17” or “18”) adj1 (“year* old*” or “month* old*”))).ti,ab,kw.
5	exp Pediatrics/ or adolescent/ or young adult/ or exp child/ or exp infant/
6	4 or 5
7	(“complex care” or CMC* or CSHCN* or CYMC* or “medically complex” or “medical complexity” or “medical complexities” or “medically fragile” or life-limit* or “life limiting” or “life limited” or life-threat* or “life threatened” or “life threatening” or life-short* or “life shortening” or “life shortened” or “multiple conditions” or “chronic condition” or “chronic conditions” or “complex condition*” or “care coordination” or co-morbidit* or comorbidit* or multi-morbidit* or multimorbidit* or “technology dependence” or “technology dependent” or “high intensity care” or “neurodevelopmental disabilit*” or “neuro-developmental disabilit*” or “neurodevelopmentally disabled” or “neuro-developmentally disabled” or “global developmental delay” or GDD or “enteral nutrition” or “parenteral nutrition” or ventilat* or “mechanical ventilation” or “neurological impairment” or “neurological impairments” or “neurologically impaired” or “rare disease*” or “rare disorder*” or “rare condition*” or “genetic disease*” or “genetic disorder*” or “genetic condition*” or “special need” or “special needs” or “technology dependent” or “technology dependence” or “technologically dependent”).ti,ab,kw.
8	rare diseases/ or exp Comorbidity/ or exp neurodevelopmental disorders/ or enteral nutrition/ or Parenteral Nutrition, Home/ or exp Ventilators, Mechanical/
9	7 or 8
10	(prepare* or readiness or ready or competen* or proficien* or knowledge* or skill* or able or abilit* or confiden* or “nurs* attitude*” or “nurs* view*” or “nurs* opinion*” or “professional development”).ti,ab,kw.
11	(((home or respite or communit* or primary) adj2 (care or “health care” or healthcare or nurs*)) or ((personal or paid) adj3 caregiv*) or “personal care aide*”).ti,ab,kw.
12	home health aides/ or exp home care services/ or patient care planning/ or primary health care/ or transition to adult care/ or transitional care/ or patient navigation/
13	11 or 12
14	3 and 6 and 9 and 10 and 13
15	limit 14 to “all child (0 to 18 years)”

This scoping review will consider experimental and quasi-experimental study designs, including randomized controlled trials, nonrandomized controlled trials, before-and-after studies, and interrupted time-series studies. In addition, analytical observational studies, including prospective and retrospective cohort studies, case-control studies, and analytical cross-sectional studies, will be considered for inclusion. This review will also consider descriptive observational study designs, including case series, individual case reports, and descriptive cross-sectional studies, for inclusion. In addition, qualitative studies using methods such as phenomenology, grounded theory, ethnography, qualitative description, action research, and feminist research will be considered. In addition, any kind of systematic reviews that meet the inclusion criteria will also be considered. Gray literature, such as dissertations and theses, opinion papers, and conference presentations, will also be considered for inclusion in this scoping review. However, sources such as theoretical or conceptual papers, books, or book chapters will not be included.

The search strategy will aim to locate both published and unpublished studies. An initial limited search of MEDLINE (Ovid) and CINAHL (EBSCO) was undertaken to identify articles on the topic. The text words contained in the titles and abstracts of relevant articles and the index items used to describe the articles were used to develop a full search strategy for MEDLINE via Ovid. The search strategy, including all identified keywords and index terms, will be adapted for each included database and/or information source. The reference list of all included sources of evidence will be screened for additional studies. The databases to be searched include MEDLINE, CINAHL, Scopus, ProQuest Nursing & Allied Health, PsycINFO, Cochrane Central Register of Controlled Trials, and Cochrane Database of Systematic Reviews. Gray literature search will include dissertations and theses, opinion papers, and conference presentations. The same search strategy will be applied to ProQuest Dissertations & Theses. Papers published in any language will be included. Although the team primarily uses English as its working language, DeepL translator (DeepL) will be used for the initial translation of non–English-language

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articles. To ensure translation accuracy and quality appraisal, translated content will be reviewed by at least one bilingual reviewer or a native speaker familiar with the subject matter, when available. Professional translation or consultation with a language expert will be sought to validate meaning and context, where necessary.

The search strategy for this protocol was developed by author JT in consultation with a nursing librarian AM from the University of Windsor to scope out relevant studies from both published and gray literature. Keywords and search terms relating to pediatric home care and care providers were developed and adapted from published search terms. A draft search strategy for MEDLINE (Ovid) is presented in Table 1. No date restriction will be imposed on the searches, as the literature on home care for children is limited. However, studies published before 2000 will be carefully assessed for relevance, and findings will be interpreted in light of changes in pediatric care practices, health systems, and home care models over time.

Following the search, all identified citations will be collated and uploaded into Zotero (version 6.0.36; Corporation for Digital Scholarship and Roy Rosenweig Center for History and New Media), and duplicates will be removed. Potentially relevant sources will be retrieved in full, and their citation details will be imported into Covidence (Veritas Health Innovation) for screening. A 2-stage review will be conducted to screen the articles. In the first stage, 2 independent reviewers will screen articles for relevance based on the title and abstract. In the second stage, 2 reviewers (JT and EC) will perform independent full-text reviews of articles. Any disagreements among the reviewers at each stage of the selection process will be resolved with an additional reviewer (or reviewers). Reasons for excluding sources of evidence at full text that do not meet the inclusion criteria will be recorded and reported in the scoping review. Results of the screening process will be presented in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) 2020 flow diagram [30].

Data will be extracted from the articles included in this scoping review. A pilot test will be undertaken by 2 or more members of the review team on at least 4 articles using a data extraction tool developed by the reviewers to ensure reliability and accuracy in capturing data. After this initial review, articles will be reviewed by 2 or more independent reviewers. Any disagreements among reviewers will be resolved with additional reviewers. The extraction tool will provide an overview of knowledge and practice gaps to inform education, training, and service delivery in home and community care.

The extracted data will include specific study details, such as sample characteristics, data collection and analysis, results, and other findings. The draft data extraction tool will be refined as necessary during the data extraction process. Any refinement will be detailed in the scoping review. Findings will then be organized in a spreadsheet format.

The PRISMA-ScR checklist will guide the reporting of the results in this scoping review. To answer review question 1, characteristics (eg, age, sex, types of diagnosis, time since diagnosis, types of medical devices, etc) will be described using frequency counts, percentages, mean, and SDs. Similarly, for review question 3, frequency counts and percentages will be used to summarize all reported influencing factors identified through quantitative data. Where available, quantitative findings related to influencing factors will also be analyzed thematically.

A qualitative descriptive approach will be used to address review questions 2 and 3. Relevant findings from included studies will be extracted and coded inductively, and thematic analysis will be conducted to identify and group key patterns in the perspectives of home care providers regarding their readiness to care for children and youth with medical complexities. For review question 4, reported strategies or recommendations to enhance provider readiness will be charted and thematically categorized. Finally, we will use different knowledge translation strategies to share results, including but not limited to open access publication in a peer-reviewed journal, presentation at home and community care conferences, and infographics to share our findings via social media such as X (formerly Twitter) and Instagram.

Results

As of May 2025, data screening for the scoping review is underway. This review will identify key factors influencing provider readiness to care for children and youth with medical complexities at home, including training needs, system-level supports, and role-specific challenges. The analysis will highlight gaps in pediatric-specific competencies and workforce preparation, informing future efforts to strengthen home care capacity and provider support. Results are expected to be published in winter 2026.

Discussion

Anticipated Findings

This scoping review protocol addresses a critical knowledge gap in understanding provider readiness for pediatric home care. Despite the increasing prevalence of children and youth with medical complexities receiving care at home, research on provider preparedness has not kept pace with this trend [1,16]. While advances in pediatric medicine have improved survival rates and shifted care from hospital to home settings, current literature on provider readiness exists in isolation across different professional groups and care contexts, limiting understanding of broader workforce capacity issues [4-6]. This fragmentation is particularly problematic in Canada, where publicly funded home care systems vary significantly across provinces, with little comparative analysis on provider preparedness [9,14,15]. Using Weiner's theory of organizational readiness for change as a guiding framework, this review recognizes that readiness extends beyond individual competence to encompass organizational supports and motivational factors, providing a structured lens for systematic synthesis that can inform targeted interventions [23]. While this review focuses on provider factors, the ultimate beneficiaries are children and youth with medical complexities and their families who depend on competent, confident home care providers for safe and effective care delivery [11,12]. The consequences of inadequate provider readiness extend beyond immediate care quality to affect family stress, caregiver burden, and health care usage

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patterns, and the review's focus on role-specific challenges recognizes that different health care providers bring unique skills and face distinct challenges in pediatric home care contexts [8,13,21,22].

Methodological Considerations and Strengths

The choice of scoping review methodology is particularly appropriate for this topic given the exploratory nature of the research questions and the anticipated heterogeneity in study designs, populations, and outcomes [28,29]. Unlike systematic reviews that focus on specific, well-defined questions with comparable outcomes, scoping reviews are designed to map the breadth of evidence and identify key concepts, gaps, and future research directions, which is essential when examining provider readiness where definitions, measurement approaches, and contextual factors likely vary significantly across studies [28]. The comprehensive search strategy developed in consultation with a nursing librarian ensures broad coverage of relevant databases and gray literature sources, while the inclusion of non–English language publications with translation protocols addresses potential language bias given the international scope of pediatric home care challenges [31]. Studies from 2000 onward will be included to ensure findings reflect current pediatric care practices and home care models, as earlier studies may not adequately represent the current landscape of provider roles and care delivery approaches. The 2-stage screening process with independent reviewers and conflict resolution mechanisms enhances the rigor and reliability of study selection, and the use of Covidence for screening management and pilot testing of data extraction tools further strengthens the methodological approach, with these quality measures being crucial given the anticipated complexity and heterogeneity of the literature base [30].

Anticipated Challenges and Limitations

Several challenges are anticipated in conducting this review. The heterogeneity in how "readiness" is defined and measured across studies may complicate synthesis efforts, as provider readiness has been conceptualized variously as confidence, competence, preparedness, or capability, with measurement approaches ranging from self-report surveys to observational assessments [26,27]. Additionally, variation in health care systems, particularly between publicly funded systems like Canada's and other models, may affect the generalizability of our findings. However, this diversity also represents an opportunity to identify universal themes and context-specific factors that influence provider readiness [9]. Finally, focusing on published literature may introduce publication bias, where unfavorable or inconclusive findings may be less likely to appear. Despite the inclusion of gray literature and translation protocols, some relevant non–English-language studies may still be missed.

Implications for Policy and Practice

The findings from this review are expected to have significant implications for multiple stakeholder groups. For policymakers, the synthesis will provide evidence to inform workforce planning, funding allocation, and regulatory frameworks for pediatric home care, while health care organizations and home care agencies will benefit from identifying organizational factors that contribute to provider preparedness to inform quality improvement initiatives and staff development programs [32,33]. For educators and professional bodies, identifying competency gaps and training needs will inform curriculum development and continuing education programs, with an understanding of how readiness varies across health care roles, enabling the development of role-specific educational interventions and competency frameworks [34]. For researchers, this review will identify methodological approaches, outcome measures, and research gaps that can guide future investigation, with the synthesis of existing measurement approaches potentially contributing to the development of more standardized tools for assessing provider readiness in pediatric home care contexts.

Future Research Directions

This scoping review will identify important areas for future research, including gaps in understanding specific provider types, care contexts, or populations of children and youth with medical complexities. The synthesis may reveal a need for more robust measurement tools for assessing provider readiness or longitudinal studies examining how readiness changes with experience and training over time. Additionally, the review may identify a need for intervention studies that test strategies for enhancing provider preparedness in real-world settings and implementation science studies that examine how evidence-based strategies can be effectively translated into practice across different organizational contexts. Understanding what works and how to implement effective strategies in diverse settings will be crucial for translating research findings into improved outcomes for children and youth with medical complexities.

Conclusions

As the care of children and youth with medical complexities shifts increasingly to the home setting, understanding provider readiness becomes essential to ensuring safe, coordinated, and effective care. This scoping review will synthesize current evidence on how readiness is defined, perceived, and influenced across home care roles. Results will guide further efforts in policy, workforce training, and service planning to better equip providers and support families navigating complex home care needs.

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Authors' Contributions

Conceptualization: JT, MS, AM, and EC
Data curation: AM
Methodology: JT, MS, and EC
Project administration: JT
Writing—original draft: JT
Writing—review and editing: MS, AM, and EC

Conflicts of Interest

None declared.

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Abbreviations

JBI: Joanna Briggs Institute
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Salivary MicroRNAs as Potential Noninvasive Biomarkers for the Diagnosis of Nasopharyngeal Carcinoma: Protocol for a Scoping Review

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Abstract

Background: Nasopharyngeal carcinoma (NPC) is the fourth-most-prevalent cancer in both Indonesia and Asia. Globally, an estimated 133,354 cases and 80,008 deaths were attributed to NPC in 2020. Early diagnosis plays a key role in managing NPC. Molecules found in bodily fluids, such as saliva, contain compounds (including microRNAs [miRNAs]) that can aid in detecting diseases like NPC. More studies on the expression, role, use, and accuracy of salivary miRNAs as potential diagnostic biomarkers of NPC are needed.

Objective: This protocol provides a framework for conducting a scoping review aimed at mapping the expression, role, use, and diagnostic accuracy of specific salivary miRNAs as potential diagnostic biomarkers of NPC.

Methods: The guidelines established by the JBI will be followed, which include defining the research questions, identifying relevant studies, and selecting studies based on titles and abstracts. The process will involve charting the data; collating, summarizing, and reporting the findings; and consultation. The synthesis will specifically examine the expression, role, use and accuracy of salivary miRNAs as potential diagnostic biomarkers of NPC. Both quantitative and qualitative analyses will be performed.

Results: The selection of studies based on keywords was completed in August 2024, and the study screening and review processes were finished by November 2024. The drafting of the scoping review manuscript is currently underway. The development of this scoping review protocol was supported by funding from the Centre for Higher Education Funding and the Indonesia Endowment Fund for Education.

Conclusions: The findings of this study will offer a comprehensive overview of the expression, role, use, and diagnostic accuracy of salivary miRNAs as potential diagnostic biomarkers of NPC. The findings of this review are expected to serve as a basis for further research.

Trial Registration: Open Science Framework k3prh_v1; https://osf.io/preprints/osf/k3prh_v1

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KEYWORDS

nasopharyngeal carcinoma; microRNA; miRNA; biomarker; saliva; diagnosis

Introduction

Background

Nasopharyngeal carcinoma (NPC) is a malignant cancer that arises from the epithelium of the nasopharynx. The global incidence of NPC is rising; despite this, mortality rates and disability-adjusted life years are decreasing. The heaviest burden of NPC is in regions with a high-middle or middle sociodemographic index [1]. This cancer is prevalent in Indonesia, southern China, Southeast Asia, and North Africa [2]. Indonesia ranks as the third-highest country in terms of mortality due to NPC, reaching 3220 deaths in 2019 [3].

Diagnosing NPC is challenging. The nasopharynx is in the postnasal space, which is difficult to access with simple examinations. Additionally, the nasopharynx often has a normal lymphoid epithelium that is hard to distinguish from NPC. Clinical appearances of NPC are often nonspecific, leading to missed or delayed diagnoses [4]. Survival rates have not significantly improved in recent decades. This is due to the majority of cases being diagnosed at advanced clinical stages and the high treatment failure rates associated with late diagnosis [5]. Treatment for NPC at an early stage has a much better prognosis compared to the advanced stages [6]. Therefore, early detection is crucial in managing NPC [7].

MicroRNAs (miRNAs) are small molecules consisting of nucleotides with a single strand. These small RNA molecules regulate protein production from messenger RNA (mRNA) [8]. Research has reported that changes in miRNA expression are closely related to carcinogenesis, including in NPC. These molecules play a role in the transformation of normal epithelial cells into neoplastic cells [9]. miRNAs contribute to the increased migration and invasion of NPC cells by upregulating messenger RNA that encodes extracellular matrix proteins. Certain miRNA alterations also downregulate the expression of several tumor suppressors, and they affect cell proliferation, colony formation, migration, and invasion in vitro [10].

Saliva is an easily accessible bodily fluid and one example of a noninvasive sample that has the potential for biomarker detection in NPC. Saliva contains more than 3000 types of RNA that can be used as biomarkers for the noninvasive diagnosis of NPC [7]. Therefore, the molecules contained in saliva can potentially be used to detect several diseases, including NPC. [11]

Most previous studies have explored alternative methods for the detection of NPC. These investigations and reviews have primarily focused on tissue biopsy, various molecular markers found in tissue samples, and other invasive techniques [12-19]. There is no comprehensive review that has specifically examined and combined the use of salivary miRNAs as a noninvasive modality for NPC detection. Our scoping review aims to bridge this gap by providing an up-to-date synthesis of current evidence and identifying new areas in using salivary miRNAs as noninvasive tools for diagnosing NPC.

Early detection remains a clinical challenge due to the deep anatomical location of NPC and the nonspecific initial symptoms. While tissue biopsy remains the gold standard for diagnosis, it is invasive, often delayed, and limited by accessibility and patient compliance. These limitations point to the urgent need for noninvasive, reliable diagnostic alternatives. Recent advances in molecular oncology have highlighted the potential of miRNAs as promising noninvasive diagnostic biomarkers of NPC. Among various bodily fluids, saliva has emerged as an attractive medium for biomarker discovery due to its noninvasive collection and ease of storage. Several studies have started to look at the mechanisms underlying new diagnostic methods for NPC, but most of the results still mainly focus on tissue biopsy and other methods that are more invasive, and there is no comprehensive overview of the findings.

To address this gap and provide a comprehensive overview of the current landscape, this scoping review will explore the following topics:

- Mapping the expression of miRNA in the saliva of patients with NPC
- Mapping the role, use, and accuracy of specific salivary miRNAs as potential noninvasive diagnostic biomarkers for patients with NPC

Objectives

This protocol is designed to guide a scoping review by outlining research objectives, methods, study selection, and data extraction. The objectives of this scoping review protocol are as follows:

- Identify and understand the expression of salivary miRNAs in patients with NPC
- Understand the role of specific miRNAs in NPC as potential noninvasive diagnostic biomarkers of NPC.

Methods

Overview

This scoping review will be carried out in accordance with the JBI scoping review methodology [20]. There are six steps: (1) define the research questions; (2) identify relevant studies; (3) select the studies; (4) chart the data; (5) collate, summarize, and report the results; and (6) consult [21]. The PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses Extension for Scoping Reviews) checklist will be used [22]. Searching the literature, refining the search strategy, assessing articles for inclusion, and collecting pertinent data will be done in an iterative fashion.

Protocol Registration and Report Information

A PRISMA-ScR checklist is provided in Multimedia Appendix 1. The checklist is an effective tool for guiding the reporting of scoping studies [23]. This protocol was registered on the Open Science Framework (k3prh_v1) on April 2, 2024 [24].

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Research Questions

The research questions are as follows:

1. What is the expression of salivary miRNAs in patients with NPC?
2. What are the roles, uses, and diagnostic accuracy of specific salivary miRNAs as potential diagnostic biomarkers of NPC?

Eligibility Criteria

The research questions and eligibility criteria were designed following the population, concept, context framework (Multimedia Appendix 2). This approach supports researchers in defining the core elements of a scoping review, generating relevant search terms to investigate the topic, and choosing specific inclusion and exclusion criteria.

Population

The population of interest [25] includes patients suspected of having NPC and showing symptoms and signs of the condition but without a definitive diagnosis. For example, this could include patients with a neck lump who have not undergone a biopsy. It also includes patients from regions with a high incidence of NPC who have undergone screening to detect the disease [26].

Concept

Studies were included that investigated the diagnostic potential, biological roles, and expression patterns of salivary miRNAs as noninvasive biomarkers (ie, liquid biopsies) of NPC. This includes studies assessing their diagnostic accuracy, applicability, and clinical utility.

Context

We included research conducted in clinical or laboratory settings related to the early detection or diagnosis of NPC using salivary miRNAs.

Identifying Relevant Studies

Stage 2 of the review had 2 steps. The first involved identifying all relevant scoping reviews published up to March 2024. The search was performed in the Cochrane and Scopus databases without any time restrictions. No scoping reviews were identified focusing on salivary miRNAs as biomarkers for NPC diagnosis. The second step was to identify research on the expression of salivary miRNAs and the roles, uses, and diagnostic accuracy of specific salivary miRNAs as potential diagnostic biomarkers of NPC.

Search Strategy

A systematic search for relevant studies was conducted in 8 databases: PubMed, Google Scholar, BMJ Journal, ClinicalKey, EBSCOhost, Nature, SpringerLink, and Scopus. Gray literature was explored through GreyNet International. The selected journal databases were chosen based on their reputable indexing and accessibility from our institution, as our institution maintains subscriptions to these databases. We included Google Scholar to supplement our primary database search by identifying gray literature, preprints, and emerging studies that may not be indexed in conventional databases, which is especially useful for a developing research topic like salivary miRNAs in NPC. Additionally, manual searches were performed by reviewing references from eligible articles and other pertinent publications. All search results and the screening process were transferred to Rayyan, a free online tool for managing systematic reviews. Articles meeting the inclusion criteria were selected for inclusion (Multimedia Appendix 3). The authors used Medical Subject Headings (MeSH) terms to perform database searches with keywords associated with NPC, miRNAs, biomarkers, and saliva (Multimedia Appendix 4). The literature search strategy adhered to the PRESS (Peer Review of Electronic Search Strategies) guidelines, covering 6 essential stages: translation; use of Boolean and proximity operators; subject headings; text word searches; checking spelling, syntax, and line numbers; and applying limits and filters [27]. The search strategy was based on key elements from the PICO (population, intervention, comparator, outcome) framework to generate effective search terms [22].

Study Selection

The search results from stage 2 were transferred to Rayyan for data management, including duplicate removal and referencing. Duplicate articles were eliminated [28]. Three independent reviewers screened the titles, abstracts, and full texts according to the inclusion and exclusion criteria. Studies meeting the inclusion criteria continued to full-text screening, while those that did not were excluded. The reasons for exclusion will be detailed in the final report. Two authors conducted separate literature searches, and their results were then compared. Any discrepancies were resolved through discussion or by consulting a third researcher if necessary. Data extraction was conducted by one investigator, while a second investigator independently reviewed the data to ensure completeness and accuracy. The final selection of papers and the relevant data related to our primary question will be summarized in a PRISMA-ScR diagram [22].

Charting (Extracting) the Data

Data Extraction

Three reviewers were involved in the data extraction process to identify and discuss eligible articles for this review. Two reviewers independently conducted the literature search, and their results were compared. Any disagreements were resolved through discussion or, if needed, with the involvement of a third reviewer to make the final decision. One investigator extracted the data, while a second independently verified it for accuracy and completeness. Three experienced reviewers validated the search results. A Microsoft Excel sheet will be prepared to extract key information from the selected studies (Multimedia Appendix 5).

Data Synthesis

The JBI scoping review guideline will be used for data synthesis [29]. This synthesis focuses on the expression, role, use, and diagnostic accuracy of salivary miRNAs as potential diagnostic biomarkers of NPC. Quantitative analysis will be presented descriptively in tables, frequency distribution tables, and statistical summaries. Qualitative analysis will be presented in a narrative format to describe the expression of specific salivary

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miRNAs in patients with NPC and the role of specific miRNAs in NPC as potential diagnostic biomarkers.

We gathered key details from the included studies, such as citation information, country of origin, objectives, population, sample size, sample attributes, study methods, laboratory techniques used (eg, miRNA microarray data, reverse transcription quantitative polymerase chain reaction, the Cancer Genome Atlas), type of intervention, comparator details (including the number and characteristics of comparators), duration, outcomes, and main findings relevant to the expression, roles, uses, and diagnostic accuracy of salivary miRNAs as potential diagnostic biomarkers (ie, the review objective). Two researchers will review and validate the results of the data analysis. Any discrepancies will be addressed and resolved collaboratively.

Collating, Summarizing, and Reporting the Results

The relevant references identified in the scoping review will be imported into Mendeley, with database listings exported in RIS format, including full-text references. A PRISMA-ScR flow diagram will be used to illustrate the stages of the literature screening process for articles deemed eligible for analysis. Descriptive analysis and tabulation will be used for a narrative summarization.

Frequencies and percentages will be used to describe nominal data. The results will be presented and organized into nine main sections: (1) year of study, (2) country, (3) research objectives, (4) research methods, (5) examination techniques used, (6) population, (7) sample size, (8) comparators, and (9) key findings related to miRNAs and their relationship with the pathogenesis and diagnosis of NPC.

Consultation

Consultation can enhance the results and substantially strengthen scoping review processes and outcomes [30]. The research team will engage in discussions with consultants to review and refine the initial findings, working collaboratively to achieve a consensus. Consultation with experts in the field will be conducted after the initial data charting and initial analysis to summarize the data, validate the findings, correct conceptual errors, and enhance the interpretation of results. Biomolecular experts will be consulted if additional data or information are required.

Ethical Considerations

This review will not involve humans, animals, patients, or the public. It will compile findings from studies that have already been peer-reviewed and published. As a result, ethical clearance is not required.

Results

The selection of studies based on keywords was completed in August 2024. The study screening and review processes were finalized by November 2024. The drafting of the scoping review manuscript is currently underway, with the review expected to be completed by the end of August 2025.

This paper will highlight key findings, including study selection criteria; characteristics of the included studies; an overview of the expression, role, use, and diagnostic accuracy of salivary miRNAs as potential diagnostic biomarkers for NPC; a critical evaluation of strengths and limitations; and future research recommendations.

The scoping review is funded by the Ministry of Education through the Indonesian Educator Scholarship program (2022-2025), with no involvement from the funders in the development of the review protocol.

Discussion

Principal Findings

Early detection of NPC is crucial for improving treatment outcomes and enhancing patient prognoses. Researchers have shown that early identification of NPC leads to better treatment results, increased survival rates, and lower chances of recurrence [26].

The primary diagnostic methods for NPC rely on tissue biopsy, which is considered the gold standard. However, tissue biopsy has several limitations, as it is an invasive procedure for patients, it is not suitable for long-term monitoring due to a lack of sufficient data on the spatial and temporal variability of the tumor [13], and it can be affected by patient compliance. This highlights the importance of this scoping review protocol for identifying alternative detection methods for the future that offer comparable accuracy to tissue biopsy while being less invasive and more accessible. Thus, while tissue biopsy remains the diagnostic reference standard, our review explores the potential of salivary miRNAs as a complementary and future noninvasive tool that may overcome some of the limitations of tissue biopsy.

Saliva is a readily accessible bodily fluid and may serve as a noninvasive potential source of biomarkers, such as miRNAs, for the detection of NPC [7,26]. The use of salivary miRNAs is recognized as a noninvasive and cost-effective modality for the detection of cancers such as NPC. Saliva offers advantages in collection, transportation, and processing compared to blood or tissue samples [31].

Protocols are widely considered a crucial element in enhancing the value of research and minimizing waste [29]. Scoping review protocols are crucial, as they provide a structured framework for reviewers on the direction and implementation of the review process. A protocol can be seen as a methodological guide that outlines key components, such as inclusion criteria, the databases and search strategies for identifying studies, and the overall methodological approach [29,32]. It is strongly advised to establish protocols prior to starting a scoping review [33].

This review is expected to encounter several difficulties. This topic is a new field. The availability of articles discussing miRNAs as potential diagnostic biomarkers of NPC is still quite limited. To address this issue, the researchers plan to broaden the range of article databases used. The researchers will expand the types of studies included in this review. The novelty of this topic can also be seen as one of the advantages of this review.

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Another potential difficulty is that the medical terminology used in each article for miRNAs, NPC, and biomarkers varies greatly. To mitigate this, we will use specific keywords.

The findings of this study will offer a comprehensive overview of the expression, role, use, and diagnostic accuracy of salivary miRNAs as potential noninvasive diagnostic biomarkers of NPC. It is well established that noninvasive biomarkers of cancer can improve the quality of cancer treatment [6]. This scoping review focuses solely on the role of saliva miRNAs as potential biomarkers for the diagnosis of NPC. The findings of this review are expected to serve as a basis for further research.

Our plan for dissemination involves delivering presentations at international conferences, as well as publishing in a peer-reviewed journal. A limitation of this study is that diagnosing NPC cannot depend solely on potential biomarkers like miRNAs as the main method. Incorporating other diagnostic techniques, such as radiological imaging, will still be needed to improve the accuracy of NPC diagnosis in future research. Incorporating these variables would enable a more comprehensive analysis.

Conclusion

This scoping review protocol will provide a comprehensive overview of the existing literature on the expression of specific salivary miRNAs in patients with NPC and will map the role, use, and accuracy of miRNAs in NPC as potential diagnostic biomarkers.

Acknowledgments

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Authors' Contributions

This manuscript was conceptualized by ASW, SRI and CH. ASW drafted the manuscript. This paper was reviewed and revised by SRI, CH, DP, and SE. ASW, SRI and CH proofread the manuscript and will use the Rayyan tool for screening. The final version of this manuscript was read and approved by all authors.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-ScR (Preferred reporting items for systematic reviews and meta-analyses protocols Extension for Scoping Reviews) checklist.
[DOCX File , 48 KB - resprot_v14i1e69484_app1.docx]

Multimedia Appendix 2
PICO (population, intervention, comparator, outcome) framework.
[DOCX File , 14 KB - resprot_v14i1e69484_app2.docx]

Multimedia Appendix 3
Inclusion and exclusion criteria.
[DOCX File , 16 KB - resprot_v14i1e69484_app3.docx]

Multimedia Appendix 4
Search strategy.
[DOCX File , 18 KB - resprot_v14i1e69484_app4.docx]

Multimedia Appendix 5
Data extraction variables.
[DOCX File , 15 KB - resprot_v14i1e69484_app5.docx]

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Abbreviations

MeSH: Medical Subject Headings
miRNA: microRNA
NPC: nasopharyngeal carcinoma
PICO: population, intervention, comparator, outcome
PRESS: Peer Review of Electronic Search Strategies
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Impact of Training and Education Programs for Health Care Professionals on Video and Text-Based Meetings in Ensuring Health Care Quality: Protocol for a Scoping Review

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Abstract

Background: The use of video meetings and text-based meetings has surged and emerged as a critical tool in health care. These tools offer many benefits, such as patient prescreening, counseling services, remote patient tracking, and monitoring. With the increasing demand for technologies, health care professionals require training and educational competency development to sustain in the modern digital age. This necessitates synthesizing evidence about the existing training programs in arranging and regulating such meetings, the implementation, and reassurance about the effectiveness of these digital health meetings.

Objective: The synthesis will also uncover what training programs for health care professionals to conduct video and text-based meetings are available, and if so, how they were implemented and their impacts from the perspectives of the organization, the staff, and the patients.

Methods: The review will follow the Joanna Briggs Institute (JBI) methodology. The published studies will be searched in APA PsycInfo, PubMed, and CINAHL, and the unpublished studies through Mednar, Trove, OCLC WorldCat, Dissertations, and Theses. Studies published in English from 2003 will be considered. This review will include studies of health care professionals trained to communicate online with patients or service users, health care professionals, and health care organizations. The concept will involve online communication, such as conducting video and text-based meetings (emails, chats, and web portals), and the context will consider studies based on health care, hospitals or clinics, and primary care. A broad scope of evidence, including quantitative, qualitative, text, and opinion studies, will be considered. A total of 2 independent reviewers will screen the titles and abstracts and review the full text. Data will be extracted from the included studies using a data extraction tool developed for this study.

Results: The results will be presented in a PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) flow diagram. A draft charting table will be developed as a data extraction tool. The results will be presented as a “map” of the data in a logical, diagrammatic, or tabular form and a descriptive format. This protocol was first developed by the principal author at Linnaeus University in April 2022; however, a full search was undertaken in August 2024 as part of research development at the University of Bradford.

Conclusions: The review will identify the knowledge gaps, clarify the concepts, examine emerging evidence, and thus make recommendations for future research on video consultation and text-based meetings.

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KEYWORDS

chats; emails; health care professionals; patient encounters; text-based meetings; training and education; video conferences; video meetings; web portals

Introduction

Overview

"Telehealth is broadly defined as the use of communications technologies to provide health care at a distance" [1]. The year 2004 witnessed a revolution in telehealth with the emergence of internet-based mobile technology. This development, which included mobile phones and personal digital assistants, made the Internet more accessible than ever before [2]. It provided cost-effective ways to access internet-based technology and facilitated 2-way communications from a broader range of locations, thereby democratizing telehealth practice [3].

In the wake of the COVID-19 pandemic and the evolution of telehealth with time, the role of digital technologies in health care has been amplified. The use of computers, the internet, and mobile phones has surged, enabling remote access through video meetings and other digital tools. This surge is a direct response to the pandemic's social distancing and travel restrictions, underscoring the vital role of digital technology in maintaining health care services [4]. Along with the use of telehealth, additional forms of communication, including text-based meetings in the form of emails, chats, and web portals, have become essential to ensure that patient-related and other care-related activities can continue uninterruptedly in an unfamiliar environment [5,6]. After the COVID-19 pandemic, videoconferencing and text-based meetings have become a cornerstone of modern health care. Their easy accessibility, economic efficiency, comfort for patients, health care professionals, and the organization make them indispensable tools in the new health care landscape.

Video meetings have emerged as a critical tool in health care, facilitating family members' virtual visits to the intensive care unit. This reduces the risk of infection and ensures social distancing, thereby enhancing patient safety [7]. These meetings can also help prescreen patients, for example, those who have flu symptoms and are required to be referred to a hospital, providing counseling services virtually, such as mental health [8] and behavioral health counseling [9,10], nutrition counseling, and weight management [11]. The patients can also be followed up after a hospital stay or surgery, requiring regular checks, patient monitoring, offering advance care directives, planning, and further counseling to patients and their families. This not only ensures continuous care but also reduces the need for frequent hospital visits, thereby minimizing the risk of infection [12,13]. This service application can even benefit social care, for example, by providing a bedside doctor's visit to a nursing home, care home, or any assisted living residence without risking the patient or doctor spreading any infection [14].

The positive impact of digital technology on patient care is a reason for hope and optimism in the health care field. The improved patient outcomes may include behavioral telehealth competency improvement [15,16], behavior technician skills, patient engagement, skill acquisition [17,18], patient activation, and satisfaction [19]. Improved communication may involve connecting with patients virtually, breaking geographical barriers, and providing better accessibility for patients living in remote or underserved areas [19]. Such accessibility can minimize the need for extensive travel and enhance patient satisfaction with timely care and preventive care [16]. This powerful video consultation tool can also provide a platform for interdisciplinary collaboration among health care professionals, thus ensuring a streamlined health care process. This process may include a multidisciplinary approach, discussing complex cases, sharing insights, and making decisions for more comprehensive and patient-centric treatment plans [20,21].

With the increasing demand for technologies, tools, and applications, health care professionals are at the forefront of the digital transformation of health care. Their ability to effectively and efficiently practice medicine in the digital age is crucial [22-24]. Health care professionals, including nurses, physicians, specialists, clinicians, and practitioners, have a moral obligation to consider the consequences holistically, both intended and unintended, of digital health applications in routine clinical practice to uphold the oaths of providing patient care [25,26]. This demand further necessitates training and educational competency development for health care professionals to sustain in the modern digital age [10,27]. Developing digital health–related skills and competencies at any stage, particularly for conducting video meetings and conferences for health care professionals, is essential. The impacts of such training and education programs from the perspectives of patients, health care professionals, and the organization are of the utmost importance.

Such skills and competencies for health care professionals could include educational approaches, frameworks, or pedagogy related to understanding. This could also include applying, implementing, and evaluating the use and applications of video and text-based meetings at an individual, community, population, or society level to benefit human health and well-being. This would also answer the questions related to the ethical, legal, or social implications of health care personnel's digital skills and competencies development. Emphasis will be placed on assessing and evaluating the effectiveness and cost efficiencies of those tools and applications associated with video conferencing and how they improve health care quality.

To shape this review, we will focus on health care professionals undergoing training and education programs to conduct video and text-based meetings with patients, such as emails, chats, and web portals. This evidence synthesis will inform us about the existing types of training programs in arranging and regulating such meetings, how they were implemented, and the results of the training from the perspectives of the organization, the staff, and the patients. This proposed scoping review aligns with the strategic direction of the NHS to understand the current trends and needs of health care professionals, patients, and

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service users. It can significantly improve the quality of health care services, potentially transforming the way health care is delivered [28]. Therefore, with their potential for widespread acceptance and adoption, the review results promise to meet today's societal need, developing optimized guidance for providing information about personal and confidential patient information that can be used during a video consultation. Moreover, scoping reviews are designed to map key concepts and examine studies in a research area to provide an overview of the extent and nature of the current literature. This review aims to systematically identify and describe training programs for health care professionals to conduct online sessions with patients, making the scoping review methodology well suited to explore the available evidence without imposing strict inclusion criteria [29-31].

Despite a thorough search of reputable databases such as Campbell Systematic Reviews, the Cochrane Database of Systematic Reviews, PROSPERO, and Joanna Briggs Institute (JBI) Evidence Synthesis, no existing systematic reviews or scoping reviews on this specific topic were found. This underscores the unique and pioneering nature of our proposed scoping review, which promises to break new ground in digital health education.

Aim and Review Questions

This scoping review aims to compile and synthesize the best available evidence regarding training health care professionals to conduct video and text-based meetings (emails, chats, and web portals) with patients, service users, health care professionals, and health care organizations. We would like to know whether there are any training programs out there and, if so, how they were implemented and what their impacts are from the perspectives of the organization, the staff, and the patients.

Specifically, the review questions are as follows:

1. What training and education programs are used to train health care professionals in conducting video and text-based meetings (emails, chats, and web portals)?
2. How are those training and education programs implemented to improve the quality of care and ensure health care quality?
3. What are the impacts of such training and education programs from the perspectives of patients, health care professionals, and the health care organization?

Methods

Overview

The proposed scoping review will be conducted following the JBI methodology for scoping reviews [32].

Search Strategy

Databases will be searched for both published and unpublished studies. The approach to searching for studies for a scoping review will follow the standard 3-step method (Table 1).

Table 1. Inclusion and exclusion criteria.

Feature	Inclusion criteria	Exclusion criteria
Article type	• Conference paper • Gray literature • Early access	—[a]
Language	• English	—
Participants	• Studies involving health care staff being trained to communicate online with service users • Studies that include the implementation of training programs to train health care professionals to use online methods of communicating with service users	• Studies that do not involve health care professionals (such as university students), and studies that pertain to training health care staff using video
Concept	• Studies evaluate the impact of being trained to use online methods of communicating with patients on service users, health care professionals, and health care organizations	• Studies that do not focus on the evaluation of the training impact
Year	• Studies from 2003 through 2024	—
Context	• Studies pertaining to health care, hospitals, or clinics, primary care	—

[a]Not applicable.

The first step will be an initial limited search of relevant databases, followed by an analysis of the title and abstract text words and the index terms used to describe the article. The search for published studies will include a 2-way search strategy. One is to search the journal and reference databases, such as PsycInfo, PubMed (this database interrogates by formatting it as "MEDLINE" via PubMed), CINAHL, and Web of Science. Another is to search article-based (journal) databases, such as ACM digital library, IEEE Xplore, and BMJ Journals. The search for unpublished studies will include Mednar, Trove, OCLC WorldCat, Dissertations, and Theses. A second search will be undertaken using all identified keywords (Textbox 1) and index terms across all included databases.

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Additional search strategies, that is, citation search, specific researcher or article (eg, gold-standard article), and chain search, review reference list of the systematically selected articles, will be included to complement the search for published and unpublished papers. Studies, such as reviews (systematic, scoping, and umbrella) and letters to the editors, will be excluded. Any studies that lack ethical concerns will also be excluded. Studies published in English will be considered. Studies published from 2003 onward will be considered as the initial start for all searches to keep the dates consistent. Wireless internet-based technologies are of significant importance in the establishment of telehealth practices. To encompass more modern-day use of telehealth, this scoping review will consider research papers written in the early 2000s until the present. The collection of databases each had different publishing dates for their earliest research related to the keywords. CINAHL's earliest relevant publication was published in 1990, whereas the earliest publication on APAPsycInfo articles was published in 2003, the latest publication out of the 4 databases used. To keep the dates consistent, 2003 was selected as the initial start for all searches.

Textbox 1. A list of keywords for the search strategy.

Participants

- healthcare professional
- health worker
- healthcare staff
- healthcare provider
- clinician
- resident doctors

Concept

- video consultation
- video call
- telemedicine
- telehealth
- e-consultation
- text-based meeting
- email
- chat
- web portal
- online communication
- digital communication
- digital encounter
- training
- competenc*
- knowledge
- skill
- educational program*

Context

- healthcare
- hospitals
- clinics
- primary care

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Eligibility Criteria

This scoping review will include the following PCC (Population, Concept, and Context) framework. These mnemonics will be used as a guide (not policy); therefore, the inclusion criteria of this review will include a detailed description of types of participants, concepts, and context, as well as search strategies, data extraction, charting, analysis, and presenting the results. The eligibility criteria are listed and described in detail in Table 1.

Participants

This review will include studies of health care professionals, workers, or providers trained to communicate online with service users, other health care professionals, and health care organizations.

Concept

In this scoping review, the key concept is to evaluate the impact of online training methods of communicating, such as conducting video and text-based meetings (emails, chats, and web portals) with patients or service users, health care professionals, and health care organizations. The different formats of training will be considered (such as virtual vs in-person training and asynchronous modules vs workshops).

Context

The scoping review will consider studies based on health care, hospitals or clinics, and primary care.

Types of Sources

This scoping review will consider experimental and quasi-experimental study designs, including randomized controlled trials, nonrandomized controlled trials, before-and-after studies, and interrupted time-series studies. In addition, analytical observational studies, including prospective and retrospective cohort studies, case-control studies, and analytical cross-sectional studies, will be considered for inclusion. This review will also consider descriptive observational study designs, including case series, individual case reports, and descriptive cross-sectional studies for inclusion. Qualitative studies focusing on qualitative data will also be considered, including, but not limited to, designs such as phenomenology, grounded theory, ethnography, qualitative description, and action research. Text and opinion papers will also be considered since scoping reviews include a broad scope of evidence.

Source of Evidence Selection

Following the search, all identified citations will be collated and uploaded into EndNote 20 (Clarivate Analytics), and duplicates will be removed. A pilot test, which is conducted to ensure the effectiveness and consistency of the screening process, will be carried out. Titles and abstracts will then be screened by 2 or more independent reviewers for assessment against the inclusion criteria for the review. Potentially relevant sources will be retrieved in full and their citation details will be imported into the JBI System for the Unified Management, Assessment and Review of Information (JBI SUMARI) [33]. A total of 2 or more independent reviewers will thoroughly assess the full text of selected citations against the inclusion criteria. Reasons for excluding sources of evidence in full text that do not meet the inclusion criteria will be recorded and reported in the scoping review. Any disagreements between the reviewers at each stage of the selection process will be resolved through open and inclusive discussion or with additional reviewers. The results of the search and the study inclusion process will be reported in full in the final scoping review and presented in the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping Reviews) flow diagram [34,35].

Data Extraction

A total of 2 or more independent reviewers will meticulously extract data from papers included in the scoping review using a data extraction tool they developed. The data extracted will include specific details about the participants, concept, context, study methods, and key findings relevant to the review questions, ensuring a comprehensive review. This rigorous process instills confidence in the reliability of the results.

A draft charting table, designed to be adaptable, will be developed as a data extraction tool. The charting table will be modified and revised as necessary while extracting data from each included evidence source, ensuring the review remains flexible and responsive to the data. This adaptability ensures that the review process is responsive to the nuances of the data, providing a comprehensive and accurate review.

We will extract variables to ensure alignment with our research questions, while some variables may emerge during full-text screening; therefore, it is essential to predefine the key data extraction elements (as the protocol is structured). Clearly outlining these variables will ensure consistency in data collection, enhance transparency in the scoping review methodology, and strengthen the study's replicability. We will also follow the JBI Manual for Evidence Synthesis, which provides a basic data extraction table template to ensure completeness, methodological consistency, and adherence to best practices in data extraction [36].

Results

The results will be presented as a "map" of the data extracted from the included papers in a logical, diagrammatic, or tabular (as necessary) form and in a descriptive format that aligns with the objective and scope of the review. Some critical information that the charting table will include are (but are not limited to): year of publication, country of origin for the study, aims, study population and sample size, methodology/methods, type of intervention/comparator, duration of the intervention, and type of outcomes and how they were measured (if applicable). A clear explanation for each category will be provided, accompanied by a narrative summary describing how the results relate to the review objective and questions.

The principal author first developed this scoping review protocol as part of research development at the University of Bradford, which has been undertaking a full search since July 2024. We expect the analysis to be completed by March 2025 and the final scoping review manuscript to be submitted by August 2025,

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providing a clear timeline for the review's completion. This timeline ensures the audience is informed and prepared for the review process.

Discussion

Expected Findings

With the continuous rise of the application of digital technology, health care professionals have transformed their way of delivering patient care, collaborating, and following up on staying connected. Among all digital health care services, the most prominent advancement in recent years is the widespread usage of videoconferencing. This initiative (a scoping review) is a significant part of an international collaboration with the Region Kalmar Län, Sweden. Together, we aim to create a digital learning environment for training health care professionals to communicate with patients using only short text messages. Face-to-face workshops are crucial in this initiative, as they will enhance the digital learning environment, foster a sense of community, and promote the exchange of experiences among health care professionals. This collaboration will include patient and public involvement, arranged by the Faculty of Health Studies, University of Bradford, and already existing stakeholder involvement by the eHealth Institutes, Linnaeus University.

The improved patient outcomes may include behavioral telehealth competency improvement [15], behavior technician skills, patient engagement, skill acquisition [17], and patient activation and satisfaction [19]. Improved communication may involve connecting with patients virtually, breaking geographical barriers, and providing better accessibility for patients living in remote or underserved areas [19]. Such accessibility can minimize the need for extensive travel and enhance patient satisfaction with timely care and preventive care [16]. This powerful video consultation tool can also provide a platform for interdisciplinary collaboration among health care professionals, thus ensuring a streamlined health care process. This process may include a multidisciplinary approach—discussing complex cases, sharing insights, and making decisions for more comprehensive and patient-centric treatment plans [20].

Health care professionals need to be equipped with the skills to conduct virtual patient encounters. This involves understanding the ethical, legal, and social implications of digital health applications, particularly video and text-based meetings [22]. It also includes considerations of patient privacy and data security, the potential for increased access to care, and the impact on the doctor-patient relationship. It also involves understanding the potential for digital health to exacerbate existing health disparities or create new ones, as well as the ethical considerations of using digital tools to monitor and manage patient health. However, with time and resources constrained on the operative level in the busy sociotechnical health care environment, health care professionals cannot dedicate themselves outside their regular working hours. Their heavy workload also adds complexity to engaging and retaining skilled staff and experts within the health care organization [37]. Therefore, it is essential to set up an initial and ongoing training process on how to skillfully conduct virtual patient encounters skillfully, ideally in association with the vendors, and set aside sufficient paid time for health care professionals to be appropriately trained [28,38].

The internet, which was first used in 1983, gained popularity and usage in 1999 with the introduction of Wi-Fi on laptops and further in 2004 with the emergence of internet-based mobile technology. These milestones significantly increased the accessibility and reach of telehealth. The role of wireless internet-based technologies, such as mobile phones and personal digital assistants, in establishing telehealth practices is paramount, marking a significant shift in health care delivery [39,40]. This scoping review, aiming to capture the modern-day use of telehealth, will consider studies published from the early 2000s to the present. The significance of this review lies in its comprehensive coverage of the evolution of telehealth, providing valuable insights for health care professionals, researchers, and academics.

Strengths and Limitations

The use of the PRISMA-ScR framework is specifically designed for scoping reviews as a reporting checklist to serve as a guideline to enhance the quality, transparency, and consistency of the entire scoping review process [41] (Multimedia Appendix 1). The findings of our review, while requiring caution due to our search limitations in language and publication period, are of significant value. These findings are the result of a transparent and comprehensive strategy, which includes the standard 3-step method and gray literature for additional insights [42]. The review is a crucial step in understanding the evolution of telehealth. Each database had different publishing dates for its earliest research related to the keywords. CINAHL's earliest relevant publication was in 1990, while the earliest publication on APAPsych articles was in 2003, the latest among the 4 databases used. To maintain consistency, 2003 was chosen as the initial start for all searches, ensuring the relevance and timeliness of the research.

We acknowledge the possibility of a limited number of included studies, which may introduce bias, and we are committed to following the Evidence-based Practice Center (EPC) Methods Guide proposed by the Agency for Healthcare Research and Quality (AHRQ) to minimize this risk [43]. The scope of the review is of utmost importance, as it guides our search and interpretation of results. We must exercise caution, as most of the hits in the search may focus on training health care staff using video rather than training them on conducting video meetings with patients. It is also worth noting that articles on training health care staff in patient encounters may have been more prevalent during the pandemic (2020-2022) when digital encounters peaked.

We are committed to inclusivity to ensure the scoping review generates generalizable findings. To support the interpretation of findings and the dissemination of the review, we will hold discussions with health care professionals, patients, and the relevant public. Their perspectives are invaluable and will be integral to the review process.

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Conclusion

No current or underway scoping reviews on the topic were identified. This evidence synthesis, a collaborative effort involving researchers and practitioners, will inform us about the existing types of training programs for arranging and regulating online meetings, how they were implemented, and the training's results from the perspectives of the organization, the staff, and the patients. This review will uncover the shreds of evidence requiring diligent attention to identify the knowledge gaps, clarify the concepts, examine emerging evidence, and thus make recommendations for future research on video consultation and text-based meetings.

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Data Availability

All supporting data will be reported in the manuscript. The authors will make any raw data sets that support the results available as supplementary files.

Authors' Contributions

MSRJ contributed to conceptualization, formal analysis, investigation (second reviewer), methodology, writing—original draft, writing—review and editing, data curation. AA contributed to investigation (first reviewer), data curation, writing—review and editing, review and editing. NB contributed to investigation (first reviewer), data curation, writing—review and editing. EN contributed to conceptualization, methodology, writing—review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-ScR checklist.
[PDF File (Adobe PDF File), 645 KB - resprot_v14i1e69963_app1.pdf]

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Abbreviations

AHRQ: Agency for Healthcare Research and Quality
EPC: Evidence-based Practice Center
JBI: Joanna Briggs Institute
JBI SUMARI: JBI System for the Unified Management, Assessment and Review of Information
PCC: Population, Concept, and Context
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Conversational Systems for Social Care in Older Adults: Protocol for a Scoping Review

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Abstract

Background: Social care systems worldwide face increasing demographic and financial pressures. This necessitates exploring innovative technological solutions to enhance service delivery without substantially increasing costs. Conversational interfaces, including interactive voice response, chatbots, and voice assistants, have gained traction as a means to improve accessibility and efficiency in social care. The rapid development of large language models such as ChatGPT has further accelerated interest in conversational artificial intelligence (AI). These technologies can offer intuitive interactions, particularly for individuals with limited digital literacy. However, their real-world impact, usability, and ethical considerations in social care remain underexplored.

Objective: This scoping review aims to synthesize existing literature on the implementation, evaluation, and impact of conversational AI systems within social care settings for older adults. The review will identify best practices, current gaps, and future directions for research and implementation. Key research questions include the following: how are conversational systems implemented on a technical level, and how do older adults and their support systems use them in a social care context? What methods are used to evaluate acceptability, usability, and the impact of broad well-being in the context of older adults' social care? and What are conversational technologies' acceptability, usability, and well-being impact in the context of older adults' social care?

Methods: The review will follow the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) and Population, Concept, and Context (PCC) frameworks. A systematic search will be conducted across five databases (IEEE, Web of Science, PubMed, ACM, and Scopus) for English-language articles published from 2019 onward. Studies will be included if they empirically examine conversational systems' implementation, evaluation, or impact for older adults (aged ≥55 years) within a social care context. Two independent reviewers will screen articles and extract data. A descriptive analysis will then categorize findings across key domains such as accessibility, usability, ethical considerations, and well-being outcomes.

Results: The results will be included in the scoping review, which began in March 2025. The analysis is underway and is expected to be completed and submitted for publication by September 2025.

Conclusions: This scoping review will provide an overview of the role of conversational AI in social care, highlighting both opportunities and challenges in implementation. By synthesizing existing research, the review will inform future developments in the use of conversational agents to improve social inclusion, engagement, and well-being among older adults.

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KEYWORDS

conversational AI; social care; older adults; usability; social isolation

Introduction

Background

Social care services provide essential nonmedical support for older adults [1]. Various deployment approaches (such as community-based care programs, telecare services, and social prescribing) can offer companionship, assistance with daily activities, psychological care, and health-related guidance to older adults. However, social care systems worldwide face growing demographic and financial pressures, spurring the urgent need to leverage technological solutions to expand and improve services without prohibitive cost increases [2,3].

Conversational systems, such as interactive voice response (IVR), chatbots, and voice assistants, have emerged as a promising solution for enhancing efficiencies and broadening access to support within social care [4]. The proliferation of large language models (LLMs) such as ChatGPT has heightened public awareness of conversational artificial intelligence (AI) and accelerated the deployment of chatbots in consumer-facing services and helplines [5]. This trend coincides with evidence that information-intensive fields like health and social care may benefit substantially from voice-based interfaces, which can help streamline and personalize service provision [6,7].

Conversational technologies can simplify interactions with digital systems by offering intuitive communication, particularly for individuals with limited digital literacy or disabilities [8]. Intelligent voice assistants such as Amazon Alexa and Google Assistant have been used to provide medication reminders, offer cognitive stimulation exercises, and facilitate virtual companionship for older adults [9-11]. Similarly, chatbots have been explored to provide mental health support, help alleviate loneliness, and offer emotional assistance to older populations [12,13]. Recent studies indicate that such interfaces foster inclusion and enhance well-being among older adults, empowering them to engage more comfortably with technology [14]. This is especially relevant in settings where reliable online access or smartphone use may be challenging, as telephone-based voice interaction can reduce barriers linked to broadband availability and digital skills [6,15,16]. In social prescribing, which seeks to link individuals with nonclinical community resources that support health and well-being, the integration of voice-based conversational systems has been proposed to improve service accessibility and scale [17].

A broad literature base supports the potential of conversational systems in both health care and business contexts [18-23]. Recent systematic reviews highlight promising outcomes in user satisfaction and preliminary measures of effectiveness [19,20,23]. However, the pace of technological innovation has outstripped robust long-term evaluations of safety, efficacy, and ethical concerns [22]. Beyond technical performance, user experience factors, like trust, privacy, and perceived benefits, remain critical to adoption, particularly in sensitive domains like social care [21]. A recent systematic review of AI conversational agents in health care identified positive or mixed evidence for effectiveness and usability [24]. Still, it highlights that qualitative perceptions of these technologies could be more guarded. Many studies lacked rigorous designs or sufficient reporting, limiting conclusive assessments of their clinical and operational impact.

Given social care's complex requirements and growing resource constraints, a clear impetus exists to understand how best to use conversational systems at scale. In particular, the natural language capabilities of modern LLMs could further improve voice-based service navigation, automate routine tasks, and connect users to the right resources more efficiently [3,17]. Understanding how conversational systems can be effectively integrated into social care addresses immediate service challenges and informs the broader development of AI-based technologies tailored for sensitive, high-stakes environments.

Rationale

The existing literature broadly supports the role of digital technologies, including mobile apps, chatbots, and voice assistants, in enhancing well-being among older adults [6,14,25-27]. However, there is a notable gap in synthesized evidence regarding the specific use of conversational agents within social care, a sector already under strain due to an aging population and limited resources [28,29]. While conversational agents are considered accessible and potentially valuable in these settings [19,30], their real-world impact, effectiveness, and acceptability remain insufficiently understood. Questions persist regarding these technologies' ethical, equitable, and safe deployment in social care. A deeper understanding of their practical implementation, user experience, and broader implications is needed to ensure that they genuinely improve well-being and service accessibility.

While the boundary between social care and health care is often fluid, in this review, social care is viewed as a range of nonmedical services that support individuals' well-being, independence, and quality of life outside formal health care institutions. Accordingly, this review focuses on community-dwelling older adults rather than those residing in clinical or institutional care settings. Key goals of social care relevant to this population include reducing social isolation and loneliness, which are linked to negative health outcomes and increased mortality [31], as well as promoting autonomy through support for physical activity, nutrition, and chronic disease self-management in nonclinical settings. Additionally, as digital services increasingly mediate access to information and support, addressing digital exclusion among older adults has become an emergent component of social care policy and practice [32]. These domains collectively reflect a broader conception of well-being that extends beyond medical treatment and is increasingly recognized as essential to healthy aging.

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This review, therefore, aims to synthesize the emerging literature since 2019 on conversational systems in the age of AI (encompassing IVR, smart speakers, chatbots, and LLM-driven agents) within social care contexts to identify established best practices, current gaps, and future directions for research and implementation. To do this, the scoping review will focus on the following research questions (RQ):

- RQ1: How are conversational systems implemented on a technical level, and how do older adults and their support systems use them in a social care context?
- RQ2: What methods are used to evaluate acceptability, usability, and the impact of broad well-being in the context of older adults' social care?
- RQ3: What are conversational technologies' acceptability, usability, and well-being impact in the context of older adults' social care?

Methods

Ethical Considerations

Ethics approval is not required as data will be obtained from already published sources.

Overview of the Study Design

The review and search strategy were structured using the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) [33] and Population, Concept, and Context (PCC) frameworks (Textbox 1) [34].

Textbox 1. Population, Concept, and Context (PCC) framework.

Population

- Older adults (55 years or older)

Concept

- Voice assistants, voice interfaces, voice user interfaces, speech-based interfaces, smart speakers, conversational agents, conversational interfaces, chatbots, virtual assistants, interactive voice response

Context

- Social care, health and well-being, companionship, engagement

Search Strategy

Our review will search the following five databases to identify relevant references: IEEE Xplore, Web of Science, PubMed, ACM, and Scopus. This review focuses on technological development and user interaction, so we included computing-focused databases such as the ACM Digital Library and IEEE Xplore. To ensure broader coverage, we searched Web of Science and Scopus as general-purpose literature aggregators and PubMed to capture clinically oriented studies, including formal interventions. Relevant terms and keywords were identified for the search based on a preliminary literature examination and previous reviews on related topics. These terms were grouped into 3 themes and were searched by using the following search string structure: voice/conversational agent (abstract) AND older adults (abstracts) (Textbox 2). Given the broad nature of social care, no additional context-specific keywords were included in the search strategy. This approach was intended to maximize sensitivity and ensure that potentially relevant studies were not inadvertently excluded.

Textbox 2. Search strings.

Voice/conversational agent

"voice assistant*" OR "voice interface*" OR "voice user interface*" OR "speech-based interface*" OR "smart speaker*" OR "VUI" OR "conversational agent" OR "conversational interface" OR "conversation agent" OR "chatbot" OR "language interface" OR "virtual assistant" OR "virtual agent" OR "interactive voice response" OR "IVR"

Older adults

"older adult*" OR "senior*" OR "elderly" OR "older people" OR "aging" OR "ageing"

Inclusion Criteria

This study will include empirical research that directly examines the implementation, use, and impact of conversational systems for older adults in a social care context. To ensure relevance to recent advancements in natural language processing, only studies published from 2019 onward will be considered.

To reflect the study's aims, only papers relevant to the research questions will be included. The research must explore how conversational systems are implemented and evaluated, and their effects on older users, particularly regarding social care and well-being. While studies conducted in health care environments such as hospitals or telemedicine will not be considered, those examining the use of conversational systems for managing long-term conditions, including dementia, will be included, given their relevance to social support and daily living.

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The focus will be on research that involves direct engagement between older adults (aged ≥55 years) and conversational systems, providing insights into their practical use and reception. Studies must go beyond theoretical discussions or exploratory interviews, requiring participants to interact with the technology in a real or experimental setting.

Exclusion Criteria

Papers that do not describe original research studies, including opinions or editorials, panel discussions, conference summaries, reviews, and meta-analyses, will be excluded, as will papers that present future research plans or study protocols. Retracted articles and papers where the full text is unavailable will also be excluded. Papers that do not evaluate an entire conversational interface with older adults as study participants, such as design or development studies without user evaluation; Wizard of Oz studies without real user interactions; interviews or focus groups conducted without engagement with the technology; and studies assessing only a single feature like voice preferences rather than the overall interaction experience, will not be included.

This review focuses on text- or voice-based conversational systems where interaction occurs through natural language input. Studies involving other interaction modalities, such as smart home systems with Internet of Things integration, robots, digital pets, and avatars, will not be included. Additional interactive modalities can substantially change user experience, which aligns with other studies [35,36]. Systems integrating additional interactive elements (eg, instructional videos) will be considered only if these features do not interfere with the conversational experience.

Examples of excluded systems include smart home systems (eg, Amazon Echo that is used in a wider Internet of Things network of home devices), wearable technologies (eg, smartwatches providing health alerts without interactive dialogue), and embodied systems (eg, robots like Pepper or embodied virtual agents).

Studies evaluating technology explicitly designed for clinical or residential care settings, including hospitals, care homes, and telemedicine applications, will be excluded, as the focus of this review is limited to conversational systems in social care contexts. However, studies investigating home-based management of long-term conditions, such as dementia or Alzheimer disease, will be included if they align with social care objectives rather than medical interventions.

Finally, studies that do not explicitly connect conversational system use to well-being outcomes will be excluded. This includes research that solely examines general patterns of interaction with commercial voice assistants, such as those used for retail or routine daily tasks, unless the study specifically evaluates the system's impact on social care, inclusion, or well-being. To be included, the system must either be designed with well-being objectives in mind or assessed for its impact on improving well-being in older adults.

Screening and Article Selection

References will be exported to EndNote 21 (Clarivate), where duplicates will be identified and removed before the screening begins. The screening process will be carried out in two phases: first, titles and abstracts will be reviewed, followed by full-text screening. Two independent reviewers will screen the full texts, with any disagreements resolved through consensus. The reasons for exclusion will be recorded at each stage of screening. The screening process details will be documented in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram to ensure transparency and replicability.

Data Extraction

Three independent authors will read the full texts of all included papers and extract data into a predetermined table (see Textbox 3 for data extraction items). Any disagreements will be discussed until consensus is reached, and a senior author will be consulted if necessary.

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Textbox 3. Details of planned data extraction.

Literature

- Study title
- Author
- Year of publication
- Country of study

Technology

- Name of the system
- Does it have a voice interface? (Y/N)
- Purpose of the system as built
- Purpose of the system as evaluated
- Delivered as part of a system? (Y/N)
- How the system was used/delivered (eg, was it prescribed/self-referred)
- Technical implementation information
- Languages offered
- Target population of the system
- Target age group
- Target health condition

Evaluation

- Study design
- Main aim
- Study duration
- Sample size
- Sample demographics (age, gender, other)
- Outcomes evaluated
- Validated clinical scales used
- Other validated scales used
- Other (nonvalidated) measures
- Key findings
- How was the system used?

Data Analysis and Synthesis

A descriptive analysis will be conducted on the extracted data to provide an overview of how conversational systems are implemented and used for older adults in a social care context, how they are evaluated, and how older adults receive them. Depending on the data found in the review, specific analyses related to the outcome measures, technology used, or well-being measures may be conducted. If sufficient data is available, a thematic analysis will be conducted to summarize the qualitative data on the reception of the conversational interfaces by older adults, with subanalyses based on interface type, if applicable.

While we acknowledge the relevance of constructs such as usability, perceived usefulness, and social influence in evaluating technology acceptance, it is important to note that many existing studies on voice AI do not explicitly adopt the Technology Acceptance Model [37] or Unified Theory of Acceptance and Use of Technology [38] frameworks or similar theoretical models. Our primary aim is to outline a broad and inclusive review strategy without restricting the analysis to specific theoretical frameworks at this stage. However, we will remain attentive to these constructs during data extraction and synthesis and, where relevant, will reflect on how the included studies align with or diverge from such models.

In keeping with the methodological guidance for scoping reviews [39], this review will not include formal critical appraisal of included studies. The primary aim is to map the extent, range, and nature of research activity on this topic rather than to assess the effectiveness of interventions or synthesize outcomes in a way that would require a risk of bias assessment. As such, we will not apply formal tools. However, we will extract and report on general methodological characteristics

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(eg, study design, setting, sample size, data sources), allowing us to comment descriptively on the overall nature and apparent rigor of the evidence base.

Results

The scoping review began in March 2025, the analysis is underway, and the results will be submitted for publication by September 2025.

Discussion

Expected Results

This review aims to synthesize current knowledge about the potential of conversational systems in social care through a systematic analysis of recent medical and technology-related literature. We will examine a wide range of user studies involving older adults across various local and linguistic contexts and with technologies at different stages of development—from early prototypes to fully deployed interventions. These studies will include quantitative and qualitative findings on the impact of such systems on well-being and their usability and acceptability in different applications.

Our goal is to identify relationships and patterns in the data to determine which types of technology (eg, chatbots, IVRs, voice assistants) are most suitable for specific applications, such as addressing loneliness, improving access to health information, or supporting cognitive training. We will also explore how these applications vary across demographic groups, particularly between younger and older segments of the older adult population.

Besides age, older adults differ in education, cognitive and physical ability, mental and physical fitness, technological familiarity, race, cultural norms, and language. To reflect the importance of diversity among older adults, this review will examine how studies report participant demographics, including age distribution, education, physical and cognitive abilities, and language or cultural background. Particular attention will be paid to whether studies acknowledge these differences in their design or analysis.

In addition, we aim to examine the role of modern AI tools, such as LLMs, in the current technological landscape. While these tools offer new opportunities for more natural and engaging user interactions, they also raise significant concerns about data privacy, algorithmic bias, transparency, and trustworthiness. These issues are especially important in work involving vulnerable populations like older adults. These concerns are further compounded by this demographic's challenges with low digital literacy. Within the scope of this review, we aim to summarize how researchers and developers have approached and addressed these ethical and practical issues.

Comparison to Prior Work

Recent reviews on conversational technologies for older adults consistently highlight key benefits such as ease of use, improved companionship, and reduced social isolation [40,41]. They also agree on persistent challenges, notably learning barriers, privacy concerns, and technological limitations like speech recognition accuracy [42,43]. Furthermore, a broad consensus exists on the need for more personalized and context-sensitive solutions, especially for users with cognitive impairments [44]. Recent developments in natural language processing, with the emergence and wide proliferation of LLMs, advanced speech recognition, and improved voice synthesis, may solve some of these challenges but also pose additional challenges around privacy and ethics [45].

Additionally, many prior reviews often adopt a narrow focus, concentrating on a specific condition or technology. They demonstrate the value of conversational technologies for social care, IVR systems for data collection and service delivery [46], and smart devices aiding older adults in chronic disease management [47]. Additionally, the use of conversational systems has been examined through several targeted reviews, including telehealth solutions for chronic heart failure [48], behavioral health interventions using voice assistant technologies [23], digital coaching systems for older adults [49,50], and AI-based conversational agents promoting mental health and well-being [51]. Broader reviews provide comprehensive overviews but often concentrate on narrower subsets of literature or singular aspects like design challenges, general trends, user experience, or only commercially available technology [52-55].

We aim to offer an integrative view of recently developed or tested conversational technologies within social care, drawing explicit comparisons across diverse technologies and their practical applications. Our exploration of AI and older systems will contribute to a more in-depth understanding of the unique challenges in implementing them for social care among the older adult population.

Limitations

This review will only examine original research, meaning relevant opinions, reviews, or other short communications will not be included. As we restrict the finding to the studies with direct interactions between older people and technologies, cross-sectional studies such as population surveys, focus groups, and many participatory method studies that rely on a Wizard of Oz design are not included, despite potential usefulness for understanding such technologies' context and desirable features. Only texts available in English will be included, neglecting relevant texts in other languages and consequently introducing a potential bias toward English-speaking contexts. Additionally, the review does not include a search of gray literature, meaning it might miss conversational systems developed or deployed that were not featured in academic publishing. Nevertheless, our work will provide a valuable synthesis of existing evidence to guide future research and development.

Conclusion

This scoping review protocol outlines a systematic approach to mapping the recent literature on the use, evaluation, and reception of conversational systems within social care contexts for older adults. As social care systems worldwide contend with growing demographic pressures, there is an urgent need to understand how digital innovations, particularly voice-based

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and conversational interfaces, can support well-being, autonomy, and social inclusion among aging populations.

By following the PRISMA-ScR guidelines, this review seeks to identify the technological characteristics and implementation strategies of such systems, as well as how their efficacy, usability, and user experiences are assessed. A key emphasis will be placed on the direct interaction between older adults and these technologies in real or experimental contexts, ensuring that findings reflect actual use and reception rather than hypothetical or design-stage considerations. This review aims to provide critical insights into both the opportunities and challenges associated with these technologies, especially in the fast-paced development of related technologies in the area of natural language processing. In doing so, it will inform future research directions and contribute to developing more accessible, acceptable, and effective conversational systems tailored to the needs of older adults.

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Authors' Contributions

RBS, OH, and A Ananthakrishnan drafted the manuscript. RBS, OH, A Ananthakrishnan, A Aly, EM, CC and RBJ conceived the concept for the protocol, developed the research question, and used the Population, Concept, and Context (PCC) framework. All authors reviewed and approved the final manuscript.

Conflicts of Interest

EM is the editor in chief of JMIRx Med. All other authors declare no conflicts of interest.

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Abbreviations

AI: artificial intelligence
IVR: interactive voice response

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LLM: large language model
PCC: Population, Concept, and Context
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Interventions to Counter Health Misinformation Among Older People: Protocol for a Scoping Review

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Abstract

Background: In contemporary society, misinformation and disinformation have emerged as significant challenges, impacting various aspects of public health and societal cohesion. Some authors argue that older adults are particularly vulnerable to the effects of misinformation due to potential digital health literacy challenges. A previous review identified pedagogical approaches most commonly adopted in interventions aiming to improve the digital literacy of older adults but did not specifically address digital health literacy.

Objective: This scoping review protocol aims to explore digital health literacy interventions targeting health misinformation and designed specifically for older adults.

Methods: Following the methodology outlined by Arksey and O'Malley and the PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) checklist, this protocol delineates a systematic approach encompassing 5 stages: identification of research questions, identification of relevant studies, selection of studies, data charting, and collation of findings. Our scoping review will include peer-reviewed literature on interventions targeting misinformation for older adults. Research will be conducted on the MEDLINE (Ovid), Embase (Elsevier), PsycINFO (Ovid), CINAHL, and Web of Science databases. Gray literature will also be surveyed by performing a Google search to identify interventions and tools employed by public or private organizations, institutes, groups, or agencies. The databases and gray literature will be searched to identify relevant publications. Two members of our team will independently select publications to include in the review by using the Covidence review software (Veritas Health Innovation). The publications included will specifically address our research questions, be peer-reviewed, evidence-based, and published from January 1, 2005, in full-text English or French version. Data will be extracted from the included publications to mainly chart the intervention's objectives, types, target age groups, effectiveness, and risks reported. A thematic analysis will be conducted to categorize the study findings.

Results: The funding for this project was provided in March 2024. The research questions were identified in January 2024. The databases and gray literature search strategies were developed in February 2024. The final selection of the publications; the charting, collating, and summarizing of data; along with the reporting of findings are planned for August to September 2025. The

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findings of this scoping review will be shared through publication in an open access journal and presentations scheduled between September and December 2025.

Conclusions: This protocol will enable us to contribute to the advancement of knowledge in combating health misinformation among older adults. The results will also be utilized for the development of interventions targeting misinformation among older adults.

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KEYWORDS

misinformation; disinformation; older adults; intervention; health literacy

Introduction

Background

Misinformation and disinformation in health are significant issues because they undermine trust in public health authorities, scientists, and governments [1-4]. Health misinformation encompasses information that deviates from the established scientific consensus about a phenomenon [5]. Conversely, disinformation involves the intentional spread of inaccurate information with the aim of misleading or causing harm, while misinformation, although still incorrect, is shared without malicious intent [6]. In this protocol, the term “misinformation” will be used with regard to whether it is intended to deceive, as assessing intent can be challenging.

Health misinformation poses a threat to health, wellness, and also to democracies and social cohesion. Indeed, it can undermine trust in public health authorities, scientists, and governments; foster polarization; and fuel feelings of anxiety, fear, and depression [7,8]. Additionally, through its strong emotional appeal, it captures attention and distracts from pertinent information [9]. Health misinformation can also lead to misconceptions that may prompt potentially harmful actions [2,10]. Although its scope was highlighted by the recent COVID-19 pandemic, health misinformation is not a new phenomenon. Its negative consequences have previously been described for various public health topics such as vaccination, dietary regimes and disorders, drugs, new tobacco products, treatments for chronic diseases, and medication use [2,10-12], as well as in relation to climate change [1].

Whenever unreliable information is mentioned, the social and digital media are often called into question. Social media such as Facebook, X, Instagram, Reddit, or YouTube promote the dissemination of false information and fake news [13]. As the internet and social media become increasingly popular for finding health-related information [14], it is necessary to examine how people assess or evaluate the quality of information present on these platforms.

Older people (>60 years old) are often identified as more vulnerable to misinformation than other demographic groups due to their potential lack of necessary skills to retrieve and evaluate web-based information [15-17]. The concept of digital health literacy (eHealth literacy) is frequently mobilized in these studies. They encompass the ability to search, find, understand, and evaluate health information from electronic sources and to apply the acquired knowledge to address or resolve a health issue [18].

To address this issue, various interventions have been developed to enhance digital health literacy among older adults. Most interventions target the use of social media, online services, software, applications, and search engines and focus on older adults’ abilities to understand and evaluate web-based information [19]. A systematic review [19] identified the pedagogical approaches most commonly adopted in these interventions. The first type of approaches are formal pedagogies focused on teaching through fixed duration courses with predetermined content and objectives. These pedagogical designs often included peer learning support through collaborative tasks. The other type is pedagogies centered on the individual and their specific needs, which means they are based on the learning objectives of the participants, their experience, capabilities, or existing habits of using devices and technologies. Some studies identified in the systematic review observed an improvement in the abilities of their participants to use the internet, as well as an enhancement in their self-confidence and quality of life following the intervention, while other studies did not measure any changes. Although these interventions aimed to enhance literacy, they were not designed to specifically address digital health literacy as well as misinformation. This section can include background information such as theories, prior work, and hypotheses.

Review Objectives

The objective of this scoping review is to describe digital health literacy interventions and tools that have been implemented to counter health misinformation and that are specifically targeting older adults, thereby providing a more nuanced exploration of this critical area.

Methods

Scoping Review Methodology

Given the breadth of topics covered by our research objective, a scoping review is particularly valuable to map the body of literature because it allows for an expansive exploration of the existing literature [20]. By systematically mapping the literature, scoping reviews provide a comprehensive overview of the available evidence, including diverse sources such as academic papers and gray literature [20]. This inclusive methodology will enable researchers to identify gaps, patterns, and key concepts within the literature landscape related to digital health

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interventions developed to counter health misinformation. To enhance the potential for impact, applicability, and co-production of evidence, an advisory committee, including public health professionals from the Ministry of Health and Social Services and other organizations as well as citizen partners, will be consulted throughout the different stages of the scoping review, including the refinement of the research questions, interpretation of the results, and the development and dissemination of findings.

Protocol Design

This scoping review is based on the methodological design constructed by Arksey and O'Malley [21] and the enhanced version by Levac et al [20]. The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist [22] was also used to develop this protocol (Multimedia Appendix 1). This design consisted of 5 stages.

Stage 1: Identification of the Research Question/Questions

The research question guiding our scoping review is as follows: what digital health literacy interventions, directed specifically toward older adults, have been deployed to address or counter health misinformation? By "interventions," we are referring to various actions such as workshops, experiments, and the creation of toolkits.

Stage 2: Identification of Relevant Studies

With the collaboration of a specialized librarian (FB), we selected 5 databases relevant to our research question: MEDLINE (Ovid), Embase (Elsevier), PsycINFO (Ovid), CINAHL, and Web of Science. We identified 5 concepts to help us find relevant studies: older adults, digital health literacy, interventions, misinformation, and health. To make sure to target studies that align with the scope of our search criteria, we added the concept of "health" for PsycINFO and Web of Science, as PsycINFO is dedicated to psychology, and Web of Science encompasses multidisciplinary content. Including the term "health" in these searches helps to filter and focus on studies that are relevant to our specific area of interest in health research. We identified free-text keywords through the databases for each of the 5 concepts (Table 1) targeted by our research question.

Subsequently, we searched for corresponding controlled vocabulary employed by the MEDLINE, Embase, CINAHL, and PsycINFO databases by using their respective search tools, as this vocabulary is specific and variable between databases (Table 2). These 2 steps enabled us to establish the preliminary search strategies for each database (Multimedia Appendix 2).

Table 1. Concept-associated free-text keywords identified for search in databases.

Concept	Free-text keywords
Older adult	Older adult[a], older people, old people, old person[a], senior[a], elder[a], aged, geriatric[a]
Digital health literacy	Health literacy, medical literacy, health information literacy, eHealth literacy, digital health literacy[a], technolog[a], computer[a], ICT, information and communications technolog[a], digital illiteracy
Interventions	Interventions[a], workshop[a], training program[a], course[a], pedagogy, instruction[a], skill[a], learning, teaching, exposure[a], tool[a], resource[a], app, apps, application[a], device[a], approach[a], experiment[a], experimental research[a], prebunking, pre-emptive, debunking, reactive of fact-checking, inoculation, immunizing
Misinformation	Misinform[a], disinform[a], dis inform[a], mis inform[a], malinfor[a], mal infor[a], infodem[a], infobesit[a], rumor[a], rumour[a], hoax[a], fallac[a], conspirac[a], myth, myths, gossip[a], skeptic[a], sceptic[a], infoxication, veracity, polariz[a], polaris[a], controvers[a], denial[a], dessent[a], contest[a], deny, denier[a], alarmism, contrarianism, reinformation, false belief[a], falsehood[a], trolls, post-truth, misconception, deception, ((inaccurate, false, fake, poor quality, low quality, misleading, distorted) AND (information[a], news, communication[a]))
Health	Well-being, health, medical, public health, treatment[a]

[a]Various terminations are included.

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Table 2. Concept-associated controlled vocabulary search terms identified to search in databases.

Concept	Controlled vocabulary search terms in the databases			
	MEDLINE	Embase	PsycINFO	CINAHL
Older adult	Aged, 80 and over	Aged, very elderly	Older adulthood, geriatric patients, aging	Aged, 80 and over
Digital health literacy	Health education, health literacy, internet, digital technology, computers, computer literacy	Health literacy, internet literacy, eHealth literacy, computer literacy, social media, information technology, communication technology, digital technology, computer, technology, health education	Digital literacy, health literacy, health promotion, technology, health information, health knowledge, health education, digital information, digital health resources, internet, computers, internet usage, computer usage, information and communication technology	Health literacy, computer literacy, social media, digital technology, digital health, health information, health education
Interventions	Computer user training, problem-based learning, simulation training, cognitive training, internet-based intervention, education, mentoring, teaching, learning, media exposure, software, mobile applications, immunization	Intervention study, web-based intervention, workshop, simulation training, learning, experiential learning, skill, mobile application, devices, human experiment, experimentation, immunization	Group intervention, intervention, training, ability, adult learning, learning, cooperative learning, teaching, exposure, computer applications, mobiles applications, experimental methods, prevention, immunization	Seminars and workshops, community programs, peer assistance programs, skill acquisition, learning, teaching, media exposure, information resources, mobile applications, experimental studies, quasi-experimental studies, immunization, immunization programs
Misinformation	Deception, disinformation, infodemic, denial	Misinformation, disinformation, propaganda, information overload, infodemic, conspiracy theory, denial, deception, public opinion, information dissemination	Misinformation, deception, information dissemination, conspiracy beliefs, conspiracy theories, gossip, skepticism, denial, false beliefs	Misinformation, disinformation, information avoidance, information explosion, medical mistrust, denial (psychology), propaganda, deception, scientific misconduct
Health	N/A[a]	N/A	Well-being, health, health attitudes, health behavior, public health, public health attitudes	N/A

[a]N/A: not applicable.

In the next phase, we will perform a gray literature overview (reports, theses, working papers, blogs, research data) to identify interventions and tools employed by public or private organizations, institutes, groups, or agencies that may not appear in scientific literature and that are related to our research concepts. Free-text keywords related to our concepts identified for the bibliographic database search strategies (Table 1) will be used to search through Google. The first 100 Google search results will be screened for relevant publications. Gray literature searches will be documented in a spreadsheet, which will table the following information for each search: date of search, terms or expressions used in search, number of results found, number of results retained, and comments. We will assess the relevance of the publications from the gray literature by using a simplified checklist itemizing authority, accuracy, coverage, objectivity, date, and significance. The searching through the databases and the gray literature will be performed by a research professional (VT).

Stage 3: Selection of Relevant and Reliable Studies

The selection of the publications will be piloted on a subset of potentially relevant sources and thereafter performed independently by 2 members of the research team: the principal investigator (MV) and a research professional (VT). Publications identified in stage 2 will be exported into the bibliographic management software EndNote and the Covidence platform (Veritas Health Innovation). Using Covidence, we will remove duplicates and select the publications relevant to our research based on our inclusion and exclusion criteria (Table 3) following Levac et al's [20] methodological design. Team discussions will be held to address studies that present challenges for inclusion or exclusion. We will refine our research strategies if necessary.

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Table 3. Criteria for including or excluding publications in the review.

Criteria category	Inclusion criteria	Exclusion criteria
Type of intervention	• Interventions or tools to counter health misinformation among older people.	• Interventions or tools to counter other type of misinformation (like political) among older people or other groups of populations. • Interventions or tools to counter health misinformation among groups other than older people. • Ideas for interventions or tools (that have not been performed).
Publication information (authors' details and publication date)	• Provides author's name and publication date.	• Does not provide publication date or author's name.
Publication date	• Published on or after January 1, 2005.	• Published before January 1, 2005.
Text version	• Available in full text version.	• Not available in full text version.
Language of publication	• Available in English or French.	• Only published in language other than English or French.
Study type	• Original paper, systematic literature review, meta-analysis, scoping literature review, textbook, book, thesis, or report.	• Opinion piece, media article, written or video commentary, editorial, letter to the editor, dissertation, or conference proceeding.

Publications covering interventions or tools to counter health misinformation among older people will be included in the review in order to answer our research question. Publications covering interventions or tools to counter other types of misinformation (such as political misinformation within the context of elections) will be excluded, as our focus is solely on health misinformation. We will also exclude interventions dedicated to populations other than older adults. Publications suggesting ideas of interventions or tools (rather than describing interventions that have been implemented or tested) to counter health misinformation will be excluded. Publications not providing the author's name and publication date will not be included, as they do not provide all the information required for data extraction. Material not available in full text version or only published in languages other than English or French will be excluded due to our inability to access full content. We chose the start date of January 1, 2005, as it marks the beginning of an increase in internet usage among older adults and interest in research literature regarding media literacy among this group of population [19,23]. Peer-reviewed original papers, systematic literature reviews, meta-analyses, and scoping literature reviews will be included, as the review process provides assurance of the validity of these evidence-based publications. Textbooks, books, theses, and reports will also be considered, as they are also typically reviewed. Quantitative, qualitative, and mixed methods studies will be included to cover the various aspects of our research concepts. Primary sources will be excluded if they have already been incorporated into a selected evidence synthesis, unless the data they contain are not reported in the evidence synthesis. Opinion pieces, media articles, written or video commentaries, editorials, letters to the editor, dissertations, or conference proceedings will not be considered, as they may not have been reviewed or be evidence-based. References cited by relevant publications selected from bibliographic databases and gray literature could also be examined for additional publications to include. Given the exploratory nature of scoping reviews, it is possible that research, screening, and selection of publications may lead to the identification of new research terms or concepts or new data sources [24]. The methodology may then need to be adapted accordingly. In this case, adjustments will be noted, justified, and reported through the final review.

Stage 4: Charting the Data From the Included Studies

To document the relevant information related to our research question, we will complete a data extraction form for each included publication. As this form is being iteratively developed for this specific review, a preliminary version, which will be subject to further adjustments, is presented here (Textbox 1).

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Textbox 1. Preliminary data extraction form.

Title of publication:
Type of publication:
Author's name:
Year of publication:
Objective of the intervention:
Type of intervention:
Target age groups:
Effectiveness of the intervention:
Risks of the intervention:
Research limits:
Other:

As proposed by Pollock et al [25], the extraction form will be pilot tested independently by each of the 2 reviewers for 10 of each type of publication included in the review to ensure that the form is accurate and to make any necessary adjustments. Any discrepancies revealed by the tests will be discussed and resolved by consensus among the 2 reviewers, consulting a third team member if required. Revisions to the extraction form and justifications will be noted and reported in the final review.

Using the revised extraction form, the first reviewer will extract the data from each included publication. Data extracted from each publication will be screened by the second reviewer to validate accuracy and completeness [25]. If the extraction form needs to be further updated as part of an iterative process, these revisions and justifications will be also be noted and reported. Any inconsistencies arising occurring during data extraction will be discussed and settled by consensus between the 2 reviewers, consulting a third team member if necessary. Authors of the publications in this study could be contacted to retrieve and confirm data when needed.

The final version of the extraction form accompanied by the list and the definitions of the items extracted from publications will be made available in the final review. Data assumptions and simplifications will also be documented and presented in the final review.

Stage 5: Collating, Summarizing, and Reporting the Findings

An overview and description of all the included publications and extracted data will be presented in the final review. For each publication, the citations, characteristics, and relevant data will be reported in a tabular format. To collate those results, we will utilize qualitative methods such as thematic analysis to regroup data and identify key themes relevant to our research question and generate meaningful insights.

This scoping review will provide an overview on a broad range of interventions and tools that have been implemented to counter health misinformation and that are specifically targeting older adults. This scoping review will allow us to compare the different existing strategies, their advantages and disadvantages, their effectiveness, and their effects on older adults. Subsequently, the results will be summarized and reported in a clear and concise manner by using a narrative format or visual representations such as maps, diagrams, or tables, ensuring that important findings are accurately represented.

Results

This project was funded in March 2024. The identification of the research questions was achieved by the research team in January 2024. The literature search strategies for the bibliographic databases were iteratively developed in February 2024 by FB, VR, VT, and MV. The gray literature search strategy was developed in July 2024 by VR and MV. The search through the bibliographic databases and the gray literature is planned for May to July 2025. The final selection of the publications; the charting, collating, and summarizing of data; as well as the reporting of findings is scheduled for August to September 2025. The findings of this scoping review will be disseminated through publication in an open access journal and presentations planned for September to December 2025.

Discussion

Expected Outcomes

Our results will enhance the comprehensive overview of the literature on misinformation and contribute to advancing understanding in this field. The results will be valuable for guiding communication professionals dedicated to combating misinformation and effectively tailoring their message to the targeted population. Additionally, this scoping review marks a preliminary step in a project aimed at collaboratively developing interventions or tools with older adults to combat misinformation. The findings of this scoping review will serve as a foundational element in this endeavor.

Limitations

This protocol for a scoping review has a few limitations. Language restrictions to English and French may result in the exclusion of relevant studies published in other languages. Since this scoping review aims to map the overall landscape of research on digital health literacy interventions and tools designed for older adults to counter health misinformation, approaches and definitions of misinformation used by the

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different included publications may vary substantially. This could make it challenging to extract data, collate, summarize, and collectively report the findings gathered from the different publications. Following delineated data extraction and analysis processes will facilitate the synthesis of the findings.

Conclusions

This scoping review protocol will outline a comprehensive approach to investigate interventions aimed at addressing health misinformation among older adults. By recognizing the pervasive impact of misinformation on public health and social dynamics, this scoping review ensures a broad exploration of diverse literature sources, including gray literature, to capture a comprehensive understanding of the existing interventions. This scoping review aims to contribute to the advancement of knowledge in the field of misinformation, with implications for communication professionals and policy makers tasked with addressing this multifaceted challenge. Moreover, the protocol sets the stage for future collaborative efforts to develop targeted interventions tailored to the needs of older adults in combating misinformation. Thus, this scoping review not only serves as a critical exploration of existing literature but also as a foundational step toward meaningful intervention development and implementation.

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Authors' Contributions

Conceptualization: MV (lead), VR, VT, IS, ED, and AT (equal)
Funding acquisition: MV
Methodology: MV (lead), VR, VT, FB, IS, ED, and AT (equal)
Project administration: MV
Resources: MV
Supervision: MV
Writing – original draft: MV (lead), VR, and VT (supporting)
Writing – review and editing: MV (lead), VR, VT (supporting); FB, IS, ED, and AT (equal)

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-ScR checklist.
[PDF File (Adobe PDF File), 550 KB - resprot_v14i1e74138_app1.pdf]

Multimedia Appendix 2
Preliminary database search strategies.
[DOCX File , 20 KB - resprot_v14i1e74138_app2.docx]

Multimedia Appendix 3
Examples of prompts similar to those used for proofreading.
[DOCX File , 13 KB - resprot_v14i1e74138_app3.docx]

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Abbreviations

PRISMA-ScR: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Integrating Lived Experience Into Medical Education Related to Children With Medical Complexity or Developmental Disabilities: Protocol for a Scoping Review

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Abstract

Background: Involving people with lived experience in medical education can benefit them, their caregivers, and medical students, and may particularly impact medical education about children requiring comprehensive, individualized, multidisciplinary care, including those with medical complexity or developmental disabilities. Yet, there is no summary of how children with medical complexity or developmental disabilities, or their families or caregivers have been included in medical education for medical students, residents, and fellows. To advance the effective inclusion of lived experience in medical education related to this patient population, a synthesis of existing literature is needed.

Objective: This scoping review aims to identify and synthesize the literature on including the lived experiences of children with medical complexity or developmental disabilities and their caregivers in medical education, where in the curricular development process they are involved, and the level of engagement of people with lived experience in the process.

Methods: To complete the scoping review, MEDLINE, Scopus, PsycINFO, ERIC, Academic Search Premier, and Google Scholar were searched for studies investigating patient and caregiver involvement in medical education related to children with medical complexity or developmental disabilities. Studies involving continuing professional development or patients who are not children with medical complexity or developmental disabilities were excluded. Data will be extracted to identify the stage of curriculum development in which lived experience is included based on Kern's 6-step approach, and to examine the level of engagement in medical education of children with medical complexity or developmental disabilities, their families, or their caregivers. Data from the scoping review will be presented in tables, diagrams, or matrices to demonstrate how lived experience caring for children with medical complexity or children with developmental disabilities has been included in the 6 steps of curriculum development and to characterize the level of engagement of people with lived experience in this process. Descriptive analysis will be performed to identify the findings from the included sources pertaining to the research objective.

Results: Database searches were completed on April 19, 2024. In total, 4382 unique articles were identified and screened against the eligibility criteria in July 2024, resulting in 30 articles being included in the scoping review. Data extraction began in July 2024.

Conclusions: Our results will identify areas of improvement for medical education pertaining to the care of children with medical complexity or developmental disabilities. The findings will support and contribute to the development of medical school curricula surrounding care for children with medical complexity and children with developmental disabilities that incorporate people with lived experience in crucial roles during curriculum development. These partnerships with people with lived experience will promote more patient- and family-centered physicians, leading to better care of children with medical complexity and children with developmental disabilities.

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(JMIR Res Protoc 2025;14:e64911) doi:10.2196/64911

KEYWORDS

family as educators; family as faculty; family-centered; partnership; pediatrics; medical education; family engagement in learning; children with medical complexity; children with developmental disability

Introduction

Background

The quality and outcomes of health care are impacted by providers' knowledge and attitudes. In addition to understanding the clinical aspect of a patient's diagnosis, a provider's understanding of the patient and family's lived experience may play a role in the quality of health care provided. One way by which this could be improved is through medical education. Involvement of people with lived experience, such as patients, their families, or their caregivers, in medical education is possible and can provide new insights. Furthermore, patient and caregiver experiences have already been included in multiple settings, including both educating physicians-in-training (medical students, residents, and fellows) [1-8], as well as educating practicing physicians in the setting of continuing professional development (CPD) [9-11].

Through the incorporation of people with lived experience in curriculum design for CPD, Tajani et al [9] identified experiences that would have otherwise been left out of the curriculum, shaping the curriculum objectives to have a stronger patient focus, as well as emphasizing the role patients and their families play in their care. Unique student experiences were also observed when including adult patients in medical student education. Incorporating patient experiences into medical student education has been shown to provide students with unique insights and help them challenge assumptions they held before interacting with patients and their stories [3]. Furthermore, learning directly from patients and their caregivers has been demonstrated to help students build relationships with patients and understand challenges faced by caregivers [4], with other studies finding that students involved in sessions with patients agreed that the sessions had increased their understanding of the patient experience and the application of patient- and family-centered care [6,8]. This was also observed in the pediatric setting [2], with students who interacted with patients and caregivers writing reflections that were more patient-focused than those who did not [1].

Although there is a body of literature supporting the integration of people with lived experience's experiences in education related to adult and pediatric patients, children with medical complexity and children with developmental disabilities make up a specific subset of pediatric patients who have different experiences and care needs. Cohen et al [12] define children with medical complexity as children who have: significant health care service needs as identified by their family; at least one chronic condition that is severe or associated with fragility, whether it is diagnosed or unknown; limited function, often requiring support from technology; and high health care usage, including frequent hospitalizations, surgeries, or involvement of multiple specialists. Children with developmental disabilities have chronic impairments that are mental, physical, or both; the conditions are considered severe, must be present by the age of 22 years, are unlikely to resolve, impact multiple aspects of daily living, and lead to individuals requiring a combination of support services [13].

Due to the various needs of children with medical complexity and children with developmental disabilities, the incorporation of caregiver and patient experiences in medical curriculum development is critical. This has been demonstrated in settings of CPD [10,11], but there is a gap in understanding how it has been included in medical education for physicians in training. The methods and outcomes of involving people with lived experience in medical education must be identified to allow for effective advancement of curriculum development, specifically when designing curriculum pertaining to treating children with medical complexity and children with developmental disabilities.

As identified by previous work, the current literature on lived experiences and partnership with people with lived experience in medical education surrounding caring for children with medical complexity and children with developmental disabilities has not used consistent terms and keywords, making it difficult to identify what research and curriculum design has been completed to date [14]. A preliminary search for existing scoping reviews related to medical education involving children with medical complexity, children with developmental disabilities, and their families and caregivers was conducted in PubMed. In addition, 3 scoping reviews investigating similar education strategies were identified [15-17]; however, none of them involved children with medical complexity or children with developmental disabilities specifically. The purpose of this scoping review is to identify and synthesize literature on people with lived experience's involvement in medical education related to children with medical complexity and children with developmental disabilities.

Review Questions

Information known related to involving people with lived experience who are children with medical complexity or children with developmental disabilities, their families, or their caregivers in medical education is listed in Textbox 1.

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Textbox 1. Specific questions guiding the scoping review.

- What has been reported pertaining to the involvement of people with lived experience in medical education regarding children with medical complexity and children with developmental disability?
- What were the purposes of including people with lived experience in medical education regarding children with medical complexity and children with developmental disability?
- How were people with lived experience involved in the medical curriculum regarding children with medical complexity and children with developmental disability?
- What outcomes were measured and observed related to the impact of involving people with lived experience in medical education regarding children with medical complexity and children with developmental disability?

Methods

Overview

The Joanna Briggs Institute methodology for scoping reviews will be used for conducting the proposed scoping review [18]. The PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) will be used to report the proposed scoping review [19]. The PRISMA-P (Preferred Reporting Items for Systematic reviews and Meta-Analysis Protocols) guidelines were followed for this protocol [20]. The completed PRISMA-P checklist can be found in Multimedia Appendix 1.

Search Strategy

The review team collaborated with a research librarian (LC) to develop and execute a comprehensive search of the literature using controlled vocabulary and title or abstract terms related to the integration of the experiences of children with medical complexity and their parents or caregivers in medical education. The search was developed in MEDLINE (EBSCO) and translated into the following databases: Scopus (Elsevier), PsycINFO (EBSCO), Education Resource Complete (EBSCO), Education Resources Information Center (EBSCO), and Academic Search Premier (EBSCO) on April 19, 2024. A Google Scholar search was performed, and the first 200 results sorted by relevance were exported for screening. No date, language, or other filters were applied to the results. The full strategy for each database has been included in Multimedia Appendix 2.

Eligibility Criteria

The eligibility criteria were determined based on the purpose of this scoping review. Multiple criteria were identified based on the target population, concept, and context. Table 1 identifies the eligibility criteria, with further discussion of the criteria found below.

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Table 1. Eligibility criteria.

	Include	Exclude
Population	• Medical students • Pediatrics residents • Fellows • Interprofessional education groups, including any of the above medical learners	• Other health care professionals (nurses, physician assistants, etc) • Practicing physicians
Concept	• Patients, family, or caregivers sharing lived experiences in the curriculum • Patients, family, or caregivers involved in curriculum development or design • Need for patient, family, or caregiver involvement in the curriculum • Patients are children with medical complexity or developmental disabilities • Families are those of children with medical complexity or developmental disabilities • Caregivers are those of children with medical complexity or developmental disabilities	• Geriatric patients • Adult patients • Older patients • Patients with chronic illness who are not medically complex or have developmental disabilities • Families of the above patient populations • Caregivers of the above patient populations
Context	• Medical school • Clerkship • Residency • Fellowship	• Professional development • Continuing medical education • Patient education • Family or caregiver education
Source type	• Peer-reviewed papers	• Non–peer-reviewed papers • Conference proceedings • Conference abstracts • Grey literature • Editorials • Commentaries • Books
Language	• English	• All other languages, including those translated to English
Location	• N/A[a]	• N/A

[a]N/A: not applicable.

Participants

The review will include any studies involving the education of medical students, pediatric residents, or fellows in pediatric specialties. Studies investigating interprofessional education involving the previously mentioned groups will also be included. Studies focusing on other health care professionals were excluded due to the differences in roles of different professionals. Studies focused on the further education of practicing physicians were also excluded.

Concept

This scoping review will focus on the inclusion of children with medical complexity, children with developmental disabilities, families, and caregivers in medical education curricula. Studies that relate to people with lived experiences' involvement in curriculum development or the active participation of patients, families, or caregivers through sharing their lived experiences were included. In addition, studies investigating the need to involve patients, families, and caregivers in medical education curriculum were included. All studies involving families and caregivers that were included pertain to families and caregivers of children with medical complexity and children with developmental disabilities. Patients, families, and caregivers of pediatric patients who are not considered children with medical complexity or children with developmental disabilities were excluded, as were the lived experiences of patients, families, and caregivers of adult patients.

Context

This scoping review will focus on medical education and curricula. This was limited to the setting of learning in medical school, clerkship, residency, and fellowship. Continuing medical education coursework and other CPD trainings were excluded. Patient, family, and caregiver education were also excluded.

Types of Sources

The purpose of the scoping review is to gain an understanding of what information is known pertaining to people with lived experiences' involvement in medical education surrounding children with medical complexity and children with developmental disabilities. To do this, the scoping review will include peer-reviewed experimental studies and analytical observational studies. Editorials, commentaries, abstracts, and conference proceedings were excluded.

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Evidence Screening and Selection

Results were downloaded to a citation management software (EndNote [Clarivate]) and underwent manual deduplication by LC using the method described by Bramer et al [21]. Unique records were uploaded to the Covidence (Veritas Health Innovation) screening platform for independent review by 2 independent reviewers. Disagreements between the reviewers were resolved by a third reviewer. Full text review was then completed for studies that were not excluded based on the abstract and title. This step was also completed by 2 independent reviewers, with any discrepancies being resolved by a third reviewer. The final exclusion process will be reported using a PRISMA-ScR flow diagram [19].

Data Extraction

Data found in the papers included in the scoping review will be extracted by 2 independent reviewers using Covidence software (Veritas Health Innovation). The data extracted will include the identified need for people with lived experience involvement in medical education surrounding children with medical complexity and children with developmental disabilities, as well as how their experiences are included in medical curricula. Data involving the outcomes for medical students, residents, and fellows after taking part in these curricula will also be extracted.

A draft of the data extraction form is attached (Multimedia Appendix 3). The form will be altered throughout the extraction process as needed, with any alterations being discussed in the scoping review. Disagreements that arise between the reviewers during the data extraction process will be resolved by a third reviewer. Risk of bias will be considered by identifying papers' funding sources and other possible conflicts of interest.

Analysis

A total of 6 levels of people with lived experience's engagement were defined, as adapted from frameworks created by Smits et al [22], Burns and the National Maternal and Child Health Workforce Development Center [23], McCloskey et al [24], and Shelton et al [25]. These domains were leadership, collaborative, advisory, consultative, give information, and receive information. Details about the characteristics of each level can be found in Multimedia Appendix 4. The steps of children with medical complexity and children with developmental disabilities medical curriculum development that will be mapped to are Kern's six-step approach: (1) problem identification and general needs assessment, (2) targeted needs assessment, (3) goals and objectives, (4) educational strategies, (5) implementation, and (6) evaluation and feedback [26]. The extracted data will be analyzed using these 2 frameworks to understand people with lived experience's engagement in curricula surrounding children with medical complexity and children with developmental disabilities, as well as the steps in curriculum development that lived experience was included.

Results

The database search was completed on April 19, 2024. A total of 7466 articles were initially identified, and duplications were removed. After deduplication, 4382 unique articles were screened. Screening began on April 19, 2024. During the screening process, 4255 articles were excluded based on the title and abstract, with an additional 97 being excluded after full text review. The screening process concluded in July of 2024. In total, 30 articles met the inclusion criteria and will undergo data extraction, with publication dates ranging from 1998 to 2023. More details regarding the screening process can be further reviewed in the PRISMA-ScR flow diagram below (Figure 1).

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Figure 1. PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) flow diagram.

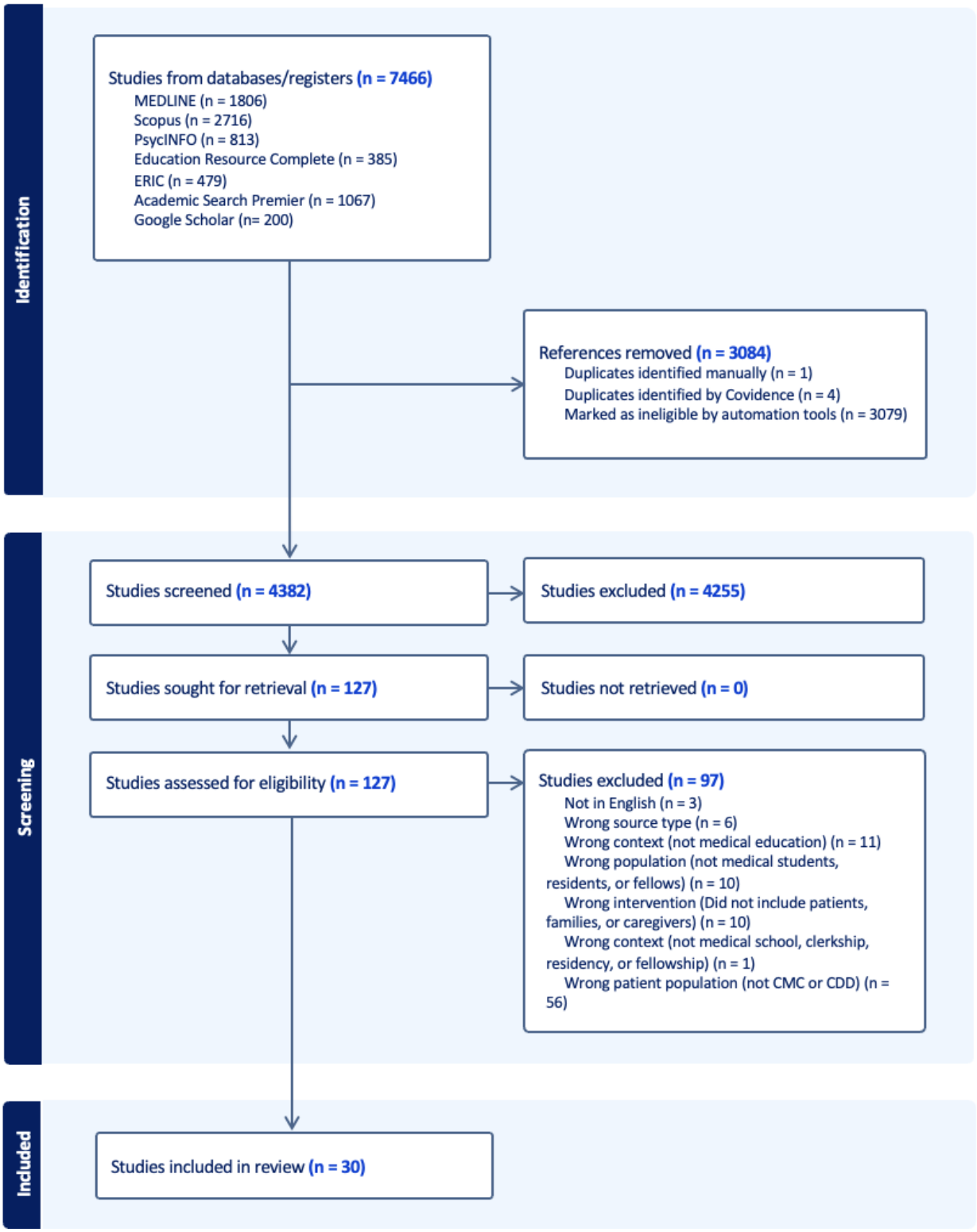

Upon completion of the data extraction, the extracted data will be presented in diagrams or tables to best illustrate the findings related to the review questions. The mapping of people with lived experience engagement against Kern's steps will be presented in a matrix (Multimedia Appendix 5). In addition to the diagrams or tables and matrix, narrative descriptions of the findings will be included. The findings will be published in a scoping review.

Discussion

Principal Findings

There is evidence supporting the benefits of including people with lived experience in medical education, from increased student comfort in discussing sensitive topics [3] to improvement in medical students' abilities to form relationships with patients [4]. Despite this, there is a gap in knowledge

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regarding people with lived experience's involvement in medical education specific to children with medical complexity and children with developmental disabilities. This scoping review will identify the ways by which people with lived experience have been involved in medical education curriculum regarding children with medical complexity and children with developmental disabilities, what part of the curriculum they were involved in, and their level of engagement. Identifying how people with lived experience are included, such as interviews or home visits, can set the groundwork for the implementation strategies of future curricula. Identifying how people with lived experience are involved will provide insight into how early in the curriculum process people with lived experience should be involved. The levels of engagement of people with lived experience identified by this review will both highlight the importance of people with lived experience's involvement and will also identify areas in which there is room for more engagement of people with lived experience in education surrounding the care for children with medical complexity and children with developmental disabilities. Outcomes of the curricula identified by the scoping review will highlight which of these methods are most successful in improving future physician readiness in providing quality care for children with medical complexity and children with developmental disabilities. By identifying how and when people with lived experience can best be partnered with in medical education regarding children with medical complexity and children with developmental disabilities, the authors hope that new curricula will be developed based on these findings to create educational experiences that will best prepare future physicians to provide care for this patient population. These findings will support curricular development across institutions, increasing the reach of improved training and care for children with medical complexity and children with developmental disabilities.

Limitations

The scoping review results will be limited by the language selection, which may exclude relevant literature that is not in English. Furthermore, gray literature will be excluded, and therefore, the results may miss medical education contributions from patients, family, and caregivers. As with any scoping review, there is also the potential that there is literature surrounding this subject that was not encompassed by the keywords used for the literature search.

Conclusions

It is the authors' understanding that this is the first scoping review focused on the involvement of children with medical complexity, children with developmental disabilities, their families, or their caregivers in medical education. It will fill in the knowledge gaps regarding what curricula regarding care for children with medical complexity and children with developmental disabilities are currently involving people with lived experience, as well as how and when people with lived experience can be involved in curricula in ways that strengthen the learning for future physicians. This scoping review will set the groundwork for the development of future curricula that can then be disseminated across the country with the hopes of improving care for children with medical complexity and children with developmental disabilities by improving the education of their future providers.

Acknowledgments

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Authors' Contributions

Conceptualization: GC, HK, DG, and NP
Data curation: LC
Funding acquisition: HK, DG, and GC
Investigation: NP, GC, DG, and HK
Methodology: NP, GC, DG, HK, and LC
Project administration: GC
Software: LC and NP
Supervision: NP and GC
Visualization: LC and NP
Writing—original draft: NP, GC, DG, HK, and LC
Writing—review and editing: NP, GC, DG, HK, and LC

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols) checklist adapted from Shamseer et al [20].
[DOCX File , 31 KB - resprot_v14i1e64911_app1.docx]

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Multimedia Appendix 2
Full search strategy used for MEDLINE, Scopus, PsycINFO, ERIC, Academic Search Premier, and Google Scholar.
[DOCX File , 16 KB - resprot_v14i1e64911_app2.docx]

Multimedia Appendix 3
Draft of data extraction form used to complete the scoping review.
[DOCX File , 17 KB - resprot_v14i1e64911_app3.docx]

Multimedia Appendix 4
Definitions for the levels of engagement of people with lived experience (PLE) in medical education.
[DOCX File , 14 KB - resprot_v14i1e64911_app4.docx]

Multimedia Appendix 5
Draft of intervention matrix to map people with lived experience (PLE) engagement levels against the step in curriculum development they are involved in.
[DOCX File , 17 KB - resprot_v14i1e64911_app5.docx]

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Abbreviations

CPD: Continuing professional development
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analysis Protocols
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Examining the Influence of Demographic and Socioeconomic Factors on Disparities in Health Care App Usage: Protocol for a Systematic Scoping Review

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Abstract

Background: The rapid proliferation of health care apps has transformed health care delivery, providing patients with unprecedented access to medical information and services. These apps facilitate remote consultations, appointment scheduling, medication reminders, and health monitoring, thereby enhancing patient engagement and improving health outcomes. Despite the widespread benefits, disparities in the adoption and usage of health care apps persist, influenced by demographic and socioeconomic factors. Understanding these disparities is crucial for designing interventions that promote equitable access to digital health tools.

Objective: This systematic review aims to identify and synthesize empirical studies on health care app usage disparities, focusing on demographic and socioeconomic factors. This review seeks to inform stakeholders about the key factors influencing app usage and provide insights to improve accessibility and effectiveness. Specifically, this review addresses the following research questions: (1) what are the key demographic and socioeconomic factors associated with health care app usage disparities? (2) how do these factors influence the adoption and utilization of health care apps? and (3) what are the barriers to and facilitators of effective use of health care apps?

Methods: This review will adhere to PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines. Eight databases—ACM Digital Library, CINAHL, IEEE Xplore, ProQuest Nursing and Allied Health Journals, PubMed/MEDLINE, ScienceDirect, Scopus, and Web of Science—were searched for studies published in English between January 1, 2014, and June 17, 2024. Eligibility criteria include journal papers focusing on health care app usage across different demographic and socioeconomic groups. Data management will involve using Zotero for reference management and Excel for screening and eligibility assessment. Two reviewers will independently extract the data and assess the study quality and risk of bias. Descriptive statistics will be used to summarize the study characteristics.

Results: As of June 2025, the review is in the screening stage. The completion of data collection is anticipated by November 2025. The final results are expected to be published by late 2025. This review aims to provide comprehensive insights into the disparities in health care app usage.

Conclusions: The findings of this systematic review will offer valuable insights into demographic and socioeconomic disparities in health care app usage, informing stakeholders on how to address these disparities. By identifying the factors influencing app adoption and usage, this review will contribute to the development of targeted interventions and policies to enhance digital health equity.

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(JMIR Res Protoc 2025;14:e63596) doi:10.2196/63596

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KEYWORDS

access to primary care; digital health; eHealth; health service accessibility; mHealth; mobile health applications, technology acceptance; telemedicine; demographic; socioeconomic factor; disparities; health care app; app usage; protocol; systematic review; medical information; health monitoring; health outcomes; effectiveness

Introduction

Rationale

The rapid proliferation of health care apps has significantly transformed health care delivery, providing patients with unprecedented access to medical information and services [1,2]. These apps facilitate remote consultations, appointment scheduling, medication reminders, and health monitoring, thereby enhancing patient engagement and improving health outcomes. The convenience and accessibility offered by health care apps are especially crucial in managing chronic diseases and ensuring continuity of care, particularly in remote and underserved areas [3].

Despite the widespread benefits, the adoption and usage of health care apps are not uniform across different population groups. Previous studies have identified significant disparities in pursuing health-related information online based on demographic and socioeconomic factors [4]. These disparities can exacerbate health inequities, as certain groups may lack the necessary resources or digital literacy to effectively use these technologies. Understanding the factors contributing to these disparities is essential for designing interventions that promote equitable access to digital health tools.

Age is a crucial factor in health care app usage. Younger individuals, with their digital proficiency, are more likely to adopt health care apps compared to older adults [5]. However, older adults, who could significantly benefit from these apps due to higher health care needs, often encounter barriers such as lack of digital literacy and skepticism toward technology [6]. This underscores the need for tailored strategies to bridge this digital divide and encourage app usage among older populations—a key disparity in health care app usage.

Gender differences also play a role in health care app adoption and usage. Studies have shown that men and women exhibit different health-seeking behaviors and preferences for digital health tools [7]. Women are more engaged in web-based health information searching, driven by social motives and enjoyment, while men are more open to virtual patient-physician relationships. Understanding these gender-based preferences can help in developing more gender-sensitive digital health solutions.

Education and income levels are significant predictors of health care app usage. Higher education levels are associated with better health literacy and greater comfort with digital technologies, leading to higher adoption rates of health care apps [8]. Similarly, individuals with higher income levels are more likely to own smartphones and have access to reliable internet, facilitating the use of health care apps [9]. Addressing these socioeconomic barriers is crucial for ensuring digital health tools reach and benefit all population segments.

Although prior studies [10-12] have investigated individual factors associated with health care app usage, such as age-related technology adoption or socioeconomic influences on digital access, existing research remains fragmented. Many studies [10,11] are context-specific, target narrow population groups, or fail to systematically compare findings across demographic and socioeconomic dimensions. Moreover, several studies [11,12] do not provide integrated frameworks that can inform policy or app design across diverse populations.

This systematic scoping review addresses these gaps by synthesizing a wide body of empirical literature to map out how demographic (age and gender) and socioeconomic (education and income) factors contribute to disparities in mobile health app usage. Unlike prior reviews [13,14] that focus on usability or technical features of apps, this review is centered on equity and access, offering practical insights for developers, health care providers, and policy makers aiming to promote inclusive digital health adoption.

The potential of health care apps to enhance health outcomes and reduce health care costs underscores the importance of addressing disparities in their usage. By identifying and understanding the factors that influence app adoption and usage, health care providers and policy makers can develop targeted interventions to promote equitable access to digital health tools. This systematic review aims to synthesize existing research on health care app usage disparities, providing a comprehensive understanding of the demographic and socioeconomic factors at play, and thereby, contributing to the development of more effective and equitable health care policies and practices.

Objectives

This protocol, adhering to PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) guidelines [15] (Multimedia Appendix 1), underpins a systematic review aiming to identify and synthesize empirical studies on health care app usage disparities. The review seeks to inform stakeholders about the demographic and socioeconomic factors influencing app usage, providing insights to improve app accessibility and effectiveness. This review addresses the following research questions (RQs).

RQ1: What are the key demographic and socioeconomic factors associated with health care app usage disparities?

RQ2: How do these factors influence the adoption and utilization of health care apps?

RQ3: What are the barriers to and facilitators of effective use of health care apps?

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Methods

Eligibility Criteria and Study Characteristics

Studies will be included in this review based on the following inclusion criteria.

1. Study type: peer-reviewed empirical journal papers (quantitative, qualitative, or mixed methods).
2. Language: published in English.
3. Time frame: published between January 1, 2014, and June 17, 2024.
4. Population: studies involving members of the general public as users of health care apps, with data disaggregated or analyzed by demographic (age and gender) or socioeconomic (education and income) variables.
5. Intervention: studies must examine health care app usage and report outcomes or observations stratified by focus on mobile health care apps used for tasks such as appointment scheduling, remote consultations, health monitoring, medication reminders, or self-management.
6. Outcomes: studies that examine usage patterns, barriers, facilitators, disparities, or adoption metrics stratified by demographic or socioeconomic factors.

Exclusion Criteria

The exclusion criteria were as follows.

1. Review papers, editorials, opinion pieces, conference abstracts, or non–peer-reviewed literature.
2. Studies that focus on clinical efficacy or technical design of apps without reporting usage by demographic or socioeconomic groups.
3. Studies that examine digital health technologies not focused on mobile apps (eg, web portals, SMS text messaging systems).
4. Studies that do not disaggregate findings by demographic or socioeconomic variables.
5. Studies that focus exclusively on provider use of apps (rather than patient or general population use).

Definition of Key Constructs

Demographic factors refer to the statistical characteristics of human populations, typically used to identify and describe population segments. In the context of this study, demographic factors include age and gender. These factors help describe who is using the health care apps and how usage varies across population groups.

1. Age refers to the chronological number of years a person has lived, often grouped into categories (eg, children, adolescents, adults, older adults) to assess patterns across the lifespan. In health app research, age is a critical factor influencing digital literacy, health needs, and technology adoption behaviors.
2. Gender refers to the socially constructed roles, behaviors, and identities that societies attribute to individuals, typically categorized as male and female. Gender can influence health-seeking behavior, comfort with technology, and preferences in health care app features and communication styles.

Socioeconomic factors relate to an individual's or group's social and economic position in the society, often influencing access to resources, services, and technology. For this review, socioeconomic factors include education level and income level. These factors affect both the ability and willingness to adopt health care apps and are central to understanding digital health disparities.

1. Education level refers to the highest degree or level of formal schooling an individual has completed. Common categories include no formal education, primary education, secondary education, and higher education. Education level influences health literacy, digital competence, and engagement with health technologies.
2. Income level refers to the total monetary earnings an individual or household receives within a specific period (typically monthly or annually). It is often classified into low, middle, and high-income brackets based on the national standards. Income level directly affects access to smartphones, data plans, internet connectivity, and affordability of health-related apps or services.

Information Sources and Search Strategy

Eight databases were searched for this systematic review. These databases are ACM Digital Library, CINAHL, IEEE Xplore, ProQuest Nursing and Allied Health Journals, PubMed/MEDLINE, ScienceDirect, Scopus, and Web of Science. These databases were selected due to their strengths as discipline-specific databases or citation indexes. All authors have institutional access to these databases. Databases were searched on June 17, 2024. See Table 1 for the search queries and the number of retrieved results. Results were limited to include journal papers written in English and published between January 1, 2014, through June 17, 2024. Keywords were searched in Medical Subject Headings (MeSH) fields in health-focused databases, CINAHL, ProQuest Nursing and Allied Health Journals, and PubMed/MEDLINE. In the other databases, keywords were searched in other metadata fields such as title, abstract, and/or keywords. As of June 2025, screening for duplicates and eligibility criteria has not yet occurred.

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Table 1. Databases, search queries, and number of studies retrieved.

Database name	Search query	Results (N=1100), n
ACM Digital Library	[[Abstract: “mobile health applications”] OR [Abstract: “digital health”] OR [Abstract: eHealth] OR [Abstract: mHealth] OR [Abstract: telemedicine]] AND [Abstract: “technology acceptance”]	2
CINAHL	MH[a] (“access to primary care” OR “health services accessibility”) AND MH (“mobile applications”) AND (“digital health” OR telemedicine)	72
IEEE Xplore	(“All Metadata”: mobile health applications” OR “All Metadata”: digital health OR “All Metadata”: eHealth OR “All Metadata”: mHealth OR “All Metadata”: telemedicine) AND (“All Metadata”: technology acceptance)	20
ProQuest Nursing and Allied Health Journals	mainsubject.Exact (“access to primary care” OR “health services accessibility”) AND mainsubject.Exact (“mobile applications”) AND (“digital health” OR telemedicine))	1
PubMed/MEDLINE	((“access to primary care” OR “health services accessibility”[MeSH[b] Terms]) AND (“mobile applications”[MeSH Terms])) AND (“digital health” OR “telemedicine”[MeSH Terms]))	6
ScienceDirect	(“mobile health applications” OR “digital health” OR eHealth OR mHealth OR telemedicine) AND (“technology acceptance”)	39
Scopus	Article title, abstract, keywords: (“mobile health applications” OR “digital health” OR eHealth OR mHealth OR telemedicine) AND (“technology acceptance”)	472
Web of Science	Topic (“mobile health applications” OR “digital health” OR eHealth OR mHealth OR telemedicine) AND Topic (“technology acceptance”)	488

[a]MH: CINAHL Exact Subject Headings.

[b]MeSH: Medical Subject Headings.

Study Records

Data Management

All 1100 studies retrieved were imported into the Zotero reference management system. After merging the studies, they will be exported to a Microsoft Excel spreadsheet to remove duplicates, screen unique papers, and select eligible papers. Relevant data characteristics (eg, author names, year of publication, type of study) will be extracted by 2 reviewers and stored in a shared OneDrive folder for systematic analysis and synthesis.

Selection Process

Two authors will independently screen all the retrieved records at both the titles/abstracts and full-text stages to ensure methodological rigor and minimize selection bias. Each study will be assessed against the predefined eligibility criteria. The studies that are not excluded will be saved to a separate folder. Subsequently, any discrepancy between the 2 reviewers will be resolved through a tie-breaker process, where a third reviewer is consulted to make the final decision. This dual independent screening process aligns with standard practices in systematic reviews to ensure objectivity and reduce the risk of bias in the study selection process. The final list of the included studies will undergo a collective review to confirm their inclusion in the systematic analysis before proceeding to data extraction and synthesis.

Data Collection Process

Data will be extracted using standardized forms by 2 independent reviewers. Key information will be recorded, including study characteristics, population demographics, socioeconomic factors, and app usage metrics. When writing the systematic review, it will be essential to ensure that the data extracted by the independent reviewers are meticulously cross-checked for accuracy and consistency. Any discrepancies between the reviewers will be resolved before moving on. This rigorous approach ensures the reliability of the data, which forms the foundation of the systematic review’s conclusions. Furthermore, the analysis will include a detailed synthesis of the findings, highlighting patterns, correlations, and potential causative factors observed in the data.

Quality Appraisal and Risk of Bias Assessment

To ensure the reliability of our systematic review, we will conduct a quality appraisal and risk of bias assessment by using the Mixed Methods Appraisal Tool (MMAT) for evaluating the methodological quality and risk of bias of all the included studies. MMAT is designed to evaluate a broad range of empirical studies, including qualitative, quantitative, and mixed methods designs [16]. Reviews that incorporate diverse study types are increasingly used to examine complex health interventions and outcomes. However, assessing methodological quality across such heterogeneous designs presents a challenge. MMAT was specifically developed to address this issue and has been positively evaluated by researchers for its adaptability and practical usefulness [17].

Two reviewers will independently assess each study to maintain objectivity. Any disagreements will be resolved through discussion or consulting a third reviewer if necessary. We will evaluate the studies based on several key factors: the appropriateness of the research design, the rigor of the data collection and analysis, and the clarity of the results. We will also consider potential biases such as selection bias, performance

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bias, detection bias, and attrition bias. The results of these assessments will be summarized in a table, highlighting the strengths and weaknesses of each study.

Data Analysis and Synthesis

We will use descriptive statistics to summarize the key characteristics of the included studies. This includes study design, population demographics, socioeconomic factors, and health care app usage metrics. They will provide an overview of the scope and variation across the included studies. We will apply standardized summary techniques to ensure consistency in data reporting. First, we will use frequency tables for categorical variables such as gender and app type. Second, we will use means or medians with ranges for continuous variables such as age. Third, we will categorize income and education levels into comparable brackets across studies.

Subgroup patterns will be explored descriptively across predefined categories to identify meaningful variations in usage trends, including (1) app type (telemedicine, medication reminders, fitness, chronic disease management), (2) age group (18-34, 35-49, 50-64, 65+ years old), (3) gender (male, female, other where reported), (4) education level (less than high school, high school graduate, college degree, postgraduate), and (5) income level (<US $25,000, between US $25,000 and US $74,999, >US $75,000).

Due to the diversity in the study characteristics, a structured narrative synthesis will be employed to integrate findings and highlight key disparities. Variations across studies will be organized thematically by subgroup characteristics and usage metrics.

Results

This study was initiated in May 2024, with preliminary data collection starting in June 2024. We anticipate completing data analysis by August 2025. The final results are expected to be published by late 2025. As of May 2025, study deduplication has been completed. From an initial pool of 1100 studies retrieved from 8 databases, 684 duplicates were removed, resulting in 416 unique papers. Title and abstract screenings are currently underway. Full-text screening and eligibility assessment are expected to be completed by November 2025. Figure 1 shows the preliminary PRISMA 2020 flow diagram [18] summarizing the study selection process to date.

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Figure 1. Preliminary PRISMA (Preferred Reporting Items for Systematic Review and Meta-Analysis) flow diagram.

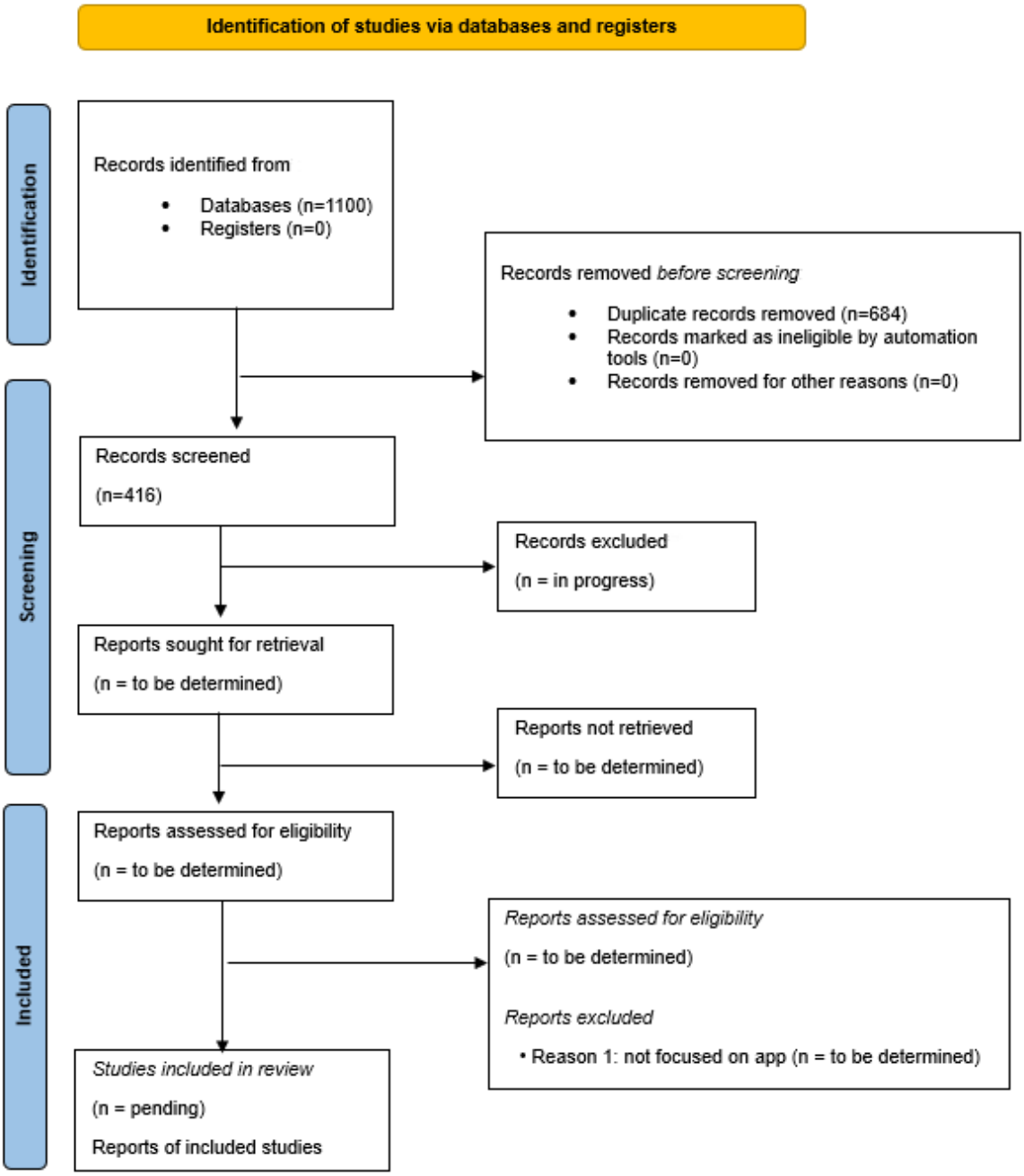

Discussion

Overview

Recent studies [19-21] have reinforced the urgency of addressing digital health disparities—particularly those amplified during the COVID-19 pandemic. Socioeconomic status continues to be a major determinant of digital health adoption, with lower-income groups and rural populations experiencing persistent barriers to access [22]. Although the pandemic accelerated overall adoption, vulnerable groups, especially those with limited digital literacy or financial resources, remain underserved [22,23]. Age and usability also play a critical role. As highlighted by Gomez-Hernandez et al [24], older adults face challenges in navigating mobile health apps due to visual, cognitive, and motor limitations. Their systematic review provides design guidelines such as simplified interfaces and training support that could significantly improve adoption rates among aging populations.

Gender emerged as a contextual but inconsistently significant factor in digital health adoption. Some studies found that women were more likely to engage with health information online and use digital tools both before and during the COVID-19 pandemic [22], while others reported no significant gender-based differences [25]. A third review acknowledged gender-related disparities in some cases but did not treat gender as a core analytic variable [24]. These mixed findings suggest that gender may interact with other social determinants and deserves further investigation in future research. Tuitert et al [22] demonstrated through a longitudinal study that pandemic-related adaptations helped reduce usage gaps among certain groups, including

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less-educated individuals. However, inequities based on income and digital access persisted, highlighting the need for ongoing interventions.

Finally, the broader systemic challenges in digital health equity must be acknowledged. As Yao et al [23] emphasize, barriers related to digital literacy, technological infrastructure, and socioeconomic status must be systematically addressed through inclusive design and targeted policies to prevent further marginalization. Together, these studies underscore the need for a comprehensive synthesis of empirical evidence. By identifying and analyzing demographic and socioeconomic drivers of health care app usage disparities, this review aims to support the development of inclusive technologies and equitable digital health strategies that can be adopted across diverse populations.

The findings of this systematic review are expected to provide significant insights into the disparities in health care app usage, influenced by demographic and socioeconomic factors. As health care increasingly shifts toward digital platforms, understanding these disparities is crucial for ensuring equitable access and utilization of health care services. The results will inform stakeholders, including health care providers, policy makers, and app developers, on how to address these disparities and enhance the accessibility and effectiveness of health care apps.

Implications for Practice

Identifying the specific demographic and socioeconomic factors influencing health care app usage can help design targeted interventions. For instance, if younger individuals are more likely to use these apps, educational campaigns can be tailored for older adults to increase their engagement. Similarly, understanding the impact of education and income levels can guide the development of more user-friendly and affordable app features, ensuring that these digital health tools are accessible to a broader population.

Policy Recommendations

This review's findings will be critical for policy makers aiming to reduce health disparities. Policies that promote digital literacy and provide subsidies or financial incentives for using health care apps could be implemented. Furthermore, regulations ensuring the privacy and security of health data are essential to building trust and encouraging app adoption among various demographic groups.

Technological Considerations

App developers can use the insights from this review to improve the design and functionality of health care apps. Features that cater to the specific needs of different demographic groups, such as language options, simplified user interfaces, and culturally relevant content, can enhance user experience and adoption rates. Additionally, incorporating feedback mechanisms within apps can help developers continuously improve their products based on user experiences and preferences.

Limitations

This systematic review may face several limitations. First, the restriction to studies published in English and within the past decade might exclude relevant studies published in other languages or before 2014. Second, the reliance on self-reported data in many studies could introduce bias. Third, although the search strategy covered a broad range of terms related to digital health, access, and technology acceptance, it may have benefited from the inclusion of additional terms aligned with the study's focus on disparities. Keywords such as technology adoption, equity, inequity, and usage could enhance the comprehensiveness of future searches, helping to capture studies that address health disparities and user behavior. Future research should consider these limitations to provide a comprehensive understanding of health care app usage disparities, thereby enhancing the scope of future reviews.

Conclusion

In conclusion, this systematic review aims to illuminate the disparities in health care app usage, offering practical insights for improving digital health equity. By addressing the demographic and socioeconomic factors that influence app usage, stakeholders can develop more inclusive and effective digital health strategies. The anticipated results will contribute to the growing body of knowledge in digital health and support the development of targeted interventions to bridge the digital divide in health care access.

Data Availability

As this is a protocol, no data have been generated yet. Upon completion of the review, the extracted dataset will be made available upon reasonable request from the corresponding author or deposited in an open-access repository where appropriate.

Authors' Contributions

Conceptualization: FA, DJM
Methodology: FA, DJM
Investigation: FA, SI
Data Curation: FA, ER
Writing Original Draft: ER, FA
Writing Review and Editing: DJM, SI, FA
Resources (Database Access and Search Strategy Support): ER
Supervision: DJM
Visualization: FA

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Validation: DJM, SI
Project Administration: DJM
All authors reviewed and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P 2015 checklist.
[DOCX File , 34 KB - resprot_v14i1e63596_app1.docx]

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Abbreviations

MeSH: Medical Subject Headings
MMAT: Mixed Methods Appraisal Tool
PRISMA-P: Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols
RQ: research question

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Protocol

Impact of the Exposome in Type 1 Diabetes: Protocol for a Scoping Review

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Abstract

Background: The recent increase in the incidence of type 1 diabetes (T1D) over the past few decades has been too rapid to be explained solely by genetic factors. It is likely influenced by environmental factors as well. Understanding these environmental factors, the exposome, is essential for identifying new disease prevention and management strategies.

Objective: This paper aims to present a protocol for a scoping review to gather current knowledge on the various dimensions of the exposome relevant to the development and outcomes of T1D, highlight existing knowledge gaps, and provide a foundation for future research.

Methods: We will follow principles from the Joanna Briggs Institute (JBI) methodology for scoping reviews and the PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) guidelines. We will search for relevant publications in 5 databases: PubMed, Embase (Elsevier), CINAHL (EBSCO), Web of Science (Clarivate), and Google Scholar. All studies on the impact of environmental exposures on T1D development or acute (hypoglycemia or hyperglycemia) and chronic (cardiovascular disease, retinopathy, neuropathy, and others) T1D complications will be collected. Two independent reviewers will then use the CADIMA (Client-Server Application for Documentation and Integrated Management of All Steps of a Systematic Review) web tool to screen records for titles, abstracts, and full texts. Data will be extracted from eligible studies by 2 independent reviewers by using a data extraction sheet, including relevant information from the eligible studies helping to answer the research question. The data extraction sheet will be completed together with a quality assessment by using JBI and other relevant tools before the synthesis of all the relevant results. Numerical and visual results will be presented using descriptive summaries to organize, describe, and interpret the findings. We will also provide a narrative synthesis of the main results focused on our objectives. This scoping review is registered with the Open Science Framework.

Results: The scoping review started in November 2024. The analysis is expected to be completed and the results submitted for publication in November 2025. The final review will report on all the studies identified and synthesized in accordance with the predefined protocol. Concerning all types of exposure, we expect to find more aspects of the specific external exposome (eg, pollutants, diet, infectious agents), particularly in young populations (children, adolescents) and possibly in utero exposition, linked to the trigger of the disease rather than in developing diabetes complications.

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Conclusions: By covering the different aspects and stages of the disease, this literature review aims to provide a comprehensive overview of the different effects of the components from the exposome in relation to T1D. This scoping review will help the scientific community understand the various aspects of the exposome in the development of T1D and its consequences. The results will be released as a peer-reviewed open-access publication and during congresses and conferences to reach the scientific community and the general public.

Trial Registration: OSF Registries 10.17605/OSF.IO/UJ5KM; https://osf.io/uj5km

International Registered Report Identifier (IRRID): DERR1-10.2196/73424

(JMIR Res Protoc 2025;14:e73424) doi:10.2196/73424

KEYWORDS

type 1 diabetes; environmental exposure; pollutants; autoimmune disease; diabetes onset; diabetes complications

Introduction

Rationale

Type 1 diabetes (T1D) is a chronic autoimmune disease characterized by the destruction of the insulin-producing pancreatic β-cells, leading to absolute insulin deficiency and manifested by the sudden onset of severe hyperglycemia leading to lifelong dependence on exogenous insulin [1]. Over the past few decades, the incidence of T1D has risen significantly worldwide and cannot be explained by genetic changes alone; it is most likely attributable to environmental influences as well [2,3]. Although lifestyle and behavioral factors are known to contribute to health and disease [4-6], growing evidence suggests that other environmental exposures may also play a critical role in the risk of chronic diseases and associated complications such as diabetes [7,8].

Emerging research highlights the complex role of the exposome, defined as the totality of environmental exposures experienced by an individual from conception onwards [9]. This exposome includes various dimensions that interact over time to influence individuals' health. It comprises the general external exposome (eg, built environment, social environment, physicochemical exposures), the specific external exposome (eg, diet, pollutants, financial status), and the internal exposome (eg, metabolic processes, microbiome). These domains are interconnected, with overlapping exposures acting cumulatively to drive disease risk and progression throughout life [10-12].

Many studies have provided valuable insights into the exposome's significant role in developing and managing chronic diseases [13]. For instance, a review found that cardiometabolic risk factors and cardiovascular disease have been linked primarily to poor air quality [14] and a wide range of other elements of the exposome [15]. In another review, ischemic heart disease progression has been linked to several dimensions from the exposome, such as air, light, acoustic pollution, soil pollution, water contamination, climate change, social stress, and infectious diseases [16]. The effect of components from the exposome such as pollutants, industrial and agricultural chemicals, toxins, lifestyle and social factors, diet, microbiome, and infection have also been reported for Alzheimer disease as well as other major neurodegenerative diseases, including Parkinson disease, amyotrophic lateral sclerosis, and multiple sclerosis [17-19]. Similarly, some studies have identified links between air pollution and heavy metals and susceptibility to the development and progression of chronic kidney disease, while associations with other dimensions from the exposome, such as chemicals and the built environment, remain understudied [20]. In the diabetes field, research has predominantly focused on type 2 diabetes (T2D) and gestational diabetes mellitus. Studies have shown exposure to ambient air pollution, persistent organic pollutants, and endocrine-disrupting chemicals play a critical role in the development of gestational diabetes mellitus [21], as well as air pollution, residential noise, and socioeconomic deprivation in the alteration of β-cells, leading to an increased risk of T2D [11,22].

Despite these interesting findings, the role of the exposome in T1D remains largely unexplored. We performed an explanatory search in relevant databases such as MEDLINE, Cochrane Database of Systematic Reviews, Open Science Framework, and PROSPERO. We did not identify current or underway scoping reviews on the exposome and its relationship to the development of T1D and its outcomes such as glycemic variability, long-term complications, and quality of life. Previous reviews have focused on specific exposures such as prenatal pollutants, diet, or viral infections [23-26]. However, the overall knowledge of the exposome remains dispersed. Even less is known about how these environmental factors impact individuals already living with T1D. Such a comprehensive understanding is essential for the identification of new strategies for disease prevention and management.

Conducting a scoping review is well-suited for this broad research question, as it allows for an exhaustive exploration, particularly for a fragmented research area. Unlike systematic reviews, scoping reviews map existing knowledge, identify research gaps, and comprehensively synthesize the available evidence [27-29]. This approach is beneficial for investigating the various environmental exposures in T1D development and its association with T1D disease outcomes, which remain underexplored.

Objectives

The purpose of this protocol study is to describe the methodology for a scoping review assessing the current understanding of the role of the exposome in T1D development and complications. In the scoping review study, we aim to describe the main components of the exposome linked to T1D, report the most effective ways to collect exposome data, and highlight the existing gaps linked to this research question.

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Methods

Protocol and Registration

This protocol was previously registered using the Open Science Framework Registries platform [30]. The scoping review will follow the Joanna Briggs Institute (JBI) methodology for scoping reviews [29,31] and the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Scoping Reviews) guidelines, shown in Multimedia Appendix 1 [32]. In addition, we will follow the guidance of the free web-based tool CADIMA (Client-Server Application for Documentation and Integrated Management of All Steps of a Systematic Review), which will be used to perform this review. CADIMA is designed to assist in conducting systematic reviews and evidence syntheses, including scoping reviews. It provides a structured workflow to manage and document the review process, facilitate collaboration, and ensure transparency and reproducibility. For a scoping review, CADIMA allows the importation of a reference list from a preliminary literature search and deduplicates records, defines eligibility criteria, screens studies (based on titles and abstracts, and full texts), extracts relevant data, and generates visual reports such as PRISMA diagrams [33].

Research Question

JBI proposes the PCC (Population/Concept/Context) framework to determine the key notions of the research question [29,31,34]. It has been determined based on the elements in Table 1 and defined as follows: which and how could environmental exposures lead to the development of the disease or complications of the disease for those who already have T1D?

Table 1. PCC (Population/Concept/Context) framework for the definition of the research question.

PCC element	Definition	Example
Population	People with T1D[a] or people who developed or will develop T1D	N/A[b]

Concept	Impact of the exposome on T1D development and on the complications in people who already have T1D	• General external exposome
		  • Socioeconomic status, living conditions, climate, weather, etc
		• Specific external exposome
		  • Work environment, chemical and physical exposure, biological and infectious agents, lifestyle, etc
		• Internal exposome
		  • Biological processes, metabolism, etc

Context	Exposures on a lifespan perspective	In utero, childhood, adolescence, adulthood, older adult life; community or hospital setting

[a]T1D: type 1 diabetes.

[b]N/A: not applicable.

Information Sources and Search

Before using the CADIMA tool, an exhaustive search for studies in various databases will be performed to identify a comprehensive corpus of relevant studies: PubMed, Embase (Elsevier), CINAHL (EBSCO), Web of Science (Clarivate), and Google Scholar, based on the key concepts of T1D and exposome. Key concepts and further ones will be associated using the classic syntactic techniques provided by PubMed. The search strategy, including all identified keywords and index terms, will be adapted for each database after several attempts to provide the most efficient source of information. An example of what will be done in PubMed as well as the strings adapted to other databases is shown in Multimedia Appendix 2. There will be no selection by language. Studies available only in the original language other than English will be translated using artificial intelligence tools and verified with native speakers when needed. Each time a paper will have to be translated in English, a native-speaking scientist from our institution will be involved to check the relevance of the translation. Additional search strategies will be employed for additional sources by using backward and forward snowballing approaches, citations from review studies, and alerts for new studies from the different database queries.

Selection of Sources of Evidence

Following the literature search, all identified studies concerning the impact of environmental exposures on the development or outcomes of T1D will be collected. All studies will be uploaded to the CADIMA tool, and duplicates will be removed. Two independent reviewers will perform the screening for titles and abstracts. After that, 2 independent researchers will select the studies by full text before extracting the data and summarizing all the relevant findings. The study eligibility criteria will be defined as follows.

1. Population: people with T1D or people who developed or will develop T1D.
2. Outcome: glycemic control variables; acute (ketoacidosis, hypoglycemia events) and chronic T1D complications (retinopathy, nephropathy, neuropathy, cardiovascular disease, and others); T1D development; T1D.
3. Exposome: general external exposome (eg, socioeconomic status, living conditions, climate, weather), specific external

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exposome (eg, work environment, chemical and physical exposure, biological and infectious agents, lifestyle) and internal exposome (eg, biological processes, metabolism), measured with sensors if applicable.

4. Exclusion criteria: no distinction between T1D and T2D, drug-induced glucose alterations (medications), review, case study.

As this work will focus on T1D, we will exclude studies on T2D or those where it is impossible to distinguish between T1D and T2D. For mixed populations, only results concerning T1D will be extracted. Studies that do not distinguish between T1D and T2D may introduce confounding factors, given their distinct etiology and pathophysiology [35-37]. The same applies to alterations in glucose levels caused by medication, which may lead to a bias in the interpretation of results, as they are not representative of the typical glycemic variability in people with T1D [38]. Finally, review studies will be excluded as they do not provide original data or specific methodologies. The same applies to case studies with limited scope for generalization [39].

Following a pilot test (consistency check to determine the agreement between reviewers when applying the selection criteria), 2 independent reviewers will screen titles and abstracts to assess them according to the study eligibility criteria defined for the review. CADIMA automatically and randomly allocates the studies to team members. The preliminary eligibility of the studies will be assessed at this stage. The selected studies by title and abstract will be evaluated for eligibility by full text. Authors of studies for which the full text is unavailable will be contacted using various communication channels (ResearchGate, email, LinkedIn) to maximize the chances of accessing the full text. During this stage, full texts will be excluded based on the eligibility criteria and for other reasons, such as being inaccessible or not presenting primary data/summary statistics. Any disagreements between the reviewers at each stage of the selection process will be solved through discussion among the reviewers, or if no consensus is reached, by involving a third reviewer. The search results and the study selection process will be fully documented in the final scoping review and presented as a PRISMA flow diagram.

Data Items

Data will be extracted from eligible papers selected for the scoping review by 2 independent reviewers by using a data extraction sheet developed with the CADIMA tool. A draft of the data to be gathered is detailed in Multimedia Appendix 3. The data extracted will include comments, article ID, study ID, author, year of publication, title, data location, and study name as predefined by the CADIMA tool (columns 1 to 8, Multimedia Appendix 3) and additional columns defined by team members according to the research question (columns 9 to 62, Multimedia Appendix 3). This draft data extraction tool will be modified and revised as necessary during the data extraction process for each eligible study. Any disagreements between the reviewers will be solved through discussion.

Critical Appraisal of Individual Sources of Evidence

The quality of the selected papers will be assessed by 2 independent reviewers by using JBI Critical Appraisal Tools [40] when provided for the specific study designs (eg, analytical cross-sectional, case-control, cohort studies, qualitative research, quasi-experimental, randomized controlled trials) and other relevant tools validated in the literature for study designs not covered by JBI, such as the National Institutes of Health and STROBE (Strengthening the Reporting of Observational studies in Epidemiology) checklists [41,42].

Synthesis of Results

We will perform an analytical approach based on the following PCC (JBI) approach [34].

1. For the population, we will record the mean age, sex distribution, and country.
2. For the concept, we will identify outcomes and exposures by specifying the type of outcome (T1D development or T1D complication) and the type of exposome by grouping according to their nature, the assessment tool.
3. For the context, we will code according to the period of exposure studied.

To ensure that the findings respond correctly to the review question and objectives and to organize and interpret the data, we will use numerical summaries and thematic synthesis [43]. To provide an overview of the included studies, we will describe the data with numerical summaries. We will present the sample characteristics such as the year of publication, geographical location, study design, and population. The exposures will be detailed in terms of exposure type (eg, environmental pollutants, occupational exposures, lifestyle factors) and exposure period (eg, in utero, childhood, adulthood). This summary will help identify current trends and gaps in the existing literature. We will also classify using thematic synthesis. This classification will provide key dimensions of the exposome based on its consensual definition about the general external exposome, specific external and internal exposome, and its associations with T1D. The results will be presented according to the outcome definition (development of T1D in the general population vs complications and outcomes in people living with T1D). We will use descriptive tables to summarize the characteristics of the studies and figures or diagrams to illustrate the distribution of the exposome dimensions related to T1D and the development and complications of T1D.

Results

Data collection for this scoping review began in November 2024. The completion of analysis and submission of results for publication are planned after 12 months from initiation. The findings will be reported as described above and submitted for publication in a peer-reviewed journal. Considering previous reviews, we anticipate finding papers that study single exposures rather than their interactions within the exposome. It is similarly possible that many more studies will focus on the effect of these exposures or of the exposome on the development of T1D. We also expect to have many more studies combining exposures when analyzing pollutants or air pollution, nutrition or else in

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utero/birth factors than combinations of other exposome types. Regarding the exposome analysis methodology, it could vary from very classical analysis to comprehensive and sophisticated methods, including machine learning and exposome-wide association studies.

Discussion

Summary of Evidence

This scoping review aims to discuss in detail the current knowledge of the impact of the exposome in the context of T1D by exploring its role in the development of the disease and its subsequent complications. We expect that the principal findings will mainly concern aspects from the specific external exposome (eg, diet, infectious agents, pollutants). We expect to find more studies on the development of T1D (in young populations and possibly in utero exposure) rather than research on T1D complications. Indeed, several reviews and meta-analyses have already highlighted specific components of the exposome and their role in the development and the evolution of the disease [44-47]. Moreover, the current research seems to focus on a single impact of specific exposures rather than the combined effect, acting as a trigger at an early stage of the disease, particularly during onset. Although these studies have led to a better understanding of how the environment can affect diabetes, further aspects of the exposome and its relationship with T1D remain underexplored. To our knowledge, this is the first literature review to explore the role of the exposome in both the development of T1D and its complications in individuals living with T1D.

Strengths and Limitations

The principal strength of this review lies in its comprehensive scope. It will provide an in-depth examination of a recent and evolving concept while covering stages of the disease. However, this approach also implies that some limitations are expected. First, as the exposome concept is new and evolving, its dimensions are not always well-defined. Additionally, the measurement methods for environmental exposures could vary a lot from objective to subjective methods, and because of this heterogeneity, it could make it challenging to summarize and define the most effective ways to collect them. Lastly, it could be difficult to interpret the findings due to the different outcomes studied in this review, including the development of the disease or its complications.

Conclusions

In conclusion, this review protocol aims to establish a methodology for a comprehensive examination of the impact of the exposome in T1D and to highlight the existing gaps in the current research. The findings are expected to provide a valuable resource for future research projects in the development of personalized strategies for the prevention and management of T1D. In order to give the broadest possible access to this research work, the results of this scoping review will be disseminated via several channels such as an open-access paper, presentations at congresses or conferences on the topic, or press releases aimed at the scientific community and the general population.

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Data Availability

All the findings from this scoping review will be made available through peer-reviewed open-access publication. All relevant documentation relating to the review will be stored in the Open Science Framework project, which has been registered under the following DOI: 10.17605/OSF.IO/UJ5KM.

Authors' Contributions

Conceptualization: GAA, GF, and MR
Funding acquisition: GF
Methodology: GAA, GF, and MR
Supervision: GAA and GF
Writing – original draft: GF and MR
Writing – review & editing: EC, GAA, GF, JPR, MR

Conflicts of Interest

None declared.

Multimedia Appendix 1

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PRISMA-ScR checklist.
[PDF File (Adobe PDF File), 101 KB - resprot_v14i1e73424_app1.pdf]

Multimedia Appendix 2
Search strategy.
[DOCX File , 21 KB - resprot_v14i1e73424_app2.docx]

Multimedia Appendix 3
Data extraction sheet.
[DOCX File , 19 KB - resprot_v14i1e73424_app3.docx]

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Abbreviations

CADIMA: Client-Server Application for Documentation and Integrated Management of All Steps of a Systematic Review
JBI: Joanna Briggs Institute
PCC: Population/Concept/Context
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Scoping Reviews
STROBE: Strengthening the Reporting of Observational studies in Epidemiology
T1D: type 1 diabetes
T2D: type 2 diabetes

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Protocol

Falls Prevention Among Older Adults in Rural Communities: Protocol for a Scoping Review

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Abstract

Background: Falls are a critical source of injury and hospitalization and leave many older adults unable to return home, especially in rural communities with limited access to health care and support services. Studying falls prevention among rural older adults is essential because they may face an increased risk of falls due to unique environmental factors, geography, and outdoor activities. Moreover, rural older adults may have limited awareness regarding fall-related risks and preventive activities.

Objective: The objective of this scoping review is to explore the literature about falls prevention from the perspectives of older adults living within a rural context. This review protocol aims to identify the search parameters and methodology that will be used in the scoping review.

Methods: This scoping review will be guided by Arksey and O'Malley's 5-step methodological framework. We will search for relevant peer-reviewed English language literature from 5 databases: CINAHL, PubMed, Academic Search Complete, PsycINFO, and Scopus. The reference lists of relevant studies will be hand-searched to identify papers. Inclusion criteria (English language, peer-reviewed journal papers, original research, focusing on rural perspectives to support falls prevention, and published from January 2013 to December 31, 2023) will be used to determine the eligibility of the journal papers. The data from the included papers will be extracted using a standardized table and analyzed using thematic analysis.

Results: This protocol was registered with the Open Science Framework on June 26, 2024. The scoping review's data collection and analysis were conducted from September to December 2024. Results from the review will be distributed through publication in a peer-reviewed journal paper, conference presentation, webinar, and a rural community workshop.

Conclusions: Understanding rural older adults' perspectives of falls prevention is critical to supporting independence and healthy aging in rural communities. This review's findings about falls prevention may have important implications for rural community leaders, policy makers, and health practitioners working to support falls prevention in rural communities.

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KEYWORDS

falls prevention; rural; older adults; aging; perceptions; protocol; scoping review

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Introduction

Falls are a substantial public health issue and a leading cause of mortality and morbidity among older adults worldwide [1]. The World Health Organization (WHO) reports that every year approximately 684,000 people die from falls [2]. A fall can be defined as an event in which an individual unintentionally comes to rest on the floor [3].

Compared to urban older adults, rural older adults report a higher risk of falls and experience a higher incidence of falls [4]. This increased risk of falls is due to differences in the physical environment, lifestyle activities, social issues, and geospatially dispersed health-related services and resources [5,6]. Rural older adults face unique challenges in accessing treatment for fall-related injuries due to limited public transportation, financial challenges, dispersed geography, and inadequate access to health care and support services [7].

Falls can lead to severe injury, dependence, death, and institutionalization among older adults [8,9] and are a critical public health issue due to their economic cost to the health care system [4,10]. The Government of Canada [11] reports that falls cost the health care system approximately CAD 2 billion (USD 1.48 billion) each year. Falls often result in debilitating injuries, require hospitalization, and leave many older adults unable to return home, especially for rural older adults with limited access to health care and support services [10,12]. Given the economic cost and the potentially life-threatening consequences of falls, there is an urgent need for research to address falls prevention within a rural context.

Current literature about rural older adults' perspectives on falls prevention in rural communities is limited. Although 2 literature reviews exist on falls, they focus primarily on rural older adults in the Australian context. For example, Boehm and colleagues [13] completed a literature review focusing on falls epidemiology in rural Australia. Similarly, Peters and colleagues [14] focused on the rural Australian context and examined paramedicine practices in supporting rural falls management. However, no existing literature reviews focus on the viewpoints of rural older adults. Moreover, existing research highlights the challenges of dissemination of fall-related programming and services in rural communities [15,16].

Given that falls are largely preventable, there is a critical need to understand rural older adults' perspectives on ways to reduce fall-related risks and injury. For example, rural older adults can provide unique insight about the contributing factors and risks to support falls prevention. By examining rural older adults' perspectives, we can develop community-informed interventions to support falls prevention and awareness within a rural context. Accordingly, this scoping review protocol outlines the methodology that will be used to examine rural older adults' perspectives on falls prevention. By focusing on the perspectives of rural older adults, this review's findings will have important implications for rural policy makers, health practitioners, and community leaders working to support rural aging.

Methods

Study Framework

This scoping review will follow Arksey and O'Malley's [17] scoping review framework and the PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) checklist (Multimedia Appendix 1) [18]. Guided by Arksey and O'Malley's framework, this study will be organized into 5 stages: (1) identification of the research question; (2) examination of relevant studies; (3) study selection; (4) data extraction; and (5) collating, summarizing, and reporting the research findings [17].

Step 1: Identification of the Research Question

The primary and secondary research questions were created to examine the existing literature on rural older adults' perspectives of falls prevention. Specifically, the primary question was developed to understand how rural older adults view falls prevention overall. The secondary questions were created to explore how rural older adults view their risk of falls and to identify what they consider to be contributing factors of falls. It is important to note that these questions focus on examining rural older adults' perspectives of prevention and risk, without focusing on fall experiences. Questions about fall experiences were avoided to align with existing research that shows that older adults focus on fall perspectives and implications rather than the fall experience itself [19]. Accordingly, it is important to emphasize that our study focuses on understanding rural older adults' perspectives of falls prevention and not experiences. We have included our primary and secondary research questions below:

1. Primary research question: What are rural older adults' perceptions about falls prevention?
2. Secondary research questions: (1) How do older adults living in rural communities perceive their risk of falls? (2) What do rural older adults identify as the contributing factors of falls? (3) What are rural older adults' perspectives of mitigation strategies to reduce falls?

Step 2: Identification of Relevant Studies

An expert librarian was consulted to recommend the most relevant databases. Based on the librarian's expertise, a broad search on EBSCO Discovery Service was conducted to identify the most applicable databases. Based on the librarian's expert guidance, 5 databases were searched: CINAHL, PubMed, Academic Search Complete, PsycINFO, and Scopus. Studies were also obtained by searching for bibliographic references of relevant studies. The time frame of the search will focus on papers published over the past 10 years from January 2013 to December 31, 2023. These dates were chosen to identify the most recent and up-to-date literature available. The keywords that were included in this search strategy are documented in Table 1. For example, the search string for CINAHL was (falls prevention or preventing falls or prevent falls or reduce falls or fall mitigation or fall risk reduction) AND (older adults or elderly or seniors or geriatrics or geriatric or seniors or aging or older people) AND (rural or rurality or underserved) AND (perceptions or attitudes or opinion or perspectives or view).

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Regarding our search terms, it is important to note that existing research shows that perspectives and experiences cannot be used interchangeably. For example, older adults tend to focus on the antecedents and consequences of falls rather than the fall experience itself [19]. Consequently, our search terms focused strategically on words related to prevention rather than experiences because our research aims to highlight the perspectives of rural older adults.

Table 1. Keyword search strategy.[a]

Concept	Keywords
Falls prevention	Preventing falls, prevent falls, reduce falls, fall mitigation, fall risk reduction
Older adults	Elderly, seniors, geriatric, geriatrics, aging, older people
Rural	Rural, rurality, underserved
Perceptions	Attitudes, opinion, perspectives, view

[a]Databases used were CINAHL, PubMed, Academic Search Complete, PsycINFO, and Scopus.

Inclusion and Exclusion Criteria

Publications will be included in this scoping review if they meet the following 4 criteria: (1) full text, peer-reviewed journal papers; (2) written in the English language; (3) published from 2013 to 2024; and (4) focus on older adults' perceptions about falls among those living in rural communities. This study will include publications with different research methods such as qualitative, quantitative, and mixed methods studies. Exclusion criteria will include the following: (1) papers that do not report on original research (such as commentaries and editorials), (2) papers published in languages that are not English, and (3) papers that do not address the research topic.

Step 3: Study Selection

Five electronic databases (CINAHL, PubMed, Academic Search Complete, PsycINFO, and Scopus) will be searched for relevant literature, and the results will be imported into Covidence software to aid in the organization and management in the review's selection and screening process [20]. Guided by the inclusion and exclusion criteria, 2 reviewers will perform the study selection process. A PRISMA diagram will be used to document the scoping review's study identification, selection, and screening process.

Step 4: Charting the Data

The data will be charted and extracted using a standardized data extraction table in Microsoft Word. The table will consist of different categories to help chart and organize the data, including the author, publication year, country of origin, purpose of the study, methods, and findings. We will also have a category to collect information to address the question-related themes, including information related to fall-related risks, contributing factors of falls, and/or mitigation strategies. Exploring this information will allow the researchers to effectively synthesize the existing information on falls prevention among rural older adults. This table will be assessed with 4 papers to ensure that the table adequately captures the data, and no missing categories are required to address the research questions.

Step 5: Collating, Summarizing, and Reporting the Research Findings

Guided by Braun and Clarke [21], we will analyze our scoping review data by using thematic analysis. Specifically, our process of thematic analysis will consist of using a deductive approach where our research process will be guided by our pre-established research questions. For examples, our codes will be guided by using our research questions (fall-related risks, contributing factors, and mitigation strategies), and our themes will be created by organizing our codes into theme and subtheme piles to ensure that our themes align with addressing our research objectives. Our theme names will be refined to ensure clarity, uniqueness, and that they provide insight into addressing each of our research questions.

Measures will be taken to support rigor in the data. For example, dependability will be accomplished by keeping a comprehensive audit trail to document the research steps and decisions made throughout the process [21]. Reflexivity will be integrated by reflecting and mitigating authors' potential biases and assumptions during the data synthesis and the development of themes. Additionally, confirmability will be incorporated through peer debriefing and reviewing interpretations to ensure the findings are representative of the data.

Results

This protocol was registered with the Open Science Framework on June 26, 2024. The scoping review's data collection and analysis were conducted from September to December 2024. Results from this review will be distributed through publication in a peer-reviewed journal paper, conference presentation, webinar, and a rural community workshop.

Discussion

Overview

Our scoping review will aim to examine the literature on rural older adults' perspectives of falls prevention. Supporting falls prevention and independence of older adults in rural communities is critical for several unique factors ranging from education to geography. More specifically, research suggests that rural older adults often lack education and awareness of falls prevention and have an increased risk of falling compared to their urban counterparts [4]. Research shows that increased risk of falls may be related to rural older adults' day-to-day activities, geography [5], and physical environments such as uneven walkways [22]. Across diverse global contexts, rural older adults often face limited treatment options due to issues of inadequate public transportation, geographical distance, social

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isolation, and reduced access to health care and support services [4,23-26]. Consequently, falls prevention is vital to supporting older adults' independence to protect themselves from issues of social isolation, loss of selfhood, and fears of dependency [27]. Additionally, falls can cause severe injury, dependence, and mortality among older adults and are costly to the health care system [2]. Each year, falls cost the health care system in Canada approximately CAD 2 billion (USD 1.48 billion) [7] and upwards of CAD 68 billion (~USD 50 billion) worldwide [26].

Although research addresses falls prevention among older adults, there is a notable lack of discussion focusing directly on the perspectives of rural older adults. However, older adults' perspectives of falls prevention are important because research shows that they have unique views regarding falls [19,28]. For example, Zecevic and colleagues [19] reported that older adults tend to focus on the causes and implications of falls, whereas researchers often emphasize the fall itself. Accordingly, the findings from this review will have important implications for rural policy makers, practitioners, and community leaders who are dedicated to addressing falls prevention in rural communities. Understanding the unique views and perspectives of older adults will inform the development of targeted strategies and actions to enhance falls prevention in rural communities.

Limitations

This scoping review will be completed in a rigorous and comprehensive manner. However, it is important to note that our review may include potential limitations. For example, our review will be limited to literature published in peer-reviewed journal papers in the English language. Thus, information in gray literature will be excluded from this study. Future reviews may expand their search to include gray literature and unpublished materials. It should be noted that future reviews using gray literature should be cautious, as gray literature is often not peer-reviewed. Another limitation is that only papers in the English language will be included in this review. However, there may be relevant peer-reviewed literature published in languages other than English. Accordingly, future research should consider examining non-English language literature on rural older adults' perspectives of falls prevention.

Conclusion

Understanding rural older adults' perspectives of falls prevention is essential to supporting independence and healthy aging in rural communities. Although research addresses falls prevention among older adults, there is a notable lack of discussion focusing directly on the perspectives of rural older adults. This scoping review on falls prevention may have important implications for rural community leaders, policy makers, and health practitioners working to support falls prevention for older adults living in rural communities.

Data Availability

The data collected during the scoping review will be available on the Open Science Framework repository and as supplementary files with our scoping review manuscript.

Authors' Contributions

MF and JDB conceived the focus and approach of the scoping review. MF wrote the first draft of the review protocol with support from JDB, AV, ZR, MSD, and MLS. All authors provided critical feedback and reviewed the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) checklist.
[DOCX File , 888 KB - resprot_v14i1e63716_app1.docx]

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Abbreviations

PRISMA-ScR: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews
WHO: World Health Organization

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Protocol

Compassion Fatigue and Burnout Among Health Care Professionals: Protocol for a Scoping Review

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Abstract

Background: Compassion fatigue and burnout among health care professionals are growing concerns, impacting the well-being of both providers and patients.

Objective: This scoping review aims to map existing evidence on the levels of compassion satisfaction, burnout, and secondary traumatic stress among health care professionals while identifying factors influencing their professional quality of life.

Methods: We will conduct a scoping review using established methods proposed by Arksey and O'Malley and Levac et al, also incorporating the recommendations of the Joanna Briggs Institute for scoping reviews and reporting guidelines. EMBASE, ERIC, PubMed, Science Direct, Scopus, and Web of Science will be searched from March 2019 to March 2024, with an update closer to the time of manuscript submission. Gray literature sources will also be searched. Publications that contain primary studies, systematic reviews, meta-analyses, and clinical guidelines addressing compassion fatigue and burnout prevention in health care professionals will be selected for inclusion. Extracted data items will include study characteristics, interventions for the prevention of compassion fatigue and burnout, measures of compassion satisfaction, burnout, and secondary traumatic stress, as well as the quality of reporting and methodology.

Results: A narrative synthesis with summary tables will be used to describe our findings. The review is expected to be completed by December 2025, and the search strategy has been developed and pilot-tested.

Conclusions: Our findings will help identify gaps in the literature with respect to compassion fatigue and burnout prevention strategies for health care professionals. This review will provide a comprehensive overview of current research, informing future interventions and policies aimed at improving health care professionals' well-being and job satisfaction.

Trial Registration: Open Science Framework r83cu; https://osf.io/r83cu

International Registered Report Identifier (IRRID): PRR1-10.2196/66360

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KEYWORDS

burnout; compassion; compassion fatigue; compassion satisfaction; fatigue; health care professionals; health care workers; professional quality of life; scoping review protocol; scoping reviews; secondary traumatic stress; stress; traumatic stress

Introduction

Overview

Compassion satisfaction among health care professionals is a crucial aspect of the quality of care provided. Compassion satisfaction refers to the positive feelings derived from caring for others and the ability to help effectively [1]. It is closely related to, yet distinct from, compassion fatigue, which can be defined as the emotional and physical exhaustion that health care workers can experience when exposed to prolonged periods of high emotional stress while caring for patients. These concepts are integral to understanding the professional quality of life of health care workers, which encompasses both positive and negative aspects of their work experience. When this satisfaction is absent, it can lead to significant negative consequences, such as burnout and secondary traumatic stress, compromising the effectiveness and quality of care offered to patients [2]. The professional quality of life of health care professionals is vital, as it directly affects their well-being and job satisfaction [3].

Recent studies have focused on examining compassion satisfaction, burnout, and secondary traumatic stress among health care professionals, revealing varying levels of these factors [3,4]. Research conducted in Brazil found that neonatal intensive care unit (ICU) nurses face higher levels of burnout compared to other ICU departments, indicating the specific challenges faced by health care professionals in this environment [5,6].

Various factors influence professional quality of life, including gender, sleep medication, education level, position, department, communication difficulty, and number of children [7,8]. These factors can impact professional quality of life in various ways. For instance, sleep medication use may indicate poor sleep quality, which can exacerbate stress and fatigue [9]. Education level and position may influence job responsibilities and autonomy, affecting job satisfaction [10,11]. Communication difficulties can lead to increased stress and potential conflicts [12]. The number of children may impact work-life balance [13]. Collectively, these factors can contribute to increased risk of burnout and decreased compassion satisfaction. Understanding these relationships is crucial for developing effective interventions to improve health care professionals' well-being and, consequently, the quality of patient care. Therefore, health care organizations should focus on implementing strategies to promote better sleep hygiene and support the overall mental health and job satisfaction of their staff [7,8].

Informal and continuous education play an important role in preventing problems related to quality of life, suggesting that professional experience accumulated over the years can be a preventive factor [14,15]. Moreover, workload has a significant relationship with burnout and well-being, where an increase in workload can elevate the risk of burnout and, paradoxically, also be associated with well-being [13,14]. Compassion, satisfaction, and burnout are statistically significant predictors of well-being, with positive and negative relationships, respectively [14,15].

Health care professionals face emotional challenges when dealing with death and providing compassionate care, such as feelings of helplessness and sadness [16]. Ethical dilemmas and moral distress are prevalent, indicating the complexity of decision-making that these professionals face [17]. Psychological resilience and organizational support are fundamental for promoting well-being and reducing compassion fatigue [18,19].

The health care work relationship is strongly marked by the ambivalence between suffering and pleasure, with the physical and mental health of professionals often at risk [20]. Scientific production on moral distress among health care professionals showed significant growth between 2015 and 2018, with most articles published in English, reflecting a growing and global interest in the topic [20].

Health care professionals often face challenges when trying to align their care with their personal belief systems, resulting in acute moral distress [21]. This phenomenon is exacerbated by the lack of adequate resources and limited coping strategies to mitigate the intense demands of work [21]. Studies also reveal a high prevalence of stress among health care professionals, with a significant proportion reporting elevated levels of stress, anxiety, and exhaustion [22]. Continuous exposure to traumatic situations and painful patient stories contributes to compassion fatigue, known as vicarious traumatization [23].

To address these challenges, interventions such as increasing qualified staff, improving multidisciplinary collaboration, and promoting a healthy organizational culture have been suggested to mitigate moral distress and improve the well-being of health care professionals [24]. Furthermore, a healthy lifestyle, including regular physical activity, has demonstrated a correlation with lower burnout symptoms and better mental well-being among professionals [25].

Objectives

The primary objectives of this scoping review are:

1. To map the existing evidence on levels of compassion satisfaction, burnout, and secondary traumatic stress among health care professionals across various health care settings.
2. To identify and analyze factors influencing the professional quality of life of health care workers, including workplace environment, workload, and organizational support.
3. To synthesize information on interventions and strategies aimed at preventing or mitigating compassion fatigue and burnout in health care professionals.
4. To identify gaps in the current literature regarding compassion fatigue and burnout prevention in health care settings, thereby informing future research directions.

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Justification

The scoping review is justified by the identification of substantial gaps in previous research, whose conclusions reverberate both in the theoretical and practical domains of the mental health field. The evidence highlighted the urgent need for comprehensive investigations addressing the prevalence of compassion fatigue among professionals in this area, as well as the need for a deeper understanding of the associated professional demands and resources [20]. Moreover, the growing consolidation of the concept of compassion fatigue signals the importance of considering the spiritual dimension in the context of mental health practices, suggesting a more in-depth analysis in this domain [21]. Therefore, the proposed scoping review aims to fill these gaps, promoting advances in scientific knowledge and providing essential subsidies for practice and the development of evidence-based interventions, aiming to improve the quality of care offered by mental health professionals.

Methods

This scoping review will be conducted according to the methodological frameworks proposed by Arksey and O'Malley [26] and Levac et al [27], also incorporating the recommendations of the Joanna Briggs Institute (JBI) for scoping reviews. The review process will follow the following steps: (1) identification of the research question; (2) identification of relevant studies; (3) study selection; (4) data extraction; (5) synthesis and reporting of results; and (6) consultation with experts.

Research Question

The research question guiding this scoping review is: "What has been published in the literature about compassion fatigue and coping with it among health care professionals in the workplace?". This review will investigate both qualitative and quantitative studies to provide a comprehensive understanding of the topic. We will examine various measures and indicators of compassion fatigue, burnout, and compassion satisfaction levels among health care professionals. These may include standardized scales such as the Professional Quality of Life (ProQOL) scale, as well as qualitative descriptions of experiences and coping strategies. By including diverse study types and measurement approaches, we aim to capture the multifaceted nature of these phenomena in health care settings.

This question was established using the Population, Concept, Context (PCC) strategy, where the Population refers to health care professionals, the Concept is "compassion fatigue and coping," and the Context encompasses "workplace." The PCC strategy is widely used to formulate research questions in scoping and systematic reviews [28].

Eligibility Criteria

The inclusion and exclusion criteria (Textbox 1) were defined based on the research question and the objective of the review, following the PCC framework:

1. Population: Health care professionals (including but not limited to doctors, nurses, allied health professionals, and mental health workers);
2. Concept: Compassion satisfaction, compassion fatigue, burnout, secondary traumatic stress, coping strategies, and interventions;
3. Context: Workplace settings in health care (hospitals, clinics, community health centers, etc).

Multimedia Appendix 1 summarizes the eligibility criteria for the scoping review.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Primary studies, systematic reviews, meta-analyses, and clinical guidelines.
- Published between March 2019 and March 2024.
- In English, Portuguese, and Spanish.
- Addressing workplace prevention for compassion fatigue and burnout in health care professionals.
- Studies addressing compassion satisfaction, burnout, and secondary traumatic stress in health care professionals.

Exclusion criteria

- Studies that do not fit the scope of the review.
- Duplicate publications.
- Letters to the editor, editorials, and opinion articles.
- Studies that do not present empirical data or are not available in full-text.

Information Sources

Searches will be conducted in the following electronic databases: EMBASE, ERIC, PubMed, Science Direct, Scopus, and Web of Science. In addition, a search for gray literature will be conducted, including theses, dissertations, government reports, and conference proceedings [29].

Search Strategy

The search strategy will use descriptors in English, Portuguese, and Spanish, combined with Boolean operators (AND, OR,

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NOT). The search terms include "health care professionals," "health workers," "health team," "burnout," "compassion fatigue," "compassion satisfaction," "professional exhaustion," "emotional exhaustion," "occupational stress," "burnout syndrome," "impact," "consequences," "prevention," "interventions," "coping strategies," "treatment," "support," "well-being," "quality of life." The search strategy will be adapted for each database to ensure comprehensive coverage.

Multimedia Appendix 2 shows the search strategy for the scoping review in the PubMed database.

Study Selection

The study selection process will be performed by 2 reviewers independently, using the Covidence reference management software [30]. Initially, titles and abstracts will be screened, followed by full-text reading of potentially relevant studies. Discrepancies will be resolved by consensus or by a third reviewer. The selection process will follow the recommendations of PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) [31] and will be presented through a flowchart.

Data Extraction

Data will be extracted using a standardized form, developed specifically for this review [32]. The form will be pilot-tested on a sample of studies to ensure its comprehensiveness and reliability. The form will include information on authorship, year of publication, country, objective, study design, population, outcomes assessed, main results, and conclusions. A total of 2 reviewers will independently extract data, with any discrepancies resolved through discussion or involvement of a third reviewer.

Multimedia Appendix 3 shows the data extraction form.

Data Synthesis

Data synthesis and analysis data synthesis will be performed narratively, with tables and graphs to summarize the findings [33]. Qualitative analyses, such as thematic analysis, may be used to identify recurring themes in the included studies [34]. We will use Braun and Clarke's (2006) framework for thematic analysis, which involves familiarization with the data, generating initial codes, searching for themes, reviewing themes, defining and naming themes, and producing the report [35]. Data synthesis will involve a narrative summary of the findings, organized thematically based on the research questions. To integrate the quantitative and qualitative data, we will use a mixed-methods approach. Quantitative data, such as prevalence rates of compassion fatigue and burnout, will be presented alongside qualitative themes to provide a more comprehensive understanding of the phenomenon. We will look for convergence, divergence, and complementarity between the quantitative and qualitative findings to answer our main research questions. Consultations with experts in the field of health care professional well-being and burnout prevention will be conducted to validate the findings and provide additional insights [27]. Expert feedback will be integrated into the final synthesis of results, contributing to the interpretation and contextualization of the findings.

Protocol Registration

This scoping review adheres to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines [36] to ensure transparency and quality of reporting (Multimedia Appendix 4). To further enhance transparency and reproducibility, the review protocol has been registered prospectively in the Open Science Framework (OSF) [37].

Ethical Considerations

As this is a scoping review of existing literature, no ethical approval is required. However, we will ensure that all included studies have adhered to ethical standards in their conduct and reporting.

Results

The search strategy will be finalized by July 2025, followed by the screening process in August and September 2025. Data extraction and analysis will occur in October and November 2025, with the final report being prepared in December 2025.

Discussion

Overview

This scoping review will provide a comprehensive overview of the current state of research on compassion fatigue, burnout, and secondary traumatic stress among health care professionals. The findings will allow us to map the levels of compassion satisfaction and its relationship with professional quality of life, focusing on the key factors that influence these outcomes, such as work environment, workload, and organizational support. In addition, interventions identified in the literature for the prevention of burnout and compassion fatigue will be summarized, offering valuable insights into potential strategies for improving health care professionals' well-being.

We anticipate that the results will highlight important trends, including the prevalence of compassion fatigue and burnout across different health care settings, and the effectiveness of interventions aimed at mitigating these issues. These data will be instrumental in identifying critical gaps in the current literature, particularly in terms of understudied populations or regions where health care systems face unique challenges.

The findings are expected to show the need for targeted strategies that address health care professionals' emotional resilience and coping mechanisms. These results may also inform the development of training programs and organizational policies aimed at reducing burnout, improving job satisfaction, and enhancing the overall mental health of health care workers.

Principal Results

Based on existing literature and background research, it is anticipated that while compassion satisfaction plays a critical role in buffering against burnout and secondary traumatic stress, there remains a lack of consistent and effective interventions specifically tailored for health care professionals. The results underscore the need for more nuanced and individualized approaches that consider the specific contexts in which health

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care professionals operate, including factors such as the department they work in, their roles, and the intensity of their workload.

This scoping review will build upon existing literature by providing a comprehensive overview of compassion fatigue and burnout across various health care professions. Previous studies, such as those by [38,39], have focused on specific health care professions or settings. Our review aims to synthesize findings across the entire health care sector, potentially revealing patterns and insights that may not be apparent in more focused studies. In addition, by including both quantitative and qualitative studies, we hope to provide a more nuanced understanding of the experiences of health care professionals and the effectiveness of various coping strategies and interventions.

This scoping review is one of the first to synthesize the literature on compassion fatigue and burnout prevention strategies across various health care settings. The importance of promoting mental health and emotional resilience through workplace interventions, including peer support and mental health programs, will likely emerge as key themes.

Limitations

One limitation of this review is its reliance on published literature from English, Portuguese, and Spanish, which may exclude studies from other languages that could contribute valuable insights. In addition, the quality of the studies included may vary, as the review does not plan to formally assess study quality, a common limitation in scoping reviews. Furthermore, the review will be confined to studies published between 2019 and 2024, which may not capture earlier works that provide foundational knowledge.

Comparison with Prior Work

Compared to previous reviews [2], this study provides a more structured and comprehensive mapping of the factors affecting health care professionals' professional quality of life. While earlier works [5] have focused on specific interventions or particular groups, such as nurses in neonatal ICUs, this review will offer a broader, cross-sectional analysis, covering diverse health care environments and professional roles. In addition, this review integrates findings from both primary research and gray literature, offering a more expansive view of the available evidence.

Implications for Practice and Research

The results of this scoping review will have significant implications for health care organizations, educational institutions, and policy makers. The identified strategies for preventing compassion fatigue and burnout can inform the development of targeted interventions and workplace policies. For researchers, this review will highlight critical gaps in the current literature, suggesting avenues for future studies, particularly in understudied health care settings or professional groups.

Conclusions

The results of this scoping review will provide essential insights into compassion fatigue and burnout prevention strategies, helping to inform future interventions and policies. These findings will be valuable for health care organizations, educational institutions, and policy makers aiming to improve health care professionals' well-being and job satisfaction. The review will also contribute to the growing body of literature on mental health in the health care workforce, offering new avenues for research and practical solutions to address these critical challenges.

By identifying key gaps in the current literature, this review will guide future research aimed at enhancing the mental resilience of health care professionals, ultimately improving the quality of care they provide to patients.

Dissemination of Results

The findings of this scoping review will be disseminated through publication in a peer-reviewed journal and presentation at relevant conferences. We will also create a summary of the findings for stakeholders, including health care administrators and policy makers, to facilitate the translation of research into practice.

Acknowledgments

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Data Availability

Data sharing is not applicable to this article as no new datasets were generated or analyzed during this study.

Authors' Contributions

CS, MN, and JA contributed to conceptualization, methodology, and writing-original draft. SC, MF, CC, ES, JM, MS, LS, and TM contributed to methodology, writing-review and editing. NC, RS, VB, AL, PF, DO, ND, CM, and GF contributed to writing-review and editing, supervision.

Conflicts of Interest

None declared.

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Multimedia Appendix 1
Eligibility criteria for the scoping review.
[DOCX File , 13 KB - resprot_v14i1e66360_app1.docx]

Multimedia Appendix 2
Search strategy for the scoping review in PubMed database.
[DOCX File , 14 KB - resprot_v14i1e66360_app2.docx]

Multimedia Appendix 3
Data extraction form.
[DOCX File , 14 KB - resprot_v14i1e66360_app3.docx]

Multimedia Appendix 4
PRISMA-P (Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols) checklist.
[DOCX File , 27 KB - resprot_v14i1e66360_app4.docx]

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Abbreviations

ICU: intensive care unit

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JBI: Joanna Briggs Institute
OSF: Open Science Framework
PCC: Population, Concept, Context
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
ProQOL: Professional Quality of Life

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Protocol

Student Mental Health in UK Higher Education Institutions: Protocol for a Scoping Review of Trends, Gaps, and Research Directions

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Abstract

Background: There is growing concern about the mental health of students in higher education institutions (HEIs) across the United Kingdom. Increasingly diverse student populations, the legacy of the COVID-19 pandemic, and variations in policies and service provision across the 4 UK nations have highlighted the need for a comprehensive understanding of student mental health. Current literature remains fragmented, with limited synthesis comparing national contexts. This protocol outlines a scoping review to systematically map the evidence base, identify key research gaps, and inform future research priorities and interventions.

Objective: The primary aim is to identify and map existing research on student mental health in UK HEIs. Specific objectives include exploring how student mental health is defined and measured, identifying risk factors, assessing support systems and interventions, and highlighting gaps in research across England, Scotland, Wales, and Northern Ireland.

Methods: This scoping review will follow Joanna Briggs Institute methodology and be reported in line with PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) guidelines. Studies will be eligible for inclusion if they (1) were conducted in the United Kingdom; (2) involved students aged 16 years and older enrolled in HEIs; (3) addressed mental health–related outcomes, definitions, or interventions; and (4) were published in English from 2005 onwards. Excluded materials include gray literature not identified during database searching. A comprehensive 3-step search strategy will be used. Initially, APA PsycInfo and MEDLINE (Ovid) will be searched, followed by a broader search across Scopus, Web of Science (Core Collection), Child and Adolescent Development Studies, and the Cochrane Library. Reference lists of the included studies will be screened for additional sources. All citations will be managed using Covidence, and study selection will involve title/abstract screening and full-text review by independent reviewers. Data extraction will include information on study design, population characteristics, mental health outcomes, measures used, interventions, and key findings. Data will be presented in tabular and narrative forms and, where appropriate, descriptive content analysis will be used.

Results: As of April 2025, preliminary searches and pilot screenings have been completed. The full database search and data charting phase will commence in June 2025. The final synthesis, analysis, and stakeholder consultation are scheduled between

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September and November 2025. The full review will be completed by December 2025, with dissemination activities planned through early 2026.

Conclusions: This review will provide a comprehensive overview of student mental health research within UK HEIs. It will highlight the key national differences, emerging themes, and underresearched areas, supporting more targeted, evidence-informed policy and practice. Limitations include language and gray literature exclusions. Nonetheless, the findings are expected to make a timely and meaningful contribution to research and intervention strategies in UK higher education.

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KEYWORDS

mental health; United Kingdom; higher education institutions; student counselling; well-being; scoping review; evidence-based; systematic search

Introduction

Background

Mental health challenges among students in UK higher education institutions (HEIs) have reached unprecedented levels, prompting urgent concerns across academic, clinical, and policy sectors [1-4]. Across England, Scotland, Wales, and Northern Ireland, students are reporting high and increasing rates of depression, anxiety, psychological distress, self-harm, and suicidality. In 2022, the UK Office for National Statistics reported that 37% of the students experienced moderate to severe symptoms of depression or anxiety—significantly higher than the general population of the same age group.

The COVID-19 pandemic has further intensified these difficulties, exacerbating pre-existing inequalities and placing increased pressure on both students and institutional mental health services [5,6]. Disruption to education, social isolation, financial strain, and heightened uncertainty have had a lasting impact on student well-being. However, mental health challenges are not evenly distributed across student groups. Underrepresented and marginalized populations, including mature students; students from ethnic minority backgrounds; lesbian, gay, bisexual, transgender, queer/questioning (LGBTQ+) students; international students; and neurodivergent students often face additional structural and cultural barriers that influence both their experiences of mental health and their ability to access appropriate support [7-9].

Moreover, there has been growing evidence of an increase in student suicides across UK HEIs, drawing national concern and prompting calls for systemic reform. Data from the Office for National Statistics and sector-specific analyses have highlighted that although student suicide rates remain lower than those in the general population, the absolute number of student deaths by suicide has risen in recent years. These findings have positioned suicide prevention as a growing policy and institutional priority, further underlining the urgency of building a comprehensive and evidence-informed understanding of student mental health in the United Kingdom [10-14].

At the same time, government policies aimed at widening access to HEIs, particularly among students with no family history of higher education, mature learners, and those entering university through vocational pathways, have resulted in increasingly diverse student populations. Although these policies have supported greater equity and inclusion, they have also placed greater demands on student support services, with no proportional increase in available resources [15]. Growing evidence suggests that only a relatively small proportion of students who experience mental health problems are likely to seek help [16-18], with help-seeking behaviors particularly low among international students [19-21].

Despite growing awareness of the mental health crisis in UK universities, several barriers continue to limit student access to timely and appropriate care. These include stigma, fears around confidentiality, culturally insensitive services, long waiting times, and uncertainty about where and how to seek support [22,23]. These issues are further complicated by the devolved nature of health and education policy in the United Kingdom, which has resulted in marked variations in the organization, funding, and delivery of student mental health services across England, Scotland, Wales, and Northern Ireland. For example, England has focused on NHS (National Health Service)-HEI partnerships through the University Mental Health Charter, aiming to embed a whole-university approach to mental well-being. Scotland has adopted a trauma-informed and rights-based framework within educational settings. Wales and Northern Ireland have developed distinct policy paths aligned with their devolved government priorities. These differences in the national strategy are set against diverse institutional and geographic contexts—including urban versus rural student populations, campus size, cultural diversity, and student mobility.

There are contextual disparities in the academic and student experience across the 4 nations, reflecting both systemic and demographic differences. In Scotland, the Commission on Widening Access and associated widening participation strategies have supported the inclusion of students from underrepresented groups. Wales and Northern Ireland have followed similar approaches to broaden access and attract international students [24,25]. These widening participation efforts are often implemented in smaller, more rural institutions, which may face unique capacity challenges and experience-related stressors. By contrast, English HEIs tend to have larger and more diverse student populations. International literature suggests that students in highly diverse cohorts may experience increased emotional strain and a lower sense of belonging, which can further impact mental health outcomes [26-28].

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Differences in tuition models and degree structures further compound these variations. Students in England and Wales typically undertake 3-year bachelor's programs and are required to pay full tuition fees regardless of residency status. In contrast, Scottish and Northern Irish students generally benefit from government-funded tuition and pursue 4-year degree programs. In Scotland, the first 2 years of study are broader and more interdisciplinary, with specialization occurring in later years. These structural distinctions in financial, academic, and cultural landscapes shape the student experience and may have important implications for student well-being; yet, they are rarely accounted for in mental health research or policy development.

Although international evidence on student mental health is extensive, UK-specific comparative research remains relatively underdeveloped. Some reviews have explored correlates of mental health and well-being among university students in the United Kingdom [29], and others have examined the association between financial stress and poor mental health outcomes [30]. However, these reviews do not distinguish among the distinctive sociopolitical, cultural, and institutional contexts of the 4 UK nations. There is a need for new work that actively compares and contrasts these national landscapes and explores how structural differences may affect student mental health. There is currently no comprehensive synthesis of the UK student mental health evidence base. This limits the ability of institutions, funders, researchers, and policy makers to make informed data-driven decisions, design inclusive support systems, or identify strategic priorities for future research and innovation.

A scoping review is the most appropriate methodology for addressing this gap. Unlike systematic reviews, which focus on narrowly defined research questions or interventions, scoping reviews are designed to map the breadth, nature, and range of available evidence [31]. This approach allows for a more inclusive and flexible understanding of how student mental health is conceptualized, studied, and supported across different institutional and policy contexts within the United Kingdom.

Scoping Review Questions

Primary Research Question

What is the current state of research on student mental health in UK HEIs, and what are the key priority areas for future research?

Secondary Research Questions

Conceptualization and Definitions

1. How is student mental health defined, conceptualized, and framed in the UK higher education context?
2. What language, models, or theoretical frameworks are used to describe mental health and well-being?

Prevalence and Risk Factors

1. What is known about the prevalence and patterns of mental health conditions among UK HEI students?
2. What risks and protective factors are associated with student mental health across different demographic and social groups (eg, ethnicity, gender, sexuality, socioeconomic background, international status, disability, neurodivergence)?

Support Systems and Interventions

1. What forms of mental health support (eg, university services, peer interventions, NHS pathways, digital tools) are described in the literature?
2. How are these services accessed, evaluated, and experienced by students?

Policy and Institutional Contexts

1. How do institutional policies and service models differ across the 4 UK nations, and how are these differences reflected in the evidence base?
2. What roles do universities, governments, and other stakeholders play in shaping mental health provision?

Methodological Scope and Gaps

1. What study designs, populations, and measures are commonly used in research on student mental health in UK HEIs?
2. What are the key gaps in the literature in terms of geography, populations, conceptual clarity, or methodological rigor?

Methods

The purpose of the scoping review method is to map a body of literature with the intention to illuminate the key characteristics, terms, methods, findings, interventions, and relevant gaps to inform future research [32-34]. The Joanna Briggs Institute (JBI) guidance on how to conduct a scoping review will be adhered to throughout [35].

Ethical Considerations

As this protocol for a scoping review involves the synthesis of previously published, publicly available data and does not include human participants, ethics approval is not required. However, the review will be conducted in line with established ethical principles for secondary research, including the accurate representation of findings, acknowledgment of original sources, and transparent reporting of results following PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) guidelines (Multimedia Appendix 1) [36].

Eligibility Criteria

Population

For the purpose of this review, the term "students" refers to individuals aged 16 years and older who are enrolled in HEIs in the United Kingdom. This includes undergraduate, postgraduate taught, and postgraduate research students across all modes of study (full-time, part-time, distance learning). There will be no upper age limit to ensure full representation of the UK HEI student population, including mature students. Students of any country of origin will be eligible, provided they are enrolled in a UK-based HEI. Studies focusing exclusively on academic staff or non-HEI student populations (eg, secondary school or further education students) will be excluded.

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Concept

This review will include studies that specifically focus on mental health, mental illness, mental disorders, or psychological distress as they relate to students in HEIs. Eligible studies must make explicit reference to HEI students in the context of mental health–related terminology, including but not limited to depression, anxiety, suicidality, self-harm, stress, and emotional well-being. Studies that explore students' personal understandings and lived experiences of mental health, where alternative terminology such as mental distress, madness, or culturally-specific terms are used will also be included, with attention to the language adopted by the participants themselves.

Context

This review will focus on research conducted within the context of UK HEIs, encompassing all 4 nations: England, Scotland, Wales, and Northern Ireland. Studies that include comparisons across these UK nations or between United Kingdom and international HEIs will also be included where relevant to the UK context.

Date of Publication

Eligible studies must have been published between 2005 and the present, covering a 20-year period. This time frame allows the review to capture changes in student mental health in response to evolving societal, institutional, and policy developments, including the widening participation agenda and the impact of COVID-19.

Types of Evidence Source

This review will include a broad range of evidence types to map the diversity of research in the field. Eligible sources include primary research studies employing qualitative, quantitative, or mixed methods designs; systematic and scoping reviews; case studies; and relevant opinion or commentary pieces that offer critical insight into student mental health in UK HEIs.

Language

Only studies published in English will be included, given that English is the primary language of instruction and publication in UK higher education and aligns with the context being reviewed.

Search Strategy

A comprehensive 3-step search strategy will be employed, consistent with the JBI methodology for scoping reviews [37,38]. An initial limited search was conducted in APA PsycInfo and MEDLINE (via Ovid) to identify relevant keywords, subject headings, and search string combinations specific to student mental health within the UK higher education context. These databases were selected for their broad coverage across psychology, psychiatry, medicine, and behavioral sciences, and their relevance to multidisciplinary research in student mental health. Building on insights from this exploratory phase, the search will be expanded to include the following databases: Scopus, Web of Science (Core Collection), Cochrane Library, and Child and Adolescent Development Studies. This approach ensures broad disciplinary coverage, capturing literature from education, health, psychology, and social sciences, and supports a comprehensive mapping of the available evidence while minimizing publication bias.

The search will be limited to studies published from 2005 to the present. This 20-year time frame was selected to capture significant shifts in UK higher education and mental health policy, including the development of national strategies, service expansion within HEIs, and the impact of the COVID-19 pandemic. The time span allows for a comparative understanding of trends over 2 decades and aligns with increasing sector-wide attention to student mental health.

Search terms were developed in consultation with an academic librarian and refined based on JBI guidance [38]. A draft version of the search strategy for APA PsycInfo is provided in Multimedia Appendix 1, and this will be further adapted for use across the selected databases. Finalized search strategies for each database will be included as supplementary material with the completed review manuscript. All retrieved references will be managed using EndNote software and imported into Covidence for deduplication, screening, and selection. The review will follow the PRISMA-ScR checklist [39] to ensure transparency and methodological rigor throughout the process.

Sources of Evidence

Prior to commencing the screening process, a calibration exercise will be conducted to ensure reliability in correctly selecting the studies for inclusion by reviewers [39]. Two levels of screening will be used to identify the sources of evidence for inclusion in the scoping review: (1) study selection—review title and abstract and (2) study screening—review the full text. The study selection will be conducted by 3 independent reviewers. Data screening, charting, and literature quality assessments will be managed using Covidence software to sift, categorize, and sort findings according to key issues and themes. Any studies identified as relevant based on the title and abstract by one or both researchers will be reviewed at full-text level. The screening process involves both reviewers evaluating the full texts of the selected studies in relation to the predetermined inclusion criteria. Where disagreement occurs between reviewers, full texts will be screened again, and discussion will take place until a consensus is met. If necessary, validation by a third reviewer will be sought. A PRISMA flowchart will be used to report the final number in the study selection process.

Data Extraction

Data extraction will be conducted using a standardized data charting form developed in accordance with the JBI guidelines and tailored to the specific aims and research questions of this review. The form will be piloted independently by 2 reviewers on a sample of 5 studies to ensure clarity, consistency, and comprehensiveness. Any discrepancies will be discussed within the review team and amendments made to the charting form as needed. For each included study, the following data will be extracted:

1. Citation details: author(s), year of publication, journal, or source
2. Study characteristics: study design, methodology, sample size, setting, and UK nation(s) covered

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3. Participant demographics: age, gender, ethnicity, student status (eg, undergraduate, postgraduate, international, first-generation, mature students)
4. Mental health focus: key concepts and definitions used; types of mental health issue or condition explored (eg, anxiety, depression, psychological distress, well-being)
5. Aims and objectives of the study
6. Measurement tools or outcome measures: instruments or self-report measures used to assess mental health (including any validated tools)
7. Key findings and themes: including prevalence data, risk and protective factors, and outcomes related to student mental health
8. Support/intervention type (if applicable): such as digital platforms, counselling services, peer support, or curriculum-integrated interventions
9. Policy and institutional context (where applicable): including links to national policies, institutional frameworks, or funding models
10. Identified gaps or research priorities: where specified by study authors
11. Funding source and any declared conflicts of interest

The extracted data will be synthesized descriptively by using a narrative synthesis approach. This will involve mapping key study characteristics and thematically analyzing findings to identify commonalities and differences in how student mental health is conceptualized, experienced, and supported across UK HEIs. Quantitative data (eg, prevalence rates, frequencies of identified risk factors) will be summarized using tables and basic descriptive statistics. Qualitative findings will be analyzed thematically by using content analysis techniques to identify recurring patterns in definitions, lived experiences, and institutional responses. Data will be mapped directly against the primary and secondary research questions. Where possible, findings will be stratified by population subgroup such as Black, Asian, ethnic minority students, neurodivergent students, LGBTQ+ students, mature learners, and international students—as well as by UK nation, to support a comparative analysis across different demographic and geopolitical contexts.

The synthesis will also highlight conceptual gaps (eg, lack of clarity or consensus around definitions of well-being, mental distress) and methodological limitations (eg, underuse of longitudinal, intersectional, participatory research designs). This will contribute to identifying evidence gaps and inform recommendations for future research directions and policy development. The process of data extraction from full-text studies will be performed by 2 independent reviewers. Discrepancies in charting will be discussed until consensus is reached; where necessary, a third reviewer will be consulted to resolve disagreements.

Results

Exploratory Research

An initial exploratory search was conducted in APA PsycInfo and MEDLINE (via Ovid) in March 2025 to identify relevant keywords, subject headings, and search combinations appropriate to the student mental health context within UK HEIs. This pilot search informed the refinement of the full search strategy and confirmed the feasibility of the review. Based on this initial phase, a revised and expanded search strategy was finalized in collaboration with an academic librarian.

As of April 2025, pilot testing of the inclusion and exclusion criteria has been completed by using a sample of 50 abstracts. The review team reached consensus on a clear eligibility framework aligned with the JBI methodology for scoping reviews [37,38], ensuring consistent application during the full screening process.

The full database search will be executed across APA PsycInfo, MEDLINE (Ovid), Scopus, Web of Science (Core Collection), Cochrane Library, and Child and Adolescent Development Studies in May 2025. Title and abstract screening will be completed by June 2025, followed by full-text review and data extraction in July and August 2025. The synthesis and analysis phases, including stakeholder consultation, are scheduled to take place between September and November 2025. The finalized review manuscript will be completed by December 2025, with dissemination activities planned throughout early 2026.

Data extracted from the included studies will be mapped descriptively to identify what is known about the key topics concerning student mental health in relation to the review's research questions. The synthesis will include frequency counts for populations, concepts, and methodological characteristics, as well as tabular summaries of study features such as participant demographics, settings, mental health focus, and institutional context. Where appropriate, content analysis techniques will be applied to examine patterns in definitions, lived experiences, and support responses across UK's 4 nations [40].

A narrative synthesis approach will be used to present key findings, supported by visual representations, including tables and charts. Data will be stratified by population subgroup (eg, mature, international, LGBTQ+, neurodivergent students) and UK nation to enable comparative analysis. This will allow for a clearer understanding of how different contexts and demographics shape mental health experiences and service access within HEIs.

A stakeholder consultation phase will follow the synthesis. This will involve presenting the findings to the broader research team and a student advisory group affiliated with the Scottish Student Mental Health Research Network (ScotSMART). Feedback will inform final refinements to the interpretation and framing of results. The results will then be disseminated to key stakeholders, including decision makers, policy developers, and academic audiences, ensuring that findings translate into actionable strategies for improving student mental health support across the United Kingdom.

Dissemination Plan

Findings from this scoping review will be disseminated through a combination of academic and nonacademic channels to ensure wide reach, stakeholder engagement, and meaningful impact. A full-length, peer-reviewed journal paper will present the complete review outcomes, methodological approach, and key

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thematic findings. In parallel, a summary report will be produced for institutional stakeholders, including universities, NHS bodies, student support services, and policy organizations across England, Scotland, Wales, and Northern Ireland.

Stakeholder-targeted dissemination will include tailored reports highlighting the review's key findings, research gaps, and actionable recommendations aligned with current priorities in the student mental health sector. These reports will be circulated to universities, health care providers, third-sector organizations, and national student mental health networks, supporting their use in practice and policy development. Academic dissemination will also include presentations at relevant national and international conferences in the fields of psychology, higher education, youth mental health, and student well-being. These may include events hosted by the British Psychological Society, Universities UK, the UK Mental Health in Higher Education Network, and global mental health research forums. Public engagement will be actively supported through a series of open-access, user-friendly outputs. These will include webinars, short-form digital summaries, and an infographic designed to communicate key insights and research gaps to a broad audience, including students, practitioners, and policy makers. Digital dissemination will also utilize institutional websites, social media platforms, and student mental health networks to enhance accessibility and visibility. To ensure real-world relevance and inclusive engagement, all dissemination materials will be co-developed with student and institutional partners, reflecting the participatory ethos that underpins this review. Input from the ScotSMART student advisory group will inform the design and framing of outputs to enhance resonance and uptake within the student community.

In line with open science principles, data management and transparency will be prioritized. All review outputs, including the finalized search strategies, data extraction forms, and synthesis tables, will be submitted as supplementary files or deposited in open-access repositories. This approach will support reproducibility, foster knowledge exchange, and maximize the long-term utility of the review findings for researchers, practitioners, and decision makers across disciplines and sectors. All dissemination materials will be co-designed with student representatives and institutional partners to ensure accessibility, relevance, and potential for real-world application. The dissemination strategy aims to inform future research, service development, and policy across UK's higher education sector.

Discussion

This protocol outlines a robust and comprehensive framework for conducting a scoping review aimed at mapping the existing evidence on student mental health within HEIs across the United Kingdom. The review will explore the multifaceted and contextually embedded challenges faced by students in England, Scotland, Wales, and Northern Ireland. It specifically considers issues such as financial strain, stigma, cultural, and structural barriers to help-seeking, and the compounding disadvantages faced by international, mature, neurodivergent, and underrepresented student groups. By focusing on these intersecting factors, the review seeks to provide a nuanced understanding of the mental health landscape across UK HEIs.

Building on prior reviews, which have often focused narrowly on intervention efficacy, singular mental health outcomes, or international student populations, this scoping review adopts a broader, more integrative approach. It extends the current evidence base by capturing a wider variety of study types and perspectives, incorporating literature from multiple disciplines, including education, psychology, sociology, and public health. This is particularly important in understanding the systemic, institutional, and policy-level influences on student well-being. Through its whole-system lens, this review will highlight both commonalities and divergences in how student mental health is experienced and addressed across UK's 4 nations.

A key strength of this protocol lies in its methodological rigor, including the use of the JBI methodological guidance for scoping reviews [37,38,41] and the PRISMA-ScR checklist [36] to enhance transparency and reporting quality. The inclusion of a multidisciplinary search strategy, consultation with an academic librarian, and pilot testing of the eligibility framework further enhances the reliability and replicability of the study. Additionally, the scoping review is distinctive in its commitment to incorporating comparative analyses across United Kingdom's devolved education systems, a relatively underexplored dimension in the existing literature.

Nevertheless, several limitations must be acknowledged. The decision to exclude gray literature may result in the omission of important contextual insights or emerging innovations that are not captured in peer-reviewed journals. Gray literature often includes institutional reports, policy briefs, or unpublished theses that could offer rich information about localized practices and lived experiences [42]. However, this exclusion is a deliberate methodological choice to ensure that the review remains manageable in scope and prioritizes high-quality, peer-reviewed evidence. The lack of standardization and variable quality in gray literature can pose challenges to data synthesis and limit the reliability of findings [43]. Another limitation is the restriction to English-language publications. Although this aligns with the dominant language of UK higher education and academic publishing, it may inadvertently exclude studies from international researchers or students working within UK HEIs who have published in other languages. However, this approach ensures feasibility within the resource constraints of the review team while maintaining focus on the linguistic context most relevant to the target population [44].

Despite these limitations, the anticipated findings of this review will make a meaningful contribution to the field. They will provide a foundation for future research by identifying conceptual and methodological gaps, including underresearched populations, neglected geographic areas, and limitations in study design such as the lack of longitudinal or intersectional analyses. Furthermore, this review will offer guidance for evaluating the effectiveness of tailored interventions and understanding how institutional structures and national policies shape student experiences. These insights will be crucial for developing evidence-informed strategies to improve mental health outcomes in HEIs across the United Kingdom.

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By synthesizing a wide range of evidence and offering a cross-national comparative perspective, this review has the potential to inform policy, guide service development, and influence institutional practices. It will serve as a critical resource for stakeholders aiming to cocreate inclusive and effective mental health strategies that are responsive to the evolving needs of diverse student populations. Moreover, the integration of feedback from stakeholders, including a student advisory group within ScotSMART, will enhance the relevance, legitimacy, and applicability of the review's conclusions.

Ultimately, this protocol establishes a timely and methodologically sound approach to understanding the state of student mental health research in the United Kingdom. In the context of growing national concern and escalating student demand for mental health services, there is an urgent need for comprehensive, contextually informed, and system-wide perspectives. This scoping review will bridge that gap by mapping the full spectrum of available evidence, highlighting where research has succeeded, and crucially, where it is still needed. In doing so, the review will support the development of coherent, equitable, and forward-looking strategies that can help transform the mental health outcomes of students across UK's higher education sector.

Acknowledgments

This review is undertaken as part of the Scottish Student Mental Health Research Network (ScotSMART), which is a research network for student mental health. It seeks to bring together academics, professional services, practitioners, and other student mental health research stakeholders to address a broad range of topics and facilitate knowledge exchange across the higher education sector. ScotSMART is funded by a research grant from the Royal Society of Edinburgh (reference 2509).

Authors' Contributions

Conceptualization and write-up of the protocol, review, and submission: NC
Reviewing and editing: AM, EL, MOT, ML, KD, CB, LH
Review and feedback of the protocol: MG
Review, update, and write-up of the protocol: SK
Reviewing and review: JM

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-ScR checklist and search strategy.
[DOCX File , 29 KB - resprot_v14i1e65594_app1.docx]

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Abbreviations

HEI: higher education institution
JBI: Joanna Briggs Institute
LGBTQ+: lesbian, gay, bisexual, transgender, queer/questioning
NHS: National Health Service
PRISMA-ScR: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews
ScotSMART: Scottish Student Mental Health Research Network

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Protocol

Addressing the Socioemotional Dimension of Medical Education: Protocol for a Scoping Review of Student-Driven Development Strategies

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Abstract

Background: The current international context, marked by complex global challenges, necessitates the rapid intervention of higher education institutions to contribute to social transformation. Medical education, in particular, is undergoing significant changes influenced by various factors, including the evolving health care environment and shifting social expectations. Socioemotional skills are increasingly recognized as essential competencies for medical professionals, contributing to better patient care, improved communication, and enhanced teamwork.

Objective: This scoping review aims to provide a comprehensive overview of the current literature on strategies employed by medical students to develop and promote their socioemotional skills in academic and hospital settings.

Methods: The review will be conducted according to the guidelines of the Joanna Briggs Institute, and the results will be presented in accordance with PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews). Eligibility criteria include studies focusing on medical students at any stage of their education, addressing strategies for developing socioemotional skills in academic or clinical contexts. Information sources include Embase, Emerald, PsycNet, PubMed, Scopus, and Web of Science, with searches conducted from January 2000 to April 2025. Gray literature sources, including ProQuest Dissertations & Theses Global, Conference Proceedings Citation Index, and OpenGrey, will also be searched. Two independent reviewers will screen titles, abstracts, and full texts. Data will be extracted using a standardized form and synthesized through narrative synthesis and thematic analysis.

Results: Results from our initial searches indicate a diverse range of literature addressing student-driven strategies for socioemotional skill development in medical education. The scoping review is progressing according to the following timeline. Protocol development and registration was completed in January 2025. Search strategy refinement was completed in February 2025. The initial database searching was expected to be completed in March or April 2025. Title and abstract screening are anticipated to be performed in May or June 2025. Full-text review and data extraction are anticipated to be performed in July to August 2025. Data synthesis and analysis are anticipated to be completed by September or October 2025. The manuscript is expected to be prepared and submitted by November or December 2025.

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Conclusions: The findings of this review may have significant implications for medical education curricula, informing the integration of socioemotional skill development alongside traditional medical knowledge and technical skills. Furthermore, the review may uncover gaps in the existing literature, highlighting areas that require further research and investigation. This scoping review will contribute to the growing body of knowledge on the importance of socioemotional skills in medical education.

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KEYWORDS

medical education; socioemotional skill; competency development; scoping review protocol; medical students; curriculum development

Introduction

In the rapidly evolving landscape of medical education, the development of socioemotional skills among medical students has emerged as a critical area of focus. This growing emphasis is reflected in the priorities of organizations such as the Association of American Medical Colleges [1] and the Accreditation Council for Graduate Medical Education [2], which increasingly recognize the importance of these skills in medical training. These skills, encompassing empathy, emotional intelligence, communication, resilience, and interpersonal effectiveness, are increasingly recognized as fundamental to providing high-quality patient care, fostering effective teamwork, and maintaining physician well-being [3,4]. As the health care environment becomes more complex and demanding, medical education must adapt to ensure that future physicians are equipped not only with clinical knowledge and technical proficiency but also with the socioemotional competencies necessary to navigate the multifaceted challenges of modern medical practice [5]. This scoping review aims to explore and synthesize the current literature on student-driven strategies for developing socioemotional skills in medical education, addressing a critical gap in our understanding of how medical students actively cultivate these essential competencies.

For the purposes of this review, we define socioemotional skills as a set of competencies that encompass the ability to recognize and manage emotions, develop care and concern for others, establish positive relationships, make responsible decisions, and handle challenging situations effectively [6]. This definition includes, but is not limited to, empathy, emotional intelligence, self-awareness, social awareness, relationship management, and responsible decision-making.

We define student-driven strategies as approaches, techniques, or practices that are primarily initiated, developed, or implemented by medical students themselves to enhance their socioemotional skills. These strategies may occur within or outside formal curricula and can include self-directed learning, peer-to-peer initiatives, extracurricular activities, or personal development practices [7]. For example, studies have explored the use of student-led support groups to address empathy, self-efficacy, and mental health stigma [8], and a scoping review shows the advantages of peer-mentoring programs, which reports academic (development of clinical confidence, skills in patient care, procedural skills, medical knowledge, interviewing and examination skills) and nonacademic (confidence, social support, peer relationships, and communication skills) benefits for both mentors and mentees [9].

Although our primary focus is on student-initiated approaches, this review also considers formal strategies that incorporate significant student feedback or input, enabling a comprehensive understanding of socioemotional skill development. This comprehensive approach allows us to examine the full spectrum of student engagement in socioemotional skill development, ranging from entirely self-directed activities to student-driven initiatives within formal educational settings. By including both formal and informal strategies, we aim to provide a nuanced understanding of how students actively participate in and shape their socioemotional skill development across various contexts in medical education. This inclusive approach will enable us to capture the diverse ways in which students engage with and contribute to their socioemotional learning, whether through self-directed efforts outside the curriculum or through active participation and modification of formal educational activities. By considering this broad range of strategies, we can better understand the interplay between institutional efforts and student-driven initiatives in fostering socioemotional competencies among future health care professionals. This review will examine the interplay between institutional efforts and student-led initiatives, analyzing how formal programs influence student strategies and how student feedback shapes institutional approaches. By considering this interaction, we can gain a deeper understanding of the socioemotional skill development in medical students.

The COVID-19 pandemic has further underscored the importance of this educational transformation, highlighting the need for flexible, resilient, and emotionally intelligent health care professionals [10,11]. Student-led strategies can play a crucial role in addressing the challenges posed by the crisis, promoting well-being, effective communication, and teamwork in high-pressure environments. In this context, understanding how medical students actively develop their socioemotional skills becomes even more crucial, particularly in terms of student-driven strategies that complement formal curricula.

This scoping review seeks to address this knowledge gap, providing insights that can inform more effective and student-centered approaches to socioemotional skill development in medical education. By identifying and categorizing the strategies used by students (objective 1), exploring the contexts in which these strategies are employed (objective 2), and examining the reported outcomes (objective 3), this review will

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provide a comprehensive overview of student-led approaches to socioemotional skill development. Furthermore, by identifying barriers and facilitators (objective 4) and highlighting gaps in the literature (objective 5), this review will inform future research and educational interventions.

The urgency during the COVID-19 pandemic forced a swift transition from the analog approach of conventional education—characterized by in-person, often paper-based, and physically interactive teaching methods—to a more digital model, even in contexts where the use of digital tools was less prevalent [12].

Despite the growing recognition of the importance of socioemotional skills in medical practice, there is a lack of comprehensive understanding of how medical students actively develop these crucial competencies. Although several reviews have examined formal curricula and interventions for socioemotional skill development in medical education [13,14], to our knowledge, no scoping review has specifically focused on student-driven strategies for developing these skills [15,16].

This scoping review aims to address this critical gap in understanding how medical students actively develop their socioemotional skills, complementing the formal curricula and institutional efforts to integrate these competencies into medical education. By exploring and synthesizing the current literature on student-driven strategies, this review seeks to provide insights that can inform more effective and student-centered approaches to socioemotional skill development in medical education.

The mental health of the students is of critical importance. Studies indicate a relationship between excessive use of social networks and higher levels of depression and anxiety in medical students [17]. Although data published on medical students' mental health during the COVID-19 pandemic have been conflicting, early detection and intervention strategies must be implemented to help them navigate challenging periods and be better prepared for other large-scale crises [12]. The integration of research and training is at the core of professional training and medical education. This integration manifests through a multifaceted approach.

1. Constructive process: it involves actively building knowledge and skills through hands-on research experiences and critical analysis of scientific literature.
2. Contextualization: the integration ensures that research activities are relevant to clinical practice and aligned with current health care challenges.
3. Formal coordination: educational institutions implement structured programs and curricula that systematically incorporate research components throughout medical training.
4. Scientific thinking: the integration aims to cultivate analytical and investigative mindsets in medical students, encouraging evidence-based practice.
5. Dialectical relationships: this approach fosters a continuous dialogue between theoretical knowledge and practical application, as well as between established medical paradigms and emerging research findings.

Through this comprehensive integration, medical education seeks to produce physicians who are not only skilled practitioners but also critical thinkers capable of contributing to the advancement of medical science [18,19]. The integration of research and training in medical education can promote the development of socioemotional skills by encouraging students to reflect on their experiences, collaborate with others, and apply ethical principles in their practice. By participating in research projects, students can develop empathy, communication skills, and problem-solving abilities, which are essential for providing patient-centered care.

Consequently, medical training requires an intertwining where the performance of teachers and the adequate management of emotions by students will positively impact the values that should accompany future professionals [20,21]. This emotional management influences professional values in several key ways:

1. Empathy enhancement: effective emotional regulation fosters greater empathy, enabling future physicians to better understand and respond to patient needs and experiences [22].
2. Ethical decision-making: improved emotional awareness contributes to more nuanced ethical reasoning, crucial for navigating complex medical dilemmas [23].
3. Resilience building: emotional management skills bolster resilience, reinforcing values such as perseverance and adaptability in challenging health care environments [24].
4. Professionalism: emotional intelligence cultivated through proper emotion management underpins professional behaviors, including respectful communication and maintaining appropriate boundaries [25].
5. Cultural competence: enhanced emotional awareness facilitates greater cultural sensitivity, aligning with values of inclusivity and equitable care [26]. The adequate management of emotions by students will positively affect the values that should accompany future professionals. Emotional management can influence ethical decision-making, resilience, and cultural competence, enabling physicians to provide compassionate, equitable, and culturally sensitive care.

By developing these emotional competencies, medical students are better equipped to embody and sustain the core values essential to compassionate, ethical, and effective medical practice.

The primary objective of this scoping review is to provide a comprehensive overview of the current literature on strategies employed by medical students to develop and promote their socioemotional skills in academic and clinical settings. Although this review primarily focuses on strategies used in academic and clinical settings, it also acknowledges the relevance of experiences in broader medical contexts such as primary care, global health, telemedicine, and public health, as these experiences can significantly influence the development and application of socioemotional skills.

Specific objectives include the following.

1. Identify and categorize the various strategies used by medical students to develop socioemotional skills.

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2. Explore the contexts in which these strategies are employed (eg, classroom, clinical rotations, extracurricular activities).
3. Examine any reported outcomes or effectiveness of these student-driven strategies.
4. Identify potential barriers and facilitators to student-driven socioemotional skill development.
5. Highlight gaps in the current literature and areas for future research.

The findings of this review have the potential to significantly impact medical education by (1) informing the design of more effective and student-centered approaches to socioemotional skill development in medical curricula, (2) identifying potential barriers and facilitators to skill acquisition from the student perspective, (3) highlighting informal learning opportunities that can be leveraged in formal educational settings, and (4) guiding future research on the effectiveness of various strategies for developing socioemotional skills.

By comprehensively examining this underexplored aspect of medical education, our scoping review will contribute to the growing body of evidence supporting the integration of socioemotional skill development in medical training, ultimately leading to better-prepared health care professionals and improved patient care.

Methods

Study Design

This scoping review protocol has been developed based on the methodological framework outlined by Arksey and O'Malley [13], further refined by Levac et al [14], and the Joanna Briggs Institute Manual for Evidence Synthesis [15]. This review will be reported in accordance with PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) [16]. The scoping review protocol was registered on the Open Science Framework.

Review Question

The scoping review question was developed by applying the population, concept, and context framework [27,28]: what has been published about the strategies for developing or promoting (concept) socioemotional skills (context) in medical students (population)?

Eligibility Criteria

Studies will be included if they meet the following criteria.

1. Population: medical students at any stage of their undergraduate or graduate medical education.
2. Concept: strategies, approaches, or methods used by students to develop or enhance socioemotional skills. These may include, but are not limited to, communication, empathy, emotional intelligence, teamwork, leadership, and self-awareness.
3. Context: academic settings (eg, classrooms, simulation centers) and clinical environments (eg, hospitals, clinics) where medical education takes place. This includes both formal educational activities and informal or extracurricular contexts where students engage in socioemotional skill development.
4. Study design: all types of primary research studies (qualitative, quantitative, and mixed methods), as well as review papers and gray literature (eg, theses, conference proceedings).
5. Time frame: studies published from January 2000 to the present, to capture contemporary approaches in medical education.
6. Language: studies published in English, Spanish, or Portuguese.

Studies will be excluded as follows.

1. Focus solely on formal curricular interventions implemented by faculty without student input or initiative.
2. Address only the development of clinical or technical skills without consideration of socioemotional competencies.
3. Involve health care professionals other than medical students (eg, nursing students, practicing physicians) as the primary population of interest.

The criteria mentioned above can be revised according to the available literature [13]. Although our primary interest lies in student-driven strategies, we recognize that these can occur within both formal and informal educational contexts. Therefore, our review will include studies that examine (1) entirely self-directed or informal activities initiated by students outside of the formal curriculum, (2) student-led or student-modified activities within formal educational settings, and (3) formal educational strategies that incorporate significant student input or allow for substantial student agency in skill development.

By including this range of contexts, we aim to capture the full spectrum of student engagement in socioemotional skill development. During the analysis phase, we will distinguish between these different types of strategies to provide a comprehensive understanding of how students actively participate in developing their socioemotional skills across various educational contexts.

Types of Sources

The bibliographical research will be performed using the following databases: Embase, Emerald, PsycNet, PubMed, Scopus, and Web of Science. The search strategy was developed by a librarian expert in the subject and will be conducted using keywords in English, Spanish, and Portuguese to ensure comprehensive coverage of the literature. A comprehensive search strategy will be developed in consultation with a health sciences librarian. The strategy will include a combination of Medical Subject Headings (MeSH) terms and keywords related to medical students, socioemotional skills, and development strategies. The search strategy will be initially developed for MEDLINE and then adapted for other databases. A draft search strategy for MEDLINE is provided in Textbox 1.

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Textbox 1. Search strategy.

("Medical Education" OR "Medical School*" OR "Medical Student*" OR "Medical Universit*" OR "Medical Facult*") AND ("Competency-Based Education" OR "Competency Based Education" OR "Education, Competency-Based" OR "Competency-Based Educations" OR "Education, Competency Based" OR "Educations, Competency-Based" OR "Educación Basada en Competencias") AND ("Socioemotional Skills" OR "Social Skills" OR "Interpersonal Skills" OR "Emotional Intelligence" OR "Empathy" OR "Self-awareness" OR "Social Awareness" OR "Relationship Management" OR "Affective Skills" OR "Emotional Competence" OR "Social Competence" OR "Emotional Regulation" OR "Social-Emotional Learning" OR "SEL") AND ("Student-driven" OR "Self-directed Learning" OR "Peer-to-peer Learning" OR "Student-initiated" OR "Extracurricular Activities" OR "Personal Development" OR "Student-led" OR "Self-regulated Learning" OR "Autonomous Learning" OR "Independent Learning" OR "Student Agency" OR "Student Empowerment")

To ensure a comprehensive search that captures both socioemotional skills and student-driven strategies, we have expanded our search terms. For socioemotional skills, we have included terms such as emotional intelligence, empathy, self-awareness, social awareness, relationship management, and affective skills. To capture student-driven strategies, we have incorporated terms such as self-directed learning, peer-to-peer learning, student-initiated, extracurricular activities, and personal development. Additionally, we have refined our search to focus specifically on medical students by including terms such as medical education, medical school, and medical students instead of broader higher education terms.

Additionally, we will search for gray literature by using ProQuest Dissertations & Theses Global, Conference Proceedings Citation Index (via Web of Science), and OpenGrey. Literature analysis will begin after identifying suitable studies and removing duplicates. The search strategy will be adequately refined if the literature list is found to be inappropriate [15,27].

Study Selection

All identified citations will be collected and uploaded to the online Rayyan platform following the search strategy [29], and duplicates will be removed. Titles and abstracts will be selected and evaluated by 2 independent reviewers according to the review inclusion criteria. Potentially relevant sources will be fully retrieved.

The full text of the selected citations will be assessed against the inclusion criteria by 2 independent reviewers. Reasons for excluding full texts that do not meet the inclusion criteria will be recorded and reported in the review. At any selection stage, disagreements between reviewers will be resolved through discussion or with the mediation of a third reviewer. The search results and the study inclusion process will be represented according to PRISMA-ScR guidelines [16,30]. The complete PRISMA-Protocols checklist is provided as Multimedia Appendix 1 to ensure transparency and reproducibility of our review protocol. The research team will discuss the data selection results and develop a data extraction table after reaching a consensus.

Data Charting

The data extraction instrument will be decided a priori, developed, and used to extract data from the included studies [13,28,30]. A standardized data extraction form will be developed and piloted on a sample of 5-10 included studies. Two reviewers will independently extract data from each included study. Any discrepancies will be resolved through discussion or consultation with a third reviewer. The following data will be extracted from each included study.

1. Study characteristics (author, year, country, study design)
2. Population characteristics (sample size, stage of medical education)
3. Context (academic setting, clinical setting, or both)
4. Socioemotional skills addressed
5. Description of student-driven strategies or approaches
6. Reported outcomes or effectiveness (if available)
7. Barriers and facilitators to strategy implementation (if reported)
8. Key findings and conclusions

Multimedia Appendix 2 shows the data extraction instrument. During data extraction, the draft tool will be modified and revised if necessary. Extraction will be performed using a double-blind scheme [28,31].

Data Analysis

The data will be aggregated into themes, qualitatively described, and may be graphically represented. The final decision on the means to represent the results will be made based on the findings after the screening is completed [13,15,30]. The thematic analysis will follow the 6-phase approach outlined by Braun and Clarke (2006) [32]: (1) familiarization with the data, (2) generating initial codes, (3) searching for themes, (4) reviewing themes, (5) defining and naming themes, and (6) producing the report. Two independent reviewers will conduct the initial coding using NVivo software (QSR International) to ensure consistency and rigor. The coding process will be inductive, allowing themes to emerge from the data rather than fitting into a pre-existing coding frame. However, given that this scoping review will analyze diverse types of data extracted from published studies—including study characteristics, population details, intervention descriptions, and reported outcomes—our thematic analysis will be adapted to focus on identifying overarching themes related to student-driven strategies for socioemotional skill development in medical education. Specifically, the initial coding will involve categorizing the extracted data based on the type of strategy employed (eg, self-directed learning, peer-to-peer initiatives), the context in which it is implemented (eg, academic, clinical), and the socioemotional skills targeted (eg, empathy, resilience). Subsequent theme development will focus on synthesizing these categories to identify common patterns, key components, and potential mechanisms underlying the effectiveness of different student-driven strategies. This approach will allow us to move beyond a mere summary of individual studies and generate a more holistic understanding of how medical students actively develop their socioemotional skills.

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A codebook will be developed and refined throughout the analysis process, with clear definitions and examples for each code and theme. To enhance trustworthiness, we will employ member checking with a subset of the included studies' authors and engage in ongoing critical reflection and discussion among the research team. The final thematic framework will be reviewed by all the team members to ensure that it accurately represents the data and addresses the research objectives. This is a scoping review, and a formal quality assessment of the included studies will not be conducted. However, we will provide a narrative summary of the overall nature and quality of the evidence base.

Our analysis will account for the diverse types of study designs and sources included in this scoping review. We will employ a stratified approach to manage and analyze different types of evidence: (1) primary research studies (quantitative, qualitative, and mixed methods) will be analyzed based on their methodological approach, key findings, and relevance to student-driven strategies for socioemotional skill development; (2) review papers will be examined for their synthesis of existing evidence, key themes, and gaps identified in the literature; (3) conference proceedings will be analyzed for the emerging trends, innovative approaches, and preliminary findings that may not yet be published in peer-reviewed journals; and (4) guidelines and recommendations from scientific societies will be assessed for their practical implications and alignment with student-driven approaches.

To manage potential overlap between sources, particularly between primary studies and reviews, we will cross-reference the included studies and note any instances where the same primary data are reported in multiple sources. In such cases, we will prioritize the most comprehensive or recent report of the data.

The double-blind scheme mentioned earlier refers to a process where 2 reviewers independently extract data from each included study. To elaborate on this process: (1) two reviewers will independently extract data from each included source by using the predetermined data extraction form; (2) the reviewers will be blinded to each other's extractions to prevent bias; (3) after completing the independent extractions, the reviewers will compare their results; (4) any discrepancies in the extracted data will be discussed and resolved through consensus; and (5) if consensus cannot be reached, a third reviewer will be consulted to make a final decision. This rigorous approach ensures the accuracy and reliability of the data extraction process, minimizing potential bias and errors.

Results

The scoping review is progressing according to the following timeline. Protocol development and registration was completed in January 2025. Search strategy refinement was completed in February 2025. The initial database searching was expected to be completed in March or April 2025. Title and abstract screening are anticipated to be performed in May or June 2025. Full-text review and data extraction are anticipated to be performed in July to August 2025. Data synthesis and analysis are anticipated to be completed by September or October 2025. The manuscript is expected to be prepared and submitted by November or December 2025. As of April 2025, we have completed the protocol development, search strategy refinement, and initiated the database searching. Preliminary results from our initial searches indicate a diverse range of literature addressing student-driven strategies for socioemotional skill development in medical education. The next steps involve screening titles and abstracts to identify relevant studies for full-text review. The final results, expected by December 2025, will include a comprehensive mapping of student-driven strategies, identifying gaps in current knowledge, and recommendations for future research and curriculum development in this field. In our final analysis and presentation of results, we will employ a multifaceted approach to illustrate the complex relationships among student-driven strategies, educational contexts, and outcomes.

1. Conceptual framework: we will develop and present a comprehensive conceptual framework that visually maps the interrelationships between the identified strategies, contexts, and reported outcomes.
2. Network analysis visualization: a network diagram will be created to demonstrate the connections and potential synergies between different strategies and their contexts.
3. Strategy-context matrix: we will construct a matrix cross-tabulating student-driven strategies against various contextual factors and reported outcomes, facilitating the identification of patterns and trends.
4. Temporal analysis charts: where longitudinal data are available, we will create timelines or trajectory maps to illustrate the evolution of strategies over the course of medical education.
5. Comparative strategy charts: we will develop comparative charts highlighting the relative strengths, limitations, and contextual dependencies of different student-driven strategies.
6. Thematic concept maps: using thematic analysis techniques, we will create concept maps illustrating key themes and subthemes emerging from the literature.

These analytical approaches will be complemented by a narrative synthesis to provide a rich, contextual understanding of the landscape of student-driven socioemotional skill development in medical education. This multidimensional analysis will facilitate the identification of best practices, knowledge gaps, and future research directions.

Discussion

Anticipated Significance

This scoping review will provide a comprehensive overview of student-driven strategies for developing socioemotional skills in medical education. By synthesizing the available evidence, we anticipate that this review will (1) inform medical educators and curriculum developers about effective student-centered approaches to socioemotional skill development, (2) highlight innovative strategies that could be incorporated into formal medical curricula, (3) identify potential barriers and facilitators to socioemotional skill development from the student

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perspective, and (4) guide future research by identifying gaps in the current literature and areas requiring further investigation.

Potential Implications

The findings of this review may have significant implications for medical education.

1. Curriculum development: results may inform the integration of student-driven approaches into formal curricula, potentially enhancing the effectiveness of socioemotional skill training.
2. Student support: understanding student-initiated strategies can help educators better support and facilitate student efforts in developing these crucial skills.
3. Assessment methods: insights into student-driven approaches may inform the development of more authentic assessment methods for socioemotional competencies.
4. Educational policy: findings may influence educational policies related to the incorporation of socioemotional skill development in medical education standards and accreditation criteria.

Strengths and Limitations

The strengths of this review include its comprehensive search strategy, inclusion of multiple languages, and focus on an underexplored aspect of socioemotional skill development in medical education. However, potential limitations include the possibility of missing relevant studies due to language restrictions and the challenge of synthesizing diverse types of evidence.

Socioemotional skills are increasingly recognized as essential competencies for medical professionals, as they contribute to better patient care, improved communication, and enhanced teamwork [33]. These skills encompass a wide range of abilities such as empathy, emotional intelligence, resilience, and interpersonal communication, which enable physicians to navigate the complex and emotionally demanding nature of their work [34,35].

Despite the growing awareness of the importance of socioemotional skills in medical education, there is limited research on the specific strategies employed by medical students to develop and promote these skills. This scoping review aims to address this gap by providing a comprehensive overview of the current literature on the various approaches used by medical students to cultivate their socioemotional competencies in academic and hospital settings.

Conclusions

This scoping review will provide a comprehensive overview of student-driven strategies for developing socioemotional skills in medical education. By mapping the current literature and identifying gaps in knowledge, this review will contribute to the growing body of evidence on the importance of socioemotional competencies in medical practice and inform future educational interventions and research directions.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P (Preferred Reporting Items for Systematic review and Meta-Analysis-Protocols) checklist.
[DOCX File , 32 KB - resprot_v14i1e66757_app1.docx]

Multimedia Appendix 2
Data extraction instrument.
[DOCX File , 16 KB - resprot_v14i1e66757_app2.docx]

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Abbreviations

MeSH: Medical Subject Headings
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Health Care Professionals' Experiences and Opinions About Generative AI and Ambient Scribes in Clinical Documentation: Protocol for a Scoping Review

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Abstract

Background: Generative artificial intelligence (GenAI) leverages large language models (LLMs) that are transforming health care. Specialized ambient GenAI tools, like Nuance Dax, Speke, and Tandem Health, "listen" to consultations and generate clinical notes. Medical-focused models, like Med-PaLM, provide tailored health care insights. GenAI's capability to summarize complex data and generate responses in various conversational styles or literacy levels makes it particularly valuable since it has the potential to alleviate the burden of clinical documentation on health care professionals (HCPs). While GenAI may prove to be helpful, offering novel benefits, it comes with its own set of challenges. The quality of the source data can introduce biases, leading to skewed recommendations or outright false information (so-called hallucinations). In addition, due to the conversational nature of chatbot responses, users may be susceptible to misinformation, posing risks to both safety and privacy. Therefore, careful implementation and rigorous oversight are essential to ensure accuracy, ethical integrity, and alignment with clinical standards. Despite these advances, currently, no review has investigated HCPs' experiences and opinions about GenAI in clinical documentation. Yet, such a perspective is crucial to better understand how these technologies can be safely and ethically adopted and implemented in clinical practice.

Objective: We aim to present the protocol for a scoping review exploring HCPs' experiences and opinions about GenAI and ambient scribes in clinical documentation.

Methods: This scoping review will be carried out following the methodological framework of Arksey and O'Malley and the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Scoping Reviews) checklist. Relevant papers will be searched for in PubMed, IEEE Xplore, APA PsycInfo, CINAHL, and Web of Science. The review will include studies published between January 2023 and September 2025. Studies will be included that represent original peer-reviewed work that explores HCPs' experiences and opinions about the use of GenAI or ambient scribes for clinical documentation. Data extraction will include publication type, country, sample characteristics, clinical setting, study aim, study design, research question, and key findings. Study quality will be assessed using the Mixed Methods Appraisal Tool.

Results: The results will be presented as a narrative synthesis structured along the key themes of the evidence mapped. Data will be collated and presented in charts and tabular format. Findings will be reported in a peer-reviewed scoping review.

Conclusions: This will be the first scoping review that considers HCPs' experiences and opinions about GenAI and ambient scribes in clinical documentation. The results will clarify how HCPs use—or avoid using—GenAI in daily health care work. This

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insight will help address perceived benefits, risks, expectations, and uncertainties. It may also reveal key research gaps in the field.

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KEYWORDS

artificial intelligence; AI; generative artificial intelligence; GenAI; ambient scribes; health care professionals; clinical documentation; attitude; scoping review

Introduction

Background

Generative artificial intelligence (GenAI), a subset of artificial intelligence (AI), leverages large language models (LLMs) to learn patterns from vast datasets and generate novel content [1-3].

In health care, the use of GenAI tools for clinical documentation is growing, primarily scribes and chatbots. Examples of ambient AI scribes, also known as ambient voice technology, in the market include Nuance Dragon Ambient eXperience by Microsoft [4], Speke by ScribeAmerica [5] and Tandem Health [6], among others.

Chatbots range from general purpose models that are not clinically validated, such as OpenAI's ChatGPT, to medical-specific ones, like Med-Palm, developed by Google Research [7], which is pretrained on medical data and has undergone clinical benchmarking in clinical settings.

Applied to health care, these tools may help clinicians with documentation tasks and reduce administrative burdens, which are known drivers of burnout [8-10]. These tools may also improve accessibility for patients [11,12] by synthesizing complex data and writing responses in a desired conversational style or literacy level [13,14], ultimately improving the overall efficiency of health care services [13,15].

The adoption of GenAI in health care, however, also raises significant concerns [15,16]. AI outputs can be biased, potentially exacerbating ageism, racism, or gender discrimination in health care due to omissions and biases present in the training data used [17-20]. Such "algorithmic biases" can result in unfair suggestions and discriminatory advice. Even in passive use cases, such as ambient scribes that transcribe clinician-patient interactions, bias may emerge in how speech is transcribed, summarized, or prioritized, potentially misrepresenting certain dialects, accents, or phrasing more commonly used by specific demographic groups. This could affect the completeness or accuracy of documentation and introduce disparities into medical records. These tools may also generate dangerous medical advice and can produce incorrect information called "hallucinations" [20,21]. Users may be vulnerable to misinformation because of the compelling, rapid responses offered, which could further endanger privacy and safety [16,22].

Previous reviews have examined the perspectives of health care professionals (HCPs) on AI use in clinical settings, focusing on its roles in decision-making, efficiency, quality of care, and documentation systems [23,24]. Others have explored perceived benefits and concerns, such as bias, transparency, data privacy, and safety, as well as factors influencing AI adoption, including barriers and facilitators influencing AI adoption [25-28]. Additional review studies have investigated HCPs' overall understanding and experiences with AI, mapping the broader implications of emerging AI-powered technologies across the health care landscape [29,30]. However, none of these reviews have specifically examined the lived experiences, perceptions, or opinions of HCPs, particularly frontline clinicians, regarding the use of GenAI in clinical documentation and decision-making.

Added to this gap, survey research indicates important trends and insights in relation to the adoption of technological tools for clinical documentation. Namely, HCPs both desire and expect technological tools to alleviate their administrative burdens [8-10].

Theoretical framing is also required to better explore barriers and facilitators to GenAI uptake in clinical documentation. For example, the technology acceptance model (TAM) provides one useful framework to examine this gap, highlighting perceived usefulness and ease of use as key factors influencing technology adoption [31].

To address this theoretical and empirical gap, we have planned a scoping review to systematically map the current evidence on HCPs' experiences and opinions of GenAI use in clinical documentation. This manuscript presents the protocol detailing the methodology and approach that will guide the review.

Study Objectives

This scoping review aims to explore HCPs' perspectives on the use of GenAI tools, such as chatbots and ambient AI, specifically for clinical documentation, by synthesizing existing evidence on their experiences and opinions and identifying gaps to guide future research.

To achieve this aim, the following objectives have been developed: (1) to identify, collate, and summarize existing evidence on HCPs' experiences of GenAI tools, including chatbots and ambient AI, on clinical documentation; (2) to assess HCPs' opinions about, and perceived impact of, GenAI on documentation efficiency, quality, privacy, and the potential harms and benefits for HCPs and patients; and (3) to identify research gaps to inform future investigations into HCPs' experiences and opinions on the use of GenAI and ambient AI for clinical documentation.

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Methods

Scoping Review

A scoping review is well-suited for exploring emerging fields like GenAI in clinical documentation, as it maps the existing literature, identifies key themes, and highlights gaps in knowledge. Unlike a systematic review, which focuses on a narrowly defined question with strict inclusion criteria, a scoping review provides a broader overview, capturing diverse perspectives, methodologies, and contexts [32]. This approach is valuable for informing future research directions and policy considerations in a rapidly evolving technological landscape [32]. We will carry out a scoping review using the framework proposed by Arksey and O'Malley [32], consisting of the following five stages: (1) identifying the research question, (2) identifying the relevant studies, (3) selecting eligible studies, (4) collecting data, and (5) summarizing data and synthesizing results. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews (PRISMA ScR) checklist will be used to report the review [33,34]. The final publication will emphasize any further changes made to the study design.

Stage 1: Identifying the Research Question

Based on the objectives and iterative discussions within the research team, we agreed on the primary research question (RQ) and 8 secondary RQs.

Primary RQ

What is known from the literature about the uptake, experiences, and opinions among HCPs regarding the use of GenAI, including ambient AI, in clinical documentation?

Secondary RQs

The eight secondary RQs are as follows:

1. To what extent have HCPs adopted GenAI chatbots and ambient scribes for clinical documentation?
2. What drives HCPs' adoption of GenAI chatbots and ambient scribes?
3. What are the key themes and recurring patterns in HCPs' interactions with GenAI and ambient scribes in clinical documentation?
4. How do HCPs perceive the benefits and challenges of using GenAI and ambient scribes in documentation?
5. What ethical considerations and concerns do HCPs raise regarding the integration of GenAI and ambient scribes in documentation?
6. Is the use of GenAI and ambient scribes for documentation associated with HCPs' perceptions about efficiency, workflow, and job satisfaction?
7. What gaps exist in the literature regarding HCPs' experiences and opinions about GenAI and ambient AI in clinical documentation?
8. How do HCPs' experiences or opinions vary depending on the type of GenAI system or architecture (eg, consumer LLMs, ambient AI scribes, speech-to text, and voice-activated, domain-specific models) used in clinical documentation?

What Are Experiences and Opinions?

For the purposes of this review, we denote experiences as any direct, practical interaction with a GenAI tool available on the market that is used by an HCP for clinical documentation. We interpret opinions to refer to any expressed thoughts or perceptions about these tools, including views formed without direct use, as well as perceived implications or consequences. The initial definitions of "experience" and "opinion" are provided in Textbox 1.

Textbox 1. What do we mean by health care professionals' experiences and opinions?

Experiences

This refers to health care professionals' direct, practical interactions with generative artificial intelligence tools: what they did, observed, or encountered while using them.

Opinions

This refers to health care professionals' personal judgments, beliefs, or attitudes about the usefulness, effectiveness, or impact of these tools.

We used the SPIDER (sample, phenomenon of interest, design, evaluation, research type) [35] framework to systematically formulate our research questions and guide the selection of relevant studies, as summarized in Table 1. During the preliminary test searches conducted for the scoping review, the research team observed that setting limitations on the study design within the SPIDER framework excluded relevant articles. These exclusions were due to several studies' metadata either not identifying the design or providing insufficient detail. As a result, we decided to remove the "design" element from the search strategy. This modification maximizes the retrieval of relevant data by ensuring no design constraints are applied in the search string. The "design" element will be retained during screening and synthesis to manage heterogeneity and preserve focus.

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Table 1. SPIDER (sample, phenomenon of interest, design, evaluation, research type) framework.

SPIDER dimension	Description
Sample	Health care professionals (eg, doctors, nurses, and dentists)
Phenomenon of interest	Use of GenAI[a], including apps and ambient scribes, to write documentation
Design	No limitations during the search stage
Evaluation	Experiences and opinions
Research type	Qualitative methods, quantitative methods, or mixed methods

[a]GenAI: generative artificial intelligence.

Stage 2: Identifying Relevant Studies

The PRISMA flow diagram [34] outlines the planned multistage screening process for identifying relevant studies (Figure 1). As this is a protocol, the flowchart includes placeholders marked "n=0" to indicate that specific data (eg, number of records screened or excluded) are not yet available, since the formal search and selection process has not been conducted. An experienced research librarian from Uppsala University, Sweden, will handle the deduplication procedure.

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram: a step-by-step illustration of the multistage screening process for source selection in the scoping review, created using the Shiny web-based tool [36,37]. All numbers are set to 0 as placeholders since the review has not yet been conducted.

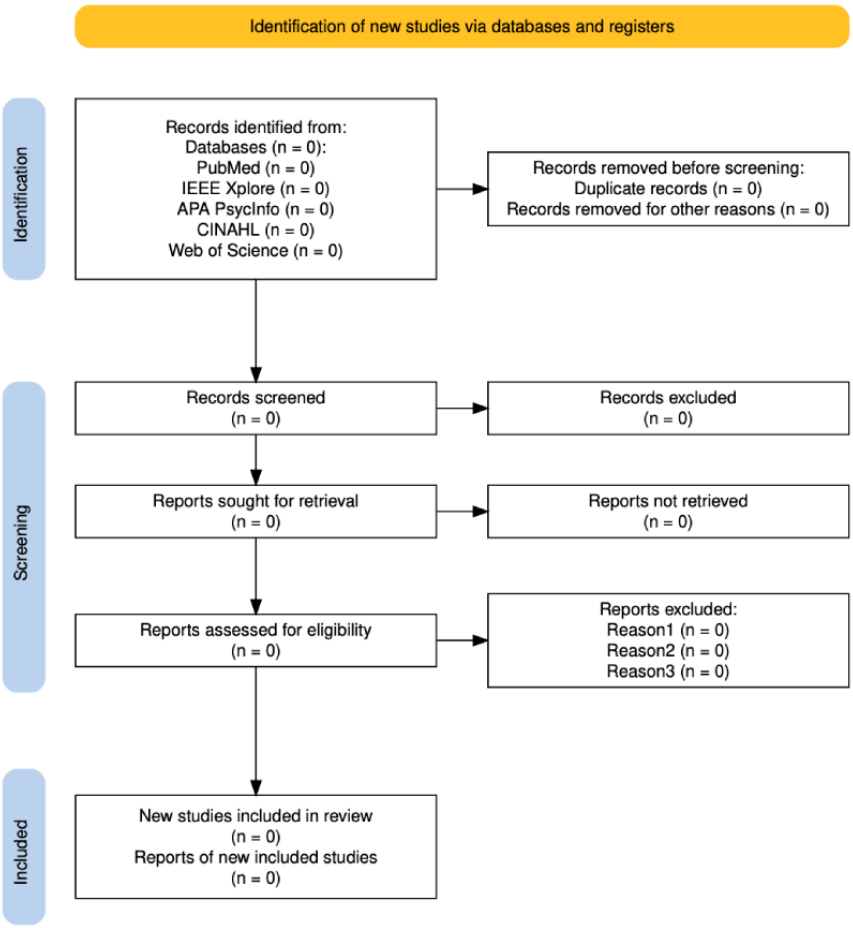

The search strategy was developed through an iterative process by CGS and the Uppsala University library. The first list of search phrases was compiled using seed references, and it was further refined through conversations between the library and CGS. It is composed of four main concepts: (1) HCPs, (2) GenAI, (3) clinical documentation, and (4) experiences and opinions. These concepts were combined with the Boolean AND and OR operators, as shown in Textbox 2. The literature search will be done in the following five databases: PubMed, IEEE Xplore, APA PsycInfo, CINAHL, and Web of Science. The search terms were tailored to different databases. The whole search query is available in Multimedia Appendix 1.

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Textbox 2. Key concepts of the search strategy.

Health care professional search string

"Health Personnel"[Mesh] OR "Medical staff"[Mesh] OR "health personnel"[Title/Abstract] OR "medical staff"[Title/Abstract] OR "healthcare professional*"[Title/Abstract] OR "health care professional*"[Title/Abstract] OR HCPs[Title/Abstract] OR "healthcare worker*"[Title/Abstract] OR "health care worker*"[Title/Abstract] OR "health care provider*"[Title/Abstract] OR "healthcare provider*"[Title/Abstract] OR physician*[Title/Abstract] OR nurs*[Title/Abstract] OR clinican*[Title/Abstract]

Generative artificial intelligence search string

"Artificial Intelligence"[Mesh] OR "Natural language processing"[Mesh] OR GenAI[Title/Abstract] OR chatbots[Title/Abstract] OR ChatGPT[Title/Abstract] OR "artificial intelligence"[Title/Abstract] OR AI-based[Title/Abstract] OR "natural language processing*"[Title/Abstract] OR "summarization tools"[Title/Abstract] OR "machine intelligence"[Title/Abstract] OR AI[Title/Abstract] OR "ambient intelligence"[Title/Abstract] OR "ambient scribes"[Title/Abstract]

Clinical documentation search string

"Documentation"[Mesh] OR "Medical records systems, computerized"[Mesh] OR "Electronic Health Records"[Mesh] OR "Health Records, Personal"[Mesh] OR "Patient Discharge"[Mesh] OR "Patient Discharge Summaries"[Mesh] OR documentation*[Title/Abstract] OR "medical record*"[Title/Abstract] OR "clinical note*"[Title/Abstract] OR "medical note*"[Title/Abstract] OR "clinical record*"[Title/Abstract] OR "patient discharge*"[Title/Abstract] OR "health record*"[Title/Abstract] OR "patient record*"[Title/Abstract]

Experiences and opinions search string

"Attitude of Health Personnel"[Mesh] OR "Attitude"[Mesh] OR experience*[Title/Abstract] OR opinion*[Title/Abstract] OR attitude*[Title/Abstract] OR efficiency[Title/Abstract] OR quality[Title/Abstract] OR "patient understanding"[Title/Abstract] OR "ethical implication*"[Title/Abstract] OR "privacy implication*"[Title/Abstract] OR perception*[Title/Abstract] OR reaction*[Title/Abstract] OR response*[Title/Abstract

Stage 3: Selecting Eligible Studies

Inclusion and Exclusion Criteria

The inclusion and exclusion criteria, as shown in Textbox 3, were defined by the entire research team and will be applied in the study selection process. The SPIDER framework was used to define the eligibility criteria for study inclusion and exclusion, organized by sample, phenomenon of interest, design, evaluation, and research type. Additional criteria included setting, time period, and language. This review will include formally published peer-reviewed journal articles and conference papers that have undergone peer-review, and it will exclude gray literature, opinion pieces, letters, protocols, reviews, and other publications that do not represent original research. Exceptions will be made for cases where a source includes original data along with adequate methodological and analytical details.

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Textbox 3. Inclusion and exclusion criteria.

Inclusion criteria

- Sample: health care professionals (HCPs) as participants, including but not limited to physicians, nurses, dentists, and other clinical staff
- Phenomenon of interest: use of generative artificial intelligence (GenAI) and ambient scribes for clinical documentation
- Design: case studies, surveys, focus groups, and interviews; pilot programs, ethical and legal considerations, and longitudinal studies
- Evaluation: studies that explore HCPs' experiences and opinions regarding the use of GenAI or ambient scribes for clinical documentation
- Research type: original, peer-reviewed studies presenting empirical data, including qualitative, quantitative, or mixed methods designs
- Setting: all medical disciplines, all health care settings, no location restrictions
- Time period: published between January 2023 and September 2025
- Language: studies published and available in English

Exclusion criteria

- Sample: HCPs not included as participants
- Phenomenon of interest: no use of GenAI or ambient scribes for clinical documentation
- Design: studies that do not use quantitative, qualitative, or mixed methods designs, or that focus solely on ethical, legal, or policy considerations without reporting HCPs' experiences or opinions
- Evaluation: studies focused solely on the quantitative measurement or assessment of the effectiveness, accuracy, or performance of GenAI tools, without addressing HCPs' experiences or opinions
- Research type: studies that are not empirical research, including reviews, such as systematic, scoping, and meta-analyses; gray literature, including opinion pieces, protocols, and reviews; and gray data, such as websites, tweets, and blogs
- Setting: not medical discipline or health care setting
- Time period: published before January 2023
- Language: studies published in a language other than English

Mixed methods studies will be included if they contain quantitative and/or qualitative data relevant to HCPs' experiences or opinions on the use of GenAI tools for clinical documentation.

No geographic limitations will be applied to ensure a comprehensive overview of global perspectives. Due to resource constraints, the study will exclusively include articles published in English. The research team acknowledges that this approach limits the inclusion of studies conducted in different parts of the world and published in other languages. This will potentially introduce language bias and lead to the underrepresentation of diverse global perspectives. Efforts to mitigate this are described in the Strengths and Limitations subsection.

Study Selection Process

We will perform collaborative, blinded screening of abstracts and titles using Covidence (Veritas Health Innovation) [38]. Every member of the research team will take part in this procedure, and at least two people will review each record in the result set. The entire texts of the relevant studies will be considered when discussing discrepancies. A third reviewer will be involved and given the authority to decide whether to include or exclude the study in the event that differences cannot be settled.

Stage 4: Collecting Data

After selecting the studies to include, metadata (eg, title, authors, and publication year) of the remaining records will be exported and summarized to Google Sheets for further processing. The spreadsheet will be extended with the following parameters, based on the studies' full texts: publication type, country, sample characteristics, clinical setting, study aim, study design, research question, and key findings. This will allow us to extract and organize relevant data from included studies. The results will be presented in diagrams or tabular format for a clear and comprehensive visualization. While no design restrictions will be applied during the search phase to ensure broad retrieval of relevant studies, study design will be evaluated during the screening and data charting processes. To manage potential heterogeneity, included studies will be grouped according to their methodological design (eg, qualitative, quantitative, or mixed methods) and analyzed within these categories during the synthesis phase. This approach allows us to preserve the comprehensiveness of the search while maintaining analytical clarity and relevance in reporting.

All members of the study team will participate in the data extraction process. Additionally, the first author (CGS) will verify that the data extraction is accurate and comprehensive. The Mixed Methods Appraisal Tool (MMAT) [39] will be used to evaluate the studies' quality and methodological rigor. All studies included will be graded by two researchers separately, and their findings will be approved by a third independent researcher who will be consulted if no consensus can be obtained.

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Stage 5: Summarizing Data and Synthesizing Results

Narrative Synthesis

Study results will be extracted from the full texts by the lead author (CGS) and summarized into two formats: (1) a reduced format within a textbox, providing an overview of the findings from all included studies, and (2) a detailed narrative synthesis. The narrative data will be analyzed independently by at least two researchers using thematic analysis following the 6-phase framework of Braun and Clark [40].

We will adopt a hybrid approach to theme development: initial deductive codes will be informed by the research questions, particularly focusing on HCPs' experiences and opinions, but we will also remain open to inductive themes that emerge from the data during analysis.

At least two researchers will code the data independently using Google Sheets to facilitate coding, organization, and comparison. An initial coding framework will be developed and refined through iterative discussion. Intercoder reliability will be enhanced through regular consensus meetings, and discrepancies will be resolved collaboratively. Final themes will be reviewed and approved by the full research team to ensure consistency and analytical rigor.

We aim to identify patterns and relationships within and across studies, as suggested by Levac et al [33], in order to explore HCPs' perspectives on the potential of both GenAI apps and ambient AI tools to reduce documentation burdens in creating clinical notes. This analysis will examine associated benefits (eg, clarity, speed, and ability to translate complex medical information), risks (eg, mistakes, biases, and patient privacy), and opinions based on HCPs' experiences. Ethical, legal, and privacy concerns will be coded as distinct themes to ensure focused attention on these sensitive issues. In assessing the methodological rigor of the studies, we also envisage the potential to identify research gaps; for example, we predict there may be perceived privacy and ethical concerns pertaining to the potential for errors and liability associated with these tools.

Assessing the Robustness of the Synthesis

The robustness of the narrative synthesis depends on the quality of the included studies as well as on the trustworthiness of the synthesis [41]. In order to minimize bias, we will conduct the study quality appraisal through MMAT [39] to ensure that studies of equal technical quality are given equal weight.

Ethical Considerations

This study is not subject to ethical approval since only publicly available data material will be used within the scoping review methodology.

Results

The results of this scoping review will be presented in both narrative and tabular formats. The narrative synthesis will reflect key themes emerging from the literature on HCPs' experiences and opinions regarding the use of GenAI and ambient AI tools in clinical documentation. These themes will include perceived benefits (eg, clarity, efficiency, and support for complex tasks), risks (eg, errors, bias, and privacy concerns), and practical or ethical considerations as reported by the participants. Descriptive study characteristics (eg, publication type, country, sample characteristics, clinical setting, study aim, study design, research question, and key findings) will be summarized in tables or diagrams.

In addition, findings will be organized using the TAM to interpret patterns related to perceived usefulness, ease of use, and behavioral intention. Where relevant, ethical, legal, and privacy considerations reported in the literature will be highlighted and mapped in relation to technology adoption and implementation dynamics.

Discussion

Anticipated Findings

This scoping review is expected to provide a comprehensive overview of the current evidence on HCPs' experiences and opinions regarding the use of GenAI tools in clinical documentation. By systematically mapping this literature, we aim to identify prevailing themes as well as significant knowledge gaps. For example, we anticipate insights into perceived risks related to patient safety, bias, and data protection, as well as ethical and privacy concerns that may influence technology acceptance and use in clinical settings.

By applying the TAM as a guiding framework, we will interpret patterns across studies related to perceived usefulness, ease of use, and behavioral intention to adopt GenAI tools. This approach may reveal aspects such as usability challenges or contextual factors shaping HCPs' readiness to integrate these technologies.

Furthermore, our review could help clarify how ethical considerations overlap with user acceptance, practical implementation, and broader sociotechnical dynamics that influence GenAI uptake in health care. This integrated perspective can inform targeted strategies to support safe, ethical, and effective adoption of GenAI tools in clinical practice.

Finally, applying the MMAT to assess study quality will support a more robust and trustworthy narrative synthesis by contextualizing findings within the methodological strength of the available evidence.

Comparison to Prior Work

Several reviews have explored HCPs' perspectives on AI in clinical settings. Ayorinde et al [23] conducted a systematic review synthesizing experiences with non–knowledge-based AI tools in decision-making. Bracken et al [24] focused on the efficiency, quality, and stakeholder views of AI-driven documentation systems using measurable outcomes. Buchanan et al [29] mapped emerging AI-powered health technologies and their implications for nursing across clinical, administrative, policy, and research domains. Chustecki [25] used a narrative review to examine benefits and concerns related to AI in health care, including bias, transparency, data privacy, and safety. Hassan et al [26] and Lambert et al [27] conducted scoping and integrative reviews, respectively, to identify barriers and

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facilitators to AI adoption and acceptance among HCPs. Sahoo et al [28] highlighted perceived pros and cons of AI in health care, while Shinners et al [30] explored HCPs' understanding of and experiences with AI in care delivery. While these reviews broadly explore HCPs' perspectives on AI, none specifically address their experiences and opinions on the use of GenAI for clinical documentation.

Strengths and Limitations

Given that GenAI tools are increasingly being heralded as valuable in clinical documentation, this scoping review examines an urgent topic. By synthesizing HCPs' experiences and opinions, it strives to obtain insights on implementation and uptake of these tools. These findings can guide future research and support the safe integration of GenAI in health care.

As GenAI rapidly evolves, a potential limitation of the study is that the findings may soon become outdated. Additionally, the exclusion of non–English-language studies might lead to the omission of relevant research. This may limit the generalizability of the findings and introduce a Western-centric bias, particularly given the global scale of GenAI adoption in health care. This constraint may overlook relevant insights from non–English-speaking countries. While resource limitations prevent full inclusion of non–English-language literature, studies with English-language abstracts will be screened when available to partially mitigate this limitation. Furthermore, the exclusion of gray literature means that some studies will be overlooked. Nevertheless, our search strategy is designed to identify the most comprehensive and high-quality evidence.

Future Directions

Our scoping review aims to map current research on this issue. This approach aims to clarify how HCPs are—or are not—integrating GenAI into their daily work, helping to identify perceived benefits, risks, expectations, and uncertainties. Results also may help to identify research gaps in this field.

Dissemination Plan

To ensure the findings of this scoping review reach relevant stakeholders and contribute meaningfully to practice, policy, and future research, we plan to implement a comprehensive dissemination strategy. This will include publishing the results in a peer-reviewed, open-access journal and presenting them at relevant academic conferences and professional meetings.

Conclusion

This scoping review will systematically map the existing literature on HCPs' experiences and opinions regarding the use of GenAI tools in clinical documentation. By identifying key themes, knowledge gaps, and patterns related to technology acceptance, the findings will help inform future research, policy, and practice. The integration of the TAM as a guiding framework, along with focused attention on ethical and practical considerations, will provide a structured lens for interpreting the literature. Ultimately, this review aims to support the safe, effective, and ethical implementation of GenAI in health care settings.

Acknowledgments

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Data Availability

As this is a protocol, no data have been collected or analyzed to date. The scoping review will use data from publicly available sources, retrievable through the following databases: PubMed, IEEE Xplore, APA PsycInfo, CINAHL, and Web of Science.

Authors' Contributions

CGS drafted the manuscript. CGS and CB were responsible for the conception of the study. All authors read the paper, provided feedback on it, and approved it for submission.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Adapted search strategies for each database.
[DOCX File , 26 KB - resprot_v14i1e73602_app1.docx]

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Abbreviations

AI: artificial intelligence
GenAI: generative artificial intelligence
HCP: health care professional
LLM: large language model
MMAT: Mixed Methods Appraisal Tool
PRISMA ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RQ: research question
SPIDER: sample, phenomenon of interest, design, evaluation, research type
TAM: technology acceptance model

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Protocol

The Impact of Young and/or Exercised Blood Plasma Transfusions in Individuals With Neurodegenerative Conditions: Protocol for a Scoping Review

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Abstract

Background: The prevalence of neurodegenerative conditions is expected to continue to rise, with current treatments largely focused on the management of symptoms and not disease progression. Exercise is a therapy that has significant favorable effects on several of the modifiable risk factors that influence the development/progression of some neurodegenerative conditions. However, there are significant barriers to exercise for this population, warranting consideration of alternative or adjunct therapies. Blood plasma transfusion is an emerging nonpharmaceutical/nonexercise therapy that may have positive benefits on people and animal models with neurodegenerative conditions.

Objective: The aim of this study was to investigate and synthesize the literature on the impacts of young or exercised blood plasma transfusions in people and animal models with neurodegenerative conditions.

Methods: We will include studies that have explored the impacts of young or exercised blood plasma transfusions in adults or animal models with neurodegenerative conditions. PubMed Central, MEDLINE, Cochrane Database of Systematic Reviews, Scopus, ProQuest, SPORTDiscus, PROSPERO, and multiple unpublished sources, including book chapters, conference papers, and theses, will be searched to include literature from January 2004 to May 2024, written in English. Studies will be screened by 2 independent reviewers; a third reviewer will be used to resolve any conflicts. Data will be extracted into a modified charting tool and will be presented in a graphical or tabular format combined with the appropriate narration.

Results: As of June 2024, the literature search has been completed. After searching listed databases, 3646 citations and 13 gray literature studies were identified, of which 1432 duplicates were removed.

Conclusions: To the best of our knowledge, this study will be the first study with the aim of investigating the literature on the impacts of young or exercised blood plasma transfusions in individuals with neurodegenerative conditions.

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(JMIR Res Protoc 2025;14:e65935) doi:10.2196/65935

KEYWORDS

neurodegenerative conditions; plasma transfusion; young plasma; exercised plasma; aged; population; concept; context

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Introduction

Background

Neurodegenerative conditions such as Parkinson disease, Alzheimer disease, motor neuron disease, and multiple sclerosis are a form of neurological condition affecting more than 3 billion people worldwide [1]. With a growing and aging population, the prevalence of neurodegenerative conditions is expected to continue to rise [2]. Neurodegenerative conditions refer to a collection of conditions that are primarily characterized by neuron dysfunction and loss [2]. An important feature of many neurodegenerative conditions is the involvement of proteins with altered physicochemical properties, commonly referred to as misfolded proteins [3], resulting in altered function and/or intracellular or extracellular accumulation of the proteins [2].

Treating these conditions is challenging, as relatively little is known about their etiology and pathophysiology [4]. Therefore, therapeutic interventions typically focus on the management of symptoms or reducing the impact of impairments rather than on disease progression [5]. Nevertheless, there is some evidence showing that the development of some neurodegenerative conditions is a direct or indirect result of modifiable risk factors [6]. Some of these risk factors include diabetes, hypertension, obesity, depression, and physical inactivity [6]. Exercise is a modality that has been shown to have significant favorable effects on all of these modifiable risk factors [6]. Exercise is also a well-established method of positively influencing brain cognition, neurogenesis, and plasticity [7]. However, there are significant barriers to exercise in neurodegenerative populations that lead to poor long-term exercise adherence [8,9]. Barriers include low outcome expectation, fear of falling, functional or physiological impairment, and lack of time [8,9]. Therefore, alternative/adjunct therapies are warranted that may overcome the barriers to exercise while still providing similar benefit.

Blood transfusion of plasma from young (young plasma) or athletic (exercised plasma) individuals is emerging as a potential therapy to alleviate symptoms and potentially progression of some neurodegenerative conditions [6,10,11]. Young plasma transfusions have been shown to be safe and well tolerated in both humans and animals, with minimal adverse events or reactions [12-14]. A study in a mice model has demonstrated that young plasma transfusions can reverse some of the various age-related changes in the mouse brain, including, but not limited to, hippocampal neurogenesis and improved cognition [15]. Similar findings have been reported in clinical human studies with young plasma or therapeutic plasma exchange [16]. Specifically in humans, platelet-rich plasma infusions have been shown to reduce neuroinflammatory compounds, including tumor necrosis factor-α, which has a systemic anti-inflammatory effect [12,17].

Conversely, there is limited research on the safety, tolerability, and impacts of exercised plasma transfusions in human and animal models [6]. Specifically in humans, only 1 study protocol [6] has been published to investigate the safety and efficacy of exercised plasma transfusions in patients with Alzheimer disease. That study is currently in progress and is expected to be completed in 2026 (NCT05068830). There is some animal model research on the safety, tolerability, and impacts of exercised blood plasma transfusions in neurodegenerative conditions [11]. One trial found that exercised blood plasma transfusions from aged and exercised donor mice conferred the beneficial effects of exercise on cognition and hippocampal neurogenesis in aged sedentary mice [11]. Therefore, the aim of this scoping review is to investigate, synthesize, and present the current research literature on the impacts of blood plasma transfusions (young or exercised) in people and animal models with neurodegenerative conditions and to identify gaps in the existing research literature and areas for future inquiry.

A preliminary search of PubMed, the Cochrane Database of Systematic Reviews, Google Scholar, and Joanna Briggs Institute (JBI) Evidence Synthesis was conducted, and no current or underway systematic reviews or scoping reviews on the impacts of young and/or exercised blood plasma transfusions in people or animal models with neurodegenerative conditions were identified. Our preliminary search identified a systematic scoping review, which investigated the safety and efficacy of replacement fluids in therapeutic plasma exchange [16]. However, the impacts of young and/or exercised plasma in neurodegenerative conditions has not been explored in that study [16].

Review Objectives

The objectives of this scoping review are as follows.

1. Synthesize the literature on the impacts of young or exercised blood plasma transfusions in people and animal models with neurodegenerative conditions.
2. Identify the gaps in the existing literature and areas for future research on the impacts of young or exercised blood plasma transfusions in people and animal models with neurodegenerative conditions.

Review Questions

The research questions of this scoping review are as follows.

1. What are the impacts of blood plasma transfusions (young or exercised) in people or animal models with neurodegenerative conditions?
2. What is known about the safety and tolerability of young or exercised plasma transfusions in people or animal models with neurodegenerative conditions and what physiological parameters are measured to monitor the safety and tolerability of this therapy?
3. What are the protocols implementing young or exercised plasma transfusions in people or animal models with neurodegenerative conditions (intervention period, dosage, donor parameters)?
4. What are the barriers and facilitators to the implementation of plasma transfusions (young or exercised) in people or animal models with neurodegenerative conditions?
5. What is the cost-effectiveness of young or exercised blood plasma transfusion in people with neurodegenerative conditions?

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Methods

The proposed scoping review will be conducted in accordance with the JBI methodology for scoping reviews and the PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) guidelines (Multimedia Appendix 1) [18,19].

Inclusion Criteria

Participants

Only studies that included adults or animal models with neurodegenerative conditions will be considered. Adults and animal models with any one of the following neurodegenerative conditions will be included: Parkinson disease, Alzheimer disease, motor neuron disease, vascular dementia, Lewy body dementia, multiple sclerosis, prion disease, amyotrophic lateral sclerosis, Huntington disease, and spinocerebellar ataxia. Additionally, aged adults or animal models will be included, as aging is the single greatest contributing risk factor to the development of neurodegenerative conditions [20].

Concepts

The key concepts that will be addressed are the impacts of blood plasma transfusions in individuals with neurodegenerative conditions, plasma exchange/transfusion, young plasma, and exercised plasma. The following are the working definitions of the concepts used in the scoping review.

Plasma Exchange/Transfusion

Plasma transfusion is a blood plasma replacement therapy. Typically, patients' blood is removed via an intravenous needle into an exchange machine via tubing, which separates the various components of blood, including removing the plasma. The exchange machine then adds a plasma substitute, which can include young plasma or exercised plasma. Lastly, the new plasma is returned to the patient through the tubing.

Young Plasma/Exercised Plasma

Young plasma is blood plasma drawn from young individuals. In human trials, healthy individuals aged 18-30 years are usually considered young donors [12]. In animal models, specifically mice trials, healthy individuals aged 3-4 months are usually considered young donors [15].

Exercised plasma is blood plasma drawn from athletically fit individuals. As this is a new therapy, there is limited research on donor criteria. However, of the available protocols, donor inclusion criteria includes healthy male donors, aged 18-40 years, with a maximal oxygen uptake of ≥55 mL/kg/min, and a BMI of ≤27 kg/m^2 [6]. In animal models, specifically mice, donor inclusion criteria included healthy, aged (18 months old) mice who were given continuous access to a running wheel for 6 weeks [11].

Context

The context for this scoping review will be the globally published and unpublished research on the impacts of blood plasma (young or exercised) transfusions in people or animal models with neurodegenerative conditions.

Types of Studies

This scoping review will consider both experimental and quasi-experimental study designs, including controlled and noncontrolled studies (randomized controlled trials, controlled clinical trials, nonrandomized controlled trials, and pre-post studies). Although randomized controlled trials are preferred, other study types will be included, as not all research questions can be answered with a randomized controlled trial. Systematic reviews that meet the inclusion criteria will also be considered depending on the research question. In addition, protocol-only papers will be included to allow a deeper understanding of protocol development. The search for unpublished studies will include book chapters, conference papers, and theses. However, unpublished studies will be excluded if a published study is available. Only studies written in English will be considered due to time and resource constraints. Studies related to the topic published between January 2004 and May 2024 will be considered to capture the modern use of blood plasma transfusions. Papers focused on any of the following aspects of blood plasma transfusion will not be considered.

1. Use of other types of plasma or replacement fluids that are not young or exercised plasma or if the use of young or exercised plasma is not specified.
2. Application in nonneurodegenerative conditions or a neurodegenerative condition that is not listed above.

Search Strategy

The search strategy will aim to locate both published and unpublished studies. A 3-step search strategy will be utilized. An initial limited search of PubMed and Google Scholar using keywords (Textbox 1) will be undertaken to identify the studies on the topic. The text words contained in the titles and abstracts as well as the index terms of relevant studies will be used to develop a preliminary search strategy (Multimedia Appendix 2) tailored to each information source.

Subsequently, this preliminary search strategy will be used to search for the following sources of research that will be scoped for this review.

1. Electronic databases: PubMed Central, MEDLINE, Cochrane Database of Systematic Reviews, Scopus, ProQuest, and SPORTDiscus.
2. Trial registries: PROSPERO.
3. Unpublished studies: the search for unpublished studies will include book chapters, conference papers, and theses.

The search strategy, including all the identified keywords and index terms, will be adapted for each included database and/or information source. The reference list of all the included sources of evidence will be screened for additional studies.

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Textbox 1. Development of the population, concept, context search terms for the preliminary search.

Population

- Neurological patients
- Neurodegenerative
- Neurological models
- Parkinson disease
- Alzheimer disease
- Motor neuron disease
- Prion disease
- Dementia
- Amyotrophic lateral sclerosis
- Multiple sclerosis
- Huntington disease
- Spinocerebellar ataxia

Concept

- Plasma transfusion
- Plasma exchange
- Blood plasma transfusion
- Therapeutic plasma exchange
- Blood component transfusion
- Infusion
- Transfusion medicine
- Plasma infusion
- Plasmapheresis
- Exercised plasma
- Exercise trained donors
- Young plasma
- Young fresh frozen plasma
- Blood factor transfer

Context

- Therapeutic effects
- Efficacy
- Effects
- Tolerability
- Rejuvenative
- Improve

Study Selection

Following the search, all identified citations will be collated and uploaded into Endnote version 21.2/2024 (Clarivate Analytics) and duplicates removed. Titles and abstracts of potentially relevant sources will be retrieved, and their citation details will be imported into the Covidence systematic review software, Veritas Health Innovation. Following a pilot test, titles and abstracts will then be screened by 2 independent reviewers (MJK and ERC) for assessment against the inclusion criteria for the review.

The full text of the selected citations will be assessed in detail against the inclusion criteria by 2 or more independent reviewers. The reasons for exclusion at full text will be recorded. Any disagreements that arise between the reviewers at each stage of the selection process will be resolved through discussion

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or with an additional reviewer (JSR). The results of the search and the study inclusion process will be reported in full in the final scoping review and presented in a PRISMA flow diagram [19,21].

Data Extraction

Data will be extracted from the included papers by 2 or more independent reviewers by using the standardized data extraction tools available in JBI SUMARI [18]. The data extracted will include specific details about the participants, concept, context, study methods, interventions, and key findings relevant to the review questions. Based on the contributions of Kohli et al [16] and Teferra et al [22] and considering the keywords, a modified preliminary data extraction tool is proposed (Multimedia Appendix 3). The draft data extraction tool will be modified and revised as necessary during the process of extracting data from each included evidence source. Any disagreements between the reviewers (MJK and ERC) will be resolved through discussion or with an additional reviewer (JSR). Where required, authors of papers will be contacted to request missing or additional data.

Data Presentation/Analysis

According to the population, concept, context framework (Textbox 1) that has been outlined in this scoping review protocol, the extracted data will be presented in a graphical or tabular format combined with appropriate narration. The extracted information will be presented in categories, as described in Multimedia Appendix 3. If any additional information needs to be categorized, it will be categorized at the time of review. The narrative summary will include the objectives, aims, results of review questions, and concepts. A summary of the findings will be used to provide an overall description of the included studies. The scoping review will address the various elements of the research questions established and identify gaps for further research. The chosen method of data analysis and presentation was selected because of the broad scope of the included participants/studies to allow for multiple types of transfusions and neurodegenerative conditions to be included and the relatively new nature of the field. A PRISMA flow diagram (Multimedia Appendix 4) was modified to report the results of the literature search [19].

Results

As of June 2024, the literature search has been completed. After searching the listed databases, 3646 citations and 13 gray literature studies were identified, of which 1432 duplicates were removed. Subsequent abstract screening (completed by MJK and ERC) and full-text review (MJK, ERC, JSR) were completed and submitted for publication in June 2025. The search and screening results are summarized in the PRISMA flow diagram (Multimedia Appendix 4) [19].

Discussion

Overview

Previous research has demonstrated that young and/or exercised blood plasma transfusions may have therapeutic benefits in people [12] and animal [11] models with neurodegenerative conditions. However, studies report conflicting outcomes [11,12,23]. For example, a recent study showed positive benefits on neurogenesis after the administration of exercised plasma [11]; however, another similar study found no significant benefits on neurogenesis [23]. Thus, the impacts of young and/or exercised blood plasma transfusions in individuals with neurodegenerative conditions remain unclear. Further to this, exercised blood plasma has been postulated to potentially be superior or have a greater effect in certain neurodegenerative conditions (Alzheimer disease) when compared to young blood plasma [6]. The primary aim of this scoping review is to therefore investigate, synthesize, and present the current research on the impacts of blood plasma transfusions (young or exercised) in people and animal models with a neurodegenerative condition. This scoping review will also identify gaps in the existing research literature and areas for future inquiry.

Our results will outline the similarities and differences between the included studies on the impacts of young and/or exercised blood plasma transfusions and identify common trends between them. These factors are important to inform future research and any potential future implementation of young and/or exercised blood plasma transfusions in the treatment/management of neurodegenerative conditions.

To the best of our knowledge, this will be the first study to systematically scope and synthesize the literature on the impacts of young and/or exercised blood plasma transfusions in individuals with neurodegenerative conditions. This scoping review will have several limitations, including omitting studies that do not specify the population, type, or age group of the plasma donors used, which may potentially exclude relevant studies. Additionally, only including studies written in English is another limitation by potentially excluding relevant research published in other languages.

Conclusion

Overall, this scoping review aims to synthesize the current research on young and/or exercised blood plasma transfusion in people/animal models with neurodegenerative conditions. This work may inform future research and aid in the development of increasing robust studies to elucidate the effectiveness of these types of plasma transfusions in people/animal models with neurodegenerative conditions.

Data Availability

All data relevant to this study are included within this paper or uploaded as Multimedia Appendices 1-4.

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Authors' Contributions

Conceptualization: MJK and JSR
Writing – original draft: MJK
Writing – review & editing: MJK, JSR, ERC, LD, BL, CD, RC, AB

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-ScR checklist.
[DOCX File , 53 KB - resprot_v14i1e65935_app1.docx]

Multimedia Appendix 2
Preliminary search strategy for scoping review.
[DOCX File , 14 KB - resprot_v14i1e65935_app2.docx]

Multimedia Appendix 3
Preliminary data extraction tool.
[DOCX File , 14 KB - resprot_v14i1e65935_app3.docx]

Multimedia Appendix 4
PRISMA flow diagram: search results and study selection and inclusion process.
[DOCX File , 39 KB - resprot_v14i1e65935_app4.docx]

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Abbreviations

JBI: Joanna Briggs Institute
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Recommender Systems in Health Professions Education: Protocol for a Scoping Review

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Abstract

Background: In health professions education (HPE), the concept of precision education is being explored, with the intention of tailoring learning experiences to the unique needs of learners. Recommender systems can assist academic decision-making. They can be used to personalize content delivery, suggest appropriate learning pathways, propose schedules, recommend suitable institutes, supervisors, and courses, and provide learner feedback. Given abundant learning resources, selecting the right one can be daunting. Recommender systems may address this challenge by offering tailored suggestions that align with learners' requirements and abilities.

Objective: This study aims to examine the literature related to the use of recommender systems in HPE.

Methods: This review will be conducted following the methodological framework proposed by Arksey and O'Malley. A comprehensive search will be conducted across the MEDLINE, CINAHL Plus with Full Text, ERIC, Academic Search Premier, and Web of Science databases, as well as gray literature sources including arXiv and Google Scholar. These searches will focus on the period from January 2000 to February 2025. In addition, backward and forward citation searching will be carried out. Articles will be screened independently by 2 reviewers; discrepancies resolved by consensus or a third reviewer. The selection process will involve an initial screening of titles and abstracts to identify potentially relevant articles. If initial screening is inconclusive, full-text review will ensure articles meet inclusion criteria. The main eligibility criteria for inclusion in the review are studies involving health professions students or educators, focusing on the concept, development, or application of recommender systems. Data extraction will be performed using a customized data charting template covering article, study, and recommender system details. The extracted data will be analyzed and displayed in both tabular and graphical formats, supplemented by a narrative interpretation. The findings will be synthesized by mapping the existing literature to identify key concepts, research gaps, and types of evidence, highlighting similarities and differences in how recommender systems are applied in HPE. This reporting will be in accordance with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines. Data extraction and analysis will be conducted using Covidence.

Results: The current phase of the study involves selecting studies for the scoping review as specified in this protocol. The search, screening, and data extraction will begin in February 2025. The results of the study and the submission of a manuscript for peer review are expected in the winter of 2025.

Conclusions: This study aims to comprehensively map the extent of recommender systems in HPE. By identifying effective practices and existing gaps, it will serve as a valuable resource for health professions educators, enabling them to make informed decisions about integrating these systems into educational applications.

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KEYWORDS

recommender systems; precision education; personalized learning; health professions education; HPE

Introduction

Overview

The magnitude of medical information and learning resources available online, while advantageous to the user, can also be overwhelming [1-4]. The sheer volume and varying quality can lead to information overload [5-7]. This can be a stressor, making it difficult for one to evaluate the relevance and quality of the information available, ultimately impacting the individual and inhibiting effective decision-making [8-10]. In addition, there are concerns about the credibility and validity of medical and health-related information found on widely used information-sharing platforms [11,12]. A systematic review by Wang et al [13] showed an increasing trend in health-related misinformation on topics such as vaccination, Ebola, and Zika virus. Coincidentally, the article was published a month before the COVID-19 pandemic started making headlines, which itself garnered attention from online "misinformation superspreaders" [14]. Furthermore, YouTube has been identified as a source of misinformation regarding the human papillomavirus vaccine [15]. Studies have also highlighted the spread of cancer misinformation on Facebook [16,17], misinformation related to e-cigarettes and nicotine on Twitter [18], and misinformation about rheumatoid arthritis across various platforms [19]. These issues are problematic because they can lead to public health risks, such as vaccine hesitancy [20], poor disease management [21], and the spread of harmful health practices [22].

In response to these challenges of information overload and the accuracy of information, recommender systems are emerging as a powerful tool [23-25]. Recommender systems, also known as recommendation systems, platforms, engines, or algorithms, are essential tools in information filtering and personalization [26,27]. Their use can improve user experiences, boost engagement, and aid decision-making [28]. A seminal article by Resnick and Varian [29] characterized a recommender system as one in which recommendations are provided as inputs by people, which the system then aggregates and directs to appropriate recipients. Burke [30] described them as systems that generate tailored recommendations or assist users in a personalized way to choose from an array of options. These systems use algorithms to tailor recommendations by filtering, curating content, and guiding the user toward pertinent resources [31,32]. Thus, recommender systems play a pivotal role in alleviating the burden of information overload.

Recommender systems have already seamlessly integrated into our everyday lives. Serving as intelligent guides, they suggest relevant content to users in contexts ranging from social media to e-commerce and streaming services. According to a report by MacKenzie et al [33], 35% of Amazon purchases and 75% of Netflix viewing choices can be attributed to recommendations by such algorithms. In recent years, approaches such as machine learning, natural language processing, and deep learning [34-37] have brought advancements to recommender systems. These systems are not only prevalent in commercial applications but are also increasingly being adopted in educational settings [38,39]. A recent systematic review by Thongchotchat et al [40] found that while attribute- or characteristic-type recommender systems dominate education, there is an emerging trend of varied systems, including hints, clues, prompts, and tutoring, but these are in the early stages and require exploration and development. Combining theories of learning styles may enhance the flexibility and effectiveness of recommendations [40]. A recent bibliometric analysis [39] noted an increase in research dedicated to exploring recommendation techniques with the objective of enhancing the accuracy of recommendations made by educational recommender systems, driven by the ever-increasing amount of available learning resources. Large language models (LLMs) now enhance conversational recommender systems by leveraging their contextual understanding, potentially improving recommendation quality [41,42]. Recommender systems fall under 1 of 4 types of filtering approaches [43-45]. Table 1 provides a detailed description of each type, including its respective strengths and limitations, as well as examples.

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Table 1. Comparison of recommender system filtering types.

Filtering type	Description	Strengths	Limitations	Examples
Content	A recommendation is made based on user characteristics or past behavior (ie, a user's data) [46].	• Gray sheep: adapts to users with unique profiles [47]. • Recommendations can be shared without the user sharing a profile, thereby ensuring privacy [48]. • Can recommend new, rare, or unpopular items [49].	• Lack of serendipity: may not suggest unexpected items, as it does not rely on data from other users [50]. • New user problem: difficult to make recommendations in the absence of historical data to understand the user [51].	A study app that recommends quiz questions similar to those the user is practicing.
Collaborative	A recommendation is made by identifying patterns among similar users [52].	• Leverages the power of the collective user behavior [53]. • Can recommend items that a user may not have found independently [54].	• Cold start problem: difficult to make recommendations with little or no historical data [55]. • Sparsity: many user-item interactions may be unknown [56]. • May only recommend popular items [57]. • Raises privacy concerns, as data must be shared [27]. • Gray sheep: Not effective for users with unique profiles [58].	A clinical skills training app that recommends practice scenarios frequently used by other students.
Knowledge	A recommendation is made based on explicit domain user knowledge and recommendation criteria [59].	• Useful when there is explicit knowledge about an item or user preferences [60]. • New item problem: can be managed effectively, as it does not rely on past user-item interactions [61].	• Knowledge acquisition bottleneck: requires explicit knowledge, which may not always be obtainable [62]. • Lack of serendipity: may not suggest unexpected items, as it relies on the user's requirements rather than on data from other users [63].	An advising system that recommends research opportunities and projects based on a student's academic background and research interests.
Hybrid filtering	This approach uses ≥2 filtering techniques [30].	• Combines techniques to overcome the limitations of a single approach [64].	• Sensitive to the strengths and weaknesses of the techniques used [65].	A study platform that, for learners of a specific module, may adopt a hybrid approach— (1) content-based: recommend additional resources similar to those used in the module, and (2) collaborative-based: recommend resources that other learners studying the same module found helpful.

Recent Advances in Artificial Intelligence and LLMs in Recommender Systems

The integration of generative artificial intelligence and LLMs has advanced the development of recommender systems. These technologies enhance natural language processing, facilitate natural-sounding dialogues, and improve recommendation accuracy and user interaction experiences [66-68]. Approaches such as retrieval-augmented generation models combine retrieval models and generative models to integrate specific knowledge sources, aiding complex recommendations while also addressing issues such as hallucinations and cold starts [69,70]. These advances, however, are not just restricted to text-based systems. Multimodal recommender systems are emerging in popularity, integrating various types of input data such as text, image, and audio. By leveraging the capabilities of LLMs to process this multimodal data, more comprehensive and accurate recommendations are possible [71,72]. Despite these advancements, challenges remain. Biases in LLM-based recommendations [73] and ethical concerns continue to pose challenges [74]. As these systems continue to evolve, they will offer more efficient and personalized solutions.

Merits and Use Cases in Health Professions Education

Learners in health care seek reliable materials for their education online [75,76], while others turn to the internet to understand their health conditions, treatment options, and preventive measures [77-81]. YouTube, a popular educational resource among health profession students [82,83], raises concerns for health care educators regarding the quality of information

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presented to students. This concern is supported by findings from Helming et al [84], who found that many YouTube videos on medical education are of low quality, even those created by academic physicians. Metrics such as views and likes, while popular among learners for navigating their choices, can be superficial and unreliable indicators of quality or accuracy [11,83,85]. Similarly, a study by Camm et al [86] found no correlation between video quality as assessed by a scoring tool and commonly used preference metrics (ie, hits, likes, dislikes, or search page rankings). When it comes to the videos recommended by the platform, the rationale behind the algorithm for suggesting specific content remains unclear? By developing a proprietary recommender system curated by experts in the subject matter, the suggested information and learning resources could be moderated, ensuring the quality and relevance of the materials recommended to learners.

Educational recommender systems are information systems designed for use in educational settings to recommend various resources to different stakeholders, including learners, educators, researchers, and others [87]. Leveraging advanced algorithms and data analytics, educational recommender systems provide tailored recommendations that enhance the educational experience by addressing individual learner needs and preferences [1,38]. They facilitate efficient resource discovery, aiding personalized learning and informed decision-making in academic applications [38,40]. These systems are used in a variety of ways, with the goal of assisting students with academic decisions. They are used to recommend suitable institutes, study topics, and courses [88-90]. They can be used to propose personalized syllabi and scheduling [91-93], learning materials [94-97], scholarships [98], supervisors [99], and career paths [100]. These systems can also be used to offer learners feedback on summative assessments [101]. In education, personalized learning centers on learners, acknowledging their inherent differences—variations in strengths, weaknesses, and learning preferences [102]. This recognition of differences suggests that a uniform or "one-size-fits-all" approach may not be optimal for all learners. Koestner et al [103] conducted a meta-analysis that revealed that learners are more likely to achieve their goals when those goals are (1) self-concordant and (2) accompanied by an implementation plan. The concept of agency, as defined by Bandura [104], refers to the capacity to initiate actions with intention and purpose. In education, this concept manifests as learner agency—a framework that embodies self-directed learning [105,106]. Learners actively pursue knowledge aligned with personal goals and interests, facilitated by strategic guidance from educators [107,108]. Educators play a crucial role in this process by providing the necessary guidance and support to ensure that learners have access to high-quality and relevant resources. In addition to the information overload highlighted earlier, learners may sometimes be unaware of what to search for [109]. Deschênes [110] highlighted that recommender systems are valuable for curating educational resources tailored to the needs of individual learners, empowering informed choices, guiding learners to resources (that they may not have encountered unprompted), and fostering an environment conducive to autonomous yet guided education.

While the topic of recommender systems has been extensively studied in both health care [111,112] and education [113-115], to the best of the authors' knowledge, there appears to be a gap in the literature regarding their application in health professions education (HPE). For example, a topic search (covering the title, abstract, and keywords) on Web of Science using the terms "recommender system*" and "health professions education" returned only 2 articles. This scoping review aims to comprehensively map the extent of recommender systems in the HPE domain.

Practical Implementations in HPE

In reviewing the literature for applications of such systems in HPE, several innovative implementations with diverse purposes have been identified. One system provides adaptive, competence-based recommendations tailored to each student's unique needs [116]. Another is used to evaluate nursing competencies and to recommend targeted learning materials to address skill gaps [117]. Liou and Chen [118] presented an e-learning platform that recommended personalized learning activities for medical interns. Another system assists second-language nurses in patient care charting by suggesting optimal terms during documentation [119]. Liou [120] introduced a recommender system for an online discussion forum that personalized article recommendations based on individual preferences.

Objectives

This scoping review aims to identify the different use cases of recommender systems in HPE. In addition, this review aims to determine the filtering techniques used by these systems, analyze their attributes or features, and explore the user experiences of both learners and educators. Furthermore, this review seeks to identify gaps in the current literature and provide suggestions for future research on the use of recommender systems in HPE.

Methods

Ethical Considerations

This study is based on the analysis of published literature, both scientific and gray. It does not involve patients, medical research, or any type of personal information, and, as such, no ethics approval is required. The results of this scoping review will be submitted for publication in a peer-reviewed international journal and presented at scientific meetings and conferences related to HPE.

Protocol Design

Overview

Scoping reviews have gained popularity in recent years as a research methodology [121]. The objective of a scoping review is to identify and map the evidence available on a given topic [122]. Munn et al [123] elaborated on the objectives of conducting a scoping review by outlining six distinct components: (1) catalog the breadth of evidence available, (2) clarify concepts or definitions, (3) examine how the available research is conducted, (4) identify key characteristics of the topic, (5) ascertain the feasibility of conducting a systematic review, and (6) identify gaps in the existing literature. The

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methodology used in this scoping review is based on that of Arksey and O'Malley [122]. To ensure rigor, quality, and reproducibility, a recommended checklist [124,125] will be followed: the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) [126]. The output will be displayed using a flow diagram.

Stage 1: Identifying the Research Question

The objective of this scoping review is to gain a better understanding of the current use of recommender systems in HPE. Specifically, we will investigate the following questions:

1. How are recommender systems being applied in HPE? That is, what is the recommendation element?
2. What filtering technique or techniques are used by recommender systems in HPE?
3. What are the attributes or features of these HPE recommender systems?
4. What are the experiences of users, that is, learners and educators in the health professions, regarding the use of recommender systems?
5. What are the gaps in the current research on the use of recommender systems in HPE?

Stage 2: Identifying Relevant Studies

A literature search will be conducted across the selected databases, consisting of the medical-specific source (MEDLINE), the nursing and allied health database (CINAHL Plus with Full Text), the educational search engine (Education Resources Information Center), and the multidisciplinary databases (Academic Search Premier and Web of Science). Gray literature will be searched via the arXiv repository for preprints and Google Scholar. For gray literature sources, we will review the first 100 results, ranked by the platform's relevancy sorting feature. For Google Scholar, the searches will be limited to article titles, an approach recommended by Haddaway et al [127] for conducting systematic reviews. This comprehensive approach will ensure a high-quality literature review by retrieving a wide range of potentially relevant articles from a broad multidisciplinary perspective.

A search-string development strategy will be developed in accordance with the 3-step recommendations provided by the Joanna Briggs Institute [128]. First, an initial limited search will be conducted in 3 databases: Academic Search Premier, CINAHL, and MEDLINE, with the relevance of the terms used being evaluated. Next, the text in the returned articles (titles, abstracts, and keywords) will be analyzed. A comprehensive search will then be performed using these terms across the databases. Finally, citations in the retrieved results will be manually reviewed to identify any additional relevant studies not captured in the database or gray literature searches.

The search strategy will include title and abstract searches with terms related to HPE and recommender systems, connected using Boolean operators (AND, OR, and NOT). Controlled vocabulary terms (eg, Medical Subject Headings [MeSH] terms, subject headings, or subject terms) will be used when available in the database to enhance the search, independent of the title and abstract search parameters. These terms will help identify synonyms and related concepts, thereby broadening the search scope. Truncations (or stemming) will be used to capture the root of words, ensuring that different endings of the term of interest are included. For example, using "recommend* system" would capture "recommendation system," "recommender system," and "recommending system." In addition, we will implement word proximity searches to ensure that terms of interest are situated within a specified number of words from each other. This approach will allow us to capture relevant phrases and contexts that are not caught through truncation alone. For example, when we search for "recommender N2 system*," articles in which "recommender" appears within 2 words of any variation of "system" will be returned. For instance, it would capture a sentence such as, "The recommender model system enhanced student learning outcomes," which would otherwise be missed.

The following are examples:

1. TI = (recommender NEAR/2 system* OR recommendation NEAR/2 system*) OR AB = (recommender NEAR/2 system* OR recommendation NEAR/2 system*)
2. TI = (medical OR nurs*) OR AB = (medical OR nurs*)
3. 1 AND 2

This example includes a title and abstract search, making use of Boolean operators (AND and OR), stemming (eg, recommend*), and proximity search (eg, NEAR/2).

The search period will span from January 2000 to February 2025. Our decision to start the scoping review in 2000 is informed by existing literature on recommender systems in education. The systematic review by Urdaneta-Ponte et al [129] focused on literature from 2015 onward, while the work by Kamal et al [89] covered 2011 onward. The literature review by Lampropoulos [114] traced studies on the use of recommender systems in education back to 2001. By selecting the earliest date from these studies, we establish a conservative starting point, minimizing the risk of overlooking relevant literature. The search strategy targets students and educators in specific health professions, including medicine, nursing, dentistry, pharmacy, public health, allied health, clinical education, veterinary medicine, paramedical sciences, occupational therapy, physiotherapy, speech therapy, audiology, mental health, biomedical sciences, nutrition, dietetics, midwifery, chiropractic, and podiatry. The inclusion criteria will be limited to studies reporting on the concept, development, or application of recommender systems applied to diverse educational or training offerings designed for these health professions students or educators (eg, undergraduate, postgraduate, continuing professional development). Studies involving mixed populations, that is, health professions and non–health professions students, will be excluded. For a detailed view of how search lines 1 and 2 in the example above are combined, a sample search strategy can be found in Multimedia Appendix 1.

All identified references will be imported into the reference management software, EndNote [130], to merge and manage the citations and remove any duplicate entries. Once the data cleansing is complete, the citations will be imported to

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Covidence [131] for the study selection screening and charting stages.

Stage 3: Study Selection

Next, a 2-stage screening process will be implemented. The first stage involves scanning titles and abstracts to identify relevant articles. To be eligible for the second stage, the title or the abstract (or both) must (1) focus on the use of recommender systems and (2) target HPE. The second stage involves a full-text review of articles. In both stages, reviewers will screen articles against the eligibility criteria outlined in Textbox 1. Any uncertainty about whether an article should be included during the initial screening will result in its progression to the full-text review stage. Disagreements about the relevance of an article during the full-text review will be discussed among the reviewers, and if no consensus is reached, a third reviewer will be consulted to decide whether to include the article. The reasons for excluding the articles will be documented in the scoping review report.

Textbox 1. Full inclusion and exclusion criteria.

Inclusion criteria

- Population: studies involving health profession students or educators (including undergraduate, postgraduate, and continuing professional development [CPD]).
- Concept: studies focused on the concept, development, or application of recommender systems.
- Context: any geographic location
- Types of evidence: all primary studies of all designs; systematic reviews; full-text conference proceedings; full-text articles; articles published from 2000 to February 2025
- Language: any

Exclusion criteria

- Population: studies that exclude health profession students or educators (eg, those centered on patients or the public); studies with mixed populations (ie, health professions and non–health professions students)
- Concept: studies that do not address recommender systems (eg, studies focused on unrelated technologies)
- Context: none
- Types of evidence: articles published before 2000; meeting abstracts

Stage 4: Charting the Data

Data extraction will be conducted by 2 independent reviewers (reviewers 1 and 2) to ensure consistency and reliability. A standardized data extraction form, developed by the research team and configured in Microsoft Excel, will be used to chart the relevant data from all included studies (Table 2). The extracted data will cover 4 domains: article details, study details, specifics of the recommender system, and user experience. Each domain will be carefully examined to ensure that the collected data aligns with the research questions, and discrepancies will be noted for further analysis.

For article details, information such as article type (eg, original research, review, and case study), authors' names, affiliations or institutions, year of publication, and the country of the study's origin will be included to help contextualize the study within the broader literature. The study details will cover the study design (eg, observational, longitudinal, randomized controlled trial, and qualitative), the primary objective of the study, participant demographics, and the main outcomes of the study, providing insights into methodologies and key findings. In addition, details about the recommender system will be documented, including its application (ie, what it is recommending), the filtering techniques used, the attributes or features of the recommender system, and the user experiences of learners and educators, revealing practical applications and features, as well as highlighting user feedback. Data charting will be conducted using Covidence, a cloud-based resource for scoping review management.

This form will be piloted on a subset of articles to assess its effectiveness. For instance, certain important characteristics of the articles may not be captured by the current items, requiring adjustments to the instrument. The full-text reviewers will be asked during the pilot stage to identify any additional variables that should be considered for charting, and the form will be revised if deemed necessary. Any disagreements between the reviewers will be resolved through discussion, with a third reviewer (reviewer 3) acting as an arbiter if necessary.

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Table 2. Data charting instrument.

Domain and subdomain	Description or examples
Article	
Article type	Original research, review, and case study
Authors	List of authors' names
Affiliation	List of authors' affiliations or institutions
Year of publication	Year the article was published
Country	Country of the study's origin
Limitations	Any limitations described or observed in the article
Study	
Study design	For example, observational, longitudinal, randomized controlled trial, and qualitative
Aim	Primary objective or purpose of the study
Participants	Who were the participants in the study?
Outcomes	Main results of the study
Recommender system	
Element	How is the recommender system being applied? That is, what is it recommending?
Technique or techniques	What filtering technique or techniques are used by the recommender system?
Attributes	What are the attributes or features of these health profession education recommender systems?
User experience or experiences	What are the experiences of users (ie, learners and educators) in the health professions regarding the use of recommender systems?

Stage 5: Collating, Summarizing, and Reporting the Results

Data will be analyzed and summarized, with the study characteristics presented in both tabular and graphical formats, accompanied by a narrative interpretation. To ensure thorough synthesis, we will use a framework that categorizes the data according to our research questions. This will involve mapping the extracted data to each question, identifying patterns, and summarizing the aggregated evidence. For example, we will compare the filtering techniques (eg, content, collaborative, knowledge, or hybrid) used across different studies to understand their application in various HPE contexts. We will create summary tables that outline the key findings from the included studies for each research question. This approach will help us systematically present the different use cases and characteristics. In reporting our results, we will highlight the similarities and differences in how recommender systems are applied in HPE and identify research gaps through a comparative analysis of the studies and their applications. Arksey and O'Malley [122] suggest an optional sixth stage—stakeholder consultation—to gather feedback on the findings uncovered during the scoping review. Although we acknowledge the value of this step, this scoping review is part of a larger study that will later include a qualitative component involving stakeholders. Therefore, this scoping review will not include a stakeholder consultation.

Table 3 provides an estimated timeline for this scoping review. This timeline is designed to balance the thoroughness required for a comprehensive literature review with the need for timely completion to maintain the relevance of our findings to the academic community.

Table 3. Data charting instrument.

Stage	Description	Estimated completion date
1	Identifying the research question	October 2024
2	Identifying relevant studies	February 2025
3	Selecting studies	June 2025
4	Charting the data	September 2025
5	Collating, summarizing, and reporting the results	November 2025

Results

The study will begin the phase of selecting studies for this review as outlined in the protocol, including the processes of search, screening, and data extraction, in February 2025. We anticipate completing the study and submitting the manuscript for peer review by the winter of 2025. This review aims to provide a detailed overview of the various applications of recommender systems in HPE, including the filtering techniques used and the specific features of these systems.

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Discussion

Anticipated Findings

The anticipated findings of this scoping review are expected to provide valuable insights into the diverse applications and potential benefits of recommender systems in HPE. These systems can significantly enhance learning experiences by personalizing the content to the unique needs of individual learners. By providing tailored recommendations, these systems can help bridge knowledge gaps, reinforce learning, and support continuous professional development. The expected findings will provide insights into the experiences of both learners and educators, identifying applications and implementation challenges. The scoping review aims to evaluate existing evidence and identify gaps in the literature concerning the use of recommender systems in HPE.

Comparison to Prior Work

Previous studies have highlighted the benefits of recommender systems in various educational contexts of HPE (116-20). A continuously growing number of learning resources has created a need for these systems in education [23-25,39]. Digel et al [38] reported that engaging users in the development process of such systems is crucial to ensure their acceptance and use. It is anticipated that the applications and implementation challenges identified through this scoping review will help health profession educators in developing future systems. This review will build on these findings by specifically focusing on their use with HPE and identifying unique challenges and opportunities in this field.

Strengths and Limitations

A strength of this review is its comprehensive methodology, which includes a thorough search across multiple scientific databases and gray literature sources. This approach ensures a broad and inclusive overview of the existing literature. However, some limitations should be acknowledged. First, because the screening processes for scoping review do not assess the quality of the included studies, the robustness of the evidence presented may be impacted [132]. In addition, by focusing exclusively on studies published from 2000 onward, the review may overlook earlier research that could offer valuable insights and increase the potential for systematic bias [133]. Furthermore, while the aim is to cover a broad range of studies related to recommender systems, this breadth may come at the cost of a lack of depth in the analysis [134], making it difficult to draw specific conclusions. Publication bias, in which the likelihood of a study being published is influenced by the nature and direction of its results, creates a systematic difference between published and unpublished studies. Although incorporating gray literature in our study helps mitigate this bias, it does not fully eliminate it, as studies with positive or significant outcomes are still more likely to be published [135].

Dissemination Plans

The dissemination strategies for the findings of this scoping review will include publication in a peer-reviewed journal and presentations at national and international conferences. The dissemination activities will commence in the winter of 2025 with the manuscript submission.

Conclusions

While recommender systems have been extensively studied in health care and education, there is a significant gap in the literature regarding their application in HPE. To the best of our knowledge, this is the first comprehensive exploration of recommender systems specifically focused on HPE. This scoping review aims to thoroughly map the extent and various applications of these systems within this domain. By identifying effective practices and highlighting existing gaps, this review will serve as a valuable resource for health professions educators, enriching academic discourse and providing practical guidance for effective implementation in HPE.

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Data Availability

Data sharing is not applicable to this paper as no datasets were generated or analyzed during this study.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy for the MEDLINE database.
[DOCX File , 24 KB - resprot_v14i1e69979_app1.docx]

Multimedia Appendix 2
PRISMA-ScR Checklist.
[DOCX File , 37 KB - resprot_v14i1e69979_app2.docx]

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Abbreviations

HPE: health professions education
LLM: large language model
MeSH: Medical Subject Headings
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Current Status and Challenges of Planetary Health Education: Protocol for a Scoping Review

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Abstract

Background: The impacts of climate change, such as air pollution and abnormal weather, are becoming more apparent and threatening to human health. In response, the concept of planetary health was proposed in 2015 based on the recognition that human and earth health are closely related and that the general public needs to improve the health and sustainability of the ecosystems through a comprehensive approach. As economic development and human longevity progress, the burden on the earth's environment will increase; however, systematic methods for education and planetary health practices have not yet been established.

Objective: This study aims to clarify the current status and challenges of planetary health–related education. Specifically, it seeks to identify and analyze both existing educational programs that have already been implemented and evaluated, as well as those that have not yet been systematically assessed, providing insights for future curriculum development.

Methods: A scoping review based on PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines will be conducted using the Population-Concept-Context framework. Without a defined target period, original papers and conference proceedings published in PubMed, CINAHL, EMBASE, Web of Science, Scopus, Google Scholar, and the Cochrane Central Register of Controlled Trials will be searched, and the findings will be disseminated through peer-reviewed publications and conference presentations. Studies with descriptions of planetary health education are included, while review papers and studies published in languages other than English or Japanese are excluded.

Results: As of August 2025, 28 studies had been selected. Data collection was carried out between May 2024 and July 2025. Preliminary data analysis will be conducted again in September 2025. The results are currently being prepared for publication and are expected to be published by October 2025.

Conclusions: This study will identify the current status and challenges of planetary health education. The findings will contribute to developing future curricula that promote ecosystem health and sustainability.

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KEYWORDS

public health education; climate change and health; educational frameworks; competency-based education, interdisciplinary education

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Introduction

Climate change poses a significant threat to human health and well-being, and the United States Centers for Disease Control and Prevention has identified air pollution, extreme weather events, heat waves, water quality deterioration, and increased allergens as potential consequences [1]. In 2015, The Rockefeller Foundation and The Lancet proposed the concept of planetary health. This concept emphasizes the inseparable relationship between human and planetary health and provides a holistic approach to comprehensively improving and maintaining the health of all ecosystems [2,3]. It is important to distinguish planetary health from related concepts such as "One Health" and "sustainability education." Although One Health primarily focuses on zoonotic diseases and the interconnected health of humans, animals, and ecosystems, and sustainability education broadly addresses environmental justice and resource management, planetary health emphasizes the interdependence of human health and the state of the earth's natural systems. This concept is not only concerned with protecting the global environment but also includes recognition of inequalities and injustices. In particular, many low-income communities tend to be more vulnerable to the severe impacts of climate change [4], and the need to address both environmental inequality and social injustice simultaneously is emphasized. International organizations such as the Planetary Health Alliance are working to understand the interplay between the environment and health and to promote education and training to address these issues [5].

The importance of planetary health education is increasingly recognized; yet, significant gaps remain in its global implementation. Previous studies have reported that the adaptation to planetary health education policies has been slow, with a lack of faculty expertise and an emphasis on treatment rather than prevention, which has become a significant barrier to curriculum integration [6]. Furthermore, there is limited information on how cultural, socioeconomic, and political factors should be integrated into planetary health education curricula.

In particular, challenges specific to planetary health education include the absence of standardized competencies, the fragmented incorporation of content into existing health or environmental curricula, and a lack of interdisciplinary collaboration in curriculum development and delivery. These challenges hinder the development of cohesive educational strategies needed to prepare students as future leaders in addressing climate-related health issues. Against this background, how to integrate planetary health education into broad university-wide curricula as well as specialized programs such as medical, science, and teacher education is recognized as a critical challenge moving forward.

Therefore, this study aims to clarify the current status and challenges of planetary health–related education. We hypothesize that planetary health education at universities is not yet systematically organized, and there is considerable variation in the educational content, objectives, and teaching methods among programs. Specifically, we seek to identify both educational programs that have already been implemented and evaluated as well as those that have not yet been systematically assessed while also examining the educational objectives, teaching methods, and resources. This study will focus on how planetary health is taught to university students, educators, and health care professionals, all of whom have the potential to become future leaders and key contributors to societal well-being. The study will further examine the differences and challenges in planetary health education across general education courses and specialized programs at the university level. By doing so, this study aims to explore the effectiveness of these educational approaches and identify strategies for improving and advancing planetary health education. The focus of this study is on university and professional education curricula, with secondary education excluded from the scope. The reason for excluding secondary education (middle and high school levels) is that the specialized content of planetary health is more commonly taught at the university level. Education at the secondary education level tends to focus on developing basic awareness of environmental issues, and the concept of planetary health is often not fully developed at these stages. Therefore, this study focuses on university and professional education.

The results of this study will be shared with the author's affiliated educational institution and collaborating researchers in various countries, and these results will be used in the design and improvement of planetary health education programs at each institution.

Methods

Study Design

This scoping review will investigate how planetary health education is being implemented. The research protocol follows the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) [7] guidelines.

Identifying the Research Question

This study will aim to clarify how the concept of planetary health is incorporated into educational programs. Based on our findings, we plan to develop and implement educational programs in the future. The concept of planetary health used in this study was jointly introduced by The Rockefeller Foundation and The Lancet. Our research question is: what are the current status and challenges of planetary health education? For scoping reviews, the Population, Concept, Context framework will be used [7]. In this study, the components defined are as follows.

Population: students, educators, and health care professionals.

Concept: the current state and challenges of planetary health education, its delivery methods, content, program design, and curriculum.

Context: geographic location (country, region), educational settings (university, public educational institutions, online platforms), cultural or political background, and specific socioeconomic context in which education is conducted.

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Identifying Relevant Studies

To identify potentially relevant and gray literature, databases such as CINAHL, Scopus, EMBASE, Ichushi-Web, PubMed, and OpenGrey will be searched without setting a specific time frame. All the references will be imported into Rayyan and Microsoft Excel for deduplication and screening. The PubMed search strategy will be adopted as the primary search approach, and the search strategies for other databases will align with this strategy to ensure consistency across platforms. The preliminary search string will be as follows: ("Planetary health"[title/abstract]) AND (education[MeSH terms])

We will include all relevant studies published up to March 2025 to ensure comprehensive topic coverage. No lower limit on the publication date was set. Studies with descriptions of planetary health education are included, while review papers and studies published in languages other than English or Japanese are excluded.

Study Selection

The studies included in this scoping review will address the integration of planetary health into educational programs, specifically targeting university students and professionals, excluding middle and high school students. Eligible literature will consist of original research studies, gray literature, and conference proceedings. Reviews, letters, comments, and books will be excluded. No restrictions will be applied regarding the study design. Study selection will be conducted using Rayyan and Excel (Microsoft Excel, version 16.35). Two reviewers will independently screen the studies based on titles and abstracts during the initial screening by using the eligibility criteria. The eligibility criteria will be assessed by 2 reviewers, and any discrepancies will be resolved through discussion or third-party adjudication. Subsequently, 2 reviewers will independently review the full texts of the studies that meet the eligibility criteria based on their titles and abstracts. In cases where the 2 researchers are uncertain of their judgments, a third researcher will be consulted to provide a definitive decision. The reasons for excluding studies after full-text review will be documented. The study selection process is summarized in a PRISMA flow diagram (Figure 1).

Figure 1. Flowchart of the study selection process.

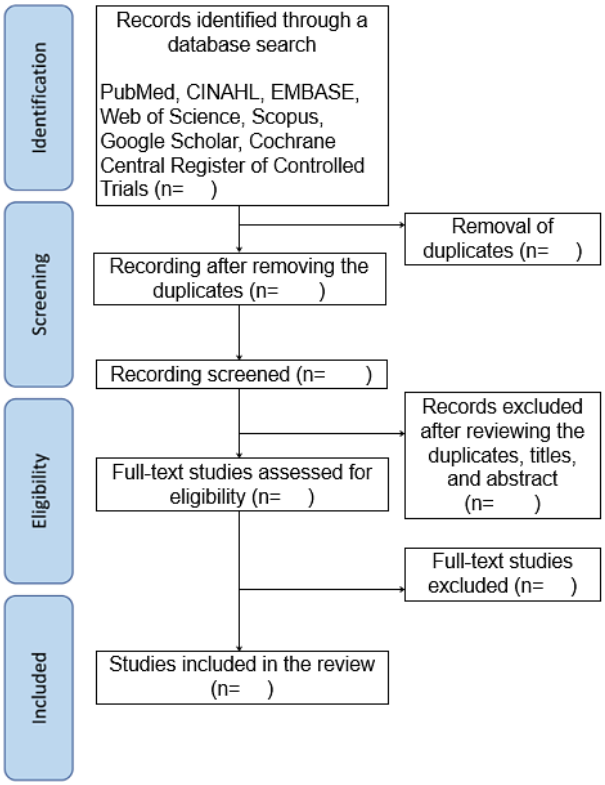

Charting the Data

The data extraction process involves Rayyan and Microsoft Excel. To provide an overview of the trends in the selected literature resulting from the searches, we will create a table based on Garrard's [8] metric approach. The selected papers will be listed chronologically and organized into 8 topics: author(s), publication year, country, objectives, study design, participants, survey items, and results. In order to consider the influence of the cultural, socioeconomic, and political factors on planetary health education, we will also examine in detail how the differences in the educational environments across regions as well as the social and cultural backgrounds of each region are reflected in the educational programs. Specifically, we will analyze how each country's educational systems and policies, region-specific social issues, and cultural values influence the introduction and implementation of planetary health education. By comparing and examining these factors, we aim to strengthen the applicability of this study in different educational settings. When conducting the analysis, we will carefully address the variations in the terminology, limited data availability, and differences in the educational systems across

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regions. Additionally, when comparing the results, we will carefully consider the educational environments and the policies specific to each region. To strengthen the evaluation of the impact of planetary health education, this study will also discuss how the effectiveness of the programs can be assessed. Potential evaluation criteria will include measures such as students' retention of knowledge, behavioral changes, and the adoption of planetary health curricula by educational institutions. By considering these outcome-based evaluations, we aim to gain a more comprehensive understanding of the educational impact of planetary health initiatives. These aspects will be included in the review to provide a clearer picture of the outcomes associated with planetary health education.

Result Collation, Summarization, and Reporting

Given that the methodologies and the study populations of the various studies included in this scoping review will differ, the analysis of the results will depend on the type of data collected. Further, the identified studies will be analyzed using qualitative methods. Where feasible, the results will be categorized within the domains proposed by the Planetary Health Education Framework [9], which are outlined in 5 foundational areas. Based on the 5 foundational areas of this framework, the selected studies will be categorized and compared, clearly identifying the educational outcomes and challenges within each area to evaluate the effectiveness of planetary health education. Furthermore, by using the framework, we aim to ensure consistency in data interpretation and to systematically understand the educational impacts across different regions and educational systems.

Ethics and Dissemination

As this scoping review will not require any intervention or population recruitment, approval from a research ethics board was not necessary. The results of this scoping review will be disseminated through peer-reviewed publications and conference presentations. This will allow us to make recommendations for the future development of educational programs related to planetary health in universities.

Results

As of August 2025, 28 studies had been selected. Data collection was carried out between May 2024 and July 2025. Preliminary data analysis will be conducted again in September 2025. The results are currently being prepared for publication and are expected to be published by October 2025.

Discussion

The strength of this scoping review lies in its ability to identify current gaps and to provide a foundation for the development of curricula that integrate human health and planetary health. These findings are expected to contribute to the construction of sustainable educational strategies that emphasize both ecosystem and human health. However, this study is limited to published research and cannot cover the curricula of all educational institutions. As a result, it may not be possible to fully clarify the current state and challenges of planetary health education. Moreover, we acknowledge that the scope of the published literature may introduce risks of institutional and publication biases as well as the dominance of Western-centric frameworks influencing educational content. Such biases may limit the representation of diverse educational models and regional perspectives, particularly from non-Western countries where planetary health education may be emerging differently. In addition, this study limited the literature search to publications in Japanese and English. This decision was made because the research team is proficient in these languages, allowing for accurate and reliable analysis without the risk of misunderstandings or loss of nuance through translation. In the future, as collaborators from countries such as Indonesia, Vietnam, Thailand, and Malaysia join the team, we plan to expand the scope to include literature published in other languages. Recognizing these limitations, we intend to address these issues in future studies by collaborating with researchers from diverse geographical and cultural backgrounds to expand the scope and the inclusivity of the educational frameworks reviewed.

With economic development and human longevity progressing, modern society is placing an unprecedented burden on the environment. The United Nations Development Program's Planetary Pressures–adjusted Human Development Index, introduced in the 2020 Human Development Report, is one attempt to quantitatively assess this global challenge [10]. Although Europe leads the Planetary Pressures–adjusted Human Development Index rankings, Southeast Asian countries have reported a lack of sufficient environmental and health initiatives. Climate change performance indicators evaluate international policies across 4 categories: greenhouse gas emissions, renewable energy, energy use, and climate policies. Although no country meets all the criteria, the European Union has received high ratings, while Southeast Asian nations such as Thailand, Vietnam, and Indonesia have demonstrated low performance, with Japan and Malaysia also rated very low. The average temperature in this region has risen by 0.14 °C to 0.20 °C per decade since the 1960s, with projections of further temperature increases and more frequent heatwaves [10].

These challenges underscore the importance of comprehensive planetary health education. Although various models have existed, such as the "One Health" programs focused on zoonotic diseases and sustainability programs addressing food security and environmental justice [11], there are limited programs specifically focused on planetary health. According to previous research, more than 95 universities and organizations are promoting education and research related to planetary health [12]. However, many of these efforts remain confined to specific academic disciplines or fields, and there are still challenges in developing comprehensive curricula that adopt an interdisciplinary approach. Furthermore, integrating planetary health into existing curricula has been reported to face barriers such as a lack of educator expertise and insufficient understanding within educational institutions [6]. The current status and challenges of planetary health education presented in this scoping review can help deepen our understanding of the obstacles educators face as well as provide guidance for institutions to implement effective curriculum reforms.

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Moreover, this study is expected to contribute to building a foundation for more effective educational strategies by emphasizing the importance of interdisciplinary approaches and offering insights into how to integrate planetary health into educational systems. Additionally, it is anticipated that this research will lay the groundwork for future educational programs to better adapt to regional needs and incorporate the concept of planetary health comprehensively into educational settings.

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Authors' Contributions

Conceptualization: YS (lead), NT (equal), KS (equal)
Data curation: YS (lead), NT (equal), KS (equal), MK (equal)
Formal analysis: YS (lead), KS (equal)
Funding acquisition: YS (lead)
Investigation: YS (lead), KS (equal)
Methodology: YS (lead), NT (equal), KS (equal)
Project administration: YS (lead), NT (equal), KS (equal)
Resources: YS (lead), NT (equal), KS (equal)
Supervision: NT (lead), MK (supporting)
Validation: YS (lead), NT (equal), KS (equal), MK (equal)
Visualization: YS (lead), KS (equal)
Writing – original draft: YS (lead), KS (equal)
Writing – review & editing: YS (lead), NT (equal), KS (equal), MK (equal)
NT also served as a co-corresponding author for this study.

Conflicts of Interest

None declared.

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Abbreviations

PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Determining the Intersection of Social Prescribing in Social Work Practice: Protocol for a Scoping Review

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Abstract

Background: Social prescribing is a nonclinical intervention used in various health care settings to improve health outcomes of individuals by attending to the social determinants of health and broader social factors. Prevalence of social prescribing has increased globally over the past decade, leading to the creation of new organizations and networks dedicated to social prescription. Although social workers comprise one of the largest providers of social and mental health services sectors, there remains little guidance how social workers can integrate social prescribing in practice.

Objective: The objectives of this scoping review are 3-fold. The objectives of this scoping review are to (1) systematically scope the literature on social prescribing and social work and identify scholarly gaps in the literature, (2) identify the role of social work in social prescribing, and (3) describe how social workers are integrating and engaging in social prescribing in clinical practice.

Methods: The review follows the 5-stage scoping review framework from Arksey and O'Malley (2005), which was later enhanced by Levac et al in 2010. The review will examine both academic and grey literature. We will search for studies in the following databases: MEDLINE, Embase, PsycINFO, CINAHL, Social Services Abstracts, and Social Work Abstracts. Grey literature will be searched using Google with a focus on social prescription organizations, social prescription conferences, and Canadian social prescription reports. All studies must be in English and there are no date restrictions. Title and abstract screening, assessment of full-text review, and data extraction will be conducted by 2 independent reviewers. Data will be extracted into a chart format, which will be analyzed for data summarization and synthesis.

Results: The results of the study and submission of a manuscript for peer review are expected in October 2025. The results of the scoping review are expected to contribute to an understanding of how social workers employed in health care can integrate social prescribing in their practice.

Conclusions: To the authors' knowledge, this is the first scoping review undertaken on the topic of social prescribing and social work. Findings from the scoping review will inform the future development of guidelines to support the integration of social prescription in social work practice.

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KEYWORDS

social prescription; social conditions; systems navigation; systematic review; social work

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Introduction

The field of social prescribing has gained momentum over the last decade, with social prescribing becoming increasingly prevalent across more than 20 countries, including Canada, the United States, Australia, the United Kingdom, and elsewhere [1,2]. There has been a rise of new social prescribing organizations and networks established across the globe [2], such as the World Health Organization– and United Nations–linked Global Social Prescribing Alliance [1], the Social Prescribing Network [3], the National Academy for Social Prescribing [4], and the Canadian Institute for Social Prescribing [5]. Originating in the United Kingdom, social prescribing refers to a process of care that connects patients to nonmedical services and enhances health and well-being [6,7]. According to the Social Prescribing Network, social prescribing is defined as "enabling health care professionals to refer patients to a link worker, to co-design a nonclinical social prescription to improve their health and well-being" [8]. Various definitions of social prescribing exist; however, one commonality across different definitions is that social prescribing is considered a nonclinical intervention [2,9]. Although the Social Prescribing Network and the World Health Organization situates social prescribing within a health care setting involving a health care provider [8,10], Muhl et al [2] hold a more expansive view and assert that social prescribing can occur in nonmedical community settings. Inherently, the essence of social prescribing is attendance to the social determinants of health, health equity, and the broad health-related social factors that influence health outcomes [2,7]. This aligns well with social work, which takes a holistic approach by looking at how history, the environment, social structures, and other factors impact the health of individuals.

Social work is a practice-based profession that responds to the needs of individuals, families, and communities by focusing on improving health and social well-being [11,12]. As one of the largest groups of health and social service professionals [11,13], social workers have a long-standing history of practice in a broad range of health settings, such as hospitals, primary health care, community mental health, public health, social services, nonprofit organizations, and elsewhere [14]. Notably, health was one of the earliest areas of practice for social work and continues to be one of its largest practice domains [15,16]. Guided by foundational values of social justice, human rights, respect for diversity, and collective responsibilities, social work inherently strives for health equity and alleviation of existing and future disparities [14,17-19]. The person-in-environment perspective guides social workers to bring a crucial understanding of the disparities and inequities that manifest as health and mental health conditions, with practice aimed at addressing the range of nonmedical psychosocial factors that impact health and well-being [14]. Social workers fulfill many roles with crisis management, service coordination, case management, problem solving, discharge planning, systems navigation, resource allocation, and community mobilization as core functions [16,17,20]. Furthermore, social workers often engage in referrals to community resources to attend to the socioeconomic factors impacting the health of individuals [21]. This is aligned to social prescribing, which recognizes the importance of nonmedical services that are often beyond the scope of health care professionals [7]. At the same time, there are no standards for how social prescribing occurs or who is involved throughout the process of social prescription [7]. Despite the similarities in focus, it is unclear how social work and social prescription are related or intersect to inform one another. From a health systems design perspective, having clarity about the roles and functions of similar types of services and providers can "optimise human well-being and overall system performance" [22].

The objectives of this scoping review are to (1) systematically scope the literature on social prescribing and social work and identify scholarly gaps in the literature, (2) identify the role of social work in social prescribing, and (3) describe how social workers are integrating and engaging in social prescribing in clinical practice. This work will constitute the first step in the development of guidelines to explain how social prescription and social work are aligned. By doing so, this information will help provide guidance to social workers and other leaders in health care in determining how social work practice can best integrate social prescription in practice and how health care organizations who are implementing social prescription can use social workers for this function. Furthermore, the knowledge gained will inform future research directions that can also shift clinical practice and policy.

Methods

Protocol Design

Using scoping review methods, our study is helping to provide a broader understanding of social work's engagement in social prescription. A scoping review is a method of knowledge synthesis that maps key concepts and evidence related to a defined field of research by systematically searching and synthesising existing knowledge [23]. Systematically mapping a subject field is particularly useful when minimal literature exists for a particular topic or when the examination is on a complex or nonhomogeneous topic [23-25]. Scoping reviews provide an opportunity to identify key concepts and evidence that can help guide clinical practice [24]. Knowledge synthesis, including scoping reviews, is necessary for advancing health care practices and can help knowledge users—in this case social workers—increase integration of efficient evidence-based decisions in clinical practice [23]. The study adheres to the PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) checklist, and no protocol was registered. In alignment with scoping review designs, no quality appraisal will be performed on included sources.

Following recommendations from Colquhoun et al [23], our methods for this study are based on a 5-stage scoping review framework proposed by Arksey and O'Malley [24] and enhanced by Levac et al [26]. The five stages informing our review are (1) identifying the research question, (2) identifying relevant studies, (3) selecting studies, (4) charting the data, and (5) summarizing data and synthesizing results [24,26]. We consider this an appropriate framework for our current study

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due to the infancy of the topic and scarcity of evidence-based studies.

Stage 1: Identifying the Research Question

Levac et al [26] recommend clarifying stage 1 [24] by combining a broad research question with a clear scope of inquiry that defines the concept and target population to clarify the focus of the scoping review. Levac et al [26] also recommend developing the research question with the intended outcome of the scoping review in mind to help determine the purpose of the study. In this case, the purpose of this scoping review is to provide clarity about the ways that social work has been involved in social prescribing that may contribute to clinical practice guidelines that are currently absent. Through consultation, the research team has defined the overarching research question as, "In what ways has social work been involved with social prescribing?" In addition, the two subquestions guiding this scoping review are as follows: (1) "How has social work contributed to the role of social prescribing?" and (2) "How are social workers integrating and engaging in social prescribing in clinical practice?"

Stage 2: Identifying Relevant Studies

In stage 2 [24] we seek to identify available literature on social prescription that includes mention of social work. Levac et al [26] recommend strengthening stage 2 by assembling a suitable research team with combined content and methodological expertise to ensure successful completion of the scoping review. We have followed this suggestion and have assembled a team that combines expertise in social prescribing (RA, KA, TDV, and SO), social work practice in health care (RA, KA, TDV, RB, SM, and MRL), and scoping review methodology (RA, SL, KA, TDV, and BW). We have also identified 2 graduate-level research assistants who will participate in all phases of the scoping review (SM and MRL).

A search strategy will be implemented to identify literature discussing both social prescription and social work. This strategy, developed by a social sciences librarian (BW) and peer-reviewed by an independent health science librarian using the Peer Review of Electronic Search Strategies framework [27] for use in MEDLINE (Ovid) will then be translated for use in 5 additional databases including CINAHL, Social Work Abstracts, Social Services Abstracts, Applied Social Sciences Index and Abstracts, and Scopus. The goal of this search will be to locate all articles in the social work and health science literatures with relevant text words appearing in the title, abstract, and author-supplied keyword fields. Relevant controlled vocabulary will also be used to increase search sensitivity. All text words and subject headings have been determined collaboratively with the research team. No restrictions on publication date, language, or geographical location were applied to ensure the comprehensive capture of relevant literature. The pilot MEDLINE search is shown in Table 1.

Table 1.

Search statement	Results
(social work* or socialwork*).tw,kf.	21,074
exp Social Work/ or Social Workers/	20,346
(social work* or socialwork*).tw,kf. OR exp Social Work/ or Social Workers/	33,861
(prescrip* or prescrib*).tw,kf.	317,451
(social work* or socialwork*).tw,kf. OR exp Social Work/ or Social Workers/ AND (prescrip* or prescrib*).tw,kf.	469
link work*.tw,kf.	246
community connector*.tw,kf.	24
link work*.tw,kf. OR community connector*.tw,kf.	269
(social work* or socialwork*).tw,kf. OR exp Social Work/ or Social Workers/ AND (prescrip* or prescrib*).tw,kf. OR link work*.tw,kf. OR community connector*.tw,kf.	715

A search in each database was conducted, and results were exported to the literature review management software Covidence [28] for deduplication and screening. While a total of 10,416 citations were exported from 6 databases, deduplication left 2543 unique sources to be screened. Full search strategies across all 6 databases are available on request.

In addition, a grey literature search will be conducted to identify any relevant reports using the following steps: (1) review of websites belonging to any agencies or associations mentioned in articles included in the sample; (2) review of websites belonging to national and international social prescription associations; (3) review of any conferences, symposiums, or gatherings specific to social prescription; and (4) review of all grey literature in Canada that is focused on social prescription. The grey literature search will capture reports created by professional associations and health care organizations pertaining to social prescription and social work.

Terms will be searched as keywords in the titles, abstracts, and subject headings as appropriate. Search results will be downloaded and imported into the web-based platform Covidence [28].

Stage 3: Selecting Studies

In stage 3 [24], the review process will be comprised of two levels of screening: (1) a title and abstract review, and (2) a full text review. The stage 3 inclusion criteria guiding publication types acceptable for review are broad and inclusive of all peer-reviewed publications such as original research, case

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reports, literature reviews, technical guidelines, and commentary papers. Only articles published in the English language will be included at this stage. No date limits will be applied, and no limits on geography will be applied.

For the first level of screening, the 2 graduate-level research assistants (SM and ML)—working under supervision of the lead author (RA) and the project coordinator (SL)—will independently conduct title scans and abstract reviews to assess eligibility against the inclusion criteria. Disagreements regarding the inclusion of articles in the title and abstract reviews will be decided by the lead investigator or project coordination. Articles that are considered relevant by both research assistants will be included in the full text review. During full text screening, both research assistants will assess each article to determine eligibility. Any discordant full text articles will be reviewed by both the research assistants and the lead investigator or project coordinator to determine whether they meet the inclusion or exclusion criteria. A hand search of reference lists of the articles included in the sample will be conducted and included in our screening process.

Relevant studies will be assessed against the following inclusion criteria: (1) the words social prescription (inclusive of search terms) and social work (inclusive of search terms) are used in the title or abstract and (2) social prescription is a key focus of the article. Any type of study design will be included, as well as commentary articles. We will follow the recommendation by Levac et al [26] to approach stage 3 as an iterative process that includes regular team meetings to discuss the criteria for study inclusion and exclusion throughout the study process. Screening will occur using Covidence [28].

Stage 4: Charting the Data

To guide stage 4 [24], a data collection instrument will be generated by the research team to extract characteristics from the sample. We will extract data from all studies included in the scoping review. Example of categories that will be included on the data charting form include but are not limited to authorship, publication year, type of article (eg, original study or commentary paper), study design (qualitative, quantitative, or mixed), geographical origin of study or article, definition of social prescription, social prescription activities, description of practice setting (community-based, hospital, primary care, or web-based), description of social work activities related to social prescribing, type of practice location, and patient population characteristics. This form, created in Microsoft Excel, will be created with input by the research team as per the recommendation by Levac et al [26] that the research team collectively determine variables to extract from the data and collaboratively develop the data charting form to effectively answer the research questions. Data extraction will be conducted by the 2 graduate-level research assistants working under the supervision of the lead investigator and project coordinator.

Stage 5: Summarizing Data and Synthesizing Results

The focus of stage 5 [24] will be to provide a synthesis and summary of the results. An inductive qualitative content analysis is generally descriptive in nature and appropriate to guide analysis of this scoping review data [29]. Following data charting, the findings from the selected sources will be synthesized, with an emphasis on identifying recurring themes relevant to the objectives of the review. This aligns with the aims of scoping reviews to provide a map of concepts underpinning the research, key sources, and types of research [30]. Levac et al [26] suggest breaking stage 5 into the following three smaller steps: (1) analysis, (2) reporting of the results pertaining to the overall study purpose and research question, and (3) consideration of the meaning of the results and discussion of the potential implications that the findings may have on future research, clinical practice, and policy.

Ethics and Dissemination

This study will be the first step toward developing guidelines for social workers pertaining to social prescription. Research ethics approval is not required given that we are collecting data from publicly available sources. The results of this scoping review study will be disseminated through a conference presentation that engages an audience of social work practitioners in health care and a peer-reviewed publication. Most members of the research team have established relationships with social work and health care networks, which will also be used to disseminate the findings. Our aim is to use the results from this scoping review to guide future research on social prescription with social workers.

Results

The scoping review commenced in February 2025. The formal literature search was completed in February 2025 with the exception of the addition of “community connectors,” which was added to the formal literature search in July 2025. The process of screening all articles was completed in March 2025 with the exception of articles identified with the updated term “community connectors,” which was completed in July 2025. We are currently in the process of conducting the grey literature search. The results of the study and submission of a manuscript for peer review are expected in October 2025. The results of the scoping review are expected to contribute to an understanding of how social workers employed in health care can integrate social prescribing in their practice. Gaps in social work practice and social prescribing may also emerge.

Discussion

Overview

This scoping review addresses an important gap in understanding the role of social workers in social prescribing. Although a core focus of social workers’ roles in various settings is on addressing the social determinants of health [14,31,32], such as issues related to financial challenges and insecure housing, research to inform social workers’ uptake of social prescribing in practice appears minimal. While advances in social prescribing have been made, current literature aimed at informing and guiding social workers in the practice of social prescribing appears absent. Given social workers’ historical expertise in addressing the social dimensions of health, providing mental health care, working with complex client situations, and doing systems navigation and resource allocation,

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there is much that the discipline of social work can add to the social prescribing literature and practice. This scoping review intends to identify the role of social work in social prescribing and explain how social workers can integrate social prescribing in clinical practice.

Given the exploratory nature of the research questions and the anticipated variability in study designs, populations, and outcomes, a scoping review represents a well-suited methodological approach for this topic. The use of gray literature will supplement the search to find pertinent information not found in the databases and will include literature that may be guiding social prescribing in various health and community settings. This scoping review will constitute an important first step in the development of practice guidelines for social workers and social prescribing. The findings will assist leaders in health care in determining how to allocate social work resources pertaining to social prescribing.

Limitations

The scoping review has some limitation. First, the search is limited to sources available in English, meaning that sources not written in English will not be included, thus limiting generalizability. Although acceptable within the context of scoping reviews, studies included in the sample will not be evaluated for quality or methodological rigor.

Conclusions

The scoping review will assist in the further development and implementation of social prescribing by providing a foundation by which to develop guidelines for social work practice. These results will be disseminated at a national social work conference and will be published in a health care journal. This scoping review aims to address a gap in the literature and provide guidance on the implementation of social prescribing practices in health care.

Data Availability

The datasets generated or analyzed during this study will be made available in the final manuscript. All data will be attained from publicly available sources.

Authors' Contributions

RA, SL, TDV, RB, and KA contributed to the conceptualization of study. RA led the development of the methodology with input from SL, TDV, and KA. BW led data curation with assistance from SL, SM, and MRL. Formal analysis will be conducted by RA, SL, and SM. Project administration and supervision were conducted by RA and SL. All authors contributed to writing the original manuscript and reviewing and editing the final version.

Conflicts of Interest

None declared.

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Abbreviations

PRISMA-ScR: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Viral Load Suppression Associated With Undisclosed HIV Status Among Adolescents Aged 10 to 19 Years Living With HIV in Low- and Middle-Income Countries: Protocol for a Scoping Review

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Abstract

Background: HIV and AIDS remain a major health problem in sub-Saharan Africa and are particularly prevalent in children and adolescents. The prevalence of undisclosed HIV status among adolescents is also a challenge worldwide.

Objective: This scoping systematic review aims to synthesize the existing literature to address viral load suppression among adolescents living with HIV who have not disclosed their HIV status in low- and middle-income countries.

Methods: A comprehensive search of PubMed, MEDLINE, Google Scholar, and ScienceDirect from 2010 to 2024 will be conducted. This review will conduct evidence synthesis from the published literature on a research question regarding viral load suppression associated with undisclosed HIV status among adolescents living with HIV. The population, concept, and context framework was considered more useful in guiding this study. A random sample of 12 articles will be assigned to the 2 reviewers to pretest the data extraction tool.

Results: The initial search was conducted for articles published from March 1, 2010, to December 31, 2024, and 3174 articles were returned in total. After deduplication, of the 3174 articles, 1147 (36.14%) abstracts were reviewed, and 98 (3.09%) articles have been included in full-text review. Most of the results indicated that disclosure of HIV status is positively associated with the holistic well-being of adolescents. Among adolescents, the provision of social and psychological spaces helps them vent problems, whereas behavior change interventions are essential to reduce the likelihood of unsuppressed viral load and the risk of HIV transmission among adolescents in the context of antiretroviral therapy education and counseling.

Conclusions: The findings will be key in informing practices, programs, and decision-making for the integration of services for adolescents living with HIV to address the issue of HIV disclosure for the achievement of viral load suppression.

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KEYWORDS

evidence synthesis; scoping review; HIV; undisclosed; viral load suppression; adolescents

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Introduction

Background

In recent decades, the global HIV landscape has changed, and major milestones have been achieved in both HIV treatment and prevention. Despite these significant advances, it has been reported that 28% of people living with HIV are not virologically suppressed [1]. Unsuppressed viral load (VL) is associated with an increase in the risk of AIDS progression [2]. In certain groups, the risk of nonsuppression of the HIV virus is higher [3]. HIV and AIDS remain a major health problem in sub-Saharan Africa and are particularly prevalent in children and adolescents [4].

HIV VL measurement is a key indicator in the clinical management of the HIV virus in people who are infected. Since 1996, it has been demonstrated that the VL threshold is a way of measuring the response to antiretroviral therapy (ART) and identifying patients with virological suppression or its failure [5,6]. Frequent tests are recommended as part of the management of nonsuppression and failure events, which may vary according to guidelines [7,8]. VL results are classified as undetectable (no VL detected on the test used), suppressed (≤1000 copies per mL), or unsuppressed (>1000 copies per mL) [9]. In 2023, the World Health Organization issued updated policy guidelines on the role of HIV eradication in improving health for people living with HIV and reducing HIV transmission by recommending regularly monitoring VL to detect early treatment failures. Although a threshold of >50 copies per mL was introduced, currently, the World Health Organization still considers an individual with a VL of >1000 copies per mL in 2 consecutive tests to be virally unsuppressed [7].

HIV infection in women heightens the risk of transmitting the virus to the foetus. Such vertical transmission may occur during pregnancy via the placenta, during childbirth through exposure to maternal body fluids, or after birth through breastfeeding in Walters et al [10]. The vertical transmission was mainly perinatal, whereby a mother transmitted HIV to their child during pregnancy, childbirth, or breastfeeding [11]. In 2022, approximately 1.2 million pregnant women were infected with HIV, and without treatment, between 15% and 30% of infants contracted HIV during pregnancy, labor, or birth and 5% to 15% contracted HIV during breastfeeding [12]. With an expansion of the rollout of prevention of mother-to-child transmission (MTCT) services, mothers' VLs are likely to be suppressed through antiretroviral medication during the breastfeeding period, so the rate of MTCT of HIV could be <2% [13]. In the same year (2022), the global progress toward the elimination of MTCT was reported to be stagnated despite women with HIV receiving ART [12]. However, between 2021 and 2022, the global MTCT rates showed a slow decline after several years [14]. Several studies have highlighted that, despite efforts to reduce MTCT rapidly among HIV-exposed infants and eliminate it, the vision of a new generation without HIV has not yet been achieved [14-16].

Because of the effectiveness of ART expansions, many children living with vertically acquired HIV are now living longer to reach adolescence (10–19 years) and early adulthood [17]. By the time they reach the developmental transition period of adolescence, they have been living for a decade with a chronic disease [18,19]. Adolescents aged 10 to 19 years account for approximately 16% of the world's population. In 2021, there were 1.7 million adolescents living with HIV, representing 5% of the population living with HIV worldwide [20]. Approximately 140,000 new HIV infections in the world were reported in 2022 among young people aged 10 to 19 years, with approximately two-thirds of all HIV infections occurring in sub-Saharan Africa, although high HIV rates were also reported in Eastern and Southern Africa [21].

The literature reveals that adolescents living with vertically acquired HIV experience poorer HIV-related outcomes, such as virologic treatment failure and poorer retention in care [22,23]. It has been highlighted that many children and adolescents living with HIV are enrolled in HIV care without knowledge of their HIV status for various reasons, such as considering that the child is still too young to understand, stigmatization, or fear of disclosing the mother's or child's HIV status [24,25].

HIV status disclosure is a well-known important factor determining physical and mental health outcomes for patients with HIV at any age, and it is a challenge that continues to be faced [26]. The disclosure of HIV status to children is a difficult task for parents and caregivers as it is emotional and can be linked to positive or negative health outcomes [25,26]. Care providers who delay disclosure to children identify several factors for doing so, such as concerns about negative reactions of children and inappropriate disclosure to others that may result in shame, stigmatization, and discrimination related to HIV [26,27]. Disclosure of HIV status to infected children holds several benefits, yet rates of disclosure remain low, posing challenges worldwide [28], and many infected children do not know their diagnosis even though they regularly attend clinics and receive ART [28].

HIV status disclosure is an ongoing process and can be conducted in phases. Partial disclosure to children or adolescents can take place when the child reaches the ages of 5 to 9 years, full disclosure can take place at the ages of 10 to 12 years, and psychosocial support to transition to other relevant programs can be provided at the ages of 13 to 19 years [29]. A study conducted in Uganda showed that up to 30% of HIV-infected children aged 5 to 17 years achieved full HIV status disclosure, and a similar study in Zimbabwe reported that 27% of HIV-positive children aged 9 to 15 years received full disclosure [29].

Two South African studies found that adolescents find it difficult to adhere to any ART medication regimen in the long term compared to adults. As a result, they face unsuppressed VL and virological failure [30]. With the engagement in high-risk behaviors, some adolescents who are infected with HIV fail to respond optimally to antiretroviral medications, with only 24% achieving and maintaining undetectable VLs [31]. Adolescents face distinctive challenges in taking ART because of failure to take their condition seriously, disclosure concerns, and stigma [19].

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Objectives

Although large studies on the efficacy of ART in HIV-infected adults and children have been conducted, relatively fewer data have been collected and synthesized describing how disclosure affects virological outcomes among adolescents aged 10 to 19 years on ART [31]. A scoping review is especially suitable for this topic as it enables the mapping of existing literature, identification of research gaps, and synthesis of various pieces of evidence related to the suppression of VL among adolescents with undisclosed HIV status. It might highlight gaps in knowledge about the psychological, social, behavioral, and clinical factors affecting medication adherence and VL suppression of adolescents with nondisclosed status. Given the relatively sparse focus on this subgroup between 2010 and 2024, there might be limited consolidated data and systematic reviews. Hence, this scoping review aims to systematically synthesize existing evidence on the relationship between nondisclosure and VL suppression among adolescents aged 10 to 19 years living with HIV. In addition, this review may propose personalized strategies, including initiatives to improve medication adherence and VL suppression, while respecting confidentiality and addressing stigma.

Methods

Overview

Scoping reviews are increasingly used as an effective and systematic method for the synthesis of knowledge [32]. It is a form of evidence synthesis that systematically determines and maps the scope of evidence available on a specific topic, field, or concept, often irrespective of the source of primary research or nonempirical evidence within or across a particular context [33]. Often, a scoping review is carried out to clarify concepts and functional definitions and inform future research [34-36]. A scoping review is particularly suitable for addressing broad research questions, to increase the understanding of the widely used approach to the search for information, but which have not yet been thoroughly examined [37,38].

This scoping review will be guided by the evidence-based methodology described by Khalil et al [39] based on the well-known framework and methodology by Arksey and O'Malley [40]. This framework comprises five phases, namely, (1) identifying the research question, (2) identifying relevant studies, (3) identifying the study selection criteria, (4) charting the data incorporating both quantitative and qualitative thematic analysis, and (5) collating, summarizing, and reporting the results.

As far as we know, no specific scoping review has been published addressing the relationship between HIV status nondisclosure and VL suppression among adolescents aged 10 to 19 years living with HIV. This proposed scoping review will address this study gap.

Review Process

Phase 1: Identifying the Research Question

This scoping review will form the basis for synthesized knowledge that will present a broad overview of the evidence on this research topic. The concepts that will assist in this review will be mapped systematically and logically while searching, selecting, and synthesizing existing data [35]. The primary research question to guide this review will be the following: what is the extent and nature of evidence regarding VL suppression among adolescents aged 10 to 19 years living with HIV who have not disclosed their HIV status in low- and middle-income countries?

The secondary research questions, outlined in Table 1, will help in mapping the existing literature comprehensively while identifying gaps in knowledge about this population.

Table 1. Secondary research questions.

Characteristic	Research questions
Clinical and treatment outcomes	• What are the prevalence rates of viral load suppression among adolescents with undisclosed status compared to those who have disclosed their status? • What is the relationship between the degree of disclosure and viral load suppression outcomes?
Disclosure-related factors	• What are the barriers to HIV status disclosure among adolescents and how does this impact viral load suppression? • How does fear of disclosure affect treatment engagement and viral load suppression outcomes?
Psychosocial and behavioral factors	• What psychosocial factors influence viral load suppression among adolescents with undisclosed status living with HIV? • What role does social support play in achieving viral load suppression among adolescents with undisclosed status?
Health care system and support factors	• What interventions are most effective for achieving viral load suppression among adolescents with undisclosed status? • What support services are associated with improved viral load suppression in this population?

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Phase 2: Identifying Relevant Studies for Scoping Review Eligibility

Overview

This scoping review will be guided by the population, concept, and context framework recommended by the Joanna Briggs Institute. The 3 elements of this scoping review eligibility framework, namely, population, concept, and context [40], will be used to guide the establishment of the inclusion and exclusion criteria. The adapted population, concept, and context framework is illustrated in Table 2.

Table 2. Scoping review protocol design adapted to the population, concept, and context (PCC) framework.

PCC element	Description	Operational definition
Population	Adolescents aged 10-19 y living with HIV	• Any individuals aged 10-19 y who have been diagnosed with HIV and may or may not be receiving ART[a].
Concept	Viral load suppression related to undisclosed HIV status	• Viral load suppression refers to an HIV viral load of <1000 copies per mL, although thresholds may vary by national guidelines. • Undisclosed HIV status involves adolescents who are unaware of their diagnosis due to nondisclosure, partial disclosure, or delayed disclosure by caregivers.
Context	LMICs[b]	• The context refers to LMICs as classified by the World Bank at the time of each study's publication, which includes health system factors, cultural norms, stigma, legal frameworks regarding consent for disclosure, and caregiver roles in adolescent HIV care.

[a]ART: antiretroviral therapy.

[b]LMIC: low- and middle-income country.

Synthesis of Eligibility Criteria

The inclusion and exclusion criteria to be considered for this scoping review will be based on accessible full-text published articles that are peer reviewed and in English. All quantitative, qualitative, and mixed methods studies conducted among adolescents aged 10 to 19 years living with HIV regardless of disclosure status in low- and middle-income countries will be included. The search databases will consider published data from 2010 to 2024 onward up to the time of the scoping review. The studies may be cross-sectional surveys or observational or interventional in design or include randomized controlled trials.

Any studies that do not meet the eligibility criteria, such as gray literature, systematic reviews, meta-analyses, case reports, editorials, commentaries, or opinion pieces without primary data and populations aged <10 and >19 years, will be excluded.

Search Strategy

To ensure a comprehensive assessment of the content, a search of PubMed, MEDLINE, Google Scholar, and ScienceDirect from 2010 to 2024 will be conducted. The authors will conduct a systematic literature search by consulting the Sefako Makgatho Health Sciences University's online library. Keywords such as "HIV," "disclosure," "viral load suppression," "adolescents living with HIV," "adolescents on antiretroviral treatment," and "primary caregivers" will be used for the literature search. All the identified articles meeting the inclusion criteria will be listed in the reference list. The following search strategy will be used:

> *[("HIV" OR "Human Immunodeficiency Virus") AND ("viral load suppression" OR "viral suppression") AND ("undisclosed HIV" OR "undisclosed HIV status" OR "HIV status not disclosed") AND ("adolescents" OR "adolescents" OR "teenagers" OR "youth") AND ("low-middle income countries" OR "low-income countries" OR "middle-income countries"]*

Phase 3: Study Selection

The selection process of documents will be guided by the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) model [40]. Two reviewers in this study will independently screen the titles, abstracts, and full texts of the retrieved articles to identify whether studies meet the inclusion criteria. If discrepancies arise and they fail to reach consensus through discussions, an independent reviewer to mediate the situation will be considered. The results of the search will be presented in a PRISMA-ScR flow diagram.

Phase 4: Charting the Data

Data from eligible studies will be charted independently by 2 researchers using a standardized data extraction tool. The chart will capture the relevant information using key study terminology and characteristics, such as the participant demographics, study objectives, study setting, population, and key results of the studies reviewed. This chart will be used to capture such information for each article [41]. The process will include reviewing the entire text to identify the variables relevant to this scoping review.

Virtual training sessions will be held for reviewers involved in the scoping review focusing on research objectives and questions, inclusion and exclusion criteria, key concept definitions, and the use of evaluation and data extraction tools. The Rayyan (Qatar Computing Research Institute) web-based software screening tool will be used to identify and remove duplicates, and the reviewers will be trained on its use.

The deduplicated results of the screening, including a unique ID, title, author, and abstract, will be evaluated in 2 phases in the Rayyan web-based software. First, the titles and abstracts

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of the articles retrieved from the search will be independently evaluated by 2 reviewers to determine the relevant records. Relevant records that at least one reviewer has classified as *included* or *insecure* will be moved to the second screening round. In the second phase, the complete texts of the relevant documents will be retrieved and independently checked to ensure that they meet the a priori defined study inclusion criteria.

Interrater agreement refers to the degree of coherence or agreement between ≥2 reviewers in the process of screening and data extraction. In this scoping review, a random sample covering 10% of the retrieved citations for pilot-testing will be assigned to the 2 reviewers, who will independently screen the titles and abstracts. The interrater agreement will be calculated using the Stata statistical software (version 19; StataCorp), and the Cohen κ statistical measurement will be used to assess the reliability or agreement between the 2 reviewers during the piloting phase. A κ value of ≥0.7 will be considered acceptable, indicating a substantial agreement. If the agreement is below the acceptable threshold, the criteria will be reviewed, additional training will be provided, and the pilot-testing will be repeated until a satisfactory agreement has been reached. Modification and merging will follow when an agreement is reached. Should conflict still arise, a mediator will be approached to facilitate agreement until a consensus is achieved.

Phase 5: Collating, Summarizing, and Reporting the Results

This scoping review will synthesize extracted data following thematic analysis for qualitative data and frequency analysis with counts and percentages for quantitative data to summarize the existing knowledge on the association between VL suppression and undisclosed HIV status among adolescents who acquired the infection through vertical transmission in low- and middle-income countries. A coding framework for qualitative studies will be developed by the 2 reviewers, whereas tables, charts, and diagrams will be used to capture data from the articles. Manuscripts will be written and submitted for peer review and for publication in a selected accredited journal. Conference posters will be designed and presented. The results will also be presented orally at relevant health care–related conferences locally and internationally. The findings will also be shared with the various stakeholders in the Department of Health in South Africa locally and nationally, including various nonprofit organizations responsible for youth-friendly services.

Ethical Considerations

All articles that will be included in this review must provide a statement indicating that their study was subjected to ethical review and that the required ethics approval was obtained. The protocol will not be registered with PROSPERO. However, it will be published in a peer-reviewed journal.

Results

This scoping review is currently in the study selection phase. Preliminary electronic database searches were conducted on January 3, 2025, yielding a total of 3174 records. On the basis of the inclusion and exclusion criteria, of the 3174 records, 2027 (63.86%) were excluded during this stage. After removing duplicates, 1147 unique records remained for title and abstract screening. Of the 1147 unique records, 98 (8.54%) articles have been identified for full-text review, which constitutes the next step in the selection process aimed to be completed by December 2025 (Figure 1).

Figure 1. PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) flow diagram example for this scoping review (self-developed).

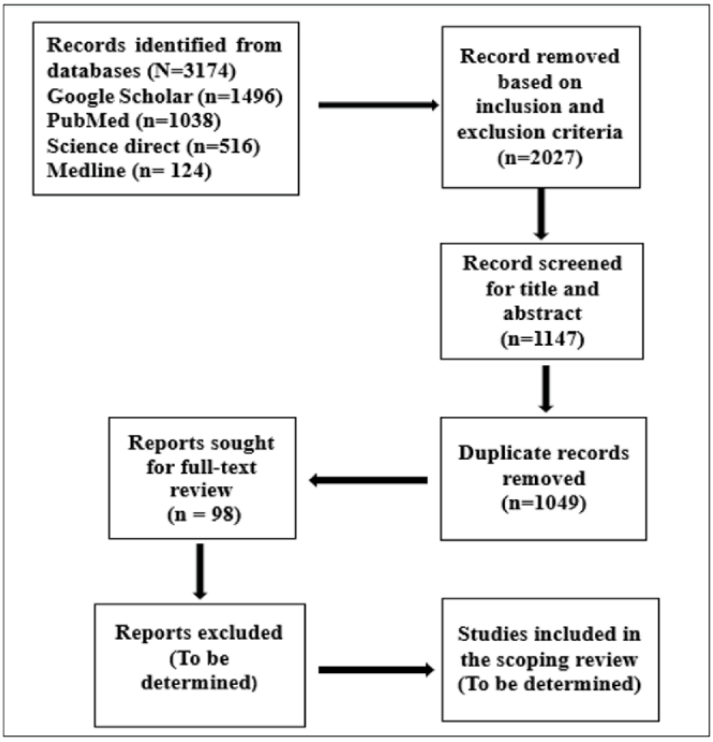

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Preliminary screening results show that almost 1 in 2 adolescents living with HIV were diagnosed and put to HIV care before the age of 10 years. Many adolescents living with HIV do not correctly adhere to ART because they are not informed about their HIV-positive status. The lack of disclosure causes confusion as some adolescents living with HIV think that they are correctly handling the conditions they have been falsely informed they have instead of HIV. Status disclosure has been found to positively elevate the holistic well-being of adolescents living with HIV. Moreover, disclosure of HIV status can improve quality of life, social support, immune recovery, and adherence to ART, but nondisclosure increases the risk of loss of follow-up and represents an important obstacle to achieving VL suppression. The provision of social and psychological spaces helps adolescents living with HIV vent problems, whereas HIV disclosure rules in health care facilities are key positive factors influencing the disclosure of HIV status to adolescents.

The preliminary screening results show that behavior change interventions are essential to reduce the likelihood of VL nonsuppression and the risk of HIV transmission among adolescents in the context of ART education and counseling. The results point to the importance of addressing psychosocial challenges in combination with medical treatment to facilitate adherence to ART and the achievement of VL suppression

Discussion

Expected Findings

This scoping systematic review aims to review and synthesize the existing literature to address VL suppression in adolescents with undisclosed HIV status; the prevalence of undisclosed HIV status among adolescents remains a challenge worldwide. Several studies indicate that poor VL suppression challenges following undisclosed HIV status vary widely among adolescents in various parts of the world [42-44].

It is imperative to review and analyze existing evidence from various parts of the world to provide a summary that will give us the full picture of the phenomenon. This scoping review will provide summary results by subgroup, such as low- versus middle-income countries, sex, and age categories, and describe factors associated with disclosure status. As adolescents aged 10 to 19 years are increasingly observed not to disclose their HIV status, which is an important factor in suppressing VL, it is necessary to deeply understand this complex problem [29,45]. Despite significant advances in HIV treatment and strategies to improve adherence, many adolescents choose not to disclose due to stigma, fear, or social pressure [46-48], which can have a negative impact on the results of VL suppression.

Most existing literature demonstrates that the probability of achieving VL suppression increases in adolescents who have an idea of their HIV status as compared to those who do not have an idea of the medication they are taking [19]. Understanding the interaction between nondisclosure and VL suppression is important to come up with appropriate interventions to meet adolescents' social, medical, and psychological needs [3,49]. Poor VL suppression among adolescents living with HIV continues to hold back the attainment of Sustainable Development Goals and the ending of the HIV epidemic by 2030 [50-52]. Addressing these challenges will significantly improve the health status of adolescents living with HIV and contribute to the global goal of ending the AIDS epidemic.

The available evidence highlights that nondisclosure is among several factors that contribute to poor VL suppression [53]. However, the variations in factors that contribute to poor VL suppression among adolescents living with HIV are unclear in the specific context of HIV status disclosure as there is no scoping review on this topic. Full disclosure occurs when the child has reached the appropriate maturity and is prepared to fully understand HIV status [28]. In some instances, it was found that adolescent-friendly services reduce known barriers to HIV disclosure [54]. Although the evidence is not conclusive, knowing one's HIV status and disclosure to others can improve adherence to ART. Although adolescents with HIV are faced with many situations in which they have to handle disclosure, they must learn how to cope with their own HIV status. Adolescents who better understand the issue of disclosure can disclose their status more easily than people who do not [46]. Disclosing HIV status can indirectly improve VL by enhancing compliance with treatment.

Therefore, this review will be key in providing summary findings about the prevalence of unsuppressed VL and the relationship with undisclosed HIV status among adolescent population groups. The outcomes will be key in informing health research in this field, especially research directed toward designing context-specific interventions against these challenges. It will also inform HIV and AIDS–related policies concerning VL suppression and HIV status disclosure in various settings.

Foreseeable Limitations

This study will be limited to adolescents aged 10 to 19 years who acquired HIV vertically from their biological mothers. This scoping review will only include studies published in English. It will only cover studies published from 2010 up to the date the scoping review will be conducted. This review might be limited by the availability and quality of the data extracted from the eligible studies, which might impact the accuracy and completeness of the findings. There is a high possibility that our search strategy will omit relevant studies, and we will mitigate this risk by extending the search to multiple online databases and manually searching review articles from the institutional library.

Conclusions

A scoping review is an emerging approach compared to systematic reviews and meta-analyses in terms of its purpose and aims. A scoping review aims to provide an insight into the available research without providing outcomes and guide clinical decision-making and interventions. A comprehensive search of PubMed, MEDLINE, Embase, Google Scholar, and ScienceDirect from 2010 to 2024 will be conducted, and the PRISMA-ScR framework will be adopted to ensure a comprehensive search of eligible articles that is rich in content relevant to the study. This scoping review will synthesize

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existing knowledge on HIV status disclosure and VL suppression among adolescents living with HIV regardless of whether the transmission occurred during pregnancy, during childbirth, or after birth through breastfeeding. This review will incorporate a range of study contexts to comprehensively summarize and synthesize evidence with the aim of informing practices, programs, and decision-making for the integration of services for adolescents living with unknown HIV status and facilitating the issue of HIV disclosure for undetectable VL achievement. Moreover, this scoping review might provide directions for future research priorities.

Authors' Contributions

Conceptualization of the protocol was carried out by MPL. Methodology was developed by MPL and OO. Project administration was managed by MPL. Preparation of the original draft was done by MPL, while review and editing were performed by OO. All authors have read and approved the final version of the manuscript for publication.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-ScR checklist.
[DOCX File , 1628 KB - resprot_v14i1e75838_app1.docx]

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Abbreviations

ART: antiretroviral therapy
MTCT: mother-to-child transmission
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
VL: viral load

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Protocol

Predicting In-Hospital Cardiac Arrest Using Machine Learning Models: Protocol for a Scoping Review

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Abstract

Background: In-hospital cardiac arrest (IHCA) remains a public health conundrum with high morbidity and mortality rates. While early identification of high-risk patients could enable preventive interventions and improve survival, evidence on the effectiveness of current prediction methods remains inconclusive. Limited research exists on patients' prearrest pathophysiological status and predictive and prognostic factors of IHCA, highlighting the need for a comprehensive synthesis of predictive methodologies.

Objective: This scoping review aims to synthesize and critically evaluate the quality and quantity of clinical features and machine learning (ML) models for predicting IHCA. The review will evaluate temporal characteristics, predictive and prognostic values of prearrest clinical features, and model performance metrics.

Methods: This scoping review follows the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines and aims to synthesize studies that used ML algorithms to predict IHCA published between April 2009 and April 2024. We will conduct a comprehensive search using 4 major databases: PubMed, Web of Science, IEEE Xplore, and Embase. The inclusion criteria are peer-reviewed, English-language studies that explore ML applications for predicting IHCA in adult patients (aged ≥18 years). Exclusion criteria include review articles, preprints, non–English-language studies, and studies without specific ML metrics for IHCA prediction. Two independent reviewers will conduct the screening and data extraction using Rayyan for deduplication and ensuring study eligibility. Descriptive statistics will be used to summarize the data, and a narrative synthesis will provide insights into the clinical features used in the models, the performance metrics, and any gaps in the literature.

Results: A total of 2479 records were identified between April 2009-April 2024. After removing duplicates and conducting screening, 16 studies have been included in the review. Data extraction and synthesis are ongoing and are expected to be completed by June 2025. The anticipated results from this review will provide a comprehensive overview of the clinical predictors of IHCA used in ML models, including commonly reported clinical features such as vital signs, biomarkers, and comorbidities. We expect to highlight variations in data quality and quantity across studies, which may influence model performance.

Conclusions: This study will contribute to advancing ML applications for IHCA prediction by addressing data challenges and promoting standardization to improve the clinical decision-making process. The results of this review are expected to inform future studies; promote consistency in the reporting of clinical features; and, ultimately, enhance the decision-making process in clinical settings, potentially leading to better outcomes for patients experiencing IHCA.

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KEYWORDS

machine learning; electronic health records; artificial intelligence; AI; cardiac arrest; predictive value; resuscitation

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Introduction

In-hospital cardiac arrest (IHCA)—defined as the absence of a pulse and need for defibrillator shocks and/or chest compression in a patient admitted to an inpatient bed—remains a significant public health challenge in the United States, with approximately 292,000 cases occurring annually [1-3]. Mortality rates for IHCA are 80% for patients with nonshockable rhythms and 55% for those with shockable rhythms, and 1-year survival after IHCA is only 13% [2,4,5]. Despite documented differences between IHCA and out-of-hospital cardiac arrest (OHCA) [6], treatment guidelines for the 2 types remain the same. IHCA has been less studied compared to OHCA, with a recent study reporting 61 published randomized controlled trials involving OHCA compared to only 15 for IHCA (2015-2022) [7]. Most IHCA studies have focused on patient outcomes during or after resuscitation, with limited research into the complex prearrest pathophysiological changes. However, recent evidence has challenged traditional assumptions about the causes of IHCA (eg, hypoxia). Conditions such as sepsis or infection and heart failure, which lead to circulatory and respiratory collapse, have been identified as significant contributors that enhance our understanding of IHCA causes [8]. A deeper understanding of the complex pathophysiological changes and factors contributing to IHCA would enable the development of more accurate tools, early initiation of preventive measures, and more effective treatment strategies.

Early identification of high-risk patients could facilitate the implementation of preventive interventions to reduce mortality and potentially improve 1-year survival rates. However, evidence regarding the effectiveness of current prediction methods (eg, scoring systems) and the establishment of practices for preventing IHCA remains inconclusive [9,10]. Heterogeneity in settings; subgroups, including small sample sizes (eg, patients with cardiac arrest); and methodologies, including lack of high-quality validation in common diseases that cause mortality (eg, cardiovascular diseases), as well as insufficient reporting, make the scoring system suboptimal to predict patient deterioration and cardiac arrest [9,11-13]. Moreover, the effective role of rapid response teams (RRTs) in preventing IHCA remains controversial. A crucial factor in preventing IHCA is the identification of deteriorating signs by the clinicians and activation of RRTs. Delayed activation or failure to activate RRTs has been associated with increased mortality [14]. Furthermore, a study by the investigators of the American Heart Association's Get With the Guidelines–Resuscitation (GWTG-R) program did not support the role of RRTs in preventing hospital mortality among 56 hospitals (5.1 million hospitalizations) from 2000 to 2014 [15]. Moreover, a systematic review reported inconsistent findings to support the role of RRTs in cardiopulmonary arrest mainly due to its various definitions in studies (eg, code blue and respiratory arrest). A meta-analysis was not conducted due to heterogeneity of the study designs (eg, data collection and sample characteristics) [16]. Randomized trials also had limited support for or did not support the role of early warning scores or RRTs in adverse events, cardiac arrest, and hospital mortality [17].

IHCA prediction has been challenging. One of the most important barriers is lack of publicly available prearrest data [18], in particular diagnostic tests, treatments (eg, medications), and physiological measures (eg, laboratory test results). The GWTG-R program of the American Heart Association [19] is a national registry that collects resuscitation data from approximately 20% of all hospitals across the country. The quality of care has improved for patients with IHCA by enhancing resuscitation guidelines and standard of care using data from the GWTG-R program. However, no longitudinal clinical data that provide an insight into the pathophysiological prearrest status (eg, laboratory test results and medications) can be found in any public cardiac arrest or resuscitation registries. Our understanding of underlying pathophysiological statuses that progress to instabilities and, ultimately, lead to cardiac arrest continues to be limited. Electronic health records (EHRs) and monitoring systems (eg, telemetry) at hospitals contain digital and time-series data that can be used to generate timely predictions. However, the presence of limited retrospective prearrest studies (eg, involving laboratory test results and medications) may indicate a complex and time-consuming process for data mining in EHRs [20-24]. Consequently, there has been no prospective study using vast digital data from hospitals to predict IHCA. Another challenge in predicting IHCA is the heterogeneity in IHCA data as the function of patients' clinical characteristics (eg, medical-surgical diagnoses) and hospitals' characteristics (eg, urban vs rural), particularly in methods of calculating (eg, BMI), presenting, and reporting clinical data. For example, there are different critical values for laboratory test results across health care settings [25,26]. The phenotyping approach of EHR data can be one option for some of these challenges because one size does not fit all. External validations of predictive tools can be limited without phenotyping the clinical data. Other important challenges are missing data and concerns about data accuracy. For example, vital signs recorded in the EHR are frequently used to develop clinical tools (eg, early warning scores) for predicting IHCA. However, these measures depend on bedside clinicians' documentation, and studies have raised concerns about their accuracy and completeness [27,28].

Nevertheless, EHRs are an important source of big data for developing machine learning (ML) models to predict adverse health events. ML, a branch of artificial intelligence, uses algorithms to recognize patterns in large, diverse datasets and predict outcomes [29]. Unlike traditional statistical methods, which are limited to linear relationships between variables, ML can learn automatically to uncover complex, nonlinear relationships and aims to make the prediction as accurate as possible in massive datasets adjusting to the scale of the data without compromising the performance [30]. This makes ML well suited for IHCA prediction. The growing availability of EHR data enables the creation of predictive models that may offer more nuanced insights into the factors leading to IHCA. Despite the increasing use of ML, this field remains challenging as the quality and accuracy of EHR data are essential to ML's success [30-34]. Because the accuracy of ML predictive models depends heavily on unbiased and diverse training data, investigators developing these models must have a comprehensive understanding of the known causes of the event

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or condition they are predicting, characteristics of the targeted population, and confounding variables (eg, sex differences), as well as access to a large, accurate set of time-series data.

Despite the clinical and organizational challenges to studying IHCA, such as missing or inaccurate data, the number of studies using ML models to predict IHCA has been increasing in recent years. However, there is limited IHCA review literature (eg, systematic reviews) examining the prognostic and predictive prearrest factors for IHCA. Only 1 systematic review study [35] was found that evaluated the performance of ML models in predicting IHCA by comparing them with a clinical predictive tool (ie, modified early warning score), and it concluded that ML models were superior. The quality and quantity of input data were not examined in this study; instead, the emphasis was on evaluating the performance of the ML models. Furthermore, several selected studies included composite outcomes (eg, combination of death, cardiac arrest, and unit transfer) and did not provide separate ML metrics specifically for predicting IHCA. This review was conducted in 2020 and did not include literature published in the past 4 years. In addition, the term "in-hospital cardiac arrest" was not used as one of the search keywords for finding the ML articles.

Given the increasing use of ML models in predicting IHCA and the clinical and organizational challenges associated with this emerging field, it is imperative to conduct a scoping review to identify gaps in current ML studies. These challenges include missing data and the complexities of working with EHRs in clinical settings. To the best of authors' knowledge, no existing scoping review has synthesized and critically evaluated the quality and quantity of selected features used in ML models for predicting IHCA. This includes aspects such as patient characteristics, the temporal characteristics of collected data (eg, time of IHCA), the predictive value of prearrest clinical features, and the performance metrics of ML models. Population representativeness is essential in constructing ML models because findings then can be generalized to similar populations. Historically, women have been underrepresented in cardiovascular clinical trials, and they only represent 30% to 40% of the total population participating in sudden cardiac arrest studies [36,37]. Furthermore, there are physiological differences between men and women that are reflected in their signs and symptoms. For example, there is a higher rate of respiratory insufficiency before cardiac arrest and a lower rate of obstructed coronary artery disease after cardiac arrest in women than in men [38]. Therefore, adequate sample sizes of men and women considering their physiological differences should be considered before and during the construction of ML models (eg, training). Selection of other demographic characteristics (eg, race) should also be part of sample construction to enhance population representativeness. Another important issue in synthesizing ML studies is the presence of tools that interpret the findings and their implications in clinical practice. We will evaluate not only the quality of the data but also their relevance to clinical practice. Findings from this scoping review will not only highlight these gaps but also provide practical recommendations for standardized reporting of clinical features as integral components of ML modeling. Such standardization is crucial for improving the accuracy and applicability of ML models in clinical decision-making processes to improve the quality of patient care.

This need for standardization becomes even more evident when considering IHCA, which is a multifactorial event characterized by dynamic and complex physiological processes often involving nonlinear interactions between time-sensitive variables such as heart rate variability (HRV), oxygen saturation, and blood pressure. Traditional statistical models are typically limited by assumptions of linearity and variable independence, which constrain their ability to model such complexity. Recent work by Lee et al [39] developed and validated a real-time ML model using electrocardiogram-derived HRV metrics in intensive care unit patients and demonstrated that ML models can effectively capture nonlinear and time-dependent patterns in prearrest physiology. Their model, which used a gradient boosting algorithm, achieved an area under the receiver operating characteristic curve of 0.881 and significantly outperformed a traditional clinical parameter–based model (area under the receiver operating characteristic curve=0.735; $P<.001$), underscoring the advantage of ML in managing IHCA prediction complexity [39]. In addition, the same study highlights how ML models incorporate nonlinear HRV measures (eg, triangular interpolation of the NN interval, HRV triangular index, and inverse of average length of the acceleration and deceleration segments), which have shown predictive value but are often not feasible to model using standard regression approaches. Furthermore, evidence from Akintoye et al [40] demonstrates a nonlinear association between hospital cardiopulmonary resuscitation volume and IHCA survival, where survival peaked at a moderate volume threshold and declined at higher volumes, suggesting complex institutional and systemic interactions that ML models are well suited to accommodate hospital volume and cardiopulmonary resuscitation. These findings collectively strengthen the appropriateness of ML approaches in this context and support our rationale for focusing the scoping review on ML-based IHCA prediction models.

Methods

This scoping review will be conducted using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines developed using checklists from the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews), and the protocol was developed following the PRISMA-P (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols) [41,42].

Review Questions

Our review questions are as follows:

1. What are the quality and quantity characteristics of clinical data used to construct ML models?
2. What are the common clinical predictors among multiple ML models?
3. What are the strongest predictive metrics for occurrence of IHCA?

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Ethical Considerations

This review will not involve direct contact with human participants. All clinical data (ie, laboratory test results and vital signs) used in ML model construction will be presented as aggregated and deidentified data from previously published studies. This protocol was registered in the Open Science Framework on November 16, 2024 [43].

Eligibility Criteria

The focus of this review is to synthesize the clinical features used to construct ML models and evaluate the performance of these models in predicting IHCA.

The inclusion and exclusion criteria are as follows. We will include only peer-reviewed, English-language studies published between April 2009 and April 2024 that used ML algorithms to predict IHCA. The selection of 2009 as the starting year for our search was based on significant advancements in ML applications within health care around that time. In 2009, a prominent national report indicated that only a small proportion of US hospitals had adopted a "basic" EHR system [44]. In addition, the Health Information Technology for Economic and Clinical Health Act provided incentives for health care providers who used EHRs. This period marked the beginning of more widespread adoption of EHRs and the integration of advanced computational methods, which facilitated the application of ML algorithms in clinical settings. These technological advancements enabled more accurate and efficient prediction models for IHCA. Therefore, studies published after 2009 are more likely to reflect the current state of ML applications in predicting IHCA [45,46]. We will exclude the following types of articles:

1. Reviews (eg, systematic reviews and meta-analyses)—while review articles will be excluded from the formal selection, we will use them as supplementary resources to identify additional relevant studies that may not have been captured in our initial search, which will allow us to ensure a more comprehensive inclusion of relevant literature
2. Preprints, conference proceedings, theses, and dissertations
3. Studies published in foreign languages, abstract-only studies, opinions, letters to the editor, commentaries, short communications, and patents

Regarding the patient population, only studies involving adults aged ≥18 years who have experienced IHCA will be included. There will be no restriction based on sex, gender, geographic location, race, or types of ML techniques used. We will use the Utstein Out-of-Hospital Cardiac Arrest Resuscitation Registry Template definition of IHCA [1], which refers to the delivery of defibrillator shocks or chest compressions to a patient admitted to an inpatient bed. Studies that do not adhere to this definition or that did not collect data from hospitals or medical centers will be excluded. In addition, studies that include cases of death or sudden death without resuscitation or OHCA and animal studies will be excluded.

Regarding study outcomes and ML metrics, some studies list composite outcomes, including IHCA, admission to intensive care units, and patient deterioration. We will include studies that report ML metrics for predicting IHCA, even when they are part of a composite outcome, as long as the prediction of IHCA is clearly specified and distinguishable from other outcomes. This approach will allow us to capture a broader range of clinically relevant studies while maintaining focus on IHCA prediction.

Information Sources

Four reputable databases were searched: PubMed (biomedical research), Web of Science (a global citation database in the sciences, arts, and humanities), IEEE Xplore (for technology and engineering research), and Embase (medical research). The following 2 sets of search terms—"in-hospital cardiac arrest" and "machine learning"—were entered into the databases connected using AND after several trials to select different text words.

Search Strategy

Before protocol registration on the Open Science Framework in November 2024, we conducted a preliminary exploratory search to refine the search terms, databases, and feasibility of conducting this review. While this process involved screening a small set of articles for pilot-testing purposes, the formal and comprehensive literature search used for study inclusion and data extraction was carried out after protocol registration. This preregistration phase did not influence the core research objectives, inclusion and exclusion criteria, or data extraction domains. An interprofessional informationist team member worked with disciplinary faculty and created the base search to refine key concepts. The informationist completed a pilot search in PubMed, which a team member screened to determine retrieval accuracy for key articles on IHCA and ML. For example, we initially selected the following search terms and keywords using the MeSH (Medical Subject Headings) database:

("In-hospital cardiac arrest" [text word] OR "In-hospital cardiac arrest" [tiab] OR "cardiopulmonary resuscitation" [text word] OR "heart arrest" [text word] OR "sudden cardiac death" [text word] OR asystole [text word] OR heart arrest [MeSH] OR asystole [MeSH] OR cardiopulmonary arrest [MeSH] OR arrest, cardiopulmonary [MeSH]) AND ("Artificial intelligence" [text word] OR "artificial intelligence" [tiab] OR Artificial intelligence [MeSH] OR Intelligence, Artificial [MeSH] OR Computational Intelligence [MeSH] OR Intelligence, Computational [MeSH] OR Machine Intelligence [MeSH] OR Machine Learning [MeSH] OR Deep Learning [MeSH] OR Supervised Machine Learning + [MeSH] OR Unsupervised Machine Learning [MeSH]) 2009-2024

Each trial was conducted using carefully selected keywords involving Boolean operators and MeSH options along with other text words with or without the assigned years (2009-2024), which produced a set number of articles. These articles were reviewed by a team member with expertise in IHCA and familiarity with ML techniques. A discussion was then initiated between the informationist and the team member to improve search terms for targeted peer-reviewed articles in PubMed. This process was iterated 7 times, producing a range of published articles from 95 to 2004. On the basis of the search sensitivity, revisions were made to the search query, which was then translated from PubMed into 3 additional databases—Web

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of Science, Embase, and IEEE Xplore—for hand searching. A second research librarian will conduct a full Peer Review of Electronic Search Strategies review of the search and will recommend revisions.

Screening

All search results will be downloaded and exported into Rayyan (Qatar Computing Research Institute) for deduplication. Automated tools in Rayyan will be used to identify and remove duplicates. Once duplicates are removed, the titles and abstracts will be screened according to the exclusion criteria, and the articles that do not meet the criteria will be excluded. The full texts of the remaining articles will then be reviewed to determine eligibility, with reasons for exclusion recorded and reported in the final scoping review. Two reviewers will independently conduct the screening process using the Rayyan application. Any disagreement between the reviewers will be resolved through discussion, with input from experts in resuscitation and data sciences. The results of the search (ie, the included articles) will be presented in a PRISMA flow diagram.

Data Extraction and Main Data Elements

Our review aims and questions will guide the types of data elements for extraction. The targeted data elements will be identified and extracted from the eligible full texts of the articles by 2 team members who will record them as variables in a developed template using Microsoft Excel. We will have several sheets within a Microsoft Excel file to complete data charting (eg, demographics and biomarkers). The Microsoft Excel file can be considered our tool and will be revised as necessary during the extraction phase. The extracted data will be reviewed by the third team member for accuracy. To resolve any conflict, a discussion among all these team members will take place to reach consensus. A list of data elements for future extraction is presented in Figure 1, which includes study characteristics, ML metrics, medical diagnosis, inclusion and exclusion criteria, vital signs, population characteristics, laboratory test results, and definitions and number of outcomes. We specifically pay attention to 2 important criteria, including representativeness of the population by examining the sample sizes in subgroups (eg, men and women) of the total population and in the construction of ML models (eg, training and testing phases). The physiological differences between men and women that are represented by their signs and symptoms will also be evaluated. We will also determine the interpretability of the clinical data through the utility of different tools, including Shapley additive explanations.

The vital sign metrics comprise heart rate or pulse rate, systolic blood pressure, diastolic blood pressure, respiratory rate, temperature, and oxygen saturation. These metrics were selected after reviewing the literature [27,47,48] and a discussion among 2 investigators in this scoping review with medical knowledge and expertise (MA and KB). For example, oxygen saturation is typically not included in its traditional format [49], or certain vital sign metrics were not selected in some studies (eg, diastolic blood pressure) [47,48]. We decided to incorporate all vital sign metrics to comprehensively evaluate the quality and quantity of the clinical data.

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Figure 1. Names of the variables that will be extracted from the selected articles. ML: machine learning.

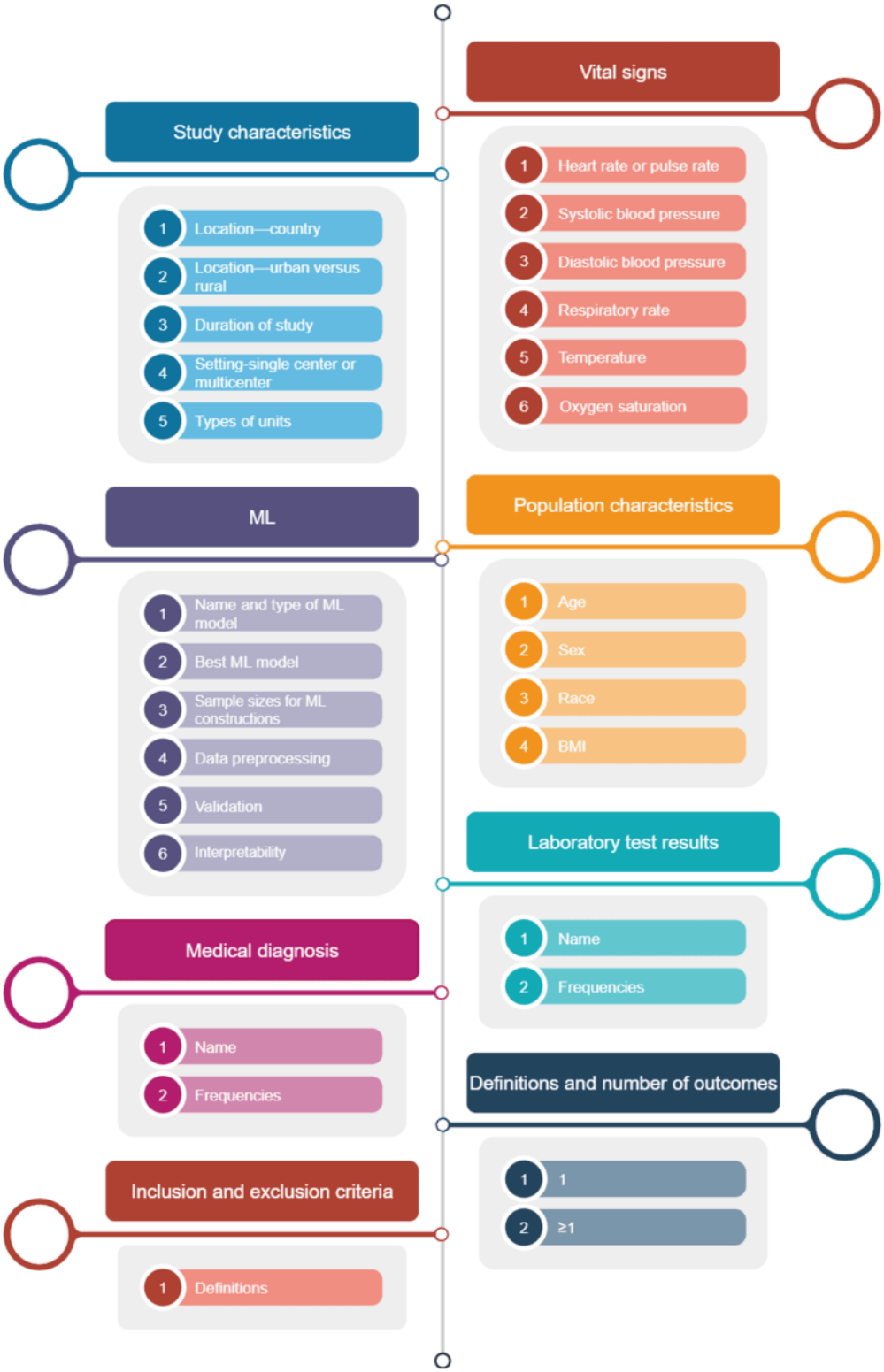

Data Analyses and Presentation

Descriptive statistics, including numbers, percentages, means, and SDs, will be reported to quantify the selected variables, and a comprehensive narrative will provide a detailed synthesis of variables across the articles. We will extract clinical features used in ML models for predicting IHCA, including patient demographics (eg, age and sex) and medical histories (eg, diagnoses), vital signs, laboratory test results, and all other available data. We will also gather information regarding the data sources (eg, EHRs and registries) and the methods used to handle missing or incomplete data. We will evaluate the number of features included in the models and the sample sizes used for constructing ML models. The number and type of all ML models (ie, traditional vs deep neural network) will be presented in a graph. The metrics of ML model performance will be presented in a table including the area under the curve, sensitivity, specificity, negative predictive value, positive

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predictive value, accuracy, precision, and F_1-score (Figure 2). We will compare the performance metrics of different ML models to understand how data quality influences model outcomes. Subgroup analyses will also be conducted to evaluate the effects of different types of clinical data (eg, vital signs vs laboratory test results) on predictive performance. To ensure alignment with our review objectives, the synthesis of extracted data will be directly mapped to the review questions. We will group and summarize findings on the geographical distribution of studies, data quality and quantity, shared clinical predictors, and performance metrics using descriptive statistics (eg, frequency, percentages, means, and SDs, described previously) and a narrative approach. This dual synthesis strategy will allow us to highlight patterns in ML model inputs and outputs, methodological heterogeneity, and gaps in reporting practices. Figure 1 outlines the core variables identified for extraction and synthesis, reinforcing the linkage between data elements and our research questions.

Figure 2. Performance metrics of machine learning models. AUC: area under the curve; NPV: negative predictive value; PPV: positive predictive value.

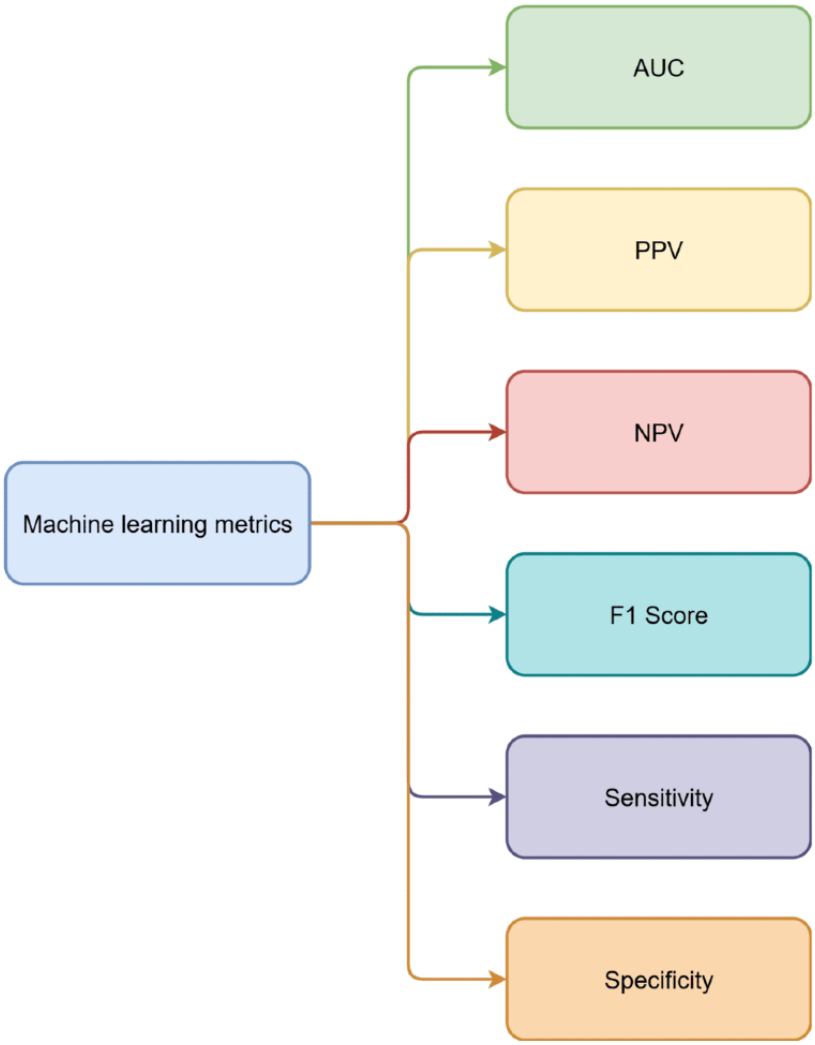

Results

A total of 2479 records were identified from 4 databases (Embase, PubMed, Web of Science, and IEEE Xplore). After removing 20.61% (511/2479) duplicates, 1968 titles and abstracts were screened. Of these 1968 titles and abstracts, 83 (4.22%) full-text articles were assessed for eligibility, and 16 (19%) studies have been included in the final synthesis. Data extraction and analysis are ongoing and expected to be completed by June 2025. We will present our work in national meetings relevant to the topic of cardiac arrest and resuscitation and submit our findings to a peer-reviewed journal to share knowledge and increase the awareness of the state of the art in predicting IHCA using artificial intelligence.

The results will address each of our questions by providing specific findings presented as descriptive statistics and a detailed narrative summary. We created a comprehensive search strategy to identify studies that used ML models to predict IHCA. Our work will be presented as a scoping review that contains detailed and aggregated information summarizing data using tables and graphs. Figure 3 shows project milestones and associated timelines.

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Figure 3. Gantt graph showing the project milestones and associated timelines. PRESS: Peer Review of Electronic Search Strategies.

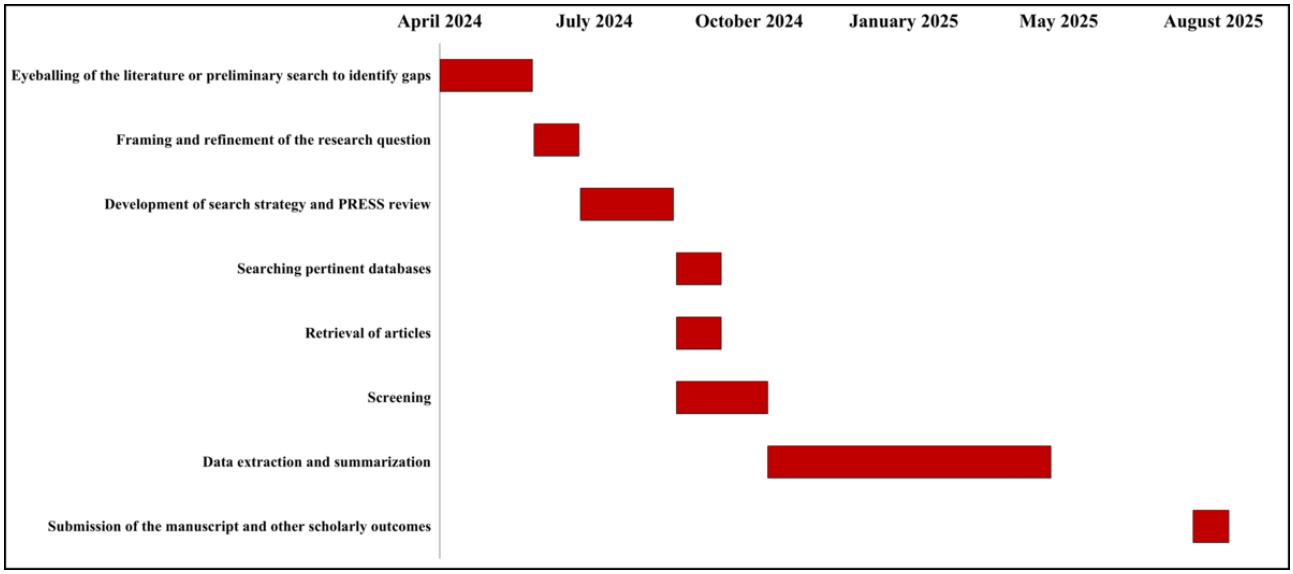

Discussion

Anticipated Findings

We will conduct a comprehensive evaluation of the clinical features extracted from EHRs for each phase of ML model development, including training, validation, and testing. This evaluation will focus on assessing population diversity, such as age, sex, race and ethnicity, and comorbidities, to ensure inclusivity and representation in model development. Recognizing that EHR data often contain time-series information, we will thoroughly analyze the temporal characteristics of clinical features, particularly in relation to the timing of IHCA onset. This includes exploring patterns, trends, and critical time points that could enhance the predictive power of ML models.

Furthermore, we will identify and discuss the significance of commonly reported predictors across studies, such as vital signs, laboratory test results, and comorbid conditions, and critically evaluate their clinical implications. This will provide insights into the relevance of these predictors in the context of IHCA and their potential utility in real-world clinical settings.

Special emphasis will be placed on enhancing the interpretability of ML models, addressing the *black box* challenge often associated with these approaches. Techniques such as feature importance analysis, visualization of decision pathways, and integration of domain knowledge will be explored to improve the transparency and usability of ML predictions. The discussion will also cover the metrics and methodologies for optimizing model performance, including sensitivity, specificity, precision, recall, and calibration, with a focus on their implications for clinical decision-making and patient outcomes. Through this synthesis, we aim to support the standardization of reported clinical features and methodologies in the development of predictive ML models for IHCA. This standardization will facilitate comparability across studies; enhance reproducibility; and, ultimately, contribute to the broader adoption of ML tools in clinical practice for early detection and prevention of IHCA.

Strengths and Limitations

This study will have several strengths and limitations. Among its strengths, it will provide a comprehensive analysis of clinical features extracted from EHR data considering population diversity and temporal dynamics. This ensures that the findings are inclusive and applicable across varied patient populations. The focus on temporal characteristics is another strength as it addresses the critical aspect of timing in predicting IHCA, enabling better anticipation of adverse events. In addition, this study places significant emphasis on interpretability, tackling the *black box* nature of ML models and ensuring that results are transparent and usable by clinicians, fostering trust and adoption in health care. Furthermore, the synthesis of predictors and features across studies will support standardization in reporting practices, enhancing reproducibility and comparability in ML model development. The emphasis on clinical relevance will bridge the gap between technical advancements and practical implementation, whereas considerations of population diversity will promote equity and reduce biases in predictive models.

However, this study will also face certain limitations. The quality, completeness, and standardization of EHR data, which can vary across institutions, may impact the analysis and model performance. Despite efforts to include diverse populations, biases in available datasets could limit the generalizability of findings, especially for underrepresented groups. While interpretability is emphasized, some ML models may remain opaque due to their inherent complexity. In addition, a scoping review has inherent limitations that stem from its methodology and objectives, which focus on mapping existing literature rather than providing definitive answers to specific research questions. One primary limitation is the lack of depth in analysis as scoping reviews typically do not involve a critical appraisal of the quality of the included studies. This means that studies with varying levels of rigor may be included, potentially affecting the reliability of the findings. In addition, the heterogeneity of evidence, including diverse study designs, populations, and outcomes, can make it challenging to synthesize findings into cohesive conclusions. Unlike meta-analysis, scoping reviews

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do not perform formal meta-analyses or provide pooled effect estimates, limiting their ability to quantify relationships or provide definitive conclusions. The broad scope of this scoping review may also introduce selection bias as the inclusion of studies depends on the search strategy, availability of data, and reviewer judgment. Moreover, this scoping review will rely heavily on published and accessible literature, potentially overlooking unpublished studies, gray literature, or ongoing research, leading to publication bias. Despite these challenges, this study provides valuable insights and a balanced contribution to the development and evaluation of ML models for predicting IHCA.

Conclusions

Our scoping review will add to the body of IHCA literature by synthesizing different aspects of ML studies to predict IHCA. This will be our first step to comprehend the complexity of ML studies and promote realistic options for the clinical decision-making process.

Acknowledgments

The authors would like to acknowledge Jane Morgan Daniel at the University of Florida library for assistance with developing the search strategy and for conducting the Peer Review of Electronic Search Strategies review. The authors did not use artificial intelligence for any portion of manuscript generation.

Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization was undertaken by MA. Methodology and project administration were undertaken by MA, BS, KB, and XG. Investigation, resources, and data curation were undertaken by MA, BS, LB, FMR, NAA, JC, and RM. Writing—original draft preparation was conducted by MA, BS, KB, and XG. Writing—review and editing and visualization were undertaken by MA, BS, LB, FMR, NAA, JC, RM, and KB. Supervision was handled by KB and MA.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-P checklist.
[DOCX File , 31 KB - resprot_v14i1e69716_app1.docx]

Multimedia Appendix 2
PRISMA-ScR checklist.
[DOCX File , 109 KB - resprot_v14i1e69716_app2.docx]

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Abbreviations

EHR: electronic health record

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GWTG-R: Get With the Guidelines–Resuscitation
HRV: heart rate variability
IHCA: in-hospital cardiac arrest
MeSH: Medical Subject Headings
ML: machine learning
OHCA: out-of-hospital cardiac arrest
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-P: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
RRT: rapid response team

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Protocol

Strategies for Tailoring Patient-Centered Technologies Across the Cancer Continuum: Protocol for a Scoping Review

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Abstract

Background: In the United States, cancer is more prevalent in racial and ethnic minority groups and in rural-dwelling and low-income people. Compared with White people of non-Hispanic descent, Black and African American people have higher cancer mortality and Hispanic people are more likely to be diagnosed with infection-related cancers. In addition, people who live in persistent poverty areas are more vulnerable to cancer mortality. Tailoring health information technologies (HITs) can help bridge health inequities by providing these populations with relevant health information and cancer care. Cultural tailoring in health care involves adapting interventions to reflect a population's values, history, and attitudes that influence behavior.

Objective: The goals of the current study are as follows: 1) to understand what elements of tailoring HITs are most effective among different underserved populations, 2) to identify ways of incorporating these elements to improve the acceptability and effectiveness of technology-based interventions, and 3) to develop a framework to tailor HITs to underserved populations and improve engagement and acceptability.

Methods: A scoping review will explore how HITs have been culturally tailored to underserved populations using PubMed, Scopus, and Web of Science database searches. Our search strategy will include terms and medical subject headings associated with the categories of cancer, HITs, tailoring, and underserved populations. We will also perform a snowball search of the references of included studies. We will include quantitative and qualitative peer-reviewed, English-language studies from the United States that examine efforts to tailor HIT interventions to improve their acceptance, use, and usability among underserved populations. Predefined inclusion and exclusion criteria will be applied for study selection. For each included study, we will extract the following data: study design, cancer type, underserved population of interest, details of the technology used, study methods, sample size, study outcomes, user acceptability, and tailoring and targeting strategies. The data will be summarized descriptively and analyzed thematically.

Results: Preliminary searches following this strategy yielded a total of 784 citations (after removing duplicates) that will each be reviewed by at least 2 reviewers for inclusion. This protocol was submitted before data collection. The search strategy, citation screening, and data extraction will commence in accordance with the PRISMA-ScR (Preferred Reporting Items for Systematic

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Reviews and Meta-Analyses extension for Scoping Reviews) guidelines and the published protocol. Findings will be expected by the spring of 2026.

Conclusions: There is a need to develop more accessible HITs for underserved populations. This scoping review will inform researchers, providers, and developers working on cancer-specific HITs for underserved populations, such as racial and ethnic minority groups, rural-dwelling residents, and low-income populations. By summarizing evidence on tailoring strategies by population and delivery mode, the review aims to support the development of more effective and acceptable technologies.

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KEYWORDS

scoping review; health information technology; tailoring; cancer continuum; underserved populations

Introduction

Background

In the United States, over 18 million Americans are cancer survivors [1]. Although cancer is a disease that can affect anyone, some populations are more at risk of developing and dying from cancer than others. In particular, individuals who identify as being part of an underrepresented racial or ethnic minority group, live in a rural geographic area, or belong to a lower socioeconomic status have the highest risk of cancer. For example, African American men and women have higher cancer mortality and a lower 5-year survival after diagnosis compared with White men and women of non-Hispanic descent [2]. Additionally, compared with White individuals of non-Hispanic descent, Hispanic or Latino people are more likely to be diagnosed with cancers caused by infections [3]. Together, these findings underscore the urgent need for targeted interventions to reduce cancer disparities and improve cancer-related outcomes within these populations.

Various forms of health information technology (HIT) may offer a way to reach underserved populations. HIT is often defined as the "application of information processing involving both computer hardware and software that deals with the storage, retrieval, sharing, and use of health care information, data, and knowledge for communication and decision making" [4]. As such, it commonly refers to provider-facing electronic systems such as electronic health records, patient-facing personal health records, and other tools such as computerized provider order entry. However, there are other patient-facing technologies (hereafter referred to as patient-centered technologies) such as telehealth, mobile health (mHealth) apps, and patient portals [5]. These patient-centered technologies provide novel and promising ways to educate healthy individuals and patients with cancer on topics ranging from cancer prevention to managing a cancer diagnosis. These technologies are not always developed, however, with the populations of interest in mind. As a result, there is mixed evidence on how effective these technologies are among these populations [5]. Several factors influence the acceptability of HITs among patients with cancer, including age, educational achievement, and access to the internet [6]. For example, while mobile devices can help patients coordinate their health care through text message reminders, a systematic review conducted by Tarver et al [5] noted that underserved populations such as Black patients with cancer are not always up to date on how to use text messaging. Factors such as this can impact the effectiveness of these technologies and highlight the importance of bettering our understanding of different populations and the factors to consider when developing and implementing interventions designed to reach them.

An important and understudied element of intervention design is tailoring technologies based on elements such as the race, ethnicity, and language with which people identify. Tailoring is defined as any combination of techniques and information designed to target a single person based on traits that are unique to that person and connected to the desired outcome that is generated through an individual evaluation [7]. As an example, compared with a lay health advisor intervention, a tailored print and video intervention increased multiple colorectal cancer prevention efforts, such as fruit and vegetable consumption, recreational physical activity, and fecal occult blood testing screening, among a sample of African American church members [8]. This highlights the potential of tailored interventions in the prevention and early detection of cancer.

While the existing literature has largely focused on tailoring printed materials, less attention has been paid to the tailoring of HITs. A study done by Vilaro et al [9] noted that virtual health assistants tailored to Black women increased cancer screening in that community. While race and ethnicity are important elements to examine, culture is another essential component. Racial and ethnic minority populations may be distrustful of formal health services, contributing to their reliance on previously acquired cultural beliefs about health care [10-12]. An awareness of these barriers can aid in the development of interventions to help mitigate challenges and better engage these patient populations.

Furthermore, most studies demonstrated that the incorporation of HIT was linked to increased cancer knowledge; however, common shortcomings included a lack of language adjustment and tailoring to specific populations. For example, one study reported that a specific multimedia program (CancerHelp) [13] improved patient care for underserved populations by increasing their cancer knowledge. However, the program did not have a Spanish language version, thus excluding Spanish-speaking individuals who lack English proficiency. This issue highlights the need for researchers and care providers to work with developers to design interventions with the populations of interest in mind. When stakeholders take the needs and perspectives of these populations into consideration during the

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implementation of HITs, they are able to design solutions that lead to increased engagement [14]. Understanding how a population's culture influences health behavior is necessary to develop HITs.

The purpose of the current study will be to systemically review current evidence on the tailoring of patient-centered technologies to underserved populations in the context of cancer care.

Research Question

This review will seek to answer the question, "How can patient-centered technologies be tailored to engage underserved populations across the cancer continuum?" More specifically, we are interested in understanding the following aspects:

1. The importance of tailoring among underserved populations.
2. What elements of tailoring are most effective for different populations and at different points along the cancer continuum.
3. How tailoring can be used to address issues and barriers faced by underserved populations.
4. How to identify strategies to improve engagement.

Methods

Overview

This scoping review protocol was informed by the methodological framework developed by Arksey and O'Malley [15]. This framework guided the following steps: (1) identifying the research question, (2) identifying relevant studies, (3) study selection, (4) data charting, and (5) collating and reporting results [15]. The scoping review methodology was chosen as it is ideal for mapping a body of literature on a topic and identifying knowledge gaps [16]. We present steps 1 through 5 of our scoping review below.

Step 1: Identifying the Research Question

As mentioned previously, the main research question that will guide our scoping review is, "How can patient-centered technologies be tailored to engage underserved populations across the cancer continuum?" Our scoping review will aim to extract information related to tailoring technologies for different populations along the cancer continuum and synthesize the available evidence, thereby creating a framework that can be used to develop or enhance technologies seeking to better engage populations of interest.

Step 2: Identifying Relevant Studies

Search Strategy

The database search will be conducted using the electronic databases PubMed, Scopus, and Web of Science. These databases were chosen because they index and abstract the major health and medical journals and scholarly literature. Keywords were developed from existing literature in addition to medical subject heading (MeSH) terms to identify eligible studies. Keywords will include relevant terms corresponding to categories related to the disease class of cancer, underserved populations, cultural tailoring or targeting, and types of HITs. A full list of the keywords can be found in Table 1. In addition, we will perform a snowball search method by reviewing the references of the final list of included studies to ensure all relevant studies were captured.

Table 1. Operationalization of the search terms. Search terms within each category will be combined with OR. Search terms between categories will be combined with AND.

Category	Search terms
Cancer	Cancer*[a] OR neoplas* OR carcino* OR onco* OR malignan* OR tumour OR tumor OR hematolog* OR haematolog* OR lymphoma OR leukemia OR leukemia OR leukaemia
Underserved populations	"Minority Health" OR "Healthcare Disparities" OR "Health Status Disparities" OR Poverty OR "low income" OR Ethnic* OR race OR racial OR disparit* OR minorit* OR underserved OR underrepresented OR inequalit* OR rural OR hispanic* OR mexican* OR latin* OR african* OR black* OR asian OR indian* OR alaskan* OR "alaska* native" OR "native american*" OR inuit OR "pacific islander" OR immigrant
Tailoring	personaliz* OR personalis* OR individualiz* OR individualis* OR tailor* OR customiz* OR customis* OR "linguistically target*" OR "culturally target*" OR "patient target*"
Patient-centered health information technologies	"health information technology" OR "health it" OR "electronic health records" OR "electronic health record" OR "electronic medical record" OR "personal health record" OR "personal medical record" OR "patient accessible record" OR "patient portal" OR "patient internet portal" OR "decision support" OR "clinical reminder" OR "electronic reminder" OR "reminder system" OR "m-health" OR "mhealth" OR "mobile technolog*" OR "mobile health" OR "cell phone" OR "cellular phone" OR "smartphone" OR "mobile phone" OR "mobile device" OR "text message" OR "cd-rom" OR "dvd" OR "computer based" OR "computer-based" OR "internet-based" OR "web-based" OR "web based" OR "e-health" OR "ehealth" OR "tablet" OR "telemedicine" OR "telehealth" OR "teleoncology" internet

[a]The asterisk (*) denotes truncated terms. For example, minority groups identified as being underserved will be captured using the following truncated keywords: black* and african* for Black or African American groups and hispanic*, mexican*, and latin* for Hispanic or Latino groups.

Definitions

Patient-Centered Technologies

Patient-centered technologies are HIT applications that are patient-facing, making them "well suited to engage patients, promoting a more active role for patients in health care" [17]. For the purposes of this review, we are interested in including studies using personal health records or patient portals, mHealth, telehealth, and the Internet and access to websites.

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Tailoring

Cultural tailoring is defined as any combination of information intended to reach one specific person based on characteristics unique to that person related to an outcome of interest derived from a personal assessment [7].

Targeting

Targeting is defined as the development of interventions for a defined population subgroup. This approach takes into account the various shared characteristics, such as culture, of the subgroup's members [18].

Underserved Population

Medically underserved populations are groups who may face economic, cultural, or linguistic barriers to medical care services [19]. For the purposes of this review, we will focus on racial and ethnic minority groups, individuals of lower socioeconomic status, and people residing in rural geographic areas.

Inclusion and Exclusion Criteria

We will include peer-reviewed journal articles published in the English language and studies conducted in the United States. We will include both qualitative and quantitative studies for insights on patient perspectives as well as the effectiveness of the interventions. In addition, we are interested in studies that explore efforts to tailor or target the design of interventions to improve their acceptance, use, and usability among underserved populations.

Conversely, we will exclude nonempirical studies such as commentaries, editorials, letters-to-the-editor, conference abstracts, and protocols. In addition, we will exclude international studies due to sociocultural differences across countries. We will also exclude other reviews. If the search identifies other reviews on similar topics, we will, however, search their reference lists as part of our snowball strategy to identify additional articles.

Step 3: Study Selection

Studies will be selected using a 2-step inclusion process. The title and abstract for each citation will be reviewed in step 1. If the title or abstract is classified as a systemic review or protocol, does not incorporate HITs, does not focus on cancer, is conducted outside of the United States, or is published in a language other than English, the study will be excluded. In step 2, the full-text articles of the remaining citations will be retrieved for review. Similarly, we will exclude citations that do not meet our inclusion criteria.

During the review process, 2 reviewers will review each citation's title and abstract (step 1) and full-text article (step 2). The use of 2 reviewers has been found to increase the reliability of article selection. When the inclusion criteria are unclear during title and abstract review, reviewers will err on the side of inclusion during step 1, progressing it to step 2. A full-text review will then determine eligibility. For example, if an abstract met the criteria of using HIT to improve breast cancer knowledge among American women, but did not specify the inclusion of underserved individuals, it would not be excluded. It would move forward to the next step so that the full-text article could be reviewed to ascertain eligibility.

Step 4: Data Charting

A team of 4 reviewers (WT, DB, PJ, and MB) will perform the data charting process with each article being reviewed and extracted in pairs. A standardized form will be developed and used to extract data from the included studies for evidence synthesis. Systematically extracted information will include the following information from each included study: study design, cancer type, the underserved population of interest, the type of technology used, details of the technology used, study methods, sample size, study outcomes, indicators of user acceptability, and methods used to tailor and target interventions. Additional variables may be added during the data collection and analysis phases. Two reviewers will independently extract data from each study. Disagreements will be resolved through discussion with the study team. If needed, missing information relevant to our review will be requested from the studies' authors.

Step 5: Collating and Reporting Results

After extracting data as described in step 4, we will create descriptive and numerical summaries of the studies that meet our inclusion criteria. Study characteristics will be presented in a tabular form and narratively summarized within the text. Gaps in the literature will be identified by using comparative analysis of study participant characteristics, study designs used, and HITs studied.

The qualitative data that we extract pertaining to tailoring effects will be subjected to thematic analysis according to the inductive-deductive approach described by Clarke and Braun [20]. This approach will guide us to identify themes and commonalities in how HIT is tailored. As a team, we will discuss and develop these descriptive themes until we reach consensus. As we present our findings, we will also highlight similarities and differences in how HIT is tailored for different populations of interest. In summary, we will follow a three-stage process including the following steps: (1) coding of the findings and results of the included studies, (2) organization of the codes into related areas, and (3) development of analytical themes. These data will be descriptively summarized in tables by theme and narratively reported.

This scoping review will synthesize both quantitative and qualitative research. As a result, a meta-analysis will not be feasible due to the expected variability in study designs, methodologies, and outcome measures.

Results

This protocol was submitted before data collection. The search strategy, citation screening, and data extraction will commence in accordance with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines [21] and the published protocol. Findings will be expected by the spring of 2026. A preliminary search produced a total of 1395 articles. Duplicate records (n=221) were removed, leaving a total of 784 unique articles. The inclusion and exclusion criteria will be strictly followed in performing the forthcoming study selection. The data will be

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summarized narratively to assess the elements of tailoring patient-centered technologies to underserved populations.

Discussion

Rationale for the Study

To our knowledge, this is the first scoping review examining the tailoring of patient-centered technologies for underserved populations across the cancer continuum. Despite the widespread use of patient-centered technologies for health, research in this area is limited. This scoping review aims to address this important knowledge gap by synthesizing existing evidence and identifying areas for future research. A clear understanding of which tailoring methods can be used in the development of patient-centered technologies will enable effective decision making by policymakers, researchers, clinicians, and developers. In addition, it will provide these stakeholders with a framework for understanding the most effective methods and modes of delivery to use for specific populations of interest. Thus, this review will inform the creation of more effective and engaging tools. These results will further extend the knowledge gained from a previous systematic review, which found that patient-centered technologies seem to be more effective when tailored to the populations of interest [5]. This protocol was informed by established PRISMA-ScR guidelines to conduct systematic and scoping reviews [21,22].

Strengths and Limitations

Given the breadth of this proposed scoping review, we anticipate challenges and have outlined mitigation strategies in this protocol. The first challenge relates to the inconsistent language used in studies that may incorporate tailoring in their development process. We constructed our search strategy to address this by expanding it to include keywords related to targeted interventions and personalizing or customizing interventions.

Second, we anticipate limited descriptions of patient-centered technologies and how they were developed and tailored. Authors may not adequately detail the development and tailoring process of their technologies. If needed, we will contact study authors with the intent of obtaining additional information to mitigate this challenge.

Conclusions

When implementing patient-centered technologies for underserved populations, cultural backgrounds should be considered along with effective methods of tailoring and modes of delivery. This review will aim to present a summary and analysis of the existing evidence on tailoring HITs to underserved populations. We believe this review will be an invaluable aid and reference to researchers, providers, and developers aiming to develop or enhance cancer-specific HITs for racial and ethnic minority groups, populations residing in rural areas, and people with low income. The result of this scoping review of cancer-specific patient-centered technologies will be a detailed summary of the evidence for tailoring these technologies organized by underserved populations of interest and modes of delivery. By providing a structured summary of the evidence base for cancer-specific patient-centered technologies, this review aims to inform and facilitate studies developing and implementing these technologies, ultimately contributing to their improved acceptance and effectiveness.

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Authors' Contributions

All authors contributed to the design of this protocol. WT and EP initiated the project. WT drafted the protocol and will be responsible for manuscript preparation. WT, DB, PJ, MB, TP, EPK, and EP contributed to the study design and methodology and will provide critical revision of the manuscript. All authors have read, refined, and approved the final manuscript.

Conflicts of Interest

EP is a multiple principal investigator on grants to the institution unrelated to this work from Genentech, Pfizer, Merck Foundation, Guardant Health, and Astra Zeneca. She also serves on advisory boards for Merck, GlaxoSmithKline, and Novartis.

Multimedia Appendix 1
PRISMA-ScR checklist.
[DOCX File , 110 KB - resprot_v14i1e73705_app1.docx]

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Abbreviations

HIT: health information technology
MeSH: medical subject heading
mHealth: mobile health
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Perceptions of Occupational Risk and Adherence to Tuberculosis Prevention Among Health Care Workers: Protocol for a Scoping Review

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Abstract

Background: Tuberculosis (TB) is a major public health problem around the world. Health care workers (HCWs) are at a much higher risk of contracting TB because they are often working around sick people in clinical settings. Even though HCWs play a key role in controlling TB, we still do not fully understand how they see this risk and how it affects their willingness to follow preventive measures.

Objective: This study aims to examine the existing body of knowledge on HCWs' perceived risks of TB and how these perceptions impact their adherence to TB prevention measures. The results of this scoping review will identify gaps in the current literature that should inform policy and practice and guide future research studies to optimize TB prevention among HCWs.

Methods: This scoping review will be conducted following the framework proposed by Arksey and O'Malley, incorporating the recent advancements. This approach involves 6 key stages: identifying the research question; identifying relevant studies; selecting studies; charting the data; collating, summarizing, and reporting the results; and consulting with stakeholders.

Results: As of June 2024, 1345 records were identified (1234 from databases and 111 from other sources), and 667 duplicates were removed. The remaining 678 records were screened by title and abstract, with 216 progressing to full-text review. After applying the eligibility criteria, 42 studies were included in the final analysis. Screening and full-text assessments were conducted between September and October 2024. Data extraction and thematic analysis were performed in winter 2024. The final data synthesis stage is expected to be completed by 2025.

Conclusions: HCWs' perceptions of risk have a considerable effect on how well they follow TB prevention measures such as using personal protective equipment and undergoing health screenings. Lack of resources, lack of training, and the stigma around TB are some of the main barriers to TB prevention adherence. The thematic analysis showed that adherence levels were different depending on the support offered by the institution and the TB knowledge level and perception of each HCW. Although TB treatment has become more effective, nosocomial infections are still a big concern, especially in low- and middle-income countries like Indonesia, where HCWs are more likely to have latent TB infections. This review shows how important it is for HCWs to understand how TB prevention behaviors work. To improve HCW adherence, the gaps in institutional support, stigma, and training must be filled. Future interventions should be based on the specific problems found in low- and middle-income countries. This will make health care safer for everyone around the world.

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(JMIR Res Protoc 2025;14:e64037) doi:10.2196/64037

KEYWORDS

health care worker; tuberculosis; occupational risk; perceptions; TB prevention

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Introduction

Tuberculosis (TB) remains a major global public health issue and a particular concern among health care staff in the high-risk environment of clinical settings. Health care workers (HCWs) are at the forefront of TB control and consequently to occupational *Mycobacterium tuberculosis* exposure. Compared to the general population, HCWs are at a higher risk of TB infection, as the dependent factor of the World Health Organization (WHO) has estimated HCWs to be approximately 2-3 times more likely to become infected with TB. Earlier landmark research published in 2001 had provided evidence that TB can be transmitted through air in health care environments [1-3]. Thus, we need control measures to reduce this risk.

TB has the largest impact in low- and middle-income countries (LMICs), as >95% of TB-related deaths occur in LMICs. Only 8 LMICs account for two-thirds of the global caseload, and one of them is Indonesia [4,5]. The risk of HCWs developing TB is much higher than that of the general population [6-8]. A systematic review of 111 studies showed that the prevalence of latent TB infections (determined by the tuberculin skin test) among HCWs in LMICs ranged from 14% to 98%, with the mean prevalence being 49% [9,10]. High regional variability has been observed in the annual incidence of latent TB infections among HCWs, ranging from 0.5% to 14.3% [11,12].

Occupational risk perceptions can be compromised [13,14], contributing to nonadherence to proven effective TB prevention regimens (eg, personal protective equipment, regular enrollment in health screenings). Although there has been a notable advancement in the treatment of TB, nosocomial or hospital-acquired TB infections remain a considerable occupational risk, particularly with the complex interplay of multidrug-resistant TB and HIV/AIDS in clinical settings [15,16]. Studies have shown that HCWs' TB preventive behaviors widely differ and are determined by their risk perceptions, knowledge levels, and institutional support. For example, HCWs at a higher risk of TB are generally more engaged in preventive behaviors [17,18]. Yet, persistent barriers remain, such as insufficient personal protective equipment, poor ventilation, and TB stigma [19,20]. Such gaps warrant strategic mapping of existing literature on HCWs' perceptions and practices to inform future interventions. Our objective is to synthesize existing literature on HCWs' perceptions of occupational risk and adherence to TB preventive routine measures in order to identify widespread themes and gaps in the research and provide an overview of the factors informing these perceptions and behaviors. This study aims to examine the existing body of knowledge on HCWs' perceived risks of TB and how these perceptions impact their adherence to TB prevention measures. The results of this scoping review will identify gaps in the current literature that should inform policy and practice and guide future research studies to optimize TB prevention among HCWs.

Methods

Study Design

This study is a scoping review protocol and does not involve a randomized controlled trial; therefore, trial registration is not applicable. This review will be conducted following established methodological frameworks by Arksey and O'Malley [14], with enhancements by Levac et al [21], and guided by the Joanna Briggs Institute methodology for scoping reviews [22]. This approach involves 6 key stages: identifying the research question; identifying relevant studies; selecting studies; charting the data; collating, summarizing, and reporting results; and consulting with stakeholders. The PRISMA-ScR (Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews) checklist is shown in Multimedia Appendix 1.

Key Stages of the Study

Stage 1: Identifying the Research Question

The primary research question guiding this scoping review is as follows: how do HCWs perceive their occupational risk of TB and what factors influence their adherence to TB prevention and control measures? This question aims to explore the breadth of literature on HCWs' risk perceptions and their impact on preventive behaviors.

Stage 2: Identifying Relevant Studies

The review will apply the Joanna Briggs Institute approach [23] to identify the suitability of the papers (Table 1). A comprehensive search strategy will be employed to identify relevant studies. Key databases, including PubMed, MEDLINE, EBSCO, Scopus, and Web of Science, will be searched. Keywords and search terms will include combinations of the following: HCWs, health personnel, tuberculosis, TB, occupational risk, perceptions, attitudes, awareness, knowledge, prevention, control measures, adherence, and compliance (Table 2). Both peer-reviewed studies and grey literature will be considered to ensure a wide scope of information (Figure 1).

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Table 1. Search strategy for the perceptions of occupational risk and adherence to tuberculosis prevention among health care workers.

Strategy	Criteria
Population	• HCWs[a], including doctors, nurses, laboratory technicians, and support staff, directly involved in patient care • Currently employed in health care settings such as hospitals, clinics, or health centers • A minimum of 6 months of experience in a health care setting • Willingness and ability to provide informed consent to participate in the study
Concept	• Studies exploring HCWs' perceptions of occupational tuberculosis risk and/or adherence to tuberculosis prevention and control measures
Context	• Studies conducted in any health care setting (hospital, primary care, clinic) and in any country
Type of source	• All research designs: observational studies, randomized controlled trials, systematic reviews, case studies, qualitative studies, clinical guidelines. The following were excluded: publications in the form of editorials, letters to the editor, comments, and case reports/narrative case reports.

[a]HCW: health care worker.

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Table 2. Keywords and queries used for identifying the studies on the perceptions of occupational risk and adherence to tuberculosis prevention among health care workers.

Database	Keywords	Query
MEDLINE	• Health care workers: health care personnel, health care professionals, medical staff, clinical staff, doctors, nurses, laboratory technicians • Perceptions: perception, awareness, belief, attitude, understanding • Occupational risk: occupational risk, workplace exposure, job hazard, professional risk • Tuberculosis: tuberculosis, TB, Mycobacterium tuberculosis • Prevention: prevention, infection control, protective measures, preventive practices, adherence, compliance	((“Health Personnel”[MeSH] OR health care workers OR medical staff OR clinical staff OR doctors OR nurses OR laboratory technicians) AND (“Perception”[MeSH] OR perception OR awareness OR belief OR attitude OR understanding) AND (“Occupational Exposure”[MeSH] OR occupational risk OR workplace exposure OR job hazard OR professional risk) AND (“Tuberculosis”[MeSH] OR tuberculosis OR TB OR Mycobacterium tuberculosis) AND (“Infection Control”[MeSH] OR prevention OR protective measures OR preventive practices OR adherence OR compliance))
Scopus	• Health care workers: health care personnel, health care professionals, medical staff, clinical staff, doctors, nurses, laboratory technicians • Perceptions: perception, awareness, belief, attitude, understanding • Occupational risk: occupational risk, workplace exposure, job hazard, professional risk • Tuberculosis: tuberculosis, TB, Mycobacterium tuberculosis • Prevention: prevention, infection control, protective measures, preventive practices, adherence, compliance	KEY (“health care personnel” OR “health care professionals” OR “medical staff” OR “clinical staff” OR doctors OR nurses OR “laboratory technicians”)) AND (TITLE-ABS-KEY (perception OR awareness OR belief OR attitude OR understanding)) AND (KEY (“occupational risk” OR “workplace exposure” OR “job hazard” OR “professional risk”)) AND (KEY (“tuberculosis” OR TB OR “Mycobacterium tuberculosis”)) AND (TITLE-ABS-KEY (prevention OR “infection control” OR “protective measures” OR “preventive practices” OR adherence OR compliance))
EBSCO	• Health care workers: health care personnel, health care professionals, medical staff, clinical staff, doctors, nurses, laboratory technicians • Perceptions: perception, awareness, belief, attitude, understanding • Occupational risk: occupational risk, workplace exposure, job hazard, professional risk • Tuberculosis: tuberculosis, TB, Mycobacterium tuberculosis • Prevention: prevention, infection control, protective measures, preventive practices, adherence, compliance	(“health care personnel” OR “health care professionals” OR “medical staff” OR “clinical staff” OR doctors OR nurses OR “laboratory technicians”) AND (perception OR awareness OR belief OR attitude OR understanding) AND (“occupational risk” OR “workplace exposure” OR “job hazard” OR “professional risk”) AND (“tuberculosis” OR TB OR “Mycobacterium tuberculosis”) AND (prevention OR “infection control” OR “protective measures” OR “preventive practices” OR adherence OR compliance))
Google Scholar	• Health care workers: health care personnel, health care professionals, medical staff, clinical staff, doctors, nurses, laboratory technicians • Perceptions: perception, awareness, belief, attitude, understanding • Occupational risk: occupational risk, workplace exposure, job hazard, professional risk • Tuberculosis: tuberculosis, TB, Mycobacterium tuberculosis • Prevention: prevention, infection control, protective measures, preventive practices, adherence, compliance	“health care workers” OR “health care professionals” OR “medical staff” OR “clinical staff” OR doctors OR nurses OR “laboratory technicians” AND perception OR awareness OR belief OR attitude OR understanding AND “occupational risk” OR “workplace exposure” OR “job hazard” OR “professional risk” AND tuberculosis OR TB OR “Mycobacterium tuberculosis” AND prevention OR “infection control” OR “protective measures” OR “preventive practices” OR adherence OR compliance

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Figure 1. Search strategy.

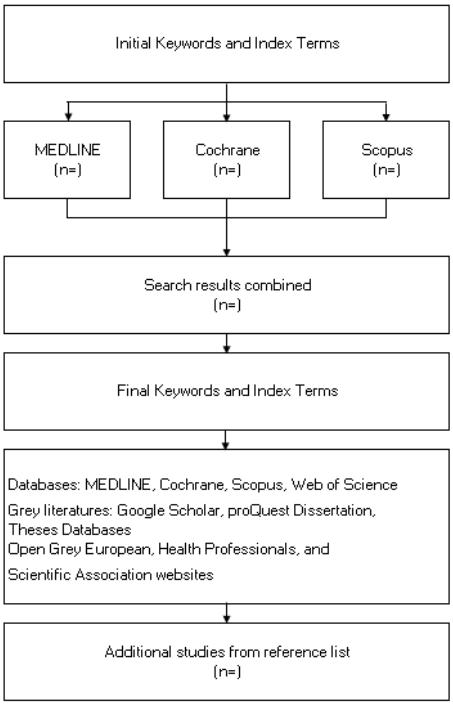

Stage 3: Study Selection

The selection process will involve a 2-step approach. Initially, titles and abstracts will be screened for relevance by 2 independent reviewers. Studies that meet the inclusion criteria will proceed to full-text screening. The inclusion criteria will encompass studies focusing on HCWs' perceptions of TB risk, research examining adherence to TB prevention and control measures, publications in English, and studies published from 2000 onwards to capture recent trends and advancements (Table S1 in Multimedia Appendix 2). Discrepancies between reviewers will be resolved through discussion or by consulting a third reviewer (Figure 2).

Figure 2. PRISMA-ScR flow diagram for the study selection.

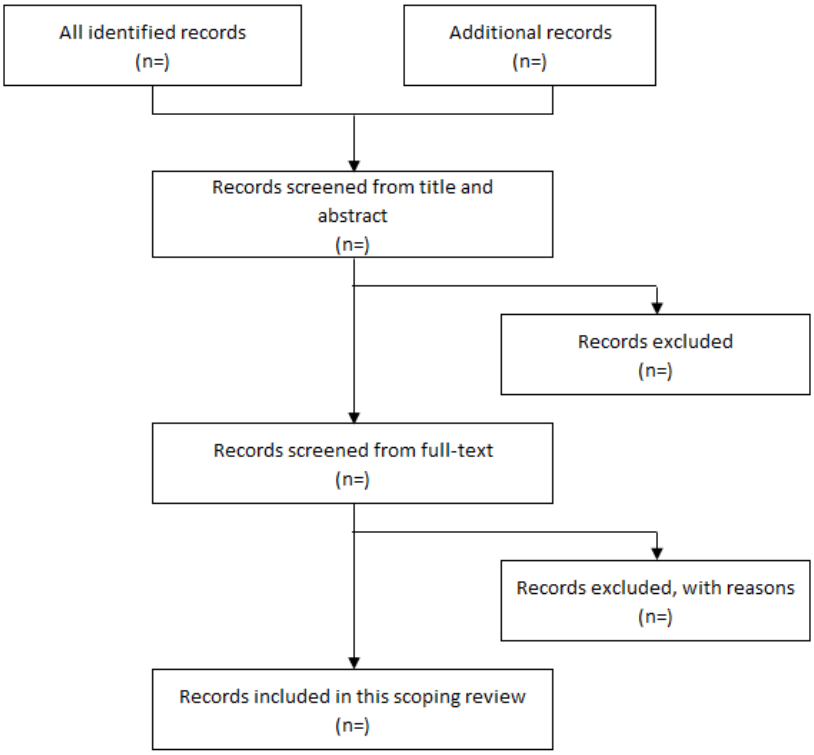

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Stage 4: Charting the Data

Data extraction will be performed using a standardized charting form (Table S2 in Multimedia Appendix 2). Key information to be extracted on the characteristics of the study include the author(s), year, country, and study design; participant details, including the sample size, health care role, and setting; perceptions of TB risk; factors influencing the adherence to TB prevention measures; and main findings and conclusions. This iterative process will allow for continuous refinement of the data extraction form as necessary.

Stage 5: Collating, Summarizing, and Reporting Results

The extracted data will be collated and summarized to provide an overview of the existing literature. This will involve a descriptive numerical summary and a thematic analysis. The numerical summary will outline the study characteristics, while the thematic analysis will identify common themes related to HCWs' perceptions of TB risk and factors influencing their adherence to prevention measures. This stage aims to highlight the key findings, identify gaps in the literature, and suggest implications for policy and practice.

Stage 6: Consultation With Stakeholders

To enhance the relevance and applicability of the findings, we will conduct consultations with stakeholders such as health care professionals, TB experts, and policymakers. These consultations will provide additional insights, validate the findings, and offer practical recommendations for improving TB prevention and control in health care settings. Stakeholder feedback will be integrated into the final report to ensure that it addresses real-world concerns and needs. By adhering to this structured and systematic methodology, this scoping review will provide a comprehensive understanding of HCWs' perceptions of occupational TB risk and the factors influencing their adherence to preventive measures.

Data Synthesis and Thematic Analysis

We will explore patterns in how HCWs think about the risk of occupational TB and how well they follow TB prevention and control measures by performing a thematic analysis of the qualitative and quantitative data we collected. The process will be based on Braun and Clarke's 6-phase framework [24] for thematic analysis. The 6 steps are as follows: (1) getting to know the data, (2) making initial codes, (3) looking for themes, (4) reviewing themes, (5) defining and naming themes, and (6) writing the report. We will organize the data in order and analyze with NVivo (version 14; QSR International) to help with coding and developing themes in a systematic way. Each reviewer will code each study on their own. If they do not agree, they will talk about it or, if necessary, have a third reviewer to help. Thereafter, the codes will be arranged into groups, and then those groups will be used to develop overarching themes.

We will maintain an audit trail to make the analysis open and trustworthy, and we will hold regular team meetings to talk about new themes and make sure everyone agrees. There will be both descriptive and analytical themes in the synthesis, which will show what people think is a risky job, how they act in response to it, what helps and hurts, and how these things change in different health care settings. The last themes will be tweaked to fit the review's goals, and the results section will show them with evidence from the studies that were used. We will consider heterogeneity across data sources by stratifying findings based on key study characteristics such as geographic region, health care setting (eg, hospital vs primary care), type of HCW, and study design (quantitative, qualitative, or mixed methods). This stratified approach will help us capture the variations in HCWs' perceptions and adherence to TB preventive measures across different contexts.

Ethical Considerations

As this study is a scoping review that involves the synthesis of data from publicly available literature and does not include any research involving human participants, identifiable personal data, or animals, an ethics review board assessment was not required. According to institutional and international guidelines, including the Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans (article 2.2) and equivalent regional policies, research that does not involve interaction with humans or access to nonpublic identifiable data is exempt from formal ethical review. Therefore, no application was submitted to an ethics committee for this protocol.

Results

The electronic database search was completed in June 2024, initiating the research team's review of HCWs' perceptions of occupational TB risk and related preventive behaviors. A total of 1345 records were identified (1234 from databases and 111 from other sources), and 667 duplicates were removed. The remaining 678 records were screened by title and abstract, with 216 progressing to full-text review. After applying eligibility criteria, 42 studies were included in the final synthesis. Screening and full-text assessments were conducted between September and October 2024. Data extraction and thematic analysis were performed in winter 2024. This review summarizes key findings, including study characteristics, participant roles and settings, risk perceptions, factors influencing adherence to TB prevention measures (such as personal protective equipment use, routine screening, and institutional support), and barriers such as stigma and poor infrastructure. At the time of submission in February 2025, the study was in the final data synthesis stage.

Discussion

Overview

The findings of this scoping review are expected to offer several real-world applications for health care systems, particularly in high TB burden countries. By identifying the key factors influencing HCWs' perceptions of occupational TB risk and their adherence to preventive measures, this review will support the development of targeted, evidence-informed interventions aimed at improving workplace safety. Policymakers and hospital administrators can utilize these insights to strengthen institutional policies—such as the provision of adequate personal protective equipment, regular TB screening, and comprehensive training—while also addressing structural and psychosocial barriers, including TB-related stigma. Additionally, this review

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will provide a valuable foundation for researchers and TB program implementers to design context-sensitive strategies that enhance infection control efforts, protect frontline health workers, and ultimately reduce nosocomial transmission of TB. The synthesis of diverse study contexts and health care settings will further ensure that the recommendations are adaptable and applicable across a range of health system environments.

In addition, this review highlights the interaction between individual and organizational factors in influencing HCWs' preventive actions. It is essential to consider, in addition to the resources being available, that adherence is mediated by perceptions of support from the institution in addition to the presence of a work culture that is supportive. Stigmas associated with TB, barriers to accessing human resources and workload pressures, and insufficient comprehensive training programs are other hindrances that contribute to the observed situation. The translation of these results further outlines the knowledge gap in the current literature and highlights contributory ideas to better fit potential interventions for this demographic. If these barriers are addressed through improved policies, capacity development/training initiatives, and institutional reforms, there can be a significant improvement in adherence to TB preventive measures, which could reduce the occupational risk of TB among HCWs across the world.

Strengths and Limitations

This scoping review has some strengths. First, it has a wide scope of included study designs (qualitative, quantitative, and mixed methods) and sources that ensure a comprehensive evidence base. The addition of peer-reviewed papers and grey literature also provides a wide range of data. Second, the methodology follows the Arksey and O'Malley [14] framework, with enhancements by Levac et al [21], and guided by the Joanna Briggs Institute methodology for scoping reviews [22] to ensure rigor and transparency. Third, engagement with health care professionals, TB specialists, and policymakers increases the real-world relevance and applicability of the results. Fourth, and particularly important, by considering data from HCWs in low-, middle- and high-income countries, the results are globally relevant and add weight to a global case for policy and practice based on evidence. Finally, the review findings have potential implications for the design of targeted interventions that could enhance TB prevention and adherence among HCWs.

However, this review also had a few limitations. First, limiting the review to English language publications may miss pertinent studies published in other languages. Second, by restricting the review to studies published from 2000 onwards, earlier research and historical trends may have been overlooked. Third, using published studies may be subject to publication bias by excluding unpublished or not publicly accessible data. Fourth, differences in design, population, and setting of the included studies' designs make data synthesis and comparison challenging. Finally, although independent reviewers strived to reduce potential bias, the interpretation of themes in this thematic analysis represented somewhat subjective accounting. These limitations should be borne in mind when interpreting the findings of the review.

Conclusion

This scoping review is the first of its kind, to our knowledge, focusing on presenting methodological and technical guidance on assessing and understanding HCWs' perceptions of occupational TB risk and adherence to preventive measures. This scoping review will systematically map the existing literature to address critical knowledge gaps and provide a comprehensive overview of the factors influencing HCWs' behaviors across different health care settings. These findings will guide policymakers, health care institutions, and researchers in formulating targeted strategies and interventions to improve TB prevention and control efforts, particularly in high-burden areas. The findings from this review will support upcoming research and operationalization to be implemented to ensure the safety and wellness of the primary receptors of frontline risk, that is, humanitarian health workers, across the globe.

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Authors' Contributions

Conceptualization: AF (lead), AA (equal)
Data curation: AF
Formal analysis: AF (lead), EAP (supporting)
Funding acquisition: AF
Investigation: AA
Methodology: AF, AA
Project administration: AF (lead), AA (equal), EAP (supporting)
Resources: EAP
Supervision: AF
Validation: AA
Visualization: AA (lead), EAP (supporting)
Writing – original draft: AF (lead), AA (supporting)
Writing – review & editing: AF (lead), AA (supporting), EAP (supporting)

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Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-ScR checklist.
[PDF File (Adobe PDF File), 571 KB - resprot_v14i1e64037_app1.pdf]

Multimedia Appendix 2
Study selection and data extraction.
[DOCX File , 18 KB - resprot_v14i1e64037_app2.docx]

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Abbreviations

HCW: health care worker
LMICs: low- and middle-income countries
PRISMA-ScR: Preferred Reporting Items for Systematic reviews and Meta-Analyses extension for Scoping Reviews
TB: tuberculosis
WHO: World Health Organization

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Protocol

Machine Learning in Health Economic Evaluations: Protocol for a Scoping Review

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Abstract

Background: In recent years, the development of machine learning (ML) applications has increased substantially, indicating the potential role of ML in transforming health care. However, the integration of ML approaches into health economic evaluations is underexplored and has several challenges.

Objective: This scoping review aims to explore the applications of ML in health economic evaluations. This review will also seek to identify some potential challenges to the use of ML in health economic evaluations.

Methods: This review will use PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) methods. The search will be conducted on MEDLINE (Ovid), Embase (Ovid), IEEE Xplore, and Cochrane Library databases. The eligibility criteria of the selection process will be based on the study types, data sources, methods, and outcomes (SDMO) framework approach.

Results: The database search yielded 4141 records after removal of retractions and duplicates. Title and abstract screening of 3718 records has been completed, resulting in 30 reports retrieved for eligibility assessment. Data extraction and charting are currently in progress. The results will be published in peer-reviewed journals by the end of 2025.

Conclusions: This review will help to build up the current understanding of how ML applications are integrated in health economics evaluations. This will also explore the potential barriers to and challenges of using ML in health economics evaluations.

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KEYWORDS

machine learning; economic evaluations; health economics; cost-effectiveness analysis; economic modelling

Introduction

Background

Machine learning (ML) is a growing area in economic evaluation of health care interventions, improving predictive accuracy and resource allocation [1,2]. ML is a subfield of artificial intelligence that comprises statistical techniques that allow algorithms to learn from data and improve performance without being explicitly programmed [3,4]. In contrast, health economic evaluation provides a structured approach for comparing the costs and consequences of health care interventions to provide information in identifying the most efficient use of resources [5,6]. ML models use extensive real-world data, such as patient demographics, clinical backgrounds, treatment responses, and health care resource usage, to evaluate numerous parameters.

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The rapid nature of ML evaluation also allows for efficient and accurate determination of the important parameters that are considered when comparing 2 health care interventions. These may include costs of medicines or technologies, prevalence of illnesses, or the effectiveness of different treatments [7-10]. ML has significant potential to enhance health economic evaluations [9-19]; however, further exploration is required to fully understand its methodological integration and practical implications.

Despite the growing interest in ML across health research, its application within the domain of the health economic evaluation process remains limited and underexplored. Existing literature tends to focus broadly on ML applications in health outcomes research, often emphasizing prediction, diagnosis, or economic impact rather than incorporating it in the health economic evaluation process [1,2,20]. For example, a scoping review reported that 42% of studies using ML in economic evaluations focused on clinical event prediction, 22% on treatment outcomes, 16% on health care resource utilization, and 3% on cost prediction [1].

Understanding how ML is currently used in health economic evaluation is essential to ensure methodology transparency and understanding how ML could be integrated into the economic evaluation. An example of this is the research that analyzed the cost-effectiveness of high-flow nasal cannula therapy versus continuous positive airway pressure for acutely ill children using ML in data analysis [10]. The analysis indicated that high-flow nasal cannula therapy is more cost-effective for male infant patients and patients without severe respiratory distress, as it has an incremental net monetary benefit of £5310 (US $6590)overall [10]. Another example is in the case of breast cancer screening in which an ML-based risk-stratified model might save £60.4-85.3 million (US $74.9-105.9 million) per year while improving health outcomes compared to traditional screening [19]. Furthermore, applying risk assessment models can save costs while increasing value by identifying patients who can be safely discharged from the emergency room [18]. Additionally, ML techniques have shown promise in addressing nonlinear relationships and high-dimensional datasets that challenge traditional regression-based approaches [9,14,15]. For example, combining linear regression with feature selection methods such as lasso, random forest, and extreme gradient boosting has improved predictive performance in modelling complex health care costs [9,14,15]. There is a growing recognition that ML could strengthen several dimensions of economic evaluation, including the ability to capture patient heterogeneity, perform risk-stratified analysis, optimize model inputs, and handle complex data [9-19].

To the best of our knowledge, there are no previous reviews that directly explore the use of ML in health economic evaluation. However, ML has the ability to improve the health economic evaluation process through analysis of patient heterogeneity, model parameter optimization, and risk-stratified analysis [10,12,16,18]. To address this gap, this review aims to examine how ML has been applied in economic evaluations in health care and to explore the potential barriers and opportunities of using ML in the field of health economic evaluation. Guided by this aim, the review is structured around the following research questions:

1. How have ML techniques been applied within the process of health economic evaluations?
2. Which technical components of full economic evaluations (eg, model calibration, parameter estimation, heterogeneity analysis, uncertainty quantification, and metamodeling) have incorporated ML methods?
3. What challenges and barriers have been reported in applying ML within health economic evaluations?

Objectives

The aim of this scoping review is to identify ML applications in the health economic evaluation process. Specifically, it maps how ML techniques are integrated into the technical components of full economic evaluations, such as model calibration, parameter estimation, heterogeneity analysis, uncertainty quantification, and metamodeling, regardless of the clinical or health sector context. The output will focus on the methods adopted and the challenges and barriers faced.

Methods

Overview

This scoping review follows Levac's [21] recommended update to the Arksey and O'Malley scoping review framework to ensure a systematic and rigorous approach to evidence synthesis [22]. The PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines inform the reporting of the review [23]. The final report will include a PRISMA-ScR checklist (Multimedia Appendix 1).

Search Strategy and Study Selection

A comprehensive literature search will be conducted on MEDLINE (Ovid), Embase (Ovid), IEEE Xplore, and the Cochrane Library. We will consult with information specialists to improve the search strategy. The search will use Medical Subject Headings (MeSH) terms with Boolean operators (AND, OR). The preliminary search approach is shown in Multimedia Appendix 1.

Eligibility Criteria

This review will adopt a study types, data sources, methods, and outcomes (SDMO) framework approach [24]. This framework is used to make sure that the studies included in the selection process are relevant. The eligibility criteria are presented in Table 1. We included peer-reviewed, full-text articles and relevant conference abstracts that applied ML techniques within full economic evaluations. All health care settings were eligible, with no restrictions on publication year. Only studies published in English were considered.

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Table 1. Eligibility criteria.

Category	Inclusion criteria	Exclusion criteria
Types of studies	Quantitative studies and economic evaluations.	Opinion pieces, editorials, and studies without economic evaluation.
Types of data	All types of data, including EHRs[a], claims databases, clinical trial data, administrative health care datasets, and simulated or hypothetical data.	None.
Types of methods	Studies that use supervised, unsupervised, reinforcement learning, or deep learning models for economic evaluations.	Studies using ML[b] for disease prediction or clinical decision-making without economic evaluations.
Outcomes	Studies that evaluate health economic results such as ICERs[c], QALYs[d], utility scores, cost predictions, and health resources.	Studies without economic evaluation outcomes.

[a]EHR: electronic health record.

[b]ML: machine learning.

[c]ICER: incremental cost-effectiveness ratio.

[d]QALY: quality-adjusted life year.

Screening and Article Selection

All references identified from database searching were first imported into EndNote [25] for reference management, with removal of duplicate references, and then uploaded to Rayyan [26]. Two independent reviewers (AK and HA) will screen titles and abstracts based on the eligibility criteria, working blinded and independently in different locations on separate copies of the database. Discrepancies will be resolved through discussion or consultation with a third reviewer.

Although a formal calibration exercise was not conducted, both reviewers (AK and HA) discussed the initial records to ensure a shared understanding of the inclusion and exclusion criteria. These criteria served as the guiding reference throughout the screening process. Consistency was maintained throughout the screening process via ongoing communication, with discrepancies resolved through discussion and, when necessary, adjudication by a third reviewer. Interrater agreement statistics were not calculated, but reviewer alignment was tracked throughout.

Data Extraction and Analysis

A structured data extraction form will be developed a priori and piloted to ensure consistency and reproducibility in capturing relevant study characteristics and to understand the gap in applying ML in health economic evaluation. Data will be managed using Microsoft Excel, allowing for systematic organization, coding, and retrieval of key information.

Two independent reviewers will perform data extraction, ensuring interreviewer reliability. Any discrepancies in extracted data will be resolved through discussion or, if necessary, by consulting a third reviewer. The extracted information will include the key domains described in Table 2.

Table 2. Key domains for extracted information.

Domain	Description
Study characteristics	Authors, year of publication, country, study design, study objective, study setting, and data sources.
Economic evaluation	Type of economic evaluation, such as cost-effectiveness analysis and cost-utility analysis, in addition to how the economic evaluation was carried out (alongside a clinical trial or economic decision models).
ML[a] methodology	Type of ML approach used, such as supervised learning, deep learning, or reinforcement learning algorithms.
Outcomes	All economic evaluation outcomes, including ICERs[b], QALYs[c], utility scores, cost predictions, and health care resource allocation.
Challenges and limitations	Identified ML implementation barriers such as computational complexity, data security, and data availability.

[a]ML: machine learning.

[b]ICER: incremental cost-effectiveness ratio.

[c]QALY: quality-adjusted life year.

Data Synthesis

Data will be synthesized narratively using descriptive analysis. Studies will be categorized based on ML methodologies, economic evaluation type, and key outcomes. Narrative analysis will identify the themes that serve as opportunities or barriers to the application of ML in economic evaluations. In addition to narrative synthesis, we will also consider presenting findings using appropriate visual summaries, such as tables, flow charts, and descriptive figures.

The extracted data will be synthesized narratively using both descriptive and thematic approaches. Studies will first be categorized based on key characteristics, including study design, clinical area, data sources, ML methodology, type of economic

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evaluation, computational complexity, data security and availability concerns, and the context and stage of ML application within the economic evaluation process. Subsequently, a thematic analysis will be conducted to identify recurring methodological patterns, innovations, and implementation challenges. Themes will be developed inductively and refined through team discussion.

Results

The preliminary search conducted in April 2024 yielded 4141 records from the selected databases, namely, MEDLINE (Ovid), Embase (Ovid), IEEE Xplore, and the Cochrane Library. Results will be disseminated through publication in a peer-reviewed journal by the end of 2025. The database searches are ongoing, and the PRISMA-ScR flowchart (Figure 1) illustrates the study selection process. The flowchart will be updated upon completion of full-text screening and data extraction. Based on an initial scan of titles and abstracts, the retrieved studies appeared to include a range of designs, including simulation-based modelling studies, retrospective cohorts, and hybrid designs that integrate trial data with economic models. Thematically, many studies applied ML for tasks such as model calibration, parameter estimation, heterogeneity analysis, uncertainty quantification, and metamodeling.

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram of the study selection process.

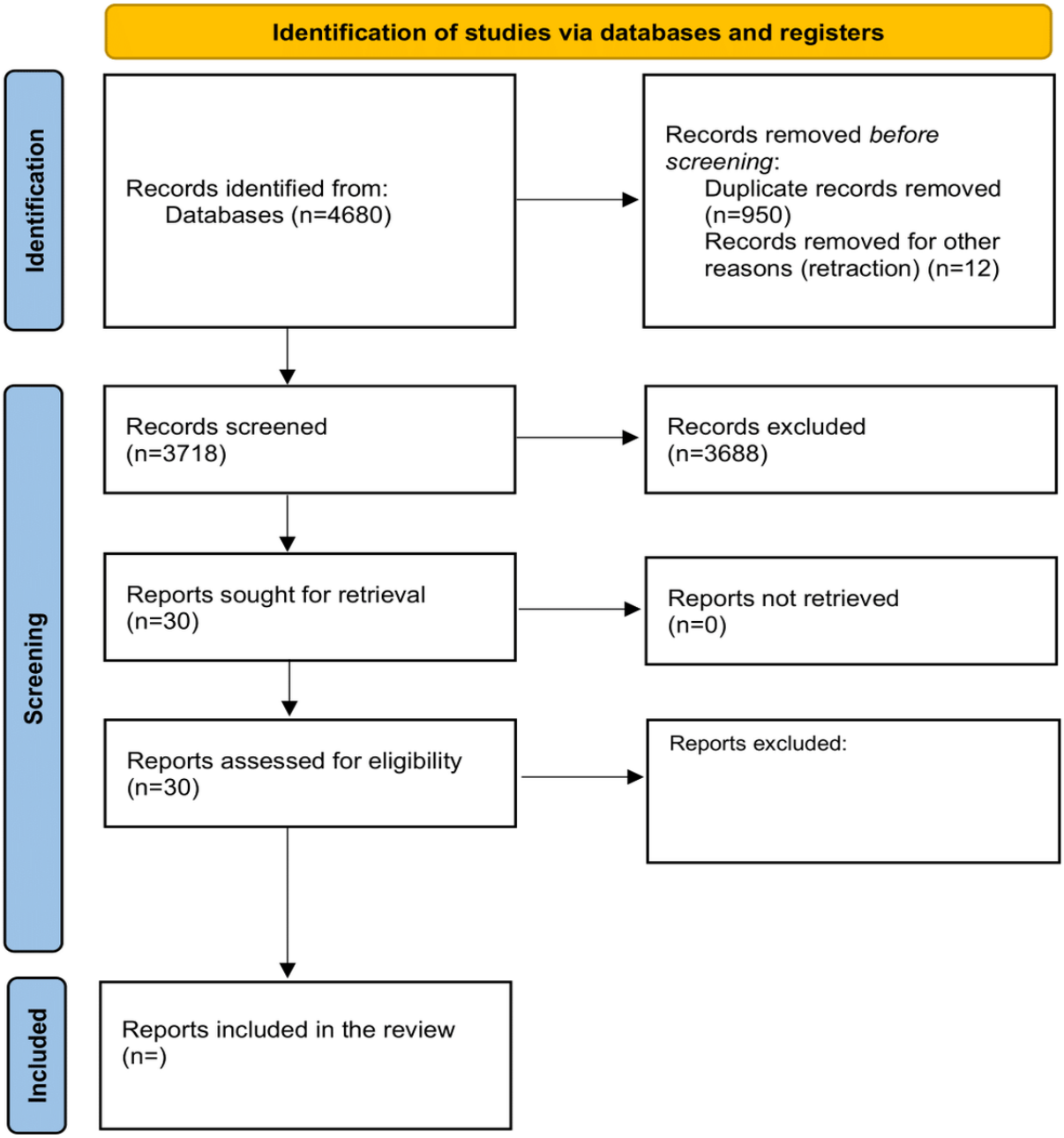

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Discussion

Anticipated Findings

This scoping review is expected to identify how ML methods have been applied within health economic evaluations, particularly in areas such as model calibration, parameter estimation, heterogeneity analysis, uncertainty quantification, and metamodeling. By synthesizing this evidence, the review will map current practices and highlight methodological gaps that could inform future development of economic evaluation frameworks.

Most previous reviews examine how ML algorithms improve prediction, diagnosis, and economic impact; none have specifically explored ML in the context of the health economic evaluation process [1,2,20]. To the best of our knowledge, there is a lack of reviews on applying ML in the health economic evaluation process. This scoping review will seek to provide more comprehensive evidence on how ML is incorporated in the health economic evaluations process, what opportunities and barriers ML could face in the health economic evaluations process.

In this review, we aim to explore the existing literature in an unbiased manner; however, there are several limitations that should be acknowledged. For instance, not including grey literature may lead to missing relevant evidence from conference proceedings and other nonindexed sources. This decision was made to enhance the rigor and reliability of findings. Moreover, restricting the search to English-language publications may introduce language bias and miss relevant studies published in other languages [27]. Furthermore, this review did not assess the quality or risk of bias of the included studies, which allowed for a broad inclusion of relevant literature.

The findings of this scoping review may guide the design of future systematic reviews and comparative analyses that directly assess the effectiveness of ML-based versus traditional approaches in health economic evaluation. It may also highlight methodological areas where further research is required, such as handling of heterogeneity, validation of ML-based models, and transparency in reporting.

Conclusions

This scoping review will explore how ML applications could be incorporated into the health economic evaluation process. This review will identify opportunities and barriers for this research. This can help us to understand the possibilities of applying ML in the health economic evaluation. By mapping current practices, the review will contribute to a clearer understanding of the role of ML in areas such as model calibration, parameter estimation, heterogeneity analysis, and uncertainty quantification. The findings will help inform the design of future systematic reviews and comparative studies, and guide methodological research aimed at strengthening the integration of ML into economic evaluation frameworks. Results will be disseminated through a peer-reviewed journal article, academic conference presentations, and professional networks in health economics and data science, and will be communicated to relevant stakeholders, including policymakers and researchers interested in ML applications in health economics.

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Authors' Contributions

Conceptualization: HD, GSS
Methodology: HD
Supervision: AK, EM, GSS
Writing – original draft: HD
Writing – review & editing: HD, AK, RB-S, RP, AA, CC, VR, EM, GSS

Conflicts of Interest

EM is an Editor in Chief of *JMIRx Med*. All other authors have no conflicts of interest.

Multimedia Appendix 1
PRISMA-ScR checklist and detailed search strategy.
[DOCX File , 23 KB - resprot_v14i1e77494_app1.docx]

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Abbreviations

MESH: Medical Subject Headings
ML: machine learning
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
SDMO: study types, data sources, methods, and outcomes

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Protocol

Workplace Health Interventions Targeting Cardiovascular Diseases and Diabetes Mellitus for Blue-Collar Workers: Protocol for a Scoping Review

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Abstract

Background: Cardiometabolic diseases, such as cardiovascular diseases (CVD) and diabetes mellitus (DM), represent a global health issue, causing significant premature mortality and disability. Blue-collar workers, who often face a higher exposure to risk factors (eg, smoking, poor diet, and lack of physical activity), are particularly vulnerable to these diseases. Workplace health promotion plays a crucial role in mitigating this risk, yet the scope and the characteristics of interventions targeting this specific workforce remain unclear.

Objective: The objective of this scoping review will be to assess the extent and characteristics of workplace health promotion interventions aimed at preventing cardiometabolic diseases and their risk factors in blue-collar workers.

Methods: The review will follow the JBI methodology for scoping reviews. A search of MEDLINE, Scopus, Embase, and the Cochrane Database as well as grey literature will be conducted. The search strategy is designed to capture relevant studies published since 2014 in English, Spanish, Italian, and Polish. Eligible study designs include experimental design (eg, randomized controlled trials), observational studies (eg, longitudinal studies), qualitative research, and mixed-method approaches as well as other formats present in grey literature (eg, reports). This review will include studies focusing on health promotion interventions involving adult blue-collar workers (aged ≥18 years) currently employed, with at least 60% of participants being blue-collar employees. The interventions of interest are workplace health promotion strategies targeting CVD, DM, or their risk factors, such as hypertension, obesity, and smoking. Each paper retrieved will be screened for inclusion by at least 2 reviewers. Disagreements between the reviewers will be resolved through discussion with the other reviewers. Studies focusing on noninterventional contexts, mental health, or ergonomic safety will be excluded. Data will be extracted and analyzed using qualitative and quantitative methods, with a focus on intervention types, participant characteristics, and outcomes.

Results: The study began in March 2024 and the full scoping review report is expected to be ready in September 2025.

Conclusions: The scoping review presented in this protocol can contribute to filling the knowledge gap by mapping the current state of workplace health promotion interventions aimed at preventing CVD and DM and modifying relevant risk factors in the blue-collar workers' group.

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Trial Registration: Open Science Framework hdrq4; https://osf.io/hdrq4
International Registered Report Identifier (IRRID): DERR1-10.2196/74248

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KEYWORDS
blue-collar workers; cardiovascular disease; diabetes mellitus; workplace health promotion; workplace health interventions; chronic disease prevention; occupational health; public health

Introduction

Cardiometabolic diseases, including cardiovascular diseases (CVD), diabetes (DM) and nonalcoholic fatty liver disease [1], are a leading health problem on a global scale, being the most common cause of premature mortality and disability [2,3]. In 2019, it was estimated that over half a billion people in the world suffered from CVD, and 18.2 million died from this cause [4]. In the case of DM, the number of patients was estimated at 529 million people; over the years 2010-2021, DM experienced the most rapid growth among the causes of health loss after adjusting for age and population size [3]. Although older age is one of the most important risk factors for cardiometabolic diseases [5,6], it is estimated that up to one-third of deaths due to circulatory system diseases occur before the age of 70 [7]. Moreover, available research indicates that CVD and DM are some of the main causes of early exit from paid work [8,9], making it a burden to the health system as well as to the national, regional, and global economy.

To address this challenge, several initiatives have been launched to allow for a better understanding of the determinants leading to CVD and DM and increase the effectiveness of preventive measures both on the individual and social levels. One such initiative is the Joint Action on Cardiovascular Diseases and Diabetes (JACARDI), implemented under the EU4Health Program of the European Commission [10]. JACARDI's objective is to support EU countries in reducing the burden of CVD and DM and related risk factors while ensuring health systems' sustainability and equity. JACARDI aims at enhancing and promoting the implementation of best practices and pilot testing of innovative practices throughout the whole patient journey. One of the JACARDI Work Packages aims at supporting the labor participation of people living with noncommunicable diseases, particularly with CVD and DM and related risk factors, by identifying issues affecting labor participation and testing systemic and organizational solutions to improve inclusion, retention, and return to work, and support well-being at the workplace. Within the broader JACARDI objectives, this scoping review will focus specifically on CVD and DM prevention.

Considering how heterogenous working population is in terms of exposure to risk factors for CVD and DM, this scoping review will focus on blue-collar workers, a group of employees that generally includes people who perform low-complexity manual work, usually not requiring advanced qualifications or higher education [11]. Numerous studies indicate that these workers are more likely to be diagnosed with obesity, hypertension, and dyslipidemia [12,13] and are more exposed to behavioral risk factors associated with lifestyle, such as smoking, alcohol consumption, poor eating habits, and lower levels of physical activity [14,15]. For this reason, health promotion is pivotal in preventing CVD and DM and mitigating their effects. Indeed, in the case of the working-age population, workplace health promotion, understood as combined efforts of employers, employees, and society to improve the health and well-being of people at work [16], becomes a very important vehicle for change. Therefore, identifying the scope and characteristics of interventions undertaken in the workplace environment to tackle the burden of CVD and DM risk factors is a necessary first step in the way to fully exploiting the potential of the working environment to improve the population's health.

The scope of literature on health promotion interventions aimed at preventing CVD and DM in blue-collar workers is currently unknown. A preliminary search of PubMed, Scopus, Embase, and the Cochrane Database of Systematic Reviews was conducted and no current or underway systematic reviews or scoping reviews on this specific topic were identified. During the search, several cases of reviews with similar topics were found that differ from this scoping review due to their reference to the general population of employees [17-21] or their focus on one type of intervention (ie, behavioral interventions) or disregarding "diabetes" as a keyword [17,21,22].

Providing a critical review of specific workplace health interventions targeting blue-collar workers can help stakeholders identify which actions can be rolled out to prevent CVD and DM in workplace settings. For these reasons, the objective of this scoping review is to assess the extent and characteristics of workplace health promotion interventions aimed at preventing CVD, DM, and their risk factors in blue-collar workers, consistent with JACARDI's objectives. The ultimate aim is to provide a comprehensive overview of the most frequently implemented interventions and prevention strategies in addressing the risk factors for CVD and DM and to examine potential variations in intervention approaches across different geographical settings and sectors.

Methods

Overview

This scoping review will be conducted in accordance with the JBI methodology for scoping reviews [23] and will be reported following the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist [24]. The identification and the examination of the research question is based on the Participant, Concept, Context (PCC) framework. This scoping review was registered on Open Science Framework. The planned study period is May 2024 to September 2025.

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Participants

This review will include studies that involve adult (aged ≥18 years) blue-collar workers (with jobs listed by the International Labor Organization under codes 6, 7, 8, and 9) who are currently active in the labor setting. In case of mixed study groups including blue-collar, white-collar, and pink-collar workers, we will include a study when blue-collar workers constitute at least 60% of participants. Studies where the proportion of blue-collar workers is impossible to determine will also be excluded. Studies involving retired or sick workers or unemployed persons will be excluded.

Concept

This scoping review will focus on health promotion interventions that target CVD and DM disease or their risk factors (ie, hypertension, dysglycemia, dyslipidemia, overweight and obesity, smoking, alcohol, physical inactivity, and unhealthy diet including insufficient consumption of fruits and vegetables) [7,25]. We are interested in studies focusing on the evaluation of the results or the methodology of the following health promotion interventions: (1) health education, (2) prevention of risk factors and diseases or elimination of exposures (primary prevention), (3) disease or risk factor detection or screening (secondary prevention), and (4) health policy changes (eg, changes in infrastructure). We will consider health promotion interventions that entail both voluntary and compulsory participation.

We will exclude studies that report the context of an intervention (without direct connection to intervention results or the methodology), and those that report interventions primarily focusing on: (1) mental health (eg, stress, burnout, and depression), (2) musculoskeletal problems, (3) sun or skin protection, (4) violence or harassment prevention, (5) infections (vaccination and hygienic behaviors), (6) sexual behaviors, and (7) pollution.

Context

This review will consider studies that involve health promotion interventions carried out or initiated in workplaces among blue-collar workers. The review will not be limited to any specific country or work setting.

Types of Evidence

This scoping review will consider empirical studies describing interventions that present quantitative, qualitative, or mixed-method results. Both experimental and quasi-experimental study designs including randomized controlled trials, nonrandomized controlled trials, before and after studies, and interrupted time-series studies will be eligible. Qualitative studies will be considered including, but not limited to, designs such as ethnography and action research, provided they involve an intervention with measurable results.

Studies published in English, Spanish, Italian, or Polish will be included, as these are the languages the participating researchers are proficient in. Additionally, to cover the last 10 years of literature and limit variations in technology availability, only studies published since 2014 will be considered.

A summary of the eligibility criteria is reported in Table 1.

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Table 1. Eligibility criteria.

Category	Criteria
Participants	
Include	• Blue-collar workers (ILO[a] codes 6, 7, 8, and 9). • Adults (aged ≥18 years). • Current active workers. • In mixed study groups including blue-collar, white-collar, and pink-collar workers, only those where blue-collar workers constitute at least 60% of participants.
Exclude	• Retired workers. • Workers on sick leave. • Unemployed individuals.
Concept	
Include	• A past or ongoing health promotion intervention targeting CVD[b] and DM[c] or their risk factors (ie, hypertension, dysglycemia, dyslipidemia, overweight and obesity, smoking, alcohol, physical inactivity, and unhealthy diet). • Interventions including health education, prevention of risk factors and disease, elimination of exposures, screening, and health policy changes.
Exclude	• Studies focused on the context of an intervention (not directly connected to intervention results or methodology). • Interventions primarily focusing on mental health (stress, burnout, and depression), musculoskeletal problems, sun or skin protection, violence or harassment prevention, infections (vaccination and hygienic behaviors), sexual behaviors, and pollution.
Context	
Include	• Workplace health interventions (taking place at the workplace or initiated at the workplace but performed outside).
Exclude	__[d]
Study characteristics	
Include	• Empirical studies (quantitative, qualitative, and mixed-method studies). • Original research. • Articles, books, reports, and grey literature. • Published online and free to access. • Written in English, Italian, Polish or Spanish. • Published after 2013.
Exclude	• Study protocols. • Reviews, systematic reviews, scoping reviews, and umbrella reviews.

[a]ILO: International Labor Organization.

[b]CVD: cardiovascular disease.

[c]DM: diabetes mellitus.

[d]No specific exclusions.

Search Strategy

The search strategy aims at locating published documents. A 3-step search strategy will be used in this review. First, an initial limited search of MEDLINE (PubMed) and Scopus will be undertaken to identify articles on the topic. To ensure a comprehensive search, a variety of terms associated with blue-collar occupations will be incorporated. Additionally, the International Classification of Occupations will be used to delineate jobs classified as blue-collar. Specifically, categories 6, 7, 8, and 9 will be selected based on previous reviews [26] that identified these categories as blue-collar. In addition, diverse terms describing interventions and each specific outcome of interest will be included. The search strategy will be developed through an iterative process involving the creation and testing of multiple search strings including terms with various degrees of generality. The researchers will prepare an initial list of general terms reflecting the elements of the PCC framework (eg workplace, intervention, blue-collar, and cardiovascular). Next, they will begin the search in the 2 databases using combinations of the initial terms. If any relevant publications are identified this way, their abstracts and keywords will be screened for additional terms (eg, synonyms, alternative spellings, and subgroups of the initial concepts). All terms identified in the process will be added to the relevant PCC categories and pretested in strings. The final search strings will be selected from among those yielding a manageable number of results with a big proportion of potentially relevant results. This means that strings that will retrieve approximately 200–300 records and more than 60% entries will be potentially relevant upon title and abstract screening and kept. This threshold is intended to ensure feasibility while preserving

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comprehensiveness. Finally, the full search strategy will be adapted for each of the included databases: MEDLINE (PubMed), Scopus, Embase, and Cochrane Library (Cochrane CENTRAL). The final search string will be formulated to ensure that the included terms are located specifically within the title or abstract fields. As an example, the search keywords applied to the Embase Database on June 6, 2024, are reported in Textbox 1.

To ensure a comprehensive review of relevant sources not indexed in traditional databases, we will incorporate sources of grey literature, encompassing international organizations such as the World Health Organization, the European Agency for Safety and Health at Work, and the National Institute for Health and Care Excellence. We will also look for relevant national resources from Poland, Italy, and Spain, which are the countries of the researchers carrying out this scoping review and involved in JACARDI. These include governmental and institutional databases on health, labor, and occupational safety, such as the Polish National Institute of Occupational Health, the Italian Ministry of Labor, and the Spanish National Institute of Health and Safety at Work. If any relevant search terms are identified in these sources, they will be added to the search strings pretested in the 4 academic databases.

Textbox 1. Search keywords applied to the Embase Database on June 6, 2024.

1. manual OR unqualified OR unskilled OR semi-skilled OR middle-skilled OR low-skilled OR low-wage OR “low wage” OR forestry OR fishery OR agricultural OR hunting OR craft OR building OR metal OR handicraft OR printing OR equipment OR electronics OR telecommunications OR “food processing” OR woodworking OR garment OR ship OR laundry OR cleaning OR mining OR construction OR manufacturing OR transport OR storage OR “food preparation” OR “street sales” OR elementary. ti,ab.
2. workers OR employees OR workforce OR staff OR personnel OR labo*rers. ti,ab.
3. 1 AND 2.
4. blue-collar OR bluecollar OR “blue collar” OR labo*rers OR wage-earn* OR gardeners OR “crop grow*” OR “animal produc*” OR “crop produc*” OR hunters OR trappers OR farmers OR fishers OR gatherers OR finishers OR painters OR cleaners OR moulders OR welders OR blacksmiths OR toolmakers OR mechanics OR repairers OR printers OR installers OR electricians OR “wood treaters” OR “cabinet-makers” OR “plant operator*” OR “machine operators” OR assemblers OR drivers OR “deck crew*” OR helpers OR “street vendors” OR “refuse workers”. ti,ab.
5. 3 OR 4.
6. workplace*, work-place OR worksite*, work-site OR “work place” OR “work site” OR occupational. ti,ab.
7. “intervention” OR “program” OR “programme” OR “project” OR “trial” OR randomi?ed OR “RCT” OR “experiment”. ti,ab.
8. health OR wellness OR well-being OR wellbeing. ti,ab.
9. 6 AND 7 AND 8.
10. whp. ti,ab.
11. 9 OR 10.
12. 5 AND 11.
13. limit 12 to original research.
14. Limit 13 to publication year from 2014 to 2024.

Study Selection

All identified citations will be collated and uploaded into Covidence systematic review software (Veritas Health Innovation), and duplicates will be removed. Then, each title and abstract will be screened by 2 independent reviewers following the inclusion criteria for the review. Potentially relevant resources will be sent to the full text analysis section, where they will be thoroughly evaluated against the inclusion criteria by 2 independent reviewers. Reasons for exclusion of sources at the full text analysis will be recorded and reported in the scoping review. Any disagreements between reviewers at each stage of the selection process will be resolved by involving a third reviewer.

A preliminary version of the PRISMA flow diagram [27] is shown in Figure 1 (checklist provided in Multimedia Appendix 1). The full version including total results of the study inclusion process will be reported in the final scoping review.

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Figure 1. Preliminary PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram.

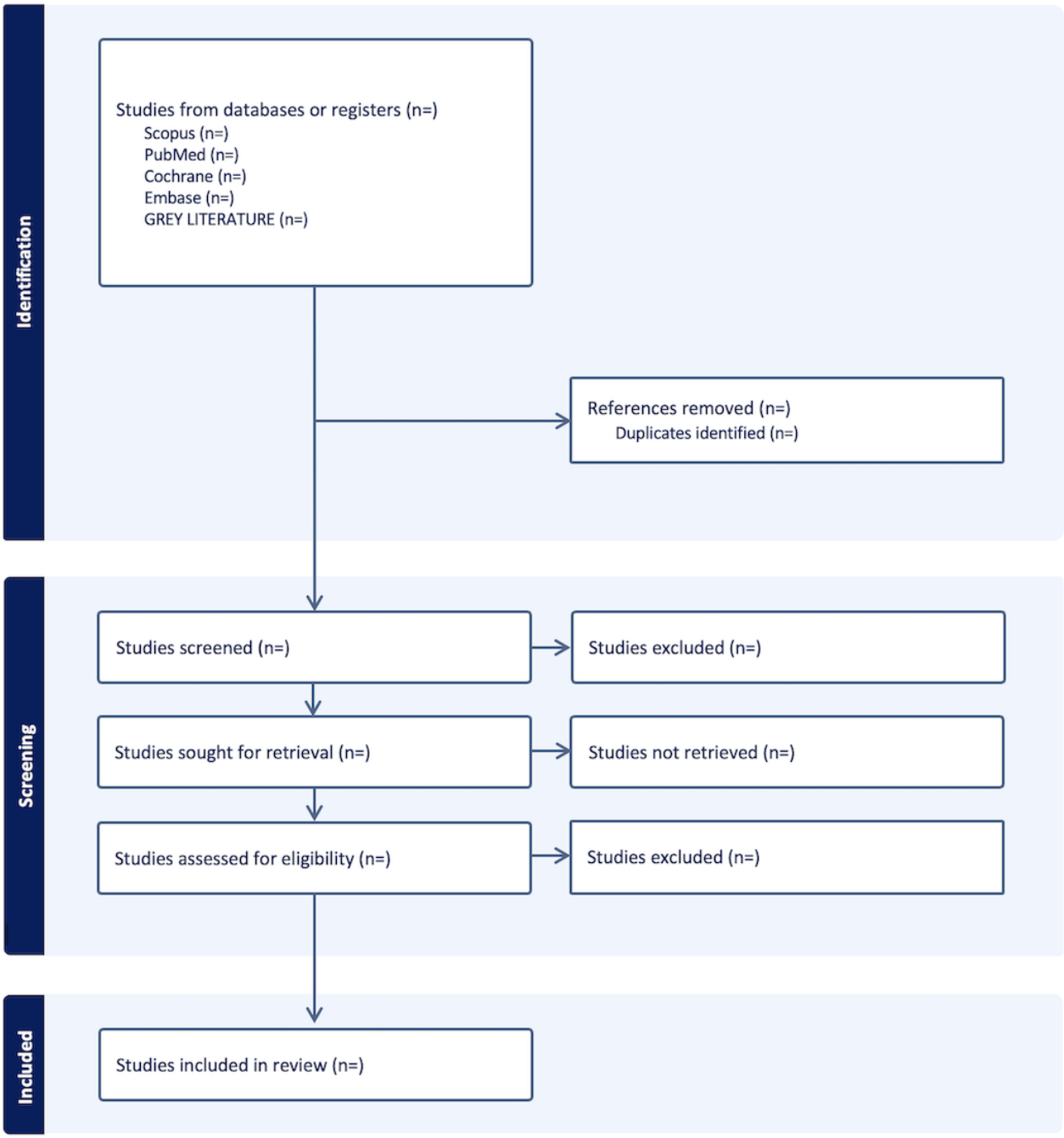

Data Extraction

Data will be extracted from papers included in the scoping review by 2 independent reviewers using a data extraction table developed in Covidence by the authors; a third reviewer will check for consistency and will resolve any disagreements. The extracted data will encompass specific information regarding the participants, concept, context, study methods, source type, type of intervention, target group, and key findings pertinent to the review question. To ensure the proper functioning and suitability of the data extraction table, an initial extraction will be conducted on 5 of the evidence sources selected and then the appropriateness of the extraction table will be discussed. The following data will be extracted:

- Authors and date
- Title
- Geographical location
- Source type
- Intervention title
- Language
- Aim
- Type of research
- Study design
- Industry
- Professions
- Targeted population
- Number of participants
- Number of blue-collar workers
- Mean age and percentage of men

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- Type of intervention
- Theoretical framework
- Diseases targeted
- Risk factors targeted
- Intervention content
- Findings

The data extraction table will be modified and revised as necessary throughout the process of extracting data from each included evidence source. Any modifications will be detailed in the scoping review.

Data Analysis and Presentation

We will use quantitative and qualitative content analysis to document the intervention characteristics, participant characteristics, and reported outcomes. The unit of the analysis will be the intervention. We will present the extracted data graphically along with a narrative summary, which will accompany the results and will describe how the results relate to the review's questions and objectives. For intervention characteristics, we will focus on type of intervention, implementation year, intervention setting, and diseases and risk factors targeted. For participant characteristics, we will focus on gender, age, and profession, whereas for the reported outcomes specifically, we will focus on the health-related changes (especially improvements) identified in blue-collar workers.

Ethical Considerations

No ethical approval is required for this scoping review since it involves the analysis of already published data. The results of this study will be published in a peer-reviewed journal and discussed at scientific conferences. A summary of the study findings will also be developed to inform the work of the pilots of the work package on labor participation of people living with noncommunicable diseases within JACARDI.

Results

The study began in March 2024 and the full scoping review report is expected to be ready in September 2025.

Discussion

This protocol outlines the methods for a scoping review aimed at mapping and thoroughly describing health promotion interventions implemented or initiated in the workplace. While the review will share its focus on blue-collar workers with a few previous studies [22,26,28,29], it will differ by embracing all kinds of workplace interventions and by limiting its scope to those targeting CVD, DM, and their risk factors. The review will provide an insight into which risk factors and diseases are more frequently targeted, as well as which strategies are more frequently implemented. Moreover, it will highlight potential heterogeneity in interventions carried out in different geographical locations or in different sectors. This will be useful to guide pilots within JACARDI and to provide policymakers and companies with a better understanding of potential interventions for CVD and DM prevention.

The scoping review has some potential limitations. First, the review will be restricted to publications in English, Italian, Spanish and Polish, reflecting the languages spoken by the research team. This might result in underrepresentation of studies from other countries, notably from studies carried out in Asia, Africa, or South America. Moreover, by excluding interventions targeting mental health and musculoskeletal disorders, we may have missed integrated health promotion programs common in blue-collar workplaces. A quality assessment of the studies included is not planned as part of the scoping review. Although it might provide interesting information, it is beyond the scope of this study, which aims to describe the scope and content of the interventions described in the studies.

Despite the increasing implementation of workplace health promotion programs, there is currently a lack of synthesized evidence on their scope, characteristics, and effectiveness for this specific workforce. Given the significant burden of CVD and DM on public health and the global economy, it is crucial to better understand how occupational interventions can reduce these risks in vulnerable working populations. The scoping review can contribute to filling the knowledge gap by mapping the current state of workplace health promotion interventions aimed at preventing CVD and DM and modifying relevant risk factors in the blue-collar worker group.

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Authors' Contributions

EC and AL contributed to the conception and design of the work. AL, EC, KK, PR, CDG, MF, GB-M, CM-A, AA-Á, and DBB collaboratively developed the protocol and the search strategy. CDG, MF, FT, KK, AA-Á, and AL drafted the primary text. All authors reviewed the manuscript and agreed to the published version of the manuscript. EC is the guarantor.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Preliminary PRISMA-ScR checklist.
[DOCX File , 25 KB - resprot_v14i1e74248_app1.docx]

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Abbreviations

CVD: cardiovascular diseases
DM: diabetes mellitus
JBI: Joanna Briggs Institute
PCC: Participant, Concept, Context framework
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses

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Protocol

Time for Clarity in Exploring the Evidence and Key Concepts of Human-Centered Design in Digital Health Care: Protocol for a Scoping Review

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Abstract

Background: Human-centered design (HCD) methodologies such as design thinking (DT), user-centered design, cocreation, and participatory design (PD) have been adopted to facilitate user and stakeholder involvement in the development of eHealth applications. However, there is frequent confusion around these methodologies, leading to the fragmentation of the discourse and limited integration opportunities. The absence of an empirically grounded framework for HCD limits research and theoretical consensus, particularly in the highly regulated context of eHealth solution development. For this scoping review, the term HCD will be used as an umbrella term, under which the terms user-centered design, patient-centered design, cocreation, co-design, PD, and DT will be used in this protocol.

Objective: In this paper, we describe a protocol for a scoping review that aims to explore and analyze the scope, definitions, key concepts, and motivations reported in peer-reviewed studies that have applied stakeholder engagement methods such as HCD, PD, or DT in developing eHealth applications.

Methods: A team of 3 reviewers will conduct this scoping review to identify and synthesize key concepts at the intersection of HCD methodologies and their application to the development of eHealth applications. We will follow the Joanna Briggs Institute methodology for scoping reviews and the guidelines for conducting systematic mapping studies in software engineering. The reporting of the results will be guided by the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) extension. This review will include only primary studies reporting on the experience, challenges, and applicability of HCD for the design and development of eHealth applications, identified through the PubMed, IEEE Xplore, Web of Science, Scopus, PsycINFO, CINAHL, and ACM Digital Library databases, and limited to articles from the past 10 years.

Results: A preliminary search applying the search strategy resulted in 826 records. The search was initiated in March 2025. Title and abstract screening will conclude by mid-2025, followed by full-text screening, data extraction, and analysis in the second half of 2025. Results are expected to be submitted for publication in the first half of 2026.

Conclusions: This protocol describes a systematic approach for conducting a scoping literature review, aimed at synthesizing definitions, concepts, and methodologies related to HCD in eHealth application development. This review aims to identify research gaps and trends to guide the future of mobile health innovation, with a focus on improving adoption and long-term sustainability, particularly from the perspective of technologies for vulnerable populations.

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KEYWORDS

patient-centric health care; user experience; user interface; usability; mobile health; mHealth human-centered design; design thinking; scoping review; participatory design; generative artificial intelligence; GenAI

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Introduction

Background

According to a report by the Institute of Medicine, today's health providers have access to more research findings and more technology than ever before. However, there are serious concerns about the inadequate quality of health care, driven by four key factors: (1) the growing complexity of science and technology, (2) the increase in prevalence of chronic conditions as people live longer, (3) a decentralized, inefficient health care delivery system, and (4) challenges in leveraging information technology, as patients increasingly seek health-related information and advice online [1]. Human-centricity, which emphasizes health care solutions that are humane and respectful of the needs and preferences of individuals, is 1 of 6 key factors needed to close this quality gap in the new era of health care [1].

Adoption of eHealth Solutions

When developed correctly, eHealth applications can facilitate self-care promotion, enable informed decision-making, foster patient engagement and empowerment, and ultimately improve patients' satisfaction and health outcomes [2,3]. eHealth solutions entail various digital technologies for health management and care and may include telehealth applications, such as videoconferencing for medical consultations; electronic health records for storing, managing, and accessing patient health information; mobile health (mHealth) apps, such as medication reminders, diabetes self-management, mental health apps, and artificial intelligence (AI) algorithms [4,5].

Despite their potential, the rapid and costly development of digital health technologies frequently leaves no space for user involvement in the design process, leading to solutions that fail to address real-world needs [6,7]. Consequently, low adoption rates result in significant technological waste [8-12].

Moreover, patient expectations for eHealth solutions are very high, as users expect these applications to provide a similar user experience to their shopping, messaging, or banking solutions. However, the low adoption rates demonstrate that eHealth applications still have a steep path ahead [11]. Similarly, health care professionals expect eHealth applications to integrate into their workflow easily, allowing more time for patient care [12]. In reality, many health care professionals spend large amounts of their time working with IT systems that do not add value to the quality of care [13,14].

Methods for Stakeholder Engagement: Design Thinking, Human-Centered Design, and Participatory Design

The importance of human-centricity—placing patients, caregivers, and health care professionals (ie, physicians, nurses, and other medical staff) at the heart of the development process [15-17] to truly meet their needs and expectations—is acknowledged but rarely applied to eHealth applications [18]. Methods such as human-centered design (HCD), design thinking (DT), cocreation, and participatory design (PD) have been adopted in other industries to address this issue by helping software developers incorporate the needs, experiences, and feedback of end users and stakeholders in the development process of digital applications in general. A recent systematic literature review by An et al [19] reported studies of eHealth applications comparing traditional interventions to HCD interventions, where the latter showed greater satisfaction, usability, and effectiveness.

HCD Approach

The term HCD has been defined in the International Organization for Standardization (ISO) standard 9241–220 as an approach to systems design and development that aims to make interactive systems more usable by focusing on the understanding of interactions among humans and other elements of a system to optimize human well-being and overall system performance [20]. The term *HCD* goes beyond *user-centered design (UCD)* to foster the involvement of other stakeholders, not only those typically considered users, throughout design and development activities [6,21].

DT Methodology

The DT methodology is an iterative, nonlinear, and human-centered method that helps incorporate users' needs and feedback throughout the development process. DT has been recognized as a problem-solving methodology and a driver of innovation and change [22-25]. According to Stanford school, the 5 phases of the process are empathy, define, ideate, prototype, and test [26].

On a practical level, DT has been interpreted as a trilogy of interlinked modes: (1) a process with a sequence of steps, (2) a toolbox with a collection of methods, and (3) a mindset with a set of human-centered principles [27,28].

Over the last 40 years, researchers at Stanford University have studied this methodology, which has spread to other universities, such as Aalto (Finland), Potsdam (Germany), and St Gallen (Switzerland). It has been adopted in the private sector across many industries such as business, fintech, hospitality, education, and aviation, to solve complex problems [22,29,30]. Examples of adopters are major companies such as Deutsche Bank, Procter & Gamble, Google, Apple, and SAP [18]. More recently, DT has emerged as a critical tool to drive innovation in health care [5,6,19,22,31-35]; however, when considering the scope of all ongoing research, development, and innovation in health care, DT has been applied sparsely [12,20].

Cocreation and Co-Design

A core principle of DT is radical collaboration, also known as cocreation, which emphasizes trust-building within design teams and among stakeholders, ensuring that all participants actively contribute and learn from one another throughout the design process [36,37]. This principle relies on flexibility in thinking, creativity, and openness to new ideas and perspectives [38].

PD Approach

PD has been defined as a human-centric approach to technology development guided by the enhancement of workplace democracy, mutual learning, and empowerment [12], and as a toolbox for engaging users to deliver better products [24]. The principles of stakeholder participation are aligned with

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participatory ergonomics and other PD methods, such as experience-based design [39].

A Wicked Problem

The DT method has been criticized for lacking theoretical and methodological rigor [24,40,41]. The literature often presents DT as vague and sometimes ambiguous [42] or as "a practice rather than a precise science" [43]. Other descriptions and theoretical foundations provide a more specific definition of DT as a methodology suited for use in broad and multidisciplinary settings [23,25,44-52]. Furthermore, there is often confusion between DT, HCD, UCD, PD, patient-centered design, gamification, and agile methods [30], which leads to the fragmentation of the discourse and missing opportunities for integration. The absence of an empirically grounded framework for HCD limits research and theoretical consensus, particularly in the highly regulated context of the development of eHealth applications [23,53-55].

Several studies report (1) the lack of coherent evidence- and theory-driven methodologies that promote user and stakeholder involvement in the development process of eHealth applications [5,21-24] and (2) the need for more cocreation between vendors and stakeholders in the development process of eHealth applications [56,57]. These 2 conditions are paramount factors for adoption. They highlight the need to clarify the key concepts and key characteristics related to the methods promoting human-centricity and stakeholder engagement.

HCD methodologies can be particularly valuable in the context of eHealth applications, and their use is expected to increase, as they ensure that the software solutions are not only technically robust but also focused on user needs and real-world contexts, leading to more effective and widely adopted developments [19,22,34]. Conversely, the overall understanding and specific steps on how the HCD processes are applied in complex and highly regulated environments, such as digital health care, remain underexplored. Furthermore, the empirical evidence on the application of the methods within the eHealth sector is surprisingly limited in comparison to other industries [5,58,59], especially concerning solutions for vulnerable patient groups [60].

Goal of This Review

This scoping review will act as a stepping stone in developing a methodological framework by (1) characterizing the extent to which primary studies reported in peer-reviewed articles that are publicly available in the literature have adopted HCD for the development of eHealth applications and (2) mapping the quantitative and qualitative evidence to shed light on the methods, tools, and principles that have been used in the context of HCD approaches to inform the development of eHealth applications.

Our goal with this review is to reduce ambiguity around the concepts of HCD in the context of the software development of digital health applications and to empower researchers to develop solutions that place the needs of users and stakeholders at the forefront instead of being "lost in translation" amid the confusion of the terms, while maintaining compliance.

Review Questions

Guided by the ultimate goal of creating a methodological framework, this review explores *what key concepts and instruments of HCD are available and how they are being applied in the context of the software development of eHealth applications*. This high-level question is broken down into 4 specific review questions (Table 1).

Table 1. Review questions (RQs).

RQs	Subquestions
RQ1. Concept: what is HCD[a]?	Which theoretical frameworks, key concepts, and terms of HCD have been used in the reported studies?
RQ2. Process: in what ways is HCD being used?	Which HCD tools, processes, and mindsets have been applied in the studies, and what approaches have been used to evaluate the application of HCD methodologies?
RQ3. Motivation: why is HCD applied?	Why do teams choose HCD methodologies over other methodologies?
RQ4. General: where, when, and who is applying the method?	In which geographical locations (based on author affiliation and domains of health care) have the studies applying the HCD methodologies been published?

[a]HCD: human-centered design.

Methods

Overview

We have chosen to conduct a scoping review of the literature, which is a systematic and effective method for identifying and synthesizing key concepts and methods in the literature on a given topic, with the purpose of summarizing and mapping the available evidence. Unlike traditional systematic reviews, scoping reviews do not aim to produce a critical appraisal of the literature but rather to provide an overview or map of the available evidence [61].

This scoping review will follow the Joanna Briggs Institute methodology for scoping reviews [62] and the guidelines for conducting systematic mapping studies in software engineering [63]. This protocol consists of 5 stages: (1) defining the review question; (2) identifying relevant studies or developing a search strategy; (3) study screening and selection; (4) extracting and charting the data from the studies included; and (5) collating, summarizing, and reporting the data.

The reporting of the results will be guided by the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews).

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Search Strategy

The studies will be identified initially through searches of the following 7 online databases: PubMed, IEEE Xplore, the Web of Science Core Collection, Scopus, APA PsycINFO, CINAHL, and the ACM Digital Library. These databases were considered because they cover the technical and clinical literature, as well as aspects such as psychology, design, human-computer interaction (HCI), and implementation science, reflecting the multidisciplinary nature of the literature.

Key concepts and domains were identified based on a preliminary literature review of key articles known to the authors. The keywords contained in the abstracts and titles led to several search terms that were clustered into three main themes, following the concept and context outlined in the inclusion criteria: (1) HCD, (2) eHealth, and (3) technology and development. The related key concepts for the 3 themes are presented in Table 2. These key terms will serve as the basis for the search in each of the databases.

Table 2. Search strategy and key terms.

Domain and context	Search strings[a]	Controlled terms
Human-centered design	(“Design Thinking” OR “Human Centered Design” OR “User Centered Design”[MeSH[b]] OR “Co-design” OR “Participatory Design” OR “Service Design”)	“User-Centered Design”[MeSH]
eHealth	(“eHealth” OR “telemedicine” [MeSH] OR “mHealth” OR “Health Informatics” [MeSH] OR “digital health” OR “remote monitoring”)	“Telemedicine” [MeSH]; “Health Informatics” [MeSH]; “Digital Health” [MeSH]
Technology and development	(“Software Design” [MeSH] OR “User Experience” OR “technology development” OR “user requirements” OR “Digital Technology” [MeSH]	“Digital Technology” [MeSH]; “Software Design” [MeSH]

[a]All domain search strings were combined using the Boolean operator AND.

[b]MeSH: Medical Subject Headings.

The search terms have been tested term by term for relevance and performance in PubMed. We tested the search results by adding and removing search terms to identify the most relevant ones, observing the number of results added by a specific term to the results, and determining the versions of the search that should be moved forward for relative recall testing. Terms that did not add any unique results were removed to streamline the search terms.

For additional validation, different versions of the search strategy were created to test the performance of a broad versus narrow interpretation of the terminology and the best-suited PubMed field tags (eg, [ti], [tiab], [tw]). Ultimately, each search term was tested multiple times to determine the types of studies returned before being included in the final search terms. The final search string has been peer reviewed by a librarian.

Due to time and resource limitations, articles will not be screened for additional studies (snowballing). The search will be limited to the last 10 years of publication.

Inclusion Criteria

Population

No restrictions are applied to participants in this scoping review.

Concept

The object of this scoping review will be the exploration of HCD methodologies, with a focus on DT as a methodology to design, develop, describe, report, or document experiences during the software development of eHealth applications. Articles will be included if two premises are fulfilled: (1) the research article has the main focus on conceptualizing HCD methodologies, either through definition, descriptive methods, attributes, or relationships, and (2) the concepts are used in relation to the development of software applications in the area of eHealth, medical informatics, and digital health care.

Context

The studies considered for this review will include studies in all health care settings and areas of medicine in the private or public sector, as long as the eHealth applications are intended for medical purposes, such as diagnosis, prevention, monitoring, therapy, or rehabilitation. However, studies reporting on the development of programs or education in the broader sense of health care will not be included in the review.

Types of Evidence Sources

This review will include all peer-reviewed primary research articles that apply and report on the application of HCD and methods that have used the HCD methodology for eHealth applications. The review will not include any peer-reviewed methodology articles, literature reviews, meta-analyses, guidelines, or opinion articles reporting on HCD.

Furthermore, articles published between 2015 and 2025 in English, Spanish, and German will be included, as LM is fluent in these languages. An overview of the inclusion and exclusion criteria is provided in Textbox 1.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Peer-reviewed articles, including conference proceedings, published in open-access journals or journals accessible to the author
- Primary studies or empirical studies reporting on experiences, challenges, applicability of human-centered design (HCD) for the design and development of eHealth applications
- Written in English, German, or Spanish
- Published between 2015 and 2025

Exclusion criteria

- No abstract available
- No full text available
- Published in a language other than German, English, or Spanish
- Literature reviews, methodological articles, opinion articles, theoretical articles, or meta-analyses
- Studies already evaluated in one of the reviewed articles (duplicates)
- Studies in which HCD is not mentioned in the title or abstract, not conceptualized, not clearly operationalized, or lacking a theoretical underpinning
- Not relevant to medical informatics or digital health

Study Screening and Selection

On the basis of the inclusion criteria in Textbox 1, all retrieved articles will be organized using the bibliographic reference management software Zotero, and any duplicates will be removed. Zotero will be used for the initial screening of titles and abstracts. Selected articles will be imported into the software for qualitative and mixed methods analysis, and MaxQDA [63] will be used for full-text analysis.

To limit the risk of selection bias and interpretation bias, we will use a triangulation approach in which 3 reviewers will be involved in the screening and adjudication process. Two reviewers, 1 human and 1 AI robot screener (Nested Knowledge [64]), will independently screen the data. The AI robot screener (second reviewer) will be trained with a set of 50% of the records to ensure accuracy. A third reviewer (a human expert in medical informatics) will compare the robot screening results to the screening decisions of the first reviewer (human) and will adjudicate any conflicts.

As an additional layer to limit interpretative bias, the third reviewer will randomly select 30% of the included studies for an additional independent review of the screening process, ensuring consistency and reliability in data extraction. In case of disagreement, the corresponding article will be reviewed by a fourth reviewer (an expert in medical informatics), who will act as a mediator.

Careful record keeping will be maintained through a standardized screening table documenting reasons for rejection, which will be used by all authors to minimize potential bias and allow for transparency. This table will be made publicly available as part of the results publication. Reasons for exclusion of the full-text articles will be documented and reported in the scoping review in a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram. To ensure consistent and accurate assessments and the performance of the AI model, statistical parameters such as interrater reliability, recall, and accuracy will be evaluated and reported.

Data Extraction and Charting

A data charting table, including general study characteristics and variables related to the concept, context, review questions, and key concepts, will be included in the review.

To validate the completeness and accuracy of the data charting table, a pilot extraction process will be conducted for 10 of the selected articles. The data will be extracted in parallel by the 2 human reviewers, and any uncertainties that arise will be discussed. If necessary, the data charting table will be adjusted accordingly.

After validating the data charting table, the full charting of the data will be done by 1 reviewer with random quality checks by the second reviewer, who will review 30% of randomly selected articles and compare them to the results obtained by the first reviewer to ensure consistency. Any uncertainties or disagreements will be discussed between the 2 reviewers until consensus is reached. If a decision cannot be made, a third reviewer will act as a mediator. The data charting table will be made publicly available as part of the results publication.

On the basis of the prereviewed literature and acknowledging the ambiguity surrounding HCD terminology, the authors will adopt a deductive approach, deriving subcodes from the selected studies and structuring them within a framework. The main codes will be generated inductively, aligned with the predefined review questions (Table 1). Careful record keeping will be supported through the standardized charting table, which will be used by all authors to minimize potential bias.

Examples of items to be included in the data charting table are: (1) general characteristics of the study (eg title, year, and country), (2) concept (terms and theories used in connection with HCD in the reported studies), (3) process (tools, mindset and life cycle of HCD applied in the reported studies), (4) motivation (why teams choose HCD methodologies over other

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methodologies); and (5) evaluation (which practices have been used to evaluate the application of HCD methods in the reported studies)

Data Collating, Summarizing, and Reporting

This review will follow a mixed methods approach. The data will be analyzed using descriptive statistics for all quantitative data items, such as sample size, sample demographics, and the methodological approach. The data items of a qualitative nature will be analyzed using the methodology developed by Mayring for qualitative content analysis, which aims to systematically code and organize the data based on a structured coding framework consisting of categories that can be generated deductively and inductively [64].

The information for each extracted field will be tabulated, grouped by themes and subthemes, and illustrated visually. To create a compelling presentation of the findings, the data will be available in tabular form, accompanied by graphic visualizations in the form of evidence maps where possible, and a narrative summary.

Results

A preliminary search applying the key terms (Table 2) in all 7 databases resulted in 826 records. The search was initiated in March 2025. Title and abstract screening will conclude by mid-2025, followed by full-text screening, data extraction, and analysis in the second half of 2025. The results are expected to be submitted for publication in the first half of 2026.

Discussion

Anticipated Findings

This protocol outlines a systematic approach for conducting a rigorous scoping literature review, aimed at summarizing the current evidence in the form of evidence maps, helping readers identify where evidence exists and where gaps remain, and understanding the terms, definitions, and methodologies of HCD and related participatory approaches in the development of eHealth technologies. This knowledge may help reduce confusion, facilitate interdisciplinary collaboration, and support the implementation of HCD methodologies.

We anticipate identifying patterns in how these methodologies are applied across different phases of the development process, target populations, and health domains. A particular focus will be placed on understanding whether and how these methods are used in the context of vulnerable or underserved populations, such as children, older adults, or individuals with cognitive or mental health conditions.

We expect to identify research gaps and trends that will inform the current and future development of mHealth technologies to enhance their adoption and sustainability.

Comparison to Prior Work

Several studies have examined the role of HCD and other stakeholder engagement methodologies in health care. Kauppinen et al [5] investigated the potential of HCD to enhance the benefits of health care software projects; the results of this review are pending. Jacob et al [65] synthesized the literature on patient adoption of health applications, emphasizing the importance of sociotechnical factors, inclusive design, integration into the patient journey, and comprehensive education and support. Leary et al [38] reported that clinical providers should be proficient in DT to create effective health interventions, noting inconsistencies in its application. Nimmanterdwong et al [66] demonstrated that HCD can yield positive outcomes for older adults while highlighting the need for more rigorous, goal-oriented studies in mHealth for this population. Altman et al [22] found HCD-based interventions to be more usable and effective than conventional approaches, showing that methodological and quality limitations are barriers to their implementation. An et al [19] found that DT can produce usable, acceptable, and effective mHealth applications and recommended standardizing HCD practices to improve sustainability and integration into development processes.

In summary, this scoping literature review builds on previous research by exploring how HCD methodologies have been implemented to develop eHealth applications. While earlier work in the field often focused on a single methodology or specific health condition or technology, few studies have offered a comprehensive overview of the diverse HCD-related approaches used in eHealth. Our review adopts a broader methodological spectrum, encompassing UCD, patient-centered design, cocreation, co-design, PD, and DT. Furthermore, by including work from multiple disciplines, such as health informatics, HCI, and implementation science, we aim to complement the existing literature by identifying both common practices and underexplored areas in the design of human-centered digital health solutions.

Strengths and Limitations

A key strength of this protocol is the use of a comprehensive and interdisciplinary search strategy, incorporating both controlled vocabulary (eg, Medical Subject Headings [MeSH] terms) and free-text keywords across multiple databases spanning health, psychology, and computer science. Despite efforts to balance sensitivity and precision, the broad scope of terms such as “technology,” “DT” [50,52] or “user experience” may result in the inclusion of studies only marginally relevant to HCD in eHealth.

One limitation of this study is that, as with all scoping reviews, the lack of methodological quality appraisal may limit the ability to make definitive claims about the effectiveness of specific approaches. In addition, due to time constraints, backward and forward citation tracking will not be performed.

LM will lead the data collection and analysis processes, is trilingual in Spanish, English, and German, and self-identified at the time of drafting this manuscript as a woman and an ethnic minority scholar of Latin American origin living in Germany. BS self-identified as a Caucasian male born and raised in Germany; he speaks German, English, Swedish, and French; and contributed to refining the theoretical framework. LM and BS contributed to conceptualizing the study. However, it is likely that our backgrounds may influence the interpretations of the data. To minimize this bias, LM and BS will make efforts to take notes on all preconceptions that arise during study

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inclusion in order to limit these existing assumptions during the data collection and analysis processes.

Future Directions

The findings of this scoping review may inform the development of best practice guidelines for researchers and practitioners seeking to apply HCD methods in digital health. They may also point to the need for greater methodological transparency and interdisciplinary collaboration in this domain. We expect that this review will highlight important gaps in current research, such as the limited inclusion of vulnerable populations in co-design processes or the inconsistent reporting of HCD methods. This paper is part of a larger research project, and more specific research activities will be described in separate papers.

Dissemination Plans

We plan to disseminate the final results through multiple channels. In addition to submitting the findings for open-access publication in a peer-reviewed journal, we will present the results at relevant conferences in digital health, HCI, and implementation research. The findings will also be shared with design and clinical stakeholders through webinars, workshops, and summaries tailored to practice-oriented audiences.

Data Availability

Data sharing is not applicable to this study as no datasets were generated or analyzed during the preparation of this manuscript.

Authors' Contributions

BB, BS, and LM contributed to the conceptualization, study design, and methodology. BS provided supervision. BS and LM drafted the original manuscript. BS and LM also contributed to writing, reviewing, and editing.

Conflicts of Interest

None declared.

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Abbreviations

AI: artificial intelligence
DT: design thinking
HCD: human-centered design
HCI: human-computer interaction
ISO: International Organization for Standardization
MeSH: Medical Subject Headings
mHealth: mobile health
PD: participatory design
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
UCD: user-centered design

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Protocol

Facilitators of and Barriers to Resilience Among Black Children and Youth in Canada and the United States: Protocol for a Scoping Review

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Abstract

Background: Black children and youth disproportionately experience systemic discrimination, racism, stereotypes, and academic streaming, which negatively affect their well-being. Although they often demonstrate high aspirations and resilience, dominant narratives remain deficit-based, emphasizing challenges over strengths. The limited research on resilience among Black children and youth in Canada restricts the development of informed policy and future scholarship.

Objective: This scoping review aims to identify, describe, and synthesize existing evidence on the facilitators of and barriers to resilience among Black children and youth in Canada and the United States. Given the shared histories of anti-Black racism and similarly structured systems, such as education, health care, and child welfare, the scope of this study extends to the United States to offer relevant insights that can help inform policy, practice, and future research in both contexts.

Methods: This review will be guided by a methodological framework for scoping reviews proposed by Arksey and O'Malley and advanced by Levac and colleagues. We searched 4 multidisciplinary electronic databases (CINAHL, Ovid MEDLINE, ERIC, and PsycINFO) for relevant reports. The Thesis and ProQuest Dissertations and Theses Global database will also be searched for unpublished student theses and dissertations. Two independent researchers will complete the screening process. Using the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines, the findings will be synthesized quantitatively and qualitatively through thematic analysis.

Results: Data screening is ongoing and will be followed by data extraction, analysis, and the drafting of the final manuscript for peer-reviewed publication.

Conclusions: This scoping review will generate critical insights into the multifaceted factors that support or hinder resilience among Black children and youth in Canada and the United States. By centering intersectionality and community-engaged approaches, the findings will inform equity-oriented policies, culturally responsive practices, and future research that amplifies the strengths of Black young people. Ultimately, this scoping review will contribute to disrupting systemic inequities and supporting the flourishing of Black children and youth across diverse contexts.

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KEYWORDS

Black children and youth; resilience; Canada; United States; well-being

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Introduction

Background

Black children and youth disproportionately encounter systemic discrimination, racism, stereotypes, and academic streaming [1-3], which are challenges that lead to disparities in education, health, and economic opportunity. These disparities include low educational attainment, overrepresentation in the criminal justice system and welfare system, and poor physical and mental health [4-6]. Collectively, these negative outcomes reinforce persistent socioeconomic disparities between Black youth and their peers from other racial and ethnic backgrounds.

Despite these challenges, research shows that Black children and youth often hold high aspirations for their future [7,8]. However, systemic discrimination and racism can hinder their ability to pursue and realize these goals. One study found that students belonging to visible racial or ethnic minority groups were more likely to aspire to attend a university compared to their peers belonging to nonvisible racial or ethnic minority groups [9], a finding that has been replicated in other studies [10]. Even as they strive to achieve their aspirations, Black children and youth are often subjected to deficit-based narratives that reinforce negative stereotypes [8,11].

In response to these barriers and challenges, many Black children and youth engage in strategies that foster resilience, which is the capacity to thrive amid adversity [12]. Resilience has been conceptualized in multiple ways, including the ability to access and effectively use psychological, social, cultural, and physical resources [13] as well as a set of interconnected processes between individuals and systems that enable the use of these resources to achieve positive outcomes [14]. These conceptualizations align with the biopsychosocial model of human development proposed by Bronfenbrenner [15]. While some of the definitions mentioned earlier emphasize individual capacities, others highlight the systemic and relational processes involved in fostering resilience. For this study, we define resilience in Black children and youth as (1) a dynamic process; (2) a set of capacities; and (3) a range of outcomes that enable them to adapt, cope, and flourish despite ongoing exposure to systemic adversity. This highlights the role of cultural identity, community support, and lived experience in shaping how resilience is expressed and sustained among Black children and youth.

Although there is a growing body of research focused on the experiences of Black children and youth in Canada and the United States [10,16-18], targeted studies on resilience remain relatively sparse. In the Canadian context, especially, there is a notable lack of synthesized evidence on the factors that support or hinder resilience. While recent reviews have explored mental health and general health among Black youth [19-21], these studies represent only a subset of the broader social, structural, and cultural conditions shaping resilience. On the basis of a preliminary review of the literature and to the best of our knowledge, no existing literature, no existing literature reviews have systematically examined the factors influencing resilience among Black youth in Canada. This represents a critical gap. Accordingly, this review aims to fill that gap by synthesizing evidence on the complex and intersecting dynamics that shape resilience in this population.

Due to the limited Canadian literature, we expand the scope of this review to include the United States, providing a broader base of evidence to inform policy, practice, and future research in both countries. While Canada and the United States differ in population size, health care systems, immigration pathways, and social policies [22-24], they share critical historical and structural features [25]. Both are settler-colonial states with enduring legacies of anti-Black racism and face parallel challenges in advancing racial equity in health, education, and social services. Their geographic proximity, common language, and history of cross-border policy exchange further support the value of reviewing literature from both contexts. In light of these contextual differences and similarities, there are opportunities to illuminate resilience processes that may be transferable or adaptable to the Canadian context.

Objectives

By examining findings from Canada and the United States while attending to their distinct systemic and cultural environments, this review aims to inform Canadian policy through both context-specific and comparative insights.

Therefore, this review aims to identify, describe, and synthesize existing evidence on the facilitators of and barriers to resilience among Black children and youth in Canada and the United States. Importantly, we recognize the heterogeneity within Black populations, including the diverse experiences of first-, second-, and later-generation migrants from continental Africa and the Caribbean as well as descendants of survivors of the trans-Atlantic slave trade [26]. While their backgrounds are varied, shared racialization and phenotypic similarities often expose them to similar patterns of discrimination and exclusion.

Methods

Theoretical Lens

This scoping review will be guided by an intersectionality-based theoretical lens, which provides a critical framework for understanding how overlapping systems of oppression, such as race, class, gender, immigration status, and age, interact to shape the lived experiences of Black children and youth [27-29]. This lens enables a more nuanced exploration of resilience by recognizing that it is shaped not only by individual or cultural factors but also by the intersections of structural and systemic inequities. By applying this approach, we will be sensitive to the complexity and diversity within Black communities, moving beyond one dimensional analyses and highlighting how multiple identities and contexts contribute to both vulnerabilities and sources of strength [30,31].

Researchers' Positionality

Our research team includes Black Ghanaian, Nigerian, and Canadian scholars with disciplinary backgrounds in nursing and health geography, representing diversity across gender and generational age. The project is supervised by a Canada Research Chair in Black and Racialized People's Health with recognized expertise in the well-being of Black children and

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youth. Two undergraduate Black and racialized youth research assistants are actively involved in the project, contributing lived experience and critical reflections that inform this study's design and focus. We have established a Black youth advisory committee for stakeholder consultation and feedback on data interpretation and synthesis. Our intersecting positionalities as racialized, migrant, and health equity scholars enable us to critically engage with the structural conditions shaping the well-being of Black youth and children. We recognize the complexities of our proximity to and distance from this population and will engage in reflexive dialogue to address how our identities and assumptions shape the research process. We reject claims to absolute objectivism and instead embrace a standpoint rooted in care, equity, and justice.

Design

This review will be guided by the methodological framework for scoping reviews proposed by Arksey and O'Malley [32] and advanced by Levac et al [33]. This framework involves five key stages: (1) formulating a research question; (2) identifying relevant studies; (3) selecting studies; (4) organizing and extracting data; and (5) compiling, summarizing, and reporting the findings.

Formulating the Research Question

The research question for this scoping review was developed in response to gaps identified in the existing literature on the well-being of Black children and youth. Specifically, we seek to answer the following research question: What individual, community, relational, and cultural factors facilitate or hinder resilience among Black children and youth in the context of systemic adversity in Canada and the United States?

Identifying Relevant Studies: Search Strategy

This scoping review will use a search strategy designed to locate both published and unpublished empirical reports. A preliminary search on relevant electronic databases (CINAHL, Anthropology Plus, Criminal Justice Abstracts, LGBTQ+ Source, MEDLINE, Health Source: Nursing/Academic Edition, and ERIC) was conducted using a search strategy on May 19, 2025 (Multimedia Appendix 1).

The research team consulted a health sciences librarian to refine the search strategy. The preliminary search revealed significant overlaps between domain-specific databases. To ensure practical feasibility and comprehensive content coverage, the initial list of databases was reduced to 4 major electronic databases. This decision was made to maintain methodological rigor while ensuring a manageable and transparent review process by prioritizing databases that offered the most comprehensive and nonredundant coverage. Specifically, CINAHL and Ovid MEDLINE were chosen for their health focus (eg, medicine, clinical sciences, public health and epidemiology, nursing, biomedical sciences, health services research, psychology and behavioral sciences, and medical education), while ERIC and PsycINFO were selected for their focus on education and psychology (eg, educational psychology, gender, sexuality, cultural studies, stress and resilience, social work, and developmental psychology). This combination ensures a robust multidisciplinary approach, as these major databases already include a significant portion of the sociological, kinesiological, and social work literature relevant to the topic. For example, MEDLINE and PsycINFO cover not only their core disciplines but also content on social phenomena and behavioral sciences, which encompasses much of the research on resilience and systemic adversity.

To minimize publication bias, the team will also search for gray literature, including unpublished theses, dissertations, and relevant nongovernmental organizations and government documents. In addition, the reference lists of included studies will be reviewed to identify any further sources. The search strategy will be rerun before the final analysis and manuscript submission to capture any newly published relevant studies for inclusion in the final report (Multimedia Appendix 2).

Selecting Studies: Inclusion and Exclusion Criteria

We will include original primary research studies with quantitative, qualitative, or mixed method designs using the population, concept, and context framework (Table 1 and Table 2) [34,35]. We will include studies conducted in English from 2000 to the present to reflect the widespread adoption of multisystemic and intersectional resilience frameworks in the 21st century and ensure the relevance of generated evidence for contemporary policy and practice, particularly following heightened awareness and advocacy around racial injustices. Excluding French and other non-English studies may limit the comprehensiveness of this scoping review. While this decision reflects practical resource constraints, we acknowledge the transnational nature of Black communities and Canada's bilingual context. Consequently, valuable perspectives, particularly from Francophone Canadians, may be missed. We will exclude nonresearch reports (eg, editorials, commentaries, and opinions). Conference abstracts will also be excluded from formal extraction, analysis, and synthesis, as inconsistencies between an abstract and the full report are common [36]. However, relevant abstracts may be examined informally to identify emerging topics, geographic trends, or shifts in research focus over time. This information may be used to inform the discussion of gaps and future research priorities.

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Table 1. Population, concept, and context (PCC) framework.

PCC element	Definition
Population	Black children and youth aged between 0 and 24 years (broadly defined to include diverse populations from continental Africa, the Caribbean, and descendants of those enslaved through the trans-Atlantic slave trade)
Concept	Resilience, which includes processes, capacities, and outcomes among Black individuals despite exposure to significant stress or hardship (Table 2)
Context	Canada and the United States

Table 2. Operationalized dimensions of resilience for study screening.[a]

Resilience dimension	Operational definition	Indicators for inclusion	Example
Process	A dynamic process of adapting to, coping with, or resisting adversity over time	Describes how Black children and youth adapt to systemic adversity; longitudinal or developmental analysis of coping or adaptation; includes mechanisms or trajectories	A study examining how Black adolescents navigate school discrimination over several years
Capacities (resilience factors)	Individual, relational, or contextual characteristics that support or promote positive adaptation in the face of adversity	Mentions protective or promotive factors such as self-efficacy, cultural identity, community support, family cohesion, mentorship, and religious or spiritual beliefs	A study exploring the role of Black cultural identity in coping with racial profiling
Outcomes	Observable behavioral, psychological, developmental, or social manifestations of resilience	Includes positive outcomes such as academic engagement, leadership, self-esteem, positive identity, social competence, and adaptive functioning	A study reporting improved academic performance despite exposure to racism

[a]Studies that use the term *resilience* superficially or metaphorically without linking it to defined outcomes, capacities, or processes will be excluded.

Organizing and Extracting Data: Data Management, Evidence Extraction, and Reference Management

After completing the database search, we will remove all duplicates and transfer the reports to Covidence (Veritas Health Innovation) software for systematic reviews. We will conduct a 2-step screening process on the articles. First, 2 independent reviewers will screen the titles and abstracts to identify relevant reports using the inclusion and exclusion criteria. Second, the same reviewers will assess the full texts of potentially relevant studies. Throughout the screening process, the research team will meet to discuss conflicts and will resolve them through consensus. To ensure consistency and minimize subjectivity, particularly given the multidimensional nature of resilience, reviewers will use a full-text screening tool (Multimedia Appendix 3). This guide includes clear inclusion rules and examples of resilience-related processes and outcomes (eg, effective coping, cultural adaptation, social connectedness, and religious coping) based on the definition outlined in the population, concept, and context framework.

A data extraction tool will be piloted to determine its suitability and will be modified if necessary for use in data extraction (Multimedia Appendix 4). Following that, the independent reviewers will extract data from all reports that will be included in this review. The extracted data will include specific details about the author names and publication dates, country of origin, purpose and aims of the study, design and methods, type of adversity, findings, resilience facilitators, resilience barriers, implications, and research limitations [37]. If possible, we will contact the authors of the included reports via their email contact information if there are missing data [38]. Missing data will be categorized as "not reported" if attempts to retrieve them are not successful. In alignment with the option not to appraise the quality of included studies by Arksey and O'Malley [32], we will not conduct quality appraisal, as our goal is not to make judgments about the quality of evidence but to map the breadth of literature on this topic.

Compiling, Summarizing, and Presenting the Findings

We will present the results of the screening process and reasons for the exclusion of reports from the full-text screening in the final report using the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) [39] guidelines. We will use descriptive statistics to analyze the frequencies of the characteristics of studies included in this review and the quantitative findings from quantitative and mixed methods studies. The frequencies of included studies with similar characteristics, such as country of origin, range of publication dates, and study designs, will be tallied and presented using graphs and tables.

Guided by an intersectionality-based theoretical lens [27], we will analyze the extracted data from qualitative studies using a thematic approach [40] in NVivo (Lumivero) software. Initially, the project lead and research assistants will conduct open inductive coding of the first 5 extracted reports to categorize emerging evidence on resilience facilitators and barriers. The broader research team will then meet to review and discuss the initial codes, refining them collaboratively into a preliminary coding framework.

This coding framework will be used to guide analysis of the remaining data while still allowing for inductive modification

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as new themes emerge. Codes will be grouped into themes and subthemes based on recurring patterns, contextual factors, and intersectional considerations. The team will engage in regular analytical meetings, ensuring that multiple perspectives inform the interpretation of findings and reduce individual bias. Reflexive discussions with the 5-member advisory youth committee will also be used to interrogate assumptions and positionality throughout the analytic process. To ensure the review maintains relevance for Canadian policy and practice, we will categorize and analyze Canadian and US studies separately during data charting. Thematic comparisons across both contexts will be conducted to identify shared patterns as well as context-specific distinctions. Data from the United States will be interpreted with attention to its unique contextual conditions while also highlighting elements that may be transferable or adaptable to the Canadian landscape.

We will use a narrative approach to organize findings by study design (qualitative, quantitative, or mixed methods). Themes will be organized into overarching categories such as individual, relational, community, and structural levels, in alignment with our biopsychosocial and intersectionality-informed lens. This layered synthesis will allow us to present an integrated understanding while noting where and how methodological differences shape insights. We will synthesize the findings into a final report with general conclusions and recommendations as well as limitations.

Ethical Considerations

This study did not require ethics approval because data will be obtained from already published sources and does not include direct involvement of human participants. However, we recognize that ethical considerations remain important, especially given the sensitive nature of topics such as childhood trauma, racism, mental health, sexual orientation, disability, and other marginalized social identities. We are mindful of the potential for research to inadvertently reinforce stigma, a risk we seek to mitigate by emphasizing community strengths. Our approach aims to present the evidence with respect and sensitivity, centering the lived experiences of Black children and youth within their broader sociohistorical contexts.

Reporting Standards

This protocol has been submitted for registration and will be embargoed on the Open Science Framework. This will become publicly accessible upon journal publication [41].

Results

The research team finalized the conceptualization of this scoping review protocol in June 2025. The comprehensive literature search was completed on July 16, 2025, in consultation with a health sciences librarian. This search yielded 5944 reports, of which 725 (12.20) duplicates were identified and removed using Covidence (Figure 1). We anticipate completing data screening, selection, extraction, and analysis by September 2025. The final report will be submitted for publication in a peer-reviewed, open-access journal.

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Figure 1. PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) flowchart.

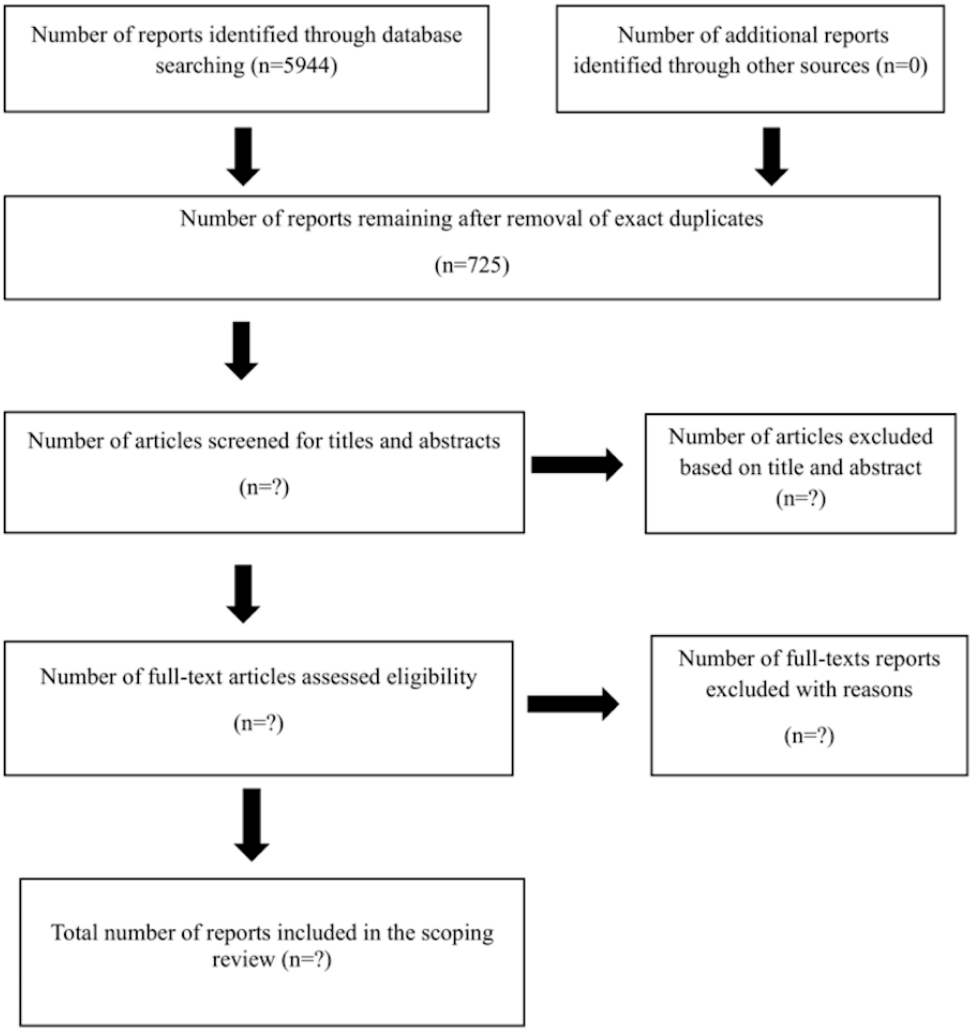

Discussion

Anticipated Findings

This scoping review is expected to identify and synthesize key facilitators of and barriers to resilience among Black children and youth in Canada and the United States. We anticipate identifying a broad range of individual, relational, community, and structural factors that enable or constrain resilience. These factors include, but are not limited to, cultural identity, family cohesion, mentorship, experiences of racism, and systemic barriers in education and health care. We also expect that resilience processes and outcomes will vary based on intersecting social identities (eg, gender, immigrant status, and socioeconomic position), revealing the need for nuanced and tailored interventions.

Unlike previous reviews, which focused primarily on mental health and general health outcomes among Black children and youth [19-21], this review positions resilience as both a process and an outcome, incorporates an intersectionality lens, and situates findings within structural and cultural contexts, offering a more holistic understanding of resilience. By situating resilience within structural and cultural contexts, this work addresses critical gaps in the literature and builds on earlier efforts to understand how systemic inequities shape Black youth resilience. Finally, this review aligns with ongoing national efforts to improve outcomes for Black communities in Canada, particularly in response to enduring racial inequities and those highlighted during the COVID-19 pandemic [42].

Strengths and Limitations

A key strength of this review is its comprehensive and multidisciplinary approach, informed by health, education, social science, and community perspectives. This study is also strengthened by its grounding in Black-led research, community engagement, and critical theoretical frameworks, including intersectionality and the biopsychosocial model developed by Bronfenbrenner. Our study has a few limitations. Excluding articles published in French may limit the comprehensiveness of this scoping review, given that Canada is a bilingual country. Consequently, the findings will primarily reflect evidence available in English-language studies. In addition, the concept of resilience is inherently complex and interpreted differently across various disciplines [43]. This inherent variability could pose challenges during the screening and data extraction phases when identifying resilience facilitators and barriers. To mitigate this, we will apply operationalized dimensions of resilience (Table 2) and use a reflexive, consensus-driven approach within the research team during data screening and extraction.

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Implications for Future Research

Future research should adopt bilingual or multilingual approaches to incorporate Francophone communities and perspectives, thereby enhancing inclusivity and representativeness. Expanding resilience research across diverse cultural and structural contexts will be critical for developing effective, equity-driven policies and programs.

Dissemination Plan

To maximize the impact and accessibility of our findings, we will disseminate results through both academic and community channels. These include publication in a peer-reviewed journal, presentations at relevant conferences (eg, the Black Child and Youth Summer Institute), and cocreated knowledge translation products (eg, podcasts and summary briefs). Our Black youth advisory committee will play an active role in codeveloping these outputs to ensure they are accessible, culturally resonant, and action oriented for advocacy organizations, educators, community groups, and policymakers.

Conclusions

By moving beyond deficit-oriented frameworks, this scoping review protocol centers the strengths, strategies, and structural contexts that shape how Black young people navigate systemic adversity. Guided by intersectionality and grounded in community-engaged scholarship, this review will offer a multidimensional synthesis of the processes, capacities, and outcomes that support or hinder resilience. In doing so, this study will inform culturally responsive, equity-driven policy and practice interventions that reflect the lived realities and aspirations of Black youth. The findings will contribute critical knowledge to disrupt systemic inequities and advance health, educational, and social justice for Black children and youth.

Acknowledgments

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Authors' Contributions

Conceptualization: EAM, BS
Methodology: EAM, GAA, BS
Project administration: EAM
Resources: BS
Supervision: BS
Writing—original draft: EAM
Writing—review and editing: BS, GAA

Conflicts of Interest

None declared.

Multimedia Appendix 1
Preliminary search strategy.
[DOCX File , 14 KB - resprot_v14i1e80859_app1.docx]

Multimedia Appendix 2
Final comprehensive search strategy.
[DOCX File , 16 KB - resprot_v14i1e80859_app2.docx]

Multimedia Appendix 3
Full-text screening tool.
[DOCX File , 504 KB - resprot_v14i1e80859_app3.docx]

Multimedia Appendix 4
Data Extraction Table.
[DOCX File , 17 KB - resprot_v14i1e80859_app4.docx]

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Abbreviations

PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Experiences of Pregnant Women With a Positive HIV Status in Sub-Saharan Africa: Protocol for a Scoping Review

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Abstract

Background: The World Health Organization reports that HIV and AIDS remain a significant public health concern in sub-Saharan Africa, which hosts over 60% of the global population of people living with HIV. Among these, there were 1.2 million pregnant women with HIV in 2023 who likely experienced challenges related to the pregnancy itself, the fear of infecting their newborn babies, and issues related to HIV stigma and disclosure. However, their experiences have not been summarized to inform tailored interventions to assist them in their journey to delivery.

Objective: This scoping review aims to synthesize the existing evidence related to the experiences of pregnant women with an HIV-positive status in sub-Saharan African countries.

Methods: A review of the relevant literature will be guided using the Joanna Briggs Institute methodological framework for scoping reviews. Studies will be eligible for inclusion if they report on reactions to a new HIV diagnosis and the management of these reactions. All eligible studies from 2014 to 2025 in English and French will be included. The following databases will be used for the search: PubMed, MEDLINE, EBSCOhost (CINAHL with Full Text), Scopus, and Web of Science. All identified records will be collated and uploaded into EndNote X21 for management. Eligible studies will be screened by 2 independent reviewers, and disagreements will be solved through discussion. Data extracted via a validated data extraction form developed for this review will be analyzed using content analysis and presented in a narrative format. NVivo (version 12) will be used to facilitate the data analysis process. This protocol is aligned with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines.

Results: We will include studies on timely intervention with antiretroviral therapy, close medical monitoring, careful planning around delivery, and comprehensive support for both mother and child. The findings will be disseminated through medical education conferences and publications. The database search was completed in March 2025, and the results are expected to be published in December 2025.

Conclusions: This review will provide a comprehensive narrative of the experiences of pregnant women with a positive HIV status in sub-Saharan Africa and how they react when they are first diagnosed with HIV, as well as how they manage the news. It is anticipated that there will be evidence of mixed reactions to and balanced management of a new HIV diagnosis among pregnant women.

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KEYWORDS

HIV and AIDS; pregnancy; antenatal; experiences; sub-Saharan Africa

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Introduction

The World Health Organization reports that HIV and AIDS remain a significant public health concern worldwide, with sub-Saharan Africa (SSA) disproportionately affected [1]. Worldwide, 39.9 million people were living with HIV in 2023, with 44% of all new HIV infections among women and girls and 62% of all new HIV infections in SSA. Moreover, approximately 1.3 million pregnancies occurred in 2023 among people with HIV worldwide, with high rates of HIV among pregnant women in SSA [2]. Efforts have been made to decrease the impact of HIV on people's lives [3], including strides to reduce the HIV incidence in newborns. Prevention of mother-to-child transmission programs have been aligned with the Joint United Nations Programme on HIV/AIDS 90-90-90 targets launched in 2014 and updated in 2021 to 95-95-95, whereby 95% of HIV-positive people should know their HIV status, 95% of people diagnosed with HIV should receive sustained antiretroviral therapy (ART), and 95% of people on ART should achieve viral suppression by 2030 [4]. The success of ART has resulted in a diminution of the perinatal transmission of HIV [5].

However, there is still stigma and discrimination attached to HIV and AIDS. Moreover, the initial diagnosis of HIV and AIDS, similar to any other life-threatening disease, causes patients to experience several distressing psychological and emotional states of mind. These include denial, fear of the consequences, emotional shock, hopelessness, and guilt [6]. Previous studies have shown that people living with HIV are vulnerable to mental health problems, including depression [7-9]. Equally, pregnant women are twice as likely to develop depression [10]. This is because pregnancy is a period in which physiological, hormonal, social, and psychological changes occur [11]. These changes may cause more concern in women living with HIV. In addition to coping with the effects of pregnancy and dealing with the anxieties of childbirth [12,13], they have concerns related to HIV disclosure, stigma, and fear of infecting the unborn child [14]. This is exacerbated in unplanned pregnancies [15]. Therefore, understanding the lived experiences of newly diagnosed HIV among pregnant women is essential.

HIV infection in pregnancy is associated with increased maternal, fetal, and neonatal complications, which can lead to maternal and infant mortality [16,17]. Moreover, some pregnant women face unique challenges in accessing HIV care due to societal stigma and their personalized health needs [18], although most SSA countries have adopted compulsory HIV testing during antenatal visits [19]. Studies have reported that being diagnosed with HIV during pregnancy can negatively affect interpersonal relationships [20], leading to emotional turmoil due to the dual challenges of pregnancy and an HIV diagnosis [21], and amplify shock and disbelief in the case of a lack of symptoms despite the positive result [22]. Furthermore, partner disclosure becomes more difficult during this time [23] and can trigger negative reactions such as violence and separation [24].

Although efforts to prevent initial HIV infection in pregnant women are important in preventing perinatal transmission [25], equally important are efforts to ensure that pregnant women who receive the news of an HIV-positive status are able to manage it [21]. One could assume that the reactions to and the experiences of a diagnosis of HIV of any HIV-infected person are similar to those of HIV-infected pregnant women. However, unless this is explicitly investigated, knowledge of the extent to which the experiences can differ is limited. In addition, emotional and social challenges following an HIV diagnosis can lead to poor adherence to ART [26], whereas better handling of a new diagnosis of HIV could greatly buffer psychosocial and mental health and help facilitate health care seeking and retention [27]. This makes understanding pregnant women's lived experiences in managing their HIV status essential to developing tailored interventions that can support their journey to delivery [5].

Despite studies describing the experiences of pregnant women with diagnoses of HIV, as of January 2025, a preliminary search of PROSPERO, the Cochrane Database of Systematic Reviews, *JBI Evidence Synthesis*, and the Open Science Framework indicates that there are no previous or ongoing scoping reviews that summarize pregnant women's experiences related to HIV antenatal care (ANC) in SSA or their reactions to the news of a positive HIV status. One recent review conducted on HIV ANC focused on factors associated with HIV testing during ANC [19], and another was conducted on the childbirth experience of women living with HIV [14] but not during pregnancy or in SSA. Therefore, the proposed scoping review will explore the experiences of pregnant women with an HIV-positive status in SSA countries, with a focus on their reactions to the news as well as the disclosure of their status.

On the basis of the aforementioned objective, the following research questions have been developed:

1. What types of evidence have been published regarding the experiences of pregnant women with a positive HIV status?
2. What are pregnant women's reactions to the news of their HIV-positive status?
3. What are the experiences of an HIV-positive status among pregnant women?

Methods

We will conduct the proposed scoping review according to the Joanna Briggs Institute methodology for scoping reviews and adhere to the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) reporting guidelines [28].

Registration

This review is registered with the Open Science Framework repository [29].

Eligibility Criteria

Overview

Eligibility criteria for this scoping review will draw from the Joanna Briggs Institute mnemonic for the formulation of scoping

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review questions describing the population, concept, and context of the study [30]. For studies to be included, they should meet the following criteria: be available in full text in English or French; be related to HIV ANC; focus on reactions, experiences, and disclosure; and be published between January 2014 and February 2025. Studies will be excluded should they not be available in full text; focus on HIV among women in the postpartum period; not include reactions, experiences, or disclosure; be published outside the identified search period; or not be available in English or French. Textbox 1 summarizes the inclusion and exclusion criteria.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Population: studies conducted on pregnant women living with HIV
- Concept: experiences of pregnant women, reactions to the news of an HIV diagnosis, and disclosure of HIV status
- Context: studies conducted in sub-Saharan Africa (SSA)
- Time frame: studies conducted from January 2014 to March 2025
- Language: studies published in English or French

Exclusion criteria

- Population: studies conducted on pregnant women with a negative HIV status, studies conducted on postpartum women, and studies conducted on any other women with an HIV-positive status
- Concept: factors associated with HIV antenatal care, prevalence and incidence of HIV antenatal care, and any other outcome different from the primary outcomes that refers to experiences of HIV-positive pregnant women
- Context: studies conducted outside of SSA
- Time frame: studies conducted before 2014
- Language: studies published in any other language apart from English or French

Population

For this scoping review, we will source all relevant peer-reviewed articles regarding pregnant women with a positive HIV status. We will exclude studies on pregnant women with a negative HIV status and on women with a positive HIV status in the postpartum period.

Concept

This review focuses on HIV antenatal experiences when the woman is either newly diagnosed with HIV or is a person living with HIV who is pregnant.

Context

The context of the study is SSA, which was chosen because the number of new HIV infections among adolescents and young women in the region remains exceptionally high [31].

Time Frame

Eligible studies conducted from January 2014 to March 2025 will be included because it was in 2014 that the Joint United Nations Programme on HIV/AIDS 90-90-90 target was launched.

Types of Sources

We will seek all peer-reviewed literature related to the study objectives. We will consider experimental and quasi-experimental study designs, including before-and-after and interrupted time-series studies. In addition, we will include analytical observational studies, including prospective and retrospective cohort studies, case-control studies, and analytical cross-sectional studies, as well as descriptive observational study designs, including case series, individual case reports, and descriptive cross-sectional studies. Qualitative studies will also be included but not limited to any qualitative design. In addition, systematic reviews will also be considered for inclusion in this scoping review. However, gray literature (dissertations), conference abstracts, commentaries, study protocols, and book chapters will not be included. We will also conduct a hand search of all included articles' reference lists to identify any additional relevant studies.

Search Strategy

In this review, we will use a 3-step search strategy. First, we conducted an initial limited search in PubMed and examined the words in the title and abstract, index terms, and keywords of several papers to identify search terms (Multimedia Appendix 1). We will then devise the list of search terms and review these with the librarian at the Durban University of Technology to develop a full search strategy for PubMed. On the basis of those keywords, we will systematically search 4 electronic databases: PubMed and MEDLINE, EBSCOhost (CINAHL with Full Text), Scopus, and Web of Science. We will adapt the search strategy, including all identified keywords and index terms, for each included database or information source. We will review peer-reviewed journals for primary studies with a clear empirical base using qualitative, quantitative, and mixed methods addressing the research questions. In addition, we will search for articles through the "cited by" search. Once article review is completed, we will search the reference lists of all the included articles to identify additional articles.

We will also use the university's interlibrary loan system to retrieve some of the full-text articles. We will thereafter send

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an email and then a reminder to the corresponding authors of articles whose full texts are not available. We will only send 2 reminders to authors as we want to complete the review in 3 months. If there is no response after a reasonable time, the articles will be excluded from the review. We will report the outcomes of contacting the authors in terms of how many reminders were sent, how many authors responded, and how many authors shared the requested full texts. The first search was conducted in March 2025, and an updated search will be conducted in June 2025 before the final synthesis.

To conduct the search, we will combine the following keywords: "HIV" AND "pregnancy" AND "sub-Saharan Africa." We will use Boolean terms (AND, OR, and NOT) to separate the keywords. We will also use wildcards and truncations to accommodate variations in the different databases. The search strategy will be piloted by independently reviewing 10 articles to examine interrater reliability and resolve early issues before the full collection of articles. This is to check the appropriateness of selected electronic databases and keywords. We will modify the syntax where needed. We will use the services of an experienced information specialist to ensure that a robust review search strategy is followed. To compile all relevant evidence sources and identify and remove duplicate records, the EndNote X21 reference manager (Clarivate Analytics) will be used to import and manage eligible studies.

Study and Source of Evidence Selection

Following the search, we will collate and upload all identified records into EndNote X21, and thereafter, we will use the Rayyan systematic review software (Qatar Computing Research Institute) to remove duplicates. Two authors will screen the titles and abstracts independently using Rayyan according to the eligibility criteria. We will then retrieve potentially relevant sources in full. Thereafter, 2 authors will assess the full texts of the identified reports independently against the inclusion criteria using Rayyan. The 2 screeners have received the following instructions: "Your role is to systematically screen the titles and abstracts (and potentially full texts) of studies identified in our literature search to determine their relevance and eligibility for inclusion in our review, based on the predefined inclusion and exclusion criteria. Please familiarise yourself with the review protocol, specifically the section detailing the inclusion and exclusion criteria. This document outlines the specific criteria that must be met for a study to be included in the review. Initially, screen titles and abstracts will be screened to determine if a study potentially meets the inclusion criteria. If there is any doubt, include the study for further screening. A study should be included if it meets all the inclusion criteria and none of the exclusion criteria. A study should be excluded if it fails to meet one or more of the inclusion criteria or if it meets one or more of the exclusion criteria. Document your screening decisions (include/exclude/maybe) and provide a brief reason for each decision." We will record the reasons for the exclusion of sources of evidence that do not meet the inclusion criteria at the full-text stage. During screening, journal names, authors, and publication years will not be hidden from screeners because the Rayyan software does not blind such information. Any disagreements that arise between the reviewers at each stage of this process will be resolved through discussion until a consensus is reached. To minimize bias during the screening rounds, the 2 authors will independently screen all sources, and a coefficient of agreement will be calculated at each round. If the coefficient is <50%, the 2 screeners will discuss the eligibility criteria to obtain a better understanding.

Quality Appraisal

Two authors will independently appraise the quality of all full-text peer-reviewed studies included in this review using the Mixed Methods Appraisal Tool version 2018 [32] by rating each item using "yes," "no," or "can't tell." We chose the Mixed Methods Appraisal Tool as it allows for the appraisal of qualitative, quantitative, and mixed methods studies using the same tool [32]. It has also undergone recent evaluations to inform its usefulness and content validity [33].

Data Extraction

Two authors will independently extract data from papers included in the scoping review using a data extraction tool on Google Forms developed by the reviewers (Multimedia Appendix 2). The Microsoft Excel spreadsheet outputs will be shared among the authors for discussion and validation before data synthesis. They will extract specific details such as (1) metadata (authors, year of publication, and country), (2) study methods and sample size, (3) reactions, (4) experiences, (5) disclosure, and (6) any other significant findings. Before data extraction, the 2 screeners will receive the following instructions: "Extract data from each included study. Carefully extract all relevant data from the included studies, as outlined in the extraction form. Be thorough: Ensure that all required data points are extracted, even if they are not immediately obvious. Document any missing data: If a piece of data is missing, clearly document that in the extraction form. Record the source: Always indicate the source of the data (specific paragraph, table, figure)." They will also pilot-test the tool on 5 articles and then modify it if the extraction alignment is poor or if changes are needed. We will also revise it as necessary while extracting data from each included evidence source. The screeners will detail all modifications to the data extraction tool in the final scoping review. Finally, a Cohen κ coefficient will be calculated to measure the agreement between the 2 data extractors. A κ value of 1 will indicate perfect agreement, whereas a value of 0 will indicate an agreement no better than chance.

Ethical Considerations

Ethics approval is not required at this stage, as we will synthesize published literature only.

Data Analysis and Presentation

All the authors will be involved in the synthesis, and there will be no procedure to blind synthesists. One author will synthesize the extracted data, and the other 2 will validate the synthesis. The first author is a native French speaker and will read and understand all eligible studies published in French. We will adopt a descriptive approach, using thematic analysis for data summarization and reporting as suggested by Braun et al [34]. We will present the findings of the included studies related to the experiences and challenges encountered by pregnant women

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with a positive HIV status using a narrative approach. This approach was chosen because our research questions focused on understanding the experiences of pregnant women with an HIV-positive status in SSA, and narrative synthesis is well suited for exploring qualitative data and providing a rich, contextualized understanding. Given the heterogeneity of the potential studies, a narrative synthesis will allow us to explore the variations in findings across different study settings and populations. Although a meta-analysis could have been conducted for quantitative studies, the lack of comparable outcome measures across all studies made it unsuitable for our review. Therefore, a narrative synthesis was chosen to provide a more holistic interpretation of the findings. We will also report on any other emerging themes.

Results

Pregnant women's reactions to and experiences with an HIV-positive status will be extracted from the included articles, and data will be analyzed to develop a comprehensive model for effective management of HIV during pregnancy that will include reports on timely intervention using ART, close medical monitoring, careful planning around delivery, and comprehensive support for both mother and child. As of May 2025, the database search and title and abstract screening have been completed. The results paper is expected to be published within the next 6 months. As of October 2025, the data search and screening of titles, abstracts, and full-texts have been completed. The results paper is expected to be published in December 2025. We will report the results of the search and the study inclusion process in a PRISMA-ScR flow diagram [35] (Figure 1).

Figure 1. PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flowchart. As of October 2025, the data search and screening of titles, abstracts, and full-texts have been completed.

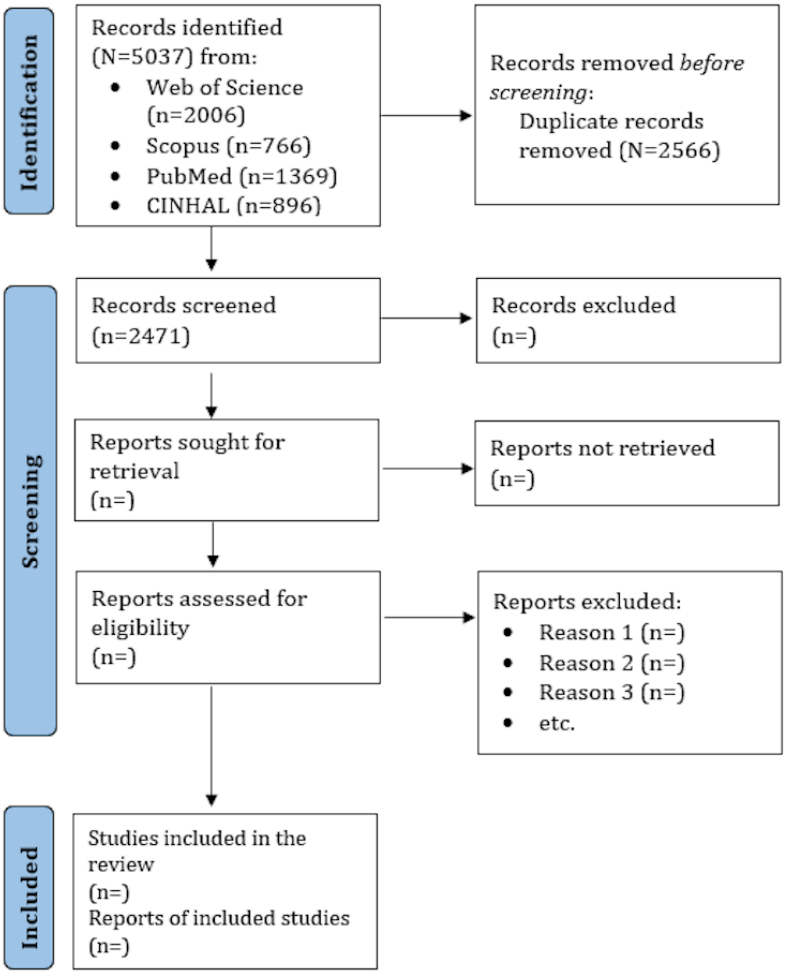

Discussion

Expected Findings

This scoping review will be an overview of the current state of knowledge and research activities on the experiences of pregnant women with a positive HIV status in SSA, where HIV ANC has different characteristics. This review has the potential to contribute to achieving the United Nations' goal of ending AIDS as a public health threat by 2030, as well as the Sustainable Development Goal (SDG) of reducing maternal and neonatal mortality related to AIDS by informing strategies to enhance culturally sensitive counseling and improve prevention of mother-to-child transmission outcomes. The results of this study will be, to the best of our knowledge, the first synthesis of the experiences of pregnant women with regard to HIV ANC. This

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review will identify challenges faced by pregnant women with a positive HIV status as HIV in pregnancy does not always mitigate the positive feelings toward childbirth and motherhood [14]. Moreover, some women discover their pregnancy and HIV-positive status simultaneously [21], placing them in a difficult position. The results of this review will also highlight strategies implemented by women to disclose their HIV-positive status to their families. Finally, the results of this review will inform a study that aims to address HIV-positive status in unplanned pregnancies in South Africa, which has one of the highest HIV prevalence rates worldwide, with approximately 7.5 million people living with HIV [36].

Policy and Practical Implications

This scoping review aims to provide insights into the experiences of HIV-positive pregnant women in African countries. It will be instrumental in identifying key gaps and challenges in their pregnancy journey, as well as in HIV-related future research.

By linking the anticipated results to the SDGs, this review aligns with SDG 3, particularly targets 3.1 and 3.3, by addressing the intersecting challenges of maternal health and HIV. It also contributes to SDG 5.6 through its focus on reproductive health rights and gender-sensitive health care delivery. The findings will have both policy and practical implications for integrated HIV and maternal care services, stigma reduction, and improved retention in care for HIV-positive pregnant women. Health care providers are expected to benefit from the insights that this scoping review will provide regarding individualized needs for effective support of these women. This will improve HIV ANC. Furthermore, this review will emphasize the importance of community involvement in supporting and understanding HIV-positive journeys.

Potential Challenges and Limitations

This review includes only studies published in English or French, which may exclude relevant research in other languages and limit the comprehensiveness of the findings. Furthermore, it focuses on studies published and indexed in selected databases, potentially overlooking unpublished research.

Data Availability

All data generated and analyzed will be included in the published scoping review article and will be available on request.

Authors' Contributions

All authors contributed equally to this study. All authors approved the final version to be published, agreed with its publication, and agreed to be accountable for all aspects of the work.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Pilot search.
[DOCX File , 14 KB - resprot_v14i1e76971_app1.docx]

Multimedia Appendix 2
Data extraction form.
[DOCX File , 14 KB - resprot_v14i1e76971_app2.docx]

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Abbreviations

ANC: antenatal care
ART: antiretroviral therapy
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
SDG: Sustainable Development Goal
SSA: sub-Saharan Africa

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Protocol

Physical Activity Interventions for Patients With Poststroke Fatigue: Protocol for a Scoping Review

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Abstract

Background: Poststroke fatigue (PSF) affects nearly 50% of stroke survivors, severely impacting functional recovery and quality of life. Physical activity (PA) interventions show promise in mitigating fatigue, yet evidence remains fragmented across study designs and intervention types.

Objective: This scoping review aims to systematically map the literature on PA interventions for PSF, identifying key concepts, evidence gaps, and implementation characteristics to guide future research.

Methods: Using a 5-step framework, we will search PubMed, Web of Science, Scopus, Embase, PsycINFO, CINAHL, and the Cochrane Library from the inception of the databases to 2025. Gray literature and trial registries will be included. Two reviewers will independently screen titles, abstracts, and full texts using predefined criteria. Data extraction will focus on intervention components, fatigue assessment tools, and implementation outcomes.

Results: Initial searches identified 8268 articles. The study selection process is expected to finish in February 2026, and the manuscript will be submitted in June 2026.

Conclusions: The conduct of this scoping review is expected to synthesize a fragmented evidence base, providing a clear evidence map of PA interventions for PSF. The findings will identify key gaps and inform the design of future definitive studies and evidence-based clinical guidelines, ultimately contributing to improved care for stroke survivors experiencing fatigue.

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KEYWORDS

stroke; fatigue; scoping review; poststroke fatigue; physical activity; exercise; rehabilitation; protocol; knowledge synthesis; scoping literature review

Introduction

Stroke refers to a group of cerebrovascular diseases characterized by sudden onset and rapidly developing focal or diffuse neurological deficits caused by organic brain injury [1]. Stroke is the second leading cause of death worldwide, accounting for 11.8% of global mortality [2-4]. It is marked by high incidence and mortality rates, significantly impairing patients' quality of life [5]. Its complications significantly impact patients' long-term functional recovery [6], with poststroke fatigue (PSF) being one of the most prevalent and direct contributing factors.

PSF is defined as a multidimensional sensorimotor, affective, and cognitive experience characterized by early-onset exhaustion and a lack of energy, which manifests as a feeling of weariness during physical or mental activity and cannot be alleviated by rest [7]. A meta-analysis [8] has identified 5 core characteristics of PSF: lack of physical strength to perform activities, abnormal need for prolonged sleep, easy fatigability after activity and abnormal need for rest, unexplained and unpredictable fatigue sensation, and increased stress sensitivity. These symptoms

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must be prominently present daily or frequently during at least 2 weeks within the past month.

PSF is a pathological, chronic, and persistent syndrome of physical and mental exhaustion experienced by stroke survivors [9]. Different studies have reported markedly divergent prevalence rates for PSF, ranging from 23% to 85% [10]. This significant heterogeneity primarily stems from some key factors. Foremost, the absence of standardized clinical diagnostic criteria and validated assessment scales for PSF results in substantial prevalence variations across studies using different measurement tools [11]. As a recent systematic review and meta-analysis [12] reported, the global pooled prevalence of PSF in stroke survivors was 46.79%.

PSF directly impedes stroke rehabilitation progress and severely compromises patients' quality of life [13,14]. A prospective cohort study [15] found that PSF is a factor associated with the inability to return to work in patients younger than 60 years. PSF also significantly influences every domain of health-related quality of life and increases the caregiving burden placed on families and society [16]. Despite its high prevalence and substantial impact, the underlying mechanisms of PSF remain poorly understood, and effective management strategies are limited. However, insufficient attention has been paid to patients with PSF in clinical practice, which directly affects patient prognosis.

Current PSF management strategies consist of pharmacological and nonpharmacological interventions, with nondrug approaches being the principal method due to limited evidence supporting medication efficacy [17]. Bivard et al [18] suggested that PSF can be alleviated through pharmacological treatment, whereas Poulsen et al [19] found that medication has no effect on PSF. De Doncker et al [20] administered transcranial direct current stimulation to patients with PSF, resulting in marked improvement in their fatigue. Nguyen et al [21] concluded that cognitive behavioral therapy can improve fatigue symptoms more effectively than routine treatment among patients who have experienced a stroke. To date, evidence regarding the effectiveness of any intervention to treat or prevent PSF is still lacking [22]. Meanwhile, multiple studies [22,23] have suggested physical activity (PA) as a nonpharmacological intervention for PSF; however, this topic has not been systematically investigated in a review.

PA is a simple and easily implementable intervention for managing PSF. The American Heart Association and American Stroke Association's statement [24] for health care professionals notes that PSF may be exacerbated by a sedentary lifestyle, and regular PA may help reduce PSF. Previous studies [25-27] have indicated that PA level is a determinant of PSF, with higher levels of PA associated with reduced fatigue severity. A meta-analysis [28] also revealed associations between higher PSF and lower PA. A pilot study [29] found that mobile health–based interventions have the potential to improve fatigue in patients who have experienced stroke. Exercise may improve several peripheral factors, such as decreased aerobic capacity and muscle atrophy, and central system dysregulations, including changes in cerebral blood flow, altered cellular energy reserves, and abnormal neural circuit activity, all of which could potentially contribute to PSF [30,31].

PA interventions have shown promise in managing fatigue in various clinical populations, including cancer survivors [32-34] and individuals with chronic fatigue syndrome [35,36]. However, the evidence for the effectiveness of PA interventions specifically targeting PSF is fragmented and has not been systematically synthesized. The heterogeneity in exercise interventions and outcome assessments precludes a systematic review, making a scoping review the most appropriate alternative. A scoping review is an ideal methodology to map the existing literature, identify gaps in knowledge, and provide a comprehensive overview of the types of evidence available. This scoping review protocol outlines a systematic approach to examining the scope and nature of PA interventions for PSF. Therefore, the purpose of this scoping review is to map PA intervention characteristics, delivery methods, and outcomes reported in PSF research.

Methods

Study Design

The scoping review will be conducted following the methodological framework proposed by Arksey and O'Malley [37], which includes the following five stages: (1) identifying the research question; (2) identifying relevant studies; (3) selecting studies; (4) charting the data; and (5) collating, summarizing, and reporting the results. This protocol has been designed in accordance with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) [38]. The PRISMA-ScR guidelines have informed the structure and reporting of this protocol and will guide the conduct and final reporting of the full review. As part of the scoping review process, we follow the guidelines set by the Joanna Briggs Institute [39]. Open Science Framework has registered the protocol for the study, which will begin in December 2025 and end in February 2026.

Review Questions

Following preliminary literature screening, the research team established the study question through collaborative team discussions and specialist consultation. The primary research questions guiding this scoping review are as follows: (1) What are the characteristics of the PA interventions (eg, type, frequency, intensity, duration, session length, and total weeks) that have been used to manage PSF? (2) What is the volume and nature of the available evidence (eg, study designs and methodological quality), and what subpopulations of stroke survivors have been included in these studies? (3) What are the reported effects of PA interventions on fatigue severity and related domains (eg, physical function, mood, and quality of life), and what measurement tools are used to assess these outcomes? (4) On the basis of the mapping of existing evidence, what are the implications for developing optimal PA interventions and for designing future definitive trials for PSF?

Ethical Considerations

Ethics approval is not required because this review will use secondary data synthesis without primary data collection.

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Furthermore, all analyzed data originate from publicly accessible sources, thereby eliminating confidentiality concerns and ensuring compliance with data protection regulations. Future dissemination of this work will include presentations at scientific meetings and publication in peer-reviewed journals.

Search Strategy

A comprehensive search strategy will be developed in consultation with a medical information specialist. We will search the following electronic databases: PubMed, Web of Science, Scopus, Embase, PsycINFO, CINAHL, and the Cochrane Library. The search strategy will include a combination of Medical Subject Headings (MeSH) terms and keywords related to stroke, fatigue, and PA. Relevant subject headings and terms associated with the following concepts may be included in the search: (1) stroke, post stroke, poststroke, cerebral infarction, cerebral hemorrhage, hemorrhagic stroke, ischemic stroke, brain ischemia, brain infarction, and cerebrovascular accident; (2) fatigue, asthenia, lassitude, lethargy, tired, weak, and exhaust; and (3) sport, exercise, PA, movement, physical exercise, aerobic training, resistance training, exercise rehabilitation, walk, and step counts.

A Boolean search strategy (using operators such as AND and OR) will be used to merge these terms into queries optimized for specific databases or search engines. Reference lists of relevant articles will also be hand searched to identify additional studies. To ensure the validity and scientific rigor of the search strategy, we first conducted a preliminary search in PubMed, restricting the search terms to titles and abstracts while incorporating both keywords and MeSH terms. During the formal search phase, the search queries constructed in PubMed were refined and subsequently adapted for use in other databases to enable a comprehensive literature retrieval. The complete search strategy can be found in Multimedia Appendix 1. The search period will cover the period from the inception of the databases to December 31, 2025.

Study Selection

Following initial retrieval, records will be aggregated in EndNote (Clarivate) for reference management and deduplication [40]. The cleaned dataset will then be transferred to Covidence (Veritas Health Innovation Ltd), which will serve as the primary tool for managing study selection and documenting the review workflow [41]. Two reviewers will independently screen the titles and abstracts of the identified studies for potential inclusion. A satisfactory interrater agreement ($\kappa \geq 0.80$) is required in this process. Full-text articles will be retrieved for studies that appear to meet the inclusion criteria or where there is uncertainty. The same 2 reviewers will then independently assess the full-text articles for final inclusion. Any disagreements will be resolved through discussion or by consulting a third reviewer. The search results and study screening process will be fully summarized according to PRISMA-ScR [38].

Eligibility Criteria

The population, concept, and context framework [42] will be used in this study to define the inclusion criteria, which is a structured approach used in evidence synthesis.

Types of Participants

The study participants were rigorously selected based on the following inclusion criteria: (1) all individuals had received a formal clinical diagnosis of stroke, as confirmed through standardized diagnostic protocols; (2) participants were required to be aged ≥18 years at the time of enrollment, ensuring legal adulthood and capacity to provide informed consent; and (3) patients were diagnosed with ischemic stroke, hemorrhagic stroke, transient ischemic attacks, or minor stroke.

Concept

Any type of structured PA intervention, including but not limited to aerobic exercise, resistance training, balance training, and functional mobility training, meets the criteria. Studies where PA is part of a multicomponent intervention will also be included if the PA component can be clearly identified. Given the diverse definitions and measurement tools for PSF, it is impossible to establish a single definitive standard from a global perspective [43]. Therefore, any literature will be included if it has clear diagnostic criteria and assessment for fatigue.

Context

This study will have no restrictions on language or publication date. All non-English literature will be translated into English, and then the results can be integrated. Interventions conducted in all health care and community settings will be included.

Types and Sources of Literature

In addition to electronic databases, we will search gray literature sources, including Google Scholar, ClinicalTrials.gov, and ProQuest Dissertations.

Exclusion Criteria

The exclusion criteria encompassed unavailable full-text articles despite exhaustive retrieval efforts, duplicate publications identified through author names, and datasets. Secondary literature, such as systematic reviews, narrative reviews, case reports, study protocols, opinion pieces, conference abstracts, commentaries, discussion papers, and publications with incomplete datasets, will also be excluded.

Data Extraction

A data charting form will be developed to extract relevant information from the included studies. The form will be piloted on a small sample of studies and refined as necessary. Data to be extracted will include the following information:

- Study characteristics (author, year, country, and design)
- Participant characteristics (fatigue severity, sample size, age, gender, time since stroke, and severity of stroke)
- Intervention components (type, frequency, duration, intensity, setting, and technology use)
- Outcome measures used to assess fatigue and intervention results
- Implementation (dropout rate and safety events)
- Key findings related to the effectiveness of the intervention on fatigue

The complete data charting form can be found in Multimedia Appendix 2. Any discrepancies or challenges encountered during

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the data extraction process will be discussed within the research team. Revisions to the form will be made by consensus only when necessary to capture the data relevant to the review questions.

Critical Appraisal of Individual Sources of Evidence

Notwithstanding that quality appraisal is not an essential step in scoping reviews, the included studies in this research will still be evaluated to ensure the robustness of the findings. Two reviewers will independently assess methodological quality of included studies using the enhanced Mixed Methods Appraisal Tool (MMAT). The decision to use the MMAT was motivated by the need to evaluate an anticipated combination of quantitative and qualitative evidence [44]. Its use of 5 core criteria ensures a methodologically rigorous yet efficient assessment. Any discrepancies in quality ratings will be resolved via consensus discussion. Consistent with the purpose of a scoping review to map the available evidence, no studies will be excluded based on quality assessment. Instead, the results of the MMAT appraisal will be used to characterize the overall methodological strengths and limitations of the evidence base. These findings will explicitly inform the interpretation of the review's results, helping to contextualize the reported outcomes. Furthermore, identified gaps in methodological rigor will form the basis for recommendations for future primary research.

Analysis and Reporting

The results of this scoping review will be reported in accordance with the PRISMA-ScR guidelines. Following data extraction using a standardized form, a narrative synthesis will be conducted and structured around a predefined analytical framework that directly addresses the research questions. This framework will organize the findings by key themes, namely the characteristics of the PA interventions (eg, type, dosage, and delivery), the properties of the available evidence base (eg, study designs and populations), and the reported outcomes alongside the measures used. Within this structure, quantitative data will be summarized descriptively, whereas any qualitative findings will be analyzed using systematic, inductive content analysis. The synthesized evidence will be presented through narrative summaries, tables, and figures, culminating in a descriptive summary that discusses the implications for clinical practice and future research while explicitly highlighting the identified gaps in the literature.

Results

A total of 8268 records have been identified through electronic database searches, and 4589 (55.5%) unique records remain after deduplication (Figure 1). As of November 2025, the literature screening process is still ongoing. Gray literature sources have not yet been searched. The study selection process is scheduled for completion in February 2026. Data analysis and manuscript writing are anticipated to be finalized by May 2026. Manuscript submission and peer review are expected to occur in June 2026.

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Figure 1. Flow diagram of study selection process.

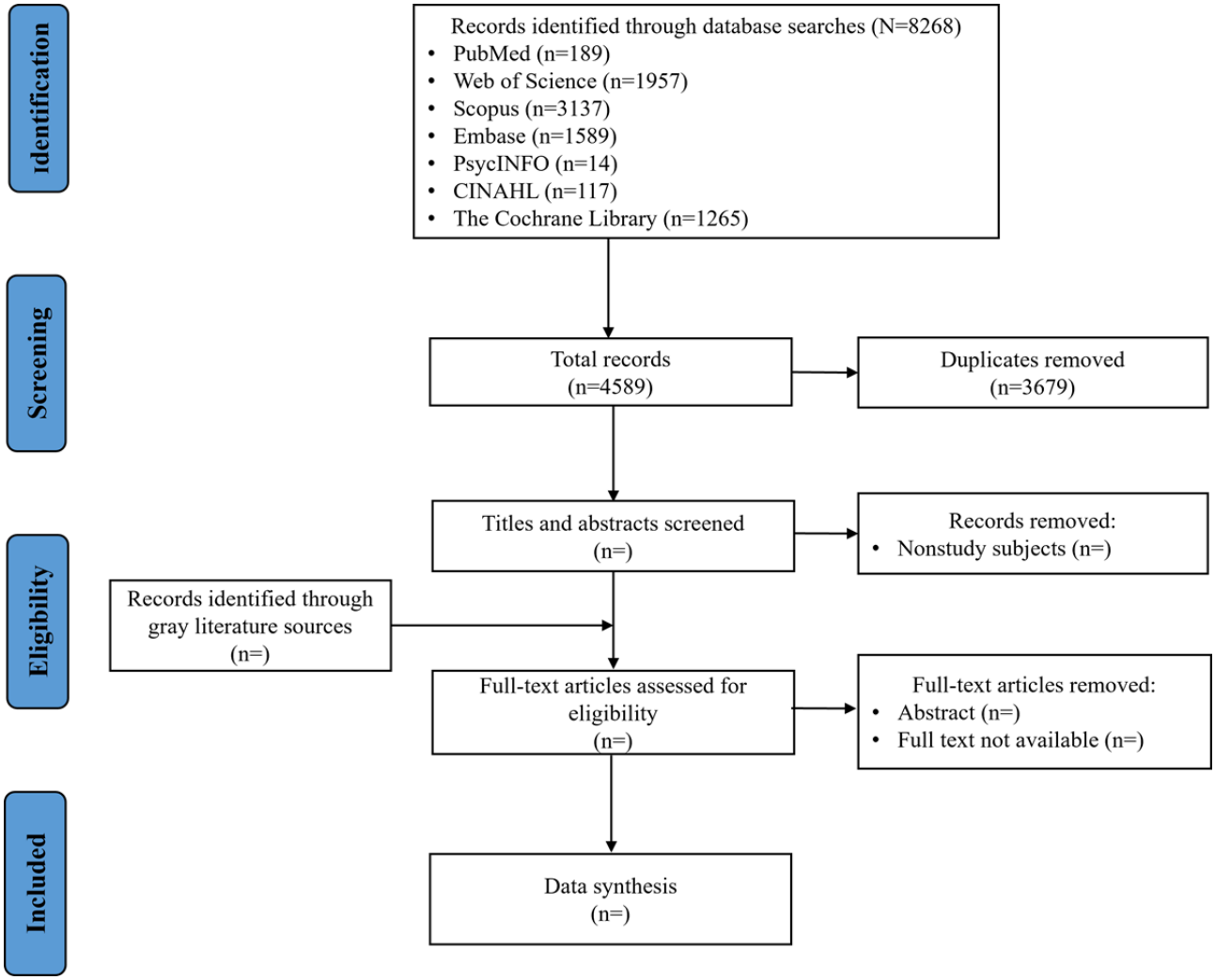

Discussion

Anticipated Findings

Upon completion, this scoping review is anticipated to generate a systematic map of the existing literature on PA interventions for PSF. We hypothesize that our findings will reveal a heterogeneous and evolving evidence base, characterized by a wide variety of PA intervention types, dosages, and delivery modes. It is expected that the available studies will encompass diverse patient populations across different stroke recovery stages, using a range of fatigue assessment tools. A key anticipated finding is the identification of significant gaps in the literature, particularly regarding the optimal components and dosing of PA interventions for PSF, the mechanisms through which PA may alleviate fatigue, and the specific subpopulations of stroke survivors who may benefit most.

Comparison With Prior Work

To our knowledge, this will be the first scoping review to systematically map the entire landscape of PA interventions specifically for PSF. While previous systematic reviews have focused on the general association between PA and fatigue or have examined interventions for PSF broadly, this review will provide a dedicated and detailed characterization of PA as a distinct intervention category. The findings will complement existing knowledge by offering a comprehensive overview of intervention characteristics and implementation contexts, which can inform the design of more targeted and effective future trials. This work will situate itself within the broader context of nonpharmacological PSF management, potentially clarifying the unique role of PA compared to other approaches such as cognitive behavioral therapy or neuromodulation.

The findings of this review are expected to directly inform future research by pinpointing specific evidence gaps. These may include the need for high-quality randomized controlled trials to determine optimal PA prescription, studies exploring the biological and psychological mechanisms of action, and research focused on underrepresented stroke subgroups. On the basis of mapped evidence, we will formulate concrete recommendations for the key components and design of such definitive trials.

Strengths and Limitations

A strength of this scoping review is the comprehensive search strategy that includes multiple databases and gray literature sources, which will help to ensure that a wide range of studies are identified. The use of independent screening by 2 reviewers will enhance the reliability of the study selection process. In addition, the conduct of a meta-analysis was not feasible with the available quantitative data, which hindered the advancement of recommendations for an optimal exercise regimen. Finally,

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there may be potential challenges in synthesizing highly heterogeneous interventions.

Conclusions

In conclusion, this scoping review protocol outlines a systematic approach to examining the scope and nature of PA interventions for PSF. However, the study implementation requires strict adherence to guidelines, ensuring rigor, preventing outcome bias, and addressing potential feasibility constraints. The execution of this review is expected to consolidate a currently fragmented body of literature, providing a valuable resource for researchers, clinicians, and policymakers. The findings will contribute to a better understanding of the current evidence base and inform future research and clinical practice in this important area of stroke rehabilitation.

Data Availability

The datasets generated or analyzed during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization: DC, XJG
Methodology: DC, XJG
Supervision: XJG
Writing—original draft: DC, LL, LJ, XJG
Writing—review and editing: DC, LL, LJ, XJG

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[PDF File (Adobe PDF File), 90 KB - resprot_v14i1e80703_app1.pdf]

Multimedia Appendix 2
Data charting form.
[PDF File (Adobe PDF File), 76 KB - resprot_v14i1e80703_app2.pdf]

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Abbreviations

MeSH: Medical Subject Headings
MMAT: Mixed Methods Appraisal Tool
PA: physical activity
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews
PSF: poststroke fatigue

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Protocol

Digital Information Sharing Before Consultations in General Practice: Protocol for a Scoping Review

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Abstract

Background: Digital tools that enable patients to submit information before consultations, such as Accurx and eConsult, are increasingly used in general practice. These systems aim to streamline workflows, improve documentation, and optimize consultation efficiency. However, evidence about their implementation, impact on health inequalities, and health care outcomes remains limited and fragmented.

Objective: This study aims to map and synthesize the evidence on digital tools used for preconsultation information sharing in family or general practice.

Methods: This scoping review will follow the Joanna Briggs Institute framework and the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines. Searches were conducted on May 12, 2025, in MEDLINE (Ovid), Embase (Ovid), CINAHL (EBSCOhost), and the Cochrane Library. Gray literature will be identified via Google Scholar and the National Health Service or government websites. Eligible studies will describe or evaluate digital tools used to collect information from patients before general practice consultations. Two independent reviewers will conduct screening and data extraction. Data will be analyzed using narrative synthesis.

Results: Database searches identified 6991 records, with 4536 (64.88%) remaining after deduplication. Screening began in June 2025. Full-text screening was completed in November 2025, with data extraction and synthesis planned for completion by February 2026. Results will be submitted for publication in early 2026.

Conclusions: This review will summarize evidence concerning the use of digital tools for preconsultation information sharing in general practice. Findings will inform implementation, research priorities, and service improvement in digitally supported care.

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KEYWORDS

digital health; online consultation; preconsultation information sharing; asynchronous communication; Accurx; eConsult; general practice; telehealth; primary care; scoping review; artificial intelligence; AI

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Introduction

Rationale

Digital tools that enable patients to share information before health care consultations have become increasingly common, particularly in general practice. Systems, such as Accurx, allow patients to submit descriptions of symptoms, photographs, or queries, facilitating asynchronous communication between patients and clinicians [1,2].

Before the COVID-19 pandemic, online consultation systems were already in place in the United Kingdom and elsewhere [3-5]. These typically involved patients submitting online forms that described their clinical or administrative needs, which were reviewed by health care staff who resolved the issue directly or arranged a follow-up via telephone, online messaging, or a face-to-face consultation. Early studies, predominantly from the United Kingdom, focused on implementation, user experience, and the potential of these systems to increase efficiency and manage workload.

A recent systematic review of studies up to 2022 examined asynchronous telemedicine (also known as the "store-and-forward" technique, where clinical data, such as text or images, are transmitted and interpreted later) in general practice. It found that asynchronous telemedicine can support effective diagnosis, prescribing, and timely care, with increased use after the COVID-19 pandemic. However, evidence remains limited by heterogeneity and small study sizes, with gaps in reporting on safety, equity, and cost-effectiveness [6]. There are also concerns that digital exclusion may exacerbate health inequalities.

Since the COVID-19 pandemic, there has been a substantial acceleration in the adoption of digital technologies across primary care, including increased use of artificial intelligence–enabled tools to support triage, decision-making, and patient communication. Digital transformation is also a priority for improving care and reducing costs, as outlined in the UK government's digital health and social care plan [7]. In particular, the National Health Service (NHS) aims to "put digital tools in place so patients can be supported with high-quality information that equips them to take greater control over their health and care" [8].

At the same time, the structure and delivery of general practice have changed, now offering a wider and more complex range of services provided by an expanded multidisciplinary team. This includes incorporating allied health professionals, such as physiotherapists, pharmacists, paramedics, and physician assistants (formerly known as physician associates), reflecting a move toward team-based, digitally supported models of care.

While these technologies aim to improve efficiency and patient experience, the breadth, mechanisms, socioeconomic impacts, and health outcomes of such digital tools remain underexplored [9]. Therefore, we aim to map the available evidence on digital preconsultation information sharing in general practice settings.

Objectives

This scoping review will follow the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews) guidelines [10] (Multimedia Appendix 1). The objectives are to (1) identify and map digital methods used for information sharing before telephone, virtual, and face-to-face consultations in general practice; (2) describe the characteristics, implementation contexts, and reported impacts and outcomes of such systems; (3) explore the range of digital tools (eg, Accurx and eConsult) used; and (4) identify gaps in the current literature that require further empirical research or systematic review.

Review Questions

This review will be guided by the following questions, using the Joanna Briggs Institute population, concept, and context framework [11]:

- What digital tools (concept) are used to collect information before health care consultations in general practice (context)?
- In which patient populations (population) are these tools implemented?
- What are the reported experiences and outcomes (concept) of using these tools in general practice (context)?
- What methodological approaches have been used to evaluate their implementation or effectiveness (concept) in general practice (context)?
- What is the evidence on the effects on health inequalities and health outcomes (context)?

Methods

Eligibility Criteria

Studies will be selected according to predefined inclusion and exclusion criteria (Textbox 1), designed to identify relevant literature on digital tools used for information sharing before consultations in general practice.

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Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Studies describing or evaluating digital, online, or virtual tools used to gather information before consultations (eg, face-to-face, telephone, or video)
- Tools combining patient-entered data with algorithmic triage (eg, eConsult, askmyGP, and Accurx), provided they allow patients to submit information before clinician review
- Studies conducted in family or general practice settings
- All study designs, including qualitative, quantitative, and mixed methods
- Publications in English
- Studies from any country

Exclusion criteria

- Synchronous telemedicine, including remote telephone and virtual consultations (audio only or video consultations)
- Studies in primary and community settings, which are not part of family or general practice (eg, community nursing, pharmacy, dental care, optometry, and mental health services), with the context of interest being general practice, including general practitioner–led teams but excluding independent community or pharmacy-only services
- Studies focused only on remote consultations without a preconsultation component
- Tools limited to automated decision support (eg, back-end artificial intelligence decision aids used only by clinicians) without patient input
- Telemonitoring interventions
- Interactions solely between health care professionals
- Editorials, commentaries, opinion pieces, study protocols, case reports, conference abstracts, research theses, and policy documents

Information Sources and Search Strategy

A structured literature search was conducted on May 12, 2025, across 4 electronic databases: MEDLINE (via Ovid), Embase (via Ovid), CINAHL (via EBSCOhost), and the Cochrane Library. Searches were limited to studies published from January 2021 onward to reflect the rapid evolution of digital tools in general practice. The strategy combined terms related to general practice (eg, “primary care,” “general practitioner,” and “family medicine”) with terms describing digital and asynchronous consultation methods (eg, “Accurx,” “eConsult,” “online consultation,” “remote consultation,” and “telemedicine”).

Gray literature and policy documents will be identified through targeted searches of Google Scholar and relevant NHS or government websites. The database searches yielded 6991 records, with 4536 (64.88%) remaining after deduplication. The complete search strategy is provided in Multimedia Appendix 2.

The search was restricted to studies from January 2021 onward to capture post–COVID-19 pandemic acceleration of digital preconsultation systems. Earlier literature has been summarized in previous reviews of online consultation tools conducted before or during early COVID-19 phases [3-6]. As a sensitivity check, we will screen a sample of highly cited pre-2021 records to confirm no new concepts have been omitted. Non-English studies with English abstracts will be considered at the abstract level.

Selection of Sources of Evidence

Three researchers will screen all titles and abstracts against the eligibility criteria. There will be an initial pilot phase to operationalize and standardize definitions to optimize levels of agreement. To ensure consistency, an initial 20% of the titles and abstracts will be independently screened in duplicate to calibrate reviewers and estimate interrater agreement (target Cohen $\kappa \geq 0.8$) [12]. If the agreement falls below this threshold, the proportion screened in duplicate will be increased. Screening will be managed in Rayyan [13], with automated deduplication and tracking via EndNote (Clarivate). All full-text articles will undergo duplicate screening. Any discrepancies will be resolved through discussion or adjudication by a third reviewer.

Definition of Key Concepts

General practice is the first point of contact in the health care system. It provides a range of services, including diagnosing and treating medical conditions, managing long-term illnesses, prescribing medicines, delivering vaccinations, promoting health, and referring patients for specialist care. General practice includes general practitioners (GPs), nurses, allied health professionals (eg, pharmacists, physician assistants, and physiotherapists), and administrative staff working as part of a multidisciplinary team [14].

Consultation is defined based on a theoretical framework derived from the model of the patient-centered consultation proposed by Stewart et al [15]. This model provides the most widely cited definition of consultation in UK primary care. It encompasses the following elements: (1) exploring both the disease and the illness experience; (2) understanding the whole person; (3) finding common ground regarding management; (4) incorporating prevention and health promotion; (5) strengthening the physician-patient relationship; and (6) “being realistic” and recognizing personal limitations and practical constraints, such as the availability of time and resources

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Digital refers to "the use and transfer of information using devices and technology, such as computers and smartphone applications, and the infrastructure and processes used to do so" [16].

Telemedicine "is the use of telecommunication and information technology for the purpose of providing remote health assessments and therapeutic interventions" [17].

Synchronous telehealth refers to real-time communication between a patient and a health care professional in different locations, using audio or video technology [18].

Asynchronous telehealth refers to the use of digital tools that enable the collection and review of clinical information, such as text, images, or data, at a later time. This includes store-and-forward systems as well as online patient queries submitted via portals or apps [18]. This is a communication where clinician review occurs later and not in real time.

Preconsultation information sharing refers to any digital submission of information that precedes synchronous clinical interaction.

Demographic factors refer to the characteristics of populations that help describe who is using digital tools and how use may vary. In this review, demographic factors include age and sex or gender.

Socioeconomic factors refer to an individual's social and economic position, which may influence access to and engagement with digital health services.

The following definitions apply:

- Age refers to the patient's chronological age, which may affect digital literacy, health needs, and engagement with technology.
- Gender refers to socially constructed roles and identities (eg, male, female, or nonbinary), which can influence health-seeking behavior and communication preferences.
- Education level reflects the highest level of formal education completed and may affect digital competence and health literacy.
- Income level refers to an individual's or household's financial resources, which can shape access to technology, internet connectivity, and health services.

Data Collection Process

Data will be extracted using a prepiloted data charting form developed by the review team. There will be an initial pilot phase using the form to operationalize and standardize definitions and optimize levels of agreement. Two reviewers will independently extract data from all included studies. Discrepancies will be resolved through discussion or by a third reviewer, if needed. Extracted data will include authors, year, country, study design, health care setting, description of the digital tool or system, target population, implementation features, outcomes measured, and key findings. Extracted data will be cross-checked against predefined review questions and outcome categories to ensure consistency and accuracy.

Synthesis of Results

Extracted data will be summarized in tabular and narrative form. Thematic analysis will be used for qualitative data, and frequency counts will be used to summarize key characteristics across studies. Qualitative findings will be organized using a deductive framework derived from established domains in digital health evaluations: access and equity, workload or substitution, timeliness, safety, usability, costs, and implementation context. A preliminary codebook will be piloted on 10 studies and refined iteratively. Quantitative outcomes will be tabulated descriptively by study design and population subgroup (eg, age, deprivation, ethnicity, rurality, and digital exclusion).

Quality Appraisal and Risk of Bias Assessment

Although formal quality assessment is not mandatory in scoping reviews, we will use the Mixed Methods Appraisal Tool (MMAT; version 2018, Canadian Intellectual Property Office) to assess the methodological quality of included studies. The MMAT is designed to appraise qualitative, quantitative, and mixed methods studies within a single tool, making it well suited to the diverse evidence base anticipated in this review. Given the likelihood of heterogeneity in study designs, the MMAT provides a consistent and structured approach to assess study rigor (without excluding studies based on quality) and supports transparent reporting of study limitations [19]. Two reviewers will independently assess the methodological quality of all included studies using the MMAT [19]. Disagreements will be resolved through discussion or by a third reviewer, if needed.

Dissemination

Findings will be disseminated in a peer-reviewed journal and at an academic conference. The results may inform future implementation strategies and areas for targeted evaluation.

Results

This scoping review began in May 2025. Full-text screening and final eligibility assessments were completed in November 2025. Data extraction and analysis will be conducted between December 2025 and February 2026, with findings to be submitted for publication in a peer-reviewed journal in early 2026.

On the basis of previous research, we anticipate considerable heterogeneity in study design, populations, and outcome measures. However, more recent and larger-scale evaluations are also likely to be included, reflecting the increasing adoption of asynchronous digital information-sharing tools in primary care. This review aims to improve understanding of how patients share information digitally before consultations and the implications for quality, safety, equity, and clinical outcomes in general practice. Figure 1 summarizes the study selection process using the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram [20].

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Figure 1. Preliminary PRISMA flow diagram. *Automation tools: Rayyan and EndNote (Clarivate).

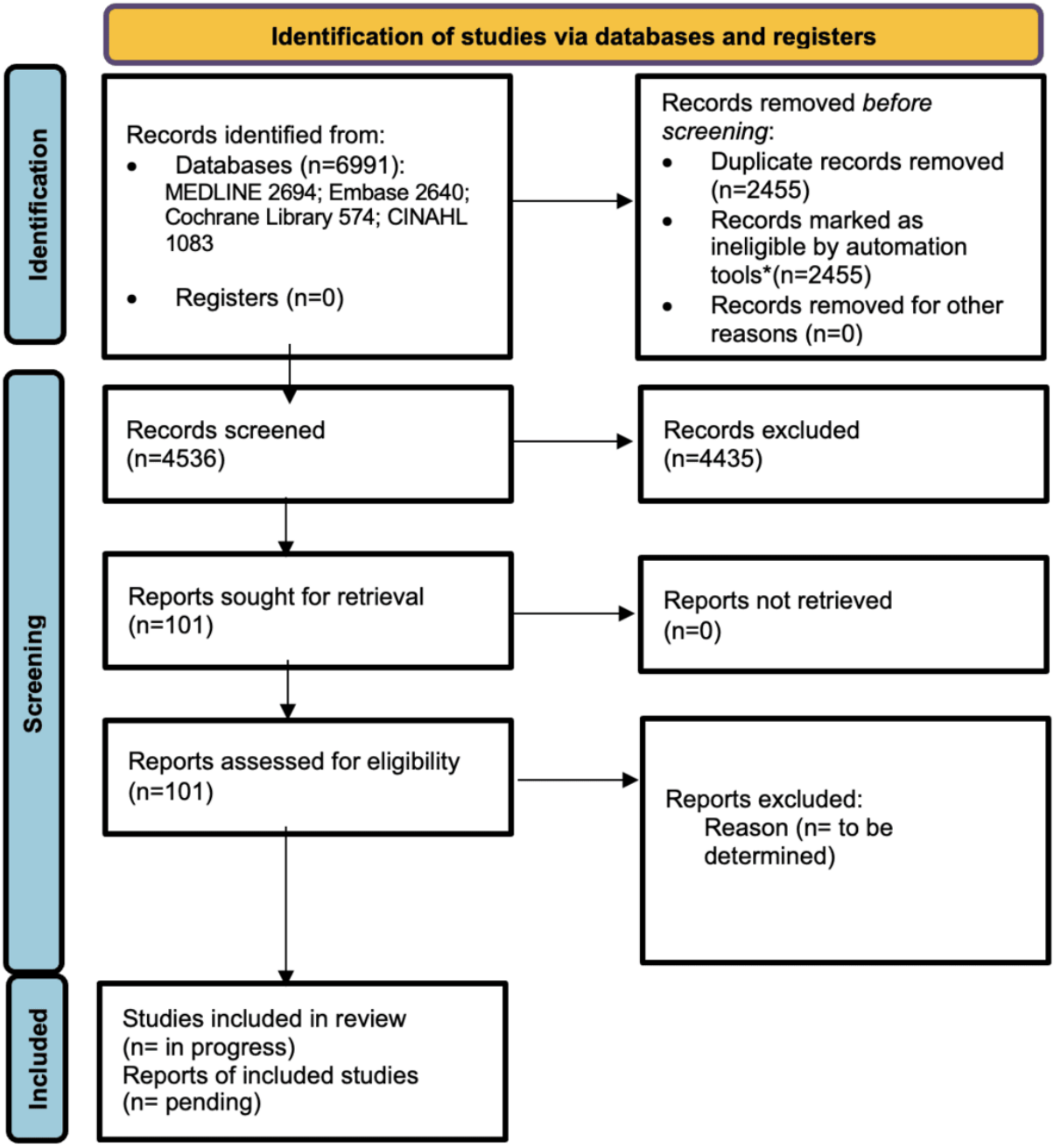

Discussion

Anticipated Findings

This review will summarize evidence concerning the use of digital tools for preconsultation information sharing in general practice. Findings will inform implementation, research priorities, and service improvement in digitally supported care and could impact health inequalities.

Strengths and Limitations

This review will be the first scoping review to systematically map the evidence on digital tools used for preconsultation information sharing specifically within general practice, following their widespread adoption in the wake of the COVID-19 pandemic. It will use a comprehensive search strategy across multiple databases; follow the PRISMA-ScR guidelines; and apply the Joanna Briggs Institute population, concept, and context framework to guide study selection. The inclusion of all study designs and the use of MMAT will allow for consistent assessment of methodological quality across heterogeneous evidence.

However, as a scoping review, it will not include a meta-analysis. Quality appraisal will support interpretation but not be used to exclude studies. In addition, the focus on general practice may limit the generalizability of findings to other health care settings. Partial duplicate screening risks missing eligible

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studies. However, our approach involves an initial 20% dual screening with interrater reliability checks (target κ≥0.8) and verification by a third reviewer when discrepancies arise.

Comparison With Other Studies

A range of digital tools has been introduced in general practice to allow patients to share information before consultations. A retrospective evaluation in Spain found that eConsulta (an asynchronous teleconsultation tool) could avoid in-person appointments in up to 87.9% of cases, particularly for test results, medical queries, and repeat prescriptions. However, 27.7% of interactions represented additional demand, potentially stimulated by ease of access [4].

In England, similar platforms (eg, webGP, askmyGP, Tele-Doc, and eConsult) have been piloted and studied with mixed outcomes before the COVID-19 pandemic. A mixed methods evaluation of webGP piloted across 6 practices in Devon revealed low uptake, with GPs judging that 72% of the online requests still required a telephone or face-to-face consultation. While patients found the system broadly acceptable, it shifted responsibilities between patients and practice staff, introducing tensions with existing workflows [3]. A retrospective study analyzing data from 9 UK practices using askmyGP found that use was highest among female individuals and those aged between 25 and 34 years. Online activity peaked early in the week and during morning hours. Most consultations were for medication-related or administrative reasons. While some patients reported convenience and ease of use, these benefits were context dependent [5].

Other studies highlighted implementation challenges. For example, Tele-Doc uptake was limited, with increased responsibility placed on patients and administrative staff [21]. A 15-month pilot across 36 practices, uptake of eConsult was low (mean 2 consultations per 1000 patients per month), with most consultations occurring during working hours. Most patients were women (64.7%), with a median age of 39 years. The most common reasons were administrative requests and infections. Approximately 70% of the patients received a follow-up via telephone or face-to-face, and the average cost per e-consultation response was £36.28 (about US $49.20), mainly driven by subsequent face-to-face or telephone consultations [22].

A sequential mixed methods evaluation of eConsult use in Devon and Cornwall found that while COVID-19 led to increased use, concerns remained about usability, repetitive forms, and the lack of continuity. Older adults had lower uptake despite being frequent users of face-to-face care. Only 3% of the consultations included feedback forms, and GP websites often failed to meet accessibility standards [23]. A 6-month evaluation across 11 practices in Scotland found that eConsult largely met expectations as an additional access route to GP services but there was less certainty in its ability to promote self-management. Uptake was low, and successful implementation required strong internal leadership and process protocols [24].

An analysis of NHS clinical commissioning groups' annual reports in England revealed wide variation in digital capabilities across regions [25]. Using a digital options framework, 3 clusters of digital maturity were identified: digitally disengaged, digitally engaged, and digital torchbearers. Despite national policies promoting digital transformation, almost half of clinical commissioning groups, particularly in London, were classified as digitally disengaged. The study suggested that improving digital health literacy and inclusion efforts is as important as advancing technical innovations [25]. Evidence from the Netherlands also suggests that digital tools may increase overall consultation rates and associated costs, potentially reflecting greater accessibility [26].

A systematic review using normalization process theory identified key factors influencing the successful implementation of asynchronous online platforms. Although patients valued the convenience of digital consultations and health care staff felt confident using the platforms, integration issues, increased workload, usability problems, and concerns about confidentiality and health inequities prevented embedding into routine practice. Recommendations included improving platform usability, integration with clinical systems, and targeted support for different patient groups [27]. In addition, digital preconsultation systems may inadvertently widen access gaps. Patients with limited English proficiency, low health literacy, or limited digital access could find these platforms more difficult to use, leading to differential engagement and outcomes. Understanding how such tools affect equity of access will be a critical dimension of future evaluation.

Implications for Practice and Research

This review will offer a comprehensive synthesis of how digital tools are used to collect patient information before consultations in general practice. Findings will inform clinicians, commissioners, and policymakers about the range and characteristics of preconsultation digital tools, their implementation contexts, and reported outcomes. This may guide more effective integration of asynchronous digital tools into general practice workflows and highlight implications for workload, access, and patient experience. The review will also identify evidence gaps and inform priorities for future evaluation and implementation research, particularly about safety, equity, and system-wide adoption.

Conclusions

Asynchronous digital tools for preconsultation information sharing are becoming increasingly integrated into general practice. However, the evidence on their design, use, and impact on health inequalities remains fragmented. This review aims to map the existing literature and provide a foundation for future research and implementation strategies that support the safe, equitable, and effective use of digital tools in general practice.

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Data Availability

Data are supplied in supporting files available for download along with the published manuscript.

Authors' Contributions

Conceptualization: SJG, MSR
Methodology: MSR, MK, ZS, IK, HD-M, PO, SJG
Supervision: SJG
Writing—original draft: MSR
Writing—review and editing: MSR, MK, ZS, IK, PO, HD-M, SJG

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-ScR checklist.
[DOCX File , 115 KB - resprot_v14i1e82649_app1.docx]

Multimedia Appendix 2
Complete search strategy.
[DOCX File , 19 KB - resprot_v14i1e82649_app2.docx]

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Abbreviations

GP: general practitioner
MMAT: Mixed Methods Appraisal Tool
NHS: National Health Service
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses Extension for Scoping Reviews

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Protocol

Use of Head-Mounted Inertial Sensors for Mobility Tasks: Protocol for a Scoping Review

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Abstract

Background: Human activity recognition (HAR) is the use of technology to detect a person's movements. Sensors can be passive like cameras monitoring an area, or active like those attached to a person's watch. HAR is a burgeoning field whose uses span from personal health tracking to at-home physical degradation monitoring. The benefit of having sensors attached to a person for constant HAR tracking can be seen in the personal fitness field where people track their number of steps or distance ran. For older adults, HAR can be used in combination with mobility tasks like sit-to-stand, timed-up-and-go, and other tasks to monitor a person's ability to be self-sufficient and to live alone at home. Together, HAR and mobility tasks are an effective method to measure health, especially in older adults. Consumer wearables like Fitbits and Apple watches are currently being used to measure many of these mobility tasks. The wide adoption of these devices is a result of their ease of use and simplicity. Despite this, most wearables go unused shortly after purchase. A potential solution is the use of consumer devices that are already adopted like headphones or hearing aids. These devices can perform the same measurements as the wearables but have the advantage of being used for other reasons than health monitoring. Despite this, no scoping review has summarized the current capabilities of what can be done using head-worn sensors.

Objective: We aim to understand how head-worn devices have been used to monitor dynamic mobility tasks and if they have been compared to traditional methods (like smartwatches or in-sole sensors).

Methods: This scoping review will be guided by the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) framework. There is no time limit to when the papers must have been published. The databases included in the search are PubMed, Engineering Village, SCOPUS, and Web of Science. Using pre-established inclusion and exclusion criteria, 2 reviewers will screen each paper. We will follow 3 stages of the screening process: abstract and title screening, full-text screening, and full-text data extraction.

Results: The search will be started once this scoping review protocol is published.

Conclusions: Head-mounted devices have become part of everyday life and many already contain accelerometers or inertial measurement units. This scoping review will examine how these sensors have already been used in research to measure mobility tasks, and determine how consumer devices can be adapted to improve the lives of regular people.

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KEYWORDS

inertial sensor; mobility; accelerometer; human activity recognition; inertial measurement unit; sensor; wearable device, scoping review

Introduction

Background

Physical activity is defined as the energy expenditure from bodily movement [1] and has been shown to help prevent heart disease, type 2 diabetes, and many other ailments [2]. Given the health implications, enabling a person to track their own physical activity to help them reach the recommended levels can have positive effects on their health [3]. Similarly, this tracking can also be harnessed by medical professionals to identify where problems may stem from or to monitor a patient's adherence to a prescribed medical routine. Physical activity is especially important for older adults as a sedentary lifestyle increases the percentage of body fat and decline of lean body mass, causing a positive feedback loop [1]. At-home monitoring of one's physical activity levels can facilitate preventative action and enable tracking of their progress over time [4]. This technology relies on human activity recognition (HAR)—a field of research focused on detecting what a person is doing by using sensors. Closely tied to physical activity is a person's mobility level, which is the ability to move independently through the day [5]. Without a certain level of mobility, a person cannot perform physical activity to prevent health degradation. In a clinical setting, a person's level of mobility can be assessed using mobility tasks like sit-to-stand (STS), timed-up and go (TUG), and six-minute walk tasks. Unlike activity levels, these tasks have normative scores that are used as part of the assessment [6]. This review will include both clinical mobility tasks along with generic physical activity detection.

HAR systems can be implemented using environmental sensors (like cameras) or body-worn devices, each with distinct advantages and limitations. Camera-based systems face challenges with framing, clothing variations, and lighting conditions that can affect algorithm performance [7]. Wearable devices circumvent these issues by directly capturing body movement through inertial measurement units (IMUs), which record tri-axial acceleration and angular velocity data [8]. These sensor data enable extraction of basic activity metrics like step counts [9] and energy expenditure [10], as well as detailed gait parameters including walking speed, step length, cadence, and step symmetry. These gait characteristics have clinical significance, with research showing disease-specific patterns such as prolonged stance times following stroke [11], reduced medial-lateral acceleration after concussion [12], and shuffling gait patterns in Parkinson disease [13]. While walking speed has been used as an effective metric to measure a person's physical health [14], other movements are used in medical testing. An example of this is a 5 times STS test that is used for determining fall risk in patients with Parkinson disease [15]. Several mobility tests can be performed, like a 5 times STS test, six-minute walk test [16], and the TUG test [17], to name a few. These tests provide data for extracting the gait characteristics mentioned earlier. In this review, we will attempt to include all mobility tests by searching for generic terms like walking, mobility transition, and others, along with some named mobility tests mentioned above.

Despite the many ways people can benefit from using wearables, these devices often see a low adoption rate. Participants in studies investigating why people would abandon their devices often mention that they are not the target users for these devices [18]. Since these devices are purchased with the intent of physical activity tracking [19], the person loses interest in the device if they stop exercising. Even if the person is not exercising, the benefits of monitoring the person's activity levels do not change. Instead, the wearable device they use for physical activity tracking should have some primary purpose that will cause them to adopt the device in the long term. Examples of such devices are hearing aids and earbuds. Hearing aids are often needed and used by older adults [20] who would benefit from physical activity monitoring. Although there is a large need for using hearing aids, there is still difficulty with their adoption for similar reasons as wearables [21]. Despite this problem, if the older adults who use hearing aids also adopt physical activity monitoring, there would still be a large benefit.

Earbuds are another popular but less suitable option. Since they are not worn the entire day, they will not capture as much data as hearing aids. Unlike hearing aids, many people use earbuds when they exercise, creating an opportunity to capture still important and usable data.

Head-mounted devices provide a unique challenge compared to other wearables. Unlike other locations of the body, the head's stability is important for movement of the body [22]. Because of this, the acceleration signals are attenuated as they pass through the trunk [23,24]. This causes the head acceleration signals to have a lower frequency [23] than other locations like the trunk. This attenuation process is also not uniform, with some directions having more attenuation than others [23]. Furthermore, there are differences in the effectiveness and method of attenuation as the person ages [25,26] and between genders [27,28]. When moving out of the laboratory into free-living environments, many characteristics in the data can change in unexpected ways. Knowing this, we intend to investigate what can be done using head-worn sensors for gathering data on activity levels and mobility tasks.

Prior Work

To our knowledge, no scoping review has focused on the use of head-worn IMUs for mobility tasks. The closest is Ionut-Cristian's [29] scoping review, which focuses on head motions quantified by IMUs. Their review covered all movements with a focus on head gestures and their integration in augmented reality. Their goal was to contextualize IMU technology for helping people with partial or total paralysis. This review will focus on any paper using head-worn IMUs for capturing the previously discussed mobility tasks.

Our motivation stems from our previous work in using IMUs in hearing aids for step counts, TUG, and STS [30,31]. When

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undertaking that work, there was no clear approach for HAR and mobility task analysis for head-worn sensors. Given the difference in signal information from other body parts, we believe that covering what has been done in this area is important for the field.

Research Questions

The aim of this scoping review is to summarize previous work investigating the use of head-mounted IMUs for gathering mobility measures. Specifically, we aim to identify (1) the outcome measures that can be assessed with head-mounted sensors, (2) the methods for computing these measures, and (3) what devices are used for data acquisition.

Methods

Study Design

A preliminary search was performed for related reviews, from which we found the earlier mentioned review [29]. We then met with an academic librarian to help prepare for undertaking the search. The reporting and writing of the scoping review will be guided by the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist.

Search Strategy

Based on a meeting with the librarian, we iteratively developed our keywords. We carried out the search based on our initial assumptions and then extracted keywords from the relevant articles. The initial search was conducted within IEEE Xplore. The full list of searched terms is included in search strategy (Multimedia Appendix 1). The search was split into three concepts: (1) the mobility task (eg, gait, walk, STS, and TUG), (2) the mounting location or device used (eg, head-mounted device; earables, mastoid, or AirPods [32]; Google Glasses [33]; eSense [34]; and OmniBuds [35]), and (3) the sensor used (eg, IMU, gyroscope, and accelerometer). Mobility task–related keywords have been worded to capture all possible activities and are not restricted to “known” movement sets. The search query has been worded this way to capture movements that may not be directly related to clinical health tests but are still relevant to this review. The databases included in the completed search term list were PubMed, Engineering Village, SCOPUS, and Web of Science. We did not include IEEE Xplore, as it is included within several of the listed databases.

Throughout the search, we used Boolean operators. An example of a search for Engineering Village is provided in Textbox 1. We used the same search approach for each database with the addition of a NOT operator where appropriate.

Textbox 1. An example of a search on Engineering Village.

(stair* OR ascend* OR descend*) AND (accelerometer OR gyro*) AND (”hearing aid” AND earable* AND earbud*)

Inclusion Criteria

Textbox 2 lists the inclusion criteria for identifying articles included in the scoping review. We chose the mobility tasks through a combination of our interest in clinical outcomes, what was found in our preliminary search, and previous work we had undertaken [30,31]. Head-worn devices that used an accelerometer in combination with other sensors like gyroscopes, magnetometers, pressure, etc, were included.

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Textbox 2. Inclusion criteria.

Population

- Adults.

Mobility task

- Gait, walking, and running.
- Sit-to-stand task, timed-up-and-go task, Berg Balance Test, Six-minute walk task, and the 10-meter walk task.
- Ascending or descending the stairs.
- Human activity recognition or activity classification.
- Mobility tests.
- Balance and stability.

Mounting location or branded devices

- Attached to the ear, including earbuds, hearing aids, and earables.
- Secured to the head using bands and/or straps.
- Glasses with sensors attached or embedded.
- AirPods, OmniBuds, eSense, or Google Glasses.

Device Types

- Any device that measures inertial movement including accelerometers and inertial measurement units.

Expected outcome measures

- Types of movements classified (eg, walking vs running vs standing).
- Gait parameters extracted (eg, speed, cadence, and stride length).
- Step count.
- Mobility task–specific variables (eg, time to complete the sit-to-stand task).

Limits

- Language: English

Exclusion Criteria

Textbox 3 lists the exclusion criteria. We excluded articles that reported on the use of multiple sensors where data recording and analysis included fusion with results from a non–head-mounted sensor. An example is the use of a chest-worn IMU in combination with a head-worn IMU.

Textbox 3. Exclusion criteria.

Population

- Children.
- Animals.
- Simulations.

Mobility task

- Gestures like nodding and shaking the head.
- Chewing, speaking, and smiling or other related mouth activities.

Mounting location

- Sensor fusion between a head-mounted device and a device at any other location.

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Study Screening and Selection

Using the set-out criteria, 2 authors (WS and GM) will independently screen the identified articles. The online software DistillerSR [36] will be used for all parts of the search, including title/abstract screening, full-text screening, and data extraction. The complete extraction sheet is provided in Multimedia Appendix 2, but it was implemented inside of DistillerSR. Any conflicts will be resolved through discussion between the authors until consensus is reached.

Results

The data collection process has begun, and we expect the results to be published in spring of 2026.

Discussion

Principal Results

Currently, extensive research is being carried out on head-worn sensors for mobility tasks. While there has been successful work on implementing step counting [37-40], gait parameter extraction [41-48], the use of virtual reality headsets [49,50], and hearing aid integration [51], there is no comprehensive synthesis of the current state of the research. Presenting a review of this field would be beneficial to show what algorithms have been implemented and what metrics are being used.

The use of head-worn sensors represents an opportunity to capture users' physical health data through devices already integrated into daily routines. The sensors are embedded in commercial products, making them more likely to be adopted by users. With these sensor data, we can track a person's activity levels for personal use or support clinical assessments of mobility function.

However, placing sensors on the head, as opposed to other locations, presents unique technical challenges compared to traditional wrist-worn devices. Head-mounted IMUs capture attenuated acceleration signals, with the degree of the signal dampening varying across individuals due to differences in body mechanics. For reliable health assessments, we must ensure that mobility parameters can be accurately extracted despite these signal characteristics.

This scoping review aims to summarize current approaches for capturing mobility data from head-worn sensors. We will examine the algorithms used, the types of data collected, and sensor placement considerations to provide a comprehensive understanding of current capabilities and limitations.

Limitations

There may be limitations to what questions this scoping review can answer. Since the wearable field is so rapid and unstructured, we may miss relevant papers. An example of this is the consequence of using abbreviated product names that mask the device's purpose, making us rely on the tagging system of the databases we searched.

Conclusions

Human activity recognition is a burgeoning field with many consumer products and companies focusing entirely on the problem. This scoping review aims to answer questions on how sensors in head-worn devices have been used to solve activity detection for various health purposes and then discuss where future research should be focused.

Data Availability

The extraction table data will be made publicly available upon publication of the scoping review.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Search strategy.
[DOCX File , 15 KB - resprot_v14i1e67628_app1.docx]

Multimedia Appendix 2
Data extraction methods.
[DOCX File , 29 KB - resprot_v14i1e67628_app2.docx]

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Abbreviations

HAR: human activity recognition
IMU: inertial measurement unit
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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STS: sit-to-stand
TUG: timed-up-and-go

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Protocol

Assessing the Readiness of Local Vaccine Manufacturing in African Countries: Protocol for a Scoping Review

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Abstract

Background: Although Africa experiences the highest burden of infectious diseases, the continent currently produces less than 1% of its vaccine needs. In 2021, the African Union set a target to locally produce at least 60% of the continent's vaccine needs by 2040. However, at the time of developing this scoping review protocol, there is no consolidated, evidence-based framework for assessing national or regional "readiness" to establish or scale vaccine production.

Objective: This protocol aims to describe a methodological approach that will be used to review existing literature to identify, map, and synthesize the existing evidence on all relevant frameworks, indicator sets, and policy documents (global or national) developed pre- and post–COVID-19 pandemic (January 1, 2010, to December 31, 2025) that addresses readiness for local human vaccine manufacturing with focus on African countries.

Methods: This scoping review will be conducted and reported in accordance with the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines, following the 9-step framework outlined in the Arksey and O'Malley methodology and further informed by guidance from the Joanna Briggs Institute. We will search MEDLINE (PubMed), Scopus, Web of Science, Africa-focused databases (eg, Africa-Wide Information, African Index Medicus, and African Journals Online), and gray literature. Eligibility criteria will follow Population, Concept, and Context guidelines (Population: 55 African Union member states; Concept: readiness frameworks, indices, indicators, and policies for human vaccine manufacturing; Context: African national or regional initiatives or global frameworks applied to Africa). Materials in English, French, Portuguese, or Arabic will be included. Publication types will be limited to frameworks, policies, guidance, and reports. Two reviewers will perform calibrated dual screening (Cohen κ) and standardized data charting. We will create an evidence map and inductive thematic synthesis using a vaccine-specific Political, Economic, Social, Technological, Legal, Environmental, plus Market taxonomy. Consistent with the guidance by the Joanna Briggs Institute, critical appraisal will not be performed. An optional expert consultation will help identify missed sources and validate domains.

Results: Ethics approval for the expert consultation component was obtained from the University of Geneva Research Ethics Committee (application submitted May 21, 2025; approval September 9, 2025). The initial search strategy has been finalized, and pilot searches were completed (May-August 2025). The screening calibration is planned; dual-review title and abstract screening begins in December 2025, with full-text screening and data charting scheduled for January-March 2026. Thematic

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synthesis and expert consultation are planned from April to May 2026. We anticipate submitting the completed scoping review paper by June or July 2026.

Conclusions: This review will generate Africa's first continent-focused evidence map of vaccine-manufacturing readiness, compiling indicators by domain, comparing frameworks, identifying gaps, and informing a multidomain Country Readiness Assessment Index for policy and investment decisions.

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KEYWORDS

vaccines; manufacturing; readiness; Africa; frameworks; indicators; scoping review; PRISMA-ScR; Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews; policy; capacity building

Introduction

Background

Despite substantial scientific contributions of African researchers in vaccine research and development (eg, HIV Vaccine Trials Network/South African AIDS Vaccine Initiative for HIV, South African Tuberculosis Vaccine Initiative–led tuberculosis trials, and pivotal COVID-19 vaccine studies in South Africa), local vaccine manufacturing capacity across Africa remains minimal [1], currently supplying less than 1% of the continent's needs [2]. This heavy reliance on imports was starkly highlighted during the COVID-19 pandemic, when African countries faced delayed access to vaccines due to external supply constraints [2,3]. In response, the African Union and Africa Centres for Disease Control and Prevention (Africa CDC) have set an ambitious goal: by 2040, 60% of vaccines needed in Africa should be produced locally [1]. Achieving this target is critical for health security and equity, as it would reduce dependence on global supply chains and improve the continent's ability to respond to epidemics.

Country-level experiences reveal significant variation in vaccine manufacturing "readiness." South Africa, through firms like Biovac and Aspen Pharmacare, has demonstrated higher readiness in several domains, including regulatory maturity, fill-finish capacity, and active technology transfer partnerships [2,3]. Senegal's Institut Pasteur de Dakar highlights both legacy strengths and persistent gaps, combining long-standing yellow fever vaccine production capability with newer platform investments and ongoing challenges in supply chain resilience and financing [3,4]. More recently, countries like Rwanda and Ghana have launched national vaccine manufacturing strategies; yet, they remain in the early stages of building infrastructure, policy frameworks, and regulatory systems necessary to translate political commitment into operational capacity [5,6].

These examples underscore the diversity of readiness across African countries. However, despite growing momentum and multiple global initiatives and frameworks (eg, the Partnership for African Vaccine Manufacturing [PAVM] Framework led by Africa CDC to boost Africa's vaccine manufacturing ecosystem, World Health Organization's (WHO) Regional Framework for strengthening local production [7], Gavi, the Vaccine Alliance African Vaccine Manufacturing Accelerator platform [8]), there is no standardized, multidomain tool for assessing a country's vaccine manufacturing readiness. That is, no consolidated framework or index exists that integrates indicators spanning technical infrastructure, policy environment, regulatory maturity, supply chain, workforce, and financing systems [9].

Literature Gaps

To address this gap, we conducted a search between May and August 2025 across PubMed, major gray literature repositories, Open Science Framework, and International Prospective Register of Systematic Reviews for completed or ongoing evidence syntheses on this topic (Multimedia Appendix 1). No published or registered scoping or systematic review with an equivalent scope was identified. Recently, although reports and commentaries have begun to catalog facilities, map pipelines, or describe enabling factors for vaccine production in Africa, the existing literature falls short. First, most outputs are single-domain (eg, regulatory benchmarking, financing mechanisms, or facility counts) and do not integrate across technical, regulatory, workforce, policy, and supply chain dimensions to yield a country- or a regional-level picture of "readiness." Second, indicators are heterogeneous and inconsistently defined across sources, limiting comparability and precluding aggregation into a standardized index. Third, many assessments are cross-sectional (often COVID-19 era snapshots), providing little longitudinal insight into how readiness evolves. Fourth, several influential sources are gray literature or program documents with unclear methods, limited transparency on indicator selection or weighting, and minimal external validation. Fifth, most frameworks are not tailored to the African policy environment (eg, procurement modalities, regional market-shaping initiatives, and technology-transfer pathways), reducing their applicability. Finally, few publications explicitly link measured domains to actionable thresholds (what constitutes "ready enough") [3,4,10,11]. These limitations underscore the need for a scoping review to systematically map concepts, indicators, and gaps across sources, and to inform the development of a transparent, multidomain Country Readiness Assessment Index (CRAI) suitable for African contexts.

Rationale of the Scoping Review

A scoping review is therefore warranted for 3 key reasons. First, the concept of vaccine manufacturing "readiness" is multidimensional and inconsistently defined across sources ranging from regulatory maturity to workforce capacity,

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financing, and policy frameworks [3,4]. Scoping reviews are particularly suited to clarifying key concepts, mapping the breadth of available evidence, and identifying gaps in complex or emerging fields. Second, the available literature is heterogeneous, spanning peer-reviewed studies, technical reports, policy documents, and organizational frameworks. Systematic reviews are designed to answer narrowly focused questions on intervention effectiveness, whereas a scoping review can accommodate this diversity of evidence and synthesize it into a coherent map [12-14]. Third, no published or registered review has yet consolidated frameworks, indicators, and policies for assessing vaccine manufacturing readiness in Africa, despite clear demand from regional bodies, such as the African Union and Africa CDC, for standardized tools [3,4]. Conducting a scoping review will therefore establish the evidence base required to guide the development of a tailored readiness index and inform policy and investment priorities.

Definition of Readiness

For the purposes of this review, readiness is defined as the extent to which a country has the foundational systems and conditions to initiate or scale local vaccine production [15]. These include regulatory capacity, enabling policies, physical infrastructure, supply chain systems, financing mechanisms, and skilled workforce availability. This review will focus specifically on readiness, as this concept is both amenable to scoping review methodology and grounded in accessible evidence sources, such as policy documents, technical reports, and regulatory tools. In contrast, related concepts like capability (operational performance) and viability (economic sustainability) rely on proprietary or facility-level data that are not consistently available [16,17].

Scoping reviews are designed to clarify concepts, collate heterogeneous evidence, and identify gaps rather than to assess operational performance or economic feasibility. Accordingly, focusing on readiness enables the review to generate a comprehensive knowledge map that is both methodologically sound and directly relevant for informing policy and investment priorities in Africa [18].

The findings from the scoping review will directly inform the subsequent development of a CRAI for vaccine manufacturing in Africa. By systematically mapping the dimensions of readiness described across peer-reviewed studies, organizational frameworks, and policy documents, the review will identify common domains, indicators, and measurement approaches that can serve as building blocks for the CRAI. Gaps revealed through the review will highlight where new indicators or methodological innovations are required. In this way, the scoping review functions not only as a synthesis of existing knowledge but also as a methodological foundation for designing and validating a tailored, multidomain tool to evaluate readiness at the country or regional level.

Scope and Unit of Analysis

Our unit of analysis is the country, not the industry. Vaccine manufacturers operate within and are constrained by the political, regulatory, and socioeconomic context of their host countries; therefore, durable manufacturing capacity depends on country-level readiness. Assessing readiness at this level enables governments to identify priority gaps, target interventions, build capabilities, attract strategic investment, and foster international collaboration, laying the groundwork for vaccine self-sufficiency and stronger public health resilience by 2040.

Ultimately, CRAI responds to the urgent need for evidence-informed strategies to build Africa's vaccine production capacity, will serve as a tool for benchmarking, strategic planning, and resource mobilization to support Africa's vaccine manufacturing ambitions.

Review Objectives

The objectives of this scoping review protocol are (1) to describe a methodological approach that will be used to review existing literature to identify, map, and synthesize the existing evidence on all relevant frameworks, indicator sets, and policies related to readiness for local human vaccine manufacturing in African countries; (2) derive and validate a taxonomy of readiness domains and indicator set from included sources; and (3) produce standardized outputs including a framework-mapping table, theme×frequency summary, and a master indicator catalog to inform construction of a CRAI (Multimedia Appendix 2).

In alignment with the Joanna Briggs Institute (JBI) scoping review methodology, we aim to broadly explore all relevant concepts and evidence on this topic [13,14,18,19]. We adopted the JBI enhancement for conduct because it provides operational, step-by-step guidance tailored to scoping reviews covering Population, Concept, and Context (PCC) framing, eligibility specification, search or selection, standardized data charting, and stakeholder consultation, thereby supporting methodological consistency across heterogeneous evidence. Specifically, the review will chart the characteristics of any published materials that define or assess a country's readiness to produce vaccines locally. This includes global-level frameworks or readiness indices proposed by organizations such as WHO, Gavi, Coalition for Epidemic Preparedness Innovations, as well as national strategies, policy documents, and academic studies from or about specific African countries. By mapping these sources, the review seeks to understand the dimensions commonly considered part of "manufacturing readiness" (regulatory readiness, technical infrastructure, workforce, financing, supply chain, etc), and to summarize how readiness has been measured or conceptualized to date. Ultimately, the objective is to produce a comprehensive overview that will inform the development of a new composite readiness index for vaccine manufacturing in Africa.

Methods

Conceptual Framework

We will adapt and use a vaccine-specific taxonomy, which is Political, Economic, Social, Technological, Legal, Environmental, plus Market (informed by Political, Economic, Social, Technological, Legal, Environmental [20] model), to structure data charting and synthesis. Each domain is defined for human vaccine manufacturing readiness, with illustrative indicator examples (used only as guides; final indicators will

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be those extracted from sources. The indicative domains include Policy and governance, Economic and financing, Social and workforce, Technology and infrastructure (including drug substance and drug product functions, Legal: intellectual property and regulatory systems, Environmental and utilities (energy, water, and waste), and Market and demand. Examples include presence of a national strategy or roadmap (Policy and governance), viability-gap funding or guarantees (Economic and financing), Good Manufacturing Practice–trained workforce capacity (Social and workforce), drug substance bioreactor availability (Technology and infrastructure), Good Manufacturing Practice and Quality Assurance statutes (Legal), National Regulatory Authority maturity / African Vaccine Regulatory Forum participation or WHO Prequalification track record (intellectual property and regulatory systems), stable power and effluent management (Environmental and utilities), and multiyear offtake commitments (Market and demand).

Study Design

This scoping review was developed based on the Arksey and O'Malley scoping review methodology and further informed by guidance from the JBI [14,18,19]. The JBI's enhanced framework expands the 6 stages of Arksey and O'Malley into nine distinct stages for undertaking a scoping review: (1) defining the review question, (2) developing the inclusion and exclusion criteria, (3) describing the search strategy, (4) searching for the evidence, (5) selecting the evidence, (6) extracting the evidence, (7) charting the evidence, (8) summarizing and reporting the evidence, and (9) consulting with relevant stakeholders. For details, see Multimedia Appendix 3 on operationalization of JBI steps for vaccine-manufacturing readiness.

Step 1: Defining the Review Question

The overall main research question was defined as "What frameworks, indicators, or policies have been documented that relate to a country's or regional readiness for local vaccine manufacturing in African countries?" This broad question will be addressed by mapping evidence across various sources. In addition, we will consider the subquestions listed in Textbox 1 to ensure comprehensive coverage of the topic.

Textbox 1. Review subquestions.

Subquestions

- Which frameworks or models (conceptual or analytical) have been proposed to assess or guide vaccine manufacturing capacity or readiness, low- and middle-income countries, or in Africa?
- What indicators or indices have been used to measure readiness or enabling factors for local vaccine production (eg, multifactor readiness indices, assessment checklists, and benchmarking tools)?
- What policies, strategic plans, or initiatives have African countries implemented to enhance their readiness for vaccine manufacturing, and what do these documents identify as key readiness criteria or challenges?
- How do initiatives (by the World Health Organization, Gavi, Coalition for Epidemic Preparedness Innovations, etc) define or support "readiness" for vaccine manufacturing, and how are these frameworks being applied or adapted in African contexts?
- What gaps exist in the current literature and frameworks regarding vaccine manufacturing readiness, especially in areas such as regulatory systems, technology transfer, supply chains, financing, human capital, or partnerships?
- Are there lessons learned or failed attempts at vaccine manufacturing in Africa?

These questions collectively aim to capture both the content (the existing indicators, frameworks, and policies) and the context (who developed them, for what purpose, and applicability to Africa). The scoping review approach, with its broad question, is appropriate here since our goal is to map concepts and evidence rather than to answer a narrow effectiveness question [13,14]. As recommended for scoping reviews, we maintain a broad scope but with clearly articulated key concepts (PCC) to guide the search and selection of evidence [13,14,18]. The resulting review will address these questions above and highlight areas where evidence is abundant or lacking.

Step 2: Identifying the Relevant Studies (Defining the Inclusion and Exclusion Criteria)

To identify eligible studies and gray literature for review, we will apply the eligibility criteria outlined in Table 1, following JBI guidance on clearly specified inclusion criteria for scoping reviews [13,14,18]. Gray literature characteristics will be captured with Authority, Accuracy, Coverage, Objectivity, Date, and Significance descriptors [21].

We will apply the JBI's PCC framework to define and identify the inclusion criteria for this scoping review [13,14,18]. The PCC elements are outlined in Table 1.

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Table 1. Elements of the PCC (Population, Concept, and Context) framework.

Criterion	Include	Exclude
Population	Literature on any of the 55 African Union member states, multi-country or continent-wide African analyses, and global studies that report African data.	Studies with no African country data
Concept	Frameworks, indices, indicator sets, and policies that define or measure readiness for human vaccine manufacturing (infrastructure, regulatory, workforce, supply chain, finance, and markets). We defined the concept of readiness as the structural and system preconditions to initiate or scale human vaccine manufacturing. We will include items on capability or viability only when they explicitly define or operationalize readiness or contain readiness-measurable indicators.	Generic pharmaceutical and medicines manufacturing capacity papers, unless they contain vaccine-specific indicators. For example, papers focused solely on nonvaccine medicines (small-molecule active pharmaceutical agents, oral solids, and injectables unrelated to vaccines), medical devices, or diagnostics, with no vaccine-specific indicators.
Context	National or regional African initiatives; global guidance explicitly referencing Africa's manufacturing goals.	Veterinary-only production and manufacturing readiness in other continents (unless used purely for comparison).
Publication type	Peer-reviewed articles, government, agency, international governmental organization reports; strategy documents; theses; conference papers, registered preprints, and key repositories (eg, SABINET, institutional repositories, or ministries' websites).	Opinion or commentary without a framework or indicators, veterinary-only, non-African with no Africa application, basic research and development with no readiness link.
Language	English, French, Arabic, Portuguese (title and abstract screening used machine translation [DeepL/Google] for non-English records to enable first-pass triage.	All other languages.
Time frame	Publication years from January 1, 2010, to December 31, 2025. Pre- and post–COVID-19 era surge and policy momentum.	Publications before 2010.
Setting	Human vaccine manufacturing across the full value chain (antigen to fill-finish).	Downstream procurement, logistics, and service-delivery topics.

Steps 3 And 4: Describing the Search Strategy and Searching the Evidence—Search Strategy

Following the JBI-recommended methodology, we will implement a three-step search strategy to identify both published and gray literature sources [13,14]. The search strategy will be developed with the guidance of a reference librarian and adapted for other databases using appropriate controlled vocabulary and syntax. The search strategy will be designed to be comprehensive, aiming to capture the full scope of literature on our topic within practical limits [13]. The planned steps are listed below

Limited Search

First, we will conduct an initial exploratory search in 2 or more relevant databases, such as MEDLINE (via PubMed), using preliminary keywords related to vaccine manufacturing and readiness. An example of our initial search string in PubMed might include terms such as "vaccine manufacturing" OR "vaccine production" AND readiness OR capacity OR capability OR preparedness OR "local production" AND Africa OR African OR specific country names. We will examine the titles, abstracts, and index terms of the results from this initial search to refine our understanding of how relevant literature is described. This will help identify additional keywords, synonyms, and subject headings. For instance, we might discover terms like "vaccine industrialization," "pharmaceutical manufacturing capacity," or specific program names (eg, PAVM) that should be incorporated.

Comprehensive Search

Using the insights from Step 1, we will craft a more detailed search strategy and apply it across all selected information sources. This will include multiple bibliographic databases. We anticipate searching MEDLINE (PubMed), Scopus, and Web of Science. We will also search region-specific databases or repositories, such as Africa-wide Information, African Index Medicus, or African Journals Online, to capture research published in African journals. The database search strings will combine keywords and controlled vocabulary (eg, Medical Subject Headings terms like "Drug Manufacturing" or "Vaccines" and terms for readiness or capacity). We are developing and improving a search strategy in PubMed. For details, see Multimedia Appendix 4 to retrieve relevant literature.

We will tailor the search syntax for each database (using MeSH [Medical Subject Headings] in PubMed, etc, where appropriate). We will apply date and language limits. In addition to journal databases, we will search for gray literature systematically. This includes targeted searches of organizational websites and document repositories.

Reference List Search and Expert Recommendations

In Step 3, we will examine the reference lists of all included sources (backward reference checking) to identify any additional publications we might have missed. We will also use forward citation tracking on key articles or frameworks (using tools like Google Scholar's "cited by" feature) to find more recent works that cite known references. Moreover, as part of our methodology (and aligning with expert consultation plans described later), we will ask experts in the field to suggest any

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seminal or unpublished materials. This could include, for example, an expert alerting us to a forthcoming government policy or a workshop report that may not be indexed online. Any such sources that meet our inclusion criteria will be pursued. Throughout the search process, we will use an iterative approach: if we identify new keywords or acronyms (eg, if we find an index called "Vaccine Manufacturing Readiness Index" hypothetically, we would add that term to our search), we will rerun searches as necessary. All search strategies (database-specific strings and a list of gray literature sources searched) will be documented fully in the final protocol and subsequent report. Our goal is to ensure the search is as comprehensive as possible within resource limits, capturing published peer-reviewed studies, relevant conference papers or theses, and policy and strategy documents from the gray literature.

Step 5: Selection of Sources of Evidence

We will follow a transparent and rigorous selection process to screen the search results and determine the final set of sources for inclusion (see completed PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist, mapping each item to study sections provided in Multimedia Appendix 5). The selection will proceed in multiple stages, using a PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) flow diagram to report the process.

Data Harmonization and Deduplication

All records retrieved from the various searches will be imported into a reference management software (Zotero). Duplicate records will be identified and removed before screening. We will also integrate results into a systematic review management tool (such as Covidence) to facilitate screening and collaboration among reviewers. We will maintain a master indicator registry that assigns a unique ID to each distinct readiness indicator or framework. All extracted criteria will be mapped to unique IDs, and counts will be computed at the unique-indicator (unique ID) level, not per document, while preserving full source provenance. Overlaps (eg, WHO and AU citing the same criterion) will not be double-counted: exact and near-duplicate items will be merged under a single unique ID.

Title and Abstract Screening

Two reviewers (UAA and KJU) will independently screen the titles and abstracts of all retrieved records against the inclusion criteria. We will develop a screening guide based on our PCC criteria to ensure consistency. For example, any record not mentioning vaccines or not related to Africa will be quickly excluded at this stage. If information in the title or abstract is insufficient to determine inclusion, we will err on the side of inclusion and carry it forward to full-text screening to avoid premature exclusion. The two reviewers will label each record as "include," "exclude," or "unsure." We will then compare decisions and resolve any conflicts through discussion. In cases of disagreement that are not easily resolved, a third reviewer (CAN) will be available to arbitrate. Having at least two independent reviewers throughout the selection process will minimize bias and improve reliability [13]. We will keep a log of reasons for exclusion at the full-text stage, but not at the title or abstract stage, where the volume is larger, and reasons may be generic.

Full-Text Screening

We will obtain abstracts and the full texts (if available) of all records that passed the title or abstract stage or were marked as "unsure." Each full-text document will then be assessed in detail by two independent reviewers (UAA and KJU) for eligibility. We will use a predefined form to evaluate inclusion criteria on full text (confirming the population is African or relevant to Africa, the concept is vaccine manufacturing readiness, etc). Reasons for exclusion will be recorded for each excluded full-text article (common reasons might be "Not about vaccine manufacturing readiness," "Not focused on Africa," or "Opinion piece with no framework or data").

Final Inclusion

After full-text screening, we will have the final list of sources to be included in the review. We will document the number of sources included, as well as numbers excluded at each stage, with reasons (to be presented in the PRISMA-ScR flow diagram in the eventual review report). The inclusion of multiple reviewers and clearly defined criteria will enhance the methodological rigor of the selection process, ensuring we systematically identify relevant evidence while reducing the chance of omission due to error or bias.

We also plan a calibration exercise at the start of screening: the team will pilot screen a sample of titles or abstracts (50 references) together and compare decisions to refine the application of the criteria. Similarly, a pilot of a few full-text reviews will be done to standardize interpretation. This training set will help clarify any ambiguities in the criteria and improve consistency. All these steps follow best practices for scoping reviews to ensure a robust selection of evidence [13].

Steps 6 and 7: Extracting and Charting the Evidence—Data Extraction and Charting Process

We are creating a data extraction form in Microsoft Excel that will be used to extract relevant data from all included studies. We shall first pilot the form on a variety of a few studies. Key data elements outlined in Table 2 will be extracted by UAA and KJU.

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Table 2. Data items.

Data items	What will be captured?
Bibliographic info	Authors, year, title, source, publication type
Geographic focus	Country or region covered (eg, Kenya, multicountry, Africa-wide, and global)
Aim or purpose	Stated goal (new framework, capacity evaluation, policy analysis, etc)
Conceptual framework	Named model or pillars, or components of readiness, if provided
Indicators or criteria	Specific readiness measures listed (eg, National Regulatory Authority maturity, and workforce size)
Composite index	Existence, construction, and any scores or rankings of a readiness index
Key findings	Main facilitators or barriers, or conclusions relevant to readiness
Contextual factors	Noted enablers or constraints (tech transfer, raw-material supply, etc)
Recommendations	Actions or policy steps the source proposes to improve readiness
Stakeholder roles	Governments, industry, donors, or others identified, and their roles
Evidence type	Methodology (review, case study, survey, expert consultation, etc)

Data Items to Extract

For each included source (whether a journal article, report, or policy document), we plan to chart details listed in Table 2 (with adjustments as needed by source type).

Data Charting, Calibration, and Interrater Agreement

Two reviewers (UAA and KJU) will independently chart each source using a piloted form, reconcile by consensus, and monitor reliability (Cohen $\kappa \geq 0.70$). Charting will be iterative and reflexive: any field changes will be logged and applied retroactively to all previously charted sources. All data will be kept in a single versioned database. Before formal screening, 2 reviewers (UAA and KJU) will pilot the criteria on 50 titles or abstracts and 30-40 full texts. We will measure interrater reliability using Cohen kappa and percent agreement, aiming for $\kappa \geq 0.70$ at the title or abstract and $\kappa \geq 0.75$ at the full text. If thresholds are not met, we will refine the criteria and recalibrate. Disagreements will be resolved by consensus with a third reviewer (CAN) arbitration. All decisions and updates will be logged.

Step 8: Collating, Summarizing, and Reporting the Evidence—Analysis and Synthesis of Results

The extracted data will be analyzed using descriptive and thematic synthesis techniques appropriate for scoping reviews. Our approach will align with the JBI guidance to both quantitatively summarize the characteristics of included sources and qualitatively synthesize the emergent themes. The analysis will proceed in the following manner:

1. First, we will synthesize the evidence using a hybrid deductive–inductive thematic approach. We begin with an a priori codebook derived from a readiness taxonomy (PESTLE domains, regulatory-maturity elements, and vaccine manufacturing functions such as research and development, drug substance, and fill-finish). Two reviewers (UAA and KJU) will pilot code approximately 10% of sources to develop the codebook, resolve discrepancies, and finalize code definitions and inclusion and exclusion rules.
2. Descriptive (quantitative) summary: we will produce a numerical summary of the included evidence. This will include counts and frequencies, such as the number of sources by publication type (eg, X peer-reviewed articles, Y policy papers, and Z reports), by year of publication (to see trends over time), and by country focus (how many sources focused on South Africa, how many were multi-country, etc). We will likely present a table or a chart of the distribution of sources across countries and across source types. We will also enumerate the distinct frameworks or indices identified. For example, if we find 3 major global frameworks and, say, 5 country-specific frameworks, we will note that. Additionally, we might count how many sources mention certain domains of readiness, for example, if 90% of sources mention “regulatory capacity” as important, whereas only 50% mention “environmental factors,” that is an insight. This quantitative mapping provides a landscape view of the literature.
3. Thematic analysis (qualitative synthesis): we will conduct a content analysis of the data we charted to identify key themes and categories pertaining to vaccine manufacturing readiness. Using an inductive approach, the review team will examine the extracted data (especially the framework components, indicators, and recommendations from each source) and group similar items together. Likely themes (to be confirmed by the data) might include Policy and governance (eg, presence of national vaccine manufacturing plans, political economy drivers, partnerships, political will, and regulatory frameworks), Infrastructure and Technology (eg, existing manufacturing facilities, research and development labs, and cold chain infrastructure), Human Capital (skilled workforce availability and training programs), Regulatory Systems (strength of National Regulatory Authority and regulatory pathways for licensure), Financing and Investment (availability of funding, incentives for manufacturers, and public-private partnerships), Supply Chain and Inputs (access to raw materials, supply of equipment and consumables), Demand and Market (guaranteed demand via procurement, market size, and regional purchasing pools), Partnerships and External Support (tech transfer agreements, international

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support like from WHO or donor funding), and other contextual factors (like public acceptance, geopolitical stability, etc, if mentioned). We will not impose these categories a priori but will derive them from repeated patterns in the data (although they are informed by known frameworks like PESTLE). For each theme, we will collate what the literature says: for example, under Regulatory Systems, we might summarize that "Many sources emphasized the importance of a mature regulatory authority for vaccine licensure; however, only a few African countries have attained WHO Level 3 regulatory maturity [22,23], indicating a gap in readiness." Under Financing, we might note how various initiatives propose innovative financing or that Gavi/African Development Bank investments are crucial. We will also identify any specific indicators that fall under each theme, to potentially create a master list of indicators grouped by domain. This qualitative synthesis will allow us to present a narrative of what readiness entails according to existing evidence, and where emphases differ. For example, global frameworks might stress regulatory and tech transfer, while national policies might also stress workforce training or infrastructure building.

4. Comparison and gaps: part of our analysis will involve comparing frameworks and sources to see where they converge or diverge. If multiple frameworks exist, we will compare their components side by side. We will highlight any gaps in the literature, areas that are important for readiness but are not well covered. For example, if we find abundant information on technical capacity but very little on community acceptance or on environmental considerations for manufacturing, we will note that as a knowledge gap. Another gap might be the lack of any comprehensive index that aggregates these factors quantitatively, reinforcing the rationale to develop one. We will also identify if there are any best practices or success factors repeatedly cited (eg, "strong government commitment" comes up in nearly all sources, indicating a consensus that political support is key) [1].
5. Use of consultation input: if, during our expert consultation (described below), we receive additional input (eg, experts pointing out missing factors or newly released documents), we will incorporate that into the analysis. For instance, an expert might inform us about an ongoing WHO initiative to create a manufacturing readiness index, and we would then include whatever information is available about that and consider it in our synthesis, even if it was not in published literature yet.
6. The synthesis will be presented both narratively and with the aid of tables or figures. We anticipate creating:
   - A summary table of identified frameworks/indices, listing their origin, purpose, and components.
   - A figure or schematic that illustrates the common domains of readiness (perhaps a conceptual diagram showing overlapping domains from different sources).
   - A PRISMA flowchart (for the selection process, as mentioned).

By collating and summarizing in this way, the scoping review will "provide a map of what evidence has been produced" on vaccine manufacturing readiness [13,14] We are not assessing the quality of evidence per se (scoping reviews typically do not exclude based on quality), but we may comment on the nature of evidence (eg, noting if most of it is commentary vs data-driven). This comprehensive synthesis will directly inform identifying which factors to include in a new readiness index and where to focus further primary research (such as expert interviews to probe gaps). All analysis steps will be documented to ensure transparency in how we moved from raw data to our conclusions.

Step 9: Expert Consultation and Validation

Overview

Consulting with content experts and stakeholders is an optional but highly valuable stage in scoping review methodology [19,24]. We have planned an expert consultation component as part of this review to enhance its validity and relevance. The consultation serves 2 main purposes: (1) to ensure our search and included sources are comprehensive, and (2) to help interpret and validate the findings, especially in terms of practical significance for policy and index development.

Timing and Participants

We intend to engage experts after an initial draft of our evidence map is prepared (ie, after we have preliminary results from the literature). The experts will include individuals who are deeply involved in vaccine manufacturing initiatives or policy in Africa and globally. Potential participants are officials from organizations like Africa CDC's vaccine manufacturing programs, WHO and Gavi representatives involved in local production, leaders of vaccine manufacturing companies or institutes in Africa (eg, Institut Pasteur Dakar, Biovac in South Africa, and the new Ghana Vaccine Institute), and researchers who have published on pharmaceutical manufacturing capacity. We may also include representatives from funding bodies (World Bank and African Development Bank) who have a perspective on readiness investments. We will use purposive sampling to survey approximately key experts (2-3 per sector), expanding via snowball sampling as needed, and will stop at thematic saturation (ie, when additional interviews yield no substantively new insights), to capture a broad range of perspectives.

Consultation Methods

We will use a flexible approach, possibly surveys. We will prepare a summary of our scoping review findings (eg, a short presentation or summary document highlighting identified frameworks and preliminary themes) to share with the experts in advance. During the consultation, we will seek feedback on several points:

1. Completeness of the literature: we will ask if they are aware of any important frameworks, reports, or data sources that we might have missed in our search. Experts might point us to very recent or in-press materials or even internal documents that could be relevant. If any new sources are identified, we will attempt to obtain them and consider them for inclusion post hoc (provided they meet criteria).

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2. Interpretation of findings: We will present the themes and domains of readiness we have extracted and ask if these resonate with their experience. Do they agree that these are the key elements of readiness? Are there factors that the literature does not emphasize but are critical in practice?
3. Validation of framework for index development: since this scoping review feeds into developing a readiness index, we will use expert input to validate which indicators or domains should likely be included. If our literature-based framework has, say, 6 domains (policy, infrastructure, workforce, etc), we will query if these cover all critical areas. Experts might also suggest how to prioritize among them or note if any proposed indicator is not a good measure in reality. This does not change the scoping review results per se, but it adds a layer of practical validation that we will report on.
4. Feasibility and data for indicators: experts might also provide insight on how certain indicators could be measured (or whether data exists), which is useful context for the next research phase.

We will document the expert consultation process and integrate it with the scoping review in two ways. First, any new sources or gray literature identified will be added to the review if possible (with an addendum search if needed). The protocol allows for this consultation stage to inform the search as an iteration. Second, in our scoping review report, we will include a section on "Consultation Results" where we summarize the key suggestions or affirmations from the experts. For example, if experts unanimously highlight the importance of a regional pooled procurement mechanism as a readiness factor (even if only a couple of documents mentioned it), we will note that the consultation reinforced this point, adding credibility. Consultation in scoping studies is known to help inform or validate findings [11], improving the usefulness of the review for end users.

By moving beyond literature alone and involving stakeholder voices, we align with an expanded methodology for scoping reviews that values knowledge user engagement. This is especially important in a dynamic, policy-driven field like vaccine manufacturing in Africa, where some knowledge may reside in practice networks or recent initiatives not yet published. The expert consultation thus serves as a bridge between evidence and real-world application, ensuring that our review outputs are not only academically thorough but also grounded in current initiatives and expert consensus. All consultation activities will be conducted in an ethical manner, obtaining consent from participants and making it clear that their input is for the research purposes of refining our understanding. Any potential conflicts of interest (eg, an expert heavily promoting a particular index) will be managed by cross-referencing with evidence from other sources.

Reporting and Dissemination

Overview

This scoping review will be reported in accordance with the PRISMA-ScR guidelines [24]. We will ensure all the key reporting items are addressed, including a clear description of our background, objectives, eligibility criteria, search strategy (with search strings for at least one database provided), selection process, data charting methods, and results of the review. All sources of information will be properly cited, and any protocol deviations will be noted. In the scoping review paper, we will also include the statement: "The objectives, inclusion criteria, and methods for this scoping review were specified in advance and documented in a protocol," along with a reference to this protocol.

For dissemination, there are multiple avenues:

- Academic publication: We intend to publish the scoping review in a peer-reviewed journal. We will also make the published article open access for broader reach.
- Stakeholder engagement beyond academia: to facilitate policy and practice uptake, we will prepare a 2-4 page policy brief and slide deck tailored for African stakeholders (eg, Africa CDC or PAVM, World Health Organization Regional Office for Africa [WHO AFRO], National Regulatory Authorities, National Immunization Technical Advisory Groups, Ministries of Health and Industry, regional economic communities, and relevant manufacturer associations). We will seek opportunities to present findings in Africa CDC or WHO AFRO webinars or technical convenings and at regional forums (eg, the Vaccine Alliance African Vaccine Manufacturing Accelerator platform and PAVM working groups). Where feasible, we will conduct targeted briefings with priority audiences (eg, regulatory and industrial policy units) to discuss how mapped readiness domains can inform ongoing initiatives.

Throughout dissemination, we will emphasize how this scoping review fills a crucial knowledge gap and sets the stage for evidence-based interventions. By documenting existing frameworks and indicators, we can help avoid duplication of efforts and encourage stakeholders to coalesce around best practices identified. We anticipate the review becoming a reference for groups like the African Union, WHO AFRO, or national task forces when they articulate what needs to be done to enable vaccine manufacturing, essentially providing a menu of factors and examples gleaned from the literature.

Measuring Dissemination Success

To assess whether dissemination reaches intended audiences and informs practice, we will track (1) bibliometrics (citations, downloads, and Altmetric attention); (2) stakeholder engagement metrics (attendance at briefings or webinars, requests for follow-up or technical assistance, distribution of the policy brief or slide deck); (3) evidence of policy or practice uptake (citations or references in AU, Africa CDC, WHO AFRO or national strategy documents, inclusion in guidance and roadmaps, and invitations to contribute to working groups); and (4) early indicators of application (eg, references to the review's domains in country assessments or pilot use to scope a readiness index).

Ethical Considerations

Although this scoping review does not collect primary health or patient data, the planned expert consultation component involves human participants. The expert consultation component received approval from the University of Geneva Research Ethics Committee with decision form number

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CUREG-2025-05-87 (application submitted May 21, 2025, and approval received September 9, 2025). Written informed consent will be obtained, and data will be anonymized and securely stored.

Results

The protocol is registered on the Open Science Framework. The initial search strategy has been finalized, and pilot searches were completed (May-August 2025). We are currently reviewing and scoping more abstracts and literature from peer-reviewed journals and gray literature. The screening calibration set (n50) will be prepared. Dual review title or abstract screening begins December 2025, with full-text screening and data charting scheduled for January-March 2026. Thematic synthesis and expert consultation are planned for April-May 2026. We anticipate submitting the completed scoping review manuscript in June or July 2026.

Discussion

Expected Findings

This scoping review will generate the first continent-focused evidence map of vaccine-manufacturing readiness in Africa. It goes beyond single-domain inventories to produce a multidomain taxonomy and master indicator catalog. The predefined outputs (framework-mapping table, theme-frequency summary, and indicator catalog) translate fragmented evidence into decision-oriented products. Methodologically, rigor is supported by PCC-based eligibility, dual-reviewer screening with calibration, descriptive mapping plus inductive thematic analysis, and a targeted expert consultation (5-10 informants) to validate domains and surface missed sources. Anticipated insights include (1) areas of consensus across domains (regulatory, infrastructure or technology, human capital, finance, inputs, demand or market, partnerships, and governance/context), (2) gaps (eg, inputs, energy reliability, environmental compliance), and (3) a shortlist of candidate pillars or indicators for a CRAI.

Limitations

There are a few limitations to this scoping review. Article inclusion is restricted to papers published in English, French, Portuguese, and Arabic. Local language items may be missed, partly mitigated via regional portals and expert flagging. Gray literature heterogeneity limits methodological appraisal, consistent with JBI. No formal critical appraisal will be performed. The review offers a cross-sectional snapshot, and late-emerging initiatives may fall outside the window.

Conclusions

This scoping review protocol has detailed a rigorous approach, following JBI methodology, to map the landscape of vaccine manufacturing readiness in African countries. By clearly outlining our objective, question, inclusion criteria, search methods, selection, data charting, analysis plan, and consultation strategy, we aim to ensure the review process is transparent and reproducible. The ultimate outcome will be a comprehensive knowledge synthesis that not only contributes to academic literature but also supports practical policy and strategy development toward Africa's vaccine self-sufficiency goals [1]. The protocol and subsequent review will be valuable steps in a larger research endeavor to develop and validate a readiness index for vaccine manufacturing in Africa, guiding investments and actions in the coming years for strengthening health security on the continent.

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Data Availability

Data sharing is not applicable to this article as no datasets were generated or analyzed during this study.

Authors' Contributions

Conceptualization: UAA (lead), NR (equal), JN (supporting)
Data curation: UAA
Formal analysis: UAA (lead), KJU (supporting)
Investigation: UAA
Methodology: UAA, CAN, NR, JN
Project administration: UAA (lead), NR (equal), KJU (supporting)

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Supervision: NR
Validation: NR
Visualization: UAA (lead), KJU (supporting)
Writing – original draft: UAA (lead), KJU (supporting), CAN (supporting)
Writing – review & editing: UAA (lead), CAN (supporting), KJU (supporting), JN (supporting)

Conflicts of Interest

None declared.

Multimedia Appendix 1
Existing tools on vaccine manufacturing readiness.
[DOCX File , 21 KB - resprot_v14i1e81231_app1.docx]

Multimedia Appendix 2
Thematic synthesis output (domains, indicators, and frequency across sources).
[DOCX File , 16 KB - resprot_v14i1e81231_app2.docx]

Multimedia Appendix 3
Operationalization of JBI steps for vaccine-manufacturing readiness.
[DOCX File , 29 KB - resprot_v14i1e81231_app3.docx]

Multimedia Appendix 4
Search strategy.
[DOCX File , 15 KB - resprot_v14i1e81231_app4.docx]

Multimedia Appendix 5
PRISMA-ScR flow diagram.
[DOCX File , 16 KB - resprot_v14i1e81231_app5.docx]

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Abbreviations

Africa CDC: Africa Centres for Disease Control and Prevention
CRAI: Country Readiness Assessment Index
JBI: Joanna Briggs Institute
MeSH: Medical Subject Headings
PAVM: Partnerships for African Vaccine Manufacturing
PCC: Population, Concept, and Context
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews
WHO: World Health Organization
WHO AFRO: World Health Organization Regional Office for Africa

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Protocol

Workplace Loneliness Experience Among Older Professionals (Aged ≥50 Years) in the Context of Digitalization: Protocol for a Scoping Review

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Abstract

Background: Workplace loneliness—defined as the perceived absence of meaningful social relationships at work—can have a negative impact on the well-being, engagement, and productivity of employees. Older professionals (aged ≥50 years) may be particularly vulnerable to workplace loneliness in the context of accelerated digitalization, which may create obstacles to inclusion, communication, and collaboration. Despite growing interest in this phenomenon, no comprehensive synthesis has yet examined how digital tools and transformations affect loneliness among older workers or what interventions have been implemented to address it.

Objective: This scoping review aims to systematically map the existing literature on workplace loneliness among workers aged 50 years or older, with a particular focus on how digitalization influences these experiences. The review will also identify digital tools associated with loneliness and explore organizational interventions to reduce loneliness among this demographic.

Methods: This scoping review will follow the methodological framework by Arksey and O’Malley and the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) reporting guidelines. A comprehensive search will be conducted in multiple databases (MEDLINE, Scopus, Web of Science, and APA PsycINFO) and gray literature. Eligible studies will (1) include workers aged 50 years or older, (2) address workplace loneliness or related constructs in professional contexts, and (3) be situated in digitalized work environments (eg, remote or hybrid work, digital tools, and information and communications technology systems). Study selection, data extraction, and quality assessment will be conducted independently by at least 2 reviewers. Data will be charted using a predefined template covering study characteristics, theoretical frameworks, the digital context, loneliness measures, and intervention strategies and synthesized narratively and thematically.

Results: As this is a scoping review protocol, results are not yet available. A preliminary search conducted in June to July 2025 across MEDLINE, Cochrane Library, and Web of Science yielded 450, 1, and 47 potentially relevant records, respectively. No

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systematic or scoping reviews were identified on workplace loneliness among older workers in digitalized contexts. One review addressed video calls for nonworking older adults, reporting very low-certainty evidence. The planned review will apply the PRISMA-ScR guidelines to synthesize evidence on digitalization's role in, technologies associated with, and organizational interventions to mitigate workplace loneliness for professionals aged 50 years or older.

Conclusions: This scoping review will systematically examine how digitalization shapes workplace loneliness among professionals aged 50 years or older and identify organizational interventions that address it. The synthesis will refine conceptual understanding, highlight critical evidence gaps, and inform the development of socially supportive digital work environments for aging workforces.

Trial Registration: Open Science Framework 6p4ak; https://osf.io/6p4ak

International Registered Report Identifier (IRRID): DERR1-10.2196/81843

(JMIR Res Protoc 2025;14:e81843) doi:10.2196/81843

KEYWORDS

workplace loneliness; digital tools; digital technology; older workers; scoping review

Introduction

Background

As workplaces become increasingly reliant on digital communication technologies, older workers (aged ≥50 years) may experience challenges in adapting, which can influence their sense of belonging and overall workplace experience [1]. This issue is significant given the crucial role of older professionals in mentoring and knowledge transfer. Many expect to remain in the workforce for 15 years or more; therefore, ensuring their inclusion and connectedness is vital [2-4].

The aging workforce represents a global demographic shift. United Nations projections indicate that the number of older working-age individuals (aged 55-64 years) will rise by nearly 49% between 2021 and 2050 and by 68% by 2100 [5]. As people live longer and work later, organizations face new challenges in sustaining well-being and productivity. One key concern is workplace loneliness, which can affect older employees' satisfaction, engagement, and performance [6].

Workplace loneliness refers to the perceived absence of meaningful social relationships at work, encompassing both emotional and social isolation [7,8]. It is associated with reduced job satisfaction, lower engagement, and diminished performance [9,10]. Loneliness is not merely physical separation but a subjective sense of disconnection stemming from unmet social needs [11-13]. While loneliness has often been studied as an individual experience, organizational factors such as leadership, culture, and communication systems play an equally important role. The digitalization of work—through online platforms, automation, and remote communication—has transformed how employees interact [14]. While these innovations offer several benefits, including increased flexibility and efficiency, they can also contribute to workplace stress, strain, and negative impacts on social connection, particularly among older workers who may struggle to adapt to rapidly changing technological environments [15].

Sociocognitive models argue that loneliness emerges when there is a mismatch between expected and actual social interactions, which are shaped by self-perception, cognitive biases, and attributional tendencies [16]. Life span developmental theories emphasize that older adults may become more selective in their social investments, focusing on emotionally meaningful interactions over broader social networks [17]. In organizational theory, structural factors such as hierarchical distance, leadership style, and digital communication norms can buffer or intensify loneliness [18]. Together, these frameworks highlight the interplay between individual psychology and workplace structures in shaping later-career experiences.

Older employees (aged ≥50 years) often face distinctive challenges in digital environments. Low digital literacy can create feelings of exclusion and limit communication, leading to weaker professional ties [19]. The expansion of remote and hybrid work since the COVID-19 pandemic has further intensified reliance on digital interaction, potentially increasing isolation among older workers [20]. While workplace loneliness is often viewed through a negative lens, recent scholarship has called for a distinction between distressing loneliness and restorative solitude. Solitude, when chosen rather than imposed, can foster creativity, emotional regulation, and a sense of autonomy [21,22]. For older professionals, the ability to step back from constant digital interaction may offer moments of reflection and recharge, contributing to their well-being and professional insights [23]. Therefore, organizations should be cautious not to pathologize every experience of being alone, recognizing that solitude can, in some cases, act as a psychological resource [24].

The effects of workplace loneliness are significantly shaped by how the concept is operationalized. When defined narrowly as a painful emotional experience due to unwanted isolation, loneliness is consistently linked to negative outcomes, including stress, depression, and disengagement [25]. However, broader definitions that include aspects of solitude or intentional aloneness reveal a more ambivalent picture. For instance, individuals high in introversion may prefer limited social interaction yet remain satisfied and productive [26]. Understanding these definitional boundaries is crucial for interpreting empirical findings and designing nuanced interventions that distinguish between detrimental loneliness and adaptive solitude.

Recent scholarship emphasizes that workplace loneliness is qualitatively distinct from general loneliness as it emerges from the specific relational and structural dynamics of professional environments [27]. This distinction is important as

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context-specific drivers such as organizational culture, leadership behavior, and the integration of digital tools can shape loneliness in ways not captured by general measures [28,29]. In older workers, reduced opportunities for informal interaction in digitalized workplaces may impact both psychological well-being and job engagement. Furthermore, social isolation in professional contexts has been associated with higher turnover rates and diminished organizational commitment, which can disrupt workforce stability [30].

Although digital technologies can foster connectivity, their benefits are unevenly distributed. Employees with lower digital literacy risk exclusion and marginalization [31]. Conversely, inclusive communication strategies, empathetic leadership, and targeted digital skill training can help counteract these effects [32,33]. Consequently, the literature underscores the need to design digital inclusive workplaces that balance efficiency with human connection, ensuring that older workers remain integrated, valued, and engaged in an increasingly digital working world [34].

Goal of the Research

This scoping review aims to address the research gap in understanding workplace loneliness among older workers (aged ≥50 years), with a particular focus on the influence of digitalization. It will synthesize state-of-the-art evidence to explore how digitalization shapes these experiences—both positively and negatively—and identify effective, documented interventions to reduce workplace loneliness. By charting the existing literature and examining organizational strategies, the review will offer practical insights for supporting the aging workforce and enhancing their work experience in increasingly digital environments.

Methods

Guidance and Framework

To ensure methodological rigor and transparency in the reporting of this scoping review, we will follow the PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) guidelines [35]. This protocol closely follows the structure and reporting logic applied in recent related work within the DIGI-net network, particularly the methodological approach described by Spijker et al [36]. Their work provided a valuable reference point for consistency and transparency in the scoping review design. Methodologically, this scoping review will be conducted following the guidance of Arksey and O'Malley [37] and guided by the recommendations of Levac et al [38], consisting of the following stages: (1) defining the research question, (2) identifying pertinent studies, (3) selecting studies based on inclusion criteria, (4) extracting and synthesizing data, and (5) summarizing and presenting the results. The checklist for this protocol is provided in Multimedia Appendix 1 [39].

Protocol and Registration

This protocol was developed before conducting the full electronic literature search, which included identifying existing scoping reviews and pilot-testing search terms (see details below). This study was registered with the Open Science Framework [40].

Stage 1: Identifying the Research Questions

We posed the following overarching research question: how does workplace digitalization influence experiences of loneliness among older workers (aged ≥50 years)? To address this, we also formulated three specific questions: (1) what is known from the existing literature about workplace loneliness in older workers in the context of digitalization? (2) What digital tools are used, and are they directly linked to or mediate experiences of loneliness? (3) What interventions have proven effective in reducing workplace loneliness among older professionals, and how have organizations implemented them?

On the basis of these research questions, we defined the population, concept, and context (PCC) criteria to clarify the focus of this scoping review and guide an effective search strategy [38] (Textbox 1 [41-46]). Regarding the population, our review will focus on studies involving older workers aged 50 years or older.

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Textbox 1. Definitions of the inclusion criteria regarding population, concept, and context for this scoping review.

Population: older workers

1. In this review, older workers are defined as individuals aged 50 years or older who were actively engaged in paid employment at the time the study was conducted. This threshold aligns with previous research identifying 50 years or older as a meaningful demarcation of later-stage employment due to physiological, career, and social transitions associated with aging [41].
2. Studies will be eligible if they focus entirely on participants aged 50 years or older or if they include this age group in a way that allows for separate analysis of findings by age. When age is reported in ranges, the lower bound of the relevant category must include 50 years (eg, 50-59 years). The decision to adopt this threshold is grounded in evidence of the growing representation of this demographic in the labor market and their diverse employment trajectories and motivations [42].
3. If age is reported as a continuous variable, inclusion will apply only when the reported descriptive statistics (eg, range, mean, or median) indicate that the sample includes participants aged 50 years or older. Studies focusing exclusively on younger adults (<50 years) or on individuals who are retired or not engaged in paid professional work will be excluded.

Concept: workplace loneliness

1. Eligible studies will examine workplace loneliness, professional isolation, solitude, or emotional disconnection as they occur in relation to professional roles and structures.
2. Workplace loneliness is understood as a subjective experience of social isolation or lack of meaningful connection with colleagues, distinct from but related to social or personal loneliness [43]. It has been linked to reduced engagement, decreased performance, and health risks in organizational settings.
3. Studies focusing solely on non–work-related loneliness (eg, familial or social) will be excluded, as will those examining workplace factors without specific reference to loneliness or isolation.

Context: digitalized work environments

1. Digitalized work environments refer to professional settings in which work tasks, processes, and communication are mediated or transformed through the use of digital technologies. This includes but is not limited to remote and hybrid work arrangements, the use of digital communication platforms (eg, Zoom and Microsoft Teams), and the integration of information and communications technology in everyday operations [44].
2. Digitalization encompasses the adoption of digital workplaces, automation, and broader digital transformation initiatives, which can reshape organizational structures [45] and influence the nature of professional relationships [46].
3. For the purposes of this review, digitalized work environments are defined as any setting in which digital tools or systems play a central role in enabling, organizing, or delivering work. Studies that do not address digitalization or that examine purely traditional, nondigital workplaces will be excluded.

Stage 2: Identifying Relevant Studies

This stage will involve a comprehensive and systematic search to identify relevant studies that meet the eligibility criteria defined in stage 1. The search strategy will be developed in accordance with the Joanna Briggs Institute Manual for Evidence Synthesis [47] and guided by the PCC framework, ensuring both breadth and focus in capturing appropriate evidence related to the review objectives. Our initial search on the main databases (ie, MEDLINE, Cochrane, ProQuest [including Dissertations and Theses Global], Web of Science, Scopus, APA PsycINFO, and ERIH PLUS) yielded no ongoing or completed systematic or scoping reviews on this topic.

To enhance comprehensiveness, the final search will also include additional databases, such as Embase, CINAHL, IEEE Xplore, and the ACM Digital Library, which index studies relevant to health, technology, and workplace digitalization. Further searches may be conducted in relevant gray literature repositories and institutional sources if deemed necessary during the screening process.

The search terms to be used are as follows: (“workplace loneliness” OR “occupational loneliness” OR “job-related loneliness” OR “professional isolation” OR “workplace isolation” OR “social isolation at work” OR “loneliness at work” OR “employee loneliness” OR “staff loneliness” OR “colleague isolation” OR solitude OR “workplace solitude” OR “professional solitude”) AND (“older professional*” OR “older employee*” OR “older worker*” OR “senior professional*” OR “senior employee*” OR “senior worker*” OR “aging professional*” OR “ageing professional*” OR “aged worker*” OR “older adult*” OR “older staff” OR “elderly worker*” OR “elderly employee*” OR “older personnel”) AND (“digitalization” OR “digitalisation” OR “digital transformation” OR “digital technology” OR “information and communication technology” OR ICT OR “technology adoption” OR “digital tools” OR “online communication” OR “virtual communication” OR “digital” OR app* OR web OR internet OR tech* OR “social media” OR chat OR online* OR cyber OR virtual OR “computerized” OR “computerised” OR electronic)

In our search query, we introduced symbols specific to Boolean operators such as OR to encompass a broad range of related loneliness and digital technology concepts and terms referring to older workers. We also used the AND Boolean operator to overlap and identify studies that contain all the main concepts. Finally, in constructing our search strategy, we used the asterisk (*) symbol as an end-of-root-word truncation mark.

A preliminary search conducted in June 2025 and July 2025 in PubMed, Cochrane, and Web of Science Core Collection yielded 450, 1, and 47 results, respectively. Of all the studies, only 1 review included older people and digital technology use. A

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systematic review assessed the effectiveness of video calls in reducing loneliness and social isolation among adults aged ≥65 years [48]. However, this review did not focus on workers or workplace settings; instead, the included studies were all conducted in nursing homes with nonworking older adults. Despite evaluating digital technology use, particularly video calls via internet-enabled devices such as smartphones, tablets, and laptops, it found very low-certainty evidence that these interventions reduce loneliness, social isolation, or depression. Other studies identified focus on technology use as an interventional tool and are not specific to any occupational setting but rather to the general population [49,50]. This search strategy will be adapted for other databases (eg, Scopus, APA PsycINFO, and Web of Science [all collections]) using appropriate syntax and indexing systems. The final version of the search strategy will be documented in accordance with PRISMA-ScR and Joanna Briggs Institute reporting standards. Our search will be limited to studies published in English.

Stage 3: Study Selection and Eligibility Criteria

After removing duplicate references in stage 2 using a reference management tool, the remaining citations will be imported into Covidence (Veritas Health Innovation) for systematic screening. The selection procedure will take place in 2 sequential stages. First, titles and abstracts will be screened. Second, the full texts of potentially eligible studies will be reviewed. Each record will be independently assessed by 2 reviewers at both stages in accordance with the predefined eligibility criteria. Studies that clearly meet these criteria, as well as those for which relevance is uncertain, will advance to the full-text stage.

Considering the expected number of search results, the screening workload will be distributed among all coauthors. Covidence will facilitate the allocation of records, the identification of conflicts, and the documentation of decisions. Any conflicts flagged by the software will be resolved through the involvement of a third reviewer. The research team will meet regularly online to address methodological questions and ensure consistent application of the inclusion and exclusion criteria throughout the process.

The overall selection workflow will be presented in a PRISMA-ScR flow diagram, which will also include the reasons for excluding studies at the full-text stage. Eligibility criteria are organized according to the PCC framework and complemented with additional parameters such as source type, language, time frame, work status, and outcomes of interest, as shown in Textbox 2.

Textbox 2. Eligibility criteria for the scoping review.

Inclusion criteria

1. Population: professionals aged 50 years or older or studies with age-disaggregated data allowing for analysis of this group
2. Concept: workplace loneliness, professional isolation, solitude, or emotional disconnection in professional settings
3. Context: digitalized work environments (eg, remote or hybrid work, digital communication platforms, automation, and digital transformation)
4. Setting: professional or organizational contexts involving paid employment
5. Study type: original studies with any design or data type (quantitative, qualitative, or mixed methods), including dissertations and organizational reports with empirical data
6. Publication status: peer-reviewed journal articles, conference proceedings, dissertations, and reputable gray literature (eg, reports from reputable organizations)
7. Publication language: English
8. Time frame: published from 2000 onward
9. Full-text availability: full text accessible for review

Exclusion criteria

1. Population: studies focusing exclusively on younger workers (aged ≤49 years) or on retirees not engaged in professional work
2. Concept: general or personal loneliness unrelated to the workplace or studies on workplace factors without specific reference to loneliness or social disconnection
3. Context: nondigitalized work environments or settings without reference to technology-mediated changes in the workplace
4. Setting: informal, nonprofessional, or volunteer work contexts
5. Study type: protocols, narrative reviews, systematic reviews, opinion pieces, editorials, or nonempirical publications
6. Publication status: unpublished studies lacking peer review and low-quality gray literature without empirical data
7. Publication language: languages other than English
8. Time frame: published before 2000
9. Full-text availability: full text not accessible for review

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Stage 4: Charting the Data

The protocol authors developed and refined the initial data charting form. Levac et al [38] state that data extraction is an iterative process. Thus, we may revise the data charting form over time as we gain a better understanding of the data related to the research questions. Specifically, we may include extra items that are relevant for answering the research questions in the form. It was recommended that 2 researchers conduct a pilot test on 7 articles to assess the data extraction form [51]. Before implementation, the research team will review and discuss the charting form to check that it is complete and comprehensive. After piloting and refining the form, data will be extracted independently by 2 reviewers using a Microsoft Excel spreadsheet. Disagreements or inconsistencies in data extraction will be managed through the involvement of a third reviewer from the research team.

Data extracted from each included study will cover key bibliographic information (eg, author, year, and country or region); study characteristics (eg, design, population, sample features, and theoretical framework); and findings relevant to the review objectives, including definitions and measures of loneliness, digitalization context, key results, and intervention details when applicable. A comprehensive list of data items and their descriptions is provided in item 11 of the PRISMA-ScR checklist (Multimedia Appendix 1).

Stage 5: Collating, Summarizing, and Reporting the Results

Following the guidance proposed by Levac et al [38], the fifth stage of this review will involve three interconnected activities: (1) synthesizing the evidence through both descriptive numerical summaries and qualitative thematic analysis; (2) examining the extracted data to identify results that address the primary research question, which will be presented in a narrative format; and (3) interpreting the findings in light of the supplementary research questions, with consideration of their practical relevance and potential policy implications.

Alongside the narrative synthesis, structured tables will be used to present an organized summary of the main results. The reporting of findings will follow the PRISMA-ScR guidelines [35] to ensure methodological transparency and consistency.

Quality Assessment

According to Peters et al [52], the screening and inclusion procedure of many scoping reviews involves a broad range of sources. They also point out that formal risk-of-bias assessments, statistical pooling (meta-analysis), and evidence quality evaluations are not part of scoping reviews [52]. This scoping review will not formally evaluate the methodological quality or risk of bias of the included studies because the goal of this research is to map the body of literature on workplace loneliness among employees aged 50 years or older in a systematic manner, with a particular focus on how digitalization affects these experiences.

Results

As this is a scoping review protocol, no results are available at this stage. The planned review will follow the PRISMA-ScR reporting guidelines to systematically map and synthesize evidence on workplace loneliness among professionals aged 50 years or older in digitalized work contexts. We anticipate identifying a wide range of empirical and conceptual studies exploring how digital tools, communication practices, and organizational changes influence older professionals' social experiences at work.

The results of our inquiry will be disseminated through a scoping review, with the selection process illustrated in a PRISMA-ScR flow diagram. An anticipated version of the PRISMA-ScR flowchart has been included in Multimedia Appendix 2 to depict the planned study selection process. Numerical data will be added upon completion of the review. Extracted data will be presented in structured tables summarizing study characteristics and key variables (eg, digital context, age, and sector) and expanded upon in a thematic narrative synthesis. This synthesis will address the primary research question (how does workplace digitalization influence experiences of loneliness among older workers?), as well as the following subquestions: (1) what is known from the literature about workplace loneliness in older professionals in the context of digitalization? (2) Which digital tools are associated with or mediate experiences of loneliness? (3) What organizational interventions have been effective in reducing workplace loneliness among older professionals, and how have they been implemented? Where possible, subgroup trends by gender, sector, or region will also be highlighted. The review aims to provide a comprehensive map of current knowledge and identify priority areas for future research.

Discussion

Existing Evidence and Research Gap

The existing literature suggests that, while the effects of digitalization on older workers are increasingly documented, workplace loneliness remains a relatively neglected focus of investigation. Previous studies have tended to examine aging, digital skills, or occupational well-being in broader terms, but few address the specific emotional and relational consequences of digital transitions—such as reduced informal contact, social disconnection, or perceived isolation—among professionals aged 50 years or older [27-29]. The evidence base is fragmented across disciplines, including public health, education, management, and digital sociology, with limited cross-sectoral synthesis.

Recent empirical research further indicates that workplace loneliness can diminish employees' work engagement, which in turn increases job dissatisfaction; however, this relationship may be buffered in individuals with a stronger need to belong [1]. Therefore, understanding both the direct and indirect effects of workplace loneliness on subjective well-being, as well as the personal and organizational factors that mitigate its impact, remains an important research priority [43].

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Evidence specifically addressing workplace loneliness in digital contexts is scarce, and available evidence varies regarding the role of digital tools such as videoconferencing, instant messaging platforms, or collaborative applications in fostering social connectedness. For some older workers, these technologies act as enablers of engagement, whereas for others—particularly those with lower digital literacy—they may inadvertently exacerbate feelings of exclusion and marginalization [31,32,53]. Contextual factors such as organizational culture, leadership style, and opportunities for informal interaction appear to significantly moderate these outcomes [30,33].

The paucity of targeted studies presents both a challenge and an opportunity. The challenge lies in the absence of comprehensive conceptual frameworks explicitly linking workplace loneliness to digital transformation among older professionals. The opportunity lies in the potential to design and evaluate targeted strategies—such as structured digital skill training, leadership-led initiatives to enhance social connection, and workplace policies promoting inclusive communication—that could strengthen older workers' social integration and mitigate loneliness in increasingly digitalized work environments [54-56].

Limitations

Our inclusion criteria restrict the review to studies providing empirical evidence published in English. This language limitation may introduce bias toward research conducted in anglophone or Western contexts and could affect the diversity of perspectives represented. Moreover, the existing body of literature directly addressing the intersection of workplace loneliness, digitalization, and older workers is notably limited. This scarcity presents both a challenge and an opportunity: while it constrains the available evidence for synthesis, it also underscores the novelty of the topic and the potential for this review to highlight significant gaps in current knowledge.

The term *workplace loneliness* was selected as the core concept for its alignment with our research objectives. The search strategy, developed in collaboration with an information specialist, incorporated both controlled vocabulary and free-text keywords to maximize coverage. Controlled terms ensure consistency in indexing, whereas free-text keywords capture variations in author language and disciplinary framing. Nonetheless, given the variability in terminology and the evolving nature of research in digitalized work environments, it remains possible that some relevant studies will not be retrieved despite these measures.

Comparison With Previous Work

This scoping review protocol on workplace loneliness among older professionals (aged ≥50 years) in the context of digitalization uniquely addresses a gap not covered by previous literature syntheses. Previous reviews have largely examined loneliness and digital technologies among older adults in general without focusing specifically on those engaged in professional roles within digitally transforming workplace environments, such as the reviews on loneliness at work listed in Table 1. For example, Chen et al [50] investigated the effects of online social networking and information and communications technology tools on loneliness and mental health among older adults aged 50 to 83 years, but their work concentrated on community or home settings rather than workplace contexts. Similarly, Noone et al [48] assessed the impact of video calls on loneliness in adults aged ≥65 years residing in care homes, finding very low-certainty evidence and no applicability to professional environments. Hoang et al [49] provided a broader mapping of digital interventions—ranging from social media to virtual reality and assistive technologies—designed to reduce social isolation in older adults but excluded employment-related experiences.

Table 1. Selected systematic reviews on digital technologies for loneliness among older people at work.

Review	Population age (years)	Digital technologies	Type of loneliness
Noone et al [48], 2020	≥60	Video calls using Skype, FaceTime, and Zoom to connect with family members, friends, and health professionals	Loneliness (subjective): feelings of being alone or lacking companionship; social isolation (objective): lack of social contact or interaction
Chen et al [50], 2022	50-83	Online social networking sites such as Facebook and Twitter; communication tools: email, Skype, and instant messaging; information and communications technology generally, including forums and support groups; computer-mediated communication in some cases	Social isolation (objective): lack of social contacts or infrequent interaction; loneliness (subjective): perceived lack of meaningful connection; emotional loneliness (missing close or intimate relationships); social loneliness (lack of broader social network)
Hoang et al [49], 2022	≥60	Communication technologies: video calls, social media, and messaging platforms; social engagement platforms: online communities and forums; assistive and ambient technologies: robotic pets and virtual assistants (eg, Alexa)	Loneliness (subjective): feelings of being alone and disconnected; social isolation (objective): reduced or infrequent social contact

Few studies address the emotional and relational consequences of workplace digitalization—such as loss of informal contact, perceived isolation, or reduced social integration—in professionals aged 50 years or older. This clear research gap underscores the need for a focused synthesis that can clarify conceptual boundaries, identify sector-specific risk factors, and assess effective intervention strategies. This scoping review aims to provide such an integrated understanding and inform evidence-based approaches for fostering social connectedness among older professionals in increasingly digitalized work settings.

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This review is distinguished by its emphasis on workplace digitalization, including remote work models, digital communication platforms, and automation, and its targeted focus on older workers still engaged in paid employment. Grounded in sociocognitive, life span developmental, and organizational theories, it conceptualizes loneliness as a context-dependent construct shaped by digital communication norms, leadership, and individual adaptation. Furthermore, the review aims to not only document digital tools associated with loneliness but also map interventions implemented by organizations to mitigate its effects. By focusing on professional inclusion and adaptation in the digital era, this review offers both theoretical and applied contributions to aging, organizational behavior, and digital workplace research.

Conclusions

This scoping review will systematically investigate the ways in which digitalization influences the experience of workplace loneliness among professionals aged 50 years or older. By mapping the existing empirical and conceptual literature, the review will identify how digital tools, communication practices, and organizational changes contribute to shaping social connection—or the lack thereof—within professional settings. In doing so, it will provide a nuanced account of the interplay between technological transformation and the relational dynamics of later-stage careers.

Beyond documenting patterns in the evidence, the synthesis will also examine organizational strategies and interventions aimed at reducing workplace loneliness in digitally mediated environments. This dual focus will allow the review to refine conceptual clarity; uncover significant gaps in current knowledge; and offer insights that can guide the design of inclusive, socially supportive digital work environments. In turn, these findings have the potential to inform both policy development and practical initiatives that address the unique needs of an aging workforce.

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Authors' Contributions

LIT-P contributed to conceptualization, methodology, formal analysis, investigation, data curation, validation, visualization, supervision, project administration, writing—original draft, and writing—review and editing. CMT contributed to conceptualization, methodology, supervision, funding acquisition, resources, writing—original draft and writing—review and editing. MPB contributed to conceptualization, methodology, formal analysis, writing—original draft and writing—review and editing. ŞA contributed to investigation, writing—original draft and writing—review and editing. AI contributed to investigation, writing—original draft and writing—review and editing. RPH contributed to investigation, writing—original draft and writing—review and editing. All authors read and approved the final version of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) checklist.
[PDF File (Adobe PDF File), 336 KB - resprot_v14i1e81843_app1.pdf]

Multimedia Appendix 2
Anticipated PRISMA-ScR (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews) flow diagram.
[PDF File (Adobe PDF File), 287 KB - resprot_v14i1e81843_app2.pdf]

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Abbreviations

PCC: population, concept, and context
PRISMA-ScR: Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews

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Protocol

Remote Lifestyle Intervention to Reduce Postpartum Weight Retention: Protocol for a Community-Engaged Hybrid Type I Effectiveness-Implementation Randomized Controlled Trial

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Abstract

Background: Maternal obesity is associated with significant racial disparities. People who identify as non-Hispanic Black and Latinx are at the highest risk related adverse short- and long-term health outcomes (eg, hypertension in pregnancy and postpartum weight retention). Remote lifestyle interventions delivered during and after pregnancy hold promise for supporting healthy weight outcomes; however, few are tested in groups of people who self-identify as non-Hispanic Black and Latinx or address the neighborhood-level and psychosocial factors driving maternal health disparities. Implementing remote lifestyle interventions within community-based programs that serve birthing people may optimize trust and engagement, promote scalability and sustainability, and have the broadest public health impact.

Objective: The goal of this trial is to test the effectiveness of a culturally adapted remote lifestyle intervention (Healthy for Two–Home Visiting) implemented within home visiting compared to usual home visiting services on postpartum weight retention among pregnant or postpartum individuals, in particular those who identify as non-Hispanic Black and Latinx. Facilitators and barriers to implementation of the intervention within home visiting will be examined.

Methods: We describe the rationale and protocol for this hybrid type I effectiveness-implementation randomized controlled trial. In this paper, we highlight the community-engaged approach and trial design features that enable the implementation of the intervention within home visiting and demonstrate its applicability to the target population. Participants will be 360 pregnant individuals with overweight or obesity enrolled between 20 and 33 weeks of gestation and randomized 1:1 to Healthy for Two–Home Visiting or usual home visiting services. The primary outcome is weight retention at 6 months post partum, calculated as 6-month postpartum weight minus earliest pregnancy weight (≤18 wk of gestation). The measures of implementation include intervention feasibility, acceptability, reach, adoption, and fidelity. Throughout the paper, we highlight the community input used to improve intervention effectiveness and study implementation and as a strategy to promote maternal health equity.

Results: This study was funded in June 2021, and recruitment began in April 2023. As of November 2024, we enrolled 90 participants. Data collection to assess the intervention's effectiveness is expected to end in June 2026. Implementation evaluation is expected to conclude in December 2026.

Conclusions: This hybrid type I effectiveness-implementation randomized controlled trial integrates a culturally adapted remote lifestyle intervention into early home visiting services to examine its effectiveness on postpartum weight retention compared to usual home visiting. We anticipate that the study results will enable an understanding of the drivers of successful implementation

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within a community-based setting to maximize the future sustainability and dissemination of a strategy for reducing long-term obesity and other maternal health disparities.

Trial Registration: Clinicaltrials.gov NCT05619705; https://clinicaltrials.gov/study/NCT05619705

International Registered Report Identifier (IRRID): DERR1-10.2196/62847

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KEYWORDS

pregnancy; obesity; postpartum weight retention; remote lifestyle intervention; home visiting; mobile health; mHealth app; community-engaged research; implementation science; health disparities; maternal health

Introduction

Background

Maternal obesity is a persistent public health concern, with widening racial and ethnic inequities [1-3]. In the United States, 57% of women who self-identify as non-Hispanic Black and 47% of women who self-identify as Latinx, Hispanic, or of Spanish origin (hereinafter referred to as Latinx) have obese status compared to 38% of people who identify as non-Hispanic White [4]. Nearly 50% of pregnant people who identify as non-Hispanic Black or Latinx exceed the recommended guidelines for gestational weight gain (GWG), contributing to adverse maternal and infant health outcomes (eg, hypertension in pregnancy, preterm birth, and maternal mortality) [5-8], as well as an estimated economic impact of up to US $32 billion from conception through the offspring's first 5 years of life [9]. It is imperative to focus public health prevention efforts on non-Hispanic Black and Latinx pregnant individuals who are most susceptible to worsening obesity (ie, postpartum weight retention [PPWR]) [10-13] and other long-term health problems, including cardiovascular disease [14-17]. Pregnancy offers an opportunity to initiate healthy behaviors that limit GWG and its associated health risks because individuals are motivated to have a healthy baby [18]. This ideal window for health promotion extends to the period after birth when it is critical to sustain healthy changes and improve care transitions, especially among individuals with known barriers to health care access and quality [19]. These individuals have increased exposure to negative social determinants of health (eg, environmental, financial, cultural, and linguistic barriers; racism; limited health literacy; and inadequate insurance coverage), which impacts postpartum visit attendance [20,21] and further exacerbates health risk [22-24].

Counseling and lifestyle interventions during and after pregnancy are a recommended and well-established strategy for limiting GWG [25-28] and reducing PPWR [29-32], and their implementation is being tested in real-world settings; for example, our team is testing a remote health coaching intervention to limit GWG integrated into prenatal care clinics [33,34]. However, there are several evidence gaps. First, few interventions have been tested in racial and ethnic minority groups [32,35], with especially low representation of Latinx individuals [36]. Second, few interventions have been implemented and tested in community-based settings where pregnant and postpartum individuals considered high risk access safety net services. Finally, interventions that address health-constraining social factors that contribute to disparities in maternal health outcomes are limited [31,37,38].

Importantly, implementing effective remote lifestyle interventions within community-based programs that pregnant individuals access and trust may optimize their benefits, promote scalability and sustainability, and have the broadest public health impact. Home visiting is an evidence-based public health strategy targeting pregnant individuals considered high risk and families with children aged up to 5 years. Home visitors provide health education, promote positive parenting and early learning, and link families with needed community resources and social support [39]. Early home visiting has been shown to prevent child abuse and neglect, improve maternal and child health, enhance family socioeconomic status, and promote child development and school readiness [40]. Early home visiting is an ideal setting for delivering lifestyle interventions for pregnant and postpartum individuals because home visitors are uniquely positioned to address social and environmental factors impacting health behavior (eg, neighborhood food availability and walkability) [39]. A recent randomized trial testing a lifestyle intervention embedded in early home visiting services showed lower GWG and PPWR up to 12 months, greater achievement of 5% weight loss, smaller waist circumference, and reduced sugar intake at 12 and 24 months [41], as well as greater success in reducing access to sugar-sweetened beverages in the home up to 24 months [41,42].

Objectives

The goals of this paper are to (1) describe the design of this hybrid type I effectiveness-implementation randomized controlled trial testing the effectiveness of the Healthy for Two–Home Visiting (H42-HV) remote lifestyle intervention integrated into home visiting compared to usual home visiting services on PPWR among pregnant and postpartum individuals; (2) highlight the design features of this trial that enable its implementation within home visiting and the applicability of the intervention to the target population, in particular those who identify as Latinx and non-Hispanic Black; and (3) highlight our application of a community-engaged approach to the conceptualization and design of the study to improve intervention effectiveness and study implementation and as a strategy to promote maternal health equity.

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Methods

Study Design, Aims, and Hypothesis

We designed this hybrid type I effectiveness-implementation randomized controlled trial to test the effect of the H42-HV lifestyle intervention integrated into home visiting from mid- to late pregnancy (20-33 wk) through 6 months post partum, compared to usual home visiting services, among pregnant and postpartum individuals with overweight or obesity. The primary outcome is PPWR calculated as 6-month postpartum weight minus prepregnancy (≤18 wk of gestation) weight. Additional measures of effectiveness include GWG and maternal health behaviors, wellness, and health care use. Our main hypothesis is that participants in the H42-HV arm will have lower PPWR than those in the usual home visiting services arm.

Hybrid type I effectiveness-implementation trials assess the primary outcome of clinical effectiveness and evaluate implementation strategies of the intervention as secondary outcomes to better understand facilitators and barriers to real-world dissemination. This hybrid approach could efficiently and in a timely fashion inform the pathways from translation of evidence into practice upon establishing the effectiveness of the intervention, guide future sustainability efforts, and facilitate greater subsequent public health impact [43,44]. To this end, the study will also examine home visiting organizational factors that could impact the implementation of the intervention. We will use the practical, robust implementation and sustainability model (PRISM) framework [45] and domains from the Consolidated Framework for Implementation Research (CFIR) [46] to assess intervention feasibility, acceptability, reach, adoption, and fidelity.

The protocol has been registered with ClinicalTrials.gov (NCT05619705).

Application of a Community-Engaged Approach

We used a community-engaged research approach to inform the conceptualization and design of the study, including the adaptation of the H42-HV intervention and its integration into early home visiting services. On the basis of the continuum of community engagement in research [47], our level of engagement is best characterized as community participation because the community was actively engaged with a defined role in all stages of the research process. Prior studies clearly demonstrate the importance of early and sustained stakeholder involvement to develop and implement remote health interventions for underserved populations [48-50]. The study principal investigators (WLB and KMB) engaged home visiting stakeholders while developing the proposal and, once funded, used a variety of strategies to establish and sustain 2-way engagement, communication, and information sharing. All aspects of the study were enhanced by feedback from a diverse group of stakeholders who serve individuals identifying as Latinx or non-Hispanic Black, including regional and state leaders in home visiting and participating home visiting program managers and home visitors. Stakeholders also included current or recently pregnant individuals who identify as Latinx or non-Hispanic Black and participate in home visiting services.

During the conceptualization phase, we met with state and program leaders to gather information about the relevance of the intervention and its alignment with state and program public health priorities. We also explored the feasibility and acceptability of implementing the intervention within the home visiting setting. In the planning phase of the study, we established a translation and cultural adaptation team of primarily native Spanish-speaking maternal and child health professionals (ie, dietitian, midwife, and nurse) and health professional students (ie, those studying nursing and medicine) to translate and adapt the H42-HV intervention for Spanish-speaking individuals (the adapted version is called Sanos los Dos).

Once funded, we established a coordinating council with home visitors, leaders from participating programs, and Spanish- and English-speaking community members. Regular meetings with the coordinating council informed all aspects of the study protocol as well as implementation measures, recruitment processes, intervention adaptation, and safety protocols. We asked for specific feedback about the referral process, recruitment materials (flyers and videos), intervention approach and messaging, cultural adaptability, and community resource needs through semistructured one-on-one interviews (6 with home visiting program leaders and 7 with coordinating council members). We performed end-user testing of the H42 mobile health (mHealth) app (Figure 1). We conducted 6 interviews with parents and 2 with home visitors, applying a process known to impact the usability and engagement of culturally adapted digital health tools [49,51].

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Figure 1. Healthy for Two mobile health app.

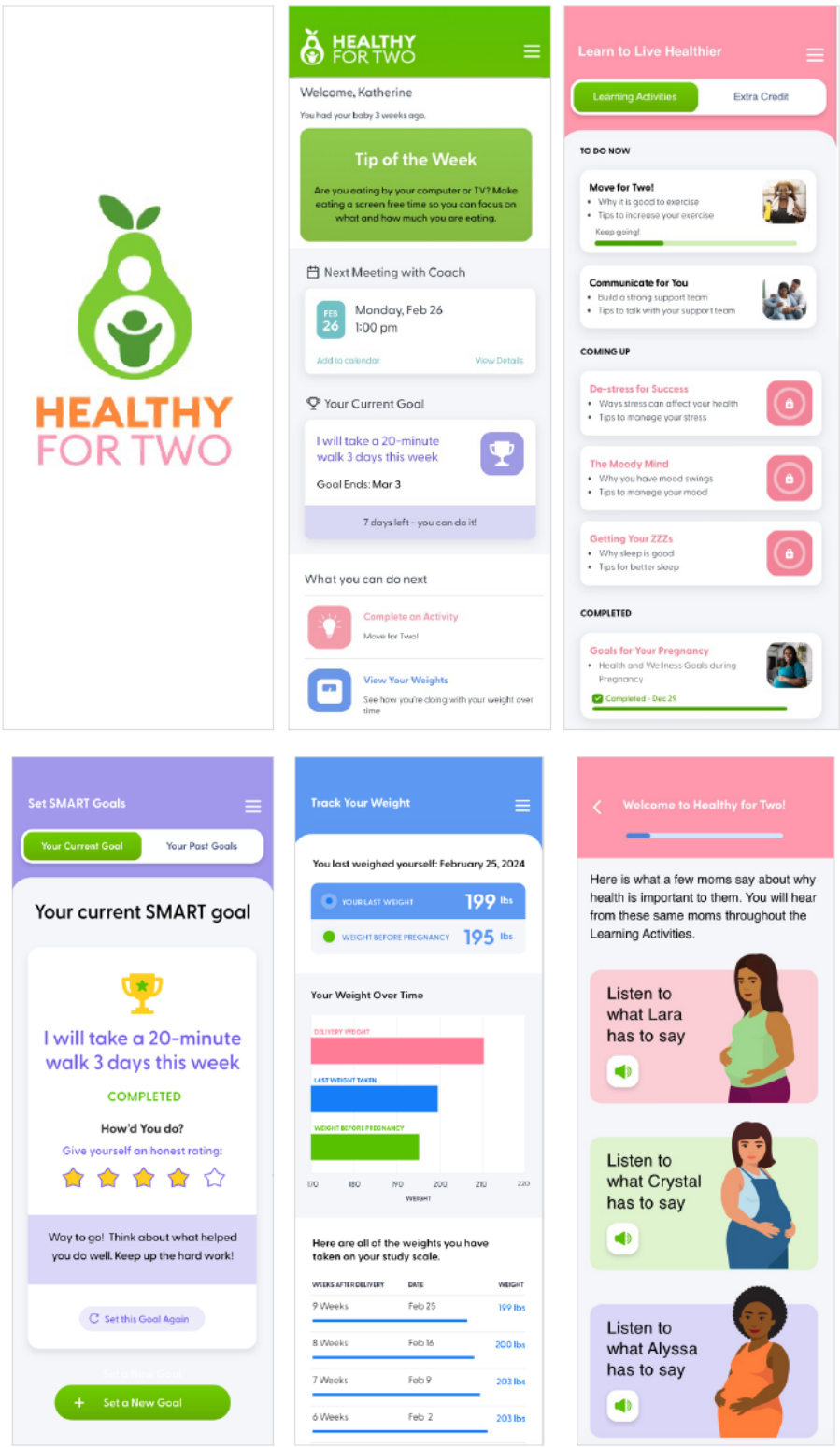

Overall, the feedback highlighted facilitators and barriers to the integration of the H42-HV intervention into home visiting programs and identified strategies for recruitment, adaptations to meet the language and cultural needs of individuals who identify as Latinx and non-Hispanic Black, and effective coordination between the home visitor and health coach. We describe how we addressed feedback from the coordinating council and the additional stakeholders in each of the following subsections.

Home Visiting Programs and Setting

In the formative phase of the trial, we engaged with 7 home visiting programs from across 5 counties in Maryland, United States, that serve predominantly pregnant and postpartum individuals who identify as Latinx or non-Hispanic Black, speak English and Spanish, and have low incomes and literacy levels. Once we launched recruitment, we invited additional early home visiting programs to refer participants to be screened and enrolled in the study. We did not limit ourselves to a particular

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model of home visiting and included evidence-based and non–evidence-based models [39]; for example, the partnering home visiting models include but are not limited to Healthy Families America, Healthy Start, Nurse Family Partnership, and Babies Born Healthy. Depending on the model, home visitors are either nurses or paraprofessionals. Participating home visiting models enroll families in early pregnancy and follow them 6 months to 5 years post partum, but the frequency and intensity of home visits vary by model.

Participant Eligibility

As this is an effectiveness trial, we apply the broadest eligibility criteria to enhance generalizability [43,44,52]: age ≥18 years, singleton pregnancy between 20 and 33 weeks of gestation, and planning to enroll in home visiting services at 1 of the study's participating sites. We are focusing this study on individuals who are overweight or obese (BMI ≥25 kg/m^2) before pregnancy as they are at the highest risk for future cardiometabolic disease [53], and we are excluding conditions that may impact an individual's ability to medically or physically participate in the intervention if randomized to that arm (eg, advised not to exercise by provider or diagnosed with type 1 diabetes). Textbox 1 presents additional eligibility criteria.

Textbox 1. Eligibility criteria.

Inclusion criteria

- Age ≥18 y
- 20-33 wk of gestation
- Prepregnancy BMI ≥25 kg/m^2 (calculated based on self-reported prepregnancy height and weight)
- Able to provide informed consent
- English or Spanish speaking
- Intention to enroll in early home visiting services at a participating site
- Ability to complete telephone-assisted screening and electronic consent

Exclusion criteria

- Diagnosed with type 1 diabetes
- Pregnant with multiple fetuses
- Advised not to engage in exercise by medical provider
- Not cleared by the study's clinicians or home visiting program staff
- Planning to relocate outside of Maryland in the next year
- Active substance abuse (except marijuana)
- Psychiatric or substance use–related hospitalization in the past year
- Active eating disorder

Evidence shows that starting an intervention early in pregnancy has the greatest impact on pregnancy outcomes and GWG [54,55]. However, many home visiting programs rely on several steps to occur before services can begin, that is, entry in prenatal care, referrals from clinic, screening by outside agency for eligibility, and outreach by home visiting program. In response to input from participating home visiting programs, we selected a broad enrollment window during pregnancy (20-33 wk of gestation) and will continue intervention delivery through 6 months post partum. Given state and program leader feedback about the potential for home visiting enrollment in late pregnancy, we selected the primary outcome as return to prepregnancy weight or below because PPWR is a risk factor for future obesity.

Screening and Recruitment

With feedback from home visiting program partners (refer to the Application of a Community-Engaged Approach subsection), we designed the role of home visitors to be low touch and aligned with the procedures they already use in their program and visits. Figure 2 outlines the study design and recruitment procedures. Home visiting staff inform potentially eligible clients about the study via conversation, email, or SMS text message using a "toolkit" of different materials available in English and Spanish to accommodate program, staff, and client needs and preferences (eg, suggested dialogue, paper flyers or postcards, and an informational video lasting 2-3 min). All recruitment materials include a link and QR code to an "electronic interest form" (to be completed by clients or home visitors on their behalf) that requests basic eligibility information to preemptively exclude clients aged <18 years and >33 weeks of gestation, as well as additional details to facilitate the next steps of the screening process.

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Figure 2. Study design and recruitment procedures. mHealth: mobile health.

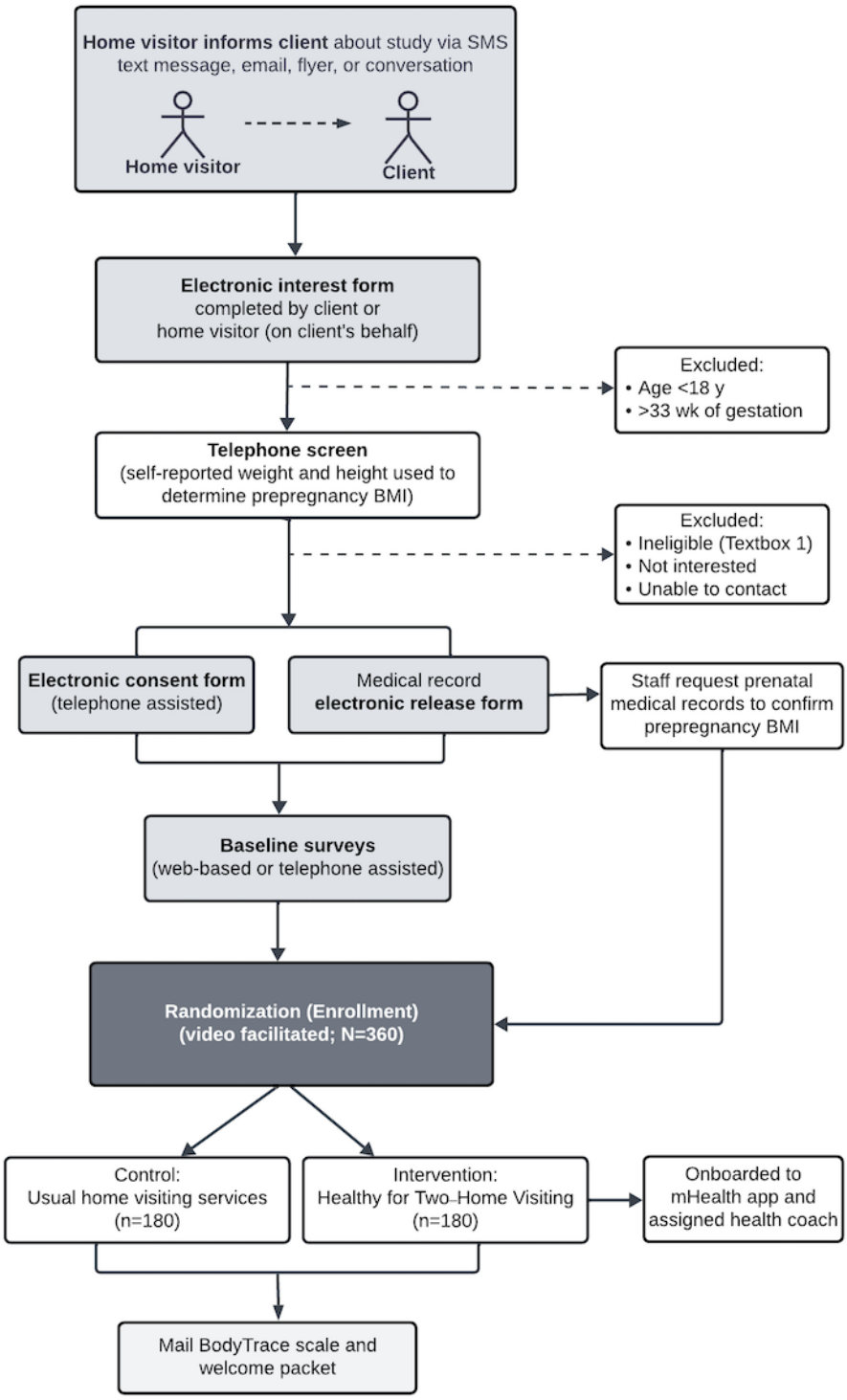

Upon receiving a completed "electronic interest form," research staff reach out to the potential participant via telephone to further assess interest and screen for eligibility. After confirming eligibility, research staff complete a telephone-assisted electronic consent process that includes obtaining a signed authorization for the release of medical records, including prenatal and infant records as well as claims data. After consent is obtained, study staff immediately request prenatal clinic records for height and prepregnancy weight measurements to confirm BMI criteria, and participants complete web-based or telephone-assisted baseline data collection surveys. Once these steps are complete, consented participants meet virtually with staff for a video-facilitated randomization (enrollment) visit. At randomization, participants receive instructions for taking home weight measurements using a study-provided smart scale shipped to their home; intervention participants are oriented to the H42 mHealth app and provided the name of their health coach. In response to home visitors' interest in the result of each client they refer (ie, ineligible, unable to contact, or enrolled), we provide them with the option to "opt in" to live email updates on referral outcomes.

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Randomization and Blinding

A total of 360 participants will be randomized 1:1 to the H42-HV arm or comparison arm. Randomization is stratified by home visiting program region+primary language served (ie, central Spanish or English, capital Spanish or English, eastern Spanish or English, southern Spanish or English, or western Spanish or English) and BMI (≥30 kg/m^2 vs 25-29.9 kg/m^2) and within each stratum using randomly varying block sizes of 2, 4, and 6. The randomization scheme was generated using Stata (version 17.0; StataCorp LLC) and imported into REDCap (Research Electronic Data Capture; version 14.0.31; Vanderbilt University) [56,57]. Assignment remains masked until a participant is randomized. Due to the nature of this lifestyle intervention, participants, home visitors, the intervention team, and the safety monitor will not be blinded to randomization assignment after randomization. Until the end of the trial, all nonintervention study staff and coinvestigators, including the principal investigators and data collectors, will remain blinded, with the exception of the lead biostatistician.

H42-HV: Intervention Design and Approach

Overview

The intervention was adapted from our previously designed and pilot-tested remotely delivered lifestyle intervention (called Healthy for Two/Healthy for You) to limit GWG and PPWR in a racially diverse population with low literacy [33,34]. The person-centered intervention uses a standard behavioral approach to weight management [58], teaching strategies aligned with social cognitive theory, such as self-monitoring, goal setting, and problem-solving [59]. The overarching goal of the H42-HV intervention is for participants to have lower PPWR 6 months after delivery.

Intervention Components and Adaptations

Overview

We used an iterative approach for translating and adapting intervention content and technologies using feedback from our key stakeholders (refer to the Application of a Community-Engaged Approach subsection). In addition to shifting intervention timing and focus to the postpartum period, we reframed messaging about program goals to achieving "overall health and wellness" versus a "healthy weight." Consistent early feedback from home visitors suggested that strong internalized weight biases among their clients may impact intervention engagement and acceptability. Weight stigma is pervasive in health care settings, has detrimental impacts on overall health and the use of health care services [60,61], and has more recently been regarded as a social determinant of poor birth outcomes [62]. Textbox 2 summarizes the adapted components of H42-HV.

Textbox 2. Healthy for Two–Home Visiting intervention components.

Person-centered health coaching (English or Spanish)

- 10 total telephone or video meetings (4 pregnancy, 6 postpartum) lasting approximately 30 min using a person-centered approach, plus 2 as-needed "boosters"
- Starts between 20 and 33 wk of gestation and continues through 6 mo post partum
- Coaches have access to a mobile health (mHealth) coaching interface to view participant app engagement and health progress (refer to the H42 mHealth App subsection)

Self-weighing via a home smart scale

- Participants self-weigh at least once weekly on a cellular-enabled home smart scale
- Paper and electronic "wellness journal" available to self-monitor diet and exercise

H42 mHealth app (hosts web-based learning and goal-setting activities, smart scale weight displays, and 2-way participant-coach messaging; promotes engagement via dynamic in-app messages and email reminders)

- Learning activities: 10 educational modules focused on diet, exercise, social support, stress, mood, and sleep. Learning methods include the following: simple, brief education on core topic; audio quotes from 3 ethnically diverse mothers describing personal challenges or successes and behavioral strategies that help them meet health and wellness goals; 5 simple multiple-choice quiz questions to reinforce key concepts; open-ended free-text questions, ranging from 4-9 total per learning activity, to promote goal-oriented thinking, problem-solving, and identification of barriers and successes.
- Add-on learning: videos and external links covering topics such as breastfeeding, gestational diabetes, and smoking cessation
- Goal setting activity: tool that aids participants in setting their own specific, measurable, achievable, relevant, and time-bound (SMART) goals and rating their progress
- Weight display: real-time view of home smart scale weights with feedback to support goal of returning to prepregnancy weight
- Coach-participant messaging: synchronous communication stream primarily used for scheduling and delivery of individualized intervention content (ie, PDF files, images, etc)
- Home page: personalized summary to facilitate intervention adherence (ie, date and time of upcoming coach meetings, most recent coach message, reminders to weigh) and engagement (ie, seasonal health or wellness "Tip of the week")
- Coach and coach manager interface: coach interface with dynamic access to participant weight data and engagement with app (ie, SMART goals, free-text entries); coach manager interface with real-time access to participant and group-level data for individualized case management and ongoing support and management of all coaches

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Person-Centered Health Coaching

The cornerstone of the H42-HV intervention is *health coaching* using an evidence-based person-centered approach [63] aimed at enhancing participants' intrinsic drive to make health-related behavior changes (diet, exercise, and stress management). Participants complete up to 12 coach meetings (10 planned plus 2 as-needed "boosters") via video or telephone when they join the study (between 20 and 33 weeks of gestation) through 6 months post partum. Coaches aim to complete 4 meetings during pregnancy and 6 meetings post partum, with flexible cadence to account for varying enrollment dates. The frequency of coach meetings is consistent with similar interventions showing an effect on PPWR [29,33,64] and based on evidence that moderate- (ie, ≥6 contacts) to high-intensity (ie, ≥12 contacts) lifestyle interventions have the greatest effect on GWG [26,65]. Coaches receive enhanced training on weight bias and cultural sensitivity as well as supporting behavioral changes in the context of common social and environmental barriers such as food insecurity and neighborhood safety.

Health Behavior Tracking (Self-Weighing via Home Smart Scale)

Participants are instructed to weigh themselves weekly on a *cellular-enabled home smart scale* (Body Trace; BodyTrace, Inc) [66] that transmits live data to the H42 mHealth app and coach interface described in detail in the next subsection. Coaches emphasize that self-weighing is a core tool to assess progress, similar to monitoring one's exercise minutes and the type and amount of food and drinks consumed. Participants have the option to track and share diet and exercise behaviors with their coach as well as daily ratings of their mood and sleep using a simple paper "wellness journal" or "electronic wellness journal" delivered daily or weekly via SMS text message or email.

H42 mHealth App

Our team designed the *web-based mHealth app* (Figure 1) *and coach interface* based on intervention content tested in past trials [33,34]. The H42 mHealth app is accessible via mobile phone and delivers education tailored to a <6th-grade reading level [67-69] via interactive learning activities that provide guidance on making healthy lifestyle changes in the context of common environmental barriers (eg, eating healthy on a budget and low-cost ways to manage stress). Supplemental health topics (eg, breastfeeding, infant health, and depression) are also available because our formative research and work by others suggested that pregnant and postpartum people across races are more likely to use digital health tools that offer credible, perinatal-specific health information beyond nutrition and exercise [70,71]. The mHealth app contains a goal-setting activity, facilitates 2-way participant-coach communication, displays smart scale data, and promotes adherence and engagement via dynamic in-app messages and email reminders (Figure 1). End-user testing of the English and Spanish versions of the app completed in preparation for the trial (the testing involved 3 English-speaking and 3-Spanish speaking parents and 2 bilingual home visitors) generated reactions to app design and images, usability, interactive functionality, cultural appropriateness, and effectiveness. Consistent feedback gathered (and addressed) included preferences for a brighter color palette, more images, less text and fewer numbers, more traditional Latinx food options, larger-sized body types, simpler graphics (ie, bar graph vs line graph), and a stronger representation of family (ie, households with multiple children). If cost is a barrier, the study subsidizes web-based access (eg, by providing data cards).

The *coach/coach manager interface* provides dynamic access to participant smart scale weights and app activity (ie, goals and free-text responses) as well as food and exercise data for those who choose to track these behaviors using the "electronic wellness journal" that syncs data to the interface. The interface additionally serves as a documentation and scheduling tool. A coach manager interface provides individual and aggregate summary data to facilitate regular participant oversight, ongoing support, and the management of coaches and intervention adherence monitoring throughout the study.

Usual Home Visiting Services Comparison

Participants randomly assigned to the comparison arm receive usual home visiting services per agency guidelines and requirements. In addition, we provide a brief, publicly available educational video on urgent maternal warning signs [72,73]. Private, staff-monitored Facebook groups are offered to disseminate information on healthy pregnancy and allow for community building and retention for both groups (usual home visiting services and H42-HV). Both groups are also provided county-specific resource lists with information on green spaces, food banks, mental health resources, medical centers, and intimate partner violence support. This resource list is available as an electronic map (using Google Maps) and a paper version.

National Institute on Minority Health and Health Disparities Research Framework Adaptation for the H42-HV Intervention

We adapted the National Institute on Minority Health and Health Disparities research framework [74] to depict the multilevel influences (individual, interpersonal, community, and societal levels) that embedding the remote intervention into early home visiting services has on health outcomes and disparities, including the social determinants of health (Figure 3). The H42-HV intervention impacts *individual-level* factors by promoting a healthy lifestyle in women with cardiovascular risk factors, regardless of insurance coverage or health literacy. While coaches provide education and strategies for making healthy changes (ie, adding fruits and vegetables to participants' diet), home visitors address context-specific barriers (eg, healthy food availability) and leverage context-specific assets (eg, local food banks) to increase success at achieving behavioral goals. At the *interpersonal level*, home visitors provide social support and connect participants with social support networks that promote a healthy lifestyle and provide tools to navigate family or peer norms, while health coaches teach participants effective communication skills to strengthen the support they receive from their existing network (eg, home visitors, health care providers, family members, and peers) and tailor this support toward making healthy changes. The H42-HV intervention addresses *community*- and *societal-level* influences by connecting participants with local resources and promoting

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parent and infant use of health care services (eg, postpartum care and primary care). Ultimately, the study is designed to promote a holistic approach to reducing cardiometabolic health inequities among birthing people.

Figure 3. National Institute on Minority Health and Health Disparities research framework adaptation for the Healthy for Two–Home Visiting intervention.

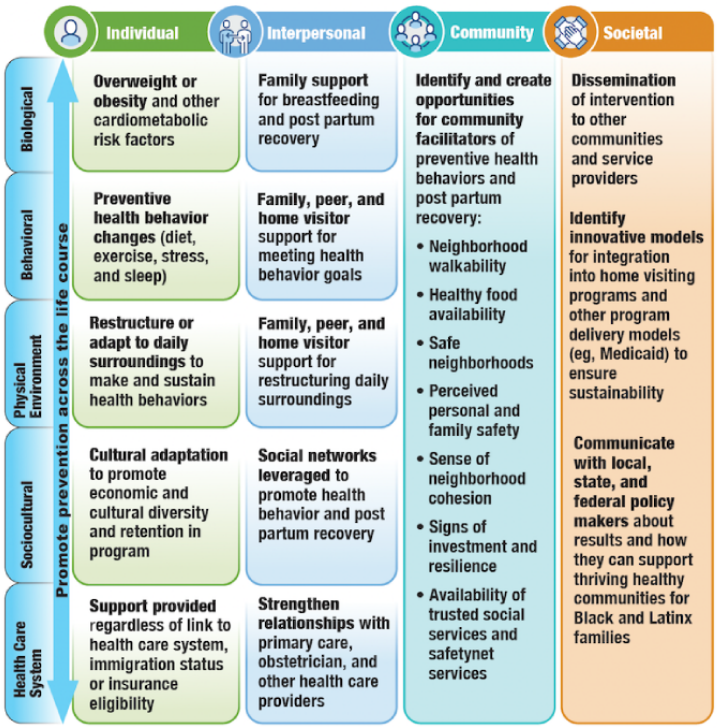

Data Collection and Data Sources

Effectiveness Measures and Methods

Tables 1 and 2 summarize the methods of measurement and timing aimed at improving access and retention as well as minimizing participant burden (also refer to Figure 4). Early conversations with home visiting program leaders indicated that home visitors would not have time to collect study data; therefore, data collection procedures were designed to not involve home visitors. Data are collected through 4 methods: a cellular-enabled home smart scale, medical record review, web-based surveys via REDCap, and Medicaid claims data.

Table 1. Schedule of intervention effectiveness measures: electronic medical record review, smart scale, and Medicaid claims.

Measure	Pregnancy		Post partum			
	Baseline[a]	37 wk	Delivery[b]	2 mo	4 mo	6 mo
Maternal weight and height	Electronic medical record review	Smart scale	—[c]	Smart scale	Smart scale	Smart scale
Labor and delivery discharge summary from outside hospitals	—	—	Electronic medical record review	—	—	—
Infant weight and length from pediatric practices	—	—	Electronic medical record review	—	—	—
Maternal and infant health care use				Medicaid claims	Medicaid claims	Medicaid claims
Home visiting use and safety net services				Medicaid claims	Medicaid claims	Medicaid claims

[a]Baseline window: 20 to 33 wk of gestation.

[b]Delivery through 2 wk post partum.

[c]Not applicable.

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Table 2. Schedule of intervention effectiveness measures: web-based surveys.

Measure	Pregnancy		Post partum		
	Baseline[a]	Delivery[b]	2 mo	4 mo	6 mo
Web-based surveys					
Demographics and medical history [75-78]	✓	✓[c]			
Dietary behaviors [79]	✓				✓
Physical activity [80]	✓		✓		✓
Depression and anxiety [81]	✓	✓	✓	✓	✓
Brief Perceived Stress Scale [82]	✓		✓	✓	✓
Brief Pittsburgh Sleep Quality Index [83]	✓		✓	✓	✓
Functional Social Support Questionnaire [84]	✓		✓		✓
Social determinants of health [76,78]	✓				
Everyday discrimination [85]	✓				
Tobacco, marijuana, and alcohol (PRAMS[d]) [86]	✓				✓
Pregnancy intention (PRAMS) [86]	✓				
Usual source of (maternal) care (PRAMS) [86]	✓				✓
Experiences with care (PRAMS) [86]		✓			
Infant care (PRAMS) [86]		✓	✓		
Postpartum visit attendance and support (PRAMS) [86]				✓	
Postpartum contraception (PRAMS) [86]				✓	✓
Breastfeeding intention and practices (PRAMS) [86,87]			✓	✓	✓
Use of community and safety net services: Supplemental Nutrition Program for Women, Infants, and Children (PRAMS) [86]			✓	✓	✓
Engagement with home visiting			✓	✓	✓
Safety survey		✓	✓	✓	✓

[a]Baseline window: 20 to 33 wk of gestation.

[b]Delivery through 2 wk post partum.

[c]Infant race and ethnicity collected at delivery.

[d]PRAMS: Pregnancy Risk Assessment and Monitoring System.

Figure 4. Data collection and retention.

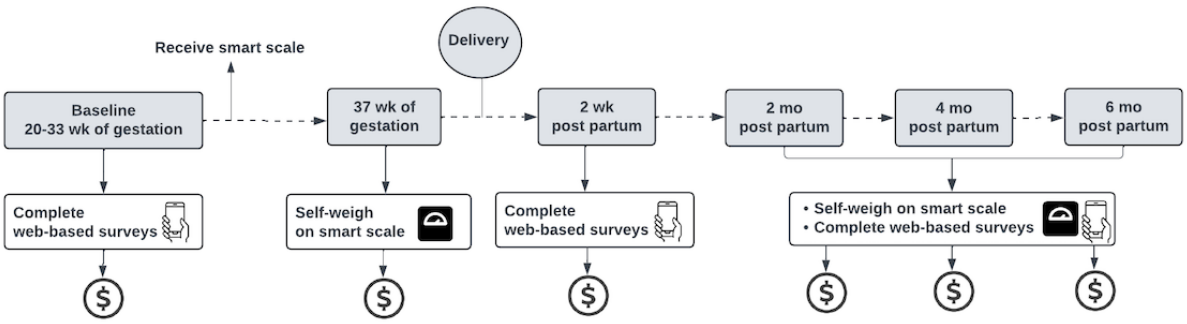

Assessment and Verification of Maternal Weight Using a Smart Scale

Smart scale weights are collected at 4 time points: 37 weeks of gestation; and 2, 4, and 6 months post partum (Table 1). Participants are instructed to weigh themselves in light indoor clothes without shoes on their home smart scale (BodyTrace [66]). The smart scale transmits data to the study team via cellular connectivity (no Wi-Fi or cellular plan is required), which is ideal for rural client communities with intermittent Wi-Fi or those with reduced access to cellular data or inconsistent data plans. The BodyTrace smart scale was selected

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because it demonstrates good concordance with in-person assessments [88,89] and has been used in several large weight management trials [90,91], including those with racially diverse populations with low incomes and literacy levels [92-94]. The scale is mailed to participants' homes after randomization, and brief SMS text reminders to weigh are sent at each study assessment time point (ie, "Time to step on your scale"). Staff monitor weight data transmitted to the study's REDCap server in real time and reach out to participants with no weight by the middle of each designated assessment "window," which ranges from –10 days to +10 days at designated study outcome assessment time points. Staff also monitor battery power and the strength of the cellular connection to assist participants with related issues, as needed. To mitigate the disruption that environmental factors (eg, potential for multiple users or scale displacement) can have on data quality, we programmed a dynamic weight cleaning procedure that requires participants to confirm questionable weights by responding to a 1-question survey sent via SMS text message. For intervention participants, this cleaning procedure ensures real-time accuracy of the weight graphs in the H42 mHealth app, as well as automated reminders, including in-app messages that prompt participants to weigh if a confirmed weight is not available after 7 days. After 14 days, coaches are notified to conduct personalized outreach to remind participants to weigh themselves.

Obtaining Medical Records and Abstracting Information on Prepregnancy Weight

Participants consent to pre- and postnatal medical record release for themselves and their infant from before pregnancy through 1 year post partum (Table 1). We use a secure electronic fax system (OpenText Fax; Open Text Corporation) to request medical records from prenatal clinics, offices, and hospitals. "Prepregnancy" weight is defined as the earliest measured weight obtained from medical records up to 18 weeks of gestation; when not available, we use self-reported weight. We also abstract height, parity, and comorbid conditions from medical records.

Web-Based Surveys

We used REDCap to build and design web-based surveys using standard instruments selected to minimize participant burden and enable completion at home (Table 2). Collectively, surveys take 10 to 20 minutes to complete, depending on the total number and length of those designated at each time point; staff-led telephone-assisted surveys are available, when preferred.

Demographics and Social Determinants of Health

Maternal and infant demographics and social determinants of health are collected using standard questions from the PhenX toolkit [78], the 2020 US Census Informational Questionnaire [75], and the Accountable Health Communities Health-Related Social Needs screening tool [77]. Additional common data elements, using standard and commonly used measures related to participant characteristics and social determinants of health, were incorporated, as required by the National Institutes of Health–Health Equity and Action Network for data harmonization at the National Institutes of Health Multiple Chronic Diseases Disparities Research Consortium [76]. Experiences with chronic, routine discrimination [95] are assessed using the 9-item Everyday Discrimination measure [85], which demonstrates good reliability (Cronbach α=0.88) and is shown to be a strong and consistent predictor of health and well-being [85].

Maternal Health Behaviors, Attitudes, and Experiences

Dietary intake is assessed as estimates of servings of fruits and vegetables, added sugars, whole grains, fiber, and calcium using the 26-item Dietary Screener Questionnaire [79], which demonstrates agreement with 24-hour dietary recalls [96]. Exercise frequency and intensity are measured using the 7-item International Physical Activity Questionnaire–Short Form, which has acceptable reliability (pooled ρ=0.76) and some agreement with the accelerometer standard (pooled ρ=0.30) in a diverse sample [80].

Mood is assessed using the 10-item Edinburgh Postpartum Depression Scale for postnatal depression, which illustrates moderately high validity (sensitivity=85%, specificity=77%) and split-half reliability (r=0.88) in the original sample of 60 mothers [81]; these results have been confirmed in other validation studies [97]. We measure stress using the 4-item Brief Perceived Stress Scale [98], which is a shortened version of the original 14-item scale [82] and has acceptable psychometric properties [99]. We assess sleep using the 6-item Brief Pittsburgh Sleep Quality Index [83], which shows good internal consistency (Cronbach α=0.79, McDonald ω=0.91) and adequate validity (sensitivity=76%, specificity=77%) in a large population-based sample [83]. Perceived social support is quantified using the 8-item Duke-UNC Functional Social Support Questionnaire [84], which has favorable test-retest reliability (r=0.50-0.85) and is significantly correlated with other social support measures [84].

Several questions from the standard and core measures of the Pregnancy Risk Assessment and Monitoring System (PRAMS) [86] assess pregnancy and breastfeeding intentions and practices, contraception, substance use (tobacco, marijuana, and alcohol), and experiences with or use of health care before and after birth.

Infant Health, Sources of Care, and Feeding Practices

Infant overall health, feeding, and sources of care are assessed using the PRAMS [86] and Infant Feeding Practices Survey [87]. The use of community and safety net programs (ie, Supplemental Nutrition Program for Women, Infants, and Children) is also measured using the PRAMS [86].

Engagement With Home Visiting Services

Engagement with home visiting services and the frequency of contacts with home visitors will be collected at all postpartum time points to assess the "dose" of home visiting during the study.

Intervention Satisfaction

Intervention participants complete a satisfaction survey at the end of the study using an adapted survey tool administered and reported on in previous trials [33,34].

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Medicaid Claims Data

We will request Maryland Medicaid claims data for all consented participants with Medicaid to assess maternal and infant health care use outcomes (ie, attendance at prenatal care visits, postpartum visit, primary care visits, infant visits, and receipt of infant vaccines) via a data use agreement with the Maryland Department of Health (Table 2).

Implementation Process Measures and Methods

Overview

Measures to evaluate the implementation are based on the PRISM framework [45] and domains from the CFIR [46]. Table 3 outlines all implementation outcomes and measures.

Table 3. Implementation process measures and methods.

PRISM[a]+CFIR[b] domains	Implementation process measure	Data collection method (before, during, and after the trial)
Organizational perspectives	Home visiting program perceived usability, adaptability, and relative priority of the intervention	Surveys before and after program orientation; focus groups after the trial
Organizational characteristics (inner setting from the CFIR)	Home visiting program culture, management support and cooperation, systems, training, staffing, and incentives	Home visiting leader surveys before the trial
External environment (outer setting from the CFIR)	Home visiting program regulatory environment (policies and incentives); patient needs and resources	Home visiting leader surveys before the trial; county reports; census and county rankings database
Reach	Total number of clients enrolled out of those screened and eligible; total number of clients enrolled out of new pregnant clients enrolled in the home visiting program	Study recruitment and enrollment data; home visiting program leader surveys after the trial
Implementation (engaging, reflecting, and evaluating process from the CFIR)	Engagement of program leaders in implementation process; qualitative feedback on the progress and quality of the implementation	Coordinating council, formative interviews with home visiting program leaders, focus groups, and research team discussion and reflection throughout the trial
Adoption	Proportion of sites across the state that opt to participate in the study; adoption of training and recruitment procedures; level of involvement supporting intervention participants	Home visiting staff focus groups after the trial; review of study recruitment and enrollment data
Fidelity of the intervention (coach and participant)	Coach adherence to meeting guides and patient-centered approach; participant adherence to intervention components and perceived acceptability	Review of audio-recorded coach meetings during the trial; reports from data management systems; participant acceptability survey after completing the study

[a]PRISM: practical, robust implementation and sustainability model.

[b]CFIR: Consolidated Framework for Implementation Research.

Organizational Perspectives

To support state and program leader feedback gathered during the conceptualization phase of the study (refer to the Application of a Community-Engaged Approach subsection), home visitors' perspectives of the intervention were assessed via survey before and after a 1-hour study staff–led orientation (an overview of study goals, design, and referral procedures) that they received before the trial. They rated the importance of, and the need for, resources to address various health-related topics (eg, nutrition and exercise) with their clients before the training and after they rated intervention acceptability, appropriateness, and feasibility [100]. At the end of the study, we will conduct 2 focus groups with home visitors from participating programs to further explore the perceived usability, acceptability, and adoption of the intervention. Interview guides will be developed using the PRISM framework [45] and include questions assessing facilitators and barriers to implementation.

Organizational Characteristics (Inner Setting From the CFIR)

Features of home visiting programs through which the implementation process will proceed and features that may support or impede the programs' ability to successfully implement the intervention (eg, structure, enrollment, staffing, service modality, and curriculum) were assessed before the trial using a survey completed by home visiting program leaders.

External Environment (Outer Setting From the CFIR)

The county-level economic, political, and social contexts within which the home visiting programs reside and which may affect their ability to successfully implement the intervention (eg, social determinants of health, obesity rates, demographics, reimbursements, and health and wellness resources) will be assessed before the trial using a survey completed by home visiting program leaders and publicly available data from county reports, US Census Bureau data [75], and a county rankings database [101].

Study Reach

We will quantify study reach as (1) the total number of clients enrolled in the study out of new pregnant clients enrolled in home visiting during the enrollment period and (2) the total number of clients enrolled in the study out of those screened and eligible for the study.

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Implementation (Engaging, Reflecting, and Evaluating)

We will measure implementation through a combined strategy of gathering feedback from home visiting programs about the progress and quality of the implementation and holding regular debriefings with personnel and team about progress and experience.

Adoption of Intervention

We will track the proportion of home visiting sites across the state that opt to participate in the study and assess the level of involvement in study procedures and the intervention via survey and home visitor focus groups after the trial.

Fidelity of the Intervention: Coach and Participant Adherence (During and After the Intervention)

We will examine intervention fidelity and its impact on the primary outcome using common procedures applied in multicomponent remote lifestyle intervention trials [102,103]. Health coach fidelity to a participant-centered approach and standard meeting components (eg, reviewing successes and progress as well as setting goals) will be measured using an iterative quality assurance process of sampling and reviewing audio-recorded coach meetings. We will track participant adherence to each component of the intervention (coach meetings, mHealth app, and smart scale use) and intervention acceptability using an end-of-study survey.

Retention Strategies for Participants

On the basis of our experience with recruiting and retaining pregnant women, we will use several methods to achieve high retention, including rapport building, sending birthday and birth cards, and using email and SMS text message reminders based on each participant's preferred method of contact. Participants will be provided gift cards after each data collection visit: US $10 at enrollment; US $10 at 37 weeks of gestation; US $15 at 2 weeks post partum; and US $20, US $25, and US $30 at 2, 4, and 6 months post partum, respectively (Figure 4). As participants will be engaged in home visiting and consider the program part of their care, we anticipate low risk for loss to follow-up.

Methods for Ongoing Home Visitor and Community Engagement

Home visitor engagement will involve monthly recruitment updates shared with sites and site supervisors, raffle incentives, ongoing training opportunities on topics of interest, and brief one-on-one "check-ins" between a study team member and home visitor "site champion" aimed at quickly mitigating concerns or struggles pertaining to study procedures. Community engagement throughout the trial will involve quarterly newsletters to all stakeholders (ie, coordinating council members and state-level leaders), including home visitor and community member "spotlights" and participant success stories. In addition, each home visiting site will receive an annual financial incentive.

Analytic Approach

Sample Size and Power Estimates

With 360 participants, our objective is to determine the minimum detectable difference (MDD) for the primary outcome of PPWR between the 2 study groups. Our assumptions are as follows: a 2-tailed type I error rate of 0.05, a type II error rate of 0.10, and ≥70% follow-up for the main outcome of PPWR at 6 months. On the basis of the past experience [33] and published literature, we anticipate <30% loss to follow-up for 6-month weight measurements, consequential to various forms of dropout (eg, lost to follow-up). With this dropout rate and the assumption that the dropout is consistent with missing at random, we expect to randomize 360 participants (n=180, 50% per arm) to retain an effective sample size of 252 participants (n=126, 50%/arm) for our primary outcome. SDs for the MDD evaluation were informed by previous studies of similar combined diet-exercise lifestyle interventions to limit weight gain in pregnancy and promote postpartum weight loss [26,41,104,105]. Under these considerations, the resulting MDDs range from 2.3 to 3.6 kg with corresponding SDs for PPWR of between 5.5 and 8.8 kg.

Main Analytic Model for the Primary Outcome of PPWR

Analysis will follow the intention-to-treat principle. The main analysis will assess the between-group difference in PPWR (the difference between earliest pregnancy weight and weight at 6 mo post partum) using a mixed effects model characterized by a mean model relating the outcome to the predictors and a variance-covariance model addressing variance of all available longitudinal weight outcomes and correlation between outcomes measured over time within individual. The predictors in the mean model will include a group indicator (0 for the comparison arm and 1 for H42-HV) as well as 3 binary indicators for 2-, 4-, and 6-month postpartum visits, respectively, with baseline visit as the reference, and the corresponding group-by-visit interaction terms, adjusting for study sites (region and primary language served) and baseline BMI category used for randomization stratification, as fixed effects. The regression coefficient of the group by 6-month postpartum weight interaction term will estimate the intervention effect on the primary outcome, that is, mean difference in PPWR at 6 months between the intervention and control groups. We will use an unstructured variance-covariance model to allow full flexibility on outcome variances and longitudinal correlations for the repeatedly measured weight data. A model-based 2-tailed t test will be used to evaluate the intervention effect and derive the associated 95% CI. The Kenward-Roger approximation will be used to calculate the df for the t test, with $P<.05$ considered statistically significant [106].

Data from all randomized participants will be used in this analysis, with missing data included using a software-specified missing indicator. The main analysis will assume that outcome data are missing at random and use an observed data likelihood approach implemented through the mixed effects regression model, where baseline characteristics associated with the probability of missing outcome data will be further adjusted for in the mean model. Sensitivity analysis through multiple

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imputation of missing outcome data under plausible missing-not-at-random scenarios will be conducted to evaluate the robustness of the findings from the main analysis conducted under the missing-at-random assumption.

Secondary Outcomes and Additional Analyses

Secondary outcomes include maternal, infant, and organizational process outcomes. For secondary maternal outcomes, available data from all randomized individuals will be included. Between-group differences in GWG (defined as the difference between the weight at 37 weeks of gestation and prepregnancy weight) and infant weights will be assessed using the same mixed effects modeling approach as described for the primary outcome, with separate models for each outcome. Between-group differences in the binary outcomes of diet, exercise, breastfeeding, and women's wellness measures (depression, sleep, stress, and social support) will be described between the H42-HV and comparison arms using standard cut points for the scales and modeled using logistic regression model–based longitudinal models implemented through a generalized estimating equations approach [107]. The mean models will similarly use the group indicator, visit indicators, and the corresponding group-by-visit interaction terms, adjusting for the variable used to stratify the randomization. Robust variance estimates will be used for statistical inferences to derive 95% CIs for the population-average estimates and corresponding *P* values. Conforming to recommended maternal postpartum care use and well-baby care use over time will separately be modeled using a similar generalized estimating equations approach as described for the longitudinal binary outcomes.

Exploratory Analyses for the Heterogeneity of the Intervention Effect

We will explore for potential moderators of intervention effects by conducting subgroup analyses based on baseline survey data (race, ethnicity, home visiting program characteristics, baseline BMI category [overweight or obese], language spoken at home, low English proficiency, income, and education level) and examining effect modification by adding appropriate interaction terms to the primary mixed effects model. We do not expect the intervention effects to vary across subgroups, and we will interpret carefully any observed heterogeneity, or lack thereof, given the exploratory nature of these analyses.

Safety Surveillance and Monitoring

For active surveillance, a safety medical officer will oversee the postdelivery review of medical records, including labor and delivery notes and infant discharge summaries. We will administer safety surveys after delivery and at 2, 4, and 6 months post partum to enable tracking of all maternal and infant hospitalizations, emergency department visits, and labor and delivery triage evaluations (Table 2). We have developed protocols to alert the team and manage high levels of depressive symptoms or interpersonal violence (Table 2). The Johns Hopkins Institutional Review Board is required to review all serious safety events. In addition, the study has a sponsor-approved data safety and monitoring plan, and oversight from the Mid-Atlantic Center for Cardiometabolic Health Equity Data and Safety Monitoring Board that meets twice a year to review study progress, intervention adherence, and adverse events (mild, moderate, and severe).

Ethical Considerations

The protocol received initial approval from the Johns Hopkins Institutional Review Board in June 2022 (IRB00307430) and was determined to be minimal risk. Standard continuing reviews occur yearly; protocol amendments are also reviewed and subsequently updated in the ClinicalTrials.gov registry. During the informed consent process (refer to the Screening and Recruitment subsection), participants are made aware of their right to privacy and confidentiality and are informed that all health information is deidentified or stored on secure servers. They are also advised that they can withdraw from the study at any time without consequence from the research team and medical or home visiting services, and if this occurs, Johns Hopkins may use any data collected before withdrawal. Participants will be provided gift cards after each data collection visit (for details, refer to the Retention Strategies for Participants subsection). In addition, each home visiting site will receive an annual financial incentive.

Results

This study was funded in June 2021, and recruitment began in April 2023. As of November 2024, we enrolled 90 participants. Data collection to assess the intervention's effectiveness is expected to end in June 2026. Implementation evaluation is expected to conclude in December 2026.

Discussion

Anticipated Findings

We designed this hybrid type I effectiveness-implementation randomized controlled trial to test a remote lifestyle intervention for weight management during pregnancy and post partum in a community-based setting that serves individuals who identify as Latinx and non-Hispanic Black. The goal of this hybrid trial is to evaluate the effectiveness of a newly adapted remote lifestyle intervention (H42-HV) and effectively integrate the intervention into early home visiting services to reduce PPWR. We hypothesize that participants who receive the H42-HV intervention will have a lower mean difference in PPWR at 6 months than control group participants. This would add to the limited evidence supporting the effectiveness of counseling and lifestyle interventions during and after pregnancy in minimizing GWG [25-28] and reducing PPWR [29-32] among racial and ethnic minority groups [32,35]. Furthermore, because few counseling and lifestyle interventions for pregnant and postpartum people have been tested in community-based settings, the use of implementation science methods will enable the gathering of important data about the facilitators and barriers to implementing the intervention in the early home visiting setting and among this population considered vulnerable. Early home visiting programs hold promise to be an ideal setting to integrate lifestyle interventions because of their unique ability to address relevant social and environmental conditions impeding healthy behaviors (eg, access to healthy foods and transportation), as well as support and improve transitions to

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postpartum care. We anticipate that our study findings will demonstrate feasibility comparable to that reported in another trial of a lifestyle intervention embedded into early home visiting [41,42]. Through the implementation science approach, we will also provide evidence to support policy translation, including the expansion of H42-HV delivery into other US states' home visiting programs, and into Medicaid Managed Care coaching and case management programs as Medicaid coverage expands into the postpartum period in more states [108].

Strengths and Limitations

A major strength of the trial's design is the community-engaged approach, which began during the grant conceptualization and preimplementation phases to inform project design. Community-engaged research approaches have increased dramatically in the last few decades and are linked with statistically positive outcomes and success in recruiting and retaining racially and ethnically diverse populations experiencing marginalization [109-111]. Community-engaged research has many benefits, including ensuring intervention appropriateness, acceptability, and applicability [112-115]; ensuring that study methods and intervention are properly adapted to the population of interest [114,116,117]; and promoting trust, transparency, and bidirectional learning between research teams and stakeholders [112,118,119]. Adopting this approach has already guided key research design decisions, including (1) limiting the primary role of home visitors to the recruitment of study participants to minimize impact on workflow, (2) enrolling participants during mid- to late pregnancy (20-33 wk) to align with client enrollment in home visiting programs, (3) defining the primary outcome as weight retention at 6 months post partum to allow time for increased support during the postpartum period, and (4) focusing study goals and messaging on achieving "overall health and wellness" versus a "healthy weight" to minimize the effects that weight bias internalization may have on recruitment and intervention acceptability. Using remote data collection procedures was another important design consideration (ie, smart scale and access to prenatal medical records), given the transportation barriers of home visiting clients living in rural locations and anticipated challenges they might have in reporting their height and weight to confirm eligibility—an issue that was confirmed soon after study launch. We anticipate that the continued involvement of our coordinating council as well as other methods of community engagement will drive future decisions about the interpretation of data and dissemination of findings.

The iterative process of end-user interviews that informed the design, features, and functionality of the H42 mHealth app was especially valuable for adapting and improving it, including methods for incorporating weight goals and progress (ie, simple, colorful graph versus weight change statistics) and translating the interactive goal-setting activity for Spanish-speaking participants. Comprehensive measures of adherence to coaching, the H42 mHealth app, and the smart scale are a major strength of the study, given the growing complexity of remote lifestyle intervention packages and the critical need to differentiate the effects of unique components [27]. Similarly, access to robust engagement metrics for distinct mHealth app features (ie, interactive goal setting, coach messaging, access to weight data, comprehension quizzes, and educational videos) may build upon the patterns of website engagement characterized by Power et al [120] in a sample of individuals with low-income status who identified as Latinx; of note, in this particular study, website engagement was a strong predictor of weight retention at 6 months post partum.

The design of our study has limitations that could impact the interpretation of the results. First, control participants will have access to a scale for data collection, and regular self-weighing is a key component of behavioral weight management [58]. From a health equity and ethical perspective, we decided that we would refrain from instructing control participants not to weigh themselves outside of data collection and, instead, statistically control for the number of measured weights across the groups. Nonetheless, given the enhanced level of engagement with self-weighing in the intervention group (ie, reminders, ability to view progress on the app, and feedback from the coach), we expect the frequency of weighing in the control group to be significantly lower, and frequency is the strongest known predictor of overall weight change [121]. Another limitation is our limited ability to formally measure and control for the varying levels of support that the home visitors offer clients throughout the trial, which may differentially impact behavior change (eg, addressing access to healthy food and discussing a healthy lifestyle). This lack of control precludes our ability to measure intervention effectiveness for a Latinx and non-Hispanic Black, English- and Spanish-speaking sample considered high risk outside of the context of home visiting. Although home visitors were intentionally removed from intervention delivery, early feedback conveyed a preference among some home visitors to be actively involved, specifically with the ability to access SMART goals (assuming clients' permission). The differences in home visitor training (ie, nurse vs paraprofessional), curriculum, and the intensity of home visiting models in the trial (ie, frequency of visits ranging from weekly to 2 visits total during the first 6 mo post partum) may also differentially impact client success. We expect qualitative data on intervention adoption captured in focus groups after the trial to enhance our understanding of the potential role home visitors play in moderating intervention effects and will leverage these insights for future trial designs and intervention adaptions.

Conclusions

There is a critical need to develop effective lifestyle interventions for pregnant and postpartum individuals who identify as Latinx and non-Hispanic Black and experience the greatest risk for adverse pregnancy outcomes. This study has the potential to provide a high-quality assessment of the effectiveness of a remote lifestyle intervention for a Latinx and non-Hispanic Black population considered high risk and highlight facilitators and barriers to its implementation in a grounded service strategy specifically geared toward improving maternal and infant health. We expect the study to yield important findings that aid in refining future lifestyle intervention approaches for pregnant and postpartum people, particularly those who identify as non-Hispanic Black and Latinx, and facilitate scalability in community-based settings,

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ultimately improving maternal and infant long-term health and promoting health equity.

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Data Availability

The datasets generated and analyzed during this study will be available from the corresponding author on reasonable request.

Authors' Contributions

Conceptualization: KMB (lead), WLB (lead)
Data curation: LMM (lead), CDM (supporting)
Funding acquisition: KMB (lead), WLB (lead)
Investigation: KMB (lead), WLB (lead), LMM (supporting), CDM (supporting), LEA (supporting), JWC (supporting), NKJ (supporting), AS-U (supporting)
Methodology: KMB (lead), WLB (lead), LMM (supporting), CDM (supporting), JWC (supporting), NKJ (supporting), NYW (supporting)
Project administration: KMB (lead), WLB (lead), LMM (supporting)
Resources: AS-U (supporting)
Supervision: KMB (lead), WLB (lead), LMM (supporting), CDM (supporting), JWC (supporting), NKJ (supporting)
Writing (original draft): LMM (lead), KMB (supporting), WLB (supporting)
Writing (review and editing): LMM (lead), KMB (lead), WLB (lead), CDM (supporting), LEA, (supporting), JWC (supporting), NKJ (supporting), AS-U (supporting), KAC (supporting), NYW (supporting)

Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report from the National Institute on Minority Health and Health Disparities Special Emphasis Panel - National Institute on Minority Health and Health Disparities - Centers for Multiple Chronic Diseases Associated with Health Disparities: Prevention, Treatment, and Management (P50) ZMD1 MLS (A1) (National Institutes of Health, USA.
[PDF File (Adobe PDF File), 226 KB - resprot_v14i1e62847_app1.pdf]

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Abbreviations

CFIR: Consolidated Framework for Implementation Research
GWG: gestational weight gain
H42-HV: Healthy for Two–Home Visiting
MDD: minimum detectable difference
mHealth: mobile health
PPWR: postpartum weight retention
PRAMS: Pregnancy Risk Assessment and Monitoring System
PRISM: practical, robust implementation and sustainability model
REDCap: Research Electronic Data Capture
SMART: specific, measurable, achievable, relevant, and time-bound

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Protocol

Adaptive Just-in-Time Intervention to Reduce Everyday Stress Responses: Protocol for a Randomized Controlled Trial

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Abstract

Background: Personalized approaches to behavior change to improve mental and physical health outcomes are needed. Reducing the intensity, duration, and frequency of stress responses is a mechanism for interventions to improve health behaviors. We developed an ambulatory, dynamic stress measurement approach that can identify personalized stress responses in the moments and contexts in which they occur; we propose that intervening in these stress responses as they arise (ie, just in time; JIT) will result in positive impacts on health behaviors.

Objective: This study aims to (1) use an experimental medicine approach to evaluate the impact of a smartphone-delivered JIT stress management intervention on the frequency and intensity of person-specific stress responses (ie, stress reactivity, nonrecovery, and pileup); (2) evaluate the impact of the JIT intervention on the enactment of health behaviors in everyday life (physical activity and sleep); and (3) explore whether changes in stress responses mediate the interventions' effects on health behaviors.

Methods: In a 2-arm phase 2 clinical trial, we will enroll 210 adults in either a JIT stress management intervention or an active control condition. For 4 weeks, participants will complete 8 brief smartphone surveys each day and wear devices to assess sleep and physical activity. After a 1-week run-in period, participants will be randomized into the JIT intervention or an active control condition for 2 weeks. Participants in the JIT intervention will receive very brief stress management activities when reporting greater than typical stress responses, whereas control participants will receive no personalized stress management activities. Participants enrolled in both conditions will engage in self-monitoring for the entire study period and have access to a general

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stress management education module. Self-report outcomes will be assessed again 1 month after the intervention. We will use mixed-effects models to evaluate differences in person-specific stress responses between the intervention and control groups. We will conduct parallel analyses to evaluate whether the intervention is associated with improvement in health behavior enactment (ie, sleep and physical activity). The Pennsylvania State University Institutional Review Board approved all study procedures (STUDY00012740).

Results: Initial participant recruitment for the trial was initiated on August 15, 2022, and enrollment was completed on June 9, 2023. A total of 213 participants were enrolled in this period. Data are currently being processed; analyses have not yet begun.

Conclusions: We anticipate that this research will contribute to advancing stress measurement, thereby enhancing understanding of health behavior change mechanisms and, more broadly, providing a conceptual roadmap to advance JIT interventions aimed at improving stress management and health behaviors.

Trial Registration: Clinicaltrials.gov NCT05502575; https://clinicaltrials.gov/study/NCT05502575

International Registered Report Identifier (IRRID): DERR1-10.2196/58985

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KEYWORDS

stress; stress responses; stress management; just-in-time adaptive intervention; sleep; physical activity; behavior change; experimental medicine approach

Introduction

Background

Broadly defined stress processes (eg, chronic stress and allostatic load) are associated with an increased risk for poor mental and physical health outcomes [1]. Traditional research on this topic tends to focus on between-person assessment examining, for example, whether those with more major life events or more chronic stressors for relatively long periods have worse health. However, chronic stress is characterized by a series of repeated acute events, each including exposure to stressors and slow and delayed recovery from stressful events [2]. Thus, to effectively characterize and intervene in stress processes, a granular measurement of acute stress is needed that uses a personalized, within-person approach. In this case, the goal is to understand an individual's stress experience at a given moment compared to another moment (eg, their normal resting state). Such an approach captures the dynamic and temporal nature of the stress experience that occurs within an individual as they navigate their natural environment. Furthermore, this within-person approach to capturing stress experiences affords the opportunity to identify and intervene in such processes before, or at the onset of, their occurrence to attenuate the association between stress and poor health outcomes [3-5].

To help advance stress measurement approaches, we developed and refined methods for the self-report assessment needed to measure and characterize how individuals experience stress in their everyday lives in a way where each stress event can be adequately captured and studied [4,5]. We proposed that a stress event can be broken down into distinct components. Specifically, our approach focuses on assessing events that elicit immediate emotional and cognitive responses (ie, reactivity), the degree to which we adapt and recover (ie, recovery), and the temporal patterns of responding to and recovering from multiple stressors over time (ie, pileup). This assessment strategy took a within-person approach that permitted the repeated assessment of stress experiences close to their occurrence. It estimated how these stress response components (ie, reactivity, recovery, and pileup; RRP) unfold with time and in natural contexts. We demonstrated the utility of assessing these specific components of the stress responses (ie, RRPs) across 3 indicators (ie, negative affect, perseverative cognition, and subjective stress) to index "moments of risk," where such moments are specific to a person and context [6-8]. Furthermore, we were able to link specific stress response targets to health behaviors (ie, sleep and physical activity) both within and between individuals [9,10]. Given that these stress response components and indicators are related to the enactment of health behaviors in everyday life, we contend that they may be potent targets for intervention, and we aim to test this using the experimental medicine approach [11-13].

There is growing awareness and need for better personalized and precision medicine approaches in the behavioral sciences [14]. Advances in smartphone technology (ie, apps, location, and activity) and the widespread use of mobile and sensing devices have led to the development of ecological momentary interventions that use contextual information and self-report data to match intervention content to contextual needs and deliver that content in real time [3,15]. A just-in-time (JIT) intervention framework advances this approach using rule-based algorithms to deliver the right intervention at the right time based on prespecified triggers (eg, specific variable, context, or combination of variables and context).

We suggest that our stress response assay is well suited to inform the JIT and related interventions. First, our approach is highly personalized in deriving person-specific estimates of momentary or daily risk. We have chosen to not implement static threshold–based general rules applied across all individuals; for example, with the intervention content delivered when some predetermined threshold value is exceeded (eg, a score of ≥6 on a 7-point scale) or when individuals report being in a specific location deemed risky. Although intervention delivery using this method may still benefit the recipient, it does not fully allow for adaptation to the individual with time or across changing contexts. The approach proposed in this protocol, and in some of our previous work [4,5], goes beyond using group or

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sample-level fixed-risk estimators, providing an adaptive and individualized framework to identify moments of maladaptive stress responses across several key indicators specific to the person. Second, we have developed, tested, and refined an intervention algorithm that uses our stress assay to process real-time information to identify and provide personalized intervention content as stress targets arise. This approach includes providing intervention content matched to general availability and the intensity and frequency of the individual's experience. We propose that the implementation of this stress assay and the JIT intervention framework has the potential to inform approaches to individualized stress management, intervention design, and implementation science more broadly.

Aims

This study aims to determine the effectiveness of a JIT stress management intervention, delivered via a study smartphone, on the outcomes of stress responses, sleep, and physical activity. This study will leverage our optimized stress assay to identify moments of risk and deliver empirically derived multimodal JIT intervention content in everyday life, with the aim of modifying stress response components (ie, RRPs) across multiple indicators (ie, negative affect, preservative cognition, and subjective stress) to subsequently produce positive change in daily physical activity and night sleep. Using the experimental medicine approach within the context of a phase 2 clinical trial, our primary aim is to evaluate the impact of a 2-week smartphone-delivered JIT intervention (relative to an active control consisting of self-monitoring and stress management education) on the frequency and intensity of stress responses (RRPs), as measured by (person-specific) negative affect, perseverative cognition, and subjective stress. Our secondary aim is to evaluate the impact of the JIT intervention on the enactment of health behaviors in everyday life (ie, daily physical activity and night sleep). Our third aim is to explore whether the interventions' effects on health behaviors are mediated by changes in our target mechanism (RRPs).

Methods

Project Overview and Trial Design

This study is a 2-arm phase 2 clinical trial (ClinicalTrials.gov NCT05502575). The study has 2 phases (Figure 1), including a 1-week baseline eligibility "run-in" period (phase 1), followed by a 2-week randomized controlled trial (phase 2) for those eligible after phase 1, with a 1-week observational interval following the intervention.

Figure 1. Study design. JIT: just in time.

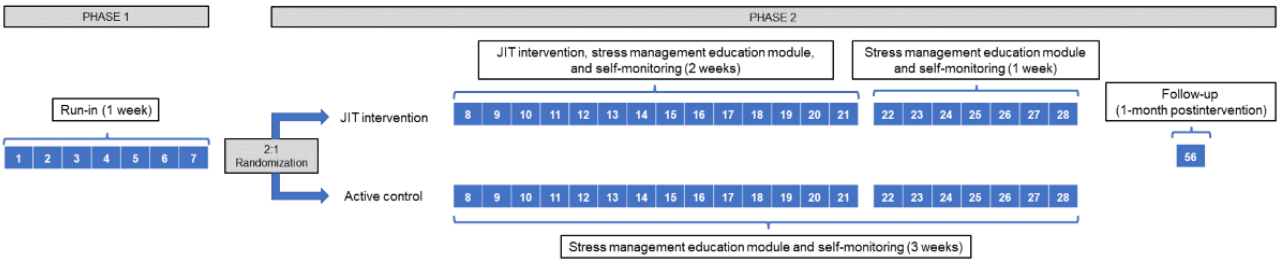

Ethical Considerations

The Pennsylvania State University Institutional Review Board approved all study procedures (STUDY00012740). All participants provided informed consent. All study data are deidentified and encrypted. Participants were compensated equitably for participation according to what study phases and components they completed, as detailed in the Procedures section.

Phase 1

Phase 1 of this study serves 3 primary purposes. First, it is a data-capture period that enables us to collect individual baseline data on each participant to be used to inform the JIT intervention algorithm in phase 2. Second, it allows us to screen for participant compliance with the protocol and ensure that those enrolled in phase 2 meet minimum standards for data completeness (ie, >70%). Third, this period allows us to exclude participants who do not regularly report stress during everyday life and thus may not be impacted by our intervention.

Phase 2

Phase 2 is the clinical trial portion of the study and will serve as the between-group test of our JIT intervention on night sleep and physical activity. This study phase will be initiated immediately following phase 1 and is 3 weeks long. Participants who are eligible for phase 2 will be randomized into one of two conditions as follows: (1) JIT intervention (ie, JIT stress management, self-monitoring, and web-based stress education module) or (2) active control (ie, self-monitoring and web-based stress education module). The first 2 weeks of phase 2 are the active intervention period, while the final week is a self-monitoring period.

Participants

To examine the impact of our intervention on our primary outcomes without the influence of age-related stressors or increased probability of health comorbidities that could impact our measures of sleep and physical activity, our target population will be generally healthy middle-aged adults. Specifically, we will recruit English-speaking men and women aged 35 to 65 years who report good general health and are free of physical limitations from the mid-Atlantic region of the United States.

We will exclude people who report (1) residing in the same household as current or former participants (to prevent any contamination of the intervention or unblinding of condition allocation); (2) an inability to answer smartphone survey SMS text messages due to restrictions or policies in the workplace; (3) a diagnosis of a mental health condition that required a

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medication adjustment or hospitalization within the last 3 months; (4) being a primary caretaker for a parent, child, and family member who is severely disabled; (5) employment that requires shift work as this will result in abnormal sleep patterns; (6) a diagnosis of sleep apnea, use of a continuous positive airway pressure machine, or score above threshold on STOP-BANG; (7) the use of physician-prescribed pharmaceutical sleep aids or over-the-counter sleep aids for ≥3 days per week; (8) an inability to be physically active or who have medical contradictions for physical activity; or (9) physical exercise of ≥200 minutes per week at a moderate or vigorous intensity or ≥10 hours of walking per week as this raises the possibility of ceiling effects on activity.

Recruitment and Screening

Participants will be recruited through advertisements posted in the local communities (eg, community centers, grocery stores, libraries, and cafés), online channels (eg, social media and study recruitment websites), and mailed flyers. Interested participants can contact the study team via phone or email and will be given a brief study overview. Participants can also access study information and preliminary web-based screening forms using a link on the recruitment materials. Individuals interested in participating will be screened to determine eligibility and scheduled for an introductory training session if eligible. All screening and scheduling will be conducted via phone using a script.

Randomization

Randomization for this study will occur upon enrollment into phase 2 using discrete codes entered into the smartphone app by a research assistant blind to study goals. Participants will be allocated on a 2:1 ratio that favors the JIT intervention condition to provide a sample size large enough to support our planned analyses. To balance participant characteristics within the study conditions, participants will be equally randomized across 3 age categories (including those aged 35 to 44, 45 to 54, and 55 to 65 years) and by sex (male and female). Masking of the participant group identities from the training personnel, data collectors, and analysts will be used. Group assignments will be unmasked for analysis when the trial is complete and after all data have been entered.

Sample Size

Our initial power calculations suggest that our study target for participants enrolled in phase 2 should be 210 (n=140, 66.7% assigned to the JIT intervention condition and n=70, 33.3% assigned to the active control condition). In our previous work with a similar assessment schedule, we observed compliance rates of >70% on the momentary surveys and >80% on the device wear time across 2 weeks in 95.2% (120/126) of the participants (unpublished data). Of those participants, the lowest quartile reported approximately 3 stressor events across 2 weeks. Thus, we estimate that approximately 15% of participants enrolled in phase 1 will not qualify for phase 2 due to no reported stressors or low compliance rates with study procedures. It is also likely that some participants may choose not to continue participation in phase 2 even if they are eligible due to the intensive assessment schedule. We estimate that refusal will account for 25%, and an additional 10% of those participants may either drop out during phase 1 or become ineligible. Thus, we estimate that up to 50% of the participants enrolled in phase 1 may not continue to phase 2. Therefore, we expect to recruit and enroll approximately 450 participants in phase 1 to reach our target of 210 participants in phase 2.

Equipment

Study Smartphone

All study participants will be provided with an Android LG Rebel 3 smartphone. The smartphones will be preloaded with the MovisensXS app (Moviesens GmbH [16]), a secure assessment app that delivers, collects, and uploads the study smartphone surveys to a secure server. Devices will also be preloaded with the stress management intervention content. Each phone will have an active data plan and Wi-Fi capability to allow instantaneous survey uploads, intervention delivery, and access to the web-based stress education modules. Participants will only have access to the smartphone functions relevant to the study procedures, and all other smartphone capabilities will be locked.

Device-Assessed Sleep

Objective sleep outcomes will be collected using the Actiwatch Spectrum Plus (Philips Respironics [17]). Participants will be asked to wear the water-resistant Actiwatch on their nondominant wrist for the study's duration, only removing the device when bathing or swimming. This device measures wrist movement time series using the digital integration method and will be configured to collect activity data at 32 Hz. At study completion, data from the Actiwatch will be processed to detect off-wrist periods and downloaded in 15-second epoch files using the Respironics Actiware software (version 6.0.9; Philips Respironics).

Device-Assessed Physical Activity

Participants will be asked to continuously wear a water-resistant ActivPAL4 activity monitor (PAL Technologies [18]) for the duration of the study. The ActivPAL4 monitor will be adhered to the midline of either thigh, halfway between the knee and hip, with adhesive tape. Participants will be instructed to remove the device only if bathing or swimming and will not be required to charge the device. This device uses an inclinometer and accelerometer to measure posture and activity intensity to quantify the time spent sitting, lying, standing, or stepping. Activity data will be collected at 20 Hz, with device data downloaded and processed using the PALbatch software (version 8.10.11.54; PAL Technologies).

Procedures

Phase 1 (Run-In Period)

Phase 1 of this study is 1 week in duration. Participants will attend a 90-minute introductory training session with a research assistant. During this visit, participants will take part in an informed consent procedure. They will be notified that they may be invited to another longer study after they have completed the 1-week study. However, no further information about the study or eligibility criteria for participation will be provided.

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After informed consent is obtained, participants will participate in a study protocol training session to learn how to use the study smartphone to answer surveys. Each participant will be able to practice the surveys with a research assistant to ensure that they understand the survey items and how to operate the smartphone. Participants will also receive instruction on properly adhering and caring for the wrist-worn actigraphy device and the physical activity monitor. Finally, they will be asked to complete a demographics survey and baseline questionnaires. Each participant will receive a quick reference participant booklet that reviews relevant survey and device information.

During the 1-week study period, participants will be asked to complete 8 brief smartphone surveys per day that are delivered to the study smartphone, including 1 survey upon waking in the morning, 6 surveys delivered randomly throughout the day between 8 AM and 9 PM, and 1 survey at the end of the day before going to sleep. Participants will continuously wear the actigraphy and physical activity devices for the entire week. At the end of the 1-week study period, participants will attend a second session to return their devices and receive compensation (up to US $100). At this time, research assistants will assess survey and device data for compliance and completeness to determine whether the participant meets the criteria for eligibility into phase 2.

Eligibility for Phase 2

Survey data from phase 1 of the study will be used to inform the delivery of the JIT intervention in phase 2. Therefore, it is essential for participants who enter phase 2 to meet the minimum criteria for complete data on which to apply our intervention rules. For this reason, we will assess participant compliance with the study procedures and data completeness before inviting participants into phase 2. Specifically, participants who complete phase 1 will be eligible for phase 2 if they (1) return all study devices, (2) report at least 1 stressor in their surveys during the 1-week run-in period, (3) meet an acceptable rating threshold for survey compliance (ie, >70%), and (4) have valid accelerometry data for at least 5 nights during the 1-week study period. Given that these compliance checks will be conducted during a brief session, the physical activity data will not be assessed for completeness as it requires considerable time to download and review.

Once all devices are obtained and compliance checks are done, participants will be compensated according to completed study procedures. At the time of compensation, each participant will either be dismissed or invited to participate in phase 2 of the study. Those deemed eligible to participate in phase 2 will receive a brief overview of study procedures. They will participate in the consent procedure for phase 2 and a refresher training session if interested. If they are not interested, they will be dismissed.

Phase 2 (Clinical Trial)

Phase 2 will be initiated immediately following phase 1. The study procedures for phase 2 are similar to phase 1 (ie, 8 smartphone surveys per day and wearing study devices) but also involve randomization into either the JIT intervention condition or the active control condition. Participants will undergo another informed consent procedure and a brief review on using the study smartphones and how to wear and care for the study devices. All participants will be notified during the session that they will have access to web-based stress management education modules on the home screen of their smartphone (refer to Active Control Condition section); they may also receive additional prompts delivered to their smartphone and will be asked to follow all instructions provided to them to the best of their ability.

Given that both the participants and researchers will be blind to condition allocation, no training specific to interacting with the JIT intervention materials will be provided to participants. Importantly, no specialized training or instruction is required to participate in the intervention condition as all necessary instructions will be provided on the device when the intervention content is delivered. We adopt this approach as it may facilitate the scaling up of intervention delivery in the future (eg, by not requiring in-person or online training). After the phase 2 training session, participants will attach their study devices and continue to answer surveys delivered across the 3-week study period.

For the first 2 weeks of the 3-week study period, participants randomized into the JIT intervention condition will complete the 8 smartphone surveys per day, wear the 2 study devices continuously, and receive multimedia JIT intervention content to their smartphone during moments and days identified as appropriate for intervention (Figures 2 and 3). Participants randomized into the active control condition will continue to complete 8 smartphone surveys daily and continuously wear the 2 study devices. However, they will not receive any personalized stress management content. Participants in both conditions will have access to web-based stress management education information regarding the causes, consequences, and remediation of stress. This information was developed and curated by stress experts on our team (JMS, MJZ, and JAJ; ie, representing an informational standard of care) and will be available on study smartphones for the entire 3-week study period.

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Figure 2. Just-in-time intervention algorithm. EOD: end of day. NA: negative affect; PC: perseverative cognition; RRP: reactivity, recovery, and pileup; SS: subjective stress.

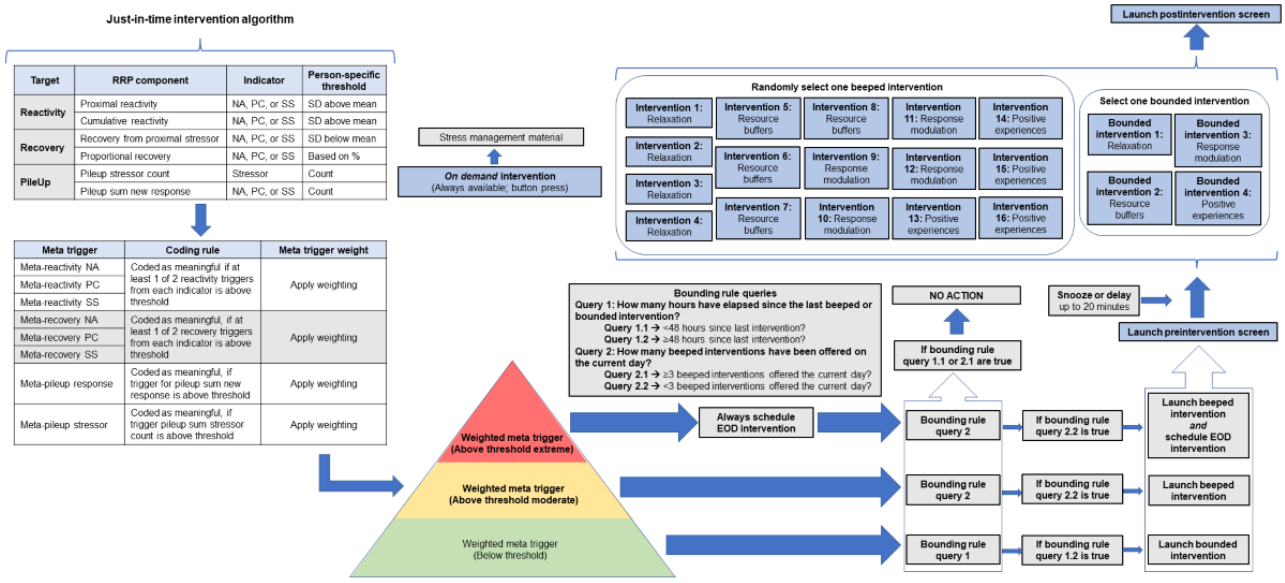

Figure 3. End-of-day (EOD) intervention algorithm. EMA: ecological momentary assessment; NA: negative affect; PC: perseverative cognition; RRP: reactivity, recovery, pileup; SS: subjective stress.

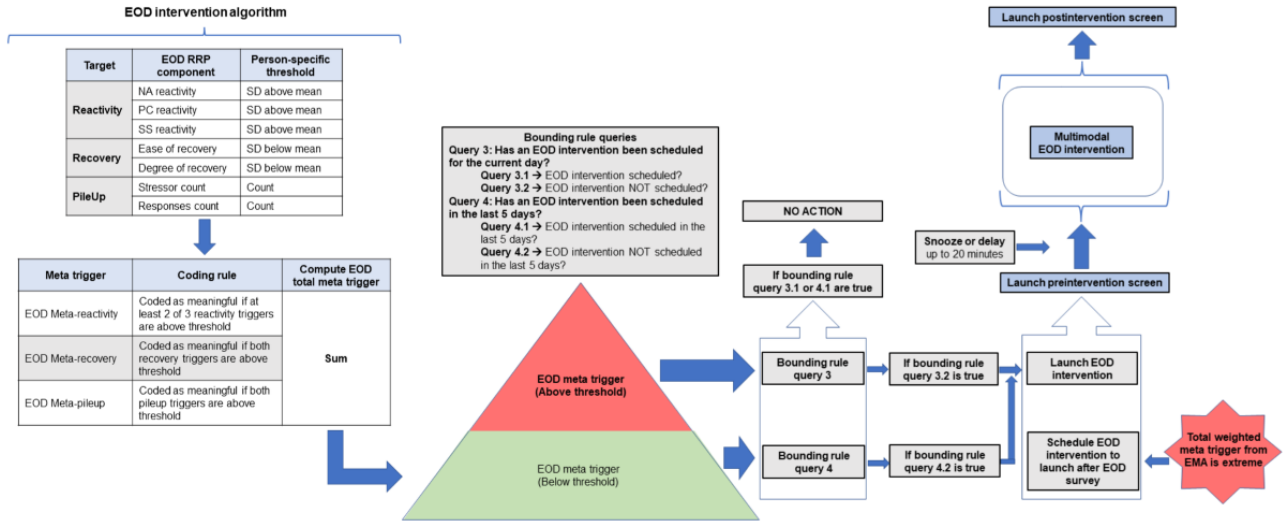

During the final week of the 3-week study period, the delivery of the JIT intervention content will cease (access to the web-based stress management education module will continue), and participants in both conditions will continue to engage in self-monitoring only. This final week of self-monitoring will provide information about the short-term impact of the JIT intervention and the immediate effects of tapering JIT intervention content. It will also evaluate whether any effects persist in whole or in part once the JIT intervention ceases. At the end of the 3-week study period, participants will attend a final session to return their devices and debrief about the study. A research assistant will assess participant compliance with the study procedures, and participants will receive their earned compensation of up to US $300 for phase 2.

Follow-Up

One month after the completion of phase 2, participants will be invited via email to complete a web-based follow-up self-report survey to assess changes in stress, sleep, and physical activity with measures capturing key study constructs. Participants will have 1 week to complete this survey to receive US $15 compensation.

Measures

Demographics

At baseline, participants will provide information on the following demographic characteristics: sex, age, race, ethnicity, education level, current work status, household income, subjective social status, marital status, number of adults and children in the home, and height and weight (ie, BMI). We will also inquire about active gymnasium memberships and the use of wearables and smartphone apps for sleep and physical activity.

Baseline and Follow-Up Measures

The measures selected for this study are intended to capture a broad range of constructs that may impact stress and stress

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responses in everyday life, including personality, mood and affect, tendencies for ruminative and perseverative thinking styles, social support, and current stress. These person-level factors will help characterize our sample and may serve as potential explanatory variables for treatment response heterogeneity. We are also capturing information on current health status and preintervention and follow-up measures of self-reported sleep behaviors and sleep disturbance, physical activity behaviors, and physical activity intention or automaticity. The measures being assessed in this study and their assessment schedule are summarized in Table 1.

Table 1. Study measures.

Construct and scale name	Baseline	Follow-up
Health status (SF-36[a] [19])	✓	✓
Social support (Social Support Questionnaire [20])	✓	✓
Personality		
The Satisfaction with Life Scale [21]	✓	
Life Orientation Test-revised [22]	✓	
Big Five Inventory [23]	✓	
Rosenberg Self-Esteem Scale [24]	✓	
Mood and affect		
Positive and Negative Affect Scale [25]	✓	✓
Toronto Alexithymia Scale [26]	✓	
Perseverative cognition		
Recent Perseverative Cognitions	✓	✓
Perseverative Thinking Questionnaire [27]	✓	
Rumination-Reflection Questionnaire (Rumination subscale) [28]	✓	
Stress		
Recent stress	✓	✓
Current stress	✓	✓
Stress mindset [29]	✓	✓
Impact of Events Scale [30]	✓	✓
Perceived Stress Scale [31]	✓	✓
Sleep		
Insomnia Severity Index [32]	✓	✓
Pittsburgh Sleep Quality Index [33]	✓	✓
Physical activity		
International Physical Activity Questionnaire [34]	✓	✓
Physical activity intentions	✓	✓
Generic Multifaceted Automaticity Scale [35]	✓	✓
Acceptability (General acceptability)		✓

[a]SF-36: 36-Item Short Form Survey Instrument.

Smartphone Surveys

Overview

The smartphone surveys in this study capture momentary and global ratings of stressful events, subjective stress, positive and negative affect, perseverative cognitions, and health behaviors as participants go about their daily lives. There are 2 types of smartphone surveys in this study, including those that are self-launched by the participant by button press within the smartphone app (ie, morning and evening surveys) and those that are automatically delivered to the participant at semirandom intervals throughout the day (ie, beeped surveys). The self-launched surveys serve as broader retrospective assessments of these outcomes across the day. In contrast, the beeped surveys are meant to capture more proximal assessments of these outcomes in the contexts in which they occur (at the moment). The information collected in the smartphone surveys will be used to derive our indicators of stress in real time and inform the delivery of JIT intervention content (Figures 2 and 3).

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Morning Survey

Participants will be asked to launch and complete the morning survey each day within 30 minutes of waking. This survey will assess the duration and quality of the previous night's sleep, current stress, affect, perseverative cognitions, plans for physical activity, and expectations for the day ahead.

Beeped Surveys

The beeped surveys will be automatically delivered to participants at 6 random times each day between 8 AM and 9 PM during the study period and are scheduled at semirandom intervals (1 to 4 hours apart; typically 2.5 hours apart) to capture most waking hours. These brief surveys assess the participant's current location, activities, social interactions, recent stressors, affect, perseverative cognitions, and physical activity (duration and intensity). Participants can delay (up to 15 minutes) or dismiss any survey if they cannot complete it at the indicated time.

Evening Survey

Participants will be asked to complete the evening survey each night before going to bed and instructed to think about their entire day (ie, from waking up) when completing the survey. This survey assesses stressful experiences and reactions to them; overall day-level affect and perseverative cognitions; physical activity (duration and intensity); consumption of caffeine, nicotine, and alcohol; use of backlit devices before going to bed; and daytime nap duration.

Objective Sleep

Two research staff (who have been satisfactorily trained on scoring sleep data by a sleep expert on our team) will independently score downloaded data from the sleep watch. Sleep intervals and relevant sleep outcomes will be derived using a previously validated algorithm [36]. Outcomes will include total sleep time, wake after sleep onset, sleep efficiency, and nap count or frequency and duration. Total sleep time will be calculated by the number of minutes between sleep onset and awakening. Wake after sleep onset is the total time spent being awake between sleep onset and awakening. Finally, sleep efficiency will be calculated as the proportion of actual sleep from sleep onset to awakening relative to the total sleep duration interval (%). Naps will be delineated as other sleep periods >30 minutes in length that occur outside of the main nighttime sleep period.

Objective Physical Activity

The physical activity data will be aggregated into 1-minute epochs. Using the sleep and wake times from the sleep data, all sleep periods will be excluded in the subsequent data aggregation process. Furthermore, any continuous sitting or standing events that are >5 consecutive hours will be classified as nonwear and will also be excluded. The remaining valid wake period will be classified into either time spent sedentary, standing, or stepping. Time spent stepping will further be classified into time spent in light physical activity or moderate to vigorous physical activity using the 100 steps per minute cut point [37]. Other relevant objective physical activity outcome variables will include step count and number of sit-to-stand transitions. The physical activity data will be further aggregated depending on the level of analysis as necessary (eg, hourly, daily, and person-level summary).

JIT Intervention

General Approach

In line with the principles of the JIT intervention approach, our goal was to develop empirically supported stress management content that is delivered during particularly stressful moments. It uses a nudge framework [38] to help a person reorient to a nonstress state via improved affect and reduced perseverative and maladaptive cognitions. More broadly, each nudge aims to help build a diverse toolkit of stress management skills that can be implemented in everyday life. Furthermore, this allows us to implement a personalized approach to intervention delivery using real-time information specific to the individual at a given moment to deliver content at moments of presumptive risk or need [39].

Intervention Content

The development and testing of our intervention content have been described previously [40]. Briefly, we developed our intervention content within 4 broad categories: relaxation, response modulation, positive experiences, and resource buffers.

Relaxation

These techniques aim to shift the body from a state of elevated or negative arousal to a relaxed or neutral state. Participants could do controlled breathing, deep breathing, progressive muscle relaxation, or an object-focused meditation.

Response Modulation

These techniques aim to promote self-regulatory behavior, in particular, to manage emotions, promote efforts to change thoughts and associated emotions to a more positive meaning, reduce impulsive behavior, and focus attention away from emotion-eliciting situations or thoughts. Participants could perform a reappraisal task to learn how to rethink negative situations, an attentional deployment task to train them to focus on positive stimuli, a third-party observer task that asks them to imagine how an outsider would view their stress, or an affect labeling task to encourage the ability to use words to self-describe negative emotional events.

Positive Experiences

This category aims to facilitate engagement in activities that can induce positive mental states. Participants could imagine saying positive statements to themselves, reacting to positive imagery, engaging in a gratitude exercise, or a reminiscing task that engages them to relive a positive event in their lives.

Resource Buffers

This category aims to increase the quality of life at the moment to enhance function and resilience. Participants could engage in a self-affirmation task to embrace those facets of their life that are most positive, a self-efficacy task to encourage them to find moments they have successfully dealt with life events, a social comparison task that allows them to learn from others who have successfully dealt with stress in their lives, or a best

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possible self activity (imagining an idealized version of themselves and how they might achieve that self).

Intervention Types

Overview

The intervention content was developed to be appropriate for everyday life, including the consideration of general availability to engage with the intervention content. Therefore, we developed 2 intervention types of differing lengths and time of day availability, and all content was intended to be displayed to the participant on a smartphone. Each activity is intended for the participant to do independently, not requiring interaction with others.

Microinterventions

These very brief interventions (ie, microinterventions) are no more than 1 to 2 minutes in duration. This suite of microintervention content includes 16 brief videos, including 4 microinterventions across each of the 4 categories described above. For any given participant randomized into the JIT condition, when an intervention moment is identified (refer to Intervention Delivery section), 1 of the 16 microinterventions will be randomly selected from the suite of videos and presented to them on the smartphone. To maximize engagement and increase the potential for exposure to the different skills and activities, each time an intervention is delivered, it will not be placed back in the pool of available videos for potential delivery until all 16 videos have been used.

Once a microintervention is initiated, participants will receive an audible alert from the phone, and once activated, they will be notified that their stress levels appear elevated and that a recommended intervention is available to help reduce their stress. Next, they will receive a description of the activity they will engage in and how to be prepared to do it most effectively. They will then initiate the intervention video on the smartphone and follow the guided instructions. Each activity is designed so that previous training is unnecessary, but continued engagement may increase one's enjoyment and ease in doing the activity. At the end of each intervention, we will ask the participant to consider what worked with the intervention and plan how to use it in a future moment of stress. To this end, participants must consider when they are stressed and thus engage in some self-monitoring of their behaviors. Furthermore, by encouraging participants to use the activity on their own, they may be more likely to practice and improve their skills.

End-of-Day Intervention

We also wanted to provide a longer, more comprehensive intervention that covered the various domains of our broader intervention approach while providing an opportunity for more focused skill-building. This 20-minute singular intervention will be delivered in the evening when people may have more time to engage in the focused activity. It comprises multimodal components that cover several broad domains and represents a progression of many of the techniques and categories noted above. The goal is to guide an individual through more extensive training to reduce stress via improved affect and reduced perseverative cognitions. It is intended to be repeated to build general skills in the broad domains it covers. Similar to what was outlined previously, participants will receive stressor-focused framing before and after the intervention.

Intervention Delivery

As described earlier, in our previous work, we developed a stress assay that used self-reported survey data on different stress response indicators (ie, negative affect, perseverative cognitions, and subjective stress) and several stress targets (ie, RRPs) to be able to derive person-specific means and SDs [4,5]. Using this information, we were able to establish person-specific thresholds that would indicate meaningful derivations from an individual's norm (ie, identifying when they are stressed), as well as moments or days that were associated with poor health behavior enactment (eg, sleep and physical activity [9,10]). In this study, we aim to use this assay to identify "moments of risk" and intervene "just in time" to prevent downstream impacts on our health behaviors of interest (ie, sleep and physical activity). To provide intervention content at these moments of elevated stress while also maximizing the probability of participant engagement with the intervention content, we developed several pragmatic principles and boundaries to guide our intervention delivery. We refer to these general principles and rules as our intervention algorithms. These algorithms, when paired with the smartphone survey data in real time (ie, uploaded from the smartphone to the study server via mobile data plan), allow us to process the participant's survey data, aggregate the information across moments and days, provide a solution (ie, trigger) for whether or not intervention content should be delivered to the participant at that moment, and subsequently deliver the content to the participant, all in near real time.

To provide us with the greatest opportunity to interfere with current or ongoing stress responses and to maximize the probability of availability, we decided that interventions would only be delivered immediately following the completion of a survey (beeped or evening). This ensures that the participant is near their study smartphone should an intervention be delivered. It also allows us to intervene in active or ongoing stress responses in the contexts in which they occur. Although this approach has some limitations, such as requiring the individual to have the mental resources to engage with the intervention during periods of elevated stress, it was chosen in an attempt to optimize intervention impact and participant engagement. This approach also provides a natural connection between this study's intervention and survey types.

We have created 2 overlapping intervention algorithms to match intervention types (ie, microinterventions and end-of-day intervention) to survey data (ie, beeped and evening) while accounting for participant availability and burden. We developed the JIT intervention algorithm (Figure 2) to process information from the beeped surveys and trigger brief microinterventions during the day. Then, we developed the end-of-day intervention algorithm (Figure 3) to process information from the evening survey and trigger the longer end-of-day intervention. These algorithms, when combined, allow us to leverage our stress assay to detect moments of elevated stress responses in individuals at both the moment and day level, providing brief interventions in the moment or longer and more focused

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interventions at the end of the day, when there are generally fewer daily demands on an individual.

In broad terms, the intervention algorithms use survey data from phase 1 to derive person-specific thresholds for each participant to inform intervention delivery in phase 2. This approach highlights the importance of selecting highly adherent participants to continue to phase 2 of the study. Once enrolled in phase 2, person-specific thresholds will be continuously updated as surveys are completed and intervention content is delivered. When survey data are collected from participants throughout the day and in the evening, it will be automatically uploaded and processed in the algorithm in real time to determine whether a participant's state indicates elevated stress levels. The algorithm will access all previous responses preceding that specific moment and the person-specific thresholds to do this. This information will then be combined with the current survey data to determine whether there is a meaningful deviation from an individual's norm. Each meaningful score will be weighted and combined with other meaningful scores for that specific moment to derive a weighted summary risk score. Each moment's risk level will then be evaluated based on the weighted summary risk score. Depending on this score, an intervention may be delivered to a participant at that moment, and, in some cases, a longer intervention may also be scheduled for delivery at the end of the day. This process will be repeated continuously for each participant as survey data are uploaded.

As an initial attempt to manage participant expectations and burden in this study, we incorporated a set of rules that will govern the upper and lower limits of intervention delivery (ie, ensure both a minimum and maximum frequency) and serve 2 purposes. First, our lower bound rules ensure that at least some intervention material is pushed out to each participant who is randomized into the JIT intervention condition, even in the absence of person-specific elevated stress. This includes providing a microintervention at least every 48 hours, regardless of whether elevated stress levels triggered an intervention, and an end-of-day intervention at least once every 5 days. We think this approach will keep participants engaged while providing a minimum "dose" of intervention content. We are also aware that participants in this study may experience stress below our intervention threshold (especially as their time and exposure to intervention content progresses) or that we may miss some stress responses or events with our survey schedule. Therefore, providing some minimum level of intervention content could provide the skills or resources to maintain the treatment effect, prevent future stress responses, or buffer any ongoing subthreshold stress. Second, the upper bounds of our intervention delivery will prevent us from overwhelming participants should they experience a bout of frequent or intense stress. To prevent undue participation burden related to engaging in microintervention content, we will limit microinterventions to a maximum of 3 on any given day (between 8 AM and 9 PM). We will provide the option to dismiss or delay any intervention for up to 20 minutes. We will have access to the uptake of all intervention content, including the date and time it was delivered and initiated by the participant, its duration, and the completion time.

Active Control Condition (Self-Monitoring and Stress Management Education)

In this study, participants enrolled in the active control condition will engage in self-monitoring for the duration of phase 2. Although there is some evidence that self-monitoring on its own might be a strategy for reducing negative affect and perseverative cognition [41], we wanted to provide a more stringent test of the "just in time" aspect of our stress management intervention. Therefore, we decided to bolster our comparison condition by providing access to a stress management education module comparable to any usual care stress management resource that an individual could access if needed. With this in mind, we developed 8 brief readings and tips that focused on stress education and the impact of stress in everyday life and adapted these materials into a web-based reading or reference module [40]. All participants enrolled in phase 2 of the study will have access to this module on the home screen of their study smartphone. If the module link is activated, they will be provided with a summary of the purpose of the module, followed by a list of 8 topics they can choose. Each module will take about 2 minutes to read and is followed by a brief, generic stress management tip that can be incorporated into everyday life. The stress management tips were derived from the same 4 categories outlined earlier, with 2 activities from each of the 4 categories included in the module. Participants will have access to this module 24 hours per day for the entirety of phase 2 and can access the readings as often as they want. User statistics will be collected each time a participant accesses the module, including the topics accessed, the number of times the module is accessed per day across the study, and a singular item about acceptability.

Proposed Analyses and Analytical Approach

All collected data will be subjected to a rigorous data-cleaning procedure to identify invalid data points (eg, out-of-range, implausible, and outlier variables will be scrutinized). General descriptive statistics (ie, mean, median, percentages, and SD) will be used to characterize the study sample. To evaluate the effect of the smartphone-delivered JIT intervention on RRP (specific aim 1), we will use mixed-effects models to evaluate any significant differences in RRP scores between the 2 study groups (ie, intervention group vs control group). In addition to the main effect differences between the 2 groups, we are interested in the potential cumulative effect of receiving multiple interventions across the 2-week study duration (testing a "dose" effect of the microinterventions) or whether potential benefits do not occur immediately but rather develop during the intervention period (eg, if it takes some time for the JIT intervention to lower stress responses). To evaluate this latter effect, we will test the group-by-time interaction effect in a multilevel (eg, momentary RRP nested within days, days nested within person, and person nested in group) mixed effect model. Analyses will be conducted using the SAS statistical program (version 9.4; SAS Institute Inc).

For our second aim, evaluating whether the intervention is associated with improved health behavior levels (ie, sleep and physical activity), we will use the same approach described for our first aim. That is, we will evaluate the overall treatment

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effect and how this effect changes with time. Unique in this evaluation, we will test these relationships using continuous outcome (ie, the amount of time spent on these health behaviors) as well as the likelihood of meeting the threshold for recommended levels of physical activity (≥150 minutes of moderate to vigorous physical activity/week) and sleep (>7 hours/night). That is, we are interested in finding out whether participants who receive the innovative JIT intervention were more likely to meet recommended levels of physical activity or sleep.

Finally, we will test whether changes in RRPs mediate the group-level effects of the intervention on health behaviors. In other words, we want to evaluate whether any benefits observed in health behaviors are due to the changes in stress responses (RRPs). All evaluations will be conducted using an intent-to-treat analysis, with imputation conducted for missing data as appropriate, and a per-protocol (completers) analysis. Given the large number of analyses planned, we will evaluate and implement appropriate methods to reduce the likelihood of false positives (eg, false discovery corrections). Theoretically informed but more exploratory analyses will be conducted to examine if there are individual difference moderators of observed effects.

Results

Participant recruitment for the trial was initiated on August 15, 2022. Initial enrollment was completed by June 9, 2023, with 213 participants enrolled. Each of the multiple data sources (eg, ecological momentary assessment survey reports, physical activity, and sleep) is being cleaned and processed for use. Study analyses have not yet begun.

Discussion

Principal Findings

In this trial, we will evaluate the effectiveness of a JIT stress management intervention, delivered via a study smartphone, on the outcomes of stress responses, sleep, and physical activity. We hypothesize that those receiving the JIT intervention and standard stress management material will show better stress response processes, greater engagement in physical activity, and better sleep than those receiving only standard stress management material.

This study will provide valuable insight into the potential utility of characterizing, in a personalized manner, components of everyday stress responses and using individualized moment and day-level risk indicators to deliver JIT stress management microinterventions (relative to generic stress management educational materials coupled with intensive self-monitoring). The JIT stress management microintervention condition is predicted to enhance stress response (ie, reduced reactivity, better recovery, and less pileup) across multiple indicators (subjective stress, affect, and cognitions) relative to the control condition. In turn, it is thought that enhanced stress response processes will allow individuals to successfully engage in more positive health behaviors; namely, the group receiving the JIT intervention will exhibit more physical activity, less sedentary time, and improved sleep.

Our stress response components (RRPs) have been developed based on preliminary work and theoretical considerations; however, it is important to note that both their specific implementation (eg, the level at which momentary risk is presumed) and how they are used to trigger JIT microintervention can be readily adapted. Thus, this study is not intended to serve to finalize or concretize the specific implementation of this approach or the intervention itself (eg, the triggering algorithm and microintervention content); rather, it is meant to serve as a foundational proof-of-concept demonstration of this approach that can (and should) be adapted, refined, and tailored by others to specific samples, contexts, and research or clinical questions. It may also be fruitful to consider matching microintervention content to the nature or type of stressor experienced and the context (eg, location and social features) in which it was experienced.

This trial requires a high level of engagement by participants. Although there is the presumptive benefit of receiving stress management to enhance motivation and no side effects as might be experienced in a pharmaceutical trial, there is the requirement of actively responding to multiple brief surveys each day for a lengthy period. Clearly, this raises the possibility of self-selection, biasing the type of person who ultimately enrolls in the study. If the results of this trial indicate positive benefits for our primary outcomes, participant burden will have to be carefully considered moving forward to address issues related to generalizability and potential for dissemination.

Several other domains represent exciting future directions for this line of work to continue to refine, extend, and enhance the JIT microintervention approach we have developed. For example, developing and implementing additional stress target measurement indicators (eg, physiology and positive affect) for inclusion in the stress assay should be possible. Similarly, this work can be extended to encompass various health behaviors at different temporal scales. This stress assay can be used for intervention in “intensive” ways and integrated into more standard intervention formats (eg, face-to-face). For example, it can generate a highly reliable between-person risk indicator for risk stratification; moreover, our assay will provide risk components to allow personalized (precision) approaches to (standard) intervention. The time-varying nature of the stress assay would also allow for the development and implementation of not only JIT but also adaptive interventions, ones that “learn” what is effective for each individual and deliver what is most helpful for that individual at that moment (or stressful moments anticipated to occur in the near future).

Conclusions

This trial evaluates the effects of a novel, personalized JIT stress management intervention on everyday stress responses and the enactment of physical activity and sleep behaviors. Overall, we hypothesize that we will see the benefits of intervention over our active control condition and hope that this stress assay and adaptive JIT intervention approach will prove a valuable assessment and intervention tool for measuring and treating stress and stress-related disorders.

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Acknowledgments

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Data Availability

The datasets generated during and analyzed during this study are not yet publicly available while data analysis is ongoing but are available from the corresponding author on reasonable request.

Authors' Contributions

The study was conceptualized by MJZ, MJS, DMA, OMB, DEC, RSS, SBS, CNS, PAG, and JMS. The stress assay was developed by MJZ, MJS, DMA, OMB, DEC, DM-C, JK, RSS, SBS, MJLT, and JMS, and the intervention content was developed by JAJ, MJZ, DEC, CNS, EMR, PAG, and JMS. The intervention algorithm was developed by JAJ, MJZ, MJS, DMA, DM-C, JK, RSS, SBS, MJLT, and JMS. The trial implementation was performed by JAJ, EMR, NLS, and JMS. All authors reviewed and approved the manuscript before submission.

Conflicts of Interest

Outside of this work, OMB received subcontract grants to The Pennsylvania State University from Proactive Life LLC (formerly Mobile Sleep Technologies) doing business as SleepSpace (NSF/STTR #1622766, NIH/NIA SBIR R43-AG056250, R44-AG056250).

Multimedia Appendix 1
Peer review report from the Science of Behavior Change Common Fund Program - National Institutes of Aging (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 99 KB - resprot_v14i1e58985_app1.pdf]

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Abbreviations

JIT: just-in-time
RRP: reactivity, recovery, and pileup

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Protocol

Comparative- and Cost-Effectiveness Research Determining the Optimal Intervention for Advancing Transgender Women With HIV to Full Viral Suppression (Text Me, Alexis!): Protocol for a Randomized Controlled Trial

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Abstract

Background: Many transgender women with HIV achieve suboptimal advancement through the HIV Care Continuum, including poor HIV health care usage, retention in HIV medical care, and rates of viral suppression. These issues are exacerbated by comorbid conditions, such as substance use disorder, which is also associated with reduced quality of life, increased overdose deaths, usage of high-cost health care services, engagement in a street economy, and cycles of incarceration. Thus, it is critical that efforts to End the HIV Epidemic include effective interventions to link and retain transgender women in HIV care through full viral suppression.

Objective: This study builds on the promising findings from our two Health Resources and Services Administration-funded demonstration projects, The Alexis Project and Text Me, Girl!, which used peer health navigation (PHN) and SMS text messaging, respectively, for advancing transgender women with HIV to full viral suppression. Though the effectiveness of both interventions has been established, their comparative effectiveness, required resources or costs, cost-effectiveness, and heterogeneous effects on subgroups, including those with substance use disorder, have not been evaluated. Given the many negative personal and public health consequences of untreated or undertreated HIV, and that HIV services for transgender women are frequently delivered in resource-limited, community-based settings, a comprehensive economic evaluation is critical to inform decisions of stakeholders, such as providers, insurers, and policy makers.

Methods: Text Me, Alexis! is a 3-arm randomized controlled trial. Participants (N=195) will be randomized (1:1:1) into: PHN alone (n=65), SMS text messaging alone (n=65), or PHN+SMS text messaging (n=65). Using the same time points as the Health Resources and Services Administration demonstration projects, the repeated-measures design will assess participants at baseline, 3, 6, 12, and 18 months post randomization. Over the course of the 90 days, participants in the PHN arm will receive unlimited navigation sessions; participants in the SMS text messaging arm will receive 270 theory-based SMS text messages (3 messages daily) that are targeted, tailored, and personalized specifically for transgender women with HIV; and participants in the PHN+SMS text messaging arm will receive a combined PHN and SMS text message intervention. The desired outcome of Text Me, Alexis! is viral suppression and cost-effectiveness.

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Results: Recruitment began on April 10, 2024, and the first participant was enrolled on April 11, 2024. Data collection is expected to be completed in July 2027. Primary outcome analyses will begin immediately following the conclusion of the follow-up evaluations.

Conclusions: Transgender women are a high-priority population for reaching End the HIV Epidemic goals. Findings have the potential to improve individual and population health outcomes by generating significant improvements in viral suppression among transgender women and guiding service provision and public policy.

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KEYWORDS

HIV/AIDS; transgender women; SMS text messaging; peer health navigation; HIV Care Continuum

Introduction

Background

Current national data suggests that over 14% of transgender women in the United States are currently living with HIV [1], a rate at least 30 times higher than that observed in the general population aged 13 years and older (0.44%) [2]. National data on transgender women with HIV demonstrate lower rates of linkage to HIV care, retention in care, antiretroviral therapy (ART) uptake, ART adherence, and viral suppression than cisgender men and women [3,4]. Thus, any concerted effort to End the HIV Epidemic must include effective interventions to link and retain transgender women in HIV care through durable viral suppression [5,6]. The HIV prevalence rate of transgender women in Los Angeles County (LAC) exceeds national prevalence estimates, with an estimated 33% of transgender women with HIV, of whom only 58% achieved sustained viral suppression in 2022 [7]. As such, transgender women have been identified as a high-priority population, and LAC as a priority county for Ending the HIV Epidemic [6-8].

Transgender women in the United States experience numerous barriers to retention in HIV care, ART adherence, and viral suppression, including structural determinants of health, such as poverty and housing instability [9,10]; lack of access to health insurance [11]; transphobic stigma and discrimination from providers, including HIV specialists [11-13]; and disproportionate rates of individual-level health disparities including lack of perceived support [14], experiences of violence [15], cycles of incarceration [10,16], and untreated or undertreated substance use disorders (SUD) and mental health disorders, which are highly comorbid [17,18]. A 17-year comparison study in LAC demonstrated that these conditions have worsened among transgender women, with decreased levels of income and housing stability, increased incidents of physical harassment and abuse, and increased rates of HIV and sexually transmitted infections [19].

Evidence demonstrates that transgender women who are successfully linked and retained in HIV care go on to achieve rates of viral suppression similar to that of cisgender men and women, confirming linkage and retention to HIV care as critical intervention outcomes [20,21]. Among transgender women, access to gender-affirming resources and care [6,13], greater medication self-efficacy [22], and tailored HIV messaging (eg, addressing fears of ART or hormone drug-drug interactions) [23-25] are all associated with higher odds of ART uptake and adherence.

As an intervention modality, peer health navigation (PHN) is considered generally well-suited for application among transgender women, as it can be tailored to each participant's needs, and is premised on increasing participants' self-efficacy [20,26,27]. Interventions including PHN have been shown to be efficacious in improving rates of HIV care engagement, ART adherence, and viral suppression among transgender women [28-30]. However, due to the intensity of PHN, some transgender women may prefer a lower-intensity intervention such as SMS text messaging to deliver gender-affirming, transspecific SMS text messages, which are based on theories to improve self-efficacy and avoid or reduce health risks. SMS text messaging is a viable option since telehealth and technology-based interventions have demonstrated both acceptability and effectiveness among transgender women [23,28,29,31,32].

The promising findings gleaned from our team's two Health Resources and Services Administration-funded Special Projects of National Significance demonstration projects guided the Text Me, Alexis! randomized controlled trial design. Reback et al [33] demonstrated that increased attendance to PHN sessions was associated with significant and sustained (ie, through 18 months) achievement of both behavioral (coefficient range 0.12-0.38) and biomedical (coefficient=0.10) HIV milestones (all $P \leq .01$); 85% were linked to HIV care, and 83% of the participants that enrolled detectable and achieved a 1 log viral load reduction went on to achieve viral suppression [28]. Additionally, Reback et al [24] produced significant and sustained (ie, through 18 months) overall increases in ART uptake, self-reported ART adherence as "excellent," and achievement of an undetectable viral load defined as 200 copies/mL (49% vs 77%, 5% vs 38%, 35% vs 52%, all $P \leq .001$) [25]. The Alexis Project has been included in the Substance Abuse and Mental Health Services Administration's intervention guide for persons with substance use and mental health disorders, and Text Me, Girl! has been included in the Ryan White HIV/AIDS Best Practices Compilation. Thus, the appropriate next step was Text Me, Alexis!, the randomized controlled trial to simultaneously assess the relative efficacy of these interventions, and their respective costs and benefits to determine their efficiency and inform widescale implementation.

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An economic evaluation was included to inform "real-world" resource allocation decisions faced by relevant stakeholders. Economic value (ie, the extent to which a stakeholder's resources are efficiently allocated) is a fundamental concern for any intervention targeting transgender women with HIV, given the number of persons in need and the fact that services for transgender women are frequently delivered in resource-limited, community-based settings [3,19,20].

Primary and Secondary Aims

The primary aim of the Text Me, Alexis! study is to determine the comparative effectiveness of PHN alone, SMS text messages alone, and PHN+SMS text messaging combined with the goal of viral suppression and cost-effectiveness, and to identify the resources (eg, time and materials) required to prepare for, implement, and sustain each intervention, and estimate the associated costs. Further, the study will conduct a comprehensive cost-effectiveness analysis to determine the relative value of each intervention from the health care–sector, state policy makers, and societal perspectives. The secondary aim of the study is to determine heterogeneous intervention effects of PHN alone, SMS text messaging alone, and PHN+SMS text messaging due to social and structural determinants of health (eg, poverty, housing insecurity, food scarcity, educational attainment, and lack of insurance) and differing individual-level characteristics (eg, racial or ethnic identity, age, SUD—by type, and time since HIV diagnosis) among transgender women with HIV.

Methods

Study Design

Following screening, informed consent, and baseline assessment, participants (N=195) are randomized (1:1:1) into: PHN alone (n=65), SMS text messaging alone (n=65), or combined PHN+SMS text messaging (n=65). The 3-arm repeated-measures design will assess participants at baseline, 3 (immediate effects), 6, 12 (sustained effects), and 18 (distal effects) months post randomization to determine the relative effectiveness of the interventions, including heterogeneous treatment effects across subgroups and over time, the implementation and sustainment costs of each intervention, and their cost-effectiveness relative to one another. The study uses an "intent-to-treat" design whereby all assessments are administered to all participants regardless of their level of participation or retention in the study (Figure 1).

Figure 1. Comparative-effectiveness and cost-effectiveness design. PHN: peer health navigation.

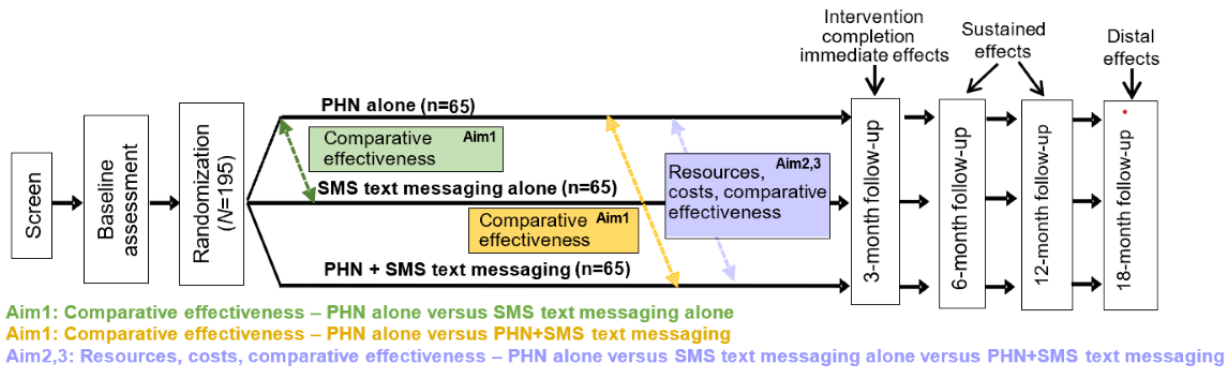

Study Arms

PHN

PHN is based on the theoretical foundation of social cognitive theory (SCT). Participant-centered PHN helps to (1) identify barriers to HIV care, (2) identify and link participants to needed auxiliary services, and (3) increase participants' self-efficacy in working with HIV care providers and other social service and treatment facilities. PHNs do not provide counseling or psychotherapy; they work with each participant to successfully navigate complicated health care and social service systems. The PHN intervention uses an individualized, participant-centered treatment plan with the goals of removing multiple and complex barriers that can impede linkage to and retention in HIV care and medication adherence to achieve virological suppression. Each participant works with a PHN to develop a participant-centered treatment plan and get linked to HIV care or other needed auxiliary physical, mental health, and psychosocial services (eg, hormone therapy, dental care, hepatitis testing or care, SUD treatment, mental health treatment, legal services, and job training or development; Figure 2). A priority of the first session is to schedule an HIV care appointment for the participant if needed. The PHN also works with each participant to establish HIV self-efficacy regarding her treatment plan. To establish an immediate connection, participants are introduced to a PHN immediately following randomization. PHN sessions are unlimited for 90 days.

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Figure 2. PHN intervention delivery system. ART: antiretroviral therapy; IPV: intimate partner violence; PHN: peer health navigation; STI: sexually transmitted infection.

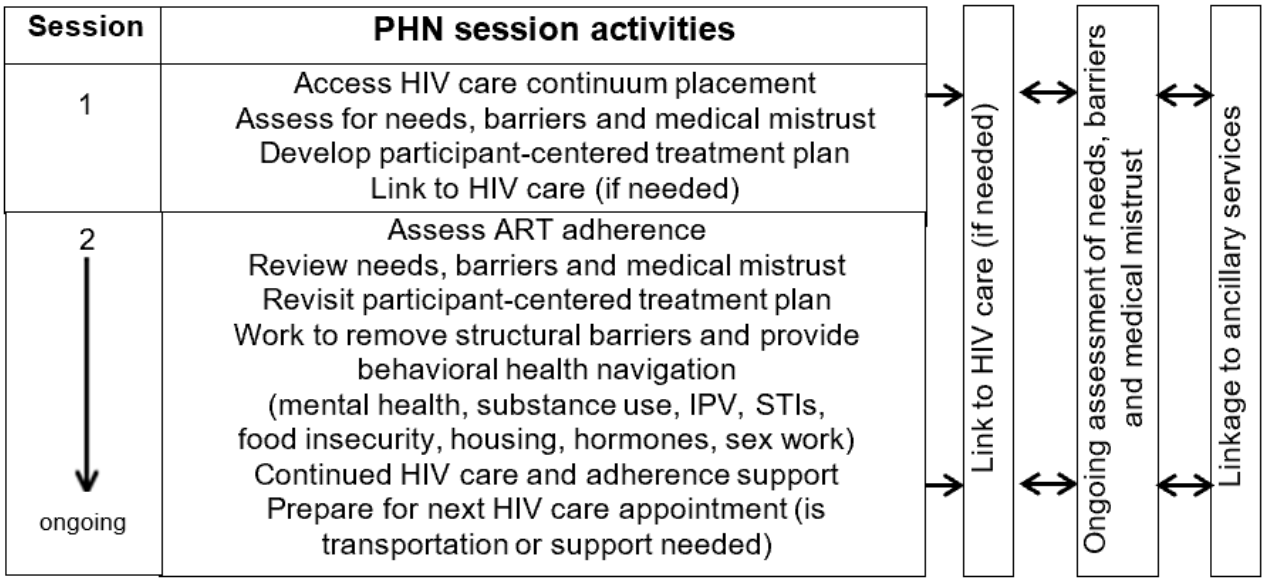

SMS Text Messaging

The SMS text messages are based on, and equally distributed across, three theories: social support theory (SST) [34-36], social cognitive theory [37,38], and health belief model (HBM) [39]. Table 1 illustrates how the SMS text message library was developed to have a theoretical foundation and be transculturally responsive. Participants receive three daily, theory-based SMS text messages for 90 days (270 unique scripted messages); participants do not receive the same scripted SMS text message twice. SMS text messages are evenly arrayed across: (1) HIV Care Continuum (HIV positivity/physical and emotional health, linkage/retention in HIV Care, and ART adherence/viral load suppression); and (2) theoretical foundation (SST, HBM, or SCT; Table 2).

SMS text messages are transmitted through gradual automation administration daily, including weekends, in real time, within a 10-hour period, and every 5 hours. Optimum hours were determined to be noon, 5 PM, and 10 PM, though participants may personalize the schedule to any 10-hour period and can choose to have the messages delivered through their cell phone or email. Both dosing (ie, three messages per day) and timeframe (ie, 10 hours) were determined during our prior SMS text messaging studies [23,25]. The intervention was designed to be cost-efficient, sustainable, and easily scaled by health clinics or community agencies. The automated SMS text message delivery system was developed by Dimagi [40]. Participants are asked to notify a research assistant immediately if they lose their cell phone or change their phone number or email address.

Table 1. Sample Text Me, Girl! SMS text messages: displays theoretical foundation, HIV Care Continuum placement, and adaptation from a general message to a transspecific message.

Theoretical foundation	HIV Care Continuum	General message	Transspecific message
Social support theory	HIV positivity/physical and emotional health	Take care of yourself	Trans pride is taking care of yourself
Health belief model	Linkage/retention in HIV care	See your doctor	Protect your trans beautiful body, see your doctor
Social cognitive theory	ART[a] medication adherence	Take your meds	Take your meds, girl! You can do it!

[a]ART: antiretroviral therapy.

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Table 2. SMS text message content by theoretical foundation.

	HIV Care Continuum			Total
	HIV positivity/physical and emotional health	Linkage/retention in HIV care	ART[a] adherence/viral load suppression	
Theoretical foundation				
Social support theory	30	30	30	90
Health belief model	30	30	30	90
Social cognitive theory	30	30	30	90
Total	90	90	90	270

[a]ART: antiretroviral therapy.

PHN+SMS Text Messaging (Combined)

Participants in the PHN+SMS text messaging arm receive the same PHN and SMS text messaging interventions described above, but in concert to determine the effectiveness of the combined intervention when compared to PHN or SMS text messaging alone.

Theoretical Mechanisms of Behavioral Change

The theoretical foundations of the interventions serve as mechanisms of behavior change, increasing advancement through the HIV Care Continuum and maximizing potential public health impacts.

SST

According to SST, social support encompasses instrumental, emotional, and informational assistance. These forms of social support have been shown to mediate the relationship between stressful events and health outcomes [34-36].

HBM

HBM asserts that believing specific health behaviors can reduce threats to health predicts one's likelihood of engaging in protective health behaviors. The HBM is most effective when informative messages are culturally appropriate to the target population [39].

SCT

SCT posits interactive causal relationships among personal determinants, behavior, and environmental influences [37,38], and is designed to improve participant self-efficacy. Effective HIV care interventions must increase individuals' self-efficacy and guide them in developing self-regulation skills, offer practice and feedback opportunities, and engage resources to maintain health-promoting behavior change.

Participants

Inclusion criteria are (1) identifying as a transgender woman; (2) being 18 years or older; (3) having a verified HIV-positive serostatus; (3) not currently in HIV care, or had not had an HIV care visit in the previous 6 months, or had a viral load of ≥200 copies/mL on her last laboratory test result, or not currently prescribed ART, or prescribed ART but does not rate her ability to take all her medications as "excellent"; and (4) ability to receive daily SMS text messages on either a personal cell phone or via an email account. Potential participants must be able and willing to provide informed consent and comply with study requirements. Individuals are excluded if they do not meet all eligibility criteria.

Recruitment and Enrollment

Six recruitment strategies are used to ensure a diversity of participants are enrolled. (1) Web-based: banner ads and digital flyers will be placed through geo-mapping on appropriate websites and social media platforms and are optimized for mobile platforms at 300×250 pixels. (2) Print media: local ads will be placed in print media for transgender women. (3) Outreach: 2 research assistants conduct outreach in identified areas where transgender women congregate. Optimal sites, days, and times have been identified, including bars or clubs, motels, parks, boulevards, street corners, mini markets, boutiques, wig shops, electrolysis offices, salons, and lingerie stores. Outreach locations are continually modified through ongoing community mapping and input from the Community Advisory Board. (4) Poster advertisement and club cards: posters are placed throughout the research site and community collaborating sites to inform potential participants how to receive further information. Club cards will be distributed at dance clubs, bars, and transspecific events. (5) In-reach: potential participants often drop into the research site to inquire about services or to receive a daily hot meal. (6) Long-chain referral: current study participants are asked to recruit a maximum of three potential new participants. All recruitment and promotional activities are discussed at Community Advisory Board meetings.

Potential participants who inquire about the study are scheduled for intake within 48 hours. At intake, potential participants are screened for eligibility, complete the informed consent process, and take an informed consent quiz to verify their understanding of study procedures. At baseline, potential participants complete the baseline assessment, collect biospecimens, and are randomized to an intervention arm. Potential participants are considered enrolled and given a study ID number following randomization.

Randomization

Stratified block randomization with random block sizes is used to assign participants to each of the 3 study arms. To ensure balance with respect to certain covariates, participants are grouped by three stratification factors: (1) age (<35 and ≥35

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years), (2) race or ethnicities (Latinx, all other race or ethnicities), and (3) HIV Care Continuum placement (linked, not linked to HIV care). Block randomization helps ensure balance in the number of participants assigned to each arm, while random block sizes make the sequence of assignments less predictable to research staff.

Measures

All data will be collected on an audio computer-assisted self-interview administered via the Qualtrics system. The following describes the measures used to address the study's specific aims.

Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)

The *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) diagnostic items are necessary to make a determination of mild, moderate, or severe SUD. These findings are used to describe the sample characteristics and to determine the extent and effects of these individual-level health disparities as barriers to advancement along the HIV Care Continuum.

HIV Health Assessment

The assessment records demographics (eg, sexual identity, age, and race or ethnicity), educational attainment, housing status, access to insurance, HIV treatment status (including the position in the HIV Care Continuum), HIV medication status (including medication type and dose), and self-reported ART adherence.

The Los Angeles Transgender Health Survey

The instrument consists of seven modules: screening, sociodemographic characteristics, health care access and medical history, sexual behaviors (at all stages of gender transition), drug and alcohol use, legal and psychosocial issues, and HIV prevention.

Substance Use Frequency

This brief assessment assesses substance use, injection drug use, and injection protocols in the past 30 days.

HIV Treatment Adherence Self-Efficacy Scale

The HIV Treatment Adherence Self-Efficacy Scale (HIV-ASES) consists of 12 items assessing participants' self-efficacy to adhere to their HIV medication regimen, to measure behavior change associated with SCT [41].

HIV Treatment Optimism Scale

The HIV Treatment Optimism Scale is a 19-item scale associated with components of the HBM (perceived susceptibility to disease, perceived severity of the disease, perceived benefits of preventive behavior, and barriers to preventive behavior) [42].

Inventory of Socially Supportive Behaviors

The Inventory of Socially Supportive Behaviors (ISSB) is a 40-item scale measuring instrumental, emotional, and informational dimensions of SST [36,43].

Rapid HIV Antibody Test

Potential participants are administered a rapid HIV antibody test (INSTI HIV 1/HIV 2) during the screening process to verify HIV-positive status. Participants who show documentation of HIV-positive serostatus (eg, laboratory results, ART prescription) are not given an HIV antibody test.

Urine Drug Screen

Urine samples are tested using a 5-panel urine dip card [44], with drug detection cut-off values at: amphetamines (1000 ng/mL), cocaine (300 ng/mL), opiates (300 ng/mL), methamphetamines (500 ng/mL), and tetrahydrocannabinol (50 ng/mL). Valid samples are indicated by the temperature of the sample (33 °C to 36 °C) [44].

Viral Load Test

Participants receive a viral load test at each time point to assess virologic suppression or control as indicated by an undetectable HIV-1 level on the Aptima HIV-1 Quant Dx assay, which is the lower limit of quantification of ≤30 copies/mL [45]. Participants who access their electronic health records and provide viral load results within 14 days of the assessment are not reassessed with viral load testing performed as part of the study.

Drug Abuse Treatment Cost Analysis Program

The Drug Abuse Treatment Cost Analysis Program is a standardized, customizable tool designed to help identify intervention resources across diverse settings for the purposes of estimating the implementation and sustainment costs associated with the intervention [46].

Nonstudy Medical and Other Services

The usage of health care services by participants is self-reported using a time-anchoring methodology via the Nonstudy Medical and Other Services form [47-49]. Health care services will include nonstudy: HIV care, inpatient, outpatient, and emergency department services; SUD treatment medications; residential and outpatient SUD treatment days; hospital SUD detoxification days; and mental health treatment visits. This information is measured for the 90 days prior to baseline, then "since the last assessment." The use of nonmedical and other resources required for the economic evaluation from state policy maker and societal perspectives (eg, criminal-legal, labor productivity, and travel time to medical care) is also self-reported and collected via the Nonstudy Medical and Other Services form.

Patient-Reported Outcomes Measurement Information System-Preference

The PROMIS (Patient-Reported Outcomes Measurement Information System)-Preference (PROPr) measures a participant's health-related quality-of-life across the following PROMIS domains: cognitive function abilities, depression, anxiety, fatigue, pain interference, pain intensity, physical function, sleep disturbance, and ability to participate in social roles and activities [50-52]. The PROPr is also capable of generating a health utility index value, based on the participant's scores for each domain, that represents the general US

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population's preference for the respondent's current health state. PROPr has 5 levels for each domain, ranging from "no problems" to "extreme problems." The health-utility value produced by PROPr can range from –0.022 to 1, where 0 represents death, 1 represents perfect health, and values below 0 represent states perceived to be worse than death. The health-utility value is used to calculate quality-adjusted life-years (QALYs) [50,53].

Statistical Analyses

Aim 1

The primary outcome of HIV care will be viral suppression (defined as less than 200 copies/mL). Secondary outcomes include the HIV-ASES, the HIV Treatment Optimism Scale, the ISSB, and urine drug screen results (test results for each of the 5 substances identified in the urine drug screen will be treated as different indicators). These outcome variables will be assessed at baseline and 3, 6, 12, and 18 months post enrollment. The resulting dependent variables will fall into one of two categories: (1) dichotomous variables (primary outcome: virologic suppression, and secondary outcome: urine drug screen results), assumed to follow a binomial distribution; or (2) continuous random variables (secondary outcomes: HIV-ASES, HIV Treatment Optimism Scale, ISSB scores), assumed to follow a normal distribution. All distributional assumptions will be evaluated prior to the conduct of analyses, and statistical methods chosen accordingly. Each of these dependent variables will be separately regressed on treatment condition (PHN alone vs SMS text messaging alone vs PHN+SMS text messaging), a set of baseline covariates (individual-level demographic characteristics), and time-varying covariates (social and structural determinants of health), using hierarchical linear regression where responses at each time point are nested within individuals. All analyses will be conducted on available study-related data from all participants, regardless of whether or when they drop out of treatment. The effect of interest will be a time × treatment condition interaction effect which will estimate the differential course and impact of the three intervention modalities over the follow-up period.

A generalized linear mixed model (GLMM) [54-56] will be used to conduct analyses of all outcomes following an intent-to-treat approach. The GLMM is an ideal statistical procedure for analyzing a broad class of longitudinal outcomes, including costs. As described above, key indicators of HIV care will be regressed on treatment conditions and a series of baseline and time-varying covariates. Treatment condition will be used to predict the slope of time, creating a time × treatment interaction term that is the effect of interest in the proposed study. We will also report on the relationships between time-varying covariates and the outcome measures, including time-shifted analyses where the value of the covariate at a previous timepoint is used to predict the outcome measure at a subsequent timepoint. Hypothesis testing for any given outcome will involve fitting the statistical model of interest and testing the effect of interest, as well as all other estimable effects in the model. We will use an iterative model-building approach where the simplest model is fit to the data first, and additional explanatory factors are added iteratively, in order of theoretical importance. Likelihood ratio tests are used to determine if the more complicated of the 2 models is a significant improvement over the simpler model. Variables of interest such as those specified in Aim 1 will always be included in the final model as the statistical tests of those parameter estimates (be they significant or nonsignificant) are of primary interest to this study.

Aims 2 and 3

The economic analyses will follow well-established guidelines [57-59]. The study will incorporate all resources or costs associated with the PHN, SMS text messaging, and PHN+SMS text messaging interventions from the health care sector, state policy maker, and societal perspectives [58-60]. The health care sector perspective includes all formal medical costs incurred by the system on behalf of participants, including the cost of the intervention, and participant out-of-pocket costs. The state policy maker perspective is crucial to informing resource allocation decisions on behalf of the public, who is primarily responsible for funding health care among this underserved population, given data indicating that most transgender women are either public health care insurance beneficiaries or uninsured [11,19]; moreover, the direct costs associated with criminal-legal resources, social safety-net programs, etc are paid for using public funds. In addition to the resources or costs included in the state policy maker perspective, the societal perspective accounts for those associated with untreated or undertreated HIV and comorbid conditions, such as premature mortality, reduced labor productivity, and those incurred by victims of crime [61,62].

The resources required to implement and sustain each intervention in a "real-world" setting (Aim 2) will be estimated using a detailed microcosting analysis, guided by a tailored version of the Drug Abuse Treatment Cost Analysis Program. The microcosting analysis will consist of gathering relevant administrative data and conducting semistructured interviews with site personnel in order to capture quantitative data regarding the resources (time and materials) used to deliver the interventions. The intervention implementation phase is considered to be the time period from conception (including planning activities) until the "steady state." Resources will be categorized as "fixed start-up" (incurred once), "time-dependent" (recurring, but does not vary with the number of participants), and "variable" (used every time a participant is served). The site visits and initial interviews will be conducted early in the study (~6 months following the first randomization). Follow-up interviews will be conducted virtually upon the study reaching a "steady state" (~12 months following the initial interview), to identify the time-dependent and variable resources required to sustain the intervention. "Steady state" will be determined with the assistance of site personnel. Implementation and sustainment costs will be estimated by assigning nationally representative price weights to the identified resources [58]. Research-specific costs will be excluded.

After estimating the implementation and sustainment costs associated with each intervention (PHN, SMS text messaging, and PHN+SMS text messaging), the relative value of each will be estimated according to the stakeholder perspective. This

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process entails capturing all relevant resources used by participants in each arm, assigning nationally representative price weights to them, estimating the predicted mean costs, and testing for differences between resource categories. Estimating the incremental costs between arms according to resource category allows for a careful evaluation of the downstream savings resulting from improvements in HIV care and reductions in related risk behaviors. These include savings resulting from reduced usage of high-cost health care (eg, emergency department visits and inpatient stays) and criminal-legal resources, as well as increased labor and other forms of productivity. Price weights will be derived from sources reflecting national "real-world" costs faced by state policy makers and society.

The primary outcome of the cost-effectiveness analysis (Aim 3) will be the incremental cost-effectiveness ratio (ICER), which will be calculated as the incremental, predicted-mean cost of a given intervention relative to an alternative, divided by the incremental predicted-mean effectiveness of the 2 interventions. The primary measure of effectiveness for the economic evaluation will be QALYs. The secondary measure of effectiveness will be advancement along the HIV Care Continuum. The QALY is a measure that combines the health-related quality-of-life associated with an individual's health state and the time spent in that state and is recommended as the primary effectiveness measure in economic evaluation studies due to its ability to be compared across interventions and disorders [58,63]. In addition, generally accepted thresholds for defining value have been established for QALYs, unlike clinical measures [64,65]. The HIV Care Continuum is an important and widely accepted model or tool for assessing HIV care outcomes at both an individual and a public health level; thus, the additional cost required to achieve a one-step increase along the HIV Care Continuum for the average transgender woman with HIV will be a critically important clinical and policy-relevant measure. Two ICERs (one for each effectiveness measure) will be calculated for each stakeholder perspective at both 3 months (intervention completion; immediate effects) and 18 months (distal effects).

To help address censored data, we will model the person period and estimate all regressions using a multivariable GLMM. Separate regressions will be estimated to predict the mean value for each resource category, at each time period, by study arm. The statistical method of recycled predictions will be used to obtain the final predicted mean values [58]. Similarly, individual regressions will be used to predict the health utility index value and HIV Care Continuum steps gained for each participant, at each time point. QALYs gained will be estimated using the predicted health utility values and the area under the curve methodology [58]. The most appropriate distributional and link functions for each GLMM regression will be chosen according to the fit of the observed data [58].

To account for sampling uncertainty in point estimates, the *P* values and SEs will be estimated using nonparametric bootstrapping techniques within the multivariable framework combined with methods to address missing data based on recommended approaches [66]. All monetary values will be adjusted for inflation, and all measurements obtained beyond 12 months of baseline will be discounted for time preference using the recommended rate of 3% [58,65].

The most cost-effective strategy for each outcome measure (QALYs; HIV Care Continuum placement) will be determined using the rules of strong and extended dominance. Parametric methods based on parameters obtained from bootstrapping will be used to estimate cost-effectiveness acceptability curves for each ICER, which illustrate the probability that an intervention is cost-effective for different value thresholds [57].

Power Analysis

A simulation approach was used to conduct the power analysis and determine that N=195 (65 per arm) was an appropriate sample size to detect the effect of each intervention on our primary outcome, and the likelihood of virologic suppression over time [67]. Power by simulation is more flexible than traditional approaches because it can estimate power under a wide variety of circumstances, including when these assumptions are not met.

Ethical Considerations

All study procedures are approved by the Western Institutional Review Board (Study #1352118; Institutional Review Board Tracking #20231531). This trial has been registered at ClinicalTrials.gov under the number NCT06408350. All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Informed consent was obtained from all individual participants included in the study.

Results

Recruitment began on April 10, 2024, and the first participant was enrolled on April 11, 2024. Recruitment spans approximately 33 months; enrollment goals are approximately 6 enrolled participants per month. Data collection, including all follow-up assessments, is expected to be completed in July 2027.

Discussion

Principal Findings

Many transgender women have suboptimal advancement through the HIV Care Continuum, including poor HIV health care usage, retention in HIV medical care, and rates of viral suppression; moreover, these issues are exacerbated by comorbid conditions such as SUDs. The Text Me, Alexis! study is a comparative-effectiveness research trial with a comprehensive economic evaluation that builds upon the promising findings of two Health Resources and Services Administration-funded demonstration projects in order to identify the optimal intervention for advancing transgender women with HIV to full viral suppression. Though the effectiveness of the demonstration projects has been established, their comparative effectiveness, required resources or costs, cost-effectiveness, and heterogeneous effects on subgroups, including those with SUDs, have not been evaluated.

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Challenges

There are several challenges to the Text Me, Alexis! study. First, housing instability, substance use, engagement in sex work, and other individual-level, social, and structural disparities may interfere with study participation. The PHN alone and PHN+SMS text messaging arms were designed to address these issues and work with each participant to assess and minimize or remove barriers and link participants to an array of ancillary social services. Additionally, in the demonstration project, despite experiencing several health disparities including low educational attainment, low income, and housing instability, SMS text messaging alone demonstrated significant improvements in ART uptake, ART adherence, and achievement of an undetectable viral load, which were durable through 18-month follow-up. Second, episodes of short-term incarceration may interrupt study progress and follow-up assessment rates, due to factors such as actual or perceived participation in the street economy, or minor homeless infractions. Study staff monitor the public records database for participants who miss appointments. When an incarcerated participant is found, we begin a correspondence with the participant immediately upon release. Third, loss of ART or selling ART due to lifestyle needs ("diversion")—ART adherence will be stressed through the participant-centered treatment plan and via adherence-specific SMS text messages, including strategies for keeping medication safe, and a discussion on how ART adherence outweighs selling the drug. Finally, fear of drug-drug interaction—some participants may be concerned about ART and gender-affirming hormone therapy interactions and prioritize gender-affirming hormone therapy over ART uptake or adherence. These concerns will be acknowledged and corrected in PHN sessions and SMS text messages.

Conclusions

The public health significance of Text Me, Alexis! has the potential to be quite profound, as comparative- and cost-effectiveness research trials are critical steps in the development and adoption of scalable and effective HIV care intervention, especially among key populations that rely on service provision in resource-limited, community-based settings.

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Data Availability

The datasets generated during or analyzed during this study are available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Authors' Contributions

CJR and SMM conceived of the study design and wrote the original draft of the manuscript. TB wrote the statistical analysis sections for Aim 1 and the secondary aim; SMM and AJ wrote the statistical analysis sections for Aims 2 and 3. RJL provided oversight on all sections related to medication adherence and viral suppression. MJL, RPM, DR, and PJJ reviewed and edited the manuscript.

Multimedia Appendix 1
Summary Statement Peer Review Comments.
[PDF File (Adobe PDF File), 143 KB - resprot_v14i1e65313_app1.pdf]

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Abbreviations

ART: antiretroviral therapy
DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)
GLMM: generalized linear mixed model
HBM: health belief model
HIV-ASES: HIV Treatment Adherence Self-Efficacy Scale
ICER: incremental cost-effectiveness ratio
ISSB: Inventory of Socially Supportive Behaviors
LAC: Los Angeles County

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PHN: peer health navigation
PROMIS: Patient-Related Outcome Measurement Information System
PROPr: PROMIS-preference score
QALY: quality-adjusted life-year
SCT: social cognitive theory
SST: social support theory
SUD: substance use disorder

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Protocol

Self-Management Strategies for Low Back Pain Among Horticulture Workers: Protocol for a Type II Hybrid Effectiveness-Implementation Study

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Abstract

Background: Low back pain (LBP) is highly prevalent and disabling, especially in agriculture sectors. However, there is a gap in LBP prevention and intervention studies in these physically demanding occupations, and to date, no studies have focused on horticulture workers. Given the challenges of implementing interventions for those working in small businesses, self-management offers an attractive and feasible option to address work-related risk factors and manage LBP.

Objective: This study will (1) investigate the effectiveness of self-management strategies for nursery and landscape workers by comparing within-subject control and intervention periods and (2) determine if adoption and effectiveness differs between participants randomly assigned to review self-management videos only and those who also receive multimodal implementation support. We will also identify contextual factors impacting effectiveness and implementation.

Methods: A pragmatic, mixed methods, hybrid effectiveness and implementation design will be used to compare back pain with work tasks, disability, medication and substance use, and psychological factors between a baseline control and intervention periods. We aim to recruit 122 English- and Spanish-speaking horticulture workers with back pain, 30 supervisors, and 12 focus group participants. Participants will review short video modules designed to increase awareness of opioid risk and introduce self-management and ergonomic choices and use 1 self-management and 1 ergonomic strategy for 10 weeks. They will be randomly assigned to 2 implementation groups: video modules only or video + multimodal personalized support (checklist guidance, review of video feedback for ergonomic problem-solving, and text message reminders). Questionnaires will be administered at 3-month time points: baseline, pre- and postintervention, and at 3 and 6 months. Qualitative analysis of field notes, open-ended comments, and focus groups will expand understanding of results with comprehensive documentation of the context, barriers and facilitators, and reasons for adoption.

Results: The project was funded on September 29, 2023 (Centers for Disease Control and Prevention National Institute of Occupational Health and Safety, CDC NIOSH; U54OH011230-07S1), as a core research grant for the Southeast Coastal Center for Agricultural Health and Safety. The design, creation, and editing of English and Spanish videos was completed in June 2024 after comprehensive formative evaluation. Enrollment began in June 2024 with anticipated completion in 2027.

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Conclusions: We hypothesize that both self-management interventions will result in reductions in work task pain and disability and that the video enhanced with multimodal personalized support will result in greater reductions than the video alone. If self-management is effective, mitigating pain positively impacts quality of life, productivity, and retention, while increasing the use of nonpharmacological alternatives to opioids addresses an important public health issue. Implementation aims will help inform reasons for results, barriers and facilitators, and potential for similar interventions in these and similar industries with physically challenging outdoor work.

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KEYWORDS

low back pain; self-management; implementation; horticulture workers; video training; video feedback; text message reminders; agriculture; ergonomic; nonpharmacological

Introduction

Background

Low back pain (LBP) is the most common musculoskeletal disorder among agricultural and horticultural workers [1-5], negatively impacting worker's physical and mental health, increasing absenteeism, and shortening work longevity [6-11]. Further, LBP contributes to lower productivity, loss of experienced workers, and increased workman's compensation costs. The financial impact of high out-of-pocket costs and lack of paid leave often drive agricultural and horticulture workers to seek pain relief from prescription medications and illicit substances [12-14]. In one study of farmers with LBP, 71% relied on pain medication without consulting a physician compared to only 35% of white-collar workers [15].

Viable alternatives to pharmacological management of LBP have never been more important [16,17]. Despite guidelines recommending nonpharmacologic management, opioids are commonly prescribed for work-related injury and pain more frequently than for nonoccupational musculoskeletal disorders [18-22]. Although opioid prescribing has declined gradually since 2010, opioid fatalities from prescription and illicit synthetic opioids have continued to rise [20,23]. The precipitous increase in opioid overdose associated with fentanyl manufactured in clandestine laboratories [23,24] has elevated the importance of highlighting and promoting uptake of nonpharmacological alternatives for management of LBP [20]. In rural areas, opioid prescription rates are particularly high [25], and access to nonpharmacologic treatment options is limited [16]. A preliminary study supporting this protocol found that over half of agricultural workers (n=129) reported using opioids at some point [14]. Of those who had used opioids, most (77%) reported they received a prescription for a work-related injury. Participants explicitly linked work hazards and chronic pain with increased risk of opioid dependence, citing the need to continue working and "live with pain" as a cultural norm contributing to the problem [14]. While progression to opioid use disorder is complex, opioid misuse has devastating effects on health and work. A systematic review of the impact of prescription medications for occupational musculoskeletal injuries found that opioid use was associated with slower return to work, longer duration of disability, poorer self-reported work function, and poorer functional improvements [26]. Opioid prescriptions within the first 2 weeks of a work-related injury, opioid use for longer than 7 days, and higher dose supplies are associated with subsequent work disability or delayed recovery and greater work loss [26]. Owners of nursery and landscaping businesses in Florida reported problems with turnover, frequent absences, and low productivity among workers who used opioids, resulting in decreased labor availability [14]. Landscape and nursery work characteristics including low skill discretion, job strain (low control and high demand), high physical effort, and heavy lifting are risk factors for opioid use disorder [27]. Few opioid prevention efforts have been focused on underlying work-related factors such as musculoskeletal pain [18,28]. The substantial worker and employer burden of LBP in the horticulture industry and the devastating effects of opioid dependency highlight the need for efforts to manage and limit LBP and reduce unwarranted opioid use for musculoskeletal injury. Strategies to (1) increase workers' awareness of the risks and consequences of opioid use, (2) encourage workers to discuss options with health care providers after more acute injuries, and (3) provide alternatives for nonpharmacological strategies to manage pain or limit ergonomic stress [28] may increase knowledge and self-efficacy while reducing stigma [20,28].

Self-management is defined as the ability to manage pain, treatment, psychosocial, and lifestyle implications of a chronic condition [29,30], with the overall goal for individuals to safely manage symptoms and lifestyle without seeking unnecessary medical intervention [30-33]. Encouraging active involvement and empowering individuals to select options to manage work-related pain tailored to each worker's circumstances and preferences encompasses the principles of self-management for chronic conditions [6]. Effective self-management strategies should optimize pain coping strategies to manage and reduce symptom exacerbation through problem-solving [30]. Self-management is recommended for the management of chronic LBP in a number of guidelines and strategic initiatives [16,34,35], with moderate effectiveness for pain, and small to moderate effectiveness for pain-related disability reported in a systematic review and meta-analysis [36]. Increasing self-management of chronic pain that frequently limits work activities is one of the Health People 2030's targets [35]. However, most studies investigating effectiveness of self-management approaches have involved patients receiving

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clinical care rather than groups who continue to work in physically demanding occupations. Self-management skills such as problem-solving, action planning, self-tailoring, and self-monitoring may provide a worker-centered approach for horticulture workers to promote self-efficacy and coping skills for adjusting work activities and managing pain [29,30,37].

There are limited training initiatives to address musculoskeletal pain for horticulture workers and most workers rely on supervisor's advice or learning by experience. Many studies have concluded that education can positively influence work-related musculoskeletal pain by promoting behavioral change, modifying health beliefs, and improving attitudes, although gaps in optimal implementation persist [38]. Although some studies reported additive effects of improving physical activity or ergonomic adjustments [38], none focused on agriculture, nursery, or landscape workers. Collectively, there is a crucial need to determine optimal implementation of effective self-management programs for workers, especially for those who do not have resources to receive treatment in typical health care settings [39,40]. Therefore, examining the effectiveness of training to assist workers with learning self-management and ergonomic strategies will provide valuable information, while studying implementation outcomes will help determine engagement, adoption, and feasibility.

Prior Work

This protocol builds from a preliminary study of streamlined individualized participatory ergonomic (PE) methods in clam aquaculture workers with similar physically challenging work [39,41]. Workers with chronic LBP were introduced to ergonomic concepts to reduce risk, selected 3 pertinent and acceptable strategies from a list, reviewed videos, and received text reminders. Significant improvements in disability, work-task pain, pain anxiety, and coping compared to baseline were observed ($P<.05$; n=19), with pain improvements greater than published minimal detectable change for 74% of the participants. The methods were both feasible and acceptable. These promising results led to recommendations to establish whether these approaches are effective in a larger cohort over longer timeframes, in different contexts, and with follow up [39].

We will investigate the effectiveness of self-management and ergonomic individual choices along with behavior change support for nursery and landscape workers. The first aim is to determine if self-management videos combined with multimodal personalized support is more effective than self-management videos alone for improving LBP management among horticulture workers. We hypothesize that compared to the video modules alone, the combined multimodal personalized support will result in (1) greater reductions in work task pain and disability, (2) lower prevalence of high-impact chronic pain, (3) greater reduction in substance use to manage pain, (4) greater reeducation in pain anxiety and depression, and (5) improved coping and self-efficacy. The second aim is to identify contextual factors that impact engagement, adoption, effectiveness, and implementation of nonopioid alternatives for LBP self-management. Understanding the external context and individual and team characteristics will help explain the results, provide important implementation perspectives, and inform translation.

Methods

Study Design

The exploration and preparation phases of the study were started in 2023, with the video training module creation, evaluation, modifications, and production completed in June 2024. A 2-arm pragmatic randomized controlled hybrid type II effectiveness and implementation study [42-44] will be conducted using mixed methods and a within-subject control period. The Standards for Reporting Implementation Studies (StaRI) standards checklist is included in Multimedia Appendix 1.

Ethical Considerations

The study was approved by the University of Florida Institutional Review Board (IRB202300756) and registered as a clinical trial through ClinicalTrials.gov (NCT06153199). Participants will be compensated for their time. Workers will receive US $25 for the baseline data collection and US $50 for subsequent steps for a possible total of US $225, while supervisors or owners will receive US $50 for the 2 data collection sessions for a possible total of US $100.

Employers will provide permission to discuss the study with workers and to conduct the study in the workplace. After determining eligibility, research staff will describe the purpose of the study, study-related procedures, risks, and benefits, and participants will sign an informed consent if they agree to participate. We will ensure that participants understand that participation is voluntary and that they can withdraw from the study at any time without consequences. A Certificate of Confidentiality (42 USC §241(d)) will protect participant privacy related to potentially sensitive information about the use of pain medication and other substances. If individual workers are not eligible or do not want to participate, they will be able to view the educational videos with their teams. If participants who are randomly assigned to the intervention enhanced with multimodal support are not comfortable being videotaped, we will provide deidentified video clips of other workers with blurred faces performing tasks similar to the tasks they have identified as difficult due to pain.

Recruitment

Recruitment Methods

We will recruit nursery and landscape workers in Florida through community partners and contacts from the Southeastern Coastal Center for Agricultural Health and Safety. We will use direct communication, email lists, websites, word-of-mouth referrals, and community meeting announcements to identify employers who are interested, followed by presenting the study to workers. We will recruit workers with a range of disability, pain impact, and persistence, anticipating that participants will be primarily male, with higher numbers of female participants in the nursery teams, and that approximately 50% will identify Spanish as their first language. Initial contact and permission will be through owners and supervisors to enroll nursery and landscape businesses and their employees.

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Inclusion and Exclusion Criteria

Criteria for inclusion are (1) working full time (30 hours or more per week) in nursery or landscape businesses, (2) 18 years of age or older, (3) English or Spanish speaking, and (4) experiencing continuous or intermittent LBP over the past 3 months. We will exclude individuals who (1) report history of trauma, major spine surgery, or spinal nerve blocks in the past year; (2) are seeking disability or workmen's compensation, or (3) self-disclose pregnancy.

Sample Size Projections

A priori sample size was calculated using data from the pilot study comparing pain and disability measures pre and post–self-management PE interventions for 19 seafood workers [39]. For each participant and pain or disability outcome, averages of 4 baseline measurements and 2 postintervention measurements were used to calculate the difference in pre- to postintervention outcomes. Mean changes over a control period are assumed to have a mean 0 difference but share the same SD as the intervention period. Changes over the 2 periods for the same person are assumed to be independent. Data were simulated from a simple linear mixed model (LMM):

$$Y_{ijk} = \alpha_i + \beta_1 X_{ijk} Z_{ijk} + \beta_2 (1 - X_{ijk}) Z_{ijk} + \varepsilon_{ijk}$$

In this model equation, Y_{ijk} is the outcome of observation period k of individual j in cluster i, X_{ijk} indicates the intervention group (1: video + support, 0: video), Z_{ijk} indicates the intervention period (1: intervention period, 0: baseline period), α_i is the random intercept of cluster i, and ε_{ijk} is the error term. The variance of α_i was set as 5% of ε_{ijk}, such that the intraclass correlation is close to 0.05. For each set of simulated data, a generalized estimation equation model was used to test the null hypothesis β_1=0. We ran 1000 simulations to calculate the power for each of the different settings of the number of clusters and cluster sizes. Table 1 shows the power based on individual randomization. Fitting a LMM yielded comparable results. The planned enrollment of 102 participants (24 clusters) will provide adequate power for the primary outcomes, pain with most difficult work activities and total disability. An additional 20% enrollment for attrition results in a total anticipated sample of 30 clusters and 122 participants (teams of 3-5 participants) for the comparative effectiveness goals.

Table 1. Statistical power (%) based on individual randomization for differentiating between the 2 implementation groups using preliminary data.

Number of clusters	Cluster size	Projected Sample size	Power (%) calculated using results from Dunleavy et al. [39].			
			Pain with most difficult work activities (mean –16.1, SD 18.8)[a]	Average pain (mean –5.2, SD 17.3)[a]	Total disability (mean –2.5, SD 3.5)[a]	Difficulty level with most problematic work activity (mean 9.0, SD 28.5)[a]
20						
	3	60	96.9	28.4	88.7	33.8
	5	100	99.8	43.9	98.3	49.5
	10	200	100	73.5	100	73.5
25						
	3	75	98.9	32.3	93.3	40.7
	5	125	100	48.6	99.4	57.5
	10	250	100	80	100	84
30						
	3	90	99.5	38.2	97.1	44.3
	5	150	100	56.3	99.8	64.4
	10	300	100	87.3	100	88.8

[a]Mean difference, SD from Dunleavy et al [39].

Target Enrollment and Randomization

Our target enrollment of 122 workers will be recruited over 3 years starting in June 2024 with anticipated completion in 2027. For each team, we will enroll at least 1 supervisor or owner to provide support and comments on the overall feasibility and results, for 30 supervisors. In year 4, we will also invite 12 stakeholders to participate in focus groups (see aim 2) for a total expected enrollment of 164. Participants will be randomized to one the intervention groups after the baseline control period using stratified block randomization by type of work (nursery, landscape), and within each employer group to ensure a 1:1 distribution. The random assignment table was created prospectively by the statistician and participant numbers are generated in the REDCap (Research Electronic Data Capture) software (version 9.1.1; Vanderbilt University) [45] when baseline data are downloaded to reduce the risk of bias. Participants will receive incentives after completion of the surveys, training, and interviews.

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Data Collection

Timelines

Five measurement periods will allow longitudinal comparison of change from the within-subject control period (10 weeks), across the pre- and postintervention period (10 weeks), and follow-up (3 and 6 months; Figure 1).

Figure 1. Timelines.

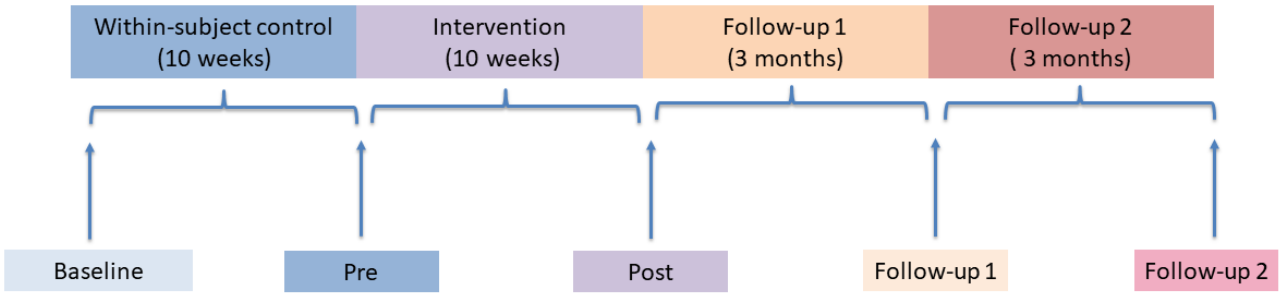

Questionnaires

Questionnaires in English or Spanish will be administered in the workplace on tablets using the REDCap platform [45]. The REDCap is a secure, web-based software platform with questionnaire support and data management functions [45]. Primary dependent variables will be collected at all timepoints—pain (severity, interference, and persistence); pain with specific work tasks; disability; work ability; and pain medication use [46-51]. Affective or cognitive characteristics impacting adoption and effectiveness (secondary dependent variables or potential confounders) such as coping, fear, anxiety, and depression will also be collected [52-55]. Branching logic will be used to pipe answers for the most difficult work activities and choices of strategies into subsequent questionnaires. In addition to demographics, medical and work characteristics will be collected. Disability will be assessed using Roland-Morris Disability Index [49], Patient Specific Functional Index (PSFS) for work tasks considered most difficult due to back pain [39,50,56-58], and Work Ability Index instruments [48]. Pain constructs from the National Pain Strategy recommendations (severity, interference, persistence, and impact) [46,47], along with pain with the specific work tasks identified in the PSFS, will be measured using Likert scales [39]. Substance use will be recorded using the National Institute on Drug Abuse quick screen [23] with additional questions on over-the-counter pain medication and other substances. Affective and cognitive measures include the Pain Anxiety Symptom Scale [53], Center for Epidemiological Studies Depression Scale short form [52], Coping Strategy Questionnaire [55,59,60], and Self-Efficacy for Chronic Condition management short form [54]. Instruments were translated by a certified translation agency if validated Spanish versions were not available.

Qualitative Methods

Understanding the context (circumstances and unique factors surrounding the study) will help explain results and provide implementation outcomes [43,61,62]. We will use relevant components of the Exploration, Preparation, Implementation, Sustainment conceptual framework, including inner (individual and team) and outer (industry, regulations, and environment) contextual factors (Figure 2) [63]. Qualitative data will be compiled from (1) researcher observations and field notes; (2) anchor-based and open-ended questions reflecting engagement (opinions of intervention delivery and support, recommendations to others), adoption (use of strategies in past 7 days), and feasibility (ease of use, barriers and facilitators); (3) perceived effectiveness (including global rating of change); (4) supervisor and worker comments; and (5) data collected during final stakeholder focus groups (Figure 3). Spanish-speaking research team members will contribute to observations and if needed, will translate comments. We will record comments, expansions, and clarifications and will ask workers specifically about the acceptability of introducing information about opioid risk and self-management at home and in the workplace. Supervisors and owners will be asked to provide their opinions from an organizational perspective. Recommendations will be confirmed, prioritized, and expanded ensuring robust and iterative analysis.

In addition, 2-3 focus groups will be conducted during the last quarter of the study. Industry representatives, employers, supervisors, and select participants will be invited to contribute their opinions. We will invite industry leaders committed to support wide-spread dissemination and translation of interventions, and workers able to comment on their real-world perspectives with 1 focus group conducted in Spanish. Focus group questions will help explain findings and patterns identified throughout the study and generate recommendations for future interventions. Question prompts will reflect any similarities or differences generated from earlier data analysis to confirm themes and conclusions, further ensuring triangulation and rigor. Interview and focus group recordings will be recorded using participant numbers only, transcribed, and translated if appropriate [64]. Comprehensive data analysis will be conducted progressively throughout the study, contributing to triangulation and trustworthiness of the qualitative analysis [64,65].

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Figure 2. Contextual framework: selected components from the EPIS (Exploration, Preparation, Implementation, Sustainment) Model.

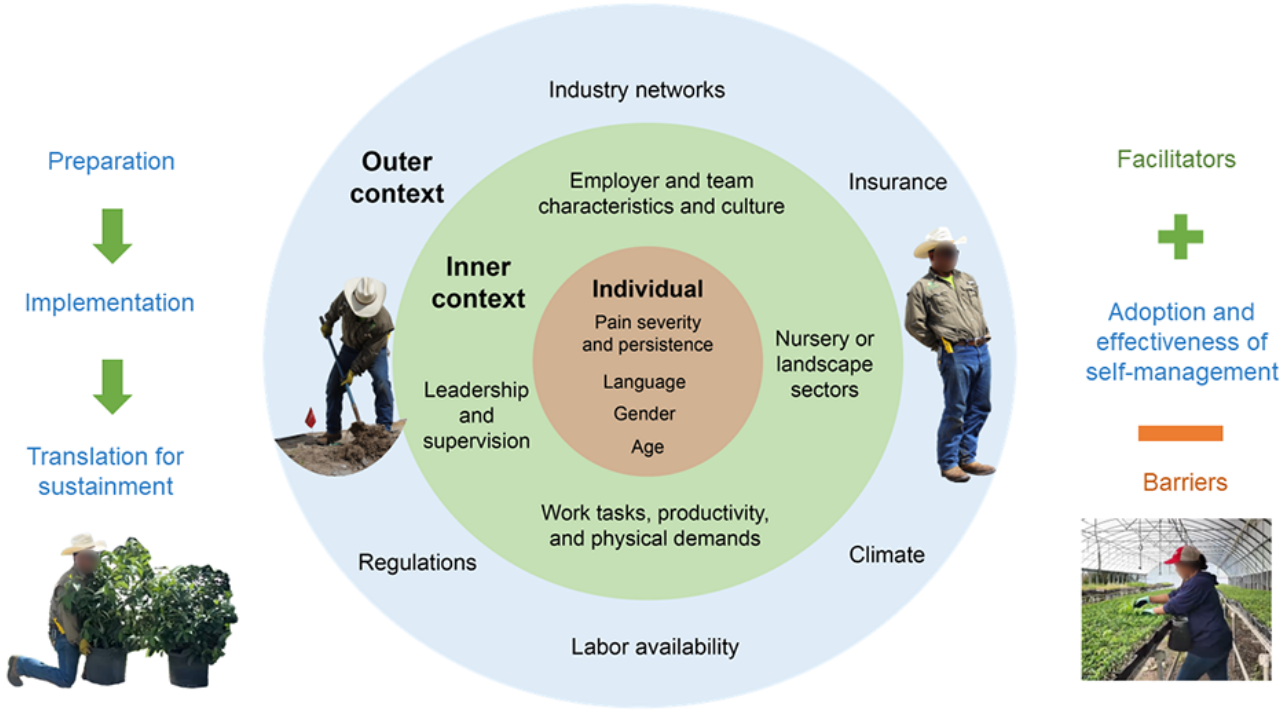

Figure 3. Qualitative methods.

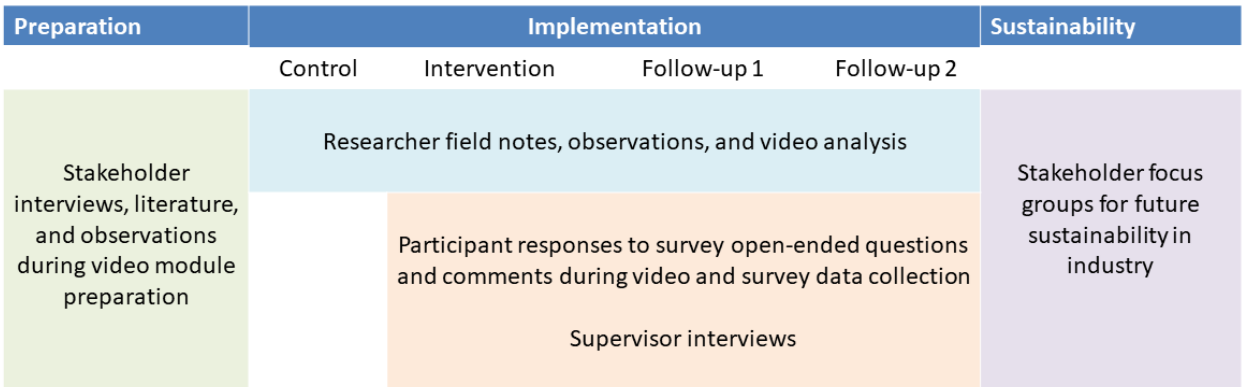

Risk Exposure for Tasks

Participants will be videotaped while performing their self-identified most difficult work tasks at baseline and after the intervention. After categorizing video clips by tasks, subtasks, and variations using hierarchical task analysis, the risk for each task will be categorized using the Rapid Entire Body Assessment (REBA) checklist [59,60]. The REBA is a commonly used measure to reflect ergonomic risk in the workplace and reflects extreme postures in tree nursery workers better than other observational instruments [66]. We will use a software system (Tumeke) [67], which identifies and reports the REBA for the postures and movements in the cycle with the highest risk to help with consistency of analysis. The risk assessment measures will be documented for specific tasks rather than used to compare individual change due to the variability of tasks and potential difficulty capturing the exact same tasks for all participants. Tasks will be recorded as changed or unchanged.

To further understand the impact of work adjustments and variations, simulations of various ergonomic scenarios will be conducted in laboratory settings with 3D analysis. Tasks with multiple variations and those which are changed will be selected and replicated. These simulations will involve creating different work environments and task setups to replicate the typical conditions encountered by the participants. By analyzing these simulated scenarios, we aim to identify potential ergonomic improvements and assess relative risk for variations of the tasks rather than evaluating individual change.

Intervention

Video Training Module Design and Preparation

Three short video modules were created specifically for nursery and landscape workers, tasks, and environments. The instructional design was informed by stakeholder discussions, review of current evidence, targeted in-depth interviews with industry experts (insurance safety consultants, association leadership, owners, supervisors, and workers; n=15), and work

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observation conducted during the preparation phase. Stakeholders also completed surveys which helped prioritize a preliminary list of work tasks considered most problematic for back pain.

Nursery and landscape worker characteristics informed design of multimedia visual representation of work activities and content with representation of genders and ethnicities in the videos and resource materials. Scripts were designed and evaluated for language consistent with lower than eighth grade literacy level to meet the lowest anticipated educational level, while structure and organization to reduce cognitive load, and design accounting for multiple language versions was built in from the first draft (Textbox 1).

The videos emphasize the importance of managing and limiting pain using active nonpharmacological self-management and conserving work longevity to facilitate ongoing support of family. The modules cover (1) the need to manage pain without relying on medication and substances, as well as the risk of opioid use; (2) self-management strategies for pain at home and at work (general exercise, specific back exercise, nutrition and hydration, deep breathing and positive thinking, rest, relaxation, and sleep); and (3) work-specific ergonomic strategies to address physical risk factors during nursery and landscape tasks. The videos encourage selection of relevant strategies for pain management of exacerbations, emphasize prevention through lifestyle and behaviors such as exercise, nutrition, and sleep, and proactively planning work tasks and adjusting movement to minimize risk (Figures 4 and 5). Sector-specific video clips of relevant work activities were filmed in nursery and landscape work settings and represent workers with a mix of genders and ethnicities, along with key stakeholder commentary to provide relevance.

Textbox 1. Design choices matched to characteristics.

Multimedia visual representation

- Videos and narration; minimal use of text with simple language, short sentences, images to represent key concepts, and advance organizers [68,69].
- Check list support materials (print) [68,69].
- Infographics and resource materials.
- Text messages include graphics and gifs for movement.

Health literacy and cognitive load considerations

- Literacy levels lower than eighth grade [68,70].
- Organization to maximize working memory and reduce cognitive load using advance organizers, smaller “chunks” and grouping of concepts [71].
- Graphics to represent choices as advance organizers.
- Short modules to minimize overload.
- Encouragement to choose relevant options for self-efficacy.
- Message design and visual representation, for example, focus on positive options for movement and work adjustments rather than what not to do or representation using symbols with negative connotations such as red crosses.
- Contrasting recommended movement in color with those that should be adjusted in black and white video.
- Music and screen transitions to divide concepts.

Multiple languages

- English version design and initial formative evaluation to identify and adjust vocabulary and grammar difficult to translate into Spanish.
- Length of clips adjusted to time needed for Spanish narration using transitions.

Feasibility for workplace

- Video delivered on iPads in 5-minute modules to maintain attention to use in the field for “toolbox” talks, team discussions, or as part of general safety meetings.
- Options based on the work and team location rather than requiring classroom settings to promote feasibility.

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Figure 4. Self-management strategy options.

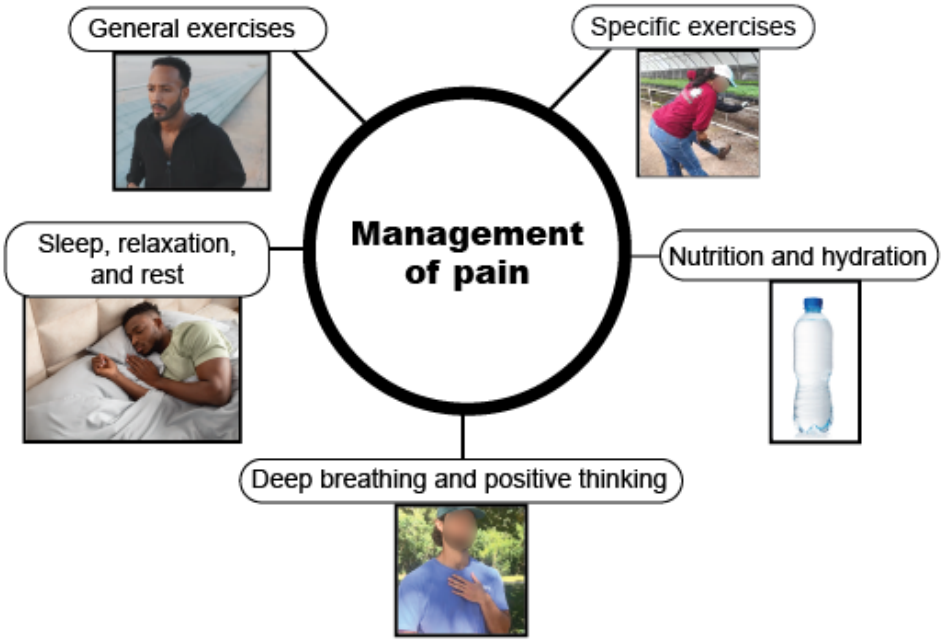

Figure 5. Ergonomic strategy options.

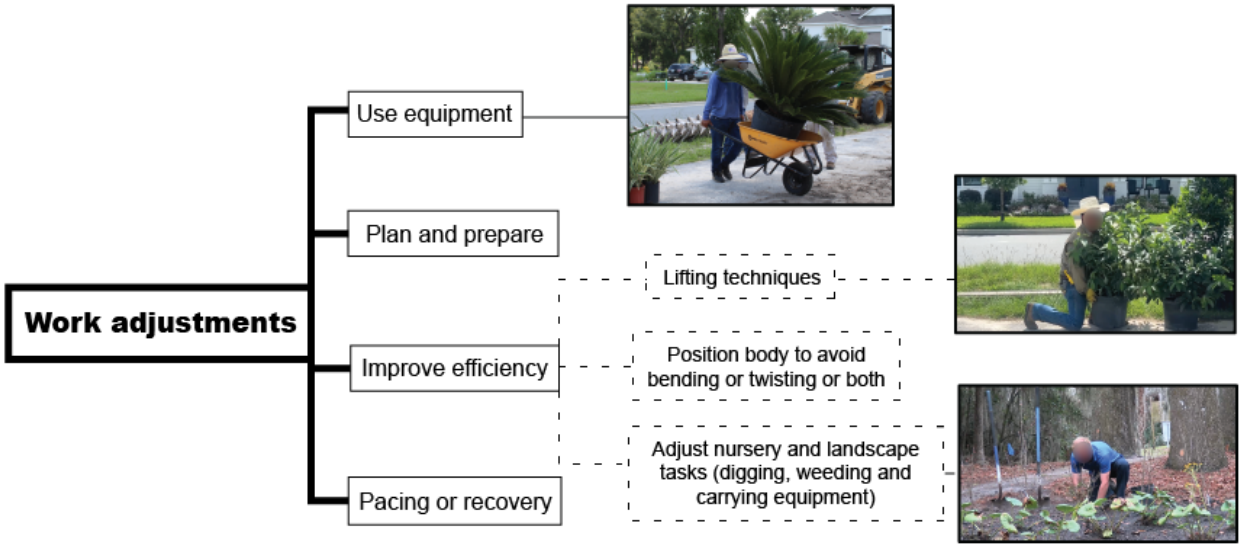

Video Formative Evaluation

The design incorporated iterative feedback from instructional design and health literacy experts and input from the research team who have expertise in pain management, rehabilitation, psychology, opioid misuse, and ergonomics. The scripts were evaluated for health literacy and inclusivity, followed by formative review by the experts in our multidisciplinary team. The adjusted English script was evaluated by owners, supervisors, workers, communication and industry experts, as well as bilingual stakeholders for words and concepts that are difficult to translate.

Supervisors, workers, and outside stakeholders (n=27) reviewed the video for content, format, representation, understanding, and provided comments. Additional video clips were added, and some content reorganized for flow and organization to reduce cognitive load. Final narration was completed after the second revision. The script was translated into Spanish by a certified agency and reviewed again for consistency, language, messaging, and cultural acceptability, prior to adding the Spanish narration and titles. Spanish speaking supervisors, workers, and stakeholders (n=12) also evaluated the Spanish videos with minor changes.

Self-Management and Ergonomic Options and Implementation Strategies

The self-management and ergonomic options (Figures 4 and 5) and implementation strategies (Table 2) were selected using evidence, stakeholder interviews, and established theoretical frameworks (health beliefs [72,73], self-determination [74-76], social cognitive [77,78], and Bronfenbrenner's Ecological Systems Theories [79]). The theoretical frameworks will help to interpret effectiveness outcomes for the group and for

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different subgroup characteristics and determine if interventions are modifiable to fit with internal and external contexts [80].

After the within-subject control period, participants will be randomly assigned to 1 of the 2 implementation arms. Workers in both groups will view the tailored educational video modules in the workplace and select 1 self-management (Figure 4), and 1 ergonomic strategy (Figure 5), to use during the 10-week intervention period. Workers assigned to the arm enhanced with additional support (video + support) group will be provided checklists to use while reviewing the videos and asked to consider strategies they do not use or could use more frequently [81]. To assist workers with problem-solving, participants in this group will be shown video recordings of their own work and encouraged to problem-solve ergonomic alternatives [39,41,81]. Finally, the workers in the video + support group will receive weekly SMS text message reminders to support their specific choices. These automated messages will be delivered using the Mosio text platform [82] at the beginning (ergonomics) and at the end (self-management) of the week. The messages are preprogrammed and will include graphics and gifs to represent concepts from the videos. Supervisors will also be asked to support workers for ergonomic choices and provide their opinions of engagement, adoption, and feasibility.

Table 2. Implementation outcome measures.

Implementation strategy	Engagement	Adoption	Feasibility
Tailored short educational video modules delivered in the workplace using iPads	• Acceptability, relevance—questions during or after training • Opinions of the videos and delivery	• Number of ergonomic and self-management strategies used • Frequency of strategy use • Intent to use strategies in the future	• Ease of use of strategy • Facilitators or barriers • Time for delivery • Feasibility in the workplace environment
Worker choice of preferred strategies matched to self-identified most difficult work tasks	• Acceptability	• Number of ergonomic and self-management strategies used • Frequency of strategy use • Intent to use strategies in the future	• Ease of use • Barriers and facilitators
Supervisor involvement	• Supervisor engagement (observation)	• Uptake and involvement of workers from supervisor's perspectives	• Supervisor interviews—feasibility, reasons for adoption, fit with organization, and environment • Barriers and facilitators
Visual feedback for positions and movements	• Qualitative comments and questions during review of video	• Use of strategies	• Time • Recognition of positions and postures • Opinions of relevance and acceptability
Ergonomic problem-solving	• Involvement in problem-solving • Supervisor comment discussion among workers	• Use of strategies	• Opinions of ergonomic strategies and problem-solving • Supervisor observations of suggestions for work tasks, changes in work practices
Text message reminders including images and gifs	• Questions and return texts		• Feasibility for workers • Opinions of text messages

Data Analysis

Aim 1

LMMs or generalized linear mixed models (GLMM) will be used to compare within-subject changes in the primary and secondary outcomes (1) over time (baseline, pre, and post) between the intervention periods and the control period and (2) between video and video + support interventions, depending on the distributional feature of the outcome. A general regression structure will be used:

$$g(EY_{ijk}) = \alpha_i + \gamma_j + \beta' X_{ijk}$$

In this equation, Y_{ijk} is the change of the outcome over observation period k of individual j in cluster i; $g(EY_{ijk})$ is the link function for the mean of Y_{ijk}; α_i and γ_j are random intercepts specific to cluster i and individual j, respectively; and X_{ijk} and β are vectors of covariates and associated coefficients. X_{ijk} indicates intervention (1: intervention video+support, 0: control video only), and baseline characteristics (demographics, occupation, and baseline pain or disability levels). For continuous outcomes that are symmetrically distributed (after transformation), the following traditional LMM will be used:

$$Y_{ijk} = \alpha_i + \gamma_j + \beta' X_{ijk} + \varepsilon_{ijk}$$

where ε_{ijk} are normal random errors. For skewed continuous outcomes, a GLMM with a gamma distribution will be used. Intervention effects will be represented by mean differences in the continuous outcome between the comparison groups. For

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categorical outcomes such as prevalence of chronic high impact pain, we will either dichotomize the outcome and fit a logistic mixed model or directly fit a Bayesian multinomial logit model that is available in the R package. Intervention effects will be represented by odds ratios. We will also reparameterize the model to obtain relative risks for measuring intervention effectiveness. These models will account for correlations within each team, as well as within each subject. Results will be verified by general estimating equation models in case within-team or within-subject correlation structures are mis-specified. Missing values for either outcome or covariates will be managed by multiple imputation or the Expectation-Maximization algorithm.

Aim 2

Qualitative analysis will help explain effectiveness and implementation outcomes concurrently [43,61]. Contextual factors that support or hinder engagement, adoption (use of interventions), feasibility, and effectiveness will be described. We will examine general barriers and facilitators and specific patterns for workers in the nursery and landscape sectors. The qualitative analysis will be used to develop a comprehensive matrix of team context, organization, and individual characteristics to explain effectiveness of interventions and implementation results. Using directed deductive content analysis, initial codes will be developed from analysis of preparatory interviews for (1) contextual factors; 2) barriers and facilitators contributing to the degree of impact of the interventions; and (3) opinions of ease of use, overall satisfaction, and reasons for engagement, adoption, and feasibility results. We will use NVivo qualitative analysis software (version 14; Lumivero) to code content and identify categories and subcategories to describe patterns and relationships that emerge. We anticipate comparing themes for (1) intervention groups, (2) participants with different degrees of pain severity and persistence, (3) individuals and teams who adopt and implement the strategies consistently compared to those who do not, (4) individuals who respond positively to the interventions compared to those who do not improve, and (5) subsectors of the industry. Once themes are identified, interconnections, interactions, and relationships will be described and explained. Recommendations for future implementation and sustainability will be confirmed and prioritized.

Results

Preparatory literature searches, stakeholder interviews, and observations were started in January 2023 and completed in August 2023. The stakeholder interviews confirmed the limited formal training for prevention of musculoskeletal repetitive strain injury and overall need for addressing LBP in the industry. The project was funded on September 29, 2023 (CDC NIOSH U54OH011230-07S1), as a core research project for the Southeast Coastal Center for Agricultural Health and Safety. The video recording and creation started in April 2023 and was completed in June 2024. Formative evaluation of drafts 1 and 2 of the videos, revisions, translation into Spanish, and narration were completed in April 2024, and final video edits were completed in June 2024. The first group was enrolled in June 2024. As of December 6, 2024, we have enrolled 14 participants and 4 supervisors from 3 employers. Data collection is anticipated to be completed in late 2027 or early 2028 with plans for final analysis and dissemination of findings shortly thereafter. Qualitative data for Aim 2 will be coded and analyzed progressively for team characteristics and trends.

Discussion

Importance of Study Findings

In this paper, we present the protocol for a randomized within-subject controlled hybrid intervention study with coprimary aims to examine the effectiveness of self-management videos combined with multimodal personalized support compared to self-management videos alone for improving LBP and disability in nursery and landscape workers, as well as to identify contextual factors that impact implementation including engagement, adoption, effectiveness, and feasibility. Improving self-management strategies to reduce transition from intermittent to high-impact chronic LBP will contribute to important Healthy People 2030 objectives [35] while addressing research and practice gaps to mitigate musculoskeletal pain.

In nursery and landscape businesses, prevention of musculoskeletal injuries has not typically received high priority. Despite the size and growth of the industry, horticulture has rarely been included with other agriculture sectors in studies addressing musculoskeletal injury prevalence [5] or risk factors [5,6]. There is a death of intervention studies to prevent or mitigate LBP in agriculture [2,10,66], with few intervention studies specifically targeting nursery and landscape populations [5]. Feasible, easily implemented interventions to manage pain and reduce risk factors are essential for small businesses in the horticulture industry who face major challenges with labor availability. Variability in work environments, seasonal fluctuation in workloads, weather constraints, and productivity requirements make the adaptability, efficiency, and ease of adoption paramount for any training intervention. Current “training on the-job” from more experienced workers and supervisors is challenging with turnover and difficulty retaining experience workers who can pass on best practices. Efficient delivery methods providing structured evidence-based information and strategies would provide consistency. Short videos tailored for both sectors are a pragmatic option to address the needs while remaining flexible for work priorities and productivity. This study will contribute to knowledge about the effectiveness of interventions specifically tailored to the characteristics, work tasks, and work settings for these workers.

Awareness of the risks and consequences will highlight the importance of nonopioid alternatives [14]. Opioid education is not effectively integrated into workplace safety training but embedding discussion of opioid risk within a more holistic approach to prevention and mitigation of LBP may promote help-seeking behavior and reduce stigma and communication barriers [20]. Introducing the risk of opioids along with options to manage pain using self-management and ergonomic alternatives is likely to be received more positively than opioid education alone.

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Awkward postures, repetitive actions, and intermittent lifting, digging, or shoveling have been identified as inherent ergonomic risk factors for landscape workers [5]. Similar risks are present in nursery work with awkward stooped trunk postures, repetitive low load lifting, and intermittent heavy lifting [10,11]. Larger companies often have more access to mechanical equipment, while small work units seldom have sufficient resources for major engineering redesign recommended in the NIOSH hierarchy of controls [6]. Modifying the way people work or reinforcing the use of available equipment in small businesses is, therefore, more realistic than major equipment modifications. Typically, smaller companies do not have access to ergonomic and safety experts, and may not provide health care benefits. Feasible, easily implemented interventions to manage pain and reduce risk factors are, therefore, needed for businesses in the nursery and landscape industry.

PE approaches involve workers in identifying possible solutions to reduce work-related stress and have been used in a variety of ways in large manufacturing, construction, and health care settings [83-86]. The evidence for effectiveness of PE in large corporations is mixed for group changes for time off work, return to work, self-assessed productivity, and prevalence of LBP [85,87-94]. In contrast, PE has been found to improve overall perceived health, decrease back pain intensity, and reduce absences due to back pain [94]. Comprehensive PE interventions are often time-consuming and challenging to implement across large corporations. Solutions suggested by workers may be feasible, but changing organizational processes can be difficult. Thus, PE has been suggested to be especially beneficial for small teams, enterprises with restricted finances, and rural or less developed areas [86,95,96]. Although PE has not been studied extensively in agricultural settings [39,41,86,95,96], there is some evidence of lowered ergonomic risk and improved management of symptoms among farmers [86]. In another study, construction workers reported significantly less general fatigue after a typical workday, and increased influence on their work compared to controls [81]. A modified approach to encourage workers to choose relevant options for changing their work activities to minimize ergonomic stresses may be feasible to empower nursery and landscape workers to manage back pain [40].

In this study, changes in the primary (pain, disability, and medication use) and secondary (pain-related anxiety, coping, self-efficacy) measures from the preintervention to postintervention timepoints will be compared to a within-subject baseline within-subject period. We will also compare 2 forms of training implementation—video modules alone and video enhanced with multimodal personalized support. We hypothesize that the video + support will facilitate greater engagement, and increased adoption, thereby contributing to greater reductions in work task pain and disability compared to a baseline control period than the video alone. If either intervention is effective, mitigating pain and enhancing knowledge, skills, and attitudes to manage pain successfully is likely to impact quality of life, productivity, and retention. Improvements in pain and disability could result in decreased use of pain medication and other substances, important outcome public health priorities. Even if observed differences are not significant, identifying characteristics of those who respond will contribute evidence for preventing the transition from low to high-impact chronic pain. The mixed methods will help explain results and surrounding inner and outer contextual factors, facilitators and barriers contributing to implementation success for individuals, teams, and specific strategy choices [44]. Qualitative analysis will also inform recommendations and provide ideas for sustainability of effective interventions. Analysis from multiple perspectives will also help explain emerging or complex factors inherent with the dynamic workplace environment and business models, to guide decisions for others considering these approaches. If self-management is effective for horticulture workers (or specific subgroups), simultaneously studying implementation outcomes (engagement, adoption, and feasibility) will facilitate translation of the intervention from research to practice and scaling to the workforce. Potential limitations that may impact the success of this study are consistent with other hybrid effectiveness implementation studies. First, although we anticipate that our recruitment goals are achievable, external factors such as productivity requirements may impact owner and supervisor willingness to allow workers to participate. As attrition is expected, we plan to enroll additional participants to achieve adequate power. We will emphasize benefits for employers such as limiting absenteeism, improving retention, and reducing potential risks of medication or substance use to manage pain while working. Second, we also anticipate that owners and supervisors who agree to participate are already committed to supporting workers. This may result in a sample of workers associated with positive contextual factors that may not be generalizable to all employers. However, these factors will be documented to help interpret results from an implementation perspective. Third, weather and seasonal variations are likely to impact productivity and, therefore, willingness to participate, particularly for landscape companies. These factors will also impact scheduling for data collection, for example, hurricane or weather delays. We have built in a 2-week window for data collection to accommodate the scheduling but there may be a need for additional flexibility. Finally, cultural, language, and educational literacy variations are expected. All instruments and materials have been translated and checked thoroughly while research assistants who speak Spanish fluently are essential.

Conclusions

Interventions to reduce the burden of LBP that consider the unique characteristics and business models within the nursery and landscape sectors are lacking. Given the high incidence of LBP, the risk of opioid use, impact on labor availability and productivity, and the limited attention to musculoskeletal disorders in these sectors, this study will provide valuable information to address both employer and worker needs. The hybrid type II effectiveness and implementation study will investigate the effectiveness of self-management interventions for pain and disability, along with the engagement, adoption, and feasibility, for 2 forms of implementation while also documenting the context, facilitators, and barriers for nursery and landscape businesses [44]. Increased awareness of opioid risk and options for alternate nonpharmacological strategies to manage pain will also provide an important contribution to a

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high priority public health challenge. We anticipate self-management will result in reduced pain and disability. Further, targeting self-management can empower workers and improve pain coping, reducing pain anxiety, depression, and associated use of pain medications. Short video training modules presenting realistic strategies to manage pain and limit work stress are likely to be feasible in the workplace while multimodal personalized support is likely to facilitate engagement and adoption of context-specific solutions. The qualitative methods used will help elucidate whether these options are feasible for small- to medium-sized horticulture businesses, document barriers and facilitators, and describe the inner and outer contextual factors influencing adoption and effectiveness. If the video and multimodal personalized support intervention is more effective than viewing training modules alone, this knowledge will inform best practices and may be easily adapted for other physically challenging agricultural sectors.

Acknowledgments

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Data Availability

Deidentified data will be made available to researchers upon written request. A data-sharing agreement will be developed and signed that provides commitments to (1) use the data only for research purposes and not to identify any individual; (2) securing the data using appropriate computer technology and security protocols; and (3) destroying or returning the data after analyses have been completed. This data sharing plan may be modified as recommended by the funding agency or university policies at the time of study completion.

Authors' Contributions

Study conceptualization, funding acquisition, and methodology was performed by KD, JMB, BH, KKG, and HLR. The data analysis plan was developed by KD, JMB, BH, KKG, HLR, and YY. with project administration contributions from KD and JMcB. The original draft was created by KD, with full writing, review and editing completed by KD, JMB, JMcB, KKG, HLR, and YY. All authors reviewed and approved the submission.

Conflicts of Interest

None declared.

Multimedia Appendix 1
STARI (Standards for Reporting Implementation Studies) checklist.
[PDF File (Adobe PDF File), 140 KB - resprot_v14i1e64817_app1.pdf]

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Abbreviations

CDC: Centers for Disease Control and Prevention
GLMM: generalized linear mixed model
LBP: low back pain
LMM: linear mixed model
NIOSH: National Institute of Occupational Health and Safety
PE: participatory ergonomic
PSFS: Patient Specific Functional Index
REBA: Rapid Entire Body Assessment
REDCap: Research Electronic Data Capture
StaRI: Standards for Reporting Implementation Studies

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Protocol

Novel Smartphone App and Supportive Accountability for the Treatment of Childhood Disruptive Behavior Problems: Protocol for a Randomized Controlled Trial

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Abstract

Background: Although evidence-based treatments have been developed for childhood behavior problems, many families encounter barriers to treatment access and completion (eg, local availability of services, transportation, cost, and perceived stigma). Smartphone apps offer a cost-efficient method to deliver content to families.

Objective: The aim of this study is to evaluate the effectiveness of the UseIt! mobile health system as both stand-alone and coach-assisted interventions via a randomized controlled trial. The UseIt! System is designed to reduce disruptive behaviors in young children.

Methods: A nationwide sample of parents of children aged 5 years to 8 years with disruptive behaviors (N=324 dyads) are randomly assigned to the stand-alone app (UseIt!; n=108), the coach-assisted app (UseIt! plus supportive accountability; n=108), or the control app (mindfulness app; n=108). The UseIt! App provides parents with tools and troubleshooting to address disruptive behaviors, along with a behavior diary to track behaviors and strategies over time. The coach-assisted condition includes a bachelor's level paraprofessional who provides weekly phone calls to promote engagement with the app. The control condition is composed of a mindfulness app. The web-based, self-assessed outcome measures (post treatment and 6-month follow-up) include measures of app usage, parenting knowledge (eg, knowledge of parent management training and cognitive behavioral therapy skills), and strategies (use of evidence-based parenting strategies), symptom reduction (eg, behavior problems), and parent mental health (eg, anxiety, stress, and depression). We hypothesize that both intervention conditions will show greater parent knowledge and use of skills along with greater symptom reduction relative to the control condition. Further, we hypothesize that those assigned to the coach assisted condition will report greater knowledge, skill use, and symptom reduction than the stand-alone app. We will use intent-to-treat analyses to regress outcomes on study conditions to evaluate for differences across conditions.

Results: Recruitment of study participants began in December of 2022 and is ongoing. We have recruited over half of our intended sample of 324 parent-child dyads (n=214) as of December 2024. These dyads have been randomly allocated to each of the intervention conditions, with 71 assigned to the coach-assisted condition, 72 assigned to the stand-alone app, and 71 assigned to the control app condition. Data collection is projected to be completed by late 2026.

Conclusions: The current study aims to address a gap in the literature regarding the feasibility, effectiveness, and utility of a smartphone app that includes a coach-assisted arm. Digital therapeutics have the potential to enhance the reach and scalability of skills-based psychosocial interventions. Findings from this study will advance scientific knowledge and have implications for clinical practice.

Trial Registration: ClinicalTrials.gov NCT05647772; https://clinicaltrials.gov/study/NCT05647772

International Registered Report Identifier (IRRID): DERR1-10.2196/67051

(JMIR Res Protoc 2025;14:e67051) doi:10.2196/67051

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KEYWORDS

mobile health; disruptive behaviors; parent management training; randomized controlled trial; externalizing behavior

Introduction

Background and Rationale

In the United States, approximately 1.5 million school-age children meet *DSM-5* (*Diagnostic and Statistical Manual of Mental Disorders* [Fifth Edition]) diagnostic criteria for a disruptive behavior disorder (DBD) [1]. DBDs, a category of disorders that broadly involves problems concerning the self-control of behaviors (eg, conduct disorder [CD] and oppositional defiant disorder [ODD]), account for more than half of all mental health referrals for children [2,3]. Longitudinal studies reveal that these problems in early childhood can be risk factors for persistent problems later in life, including substance use disorders and internalizing disorders, if left untreated [4]. DBDs are typically treated with psychosocial evidence-based therapies [5] that include parent management training (PMT) skills (eg, praise, rewards, consequences, and time-outs) and cognitive behavioral therapy (CBT) skills (eg, problem-solving and emotion labeling) [6]. Meta-analyses point to the substantial effectiveness of these interventions at reducing symptoms and maintaining treatment gains over time [7,8]. Despite the effectiveness of evidence-based treatments, many families do not have access to these services, and often stop attending or fail to practice new skills between sessions. Barriers to access include local availability of services, transportation, cost, and perceived stigma. Barriers to noncompletion include poor motivation and low engagement, along with competing demands for time, transportation problems, and copayment costs [9].

The Promise of Digital Therapeutics

Recent advances in technology, in particular mobile health (mHealth) systems, have the potential to overcome these barriers and promote better data collection for researchers [10]. mHealth technologies, including smartphones, create an opportunity to develop personalized interventions that are delivered to families in their day-to-day settings [11]. A smartphone-based mHealth system has numerous potential advantages for improving access to, and engagement in, evidence-based treatments for childhood behavior problems. Such applications can deliver content to improve understanding of skills, provide opportunities for learning through skills practice, and give feedback to families regarding areas for improvement [12,13]. In a recent meta-analysis, of 25 clinical trials, mobile technology use was associated with superior treatment outcome across all study designs and types of control conditions (effect size=.34) [14]. mHealth technologies can also be used to collect data on between-session treatment adherence and skills practice. Evaluating the extent to which patients and families are using the skills they are learning outside of treatment sessions is especially important for psychosocial treatments for disruptive behavior problems which are overwhelmingly skills-based. Remote digital assessments have many advantages over traditional retrospective self-reports including reduced recall bias, the ability to obtain a more representative sample of behavior across situations and contexts, and the ability to track changes in behavior [15-17].

Rigorous evaluations of mHealth interventions targeting child behavioral concerns are in their nascent stage. A 2024 systematic review of mHealth interventions targeting behavioral problems in youth indicated a wide range of effect sizes, from small to large, across the 11 studies reviewed. Most sample sizes were small (ie, less than 100), and the few larger studies did not focus on clinical outcomes (eg, satisfaction, acceptability, and app usage, without behavioral outcomes) [18]. Other recent studies reflect similar findings (ie, improvements in child and parental symptoms, with a wide range of effect sizes), but have similar limitations (ie, small sample sizes, outcome measures focused on satisfaction or acceptability of apps rather than empirically based measures of symptom improvement) [19-22].

The Role of the Coach in mHealth

There is growing evidence in the field of digital therapeutics that some degree of human interaction is important to sustain app usage and achieve meaningful outcomes [23-25]. Although various models have been proposed, the “Coaching” model affords many of the benefits of human interaction (eg, support and accountability) at a level of service that remains highly scalable [23]. Mohr’s Supportive Accountability (SA) Model, which is flexible and can be tailored to clinical conditions and service users, details that the intervention is supported by a coach who provides a social presence and accountability to boost motivation and engagement. Effectiveness studies have shown that various paraprofessionals can successfully be trained as coaches for a wide range of interventions and clinical populations [23].

Previous Pilot Trials of the UseIt! mHealth System

The UseIt! app combines aspects of PMT and CBT to provide parents with evidence-based skills to decrease disruptive behaviors in their children. To date, we have completed 2 pilot randomized controlled trials (RCTs) to test preliminary target engagement and effectiveness of the UseIt! mHealth system. The first trial tested the UseIt! mHealth system as a stand-alone intervention (N=34). Parent-child dyads enrolled in the study and were randomly assigned to either the UseIt! mHealth app condition (n=17) or to a waitlist condition (n=17). Overall, results supported the feasibility of the intervention, but attrition was high in the waitlist control group. This informed our decision to have an active control group rather than a waitlist control group in the current study. The second pilot trial tested the UseIt! mHealth system as an adjunct to therapy in community settings (N=39 parent-child dyads). Though treatment targets moved in the expected direction, high clinician turnover in community settings limited the sustainability and scalability of this approach. This informed our decision to include a bachelor’s level paraprofessional “coach” rather than a clinician in this study.

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Study Aims and Hypotheses

Primary Aim

We aim to evaluate the effectiveness of the UseIt! mHealth system as both a stand-alone (n=108) and coach-assisted (n=108) intervention compared with a control app condition (n=108). We expect that (1) the 2 UseIt! intervention conditions will score higher on parenting knowledge (primary outcome) and show greater posttreatment reductions in disruptive behavior symptoms (secondary outcome) compared with the control condition, and (2) the coach-assisted UseIt! condition will score higher on parenting knowledge and show greater posttreatment reductions compared to the stand-alone UseIt! condition.

Secondary Aims

We will also test mechanisms of therapeutic change. In particular, we will test whether gains in knowledge of parenting skills are associated with reductions in disruptive behavior symptoms. Finally, we aim to evaluate the effectiveness of the components of UseIt! mHealth system. We will compare app usage across the stand-alone and coach-assisted conditions and test whether the app usage indices are associated with target engagement, knowledge of parenting skills, and symptom reduction at post-treatment. We expect that families who use the app more often will have higher skill acquisition and usage scores at post treatment ("dose" effects) though we do not have specific hypotheses regarding individual app features.

Methods

The UseIt! Smartphone App

The UseIt! system includes a free cross-platform mHealth app that runs on both iOS and Android devices. The app is securely connected to a portal where app feature usage is stored. The portal was designed for the research team to track and monitor the usage of the app by parents. The app contains six features: (1) a troubleshooting guide that provides detailed skill recommendations for problem situations, (2) a behavior diary for tracking behaviors and skills used each day, (3) a digital library that provides definitions and instructions for each skill, (4) a point counter for parents to award points to their children, (5) a skills-alarm for reminding parents to practice the various skills, and (6) a timer for use with parenting skills (eg, time-outs, managing screen time, routines). Users can examine diary entries, viewpoints awarded, and set the skills alarm through the app. See Figure 1 for a screenshot of the app's home page.

Figure 1. Home page of the UseIt! smartphone app.

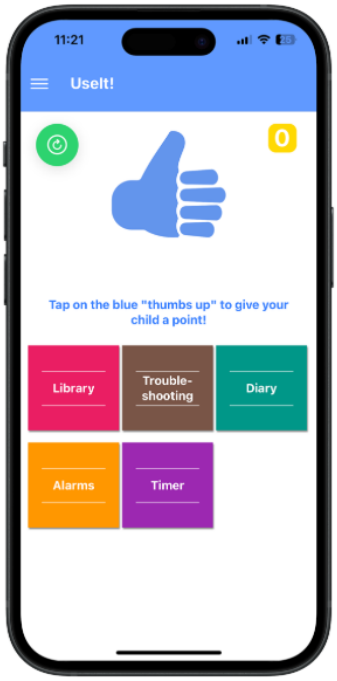

Troubleshooting Guide

The UseIt! troubleshooting guide contains information to help parents effectively respond to problem behaviors. Parents are presented with a list of potential negative behaviors (eg, bullied or fought). After selecting a behavior, appropriate skill options (eg, time-out) are displayed with tips to effectively apply each skill. Once a skill has been used and the behavior has stopped, parents are reminded to praise their child for positive behaviors (Figure 2).

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Figure 2. Troubleshooting guide.

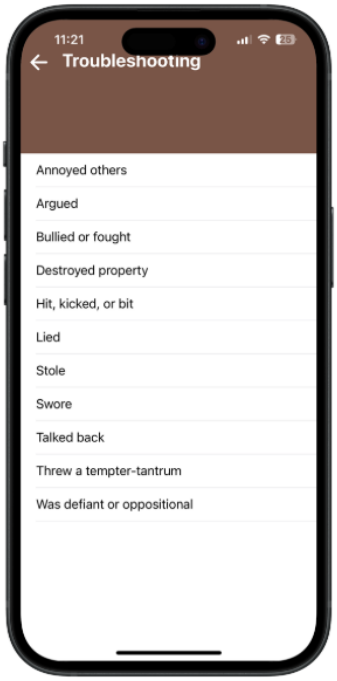

Behavior Diary

The behavior diary cues participants (via a notification) to complete a series of questions about behaviors and PMT and CBT skills used each day. The results are displayed graphically and can be reviewed by the user to track progress over time. This allows the user to keep track of what skills the family has tried for different behaviors (both positive and negative child behaviors) and which ones have been helpful in various contexts (Figure 3).

Figure 3. Daily behavior diary.

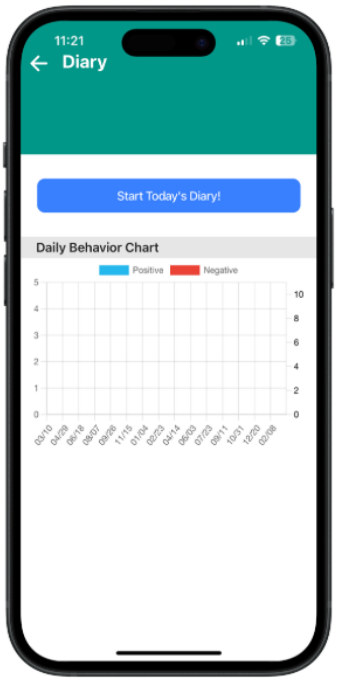

Digital Library

The UseIt! digital library provides detailed information about using strategies for positive and negative child behavior. Each skill is defined and presented with tips for how and when to effectively use each skill. The digital library contains more information than the troubleshooting guide and is designed as an information source for reviewing PMT and CBT topics (Figure 4).

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Figure 4. Digital library.

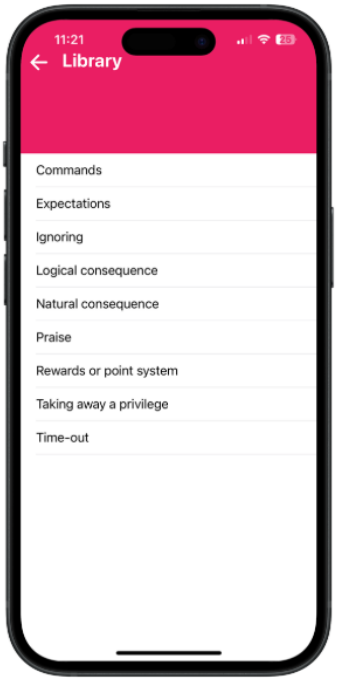

Point Counter

Treatment for disruptive behavior disorders typically includes prizes for treatment adherence, positive behaviors, and skill use. Parents can award points to children for target behaviors (eg, cleaning dishes) and skill usage. The UseIt! point counter features an on-screen button ("Give your child a point") which parents press to reward their child with a point. The feature functions as a digital rewards program that parents can use to keep track of points and reward their children. See Figure 1 for a view of the point counter window.

Skills Alarm

Skills alarms can be set at any time via the app. Users can set dates and times for notifications to activate. These notifications remind parents and children to practice specific skills throughout the week (eg, "remember to praise your child"). Parents are able to view a list of active and inactive alarms (Figure 5).

Figure 5. Skills alarm.

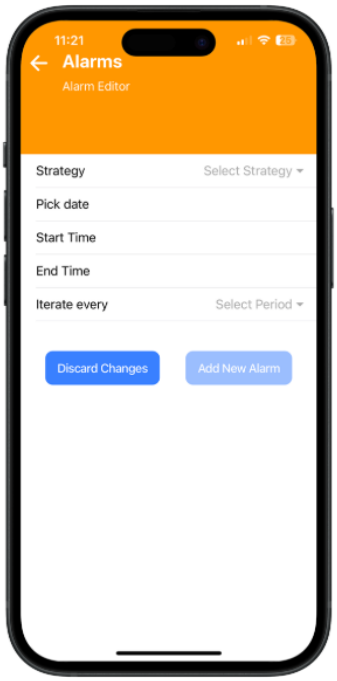

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Timer

Timers can be set for use with a variety of skills (eg, time-outs, screen time management, and routines) to promote use of the skills.

Recruitment

We use a 2-pronged recruitment strategy to maximize enrollment. The two recruitment avenues are (1) the Clinical and Translational Science Institute patient registry (Pitt+Me) at the University of Pittsburgh and (2) BuildClinical. The Clinical and Translational Science Institute patient registry (Pitt+Me) is an institutional research participant registry that uses enhanced study descriptions and social media to engage the community in research. BuildClinical is a clinical trial recruiting system that helps investigators recruit participants for clinical trials more efficiently. Using study-specific digital advertisements displayed on search engines, health websites, and social media platforms, BuildClinical generates participant referrals. BuildClinical also provides tools to streamline the recruitment and prescreening process. The platform stores information in a HIPAA (Health Insurance Portability and Accountability Act)-compliant manner and allows for remote enrollment.

Participant Eligibility

Inclusion criteria for this study are that (1) parents or guardians must have a child between the ages of 5 and 8 years, (2) the child must be above the 90th percentile for either or both ODD and CD on the Vanderbilt Assessment Scale, (3) the child must be in residence with the parent or guardian for at least 80% of the time, (4) the parent or guardian must consent to study participation, and (5) the parent or guardian must have a smartphone device with daily internet access. Exclusion criteria are the child (1) having a known preexisting behavioral or mental health diagnosis requiring alternative treatment (eg, bipolar disorder, major depression, and pervasive developmental disorder) or (2) currently receiving treatment for childhood disruptive behavior.

Sample Size Determination

Power analyses were conducted in PASS (version 13.0.8; NCSS) to ensure that the sample size is adequate to test the primary hypotheses with adequate statistical power. All analyses assumed 0.80 power and 2-sided tests. Estimated sample sizes are determined based on an assumed 5% attrition and missing data post treatment (102 per group) and 10% total attrition at 6-months (97 per group). Using an analysis of covariance approach to test for differences across 3 groups post treatment (n=108 each) and assuming R^2=0.20 from 5 covariates, we expect 0.80 power (α=.05) to detect an effect size difference of Cohen f=0.16 among the 3 groups, f=0.14 (d=0.28) between both UseIt! treatment groups versus the control group, and f=0.18 (d=0.36) between any 2 groups.

Design

The study is a RCT with 3 conditions. Parents of children aged 5 to 8 years (n=324) are randomly assigned to one of 3 conditions: a stand-alone UseIt! app condition, a UseIt! app and Coach condition, and a control app condition (Smiling Mind app). Data are collected via web-based surveys at baseline, post treatment (4 months after baseline), and at 6-month follow-up. Randomization takes place after the baseline is completed.

Study Conditions

Stand-Alone UseIt! App Condition

Participants are assigned to the UseIt! App as a stand-alone intervention for 4 months.

UseIt! App + Coaching Condition

Participants are assigned to the UseIt! App and are provided with an mHealth "Coach" for 4 months. The primary objective of the coaching condition is to promote engagement with the UseIt! mHealth platform. The mHealth coach is a bachelor's-level paraprofessional with a degree in psychology or an allied discipline (eg, social work) who provides support to parents in the coach-assisted condition. We selected a bachelor's-level coach over a master's-level coach to enhance the scalability of this intervention condition. The coach uses the SA coaching model using the training guidelines outlined by Dopke and colleagues [26]. During the intervention phase of the study, parents are contacted by the coach once per week by phone and also allowed to contact the coach during regular business hours. The coach provides motivation and accountability but does not provide therapeutic or clinical support. The primary goal of the coach is to increase participant engagement with the UseIt! mHealth system. Specific coaching content and tasks include (1) social support, (2) promoting engagement with the app, (3) goal setting (4) monitoring progress, and (5) encouragement and motivation. Parents are provided with appropriate referrals for any crises. The coach is instructed to respond to questions that lie outside the domains of motivation and accountability (ie, content-specific therapeutic support) by redirecting the parent to the content-specific app features (ie, Troubleshooting and Library). Only the parents interact with the coach. To maintain the scalability of the condition, the target time spent with each family is 15-30 minutes per week. The coach maintains a "coach-log" to track the frequency, duration, and content of contact with each participant.

Control Condition (Smiling Mind App)

Parents in the control app condition are assigned to use a mindfulness app called Smiling Mind [27] for 4 months. We selected a mindfulness app because it is an active control condition, but one that we do not expect to engage the same treatment targets as the UseIt! mHealth system. Meta-analytic findings indicate that mindfulness-based interventions for school-age children are associated with medium to large effect sizes for disruptive behaviors [28]. For parents, dispositional mindfulness has been found to be associated with lower rates of children's externalizing and internalizing problems [29], and a mindfulness-based program was associated with decreased parent reports of child attention-deficit/hyperactivity disorder symptoms and decreased parental stress [30]. Other studies with youth found that a combined approach (parent and youth mindfulness training) improved externalizing problems and attention [31]. As an active control condition, we expect that a mindfulness app will likely have some influence on parenting

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and child behavior. This provides us with a rigorous control condition while also allowing us to test the specificity of target engagement. We expect the Smiling Mind app will only enhance mindfulness, but not PMT and CBT skills (other than mindfulness). We selected the Smiling Mind app [27] in particular because (1) it can be downloaded at no cost, (2) it is available for both Android and Apple (iPhone) devices, and (3) app-use can be tracked.

Study Procedures and Randomization

Participants provide their contact information to the Pitt + Me or BuildClinical systems after accessing the study advertisement. Trained research assistants then contact families and conduct the initial screening to determine study eligibility. If determined eligible, a future call is scheduled to obtain consent from the parent, and assent from the child to participate. After consent, parents are provided a Qualtrics link to complete the initial baseline assessment. After completion of the assessment, families are randomly assigned to group 1 (standalone UseIt! app; n=108), group 2 (UseIt! app + coach; n=108), or group 3 (control app condition; n=108). We use stratified randomization to ensure that the groups are equivalent on key clinical features (screening severity and referral source (ie, Pitt + Me or BuildClinical). Parents assigned to the Coach condition are walked through the initial setup and login process, along with a brief training on how to use the applications over the phone. Families can be set up and trained in approximately 30 minutes. If parents cannot be reached after 3 weeks, instructions are sent via email. Parents assigned to the stand-alone UseIt! app condition are sent a tutorial video with the same information. Parents use the app condition assigned for 4 months before the administration of the posttreatment assessment, via Qualtrics. Six months following the posttreatment assessment, parents again are prompted to complete the 6-month follow-up assessment via Qualtrics.

Measures

Table 1 for a summary of study constructs, measures, and assessment time points.

Table 1. Measures.

Construct	Measure or instrument	Time point
PMT[a] and CBT[b] skill knowledge	Knowledge of Effective Parenting Test	Baseline, post treatment, 6-month follow-up
Symptom severity	Vanderbilt Assessment Scale	Baseline, post treatment, 6-month follow-up
Parenting practices	Alabama Parenting Questionnaire	Baseline, post treatment, 6-month follow-up
Parent depression	7-item Generalized Anxiety Disorder Scale	Baseline, post treatment, 6-month follow-up
Parent anxiety	9-item Patient Health Questionnaire	Baseline, post treatment, 6-month follow-up
Parenting stress	Parental Stress Scale	Baseline, post treatment, 6-month follow-up
Social support	Social Provisions Scale	Baseline, post treatment, 6-month follow-up
PMT and CBT skill use	Parenting Skill Use Diary	Baseline, post treatment, 6-month follow-up
App use	Automatically recorded	Active app phase
Mindfulness	Mindful Attention Awareness Scale	Baseline, post treatment, 6-month follow-up
Service use	Service Assessment for Children and Adolescents	6-month follow-up
Supportive accountability	Supportive Accountability Inventory	Post treatment (coach condition only)
Usability	Post-Study Usability Questionnaire	Post treatment
Technological literacy	Technology Self-Assessment Tool	Baseline

[a]PMT: parent management training.

[b]CBT: cognitive behavioral therapy.

Primary Outcome: PMT and CBT Skill Knowledge

The knowledge of effective parenting test [32] is a 21-item measure of parental knowledge of effective parenting skills. The measure was developed as a potential treatment target for evidence-based psychosocial treatments of disruptive behaviors in children. The knowledge of effective parenting test assesses parental knowledge of domains including praise, rewards and point systems, attending and ignoring, commands and expectations, consequences, and time-outs. Parents are presented with a series of video and text-based parenting scenarios and questions with 4 multiple-choice response options. Scores range from 0 to 21. The measure has good reliability (Cronbach α=0.84). The measure has also demonstrated convergent validity with other measures of parenting knowledge and parenting-related constructs (eg, child behavior and parental psychopathology).

Secondary Outcomes

Symptom Severity

The Vanderbilt Assessment Scale-Parent Report (VASPR [33]) is a 55-item parent-report screen for attention-deficit hyperactivity disorder (ADHD), ODD, and CD. It also includes 7 items on internalizing symptoms and 8 items on school performance and social functioning. Symptom items are rated using a 4-point scale and the performance items are rated on a

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5-point scale. The measure has Cronbach alphas ranging from 0.79 to 0.95 and strong evidence of construct validity.

Parenting Practices

The Alabama Parenting Questionnaire (APQ [34]) is a 42-item measure that assesses five dimensions of parenting: (1) positive involvement, (2) monitoring, (3) positive discipline, (4) consistency, and (5) corporal punishment, using a 5-point scale ranging from 1 to 5. The internal consistency of the scale is acceptable with α values for the 5 domains ranging up to .80. The measure has well-established construct validity.

Parent Depression

The Patient Health Questionnaire-8 (PHQ-8 [35]) measures symptoms of depression using a 4-point scale from "not at all" to "nearly every day." Total scores range from 0 to 24. The measure has a reported Cronbach α of .82 and strong construct validity.

Parent Anxiety

The General Anxiety Disorder-7 Scale (GAD-7 [36]) is a 7-item measure of anxiety. Items are rated on a 4-point scale from "not at all" to "nearly every day." The measure includes an item to assess the duration of anxiety symptoms. The measure has excellent internal consistency (Cronbach α=0.92), good test-retest reliability (intraclass correlation [ICC]=0.83), and strong convergent validity with other measures of anxiety.

Parenting Stress

The Parental Stress Scale (PSS [37]) is an 18-item measure of stress related to parental experiences. Items are rated on a 5-point scale from "strongly disagree" to "strongly agree." Scores range from 18 to 90. The internal consistency of the scale is acceptable with a Cronbach α of 0.83, a test-retest reliability of 0.81 (ICC), and strong convergent validity of both other parental stress measures (ie, Parental Stress Index), and other measures related to parenting stress (eg, loneliness, marital satisfaction, and social support).

Social Support

The Social Provisions Scale [38] is a 24-item measure that assesses 6 dimensions of support, including attachment, social integration, opportunity for nurturance, reassurance of worth, reliable alliance, and guidance. The measure uses a 5-point scale ranging from 1 to 4, strongly disagree to strongly agree. The measure has been validated across samples, with Cronbach α ranging from 0.65 to 0.76 for the 4 subscales, and a total reliability estimate of 0.91. The measure also demonstrated convergent validity with related measures of social support.

PMT and CBT Skill Use

The Parenting Skill Use Diary [39] assesses daily use of parenting skills in everyday parenting contexts (eg, child sharing and helping, hitting, and fighting). Respondents are presented with a checklist of behaviors to report on for the past week. For each behavior they select, they are next asked to identify which skills (eg, praise, reward, time-out, and loss-of-privilege) they used in responding to the behaviors. The instrument has demonstrated the ability to capture significant between-person variability in appropriate PMT skills. A weekly summary score discriminated between parents or guardians whose children screened positive versus negative for CD (area under the receiver operating characteristic curve [AUC]=0.72) and ODD (AUC=0.70).

App Use

Parents assigned to both UseIt! conditions (ie, stand-alone app and coach conditions) have their data stored on the secure portal, accessible to the research team. We collect the behavior diary tracked by parents, which displays data on child behavior (both positive and negative) along with CBT and PMT skills. We are also collecting data on time spent on the app along with modules accessed. App usage (eg, modules used and time spent) is also tracked for the Smiling Mind app (control condition).

Mindfulness

The Mindful Attention Awareness Scale [40] is a 15-item scale designed to assess core characteristics of mindfulness. Parents are asked how often they are engaging in a variety of mindfulness-related behaviors, such as finding it difficult to stay focused on what is happening in the present moment, finding themselves preoccupied with the future or past, and not noticing feelings of physical tension or discomfort until the really grab their attention. The measure's response scale ranges from 1 (almost always) to 6 (almost never). The measure is scored as an average of all 15 items. The measure has adequate validity (Cronbach α=0.87 and convergent validity with other measures of mindfulness (eg, mood disturbances and stress).

Service Use

An abbreviated version of the Service Assessment for Children and Adolescents (SACA [41]; 25 items) was used to measure mental health service usage. The SACA asks about various inpatient and outpatient treatment services for mental or behavioral health problems that have been used by the child in the past 6 months [41]. Most items are yes or no questions. The measure is a widely used research tool with strong evidence of reliability and validity.

Supportive Accountability

The Supportive Accountability Index (SAI [42]) is an 8-item measure of how well a given platform functioned to help keep parents accountable to accomplish a given goal. The measure was included to assess the effectiveness of the Coach in the coach condition of the app in helping to keep parents accountable with skill learning and use. Items are rated on a 1-7 scale, from 1=strongly disagree to 7=strongly agree. Total scores are summed, ranging from 8-56. The measure has acceptable validity (Cronbach α=0.68) and good convergent and divergent validity.

Usability

The 19-item Post-Study System Usability Questionnaire (PSSUQ [43]) is used to assess overall user satisfaction with the UseIt! apps. Internal consistency of the PSSUQ is excellent (α=.91 to .96).

Technological Literacy

The Technological Self-Assessment Scale (TSAT [44]) is a 13-item parent report screen for technological ability. The

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measure was created for this study by the research team to provide an indicator of parent knowledge and experience with their computers and phones. For example, items ask parents if they know how to search for information on the internet if they have ever downloaded an app, and if they have social media accounts. Items are scored Yes or No, and scores range from 0 to 13.

Data Analyses

Primary Analyses

Our primary analytic strategy will use intent-to-treat analyses. We will examine reasons for any missing data and perform multiple imputation (eg, Multiple Imputation for Chained Equations [45]) for data missing at random. To evaluate the effectiveness of the UseIt! mHealth system as both a stand-alone (n=108) and coach-assisted (n=108) intervention compared to a control app condition (n=108), we will regress the primary and secondary outcomes on the study condition. We will also perform a priori tests to compare both UseIt! groups to the control and to compare the coach-assisted and stand-alone UseIt! groups. Cohen *d* effect sizes will be estimated for between-group differences as well as pre-post changes within each group.

Secondary Analyses

We will also test whether gains in knowledge of parenting skills are associated with symptom reduction. We will regress the posttreatment knowledge of parenting skills on study condition, pretreatment knowledge, and their interaction. We will also compare app usage across stand-alone and coach-assisted conditions and test whether the app usage indices are associated with target engagement and symptom reduction at post-treatment. App usage outcomes will include the number of each of the app features that are used, along with frequency and duration (in minutes). We will use generalized linear models with the appropriate link (eg, log link for count data and identity link for continuous outcomes) to regress each usage outcome on study condition (stand-alone versus coach).

Ethical Considerations

Ethical approval has been obtained from the institutional review board at the University of Pittsburgh (protocol # STUDY22030138). Informed consent from parents is obtained by trained research staff. So as not to artificially inflate the rates of app usage, participants are not compensated for using the app but only for assessments completed. Participants in each condition are compensated US $20 for baseline assessment completion, US $40 for the postassessment, and US $60 for the 6-month follow-up assessment. All study data are deidentified and stored securely.

Results

The study was funded in September 2022. Study recruitment began in December 2022. As of December 2024, we have recruited over half (n=214) of our target sample of 324 parent-child dyads. Of these, 72 parents have been assigned to the stand-alone condition, 71 to the coach condition, and 71 to the control condition. Recruitment is ongoing and completion is expected in another 12 to 14 months. Follow-up data collection is expected to be completed by the end of 2026. Figure 6 displays the trial flowchart for this study.

Figure 6. Trial flowchart. FU: follow-up.

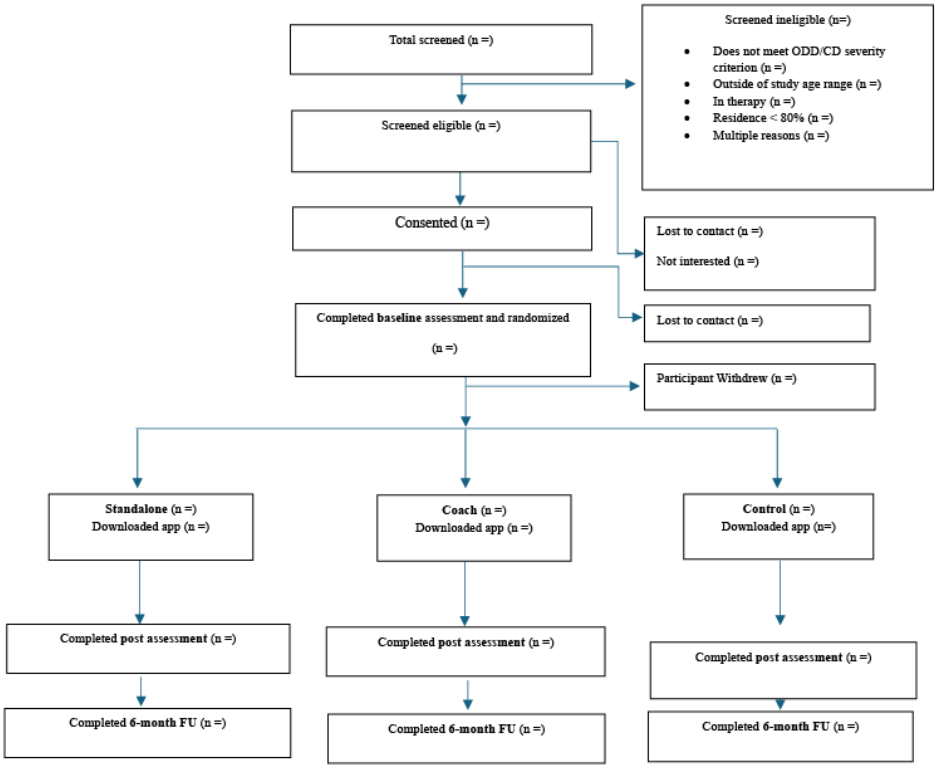

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Discussion

mHealth parenting programs have the potential to improve outcomes for parents and children [14]. Further, supportive accountability, defined as a degree of human interaction throughout the program, has the potential to enhance outcomes for mHealth interventions by increasing motivation and engagement [23]. The current study aims to add to the literature base on effective mHealth interventions to treat disruptive behaviors in children. The study will allow us to test the degree to which the UseIt! app can modify parenting (ie, skill acquisition and usage) and whether such target engagement is associated with symptom reduction. The UseIt! mHealth system also allows researchers unique access to data on child behaviors and parent skills tracked on a daily basis. This data will not only allow parents to track behaviors and skills for themselves (allowing parents to visualize progress) but will also allow researchers a system to track change over time. The coaching model used in the study is highly scalable, providing a flexible model of coaching that can be tailored to a variety of clinical conditions and service settings. We expect that those assigned to the coach condition will have the largest increases in parent knowledge and skill use, along with the largest decreases in child behavior problems. We also expect that those assigned to the UseIt! stand-alone app condition will report greater improvements in parent knowledge, skill use, and child behavioral concerns, compared with the control app condition.

Strengths and Limitations

This study has several strengths and adds to the existing literature. To our knowledge, it is the largest RCT of an mHealth smartphone-based app targeting child behavioral concerns to date. The trial adds to the literature base of the SA model [23] and aims to provide preliminary evidence to the effectiveness of the model in the context of a smartphone-based app targeting parents. We selected clinically relevant outcome measures for the trial, including validated measures of parenting knowledge, parent skill use, parent mental health, and child behavior problems. We also collect app usage data, both for use as a moderator of intervention effects, and to inform future work to promote increased usage in other studies. A few limitations are also worth noting. First, we expect up to 10% attrition over the course of the study. We have taken several steps to minimize attrition, including increasing participant compensation at each time point. We also factored 10% attrition into our power analysis to determine sample size, ensuring that the trial will still be fully powered. Another limitation is that outcome measures are based primarily on parent report. This limitation is mitigated by substantial evidence that parents are accurate reporters of child behavior problems.

Conclusions and Future Directions

In summary, the current study aims to address a gap in the literature regarding the feasibility, effectiveness, and utility of a smartphone app that includes a coach-assisted arm for treating disruptive behaviors in young children. Digital therapeutics have the potential to enhance the reach and scalability of skills-based psychosocial interventions, as even small effects can be meaningful on a population level if the intervention can be delivered efficiently on a large scale at a low cost. The UseIt! mHealth system is able to deliver therapeutic content to parents across a variety of settings and has the potential for meaningful impact. Findings from the current trial will advance scientific knowledge and have the potential to enhance clinical practice.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer-review report from CPDD - Child Psychopathology and Developmental Disabilities Study Section (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 127 KB - resprot_v14i1e67051_app1.pdf]

Multimedia Appendix 2
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 620 KB - resprot_v14i1e67051_app2.pdf]

Multimedia Appendix 3
Spirit Checklist.
[DOC File , 121 KB - resprot_v14i1e67051_app3.doc]

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Abbreviations

ADHD: attention-deficit/hyperactivity disorder
APQ: Alabama Parenting Questionnaire
AUC: area under the receiver operating characteristic curve

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CBT: cognitive behavioral therapy
CD: conduct disorder
DBD: disruptive behavior disorder
DSM-5: Diagnostic and Statistical Manual of Mental Disorders (Fifth Edition)
GAD-7: General Anxiety Disorder-7 Scale
HIPAA: Health Insurance Portability and Accountability Act
mHealth: mobile health
ODD: oppositional defiant disorder
PHQ-8: Patient Health Questionnaire-8
PMT: parent management training
PSS: Parental Stress Scale
PSSUQ: Post-Study System Usability Questionnaire
RCT: randomized controlled trial
SA: Supportive Accountability
SACA: Service Assessment for Children and Adolescents
SAI: Supportive Accountability Index
TSAT: Technological Self-Assessment Scale
VASPR: Vanderbilt Assessment Scale-Parent Report

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Protocol

Healthy Mom Zone Adaptive Intervention With a Novel Control System and Digital Platform to Manage Gestational Weight Gain in Pregnant Women With Overweight or Obesity: Study Design and Protocol for a Randomized Controlled Trial

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Abstract

Background: Regulating gestational weight gain (GWG) in pregnant women with overweight or obesity is difficult, particularly because of the narrow range of recommended GWG for optimal health outcomes. Given that many pregnant women show excessive GWG and considering the lack of a “gold standard” intervention to manage GWG, there is a timely need for effective and efficient approaches to regulate GWG. We have enhanced the Healthy Mom Zone (HMZ) 2.0 intervention with a novel digital platform, automated dosage changes, and personalized strategies to regulate GWG, and our pilot study demonstrated successful recruitment, compliance, and utility of our new control system and digital platform.

Objective: The goal of this paper is to describe the study protocol for a randomized controlled optimization trial to examine the efficacy of the enhanced HMZ 2.0 intervention with the new automated control system and digital platform to regulate GWG and influence secondary maternal and infant outcomes while collecting implementation data to inform future scalability.

Methods: This is an efficacy study using a randomized controlled trial design. HMZ 2.0 is a multidosage, theoretically based, and individually tailored adaptive intervention that is delivered through a novel digital platform with an automated link of participant data to a new model-based predictive control algorithm to predict GWG. Our new control system computes individual dosage changes and produces personalized physical activity (PA) and energy intake (EI) strategies to deliver just-in-time dosage change recommendations to regulate GWG. Participants are 144 pregnant women with overweight or obesity randomized to an intervention (n=72) or attention control (n=72) group, stratified by prepregnancy BMI (<29.9 vs ≥30 kg/m^2), and they will participate from approximately 8 to 36 weeks of gestation. The sample size is based on GWG (primary outcome) and informed

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by our feasibility trial showing a 21% reduction in GWG in the intervention group compared to the control group, with 3% dropout. Secondary outcomes include PA, EI, sedentary and sleep behaviors, social cognitive determinants, adverse pregnancy and delivery outcomes, infant birth weight, and implementation outcomes. Analyses will include descriptive statistics, time series and fixed effects meta-analytic approaches, and mixed effects models.

Results: Recruitment started in April 2024, and enrollment will continue through May 2027. The primary (GWG) and secondary (eg, maternal and infant health) outcome results will be analyzed, posted on ClinicalTrials.gov, and published after January 2028.

Conclusions: Examining the efficacy of the novel HMZ 2.0 intervention in terms of GWG and secondary outcomes expands the boundaries of current GWG interventions and has high clinical and public health impact. There is excellent potential to further refine HMZ 2.0 to scale-up use of the novel digital platform by clinicians as an adjunct treatment in prenatal care to regulate GWG in all pregnant women.

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KEYWORDS

pregnancy; gestational weight gain; physical activity; healthy eating; overweight; obesity; intervention

Introduction

Background

High maternal prepregnancy BMI and high gestational weight gain (GWG) elevate the risks for poor pregnancy outcomes (eg, gestational diabetes and hypertension) and fetal outcomes (eg, large for gestational age birth weight) [1-6]. High BMI and GWG may also "program" the child's metabolism for life [7,8] and increase the future risks for obesity and type 2 diabetes in both mothers and their offspring [1-6]. As such, managing GWG has high clinical and public health significance, and it can improve maternal health and impact the etiology of obesity or diabetes in offspring at a crucial time in the life cycle [1-6,8].

Guidelines from the Institutes of Medicine (IOM) [1] and National Academy of Medicine [2] recommend that the optimal total GWG should be based on a woman's prepregnancy BMI category (ie, overweight: 6.8-11.3 kg; obese: 5.0-9.1 kg). However, evidence from a meta-analytic review including over 1 million pregnant women found that nearly 50% of women exceeded their recommended goals [9], and this was prevalent among those with normal weight as well as those with overweight or obesity. Furthermore, data from a meta-analysis of almost 200,000 women from 25 international cohort studies in the LifeCycle Project [6] showed the highest risk for adverse outcomes among women with both high BMI and high GWG. Given these concerns as well as the rapidly changing landscape of health care delivery since the COVID-19 pandemic, there is a critical and timely need for scalable approaches to effectively regulate GWG. One such strategy that may reach more pregnant women and reduce the burden on prenatal clinicians who monitor GWG is an automated approach that relies on a digital platform with remote delivery and passive remote data collection to monitor and effectively and efficiently regulate GWG.

Prior Work

Our team's prior work successfully constructed energy balance models to predict maternal GWG [10] and infant birth weight [11]. Expanding the work of Thomas et al [12], we built a novel dynamic mathematical model of energy balance and behavior to predict GWG [13,14]. It describes how physical activity (PA) and energy intake (EI) behaviors are influenced by social cognitive determinants (attitude, subjective norm, perceived control, intention, and self-regulation) [15-17] and depicts how components (ie, education, behavior coaching, goal setting, nutrition counseling, and engaging in PA and healthy eating activities) impact PA and EI social cognitive determinants and behaviors to regulate GWG. We also explored how the energy balance model could be extended to explain infant birth weight [11,18].

Prior research has shown that behavioral interventions can impact GWG [19-27] and more specifically that participants who received behavioral intervention components (eg, counseling, guided PA, and prescribed diet) had a lower mean GWG, decreased likelihood of exceeding GWG guidelines, and lower risk for adverse maternal and infant outcomes [20]. There was also evidence for a dose-response relationship whereby intensive interventions with more subject contact were associated with a stronger impact on GWG [20]. Moreover, the findings from qualitative and prospective cohort studies support an intensive approach to managing GWG in pregnant women with overweight or obesity because they may be more likely than women with underweight or normal weight to overestimate the amount of weight they should gain, underreport EI, and have low motivation to engage in PA on their own [28-41]. Taken together, there is ample evidence from the literature for an approach that considers the unique needs of pregnant women with overweight or obesity and personalizes intervention dosages to regulate GWG.

Many GWG interventions use a "one size fits all" approach and are not designed to consider individual variability in how women gain weight over the course of gestation. Our approach adapts personalized dosages for each woman in a way that gives more intensive treatment only to the women who need more assistance to regulate GWG. We piloted a proof-of-concept study [42] and feasibility-initial impact randomized trial [8,10,19,43-45] to examine the impact of the Healthy Mom Zone (HMZ) intervention on GWG. The social cognitive theory–based components [15-17] noted above were designed with the Multiphase Optimization Strategy [46] translational science framework [47-50], and control systems methodology [51-55],

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with the long-term goal to scale-up use by clinicians as an adjunct treatment to prenatal care in order to regulate GWG. This multiphase approach [46] builds an intervention in a principled manner whereby key constraints expected to impact scalability (eg, implementation feasibility and subject or staff burden) are considered from the start so that the end goal is an optimized (effective and efficient) and scalable intervention that delivers the best possible outcome [46]. Our translational science framework [47-50] guided by the Quality Implementation Framework [49] and Quality Implementation Tool [50] aligns with the paradigm shift in the literature to prospectively examine implementation markers (eg, subject acceptability, dosage exposure, and staff burden) from the start of an intervention to identify and resolve challenges during delivery that impact efficacy and scalability [49,50].

Our feasibility trial that randomized 31 pregnant women with overweight or obesity to the adaptive GWG intervention (delivered in person or remotely) or a control group over the course of pregnancy and used mobile health tools and online surveys to measure study outcomes showed high measurement compliance (85%), low burden (eg, average 1 min per day to complete measures), and low attrition (3%) [19]. The control system driven by decision rules and a woman's observed GWG informed when to adapt dosages (GWG within goals [1,2], maintain dosage; GWG greater than goals, adapt dosage) [19]. Participants in the intervention group had a 21% lower mean GWG and were more likely to have GWG within goals than controls. Exploratory analyses showed promise for the HMZ intervention to impact secondary outcomes, including PA minutes, active kcal, EI kcal, and PA and EI social cognitive determinants. Furthermore, maternal nighttime awakenings were related to higher GWG [45], and maternal eating behaviors (uncontrolled eating or restraint) were related to GWG and infant birth weight [44].

Because our long-term goal is to deliver the best possible impact on GWG and maternal or infant outcomes and develop an approach that is scalable for future use in the real world, we used these feasibility findings to make refinements to the intervention content (eg, promoting healthy sleep or eating behaviors), delivery (all content available for remote delivery to ensure scalability), and decision process for evaluating and predicting GWG. More specifically, our initial control system was manually operated (ie, plotted each woman's weight in individual participant files) and not particularly scalable. We thus improved this system by designing a new model-based control system with a hybrid model predictive control algorithm and our dynamic model of energy balance and behavior (Figure 1) [10,13,56]. This enables projections of within-person GWG over time (even when data are missing at the current time point) and has been found in past studies to yield robust personalized suggestions and accurate inferential results even with missingness [56-68]. We also built an architecture for a novel digital platform that makes it possible to deliver just-in-time recommendations directly to a subject in ways that target a broader array of outcomes and can reach more women. The platform provides a web-based interface equipped with secure user access control that automates the linkage of subject data collected with mHealth tools to the new model-based predictive control system that implements a Control Optimization Trial approach [10,51] consisting of semiphysical system identification and Hybrid Model Predictive Control. The platform displays graphical or numeric summaries of a woman's past weight, behaviors (eg, PA, EI, and sleep), social cognitive determinants, and other factors; computes optimized dosage changes across multiple maternal variables; and produces a host of personalized PA or EI strategies to regulate GWG. This refined version of the intervention is denoted HMZ 2.0.

In order to activate recruitment, examine participant compliance with the measurement protocol, pilot test the HMZ 2.0 data transfer pipeline, examine intervention session delivery and user acceptability of the digital platform, and conduct simulations for controller-recommended dosage changes, we conducted a 28-day pilot study.

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Figure 1. Dynamic model of energy balance and behavior to predict gestational weight gain (GWG). The intervention components are education, counseling, goal-setting, self-monitoring, and physical activity (PA)/healthy eating (HE) active behavior strategies (eg, guided activity sessions and cooking demonstrations). The figure depicts the block diagram of the closed-loop control system framework for managing GWG in pregnant women with overweight or obesity and describes the influence of intervention components, baseline intervention dosage, and gestational age (GA) on GWG. The participant model consists of 2 behavioral models targeting PA and energy intake (EI) behaviors, respectively, and an energy balance model. Outputs from the behavioral models serve as inputs to the energy balance model, which calculates changes in GWG by assessing the difference between EI and energy expenditure. The hybrid model predictive controller (HMPC) uses filtered signals of set point and measured disturbances (baseline intervention dosage and GA). A Type-I filter is used to filter the baseline, represented by a binary signal that indicates the preintervention phase (0) or the intervention phase (1). In contrast, a Type-II filter is used to filter the set point and GA. The HMPC-based optimizer determines a sequence of control actions, referred to as PA and HE dosage augmentations. BS: baseline; IOM: Institutes of Medicine.

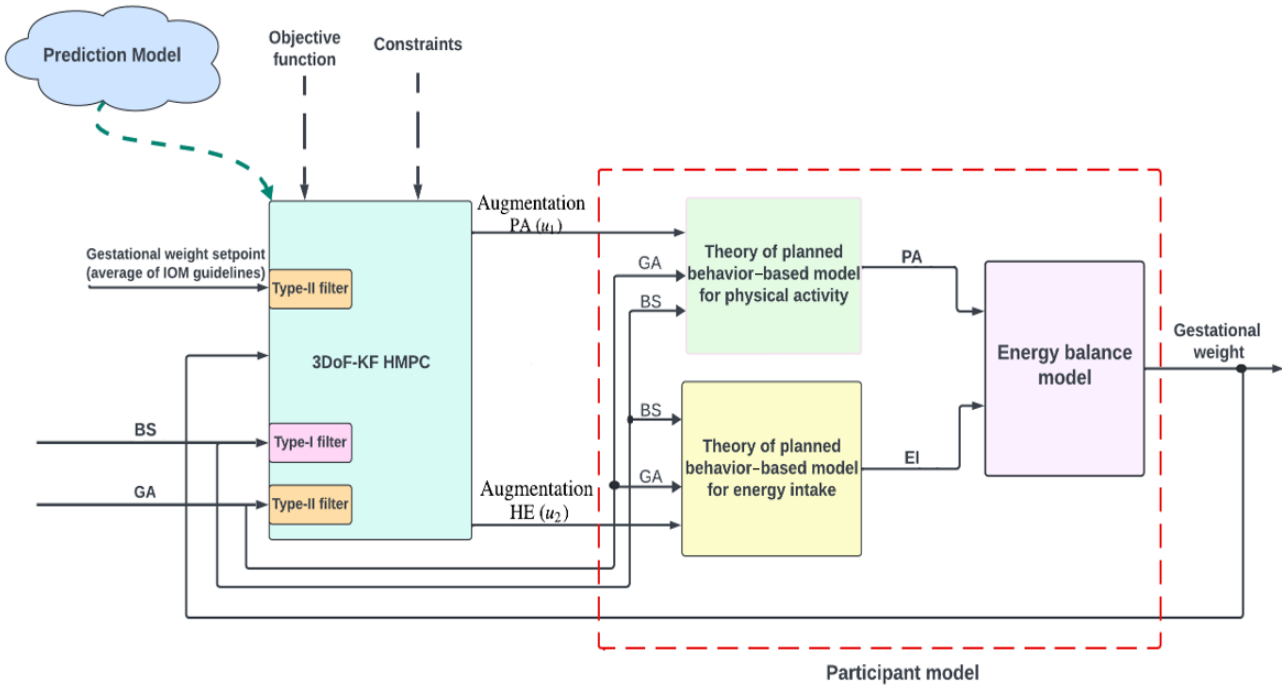

HMZ 2.0 Pilot Study Results

We recruited and enrolled 10 pregnant women (mean age: 32.1 years; mean gestational age at enrollment: 14 weeks). Participants completed the HMZ 2.0 preintervention measurement protocol lasting 7 to 9 days (depending on the day of enrollment), completed daily and weekly study measures over a 3-week period while also participating in three 60-minute weekly intervention sessions (content from the first 3 weeks of the HMZ 2.0 baseline intervention) delivered by a trained staff member through the HMZ 2.0 digital platform, and completed the postintervention measurement protocol (7-9 days) and a poststudy brief interview to understand user acceptability. The results of this pilot study are presented below.

We had 59 participant contacts, of which 31 (53%) were assessed for eligibility and 10 (32% of eligible participants) were enrolled in the pilot study. Successful recruitment of participants involved social media (30%), community-based flyers and handouts (eg, campus locations and local events such as farmer's markets; 30%), word of mouth (20%), and clinic referrals (20%).

Participant compliance with the HMZ 2.0 measurement protocol was excellent, with compliance rates of 88% for the daily or weekly online surveys and MyFitnessPal app, 92% for using the Fitbit Aria Wi-Fi scale each day to assess weight, and 98% for wearing the Fitbit Charge 6 monitor each day to assess PA, sedentary behavior, and sleep behaviors. Moreover, the flow of data through the HMZ 2.0 pipeline was exceptional. Data transfer from devices and Research Electronic Data Capture (REDCap) to the digital platform was smooth, with <2% evidence of technical problems or glitches, and 100% of problems were resolved without issue.

A total of 30 intervention sessions (3 per participant) were delivered, of which 80% (24/30) were delivered with a hybrid approach (in person with the platform) and 20% (6/30) were delivered with a fully remote approach using Zoom and the platform. Attendance and compliance with the sessions were 100%. All the women (10/10, 100%) liked the utility of the HMZ 2.0 digital platform, and 90% (9/10) liked to see their real-time data and set weekly goals with trained study staff. In the poststudy brief interview, 1 woman commented that it was "nice to use [the platform] prior to sessions so I was able to come prepared and ask questions." Another woman said, "The platform was easy to move from page to page." A third woman noted, "We covered different topics during the sessions, so I liked being able to go back to the platform and look at the content again." The participants also provided constructive feedback on the platform and suggested the following refinements: soften the color scheme on the website pages, include a page with session schedule and location information, and include a link to directly email the study staff to reduce the burden of looking through study materials for contact information. The platform was refined to address these concerns.

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Simulations to illustrate the estimated model are presented in Figure 2, which shows the Control Optimization Trial framework for the recommended dosages within the system identification phase, adhering to the 2-week and 3-week delay. The first panel displays the participant's weight in pounds (black solid line) and the setpoint (solid magenta line), which indicates the mean of the IOM guidelines (dashed red line) [1]. Different colors are used to represent the various intervention phases. The preintervention phase lasts for 7 to 9 days (9 days in this case), followed by a 2-week baseline period. During both the preintervention and baseline phases, no augmentations or dosages are administered. The first dosage is recommended after 2 weeks in the dosage 1 phase, starting on gestational day 126. The second dosage follows 2 weeks after dosage 1 in the dosage 2 phase. The second panel contains 2 subpanels: one for the manipulated variable augmentation PA and another for PA kcal. The last panel similarly includes subpanels for augmentation healthy eating and EI kcal. The simulation results show that the hybrid model predictive controller effectively manages the participant's weight within the IOM bounds once the controller is activated. As illustrated, both in the system identification and controller phases, recommendations for PA or healthy eating dosages lead to reduced EI (healthy eating dosage recommended) or increased PA (PA dosage recommended), ultimately facilitating weight reduction through decreased EI and increased PA.

After the dosage 2 phase, the controller phase begins, during which the controller recommends further dosages based on predicted participant weight and the logic outlined in Figure 3, which illustrates the conceptual framework for the controller's augmentation or dosage recommendations, operating similarly to a finite state machine. Each state is represented by 2 digits: the first digit denotes augmentation PA (PA dosage) and the second digit indicates augmentation EI (healthy eating dosage), and either the PA dosage or EI dosage is updated at any given time. The controller recommends dosages with a minimum user-specified delay of 2 weeks between all dosages, except between dosage 2 and dosage 3, where a 3-week delay is specified. Transitions between dosages are governed by an auxiliary signal a_k. If a_k equals 1, the controller can transition from the current dosage state to the next; otherwise, it remains in the current dosage state.

Figure 2. Simulation illustrating the various stages of the control optimization trial implemented in the Healthy Mom Zone (HMZ) 2.0 intervention using an estimated model of an HMZ 1.0 representative participant. EI: energy intake; HE: healthy eating; HMPC: hybrid model predictive controller; IOM: Institutes of Medicine; PA: physical activity; RMSE: root mean square error.

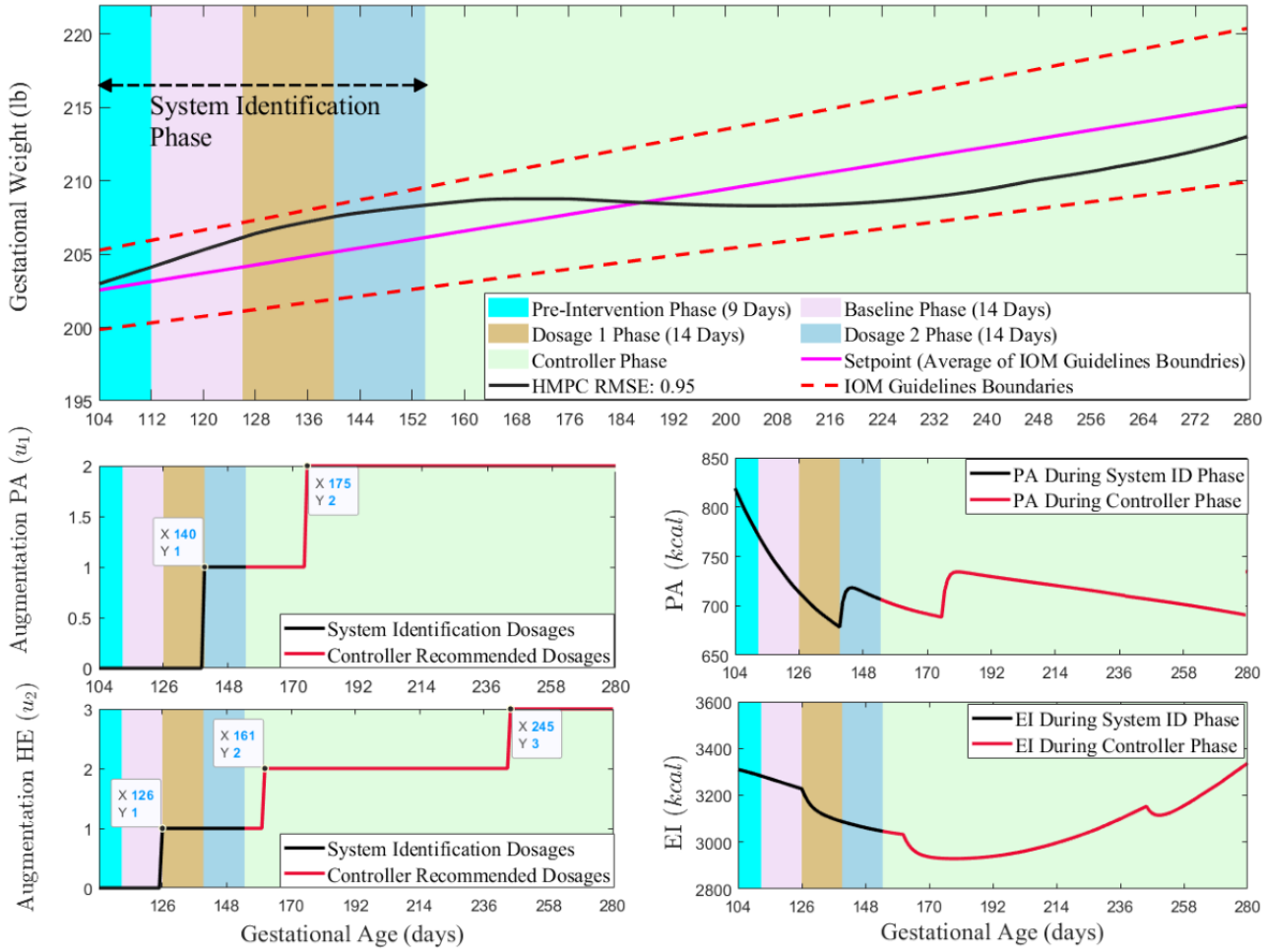

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Figure 3. Dosage sequence pattern for the hybrid model predictive controller within the Healthy Mom Zone (HMZ) 2.0 intervention.

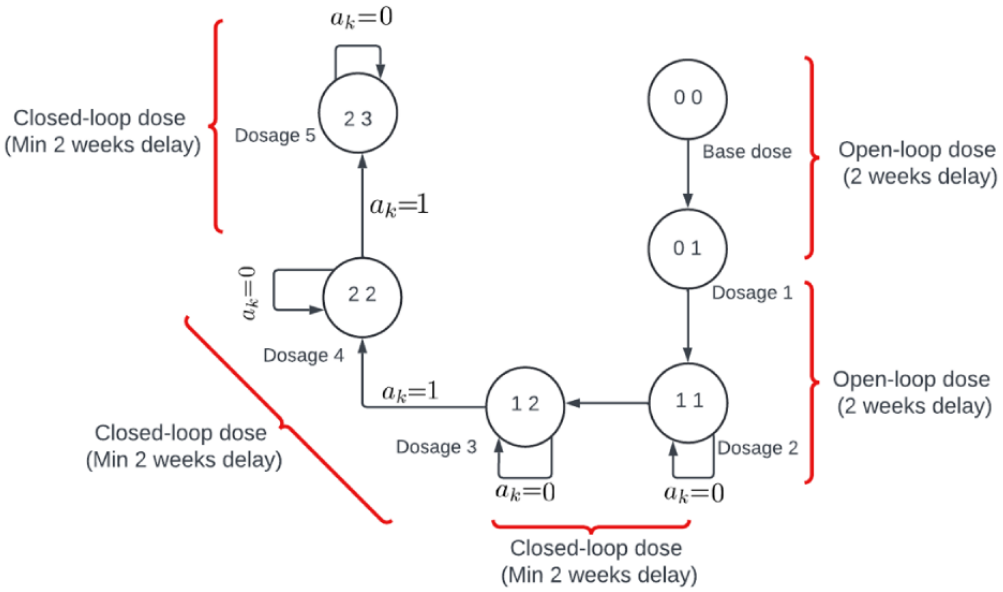

Goal of This Study

The goal of this study is to describe the protocol for a randomized controlled optimization trial to examine the efficacy of the enhanced HMZ 2.0 intervention with the new automated control system and digital platform to regulate GWG and influence secondary maternal and infant outcomes while collecting implementation data to inform future scalability. Aim 1 is to examine the efficacy of the intervention in terms of GWG (primary outcome) and maternal PA and EI behaviors and social cognitive determinants on comparing intervention and control groups. It is hypothesized that the intervention group will (1) have lower pre- to postintervention GWG and be more likely than controls to achieve GWG within the guidelines [1,2], and (2) have higher PA kcal (and total kcal) and PA or EI determinants and lower EI kcal than controls. Aim 2a is to measure pre- to postintervention differences in secondary maternal sleep and eating behaviors. It is hypothesized that the intervention group will have fewer nighttime awakenings and less uncontrolled eating than controls. Aim 2b is to examine the impact of the intervention on birth weight and adverse pregnancy, labor, and delivery outcomes. It is hypothesized that the intervention group will show lower birth weight adjusted for gestational age and will have lower occurrences of adverse pregnancy, labor, and delivery outcomes than controls. Aim 3 is to examine the impact of implementation markers on intervention efficacy in terms of GWG and secondary outcomes. It is hypothesized that subject engagement, acceptability, dosage exposure, and staff burden or acceptability will moderate the effect of the intervention on study outcomes. This information will inform how to scale-up the HMZ 2.0 intervention for future use by prenatal clinicians.

Methods

HMZ 2.0 Intervention Description

HMZ 2.0 is a multidosage, individually-tailored, adaptive intervention with social cognitive theory and behavior components [15-17]. The “baseline dosage” is delivered to all intervention participants, and it consists of up to 24 weekly modules (depending on gestational age at study enrollment) including the following:

- Education: Knowledge-based content on meeting guidelines (GWG, PA, EI, sleep behaviors, and good sleep hygiene) [1,2,69-75]; mood (eg, depressive symptoms, stress, and anxiety); safely engaging in prenatal exercise; and awareness of stressful situations that prompt uncontrolled and emotional eating, hunger cues, cravings, and mindful eating choices [76,77]. We also provide knowledge about recently published evidence-based studies on how a mother’s health impacts her baby (eg, sleep, brain development, and food preferences) and developmental milestones (eg, when eyebrows develop), which is shared over the course of the intervention. Our pilot work [42] demonstrated that women specifically asked for education materials that provided this information.
- Personalized behavior coaching or counseling: Individually tailored behavior coaching from a prenatal fitness instructor and registered dietitian on GWG, PA, and EI that uses information and feedback from a woman’s prior week to inform the future week’s motivational cues and strategies to increase PA, improve diet quality, and overcome barriers (this can be delivered in person or through a remote synchronous or asynchronous approach for future scalability).
- Goal setting and action planning: Guided and self-selected PA and EI goals [69-71,78] using implementation intentions to target when, where, and how each woman will work toward goals and how these PA or EI goals relate to GWG. Example goals include targets for daily steps (eg, 10,000 steps) and activity time (eg, 30 minutes), as well as fruit or vegetable intake for lower energy density [79] and increasing water intake to maintain good hydration [80,81]. HMZ trimester-specific prenatal PA and recipe booklets (developed by our team) provide detailed examples for PA (eg, 150 min/week of moderate-intensity activities; 10,000 steps/day) and EI kcal goals [78].

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- Self-monitoring: Women use mHealth tools (eg, Wi-Fi weight scale, activity monitor, and dietary intake app) to self-monitor GWG, PA, or EI [82]. The HMZ digital platform visually displays their daily or weekly data. Feedback is given to each woman on how to use the devices and self-monitor their behaviors in relation to their GWG and PA or EI goals [19,43,78,83].

Adaptive Intervention Dosage Changes

The model-based predictive control algorithm in the HMZ 2.0 digital platform continually and automatically evaluates GWG. It relies on a dynamic model and solving a receding horizon online optimization problem that identifies when a woman's forecasted GWG is anticipated to exceed the GWG guidelines [1,2,84-86], and based on a structured sequence of decisions that form part of the model, a dosage change is recommended (Figure 4). Only women who have a forecasted need for added support to regulate GWG will receive adaptive dosages in addition to the baseline intervention. Dosages are additive such that a woman receives more intensive support for eating healthy and engaging in PA with each adaptation up to a maximum of 5 adaptive dosages. The web-based user interface provides an easy and intuitive way to integrate expert-supervised dosage change recommendations to regulate GWG. The HMZ 2.0 prenatal fitness instructor and registered dietitian review the participant's data and recommend individually tailored behavioral strategies that are delivered through the HMZ 2.0 digital platform. Each woman's unique preferences and past successes with PA or EI strategies are considered when customizing the dosage adaptation to promote engagement, enjoyment, and compliance, which can in turn influence GWG. These active learning strategies include, for example, multiple PA-guided workouts with a variety of prenatal cardiovascular and resistance training exercises (preapproved for safety and with physician consent for participation) [69,70], as well as healthy eating cooking demonstrations, portion size control strategies to substitute high energy density foods with low energy density options such as water-rich fruits or vegetables [43,71], using food scales and portion size containers, customized grocery planning, and meal replacements. There are a host of easy-to-adopt and practical recommendations for integrating PA or EI strategies into daily life (eg, walking in 5- to 10-minute increments throughout the day to increase PA kcal by 200 kcal/day, reduce sitting by 5 min/hour from 9 AM to 5 PM, and replace 8 ounces of whole milk with skim milk to reduce EI kcal by 100 kcal/day) to facilitate behavior change while adhering to safety standards [69,70]. All dosages can be delivered in person or through a remote approach (synchronous and asynchronous for selected sessions), depending on the participant's preference.

Figure 4. Healthy Mom Zone (HMZ) 2.0 adaptive intervention design. Participant weight is measured daily and continuously evaluated against the Institutes of Medicine (IOM) gestational weight gain (GWG) ranges. All intervention women will receive the baseline intervention plus step-up 1 plus step-up 2 during the system identification open-loop experiment. Dosages 3 to 5 are delivered to selected intervention participants based on hybrid model predictive controller (HMPC) decisions in the closed-loop experiment. HE: healthy eating; PA: physical activity.

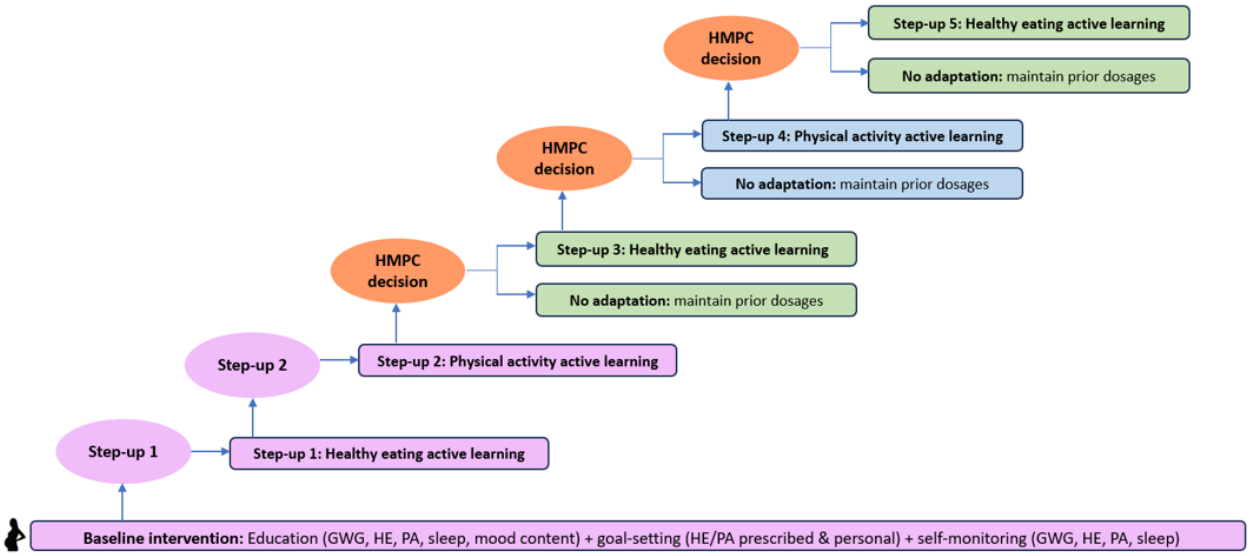

HMZ 2.0 Automated Data Pipeline and Digital Platform

The data pipeline for HMZ 2.0, illustrated in Figure 5, is orchestrated by Apache Airflow [87], a workflow management platform, where daily jobs are scheduled, including (1) retrieving deidentified data from various sources, such as the application programming interface (API) of the REDCap [88] database; (2) preprocessing survey data, including aggregating subscales and back-calculating EI [89,90]; (3) imputing missing data via multiple imputation [91,92] and machine learning–facilitated [93-95] techniques programmed into the platform; (4) feeding the imputed data into the advanced hybrid model predictive control system to generate the adaptive decision-making process; and (5) continuously monitoring errors and warnings in the Airflow monitoring dashboard during steps 1-4, scanning data quality, and initiating automated alerts that notify different pillars of the study team based on the issue type. As the participants in the study cohort change with time, tasks for each new participant are dynamically created. The scripts are version controlled, and data generated throughout the pipeline are saved in a PostgreSQL relational database to ensure data reproducibility. The HMZ 2.0 web-based platform has been

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built with Django, an advanced Python web framework to scale-up future production and access (see Figure 6 for the digital platform architecture and website examples). Heterogeneous user interfaces have been built for study staff (and future clinicians), participants in the intervention group, and participants in the control group. The web-based platform provides an access-controlled admin dashboard where authorized users can manually update settings, curate data, or export deidentified datasets for further analyses. For example, during intervention sessions, study staff can access participants' general information, data, educational content, goals, and intervention dosages, and participants will have access to selected resources that are tailored to their specific needs.

Figure 5. Healthy Mom Zone (HMZ) 2.0 data transfer pipeline. API: application programming interface; GWG: gestational weight gain; HMPC: hybrid model predictive controller. *Real-time deidentified 24-hour data stream into REDCap, **Access control (user ID) by authorized study staff, ***Access control (user ID) by intervention study staff (and in the future, dissemination to clinicians).

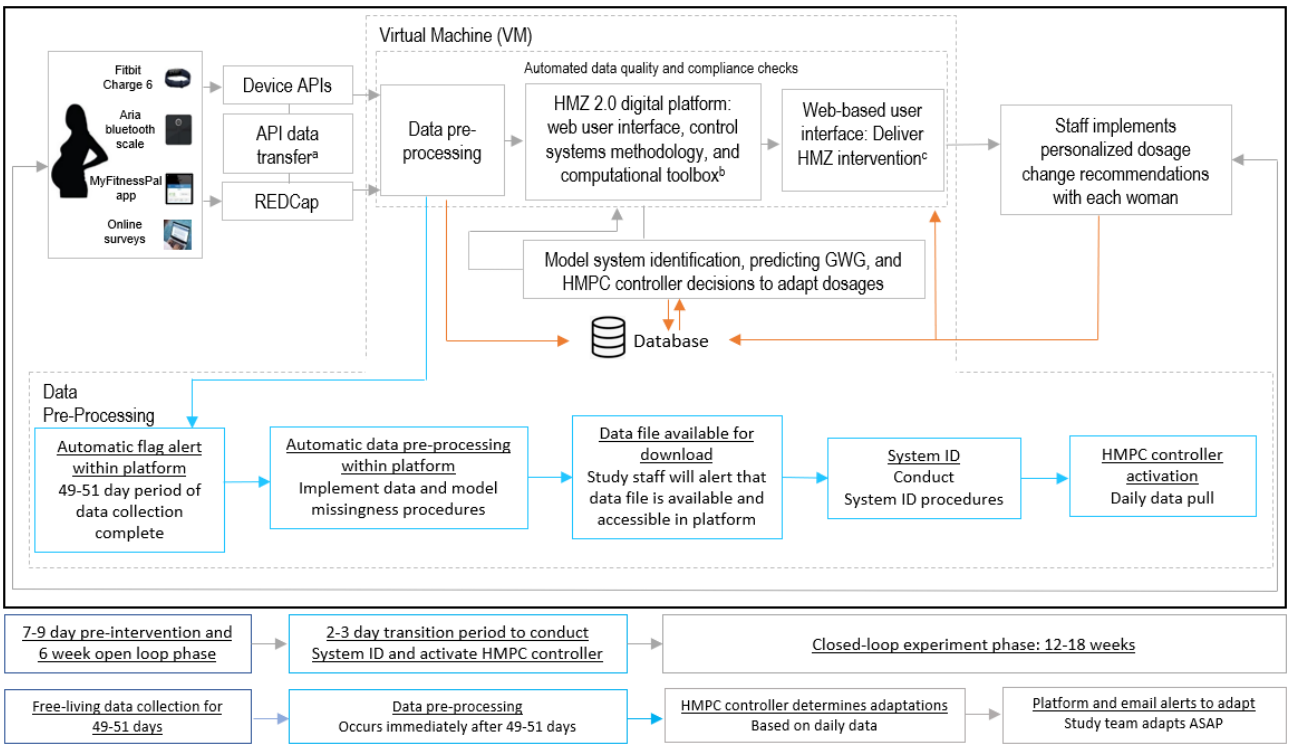

Recruitment

Recruitment began in April 2024 and will continue through May 2027. Pregnant women with overweight or obesity (N=144) are being recruited for this study. Our team has extensive expertise with recruiting pregnant women. Our past studies have yielded over 3100 subject contacts, with recruitment rates of 84%-92% across our studies [19,96-102]. Well-established methods from our past studies are used for recruitment procedures as follows:

- Clinic: Nurses identify eligible women at the 1st prenatal visit (eg, appointment schedule and electronic health record) and refer them to the study team for screening. A study flyer with study contact information and a QR code is included in the clinic's prenatal packet and posted in exam rooms.
- Community: Study flyers are posted in local areas (eg, daycares and churches) and hospitals, and shared at community events (eg, farmer's markets and celebratory events).
- Social media: Study information is shared on Facebook, Instagram, X, YouTube, and study websites.

Using well-established procedures from our past studies [19,96-102], interested participants, regardless of recruitment method, are screened for eligibility. If interested, participants scan a QR code that directs them to a REDCap survey to complete a screening questionnaire or they send a message by email, text, or voicemail, and a trained study staff member will reply to complete the screening questionnaire over the phone.

The staff member reviews the participant's responses to determine eligibility. The inclusion criteria are as follows: age range 18-45 years; singleton pregnancy with ≥8 and <18 weeks gestation; any parity; any race or ethnicity; BMI of 24-45 kg/m^2 (>40 with provider consent); have not gained >25% of total GWG (based on BMI and IOM guidelines) from prepregnancy to the date of enrollment [103]; able to read or understand English; access to a computer or phone; able to attend sessions either on-site or remotely; randomization to conditions; no absolute contraindications to PA (and presence of relative contraindications only with health care provider consent to participate); and not a current heavy smoker (>20 cigarettes per day) [19,69-71] . The exclusion criteria are as follows: outside the age, BMI, gestation, or GWG range; not able to participate (cannot read or understand English, no access to a phone or computer to attend sessions remotely, and cannot use a device or service assistance); absolute contraindications to PA [69-71] or relative contraindications to PA noted by the participant's health care provider as precluding study participation; current

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heavy smoker (>20 cigarettes per day) at study entry; and multiple pregnancy. Eligible women are scheduled for the preintervention assessment. Women not meeting the eligibility criteria are thanked for their time and given information on other studies that may be of interest.

Safety Considerations

Prior to enrollment, a study team member informs the participant's health care provider about their potential participation and obtains consent from each provider. The provider completes the consent form (hard copy or REDCap link) confirming eligibility for participation, and the participant is officially enrolled. This process is repeated at mid-study (eg, between the 2nd and 3rd trimesters) to ensure the participant does not have any new medical conditions that may impact study participation.

Because this study includes pregnant women, a vulnerable population as defined by the National Institutes of Health, there is a Data Safety and Monitoring Board with experts in obstetrics and gynecology, prenatal weight gain, PA and nutrition interventions, and fetal growth that will: (1) review the study methodology and procedures, data on recruitment, enrollment and adherence to the inclusion/exclusion criteria, and participant's progress through the study; (2) assure the safety of the study participants; and (3) make recommendations to the research team. Adverse events that the Data Safety and Monitoring Board will be notified of and oversee include: (1) insufficient GWG: indicators of insufficient GWG are weight loss of less than 3% in a week or 0% weight gain in a 4-week cycle [104]; (2) depressive symptomology: all women regardless of initial preintervention assessment scores will be given resources on managing depressive symptoms and a comprehensive list of available resources and supportive services, and depressive symptoms will be monitored monthly [105]; and (3) absolute or relative contraindications to exercise [69-71].

Participants in the intervention group complete verbal assessments of pregnancy symptoms (eg, mild muscle cramping, headaches, and symptoms of labor) and contraindications to exercise (eg, bleeding, severe abdominal cramping, nausea, etc) during activity sessions. The study safety protocol includes steps to understand symptoms, ratings of perceived exertion, and responses if appropriate, including stopping the activity, seeking medical attention, and calling a participant's emergency contact and provider. If a woman experiences a contraindication to PA in pregnancy that precludes her continued participation, she will remain in the study and complete measures as appropriate (intent to treat) but will not engage in PA until provider consent to return to activity is obtained. We also monitor changes in health status and health symptoms. For example, women who develop gestational diabetes during the study will remain in the study and receive the standard of prenatal care by their obstetrician or health care provider, in which an established standard of care plan is provided for the treatment and management of gestational diabetes.

Ethical Considerations

This study has been approved by the Pennsylvania State University Institutional Review Board (IRB; STUDY00019075), and Arizona State University is an IRB-approved participating site (SITE00001437). All members of the study team have appropriate CITI training certifications. Any and all changes made to the protocol will be communicated to participants and other relevant individuals or parties immediately. All study participants provide their informed consent prior to enrollment into the study with the option to decline enrollment or stop participation at any time. Data collected are deidentified, and access is only granted through lock and key as well as secure accounts with passwords. Participants are compensated up to US $250 in gift cards for either Target or Walmart. Compensation is provided based on the completion of study milestones, such as completing the pre- and postintervention assessments, allowing electronic health record data to be extracted, and attending and completing more than 85% of study sessions and the measurement protocol. Both the intervention and control group participants can receive the same amount of compensation. This study is registered at ClinicalTrials.gov (NCT05807594).

Randomization Procedures

A trained staff member randomizes each participant after the preintervention measures via a randomization module in REDCap [88]. The study's biostatistician has developed the randomization scheme using variable-size random permuted blocks to ensure the number of subjects in each group is balanced after each set of *B* randomized subjects, where *B* is block size. The biostatistician programs the REDCap module, and the remaining study staff do not have access to the randomization scheme. Randomization to control (n=72) and intervention (n=72) groups uses 1:1 allocation; subjects are entered consecutively. Randomization is stratified by prepregnancy BMI status (<29.9 vs ≥30 kg/m^2). A staff member calls each woman to inform her of study assignment. She is then provided with study information and education materials for her group assignment. The investigator is blinded to intervention assignments.

Treatment Conditions

Intervention Condition

Women randomized to the intervention group receive the HMZ 2.0 intervention, described in detail above in the section "HMZ 2.0 Intervention Description," which includes the baseline intervention (education, personalized behavior coaching or counseling, goal setting or action planning, and self-monitoring) and adaptive intervention dosage changes (for the participants who need them). This baseline intervention continues through the duration of the study. Each week over the course of the study, GWG is monitored and evaluated against the recommended upper and lower bounds of the IOM GWG guidelines [1]. Depending on each participant's response to the baseline intervention (eg, GWG within or above guidelines) and her forecasted GWG, the automated control system may recommend a dosage change to adapt the intervention. This adaptive dosage begins after the first 4 weeks of the baseline

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intervention (to allow the participants to get used to the intervention and reduce burden) and includes EI and PA active learning interactive components that "step-up" the intensity of the dosage. Dosage change recommendations are automatically delivered through the HMZ 2.0 digital platform (architecture of the platform is described above); staff implement the recommended dosage change with the participant. As illustrated in Figure 6, there are up to five dosage "step-up" adaptations that can be recommended by the automated control system to regulate GWG.

Figure 6. Healthy Mom Zone (HMZ) 2.0 digital platform architecture and website examples. API: application programming interface; HMPC: hybrid model predictive controller.

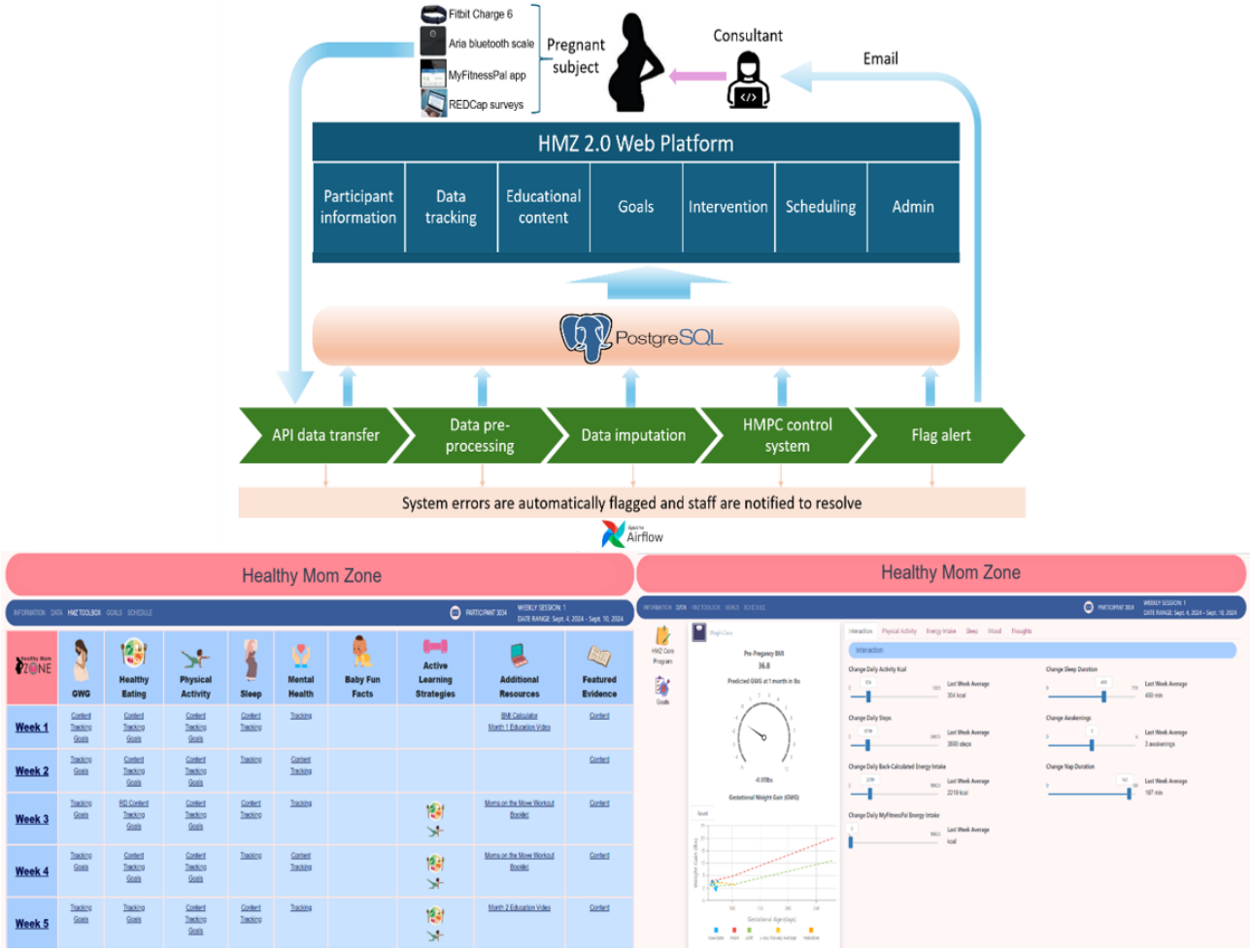

Attention Control Condition

Consistent with guidelines for comparator groups [106], all women in the study receive prenatal care offered by recruitment sites with routine provider visits, counseling about prenatal behaviors (eg, no smoking), and clinical oversight of health. To match attention to the intervention group, women in the control group receive (for the first 4 weeks of the study) one-on-one weekly education sessions delivered by trained study staff, and thereafter, they receive monthly education content delivered as asynchronous videos and get check-in support from study staff (eg, phone, text, and email) for the remainder of the study. Content includes topics, such as preparing for labor or delivery; benefits of behavioral pain management strategies (eg, mindfulness-based relaxation, imagery, music, massage, and deep breathing) to regulate pain after childbirth with nonpharmacological approaches [107]; and baby or child safety, health and development, behaviors, and nutrition. Content is drawn from evidence-based guidelines and materials designed by members of the study team for a patient-provider toolbox to reduce opioid pain management use after childbirth [107], as well as The American Academy of Pediatrics, The March of Dimes, The Centers for Disease Control, and The American College of Obstetrics and Gynecology [108-111]. The matched control group education content is also provided to the intervention group as supplemental material.

Both the intervention and control groups receive the same measurement protocol and frequency of measurement to understand and compare the impact of the intervention on primary and secondary study outcomes. Data are collected from each participant daily (GWG: Aria Wi-Fi scale [112]; PA, sedentary behavior, or sleep: Fitbit Charge 6 monitor [112], logs for device wear time, and PROMIS Sleep Disturbance [113,114] assessment; and self-reported hydration behaviors); weekly (self-reported online in REDCap; social cognitive determinants and EI diet quality: MyFitnessPal app on 2 weekdays and 2 weekend days) [19,115]; and monthly (self-reported online in REDCap; eating behaviors [19,116,117], psychosocial measures, cognition, pain, and temperament measures).

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Control Optimization Trial Procedures

Control systems methodology [51-54] in a novel Control Optimization Randomized Controlled Trial (RCT) [51] is used to test the efficacy of the enhanced HMZ 2.0 intervention with a novel digital platform and a new automated control system to regulate GWG and influence secondary outcomes. This idiographic approach uses individual dynamic models (integrating behavioral and energy balance models) informing how each woman responds to HMZ 2.0 to make personalized decisions about intensifying dosages to regulate GWG. We are not aware of any other studies using this unique strategy to regulate GWG. Women start the intervention with an "open-loop" experimentation phase and receive the HMZ 2.0 baseline intervention (dosages are not yet adapted during this time). Semiphysical models estimated using concepts from system identification [85,118-120] allow individual energy balance and behavior models to be built for each subject [51]. Model and dosage personalization is further enhanced by leveraging our team's expertise in time-varying dynamic systems (systems that show changes in statistical properties over time) and multilevel models that integrate individual- and group-based dynamics and missing data issues [56-68]. Model components are measured with real-time data procedures to predict corresponding deviations from each woman's target GWG range: overweight, 6.8-11.3 kg total and 0.23-0.32 kg/wk; obese, 5.0-9.1 kg total and 0.18-0.27 kg/wk [1,2]. Model estimation is used to confirm individual models and identify if certain constructs provide maximum impact for the control system. The goal of this open-loop phase is to arrive at a set of personalized dynamic models that capture the effects of dosage augmentations, gestational age, and the baseline intervention. Once the models are identified and the controller commissioned, models will not be updated, but the tuning parameters can be adjusted, if necessary. While there is no set threshold of data compliance for building individual models (models can be built with as little as 50% missing data handled with maximum likelihood estimation) [56-68], we will rely on strategies to achieve high compliance (90%; 10% missing data) similar to that in our feasibility study [19].

These personalized individual energy balance and behavior models are used in the "closed-loop" experimentation phase for the rest of the study period during which a woman's responsivity to HMZ 2.0 is considered and dosages are adapted to regulate GWG. Continuous mHealth data are automatically linked to the control system, which considers GWG over a prediction horizon to minimize discrepancies between a woman's observed GWG and her goal [1,2]. It considers the anticipated rate of GWG change as predicted with the individual model. Currently trained with data from the feasibility trial [19] and pilot data collected on HMZ 2.0 participants, the control system uses the values of each woman's modifiable factors (eg, PA or EI kcals) in the current week to simulate ways in which these behaviors can be "controlled" or altered to drive GWG closer to the goal in the following week. We are cognizant of potential system identification issues that may arise with limited data available from each subject. If needed, selected parameters from the energy balance models can be constrained to be invariant across subjects to borrow strengths from other subjects and aid model estimation [121,122]. We will identify the optimal balance between control system performance (how well it can produce desired effects as efficiently as possible) and robustness (how well it can produce desired performance under disturbances and uncertainty; eg, poor compliance, change in responsiveness to dosages, and measurement variability) [10,51]. The controller has tuning parameters that allow adjustment of how fast or slow the control system makes recommendations to enable a judicious balance between effectiveness and responsiveness. Computations are performed with toolkits in MATLAB (MathWorks) and IBM ILOG CPLEX Optimizer. Study staff work with subjects to address concerns or technical issues. We will also explore how the individual subject data may inform modifications to the maternal energy balance and behavior model [10,19] and infant birth weight model [11,18].

Primary and Secondary Outcomes

Table 1 summarizes the HMZ 2.0 measurement protocol and timepoints. More details of the primary and secondary outcomes are provided below.

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Table 1. Healthy Mom Zone 2.0 measurement protocol and timepoints.

Variable measure	Timepoint
Energy balance model outcomes	
GWG[a] /weight (primary outcome)	
High precision adult scale (10 s)	Pre- and postintervention
Aria Wi-Fi Smart Scale (15 s)	Pre- and postintervention and daily
Prenatal records: total GWG	Pre- and postintervention
PA[b] and sedentary behavior	
Fitbit Charge 6: activity kcal (passive)	Pre- and postintervention and daily
ActiGraph GT3X: activity min (passive)	Pre- and postintervention and daily
PA log: monitor wear time (1 min)	Pre- and postintervention and daily
Resting metabolic rate	
Predicted equation	Pre- and postintervention and daily
EI[c]	
EI kcal: back-calculation method	Pre- and postintervention and daily
EI diet quality: MyFitnessPal app (5 min)	Pre- and postintervention and monthly
PA or EI social cognitive determinants	
Attitude, subjective norm, perceived behavioral control, and intention (3 min)	Pre- and postintervention, daily, and weekly
Behavioral, normative, or control beliefs (2 min)	Pre- and postintervention and monthly
Retrospective self-regulation (1 min)	Pre- and postintervention, daily, and weekly
Secondary outcome measures	
Sleep behaviors	
Pittsburgh sleep quality index (2 min)	Pre- and postintervention and monthly
FitBit Charge 6: sleep behaviors (passive)	Pre- and postintervention and daily
Sleep log: sleep behaviors (30 s)	Pre- and postintervention and daily
PROMIS Sleep Disturbance (30 s)	Pre- and postintervention and daily
Eating behaviors	
3-factor eating inventory: cognitive restraint, disinhibition, and hunger (3 min)	Pre- and postintervention, weekly, and monthly
Maternal-infant labor or delivery and adverse pregnancy outcomes	
Diagnoses of gestational diabetes, insulin use, preeclampsia, and depression	Postintervention only (at delivery)
Labor or delivery issues and other complications	Postintervention only (at delivery)
Infant APGAR score and mode of delivery (vaginal or cesarean)	Postintervention only (at delivery)
Infant birth outcomes	
Birth weight (adjusted for gestational age at delivery), length, sex, gestational age at delivery, and date of birth in the electronic health record	Postintervention only (at delivery)
Clinical and safety protocol measures	
Height	
Stadiometer (5 s)	Preintervention only
Blood pressure	
Screen for preeclampsia (2 min)	Preintervention only
Demographics, medical history, and obstetric history	
Age, race or ethnicity, income, education, medical or pregnancy history, etc (7 min)	Pre- and postintervention
Depressive symptoms and monitoring health	

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Variable measure	Timepoint
Center for Epidemiological Studies Depression Scale (3 min)	Pre- and postintervention and monthly

[a]GWG: gestational weight gain.

[b]PA: physical activity.

[c]EI: energy intake.

Primary Outcome

Participant GWG

Weight and GWG are assessed daily at preintervention, during the intervention, and at postintervention at home using the Fitbit Aria Wi-Fi Smart Scale [112] (weights are wirelessly uploaded to an online program). GWG is standardized, and the target weight gain is determined for each woman based on the BMI status (overweight, 14.1-22.7 kg; obese, 11.3-19.1 kg) [1,2]. For the criterion measure to determine when to adapt the intervention, weight gain is calculated to determine if a woman is gaining less than her goal, at the exact amount of her goal, or more than her goal. GWG over the course of the study is calculated as the last measured weight during the study subtracted by the first measured weight during the study. Weight at enrollment is measured, and prepregnancy weight and GWG from the first prenatal visit to the last predelivery weight are abstracted from clinical records.

Energy Balance and Behavior Model Primary Constructs

PA and Sedentary Behavior

PA and sedentary behavior are assessed daily at preintervention, during the intervention, and at postintervention. Participants wear the wrist-worn Fitbit Charge 6 [112] 24 hours per day from the preintervention assessment until the end of the postintervention assessment. The Fitbit Charge 6 allows for continuous passive (low subject burden) PA assessment in the energy balance model [12] to predict GWG. The device measures total kcal, activity kcal, steps, and minutes in sedentary, light, or moderate PA. The waist-mounted ActiGraph GT3X [123] is worn at pre- and postintervention and for the first 2 weeks of the open-loop phase during waking hours to assess PA and sedentary behavior (activity kcal, steps, and minutes in sedentary, light, or moderate PA). Participants track their PA and monitor wear time by completing a self-report PA log and the Leisure Time Exercise Questionnaire [124] daily for cross-validation of the Fitbit data [125].

EI Behavior: Back-Calculation Estimation

EI is estimated daily at preintervention, during the intervention, and at postintervention from measured weight (Aria Wi-Fi scale) [112], PA (Fitbit Charge 6 activity monitor) [112], and resting metabolic rate (RMR), with k=1, 2,… N relating to day 1 to day N. T is the sampling time (T=1 day) [8,12,68-71], and RMR is estimated daily as follows:

$$eRMR = 0.1976W^2 - 13.424W + 1457.6 \quad \textbf{(1)}$$

The noise in weight is small relative to the total weight, but the extent of this noise can affect the calculated rate of GWG per day, so a 5-day moving average filter is used to preprocess (smooth) measured weight before “true” daily EI is estimated [117-119]:

Our team effectively used this back-calculation method for estimating EI in the HMZ proof-of-concept study [42] and feasibility-initial impact randomized trial [8,10,19,43-45].

Secondary Outcomes

Secondary Energy Balance and Behavior Model Constructs

The following aspects are considered:

- Theory of Planned Behavior [15,126]: Involves healthy eating or limiting unhealthy eating, PA attitude, subjective norm, perceived behavioral control, intention, and beliefs. The Theory of Planned Behavior constructs in the dynamic model of energy balance and behavior [13-17] inform individualized model-based interventions for each intervention participant. Participants complete online surveys daily at pre- and postintervention and during the open-loop phase, and daily and weekly during the intervention to assess their attitude, perceived behavioral control, subjective norm, intention to eat healthy and limit unhealthy eating, and participation in PA. Participants complete a one-time online survey at pre- and postintervention and monthly to assess their beliefs about eating healthy, limiting unhealthy eating, and participating in PA.
- Retrospective self-regulation for EI or healthy eating and PA [17]: Retrospective self-regulation in the dynamic model of energy balance and behavior [13-17] informs individualized model-based interventions for each intervention participant. Participants complete two 6-item online surveys daily at pre- and postintervention and during the open-loop phase, and weekly during the intervention to determine how good they are at regulating their EI or healthy eating and PA and how these behaviors impact GWG over the course of pregnancy.

Maternal Health

Participants complete the following measures at preintervention, during the intervention, and at postintervention:

- Diet composition or quality and eating behaviors: Participants use the MyFitnessPal online app on 2 weekdays and 2 weekend days at pre- and postintervention, weekly during the first 2 weeks of the open-loop phase, and once a month during the intervention to assess their diet composition and quality. This information aids in personalized counseling of diet quality for the intervention group [19]. The Three Factor Eating Questionnaire

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[116,117] is completed at pre- and postintervention, weekly during the open-loop phase, and monthly during the closed-loop phase and is used to assess 3 dimensions of eating behaviors: dietary restraint (cognitive control of eating behavior), dietary disinhibition, and susceptibility to hunger.

- Sleep behaviors: The Pittsburgh Sleep Quality Index [127] assesses the quality and patterns of sleep and measures subjective sleep quality, sleep latency, sleep duration, habitual sleep efficiency, sleep disturbances, use of sleeping medication, and daytime dysfunction. The PROMIS Sleep Disturbance short-form survey [113] assesses difficulties and concerns with getting to sleep and staying asleep; evaluates the perceptions of the adequacy of and satisfaction with sleep; and measures sleep quality, sleep depth, and restoration associated with sleep. Participants also complete a daily self-report sleep log [128] to measure time to sleep and wake, minutes of sleep, nighttime awakenings, time spent awake after sleep onset, daytime naps, and daytime nap duration, and wear the Fitbit Charge 6 Activity Monitor [112] each night to assess time to sleep and wake, minutes of sleep, nighttime awakenings, and light and deep rapid eye movement sleep.

Maternal and Infant Outcomes

Prenatal, labor, and delivery data will be abstracted from the participant's electronic medical record. Maternal and infant outcomes include: mode of delivery (vaginal or cesarean), adverse pregnancy outcomes (eg, diagnosis of gestational diabetes, insulin use, preeclampsia, depression, labor or delivery issues, and other complications), birth weight, length, sex, gestational age, date of birth, APGAR score, and any complications related to the infant during labor and delivery. In the event that labor or delivery data are missing or unavailable from the medical record, the investigators will obtain information from the participant's self-report.

Implementation Marker Procedures

Our team has ample experience with evaluating program implementation [96-98,129-133], including in the HMZ proof-of-concept study [42] and feasibility trial [19]. The Quality Implementation Framework [49] and Quality Implementation Tool [50] will guide examination of the following markers:

- Subject engagement and participation: Fidelity monitoring evaluations are conducted for each subject and staff after each session. A trained staff observer reviews video recordings of 50% of intervention and attention control sessions and follows a review checklist to measure engagement (degree of subject responsiveness with content, discussion, and activities) [134,135].
- Subject acceptability: Subjects and staff complete weekly checklists to assess attendance (0%-100% attendance at pre- and postintervention assessments; 0%-100% attendance at intervention and attention control sessions), compliance (0%-100% compliance with mHealth tools and surveys during free-living pre- and postintervention sessions and over the course of the study for all subjects; 0%-100% compliance with attention control or HMZ 2.0 activities), and quality and completeness of data (0%-100% of usable data for each subject).
- Dosage exposure is assessed by (1) weekly checklists completed by subjects or staff regarding the amount of program content delivered or received (goal 85%+ coverage) [19]; (2) fidelity monitoring by a trained staff observer who reviews video recordings from the same sample of 50% of video recordings noted above; and (3) tracking of the number of dosage changes determined by the model-based control system, number of days between dosage change recommendation and implementation by staff, and number and type of PA or EI strategies suggested or used.
- Staff engagement: Fidelity monitoring is conducted by a trained staff observer who reviews video recordings from the same sample of 50% of video recordings noted above and follows a checklist to measure engagement (enthusiasm, preparedness, session delivery effectiveness, and responsiveness to the subject).
- Staff burden: Weekly checklists are completed by staff for the amount of time spent preparing for sessions, responding to or following up with subjects, and using the HMZ 2.0 digital platform, and for issues with delivering dosage recommendations to the subjects.
- Study delivery costs: A trained staff member tracks and calculates the time and financial costs of the study. Postintervention semistructured interviews with HMZ 2.0 subjects elicit key facilitators and barriers to study participation. The interview guide has been developed with standard procedures [136,137] from our past studies [10,19,42-45,107,138-140]. Expert feedback will be obtained from key clinician stakeholders (ie, registered dietitians, nurses, obstetrics or gynecology providers, etc) on the strengths and limitations of using the HMZ 2.0 digital platform, potential barriers to scaling-up use in prenatal care (eg, clinician beliefs about technology and connectivity issues), and suggestions for improvements. This valuable feedback will be used to make additional refinements to HMZ 2.0 to scale-up future use by prenatal care clinicians.

Statistical Analysis

For study aims 1 and 2, time series methodology will be used on a subject basis (ie, cubic polynomial spline 3-lag auto-regressive models with maximum likelihood as the estimation method) followed by a fixed effects meta-analytic approach to combine information in order to compare the intervention group to the control group [141-143]. Mixed effects models will be used when the meta-analytic approach does not fit the data [56,62-65]. Potential confounding variables (eg, maternal age, parity, and income; infant sex; and adverse maternal-infant outcomes) [6,144] will be included in the models as covariates when appropriate. We will explore the extent to which prenatal sleep and eating behaviors impact postintervention GWG, PA, or EI and infant birth weight to inform modifications to the maternal energy balance and infant birth weight models. The intent-to-treat principle will be followed. Our statistical approach is robust if data are missing at random (multiple imputation will be considered if missing data are problematic) [145]. Hypothesis tests will invoke a

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2-sided significance level of .05. Analyses for the synthesis of mHealth data and the predictive control system are informed by MATLAB toolkits and past experience [51,146,147]. Model personalization will use control-theory models, and requisite computations will be performed for optimal dosage changes [112,113,128,148-150]. For study aim 3, descriptive statistics will be used to examine the percentage and frequency for implementation markers. Formative methods will be used to organize, code, and rank order interview data [136,137]. Study findings will be used to further optimize HMZ 2.0 for effectiveness and scalability. Data will be collected and stored in REDCap [88]. Deidentified data will be exported from REDCap [88] to statistical packages. Subject confidentiality will be maintained with subject IDs. Data security is ensured with Penn State standard procedures.

Power Calculations

The primary outcome is GWG: absolute difference between the intervention and control groups for the mean change in GWG from the start to the end of the trial. From our feasibility study [19], we found that the difference between the intervention and control groups with respect to the absolute mean change in GWG from the start to the end of the trial was 1.9 kg (SD 4.9 kg), with an approximately 21% relative reduction for the intervention group compared to the control group. We compared the mean change in our feasibility trial [19] to that in several other GWG studies comparing intervention and control groups [29,151-154] and found that the intervention group gained on average 1.8 kg less than controls (range: 1.1-3.1 kg). The sample size of 144 randomized to the intervention (n=72) and control (n=72) groups in the proposed research is informed by our feasibility trial showing a mean difference of 1.9 kg (SD 4.9 kg), a 21% relative reduction in GWG in the intervention group compared to the control group, and a 3% dropout. Given our experience with the feasibility trial [19], the series of refinements that we performed following the feasibility trial (eg, adding content on sleep and eating behaviors given their effects on GWG; modifying all content for remote delivery given 100% compliance found for remote sessions in the feasibility trial; replacing the initial control system to make dosage change decisions with the new, automated, dynamic model-based predictive control system that outperformed the initial system for regulating GWG; and adding the novel HMZ 2.0 digital platform to adapt dosages), and the findings from our HMZ 2.0 pilot study (average weekly GWG over the 4-week study period: 0.3 kg, SD 0.4 kg; overall GWG from pre- to postintervention: 1.2 kg, SD 0.8 kg), we expect the HMZ 2.0 intervention to be more effective. We anticipate that our mean difference will be closer to what a recent study [155] found for the mean difference in GWG between the intervention and control groups (mean 3.6 kg, SD 5.7 kg). Conservatively, considering this larger SD of 5.7 kg and anticipating a larger dropout rate of 10%, the sample size of 144 yields 80% statistical power with a 2-sided significance level of .05 to detect an absolute difference of at least 2.9 kg in GWG between groups. Sample sizes for semistructured interviews are adequate to observe data saturation [136,137,141].

Results

HMZ 2.0 Control Optimization Efficacy RCT

Recruitment began in April 2024 and will continue through May 2027. All data are expected to be collected by December 2027. Currently, we have 193 participant contacts, of which 119 (91%) have been assessed for eligibility and 12 (50% of eligible participants) are enrolled in the RCT (Figure 7). Full results will be uploaded on the ClinicalTrials.gov website at the end of the trial, which is anticipated in January 2028.

Figure 7. Healthy Mom Zone (HMZ) 2.0 CONSORT (Consolidated Standards of Reporting Trials) diagram.

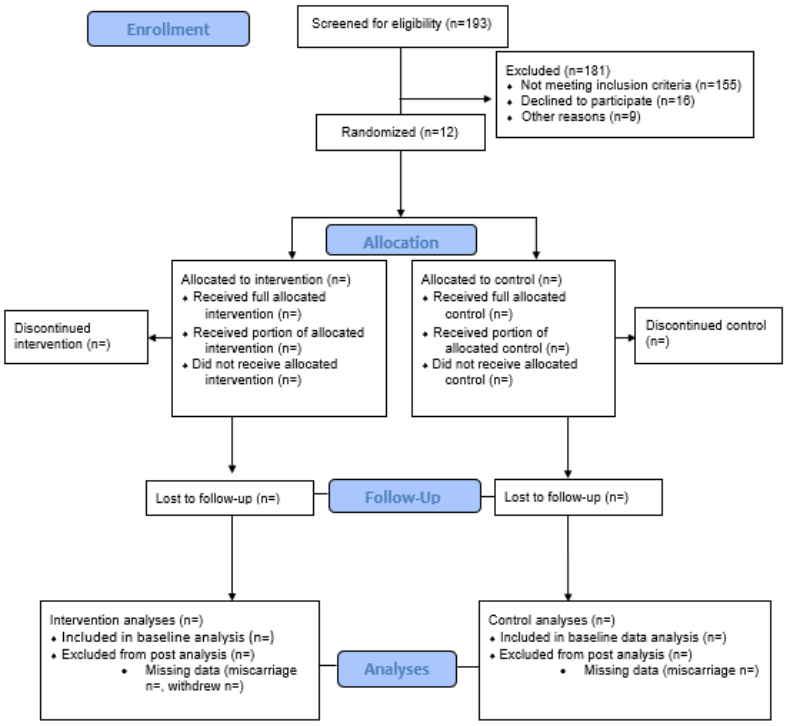

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Discussion

Overview

To our knowledge, there are no other adaptive behavioral interventions aiming to regulate GWG with a theory-driven, energy balance model–based predictive control system, highlighting the novelty of our approach. We have made every effort to obtain robust and unbiased results in this trial. We have established the proof-of-concept and tested the feasibility of the intervention dosages, safety protocols, and strategies to retain subjects for this trial. The hypotheses to be tested are based on a sound foundation of preliminary data [10,11,13,14,19,42-45,140]. We have also pilot tested several aspects of HMZ 2.0. Findings from the HMZ 2.0 pilot study showed successful recruitment from multiple methods, excellent participant compliance with the measurement protocol and transfer of data from devices and online surveys to the digital platform, user acceptability of intervention sessions delivered through the platform, and utility of the predictive controller for informing dosage change decisions. We will use a randomized study design for the control optimization trial to test the efficacy of the HMZ 2.0 intervention and automated data pipeline and digital web-based platform compared to an attention control group. Data will be collected from all subjects to measure primary and secondary outcomes with valid and reliable measures. We will show the reproducibility of mHealth measures by having all subjects complete the same measures over time. Intervention content, measurement and implementation evaluation protocols, and intervention materials are available for reproducibility. The HMZ 2.0 digital platform and new model-based predictive control system have been built in MATLAB Compiler for reproduction with limited license restrictions. The HMZ 2.0 digital platform is a central hub for the automated data pipeline and web interface for intervention delivery. The data pipeline uses Apache Airflow for robust and dynamic scheduling and implements a multilayer real-time monitoring system. The web interface leverages the Django framework to deliver a rich user experience with role-based access control. The digital platform greatly improves the efficiency of this collaboration study by facilitating information sharing and reducing the turnaround time among researchers, consultants, and patients. Since both Airflow and Django are readily scalable (eg, through parallelism and caching), this digital platform can easily accommodate scale-up in the future.

Limitations

There are many strengths of this study, including clinical and public health significance, novel methods, introduction of the HMZ 2.0 digital platform and model-based predictive control system with personalized dynamic energy balance models for each subject to automate dosage changes and predict GWG, use of a back-calculation method to estimate EI, pilot data [10,11,13,14,19,42-45,140] to support the rigor and reproducibility of the proposed methods, and strong potential for future scalability. Despite these strengths, participant compliance in RCTs is an ongoing challenge, and thus, we have incorporated strategies (eg, staff support, easy passive data collection, and remote delivery of the intervention) to facilitate compliance. We have also worked through technical aspects of the data pipeline and digital platform to reduce technical challenges. Lastly, there is a risk that the HMZ 2.0 study may be underpowered based on the assumptions used in the sample size estimation, but this is true for any power analysis.

Conclusions

The approach involving the HMZ 2.0 intervention and use of a control optimization trial [46] to examine the efficacy of the intervention in terms of GWG and related maternal-infant outcomes expands the boundaries of GWG interventions, uses novel methods and automated decision making, and has clinical and public health impacts in a high-risk population of pregnant women with overweight or obesity and their offspring. There is excellent potential to further refine HMZ 2.0 in the future to regulate GWG in women of all BMI categories and scale-up HMZ 2.0 for use by clinicians as an adjunct treatment in prenatal care. There may also be a way to optimize the digital platform in the future so that it can be safely and directly used by pregnant women. HMZ 2.0 may also serve as a model for how the control systems methodology and a digital platform can be used to automate dosage change decisions for other behavior interventions such as those involving regulation of diabetes, weight loss, and related health outcomes.

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Data Availability

Data cannot be shared publicly because the data collected from human subjects have not been approved for public sharing. Moreover, since the data are of human subjects, a data transfer agreement is needed. Data are available from the principal investigator DSD (dsd11@psu.edu or 814-863-0456) and the Pennsylvania State University Office for Research Protections (orp@psu.edu or 814-865-1775) for researchers who meet the criteria for access to confidential data.

Authors' Contributions

DSD was responsible for intellectual design, framework, and writing of the manuscript, and organized and led a team for co-writing and providing insights on sections. AMP was responsible for co-writing the methods and results, figures, tables, and references, and provided edits to the manuscript. DER was responsible for assistance with the framework of the manuscript, provided insights on control systems engineering aspects of the paper, and provided edits to the overall manuscript. JSS and AMM were responsible for providing insights on the healthy eating aspects of the Healthy Mom Zone (HMZ) intervention and provided edits to the overall manuscript. SC was responsible for providing insights on intervention personalization, data collection, and analysis descriptions, and provided edits to the overall manuscript. CL and DS were responsible for providing insights on HMZ digital platform description and provided edits to the overall manuscript. JMP was responsible for providing insights on HMZ recruitment and retention descriptions, and provided edits to the overall manuscript. AK was responsible for co-writing of the analysis, power, and sample size descriptions, and provided edits to the overall manuscript. OK was responsible for providing insights on control systems engineering aspects of the paper and developing the figures and figure descriptions, and provided edits to the overall manuscript.

Conflicts of Interest

AK owns stock in Merck, a pharmaceutical company. However, Merck was not involved with this particular manuscript.

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Abbreviations

EI: energy intake
GWG: gestational weight gain
HMZ: Healthy Mom Zone
IOM: Institutes of Medicine
IRB: Institutional Review Board
PA: physical activity
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
RMR: resting metabolic rate

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Protocol

Acceptability and Preliminary Efficacy of a Novel Web-Based Physical Activity for the Heart (PATH) Intervention Designed to Promote Physical Activity in Adults With Obesity: Protocol for a Pilot Randomized Controlled Trial

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Abstract

Background: Even in the absence of weight loss, any level of physical activity (PA) can reduce the risk of cardiovascular disease among individuals with obesity. However, these individuals face multifaceted barriers that reduce their motivation and engagement in PA. They prefer programs that are convenient, fun to engage in, and feature people who they can relate to. Yet, there is a paucity of PA interventions that are designed to incorporate these preferences. We designed the web-based PA for The Heart (PATH) intervention to address this gap.

Objective: This study aimed to describe the protocol of a study that aims to examine the acceptability and preliminary efficacy of PATH intervention among insufficiently active adults with obesity aged at least 18 years.

Methods: This is a 6-month pilot randomized controlled trial (RCT), using a parallel design with 1:1 allocation to intervention or control group. The PATH intervention group is given access to the PATH platform, but the resources each participant can access are tailored according to their baseline fitness level. Control group receives a self-help PA handout. Both groups self-monitor their PA using Fitbit (Google) and have Zoom (Zoom Video Communications) meetings twice a month with either the health coach (intervention) or study coordinator (control). The outcomes at 6-months include acceptability, changes in PA, and cardiometabolic risk from baseline to 6-months.

Results: We screened 763 individuals for eligibility and 89 participants were enrolled and randomized to the intervention (45/504, 50.6%) and control arms (44/504, 49.4%). The average age was 48.7 (SD 12.17) years, and most participants were female (81/504, 90.1%), Black (45/504, 50.6%), and non-Hispanic (83/504, 93.3%). No systematic differences in baseline characteristics were observed between the study arms. The 6-month intervention is currently underway, and the completion of follow-up data collection is expected in February 2025, with results to be published soon after.

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Conclusions: The PATH intervention offers a promising, evidence-based approach to overcoming the barriers that have hindered previous PA programs for adults with obesity. It can support new and existing programs to foster long-term maintenance of health-enhancing PA.

Trial Registration: ClinicalTrials.gov NCT05803304; https://clinicaltrials.gov/study/NCT05803304

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KEYWORDS

obesity; physical activity; cardiometabolic risk, body positivity, cardiovascular fitness, self-efficacy

Introduction

Only about 14% of adults with obesity attain the minimum levels of physical activity (PA) recommended by public health guidelines to achieve health benefits [1-3].Low levels of PA contribute to the high population burden of cardiovascular disease (CVD) as they increase the relative risk of stroke, coronary heart disease, and diabetes by 60%, 45%, and 30%, respectively [4-6]. Even in the absence of weight loss, regular PA can significantly reduce the risk of CVD among individuals with obesity [3,7,8]. However, individuals face complex and multifaceted barriers that reduce their motivation and engagement in regular PA for meeting current recommendations [9,10].

Barriers to PA associated with obesity include stigma, shame, poor fitness, and low self-efficacy. These evoke fears of embarrassment and pain, contributing to aversion and avoidance of PA [10-12]. To mitigate these barriers, web-based PA programs targeting adults with obesity have been developed. Preliminary data suggest improved retention for online programs, but the effects on PA are heterogeneous [13]. Limitations of these interventions include the absence of human contact, “one-size-fits-all” strategies, unmet weight-loss expectations, and generic content that fails to address barriers associated with obesity [10,14]. We [15] and others [9,10] have reported that individuals with obesity prefer programs that are convenient, fun to engage in, and feature people who they can relate to with respect to body size, fitness level, and age. Yet, there is a paucity of web-based PA programs that are intentionally designed to flexibly incorporate these preferences [10,16,17].

To address the limitations of previous interventions, our research team designed the web-based PA for The Heart (PATH) intervention. PATH leverages openly accessible platforms, such as YouTube (Alphabet Inc), to provide workout videos that match the specific preferences expressed in our formative studies and the extant literature. In developing PATH, we used an iterative bottom-up approach where our target population was engaged in the selection and rating of the workout videos. Then, highly rated workouts (≥3.5/5 stars) were vetted by the study team for content relevance and safety and then curated on our PATH website in 3 intensity levels (beginner, intermediate, and proficient) to foster gradual progression from low- to high-intensity PA. We added backend features that enable a remote health coach to help users set their PA goals and select a PA regimen that is safe for their fitness level. Each PATH user has a personalized dashboard displaying their recommended workouts and progress toward their PA goals.

We have successfully beta-tested the PATH platform (N=25) and completed a 12-week feasibility study where we met our recruitment goal (N=82) and attained excellent retention (96%). Intervention engagement was high, and the PATH group significantly increased objective moderate to vigorous PA (MVPA) indicating preliminary efficacy [18]. The feedback we obtained from this study included the need to provide resources that can help participants improve their diet, provide feedback on cardiometabolic health indicators, and the need to improve our machine learning algorithm designed to keep the PATH platform up to date.

We used this feedback to further refine the PATH platform by curating nutritional resources focusing on improving diet quality and added a user-facing dashboard with feedback on 5 measures of cardiovascular health including physical activity, blood pressure (BP), weight, heart rate, and sleep efficiency. Also, we optimized the platform’s machine learning algorithm (PATH Fresher) that continually identifies new workout videos that match those preferred by the PATH users to be used in future updates of the platform.

This study describes the latest protocol (version #7, 12/16/2024) of a 6-month pilot randomized controlled trial (RCT), using a parallel design with 1:1 allocation to intervention or control, and designed to assess the preliminary efficacy of the optimized PATH intervention for promoting adherence to PA guidelines among 88 insufficiently active adults with obesity. We hypothesized that participants who are randomized to the optimized PATH intervention will show greater increases in PA at 6 months compared with those assigned to the attention control group. We also hypothesized that the optimized PATH intervention group will have a more favorable cardiometabolic risk profile at 6 months compared with the attention control group.

Methods

Study Design

This is a 6-month, ongoing parallel group RCT including 89 participants with insufficient activity and obesity who are randomized 1:1 to either the PATH intervention or an attention control group. The PATH intervention group are given access to the PATH platform, but the resources each participant can access are tailored according to their baseline fitness level (details described below under optimized PATH intervention).

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In addition, the intervention group receive text and or email reminders to log into PATH and do their workouts based on their preferred schedule and will have twice per month online meetings with fitness coaches to monitor progress and review PA goals. The control group receives the Be Active Your Way booklet which is an evidence-based self-help resource for promoting PA [19] and twice per monthly online meetings with the study coordinator to check-in on their progress in the study and maintain contact. The staff members conducting the study assessments are blinded to randomized group allocation.

Setting and Participants

The study is conducted at Emory University, with participants recruited primarily from the Atlanta metro region. Eligibility criteria include reliable access to the internet, age ≥18 years, BMI ≥30 kg/m^2, successful self-monitoring of PA (≥4 days with ≥10 hours wear time) via a waist-worn ActiGraph accelerometer during a run-in period, and classification as insufficiently active according to the PA Guidelines (<150 min of MVPA per week) based on self-reported PA from the Behavioral Risk Factor Surveillance System PA questionnaire [20]. Exclusion criteria include current participation in a lifestyle modification or weight loss study, pregnancy or intention to become pregnant within 6 months, mobility restrictions, use of implantable electronic medical devices, or any condition that requires supervised PA (eg, stroke). Those with any condition that the PA Readiness Questionnaire (PAR-Q+) [21] identifies as requiring primary care provider review before engaging in unsupervised PA will be required to obtain medical clearance before they are enrolled in the study.

Recruitment

Overview

To obtain our target sample (N=89), we leverage resources available to Emory investigators, including Georgia Clinical and Translational Science Institute, Research Match (registry of research volunteers), electronic mailings, announcements on social media sites, and fliers posted in the community. We are also recruiting from primary care practices affiliated with Emory Health care, with an aim to recruit a diverse sample that includes ≥25% men and ≥30% racial and ethnic minorities.

Screening and Online Questionnaires

Individuals who respond to recruitment solicitations are directed to a web link that provides a brief overview of the study and eligibility criteria. Those who are eligible are guided to follow a link to complete 9 brief questionnaires which are outlined with their validation references in Table 1. For participant convenience, the questionnaires are administered via the REDCap (Research Electronic Data Capture; Vanderbilt University) platform so that they can be completed online in one or multiple sittings within 30 minutes. Data from the questionnaires are used for eligibility screening and will eventually allow us to examine the impact of sleep disturbance, health status, stress, and risk of depression on study outcomes. The eligibility criteria are embedded within the online surveys so that the data collection is terminated when a potential participant enters information that makes them ineligible (eg, history of stroke). Those who complete the REDCap questionnaires and remain eligible for the study are scheduled for a 20-minute phone interview, during which the Mediterranean Eating Pattern for Americans [22] screener and the PA questionnaire [20] are administered by an interviewer. Those who do not meet current PA guidelines (<150 min of MVPA per week) are scheduled for a 15-minute phone call to set up the technology that they will be using in the study.

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Table 1. The questionnaires and assessment schedule.

Questionnaires and scheduled assessments	Baseline	6 months
Screening, health history, and lifestyle questionnaires		
Sociodemographic and medical history questionnaires	✓	✓
PA[a] readiness questionnaire (PAR-Q+) [21]	✓	✓
Poffenbarger exercise habits questionnaire [23]	✓	✓
Barriers Self Efficacy Scale [24]	✓	✓
PROMIS SF[b] sleep disturbance questionnaire [25]	✓	✓
PROMIS SF sleep-related impairment questionnaire [25]	✓	✓
Center for Epidemiologic Studies Depression Scale (CES-D) [26]	✓	✓
NIH[c] toolbox perceived stress [27]	✓	✓
EQ-5D health status instrument (EQ-5D-5L) [28]	✓	✓
Questionnaires measuring PA and potential PA mediators		
Mediterranean eating pattern for Americans questionnaire [22]	✓	✓
BRFSS[d] physical activity questionnaire [20]	✓	✓
All of us research program lifestyle survey (smoking and alcohol)	✓	✓
Exercise Self-efficacy Scale [29]	✓	✓
Self-regulation Questionnaire [30]	✓	✓
Physical Activity Enjoyment Scale [31]	✓	✓
Social Support for Exercise Scale (SSES) [32]	✓	✓
Multidimensional Outcome Expectations for Exercise Scale [33]	✓	✓
Medication history and cardiometabolic assessments		
Medication history	✓	✓
Zoom supervised self-administered blood pressure	✓	✓
Zoom supervised self-administered weight	✓	✓
Zoom guided self-administered waist circumference	✓	✓
Self-reported data for PA index (frequency, intensity, and duration) [34]	✓	✓
Zoom supervised dry blood spot sample collection for HbA1C[e], adiponectin, and lipids (total, LDL[f], and HDL[g] cholesterol)	✓	✓
CVD[h] risk score computed using ASCVD[i] risk calculator [35]	✓	✓
Heart health score computed using life's essential data	✓	✓
American diabetes association risk score [36]	✓	✓
Fitbit charge 5 data on PA (continuous)	✓	✓
ActiGraph GT3X accelerometer data on MVPA[j] (7 days)	✓	✓
Users' feedback		
System Usability Scale [37] and post-intervention survey		✓

[a]PA: physical activity.
[b]PROMIS SF: Patient-Reported Outcomes Measurements Information System.
[c]NIH: National Institutes of Health.
[d]BRFSS: Behavioral Risk Factors Surveillance System.
[e]HbA_{1c}: hemoglobin A_{1c}.
[f]LDL: low-density lipoprotein.
[g]HDL: high-density lipoprotein.
[h]CVD: cardiovascular disease.
[i]ASCVD: atherosclerotic cardiovascular disease.

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[j]MVPA: moderate to vigorous PA.

Technology Set-Up, Informed Consent, and Mediation

Before the technology set-up phone call, we provide potential participants with email instructions on how to install Zoom (Zoom Video Communications; for assessments and coaching), Withings (weight, BP), and Fitbit (PA) apps. During the phone call, the study staff members verified the software installation and provided login credentials for the apps. Next, study staff members review the study procedures and those still interested in the study receive a copy of the informed consent to review and sign via REDCap. Those who consent are asked to complete the All of Us Research Program Lifestyle Survey as well as questionnaires assessing exercise self-efficacy [29], self-regulation [30], PA enjoyment [31], social support [32], and outcome expectancy [33] (Table 1). These validated questionnaires are frequently used to identify facilitators and barriers [29-33] that are known to influence PA and cardiovascular outcomes [38-41]. These questionnaires can be completed in REDCap within approximately 30 minutes and will be repeated at the 6-month follow-up visit. An optional Adverse Childhood Experiences questionnaire will be used to explore difficult childhood experiences that may impact variables of interest in the study. The participants will be asked by the study staff members to give their verbal consent to receive this questionnaire at the end of the study assessment.

Baseline Assessment Via Zoom

Participants who meet all eligibility criteria during screening are scheduled for a baseline assessment via Zoom. Before the assessment, each participant will receive a package with all supplies including a Dry Blood Spot Kit, Fitbit Charge 5, ActiGraph GT3X, Withings Arm BP Monitor, Withings Scale, Perfect Waist Tape Measure, and Stretch Band. During the Zoom visit, the study staff members review the data in the PA readiness questionnaire (PAR-Q+) [21], to ensure that individuals who need primary care practitioner clearance obtain it before they are randomized to the intervention or attention control condition. We use the HIPAA (Health Insurance Portability and Accountability Act)-compliant online Fax (SRFax, Ziff Davis Inc) to send and receive faxes on behalf of participants.

The assessments commence with the study staff members reviewing the waist circumference self-measurement video and guidelines developed by the International Chair on Cardiometabolic Risk [42]. The staff members instruct the participants to go to a private location where they can measure their waist on bare skin using the Perfect Tape Measure. The participant shows the locked tape measure to staff members via the camera. There is evidence for strong correlation coefficients (0.8 to 0.9) between self and technician-measured waist circumference using this method [43-47]. Next, the staff members instruct the participant to wear light clothing and stand on the smart scale footpads with their bare feet to measure weight, percentage body fat, percentage body water, muscle, and BMI. The study team obtains these device-recorded measures via the Withings application programming interface (API) with the PATH platform.

We use the clinically validated Withings Arm BP Monitor for self-measurement of BP [48]. The smart monitor has a one-touch easy-to-read digital screen and a cuff that fits an arm circumference of 22-42 cm (larger cuffs available on request). Staff members will instruct the participant to apply the cuff on the bare left arm, then sit in a chair with both feet resting flat on the floor, with the back straight and supported. After 5 minutes of rest with the left arm resting on a flat surface at heart level, participants will be asked to turn on the BP machine and take 3 measurements at 1-minute intervals. The study team will immediately access the device-recorded BP via Withings API with the PATH platform. Participants with elevated BP (>130/80 mm Hg) will be referred to their primary care practitioner, with a request to update the study team if treatment is initiated. Those with severe hypertension (BP ≥180/110 mm Hg) will be asked to seek urgent medical attention before re-evaluation of their eligibility.

Blood samples for measurement of adipokines (tumor necrosis factor alpha [TNF-α], monocyte chemoattractant protein 1 [MCP-1], interleukin [IL]-1 beta [IL-1β], and IL-6, leptin, and adiponectin) and lipids (low-density lipoprotein [LDL], high-density lipoprotein [HDL], and total cholesterol) are collected via volumetric absorptive microsampling approach using Mitra dry blood spot kits [49]. Study staff members supervise participants collecting the fingerstick sample following the steps outlined in the sample collection tutorial [50]. The samples are mailed by each participant to the laboratory using the included return address. Once at the laboratory, the samples are stored at –80° C and will be processed at the end of the study using established protocols for analysis [51].

Run-In Period

At the end of the baseline assessment, the staff members will instruct participants to wear the ActiGraph GT3X on their waist and Fitbit on their wrist to monitor PA for a 7-day run-in period. The run-in period will help potential participants appreciate study expectations and will provide objective data on baseline MVPA. Individuals will need to wear the Fitbit and ActiGraph GT3X for ≥10 hours on ≥4 days to be eligible in the study [52].

Randomization and Orientation

After the successful completion of the run-in period, nonblinded staff members randomize eligible participants with equal allocation (1:1) to either the PATH intervention or the attention control arm using the REDCap randomization software. Group assignments are generated via a REDCap stratified randomization scheme to achieve a balance between the treatment and control groups regarding age (18-45, 46-64, and ≥65 years), sex (male or female), and race (White or racial and ethnic minorities). The Randomization scheme was developed by the study statistician. After randomization, a study staff member meets with each participant on Zoom to orient them to their randomized group resources. If blinded staff members inadvertently become unblinded, the incident will be noted in the study's log, and they will not conduct end-of-study assessments on the participant. Participants in both groups are

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instructed to wear Fitbit on their nondominant hand during the study using a 24-hour wear protocol.

The PATH Intervention

A health coach will provide each participant with a password-protected profile to access the PATH website and a detailed orientation on how to use all the resources included in PATH. In addition, the health coach will meet remotely with each participant twice per month. The PATH intervention provides counsel and guidance to participants in the development of multiple behavior change strategies to promote long-term adherence to the minimum threshold of PA Guidelines (150 MVPA min/week). The Fitbit and Withing APIs are integrated with our PATH platform to enable near-real-time monitoring of the participant's progress. The interface also enables us to capture longitudinal trends in PA and to display the progress toward their PA goal on each participant's dashboard. The coach will work with each participant in the treatment group to develop their PA prescription guided by the FITT-VP (frequency, intensity, type, time, volume, and progression) principle [53], which recommends the frequency, intensity, duration, type, volume, and progression of PA. Although there are no established standards on how to increase PA, available evidence suggests that it is safe to increase MVPA by 10 minutes per week [54]. Although the weekly MVPA goal translates to about 1000 steps of moderate activity per week [55], the participants are asked to target 500 additional steps per week to make sure that the goals are safe for everyone, including those with morbid obesity.

The coach works with each participant to develop a tailored plan geared toward increasing MVPA by ~10 minutes per week with each coaching encounter. Given the scheduled 12 coaching encounters during the 6-month study period, participants at all levels of fitness will have a chance to develop a PA regimen that is adherent to the PA Guidelines. Participants with relatively high baseline PA are advised to target the higher threshold of the PA Guidelines (300 MVPA minutes per week). Our PA prescription process begins by identifying a suitable PATH level for each participant based on their estimated cardiorespiratory fitness level, which is estimated using a predicted maximum rate of oxygen consumption during incremental exercise (VO_2 maximum) [53]. The VO_2 maximum is predicted using a validated, nonexercise prediction model for peak VO_2 whose covariates include sex, age, waist circumference, resting heart rate, and PA index [34].

Individuals with a predicted VO_2 maximum in the ≤35th percentile for their age and gender are considered for assignment to the Beginner PATH level (includes light-intensity PA metabolic equivalents [METs] of <30 METs). Those with VO_2 maximum above the 35th percentile rank are assigned to the intermediate PATH level, which includes moderate-intensity workouts (3.0-5.9 METs) in addition to the Beginner PATH content. Based on our pilot experience, it is unlikely that a participant will be assigned to begin at the Proficient PATH level which includes vigorous-intensity workout videos (≥6 METs). Rather, participants will be given access to the level based on their rating of perceived exertion (RPE) scores at the intermediate level and coach evaluation. The coach can change the PATH level based on their assessment of the participant's capabilities during the meetings.

After assigning the PATH fitness level, the health coach guides each participant in selecting their weekly PA goal and helps them start slowly with a plan to establish regular exercise frequencies of 3-5 days per week. The coach also guides participants to select activities with intensity to help them progress along the PA continuum (ie, from inactive to light PA and then MVPA). To foster safety, participants are instructed to use the RPE Scale [56] as a guide for adjusting the intensity of their PA regimen. The scale ranges from 6 (no exertion at all) to 20 (maximal exertion) and is embedded within each workout video on PATH. The coaches will also help participants set up Fitbit safe heart rate zones based on their fitness levels, with a goal of progressing to the Cardio Zone (70% and 84% of maximum heart rate) by the end of the study.

Participants are asked to use workouts that elicit perceived exertion ratings between 12 and 14 (ie, moderate intensity) on the RPE Scale. The coach reviews progress made every 2 weeks. More intensity is allowed, including the transition to the next PATH level, when most workouts within the assigned PATH level are perceived to be "fairly light" (≤11 on the RPE Scale). If a participant forgets to rate their workouts, their heart rate during the workout sessions is reviewed during the coaching session, and a goal that aligns with each person's capabilities is discussed between the health coach and participant. This method ensures the prescribed regimen is based on ability and fitness status. Although the health coach provides examples of workout videos that could help participants attain their personalized goals, each participant has access to all resources within their PATH level and is encouraged to select a regimen that includes their preferred workout videos and other types of PA appropriate for their fitness level. The workouts that are recommended by the health coach and those selected by each participant as favorites are featured on their PATH dashboard alongside the self-monitoring data (Figure 1).

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Figure 1. Participants' physical activity for the heart platform dashboard.

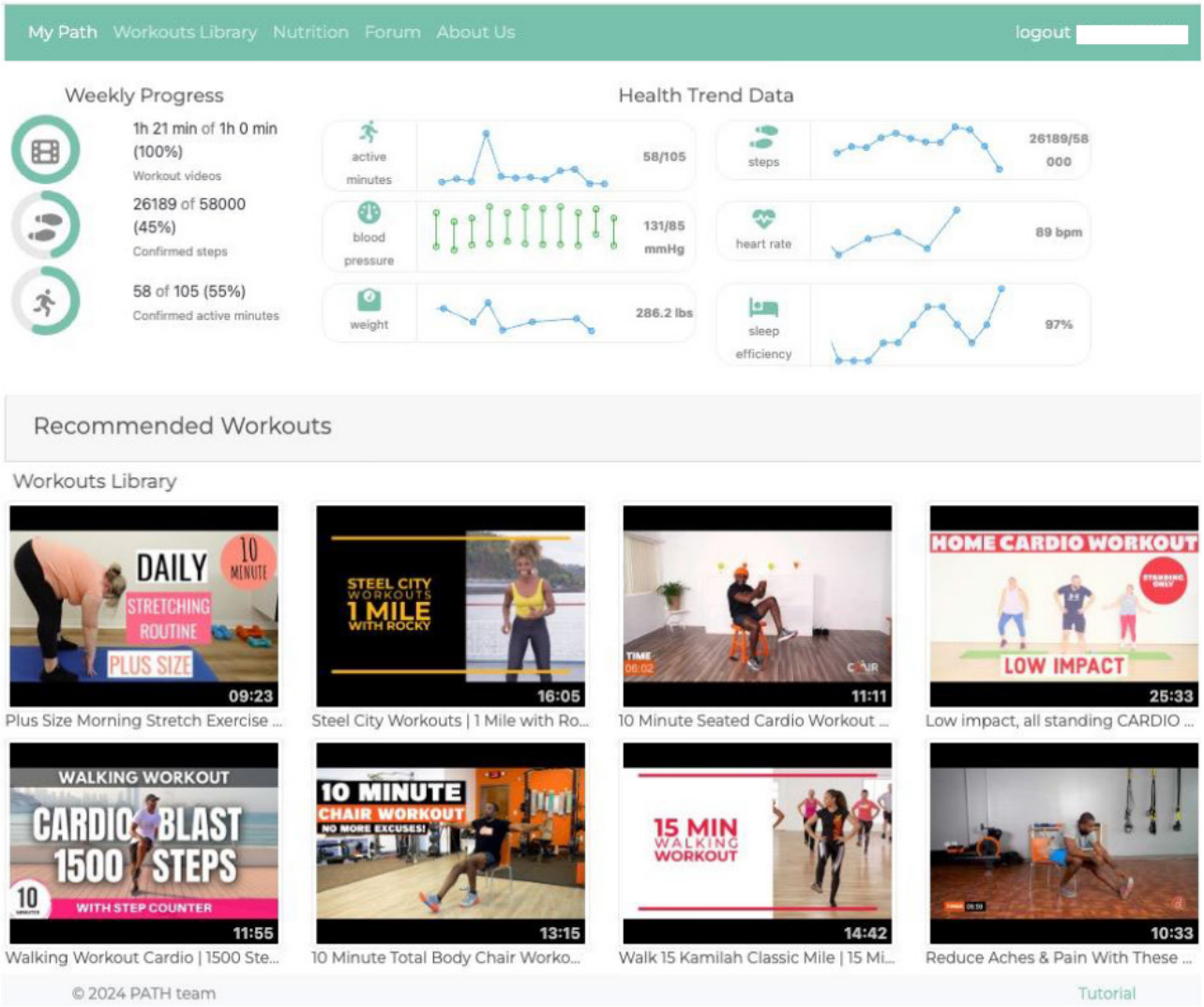

The PA prescription is revised during the online meetings with the coach to reflect the progress made toward the study goal. Those who attain adherence to the PA Guidelines within the first 3 months will achieve the study goal and their plan for the remaining 3 months will be to maintain the improved PA regimen. However, each participant can opt to continue with a gradual increase in PA duration and intensity. To simplify access and support maintenance of PA, the workout videos are organized into categories (eg, walking, dance, and steps aerobics) and can be sorted by duration and METs. To reduce the risk of injury, the amount and intensity of PA are increased gradually, with emphasis on duration followed by intensity per the American College of Sports Medicine [53]. The coach, in consultation with the principal investigator (PI), may discontinue or modify any participant's PA prescription in response to the potential for harm, participant request, or improving or worsening disease. To complete the PA prescription, participants are asked to suggest their preferred schedule for receiving motivational PA reminders (eg, "Remember to work out on PATH today! Exercise doesn't have to leave you exhausted for it to make a difference in your health — M. Richardson"). The short motivational messages are randomly selected from a bank with >270 vetted messages. Also, participants are asked to provide a schedule for the Zoom meetings with a health coach to monitor progress and revise PA goals. During the study, the participants are encouraged to share their experiences on the PATH community forum to foster community and social support. An end-of-study survey will capture feedback on participant experiences and the most helpful aspects of the PATH intervention resources.

The Control Condition

After randomization, study staff members schedule a Zoom meeting with each control group participant where they are guided to use their tracker and Be Active Your Way Guide [19]. They also schedule a check-in meeting with them every 2 weeks, with the intention to keep the contact between the groups as similar as possible.

Protocols for Both Treatment and Control Arms

During the twice per month meetings with intervention and control groups, the participants receive early morning reminders to empty their bladder and step on the scale before meeting with the study staff members who supervise BP measurements on Zoom. These data are used to monitor trends in BP, weight, and body composition during the study period. Both the intervention

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and control arms receive an email with a brief PDF addressing 1 diet component every 4 weeks. The diet information is also available to them as modules on the PATH platform (control group access on PATH is limited to the nutritional resources). At the end of the 6-month study assessments, both control and intervention group participants are given the option to continue using the PATH platform at their convenience without any interaction with the coaches.

Study Outcomes

Indicators of PATH Fresher Algorithm's Effectiveness in Identifying Workouts That Match User Preferences

Effectiveness of the PATH Fresher algorithm will be indicated by its ability to analyze PATH users' data, spin up new browser sessions in the background to activate the YouTube recommender system, and select new workouts like those highly rated (≥3.5/5 stars) by study users. At the end of the study, the coaches will vet the new workouts recommended by the PATH fresher algorithm. The acceptance of ≥50% of the top twenty recommended workouts for inclusion in PATH will indicate the effectiveness of the PATH fresher algorithm. The systems usability survey [37] will be completed by participants to survey satisfaction with the PATH platform.

Acceptability of the Disseminated Educational Resources Focusing on Improving Diet Quality

The resources will be curated from an extensive library of standard behavioral treatment content previously developed and validated by the SMARTER study team [57,58]. Their acceptability will be indicated by 70% of the participants rating the materials as helpful via a researcher-developed end-of-study survey (Multimedia Appendix 1).

Measures of PA and Adherence to PA Guidelines

The efficacy of PATH in enhancing adherence to PA guidelines will be evaluated at 6 months using MVPA data collected using the Actigraph GT3X device [59] worn on the waist for 7 days at 6 months. Adherence to PA guidelines will be defined as achieving ≥150 minutes of MVPA per week. Percent change in adherence will be calculated as follows: ([postintervention MVPA–baseline MVPA]/recommended MVPA×100). Between-group differences in % change in adherence and the proportion of individuals who attain the recommended MVPA will be evaluated. Established and novel methods will be used to process ActiGraph data which will be considered valid if ≥4 days with ≥10 hours of wear time are measured [59]. ActiGraph GT3X nonwear time was defined using the Choi wear time validation algorithm [60]. Fitbit valid data were indicated by ≥4 days with ≥500 steps per day as recommended by Thorndike et al [61] and Bizhanova et al [62]. Sustained PA engagement will be evaluated via Active Zone Minutes data collected via Fitbit Charge 5 and will be analyzed via the adherence strategy described above. Validation studies suggest that Fitbit is ideally suited for long-term self-monitoring of PA due to its user-friendliness and extensive use in RCTs [63].

Measures of Cardiovascular Outcomes

Cardiovascular outcomes will be indicated by change from baseline to end of 6-month study post intervention in CVD risk score calculated using the 2013 Atherosclerotic Cardiovascular Disease Risk Calculator [35]. The algorithm provides sex- and race-specific estimates for the first CVD events. The scores range from 0% to 100% with higher scores representing poor cardiovascular health status. The composite risk factors included in the algorithm are age, total and HDL cholesterol, systolic blood pressure (including treated or untreated status), diabetes, and current smoking status. These will be measured using the protocols outlined under baseline assessment. The main outcome will be between-group differences in risk score change from baseline. We will use the same strategy to evaluate changes in independent risk factors for CVD (secondary outcomes): waist circumference, weight, BP, Life's Essential 8, hemoglobin A_{1c} (HbA_{1c}), adiponectin, and lipids (total, low-density lipoprotein, and HDL cholesterol).

Sample Size Justification

Given our repeated measures study design, we anticipate some participant attrition. To ensure sufficient sample size with complete assessment through 6-months follow-up, we plan to enroll 88 participants (44 per treatment group) retaining at least 76 participants (38 per treatment group) assuming a 14% attrition through the 6-month follow-up based on attrition rates observed in the literature [64]. When estimating within-group changes to describe the effect of PATH on study outcomes using either proportions or means, with at least 38 participants per treatment group (76 total), we would have at least 80% power to detect small-to-medium effect sizes for the efficacy of the PATH intervention. For PA, this corresponds to a mean difference of 20 minutes of MVPA or 13.3% absolute change in terms of adherence to PA guidelines. For CVD risk factors, linear contrasts from either linear or generalized linear mixed modeling will be specified and estimated to compare the treatment groups on the 6-month change in CVD risk scores and risk factors at test wise (Bonferroni-adjusted) significance level of .05.

Statistical Analysis

Data will be analyzed using SAS (version 9.4; SAS Institute) to conduct exploratory data analyses for data screening, including missing data assessment, as well as repeated measures modeling, and modeling of attrition. Mplus (version 8.8; Muthén and Muthén) will be used for mediational analyses to explore possible mechanisms of action of the PATH intervention. Data will first be carefully screened with the results of these preliminary analyses informing the final analysis strategies to be applied to address study aims and exploratory analyses. Although hypotheses are stated as directional, hypothesis testing will be nondirectional with the significance level set to .05 and CI estimation at 95%. The randomness of missing data will be investigated using information on participant characteristics to help discern patterns in the missing data, identify possible missing data mechanisms, and inform strategies to handle missing data. If data are not missing at random, we will apply multiple imputations and 2 extreme case scenarios (worst or best case) to address missing data. If nonrandom missingness is suspected, we will use selection or pattern mixture modeling to explore the sensitivity of results to the assumed missing data patterns.

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An intent-to-treat (ITT) approach will be used to test the efficacy of the PATH intervention on the distal outcome of adherence to the PA guidelines over time. Since key study end points are assessed at multiple time points, repeated measures modeling (eg, linear or generalized linear mixed modeling methods and or marginal modeling using generalized estimating equations as appropriate, both assuming a normal error structure) will be used to test the efficacy of the PATH intervention on the measures of adherence to the PA guidelines over time (baseline [0 months], and 6 months [long-term] follow-up). To test the hypothesis that the PATH intervention group will have greater adherence to PA guidelines compared with the attention control group, linear contrasts will be specified and estimated to compare adherence to PA guidelines between the treatment groups at 6 months relative to baseline values, respectively. The test wise significance level will be set to .05 (Bonferroni-adjusted). Point and interval (95% CIs) estimates based on linear contrasts will also be computed as both unstandardized and standardized effect sizes of the efficacy of the PATH intervention.

Analysis Strategy to Compare the Effects of the PATH Intervention on CVD Risk Factors

A similar repeated measures modeling approach as outlined above will be used to evaluate the efficacy of the PATH intervention compared with the attention control condition on CVD risk factors including CVD risk score, weight, BP, waist circumference, HbA_{1c}, and lipids at 6-month follow-up. These measures of CVD risk are either interval or ratio scaled, and a normal error structure (or following a suitable data transformation) will be assumed when modeling. As necessary, generalized linear mixed modeling assuming a binomial error will be applied to model CVD risk factors dichotomized based on clinically meaningful cut points. To test the hypothesis that the PATH intervention group will have a greater reduction in CVD risk score versus the control group, linear contrasts will be specified and estimated to compare the treatment groups on the change in CVD risk scores at 6-months follow-up relative to baseline values at a test wise significance level of .05 and CI estimation at 95%.

Data Management

Overview

All technologies to be used in this study, including the AWS web hosting platform, PATH website, Twilio, SR Fax, ActiGraph GT3X, Fitbit, and Withings apps were reviewed and approved by Emory University's Enterprise Information Security Team. The entire data collection infrastructure, including the REDCap and PATH platforms, were tested by the study team before it was deployed for data collection. Data will be stored on a password-protected computer with access limited to the staff members who monitor participants' adherence and safety, and the data management team. Access to the master list of participant names and ID numbers will be limited to the staff members who conduct the screening and intervention procedures as they need to interact with these individuals on a name basis. The staff members who do not interact with participants are blinded to name and treatment assignment. The primary outcomes will be shared in scientific conferences and peer-reviewed publications. Investigators seeking to use the deidentified data will sign a data user agreement with Emory University.

Plans to Monitor the Data to Ensure Safety of Participants and Data Integrity

A data safety and monitoring plan will be implemented to ensure the safety of all participants involved in the study and to ensure the validity and integrity of the collected data. The PI and biostatistician (in conjunction with the project coordinators and staff members), will be responsible for the execution of this plan under the oversight of a safety officer and the institutional review board (IRB). The safety officer will act in an advisory capacity to the PI and the National Institutes of Health program director. All adverse events will be documented in REDCap and reported in publications. Major adverse events will be reported to IRB following established protocols. To posttrial care or compensation for harm will be provided. The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist is provided in Multimedia Appendix 2.

Ethical Considerations

The Emory IRB approved the study protocol before beginning the study (IRB approval #STUDY00005168). Written informed consent is obtained from all participants before participation in study procedures. Data is collected using the encrypted and password-protected REDCap and PATH platforms. Identifiable data is only stored in REDCap and is deidentified before being exported for analysis. Confidentiality will be ensured by the use of a simple ID number, which is not encoded to denote other variables. Participants received US $100 compensation and were allowed to keep their Fitbit tracker and Smart Scale for their participation in the study.

Results

We screened 763 individuals for eligibility and 89 participants were enrolled and randomized to the intervention (45/504, 50.6%) and control arms (44/504, 49.4%). The average age was 48.7 (SD 12.17) years, and most participants were female (81/504, 90.1%), Black (45/504, 50.6%), and non-Hispanic (83/504, 93.3%). No systematic differences in baseline characteristics were observed between the study arms. The 6-month intervention is currently underway, and the completion of follow-up data collection is expected in February 2025, with results to be published in the Spring of 2025. Figure 2 presents the CONSORT (Consolidated Standards of Reporting Trials) flow diagram with the screening, enrollment, and randomization details.

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Figure 2. The CONSORT flow diagram.

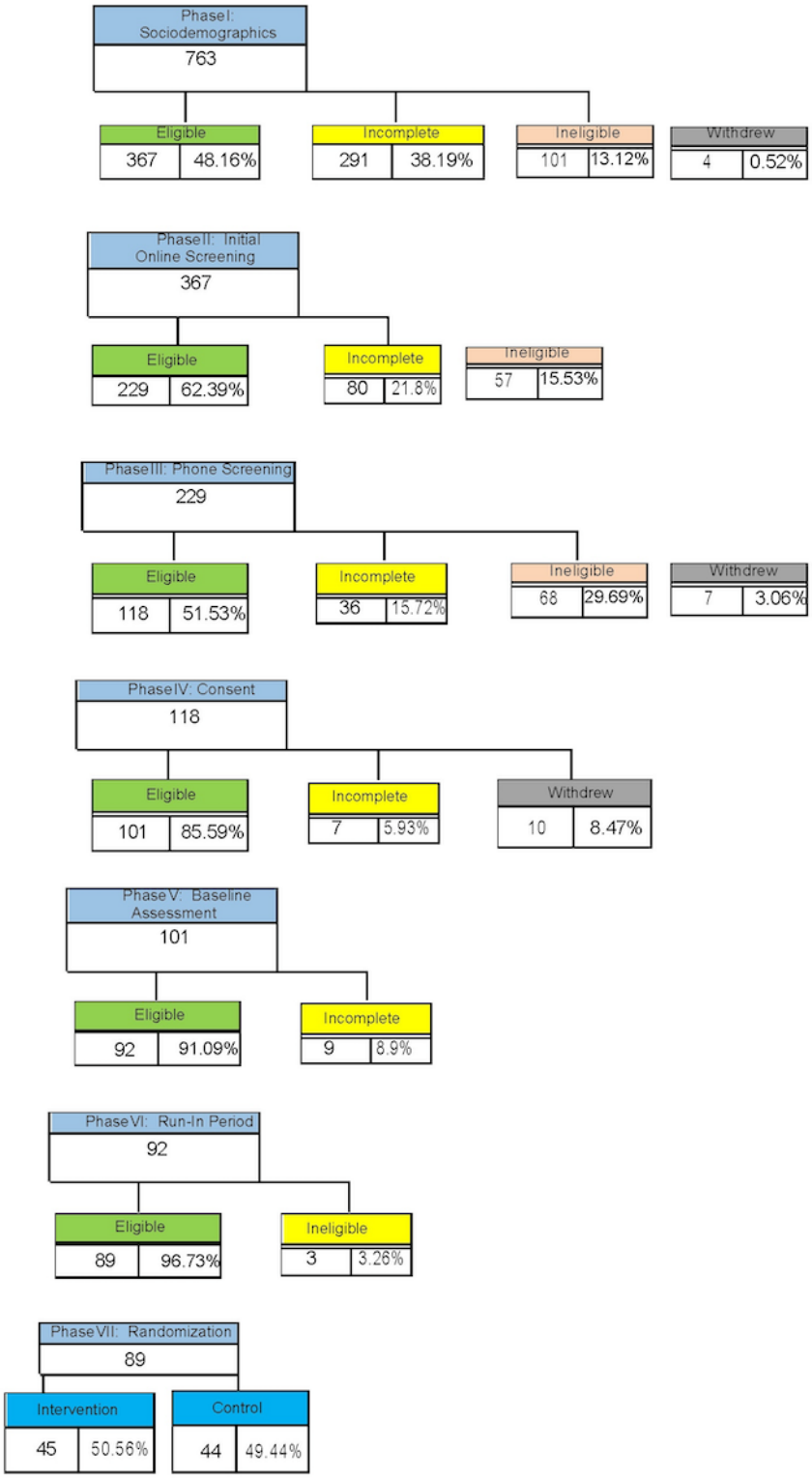

Discussion

Anticipated Findings

The significance of addressing physical inactivity in adults with obesity cannot be overstated. The PATH intervention is testing a novel strategy for addressing the multifaceted barriers to PA among adults with obesity. Our study protocol is grounded in the understanding that traditional PA programs often fail to engage this population because they do not address their unique barriers to PA including stigma, poor fitness, low self-efficacy, unmet weight loss expectations, and limited access to relatable exercise programs [10,15]. By engaging users via tailored workout videos, online coaching, and digital self-monitoring tools, the PATH intervention offers a scalable, participant-centered, and highly accessible solution to address barriers to PA engagement among individuals with obesity. The weight-neutral messaging included in PATH programming is

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intentionally designed to help participants focus on getting active without being discouraged by limited weight loss progress.

Preliminary evidence from formative studies suggests that the PATH intervention is promising in promoting PA engagement and adherence among adults with obesity [18]. The integration of personalized online coaching with a highly accessible and user-friendly web-based platform addresses key limitations of previous web-based and mobile health (mHealth) PA interventions, which often lacked the individualized support necessary to sustain long-term behavior change [10,14,16]. Our approach in this RCT aligns with that used in recent studies that have highlighted the importance of combining technology with human interaction to promote engagement and adherence in PA programs [14,18]. Moreover, the use of validated smart digital tools (eg, Fitbit tracker, Withings scale, and BP monitor) that are interfaced with the user-facing dashboard on PATH facilitates near–real-time accurate monitoring of multiple cardiovascular health indicators without increasing participant burden. These tools enable the coaches to offer timely feedback and appropriate support during online coaching sessions, helping the participants maintain PA engagement over time.

If successful in promoting PA adherence, the PATH intervention could provide a practical, scalable option that health care providers can recommend to patients who struggle with PA adherence, especially those with obesity. Because PA has been shown to reduce the risk of CVD even without weight loss [8], the PATH intervention has the potential to play a critical role in improving health outcomes in this high-risk population. The program's weight-neutral messaging encourages the participants to focus on being active with the goal of achieving cardiovascular health benefits, even if no weight loss is attained. This careful messaging is intended to mitigate unmet weight loss expectations, which are a major impediment to long-term adherence to PA in this high-risk population [12].

Understanding the mechanisms of action underlying the efficacy of PATH is highly significant. In this study, we are examining factors such as self-efficacy, social support, and outcome expectations to gain more insights into how the PATH intervention facilitates behavior change. These data will inform further refinement and optimization of the PATH platform. The next phase of optimization could leverage novel digital health technologies such as artificial intelligence for enhanced personalization to further improve the engagement and efficacy of the PATH intervention. This presents a promising opportunity for providing a more tailored and engaging experience for users, which aligns with the growing trend of technology-enhanced preventive health solutions.

This study has a few limitations that are worth acknowledging. The relatively small sample size may limit the generalizability of findings, and our eligibility criteria may favor participants with higher levels of digital literacy and access to technology. Future research should focus on addressing these limitations by conducting larger-scale trials that evaluate long-term efficacy and sustainability of PA adherence, with proactive strategies to reach populations with limited digital access. Our next logical step will be to conduct a full-scale RCT which will be adequately powered to examine if the PATH intervention can increase long-term PA and cardiometabolic health in adults with obesity. After large-scale efficacy trials, comparative effectiveness studies may be needed to determine how PATH performs relative to other web-based, in-person, or hybrid PA interventions to identify the most effective strategies for promoting PA adherence in adults with obesity. In addition, evaluating the cost-effectiveness of PATH compared to traditional PA programs or other web-based or mHealth interventions is also necessary to examine its value as a sustainable solution in real-world settings.

Moreover, future research should explore how the PATH platform can be further tailored to meet the needs of specific subgroups, such as older adults, individuals from diverse cultural backgrounds, or those with comorbidities like diabetes or hypertension. This will enhance the intervention's relevance and effectiveness for a broader range of individuals. Then, future studies can explore how the PATH intervention can be availed to health care systems to facilitate seamless referral of sedentary high-risk patients by clinicians, making PATH a more practical tool for promoting PA in routine clinical practice. Currently, there are very few options for structured PA programs that health care providers can refer their patients to beyond physical therapy.

Conclusion

In conclusion, the PATH intervention offers a promising, evidence-based approach to overcoming the barriers that have hindered previous PA programs for adults with obesity. For instance, most of the existing supervised PA programs, such as cardiac rehabilitation are usually short-term and address recovery to a baseline–rather than long-term maintenance of health-enhancing PA. By incorporating user preferences, human support, and a flexible, scalable web-based platform, the PATH intervention is poised to significantly improve PA adherence and reduce the risk of CVD in this high-risk population. If the PATH program proves to be efficacious in promoting PA among individuals with obesity, it could be an option for referral at the end of cardiac rehabilitation to promote and maintain a regular PA regimen. The findings from this RCT will contribute valuable insights to the field of research focusing on behavioral interventions to manage obesity, with potential implications for reducing the burden of obesity-related diseases. This aligns with the broader goal of preventive health care models that emphasize lifestyle modification as a cornerstone for managing chronic diseases [12,65].

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Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
The Informed Consent.
[PDF File (Adobe PDF File), 516 KB - resprot_v14i1e67972_app1.pdf]

Multimedia Appendix 2
The SPIRIT checklist.
[DOCX File , 46 KB - resprot_v14i1e67972_app2.docx]

Multimedia Appendix 3
Peer-review report from the Lifestyle Change and Behavioral Health Study Section (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 103 KB - resprot_v14i1e67972_app3.pdf]

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Abbreviations

API: application programming interface
BP: blood pressure
CONSORT: Consolidated Standards of Reporting Trials
CVD: cardiovascular disease
FITT-VP: frequency, intensity, type, time, volume, and progression
HbA1c: hemoglobin A1c
HDL: high-density lipoprotein
HIPAA: Health Insurance Portability and Accountability Act
IL: interleukin
IRB: institutional review board
ITT: intent-to-treat
LDL: low-density lipoprotein
MCP-1: monocyte chemoattractant protein 1
MET: metabolic equivalent
mHealth: mobile health
MVPA: moderate to vigorous physical activity
PA: physical activity
PAR-Q+: PA readiness questionnaire
PATH: Physical Activity for the Heart
PI: principal investigator
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
RPE: rating of perceived exertion
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TNF-α: tumor necrosis factor alpha
VO2 maximum: maximum rate of oxygen consumption during incremental exercise

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Protocol

Theory-Based Social Media Intervention for Nonmedical Use of Prescription Opioids in Young Adults: Protocol for a Randomized Controlled Trial

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Abstract

Background: The nonmedical use of prescription opioids (NMUPO) in young adults in the United States is concerning and is robustly influenced by many psychosocial factors. Given the advantages of flexibility, wide coverage, and real-time responses and assessment, using social media appears to be a promising and innovative approach to delivering psychosocial intervention to young adults. However, few theory-based social media interventions are available for NMUPO targeting this at-risk population.

Objective: Guided by the information-motivation-behavioral skills model, the proposed research aims to address critical gaps by theoretically exploring psychosocial content associated with NMUPO among young adults via formative assessment. These findings will then be used to develop and evaluate the feasibility and preliminary efficacy of a peer-led social media intervention to reduce NMUPO among young adults.

Methods: The proposed study will comprise serial research activities. First, formative research will be conducted through semistructured interviews among 30 young adults engaged in NMUPO. Qualitative data will be synthesized using a pragmatic approach for identifying psychosocial content associated with NMUPO. Second, qualitative findings will be used for developing a peer-led social media intervention to reduce NMUPO among young adults by integrating promising psychotherapy principles and incorporating them with well-trained recovery coaches. Third, the social media intervention will be evaluated through a 12-week randomized controlled trial among 70 young adults (n=35, 50% in the intervention group and control group) engaged in NMUPO via mixed methods, including pre- and postintervention surveys, social media paradata (eg, time-series reactions to posts) collection, and ecological momentary assessment during the intervention. The control group will not receive an intervention but will complete the pre- and postintervention surveys. The primary outcomes will be feasibility, usability, and acceptability, while the secondary outcomes will be psychosocial and behavioral measures, such as past–3-month NMUPO, intention, psychological distress, self-efficacy, resilience, and coping strategies.

Results: The proposed study was funded in May 2024. Social media campaigns have received responses from a total of 379 individuals, with 24 (6.3%) identified as eligible. As of February 10, 2025, we have completed formative interviews with 8 eligible participants.

Conclusions: The proposed study will be one of the first efforts to develop and deliver a theory-based peer-led intervention on social media, incorporating empirical findings on the psychosocial mechanism of NMUPO. The findings of the proposed study

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will provide valuable insights into opioid risk reduction for young adults through an innovative approach. If the tested trial is found to be feasible, the proposed study will contribute to future scaled-up and fully powered psychosocial interventions among young adults and other key populations at risk for NMUPO.

Trial Registration: ClincialTrials.gov NCT06469749; https://clinicaltrials.gov/study/NCT06469749

International Registered Report Identifier (IRRID): DERR1-10.2196/65847

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KEYWORDS

nonmedical use of prescription opioids; opioid misuse; young adults; social media; psychosocial intervention; randomized controlled trial; mixed methods

Introduction

Background

The nonmedical use of prescription opioids (NMUPO) is a critical public health concern in the United States, and young adults are particularly susceptible to this behavior. NMUPO refers to the aberrant use of prescription opioids in a manner other than as prescribed [1-3]. Substance use literature has paid increasing attention to NMUPO owing to its adverse consequences. National US data have shown a substantial increase of opioid-related overdose deaths, from <5000 in 1999 to >100,000 in 2023 [4,5]. NMUPO has also led to extensive medical costs in the United States (US $78.5 billion annually) [6]. Young adults (aged between 18 and 25 y) are at a high risk for NMUPO. In 2019, 5.5% of young adults in the United States engaged in past-year NMUPO, compared to 2.3% to 3.5% for other age groups. This rate was even higher among those who were not enrolled in college (6.3%) [7]. Besides the risk of overdose and dependence, NMUPO is associated with other negative outcomes, including health-jeopardizing behaviors (eg, driving under the influence), sexual risk behaviors, and suicide attempts [1,8-11]. In response to this issue, many US jurisdictions have launched initiatives to monitor prescription opioids [12]. Despite an obvious reduction in the prescribing rate (eg, 47% in 2019 to 38% in 2023) [12], NMUPO-related deaths remain high (>100,000 in 2023). Notably, NMUPO is strongly linked with the initiation of heroin and synthetic opioid use (eg, fentanyl) in young adults, posing a substantial risk for the development of substance use disorder (SUD) and overdose [13]. Hence, interventions targeting young adults are urgently needed to address NMUPO, and those should be delivered beyond the college population [14].

Interventions for NMUPO in young adults should take psychosocial factors into account. NMUPO literature has identified several important psychosocial factors associated with NMUPO in young adults, including perceived stress (eg, academic strain and traumatic stress), psychiatric distress (eg, depression and anxiety), perception of risk, peer and family influences, and sensation seeking [15-18]. Tam and his colleagues' previous research on NMUPO in college students has indicated several additional factors that reduce risk for NMUPO, such as psychological resilience, positive coping, outcome expectancies, and self-esteem [10,19-21]. Importantly, psychosocial factors robustly contribute to NMUPO. A meta-analysis study revealed that pooled effect sizes of psychosocial factors on NMUPO (odds ratios 2.14-2.45) were higher than those of somatic symptoms (odds ratio 0.81-1.76), which are traditionally viewed as major NMUPO determinants [22]. These findings indicate that interventions should be guided by a structured framework between psychosocial factors and health actions for NMUPO.

There are a handful of interventions that have been recently developed to address psychosocial aspects of NMUPO in young populations [23-25]. Although these programs have shown some efficacy, they encounter numerous challenges. First, most programs have been adapted from existing substance use interventions that were not originally designed for NMUPO. For example, some content specific to opioids (eg, the risk for overdose and pain relief expectancy) are absent from these programs, yet these factors significantly contribute to health action related to NMUPO. Second, most programs were delivered in schools and failed to target young adults who did not attend college or were difficult to reach. Third, the flexibility of these interventions was limited because they were delivered by professionals in an in-person setting. Furthermore, literature on substance misuse prevention in young adults has revealed several drawbacks to the in-person context, such as limited trust and fear of being stigmatized [26]. These challenges highlight the critical need for an innovative intervention that is based on psychosocial theory, tailored to the NMUPO context, and flexible in real-world settings.

Psychosocial Theoretical Framework for an NMUPO Intervention

To guide an intervention addressing psychosocial aspects of NMUPO, a theoretical framework (Figure 1) was developed based on the information-motivation-behavioral skills (IMB) model [27]. The IMB model has been applauded for its strength in considering a straightforward path diagram for health behavior changes [28]. This model emphasizes that health behavior changes are driven by 3 arrays of psychosocial constructs—information, motivation, and behavioral skills. Information refers to knowledge contributing to a prerequisite for enacting the changes (eg, misinformation of opioids). Motivation includes 2 belief components: personal motivation (eg, outcome expectancies and risk perceptions) and social motivation (eg, social norms and support). Behavioral skills stand for cognitive capacities (eg, self-efficacy and resilience) and behavioral skill sets necessary for adopting the changes (eg, coping or self-regulation skills) or for managing barriers (eg, stress management) [27,28]. Information and motivation can directly affect the target behavior as well as indirectly affect it

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through the acquisition of adjacent behavioral skills. Such a well-structured framework offers clear guidance for intervention practices and suggests that intervention delivery could benefit from targeting information and motivation factors in the initial sessions, along with enhancing the role of behavioral skill training gradually in the intervention. For instance, initial efforts ought to address misinformation and outcome expectancies of substance use, and, as the intervention progresses, sessions should facilitate action by helping participants develop planning strategies and coping skills. Indeed, existing evidence has shown the efficacy of IMB-guided interventions in reducing substance use (ie, tobacco and illicit drugs) [29-32]. Thus, the IMB model is an ideal theoretical choice for developing an intervention for NMUPO.

Figure 1. Theoretical framework for the proposed study. NMUPO: nonmedical use of prescription opioids.

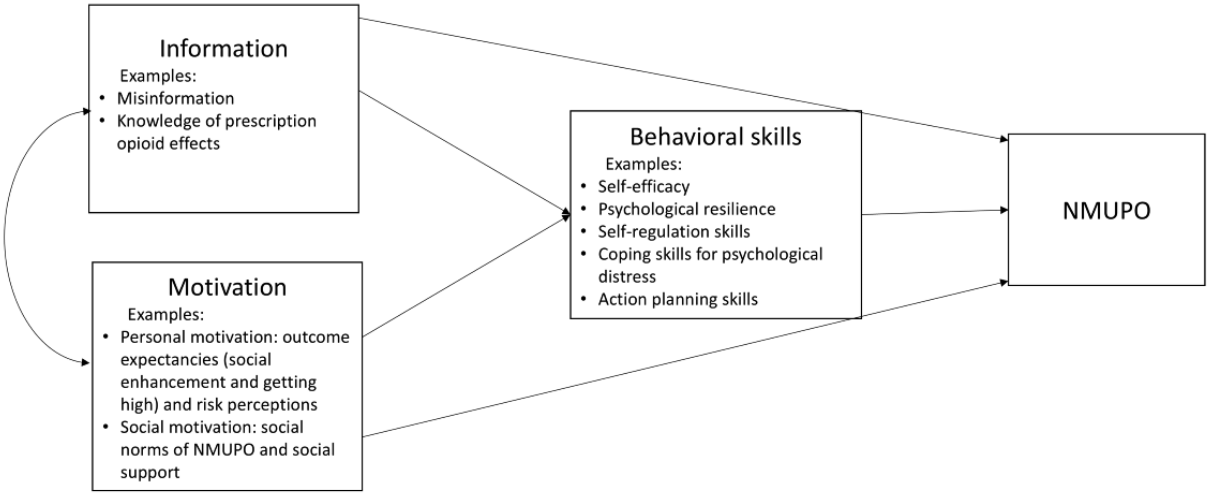

Social Media as a Promising Platform for an NMUPO Intervention Targeting Young Adults

The rapid development of social media technologies provides a novel tool for substance use interventions. Increasing substance use literature has highlighted the significant potential of social media, in which individuals can obtain substance use knowledge, communicate their experiences and thoughts of substance use problems, and seek out social support from peers with similar problems through available networks or groups [33,34]. It is worth noting that social media offers distinct merits in addressing existing challenges in interventions for NMUPO in young adults. First, recent research has validated the use of social media to reach people who engage in NMUPO from multiple venues across the United States [35,36]. Ubiquitous connectivity enables interventions to deliver content remotely to young adults who are not enrolled in college and, therefore, not able to access traditional models of education on safe substance use. Second, social media allows interactive posts in multiple formats (eg, texts, images, polls, and videos) and with customized functions (eg, internet-based goal setting tools and notifications) without time restrictions. This can facilitate exposure to intervention content at the time when participants choose to engage [37]. Third, social media technologies are applicable to timely measurements, such as ecological momentary assessment (EMA) and paradata (eg, auxiliary data of engagement [frequencies of shares, comments, and “likes,” etc] analyses) [38,39], which allow tracking of intervention usability and acceptability on specific modules in real time. Extant literature has shown that EMA has been applied in intervention research for substance use reduction and psychosocial improvements [40]. Fifth, social media is extremely popular among young adults. The latest national data indicate that 72% of US adults use social media, most of whom are young adults (84%) who use it daily (70%) [41].

Another notable feature of social media is that it is significantly favorable for the peer role model, which has been a robust intervention approach for reducing substance use, particularly among young adults [42]. Existing evidence has demonstrated that social media interventions are effective in promoting behavior change for stigmatizing behaviors, including substance use, with perceived peer influence and support playing an important role in the change [43]. Accordingly, emerging peer-led intervention programs have been initiated on popular social media platforms among young adults (ie, Instagram [Meta Platforms, Inc], Facebook [Meta Platforms, Inc], Snapchat [Snap Inc], and Twitter [subsequently rebranded X; X Corp]) and have indicated good feasibility and preliminary efficacy in reducing various substance use behaviors (eg, risky drinking, cigarette use, and cannabis use) [37,42-47]. Notably, promising findings have also been reported for NMUPO reduction. Young et al [45] conducted a pilot study of a peer-led trial on Facebook for patients with chronic pain, who were randomly assigned to the peer-led intervention group or the control group (with no peer leaders) The preliminary results suggested higher engagement and more discussion on NMUPO and coping in the intervention group than in the control group. Taken together, the advantage for the peer role model with other promising aspects, social media appears to be a promising platform for NMUPO intervention among young adults, and such programs would be strongly powered by psychosocial theory–guided content and peer-led modules.

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The Aims of This Study

Overview

This study proposes to develop and pilot-test a theory-guided, peer-led social media intervention on Instagram as well as examine its feasibility and preliminary efficacy among young adults engaged in recent NMUPO via a randomized controlled trial (RCT). The assessments will use mixed methods to collect various types of data, including qualitative assessment of semistructured interviews; psychometric measures in pre- and postintervention surveys; real-time paradata on social media platforms; and brief, timely measures in EMA surveys during the intervention. The specific aims are mentioned below.

Aim 1

Aim 1 involves conducting a formative study to inform a theory-based social media intervention for NMUPO among young adults in the United States. By collaborating with 4 peer leaders trained as "recovery coaches," the proposed study will recruit 30 young US adults (aged 18-25 y) who engage in NMUPO from social media (eg, Instagram) and conduct in-depth semistructured interviews to explore psychosocial content associated with NMUPO. The interviews will be guided by the IMB model.

Aim 2

Aim 2 involves developing a theory-based social intervention to reduce NMUPO among young adults. The intervention will be developed upon findings from the formative study and based on several promising strategies (eg, peer support group, ambivalence resolving techniques, interactive training modules, internet-based goal setting, and video modeling). It will be delivered via Instagram private groups by peer leaders, with close supervision provided by experts and clinicians in the fields of health psychology and addiction medicine.

Aim 3

Aim 3 involves testing the feasibility and preliminary efficacy of the theory-based social media intervention with a randomized controlled design for NMUPO among young adults. Participants who engage in recent NMUPO will be randomly assigned to 1 of the 2 parallel groups, including the intervention group (35/70, 50%) and control group (35/70, 50%), using a 1:1 allocation ratio. The intervention will be evaluated in terms of feasibility, usability, acceptability, engagement, dose, and preliminary efficacy using mixed methods (eg, surveys, EMA, paradata, and semistructured interviews). During the intervention, EMA (a prompt every 2 days) will assess the acceptability and usability of individual modules. Preliminary efficacy will be tested on behavioral outcomes (ie, past-month NMUPO) and psychosocial factors (eg, outcome expectancy, self-efficacy, action or coping planning, resilience, and psychiatric symptoms).

Methods

Research Settings and Participants

Research Platforms

The proposed formative and intervention study will be conducted on Instagram, which is a popular social media platform for young US adults (71% use) [41,48] and home to many support groups for substance use prevention and reduction [49,50]. Recruitment sites will expand to Snapchat and Facebook (>65% use) [41], which are identified as useful recruitment sources for substance use prevention in young US adults [51,52]. As a pilot study for a cross-platform trial, the module prototypes will be developed based on Instagram features available on other platforms (eg, live streaming, voting polls, group chatting, and multimedia posting). Recent interventions developed on these features indicated efficacy on behavioral changes, including drug use [37,45,46,53-56].

Peer Leaders

The study will engage 4 peer leaders who are serving in recovery programs at substance use–related associations or communities for young adults (ie, Gamecock Recovery at the University of South Carolina). The study takes advantage of this model in various aspects, including recruitment and intervention development or delivery. Eligible leaders will be those who are (1) aged between 18 and 25 years, (2) formally trained as a recovery coach (>40 h), (3) have had successful recovery from opioid misuse or opioid use disorder, and (4) use social media (eg, Instagram, Facebook, and Snapchat) on a daily basis. The health psychologist and addiction treatment experts and doctoral-level clinical psychology trainees at the Integrated Care for Recovery (I-CaRe) Training Center at the University of South Carolina will provide training and ongoing support for the peer leaders. e-gift cards will be provided to compensate for their time (US $2 for each recruitment; US $30/h for intervention).

Participants and Recruitment

Participants for the formative study and intervention trial will be those who meet the following inclusion criteria: (1) aged between 18 and 25 years, (2) US residents, (3) engaged in NMUPO in the past 3 months, and (4) using Instagram at least 3 times a week in the past 3 months. NMUPO refers to the occurrence of the following behaviors (1 time or more): (1) taking a prescription opioid without a prescription, (2) taking more doses than prescribed, and (3) using opioid for a nonmedical reason (eg, getting high) [1-3]. Individuals will be excluded if they report (1) receiving substance use interventions in the past 3 months, (2) being diagnosed with SUD, or (3) not being proficient in English. We anticipate a total sample size of 100, with 30 for the formative study and 70 for the intervention trial.

The entire recruitment procedure is presented in Figure 2. Recruitment will be conducted using two strategies: (1) peer outreach and (2) advertising campaigns. For the peer outreach approach, peer leaders will distribute recruitment advertisements via online social networking (eg, posting advertisements on their social media accounts and inviting subscribers to repost the advertisements). Peers can also send direct invitations to young adults who they personally know to be eligible for the study. For advertising campaign approaches, we will target the accounts (on Instagram or Facebook) of colleges, local young adult communities (eg, trade unions), and substance use support groups. Upon approval from their group administrators, we will post advertisements in the groups. In addition, we will develop

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targeted advertising using Ads Manager (Meta Platforms, Inc) [57]. The advertisements will display research-relevant images, hashtags, and headings, which are tailored to engaging content for young adults. To ensure appropriateness, the advertisements will be reviewed by a community advisory board. The advertisements for aim 3 will be improved in line with formative research. The Ads Manager will also determine the range of the advertisement campaign in terms of age, time, and locations (ie, the United States). The designed advertisements will be delivered in various formats dependent on the platforms, such as linear posts within personal feeds on Instagram, news feeds on Facebook, and stories on Snapchat. To ensure representativeness, recruitment will be stratified based on key demographics (eg, gender, race or ethnicity, and education) in line with the latest US national data on NMUPO [58]. The advertisements will navigate potential participants to a web-based sign-up survey on REDCap (Research Electronic Data Capture; Vanderbilt University), which is a secured web-based platform monitored by the University of South Carolina. The prescreening survey will include questions in terms of age, past–3-month NMUPO (National Institute on Drug Abuse [NIDA]–Modified Alcohol, Smoking and Substance Involvement Screening Test [59]), US residency, use of social media, and SUD diagnosis or treatment history. Participants who are identified as eligible will provide their preferred contact method (eg, Zoom [Zoom Communications, Inc]) in the survey for a brief preinterview online meeting with the study team for a fraudulent screening. Such a screening will be conducted by checking for inconsistencies in their responses, requesting time-stamped screenshots to prove their locations, and asking for information (eg, brand names) of prescription opioids that they have been using. Eligible participants with no fraud responses will then be invited to complete web-based informed consent. Young adults enrolled in the study will be provided with instructions for interviews (aim 1) or intervention (aim 3).

Our recruitment approaches are considered feasible according to existing data. Feasibility research examined the advertising campaign approach on Facebook to reach young adults engaged in NMUPO, showing that it successfully recruited 689 participants over 2 weeks (91% past-year misuse) [35]. The US national data indicate that the majority of young people with NMUPO do not have SUDs (2801/3257, 85.9%) [60]. Previous substance use studies indicated retention rates of 75% to 93% among young adults reached by social media [46,53,61].

Figure 2. CONSORT (Consolidated Standards of Reporting Trials) flowchart of the proposed study. EMA: ecological momentary assessment; IMB: information-motivation-behavioral skills; NMUPO: nonmedical use of prescription opioids; RCT: randomized controlled trial.

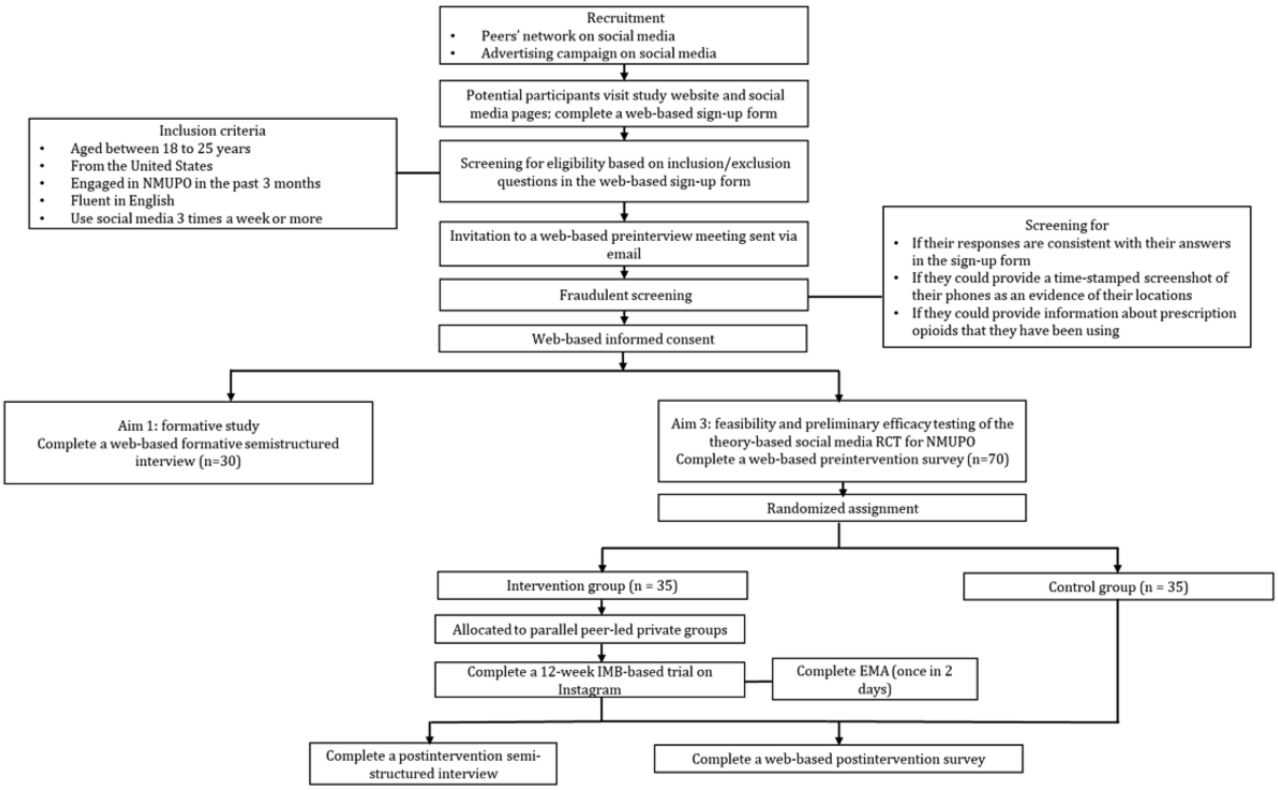

Study Design and Procedures

Aim 1: Formative Study

Young adults who are social media users (eg, Instagram and Facebook) and indicate NMUPO will be invited to web-based 60-minute individual semistructured in-depth interviews. The interview guide will be based on the IMB model and aim to (1) identify NMUPO patterns (eg, drug classes and individual behaviors), (2) understand psychosocial factors contributing to reducing NMUPO, (3) extract vivid examples related to psychosocial content, (4) identify planning processes and coping skills facilitating the change, (5) assess the feasibility and acceptability of social media to manage NMUPO, and (6) review recruitment advertisements. This will provide the foundational knowledge and materials to develop specific content (eg, video and posts) for the intervention. The interviewers will be trained research assistants from the fields of psychology or public

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health. As suggested by the guideline of qualitative research [62], the sample size will be 30 young adults.

Interviews will be audio recorded, transcribed, and coded using a pragmatic approach. The framework analysis [63] will be performed via a deductive process, including five key steps: (1) familiarizing the data, (2) developing a coding scheme, (3) condensing and structuring the data, (4) rearranging the coded data and comparing patterns, and (5) mapping and interpretation [64]. A codebook will be developed based on step 2 as a guide for coding. Coding disagreements will be resolved through group discussion. Data analysis will be conducted on NVivo (version 11.0; Lumivero). Interrater reliability will be assessed throughout the coding process with a goal of ≥0.80 [65].

Aim 2: Intervention Development

Intervention Strategies

The intervention will apply various principles in psychotherapy. The intervention materials (texts, videos, and images) and activities will be developed using the findings from the formative study. To address particular factors in the IMB model, it will be based on peer support for behavioral change, motivational interviewing (MI) [66], cognitive behavioral therapy (CBT) [67], and solution-focused therapy (SFT) [68], which have been widely applied in substance use interventions [69-71]. Peer support is promising for facilitating social support and skill coaching [72]. MI is used to resolve cognitive ambivalence (eg, positive expectancies of substance use vs the benefits of making change), which is particularly beneficial for promoting motivation [73]. CBT is widely applied to distress management by reframing negative thoughts and facilitating adaptive coping [74]. SFT emphasizes a focus on problem-solving and is favorable for setting concrete goals (action planning) [75,76]. This content and these activities will be packed in different modules.

Incorporating inputs from peer leaders, the video content will follow a video prompting strategy [77]. Videos will feature peer leaders and involve breaking tutorials into steps, allowing young adults to learn and rehearse cognitive and behavioral skills in a sequential fashion. For example, guided by CBT, a peer leader may lead participants may lead participants to reflect on the context, thoughts, and consequences, related to their last experience of NMUPO, and then practice adaptive responses (eg, positive reframing and replacement behaviors). Video prompting has been effective for skill coaching in young adults [78].

Intervention Components

Overview

The proposed intervention components are guided by the IMB-based conceptual framework (Figure 1), with each component targeting specific factors derived from 3 psychosocial constructs (ie, information, motivation, and behavioral skills). As outlined in the framework, the pacing of intervention is structured to prioritize addressing information and motivation factors during the initial phases, while later sessions progressively promote behavioral skill training that contributes to psychological distress management and NMUPO reduction. Incorporating Instagram functions, the intervention platform is proposed to consist of four intervention modules, including (1) NMUPO knowledge module, (2) self-care module, (3) internet-based goal setting or monitoring module, and (4) peer support module (Figure 3). These are planned, and final content will be informed by or modified in line with the formative research. The research team will work closely with the community advisory board and peer leaders to ensure appropriate content and language. The intervention will last 12 weeks according to previous social media trials (typically 8-12 wk) [37,44,79-86]. Clinicians will review the intervention materials and ensure the scope is appropriate. Content will be prompted daily as suggested by the IMB model (eg, initially focus on information and motivation factors and gradually enhance the role of behavioral skills).

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Figure 3. Planned intervention modules and strategies. I-CaRe Training Center: Integrated Care for Recovery Training Center; IMB: information-motivation-behavioral skills; NMUPO: nonmedical use of prescription opioids; PI: principal investigator; WDC: Web Development & Communication.

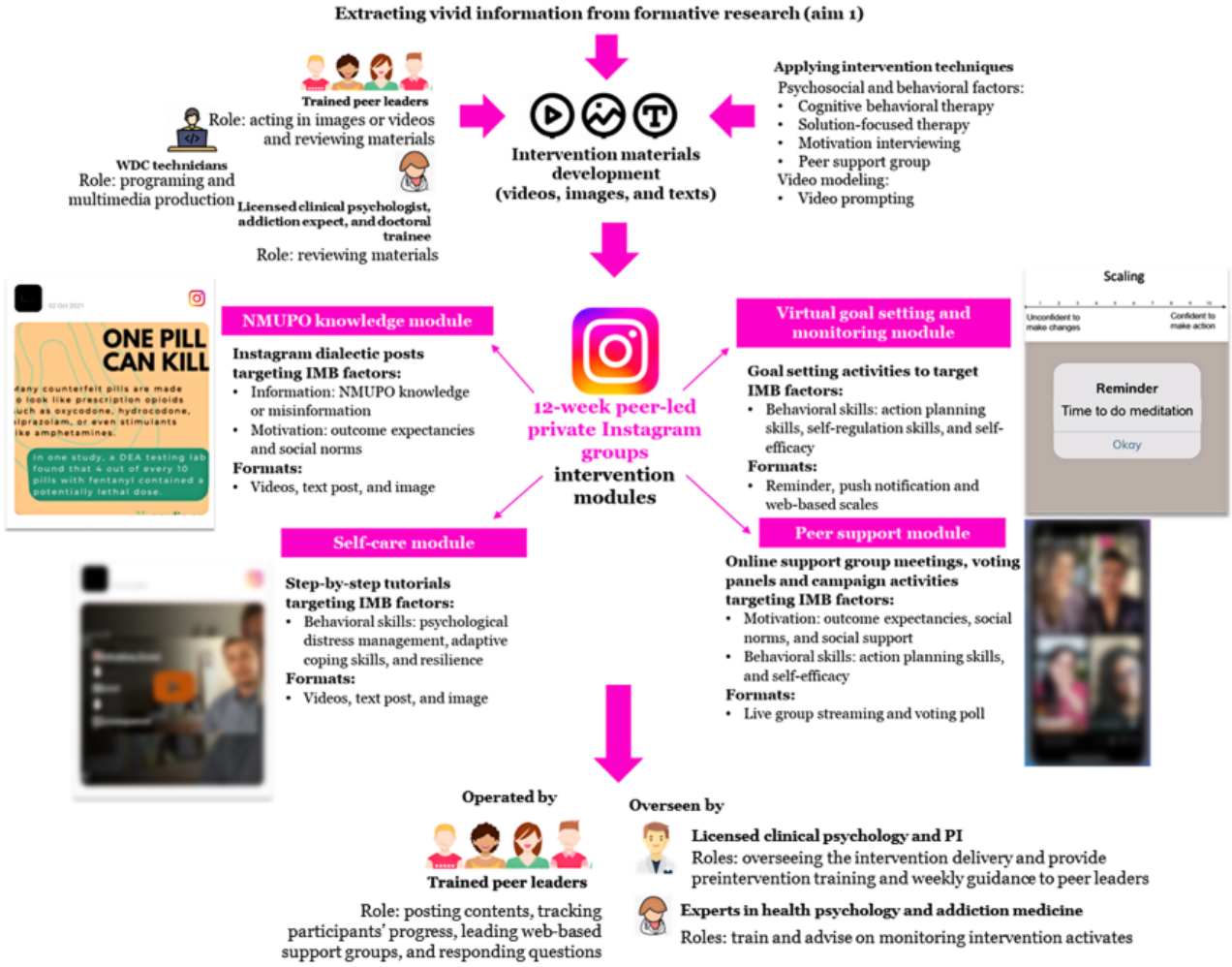

NMUPO Knowledge Module

A self-paced psychoeducation module will be developed targeting information and motivation factors. This module will provide the latest information about prescription opioids (eg, illicit manufacture and the role of fentanyl, naloxone, and xylazine) and the harms of NMUPO, introduce the benefits of use reduction, and clarify misconceptions. Each component will display vivid stories drawn from the formative study and delivered via multiple formats, including images, videos, and text. Participants can react to the posts by leaving comments or by liking the posts. The majority of the content will be based on MI strategies (eg, ambivalence resolution). This media campaign strategy, combined with prevention education, has been identified as an essential approach for reducing NMUPO in young adults [25].

Self-Care Module

This module will provide tutorial materials on behavioral skills for managing psychological distress and identifying strengths to make changes. Material formats (videos, texts, and images), duration, and content will be determined by the findings from the formative study. For example, serial 3-minute tutorial videos will introduce CBT strategies for reframing negative thoughts (eg, "I'm a total failure") and exploring intrapersonal or interpersonal strengths (eg, resilience). Tutorials will be step-by-step based, allowing participants to role-play and rehearse, presented with vivid examples extracted from the formative research (aim 1). Such a self-guided CBT component has proven effective in reducing psychiatric distress [87].

Internet-Based Goal Setting or Monitoring Module

This module aims to enhance action planning skills to reduce NMUPO. Specifically, it will assist young adults with setting personalized goals associated with NMUPO reduction and tracking progress toward meeting the goal. Web-based activities will be developed using SFT strategies. For example, the video will guide using scaling questions, which help participants identify their confidence levels to stop NMUPO and make a realistic plan based on it. Participants will then be instructed to explore barriers and their corresponding coping strategies for moving up the scale. Peer leaders will track their progress and provide support via online support group meetings. In addition, tutorials will instruct participants to set daily reminders or notifications on their devices (eg, mobile phone) to monitor the progress. This virtual self-monitoring has been a promising strategy to manage psychiatric distress and substance use [88].

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Peer Support Module

This module will provide interpersonal activities for discussing NMUPO, sharing strategies, monitoring progress, providing social support, and increasing self-efficacy to take action, with themes based on the aim 1 findings. Activities include weekly (30 min) online support groups, discussion polls, and campaign activities. Online support groups are live video meetings led by peer leaders and assisted by doctoral-level clinical psychology trainees at the I-CaRe Training Center, who will be overseen by a licensed clinical psychologist and principal investigator (PI), under supervision from experts in health psychology and addiction medicine (SH and AHL). Each meeting will discuss personal practices related to content in that week. Peer leaders will use techniques (eg, active listening, insights, and interpretation) [26] to facilitate cohesion and provide feedback. Discussion polls will be voting activities (eg, selecting adaptive coping skills), aiming to stimulate discussions. Campaign activities will be held weekly with target-orientated themes (eg, "#healthy coping challenge") to boost posting. Participants will be encouraged to leave comments and peer leaders will promptly provide feedback.

Intervention Encouragement and Monitoring

Several strategies that are shown to be useful for enhancing engagement will be used [82,84,89-92]: (1) reminder notifications (via Instagram or emails); (2) prompt replies to participants' messages; and (3) biweekly prize draws of US $25 gift cards for those who post, attend meetings, and reply on the panels. The intervention will be overseen by PI and a licensed clinical psychologist at the I-CaRe Training Center, under supervision from experts in addiction medicine and psychotherapy for SUD. They will provide preintervention training (eg, skills in MI or CBT techniques and findings from aim 1) and weekly guidance to peer leaders. They will also advise on referrals to link participants to licensed mental and behavioral health professionals in their states of residence if necessary. The doctoral-level psychology trainees at I-CaRe Training Center will support intervention delivery by (1) ensuring conversations are intervention related and banning inappropriate content; (2) promptly replying to participants' comments; and (3) monitoring participants' safety (eg, emotional reactions to the posts and in the online group meetings) and offering referrals for outside psychological services, if needed. They will also be responsible for reporting adverse events to the PI if observed.

Aim 3: Intervention Feasibility and Preliminary Efficacy Evaluation Study

RCT Design

The intervention modules will be tested through an RCT design using mixed methods in 70 young adults who engage in NMUPO [93]. The primary purpose is to determine acceptability, usability, feasibility, and initial efficacy. Participants reached by peer leaders or advertisements on social media will be navigated to a screening survey on REDCap and scheduling a meeting with the research team for informed consent. Participants will be required to comply with the user safety agreement. Participants will be randomly assigned to the parallel intervention (35/70, 50%) or control group (35/70, 50%) using computer-generated random numbers. Participants are blinded to the randomized assignments. Intervention group will be guided to join Instagram peer-led private groups (n=10-15 each). Participants will be asked to provide their Instagram accounts to their assigned peer leaders for participating in intervention activities. Peer leaders will set up private and independent groups via their Instagram accounts and will send direct invitations to their assigned participants to join groups. Once group membership is confirmed, peer leaders will post intervention materials and lead group activities according to the plan as developed in aim 2. Private groups will synchronously deliver intervention packages over 12 weeks. To ensure confidentiality, participants will be assigned unique study IDs, which will be used for data collection and intervention activities. The intervention group will participate in data collection through multiple formats, including Instagram paradata, pre- and postintervention surveys, EMA surveys, and postintervention semistructured interviews.

The control group will not engage in any intervention activities but will complete the pre- and postintervention surveys.

Web-Based Pre- and Postintervention Surveys

The web-based pre- and postintervention surveys will be developed and administered on REDCap [94] to measure demographic variables as well as psychosocial and behavioral factors outlined in the IMB-based conceptual framework. Factors include NMUPO behaviors (past–3-month NMUPO) and information- and motivation-related factors (ie, NMUPO knowledge, NMUPO risk perception, outcome expectancies, self-efficacy, psychological distress, resilience, and other substance use). Web-based surveys will be conducted among participants in both the intervention and control groups. Participants will receive survey links via inbox messages to the Instagram accounts they provide for the study. The preintervention survey will be sent 2 weeks before the intervention (baseline), and the postintervention survey will be sent in the week immediately following the intervention (12-week follow-up). The survey will be self-administered and take approximately 20 to 30 minutes to complete. If participants cannot complete the surveys at one time, they can save their responses, and the platform will generate a code that allows them to resume the survey within the same week. The survey will also provide forward and back buttons, allowing participants to review and change their responses before they submit their surveys. Study IDs and filling time will be collected for determining duplicate entries. e-gift cards will be provided for the completion of surveys (baseline and 12 weeks; US $30 each).

Use of EMA

EMA will be used through brief evening surveys to screen the prompt acceptability and usability (the Usefulness, Satisfaction, and Ease of use questionnaire) [95] and the dose of particular modules in the intervention group. The EMA survey will be conducted once every 2 days during the intervention. The daily EMA is widely used in behavioral trials [39]. Data will be collected via a 20-second survey on a smartphone app (ExpiWell), which is user-friendly and customizable for EMA development and implementation [96]. A prompt will be sent

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at the moment for assessment and tailored for the intervention materials in the past 2 days. A reminder will be provided if no response is made in 30 minutes. For safety purposes, if an EMA occurs during an incompatible activity (eg, driving), participants will be instructed to ignore or postpone the prompt.

Postintervention Semistructured Interviews

At week 12, participants will join semistructured interviews measuring (1) feasibility, usability, and acceptability and (2) reactions to the content, format, concepts, visual presentation, assessments (survey and EMA) and adaptation to other platforms. The interview guide will be based on mobile health (mHealth) studies [97]. The interview will be audio recorded and take approximately 60 minutes via an online meeting application (eg, Zoom).

Measures

Mixed Methods Measures for Primary Outcomes: Intervention Feasibility Outcomes

Multiple forms of data will be collected within 12 weeks during the intervention for the intervention feasibility evaluation.

Feasibility, Acceptability, and Usability

Mixed methods will be used. Acceptability will be assessed using EMA on Likert items that rate how helpful the module is (1=not at all to 5=extremely). Usability will be measured using EMA on the Usefulness, Satisfaction, and Ease of use questionnaire [95], which assesses perceived usefulness, satisfaction, and ease of use for the module. At week 12, participants will join semistructured interviews measuring (1) feasibility, usability, and acceptability and (2) reactions to the content, format, concepts, visual presentation, assessments (survey and EMA), and adaptation to other platforms. The interview guide will be based on mHealth studies [97].

Engagement

Paradata on participants' interactions with specific modules will be collected, including their frequency of reactions (ie, comments, "likes," questions, and replies on specific posts) and personal posts to Instagram groups [37]. Retention will be assessed by calculating the percentage of participants engaging in the group at varying time points. Data will be collected in real time.

Dose of Intervention

Participants' engagement in particular intervention modules will be measured in EMA surveys as guided by dose operationalization for mHealth interventions [98]. Dose for specific modules will be assessed in three domains (1 yes or no item each): (1) intervention actions (if viewing a post), (2) participant actions (if practicing a skill or completing an assignment), and (3) behavioral target actions (if adopting skills outside of the intervention).

Web-Based Surveys for Demographic Variables and Secondary Outcomes: Psychosocial and Behavioral Outcomes

The web-based surveys will measure demographic factors and psychosocial and behavioral factors outlined in the IMB-based conceptual model (Figure 2).

Demographic Characteristics

In the baseline preintervention survey, participants will be asked to report their background information regarding gender (ie, man, woman, transgender, or other), race or ethnicity (eg, White or African American or Black), age (y), socioeconomic status, education, family or household characteristics, and physical health status (Patient Health Questionnaire-15) [99].

NMUPO Measurement

The past–3-month NMUPO will be measured using relevant items from the Tobacco, Alcohol, Prescription medication, and other Substance use tool [100]. The scale includes 2 sections, with a screener followed by a brief assessment. The screener contains 1 item asking the frequency of NMUPO (ie, used just for feeling, more than prescribed, or without a prescription) with 5 response options (daily or almost daily, weekly, monthly, less than monthly, or never). Participants with a response other than "never" will be led to the brief assessment, including 3 dichotomous questions regarding their level of use, dependence, and concern from others related to the past–3-month NMUPO. The sum score of the brief assessment will be calculated, with a higher score indicating a greater level of NMUPO.

NMUPO Knowledge

Information about NMUPO and relevant topics, such as misconceptions, the role of fentanyl, naloxone, and xylazine, will be assessed using the NMUPO knowledge scale [61]. This scale will be developed according to the measure in POP4Teens and the formative study. This scale is proposed to include 15 statements related to opioids or NMUPO. Participants will be asked to determine if a statement is true or not (0=false and 1=true). Responses will then be rated by the research team, with higher scores indicating better knowledge of NMUPO.

Outcome Expectancies

Beliefs on positive or negative consequences of engaging in NMUPO will be assessed using a scale adapted from the Behaviors, Expectancies, Attitudes, and College Health Questionnaire [101]. A total of 50 items will be scored on a 5-point Likert-type scale ranging from 0 (not at all) to 4 (very often or always), with higher sum scores standing for the greater level of expectancies. The scale consists of 8 dimensions related to specific expectancies of opioids, including pain reduction, tension reduction, academic preference, emotion enhancement, social enhancement, guilt and dependence, cognitive impairment, and physical discomfort.

NMUPO Risk Perception

Perceived susceptibility and severity of engaging in NMUPO will be assessed using the Perceived Risk Scale for Prescription Drug Abuse [102]. This scale includes 5 items with 4 rating options (1="strongly disagree" and 4="strongly agree"). The

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sum score will be generated, with a higher score indicating a greater level of perception risk for NMUPO.

Action Self-Efficacy and Coping Self-Efficacy

Perceived control on making actions to stop or reduce NMUPO or confidence on coping with barriers against the actions will be assessed using an adapted version of the Self-Efficacy Scale [103]. A total of 6 items will be rated on a 5-point Likert scale (1=strongly disagree and 5=strongly agree) and can be organized into 2 subscales (coping self-efficacy and action self-efficacy) with 3 items each. The sum scores will be generated for each subscale, with higher scores indicating greater levels of self-efficacy.

Psychological Distress

Depression and anxiety symptoms in the past 2 weeks will be assessed using the Patient Health Questionnaire-9 [104] and Generalized Anxiety Disorder-7 [105], respectively. The Patient Health Questionnaire-9 is composed of 9 items asking the frequency of depressive mood experiences (eg, “feeling down, depressed, and hopeless”), while the Generalized Anxiety Disorder-7 comprises 7 items assessing the frequency of feelings of nervousness or worry (eg, “not being able to stop or control worrying”). Two scales have 4 response options ranging from 0 (not at all) to 4 (nearly every day). Sum scores for 2 scales will be generated, with higher scores indicating greater levels of depression or anxiety.

Resilience

The Connor-Davidson Resilience Scale will be used for assessing psychological resilience [106]. This scale has 25 items asking about personal capacities in response to stress, including tenacity, tolerance of negative affect, positive acceptance of change, and positive view of adversities. Items will be rated on a 5-point scale (1=not at all and 5=nearly all the time). The sum score will be generated, with a higher score indicating a greater level of resilience.

Other Substance Use

The engagement in the use of alcohol, illicit drugs, and cigarettes in the past 3 months will be assessed using the NIDA-Modified Alcohol, Smoking and Substance Involvement Screening Test [59]. The scale includes 12 dichotomous items (0=no and 1=yes) asking if a participant has engaged in using or misusing any of 12 individual substances.

Data Analysis

The intervention trial will use multiple data analytic methods according to the format of the data.

Qualitative Analyses

Postintervention interviews will be audio recorded, transcribed, and coded using a pragmatic approach. The framework analysis [63] will be performed via a deductive process, including five key steps: (1) familiarizing the data, (2) developing a coding scheme, (3) condensing and structuring the data, (4) rearranging the coded data and comparing patterns, and (5) mapping and interpretating [64]. A codebook will be developed based on step 2 as a guide for coding. Coding disagreements will be resolved through group discussion. Data analysis will be conducted by the PI and graduate assistants on NVivo (version 11.0). Interrater reliability will be assessed throughout the coding process with a goal of ≥0.80 [65]. Analyses for postintervention interviews will synthesize the comments on feasibility, acceptability, and usability of the intervention, as well as summarize suggestions for improvements.

Quantitative Analyses

Bivariate Analyses

Data of web-based surveys (ie, before and after intervention) will be screened for missing data, outliers, and normality. If data are not missing (completely) at random or have a high missing rate (>5%), multiple imputation will be used [107]. Transformations will be conducted if violating normality (square root for moderate skew or log for greater skew). Attrition tests will be used (ie, chi-square tests and ANOVA) on demographics and outcomes at baseline. Descriptive statistics will be reported on primary (feasibility outcomes) and secondary outcomes (psychosocial and behavioral outcomes).

Multivariate Analyses

Preliminary outcomes from baseline and 12 week will be tested using repeated measures analysis of covariance, controlling for demographics. EMA data will be tested using multilevel modeling (ie random-coefficient regression model) to examine intervention usability and acceptability, capable of incorporating tests of time-serial characteristics, including linear trend over time and cyclicity. Before multilevel modeling, unconditional means models will be tested for between- and within-participant variation in each measure and determination of appropriate within-person error covariance structure [108].

Mixed Method Analysis

Qualitative and quantitative data on feasibility will be triangulated with a complementary proposition [109], in which the qualitative findings will provide in-depth understanding for the quantitative results in terms of intervention feasibility outcomes.

Power Analysis

The primary aim is to evaluate the feasibility, acceptability, and usability of the intervention to support a future large-scale RCT. According to the guidance for pilot intervention studies [110], it is suggested a minimum sample of 30 per group for the feasibility evaluation. In terms of the aim for the preliminary efficacy evaluation (ie, secondary outcomes of psychosocial and behavioral factors associated with NMUPO), we estimate an effect size according to a previous review on digital interventions for illicit drug use [111] and found small-to-medium effect sizes (Cohen d=–0.17 to –0.34) with a 6-month follow-up assessment. G-power analysis [112] estimated a sample size of 10 to 35 per arm for an RCT (repeated measures analysis of covariance). According to previous mHealth trials for substance use with retention rates ranging from 75% to 93% [46,53,61], a sample of 70 appears to be feasible and provides adequate power for proposed analytic plans. Despite a small sample size, this is appropriate for the aim of developmental research.

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Project Timeline

A detailed study timeline is shown in Table 1.

Table 1. The project timeline.

	Year 1	Year 2	Year 3	Year 4	Year 5
Phase 1: formative study (aim 1)	✓	✓			
Literature review and assessment development (ie, surveys and semistructured interviews)	✓				
IRB[a] submission	✓				
Peer leader recruitment, participant recruitment and assessment, and community advisory board establishment	✓				
Transcription and data analysis or extraction		✓			
Phase 2: intervention development (aim 2)		✓	✓		
Development of multimedia files or features based on data from formative research		✓			
Establishment of IMB[b]-based intervention module packages		✓	✓		
Development of prototype for social media groups and pages (ie, Instagram [Meta Platforms, Inc])			✓		
Peer leaders' and administrators' training (doctoral clinical psychology trainees)			✓		
Phase 3: intervention feasibility and preliminary efficacy evaluation study (aim 3)			✓	✓	
Participant recruitment, preintervention assessment, and randomized controlled trial assignment			✓		
Delivery of intervention			✓		
EMA[c] surveys and paradata collection			✓		
Postintervention assessment and interviews				✓	
Data analysis				✓	
Revisions based on participants' feedback				✓	
Dissemination and disclosure of research findings				✓	✓
Preparation and submission a research proposal for a large-scale intervention effectiveness evaluation with a randomized controlled trial design				✓	✓

[a]IRB: institutional review board.

[b]IMB: information-motivation-behavioral skills.

[c]EMA: ecological momentary assessment.

Ethical Considerations

All data (ie, qualitative and quantitative) and materials (including video, images, and comments) collected or generated in the proposed study are deidentified and stored on a password-protected drive to ensure confidentiality. Intervention materials will be only delivered in private Instagram groups, which are not accessible to public users. Before their participation, all participants are provided with informed consent that explains the study's purposes, voluntary nature, and confidentiality. Participants are allowed to withdraw from the study at any time. Participants will receive e-gift cards for the completion of formative interviews (US $50) and each intervention assessment (preintervention and postintervention; US $30 each). The prorated incentive will be given according to the completion of EMA during the intervention period (eg, US $25 e-gift card for a 100% completion; US $15 for a 67% completion). Biweekly random prize draws of US $25 gift cards for these who post, attend meetings, and reply on the panels. At the end of the intervention, US $60 e-gift cards will be provided to participants who complete 90% of tasks during the intervention.

As a multiphase study, the protocol is reviewed by the research ethics boards in a sequential manner. A protocol for a formative interview study (aim 1) has been submitted to relevant institutional boards for review. Detailed information on the ethical approval and recruitment progress is provided in the subsequent sections. The protocol has been developed and reviewed in accordance with the SPIRIT (Standard Protocol Items: Recommendations for Intervention Trials checklist; Multimedia Appendix 1). The protocol of the formative study (aim 1) has been approved by the Institutional Review Board for Human Research at the University of South Carolina (#Pro00135306).

Results

The protocol was funded in May 2024 by the NIDA under the award number 1K01DA058768-01A1. The research team has

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developed a social media campaign (eg, Facebook and Instagram) to facilitate recruitment for formative qualitative interviews. As of February 10, 2025, the study has received 379 responses, with 24 (6.3%) completing screening interviews. In total, 8 participants who are identified as eligible for the study have consented and completed formative interviews (Figure 4).

Formative interviews (aim 1) are expected to be completed by May 2025. The completion of formative qualitative analyses and intervention module development (aim 2) is anticipated by May 2027. A protocol for an intervention study (aim 3) will be submitted to the Institute Review Board for Human Research for review in early 2027. Upon receipt of an approval, the recruitment of the RCT will be initiated in late 2027, and the intervention will be conducted in early 2028. The intervention feasibility and preliminary efficacy (aim 3) will be finalized by the middle of 2028. Data analyses and manuscript development of the intervention will be completed by the end of 2029.

Figure 4. Recruitment progress for the formative study (aim 1) as of February 10. NMUPO: nonmedical use of prescription opioids.

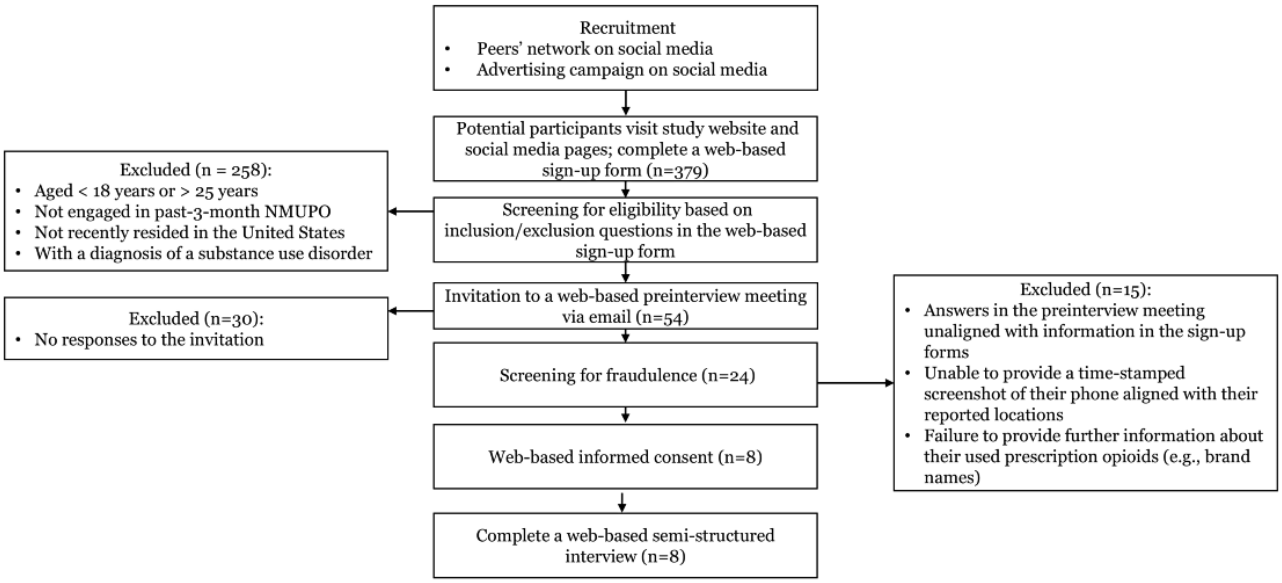

Discussion

Anticipated Findings

In response to the growing evidence on psychosocial aspects of opioid addiction and relevant disorder concerns in the United States, this proposed study aims to apply a psychosocial theoretical framework and peer role model techniques to develop and implement an evidence-based intervention for reducing NMUPO risk in young US adults. The intervention will be established through a serial research activity, from a formative semistructured in-depth interview study to feasibility evaluation of a 12-week interactive peer-led trial. By leveraging the merits of social media, the proposed intervention study will be powered by adopting innovative approaches, including a tailored recruitment strategy (eg, paid advertisement campaigns), intervention delivery that transcends time and space constraints, and the application of mixed methods and time-series assessments (eg, paradata and EMA measures). As one of the first attempts to deliver peer-led interventions on social media specifically targeting NMUPO, the findings from this mixed methods design will offer valuable insights into the use of innovative approaches for reducing opioid risk among young adults. In line with previous intervention studies for NMUPO on social media [45], we anticipate that our intervention will yield high feasibility outcomes. In particular, the mixed methods assessments for the intervention group will demonstrate (1) high feasibility, acceptability, and usability on all intervention modules among young adults across 12 weeks and (2) high engagement, especially for the modules in the interactive formats, such as discussion polls and live streaming group meetings. We also anticipate significant preliminary intervention efficacy on the NMUPO-related and psychosocial behavior outcomes. Compared to the control group, the intervention will report (1) decreases in past–3-month NMUPO and other substance use (eg, alcohol, illicit drugs, and cigarettes), (2) decreases in psychological distress, (3) changes in outcome expectancies (eg, increased physical discomfort and decreased pain reduction), (4) increases in NMUPO knowledge and NMUPO risk perception, and (5) increases in resilience and self-efficacy (ie, action and coping).

Notably, the proposed intervention will be developed and implemented based on qualitative findings on the psychosocial mechanism of NMUPO, incorporating tailored psychotherapy strategies, such as CBT, MI, and peer role models. As highlighted in recent research, NMUPO in young adults is robustly driven by psychosocial factors, with influences comparable to biological and medical factors, which are traditionally viewed as prominent determinants [22]. However, scant theory- and evidence-based intervention programs have been designed to empower psychosocial skills for young US adults, especially for those who have engaged in NMUPO but do not develop addiction or SUDs. As a pilot trial, our feasibility evaluation will contribute to emerging practices of opioid use disorder prevention within social media settings, particularly through the implementation of peer-led groups [45,46]. In addition, preliminary efficacy on psychosocial measures will contribute to the growing literature on psychosocial aspects of NMUPO and offer clinical evidence for using psychosocial

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intervention to manage the risk of opioid misuse in the young population. The success of the proposed trial should underscore the potential of leveraging social media as a feasible tool for delivering secondary prevention programs targeted at group-based psychosocial skill training for young people at high risk of SUD.

The proposed study has several methodological limitations. First, the generalization of our findings will be limited by the convenient sampling approach. Second, because most evaluations in this study will be based on self-reported measures, results could be subject to response bias (eg, social desirability and recall bias). Third, our EMAs could impose additional burdens on participants due to the frequent prompts for assessments in real time. Fourth, our efficacy findings could be limited in assessing long-term effects given a pre- and postevaluation design. Fifth, since the planned content for all peer-led groups will be identical and delivered concurrently, our analyses could not examine the efficacy of specific intervention modules. Sixth, given a program will be delivered on Instagram, our findings will be limited to Instagram users, and the format and presentation of the intervention content will be constrained by the platform's available features and functionality. Seventh, our peer leaders could also have limitations. They are recruited solely from local agencies within a single state (South Carolina). In addition, although they will be supported by clinicians (eg, licensed clinical psychologists and physicians in addiction medicine), their service may be subject to disparities in the quality of support. To address those, our future plan is to conduct a scaled-up cross-platform social media RCT study with a design of the multiphase optimization strategy and longitudinal measures. The intervention will be provided by a team of peer leaders, comprising recovery coaches with expertise in opioid misuse from various states across the United States.

The proposed intervention might encounter several potential challenges related to social media, including inefficient recruitment (eg, scams) and intervention delivery affected by the policy changes to social media platforms. Several contingency plans will be used if these occur. To address recruitment challenges, the eligibility of participants will be thoroughly evaluated by a 2-step approach. Young adults who have signed up for participation via social media will be navigated to complete a screening survey regarding their age, current NMUPO, history of SUDs, and their preferred online meeting methods. The research team will then contact the participants by their preferred methods and evaluate their eligibility in person. In addition, the recruitment plan will be supplemented by additional in-person approaches, including a snowball strategy (ie, allowing participants to invite eligible peers), and an outreach approach (ie, advertising at local young adult communities, colleges, and associations). To address the policy challenges to social media, the research team will transfer multimedia files to a publicly available but password-secured platform (eg, Discord [Discord Inc]), which also allows member reactions, and implement all interactive activities (eg, live streaming) via alternative social media applications (eg, WhatsApp [Meta Platforms]).

Guided by a theoretical framework, the proposed intervention study is dedicated to reducing NMUPO behaviors and the risk for opioid-related addiction and disorders by empowering psychosocial competencies among young adults via the application of social media. The proposed program is informed by substantial literature on NMUPO in young adults and formative qualitative findings of psychosocial mechanisms associated with NMUPO behavior management. Findings from rigorous methods are anticipated to inform a future scaled-up RCT study to optimize intervention content and effectiveness of a fully powered cross-platform social media intervention.

Study Dissemination

To promote the academic and social benefits of the proposed intervention study, several strategies will be used to disseminate the study findings. First, the findings will be published in international and national scientific journals and presented at national and international scientific meetings or conferences held by SUD research institutes. Second, the access to the deidentified data will be available for registered users through our selected data repository, the Interuniversity Consortium for Political and Social Research, with high security standards. Third, documentation and support materials regarding the intervention will be available at ClinicalTrials.gov and compatible with its protocol registration data elements. Fourth, we will capitalize on social media and professional networks that can increase the research and accessibility of findings, such as webinars, files, and videos available on websites and publicly available channels (eg, YouTube [Google LLC]), to increase the visibility and impact of the scientific publications and presentations. We hope that the anticipated success of the proposed intervention will prompt policy attempts for prescription drug intervention and treatments. The lessons learned from the proposed study and the intervention strategies tested can be scaled up to reduce NMUPO risk in young adults and other high-risk populations.

Acknowledgments

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Data Availability

The (deidentified) datasets generated or analyzed during this study will be available in the Data Sharing for Demographic Research data repository hosted at the Interuniversity Consortium Political and Social Research.

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Authors' Contributions

CCT is the principal investigator of this project and led the study design as well as manuscript development. AHL, SH, SDY, and XL contributed significantly to the conception and design of the study. SDY and XL contributed significantly to the editing of the manuscript. All authors reviewed and provided comments to improve the manuscript and final approval of the manuscript.

Conflicts of Interest

SY is an advisor to digital health startups and a consultant to SBIRs grant to help opioid use disorder researchers. The remaining authors have no conflict of interest to declare.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Intervention Trials) checklist for the proposed study.
[PDF File (Adobe PDF File), 75 KB - resprot_v14i1e65847_app1.pdf]

Multimedia Appendix 2
Peer-review report from the IPTA–Interventions to Prevent and Treat Addictions Study Section, National Institute on Drug Abuse (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 164 KB - resprot_v14i1e65847_app2.pdf]

Multimedia Appendix 3
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 312 KB - resprot_v14i1e65847_app3.pdf]

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Abbreviations

CBT: cognitive behavioral therapy
EMA: ecological momentary assessment
I-CaRe: Integrated Care for Recovery
IMB: information-motivation-behavioral skills
mHealth: mobile health
MI: motivational interviewing
NIDA: National Institute on Drug Abuse
NMUPO: nonmedical use of prescription opioids
PI: principal investigator
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SFT: solution-focused therapy
SPIRIT: Standard Protocol Items: Recommendations for Intervention Trials
SUD: substance use disorder

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Protocol

Stress Management Among Caregivers of Detained Youth: Protocol for Randomized Controlled Trial of the RAISE Web-Based mHealth App

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Abstract

Background: Detained adolescents exhibit high rates of behavioral health needs, yet few receive treatment during detention or community re-entry. Once adolescents are released into the community, caregivers must mobilize significant resources and overcome barriers to facilitate their treatment engagement. Parenting stress is often heightened during this forced separation and the re-entry transition. Parenting stress is associated with greater perceived barriers to treatment and, for adolescents who begin treatment, less therapeutic change and premature treatment dropout. Interventions designed to support caregivers of detained adolescents in managing their stress while navigating the juvenile legal system are urgently needed, and mobile health (mHealth) interventions offer promising, scalable approaches. RAISE (Reducing pArentIng StrEss) is a web-based application co-designed with caregivers of detained adolescents to reduce caregiver stress and promote postrelease adolescent behavioral health services use.

Objective: This study will evaluate the effectiveness of RAISE in reducing caregiver stress and promoting adolescent behavioral health services use following release from detention.

Methods: A randomized controlled trial with 60 caregivers of detained adolescents (ages 12-17 years) across the United States will be conducted. Caregivers will be recruited through passive and active techniques and randomized to receive RAISE (intervention) or an informational brochure (comparison). Self-assessment questionnaires will be completed at baseline and 3- and 6-month follow-up timepoints. The fully automated RAISE intervention includes an 8-week stress reduction intervention, self-monitoring and affirmational SMS text messaging, and resources related to navigating the juvenile legal system. Assessments include empirically validated measures of parenting stress, mindful parenting, parenting self-efficacy, adolescent services use, motivation for youth treatment, caregiver behavioral health, sociodemographics, and RAISE usability (intervention only). Caregivers will also participate in a semistructured qualitative exit interview at the 3-month (postintervention) timepoint. Descriptive statistics will examine recruitment, randomization, assessment, retention, and application usability. Independent samples *t* tests and chi-square analyses will determine whether randomization was successful based on multiple background variables; group differences will be accounted for in outcome analyses. Regression analyses will be used for outcome analyses, with an intent-to-treat design; analyses will include intervention group as a predictor and control for the baseline level of the outcome, application usage, and demographic characteristics. Potential moderators and mediators of intervention effects will be explored.

Results: We propose the enrollment of 60 caregivers by April 2025, final data collection by September 2025, and submission of main findings for publication in December 2025.

Conclusions: This study will provide empirical evidence regarding the impact of an mHealth stress reduction intervention co-designed with caregivers of detained adolescents. Findings will be informative for legal systems regarding how best to support

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caregivers of detained adolescents and the impact of reducing caregiver stress on adolescents' linkage to behavioral health services following their release into the community.

Trial Registration: ClinicalTrials.gov NCT05032742; https://clinicaltrials.gov/study/NCT05032742

International Registered Report Identifier (IRRID): DERR1-10.2196/67511

(JMIR Res Protoc 2025;14:e67511) doi:10.2196/67511

KEYWORDS

adolescence; community engagement; digital health technology; incarceration; mindfulness; randomized clinical trial

Introduction

Background

Although rates of youth incarceration have declined over the past decade, the most recent publicly available data show that in 2021, the United States incarcerated over 24,000 young people [1]. This relatively low number, compared to historical rates (eg, in 2019, there were over 35,000 youth detained), is in part due to the COVID-19 pandemic, which had significant impacts on juvenile legal system facilities and reporting of data related to youth in placement [1].

Detained adolescents are disproportionately male, from racially minoritized backgrounds, and most commonly incarcerated for delinquent (violent, property, etc) rather than status (ie, behaviors criminalized for minors but not adults) offenses [2]. About two-thirds of detained males and three-quarters of detained females have a diagnosable psychiatric condition [3], with nearly half meeting criteria for a substance use disorder. Many have co-occurring substance use and psychiatric disorders, increasing their risk for substance-related recidivism [4], persistent reoffending [5], and antisocial activity [6].

Behavioral health treatment is effective at improving adolescent behavioral health (eg, reducing substance use and improving mental health) and legal outcomes, with research consistently demonstrating that treatment involving adolescents and their caregivers is most efficacious in offsetting maladaptive trajectories of risk behavior [7,8]. Yet, few adolescents with behavioral health needs receive services or referrals during detention or community re-entry [9], and legally involved adolescents and their caregivers face multiple barriers to accessing community-based treatment. Adolescent behavioral health treatment access and engagement are multifaceted issues. At the individual level, adolescents and caregivers may experience stigma about accessing behavioral health services, not trust service providers, or may not feel services are needed [10,11]. At the structural level, factors such as lack of available providers, transportation, and insurance access can also impact access [10]. Ultimately, caregivers must often mobilize significant resources to facilitate adolescent engagement in community-based behavioral health treatment (transportation, childcare, etc); this can be challenging when juggling the stress of caring for a legally involved adolescent. As such, few legally involved adolescents in need of treatment actually receive any of the empirically based services available [9]. Detention is a critical window in which adolescents and their caregivers can be linked with treatment, yet as a nation, we are largely failing to use this opportunity.

Parenting Stress

Among the potentially malleable factors contributing to adolescent treatment engagement is parenting stress (ie, stress reaction to demands of parenting), a well-documented impediment to treatment engagement, treatment progress, and a predictor of adverse youth outcomes such as substance misuse. Parent-child relationship (P-C-R) stress theory [12,13], one of the most widely tested and empirically supported parenting stress theories, posits that parenting stress arises from 3 domains: (1) parent (P); (2) child's behavior (C); and (3) parent-child relationship (R). Each domain is associated with functional outcomes (eg, P with parent psychopathology [14,15], C with child behavior problems and psychopathology [16,17], R with parent-child relationship conflict [18,19]), which degrade the quality and effectiveness of parenting behavior and lead to increases in child emotional and behavioral problems. P-C-R theory proposes bidirectional effects (eg, child's behavioral difficulty increases over time and parenting stress increases, resulting in further problems with parenting and child well-being; parent mental health leads to impaired parenting and increases child behavioral problems, which increases parenting stress). Caregivers' reactions to the stress of parenting are key in propelling the process forward. For caregivers of legally involved adolescents, stress can be amplified by separation from their detained child and navigating the expectations imposed by the carceral system.

Parenting stress is associated with greater perceived barriers to treatment (eg, perceived relevance) [20], less therapeutic change among youth during treatment [21], and premature treatment dropout [20,22,23]. Highly stressed parents tend to report less parenting self-efficacy [24] and more negative parenting practices [25] that increase youth risk for substance misuse [26]. Higher parental stress has been associated with greater motivation for youth treatment (ie, recognition that the youth has a problem and caregiver readiness to participate in their treatment), particularly when caregivers perceive youth to have more severe symptoms [27]. Among caregivers of legally involved adolescents in the community, caregivers experiencing more mental health distress tend to be more likely to recognize when their child is experiencing a behavioral health problem [28]; however, for caregivers of adolescents who are mandated to treatment by the courts, recognition of youth behavioral health problems has been shown to be lower compared to those referred by other sources (self, school, etc) [27]. Caregivers of adolescents re-entering the community following detention face a myriad of stressors and demands, for example, ensuring their youth adheres to probation requirements (eg, can include enrollment in school, court-mandated community service, and

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court-mandated service participation). Among the range of problems that adolescents re-entering the community are facing, caregivers may be less likely to recognize the need for behavioral health treatment as a priority. Disrupting the parent-child relationship cycle by reducing parenting stress has the potential to increase caregivers' self-efficacy to engage in effective parenting strategies needed to overcome barriers in facilitating adolescent treatment engagement and to recognize when their youth needs behavioral health intervention.

One promising method of reducing parenting stress is through mindfulness-based interventions [29]. Mindfulness, "the practice of focusing full attention on the present moment intentionally and without judgment" [30], is posited to reduce perceived and biological stress reactivity by increasing awareness of and ability to tolerate thoughts and emotions. Evidence suggests that in-person mindfulness-based parenting interventions increase mindfulness, decrease parenting stress [31,32], and improve parent-adolescent relationship quality among highly stressed parents [33]. Decreasing parenting stress, starting while adolescents are in detention, has the potential to enhance caregivers' ability to facilitate adolescent engagement in community-based behavioral health treatment during re-entry; possible mechanisms of action (Figure 1) include increases in caregivers' parenting self-efficacy (ie, beliefs about one's ability to carry out parenting roles [34]) and motivation for adolescent-focused treatment.

Figure 1. Hypothesized model of intervention effects.

mHealth Technology Approaches to Intervention

Parenting stress is a malleable individual-level target that can be addressed using approaches that circumvent barriers to treatment access, such as digital mobile health (mHealth) technology. Research with postpartum mothers experiencing parenting stress and parents of primary school students provides initial support for the effectiveness of self-guided, web-based mindfulness and self-compassion training programs [35,36]. Increasing available providers, reducing the cost of services, and improving reliable transportation access can also enhance treatment accessibility but require intensive, long-term system and policy-level interventions.

Using mobile phones to deliver health (mHealth) interventions is a viable method for caregivers of legally involved adolescents, who commonly cite time, transportation, agency or program issues, and distrust of professionals as barriers to accessing in-person services [10]. mHealth technology refers to "the use of mobile devices, such as mobile phones, tablet computers, and personal digital assistants to provide medicine, public health, and health services" [37] and is an efficacious, low-cost way of reaching underserved populations to engage them in and deliver quality care [38]. mHealth circumvents many barriers caregivers of legally involved adolescents report, including transportation and time (eg, accessible from any internet-connected device at one's convenience). mHealth is widely used and effective at increasing communication, monitoring, and education, to reduce the burden of diseases associated with poverty, to improve access to health services, clinical diagnosis, and treatment adherence, and for chronic disease management [39,40]. mHealth allows for instantaneous and portable access and, in some cases, direct communication with providers [41]. Research indicates caregivers of legally involved adolescents and juvenile legal system stakeholders are interested in mHealth treatment [2,42,43], making it a likely acceptable approach for them. Using mHealth apps with caregivers of legally involved adolescents is, therefore, one potentially efficacious way to reduce parenting stress, circumvent well-documented barriers to treatment, and ultimately increase adolescent engagement in community-based behavioral health treatment.

Participatory Co-Design Approaches to mHealth Intervention Development

Caregivers of detained adolescents have unique factors that require consideration when designing interventions and should be involved in the development process. Of note, caregivers often feel blamed for their child's involvement in the system, internalize the stigma of being a "bad parent" [44], and feel overwhelmed by not understanding the court system and concerns for their child [44]. Further, they often harbor mistrust in the legal system, in part stemming from systemic racism [45] and a history of difficulty accessing effective community services and supports [46]. They are typically not included in or consulted regarding the development of interventions to help them, and as such, many existing interventions are not feasible or acceptable to them. Efforts to create relevant and accessible interventions must include their direct perspectives and buy-in to be successful.

Based upon principles of Community Partnered Participatory Research [47] and user-centered design [48,49], participatory informatics [50] is an approach to technology co-development that does not require technological expertise and includes users as equitable members in the design process. Involving caregivers in the design process increases the chances the mHealth intervention will be suitable for their needs, more satisfactory [49], and ultimately more effective at facilitating youth engagement in behavioral health treatment post release (via caregiver-level mechanisms of action; Figure 1).

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Study Objectives

This study will be the first to evaluate a mHealth intervention (RAISE app), designed through participatory co-design approaches with caregivers of detained adolescents, specifically focused on supporting caregivers of detained adolescents in managing their own stress while navigating the juvenile legal system. Using a randomized controlled trial (RCT) design, the primary goal of the study is to assess the feasibility, acceptability, and preliminary impact of the RAISE intervention on proximal caregiver outcomes (eg, parenting stress, parenting self-efficacy, and motivation for youth treatment) and more distal adolescent community-based treatment engagement outcomes.

RAISE App

The RAISE app was co-designed using participatory informatics approaches and the secure, web-based Chorus platform (Chorus Innovations, Inc) [51]. The Chorus platform provides a simple, visual, web interface to create interactive mHealth apps without requiring programming skills. Chorus includes interactive voice, texting, and mobile-based web app capabilities and is accessible from any device with internet browsing capabilities.

The co-design process is described in detail elsewhere (Folk et al, unpublished data). In brief, 6 caregivers of adolescents (12-18 years old) who had been detained in juvenile hall within the past year (including 50% currently detained) participated in 9 co-design sessions. Caregivers met either individually (n=2) or in pairs (n=4) with members of the research team to provide in-depth input regarding the needs of caregivers with detained adolescents, perspectives on acceptable intervention approaches (including reviewing mindfulness-based stress reduction approaches), and to develop and refine all RAISE app content. Once an initial version of the RAISE app was developed, co-designers and 6 new caregivers tested the app over a 3-month period and participated in 3 feedback sessions. The app was then refined in preparation for the current pilot trial.

The web-based RAISE app contains: (1) an 8-week stress-reduction intervention adapted from a mindful parenting curriculum [33]; (2) self-monitoring SMS text messages related to stress, mindfulness, and parenting self-efficacy (daily for the first 8 weeks, then reducing to 3 times per week for 3 weeks and weekly for the final 12 weeks); (3) weekly motivational SMS text messages, written by co-designers; and (4) resources related to navigating the juvenile legal system and accessing behavioral health treatment. Example pages within the RAISE app are displayed in Figure 2. The RAISE intervention is entirely self-guided, and the app can be accessed as frequently as a caregiver chooses; new content is released weekly for the 8-week stress-reduction intervention, with the option to revisit prior weeks' material at any time. Each module contains mixed-media approaches to instruction, including audio-recorded exercises, videos (animated, with the exception of a yoga instruction video filmed by a live person), images, written text, and writing prompts to reflect on the content. The app will be "frozen" to changes during the trial (with the exception of addressing any unanticipated bugs), so all participants receive the same version of the intervention. During the informed consent appointment, users randomized to RAISE will set up an account with the assistance of a research assistant and be shown a tutorial video with key application features (which is also available in the app for their viewing at any time); no additional training is provided, however, if users experience technical difficulties with the application, they can contact the research team for support.

Figure 2. Select pages of RAISE application.

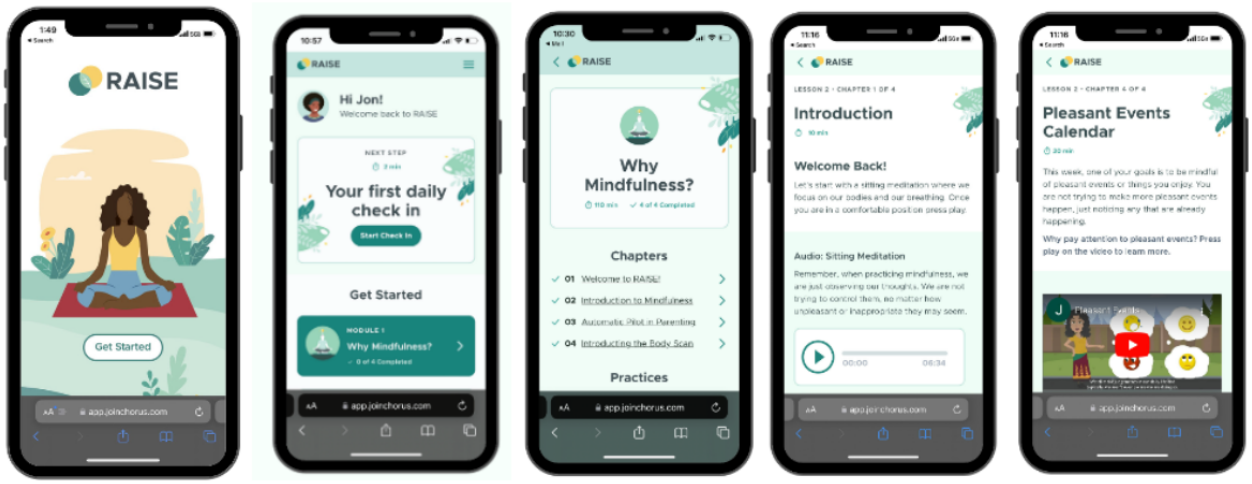

Hypotheses

We hypothesize that caregivers receiving the RAISE intervention will experience reductions in their parenting stress and that their adolescents will be more likely to initiate behavioral health services post release. We will explore hypothesized mechanisms of intervention impact (eg, mindful parenting, parenting self-efficacy, and motivation for youth treatment) as well as potential moderators (eg, gender, race, and ethnicity).

Methods

Study Design

Caregivers of detained adolescents (N=60) will participate in the RCT to assess the preliminary impact of the RAISE

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intervention on caregiver stress and adolescent behavioral health services use post release. A study flow diagram is displayed in Figure 3. Caregivers of adolescents (12-17 years old) in placements mandated by the juvenile legal system will be enrolled in the study and randomized to either the RAISE intervention or to receive an informational brochure (comparison). Enrolled caregivers will complete a computerized set of questionnaires (on a tablet device, mobile phone, PC, or laptop computer) at baseline and 3- and 6-month follow-ups. The trial has been registered with ClinicalTrials.gov (NCT05032742) (Multimedia Appendices 1 and 2).

Figure 3. Study flow diagram.

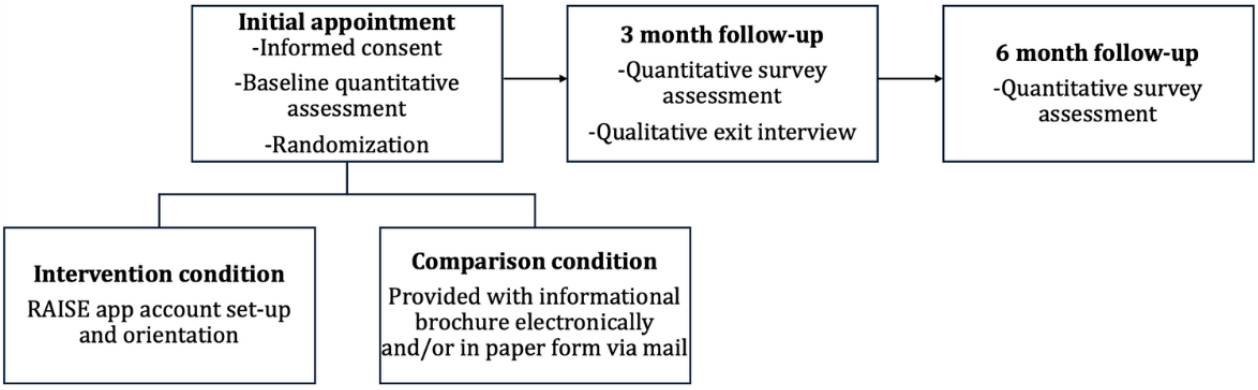

Study Sample Size Determination

The main overall study focus is on the feasibility and acceptability of the codevelopment process and RAISE intervention; however, we will examine the direction of effects through this pilot RCT and cautiously consider effect size to inform sample size determination for a subsequent phase 2 efficacy trial. As with most pilot studies, these analyses are underpowered (for primary analyses considering a sample of 60 participants with α=.05, 4 of predictors, and estimating a medium effect size (Cohen f^2=.15), power=.62). There are notable concerns with calculating effect sizes based upon pilot studies, including potential for overestimating and underestimating effects [52]. Given that we anticipate small to medium effect sizes, we followed published guidance to determine a planned enrollment of 30 participants per study arm [53].

Intervention Condition (RAISE)

Caregivers (n=30) who are randomized to the RAISE intervention will receive access to the web application for a 6-month period. The first 3 months are considered the main intervention window, as this is the timeframe when the 8-week stress reduction intervention content is intended to be completed. Caregivers have the option to revisit this material at any time during the 6-month access period, and use of all RAISE app features is captured in app logs. Caregivers can access the web application on any device with an internet browser and log in using a unique username and password. RAISE is provided at no cost to participants.

Informational Brochure Condition (Comparison)

Caregivers (n=30) who are randomized to the comparison condition will receive an informational brochure about the juvenile legal system. Content for the brochure was adapted from existing guides distributed to caregivers by local jurisdictions in partnership with juvenile legal system professionals [54].

Recruitment

Enrollment for the trial commenced in October 2023 and is anticipated to conclude by April 2025. Caregivers are recruited through passive and active techniques. Flyers and business cards with a QR code, which when scanned directs to an online eligibility survey and video explaining the study, are posted in public places (detention center waiting areas, court buildings, etc) and distributed electronically by legal system partners (probation officers, attorneys, behavioral health clinicians, etc). Study staff also recruit caregivers through active means, specifically by talking directly with families during family visitation in detention centers. Caregivers who provide their contact information and permission to be contacted by the study team are offered an opportunity to learn more about the study by meeting with a research assistant either remotely via Zoom or in person. Caregivers who are eligible and interested in participating complete an informed consent discussion with a research assistant and the baseline assessment before randomization (Multimedia Appendix 3).

Inclusion and Exclusion Criteria

Eligible caregivers must be the parent or legal guardian of an adolescent who (1) is currently detained by the juvenile legal system, (2) is 12-17 years old, (3) has an identified substance use or substance use and co-occurring mental health need, and (4) will ultimately be released into the community to the care of the enrolled caregiver. Computer or internet literacy is not an inclusion criterion for the study. Given that adolescents within this population are not always raised or cared for by their biological parents, we use the term “caregiver” to define the adult who has principal responsibility for the raising and care of the adolescent, and who can provide legal consent and enrollment in services and research studies. In addition, detention by the juvenile legal system can include secure facilities such as juvenile detention centers or alternative placements such as group homes, which are less secure, but where youth are not technically allowed to leave freely.

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Randomization

Participants will be randomized (using the REDCap [Vanderbilt University] randomization module [55,56]) to either the RAISE intervention group (30/60, 50%) or the informational brochure comparison group (30/60, 50%) directly after consent and completion of the baseline assessment. Randomization is blocked (to avoid "runs" of assignment to the same condition) and stratified by gender to ensure balance between the 2 conditions (because most caregivers are anticipated to identify as women). The randomization table is generated by a biostatistician and is not visible to the research assistant before assignment; no blinding was used. Participants will not be told which condition is the intervention of interest, but during the informed consent discussion are informed that they may be invited to test a mobile app.

Ethical Considerations

This study was approved by the Institutional Review Board at the University of California, San Francisco (#20-32010) and certified by the Office for Human Research Protections. Caregivers will provide informed consent before completion of their baseline assessment during an appointment with a research assistant. Study data do not contain personally identifiable information and are coded with a unique study identification number; a list linking study identification numbers to specific participants is securely maintained and only accessible to trained study staff. Each participant will be offered a US $40 gift card as compensation for their time for each survey or interview completed (total possible compensation: US $160). A Data Safety and Monitoring Board was formed before the initiation of the RCT and includes 4 members with expertise in clinical trials, mental health research with underserved populations, and research with youth and families. Adverse events will be reported and managed in accordance with the institutional review board and the funder's requirements.

Data Collection

Self-report data will be collected from caregivers through electronic quantitative surveys administered via REDCap (3 times total) and one-time qualitative interviews.

Quantitative Measures

Parenting Stress

The 90-item Stress Index for Parents of Adolescents [57] assesses caregivers' perception of stressful areas in caregiver-adolescent interactions, including the relationship between stress and adolescent-caregiver characteristics, the quality of adolescent-caregiver interactions, and stressful life circumstances.

Mindful Parenting

The 8-item Interpersonal Mindfulness in Parenting Scale [58] assesses present-centered emotional awareness in parenting, present-centered attention in parenting, nonreactivity or low reactivity in parenting, and nonjudgmental acceptance in parenting.

Parenting Self-Efficacy

The 20-item Parenting Self-Efficacy Scale [59,60] assesses caregivers' perceived parenting ability across 3 dimensions: parental connection, behavioral influence, and psychological autonomy.

Adolescent Services Use

The Child and Adolescent Services Assessment [61] obtains information about service use for mental health and substance use needs across multiple sectors (eg, schools and the legal system), including details about the type of treatment facility, professional discipline of provider(s), outpatient services, and out-of-home placements. We adapted this instrument to also assess whether services were mandated by the legal system. Outcomes of focus will include whether the adolescent completed any behavioral health services following release into the community (yes or no) and whether they complied with mandated services (yes or no). Barriers to adolescent services are also assessed (16 barriers; language, transportation, cost, stigma, etc). The assessment focuses on the 3 months before the adolescent's detention (at baseline) and for follow-ups in the 3 months since the last assessment.

Motivation for Youth's Treatment

The 8-item Motivation for Youth's Treatment Scale [27] assesses intrinsic motivation for youth treatment through 2 subscales: (1) recognition that the youth has a problem and (2) readiness to participate in the youth's treatment.

Caregiver Behavioral Health

The 23-item DSM-5 Level One Cross Cutting Symptom Inventory [62] assesses psychiatric symptoms (depression, anxiety, mania, psychosis, etc) and substance use during the past 2 weeks.

Acceptability of the RAISE App

For caregivers randomized to the RAISE condition only, the 18-item mHealth App Usability Questionnaire for Standalone mHealth Apps [63] assesses the acceptability (ie, ease of use, interface and satisfaction, and usefulness) of the RAISE app.

Sociodemographic Characteristics

We will collect data on caregiver race, ethnicity, gender, education, income, and adolescent history of legal involvement.

Application Use Metrics

We will extract use metrics from the Chorus platform. Metrics will include the number of days of use, number of modules completed, time spent practicing mindfulness exercises, and responses to self-monitoring messages sent by the application.

Qualitative Interviews with Caregivers

All caregivers (both conditions) will be invited to participate in a one-time qualitative interview at the time of the 3-month follow-up assessment. Interviews will focus on the feasibility, acceptability, and satisfaction with the RAISE app and informational brochure conditions (Multimedia Appendix 4).

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Statistical Analysis

Quantitative Analysis

Analyses will be conducted using IBM SPSS Statistics software. Descriptive statistics will be used to examine issues related to recruitment (eg, sufficient numbers of caregivers consenting and pace of recruitment), randomization (eg, whether participants are willing to be randomized), assessment (eg, valid, reliable, acceptable, and complete), and retention (eg, rates of follow-up assessment completion). Preliminary analyses will examine whether the randomization process was successful, comparing groups on multiple background (gender, race, etc) and baseline (parenting stress, caregiver mental health, etc) variables through independent samples *t* tests (continuous variables) and chi-square analyses (categorical variables). If there are group differences, subsequent analyses will be run both with and without accounting for these variables. Efforts will be made at each stage of analysis to assess the importance of race and gender. Initially, means, distributions, and reliabilities for all major measures will be examined separately by race and gender. Any observed differences across demographic subgroups will be considered in the interpretation of substantive analyses. The proportion of missing data will be examined before outcome analyses to determine whether a complete case analysis is appropriate or whether multiple imputation is warranted (eg, if there is a large proportion of missing data, ie, >5%; if there are patterns in missingness based on demographic factors) [64].

RAISE User Engagement and Acceptability

RAISE app use metrics will be generated through logs from the Chorus platform. The use metrics will be examined in relation to the outcomes of interest (eg, changes in parenting stress) through bivariate correlations and linear regression and included as control variables when examining intervention effectiveness. Average response rates to daily ratings will be examined, as well as factors that relate to response rates (age, gender, race, mental health, substance use, etc) through bivariate correlations (eg, age) and independent samples *t* tests (eg, gender).

Descriptive statistics will be used to examine ratings of application usability (eg, ease of platform use) and acceptability of intervention components (content, mindfulness exercises, daily ratings, etc) on the mHealth App Usability Questionnaire for Standalone mHealth Apps [63].

RAISE Effectiveness

Outcome analyses will focus on proximal caregiver-level outcomes, including mindful parenting, parenting stress, parenting self-efficacy, perceived barriers to youth treatment, and motivation for youth treatment. Secondary distal outcomes will include adolescent treatment initiation and retention. Linear regression will be used for continuous outcomes (ie, mindful parenting, parenting stress, perceived barriers to youth treatment, motivation for youth treatment), logistic regression for 3- and 6-month follow-up dichotomous outcomes (ie, treatment initiation and adherence to mandated treatment), and Poisson or negative binomial regressions for count outcomes (ie, number of treatment sessions attended). All analyses will include the intervention group as a predictor and control for baseline level of the outcome variable, application usage, and demographic characteristics (determined during preliminary analysis). Potential moderators and mediators of intervention effects will be explored using the PROCESS macro in SPSS, which uses a regression framework. Moderation analyses will involve computing interaction terms of intervention group (intervention vs comparison) by key demographic factors (eg, caregiver age, gender, race, mental health, substance use, and youth age, centered before computing interaction term for continuous variables). Mediational effects will examine the impact of intervention group on key proximal outcomes assessed at 3 months (ie, mindful parenting, parenting stress, parenting self-efficacy, perceived barriers to youth treatment, and motivation for youth treatment) and their impact on distal youth treatment engagement and retention outcomes assessed at 6 months. An “Intent to Treat” design, where all initially assigned to the intervention group are included in analyses, whether or not they used the intervention, will be used.

Qualitative Analysis

Individual interviews will be digitally recorded and transcribed verbatim. Transcripts will be loaded into ATLAS.ti (ATLAS.ti Scientific Software Development), a qualitative analysis software for coding, text retrieval, intensive data management, and analysis. Interviews will be coded using inductive thematic analysis. An initial codebook will be developed based on the interview guides and corresponding transcripts. To improve reliability and ensure adequate intercoder agreement, the study principal investigator and research assistant will compare coding patterns and refine the codebook until consensus is reached, and then generate memos to highlight connections between codes and subcodes. Quotations will be compiled, and concepts and relationships pertinent to core themes will be developed. We will seek out and compare unique themes relevant to analytic subgroups (eg, age, gender, race, and ethnicity) to capture important thematic group differences. Final codes and memos will be compared and combined into overarching themes and subthemes. Themes will be discussed, refined, and named for the final analysis.

Results

The study was funded by the National Institute on Drug Abuse on April 1, 2021. The trial is open and recruiting. We propose the enrollment of 60 caregivers by April 2025 and final data collection by September 2025. After final data analysis and writing of the results, manuscripts will be submitted to appropriate journals for dissemination. We anticipate submitting the main findings for publication by December 2025.

Discussion

Summary

This study is a protocol for an RCT testing an empirically derived mHealth app (RAISE) to support caregivers of detained adolescents in managing their stress and linking their adolescents with behavioral health treatment post release. The RAISE intervention includes mindfulness-based stress reduction techniques tailored specifically for caregivers of detained

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adolescents, informational resources for navigating the legal system and accessing mental health care, and self-monitoring and motivational messages. The RAISE intervention builds on prior research linking parenting stress and youth treatment engagement. Among caregivers of legally involved youth specifically, existing evidence suggests caregivers of youth court-mandated to treatment may be less likely to recognize their adolescent has a behavioral health problem [27] and that caregivers experiencing higher levels of their own mental health distress are more likely to recognize their child's behavioral health needs (ie, youth problem recognition) [28]. Mindfulness-based stress reduction interventions have been shown to be effective for highly-stressed caregivers of adolescents [32,33], though investigations into the effects of addressing parenting stress among caregivers of detained youth on subsequent youth treatment engagement is limited. We anticipate that caregivers in the RAISE condition will report greater reductions in their parenting stress, as well as increased self-efficacy and motivation for their adolescent to engage in treatment (as mechanisms for youth behavioral health treatment engagement following release), compared to caregivers in the informational brochure condition.

Strengths of this study include the use of an RCT design to maximize internal validity and scientific rigor, the use of empirically supported intervention models (eg, mindfulness-based stress reduction), and the incorporation of mixed methods data collection and analysis to understand the intervention's effectiveness. This study builds off prior participatory co-design work to create the RAISE app, which we anticipate will enhance intervention relevance and usability. A potential limitation is the reliance on self-report for primary outcomes, as we are unable to collect electronic health record data as collateral for service use due to the national recruitment approach. Furthermore, sample size may limit the current potential to analyze outcomes based on placement type and length of separation, which could be relevant to the intervention impact. We will descriptively explore these factors to inform a future larger trial.

Conclusions

The current study aims to advance our understanding of how to support caregivers of detained adolescents in managing their parenting stress and the impact of doing so on their adolescents' postrelease engagement with behavioral health services. Use of a mHealth intervention approach has the potential to increase scalability, and the current trial will provide insight into whether caregivers of detained adolescents find such an approach feasible and acceptable to use. Findings will inform a future large-scale hybrid trial and be used to provide empirically driven recommendations for systems related to supporting caregivers of detained adolescents.

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Data Availability

Data sharing is not applicable to this study because no datasets have been generated or analyzed yet for the preparation of this protocol study. After analysis and dissemination, data generated and analyzed in the RCT will be available from the corresponding author upon reasonable request.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist.
[DOC File , 125 KB - resprot_v14i1e67511_app1.doc]

Multimedia Appendix 2
CONSORT E-HEALTH checklist.
[PDF File (Adobe PDF File), 497 KB - resprot_v14i1e67511_app2.pdf]

Multimedia Appendix 3
Caregiver consent form for the randomized controlled trial.
[PDF File (Adobe PDF File), 171 KB - resprot_v14i1e67511_app3.pdf]

Multimedia Appendix 4

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Caregiver exit interview guide.
[DOCX File , 18 KB - resprot_v14i1e67511_app4.docx]

Multimedia Appendix 5
Peer review report by the IPTA Interventions to Prevent and Treat Addictions Study Section (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 147 KB - resprot_v14i1e67511_app5.pdf]

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Abbreviations

mHealth: mobile health
RCT: randomized controlled trial

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Protocol

Optimizing and Testing an Individualized and Adaptive Physical Activity Digital Health Intervention: Protocol for a Control Optimization Trial Embedded Within a Randomized Controlled Trial

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Abstract

Background: While effective physical activity (PA) interventions exist, interventions often work only for some individuals or only for a limited time. Thus, there is a need for digital health interventions that account for dynamic, idiosyncratic PA determinants to support each person's PA. We hypothesize that supporting individuals with their personal PA goals requires a personalized intervention that both supports each person in forming daily habits of walking more and develops personalized knowledge, skills, and practices regarding engaging in exercise routines. We operationalized these adaptive features via a digital health intervention called YourMove that uses a control systems approach to support personalized habit formation and a self-experimentation approach to develop personalized knowledge, skills, and practices.

Objective: The primary aim is to evaluate differences in minutes of moderate to vigorous PA (MVPA) per week at 12 months comparing our personalized intervention, called YourMove, with an active control that is similar but without personalization of the intervention components and mimics best-in-class digital health worksite wellness programs.

Methods: The YourMove study is a 12-month randomized controlled trial that involves 386 inactive adults aged 25 to 80 years. All participants receive (1) a Fitbit Versa smartwatch and corresponding smartphone app; (2) weekly PA goal suggestions and feedback, behavior change strategies, and reminders via SMS text messaging; and (3) up to US $50 in incentives for reaching daily step goals. Participants randomized to the active control group, modeled after worksite wellness programs, receive all the elements described in addition to a static daily step goal and static point rewards. Participants randomized to the intervention group receive (1) a habit formation element with daily personalized step goals and personalized point rewards generated through a control optimization trial approach and (2) a knowledge, skill, and practice development element featuring a self-guided

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self-experimentation tool that helps individuals find strategies to improve MVPA. The primary outcome is objectively assessed weekly minutes of MVPA via an ActiGraph monitor.

Results: Recruitment began in October 2022 and concluded in August 2024. Data collection will conclude in August 2025, with results expected by early 2026.

Conclusions: We hypothesize that the intervention group will show greater improvement in MVPA than the active control group at 12 months. If the hypothesis is supported, this will provide compelling evidence to suggest that personalized and perpetually adaptive support can enhance PA more effectively than intervention elements commonly used in digital health worksite wellness programs. If the trial is successful, the results will provide justification to explore both the control optimization trial approach and self-experimentation approach for other complex, idiosyncratic, and dynamic behaviors such as weight management, smoking, or substance abuse.

Trial Registration: ClinicalTrials.gov NCT05598996; https://clinicaltrials.gov/study/NCT05598996

International Registered Report Identifier (IRRID): DERR1-10.2196/70599

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KEYWORDS

physical activity; digital health; optimization trials; control optimization trial; randomized controlled trial

Introduction

Significance of the YourMove Intervention

Strong evidence indicates that physical activity (PA) reduces the risk of a variety of cancers (eg, bladder, breast, and colon) [1-5] and cardiovascular disease [6] and improves glycemic control [7]. The 2018 Physical Activity Guidelines recommend 150 minutes per week of moderate to vigorous PA (MVPA) and emphasize taking an adequate amount of steps each day as a behavioral target [8]. However, only a third of adults meet these guidelines for PA [9-17]. As inactive adults are at high risk of developing cancers [4,5] and other chronic diseases, PA is a key behavior to target for this population [8], which suggests the need for PA interventions.

Digital-based interventions show great promise for promoting health behavior change [18], and as a result, many PA interventions are being developed via digital technology [19,20]. While effective digital health interventions (DHIs) for PA exist, many have significant limitations that result in gaps between hoped for results and actual outcomes. In particular, previous research shows that DHIs for PA have a moderate short-term effect on PA, are acceptable with good adherence when used in research studies [5,21-28], and show meaningful 12-month results with effect sizes of 0.2 relative to comparators [29,30]. However, these interventions were found to only be effective for certain populations or for a limited period [31-33]. This can be partially explained by the idiosyncratic nature of PA, with prior work indicating that individuals' PA is influenced by different factors [34,35]. In addition, PA is dynamic in that individuals can engage in PA for a time, but then an event may occur that prompts inactivity [24,36-44]. Our prior work shows that individual (eg, stress and busyness) and contextual (eg, day of the week and the weather) factors have different relationships to PA for each person [34,35] and these predictors change over time [9-16,45]. These findings point to the need for interventions that account for dynamic, idiosyncratic PA determinants to support each person's PA.

We refer to DHIs for PA that adapt the support provided to individuals' unique and changing needs as personalized and perpetually adaptive interventions [24,46]. While the approach that the team has developed to create scalable, personalized, and perpetually adapting DHIs described in prior work shows promise [47,48], a randomized controlled trial (RCT) will produce valuable evidence for examining the degree to which this approach is a meaningful improvement relative to a comparator modeled after a digital health worksite wellness offering.

Purpose of This Paper

The purpose of this paper is to describe the research protocol of the YourMove study, which tests the YourMove intervention via an RCT. This paper is organized as follows: (1) an explanation of the approach that was used in the YourMove intervention to increase MVPA by operationalizing personalized and perpetually adapting support, namely, the use of control systems methods to support habit formation with respect to walking and a self-experimentation approach to support knowledge, skill, and practice development; (2) a description of the YourMove trial methods, including study aims, participant recruitment, intervention procedures, measurement follow-up, and the statistical analysis plan; and (3) the implications of YourMove regarding future research on optimization of DHIs for PA.

Methods

Aims

The primary aim of the YourMove trial is to evaluate differences in minutes of MVPA per week at 12 months comparing the personalized and perpetually adapting YourMove intervention against an active control that was designed to mimic current worksite wellness offerings for fostering PA. We hypothesize significantly higher minutes of MVPA per week at 12 months compared to baseline in the YourMove intervention group relative to the control group measured via the ActiGraph GT3X+ [49-51]. The secondary aims include examining continuous daily measures (ie, steps per day) via a Fitbit Versa (Google) smartwatch [52] and daily intervention engagement. In addition, comparing baseline and 6- and 12-month follow-up

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measures, we will examine metabolic syndrome–related health outcomes directly related to cancer risk (ie, submaximal oxygen consumption, BMI, and body composition), psychological variables (ie, quality of life, anxiety, and depression), and the percentage of individuals that meet and maintain 150 minutes per week of MVPA.

Study Design

The YourMove study is an RCT with a sample of 386 inactive adults aged 25 to 80 years. Participants are randomized to either the YourMove intervention or active control group. The primary outcome is change in minutes per week of MVPA at 12 months relative to baseline as measured via the ActiGraph activity monitor [49-51] using standard procedures [53,54]. Assessments of these constructs are conducted through a combination of in-person measurement at the Exercise and Physical Activity Resource Center (EPARC) at the University of California, San Diego (UCSD), and continuously via the Fitbit smartphone app and wearable PA monitor.

Innovation of the YourMove Intervention

Overview

The YourMove intervention seeks to be a scalable DHI to improve MVPA by providing personalized and perpetually adapting support via (1) a control optimization trial (COT) systems engineering approach to support habit formation regarding daily steps and (2) a self-guided self-experimentation approach for developing personalized knowledge, skills, and practices to exercise regularly [48].

Prior work demonstrates the value of individuals receiving health coaching from a person. A key advantage of a human health coach is that they can listen carefully to a person to ensure that they can personalize their approach and suggestions for each individual and adapt to them over time as their needs change. These characteristics are not easily replicated within current DHIs as present-day DHIs mostly rely upon a priori decision rules and policies to guide adaptation. Within the DHI tested in this RCT, the team incorporated 2 approaches to achieve personalization and perpetual adaptation that are not common in current DHIs. One uses methods from control systems engineering to address the challenge, and the other incorporates the person themselves as the ultimate arbitrator on whether something is working for them via a self-guided self-experimentation tool. Each approach will be described, with a particular focus on how it offers personalized and perpetual adaptation that better mimics what a human coach could normally provide.

A Control Systems Approach for Fostering Walking Habits

This study uses a control systems approach, which the team has labeled a COT, to help people develop walking habits in a personalized and perpetually adapting way. It is based on the well-established field of control systems engineering, which is pervasive and embedded within a range of well-known technologies such as pacemakers, climate control, and robotics, yet it often goes unnoticed as a hidden technology [55,56]. Control systems engineering focuses on decision-making in systems that change over time. COT is an approach for creating personalized and perpetually adapting interventions via the development of individualized protocols for each person that has 2 key phases. The first phase is for each participant to take part in an embedded system ID [57-59] experiment (which is an N-of-1 trial design). The purpose of this initial phase is to develop personalized computational dynamic models to guide personalization. After this phase is completed, the next stage involves the use of these personalized dynamic models within a control systems engineering–based decision-making algorithm called a controller [60-62] to enable daily, perpetual adaptation.

We specifically apply our COT approach for personalization and perpetual adaptation to 2 well-recognized behavior change techniques (BCTs): goal setting and positive reinforcement. We hypothesize that this approach to personalization and perpetual adaptation can facilitate (1) improved adherence as persons will experience receiving the “right” support over time; (2) enhanced cultivation of walking habits as adjustments are made in context and over time, thus plausibly improving habit formation; and (3) increased likelihood of maintenance via the creation of resilient walking habits that, plausibly, are more likely to be maintained even after sessions of use of the intervention.

Turning back to our health coach analogy, our COT approach for creating a personalized and perpetually adaptive DHI is an automated way to achieve many desirable attributes that, in the past, only a health coach could provide. A good health coach has several attributes: (1) a clear sense of what meaningful behavioral targets are, such as PA guidelines; (2) the ability to actively monitor a person’s behavior; (3) awareness of a person’s broader life circumstances and how those circumstances influence their behavior; (4) a repertoire of evidence-based BCTs that can be used and adapted to each person; and (5) the capacity to learn about a person and continuously adjust support based on their changing needs. Similarly to an effective health coach, our COT-based intervention has the following capabilities: (1) ambitious and achievable step goals based on participant-specific models and the performance of each participant on the most recent days that strive toward fostering steps per day that are recognized as conferring health benefits (eg, 8000 steps per day) [63-65]; (2) continuous monitoring of steps per day via a Fitbit Versa smartwatch; (3) monitoring of other facets of a person’s life (eg, weather patterns, daily stress, and busyness); (4) use of multiple BCTs (ie, goal setting, provision of feedback, positive reinforcement, self-monitoring, prompting of intended action, action planning, and education process) that adapt to a person’s changing needs; and (5) prediction of how a person will respond to support each day, with subsequent monitoring to test the accuracy of each daily prediction and results on accuracy incorporated into future predictions, thus operationalizing learning about each person. These components are delivered to intervention participants via a study-specific Fitbit watch face and ecological momentary assessment (EMA) prompts, shown in Figure 1.

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Figure 1. YourMove intervention Fitbit watch face, daily step goal prompts, and ecological momentary assessment.

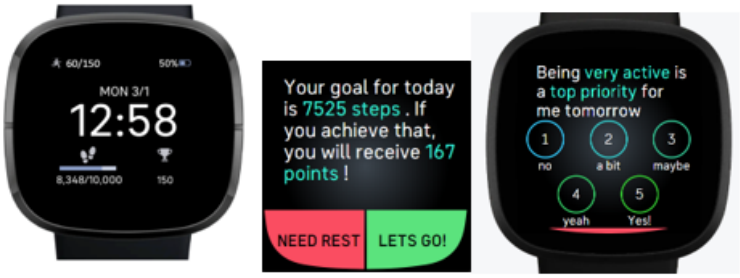

Using our previously developed and vetted dynamic model of social cognitive theory (SCT) and insights from running N-of-1 system ID experiments with each person, our COT-based intervention can use continuous monitoring of steps per day and other individual factors to make predictions on each person's response to different intervention adaptations considering a person's current state and context. On the basis of those predictions and matching to the desired state (eg, 7500 steps per day being maintained), the system performs N-of-1 adaptations related to suggested goals, feedback offered if goals are not met, and the amount of reward given. For example, our controller can adjust (1) the suggested daily step goal and (2) the reward points offered each day when goals are met or not.

This COT approach mimics how a health coach may hypothesize about a person's response to different BCTs. The discrepancy between a controller's prediction and a person's actual response is incorporated into future decisions of the controller. For example, if a person starts to be less responsive to suggested goals, the controller may increase the reward that a person will receive for meeting a goal to increase a person's incentive to meet suggested goals. In sum, our COT approach is a robust, systematic, scalable approach for providing many key benefits of a health coach via an automated tool. The following sections provide more details on how this was operationalized.

Self-Experimentation to Cultivate Personalized Knowledge, Skills, and Practices

In this study, we developed a self-guided self-experimentation tool titled Reflect to support participants in developing personalized knowledge, skills, and practices [48] related to exercising. To do so, the Reflect tool mimics a typical health coaching session using a logic-based survey design on Qualtrics (Qualtrics International Inc). Follow-up questions, feedback, and advice are contingent on participants' responses, shown in Figure 2. To build knowledge and skills, participants are guided through a series of questions to identify personal MVPA goals, exercises to meet their MVPA goals (eg, walking, running, and recreational sports), strategies that work well in general for helping people engage in exercise (eg, strategies to do before, during, and after exercise), and basic instructions on how to try out the strategy for a week to see whether it works. Strategies are framed as short-term experiences, or "experiments." Participants are asked to use personal judgment to decide which strategies to try and then use their experience while experimenting to define whether a strategy is successful. This contrasts with more common approaches such as our COT approach, which seek to have the technology define whether a person is successful. The Reflect tool is outlined for participants in a 3-minute informational video and accompanying text description to view before using the Reflect tool initially and as needed throughout the intervention, as shown in Figure 3.

Following completion of the tool, participants receive an automated summary of their developed plan for the week via email. Throughout the week, whenever a bout of exercise is detected via Fitbit, participants are prompted on their smartwatch to indicate whether they tried their Reflect strategy and, if so, whether the strategy was useful. Examples of this follow-up with participants after the use of the Reflect tool are shown in Figures 4 and 5. Depending on responses, participants are invited to return to Reflect to try out different strategies and continue with the process. For example, if the person rates the strategy as working well, this is acknowledged, and they are invited to go back and work on other strategies that might also help if they thi`nk they need more support. However, if a person rates a strategy as not helpful, they are also invited back to the Reflect tool to try something different. Through this, the system aligns with the priorities and interests of the individual, trusting them to determine whether a strategy is helpful for them. This personalized and perpetually adapting approach guides participants toward strategies that might help them and are aligned with their self-interests and evolving PA goals, much like how a health coach might do so in a session. Details about the contents of the Reflect tool can be found in Multimedia Appendices 1-7.

With these approaches, Reflect helps participants develop a personal health practice related to exercise. Contrary to habit formation, as targeted using the COT approach to improve daily steps, with Reflect we aim to cultivate an exercise practice by having participants be engaged in the process of determining what strategies work best for them and refining and personalizing strategies for themselves as needed.

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Figure 2. Example interface from YourMove Reflect tool.

Figure 3. Participant introduction to YourMove's Reflect self-guided self-experimentation tool.

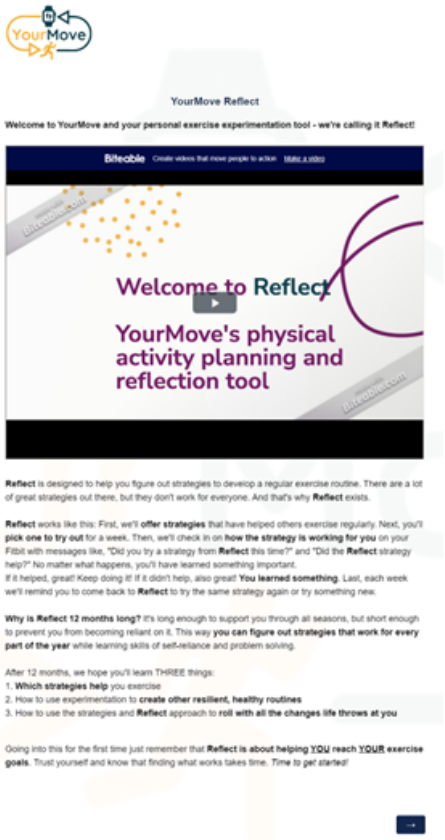

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Figure 4. YourMove Reflect tool response summary.

Figure 5. YourMove Reflect tool Fitbit watch face follow-up prompts.

Comparator Selection

When selecting a meaningful comparator, it is critical to identify one that best serves the trial's primary purpose [66]. To do so, we chose to compare the YourMove intervention to an active control that both could be viably deployed in real-world settings as a worksite wellness program and incorporated intervention components that, in previous literature, have been shown to be valuable for producing meaningful results in DHIs for PA. The YourMove intervention, as described, is a DHI designed to offer personalized and perpetually adapting support to both support habit formation related to walking and cultivate personalized knowledge, skills, and practices in exercising. On the basis of our already tested DHIs [35,67], the YourMove and active control groups both include education, weekly planning, PA history, motivational messaging, and implementation intentions through weekly SMS text messages. Both groups will also include the goal setting and feedback, self-monitoring, and positive reinforcement BCTs, as well as equal financial incentives (US $50) for meeting daily step goals, with the key difference being in how these 3 BCTs are provided in the 2 groups. On the basis of this, our trial provides a strong mechanistic comparison. In addition, our comparator was designed to mimic currently scaled standard-of-care DHI worksite wellness offerings. With this, the results of this trial are valuable for understanding ways for determining both whether our specific strategies for delivering personalized and perpetually adapting interventions are effective and whether they perform better than an intervention that mimics current worksite wellness offerings. Table 1 provides a summary of the

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key common and different features between the YourMove intervention and our active control, which was designed to control for common offerings commonly available in digital health PA interventions (eg, self-monitoring, financial incentives for meeting step goals, and receiving a Fitbit). The Active Control section provides more details on the active control condition.

Table 1. Summary of features in the active control and the YourMove intervention.

Intervention feature	Active control	YourMove intervention
Digital technology tool		
Fitbit Versa smartwatch	✓	✓
Smartphone app	✓	✓
Financial incentives—receiving up to US $50 for meeting their suggested step goals	✓	✓
Tailored SMS text messaging support		
Weekly PA[a] goal and feedback	✓	✓
PA behavior change strategy	✓	✓
Midweek PA goal feedback	✓	✓
Reminder to complete the Reflect tool		✓
Daily support		
Daily step goal	✓	✓
N-of-1 adapted?		✓
Daily points contingent on goal being met	✓	✓
N-of-1 adapted?		✓
Daily EMA[b] both for self-monitoring and to measure SCT[c] constructs that inform N-of-1 adaptation		✓
PA reflection tool		✓
Adherence support—check-ins to support adherence to measurement	✓	✓

[a]PA: physical activity.

[b]EMA: ecological momentary assessment.

[c]SCT: social cognitive theory.

Ethical Considerations

Overview

This study was approved by the Human Research Protections Program at UCSD (protocol 200733) and is registered on ClinicalTrials.gov (NCT05598996). In addition to these requirements, the study team engaged in several additional steps to ensure that the study was conducted with the highest degree of ethical practices to balance out a range of often competing requirements related to (1) ethical best practices (honoring autonomy, beneficence, and justice), (2) risks and benefits both for individuals and society at large with respect to conducting the research study, (3) data management and corresponding ethical issues inherent to commercially available digital health tools (eg, managing privacy and data sharing issues), (4) assessment of the state of the science to guide decision-making on the type of evidence production that is appropriate, and (5) system usability and fit into a person's real-world context.

Informed consent was obtained from each participant during the baseline visit. Before this in person consent discussion, individuals were directed to a web-based screening form to review the study purpose, procedures, risks, and benefits and respond to eligibility questions. Eligible individuals were contacted by phone to verify their responses and to schedule a baseline visit. Data from Fitbit Versa devices were continuously and securely transmitted to Fitbit servers, retrieved by Fitabase, and stored on a Fitabase secure server. De-identified data were downloaded for analysis and stored on password-protected servers at the EPARC, with no personally identifiable information was linked to the device-captured data. EPARC servers were accessible only to study staff involved in the measurement of study participants and analysis of study data. Researchers using commercial devices for digital health research have a responsibility to understand and evaluate how vendors manage participant data, especially when data remain on third-party servers even after being exported to platforms like Fitabase. In this study, the decision to use Fitbit was made prior to the company's acquisition by Google, at a time when Fitbit's privacy policy reflected stronger consumer protections. Participants received financial incentives for both participation and measurement adherence. For the intervention phase, participants in both arms could earn up to US $50 over 12-months based on points awarded for meeting daily step goals. Intervention participants received personalized daily goals and point values generated by a control algorithm, while control participants received a fixed daily goal of 10,000 steps and static point values (150 points/day). In both groups, 1000 points

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equaled US $1. To encourage retention, participants received US $25 and US $50 for attending the 6- and 12-month follow-up measurement visits, respectively. Thus, participants could earn between US $75 (measurement incentives only) and US $125 (maximum incentives for both measurements and step goals). Participants who completed at least one month of the study were allowed to keep the Fitbit Versa device (valued at US $230) A full review of the ethical and design work that the team conducted to prepare this study is beyond the scope of this protocol paper but is an important and complementary set of activities that was a central part of this study. Key activities that the team conducted included (1) active use of the Digital Health Checklist [68] as a general guide for thinking through and making initial decisions about technology selection, design decisions for the technology, and decisions about other ways of balancing the often competing demands outlined previously; (2) conducting a series of human-centered design workshops that invited prospective participants to engage with and provide the team with feedback on possible design decisions for the technology (eg, selection of the Fitbit vs other devices and design options that balance the desire for honoring the autonomy of participants while minimizing burden); and (3) applying for and receiving a bioethics administrative supplement specifically focused on developing guidance specific to strategies for improving consent communications about the complexities of the control algorithm to participants. The consent research aimed to enable prospective participants to make truly informed decisions about the use of digital technologies in their own lives [69]. The results of the first 2 activities are summarized in the following section, and the results of the third set of activities are reported elsewhere [69-72].

Summary of the Results of Engaging With the Digital Health Checklist

Overall, our activities resulted in the selection of the Fitbit based in part on the ethical and data management practices that are used at Fitabase, which was the digital health technology company that ultimately operationalized many of the key elements of our overall study protocol. In addition, our team devised a robust and comprehensive set of activities that were all designed to ensure that participants engaged with sets of questions to assess potential risks of participating (which largely related to potential risks that arise if a person has health challenges that would result in increasing the likelihood of adverse events due to exercising) and also helped participants make informed decisions, including the use of a motivational interviewing–style approach to informed consent that involves asking participants to develop their own personal list of the pros and cons of both participating and not participating in the study before making a final informed consent decision. In addition, our entire algorithm development process was explicitly established to be able to align with and learn each person's priorities, interests, and goals and, from there, align with a person's context and needs. This was done via the mixed use of both the COT approach for creating a personalized (via system ID) and perpetually adapting (via the control algorithm) approach that is all enacted in a purely idiographic (ie, N-of-1) way. This approach reduces the risk of a systemic bias of an algorithm developed nomothetically (eg, an algorithm that was trained on persons with largely light skin creating a systematic bias that reduces confidence in the results when used with persons with darker skin) as there is no requirement for all participants to have the same computational algorithm to guide personalization or the same enactment of the control algorithm to support personalization. Moreover, we included our self-experimentation Reflect tool with the explicit goal of inviting persons to cultivate their knowledge, skills, and practices for exercising, with the ultimate judge on whether a strategy is a good one being the person themselves. Through examining the key questions and challenges of the Digital Health Checklist, the team concluded that we had produced a digital health tool that could be implemented in a way that, most critically, honors individual autonomy; leans toward beneficence in the form of aligning the success of the intervention strategies directly with the goals of the person, accounting for their personal assets and constraints; and honors justice in the form of advancing an algorithmic and self-experimentation approach that, at its core, can align with each person's unique needs while also being automated and, thus, scalable, thus providing a pathway for advancing justice in the implementation of digital health tools.

Eligibility Criteria

The targeted population were inactive adults interested in increasing their weekly PA. Inclusion criteria were (1) age of 25 to 80 years; (2) intention of being available for a 12-month research study; (3) willingness and ability to attend 3 measurement visits at UCSD over the 12-month RCT; (4) PA deficiency (<150 MVPA minutes per week and <75 vigorous PA minutes per week based on the International Physical Activity Questionnaire) [73]; (5) passing the conditional logic of the Physical Activity Readiness Questionnaire–Revised (PAR-Q) [74], which screens for PA readiness, OR being approved by their physician if they did not pass the PAR-Q; (6) BMI between 18 and 40 kg/m^2; (7) willingness and ability to use a smartphone and SMS text messaging; (8) willingness and ability to use the Fitbit Versa smartwatch and app; (9) willingness and ability to walk and engage in moderate-intensity activities; and (10) ability to speak English. Exclusion criteria were (1) a mechanical medical implant, (2) enrollment or plans to enroll in a PA program during the study period, and (3) psychiatric or medical conditions that prohibited compliance with the study protocol.

Recruitment, Enrollment, and Retention

A diverse sample of prospective participants were recruited in the San Diego region via digital advertisements, targeted social media advertisements, posting of print and digital flyers at UCSD and community centers, emails sent by community public health partners, and county-wide events via tabling. Interested individuals were directed to complete a web-based screening form through the study's secure REDCap (Research Electronic Data Capture; Vanderbilt University) database hosted at UCSD [75] that provided further details about the study and criteria for participating. Individuals were then asked eligibility questions, including their age, BMI, and current PA behavior via the International Physical Activity Questionnaire [73], and study staff followed up accordingly.

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Prospective participants who did not meet the eligibility requirements received an email notifying them and thanking them for their interest in the study. Prospective participants who met the eligibility requirements received a call from a trained research staff member notifying them that they may be eligible to participate, informing them about the study details, explaining that they may be randomized to an active control group, and confirming the information provided in the web-based screening form. Because participants engaged in a submaximal treadmill test, those eligible were also prescreened for exercise testing using the PAR-Q [74]. Those who did not pass the conditional logic of the PAR-Q were required to obtain approval from a physician before participation. In addition, prospective participants who reported ≥3 American College of Sports Medicine risk factors [76] were referred to the study physician to determine how to proceed with exercise testing. The study physician determined whether the participant could (1) take part in exercise testing as normal, (2) take part while being monitored by an electrocardiogram, or (3) take part with clearance from the participant's physician. Once prescreening procedures, shown in Figure 6, were completed and the prospective participant was deemed eligible, they were invited to schedule a baseline measurement appointment at the EPARC at UCSD. This entire prescreening process reflected our commitment to truly informing our prospective participants of the opportunities and potential risks, with risk assessment taking place on their behalf to ensure that they had all the information they needed to decide. With this information, prospective participants were then provided with the final written informed consent document to review it and ask questions about the study; if they agreed, they signed the consent form to conclude the enrollment process. Following written consent, the baseline measurements took place.

Figure 6. Pre-enrollment screening and exercise testing procedures for YourMove. ACSM: American College of Sports Medicine; APMHR: age-predicted maximal heart rate; CV: cardiovascular, MD: medical doctor; PAR-Q: Physical Activity Readiness Questionnaire.

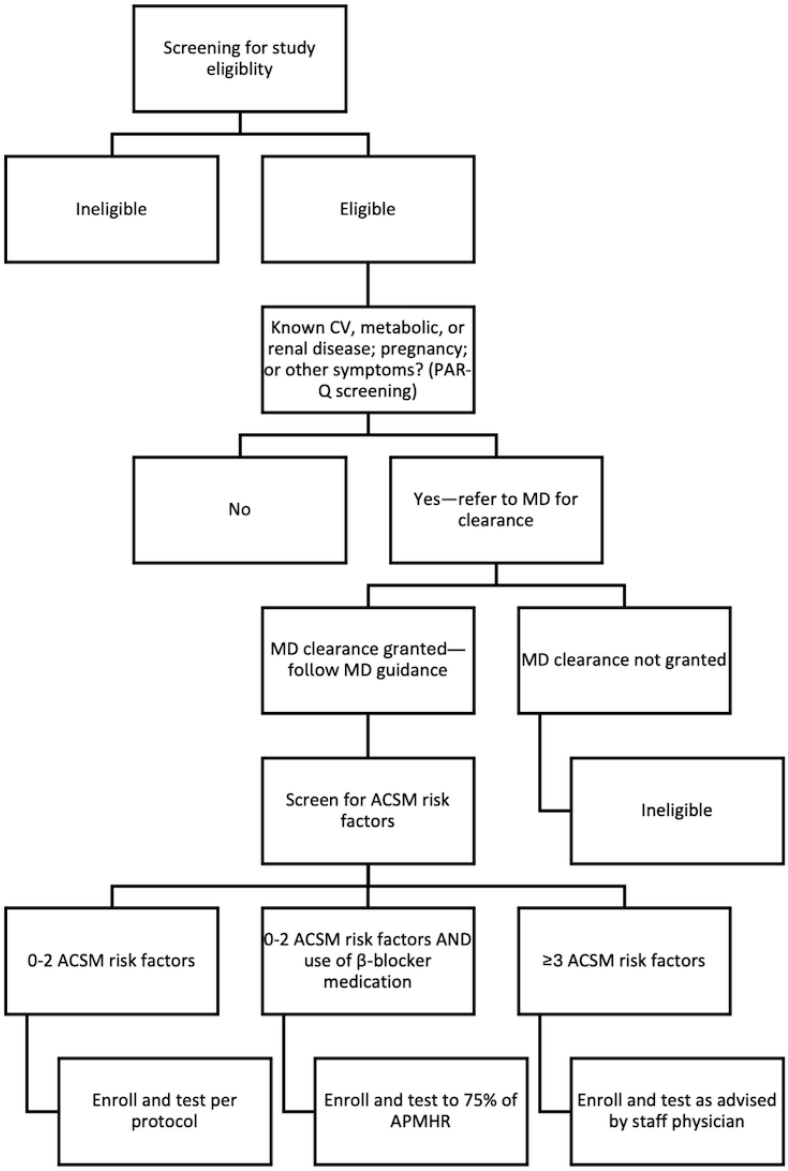

After eligibility, consent, and BMI were confirmed and baseline measurements were completed, participants were randomized to either the YourMove intervention or the active control at a ratio of 1:1 stratified by sex. The biostatistics team generated

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an electronic randomization list using the latest version of the statistical software platform R (currently version 4.1.2; R Foundation for Statistical Computing [77]). The pseudorandom seed was saved so that the code could be validated and the sequence regenerated if necessary.

To meet enrollment targets and increase retention, each participant was provided with a Fitbit Versa smartwatch and gift card incentives throughout the study. At the baseline measurement visit, after enrollment and randomization, participants received a Fitbit Versa. The device is theirs to keep upon completing at least 1 month of participation in the study. To maximize the likelihood that participants will continue with follow-up measurement visits and stay in the study, US $25 and US $50 gift cards are provided at the completion of the 6- and 12-month measurement visits, respectively, for a total of US $75. Participants in both the YourMove intervention and active control groups also receive up to US $50 over the 12-month study contingent upon meeting their assigned step goals and based on the number of points assigned to them each day. For the YourMove intervention, goals and points are assigned based on, first, the system ID experiment (to generate a personalized computational model) and then on the control algorithm to support perpetual adaptation (which, overall, we refer to as the "COT approach," a term that we will use when referencing the overall approach regardless of phase). Daily step goals for each participant are estimated to be challenging for the person but also possible based on their step data history and predictions from the COT approach. In addition, daily points are assigned by the COT approach, with the phase 2 control algorithm set to lean toward providing the fewest number of points needed to facilitate a person meeting their step goals on any given day. For the active control, daily step goals are 10,000 steps per day. Points remain static at 150 points per day. For both groups, 1000 points equal US $1, and the maximum amount that each participant can earn over the course of the 12-month study is US $50. The minimum monetary compensation that a participant can receive for completing the study (both in the intervention and control conditions) is US $75 by completing only the measurement visits, and the maximum monetary compensation is US $125 by achieving the maximum of US $50 for reaching the daily step goals and US $75 for completing each measurement visit.

Measurement Protocol

Overview

Outcomes are measured at baseline and the 6- and 12-month follow-up. The primary outcome measure, minutes per week of MVPA, is assessed via the ActiGraph GT3x+ [49-51] using standardized procedures [50,53]. Participants are instructed to wear the device continuously during their waking hours for 7 days except while bathing or swimming. Minute-by-minute estimates of activity are categorized into intensity-weighted summaries (ie, sedentary, light, moderate, and vigorous) of PA using previously validated calibration thresholds as well as cutoff points used in national surveillance systems [49,50]. Steps per day are also determined using a proprietary algorithm from ActiGraph that has been independently validated [51].

Secondary outcome measures include anthropometric and physiological measures, behavioral measures, psychological measures, related lifestyle factors, and overall participant experience and satisfaction. Anthropometric and physiological outcomes are measured using the following standardized procedures and conducted by trained staff: (1) body weight is measured to the nearest 0.1 kg using a calibrated digital scale; (2) height is measured to the nearest 0.1 cm using a stadiometer; (3) BMI is calculated from the height and weight measurements as kg/m^2; (4) waist and hip circumference is measured to the nearest 0.1 cm using stretch-resistant measuring tape; (5) body composition is measured through bioelectrical impedance analysis using a Tanita DC-430U dual-frequency total body composition analyzer; (6) grip strength is measured to the nearest 1 kg using a grip strength dynamometer (JAMAR; model 081669928); (7) flexibility is measured using a sit-and-reach box; (8) gait speed is measured using a 25-foot walk test; (9) the Short Physical Performance Battery and Timed Up and Go test will be conducted in participants aged ≥50 years to assess lower extremity strength, transitional movements, balance, fall risk, and mobility; and (10) the submaximal graded exercise test is conducted on a treadmill using a walking protocol.

Behavioral measures include the Global Physical Activity Questionnaire; Physical Activity Neighborhood Environment Scale; Sedentary Behavior Questionnaire; Social Support for Exercise Survey; and other surveys assessing sleep, perceptions and intentions related to exercise, and PA change strategies used in previous behavioral health research. Psychological measures include the Rosenberg Self-Esteem Scale, Center for Epidemiological Studies Depression Scale, Spielberger State-Trait Anxiety Inventory, and Quality of Well-Being Scale. Other related lifestyle factors are measured using the Social Determinants of Health Toolkit, RAND Homelessness Survey, and Customary Drinking and Drug Use Record. Participant experience and satisfaction is measured using the Twente Engagement With eHealth Technologies Scale and the User Burden Scale.

Continuous measures include PA, intervention engagement, and SCT constructs and key process variables. PA is measured as steps per day and minutes of MVPA through the Fitbit Versa smartwatch. Quantitative markers of engagement for all participants include use of the Fitbit smartwatch and smartphone app and progress toward daily step goals and accompanying accrual of points. Additional markers of engagement for participants receiving the YourMove intervention include adherence in responding to daily EMAs. Participant responses to daily EMAs enable measurement of SCT constructs for our dynamic SCT model, described in the YourMove Intervention section, and key process variables. Key SCT constructs and process variables include (1) behavioral outcomes (ie, sleep, mood, physical fitness, and physical appearance), (2) busyness, (3) stress, (4) typicalness of the day, (5) internalized cue to action, (6) commitment to goal, (7) self-efficacy for meeting the daily goal, and (8) outcome expectancies (ie, sleep, physical appearance, mood, concentration, and physical fitness). The timeline for outcome measurement are shown in Figure 7.

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Figure 7. A timeline for outcome measurement. *Primary outcome measure; EMA: ecological momentary assessment; MVPA: moderate to vigorous physical activity; SCT: social cognitive theory.

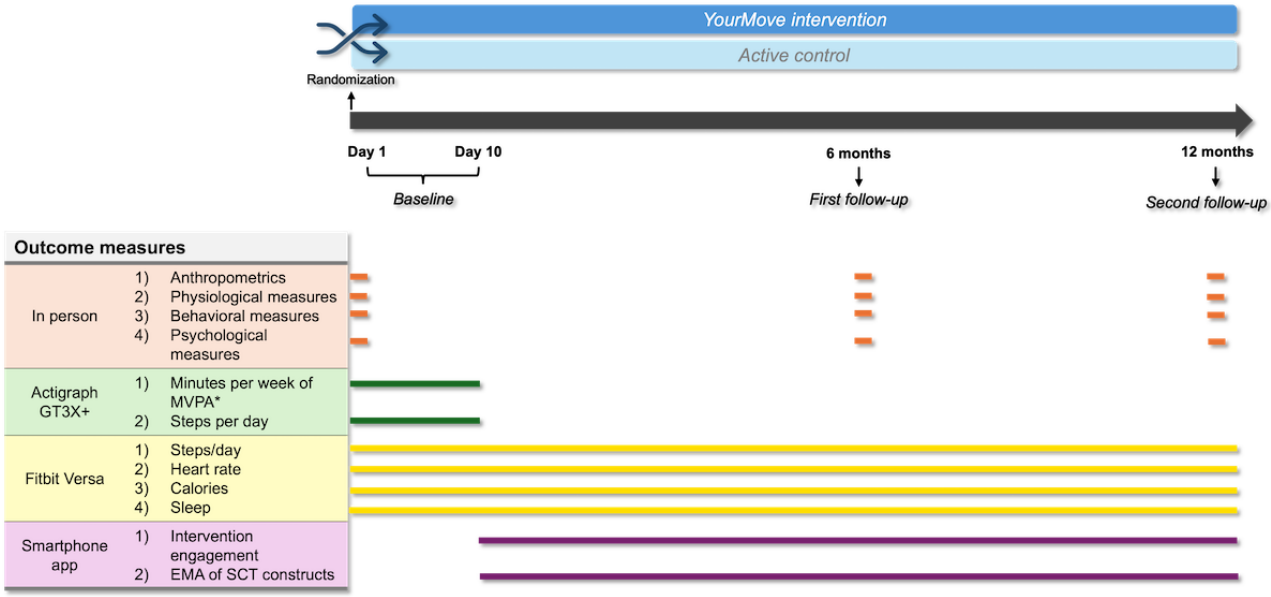

Fitbit Versa Smartwatch and Smartphone App

All participants receive a consumer-level Fitbit Versa smartwatch and corresponding smartphone app. The Fitbit Versa is a wrist-worn device that objectively measures PA through its triaxial accelerometer, optical heart rate monitor, and altimeter. Upon syncing the device, participants can view PA measurements, including steps and MVPA, on the Fitbit smartphone app. Data collected from the Fitbit smartwatch are passively and securely streamed to the Fitbit website. They are then retrieved using Fitabase [78], a web-based application developed by Small Step Labs LLC. This allows for the simultaneous collection of high-resolution Fitbit data from large numbers of participants and integration with the COT approach controller and SMS text messaging system. Fitbit was chosen as the digital technology tool as it was deemed the most viable technology platform that balanced the various constraints of the study with respect to privacy, access and usability, data management, and risks and benefits. The digital health checklist mentioned previously was used to guide decision-making specific to our wearable device selection.

Financial Incentives for Meeting Daily Step Goals

On the basis of a review of worksite wellness programs and the literature [79-81], we found that it is plausible to assume that worksite wellness offerings will provide both wearable devices to employees and financial incentives for meeting health targets. On the basis of a review of options (coupled also with our design work described previously), we determined that US $50 in financial incentives for meeting step goals was a fiscally viable target that could be scaled and implemented at scale within worksite wellness offerings. On the basis of this, participants in both the YourMove intervention and active control are eligible to receive up to US $50 for meeting their suggested step goals. In both groups, 1000 points translate to US $1, but the approach for establishing the daily suggested step goal and number of available points varies across the 2 groups, described in detail in the following sections.

Tailored Text Messaging Support for Exercising

All participants receive a weekly exercise goal and feedback, behavior change strategies, and reminders to wear the Fitbit Versa smartwatch via the Fitabase SMS text messaging system. In total, 3 to 4 SMS text messages are delivered each week and follow a consistent weekly schedule, shown in Multimedia Appendix 8. Each week, participants are encouraged to achieve 150 minutes of MVPA. While this static goal is not adjusted dynamically as with the controller-generated daily step goals, participants receive personalized, tailored feedback on progress toward reaching the goal based on data collected from the Fitbit Versa smartwatch. In addition, in instances in which a participant exceeds the goal, tailored feedback encourages achieving 300 minutes of MVPA, which is associated with additional health benefits [63-65]. The behavior change strategies focus on physiological characteristics, behavioral drive, motivation, opportunity, and resiliency conditioning. Finally, if no data have been collected from the smartwatch, participants are reminded to wear their watch in lieu of weekly midweek and end-of-week feedback.

YourMove Intervention

Overview

For the week following randomization, participants are instructed to engage in their normal level of PA to establish a baseline measured by wearing the ActiGraph activity monitor and Fitbit smartwatch. During this time, participants do not receive any intervention components. Afterward, participants assigned to the YourMove intervention group receive (1) the Fitbit Versa and corresponding smartphone app, (2) daily personalized step goals with corresponding point rewards generated using our COT approach, (3) the weekly PA goal (150 minutes of MVPA per week) with accompanying motivational and informative content via SMS text messaging, and (4) the Reflect tool delivered via Qualtrics. Each of these components is discussed in detail in the subsequent sections.

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The COT Approach for Setting Step Goals and Point Rewards

Our COT approach for creating a personalized and perpetually adapting DHI includes three phases: (1) baseline (to obtain an initial estimate of the median steps per day that the person engages in, which is the starting reference that is used in the next phase), (2) system ID (to enable the development of a computational model for each person that could be used in the next phase to provide personalized support), and (3) controller (which can use insights gleaned from the previous 2 phases to support perpetually adapting support, including the possibility of a person moving between states of behavioral initiation and maintenance of PA). On the basis of this, each phase sets step goals and point rewards differently (shown in Figure 8).

Figure 8. Control optimization trial simulation illustrating the system ID (cyan) and control phases for a representative participant. White regions denote the controller initiation state, whereas green regions denote the maintenance state. GA: goal attainment.

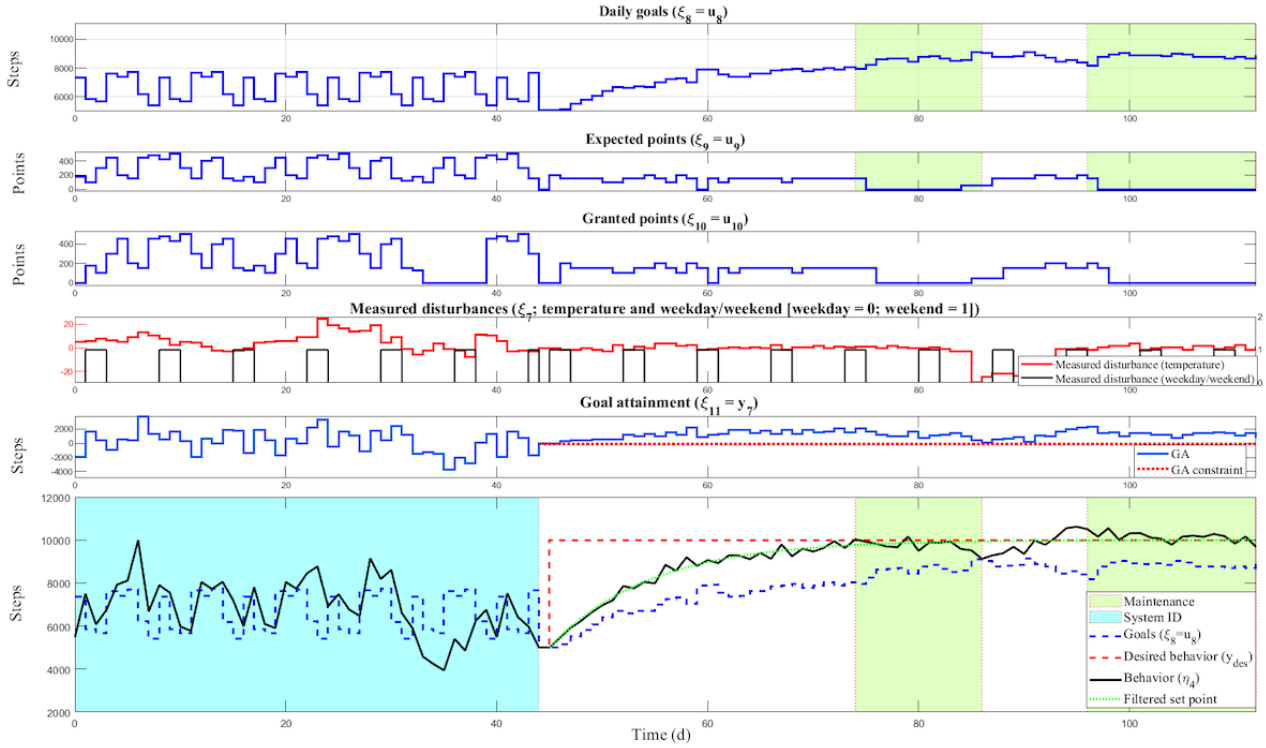

Phase 1: Baseline

The purpose of this phase is to obtain an estimate of a person's median steps per day before receiving any active intervention save for the Fitbit Versa itself. To do this, participants are asked to wear the Fitbit smartwatch for 10 days but otherwise do not receive any other type of support. Participants are also asked to engage in their normal PA activities to the best of their abilities. Neither suggested daily goals nor points are provided to participants during this phase.

Phase 2: System ID

The purpose of phase 2 is to create a personalized dynamic model that is meant to represent each person related to engaging in steps per day. Thus, phase 2 of our overall COT approach is how we operationalize our approach to personalization.

In phase 2, an "open-loop" system ID experiment is conducted. This approach is "open loop" because the pseudorandom input signals used to define the suggested step goals and points that a person receives each day do not change based on whether a person meets their suggested step goals (it becomes a "closed-loop" response when a person's capacity to meet suggested step goals is considered, which occurs in phase 3).

In the open-loop system ID experiment phase, each person receives their own suggested step goals and points each day, and each day, the suggestions are experimentally varied. For example, if a person's median steps per day are 4000 (determined from phase 1 initially), then a person, over a 22-day cycle, some days will receive suggested step goals that are experimentally varied and could fit within the range of their median steps (eg, some days they are suggested to walk 4000 steps) and some days will receive more challenging step goal suggestions (eg, striving for double their baseline median, targeting 8000 steps per day). In addition to step goals, each person receives experimentally varied expected points that that they could receive if they meet their suggested step goal for that day, with the range of expected points being between 0 and 500 on any given day. Thus, for example, one day a person may not receive any points for meeting a goal, whereas on other days, they may receive 500 points for meeting a suggested step goal. In total, 1000 points equal US $1, and the accumulation of 5000 points enables a person to cash in their points for a gift card (up to US $50 in total over the 12-month intervention period). The dollar value was selected in part as it is an amount that has been used in worksite wellness programs and other offerings, thus establishing a plausible incentive structure that could be scaled and that was also used in the control group.

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Step goals are minimally personalized in that they are all calculated in reference to a person's median steps per day. Thus, for example, in the first cycle of the system ID experiment, the 10 days of the baseline phase are used to calculate the median steps per day as the reference for defining the lower range of a person's suggested steps per day goal. Points are not personalized in this phase (eg, a person receives suggested points each day ranging from 0 to 500 points).

Pseudorandom input signals are used to dynamically and experimentally vary suggested step goals and points. Within a system ID experiment, a key concept is the notion of a cycle. A cycle is used to define the length of time needed coupled with other constraints (discussed in the following section related to input signal design) to ensure sufficient excitation of variance at a sufficient length of time to generate a computational model of the dynamic system for each individual. For this, key considerations include designing an input signal within a given cycle to have confidence that enough variations (some days with high goals, some with low suggested goals, and some with intermediate goals and, similarly, some days with a high number of points, an intermediate number of points, or no points) exist to create an estimate of the influence of steps goals and points for each person over time and across variations in context. In addition, a cycle needs to be long enough to ensure that the 2 intervention input signals are orthogonal to one another and not aligned with any known temporal patterns (eg, they do not align with a 7-day weekly cycle, which would make it impossible to disambiguate the influence of the intervention option relative to the impact of day of the week).

Within system ID experiments, replication occurs in the form of repeating the cycle multiple times. With this, the dynamic system model for each person can be produced, with cycles used to estimate the dynamic system model and then validate the predictions made for each, in line with previous protocols and strategies used and described by the study team [34,35,47]. As described in the following section and in prior work, the team engages in a sort of power calculation but with the focus not on estimating the number of participants needed but, instead, on the length of a cycle and total number of cycles that would be needed to produce a reliable and valid dynamic model for understanding and predicting each person's walking behavior.

Once data are collected for the last day of the system ID phase, auto-regressive model with exogenous input [57-59] data analysis takes place to produce the dynamic system model for each person as our concrete approach for personalizing the YourMove intervention to each participant. Auto-regressive models with exogenous input are dynamic extensions of basic regression models. This modeling approach paired with discrete simultaneous perturbation stochastic approximation [82] provides the means to identify key variables that are predictive of each person's steps per day over time [83]. Discrete simultaneous perturbation stochastic approximation, as described in the team's prior work [84], is an analytic technique that can be used to overcome the need for exhaustive computational searches of all possible dynamic system models for each person. This is important because exhaustive searches (which was the team's initial approach to this [34,35]), when scaled, result in a level of computational load that would be impractical. With this final step, the team has produced dynamic models in a way that can be fully automated and fit into real-world constraints (eg, the team was able to run all required analyses and computations for all participants in the trial overnight to ensure that every person received their own personalized suggestions every day). Through this, we have not only produced a scientifically plausible approach but also created the technology infrastructure and sets of methods that would be required for the full scalability of our approach. More details on this approach within YourMove have been published elsewhere [83,85,86].

Technical Details Regarding the Input Signal Design

At a high level, the basic idea of our input signal design is to experimentally vary suggested step goals and points for each person over time. The general logic is that, if one wants to understand the impact of changing something, they need to vary it, particularly across variations in context.

Turning to the technical design of this approach, in this open-loop system ID experiment, pseudorandom multi-sine input signals are designed for each of the independent intervention components (eg, goal setting and expected points). Following the guidelines presented in previous literature on systems archetypes [87], the effective frequency range can be specified by selecting the design parameters based on the estimated range of the dominant time constant of the system, and , and other user-defined parameters to dictate the covered high- and low-frequency content (α_s and β_s, respectively), as seen in equation 1:

In this equation, ω_* and ω^* represent the lower and upper bounds of the effective frequency range. Input signal design is an iterative process that requires some knowledge of the system dynamics of interest. In this work, a priori knowledge from analyzing the experimental data from previous studies, particularly the JustWalk intervention [35], is leveraged. In YourMove, the selected guideline parameters for the estimated dominant time constant have been set to . Moreover, to cover a wide range of low- and high-frequency content, the values for the user-defined coefficients have been chosen as β_s=3.5 and α_s=1.

YourMove's input signal is designed using a shifted approach, which implies that it is generated for only 1 input and then shifted relative to the other inputs to increase statistical independence. Shifting of the input signal introduces differences in phase that promote orthogonality. The advantage of this approach is that it results in shorter cycles than the zippered approach, which was applied in the JustWalk study [35], for the same number of excited harmonics. As can be observed in Figure 9A, the overall duration of the designed input signals was selected as 22 days to allow for the execution of more cycles designated for the system ID experiment within the duration of the study.

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Figure 9. Single cycle of shifted multi-sine signals used in the system ID phase—(A) scaled time domain and (B) power spectral density.

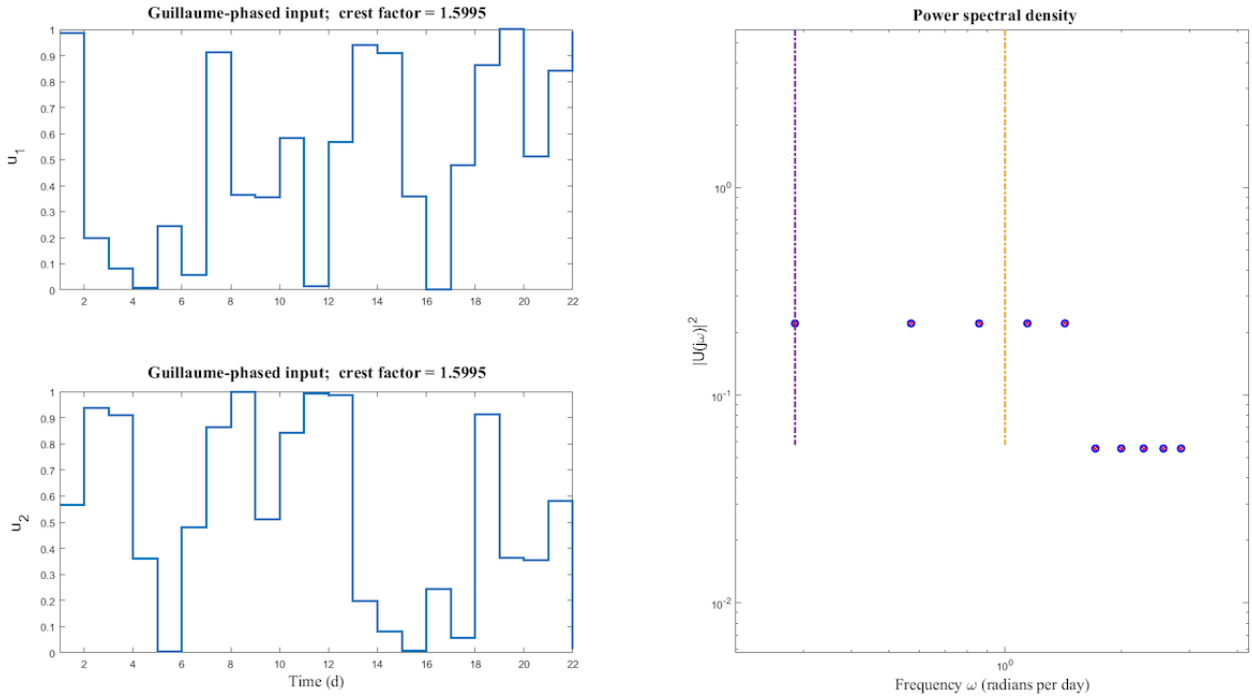

This cycle length was also selected to allow for 5 excited harmonics in the designed input signals, as shown in Figure 9B. Because the signals for the 2 input channels are shifted copies of one another, they share the same Fourier coefficient values for all harmonics. Consequently, both signals have equally excited harmonics at the same frequencies, as can be observed in Figure 9B from the overlapping sinusoidal harmonics.

Phase 3: Controller

The final phase of our COT approach is when we "close the loop" and explicitly seek to offer personalized and perpetually adaptive support to each person. This is all done via the use of a controller, as used within control systems engineering. The key design focus of the controller is to monitor and be capable of supporting individuals in flowing between what the team labeled as "initiation" and "maintenance" states. By an initiation state, we refer, conceptually, to states in which a person's walking habit is either in development or not observed as stable. By a maintenance state, we refer, conceptually, to a state in which a person appears to be engaging in a regular walking habit in that they engage in meeting targeted levels of suggested steps per day goals appropriate for their age group with minimal to no support provided by the YourMove intervention (ie, minimal suggestions related to goals and steps, including some days when neither is provided to a person).

Critically, the controller treated these as states, not stages. Through this, the controller did not make any assumptions about the possible continuation of engaging in the maintenance state in perpetuity once an initial detection of a person meeting the maintenance state was observed. This decision was made based on the well-observed phenomenon of persons lapsing (having brief moments when they no longer meet their targeted step goals but relatively quickly return to the maintenance state), relapsing (moments when a person no longer meets targeted step goals and this lack of achievement then continues), and prolapsing (moments when a person no longer meets a targeted step goal but then translates that moment into a sort of teachable moment that results in a strengthened walking habit). In addition, the team wanted to ensure that the controller could be responsive to known variations that occur in a person's life, such as becoming sick, going on vacation, or other things (which a person can report each day after a step goal is suggested; see Figure 1 and the prompt to "take rest," which then asks a follow-up question on reasons for rest, including illness and vacation). While this approach was used throughout, it was particularly valuable and important during the controller phase to enable personalization and perpetual adaptation.

The general logic of the control algorithm is that it uses a person's previous data on steps per day with a particular emphasis on the previous 7 days coupled then with the use of the personalized dynamic model made for each person to run a series of simulations. These simulations vary plausible suggested step goals and points that could be provided to the person for the following day and into the future. Simulations also include seeing plausible intended and unintended consequences of different decisions that the controller could make on a person's activity weeks and months into the future. With all these simulations run, the controller then selects an intervention (ie, a suggested daily step goal and corresponding points) that it estimates as the most likely to help a person develop a walking habit while not overwhelming them or inspiring them to give up on the use of the overall YourMove intervention. The controller does this every night and, based on this, decides every day. Thus, each day becomes a sort of mini experiment that the controller engages in. Over time, this information on the predictive capacity and ability of the controller to engage in decisions that result in helping a person develop a walking habit without overwhelming them (eg, having them stop using YourMove) is incorporated into the controller's simulations. With this, the controller is capable of enacting a highly

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personalized and perpetually adaptive approach for supporting individuals in developing walking habits.

Turning now more toward the technical details that undergird the controller, first, it is critical to note that the decision-making control algorithm operates differently in each state. For behavioral initiation, the decision-making algorithm strives for appropriate daily step goals using the general approach described previously. When it comes to the behavioral maintenance state, the decision-making algorithm switches from not only seeking to optimize for steps to also minimizing the use of the financial reward component while steps are maintained. This process requires an additional logical condition that is related to consistently achieving desired levels of healthy behavior or, put more plainly, our approach for operationalizing when a person is or is not in the maintenance state. We defined a person as being in the maintenance state when they consistently reach ≥9500 steps per day for 6 out of the previous 7 days. When this condition is met, the point intervention component is reduced or deactivated by adjusting the decision-making algorithm's tuning parameters. On the other hand, the positive reinforcement intervention component can be reactivated when the logical condition is no longer met, enabling responsiveness to lapse [88,89]. The decision-making algorithm bases its reduction of interactions on behavioral theory, specifically a thinning reinforcement schedule of points and other strategies (eg, minimize suggested goals each day to internalize targets) to help facilitate habit formation [90-92].

When there is a discrepancy between the decision-making algorithm's prediction and a person's actual response, the decision-making algorithm will systematically use approaches that the person appears more responsive to. These approaches are applied through a robust three-degree-of-freedom Kalman filter-based hybrid model predictive control (3DoF-KF HMPC) [85,86,88,89], biasing the decisions toward what a person has been responsive to most recently (instead of what worked earlier in the intervention). The optimization objective function for the controller is expressed in equation 2:

In this equation, denotes the outputs, and represent controller decisions with both continuous and discrete elements. and are binary and discrete auxiliary variables that convert discrete and logical decisions into their equivalent linear inequality constraints represented in equation 3:

$$E_5 \geq E_2\delta_k - E_4y_k - E_1u_k + E_3z_k + E_dd_k - E_6u_{k-1} - E_7y_{k-1}$$

in equation 2 represents the slack variables implemented to soften output constraints. The desired target for each variable is described by $*_r$. Matrices W_y, $W_{\Delta u}$, and W_s are the penalty weights on the output error, move size, and slack, respectively, whereas W_u, W_δ, and W_z are the penalty weights on manipulated variables, auxiliary binary variables, and auxiliary discrete variable targets, respectively. The move horizon and the prediction horizon are denoted by m and p, respectively.

On each day of the closed-loop intervention, denoted by k, mixed-integer quadratic programming is used to make personalized intervention decisions by solving the optimization problem in equation 2 subject to the logical and categorical constraints presented in equation 3 and the following input and output constraints:

$$y_{\min} - \Psi_{k+j} \leq y_{k+j} \leq y_{\max} + \Psi_{k+j},\ j=1,\ldots p$$

$$u_{\min} \leq u_{k+i} \leq u_{\max},\ i=0,1,\ldots m-1$$

$$\Delta u_{\min} \leq \Delta u_{k+i} \leq \Delta u_{\max},\ i=0,1,\ldots m-1$$

$$\Psi_{k+J} \geq 0,\ j=1,\ldots p$$

Variations in the control strategies are implemented at different stages of the closed-loop intervention as part of the decision-making algorithm. This is achieved by reconfiguring the controller and adjusting tuning parameters based on the participant's performance in the previous 7 days of the intervention. Figure 10 summarizes the "digital PA coach tuning" algorithm used in this study. A more detailed description of the algorithm is presented in previous literature [85,93].

In addition to maintenance reconfiguration, the devised decision-making algorithm tightens the constraints based on how many days that person failed to meet the daily goals to ensure the delivery of *ambitious yet achievable* goals. For example, if the participant misses the goals for 3 to 4 days, the decision-making algorithm softly tightens the constraint for goal attainment. If the person misses the goals for ≥5 days, the decision-making algorithm constrains the daily goal to a maximum of 2000 steps per day above the average of the previous 7 days. In sum, the decision-making algorithm in our study is a robust, systematic, scalable approach for providing many key benefits of a lifestyle coach via an automated tool.

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Figure 10. Summary of the logic used in controller reconfiguration and tuning. GA: goal attainment.

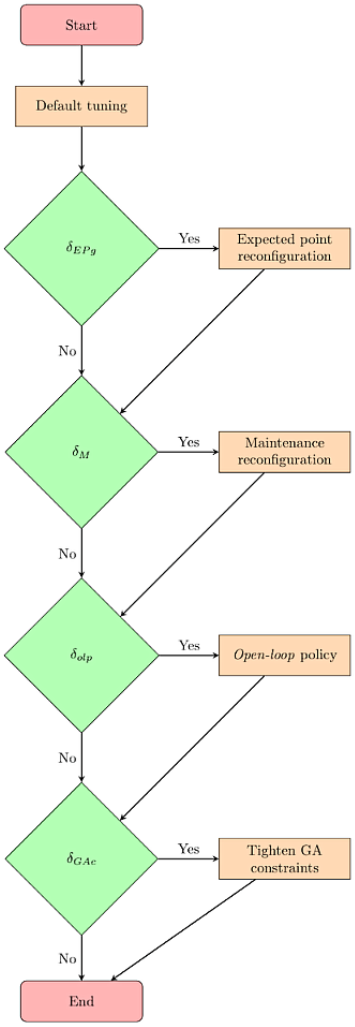

PA Planning and Reflection Tool

Participants are prompted to complete a self-guided self-experimentation tool titled Reflect via Qualtrics [94] weekly for the first 8 weeks and monthly thereafter. In addition, Reflect is available for participants to complete more often if preferred. At the start of the survey, participants are asked to reflect on their progress toward their weekly exercise goal delivered via SMS text message. Next, participants are provided with a list of various types of exercises that can be done to achieve MVPA (eg, biking and circuit training). On the basis of their selections, participants are then prompted to create a plan to reach their weekly goal. Each time the tool is completed, participants have an option to keep their exercise choices the same as their previous selections or make changes depending on their previous experiences. Participants then choose which exercise strategy they would like to experiment with over the following weeks. As explained to participants, the strategies are designed to help achieve the previously developed exercise plan and, ultimately, reach the weekly exercise goal. Each time a participant completes the tool, they are asked to reflect on their experiences experimenting with the strategy and, contingent on their reflections, prompted to either continue experimenting with the strategy or try another. Following the completion of Reflect, participants are emailed a summary of their responses to encourage adherence to their exercise plan and strategy experimentation. In addition, EMA messages are sent to a participant after completing at least 10 minutes of MVPA to prompt further reflection on their experiences with exercise and experimenting with the Reflect strategy, shown in the Self-Experimentation to Cultivate Personalized Knowledge, Skills, and Practice section (Figure 5).

Active Control

In addition to all the common elements described in the previous sections (eg, Fitbit smartwatch, US $50 in incentives for meeting step goals, and tailored SMS text messaging support), participants assigned to the active control group, similarly to those assigned to the YourMove intervention group, are instructed to engage in their normal level of PA for 1 week to establish a baseline, shown in Figure 7. This is followed by the intervention phase, during which participants receive a daily step goal along with an accompanying number of points earned each day that they reach their goal. Unlike the YourMove intervention, the daily step goal and accompanying number of points is kept fixed (10,000 steps per day and 150 points per day, respectively). The goal is delivered to participants via the standard Fitbit app features, and points are communicated via email. Participants also receive a weekly PA goal and the same accompanying motivational and informative SMS text messages

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as those for the YourMove intervention group described previously. Finally, the active control condition does not include the self-guided self-experimentation tool (Reflect) featured in the YourMove intervention condition.

Data Management and Quality Assurance

Most study data will be collected, managed, and stored using the secure web-based tool REDCap hosted at UCSD [75]. REDCap provides an interface for data entry and storage, audit trails for tracking data input and changes, automated export procedures for data downloads to common statistical packages, and procedures for importing data from external sources. Furthermore, data are deidentified using a unique trial identification number assigned to each participant and kept confidential.

Clinical Trial Integrity Practices While Accounting for the Need to Tune the Controller

As described in the Phase 3: Controller section, controller tuning is a common practice within control systems engineering and involves refining the controller for targets such as performance and robustness based on real-world observation. In this case, the key focus was on controller robustness. Robustness focuses on ensuring that the controller is programmed to be able to offer appropriate response options to the diversity of responses of those who will use the controller. Robustness is a critical target within control systems engineering. Critically, the tuning work focuses on refining how the controller responds to all participants, with any tuning changes made across all participants. Controller tuning is a common strategy used in control systems engineering and, thus, its lack of inclusion would result in an inappropriately tested control systems–driven behavioral intervention (ie, it would not reflect an appropriately operationalized COT approach). This is because, if controller tuning were excluded, the control system that is implemented would not be a rigorous implementation of standard procedures used in control systems engineering.

Controller tuning is not a normative requirement within traditional clinical trial work. Therefore, the team needed to develop an approach to guaranteeing clinical trial integrity to ensure the trustworthiness of the results of the RCT while simultaneously enabling the control systems team to engage in the required “tuning” work to ensure that we followed best practices from control systems engineering. Thus, the team developed the following sets of rules and procedures for data monitoring and fidelity that were reviewed and approved by the full study team (ie, all coauthors on this paper) before any data were collected.

At a high level, from the perspective of the RCT, control systems tuning was treated as part of the overall intervention package. With this stated explicitly, it is critical to note that, while the system we developed is scalable and automated, it does require a human to actively monitor the system to engage in tuning. We referred to this role as the “digital health PA tuning coach” described previously. From a scalability perspective, we assumed that any digital health implementation of this would include a staff member with the requisite data science and control systems expertise to fulfill this role on any scaled platform. Thus, this digital health PA tuning coach role, which was fulfilled by one of our team members conducting this set of activities as a part-time set of their total tasks, is another key element of the YourMove intervention that would need to be considered for any future implementation. On the basis of common practices in digital health and digital therapeutics companies, we postulate that it is a fair assumption that any digital health tool requires the right staffing to implement it at scale.

With the assumption that it is reasonable that data science expertise capable of tuning the controller will be present in a digital therapeutics company implementing our team’s approach, our team developed protocols to enable this digital health PA tuning coach role to be involved while not compromising the integrity of the clinical trial. Again, at a high level, a priori plans for maintaining clinical trial integrity included a clear separation of team personnel among (1) those who gather primary and secondary outcome data; (2) our study statistician and those conducting the primary analyses for the clinical trial; (3) those managing the study participants and, thus, who have awareness of group allocation by necessity of the behavioral trial design; and (4) the control systems engineering team tasked with implementing the standard practice of tuning the controller during the trial.

The following procedures for ensuring clinical trial integrity were established. First, eligible participants were randomly allocated to 1 of 2 conditions, YourMove or active control. The study statistician, without knowledge of participant characteristics, created a priori a computer-generated list involving block randomization accounting for sex as a biological variable. This randomization was used to assign participants to study conditions. Second, allocation concealment has been and will be maintained via the staff gathering clinical trial measurements, including the primary outcome measure of ActiGraph-assessed MVPA and physiological secondary laboratory-based outcomes (eg, BMI and submaximal oxygen consumption), remaining blinded to group allocation. Thus, the principal investigator (PI; EH) did not and will not have access to primary and secondary outcome data and will remain blinded to group allocation. Furthermore, the study statistician and all coinvestigators have remained and will remain blinded to primary and secondary outcome data while they are being gathered. Third, no data cleaning or analyses of primary and secondary laboratory-based outcomes have taken place or are planned until study completion save for basic data quality checks conducted by those who gathered the primary and secondary outcome data. No group comparisons, including possible comparisons with Fitbit or other data, are planned nor will be conducted until study completion. Group allocation will be revealed only after the primary analysis is completed.

Regarding enabling controller tuning while maintaining clinical trial integrity, the team responsible for controller tuning had no access to primary and secondary outcome data; the team tasked with tuning the controller were and will be unable to influence acquisition of the primary and secondary outcome data; study staff responsible for implementing the randomization procedure and, thus, aware of group allocation were not and will not be included in controller-tuning activities, remaining blind to those

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activities; the team responsible for tuning will not be able to run any analyses comparing differences between randomized groups; all tuning will use idiographic or N-of-1 analyses used as part of standard control systems engineering techniques for tuning a controller using data that the controller uses to make decisions, including steps per day as measured via Fitbit, EMA data, and weather data; a coinvestigator (PK) will be involved in all tuning discussions and provide behavioral insights to guide the tuning decision-making process, with final decision-making on the controller conducted by the multiple PI (DER); and the study PI (EH) will only take part in a limited matter regarding controller tuning. Specifically, the PI (EH) will only collaborate with the control systems engineering team during the final stages of publishing the tuning activities. These publications will report on only a selected subset of analyses conducted ideographically. These will be selected by the tuning team specifically because of their use in tuning the controller. Any results on tuning will not include results from all participants in the intervention condition to reduce possible risk of creating a bias regarding the integrity of the clinical trial. No analyses will be conducted within the control group dataset until after completion of the clinical trial.

Statistical Analysis

Overview

For the comparison of a 12-month change in minutes per week of MVPA from baseline between the intervention and control groups, a 2-sided, 2-sample 2-tailed *t* test with a significance level of .05 (or a nonparametric approach such as the Wilcoxon rank sum test if parametric assumptions fail) will be conducted. In general, analyses will incorporate the intention-to-treat principle, which includes all participants who are randomized in the analysis. A mixed model for repeated measures (MMRM) will also be considered. The dependent variable in the MMRM is the change from baseline in minutes per week of MVPA at each postbaseline visit (6 and 12 months). Independent variables in the MMRM include study arm, visit (as a categorical variable), arm-by-visit interaction, minutes per week of MVPA at baseline, and potential covariates of interest (eg, baseline BMI, sex, age, ethnicity and race, marital status, parental status, employment status, and smoking status) that are determined a priori. Potential covariates significantly associated with outcome ($P<.10$) will be included in a multivariable logistic regression model. To avoid inflation of the type I error, we will use permutation tests for inference. Missing data will be evaluated. If the missingness is not random (nonignorable), multiple imputation or propensity weighting will be considered. There will be no planned interim analyses for efficacy or futility conducted for this study. In addition, a frequency table comparing the arms in terms of meeting the guidelines (dichotomized as *yes* or *no*) will be created, and a Fisher exact test will be conducted. Furthermore, a generalized estimating equations regression will be conducted with meeting the guidelines (*yes* or *no*) as the dependent variable and visit, arm, and visit by arm as interaction terms in the model using an appropriate correlation structure adjusted by similar covariates to those of the primary aim. Statistical analyses will be conducted using the statistical software R (version 4.1.2).

Power Considerations

Our sample size (N=386) provides sufficient power for our primary aim. On the basis of a 2-sided, 2-sample *t* test, with a sample size of 193 in each arm (386 participants in total) and a type I error (α) of .05, we achieve 80% power to detect a standardized effect size [1-3,8,9] of 0.32 for comparing a month 12 change from baseline in minutes per week of MVPA between arms, accounting for an attrition rate of 20% in measurement (ie, completing the ActiGraph measurement battery at 12 months but not necessarily adhering to the use of the DHI; Table 2). We have powered for a 0.32 effect size, through which we anticipate a change from baseline of 45 minutes of MVPA after 12 months in the control arm and a 75-minute change from baseline in MVPA for the intervention arm assuming a pooled SD of change of 94 minutes and a mean change score difference of 30 minutes per week of MVPA.

Table 2. Sample size and power (2-sided α=.05).

Power	Effect size	Sample size per group	Overall sample size	Overall sample size considering 15% attrition	Overall sample size considering 20% attrition
0.8	0.32	154	308	362	386
0.8	0.36	122	244	288	306
0.8	0.4	99	198	234	248
0.85	0.32	176	352	414	440
0.85	0.36	139	278	328	348
0.85	0.4	113	226	266	284

To develop this power calculation, we examined effect sizes from 3 different studies available at the time of study design [26] plus our own previous formative research results [93,95-98] to establish an effect size of 0.32 as reasonable. When combined, previous studies and formative research results address power considerations related to using similar measurement batteries, detecting meaningful effects at 12 months between 2 active interventions and plausibly meaningful effects to be anticipated when comparing our YourMove intervention approach to our active control. First, these estimates are consistent with those of the study by Lynch et al [98], which we used as a reference as it conforms to effects that we observed in our formative research. It evaluated a technology-based intervention and used a similar measurement protocol, particularly an ActiGraph monitor, to assess minutes per week of MVPA. That said, the trial did not assess differences at 12 months, nor did it compare

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2 active interventions. As such, we used the Community Health Advice by Telephone trial as a second reference, whereby an effect size of 0.32 (ie, the same effect size as that for our study) was also observed as the difference between 2 active and successful PA interventions at 12 and 18 months after baseline, with one being a technology-based intervention and the second being a human-based intervention [97,99]. As our RCT includes an active goal-setting intervention, we also examined effect sizes in a third trial by previous studies [95,96]. Specifically, Adams et al [95] conducted a trial comparing adaptive step goals to static step goals (ie, 10,000 steps per day) and also immediate reward provision versus delayed reward provision (with both groups, similarly to ours, receiving gift cards if they met a daily step goal target). Results indicated that all conditions significantly increased by, on average, 2389 steps per day over 4 months (which aligns with our pilot study of JustWalk version 1 of 2651 steps per day [100] at 3 months). Results further indicated a significant difference at intervention completion favoring immediate over delayed reward (with immediate reward in alignment with our protocol) and an effect size of 0.32 comparing these 2 active interventions. The condition most similar to our intervention condition (ie, adaptive goals+immediate feedback) exhibited gradual increases in steps across the intervention, including until study end, which supports our assertion of the value of gradual habit formation. In our pilot study, we had 5% attrition over 3 months, and the study by Adams et al [95] had an attrition rate of 11% at 4 months. On the basis of this, our oversampling to support up to 20% attrition at 12 months is justifiable, particularly when considering the use of the ActiGraph monitor for assessment instead of using a measurement approach that is linked to the intervention in some way. In summary, based on the overall state of the science, being able to detect an effect size of 0.32, which equates to a change difference of 30 minutes per week of MVPA between YourMove and the active control via ActiGraph at 12 months, would illustrate both a clinically meaningful difference and also a difference that is conservative enough to be observable between 2 active interventions based on prior work.

Results

The YourMove study was funded in July 2020 and received institutional review board approval on July 1, 2020. Recruitment and enrollment began in October 2022, and a total of 386 participants were enrolled by August 2024. Data collection is ongoing and expected to conclude by August 2025. Data analysis has not yet begun, and results are anticipated in early 2026.

Discussion

Overview

Our prior work has emphasized the need for personalized interventions that can adapt dynamically to each individual's evolving context and behavioral patterns. We observed that internal factors (eg, stress and busyness) and external factors (eg, the weather and day of the week) influence PA in ways that vary not only across individuals but also within individuals over time. These findings align with and extend previous research showing that DHIs for PA tend to yield moderate short-term effects and are generally acceptable, yet their benefits often diminish over time and are typically limited to specific subpopulations. Together, this evidence underscores a critical gap in current intervention design—the need for approaches that are responsive to the inherently dynamic and idiosyncratic nature of PA rather than relying on static behavior change assumptions.

To address this gap, the YourMove DHI integrates two core components: (1) habit formation mechanisms driven by the team's proposed COT approach and (2) knowledge, skill, and practice development components via a self-experimentation approach modeled after the Schraefel et al [48] experiment in a box (XB) approach to improve MVPA. There are many potential contributions of this work. First, our intervention is the first scaled deployment and testing of the team's overall COT approach, described previously. Designed to be highly scalable for improving behaviors and reducing chronic disease risk, if effective, it could be used widely through smartwatch and smartphone technology. In addition, this study will be a rigorous evaluation of the COT approach via an RCT. If our approach to offering personalized and perpetually adaptive support is helpful for PA, it will provide justification for extending the approach to other health behaviors that are dynamic and idiosyncratic, such as weight loss or addiction.

Previous Research That Informed Our COT Element

As a proof of concept for the COT approach used in YourMove, system ID techniques were used to develop an idiographic dynamic model using participant data from the team's previous study, Just Walk [89], which included an intervention aimed at promoting walking behavior among sedentary adults. While YourMove builds on foundational insights from Just Walk, it represents a deliberate and planned expansion of the original work. Notably, this protocol includes a broader age range (adults aged ≥25 years) and is not limited to individuals who are overweight or obese, as was emphasized in earlier protocol versions and peer-reviewed materials. These changes were implemented in response to iterative design work that was explicitly outlined in the funding grant and intended to enhance generalizability and future scalability. In addition, while both studies center on mobile health–based PA promotion, YourMove incorporates new components, including a knowledge, skill, and practice self-experimentation element and broader COT infrastructure to support real-time N-of-1 adaptation that is both guided by the controller and self-guided. These deviations from the original protocol are intended to enhance generalizability and reflect iterative improvements informed by the design work that was part of the funding grant.

On the basis of this formative work, we conducted a number of analyses intended to lead to more predictive models that informed intervention development and decision policies for a personalized and perpetually adapting intervention. The estimated model was subsequently used to evaluate a control-oriented decision-making algorithm designed for an adaptive DHI that promotes PA in sedentary adults within a simulation environment [89]. The decision-making framework

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was based on 3DoF-KF HMPC formulation, incorporating a mixed logical dynamic framework to represent categorical and logical decisions within the policy. A three-degree-of-freedom tuning approach was implemented, allowing for independent adjustments for response speed to set point tracking and disturbance rejection, both measured and unmeasured. Simulation results highlighted the integration of system ID and the HMPC controller formulation, demonstrating the potential for optimal and personalized PA interventions—a crucial step toward large-scale dissemination of behavioral interventions for PA promotion. The estimated model displayed strong predictive capabilities while maintaining a good fit to the data. This model was used as the predictive component in simulations to assess the efficacy of the 3DoF-KF HMPC framework in delivering individualized PA interventions. Simulation outcomes showed the HMPC algorithm to be highly effective in guiding personalized PA interventions. In addition, within the HMPC algorithm, the controller was reconfigured to support a maintenance phase, reducing or eliminating financial incentives to help participants sustain healthy PA levels without dependence on rewards [48].

Thus, the YourMove study described in this protocol is the logical next step in this systematic line of research meant to develop ways to use control systems engineering methods to guide the creation of personalized and perpetually adaptive interventions. The results of this trial will provide a robust nomothetic test of the value of the many decisions and efforts of the team to create a robust operationalization of this type of personalized and perpetually adapting intervention. Significant results suggesting improvements in MVPA relative to an active control will provide compelling evidence for both digital health and digital therapeutics companies to consider incorporating this algorithmic approach into their tools. In addition, these results will provide justification for the continued development and expansion of the use of control systems engineering approaches for providing highly personalized and perpetually adaptive interventions for individuals, thus filling a critical gap in care, namely, the capacity to provide the “right” type of support that is appropriate for each person over time.

Previous Research Informing Our Self-Experimentation Tool

The Reflect tool was based on the XB framework developed by Schraefel et al [48]. Contrary to common digital health tools that seek to provide the solutions for participants, the XB approach allows participants to experiment with general health heuristics to discover what is useful for themselves. Through self-experimentation, an individual can build knowledge, skills, and practice to transform a general health heuristic (eg, national guidelines for PA) into a personal health heuristic (eg, a regular exercise routine that adapts to different contexts) [48]. Aligned with self-determination theory, the XB framework gives a participant the opportunity to develop autonomy to determine and use strategies that work for them without pressure to adopt ones that are not useful [100]. In this way, participants are the agents of achieving desired behavior change rather than the intervention or technology itself.

This work also aligns with other frameworks of self-experimentation such as the personal science framework [101] and self-study [102]. Personal science is illustrated by a cycle of five activities in which individuals examine their personal health by (1) *asking questions* unique to their health status and behaviors; (2) *designing* to discover and apply necessary changes; (3) *observing* to self-track meaningful data; (4) *reasoning* to reassess questions, designs, and observations; and (5) *discovering* what is helpful or needs further questioning [101]. Similarly, self-study involves experimentation and tracking at an individual level to establish autonomy and make meaningful impacts on one’s health [48]. By using the XB and personal science frameworks and self-study, Reflect is a tool in the YourMove intervention designed to promote intrinsic discovery of personal PA health heuristics to enable resilient PA practice.

While this intervention component was a secondary element to the overall intervention, if our trial results suggest significant differences in our active intervention relative to the control, it will provide empirical justification for continued study and exploration on ways in which self-experimentation approaches can be developed within digital health and digital therapeutics tools. We see particular value in this approach as a strategy for ensuring the ethical use of these digital technologies via an explicit incorporation of the person determining whether an intervention is working for them based on their own self-experiments.

Study Limitations

Several limitations inherent to RCTs on behavioral interventions should be acknowledged. First, due to the nature of digital behavioral interventions, observer bias may have arisen as it is challenging to achieve full blinding in these types of studies. Second, the primary outcomes were measured at discrete time points, providing only snapshots of behavior change over the study period. This approach may lack sensitivity to capture the dynamic, continuous changes in behavior that occur within individuals (although the team can overcome this via the use of Fitbit data as a secondary check). Third, this study did not use a fully random sampling approach for recruitment, which may limit the generalizability of the findings, although the approaches do conform to standard practices for behavioral interventions. Finally, as is the case with any RCT, there are potential limitations in internal validity, including potential unmeasured confounding variables and issues related to participant adherence, which are common in behavioral intervention trials.

Conclusions

Overall, this work will examine whether the team’s hypothesized approach to creating a personalized and perpetually adaptive DHI can result in increased MVPA in comparison to an active control condition that is meant to control for common behavioral strategies (eg, self-monitoring, goal setting, financial incentives, and psychoeducation) while also mimicking common digital health worksite wellness offerings that were available and common when the study was being designed. This research marks an important step toward developing scalable solutions

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for sustainable, personalized, and perpetually adapting PA support.

Acknowledgments

This study was funded by the National Cancer Institute (5R01CA244777). The National Institutes of Health peer review report is provided in Multimedia Appendix 9.

Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

MEM, JG, KP, CN, SJ, DER, PK, and EH conducted the theoretical foundation work and simulations. MK, MEM, JP, SM-A, MH, DER, PK, and EH developed the intervention. JP, MEM, and PK developed the technical systems, including the server and mobile app. MK, SM-A, SDLT, and MH conducted recruitment and interviews and worked on the trial logistics. SM-A, MEM, JP, SB, OK, and MH monitored the participants, communicated with them if necessary, and executed the adherence protocol. MEM, SB, OK, and DER developed the system ID programs. DER, PK, and EH provided guidance at each stage of the study. All authors contributed to the writing of the manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
YourMove Reflect tool for week 1.
[PDF File (Adobe PDF File), 466 KB - resprot_v14i1e70599_app1.pdf]

Multimedia Appendix 2
YourMove Reflect tool week 1 summary email.
[PDF File (Adobe PDF File), 324 KB - resprot_v14i1e70599_app2.pdf]

Multimedia Appendix 3
YourMove Reflect tool for the follow-up weeks.
[PDF File (Adobe PDF File), 975 KB - resprot_v14i1e70599_app3.pdf]

Multimedia Appendix 4
YourMove Reflect tool summary email for the follow-up weeks.
[PDF File (Adobe PDF File), 199 KB - resprot_v14i1e70599_app4.pdf]

Multimedia Appendix 5
YourMove Reflect tool experiment strategies.
[PDF File (Adobe PDF File), 58 KB - resprot_v14i1e70599_app5.pdf]

Multimedia Appendix 6
Reflect tool week 1 survey video.
[MP4 File (MP4 Video), 146273 KB - resprot_v14i1e70599_app6.mp4]

Multimedia Appendix 7
Reflect tool survey video for the follow-up weeks.
[MP4 File (MP4 Video), 154472 KB - resprot_v14i1e70599_app7.mp4]

Multimedia Appendix 8
Weekly schedule and examples of SMS text messages delivered in the YourMove intervention.
[PNG File , 520 KB - resprot_v14i1e70599_app8.png]

Multimedia Appendix 9
Peer-review report from PRDP - Psychosocial Risk and Disease Prevention Study Section (National Institutes of Health, USA).

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[PDF File (Adobe PDF File), 215 KB - resprot_v14i1e70599_app9.pdf]

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Abbreviations

BCT: behavior change technique
COT: control optimization trial
DHI: digital health intervention
EMA: ecological momentary assessment
EPARC: Exercise and Physical Activity Resource Center
HMPC: hybrid model predictive control
MMRM: mixed model for repeated measures
MVPA: moderate to vigorous physical activity
PA: physical activity
PAR-Q: Physical Activity Readiness Questionnaire–Revised
PI: principal investigator

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RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SCT: social cognitive theory
UCSD: University of California, San Diego
XB: experiment in a box

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Protocol

Addressing Youth Mental Health Through Schools and Primary Care Clinics Using the Connected for Wellness Mobile App: Protocol for a Stepped-Wedge Trial

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Abstract

Background: Youth in the United States are experiencing rising rates of anxiety, depression, and other mental health challenges, yet many remain underserved due to systemic barriers such as poverty, limited access to care, and shortages in the mental health workforce. Schools and primary care clinics are trusted, community-based settings that offer strategic opportunities for early identification, prevention, and intervention. As part of a public health approach, integrating digital mental health tools into these settings can support broad access, enhance mental health literacy, and promote help-seeking behaviors among all students. When co-designed with youth and embedded within existing care systems, these tools offer a scalable, proactive solution to support well-being across diverse school-aged populations.

Objective: This protocol describes the design and implementation of a stepped-wedge clinical trial to evaluate the Connected for Wellness mobile app, a youth- and caregiver-facing digital mental health intervention. Developed using participatory informatics and human-centered design principles, the app provides culturally relevant content in English and Spanish. Features include self-guided wellness activities, well-being screeners, psychoeducational videos, and localized service directories. Machine learning algorithms personalize content recommendations based on user inputs and behavioral patterns.

Methods: This trial uses a stepped-wedge cluster randomized design across 20 community-based sites (10 high schools and 10 primary care clinics) in 2 counties in California. These counties were selected for their high proportions of underserved youth populations. All youth aged 13 to 22 years and their caregivers will be invited to access the app. Sites are randomized into 2 implementation waves. The app is introduced site-wide as a universal public health intervention supported by on-site navigators and peer ambassadors. The primary outcomes are derived from a cascade-of-care framework, including identification of mental health need, referral to services, initiation of services, and engagement (defined as ≥3 treatment visits). Data will be collected via anonymous in-app analytics, monthly World Health Organization–Five Well-Being Index assessments, and deidentified electronic health and administrative records. Generalized linear mixed models will be used to evaluate differences in cascade outcomes between pre- and postimplementation phases while accounting for clustering and site-level variability.

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Results: As of May 2025, the mobile app has been finalized, institutional review board approvals have been secured, and all study sites have been recruited. Participant recruitment is projected to begin in August 2025. Data collection and initial analyses will begin in early 2026, with preliminary findings expected by October 2026.

Conclusions: This study tests a novel digital health intervention integrated into trusted care systems. If effective, the Connected for Wellness mobile app may serve as a scalable strategy to reduce disparities in mental health care access and engagement for youth across the United States.

Trial Registration: ClinicalTrials.gov NCT06122688; https://clinicaltrials.gov/study/NCT06122688

International Registered Report Identifier (IRRID): PRR1-10.2196/73721

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KEYWORDS

mobile app; co-design; youth mental health; participatory informatics; stepped-wedge design; mental health disparities; wellness; prevention; primary care; school mental health

Introduction

Background

Could a mobile mental health app designed for youth and caregivers help address mental health service barriers? For decades, research has documented the ongoing and persistent inequities in mental health care access for many populations, including both rural and urban [1-3]. Innovative aspects of the clinical trial protocol reported in this paper include using a mobile app codeveloped with youth and families through participatory informatics to drive technological innovation considering youth and caregiver priorities regarding customizable features and in-app resources.

Our previous work supports the hypothesis that mobile apps and other digital health interventions are effective for delivering mental health and prevention services provided that they meet the needs and preferences of end users [4]. These interventions can be successfully implemented within child-, adolescent-, and family-serving systems of care. Unlike clinicians' time, technology offers a nonconsumable strategy (ie, available asynchronous content vs scheduled therapist time) for improving mental health care access [5]. The United States has witnessed an increasing need for youth mental health services, especially for stress-related challenges [6,7] and populations disproportionately affected [8]. National data reveal that, after controlling for sociodemographics, severity of symptoms, income, and health insurance, Black and Latino youth with similar needs as White youth were almost half as likely to receive mental health services [3].

Barriers to care exist across multiple levels, including cultural, community, family, and systemic factors. For instance, Latino caregivers may perceive children's behavioral challenges as issues to address within the family, struggle with the lack of linguistically and culturally appropriate services, or experience stigma and perceptions of mental health needs that differ from those of mental health care providers [9]. Rural communities of all backgrounds are also underserved. These systematic factors contribute to reduced use of mental health services even in high-risk populations, underscoring the need for focused interventions that can both help mental health symptoms and risks and promote and facilitate engagement with services [10].

Mobile app interventions, integrated into trusted community settings such as schools and primary care clinics, offer scalable solutions to improve access to youth mental health care. To be effective and acceptable, apps need to include features and content that are designed to be engaging for and address the needs of diverse groups [11]. Despite the proliferation of digital health interventions for youth across a range of delivery methods (eg, websites, apps, games, robots, and virtual reality) [12], few are co-designed with the intended users in mind [13]. Furthermore, the methods used for youth and caregiver collaboration in the design process vary widely [14]. This is unfortunate as studies have demonstrated high levels of acceptability among youth for engaging with mobile health app interventions [15]. These tools can be important nonconsumable and scalable approaches for delivering mental health prevention and wellness tools [16]. When mobile mental health apps are used to expand access to mental health education and prevention resources, youth may be more likely to initiate and engage in help-seeking behaviors, and families may report greater satisfaction with care and perceive services as more appropriate once they engage [17].

Accessibility to mobile apps is another important consideration [18,19]. Use of cross-platform frameworks such as React Native [20] can ensure that an app is easily available to a wide community of users while retaining a single codebase for agile development. Mobile apps can also be integrated effectively with school-based and primary care services. Schools and primary care clinics are critical health care and mental health service providers [21], especially for underresourced populations [22]. Pediatric primary care is widely recognized as an important setting for identifying and managing youth mental health needs given that most youth make at least one medical visit annually [23]. In addition, access to mental health supports has often been expanded through educational settings [24], including the adoption of whole-school, multitiered systems of support that provide school-wide preventive interventions and mental health services through school-based health clinics and programs [25].

Overview of the Connected for Wellness Mobile App

In an effort to address the barriers to care for youth, a co-designed mobile app called Connected for Wellness was created with adolescents and their caregivers. The development of the Connected for Wellness mobile app and its predecessor,

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Connectd for Schools [26], is grounded in participatory informatics approaches. *Participatory informatics* [27] is an approach to technology codevelopment that combines best practices from community-partnered participatory research [28] and end user–centered participation in technology design [29]. This approach addresses community health priorities by including intended users as equitable partners throughout the design process. The codevelopment of the Connected for Wellness mobile app with youth and caregivers was led by the scientific team that includes diverse, multilingual research staff, child and adolescent psychiatrists, psychologists, technology development experts, and student researchers. The content includes engaging videos created by and representing diverse youth and caregivers in English and Spanish (details on the codevelopment process and protocols are reported elsewhere). In its final form, Connected for Wellness has four key components: (1) mental health and wellness education, (2) self-assessment tools, (3) emotion regulation and coping strategies, and (4) site-specific and community resources. The home page features a Get Help Now button that directly connects the user to 911 for those who need immediate assistance. The community resources include an embedded link to FindHelp, which is searchable by zip code. In addition to listings of financial assistance and free and reduced-cost food, housing, and health care, FindHelp also features helplines for specific needs such as domestic violence assistance and for communities that are particularly underserved. Given our priority to ensure that the app is widely accessible, we also developed a PDF document that provides all app content for anyone who is using a screen reader or prefers reading along.

The app includes optional notifications, inspirational messages, and interactive components to promote ongoing engagement. In addition, the co-design process led to the development of an app that prioritizes user confidentiality and safety. The app allows for anonymous use, does not include 2-way communication, and avoids open-text response fields, minimizing the risk of exposing sensitive personal information and ensuring that users can engage with the content privately and safely. We collaborated with both English- and Spanish-speaking communities to develop Connected for Wellness content in both languages. Table 1 outlines the app's features and pathways and includes images of the app's user interface.

To enhance customization and interactivity for both youth and caregivers, the Connected for Wellness mobile app uses collaborative filtering techniques [26] to intelligently recommend wellness skills and supportive resources to study participants. One approach, a content-based (*item-item*) method, automatically suggests skills based on previously viewed skills and the metadata associated with them. For example, the app clusters content related to similar topics—such as sleep health or emotion regulation—by analyzing descriptions, titles, and other metadata, allowing it to recommend new wellness skills that are semantically similar to those the user has already explored.

In addition, the app uses a peer-based (*user-user*) approach, which identifies users with similar engagement patterns and recommends resources that those similar users have found helpful but the current user has not yet accessed. A second layer of intelligence involves user classification, where youth responses to in-app wellness screeners trigger tailored protocols and personalized content recommendations based on their identified needs. Specifically, Connected for Wellness includes the World Health Organization–Five Well-Being Index (WHO-5) [30], a short questionnaire that measures a person's well-being over the previous 2 weeks and is suitable for children aged ≥9 years. Users can access this questionnaire on their own and will be reminded to complete it monthly through a notification. Higher scores on the WHO-5 indicate better mental well-being, whereas lower scores indicate potential risk of mental health concerns. After responding to the well-being questions, users receive a well-being score categorized as low, moderate, or high. On the basis of their score, they are provided with personalized well-being activities and suggestions, which can be saved in the app's Toolbox section for easy access later. For example, a user who scores low on the WHO-5 will receive recommendations for professional help seeking, along with evidence-based strategies to support well-being, such as behavioral activation and emotion regulation techniques. Figure 1 illustrates how the WHO-5 normed scoring system guides the Toolbox recommendations and suggestions for help seeking provided to users based on their check-in results (ie, scores on the WHO-5: green for high well-being, yellow for moderate well-being, and orange for low well-being).

The primary objective of this study is to evaluate the effectiveness of the Connected for Wellness mobile app in enhancing youth engagement with mental health services when implemented in schools and primary care settings. This study aims to leverage the app's ability to deliver evidence-based, culturally and contextually relevant information to address key barriers to mental health care, including stigma, limited accessibility, and the need for youth autonomy and confidentiality.

In addition, this study will explore how the app—co-designed with input from both youth and caregivers—enhances engagement with mental health support services and fosters help-seeking behaviors among youth and their families. Our main hypothesis is that the Connected for Wellness app will improve cascade-of-care outcomes compared to usual care. Specifically, we expect that youth at sites implementing the intervention will seek help more often, be screened more frequently, and be more likely to attend at least 3 mental health sessions if identified as needing services. If effective, the app has the potential to be a scalable tool for supporting youth mental health in community-based settings such as schools and primary care clinics and advancing public health approaches to connecting youth with care.

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Table 1. Features of the Connected for Wellness mobile app for youth and caregivers.

Feature (English and Spanish)	Description	Examples
Pathways	Brief videos and quick tips on well-being topics	• Getting better sleep • Improving communication • Grief and loss • Social connectedness • Relaxation • Managing emotions • Academic stress • Mental health help seeking
Self-assessments	Short questionnaires to gauge sleep and well-being (for youth and caregivers) and social determinant of health needs (for caregivers)	• WHO-5[a] • PROMIS[b] sleep items • Social determinant of health questions
Directory	Site-specific, local, and national resources with direct dial, maps, and information about resources	• Hotlines • Helplines • Clinic- or school-specific mental health and social resources located on-site • Community resources (FindHelp)
Toolbox	Over 500 well-being activities and suggestions that can be saved in the "Toolbox"	• Brief suggestions based on well-being frameworks that include domains of physical, psychological, emotional, spiritual, relational, professional, and cultural well-being

[a]WHO-5: World Health Organization–Five Well-Being Index.

[b]PROMIS: Patient-Reported Outcomes Measurement Information System.

Figure 1. World Health Organization–Five Well-Being Index (WHO-5) well-being check-in responses.

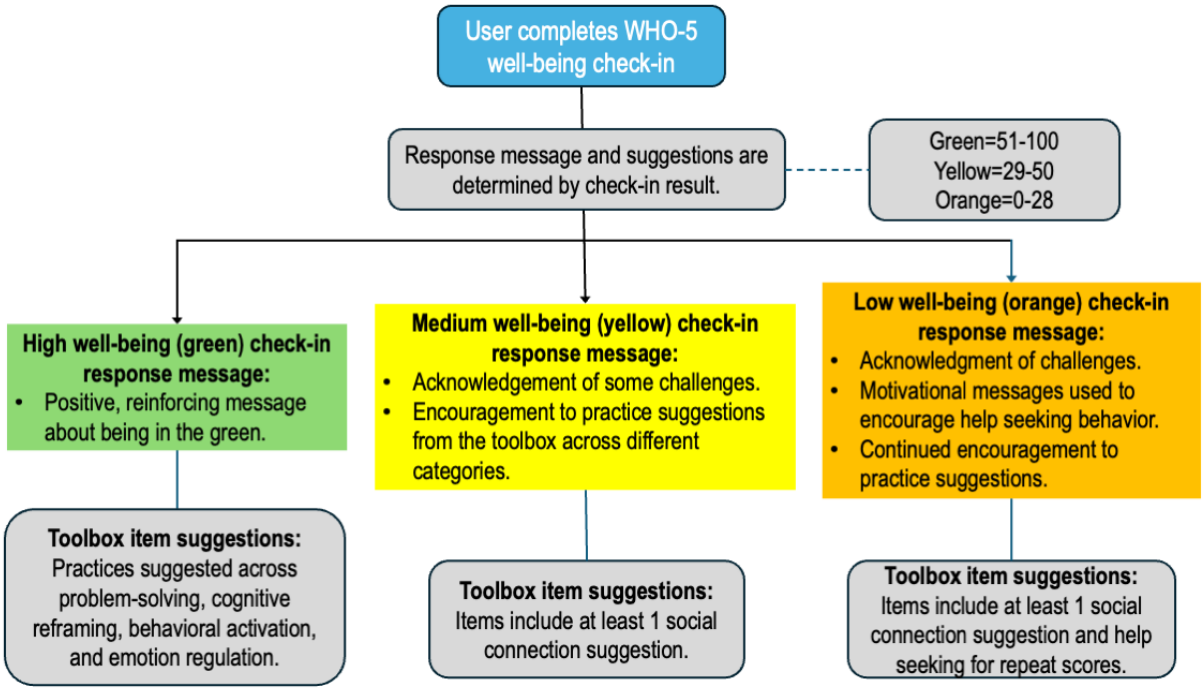

Methods

Objectives

This study protocol was developed in response to the National Institutes of Health, and the study was funded in August 2023 by the National Institute of Mental Health and will be completed by June 2027. In this section, we present the protocol for implementation of the mobile app using a stepped-wedge design in 10 schools and 10 clinics.

Stepped-Wedge Design

We use a stepped-wedge design, a type of cluster randomized trial that involves clusters (such as groups of clinics or schools) randomly assigned to different time points (ie, waves) to begin

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receiving the intervention [31]. The rationale for the stepped-wedge design includes its effectiveness in testing health care delivery models and related outcomes for systems of care, particularly when randomization at the individual level is not feasible [32]. A stepped-wedge design is also ideal when an intervention must be rolled out gradually due to logistical, financial, or ethical constraints, ensuring that all groups eventually receive the intervention. It is particularly useful for evaluating complex, systemic, or behavioral interventions when simultaneous initiation of the intervention is not feasible. Because the goal is to offer the intervention to all youth and caregivers at participating study sites, 2 clusters—consisting of 5 schools and 5 primary care clinics per wave—are randomly assigned to 2 different implementation waves. All clusters begin in the control condition, with the Connected for Wellness mobile app intervention introduced to schools and clinics at predetermined time points. By the end of the trial, all clusters will have received the intervention, allowing for a stepped implementation across the sites. Stepped-wedge designs are becoming increasingly popular for testing health care delivery models [33] and are an innovative approach for evaluating the public health impact of mobile apps delivered as universal or tier 1 interventions in youth- and family-serving systems of care [34].

Setting and Participants

This study will include youth aged 13 to 22 years (to include the range of possible ages in high school) and will be implemented across 10 public high schools and 10 community-based primary care clinics in 2 regions in California, United States. Caregivers will also be invited to use a version of the app for support of their child and their own well-being; however, this study does not monitor caregiver outcomes. Study sites will include urban and rural regions. The investigators will collaborate with one large school district and a network of primary care clinics that are part of a Federally Qualified Health Center system serving desert and rural regions. The schools and primary care clinics have existing peer support leaders or family navigators, who will integrate the Connected for Wellness app into their usual care in supporting students and caregivers in accessing mental health services and resources, encouraging help seeking, and using the in-app wellness skills.

Recruitment Strategy and Site Selection

Schools and clinics were selected based on (1) geographic (urban and rural) and full demographic representation, (2) service to communities with high proportions of underserved youth (including low-income White, Latino, Black, and Asian backgrounds), and (3) existing collaborations with the investigative team. Sites had to demonstrate adequate infrastructure, including wellness navigators, school-based health centers, or peer educator programs. Recruitment within each site will involve promotional campaigns, informative sessions, videos, and peer navigator outreach.

Existing Peer-to-Peer and Navigator Models

The high schools partnering with this study have an existing peer-to-peer model in which high school students are trained in a *community health framework* to deliver health and mental health education on topics relevant to their adolescent peers. This model targets health disparities by promoting wellness and reducing barriers to care within a culturally appropriate and community-centered approach [35,36]. Trained students lead school-wide campaigns to promote awareness and education with support from adult allies. In addition, each school has wellness navigators who will play a key role in integrating the mobile app into both school-wide educational efforts and individual support provided to students and caregivers. The primary care clinics participating in this study also have bilingual case managers and family navigators who will promote app use. These support specialists will be partnering with youth and families to help them access mental health information, develop wellness skills, and navigate linkages and referrals to care and community resources through the app.

Participant Eligibility Recruitment, Consent, and Monitoring

For the study sites, 10 schools and 10 primary care clinics have been recruited to use the Connected for Wellness app site-wide, entering the study in 2 randomized cohorts (see Multimedia Appendix 1 for study timeline). All youth and caregivers at each intervention site will be offered the mobile app. Each site will have a site ID code to access the app. All youth aged 13 to 22 years at the site will be invited to participate in the study by using the mobile app. We will use an information kick-off event, other mental health and promotional events, website links, and videos that provide information about the study. Navigators, site champions, and peer ambassadors will also promote the app and help with downloads for participants requesting help (eg, caregivers who are less comfortable with technology). After all youth or caregivers download the app, they will choose their preferred language (English or Spanish) and role (student or caregiver).

As approved by the institutional review board (IRB) for this study, participants will then complete the in-app consent process, which presents study information in both video and text formats along with comprehension questions to ensure that participants understand the consent process. Only those who answer the questions correctly and indicate their willingness to proceed will gain access to the app. To maximize anonymity—a priority identified during the codevelopment phase—users do not enter any personally identifying information (such as name, email, date of birth, or password). Investigators will regularly review anonymous app data and maintain an aggregated dashboard by site, including demographic characteristics of app users. The dashboard will also capture app use patterns. Using insights from enrollment and app use data, the research team will work closely with school and primary care clinic study champions to actively promote study participation and engagement across the sites.

Primary Outcomes: Cascade-of-Care Framework

The primary study outcomes are based on the cascade-of-care framework that focuses on population-level health needs and tracks individuals across relevant stages of a health care continuum [37,38]. Originally developed by the Juvenile Justice–Translational Research on Interventions for Adolescents

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in the Legal System [39,40], the steps in the cascade of care are identification of a behavioral health need, referral to behavioral health care, initiation of services, and engagement with services (>3 visits). The cascade of care has been adapted for youth in foster care [41]; this version was used for this study. Data on each step of the cascade of care will be obtained from deidentified electronic medical records and administrative data at the individual youth level from each of the study sites. This approach, which uses established databases, will enable comparison of cascade-of-care outcomes after implementation to data that were collected before preimplementation years. As detailed in the analytic plan in the Data Analysis section, individual-level data will be aggregated to the site level to test the hypothesis that implementation of the Connected for Wellness mobile app intervention is associated with improvements in youth progression through the cascade of care compared to the (preintervention) control condition. Improvements in the cascade of care are an established public health outcome as they help identify gaps in care and assess the effectiveness of the mobile app intervention. At a population level, in schools or primary care clinics, examining the cascade can inform how well an intervention improves youth access, engagement, and outcomes for a specific population and whether the intervention effectively addresses their unique needs and disparities. Statistical power was determined relative to the current level of each of the cascade outcomes (identification of mental health need, match to services, and initiation of services) in the sites as reflected in administrative data. Power was calculated separately for each cascade outcome. With a power of 0.8, an α value of .05, and 2-tailed tests, the planned design and sample sizes enable detection of small differences between the intervention and control conditions in all the cascade outcomes (2%-10%). Table 2 shows the operational definitions for the cascade-of-care outcome variables, and Table 3 shows the definitions, data collection, and outcomes.

Table 2. Cascade-of-care model based on Connected for Wellness triage outcomes.

Step	Rate	Operational definition
Youth at site (step a)	(a)	Total number of youth enrolled at a high school campus or on a patient panel at the primary care clinic site
Need identified (step b)	(b/a)	Subset of total enrolled youth (step a) who complete mental health and social determinant of health needs identification at school or the primary care clinic
Matched to services (step c)	(c/b)	Subset of youth with needs (step b) who receive a referral
Initiated services (step d)	(d/c)	Subset of those referred to services (step c) who initiate services (eg, first treatment session)
Engaged in services (step e)	(e/d)	Subset of those who initiate services (step d) who have ongoing sessions (≥3 visits)

Table 3. Primary outcomes based on the cascade-of-care framework and covariates for generalized linear mixed model (GLMM) analysis.

Cascade step	Operational definition and data description	Covariates in GLMM
Need identified	Youth who completed self-assessments or were flagged by navigators	Age, gender, race, ethnicity, site type (school vs clinic), and urban or rural
Matched to services	Referral documented in site records or follow-up logs	All the aforementioned covariates+previous mental health history if available
Initiated services	Attended first mental health appointment	Same as the previous covariates
Engaged in services	≥3 treatment sessions attended	Same as the previous covariates+time since app onboarding

Ethical Considerations

This study has been reviewed and approved by the IRB at the University of California, Riverside (protocol 30090). All study procedures involving human participants adhere to institutional and national ethical standards. Informed consent is obtained via the app using both video and text formats. Participants complete comprehension questions to ensure understanding. Only youth who correctly answer the questions and indicate consent may proceed. Parental consent is required for youth aged <18 years and per institutional policy. No personally identifying information is collected. Data are fully anonymized, and site-level dashboards track aggregate use only. App use is voluntary, and users remain anonymous throughout. Participants are not compensated for using the app, which is designed as a universal public health intervention. Site staff (peer ambassadors and navigators) may receive stipends through partner institutions. No images or materials in this study contain identifiable participant information.

Data Monitoring Plan

A data safety monitoring board (DSMB) will oversee the study to ensure participant safety, data integrity, and protocol adherence. The DSMB will review cumulative data at scheduled intervals and advise on any modifications needed to protect participants. The study team will conduct routine internal data quality checks, with any protocol deviations or serious concerns reported promptly to the DSMB and IRB.

Data Management Plan

Study data will be collected using HIPAA (Health Insurance Portability and Accountability Act)-compliant, encrypted platforms, with all records linked to unique participant IDs to ensure confidentiality. Data will be stored on secure, password-protected institutional servers with regular backups. Data management procedures—including entry, coding,

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cleaning, and storage—will follow standard operating procedures and be documented for transparency and reproducibility.

Plan for Collection and Reporting of Harms

All adverse events will be systematically recorded and reported per IRB and National Institutes of Health guidelines. Study personnel will be trained to monitor and respond to participant distress or risk disclosures, with serious adverse events reported to the DSMB and IRB within 48 hours. The DSMB will review all safety reports and provide recommendations for continuation or modification of study procedures as needed.

Data Access and Use

Access to identifiable data will be limited to authorized study staff approved by the IRB. All data use will comply with established data use agreements with the participating schools and clinics.

Dissemination Plan

All dissemination materials—including publications, presentations, and community reports—will be reviewed to ensure participant confidentiality and adherence to ethical standards. Community-facing materials will be developed in accessible formats and, when appropriate, cocreated with community partners.

Data Analysis

Analyses will be conducted using the SAS statistical software (version 9.4; SAS Institute) [42]. Preliminary analyses will include examination of descriptive statistics, distributions, and internal consistency reliability of scaled measures. The primary hypotheses are that the Connected for Wellness mobile app will improve all cascade outcomes relative to the usual care control condition. Specifically, we hypothesize that the mobile app will affect site-level increases in the progression through the defined cascade of care, as defined in Table 2 (eg, youth at sites implementing the Connected for Wellness mobile app intervention will engage in more help seeking and be screened more frequently, and once screened and identified as needing mental health services, youth will be more likely to attend at least 3 sessions as compared to the control conditions [before implementation of the mobile app intervention]).

These hypotheses will be tested within a generalized linear mixed model (GLMM) framework implemented using the SAS PROC GLIMMIX statement. These models accommodate variously distributed dependent variables, including dichotomous outcomes such as those reflecting the cascade-of-care outcomes, and account for correlations among measurements of the same participants and nesting of youth within sites. Models will use a binomial distribution and a logit link function. All tests will be 2-tailed with a significance level of P=.05. For dichotomous outcomes, we will use a binomial distribution with a logit link function.

The GLMM models will include county and intervention (vs control) as fixed effects, with site and youth as random effects. Study month will be treated as a continuous variable to account for potential secular trends. The primary focus will be on the intervention effect. For youth with mental health need, we will also examine time-to-event outcomes (eg, days to service initiation) using Poisson models with a log link function. If overdispersion is detected, we will use a negative binomial model. The relative risk ratio for intervention will indicate whether the app reduces time to service matching and initiation. To address heterogeneity, the GLMM will include random intercepts for sites and fixed effects for county and wave. We will test for interactions between intervention status and site characteristics (eg, urban vs rural and school vs clinic). We will also conduct stratified analyses by key demographic variables (race and ethnicity, age, and gender) to explore subgroup effects.

Results

As of May 2025, preparatory activities have been completed. These include finalization of the Connected for Wellness mobile app, IRB approvals, staff training, and recruitment of 20 participating sites (10 schools and 10 clinics randomized to cohorts). App deployment and participant recruitment are expected to begin between August 2025 and September 2025. App data collection and analysis of both app data and administrative data from the sites will begin in early 2026. Preliminary analyses are anticipated for October 2026. No results related to the study hypotheses are available at this time, but baseline engagement metrics and user demographics will be summarized once data are available. IRB approval was granted on July 1, 2025.

Discussion

Expected Findings

Innovative aspects of our clinical trial include the use of a mobile app codeveloped through participatory informatics integrating youth and caregiver priorities into its design to ensure that it addresses their specific needs. The app incorporates machine learning–driven, customizable features that offer personalized mental health resources focusing not only on mental health but also on addressing social determinants of health, such as housing and educational needs. By promoting local resources and providing tailored, real-time suggestions, the app helps bridge gaps in both mental health care and social services, ensuring that youth and caregivers can access the support they need in their everyday environments.

The growing body of evidence on mobile apps for mental health highlights their potential to improve access to care, engagement, and outcomes, particularly for underserved populations. While mobile health app technologies are increasingly recognized as scalable and accessible tools, their effectiveness is often dependent on personalization and relevance to the user's context. Few studies have focused on participatory, co-design approaches tailored for youth and caregivers, which is where our study stands apart. By integrating machine learning, the app can dynamically adjust to the needs of each user, positioning it as an innovative solution in the field of mobile health.

Low-income populations, who often face barriers to accessing traditional health care [2], demonstrate high levels of cell phone and mobile internet use [43]. This provides a unique opportunity for mobile apps to address health care disparities. Research has

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shown that emergency departments increasingly serve as safety nets for underserved populations, especially for low-acuity conditions that could be managed in primary care settings. Mobile app tools designed to connect individuals with timely medical advice could reduce emergency department use, improving overall health care access [44]. While the potential exists, understanding the feasibility of underserved populations engaging with mobile apps to improve mental health care is essential [45]. A recent review of 36 trials conducted among youth found that, while mobile apps show promise in addressing issues such as depression, anxiety, and substance use, the evidence remains uncertain or limited [46]. Most of the studies included in the aforementioned review were small in scale, focused primarily on efficacy for youth already identified as at risk of depressive symptoms, and highlighted the need for larger trials to assess effectiveness and explore subgroup differences. Our study aims to address these gaps in scientific literature by testing a comprehensive, participatory, and machine learning–driven mobile app designed to improve wellness practices as a form of prevention while also improving service use outcomes for youth. This study places a strong emphasis on population health, embedding the intervention within school and primary care clinic settings.

Limitations

The stepped-wedge design offers several advantages, including the ability to evaluate the intervention's effectiveness while ensuring that all students in a high school or primary care clinic have the opportunity to access the wellness and prevention components of the app along with peer and family supports. It also allows for the assessment of temporal trends and the potential for learning or adaptation over time. However, this design also has limitations. The sequential implementation of the intervention may introduce biases such as those arising from differences in timing or external events affecting specific sites. Although the mobile app helps ensure fidelity by providing a standardized intervention across sites, the design still requires careful planning to manage logistical complexities and ensure consistency in implementation across diverse settings. Finally, variability in site readiness and capacity to implement the intervention highlights the need for robust support and ongoing monitoring of study sites. This includes tracking factors such as staff size, mental health service capacity, and the presence of existing peer-to-peer programs throughout the study.

Conclusions

If successful, this study will demonstrate how mobile apps can serve as universal mental health and prevention tools, complementing existing behavioral health resources and community strategies such as peer support and family navigation programs. The mobile app–supported public health approach offers an equitable, scalable solution that has the potential reach and effectiveness to significantly improve public health outcomes and could reduce mental health care stigma among underserved communities.

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Data Availability

The datasets generated or analyzed during this study are not publicly available because they include administrative data owned by partnering schools and primary care sites, both of which are obligated to protect the privacy of minors.

Authors' Contributions

LRF, SK, MVP, MT-S, and MS led the conceptualization, methodology, implementation approach, and app development. LRF and SK led the funding acquisition, project administration, and supervision. RI-M and JBF contributed to conceptualization. MS and HA developed the methodology and formal statistical analysis. GB led the software programming and technical development of the Connected for Wellness app. JCG assisted with the methodology of the World Health Organization–Five Well-Being Index well-being workflow and app responses. All authors contributed to writing—original draft and review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Project Timeline for Stepped-wedge trial of the Connected for Wellness mobile app.
[DOCX File , 53 KB - resprot_v14i1e73721_app1.docx]

Multimedia Appendix 2

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Peer-review report by ZRG1 MOSS-T (50) Center for Scientific Review Special Emphasis Panel RFA-RM-21-021: UNITE Transformative Research to Address Health Disparities and Advance Health Equity (U01), National Institute of Mental Health (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 137 KB - resprot_v14i1e73721_app2.pdf]

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Abbreviations

DSMB: data safety monitoring board
GLMM: generalized linear mixed model
HIPAA: Health Insurance Portability and Accountability Act
IRB: institutional review board
WHO-5: World Health Organization–Five Well-Being Index

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Protocol

Improving Access to Specialty Care for Rural Children Using Enhanced Hearing Screening and Specialty Telehealth Follow-Up in Rural Kentucky Schools: Protocol for a Hybrid Effectiveness-Implementation Stepped Wedge, Cluster-Randomized Controlled Trial (Appalachian STAR Trial)

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Abstract

Background: Rural populations are disproportionately affected by preventable childhood hearing loss, which is associated with speech and language delays, impaired social development, and decreased educational attainment. Rural schools are critical access points for preventive health screenings such as hearing screening, but variable screening implementation, loss to follow-up, and scarcity of specialists in rural areas diminish program effectiveness. We seek to implement a school-based telehealth intervention to increase access to specialty hearing care for children in rural Kentucky.

Objective: The Appalachian Specialty Telemedicine Access for Referrals (STAR) trial will assess effectiveness and implementation of the novel, evidence-based STAR model, consisting of 3 core components: (1) enhanced hearing screening; (2) specialty telehealth follow-up; and (3) streamlined communication between schools, health care providers, and parents and caregivers.

Methods: Adaptation of the STAR model for rural Kentucky will occur in the first 2 years, followed by a phased rollout of the intervention using a stepped wedge, cluster-randomized design among kindergartners enrolled in approximately 63 schools in 14 counties of rural Kentucky. School districts were identified based on scientific and community input, as well as geographic proximity to state-run clinics, which provide audiology evaluation free of charge. School districts were randomized into 2 sequences using constrained randomization to balance baseline covariates, such as kindergarten enrollment and number screened. This hybrid type 1 effectiveness-implementation trial will evaluate effectiveness of the STAR model compared with usual hearing screening and usual follow-up process using an intention-to-treat approach with generalized estimating equations. Barriers and

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facilitators to implementation of the intervention will be identified using a mixed methods approach. The primary effectiveness outcomes are the (1) proportion of kindergarteners screened and (2) proportion of referred kindergarteners who receive specialty follow-up within 60 days of screening. Implementation outcomes include assessment of factors affecting successful integration of the STAR model. Iterative adaptation of the intervention will be performed at prespecified time points to maximize implementation outcomes.

Results: The trial began in September 2022 and is expected to conclude in May 2026. Final data analysis is planned to begin in June 2026, and publication of results is expected in 2027.

Conclusions: The STAR model addresses issues related to identification of hearing loss, loss to follow-up from screening, and access to specialty care in rural Kentucky. Effectiveness outcomes may inform future policy for school hearing screening, including adoption of evidence-based protocols to address preventable childhood hearing loss and integration of school-based specialty telehealth follow-up to improve follow-up. Implementation aims may maximize the STAR model's adaptability and overall fit. Community input and systematic adaptation will ensure consideration of unique needs and priorities of rural Kentucky counties. If successful, the STAR model could be scaled across rural America and applied to other preventable child health conditions.

Trial Registration: ClinicalTrials.gov NCT05513833; https://clinicaltrials.gov/study/NCT05513833

International Registered Report Identifier (IRRID): DERR1-10.2196/77630

(JMIR Res Protoc 2025;14:e77630) doi:10.2196/77630

KEYWORDS

hearing loss; health disparities; specialty care; rural health; telehealth; telemedicine; school; children; hearing screening; randomized controlled trial; cluster-randomized trial; stepped wedge; implementation

Introduction

Background

Individuals living in rural communities experience worse health outcomes beginning early in life, making health interventions targeting young children essential to improve health in rural communities [1-5]. Limited access to health care in rural areas is a major contributor to these differences [6-8]. Ear and hearing health constitutes a prime example of how geography can affect health outcomes. Untreated childhood hearing loss has serious long-term consequences, including speech and language delays, worse academic performance, lower literacy, impaired social skills, and reduced higher education and employment opportunities [9-12]. Children with even mild hearing loss have lower quality of life and worse behavioral outcomes than peers with normal hearing [13,14]. The World Health Organization (WHO) estimates that up to 60% of childhood hearing loss is due to preventable causes, such as untreated otitis media, and this estimate rises to 75% in resource-constrained settings such as rural communities [9,15]. Low socioeconomic status, lack of insurance, and geographic barriers to accessing specialty care are associated with poorer outcomes in rural patients with ear or hearing conditions [16-19]. As such, childhood hearing loss and its predisposing conditions disproportionately affect rural and other underserved populations and constitute a critical intervention point to prevent more intractable long-term health and social disadvantage [16,20-22].

Schools serve as an essential access point for health screening and preventive interventions for rural American children. Over 95% of children attend school during critical years of social and intellectual development, making schools an ideal location for preventive health screenings recommended by the American Academy of Pediatrics [23-25]. School nurses and teachers engage daily with rural children, strengthening their potential as key implementation partners for preventive health programs. In the United States, school-based hearing screening programs are designed to identify cases of acquired or later-onset childhood hearing loss [26]. Although school screening can support early evaluation and treatment of childhood hearing loss and may be cost-effective [27], challenges remain with implementation, such as a lack of standardized screening protocols and frequent loss to follow-up. Further, the necessary diagnosis, treatment, and monitoring provided by audiologists and otolaryngologists are not available in primary care [28,29].

The Appalachian Specialty Telemedicine Access for Referrals (STAR) trial seeks to combine the potential of the school as the primary location for preventive health services with telehealth specialty follow-up to improve access to specialty care in rural areas. Telehealth has increasingly been used within innovative programs designed to enable access to specialty care among rural populations with a dearth of health care resources [30-32]. Our group previously conducted a randomized trial in rural northwest Alaska which was, to our knowledge, the first to integrate telehealth into an intervention to address loss to follow-up from screening and provide better access to specialists in rural areas [33]. This Patient-Centered Outcomes Research Institute (PCORI)–funded trial used the existing telehealth infrastructure in rural clinics within the Tribal health system of rural Alaska for follow-up from school hearing screening (Figure 1). Several key findings from that randomized trial have contributed to the development of the STAR model. First, although infection-related hearing loss is common in rural communities and other countries have begun to incorporate tympanometry into national screening protocols [34], current screening protocols in the United States do not yet include a middle ear assessment that is essential for detecting infection-related hearing loss. Our trial found that the addition of tympanometry significantly increased sensitivity compared with usual school screening [33]. Second, telehealth specialty follow-up more than doubled the likelihood of a child receiving follow-up care, and that care happened over 17 times faster on

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average with telehealth than with usual follow-up. Third, based on qualitative interviews with stakeholders, we found that success of the telehealth intervention varied depending on clinic capacity, personnel and ownership, awareness, and communication between schools and clinics [35], and a key recommendation was to provide telehealth capacity directly within the school setting. As a result, the STAR model incorporates (1) enhanced hearing screening with tympanometry; (2) school-based specialty telehealth follow-up; and (3) streamlined communication between schools, health care providers, and families (Figure 2).

Figure 1. Comparison of follow-up pathways following school hearing screening, with data for the first 2 rows provided from a trial in northwest Alaska [35]. STAR: Specialty Telemedicine Access for Referrals.

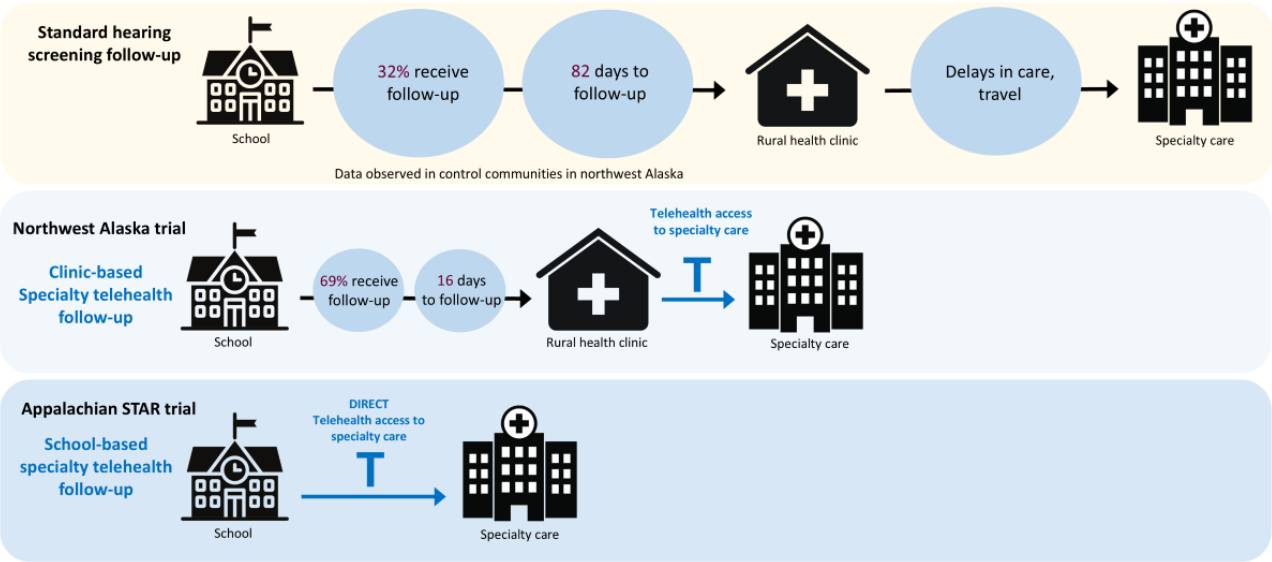

Figure 2. Core components of the Specialty Telemedicine Access for Referrals (STAR) model.

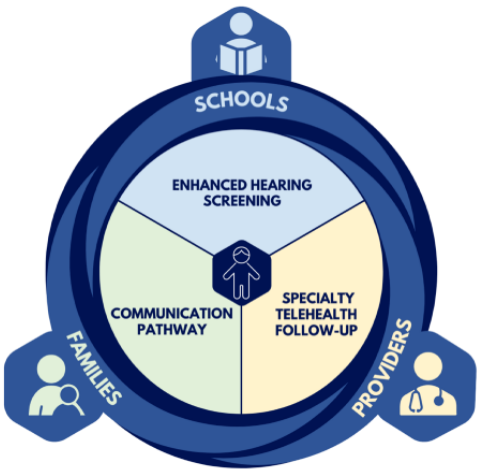

In the Appalachian STAR trial, we seek to address the implementation factors identified in our prior trial and translate the STAR model for application in a broader rural context. Prior work by members of our group has established that residents of rural Appalachian Kentucky communities experience delays in access to ear and hearing specialty care and have overall worse ear and hearing outcomes [16,18,20]. Based on this prior work and community input, we selected the rural Appalachian communities of eastern Kentucky as the setting for translation of the STAR model. We adapted the evidence-based STAR model initially designed in rural indigenous Alaskan communities to meet the unique needs and cultural context of these rural Kentucky populations by using the systematic evidence-based ADAPT-ITT framework [36]. The ADAPT-ITT model was selected to guide this process because it is a method to facilitate adaptation of existing evidence-based interventions for novel situations and environments. We also engage community members and stakeholders in the implementation evaluation, forming the basis for community involvement in sustainable implementation of the STAR model in Appalachia and expansion into other regions of rural America.

Aims

The effectiveness and implementation of the STAR model are being assessed via 3 distinct aims. Aim 1 used community engagement strategies to inform the adaptation of the STAR model to meet the unique needs of communities and schools in rural Kentucky prior to implementation using the ADAPT-ITT framework [36]. Aim 2 evaluates effectiveness of the STAR model via a nested stepped wedge, cluster-randomized trial in

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14 counties (approximately 63 schools) in rural Kentucky, comparing the STAR model with usual hearing screening and follow-up processes. Finally, Aim 3 assesses implementation factors and outcomes in rural Kentucky schools to drive further adaptations during the trial and inform overall scalability of the STAR model.

Hypotheses

We conservatively hypothesize that the probability of being screened for hearing loss will be greater for children in schools that receive enhanced hearing screening via the STAR intervention compared with those with usual hearing screening. We further hypothesize that the probability of specialty follow-up within 60 days of screening for children who are referred will be greater in schools that have implemented both enhanced hearing screening and the specialty telehealth follow-up compared with those that have only implemented enhanced screening [37].

Methods

Study Setting

The Appalachian STAR trial assesses effectiveness among kindergartners (~3600/year) attending 63 elementary schools in 14 participating counties in rural eastern Kentucky. This region was chosen based on feedback from scientific and community stakeholders with a long-standing partnership in this region (Figure 3). Participating counties have long been classified as persistent poverty counties and are among the poorest in the United States, with most children considered underserved, rural, and socioeconomically disadvantaged. Like many rural areas of the United States, the region has limited access to specialty care. Hearing screening is required for all children at entry into elementary schools in Kentucky [38] but is currently variably implemented across school districts [39]. Children who receive referrals from school hearing screening programs can undergo diagnostic audiology evaluation at clinics administered by the Office of Children with Special Healthcare Needs (OCSHCN) free of charge, though the program is currently not well-utilized. After receiving community input, participating counties were selected based on close proximity to 2 eastern Kentucky counties with an OCSHCN clinic. Personnel at these clinics will facilitate the specialty telehealth follow-up component of the STAR intervention (Figure 4).

Figure 3. Schematic of the study phases for the Appalachian Specialty Telemedicine Access for Referrals (STAR) trial. CFIR: Consolidated Framework for Implementation Research; GEE: generalized estimating equation.

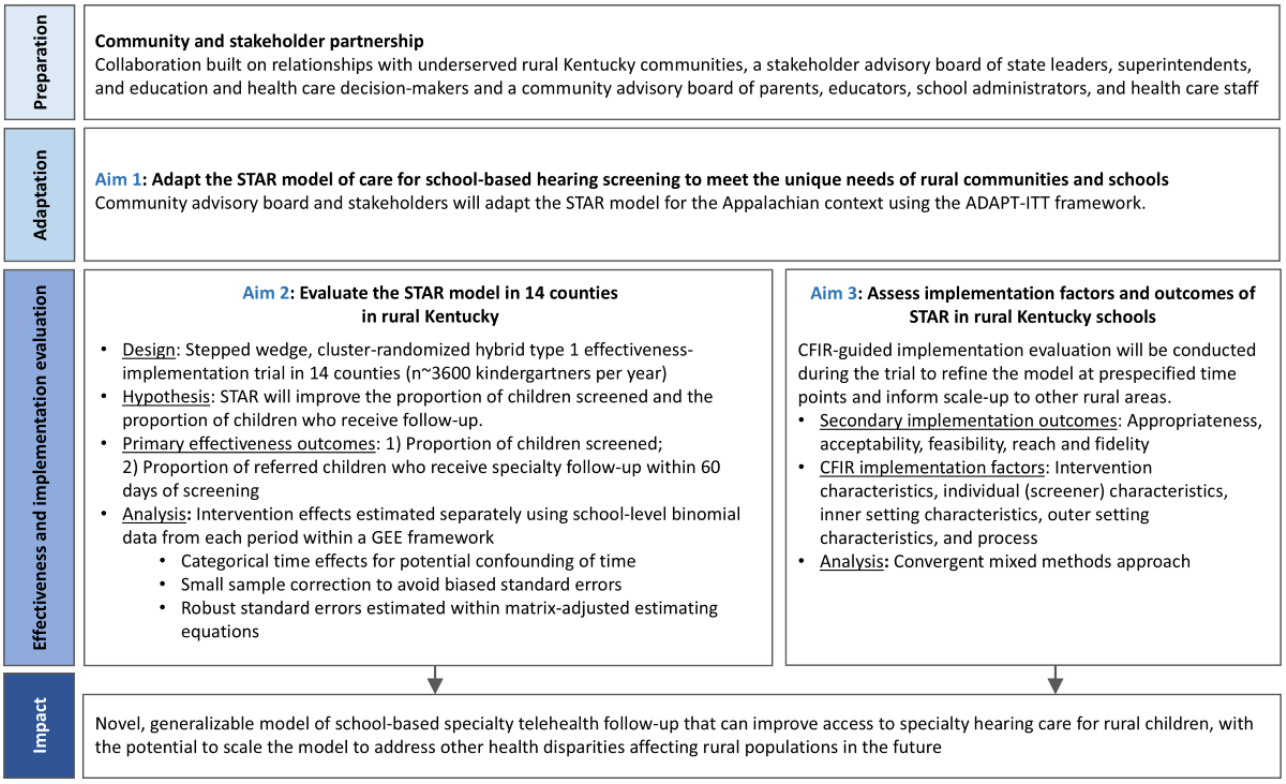

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Figure 4. Map of Kentucky counties participating in the Appalachian Specialty Telemedicine Access for Referrals (STAR) trial (indicated in blue), including counties with state-run specialty clinics (denoted with a star).

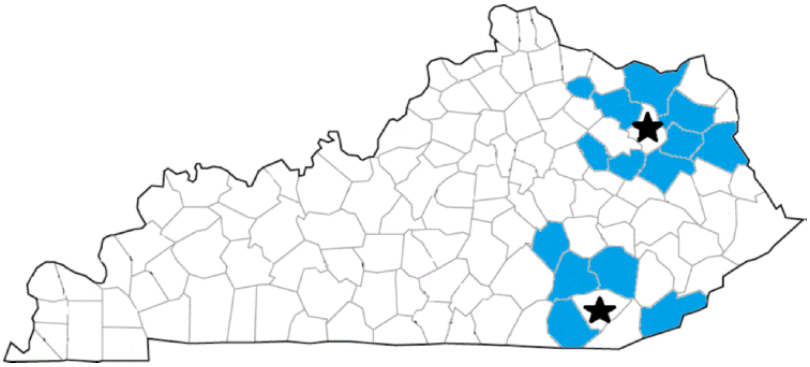

Stakeholder Feedback

This study builds on strong community engagement and stakeholder partnership. The scientific team has been meeting regularly since study inception with a community advisory board (CAB) comprised of parents, educators, school administrators, and health care providers, as well as a stakeholder advisory board (SAB) comprised of superintendents of the participating school districts and key representatives from the Kentucky Department of Education, OCSHCN, Cabinet of Health and Family Services, and Department of Medicaid Services. In Aim 1, we engaged participating communities and incorporated the preferences and perspectives of parents, providers, educators, school administrators, the CAB, and other stakeholders to adapt the STAR model for rural Kentucky using the ADAPT-ITT framework [36]. During and after STAR model deployment in the stepped wedge cluster-randomized trial (Aim 2), stakeholders provide feedback on their experiences with the STAR model. This feedback is being used to develop iterative refinements at predefined time points during the trial and ensures the design of the STAR model is informed by community engagement (Aim 3). Refinements include implementation-related elements of the model, such as how informed consent for telehealth follow-up is obtained and how training materials are designed or delivered. Changes are not being made to the core components of the STAR model. Implementation is being systematically evaluated to assess adoption, acceptability, fidelity, and implementation costs [40,41].

Study Design

The Appalachian STAR trial began with adaptation of the STAR model for the local context informed by feedback from community partners in rural eastern Kentucky counties (Aim 1; Figure 5). A hybrid type I design is being used to test the effectiveness of the STAR intervention on hearing screening and specialty follow-up (Aim 2). The study is also evaluating the implementation of the STAR intervention using both qualitative and quantitative methods (Aim 3). All schools in participating counties continued with hearing screening and referral according to the current practices for that county for the first 2 years to determine baseline screening and follow-up. This is followed by a phased rollout of the STAR model (ie, first enhanced hearing screening then specialty telehealth follow-up), with an implementation evaluation ongoing throughout the trial.

Figure 5. Appalachian Specialty Telemedicine Access for Referrals (STAR) trial timeline.

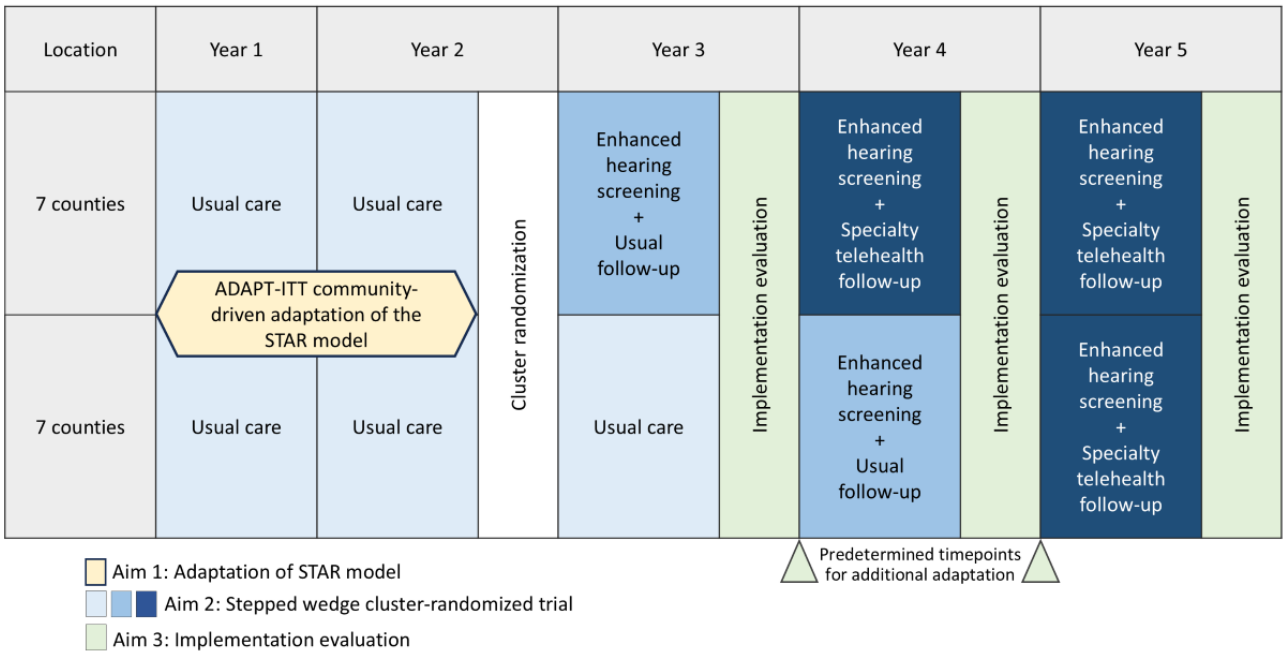

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The Appalachian STAR trial consists of a 2-sequence stepped wedge cluster-randomized trial, with 7 of the 14 county school districts randomly assigned to each sequence. A stepped wedge design with county-level cluster randomization was chosen based on feedback from community partners during initial conception of the study to ensure that all participating counties will eventually receive the STAR model. Furthermore, the stepped wedge design allows for sequential implementation of the screening and follow-up components of the STAR model, facilitating gradual integration of new technology and procedures into existing school and health systems. Consistent with this design, in each sequence, enhanced hearing screening is being rolled out first, followed by the addition of specialty telehealth follow-up. As shown in Figure 6, the key difference between the 2 sequences is that rollout of each of the 2 components is 1 year later in Sequence 2 than in Sequence 1. Consequently, there are 2 nested designs within the overall stepped wedge trial: a complete stepped wedge design to evaluate the screening component and an incomplete stepped wedge design to evaluate the specialty telehealth follow-up component (Figure 6).

Figure 6. Graphic of complete and incomplete stepped wedge trial designs for the screening and follow-up outcomes.

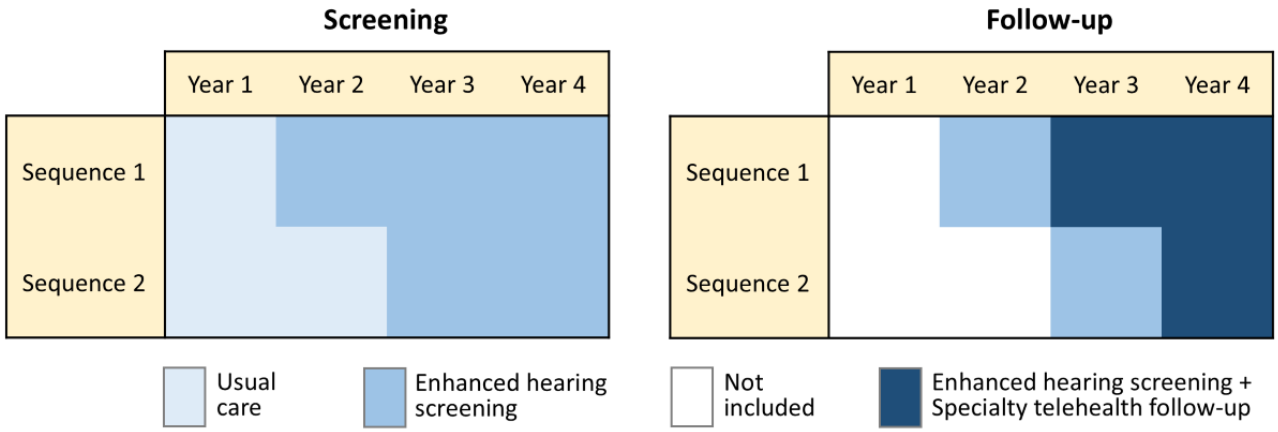

Publicly available screening data from the Kentucky Department of Education suggest that current (usual) screening procedures vary significantly by county, which can result in significant variation by county in referral rates [39]. The nested design will assess follow-up outcomes for each sequence only after enhanced hearing screening is implemented, ensuring that hearing screening practices are consistent and comparable between participating counties. For the screening component's complete stepped wedge design, Year 2 served as the baseline data collection period for the outcome of proportion screened, with all counties providing usual hearing screening according to state regulations. In Year 3 of the study, elementary schools in the 7 counties randomized to Sequence 1 provided enhanced hearing screening to all kindergartners, while schools in the 7 counties randomized to Sequence 2 continued to provide usual hearing screening. In Years 4 and 5, counties in both sequences will provide enhanced hearing screening. For the specialty telehealth follow-up component's incomplete stepped wedge design, Year 3 serves as baseline for counties in Sequence 1, and Year 4 will serve as baseline for counties in Sequence 2, with elementary schools providing enhanced hearing screening and the usual follow-up process during each of these periods. Counties in Sequence 1 will provide specialty telehealth follow-up in Years 4 and 5, while counties in Sequence 2 will provide specialty telehealth follow-up in Year 5. The detailed trial protocol and the statistical analysis plan will be made available upon request and will be included as supplemental documents when publishing trial findings.

Ethical Considerations

Human Subject Ethics Review

The study was approved by the University of Kentucky Institutional Review Board (IRB# 71393), with the University of Arkansas for Medical Sciences and Duke University IRBs serving as relying IRBs.

Adaptation and Implementation of Informed Consent

Informed consent procedures and study enrollment for Aim 1 (adaptation) were conducted by trained research personnel preceding the interview. A member of the study team reviewed the consent form with the participant and answered any questions. A copy of the consent was provided to the participant. The same procedures are being used for Aim 3 (implementation evaluation).

Trial Informed Consent

Per standard practice with school screening programs in public schools, children entering elementary school in participating schools receive the state-mandated hearing screen unless parents opt out. For the specialty telehealth follow-up, parental consent will be obtained in the form of a consent-to-treat document implemented in partnership with the OCSHCN clinic performing the telehealth follow-up. The informed consent was developed and adapted based on the feedback from Aim 1. The consent form for the specialty telehealth follow-up will be added to school enrollment paperwork. Child assent for the hearing screening will be conducted per usual procedures at the school, which involves stopping screening if a child shows unwillingness to participate. Similarly, should a child show unwillingness to participate during the specialty telehealth

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follow-up (eg, pushing the probe away, crying), the intervention will not be completed.

Privacy and Confidentiality

Primary outcome data for this trial will be obtained at the state level. The Kentucky Department Education, Cabinet for Health and Family Services, and Department of Medicaid Services will provide data to an honest broker. The honest broker will link children across data sets and de-identify the data before sharing with the research team for analysis. All data for the trial will be stored on secure servers with access limited to the study team. For Aims 1 and 3, all identifiable data are stored locally on secure servers at the University of Kentucky, and de-identified transcripts are being used for analysis.

Compensation Details

For Aim 1, participants received US $25 for participating in an interview or focus group. For Aim 3, participants receive US $25 for completing an interview or focus group each year of the trial that they participate. Children enrolled in the trial do not receive compensation, as they are participating in state-mandated hearing screening or school-based specialty telehealth follow-up with parental consent.

Preliminary Adaptation

The core components of the STAR model include enhanced hearing screening; specialty telehealth follow-up; and streamlined communication between school staff, health care providers, and parents and caregivers. To tailor the STAR model to the Appalachian context, engagement with key stakeholders, including parents, educators, health care providers, and the CAB, guided adaptation of STAR using the ADAPT-ITT framework [36] during Years 1 and 2. Stakeholders were engaged in semistructured interviews addressing perceptions related to current school hearing screening, the referral process, and health care experiences with follow-up in the community (Multimedia Appendix 1). Stakeholders reviewed the core components of the STAR model and provided preferences regarding content, delivery, and potential challenges with each component. Rapid analysis of the resulting qualitative data directly informed adaptations [40,41]. Various aspects of the STAR model and its adaptations were presented to the CAB in the context of a theater test, with the goal of ensuring that the adapted STAR model is acceptable for the target population [36].

Trial Participant Recruitment

All children enrolled in kindergarten at schools in the participating 14 counties are eligible to participate regardless of age, sex, race, or ethnicity (approximately 3600 children/year for a total of 14,400 children over 4 years). Inclusion in the trial is limited to school-aged children because the interventions being tested are specifically intended to improve hearing screening and access to care in rural schools. For children enrolled in kindergarten in a participating school, there are no additional exclusion criteria, such as age restriction, for study participation. We therefore anticipate enrolling children as young as 4 years and as old as 7 years. Children of families who opt out of screening will not be included in screening, per standard practice in participating schools. Children of families who decline to participate in the specialty telehealth follow-up will receive the usual follow-up.

In 2021-2022 (Year 1), all schools from the 14 participating counties were invited to participate in the trial in close collaboration with the Kentucky Commissioner of Education and the SAB. The commissioner worked with superintendents from the 14 participating counties (approximately 63 total schools), many of whom are also serving on the SAB, to finalize participation in the trial. The CAB guided integration of study information into consent documents that parents sign annually for school-based health programs, including hearing screening. Methods for parental communication were developed during the adaptation and theater testing in Aim 1.

Retention and attrition are not concerns in this trial because the design only requires participation once during annual kindergarten hearing screening. The trial will span Years 2-5 (2022-2026), and because of the natural advancement of children each academic year, new kindergartners participate each year of the trial, thus minimizing concerns for retention. Furthermore, data for the trial will be obtained at the population level from health and education entities and not from individual participants.

Adaptation and Implementation Aims Recruitment

Participants in Aim 1 and Aim 3 include educational staff, parents, and key stakeholders from the 14 participating rural eastern Kentucky counties. Recruitment for Aim 1 occurred through a purposive sampling method, with the dual goal of reaching saturation and achieving diverse representation within each group. Similar recruitment is being used for Aim 3. Informed consent procedures and study enrollment are conducted by trained research staff. Participants fall into 3 major categories: (1) education stakeholders, (2) health care stakeholders, and (3) parents of early elementary-aged children and other key stakeholders.

Education stakeholders, including elementary school teachers, school nurses, administrative staff members, and speech-language pathologists involved in school hearing screening, were recruited using purposive sampling procedures for Aim 1. We aimed to achieve representation of several different types of staff, different counties, and different school sizes. For Aim 3, we are recruiting staff who are directly involved in delivering the STAR model in schools.

Health care stakeholders, including audiologists, otolaryngologists, and OCSHCN staff, were recruited using our professional networks of CAB members for Aim 1. We accessed perspectives from several groups of providers who work directly with children and their families. For Aim 3, we will prioritize health care providers who are directly involved in delivering specialty telehealth follow-up.

Parents of early elementary-aged children and other key stakeholders were recruited using purposive sampling procedures for Aim 1. Potential participants were identified by participating county educators, school board members, our OCSHCN co-investigator, CAB members, or other parent participants. For Aim 3, we are focusing on recruiting parents of children who participate in the STAR model.

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Randomization and Masking

County school districts (n=14) were randomized to 1 of 2 sequences using constrained randomization, which was used to balance important baseline covariates between sequences to increase statistical power and improve internal validity of the trial [42]. This involved calculating a balance score for each allocation and incorporating into the balance metric candidate covariates expected to be correlated with the primary outcomes (chosen a priori by study team consensus), including kindergarten enrollment per county (from 2021-2022 school year), number of kindergarteners screened per county (2021-2022 school year), and nearest OCSHCN clinic (as the stratification variable). Because the number of schools can vary widely by district, any allocations where either sequence included more than 36 schools (32 per sequence would be exactly balanced) were excluded. Of the remaining allocation schemes, the 5% with the best (ie, lowest) balance scores were kept. In the case where balance scores were tied at the 5% cutoff, ties were also included in the set of possible allocations. Independent statisticians performed the final randomization, and study statisticians will remain blinded to allocation until the primary analysis is complete. The allocation cannot be masked for other study team members, school staff, or parents for logistical reasons, but allocation is only revealed when required.

Interventions

Intervention Condition: Enhanced Hearing Screening

Each kindergartener receives enhanced hearing screening once during the normal school screening period. The enhanced screening involves otoacoustic emissions (OAE) and tympanometry. This screening regimen was selected based on systematic reviews, practice guidelines for school screening, and results from our previous northwest Alaska trial [43-45]. Among various hearing screening protocols tested in our Alaska trial, regimens that included tympanometry were the most accurate. In particular, screening protocols incorporating tympanometry are the most sensitive in the detection of infection-related hearing loss, which is often observed in rural environments [44]. For children ages 3 years to 6 years, OAE and tympanometry performed better than pure-tone screening and tympanometry due to the challenges of getting young children to follow directions with participation-based audiometry tests [44]. Given that kindergarteners are the focus of the Appalachian STAR trial, we therefore selected OAE over pure-tone screening for this screening protocol.

OAE screening is conducted at 2, 3, 4, and 5 kHz frequencies, with 3 of 4 frequency pass criteria [46]. Criteria for referral include failure at 2 or more frequencies, with the test producing a pass or refer result. For tympanometry screening, criteria for referral include generation of a type B (flat) tympanogram or negative pressure less than –200 decapascal (daPa) per standard clinical guidance [47]. Results for tympanometry screening are displayed as a pass or refer result. A child is considered a referral if they do not pass OAE or tympanometry screening for one or both ears.

A hearing screening kit custom-designed for laypersons, such as teachers and school nurses who do not have specialized training in hearing, is provided to each school to implement the enhanced hearing screening, with districts retaining the equipment after conclusion of the trial. The STAR model screening kit includes all the tools necessary to complete the enhanced hearing screening, including tympanometry and OAE. Districts determine the appropriate staff members to conduct the enhanced hearing screening. This staff includes school nurses, speech-language pathologists, and/or teachers. Identified staff at each district receive training on the use of the hearing screening kit as part of the adapted STAR model procedures. Technology support and training are offered throughout the school year to support screening efforts. Because the screening equipment provides a pass or refer result, no clinical judgement is required for interpretation.

Control Condition: Usual Hearing Screening

Schools in the control condition continue usual hearing screening, with protocols varying by school. During Aim 1, we determined the screening protocols, devices, and practices used across participating schools.

Intervention Condition: Specialty Telehealth Follow-Up

Details of the specialty telehealth follow-up intervention were determined based on stakeholder feedback in Aim 1 and input from the CAB. Follow-up will be conducted only for children who refer (eg, fail) either OAE or tympanometry screening. Specialty telehealth follow-up will be conducted by school staff according to each school district's preferred assignment of responsibilities; these individuals may include teachers, speech-language pathologists, or school nurses. Although details of the specialty telehealth follow-up will be determined during the adaptation phase of the STAR model, elements will include a lay-friendly platform that connects to tools, such as an otoscope for taking images of the ears; tympanometry; additional hearing testing; and possibly vital signs such as blood pressure and temperature. If a child receives a referral from hearing screening, school staff will complete the established procedure for the specialty telehealth follow-up with an audiologist. This will consist of asynchronous transfer of screening information (such as images of the ears) from school staff to an audiologist affiliated with a state-run OCSHCN clinic. The audiologist will provide a clinical assessment and recommendations for management to the school, family, and primary care provider. Results of the audiologist consult will be provided back to the school using the STAR model technology platform. Families will also receive results through email or SMS text messaging, from which a report can be viewed, printed, and shared if desired.

Control Condition: Usual Follow-Up

The control condition for specialty telehealth follow-up will be the usual process followed in Kentucky schools, which typically consists of a letter notifying parents that their child received a referral from screening and will need follow-up. Year 3 is the comparator for Sequence 1 counties, and Year 4 will be the comparator for Sequence 2 counties. As is currently standard across Kentucky and nationally, parents will be responsible for

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arranging follow-up for their child. State-run OCSHCN clinics see children who receive referrals from school screening for follow-up free of charge as standard practice, and this resource will continue to be available to families within the usual care sequence.

Implementation Approach

Overview

Certain components of the implementation process were developed as part of Aim 1. Based on stakeholder feedback through qualitative interviews and CAB and SAB meetings, we adapted additional features of the STAR model to facilitate integration of enhanced hearing screening and specialty telehealth follow-up within the rural Appalachian school system. Major components of the implementation strategy designed a priori to Aim 1 stakeholder feedback are described in the following sections.

Screening Equipment

The overall intent of the STAR model is to deliver an all-in-one solution for school hearing screening. All equipment, accessories, consumable supplies, and supplementary materials are delivered in a single case. As core components of the intervention, an OAE device and a handheld tympanometer are included in the equipment. For the purpose of conducting the specialty telehealth follow-up intervention, screening kits will additionally include an otoscope. Otoscopes will be used by school screeners for children who are referred for screening to obtain images of the ears. These images will be asynchronously reviewed remotely by an OCSHCN audiologist in conjunction with screening results. We collected stakeholder feedback during Aim 1 to select the best existing software and hardware solutions and customized a novel platform to meet the needs of local partners.

Training and Technical Assistance

STAR enhanced hearing screening is intended to be delivered by existing school staff who may or may not have previously been engaged in other forms of hearing screening. These screeners may include school nurses, speech-language pathologists, and teachers who have varying degrees of clinical knowledge and skills. As such, the training is designed to be lay-friendly and tailorable to the needs of each county's screener population.

Training sessions occur at each district, last 1 hour to 2 hours, and are delivered either in person or virtually. Content for education staff includes the use of the technology and performance of the screening tools. Content for clinical partners will cover the technology platform for specialty telehealth follow-up, which will include asynchronous review of hearing screening results and otoscopy images. Training is designed to be tailorable to the preferences of each county, with a variety of usable models (eg, direct training of all screeners, train-the-trainer approach). Per community preferences, the team developed materials that can be referenced and reviewed outside of training sessions at screeners' convenience. Screeners receive a certificate attesting to their completion of training for the STAR enhanced hearing screening protocol. The study staff maintain a log of training attendees and verification of screeners as part of the fidelity measures.

The study team supports a dedicated phone line and email address for communication with school and clinical partners. This line is staffed during regular business hours. The study team aids with coordination of study logistics and troubleshooting of equipment and software. However, given the implementation aims of this study to be a community-administered intervention, the study team refrains from directly administering hearing screening or providing clinical review of data.

Implementation Adaptation

As defined within Aim 3 and guided by ADAPT-ITT, data-driven process adaptation occurs at predetermined time points after each school year (Figure 5). At these time points, the study team analyzes feedback from qualitative data and from CAB discussions to identify potential modifications to the STAR model. Core components of the STAR model remain unchanged to ensure adequate measurement of the effectiveness of the intervention. Enhanced hearing screening for kindergarteners will always involve OAE screening and tympanometry, and there will always be a pathway for specialty telehealth follow-up. However, certain elements of the intervention and its implementation approach are subject to change, based on qualitative feedback. Potential adaptations may include changes to training activities, the consent process, time and location of screening, screening personnel, screening hardware, school and clinical software interfaces, and communication pathways. Adaptations to STAR intervention technologies will be deployed uniformly across sequences and schools to ensure consistency in the enhanced hearing screening process. However, adaptations to screening personnel, training activities, and time and location of screening are tailorable according to individual county preference and may vary within or between sequences. This is to ensure that the STAR intervention fits within the existing infrastructure of each rural county and is deployed in line with community preferences.

Both formal qualitative data from interviews and informal discussions from CAB meetings are being used to gather feedback on proposed changes during implementation adaptation. We will query whether modifications improved the desired implementation outcomes and successfully addressed issues raised in the prior year to determine whether these modifications are maintained, modified further, or discarded between years. Through this process of iterative feedback and revision, periodic implementation adaptation is anticipated to not only improve the STAR implementation process with each iteration but also expand the range of tailorable variations to fit community needs. This will reinforce the overall flexibility and scalability of the STAR model within the implementation aim of this trial.

Primary Outcomes

The trial has 2 primary outcomes: (1) proportion of kindergarteners screened for hearing loss and (2) proportion of referred kindergarteners (ie, those who did not pass screening)

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who receive specialty follow-up within 60 days of screening date

Prior to the rollout of enhanced screening, we collected baseline data during Year 2 (2022-2023) from education and health care agencies on the primary outcomes, including proportion of children screened for hearing and the proportion of referred children who received specialty follow-up. Proportion of children screened will be measured through school-based reporting mechanisms already used to monitor school-based health programs across the state. Schools will keep a record of children referred from screening per current practice in each school.

An electronic health record query of ear and hearing visits at state-run OCSHCN clinics, which are the primary source of specialty ear and hearing care for counties participating in the trial, will be used to indicate successful initiation of specialty services. We will also obtain Medicaid claims data on ear and hearing encounters for those who may seek services outside of OCSHCN clinics. Based on our previous trial, collecting electronic health record data for 60 days from screening date is sufficient to determine differences in rates of follow-up [37,48].

Implementation Outcomes

To successfully implement the STAR model and prepare for scale-up beyond the participating counties, it is essential to understand the dynamic factors within schools, communities, and health care settings that influence implementation outcomes of the STAR model. Understanding these factors is essential to sustain STAR within rural Kentucky schools, as well as to develop implementation strategies to sustain and scale the STAR model beyond rural Kentucky.

For this trial, we are using the taxonomy of implementation outcomes by Proctor et al [49] to assess acceptability, appropriateness, feasibility, reach, and fidelity of the STAR model at the school level, as defined in Table 1. A multilevel, mixed methods assessment is being used to assess implementation factors and outcomes. Quantitative data sources include trial process records, surveys, and existing county- or school-level artifacts (eg, communication documentation with parents). Qualitative data sources include interviews or focus groups with a subset of the stakeholders, including educational staff, health care providers, and parents. The number of participants planned for interviews is based on predetermined targets regarding numbers needed to attain saturation and representation of key perspectives. Interviews occur annually beginning in 2023-2024 to understand implementation factors influencing each component of the STAR model as it is rolled out in phases in participating counties. Stakeholders are engaged in quantitative and qualitative data collection at multiple time points that are applicable within trial operations. Data collection will occur after enhanced hearing screening is completed in schools for educational staff and after specialty telehealth follow-up has concluded for health care staff and parents.

Table 1. Implementation outcome measures for Aim 3 of the Appalachian Specialty Telemedicine Access for Referrals (STAR) trial.

Implementation outcome	Definition	Data source	Data collection timing[a]
Appropriateness, acceptability, feasibility	STAR model is appropriate, acceptable, and feasible for participating schools	Brief questionnaires (ORIC[b], IAM[c], AIM[d], FIM[e]) [45,46] for all implementation actors at schools	For questionnaires on enhanced screening: Year 3 for Sequence 1 and Year 4 for Sequence 2; for questionnaires on specialty telehealth follow-up: Year 4 for Sequence 1 and Year 5 for Sequence 2
Reach	Representativeness of children reached by the STAR model based on demographic factors such as race/ethnicity and county	STAR process records, school data	Annually during Years 3-5
Fidelity	Extent to which core components of the STAR model are implemented as intended, contextualized using the CFIR[f] framework of factors influencing fidelity [41].	Interviews with education and health care stakeholders, parents	Annually during Years 3-5
Fidelity	Degree of adherence to core components; adherence thresholds will be determined as core components are finalized through theatre testing	Fidelity checklist filled out by school or study staff	Annually during Years 3-5

[a]Year 3 is the 2023-2024 academic year; Year 4 is the 2024-2025 academic year; Year 5 is the 2025-2026 academic year.

[b]ORIC: Organizational Readiness for Implementing Change.

[c]IAM: Intervention Appropriateness Measure.

[d]AIM: Acceptability of Intervention Measure.

[e]FIM: Feasibility of Intervention Measure.

[f]CFIR: Consolidated Framework for Implementation Research.

Appropriateness, Acceptability, and Feasibility

To assess appropriateness, acceptability, and feasibility, key informants complete modified versions of the following brief, validated questionnaires: Intervention Appropriateness Measure, Acceptability of Intervention Measure, Feasibility of Intervention Measure, and Organizational Readiness for Implementing Change [50,51]. Surveys are completed annually to assess outcomes across various STAR components as they are rolled out. We will bolster our understanding of

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appropriateness, acceptability, and feasibility through qualitative feedback from key informants. Probes have been developed to yield perspectives on the fit of the STAR model within school contexts, competing priorities, and ease of use.

Reach

We are evaluating the representativeness of children reached by the STAR model based on demographic factors such as race/ethnicity and county. This will provide valuable context for the primary outcomes, which measures overall proportions of children reached by the screening and specialty telehealth follow-up components of the STAR model.

Fidelity

We are evaluating fidelity by assessing adherence to the intervention, as well as the context for how the intervention is implemented [49]. We are using several sources of pragmatic real-world data. To reduce implementer burden, fidelity is primarily assessed by the research team using a structured fidelity checklist of the intervention's core components. In addition to the use of checklists, fidelity to the specialty telehealth follow-up component will also be measured by assessing time to specialty follow-up through comparison of the date of specialty ear and hearing encounter to the date of screening. This measure will provide additional context to the second primary outcome by measuring the average time to follow-up as a numeric variable rather than as a categorical variable (ie, follow-up within 60 days or not).

Last, fidelity is assessed using qualitative data collection during semistructured interviews. For educational staff, probes have been developed to ask about how various facets of the STAR intervention were used (ie, which grade levels were screened, what screening tests were used, referral criteria, and parental communication method). Similarly, for health care staff, probes may ask about whether follow-up care was completed using the telehealth interface developed for the STAR intervention. On an annual basis, quantitative and qualitative data will be compared to develop reports on fidelity at the individual school level and to support adaptations.

Implementation Factors

This effectiveness-implementation trial includes adaptation phases both before and between the key years of the STAR intervention deployment (ie, Years 3-5). The adaptation process uses targeted modifications to the STAR implementation approach derived from qualitative feedback from key stakeholders. First, we will seek to develop an explanatory model for the aforementioned implementation outcomes by analyzing various implementation factors. The primary data source for this component of the implementation evaluation will include the semistructured interviews and focus groups conducted with key informants during each school year. Using the Consolidated Framework for Implementation Research (CFIR) [41], we will operationalize multiple factors that influence implementation outcomes in the school setting in 4 domains: components of the STAR model (Intervention), how it is implemented (Process), the school environment for implementation and integration with the health care setting (Inner Setting), and the external policies and people facilitating implementation (Outer Setting; Table 1). These implementation factors will be analyzed with respect to each component of the STAR model to inform adaptations and scalability [40].

Statistical Analysis

Sample Size

To calculate power for a cross-sectional stepped wedge design with a binary outcome, we used the approach from Hemming et al [52,53] based on a comparison of 2 proportions, incorporating design effects to account for clustering by county school district, repeated measures on the same cluster, and *t*-based inference to accommodate the small number of clusters (ie, 14 counties). The design is cross-sectional rather than cohort because data are collected from different children each year of the study. Assumptions for power calculations for the primary outcomes are summarized in Table 2.

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Table 2. Power calculation assumptions for primary outcomes of the Appalachian Specialty Telemedicine Access for Referrals (STAR) trial.

Parameter	Enhanced hearing screening	Telehealth specialty follow-up
Outcomes and intervention effect		
Outcome	Screening	Specialty care within 60 days of referral
Kindergarteners included in analysis	All	Those screened and referred
Proportion in control periods, %	36[a]	20
Proportion in intervention periods, %	56	60
Intervention effect, percentage point	+20	+40
Sample size assumptions		
Total kindergarteners per year, n	3635[b]	101[c]
Clusters (counties) per sequence, n	7	6[d]
Median cluster size (m)	201	6
Cluster size CV[e]	0.73	0.91
Correlation structure assumptions[f]		
Within-period ICC[e]	0.10	0.10
Correlation structure over time	2-period decay	2-period decay
Cluster autocorrelation (CAC)	0.8	0.8
Calculated power[f], %	>90	90

[a]Based on population weighted average of 2018-2019 reported county level screening rates.

[b]Based on 2019-2020 county level kindergarten enrollment in 14 counties.

[c]Based on assumption that each of the 2018-2019 reported county level screening rates improved 20 percentage points and the referral rate was approximately 5% in all counties.

[d]Based on previous data, 1 county expected to have 0 referrals. The power calculation was thus conservatively based on one county being excluded from each of the 2 trial sequences.

[e]CV: coefficient of variation.

[f]Conservative assumptions estimated based on the method by Hayes and Moulten [54] to estimate the within-period intracluster correlation coefficient (ICC) using published data at the county level.

[e]ICC: intracluster correlation coefficient.

[f]Based on comparison of 2 proportions within a stepped-wedge design [55,56].

Screening Outcome

Power for the screening outcome was calculated based on kindergarten enrollment from the 2019-2020 school year (n=3635) and screening rates reported from the 2018-2019 school year due to lags in screening data availability and concern for the potential impact of COVID-19 on school-based preventive health screenings. Data from all 14 participating county school districts were used, with an expected median annual county kindergarten enrollment (ie, cluster-period size) of 200, a baseline screening rate of 36%, and a coefficient of variation (CV) of cluster size of 0.73.

We estimated a within-period intracluster correlation coefficient (ICC) using a formula based on the CV of the outcome. The CV was estimated using a published strategy [54]: County-specific proportions of the screening outcome were assumed to be normally distributed, centered on the control arm proportion with a between-cluster standard deviation derived from an assumed range for 95% of the county-specific proportions (ie, for a width of ~$4\sigma_B$). Given the wide range of 2018-2019 county-specific screening rates reported, we estimated a likely half-width of 30% for the interval around the baseline screening rate of 36% (π). Using the published strategy based on the following formula, $ICC=(\sigma_B^2)/[\pi(1-\pi)]$ yielded a corresponding ICC of ~0.10. We conservatively assumed a cluster autocorrelation of 0.8 and a 2-period decay structure between measurements within the same cluster over subsequent time periods. We assumed a 2-period decay structure in the design phase rather than an alternate less realistic structure such as exchangeability to protect against an underpowered trial [55,56].

Given a 2-sided α of .05, with the aforementioned cluster-period size and clustering assumptions and assuming a complete stepped wedge design with 2 sequences of 7 clusters (counties) each (Figure 6), the study will have greater than 90% power to detect an increase in screening of 20 percentage points (36% vs 56%) using a 2-sided test of difference in proportions [52,56,57].

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Follow-Up Outcome

To calculate power for the follow-up outcome, it was necessary to estimate the number of students who will be referred for follow-up each year in each county. To do this, we multiplied the assumed county-level screening proportion under enhanced hearing screening (56%) by the expected county-level kindergarten enrollment and by the expected referral rate of 5% (a conservative assumption given the lack of current referral data in Kentucky). It is possible that, even after the introduction of enhanced screening, one of the smaller counties may have zero referrals. With this assumption, we expect a median cluster-period size of 6 referred children (ie, per county per year), a CV of cluster size of 0.91, and 6 counties per sequence (Figure 7).

Figure 7. Estimating cluster size for specialty telehealth follow-up outcome based on prior school data.

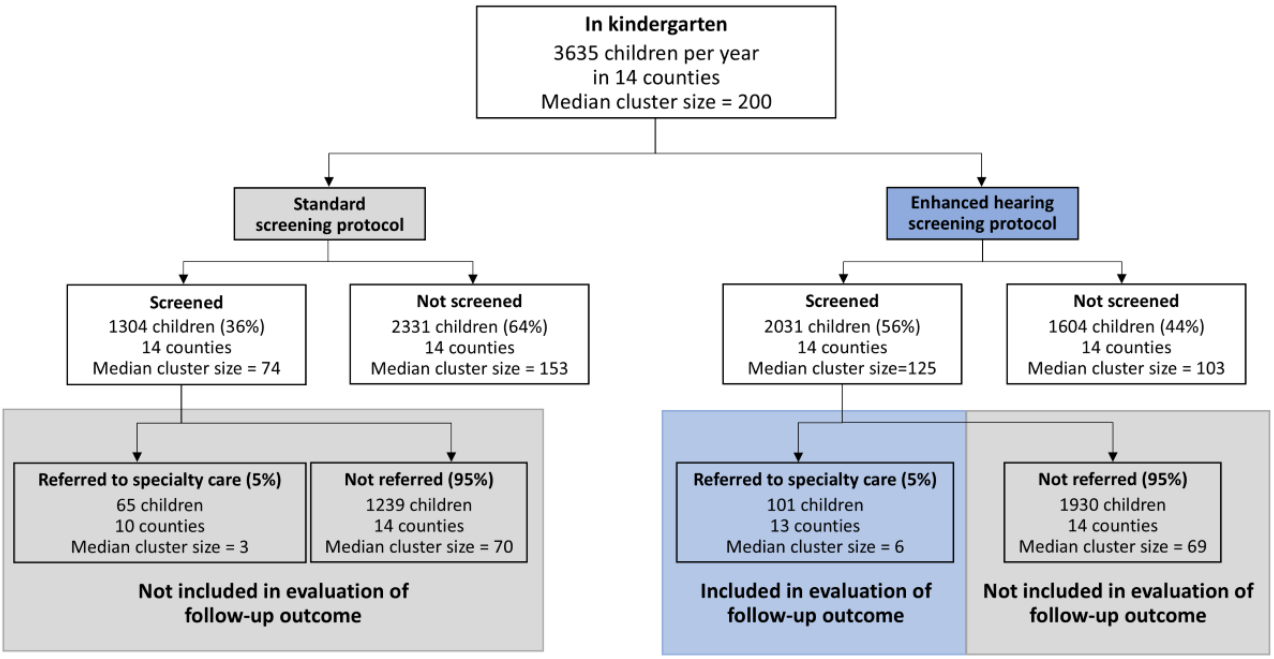

To be conservative, we assumed the follow-up outcome proportion to be 20% for children in the control condition (ie, enhanced hearing screening only). With similar assumptions about ICC (0.10) and cluster autocorrelation (0.80) as for the screening outcome, a 2-sided α of .05 and assuming an incomplete stepped wedge design with 2 sequences of 6 clusters each (Figure 6), the study will have 90% power to detect an increase of at least 40 percentage points in the proportion of referrals resulting in specialty care (ie, 20% vs 60%).

Analysis of the Primary Effectiveness Outcomes

For analysis of the first primary outcome (proportion of children screened for hearing loss), the intention-to-treat population will be all students enrolled in kindergarten at the elementary schools across 14 counties of eastern Kentucky participating in the study, at the time of their school's screening for hearing loss, over Years 2-5. For analysis of the second primary outcome (proportion of referrals resulting in specialty follow-up within 60 days of the date of screening), the intention-to-treat population will be all kindergarten students referred for follow-up during their school's enhanced hearing screening period (Years 3-5 for the first sequence, Years 4-5 for the second sequence), regardless of whether their parent or guardian opts in to the specialty telehealth follow-up intervention.

Child-level outcomes will be analyzed using generalized estimating equations (GEEs) in order to accommodate correlation within counties and schools that is expected to arise due to the repeated cross-sectional data obtained over time. Moreover, the GEE approach will provide population-averaged intervention effects that are relevant to public health implementation [58,59]. More specifically, binary outcomes at the child level will be analyzed assuming a binomial outcome distribution and will include the following terms: an indicator for whether the county (ie, cluster) is observed under the usual care or intervention condition during the cluster-period; time effects to account for the potential confounding effect of time and fixed effects for the variables used in the constrained randomization procedure (kindergarten enrollment, baseline screening rate, and which OCSHCN clinic serves the county); and prespecified adjustment for sociodemographic characteristics (eg, gender, race, ethnicity, and free-reduced lunch eligible) of children to account for potential confounding.

Results will be reported on the relative scale as risk ratios, and absolute effects will be reported as risk differences, both with 95% confidence intervals [60]. To do this, the identity- and log link will be used to estimate absolute and relative effects, respectively. In the event of issues with convergence of either the log-binomial or identity-binomial GEE models, we will use the modified Poisson approach [61] with log or identity link, as needed. If further convergence issues arise with the log link, we will instead use the standard logit-binomial GEE and report odds ratios as the estimate of a relative effect, and if further convergence issues arise with the identity link, the Gaussian distribution will be used with identity link to estimate absolute effects [62]. Standard errors will be estimated using the robust sandwich variance estimator using appropriate small-sample

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corrections to obtain valid standard errors [63]. The GEE approach assumes that data are missing completely at random, thus this assumption will be checked.

Within-period ICCs will be calculated and reported based on baseline outcome levels across all counties. Given that the overall intervention (enhanced school hearing screening plus specialty telehealth follow-up) will be considered effective if both tests are significant, a 5% significance level will be used for each of the 2 primary outcomes with no alpha penalty [64].

Missing Data

Missing data for the screening outcome will likely be in the form of loss of reporting from some schools or from closing or merging of schools. Detection of missing data at the child level will not be possible, as children enrolled but not present will count as not being screened. Missing data for the specialty follow-up outcome may occur if referred children move out of the region or receive follow-up care from providers outside our data observation scope. Child-level enrollment date ranges will help us determine if the former has happened, but we cannot track the latter. Therefore, our analysis will assume that, if a specialty follow-up visit is not recorded in our data (and the child remains enrolled in a regional school), the visit did not take place. Depending on the pattern of missingness at the school level, we may use an inverse probability weighting or multiple imputation approach. We will use complete case analysis only if data loss is thought to be missing completely at random.

Qualitative Analysis

Interviews and focus groups are recorded, transcribed, and analyzed manually or using Atlas.ti qualitative software depending on the volume of data collected at each analysis phase. Administrative data, including CAB meeting notes and communication logs between sites and study staff, are also included in content analyses. Coders use an iterative process to develop a framework, categories, and coding plan for each phase of analysis. Interview and focus group transcripts are coded with respect to established CFIR domains [40,41]. To ensure intercoder reliability, discrepancies are resolved through discussion among the qualitative analysis team. The study co-investigators review the content generated from analysis.

A multiphase mixed methods design is being used to evaluate program implementation and targeted adaptation. Quantitative and qualitative data will be combined to inform predetermined implementation outcomes of appropriateness, acceptability, feasibility, reach, and fidelity. Rapid content analysis of qualitative data will be integrated with descriptive analysis of quantitative data consistent with a mixed methods design.

Monitoring and Risk Assessment

The STAR model poses minimal risk for participating children and introduces no more than ordinary risk encountered during a routine ear and hearing exam. Since this is a minimal risk study, a Data Safety Monitoring Board is not required; however, a Data Safety Monitoring Plan is in place.

Data Management and Security

Data and consents from the qualitative aspects of the study are stored in a secure Research Electronic Data Capture (REDCap) database locally at the University of Kentucky. Study personnel obtain consent and manage the coding system linking participant names to identification numbers, which is maintained in an encrypted, password-protected database separate from the data. Trial data are obtained at the population level, with a limited data set that links school hearing screening results and ear and hearing encounters. All identifying data for the trial are removed, and unique identifiers are assigned prior to receipt by the study team. There are no key linking identifiers to trial data. The database design incorporates all necessary logic and range checks and prompts. The data manager is responsible for ensuring the accuracy, completeness, legibility, and timeliness of the data reported. The University of Arkansas for Medical Sciences serves as the data coordinating center, housing the secure research database and overseeing the data architecture, sharing, and management.

The multiple principal investigators (MPIs) verify that all study data generated, documented, and reported are compliant with the protocol and the applicable regulatory requirements for good clinical practices. Despite population-level data collection for the trial, interval quality assurance audits are conducted and overseen by the MPIs. Reports are developed at regular intervals to monitor data accuracy. Monitoring is conducted using web-based data validation rules and data manager review.

The MPIs are responsible for ensuring participant safety for the study. Although no adverse events are anticipated during data collection for the adaptation and sustainability evaluation of the STAR model, should an individual experience any sensitivities during an interview, the interviewers are trained for an appropriate response, including concluding the interview early. An iterative process has been put into place to adapt interview questions and study personnel training as needed to address this possible risk. In the case of an adverse event or unanticipated problem, such as breach of confidentiality, the MPIs will be notified within 24 hours. If required, the MPIs will report the adverse event or unanticipated problem to the appropriate IRB within 7 days and will determine necessary action, from changes to the protocol to cessation of activity, in compliance with IRB oversight.

Dissemination Plan

This study complies with the National Institutes of Health (NIH) Data Sharing Policy, Policy on the Dissemination of NIH-Funded Clinical Trial Information, and the Clinical Trials Registration and Results Information Submission rules. The trial was registered at ClinicalTrials.gov, and results from the trial will be submitted to ClinicalTrials.gov. Adhering to the community-based nature of the proposal, results will be shared with Kentucky communities. Dissemination efforts will be made at the end of the trial to communicate study findings to members within each of the participating communities. We will also make our results available to the broader scientific community through presentations at regional and national scientific meetings, as well as through publications. The input and collaboration of others studying similar scientific questions in this discipline will be welcomed. All finalized data sets, protocols, and study materials will be made publicly available upon request with

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necessary approvals and execution of a formal data use agreement.

Results

The stepped wedge trial began in September 2022 with baseline data collection. Adaptations of the STAR model were completed by summer 2023 based on data collected as part of Aim 1. Randomization was conducted in 2023, and the phased rollout of the STAR model began in the 2023-2024 academic year. The trial is expected to conclude in May 2026. Final data analysis is planned to begin in June 2026, and publication of results is expected in 2027.

Discussion

Appalachian STAR Trial

The Appalachian STAR trial represents a unique opportunity to demonstrate that school-based telehealth can improve access to specialty hearing care for rural children. Pediatric ear and hearing care constitutes a critical area for intervention, as the WHO estimates that up to 75% of childhood hearing loss is preventable in underserved communities, and the repercussions of untreated childhood hearing loss continue into adulthood [14,15,65-67]. Kentucky and greater Appalachia exemplify how rurality often predisposes to worse ear and hearing outcomes due to limited access to specialty care [16-18,20].

This trial places communities at the center, using formative work and implementation evaluations to adapt and implement a community-informed intervention designed to be sustainable and scalable. Community partnership in this trial spans active CAB involvement to engagement with school staff and leadership, health care providers, and parent partners. Strong partnerships at the state level and support for this study from Kentucky state leadership and stakeholders have set the stage for sustainability and scalability of the STAR model. The study also leverages existing infrastructure and programs in state-run clinics, facilitating follow-up and removing barriers to care through creation of a model that can be replicated for other preventive screenings within the state.

The Appalachian STAR trial is designed to fill gaps in the evidence to influence school screening policy and evaluate a novel intervention with significant potential to broadly change access to specialty care for rural children. There is currently no national standard for school hearing screening, with different states and even different counties within a single state variably implementing screenings with a range of protocols. This trial evaluates the effectiveness and implementation of an evidence-based enhanced hearing screening protocol that incorporates tympanometry, a middle ear assessment we have previously shown significantly improves the accuracy of screening in rural Alaskan communities where infection-related hearing loss is common [44]. The Appalachian STAR trial will be the first to evaluate the effectiveness of this screening protocol when conducted by school-based screeners in an environment that is prototypical of other rural contexts in the United States. As a result, evidence from this trial may inform policy change and implementation of a standardized, evidence-based school screening protocol statewide in Kentucky and across other rural states, placing Kentucky at the forefront of transforming preventive school hearing screenings throughout the United States. Our second primary outcome will establish the effectiveness of specialty telehealth follow-up in the school setting, while our supplemental implementation aims will inform the overall adaptability and scalability of the STAR model. It is critical to understand the various implementation factors that facilitate successful integration of this model of care delivery into rural schools and clinical contexts. Once proven successful with hearing, the STAR model could be applied to address multiple serious health disparities that begin in childhood and affect underserved rural populations for a lifetime, such as vision loss, behavioral health, development, and obesity [68].

Limitations

A pragmatic stepped wedge trial design such as ours often imposes challenges to maintain internal validity while ensuring broad applicability of the intervention in a real-world setting. To enhance internal validity, we balanced important covariates between the sequences that are expected to be correlated with the primary outcome. Cluster-randomized trials have inherently lower power than parallel design trials; however, this design is important for testing an intervention that is intended to be implemented at the school level. Based on the anticipated sample size, we expect to have sufficient statistical power to detect effects of the primary outcomes. One limitation inherent in the study design is that it is not possible to mask participating schools and parents to allocation. A high degree of collaboration with community stakeholders is needed for integration of the STAR model in rural schools, and parents receive information about the program at the start of the academic year. However, the statistical team is masked to allocation until primary analysis is complete, and allocation is only revealed to members of the study team who need the information for managing the logistics of implementation. Another potential challenge is ensuring intervention fidelity across counties. Implementation of the STAR intervention involves screeners gaining familiarity with new technology and screening protocols, which could lead to inconsistent adoption. We have put several safeguards in place to avoid this, such as the development of training materials and incorporation of fidelity checklists. Additionally, there are 2 prespecified time points during the trial when community feedback from the Aim 3 implementation evaluations can be used to adapt the solution to address various implementation factors that may affect fidelity, improving overall success of integration and providing key insights on various modifiable components of the protocol to maximize uptake (Figure 5). These obstacles are not exclusive to this study and are common to other effectiveness-implementation trials.

Conclusion

The Appalachian STAR trial is evaluating a new model of care that has great potential to improve access to specialty care for rural children. The evidence generated on school hearing screening may influence policy in Kentucky and other rural states, and, if effective, this novel model of specialty telehealth follow-up could be generalized to other preventable health disparities beyond hearing.

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Acknowledgments

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Data Availability

All finalized data sets, protocols, and study materials will be made publicly available upon request with necessary approvals and execution of a formal data use agreement.

Authors' Contributions

SKR, ET, AP, MSG, NS, MB, and SDE contributed to study conception and design. TS, SD, and SDE were major contributors to writing and preparing the manuscript. ET, AP, and DA contributed to the statistical design and analysis plan, including relevant sections of the manuscript. TS, JPB, and HL contributed to study implementation science design and analysis plan, including relevant sections of the manuscript. MB and SDE are the multiple principal investigators (MPIs) of the study, providing oversight on overall study conception and design. All authors read and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Aim 1 Interview Guides.
[PDF File (Adobe PDF File), 844 KB - resprot_v14i1e77630_app1.pdf]

Multimedia Appendix 2
SPIRIT Checklist.
[PDF File (Adobe PDF File), 130 KB - resprot_v14i1e77630_app2.pdf]

Multimedia Appendix 3
Peer review report by ZRG1 MOSS-*t* (50) - Center for Scientific Review Special Emphasis Panel RFA-RM-21-021: UNITE Transformative Research to Address Health Disparities and Advance Health Equity (U01) (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 160 KB - resprot_v14i1e77630_app3.pdf]

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Abbreviations

CAB: community advisory board
CFIR: Consolidated Framework for Implementation Research
CV: coefficient of variation
GEE: generalized estimating equation
ICC: intracluster correlation coefficient
IRB: institutional review board
MPI: multiple principal investigators
NIH: National Institutes of Health
OAE: otoacoustic emissions
OCSHCN: Office for Children with Special Health Care Needs
PCORI: Patient-Centered Outcomes Research Institute
REDCap: Research Electronic Data Capture
SAB: Stakeholder Advisory Board
STAR: Specialty Telemedicine Access for Referrals
WHO: World Health Organization

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Protocol

Health System–Level Implementation of Digital Health Support for People Living With HIV and Substance Use Disorders: Protocol for a Cluster-Randomized, Stepped-Wedge Clinical Trial

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Abstract

Background: People living with HIV who are affected by substance use disorders and other social vulnerabilities are less likely to achieve and sustain viral suppression. Supporting these patients with mobile health systems can provide additional social and behavioral support that may improve HIV outcomes in these populations.

Objective: This study aims to implement and evaluate an evidence-based digital health system (antiretroviral therapy care coordination; ART-C) to improve HIV viral suppression and reduce missed clinic visits within a multisite HIV care program.

Methods: ART-C will be implemented in 8 HIV medical home clinics operated by Vivent Health in Colorado, Missouri, Texas, and Wisconsin. All patients receiving HIV care across the system will be invited to use a customized version of the Connections smartphone app to join a virtual community of peers living with HIV. A subset of patients with substance use disorder will be recruited to use enhanced features of the app, allowing sharing of information about substance use and other social determinants of health with their care team. Effectiveness and implementation outcomes will be evaluated using a stepped-wedge clinical trial design. Effectiveness will be evaluated by comparing missed visits and viral nonsuppression rates before and after the intervention. Implementation will be evaluated using a mixed methods approach based on the reach, effectiveness, adoption, implementation, and maintenance framework.

Results: Funding was received April 2022 with data collection beginning December 6, 2023. Data collection is anticipated to end in 2027 with data analysis and results expected late 2027. As of submission of the manuscript, 86 participants were recruited. Of the 6710 patients with health record data available 2 years before the trial began, 1723 (25.68%) had a substance use disorder, 2825 (42.1%) missed at least 2 care visits, and 1354 (20.18%) had at least 1 detectable HIV RNA test (viral load ≥200 copies/mL), leaving 3816 (56.87%) eligible individuals. Analysis of preimplementation data demonstrated that patients had a mean of 4.1 (SD 2.1) to 7.8 (SD 5.5) care visits across all 8 Vivent Health sites, with 45% to 70% of patients missing at least 1 visit. Patients underwent a mean of 2.2 to 4 HIV RNA tests, and 14% to 37% of patients across clinics had at least 1 nonsuppressed HIV RNA result. Primary analyses are expected to be completed by 2028.

Conclusions: This study will evaluate the effectiveness of and implementation strategies for a mobile health–based intervention to support patients with HIV, substance use disorder, and related challenges in engaging in care and achieving viral suppression.

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KEYWORDS

HIV; antiretroviral agents; substance-related disorders; medication adherence; digital health; case management; mobile phone

Introduction

Background

Clinical implementation and global scale-up of antiretroviral therapy (ART) for HIV have transformed one of the deadliest pandemics in human history into a chronic disease management challenge. Before 2003, HIV and AIDS were a leading cause of death among young adults worldwide. In recent decades, however, effective treatment and systems of care have demonstrated such an impact that the World Health Organization has declared HIV elimination to be a realistic global health goal [1].

Elimination of HIV transmission through effective treatment (also referred to as "treatment as prevention") can only be achieved through universal access to treatment and sustained viral suppression (defined as plasma HIV RNA levels that are lesser than the detection threshold of 200 copies/mL) for nearly all persons living with HIV [2]. Unfortunately, in the United States, only 62.7% of persons diagnosed with HIV infection had viral suppression in 2017 [3], a level that falls substantially short of the 95% goal set by the US Department of Health and Human Services for ending the epidemic [4].

Patients and communities impacted by substance use disorders (SUDs) and related social and behavioral vulnerabilities are significantly less likely to experience sustained HIV suppression [5-8]. In a cohort of people who inject drugs followed for a median of 8.7 years, only 30% were retained in care every year they were in the study [9]. Of those who reported receiving ART during the study, 86% achieved viral suppression during at least 1 study visit; however, only 12% were found to have achieved viral suppression at every study visit after ART initiation, meaning nearly 9 in 10 patients experienced virologic failure during their treatment [9].

Previous research has demonstrated that the determinants of suboptimal HIV treatment outcomes are heterogeneous and complex [10], suggesting that ending the HIV epidemic will require the implementation of multifaceted strategies to support vulnerable patients throughout their life course. Fortunately, systems of HIV care that address social determinants of health can help address these complex needs. Data from the Health Resources and Services Administration (HRSA) Ryan White HIV and AIDS Program (RWHAP) [11] showed that 85% of individuals who had at least 1 medical visit to a clinic funded by RWHAP during 2017 had achieved viral suppression [12]. A study on service delivery in RWHAP-funded facilities found that they were more likely to provide case management, mental health, substance use, and other support services compared to non–RWHAP-funded clinics, and patients attending these facilities were more likely to receive these services [13].

The Need for Just in Time Strategies for Monitoring and Responding to Social Determinants of Health in HIV Care Settings

While clinical factors, such as antiretroviral adherence [14] and retention in care [15] are well understood to be proximal determinants of viral suppression, nonclinical factors, such as poverty [16], lack of health insurance [17], homelessness [18], food insecurity [19], and criminal justice involvement, also influence HIV care outcomes. In 1 community-based cohort study of predominantly African American people with HIV who inject drugs, participants who achieved viral suppression after initiating ART had a 1-in-4 risk of experiencing viral rebound (ie, virologic failure) during any 6-month interval [20]. In that study, loss of viral suppression was more common if participants reported recent incarceration, daily injection drug use, or homelessness, demonstrating how time-varying social and behavioral factors can signal vulnerability to treatment interruptions Other patient-level factors that have been consistently correlated with treatment interruptions include depression and anxiety [21], low self-efficacy, internalized HIV-related stigma [22], and inadequate social support [23].

A major challenge to addressing HIV-related health disparities is the tendency for patients to miss appointments during periods of greatest vulnerability. Research using electronic health record (EHR) data shows that treatment failure is predictable based on individual-level characteristics documented in the EHR [24,25]. However, the social, behavioral, and structural factors that increase the risk of treatment disruption and require the timely provision of support to ensure care retention are not typically captured in EHRs. Therefore, health care providers do not generally have timely access to data that would help them provide support when it is most needed. As a result, most disruptions in ART are detected only after a lapse in care has already occurred. The fact that previous treatment disengagement and virologic nonsuppression are 2 strong predictors of future care disengagement [24,25] further underscores the need to interrupt the cycle of treatment disruption and find new ways to support retention.

Digital Health Approaches to Addressing Disparities in HIV Care

Real-time monitoring of patients with digital health systems can provide a platform to provide timely support and linkage to needed services. A suite of demonstration projects supported by HRSA's Special Projects of National Significance explored the beneficial roles of social media and mobile health (mHealth) interventions, finding promise in three domains: (1) managing HIV care with subthemes of medical information accessibility, reminders, and self-efficacy; (2) fostering feelings of support and personal connectedness; and (3) helping alleviate negative feelings about status and mitigating HIV-related stigma [26].

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Technology can empower patients with direct delivery of individualized motivation, education, and support [27]. Wireless technologies remove the barriers of time and distance between patients and health care providers; this is especially important for patients with SUD and other populations that are hard to reach and difficult to keep engaged in care. Digital health technology offers great potential for collecting higher-quality data related to care delivery and health outcomes, and facilitating more effective collaboration among HIV care providers.

In this paper, we describe a hybrid implementation effectiveness trial of a clinic-based intervention that seeks to leverage the numerous potential benefits of digital health strategies when deployed in the context of comprehensive, patient-centered HIV care. The approach described in the Methods section was informed by a pilot study funded by the National Institute on Drug Abuse, in which 200 people living with HIV were invited to use a digital health app, the Addiction–Comprehensive Health Enhancement Support System (CHESS), for a period of 2 years [28,29]. Lessons learned from the pilot study influenced the design of key intervention elements in this study, including the use of peer mentors to boost patient engagement with the digital health system and dedicated clinic case managers to act as liaisons between app engagement and the broader HIV care team.

Methods

Overview

The goal of this project is to implement and evaluate an evidence-based digital health system to improve HIV viral suppression and reduce missed clinic visits within a multisite, comprehensive HIV care program in the United States. Using a stepped-wedge, cluster randomized trial design, we will test the effectiveness of a care coordination intervention named ART-C (antiretroviral therapy care coordination). The intervention is a multicomponent strategy that combines medical case management; peer support; and the Connections app, which is a smartphone-based platform designed to support engagement in care for people living with SUD. After conducting formative research and a community-engaged protocol development process, the trial was approved by the institutional review board (IRB) in October 2023. Protocol version 4 was approved on November 14, 2024. In this paper, we discuss the intervention, study aims and methods, and the population eligible for recruitment into the clinic-supported arm of the study.

The Connections App (CHESS Health) is based on the CHESS, a mHealth system developed at the University of Wisconsin (UW). CHESS is a suite of secure, internet-based services delivered via smartphone that promotes positive behavior change and provides social support to people engaged in care for HIV, addiction, and other complex conditions. A randomized controlled study conducted in 2014 found that Addiction–CHESS, a derivation of CHESS designed for alcohol use disorder treatment, had a significant effect on treatment retention and reduced risky drinking behaviors [30].

When implemented in a multisite HIV care program operating under a patient-centered medical home model, we hypothesize that ART-C will improve care by supporting three needs: (1) facilitating real-time, community-based capture of data reflecting social and behavioral determinants known to precede lapses in HIV care (eg, housing and food insecurity, unhealthy alcohol or drug use, or poor medication adherence); (2) improving engagement in care by increasing social connectedness among patients and between patients and peer mentors; and (3) supporting retention in addiction treatment and mental health care that promote sustained engagement in HIV care.

Study Aims

As a hybrid type 2 trial [31], the study has primary aims related to both effectiveness and implementation. The effectiveness-related aim of the study is to understand the impact of ART-C on the occurrence of virologic failure and missed clinic appointments among patients receiving HIV care. The implementation-related aim is to evaluate the deployment of ART-C within the HIV medical home model using the reach, effectiveness, adoption, implementation, and maintenance (RE-AIM) framework. We will analyze patient-, health care provider-, and clinic-level factors that influence the reach, effectiveness, implementation, adoption, and maintenance of ART-C within HIV care practices.

The hybrid trial design will simultaneously test the effectiveness of the ART-C intervention and the effect of a bundle of evidence-based implementation strategies. Our bundled implementation strategy is organized by the exploration, preparation, implementation, and sustainment framework [32]. The discrete implementation strategies that make up the bundle come from the Expert Recommendations for Implementing Change taxonomy [33].

Study Design

The stepped-wedge design is a cluster-randomized, 1-way crossover study in which all units are initially assigned to the control condition, then switched to the intervention at randomly assigned time points until all units have crossed over by the last time interval. Stepped-wedge trials enable all sites to receive enhanced services while avoiding biases associated with uncontrolled pre- and poststudy designs. A site will be considered preintervention when it is in the control condition (before ART-C implementation), and postintervention after crossover. Primary outcomes will be passively collected using data from the health system's EHR.

Study Setting and Patient Population

ART-C will be implemented within 8 HIV medical home clinics operated by Vivent Health in Colorado, Missouri, Texas, and Wisconsin. The HIV medical home model provides HIV-oriented comprehensive care to people living with HIV and encompasses primary health care, dental care, mental and behavioral health services, case management, housing, prevention or harm reduction services, and food bank services.

To describe the baseline, preintervention occurrence of study outcomes, we defined a cross-sectional sample of active patients who would be eligible to receive ART-C as of December 2023. The baseline sample excluded patients who never attended a

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medical visit, died before the time of study approval, or did not speak English.

Demographic and clinical characteristics of the study sample were captured from the Vivent Health EHR (Epic Systems Corporation). The prevalence of SUD was determined based on visit diagnoses and problem list entries in the EHR, using the *International Classification of Diseases, 10th Revision,* codes (F10-16, F19, O35.4, O35.5, O99.31, and O99.32). Patients were also classified as having SUD if they were ever prescribed a medication to treat alcohol use disorder (acamprosate, disulfiram, topiramate, or naltrexone) or opioid use disorder (methadone, buprenorphine, or naltrexone). For medications that are used for the treatment of SUD and other conditions, patients were only considered to have SUD if the prescription order was paired with an appropriate diagnosis code for alcohol use disorder or opioid use disorder.

Study Outcomes

We defined 2 study outcomes using EHR data, which will be examined at the clinic level and continually assessed during pre- and postimplementation periods. The first outcome, missed clinic visits, is defined as the proportion of appointments scheduled with an HIV care provider that a patient failed to attend and did not call in advance to cancel or reschedule. The second outcome, viral nonsuppression, is defined as the proportion of patients with an HIV RNA test result greater than the lower limit of detection (200 copies/mL) among those who received 1 or more HIV tests during the past 6 months.

These outcomes reflect the principle that optimal HIV care exists across a continuum, from timely diagnosis and linkage to care, to initiation of ART, and sustained adherence and retention in care over the life course [34]. They were selected because they have been identified as key quality improvement metrics by Vivent Health for all of its clinical sites. Missed visits are a marker of vulnerability for disengagement from care [35] and may predict loss of viral suppression [36] and subsequent mortality [37]. Viral suppression is the key indicator of a successful response to ART in all HIV care settings. Minimizing viral nonsuppression is, therefore, a main goal of national and global HIV elimination strategies [38].

Intervention Overview

The ART-C intervention consists of a bundle of digital health-supported services and traditional care coordination activities that can be used outside of the research context. When a clinic begins implementation of ART-C, all clients at the clinic immediately have the opportunity to download the Connections app and use its standard features without sharing any individual-level data with researchers. This is referred to as patient-directed engagement with the app. Individuals who use the Connections app at this level can participate in discussion forums and view resource pages alongside clients receiving services at more than 250 recovery- and prevention-oriented organizations across the United States who subscribe to the Connections app. Patients using the Connections app at this level are not considered to be research participants.

In addition to the standard level of app engagement open to all Vivent Health clients, patients with risk factors for poor engagement in care are invited to access more intensive and personalized features of ART-C as part of a research protocol. These risk factors are described in the formal participant eligibility criteria and capture a patient's HIV visit attendance history, viral load values, and self-report substance use history. Patients meeting eligibility criteria have access to additional app features and the opportunity to interact with specially trained staff who monitor activity within the Connections app and interact with study participants on a study-specific discussion board. This is referred to as the clinic-supported intervention engagement. These 2 levels of intervention engagement allow the most resource-intensive components of the intervention to be targeted toward patients at greatest risk for viral nonsuppression, while offering all patients the opportunity to participate in the online community fostered by the Connections app.

Patient-Directed Intervention Components

Peer Mentors

Peer-based support is an evidence-based strategy for supporting care engagement [39-41]. It also reduces racial and ethnic disparities in health care by addressing stigma and discrimination [42-44]. Upon implementing ART-C, Vivent Health recruited and trained 6 peer mentors living with HIV who demonstrated resilience in meeting HIV treatment goals and overcoming the effects of discrimination, addiction, or other life challenges. Candidates were identified by soliciting nominations from Vivent Health case managers and health care providers who had been oriented to the goals of the intervention. Peer mentors receive a monthly stipend (US $100) to cover phone and data services and as a token of appreciation for the valuable service they provide. Recruitment and training of peer mentors occur before the intervention starts in each clinic, using modified curricula developed for use by the HRSA-funded AIDS Education and Training Centers.

The Connections App

Developed and marketed by CHESS Health, the Connections app offers users anytime and anywhere access to a suite of digital health services, including an online community forum used by people engaged in SUD services across the United States. The recovery-oriented community forum is monitored and moderated by a peer engagement team employed by CHESS Health, consisting of trained peer support specialists who can provide feedback and support to people with SUDs. For the ART-C intervention, the research team worked with CHESS Health to build and deploy a parallel HIV care-oriented community forum, which is moderated by Vivent Health peer mentors and allows for online discussion of topics relevant to patients with and without SUDs, including medication adherence, stigma, and other challenges encountered by people living with HIV. Furthermore, the Connections app contains gamification features, where users can earn points for active engagement in the online community and for extended periods of abstinence from drugs or alcohol. The app also supports private discussions among a smaller number of users in group chats, as well as personal messages between users or between users and staff.

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Clinic-Supported Intervention Components

While the Connections app is available to the full clinic population, more intensive support involving digital health–enhanced, person-centered care coordination can only be delivered to a subset of patients due to staffing and other resource limitations. To maximize the potential impact of the ART-C intervention, the research team consulted with Vivent Health leadership to develop the eligibility criteria provided in Textbox 1 for the clinic-supported arm of the intervention.

Our target study population involves people at risk of viral nonsuppression and lapses in HIV care due to current or past substance use and history of disruptions to HIV care engagement or viral suppression, which align with these criteria.

Textbox 1. Inclusion and exclusion criteria.

Inclusion criteria

- Aged 18 years or more
- Can read and write in English
- Receiving medical care for HIV treatment at Vivent Health (confirmed by electronic health record review)
- At least 1 of the following requirements must be met based on self-report: have a self-reported lapse in medication, which is defined as missing 2 or more doses of medication within a 1-month period; have missed at least 1 appointment while receiving medical care at a Vivent Health clinic; have a history of, or current, substance use disorder, or a report that substance use has caused problems for them at some point in their life

Exclusion criteria

- Not currently having a smartphone and unwilling to obtain a smartphone
- Appearing to lack the capacity to consent, as evidenced by an inability to read, write, speak, or otherwise provide informed consent due to acute intoxication or chronic conditions

Research Care Coordinators

Two new staff members with prior employment experience in HIV medical case management were hired by Vivent Health to be fully dedicated to the ART-C intervention. The research care coordinators have a hybrid role on the Vivent Health care team: they function as research specialists, recruiting, screening, and obtaining informed consent for participants in the clinic-supported intervention, and serve as liaisons between patients who engage with app services and other health care professionals on the patients' care team. Research care coordinators are credentialed as Vivent Health case managers; have access to patients' medical records; and, with patient consent, can communicate with medical health care providers, case managers, and other staff about or on behalf of patients enrolled in the ART-C intervention.

Weekly Check-In Surveys and Red Flag Alerts

Patients enrolled in the clinic-supported intervention are sent a weekly check-in survey via the Connections app that assesses common barriers to care, medication adherence, and drug or alcohol use. The content of the weekly survey was developed and pilot-tested in previous research to provide a near real-time indication of patient experiences that may signal an increased risk of lapses in care [29]. While clients are able to reflect on and report notable barriers from the previous week, the results of these surveys will not be automatically shared with their care team. At the end of the survey, clients are required to opt in or out of having their responses forwarded to their care team for triage. Selecting to opt in means that the clinical research coordinator and care team will adhere to a predetermined escalation procedure for assisting the client with their disclosed barriers.

Participant Recruitment

On a quarterly basis, the Vivent Health data analytics group will send a list of all patients receiving HIV medical care to the ART-C study team. The list will be used to recruit for the clinic-supported intervention of the study. Patients are contacted through mass messaging campaigns using the MyChart feature of the Epic EHR system, a secure text messaging platform (Artera); direct messaging through MyChart; or direct messaging through the preferred contact method listed in their EHR. For patient privacy, patients who receive messages through mass messaging campaigns will receive a link only to the Connections app download page. Patients who receive direct messaging through MyChart or via their preferred contact method will receive a link to the eligibility survey and app download page. To participate in the study, patients must also have a smartphone and be willing to download the Connections app, which will prompt them to complete a brief questionnaire to assess eligibility for the clinic-supported intervention. Eligible patients will receive a follow-up message asking them to schedule a phone or video appointment with a research care coordinator to review the informed consent document and receive a brief orientation to the ART-C intervention and the Connections app. Patients who do not meet the eligibility criteria will receive a follow-up message informing them that they are not eligible to participate in the clinic-supported arm of the study, but they are encouraged to use the Connections app. People who download the app but do not complete the eligibility screener will receive an additional message reminding them about the opportunity to screen for eligibility for the clinic-supported intervention.

For each of the 8 Vivent Health sites, eligibility assessment and screening will continue until the accrual target is reached or until the end of the 1-year implementation period, whichever occurs first. Participants who enroll but later withdraw or are

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lost to follow-up will not be replaced by newly enrolled participants.

Data Collection

We will use the RE-AIM model to guide our overall evaluation of implementation. RE-AIM is a comprehensive framework that assesses 5 dimensions: reach, effectiveness, adoption, implementation, and maintenance [45].

The primary "reach" measure will be the percentage of Vivent Health patients with HIV who have downloaded and used ART-C, along with their sex, racial, and ethnic characteristics. The primary "effectiveness" outcomes (missed HIV care visits and viral nonsuppression) will be evaluated from clinical EHR data documenting HIV viral load results and the status (attended and missed) of scheduled HIV care visits. We will also describe Connections app use and collect quarterly surveys from patients in the clinic-supported intervention. "Adoption" at the patient level is based on research-driven metrics of meaningful use for mHealth, defined as a patient accessing any part of ART-C beyond the home page during a given week in the 12-month period after downloading the app [46].

"Implementation" will be evaluated based on fidelity to key components of ART-C at the clinic level, using quantitative and qualitative methods. We will define fidelity in two dimensions: (1) the amount of the intervention received (ie, use of the dashboard) and (2) the quality of intervention delivery (ie, the intervention participant's reflections on their experience using the dashboard and the effect it had on their approach to care delivery). "Maintenance" will be defined as follow-up on the effectiveness measures (viral load and missing visit rates) in the 6-month postintervention period.

Using qualitative interviews, we aim to gain rich insights into implementation and adoption processes at various sites from a diverse set of stakeholders involved in implementation. Data will be coded, and the analysis will help us refine the Connections app for future dissemination by determining individual and organizational conditions necessary to promote effectiveness. Interviews will be conducted with multilevel stakeholders, including study participants (10 to 20 interviews), clinic staff identified as change leaders (5 to 10 interviews), and the peer mentors (5 interviews).

Analytic Strategy: Effectiveness and Maintenance

In the stepped-wedge design, each site functions as its own control or usual care group before the implementation of ART-C. During this period, clinics treat patients with HIV using existing, standard treatment protocols and do not yet have access to the Connections app. To characterize intervention effectiveness, we will model site, time, and intervention status as predictors of primary outcomes using a repeated measures model to control for clustering by individuals and sites [47]. An indicator variable for intervention status will be modeled as 0 before intervention and 1 after ART-C is rolled out at each site. Random effects will be used to model the correlation between individuals within the same cluster (ie, site) in the stepped-wedge design. For a design with 8 clusters, 5 time points, and N individuals sampled per cluster per time interval, Y_{ijk} will be the response corresponding to individual k at time j from cluster i (i in 1,..., 7; j in 1,..., 8; k in 1,..., N) and Y_{ij} will be mean for cluster i at time j:

$$Y_{ij} = \mu + \alpha_i + \beta_j + X_{ij}\theta$$

In this equation, α_i is a random effect for cluster i, β_j is a fixed effect corresponding to time interval j, X_{ij} is an indicator of the treatment status in cluster i at time j (1=intervention; 0=control), and θ is the treatment effect. The individual-level responses of no-show rates and viral suppression are binary, so the cluster-level responses Y_{ij} are proportions with variance $\sigma_{ij}^2{}_e = \mu_{ij} * (1 - \mu_{ij})$. A variance inflation factor of 1 + (N – 1) ρ is incorporated into the analysis, where ρ is the intraclass correlation coefficient between individuals within the same cluster. Logistic generalized estimating equation (GEE) models will be determined using R statistical software (version 4.3.3; R Foundation for Statistical Computing) with geeglm (family=binomial) [48].

After establishing the base model, we will include potentially confounding and moderating factors by adding covariates, interaction terms, and weighting methods to the models. Potential clinic-level confounders will include the racial and ethnic categories, gender, age, and diagnosis of a SUD.

Power and sample size calculations will be based on the study by Hemming and Taljaard [49]. For a stepped-wedge design with 8 clusters stepped in 1 to 2 clusters at a time over 5 time periods and an assumed intraclass correlation coefficient of ρ=0.10, the design effect relative to an individual-based randomized controlled trial is 3.0. Preliminary data suggest the percentage of enrolled patients with nonsuppressed viral load (HIV RNA ≥200) before intervention to be 26.7%. On the basis of consultation with clinic leadership and pilot data from a single site, we assume a meaningful effect size to be a 10 percentage point reduction in nonsuppressed HIV RNA tests in the study sites after intervention, to 16.7%. The 8 clinical sites average 526 active patients per site per year for an estimated total of 4208 potential patients. We aim to reach approximately 15% of clinic patients using patient engagement strategies geared toward helping those patients most likely to benefit from the clinic-supported intervention. We hypothesize that the implementation strategy can effectively reach 631 (15%) patients and achieve a 68% improvement in viral load suppression among this highly vulnerable population. On the basis of these assumptions, with 3682 active patients, our power to detect a 10 percentage point reduction in nonsuppressed viral loads will be 98.5% (1–β=.985). The study will be sufficiently powered (>80%) to detect up to a 7 percentage point reduction in patients with nonsuppressed viral load.

Analytic Strategy: Reach, Adoption, and Implementation

We will assess reach by presenting descriptive statistics of the 8 clinics in the trial and comparing demographic characteristics (sex, race, and ethnicity) between patients using the app versus the overall clinic population using chi-square tests. We will assess factors of patient adoption using logistic GEE models (outcome: any meaningful use each week) and Poisson or negative binomial GEE models (outcome: days of meaningful

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use per week). Predictors of adoption will include patient sociodemographic factors (age, race and ethnicity, gender, sexual orientation, SUD history) and time-varying factors based on measures collected through weekly and semiannual surveys. Adoption will also be examined as a predictor of individual-level effectiveness outcomes for patients who enroll in the app using logistic GEE models (outcomes: viral nonsuppression and missed visit). Models will account for repeated measures using hierarchical clustering for repeated observations from patients within sites.

Interview and focus group data will be recorded and transcribed. Transcripts will be independently coded by 2 members of the research team, who will meet to discuss and resolve any significant coding inconsistencies. We will manage and analyze qualitative data using NVivo (Lumivero). We will use qualitative analysis to assess adoption at the staff level and use this information to understand potential differences in outcomes between sites related to reach, effectiveness, and implementation outcomes.

Ethical Considerations

This study was approved by the Health Sciences IRB at the UW-Madison (#2023-0938). Participants who agree to enroll in the clinic-supported arm of ART-C will provide written consent to enter the study. Documentation of consent is kept in the Department of Medicine REDCap (Research Electronic Data Capture; Vanderbilt University), which is compliant with the Health Insurance Portability and Accountability Act (HIPAA). To minimize the risks to participants, they will be provided with a paper or electronic copy of the informed consent when they initially screen as eligible to participate in the study. Participants will be informed that their participation is voluntary, that they may withdraw from the study at any time, and that they may skip any survey questions they are uncomfortable answering. We will also inform participants that being involved or discontinuing the study will not affect their access to services at Vivent Health or any treatment they are receiving. Furthermore, we have a certificate of confidentiality to protect the research team from being compelled to disclose identifiable participant information, even by a court subpoena, in any federal, state, or local civil, criminal, administrative, legislative, or other proceedings.

Study investigators developed a written protocol to assure data accuracy and protocol compliance, including data verification and protocol compliance checks. The data manager at the UW research team, in collaboration with the Department of Medicine IT, ensures that all identifiable data are stored on a UW-Madison secure, restricted drive maintained by the Department of Medicine, and that the storage is compliant with university and federal regulations. Any data generated by this study are only accessible to study team members after providing the IRB and HIPAA compliance officer a copy of their certificates of completion of the UW-Madison Human Subjects and HIPAA privacy rule online trainings. A data safety and monitoring board will not be convened for this study, which is considered a minimal risk implementation study. In lieu of a data monitoring committee, the research team will periodically evaluate the data collected for the purpose of monitoring study progress and identifying potential problems. A template will be used to present the most important summary data points (eg, number of patients screened, enrolled, and withdrawn, as well as the proportion of patients completing various study end points on time). These data will be documented and shared with the study team and principal investigators during monthly team meetings. The principal investigators will determine whether any reported problems identified by study staff represent reportable events and will notify the IRB as appropriate.

Study participants will receive US $30 for completing the baseline, 3-month, 6-month, and 9-month surveys, and US $40 for completing the 12-month survey. The maximum value for compensation for 1 participant in this study will be US $160. Participants may choose to receive their incentive either as a digital gift card, delivered by email or text message via the third-party payment platform Tremendous if they consent, or as a check sent to an address of their choosing. Participants will have the option to update their payment preference throughout the study. Compensation will be provided to participants after confirmed completion of the baseline and quarterly surveys.

Data Quality Steps and Storage

All data collection tools were created and beta tested collaboratively by study team members who have successfully completed Human Subjects Research training and annual HIPAA certifications. Testing was conducted for ease of use, clarity of questions, skip pattern logic, and duration. Instructions for completing the surveys are provided in writing at the start of the survey. Content experts were consulted during the materials drafting stage to ensure that questions are appropriate for the participant population, do not inflict any unnecessary harm or risk to participants, and were written to capture the necessary data elements. Data collection forms, such as the weekly survey and research surveys, will be directly administered to participants and programmed in a manner that participants are asked to respond to all questions to form a complete dataset, but are given an option to indicate “not applicable” or “I prefer not to answer.” Data forms limit the use of free textboxes to ensure data quality. Data will be coded, and the key linking identities to codes will be stored separately and will only be accessible to key personnel, using HIPAA-compliant servers such as REDCap. Final datasets used for analysis will be distributed by the research project manager or program administrator to study team members via a restricted drive, to which only designated research team members have access.

Protocol Changes and Communication of Findings

The UW-Madison study team consistently communicates with the participating Vivent Health locations to address any modifications to the study. Communication occurs via in-person or virtual meetings, email and phone communications, and Teams (Microsoft Corporation) for any changes related to protected health information. The research director, research supervisor, and research care coordinators at Vivent Health, who are members of the research team and oversee research projects occurring at Vivent Health, also help disseminate key study protocols and information about changes, problems, and closure of the study throughout the duration of the study.

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Results

In the 2 years before starting ART-C implementation (December 2021 to November 2023), 6710 patients received HIV-related services, including a laboratory test or scheduled visit. After excluding patients who never attended a medical visit, died before the time of study approval, or did not speak English, the resulting sample included 6035 (89.94%) patients who received HIV care in 1 of the 8 participating clinics.

Demographic and clinical characteristics of patients in the baseline sample are provided in Table 1. The majority (75%-88%) of patients at all clinics described their gender as men. The mean age of the patients as of December 2021 ranged from 41.7 (Kansas City) to 48.7 years (Denver). Self-reported race varied geographically. African American and Black individuals comprised the majority of patients in the Milwaukee and St Louis clinics, while most patients in the other 6 clinics reported as White individuals. Hispanic ethnicity was least common in St Louis (60/1409, 4.26%) and most common in Austin (210/754, 27.9%). The prevalence of SUD among active patients ranged from 4.2% (13/307; Kansas City) to 37.4% (82/219; Kenosha).

Table 2 displays the results of the baseline analysis of the 2 main study outcomes, providing the baseline level of HIV care indicators to which future, postintervention results will be compared. Over the 2 years before trial inception, patients had a mean of 4.1 to 7.8 scheduled care visits across sites, and 45% to 70% of them missed 1 or more visits. Patients had an average of 2.2 to 4 HIV RNA tests, and 14% to 37% of them had at least 1 nonsuppressed (>200 copies/mL) HIV RNA test. Multimedia Appendix 1 provides additional patient characteristics, such as HIV transmission route, sexual orientation, employment, and other features of the patient population at the clinic.

The preliminary estimate for the number of patients who are expected to be eligible for the clinic-supported research protocol is shown in Figure 1. Using the criteria described in the Methods section, we identified 1727 patients with evidence of SUD diagnosis or a previous prescription for a SUD medication during the pretrial period. On the basis of laboratory and visit data in the EHR, 1355 (22.45%) patients had 1 or more nonsuppressed HIV RNA tests, and 2798 (46.36%) patients missed 2 or more HIV care visits. We estimate that the 3816 (63.23%) total patients meeting at least 1 of these 3 criteria will be eligible for the clinic-supported version of the intervention. Table 3 provides the study enrollment and intervention implementation timeline. Primary analyses are expected to be completed by 2028.

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Table 1. Sociodemographic characteristics of patients receiving HIV care at 8 participating medical home clinics between December 2021 and November 2023 (N=6035).

Characteristics	Medical home clinics							
	Milwaukee (n=1480)	Denver (n=1453)	Green Bay (n=240)	St Louis (n=1409)	Austin (n=754)	Kenosha (n=219)	Madison (n=170)	Kansas City (n=307)
Age (y), mean (SD)	47 (13.4)	48.7 (13.1)	48.1 (12.9)	45.2 (12.3)	42.8 (12.7)	45.7 (14.3)	45.4 (13)	41.7 (12.1)
Gender, n (%)								
Women	321 (21.69)	121 (8.33)	40 (16.67)	177 (12.56)	93 (12.33)	51 (23.29)	20 (11.76)	60 (19.54)
Men	1102 (74.46)	1275 (87.75)	189 (78.75)	835 (59.26)	535 (70.96)	159 (72.6)	139 (81.76)	227 (73.94)
Other	44 (3.73)	30 (2.06)	6 (2.5)	31 (2.2)	30 (3.98)	6 (2.74)	7 (4.12)	16 (5.21)
Missing	13 (1.1)	27 (1.86)	5 (2.08)	366 (25.98)	96 (12.73)	3 (1.37)	7 (4.12)	4 (1.3)
Race, n (%)								
American Indian or Alaska Native	12 (0.81)	49 (3.37)	9 (3.75)	16 (1.14)	8 (1.06)	3 (1.37)	1 (0.59)	5 (1.63)
Asian	11 (0.74)	17 (1.17)	3 (1.25)	18 (1.28)	10 (1.33)	0 (0)	5 (2.94)	6 (1.95)
Black	798 (53.92)	203 (13.97)	41 (17.08)	741 (52.59)	213 (28.25)	85 (38.81)	42 (24.71)	129 (42.02)
Native Hawaiian or Pacific Islander	3 (0.2)	6 (0.41)	1 (0.42)	2 (0.14)	2 (0.27)	1 (0.46)	0 (0)	1 (0.33)
White	485 (32.77)	1003 (69.03)	165 (68.75)	572 (40.6)	461 (61.14)	102 (46.58)	108 (63.53)	146 (47.56)
Missing	171 (11.55)	175 (12.04)	21 (8.75)	60 (4.26)	60 (7.96)	28 (12.79)	14 (8.24)	20 (6.51)
Ethnicity, n (%)								
Hispanic	121 (8.18)	281 (19.33)	44 (18.33)	60 (4.26)	210 (27.85)	31 (14.61)	22 (12.94)	28 (9.12)
Non-Hispanic	1279 (86.42)	1100 (75.71)	190 (79.17)	1306 (92.69)	492 (65.25)	177 (80.82)	145 (85.29)	260 (84.69)
Missing	80 (5.41)	72 (4.96)	6 (2.5)	43 (3.05)	52 (6.9)	11 (5.02)	3 (1.76)	19 (6.19)
Health insurance, n (%)								
Uninsured	48 (3.24)	11 (0.77)	14 (5.83)	18 (1.28)	98 (13)	7 (3.2)	12 (7.06)	15 (4.89)
Public Insurance (eg, Medicaid)	263 (17.77)	261 (17.96)	61 (25.42)	246 (17.56)	40 (5.31)	70 (31.96)	33 (19.41)	38 (12.38)
Private insurance	197 (13.31)	461 (31.73)	47 (19.58)	309 (21.93)	89 (11.8)	25 (11.42)	40 (23.53)	23 (7.49)
Multiple payment types	966 (65.27)	718 (49.42)	117 (48.75)	834 (59.19)	526 (69.76)	117 (53.42)	84 (49.41)	231 (75.24)
Missing	6 (0.41)	2 (0.14)	1 (0.42)	2 (0.14)	1 (0.13)	0 (0)	1 (0.59)	0 (0)
Substance use disorder history, n (%)								
Yes	409 (27.64)	218 (15)	63 (26.25)	278 (19.73)	108 (14.32)	82 (37.44)	33 (19.41)	13 (4.23)
No	1071 (72.36)	1235 (85)	177 (73.75)	1131 (80.27)	646 (85.68)	137 (62.56)	137 (80.59)	294 (95.77)

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Table 2. Baseline occurrence of primary outcomes among patients receiving HIV care between December 2021 and November 2023 (N=6035).

Outcomes	Medical home clinics							
	Milwaukee (n=1480)	Denver (n=1453)	Green Bay (n=240)	St. Louis (n=1409)	Austin (n=754)	Kenosha (n=219)	Madison (n=170)	Kansas City (n=307)
Missed visit outcomes								
Clinic visits scheduled, n	11,651	12,134	1305	10,827	6380	1686	993	2236
Number of scheduled HIV care visits per patient, mean (SD)	7.1 (5)	7.8 (5.5)	4.1 (2.1)	7.4 (5)	7.6 (5.9)	5.2 (3.3)	4.3 (3.3)	5.7 (3.7)
Scheduled visits that were missed (%)	41.13	26.64	21.23	36.63	33.78	38.91	28.60	31.13
Patients with 1 or more missed visits (%)	69.57	58.90	45.48	65.85	72.90	58.72	52.16	61.83
HIV viral suppression outcomes								
HIV RNA tests completed, n	5017	4896	598	5552	2410	691	382	1147
Number of completed HIV RNA tests per patient, mean (SD)	3.3 (1.7)	2.7 (1.4)	3.1 (1.9)	2.2 (1.2)	2.1 (1.1)	3.4 (1.8)	4 (2)	3.2 (1.9)
HIV RNA tests that were nonsuppressed (%)	9.69	7.31	7.02	11.38	14.11	14.04	10.47	16.30
Patients with 1 or more non- suppressed HIV RNA tests (%)	21.65	16.86	13.91	27.05	30.65	26.09	15.73	37.18

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Figure 1. Patients represented in the baseline clinic sample and those prioritized for enrollment in the clinic-supported intervention.

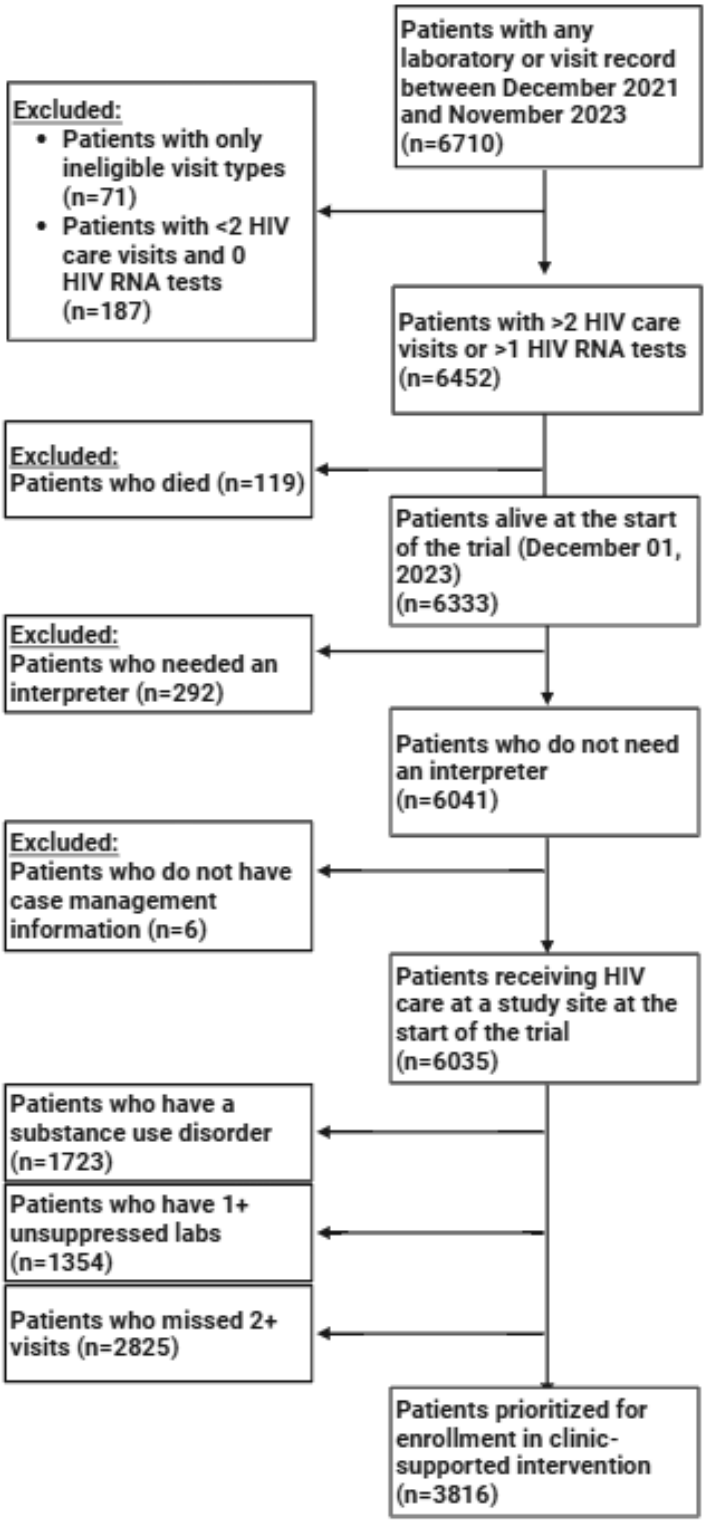

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Table 3. Study timeline.

	Year 2: March 1, 2023, to February 29, 2024				Year 3: March 1, 2024, to February 28, 2025				Year 4: March 1, 2025, to February 28, 2026				Year 5: March 1, 2026 to February 28, 2027			
	Q[a]1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Kenosha and Madison			EI[b]	EI	EI	EI	I[c]	I	I	I						
Green Bay and Milwaukee					EI	EI	EI	EI	I	I	I	I				
Denver and Kansas City							EI	EI	EI	EI	I	I	I	I		
Austin and St Louis									EI	EI	EI	EI	I	I	I	I

[a]Q: quarter.

[b]EI: enrollment and intervention.

[c]I: intervention.

Discussion

Anticipated Findings

People living with SUD are less likely to be retained in HIV treatment for a long term due to various social and structural determinants of health, signaling a need for targeted interventions to support engagement in care. Persistent disparities by race, ethnicity, and socioeconomic status underlie national estimates of viral suppression, fueling the disproportionate burden of new HIV infections occurring in people of color [50,51]. This study aims to characterize the potential impact of digital health combined with peer-based strategies for enhancing engagement in HIV and addiction treatment and care for other complex conditions. We hypothesize that implementation of CHESS within an established network of HIV clinical practices will reduce the occurrence of virologic failure and missed clinic appointments by supporting three needs: (1) facilitating real-time, community-based capture of data reflecting social and behavioral determinants known to precede lapses in HIV care (eg, housing and food insecurity, unhealthy alcohol or drug use, or poor medication adherence); (2) improving engagement in care by increasing social connectedness among patients and between patients and peer mentors; and (3) supporting retention in addiction treatment and mental health care that help maintain engagement in HIV care.

Our analysis of baseline clinical outcomes demonstrated a very high frequency of missed clinic visits across the Vivent Health network. At 7 of the 8 clinics, more than 50% of patients had 1 or more missed visits during the baseline evaluation period from December 2021 to November 2023. Missed visits represent an important target for improving HIV care and HIV-related health disparities, and improving attendance at clinic visits is an important goal of the project. The use of the Connections app may foster beneficial communication and engagement between patients experiencing barriers to care and clinic research care coordinators, who can address obstacles in real time. The findings from this study will contribute a new and innovative set of tools with a high potential impact for improving HIV viral suppression and reducing no-show visits in multiple geographic settings.

Comparison With Prior Work

Previous studies have demonstrated the feasibility and acceptance of support for medication-taking behavior [52] and increased engagement in HIV care [53], and a growing literature supports the role of mHealth in resource-limited settings [54]. Given that a large proportion of eligible patients are from racial or ethnic minority groups, have public insurance or are uninsured, and have SUDs, an mHealth intervention like the Connections app will likely be both feasible and acceptable among participants. Using a hybrid implementation-effectiveness study design will allow us to characterize the best strategies for implementing the Connections digital health app in a multisite HIV medical home while collecting data needed to assess its impact on important clinical outcomes. By facilitating social support and enhancing motivation, mHealth (digital health) interventions have shown promise for improving outcomes in addiction treatment. This study will build on previous research to determine whether similar benefits can be realized in the field of HIV care. If the intervention proves beneficial, patients may experience improved daily medication adherence and higher levels of sustained viral suppression.

Strengths and Limitations

A limitation of this study is that the Connections app was derived from an mHealth tool that was originally designed to support care for substance use, not HIV. Given the fact that not all participants may have a SUD, we have added additional components of the Connections app specifically related to HIV to engage such participants. While the centerpiece of the clinic intervention is an established, theory-based mHealth app, the expected impact of the mHealth component derives from its integration with the multiple services and social support delivered as usual care. We aim to maximize opportunities for patient engagement in the mHealth intervention by providing access to the Connections app for all clinic patients living with HIV and implementing a more intensive clinic-supported intervention designed to reach the highest-risk patients. The

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Connections app will generate alerts based on responses to weekly surveys that indicate a patient is at risk for lapses in care. On the basis of these alerts, research care coordinators will facilitate communication about emerging challenges with members of Vivent Health staff in the participant's respective clinic.

Future Directions

Reducing the risk of community-level transmission of HIV requires systems to prevent lapses in ART adherence and improve access to services when patients are not virally suppressed. Moreover, clinic-level interventions must be sustainable over the long term to support patients' need for lifelong treatment. If this trial demonstrates a beneficial impact on HIV care outcomes as anticipated, future research will be needed to optimize patients' long-term retention in similar mHealth-based initiatives. Furthermore, cost-benefit studies will be needed to clarify the resources required to sustain novel strategies for supporting vulnerable patients.

Acknowledgments

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Data Availability

The datasets generated for this analysis and subsequent study are not publicly available due to the presence of protected health information. Data are available upon request and must be submitted on an individual basis to the University of Wisconsin–Madison.

Authors' Contributions

RPW, AQ, and CF conceptualized the project, developed the protocol, and supervised the study. RPW and HKB wrote the first draft of the manuscript. HKB and REG conducted data analysis. LSP, CL, ES, MW, and RM contributed to the development of the intervention protocol and content of the mobile health app and intervention app; advised on implementation, data collection, and analysis; and contributed to the manuscript. REG, HKB, and MPM contributed to the description of planned statistical analyses. All authors have read, revised, and approved the manuscript.

Conflicts of Interest

AQ has a shareholder interest in CHESS Health, a company that disseminates software technology to the addiction treatment field. AQ also consults on the implementation of evidence-based healthcare interventions for the non-profit NIATx Foundation. These relationships are managed by the University of Wisconsin–Madison's Conflict of Interest Committee.

Multimedia Appendix 1
Additional sociodemographic and behavioral characteristics of patients at each study clinic during the 2 years before trial implementation, December 2021 to November 2023.
[DOCX File , 11 KB - resprot_v14i1e69842_app1.docx]

Multimedia Appendix 2
SPIRIT Checklist.
[DOCX File , 39 KB - resprot_v14i1e69842_app2.docx]

Multimedia Appendix 3
Peer-review report .
[PDF File (Adobe PDF File), 150 KB - resprot_v14i1e69842_app3.pdf]

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Abbreviations

ART: antiretroviral therapy
ART-C: antiretroviral therapy care coordination
CHESS: Comprehensive Health Enhancement Support System
EHR: electronic health record
GEE: generalized estimating equation
HIPAA: Health Insurance Portability and Accountability Act
HRSA: Health Resources and Services Administration
IRB: institutional review board
mHealth: mobile health
RE-AIM: reach, effectiveness, adoption, implementation, and maintenance
REDCap: Research Electronic Data Capture
RWHAP: Ryan White HIV and AIDS Program
SUD: substance use disorder
UW: University of Wisconsin

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Protocol

Mobile Telehealth Intervention to Support Care Partners of Patients With Alzheimer Disease and Related Dementias (I-CARE 2): Protocol for a Randomized Effectiveness Clinical Trial

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Abstract

Background: Nearly all individuals with Alzheimer disease and related dementias (ADRD) experience behavioral and psychological symptoms of dementia (BPSD), which include symptoms such as agitation, wandering, delusions, and hallucinations. Care partners (a person, often a family member, who provides care and support to someone with ADRD) struggle to manage BPSD, making symptom management a critical focus of intervention research. Our team has developed a mobile telehealth intervention (Brain CareNotes) to help care partners manage BPSD.

Objective: This paper outlines a protocol for a randomized controlled trial of 160 care partners of patients with ADRD to test the effect of Brain CareNotes on care partner burden and patients' BPSD.

Methods: Participants will be recruited from partner health systems in Indiana, United States, by word of mouth, and through community outreach efforts. They will be randomly assigned to use either the Brain CareNotes mobile app intervention—which helps care partners manage BPSD through the support of a care coach, written and visual materials on developing care skills, and BPSD measurement and tracking—or an education-only mobile app control for 12 months. Data will be collected over the phone at baseline, 6 months, and 12 months. Primary outcomes assessed for this trial are (1) care partner burden and (2) patients' BPSD. Secondary and exploratory outcomes assessed include care partner depressive symptoms, patient and care partner acute care use, intervention usability and acceptability, and intervention use. The trial will also collect patient and care partner demographics and measure care partner self-efficacy, care partner social support, patients' ADRD severity, and patients' functional abilities.

Results: As of March 2025, we have enrolled 159 participants, and 42 have successfully completed the study.

Conclusions: Brain CareNotes is a unique mobile app intervention to support care partners in managing BPSD. Due to the scalability of mobile health interventions, if Brain CareNotes is shown to be effective in reducing caregiver burden and patients' BPSD, it has the potential for widespread adoption to support many ADRD care partners.

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KEYWORDS

Alzheimer disease; dementia; behavioral and psychological symptoms of dementia; caregivers; technology; mobile telehealth intervention; protocol; randomized controlled trial

Introduction

The National Plan to address Alzheimer disease and related dementias (ADRD) identifies behavioral and psychological symptoms of dementia (BPSD) as a critical focus of intervention research [1]. BPSD include both behavioral (eg, agitation, aggression, and wandering) and psychological (eg, delusions and hallucinations) symptoms [1]. Almost everyone with ADRD will experience BPSD, yet care partners (nonprofessional caregivers who are often family members of the person with ADRD) report having unmet needs for support with BPSD [2-5]. BPSD are often poorly managed, increasing the risk of avoidable hospitalizations, morbidity, mortality, and nursing home placement [4,6-12]. Care partners struggle to manage BPSD on their own, especially as conditions and symptoms change, leading to increased care partner stress, depression, and risk of mortality [12-15].

The PREVENT randomized controlled trial (R01HS010884) developed and evaluated a BPSD intervention that included care partner–facing materials and BPSD measures [16]. The intervention significantly reduced care partner burden and patients' BPSD after 12 months when compared with augmented usual care [16]. The PREVENT intervention was then translated into a self-sustained clinical service called the Aging Brain Care clinic [17-20], which demonstrated the ability to hire, train, and use empathetic, nonclinically trained community health workers as care coaches to assist care partners with BPSD management. The Aging Brain Care clinic has had positive effects on BPSD and caregiver burden outcomes [18], but there are barriers to implementing a clinic-based intervention at scale (eg, reliance on in-person encounters, limited clinic operating hours, and the need to employ local clinicians) [17-22].

The National Institute on Aging's published priorities call for technological interventions for ADRD care [23]. Remote technology (hereafter referred to as telehealth) solutions are especially desired because they can substitute for or extend clinic-based programs, which are costly, hard to scale, and hampered by rising staffing shortages [24]. With record rates of telehealth and mobile app use, now is the time to rigorously investigate technology-based remote interventions for managing BPSD.

Our team developed Brain CareNotes, which distills the Aging Brain Care Model [16,17] into a secure mobile telehealth app for care partners to manage BPSD with the aid of a remote care coach. It was professionally developed in collaboration with care partners, clinical staff, and leaders in the Aging Brain Care clinic but designed for scalability and broad use across settings. To our knowledge, Brain CareNotes is the first app of its kind [25] and delivers remote care support, BPSD measurement and tracking, psychoeducation, and person-centered care planning. Brain CareNotes was pilot tested with 53 care partners of patients with ADRD [26,27] and was demonstrated to be usable and acceptable by care partners. Although not statistically significant, the pilot test also indicated that Brain CareNotes may be effective in reducing care partner burden and patients' BPSD.

The aim of this study is to test the effectiveness of Brain CareNotes in a larger-scale, randomized, parallel group clinical trial. Figure 1 depicts the study's conceptual model (shaded sections are investigated in the current trial) based on the best-practice models of ADRD care [28,29]. Like PREVENT and the Aging Brain Care clinic, we anticipate that Brain CareNotes will decrease care partner burden and patients' BPSD (study primary outcomes), while also lowering care partner depressive symptoms (study secondary outcome). It is hypothesized that improvements in these outcomes will also decrease the acute care use of both patients with ADRD and their care partners (secondary outcome). Care partner self-efficacy and social support are also being measured as the hypothesized primary social-behavioral mechanisms mediating the efficacy of Brain CareNotes [30,31].

Figure 1. I-CARE 2 conceptual model. BPSD: behavioral and psychological symptoms of dementia.

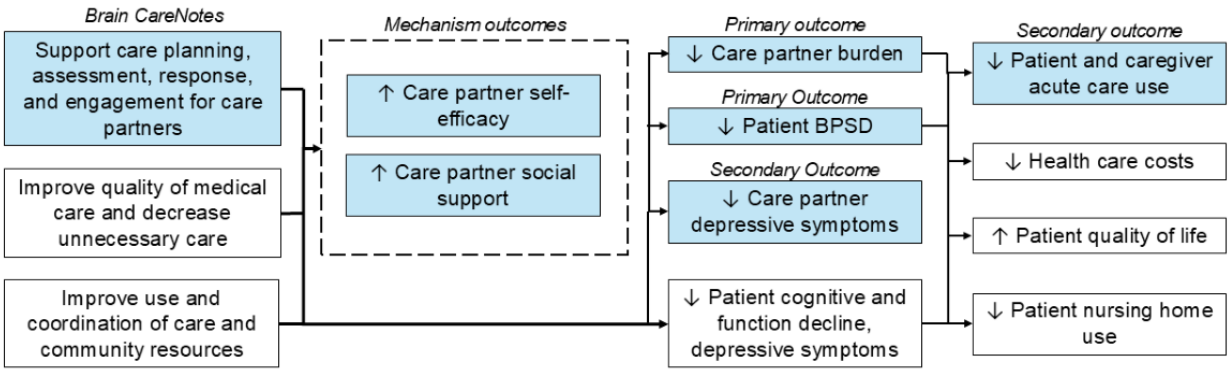

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Methods

Study Design

This study is a randomized controlled trial of 160 ADRD care partners to evaluate the real-world efficacy of Brain CareNotes on the primary outcomes of care partner burden and patients' BPSD; patients with ADRD are not enrolled in the study, only their care partners are enrolled. Participants will be recruited from 2 health systems, by word of mouth, and from community outreach efforts and randomized to receive either the Brain CareNotes intervention or an education-only attention control app. Participants will remain in the study for 12 months.

The primary objectives of this trial are to test the effect of Brain CareNotes on (1) care partner burden and (2) patients' BPSD after 12 months of use. Both primary outcomes will be assessed using the care partner-reported Neuropsychiatric Inventory (NPI) [32,33].

The secondary objectives are to test the effect of Brain CareNotes on (1) care partner depressive symptoms and (2) patient and care partner acute care use at 12 months. For care partner depressive symptoms, we will use the researcher-administered 9-item Patient Health Questionnaire-9 [34,35]. Acute care use data will be obtained from participant self-reports to identify both their and the patients' hospital and emergency room visits that occurred within 12 months of enrollment.

To measure the predicted social-behavioral mechanisms mediating the efficacy of Brain CareNotes, we will also measure (1) care partner self-efficacy and (2) care partner social support at baseline, 6 months, and 12 months. These are measured using the Revised Scale for Caregiving Self-Efficacy [36] and the Multidimensional Scale of Perceived Social Support (MSPSS) [37], respectively.

App use, acceptability, and usability will also be obtained from participant self-reports at 6 and 12 months. App usability will be assessed using the Simplified System Usability Scale [38], and app acceptability will be assessed using the Behavioral Intention Questionnaire [39-41]. To track participant and patient characteristics, we will collect demographics for both the participant and the patient and assess patient functional abilities and dementia stage by having the participant complete the Functional Activities Questionnaire (FAQ) [42] and the Quick Dementia Rating System (QDRS) [43]. We will also share an app use questionnaire consisting of 2 questions: (1) "Over the last six months, how often have you used the app?" (2) "Over the last six months, when you have accessed the app, how long have been on it?"

Study outcomes are summarized in Table 1.

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Table 1. I-CARE 2 study outcomes.

Outcome type and domain	Measure
Primary	
Care partner burden	NPI[a] caregiver distress subscore
Patients' BPSD[b]	NPI
Secondary	
Care partner depressive symptoms	PHQ-9[c]
Care partner and patient acute care use	Self-report hospital and emergency room visits
Mechanism	
Care partner self-efficacy	Revised Scale for Caregiving Self-Efficacy
Care partner social support	MSPSS[d]
Process	
App use	In-app activity logs (intervention only), app use questionnaire (both groups)
App acceptance	Behavioral Intention Questionnaire
App usability	Simplified SUS[e]
Patient characteristics	
Functional abilities	FAQ[f]
Dementia stage	QDRS[g]
Patient demographics	Participant report
Participant characteristics	
Care partner demographics	Self-report

[a]NPI: Neuropsychiatric Inventory.
[b]BPSD: behavioral and psychological symptoms of dementia.
[c]PHQ-9: 9-item Patient Health Questionnaire.
[d]MSPSS: Multidimensional Scale of Perceived Social Support.
[e]SUS: System Usability Scale.
[f]FAQ: Functional Activities Questionnaire.
[g]QDRS: Quick Dementia Rating System.

Setting and Participants

This study has a planned enrollment of 160 care partners of patients with ADRD. There will be 80 participants in the intervention arm and 80 in the attention control comparator. We will obtain lists of eligible care partners' contact information from partner health systems in Indiana, United States, including (1) primary care clinics at Indiana University Health (a nonprofit academic health care system), (2) Healthy Aging Transition Services clinics at Community Health Network (a nonprofit health care system), and (3) Eskenazi Health (a public health care system with special emphasis on vulnerable populations in Indiana). Care partners will be identified either by searching patient databases for patients with an ADRD diagnosis (the care partner will be their contact person) or by working with health care professionals at specific clinics to identify potentially eligible care partners. We will also distribute study information at conferences, in communities of interest, and by word of mouth (Multimedia Appendix 1). In addition to these recruitment efforts, our study is listed in databases such as ClinicalTrials.gov and Indiana University's All IN for Health study listings. These postings reach potential participants statewide, nationwide, and internationally. We will consider international participants on a case-by-case basis and take into account international research ethical standards.

Sample Size

The sample size was determined to achieve at least 80% power to detect group differences on both primary outcomes: care partner burden and BPSD. Adequate power required 64 participants per group (or N=128 in total) based on previous work [16]. Conservatively estimating 75% retention, a target total of 160 was set.

Intervention Description

The Brain CareNotes mobile telehealth app (Figure 2; [44]) is used by care partners for BPSD management. It includes remote communication with an external human support person—a care coach—as well as features for users to independently perform health-related activities (Textbox 1 [45,46]).

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Figure 2. Brain CareNotes features.

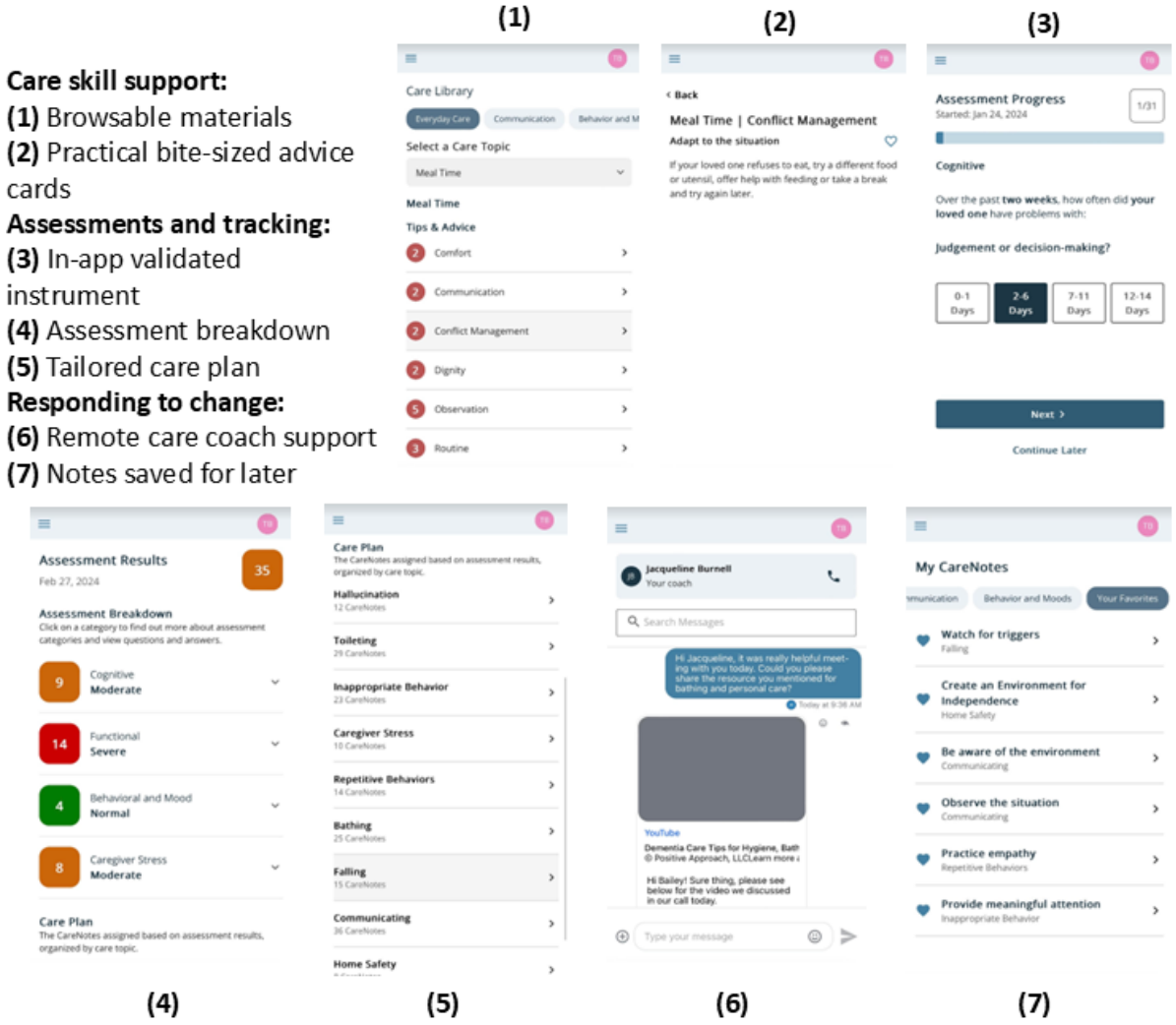

Textbox 1. Brain CareNotes mobile telehealth app features.

- Care skill support features: users have 24/7 access to written and visual materials on developing care skills. These materials cover a range of topics, including (1) care partner burden, (2) understanding the patient with memory loss, (3) exercise, (4) personal care, (5) behaviors, (6) safety, and (7) delirium.
- Care coach support: each care partner user is assigned to a personal care coach employed by the study team. Care coaches operate remotely using a mobile phone or computer-based secure and HIPAA (Health Insurance Portability and Accountability Act)–compliant portal. Care coaches perform the following tasks daily: (1) monitor, respond to, and initiate messages to and from Brain CareNotes users; (2) address user activity, including new assessments; and (3) schedule and conduct biweekly or monthly phone calls with the care partner.
- Assessments and tracking: every 2 weeks, users are prompted to self-administer the Healthy Aging Brain Care Monitor [45,46]. Once an assessment is completed, results are immediately displayed in easy-to-read, color-coded visualizations with interpretation of whether scores are normal, mild, moderate, or severe. Past measurements can be displayed on demand to compare recent scores and assess change over time. Care coaches receive daily notifications when an assessment was completed or a message was received from a care partner.
- Responding to change over time: Brain CareNotes has bidirectional secure messaging, allowing unpaid care partner users to communicate back and forth with the care coach or for the care coach to initiate a conversation. Moreover, when a care partner reports a patient or care partner symptom, the app generates a set of specific CareNotes associated with each reported symptom.

Participants randomized to receive Brain CareNotes will be sent a HIPAA (Health Insurance Portability and Accountability Act)–compliant link to create an app account on their personal device. This researcher-generated link is required to gain access to Brain CareNotes. If the participant does not have a mobile device meeting the minimum technical requirements, a smartphone with an unlimited network data plan from AT&T, along with unlimited text messaging and pooled voice minutes, will be provided for the duration of the study.

An unmasked research assistant will guide the participant through loading the Brain CareNotes app or attention control app on the participant's personal smartphone or on a smartphone provided by the study. The unmasked research assistant will

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provide written (and verbal, if requested) instructions on app use. They will provide as-needed technical assistance when requested in person or by phone and receive biweekly reminders to engage with their assigned app.

Description of the Attention Control App

Participants randomized to the attention control group will receive the Dementia Guide Expert app, an existing BPSD mobile app freely available in the Google and Apple app stores. It was developed by the ENGAGE-IL initiative at the University of Illinois at Chicago (Health Resources and Services Administration grant U1QHP28730). Dementia Guide Expert provides education only, with no interactive BPSD management support, coaching, assessment, or external response. It contains "evidence-based expert information on what dementia is, types, contributing factors, risks, symptoms, stages, diagnosis, tests, treatment, management, communication techniques, and links to resources and support services" [47]. We will use an attention control comparator to mimic the intervention group's use and access to technology, frequency and type of contact with research staff (ie, for installation and technical support), and expectancy of benefit [48].

Inclusion and Exclusion Criteria

Eligibility will be assessed using a screening questionnaire (Textbox 2).

Textbox 2. Inclusion and exclusion criteria.

Inclusion criteria

- Self-identified primary care partners of patients diagnosed with Alzheimer disease and related dementias (ADRD; at any stage) who are receiving primary care and community dwelling
- Participants are English literate

Exclusion criteria

- Participants cannot speak English
- They are involved in another trial that would prevent or interfere with study objectives (eg, another trial with an intervention aimed at reducing caregiver burden)
- Participants have a sensory or other impairment prohibiting the use of a mobile touchscreen device or another study activity (after correction).
- The patient with ADRD is a permanent resident of an extended care facility (eg, a nursing home, hospice facility, or locked memory unit of an assisted living facility).

Recruitment and Retention

We will obtain lists of eligible care partners' contact information from partner health systems or work with the health system to contact potentially eligible individuals as approved by the Indiana University Institutional Review Board (IRB), health system IRB (when applicable), and health system leadership. We will also obtain contact information for potential participants via word of mouth.

Research staff will call eligible care partners to determine if they are interested in study participation. Screening for eligibility will be conducted by phone or in person, when necessary, using a scripted questionnaire assessing eligibility. Data collection will occur remotely over the phone or videoconferencing software to minimize the burden on study participants. Research staff will also maintain engagement through regular contact with participants.

Ethical Considerations

This trial is approved by the Indiana University IRB (15749) and is registered on ClinicalTrials.gov (NCT05733520). Indiana University Health system has approved the study through their internal approval system (they do not have an independent IRB), and the Community Health Network IRB has approved the distribution of study recruitment materials in their clinics. All protocol modifications will be approved by the IRB before implementation.

Informed consent will be obtained from participants by a research staff member. Individuals will receive verbal and written information about consent and offered a chance to have all their questions answered. Each participant will provide verbal documented consent over the phone.

As there will be no researcher interaction with the patient with ADRD or direct data collection from them, patients with ADRD will not be considered study participants or consented into the study.

Participants may withdraw from or discontinue the study at any time, including following the death of the patient with dementia or their placement in an extended care facility, by contacting a member of the research team. Participants may also be withdrawn, with notification, from the study to protect data integrity or if there is a danger to their or the research team's safety related to continued participation. The risks of participation in this trial are expected to be minimal. Research personnel will be IRB approved and will have completed human subjects training, regular education, and updates on HIPAA regulations. Data will be stored in REDCap (Research Electronic Data Capture; Vanderbilt University), which is a widely used and secure browser-based, metadata-driven electronic data capture software solution and workflow methodology for designing clinical and translational research databases. Participants will be given a unique study ID to protect confidentiality and will not be identified in reports. Data collected through the Brain CareNotes app will be housed on HIPAA-compliant, secure cloud-based servers. Direct access

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to the app requires the user to input their email or phone number to which a one-time log-in code will be sent. After their first log-in, participants will also have the option to use their smartphone's built-in biometric authentication (eg, fingerprint or facial recognition) to access the app. The only changes to log-in protocols will be those that result in equal or better security.

Randomization

We will use a permuted block randomization scheme implemented within REDCap. Randomization will be stratified by recruitment source. Participants will be randomized after the baseline assessment by unmasked research staff. Research personnel masked to the randomization of individual participants will perform all primary and secondary data collection at the 6- and 12-month follow-ups. Participants will not be informed which app is the intervention and which is the control.

Assessments and Outcomes

A research staff member will perform a baseline assessment with the participant before randomization and follow-up assessments at 6 and 12 months, as shown in Table 2. The research staff completing primary and secondary data collection for the 6- and 12-month follow-up assessments will be masked to the treatment condition. The research staff completing usability and acceptance data will be unmasked to the treatment condition. All assessments will be scheduled and conducted remotely over the phone or with videoconferencing software (eg, Zoom; Zoom Communications, Inc) or in person when necessary. Participants will receive US $25 per assessment period with an additional US $25 bonus if they complete all 3 assessment periods (for up to US $100 for the entire study).

Table 2. Assessment completion schedule.

	Baseline	Month 6	Month 12
Patient functional abilities (FAQ[a])	✓		
Patient dementia stage (QDRS[b])	✓		
Patient Care partner demographics	✓		
Neuropsychiatric Inventory	✓	✓	✓
Care partner depressive symptoms (PHQ-9[c])	✓	✓	✓
Care partner acute care use		✓	✓
Patient acute care use		✓	✓
Care partner self-efficacy	✓	✓	✓
Care partner social support (MSPSS[d])	✓	✓	✓
App usability (SUS[e])		✓	✓
Behavioral Intention Questionnaire		✓	✓

[a]FAQ: Functional Activities Questionnaire.

[b]QDRS: Quick Dementia Rating System.

[c]PHQ-9: 9-item Patient Health Questionnaire.

[d]MSPSS: Multidimensional Scale of Perceived Social Support.

[e]SUS: System Usability Scale.

The primary outcomes assessed are (1) patients' BPSD and (2) care partner burden. The secondary outcomes assessed are (1) care partner depressive symptoms and (2) patient and care partner acute care use.

Care partner burden and patients' BPSD will be determined using the NPI [32,33], administered by research staff to the participant at baseline, 6 months, and 12 months. The NPI has been adopted by the Alzheimer's Disease Cooperative Studies Group [49,50] to obtain information in 12 behavioral areas including delusions, apathy, hallucinations, disinhibition, agitation, depression, aberrant motor behavior, anxiety, nighttime behavior, and euphoria [32,33]. The NPI has both content and concurrent validity as well as between-rater, test-retest, and internal consistency reliability [32].

Care partner depressive symptoms will be assessed using the PHQ-9 [34,35], administered by research staff at baseline, 6 months, and 12 months. The PHQ-9 is a 9-item depression scale that has good internal consistency and test-retest reliability as well as convergent, construct, criterion, procedural, and factorial validity for the diagnosis of major depression [34,35,51-53].

We will also ask participants to self-report any acute care use in the preceding 6 months by themselves or the patient with ADRD during the 6- and 12-month follow-up visits.

Additional Data Collection

To collect contextual information regarding the severity of the care recipient's dementia, we will assess the care recipient's functional abilities and dementia stage at baseline. The FAQ [42] and the QDRS [43] will be administered by research staff to the participant at baseline to assess the cognitive and functional status as well as the dementia severity of the patient with ADRD.

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We will also collect patient and participant demographics at baseline, including age, sex, gender, race, ethnicity, education level, income, and living situation.

In addition to the primary and secondary outcomes, we will also measure (1) care partner self-efficacy, (2) care partner social support, (3) app acceptance, and (4) app usability throughout the study.

Care partner self-efficacy will be measured using the Revised Scale for Caregiving Self-Efficacy [36], and care partner social support will be measured by the MSPSS [37]. They will be administered by research staff to the participant at baseline, 6 months, and 12 months. Both scales have been validated in ADRD care partner samples, have strong psychometric qualities yet are brief, and measure constructs hypothesized and shown to act as the mechanisms of action for other psychosocial ADRD care partner interventions [30,31].

For both the control and intervention apps, we will assess app acceptance and app usability with surveys at the 6- and 12-month follow-ups. We will assess usability using the Simplified System Usability Scale [38], a 10-item questionnaire answered on a 5-point Likert scale (from strongly disagree to strongly agree). Technology acceptance will be assessed using the Behavioral Intention Questionnaire, a 4-item questionnaire using a 7-point response scale from 0 (not at all) to 6 (a great deal) [39,40].

Analyses

At 12 months, the NPI Caregiver Distress scale will be compared between study groups using an analysis of covariance model with fixed effects for Brain CareNotes (vs attention control), health system, age, sex, race, recruitment source, and baseline values for NPI Caregiver Distress and NPI Total Score scales. For between-group comparisons, the difference in least squares means, corresponding SE, 2-sided 95% CIs, and 2-tailed *P* value will be derived from this analysis of covariance model and presented. Within-group change (least squares) means, corresponding SEs, 2-sided 95% CIs, and 2-tailed *P* values will also be presented. Standard model diagnostics will be performed to assess the validity of the proposed model; these diagnostics will include an examination of the residuals for normality, linearity, and homoscedasticity as well as testing for the significance of the intervention by baseline values interaction term to examine if intervention effect differs depending on the baseline levels of NPI Caregiver Distress or NPI Total Score scales.

The NPI Caregiver Distress scale will also be analyzed using a generalized linear mixed model (GLMM) [54,55] with an identity link function. GLMM allows us to analyze longitudinal data at each time point (baseline, 6 months, and 12 months) adjusting for multilevel dependencies within an individual (nested in the study group) and to explore additional covariates as mentioned earlier. Random intercepts, slopes, and fixed covariate effects will be estimated as needed. Time will be modeled as a continuous and categorical variable to model linear and nonlinear changes in care partner burden, respectively. The interaction between study group and time (ie, days between assessments) will be tested to determine if the rate of change in care partner burden is different between study groups. Standard model diagnostics will be performed to assess the validity of proposed models; these diagnostics will include examining the residuals for normality, linearity, and homoscedasticity and testing for the significance interaction term of the intervention by the baseline levels of the NPI Caregiver Distress and NPI Total Score scales. The variance-covariance structure of the random effects will be dependent on the variability among participants within groups. A preliminary test will be conducted to assess the significance of the homogeneity of variances [56] for within-group differences.

Analysis for patients' BPSD and care partner depressive symptoms will be the same as for care partner burden, using the NPI Total Score scale and PHQ-9, respectively.

Acute care use will be analyzed as a dichotomous outcome (ie, yes or no for at least 1 emergency department or hospital visit—cumulative incidence) using a generalized linear model, specifically, a log-binomial regression model with fixed effects for Brain CareNotes (vs attention control), strata, and covariates described earlier. For the between–study group comparison, the estimated risk ratio (relative risk), SE, 95% Wald CI, and *P* value will be presented. Standard model diagnostics to assess final model validity and assumptions will be implemented.

As in the primary analysis, we will use a GLMM [54,55] with a log link function to model cumulative incidence. In addition, a Poisson model (GLMM with log link function and offset variable for follow-up duration) will be examined to model the incidence rate of acute care visit counts during the 12-month follow-up period.

The potential for 3-way and 2-way interactions will be examined to identify participant characteristics associated with increased benefit of the intervention. If statistically significant interactions are observed, additional intervention effect results will be presented as subgroup analyses to highlight intervention effect modifiers on primary and secondary outcomes separately.

Measures related to improved psychosocial outcomes (ie, social support and self-efficacy) will be tested as a potential mediator or moderators of intervention effects. We will also examine baseline characteristics (eg, sex and age) related to psychosocial outcomes as potential intervention effect moderators.

Similarly, mechanism measures (MSPSS and Revised Scale for Caregiving Self-Efficacy) will be evaluated for their potential mediation effect on the primary and secondary outcomes. We will also use investigate patient characteristics (FAQ or QDRS) as potential moderator. All analyses related to study primary, secondary, and mechanism outcomes will be performed by researchers masked to treatment condition.

Linear regression and classification and regression trees will be used to examine the effect of intervention timing, participant ratings on usability, acceptance, and actual use of technology on intervention efficacy.

Handling Missing Data

Our general approach to missing data involves using all observed information while not exaggerating the precision of findings

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based on incomplete data [57,58]. All variables described for our final regression models will be used in our imputation procedures, that is, outcome measures, intervention condition, baseline outcome variables, strata variables (sex and race), age, and health system. The study group participant data will be imputed separately [59]. Multivariate imputation by chained equations methods using PROC MI and MIANALYZE procedures in SAS (SAS Institute) will be used to create multiple imputations for multivariate missing data (eg, continuous, binary, unordered categorical, and ordered categorical data) based on a fully conditional specification, where each incomplete variable is imputed by a separate model [60]. All missingness (nonresponse, attrition, or loss to follow-up) will be treated the same way for our benchmark analysis. Sensitivity analyses will be explored where reasons for attrition are accounted for in the generation of imputed covariate and outcome values. All variables (ie, outcome and baseline characteristics) described in the aforementioned models will be used for imputation procedures. The number of datasets to be imputed will be determined using the quadratic rule [61].

Data and Safety Monitoring Plan and Board

The principal investigators (PIs), along with the independent data and safety monitoring board (DSMB), will be responsible for data and safety monitoring during the duration of the study. PIs will work to ensure the daily safety of participants, while the DSMB will advise PIs and National Institute on Aging program staff on the safety of participants, potential study risk and benefits, the ethicality of the study, scientific integrity, and participant recruitment.

The study team will meet with PIs on average at least every 2 weeks to discuss the ongoing progress of the study, data collection, and participant safety. Any reportable events will be discussed and reported within 48 hours (about 2 days). PIs will work will research staff to submit a written report to the DSMB every 6 months, unless otherwise recommended by the DSMB. This report will include study updates on the following: participant recruitment, accrual, randomization, and retention; treatment delivery and fidelity; data collection and quality; any adverse events that have occurred; and any protocol deviations that have occurred.

All participant data will be compiled and stored in the study's HIPAA-compliant REDCap databases. Participant contact information will be collected from partner health system's electronic databases and manually entered by the data management team. Participants' survey responses, acute care use, and adverse events will be collected during assessment administration and entered directly into the database. App use will be estimated via app server queries that will be stored in IRB-approved databases. All data will be routinely reviewed for errors and cleaned by the data management team.

Results

From May 2023 to March 2025, we have enrolled 159 participants, and 42 have successfully completed the study. Data analysis will begin once the final participant has completed their involvement in the study (estimated in spring 2026), and we anticipate results of these analyses will be published in late 2026 or early 2027. Results will be available to participants and the public on the study's ClinicalTrials.gov (NCT05733520) page, and participants will be reminded of that link 1 month before their completion of the study.

Discussion

Anticipated Findings

This paper presents the protocol for a randomized controlled trial to test the efficacy of a mobile app to support care partners of patients with ADRD in managing BPSD. We hypothesize that, relative to the education-only attention control, care partners randomized to Brain CareNotes will have lower caregiver burden and will report lower care recipient BPSD. We also anticipate that care partners in the intervention group will report lower depressive symptoms, lower acute care use, increased self-efficacy, and increased social support.

Supporting care partners of patients with ADRD is a public health imperative [62]. BPSD occur commonly among patients with ADRD, and care partners often lack support for BPSD management [2-5], meaning there is a significant need for interventions to support care partners in this area. Mobile telehealth interventions—such as the intervention described in this study—are scalable solutions with the possibility of supporting large numbers of care partners in a variety of situations, for a lower cost. Brain CareNotes has the potential to be a scalable, effective intervention for BPSD management as it transforms other evidence-based interventions into a mobile app with the potential to be used by large numbers of care partners without constraints on geography, time of day, or clinic access.

Limitations and Potential Challenges

There are some limitations and potential challenges to this study. First, while we have had success in recruiting participants on time, there are concerns about retaining participants in the study for the entire 12-month duration. Sample size was calculated assuming a 75% participant retention rate, as the 6-month pilot had 85% of participants complete the study. However, the likelihood of care recipient death or nursing home placement increases with the duration of the study, and this may impact our ability to retain as many participants as previously anticipated. In addition, our team does not have the ability to control the "dosing" of the intervention that participants receive, as they are able to use Brain CareNotes at their own discretion. This means that those randomized to the intervention group likely have differing app use patterns, which could affect its efficacy. While this is reflective of real-world use patterns of commercially available mobile apps, we are attempting to control this by sending app use reminders to participants in both the intervention and control groups every 2 weeks. Currently, Brain CareNotes is a website optimized for mobile viewing, so it is compatible with all mobile devices that can access the internet through a browser. In the future, it could be adapted into an app and made widely available on public app marketplaces (eg, Apple App Store and Google Play Store) for download onto a mobile device. While there are costs associated with Brain CareNotes once built (eg, technology maintenance

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and security and care coach compensation), it is likely that these costs are lower than other types of interventions. In addition, a mobile telehealth intervention like Brain CareNotes can remove some barriers to care partners (eg, geography) accessing BPSD support.

Conclusions

Brain CareNotes distills the Aging Brain Care Model into a mobile app, and its historical BPSD tracking and care coach support features make it a unique mobile intervention to support care partners in managing BPSD. Due to the scalability of mobile health interventions, if Brain CareNotes is shown to be effective in reducing caregiver burden and patients' BPSD, it has the potential for widespread adoption to support a large number of ADRD care partners.

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Data Availability

Access to the study data will be facilitated in collaboration with the Global Alzheimer's Associated Interactive Network (GAAIN). As a GAAIN Data Partner, data from this study will be shared in aggregate through the GAAIN portal [63].

Authors' Contributions

JRH contributed to drafting, reviewing, and editing the manuscript; project administration; and supervision. BG and MJR contributed to drafting the manuscript, with BG also involved in reviewing and editing the manuscript and investigation and MJR in project administration and supervision. LG-A handled data curation, formal analysis, software, and manuscript review and editing. RSZ contributed to methodology and manuscript review and editing. ZB and JB participated in drafting the manuscript and conducting the investigation. EJJ secured funding. MB contributed to conceptualization, methodology, supervision, and funding acquisition. RJH was involved in conceptualization, methodology, project administration, supervision, funding acquisition, and manuscript review and editing.

Conflicts of Interest

MAB serves as a chief scientific officer and cofounder of BlueAgilis and the chief health officer of Mozyne Health, Inc. He has equity interest in Blue Agilis, Inc and Mozyne Health, Inc. He sold his equity in Preferred Population Health Management LLC and MyShift, Inc (previously known as RestUp, LLC). He cofounded Digicare Realized that was folded without any financial gain. He serves as an advisory board member or consultant for NeuroX, Emirates Health Services; Eli Lilly and Co; Eisai, Inc; Merck & Co Inc; Biogen Inc; and Genentech Inc. These conflicts have been reviewed by Indiana University and have been appropriately managed to maintain objectivity. RJH is founding co-owner of CareNotes, LLC.

Multimedia Appendix 1
Study information sheet.
[DOCX File , 35 KB - resprot_v14i1e73387_app1.docx]

Multimedia Appendix 2
Grant peer review comments from ZAG1 ZIJ-D (M2) - National Institute on Aging Special Emphasis Panel Dementia Care (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 106 KB - resprot_v14i1e73387_app2.pdf]

Multimedia Appendix 3
CONSORT-eHEALTH checklist (V 1.6.1).
[PDF File (Adobe PDF File), 6553 KB - resprot_v14i1e73387_app3.pdf]

Multimedia Appendix 4
SPIRIT checklist.
[PDF File (Adobe PDF File), 118 KB - resprot_v14i1e73387_app4.pdf]

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Abbreviations

ADRD: Alzheimer disease and related dementias
BPSD: behavioral and psychological symptoms of dementia
DSMB: data and safety monitoring board
FAQ: Functional Activities Questionnaire
GAAIN: Global Alzheimer's Associated Interactive Network
GLMM: generalized linear mixed model
HIPAA: Health Insurance Portability and Accountability Act
IRB: Institutional Review Board
MSPSS: Multidimensional Scale of Perceived Social Support
NPI: Neuropsychiatric Inventory
PHQ-9: 9-item Patient Health Questionnaire
PI: principal investigator
QDRS: Quick Dementia Rating System
REDCap: Research Electronic Data Capture

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Protocol

Leveraging Aging Service Providers to Support Internet-Based Cognitive Behavioral Therapy for Depression in Homebound Older Adults: Protocol for a Type 1 Hybrid Effectiveness-Implementation Randomized Controlled Trial

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Abstract

Background: Homebound older adults face a high burden of depression and substantial barriers to accessing mental health treatments. Few interventions address their specific needs. Empower@Home, an internet-based cognitive behavioral therapy program, was co-designed with stakeholders and tailored to older adults. The program includes 9 self-paced online sessions to be completed within 12 weeks, augmented by telephone-based human support. Efficacy studies have demonstrated its acceptability and effectiveness in reducing depression when supported by trained research staff. However, its real-world effects and feasibility for integration into community aging service settings remain unknown.

Objective: This study aims to assess the real-world effectiveness of Empower@Home integrated into aging services, using nonclinician agency staff as coaches to support older adults. A secondary objective is to evaluate the implementation process through a qualitative process evaluation.

Methods: The study is a type 1 hybrid effectiveness-implementation trial with a 2-arm randomized controlled design. A total of 256 homebound older adults will be recruited from 3 community aging service agencies, and agency staff will be trained as coaches to support internet-based cognitive behavioral therapy use. Participants in the treatment group will receive Empower@Home immediately, while the control group will receive biweekly friendly calls and enhanced care as usual, including the provision of psychoeducational materials and usual care. Outcomes will be assessed at baseline, after the intervention (12 weeks), and at 2 follow-up points (24 and 36 weeks). The primary outcome is a change in depressive symptoms as measured by the 9-item Patient Health Questionnaire. Secondary outcomes include changes in social isolation, health-related quality of life, disability burden, pain intensity, and anxiety symptoms.

Results: Institutional review board approval was obtained in August 2024, and recruitment began in October 2024. Recruitment is expected to conclude by April 2028. Upon trial completion, the effectiveness of Empower@Home on primary and secondary outcomes will be analyzed.

Conclusions: This study will provide critical insights into the real-world effectiveness of Empower@Home. If successful, this study will provide a scalable, cost-effective model for integrating technology-assisted mental health treatments into community aging services, thereby improving access to care for an underserved, hard-to-reach population.

Trial Registration: ClinicalTrials.gov NCT06584422; https://clinicaltrials.gov/study/NCT06584422

International Registered Report Identifier (IRRID): DERR1-10.2196/72953

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(JMIR Res Protoc 2025;14:e72953) doi:10.2196/72953

KEYWORDS

depression; older adults; homebound; eHealth; mHealth; digital mental health; internet intervention; internet-based cognitive behavioral therapy; iCBT; implementation effectiveness; aging services

Introduction

Background

Depression among homebound older adults is a critical yet often overlooked public health issue [1,2]. Research has shown that 50% of homebound older adults experience clinically significant depression. Of these, 14% face major depression, a rate 7 times higher than that of their non–homebound counterparts [3,4]. Regardless of its severity, untreated and undertreated depression has serious health consequences for older adults. It can increase the risk of suicide, physical disabilities, cognitive impairment, hospitalizations, and premature mortality [5-8]. Compounding these challenges, homebound older adults often face substantial access barriers to mental health services due to socioeconomic disadvantages and physical disabilities [9-11].

Late-life depression can be effectively treated with antidepressants, psychotherapies, or a combination of both [12,13]. However, the aging process is often associated with an increased risk of chronic illness, functional limitations, social isolation, and reduced coping resources. Psychotherapies can be particularly useful as they address symptoms and teach coping skills to better address these challenges [10,14]. Unfortunately, few older adults receive psychotherapy treatments due to stigma, a shortage of trained mental health providers, and systemic barriers, including inadequate insurance coverage for subthreshold depression [15-17]. Without proper treatment, depression and physical disability can reinforce each other, ultimately worsening both health and overall quality of life [6].

Aging Network agencies have unmatched reach to the target population, covering nearly every community in the United States and serving more than 8 million older Americans annually. Consequently, integrating mental health treatment into the Aging Network holds significant potential to increase access to mental health services for homebound older adults [10]. Previous research has already demonstrated that nonclinician aging service providers can be effectively trained to deliver a range of depression interventions, including those based on behavioral activation, psychoeducation, problem-solving, and depression self-management [18-25]. For example, Choi et al [26] showed that aging service providers could effectively administer behavioral activation via teleconference [27]. However, depending on these providers to directly administer structured treatments poses several challenges, such as limited expertise in depression care, heavy caseloads, and frequent turnover.

Leveraging digital mental health interventions (DMHIs), particularly internet-based cognitive behavioral therapy (iCBT), is a promising solution to these challenges. When paired with human support, iCBT is as effective as face-to-face CBT [28-30]. Through packaged online lessons, iCBT consistently delivers core therapeutic techniques to patients. Implementing iCBT in aging service agencies shifts providers from direct treatment delivery to supportive roles, thereby reducing training demands and time commitments without compromising CBT fidelity. This makes iCBT a more feasible and scalable approach.

Despite their potential, iCBT programs face significant challenges with user engagement, particularly among older adults. Completion rates have been low, with an average of 17% in self-guided iCBT [31] and 65% in human-support programs [32]. For homebound older adults, engagement barriers are often exacerbated by usability challenges, including text-heavy, academic content and interfaces that are not designed with older users in mind. For example, in our evaluation of an evidence-based iCBT program, only 1 in 4 homebound older adults completed the program, even with weekly in-home support [33]. These findings underscore the urgent need for iCBT programs tailored to older adults.

Although several iCBT programs have been designed to address older adults' needs, none are widely available to US consumers [34-36]. To address this gap, we developed Empower@Home, an iCBT program explicitly tailored for older adults. Created in collaboration with key stakeholders, the program uses plain language, integrates text with visuals, incorporates age-relevant examples, and features a simplified user interface. Preliminary studies found Empower@Home to have superior usability compared to other iCBT programs. In addition, feasibility trials demonstrated exceptional program completion rates and significant reductions in depressive symptoms when participants were supported by lay coaches [37-40]. However, it remains unclear whether Empower@Home will be equally effective when integrated into real-world community aging services and supported by aging service providers.

Objective

The primary aim of this study is to evaluate the real-world effectiveness of Empower@Home, an iCBT program tailored to older adults with depression when supported by aging service providers. A mixed methods approach will be used, incorporating structured surveys and semistructured interviews to examine intervention outcomes and underlying mechanisms. The secondary aim is to identify implementation barriers and facilitators through a qualitative process evaluation. This study builds on previous efficacy trials demonstrating the acceptability and effectiveness of Empower@Home. It takes a critical next step by transitioning the intervention from an academic setting into community-based aging services, thereby assessing its real-world impact and the feasibility of training aging service providers to act as coaches or human supporters for iCBT.

Intervention Model

The design of Empower@Home incorporates user-centered and community-participatory research principles [37]. The

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intervention was designed with input from homebound older adults, therapists, and more than 30 aging service providers, undergoing multiple iterative refinements based on testing and feedback [37-39]. Empower@Home consists of 9 sequenced online lessons, each lasting 20 to 25 minutes, featuring didactic content delivered through short videos, voice-over instructions, interactive exercises, and motivational quotes. These lessons are grounded in evidence-based CBT manuals [41-43] and focus on core CBT skills: "Doing Tools" for behavioral activation and problem-solving, "Thinking Tools" for cognitive restructuring, "Feeling Tools" for relaxation and mood monitoring, and "Communication Tools" for effective communication [41].

The content is specifically tailored to the unique needs of homebound older adults, incorporating age-relevant examples informed by stakeholder input and prior research [44-46]. Each lesson integrates a mini animated story centered on a homebound older woman, Jackie, facing common health challenges within the target demographic. According to persuasive design principles, interactive, engaging, and immersive interventions are more effective in promoting behavioral change [45]. Entertainment education theories further suggest that narratives can reduce resistance to behavioral modifications by fostering emotional engagement and personal reflection [46]. Jackie's story encourages users to identify with the character, adopt story-aligned behaviors, and improve treatment engagement. Qualitative interviews with past participants indicated mixed identification with the storyline but suggested that it enhanced engagement [40].

Aligned with best practices for age-friendly digital design [47], the program features a streamlined interface with large buttons, text-labeled icons, high-contrast colors, and intuitive navigation. Online lessons are complemented by a large-print workbook containing session summaries, additional psychoeducational materials, wellness resources, and home practice instructions. Designed with older adults in mind, the workbook features large text, images of diverse older adults, and a visually appealing layout. Prior studies highlighted the workbook's importance, noting its familiar format, aesthetic appeal, and utility as a convenient reference for completing and revisiting exercises and lessons [40].

To address real-time support needs and technological challenges, we introduced "Empower Coaches," laypersons who provide weekly support calls to enhance program personalization, guided by the Efficiency Model of Support [37]. Our target demographic favors this human interaction over purely automated systems. Supported iCBT programs consistently demonstrate better engagement and clinical outcomes than those without support [30-32]. While many iCBT programs rely on therapists with specialized mental health qualifications, using aging service providers as iCBT supporters offers an innovative and practical solution. This strategy leverages aging service providers' existing relationship with the target population and aligns with the staffing structures of aging service agencies, ensuring widespread and accessible support. Prior research has successfully trained aging service providers to administer psychotherapy and multicomponent interventions directly [18-25], suggesting that training aging service providers as coaches is also likely feasible.

Our approach focuses on equipping service providers to support iCBT, a role that does not require extensive specialized training and is less time-intensive than acting as lead interventionists. Our previous efficacy studies showed that Empower@Home, supported by undergraduate and graduate students in psychology, social work, or related fields, was acceptable and efficacious based on both qualitative and quantitative outcomes [38,40]. However, no studies have examined the feasibility of training aging service providers such as case workers and community health workers to support iCBT or integrating iCBT into aging service settings. This study aims to fill that gap.

Our team developed a structured coaching guide based on experiences from pilot studies. The guide outlines coaching tasks, provides tips, and includes CBT teaching points aligned with session content. Coaches conduct weekly check-ins, which can be completed over the phone or in person, allowing flexibility and greater efficiency. For example, coaches with scheduled home visits can incorporate coaching sessions into the visit without requiring additional scheduling. On the basis of prior research and our experience, coaching support typically includes providing motivation, encouragement, homework review, assistance with applying tools, and technical support. In line with the efficiency model of support [48], coaches are encouraged to personalize their approach for each client—for instance, offering to complete part of the program alongside an unmotivated participant. The length of coaching sessions can be adapted to meet participants' needs and preferences, ranging from 5 minutes to an hour.

Coach training includes reviewing all Empower@Home online sessions (approximately 4-5 hours), supplemented with didactic videos introducing each session and its techniques. In addition, coaches attend a live, in-person training workshop lasting approximately 4 hours, where they observe demonstrations of coaching sessions and receive clarification on operating logistics. The total training requirement is approximately 9 to 10 hours per coach. Biweekly coach support meetings are offered throughout the study to provide ongoing support. While previous studies limited the intervention period to 10 weeks, this project extends it to 12 weeks to accommodate the frailty of the target population, who may face additional barriers such as hospitalizations that could delay program completion.

Methods

Preliminary Study

The procedures outlined in this protocol, including recruitment, assessments, coaching call logistics, and device management, have been tested and refined through feasibility and efficacy studies conducted in 2022 to 2023. A pilot randomized controlled trial (RCT) with 70 participants, supported by trained research assistants, demonstrated that the program was significantly more effective in reducing depressive symptoms compared to biweekly friendly calls, with a medium between-group effect size (Cohen d=0.7) [38]. Program adherence was high, with approximately 90% of participants

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completing all sessions within 10 weeks [39]. Participants reported high satisfaction with the program, and themes from qualitative interviews supported the quantitative findings, further highlighting the program's positive effects [40]. However, positive findings from small-scale pilot studies may not always translate into comparable outcomes in real-world settings or larger studies. This trial evaluates whether these promising results can be replicated in a community-based, real-world implementation context.

Study Setting

The University of Michigan will be the primary study site, collaborating with community agencies serving older adults. All participants will be ≥60 years and are expected to be predominantly low-income individuals. They will complete the intervention at home, with all assessments and technological support provided remotely by phone.

Eligibility Criteria

To participate in the trial, individuals must be at least 50 years old, eligible to receive services at the participating community agency, and have mild or greater depressive symptoms, defined as a score of ≥8 on the 9-item Patient Health Questionnaire-9. Participants will be excluded if they meet any of the following criteria: (1) probable cognitive impairment, indicated by a score of ≥12 on the Blessed Orientation-Memory-Concentration Test [49]; (2) non-English speakers; (3) moderate to high suicide risk, as assessed by the Columbia-Suicide Severity Rating Scale [50]; (4) terminal illness with a life expectancy of fewer than 6 months or unstable physical health; (5) visual impairment that prevents the use of a screen, even with corrective measures (self-reported); (6) current or recent substance use, as indicated by a score of ≥2 on the CAGE-Adapted to Include Drugs Substance Abuse Screening Tool [51]; (7) diagnosis of a psychotic disorder (self-reported); and (8) active psychotherapy (more than once a month) or initiation of new therapy within the past 3 months. The study will not exclude participants based on race or gender. While completing the intervention requires a tablet and internet access, participants are not required to have their own. Those without a tablet or internet access will be provided with both at no cost for the active intervention period.

Recruitment and Compensation

Participants will be recruited on a rolling basis, primarily through referrals from participating community agencies. Two of these agencies are Area Agencies on Aging (AAAs), which may refer existing clients enrolled in their programs, such as case management, caregiver services, or Meals on Wheels. In addition, AAAs may refer new clients or individuals seeking information from the agency, as providing information is a key role of AAAs.

To support participant recruitment, participating agencies receive a 20-minute online training covering eligibility criteria and referral procedures. The research team also designed a prescreening form that includes the PHQ-9 and additional brief screening items to improve referral accuracy. On the basis of prior experience, approximately half of the individuals passing the prescreening will qualify for the study. All prescreening and referral forms are hosted online and optimized for efficiency.

After receiving referrals, study personnel will contact potential participants by phone to complete a more detailed eligibility screening. This initial screening typically takes 20 minutes but may take longer if a complete suicidal ideation assessment is needed. Participants who agree to participate will provide recorded verbal consent, while those who decline will be referred back to their case managers or agency when feasible. In addition, participants can self-refer for eligibility screening through advertisements on social media platforms and by word of mouth.

Qualified participants will be compensated up to US $140, including US $30 for each survey assessment and US $20 for the qualitative interview. Compensation is prorated based on completed assessments (eg, participants completing only the baseline assessment will receive US $30).

Study Design and Randomization

Eligible and consented participants will be randomly assigned to the treatment or control group in a 1:1 ratio. Block randomization, stratified by participating community agencies, will be used to assign participants. Each site has 9 blocks of 10 participants. The study statistician (JNJ) created the randomization sequence, and sealed envelopes were prepared by a research assistant who was not involved in the randomization process. The lead project coordinator will conduct the randomization using these sealed envelopes.

Both groups will follow the same assessment schedule, including a comprehensive baseline assessment, a postintervention or control assessment at 12 weeks, and follow-up assessments at 24 and 36 weeks. Both groups will continue to receive usual care from their referring agency. Participants in the control group will receive the intervention after completing their final follow-up assessment. Due to the nature of the intervention and study design, blinding participants and evaluators to group assignments is not feasible. However, assessors will remain blinded to group allocation whenever possible.

Control Condition

The attention control condition provides participants with a comparable amount of phone contact as the intervention group, including 15- to 25-minute companionship calls ("friendly calls") every other week. These calls are conducted by research team members and focus on providing social interaction and support without introducing CBT-related content or structured therapeutic interventions. To ensure safety and align with the biweekly PHQ-9 assessments conducted in the intervention group as a part of the online program, participants in the control group will complete a telephone-administered PHQ-9 assessment every 2 weeks as a part of the friendly calls. In addition, participants in the control group will continue receiving regular social services from the participating agency. They will receive a psychoeducational handout containing information about depression and a list of community resources for further support.

Safety Monitoring and Discontinuation

Participant safety is a top priority in this study, with procedures in place to monitor and address any significant clinical changes.

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Biweekly assessments of depressive symptoms using the PHQ-9 serve as both clinical outcome measures and safety checks. A clinically significant worsening of symptoms, defined as a 5-point or greater increase in the PHQ-9 from baseline, triggers a multistep review process. This process includes automated alerts in our electronic data-capturing system and in-depth risk assessments by the project coordinator, a licensed clinical social worker. While such occurrences are rare—less than 3% of participants experienced a 5+ point increase during pilot studies—persistent or worsening symptoms over 4 weeks may lead to discontinuation. Similarly, any new or increased endorsement of suicidal ideation on item 9 of the PHQ-9 prompts immediate follow-up using the Columbia-Suicide Severity Rating Scale, following an established protocol to ensure participant safety.

Participants may also be withdrawn from the study if their physical health conditions worsen unrelated to the intervention, compromising their ability to participate safely (eg, repeated hospitalizations). Such decisions are informed by input from the participant, agency coaches, and family members. In all cases of withdrawal, the study team collaborates with partnering community agencies to connect participants to appropriate treatment, including pharmacotherapy and locally available psychosocial resources. Final discontinuation decisions will be made by the core research team managing human participants, including the principal investigator and the 3 project staff.

Data Management and Storage

All study data collected through surveys or structured observations will be entered directly by project staff into REDCap (Research Electronic Data Capture; Vanderbilt University) [41]. Agency coaches will also complete a structured coaching form hosted on REDCap. During the active intervention, participants will complete the PHQ-9 every other week as part of the online therapy lessons. These assessment data will be securely stored in a HIPAA (Health Insurance Portability and Accountability Act)–compliant database hosted by the University of Michigan. Recordings of qualitative interviews will be stored on Dropbox in compliance with the University of Michigan's safe computing guidelines for handling sensitive research data. In addition, meeting minutes and other program administrative records, which do not contain participant identifying information, will be stored on Google Drive.

Measures

Primary Clinical Outcomes

All key outcome measures are summarized in Table 1. The primary outcome is changes in depressive symptoms, assessed using the PHQ-9, a widely used screening tool in primary care, community agencies, and iCBT studies [52]. Each participant will complete the PHQ-9 up to a total of 9 times: at screening (T0), postintervention at 12 weeks (T2), and follow-up assessments at 24 weeks (T3) and 36 weeks (T4), along with up to 5 biweekly assessments between baseline (T1) and postintervention period (T2). For participants in the intervention group, PHQ-9 assessments will be embedded within the online program and completed during sessions 1, 3, 5, 7, and 9. Control group participants will complete these assessments via telephone at corresponding intervals. In addition, the 7-item Hamilton Depression Rating Scale (HAMD; HAMD-7) will be used as a secondary measure to evaluate the intervention's clinical effectiveness. The HAMD-7, an abbreviated version of the HAMD-17, is shown to be equally effective in assessing remission in patients with major depressive disorder [53]. It was chosen to reduce participant burden and to enhance the feasibility of telephone-based administration. The participant flowchart is presented in Figure 1.

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Table 1. Key study measures and time points.

Measurement domain	Instrument	Baseline (T1)	Biweekly	Post (T2)	Follow-up (T3)	Follow-up (T4)
Primary clinical outcomes						
Depressive symptoms	PHQ-9[a]	✓	✓	✓	✓	✓
Depressive symptoms	HAMD-7[b]	✓		✓	✓	✓
Secondary clinical outcomes						
Anxiety	GAD-7[c]	✓		✓	✓	✓
Social isolation	DSSI-10[d]	✓		✓	✓	✓
Health-related quality of life	EQ-5D-5L	✓		✓	✓	✓
Disability burden	WHODAS 2.0[e]	✓		✓	✓	✓
Pain	PEG[f]	✓		✓	✓	✓
Treatment mechanisms						
CBT[g] skills acquisition	CBTSQ[h]	✓		✓		
Behavioral activation	BADS-SF[i]	✓		✓		
Dysfunctional attitudes	DAS-SF2[j]	✓		✓		
Social engagement	SEAQ[k]	✓		✓		
Psychological flexibility	AAQ-II[l]	✓		✓		
Digital alliance	D-WAI[m]			✓		
Narrative engagement	NES[n]			✓		
Character identification	EDI[o]			✓		
Coaching fidelity	Study-specific			✓		
Autonomy	BNSQ-S[p]	✓		✓		
Feasibility and acceptability						
Treatment adherence	Session completion			✓		
Treatment acceptability	TEI[q]			✓		

[a]PHQ-9: 9-item Patient Health Questionnaire.
[b]HAMD-7: 7-item Hamilton Depression Rating Scale.
[c]GAD-7: 7-item Generalized Anxiety Disorder.
[d]DSSI-10: 10-item Duke Social Support Index.
[e]WHODAS 2.0: WHO Disability Assessment Schedule 2.0.
[f]PEG: Pain, Enjoyment of Life and General Activity.
[g]CBT: cognitive behavioral therapy.
[h]CBTSQ: Cognitive-Behavioral Therapy Skills Questionnaire.
[i]BADS-SF: Behavioral Activation for Depression Scale–Short Form.
[j]DAS-SF2: Dysfunctional Attitudes Scale–Short Form 2.
[k]SEAQ: Social Engagement and Activities Questionnaire.
[l]AAQ-II: Acceptance and Action Questionnaire.
[m]D-WAI: Digital Working Alliance Inventory.
[n]NES: Narrative Engagement Scale.
[o]EDI: Identification with Characters Scale.
[p]BNSQ-S: Basic Needs Satisfaction in General Scale.
[q]TEI: Treatment Evaluation Inventory.

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Figure 1. Participant flow. *Accounting for a cumulative 20% attrition rate from baseline to T4.

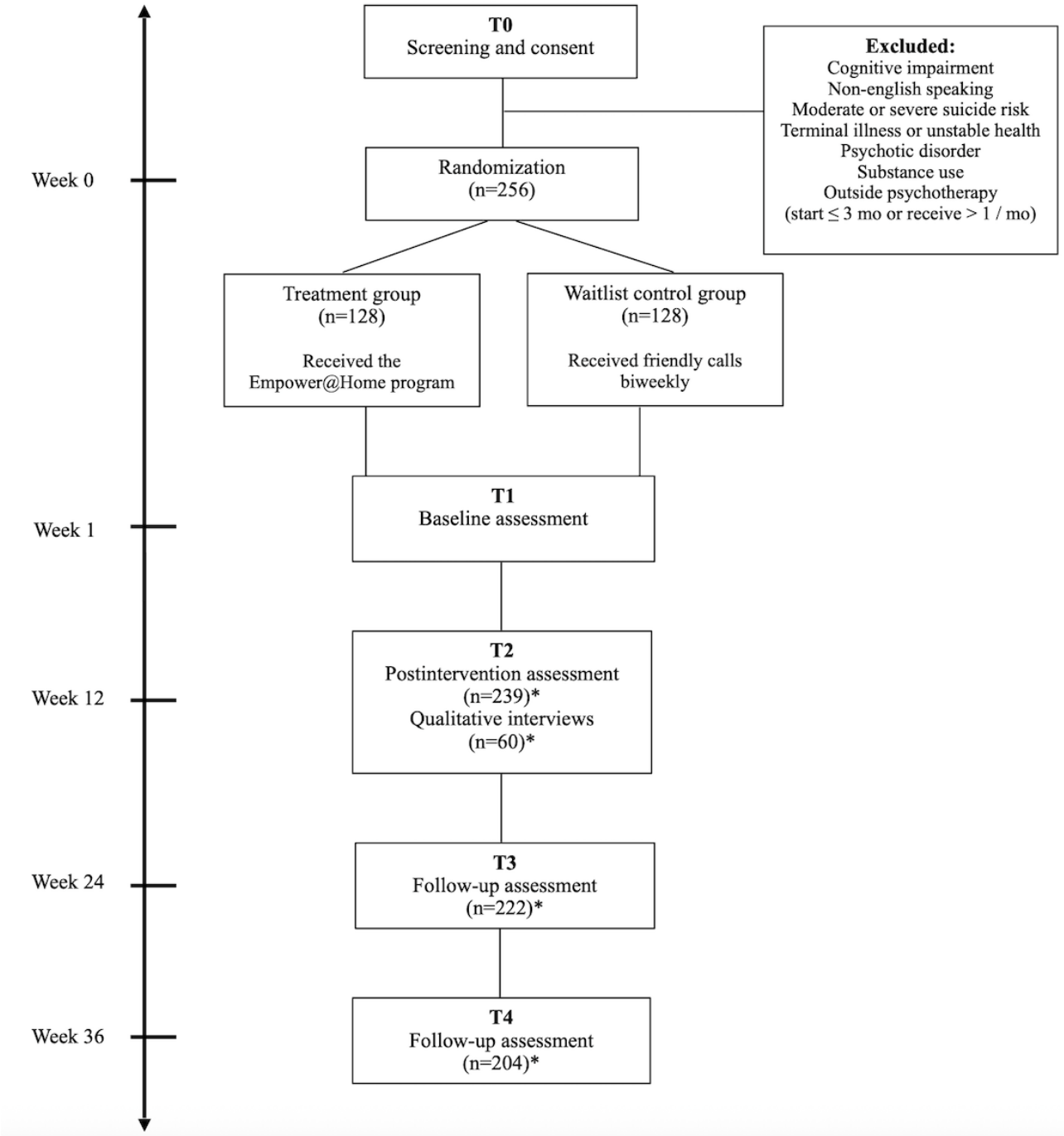

Secondary Clinical Outcomes

The secondary clinical outcomes, listed in Table 1, include changes in anxiety, social isolation, quality of life, disability burden, and pain severity, assessed at 4 time points (T1-T4). These outcomes were chosen for their significant impact on the quality of life of older adults with chronic illnesses and disabilities, aligning with prior research on geriatric depression treatments [20,54].

Anxiety will be assessed using the Generalized Anxiety Disorder-7, a measure that has been validated in older adults [33,55]. Participants answer 7 questions probing the frequency of their anxiety symptoms rated on a 4-point Likert scale ranging from “not at all” to “nearly every day.” The Generalized Anxiety Disorder-7 scale has demonstrated 89% sensitivity and 82% specificity in detecting generalized anxiety disorders in primary care patients [37].

Social isolation will be assessed using the Duke Social Support Index 10-item scale, which evaluates social interaction and satisfaction with social support in older adults [56].

Quality of life will be measured using the EQ-5D-5L scale [57]. Participants rate their ability to perform tasks in 5 domains—mobility, self-care, usual activities, pain, and anxiety or depression—on a 5-point Likert scale ranging from “no problem” to “extreme problem or unable.” Responses will be converted into utility values using a US population–specific algorithm [58].

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Disability burden will be assessed using the WHO Disability Assessment Schedule 2.0 12-item survey, which examines difficulty performing activities across 6 domains: cognition, mobility, self-care, getting along with people, life activities, and societal participation. Responses range from "none" to "extreme or cannot do" [59].

Pain severity will be evaluated with the Pain, Enjoyment of Life and General Activity scale, a 3-item measure that assesses pain intensity and its interference with enjoyment of life and general activity. Each item is rated on a scale from 0 to 10 [60].

Treatment Mechanisms

Overview

We hypothesize that the intervention operates through multiple mechanisms grounded in CBT, entertainment persuasion, and self-determination theories. CBT principles suggest that depression stems from maladaptive thoughts and behaviors; thus, improved CBT skills, behavioral activation, and reduced dysfunctional attitudes are expected to mediate treatment effects [61]. The animated Jackie storyline aims to enhance engagement, fostering a connection with the narrative and program [46]. In addition, the coach-client rapport, aligned with the common factors theory, is hypothesized to mediate outcomes through the therapeutic bond and satisfaction with coaching [62]. Self-determination theory highlights the importance of autonomy, competence, and relatedness in fostering motivation and well-being [63].

CBT-Related Factors

Jacob et al [64] developed the 16-item Cognitive-Behavioral Therapy Skills Questionnaire to assess the use of CBT skills such as cognitive restructuring and behavioral activation. We modified the scale to 14 items by removing 2: "Identify stressors that led me into treatment," as participants were not recruited from clinical settings, and "Catch myself when I jump to conclusions," as the preprogram assessment occurs before participants are introduced to this concept, enhancing reliability. Item wording for the remaining 14 items was simplified for readability, for example, "Identify risk factors for relapse" was revised to "Identify warning signs that trigger bad mood, depression, or anxiety." Participants rate their frequency of activities such as organizing plans, motivating themselves, and socializing on a 5-point Likert scale from "never" to "always."

The 9-item Behavioral Activation for Depression Scale–Short Form evaluates activation and avoidance behaviors consistent with Behavioral Activation theory [65]. Each item is rated on a 7-point scale from 0 ("not at all") to 6 ("completely"), with higher scores reflecting greater activation.

The 9-item Dysfunctional Attitudes Scale–Short Form 2 is a self-report measure for assessing the presence and intensity of rigid or maladaptive beliefs [66]. We adapted the original 4-point Likert scale ("totally agree," "agree," "disagree," and "totally disagree") to a 5-point Likert scale ranging from "strongly disagree" to "strongly agree" to be consistent with the other measures in the study.

The 10-item Social Engagement and Activities Questionnaire was developed to assess social engagement in homebound older adults, accounting for physical and functional limitations. Participants report the frequency of activities such as socializing, volunteering, attending religious services, and participating in recreational or educational events over the past month. Responses are scored on a 6-point scale (0-5) for each item [67].

Entertainment or Engagement-Related Factors

The Digital Working Alliance Inventory is a 6-item measure that asks participants to rank their experience using a DMHI [68]. Responses are scored using a 5-point Likert scale from "strongly agree" to "strongly disagree." The word "app" from the original Digital Working Alliance Inventory scale was modified to "program" to reflect that the intervention is accessed online rather than through a mobile app.

The 12-item Narrative Engagement Scale assesses the audience's mental models, particularly their enjoyment and understanding of a story, using a 5-point Likert scale ranging from "strongly agree" to "strongly disagree" [69]. The scale includes 4 domains, each measured by 3 items: narrative understanding, attentional focus, narrative presence, and emotional engagement. For this study, we retained all 3 items from the emotional engagement domain but selected only one item each from the narrative understanding, attentional focus, and narrative presence domains.

The Identification with Characters Scale consists of 14 items that help identify different levels of relatedness and connectedness the viewer has to a film [70]. We adapted the original 5-point scale ("1 = not at all" to "5 = very much") to a 5-point scale ranging from "strongly disagree" to "strongly agree" for consistency with other questions. In addition, "characters" was replaced with Jackie's name (eg, "I felt like I was similar to Jackie").

Coach-Related Factors

Coaching fidelity (client report) will be assessed using a 9-item scale developed specifically for this study. Some items were adapted from the Therapist's Interpersonal Style Scale [71] to align with the study context, emphasizing aspects of coaching that reflect therapeutic alliance and its potential influence on treatment outcomes. Example items include "The feedback I receive from my coach is helpful," "My coach is trustworthy," and "My coach makes the program more personalized and relevant to my situation and needs." Participants will rate their agreement with each statement on a 5-point Likert scale ranging from "strongly agree" to "strongly disagree."

Self-Determination

The Basic Needs Satisfaction in General Scale is a 16-item questionnaire designed to assess satisfaction with 3 fundamental psychological needs: autonomy, competence, and relatedness. Autonomy pertains to an individual's desire to perceive their actions and subsequent consequences as self-determined, rather than being subject to external influences or control [72]. Competence refers to the inherent desire to experience a sense of efficacy and proficiency in executing tasks of varying complexities [73]. Relatedness refers to the inherent human desire for social connection, support, and caring from others [73]. According to the self-determination theory, all 3 needs must be fulfilled to achieve psychological well-being [72].

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Consistent with the responses of other measures used in this study, participants respond on a 5-point scale ranging from "strongly agree" to "strongly disagree" [74].

Acceptability will be assessed by the number of sessions participants completed (ie, adherence) and the Modified Treatment Evaluation Inventory (TEI) developed explicitly for evaluating geriatric depression treatment [75]. The TEI has 11 items, including 8 positively worded items and 3 negatively worded items. We modified the TEI by rephrasing the original TEI items from questions to statements and reducing the responses from a 7-point Likert scale to a 5-point Likert scale to ease respondents' burden. The modified TEI yields total scores ranging from 11 to 55, where a score of ≥32 suggests positive attitudes toward the treatment.

Implementation Fidelity Monitoring

Implementation fidelity is essential for evaluating interventions delivered in real-world settings. While the online program ensures consistent delivery of core CBT concepts, coaching support naturally varies due to its personalized nature. We used 3 methods to assess fidelity in this context: coach self-reports, in vivo observations of coaching calls, and fidelity check-in calls with clients.

Coach self-reports capture the coach's perspective on each session. Coaches document session duration, delivery mode (phone, virtual, or in-person), and types of support provided, selecting from a checklist including application, education, motivation, personalization, and technology assistance. In addition, the coaches respond to close-ended questions assessing adherence to session tasks outlined in the coaching guide, such as "Did you review in-session exercises as outlined in the coaching guide?" with response options of all, most, some, or none.

In vivo observations involve trained research team members evaluating at least one coaching session per client, selected randomly using a predetermined random sequence. Observers join sessions via 3-way calls to assess fidelity in real time. A structured rating guide, developed specifically for this study, includes items adapted from the literature and validated scales such as the United Kingdom Alcohol Treatment Trial Process Rating Scale [76] and the Therapist's Interpersonal Style Scale [71]. The guide comprises items across 3 domains: session management, adherence to the coaching guide, and coaching style. Key items under session management and adherence to the coaching guide include collaborative agenda-setting, reviewing exercises, checking goal progress, and providing personalized feedback. Coaching style is rated based on factors such as engagement, empathy, reflective listening, and collaboration. Each item is scored on a 4-point scale from excellent to poor. The instrument includes detailed instructions for rating each item. To ensure reliability, 2 research staff independently rated coaching call recordings from pilot studies, compared their ratings, and resolved discrepancies to refine the scale and its instructions for consistency.

Qualitative Interviews

After completing the intervention, approximately half of the intervention group will take part in a semistructured qualitative interview lasting approximately 30 minutes. These interviews will explore several domains, including participants' overall experience with the program, engagement barriers and facilitators, and their experience with the coaching component. Interview questions are available in Multimedia Appendix 1.

In addition, all Empower Coaches, their immediate supervisors (who also serve as site principal investigators for institutional review board [IRB] purposes), and other relevant agency staff involved in implementation will be invited to participate in qualitative interviews during the final year of data collection. These interviews will gather insights into how the intervention functioned, what modifications were or should be made, and how well it integrates into routine provider workflows. The updated Consolidated Framework for Implementation Research [77] will guide the design of qualitative interview protocols and data analysis.

Sample Size

All parameters for the power analysis were based on the pilot RCT conducted in 2023, with an original sample size of 70, with 35 in the treatment group and 35 in the control group. At the time of this analysis, a total of 440 data points across the 7 time points had been collected. Time 7 data had been collected from 63 participants, 33 in the treatment and 30 in the control group. A linear mixed model using *lme* from R package *lme4* showed a treatment by time effect of −0.69, $P<.001$. These pilot data were used in the R package *simr* with the effect size conservatively set to approximately one-half of that found in pilot study, −0.35. With a sample size of 192, there was a power of 0.91 to detect the effect of −0.35 for the treatment by time parameter. Assuming 25% attrition, we will aim to recruit 256 participants.

Analytic Plan

Primary Analyses

The primary analyses will use an intention-to-treat approach, including all individuals who completed the baseline interview and were randomized. If sufficient variability in participation or dropout is observed, secondary analyses will incorporate measures of intervention dosage (ie, adherence) as covariates to account for differences in engagement with the intervention.

Linear mixed effects models will be used to examine differences between the treatment and control groups over time. All outcome variables will be assessed for normality, and transformations will be applied if needed. Parameter estimates for the interaction between group membership and time will determine whether the treatment group demonstrates significantly different changes over time compared to the control group. Various covariance structures will be evaluated to identify the best-fitting model, and nonlinear time functions (eg, quadratic) will also be explored.

Mediation Analysis

Latent growth curve modeling will be used to assess whether proposed mediators—CBT-related, engagement-related, and coach-related factors—explain the primary treatment effect [78]. These models will be estimated using Mplus software. According to Cheong [79], latent growth curve models with 5

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measurement points show minimal bias and sufficient power to detect mediation effects, particularly when the R^2 (the proportion of variance in mediator and outcome variables explained by growth factors) is moderate or high. In this study, 7 measurement points will be used in mediation analysis (T1, T2, and 5 in-app assessments), making the estimates conservative as power increases and bias decreases with additional measurements. On the basis of guidance from Cheong [79], assuming a medium effect size and moderate R^2, the sample size of 192 will yield power of 0.8 to detect the mediation effect, indicating adequate statistical power for the analysis.

Qualitative Analysis

Third-party transcription services will be used to transcribe recorded qualitative interviews. Coding and theme extraction will follow the methodology proposed by Saldaña [80] for qualitative analysis. In the first coding cycle, a combination of a priori codes from preliminary studies and inductively developed new codes will be used to analyze transcripts. Two trained research staff will independently review a random subset of transcripts to ensure coding consistency. This process will continue until a satisfactory level of agreement is reached, at which point, the finalized codebook will be applied to the remaining transcripts. During the second coding cycle, patterns and relationships among initial codes will be identified, with codes being grouped into broader themes or concepts through an iterative process. Data analysis will be conducted using Dedoose, which supports essential qualitative analysis tasks such as coding, creating memos, and diagramming.

Ethical Considerations

The study protocol was approved by the University of Michigan Health Sciences and Behavioral Sciences IRB (HUM00254688). Participants provide verbal consent, which is recorded after receiving information about the study's purpose and potential outcomes. Written consent was waived because the study does not involve in-person contact and would not require written consent outside of the research context. After verbal consent, a written copy of the informed consent is mailed to participants. If a participant opts out of recording consent, they receive the consent form by mail along with return postage to send back the signed document. Participants receive compensation for their time completing the study surveys, up to US $140 in total paid via check or gift card. Participant contact information is kept for the purposes of follow-up during participation and is kept separately from study data using REDCap, a HIPAA-compliant secure platform. Deidentified study data will be uploaded to the National Institute of Mental Health Data Archive, in accordance with the sponsor's requirements. Participants are asked for their consent to retain their deidentified study data after the study conclusion. After the research data are verified and all payments have been processed to participants, identifiable data will be deleted within 6 months of the study conclusion and research records of those who consented will be kept as a deidentified dataset.

Results

Funding for this project was awarded in July 2024. IRB approval was obtained in August 2024. Enrollment began in October 2024 and is anticipated to be completed in April 2028. The trial is registered at ClinicalTrials.gov (NCT06584422).

Discussion

Anticipated Findings

To our knowledge, this study represents the first hybrid type 1 implementation-effectiveness RCT of an aging service provider–supported iCBT intervention for low-income homebound older adults with depression. We hypothesize that the Empower@Home intervention will reduce depressive symptoms and improve psychosocial functioning and health-related quality of life when supported by aging service providers.

Despite the availability of numerous iCBT programs, very few are explicitly designed for older adults [35,36,81,82], a population more sensitive to usability challenges. Our previous experience testing generic iCBT programs with low-income homebound older adults revealed numerous usability issues, such as hard-to-read text, buttons placed too close together, icons without labels, required text entry fields, and complex interfaces, leading to frustration and low program completion [33,34]. Even college-educated and computer-literate older adults report challenges with technology, such as text entry, when interacting with iCBT programs [83]. Having a streamlined, user-friendly, and accessible user interface is critical to the experience of older adult consumers. In addition to user interface, experts have articulated the need for procedural and content modifications to CBT that address differences in thinking styles and age-related adjustment [84]. In our previous study, older adult users described a general adult iCBT program as, "This isn't meant for someone my age," due to the lack of relatable case stories or examples that reflected their life experiences [44]. Furthermore, the real-world effectiveness of these programs has often been limited by difficulties in achieving consistent and meaningful user engagement outside of academic settings [85]. This study addresses these gaps by tailoring an iCBT program specifically for older adults and embedding it within community-based aging services supported by trained aging service providers.

This study makes 2 significant contributions to the field. First, it provides crucial evidence on integrating iCBT with training community providers, such as aging service staff, to offer human support. This approach tests the feasibility and effectiveness of using providers already embedded in the community to deliver iCBT in real-world settings. While our prior efficacy trials demonstrated that layperson-supported iCBT can succeed in highly controlled academic environments, this study explores whether those results can be replicated in community settings.

Using nonclinician providers has been recognized as a key approach to expand the geriatric mental health workforce [16]. Leaders in geriatric mental health have demonstrated that nonclinician aging service providers can be trained to effectively provide behavioral interventions for depression [20-25]. However, none of the previous studies tested DMHIs. In addition to filling the gap regarding aging service staff–supported DMHIs, this study also provides importance insights into

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implementation issues, which remains an underexplored area of research. We will gather information on the implementation process and address questions about treatment fidelity. Specifically, we will examine whether aging service providers can consistently follow the intervention protocol and quality of coaching. We anticipate larger variation in implementation fidelity in this real-world effective study than that observed in our previous studies with student coaches in a controlled academic setting. Interestingly, the intergenerational aspect of using student coaches in past trials may have played a unique role that providers with existing relationships with their clients might not replicate. Therefore, it is important to verify that the program will be effective in real-world settings. The findings will lay the groundwork for future large-scale implementation and scalability efforts.

Second, our previous efficacy trials showed exceptional program engagement, with 90% of participants completing the program—a stark contrast to the average completion rates reported in meta-analyses. For example, one meta-analysis of 40 iCBT studies found that 57% of participants dropped out [86]. More recent systematic reviews have shown that completion rates average 17% for self-guided DMHIs [87] and 65% for therapist-supported interventions [32]. In addition, use rates often drop sharply when these interventions are implemented outside controlled study conditions [86,88]. While our earlier qualitative studies offered insights into high engagement [40], many factors contributing to this success remain unknown. In this study, we will examine engagement-related, coaching-related, and CBT-related mechanisms to better understand treatment pathways. These findings could provide broader insights into overcoming engagement challenges in DMHIs.

The rapid evolution of digital mental health technologies, particularly with advancements in artificial intelligence, underscores the importance of addressing the digital divide. Without careful consideration, these innovations risk further marginalizing underserved populations, including low-income older adults. This study demonstrates how technology can be leveraged alongside existing service delivery infrastructures to address unmet mental health needs. It provides a critical data point on effectively integrating DMHIs into community settings effectively.

Finally, this study is particularly timely given the long-term mental health consequences of the COVID-19 pandemic [89], which have disproportionately affected vulnerable populations such as homebound older adults. By addressing engagement and implementation challenges, this research contributes to the ongoing effort to close mental health disparities and ensure equitable access to effective treatments.

Strengths and Limitations

This study has several notable strengths. The intervention was iteratively developed, incorporating patient and provider feedback, and was tested using a rigorous randomized design. It uses laypersons as interventionists and is implemented in real-world community settings, thus enhancing its practical relevance. The study includes a 36-week follow-up period to assess long-term effects and focuses on an underserved, hard-to-reach population with significant unmet mental health needs.

However, the study also has limitations. While it is fully powered at the individual participant level to detect both treatment effects and mediation effects, it is not powered to detect differences at the coach or site level. Our plan includes only 3 community sites, and each site is expected to have 2 coaches. Preliminary analyses of the first 50 enrolled participants already show variation in participants' backgrounds across sites. These differences may stem from multiple factors, including regional variation (eg, Metro Detroit vs a predominately rural county), differences in clientele given agencies' priorities, and methods agency staff use to identify clients. For example, we have observed initial patterns in baseline depression burden across sites, likely influenced by agency-specific outreach and referral strategies. In addition to differences in clientele, we have also observed qualitative differences across sites in organization culture, leadership style, communication, and internal processes (eg, incentives for coaches and allocation of protected time for coaching). These factors may influence how coaching is delivered and the fidelity of the intervention implementation across sites. To rigorously evaluate these contextual factors, future studies should adopt implementation-focused designs with a larger number of community organizations and randomization and the site level, if comparing different implementation strategies. Similarly, coach-level differences, such as variations in qualifications and experiences, may also affect coaching fidelity. However, in this study, coach assignment within each site is not randomized. Instead, clients are matched to coaches based on a combination of preference and convenience. For example, if coach A referred a client, coach A is typically assigned to coach that client. In other cases, the assignment may depend on coach availability—such as assigning coach B because they have time to take on a new client. As a result, coach-level differences are confounded by client-level characteristics, making it impossible to draw causal conclusions about the effectiveness of individual coaches. To accurately assess coaching effectiveness across different coaches, clients would need to be randomly assigned to coaches in future studies.

Another limitation to consider is the difference in how the PHQ-9 is administered between the treatment and waitlist groups during the intervention period. Treated participants complete the PHQ-9 on their own through the online program platform (self-administered). In contrast, waitlisted participants complete the PHQ-9 over the phone with research staff, as they do not have access to the online platform. This introduces a systematic difference in the mode of administration, which could potentially influence how participants respond and score on the PHQ-9. Importantly, this difference only affects the repeated PHQ-9 scores used in the mixed effects models. It does not impact our primary outcome analysis, which is based on the change from baseline to posttest scores, both of which are administered verbally by trained research staff for all participants, regardless of group. To further assess whether the mode of administration introduces bias, we will compare participants' baseline PHQ-9 scores (administered by staff) with their in-app self-assessment scores.

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Conclusions

This study offers some of the first evidence on integrating DMHIs into aging services. If successfully implemented, this innovative approach could help bridge the digital divide and address mental health disparities among homebound older adults. In addition, the findings have broader relevance for other DMHIs and populations with physical disabilities or access barriers who continue to face significant barriers to mental health care.

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ChatGPT 4o, a generative artificial intelligence tool developed by OpenAI, was used during the writing process solely as an editing aid to enhance the clarity of human-generated drafts. The tool was typically prompted with phrases such as “Can you make this text clearer?” All original content was written by the authors, who reviewed and made independent decisions about whether and how to incorporate suggestions provided by ChatGPT.

Data Availability

The datasets generated during this study will be available in the National Institute of Mental Health Data Archive (NDA) repository.

Authors' Contributions

XX was involved in conceptualization, data curation, resources, and supervision. JNJ, RA, and XX were involved in methodology. ST and SA were involved in project administration. XX, XZ, EN, SA, and ST were involved in writing the original draft. RA, JNJ, SP, SH, and JAH were involved in reviewing and editing the draft.

Conflicts of Interest

XX led the design of Empower@Home. SA contributed to the design of Empower@Home.

Multimedia Appendix 1
Interview guide.
[DOCX File , 15 KB - resprot_v14i1e72953_app1.docx]

Multimedia Appendix 2
CONSORT-EHEALTH (V 1.6.1) checklist.
[PDF File (Adobe PDF File), 1222 KB - resprot_v14i1e72953_app2.pdf]

Multimedia Appendix 3
Peer review report from the EMHI - Effectiveness of Mental Health Interventions Study Section, National Institute of Mental Health Initial Review Group. National Institute of Mental Health (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 135 KB - resprot_v14i1e72953_app3.pdf]

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Abbreviations

AAAs: Area Agencies on Aging
DMHI: digital mental health intervention
HAMD: Hamilton Depression Rating Scale
HIPAA: Health Insurance Portability and Accountability Act
iCBT: internet-based cognitive behavioral therapy
IRB: institutional review board
PHQ-9: 9-item Patient Health Questionnaire
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
TEI: Treatment Evaluation Inventory

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Protocol

Evaluating and Optimizing Just-in-Time Adaptive Interventions in a Digital Mental Health Intervention (Wysa for Chronic Pain) for Middle-Aged and Older Adults With Chronic Pain: Protocol for a Series of Randomized Trials

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Abstract

Background: On a population level, digital mental health interventions effectively reduce depression and anxiety symptoms. However, middle-aged and older adults with chronic pain and coexisting depression or anxiety have not been adequately represented in digital mental health studies.

Objective: The goal of this study is to refine an existing mobile, digital mental health intervention (Wysa for Chronic Pain) that addresses symptoms of depression, anxiety, and coexisting chronic pain for the unique challenges and technology use patterns of middle-aged and older adults.

Methods: Using a mixed methods, human-centered design approach and a series of randomized trials, we will test and iteratively refine just-in-time adaptive interventions (JITAIs) that are designed to increase engagement with a digital mental health intervention. Participants will be aged 45 years or older, endorse at least moderately severe depression or anxiety symptoms (Patient Health Questionnaire-9 or Generalized Anxiety Disorder-7 score ≥10), and have coexisting chronic pain (ie, pain on most days or every day in the past 3 months), and live in the United States. In this open, web-based trial, participants will all receive Wysa for Chronic Pain (by Wysa), which uses a behavioral activation framework and encourages users to work toward pain acceptance. The fully automated intervention also includes cognitive behavioral therapy, mindfulness, and sleep tools, among others. In each trial, participants will be randomized during a maximum 12-week study period to receive versus not receive novel JITAIs that are intended to reduce navigation burden and improve usability (and subsequent engagement and clinical effectiveness). The JITAIs are being designed with iterative user feedback, guided by the Discover, Design/Build, and Test framework and the Behavioral Intervention Technology model. The proximal outcome for each JITAI is related to engagement with Wysa for Chronic Pain after JITAI delivery (compared to when no JITAI is delivered). The primary distal clinical outcome is the Patient Health Questionnaire Anxiety and Depression Scale. Based on statistical analysis that is triangulated with qualitative feedback from a subsample of trial participants, the JITAIs will be iteratively refined and retested in subsequent microrandomized trials until retesting of refined adaptations no longer yields meaningful improvement in immediate engagement or a maximum of 5 total trials have been completed.

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Results: Institutional review board approval was obtained on April 11, 2025. The first participant was enrolled on June 2, 2025, and recruitment is expected to conclude in 2026.

Conclusions: Completion of this project will result in iteratively refined JITAIs that are designed to improve usability and engagement with a digital mental health intervention by middle-aged and older adults with depression or anxiety and coexisting chronic pain.

Trial Registration: ClinicalTrials.gov NCT06978166; https://clinicaltrials.gov/study/NCT06978166

International Registered Report Identifier (IRRID): PRR1-10.2196/77532

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KEYWORDS

anxiety; chronic pain; depression; digital mental health intervention; engagement; human-centered design; just-in-time adaptive intervention; microrandomized trial; middle-aged adults; older adults

Introduction

Background

The prevalence of chronic pain increases with age, and among the 26% of middle-aged and 31% of older adult Americans with chronic pain, up to half experience depression or anxiety [1-4]. At a population level, digital mental health interventions effectively address many access barriers to mental health care and reduce depression and anxiety symptoms [5-10]. However, middle-aged and older adults with coexisting chronic pain have not been adequately represented in digital mental health intervention studies. This gap is important to address for these populations for multiple reasons: (1) chronic pain reduces the effectiveness of stand-alone mental health treatment unless a person's pain is simultaneously addressed [11,12]; (2) physical and mental health–related disability in these older age groups has unique downstream effects, such as reductions in the workforce, impact on dependent children, and strain on caregiver availability [13-17]; and (3) use of technology in these age groups is widespread and growing, but these users have unique digital health needs and preferences [5-7,18-21]. Compared to younger users, middle-aged and older adults have unique needs for mental health interventions. For example, they prefer more access to real-time support that supplements automated instructions; they have a greater interest in interventions that address multimorbidity; they prefer different screen layouts due to age-related changes in visual acuity, eye tracking patterns, and dexterity; and they may benefit from more "push" notifications because they check their phones less frequently, and some have age-related cognitive deficits that reduce their ability to independently navigate through apps [18,22-26].

Wysa for Chronic Pain

Wysa is an established, evidence-based mobile app with over 6.5 million users, and it has the potential to meet the digital mental health care needs of middle-aged and older adults [27,28]. It is available directly to consumers through free and paid subscriptions, and some versions of the platform are covered by select employers and insurers. It delivers evidence-based mental health therapeutic techniques like cognitive behavioral therapy through an artificial intelligence–based chatbot [29,30]. Wysa for Chronic Pain is a specific version of the platform for people with mental health symptoms and coexisting chronic pain [31]. Preliminary studies have demonstrated encouraging signals of effectiveness for Wysa for Chronic Pain among adults across the age spectrum [32-34]. However, middle-aged and older adults specifically identified barriers to engagement related to navigation difficulty within Wysa for Chronic Pain [34].

Just-in-Time Adaptive Interventions

Just-in-time adaptive interventions (JITAIs) are a unique approach that uses prespecified triggers and leverages user data to deliver a digital intervention, specifically when a person is most in need and receptive to the intervention [35-37]. For instance, a user who is trying to increase physical activity may receive a daily smartphone prompt to encourage physical activity, but only if passive sensors from the smartphone detect that the user is not already active, is not driving or riding in a vehicle, and has not yet met their step goal for the day [38]. Because JITAIs can be pushed to a user when they are most relevant (rather than requiring user-led navigation), JITAIs are particularly appropriate for people with difficulty navigating digital tools. In academic studies, JITAIs have shown promise in driving engagement and improving effectiveness to increase emotional regulation, exercise, and other healthy behaviors; however, the use of JITAIs in commercial digital mental health interventions is relatively novel [39-42].

Goal of This Study

We are conducting a large-scale, 3-phase project using human-centered design and the Discover, Design/Build, and Test (DDBT) framework to optimize an existing digital mental health intervention (Wysa for Chronic Pain) for middle-aged and older adults with depression or anxiety and coexisting chronic pain [43]. In the first project phase, we conducted semistructured interviews and usability testing among this target user population. During that process, novel JITAIs for Wysa for Chronic Pain were developed using the Behavioral Intervention Technology (BIT) model [36,44], which links established behavior change strategies with technology-related design and implementation factors—for example, timing, medium (text, audio, or video), and complexity of intervention delivery—that affect engagement and subsequent effectiveness of a digital health intervention [44,45].

This study protocol outlines the second project phase. In a series of traditional and microrandomized trials (MRTs) that are interspersed with qualitative feedback from a subgroup of trial

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participants, the goal of this study is to test and optimize the effectiveness of the novel JITAIs to increase engagement among middle-aged and older adults with Wysa for Chronic Pain. The central hypothesis is that incorporating these JITAIs will increase engagement with Wysa for Chronic Pain by improving usability and, subsequently, will improve depression and anxiety symptoms in this population. After completion of this phase, the third project phase will be a pragmatic, hybrid type 1 effectiveness-implementation trial during which the final JITAIs will be fully integrated into the Wysa for Chronic Pain user experience.

Methods

Study Design and Setting

In this remote, single-site, mixed methods study, we will conduct a series of randomized trials interspersed with semistructured interviews (Figure 1). The first trial will be a traditional 4-week, 2-arm randomized controlled trial in which participants receive "Wysa for Chronic Pain with JITAIs" or "Wysa for Chronic Pain without JITAIs." The primary purpose of this first trial is to obtain preliminary information regarding the frequency that (1) the prespecified criteria (ie, decision rules) are met for each JITAI and (2) participants engage with each JITAI. These quantitative data, coupled with qualitative data from semistructured interviews with a subgroup of trial participants, will guide the final design (and particularly the initial randomization probabilities) of a subsequent 12-week MRT. MRTs were developed as a novel study design by Susan Murphy and colleagues [46] to rigorously study JITAIs. In an MRT, each participant is repeatedly randomized multiple times during the course of the trial. For example, randomization can be related to (1) receiving one versus another JITAI (or none at all) when fixed prespecified criteria are met or (2) variations in the prespecified criteria or delivery of a JITAI (eg, timing for the decision rule, timing of JITAI delivery, JITAI language, etc). In this way, both between-participant and within-participant comparisons can be made, which increases the efficiency of the trial. Furthermore, time-varying effects of a JITAI can be studied with an MRT, for instance, to evaluate a JITAI's impact on engagement during the first day of app use (when engagement is typically high) compared to the tenth week of app use (when engagement is typically lower) [46].

Figure 1. Study design. JITAI: just-in-time adaptive intervention; MRT: microrandomized trial; RCT: randomized controlled trial.

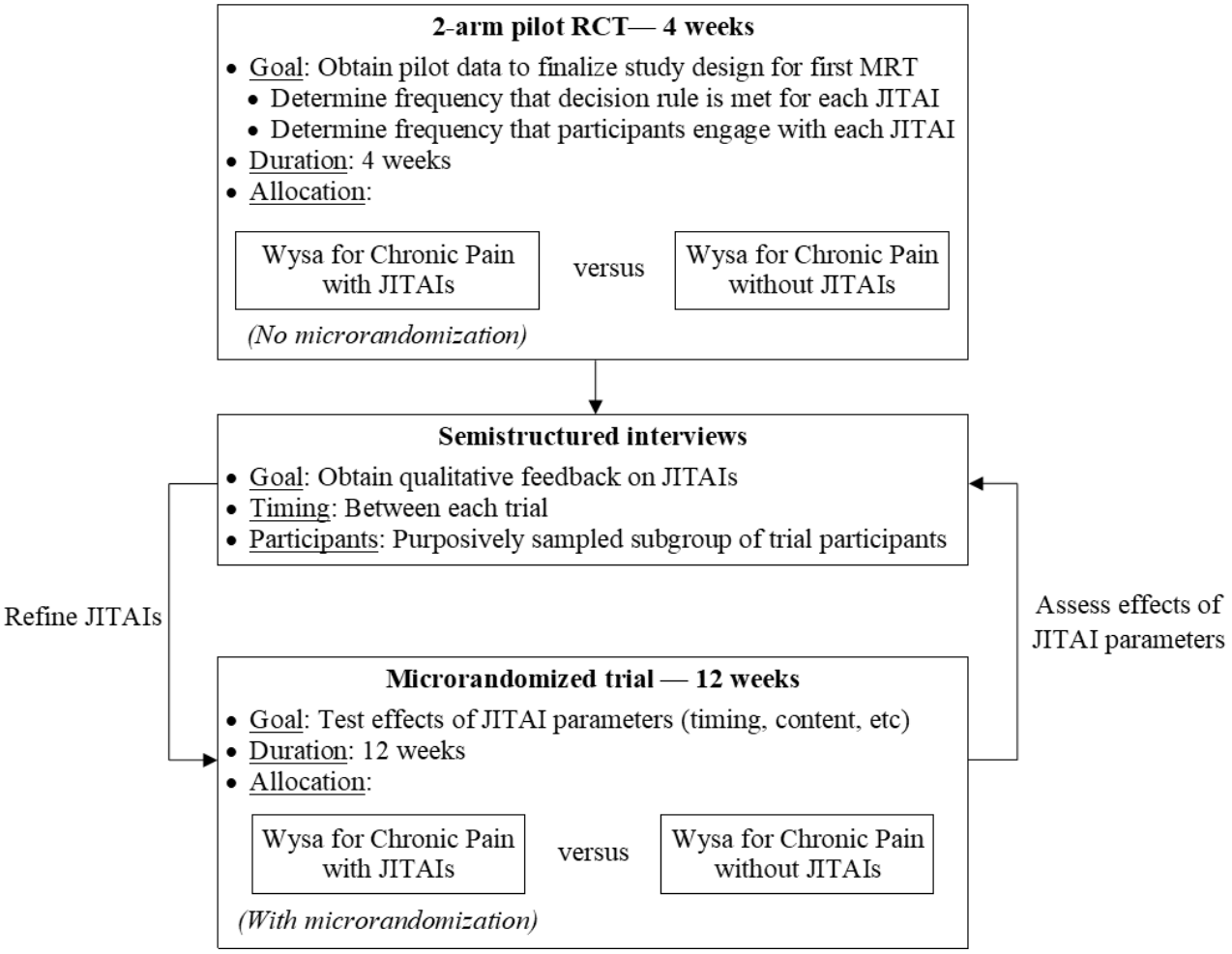

We anticipate performing 2-4 MRTs as part of this study, depending on opportunities that we identify for continued JITAI refinement based on our quantitative and qualitative findings after each trial, within the limitations of time and budget constraints. Each MRT will include 2 arms (Figure 2). Participants in the "Wysa for Chronic Pain with JITAIs" intervention arm will be randomized every time they meet prespecified criteria (ie, decision rules) for the JITAIs under

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investigation, whereas participants in the "Wysa for Chronic Pain without JITAIs" control arm will never receive JITAIs, regardless of whether they meet the prespecified criteria. Inclusion of a control arm in each trial will facilitate accounting for time-varying factors (eg, refinements to the Wysa for Chronic Pain user experience that are unrelated to the JITAIs) and enable additional secondary analyses.

Figure 2. Participant flowchart for each microrandomized trial (MRT). JITAI: just-in-time adaptive intervention.

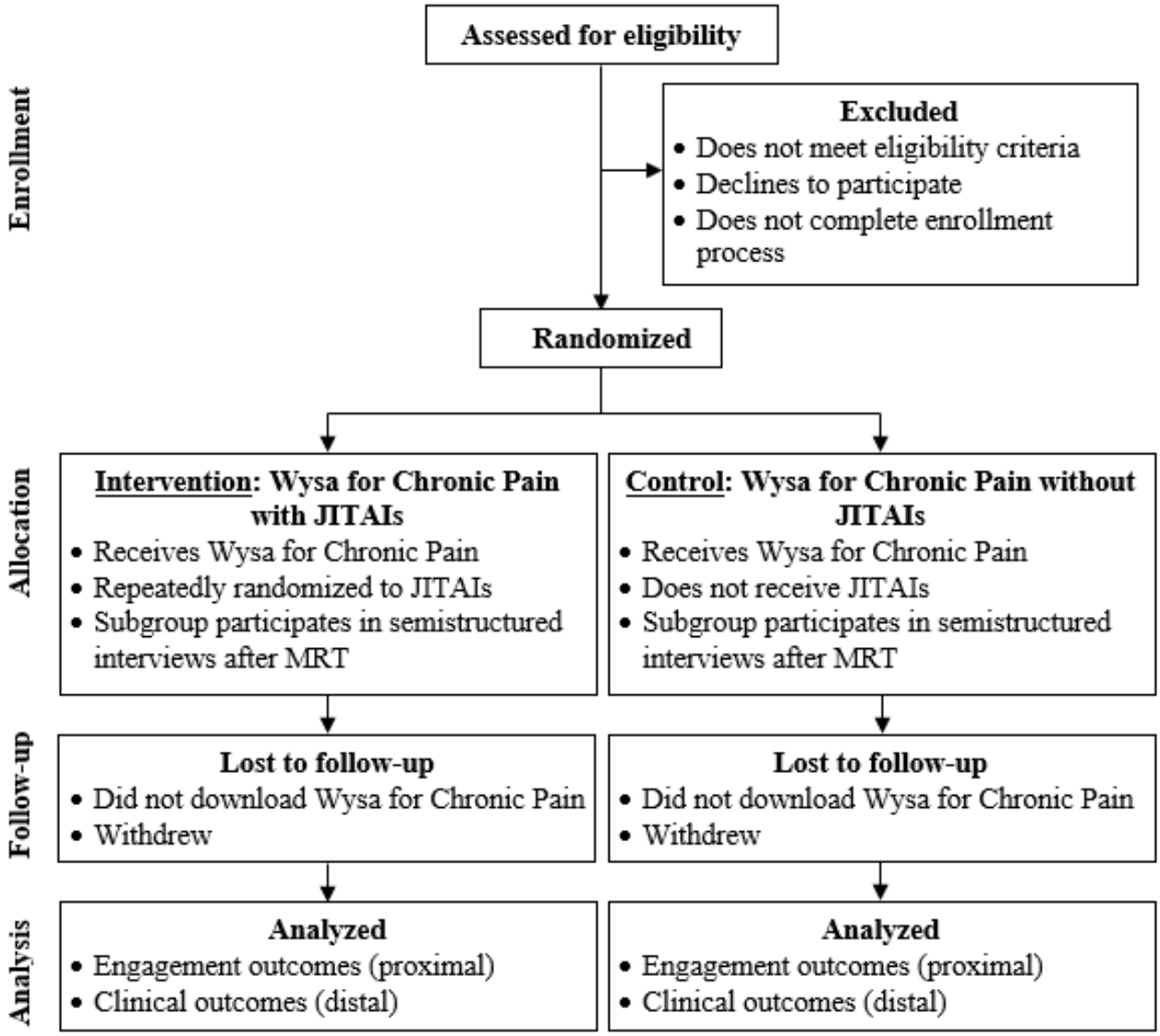

Participants

Eligibility Criteria

Eligibility criteria were selected to be pragmatic and reflect the broad target population for Wysa for Chronic Pain while also being mindful of which variables can reliably be collected in an entirely remote study (Textbox 1).

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Textbox 1. Eligibility criteria.

Inclusion criteria

- Aged 45 years or older
- At least moderately severe depression or anxiety symptoms (Patient Health Questionnaire-9 or Generalized Anxiety Disorder-7 score ≥10) [47,48]
- Chronic pain (ie, pain on most days or every day in the past 3 months) [2]

Exclusion criteria

- Frequent active suicidal ideation [49]
- No access to a mobile device
- Not living in the United States

Sample Size

Sample size calculations were performed at a 5% significance level to detect an effect in the primary study outcome between the 2 study arms. Because the primary outcome for each JITAI is related to engagement (which is automatically captured by the Wysa platform and does not require participant report), we assumed a 10% attrition rate (conservatively assessed as occurring at baseline but after downloading Wysa for Chronic Pain). In the initial 4-week pilot trial, we will enroll 29 participants into each of the 2 arms (58 participants total). This will provide 80% power to detect a large effect size (Cohen d=0.8).

Sample size determinations for the subsequent 12-week MRTs will be dependent on analysis after each preceding trial, but it is anticipated that control groups for analysis will be pooled by including the control groups from previous trials. For the first MRT, we preliminarily anticipate enrolling 75 participants into the "Wysa for Chronic Pain with JITAIs" intervention arm and 46 participants into the "Wysa for Chronic Pain without JITAIs" control arm (121 total participants recruited). In the intervention arm, clipped Thompson sampling will be used to make intervention assignments with the clipping rate set at 10%. This would provide 80% power to detect a moderate to large effect size (Cohen d=0.5). For the second MRT, we preliminarily anticipate enrolling 120 participants into the intervention arm and 55 participants into the control arm (175 total participants recruited). Clipped Thompson sampling will again be used in the intervention arm, with a 10% clipping rate. This would provide 80% power to detect a moderate to small effect size (Cohen d=0.4). Sample sizes for any additional MRTs will follow a similar calculation process.

Randomization

Allocation to Interventions

For the initial 4-week pilot trial, a computer-generated random sequence will be used to randomize participants to 1 of the 2 study arms. Stratification (eg, by age, sex, or symptom severity) or block randomization may be considered for the subsequent MRTs based on analysis from the preceding trials. A study statistician will generate the allocation sequences, and participants will be assigned to study arms automatically after they pass the web-based eligibility screen, review the study procedures, and complete the baseline study questionnaires; no direct involvement by study team members is required for study arm assignment. Criteria for discontinuing or modifying allocated interventions are described in Multimedia Appendix 1.

Blinding

Study team members involved in outcome assessment and data analysis will not be blinded to participants' intervention assignment because (1) the primary proximal outcomes related to immediate app engagement will be collected automatically and in real time throughout each trial and (2) the study outcomes will not be analyzed until a given trial is complete. Trial participants cannot definitively be blinded to their intervention assignment because the notification experience within Wysa for Chronic Pain will differ between the 2 intervention arms. Nevertheless, all participants will receive the same Wysa for Chronic Pain therapeutic content, participants will not explicitly be notified which study arm they are assigned to, and participants in the intervention arm with JITAIs will not necessarily be aware when a notification (or lack thereof) from Wysa for Chronic Pain is related to a JITAI under investigation.

Interventions

Wysa for Chronic Pain

The overarching digital intervention is Wysa for Chronic Pain, developed by Wysa for mobile devices (Multimedia Appendix 1). The general Wysa platform delivers cognitive behavioral therapy, dialectical behavioral therapy, motivational interviewing, mindfulness training, deep breathing, and sleep tools (eg, meditations, sleep hygiene education [29,30]) through an artificial intelligence–based chatbot that uses a combination of rule-based decision-making, natural language understanding, and large language models to facilitate maximally nuanced, personalized conversations. Wysa for Chronic Pain also specifically delivers therapeutic content related to behavioral activation and pain acceptance (ie, "acknowledging that one has pain, giving up unproductive attempts to control pain, acting as if pain does not imply disability, and committing one's efforts toward living a satisfying life despite pain"; Figure 3) [50-53]. It uses push notifications to encourage user engagement and also allows for independent exploration of self-care tools by users. The version of Wysa for Chronic Pain that will be tested in these trials is fully automated.

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Figure 3. Screenshots of Wysa for Chronic Pain.

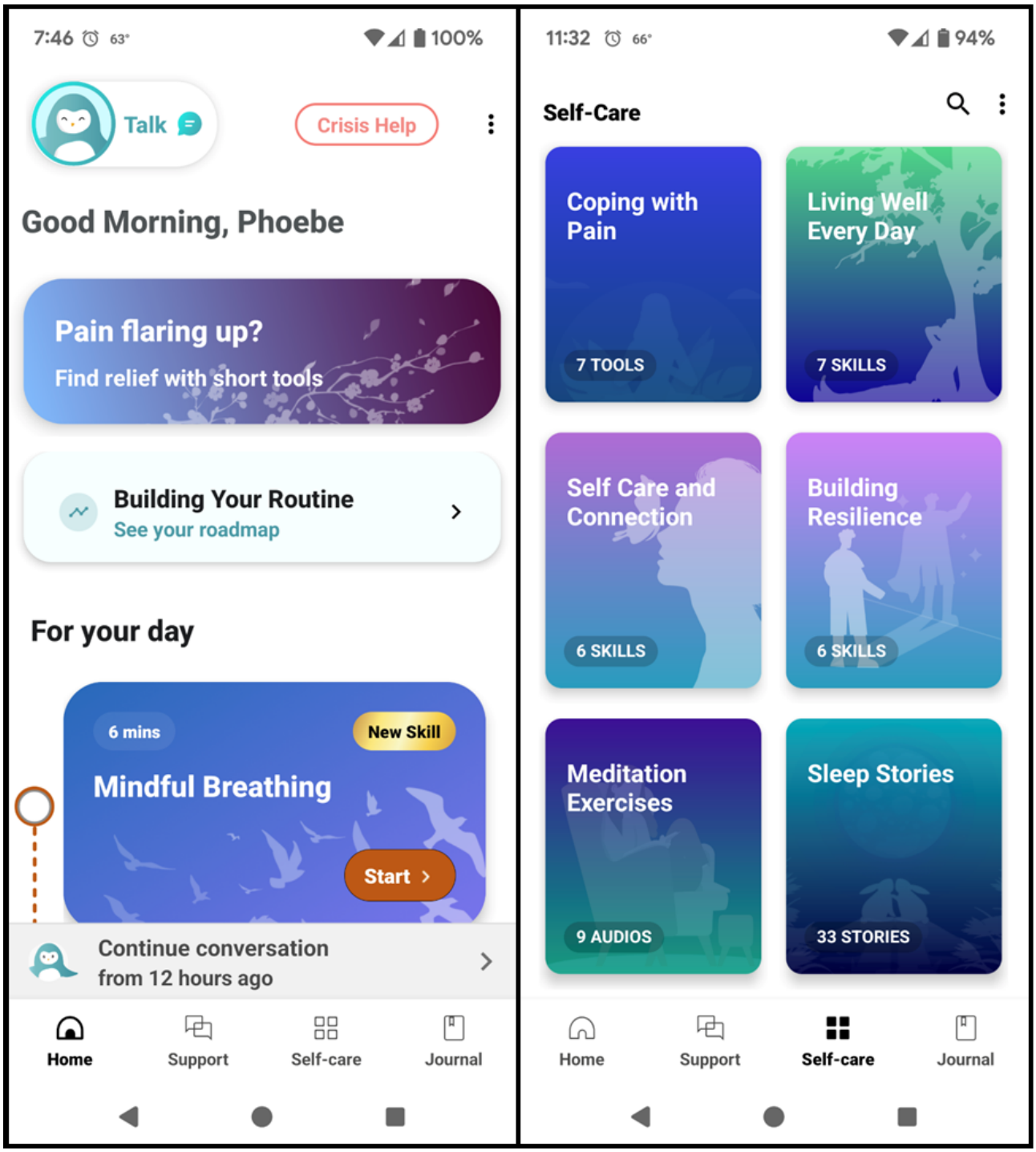

JITAIs Descriptions

Multiple JITAIs will be tested in the trials. Table 1 describes the JITAIs that will be tested in the first trial, but the final plan for each subsequent trial will be refined based on findings from the preceding trials and semistructured interviews. Each proposed JITAI in Table 1 involves the delivery of one or more push notifications to the participant. The notifications are intended to improve engagement in numerous ways, such as directing a user to a relevant therapeutic tool, adjusting the Wysa for Chronic Pain experience and frequency of scheduled notifications in order to meet the user's demonstrated preferences and to reduce notification fatigue, and increasing the frequency of scheduled notifications when mental health symptoms have recently worsened.

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Table 1. Description of initial just-in-time adaptive interventions (JITAIs) to be tested in the microrandomized trials.

JITAI name	Purpose	Decision rule: tailoring variables and cut points	Decision rule: intervention[a]
Onboarding	Increase onboarding completion rates	If the user downloaded the app but did not complete onboarding within 24 hours of download	Then, send a notification that encourages the user to finish onboarding. The notification directs the user back to the onboarding screen. When possible, the notification is personalized based on information the user shared thus far during onboarding.
Short disengaged	Motivate a user to engage using messages or content that resonates with the user	If no app engagement for 24 hours	Then, send a personalized notification regarding a challenge the user endorsed at onboarding or during a previous conversation. The notification directly opens to a relevant tool.
Long disengaged	Respect that users' preferred or needed frequency of engagement may fluctuate based on symptom severity and life events	If no app engagement for 7 days	Then, send an "FYI[b] or opt back in"[c] notification, and stop all notifications for 3 days. After 3 days, send a notification with a tool that was previously helpful or that has not been used yet but should be relevant based on challenges reported at onboarding. Then resume the previous notification schedule.
AM check-ins only	Personalize push timing to users' demonstrated preferences	If no engagement with PM check-ins but ≥1 engagement with AM check-ins within the last 7 days	Then, send an "FYI or opt back in" notification, stop daily "PM check-in" notifications, and move the "activity tracking and mood reflection" task to the AM check-ins.
PM check-ins only	Personalize push timing to users' demonstrated preferences	If no engagement with AM check-ins but ≥1 engagement with PM check-ins within the last 7 days	Then, send an "FYI or opt back in" notification, stop daily "AM check-in" notifications, and move the "activity scheduling and planning" task to the PM check-ins.
Sporadic engagement only	Personalize push timing and content to users' demonstrated preferences (eg, engagement only during pain or mood symptom flares)	If no engagement with AM or PM check-ins, but ≥1 user-led engagement within the last 7 days	Then, send an "FYI or opt back in" notification, and stop daily "AM check-in" and "PM check-in" notifications. Instead, each day, send a single personalized notification that directs the user to a tool that was previously helpful or that has not been used yet but should be relevant based on challenges the user reported at onboarding.
Mental health flare[d]	Offer increased support when most needed	If PHQ-4[e] score worsens compared to the preceding PHQ-4 score, and the user's current push notification frequency is less than twice daily	Then, send an "FYI or opt out" notification, and increase notification frequency back to twice daily (ie, AM and PM check-ins).

[a]For the "onboarding" and "mental health flare" JITAIs, the intervention will be delivered immediately after the decision rule cut points are met. For all other JITAIs, the intervention will be sent after a strategic delay. If the user's previous 3 engagement events with the app are within the same 6-hour interval of the day, the initial notification of the intervention will be sent at the time of day equal to the average of the user's last 3 engagement events (ie, when the user has historically been more likely to engage). Otherwise, the notification will be sent at the last time of day the user entered the app.

[b]FYI: for your information.

[c]If the "opt back in" or "opt out" option is selected, the rest of the intervention is not delivered, the countdown clock for the decision rule resets, and a single personalized notification is sent that directs the user to a tool that was previously helpful or that has not been used yet but should be relevant based on challenges the user reported at onboarding.

[d]The "mental health flare" JITAI overrides any engagement-related JITAIs, which would otherwise reduce the frequency of push notifications to the user.

[e]PHQ-4: Patient Health Questionnaire-4, a 4-item measure to assess depression and anxiety symptom severity [54,55]. Users are prompted to complete the PHQ-4 once weekly as part of a weekly assessment and progress report.

Among participants in the "Wysa for Chronic Pain with JITAIs" intervention arm for each trial, each time they meet prespecified criteria per the JITAIs' decision rules, they may receive the JITAI. In the initial 4-week pilot trial, they will receive the respective JITAIs described in Table 1 each time they meet the prespecified criteria. In the subsequent MRTs, they will be randomized to receive the respective JITAI, a variation of the JITAI (eg, different timing or content), or no JITAI at all. When the prespecified criteria are not met, participants will not receive a JITAI-related notification or any JITAI-related interventions. Several JITAIs are anticipated to be tested simultaneously in each MRT.

Concomitant Care

Participants will not be restricted from engaging in any concomitant care during the trial, including mental health or chronic pain treatments. Participants will be asked to self-report whether (and what types of) medication they take for their mental health or pain at baseline, and they will be asked whether and how their medication regimens have changed at each

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follow-up time point. They will also be asked to report whether they had any pain procedures or psychiatry, counseling, or physical therapy visits during each follow-up period.

Outcomes

The purpose of each JITAI is to increase engagement with Wysa for Chronic Pain by improving usability. Therefore, the outcomes of greatest importance in these randomized trials are the proximal outcomes related to engagement (Table 2). All proximal engagement outcomes will be collected automatically for all participants through Wysa platform's established infrastructure, regardless of whether participants complete follow-up study questionnaires.

Table 2. Proximal outcomes for each of the initial just-in-time adaptive interventions (JITAIs) to be tested in the microrandomized trials.

JITAI name	Proximal outcomes	Outcome type	Target engagement time interval
Onboarding	Completion of onboarding	Binary	24 hours
Short disengaged			24 hours
Primary outcome	Any engagement[a]	Binary	
Secondary outcome	Content engagement[b]	Continuous	
Long disengaged			4 days
Primary outcome	Any engagement	Binary	
Secondary outcome	Content engagement	Continuous	
AM check-ins only			7 days
Primary outcome	Daily engagement[c] with the "activity tracking and mood reflection" task	Continuous	
Secondary outcome	Change in content engagement compared to the 7 days preceding	Continuous	
PM check-ins only			7 days
Primary outcome	Daily engagement with the "activity scheduling and planning" task	Continuous	
Secondary outcome	Change in content engagement compared to the 7 days preceding	Continuous	
Sporadic engagement only	Change in content engagement compared to the 7 days preceding	Continuous	7 days
Mental health flare	Change in content engagement compared to the 7 days preceding	Continuous	7 days

[a]"Any engagement" is operationalized as opening the app during the target engagement time interval.

[b]"Content engagement" is operationalized as the total number of tools, conversations, and check-ins the user engaged with during the target engagement time interval.

[c]"Daily engagement" is operationalized as the total number of days the user completed the task of interest during the target engagement time interval.

Distal clinical outcomes will be collected through a self-reported electronic questionnaire. The primary distal outcome will be the Patient Health Questionnaire Anxiety and Depression Scale (PHQ-ADS) [56,57], which is a combination of the Patient Health Questionnaire (PHQ-9) and Generalized Anxiety Disorder-7 (GAD-7) [47,48]. This single measure captures symptoms from both mental health conditions, which Wysa for Chronic Pain is primarily intended to address. Of note, values of these distal clinical outcomes will be the same across all JITAIs tested. In this formative project, analysis of changes in clinical outcomes from baseline to the final follow-up time point will not directly shed insight into the clinical effectiveness of each JITAI but rather will provide insight into the effectiveness of the entire Wysa for Chronic Pain intervention as it is iteratively refined between randomized trials.

In accordance with the National Institute of Mental Health's (NIMH) experimental therapeutics approach, measures of clinical mechanisms of action will also be collected electronically through self-report (Table 3). We have previously reported signals of mediation by the 3 proposed clinical mediators of behavioral activation, pain acceptance, and sleep quality [53].

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Table 3. Operationalization of mediators and outcomes.

Construct	Measure
Clinical mediators	
Behavioral activation	BADS-SF[a] [58]
Pain acceptance	CPAQ-8[b] [59,60]
Sleep difficulty	AIS[c] [61]
Outcomes	
Engagement (proximal)	
Immediate engagement[d] (primary outcome)	See Table 2 for JITAI[e]-specific definitions
Engagement need[d]	Number of times that the decision rule criteria were met to trigger each JITAI
Engagement dose	
Touches	Number of times a user interacted with Wysa for Chronic Pain (eg, opened a notification, navigated through the app, sent a message to the chatbot, etc)
Sessions started	Number of times a digital tool session was opened (even if not completed)
Sessions completed	Number of times a digital tool session was completed
Retention	Number of days from onboarding until the last day of engagement with Wysa for Chronic Pain
Engagement content	Number of interactions in which the participant engaged with each of the following tool types: digital cognitive behavioral therapy tools, digital mindfulness and meditation tools, and digital sleep tools
Clinical (distal)	
Depressive and anxiety symptoms[f] (primary outcome)	PHQ-ADS[g] [56,57] (Combination of PHQ-9[h] and GAD-7[i])
Disability	WHODAS 2.0[j]
Quality of life	Global QOL[k] [62]
Pain interference	BPI[l], Pain Interference domain [63]

[a]BADS-SF: Behavioral Activation for Depression Scale-Short Form.

[b]CPAQ-8: Chronic Pain Acceptance Questionnaire-8.

[c]AIS: Athens Insomnia Scale.

[d]These measures will have unique values for each just-in-time adaptive intervention tested. Values for all other measures will be the same across all JITAIs tested.

[e]JITAI: just-in-time adaptive intervention.

[f]PHQ-9 and GAD-7 scores will also be reported separately [47,48].

[g]PHQ-ADS: Patient Health Questionnaire Anxiety and Depression Scale.

[h]PHQ-9: Patient Health Questionnaire-9.

[i]GAD-7: Generalized Anxiety Disorder-7.

[j]WHODAS 2.0: World Health Organization Disability Assessment Schedule 2.0.

[k]Global QOL: Global Quality of Life Scale.

[l]BPI: Brief Pain Inventory.

The primary end point for each MRT will be 12 weeks, which is a common end point for digital mental health trials to assess durability (Table 4) [6]. Because engagement is known to rapidly wane with digital interventions (and to facilitate mediation analyses), patient-reported measures will also be assessed at 4 and 8 weeks.

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Table 4. Timing of data collection for each microrandomized trial.

Measure	Baseline	Week 4	Week 8	Week 12[a]
Participant characteristics	✓			
Clinical mediators	✓	✓	✓	✓
Outcomes				
Engagement (proximal)		✓	✓	✓
Clinical (distal)	✓	✓	✓	✓

[a]Primary end point.

Data Collection and Management

Qualitative Interviews

Qualitative feedback will be obtained from a subgroup of approximately 5-10 trial participants through semistructured interviews after each trial. Participants will be asked to share perceptions of the strengths, limitations, and suggestions for improvement related to the JITAIs. Participants will be purposively sampled to represent a range of sociodemographic characteristics and engagement patterns. The interviews will occur through secure audio and video recording hosted by a HIPAA (Health Insurance Portability and Accountability Act)–compliant Zoom (Zoom Communications, Inc) platform. Recording files will be stored on the study institution's encrypted cloud server, Box (Box, Inc).

Retention Strategies

To improve retention, participants will be asked to complete the baseline study questionnaires immediately after the recruitment and enrollment process [64]. They will receive electronic gift cards for each time point that they complete all study questionnaires, but participants will not be paid for their level of engagement with the intervention since this is an outcome of interest. Rather, engagement will be monitored for all participants, regardless of whether they complete study questionnaires through the final study time point. A study team member will reach out to a trial participant by phone call, SMS text message, or email for reminders as needed if the participant does not complete electronic study questionnaires despite repeated automated prompts.

Statistical Methods

Primary Outcome

The main purpose of the initial 4-week pilot trial is to determine the initial randomization probability for each JITAI in the first MRT for the "Wysa for Chronic Pain with JITAIs" intervention arm (ie, to construct a robust informative prior, also called a warm start, for each JITAI). We will also perform between-group comparisons of the primary proximal outcome for each JITAI between the intervention versus control arm (ie, comparison of the primary engagement outcome during the target engagement time interval between participants in the intervention arm when they met prespecified criteria and received JITAIs vs participants in the control arm when they met the same prespecified criteria but did not receive JITAIs). In the subsequent MRTs, analysis of the primary proximal outcome for each JITAI will account for both between-group and within-participant comparisons because participants in the "Wysa for Chronic Pain with JITAIs" arm may have met the prespecified criteria for any given JITAI multiple times during the study period. A secondary analysis of each MRT will also be performed to again construct a prior (warm start) for the subsequent MRT, for instance, centered at the estimated optimal JITAI strategy.

Interim Analyses

Interim analyses will be performed to ensure the specified randomization probabilities are producing a sufficient frequency of JITAI delivery to facilitate analysis of the primary outcomes, and randomization probabilities may be updated as needed throughout the trials. No interim analyses of the study outcomes will be performed. Given the relatively short duration and low risk of each trial, early stopping of a trial will only be considered if the data safety monitoring board (DSMB) determines that the intervention is contributing to one or more serious adverse events (SAEs), and the risks of continuation of the study outweigh the potential benefits to the enrolled participants. This is because the risk of harm from the intervention is low, and all participants will be receiving the same established therapeutic content. Sustained engagement and treatment effects are important secondary analyses, and early cessation of trials would jeopardize these analyses.

Additional Analyses

In a secondary analysis, we will evaluate whether the JITAIs' effects on engagement vary with time based on the week of the study. The distal clinical outcomes in Table 3 at weeks 4, 8, and 12 will be analyzed using mixed-effects models to test for moderating effects of participant characteristics—for example, age group (middle-aged: 45-64 years vs older adult: 65 years or older), sex, race and ethnicity, depression or anxiety severity [6], and chronic pain duration—and engagement with the Wysa app (ie, total dose, duration, and content) by including these as interaction terms.

We will also estimate optimal JITAIs for the distal clinical outcomes using methods from reinforcement learning [65,66], and we will evaluate the appropriateness of engagement as a surrogate for long-term clinical outcomes by comparing the performance of an optimal JITAI that targets engagement with one that is optimized for the distal clinical outcomes of interest.

Other secondary analyses will include development of models that predict the likelihood that a user will disengage with Wysa for Chronic Pain; descriptive analyses of the estimated optimal JITAI (eg, if, when, and for whom a JITAI should be

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recommended); and testing for heterogeneity across patients (ie, comparing the performance of a JITAI rule developed from data pooled across all participants to the performance of a rule learned from each participant's individual trajectory of data).

Our experimental therapeutics model will be assessed by evaluating for associations between engagement with tools related to each therapeutic target (ie, behavioral activation, pain acceptance, and sleep quality), patient-reported improvement in the corresponding target (ie, clinical mediators), and subsequent improvement in distal clinical outcomes. We will also investigate whether and how these associations vary across patient characteristics, such as age, depression or anxiety severity, pain interference severity, and self-reported digital savviness.

Missing Data

Once randomized participants download the Wysa for Chronic Pain app and initiate onboarding, proximal engagement outcomes will be automatically collected by the Wysa platform, regardless of how much or even whether a participant engages with Wysa for Chronic Pain during the rest of the study period, so these data points are not expected to be missing. For participant-reported questionnaire data, all questions will be designed as "required," but participants will have the option to select "prefer not to answer" for sensitive descriptive variables. In these situations, "prefer not to answer" will be treated as a distinct covariate category in the analyses (rather than as missing data) since it will not necessarily be selected at random and may represent a distinct subgroup of participants. Multiple imputation for sequential randomized trials will be used to address missing data, for instance, if a participant does not complete questionnaires at a follow-up time point or withdraws from the study [67].

Qualitative Analysis

Recordings of participants' interviews will be professionally transcribed. A hybrid inductive-deductive coding approach will be used, with the BIT model as a framework. At least 2 team members will be involved in thematic analysis. The primary goal of the qualitative analysis is to identify opportunities for refinement of the JITAIs (eg, decision rules, intervention options, intervention language, etc) to improve their usability and effectiveness.

Data Sharing Plans

Deidentified participant-level data will be shared through the NIMH Data Archive. Access to the dataset will be managed by the NIMH Data Archive.

Oversight and Monitoring

Trial Steering Committee

Collectively, the trial steering committee includes expertise in geriatric mental health, chronic pain, qualitative and implementation research, and biostatistics, with particular expertise in JITAIs and MRTs. One or more members of the committee will meet with Wysa's project leads at least biweekly on average.

Data Safety Monitoring Board

The DSMB consists of 3 members, collectively with expertise in mental health, chronic pain, behavioral interventions, biostatistics, and clinical trials. Led by a chairperson, the DSMB's role is to review safety data and provide recommendations about starting, continuing, modifying, or stopping the study, taking into account the following considerations: participant safety, achievement of recruitment targets, research team adherence to applicable protocol requirements, and the completeness, quality, and analysis of safety assessments. The DSMB members are independent from the study funder, trial steering committee, and research team, and they are free from conflicts of interest related to the study intervention. The DSMB met before enrollment of the first participant in the first trial and will meet before launching each subsequent trial, or more frequently if new information raises questions regarding safety.

Adverse Event Reporting

Study participants will be encouraged to report any real or perceived adverse events to the research coordinator through telephone or email. These instructions will be included on the study information sheet, in addition to other electronic study materials provided to participants. The coordinator will record all reported events in an adverse event log (including the participant's name, date, and event description), which will be hosted in the study's secure Research Electronic Data Capture (REDCap) database [68,69]. If a participant expresses thoughts of self-harm with a plan, means, and intent to carry out the plan through communication with a study team member, a member of the study team will call the participant within 1 business day with the goal of ensuring the participant has access to the appropriate crisis resources. The study coordinator will also notify one or more of the study investigators within 2 business days if an SAE is reported directly from a study participant or from someone on behalf of a participant. SAEs include death; hospitalization; suicidal or homicidal action or ideation with a plan, means, and intent to carry out the plan; new psychosis; new substance dependence; or permanently disabling event. Examples of non-SAEs include worsening anxiety or depression symptoms, newly recognized need for professional behavioral health care, and difficulty with intervention technology. Within the Wysa for Chronic Pain platform, Wysa will also track (1) crisis events that are instances when the app detects user input that is suggestive of suicidal or self-harm intent and then the user confirms this thinking on follow-up questioning by the app and (2) instances in which a user navigates to a crisis hotline from within the app. In these instances, the Wysa platform's standard safety protocols will automatically be implemented and will direct users to national crisis hotlines.

Any serious event that is deemed by the study investigators to be attributable or possibly attributable to the study intervention will be reported to the institutional review board (IRB) within 24 business hours and to the DSMB within 5 business days of the knowledge of occurrence. In accordance with NIMH policy, any deaths or SAEs that are deemed related to study participation will also be reported to the NIMH within 5 and 10 business days, respectively. These actions and the dates of

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implementation will be recorded in the adverse event log. If an SAE that is attributable to the study occurs, immediate changes to the study consent form and protocol will be made if indicated. Otherwise, each quarter, the study investigators will classify any reported events as “serious” or “nonserious” and as “attributable,” “possibly attributable,” or “nonattributable” to the study intervention.

Protocol Modifications

Any proposed major protocol modifications will be approved by the DSMB and IRB and then communicated to relevant parties through updates to the ClinicalTrials.gov registration or direct communication with participants, as relevant.

Dissemination Plans

Study results will be submitted for publication in peer-reviewed scientific journals and for presentation at academic conferences, as appropriate. Aggregate study results will also be shared through ClinicalTrials.gov. Furthermore, study results will inform the development of a final refined Wysa for Chronic Pain intervention, which will ultimately be available for widespread public use.

Ethical Considerations

Participants will be recruited from the general direct-to-consumer Wysa platform, potentially as well as from other sources, such as free and publicly available online support groups and research registries (Multimedia Appendix 1). Given the minimal risk of this study, a waiver of written documentation of informed consent will be used. Instead, potential participants will receive a study information sheet that includes all elements of consent and is presented through the study institution’s secure, HIPAA-compliant, web-based REDCap system [68,69] (Multimedia Appendix 2). IRB approval for the study has been obtained by Advarra, Inc (Pro00085039). Participants will receive a US $25 electronic gift card for each time point that they complete all study questionnaires (eg, baseline, week 4, week 8, and week 12; maximum US $100 for full participation in the MRT). Participants who also complete a semistructured interview will receive an additional US $30 gift card.

Results

This study was funded on March 4, 2024, by the NIMH as part of grant R01MH131989. IRB approval was obtained on April 11, 2025 (protocol version 1: March 26, 2025). The first participant was enrolled on June 2, 2025, and recruitment is expected to conclude in 2026.

Discussion

Significance and Directions for Future Research

This study is an intermediate step in the adaptation and dissemination of a digital mental health intervention that is iteratively co-designed with user input, rigorously tested, and then rapidly made available to the target population. After completion of this study, we will conduct a pragmatic, hybrid type 1 effectiveness-implementation study as the final refined version of Wysa for Chronic Pain is launched for widespread use. This process will facilitate real-world assessment of the effectiveness and reach of the intervention, and it will enable rapid, global availability of the intervention for people in need.

We anticipate that the process and results of this study will also lead to more generalizable insights. For instance, our process can serve as a reproducible, precision medicine approach to tailor digital mental health interventions for people with other medical comorbidities that frequently coexist with mental illness (eg, cancer, diabetes, stroke, heart disease, and lung disease) [70]. Additionally, we hope to identify human-centered design insights that are generalizable to other behavior-based digital health interventions for middle-aged and older adults, such as for symptom tracking, medication adherence, and medical visit reminders [71].

Limitations

A limitation inherent in most trials involving a digital health intervention is that findings from this study will be most generalizable among people who have a base level of comfort and interest in using technology for health-related purposes. Nevertheless, especially as technology use continues to rapidly increase in this large and growing population [20], the results of this study will still be applicable to a meaningful proportion of middle-aged and older adults. For this pragmatic and somewhat formative study, results will also need to be interpreted in the context that (1) participants are permitted to receive additional treatment beyond what is delivered by the digital intervention and (2) multiple secondary outcomes are being assessed, which increases the likelihood of type 1 errors for these outcomes (but not for the singular primary outcome for each JITAI). Finally, as with most behavioral interventions, participants cannot be blinded.

Conclusions

Completion of this mixed method series of randomized trials and semistructured interviews will result in iteratively refined JITAIs that are designed to improve usability and engagement with a digital mental health intervention by middle-aged and older adults with depression or anxiety and coexisting chronic pain. The methodological approach and the usability-related insights that are identified from this study can also be used for the development and refinement of other digital behavioral interventions for similar populations.

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Authors' Contributions

ALC conceived of the study and led the development of the protocol. SMH and JA contributed to the study design. EBL and JPM directed the statistical analysis plan. All authors contributed to and reviewed the final manuscript.

Conflicts of Interest

The study team is independent and distinct from the developers and owners of the Wysa for Chronic Pain intervention. Wysa conceived of and developed the original Wysa for Chronic Pain intervention. Based on user and participant feedback obtained by the study authors as part of grant R01MH131989, Wysa built the just-in-time adaptive interventions that will be tested in this study into its platform. Chaitali Sinha is the chief clinical research and development officer at Wysa, and she is a coinvestigator on grant R01MH131989. Wysa will also facilitate data collection for this study in its platform and share the data with the study authors. Wysa was not involved in the development of the statistical analysis plan, and Wysa will not contribute to data analysis, final interpretation of the data, or final approval for publication of prespecified analyses and outcomes.

Multimedia Appendix 1
Additional study details.
[DOCX File , 23 KB - resprot_v14i1e77532_app1.docx]

Multimedia Appendix 2
Study information sheet.
[DOCX File , 60 KB - resprot_v14i1e77532_app2.docx]

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Abbreviations

BIT: Behavioral Intervention Technology
DDBT: Discover, Design/Build, and Test
DSMB: data safety monitoring board
GAD-7: Generalized Anxiety Disorder-7
HIPAA: Health Insurance Portability and Accountability Act
IRB: institutional review board
JITAI: just-in-time adaptive intervention
MRT: microrandomized trial
NIMH: National Institute of Mental Health
PHQ-9: Patient Health Questionnaire-9
PHQ-ADS: Patient Health Questionnaire Anxiety and Depression Scale
REDCap: Research Electronic Data Capture
SAE: serious adverse event

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Protocol

Acute Next-Day Effects of Alcohol Use on Daily Cognitive Functioning Among Young Adults: Protocol for a 21-Day Diary Study

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Abstract

Background: Young adults exhibit the highest rates of binge drinking and heavy alcohol use of any age group. Blackout drinking, or alcohol-induced memory loss, is a negative consequence of heavy drinking and is common among young adults. Alcohol use has been found to affect postintoxication cognitive functioning, especially among those who have experienced blackout drinking. However, there have been a limited number of studies that have assessed alcohol use and cognitive functioning via ecological momentary assessment (EMA). This methodology allows researchers to have a better understanding of the association between alcohol use and next-day cognition as well as blackout drinking and potential moderators between these associations.

Objective: The primary objective of the current study is to examine the association between alcohol use and next-day cognitive functioning among young adults. Multiple indices of alcohol use including blackout drinking and cognitive functioning will be examined. Additionally, moderators of these associations (at the day- and person-levels) will be examined. Potential moderators include other substance use, sleep, mood, hangover symptoms, and participant characteristics (eg, baseline alcohol use severity).

Methods: Eligible participants had to be aged between 18-25 years, a current university or college student, residing in the Eastern time zone, endorsing heavy episodic drinking at least 2 times in a typical month, and reporting a blackout drinking episode at least once in the previous year. After completing a web-based screening survey, eligible participants were directed to a web-based baseline survey that asked about alcohol use, self-reported cognitive functioning, objective cognitive assessments, and demographic information. Participants were then sent 5 surveys a day for 21 consecutive days, which asked about substance use, sleep, mood, and self-reported and objective cognitive functioning. Multilevel models will be used to examine day-level associations between alcohol use and cognitive functioning.

Results: A total of 304 participants were eligible, with 297 participants completing at least 1 EMA survey and cognitive assessment during the 21-day period. Data were collected between November 2023 and May 2024.

Conclusions: The primary aim of this study is to examine the association between alcohol use (including blackout drinking) and next-day cognitive functioning, with a secondary objective of identifying potential day- and person-level moderators of these associations. Findings from the study may help inform momentary interventions and identify characteristics of young adults that may put them at higher risk for experiencing negative consequences.

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KEYWORDS

alcohol use; cognitive functioning; young adults; ecological momentary assessment; blackout drinking

Introduction

Background

Rates of heavy alcohol use and alcohol use disorder peak in young adulthood around ages 18-25 years [1]. In 2023, an estimated 27% of young adults reported binge drinking (5+ drinks in a row) in the past 2 weeks, and 9% reported past 2-week extreme binge drinking or high-intensity drinking (10+ drinks in a row) [2]. An estimated 5.1 million young adults met criteria for a past-year alcohol use disorder in 2023 [1]. Even more common are acute negative outcomes of heavy drinking (eg, social-interpersonal consequences and adverse physical effects) [3]. A key negative consequence of heavy alcohol use is blackout drinking, or alcohol-induced memory loss during a drinking episode. Blackouts are common among young adults who consume alcohol, with approximately 50% reporting a lifetime history of a blackout [4]. Blackout drinking is particularly concerning given its associations with further harms from drinking, including physical injury, sexual assault, and overdose [5].

Controlled lab experiments have established the effects of alcohol use on postintoxication cognition in young adults [6,7]. Alcohol-related deficits have been identified in working memory [8], attention [9,10], psychomotor functioning [11,12], processing [13], and executive functioning [14]. Further, recent experimental evidence identified decreased volume in the posterior and central corpus callosum several days after one's 21st birthday (ie, a single heavy drinking event), even after adjusting for lifetime alcohol and cannabis use, and these effects were more pronounced among individuals who experienced a blackout during the event [15]. While this evidence suggests a link between heavy drinking and structural brain damage postintoxication, it is unclear whether heavy alcohol use also impacts daily cognitive functioning, such as working memory and attention, among young adults. Given that changes to the corpus callosum impact communication between hemispheres, heavy drinking potentially reduces functional adaptation across regions, particularly under cognitive load [16]. Cognitive and brain reserve capacities describe the potential for individuals to compensate for changes in brain structure with learned strategies to avoid experiencing declines in cognitive functioning [17,18]. Hence, this initial evidence supports early theorizing on the role of substance use in altering cognitive and brain reserve capacity [19], suggesting that alcohol and other substance use may disrupt the development of this compensatory mechanism in young adults, ultimately leading to greater functional impairment.

As noted in Pearlson [20], a critical area of further exploration is whether young adults actually experience functional cognitive consequences or disruptions in general everyday cognitive functioning as a result of heavy drinking. Particularly for young adults whose brain can typically accommodate structural changes [21,22], structural brain alterations may be reversed in the long term due to the plasticity of their brain [22,23]. A more salient indicator may be younger individuals' experiences of changes in everyday cognitive functioning [24]. Young adults who notice deficits in daily cognitive functioning may reduce engagement in cognitively stimulating activities (eg, social activities), establishing lifelong patterns of lower cognitive functioning.

Ecological momentary assessment (EMA), or collecting self-reported and behavioral data in real time and context via mobile devices, is ideal for studying functional changes in cognition. Disruptions in cognitive functioning can be small and are best captured via granular, sensitive measures in natural environments [25]. Functional changes can be observed in both objective measures (eg, executive functioning and memory) and subjective measures (eg, attentional lapses and difficulties concentrating). Beyond cognitive assessment, EMA has also been widely used for assessing alcohol use and its consequences among young adults [26,27]. Reporting on alcohol use in real time or the next morning can maximize recall of the amount of alcohol consumed [28]. Accurately identifying the number of drinks consumed in a drinking episode has important implications for identifying high-intensity drinking (8+ or 10+ drinks consumed in a day for female or male individuals, respectively) [29], which is associated with heightened risks for acute same- or next-day harms (eg, passing out or losing control) [30].

Analytically, EMA is ideal for examining the dynamic associations between alcohol use and cognition in daily life and for identifying contextual and person-level risk factors that may moderate such associations. EMA can be used to tease apart between- and within-person effects and thus isolate day-level effects of alcohol use on cognitive functioning on days with varying alcohol use intensity or experiences of blackout drinking. To date, very limited EMA or diary work has examined the role of alcohol use on cognitive functioning. In one study, higher intensity drinking was associated with difficulties in next-day self-reported attention and concentration [31], but performance-based measures of cognitive functioning were not assessed. Another EMA study examined the specific role of substance use on working memory across 7 days in a sample of young adults, finding that working memory was lower when using alcohol relative to not [32], but participants did not self-report experiences with their cognition. Among a sample of middle-aged and older adults who completed 8 days of surveys, participants self-reported their experiences with memory lapses and were more likely to have memory lapses if they drank more alcohol than the average amount they consumed [33].

As noted in prior EMA work, there is likely an acute impact of alcohol use on cognitive functioning that warrants further investigation, though several gaps in our understanding remain. First, with a more comprehensive assessment of cognitive functioning, we can determine whether the impacts of different

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levels of alcohol use are specific to a particular type of cognitive process (eg, working memory), global across cognitive processes (eg, fluid intelligence), or particular to an individual's perceptions of their ability to recruit those processes to complete daily tasks (eg, self-reported cognitive functioning). Second, through multiple assessments throughout the day, we can explore the duration of the effect of alcohol use intensity on next-day cognitive functioning (eg, do effects occur only upon waking or persist throughout the day?). Third, given the unique risks of blacking out [5,34] and the more profound structural impairments linked to blackout episodes relative to heavy drinking without blacking out [15], research exploring blackout drinking and cognitive functioning is warranted.

Aims and Objectives

Overview

Overall, even a single heavy drinking episode has been associated with short-term structural changes in the brain among a sample of young adults, and previous diary evidence suggests alcohol use may impact concentration and working memory capacity. As young adults are at higher risk of alcohol use and alcohol-related harms than any other age group, such immediate structural changes may signal a need for early prevention and intervention. Although the long-term impacts of alcohol use on the brain among young adults remain unknown, a key indicator of longer-term cognitive outcomes is observed functional impacts on young adult behavior in daily life. As such, changes in daily behaviors during this period could negatively impact cognitive health into midlife. In the current study, we collected intensive data across 21 days from a sample of young adults to explore the acute, next-day effects of alcohol use on cognitive functioning overall, across multiple timeframes, and by higher-risk drinking episodes (eg, high-intensity drinking and blackout drinking). We will also examine day-level and person-level moderators to identify moments and subgroups with greatest risk and greatest need for early targeted prevention and intervention efforts.

Primary Objective

The primary objective is to examine acute, next-day effects of alcohol use on cognitive functioning across a 21-day period for a sample of young adults. We will explore multiple indices of alcohol use (eg, whether they consumed alcohol and the number of drinks consumed) as well as higher-risk indices of alcohol use (eg, high-intensity drinking or blackout drinking) and their association with self-reported and objective measures of cognitive functioning (eg, daily memory lapses, episodic memory, and working memory).

Secondary Objectives

We will consider day- and person-level moderators of study associations between alcohol use and cognitive functioning to identify for whom and under what conditions the effects are most pronounced, which may ultimately inform targeted and real-time interventions for days and individuals at greatest risk. We will investigate other substance use, sleep, mood, hangover symptoms, and individual-level characteristics that have independent relationships with cognition or alcohol use [35-42] but have not yet been examined at the daily level among young adults who consume alcohol. Specifically, we will explore day-level moderators of hangover symptoms, mood, sleep, and prior-day cannabis and other substance use; and person-level moderators of sex, baseline alcohol use severity, and general cognitive functioning.

Methods

Participant Eligibility and Recruitment

To be eligible in the current study, participants must have: (1) been age between 18 and 25 years, (2) been currently enrolled at a 4-year college or university, (3) resided in the Eastern time zone throughout the duration of the study, (4) endorsed engaging in heavy episodic drinking (4+ or 5+ drinks in one sitting for female or male individuals, respectively) at least twice during a typical month, and (5) reported blackout drinking at least once in the past year. To verify eligibility status, participants were required to provide a ".edu" email address (ie, an email address associated with a university) and had to be within the Eastern time zone to complete the baseline cognitive tasks (to ensure participants received EMA surveys at the correct times). Participants were recruited via (1) flyers posted on campus of a large, public university and in the surrounding community, (2) email invitations to prior research participants who expressed interest in future research studies, and (3) the StudyFinder database of research studies seeking volunteers. On the study flyer, potential participants were instructed to email the study team if they were interested in seeing if they were eligible to participate.

Baseline Data Collection

Following informed consent, interested participants completed a brief web-based screener to determine eligibility. Eligible participants were automatically routed to complete a web-based baseline survey and cognitive assessments, which took approximately 30 minutes to complete. Participants completed a demographics survey; self-reported cognitive functioning items; performance-based cognitive assessments of episodic memory, executive functioning, and working memory; and self-reported typical alcohol use behavior (see Table 1 for the assessment battery). These measures represent key cognitive processes likely to impact daily functioning [43,44]. For episodic memory, participants completed a paired associates task: here, a list of 10-word pairs is presented, then participants are shown the first word of each pair and asked to recall the second. For executive functioning, participants completed a task-switching exercise categorizing objects by color (blue or green) or shape (square or rectangle) as quickly as possible based on a cue. For working memory, participants viewed 4 boxes that changed color in a random sequence and had to indicate when the same box changed colors twice in a row. Screening and baseline survey data were collected and managed with Research Electronic Data Capture (REDCap).

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Table 1. Study assessment battery.

Construct and subdomains	Assessment
Baseline assessment (approximately 30 min)	
Cognition	
Episodic memory	Paired associates [45,46]
Executive functioning	Task switching [47,48]
Working memory	N-back [49,50]
Self-reported cognitive functioning	PROMIS (Patient-Reported Outcomes Measurement Information System) cognitive functioning [51]
Alcohol use	
Quantity and frequency of alcohol use	Calendar grid of typical weekly drinking (Daily Drinking Questionnaire) [52]
Alcohol use severity	Alcohol Use Disorder Identification Test (AUDIT) [53]
Blackout drinking experiences	Alcohol-Induced Blackout Measure [54]
Demographic characteristics	Sex, age, race and ethnicity, and college education status
Daily and momentary assessments (approximately 5 min/prompt)	
Cognition (each prompt)	
Episodic memory	Modified backward number span [55,56]
Executive functioning	Modified Flanker inhibition task [57]
Working memory	Modified spatial n-back [58]
Self-reported cognitive functioning	Daily Cognitive Problems Checklist [43]
Substance use (first daily report only)	
Substance use	Checklist: all substances used the previous day (eg, alcohol, cannabis, and nicotine). If alcohol was used, report the number of standard alcoholic drinks.
Blackout drinking	Whether endorsed, “I couldn’t remember what I did/Forgot what I did” in response to, “Did any of the following happen to you as a result of your alcohol/other substance use yesterday?” [59]
Covariates or moderators	
Sleep quality (first daily report only)	Modified Pittsburgh Sleep Quality Inventory [60]
Hangover symptoms (each prompt)	Hangover Symptoms Scale [61,62]
Mood (each prompt)	Modified Positive and Negative Affect Schedule [63]
Motivation (each prompt)	Participants rate agreement with “I was motivated to perform well during this session.”
Current substance use (prompts 2-4 only)	Checklist of all substances used so far that day

Three-Week Ecological Momentary Assessment Data Collection

Follow-up surveys for the EMA portion of the study were collected online across 21 consecutive days (see Table 1 for a list of measures). Participants were sent email and text message prompts with the associated survey link daily at 11 AM, 1 PM, 3 PM, and 5 PM. The first prompt that participants completed each day included survey items about the prior day (“prompt 1”), including previous-day alcohol and other substance use, blackout drinking experiences, sleep, hangover symptoms, current mood, and cognitive functioning, plus objective (performance-based) assessments of cognition. At each subsequent assessment that day, participants reported on current substance use and mood and cognitive functioning was evaluated via both self-reported and objective cognitive measures. At the time of each prompt, participants were advised that they had 60 minutes to complete the survey questions and brief objective cognitive tasks. Average completion time per survey was approximately 3 (SD 6.12) minutes, and 90% of surveys were completed in less than 5 minutes. The EMA protocol was collected via Qualtrics. All objective cognitive assessments were collected and managed in the Gorilla Experiment Builder [64].

Participant Incentives

Participants received up to $193 for full study participation. Specifically, participants received $10 for completing the baseline survey, $2 per prompt completed, and $5 per week bonus for completing at least 20 out of 28 surveys each week.

Power Statement

We used simulations of planned multilevel models to account for dependencies in the data (SAS 9.4). For our primary

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objective (day- or moment-level associations between alcohol use and cognitive functioning outcomes), with n=300 and up to 84 surveys (21 days × 4 surveys per day), we have >80% power to detect relations between alcohol use and cognitive functioning accounting for 1% of variance. As some participants will not complete all surveys, we examined power for 80% and 50% compliance. These additional simulations resulted in power of >80% to detect the same relationship, indicating sufficient power in the presence of missing data. For secondary objectives, we are interested in differences due to day- and person-level moderators. To be conservative, we examined only scenarios with incomplete data (50% and 80%). Assuming these conditions, we can detect differences across moderators accounting for 1.7% and 1.6% of the variance, respectively.

Ethical Considerations

The institutional review board at the Pennsylvania State University approved all study procedures (#STUDY00022639). Participants provided informed consent before enrolling in the study. Study data are deidentified.

Results

Data were collected from November 2023 to May 2024. In total, 304 participants were eligible. Table 2 displays the demographic characteristics of the full sample. Of eligible participants, 97.7% (n=297) completed at least one EMA survey and cognitive assessment. Of participants who completed at least 1 EMA survey throughout the 21-day period (n=297), participants completed an average of 45 (SD 25.7) EMA surveys out of a possible 84 surveys. Average compliance for EMA surveys and cognitive assessments by prompt was as follows: 55.7% (SD 0.3%) for 11 AM, 57.1% (SD 0.3%) for 1 PM, 54.3% (SD 0.3%) for 3 PM, and 52.9% (SD 0.3%) for 5 PM. Of all possible days (6237 days), participants completed at least 1 daily survey on 73% (n=4553) of days. All primary data analyses are expected to be completed in 2026 and all primary manuscripts are expected to be submitted by 2027.

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Table 2. Demographic characteristics of the participants (N=304).

Variable	Value
Biological sex (n=304), n (%)	
Male	64 (21)
Female	240 (79)
Self-identified gender (n=304), n (%)	
Man	64 (21.1)
Woman	236 (77.6)
Gender nonconforming	1 (0.3)
Nonbinary	2 (0.7)
Transgender man	1 (0.3)
Sexual orientation (n=304), n (%)	
Heterosexual or straight	254 (83.6)
Gay	5 (1.6)
Lesbian	2 (0.7)
Bisexual	30 (9.9)
Queer	6 (2)
Asexual	1 (0.3)
Pansexual	1 (0.3)
Questioning	5 (1.6)
Age (years), mean (SD)[a]	20.34 (1.25)
Age (n=304), n (%)	
Younger than 21 years	161 (53)
21 years or older	143 (47)
Race (n=303), n (%)	
American Indian or Alaska Native	1 (0.3)
Asian	22 (7.3)
Black or African American	10 (3.3)
White	254 (83.8)
Not listed	5 (1.7)
Multiracial	11 (3.6)
Ethnicity (n=303), n (%)	
Hispanic	23 (7.6)
Not Hispanic	280 (92.4)
Race and ethnicity (n=303), n (%)	

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Variable	Value
Not Hispanic American Indian or Alaska Native	0 (0)
Hispanic American Indian or Alaska Native	1 (0.3)
Not Hispanic Asian	21 (6.9)
Hispanic Asian	1 (0.3)
Not Hispanic Black or African American	7 (2.3)
Hispanic Black or African American	3 (1)
Not Hispanic White	242 (79.9)
Hispanic White	12 (4)
Not Hispanic Not Listed	1 (0.3)
Hispanic Not Listed	4 (1.3)
Not Hispanic Multiracial	9 (3)
Hispanic Multiracial	2 (0.7)
College standing (n=303), n (%)	
First-year	53 (17.5)
Second-year	55 (18.2)
Third-year	105 (34.7)
Fourth-year	83 (27.4)
Other	7 (2.3)
Residence (n=304), n (%)	
Parent's or relative's home	17 (5.6)
College dorm or residence hall	83 (27.3)
House, apartment, or room (not college-affiliated)	202 (66.5)
Fraternity or sorority house	2 (0.7)
Typical number of drinks per week, mean (SD)[b]	13.14 (7.96)
Typical number of drinking days per week, mean (SD)[c]	2.77 (1.06)
Typical number of drinks per drinking day, mean (SD)[d]	4.73 (2.17)
Binge drinking days per month, mean (SD)[e]	5.96 (3.36)
Alcohol-Induced Blackout Measure, mean (SD)[f]	10.14 (2.89)
Blackout drinking frequency (n=304), n (%)	
Daily or almost daily	2 (0.7)
Weekly	9 (3)
Monthly	69 (22.7)
At least once in the past year, but less than monthly	224 (73.7)
AUDIT[g], mean (SD)[h]	9.25 (4.04)
Cognitive ability, mean (SD)[i]	33.03 (6.41)

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Variable	Value
Cognitive concerns, mean (SD)[j]	16.78 (6.46)

[a]The age range was 18-25 years.
[b]The range for typical number of drinks per week was 0-76 drinks.
[c]The range for typical number of drinking days per week was 0-7 days.
[d]The range for typical number of drinks per drinking day was 1-19 drinks/day.
[e]The range for binge drinking days per month was 2-18 days.
[f]The range for the Alcohol-Induced Blackout Measure score was 5-20.
[g]AUDIT: Alcohol Use Disorder Identification Test.
[h]The range for the AUDIT score was 2-28.
[i]The range for the cognitive ability score was 16-40.
[j]The range for the cognitive concerns score was 10-47.

Discussion

Anticipated Findings

Identifying the acute associations between alcohol use and blackout drinking behavior on next-day cognitive functioning, as well as the day- and person-level characteristics that moderate these associations, will provide critical information about the role of alcohol use on everyday cognitive functioning and highlight subgroups most in need of monitoring and early intervention. Findings will guide prevention and intervention programming in several key ways. Identifying whether and at what levels alcohol use impacts cognitive functioning can be used as an intervention tool: momentary interventions could incorporate timely feedback on young adults' self-reported prior-day alcohol use and objective, current cognitive functioning. Day-level moderators, such as hangover symptoms, mood, sleep, and prior-day cannabis and other substance use [35,37-40,42] may affect associations, and momentary intervention content can be tailored to participants' own risk factors and delivered in moments of greatest risk. Similarly, intervention content on typical drinking patterns and personal risk for cognitive concerns may be incorporated in existing brief motivational interventions tailored to young adults. Person-level variables that independently and synergistically impact alcohol use and cognition (eg, sex, alcohol use severity, and general cognitive functioning) [36,41] will identify higher-risk groups in need of targeted interventions.

Specific to examining blackout drinking, there have been several recent calls to include blackout-specific content in preventive interventions [4], as personalized information on typical drinking patterns, including blackout drinking, could maximize intervention impact. For some young adults, blackout drinking is associated with later drinking-related consequences [65]; thus, incorporating objective, deleterious outcomes of blackout drinking may help detect and intervene on problematic alcohol use patterns earlier. Given that brief alcohol interventions are more effective among individuals who have experienced a blackout [66], and interventions incorporating blackouts are estimated to save approximately $500,000 per year in emergency department visits [67], investigating within-person risks of blackouts and other problematic alcohol use behaviors (eg, high-intensity drinking) within this age group appears promising and impactful.

Limitations

It should be noted that future findings from this exploratory and developmental study should be interpreted with several caveats. First, generalizability to young adults who are not attending college or are attending a 2-year program may be limited as the data were from individuals aged 18 to 25 years currently attending a 4-year institution. Second, participants predominately identified as non-Hispanic White and female sex assigned at birth, which may limit the generalizability of findings to minoritized racial-ethnic groups and to men. Finally, although some of our cognitive assessments are objective performance-based, the majority of our data are based on participants' self-reports and may be impacted by social desirability or recall bias.

Conclusions

Overall, the findings will provide critical insight on the impact of alcohol use on daily cognitive functioning and will highlight subgroups and days at highest risk as targets for intervention. Results will position us to expand upon this work to (1) study young adults for a longer duration to determine whether cognitive functioning concerns accumulate over time and predict longer-term alcohol-related and cognitive problems; (2) study mechanisms underlying the link between alcohol use and cognitive functioning, including concurrent structural and functional brain changes; and (3) examine the role of day- (eg, cannabis) and person-level (eg, use severity) on the alcohol–cognitive functioning link.

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Peer review report by the Epidemiology, Prevention and Behavior Research Study Section - National Institute on Alcohol Abuse and Alcoholism (AA-2) Review Group - National Institute on Alcohol Abuse and Alcoholism (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 139 KB - resprot_v14i1e77584_app1.pdf]

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Abbreviations

EMA: ecological momentary assessment
REDCap: Research Electronic Data Capture

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Original Paper

Co-Designing Technology to Reduce Health Disparities and Address New Norms Post–COVID-19: Proposal for a Mixed Methods Community-Based Participatory Research Approach

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Abstract

Background: Everyday life has changed since the COVID-19 pandemic. Existing health disparities among underserved communities have been exacerbated. Latino and Native Hawaiian and Pacific Islander (NHPI) populations disproportionately experience health disparities, even when compared to other minority populations. Both populations have heart disease, cancer, and diabetes as the leading causes of death, and both have high rates of obesity. As we recover from the pandemic, we must consider the intersection of continued health disparities, new social norms and attitudes, and new patterns of health behavior.

Objective: The overarching goal of this project is to reduce health disparities among Latino and NHPI populations, considering new health behavior patterns, social norms, and increased technology use. The research project–specific aims are to (1) conduct key informant interviews and focus groups among Latino and NHPI populations; (2) develop and implement a community health and health behavior survey; and (3) co-design, develop, and test new technology that is meaningful and responsive to community needs and preferences.

Methods: Using community-based participatory research (CBPR) and mixed methods approaches, the interdisciplinary research team will develop new technology based on community insights (key informant interviews, focus groups, and a community health survey). With our community liaisons, we will recruit adult (18+ years old) Latino and NHPI community members from the northern region in San Diego County (ie, Oceanside, San Marcos, and Escondido), largely from culturally related groups and organizations, such as dance schools (hālaus) and churches. Qualitative data will be analyzed using directed content analysis, and quantitative data will be analyzed using descriptive and multivariate statistics. The main outcomes include the identification of community health needs, culturally appropriate interventions, desired modality of intervention strategies, and acceptability of the technology. We expect the new technology to be focused on mobile health (mHealth) smartphone apps. Components will likely include strategies to improve obesity-related health behaviors and mental health.

Results: This study received funding from the National Institute of General Medical Sciences in April 2022 as part of the Support for Research Excellence (SuRE) Program (R16). Key informant interviews and focus groups were completed in July 2023. Community health surveys were completed in August 2024. The development of the beta mHealth app began in September 2024 in partnership with California State University San Marcos (CSUSM) computer science students. Beta testing and evaluation will be completed by December 2025. The qualitative findings, identifying themes for a new mHealth app, were published in June 2025.

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Conclusions: A major strength of this study is that it works with the communities of intended impact to directly inform new innovations to promote health behaviors. This study includes unique partnerships and an interdisciplinary team of researchers, students, community members, and consultants/collaborators to inform practices that can impact health disparities among Latino and NHPI populations with technology and strategies that are innovative and effective.

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KEYWORDS

mobile health; CBPR; community co-design; academic-community partnerships

Introduction

Background

The COVID-19 pandemic has changed life as we know it. Existing health disparities were exacerbated, especially for underserved communities. In response, there has been an increase in government funding opportunities to develop and implement interventions to increase COVID-19 testing and address vaccine hesitancy. As we recover from the pandemic, we must consider the intersection of continued health disparities, new social norms and attitudes, and new patterns of behavior, particularly in how these factors impact health behavior and participation in health behavior interventions. New norms include increases in technology use, and formative research is needed to inform strategies that best capture the needs for reducing health disparities.

Many families, especially with school-aged children, were required to engage in online platforms for work and/or school, pushing our technology and its capabilities to grow faster than originally planned. While the digital divide continued to reveal itself during the pandemic and is still an important concern, the use of smartphones helps to close the gap, as smartphone usage among minority groups is comparable to non-Hispanic Whites, about 85% for adults and over 95% for teens [1,2]. Related to health, Latino/Hispanic people rely heavily on smartphones for health information and are more likely to use health apps, also known as mobile health (mHealth) [3,4]. Culturally tailored mHealth apps offer greater confidence in success [5]. Additionally, based on participant feedback from a pilot study, Native Hawaiian and Pacific Islander (NHPI) participants expressed interest in developing a mobile app that would promote health behavior change and encourage participation in intervention activities. Given the uncertainty of this "new normal," it is important to partner with communities to better understand how new habits and practices impact their health and health behaviors.

Latino and NHPI populations are some of the fastest-growing minority groups in the United States, with percent changes of 70% and 61%, respectively, between 2000 and 2019 [6]. California is an ideal location to engage with both the Latino and the NHPI communities, since it is home to more than 15 million Hispanic/Latino people and home to over 250,000 NHPI people, more than any other state, even Hawaii. In San Diego County, California, the population is over 30,000 for the NHPI community and about 1 million for Hispanic/Latino people [7]. Latino and NHPI people disproportionately experience disparities in health, even when compared to other minority populations. Both populations have heart disease, cancer, and diabetes as the leading causes of death, and both have high rates of obesity [8]. Over 81% of Hispanic Americans and 76% of NHPI people have overweight or obesity [9]. They also have the highest obesity rate compared to other groups in the United States and are more likely to be inactive, with a smaller percentage of NHPI people meeting federal physical activity (PA) guidelines compared to non-Hispanic White people [9]. Globally, out of the top 10 countries with the highest obesity, 9 were NHPI countries [10]. Diabetes is a persistent health concern among both Latino and NHPI populations. In 2018, close to 20% of NHPI adults had diabetes compared to 12.9% of African American adults, 11.5% of Hispanic adults, and 11.4% of Asian adults [9]. Serious mental illness is also a growing concern, with over 1 in 5 Latino/Hispanic people having a mental illness (about 17% of the population) and being 60% less likely to have received mental health treatment compared to non-Hispanic White people [9,11]. NHPI people also report alarming rates of serious psychological distress, at over 2 million adults between 2015 and 2016 [9]. Based on the 2020 census, 3.5% of NHPI adults experienced a serious mental illness within the past year [12]. These conditions and related health behaviors have been negatively impacted by COVID-19 restrictions, especially PA, sleep, mental health, and overall well-being [13,14]. Improving the health of Latino and NHPI communities is imperative for reducing health disparities. Moreover, working in partnership with communities will provide the best insights into appropriate, culturally relevant strategies.

Theoretical Framework

There is a growing emphasis on research that is community-based versus "community placed" [15]. This type of research translation highlights community partnership approaches in addressing health and health disparities, especially in diverse cultures. According to the Kellogg Health Scholars Program (Community Track), "CBPR (community-based participatory research) in health is a collaborative approach to research that equitably involves all partners in the research process and recognizes the unique strengths that each brings. CBPR begins with a research topic of importance to the community and has the aim of combining knowledge with action and achieving social change to improve health outcomes and eliminate health disparities" [16]. Over 15 years ago, the Institute of Medicine recommended CBPR as one of 8 new areas in public health education [17]. Sometimes referred to as "research plus" [18], CBPR not only increases the body of knowledge but also has potential to identify interventions that

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are sustainable and ready for dissemination because they have been developed with the community at stake [19].

CBPR approaches are iterative in that the process allows for the development of lasting partnerships between researchers and community members. However, critiques of CBPR include the lack of standardization in terminology, measurement, and evaluation [20]. To complement this study's CBPR approach, we will include concepts from the RE-AIM (Reach, Effectiveness, Adoption, Implementation, and Maintenance) framework, as highlighted by the National Cancer Institute's Programmatic Area of Implementation Science in the Division of Cancer Control and Population Sciences [21,22]. The RE-AIM framework, which has 5 steps for translating research into practice, has been used to translate research-based interventions into community-based programs [19,23]. RE-AIM can be used for planning, implementing, and evaluating studies. In this study, RE-AIM concepts will guide the type of formative information solicited from Latino and NHPI community members, particularly focusing on "reach," "effectiveness," and "adoption" of new technology for health behavior change. Taken together, concepts from the RE-AIM framework, along with the CBPR approach, provide a focused structure for this study.

The overarching goals of this project are to reduce health disparities among Latino and NHPI communities, especially considering new health behavior patterns, social norms, and increased technology use related to the COVID-19 pandemic. Through CBPR, we will partner with both communities to develop new technology—an mHealth smartphone app—to improve the health concerns identified by the communities (eg, obesity-related health behaviors and mental health). This project also focuses on training students who are underrepresented in biomedical research in all phases of the research and innovation development, with an emphasis on training future independent health disparities researchers and scholars. Students from diverse backgrounds and life experiences contribute to a more diverse workforce in the STEM (science, technology, engineering, and mathematics) fields. Beginning with this proposal and the academic-community partnerships established, each stage of work will continue to advance knowledge, practice, and innovative strategies for reducing disparities in Latino and NHPI communities.

Innovation

This research is novel in its responsiveness to the impact of the pandemic on health behaviors, social norms, practices, and preferences, and ultimately, how these factors influence health in communities that experience great disparities in health outcomes. A key component of this research is the development of a new technology, an mHealth smartphone app based on community insights through the CBPR process and formative research. While there have been some community-informed mHealth interventions [24-27], there is still a need to partner with communities to co-design and develop new technology, especially in partnership with underserved communities.

Our collaborative framework includes both community partners and an innovation incubator (Figure 1). Naturally incorporating the services of the California State University San Marcos (CSUSM) Innovation Hub with our senior software engineer consultant, community partners, and collaborators, this research will produce a unique experience in designing new technology for both the academic-community partners and students (underrepresented in biomedical research), highlighting excellence in research and research capacity.

Figure 1. Research team and collaboration framework; CSUSM: California State University San Marcos; PI: principal investigator.

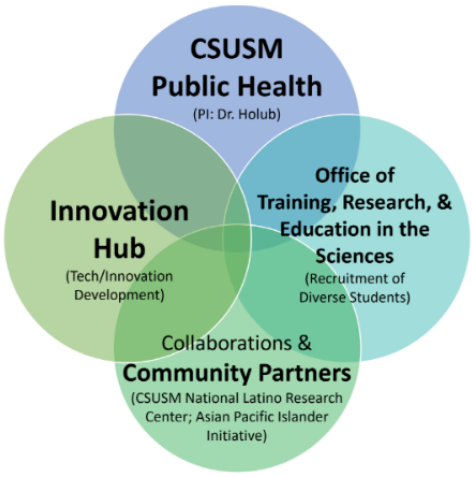

Preliminary Studies

The first Pacific Islander Community Health (PIC Health) Study began in 2013 by creating an NHPI community advisory board [28]. This formative study was funded by the American Cancer Society's Health Disparities Program. The PIC Health Study used a mixed methods approach to inform the development of appropriate strategies and culturally sensitive methods for behavior change interventions in the central/southern San Diego NHPI community. Beginning with a qualitative phase, key informant interviews and focus groups provided information for best practices for recruiting NHPI people, introducing research into the community, and cultural concepts for strategies to engage the community. The objectives of the interviews and focus groups were to identify and address potential barriers. Informed by the qualitative phase, a quantitative community health survey was developed to assess the themes identified in the qualitative phase, and other health risk behaviors, including objective measures of PA and obesity. A total of 163 (quantitative) community health surveys were collected from

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NHPI populations in central/southern San Diego; 31% (n=51) were Native Hawaiian, 20% Samoan (n=33), 47% Chamorro (n=77), and 3% (n=5) Tongan or Tahitian. Responses from the PIC Health survey (also confirmed qualitatively) indicated that interest in health topics was most similar among Native Hawaiians and Samoans, with obesity (mentioned by 65% of Native Hawaiian respondents, 60% of Samoan respondents, and 28% of Chamorro respondents) and diabetes (45% of Native Hawaiians, 52% of Samoans, and 42% of Chamorros) being the most frequently cited concerns (Holub, unpublished data, 2015). That study focused on central/southern San Diego, whereas this proposed research focuses on northern areas of San Diego with a high density of both Latino and NHPI populations, particularly Oceanside, San Marcos, and Escondido.

Based on the original PIC Health Study, a PA community-led intervention among Pacific Islander participants was conducted. This pilot study was funded by the Clinical and Translational Research Institute at the University of California, San Diego; the Academic-Community Partnership Pilot Project (2015); and the Howell Foundation for Women's Health Research, Community Engagement Initiative (2017).

The primary goal of this pilot study was to be responsive to the formative research of the PIC Health Study, indicating an interest in increasing PA among adult NHPI participants. The pilot study was a 12-week, pretest-posttest intervention study. We recruited 19 NHPI participants aged 18 years and up, among whom 15 (79%) were female and 4 (21%) were male, who did not report more than 150 minutes of MVPA in the last 7 days and who did not have medical conditions that would prohibit moderate-to-vigorous PA. The pilot study findings indicate that at 12 weeks, compared to baseline, the participants (1) had decreased BMIs by an average of 2.3 points (3.6 points for women); (2) were closer to meeting PA guidelines, increasing MVPA minutes per week by about 20 minutes (25 minutes for women), although still under the recommended 150 minutes per week (average: 137 minutes); (3) had increased their fruit and vegetable intake and decreased soda consumption; and (4) moved from "contemplation" to "action" for stages of change related to PA [29]. Key stakeholders (the community health promoter and a fitness consultant) reported that adapting to behavior change may have been difficult for some participants, and future interventions should consider mental health and coping skills strategies to supplement the fitness program.

Feedback from the pilot study led us to conduct focus groups on mental health among the pilot study participants. In 2019 and early 2020, current PA participants (as part of 2 focus groups) discussed mental health. In addition to identifying themes on mental health stigma, motivation, health-seeking behavior, and healthy mindset strategies, the theme most relevant to this proposal is the development of a mobile app for behavior change. Participants indicated that a mobile app that allows tracking of fitness progress may increase retention rates among members. In this study, participants identified the benefits of a mobile fitness app that includes promoting consistent accountability between members and instructors, promoting confidence in individuals to share fitness progress among members, and fitness educational videos to educate beginners and veteran members. One participant mentioned, "I would really like to see a tracking system, to create a consistent accountability. An accountable practice where everybody tracks where they are."

Based on the literature and preliminary studies, we expect that the proposed project will produce new technology focused on an mHealth smartphone app. Community members will guide the design, but we anticipate that the main components will include resources and strategies to improve obesity-related health behaviors and mental health. With a growing postpandemic need to better understand the intersection of continued health disparities, new social norms and attitudes, new patterns of behavior, and participation in health behavior interventions, the following specific aims were developed.

Research Project–Specific Aims

Specific Aim 1

The first project aim is to conduct key informant interviews and focus groups among the Latino and NHPI participants. Interviews and focus groups will center on gathering information, considering changing norms due to COVID-19, on attitudes, health needs, social norms, cultural beliefs, and preferences that will influence the participants' ability and willingness to partake in a health behavior intervention. We will conduct between 4 and 6 key informant interviews and 2 focus groups of 6 to 8 participants for each community.

Specific Aim 2

The second project aim is to develop and implement a community health and health behavior survey. After completing aim 1, we will develop a survey that includes emerging themes from the interviews and focus groups. Quantitative data will assess social and cultural norms, health behavior knowledge and patterns, use and acceptance of technology, and other health risk behaviors. We will survey 200 Latino and NHPI participants (about 100 from each community).

Specific Aim 3

The third project aim is to co-design, develop, and test new technology (beta version), in collaboration with the CSUSM Innovation Hub, that is responsive to community needs and preferences. Based on community feedback and in partnership, we will design and test an app that will help facilitate participation in a health behavior intervention. This app will be designed in a way that can be adapted for each community; for example, content adaptability and language options/controls. A diverse, interdisciplinary team of faculty, students, community members, and consultants will work to create a beta version of the intended product. We will recruit at least 30 participants from each community to test and use the new app. We will evaluate usability, acceptability, and the health behavior outcomes it aims to improve.

Research Capacity–Specific Aims

Specific Aim 1

The first research capacity aim is to enhance the research capacity of students who are underrepresented in biomedical research, especially toward training future independent health disparity researchers and scholars. We will work with the Office

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for Training, Research, and Education in the Sciences to recruit underrepresented students. We will recruit students from public health, nursing, human development, kinesiology (health science track), business, engineering, and other STEM disciplines. Next, we will evaluate the demographics and number of graduate and undergraduate students trained through this research in each project year, including student outcomes (eg, posters, papers, and graduate school application/acceptance rates).

Specific Aim 2

The second research capacity aim is to enhance the research capacity, sustainability, and excellence of CSUSM through meaningful collaborations between the principal investigator and the CSUSM Innovation Hub, the CSUSM National Latino Research Center (NLRC), and other campus collaborators, consultants, community partners, and community advisory boards. To ensure the continued success of these collaborations, we will evaluate attitudes, satisfaction, trust, and perceived impact of the collaboration. A survey will be carried out at the end of years 2 and 4 of the research project.

Methods

Overview of Methods

Through the CBPR process and formative research, this study focuses on reducing health disparities for Latino and NHPI communities through the co-design and development of an mHealth smartphone app in collaboration with the CSUSM Innovation Hub. Key informant interviews, focus groups, and a community health survey will be used to collect community-informed formative research. Second, this study highly involves students who are underrepresented in biomedical research with the goal of training future independent health disparity researchers and scholars. This proposal builds on interdisciplinary teams and collaborations to increase research capacity and excellence and address societal needs (Figure 1). Measures to assess underrepresented student involvement (eg, demographics, number, poster presentations, papers, and graduate school application/acceptance rates) and collaborations/partnerships (eg, attitudes, satisfaction, trust, and perceived impact of the collaboration) will be collected.

Study Research Design and Methods

Explanation

This proposal has 3 research project–specific aims and 2 research capacity–specific aims. The research project–specific aims are to (1) conduct key informant interviews and focus groups among Latino and NHPI participants; (2) develop and implement a community health and health behavior survey; and (3) co-design, develop, and test new technology (beta version), in collaboration with the CSUSM Innovation Hub, that is responsive to community needs and preferences. The research capacity–specific aims are to (1) enhance the research capacity of students underrepresented in biomedical research, especially toward training future principal independent health disparity researchers and scholars; and (2) enhance the research capacity, sustainability, and excellence of CSUSM through meaningful collaborations between the principle investigator and the CSUSM Innovation Hub, the CSUSM NLRC, and other campus collaborators, consultants, community partners, and community advisory boards. The RE-AIM Planning Tool will help guide protocol and interview development, ensuring that information is gathered related to concepts of reach, effectiveness, and adoption of new technology [21,22]. The RE-AIM Planning Tool serves as a checklist for key issues to consider when planning and developing an intervention.

Participant Recruitment

Latino and NHPI community members from the northern region in San Diego County (ie, Oceanside, San Marcos, and Escondido) will be recruited to participate in either the key informant Interviews (n=4-6 in each community), focus groups (n=6-8 each), survey (n=100 in each community), or product beta testing (n=30 in each community). Working in collaboration with the CSUSM NLRC and the Asian Pacific Islander Initiative, a Latino and NHPI community liaison will assist with participant recruitment. The participant inclusion criteria are as follows: (1) age 18 years or older and (2) identification as Latino, Hispanic, or Native of Samoa, Tonga, Hawaii, Guam, Fiji, or another Pacific Island. The NHPI participants in this study will be recruited from churches, hula “hālaus” (dance schools), and NHPI-related organizations and clubs, with support from a community liaison, who is an NHPI advocate and director of the Asian Pacific Islander Initiative. Our team has existing relationships with these organizations through her previous work. The CSUSM NLRC and collaborators will assist with recruiting Latino participants based on their long-standing relationships in the local area.

Children under the age of 18 will not be included in the proposed study because the intended health benefits are focused on and designed specifically for adult Latino and NHPI participants.

Approach and Measures

For the research project–specific aim 1 (interviews and focus groups), the purpose of the key informant interviews is to collect in-depth, qualitative information from people who are familiar with the culture and health patterns of Latino and NHPI communities. We will specifically target community leaders and members who can provide insight into the health concerns of their respective communities. These interviews will be conducted face-to-face by trained student researchers. We will conduct between 4 and 6 key informant interviews. Additionally, we will conduct 2 focus groups with 6 to 8 participants for each community (Latino and NHPI). The focus groups will gather information gained from the interviews and related to health knowledge, cultural beliefs, culturally sensitive methods to conduct research in the community, the acceptability of using new technology like health apps (mHealth), and the identification of barriers and solutions to participating in health behavior interventions. A trained student researcher will conduct and lead the focus group discussion, which will last about 1 hour. A second person will take notes, and the discussion will be audio-taped. Prior to the start of focus groups, a protocol will be developed based on key informant interviews and feedback from the research community boards (Multimedia Appendix 1). All qualitative data will be analyzed for themes to inform the development and design of a quantitative survey.

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To address research project–specific aim 2 (community health and health behavior survey), we will collect quantitative data assessing Latino and NHPI cultural norms, health knowledge and screening history, and other risk behaviors, including measures of PA, healthy eating, and obesity. We will survey approximately 100 Latino and 100 NHPI participants. The surveys will be self-administered. The measures listed are not exhaustive, as the qualitative phase of this study will help inform the development of the survey. Questions will include factors in the adoption of new technology, based on the extended unified theory of acceptance and use of technology [30], including performance expectancy, social influence, effort expectancy, facilitating conditions, perceived enjoyment, mobile self-efficacy, satisfaction, and trust [31]. Coping Skills and Cognitive Behavioral Process will be assessed using a 15-item scale [32]. Subjective PA will be assessed with the 16-item Global Physical Activity Questionnaire [33]. Sleep quality and amount will also be assessed. For demographic variables, we will collect information on the participants' age, gender, marital status, household members (children/adults), employment, household income, and education [34]. Acculturation will be measured using the 8-item Acculturation, Habits, and Interests Multicultural Scale [35]. Perceived religious influences on health behaviors will be measured using a 7-item scale developed by Holt and colleagues [36]. Partner Support will be measured using a 5-item scale [37]. Cultural values around family, respect, and gender roles are fundamental aspects among Latino and NHPI communities. Church/organization food environment around nutrition and healthy eating options during festivals and Sunday gatherings will be assessed. Other risk assessments will include Behavioral Risk Factor Surveillance System items on screening, alcohol use, smoking, and nutrition (National Cancer Institute Fruit and Vegetable Screener). Analyses and results from the qualitative and quantitative data will inform the themes, features, and general design of the new technology.

To address research project–specific aim 3 (co-design/test new technology), we will co-design, develop, and test new technology (beta version), in collaboration with the CSUSM Innovation Hub, that is responsive to community needs and preferences. Based on community feedback from aims 1 and 2 and in partnership, we will test at least one component of the newly developed mHealth smartphone app. This product will be designed in a way that can be adapted for each community (ie, with content adaptability and language options/controls). A diverse, interdisciplinary team of faculty, computer science students, community members, and consultants will work to create a beta version of the intended product. The new technology will be developed by incorporating themes and features into an app development environment. Computer science students will write code to design the app based on community input. We will recruit at least 30 participants from each community to test and use the new mHealth tool. Through feedback surveys and app demonstrations, we will evaluate the usability and acceptability of the new app and the health behavior outcomes it aims to improve (eg, obesity-related health behaviors and mental health). Additionally, we will incorporate an evaluation framework by Maar et al (2017) [38], which outlines an evaluation framework for mHealth interventions in diverse cultural settings. This framework includes the evaluation of major active components of the intervention, technology of the intervention, cultural congruence, task shifting, and unintended consequences [38]. Ultimately, the goal is to create a product for future development (in full) and testing in the project's next phase (research and funding).

Building Research Capacity

To align with this mechanism's emphasis on research capacity, this project will train undergraduate and graduate students in all aspects of this research, including conducting interviews, focus groups, and surveys, analyzing both qualitative and quantitative data, translating insights from the community to innovation development within an interdisciplinary team, and reporting the findings back to stakeholders and the communities. We will work with the CSUSM Office of Training, Research, and Education in the Sciences to recruit students who are underrepresented in biomedical research. The mission of this office is to provide a supportive multicultural environment for students in the biomedical sciences and related disciplines by sponsoring programs that focus on science education, student support services, research training, and research participation. In this regard, this campus collaboration will support the proposed research study by assisting in the recruitment of underrepresented students.

To demonstrate our commitment to training a diverse group of students who are underrepresented in biomedical research, we intentionally incorporated research capacity–specific aims, which will be measured and evaluated. To assess research capacity–specific aim 1 (training of underrepresented students), at the end of each project year, we will annually evaluate the demographics and number of graduate and undergraduate students engaged in this research project, including other student outcomes (eg, poster presentations, papers, and graduate school application/acceptance rates). We will enhance the research capacity of students from diverse backgrounds, especially toward training future independent health disparity researchers and scholars. We will also work with our campus partners to recruit students from a variety of departments, including public health (graduate students), nursing, human development, biology, kinesiology (health science track), business, and engineering. We anticipate that, across the 4-year project time, at least 20 undergraduate and graduate students will be involved in this study. This type of exposure to health disparities research that is based on the CBPR approach encourages students to pursue similar careers in health disparities research, behavioral sciences, and biomedical research.

Students will be part of interdisciplinary teams, which is tied to research capacity–specific aim 2 (meaningful collaborations). To address this aim, we will enhance the research capacity, sustainability, and excellence of CSUSM through meaningful collaborations between the principal investigator and the CSUSM Innovation Hub, the CSUSM NLRC, the Asian Pacific Islander Initiative, consultants, community partners, and community advisory boards. To ensure the continued success of these collaborations, we will evaluate attitudes, satisfaction, trust, and perceived impact of the collaboration [39]. A survey will be administered to all collaborators at the end of years 2 and 4 of the research project. A unique feature of this proposal

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is student exposure to innovation development (eg, mHealth tools) through collaboration with the CSUSM Innovation Hub. This exposes students to a diverse, interdisciplinary team spanning public health, anthropology, computer science, and entrepreneurship.

Analysis

For qualitative data, interviews from key informants and focus groups will be audio-taped, transcribed, and uploaded into ATLAS.ti (ATLAS.ti Scientific Software Development GmbH), a software used for qualitative coding and analysis. Two individuals, the principal investigator and one trained research assistant, will code and extract themes from the interview/focus group transcripts. Transcripts will be analyzed using directed content analysis to identify and categorize meaningful and detailed information about the participants' opinions, perceptions, and experiences [40]. Coding strategies will include highlighting passages for emergent themes and a priori categories derived from interviews [41]. Verification of the emergent themes will be conducted through investigator discussions using the developed coding framework. For quantitative data, descriptive statistics will be used to examine each construct in the community survey or beta testing evaluation using SPSS software (IBM Corp). We will use basic bivariate and multivariate analyses to describe the data. Depending on the type of outcome, linear or logistic regression will be used to model the relationship between health behavior outcomes and independent variables (eg, demographics, acculturation, religiosity, stress, etc). Data will be examined by race/ethnicity. We will also examine the usability and acceptability of the mHealth tool, student involvement, and the impact of the collaboration.

Project Timeline

Year 1 will be dedicated to the development of the evaluation tools, research team training and recruitment, and completion of key informant interviews and focus groups among the Latino and NHPI communities. Year 2 will focus on community health survey data collection and evaluation of all the formative research. Year 3 will focus on working with the Innovation Hub to co-design and evaluate the new technology (beta testing). Year 4 will be dedicated to finalizing the beta testing/evaluation, interpreting the findings, disseminating results (through conferences, manuscript preparation, and community presentations), and developing a Small Business Technology Transfer (STTR) application in partnership with our collaborators and Latino and NHPI community advisory boards. Student involvement will be evaluated at the end of each project year, and collaborations will be evaluated at the end of the second and fourth project years (Table 1).

Table 1. Study and evaluation timeline.

Activity	Year 1				Year 2				Year 3				Year 4			
	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4	Q1	Q2	Q3	Q4
Protocol and program development	✓	✓														
Develop evaluation tools and material	✓	✓														
Train research team (staff and students)		✓	On-go-ing	On-go-ing												
Recruit participants (Latino and NHPI[a])		✓	✓													
Key informant interviews/focus groups (RP[b] aim 1)			✓	✓												
Community health survey (RP aim 2)					✓	✓	✓									
Evaluation/analysis of formative research				✓			✓	✓								
Work with Innovation Hub to develop a product based on community feedback									✓	✓	✓					
Beta test product (RP aim 3)											✓	✓	✓			
Evaluation/analysis of beta testing														✓	✓	
Evaluate student involvement (RC[c] aim 1)				✓				✓				✓				✓
Evaluate collaborations (RC aim 2)								✓								✓
Dissemination and manuscript preparation															✓	✓
Development of STTR[d] grant with CAB[e]															✓	✓

[a]NHPI: Native Hawaiian and Pacific Islander.

[b]RP: research project.

[c]RC: research capacity.

[d]STTR: Small Business Technology Transfer.

[e]CAB: community advisory board.

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Ethical Considerations

This research falls under exemption 2 and exemption 3, as part of the Health and Human Services regulations for the protection of human participants in research [42]. Exemption 2 is met as the first phase of this research involved interviews, focus groups, and surveys among adult Latino and NHPI participants. Both the qualitative and quantitative data will be recorded in a way that the participants cannot be identified. Exemption 3 is met and applied to the last phase of this research, aimed at beta testing new technology. The new technology testing will center on usability, acceptability, and the identified health behavior it aims to change (anticipated to be benign in nature, brief, and harmless). Therefore, informed consent is waived, and participants will be provided with an information sheet (Multimedia Appendix 2).

Data will be collected in a way that cannot identify participants of this study. Research records will be kept confidential to the extent permitted by law. Participants will be identified by an ID code, and personal information from records will not be released without written permission. Participants will not be personally identified in any publication about this study. All sensitive information will be locked/secured or password-protected. Compensation for participants will be in the form of gift cards with the sum of US $30 for interviews, US $20 for focus groups, and US $10 for surveys. Multimedia Appendix 3 provides further explanations of human participant involvement, potential risks, and safety monitoring.

Results

This study received funding from the National Institute of General Medical Sciences in April 2022 (R16GM145519) as part of the Support for Research Excellence (SuRE) Program (R16). Multimedia Appendix 4 provides the review summary statement. This study also received prior approval by the CSUSM Institutional Review Board in January 2022. Recruitment began in late 2022. Key informant interviews (N=11) and 4 focus groups (N=14) were completed by July 2023. Community health surveys were completed by August 2024 (N=219). The development of the Beta mHealth app began in September 2024 in partnership with CSUSM computer science students who were completing a capstone project in fall 2024. Our project continues to collaborate with computer science students completing a capstone project in spring 2025. Beta testing and evaluation are expected to be completed by December 2025. Findings from the qualitative data (key informant interviews and focus groups), which identify themes for a new mHealth app, have been published [43]. Findings from the mHealth app beta testing are expected to be published by 2027.

Discussion

Overview

Given the COVID-19 pandemic's impact on new health behavior patterns, social norms, and increased use of technology, this proposal lays a strong foundation for collaborative co-design of new technology that advances knowledge, practice, and innovative strategies for reducing health disparities in a postpandemic context. We expect that the proposed project will produce new technology focused on an mHealth smartphone app. Community members will guide the design, but we anticipate that the main components will include resources and strategies to improve obesity-related health behaviors and mental health. A major strength of this study is that it works with the communities of intended impact to directly inform new innovations to promote health behaviors. When co-design and collaboration are priorities, the ability to design culturally tailored mHealth apps is enhanced, offering greater confidence in the success and sustainability of the intervention [5].

While there is little literature on mHealth app development for the NHPI community, there is some information on developing mHealth apps for the Latino community, and some studies have already shown the promise of culturally tailored mHealth apps for Latino/Hispanic people [44,45]. To position this proposal optimally, this work is also guided by a community advisory board and in collaboration with the CSUSM NLRC. This study includes unique partnerships and an interdisciplinary team of researchers, students, community members, and consultants/collaborators to inform practices that can impact health disparities among Latino and NHPI communities, along with technologies and strategies that are innovative and effective.

Additional strengths of this proposed project include the use of the mixed methods design, which facilitates a deeper understanding of community needs and health behaviors. Additionally, the project is guided by strong community engagement principles (ie, CBPR) and cultural relevance. Co-designing the mHealth innovation with the community creates a stronger sense of community ownership and cultural relevance. Some limitations include sample size, the need for expertise in app development beyond computer science students, and geographic constraints, as this study is focused on North County San Diego only.

After completing the objectives of this proposal, future work will focus on refining the new mHealth app and technology based on feedback from the beta version. The integration of artificial intelligence will also be timely, considering the direction of this research and technology development. Once the app is fully developed, a long-term evaluation of its impact on health outcomes will be essential to ensure the effectiveness and sustainability of the mHealth intervention. In the longer term, once the mHealth app is available to the public, the next steps will involve scaling up and addressing broader implications.

Challenges and Solutions

We recognize the challenges of academic-community partnerships and that the proposed methods may be modified as we obtain additional community input. Any needed precautions related to the pandemic will follow state and county guidelines. The current proposal is informed by preliminary studies, a focus group, and extensive experience working with both the Latino and NHPI communities. To address this potential challenge, we will carefully consider the pace at which we introduce this new study to community members. Ethical

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considerations also need attention when introducing mHealth technology, including informed consent, social implications, and privacy [46]. We anticipate that with endorsement from community leaders in our advisory board, clear/open communication, flexibility, and with great attention to cultural sensitivity, we can work to overcome these barriers.

Acknowledgments

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Conflicts of Interest

None declared.

Multimedia Appendix 1
Interview and focus group guide.
[PDF File (Adobe PDF File), 191 KB - resprot_v14i1e73927_app1.pdf]

Multimedia Appendix 2
Information sheet.
[DOCX File , 196 KB - resprot_v14i1e73927_app2.docx]

Multimedia Appendix 3
Protection of human participants.
[DOCX File , 28 KB - resprot_v14i1e73927_app3.docx]

Multimedia Appendix 4
Peer review report from ZGM1 RCB-2 (SS) - National Institute of General Medical Sciences Special Emphasis Panel, NIGMS Review of SuRE Applications (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 129 KB - resprot_v14i1e73927_app4.pdf]

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Abbreviations

CBPR: community-based participatory research
CSUSM: California State University San Marcos
NHPI: Native Hawaiian and Pacific Islander
NLRC: National Latino Research Center

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PA: physical activity
PIC Health: Pacific Islander Community Health
RE-AIM: Reach, Effectiveness, Adoption, Implementation, and Maintenance
STEM: science, technology, engineering, and mathematics
STTR: Small Business Technology Transfer
SuRE: Support for Research Excellence

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Protocol

Behavioral Nudges to Enhance Fidelity in Telehealth Sessions (BENEFITS): Protocol for Developing and Pilot Testing a Telehealth Tool to Improve Cognitive Behavioral Therapy Implementation

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Abstract

Background: The rapid expansion of telehealth provides a unique opportunity to integrate behavioral economics (BE) strategies into telehealth platforms to improve clinician fidelity to cognitive behavioral therapy (CBT)—either by enhancing clinicians' motivation to use CBT or by helping clinicians who are already motivated to act consistently on their intentions.

Objective: We will develop and evaluate "Tele-BE," a novel telehealth platform designed to nudge and incentivize clinicians to use core structural components of CBT. We focus on these structural components because they align with practices most likely to benefit from BE strategies, are delivered across diagnoses, and represent CBT competencies independently linked to improved patient outcomes.

Methods: We will refine the Tele-BE prototype in collaboration with clinicians and supervisors, who are the target end users (aim 1). Working closely with our web development team, we will field test and iteratively refine Tele-BE using rapid-cycle prototyping to optimize user experience and fine-tune the BE strategies (aim 2). The revised platform will then be evaluated in a 12-week open trial involving 30 community mental health clinicians, who will be randomized to either Tele-BE or telehealth as usual. Each clinician will deliver treatment to 2 patients, resulting in a total of 60 patient participants. All sessions will be recorded and coded to assess CBT fidelity. Clinicians and patients will complete questionnaires at weeks 1, 5, 9, and 12, with qualitative interviews conducted at the end of the trial. Primary outcomes will focus on fidelity to CBT structural components, measured via coding of recorded sessions. Secondary outcomes will include target implementation mechanisms—intentions and their determinants (attitudes, norms, and self-efficacy)—assessed using mixed methods, as well as overall CBT fidelity (aim 3). Additionally, trial data will be used to evaluate the acceptability and feasibility of Tele-BE from both patient and clinician perspectives, along with any potential ethical concerns associated with its use (aim 4).

Results: The study received National Institute of Mental Health funding in June 2024. Recruitment for aim 1 began in October 2024. As of March 2025, 6 participants had been enrolled in the initial development stage. Recruitment is ongoing, and we anticipate completing aim 1 by May 2025, after which we will prepare for aim 2 activities. We aim to complete all study data collection by the end of 2026. In accordance with our grant award, deidentified data from aims 3 and 4 will be submitted to the National Institute of Mental Health Data Archive for participants who consent to data sharing.

Conclusions: Findings will provide insight into the utility of a BE-informed telehealth platform for increasing clinicians' use of core structural CBT components, thereby improving overall CBT fidelity and patient outcomes. Results will also inform the design of future confirmatory trials.

Trial Registration: ClinicalTrials.gov NCT06601062; https://clinicaltrials.gov/ct2/show/NCT06601062

International Registered Report Identifier (IRRID): DERR1-10.2196/76035

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(JMIR Res Protoc 2025;14:e76035) doi:10.2196/76035

KEYWORDS

telehealth; behavioral economics; implementation; cognitive behavioral therapy; evidence-based practice

Introduction

Background

Telehealth for psychological interventions has existed for decades, with historically limited uptake, primarily due to strict regulations [1] and limited reimbursement [2]. COVID-19 facilitated the swift global adoption of telehealth [3], and payors have acknowledged the need to ease regulatory burdens and sustain telehealth reimbursement postpandemic [4-8]. To date, telehealth has primarily been studied as an alternative to in-person care [9-12] and as a means of supporting access to care for historically marginalized groups [13,14]. However, little research has examined how to leverage the platform to support evidence-based practices (EBPs) and patient-centered care.

Telehealth provides a unique opportunity to apply behavioral economics (BE) principles to structure therapy encounters in ways that nudge clinicians toward delivering high-quality services. BE approaches address psychological biases that influence individual decision-making [15]. These frameworks recognize that human decision-making often occurs under suboptimal conditions, leading individuals to deviate from "rational" choices in numerous ways. Classic examples of such "bounded rationality" (ie, the recognition that humans make decisions with limited cognitive resources and thus rely on heuristics [16]) include individuals failing to opt in to retirement investments that would serve their best interests (due to status quo or loss aversion bias [17]) or making suboptimal decisions in cognitively demanding situations (eg, as a result of decision fatigue or availability heuristics [15]). In health care, clinicians may be aware of the right course of action (eg, "I should deliver x treatment for y condition"), yet often choose other, less empirically supported interventions for various reasons related to environmental cues (eg, availability biases), individual cognitive styles (eg, aggregate heuristics), and other biases [18]. Research has shown that structuring environments and nudging clinicians toward recommended practices can improve quality of care [19-21]. Common BE applications include strategies that guide decision-making by providing information (eg, social reference points or peer comparisons, making key information visible), implementing structural changes (eg, changing choice defaults, altering options presented to influence the attractiveness of some choices over others), and offering cognitive assistance (eg, reminders) [18,22,23].

While BE holds strong potential to inform cost-effective, pragmatic implementation strategies that support clinicians in delivering EBPs, its role in changing mental health clinicians' behavior has received little attention. The nature of traditional behavioral health sessions—occurring behind closed doors and prioritizing privacy—makes it difficult to implement supports during encounters. The continuation of telehealth access postpandemic provides a context ripe for improving treatment delivery. Telehealth has traditionally been regarded as a medium for delivering treatment, with content and processes comparable to in-office visits [24]; however, it also offers an infrastructure well-suited to BE strategies that can optimize clinician use of EBPs, track and reward fidelity to EBPs, and make EBP use easier and more motivating.

In this study, Behavioral Nudges to Enhance Fidelity in Telehealth Sessions (BENEFITS), we will develop and pilot test an implementation strategy that leverages the technological infrastructure of telehealth encounters to nudge and incentivize clinicians to increase fidelity to the structural components of cognitive behavioral therapy (CBT). We focus on CBT because it is an EBP for many mental health conditions, and increasing clinician fidelity to CBT can enhance care quality and improve patient outcomes [25-27]. Prior research suggests that when community clinicians use CBT at all, it is often delivered with poor fidelity [28-30].

We focus on structural components of CBT for 2 reasons. First, they represent a core and distinct CBT competency [31,32] and form the backbone of CBT practice; they are delivered regardless of diagnosis. A typical CBT session begins with a brief check-in on treatment progress, a collaborative agenda, and a review of prior homework. The core of the session emphasizes intervention techniques and skills, and it concludes with planning a between-session homework practice. While the specific clinical content—such as which interventions are selected and what homework is assigned—is tailored to the patient's presentation, use of these structural components remains consistent across sessions. Structural components also support shared decision-making and facilitate the selection and tailoring of interventions to patient preferences and symptoms, thereby enhancing patient-centered care [33]. Clinical trials further suggest that these components are independently associated with improved clinical outcomes [34-37]. Our work has shown that community clinicians demonstrate consistently low fidelity to structural components [32,38], even when their intentions to deliver them are high [39].

Second, structural components are well-suited to BE strategies, which are best applied to change discrete, observable, and measurable behaviors. Leading theories of clinician behavior change [40-42], along with our prior studies [38,39], suggest 2 major reasons why clinicians trained in CBT fail to use CBT structural components—each with distinct implications for designing implementation strategies using BE approaches. First, some clinicians may have strong motivation (or intentions) to use structural components; however, aspects of their organizational setting or their patients' presentation in treatment may make it difficult to act on those intentions. For example, a patient may present with much to share, and the clinician may forget to set the agenda or be reluctant to pause the client long enough to do so. For these clinicians, effective implementation strategies should either make it easier to act on their intentions or bypass intentions altogether by making the use of structural components the default (eg, automatically sending progress

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monitoring measures to clinicians rather than requiring them to do so). Second, other clinicians may have weaker intentions to use CBT components due to factors that influence intention strength, such as holding negative attitudes about a specific component (eg, believing homework is unhelpful or irrelevant), experiencing limited normative pressure to use CBT components (eg, perceiving that one's supervisor disapproves of structured sessions), or having low self-efficacy (eg, lacking confidence in planning a homework assignment). For these clinicians, effective implementation strategies should strengthen intentions by improving attitudes, leveraging norms, or increasing self-efficacy to promote behavior change. BE offers strategies to address the mechanisms of action identified in both pathways and thereby improve clinician CBT delivery.

The field of surgery provides a useful example of the potential benefits of BE strategies for improving patient care. Surgeries are complex, requiring providers to execute highly specified procedural techniques while also knowing how and when to deviate in response to diverse problems or complications [43]. There is extensive evidence demonstrating the effectiveness of structuring surgical environments to minimize risk, optimize outcomes, and nudge surgeons to engage in safety and quality checks (eg, surgical checklists) [19,20]. Such behavioral infrastructure facilitates the delivery of high-quality care by reducing the cognitive load of remembering routine protocols [21], allowing surgeons to focus their efforts on applying clinical skill and judgment to optimally help patients. CBT structural components, when implemented correctly, provide the scaffold that supports clinicians in delivering CBT intervention techniques, which can be complex and often require adaptation [44,45] and tailoring [46] in response to patient needs that may change within and between sessions [47]. Unlike surgery, the private, in-person therapy environment has historically offered limited opportunities for BE strategies to support clinicians in delivering these structural components; therapy is typically conducted without a support team, as found in an operating room. Leveraging telehealth encounters to embed checklists and other nonintrusive nudges may reduce clinicians' cognitive load, allowing them to focus more fully on selecting and delivering interventions and skills that yield comparable benefits for their patients.

Goal of This Study

In BENEFITS, we will develop and evaluate Tele-BE, a novel telehealth infrastructure designed to nudge and incentivize clinicians to use core structural CBT components. Tele-BE is intended solely to support fidelity to the structural elements of CBT that should be present in sessions, regardless of where a patient is in active treatment (with expected exceptions such as first sessions, termination sessions, or crisis sessions). Tele-BE will remain agnostic to intervention content (ie, clinicians will be encouraged to use a CBT skill in session, but not any specific skill). Importantly, in other contexts, BE strategies have raised ethical concerns regarding coercion to engage in behaviors one might not otherwise choose [48,49]. Therefore, studying BE strategies to support mental health EBP delivery should incorporate careful consideration of participants' and end users' ethical concerns. We will address any concerns raised by clinicians or patients to ensure that clinicians do not feel undue pressure to deliver therapeutic care they consider inappropriate. Our specific aims are listed in Textbox 1.

Textbox 1. Study aims.

1. Aim 1

Design the Tele-BE prototype to increase clinician fidelity to cognitive behavioral therapy (CBT) structural components, in collaboration with 6 clinicians and 3 supervisors (target end users), guided by user-centered design principles.

2. Aim 2

Adapt and iteratively refine Tele-BE in an open field trial using rapid-cycle prototyping and testing with 5-10 clinicians and 5-10 patients.

3. Aim 3

Test the preliminary effectiveness of Tele-BE versus telehealth as usual in engaging target mechanisms and enhancing clinician fidelity to CBT in a 12-week randomized pilot trial (n=30 clinicians, 60 patients). Primary outcomes will be clinician fidelity to CBT structural components, measured via coded therapy sessions. We will also explore mechanisms of action—including intentions and determinants of intentions (attitudes, norms, and self-efficacy)—through surveys and interviews.

4. Aim 4

Evaluate the acceptability, feasibility, and ethical considerations of Tele-BE from both clinician and patient perspectives using surveys, interviews, and web analytics. We will apply mixed qualitative and quantitative methods to assess Tele-BE's impact on clinician treatment delivery, therapeutic alliance, patient satisfaction, and clinical outcomes.

Methods

Study Setting

All research activities will take place in the City of Philadelphia, building on a strong history of CBT implementation efforts in the region through the Beck Community Initiative (BCI). The BCI is a partnership with Philadelphia's Department of Behavioral Health and Intellectual Disability Services to implement high-quality CBT in the public mental health system. BCI provides training in CBT theory and strategies through intensive workshops, followed by 6 months of weekly case consultation. During the consultation phase, therapists submit recorded therapy sessions, and their CBT competence is rated in at least 4 sessions using the Cognitive Therapy Rating Scale (CTRS). Mean competence scores at the end of training (41.2) have been just above the criterion threshold for certification, highlighting substantial opportunities to further improve therapist skills even after training [50]. Importantly, BCI-trained therapists demonstrated substantial variability in their intentions

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to use CBT structural components following training [39]. Research also shows that training effects diminish over time without additional support, such as behavioral nudges [51]. Philadelphia's Medicaid behavioral health payor continues to support telehealth reimbursement, providing an ideal context in which to test the effects of BE strategies on CBT fidelity. All participants will complete a consent process with research team members before engaging in any study activities.

Conceptual Framework

Table 1 presents the target mechanisms and illustrates how Tele-BE is anticipated to map onto each, guided by leading behavioral theory to (1) strengthen clinician intentions to use CBT structural components when motivation is low, and (2) support clinicians in acting on their intentions when motivation is high. Multimedia Appendix 1 presents the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 checklist for this study.

Table 1. Proposed Tele-BE design features, target mechanisms, and implicated BE[a] principles.

Tele-BE features	Target mechanism	BE principle	Present in Tele-AU[b]?
Reminder message is sent to prompt the clinician to identify skills to review, introduce, or practice before sessions, and note identified skill in the web platform.	Intentions	Availability Bias: People tend to focus on what easily comes to mind	No; the clinician is directed to the standard telehealth interface only.
Clinicians are prompted to push out brief symptom measures while the patient is waiting for the session to start every 4 weeks.	Bypassing intentions; intention-behavior gap	Changing the Default: People will engage in behaviors that are easiest and in front of them	No; to collect patient symptom data for trial purposes, patients will be contacted by research staff directly to complete measures via SMS text message or email.
Template agenda of structural components alongside the embedded video that supports clinician pacing of session by adjusting which component is highlighted (eg, agenda is highlighted until the clinician clicks to indicate that the agenda was set, at which point homework review will highlight).	Intention-behavior gap	Reducing Choice Overload: People often avoid decisions if there are too many choices	No; the clinician is directed to the standard telehealth interface only.
Checkmarks indicating component has been completed; display adjusts as goals are reached.	Attitudes	Goal Gradients: People try harder when goals are within reach	No; the clinician is directed to the standard telehealth interface only.
Gamification (eg, badges) for goals met (eg, agenda completed >90% of the time). Tele-BE will provide automated congratulatory notifications for completing CBT[c] components and delineating them in the Tele-BE platform; exact format (eg, email vs embedded in the platform) and timing to be determined in development aims. For example, a clinician may get a notification congratulating them for preselecting a CBT skill for use 3 weeks in a row.	Attitudes	Hyperbolic Discounting: Preference for a small reward sooner over a larger reward later; Injunctive Norms: Perception of whether a behavior is approved	No
Regular feedback about elements completed from the clinical supervisor (exact timing to be refined in development). We will identify key benchmarks during our development phase to trigger a congratulatory message (if fidelity benchmark is met) or an encouraging message to increase component use (if benchmark is not met), using language refined in our P50 ALACRITY pilot trial.	Norms	Social Influence and Injunctive Norms: Perception of whether a behavior is approved	No
Downloadable summary of session activities for the clinical progress note. Information from the template agenda will be downloadable to reduce the time needed to write a session note.	Intentions and self-efficacy	Integrate Desired New Task into Existing Workflow; Make it Easy and Motivating to Use	No

[a]BE: behavioral economics.

[b]Tele-AU: telehealth as usual.

[b]CBT: cognitive behavioral therapy.

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Aim 1: Designing the Tele-BE Prototype in Partnership With Clinicians and Supervisors

Aim 1 will be conducted in 2 phases. In phase 1, we will interview 3 CBT-trained clinicians and 3 clinical supervisors who have previously received CBT training and either provide telehealth services or supervise a clinician who does. Clinicians and supervisors will not be recruited in dyads. Sample sizes are intentionally small at this stage, as the primary goal of aim 1 is to examine prototype usability to enable rapid refinement and development of the first fully functioning platform. We will present each anticipated Tele-BE feature and target mechanism (Table 1), along with initial prototypes (Figure 1), and solicit feedback on how to refine the prototype to maximize usability and engagement with target mechanisms (eg, clinician intentions, intention-behavior gap); minimize unintended negative effects on patient experience (eg, perceptions that clinicians are distracted); and ensure that Tele-BE integrates with clinical, supervision, and administrative workflows. We do not anticipate changing the structural components targeted, but we may make small adjustments to how each is described based on feedback. We will also ask whether there are additional session features that would be useful for Tele-BE to target or capture. Interviews will probe perceived motivators and barriers to adopting the Tele-BE system, including ethical concerns. For example, therapists may value the potential for improved session structure and care quality but express concern about patient perceptions of recording or about the platform infringing on their autonomy to make clinical decisions. Such feedback is critical for design and implementation planning (eg, clarifying that the interface is clinician-facing only and that clinicians can override prompts). Participants will also complete a brief demographics questionnaire to ensure that feedback is gathered from a diverse group across study phases. Recommendations from each participant will be summarized and reviewed by the larger research team to identify refinements before moving to the next phase. Results will be shared with the technology development team, which will build an initial Tele-BE working prototype incorporating this feedback. We will then reconvene the same participants for a second interview, during which they will trial the interactive prototype and suggest further refinements. All feedback will be collated and synthesized, with input echoed by multiple participants given greater weight in decisions about changes. Participants will receive US $100 in compensation for their activities, and their feedback will be integrated into the next Tele-BE iteration. Draft interview guides for aim 1, phase 1 activities are provided in Multimedia Appendix 2.

Figure 1. Prototyped mock-up of Tele-BE presession image. BE: behavioral economics.

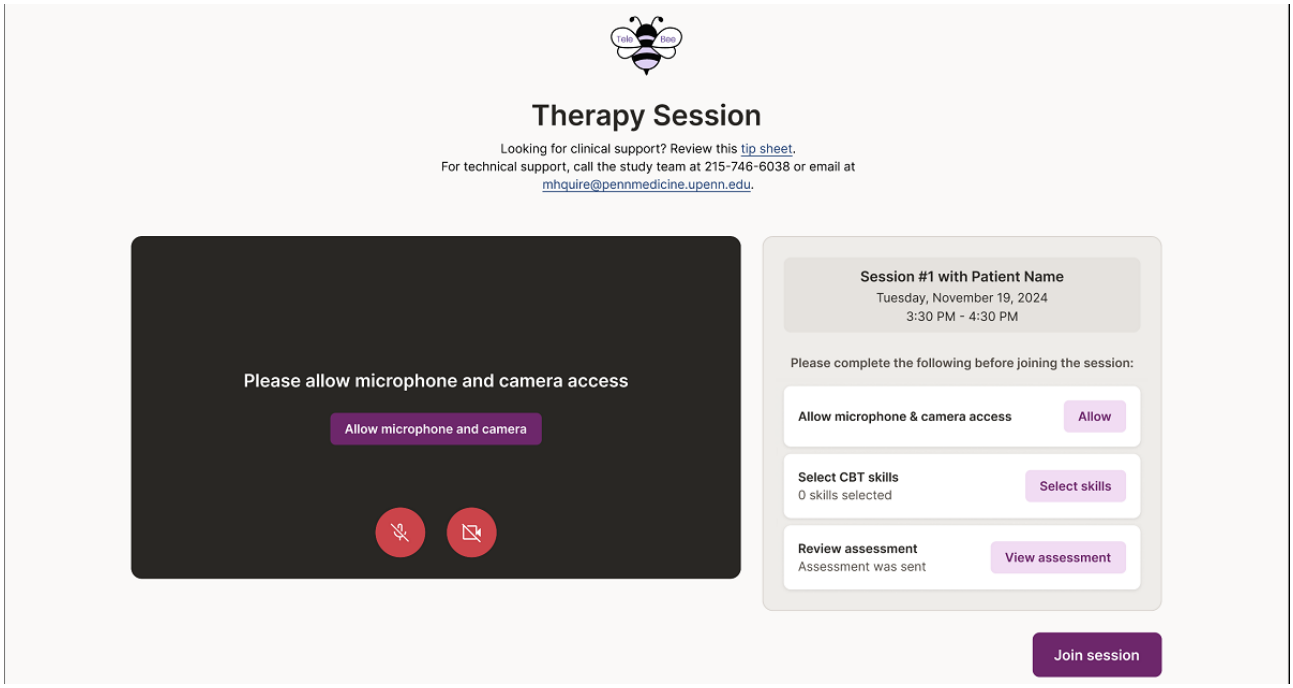

In phase 2, we will conduct usability testing with 3 newly recruited CBT-trained community clinicians, using the same eligibility criteria as in phase 1. Participants will interact 1-on-1 with a basic version of Tele-BE, with the primary objective of identifying major bugs and usability issues in preparation for aim 2. Consistent with phase 1, the small sample size is intentional, as the focus of this phase is to assess usability among clinicians, the tool's primary end users. Each clinician will meet individually with the study team and use the current version of Tele-BE for approximately 45 minutes. During this session, participants will conduct a mock therapy session with a graduate student clinician experienced in providing community-based CBT, followed by an immediate debrief to obtain feedback on both the clinician's end user experience and the "patient's" perspective. Participants' interactions with Tele-BE will be recorded using Health Insurance Portability and Accountability Act (HIPAA)–compliant videoconferencing software. Following the session, participants will complete a brief interview assessing the user experience, including learnability, acceptability, usefulness, overall satisfaction with aesthetics, perceived efficiency, and potential for integration with both clinical and supervision workflows. Semistructured interviews will probe

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each user interface element of the Tele-BE prototype. At the end of the session, participants will also complete brief quantitative measures to assess perceptions of Tele-BE, including the Acceptability of Intervention Measure (AIM) [52], a validated 4-item scale assessing the perceived acceptability of an innovation; the Feasibility of Intervention Measure (FIM) [52], a 4-item scale evaluating perceived feasibility; and the System Usability Scale (SUS), a well-established 10-item measure with strong psychometrics and sensitivity to change [53,54]. Participants will also complete a brief demographics questionnaire and receive US $75 for their participation. Collected data will identify areas for improvement in acceptability, feasibility, and usability, and refinements will be incorporated before aim 2.

Aim 2: Adapt and Iteratively Refine Tele-BE in an Open Field Trial

We will recruit 5-10 clinician-patient dyads who are already providing or receiving telehealth therapy services to engage with Tele-BE in an open field trial. The final sample size will be determined based on when saturation is reached (see below). The primary aim of this trial is to identify software bugs and evaluate usability and acceptability issues that emerge over extended use of Tele-BE, while refining our BE strategies. Secondary goals are preliminarily assessing the extent to which Tele-BE engages target implementation mechanisms and supports clinicians in delivering CBT structural components to guide further refinements. Clinicians and patients will be recruited in pairs, with participating clinicians using Tele-BE with a consenting patient of their choice for up to 4 consecutive therapy sessions or over 5 weeks of treatment, whichever occurs first. After obtaining consent, each clinician-client dyad will receive a personalized, secure link to use during their regularly scheduled telehealth sessions for up to 5 weeks. Only the clinician will require instructions on using Tele-BE. Client participants will not view the Tele-BE interface, so their telehealth sessions will appear similar to standard care.

We will use rapid-cycle methods to test and refine both the platform and the BE features developed in aim 1, with the goal of optimizing messages and visual displays. Adjustments will be made after each dyad completes aim 2 activities, continuing until feedback saturation is reached and a version suitable for formal testing in aims 3 and 4 is achieved. To streamline this process, we will use “fake back ends” to test BE strategies whenever possible, avoiding time-consuming web programming for features that may require revision. For example, study staff may message clinicians directly to simulate portal-generated messages based on feedback. The exact content of messages may evolve over time in response to participant input. Using a fake back end allows small changes across enrolled dyads to be tested more efficiently.

As noted, the Tele-BE platform is designed to be agnostic to specific CBT interventions and only nudges the use of interventions within the standard CBT session structure. A key focus of this design phase is ensuring that clinicians understand how to “override” any recommendation to use a particular structural component, maintaining full autonomy over clinical decisions. Aside from supporting Tele-BE use during already scheduled CBT sessions, research staff will provide no guidance on session conduct. Recruiting from the BCI-trained pool of therapists ensures that the CBT structure aligns with routine care. The only restriction is that clinicians will not be asked to use Tele-BE during first patient encounters or termination sessions, as these sessions may not follow the standard structure that Tele-BE is designed to support.

After each dyad’s trial period, staff will interview clinicians and patients separately about their experiences. Clinician interviews will assess system usability using the same structured interview employed in aim 1, covering learnability, acceptability, usefulness, satisfaction with aesthetics, efficiency, and workflow integration. Semistructured questions will also explore clinicians’ perceptions of how Tele-BE influenced their use of CBT structural elements, whether it produced any desirable or undesirable effects on the session or therapeutic relationship, and whether they felt comfortable overriding platform recommendations. The final portion of the interview will solicit suggestions for improving Tele-BE. Brief patient interviews will focus on the patient experience, assessing whether Tele-BE is perceived to have any desirable or undesirable effects on the therapeutic relationship or patient-centered care processes (see Multimedia Appendix 3). Clinicians will receive US $75 and patients US $25 for participating in these activities. We will use rapid qualitative analysis procedures to synthesize feedback and identify changes needed for the next testing cycle. All feedback will be reviewed with the full research team to resolve any conflicting information.

Aims 3 and 4: Evaluate the Preliminary Effectiveness of Tele-BE in Engaging Target Mechanisms and Enhancing Clinician Fidelity to CBT

Overview

Although aims 3 and 4 are scientifically distinct, study procedures will occur concurrently and are described together. We will randomize 30 clinicians who already provide individual CBT via telehealth for at least 2 clients to either Tele-BE or telehealth as usual (Tele-AU), with 15 clinicians per condition. Allocation will be balanced within organizations to ensure equal representation across conditions within each agency. Each participating clinician will deliver treatment to 2 patients over 12 weeks, the standard length for many CBT protocols, and clinician fidelity to CBT structural components will be tracked in each condition. While the primary goal is to evaluate the feasibility of our design and measurement approach for a fully powered trial, we will also measure patient symptoms, therapeutic alliance, and patient-centered care to explore preliminary clinical effectiveness outcomes and assess any potential concerns with Tele-BE (eg, clinician distraction or impact on therapeutic alliance) using mixed methods.

Participants and Procedures

We will identify at least 4 local agencies that use telehealth and have participated in system-sponsored BCI CBT training [55] as recruitment sites. A cascaded recruitment strategy, previously successful in other studies, will be employed to recruit 30 CBT-trained clinicians who treat study-eligible patients (ie, age

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14 or older, consistent with the local age of consent for mental health services; already deemed appropriate for CBT; and already using telehealth as their preferred therapy modality). In this approach, clinicians will then help select 2 patients with whom they plan to use CBT and will approach those patients about participating in the study. If a clinician has more than 2 patients with whom they plan to use CBT, 2 patients will be randomly selected from the larger pool for study participation. After obtaining informed consent, clinicians will be randomized to either the Tele-BE or Tele-AU condition. Study procedures will be identical across conditions, with the only difference being that clinicians in the Tele-BE condition will use the new telehealth tool, while those in the Tele-AU condition will use the telehealth methods established by their organization. All sessions will be video-recorded using encrypted, HIPAA-compliant technology via the clinicians' assigned telehealth platform. Clinicians and patients will complete questionnaires at 4 time points—baseline/week 1, week 5, week 9, and week 12—and participate in a qualitative interview posttrial (Table 2).

Clinicians will receive US $150 for completing study measures (US $50 for week 1 and posttrial, US $25 for weeks 5 and 9). Patients will receive US $5 per session for providing brief self-report data and allowing their sessions to be recorded, for a maximum of US $60; those completing qualitative interviews will receive an additional US $25. Clinicians and patients in both conditions will follow the same study activity schedule and complete the same assessment battery, except that participants in the Tele-BE condition will also respond to condition-specific qualitative interview questions. Compensation rates are consistent with our prior work.

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Table 2. Trial assessment schedule for aims 3 and 4.

Outcomes	Measures	Tele-BE[a]												Post
		1	2	3	4	5	6	7	8	9	10	11	12	
Aim 3 primary outcomes														
Structural component fidelity	CTRS[b] [56] and web analytics	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	N/A[c]
Aim 3 secondary outcomes														
Clinician intentions	Established stems [57]	✓	N/A	N/A	N/A	✓	N/A	N/A	N/A	✓	N/A	N/A	N/A	✓
Clinician attitudes	Established stems [57]	✓	N/A	N/A	N/A	✓	N/A	N/A	N/A	✓	N/A	N/A	N/A	✓
Clinician norms	Established stems [57]	✓	N/A	N/A	N/A	✓	N/A	N/A	N/A	✓	N/A	N/A	N/A	✓
Clinician self-efficacy	Established stems [57]	✓	N/A	N/A	N/A	✓	N/A	N/A	N/A	✓	N/A	N/A	N/A	✓
Aim 4 primary outcomes														
Acceptability	AIM[d] [58] and Interview	✓	N/A	N/A	N/A	✓	N/A	N/A	N/A	✓	N/A	N/A	N/A	✓
Feasibility	FIM[e] [58] and web analytics	✓	N/A	N/A	N/A	✓	N/A	N/A	N/A	✓	N/A	N/A	N/A	✓
Usability	SUS[f]	✓	N/A	N/A	N/A	✓	N/A	N/A	N/A	✓	N/A	N/A	N/A	✓
Aim 4 secondary outcomes														
Patient symptoms and functioning	PHQ-8[g], GAD-7[h], WHODAS[i] 2.0, and DSM[j] level 1	✓	N/A	N/A	N/A	✓	N/A	N/A	N/A	✓	N/A	N/A	✓	N/A
Therapeutic alliance	WAI-SF[k] (therapist), WAI-SF (client) [59]	✓	N/A	N/A	N/A	✓	N/A	N/A	N/A	✓	N/A	N/A	✓	N/A
Additional constructs of interest														
Contextual factors	Qualitative interview	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	✓
Clinician and patient demographics	Demographics survey	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Supervision practices	Adapted SerTIFY[l]-Supervision Form	✓	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	✓
Clinician social desirability	Edward's Social Desirability scale	✓	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Tele-BE costs	Qualitative interview and web analytics	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	✓

[a]Tele-AU: telehealth as usual.

[b]CTRS: Cognitive Therapy Rating Scale.

[c]N/A: not applicable.

[d]AIM: Acceptability of Intervention Measure.

[e]FIM: Feasibility of Intervention Measure.

[f]SUS: System Usability Scale.

[g]PHQ-8: 8-item Patient Health Questionnaire.

[h]GAD-7: 7-item Generalized Anxiety Disorder Scale.

[i]WHODAS: WHO Disability Assessment Schedule 2.0.

[j]DSM: Diagnostic and Statistical Manual of Mental Disorders.

[k]WAI-SF: Working Alliance Inventory—Short Form.

[l]SerTIFY: Self-reported therapist intervention fidelity for youth supervisor.

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Quantitative Measures: Aim 3 Primary Outcomes

The primary outcome for aim 3 is clinician fidelity to structural components of CBT. We will code all recorded therapy sessions (up to 720 sessions: 60 patients × 12 sessions) for the presence of 6 structural components: (1) discussion or review of patient symptoms, (2) homework review, (3) agenda setting, (4) skill instruction or review, (5) skill practice, and (6) out-of-session practice (homework). Coding will use items from the CTRS, a gold-standard CBT fidelity measure with 11 observer-rated items, including those indexing the specific structural components of interest (homework review and planning, agenda setting, skill instruction, and skill practice) [60]. Each CTRS item is scored on a 7-point Likert scale ranging from 0 (poor) to 6 (excellent), allowing fidelity to be defined in 2 ways: (1) the presence or absence of each component, and (2) whether each component meets a competency threshold (ie, a score of 4 or higher). Our primary focus will be on the presence/absence of each component, calculated as the sum of the binary outcomes. Presence above the competency threshold will serve as a secondary outcome. The CTRS demonstrates strong internal consistency and interrater reliability [60], as well as strong interrater agreement for general competency [32]. Importantly, the CTRS includes a subscale assessing structural competency [31], in addition to scores for specific structural components and an overall competency score.

Given the volume of recorded sessions, CTRS scores will be generated for each session using the Lyssn platform. Lyssn [61] (pronounced "listen") is a technology start-up that employs artificial intelligence (AI) to support training, supervision, and quality assurance of EBPs. Lyssn's cloud-based platform provides the following: (1) user management and organization of sessions, clinicians, and supervisors; (2) recording, playback, and annotation of audio or video from therapy sessions; (3) speech-to-text transcription; (4) AI-generated fidelity and quality metrics; and (5) data summaries and visualizations for feedback. Session recordings are automatically transcribed using Lyssn's speech recognition algorithms, which were trained on over 4000 sessions [62-64]. Using transformer-based deep neural networks [65], Lyssn developed AI-generated models for the 11 CTRS codes, trained on 2494 sessions with corresponding CTRS ratings within a cross-validation framework of training and test partitions [66,67]. Evaluation on a 30% test set of sessions, distinct from the training data, demonstrated strong predictive performance. For all but 1 code (*Understanding*, which is not a structural component of interest in this study), AI-generated predictions exceeded the 80% human reliability threshold. Using AI-generated metrics, the tools achieved 100% human-level reliability for total CTRS scores and demonstrated highly accurate reliability for individual items. Lyssn maintains an in-house coding team that continuously provides new validation and calibration data to monitor and sustain the performance of the AI algorithms.

While CTRS scores will serve as our primary fidelity metric, we will also examine self-reported fidelity to CBT structural components within the Tele-BE condition using web analytics data collected through the platform. As clinicians engage with Tele-BE, they will check off each structural component as it is completed in session or indicate if they intentionally override a component (Figure 1). This will provide self-reported data on structural component use for every recorded patient session in the Tele-BE condition. These data will allow comparison between self-reported use and Lyssn-generated CTRS scores, and provide insights into how and when clinicians override the Tele-BE infrastructure, informing aim 4 assessments of acceptability.

Quantitative Measures: Aim 3 Secondary Outcomes

Secondary outcomes are the target implementation mechanisms that align with our theorized mechanisms of action: intentions to use structural components of CBT and determinants of those intentions (Table 1). We will measure the strength of intentions separately for each structural component using established item stems from social psychology, designed to be adaptable to any behavior of interest [68]. Intentions will be assessed with 2 items on a 7-point scale, asking how willing and how likely a clinician is to use each component, with higher scores indicating stronger intentions. The 2 items will be averaged for each component. Determinants of intentions will be assessed through attitudes toward each component, measured with 4 standard semantic differential scales [40,69] (eg, 7-point scales ranging from "extremely unpleasant" to "extremely pleasant" or "extremely wise" to "extremely foolish"). Total scale scores will be computed by averaging all *z*-standardized items within each structural component, with higher scores indicating more favorable attitudes. *Norms* will be assessed using 2 standard item stems: the perception that "other people like me" will use the component, and that important others (eg, supervisors) will approve of their use, rated on a 7-point agreement scale. *Self-efficacy* will be measured with 3 statements on a 7-point scale assessing clinicians' perceived ability to perform each component (eg, agreement with "If I really wanted to, I could use an agenda"). All items will be asked separately for each structural component and aggregated for the primary analysis, with exploratory analyses examining variation by component.

Quantitative Measures: Aim 4 Primary Outcomes

Primary outcomes for aim 4 include Tele-BE acceptability, feasibility, and any potential ethical concerns raised by clinicians or patients regarding the platform. Acceptability will be assessed using the AIM [52]. Feasibility will be examined through a combination of the FIM [52] and web analytics data. Tele-BE usability will be evaluated using the SUS [53]. Psychometric support for these measures has been described above under aim 1 activities. All measures will be administered to clinicians in both conditions to allow comparison of quantitative scores for acceptability and feasibility. These measures will be supplemented with clinician and patient interviews, which will also assess potential ethical concerns, including any pressure clinicians may have felt from the platform to deviate from care they believed was in the best interest of their patients.

Quantitative Measures: Aim 4 Secondary Outcomes

Aim 4 secondary outcomes include patient-level outcomes such as therapeutic alliance, symptoms and functioning, and treatment satisfaction. During the trial, therapeutic alliance will be assessed every 4 weeks from both the patient and clinician perspectives using parallel versions of the Working Alliance

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Inventory—Short Form (WAI-SF). The WAI-SF is a validated measure consisting of 12 items that ask respondents to rate their perceptions of the therapeutic relationship on a 5-point Likert scale [56]. Patient symptoms will be assessed using the Diagnostic and Statistical Manual of Mental Disorders Level 1 Cross-Cutting Symptom Adult Measure [58] (23 items rated on a 5-point scale from 0=none/not at all to 4=severe/nearly every day, covering 13 symptom domains), the 8-item Patient Health Questionnaire [57] (8 items rated on a 4-point scale from 0=not at all to 3=nearly every day, measuring depressive symptoms), and the 7-item Generalized Anxiety Disorder Scale [70] (7 items rated on a 4-point scale from 0=not at all to 3=nearly every day, measuring anxiety symptoms). These measures will be completed by patients at 4-week intervals. Patient functioning will be assessed using the WHO Disability Assessment Schedule 2.0 (WHODAS 2.0) [59], a 12-item measure rated from 1 (none) to 5 (extremely or cannot do) across 6 domains: cognition, mobility, self-care, getting along, life activities, and participation. WHODAS 2.0 will be administered at weeks 1 and 12. Questionnaires will be sent electronically to patients at the established intervals by research staff. Patient satisfaction, including any potential ethical concerns regarding their clinician's use of Tele-BE, will be assessed qualitatively in a subsample of participants.

Quantitative Measures: Additional Constructs

We will additionally assess 3 quantitative measures: (1) supervisory practices, (2) clinician social desirability, and (3) the cost of Tele-BE. Clinician-reported CBT-specific supervisory practices will be measured at weeks 1 and 12 to identify potential differences between conditions. We adapted the Self-Reported Therapist Intervention Fidelity for Youth Supervision, originally a supervisor-report measure of supervisory practices, to be inclusive of clinicians working with adult clients and to specifically capture supervision related to CBT structural components. The adapted supervisory measure consists of 14 items rated on a 7-point scale, indicating the extent to which specific supervisory techniques are used (1=not at all to 7=extensively). Additionally, the 17-item Edwards Social Desirability Scale will be included in the baseline clinician survey as a potential covariate for clinician-reported engagement with the Tele-BE platform [71]. Finally, we will track the following cost metrics to inform more formal cost evaluations in future studies: (1) anticipated annual cost per clinician user for Tele-BE, including variation based on the number of patients with whom the platform is used—these estimates will be calculated in collaboration with our web development team to account for both base subscription costs and ongoing web maintenance;; (2) time required to train clinicians to use Tele-BE, which we expect to be minimal, tracked for each clinician and averaged at study completion; and (3) time clinicians spend logged into the Tele-BE interface, captured via web analytics.

Qualitative: Clinician Interviews (Aims 3 and 4)

All clinicians, regardless of condition, will complete interviews after their patients finish the trial period. The first portion of the interview will be identical for all clinicians and will explore perceptions of their intentions and the determinants of intentions to use CBT structural components throughout the trial. This portion addresses aim 3 questions regarding engagement of target mechanisms. Questions will be adapted from an established theory-guided qualitative interview [72], which includes items on attitudes toward an EBP, self-efficacy, perceived norms, and motivation. Questions will be asked separately for each structural CBT component of interest (Table 1). All clinicians will also be asked about barriers they encountered during the trial in using structural components, with specific probes regarding the impact of cognitive burden on delivery (eg, "To what extent, if at all, did factors like forgetting due to competing demands make it easier or harder for you to set an agenda?"). Collecting these responses from all clinicians will allow us to examine themes by condition to determine whether Tele-BE better engaged target mechanisms and reduced barriers to structural component delivery. The second portion of the interview will be administered only to clinicians randomized to Tele-BE and will address aim 4 by querying acceptability and any feasibility issues that arose. Patient interview questions may include, "How was your experience with Tele-BE? What aspects were easy or difficult to use?" We will also use self-reported fidelity data collected via web analytics to ask clinicians specific questions about how they decided to act on or override Tele-BE nudges (eg, electing not to review a planned homework) and their rationale for doing so. Clinicians will also be asked about any ethical concerns they or their patients might have, such as undue pressure to deliver structural CBT components or potential negative impacts on treatment processes. Finally, clinicians will be queried about any unanticipated resources required to engage with Tele-BE and asked to estimate how the platform influenced the time needed to prepare for or document a therapy session, informing our cost estimates.

Qualitative: Patient Interviews (Aim 4)

We will randomly select 1 patient per therapist to participate in a qualitative interview at the end of the 12-week trial period. If a patient declines, the second patient per therapist will be selected, ensuring 1 patient per therapist completes an interview. In the first half of each interview, research staff will ask patients about their perceptions of the therapeutic relationship during the trial (including any changes from before the trial), satisfaction with services received over the preceding 12 weeks, and perceived effectiveness of psychosocial treatment. This will allow comparison by condition to examine whether themes related to treatment processes differ depending on whether the clinician used Tele-BE or Tele-AU. In the second half of the interview, staff will query patients about their awareness of and perceptions regarding Tele-BE or Tele-AU and its influence on clinician behavior. Staff will then provide patients with information about Tele-BE and ask about their perceived likes and dislikes regarding their clinician's use of an enhanced telehealth interface to deliver care.

Preliminary Analyses

Data screening and analysis of missing data will be conducted following best practices. We will evaluate the psychometric properties of all scales used to assess constructs of interest (eg, coefficient alpha) to confirm adequate performance. Baseline

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variables will be analyzed as a randomization check to ensure comparable characteristics between clinicians in the Tele-BE and Tele-AU groups. We will also assess the sensitivity of our main comparisons to medium-to-large effect size imbalances between the randomized groups.

Quantitative Analyses

Aim 3 primary analyses will focus on structural component scores from the CTRS generated via the Lyssn platform, dichotomized as present or absent. An aggregate fidelity metric will be calculated for each session by summing the number of components present. We will use a linear mixed effects regression model to estimate the trajectory of completion scores over the 12 weeks of treatment. Fixed effects will include linear and quadratic time trends to capture the overall trajectory, although more flexible specifications will be considered if needed. To account for correlations arising from patients nested within clinicians, a random intercept for clinicians will be included, along with correlated residuals to address within-patient correlations over time. The model will use data from all 12 sessions to estimate time trends, as well as session means and standard errors for each session. Additionally, monthly estimates will be generated to align with participant survey intervals. As described above, we will also create an overall structural component sum score for each session by summing the total structural components rated as "completed at or above the satisfactory threshold" on the CTRS. If sufficient variability exists, we will model the time course using mixed effects models as described previously. If the score range is too narrow, we will use mixed effects ordinal regression models, with fixed and random effects specified similarly. All analyses will include patient demographics (eg, age, diagnosis) as covariates. In addition to CTRS-based fidelity measures, self-reported fidelity will be captured for the intervention group using web analytics data. The primary self-report measure will parallel the CTRS, summing the number of structural components rated as present. We will use a bivariate-response mixed effects model, treating CTRS and web-based measures as concurrent responses across the 12 weeks, to compare overall levels and trends over time between the 2 measurement methods.

To examine secondary outcomes (intentions and determinants of intentions), we will model monthly trends in clinician-reported intentions, attitudes, self-efficacy, and perceived social norms using approaches analogous to those described for fidelity measures. The primary distinction is that time will be treated as a categorical variable, reflecting the 3 assessment points rather than the 12 weekly sessions.

Missing Data Considerations

Based on ongoing prospective community mental health studies with comparable follow-up periods [73], we anticipate a clinician dropout rate of approximately 20% over 12 weeks, with minimal patient dropout among retained clinicians since patients are drawn from established caseloads. The mixed effects models described above will provide valid estimates and standard errors under the assumption that dropout is ignorable (ie, dependent only on observed outcomes and participant characteristics). We will conduct additional analyses to assess the sensitivity of our results to this ignorability assumption. Given the study's sample size, our primary focus will be on overall completion of the 12-week protocol. We will use logistic regression models to examine whether prior outcomes or baseline variables are individually associated with study completion. Variables showing strong associations with completion will be combined into a multiple logistic regression model to predict completion. Based on participant-level dropout probabilities estimated from this model, we will perform exploratory inverse probability–weighted versions of the main mixed effects models and compare intervention effect estimates from the weighted and unweighted models.

Qualitative and Mixed Methods Analyses

All interviews will be audio-recorded and transcribed for thematic analysis to complement quantitative data, allowing examination of target mechanism engagement (aim 3), Tele-BE acceptability and feasibility, and potential ethical concerns (aim 4). Given our interest in understanding clinician and patient experiences separately, interviews from these groups will be analyzed independently. Qualitative coding for both clinician and patient interviews will proceed in 6 stages. First, the coding team will familiarize themselves with the data by reading all transcripts and noting initial reactions. Team members will then debrief and share observations after reviewing all transcripts. Second, the coding team will develop an initial set of codes through line-by-line open coding of 2 randomly selected transcripts. Each team member will code the transcripts independently, then reconvene to compare codes and reach consensus. This consensus coding process enhances trustworthiness in data analysis and helps account for individual values and biases that may influence coding [74]. While reviewing the transcripts, the team will create a codebook documenting code descriptions to facilitate organization and reflection. The codebook will likely be guided by a combination of a priori areas of interest (eg, Tele-BE's impact on motivation to use structural components, acceptability of Tele-BE, and its effect on reducing cognitive burden in CBT delivery) as well as emergent themes arising directly from the data. Following codebook creation, the coding team will independently code all remaining transcripts line-by-line, compare codes, and reach consensus on coding decisions. The codebook will be iteratively updated as new codes emerge, capturing additional clinician and patient experiences revealed in the interviews. Third, the team will cluster codes based on shared patterns in content and generate themes that describe these patterns. Fourth, themes will be compared against quotes from the coded data to ensure they accurately reflect participant experiences. The team will refine themes by consolidating similar themes and breaking broader themes into subthemes as needed. Fifth, the team will finalize names and descriptions for all themes and subthemes. Finally, findings will be presented using illustrative examples from the coded data. To further enhance trustworthiness, coding team members will maintain analytic memos documenting their thought processes regarding codes, subthemes, and themes, supporting reflection on how values and biases—particularly related to Tele-BE—may have influenced coding decisions.

We will then conduct mixed methods analyses following best-practice recommendations to contextualize and interpret our quantitative findings [75-77]. Specifically, we will compare

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qualitative themes among therapists with low, medium, and high fidelity in Tele-BE, focusing on instances of overriding Tele-BE nudges, perceived ease of use, and any ethical concerns. Additionally, we will examine how patient ratings of therapeutic alliance are informed by their qualitative experiences with therapists using Tele-BE, and explore differences in patient-reported themes among therapists with varying levels of fidelity to structural CBT components.

Progression Criteria

We will examine acceptability and feasibility data, as well as trends in observed fidelity, to determine whether the pilot trial results support progression to a larger, confirmatory trial. For acceptability and feasibility, we will descriptively compare mean AIM and FIM scores between Tele-BE and Tele-AU clinicians; comparable scores would support the utility of progressing. If Tele-BE scores are notably lower than those in the Tele-AU condition, this would raise concerns regarding its acceptability and feasibility. Regarding fidelity, we will look for trends indicating (1) greater use of structural components in the Tele-BE condition relative to Tele-AU as measured by the CTRS, or (2) increased motivation to use CBT structural components in Tele-BE relative to Tele-AU, as suggested by qualitative analysis.

Ethical Considerations

All study activities will be overseen by the City of Philadelphia (protocol number 2024-58) and the University of Pennsylvania (protocol number 855355) Institutional Review Boards (IRBs). All participants will complete informed consent before participation. Identifiable data will be stored and analyzed using HIPAA-compliant, password-protected electronic systems. Participants will receive compensation for study activities as outlined above; these rates are consistent with prior work and designed to provide appropriate incentives while minimizing the risk of coercion. To address ethical considerations related to BE strategies—specifically the potential for nudges to influence participants to engage in behaviors they might not otherwise choose—we will collect data on any concerns raised by clinicians or patients. This will ensure that clinicians do not feel coerced to deliver care they deem inappropriate, and the feedback will inform future iterations of Tele-BE to prevent undue pressure in clinical decision-making.

Any modifications to the strategy or outreach materials will be submitted to the IRBs according to each institution's procedures. Any deviations from the protocol or adverse events will be documented and reported. All participants will receive a copy of their consent documentation before engaging in any study activities.

Data Safety and Monitoring

We will convene a 3-member Data and Safety Monitoring Board (DSMB) composed of independent experts with no professional or financial conflicts of interest related to the study or investigators. The DSMB will be responsible for reviewing study data for quality and integrity, ensuring adherence to the protocol, monitoring participant safety, evaluating study conduct and progress, and making recommendations regarding study continuation, modifications, or suspension/termination. The DSMB will meet before patient enrollment (ie, before aim 2) and annually thereafter for the duration of the study.

Results

The study received National Institute of Mental Health (NIMH) funding in June 2024. Recruitment for aim 1 began in October 2024. As of March 2025, 6 participants have been enrolled in the initial development stage. Recruitment is ongoing, and we anticipate completing aim 1 by July 2025, after which we will prepare for aim 2 activities. We aim to complete all data collection by the end of 2026. In accordance with our grant terms, deidentified data collected in aims 3 and 4 will be submitted to the NIMH Data Archive for participants who consent to data sharing.

Discussion

Contribution to Existing Work

The rapid expansion of telehealth [3] presents novel opportunities to address the therapy environment's infrastructure through technology, an approach previously limited by the closed-door, solitary nature of traditional therapy. This pilot randomized hybrid effectiveness-implementation trial aims to develop and evaluate the initial acceptability and feasibility of a novel telehealth tool designed to improve clinician fidelity to CBT structural components. While telehealth has long been promoted as a means of increasing patient access to CBT by expanding the pool of available providers, its potential to enhance clinicians' delivery of EBPs has not yet been fully leveraged. To our knowledge, this study represents the first effort to leverage telehealth platform infrastructure to enhance clinician delivery of EBPs, rather than treating telehealth primarily as a medium that replicates traditional face-to-face therapy. It is also among the first to apply and evaluate BE strategies for a psychosocial EBP. Our focus on the cross-cutting, transdiagnostic structural elements of CBT—rather than diagnosis-specific protocols or intervention techniques (eg, exposure therapy)—is a further point of distinction. BE strategies are particularly well-suited for changing discrete provider behaviors that are observable and measurable [15,78], and CBT structural components (eg, agenda setting) share these characteristics. This approach enables us to directly target clinician behaviors through Tele-BE in a manner that aligns with BE-informed implementation strategies. It also lays the groundwork for future research that could layer intervention-specific implementation strategies on top of those targeting structural components.

Design Considerations

Initially, we considered linking our trial phases to sessions attended rather than calendar weeks; however, most outpatient sessions occur weekly, and no-show rates are lower with telehealth [79]. These no-show rates will inform the design of future trials. We also considered including a broader set of EBPs with structural components (eg, dialectical behavior therapy), but focused on CBT due to its implementation within our partner public health system and to maintain specificity in our patient population. Other EBPs will be examined in future work. While

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we considered including supervisors in aims 2-4, we prioritized initial testing with direct end users—therapists and patients. Supervisor representation is incorporated in aim 1 design, and clinicians report on supervisory practices during the trial; follow-up trials will more formally include supervisors. We also considered limiting inclusion criteria to specific patient diagnoses for our clinical trial; however, given our focus on transdiagnostic CBT, we determined this approach would be more appropriate for subsequent trials. Additionally, we considered formally measuring organizational constructs (eg, culture and climate) in this pilot; however, our primary focus is on addressing target mechanisms of action through the BE strategies. Ultimately, we anticipate that Tele-BE will be implemented as part of broader organizational quality improvement efforts, making these organizational constructs critical to evaluate in larger, confirmatory trials.

Limitations and Efforts to Overcome Them Through Study Design

Several limitations of this study should be noted. First, although the study team aims to make Tele-BE as generalizable as possible, this pilot will not fully evaluate how it will perform across community agencies, which vary widely in resources and emphasis on telehealth service delivery [80,81]. For example, in Philadelphia, community mental health agencies differed in their capacity to transition quickly to remote care at the start of the pandemic, largely due to the costs of obtaining a HIPAA-compliant video service. To mitigate this limitation, our platform is designed to be embedded in a HIPAA-compliant web page rather than requiring a dedicated app installation, meaning clinicians will only need access to an internet browser to use it. In addition, we restrict eligibility to English-speaking patients, as our primary focus is on establishing the feasibility, acceptability, and preliminary effectiveness of Tele-BE. This restriction limits the generalizability of our findings. Finally, the 12-week duration of our pilot trial does not allow us to examine the potential for Tele-BE to support sustained fidelity over time. To address this, we will include specific questions in our aim 3 qualitative interviews with both clinicians and patients about their perceptions of using or receiving Tele-BE over a longer period, which will inform future studies on the sustainability of its effects.

Future Directions

In addition to next steps that include a fully powered evaluation of Tele-BE, future studies will extend its use to other EBPs that employ structural components and examine the durability of BE strategies (ie, whether effects persist over time), the generalizability of effects (eg, whether increases in fidelity transfer to in-person sessions conducted by the same clinicians and whether Tele-BE ultimately improves patient outcomes), and strategies for scaling up Tele-BE if it proves effective. This work will also lay the groundwork for future research to determine whether targeting structural components, rather than CBT broadly, is a more efficient way to improve fidelity across CBT protocols and, eventually, other EBPs that include structural components, such as dialectical behavior therapy. Such work also has the potential to advance the CBT and implementation science fields by enabling disaggregation of treatment effects associated with structural components from intervention technique fidelity. We will also explore additional strategies to leverage the telehealth infrastructure to make it easier and more motivating for clinicians to deliver evidence-based care, such as embedding links to CBT worksheets or tip sheets/session guides for common CBT skills delivered during sessions. Of note, Tele-BE is intended to address some, but not all, of the barriers clinicians face in delivering CBT. The nudge approach proposed here represents a low-cost, low-barrier method with substantial potential to increase clinician fidelity to a level that could meaningfully improve clinical outcomes.

Conclusions

This study will provide insight into the potential of leveraging the telehealth infrastructure to improve CBT fidelity by integrating BE strategies into the telehealth interface. If the study produces promising results, it will pave the way for large-scale testing of Tele-BE to enhance clinician CBT fidelity and patient outcomes across mental health settings that provide telehealth services.

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Authors' Contributions

EMBH, TC, DM, and KL conceptualized the study. PK, MB, and SY made meaningful contributions to the study design. EMBH and TC wrote the initial draft of the manuscript. All other authors reviewed the manuscript, provided input, and approved the submitted version. The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Conflicts of Interest

TC is an advisor and holds an equity stake in Lyssn. All other authors have no conflicts of interest to report.

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Multimedia Appendix 1
SPIRIT 2013 checklist.
[PDF File (Adobe PDF File), 144 KB - resprot_v14i1e76035_app1.pdf]

Multimedia Appendix 2
Draft interview guides for aim 1 activities.
[DOCX File , 2842 KB - resprot_v14i1e76035_app2.docx]

Multimedia Appendix 3
Draft of aim 2 interview guides.
[DOCX File , 23 KB - resprot_v14i1e76035_app3.docx]

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Abbreviations

AI: artificial intelligence
AIM: Acceptability of Intervention Measure
BCI: Beck Community Initiative
BE: behavioral economics
BENEFITS: Behavioral Nudges to Enhance Fidelity in Telehealth Sessions
CBT: cognitive behavioral therapy
CTRS: Cognitive Therapy Rating Scale
DSMB: Data and Safety Monitoring Board
EBP: evidence-based practice
FIM: Feasibility of Intervention Measure
HIPAA: Health Insurance Portability and Accountability Act
IRB: Institutional Review Board
NIMH: National Institute of Mental Health
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SUS: System Usability Scale
Tele-AU: telehealth as usual

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WAI-SF: Working Alliance Inventory—Short Form
WHODAS: WHO Disability Assessment Schedule 2.0

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Protocol

App-Based Smoking Urge Reduction Intervention for Young Adults: Protocol Combining a Microrandomized Trial and Conventional Between-Subject Randomized Trial

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Abstract

Background: Tobacco smoking is the leading preventable cause of morbidity and mortality in the United States, and young adults have high smoking rates. Although most young adult smokers are interested in quitting, they underutilize professional cessation support. Smartphones have wide reach and integration into young adults' lives, and these devices offer great opportunities to deliver cessation interventions by delivering messages suggesting coping strategies "in the moment" when smokers need cessation support.

Objective: The overall goal of this trial is to evaluate the efficacy of cognitive behavioral therapy (CBT) and mindfulness or acceptance and commitment therapy (ACT) messages for young adults targeted at specific high-risk situations for smoking.

Methods: We will conduct a microrandomized trial (MRT; within-subject randomization) to test the efficacy of CBT and mindfulness or ACT compared with control messages for reducing smoking urge up to 15 minutes after message delivery, nested in a conventional between-subject randomized controlled trial (RCT). A conventional between-subject control group of participants who will complete ecological momentary assessment (EMA) only without intervention messages will allow us to test if messages reduce cigarettes per day at the end of treatment, 3-month follow-up, and 6-month follow-up. Among MRT intervention group participants, we will explore how message efficacy may be moderated by substance co-use (cannabis, alcohol, other drugs) and exposure to specific settings (home, work, bars).

Results: As of June 2025, we had enrolled 58 participants of the target sample of 160, with 52% (30/58) assigned to the MRT group and 48% (28/58) assigned to the EMA-only control.

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Conclusions: Smoking onset is now more common among young adults than adolescents, and early cessation substantially reduces morbidity and mortality from smoking, making age-appropriate, tailored, and scalable interventions for this high-priority population even more important. Results of this trial will provide evidence on the efficacy of tailored intervention messages to help young adult smokers cope with smoking urges as an integral part of smartphone interventions. Findings will inform the field about key principles, strategies, and efficacy of situational tailoring of app-based tobacco use urge reduction messages.

Trial Registration: ClinicalTrials.gov NCT05836103; https://clinicaltrials.gov/study/NCT05836103

International Registered Report Identifier (IRRID): DERR1-10.2196/74388

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KEYWORDS

cigarette smoking; young adults; microrandomized trial; ecological momentary assessment; smartphone

Introduction

Background

Tobacco smoking is the leading preventable cause of morbidity and mortality in the United States, and young adults have high smoking rates [1]. Smoking onset is now more common among young adults than adolescents [2], and early cessation substantially reduces morbidity and mortality from smoking [3]. Although most young adult smokers are interested in quitting [4], they underutilize professional cessation support [5,6]. We need novel approaches to deliver evidence-based smoking cessation interventions to young adults [7,8]. Smartphones have wide reach and integration into young adults' lives (98% own a smartphone) [9]. These devices offer great opportunities to deliver cessation interventions by delivering messages suggesting coping strategies "in the moment" when smokers need cessation support. However, few cessation apps deliver evidence-based intervention content [10,11] and content tailored to individual needs [12-14]. Moreover, mobile smoking cessation interventions have yet to account for the impact of substance co-use (eg, alcohol, cannabis), which is frequent among young adults [15,16], on intervention effects.

One especially promising strategy for smartphone interventions is to target situations that elicit smoking urges. In our [17,18] and others' [19-22] prior work, these urges emerged as the most important triggers of smoking. The probability of smoking greatly increases as urge levels rise [23], especially among light smokers [24], who are common among young adults [25]. It is thus paramount for smartphone interventions to help young adults cope with these smoking urges. Clinical practice guidelines for smoking cessation [26] emphasize cognitive behavioral therapy (CBT) to help patients develop coping strategies for urges [27]. Mindfulness or acceptance and commitment therapy (ACT) offers a different approach, which teaches smokers psychological flexibility through accepting negative experiences [28]. Although there is evidence for the efficacy of both CBT and mindfulness or ACT smoking cessation interventions [29], it is unclear if these approaches are efficacious when implemented in real time and with young adults. The overall goal of this study is to evaluate the efficacy of CBT and mindfulness or ACT messages for young adults targeted at specific high-risk situations for smoking.

To evaluate the real-time impact of smartphone-based intervention messages on smoking urges, an alternative study design to traditional between-subject randomized controlled trials (RCTs) is needed. Microrandomized trials (MRTs) [30,31] offer an innovative factorial design appropriate for testing dynamic, context-sensitive interventions, including smartphone-based smoking cessation. Unlike static RCTs, MRTs use repeated within-subject randomizations, allowing intervention effects to be assessed across real-world situations experienced by participants as they go about their daily lives. By integrating geofence-triggered message delivery [32,33] (using GPS-defined virtual boundaries that activate messages when participants enter specific areas) and real-time data collection via ecological momentary assessment (EMA) [17,18,34,35], MRTs generate rich data on intervention message impact in near real time. This design supports causal inference and can help to identify the most effective strategies for tailoring messages to improve smoking cessation outcomes among young adults.

This study leverages a Health Insurance Portability and Accountability Act (HIPAA)–compliant mobile research platform designed for EMA studies, which enables real-time data collection, GPS tracking, and implementation of MRTs. This platform allows us to identify high-risk smoking situations using EMA, as well as time and location data; define geofences around these locations; and deliver CBT- and ACT-based intervention messages. By combining smartphone sensor data with within-subject randomization of message delivery, the platform enables us to test the causal impact of intervention messages on real-time smoking urges among young adults and addresses a critical gap in existing mobile health research.

Our team recently demonstrated the feasibility of determining high-risk situations for smoking and delivering tailored messages based on geofence triggers (virtual boundaries by GPS that trigger a message when a mobile device enters the area) [32]. Moreover, we conducted a recent successful pilot study that showed the feasibility of an app-based MRT using intervention messages triggered by geofence locations using GPS [36]. These feasibility studies inform this fully powered MRT to investigate message efficacy to reduce smoking urges and cigarette smoking behavior in young adults. The trial will address the specific aims described in the following sections.

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Aims and Hypotheses

Aim 1: To Test CBT and Mindfulness or ACT Intervention Message Efficacy for Reducing Momentary Smoking Urges (n=80)

To inform just-in-time interventions, it is crucial to test if CBT- and mindfulness or ACT-based messages can reduce momentary smoking urges. We will conduct an MRT (repeated within-subject randomizations of messages) to accomplish this [30,37]. In line with our existing protocol, participants first collect EMA data for 14 days, allowing us to determine high-risk situations for smoking. In the following intervention phase, participants receive tailored messages triggered by geofencing of participants' high-risk locations for a total of 30 days. Tailoring is based on established predictors of smoking relapse (stress and presence of other smokers) [38-40]. The MRT tests the efficacy of CBT versus mindfulness or ACT versus control messages for reducing smoking urge up to 15 minutes after message delivery. Secondary outcomes include smoking or other tobacco use (including e-cigarettes), affect, and stress.

Aim 2: To Test if Exposure to Urge Reduction Messages Results in Changes in Smoking Behavior Over Time Compared With an EMA-Only Control Group (n=80)

It is important to investigate if repeated messages in the MRT impact smoking behavior over time, in contrast to repeated assessment without messages. Thus, this study includes a conventional RCT component. Parallel to the MRT group, a control group completes EMA surveys only without intervention messages. This allows us to test if messages reduce smoking behavior. The primary outcome is number of cigarettes per day at the end of treatment, a 3-month follow-up, and a 6-month follow-up. Secondary analyses explore biochemically verified 7-day point prevalence abstinence, switching to e-cigarettes, and other tobacco outcomes. Post hoc dose-response analyses investigate the long-term efficacy of CBT and mindfulness or ACT messages on smoking behavior.

Aim 3: Explore Moderation Effects of Substance Co-Use (Cannabis, Alcohol, Other Drugs) and Exposure to Specific Location (Home, Work, Bars) on Urge Reduction Message Efficacy

A crucial research question to inform future mobile interventions is how well intervention messages work in different situational contexts and when people are co-using other substances. Among MRT intervention group participants, we will explore how urge reduction message efficacy may be moderated by substance co-use and exposure to specific settings.

Methods

Overview of Design

We will test tailored smartphone-based messages to support young adults with quitting smoking (study overview in Figure 1). Our study addresses 3 specific aims. For Aim 1, an MRT (within-subject randomization) with 80 young adult smokers will investigate the efficacy of smoking cessation messages based on CBT and mindfulness or ACT for reducing smoking urge 15 minutes after message delivery. In Aim 2, a built-in and conventionally randomized EMA-only control group will allow us to test if intervention messages result in changes in smoking behavior over time. The primary outcome will be self-reported number of cigarettes per day at the end of treatment, as well as at 3-month and 6-month follow-ups. Aim 3 will explore moderation effects of substance co-use (cannabis, alcohol, other drugs) and exposure to specific locations (home, work, bars) on urge reduction message efficacy among intervention group participants.

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Figure 1. Study overview. ACT: acceptance and commitment therapy; CBT: cognitive behavioral therapy; EMA: ecological momentary assessment.

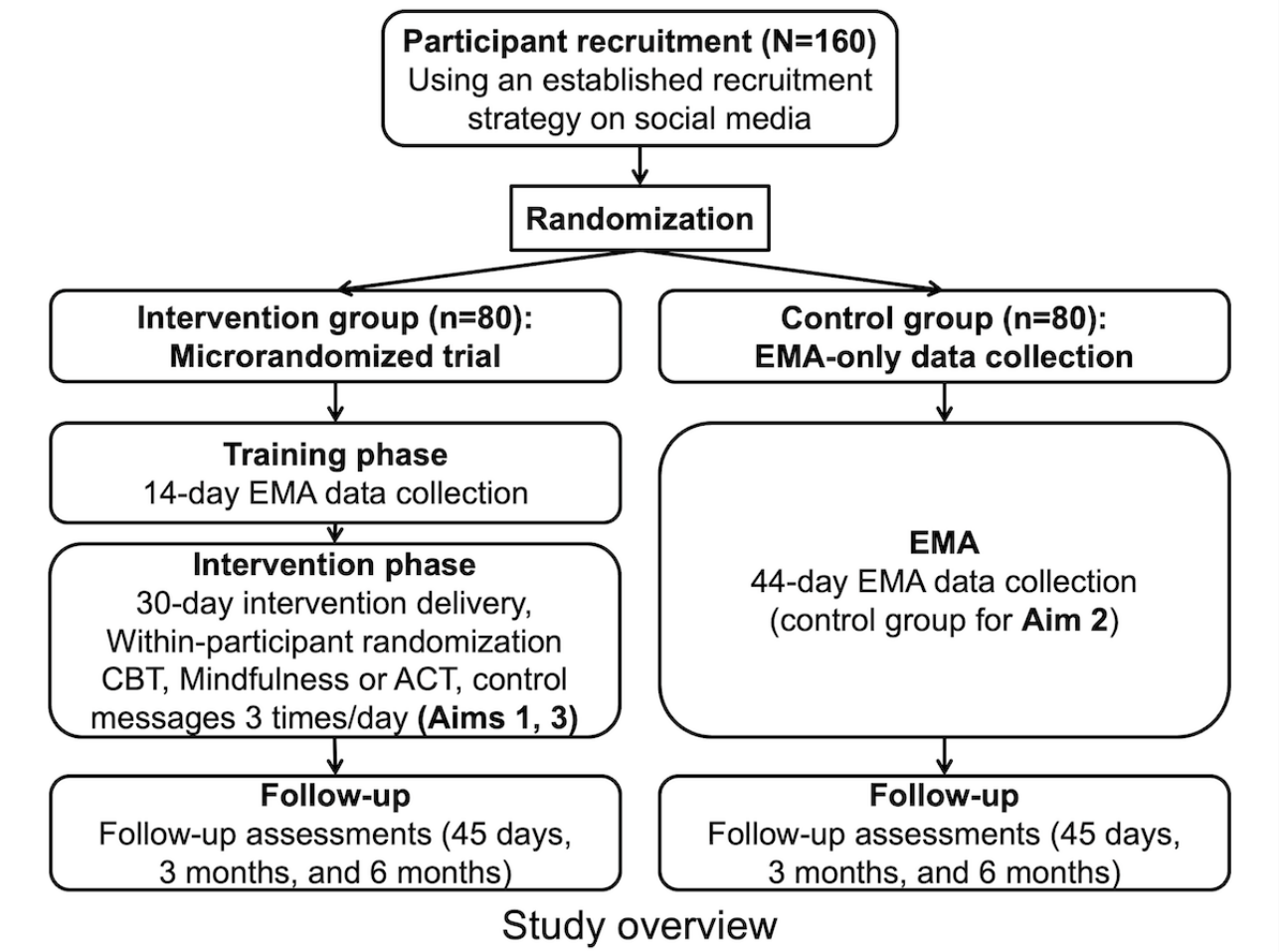

Inclusion Criteria

Participants will be young adults who (1) live in the United States, (2) read English, (3) are between 18 years and 30 years of age, (4) own a smartphone with iOS or the Android operating system, (5) have smoked ≥100 cigarettes in their lives and currently smoke at least 3 cigarettes per day on 5 or more days of the week, and (6) are planning to quit smoking within the next 30 days. There are no exclusion criteria for this study.

Recruitment

Participants will be recruited through social media advertisements, including Facebook, Instagram, Reddit, X (formerly Twitter), LinkedIn, and TikTok, a design and targeting strategy that we have previously used for recruiting diverse young adult smokers for EMA studies [18,41] and smoking cessation studies delivered through social media [35,42-44]. Additional recruitment efforts will use ResearchMatch, a nonprofit program funded by the National Institutes of Health that allows researchers from US institutions to reach out to and recruit volunteers interested in research studies. Finally, recruitment will be conducted through MyChart messages at Johns Hopkins. Eligible patients will be identified via electronic health records and will receive direct invitations through MyChart, the institution's patient portal.

Ethical Considerations

Human Subject Ethics Review Approvals

All study procedures are reviewed and approved by the institutional review board of the Johns Hopkins Bloomberg School of Public Health (IRB00013413).

Informed Consent

All participants will be required to meet eligibility criteria and provide online consent prior to study involvement. To assess understanding of the information provided in the informed consent, eligible participants will be asked a series of 3 multiple-choice questions regarding the informed consent before being able to proceed with the study. Answers will be collected, and any wrong answer will result in the potential participant being prompted to review the full consent document before attempting the consent questions again. Potential participants will not be enrolled in the study if they answer the questions incorrectly 4 times. After consenting to participate but before being enrolled into the study, participants will be required to send study staff a picture of a valid identification (eg, driver's license) that has their name, picture, and birth date to validate their age and the fact that they are a real person. Only the participant picture on the ID (headshot) will be retained for biochemical verification of smoking abstinence and will be deleted at the end of data collection.

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Privacy and Confidentiality

Participant privacy and data confidentiality will be maintained throughout the study. Screening, baseline, and follow-up survey data will be collected using the Qualtrics survey platform, and data are securely stored on Johns Hopkins servers. Moreover, the study utilizes a HIPAA-compliant mobile research platform (MetricWire Catalyst) to administer EMA surveys, capture GPS location data, and deliver intervention messages. Data collected through the app are encrypted during transmission and securely stored on the platform's servers. No personally identifiable information is stored on the participant's device. All location data are time-stamped and linked only to unique participant identifiers. Access to raw data is limited to authorized study staff. Data used for analysis are de-identified and stored on secure, access-controlled servers at Johns Hopkins. Any publications or presentations resulting from the study will use only aggregated or anonymized data. For example, location data points may be jittered or mapped to an alternative base layer to maintain participant anonymity.

Compensation Details

The study will use an incentive scheme to reward participants for high compliance with EMA prompts. Participants will receive US $2 for each day of participation in the EMA surveys (US $2 x 44 days = US $88) plus an extra incentive of US $90 if they complete at least 75% of the prompted assessments. Participants will also receive additional incentives for completion of baseline (US $10) and follow-up surveys at 3 months and 6 months (US $20 each). The maximum total incentive amount will be US $228 for participants in the trial.

Study Procedure

Randomization

We will use a dynamic minimization randomization approach to assign participants into the MRT intervention group (n=80) and EMA-only control group (n=80; Figure 1) while ensuring balance across arms on gender and nicotine dependence status. The variable known to robustly impact smoking cessation success is level of nicotine dependence (smoking within first 30 minutes after waking: yes/no) [45]. Gender will be used as additional variable to be balanced across arms. This adaptive approach recalculates imbalance scores in real time based on the distribution of previously assigned participants, assigning participants to the group that minimizes overall imbalance. Adaptive randomization using minimization will enable real-time assignment while ensuring balanced allocation of participants by key variables that may impact intervention outcomes.

Technology Implementation

For technology implementation, we will work with the Canadian company MetricWire and their Catalyst system. This company has developed a technology platform to develop, deploy, and conduct MRTs using an app on participants' own devices. MetricWire is HIPAA compliant, thus minimizing participant risk for loss of privacy. Further, we have successfully used their system in our previous EMA studies [46-52].

Intervention Messages

Intervention messages came from several previous studies [33,53,54]. Initially, these intervention messages were refined internally and combined with image content from free stock photo websites (Pexels, Unsplash). See Figures 2 and 3 for intervention message examples. Before inclusion in the trial, a total of 124 intervention messages were rated by an online Qualtrics panel of 301 diverse young adults (18-30 years old) who endorsed current cigarette smoking. Each participant rated 10 randomly selected messages (3010 total message ratings; 24.3 ratings per message) on dimensions of content, design, helpfulness for in-the-moment urge reduction, and helpfulness for quitting smoking [55]. Of these 124 messages, the 34 messages with lowest average scores on dimensions of helpfulness for in-the-moment urge reduction and helpfulness for quitting smoking were dropped, for a total of 90 messages that were retained and used in this trial. All intervention messages are available on the project Open Science Framework page [56] and in Multimedia Appendix 1.

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Figure 2. Intervention message examples for distraction and acceptance messages, including image and text content for a cognitive behavioral therapy (CBT) distraction message: "Keep your mind occupied if you get an urge. Do a mental puzzle, make your next shopping list, read a book, write a poem...you might be surprised how well occupying your mind can get rid of urges.".

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Figure 3. Intervention message examples for distraction and acceptance messages, including image and text content for an acceptance and commitment therapy (ACT) acceptance message: "Take a minute to notice what the urge feels like in your body without smoking a cigarette. Notice what is going on. See what happens. Does the urge pass?".

Participant Compliance and Incentives

Frequent assessments may lead to participant noncompliance and study attrition. Procedures are built into the study to prevent attrition over time: The app tracks participant compliance and provides feedback to participants. We will monitor compliance over time; proactively reach out to participants via calls, text messages, and email to keep them engaged; and increase contact with participants if their compliance drops below the target of a 75% response rate. We will explore potential participant problems and remind them of the importance of compliance for data quality and of the extra incentive for high compliance. Compensation details are provided in the Ethical Considerations section of the manuscript.

Treatment Conditions

Training Phase—EMA Data Collection

Baseline Survey

Initially, all participants will complete a baseline survey on the online survey platform Qualtrics to assess basic demographics; smoking and other tobacco use behavior, including e-cigarettes, nicotine dependence [57], quitting history and current quit motivation, and frequency and intensity of smoking urges; and other substance use behavior including alcohol and cannabis. Smoking-specific experiential avoidance, a measure to assess a person's willingness to experience negative mental states (eg, urges, mood, thoughts), will be assessed with the Avoidance and Inflexibility Scale [58,59]. Psychological flexibility will be assessed with the CompACT-15 [60]. Baseline measures will also include psychological distress [61].

EMA Data Collection

Before EMA data collection, participants will be contacted by phone to receive detailed instructions on how to use the EMA study app. Participants will use their own smartphones and the study app to collect data on smoking situations over the course of 14 days (EMAs of smoking situations and smartphone location sensor data). Participants will complete 3 randomly prompted EMA surveys per day and will report every time they smoke a cigarette. A random subset of these cigarette reports will trigger up to 3 EMA smoking survey prompts per day. All EMA surveys and codebooks are provided in Multimedia Appendices 2 and 3.

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EMA Momentary Surveys

Smoking urges will be recorded with a single item in accordance with recommendations from the Society for Research on Nicotine and Tobacco. Additional questions will examine internal and external aspects of the situation. The number of questions asked will be limited to ensure they do not interfere with participants' daily activities. In addition, the EMA software will log participants' geolocation based on GPS. All data will be time- and date-stamped to allow time-specific analyses and determine high-risk periods for smoking.

EMA Daily Diaries

Thorough daily diaries will be collected to assess overall cigarette, other tobacco product (including e-cigarettes), alcohol and cannabis. Questions will also assess same occasion co-use of tobacco, alcohol, cannabis, and drugs (when participants were feeling under the influence of other substance).

Purpose of the EMA Training Phase

The EMA training phase serves multiple purposes: First, it allows participants to get used to the study app that will also deliver the intervention messages, and second, the collected data will allow us to generate an individual risk profile with regard to time of day and location (by combining time stamps, GPS data, and self-reported data) with the highest likelihood of smoking for each participant. We will use geofencing to generate geospatial buffers around these high-risk locations. In combination with time-of-day information to target high-risk time periods for smoking, these geofences will trigger delivery of intervention messages when a mobile device enters the area: A message can be triggered when a participant approaches a smoking location during one of the high-risk time windows. We will use our established protocol for triggering intervention messages that we developed in previous work [32] and successfully used in a pilot trial [36]. Participants will also be prompted to self-report relevant smoking locations in the MetricWire app.

Intervention Phase—Microrandomized Trial With 80 Participants to Determine Message Efficacy

The MRT will determine if CBT and mindfulness or ACT messages are superior to control messages for reducing the primary outcome momentary smoking urges. Based on participants' training data collected in the initial 14 days of EMA monitoring, intervention messages will be delivered during time periods and at high-risk locations for smoking. In the intervention phase, participants will be prompted to complete up to 3 geofence-triggered EMAs per day for a total of 30 days. Each EMA will be followed by an intervention message, and the type of message (CBT, mindfulness or ACT, control) will be randomly selected at each time point (within-subject randomization; see Figure 4). Each intervention message will also be tailored to situational factors from the EMA-pre data. Message tailoring will focus on 2 key situational triggers stemming from our conceptual framework: (1) stress (high/low) and (2) presence of other smokers (yes/no). For each situation, characterized by a combination of these 4 possible characteristics, several messages will be placed in separate message bins (4 bins for each CBT and mindfulness or ACT message, for a total of 8 bins). Control messages will thank participants for completing an assessment. Proximate outcomes will be assessed 5 minutes to 15 minutes after message delivery and include urge levels, smoking or other tobacco product use since EMA-pre survey, affect, stress, and an evaluation of the last message (eg, perceived usefulness of message, completion of suggested activity or intervention). In addition, participants will continue completing 1 brief retrospective EMA each morning. Just like the training phase, this retrospective EMA will assess cigarette, other tobacco product, alcohol and cannabis use.

Figure 4. Flowchart for delivery of each intervention message in the microrandomized trial group. ACT: acceptance and commitment therapy; CBT: cognitive behavioral therapy; EMA: ecological momentary assessment.

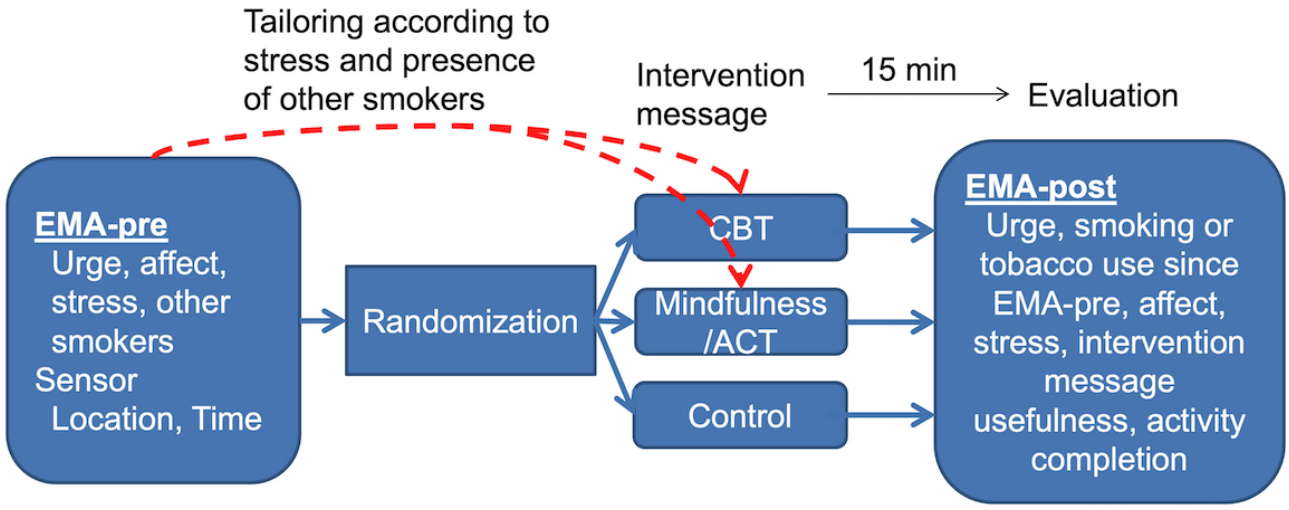

Built-in Parallel-Group RCT—EMA-Only Control Group (n=80)

A total of 80 participants will be randomized into an EMA-only control group, parallel to the MRT intervention group (Figure 1). This group will conduct a 14-day EMA-only training phase just like the MRT group but will not be switched over to the intervention phase after these initial 14 days. Instead, participants will continue the EMA-only data collection procedure for an additional 30 days (analogous to the 30-day

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intervention phase of the MRT). During these 30 days, the EMA-only control group will continue to receive 3 randomly prompted EMA surveys per day and an additional 3 EMA surveys triggered by smoking reports. By comparing this control group with the MRT intervention group, we will investigate if intervention message delivery results in changes in smoking behavior over time (see the Analytical Strategy Aim 2: To Test if Urge Reduction Messages Change Smoking Behavior Over Time section).

Measures

Primary Outcomes

The primary proximal outcome will be change in participants' ratings of smoking urge in EMA-post surveys, prompted up to 15 minutes after intervention message delivery, and controlling for the ratings in EMA-pre surveys. Urge will be assessed using a single item on a 5-point scale, ranging from 1 (very low) to 5 (very high).

The primary distal outcome will be change in self-reported number of cigarettes smoked per day in the past week from baseline to the 45-day, 3-month, and 6-month follow-ups.

Secondary Outcomes

This study will also assess several secondary outcomes. Proximal secondary outcomes will be collected up to 15 minutes after message delivery and include smoking or other tobacco product use (including e-cigarettes), change in rating of stress and negative affect in EMA-post surveys (controlling for the ratings in EMA-pre surveys), ratings of message helpfulness, and self-reported completion of intervention message recommendation. Distal secondary outcomes will be collected at the 45-day, 3-month, and 6-month follow-ups and include self-reported 7-day point prevalence abstinence from smoking, saliva cotinine–confirmed 7-day point prevalence abstinence (assessed using saliva test strips mailed to participants and photo confirmation) [44,62-64], change (reduction) in cigarettes smoked by at least 50% between baseline and each follow-up time point, tobacco quit attempts, change in frequency and intensity of smoking urges as assessed using 2 items of the Mood and Physical Symptoms Scale [65], change in psychological flexibility as assessed using the CompACT-15 [60], change in smoking-specific experiential avoidance as assessed with the Avoidance and Inflexibility Scale [58,59], and switching to other tobacco products including e-cigarettes from baseline to follow-up.

Power Calculation

Aim 1

A sample size of 80 participants receiving 3 randomized messages per day for 30 days will provide 7200 observations. Across person-days, there will be an average of 1 prompt per day for each of the 3 conditions: CBT, mindfulness or ACT, and control (balance across person-days). Power estimations were conducted using an online tool [66] specifically developed for sample size calculations for MRTs [37,67]. Assuming a message randomization probability of 1/3 (33% CBT, 33% mindfulness or ACT, 33% control), a quadratic effect over time (initially smaller as participants are getting used to the intervention, increasing over time to peak at day 20, and decreasing thereafter as participants may get desensitized) [68], and an average compliance rate of 75% linearly decreasing over time, a sample size of 80 participants will allow for detecting a standardized mean difference between CBT, mindfulness or ACT, and control conditions on the primary outcome of self-reported smoking urge of d=0.1 with a power of 0.8 and an α level of .05. This measure of effect size is a generalization of Cohen d (standardized mean difference), with the difference that the standardization is by the average standard error over the entire study, with multiple treatments for each person. A Cohen d of 0.1 is considered a small effect. A previous EMA study found that playing Tetris (analogous to a CBT distraction technique) decreased substance use urges with a mean effect size of f^2=0.12 (medium-sized effect) [69]. Given these effect sizes in the existing literature, we will be adequately powered to detect effects in Aim 1 analyses.

Aim 2

This aim will test between-group differences in number of cigarettes smoked over time among MRT (n=80) and EMA-only control group (n=80) participants. Sample size calculations were based on findings from an app-based mindfulness meditation trial for smoking reduction. This trial only delivered intervention content for 14 days (as opposed to the 30 days in this study) and found a significant reduction in 3.8 cigarettes per day in the intervention group compared with an increase in 0.8 cigarettes per day in the control group [70], which translates to an effect size of d=0.651 (f=0.326) [71]. Power estimation for between-group repeated-measures ANOVA and interactions were conducted with G-Power. Assuming an α level of .05, a sample size of 160 will allow us to detect effects in reduction of cigarettes per day of f=0.326 and larger with a power of 0.80. Multiple imputation will be used for missing data, and the full sample will be analyzed.

Data Analysis

Analytical Strategy Aim 1: To Compare CBT and ACT Intervention Message Efficacy

Aim 1 analyses to test the hypothesis of a proximal benefit of urge reduction messages will be conducted using a centered and weighted least squares method [72], which estimates treatment effects and allows inclusion of covariates. The method is similar to generalized estimating equations (GEEs) [73] and multilevel models in that it accounts for dependence of responses within individuals due to repeated measures via the use of robust standard errors. Moreover, the method takes advantage of sequential randomization to estimate causal treatment effects. The primary outcome will be participants' ratings of smoking urge in EMA-post surveys, prompted up to 15 minutes after intervention message delivery and controlling for the ratings in EMA-pre surveys. The main independent variable will be message type: CBT versus mindfulness or ACT versus a control message ("Thank you for completing the survey"). We will also test differences in efficacy between CBT versus mindfulness or ACT. We will use multiple imputation to impute missing data in EMA-post surveys.

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Secondary outcomes from EMA-pre to EMA-post surveys to be investigated include smoking in the 15-minute time window since message delivery, other tobacco product use (including e-cigarettes), as well as participant ratings of negative affect, stress, perceived message usefulness, and activity completion. The centered and weighted least squares method with robust standard errors [72] will be used to adjust for multiple observations nested within participants. The number of cigarettes per day and other tobacco product use (including e-cigarettes) as reported in the daily diary EMA will be analyzed as additional secondary outcome to investigate participants' changes in smoking and other tobacco use over time while enrolled in the MRT. As poly- and multiple tobacco product use is increasingly common among young adults, we will be able to investigate if participants are switching from cigarettes to other tobacco products (including e-cigarettes) over time.

Among MRT participants, we will explore changes in message efficacy on smoking urges over time by investigating both overall effects (across all time points) as well as linear and quadratic time trend of the intervention effect, assessed by estimating the interaction between treatment effect and day in the study with the weighted least squares method [72]. These models assess whether the relationship between a predictor and outcome changes over time. Separately for CBT and mindfulness or ACT messages, we will explore whether EMA-pre and EMA-post urge reduction changes as the intervention progresses. The same analyses will also be conducted for secondary outcomes. Analyses will provide evidence for increasing or diminishing returns of message delivery with time. Sex as a biological variable will be considered as a participant-level covariate in all models. We will also control for nicotine dependence, psychological distress, and trait negative affect.

Analytical Strategy Aim 2: To Test if Urge Reduction Messages Change Smoking Behavior Over Time

Aim 2 analyses will use data from both the MRT group (n=80) and the EMA control group (n=80). The primary outcome will be the self-reported number of cigarettes per day in the past week at the 45-day, 3-month, and 6-month follow-ups. GEEs [73] will examine cigarettes per day at each follow-up by group (MRT vs EMA-only control). Independent variables are group membership, variables that differ by group at baseline, gender, and nicotine dependence. Our previous work has shown follow-up completion rates of up to 82% of participants at the 6-month follow-up in a Facebook smoking cessation trial with young adults [43]. Again, multiple imputation procedures will be used to impute missing data at follow-up.

To compare if delivery of CBT or mindfulness or ACT messages is associated with smoking outcomes over time, we will conduct dose-response post hoc analyses. A total of 90 message randomizations per participant will result in a range of empirical distributions of message type dose. We conducted a simulation of 90 randomizations over 80 participants in R, which resulted in a range of between 18 and 42 messages of CBT or ACT or mindfulness across participants for the intervention duration. Post hoc analyses will investigate if the extent of exposure to CBT or mindfulness or ACT messages predicts smoking outcomes. These analyses will control for baseline nicotine dependence, quit motivation, and total exposure to intervention messages.

For the secondary outcomes, we will run GEE models and mixed effects multinomial logistic regression analyses to analyze longitudinal ordinal response data to model the following outcomes across time (45 days, 3 months, 6 months): (1) self-reported 7-day point prevalence abstinence (yes/no—with sensitivity analyses for missing=smoking, complete cases, and multiple imputation), (2) saliva cotinine–confirmed 7-day point prevalence abstinence (yes/no—again with sensitivity analyses for different assumptions including self-reported nicotine replacement or other tobacco product use), (3) reduction of cigarettes by 50% or more (yes/no), (4) tobacco quit attempt (yes/no), (5) switching to other tobacco products including e-cigarettes, (6) frequency and intensity of smoking urges, and (7) ACT measures of experiential avoidance and mindfulness. Independent variables are group, gender, nicotine dependence, and any variables that differ by group at baseline.

Analytical Strategy Aim 3: Explore Moderation Effects of Substance Co-Use (Cannabis, Alcohol, Other Drugs) and Exposure to Specific Location (Home, Work, Bars) on Urge Reduction Message Efficacy

Based on our data on high co-use of cigarettes with cannabis and alcohol [74-76], as well as changes in perceived reward of smoking cigarettes when under the influence of cannabis or alcohol [77-79], analyses in this aim will explore if message efficacy is moderated by substance co-use (whether a participant currently is under the influence of another substance [eg, cannabis, alcohol, other drugs]). Centered and weighted least squares models [72] similar to those for Aim 1 will be estimated with predictors of intervention message type (CBT, mindfulness or ACT, control), substance use (cannabis, alcohol, other drugs, none), and their interaction. Based on existing evidence on alcohol and cannabis co-use as barrier to cigarette smoking cessation, we hypothesize that intervention message efficacy will be reduced when participants are under the influence of another substance. However, analyses for this aim will enable us to explore if specific types of messages (CBT, mindfulness or ACT) are more helpful in co-use situations.

Moreover, we will explore aspects of intervention message-situation fit. We will test if specific locations (eg, home, work, bars) impact intervention message efficacy. Mixed models will be estimated containing the predictors of intervention type (CBT, mindfulness or ACT, control), location (home, work, bar, other locations), and their interaction. We will explore other situational characteristics and intervention message-situation fit based on affect, arousal, stress, and the presence of other smokers. We do not have specific hypotheses about moderation effects of location and other situational characteristics, but findings will inform future interventions using adaptive messages over time to improve intervention message-situation fit and intervention efficacy.

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Results

As of June 2025, we had enrolled 58 participants of the target sample of 160, with 52% (30/58) assigned to the MRT group and 48% (28/58) assigned to the EMA-only control.

Discussion

Principal Findings

This is one of the first studies that combines an MRT [30,31] using within-subject randomization and a conventional between-subject RCT design to test the real-time impact of smartphone-based intervention messages on young adult cigarette smoking outcomes. In a traditional RCT, baseline randomization does not offer protection against causal confounding due to time-varying factors and contexts in which intervention messages are delivered. Individual participants self-select into unique high-risk situations, which are impossible to control for and balance across groups in a 3-arm RCT. In an MRT, multiple within-subject randomizations will produce compositional balance in unobserved factors between the message conditions and balance of different intervention messages across participants, days, and situations. Because messages are repeatedly randomized, resulting data will allow us to assess how causal effects of messages change over time. Moreover, between-person randomized designs do not allow investigation of message-situation fit and how time-varying factors may moderate intervention effects (Aim 3). Even within participants, CBT or mindfulness or ACT messages may be more effective in different situations depending on contextual factors and between-subject randomization and assignment to exclusive CBT and mindfulness or ACT conditions would not allow us to investigate this. For these reasons, microrandomization of messages is critical for informing the development of an adaptive smoking cessation intervention. Last, MRTs are highly efficient. Due to repeated randomization within participants, effect estimations can take advantage of between- and within-subject contrasts. These within-subject comparisons allow our MRT to recruit far fewer participants than a traditional full factorial design [30]. Baseline randomization into a MRT group or control group is important to test whether repeated delivery of intervention messages improves smoking behavior outcomes over and above just repeated assessment of smoking situations over an extended period of time. To provide evidence for the long-term efficacy of CBT or mindfulness or ACT messages on smoking behavior, we will conduct post hoc dose-response analyses in Aim 2.

Limitations

Despite increasing trends in the use of novel tobacco products, including e-cigarettes, in recent years, tobacco cigarettes are still the most frequently used tobacco product. However, in a changing tobacco product landscape [80] and because of high rates of polytobacco use among young adults [6], it is important to assess the full spectrum of tobacco product use among young adults over time, to investigate if participants are switching from cigarettes to other tobacco products. Message refinement will ensure intervention messages are worded so they will be applicable to tobacco use urges beyond cigarettes. If we find in this MRT that urge reduction messages are effective for cigarette smoking urges, results could inform future intervention trials to counter urges to use other tobacco products.

In the past, we have successfully recruited young adults ready to quit in the next 30 days for smoking cessation interventions [42]. If we find that the recruitment on social media will not result in enrollment of adequate participant numbers, we will pursue additional strategies to boost recruitment, which include outreach to local schools and colleges and flyers at places young adults purchase tobacco.

Frequent assessments may lead to participant noncompliance and study attrition. Participants will be asked to complete up to 6 EMAs per day. A recent EMA study has shown that participants were equally responsive when they had to complete 1 versus 6 EMAs per day [81], suggesting that this is a feasible EMA frequency. Moreover, EMA survey length, compared with frequency, seems to have a greater impact on participant compliance [82], which means we will keep EMA surveys brief. Additional measures are built into the study to prevent attrition over time, including compliance feedback, outreach to participants, and an incentive scheme designed to promote high compliance.

Conclusions

We are testing the use of mobile technology for cancer control and prevention in an underserved, high-priority population. In the current situation of rapidly changing technology platforms as well as changes in the tobacco product landscape, it is important to conduct research that is not uniquely tied to a specific platform and tobacco product. This research builds on existing infrastructure and does not aim at developing a new smoking cessation app. Instead, results of this project will provide evidence on the efficacy of tailored intervention messages to help young adult smokers cope with smoking urges as an integral part of smartphone interventions. Findings will inform the field about key principles, strategies, and efficacy of situational tailoring of app-based tobacco use urge reduction messages. Moreover, this study will produce a database of evidence-based smoking urge reduction messages for real-time smartphone-based interventions. The logical next step after this trial is to use these messages and the results to develop and test a just-in-time adaptive intervention (JITAI) to improve tobacco product cessation among young adults. A JITAI is an intervention design that aims at providing the right type and amount of support, at the right time, by adapting to an individual's changing internal and contextual state [83,84]. This MRT will provide the necessary evidence and intervention content to inform a JITAI to support young adult tobacco use cessation.

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Data Availability

All intervention messages and study ecological momentary assessments (EMA) surveys are made available on the project Open Science Framework page [56].

Authors' Contributions

Conceptualization: JT
Funding acquisition: JT
Investigation: JD, JJCW, MRD, J Han
Methodology: JT, MRD, VZ
Resources: FN
Supervision: JT
Writing - Original Draft: JT
Writing - Review & Editing: JT, JD, JJCW, MRD, J Han, J Hamoud, FN, VZ, TM, CL, DE, MM

Conflicts of Interest

JT reports membership on the scientific advisory board of MindCotine Inc, which offers a smoking cessation program. MM served as a paid expert witness in litigation sponsored by the Public Health Advocacy Institute against R.J. Reynolds. These arrangements have been reviewed and approved by the Johns Hopkins University in accordance with its conflict of interest policies. FN is an unpaid member of the scientific committee for the Smoke Free app, an app unrelated to this study.

Multimedia Appendix 1
Intervention messages.
[XLSX File (Microsoft Excel File), 46 KB - resprot_v14i1e74388_app1.xlsx]

Multimedia Appendix 2
EMA surveys.
[DOCX File , 208 KB - resprot_v14i1e74388_app2.docx]

Multimedia Appendix 3
EMA survey codebook.
[PDF File (Adobe PDF File), 615 KB - resprot_v14i1e74388_app3.pdf]

Multimedia Appendix 4
Peer-review report from ZRG1 RPHB-V (02) - Center for Scientific Review Special Emphasis Panel Risk, Prevention and Health Behavior Integrated Review Group, National Cancer Institute and the National Institute on Drug Abuse (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 106 KB - resprot_v14i1e74388_app4.pdf]

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Abbreviations

ACT: acceptance and commitment therapy
CBT: cognitive behavioral therapy
EMA: ecological momentary assessment
GEE: generalized estimating equations
HIPAA: Health Insurance Portability and Accountability Act
JITAI: just-in-time adaptive intervention
MRT: microrandomized trial
RCT: randomized controlled trial

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Protocol

Integrating a Combination HIV Prevention Intervention Into a Widely Used Geosocial App for Chinese Men Who Have Sex With Men: Protocol for a Single-Arm Pilot and Repeated Cross-Sectional Study

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Abstract

Background: HIV disproportionately affects men who have sex with men in China. However, HIV prevention services use among this population remains limited, in part due to concerns of privacy and sexual identity disclosure. These concerns might be addressed through telehealth services.

Objective: This study was designed to assess the feasibility and acceptability of Blued+, which integrates an HIV prevention services package into a geosocial networking app commonly used by Chinese men who have sex with men.

Methods: The study design was a single-arm pilot of the Blued+ intervention among men who have sex with men, using repeated cross-sectional surveys of an external population for comparison. For the pilot study, men were recruited from Beijing and Chengdu. A 3-month standard-of-care period with measurement at enrollment and month 0 (baseline) was followed by a 12-month intervention period with measurement at months 3, 6, 9, and 12. During the intervention period, participants received the enhanced version of the Blued app (Blued+) with HIV testing, linkage to care as needed, choice of condoms and condom-compatible lubricants, and pre-exposure prophylaxis (PrEP) services. PrEP was provided through in-app counseling and prescription, followed by lab tests at local clinics and mailed medication. Three cross-sectional surveys in months 0, 6, and 12 were administered to men in Beijing and Chengdu who were not enrolled in another HIV prevention study. These participants had access to the standard Blued geosocial networking app and local health services. The primary outcome of feasibility was the uptake of home HIV testing and PrEP. The coprimary outcome of intervention acceptability was measured with the System Usability Scale.

Results: The run-in period was launched on July 15, 2022, with recruitment completed on August 24, 2022. The baseline period concluded in November 2022, and all follow-up assessments were completed by December 2023. At baseline, the pilot study enrolled 423 participants, and the cross-sectional comparison enrolled 1314 participants. Participants in the pilot were young (mean age 30, SD 7 years) and educated (324/423, 76.6% reported a college degree or higher), and most (302/423, 71.4%) reported HIV testing in the prior 3 months. Most participants (404/423, 95.5%) had heard of PrEP, and over a quarter had used PrEP (114/423, 27%). Participants in the comparison population had comparable sociodemographic characteristics, reporting HIV

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testing (501/857, 58.5%) in the prior 3 months, PrEP awareness (723/857, 84.4%), and PrEP use in the last 3 months (182/857, 15.4%).

Conclusions: This pilot study will provide preliminary evidence regarding the feasibility and acceptability of the Blued+ intervention. The study findings will provide evidence setting the foundation for future research that involves embedding prevention platforms into apps that are already widely used. If preliminary impact is observed, future research would include a hybrid effectiveness implementation trial of the intervention.

Trial Registration: ClinicalTrials.gov NCT06647173; https://clinicaltrials.gov/study/NCT06647173

International Registered Report Identifier (IRRID): DERR1-10.2196/69536

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KEYWORDS

HIV; men who have sex with men; telemedicine; mHealth; protocol

Introduction

Gay and bisexual men who have sex with men have been disproportionately affected by HIV in China [1,2], where the population of men who have sex with men was estimated to be approximately 21 million in 2018 [3]. HIV prevalence among men who have sex with men was estimated to have increased from 1% to 6% between 2001 and 2018 [4]. The estimated HIV incidence among men who have sex with men is much higher than for all other populations identified as being at risk of HIV in China since 2010 [5]. In Beijing, a cohort study of men who have sex with men documented 7.8% annual incidence [6]—a level similar to the highest incidence estimates among men who have sex with men subgroups in the United States [7]. In Chengdu, a southwestern city in China, the estimated incidence was 6/100 person-years between 2012 and 2018 [8] and 4.3% between 2018 and 2022 [9].

Despite the substantial epidemic, the use of HIV prevention services, including condoms, HIV testing, and HIV pre-exposure prophylaxis (PrEP), is low among Chinese men who have sex with men. In 2012-2016, fewer than half of men who have sex with men reported consistent condom use with male partners [10-12]. After a national intervention to expand HIV testing that started in 2007, the annual HIV testing rate increased from 21% to 38% by 2012, which was still suboptimal [13]. The suboptimal use of HIV prevention services has been associated with low self-perception of HIV risk [14] and HIV-related stigma [15,16]. To effectively control HIV transmission, a combination of multiple HIV prevention strategies, including biomedical (eg, PrEP use), behavioral (eg, HIV testing, condom, and lubricant use), and structural (eg, addressing stigma) approaches, is needed [17,18]. Therefore, adopting a combination HIV prevention approach that strategically and simultaneously leverages several types of interventions to address the specific needs of priority populations is prudent in that it is more likely to achieve comprehensive and sustained gains in HIV prevention [17].

Smart mobile devices have become ubiquitous in China and mobile apps have proliferated, offering an efficient approach to reach Chinese men who have sex with men with HIV prevention services [19]. Blued is an example of a men who have sex with men–focused app that provides dating and a wide range of HIV prevention and health information. Users can access these services anonymously and conveniently, regardless of their physical location [19]. Telehealth interventions using mobile apps have shown promising outcomes in improving practices such as consistent condom use and HIV testing to address disparities in sexually transmitted infections [20-24]. However, many innovative mHealth (mobile health) interventions that use apps have encountered challenges and issues in posttrial scale-up due to the lack of sustainable funding and limited technical expertise to support transitioning apps developed with research funding support into the marketplace [25,26]. Additionally, from the user perspective, having to manage and use many mobile apps for different purposes can result in information overload, which is associated with app use discontinuation [27]. To address these challenges, and in response to the National Institutes of Health's call to develop and evaluate the feasibility and acceptability of combination HIV prevention interventions [17,18], we adopted a low-touch digital intervention approach in this pilot study, seeking to overcome future problems with scale-up by placing the prevention platform onto a pre-existing, widely used app.

This pilot study was developed on the Blued geosocial networking (GSN) app. Blued focuses on promoting a positive and healthy lifestyle for LGBTQ+ individuals. Launched in 2012 in China, it has gained considerable popularity both within China and globally, with 6 million active monthly users in China, including over 480,000 men who have sex with men in Beijing and 221,000 men who have sex with men in Chengdu (Guodong Mi, PhD, email communication, September 2018). Blued users can share their current precise locations to connect with and date users who are near them, match with others based on user interests, share photos and videos, and broadcast live streams. In addition to being a for-profit company, Blued was founded as a community organization and remains committed to public welfare. It collaborates with various community-based organizations to provide services in HIV prevention within the men who have sex with men community and advocates for antidiscrimination.

The aim of this pilot study was to assess the acceptability and feasibility of integrating a fully featured combination HIV prevention package into a widely used GSN mobile app. Our scientific premise is that the HIV prevention services continuum for men who have sex with men should be stronger and that integrating services into a mobile app already used by Chinese

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men who have sex with men will be feasible and acceptable, providing preliminary data to inform future assessment in a hybrid effectiveness implementation trial.

Methods

Study Design

This study was a single-arm pilot with a repeated cross-sectional design as comparisons (Figure 1). This research was funded as part of the National Institutes of Health Methods for Prevention Packages Program, which was focused on the development of combination HIV prevention interventions and therefore did not allow for randomized assessment [28]. To increase rigor in the absence of randomization, we included a 3-month run-in period and a series of repeated cross-sectional surveys in an external (comparison) population to assess pilot intervention performance. The set of three comparison groups over time allows the investigation of secular trends and potential impacts of panel attrition.

Figure 1. Study design overview of a study of HIV prevention service delivery to men who have sex with men through an HIV social networking app, China, 2022-2024. PrEP: pre-exposure prophylaxis.

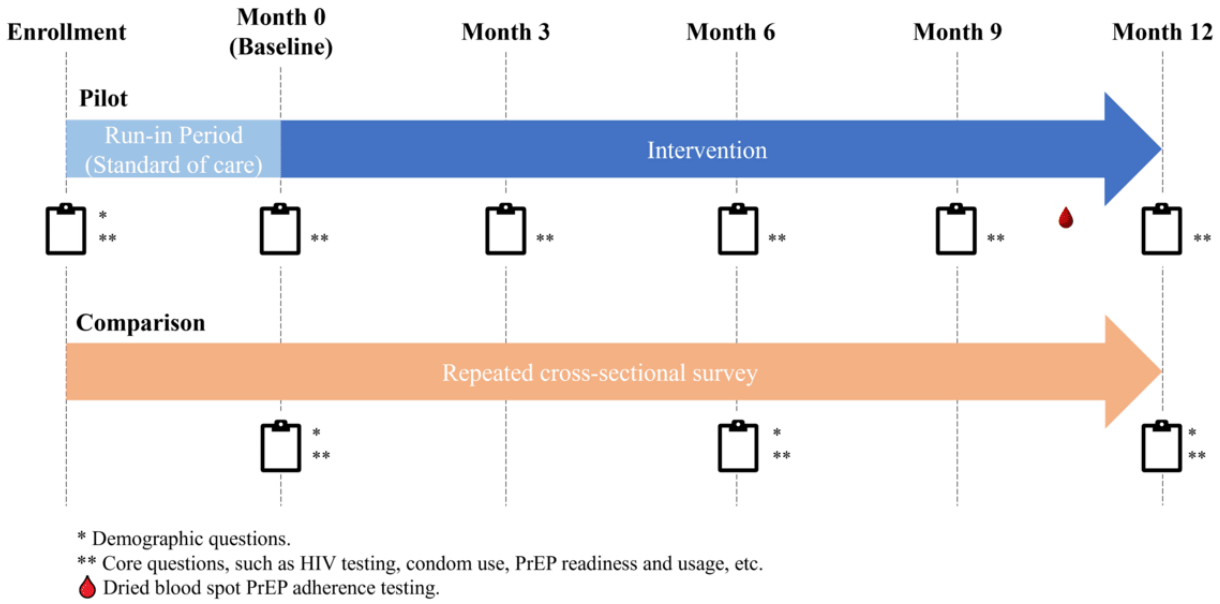

For the pilot study, a cohort of men who have sex with men was recruited from Beijing and Chengdu. Enrollment was followed by a 3-month standard-of-care (run-in) period, during which data on behaviors were collected but no HIV prevention content was provided, and a 12-month intervention period. Self-reported behavioral measures for the pilot study participants were collected at enrollment, baseline (month 0), and months 3, 6, 9, and 12. The set of three comparison groups was a series of cross-sectional surveys among men who have sex with men not enrolled in the intervention study, and administered at the same time intervals as the pilot study baseline (month 0) and months 6 and 12. Eligibility criteria for cross-sectional surveys were identical to those for the pilot study, with an additional exclusionary criterion of being enrolled in the intervention cohort. The set of three comparison groups was largely independent because they were advertised broadly to the whole city until the sample size of the study was obtained, although we did not exclude participation in subsequent comparison groups. For the intervention group, we also conducted an exploratory assessment of PrEP adherence among a subset of PrEP users willing to provide a specimen at month 12 follow-up with a blood-based biomarker test (detailed below).

Recruitment

Participants for the pilot study and repeated cross-sectional surveys were recruited using the direct message function in the Blued app. Targeted inbox messages were sent to men who lived in the Beijing and Chengdu metropolitan areas. When interested men clicked on a link in the message, they were taken to a landing page containing basic information about the study. A brief screener survey then determined study eligibility.

Eligibility

Eligible participants for both the pilot study and repeated cross-sectional surveys were registered Blued app users who self-reported male sex at birth, male gender identity, age ≥18 years, having had anal sex with a man in the last 6 months, having HIV-negative or unknown HIV status, residing in Beijing or Chengdu, not enrolled in another HIV prevention study, and being eligible for PrEP according to China's consensus statement [29]. According to the consensus statement, men who have sex with men are eligible if they ever used PrEP or postexposure prophylaxis (PEP) before or are willing to use PrEP or PEP, or meet at least one of the following four criteria in the past 6 months: (1) engaged in any condomless anal or vaginal sex, (2) injected drugs or shared needles, (3) had a serodifferent partner known to be living with HIV, or (4) were diagnosed with a sexually transmitted disease [29].

Enrollment

The advertisement and enrollment process for the pilot study and repeated cross-sectional surveys were similar. Study

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advertisements were sent as direct messages to Blued users in Beijing and Chengdu based on their log-in geolocations in the prior 3 months. Preliminarily eligible participants were asked to provide their contact information and complete the consent process. Given the remote nature of consent, we verified understanding of the key elements of the consent form with a brief quiz. Correct responses and brief explanations of key components in the consent form were shown when participants selected an incorrect option. Upon successful completion of the consent quiz, participants indicated consent by electronically affirming their decision to participate in the study.

Intervention Development

To inform intervention design, we obtained information about app preferences and user experience with the existing app, Blued. We conducted 3 in-person activity-based focus group discussions (FGDs) in Beijing with a range of 6-10 Blued users in each group in April-May 2021. The eligibility criteria were the same as the criteria above for the pilot study and the repeated cross-sectional survey. The length of Blued use ranged from 2 to 9 years. During the FGD, participants were first asked to review the HeHealth portal in the existing Blued app, including the home, condoms or lubricants, and HIV testing kits pages. Then, participants were provided with visual illustrations of concepts regarding how PrEP care components could be incorporated into the Blued+ app, including PrEP education information, PrEP screening quizzes, no-cost PrEP care and referrals, reminders, and peer communication. The FGD guide can be found in Multimedia Appendix 1. A rapid qualitative analysis of the FGDs was conducted to summarize participants' feedback on each function to inform Blued+ app development.

In general, FGD participants expressed a preference for a simple and easy-to-navigate page design. Regarding the HIV testing kits page, participants suggested a graphic display mode to present different types of test kits clearly. For condom and lubricant products, participants preferred thin condoms with good quality from reputable brands. Regarding PrEP care services to be added in Blued+, participants suggested that the page should be tailored in terms of PrEP-related information. For PrEP screening quizzes, participants were concerned about the lack of explanation about the results and emphasized the need to clarify the purpose of the quiz beyond simply encouraging people to purchase PrEP medication. To access PrEP care, most participants preferred to talk to a doctor to obtain PrEP prescriptions and medication, but they also worried about potential discrimination and stigma attitudes at in-person clinics. When considering PrEP care support services like reminders and peer communication, participants suggested that the reminder service could be offered as an optional service, but that peer communication would be unnecessary. To address concerns about PrEP efficacy, side effects, and access to prescriptions and medication, participants suggested the need for an in-app clinician for consultation, which we added to the intervention.

Standard of Care

During the 3-month standard-of-care period in the pilot study and for the cross-sectional comparison assessments, participants were able to access the existing Blued app (ie, without the additional features described above). Blued began as a community-based organization and maintains a strong community presence. This includes a network of HIV testing locations and a series of HIV testing promotion ads in Blued. In 2020, Blued started to offer a set of digital sexual health services in a for-profit model, HeHealth. It provides users with access to mailed home HIV tests, mailed standard condoms, and water-based lubricants for purchase, all in a manner similar to retail pharmacy services. HeHealth also offers pharmacy PrEP services, with users who already have a PrEP prescription from their local clinic able to receive PrEP through package delivery.

Intervention

Overview

During the intervention period, pilot study participants received the enhanced version of the Blued app: Blued+. The installation was integrated with a regular Blued app update to avoid disrupting users. A notification about the update was sent to study participants. Once study participants agreed to update the Blued app on their smartphone, the update to the enhanced Blued+ version was automatic.

The theoretical foundation that structured the integration of the HIV prevention services into this app environment was the Extended, Unified Theory of Acceptance and Use of Technology (UTAUT2). UTAUT2 is a frequently used model for the development and assessment of technology-based health interventions, with over 20,000 citations and recent validation for mobile technology assessment in China [30,31]. Domains relevant to Blued+ were performance expectancy (PE), effort expectancy (EE), social influence (SI), and habit (H) (Table 1). Blued+ sought to provide users services in a manner they deem valuable (PE), to decrease expected effort expended by using functions and design layout consistent with the existing Blued app (EE), to include health-positive messages encouraging self-care in direct messaging for social influence (SI), and to use reminder systems to help users build HIV prevention habits (H).

“Video walk-throughs” of telehealth intervention apps have been previously suggested [25]. In Multimedia Appendix 2, we provided a video walk-through of the Blued+ app to facilitate a detailed understanding of how intervention features were offered to users. Screenshots of some pages from the Blued+ app, translated into English, were presented in Figure 2. Services in the HIV prevention intervention package included PrEP provision, in-home HIV tests and linkage to care, and prevention supplies such as condoms and lubricants. Additionally, participants received weekly health messages focused on PrEP, sexual health, and self-care. All these services were provided at no cost.

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Table 1. Theoretical framework, domains, and intervention design.

UTAUT2[a] constructs	Definition	Intervention design
Performance expectancy	The degree to which an individual believes that using the system will help him or her to attain gains in health.	Provide in-home HIV testing kit, condoms, lubricant, and PrEP[b] at no cost.
Effort expectancy	The degree of ease is associated with the use of the system.	Use functions and design layout consistent with the existing Blued app.
Social influence	The degree to which using the new system is appreciated in the social network that is important to the individual.	Send highly rated health-positive messages encouraging self-care.
Habit	The extent to which people tend to perform behavior automatically because of learning.	Use health messaging to help build habits of using HIV prevention services on the enhanced Blued app.

[a]UTAUT2: Extended, Unified Theory of Acceptance and Use of Technology.
[b]PrEP: pre-exposure prophylaxis.

Figure 2. Screenshots of interventions in the Blued+ app. PrEP: pre-exposure prophylaxis.

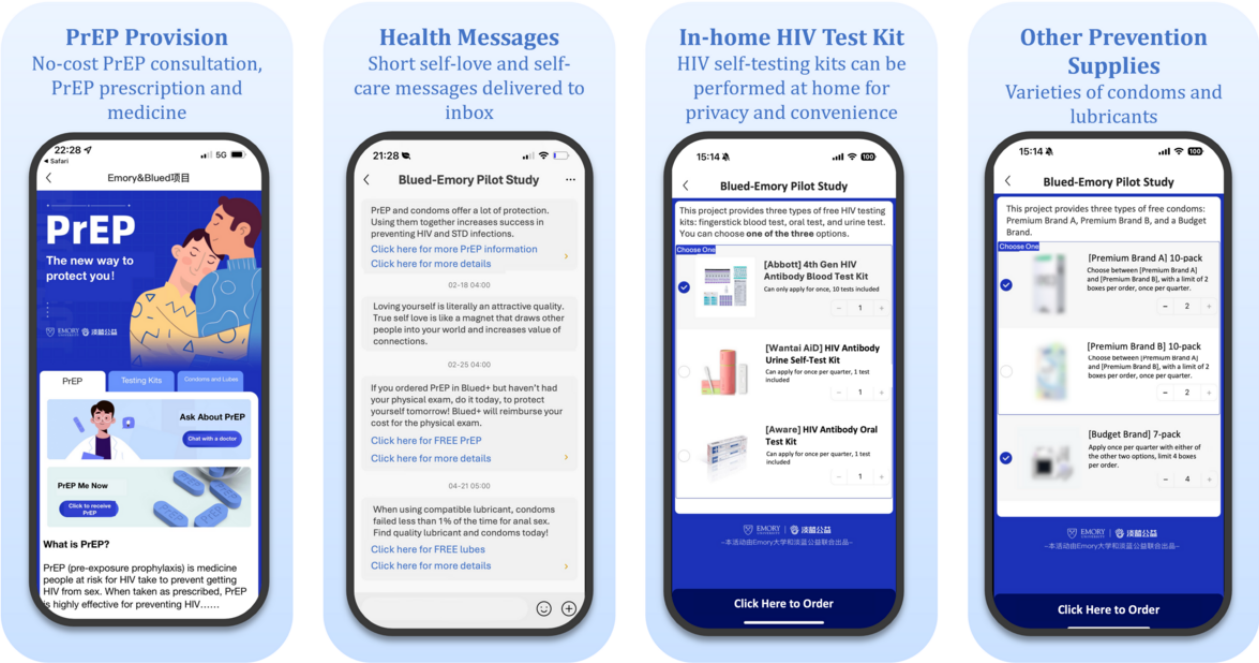

Health Messages

Health messages were adapted from a set of messages used in an app-based messaging and services intervention (M-cubed study) that was found to increase HIV testing and PrEP use among men in the United States [32]. The messages were initially translated into Chinese by staff in the research team, then reviewed and revised by staff at Blued to ensure their cultural and contextual appropriateness for Chinese men who have sex with men. Health messages in the study were sent at intervals of 1-3 weeks with a total of 29 messages sent out to each participant.

Topics included promotion of PrEP use (n=11), condom and lubricant use (n=6), HIV testing (n=6), engagement in health care (n=2), and health-positive messages encouraging self-care (n=3). PrEP use support messages included information on PrEP and PrEP medication, PrEP effectiveness, PrEP costs, side effects, dealing with PrEP stigma, and how to access PrEP. Condom use messages included traditional messages encouraging consistent condom use and encouraging condom use with lubricants for pleasure. HIV testing messages included information about rapid testing, where to get tested, and encouraging regular testing every 6 months. Messages about engagement in health care encouraged users to talk to their health care providers and offered the in-app clinician counseling option. Positive self-support messages were adapted from a set of self-care and self-love messages provided by a community PrEP educator who focused on mental well-being and harm reduction behaviors. For example, one of the self-love messages was “To love oneself is the beginning of a lifelong romance” [Oscar Wilde]. A team-based translation approach was used to translate these messages into Chinese. Two bilingual staff from the research team and two bilingual local staff members worked together to ensure the messages were accurate and culturally appropriate. For most messages, a hyperlink with an appropriate destination was included within the message. For instance, a hyperlink within a PrEP use message “Could PrEP be right for you? Chat with our Blued+ provider” would direct users to the page where they could consult with a PrEP provider. A hyperlink

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within the message "Got a hot date? Don't go unprepared. Get some free condoms and lube today!" would direct users to the page to order condoms and lubricants. A full version of all health messages with English translations can be found in Multimedia Appendix 3.

PrEP Care

The clinical eligibility for PrEP use in China are (1) laboratory-confirmed HIV-negative, (2) no contraindications to emtricitabine or tenofovir disoproxil fumarate, (3) creatinine clearance of at least 60 mL/min (reported by a laboratory), (4) willingness to adhere to a PrEP regimen, and (5) willingness to attend PrEP maintenance visits every 3 months.

Participants interested in accessing PrEP could click on the link in PrEP use messages or access services directly in the Blued+ app that schedules a PrEP counseling session with an in-app clinician. After counseling, participants who decided to initiate PrEP could get lab tests for HIV, syphilis, hepatitis B surface antigen (HBsAg), and serum creatinine from any local tier-2 or tier-3 hospital. The age and weight of the participant were collected by self-report to calculate the creatinine clearance rate. Prior to the study launch, 8 staff from Blued (4 in each city) went to a hospital of their choice and got lab tests to trial the process and estimate its cost. The cost associated with completing these lab tests was estimated to range from US $27 (190 CNY) to US $50 (350 CNY). Reimbursement for tests was sent once participants uploaded the test results to Blued+ in the app. The test results were reviewed by a study clinician, and participants were prescribed PrEP in the platform if they were eligible for PrEP. After the prescription, research staff received a notification and shipped the medication within 1 week of an order, in batches of 90 pills to cover daily PrEP use for 3 months. Participants received tracking numbers once the medicine was shipped. Participants could refill every 3 months if they received appropriate laboratory testing specified in the Chinese guidelines [29]. PrEP medicines used in this study were pills containing 200 mg emtricitabine and 300 mg tenofovir disoproxil fumarate.

In-Home HIV Test and Linkage to Care

In Blued+, participants could order in-home HIV tests by clicking a link in HIV testing health messages or clicking a tab in the Blued+ app. The ordering page was designed to be easy to navigate to reduce users' effort expectancy. Similar to the procedures for shipping PrEP medication, once the order was placed, the Blued+ pharmacy received a notification and prepared the shipment. Three types of in-home HIV test kits, using capillary blood, urine, or oral swabs, were offered to maximize participant choice. During the intervention period, each participant could order a package of 10 blood test kits, 1 urine test kit, or 1 oral test kit. The aim of offering 10 blood test kits (anticipated to be the most frequently selected option) was to provide enough test kits for the 12-month intervention period, allowing participants to test as frequently as they would like. Participants could upload photos of their test results to the app and receive free counseling (regarding the test kit and result interpretation) and linkage to care when appropriate from a study coordinator at Blued. A free message app account number of the in-app clinician was also provided to participants so that they could reach out for HIV test counseling and other related questions. Participants were able to use the Blued+ platform to voluntarily upload their HIV self-test results for further counseling. Experienced counselors would provide further explanation of the test result and referral to clinics for confirmatory tests, when necessary, through phone calls.

Other Prevention Supplies (Condoms and Lubricants)

Three types of condoms with different thicknesses and brands (ultrathin vs standard and premium vs budget brand) and water-based and silicone-based condom-compatible lubricants were available for participants to order from the platform. The types of condoms and lubricants were selected based on our target users' preferences as assessed during FGDs (see above). The ordering process for condoms and lubricants was similar to ordering HIV testing kits. When participants added condoms to their "cart" in Blued+, a note would pop up reminding them to add lubricants to use with condoms.

For condoms, each participant was offered 48 condoms per quarter. This number was based on 2-3 sexual activities per week, a common sex frequency for men who have sex with men in China [33]. The Blued+ platform allowed participants to choose luxury condoms of either premium brand A (ultrathin 20 condoms) or premium brand B (air-feel 20 condoms). This gave participants the opportunity to try different brands and thicknesses. Additionally, each participant could order 28 standard condoms from a budget brand.

It is recommended that 5-10 mL of condom-compatible lubricant be used with each anal sexual activity [34,35]. Participants were offered a total of 340 mL of lubricants per quarter, which included 1 container of water-based lubricant (100 mL) and 2 containers of silicone-based lubricant (120 mL each).

Differences Between Standard of Care and Intervention

Although the standard of care has some similarities to the intervention, there were notable differences informed in part by the study's qualitative assessments. The health page in the intervention was designed to be simpler and easier to navigate. Health messages in the intervention covered a wide range of HIV prevention–related topics and health-positive self-care messages, whereas the health messages in the standard of care only covered a narrower range of HIV prevention topics such as condom use and HIV testing, and there was no systematic delivery of these messages. For HIV prevention products, the health portal in Blued+ offered options of different condoms, lubricants, and in-home HIV test kits based on user preferences. For PrEP care access, the intervention offered in-app PrEP counseling and prescribing, and medication mailing when appropriate. All these services were provided at no cost to participants in the pilot.

Data Collection

Pilot Cohort Survey and Cross-Sectional Survey

Data were collected through Sojump, a widely used and secure online survey platform in China that offers survey design features including multiple question types and branching logic. The survey link was sent to participants through the direct message function in the Blued app. Blued user IDs, tied to

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unique phone numbers, were used to identify and exclude duplicate responses within the cohort survey as well as between the cohort survey and the repeated cross-sectional survey.

The enrollment survey included questions in the domains of (1) sociodemographic characteristics, (2) relationship status, (3) sexual history, (4) HIV and STI testing history, (5) PrEP knowledge or attitudes, (6) PrEP intention and use (including adherence), (7) HIV knowledge, (8) PrEP stigma, (9) mental health, and (10) prevention supplies order history. Sociodemographic characteristics questions were adapted from the annual American Men's Internet Survey (AMIS) [36]. HIV knowledge was assessed using an 8-item scale from the Sustainable Health Center Implementation PrEP Pilot (SHIPP) study [37]. PrEP stigma was measured using a previously validated scale [38]. Mental health was measured using the Patient Health Questionnaire for Depression and Anxiety (PHQ-4) [39]. The full enrollment survey can be found in Multimedia Appendix 4. Follow-up surveys include the domains of (1) relationship status, (2) sexual history, (3) HIV and STI testing history, (4) PrEP knowledge or attitudes, (5) PrEP intention and use, (6) prevention supplies order history, and (7) acceptability of Blued+. HIV knowledge, PrEP stigma, and mental health were only included in the month 6 and month 12 follow-up surveys because they were believed to be less labile. Acceptability of Blued+ was measured by the widely used System Usability Scale that assesses the subjective usability of products and systems [40,41]. The acceptability questions were only included in the month 12 follow-up survey. Questions in the pilot cohort survey and cross-sectional survey were identical. The average survey completion time ranged from 10 to 20 minutes across participants at each time point.

Dried Blood Spot

In addition to self-report data regarding PrEP adherence collected from the cohort survey, we conducted an exploratory assessment of the suitability and acceptability of biomarker data collection to measure drug levels in blood samples. Participants who initiated PrEP were asked at an interim visit between months 9 and 12 to visit a local laboratory for the collection of a blood specimen to create a dried blood spot to measure tenofovir diphosphate (TFV-DP) levels in plasma. For this procedure, participants were first asked to complete a supplemental survey and to receive an HIV screening test. The survey assessed PrEP pill usage in greater detail than in the cohort survey to evaluate adherence to their regimen of either daily use or on-demand use in the past 2 months. A trained phlebotomist at the designated local laboratory then collected finger-prick blood onto a paper card to create a dried blood spot card for future testing for TFV-DP. For daily pill use, TFV-DP levels provide an indicator of the mean number of days per week that PrEP is ingested over a period of approximately 1-2 months [42]. For daily users, a cut point of >700 fmol/punch TFV-DP indicates >4 doses/week and thus serves as a surrogate for substantial protection from HIV infection. For event-based PrEP users, adherence was determined by evaluating if the TFV-DP level matches with the self-report behavior data on sexual frequency.

Statistical Analysis Plan

Primary Analysis

The primary analysis will be focused on the feasibility and acceptability of the pilot intervention, assessed based on a series of benchmarks (Table 2); these benchmarks were established in 2018 when the research was first proposed. The intervention will be determined as feasible if a minimum proportion of participants receive services for home HIV testing (30%) and PrEP prescription (20%) at month 12. Minimum targets were determined based on modeling that indicate levels of service uptake required to substantially influence an HIV epidemic [43]. The intervention will be considered acceptable if it reaches a System Usability Scale rating benchmark score of “good” (≥71 out of 100). Analyses will be conducted using SAS 9.4 (SAS Institute) or similar statistical software packages.

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Table 2. Study measures, sources of data, and definitions for primary and secondary outcomes for a pilot study of integration of biomedical prevention services in an existing social networking app for Chinese men who have sex with men, Beijing and Chengdu, 2022.

Construct	Measure	Data source	Definition	Analysis
Primary outcomes				
Feasibility	Home HIV test orders	Order fulfillment	Proportion of participants sent a home HIV test	≥30%
Feasibility	PrEP[a] initiation	Clinical site data	Proportion of participants receiving a PrEP prescription	≥20%
Acceptability	System Usability Scale [40,41]	Survey	10-item scale, good score is ≥71	Good score (≥71 out of 100)
Secondary outcomes (preliminary efficacy assessment)				
HIV testing	HIV testing	Survey	Proportion of participants reporting HIV testing in the last 3 months	Descriptive, longitudinal analysis[b]
Condom use	Condom use	Survey	Proportion of participants reporting always using condoms for anal sex in the last 3 months	Descriptive, longitudinal analysis[b]
PrEP use	PrEP use [44]	Survey	Proportion of participants reported PrEP use in the last 3 months	Descriptive, longitudinal analysis[b]

[a]PrEP: pre-exposure prophylaxis.

[b]Descriptive analysis: outcome proportions over time; longitudinal analysis with generalized estimating equations or similar models to measure predictors of outcomes.

Statistical Power and Sample Size

This is a pilot study assessing feasibility and acceptability; therefore, our sample was not powered to detect significant differences in the intervention period compared to the standard-of-care period (before baseline) or to the set of three cross-sectional comparisons. A sample of 200 pilot study participants per intervention city was selected based on budget and time constraints. This sample size was also anticipated to provide estimates of key parameters with sufficient precision. For instance, a 95% CI for the prevalence of our binary benchmarks (home HIV test orders, condom package orders, PrEP medication orders) would have a half-width of 5.1 percentage points. This is calculated assuming an estimated population SD of 0.5 and Pr(w)=0.9 [45], where Pr(w) represents the probability that the width of a future CI will not exceed 95% and accounts for the fact that the SD is not known and will therefore lead to CIs that vary from sample to sample [46].

Additional Analysis

Additional analysis will include assessing preliminary efficacy with descriptive endpoints and measuring changes from baseline to intervention periods in HIV testing, condom use, and PrEP use. Descriptive analyses will include comparisons of the proportions of users reporting use of condoms, PrEP, and HIV testing in the pilot relative to the set of three comparison groups (Table 2). Longitudinal analyses will assess trends within the pilot cohort while accounting for autocorrelation, using models such as generalized estimating equations to measure predictors of the binary outcome of HIV testing, condom use, and PrEP uptake. Models will contain the 7 time periods with primary comparisons of 0-month (first baseline) measurement to 6-month (end wash-out baseline period) measurement and to 12-month (end intervention period) measurement. Time will be considered as a fixed effect to compare proportions tested across intervals, with a random intercept for individuals. TFV-DP data will be reported descriptively to provide context for the self-report PrEP use data.

Ethical Considerations

The study was approved by the Emory institutional review board (IRB00116983) and the Blued institutional review board in January 2020. Study participants completed the consent process, as described above in the Enrollment subsection, before any study activity started. Participants had the right to withdraw from this study at any time without any penalty.

A role-based access control was applied to the database storage. Participants' identifying information (eg, contact information such as Blued user IDs and phone numbers) can only be accessed by the study coordinator in China to identify and exclude duplicate responses to the cohort and cross-sectional surveys. Once the deduplication process was complete, a nonpersonally identifying study ID was used to store all study data (deidentified). Data received by other study team members, including all collaborators in the United States, were deidentified.

A compensation of US $15 (100 CNY) was provided for each of the cohort surveys and repeated cross-sectional surveys. An additional US $60 (400 CNY) was provided for each participant who completed all 6 cohort surveys in the pilot study. For each participant who completed the dried blood spot collection, an additional US $45 (300 CNY) compensation was provided.

Results

The enrollment was launched in July-August 2022. The baseline was concluded in November 2022. All follow-up assessments were completed in December 2023. As part of recruitment efforts, the study team sent out direct messages to individual app users in the study cities. The screening survey link was opened 6445 times. A total of 625 participants were screened as eligible after deduplication. Based on the prior determined

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sample size, 440 participants were contacted to be enrolled in the pilot study. After the 3-month run-in period, 423 were retained to start receiving the intervention. Retention rates at 3, 6, 9, and 12 months were 96.2% (407/423), 94.6% (400/423), 94.3% (399/423), and 94.3% (399/423). For the cross-sectional comparison, the baseline cross-sectional survey was opened 6565 times, and 857 participants were eligible after deduplication. The number of participants recruited for the 6-month and 12-month cross-sectional surveys were 764 and 747, respectively.

Sociodemographic and behavioral characteristics at baseline for each group are presented in Table 3. Participants enrolled in the pilot had an average age of 30 (SD 7.4) years. Slightly more pilot participants resided in Beijing than in Chengdu. More than two-thirds of the pilot participants had obtained at least a college degree, and about three-quarters reported working full-time. Over a third of participants had a monthly income of over US $1400, a level that is above the average income level of urban nonprivate position employees. Most participants self-identified as homosexual. In terms of behaviors, over half of the participants (265/423, 62.6%) reported having condomless anal sex in the prior 3 months. About two-thirds (302/423, 71.4%) of participants had been tested for HIV in the prior 3 months. PrEP awareness was high—nearly all participants (404/423, 95.5%) had heard of PrEP, among whom 27% (114/423) had used PrEP. Of the 114 participants who had used PrEP, two-thirds (80/114, 70.2%) had used PrEP in the prior 3 months.

Participants in the cross-sectional comparison group had similar sociodemographic characteristics to those in the pilot study, except the comparison group had a slightly higher proportion of participants residing in Beijing (565/857, 65.9%) compared to the pilot study participants (230/423, 54.4%; $P<.001$). Lower proportions of participants in the comparison group reported testing for HIV in the prior 3 months (501/857, 58.5%; $P<.001$), compared to the pilot study population. Lower proportions of participants in the comparison group also reported PrEP awareness (723/857 [84.4%] vs 404/423 [95.5%]; $P<.001$), ever PrEP use (182/857 [21.2%] vs 114/423 [27%]; $P=.02$), and PrEP use in the prior 3 months (132/857 [15.4%] vs 80/423 [18.9%]; $P=.11$).

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Table 3. Sociodemographic and behavioral characteristics of study participants in the pilot and comparison groups at baseline, Beijing and Chengdu, 2022.

	Pilot (n=423)	Comparison (n=857)	*P* value[a]
Age (years), mean (SD)	30 (7.4)	30 (7.8)	>.99
City, n (%)			<.001[b]
Beijing	230 (54.4)	565 (65.9)	
Chengdu	193 (45.6)	292 (34.1)	
Education, n (%)			.06
Postgraduate and above	89 (21)	216 (25.7)	
College or university	235 (55.6)	455 (53.1)	
Associate's degree or technical school	84 (19.9)	137 (16)	
High school and below	15 (3.5)	49 (5.7)	
Employment status, n (%)			.08
Employed full-time	328 (77.5)	675 (78.8)	
Employed part-time	31 (7.3)	38 (4.4)	
Full-time student	43 (10.2)	95 (11.1)	
Part-time student	2 (0.5)	2 (0.2)	
Unemployed or retired	13 (3.1)	42 (4.9)	
Others	6 (1.4)	5 (0.6)	
Income (monthly, in US $), n (%)			.70
>1400	173 (40.9)	365 (42.6)	
980-1400	96 (22.7)	205 (23.9)	
420-979	95 (22.5)	185 (21.6)	
<420	59 (13.9)	102 (11.9)	
Sexual orientation, n (%)			.26
Homosexual	357 (84.4)	696 (81.2)	
Bisexual	65 (15.4)	155 (18.1)	
Heterosexual and others	1 (0.2)	6 (0.7)	
Condomless anal sex, past 3 months, n (%)			.2
Yes	265 (62.6)	505 (58.9)	
No	158 (37.4)	352 (41.1)	
HIV testing, past 3 months, n (%)			<.001[b]
Yes	302 (71.4)	501 (58.5)	
No	121 (28.6)	356 (41.5)	
Heard of PrEP[c], n (%)			<.001[b]
Yes	404 (95.5)	723 (84.4)	
No	19 (4.5)	134 (15.6)	
PrEP use, ever, n (%)			.02
Yes	114 (27)	182 (21.2)	
No	309 (73)	675 (78.8)	
PrEP use, past 3 months, n (%)			.11
Yes	80 (18.9)	132 (15.4)	
No	343 (81.1)	725 (84.6)	

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[a]*t* test for age; Fisher exact test for the rest.

[b]*P*<.005, below Bonferroni-adjusted critical value.

[c]PrEP: pre-exposure prophylaxis.

Discussion

Importance of the Study

This protocol describes a pilot study assessing the feasibility and acceptability of an mHealth intervention that integrated HIV services into an existing GSN mobile app for men who have sex with men in China. A number of previous telehealth studies have developed study-specific mobile phone apps to deliver interventions [20,47,48]. Although these interventions are frequently effective in changing behaviors, few of them maintained changes over time [23]. Challenges of "translation" and obtaining "downloads" are the primary barriers to bringing the app from research into practice and maintaining the app [49]. Integrating interventions into a widely used app may overcome these challenges. Translation is a common implementation challenge. Effective health apps developed by researchers may never be translated into a sustainable model for public and long-term use [25,26]. Translating a study app into a marketable business product with sufficient profit to sustain the intervention is often out of the scope of research studies and out of the capability of researchers, who frequently lack expertise and financing to accomplish this critical task [22-24]. The challenge of downloads is that once the app is translated into the market, convincing eligible individuals to download the app may be challenging unless they are aware of the app and see a clear benefit of having it [49]. Given these barriers, we offered HIV prevention services in an app that already has a sustainable model and is widely downloaded by Chinese men who have sex with men, rather than developing a new app. To our knowledge, this is the first study incorporating interventions into a widely used GSN app for men who have sex with men. This study's results may inform future efforts to optimally leverage mHealth resources by determining the feasibility and acceptability of building prevention models into existing apps.

Stigma related to sexual orientation and HIV has been identified in other studies as a barrier for Chinese men who have sex with men accessing health care services, particularly HIV prevention services [50,51]. Moreover, prior studies found that higher levels of stigma were associated with lower awareness and use of PrEP [52,53]. In addition to sexual orientation and HIV-related stigma, stigmatization of PrEP use can be a barrier for PrEP initiation and adherence [54,55]. Therefore, our study measures possible change in HIV and PrEP stigma that could occur with the use of tailored services, although reducing stigma was not the primary intention or outcome of this pilot study.

Participants in the pilot and comparison groups were similar at baseline with respect to age, education, and income level, employment status, sexual orientation, and PrEP use. We sought to minimize differences between pilot study participants and cross-sectional comparison participants by using similar recruitment strategies in terms of advertisements, delivery, and eligibility criteria. Yet the specifics of recruitment differed slightly due to different consent forms, different lengths of participation, and different overall incentive amounts (more study activities were available for pilot participants). There were some differences in participant characteristics, with pilot participants being more likely to come from Chengdu, have recently tested for HIV, and have higher awareness of PrEP. Differences may introduce some bias in comparison, with higher levels of HIV testing and PrEP awareness, perhaps indicating higher pre-existing engagement in prevention care among pilot participants. Exploratory analyses in results assessment may seek to describe the possible impact of these differences. Ultimately, this is a pilot study, and a randomized clinical trial will be needed to determine the efficacy of the intervention if pilot results indicate feasibility and acceptability.

Limitations

The primary outcome measures of this study rely on self-report data. To account for potential social desirability and recall biases, levels of TFV-DP in the blood will be measured to provide context to the self-report PrEP use data. Given that there was no randomized control group in this pilot study due to funder requirements, there could be selection and secular time biases that are only partially addressed by our inclusion of a 3-month standard-of-care period and a series of repeated cross-sectional surveys among men who have sex with men who did not participate in any HIV prevention study as a comparison.

Conclusions

This study provides a unique opportunity for potential scalability of a novel intervention by assessing the feasibility and acceptability of integrating an HIV prevention intervention into a widely used GSN app in China. Study results can inform future research to determine the effectiveness of this type of intervention as well as implementation strategies to facilitate future adoption. If successful, app-based interventions have the potential to reach millions of men who have sex with men in China to provide sustainable HIV prevention services.

Acknowledgments

This study was supported by the National Institute for Allergy and Infectious Diseases (grant R01AI143875) and the Emory Center for AIDS Research (grant P30AI050409).

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Data Availability

The datasets are not publicly available as data analysis is ongoing but are available from the corresponding author on reasonable request.

Authors' Contributions

WH and AJS drafted the manuscript. AJS and PSS are the lead investigators and were responsible for study conceptualization and design. GM and YL were the site investigators and were responsible for overseeing study conduct in China. FY and KN were site coordinators and were responsible for participant recruitment and data collection. DS was the study statistician and was responsible for data cleaning and advanced analysis. WH, KN, and SHEK conducted the baseline descriptive data analysis. All authors read, edited, and approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
Focus group discussion guide.
[DOCX File , 33 KB - resprot_v14i1e69536_app1.docx]

Multimedia Appendix 2
Illustration video of Blued+ app.
[MP4 File (MP4 Video), 111135 KB - resprot_v14i1e69536_app2.mp4]

Multimedia Appendix 3
Health messages.
[DOCX File , 23 KB - resprot_v14i1e69536_app3.docx]

Multimedia Appendix 4
Enrollment survey.
[DOCX File , 123 KB - resprot_v14i1e69536_app4.docx]

Multimedia Appendix 5
TREND checklist.
[DOCX File , 84 KB - resprot_v14i1e69536_app5.docx]

Multimedia Appendix 6
Peer-review report by ZRG1 AARR-K (03) - Center for Scientific Review Special Emphasis Panel Member Conflict: AIDS and Related Research (National Institutes of Health, USA).
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Abbreviations

AMIS: American Men's Internet Survey
FGD: focus group discussion
GSN: geosocial networking
HBsAg: hepatitis B surface antigen
mHealth: mobile health
PEP: postexposure prophylaxis
PHQ-4: Patient Health Questionnaire for Depression and Anxiety
PrEP: pre-exposure prophylaxis
SHIPP: Sustainable Health Center Implementation PrEP Pilot
TFV-DP: tenofovir diphosphate
UTAUT2: Extended, Unified Theory of Acceptance and Use of Technology

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Protocol

The National Study of Daily Experiences: Protocol for Assessments of Daily Stress, Well-Being, Health, and Salivary Biomarkers in a Longitudinal Cohort

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Abstract

Background: Modern psychology has long recognized that understanding human behavior requires knowledge about a person's current context, which is often examined through daily diary studies. These studies offer ecologically valid insights into how everyday experiences—particularly stressors—affect health and well-being. The National Study of Daily Experiences (NSDE) addresses a critical gap by applying this approach in a large, longitudinal, and publicly accessible study that captures daily life across adulthood.

Objective: The NSDE is the largest and longest-running publicly accessible daily diary study in the United States. The purpose of this paper is to provide a guide for researchers interested in initiating similar naturalistic studies and to facilitate research using the existing NSDE data.

Methods: The NSDE includes 3510 adults (aged 24-97 years), yielding over 42,000 days of information to capture how daily life changes with age, over time, and across different cohorts, and how these daily experiences predict later health and well-being. This intensive longitudinal dataset includes an 8-day daily diary collected via phone survey, spans more than 20 years, and consists of 2 longitudinal datasets. During the daily phone interviews, participants provide reports of their experiences regarding daily events, including their stressors (Daily Inventory of Stressful Events), as well as their physical health indices, emotional experiences, and cognitive health. In addition, saliva is collected concurrently with days 2-5 of the daily phone interviews (4 collections per day for 4 consecutive days) and is used to measure biomarkers such as cortisol and alpha amylase.

Results: Recruitment began in 1995, with data collection occurring every 9-10 years. The most recent data collection is ongoing through 2027. All NSDE data are housed under the Midlife in the United States (MIDUS) study umbrella, with archived and updated datasets made available to the public on the online portal, MIDUS Colectica.

Conclusions: Results from the NSDE have refined our understanding of daily stress processes. The study's timescale has provided insight into daily life for hundreds of studies, yet much more can be learned from using these data. Microlongitudinal

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measures and combinations of factors provide for new avenues of research and promise for better understanding of health and aging. Moreover, NSDE data can be combined with datasets from neuroscience, biomarker, and macrolongitudinal subprojects from MIDUS to examine health-related processes. In addition to offering information on how to use the NSDE, this protocol serves as a resource for secondary data analyses and an outline for investigators wishing to replicate an intensive assessment design to other populations and research questions to continue to refine our understanding of how daily stress processes influence health and well-being.

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KEYWORDS

daily diary; ecological momentary assessment; publicly available data; cortisol; stress

Introduction

Background

In 1995, the Midlife in the United States (MIDUS) study was launched to examine health and well-being across middle adulthood. Embedded in the MIDUS was the National Study of Daily Experiences (NSDE), an 8-day diary study that assessed the daily behaviors, thoughts, and emotions of approximately 1500 people ranging from 25 to 75 years of age. Until then, midlife had been a relatively neglected life stage in developmental, behavioral, and social science research. Researchers focused largely on ontological changes until early adulthood, followed by a relatively smaller group examining older adults. Midlife was often characterized as a period of stability before the onset of physiological declines in older adulthood. Early life risk factors in childhood for later health were widely recognized, but few researchers were examining the importance of risk and resilience factors in midlife for predicting healthy aging [1].

The primary goal of the NSDE was to investigate the contributions of behaviors, thoughts, and emotions in daily life to functional aging processes. Key to this innovation was focusing on stress in daily life [2] and how it contributed to health, well-being, and aging. Prior research on stress in adulthood focused primarily on major life events (eg, marriage, bereavement, and retirement) and their impacts on health and well-being [3]. In contrast, daily stressors (eg, minor everyday conflicts or irritations) [4,5] received much less attention but offered considerable promise for understanding contextual factors impacting life as it is lived. Embedded in the NSDE was the Daily Inventory of Stressful Events (DISE), a set of questions that capture multiple aspects of an individual's experience that articulate stress processes [6].

The first wave of NSDE was launched with a focus on understanding how daily stressors influence daily health and well-being. The second wave of data collection, nearly 10 years later, expanded its focus on the role of daily events to include not only stressors but also daily positive events. The goals of the second data collection were to examine how data collected earlier predicted later health and to expand the study of the role of daily events (both positive and negative) to mental and physical well-being. Questions about positive events were added, as well as more questions to characterize the stressor experience. To better capture physiological mechanisms related to physical health, 4 days of saliva samples were collected with the aim of documenting diurnal patterns of cortisol, the primary glucocorticoid in humans and an ambulatory marker of stress and endocrine function. Saliva collection has many benefits in a study of this capacity, including the ability to be self-collected in the participants' natural environment, the collection is noninvasive, salivary cortisol levels are stable allowing for shipment and assay by an off-site laboratory [7], and salivary cortisol levels correlate with blood cortisol levels [8]. In addition, a further aim of this second wave was to examine how individual characteristics (personality, socioeconomic status, and caregiving status) shaped the stress response; thus, additional participants were included to gain a larger, more heterogeneous national sample.

A few years later, a new sample of adults, called the refresher sample, was collected using this same design. The purpose of this new cohort was to supplement the existing sample and examine an additional aim. In 2008, the United States had experienced the Great Recession, the biggest economic decline since World War II. Two years later, epidemiologists and demographers noticed a disconcerting trend. Life expectancy in the United States, which had been increasing steadily since it had been first recorded in 1947, started slowing in 2010 and then declined [9,10]. A main reason for this decline was excessive deaths in the United States among adults aged 45-54 years, referred to as deaths of despair (ie, deaths from drug overdoses, suicide, and alcoholic liver disease) [11,12]. Life had become more stressful, especially for people in midlife.

The collection of a refresher cohort (beginning in 2012) allowed for examination of how the daily stress process may have varied across groups assessed before and after this event. A third wave of data from people who had participated previously (NSDE3, beginning in 2016) made it possible to examine these changes longitudinally. In addition to documenting how macrolevel stressors (eg, economic and social forces) affected stress in daily life, new questions were added about daily cognition to include not only measures of daily emotional and physical well-being but also cognitive well-being. In 2023, data collection for a fourth wave of the original study and a second wave of the refresher cohort began.

Aim of This Study

Currently, NSDE consists of more than 42,000 daily interviews spanning over 20 years. Almost 300 papers and chapters have been published using NSDE data, with the number of papers

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increasing each year (see Daily Experiences Publications for Researchers [13]). These papers shed light on the contextual factors (eg, socioeconomic status) and daily experiences that shape health and well-being across the adult life span [14], but more discoveries are possible. For example, in addition to stressors, the extensive NSDE interview has allowed for examination of a broader array of individuals' daily experiences, such as exposure to nature and well-being [15], everyday discrimination and cognition [16], and the effects of daily activity diversity on cognitive and psychological well-being [17,18].

The purpose of this paper is to describe the study's design, the sample and measures, and analytic strategies necessary to test questions using this complex measurement burst study design. We do so with 2 aims: that people gain the knowledge necessary to use the publicly accessible NSDE (available through the MIDUS portal [19]), and that they consider initiating similar studies in the future, building our methods to further investigate how our daily lives exert lasting influences on our daily health.

Methods

MIDUS and NSDE Project Overview

The MIDUS study is a large, cross-project longitudinal study composed of multiple subprojects linking behavioral, psychosocial, and biological metrics to health and function across adulthood [20,21]. The NSDE is one of these embedded projects. MIDUS includes 3 waves of data beginning in 1995. The original participants have been followed at least every 10 years postbaseline (with wave 2 in 2004-05 and wave 3 in 2012-13), with new participants included in the second wave, including a city-specific subsample of Black adults, aged 35-85 years. In 2012, a "refresher sample" was recruited for new data collection and to refresh the existing pool of participants. The initial participants, as well as the subsample of Black adults, are referred to as the "core sample" and have completed up to 3 waves (with wave 4 currently in progress), whereas the refresher sample consists of a single wave (with wave 2 in progress at the time of this writing).

The NSDE is composed of a subset of participants from MIDUS (both the core and refresher samples) who consented to a series of daily interviews after having completed the MIDUS survey [22,23]. The NSDE collection is initiated about 3-6 months after the MIDUS Survey Project interview (see Data Collection Timeline for Researchers [13]), and home saliva sampling kits are sent in batches to 25-50 participants at a time. Figure 1 outlines the timing of waves for the NSDE, providing an overall picture of data collection for the core and refresher cohorts, including the number of participants, interview days, and saliva samples. This figure presents the timing of assessments collected via phone surveys and saliva samples, including our ongoing data collection.

Figure 1. Timeline of National Study of Daily Experiences (NSDE) data collection across waves. NSDE 1-4 represent the core cohort, and NSDE R1 and R2 represent the refresher cohort. Dashed lines represent data collection in progress.

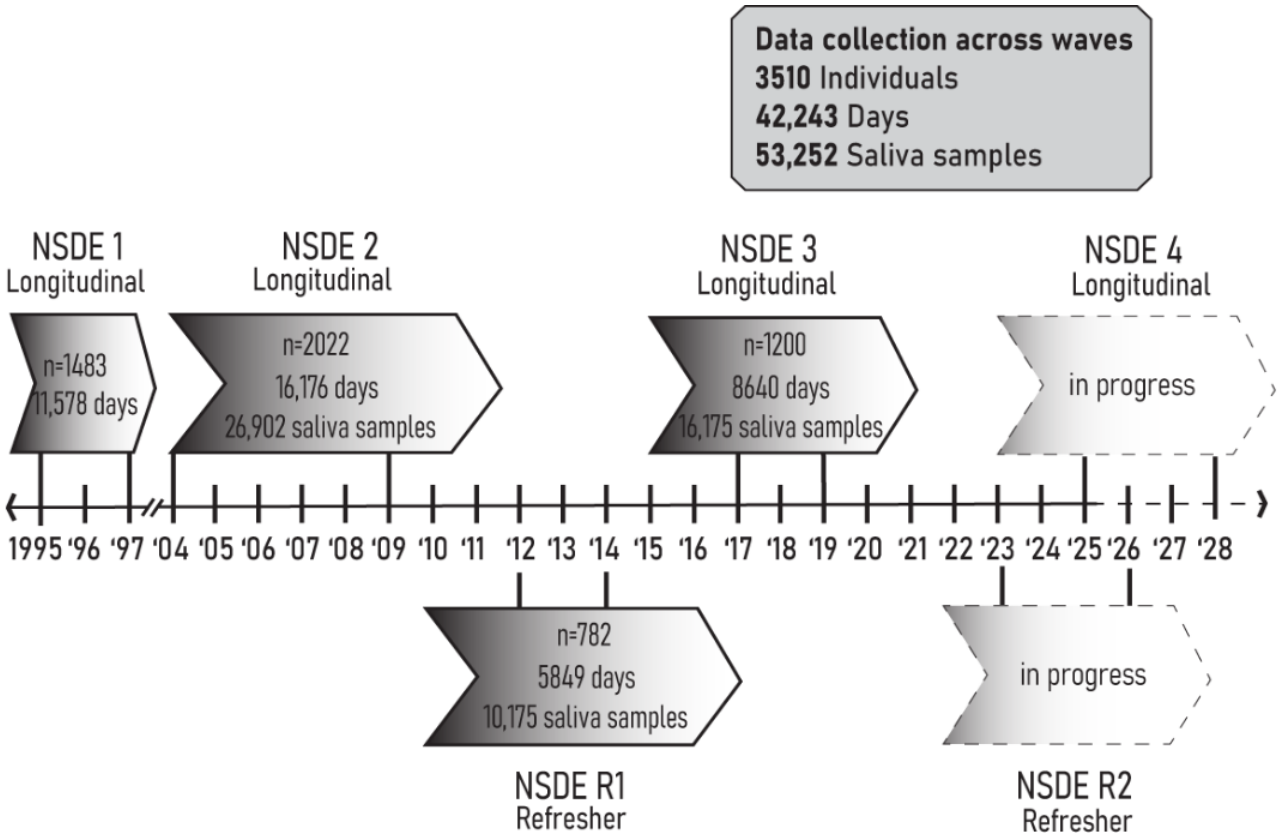

Figure 2 illustrates a focused view of the flow and design of wave 2 data collection, providing an example of how the NSDE is linked to other projects within the larger MIDUS study. At each wave, NSDE participants complete brief evening surveys via telephone interview (8 consecutive days). On the final evening of the telephone survey, participants are asked

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additional questions to reflect on their week. Saliva collection was added to the protocol beginning in the second wave (4× per day for 4 consecutive days, interview days 2-5).

Figure 2. Cross-project synergy with the National Study of Daily Experiences (NSDE). N=2022 for the core cohort and N=782 for the refresher cohort reflect maximum number of respondents at NSDE 2 (core cohort) and NSDE R1 (refresher cohort), respectively.

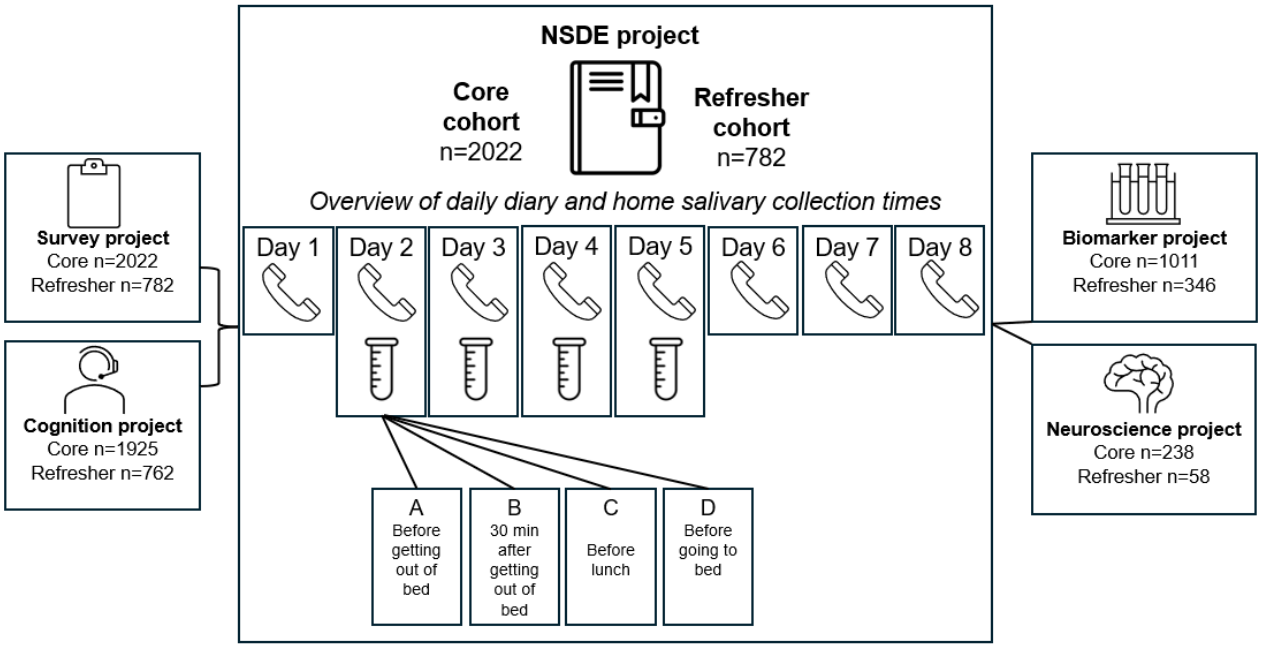

NSDE Study Sites and Participants

A central MIDUS headquarters at the University of Wisconsin–Madison currently coordinates NSDE participant selection and recruitment, which began in 1995-1996. Telephone interviews were conducted from the University of Michigan and the University of Arizona (wave 1), and then the Survey Research Center at Penn State University in all following years. Saliva samples were processed at the University of Wisconsin–Madison. Participants from the NSDE initial cohort consisted of 1483 individuals aged 25-74 years and included a nationwide sample of individuals, including siblings of the sample, oversampling from US metropolitan areas, and over 200 twin pairs [20,21,23,24]. Participant details at baseline and at the longitudinal follow-up are available [25].

Recruitment and Daily Diary Phase

Recruitment of the initial core sample of MIDUS participants used a national random-digit dialing method from working telephone banks for people in the United States. Those enrolled in wave 1 of the MIDUS study were asked to participate in additional MIDUS core projects and data collection waves. For the new refresher sample, a sampling frame consisting of all possible landline and mobile phone numbers was used. All NSDE participants selected for the 8-day daily diary protocol had previously participated in the larger MIDUS survey study. The participants were sent letters of introduction and information about requests for this study. Starting in the second wave of NSDE data collection, salivary assessment kits were included by mail. Within 1 week of sending the introductory letter and salivary kits, participants were contacted via telephone to answer any questions and enroll willing participants. The initial and final NSDE interviews last approximately 15-20 minutes, while the other 6 interviews last approximately 10-15 minutes. A computer-aided telephone interview, which enables skip patterns, open-ended probe questions, and keypunch data entry during the interview, was used for participant interviews.

Ethical Considerations

This protocol was approved by Penn State University's Institutional Review Board (PRAMS00042558), Clemson University's Institutional Review Board (2023-0053), and Northern Arizona University's Institutional Review Board (2020855). All historically collected data were deidentified before the analyses, as will future datasets currently in collection. Informed consent was obtained from all participants prior to the survey and saliva collection, and participants received the equivalent of US $25 for compensation.

Home Data Collection: Salivary Sample Kits

NSDE home saliva collection kits were designed to maximize ease of use by participants. Each kit contained a brochure, a recruitment letter addressed to the participant, and an informed consent sheet. These items highlighted the goals of MIDUS and NSDE, communicated why participants had received the kit, and provided research staff contact information. Along with these instructional materials were the following items: 16 prelabeled salivettes in a double bag with an absorbent pad, printed inserts including collection instructions, a saliva collection sheet for recording collection times, and a daily medication use form for disclosing prescription and nonprescription medication that may interfere with the interpretation of cortisol data. All items were labeled with a unique, nonpersonally identifiable kit number. An insert was included with detailed instructions about how to schedule a package pickup upon completion of the data collection, and participants were given a toll-free number should they encounter

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issues. Participants were also provided with US $25 as compensation.

Participants were instructed to provide a saliva sample at four specific times daily: (1) in the morning immediately upon waking and before getting out of bed, (2) 30 minutes after waking, (3) before lunch, and (4) before bed. The 16 prelabeled salivette swabs were sent in tubes labeled and colored to identify the day of collection (2-5) and one of the above 4 general collection times. Participants were instructed to refrain from eating, drinking, or brushing their teeth before the collection of saliva samples. They were also instructed not to use any tobacco or caffeinated products 30 minutes before collection.

To collect a saliva sample, the participants opened the prelabeled tube and tipped the container to allow the swab to fall in their mouth, taking care to avoid touching the swab with their hands. They gently rolled the swab over their tongue until fully saturated. They then placed the swab back into the tube, avoiding touching the swab, and replaced the cap on the tube. The capped tube was placed inside the provided plastic bag and stored in the fridge (4 °C). After successful saliva collection, the participants shipped the salivettes, the completed collection sheet, and the medication use form in the preaddressed mailer to the MIDUS Biological Core at the Harlow Center for Biological Psychology at the University of Wisconsin–Madison. Samples were stored at –60 °C upon receipt. Salivettes were thawed and centrifuged at 3000 rpm for 5 minutes. Cortisol concentration was determined by chemiluminescence using a commercially available immunoassay (Tecan, IBL International) with intra-assay and inter-assay coefficient of variations below 5% [26]. Per participant, cortisol levels were assayed at each of the 16 sampling times. The participant was asked to write the specific time of day in the provided space on the salivette collection tube and on the provided saliva collection sheet. The participant was provided with an instructional insert and video demonstrating proper use of the salivettes, as well as access to a toll-free 1-800 number to reach research staff if additional instructions were needed.

Measures

Measures Overview

Daily interviews included questions about experiences and events in the past 24 hours concerning time use, health behaviors, work productivity, positive and negative affect, physical symptoms, cognitive functioning, and daily stressors. Table 1 provides an overview of measures, including response options, additional operational detail, the wave each measure was first introduced, and example references. Below, we describe the main domains assessed in subcategories organized by the DISE, daily events, daily emotional experiences, daily physical health indices, daily cognitive health, and daily biomarkers. Full details of these questions are freely available [25].

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Table 1. NSDE[a] measures.

Measure	Response options	Items or operational details	Wave first introduced
Daily Inventory of Stressful Events (DISE)			
Stressor exposure [22]	Yes/no	Composite across 6 stressor types	1
Stressor type [27]	Yes/no	Arguments, avoided arguments, work, home, discrimination, network, other	1
Who was involved [28]	Multiple options	Spouse or partner, child, parent, sibling, friend, coworker, etc	1
When did it happen [29]	Yesterday/today; AM/PM	Yesterday vs today; What time of day?	1
Stressor appraisals			
Severity [30]	None at all – very	How stressful was this for you?	1
Control [31]	None at all – a lot	How much control did you have over the situation?	2
Resolution [32]	Yes/no	Is the situation resolved?	2
Resource risk [6]	None at all – a lot	Financial, health and safety, time schedule, socioemotional	1
Stressor reactivity [33]	Calculated slope	Emotional, behavioral, or biological reactions to stressors on the same day	1
Stressor residue [32]	Calculated slope	Prolonged responses extending to the following day	1
Stressor diversity [34]	Calculated index	Dispersion of stressors across multiple domains; Can be calculated using the Shannon entropy index	1
Anticipatory stress [35]	Not at all – very	How stressful do you expect tomorrow to be?	3
Daily events			
Positive events [36]	Yes/no	Interaction, work, home, network, other	2
Who was involved [36]	Multiple options	Spouse or partner, child, parent, sibling, friend, coworker, etc	2
When did it happen [36]	AM/PM	What time of day?	2
Anticipatory pleasantness [36]	Not at all – very	How pleasant do you expect tomorrow to be?	3
Emotional support exchanges [37]	Yes/no	Give or receive emotional support	1
Who was involved [37]	Multiple options	Spouse or partner, child, parent, sibling, friend, coworker, etc	1
Everyday discrimination [38]	Yes/no	9 items with follow-up reasons for discrimination (eg, race, gender, and age)	2
Time use			
Work, volunteer, assistance [39]	Hours/minutes	How much time spent working, volunteering, and providing unpaid assistance	1
Physical activity, leisure, television [40]	Hours/minutes	How much time spent on physical activity, leisure, and television	1
Daily emotional experiences			
Negative affect [41]	None of the time – all of the time	14 items for "How much of the time today did you feel...[affect item]"	1[b]
Positive affect [41]	None of the time – all of the time	13 items for "How much of the time today did you feel...[affect item]"	2
Daily physical health indices			
Health behaviors			
Cigarette smoking [42]	Quantity	How many cigarettes did you smoke?	1
Vape or e-cigarettes	Hours/minutes	How much time spent vaping or using e-cigarettes	3
Alcohol drinks [43]	Quantity	How many drinks did you have?	1
Fast food	Yes/no	Did you eat from a fast-food restaurant?	3
Self-rated physical symptoms			

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Measure	Response options	Items or operational details	Wave first introduced
Experience [44]	Yes/no	Headache, fatigue, fever, muscle weakness, chest pain, etc	1
Severity [44]	Very mild – very severe	How severe was this symptom?	2
Sleep quantity [45]	Hours/minutes	How much time did you spend sleeping?	1
Medications [46]	Yes/no	Over-the-counter or prescription allergy, inhaler, antidepressant, etc	2
Daily cognitive health			
Memory lapses			
Frequency [47]	Yes/no	Forget errand or chore, medication, appointment, someone's name	R
Irritation [47]	Not at all – very much	How much did forgetting these things bother you?	R
Interference [47]	Not at all – very much	How much did forgetting these things interfere with your routine?	R
Unconstructive repetitive thoughts [48]	None of the time – all of the time	Think about personal problems or concerns, trouble concentrating, etc	R
Daily biomarkers			
Cortisol [46]	Salivette sample	Samples drawn at wake, 30 minutes after wake, before lunch, and before bed. Can be calculated as area under the curve, cortisol awakening response, and diurnal range as examples.	2
Alpha amylase [30]	Salivette sample	Samples drawn at wake, 30 minutes after wake, before lunch, and before bed. Can be calculated as morning decline and diurnal rise slopes.	R

[a]NSDE: National Study of Daily Experiences.

[b]Wave 1 included 6 items from the Nonspecific Psychological Distress Scale. Beginning in wave 2, additional negative affect items were added from the Positive and Negative Affect Schedule. Example publications for each measure are provided in the citation next to the measure's construct.

Daily Inventory of Stressful Events

Daily stress processes are assessed using the DISE [6]. Participants are posed with stem questions to assess different types of stressors (ie, arguments, avoided arguments, work overloads, home overloads, network stressors, discrimination stressors, and other stressors). For each stressor endorsed as having occurred, participants are asked additional questions on the content classification of the stressor. Specifically, participants shared who was involved in the event (eg, spouse or partner, friend, and coworker) and when the event happened (yesterday vs today; AM/PM). Next, participants shared their appraisals of the stressor, including (1) how stressful the event was (ie, *severity*) on a scale from none at all to very, (2) how much control they had over the situation (ie, *control*) on a scale from none at all to a lot, (3) whether the situation was resolved (ie, *resolution*) with a yes or no response, and (4) the areas of life at risk due to the stressor (ie, *resource risk*: financial, health and safety, time schedule, and socioemotional). Investigators can link information from the DISE (eg, exposure to daily stressors) to other variables from the NSDE protocol (eg, negative affect) to calculate stressor reactivity (ie, emotional, behavioral, or biological reactions to stressors on the same day) and stressor residue (ie, prolonged responses extending to the following day known as residue) components of the stress process model. Investigators can also measure stressor diversity (ie, dispersion of stressors across multiple domains) by calculating an entropy index. Before ending each call, participants share their forecasting of anticipatory stress by sharing how stressful they expect tomorrow will be on a scale from not at all to very.

Daily Events

Positive Events

Daily positive events are measured with questions about the occurrence of positive experiences: positive interactions, positive experiences at work or in a volunteer position, positive experiences at home or within their social network, spending time in nature, and any other positive event [49]. For each event endorsed, participants are asked follow-up questions on who else was involved, when it happened, and additional emotional reactions. Before ending each call, participants are asked to forecast how pleasant they expect tomorrow will be on a scale from not at all to very.

Emotional Support Exchanges

Participants reported whether they gave or received emotional support and specified who was involved with these exchanges (eg, spouse or partner, child or grandchild, parent, sibling, friend, or coworker).

Everyday Discrimination

Daily discrimination is assessed using a measure adapted from Williams and colleagues' [50] 9-item Perceived Discrimination Scale. The scale was designed to capture recent experiences that involve character assaults (eg, treated with less courtesy or respect than others, treated as if inferior or dishonest) that may lead to interference with one's socioeconomic position. A

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follow-up question is asked pertaining to the reasons for the perceived discrimination (eg, race, gender, and age).

Time Use

Participants share how much time (in hours and minutes) they spent working, volunteering, providing unpaid assistance, in physical activity (lite, moderate, and vigorous), leisure activities, and watching television.

Daily Emotional Experiences

Daily positive and negative affect are measured using an adapted inventory of emotions from the Nonspecific Psychological Distress Scale developed for the original MIDUS survey coupled with questions from the Positive and Negative Affect Schedule calibrated for daily affect [51]. Each day, respondents indicate how frequently they felt each of 14 negative emotional experiences (eg, feeling so sad that nothing could cheer them up, that everything was an effort, hopeless, and lonely) and 13 positive emotional experiences (eg, enthusiastic, attentive, and proud) over the past 24 hours on a 5-point scale ranging from "none of the time" to "all of the time." The positive and negative affect measures have shown good internal consistency across both samples (core and refresher; Cronbach α in the high 0.8s and low 0.9s) and adequate between- and within-person reliabilities [52].

Daily Physical Health Indices

Health Behaviors

Each day, participants report engaging in (yes/no) and, if so, the number of cigarettes smoked, time spent vaping or using e-cigarettes, number of alcohol drinks they consumed, and whether they ate a meal from a fast-food restaurant.

Self-Rated Physical Symptoms

Daily physical symptoms are assessed using an adapted version of Larsen and Kasimatis' [53] symptom checklist. We omitted items that overlapped with the psychological distress scale (eg, "urge to cry"). The checklist asks about the occurrence and severity of 19 symptoms, including aches (headaches, backaches, and muscle soreness), gastrointestinal symptoms (poor appetite, nausea or upset stomach, constipation or diarrhea), upper respiratory symptoms (sore throat, runny nose), and menopausal symptoms (hot flashes or flushes), as well as an open-ended item. Each day, the respondents indicate if they experienced each symptom and the degree of severity on a 10-point scale from very mild to very severe. These questions predict chronic illness incidence and increased likelihood of functional limitations 10 years later [44].

Sleep Quantity

Each day, participants report the time (in hours and minutes) they spent sleeping the previous day or night.

Daily Medications

Participants reported "yes/no" to taking the following medications: over-the-counter or prescription allergy medications, steroid inhalers, oral steroids, creams or ointments containing cortisone, birth control pills, other hormonal medications, antidepressant or antianxiety medications, steroid nasal sprays, and corticosteroid injections.

Daily Cognitive Health

Memory Lapses

The Daily Memory Lapses Checklist [47] measures the frequency, irritation, and interference of memory lapses in daily life. *Frequency* was captured by respondents indicating (yes/no) whether they encountered the following prospective memory lapses (forgetting an errand or chore, medication, to finish something you started, an appointment, why you entered a room, someone's name, a word, or important information) and retrospective memory lapses (someone's name, where you put something, where something was placed, a word during a conversation, or something you wanted to remember). As a measure of *irritation*, respondents answered "How much did forgetting these things bother you?" on a scale from not at all to very much. As a measure of *interference*, respondents answered "How much did forgetting these things interfere with your routine?" on a scale from not at all to very much.

Unconstructive Repetitive Thoughts

Six items on unconstructive repetitive thoughts assessed cognitive interference each day [54]. On a scale from none of the time to all of the time, respondents shared how often they had trouble concentrating, thought about personal problems or concerns, experienced thoughts that were difficult to stop, had thoughts keep jumping into their head, thought about situations that upset them, and thought about their financial situation.

Daily Biomarkers

Cortisol

Saliva was self-collected 4 times per day for 4 consecutive days. Cortisol levels are used to determine cortisol awakening response and area under the curve. The area under the curve was determined using the raw cortisol values of each of the 16 samples compared to ground [55]. Cortisol awakening response was determined using methods described in [46] (see also [56]). These measurements are critical to assessing a blunted cortisol response, indicative of chronic stress [57]. Compliance to the saliva collection protocol was previously validated [46,58-60].

Alpha Amylase

In addition to cortisol metrics computed from the saliva samples, raw and weight metrics of alpha amylase are computed and available for each of the 16 sampling times (ie, 4 times per day—at wake, 30 minutes after wake, before lunch, and before bed) for 4 consecutive days.

Analytic Approaches and Considerations

The NSDE presents a wide range of analytic opportunities when working with its measurement burst design of microlongitudinal daily diary assessments nested within macrolongitudinal assessment waves repeated every 9-10 years. While comprehensive coverage of all analytic approaches and considerations relevant for NSDE data is outside the scope of this protocol paper, we have specified below 3 approaches that characterize past work and guide future inquiries using NSDE data.

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Opportunities for Descriptive Analysis and Aggregating Across Days of Assessment

Eight days of information provide robust metrics of a person's experiences and health beyond a single snapshot of time. Repeated measurements of time-varying constructs (ie, daily assessments of stress, affect, physical symptoms, etc) create analytic opportunities to decompose variation at between-person (eg, individual differences) and within-person (eg, day-level) levels. As one example, Scott and colleagues [52] used NSDE data as part of a coordinated analysis of intensive repeated measurement studies that descriptively demonstrated significant between-person variation, within-person variation, and reliability of daily negative affect and daily positive affect. This kind of descriptive analysis provides statistical justification for research questions and hypothesis development at multiple levels of analysis when using data sources like the NSDE.

Researchers can also aggregate values of daily experiences and health outcomes across the 8 days of assessments to create person-means that can be used to examine individual differences in person-level health outcomes. For example, Charles et al [61] averaged across study days in the NSDE 2 and NSDE R1 to create two groups of participants (a group that reported stressors vs a group that did not report any stressors across the 8 days of assessment). This between-person group variable (no stressor group vs stressor group) was then used as a predictor of person-level physical and cognitive health variables in linear regression models. This work and others document how daily assessments can be aggregated to create a person mean index relevant to study individual differences in health and well-being outcomes across the adult life span.

Analysis Focusing on Daily Dynamics Within Persons Over Time

Multilevel modeling (MLM) can flexibly manage the nested structure of NSDE data to evaluate daily dynamics within people over time [62]. Three-level MLMs can be used to model time-varying constructs (eg, stressors, affect, and physical symptoms) across study days (level 1, day level; capturing microlevel daily variation) nested within waves of assessment (level 2, wave level; capturing macrolevel changes across years) nested within persons (level 3, person level; capturing individual differences). MLM can also incorporate cohort-level differences to test specific hypotheses about how historic periods (eg, the Great Recession and the COVID-19 pandemic) impact daily experiences and daily processes (eg, stressor reactivity) as well as how these phenomena change over time.

Almeida and colleagues [22] used 3-level MLMs to model wave-level changes in daily stress processes across 20 years of adulthood (NSDE 1, NSDE 2, and NSDE 3). Stressor reactivity (the difference in negative affect on days when a stressor was reported compared with days when a stressor was not reported) was modeled at level 1 (day level), where day-level negative affect was regressed on a day-level stressor exposure variable. Macrolongitudinal changes in stressor reactivity across 20 years were modeled at level 2 (wave level), and baseline age moderation of changes in stressor reactivity was modeled at level 3 (person level). Researchers continue to leverage the adult life span samples and multiple waves of NSDE data to model age differences in constructs like stressor reactivity [63] and developmental trajectories of constructs such as affect [41] and control [31].

The NSDE provides a pivotal resource for researchers to examine daily linkages among time-varying behaviors, experiences, appraisals, and health outcomes using MLM. As one example, Cichy et al [28] leveraged 2-level MLMs to examine race differences in daily associations between family support exchanges and daily well-being, and whether family support buffered or amplified stressor reactivity. The daily diary design provided the capacity to simultaneously examine individual differences (ie, race) in the within-person associations between family support exchanges and well-being [28].

Recent Advancements in Macrolongitudinal Change in Daily Dynamics

Most prior research has primarily used a 2-step approach to examine individual differences and patterns of change among short-term within-person associations, where within-person daily associations (eg, stress reactivity slopes) are first extracted from an MLM and then subsequently included as an individual difference variable in follow-up models. Recent advances can now simultaneously model individual differences in day-level constructs (eg, stress reactivity); how that construct (eg, stress reactivity) changes over time (wave-level); and whether individual differences in the rates of change account for changes in health and well-being outcomes (person-level), modeled as random slopes within a joint modeling multilevel structural equation modeling (MSEM) framework [33,64]. Modeling these effects simultaneously within a single statistical model allows for a more computationally efficient modeling of the variability within and across levels of analysis. The MSEM approach permits a sophisticated linking of processes operating on differing timescales, where short-term daily processes that unfold over time can simultaneously be treated as antecedent and outcomes of slower developing changes in health and well-being.

Results

Since 1995, data collection has occurred every 9-10 years. The most recent data collection is ongoing through 2027. Since 1995, a total of 3510 adults, ranging in age from 24 to 97 years, have participated in the project. The NSDE has accumulated 42,243 daily interviews across multiple waves of data collection. All NSDE data are held within the online framework of the MIDUS study, with archived and continuously updated datasets made available to the research community [19].

Discussion

Impact of the NSDE

The NSDE is a foundational resource for understanding how the rhythms of daily life shape long-term psychological and physical health. This paper outlines the NSDE protocol and highlights its integration of daily diary methods, salivary biomarkers, and longitudinal health data spanning more than 20 years and involving over 3500 participants. By capturing the microlevel dynamics of stress, emotion, and social

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interaction—and linking them to long-term outcomes—the NSDE provides a uniquely rich and nuanced view of human development across adulthood. The study's methodological innovations and scientific breadth make it a critical tool for identifying biopsychosocial pathways through which everyday experiences accumulate and contribute to disparities in health, well-being, and aging.

The NSDE data have transformed our understanding of well-being across the adult life span. NSDE has tested and inspired theoretical models (eg, Daily Stress Process Model [4]) about how daily experiences influence health and mortality. For example, studies testing the Daily Stress Process Model have revealed how stressors piling up over time (ie, stressor accumulation) and of greater severity are each related to both higher levels of distress [2,64-66], and worse physical health and functioning, including greater inflammation [67,68], higher allostatic load [69], and long-term detriments to physical and mental health [33,70-72]. Using NSDE, researchers have examined how the experience of stress affects the health and well-being of some people more than others, with differences occurring as a result of age [73], socioeconomic status [74,75], sexual orientation [76], discrimination [77], and exposure to early childhood adversity [78]. Using these data, researchers have examined how stress processes change over time [22] and how they are influenced by global events, such as the Great Recession [65,79].

The above provides a few examples of the many findings from studies using NSDE, but many opportunities remain. Below, we mention several of the most pressing research questions in the field of adult development that can be addressed with available NSDE data.

Identifying Modifiable Factors Related to Cognitive Decline and Dementia

Age is the strongest risk factor for cognitive decline and for dementia. By 2060, almost a quarter of Americans will be over 65 years old, making the search for lifestyle factors that may slow cognitive decline or delay the onset of dementia a national priority. Researchers have used the NSDE in studies that document the importance of an active and varied lifestyle in predicting cognitive decline [17] and how different types of stressor exposure are related to cognitive function [80]. Yet, testable questions remain. For example, daily memory lapses, a predictor of later cognitive decline that varies by gender and education [47], are a relatively new addition to NSDE. Researchers can examine interrelationships between memory lapses and other daily activities, as well as combining information collected from other MIDUS studies to examine how they are related to physiological processes and cognitive functioning.

Understanding How Everyday Thoughts and Behaviors Influence Gene Expression

Social genomics is a relatively new area of study that focuses on how our social environment affects gene expression and functioning [81]. The NSDE includes genome-wide RNA profiles related to inflammatory and antiviral activity, as well as gene methylation to assess the pace of biological aging (epigenetic age acceleration) and epigenetic mortality risk for over 1000 people. By linking these genetic differences with daily social processes, researchers can discover the genetic mechanisms through which these daily processes are linked to cognitive, physical, and psychological well-being.

Midlife Predictors of Health in Older Adulthood

Longitudinal data have provided important insight into how earlier life experiences influence later health [82]. Most longitudinal studies, however, consist of one-time surveys that provide overall ratings that are subject to memory bias [83]. In contrast, NSDE provides insight into daily lives as they are lived and uses data from multiple days to predict health, functioning, and longevity years later. Understanding, for example, how simple daily behaviors decades earlier predict cognitive decline or greater risk for disease will help identify behaviors that have lasting influences on our health and well-being.

Changing Social and Historical Effects

In addition to studying how individual differences influence health trajectories, researchers can also examine how larger societal changes influence health and well-being. In the past several decades, for example, a greater percentage of adult children live with their parents, and a growing number of men and women are living alone [84]. NSDE examines different cohorts of adults throughout the first two decades of the twenty-first century, providing insight into how changes in social structure shape daily life. In addition, the study has followed people before and after the Great Recession. Researchers have documented historical changes in physical health and well-being [85] and how historical time periods have a greater impact on some age groups [65] that may influence people's attitudes of aging [86]. Yet, we have more to learn regarding how societal changes influence individual lives.

Data Collection Considerations and Lessons Learned From the NSDE

Any large-scale data collection presents challenges that can impact participant participation, compliance, and data quality. Standardizing collection protocols is essential when implementing naturalistic assessments of daily experiences and collecting saliva samples in people's daily surroundings (ie, ecological momentary assessment rather than a laboratory setting).

Kits with clearly labeled contents and instructions help reduce participant burden and increase compliance. Included inserts contain colorful instruction sheets with diagrams and scannable QR codes for instructional videos prepared by NSDE staff. The fillable collection sheets allowed the participants to record the day and time of salivary sample collection as well as any noted issues they encounter with that collection point (ie, dropped swab, missed timepoint, etc). Participants recorded all medications and supplements on a medication use form, allowing researchers to analyze potential correlations between medication use and measured cortisol levels. To maximize salivary cortisol reliability and reproducibility, the kit instructions emphasized proper storage of salivettes. Completed

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saliva sample shipments were tracked to ensure timely delivery and processing.

Recruitment can be difficult in a study requiring daily commitment across multiple waves of longitudinal follow-up. For initial recruitment into the NSDE, highly trained interview staff clearly communicated the study purpose and used effective strategies to reach potential participants. Participants also had access to staff for questions about the study procedures using a toll-free 1-800 number. Additionally, standardization of the telephone interview script, questions, and response choices allowed for reliable data collection across participants and cohorts. This is consistent with research that highlights the integral nature of personal engagement to increase recruitment, adherence, and retention [24].

Statistical Considerations When Using NSDE Data

With 8 days of daily diary data nested within up to 3 waves of assessment across 20 years of adulthood, analysts of NSDE data should be aware of potential design limitations when conducting their statistical analysis. Below, we briefly discuss statistical considerations when dealing with attrition across assessment waves and handling missing data in the NSDE and point the reader to didactic overviews of MLM [87] and understanding threats to validity of longitudinal designs. For example, MacDonald and Stawski [88] provide guidelines for handling attrition, retest effects, and missingness in longitudinal designs like the NSDE.

Participant attrition can be due to a multitude of factors, including busyness (no time), illness, lack of interest, relocation, or death. Participants may not complete the entire study or selectively complete certain components of the protocol. Researchers can test whether the attrition or selective missingness of certain assessments is nonrandom and the extent to which rates of change may be influenced or biased by this threat. Assessing reasons and characteristics associated with attrition as well as incorporating parameters for attrition into statistical models can improve the conclusions drawn from the analyses, inform the generalizability of the analytic sample, and isolate possible influence from attrition processes [88-90].

Missingness across days and waves of assessment can influence study results in various ways, ranging from reducing statistical power to potentially biasing parameter estimates [89]. Modern statistical approaches (eg, likelihood-based estimation and multiple imputations) can be implemented to obtain unbiased model estimates when working with missing data. As one example, full information maximum likelihood (FIML) estimation yields unbiased parameter estimates under conditions where data are assumed to be missing at random [91,92] and are based on all available information (in contrast to listwise deletion or imputed data points, FIML uses all available data and preferentially weights cases with more observations). Likelihood-based approaches such as FIML are most appropriately used on larger sample sizes [93], making the NSDE an ideal dataset for its use.

Conclusions

Daily diary studies capture the thoughts and behaviors that constitute the fabric of daily life. NSDE is an example of a daily diary study whose measurement burst design complements the wide assessment spacing of a macrolongitudinal study. In this manner, NSDE is ideal for identifying processes and capturing experiences that would otherwise be missed if just viewing health and aging from the wider assessment windows. One aim of this paper was to provide information for people interested in using the NSDE methodology for novel studies. Applying the NSDE protocol to new samples would provide a greater understanding of how daily life impacts health across different populations. A second aim was to provide information for researchers interested in using existing NSDE data. We suggested several quantitative models and future research directions for researchers interested in using NSDE to expand our knowledge of how to live healthier, longer, and more fulfilling lives. Cumulatively, these theoretical and empirical contributions highlight avenues for innovation, intervention, and application [4] and serve as examples for which research using NSDE, or applying the NSDE protocol in new studies, can continue to inform our understanding of influences of health from a microlongitudinal perspective.

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Data Availability

The datasets generated during this study are available at [19].

Authors' Contributions

Conceptualization: DMA, STC, JRP, RSS, ESC, JM
Formal analysis: RSS, ESC, JR, JM
Funding acquisition: DMA
Methodology: DMA, ESC, NC, JM
Writing – original draft: STC, RSS, ESC, JR, JSN, JCH
Writing – review and editing: DMA, STC, JRP, RSS, KEC, ESC, JR, JSN, JCH, JM

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Conflicts of Interest

None declared.

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Abbreviations

DISE: Daily Inventory of Stressful Events
FIML: full information maximum likelihood
MIDUS: Midlife in the United States
MLM: multilevel modeling
MSEM: multilevel structural equation modeling
NSDE: National Study of Daily Experiences

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Protocol

A Previsit Mobile Health App (Health-E You/Salud iTu) for Male Adolescents to Promote Sexual and Reproductive Health Care Receipt: Protocol for a Randomized Controlled Trial

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Abstract

Background: Male adolescents have significant sexual and reproductive health (SRH) needs and, despite the existence of national guidelines, their SRH care receipt remains poor. Technology-based interventions have been shown to successfully support adolescents' SRH; however, they have primarily focused on female individuals. To date, no such solutions support comprehensive SRH care delivery for male adolescents in primary care settings. Health-E You/Salud iTu (Health-E You) is a mobile web app that was originally designed for female youth and has proven to be effective in improving contraceptive care delivery and use. Adolescents access the app ahead of a clinic appointment, which contains initial screening questions, interactive knowledge items, and contraception decision support with tailored recommendations based on the users' input. The app then provides clinicians with a summary of patients' recommended SRH care.

Objective: This study aims to adapt Health-E You for use with diverse groups of male adolescents presenting for care. This protocol describes the development, testing, and evaluation of Health-E You for male youth.

Methods: This study consists of 2 stages. Stage 1 involves formative research, design, and user testing of Health-E You for male adolescents. Specifically, we implemented a youth-centered design process, using multiple rounds of qualitative data collection and engaging youth and clinician advisors to design the Health-E You app from April 2023 through April 2024. From May 2025, for approximately 6 months, we are conducting beta testing of the app with youth and its output with clinicians. Transcripts of interviews and focus groups from stage 1 will be analyzed using deductive and inductive thematic analysis to identify knowledge and skill gaps for the app to address as well as desired app features. Quantitative data will be analyzed using descriptive statistics. Stage 2 will involve a stepped-wedge cluster randomized controlled trial with 2752 participants in 8 primary care settings across the United States to assess the impact of Health-E You on sexually active male adolescents' SRH care receipt and condom use. Data will be analyzed with an intention-to-treat approach using separate mixed models for each study outcome with a random intercept to reflect clustering of patients within clinics, adjusted for clinic size.

Results: Results will include qualitative data on male adolescents' and clinicians' perspectives on SRH care receipt and delivery, respectively, and their preferences for app design. User testing will provide qualitative and quantitative data on the feasibility, acceptability, and usability of Health-E You in clinical settings. The efficacy trial will evaluate the extent to which the app improves SRH care receipt and condom use among sexually active male adolescents.

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Conclusions: The findings from this study will inform future technology-based interventions for male adolescents and improve male adolescents' SRH care receipt in primary care.

Trial Registration: ClinicalTrials.gov NCT06525064; https://www.clinicaltrials.gov/study/NCT06525064.

International Registered Report Identifier (IRRID): PRR1-10.2196/77780

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KEYWORDS

sexual health; reproductive health; primary care; mobile health; male adolescents

Introduction

Background

Male adolescents in the United States experience high rates and key determinants of sexually transmitted infections (STIs), HIV, and unintended partner pregnancy, with male adolescents belonging to racial, ethnic, and sexual minority groups being disproportionately impacted [1-3]. National guidelines recommend primary care clinicians deliver a comprehensive sexual and reproductive health (SRH) care package to all adolescents, including male adolescents. This care package includes but is not limited to preventing, screening for, and treating STIs and HIV; preventing unintended pregnancy and reproductive system–related cancers; and counseling about healthy sexual development and relationships [4-6]. However, male adolescents' SRH care receipt remains poor, with far fewer male adolescents being asked about and counseled on their sexual behavior and receiving family planning–related care compared to female adolescents [7-10]. One study showed that only 1 in 10 male adolescents received the recommended SRH care package and, when provided, care focused mainly on STIs and HIV prevention and treatment, with little emphasis on family planning [10].

Despite the need for interventions that facilitate SRH care delivery to male adolescents, we are not aware of any clinic-based interventions designed to support male adolescents' comprehensive SRH care receipt. Most clinic-based SRH interventions have been designed for female adolescents to support birth control use, STI testing, and condom use negotiation [11-15]. While female-focused approaches are well justified, addressing male adolescents' SRH needs is important for improving outcomes for *all* adolescents [16]. Existing interventions for male adolescents have focused on singular topics, such as condom use or preexposure prophylaxis for HIV, rather than the full SRH care package [17-21]. Comprehensive approaches that engage male adolescents of all genders and sexualities presenting for care are needed [22,23]. Continuing to overlook male adolescents' SRH needs not only fails to meet their health needs but also compromises their partners' health [6].

Technology-based interventions such as websites and mobile apps have been shown to successfully promote adolescents' SRH [17-20]. Such interventions allow for interactive designs that can be tailored to meet adolescents' needs while ensuring fidelity. Technology use is also ubiquitous among adolescents. They like the privacy it offers [24]; it improves their disclosure of sexual health risk behaviors [25,26], and it delivers information in ways that are perceived to be less judgmental than directly from clinicians [25-27]. While many male adolescents share that they want to talk with their clinicians about SRH, they prefer their clinician to initiate these discussions [28]. At the same time, clinicians often lack the time to have in-depth SRH conversations with male patients or feel uncomfortable doing so. The use of a technology-based intervention with male adolescents before a clinic visit may overcome some of these barriers for both adolescents and clinicians.

Health-E You/Salud iTu (Health-E You) is an interactive and individually tailored mobile web app that was originally developed to support sexually active female adolescent patients in selecting a contraceptive method that matches their personal needs and preferences and discussing contraception with their clinician. The app also prepares clinicians by sending them a confidential patient summary before the face-to-face visit. In a cluster randomized controlled trial, Health-E You significantly improved female patients' contraceptive knowledge, self-efficacy, and use of effective nonbarrier contraceptive methods [14]. While implementing Health-E You, adolescents, clinicians, schools, and community partners voiced the need for the development of an equivalent app to use with male patients.

Objective

This study protocol summarizes our approach to address vast research and care delivery gaps for male adolescents by adapting Health-E You for use with diverse groups of male adolescent patients presenting to primary care. This protocol describes the evaluation of the feasibility and acceptability of the Health-E You app; it also describes evaluating the app's efficacy on male adolescent patients' SRH knowledge, self-efficacy, and care receipt using a cluster randomized controlled stepped-wedge design as compared to usual care.

Methods

Study Design

This study consists of 2 stages (Figure 1). Stage 1 involves formative research with adolescents and clinicians to inform Health-E You app updates for use with male adolescent patients. Stage 2 involves conducting an efficacy trial to determine the impact of the updated Health-E You app on sexually active male adolescent patients' SRH knowledge, self-efficacy, contraceptive method behaviors, and care receipt. The formative work took place from April 2023 through April 2024, and the efficacy trial began in November 2025 and will last

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approximately 2 years. This study used human-centered design principles to create a youth-centered final product with input from male adolescents and clinicians to ensure the app supports addressing males' SRH. Separate from our formative research participants, described subsequently in Stage 1 Formative Research and User testing, this study is also using design team advisory groups (DTAGs) of gender-diverse male adolescents and clinicians to support the design of app content, features, and messaging; research instrument development; and recruitment strategies. This study is guided by the SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) checklist (Multimedia Appendix 1) [29].

Figure 1. Overview of the study procedures. SRH: sexual and reproductive health; T0: baseline; T1: after clinic visit; T2: 2 months after clinic visit; YCHD: youth-centered health design.

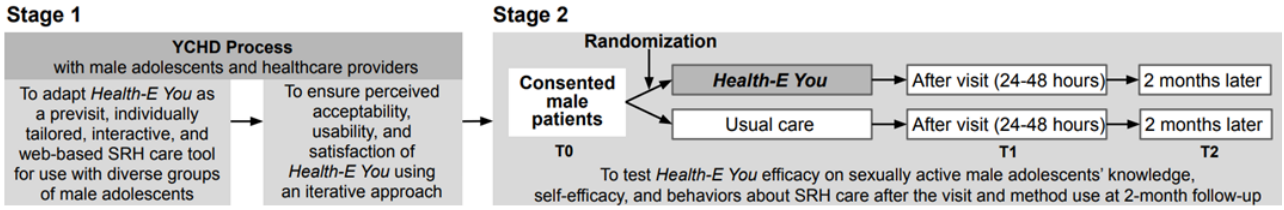

Ethical Considerations

This study has been approved by the Johns Hopkins Institutional Review Board (IRB00424416). In stage 1, eligible clinicians and male adolescents aged 18 years or older provided oral consent; parental oral consent and minor assent were obtained for eligible persons younger than 18 years. Male adolescent participants who provided consent and enrolled received a gift card of US $35, and clinicians received US $50 for their time after participation. For app testing, male adolescent participants who provided consent and enrolled received a gift card of US $50, and clinicians received US $50 for their time after participation. Stage 2 participants receive US $10 after completing the baseline survey and US $20 after completing each follow-up survey, totaling US $50 if they complete all 3 surveys. As part of our quality control process monitoring, we also have an institutional review board–approved protocol (IRB00454050) to collect online surveys before and after the intervention from clinicians and staff to provide contextual information about the trial. Each clinician or staff participant will receive a gift card of US $20 for their time after completing each survey. The protocol and consent procedures involve maintaining the privacy and confidentiality of all research subjects' data and/or identity. Survey data collected and stored through the secure Health Insurance Portability and Accountability Act (HIPAA)-compliant data management software will only be accessed by research staff. Each participant will have a unique identifier to link data between surveys and the app; participant contact information will be stored in a separate protected location that cannot be downloaded, with access limited to the research staff responsible for participant follow-up.

Stage 1: Formative Research and User Testing

Formative Research Participants and Study Setting

Male adolescents and clinicians participated in virtual focus group discussions and interviews, respectively, to inform Health-E You app updates for male adolescents. Male adolescents of any gender could participate if they were of male sex; aged 15 to 24 years; English or Spanish speaking; and able to provide informed consent and recruited via local and national youth advisory boards, youth-serving organization listservs, targeted social media posts, and referrals by enrolled participants. Clinicians could participate if they had an advanced clinical degree (eg, nurse practitioner, physician); currently practiced in the United States; served at least 10% male adolescent patients; and were recruited via professional listservs, coalitions, and conferences.

Formative Data Collection

Focus group discussions with male adolescents explored perceptions and prioritization of different SRH topics across 3 sessions, feedback on app content using draft app pages (eg, information on condom use, STI and HIV prevention, healthy relationships, family planning), and the app's look and feel after reviewing an updated interactive prototype developed based on findings from earlier sessions. Sessions were facilitated by a trained research member using a semistructured interview guide and conducted from April 2023 to February 2024. Each focus group session consisted of 2 to 5 participants, was conducted in English or Spanish, was stratified by age (aged 15-17 and 18-24 years) and gender identity (cisgender and gender expansive), and lasted approximately 60 to 90 minutes.

Interviews with clinicians explored perceptions of male adolescent patients' sexual health needs, standard SRH care delivered, and areas where the Health-E You app could support SRH care delivery to male adolescents. Before the interview, clinicians completed a brief survey about their training history and confidence in and implementation of SRH care delivery to male adolescents. Interviews were conducted from May 2023 to March 2024 by a trained research member using a semistructured interview guide and lasted approximately 60 to 75 minutes.

We conducted qualitative data collection until data saturation was reached—the point at which additional data collection does not produce new information or themes [30,31]. All qualitative data were recorded and transcribed. Findings were used to develop the Health-E You app's beta version programming by a third party.

App User Testing

We engaged our male youth DTAG members to test the app's beta version, in which they worked via the app and provided feedback on its content, design, and flow. We used this feedback to inform app refinements.

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We are subsequently conducting acceptability, usability, and satisfaction testing with 40 male adolescent patients and 10 clinicians. This pilot testing of the app started in May 2025 and will last approximately 6 months. Inclusion criteria for adolescents of any gender include male sex, aged 13 to 21, English or Spanish speaking, and able to provide informed consent. For this testing, eligible youth complete a brief baseline survey; then use Health-E You before their clinic appointment; and after their visit, complete an immediate post measurement survey (Table 1) and a debrief about their Health-E You experience to assess app acceptability, usability, and satisfaction, and any explanations for low app ratings [32-34]. Clinicians are asked to review and provide feedback on the app, including the app-generated patient summaries. Debrief sessions last approximately 30 to 45 minutes for male adolescents and 20 to 30 minutes for clinicians and are facilitated by a trained research member; the sessions are audio recorded and transcribed verbatim.

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Table 1. Measures used in app user testing[a] and efficacy trial[b].

Variables	Items, n	Content	α coefficient	T0[a,b,c]	T1[a,b,d]	T2[b,e]
Outcomes						
Knowledge about contraception methods	22	A higher score indicates higher knowledge regarding male or female contraception methods [35,36]	0.77	✓	✓	✓
Self-efficacy regarding contraceptive method use	7	A higher score indicates greater confidence in male method contraceptive use [37]	0.70	✓	✓	✓
Self-efficacy talking to a clinician	5	A higher score indicates greater self-efficacy in talking to a clinician [38]	0.83	✓	✓	✓
Contraceptive method use behaviors	15	Condom use at last sex (vaginal or anal); frequency and consistency of condom use during sex (vaginal or anal) in the past 2 months; female birth control method use at last sex (vaginal); reasons for condom use or nonuse at last sex [39,40]	—[f]	✓		✓
SRH[g] care receipt	17	Sexual history, reproductive life plan, STI[h] and HIV tests, pregnancy, and contraception history; condom and lubrication materials; SRH vaccine history; counseled on pregnancy prevention, contraception, EC[i], condoms, and PrEP[j] or PEP[k]; follow-up visit scheduled or kept [10]	—	✓	✓	✓
Follow-up visit	3	Intention to see clinician; visit occurred; reason visit did not occur	—		✓	✓
Possible moderators						
Sexual behavior history	12	Ever had sex (vaginal or anal); sex or gender of sex partners; number of partners in past 2 months	—	✓		✓
Reason for visit	1	For example, visit reasons was for well visit, sports physical, sickness, STI screen, etc [10]	—	✓	✓	✓
Background factors						
Participant background and demographics	17	Age, race and ethnicity, gender, sexual orientation, grade, self-rated mental health, parental high school completion; SRH information sources; perceived quality of SRH education from parents or school; past STI and HIV history, reproductive life plan, and partner pregnancy history; number of children [10]	—	✓		✓
Health care visit factors	5	About clinician—sex and time alone with clinician; about visit—perceived visit satisfaction and quality care receipt [41]	—	✓	✓	✓
Health-E You app process measures						
Acceptance	8	A higher score indicates greater app acceptance [33,34]	0.90		✓	
Usability	12	A higher score indicates greater app usability [32]	0.98		✓	
Satisfaction	1	A higher score indicates greater app satisfaction [33]	—		✓	
App use data	—	Amount of time spent on app content, completion, and rating	—		✓	✓

[a]Stage 1 user testing.
[b]Stage 2 efficacy trial.
[c]T0: baseline.
[d]T1: after clinic visit.
[e]T2: 2 months after clinic visit.
[f]Not available.
[g]SRH: sexual and reproductive health.
[h]STI: sexually transmitted infection.
[i]EC: emergency contraception.
[j]PrEP: preexposure prophylaxis.
[k]PEP: postexposure prophylaxis.

Formative Statistical Analysis

Collected qualitative data are being analyzed using a pragmatic approach adapted from inductive and deductive thematic analysis [42]. First, 3 study team members review transcripts to familiarize themselves with the data and then code together 2 to 3 transcripts to generate initial codes—based on discussion, interview guides, and emergent data patterns—and reach

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consensus on a codebook. Team members divide the remaining coding of transcripts, which is then reviewed by another team member. Coding questions or inconsistencies are resolved through weekly group discussions, with oversight from a senior team member, in which the team identifies, reviews, and names emergent themes related to app content, functionality, and design specifications.

We descriptively analyze quantitative data on perceived app acceptability, usability, and satisfaction and estimate the prevalence of agreement for each item within each scale (disagree and strongly disagree versus agree and strongly agree) using Stata 18 (StataCorp LLC) [43]. Any items that receive an agreement rating of less than 75% will be reviewed by the study team and DTAG members, alongside corresponding qualitative feedback, to identify possible areas of app improvement. We will then make these final improvements to the app before efficacy testing.

Stage 2: Efficacy Trial

Efficacy Trial Setting

We will conduct the efficacy trial of Health-E You at 8 primary care settings that serve male adolescents aged 13 to 21 years from November 2025 for approximately 2 years. We recruited participating clinics through professional medical organization outreach and existing relationships. This trial has been registered on ClinicalTrials.gov (NCT06525064).

Stepped-Wedge Evaluation Design

We will evaluate the app's efficacy using a cluster randomized controlled stepped-wedge design, a one-way crossover design in which all clinics will begin the study in the control phase and then transition to the Health-E You intervention [44]. This design was chosen because it allows all sites to receive the intervention over the study course. Clinics will be stratified by adolescent patient population size (large versus small) and randomized into clusters within each stratum, which will dictate when they transition to the intervention phase during the 28-month study period.

Participants

Patients in participating clinics will be eligible to participate in the trial if they are male, are aged 13 to 21 years, report having had vaginal or anal sex in the previous 12 months, are able to provide informed consent, and if their preferred language is English or Spanish.

Efficacy Trial Procedures

Consent procedures for this clinic-based study will follow state minor consent laws, which allow minors to provide consent for SRH care [45,46]. This approach upholds minor participants' right to confidential SRH care, which is codified in each participating state's minor consent laws and reiterated in national and federal clinical guidance for adolescent SRH care [4,5]. At each clinic, staff will share study materials (ie, flyers, banners, handout cards) with potentially eligible patients presenting for care that feature a QR code to the study's eligibility survey, which can be completed on any device (eg, mobile phone, tablet, computer). Eligible adolescents will be electronically directed to a multimedia consent form containing an embedded video that describes the study's purpose and design, including the number of surveys, estimated time requirements, remuneration, associated participation risks, expectations and implications of study participation, and the right to withdraw at any time without implications for their care. The video also includes a brief true or false quiz to reinforce important consent components and information on how to contact study team members (Multimedia Appendix 2).

Participants who provide consent will then be electronically autodirected to a brief baseline survey. When clinics are in the intervention phase, participants will then be autodirected to the Health-E You app after baseline survey completion. Using contact information collected at enrollment, participants will be sent a follow-up survey 48 hours after their clinic visit and then a second follow-up survey 2 months later. We use a HIPAA-compliant survey and data management software to manage all participant enrollment, data collection, and follow-up data.

Health-E You Intervention Condition

Health-E You leverages mobile web technology to privately ask patients standard screening questions about their SRH before their clinic visit; provide needed SRH information and skill development activities; and then subsequently share a patient summary of SRH needs, concerns, questions, and recommended SRH care with clinicians based on their responses. The design of Health-E You is informed by the integrated behavioral model, which asserts that behavior (eg, condom use and SRH care use) is influenced by core constructs of behavioral attitudes, perceived norm beliefs, and personal agency (Figure 2) [47]. Specifically, Health - E You aims to improve male adolescents' SRH knowledge and self-efficacy to use condoms and talk with a clinician about SRH, which collectively may result in increased SRH care receipt during their clinic visit and subsequent condom use behaviors.

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Figure 2. Conceptual framework of Health-E You intervention for male adolescents. IBM: Integrated Behavioral Model; SRH: sexual and reproductive health; STI: sexually transmitted infection; T0: baseline; T1: after clinic visit; T2: 2 months after clinic visit.

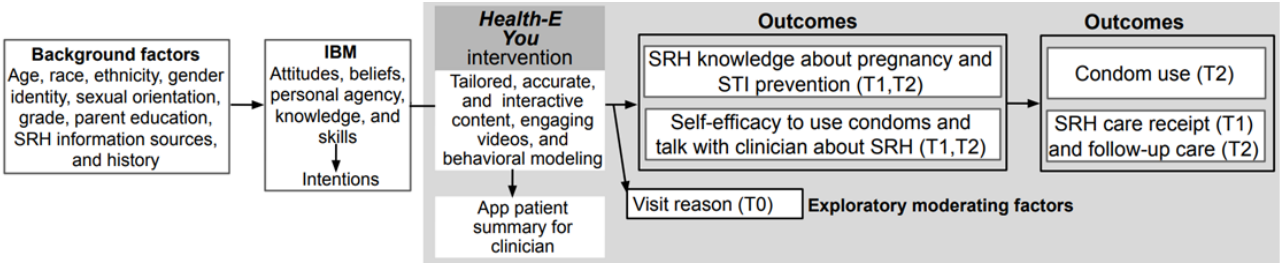

Similar to the app's original version for female adolescents, male adolescents using the Health-E You app are guided through an initial question set related to sexual behavior, sexual health history, and family planning goals (Multimedia Appendix 3). Users are subsequently directed to a core condom use and other STI and HIV prevention methods (eg, vaccines and preexposure prophylaxis) content pathway—designed to be completed in 7 to 10 minutes. The core content is multimedia and interactive to accommodate different engagement preferences and reinforce the app's messages (eg, brief condom demonstration video, interactive activity on condom use steps, animated informational videos provided by Amaze [48], videos from real clinicians and young people developed for this study, written content). Based on users' family planning goals and interests, users may also receive content on hormonal pregnancy prevention methods and, for participants expecting a child, ways to support a pregnant partner or newborn.

After completing core content, each user is presented with a summary of recommended topics to discuss with their clinician and invited to select additional SRH topics and submit questions they would like to discuss with their clinician during their visit. Users are given the option to send this patient summary to their clinician securely by email or local printing at the clinic, based on the clinic's preferred workflows. All Health-E You app data are programmed and hosted on the Drupal web-based interface and securely stored in the HIPAA-compliant Salesforce Platform (Salesforce Inc), which adheres to strict data security standards, including regular security updates.

Control Condition

When clinics are in the control condition, participants will receive care as usual.

Study Measures and Outcomes

In the baseline survey, participants are assessed for past SRH care receipt [10]; sexual behavior, including condom use [39,40]; SRH knowledge [35,36]; self-efficacy related to condom use [37] and talking to clinicians about SRH [38]; and background characteristics [10] (Table 1). At the first follow-up survey (48 hours after the visit), participants were assessed for SRH care receipt at the clinic visit, visit satisfaction, quality care receipt [41], and SRH knowledge and self-efficacy and, for participants in the intervention phase, acceptability [33,34], usability [32], and satisfaction [33] using the Health-E You app. At the second follow-up survey 2 months later, participants are assessed for the same baseline measures, including method use behaviors, and any additional app engagement (Table 1).

Retention

Strategies for participant retention from baseline through the follow-up surveys include participant remuneration, collecting multiple contacts at baseline and subsequent follow-ups (ie, phone number, email, etc), check-ins with participants between surveys, advising and providing US $5 gift cards to participants contacting us with changes in contact information, and sending reminder messages before conducting follow-up procedures [14,40].

Power and Sample Size

We generated power analyses using NCSS PASS 16 to compute minimum detectable effect sizes for condom use at last intercourse [40]. Assuming 2064 participants at the 2-month follow-up (86 participants per clinic per assessment), α of .05, power of .80, and an intracluster correlation coefficient of 0.06 (calculated from previous Health-E You data with female individuals [14]) with a baseline prevalence of 61.1% condom use at last intercourse [40], the minimum detectable difference is 12.2 percentage points, which translates to an effect size (h) of 0.26, just above the accepted threshold for a small effect size of 0.20. A baseline sample of 2752 participants (approximately 115 participants per clinic per step) will be recruited to account for 79.9% (2201/2752) retention at immediate follow-up (48 hours) and 75% (2064/2752) retention at 2-month follow-up.

Efficacy Trial Statistical Analysis

The main effects of the Health-E You intervention are being estimated using an intention-to-treat approach using separate mixed models for each study outcome, with a random intercept to reflect clustering of patients within clinics and adjustment for clinic size [49]. Each model estimates differences between the intervention and control arm in the change in each study outcome between baseline and each follow-up. This type of analysis allows for examining (1) within-individual change over time in an outcome, accounting for dependency among observations within individuals by modeling within-person error [50]; (2) between-individual variation over time [51]; and (3) between-subjects effects based on group assignment to identify significant differences in Health-E You versus usual care. We will also assess the potential moderating effect of patient demographics and adolescents' visit reason, which may influence SRH care receipt, on the study's outcomes. We are addressing incomplete data with maximum likelihood and multiple imputations [52-54]. The use of these missing replacement strategies does not mitigate loss of statistical power but does minimize bias because of attrition [55].

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Quality Control Process Monitoring

The investigative team at the Johns Hopkins School of Medicine, which is serving as the coordinating site for this multi-site randomized controlled trial, is serving as the data management team. This team will communicate any important protocol modifications to relevant parties, as appropriate, and in conjunction with the institutional review board. The investigative team comprises experts in adolescent health, male health, and evaluation research. We are using the World Health Organization's Monitoring and Evaluating Digital Health Intervention guidelines to inform this study's process monitoring of system factors, intervention quality, and intervention engagement [56]. We will assess technical functionality and stability through periodic user tests by the study team and routine app data monitoring to confirm the app is functioning as expected. We will assess intervention quality through the 48-hour follow-up survey, which will include questions on usability, acceptability, and satisfaction, including an overall app rating. We will track intervention engagement by monitoring whether participants complete core Health-E You content, opt in rates to share the patient summary with their clinician, time spent on Health-E You, and viewed content. We will provide monthly reports to participating clinics on these metrics and participant enrollment, which will provide an opportunity to gather clinic feedback to understand and address barriers with participant recruitment or sharing the patient summaries with clinicians. We will also collect online surveys before and after the intervention from clinicians and staff at each clinic about clinic workflows and visit times and postintervention about clinicians' perceived acceptability and usability of and satisfaction with Health-E You to provide contextual information about the trial.

Safety Monitoring

This study is guided by an internal data safety monitoring plan that includes staff training and monitoring related to participant privacy, confidentiality, and identification; response; and reporting of different possible events, adapted from recommendations by Horigian et al [57] (Multimedia Appendix 4). The data safety monitoring plan is managed by the principal investigator with oversight from a designated monitor external to the study team. This study is protected under a certificate of confidentiality from the National Institutes of Health that protects the research and Health-E You app data from subpoena.

Results

Findings from our stage 1 formative research and user testing will provide insights into the content, design, feature needs, and preferences of diverse male adolescents and clinicians regarding the development of an app to support young male adolescents' SRH care receipt and behaviors.

Findings from the stage 2 efficacy trial of Health-E You will provide important information on the effects of the Health-E You app on male adolescent patients' SRH knowledge, self-efficacy, and care receipt immediately after their clinic visit; condom use behaviors and additional SRH care receipt 2 months later; and acceptability, usability, satisfaction, and engagement with the app among intervention participants. Our analysis will also provide an indication of whether Health-E You produced different effects among participating male adolescents from varying backgrounds and presenting to care for different reasons. Results will be shared with participating clinics, updated on ClinicalTrials.gov (NCT06525064), and submitted for review to peer-reviewed journals.

Discussion

Anticipated Findings

There is a significant need for innovative approaches that support SRH care delivery for male adolescents. Our adaptation of the Health-E You/Salud iTu mobile web app for male adolescents offers a scalable, high-fidelity tool that primes both male adolescents and clinicians to discuss SRH, which adolescents can return to on their own time for further education and skill building. If Health-E You is found to be efficacious for male adolescents, it will provide a unique opportunity to engage male adolescent patients in much-needed SRH care.

Our iterative, human-centered design approach to adapt Health-E You for male adolescents is a strength of this study because it ensures that the app's content and features are aligned with the needs and preferences of both male adolescents and the clinicians who deliver their care. Human-centered design principles that we are implementing, such as continuous engagement, rapid prototyping, and iterative feedback, have been increasingly recognized as valuable for the design of SRH and other health interventions [58]. Furthermore, recent literature reviews suggest that engaging intended beneficiaries produces more relevant interventions and higher quality research that is more broadly disseminated [59-62].

The cluster randomized controlled stepped-wedge design in the efficacy trial of Health-E You will enable all participating clinics to receive the intervention while still maintaining rigor in estimating its effects on adolescents' SRH. If shown to be efficacious for male adolescent patients, Health-E You will likely be of use for male patients in similar settings across the United States and other clinical settings where currently no comparable strategy exists (eg, school-based health clinics, community clinics, college health services) and could be adapted for use in nonclinical settings (eg, school health classes, foster care, juvenile justice, and community-based organizations). The use of web-based technology is easy to scale up and sustain with regard to cost [63]. Ultimately, this study will contribute to advancing quality SRH care receipt for diverse groups of male adolescents and fill a critical gap that has existed for far too long without any attention.

Limitations

This study is not without limitations. Findings from our stage 1 formative research and user testing are not generalizable to all US male adolescents. This is a limitation inherent to most qualitative research studies, which prioritizes the richness and depth of data collected from participants with lived experience relevant to the research question rather than representative sampling [64]. In our stage 2 efficacy trial, we will recruit participants in primary care clinics across multiple states with diverse patient populations in an effort to approximate a sample

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that is more representative of male adolescents seeking primary care. All study participants will be volunteers and may exhibit selection biases that will be assessed and, if identified, accounted for analytically. Retention may also be an issue in the efficacy trial, though recommended strategies, such as the use of online surveys, incentives, and regular communication, will be implemented [65]. Contamination is theoretically possible; however, it seems unlikely given our clinic-level randomization and stepped-wedge design in which all clinics will start with the control condition and then transition to intervention receipt. There are also limitations to self-reported measures. It is possible responses may differ from actual behavior, although the use of such an approach is common in research such as this and well documented to be valid when assessed privately [66]. Despite these limitations, study findings will provide meaningful information on the potential for Health-E You to address key behavioral determinants of SRH and care for male adolescents.

Conclusions

This study protocol is intended to evaluate Health-E You by using a rigorous randomized stepped-wedge design to determine its feasibility, acceptability, and efficacy. If found to be efficacious, Health-E You will assist in improving SRH outcomes and care receipt for male adolescents as part of primary care.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study will not be publicly available to protect sensitive information but will be available through restricted or controlled access from the corresponding author on reasonable request.

Authors' Contributions

All authors take responsibility for the reported research and have approved the version being submitted. Each of the authors can certify that they have contributed substantially to (1) the conception and design of the study or acquisition or analysis and interpretation of data, (2) drafting this article or revising it critically for important intellectual content, and (3) final approval of the version to be submitted. All authors met the criteria for authorship and have approved the final article.
Conceptualization: AVM (lead), KT (equal), RAS (supporting)
Data curation: AVM (lead), ADS (supporting), SOS (supporting), MA (supporting), SR (supporting)
Formal analysis: AVM (lead), ADS (supporting)
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Writing – review & editing: AVM (lead), ADS (supporting), SOS (supporting), MA (supporting), SR (supporting), RAS (supporting), KT (supporting)

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT checklist.
[PDF File (Adobe PDF File), 531 KB - resprot_v14i1e77780_app1.pdf]

Multimedia Appendix 2
Link to Health-E You informed consent video for efficacy trial.
[DOCX File , 21 KB - resprot_v14i1e77780_app2.docx]

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Multimedia Appendix 3
About the Health-E You app.
[DOCX File , 21 KB - resprot_v14i1e77780_app3.docx]

Multimedia Appendix 4
Monitoring of adverse events in Health-E You efficacy trial (Stage 2).
[DOCX File , 27 KB - resprot_v14i1e77780_app4.docx]

Multimedia Appendix 5
Peer-review report from Health Services: Quality and Effectiveness Study Section (HSQE) (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 526 KB - resprot_v14i1e77780_app5.pdf]

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Abbreviations

DTAG: design team advisory group
HIPAA: Health Insurance Portability and Accountability Act
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
SRH: sexual and reproductive health
STI: sexually transmitted infection

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Protocol

Aggregating Patient Safety and Status Information in the Electronic Health Record to Support Time-Sensitive Mobility Interventions in the Intensive Care Unit: Protocol for the Design and Testing of a Clinical Decision Support Tool

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Abstract

Background: Patients who require intensive care unit (ICU) care frequently develop hospital-acquired functional decline, defined as a new or worsening loss of ability to perform self-care activities that is associated with prolonged immobility. This morbidity may persist for months to years after hospitalization but is potentially preventable through initiating mobility in the ICU using a multidisciplinary, evidence-based intervention to maintain functional status. While guidelines for ICU physical activity exist, timely identification of patients suitable for activity interventions is an ongoing challenge due to the dynamic nature of critical illness and the number of locations in the electronic health record (EHR) that clinicians need to click in and out of to synthesize patient data. Therefore, there is a critical need to develop an effective knowledge-based clinical decision support system (CDSS) interface in the EHR for efficient identification of patients appropriate for physical activity interventions and coordination of patient-specific activity plans within the ICU team.

Objective: The objective of this 2-phase project is to develop a CDSS interface for consistent translation of patient-specific data to inform evidence-based physical activity interventions delivered by registered nurses and physical therapists in ICU settings and evaluate its usability, usefulness, cognitive workload, acceptability, feasibility, and effectiveness on decision-making outcomes.

Methods: In phase 1, we will develop a usable, useful, and acceptable CDSS prototype by conducting 4 rounds of user-centered design interviews with registered nurses and physical therapists by using think-aloud and cognitive interview methods. In preparation for implementing CDSS in phase 2, we will conduct semistructured stakeholder interviews using the Consolidated Framework for Implementation Research to identify clinical workflow considerations, potential barriers, and implementation strategies. In phase 2, we will evaluate CDSS's usability, cognitive workload, acceptability, and effectiveness for activity guideline adoption in two settings: (1) a simulated EHR environment and (2) two adult ICU units in a tertiary care hospital.

Results: This study received funding in April 2024. The CDSS development phase is expected to conclude by December 2025. Data collection and analysis of CDSS evaluation are expected to begin in April 2026 and conclude by December 2028.

Conclusions: We expect the results of this multimethod process for designing, testing efficacy, and identifying barriers to real-world use to have an important positive impact on others who seek to develop safe and effective CDSSs that align with clinical workflow. Importantly, this work will complete the necessary pilot study for a subsequent multisite pragmatic clinical

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trial to scale the concurrent use of patient data with guideline recommendations at the point of care to deliver evidence-based interventions to reduce hospital-acquired functional decline and its negative, costly outcomes.

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KEYWORDS

early mobility; early ambulation; critical care; nursing; nursing informatics; decision support systems; electronic health record

Introduction

Background

New functional impairment after hospitalization for critical illness is common and persistent. More than 5 million adults are admitted to intensive care units (ICUs) each year in the United States, and more than 50% of them develop new physical health problems or hospital-acquired functional decline [1-4]. Functional decline is associated with negative outcomes during and after hospitalization, including ICU readmission, prolonged hospitalization, hospital readmission, nursing home admission, inability to return to work, and death [5-8]. These significant and long-term patient consequences demonstrate an urgent need to mitigate hospital-acquired functional decline.

The etiology of functional decline includes a combination of preexisting health status, the acute illness, and the consequences of ICU care (eg, deep sedation, immobility) [9,10]. The results of rigorous, well-designed studies demonstrate that early and routine physical activity interventions are safe and effective in improving functional recovery by the time of hospital discharge [11-13]. Multiple clinical practice guidelines recommend physical activity interventions as part of a bundle of standardized care for all patients in the ICU [14,15]. The ABCDEF bundle (Figure 1) was developed to standardize processes for coordinating and delivering evidence-based interventions in the ICU [16,17]. The early mobility ("E") bundle element describes daily, progressive physical activity interventions for physiologically stable patients, beginning with exercises in bed, transferring to a chair, and advancing to walking. The results of ABCDEF bundle implementation studies demonstrate the benefits of increased frequency and level of physical activity, decreased ICU and hospital lengths of stay, and decreased mortality [18-20]. However, reliable implementation of all elements remains challenging. A national, 68-hospital quality improvement collaborative study routinely measured ABCDEF bundle implementation performance and found that mobility was the least frequently implemented bundle element, with only 29% of patients receiving physical activity interventions beyond active range of motion [20]. To improve overall ABCDEF bundle implementation and patient outcomes, specific focus on innovative strategies to overcome barriers to physical activity is needed.

Figure 1. The ABCDEF bundle of standardized care. SAT: spontaneous awakening trial; SBT: spontaneous breathing trial.

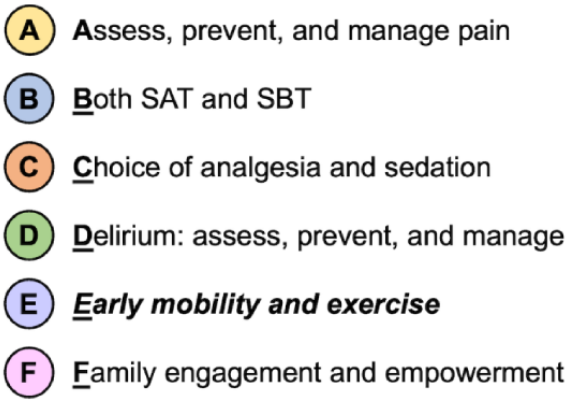

Numerous barriers to physical activity interventions have been identified and broadly classified as patient-, clinician-, unit-, protocol-, or ICU context–related barriers [21]. Strategies to address these barriers have included the use of structured quality improvement models to identify and target local barriers [22], nursing-initiated physical activity protocols to standardize patient assessment and goal setting [23], and focused interdisciplinary communication and collaboration [24,25]. However, these resources and approaches have not spread widely. A limitation to physical activity protocols is the poor usability, given the temporal and cognitive demands associated with the workflows of registered nurses (RNs). Our previous research identified that obstacles to existing RN-initiated physical activity protocols are significant—requiring time to synthesize multiple patient data elements either across different locations in the electronic health record (EHR; eg, blood pressure in vital signs documentation and vasopressor dose in the medication administration record) or scrolling through data over several hours or shifts to determine patient stability or changes in condition (eg, determining whether current ventilator settings represent an increased, decreased, or unchanged amount of respiratory support) [26].

Clinical decision support system (CDSS) interventions are particularly relevant in ICU settings to support decision-making and reduce cognitive load stemming from the large amounts of data from disparate areas of the EHR that clinicians must filter

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and process to make time-critical decisions [27,28]. CDSSs can provide data visualizations, alerts, reminders, dashboards, and decision support to augment clinicians in complex decision-making and support coordinated care delivery [29,30]. CDSSs can play an important role in the timeliness of physical activity decision-making, which significantly impacts patient outcomes. There is significant evidence that bed rest duration is associated with loss of muscle mass and strength and subsequent functional decline, which begins within 24 hours of bed rest and rapidly worsens, with a loss of up to 5% to 10% of muscle strength within 7 days of bed rest [31,32]. Nevertheless, there remains a lack of multidisciplinary EHR-integrated CDSSs designed to enhance critical thinking, promote guideline adoption, and decrease the cognitive burden of this complex decision-making process. In addition, compared to medical CDSSs, few CDSSs have been designed and tested for ICU RNs and even fewer for physical therapists (PTs) [33]. Given that physical activity interventions are delivered by multiple ICU team members, a CDSS is needed to support decision-making and physical activity care coordination across disciplines within the ICU team. Considering the low implementation of physical activity interventions during hospitalization, especially in ICU settings, it is imperative to identify methods to increase the adoption of evidence-based physical activity interventions.

Study Objectives

The overall objective of this 2-phase project is to develop and evaluate a CDSS interface for consistent translation of patient-specific data to inform evidence-based physical activity interventions delivered by RNs and PTs in ICU settings. Our team has successfully developed and validated a knowledge-based algorithm to synthesize patient data from multiple areas of the EHR with physical activity guideline recommendations (Aggregating Patient Safety and Status Information to Support Time-Sensitive Interventions in the Intensive Care Unit [ASSIST-ICU]) [34]. In phase 1, we aim to (1) develop the ASSIST-ICU CDSS interface using user-centered design (UCD) interviews with RNs and PTs and (2) develop a plan for implementing CDSS in 1 health system by interviewing key stakeholders. In phase 2, we aim to evaluate the effectiveness of the ASSIST-ICU CDSS for increasing the use of evidence-based physical activity interventions in the ICU delivered by RNs and PTs in (1) a simulated EHR environment and (2) a real-world pragmatic trial. The phase 2 secondary objectives are to evaluate the usability, usefulness, cognitive workload, acceptability, and implementation feasibility of the ASSIST-ICU CDSS.

ASSIST-ICU Algorithm Development

ASSIST-ICU is a knowledge-based algorithm using discrete nursing, respiratory therapy, and physical therapy documentation to synthesize patient data with physical activity guideline recommendations. The ASSIST-ICU algorithm was developed using an iterative process involving (1) translating expert recommendations into operational definitions, (2) identifying discrete data fields in the EHR, and (3) developing logic statements for the algorithm [35]. We used an expert consensus statement on early mobility readiness and safety criteria to develop operational definitions in 4 domains: respiratory, cardiovascular, neurological, and other [36]. An example from the respiratory domain is shown in Table 1. Each domain is evaluated using 24 hours of data to score a patient's readiness for mobility (yes or no). Overall readiness is scored as "yes" only if all domains are scored as ready for mobility; if any domain is scored as "no," the overall readiness score is "no."

Our team established content validation of the operational definitions [37], and retrospective testing of the decision support rules has been published [34]. The ASSIST-ICU CDSS will be delivered via an EHR tool. Initial feedback from focus groups will inform prototype development to include an icon that indicates readiness for mobility ("yes" or "no") with the ability to drill down to the features contributing to the score, providing details on why the patient met or did not meet the readiness elements.

Table 1. Example of algorithm development process from the respiratory domain.

Variables	Description
Expert recommendation [36]	• Clinical considerations for maintaining respiratory safety with out-of-bed exercises include that an artificial airway (eg, endotracheal tube, tracheostomy tube) is not in itself a contraindication, and SpO_2[a] should be ≥90%
Operational definition	• If a patient is receiving mechanical ventilation, the patient's most recent SpO_2 reading and the 24-hour average SpO_2 reading must be ≥90%
Data fields	• Medical device group=endotracheal tube or tracheostomy • SpO_2 row
Logic statement	• If medical device group=endotracheal tube OR tracheostomy tube, then most recent SpO_2 reading ≥90% AND 24-hour average SpO_2 reading ≥90%

[a]SpO_2: peripheral capillary oxygen saturation.

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Conceptual Framework

The theoretical basis for our study is grounded in an understanding of technology acceptance, cognitive load theory, and implementation science (Figure 2).

Figure 2. The 4 components of the study. ASSIST-ICU: Aggregating Patient Safety and Status Information to Support Time-Sensitive Interventions in the Intensive Care Unit; CDSS: clinical decision support system.

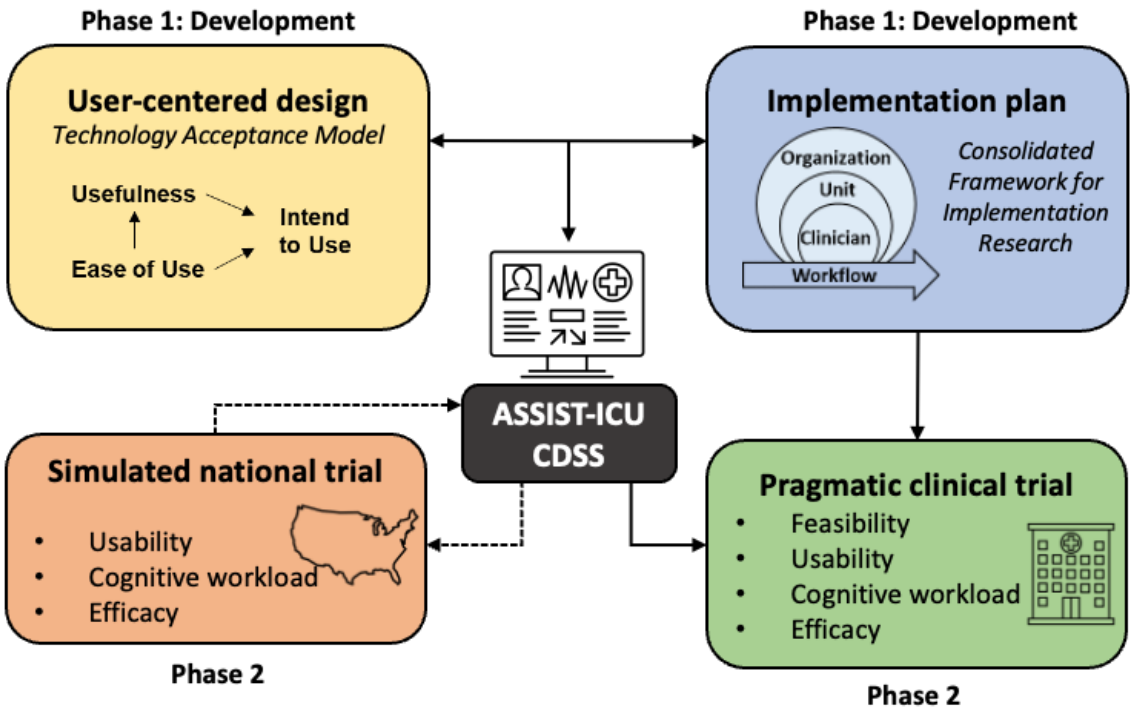

The technology acceptance model (TAM) is a widely used evidence-based model that focuses on perceived ease of use (or usability) and perceived usefulness. More than 30 years of research show that the TAM explains a substantial portion of health information technology acceptance and use [38,39]. Although multiple modifications of the TAM exist, we use the original TAM model for its parsimony, ease of use, and usefulness in explaining acceptance [40]. Cognitive load theory, a theory in use for more than 30 years, focuses on complex problem-solving when excessive cognitive load decreases decision-making performance [41,42]. A suboptimal CDSS design would increase extraneous cognitive workload and decrease a user's ability to correctly interpret the evidence presented. Given the limited amount of information humans can process in working memory before experiencing cognitive overload, our CDSS will aim to minimize extraneous cognitive load and will be evaluated using the NASA Task Load Index (NASA-TLX) [43]. Technology use is also influenced by organizational factors that are addressed by implementation science. The Consolidated Framework for Implementation Research (CFIR) organizes 39 constructs across 5 domains: innovation, outer setting, inner setting, individual characteristics, and implementation process [44,45]. This study will focus primarily on the CFIR domains of inner setting (organization and unit), characteristics of individuals (clinicians), and implementation process.

Methods

We will use a 2-phase approach using UCD and implementation science methodologies to develop a CDSS tool, implement the tool in 1 health system, and then test the tool in 2 settings (Figure 3).

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Figure 3. Details of the study's 2 phases. CDSS: clinical decision support system; EHR: electronic health record; ICU: intensive care unit.

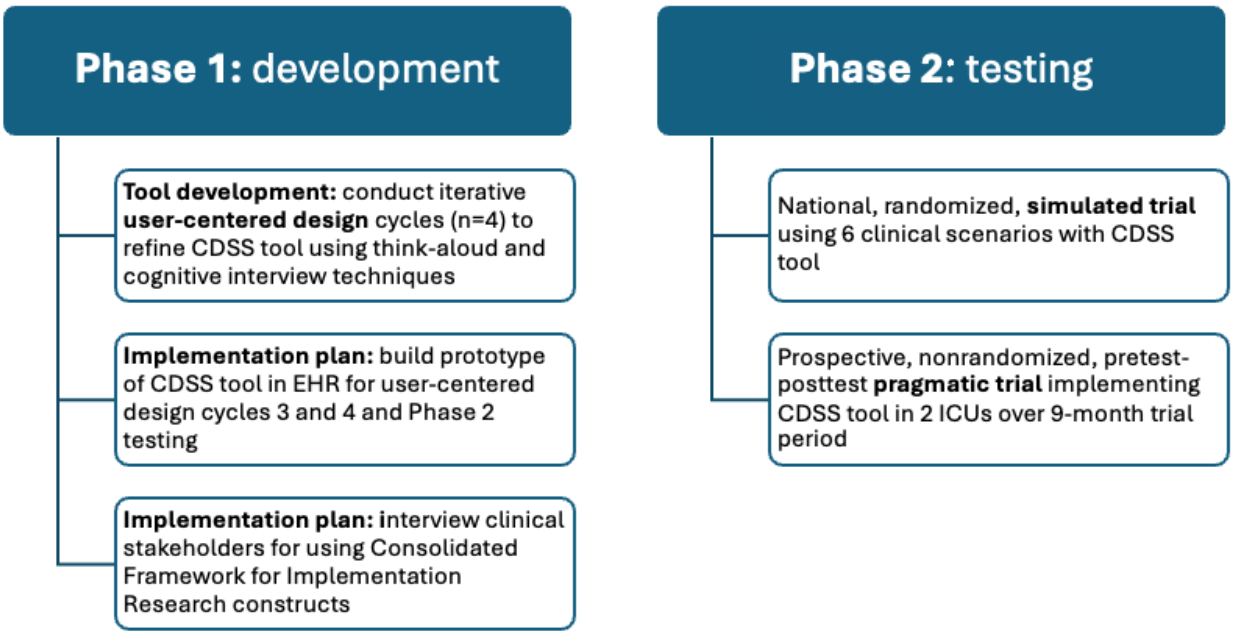

Phase 1: ASSIST-ICU CDSS Prototype Development and Implementation Plan

Iterative UCD Cycles to Design the ASSIST-ICU Prototype

We will design and iteratively revise the ASSIST-ICU CDSS prototype in a series of 4 UCD cycles with practicing critical care clinicians per cycle (n=24 RNs and PTs). We will conduct 2 types of sequential interviews—think-aloud [46] and cognitive [47] interviews—as well as a survey to assess acceptability (Multimedia Appendix 1) [38]. In the think-aloud interviews, participants will receive information about 2 patients with differing physical activity needs and will be instructed to open the prototype and navigate through the interface as they would if they were gathering clinical information in the EHR for making a clinical physical activity decision. As they explore the interface, they are instructed to vocalize about the actions they are taking and the thought processes they are using to interact with the prototype. This is a well-accepted usability method in which the clinician is not interrupted during their exploration. This method elicits users' expectations, understanding, and misunderstanding and identifies usability problems [48]. To capture interpretations and features that may have been missed during the think-aloud interview, a cognitive interview will be conducted to assess clinician understanding and interpretation of the prototype features. In this method, we systematically review the prototype interface with the clinician, feature by feature, to assess whether the feature was interpreted as the designers intended as well as to solicit design ideas. Next, to assess acceptability, the participant will complete the TAM survey (Cronbach α=0.79-0.93) [49].

The design team will analyze the findings of the interviews by rating each feature as being positive, negative, or unclear using the following deductive coding categories: (1) ease of use, (2) usefulness, (3) interpretation, and (4) satisfaction. Features with ≥25% negative or unclear ratings will be redesigned [50]. Any redesign efforts will incorporate EHR feasibility into the methods to avoid unattainable solutions. After redesign, clinician interviews will resume with a new group of participants.

ASSIST-ICU CDSS EHR Integration

After completing the UCD process, we will collaborate with the clinical informatics team at our study site to build the final prototype of the ASSIST-ICU CDSS interface in their EHR training environment. To support simulated testing, we will create real-world simulated patients with simulated data to evaluate how the data will be displayed on the screen and how clinicians can interact with the data. Our CDSS design will aim to include primarily structured data fields that are already available in the EHR to minimize creating custom documentation fields to keep the design within a Fast Healthcare Interoperability Resources infrastructure that will allow for future interoperability between sites.

ASSIST-ICU CDSS Implementation Plan

We will gather input from key stakeholders to identify clinical workflow considerations, potential barriers, and implementation strategies for the ASSIST-ICU CDSS using a descriptive qualitative design, incorporating the CFIR to inform data collection and directed content analysis [44,45]. We will interview stakeholders using a semistructured interview guide (Multimedia Appendix 2). Interview questions will focus on (1) workflow considerations, (2) role needs, and (3) implementation strategies to prepare our team and participating site for the successful evaluation of CDSS. Questions will be tailored to key stakeholders (eg, ICU director of nursing, PT director, RN informaticist, and chief medical information officer), recognizing that individuals hold different levels of influence within the organization. Interview data will be analyzed using directed content analysis [26,51]. We will review findings from the interviews to identify a follow-up plan for overcoming potential barriers and addressing workflow considerations before the ASSIST-ICU CDSS clinical trial.

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Phase 2: ASSIST-ICU Simulated Trial Design

Overview

We will conduct a simulated trial comparing the ASSIST-ICU CDSS interface with usual care (no ASSIST-ICU interface) in a simulated EHR environment. We will operationalize evidence-based decision-making through the creation of 6 expert-validated clinical scenarios. Of the 6 simulations, 3 will meet the out-of-bed safety definition, and 3 will not. All 6 simulations will be completed by each participant in a random order generated using the RAND function of Microsoft Excel. The decisions (regarding whether out-of-bed activity is safe or unsafe) will be recorded, and the number of correct decisions (range 0-6) for each participant will serve as our outcome measure of effectiveness (Table 2).

Table 2. Operationalization for scoring each clinical scenario.

	ASSIST-ICU[a] CDSS[b] recommends patient out of bed: yes	ASSIST-ICU CDSS recommends patient out of bed: no
Clinician decision to mobilize patient out of bed: yes	1	0
Clinician decision to mobilize patient out of bed: no	0	1

[a]ASSIST-ICU: Aggregating Patient Safety and Status Information to Support Time-Sensitive Interventions in the Intensive Care Unit.

[b]CDSS: clinical decision support system.

Study Participants for Simulated Trial

The inclusion criteria will be as follows: (1) licensed RN or PT, (2) at least 6 months of experience working in an ICU (to align with the advanced beginner stage of the Dreyfus model of skill acquisition [52,53]), (3) access to a tablet or computer for the design session, and (4) fluent in English. The exclusion criteria will be as follows: (1) no EHR experience in a critical care setting and (2) inability to use a cloud-based video platform.

We will recruit a sample of 50 licensed RNs and PTs (control group: n=25, 50%; intervention group: n=25, 50%) using publicly available lists from the professional state boards of 7 geographically diverse states. We will randomly select clinicians to contact. Using a modified version of the tailored design method proposed by Dillman et al [54], each selected clinician will be contacted using different modes (ie, letters, postcards, and email) up to 5 times in a 21-day cycle. For generalizability purposes, we will use a quota sampling methodology to ensure that the clinicians represent the demographics of the profession [50]. In addition to the random sample, up to 15 clinicians will be recruited using convenience sampling to assess the fidelity of ASSIST-ICU (eg, agreement between clinical scenario sequence and variable display in CDSS) in the simulated EHR.

Sample Power for Simulated Trial

The primary hypothesis to be tested in this study focuses on the efficacy of ASSIST-ICU in making evidence-based guideline physical activity decisions in a simulated EHR environment compared to no decision support. We hypothesize that participants assigned to the ASSIST-ICU intervention group will achieve a higher proportion of decisions that meet the out-of-bed safety definition. Assuming a true mean of 4.5 correct decisions out of 6 simulations (75% probability) when using the decision tool and 3 correct decisions (50% probability) when not using it, 2-sample binomial test simulations show that 25 clinicians per group will provide 99.2% power when testing for a between-group difference at α=.05.

Study Procedures and Setting

Respondents who meet the eligibility criteria will participate in an informed consent process and complete a short demographic and clinical experience survey. At the time of the scheduled test session, participants will connect via the cloud-based video platform from their homes or a quiet space of their choosing. Each participant will connect with a member of the research team and share their screen as they interact with the prototype. This will allow the visualization of computer mouse movements to show which areas and features of the prototype they are focusing on. After receiving a standardized orientation to the simulated EHR environment, the research team member will begin recording, and the clinicians will open the simulated EHR environment (with or without the ASSIST-ICU CDSS) to begin the study. The fictional patients' scenarios will be presented in their preassigned random order. After exploring the EHR environment, participants will be asked to respond whether they (1) would or (2) would not decide to move each patient out of bed that day.

Data Collection and Analysis for Simulated Trial

Clinicians will receive a score ranging from 0 to 6 based on the number of scenarios answered correctly. Participants will complete 3 brief surveys using a hyperlink in the cloud-based video platform's chat feature to assess the usability (System Usability Scale [SUS] [55]), cognitive workload (NASA-TLX [43]), and acceptability (Acceptability of Intervention Measure [AIM] [56]) of CDSS and decision-making process as a whole. The SUS is a 10-item Likert-type scale that is widely used to measure usability across a broad range of interfaces and performs well psychometrically (Cronbach α=0.70-0.92) [57,58]. The NASA-TLX is a 6-item scale that measures subjective cognitive workload in performing a specific task and is a reliable measure of cognitive workload across industries, including ICU clinicians (Cronbach α=0.83-0.92) [59]. The AIM is a 4-item Likert-type scale that measures acceptability and performs well psychometrically (Cronbach α=0.85-0.91).

Summary statistics will be calculated for the collected measures by group. Continuous measure distributions will be assessed

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for normality and reported as means and SDs or medians and IQRs, as appropriate. Categorical measures will be reported as counts and percentages for each level. A 2-sample binomial test will be used to test the null hypothesis that decision accuracy with the support tool does not differ from accuracy without it. Further between-group assessments will be conducted for SUS, NASA-TLX, and AIM scores using 2-sample 2-tailed *t* tests or the Wilcoxon rank sum test. *P* values will be reported based on 2-sided alternatives, and statistical significance will be evaluated at α=.05.

Phase 2: ASSIST-ICU Pragmatic Trial Design

The ASSIST-ICU pragmatic trial will use a prospective, nonrandomized, 2-unit pretest-posttest design. The specific components of the ASSIST-ICU CDSS and how the implementation will be operationalized, implemented, measured, and monitored for feasibility will be incorporated into the research protocol at the end of phase 1.

Study Setting and Participants for Pragmatic Trial

This study will take place at University of Iowa Health Care. Within University of Iowa Health Care, we will include 2 adult ICUs. Both units have implemented comprehensive patient physical activity programs that include protocol-based activity progression, routine PT consultation on ICU admission, and standardized activity assessment and intervention documentation for RNs and PTs in the EHR. The ASSIST-ICU CDSS will include 2 participant groups: clinicians and patients. The clinicians will include all RNs and PTs working in the selected adult ICU units. RN-to-patient ratios in the ICUs are typically 1:2, and PTs usually manage 6 to 8 patients per day. Patients will include all adults admitted to a participating ICU for at least 24 hours. As a pragmatic trial focused on decision-making at the point of care, we will not place restrictions on age, comorbidities, severity of illness, or expected discharge outcomes.

Intervention

As the trial involves using a prospective, nonrandomized, 2-unit pretest-posttest design, the ASSIST-ICU CDSS will be implemented in each ICU for a period of 9 months using a staggered approach, with 1 ICU receiving the intervention at a time. A training period will be conducted with RN and PT end users before implementation to facilitate effective use of the ASSIST-ICU CDSS and integration into existing workflows. Training will be scheduled based on each clinician's schedule and last approximately 15 minutes. In addition, resource materials will be distributed to each unit before and throughout the trial.

Data Collection and Analysis for Pragmatic Trial

Feasibility and effectiveness data will be captured via the EHR. Study data will be extracted from the EHR using EHR reports that are built from the structured data fields used to create the ASSIST-ICU CDSS. Baseline data will be collected via the reports before the intervention implementation using silent data collection. Silent data collection functionality allows CDSS logic to actively run in the system, but users do not yet have access to use the CDSS dashboard, allowing for baseline data collection.

We will evaluate key implementation and clinical outcomes by using the RE-AIM (reach, effectiveness, adoption, implementation, and maintenance) framework because it considers both the feasibility (reach, adoption, and implementation) and clinical effectiveness outcomes of the intervention (Table 3) [60].

The primary feasibility outcome will be physical activity decision-making (defined as the number of patients with out-of-bed activity documented and a corresponding CDSS designation of "safe" on a given ICU day). Secondary measures include acceptability and usability of CDSS. Acceptability (defined as the belief that an intervention is agreeable, palatable, or satisfactory [56]) and usability (defined as being appropriate for a specific context of use [55]) will be measured through online surveys. We will also evaluate potential safety events routinely reported in physical activity studies [61] and documented in the health system's patient safety reporting system, including whether the following events occurred during out-of-bed activity: fall to the floor, unplanned extubation, or line removal requiring urgent replacement.

On trial completion, all ICU RNs and PTs who worked in a study ICU will be invited to participate in a web-based survey. Usability (SUS), cognitive workload (NASA-TLX), and acceptability (AIM) will be measured and calculated in the same manner as described for the simulated trial.

We will generate histograms and bar charts to evaluate the distributions of all variables of interest and report appropriate descriptive statistics. Continuous variables will be summarized by means and SDs or medians and IQRs, as appropriate. Categorical variables will be summarized as counts and percentages. Preexisting differences in the outcome variables at baseline will be assessed using 2-sample *t* tests, the Wilcoxon rank sum test, or the Fisher exact test. Frequencies and percentages will be calculated to determine the feasibility of participation measures. A 2-sample binomial test will be used to test the null hypothesis that decision accuracy with the support tool does not differ from accuracy without it. Unit-stratified means and SDs will be calculated for SUS, NASA-TLX, and AIM scores. *P* values will be reported, and statistical significance will be evaluated at α=.05.

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Table 3. Study outcomes by RE-AIM (reach, effectiveness, adoption, implementation, and maintenance) element.

Elements and end points	Data collection
Reach	
80% of unit RNs[a] and PTs[b] participate in training	Unit participation logs
90% of unit RNs and PTs participate in trial	EHR[c] report
80% of unit RNs and PTs complete postimplementation surveys	REDCap[d]
100% of eligible patients receive CDSS[e] recommendations in participating ICUs[f]	EHR report
Effectiveness	
Ratio of safe alerts to total alerts	EHR report
Primary clinical end point: time to first out-of-bed activity	EHR report
Secondary clinical end points: highest level of activity in ICU, ICU and hospital lengths of stay, and discharge disposition	EHR report
Adoption	
Number of tool views	EHR audit log
Implementation	
Primary feasibility outcome: physical activity decision-making	EHR report
Safety: fall to the floor and accidental tube dislodgement (endotracheal or line removal)	Safety reporting system
Maintenance	
Continued physical activity practice after the clinical trial	EHR report

[a]RN: registered nurse.
[b]PT: physical therapist.
[c]EHR: electronic health record.
[d]REDCap: Research Electronic Data Capture.
[e]CDSS: clinical decision support system.
[f]ICU: intensive care unit.

Ethical Considerations

Ethics approval has been obtained for phase 1 from the institutional review board (IRB) of the University of Iowa (202503553; May 15, 2025). The study received exempt status because it involves minimal risk and met the criteria outlined in the Code of Federal Regulations (45 CFR 46). All participants will receive a study information sheet and may opt out of the study at any time. Transcript data will be deidentified, and recordings will be stored in a password-secured research data storage service. Participants in the UCD interviews will receive a US $95 gift card as an honorarium.

For phase 2, we plan to seek IRB approval before beginning the clinical trial. We plan to submit an exempt application for the virtual trial, and participants will receive a US $95 gift card as an honorarium. For the ICU trial, we plan to request an IRB waiver of informed consent for patients admitted to the ICU and clinicians, based on the premise that the trial meets the Office for Human Research Protections regulations on waivers of consent (45 CFR 46.116[f](3)). Specifically, the research involves no more than minimal risk to the participants (patients and providers engaged in data collection procedures that pose minimal risk), and the CDSS intervention is designed to increase the uptake of evidence-based care.

Results

This 2-phase CDSS development and evaluation study was funded in 2024 by the Agency for Healthcare Research and Quality (1R21HS029959-01). The developmental phase (phase 1) began in April 2024, and the CDSS trial is planned to begin in 2026, with data collection and analysis to be completed in April 2028. Phase 1 was approved by the IRB of the University of Iowa (202312543) with a waiver of informed consent, in accordance with the ethical standards of the institutional committee on human experimentation and the Declaration of Helsinki of 1975 and its latest updates. A separate IRB protocol will be submitted before beginning phase 2.

Discussion

Study Significance and Strengths

This study aims to develop and evaluate a CDSS that assists clinicians in coordinating and delivering evidence-based physical activity interventions at the point of care, with minimal extraneous cognitive workload and demonstrated feasibility of real-world trial procedures.

This study rigorously addresses the most common potential pitfalls identified with CDSSs, including usability, increased cognitive workload, usefulness, effectiveness, safety, fragmented

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workflows, and lack of spread, by using a novel sequence of methods to design and test the CDSS interface [29]. First, we use a UCD approach, considered a gold standard, which involves iterative evaluations with future system users to enable user perspectives to be incorporated into the system design to improve usefulness and usability [46,62-64]. Second, we use the CFIR implementation science framework during the design phase to understand barriers and facilitators to CDSS implementation [44,45]. Next, we conduct a virtual trial to establish the safety and effectiveness of the intervention in a simulated EHR environment before testing the feasibility of CDSS in real-world settings. Although UCD is widely used in health care, randomized tests of efficacy and rigorous testing of CDSSs in a pragmatic trial within a single study are rare. Furthermore, few CDSS studies apply implementation science theories to inform CDSS development and testing; however, designing with an implementation science lens can help identify additional modifiable barriers to address during CDSS design and implementation [65].

Despite the availability of multiple guidelines [14,36] and paper-based algorithms [23,66], there remains a lack of multidisciplinary EHR-integrated CDSSs designed to enhance critical thinking, promote guideline adoption, and decrease the cognitive burden of the complex mobility decision-making process regarding patients in the ICU. In addition, compared to medical CDSSs, few CDSSs have been designed and tested for ICU RNs and even fewer for PTs [33]. Given that physical activity interventions are delivered by multiple ICU team members, CDSSs are needed to support multidisciplinary decision-making and physical activity care coordination across disciplines within the ICU team. Considering the low implementation of physical activity interventions during hospitalization, especially in ICU settings, it is imperative to identify methods to increase the adoption of evidence-based physical activity interventions. ASSIST-ICU is expected to assist ICU clinicians in coordinating and delivering evidence-based physical activity interventions at the point of care, decrease bed rest duration, and ultimately reduce hospital-acquired functional decline.

Study Limitations

Although our study team has expertise recruiting participants for a national, internet-based clinical trial of nurses, we recognize that recruiting a multiprofessional sample may be challenging. In our prior work, we successfully recruited a national sample using state nursing board lists and a modified version of the tailored design method proposed by Dillman et al [54] that includes repeated invitations with different methods (eg, postcard or mailed letter with a small cash token) [67]. In addition, we have assembled a team with representation from both nursing and physical therapy disciplines to help optimize our reach to both professions.

Barriers beyond the focus of CDSS (efficient patient identification and physical activity coordination) may impact patient physical activity practice. We envision that this intervention may help to identify and prioritize addressing other barriers because CDSS displays patient status at the unit level, which can support unit leadership decision-making (eg, staffing or equipment needs). Without identifying patient safety for physical activity, which is a fundamental step in planning physical activity interventions, secondary barriers, such as staffing, are more difficult to plan for and address. We have selected ICUs with existing ICU activity protocols and will track unit-level barriers that may impact physical activity practice; for example, if nursing units are experiencing high levels of turnover and temporary staffing, we are prepared to modify CDSS training as needed to support unit needs.

Future Directions

The findings from this study will guide a future multisite pragmatic clinical trial to assist ICU clinicians in coordinating and delivering evidence-based physical activity interventions at the point of care. The successful completion of this study will be significant because CDSS is expected to ultimately be operable across different health systems (specified with Fast Healthcare Interoperability Resources standards), allowing for CDSS to be scaled across organizations and evaluated for clinical impact in a multicenter study. Future work will compare institutions' current standard of care with the ASSIST-ICU visualization on patient outcomes and explore institution-specific implementation needs.

Conclusions

Our study aims to develop a CDSS interface for consistent patient-specific translation of evidence-based physical activity interventions in ICU settings and evaluate its usability, usefulness, cognitive workload, acceptability, feasibility, and effectiveness on decision-making outcomes. We hypothesize that this novel interdisciplinary CDSS will increase the delivery of evidence-based recommendations for ICU physical activity. By applying UCD cycles and implementation science methods during development, we will seek to ensure that CDSS meets users' needs at the point of care and is feasible for health systems to implement in existing clinical workflows. These methods may provide a framework for developing future interdisciplinary CDSSs. The insights gained from this study are expected to provide strong justification for a subsequent multicenter study to deliver evidence-based interventions aimed at reducing hospital-acquired functional decline and its negative, costly outcomes.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study are available from the corresponding author on reasonable request.

Authors' Contributions

AK and KDL obtained funding and designed the study. HD, LK, PTE, and LFL contributed to the design of the study. AK and KDL drafted the manuscript. HD, LK, PTE, and LFL critically revised the manuscript for intellectual content. All authors have approved the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
User-centered design interview guide.
[DOCX File , 32 KB - resprot_v14i1e75752_app1.docx]

Multimedia Appendix 2
Implementation planning interview guide.
[DOCX File , 19 KB - resprot_v14i1e75752_app2.docx]

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Abbreviations

AIM: Acceptability of Intervention Measure
ASSIST-ICU: Aggregating Patient Safety and Status Information to Support Time-Sensitive Interventions in the Intensive Care Unit
CDSS: clinical decision support system
CFIR: Consolidated Framework for Implementation Research
EHR: electronic health record
ICU: intensive care unit
IRB: institutional review board
NASA-TLX: NASA Task Load Index
PT: physical therapist
RE-AIM: reach, effectiveness, adoption, implementation, and maintenance
RN: registered nurse
SUS: System Usability Scale
TAM: technology acceptance model
UCD: user-centered design

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Protocol

Transgender Men and Transmasculine One-on-One and Group-Delivered Empowerment for Targeted HIV Reduction (TOGETHR) Study: Protocol for a Digital Factorial Randomized Controlled Trial

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Abstract

Background: In the United States, transgender men and transmasculine people who have sex with men (TMSM) face an increased risk of HIV and encounter unique barriers to HIV prevention services, including preexposure prophylaxis (PrEP). Peer-based, digitally delivered support interventions that address these barriers in 1-on-1 or small-group settings may be effective in increasing PrEP engagement.

Objective: This study aims to compare the efficacy of digitally delivered individual and small-group peer-based strategies for improving PrEP uptake and adherence among at-risk adult TMSM without HIV.

Methods: The Transmasculine One-on-One and Group Empowerment for Targeted HIV Reduction (TOGETHR) study was a digital, open-label, randomized 2×2 factorial trial (1:1:1:1 randomization) of peer-delivered HIV prevention strategies designed to increase PrEP engagement in 300 PrEP-indicated TMSM without HIV. Participants were randomized to 1 of 4 conditions: (A) standard of care (SOC) package (information and PrEP locator tools), (B) SOC + PrEP for TMSM (PrEP4T; individual peer-based HIV prevention intervention), (C) SOC + LifeSkills for TMSM (LS4TM; group peer-based HIV prevention intervention), or (D) SOC + PrEP4T and LS4TM (both individual and group interventions). Interventions were delivered over a 6-week period. The study enrolled adults 18 years or older who were “transgender men or transmasculine,” sexually active with 1 or more partners who had a penis and were assigned male sex at birth, living without HIV, behaviorally at risk for HIV acquisition, and residing in geographic hot spots identified in the US Ending the HIV Epidemic initiative.

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Results: Study protocols and procedures were codeveloped with our community advisory board, including eligibility criteria, operationalization of geographic stratification, study branding, and detailed recruitment plans. Recruitment and enrollment began on April 1, 2024, and as of March 20, 2025, 103 TMSM had been enrolled. The median age was 26 (IQR 24-31) years. Among the 103 participants, 39 (37.9%) identified as Black, Indigenous, and People of Color, and 18 (17.5%) as Latine; 36 (35.0%) identified as "transgender man or trans man"; 31 (30.1%) as transmasculine; and 15 (14.6%) as nonbinary, genderqueer, or gender nonconforming. Additionally, 69 (67.0%) had at least a four-year college degree, and only 7 (6.8%) had no health insurance. Granger causality tests indicated that recruitment activities via social media (P=.006) and transgender-inclusive dating platforms (P=.02) were most effective and predicted higher baseline enrollment survey completion 2 weeks later. On March 21, 2025, the National Institutes of Health terminated the grant award, citing gender ideology and stating, "it is the policy of NIH not to prioritize such research programs."

Conclusions: This study was part of a critical research pathway to identify effective strategies for preventing HIV acquisition in TMSM, a group traditionally underserved in HIV prevention, and to inform prevention packages that incorporate peer-delivered interventions. Strong engagement with the TMSM community was central to the study's success and provided valuable insights for future HIV prevention research and practice.

Trial Registration: ClinicalTrials.gov NCT06182280; https://clinicaltrials.gov/ct2/show/NCT06182280

International Registered Report Identifier (IRRID): DERR1-10.2196/76831

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KEYWORDS

HIV prevention; transgender; preexposure prophylaxis

Introduction

HIV Epidemiology and Acquisition Risk

Transgender men and transmasculine people—those who identify as men or masculine and were assigned female at birth—have not been centered in HIV prevention efforts until recently [1-3]. Transgender people, who comprise an estimated 1.4 million US adults, are identified as a key population in the 2021-2025 US National Strategic Plan to end the HIV epidemic [4,5]. In a 2019 meta-analysis, HIV prevalence among transgender men in the United States was 3.2%—10 times greater than in the general US population [6]. Many transgender men and transmasculine people are men who have sex with men (TMSM) and engage in sexual activity with cisgender (cis) males and with partners of other genders who have a penis [7]. TMSM, especially those who engage in condomless genital or anal sex or who share needles for illicit drug use and hormones, are at risk for HIV and require tailored HIV prevention strategies [8-11]. However, no efficacious HIV prevention interventions currently exist for this population [1]. Research is needed to develop interventions that facilitate access to biobehavioral HIV prevention for at-risk TMSM, particularly those in geographic hot spots with a high HIV epidemic burden [4].

TMSM Barriers to HIV Prevention

TMSM require HIV prevention services that address their unique situated vulnerabilities and gender affirmation needs [12]. Most TMSM have not undergone genital surgery and may engage in receptive genital and anal sex, which often goes unreported to sexual health providers [8,13]. Gender nonaffirmation from cis male sexual partners is common and is associated with behavioral risk for HIV acquisition in TMSM [14]. TMSM also express concerns about concomitant preexposure prophylaxis (PrEP) and testosterone use for medical gender affirmation, which may reduce interest in and uptake of PrEP among TMSM with HIV behavioral risk [15]. Finally, TMSM are at increased risk of mental health morbidity (eg, depression, substance use), which is associated with HIV risk [7]. However, TMSM face barriers to accessing HIV prevention services, and tailored services remain lacking [15]. These barriers include discrimination that leads to care avoidance, misconceptions that TMSM are not at risk for HIV, and logistical challenges such as scheduling medical appointments [14-16]. The noninclusion of TMSM in PrEP trials and promotion further deters their use of PrEP [1]. Thus, effective HIV prevention for TMSM will need to remove barriers to care and address gender affirmation needs, while also building awareness, motivation, and behavioral skills necessary to prevent HIV among all transgender and MSM populations [17-19].

Peer-to-Peer Individual- and Group-Based Strategies for HIV Prevention

Evidence-based peer strategies that empower communities through social support, stigma reduction, and skills building are widely accepted in transgender communities [20-23]. Peer navigation interventions are individualized, using 1-on-1 sessions led by trusted peers with shared lived experiences. Peer navigation has demonstrated success in improving outcomes among people with HIV [24-32], including transgender women [33-35]. It has also been effective in increasing PrEP uptake and adherence [36-38], and shows promise for transgender women [37,39]. While peer navigation is endorsed by TMSM [17], no interventional efficacy research has yet been conducted.

Our team has previously adapted and implemented peer navigation interventions for transgender communities to increase linkages to health care services. This includes the Gender-Affirming Clinical and Public Health Model at Fenway Health (Fenway), which employs individualized 1-on-1 peer health navigation to support care engagement [32,40]. Peer health navigation typically involves 4 structured sessions over 6 months of follow-up, and evaluation of Fenway's program has demonstrated high feasibility and acceptability, with

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increased health care engagement outcomes within 60 days [41]. One-on-one sessions incorporate goal setting, skills building, assessment, planning, and navigation. Peer navigation has also been shown to increase linkage to medical, behavioral, and HIV prevention services (eg, PrEP) [41,42]. The Fenway peer navigation model has been disseminated nationally [43] and digitally [44]. Our team further replicated peer navigation with transgender people in Peru for HIV prevention [45], highlighting its adaptability, utility, and broad transferability.

Another evidence-based HIV prevention strategy used in transgender communities is group-based peer interventions, which involve peer-facilitated group sessions [20,21,23,46]. A pilot study of LifeSkills for Men (LS4M) [20], a small group–based behavioral intervention designed to reduce HIV risk and the mental health effects of stigma in TMSM, found high acceptability and positive trends in health outcomes. LS4M was adapted from LifeSkills [21], an efficacious intervention for transgender women. The LS4M curriculum consisted of 8 hours of content delivered across 4 weekly sessions. The pilot demonstrated that LS4M was feasible, highly acceptable, and associated with promising improvements over 4 months of follow-up, including increased transgender support and reductions in mental health severity, sexual risk, and gender nonaffirmation [20].

Evidence supports peer-delivered interventions for HIV prevention; however, few studies have compared individual and group formats or evaluated combined delivery [47,48]. Research is needed to assess the individual and combined effects of 1-on-1 and group-based peer-delivered strategies. Individualized interventions are tailored to the specific needs of TMSM, while group-based interventions affirm TMSM not only as individuals but also collectively as members of a community.

Conceptual Frameworks

Three conceptual frameworks informed the study (Figure 1). First, the Healthcare Accessibility Framework [49] highlights systemic and population-specific barriers to HIV prevention for TMSM, such as avoidance of care due to stigma, misconceptions that transgender men are not at risk for HIV, perceived difficulty navigating PrEP logistics [14-16], and the need for additional services (eg, mental health). It also emphasizes facilitators of access, such as health care empowerment [50]. Second, the Gender Affirmation Framework [7,51] underscores that being affirmed in one's gender is a key health determinant and that gender affirmation is not "one-size-fits-all." Many TMSM do not have or want genital surgery and are therefore at increased risk of HIV when engaging in receptive anal and vaginal sex [8,13]. Stigma and gender nonaffirmation also negatively affect HIV risk-taking and PrEP decision-making [14,52]. Gender-affirming HIV prevention that addresses TMSM-specific vulnerabilities is essential. Third, the Information, Motivation, and Behavioral Skills (IMB) model [53] is an evidence-based behavior change framework that targets increasing information (eg, PrEP knowledge), motivation (eg, attitudes, perceived benefits/risks), and behavioral skills (eg, self-efficacy) for TMSM. Effective HIV prevention for TMSM must integrate health care access, gender affirmation, and IMB constructs [17-19].

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Figure 1. Conceptual frameworks mapped to study aims. LS4TM: LifeSkills for Transgender Men and Transmasculine People; MSM: men who have sex with men; PrEP: preexposure prophylaxis; PrEP4T: PrEP for transgender men and transmasculine people; STI: sexually transmitted infection.

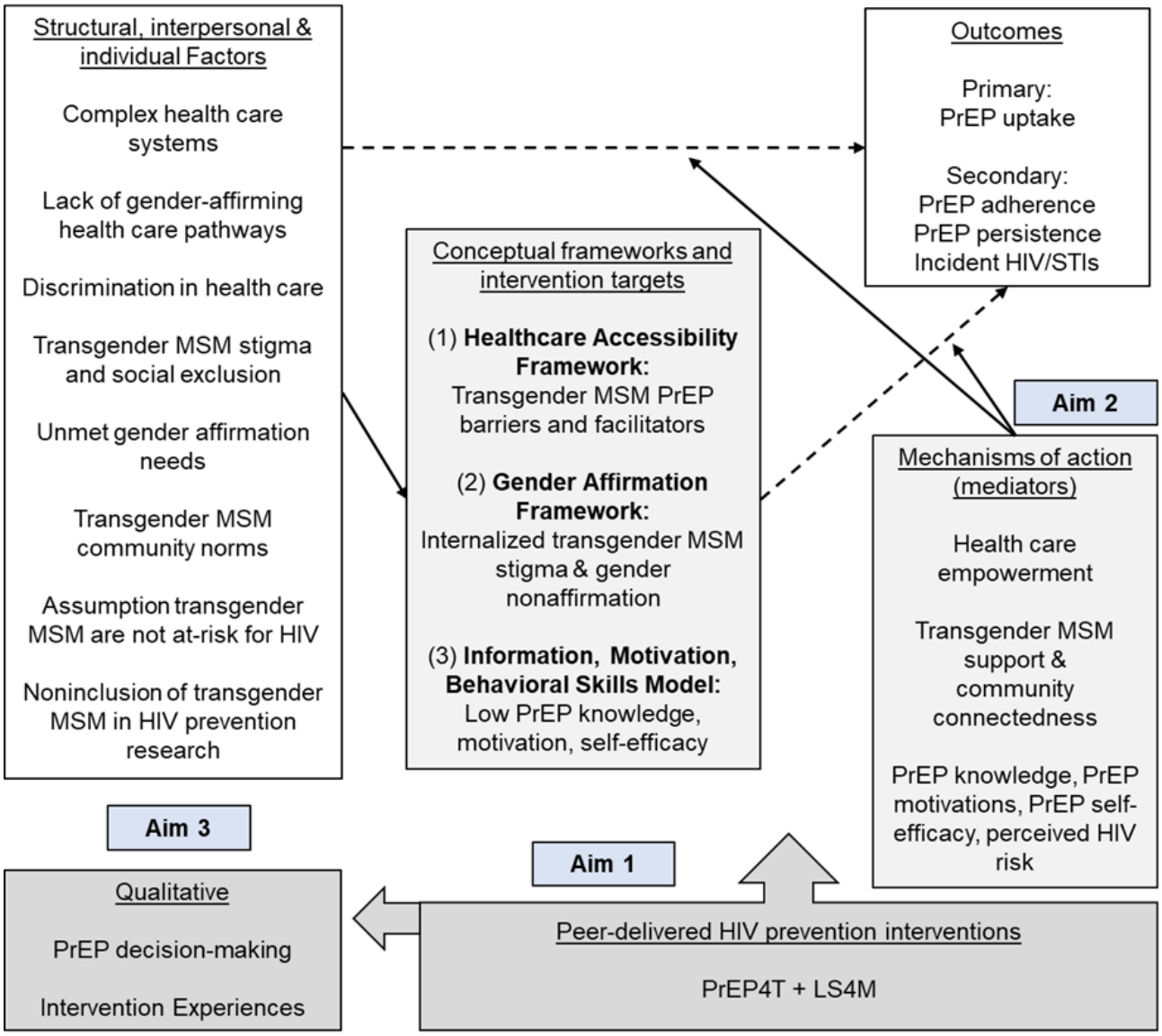

Study Objective and Aims

The goal of the Transmasculine One-on-One and Group Empowerment for Targeted HIV Reduction (TOGETHR) study was to evaluate the effectiveness of digitally delivered individual and small-group peer-based strategies in improving PrEP uptake and adherence among at-risk, HIV-negative adult TMSM.

Applying the Healthcare Access [49], Gender Affirmation [7,51], and IMB [53] frameworks, we conducted a digital, open-label, randomized 2×2 factorial trial (1:1:1:1 allocation) of peer-delivered HIV prevention strategies to increase PrEP uptake among TMSM (n=300) residing in Ending the HIV Epidemic (EHE)–prioritized geographic hot spots in the United States. The specific aims were to:

- Aim 1. Compare the efficacy of 4 peer-delivered HIV prevention strategies implemented over 6 weeks to increase PrEP uptake (primary outcome) among 300 PrEP-indicated, HIV-negative TMSM, which include
  (A) standard of care (SOC)
  digital PrEP locator and a library of syndicated HIV prevention, sexual health, and antistigma materials;
  (B) SOC + PrEP for transgender men and transmasculine people (PrEP4T; 1-on-1 PrEP peer navigation); (C) SOC + LifeSkills for Transgender Men and Transmasculine People (LS4TM; peer-delivered group-based PrEP behavioral intervention); or (D) SOC + PrEP4T + LS4TM.
- Hypothesis 1.1:
  Rates of PrEP uptake will be higher in (B) SOC + PrEP4T and (C) SOC + LS4TM conditions compared with (A) SOC (main effects).
- Hypothesis 1.2:
  PrEP uptake rates will be highest for participants randomized to (D) SOC + PrEP4T + LS4TM compared with (A) SOC (additive effects).
- Aim 2. Examine the mechanisms through which PrEP4T and LS4TM impact PrEP uptake using causal mediation analysis.
- Hypothesis 2.1:
  Health care access empowerment, transgender community support for gender affirmation, and IMB constructs will

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mediate the relationship between PrEP4T, LS4TM, and PrEP uptake.

- Aim 3. Explore PrEP decision-making processes and intervention experiences through in-depth interviews (IDIs; n=40; 10 per condition) to inform future scale-up and implementation of these interventions.

Methods

Study Design

The TOGETHR study was a collaboration between the University of Michigan and The Fenway Institute at Fenway Health. The Fenway Institute led study management, including recruitment and retention, enrollment, intervention implementation, and data collection. The University of Michigan was responsible for data analysis. Investigators from Johns Hopkins University, Duke University, Drexel University, and the University of California, Los Angeles also contributed to the study.

TOGETHR was a digitally delivered, open-label, randomized 2×2 factorial trial of peer-delivered HIV prevention strategies. The design included 2 factors: individualized 1-on-1 peer navigation (PrEP4T vs none) and group-based behavioral intervention (LS4TM vs none). The primary outcome was PrEP uptake, confirmed biologically. Secondary outcomes were PrEP adherence, defined as tenofovir diphosphate (TFV-DP) concentrations >700 fmol/punch (corresponding to >4 doses per week) [54], and PrEP persistence, defined as 2 consecutive dried blood spot (DBS) measures indicating PrEP use. Participants were randomized 1:1:1:1 to the 4 study conditions, with stratification by ethnoracial identity (Black, Indigenous, and People of Color [BIPOC] vs White non-Latine) and by Movement Advancement Project (MAP) state lesbian, gay, bisexual, transgender, and queer (LGBTQ) equality policy tally (“high, medium, or fair” vs “low or negative”) [55]. The enrollment target was approximately 50% BIPOC participants. The study protocol was developed in accordance with the 2025 Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) guidelines to ensure methodological rigor, transparency, and completeness in trial reporting [56].

TOGETHR was funded by the National Institutes of Health (NIH; R01MH129175). On March 21, 2025, however, the NIH prematurely terminated the grant, citing its focus on “gender identity.” The justification given was that, under the Trump administration (commencing January 20, 2025), “it is the policy of NIH not to prioritize such research programs." In April 20205, the American Civil Liberties Union (ACLU), Protect Democracy, and the Center for Science in the Public Interest filed a lawsuit on behalf of researchers, the American Public Health Association (APHA), and others challenging the abrupt termination of research grants on disfavored topics and populations by NIH. The current grant was included in the lawsuit. The grant was re-instated on July 9, 2025; however, litigation is ongoing and the future of the project remains uncertain [57].

Study Population: Eligibility Criteria

Inclusion criteria were (1) age ≥18 years; (2) assigned female sex at birth and identified as a “man, transgender man, or transmasculine”; (3) had sex in the past 3 months with a partner who had a penis and was assigned male sex at birth; (4) access to a smartphone or computer with internet; (5) HIV-negative at baseline (confirmed); (6) reported behavioral HIV risk in the past 3 months, including at least one of the following: (i) receptive vaginal/frontal or anal sex with an assigned male sex at birth partner with a penis; (ii) sharing needles or syringes for illicit drug use or hormones; (iii) self-reported sexually transmitted infection diagnosis; (7) residence in a US EHE-targeted geographic hot spot (48 counties, Washington, DC, San Juan, Puerto Rico—where >50% of HIV diagnoses occurred in 2016-2017—or 7 states with substantial rural HIV diagnoses; see Table S1 in Multimedia Appendix 1); (8) willing and able to provide informed consent in English; and (9) comfortable reading and conversing in English.

Community Participation: A Participatory Population Perspective

TOGETHR employed a participatory population approach, working with—rather than on—the TMSM community [58]. The study focused on peer-delivered interventions, with peers defined as “transgender men or transmasculine individuals.” Multiple investigators, all research staff interfacing with participants, and all intervention facilitators were transmasculine. A virtual community advisory board (CAB), composed of TMSM, was convened at study inception and met monthly or bimonthly via Zoom (Zoom Communications, Inc). CAB members received an honorarium for their time. The CAB played a central role in the research, collaborating closely with the study team on all aspects of the trial and serving as an essential mechanism for community consultation. The CAB provided extensive input on the interventions, study protocols and procedures, privacy and confidentiality safeguards, implementation and evaluation processes, recruitment and retention activities, dissemination strategies, and troubleshooting challenges to ensure acceptability for TMSM.

Recruitment

Participants were recruited and enrolled virtually nationwide from US EHE jurisdictions [5]. Recruitment strategies included social media (eg, closed Facebook groups, Reddit), community networking platforms (eg, Lex), paid advertisements and posts on geosocial networking dating apps (eg, Grindr), outreach through transgender health care, social, and advocacy organizations (eg, listservs, events), and peer-to-peer networks (eg, referrals from research staff, the CAB, and enrolled participants). Recruitment materials (eg, flyers, text, images, advertisements, taglines) were designed to support purposive sampling, such as geotargeting and incorporating diverse images of BIPOC and Latine MSM. Flyers and web-based advertisements directed potential participants to the study web page, where they could complete a screening form or contact the research team directly via email.

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Retention

For retention, the study team collected and regularly updated participants' contact information (eg, email, phone, mailing address, and Facebook or Instagram handles), along with the contact details of 1-3 individuals who could help locate them if needed. Participants were contacted through their preferred communication method to receive study visit reminders. Enrollment and retention were tracked in REDCap (Research Electronic Data Capture; Vanderbilt University), a secure, web-based, Health Insurance Portability and Accountability Act (HIPAA)–compliant system.

Study Procedures

Potential participants first completed a digital screener to assess preliminary eligibility. Those deemed eligible were scheduled for a virtual enrollment visit via Zoom with study staff. After eligibility was confirmed, participants completed a written informed consent process. Individuals who consented were conditionally enrolled and then completed a baseline survey and a DBS home collection kit for HIV and PrEP testing (described below). Participants who confirmed HIV negativity were fully enrolled.

After participants received eligible HIV test results, they were randomized, and study staff informed them of their assigned condition and scheduled any intervention sessions. Following communication of HIV results and randomization, all participants received an email with a password-protected link to the SOC materials housed on the study website.

Assessments and Survey Measures

Participants completed online surveys at baseline and at 3, 6, 9, 12, 15, and 18 months (Figure 2). Comprehensive surveys, lasting approximately 30 minutes, were administered at baseline, 3, 6, 12, and 18 months. The 6-month survey also included an assessment of the intervention program completed after intervention delivery. Short surveys, focused on PrEP uptake and adherence and lasting about 15 minutes, were administered at 9 and 15 months. All surveys were hosted on REDCap, a HIPAA-compliant platform.

Figure 2. Study schema and flow diagram. DBS: dried blood spot; LS4M: LifeSkills for Men; PrEP4T: PrEP for transgender men and transmasculine people.

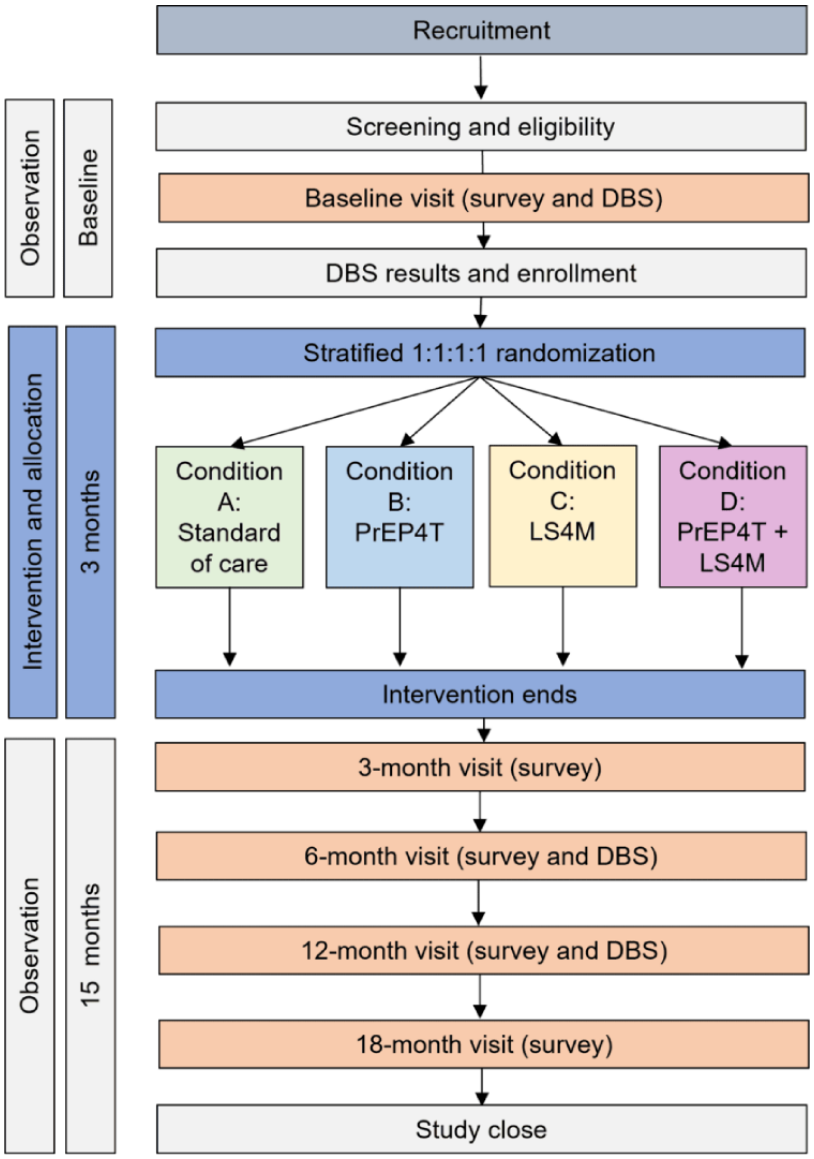

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Survey measures were guided by the Healthcare Accessibility [49], Gender Affirmation [7,51], and IMB [53] frameworks. Validated measures from transgender populations and prior research were selected to ensure comparability [59-62]. Baseline surveys included both lifetime and past 3-month recall, while follow-up surveys assessed past 3-month recall only. Domains assessed included demographics (age, race, ethnicity, gender identity, sexual orientation, education, income, housing, health insurance), gender affirmation (social, medical, legal), and unmet gender affirmation needs [59,61]. Measures included the PrEP cascade (awareness, indications, uptake, adherence, and persistence, including both daily oral and long-acting injectable formulations) [15,62]; barriers and facilitators to PrEP care [8,62]; PrEP knowledge, motivations, and preferences [8,15,63]; PrEP self-efficacy [64]; and PrEP empowerment [65]. Behavioral risk for HIV acquisition was assessed through sexual partners and practices using an adaptation of the Transmasculine Sexual Health Assessment [66], as well as injection drug use, needle-sharing behaviors, and perceived HIV risk [62]. Sexual partner communication and affirmation were measured using the Sexual Communication Self-Efficacy Scale [67] and the Gender Non-Affirmation from Sexual Partners Scale [14], respectively. Additional questions addressed HIV testing outside the study and sexually transmitted infection screening and diagnoses [61]. Mental health measures included psychological distress (Kessler-6) [68], posttraumatic stress disorder symptoms (Primary Care Posttraumatic Stress Disorder Screen) [69], resilience (Brief Resilience Scale) [70], and use of mental health services (eg, psychotherapy, support groups). Alcohol use disorder was assessed with the Alcohol Use Disorders Identification Test—Consumption [71], substance use disorder symptoms with the Drug Use Disorder Identification Test—Consumption [72], along with categories of drugs used. Discrimination was measured using the Everyday Discrimination Scale [73], which included 14 possible attributions (eg, age, gender identity, race, ethnicity). Internalized stigma [61] was also assessed. Additional measures included health care empowerment [74], health care access, utilization, and mistreatment in health care settings [60]. Social support was assessed with a short form of the Social Support Questionnaire [75], the Trans Community Connectedness subscale of the Gender Minority Stress and Resilience Measure [76], and metrics of social network size [61].

HIV Testing, Biomarker-Confirmed PrEP Outcomes, and Specimen Collection Protocol

The primary outcome was biomarker-confirmed PrEP uptake, assessed via emtricitabine triphosphate (FTC-TP) and tenofovir diphosphate (TFV-DP) concentrations in DBS. FTC-TP/TFV-DP assays were used for TFV-containing PrEP regimens approved for this population. PrEP uptake was defined as the detection of any quantifiable drug concentration. Secondary outcomes were PrEP adherence, indicated by TFV-DP concentrations >700 fmol/punch (corresponding to ≥4 doses per week) [54], and PrEP persistence, defined as 2 consecutive DBS samples showing PrEP use. Thresholds were based on the emtricitabine/tenofovir disoproxil fumarate (F/TDF) regimen and adjusted as appropriate for participants using other TFV-containing PrEP formulations (eg, emtricitabine/tenofovir alafenamide, F/TAF).

Participants self-collected DBS samples for HIV testing and PrEP level assessment at baseline, 6, and 12 months. Biospecimen processing was conducted by Molecular Testing Lab (MTL), a CAP-accredited and Clinical Laboratory Improvement Amendments–certified laboratory specializing in at-home specimen collection and processing. Participants provided a mailing address, which was validated through the US Postal Service Address Information application programming interface, and home specimen collection kits were shipped via the US Postal Service. Each kit included detailed visual instructions for specimen collection and a prepaid return mailer. Video instructions were available on the study website to guide participants through specimen self-collection. Each kit included a finger stick device, alcohol wipe, adhesive bandage, a Whatman 5-spot DBS card for HIV testing, and a Whatman 2-spot DBS card for PrEP adherence testing. Participants collected their specimens and returned the cards to the laboratory using the self-addressed, stamped envelope provided in the kit.

MTL conducted a fourth-generation HIV-1 antigen/antibody ELISA to detect HIV p24 antigen, HIV-1 (groups M and O) antibodies, and HIV-2 antibodies in human blood (sensitivity 100% and specificity 100%) (Molecular Testing Labs, unpublished data, December 2020). Biologic measures of PrEP uptake and cumulative adherence were performed only for participants who self-reported recent PrEP use. HIV test results were typically available within 14 days via the secure MTL portal, reviewed by study staff, and then shared with participants. Positive HIV results were communicated by designated clinical staff, who also contacted participants with positive DBS results to facilitate confirmatory testing. Participants with negative confirmatory results remained eligible for enrollment. PrEP levels were not reported to participants.

Study Conditions and Interventions

Overview

The 4 study conditions are displayed in Table 1.

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Table 1. Study conditions and sample size for the 2×2 factorial trial (n=300).

Study condition	Digital PrEP[a] locator and digital library	One-on-one individualized peer health navigation	Peer-delivered group-based behavioral intervention	Sample size, n
A: SOC[b]	Yes	No	No	75
B: SOC + PrEP4T[c]	Yes	Yes	No	75
C: SOC + LS4TM[d]	Yes	No	Yes	75
D: SOC + PrEP4T + LS4TM	Yes	Yes	Yes	75

[a]PrEP: preexposure prophylaxis.

[b]SOC: standard of care.

[c]PrEP4T: PrEP for transgender men and transmasculine people.

[d]LS4TM: LifeSkills for Transgender Men and Transmasculine People.

Condition A (SOC)

Participants received access to a digital PrEP locator and resource library. The SOC included linkage to the Centers for Disease Control and Prevention's (CDC's) HIV Prevention Services Locator, a national directory of HIV testing and PrEP services [8,15,77,78]. A digital library of HIV prevention, sexual health, and antistigma materials (in written and video formats) was also provided. Content was curated from multiple sources, including the CDC [79], Gate Trans Men & HIV Project, UCSF Center for Excellence in Trans Health, and the National LGBTQIA+ Health Education Center. Resources covered transgender community support (eg, support groups), sexual health (eg, contraception, DoxyPEP), HIV prevention (eg, PrEP financial assistance programs, directories of transgender-affirming PrEP providers), and other medical services (eg, gender-affirming care providers). Participants accessed the SOC resource guide on the TOGETHR website through a personal account log-in assigned after randomization. Study staff regularly updated the resources, which could be filtered by topic and location.

Condition B (SOC + PrEP4T)

This is an online 1-on-1 peer navigation. PrEP4T was an individualized, TMSM-specific intervention adapted from The Fenway Model [41], consisting of online 1-on-1 sessions between a peer navigator and a participant using a strengths-based case management manualized curriculum (Tables 2 and 3) [80,81]. Peer navigators, employed by Fenway Health and sharing transmasculine community membership with participants, were trained to provide linkages and support. Using an individualized approach, they worked to identify and address barriers, apply an asset-based frame to promote resiliencies, and pragmatically leverage these to improve biomedical HIV prevention outcomes. PrEP4T included 9 hours of content delivered across six 1.5-hour weekly sessions, with peer navigators drawing on techniques from established behavior change models (eg, Motivational Interviewing [82,83]; Transtheoretical Model [84-86]) to support PrEP-related decision-making.

Condition C (SOC + LS4TM)

This is an online peer-delivered small group–based behavioral intervention. LS4TM was a theory-based, manualized intervention designed to reduce HIV risk and address mental health–related effects of stigma for TMSM [20]. The program consisted of 9 hours of content delivered through six 2-hour small group sessions (up to 12 participants per group) held weekly for 6 weeks (Tables 2 and 3). While the total content duration was the same as PrEP4T, additional time was allotted for extended group discussions. Sessions were facilitated by staff and contractors employed by Fenway Health, all of whom shared transmasculine community membership with participants.

Condition D (SOC + PrEP4T + LS4TM)

This is an online peer-delivered combined intervention. Participants in this arm received both PrEP4*t* (1-on-1) and LS4TM (group-based) interventions in addition to SOC. Group D received a total of 21 hours of content, consisting of six 2-hour LS4TM sessions and six 1.5-hour PrEP4T sessions. These interventions were not delivered simultaneously within the same 6-week period.

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Table 2. PrEP4T[a] intervention sessions: session number, title, content, and conceptual framework guiding the intervention sessions.

Session number	Session title	Session content	Conceptual framework
1	Introduction, Background, and Goal Setting	• Build rapport with the participant • Assess the participant's background and sexual health history. • Set a realistic, sexual health–related goal for the program (eg, to start PrEP[b], to consistently communicate with partners about sexually transmitted infection testing). • Discuss factors that may impact risk for HIV among transgender men and transmasculine people.	IMB[c] and Gender Affirmation
2	HIV Transmission and Prevention	• Assess what participants know about HIV prevention and how they currently put that information into practice. • Introduce participants to the concept of harm reduction. • Fill in knowledge gaps and answer questions about HIV prevention. • Build on or reinforce participants' existing harm reduction strategies.	IMB and Healthcare Accessibility
3	Accessing PrEP and Preventive Health Care	• Discuss barriers to accessing PrEP and work with participants to identify solutions and options available to them. • Provide a brief overview of where and how participants can access postexposure prophylaxis. • Discuss preventive health care access, with an emphasis on primary care and sexually transmitted infection testing. • Address other preventive care topics, including vaccinations (human papillomavirus, hepatitis A and B), contraception, cervical and anal Papanicolaou testing, and gender-affirming care.	IMB and Gender Affirmation Healthcare Accessibility
4	Partners and Communication	• Define the key components of sexual health to help participants understand how supporting their physical, emotional, mental, and social well-being is part of sexual health. • Discuss healthy relationships, partner communication, and boundary setting; share communication strategies and practice communication skills with scripting or role playing. • Discuss self-care practices as a tool for managing stressors participants may encounter while communicating their sexual health needs to clinicians and partners, or while navigating the world as a "transgender man or transmasculine person" generally.	IMB and Gender Affirmation
5	Social Support	• Identify resources and support systems that can support HIV prevention and sexual health goals. • Use self-care practices and positive experiences of our transgender identities to build resilience.	IMB, Gender Affirmation, and Healthcare Accessibility
6	Program Summary and Wrap Up	• Summarize program framing and discuss how social stress and IMB concepts connect with the ongoing HIV prevention work the participant has been engaged in. • Identify long-term goals, as well as supports and resources participants can access after the conclusion of the program. • Solicit verbal feedback, in addition to completion of the session and program feedback forms.	IMB

[a]PrEP4T: PrEP for transgender men and transmasculine people.

[b]PrEP: preexposure prophylaxis.

[c]IMB: Information, Motivation, and Behavioral Skills.

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Table 3. LS4TM[a] (small group–based intervention) intervention sessions: session number, title, content, and conceptual framework guiding the intervention sessions.

Session number	Session title	Session content	Conceptual framework
1	Identity Recognition and Affirmation	• Provide an overview of the program. • Discuss identities and reflect on the diversity of ways participants occupy different identities. • Identify the misconceptions and stigmas that exist around the transgender men and transmasculine community, and how these have affected how people feel about their own identities. • Discuss factors that may impact risk for HIV among transgender men and transmasculine people.	Gender Affirmation
2	Let's Talk About Sex	• Inform participants about the basics of HIV transmission, barriers, and safer injection practices.	IMB[b]
3	PrEP[c] for Pleasure	• Inform participants about PrEP, postexposure prophylaxis, and contraception. • Encourage participants to consider whether PrEP may be right for them. • Identify barriers to PrEP use and uptake, and ways to navigate these.	IMB and Healthcare Accessibility
4	Barriers and Opportunities	• Learn about setting attainable goals and set a personal goal. • Identify roadblocks and structural barriers that impact individual and collective goals and constrain decision-making. • Discuss support and resources that can help to overcome roadblocks and barriers to achieving goals.	IMB and Healthcare Accessibility
5	Communication and Partner Negotiation	• Identify our rights and responsibilities in relationships. • Discuss a variety of partner communication topics relevant to transgender men and transmasculine people, including meeting partners, disclosing identities, educating partners about our transgender identities, and establishing consent and boundaries. • Brainstorm and practice healthy partner communication and negotiation skills.	IMB and Gender Affirmation
6	Tying It All TOGETHR[d]	• Highlight general sexual health concerns for transgender men and transmasculine people, including healthy sexuality and sexual pleasure. • Review the program, then revisit and revise goals moving forward. • Gather feedback from participants on the program, the curriculum, and how it was delivered.	IMB

[a]LS4TM: LifeSkills for Transgender Men and Transmasculine People.

[b]IMB: Information, Motivation, and Behavioral Skills.

[c]PrEP: preexposure prophylaxis.

[d]TOGETHR: Transmasculine One-on-One and Group Empowerment for Targeted HIV Reduction.

Incentives and Disbursement

All participants received US $30 for each comprehensive survey completed (baseline, 3, 6, 12, and 18 months) and US $10 for each short survey completed (9 and 15 months). Participants received US $20 for each self-collected HIV/PrEP test kit completed at baseline, 6, and 12 months. Participants in the PrEP4T and LS4TM arms received US $10 for each intervention session attended (6 sessions per intervention). The total compensation for participants was as follows: condition A (SOC; US $250); condition B (PrEP4T; US $310); condition C (LS4TM; US $310); and condition D (PrEP4T + LS4TM; US $370). Participants completing a qualitative interview at 9 months received an additional US $50.

Participants were compensated using ClinCard, a reloadable debit card that allowed study staff to add funds via an online portal as study activities were completed. ClinCards were mailed directly to participants' preferred addresses after study enrollment.

In the final 6 months of this 5-year study, PrEP4T and LS4TM were offered to all participants regardless of study group assignment to gather implementation data; no compensation was provided during this period.

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Qualitative Data Collection

A subset of 40 TMSM, stratified by PrEP use, was to be purposively selected for IDIs (10 per study arm) at their 9-month visit. Sampling aimed to ensure that 50% of participants were BIPOC or Latine. Additional participants could be recruited as needed to achieve data saturation. IDIs were conducted as part of the 9-month study assessment—the acute postintervention time point—to maximize recall. IDIs explored participant decision-making and experiences with PrEP and the interventions. Interviews were conducted via an online video-conferencing platform (Zoom) [87]. Each IDI lasted approximately 60-90 minutes, followed a semistructured interview guide (Multimedia Appendix 2), and was to be conducted by an interviewer trained in qualitative research and experienced in working with transgender communities.

Randomization and Blinding

Participants were randomized after their baseline HIV results were received and confirmed. Randomization was automated, computer-generated, and allocation sequences were concealed. Stratification was based on ethnoracial identity (BIPOC or Latine vs White) and MAP state LGBTQ equality policy tally ("high, medium, or fair" vs "low or negative" overall policy tally, as of October 2023; see Table S2 in Multimedia Appendix 1) [55]. The MAP state LGBTQ equality policy tally assesses over 50 LGBTQ-related laws and policies across US states (eg, nondiscrimination, health care access, religious exemptions, identity documents), providing a snapshot of the legal and policy climate for LGBTQ people [55]. Stratification was implemented to ensure balance across study arms and to facilitate subgroup analyses [88], given the disproportionate HIV burden among BIPOC or Latine versus White individuals [5] and the impact of repressive anti-LGBTQ policies on HIV prevention efforts [89]. Blinding was maintained at the statistician and investigator levels [90], but was not possible for participants or intervention staff.

Training and Quality Assurance/Quality Control

All research staff completed extensive training on the study objectives, protocol, and intervention procedures. Additional training covered transgender health, HIV, PrEP navigation, mental health crisis management, substance use, harm reduction, trauma-informed care, and addressing experiences of violence. Intervention staff training included observing and conducting mock intervention sessions. A mental health clinician, who was both a consultant and a member of the community, was available on-call to provide regular clinical supervision. Staff were also trained in human participant protections, confidentiality and privacy, informed consent, and Good Clinical Practice in accordance with federal regulations. Refresher training was conducted annually. Laboratory testing followed standardized protocols and procedures. Surveys were administered using computer-assisted self-interview methods to ensure consistency and reduce social desirability bias. Instruments were piloted to maximize comprehension, and logic checks and skip patterns were employed to minimize data entry errors. Data were reviewed regularly to ensure consistency and accuracy.

Intervention Fidelity

To ensure interventions were implemented as intended and core components were delivered according to protocol, intervention facilitators completed a checklist documenting their self-rated adherence to the intervention procedures. Session notes captured qualitative data on intervention implementation, including facilitator rapport, group dynamics, and other insights related to delivering manualized interventions. At the 6-month follow-up survey, participants reported on the intervention content they received and their experiences, including responses on the 8-item Client Satisfaction Questionnaire [91].

Statistical Analysis

Power

Factorial trials can be powered to detect either main effects or interaction effects, depending on the anticipated influence of interactions within the trial context [92]. This trial was powered to detect the main effects of the PrEP4T and LS4TM interventions. The trial was not powered to detect a PrEP4T × LS4TM interaction effect because (1) based on our conceptualization, the interventions were distinct in delivery (individualized vs group based) and content (peer navigation vs. community support and IMB strategies), and informed by preliminary studies and knowledge of the study population, we did not anticipate a combined interaction effect; and (2) any potential interaction was expected to be negligible, described in factorial trials as a minor "small quantitative interaction" [92-94]. Both PrEP4T and LS4TM were distinct, peer-delivered digital interventions that TMSM endorsed for HIV prevention in our prior research. We hypothesized that each strategy would independently increase PrEP uptake by at least 20% among TMSM, addressing the main-effects research question. Although we did not anticipate interaction effects, we hypothesized additive effects such that participants assigned to the PrEP4T + LS4TM condition would achieve the highest PrEP uptake rates. These superiority hypotheses were supported by evidence from a systematic review of peer-delivered interventions [47].

We estimated PrEP uptake rates in the SOC condition based on prior TMSM data [8,15] and conducted simulations using an SAS macro [95]. Simulations varied the number of participants per condition (n=40-120) and the magnitude of intervention effects over 18 months (20%-40%) for the PrEP4T and LS4TM conditions. Assuming 10% attrition, a total sample size of 300 (75 per condition) provided 80% power or greater to detect a 20% increase in PrEP uptake for each intervention versus SOC at a .05 significance level. We selected a 20% increase because smaller differences were not considered clinically meaningful for potential scale-up. To account for attrition, we planned to enroll 375 participants at baseline, anticipating approximately 20% loss to follow-up, resulting in 300 participants completing the study.

Data Analysis by Aim

We describe the planned analyses by aim.

Before analyses, data will be audited for quality and completeness. Descriptive statistics will be calculated, and variable distributions will be evaluated to ensure they meet the

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assumptions of planned analytic models, including detection of outliers. In this study, *t* tests and chi-square analyses will be used to assess group equivalence at baseline. Variables showing differences across the 4 groups will be considered for inclusion as covariates in the analyses. All analyses will be conducted using SAS (SAS Institute) or R (R Foundation) software, with statistical significance set at an α level of .05.

Aim 1 analyses will follow an intention-to-treat approach. Random-effects logistic regression will be used with PrEP uptake as the primary outcome. The model will include time (baseline, 6, 12, and 18 months), a categorical variable for study condition (PrEP4T, LS4TM, PrEP4T + LS4TM, with SOC as the reference), and the time × study condition interaction to test whether changes in PrEP uptake over time differ across the 3 intervention conditions compared with SOC. Baseline characteristics that differ across study conditions, as well as variables related to missingness, will be included as covariates if necessary. The primary parameter of interest is the time × study condition interaction term; a significant interaction would indicate that the rate of PrEP uptake over time differs between the intervention and SOC groups. Significant interactions will be graphed and interpreted. We hypothesize that PrEP uptake will be highest among participants randomized to condition D (PrEP4T + LS4TM). The same analytic approach will be applied to the secondary outcome of PrEP adherence. PrEP persistence will be assessed at months 12 and 18 using random-effects logistic regression, including time (12 and 18 months), study condition, and the time × study condition interaction. HIV and sexually transmitted infection incidence will be evaluated using logistic regression, with incidence between baseline and 18 months as the outcome and study condition as the predictor.

Aim 2 will use causal inference methods from epidemiology [96,97] to conduct mediation analyses and examine the mechanisms of action for the interventions. Mediation analyses will estimate the natural direct and indirect effects of proposed mediators—health care empowerment, TMSM community connectedness, and IMB constructs—on the relationship between intervention condition and PrEP uptake compared with SOC. Mediation models will be implemented using a series of random-effects logistic regression models, consistent with the approach described in aim 1.

For aims 1 and 2, patterns of missingness will be examined, and baseline responses will be compared between participants with and without missing data. Variables associated with missingness will be included in the analyses to yield valid inferences [98]. Modern missing data techniques [99] will be employed, with multiple imputation used to handle missing data, including participants lost to follow-up [100]. Sensitivity analyses will compare parameter estimates from completer-only analyses with those from multiple imputation to assess potential bias.

Aim 3 qualitative data from IDIs will be analyzed to explore PrEP decision-making and participant experiences with the interventions. An iterative analytic process will follow Crabtree and Miller's [101] 5-step approach: (1) describing, (2) organizing, (3) connecting, (4) corroborating, and (5) representing. Regular debriefing meetings with data collectors will identify preliminary findings and guide iterative data collection and analysis. An initial set of codes will be developed based on the study's conceptual frameworks of Healthcare Access, Gender Affirmation, and IMB constructs. Qualitative codes will be applied to transcripts and interview notes using qualitative analysis software by 2 independent analysts. New codes will be added as themes emerge. Summaries will be created for major themes and differences across subgroups. Descriptive quantitative survey data (eg, demographics, social and medical gender affirmation) may be used to contextualize qualitative findings. CAB members will provide ongoing input and help corroborate the qualitative results.

Data Analysis for Protocol Manuscript

Descriptive statistics were calculated for cumulative enrollment numbers, recruitment activities, screener and baseline survey completions, and sociodemographic characteristics of enrolled participants. To evaluate the effectiveness of different recruitment strategies, Granger causality tests [102] were conducted to forecast screening and baseline survey completions based on recruitment activity types; *F* tests on lagged values were used to determine whether recruitment strategies statistically predicted future screening and enrollment completions at 1- and 2-week intervals following recruitment activities, with significance set at an α level of .05. Trends over time were visualized graphically.

Ethical Considerations

The Fenway Institute at Fenway Health served as the single institutional review board of record (institutional review board protocol approval number 2023-12). Written informed consent was obtained from all participants before initiating any study procedures. Extensive safeguards were implemented to protect participant information and ensure privacy and confidentiality, including storing participant names and contact information separately in password-protected files from deidentified survey data and HIV testing results. The study was protected by a Certificate of Confidentiality from the NIH. Participants were compensated for their involvement (see the "Incentives and Disbursement" section). A Data Safety and Monitoring Board was established to oversee the trial's progress, review safety data, and provide recommendations on whether the trial should continue based on its assessment of safety and research performance. The board convened at least annually.

Results

Community Advisory Board Collaboration in Study Start-Up Activities

Overview

Monthly or bimonthly meetings of the virtual CAB ensured close collaboration and active participation with the research team. All study protocols and procedures were codeveloped and refined with CAB input to maximize acceptability for the study population. The CAB provided invaluable guidance throughout the study.

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Study Population Definitions

Discussions with the CAB focused on defining and operationalizing the study population of "TMSM" to maximize inclusivity while targeting those at risk for HIV. This included considerations of gender identity (transgender men, nonbinary people, transmasculine individuals, and other gender-diverse people), sexual orientation identity (gay, bisexual, queer, and other diverse identities), and behavioral HIV risk criteria (gender and anatomy of sexual partners).

Operationalization of Geographic Stratification

Geographic stratification for randomization was discussed, focusing on ensuring balance across EHE geographic hot spots and capturing the geo-sociopolitical climate, including policy contexts that could influence PrEP access and the lived experiences of TMSM. The decision to incorporate MAP legislative maps resulted from consultation with the CAB.

Refinement of Study Design

The initial study design included a 3-month run-in period intended to reduce study attrition and mitigate loss-to-follow-up among participants who might enroll solely to complete the baseline assessment and HIV testing for the incentive. However, the CAB recommended removing the run-in period, noting that the waiting period could discourage participation, create unnecessary anxiety while participants awaited the interventions, and erode trust with the community, given the historical mistrust in medical and research settings due to discrimination and mistreatment.

Branding and Detailed Recruitment Plan

A study logo, branding, website, and recruitment materials were developed to promote diverse participation across race, ethnicity, and geographic regions (see Tables S3 and S4 in Multimedia Appendix 1). Digital flyers and online advertisements were created in collaboration with a paid consultant who was a member of the community. A detailed, stepwise recruitment plan with targeted dates was established to implement different strategies, enabling the team to track screening and enrollment numbers and evaluate the effectiveness of each recruitment approach.

Recruitment and Enrollment

Recruitment and enrollment began on February 1, 2024. Cumulative recruitment and enrollment numbers from February 2024 to March 2025 are shown in Figure 3. Recruitment activity types are represented by colored dashed lines, while completed screeners and completed baseline surveys are shown as solid orange and blue lines, respectively.

Figure 3. Cumulative recruitment and enrollment numbers by recruitment activity type (dashed lines), completed screeners (orange line), and completed baseline surveys (blue line), February 2024-March 2025.

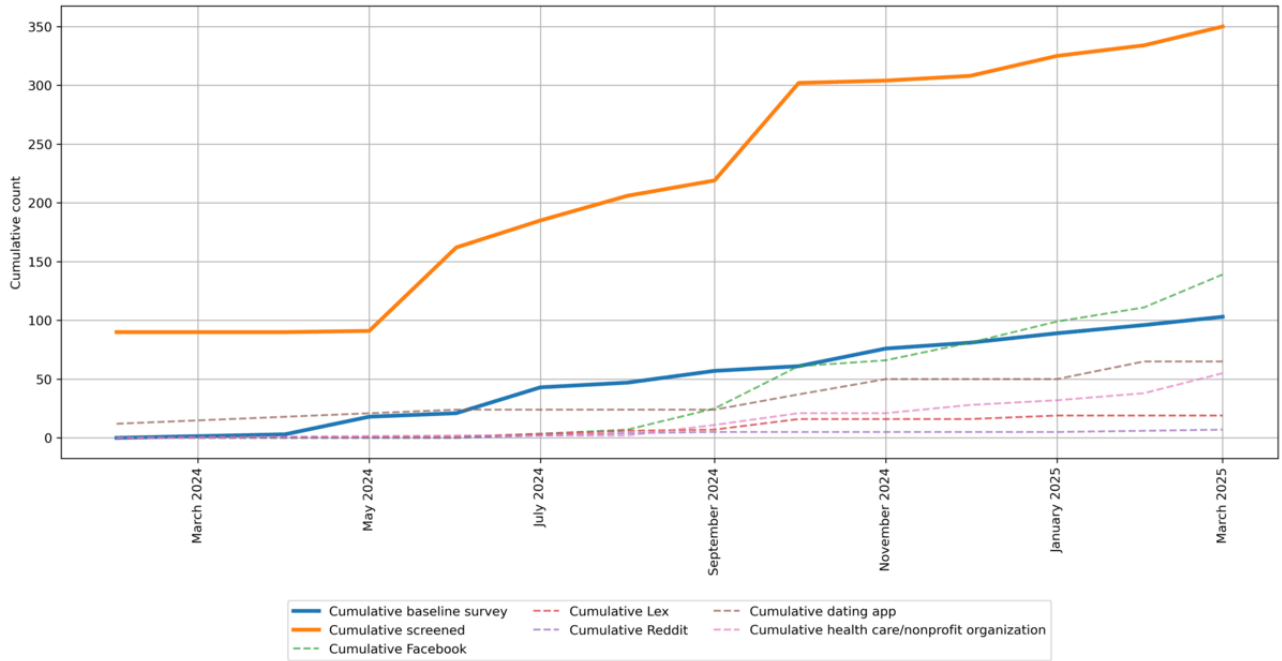

Granger causality tests were conducted to forecast screening and baseline enrollment survey completions based on recruitment activity types (Table 4). The most effective strategies for 2-week baseline survey completions were closed Facebook groups ($F_{2,23}$=6.52, P=.006) and Lex ($F_{2,23}$=4.63, P=.02). Lex also significantly predicted screening completions at both 1 week ($F_{1,26}$=10.41, P=.003) and 2 weeks ($F_{2,23}$=6.18, P=.007).

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Table 4. Granger causality test forecasting the effect of recruitment efforts[a] on screener and baseline enrollment survey completion with 1- and 2-week lag times, February 2024-March 2025.

Recruitment category	Survey type	Granger *F* test (*df*)[b] for 1-week lag	*P* value[b]	Granger *F* test (*df*) for 2-week lag	*P* value[b]
Dating app	Screened	0.40 (1, 26)	.53	0.28 (2, 23)	.76
Dating app	Baseline survey	1.70 (1, 26)	.20	1.06 (2, 23)	.36
Facebook	Screened	0.58 (1, 26)	.45	0.43 (2, 23)	.65
Facebook	Baseline survey	0.07 (1, 26)	.80	6.52 (2, 23)	*.006*
Health care/nonprofit organization	Screened	1.44 (1, 26)	.24	1.16 (2, 23)	.33
Health care/nonprofit organization	Baseline survey	2.64 (1, 26)	.12	2.05 (2, 23)	.15
Lex	Screened	10.41 (1, 26)	*.003*	6.18 (2, 23)	*.007*
Lex	Baseline survey	1.17 (1, 26)	.29	4.63 (2, 23)	*.02*
Reddit	Screened	0.43 (1, 26)	.52	0.21 (2, 23)	.81
Reddit	Baseline survey	0.48 (1, 26)	.49	2.69 (2, 23)	.09

[a]Recruitment effort represents the contacting of an organization or posting of social media or dating app advertisements.

[b]Italicized *P* values indicate statistical significance at =.05.

As of March 20, 2025, 103 TMSM were enrolled (Table 5). The median age was 26 (IQR 24-31) years. Among the 103 participants, 39 (37.9%) identified as BIPOC and 18 (17.5%) identified as Latine. The most frequently reported gender identities were “transgender men or trans man” (36/103, 35%); transmasculine (31/103, 30.1%); and nonbinary, genderqueer, or gender nonconforming (15/103, 14.6%). The majority of participants had socially, legally, and medically affirmed their gender identity. Participants reported diverse sexual orientation identities, with 67 (65%) identifying as queer, 38 (36.9%) as bisexual, 37 (35.9%) as gay, and 18 (17.5%) as pansexual (totals exceed 100% due to a “select all that apply” response format). The sample was highly educated: 69 (67%) had a 4-year college degree or higher, and 24 (23.3%) were full-time students. A small proportion (7/103, 6.8%) reported having no health insurance.

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Table 5. Sociodemographics of enrolled participants (N=103).

Sociodemographics	Values
Age in years, median (IQR)	26 (24-31)
Categorical age (years), n (%)	
18-24	36 (35.0)
25-29	33 (32.0)
30-39	28 (27.2)
40+	5 (4.9)
Missing	1 (1.0)
Gender identity (single option), n (%)	
Man	13 (12.6)
Male	1 (1.0)
Man of transgender experience	2 (1.9)
“Transgender man or trans man”	36 (35.0)
Female-to-male	3 (2.9)
Transmasculine	31 (30.1)
Nonbinary	7 (6.8)
Genderqueer	6 (5.8)
Gender nonconforming	2 (1.9)
Agender	2 (1.9)
Sexual orientation (select all-that-apply), n (%)	
Straight or heterosexual	1 (1.0)
Gay	37 (35.9)
Bisexual	38 (36.9)
Queer	67 (65.0)
Pansexual	18 (17.5)
Asexual	2 (1.9)
Demisexual	10 (9.7)
Questioning or unsure	2 (1.9)
I do not label my sexual orientation	9 (8.7)
Another sexual orientation	5 (4.9)
Racial identity, n (%)	
White	64 (62.1)
Asian	5 (4.9)
Black or African American	5 (4.9)
Latino/e or Hispanic	8 (7.8)
Multiracial	21 (20.4)
Latino/ethnicity, n (%)	
Yes	18 (17.5)
No	85 (82.5)
Health insurance type[a], n (%)	
No health insurance	7 (6.8)
Public health insurance	17 (16.5)
Private health insurance	79 (76.7)

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Sociodemographics	Values
US Census region, n (%)	
Midwest	21 (20.4)
Northeast	30 (29.1)
South	30 (29.1)
West	19 (18.4)
Ending the HIV Epidemic Area, not specified	3 (2.9)
Highest educational attainment, n (%)	
High school diploma or General Educational Development	6 (5.8)
Associate's degree/trade school certification	3 (2.9)
Some college or university	25 (24.3)
Bachelor's degree	43 (41.7)
Some graduate school	10 (9.7)
Graduate degree	16 (15.5)
Current student status, n (%)	
No	72 (69.9)
Yes, part time	7 (6.8)
Yes, full time	24 (23.3)
Outwardly express gender identity full time, n (%)	
Yes	91 (88.3)
No	12 (11.7)
Any legal gender affirmation[b], n (%)	
Yes	79 (76.7)
No	24 (23.3)
Gender-affirming hormone use (testosterone), n (%)	
Yes, within the last 3 months	94 (91.3)
Yes, but not in the last 3 months	8 (7.8)
Missing	1 (1.0)
Any history of gender-affirming surgery, n (%)	
Yes	75 (72.8)
No	28 (27.2)

[a]Participants could report more than 1 type of health insurance. If a participant reported both public and private insurance, they were coded as having private insurance. Additionally, participants who reported coverage through an employer, parents, partner, or college/university were also coded as having private insurance.

[b]Any legal gender affirmation was operationalized as having at least one identification document that listed the participant's affirmed name or gender.

Discussion

Anticipated Findings

This digital factorial trial aimed to compare the efficacy of online 1-on-1 peer navigation (PrEP4T), online peer-delivered small group–based behavioral intervention (LS4TM), a combination of 1-on-1 and group-based interventions (PrEP4T + LS4TM), and an SOC in increasing PrEP uptake and adherence among TMSM in HIV epidemic priority hot spots nationwide. It represents the first full-scale efficacy trial of peer-delivered interventions with TMSM. The study also sought to enhance understanding of the pathways linking health care access, gender affirmation needs, community connectedness, and PrEP uptake and adherence in TMSM, with potential applicability to other transgender populations. This study was part of a critical research pathway aimed at identifying strategies to prevent HIV acquisition in TMSM, a population historically underserved in HIV prevention. Key lessons include the essential role of community participation through the CAB and the effectiveness of social media and community networking platforms for recruiting and engaging this population. Findings from this study can inform future trials of HIV prevention

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packages in which peer-delivered interventions are a core component.

Limitations

Several limitations of this study should be noted. First, although the study was conducted nationwide, participants were drawn from EHE jurisdictions, limiting generalizability to the broader US population. Second, as a fully digital trial, participants were required to have access to a smartphone or computer with internet connectivity. This may have led to undercoverage of the source population and the unintentional exclusion of individuals with limited resources, restricted digital access, or intermittent technology access—groups who may also be at risk for HIV acquisition. Finally, this study cannot fully disentangle the effects of the intervention content from the additional time spent with peer navigators in the combined group. Nevertheless, the trial addresses a critical research gap by comparing individual versus group formats and evaluating the combined effects of both approaches within an at-risk and underresearched HIV epidemic population [47,48].

Conclusions

This novel study aimed to address an urgent gap in HIV prevention research for an underserved and priority population at risk in the HIV epidemic. Close collaboration and partnership with the TMSM community, along with extensive community engagement activities, were central to the study's success and provided valuable lessons for future HIV prevention research and practice with this population. Findings may also inform digital, peer-based HIV prevention strategies for other vulnerable populations affected by the HIV epidemic.

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Data Availability

Deidentified individual-level data and a corresponding data dictionary will be made available upon reasonable request, following approval of a proposal and execution of a data use agreement. External requests to access TOGETHR data undergo review and approval by the principal investigator, coinvestigators, and the Community Advisory Board. Further details and request forms can be obtained by contacting SLR via email.

Authors' Contributions

Conceptualization: SLR (lead), AIS, SWC, ALW, TP, MJM, MAM, AIM, KS, KHM
Data curation: SLR, AIM, KS, DRP (lead)
Formal analysis: SLR, DRP (lead)
Funding acquisition: SLR (lead), KHM
Investigation: SLR (lead), AIS, SWC, ALW, TP, MJM, MAM, AIM, KS, KHM
Methodology: SLR (lead), AIS, SWC, ALW, TP, MJM, MAM, AIM, KS, DRP, KHM
Project administration: SLR (SLR), AIM, KS
Resources: SLR (lead), KHM
Software: SLR, AIM, KS, DRP
Supervision: SLR (lead), AIM, KS, KHM
Validation: SLR, AIM, KS, DRP (lead)
Visualization: SLR, DRP (lead)
Writing – original draft: SLR
Writing – review & editing: SLR (lead), AIS, SWC, ALW, TP, MJM, MAM, AIM, KS, DRP, KHM

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Conflicts of Interest

AIS and TP have received consulting fees from ViiV Healthcare and Merck & Co. SWC has previously received consulting fees from ViiV Healthcare. TP and ALW receive funding from ViiV Healthcare to their institutions for unrelated observational research.

Multimedia Appendix 1
Additional analysis.
[DOCX File , 2028 KB - resprot_v14i1e76831_app1.docx]

Multimedia Appendix 2
Interview guide.
[DOCX File , 53 KB - resprot_v14i1e76831_app2.docx]

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Abbreviations

BIPOC: Black, Indigenous, and People of Color
CAB: Community Advisory Board
CDC: Centers for Disease Control and Prevention
cis: cisgender
DBS: dried blood spot
EHE: Ending the HIV Epidemic
F/TAF: emtricitabine/tenofovir alafenamide
F/TDF: emtricitabine/tenofovir disoproxil fumarate
FTC-TP: emtricitabine triphosphate
HIPAA: Health Insurance Portability and Accountability Act
IDI: in-depth interview
IMB: Information, Motivation, and Behavioral Skills
LGBTQ: lesbian, gay, bisexual, transgender, and queer
LS4M: LifeSkills for Men
LS4TM: LifeSkills for Transgender Men and Transmasculine People
MAP: Movement Advancement Project
MSM: men who have sex with men
MTL: Molecular Testing Lab
NIH: National Institutes of Health
PrEP: preexposure prophylaxis
PrEP4T: PrEP for transgender men and transmasculine people
REDCap: Research Electronic Data Capture
SOC: standard of care
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
TFV-DP: tenofovir diphosphate
TMSM: transgender men and transmasculine people who have sex with men
TOGETHR: Transmasculine One-on-One and Group Empowerment for Targeted HIV Reduction

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Protocol

Transforming Mental Health for Transgender and Gender-Diverse Young Adults Using Interventions to Drive Equity (TransHealthGUIDE): Protocol for a Digital Randomized Controlled Trial

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Abstract

Background: Transgender, nonbinary, and gender diverse (TGD) young adults face a disproportionately high mental health burden, including 2- to 4-fold increased risk of suicidality and depressive distress compared to their cisgender peers. Family and community support are protective factors that may mitigate these adverse outcomes, representing key targets for mental health interventions.

Objective: This randomized controlled trial (RCT) evaluates the effectiveness of TransHealthGUIDE, a novel digital, app-based education and support intervention aimed at reducing past 3-month suicidal ideation and past 2-week depressive distress among TGD young adults. Participants are randomized 1:1 to an immediate intervention arm or a 6-month deferred intervention arm (waitlist control).

Methods: From 2021 to 2024, a multidisciplinary team of academic and community partners conducted formative research and codeveloped a digital app containing 33 self-paced modules, communication, and interactive resources. The content is grounded in the Social Ecological Suicide Prevention Model and the Gender Minority Stress and Resilience Framework, designed to enhance family support and community connection for TGD young adults and their families. TGD young adults (ages 18-24 years) and their caregivers are prospectively enrolled and randomized in 10 US states (California, Connecticut, Illinois, Maryland, Massachusetts, New Jersey, New York, Oregon, Vermont, and Washington, DC). Participants complete self-reported surveys at baseline, 6 months, and 12 months, assessing sociodemographics, family support, community connection, suicidal ideation, depressive distress, and intervention acceptability. App usage and engagement are tracked via metadata. The target sample size is 500 TGD young adults, with 50% (n=250) identifying as people of color and 125 TGD young adult-caregiver dyads.

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Results: TGD young adult and caregiver communities, including our community advisory board (CAB), have guided all aspects of the project: study design (eg, waitlist control), survey development (eg, self-reported rather than clinician-administered suicidality measures and inclusion of social justice activism as a form of support), intervention content (eg, text, infographics, interviews with TGD people and caregivers, and simulations), and digital app safety features (eg, a quick-exit button for privacy). Recruitment and study screening began on January 21, 2025. As of May 2, 2025, a total of 149 individuals completed a study screener, with 132 (88.6%) of 149 found eligible. Enrollment visits began on April 23, 2025. As of May 2, 2025, five TGD young adults have been enrolled. Ongoing engagement with the CAB will inform iterative improvements throughout the trial.

Conclusions: Scalable, app-based interventions tailored to meet the needs of TGD young people hold promise for population-level mental health impact. This RCT—targeting suicidality and depressive distress via education and support for both TGD young adults and their caregivers—addresses a critical gap in mental health interventions for this underserved population.

Trial Registration: ClinicalTrials.gov NCT06177600; https://clinicaltrials.gov/study/NCT06177600

International Registered Report Identifier (IRRID): DERR1-10.2196/78619

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KEYWORDS

transgender; mental health; young adult; randomized controlled trial; mobile apps

Introduction

Background

Transgender, nonbinary, and gender diverse (TGD) individuals experience multiple forms of interpersonal and structural stigma and face intersectional gender-, race-, and socioeconomic-based minority stress at various levels [1-4], including within their own families [5-8], resulting in life-threatening health disparities. Suicide, one of the top 10 causes of death in the United States and the second leading cause of death among young adults [9,10], is 2-4 times more likely to affect TGD young adults compared to their cisgender peers [11,12]. Rates of depressive distress are similarly elevated among TGD young adults [11-13], as are other mental health conditions such as nonsuicidal self-injury, anxiety, and substance use [11-14].

Compounding these disparities, TGD individuals are more likely than the general population to identify as Black or Hispanic, and they frequently experience race-based health inequities [15]. For Black and Hispanic communities, which already face a disproportionately high burden of suicide compared to the general population [16], these intersecting vulnerabilities further increase risk for Black and Hispanic TGD individuals.

There is an urgent need for evidence-based interventions that address the unique mental health challenges faced by TGD young adults. Research shows that family functioning and support—including communication, satisfaction, and acceptance—are protective factors for TGD individuals' mental health [5,6,17,18]. Additionally, a strong sense of community connectedness is associated with improved mental health outcomes [19-21]. These findings emphasize the crucial role of supportive relational contexts—within families and communities—in promoting TGD individuals' well-being. Self-guided digital mental health interventions, including web- and smartphone-based apps, have demonstrated effectiveness in reducing depression and suicidality among young people [22,23]. They have also been shown to increase perceived social support [24] and are generally well-accepted by individuals experiencing mental health concerns [25]. However, to our knowledge, no evidence-based digital app intervention currently exists that is designed to reduce depression and suicidality among TGD young adults, while also engaging their caregivers or families in the process.

Study Objective and Aims

This prospective randomized controlled trial (RCT) evaluates the effectiveness of an educational and supportive app-based digital intervention in reducing suicidal ideation and depressive distress among TGD young adults across 10 US states. TransHealthGUIDE (Transforming Mental Health for Transgender and Gender-Diverse Young Adults Using Interventions to Drive Equity) is a co-designed digital app developed in partnership with TGD communities. The intervention engages, empowers, and fosters connections between TGD young adults and their families.

The primary aim of this study is to test the effectiveness of a digital app-based intervention in reducing past 3-month suicidal ideation and past 2-week depressive distress among TGD young adults and their caregivers, by comparing participants randomized 1:1 to an immediate intervention arm versus a 6-month deferred intervention arm (waitlist control).

The secondary aims are (1) to assess the impact of the intervention on family functioning (past 3-month family communication, satisfaction, and acceptance) and on community belonging and connection for TGD young adults and their caregivers, and (2) to examine the dyadic relationship dynamics between TGD young adults and their caregivers participating in the intervention.

Methods

Study Design

This is a prospective, digital RCT in which TGD young adults and their caregivers are randomized 1:1 to either an immediate intervention arm (a 6-month active intervention period followed by 6 months of observation) or a deferred intervention arm (a 6-month waitlist period followed by active intervention). Each participant is enrolled in the trial for a total of 12 months (see Figure 1). The total study duration is approximately 2 years.

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Figure 1. TransHealthGUIDE (Transforming Mental Health for Transgender and Gender-Diverse Young Adults Using Interventions to Drive Equity) study schema. Target sample size is 500 TGD young adults, with one-quarter (125 participants) in a dyad with a caregiver (target sample size of 125 caregivers). TGD: transgender, nonbinary, and gender diverse.

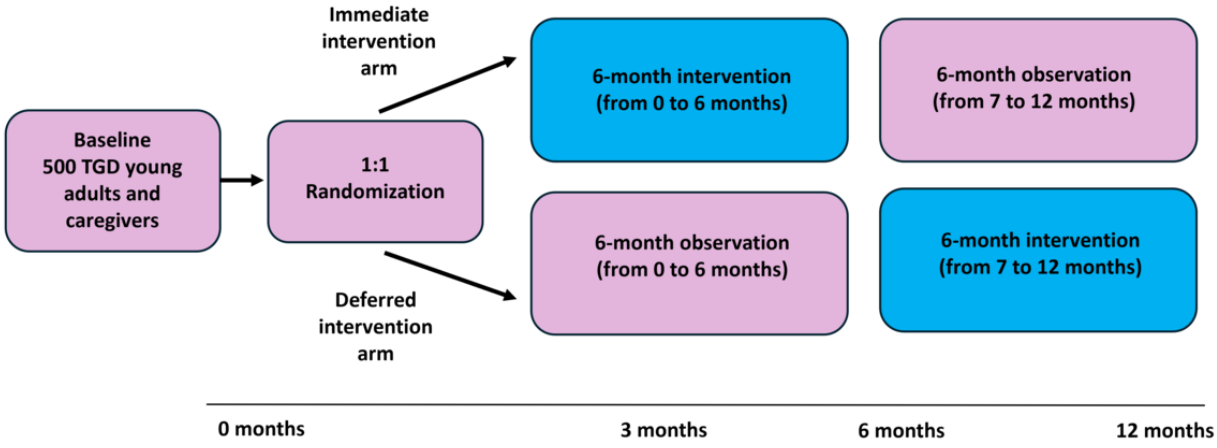

Participants in the immediate intervention arm receive full access to the TransHealthGUIDE digital app for the first 6 months. This is followed by a 6-month observation period during which they retain access to the app but receive no new intervention content or engagement prompts. Participants in the deferred intervention arm receive limited access to the app for the first 6 months, consisting primarily of curated local, regional, and national support resources. At the 6-month mark, participants in the deferred arm are granted full access to the digital app for the remainder of their participation.

Survey assessments are administered at baseline, 6 months, and 12 months to evaluate primary outcomes (past 3-month suicidal ideation and past 2-week depressive distress) as well as secondary measures.

Project History and Multidisciplinary Team

In 2021, the National Institutes of Health (NIH) Common Fund launched the "Transformative Research to Address Health Disparities and Advance Health Equity" initiative. The goal of this initiative was to support innovative, translational research projects aimed at preventing, reducing, or eliminating health disparities and advancing health equity [26]. This grant mechanism specifically supported groundbreaking interventions targeting one or more NIH-designated populations that experience health disparities in the United States. Notably, pilot data were not required; instead, emphasis was placed on the development and implementation of novel, creative interventions.

Our multidisciplinary team chose to focus on the persistent mental health disparities affecting TGD young adults, particularly elevated rates of suicidal ideation and depressive distress. To address this urgent need, we conducted extensive formative research to develop a digital, app-based intervention designed to reduce these disparities by increasing family support and community connection.

The intervention was developed through a community-engaged process and reflects the combined expertise of a multidisciplinary team with backgrounds in TGD health, educational and curriculum design, sociobehavioral interventions, digital health development, clinical trials, psychiatry and mental health, young adult developmental psychology, family systems, and TGD lived experience. TGD young adults and caregivers were actively involved throughout the development process, ensuring that the intervention was relevant, affirming, and grounded in real-world experiences.

Conceptual Framework

Digital interventions grounded in evidence-informed conceptual frameworks are more likely to be effective than those lacking theoretical design [27]. TransHealthGUIDE is informed by several evidence-based models of suicide prevention and mental health promotion tailored to meet the needs of TGD young adults.

First, the intervention aligns with the Social Ecological Suicide Prevention Model [28], addressing the multiple levels of influence—individual, interpersonal, and structural—that shape TGD individuals' experiences. Intervention content focuses on helping users navigate and cope with challenges across various contexts, including families, schools, and health care settings, while targeting key drivers of suicidality such as bullying, misgendering, and systemic exclusion.

Second, TransHealthGUIDE draws from the Gender Minority Stress and Resilience Framework [29,30], which emphasizes the impact of societal stigma, discrimination, and oppression on TGD individuals' mental health [31]. The intervention also emphasizes resilience, using a strengths-based approach to bolster self-efficacy and support-seeking behaviors [32].

Finally, the intervention incorporates an intersectional lens by explicitly addressing intersectionality [33] and centering the experiences of individuals with multiply marginalized and intersecting identities, including those related to race, ethnicity, disability, body size, gender identity, sexual orientation, neurodivergence, and religion. This intersectional framework ensures that the content remains relevant and affirming across a broad spectrum of identities and lived experiences.

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Community Consultations and CAB

In 2022, our team conducted extensive community consultations, engaging with more than 20 key stakeholders to better understand the mental health and support needs of TGD young adults and their families, identify potential intervention strategies, and establish partnerships to support future recruitment and implementation efforts. These consultations included national organizations such as the World Professional Association for Transgender Health (WPATH) and TransLine, as well as local organizations serving TGD young adults and their families within communities across the United States.

In 2023, we formally established a community advisory board (CAB) consisting of 16 members: 7 TGD young adult community members and 9 caregivers and health care providers, including mental health professionals. The CAB is geographically diverse, representing the Northeast, Mid-Atlantic, Midwest, South, and West regions, and 7 (43.8%) of 16 are people of color.

Our CAB has played a central role in guiding the project. Their input has shaped intervention content, informed recruitment and retention strategies, and contributed to the critical decisions regarding implementation of the RCT. Their ongoing engagement ensures the intervention remains grounded in lived experience and community priorities.

Formative Research

We conducted extensive mixed methods formative research to inform the study design and procedures, intervention content, digital app features and aesthetics, recruitment and retention strategies, and dissemination plans to ensure high acceptability and relevance to our target population.

Between April and August 2022, we conducted 33 qualitative interviews with a purposive sample of 13 medical and mental health care providers, 14 caregivers, and 6 TGD young adults, recruited through community partners and the team's professional and personal networks. These interviews highlighted a significant unmet need for support and education among both TGD young adults and caregivers, including a desire for accessible, accurate, expert-informed information [34].

In August 2022, we also conducted a one-time survey with 104 young adults, of whom 48 (46.2%) were people of color, recruited via the Prolific.com platform. Eligible participants were US residents aged 18-25 years who identified as TGD. The survey included both closed- and open-ended questions to explore how TGD young adults seek gender- and health-related information online. Findings revealed a high prevalence of depressive distress, with 44 (42.3%) of 104 individuals meeting criteria for clinically elevated symptoms. Low family support was a strong correlate of depressive distress, underscoring the need for interventions aimed at strengthening relationships between TGD young adults and their caregivers [18]. Participants also expressed a strong preference for receiving information through personal stories and lived experiences of other TGD people and families—an insight that directly shaped the narrative and multimedia components of our intervention [35].

Overall, our formative research revealed substantial educational and emotional support needs among TGD young adults and families, particularly regarding navigation of familial and relational dynamics and the search for affirming community connections.

Intervention Development and Content

The TransHealthGUIDE digital interactive app was developed between 2023 and 2024, drawing on insights from formative research, community consultations, ongoing CAB feedback, and the multidisciplinary team's expertise in TGD research and clinical care. The team brought together diverse areas of expertise, including provider education, digital health innovation, and computational informatics in mental health (RX); TGD research methods, clinical trials, and community-based sociobehavioral interventions (SLK-W, SLR, and SWC); suicide prevention, psychiatric care, and mental health intervention development (ASK); TGD young adult development, family systems theory, and developmental psychology (SLK-W); and instructional and curriculum design tailored to TGD populations (SWC). App design and development were carried out in partnership with Vessel Partners, a company that specializes in creating and testing app-based interventions for sociobehavioral research, with experience supporting research-grade digital tools.

The app's educational content was developed specifically for this intervention and includes text-based modules offering psychoeducational content, video narratives featuring real-life stories from TGD young adults and caregivers, and simulation-based (scripted and acted) videos, which used professional actors to portray challenging conversations between TGD young adults and caregivers, modeling best practices for communication and support.

The app includes 33 self-paced educational modules focused on reducing depressive symptoms and suicidal ideation among TGD young adults, with some modules specifically designed for caregivers. Module summaries, including titles, intended audience, and learning objectives, are provided in Table 1. Participants can access and complete modules on smartphones, tablets, or computers, in any order, and may skip or repeat modules. Each module lists an estimated completion time—most under 15 minutes—to support flexible, manageable engagement.

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Table 1. Overview of the TransHealthGUIDE[a] intervention modules, target audience, and learning objectives.

Module number	Module titles	Audience	Learning objectives (by the end of the lesson module...)
1	Introduction	TGD[b] young adults and caregivers	TGD young adults and caregivers will be welcomed and will recognize the various functionalities and features of the app.
2	Introduction: Caregivers	Caregivers	Caregivers will be able to name and recognize similarities and differences between their experiences and the caregivers highlighted in the video. Caregivers will gain insights from the video about tools they can use in their own parenting or caregiving journey.
3	Terms & Definitions	TGD young adults and caregivers	TGD young adults and caregivers will be able to define foundational sexual orientation, gender identity, and expression (SOGIE) terminology and concepts.
4	Gender Identity	TGD young adults and caregivers	TGD young adults and caregivers will be able to recognize the complexities of gender both in the present and historically; identify and name gender identities under the transgender, nonbinary, and gender expansive identity umbrellas; and foster open and empathetic communication between young people and their caregivers about diverse gender identities.
5	Names	TGD young adults and caregivers	TGD young adults will gain skills in choosing a name (if they have not already) and how to discuss name changes with their caregiver. TGD young adults and caregivers will gain the skills to locate and engage with systems and legal processes to affirm and legalize names for TGD young adults.
6	Pronouns	TGD young adults	TGD young adults will gain the skills to effectively communicate their pronouns and leverage support in settings such as home or school.
7	Gender Expression	TGD young adults and caregivers	TGD young adults and caregivers will recognize the complexities of gender expression and gain skills to respectfully engage with people outside of gender assumptions based on appearance. TGD young adults will name and recognize similarities and differences between their experiences of and desires for gender expression and those in the videos.
8	Imagining My Future	TGD young adults	TGD young adults will build a foundation of skills to foster self-compassion and care when facing challenging situations. TGD young adults will develop goal-setting skills and write gender- and relationship-related goals for the next 3 months.
9	Goals: Self & Youth	Caregivers	Caregivers will build a foundation of skills to foster self-compassion and generate a circle of support for themselves and their young person. They will define and write goals for their own growth and around engaging positively and affirmatively with their young person.
10	Dysphoria	TGD young adults	TGD young adults will gain skills to recognize and address dysphoria, as well as access support.
11	What to Expect/Transitions	TGD young adults	TGD young adults will be able to relate to the experiences shared by TGD individuals in various stages, identify key elements of psychological and social transition, and gain insights into the personal psychological benefits of the transition process.
12	Intersectionality: Identities, Communities, and Me	TGD young adults and caregivers	TGD young adults and caregivers will be able to describe intersectionality and how different identities have different levels of marginalization in society. TGD young adults and caregivers will be able to describe how stigma and discrimination impact TGD people, especially those with multiple, marginalized identities.
13	Communicating with Caregivers	TGD young adults	TGD young people will gain skills to communicate effectively, establish boundaries, and improve their relationships with their caregivers.
14	Communicating with Your TGD Loved One	Caregivers	Caregivers will gain skills to facilitate improved communication with their young person, including how to handle mistakes, begin again, and build healthy relationships with their young person.
15	Struggling to Accept	Caregivers	Caregivers will gain skills to acknowledge and appropriately process their own emotions, such as grief, confusion, and anger, without burdening their young person. They will also gain insights on how to provide support to their young person, even when struggling to accept or understand their gender identity.
16	Misgendering	TGD young adults	TGD young adults will acquire coping skills and stress management techniques to enhance their mental health and well-being when facing misgendering and other forms of transphobia.
17	Coming Out	TGD young adults	TGD young adults will develop a plan for coming out, prioritizing their safety and personal desire for privacy.
18	Navigating Coming Out	Caregivers	Caregivers will gain consent-based tools to effectively communicate about their young person's gender with close friends and extended family members, while respecting their young person's consent.

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Module number	Module titles	Audience	Learning objectives (by the end of the lesson module...)
19	Setting Health Boundaries	TGD young adults	TGD young adults will assess and acquire healthy relationship tools and boundary skills to ensure their safety and emotional well-being while potentially being treated differently.
20	Privacy & Confidentiality	Caregivers	Caregivers will be able to summarize the complexities of confidentiality and consent-based parenting that centers on their TGD young adult.
21	Healthy Peer Relationships	TGD young adults	TGD young adults will learn foundational tools for building healthy and safe relationships, including intimate, platonic, sexual, and romantic relationships. They will also gain the skills to assess their needs and activate a safety plan, including local and national resources for preventing and addressing potential harm or violence.
22	The Talk: Trans Edition	Caregivers	Caregivers will gain skills to effectively discuss sexual health, sexual orientation, and gender identity with their TGD young adult. Caregivers will be able to locate local and national resources to facilitate accurate and safe conversations about dating and sexual health topics with their young person.
23	Managing Self-Harm	TGD young adults	TGD young adults will be able to identify self-harm behaviors and triggers; will develop skills to redirect and seek help from appropriate avenues and resources; and will be able to recognize suicidal ideation and behaviors in themselves and others, when and how to seek help, and learn about appropriate resources to respond to suicidality.
24	Finding Support	Caregivers	Caregivers will build a foundation of skills to foster self-compassion and generate a circle of support for themselves and their young person. They will also gain tools related to self-harm prevention and treatment for their young person.
25	Mental Health Treatment	TGD young adults and caregivers	TGD young adults and their caregivers will recognize ways to find and access mental health care providers who meet their unique needs.
26	Talking with Providers	TGD young adults and caregivers	TGD young adults and their caregivers will learn how to interact with health care providers when seeking regular care.
27	Insurance 101	TGD young adults and caregivers	TGD young adults and their caregivers will learn how to research and navigate insurance systems.
28	Social Transition in Educational Institutions	TGD young adults and caregivers	TGD young adults and caregivers will identify best practices for creating supportive environments at educational institutions and developing gender transition plans.
29	Addressing Bullying & Discrimination	TGD young adults and caregivers	TDG young adults and their caregivers will be prepared to address bullying and harassment in educational institutions and other environments, including cyberbullying, through a law and policy lens.
30	Gender at Work	TGD young adults	TGD young adults will locate resources grounded in law & policy to build their skills in self-advocacy and protection of their rights at work.
31	Addressing Homelessness	Caregivers	Caregivers will identify and name resources available to TGD young adults who face family rejection and will gain the skills to name protective parenting practices to prevent these outcomes.
32	Homelessness	TGD young adults	TGD young adults will identify and name resources available to them when facing family rejection and will gain the skills to create a safety plan with affirming, trustworthy adults in their lives.
33	Looking Ahead	TGD young adults and caregivers	TGD young adults and their caregivers will reflect on their experiences within the app and what they have learned, and set new goals for their continuing journey.

[a]TransHealthGUIDE: Transforming Mental Health for Transgender and Gender-Diverse Young Adults Using Interventions to Drive Equity.

[b]TGD: transgender, nonbinary, and gender diverse.

Additional features of the app include: a goal-setting tool to promote self-efficacy and track progress, a community resources hub offering curated local and national supports, and moderated Q&A forums with TGD community members and expert contributors across various areas of TGD health.

Study Population and Inclusion and Exclusion Criteria

Two participant groups are being enrolled in the study: (1) TGD young adults ages 18-24 years and (2) adult caregivers of TGD young adults who are enrolled in the study. Inclusion and exclusion criteria for both groups are detailed in Table 2.

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Table 2. Inclusion and exclusion criteria for TGD[a] young adults and caregivers in TransHealthGUIDE[b].

Participant group	Inclusion criteria	Exclusion criteria
TGD young adults		
1	Ages between 18 and 24 years (inclusive)	Ages under 18 years or over 24 years
2	A person of TGD experience (transgender, nonbinary, gender diverse, or not cisgender)	Not a person of TGD experience (ie, cisgender)
3	Resides in one of the following locations: California, Connecticut, Illinois, Maryland, Massachusetts, New Jersey, New York, Oregon, Vermont, and Washington, DC	Does not reside in the 10 specified locations
4	Able to read, write, and communicate in English	Not able to read, write, or communicate in English
5	Has access to a smartphone/device or computer with internet connectivity	Does not have access to a smartphone/device or computer with internet connectivity
6	Provides informed consent to participate	Does not provide informed consent to participate
Caregivers		
1	Ages 18 years or older	Ages under 18 years
2	A parent or legal guardian of the TGD young adult during their minority	Not a parent or legal guardian of the TGD young adult
3	Has a TGD young adult aged 18-24 years enrolled in the study	Does not have a TGD young adult in the study
4	Resides in one of the following locations: California, Connecticut, Illinois, Maryland, Massachusetts, New Jersey, New York, Oregon, Vermont, and Washington, DC	Does not reside in the 10 specified locations
5	Able to read, write, and communicate in English	Not able to read, write, or communicate in English
6	Has access to a smartphone/device or computer with internet connectivity	Does not have access to a smartphone/device or computer with internet connectivity
7	Provides informed consent to participate	Does not provide informed consent to participate

[a]TGD: transgender, nonbinary, and gender diverse.

[b]TransHealthGUIDE: Transforming Mental Health for Transgender and Gender-Diverse Young Adults Using Interventions to Drive Equity.

We aim to recruit 500 participants overall, including 375 TGD young adult participants across 10 US states (listed alphabetically): California, Connecticut, Illinois, Maryland, Massachusetts, New Jersey, New York, Oregon, Vermont, and Washington, DC. Our recruitment goals include at least 50% (250 of 500 participants) identifying as people of color and at least 125 caregivers, resulting in 125 TGD young adult-caregiver pairs.

To maintain the dyadic framework of the intervention, caregivers may only participate if their corresponding TGD young adult is already enrolled. Each TGD young adult is asked to identify a primary caregiver to invite into the study, but young adults can participate in the study without a caregiver.

Caregivers must reside in one of the 10 study states due to legislative and logistical considerations. These locations were selected in consultation with experts that helped identify supportive jurisdictions for TGD young adults, ensuring a foundation of safety and feasibility for the intervention.

For TGD young adults attending college, eligibility is based on their current state of residence during the study period, not their permanent home address. TGD young adults and their caregivers can reside in different states, as long as each lives in one of the 10 eligible states.

Recruitment

Participants are recruited through a combination of community-based and digital strategies, including caregiver and young adult support groups, TGD-serving organizations, community events, and targeted listservs and newsletters. The study team also leverages personal and professional networks to connect with LGBTQIA+ (lesbian, gay, bisexual, transgender, queer, questioning, intersex, asexual) organizations and individuals.

A key goal of the study is to ensure that at least 50% of enrolled participants are people of color. To support this, we implemented the following targeted recruitment strategies. (1) Community partnerships and outreach: We collaborate with community-based organizations, clinics, and advocacy groups that specifically serve communities of color to raise awareness about the study and encourage participation. (2) Culturally responsive research team: Our team includes trained researchers who have skillsets and experience working with study participants from diverse racial, ethnic, and lived experience backgrounds to help build trust, rapport, and cultural humility in our engagement with communities of from various cultural backgrounds. (3) Diverse research team: Our team includes researchers from diverse racial, ethnic, and lived experience backgrounds to help build trust, rapport, and cultural humility in our engagement with communities of color. (4) Ongoing

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monitoring and adaptation: We continuously monitor participant demographics and adapt recruitment strategies as needed to meet our diversity and inclusion benchmarks.

Study Procedures

Potential participants are screened for eligibility online using a study-specific REDCap (Research Electronic Data Capture) screener. Those who appear preliminarily eligible are directed to a contact information form where they provide their name, email, phone number, and preferred method of contact. Study staff then follow up using the contact information provided to schedule an enrollment visit to confirm study eligibility and obtain informed consent. For individuals screened by phone, staff enter the contact information directly into REDCap during the call and schedule the enrollment visit in real time.

All enrollment visits are conducted remotely via a HIPAA (Health Insurance Portability and Accountability Act)-compliant platform, such as Zoom. Participants who meet eligibility criteria are scheduled for a virtual enrollment session during which study staff obtain informed consent using electronic consent procedures. Caregivers are only eligible to enroll if their corresponding TGD young adult has already been enrolled. During the enrollment process, the TGD young adult identifies one primary caregiver to be invited. This ensures that caregiver participation is directly linked by study staff to the corresponding TGD young adult enrollment, preserving the integrity of the dyadic intervention model.

Prior to the start of any study procedures, research staff conduct a comprehensive informed consent process. Participants are informed about the expected length of the session and advised to join from a quiet, private space with a reliable internet or phone connection. Participants are provided a copy of the informed consent form in advance or at the start of the session. A link to the informed consent form in REDCap is sent, and the document is reviewed together during the Zoom call.

Throughout the consent process, staff pause at the end of each major section to summarize key points and check for understanding. Participants are encouraged to ask questions, and staff conduct a verbal comprehension assessment by asking participants to explain back the information they have heard. These checks are repeated after key sections—particularly those on study procedures and risks—and again before signing the form. Any unclear points are rephrased to ensure clarity. Once all questions have been addressed, participants complete the electronic consent form by entering their initials and signature in REDCap. A copy of the signed document is then provided to the participant for their records.

Intervention Allocation and Randomization

Randomization occurs following completion of the enrollment visit. Participants are randomized in a 1:1 ratio to either the immediate intervention arm or the deferred arm (6-month waitlist control). TGD young adults and their caregivers who enroll as dyads are randomized together as a unit to maintain the dyadic structure of the intervention.

Randomization is conducted using an automated, computer-generated sequence within REDCap. The allocation sequence is concealed, and blinding is maintained at the analyst and investigator levels to reduce bias. Once randomization is complete, study staff notify participants of their group assignment using the participant's preferred method of contact (eg, email or phone).

Regardless of assignment, all participants receive a curated list of national and state mental health support resources.

Intervention Delivery

TGD young adults and caregivers assigned to the immediate intervention arm receive full access to the digital app. After informed consent is obtained, participants are emailed a personalized link to download the app and complete registration. Only enrolled participants are able to create an account and access the app content. Participants randomized to the deferred arm also receive immediate access to the app; however, they are initially limited to viewing the Community Resources tab, which includes local, regional, and national resources. All other features are automatically unlocked after 6 months.

The intervention supports dyadic participation, with approximately one-third of TGD young adults expected to participate alongside a caregiver. With mutual consent, TGD young adults and caregivers may choose to link their accounts. All linking is reviewed and performed manually by study staff to ensure participant privacy and data integrity.

For dyads, accounts are manually linked by research staff once both participants have downloaded the app and completed registration. If linking is requested after enrollment, the app includes a feature that allows both participants to independently provide consent for linking. Once consent is confirmed, the study team is notified, and accounts are linked manually. Linking allows for shared activities and progress tracking but is entirely optional. Participants may request to unlink their accounts at any time, and study staff will promptly honor the request. This option, along with the voluntary nature of linking, is clearly communicated during the consent process and outlined in study documentation.

Measures

Self-Reported Surveys

Online self-reported survey assessments are administered at baseline, 6 months, and 12 months (see Figure 1). Both TGD young adults and caregivers complete overlapping and complementary measures. Whenever possible, validated instruments—particularly those previously used with TGD and caregiver populations—were selected to ensure methodological rigor and comparability with existing research. All measures were pilot tested prior to implementation.

A computer-assisted self-interview is used to ensure consistency in data capture (eg, skip patterns and logic checks) and to reduce social desirability bias. Surveys are designed to take approximately 30 minutes to complete.

Survey domains include sociodemographic characteristics (age, race, ethnicity, gender identity, sexual orientation, socioeconomic status, religious affiliation, family composition, urbanicity, and nativity) [36]. Health care access and

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engagement includes general physical and mental health in the past month [37], health insurance coverage, access to primary care, unmet medical and mental health needs, and use of mental health services (inpatient, outpatient, medications, and support groups). Gender transition and journey includes age of first TGD recognition, types of gender affirmation (social, medical, legal), and family or peer disclosure and support. Family relationships are assessed via validated measures including family communication and satisfaction (Family Adaptability and Cohesion Scale III and IV) [38,39], family acceptance, and family empowerment [40]. Community belonging is measured using the Community Connectedness subscale of the Gender Minority Stress and Resilience Measure [29]. Mental health outcomes include suicidal ideation and attempts (lifetime and past 3 months) using the Columbia Suicide Severity Rating Scale (C-SSRS) [41], nonsuicidal self-injury using the SOARS (Suicidal ideation; Onset, frequency, and methods; Aftercare; Reasons; Stage of change screening and assessment of nonsuicidal self-injury) [42], depressive symptoms using the Patient Health Questionnaire-9 [43], anxiety symptoms using the Generalized Anxiety Disorder-2 [44], gender euphoria (3 items developed from qualitative research) [45], gender dysphoria via the Gender Preoccupation and Stability Questionnaire-2 [46], and substance use risk via the CRAFFT (Car, Relax, Alone, Forget, Friends, Trouble) screener [47]. Psychosocial context includes validated assessments of perceived stress [48], resilience [49], perceived social support [50], social safety [51], and perceived impact of legislative climate [52]. Social context and behavior includes bullying and social media use via questions adapted from the Youth Risk Behavior Surveillance System [53] and civic engagement using the Social Justice Scale [54]. Intervention engagement includes app engagement, acceptability [55,56], and the Net Promoter Score [57]. Caregivers complete additional assessments including the Transgender Knowledge, Attitudes, and Beliefs Scale [58]. TGD young adult-caregiver dyads complete 6 items from the Child-Parent Relationship Scale to assess the perceived impact of joint participation [59].

Digital App Usage and Metadata

Digital app usage and metadata information are collected and linked to participants' survey responses to assess engagement and evaluate the intervention's impact over time. This linkage enables a nuanced analysis of trends across the study period. The following types of app engagement data are collected: module engagement (number of educational modules completed), interactive features (frequency of engagement with interactive features such as posting, reacting or liking, and responding to posts), time spent (total time spent in the app and within specific modules), dyadic participation (dyad status, frequency of interactions between linked TGD young adult-caregiver pairs), goal-setting feature (usage and frequency of interaction with the goal setting component), log-in frequency (number of log-ins to the app), and technical issues (reports of technical difficulties or user-reported problems.) These metrics support the interpretation of intervention exposure and user experience, and inform potential improvements to future iterations of the app.

Remuneration

Participants receive a US $25 e-gift card after completing each survey at baseline, 3 months, 6 months, and 12 months, along with a US $25 bonus for completing all surveys, for a total of US $125. Payments are sent via an e-gift card to the participant's email after each survey is completed.

An e-gift card was chosen as the compensation method due to the remote nature of participant interactions. The US $25 per survey completion amount is based on feedback from the CAB, which deemed this amount appropriate for the study's context.

Safety Planning and Response Protocol

We have developed a comprehensive safety plan for participants disclosing significant distress or suicidality, specifically tailored to the needs of our study population. The safety plan outlines clear procedures for monitoring, assessing, and responding to participant distress or suicidality. It was created in consultation with multiple psychiatrists and based on established safety protocols that have been successfully implemented in other studies involving mental health assessments and potential disclosures of suicidality in at-risk populations.

A detailed safety response protocol is provided to participants during the consent process and reiterated at every survey. Participants are required to complete a comprehension quiz during the consenting process to verify their understanding of the safety protocol and response procedures. They are informed that survey submissions will not be monitored in real time and are encouraged to take immediate action if they are experiencing an emergency.

All surveys that intentionally assess suicidality, self-harm, and depression-related survey results are reviewed within a 24-hour window by the research team. Crisis management procedures and clinical assessments, as outlined in the safety protocol, are conducted by a board-certified psychiatrist using appropriate clinical interventions. If a participant's responses indicate significant distress or suicidality, a board-certified psychiatrist conducts a clinical assessment to determine the appropriate course of action.

Personalized referral information is provided to participants based on their assessment results and clinical recommendations. Participants identified as at risk for harm to themselves or others are referred to appropriate mental health services, including emergency departments or crisis hotlines. The research team does not discourage participants from seeking or continuing mental health care or treatments during the study. Participants are explicitly informed, both during recruitment and throughout the study, that their voluntary participation in the research is not a substitute for other mental health interventions.

Ethical Considerations

Boston Children's Hospital (BCH) is the prime grant awardee and serves as the primary site for study operations and implementation. The BCH Institutional Review Board (IRB) serves as the single IRB of record for the study (protocol approval number IRB-P00046532).

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The University of Michigan School of Public Health, which houses the methodology and data analysis core, and Massachusetts General Hospital, which serves as the clinical psychiatry and mental health safety core, are designated as relying sites under the single IRB structure. The study is covered by a Certificate of Confidentiality from NIH.

A data safety and monitoring board has been established to oversee the trial's progress, review safety data, and make recommendations regarding the continuation of the trial based on its evaluation of participant safety and the overall performance of the research.

Statistical Analysis

Power

The study aims to enroll 500 TGD participants between the ages of 18 and 24 years, 125 caregivers, and one-quarter of the young adult sample in a TGD young adult-caregiver dyad. The primary outcome of interest is past 3-month suicidal ideation.

Power calculations determined the sample size needed to detect a significant difference in suicidal ideation between the immediate and deferred intervention arms. To detect an effect size of at least 30% (risk ratio=0.70) in the reduction of suicidal ideation from baseline to 6 months postrandomization, a total sample size of 400 participants (200 per arm) is required to achieve 80% power at a 0.05 significance level.

We selected a 30% effect size threshold based on the assumption that smaller differences would not be clinically meaningful for public health scale-up. To account for an estimated 20% attrition rate, we plan to enroll 500 TGD young adult participants and 125 caregivers at baseline, yielding an anticipated analyzable sample of 400 TGD young adult participants and 100 caregivers.

Primary Aim Analyses

The primary outcome is suicidal ideation in the past 3 months, assessed using the 6-item C-SSRS. The C-SSRS demonstrates strong validity, with 100% sensitivity and 99.4% specificity for identifying aborted suicide attempts, and 100% sensitivity and specificity for classifying interrupted and actual suicide attempts, when compared to clinician-administered instruments [41]. The secondary outcome is depressive distress over the past 2 weeks, measured using the Patient Health Questionnaire-9, where a score of ≥10 indicates a positive screen for symptoms of clinically elevated depressive symptoms (88% sensitivity and 88% specificity for detecting major depression) [43].

Before analysis, data will be audited for quality and completeness. Descriptive statistics—including counts, percentages, means, medians, standard deviations, and ranges—will summarize baseline characteristics. Group differences at baseline will be assessed using *t* tests for continuous variables and chi-square tests for categorical variables. Variables that differ significantly between study arms may be included as covariates in subsequent models. All analyses will be conducted using SAS or R statistical software.

To evaluate intervention effectiveness, we will use an intention-to-treat approach. Poisson generalized estimating equations with a log link function will estimate the population-average (marginal) effect of the intervention on suicidal ideation from baseline to 6 months postrandomization [60]. An unstructured correlation structure will be used to account for within-subject correlations across repeated measures (baseline, 3 months, and 6 months).

The primary endpoint analysis will compare the proportion of participants reporting suicidal ideation in the past 3 months between the immediate and deferred (waitlist control) arms. The model will include a common intercept and fixed effects for the intervention arm (immediate vs deferred) and time point (3 vs 6 months). Baseline characteristics that differ significantly between groups and variables related to missingness will be included as covariates, if appropriate.

The primary estimate is the intervention arm assignment. The risk ratio will be estimated by exponentiating the intervention coefficient from the model. Wald tests with robust standard errors will be used to construct 95% CIs and test the primary hypothesis. For TGD young adult-caregiver dyads, we will adjust models to account for dyadic interdependence.

The same analytic approach will be applied to the secondary outcome of past 2-week depressive distress. Statistical significance will be determined at the 0.05 level.

Supplemental Analyses

Supplemental analyses will build on the primary analytic models to further explore the intervention's impact. (1) Dose-response effects: To assess potential dose-response relationships, digital app metadata will be incorporated into the analytic models. Specifically, fixed effects for the number of intervention sessions completed will be added to examine whether greater engagement is associated with greater reductions in suicidal ideation and depressive distress. (2) Heterogeneity of treatment effects: We will examine whether intervention effects vary across subgroups defined by race and ethnicity, gender identity, and geographic region. This will be done by including interaction terms between intervention arm assignment and each subgroup variable in the primary model [61]. Significant interactions will be graphed and interpreted to identify whether certain groups derive greater benefit, which can inform future targeted dissemination and scale-up efforts. (3) Sustained intervention effects: To evaluate whether intervention effects are maintained over time, we will analyze data from participants in the immediate arm who completed both the month 6 and the month 12 assessments. The model will estimate the marginal effect of time on past 3-month suicidal ideation between months 6 and 12. The analytic model will include a common intercept, a fixed effect for time (month 6 vs month 12), and relevant covariates. The risk ratio will be calculated as the exponential of the time coefficient.

Secondary Aims Analysis

We will explore whether hypothesized mediators at month 3 and month 6 mediate the relationship between intervention arm assignment and suicidal ideation and depressive distress at month 12. We hypothesize that factors targeted by the intervention—namely, family communication, family satisfaction, family acceptance, and community belonging—will mediate the effects of the intervention on the primary outcomes:

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past 3-month suicidal ideation and past 2-week depressive distress.

Causal mediation analysis methods [62,63] will be used to estimate the total, direct, and indirect effects of each mediator individually, followed by their combined joint effect [64]. We will also calculate the proportion mediated to determine the extent to which each mediator (or the set of mediators) accounts for the total effect of the intervention. These mediation analyses will be conducted using a series of random effects logistic regression models.

Additionally, we will explore differences in family characteristics based on whether a supportive caregiver could be identified and agreed to participate. These comparisons will offer valuable insights for refining future intervention strategies. TGD young adult-caregiver dyads also complete an additional measure to assess the impact of joint participation on the dyadic relationship. We will further examine potential differences in outcomes between linked and unlinked dyads.

Attrition Analysis

Attrition will be monitored monthly using data visualization techniques to track trends over time. Key metrics will include total enrollment, representation of target subgroups (by race, ethnicity, and geographic region), and rates of loss to follow-up. Statistical analyses will be conducted to compare participants retained in the study versus those lost to follow-up, focusing on differences in baseline characteristics.

Patterns of missingness will be systematically examined, and baseline responses will be compared between participants with complete versus incomplete data. To address potential biases due to missing data, modern missing data techniques will be used, with an emphasis on multiple imputation methods [65]. Sensitivity analyses will be conducted to compare results from complete-case analyses with those using multiple imputation, allowing for an assessment of the potential bias introduced by missing data.

Results

Community Engagement and CAB Feedback

We have maintained consistent engagement with TGD young adult and caregiver communities since the inception of the project. This collaboration has been instrumental in shaping key aspects of the study. Community feedback influenced several design elements, including the adoption of a 6-month waitlist control condition, which was deemed highly acceptable by our CAB and community partners.

Feedback from the CAB also guided the selection of survey measures—for example, prioritizing self-reported measures of suicidality over clinically administered assessments and incorporating items related to social justice and activism as a recognized form of support. The development of intervention content was similarly shaped by community input, resulting in a diverse mix of text-based information, infographics, interviews with TGD people and caregivers, and simulated scenarios. App features were refined in response to privacy and safety concerns, including the addition of a quick exit button.

We will continue to engage with the CAB throughout the intervention period to gather input and integrate community-informed improvements into the study's ongoing implementation.

Outreach

To prepare for recruitment, the outreach and recruitment team developed a comprehensive outreach protocol in collaboration with a multidisciplinary team that included communication and legal experts. Using online searches, referrals, and existing personal and professional networks, the team compiled a master list of over 225 national, state, and local organizations and listservs that serve TGD individuals, the broader LGBTQ+ community, and caregivers (eg, PFLAG).

Beginning on September 12, 2024, the team initiated outreach by contacting 209 organizations (Table 3) and conducting virtual meetings to introduce the project, establish rapport, and address questions. These meetings included the distribution of a recruitment press kit containing digital flyers, listserv-ready email content, and a guide sheet with frequently asked questions.

All organizations that participated in meetings expressed strong enthusiasm for the app, highlighting the urgent need for a resource like this among TGD young adults.

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Table 3. Outreach activities: location of organizations and listservs engaged by the TransHealthGUIDE[a] team (N=209).

Location	Outreach activities, n (%)
National[b]	23 (11.0)
California	51 (24.4)
Connecticut	13 (6.2)
Illinois	29 (13.9)
Massachusetts	29 (13.9)
Maryland	21 (10.1)
New Jersey	15 (7.2)
Oregon	14 (6.7)
Vermont	6 (2.9)
Washington, DC	8 (3.8)

[a]TransHealthGUIDE: Transforming Mental Health for Transgender and Gender-Diverse Young Adults Using Interventions to Drive Equity.

[b]National refers to outreach activities in the United States that were not state-specific.

Recruitment, Screening, and Enrollment

Recruitment and study screening were launched on January 21, 2025. As of May 2, 2025, a total of 149 TGD individuals completed the study screener, with 132 (88.6%) of 149 found eligible (Table 4). This success reflects the strategic and thoughtful recruitment plan led by the outreach team, which included tailored engagement strategies, individualized meetings with community organizations to build trust, and consistent follow-up to support interest and participation.

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Table 4. Screening, eligibility, and enrollment from January 21 to May 2, 2025.

Characteristic	Participants
Screening and enrollment cascade, n/N (%)	
Screened	149/149 (100.0)
Screen eligible	132/149 (88.6)
Contacted	101/132 (76.5)
Eligible and consented	5/101 (4.9)
Not eligible	17/101 (16.8)
Eligible, not yet consented	20/101 (19.8)
Declined before consent	6/101 (5.9)
Screening by race and ethnicity (n=149)[a], n (%)	
American Indian or Alaskan Native	7 (4.7)
Asian	15 (10.1)
Black or African American	13 (8.7)
Hispanic or Latine	29 (19.5)
Middle Eastern or North African	4 (2.7)
Native Hawaiian or Pacific Islander	2 (1.3)
White	106 (71.1)
Other	3 (2.0)
Declined to answer	7 (4.7)
Eligibility by race and ethnicity (n=132) [b] , n (%)	
American Indian or Alaskan Native	6 (4.5)
Asian	15 (11.4)
Black or African American	12 (9.1)
Hispanic or Latine	27 (20.4)
Middle Eastern or North African	4 (3.0)
Native Hawaiian or Pacific Islander	1 (0.8)
White	103 (78.0)
Other	3 (2.3)
Declined to answer	7 (5.3)
Screening by recruitment source (n=149)[c], n (%)	
Social media	5 (3.3)
Flyer	9 (6.0)
Ad	1 (0.7)
Listserv	62 (41.6)
Community organization	8 (5.4)
Health care provider	35 (23.5)
Health care clinic, hospital, or organization	31 (20.8)
Friend	8 (5.4)
Other	8 (5.4)
Eligibility by recruitment source (n=132)[d], n (%)	
Social media	5 (3.8)
Flyer	7 (5.3)

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Characteristic	Participants
Ad	1 (0.7)
Listserv	62 (47.0)
Community organization	7 (5.3)
Health care provider	33 (25.0)
Health care clinic, hospital, or organization	31 (23.5)
Friend	7 (5.3)
Other	7 (5.3)

[a]Race and ethnicity categories were a check-all-that-apply format. The 149 TGD young adults who screened reported 186 racial and ethnic identities.

[b]Race and ethnicity categories were a check-all-that-apply format. The 132 TGD young adults who were eligible reported 178 racial and ethnic identities.

[c]Recruitment source was a check-all-that-apply format. The 149 TGD young adults who screened reported 167 recruitment sources.

[d]Recruitment source was a check-all-that-apply format. The 132 TGD young adults who were eligible reported 160 recruitment sources.

The number of screened and enrolled participants by race and ethnicity and recruitment source is reported in Table 4. Overall, 28.9% (43/149) of those screened were people of color, and 22% (29/132) of those eligible were people of color. The most reported recruitment source was listservs, followed by health care provider, and health care clinic, hospital, or organization. Enrollment visits began on April 23, 2025. As of May 2, 2025, five TGD young adults have been enrolled.

Discussion

Development of a Digital Intervention to Address Mental Health Inequities

Suicidality and depressive distress are pervasive among TGD young adults [11-13], underscoring the urgent need for effective and scalable interventions to address these mental health inequities. Interpersonal and structural stigma—manifesting as minority stress at multiple levels—drives the significantly higher rates of suicidality and depressive distress experienced by TGD young adults compared to their cisgender peers [30,31]. Family functioning and support [5,6,17,18] as well as community connectedness [19-21] have been identified as key protective factors, making them critical targets for public health intervention.

Between 2021 and 2024, we worked in close collaboration with TGD young adults and families to develop TransHealthGUIDE, a digital, app-based educational and support intervention. Through extensive community engagement, formative research, and multidisciplinary input—and in partnership with a professional digital health design and development firm—we created a novel app with 33 content modules grounded in the Social Ecological Suicide Prevention Model [28] and Gender Minority Stress and Resilience Framework [29,30]. This intervention takes a relational approach to mental health and applies a strengths-based lens [32] to enhance education and social support for both TGD young adults and their caregivers.

Our ongoing collaboration with a CAB composed of TGD young adults, caregivers, and health care providers, along with ongoing community partnership activities, ensures that the research is conducted by and for TGD individuals and families. This engagement has strengthened the design and implementation of the RCT, supported recruitment and enrollment feasibility, and enhanced the acceptability and relevance of the intervention content. Our initial launch, with 149 screened and 132 eligible TGD young adults in approximately 3 months, reflects the strong interest in and pressing need for this kind of intervention.

Limitations

First, as a digital app-based intervention, an inclusion criterion for enrollment is access to a smartphone or computer with internet connectivity. Therefore, individuals with limited or no access to technology will not be represented in the study. Second, our study population is restricted to participants from 10 states selected for their supportive legislative context for TGD individuals. While mental health morbidity and mortality among TGD young adults are high in these locations, this approach restricts our reach to individuals residing in other jurisdictions. In these other jurisdictions, which may include states with states lacking legislative supports for TGD young adults, the experiences of TGD young adults may significantly differ and impact mental health risks. If the RCT demonstrates effectiveness, we will explore opportunities to disseminate the digital app more broadly.

Third, caregivers who participate in this study may be more supportive of their TGD young adults than those who do not participate, given the dyadic nature of involvement. However, based on input from the CAB, we expect heterogeneity in the level and types of support and education that participating caregivers will provide. Additionally, this study will provide valuable insights into dyadic participation and the dynamics of TGD young adult-caregiver relationships.

Conclusions

Tailored digital app-based interventions for TGD young adults are scalable and have the potential for broad public health impact, given the widespread availability of digital technology. This RCT of a novel digital app-based intervention aims to address suicidality and depressive distress in TGD young adults through education and support, involving both TGD young adults and caregivers. This approach fills a critical gap in existing mental health interventions for this population. The study findings and lessons learned from implementation will contribute to advancing mental health equity for TGD young adults and caregivers.

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Data Availability

The dataset generated is not publicly available. Deidentified data and a data dictionary will be made available upon reasonable request after the approval of a proposal and the signing of a data use agreement by involved institutions. There is a formal process for external users to request access to data, which involves a review and approval by principal investigators, coinvestigators, and a community advisory board. Further details and forms can be obtained by emailing SLR and RX.

Authors' Contributions

Conceptualization: SLR, SWC, ASK, SLK-W, RX
Funding acquisition: SLR, RX
Methodology: SLR, SWC, ASK, SLK-W, RX
Project administration: SWC, CM
Supervision: SLR, ASK
Writing – original draft: SLR
Writing – review & editing: SWC, ASK, SLK-W, CM, KK, CF, RX

Conflicts of Interest

SLR and ASK receive royalties from McGraw-Hill for editing a textbook on transgender and gender diverse health care. ASK receives royalties from American Psychiatric Association Publishing for editing a textbook of gender-affirming psychiatric care. SWC occasionally receives payments for speaking and writing on transgender health topics from for-profit companies, nonprofit organizations, and individual subscribers. SLK-W is a consultant for Paramount Global.

Multimedia Appendix 1
Peer review report from the ZRG1 MOSS-T - Center for Scientific Review Special Emphasis Panel; RFA-RM-21-021: UNITE Transformative Research to Address Health Disparities and Advance Health Equity (U01) (National Institutes of Health, USA). [PDF File (Adobe PDF File), 168 KB - resprot_v14i1e78619_app1.pdf]

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Abbreviations

BCH: Boston Children's Hospital
CAB: community advisory board
CRAFFT: Car, Relax, Alone, Forget, Friends, Trouble substance use screener
C-SSRS: Columbia Suicide Severity Rating Scale
HIPAA: Health Insurance Portability and Accountability Act
IRB: Institutional Review Board
LGBTQIA+: lesbian, gay, bisexual, transgender, queer, questioning, intersex, asexual
NIH: National Institutes of Health
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SOARS: Suicidal ideation; Onset, frequency, and methods; Aftercare; Reasons; Stage of change screening and assessment of nonsuicidal self-injury
TGD: transgender, nonbinary, and gender diverse
TransHealthGUIDE: Transforming Mental Health for Transgender and Gender-Diverse Young Adults Using Interventions to Drive Equity
WPATH: World Professional Association for Transgender Health

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Proposal

Changing the Perceived Pain Intensity in Populations With Spinal Cord Injury and With Health Disparities (HAPPINESS): Protocol for a Feasibility Study

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Abstract

Background: Chronic neuropathic pain affects 69% of adults with spinal cord injury (SCI). Medication, as a primary treatment, has insufficient benefits and significant risks for addiction and adverse effects. Of the available mind and body approaches, Qigong is the most accessible for adults with SCI, with evidence for effectiveness in reducing pain. Still, there is insufficient evidence to make recommendations for adults with SCI. Thus, the feasibility of Qigong in SCI needs to be established. We previously demonstrated feasibility in a pilot study, in which 18 non-Hispanic White adults with SCI completed a 12-week remote Qigong program. However, three additional key elements need to be addressed before performing a larger effectiveness study: (1) feasibility and acceptability of Qigong in adults with SCI with health disparities, (2) feasibility of a study design with a control group, and (3) objective outcome measures.

Objective: This National Center for Complementary and Integrative Health (NCCIH) R34 feasibility study—the HAPPINESS (Changing the Perceived Pain Intensity in Populations With Spinal Cord Injury and With Health Disparities) trial—will build upon our prior study to consolidate feasibility with a rigorous protocol. Our aims are (aim 1) to identify facilitators and barriers to participating in a Qigong study through community event meetings, focus groups, and interviews with 40 stakeholders, of whom at least 50% (n=20) have health disparities, and (aim 2) to establish the feasibility of study design and methods through prespecified targets for recruitment and enrollment, feasibility, and acceptability of design and outcomes.

Methods: For aim 1, a total of 40 SCI stakeholders—adults with SCI, caregivers, health care professionals, or other stakeholders who have experience with caring for adults with SCI—will be invited to attend community event meetings, one focus group, or an interview, where they will provide input on facilitators and barriers related to participating in a Qigong study. For aim 2, using a phase I randomized controlled trial design, 40 adults with SCI-related neuropathic pain (with at least 50% [n=20] having health disparities) will be randomized to a 12-week remotely delivered Qigong intervention (practicing at least 3×/week with the Spring Forest Qigong's "Five Element Qigong Healing Movements" video), or a short daily pain management survey, completed on a smartphone, iPad, or computer + 6-month follow-up. Feasibility benchmarks, as well as patient-reported outcome measures and objective data from the Fitbit Charge 6 watch, will be collected during the study.

Results: The first participant was recruited on August 20, 2024. Study completion is estimated on January 31, 2027.

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Conclusions: The study results will facilitate a rigorous structure to design large effectiveness studies and facilitate a clear pathway for researchers to investigate Qigong and other mind and body approaches for whole-person health in adults with chronic or neurological disorders, including those with health disparities.

Trial Registration: ClinicalTrials.gov NCT06140355; https://clinicaltrials.gov/study/NCT06140355

International Registered Report Identifier (IRRID): DERR1-10.2196/82431

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KEYWORDS

neuropathic pain; spinal cord injury; Qigong; body awareness; focus groups; protocol; qualitative; feasibility; randomized controlled trial; pain management

Introduction

Background

Chronic neuropathic pain impacts up to 69% of the 308,620 adults with spinal cord injury (SCI) [1-3]. This burning, electric, or stabbing pain can be debilitating and interfere with all aspects of life. The primary line of treatment is pain medication, but it often has insufficient benefits and carries uncomfortable side effects or risks for addiction [4,5]. In addition, there is an underrepresentation of minority groups, women, and older adults in SCI rehabilitation clinical trials [6]. For example, 14% of adults with traumatic SCI are of Hispanic origin; yet, there was an underrepresentation (<10%) of Hispanic or Latinx participants in SCI rehabilitation clinical trials in the United States between 2011 and 2020 [6].

Research showing the effectiveness of mind and body approaches for reducing pain in adults with SCI is limited to 7 studies, among which only 3 (on Yoga and Tai Chi) [7-9] looked at pain reduction, without mentioning which type of pain they were investigating [7-13]. One seated Tai Chi program was well-tolerated in adults with SCI (n=26) with reduced pain and a higher emotional and physical well-being after each session, but their weekly in-person group classes had a dropout of 60% [8].

We reported significant neuropathic pain reduction after remotely delivered Qigong in our feasibility pilot study of 18 adults with SCI-related neuropathic pain [14]. Sample sizes in the above-mentioned studies were small. Moreover, only our study [14] included adults with complete and incomplete tetraplegia, and Tsang et al [11] included adults with incomplete tetraplegia, but all others recruited adults with paraplegia only. Despite these promising results, more accessible interventions for adults with tetraplegia and larger studies are needed.

Substantial evidence suggests that mind and body treatments for physical and mental health may be particularly important for high-risk disadvantaged individuals, including racial or ethnic minorities and those with poor access to conventional treatments because of cost [15]. Factors such as offering the interventions in multiple languages, integrating feedback from participants, and designing programs that are compatible with cultural and religious beliefs would further improve the feasibility and acceptability of mind and body treatments and promote personal use [15-18]. Finally, since 2009, with the increasing opioid epidemic, the US military (Department of Defense [DoD] and Veterans Affairs) has made substantial efforts to provide multidisciplinary, holistic treatments to Veterans with chronic pain [19]. Mind and body approaches have helped military Service Members reduce their pain, improve function and self-management, and increase self-efficacy, but to what extent these approaches are used by adults with SCI to relieve neuropathic pain is unknown [19-22].

Of all mind and body treatment options, Qigong is the most accessible for adults with SCI due to the gentle movements, which can be done in standing, sitting, or lying positions, and due to its focus on breathing and body awareness [23-25]. Yet, there is insufficient evidence to make recommendations for Qigong for adults with SCI at this time. Thus, the feasibility of Qigong in SCI needs to be established. Remote delivery of Qigong is feasible for adults with SCI as it eliminates the commonly reported barriers of in-person interventions: fatigue, pain, transportation, and scheduling difficulties [26]. Moreover, our remotely delivered Qigong practice, which can be done standing, sitting, or lying down, aligns active movements to their ability level with kinesthetic imagery, that is, focusing on the feeling of moving the whole body as if in an upright position, because imagery may be an additional way to improve body awareness and reduce pain [14,25,27]. Therefore, adults with high-level tetraplegia after SCI can participate in this study because they can easily practice Qigong in their wheelchairs or lying down. In other studies, the minimum active muscle strength requirement for exercise programs often excludes these people.

Our preliminary data demonstrate the feasibility and acceptability of practicing Qigong for non-Hispanic White adults with SCI-related neuropathic pain with promising results in terms of pain relief, SCI-related symptoms, improved function, and mental well-being after Qigong practice [14,25]. Eighteen participants completed the study (18/21 enrolled; 86% retention), with 100% adherence to all study components, and 12 participants completed the 1-year follow-up. We enrolled a representative sample of women with SCI (6/18, 33%), adults 65+ years of age (7/18, 39%), living in rural areas (6/18, 33%), Veterans (3/18, 17%), adults in socioeconomic distress (12/18, 67%), and below the poverty threshold (3/18, 17%) [6,14,28]. Even though we recruited nationwide, all participants were non-Hispanic White, pointing to the need for more encompassing recruitment strategies. Participants practiced at home, at least 3 times per week for 12 weeks (123 minutes), with a Qigong video accessible via the internet (ie, the same video as proposed below). Our results showed feasibility and adherence to the intervention (138% of the required intensity

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of Qigong practice, representing 170 minutes) and no study-related adverse events.

However, despite these promising data, three additional key elements need to be addressed before performing a larger phase II effectiveness clinical trial: obtaining data from adults with SCI with health disparities on (1) feasibility and acceptability of participating in a Qigong study, (2) feasibility of the study design (including an active comparison group) and adherence to the interventions, and (3) obtaining objective outcome measures.

Purpose of This Study

This R34 feasibility study—the HAPPINESS (Changing the Perceived Pain Intensity in Populations With Spinal Cord Injury and With Health Disparities) trial—will expand on our previous study to consolidate the feasibility with a rigorous protocol that addresses those key elements, with the aims listed below.

Aim 1: To Identify Facilitators and Barriers to Participating in a Qigong Study in Adults With SCI With Health Disparities

We will hold community event meetings, focus groups, and in-depth interviews with 40 stakeholders, including at least 50% with health disparities (ie, racial or ethnic minorities, Veterans, or living in rural, underserved areas), to identify which sociodemographic, behavioral, cultural, or structural factors facilitate or hinder participation in the study.

Aim 2: To Establish the Feasibility of the Study Design and Methods of the HAPPINESS Trial in 40 Adults With SCI (With at Least 50% [n=20] With Health Disparities) Through Prespecified Targets

The targets are as follows: (1) assessing recruitment and enrollment rates and identifying facilitators and barriers to participation; (2) evaluating recruitment rates for adults with complete versus incomplete SCI to determine the ratio of incomplete versus complete SCI for recruitment estimates in the next phase II randomized controlled effectiveness trial; (3) evaluating the feasibility and acceptability of the design by assessing adherence to Qigong practice or 2-minute daily pain management surveys, study satisfaction, and attrition rates in the Qigong and active comparison groups, as well as identifying facilitators and barriers to practicing Qigong at home; and (4) evaluating the feasibility of the data collection by assessing follow-up rates of outcome measures (% completed assessments at each time point, including objective measures, and weekly and monthly pain surveys).

This R34 feasibility study addresses the National Center for Complementary and Integrative Health (NCCIH) High Priority Pain Research (NOT-AT-22-007) using complementary and integrative interventions. The outcomes of this study will facilitate a rigorous structure to design large effectiveness studies and facilitate a clear pathway for researchers to investigate Qigong and other mind and body approaches for whole-person health, including in adults with chronic or neurological disorders, and those with health disparities.

Methods

Overall Study Design

For aim 1, we will hold community event meetings (ie, education and listening sessions) in town halls and health care settings for SCI stakeholders to share information about the research and hold listening sessions. We will organize focus groups and in-depth interviews using the Consolidated Framework for Implementation Research in the Twin Cities and in South Texas. We estimate we will have 3-5 attendees if on Zoom, and 5-8 attendees if in-person. We estimate holding 3 in-depth interviews with the most informative SCI stakeholders, to better understand the facilitators and barriers to remotely delivered Qigong practice, and identify which sociodemographic, behavioral, cultural, or structural factors facilitate or hinder participation in the study as a whole, including access to a computer, iPad, or smartphone and internet needed for Qigong practice or pain management through a Qualtrics survey, and remotely delivered questionnaires. If in person, the focus groups and interviews will be held in Minnesota (University of Minnesota–Twin Cities) and South Texas (University of Texas Rio Grande Valley [UTRGV]).

For aim 2, we will organize a feasibility phase I randomized controlled trial design where 40 adults with SCI-related neuropathic pain with at least 50% (n=20) with health disparities (racial or ethnic minorities, Veterans, or adults living in rural, underserved areas) are randomized to (experimental group) a Qigong introduction class and a 12-week remotely delivered Qigong intervention, with a 6-month follow-up, or (active comparison group) they complete daily 2-minute surveys to manage their pain sent through Qualtrics, with a 6-month follow-up.

Randomization will be generated by an independent biostatistician. The outcome assessors and the biostatistician on the study will be blinded to the group allocation. We have registered this clinical trial with the National Institutes of Health (NIH) clinical trials registry. Our feasibility pilot trial follows the guidelines according to the Obesity-Related Behavioral Intervention Trials model [29] and NCCIH [30]. Based on the guidelines, we developed aims, protocol, and the following a priori feasibility benchmarks to rigorously test the methodology and feasibility of the intervention before a larger effectiveness clinical trial is conducted.

Behavioral assessments will be acquired remotely at 3 time points: at baseline, after the 12-week interventions, and at the 6-month follow-up. This 6-month follow-up period will assess behavioral changes and the sustainability of Qigong practice adherence or pain management survey adherence in daily life. In our prior study, participants enjoyed continuing Qigong practice because it helped them manage their pain [14]. Both groups will receive weekly calls during the 12-week intervention period and monthly calls during the 6-month follow-up to assess neuropathic pain (primary outcome) and neuropathic pain medication, including opioid use, adherence to Qigong practice or the pain management surveys, adverse events, illnesses, and use of health care services. Qualitative information will be collected about their adherence, adverse outcomes, if any,

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perceptions, effects, and satisfaction with the Qigong practice or pain management surveys. Ecological momentary assessments (EMAs), consisting of 2-minute Qualtrics surveys are delivered 4 times per day for 3 weeks at baseline, during the last 3 weeks of the 12-week interventions, and during the last 3 weeks of the 6-month follow-up to identify feasibility of data that can explore causal relationships between variables of mood, activity, sleep, and so on, and neuropathic pain to understand in each individual which variables increase or decrease neuropathic pain. Objective data on sleep, stress, and other information will be collected continuously with the Fitbit Charge 6 wrist device. Fitbit data will also be time-synchronized with EMA data at those 3 time points to evaluate the feasibility of data that can explore causal relationships between physiological data, behavioral data, and neuropathic pain. The study is offered in English and Spanish to increase accessibility to those for whom English may be a barrier.

The SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) 2013 checklist with recommended items to address in a clinical trial protocol and related documents (Multimedia Appendix 1) and the SPIRIT template of recommended content for the schedule of enrollment, interventions, and assessments (Table 1) are included.

Table 1. Scheduling of enrollment, intervention, and assessments.

	Study period			
Timepoint	Enrollment	12-week intervention	6-month follow-up	Close-out
Enrollment	Week 0	Week 1-12	Week 13-37	Week 38
Eligibility screen	✓			
Informed consent	✓			
Baseline assessments (Zoom questionnaires)	✓			
Allocation	✓			
Interventions				
Qigong		✓	✓	
Pain management survey		✓	✓	
Assessments				
Fitbit Charge 6 smartwatch	✓	✓	✓	✓
EMA[a] surveys	✓	✓	✓	
Zoom questionnaires	✓	✓		✓
Weekly calls		✓		
Monthly calls			✓	

[a]EMA: ecological momentary assessment.

Study Setting

The clinical trial part of the study is completely remotely delivered. The event meetings, focus groups, and interviews can be held in-person or over secure Zoom. The principal investigator (AVdW) will head event meetings, focus groups, and in-depth interviews with SCI stakeholders with emphasis on those with health disparities in Minnesota. The UTRGV team (KB and GM) will support the event meetings, focus groups, and interviews with the Hispanic community in South Texas, and provide the principal investigator (AVdW) with the transcriptions in English or Spanish with translated versions to English of the focus groups and interviews, the latter of which will be reviewed by GM to ensure cultural adaptation. We will purchase the Spring Forest Qigong Center's "Five Element Healing Movements" video and introduction class for the intervention in English or Spanish. This video will be reviewed during the meetings, focus groups, and interviews. A certified Spring Forest Qigong instructor will teach the introduction class and hold three 1:1 Zoom sessions with the participants who were randomized to the Qigong intervention group.

Participants and Recruitment

For aim 1, the inclusion criteria are 40 SCI stakeholders, which can be adults with SCI, caregivers, health care professionals, or other stakeholders who have experience with caring for adults with SCI, especially those with health disparities.

The inclusion criteria for aim 2 are persons aged 18+ years, 40 participants with an incomplete or complete SCI of ≥1 year, medically stable, and with ≥4/10 for highest neuropathic pain intensity level on the Numeric Pain Rating Scale [31]; willing to participate in a remote Qigong intervention (from any location with internet connection), fluent in English or Spanish, access to the internet and a computer, iPad, or smartphone. We aim to recruit at least 50% (n=20) of adults with health disparities (ie, racial or ethnic minorities, Veterans, or living in rural, underserved areas).

The exclusion criteria are uncontrolled seizure disorder, cognitive impairment or communicative disability (eg, due to brain injury) preventing them from following directions or from learning, ventilator dependency, major medical complications, pressure ulcers hindering prolonged sitting or lying down,

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(planning to become) pregnant or planning a major surgery during the study (given the study duration, regular Qigong practice or surveys, and frequent check-ins), regular Tai Chi or Qigong practice in the past 6 months (3×/week or more) or currently engaged in other rehabilitation programs that would influence outcomes.

We estimate recruiting 30%-40% (12-16/40) of adults with complete versus 60%-70% (24-28/40) incomplete SCI based on our prior data in SCI and on reported statistics of 23% (9/40) complete paraplegia, 15% complete tetraplegia (6/40), 22% incomplete paraplegia (9/40), and 40% incomplete tetraplegia (16/40) [32].

We will recruit from all clinical site partners within the Minnesota Regional SCI Model System, which includes hospitals, clinics, rehabilitation centers, long-term care facilities, and nursing homes in the Twin Cities and Mayo Clinic in Rochester. Specifically in the Twin Cities, we have collaborations within the Veterans Affairs (Minnesota), including the Minnesota Paralyzed Veterans, University of Minnesota Medical Center, University of Minnesota Health (M Health) Fairview, Regions Hospital, Courage Kenny Rehabilitation Institute, and Minnesota SCI associations. Health care providers will provide information to potential participants and post fliers.

M Health Fairview has a recruitment system in place where letters are sent from their system directly to patients with SCI and neuropathic pain. Patients who are interested in participating can contact the researchers. We also collaborate with the SCI patient advocacy association United to Fight Paralysis.

In 2019, a total of 530 adults with new SCI were treated in the Twin Cities clinics, with 311 receiving outpatient therapy in rehabilitation centers. In 2022, a total of 285 adults with SCI received annual evaluations, along with other visits to the Minneapolis Veterans Affairs Medical Center, totaling about 550 unique visits and 7500 encounters.

Based on the population of Hispanic origin (8.5 million) in Texas [33], and an SCI incidence rate of 54 cases per million [32,34], we expect that there are about 432 new cases of SCI per year in Texas. Our UTRGV team has committed to assisting with recruitment and retention strategies in minority groups in the Rio Grande Valley, with a 98% Hispanic population, and where almost 30% live in poverty [35,36].

There are about 200-300 adults with SCI in the Rio Grande Valley: 75-100 treated at UTRGV and >250 treated at the Rehabilitation Institute at the Doctors of the Hospital Renaissance in the Rio Grande Valley. The UTRGV team will involve Hispanic community leaders, adults with SCI, their families, caregivers, and SCI health care workers.

We will also recruit nationwide through regional and national SCI or professional organizations and will post fliers and information on relevant websites and social media. We have successfully recruited participants nationwide in our preliminary remotely delivered Qigong study [14]. Given the prevalence of 308,620 adults with SCI in the United States (with 69% neuropathic pain prevalence) and given our completely remote clinical trial part of the proposal, we have many opportunities to recruit 40 participants with SCI-related neuropathic pain (as well as 40 SCI stakeholders for aim 1), even with an estimated 30% screening failures based on inclusion and exclusion criteria.

We have also taken into account patient and public involvement. Literature shows that adults with SCI, their families, and caregivers who have experience with mind and body approaches are more likely to recommend such approaches compared to health care professionals [37]. Therefore, we have 3 SCI consultants on the team. Our Latina consultant in Minnesota will facilitate communication between the research group and the Hispanic community in Minnesota, whereas the SCI consultant in South Texas will do the same for the Rio Grande Valley region, by educating the team and facilitating the cultural acceptability of Qigong, pain management surveys, and the study protocol (including assessments) for the Hispanic community. Our Veteran SCI consultant has given input on the feasibility of Qigong practice for adults with paraplegia and tetraplegia, and the duration of remote clinical assessments. All SCI consultants will provide input throughout the study and be invited to attend quarterly meetings, where they will be informed about the progress of the study.

Interventions

Two active interventions are proposed, with different "active ingredients." More information about the interventions is given below.

The Qigong introduction class will be taught over Zoom by a Spring Forest Qigong-certified instructor. Then, participants will practice Qigong at least 3 times per week for 12 weeks with the "Five Element Healing Movements" online video with streaming access from any computer, iPad, or smartphone device, so participants can practice at home or any location with an internet connection. More details about the content of the Qigong practice can be found in our published protocol paper of the Qigong pilot study in adults with SCI-related neuropathic pain [25]. Participants log in with a unique study identification number and password onto the Spring Forest Qigong website to access the video and practice at least 3 times per week for 45 minutes per session. Their practice (time and duration of access) will be logged automatically and sent to the principal investigator (AVdW), who is level 5 (of 5 levels) in the Spring Forest Qigong curriculum, and a certified practice group leader.

Once a month, the Spring Forest Qigong-certified instructor will do a Qigong session 1:1 with each participant over Zoom to monitor their practice, address questions, demonstrate movements, and give guidance as needed to ensure quality control of the practice. We will use the recording option on the Zoom platform, and the video will be stored on our server, called the University of Minnesota secure box.

The active comparison group will receive a daily text or email message (depending on the choice of the participant) linking them to a 2-minute online Qualtrics survey to answer questions related to their pain intensity level, medications taken that day, activities that helped or hindered the pain, and free text on what they did that day that mattered to them. There are no educational or lifestyle advice components, and they will not receive any guidance on any of the active ingredients given in Qigong (ie,

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breathing, meditation, and meditative movements). Pain management has been examined through an app in multicenter trials and feasibility studies and is being used in large health care systems in Canada [38].

We will organize weekly (during the intervention) and monthly check-ins (during the 6-month follow-up) to encourage adherence. The Qigong group will also receive a 1:1 session per month with the Qigong instructor to verify the quality of practice and address any questions. The research staff will contact the participant if the pain management surveys are not completed 2 days in a row.

All participants will continue their prescribed or over-the-counter pain medication and maintain their regular standard-of-care health care appointments. However, any current regular (3 times per week or more) mind and body practices, such as Tai Chi, Qigong, or any rehabilitation programs that would influence outcomes, will not be permitted.

The study does not provide compensation for research-related injuries or unexpected urgent care.

Demographic and Clinical Outcomes

Four types of remotely delivered assessments are used in this study: (1) demographic and SCI-related medical information, (2) feasibility benchmarks, (3) patient-reported outcome measures (questionnaires and EMA surveys), and (4) objective measurements with the commercially available Fitbit Charge 6 smartwatch.

Demographic, SCI-Specific Data, and Screening

We will collect National Institute of Neurological Disorders and Stroke – Common Data Elements (NINDS-CDE) SCI-demographic, SCI-relevant general health, and SCI-specific data. We will screen participants with the Mini-Mental State Examination-short version (cutoff score <13/16) [39], and test their ability to perform kinesthetic motor imagery with the Kinesthetic and Visual Imagery Questionnaire (cutoff score <15/25 points) [40]. While imagining body parts affected by SCI may be difficult for participants at baseline, overall impaired kinesthetic imagery is rare: no adult with SCI scored below the cutoff score in our prior studies [14,41].

Feasibility Benchmarks

Our feasibility markers are consistent with models and guidelines for intervention development (Table 2) [29,42]. Based on prior publications [43-46], we will assess the following a priori feasibility markers.

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Table 2. Feasibility benchmarks.

	Feasibility item and details	Benchmark (go/no-go criteria)
Recruitment and enrollment	• Assess recruitment rates (screens and enrollment per trimester, sex, and racial outcomes). • Evaluate the recruitment rate for complete and incomplete SCI[a]. We aim to recruit 40 participants between mid-year 1 and year 2.	• The proportion of potential participants contacted who agreed to participate: 80% is excellent and 70% good. • Ratio of complete/incomplete SCI. We estimate recruitment of 30%-40% of adults with complete, 60%-70% with incomplete SCI. • Reasons for (not) participating and information collected during focus groups or interviews will help delineate facilitators and barriers to participation, including computer or internet access.
Feasibility and acceptability of the study design	• Attrition rates in the Qigong or pain management survey groups.	• Proportion of people withdrawing from the interventions. Dropout due to unrelated reasons will count as part of the general attrition. A proportion of 90% is excellent, and 80% good.
Feasibility, adherence, and acceptability of the Qigong practice	• Assess intervention adherence, average Qigong practice, at least 3×/week (123 minutes), pain management surveys (daily), and satisfaction with the Qigong practice or pain management surveys. • Identify facilitators and barriers to practicing Qigong at home or completing the pain management surveys.	• Weekly and monthly check-ins (reporting minutes/week of practice) to identify facilitators and barriers to pain management surveys or practicing Qigong. The Qualtrics website (for pain management surveys) or Spring Forest Qigong website (for Qigong practice) logs time and duration of video access. • A Spring Forest Qigong-certified instructor will do a 1:1 Qigong session with each participant via Zoom monthly for quality control and to give guidance. Feasibility: Excellent: >80% participants practice at least 2×/week; good ≥70%. For the pain management survey: completion of surveys at least 5 out of 7 days. • Dropout due to lack of interest will be counted as general attrition: 10% dropout is excellent, 20% is good.
Feasibility of adhering to the collection of quantitative measures	• % Adherence in completing all assessments during the study and in the monthly follow-up phase until 6 months postintervention. • % Adherence to wearing the Fitbit Charge 6 smartwatch and sending the data through their Fitbit app on their smartphone.	• Feasibility is 'excellent' when none of the Zoom questionnaires, EMA[b] surveys, or weekly and monthly check-ins are fully missing in >25% of the participants. • Excellent adherence: data from the Fitbit app at least 70% of the time and wearing the Fitbit Charge 6 at least 5 out of 7 days/week for at least 7 hours/day (≥80% excellent; ≥70% good).
Program satisfaction	• 3-item Client Satisfaction Scale [47]. • Ask about their intent (and frequency) to continue the Qigong practice or pain management surveys after the 12-week intervention program.	• Excellent satisfaction if ≥75% of the participants score above the scale midpoint; and good if ≥70%. • Our benchmark is ≥70% of the participants intend to continue the Qigong practice or pain management surveys after 12 weeks.
Program safety	• Assess adverse events (IRB[c]+GCP[d] reporting guidelines) and report adverse events via ACTTION[e] recommendations [48,49].	• Excellent safety: no study-related adverse events; good if there are minimal and mild adverse events (eg, muscle soreness) linked to Qigong practice in max 10% of participants, or any adverse events with the pain management surveys. We will ask about adverse events during the weekly and monthly check-in calls.

[a]SCI: spinal cord injury.

[b]EMA: ecological momentary assessment.

[c]IRB: Institutional Review Board.

[d]GCP: Good Clinical Practice.

[e]ACTTION: Analgesic, Anesthetic, and Addiction Clinical Trial Translations, Innovations, Opportunities, and Networks.

Primary Clinical Endpoints

We will use the patient-reported outcome measures of pain intensity PainDETECT [50] and the Numeric Pain Rating Scale [31] for the highest, average (ie, pain experienced most of the time), and lowest pain intensity in the prior week. The Numeric Pain Rating Scale [31] and PainDETECT [50] will be assessed weekly during the Qigong or pain management survey intervention period and then monthly during the 6-month follow-up period.

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Secondary Clinical Endpoints

To address whole-person health, all secondary outcomes, which are patient-reported outcome measures, will be assessed at 3 time points (baseline, after the intervention period, and at 6 months follow-up). In addition, we will perform EMA assessments 4 times per day for 3 weeks at baseline, during the last 3 weeks of the 12-week intervention, and during the last 3 weeks of the 6-month follow-up. The Fitbit Charge 6 smartwatch is worn all the time during the duration of the study to measure physical and emotional functioning as well as obtain objective measurements on sleep, activity, and other information such as heart rate and stress levels (heart rate variability–based measure).

Impact and Type of Pain (NINDS-CDE SCI)

The NINDS-CDE SCI International SCI Pain Basic Data Set Version 3.0 [51] assesses different types of pain, the body location, average pain intensity, and neuropathic pain interference with mood, activity, and sleep. NINDS-CDE SCI–recommended PainDETECT [50] helps identify neuropathic pain phenotypes [52].

Physical Functioning

NINDS-CDE SCI Functional Index/Assistive Technology measures function related to basic mobility, self-care, fine motor function, and ambulation [53]. For the Patient Specific Functional Scale, participants rate their ability to achieve 3 self-identified important functional activities or goals [54].

Emotional Functioning

Patient Health Questionnaire-2 is used to assess symptoms of depression in adults with SCI [55-58]. We will use the NINDS-CDE recommended SCI-Quality of Life measurement [59] subscales on pain behavior, positive affect, resilience, and ability to participate, to obtain a comprehensive view of the participant's emotional functioning [59].

Global Improvement

The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials–recommended Patient Global Impression of Change provides a measurement system with scores ranging from 1 to 7 for how a participant evaluates changes in their status, with score 1 reflecting "very much improved," and gradually decreasing to 4 reflecting "no change" and further down to 7 reflecting "very much worse" [60,61].

EMA Surveys

EMA surveys will be sent through text or email: 27 real-time questions total; 10-item Positive and Negative Affect Schedule-Short Form (PANAS-SF) [62], activity, sleep, stress, mind awareness, body awareness, pain interference, and agency (ie, control over life and control over pain) to explore the dynamics of neuropathic pain intensity in daily life [63]. Two cognitive tests will be conducted, with a duration of 30-90 seconds total: (1) attention and set-shifting: number and number/letter sequencing on a 4×4 grid, that is, 1, A, 2, B, 3... (2) spatial working memory test: remembering sequence + location of squares on a 4×4 grid. Providing EMA 4 times per day for 3 weeks is feasible in terms of participant burden, while at the same time providing enough data to perform personal causal modeling.

Objective Measurements of Sleep, Activity, and Other Information, Obtained With a Consumer Device, the Fitbit Charge 6 Watch

Our primary data will be physical activity (minutes), heart rate (every second), stress level (heart rate variability–based), and sleep (minutes). Participants will install the Fitbit app with their account and use the OAuth 1.0a protocol on a University of Minnesota website (developed by coauthor KOL) to authorize Fitbit to transfer data directly to our University of Minnesota server. Participants will leave the Fitbit app open in the background so data can be transmitted to our server. In this way, we can monitor that data is being received and that the device is being charged. KOL has used this method successfully in several studies [64,65].

Virtual delivery of questionnaires related to assessments or check-ins will be organized through our secure University of Minnesota Zoom. Participants will be encouraged to complete all scheduled virtual visits and assessments. However, missed sessions will be allowed and recorded and will not be considered protocol deviations. We had 100% adherence to Qigong training, assessments, and weekly check-ins through Zoom in our prior Qigong studies (IRB# STUDY00005656; IRB# STUDY00011997) in those who completed the study. If an EMA survey, pain management assessment, or weekly or monthly check-in is missed, measures will be taken to get the information later. There are no stop criteria for missed sessions or missed testing. The clinical trial will be completely remotely delivered.

Statistical Analyses

Sample Size Calculation

We plan on recruiting 40 SCI stakeholders (aim 1) and 40 adults with SCI-related neuropathic pain (aim 2). Stakeholders not only include adults with SCI but also caregivers and health care professionals and any other stakeholder related to adults with SCI.

Aim 1 requires a qualitative analysis, and thus, power analysis is not calculated.

The sample size for aim 2 of 40 adults with SCI-related neuropathic pain is based on our estimated accrual and enrollment rates from our prior studies on related research. Due to the nature of a feasibility study, power calculations were not conducted. With N=40, we will be able to estimate a rate for the feasibility endpoints, for example, the dropout rate, of 80% with the margin of error of the 95% CI controlled at ±10%. Based on prior literature, the sample size is sufficient to provide reliable estimates of the mean and SD of pain (primary outcome) and other outcomes, to determine the required sample size for future large efficiency studies.

Data Analysis

The demographic variables and other baseline characteristics, including sex, race, and ethnicity, will be summarized using descriptive statistics, including mean, median, SD, IQR, minimum, and maximum. Rate parameters for the feasibility markers will be estimated based on the participants who achieved each benchmark. All quantitative variables, including

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primary and secondary outcomes, will be summarized using descriptive statistics. For longitudinal outcomes, missing data will not be imputed. Mean and SD will be calculated for each outcome at each time point. Means and SDs of across-time changes (eg, pre- vs post-Qigong or pain management survey changes) and correlations will be estimated for all participants, each group, or stratum that will be used for sample size determination in future studies. Mediation analyses will explore potential mediators among variables measured with the Fitbit device for the relation between Qigong practice or pain management surveys and changes in neuropathic pain. Descriptive and feasibility data related to adults with health disparities will be investigated. Missing data will not be imputed. The % missingness will be tabulated for each time point by group, and the mechanism of missingness will be identified.

The qualitative variables (eg, focus groups, interviews, weekly and monthly check-ins) will be recorded, transcribed, and managed using NVivo (Lumivero). Coded units will be sorted into categories and analyzed for recurrent themes or patterns. Emerging categories will be reviewed for alignment with the quantitative findings. These findings will serve to reach conclusions on the feasibility, acceptability, and satisfaction of adults with SCI-related neuropathic pain in study participation and performing Qigong practice or completing pain management surveys. We will also report on conclusions relevant to adults with health disparities.

Research Team

Our multidisciplinary team has the expertise in all study aspects to successfully carry out these aims. The principal investigator (AVdW) is a NIH-funded new investigator with 27 years of expertise in body awareness research, including Qigong, and 10 years of clinical trial management, including in adults with SCI. She is responsible for the fiscal and research administration. AVdW will oversee the study design, study coordination, data management, regulatory compliance, data collection, and analysis. She will oversee the project and data manager, as well as the research assistants who are blinded to group allocation to perform the assessments. Co-investigator LRM is a SCI clinician and a DoD, NIH, and National Institute on Disability, Independent Living, and Rehabilitation Research–funded researcher with expertise in SCI clinical trial management. Co-investigator LZ is an NIH-funded biostatistician. Co-investigator KOL is an NIH-funded scientist with expertise in using EMA and the Fitbit Charge 6 smartwatch for research. He has built a program, housed on a University of Minnesota server, to download and analyze the data from the Fitbit device. At the University of Minnesota, we will have a program and data manager, experienced in working with remote teams and multiple sites, and a bilingual Latina SCI consultant, as well as a Veteran SCI consultant. Collaborators at the UTRGV are KB, NIH and DoD-funded SCI researcher; BW, SCI clinician neurologist; and GM, a bilingual (Spanish and English) NIH-funded scientist and expert in qualitative research in Hispanic communities. GM has built strong connections with this community and has experience with holding event meetings, focus groups, and interviews to effectively identify facilitators and barriers to health-related study participation and implementation [66,67]. The UTRGV team has committed to helping with the recruitment of adults with SCI in the Rio Grande Valley. They have a bilingual program manager also serving as a Spanish translator if needed, and a bilingual SCI consultant. We have ongoing collaborations with Dr Looft, associate director of Spinal Cord Injuries and Disorders Research at the Minneapolis Veterans Affairs Spinal Cord Injury Center, Minnesota (MN), for recruitment of Veterans, and with Mr Thorson at Essentia Health-Duluth (MN), a rural site for recruitment of adults with SCI.

The principal investigator and program and data manager will meet weekly, and the entire study staff will meet monthly to focus on the progress of the study until project completion. Issues requiring immediate attention across sites will be addressed either by phone, email, Zoom, or in person. The author order of publications will be based on the relative scientific contributions of the principal investigator and key personnel.

Ethical Considerations

We follow the ethical guidelines of the Declaration of Helsinki. The University of Minnesota's Institutional Review Board (IRB) approved the study (IRB#STUDY00022415). The study is registered at ClinicalTrial.gov (NCT06140355).

All protocol amendments will be submitted for IRB approval prior to implementation and communication with the participants. If applicable, a new consent form will be signed. New consent forms and protocol amendments will be sent to NCCIH at the time of yearly reporting. Prior to consenting, the consent form will be sent via an email link for review. Eligible participants will have a virtual visit with study staff to review the consent document and ask questions. We will maximize IRB-approved eConsenting and use consent through a legally authorized representative if the participant is physically unable to sign. We will not enroll minors or participants unable to consent due to an altered mental capacity.

We use the University of Minnesota Research Electronic Data Capture (REDCap) database to send out and have participants digitally sign the eConsent forms. REDCap uses a MySQL database via a secure web interface. All IRB rules and HIPAA (Health Insurance Portability and Accountability Act) rules protecting the participants' rights and confidentiality of records will be followed.

The HIPAA-eConsent forms, electronic medical record information (if applicable), and assessment data will be entered into the password-secured REDCap. EMA surveys and pain management surveys are collected on Qualtrics, and the Qigong practice is logged and sent as a Microsoft Excel file to the principal investigator (AVdW). Virtual delivery of patient-reported outcome measures will be organized through our secure University of Minnesota Zoom. Their responses, including those during the weekly and monthly phone calls, will be entered into the REDCap database. Data on REDCap will be verified by the research staff for completeness and accuracy.

Data integrity and privacy are ensured by attributing a unique study identification number to each participant. Only the principal investigator and approved research staff designees

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have access to the key, identifying participants with these codes. All data are stored on secure username and password-protected University of Minnesota servers, which are operated by the Academic Health Center's Information Systems group, and backed up daily, weekly, and monthly. Their servers provide a stable, secure, well-maintained, and high-capacity data storage environment.

Data analysis (including assessments, notes, recordings, and NVivo analysis) is stored on the University of Minnesota secure box, with two-factor authentication. The Fitbit app on their smartphone will transmit data to the Fitbit server, which pushes data to a secure University of Minnesota server (monitored by coauthor KOL). Team members interacting with participants or their data completed the University of Minnesota's training requirements for the Responsible Conduct of Research, Good Clinical Practice, HIPAA, data security, and study-specific training. They comply with all guidelines and maintain Good Clinical Practice training certificates every 3 years.

After study completion, deidentified data related to the outcomes of the aims of this project will be archived on the Dryad repository. The DOI link will be shared in the peer-reviewed publications together with the publication of the results of this study to ensure sufficient quality to validate and replicate research findings.

Regarding compensation, for aim 1, all participants receive US $50 when they complete either a focus group meeting or an interview. For aim 2, participants will receive a Fitbit that they can keep after the study ends. The participants in the Qigong group will also still have access to the Qigong video after the study has been completed. All participants receive US $200 at the end of the study and an additional US $1 for every EMA survey they have completed at the 3 time points during the study (maximum US $252).

Given that Qigong involves slow, gentle movements in standing, sitting, or lying positions, we do not expect any study-related adverse events from the treatment, similar to our experience in our preliminary studies [14,27]. We also do not expect any study-related adverse events with the pain management surveys. We will monitor adverse events weekly through direct check-in phone calls during the intervention period and monthly during the follow-up period and follow the Good Clinical Practice procedures.

Because there is minimal risk associated with this study, the IRB does not require a Clinical and Translational Science Institute data integrity monitor or data monitoring committee. The principal investigator (AVdW) and LRM (study physician) will determine whether an adverse event is expected or unexpected, if it occurs. An adverse event will be considered unexpected if the nature, severity, or frequency of the event is not consistent with the risk information previously described for the study intervention. Aside from the weekly and monthly check-ins, we will ask participants to reach out to the principal investigator or project and data manager, if (severe) adverse events occur in the period between the calls. We will follow all regulations and protocols as outlined by the University of Minnesota's IRB should this occur.

Our safety monitoring plan includes an independent medical monitor: Dr Andrew Grande, neurosurgeon at the University of Minnesota, is not associated with this research project and works independently of the principal investigator (AVdW). He is not part of the key personnel involved in this grant, nor has he collaborated or copublished with the principal investigator within the past 3 years. He is qualified to review the patient safety data generated by this study because of his unique expertise as a neurosurgeon.

Dr Andrew Grande will review all reported adverse events semiannually and as needed with the principal investigator (AVdW) to review the number and type of adverse events. The principal investigator will inform Dr Grande promptly of all study-related unanticipated problems involving risk to participants or others, serious adverse events, and all participants' deaths associated with the protocol, and provide an unbiased written report of the event to the IRB. The medical monitor will comment on the outcomes of the event or problem, and in the case of a serious adverse event or death, comment on the relationship to participation in the study. The medical monitor will also indicate whether he concurs with the details of the report provided by the study investigator. Reports for events determined by either the investigator or medical monitor to be possibly or definitely related to study participation, and reports of events resulting in death, will be promptly forwarded to the University of Minnesota's IRB and NCCIH.

Results

We report protocol version 2 and do not anticipate any further changes until trial completion. We registered and posted the trial on ClinicalTrial.gov registration (NCT06140355) on November 20, 2023. The first participant was recruited on August 20, 2024. Study completion is estimated on January 31, 2027. At this time (September 2025), 20 participants have been recruited for aim 1 (no dropouts) and 36 participants were recruited for aim 2, with 8 participants dropping out of the study.

Discussion

Anticipated Findings

With this NCCIH-funded feasibility HAPPINESS trial, we will expand on our prior study to consolidate feasibility with a rigorous protocol. We expect that the focus groups and interviews with SCI stakeholders will reveal meaningful and actionable insights regarding facilitators and barriers to Qigong, to all study components, as well as to current health care and neuropathic pain treatments. We expect to gather useful and actionable information on specific problems encountered, and cultural sensitivity to be considered in adults with health disparities (aim 1). We further expect that the study will be feasible, with both interventions being attended and feasibility established for recruitment and enrollment, including the recruitment of 50% of adults with health disparities.

Limitations

While the completely remote aspect of this study allows for recruitment nationwide and includes rural areas, we are limited to patient-reported outcome measures through Zoom and

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objective data from the Fitbit. Clinical in-person testing of sensation, movement, and function cannot be performed in this study design, given that it is a fully remote-delivered clinical trial.

Dissemination Plan

We will present the results of this study at conferences and in peer-reviewed publications. All key personnel, research staff, and stakeholder contributions will be acknowledged. We will use our connections with national SCI advocacy groups and professional associations to disseminate information about the results of the Qigong versus pain management surveys and hold dialogues with stakeholders. The results from this feasibility study will also be used for a federal grant submission for a subsequent effectiveness randomized clinical trial. We will use social media and our Brain Body Mind Lab website platform and other means to educate SCI stakeholders, including health care providers locally and nationally.

Future Directions

Assessing feasibility is the first step. The results from this study will facilitate a rigorous structure to design large effectiveness studies and facilitate a clear pathway for researchers to investigate Qigong and other mind and body approaches for whole-person health in adults with chronic or neurological disorders, including those with health disparities. Furthermore, once effectiveness is demonstrated, remotely delivered Qigong practice can easily be implemented in clinics, in the community, health care facilities, or at home.

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Data Availability

Data sharing is not applicable to this article as no data sets were generated or analyzed during this study.

Authors' Contributions

Conceptualization: AVdW
Data collection and analysis: AVdW, KOL, LZ, GM, KB
Funding acquisition: AVdW
Recruitment: AVdW, LRM, BW, KB
Supervision: AVdW
Validation: AVdW, LZ, KOL, GM, KB
Visualization: AVdW
Writing – original draft: AVdW
Writing – review & editing: AVdW, LRM, LZ, KOL, BW, GM, KB

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT checklist.
[PDF File (Adobe PDF File), 256 KB - resprot_v14i1e82431_app1.pdf]

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Abbreviations

DoD: US Department of Defense
EMA: ecological momentary assessment
HAPPINESS: Changing the Perceived Pain Intensity in Populations With Spinal Cord Injury and With Health Disparities
HIPAA: Health Insurance Portability and Accountability Act
IRB: Institutional Review Board
M Health: University of Minnesota Health
NCCIH: National Center for Complementary and Integrative Health
NIH: National Institutes of Health
NINDS-CDE: National Institute of Neurological Disorders and Stroke – Common Data Elements
PANAS-SF: 10-Item Positive and Negative Affect Schedule-Short Form
REDCap: Research Electronic Data Capture
SCI: spinal cord injury
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
UTRGV: University of Texas Rio Grande Valley

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Protocol

Brothers Building Brothers by Breaking Barriers: Protocol for a Pilot Trial of a Telehealth Social Capital Intervention for Young Black Sexual Minority Men Living With HIV

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Abstract

Background: Young Black sexual minority men are disproportionately affected by HIV, especially in the Southern United States. To address this, we developed Brothers Building Brothers by Breaking Barriers (B6) intervention with a goal of enhancing social capital and engagement in care among young Black sexual minority men living with HIV. However, we encountered challenges to feasibility in recruiting and engaging for an in-person intervention.

Objective: The objectives of this study are to iteratively adapt the original B6 intervention for telehealth delivery (Phase 1), and pilot test the intervention through a waitlist-control trial to evaluate its feasibility, acceptability, and safety (Phase 2).

Methods: In Phase 1, we used the assessment, decision, adaptation, production, topical experts, integration, training, and testing (ADAPT-ITT) framework to structure the iterative adaptation process of B6, working with a diverse study team and a Youth Advisory Board (YAB). After completing the preliminary adaptation process, we conducted initial Telehealth Brothers Building Brothers by Breaking Barriers (Tele-B6) pilot testing with a community partner organization. The result was a 5-week group-level intervention, delivered entirely remotely, consisting of a series of adapted activities to address bonding and bridging social capital, affirm intersectional identities, and engage in resilience-building processes. Following feedback integration from pilot-testing, we conducted Phase 2 with 60 young Black sexual minority men living with HIV recruited over the course of one year and who were randomized at the group level to either the immediate intervention or delayed (waitlist control) intervention group. Various data sources will be used to measure feasibility, acceptability, and safety, including surveys, postsession evaluation data, in-depth qualitative interviews, and review of medical records for HIV clinical outcomes.

Results: Phase 1, the adaptation process of B6, began in fall 2022 and was completed in spring 2023. Phase 2, the implementation of the waitlist control trial, began in spring 2023 and concluded in summer 2024. Final follow-up assessments were completed in fall 2024 and the results of the mixed methods evaluation are expected in winter 2025.

Conclusions: The adaptation process and telehealth delivery of B6 will add to the knowledge of strengths-based interventions designed to improve care engagement among young Black sexual minority men living with HIV.

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International Registered Report Identifier (IRRID): DERR1-10.2196/69961

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KEYWORDS

social capital; resilience; HIV; intervention adaptation; YB-GBSMM; sexual minority health

Introduction

Background

In the United States, sexual minority men bear the highest burden of HIV. Within this population, Black sexual minority men are disproportionately impacted; in 2022, Black and African American males accounted for 77% of HIV cases among all Black and African American persons, with 80% being attributed to male-to-male sexual contact [1]. The severity of the HIV toll among Black sexual minority men is especially evident in the Southern United States, including Atlanta, Georgia; counties in the Atlanta area make up 4 of the 48 designated high-priority jurisdictions in the national Ending the HIV Epidemic initiative [2]. Young Black sexual minority men are additionally disproportionately affected by HIV; additional 2022 surveillance data indicate that individuals aged 25-34 years accounted for 40% of all new HIV cases, and 43% of new cases attributed to male-to-male sexual contact among Black males in the United States [1]. Moreover, this same report states that Black males aged 13-24 years accounted for 49% of cases among all male-to-male sexual contact [1].

Exacerbating these existing inequities, young Black sexual minority men are observed to experience lower rates of engagement along all stages of the HIV Continuum of Care (HIV-CoC) compared with other groups [3]. The HIV-CoC is a framework outlining the steps a person living with HIV follows and consists of the following stages: HIV testing and diagnosis, linkage to HIV care, retention in HIV care, antiretroviral medication adherence, and achievement and maintenance of viral suppression [4]. Young Black sexual minority men's ability to successfully navigate the HIV-CoC is further complicated by broader, systemic factors at play. Structural racism and discrimination (including heterosexism and HIV stigma) create barriers to engagement across the HIV-CoC for young Black sexual minority men [5,6]. Specifically, HIV stigma within and outside of health care settings, logistical barriers such as insurance and transportation, and racism and discrimination that impact patient-provider relationships can all lead to decreased engagement of young Black sexual minority men across the HIV-CoC [7-10]. Social and environmental features of the Southern United States (eg, restricted Medicaid expansion, health care provider shortages, low health literacy, and higher community levels of stigma) can further impede young Black sexual minority men's abilities to realize optimal health and lead fulfilling lives [11]. Despite the existing social and structural factors working against them, many young Black sexual minority men living with HIV overcome these existing barriers and are able to successfully engage in HIV care. Enhancing these resilience processes, or successful coping despite adversity, represents an important target for interventions to support young Black sexual minority men living with HIV.

The Original (In Person) B6 Intervention Overview

Brothers Building Brothers by Breaking Barriers (B6) was created as an intervention to support resilience and ultimately improve engagement in HIV care for young Black sexual minority men living with HIV in Atlanta, Georgia [12]. The goal of B6 was to improve resilience processes by building social capital among participants [12]. The foundation of B6 was built to reflect an individual and network-level conceptualization of social capital, which is defined as the sum of benefits that can be derived from a person's resource-containing, reciprocal, and trustworthy social network connections [13].

B6 was initially developed in 2017-2018 in Atlanta, Georgia, using principles of community-based participatory research, with input from young Black sexual minority men and community leaders throughout the intervention creation process [12]. However, we encountered significant challenges with recruitment and enrollment in our initial trial of B6 as an in-person intervention; many participants who agreed to join B6 did not ultimately attend the group intervention sessions despite multiple reminders and incentives [14]. We also received feedback that participants would prefer shorter sessions over a longer period. As such, the goal of this study is to adapt B6 to telehealth delivery using a videoconference platform (Zoom; Zoom Video Communications, Inc) to suit a post–COVID-19 environment, and to address transportation and other logistical barriers. This paper describes the adaptation and evaluation protocol for the new, telehealth version of B6 (Tele-B6).

Theoretical Foundation

B6 is grounded in intersectionality, minority stress, social capital, and resilience concepts. Young Black sexual minority men living with HIV are in a unique societal position to simultaneously experience multiple intersecting layers of oppression and discrimination due to racism, heterosexism, and HIV stigma [15-17]. These external experiences with intersectional stigma and discrimination [18,19] decrease young Black sexual minority men's access to power and are manifested in a range of socio-structural barriers (eg, poverty, incarceration, and exposure to violence) that fuel disparities across the HIV-CoC for young Black sexual minority men [20-22]. In addition to logistical and material challenges stemming from these intersecting social and structural barriers, additional adverse effects are experienced through psychological consequences of such discrimination, known as minority stress. The minority stress model posits that exposure to general stressors coupled with persistent stress stemming from prejudice, stigma, and discrimination places sexual minority individuals at increased risk for negative physical and mental health outcomes [23]. Minority stress can also be experienced intrapersonally through internalization of oppressive messaging, as illustrated by research documenting associations between internalized homonegativity, low self-esteem, and mental health

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comorbidities [24-26]. Psychological distress, including that resulting from minority stress and intersectional stigma, is in turn detrimental to HIV care engagement [9,27-30]. These foundational theoretical relationships are depicted in our study's conceptual model (Figure 1).

Figure 1. Study's conceptual model of theoretical relationships.

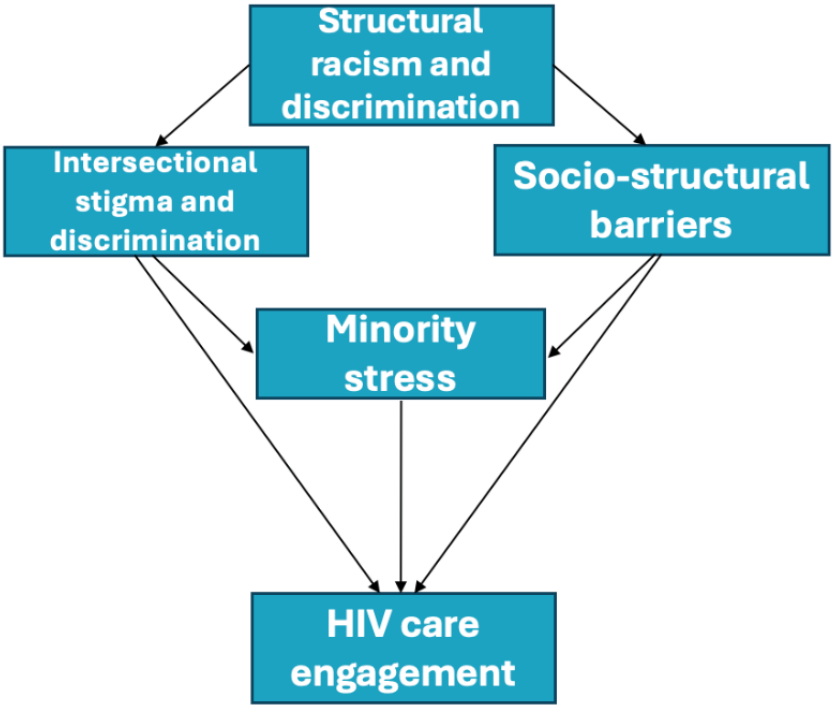

Despite facing the multitude of barriers listed above, young Black sexual minority men living with HIV can and often do thrive [31,32]. Reorienting research to focus on this positive adaptation despite adversity [33,34], or resilience processes (a dynamic process in which individuals engage to positively adapt to adversity by using their assets and resources), represents a strength-based approach to address public health problems. The development of resilience plays an important role in buffering minority stress, including: (1) individual-level resilience processes, consisting of personality traits, and beliefs that help one cope with stress; and (2) community resilience processes, through which sexual minority communities provide social resources to facilitate coping amongst their members [35,36]. Many scholars have called for resilience-focused perspectives on understanding the health of sexual minority men [37-39]. However, although several studies describe resilience processes among young Black sexual minority men in the face of systemic oppression [32,40-45], few interventions specifically focus on building resilience processes as a strategy for enhancing HIV care engagement in this population [5]. Resilience is comprised of specific processes, which can serve as intervention targets: here, we focus on identity affirmation as an individual-level resilience process, and social capital as a community-level resilience process. As previously mentioned, these intervention targets also support our efforts to embrace a strengths-based approach, via undermining the influence of prime harmful manifestations of minority stress, such as practicing identity concealment and having poor social capital, both of which have been well demonstrated and observed amongst young Black sexual minority men.

Identity Affirmation

Affirming beliefs about identity are important to individual-level resilience for racial and sexual minority youth. Positive beliefs about one's racial identity (including the centrality of race to one's self-concept, and the perception of how one's race is viewed by others) are well-established contributors to resilience processes among Black youth [46,47]. The importance of affirming racial identity has been demonstrated among young Black sexual minority men, for whom positive racial identity beliefs have been shown to decrease risky sexual behavior [48]. In a qualitative study of young sexual minority men living with HIV (n=31/54, 57% Black), Harper et al [31] identified positive affirmation of racial and sexual orientation identity as key resilience processes. Moreover, 2 additional studies that also had a geographically diverse sample of youth, which were predominantly and all Black youth, respectively, revealed that youth who endorsed positive views of their racial identity reported fewer missed HIV care appointments; while those with higher levels of internalized homonegativity and HIV stigma missed more appointments [49,50]. Identity affirmation also facilitates access to community-level resilience resources; one must embrace their identity to connect with resources within a given minority community (eg, acknowledging one's own gay identity or HIV status as a prerequisite to access lesbian, gay, bisexual, and transgender or HIV-focused organizations) [36].

Social Capital

Social capital is a community-level resilience factor with potential to improve engagement across the HIV-CoC among young Black sexual minority men. Social capital can be defined as the sum of an individual's resource-containing, reciprocal,

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and trustworthy social network connections [13,51] and is comprised of resources derived from social network connections. Social capital can improve HIV-CoC outcomes in several ways. For example, network contacts can educate one another about HIV, provide transportation assistance to appointments, and endorse health-promoting norms [52-56]. In a cross-sectional survey study, we previously demonstrated that social capital moderates the effect of depression on viral load suppression among young Black sexual minority men [57]. Others have similarly elucidated a buffering role of social capital in helping people cope with HIV stigma [53,58]. Poverty, trauma, mental health comorbidities, and structural racism can restrict young Black sexual minority men's networks and social capital accumulation [58,59]. At the same time, unique community networks are well-described among young Black sexual minority men (eg, house and ball communities natural mentoring relationships), and can provide social capital to overcome logistical barriers to care [32,60-62].

Study Objectives

The overall objective of this study is to adapt and pilot Tele-B6 as a strategy for enhancing feasibility and scalability before a larger efficacy trial. We seek to accomplish this objective via two specific aims: (1) to adapt B6 for telehealth delivery, in collaboration with young Black sexual minority men, community partners, and an advisory panel of subject matter experts; and (2) to conduct a pilot randomized controlled trial to evaluate feasibility, acceptability, and safety of the Tele-B6 intervention among young Black sexual minority men living with HIV in Atlanta.

Methods

Study Design

The current study will be completed in two phases. Phase 1, or the adaptation process of B6, has been completed. We used Wingood's and DiClemente's assessment, decision, adaptation, production, topical experts, integration, training, and testing (ADAPT-ITT) framework to inform and guide the adaptation process [63]. During this phase, the original B6 intervention was adapted for telehealth delivery, having incorporated feedback from the Youth Advisory Board (YAB) and other lessons learned from the original, in-person iteration of B6. Phase 2, the waitlist control pilot trial, has been completed. This study was conducted in line with SPIRIT (Standard Protocol Items: Recommendations for Interventional Trials) guidelines (checklist provided in Multimedia Appendix 1).

Phase 1: Adaptation Process for Telehealth Delivery

The ADAPT-ITT framework outlines a prescriptive method for adapting evidence-based interventions for new populations, including assessment, decision, adaptation, production, topical experts, integration, training, and testing. However, in the context of Tele-B6, the study setting and delivery method will change, while the target population remains unchanged (ie, young Black sexual minority men). We therefore used ADAPT-ITT as a more general guide to the adaptation of B6 into the current, telehealth version (Tele-B6), and focused our efforts on the later stages of the model (adaptation, production, topical experts, integration, training, and testing).

Adaptation and production: first, a team including research staff (2 young Black sexual minority men who cocreated the original B6 intervention and facilitated intervention sessions), the principal investigator, and a YAB member reviewed the manual closely and marked activities for deletion and consolidation or modification for the telehealth format. This subteam brainstormed potential modifications to each activity and drafted a new intervention manual for Tele-B6.

Topical experts: next, we convened the entire study team in person for a 2-day meeting, including additional study staff, investigators, and YAB members. We reviewed each activity and planned modifications in depth; thereafter, we tested new activities, and solicited feedback and ideas for any further modifications needed.

Integration, training, and testing: feedback from the 2-day full team meeting was integrated into a final manual. Supporting materials (eg, Microsoft PowerPoint presentations, worksheets, and websites) were developed and edited by the team. Next, we convened a group of Black sexual minority men through a community partner organization and conducted an initial pilot using videoconference. Feedback was solicited through a brief survey and additional modifications to procedures were made, resulting in the final Tele-B6 intervention. Finally, the 3 facilitators, all of whom identify as Black and gay persons, were prepared to lead weekly sessions by undergoing extensive training in group dynamics, which involved honing their active listening, conflict resolution, and interpersonal communication skills. Facilitators also familiarized themselves with the various features and functions of the Zoom platform to ensure they could navigate the platform as needed to conduct the intervention sessions and troubleshoot any technical issues that may arise.

Tele-B6 Intervention Description

Tele-B6 consists of weekly synchronous sessions, averaging 1-2 hours in length, in which young Black sexual minority men living with HIV engage in group discussions and activities via videoconference. Additional offline "homework" activities are also provided for participants to complete between sessions. Table 1 provides detailed information regarding Timing, Target constructs, Module title (in original B6), Module goals, and adaptations made for Tele-B6.

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Table 1. Intervention content with adaptations from original in-person Brothers Building Brothers by Breaking Barriers to Telehealth Brothers Building Brothers by Breaking Barriers.

Timing and target constructs	Module title (in original B6[a])	Module goals	Adaptations made for Tele-B6[b]
Week 1: Introductions			
	Set the stage	Introduce facilitators and participants, set expectations and create a safe space	Created a welcome video outlining the intervention's ground rules and expectations; conduct an icebreaker via Zoom
Social capital	Introduction to social capital	Explain the theoretical foundation of the intervention to participants	Updated original social capital presentation and supplemented with a humorous and engaging video to reinforce didactic material
Identity affirmation	Who am I? Multiple identities	Identify the ways in which multiple identities (eg, gay identity, Black identity, HIV-positive identity) interact	Converted to telehealth group discussion; treat activity as "homework"[c]; created an example video to share with participants; and provided activity specific supplies in enrollment bag
Week 2: Exploring self			
Social capital	Breaking communication barriers	Reflect on personal communication styles and any barriers to effective communication	Moved activity to Week 3; converted to telehealth group discussion
Coping with minority stress	Critical self-reflection and coping skills	Reflect on how individual actions impact others; discuss common stressors and positive coping strategies	Converted to telehealth group discussion; divided participants into breakout rooms to afford robust discussion; and reinforce new skills
Week 3: Building bonds			
Identity affirmation	Black gay slay: a history	Gain appreciation for the historical contributions of Black gay men in society	Moved this activity to Week 4; updated original "Black Gay Slay" presentation and B6 Jeopardy; emailed presentation to participants; treated activity (ie, presentation) as "homework"[c]
Social capital	Black gay community	Explore perceptions, stereotypes and diversity within the Black gay community	Moved this activity to Week 4 and convert to telehealth discussion using a Zoom Whiteboard or Microsoft Word document
Week 4: Building bridges part 1[d]			
Social capital	Navigating family	Gain tools to develop healthier relationships with family (birth or choice)	Converted to telehealth group discussion using a Zoom Whiteboard or Microsoft Word document
Coping with racism and discrimination	Navigating professional spaces	Build skills for succeeding in professional arenas and cultivating relationships with colleagues and supervisors	Moved activity to Week 2; converted to telehealth group discussion
Week 5: Building bridges part 2[d]			
Coping with racism and discrimination	Navigating clinical spaces	Enhance skills for navigating health care settings, share strategies for communicating effectively with providers	Converted to telehealth group discussion using a Zoom Whiteboard or Microsoft Word document
Social capital	Navigating intimate relationships	Reflect on intimate relationships; learn strategies to improve partner communication.	Divided content between Weeks 2 and 3; converted to telehealth group discussion
Week 5: Sustaining connections[e]			

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Timing and target constructs	Module title (in original B6[a])	Module goals	Adaptations made for Tele-B6[b]
Individual resilience	Individual goal setting	Set short and long-term goals for career, relationships, health.	Converted to telehealth group discussion using a Zoom Whiteboard or Microsoft Word document
Social capital	Community action	Learn strategies for activism and formulate community action plans.	Converted to telehealth group discussion using a Zoom Whiteboard or Microsoft Word document
	Conclusions	Closing ceremony, distribution of a compilation of community resources	Distributed compilation of resources during enrollment visit; provided in participant manual

[a]B6: Brothers Building Brothers by Breaking Barriers.

[b]Tele-B6: Telehealth Brothers Building Brothers by Breaking Barriers.

[c]An activity treated as "homework" means that the activity was introduced to participants at the end of a session and later discussed the subsequent session.

[d]"Building bridges" material is covered in 2 weeks—weeks 4 and 5.

[e]"Sustaining connections" material is also covered in week 5.

Phase 2: Randomized Waitlist Control Trial

Phase 2 is a waitlist control trial of Tele-B6 with 60 young Black sexual minority men living with HIV. The waitlist control design was chosen because it offers an effective way to reconcile the need to have a control group while still ensuring all participants receive the intervention, to help maximize participants' opportunities to reap potential study-associated benefits [64,65]. Following the enrollment visit, participants were randomized to either the immediate intervention (in which participants received the intervention within 2 weeks of their enrollment visit), or a delayed intervention (waitlist) condition, in which participants received the intervention 2 weeks after the 5-week program has concluded for the previous cohort of participants. See Figure 2 for the complete Tele-B6 waitlist control study design schedule.

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Figure 2. Telehealth Brothers Building Brothers by Breaking Barriers waitlist control study design schedule. Tele-B6: Telehealth Brothers Building Brothers by Breaking Barriers. T1-4: Time 1-4, at which participants are expected to complete the indicated study activities.

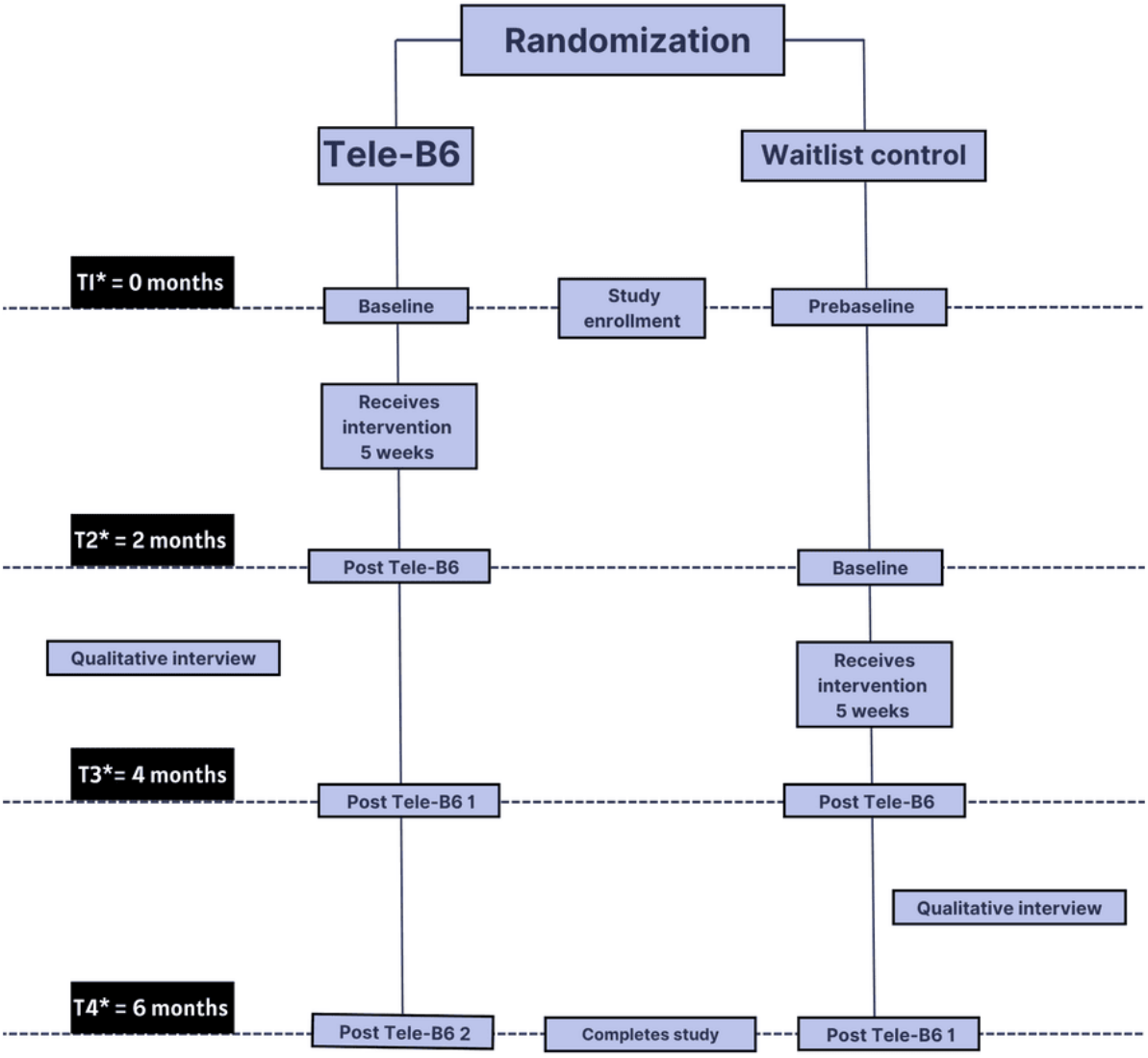

Participants

We recruited 60 participants. Participants completed an electronic screener survey housed in Research Electronic Data Capture (REDCap; Vanderbilt University) [66] to determine study eligibility. Eligible participants self-reported that they meet the following criteria: (1) Black race, inclusive of multiracial identities; (2) male gender identity, inclusive of transgender men; (3) self-identification as gay, bisexual, or nonheterosexual orientation, or any history of consensual anal or oral sex with men; (4) living with HIV; (5) age 18-29 years inclusive; (6) residence in the Atlanta Metropolitan Statistical Area; and (7) available and interested in meeting on the designated day and time over a 5-week period. Ineligible participants were excluded from study participation for the following reasons: (1) not living with HIV; (2) not having reliable internet access; (3) not satisfying the age requirement; and (4) not feeling comfortable participating in the study.

Facilitators and Intervention Staff

The B6 sessions were facilitated by 3 full-time study staff members who identify as Black sexual minority men and thus share social identities with our participants. However, as sexual minority men are not a monolith, having 3 facilitators also allowed us to offer participants different perspectives and lived experiences to connect and identify with, which enhanced the facilitators' rapport-building efforts with the participants. Of the 3 facilitators, one helped to develop and facilitate sessions for the in-person version of B6 (lead facilitator), and all 3 participated in the modifications of the intervention as well. In addition, the lead facilitator conducted trainings to ensure that all 3 were comfortable with procedures, intervention content, and evaluation procedures. Additional study team members joined the intervention sessions to provide technical assistance, and a physician member (who also identifies as a Black sexual minority men) of the study team was available for about half of the sessions to answer health-related questions that might arise, to improve the participants' patient-provider communication skills.

Setting

Enrollment and informed consent occurred in person at either the university or clinic research site. However, the intervention sessions for Tele-B6 were implemented via a secure

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teleconferencing platform (Zoom). The designated facilitators conducted the intervention from an office location on our university campus. The participants joined the intervention from any location of their choosing, and facilitators encouraged participants to join the intervention from a safe space that affords a reasonable level of comfort and privacy, given the sensitivity and nature of topics discussed (eg, experiences with discrimination, HIV serostatus, etc).

Participant recruitment has been completed. Most participants were recruited from a high-volume HIV care clinic located in Atlanta, Georgia. Other participants were recruited from advertisements on geosocial networking apps, from community-based partner organizations, and from venue-based recruitment at community locations frequented by young Black sexual minority men.

B6 Program Materials

During the enrollment visit, participants received a drawstring backpack containing the following items (Figure 3):

1. A journal and pen with the study logo: to be used for "energizer" writing activities that took place at the beginning of certain synchronous sessions.
2. A pack of coloring pencils: this was used for the Mask activity (described below).
3. A pair of headphones: this was used to help afford participants a greater sense of privacy, if necessary.
4. A battery pack: this was used to help participants to keep their devices charged while participating in the program.
5. A participant manual: this folder contained a collection of handouts, worksheets, and activities necessary to complete the program, along with listings of resources and supports aimed to assist participants meet their immediate needs (eg, currently experiencing housing and food insecurity)
6. A ClinCard: participants were compensated for completion of activities, surveys, and weekly session attendance via a reloadable debit card.

In addition to the drawstring backpack, participants were granted access to a university-affiliated, auxiliary website (managed by the facilitators) to offer another point of access to the intervention materials. By making the intervention materials available electronically, we hoped this effort would at least minimize a barrier that could restrict participant engagement (ie, not having intervention materials readily available for the weekly synchronous sessions).

Figure 3. Telehealth Brothers Building Brothers by Breaking Barriers enrollment bag and program materials.

Data Collection and Evaluation

We used a mixed methods approach to evaluate our intervention and assess our primary and exploratory outcomes**.** Data sources include an intervention log, adverse event reports, periodic electronic surveys, qualitative exit interviews, and EMR data. All data is housed in a secure location, with access to this data limited to our research team members. See Table 2 for a detailed outline of our mixed methods evaluation plan.

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Table 2. Mixed methods evaluation plan.

Outcomes, constructs, and assessment strategy	Measures (where applicable)	Timing
Primary outcomes		
Acceptability		
Qualitative interviews	• Open-ended questions adapted from original B6a exit interview guide	Exit interviews
Surveys	• Postsession eval forms (adapted from original B6)	After each group session
Feasibility		
Recruitment rates	• Rates of participation from screened and eligible participants	Continuous
Retention	• Attendance logs	Continuous
Intervention fidelity	• Structured intervention log (adapted from original B6)	Continuous
Safety		
Adverse events	• Adverse event tracking forms	Continuous
Model constructs		
Structural racism and discrimination		
Surveys	• Measures of socioeconomic status, demographics • Material resources scale [67]	0, 2, 4, 6 months
Intersectional stigma and discrimination		
Surveys	• Everyday Discrimination Scale [68] • HIV Stigma Scale - 12 (HSS-12) [69]	0, 2, 4, 6 months
Qualitative interviews	• Open-ended questions adapted from original B6 exit interview guide	Exit interviews
Socio-structural barriers		
Surveys	• Zip code to derive neighborhood measures	0, 2, 4, 6 months
Qualitative interviews	• Open-ended questions adapted from original B6 exit interview guide	Exit interviews
Individual resilience process: identity affirmation		
Surveys	• Multidimensional Model of Black Identity [70] • Lesbian, Gay and Bisexual Identity Scale [71] • Identification and Involvement with Gay Community (IGCS) [72]	0, 2, 4, 6 months
Qualitative interviews	• Open-ended questions adapted from original B6 exit interview guide	Exit interviews
Community resilience process: social capital		
Surveys	• Personal Social Capital Scale [51] • Social Capital Investment Inventory (SCII) [73] • Social Network Scale [74]	0, 2, 4, 6 months
Qualitative interviews	• Open-ended questions adapted from original B6 exit interview guide	Exit interviews
Minority stress		

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Outcomes, constructs, and assessment strategy	Measures (where applicable)	Timing
Surveys	• Mental health measures including: • Depression (CESD-R) [75] • General Well-Being (GWB) • Generalized Anxiety Disorder-7 (GAD-7) [76] • Post-Traumatic Stress Disorder (PTSD) Checklist [77]	0, 2, 4, 6 months
Qualitative interviews	• Open-ended questions adapted from original B6 exit interview guide	Exit interviews
Clinical outcomes		
HIV care engagement		
Electronic medical record (EMR) abstraction	• HIV viral load • Retention in Care (missed visits)	0 and 6 months
Surveys	• Index of engagement in HIV care [78]	0, 2, 4, 6 months

[a]B6: Brothers Building Brothers by Breaking Barriers.

Primary Outcomes: Acceptability, Feasibility, and Safety

To assess acceptability, we created intervention satisfaction evaluation surveys and administered them at the end of each weekly group discussion. We also assessed acceptability using data on participants' reactions to various program components gathered from the facilitators' intervention log. Finally, we conducted exit interviews with selected participants at the end of the 5-week intervention period to gather qualitative feedback about the structure, content, and experience of the intervention. To assess feasibility, we monitored rates of outreach, recruitment, eligibility, enrollment, attendance, retention, and assessment completion. Our goals were to achieve intervention completion rates of >80% of group sessions completed, to maintain high intervention fidelity (goal>90% fidelity on checklists), and to ensure adequate retention across the follow-up surveys (goal>80%). Fidelity assessments were also an important part of feasibility assessments: Tele-B6 facilitators completed a structured intervention log after each session to assess fidelity to intervention, time needed, and feasibility of delivering the intervention curriculum as designed. To assess safety, we monitored adverse events, including psychological or physical events occurring over the course of intervention participation.

Exploratory Outcomes

Although the primary aims of this study were to assess acceptability and feasibility, we also assessed HIV-CoC outcomes, as well as key mediators that are being targeted in Tele-B6. The selection of measures was guided by the relevant literature, our preliminary studies, and the conceptual model depicted in Figure 1.

Our eventual target outcome (in our subsequent, fully-powered study), HIV Care Engagement will be measured in terms of viral load suppression (defined as viral load measurement below 200 copies/mL at the most recent measurement before baseline, and at a data abstraction point at least 6 months post enrollment) and retention in HIV care, measured by missed visits before and after intervention participation.

Missed visits are a validated measure of retention [79]; additionally, we were not able to use the Department of Health and Human Services (DHHS) retention measure (>2 visits in 12 months, at least 3 months apart) [80] due to the limited follow-up period.

Data Collection Procedures: Surveys

We used previously validated scales with excellent documented reliability among our study population to measure key constructs in our conceptual model (structural racism and discrimination, socio-structural barriers, intersectional stigma and discrimination, and minority stress) and the resilience processes (identity affirmation and social capital) targeted in Tele-B6. We used REDCap to create and administer baseline and follow-up surveys of participants. Surveys will be administered at baseline, 2-, 4-, 6-month timepoints as outlined above. Reminders to complete surveys were sent via text message and email where needed.

Survey Procedures: surveys were self-administered by the participants remotely. We estimated that the surveys take 30 minutes to complete. Upon completion of each survey, respondents received US $25 via a reloadable debit card (ie, ClinCard).

Data Collection Procedures: Qualitative Interviews

To evaluate Tele-B6 feasibility and acceptability, as well as descriptive accounts of any impact on resilience processes and conceptual model constructs, we conducted qualitative exit interviews with a subset of participants (planned n=24 interviews). We conducted these in-depth interviews (IDIs) with a purposively selected sample of participants, including both participants who maintained high levels of engagement and those with lower levels of engagement. IDIs focused on experiences with the B6 intervention and recommended improvements. IDIs were conducted via Zoom by a trained study staff member who did not directly participate in the weekly sessions, in order to provide space for criticism if needed. Participants received an additional US $25 upon completion. All interviews were digitally recorded and uploaded to a secure server for professional transcription and analysis.

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The interviewer recorded field notes, documented salient themes to be discussed with the larger group, and explored in subsequent IDIs.

Data Collection Procedures: Facilitator Evaluations and Intervention Log

Following each weekly session, facilitators evaluated the performances of fellow cofacilitators and themselves on standard postsession evaluation forms. This data were used to help facilitators identify improvement opportunities (eg, identifying technologically savvier approaches to deliver intervention material) and acknowledge their existing strengths (eg, having facilitators who have similar shared experiences as the participants helps build trust more easily among participants). All facilitator session evaluation data were logged onto a spreadsheet and housed with study-related data. In addition, an intervention log was maintained to track changes while still ensuring intervention fidelity.

Data Collection Procedures: Clinical EMR Data Abstraction

To measure preliminary efficacy of Tele-B6 for improving engagement in care (defined using exploratory endpoints of care retention and viral suppression), we will abstract clinical data from the EMR. We will compare retention and viral suppression outcomes pre– and post–Tele-B6 and compare the intervention and control groups. At baseline and 6 months later, we will abstract viral load measurements as well as missed, scheduled, and attended appointments. Data will be entered into a secure REDCap database by trained abstractors (graduate research assistants), using standardized abstraction forms and manuals [81]. For the first 3 months of abstraction, EMR data will be abstracted by 2 study team members in parallel and examined for intercoder reliability. Differences will be discussed, and forms and manuals revised until intercoder reliability is adequate ($\kappa > 0.80$).

Statistical Analysis

Our primary outcome is focused on descriptive analyses of the acceptability, feasibility, and safety indices. We will assess intervention target outcomes (ie, retention in care and viral suppression), hypothesized mediators (eg, social capital and identity affirmation), and background variables. These measures will be used to assess feasibility and acceptability (eg, acceptability of items and length of time to complete surveys) of data collection.

Acceptability, Feasibility, and Safety

To evaluate the acceptability of the intervention, quantitative analyses of the intervention data will be descriptive and concentrate on tabulating and summarizing postsession satisfaction survey measures that feature both closed-ended and open-ended questions. As described below, we will also qualitatively analyze exit interviews conducted to assess acceptability and to identify any necessary modifications needed before a full trial. To evaluate the feasibility of the intervention, we monitored rates of recruitment and effort required (eg, number of staff hours), number of screenings conducted, and proportion eligible and agreed to enroll. We recorded the number of rescheduled, cancelled and missed sessions and assessment visits to inform estimation of staffing needs and retention protocols for a subsequent full trial. We will also assess the feasibility of verifying retention in care and viral load data by obtaining releases from participants to contact their provider or clinic by monitoring rates of verifiable EMR reports. To assess safety, we planned to tabulate and describe any reported adverse events that occurred during study participation; there were none.

Qualitative Analysis

Exit interviews were digitally recorded, deidentified, and transcribed verbatim. To support rigorous and reproducible qualitative analysis, we will practice team coding and analysis using a pragmatic thematic analysis approach [82]. Analytic steps will include (1) after each interview, interviewers will document field notes including emerging topic areas for subsequent exploration; (2) transcripts will be entered into MAXQDA (VERBI Software GmbH) qualitative software for coding and organizing data [83]; (3) we will develop a preliminary codebook to include predetermined deductive codes related to theoretical domains of interest (eg, constructs from the conceptual model) and inductive codes that emerge from the data; (4) analysts will code a subset of transcripts and compare coding, with differences discussed in team meetings until consensus is reached; (5) similarities and differences across transcripts will be examined, and codes and themes revised accordingly. We will cease developing new codes when no new themes are seen; and (6) properties and dimensions of salient themes will be summarized and interpreted in detailed analytic memos ("thick descriptions").

Ethical Considerations

All Tele-B6 procedures discussed in this protocol were reviewed and approved by Emory University's Institutional Review Board (IRB IRB00104876) and the Grady Research Oversight Committee. Eligible study participants provided informed consent to participate in this study and provided consent for study staff to access their electronic medical records (EMR) to corroborate data analyses. For security and confidentiality purposes, study data were deidentified and entered in REDCap, a Health Insurance Portability and Accountability Act (HIPAA) compliant data collection tool. During the enrollment visit, participants were informed that participation is voluntary and can withdraw from the study whenever requested. Also, throughout the duration of the study, participants were reminded of their ability to opt out of the study. Participant payments were deemed appropriate and fair by our local IRB. Participants were compensated via ClinCard (an automated and secure payment method for research participants); participants received US $50 for the enrollment visit, US $25 for each weekly synchronous session attended; US $25 for each follow-up survey; and US $25 for the optional qualitative interview.

Results

Phase 1, the adaptation process of B6, began in fall 2022 and was completed in spring 2023. Phase 2, the implementation of the waitlist-controlled trial, began in spring 2023 and is still underway; delivery of Tele-B6 will conclude in summer 2024. Final results are expected in winter 2025 (Figure 4) [84].

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Figure 4. CONSORT (Consolidated Standards of Reporting Trials) flow diagram of study participants' progress through each phase of a 2-arm randomized controlled trial.

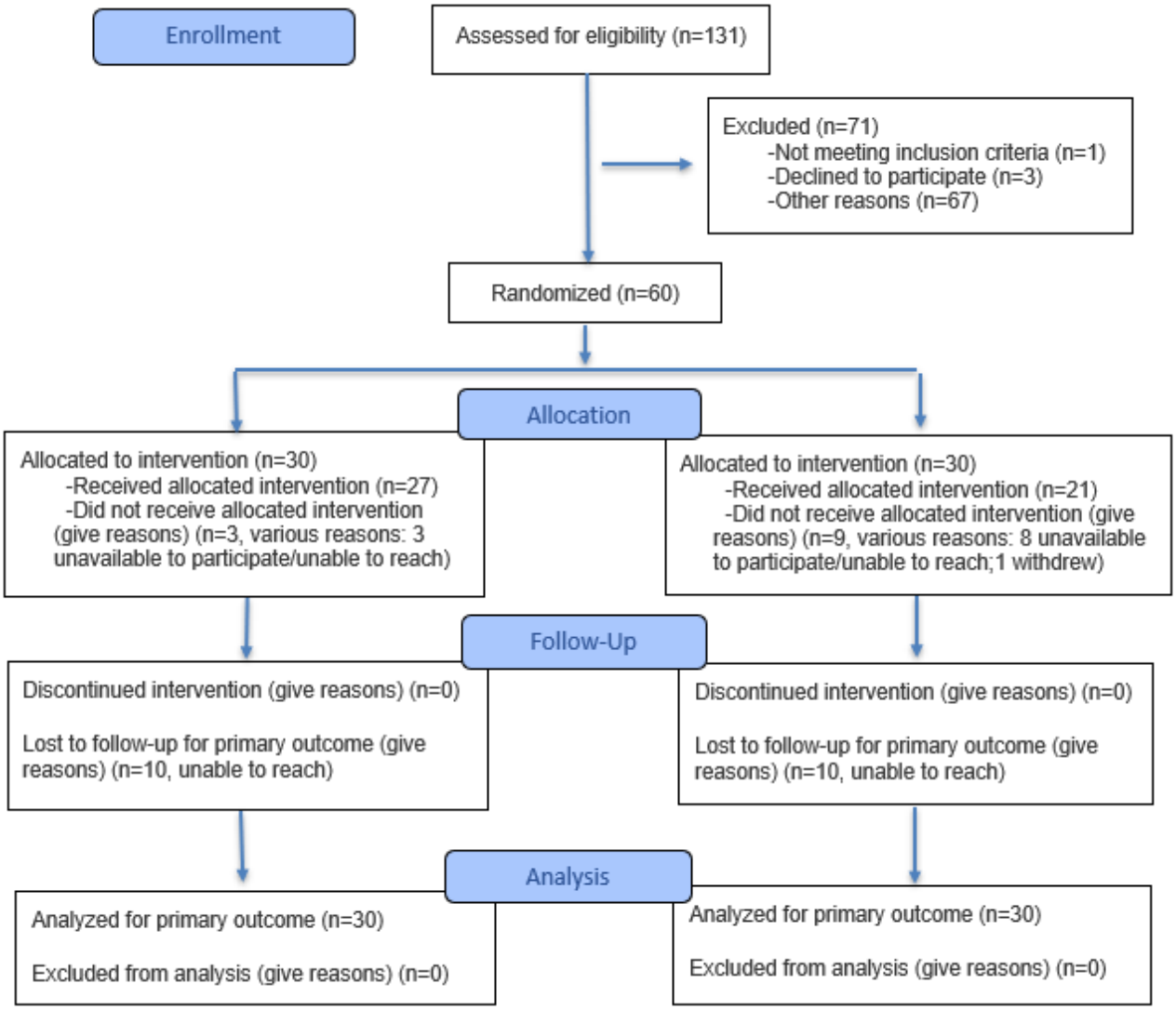

Discussion

Principal Findings

Analyses of the feasibility, acceptability, and safety of the Tele-B6 program are currently underway. Our hypothesis is that Tele-B6 will demonstrate greater feasibility, and at least equivalent acceptability and safety, compared with the in-person version of the intervention. We further hypothesize that our procedures for measuring constructs of interest (eg, social capital and general well-being) will be acceptable to participants, and that our measures will be valid and reliable in this population. If these hypotheses are correct and the aims are achieved, we will seek to test the efficacy of the intervention through a larger, fully powered randomized controlled trial.

Tele-B6 addresses scientific gaps and answers calls from other scientists to develop resilience-based and culturally aware interventions for young Black sexual minority men. Boyd et al [85] found that external resilience assets (including family support, which is thematically related to social capital) were positively related to HIV-related health behaviors. Chang et al [86] found that young Black sexual minority men gained more from a health promotion intervention with community peers if discrimination was explicitly addressed, providing support for our culturally targeted, intersectional approach. Harper et al [87] similarly found promising preliminary results in decreasing sexual risk behavior in a pilot of a critical consciousness-based intervention, with explicit cultural and developmental tailoring, for young Black sexual minority men living with HIV. Tele-B6 has the potential to add to this small but growing toolbox of strategies designed specifically for and with young Black sexual minority men, as an effort towards ending the HIV epidemic.

There is a paucity of research dedicated to recognizing and addressing the social capital needs of young Black sexual minority men living with HIV. Such efforts are critically needed considering the pervasive barriers impeding HIV care engagement for young Black sexual minority men, and suboptimal engagement levels throughout the HIV-CoC. To this end, the adaptation process and implementation of Tele-B6 adds to the limited research of interventions centering resilience building and identity affirmation to enhance HIV-CoC engagement levels among young Black sexual minority men

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living with HIV in a post-COVID-19 context. Upon analyzing our data, we will plan to disseminate results to the larger scientific community (eg, through conference presentations and scientific manuscripts), as well as to our local community and study participants through in-person and webinar-based presentations.

Conclusions

We have developed a remotely delivered version of a culturally tailored intervention, Tele-B6, which is designed to enhance the unique strengths of young Black sexual minority men who are living with HIV. Next steps will include mixed methods analysis to assess feasibility, acceptability, and safety. If our intervention meets these goals, we will seek to conduct a larger trial to test efficacy for improving mental health outcomes and engagement in medical care.

Acknowledgments

We are grateful to our community collaborators and YAB for their input into the intervention development process. We are also grateful for the participants and their contributions to this study. This study was funded by the National Institute of Mental Health (NIH/NIMH; grant R34 MH129187) and supported by the Emory Center for AIDS Research (P30 AI050409).

Data Availability

Data are available upon request. Data access is restricted to safeguard sensitive participant information.

Authors' Contributions

MOR, MB, ANJ, SD, SCOO, TT, KD, ACG, RM, KG, GWH, and SAH performed conceptualization and methodology. MOR, MB, and ANJ handled project administration. ACG, KG, GWH, and SAH contributed to funding acquisition, investigation, and supervision. MOR wrote the original draft. All authors contributed to writing – review and editing.

Conflicts of Interest

None declared.

Multimedia Appendix 1
SPIRIT 2025 checklist.
[PDF File (Adobe PDF File), 192 KB - resprot_v14i1e69961_app1.pdf]

Multimedia Appendix 2
Peer review report from the HIBI HIV/AIDS Intra- and Interpersonal Determinants and Behavioral Interventions Study Section, Risk, Prevention and Health Behavior Integrated Review Group (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 153 KB - resprot_v14i1e69961_app2.pdf]

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Abbreviations

ADAPT-ITT: assessment, decision, adaptation, production, topical experts, integration, training and testing
B6: Brothers Building Brothers by Breaking Barriers
DHHS: Department of Health and Human Services
EMR: electronic medical record
HIPAA: Health Insurance Portability and Accountability Act
HIV-CoC: HIV Continuum of Care
IDI: in-depth interview
REDCap: Research Electronic Data Capture
SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials
YAB: Youth Advisory Board

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Protocol

Optimizing an App-Based Just-in-Time Adaptive Intervention for Stimulant Use Among Sexual Minority Men Living with HIV: Protocol for a Community-Engaged Research Approach and Hybrid-Experimental Design

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Abstract

Background: In the United States, sexual minority men (SMM) are disproportionately affected by HIV. For this population, intersecting sexual minority– and HIV-related stressors add to general life stress, increasing health risks. Stress is associated with HIV progression and is linked to transmission risk behaviors, such as medication nonadherence and substance use. Substance use is a particularly important risk factor for HIV transmission; beyond injection drug use, recreational use is associated with sexual transmission risk behaviors and an increased risk of HIV among SMM. Interventions targeting stress responses may be especially useful for HIV risk reduction among substance-using SMM (SUSMM) living with HIV (LWH). Positive affect interventions have shown promise in reducing stress in the context of chronic illness, including HIV. However, few studies have examined these interventions and their potential health benefits for SUSMM-LWH.

Objective: This protocol describes a project (R34DA053999) that builds on our pilot work exploring the induction of positive affect as a potential intervention to reduce stress and improve health outcomes among SMM-LWH. This protocol aims to employ a community-engaged research approach, using the multiphase optimization strategy, to iteratively tailor our app-based positive affect intervention, TeaTime, for SUSMM-LWH.

Methods: In phase 1, we enrolled 10 SUSMM-LWH into an open-phase pilot using our existing app-based ecological momentary intervention (EMI), which employs a just-in-time adaptive intervention design. We collaborated with a community advisory board to tailor our intervention content and app design using focus group feedback. In phase 2, we conducted a pilot factorial optimization trial to assess the acceptability and feasibility of adding 2 new features that may enhance intervention design and delivery. Specifically, we piloted a 2×2 factorial design, randomizing 80 SUSMM-LWH to receive either (1) random craving prompts or (2) smartwatch integration or both or neither. Analyses will examine group differences on feasibility and acceptability outcomes, as measured by the System Usability Scale and Mobile App Rating Scale, as well as retention and engagement.

Results: The project was funded in February 2022, and data collection for phase 1 was completed in December 2023. Phase 2 was launched in July 2024, with data collection completed by August 2025. Results from phase 1 are expected to be submitted for publication by December 2025.

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Conclusions: In this protocol, we combine methods from social science, intervention science, and software development into a single innovative approach to enhance and optimize an app-based, just-in-time adaptive, EMI for SUSMM-LWH. Findings from this study will support the development of a fully optimized intervention ready for evaluation and implementation. In a future randomized controlled trial, the ecological momentary assessment design will also enable the collection of day-level data on intervention efficacy.

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KEYWORDS

mHealth; EMA; just-in-time adaptive intervention; ecological momentary intervention; ecological momentary assessment; HIV; substance use disorder; stress; behavior change; mHealth

Introduction

Background

In the United States, gay, bisexual, and other sexual minority men (SMM) are disproportionately affected by HIV compared with the general population [1]. For SMM living with HIV (LWH), intersectional sexual minority and HIV-related stress add to general life stressors, increasing health risks [2,3]. Intersectional minority stress also includes experiences of discrimination among racial and ethnic minorities [4,5], who represent a majority of the SMM-LWH population [6,7]. Because of the cumulative impact of these intersecting stressors, SMM-LWH experience significant health disparities compared with the general population [8-10]. The "cumulative stress" hypothesis asserts that chronic and acute stressors in later life have an additive impact on vulnerabilities already programmed by early life adversity [11]. Cumulative stress is hypothesized to result in increased allostatic load, operationalized as a cumulative biological burden leading to poorer health outcomes (eg, HIV progression) [12]. Furthermore, research supports a bidirectional association between psychosocial stress and HIV progression [13].

Stress is not only linked to distal outcomes (eg, HIV progression) [13,14], but is also associated with proximal behavioral outcomes that increase the risk of transmission (eg, medication nonadherence and substance use) [15,16]. Substance use is a predictor of poor HIV medication adherence [17,18], and accordingly, substance-using (SU) individuals LWH are at higher risk for HIV disease progression [19,20]. Substance use is also a particularly important risk factor for HIV transmission, as recreational use is associated with other transmission risk behaviors (TRBs), and injection drug use carries a substantially higher risk of transmission compared with other TRBs. In addition to the risk associated with injection drug use among SMM, studies show that recreational substance use is associated with sexual TRB and an increased likelihood of HIV among SMM [21-23]. As such, interventions targeting stress responses may be particularly useful for HIV risk reduction among SUSMM-LWH.

Stress is also associated with increased substance use cravings [24,25]. Even minor stressful events have been linked to heightened substance use cravings [26]. Ecological momentary assessment (EMA) studies show that daily cravings are strong predictors of subsequent substance use [27,28]. Furthermore, research suggests that cravings may mediate the association between stress and substance use [29]. This may help elucidate findings from prior studies showing a stronger link between cravings and substance use than between stress and substance use [30]. It is also important to note that, in addition to cravings induced by stress, cravings can be cue-induced [31-33]. However, studies comparing stress-related and drug-related cues on cravings have found greater subjective emotional responses and cardiovascular activity under stress-related conditions [33].

Research shows that positive affect buffers against negative stress-related health outcomes [34-36]. Positive affect refers to experiences of positive moods such as joy, interest, and alertness [37], whereas mindfulness is a state of focused, nonjudgmental awareness of one's thoughts, motivations, and behaviors [38]. Positive affect is associated with better outcomes in substance use [39] and HIV-related health [40]. Among individuals LWH, research indicates that positive affect is associated with increased odds of linkage to HIV care and treatment adherence [36]. One study also found that positive affect was linked to a significant decrease in mortality risk related to AIDS [41]. More generally, among people living with a chronic illness, positive affect interventions have shown significant effects in increasing medication adherence [42] and lowering reported stress levels related to diagnosis [43-45]. Positive affect has also been associated with lower levels of substance use [17]. Furthermore, mindfulness is positively correlated with positive affect among SMM-LWH [46].

Description of the Initial Intervention

Moskowitz and colleagues [40,47] developed an integrative positive affect intervention for people experiencing health-related stress. The intervention is based on the revised stress and coping theory [45] and the broaden-and-build theory of positive emotion [48]. These theories describe how positive emotion supports coping and well-being by building social, intellectual, and physical resources. The intervention's content, methods, protocol, and design have been published elsewhere [49]. Findings from a randomized controlled trial (RCT) demonstrate the effectiveness of this integrative intervention for people newly diagnosed with HIV [40]. The results show decreases in intrusive and avoidant thoughts related to HIV, along with increases in positive affect on a day-to-day basis [40]. Findings also indicate that the intervention's effect sizes increase over time [40].

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This intervention was recently tested with SUSMM-LWH [39,50]. Specifically, the study examined the efficacy of Moskowitz's intervention in enhancing contingency management for SMM-LWH who use methamphetamine. The pilot RCT demonstrated the feasibility of administering the intervention with SUSMM-LWH and showed significant increases in positive affect [50]. In the full RCT, participants receiving the intervention exhibited significantly higher levels of mindfulness 3 months postintervention, along with decreases in cravings and self-reported drug use [39]. This work demonstrates the promise of implementing this integrative intervention with SUSMM-LWH and its potential effectiveness in improving substance use outcomes for this population.

While the in-person delivery of this program has been effective in improving health outcomes, there has been increased interest in remote intervention delivery. Moskowitz's intervention has already been tailored for eHealth, web-based delivery [4,51]. In a recent study, the acceptability and feasibility of this web-based version were tested among individuals living with comorbid HIV and depression, and it was found to be both feasible and acceptable for this population [52].

Just-In-Time Adaptive Intervention Ecological Momentary Intervention Development

More recently, our team sought to adapt this intervention for app-based delivery. Evidence demonstrates the feasibility of mobile interventions specifically among SMM-LWH [53]. Such interventions have shown suitability, acceptability, and efficacy among SMM-LWH, as they allow a component of privacy [53]. Mobile apps can also be used to deliver ecological momentary interventions (EMIs), which provide an opportunity to offer in-the-moment support to SUSMM-LWH [54]. EMIs, much like EMAs, are delivered to participants in their daily lives; however, instead of simply collecting data, EMIs also include an intervention component. Further, this intervention content can be triggered based on participant responses to the EMA, and in this way, the delivery of the intervention is tailored to when participants need it the most [54]. This customization of intervention delivery is often referred to as a just-in-time adaptive intervention (JITAI) design.

In our proof-of-concept pilot, we adapted the evidence-based positive affect intervention's web content [40] for mobile app delivery, using an EMI delivery format and JITAI design [55]. Our JITAI EMI included 7 modules designed for positive affect induction (eg, noticing and savoring positive events, acts of kindness, behavioral activation, personal strengths, positive reappraisal, and gratitude). In this pilot, we recruited 22 SMM-LWH to engage with the app over a 90-day period. Within the app, participants had access to "on-demand" (ie, user-initiated) intervention content, allowing them to review the skills at any time. The app also delivered a daily positive message accompanied by an image from a bank of motivational quotes, each referring to one of the intervention skills. Additionally, over the course of the 90-day study, participants received a daily EMA survey that included questions about stress, positive and negative affect, and medication adherence. Depending on their survey responses, participants were randomized (at a 2:1 ratio) to receive either a brief intervention activity or a control message. Specifically, if a participant reported feeling stressed in the EMA, they were randomized to receive 1 of 32 JITAI activities. This procedure was part of the micro-randomized trial (MRT) design, which we also tested in this proof-of-concept pilot study. Selection of the specific JITAI activity to be delivered occurred through a process of further micro-randomization. Once participants were randomized to receive a JITAI activity, they were further randomized, with equal probability (P=.14), to receive an activity from 1 of the 7 modules within the app. After being randomized to a specific module, the intervention activity to be delivered at that moment was randomly selected from a bank of activities within that module. See Figure 1 for a diagram depicting our JITAI design and micro-randomization process in this study. Findings from our proof-of-concept pilot suggest that our app-based JITAI EMI is an acceptable and feasible delivery mode for SMM-LWH [55].

Figure 1. Just-in-time adaptive intervention (JITAI) design for micro-randomization in the proof-of-concept pilot. EMA: ecological momentary assessment.

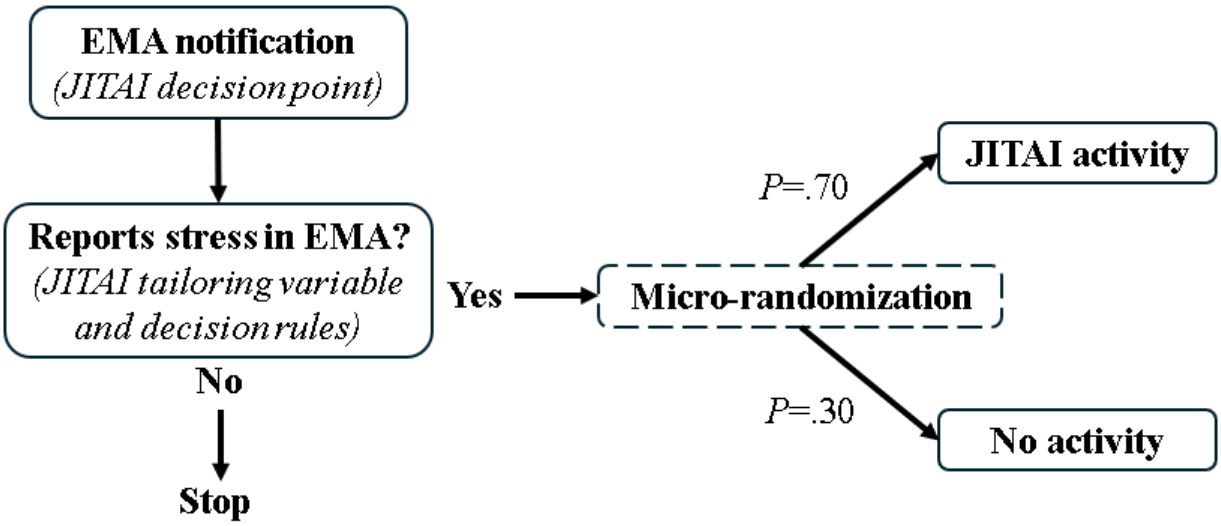

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Objectives

However, we have not yet piloted our app with SUSMM-LWH. Holding an additional marginalized identity (ie, SU) presents unique stressors and additional barriers to intervention [56,57]. For example, individuals with substance use disorders often face stigma and discrimination from health care providers [58]. This added minority stress can have a multiplicative effect when compounded by other marginalized identities (eg, racial and sexual minority status, HIV status). The JITAI EMI design is especially promising for SUSMM-LWH, given their experience of multiple intersecting stressors throughout the day (eg, microaggressions, stigma, discrimination). Further, SUSMM-LWH may benefit from the on-demand and in-the-moment support offered by an app-based JITAI EMI. As such, we aim to tailor our existing intervention content and optimize our JITAI EMI design and delivery to reduce stress and substance use among SUSMM-LWH. We also aim to further enhance our intervention by examining the acceptability and feasibility of adding new features that may improve engagement, as well as refining the app's overall design and delivery.

Methods

Overview of the Study Design

In phase 1, we conducted an open-phase pilot and engaged community members to help tailor our existing app for SUSMM-LWH. In phase 2, we piloted a randomized factorial optimization trial to assess the acceptability and feasibility of adding additional features (ie, smartwatch integration and random craving prompts) to optimize our JITAI EMI's design and delivery. We note that this project was not funded as a clinical trial and was not powered to test intervention outcomes; rather, it was designed as an acceptability and feasibility study. Accordingly, this protocol was not registered on ClinicalTrials.gov. Below, we provide an overview of the overall study design, including common approaches and procedures implemented across both phases. Specifically, we review the guiding framework, training and fidelity protocols, as well as data storage and safety procedures. We also present the eligibility criteria used across both phases. Following this, we have separately detailed the protocol and procedures for each phase. See also the CONSORT (Consolidated Standards of Reporting Trials)-EHEALTH checklist in Multimedia Appendix 1 [59].

Guiding Framework for Intervention Adaptation

Innovative Methodological Framework for Intervention Development

This study adopts a community-engaged research (CEnR) approach that integrates the Scrum Agile framework and the multiphase optimization strategy (MOST), combining methods from social science, intervention science, and software development into a single innovative approach to enhance this app-based intervention.

Community-Engaged Research

CEnR is a research approach that is particularly valuable for addressing health disparities among disadvantaged populations. In this approach, community partners are actively engaged in the research process and treated as equal collaborators throughout. CEnR establishes a partnership between researchers and communities, fostering shared decision-making at all stages of the research. It may involve a community advisory board (CAB) and incorporate feedback from other community members. In this model, the community and researchers work together to jointly explore issues relevant to the community. Such partnerships lead to the development of culturally appropriate measures and community-informed interpretations of study findings.

Scrum Agile Framework

Scrum is a form of Agile methodology used to manage multicomponent software and product development projects [60]. The Scrum model proposes that projects progress through a series of sprints. During a sprint planning meeting, the product is described in terms of the desired outcomes (ie, the features to be developed in the upcoming sprint). At the end of the sprint, these features are tested and integrated into the evolving product.

Multiphase Optimization Strategy

We approach the optimization of our JITAI EMI using the MOST framework, which involves 3 phases: preparation, optimization, and evaluation. Activities in the preparation phase include selecting components (eg, content, design features) that are candidates for inclusion in the intervention, and developing a conceptual model. Pilot testing is an important feature of this stage, including an initial proof-of-concept pilot, an open-phase pilot, and a pilot to test the feasibility of conducting a larger optimization trial. In the optimization phase of MOST, steps are taken to refine the intervention to maximize its effectiveness. This is typically achieved through a factorial optimization trial, a fractional factorial trial, a micro-randomized trial, or a combination of these methods. The MOST framework also operates on the principle of continual optimization. In the evaluation phase, the effectiveness of the optimized intervention is assessed via a standard RCT [61]. This study focused on the first and second phases of MOST (ie, preparation and optimization).

Eligibility Criteria for Phases 1 and 2

Participant Eligibility and Screening

Eligibility criteria were largely consistent across phases 1 and 2. Screening was completed using the participant's own computer or mobile device, with the survey programmed in Qualtrics (Qualtrics International Inc.). The purpose of the assessment was to collect data on self-reported demographics, health status, health behaviors, mental health, and other relevant factors to determine preliminary eligibility for the study.

Inclusion Criteria

To be eligible, individuals must (1) be at least 18 years old; (2) identify as a gay, bisexual, or sexual minority man; (3) be HIV positive; (4) have daily access to the internet via a smartphone; and (5) provide informed consent. Based on the study team's expertise and the existing literature on stimulant use among SMM, inclusion is limited to SMM-LWH reporting stimulant use. Specifically, individuals must report at least five days of

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stimulant use over a 3-month period within the past 12 months. Participants will be excluded if they report using prescription stimulants only (eg, Adderall).

Exclusion Criteria

Participants were excluded if they (1) were unable to complete surveys in English or (2) were currently enrolled in substance use treatment or an intervention study for HIV risk or drug use. The protocol required that any participant who was intoxicated or otherwise unable to provide informed consent be asked to reschedule. In phase 1, we administered the Mini-Mental Status Examination to exclude individuals showing evidence of gross cognitive impairment (ie, score <20), as such issues could compromise their ability to consent and actively participate in the study. Based on participant feedback and consultation with our investigative team, the Mini-Mental Status Examination was omitted in phase 2.

Data Collection and Measurement

Data collection measures were harmonized across phases 1 and 2. For this study, data were collected from 4 primary sources: (1) online screeners and contact surveys, (2) self-reported online surveys, (3) EMA and EMI, and (4) biometric watch data.

Harmonized Measures

Baseline and follow-up measures were harmonized across phases 1 and 2. Quantitative outcome measures for feasibility and acceptability included the System Usability Scale [62], Mobile App Rating Scale [63,64], Modified Computer Self-Efficacy Scale [65], Client Satisfaction Questionnaire-8 [66], and eHealth Acceptability Scale [67]. Additional key measures are outlined in Tables 1 and 2 [68-90].

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Table 1. Measures for the baseline and follow-up assessments (between-person measures).

Variable and between-person measures	Baseline	Follow-up
Demographic		
Age, race/ethnicity, employment, education, income, substance use, relationship status, sexual orientation, and gender	✓	N/A[a]
Stress		
The Perceived Stress Scale [68]	✓	✓
HIV-specific stress		
The HIV/AIDS Stress Scale [69]	✓	✓
Everyday Discrimination Scale (HIV) [70]	✓	✓
The HIV Stigma Scale 12-item [71]	✓	✓
Racial/sexual minority stress		
Internalized Homophobia Scale [72,73]	✓	✓
Everyday Discrimination Scale (sexual orientation, race) [70]	✓	✓
Mindfulness		
Five Facet Mindfulness Questionnaire [74]	✓	✓
The Toronto Mindfulness Scale [75]	✓	✓
Cognitive and Affective Mindfulness Scale Revised [76]	✓	✓
Self-compassion		
Self-Compassion Scale Short-Form [77]	✓	✓
Gratitude		
The Gratitude Questionnaire-6 [78]	✓	✓
Affect		
Positive and Negative Affect Schedule [79]	✓	✓
Substance use		
Drug Abuse Screening Test (DAST) [80]	✓	✓
Shortened Inventory of Problems-Alcohol and Drugs [81]	✓	✓
Depression		
Center for Epidemiologic Studies Depression Scale [82]	✓	✓
Adherence		
Simplified Medication Adherence Questionnaire [83]	✓	✓
Acceptability and feasibility		
System Usability Scale [86]	N/A	✓
Mobile App Rating Scale [88]	N/A	✓

[a]N/A: not applicable (ie, the measure was not administered at that time point).

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Table 2. Measures for the baseline and follow-up assessments (within-person measures).

Variable and within-person EMA[a] measures	Daily EMA
Stress	
EMA-Adapted Perceived Stress Scale [84]	✓
Modified HIV Stigma Scale for EMA [85]	✓
Measures of daily intersectional stigma [86]	✓
Daily discrimination related to HIV, SGM[b] identity, and race/ethnicity [87-89]	✓
Affect	
Alternative Momentary Affect Measure [90]	✓
HIV TRB[c]	
Medication adherence, previous day substance use, and sexual behavior	✓

[a]EMA: ecological momentary assessment.

[b]SGM: sexual and gender minority.

[c]TRB: transmission risk behavior.

Data Collection Tools

In both phases, screener data, contact information, and quantitative survey data were collected using the Qualtrics survey platform. Quantitative survey data were collected at 2 time points: baseline and 3-month follow-up. Our app is powered by MetricWire (Metricwire Inc), and participants used the app for 90 days, providing both EMA and EMI data via this platform. MetricWire allows the research team to download self-reported EMA data, as well as JITAI EMI engagement data (eg, intervention activity completion). In phase 2, half of the participants received a Fitbit (Google LLC), which was linked to MetricWire. Biometric inter- and intraday data were provided to MetricWire—and thus made available to the study team—via the Fitbit Research API. Qualitative interview data were also collected across both phases. In phase 1, qualitative data consisted of 3 focus groups, and in phase 2, a semistructured follow-up interview; both were audio-recorded via Zoom (Zoom Communications, Inc) and transcribed.

Ethical Considerations

Ethics Approval Statement

All procedures were reviewed and approved by the institutional review boards (IRBs) at the participating institutions: Rutgers University and New York-Presbyterian at Weill Cornell Medical Center. Specifically, Rutgers University executed a single-study IRB authorization agreement with Weill Cornell Medical College (IRB registration number: IORG0000357; protocol number: Pro2021002075).

Training, Fidelity, and Protection of Human Participants

Study staff were trained on all relevant procedures for this protocol and provided with a detailed study protocol guide, including (1) confidentiality and general guidelines for participant contact; (2) screening and scheduling protocols; (3) participant contact and tracking databases in Research Electronic Data Capture (REDCap; Vanderbilt University); (4) eligibility check and consent protocols; (5) baseline and follow-up assessment procedures; (6) semistructured interviewing; (7) data security and storage; (8) transcription procedures for qualitative interviews; and (9) monitoring the study email account, Zoom, SMS, and MetricWire instant messenger chat for participant questions.

Informed Consent

Before providing consent, all participants were informed about the study procedures, their assigned intervention condition, and the potential risks and benefits of participation. They were also informed of the protections in place to ensure that their data remained confidential and secure, and that their personal information would be protected both during the study and after its completion.

Compensation

Participants were compensated for their time and effort in the study. Monetary compensation for both phases was provided via Tango Card Rewards, which allowed participants to redeem their rewards as e-gift cards to various stores and websites. Through Tango Card Rewards, participants also had the option of receiving payment via an e-Visa card or a physical Visa card. In phase 1, participants could earn up to US $315 for completing their baseline assessment (US $50), 3 focus groups (US $50 each), 90 days of EMA (US $90, or US $1 per EMA), and a brief follow-up survey (US $25). In phase 2, participants could earn up to US $180 for completing their baseline assessment (US $50), 90 days of EMA (US $90, or US $1 per EMA), and the follow-up survey and qualitative interview (US $40).

Data Protection, Privacy, and Confidentiality

Identifiable information was collected via a contact form in Qualtrics for scheduling assessments, ensuring unique and valid responses, and compensating participants. As a data security measure, contact information was collected separately from the screener data. Specifically, the screener generates a unique participant ID. Once a participant completes the screener, eligible participants—or ineligible participants who opt to share their information for future study opportunities—are forwarded to a new Qualtrics form to provide their contact information. The contact form contains only the participant ID as embedded

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data. This unique identification number is the sole link between participant contact information and study data. As such, screener data are not stored with participant contact information on the Qualtrics server, nor are they ever downloaded as a dataset. Contact information is stored only in a dedicated contact database designed for scheduling participants, which is powered by REDCap. The study team uses a separate REDCap database to track participant activity (eg, consent completion, appointments, randomization condition, and compensation), which does not include participant contact information. All physical and electronic participant data were free of personal identifiers, with the exception of the unique identification number. Both Qualtrics and REDCap comply with HIPAA (Health Insurance Portability and Accountability Act) standards for privacy protection and use secure sockets layer encryption for all data communications.

Quantitative EMA and EMI survey data are stored on MetricWire's secure and password-protected platform. While this platform is secure, HIPAA-compliant, and uses encrypted data transmission and storage, we have taken additional precautions to ensure participant confidentiality. When participants are onboarded to the app, they are provided with an anonymous MetricWire email to log-in. Instead of using participants' names, we use their unique participant ID. As such, no participants' identifying information is provided to MetricWire, and all data stored on their platform are free of personal identifiers. Biometric data are collected via the Fitbit Sense 2 smartwatch and accessed by the study team through the MetricWire platform. To ensure data security, the study team creates a unique, anonymous university email account for each participant in the watch condition. This email account is encrypted and used to set up the participant's Fitbit account. Participants' names are not entered during account creation; only their age, weight, and height are provided to validate biometric data. Participants are then given the study email and password to log-in to the Fitbit app. Once the account is set up, MetricWire allows linking the participant's Fitbit account, providing access to deidentified biometric datasets.

Qualitative interviews were recorded using the study team's Zoom Business account, which employs secure sockets layer encryption and is HIPAA-compliant. Recordings were saved as audio only (without video) on a password-protected computer. They were then transferred to a secure university server and deleted from the local device. Recordings were saved using only the unique participant ID as an identifier, and audio files will be destroyed after quality assurance of the transcriptions is completed.

Phase 1 Procedures

Community Advisory Board

A CAB was assembled before participant recruitment for phase 1. Members were recruited from existing research CABs affiliated with 3 universities. Each CAB contributed specific expertise relevant to this study. The first CAB recruited was affiliated with the HIV Prevention Trials Network and comprised individuals LWH. The second CAB recruited was affiliated with the Adolescent Trials Network and included members of the SMM community as well as professionals working in HIV and SMM health services. Additionally, we recruited several members from an existing research CAB of stimulant-using SMM-LWH, affiliated with the START study (R01DA049843).

Recruitment and Enrollment (Phase 1)

In phase 1, recruitment, consent, baseline appointments and assessments, as well as all focus group meetings, were conducted online. An initial recruitment email was sent to past or ineligible participants from the investigative team's contact list who had consented to be contacted for future studies within the past 24 months. The email directed potential participants to our study, providing a link to a brief initial screening survey and the study's contact information. Once participants expressed interest—either by contacting us or by completing the screening survey—a study team member reached out via phone or email to schedule their baseline appointment. This approach has successfully recruited diverse samples of SMM-LWH in our previous pilot and large-scale studies. At the beginning of the baseline appointment, potential participants were provided with study information and underwent further eligibility screening. Specifically, participants' age was confirmed by presenting a valid form of identification (eg, driver's license, state-issued ID, passport, or birth certificate). Participants' positive HIV status was also confirmed through proof of an antiretroviral therapy prescription or HIV diagnosis (eg, laboratory results, prescription, or medication bottle). If deemed eligible, participants completed an online informed consent form.

Study Setting and Timeline (Phase 1)

Overview

In phase 1, all study appointments were conducted online via Zoom using the Rutgers Zoom service account. Participants completed a baseline appointment, followed by a 90-day EMI period, which included 3 focus group meetings spaced every 30 days. Participation lasted approximately 3 months. Participants received monetary compensation via e-gift cards through Tango Card Rewards for completing assessments and other study procedures, consistent with previous research. To minimize potential coercion, participants were not compensated for completing any intervention activities. This approach was intended to prevent participants from engaging in the intervention primarily for immediate monetary gain.

Baseline Assessment

During the baseline appointment, study staff conducted final eligibility screening and obtained informed consent. Participants were then introduced to the 7 modules forming the basis of the EMI through a review guide. They subsequently completed a brief (1-2 minute) guided mindfulness activity. At the end of the appointment, participants were provided a link to the baseline assessment to complete on their own device and were informed that they would be contacted once the 90-day EMI period was scheduled to begin. All final eligibility screening, informed consent procedures, and the baseline survey were programmed in Qualtrics and completed online. Participants received US $50 for completing the baseline appointment and assessment.

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Open-Phase Pilot

The 90-day EMI period began once all 10 participants were recruited and had completed their baseline appointments (approximately 1.5 months after the start of recruitment). This timing ensured that the 90 days of EMI and focus group meetings occurred on the same schedule for all participants, which is important for adhering to the Scrum Agile methodology. One week before the EMI period, participants were provided with a guide via email for downloading the app-based EMI. The guide included step-by-step instructions for installing the app on their personal mobile device, information on completing EMA surveys (eg, notifications, expiration, compensation), and guidance on completing a practice survey. Participants were also shown how to use and access each app feature, including on-demand (user-initiated) content, the resources section, and the in-app messenger. The participants' EMI periods were programmed to begin on the same date. During the 90-day intervention, EMA surveys were delivered once daily and included measures of stress, health behaviors, and mental health. Surveys were completed electronically via the MetricWire mobile app on each participant's personal smartphone. Participants received US $1 for each completed EMA survey, for a total of up to US $90 if all assessments were completed over the 90-day EMI period.

Focus Groups and CAB Meetings

After every 30 days of app engagement, participants were scheduled for a focus group meeting conducted via Zoom (audio-only). A total of 3 focus groups were held. Focus groups were led by a CAB moderator and at least one study team member, who elicited participant feedback using a qualitative focus group guide, starting with broad, open-ended questions and followed by more specific prompts. Specifically, participants reviewed the major components of the Tea Time intervention: (1) the on-demand materials, (2) the intervention activities, (3) the daily positive messages, and (4) the app design. A copy of the focus group guide is provided in Multimedia Appendix 2. In preparation for the focus groups, the research team and CAB reviewed the intervention content and prepared materials for the sessions. This included presenting participants with the intervention content as currently programmed, including screenshots of its presentation within the app and live demonstrations of various app features. Additionally, the app delivers a bank of quotes and images as a "daily positive message," which are randomly selected. These images and quotes were chosen by the research team during the proof-of-concept pilot. The CAB and research team collaborated to select new images and quotes, in addition to those currently used in the app, and presented them to the focus group for feedback. Focus groups were audio-recorded and transcribed. Participants were compensated US $50 for each focus group, for a total of US $150.

Sprints and Iterative Adaptation

As feedback was gathered, our team used iterative "sprints" following each focus group and CAB meeting to tailor and further optimize the JITAI EMI (see Figure 2). After each sprint, participants continued using the app to review updates in this cyclical approach. In accordance with Scrum Agile methodology, sprints were timeboxed to no longer than 1 month. Three planned sprints are presented in the phase 1 timeline. Consistent with Scrum methodology, a planning meeting was held at the start of each sprint, during which team members created a sprint backlog—a list of tasks to be completed during the sprint. Throughout each sprint, the Scrum team (ie, the data team) took a small set of features from concept to coded and tested functionality. At the end of each sprint, the team conducted a sprint review, during which new functionality was demonstrated to the research team and CAB, who provided feedback. Features were then tested and integrated into the evolving product.

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Figure 2. Flow for sprints and iterative adaptation in phase 1 of the study protocol. CAB: community advisory board.

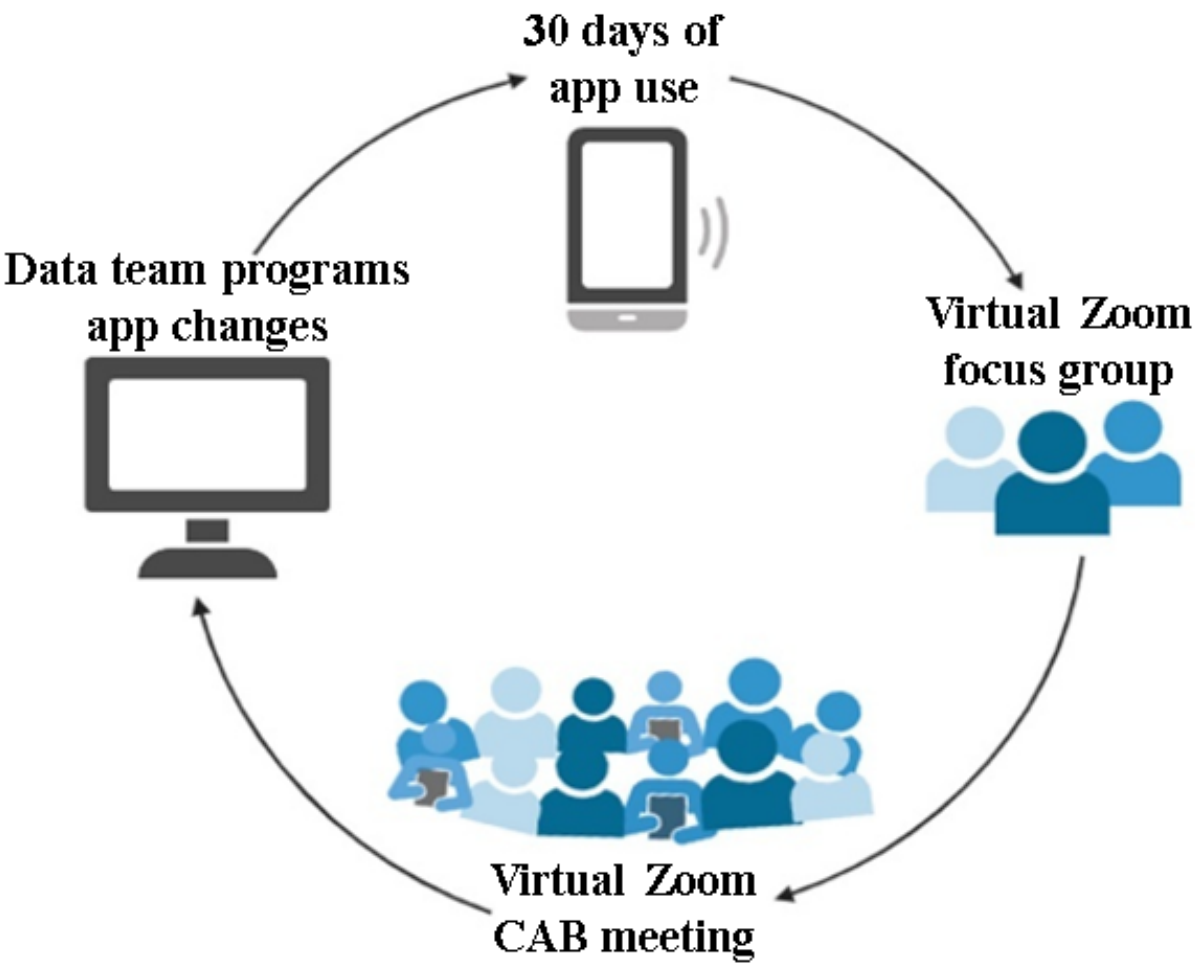

Follow-Up Assessment

Participants completed a follow-up assessment online via Qualtrics and received US $25 for their participation. The follow-up assessment included all measures from the baseline assessment, as well as additional measures to assess the acceptability and feasibility of the JITAI EMI.

Usability Testing Procedures

Following the completion of the open-phase pilot, we conducted usability testing. The data team first prepared the app for alpha testing, incorporating final changes and publishing updates so they were accessible to front-end users. Together with our CAB, we conducted usability testing to ensure the app functioned without errors and that data downloads accurately reflected our JITAI design choices (eg, micro-randomization, fixed-interval sampling). We piloted the app for 30 days, providing daily feedback to the data team as programming errors were identified. The data team addressed errors in real time, and the testing team confirmed their resolution. This 30-day period involved iterative development and refinement to finalize all changes to the app. Consistent with Scrum methodology, the team held weekly data meetings to review progress and set action items for the week. See Figure 3 for a screenshot of the app, which was finalized before the launch of phase 2.

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Figure 3. Screenshot of the finalized app, before launching phase 2.

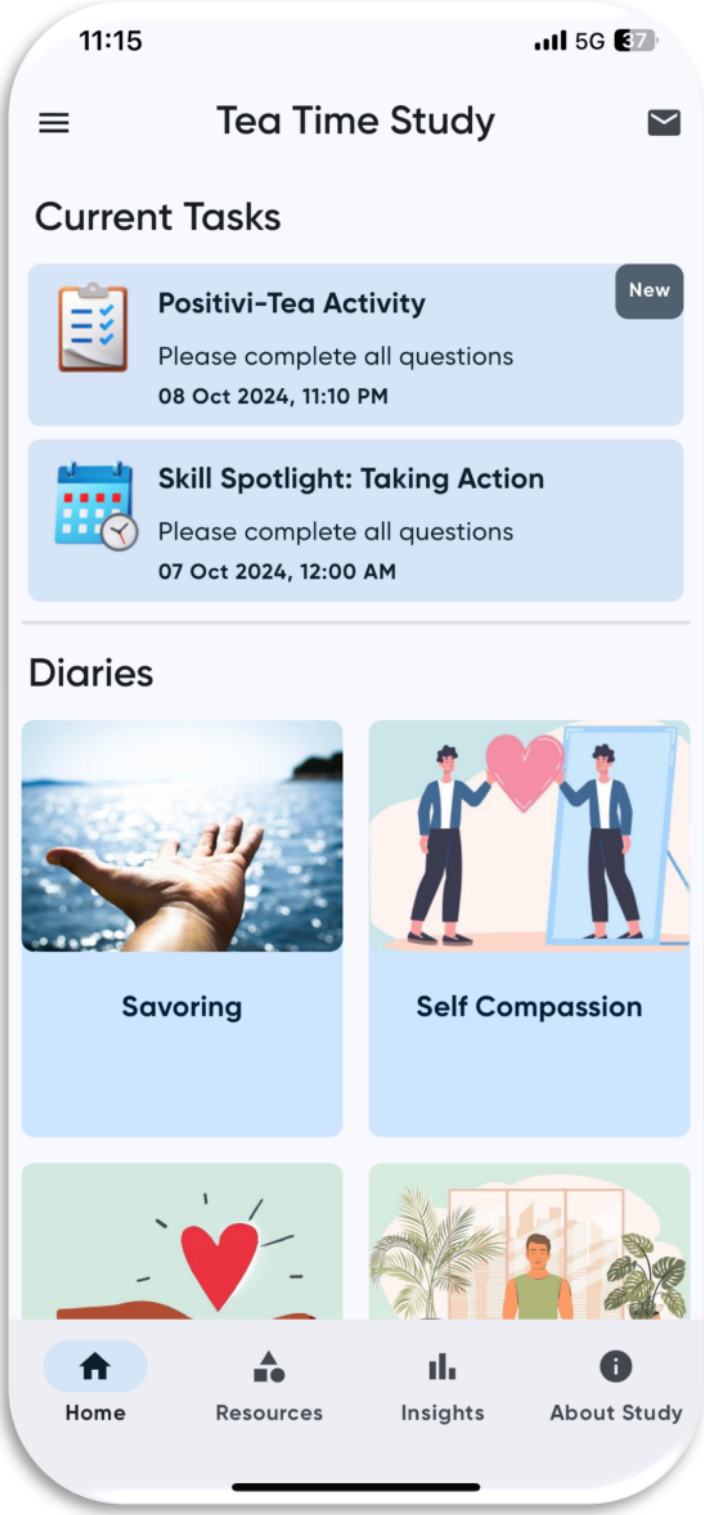

Preparation Procedures for Factorial Optimization Trial

In preparation for phase 2, we piloted study-related procedures for the factorial optimization trial. First, the data team developed all necessary data tools for the trial. This development occurred alongside usability testing and included creating a screening, contact, and tracking database in REDCap, programming the study appointment dashboard in Qualtrics, and programming the surveys required for the baseline and follow-up assessments. As part of the pilot procedures, research team members tested these databases and trained research assistants (RAs) on their use. The data team also programmed the randomizer in Qualtrics. To prepare for randomization of conditions, a second version of the JITAI EMI was developed to include random craving prompts, which only half of the participants would be assigned to receive. The research team tested all data tools, including the randomizer, to ensure that skip logic and validation functioned correctly. Three months were allotted for the

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development and testing of these data tools. Once finalized, the study investigators coordinated mock appointments with research staff to run through each condition. As part of this training, RAs practiced the baseline appointment protocol for all 4 conditions.

Phase 2 Procedures

Assessing Feasibility and Acceptability in Phase 2

In phase 2, we recruited and randomized 80 SUSMM-LWH into 1 of 4 conditions: EMI (n=20), EMI + random craving prompts (n=20), EMI with smartwatch (n=20), and EMI with smartwatch + random craving prompts (n=20). We will examine the acceptability and feasibility of adding each of these components, individually and in combination, to our JITAI EMI. Additionally, we will assess the feasibility of enrolling and retaining eligible participants in a factorial optimization trial. Finally, we are establishing proof of concept for collecting passive biometric data via smartwatches.

Recruitment and Enrollment (Phase 2)

Recruitment was conducted through both online and in-person methods (eg, provider referrals, email, social media, phone, flyers, and contact databases). All recruitment methods provided participants with a link or QR code to the brief initial screening survey or study team contact information. Participants were recruited via provider referrals, email outreach, flyers, snowball sampling, existing study contact databases, and social media ads. Referrals for participant recruitment were provided by the co-investigator. This involved reaching out to on-site providers with our informational flyer to share with potentially eligible patients, providing direct patient referrals, and placing flyers in departmental waiting areas. We also contacted past or ineligible participants from prior studies who had consented to being contacted for future research via email outreach. Flyers were additionally distributed passively through community collaborators, on-site organizations, and online listservs and mailing lists. For snowball sampling, enrolled participants were provided with a study flyer or QR code for the screening survey to share with potentially eligible individuals in their network.

Study Setting and Timeline (Phase 2)

Overview

The study timeline included a baseline appointment, a 90-day EMI period, and a follow-up appointment. A final eligibility check and informed consent were conducted at the start of the baseline appointment. Participation lasted approximately 3 months. Study appointments were conducted both online via Zoom and on-site at New York-Presbyterian at Weill Cornell Medicine in a private conference room reserved by the study team. The 90-day EMI period was completed remotely via the Catalyst by MetricWire mobile app on each participant's personal smartphone.

Randomization and Experimental Conditions

After completing the eligibility check, participants were randomized 1:1:1:1 into 1 of 4 conditions: JITAI EMI with random craving prompts, JITAI EMI with smartwatch integration, JITAI EMI with both random craving prompts and smartwatch integration, or JITAI EMI only. This followed a 2×2 factorial design. In all conditions, participants were asked to complete a 90-day EMA, and the JITAI EMI–only group served as the "control." Randomization assignments were computer-generated via Qualtrics and monitored by the data team.

Baseline Assessment

During the baseline appointment, we conducted the final eligibility screening and informed consent procedures. Participants were randomized to 1 of 4 study conditions. For all participants, we reviewed the 7 modules on which the EMI is based, and they completed a brief mindfulness activity. We also reviewed all app features (eg, user-initiated content on the home page, skill spotlight, positive messages, EMA surveys, resources section, in-app messenger), guided participants through downloading the app, and helped them complete a practice survey. Participants then completed the baseline assessment survey online via Qualtrics.

Smartwatch Assignment

Participants randomized to a watch condition received a Fitbit Sense 2 smartwatch during the baseline assessment, which was used for passive biometric data collection. Integration of the smartwatch with the MetricWire app was essential to pair EMA and biometric data; therefore, participants were provided with clear instructions on this process. The Fitbit Sense 2 can integrate with the MetricWire mobile app, allowing participants' passive biometric data to be linked with real-time, individual-level EMA data. The Fitbit collects continuous data on physiological stress reactivity, heart rate variability, heart rate, skin temperature, and blood oxygen saturation. Fitbit also provides API access, allowing MetricWire to regularly download intraday data from their server without requiring participants to visit the study site. In a recent review of smartwatch brands used in research, Fitbit was used in twice as many validation studies and was registered in ClinicalTrials.gov studies 10 times as often as other brands.

EMA/EMI 90-Day Period

Participants completed a 90-day EMA/EMI period, which was introduced during the baseline appointment and scheduled to begin the following day. The EMA and EMI were delivered via the Catalyst by MetricWire app, a leading platform for EMA data collection and JITAI EMI delivery. MetricWire offers several sensor capabilities that enable passive data collection, including smartwatch integration, as described above. While participants were compensated US $1 for each daily EMA survey, there was no monetary incentive for viewing any other app-delivered prompts, including intervention content or activities.

EMA Design Details: Planned Missing Design

Participant feedback from our proof-of-concept pilot, Positively Healthy, as well as phase 1 of this study, informed our decision to explore strategies to reduce burden and optimize EMA design. This led us to implement a Planned Missing EMA design in phase 2. A Planned Missing EMA design can reduce repetition, which in turn is expected to lower participant burden [91,92]. A Planned Missing EMA design is one in which items are intentionally omitted on alternating days. This approach not

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only reduces redundancy and participant burden but also allows researchers to maximize data collection and use validated scales. Essentially, this design provides participants with different survey items each day. The variety in survey items is expected to improve attention and engagement while reducing boredom and response fatigue, all of which can contribute to careless responding [93]. Planned Missing designs are also associated with greater quantity and quality of participant responses [94] and may reduce measurement error while improving variance in EMA data. Although this design has become increasingly popular in longitudinal research, limited studies have examined its utility in EMA [92,94,95]. In phase 2, all participants received a Planned Missing EMA design in which each item was asked two-thirds of the time, ensuring that each item had 67% complete data. This results in each pair of items for a given construct having 33% complete data for covariance estimates, which is standard for a simple matrix design [92].

EMA Design Details: Fixed Interval Schedule

Feedback from the proof-of-concept pilot also informed our decision to use a fixed-interval EMA design. During the 90 days following the baseline appointment, all participants received a daily notification to complete the EMA, which was delivered on a fixed-interval schedule. Specifically, all participants are asked to complete 1 EMA per day (approximately 5 minutes), which is delivered at 6 PM and expires at midnight, providing a 6-hour completion window. A reminder is sent halfway between the EMA's delivery and expiration if the survey has not yet been completed. In the EMA, participants report their current mood, substance use cravings, stress, and other health behaviors. A 24-hour recall is used to assess substance use and medication adherence from the previous day. Participants in the "random craving prompt" condition also received single-item EMA craving prompts 3 times per day, in addition to the once-daily evening EMA survey. These single-item craving prompts were delivered randomly within 3 time windows: 8-10 AM, 2-4 PM, and 8-10 PM, each with a 2-hour expiration window. To minimize participant burden from excessive notifications, no reminders were sent for the random craving prompts.

JITAI EMI Design Details

If participants reported stress or cravings in the EMA, they were micro-randomized to receive a JITAI activity (P=.70). The selection of a specific JITAI activity occurred through a further micro-randomization process. Once a participant was randomized to receive a JITAI activity, they were next randomized to 1 of 8 skills (P=.12), and then the JITAI randomly selected 1 activity from a bank of 4 possible activities (P=.25), each designed to help the participant practice the assigned skill.

Follow-Up Assessment

Participants completed a follow-up assessment after the 90-day EMA/EMI period. This assessment included an online survey and a semistructured qualitative interview (30-40 minutes) conducted by the RA. Interviews were conducted either in person at the Weill Cornell Medicine site or virtually using the study team's Rutgers single sign-on–secure Zoom account. All interviews were audio-recorded, either using a voice recorder or via Zoom (audio only). All participants were asked general questions regarding the acceptability of their treatment condition. Additionally, questions were tailored based on each participant's assigned condition (eg, only participants in the smartwatch conditions were asked questions relevant to that condition). A copy of the follow-up interview guide is provided in Multimedia Appendix 3. Upon completion, participants received US $40 for the follow-up assessment, in addition to compensation for any completed EMAs over the study period (US $1 per day).

Planned Analyses

In both phases of the study, we plan to conduct qualitative and quantitative analyses to assess the acceptability and feasibility of our JITAI EMI. Planned analyses will also evaluate the feasibility of the intervention design, specifically testing the implementation of an MRT embedded within a 2×2 factorial optimization trial.

Qualitative Analyses

Qualitative data will be analyzed using qualitative content analysis [96]. Sections of the interviews related to the acceptability of each condition, program satisfaction, and perceived relevance of program content will be coded separately. Feasibility will be assessed by coding participant responses to questions regarding barriers and facilitators to app engagement. Specifically, we will begin coding by first identifying indicators within participant responses. Similar indicators that emerge across participants will be grouped together and assigned tentative labels [97]. Consistent with qualitative methodology, written coding notes and memos will be maintained throughout the analysis. This process will condense participant data into a smaller set of themes [97]. Interrater reliability will be assessed using Cohen κ between 2 coders. Methodological triangulation will be used to compare quantitative and qualitative findings, further validating the acceptability and feasibility of the intervention.

Quantitative Analyses

We will first assess the feasibility of recruiting and randomizing participants into the 4 study conditions. To do so, we will develop a CONSORT diagram illustrating the enrollment cascade. Target benchmarks include more than 70% of eligible participants providing consent and over 60% of consented participants being successfully randomized [98]. We will also conduct attrition analyses to examine the proportion of randomized participants who drop out before initiating the intervention, as well as those who discontinue during the 90-day intervention period. Our target benchmark (>80%) is based on a review of retention rates in other clinical trials [99,100]. We will conduct randomization checks and examine between-group differences in attrition to ensure no significant differences exist by condition in variables such as race/ethnicity, education, income, or relationship status. Chi-square tests will be used to examine the proportion of participants in each condition who are retained through the postintervention assessment. Feasibility will also be assessed by examining adherence to each treatment condition.

For participants in the smartwatch conditions, feasibility will be defined by the rate of returned watches after the 90-day

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period. In previous EMA studies, we observed a very high return rate (74/80, 92%) among SMM-LWH. The target benchmark for this sample of SUSMM-LWH is >80%. We will also assess the feasibility of collecting passive biometric data from the smartwatches. The study will provide insight into the feasibility of collecting continuous stress reactivity data from smartwatches among SUSMM-LWH. Certain factors, such as forgetting to charge the device, may result in nonrandom missing data. We will use Fitbit's API to access stress reactivity data on their server and regularly download it to examine patterns of missing data.

Feasibility for the EMA portion of the study will be assessed across all conditions by examining the percentage of completed EMA surveys. In our pilot work, participants completed 66.19% of EMAs (median 78.21%), and our target benchmark for this study is a completion rate over 80% [101]. Adherence to the EMI will be defined as the average number of intervention activities participants completed, as well as the average number of views for positive messages and on-demand materials. In our pilot work, participants completed 83.27% of intervention activities (median 94.44%) and viewed 68.9% of daily positive messages (median 82.72%) over the 90-day period. Based on these data, as well as findings from other mobile health (mHealth) studies, our a priori target benchmark for app engagement is over 80% completion for both intervention activities and positive messages. Completion data will also be used to help identify the ideal length of the intervention. Should completion rates for the EMA or intervention activities fall below 80% over the 90-day period, we will determine the ideal intervention duration that balances maximal completion rates (≥80%) with sufficient power to detect an effect. Acceptability will be assessed using several measures. For the EMI, a score over 72.75 on the System Usability Scale is considered the benchmark for "good" or satisfactory usability [62]. Regarding app quality, an average score of 3 or higher on all subscales of the Mobile App Rating Scale is considered acceptable [64].

Exploratory/Preliminary Outcome Analyses

Although our primary aims were to assess acceptability and feasibility, we plan to leverage data collected in this study for exploratory and preliminary outcome analyses examining stress, substance use, and adherence. We will use traditional regression-based analyses to assess between-person effects, as well as main and interactive effects of random craving prompts and smartwatch integration on self-report outcomes, in addition to objective measures of substance use and adherence. We will also conduct multilevel analyses to examine within-person effects of JITAI EMI delivery on same-day substance use and adherence using lagged variables. Additionally, passive biometric data will allow us to examine stress reactivity in relation to participants' responses to random craving prompts and JITAI EMI intervention delivery.

Results

The project received funding in February 2022. Data collection for phase 1 began in October 2022 and concluded in December 2023. Phase 2 was launched in July 2024, with data collection completed by August 2025. Figure 4 presents the enrollment cascade and attrition results. Data analysis assessing acceptability and feasibility is currently in progress, with initial results expected to be submitted for publication between late 2025 and early 2026.

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Figure 4. Enrollment cascade and attrition for the phase 2 pilot factorial optimization trial. Condition 1: EMI only; condition 2: EMI + random craving prompts; condition 3: EMI + smartwatch; condition 4: EMI + random craving prompts + smartwatch. EMI: ecological momentary intervention. EMI: ecological momentary intervention.

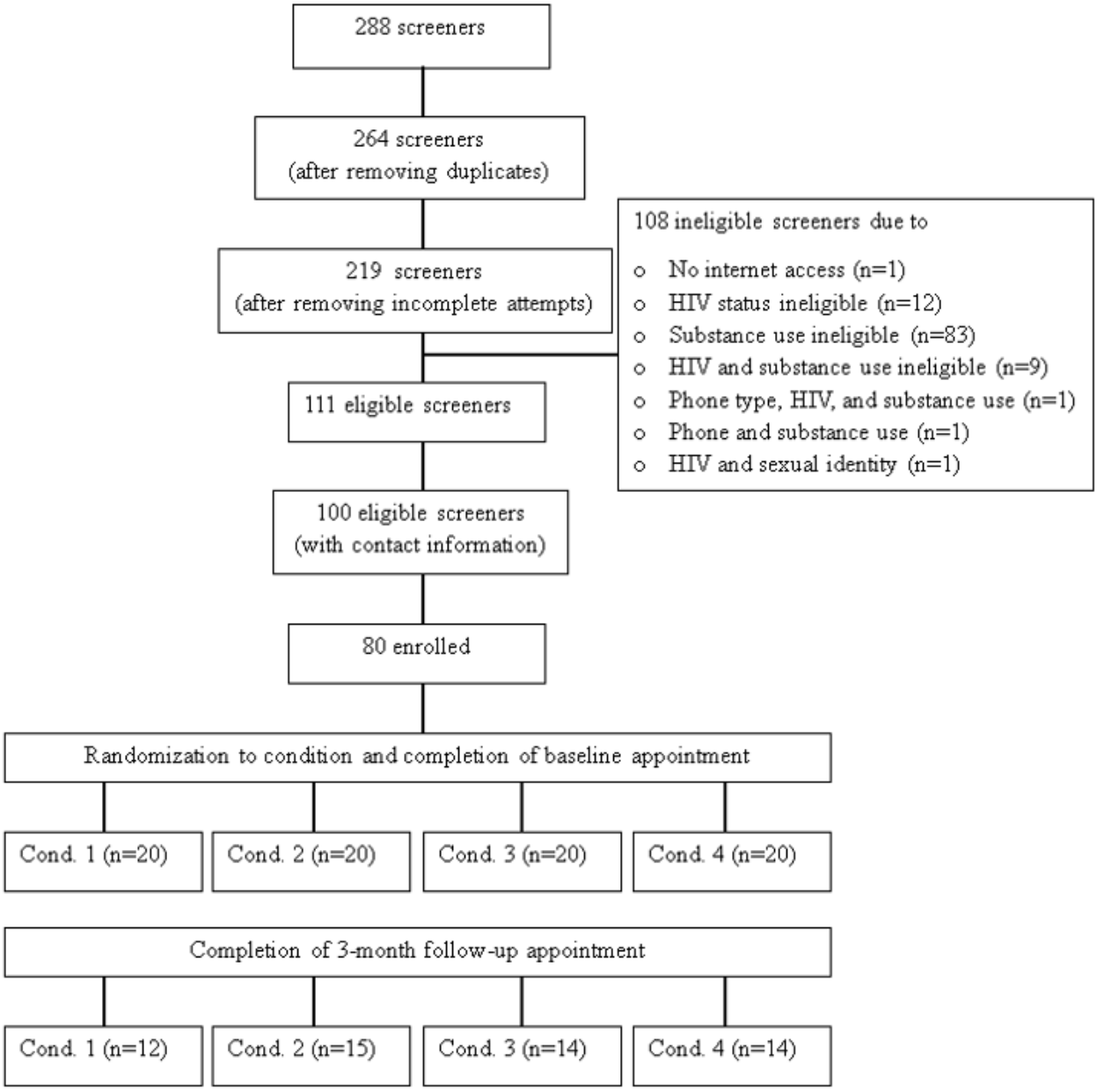

Discussion

Principal Findings

This paper outlines the study protocol for phase 1 and phase 2 of the Tea-Time study. In executing this protocol, we are tailoring our app-based EMI content and optimizing the JITAI design of the EMI. Specifically, in phase 1, we focused on adapting the intervention content to the unique needs and preferences of SUSMM-LWH. To accomplish this, we employed a CEnR approach, working closely with study participants and a CAB to guide the tailoring of our intervention. In addition to tailoring the content, we incorporated participants' suggestions for improving the system usability of the app. In phase 2, we piloted an MRT embedded within a 2×2 factorial optimization trial. Findings from the MRT will provide valuable insights, enabling further optimization of our JITAI design (eg, decision points, tailoring variables, decision rules). Findings from the randomized factorial trial will provide insights into whether smartwatch integration or random craving prompts are feasible to implement in this intervention. These findings will also clarify whether the combination of these new features is as acceptable to participants compared with either feature alone. Additionally, these data can be leveraged to assess preliminary efficacy for both proximal and distal outcomes.

Strengths and Limitations

This study takes a CEnR approach, integrating the Scrum Agile framework with MOST, thereby combining methods from social science, intervention science, and software development into a single, innovative approach to enhance this app-based intervention. In particular, our implementation of the Scrum Agile framework alongside MOST for intervention optimization strengthens both the study design and protocol. First, these 2

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approaches are highly complementary, as both propose iterative processes for adapting app-based interventions. Additionally, each provides a distinct framework to guide software development and intervention optimization. Scrum, most commonly used in technology-based fields such as computer science, is a framework for managing multicomponent software and product development projects. This framework guides us in efficiently managing data-related tasks as we program adaptations to the JITAI EMI and release different iterations of the app for alpha and beta testing. The MOST approach provides a complementary framework specific to intervention optimization, informing design choices for piloting an optimization trial of our adapted app. In essence, Scrum provides guidance on how to adapt the app, while MOST provides a framework for deciding which features should be adapted.

As part of phase 2, we are piloting the feasibility of conducting an MRT embedded within a factorial optimization trial with SUSMM-LWH. To optimize high-intensity adaptive interventions, an MRT is recommended [61,102]. The MRT is conducted under an n-of-1 framework and functions as a factorial design in which each individual is repeatedly exposed to each intervention condition over time [61]. This approach is useful for optimizing features within the JITAI EMI; however, the optimization of other features requires a standard factorial design. For example, it is not feasible to randomly assign the same participant to wear a smartwatch on some days and not others over a 90-day assessment period. Similarly, because random craving prompts are a feature of the EMA rather than the JITAI EMI, this component is also best evaluated within a standard factorial design. This combined approach to optimization is also a strength of the current protocol and will minimize the need for future optimization trials. As such, it is also cost-effective. Further, by accelerating the optimization process, we come closer to achieving a fully optimized intervention ready for evaluation and implementation. In a future RCT, the EMA design will also allow us to collect day-level data on intervention efficacy.

One potential area of concern is that participant burden [103] and response fatigue [93,104] associated with intensive repeated-measures designs threaten data validity. In addition, burden and fatigue are both associated with poorer EMA compliance [105]. Participant burden is an especially important concern for researchers working with SUSMM-LWH, as this population is already disproportionately impacted by health-related burden and other acute daily stressors. In addition, prior research shows that compliance with EMA is a challenge among substance users more generally [106] and among SUSMM [107]. Some studies have also found that racial and ethnic minority SMM and SUSMM are more likely to show poor compliance with EMA [10,108]. Poor compliance poses a significant concern regarding the feasibility of JITAI EMI delivery with SUSMM-LWH. Given that the success of a JITAI EMI relies heavily on the validity of EMA data as well as compliance with the EMA, it is important to optimize EMA methods and design before scaling up this intervention for SUSMM-LWH.

Improving EMA compliance is a vital first step in optimizing this JITAI EMI. Compliance can be improved by reducing participant burden [105]. One approach to minimize burden is to integrate ambulatory assessment into the EMA/EMI, which would facilitate passive data collection [109-111]. Smartwatches can be used to collect data such as heart rate and physiological stress responses [111], which can then be used to trigger EMI intervention content [110]. Smartwatches can also integrate with mobile apps, allowing participants to receive notifications, surveys, and EMI content directly on their watch, making engagement effortless and accessible. We expect that smartwatch integration for participants in this 2×2 trial will improve both EMA compliance and EMI engagement.

Compliance is also related to design choices [105]. In our proof-of-concept pilot, participants reported often missing their EMA due to its timing (random interval sampling) and expiration. In this protocol, we have addressed this issue by incorporating participant feedback into our EMA scheduling, moving from a random-interval design to a fixed-interval design. A fixed-interval design allows participants to set aside dedicated time to complete the EMA and may improve compliance. Of course, this change introduces certain limitations, as random-interval EMA is believed to provide better ecological validity. This is being addressed in part through our 2×2 design, which tests the integration of random-interval craving prompts in addition to the fixed-interval evening survey. Importantly, random craving prompts will trigger intervention content and will therefore be a key feature for delivering in-the-moment support for SUSMM-LWH. We expect that this combined sampling approach (eg, fixed + random interval) may further optimize our JITAI EMI.

Conclusions

Ultimately, this project aims to develop a fully optimized EMI that is both culturally relevant and acceptable to our target audience by eliminating sources of community-program mismatch in our intervention content. Additionally, we aim to further optimize the intervention by incorporating 2 additional features that may enhance engagement and effectiveness while minimizing participant burden and other potential barriers to engagement. If we are successful in these aims, this app-based JITAI EMI will offer a cost-effective intervention approach that provides SUSMM-LWH support in real time, in their daily lives, when it is most needed.

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Data Availability

The data that support the findings of this study are not publicly available due to their sensitive nature and ethical restrictions concerning participant privacy. The data are available upon reasonable request, following a review process to ensure participant confidentiality. Data requests may be sent to the first author (KMS).

Authors' Contributions

KMS, JTM, HJR, AC, and BM conceptualized and designed phases 1 and 2 of this study protocol. KMS, BM, and SG were responsible for project administration at Rutgers University. JA oversaw project administration of the study at Weill Cornell Medicine. KMS and HP designed the methodology, including data safety protocols and procedures. KMS and HP oversaw data curation, and HP developed all necessary data tools and managed data for the study. All authors assisted in writing the original draft, as well as reviewing, editing, and approving the final manuscript.

Conflicts of Interest

None declared.

Multimedia Appendix 1
CONSORT (Consolidated Standards of Reporting Trials)-EHEALTH checklist.
[PDF File (Adobe PDF File), 63312 KB - resprot_v14i1e76741_app1.pdf]

Multimedia Appendix 2
Focus group guide for phase 1.
[PDF File (Adobe PDF File), 115 KB - resprot_v14i1e76741_app2.pdf]

Multimedia Appendix 3
Qualitative interview guide for phase 2.
[PDF File (Adobe PDF File), 418 KB - resprot_v14i1e76741_app3.pdf]

Multimedia Appendix 4
Peer review report by the HIBI -HIV/AIDS Intra- and Inter-personal Determinants and Behavioral Interventions Study Section (National Institutes of Health, USA).
[PDF File (Adobe PDF File), 90 KB - resprot_v14i1e76741_app4.pdf]

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Abbreviations

CAB: community advisory board
CEnR: community-engaged research
CONSORT: Consolidated Standards of Reporting Trials
EMA: ecological momentary assessment
EMI: ecological momentary intervention
HIPAA: Health Insurance Portability and Accountability Act
IRB: institutional review board
JITAI: just-in-time adaptive intervention
LWH: living with HIV
mHealth: mobile health
MOST: multiphase optimization strategy
MRT: micro-randomized trial
RA: research assistant
RCT: randomized controlled trial
REDCap: Research Electronic Data Capture
SMM: sexual minority men
SU: substance using
TRB: transmission risk behavior

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Protocol

Assessment of Health System Readiness and Quality of Dementia Services in Peru: Protocol for a Qualitative Study With Stakeholder Interviews and Documentation Review

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Abstract

Background: Dementia is a global health priority with significant challenges due to its complex nature and increasing prevalence. Health systems worldwide struggle to address chronic conditions like dementia, often providing fragmented care. However, information about how health systems respond to the needs of people with dementia and their carers, and the quality of care provided, is scarce in low- and middle-income countries.

Objective: This study aims to assess the quality of the health system to provide diagnosis and care for people with dementia and their carers in Peru. In order to do this, the study will explore the response of the Peruvian health system to people with dementia and their carers, and explore the experiences of people with dementia of receiving their diagnosis, management, and quality of care for this condition.

Methods: This study is part of a research program called “IMPACT Salud: Innovations using Mhealth for people with dementia and Co-morbidities,” aimed at strengthening health systems to provide care for people with dementia and their carers. The study has a descriptive, cross-sectional design that uses a qualitative methodology, including stakeholder interviews and documentation review, and consists of 2 substudies, a health system assessment (HSA) and an exploration of the patient journey. The first substudy uses an HSA methodology suitable for low- and middle-income countries, conducting 160 structured interviews with 12 different stakeholder types across 3 levels of the health system (micro, meso, and macro) in 4 Peruvian regions, each with distinct geographical and urbanization profiles. The second substudy uses a patient journey methodology, which involves conducting 40 in-depth interviews with people with dementia, carers, and health care workers from the same 4 regions. The insights into the people with dementia patient and caregiver experience within the health system from the interviews will be used to produce a

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patient journey map. The analysis will be guided by the high-quality health system framework, and the findings from the HSA and patient journey will be structured using the domains included in the framework through the lens of quality of services.

Results: Data collection began in March 2024. As of the end of September 2024, a total of 156 interviews from the HSA and 38 interviews from the patient journey study have been conducted across 4 regions.

Conclusions: This study will provide a national, multilevel insight into the current operation of the Peruvian health system, including an analysis of the quality of services provided with regard to dementia diagnosis, management, and care from the perspectives of stakeholders, patients, and their carers.

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KEYWORDS

dementia; health system readiness; caregiver; comorbidities; Peru; study protocol; quality of care; comorbidity; patient journey; mHealth

Introduction

Background

Health systems worldwide face the challenge of addressing chronic conditions, which in low- and middle-income countries (LMICs) is exacerbated due to resource scarcity. LMICs often respond to diseases in isolation through vertical programs [1]. A global and integrated response to chronic conditions is needed to provide high-quality care for individuals with complex conditions [2]. Dementia is one such chronic condition, characterized as a complex disorder involving psychosocial dysfunction and vulnerability due to brain disease [3]. Dementia is a generic term that describes progressive cognitive and behavioral decline severe enough to interfere with daily life and independent function [4] and is a global health priority given its enormous human and economic costs.

Globally, the number of people with dementia is increasing. According to the World Health Organization, there are approximately 50 million people with dementia, projected to reach 75 million by 2030 [4]. Studies indicate that women are more likely to develop dementia than men [5]. Furthermore, around 60% of people with dementia live in LMICs, which are aging rapidly and have limited capacity to support them [5]. In Peru, in 2022, the Ministry of Health (MoH) attended to 13,066 people with Alzheimer disease and other dementias [6].

Health systems in LMICs are not well equipped to address dementia, often resulting in inadequate or nonexistent care. Specific challenges for the health systems and people with dementia include developing effective diagnostic services, managing cognitive and behavioral decline, handling multiple comorbidities, caregiver burden, widespread stigma, and lack of awareness about dementia. The concept of tracer conditions can help facilitate understanding the complexity of health systems and the challenges LMICs face [7,8]. Using tracers in health systems research is based on the premise that focusing on carefully selected health problems allows for the identification of weaknesses within the system and facilitates more direct insight of its performance [7,8].

Dementia affects multiple aspects of individual and family well-being, serving as an indicator of multimorbidity in both people with dementia and their carers. People with dementia have twice the number of chronic physical and mental conditions compared to those without dementia [9,10]. Dementia shares risk factors with many other common chronic diseases, including health-related behaviors (eg, unhealthy diet, smoking, and physical inactivity), as well as obesity, hypertension, diabetes, depression, and social isolation. Together, these factors account for 35% or more of the population-attributable risk (proportion of new cases of dementia due to the noted exposures). In Latin America and the Caribbean, this percentage can reach 56%, due to a combination of cultural, political, and economic factors [11].

In a broader context, addressing dementia does not mean working with a disease in isolation but rather a broader set of system-wide responses, both within and outside health care delivery structures, which can in turn contribute to achieving global goals such as Universal Health Coverage and the Sustainable Development Goals [12-16]. Abundant literature has pointed out significant deficiencies in protection systems that are relevant for addressing dementia. In Peru, despite having a specific law that addresses dementia (law no. 30795: Law for the Prevention and Treatment of Alzheimer's Disease and Other Dementias) [17], people with dementia are affected by the fragmented health care systems, shortage of human resources, limited specialized services, minimal or nonexistent long-term care, and a siloed approach to addressing diseases and health conditions.

In the vast majority of cases [18-22], support available for individuals with chronic conditions in Peru, including dementia, comes from family members, predominantly women [23], who commonly lack access to information and primary or specialized dementia care services. A study across various LMICs identified high psychological stress and caregiver burden, particularly among female carers of people with dementia [24]. Studies, such as those by Papastavrou, recognize caregiving for people with dementia as highly stressful for families, potentially leading to depression, panic disorder, anxiety, or substance use like psychotropic drugs, alcohol, and nicotine.

To date, few studies have addressed dementia in South America. Notably, the 2023 Pan American Health Organization report [25] indicates that only Chile has a national dementia plan, with underreporting in LMICs potentially reaching 90%. The 10/66 Dementia Research Group study [25] highlights the high cost

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of dementia for health systems and the negative mental health impacts on women in LMICs, who are often primary caregivers for people with dementia [26]. This underscores the need for further research on dementia diagnosis and care in LMICs and for directing it effectively toward impactful decision-making. This landscape highlights the urgent need for improved dementia diagnosis strategies in Peru and LMICs, considering the unique challenges posed by limited resources, illiteracy rates, and caregiver burden. Task-shifting approaches recommended by the World Health Organization could help bridge the gap in dementia care [4]. Additionally, addressing the social and economic impacts of dementia requires a multifaceted approach, involving collaboration between health care providers, policy makers, and community organizations. To understand the potential for such improvements on dementia diagnosis and care in Peru, a thorough exploration is needed of the existing health system and the problems that people with dementia and their carers face in daily life from a multistakeholder perspective. For these reasons, this study aims to assess the readiness to diagnose and treat dementia, as well as the quality of dementia services, in the Peruvian health system from the perspective of various stakeholders.

The study has 2 overarching objectives, which are addressed by 2 parallel substudies, respectively: a health system assessment (HSA) and an exploration of the patient journey within the health system.

Substudy 1: HSA

The HSA aims to understand the diagnosis and treatment needs of people with dementia and their carers in Peru and resources available for this, including the readiness of the health system to implement innovative mobile health (mHealth) tools for the screening and diagnosis of dementia. It will address the following research questions (Textbox 1).

Textbox 1. Research questions.

- What is the existing capacity of health workers to provide care to people with dementia and what is the quality of this care?
- What are the preconceived barriers and enablers for engaging with interventions using mobile health (mHealth) technology?
- What are the main system barriers and facilitators for the uptake of mHealth tools for supporting people with dementia and carer dyads?

Substudy 2: Patient Journey

This substudy aims to understand the journey of people with dementia to being diagnosed and receiving management for dementia and to identify opportunities to improve the diagnosis and management of dementia for people with dementia. It will address the following research questions (Textbox 2).

Textbox 2. Research questions.

- What are the experiences and challenges of providing care and unmet needs of people with dementia, their carers, and health workers?
- What are the most common barriers and facilitators to being diagnosed with dementia from the perspective of people with dementia, their carers, and health workers?
- What are the most common barriers and facilitators to receive or provide treatment and management of dementia from the perspective of people with dementia, their carers, and health workers?

Methods

Context

The IMPACT Salud research program comprises 4 distinct work packages (see Table 1), which have the overarching goal of strengthening the health system in Peru through sustainable, integrated, community-delivered, technology-enabled innovations. The expected outcomes of the overall program include improving access to diagnosis of dementia and development of a feasible and acceptable mHealth intervention for people with dementia and their carers. The first work package, the focus of this protocol manuscript, is a descriptive cross-sectional qualitative study, consisting of an HSA and an exploration of the patient journey through interviews and documentation review in order to inform future work packages of the program. The HSA will collect information on the structure and organization of the Peruvian health system, the political environment, financing, data collection and information systems, availability and affordability of medications and tests, barriers to diagnosis and treatment, service delivery in prevention and management issues, training and capacity to provide care, medical technologies and infrastructure, and perceptions of and experience with using mHealth technology.

Table 1. Work packages that comprise IMPACT Salud.

Work packages	Objective
1	Evaluate health system readiness to diagnose, treat, and support people with dementia and carers
2	Develop and implement a mobile health–enabled system for the diagnosis of dementia
3	Determine the feasibility of an intervention to treat and support people with dementia and their carers
4	Assess the economic burden of dementia and related comorbidities in Peru and estimate the costs of rolling out the diagnosis tool at a national level

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This information will be collected from diverse stakeholders from different institutions, including not only health services provision, eg, civil society and municipalities, among others, but also from policy and practice documentation. The patient journey study will complement the information gathered from the HSA from a more centered perspective of people with dementia and their carers. The insights into the experiences of both people with dementia and carers within the health system will inform the development of a journey map that visualizes these experiences. The findings from the HSA and patient journey will inform other work packages of the program and will allow for the identification of opportunities for using mHealth technology for dementia diagnosis improvement and management intervention.

Setting

Study Regions

The IMPACT Salud program is working across 4 sites in Peru (see Table 2). These include Lima, the nation's capital with over 10 million inhabitants [27], situated along the central coast. Lima holds significant importance as the country's primary city, burdened with the highest incidence of noncommunicable diseases [28]. Notable for its social disparity and cultural heterogeneity, Lima is a dynamic research locale. The second city, Huancayo, has over half a million residents [29] and is positioned in the central highlands at an elevation of 3200 meters above sea level. A pivotal hub for the economic growth of the central region, Huancayo attracts migrants from the jungle and southern highlands, primarily engaged in providing diverse services for citizens and agricultural activities. The third city, Iquitos, serves as the primary urban center in the jungle, hosting almost half a million inhabitants [30]. Characterized by diverse indigenous populations, Iquitos can only be accessed via river and air transport, resulting in an economy marked by high transportation costs. Lastly, Tumbes, located in Peru's northern most region with 265,844 residents [31], operates as a border economy due to its proximity to Ecuador. With a warm, rainy climate, Tumbes is currently experiencing heavy rainfall attributed to the “El Niño-Southern Oscillation” climatic phenomenon.

Table 2. Characteristics of the study sites or locations. Source: Instituto Nacional de Estadística e Informática (INEI)-2017—Repositorio Único Nacional de Información en Salud (REUNIS) [27-30].

Sites	Population, n	Region	Illiteracy rate in the department (15+), %	Completed high school in the department (15+), %	Most spoken language in the department	Quintile of dementia care in Peru
Lima (Metropolitan)	8,894,412	Coast	2	50.2	Spanish	1
Huancayo	545,615	Highlands (Andes)	5.3	45.5	Spanish	3
Iquitos—Maynas	149,773	Amazon Jungle	5.4	50.1	Spanish	1
Tumbes	2,154,962	Coast	4.1	48.3	Spanish	4

Health Care System

The Peruvian health care system is fragmented and complex, with health care provision and financing depending on multiple public and private entities under the oversight of the MoH. Within this fragmentation, the 2 main public health care providers are the MoH and the Social Security System (EsSalud), the last one depending financially on the Ministry of Labour and Employment Promotion [32].

This study will primarily work with the MoH, which serves 74.5% of the population [33]. Since 2007, there has been a coordinated and decentralized health system [34], which has resulted in the creation of regional health directorates and management for each region that, independently, are responsible for implementing MoH's regulations.

For the purpose of this research, we categorize the health system into 3 levels: micro, meso, and macro. The micro level encompasses primary health care services, along with any supplementary systems or organizations at the local level. The meso level includes secondary health care services and regional directorates. Finally, the macro level encompasses tertiary health care services, national directorates of the MoH, and specialized bodies.

Design

The HSA follows a Rapid Assessment Protocol (RAPIA) methodology for data collection, targeting access to care for individuals with chronic diseases in LMICs [35]. The RAPIA framework is being used for its structured approach to data collection, designed to generate information from both primary and secondary sources, including structured interviews with participants across various levels of the health system within the 4 representative regions. The interview questions were adapted to gather information on dementia, modifying the focus on medications and emphasizing inquiries about the care provided to people with dementia by their caregivers. Key attributes of this methodology include its patient-centric focus, cost-effectiveness, and provision of valuable insights for decision-makers. The rapid assessment methodology is implemented via structured interviews following a standardized questionnaire, supplemented with a review of secondary sources of information (eg, policies and national statistics), to explore 11 themes related to the Peruvian health system across the 3 levels of the health system (macro, meso, and micro). This framework will facilitate the understanding of the needs and available resources for patients with dementia and their carers. Similarly, to understand the experiences of people with dementia in receiving their diagnosis and the subsequent management of their condition, we will use the “patient journey” methodology.

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This approach is used by health care managers to identify gaps in the touchpoints between the health care system and the patient throughout the care process, such as the admission process, physical care, and appointment reminders [36]. In LMICs, "patient journeys" for noncommunicable diseases provide valuable insights for decision makers aiming to prioritize interventions and optimize disease management [36]. To carry out the "patient journey," we will conduct in-depth qualitative interviews with individuals with dementia, their caregivers, and health care professionals. This follows an example of a study on understanding poststroke care management [37]. Based on the patient journey interviews, a patient journey map will be developed to visualize the experience of people with dementia, carers, and health care workers within the health care system.

Participants and Selection Criteria

Overview

Table 3 details the different types of participants across the 2 substudies and the criteria used for purposive selection of participants. In the HSA, 14 types of key actors are participating across the macro [4], meso [3], and micro [7] levels. The patient journey involves 3 types of key actors: people with dementia, their carers, and health care workers. The aim is to achieve a comprehensive coverage of health care system stakeholders pertinent to the theme of dementia.

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Table 3. Key actors and inclusion criteria.

Level	Target institution and key stakeholder role	Inclusion criteria
Substudy 1		
Macro	• (1) Ministry of Health (eg, Mental Health Strategy, Non-Communicable Diseases Strategy, Integrated Health Insurance (SIS) Department, Planning and resources) • (2) Ministry of Financing (eg, Presupuesto por Resultados) • (3) Social Security (EsSalud) • (4) Ministry of Women and Vulnerable Populations • (5) Key opinion leaders (eg, nongovernmental organization representatives, representatives of health organizations)	• 18 years of age or older • Occupy the specified role in the Peruvian provinces of Lima, Huancayo, Iquitos, or Tumbes
Meso	• (6) Regional directorates of health • (7) Health workers of mental health public hospitals, general hospitals, and specialized memory clinics (eg, including psychologists and therapists) • (8) Nursing homes run by District Municipalities	• 18 years of age or older • Occupy the specified role in the Peruvian provinces of Lima, Huancayo, Iquitos, or Tumbes
Micro	• (9) Grass-root organizations and elderly community centers (Centro del Adulto Mayor) • (10) Community leaders and community health workers • (11) Health care workers (eg, physician, nurses, technicians, pharmacies) from primary health care facilities and community primary mental health care facilities (Centro de Salud Mental Comunitario)	• 18 years of age or older • Occupy the specified role in the Peruvian provinces of Lima, Huancayo, Iquitos, or Tumbes

Micro	• (12) People with dementia and carers	• Only for people with dementia; people with a mild dementia diagnosis who meet the following criteria:
		  • Status of dementia: people will be asked for a self-reported diagnosis of dementia. Where this is not possible, the carer will be asked to confirm. This diagnosis had to be performed by a physician in a health facility.
		  • Level of functionality: the Pfeffer Functional Activities Questionnaire (PFAQ), Spanish version, will be applied with potential participants (n=31); participants must score below 6 to participate.
		  • People with dementia should also have at least one chronic comorbidity, such as hypertension, diabetes, depression, and anxiety, among others.
		• Carers: people who are formal or informal carers, including family members that are responsible for taking care of the people with dementia. They need to have been with the people with dementia in the process of diagnosis and management and are self-recognized as carers of the people with dementia. We will also include carers of people with severe stages of dementia

Substudy 2		
N/A[a]	• (1) People with dementia	Same as substudy 1
N/A	• (2) Carers	Same as substudy 1
N/A	• (3) Health care workers	General health practitioners and neurologists

[a]N/A: not applicable.

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Sampling Method

Across the HSA and patient journey substudies, we aim to include 200 participants in total across the 4 sites through purposive sampling to recruit the required range of stakeholders across the health system. The inclusion criteria are detailed in Table 3, and the target sample size is provided in Table 4. These numbers will allow for gathering sufficient information from all regions to understand differences across the 4 settings and levels. For recruitment of people with dementia, there are specific inclusion criteria related to the stage of dementia and level of functionality. A community mapping exercise was conducted in each region to identify relevant organizations and groups from which to recruit potential participants. The purposive sampling was focused on identifying participants who represented each stakeholder type across each level of the health system as outlined in Table 4 and continued until all stakeholder types had been recruited.

Table 4. Sample size.

	Huancayo	Iquitos	Lima	Tumbes	Total
Substudy 1					
Macro[a]	—	—	—	—	20
Meso	15	15	15	15	60
Micro	20	20	20	20	80
Substudy 2					
People with dementia and carers	6	6	6	6	24
Health care workers	4	4	4	4	16

[a]The precise breakdown of participants is unclear for the 4 provinces.

Fieldwork Team

Field workers in each site were selected for their expertise in conducting qualitative interviews, their health care sector experience, and residency in the designated city of work. A total of 11 field workers have been engaged, with 9 assigned to micro- and meso-level interviews and 2 for the macro-level. A dedicated team of 2 or 3 researchers has been formed for each site, alongside a coordinator. Fieldwork team members attended 2 comprehensive training sessions, combining in-person and virtual formats. Training topics encompassed participant recruitment protocols, ethical considerations in elderly populations and dementia care, implementation of informed consent and assent procedures, an introduction to dementia from biomedical perspectives, and familiarization with the data collection materials. Upon completion of training, field workers received an operational manual detailing standardized operating procedures for data collection.

Data Collection Procedures

The study received institutional support from MoH and follows a staggered data collection approach. The process commences with higher management levels progressively authorizing interviews at operational tiers such as first-level health centers. Identification of persons with dementia (diagnosed by a health center) and their carers is facilitated through community health agents, health care center workers, and health care facility administrations. They introduce the fieldwork staff, who then administer the Pfeffer Functional Activities Questionnaire [38,39] to assess the people with dementia's functional abilities for daily activities and their possibility to participate in the interview. Scores below 6, indicating no clear impairment of functional activities, prompt interviews with both the caregiver and the person with dementia. In such cases, an informed assent is sought from the person with dementia, with informed consent obtained from the carer in their representative capacity. Figure 1 summarizes the procedure for conducting interviews with people with dementia. For other actors, specific informed consent procedures are followed prior to initiating data collection. Detailed information regarding recruitment can be found in Multimedia Appendix 1.

For the HSA, interview information will be recorded in notes on a printed version of the interview questionnaire and captured with handheld recorders. These notes will then be entered into the REDCap (Research Electronic Data Capture; Vanderbilt University) software, developed by Vanderbilt University. In this case, interviews will not be transcribed; only the recordings will be used as backup. This is due to the format of the RAPIA methodology, which advocates for a rapid analysis of information, prioritizing the perspectives of various actors rather than delving deeply into them; hence, a detailed analysis of the testimony is not necessary. On the other hand, for the patient journey, the interviews will be recorded and subsequently transcribed verbatim and coded in an Excel spreadsheet. Following coding, the information will be shared in order to seek its validation at a meeting with people with dementia and careers who were interviewed.

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Figure 1. Procedure for conducting interviews with people with dementia.

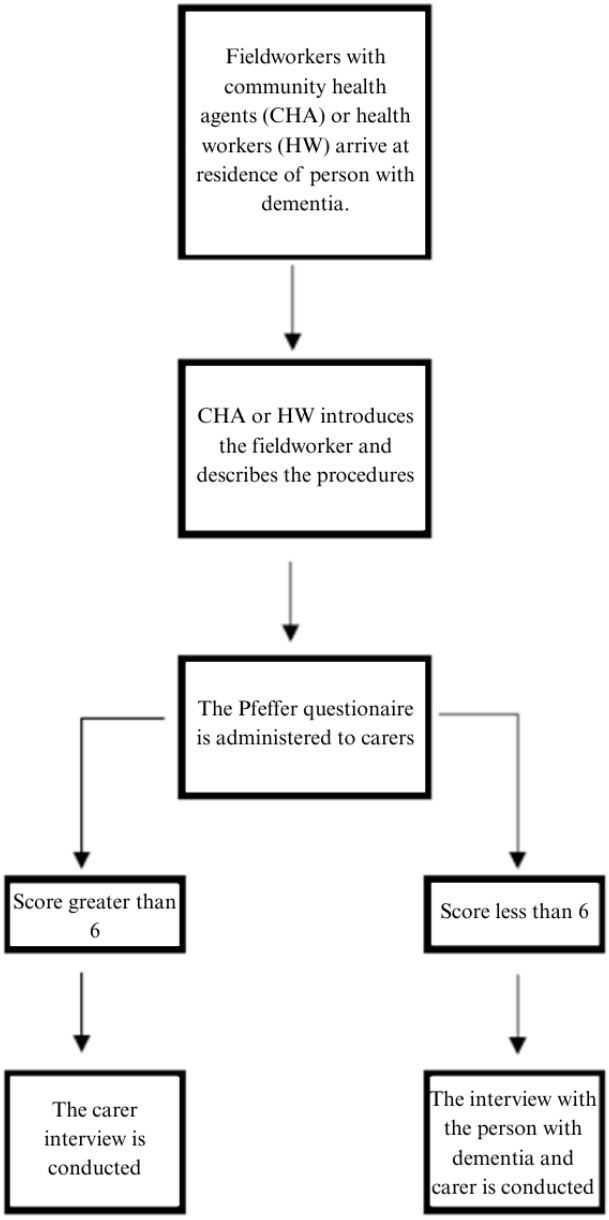

Data Collection Materials

Questionnaires with closed and open-ended questions will be used to perform the structured interviews conducted in the HSA. These instruments were originally designed to assess health systems with regard to access to insulin [35]; subsequently, they have been applied for exploring chronic diseases and neglected tropical diseases [1]. Drawing from these previous experiences, they have been adapted for this study, with questions amended or added to capture information on several key thematic areas to assess the readiness of the Peruvian health system for diagnosing and managing dementia. These thematic areas are informed by the RAPIA guidelines mentioned earlier and are outlined in more detail in Table 5, including sections and topics of the structured interview questionnaire; an example of the structured questionnaire is also provided in Multimedia Appendix 2. As per the RAPIA guidelines, interview data will be supplemented with a document review of relevant technical standards, laws, regulations, national plans, care protocols, clinical guidelines, and other materials that are publicly available. In the patient journey, we will use semistructured interview guidelines for the in-depth interviews with people with dementia, carers, and health care workers. The guidelines will explore topics to understand the diagnosis and management process of dementia and identify opportunities for improvement. The interview guide is structured into 3 stages: prediagnosis, diagnosis, and treatment [40]; an example is provided in Multimedia Appendix 3. In these stages, the number of interactions with health care personnel, the time between appointments, the emotions associated with the encounters, among others, will be collected.

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Table 5. Sections and topics of the questionnaire in the health system assessment.

Type of data	Components
General information	• Place and date • Contact information • Demographic information • Workplace and time • Occupational category
Health system structure and organization	• Units or departments responsible for people with dementia • Preparation of health personnel • Preparation to attend comorbidities • Services and organizations centered in people with dementia
Relevant policies	• Public policies and relevant policies for people with dementia
Financial issues	• Sufficient funding for prevention, diagnosis, and treatment in people with dementia • Barriers or difficulties for find funding for people with dementia • Programs or financial contributions for people with dementia and careers
Data collection and information systems	• Date registration for people with dementia • Statistic information available about people with dementia and comorbidities
Service delivery in prevention and management	• Knowledge of the available tests for people with dementia • Medications for people with dementia • Peruvian political medication for people with dementia • Knowledge of the available medication for people with dementia • Barriers or difficulties in the access of medication, tests and technology for people with dementia
Barriers for diagnosis	• Current barriers to dementia assessment • Current barriers to dementia attention • Current barriers of dementia care
Training and capacity to provide care	• Training, knowledge and capacity of health care workers in the provision and management of dementia care
Medical technology	• Infrastructure to support internet access • Infrastructure to support use of mHealth
Perceptions of and experience with using mHealth technology	• Knowledge of the tools for the dementia diagnosis • Opinion about mobile applications for disease diagnosis

Analysis Procedure

The analysis of substudy 1 HSA will follow a deductive process using coding reliability thematic analysis [41], with the aid of a structured codebook to index the information collected within the domains proposed by the high-quality health system (HQHS) framework developed by Kruk. The HQHS framework was designed to take into account the challenges of LMICs and allows for a comprehensive evaluation of service quality beyond mere access, emphasizing patient-centered care and trust in health care systems. The framework will allow us to organize and structure the results of our substudies in order to create an overall overview of the health system and the quality of services provided to people with dementia and their carers. The relevance of using this framework lies in its ability to integrate general aspects, such as access to health care centers and the number of consultations, with the patient's perception of the service's utility when describing service quality. In contrast, the analysis of the patient journey in substudy 2 will be inductive, following a framework analysis approach [42]. Analyses for both substudies will be carried out in parallel until the final phase, at which point they will be integrated to enhance the HQHS framework. The detailed analytical procedures are outlined below.

Substudy 1 will follow a 3-step process, conducted initially by 2 researchers working together on data from one site first to agree on understanding of codes and then moving to work independently on interviews from the additional sites subsequent to this. Throughout the process, the team overseeing the study will meet regularly to discuss the coding of data into the various categories and thematic areas in order to confirm understandings and address any disagreements in data coding placement (Textbox 3).

Substudy 2 will consist of 4 phases (Textbox 4).

The findings will be reported in accordance with the checklist proposed by the COREQ (Consolidated Criteria for Reporting Qualitative Research) reporting guidelines for qualitative studies [43].

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Textbox 3. Phases of the analysis for substudy 1.

- First, the data from the structured interviews and document review will be coded into the 11 themes proposed by Rapid Assessment Protocol (RAPIA; Table 5), where each theme will be structured according to the interviewees and the regions they represent.
- Next, the data from stakeholders as coded into the RAPIA themes will be cross-referenced with the components and subcomponents of the high-quality health system framework.
- The final step will involve integrating relevant information from substudy 2 into this matrix.

Textbox 4. Phases of the analysis for substudy 2.

- The first phase will involve developing an analytical framework based on codes derived from initial familiarization with the data. This familiarization process will consist of 4 meetings (one meeting per site) in which 3 researchers will listen to the interview transcripts and propose categories for analysis. The categories resulting from the first meeting will be used in the subsequent meetings, where their relevance will be evaluated.
- The second phase will involve coding all the data into the identified codes.
- The third phase will consist of summarizing data from the codes into overarching categories that represent key milestones identified as significant within the patient experience, as well as those identified by their carers and health care workers.
- These overarching category summaries will serve as the foundation for creating a patient journey map to visualize the data and for describing the subcomponents and components of the high-quality health system framework as identified in substudy 1.
- The draft patient journey map will be presented to a subsample of substudy 2 participants in each region to sense check the understanding of their experiences and inform a final version of the map and to feedback into the refinement of the overall analysis.

Ethical Considerations

The research protocol, data collection materials, and consent were initially reviewed and approved by the institutional review board (IRB) at Universidad Peruana Cayetano Heredia (UPCH) on July 20, 2023 (IRB number 209080). Subsequent amendments were approved by UPCH on October 30, 2023, and May 13, 2024, and an extension was granted on June 18, 2024, allowing data collection until June 2025. The protocol and consent forms were also approved by the Imperial College Research Ethics Committee (IRB number 6784708) on February 29, 2024, with a further amendment approved on June 11, 2024. The study will be conducted in accordance with the recommendations for physicians involved in research on human subjects adopted by the 18th World Medical Assembly, Helsinki 1964, and later revisions. Participation in the interviews will be completely voluntary; potential participants will be provided with information about what taking part will involve, and signed consent will be sought for each participant prior to collecting any data.

All invited participants have the option to decline the invitation or withdraw from the study at any time. No monetary or material compensation has been provided, other than a brochure containing general information about dementia. All collected data will be anonymized prior to analysis, in order to protect confidentiality.

In addition to the considerations mentioned earlier, specific measures to ensure ethical safeguards and to abide by local legislation will be taken in the cases of people with dementia and their carers. Assent and dissent will be respected from people with dementia, verbally or nonverbally. Also, carers who function as proxy decision makers will also be consulted about consent when the potential participant has not been able to give full consent.

Results

The IMPACT Salud program was funded in October of 2022, but the study was launched in Peru in November 2023. In the meantime, ethical approval and pilots were conducted before the implementation of both substudies. The pilot study took place from July to September 2023. The implementation of both substudies began in March 2024. As of September 30, 2024, 192 individuals have been interviewed as part of the HSA and the patient journey study from the cities of Iquitos, Huancayo, Tumbes, and Lima. Transcription and data systematization in REDCap will occur simultaneously with the administration of questionnaires and interviews. The analysis phase is scheduled to take place from October 2024 to January 2025.

Discussion

Principal Findings

This study, with its focus on both HSA and understanding the patient journey, will generate comprehensive insights into how dementia is diagnosed and managed across the diversity of the Peruvian health care system. The findings will be organized in 3 core themes from the HQHS framework, such as the process of care, quality impacts, and foundations. It is anticipated that this will reveal areas of strength in dementia care as well as areas where there are issues with quality of provision or lacking provision. This might include, for example, structural issues with financial resourcing, training of health care workers, or the existence of standardized policies and protocols. It is anticipated that there may be divergence between the experiences of stakeholders at different levels of the health system, as well as across the different regions in which the study is being conducted. Furthermore, the study will reveal insights into the facilitators and barriers to using mHealth technology in Peru for supporting better diagnosis and management of dementia.

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To date, few studies have holistically addressed dementia in South America. This work aims to serve as the foundational step in a series of studies across LMICs, particularly in Latin America, assessing health care system readiness to effectively diagnose, manage and provide care for people experiencing dementia and chronic comorbidities. As the burden of dementia and associated conditions rises among older populations in LMICs [44-46], there is a dearth of data on health care system preparedness. Additionally, the study will also address the needs of other work packages as part of the IMPACT Salud program (see Table 1).

It is important to note that using health care system evaluations from high-income nations for public health decisions in LMICs is cautioned against due to considerable disparities in home care systems, health care professional readiness, belief and health literacy, technology and infrastructure availability, as well as the political stability essential for sustained quality care. As such, this research endeavors to provide updated insights into the intricate workings of health care systems in Peru, potentially driving reforms in the health care sector. Furthermore, it aims to foster alignment among stakeholders and amplify the impact of reforms on dementia patients' lives. A notable antecedent of health care systems' responses to dementia is the STRIDE project that engages 7 countries (Mexico, Brazil, India, Indonesia, Jamaica, Kenya, and South Africa) [47]. There is one publication of this study in Mexico, and STRIDE, like IMPACT Salud, involves actors from civil society, such as the Alzheimer's Association of Mexico, its allied associations, and researchers. However, STRIDE does not directly include the participation of patients and carers as project participants, as its goal is to improve the implementation of public policies rather than gathering the needs and experiences of people with dementia in the health care system [48]. A comparative analysis of findings between these projects is planned, aiming to elucidate differences and similarities. The results of this research also aim to provide input for the development of Comprehensive Care Guidelines for individuals with Alzheimer disease and other dementias, a task that the MoH has pending since its proposal in the 2018 regulation of the Law for the Prevention and Treatment of Alzheimer's Disease and Other Dementias [17].

Also, the study has a particular focus on carers due to the significant impact of caring for a person with dementia on their mental health. Carers are 4 times more likely to experience depression and 3 times more likely to experience anxiety [49,50]. For these reasons, it is important to explore the needs of carers and possible opportunities to better support them and reduce any burden they experience. The intervention that will be adapted [51] in work package 3 of the IMPACT Salud program (Table 1) will have carers as its focus, aiming to provide guidance and tools with the aim of improving the quality of life of people with dementia and the mental health and quality of life of their carers.

Study Strengths and Limitations

The RAPIA methodology offers a diverse, multilevel, and national perspective to assess the health system, in this case having dementia as a tracer condition in Peru. While the patient journey complements this by providing insights from a patient-centered perspective about the health care system's functionality.

The HQHS framework will enable the analysis to be organized to identify structural issues (such as access, political support, and availability of qualified health care personnel), as well as relative or subjective issues contingent upon each dementia patient, caregiver, and health care provider (such as trust and service quality).

The decision of using a combination of methodological approaches is based on their focus on the end user of the health system, namely persons with dementia and their carers. Furthermore, the RAPIA methodology has the quality of being flexible to the context, allowing the addition of topics to the interview and new questions to the questionnaire [35]. Finally, the methods offer replicability benefits for researchers and health system specialists in terms of time and costs to implement.

The approach proposed in this study involves examining the macro view while also taking into account the daily lives of people living with dementia. By staying focused on these, we aim to propose solutions in the health system that have a tangible impact on people's lives. The study includes 4 sites with diverse characteristics in terms of population size, ecosystem, mother tongue, and number of people with dementia attended by MINSA; this will allow comparing the quality of the health system and experiences of people with dementia and carers, as well as opportunities in 4 highly diverse contexts within Peru.

While the study has adopted existing robust methodologies for HSA and understanding patient experience, there are potential limitations with applying these in practice. To date, the study has faced difficulties in recruiting dementia patients who meet the inclusion criteria. Our data so far indicate that most patients seek diagnosis late, resulting in worse cognitive decline than expected (a score of less than 6 on the Pfeffer functional test). This issue is compounded by the view of dementia as a normal part of aging, which discourages symptomatic individuals from seeking health care. We have partially addressed this by conducting more interviews with carers in cases where patients themselves do not meet the inclusion criteria.

Furthermore, while the setting for the research includes 4 sites with diverse characteristics to represent the various sociodemographics and cultures of Peru, this is not exhaustive, and there may be factors related to the diagnosis and management of dementia that remain unidentified by this study.

Additionally, the HQHS framework has been used previously with a survey to share information from some domains or subdomains [52]. However, there is not much published research using this framework with qualitative data, so there may be some challenges faced with this during the analysis phase.

Conclusions

This study will provide a national, multilevel insight into the current operation of the Peruvian health system, including an analysis of the quality of services provided. The findings will be structured in 3 core themes from the HQHS framework (process of care, quality impacts, and foundations) in order to

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share information about dementia diagnosis, management, and care from the perspectives of stakeholders, patients, and their carers.

Dissemination

The dissemination strategy of the IMPACT Salud program is focused on sharing the study findings with a wide variety of audiences, including the patient and carer community, health care providers, and policy makers. A variety of dissemination formats are planned, including online and in-person meetings and webinars, policy briefs and briefing notes, social media, and news communication and scientific formats including peer-reviewed journals and conferences. We will also use the project web page [53] to share information for these different audiences in a friendly format.

Acknowledgments

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Data Availability

The datasets generated or analyzed during this study will initially be available in anonymized format from the study investigators (MLP, JH, SCF, and CB) upon reasonable request, in accordance with participants' informed consent and IRB requirements. No publicly accessible repository is currently used for data sharing, but this will be developed as part of the IMPACT Salud study and more information will be available on the study website [53] in due course.

Authors' Contributions

JH, MLP, CB, JJM, and MGL worked in the first version of the protocol. FTS, MLP, JH, and DRV worked to prepare the first draft of the protocol for publication. All authors reviewed the questionnaires for the HSA and the journey map as well as reviewed and approved the current protocol. Members of the IMPACT Salud Study Group: Cecilia Anza Ramirez; María Verónica Belón Hercilla; Julio Leonardo Albitres Flores; Mariela Margarita Villegas Chavez; Javier Eduardo Sanchez Calderon; Kelly Milagros Tello Lizarraga; Lee White; Ángeles Cano Cárdenas; Matías Vega; Ioana Dobre; Martina Cesarina Edith Guillermo Roman; Pablo Fonseca; Marco Da Re

Conflicts of Interest

None declared.

Multimedia Appendix 1
Study manual detailing recruitment procedures.
[PDF File (Adobe PDF File), 95 KB - resprot_v14i1e60296_app1.pdf]

Multimedia Appendix 2
HSA (health system assessment) questionnaire example - health workers and patient caregiver.
[PDF File (Adobe PDF File), 389 KB - resprot_v14i1e60296_app2.pdf]

Multimedia Appendix 3
Patient Journey Interview Guide Example - Caregiver.
[PDF File (Adobe PDF File), 171 KB - resprot_v14i1e60296_app3.pdf]

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Abbreviations

COREQ: Consolidated Criteria for Reporting Qualitative Research
HQHS: high-quality health system
HSA: health system assessment
IRB: institutional review board
LMICs: low- and middle-income countries
mHealth: mobile health
MoH: Ministry of Health
RAPIA: Rapid Assessment Protocol
REDCap: Research Electronic Data Capture
UPCH: Universidad Peruana Cayetano Heredia

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Protocol

The First 6 Years' Experiences of a National Centralized Offspring Surveillance Setting for Dutch Children Prenatally Exposed to Maternal Cancer to Inform Future International Practice: Protocol for a Demographic Review of Referred Families and Key Lessons Learned

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Abstract

Background: Cancer during pregnancy is a rare and significant life-changing event affecting approximately 1 in 1000-2000 pregnancies. With increasing maternal age and broader application of prenatal screening programs such as the Dutch Non-Invasive Prenatal Testing, incidental detection of maternal cancer is becoming more frequent. Advancements in safe treatment options during pregnancy, supported by the International Network on Cancer Infertility and Pregnancy (INCIP), have led to fewer pregnancy terminations. Consequently, more children are exposed to chemotherapy and other cancer treatments in utero. While short-term safety has been demonstrated for many oncological agents, long-term side effects including physical, neuromotor, neurocognitive, and psychosocial impacts on offspring and their families after delivery are still being assessed. Standard settings for surveillance and care of offspring and their families have, however, never been described.

Objective: Given the importance of expertise in assessing the long-term outcomes of children, the Netherlands established the national centralized Cancer in Pregnancy (CIP) offspring outpatient clinic in 2018, which functions as a standard-of-care surveillance clinic and contributes data to the INCIP registry. Here we provide a demographic overview of referred families and to share (logistic) experiences with the national, centralized, multidisciplinary, and standardized long-term surveillance program for all Dutch children with in utero exposure to maternal cancer and its treatment.

Methods: The CIP offspring outpatient clinic is located at the Princess Máxima Center for Pediatric Oncology and provides surveillance from infancy until 18 years of age. The, relatively small dedicated team, comprising pediatric oncologists, physiotherapists, and a psychological expert, offers a 1-day, multidisciplinary assessment, including physical examinations, neuromotor tests, cardiac monitoring (for anthracycline exposure), renal and auditory screening (for platinum agents), neurocognitive testing, and psychosocial evaluation. Surveillance is aligned with international INCIP guidelines.

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Results: From May 2018 to 2024, a total of 226 children (from 221 mothers) have been referred to the CIP offspring outpatient clinic, with 465 follow-up visits completed. The most common maternal cancer types were breast, gynecological, and hematological malignancies. Most women (58%) received chemotherapy during pregnancy; 11% of them had surgery only, 3% underwent radiotherapy, 3% underwent immunotherapy, 16% received a combination of treatment modalities, and 8% did not undergo treatment during pregnancy. Anthracyclines were the most commonly used agents. Median gestational age at delivery was 37.3 weeks. Fourteen percent of the mothers died shortly after delivery, underscoring the emotional and logistical challenges for families.

Conclusions: The CIP offspring outpatient clinic provides a unique, structured approach to long-term surveillance for in utero–exposed children, which enables early detection of potential late effects and provides comprehensive family support. By sharing knowledge and experiences from the unique setting of this national centralized CIP offspring outpatient clinic, this initiative may inspire other countries in developing similar translational facilities to support affected families and improve care worldwide.

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KEYWORDS

surveillance; offspring; outpatient clinic; cancer; treatment; exposure in utero, toxic effects

Introduction

Cancer during pregnancy is rare, occurring in 1 in 1000-2000 pregnant women [1]. However, this incidence is rising as women tend to delay childbearing [2]. Also, since the introduction of the Non-invasive Prenatal Testing program in the Netherlands (in 2018), maternal cancer, often asymptomatic, is detected incidentally, even before clinical symptoms appear [3]. Hence, cancer during pregnancy is an emerging health and societal challenge, which necessitates dedicated management for the mother and child.

Several decades ago, termination of pregnancy was the standard recommendation for pregnant women with cancer. Today, however, treatment during pregnancy is often feasible and safe. The major shift in this clinical approach is based on evidence from epidemiological studies following children exposed to cancer treatment in utero, primarily led by the International Network on Cancer, Infertility, and Pregnancy (INCIP), founded in 2005 in Europe. This robust framework, now extended to 26 counties worldwide, has significantly expanded our understanding of the long-term effects of in utero exposure to chemotherapy [4-8]. While many chemotherapeutic agents are now considered safe during pregnancy, concerns remain regarding potential long-term toxicities [9-13]. Certain agents, such as anthracyclines and cisplatin, are known to cause long-term cardiotoxicity, nephrotoxicity, and ototoxicity in childhood cancer survivors [9,12,14-17]. Nevertheless, early data suggest that cisplatin may affect hearing, warranting long-term follow-up [2,8,9]. Age-specific cumulative dose limits exist, based mainly on epidemiological data, and placental transfer varies by drug [18,19]. Crucially, prematurity, and not the maternal treatment itself, has been identified as the most significant independent factor that determines affected neurocognitive and motor development in exposed offspring, but the impact of prematurity is similar to that in the healthy population [20]. Preterm birth is known to increase the risk of motor deficits such as coordination difficulties, impaired balance, and fine motor challenges, even in the absence of cerebral palsy [20,21]. Given these risks, prolonging pregnancy whenever feasible is prioritized, with additional chemotherapy courses preferred over premature delivery [2]. These data enhance our understanding and help future expecting patients with cancer and their partners to make informed decisions about the pregnancy complicated by cancer. In most countries, the available program for offspring surveillance is generally dispersed among various and often small centers. Consequently, expertise in the specific field of toxicity in the offspring after exposure to cytotoxic agents is limited.

Since 2018, Dutch pediatric cancer care has been centralized at the Princess Máxima Center, optimizing treatment outcomes and reducing toxicity [22]. Building on this model, the national Cancer in Pregnancy (CIP) offspring outpatient clinic was allowed to be hosted in this center to monitor all Dutch children prenatally exposed to maternal cancer and its treatment. The clinic offers standardized care and long-term surveillance across physical, neuromotor, neurocognitive, and psychosocial domains, integrates research on prenatal treatment effects, and serves as a knowledge hub for health care professionals. Such a centralized setting is currently not available in other countries.

In this overview, we aim to present the design of our unique clinical framework and our experiences from the first 6 years of the CIP offspring outpatient clinic. By sharing our experiences, we aim to encourage the development of similar centralized translational follow-up programs worldwide, improving care by centralization for affected families now and in the future.

Methods

Recruitment of Offspring

In 2012, the Cancer in Pregnancy advisory group ("Adviesgroep Kanker en Zwangerschap") had been established by Dutch members of the INCIP group [23]. This advisory board (Adviesgroep Kanker en Zwangerschap) has expanded its activities on an international scale now and has evolved into an international participation from countries involved in the INCIP, operating under the name ABCIP (Advisory Board on Cancer, Infertility, and Pregnancy [24]). ABCIP provides

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multidisciplinary, individualized expert advice for every pregnant patient with cancer within a few days based on evidence from the current literature [23]. This advice is then delivered to physicians responsible for these pregnant patients with cancer. The advisory group comprises a national multidisciplinary team, including oncologists, hematologists, surgeons, radiotherapists, gynecologists, obstetricians, clinical pharmacologists, and scientific researchers, and includes the pediatric oncologists and psychologists responsible for the care of children followed at the CIP offspring outpatient clinic at the Princess Máxima Center in the Netherlands. Referral of a neonate to the national CIP offspring outpatient clinic for standard-of-care follow-up at the Princess Máxima Center is always part of standard advice (Figure 1). This proactive approach identifies potential offspring already at risk in utero.

Figure 1. Translational continuum of AKZ, INCIP, and the CIP offspring outpatient clinic. The image was created using BioRender. AKZ: Adviesgroep Kanker en Zwangerschap; CIP: Cancer in Pregnancy; INCIP: International Network on Cancer Infertility and Pregnancy.

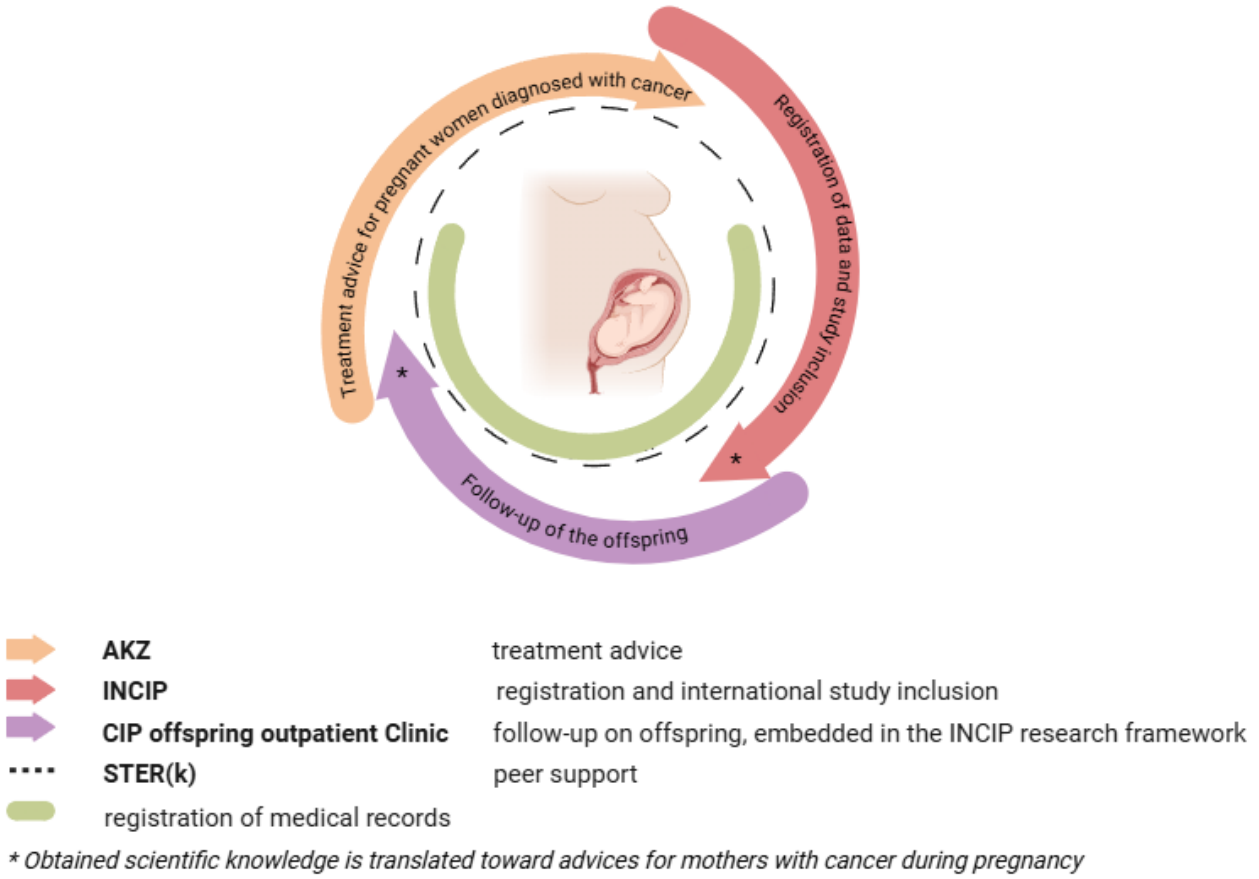

Design of the CIP Offspring Care Setting

The surveillance of offspring and their families is conducted at the long-term follow-up outpatient clinic at the Princess Máxima Center, which had been specifically established for childhood cancer survivors in 2018. This area in the hospital, uniquely suited for families exposed to cancer in utero, is separated from the area of direct patient care, thereby limiting the interaction with actively treated children with cancer. We designed this outpatient clinic with all necessary diagnostic facilities (including cardiac ultrasound, electrocardiograms, audiological testing, laboratory facility, pulmonary function testing, neuropsychological and neuromotor testing, as well as clinical consultations) within this designated area, in order to enable the performance of all tests, in 1 day, for the families' convenience, merely, on one and the same location (Multimedia Appendix 1).

The CIP offspring outpatient clinic's small multidisciplinary team (2 pediatric oncologists specialized in toxicity during and after cancer treatment, 2 physiotherapists, and a psychologist) aims to detect early deviations in physical, neuromotor, neurocognitive, and psychosocial development.

Standard of Care and Surveillance Strategy

As part of standard care, families are invited for follow-up visits at fixed intervals per the INCIP protocol. Each visit includes a physical and neurological consultation by pediatric oncologists, a neuromotor assessment by a physiotherapist, and limited blood tests for children exposed to chemotherapy in utero (with consent). Cardiac screening is added in case of anthracycline exposure; and nephrological and audiological assessment, after platinum-based exposure. Offspring of mothers with metastatic disease, especially those with histologically confirmed placental involvement, undergo abdominal ultrasounds in the first year to exclude spread of tumor cells to the liver. Identified medical or psychosocial concerns lead to referrals to appropriate specialists, including clinical geneticists, if applicable.

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Beyond the context of routine surveillance, for research purposes, internationally standardized, age-appropriate neuropsychological testing is conducted longitudinally, starting from 18 months of age and continuing thereafter [6,7]. Additionally, prior to testing, parents are invited to complete questionnaires regarding general health as well as the executive and behavioral functioning of their child, as part of the neuropsychological investigation [25,26]. All tests are pursued with informed consent. As embedded in the international INCIP research framework, upon obtaining informed consent and anonymization, all collected care data are obtained during regular follow-up care and can be used for research purposes (NCT00330447, METC NL43546.078.13) based on (parental) written informed consent from all participants. The full study protocol is available on the web [27].

Two weeks after the consultations, the results of all tests are shared with the families by telephone. Referral advice, including recommendations for interventions and support in schools, childcare facilities, or educational institutions, can be provided. For this purpose, all results of neuropsychological testing are sent to families by mail. Obviously, we closely communicate with the general practitioner of the families. If any medical, neurocognitive, or developmental concerns arise during clinical care evaluation, children and/or parents are offered to be referred to relevant expert physicians, psychologists, or pediatric physiotherapists, preferably in the region where the families reside, if available. In our experience, this is especially important in families where the mother died after delivery.

Ethical Considerations

The ethical committee of the Erasmus Medical Center Rotterdam, the Netherlands (METC NL43546.078.13) approved of the study and written (parental) informed consent was obtained for all participants. The study was performed in accordance with the tenets of the Declaration of Helsinki. The full study protocol is available on the web [27], and the study is registered in ClinicalTrials.gov (NCT00330447; first registered on May 26, 2006).

Results

In this section, we describe the experiences of the CIP offspring outpatient clinic in the first 6 years.

Epidemiology

Since the initial registration of pregnant women with cancer in the INCIP in 2005, a total of 3630 women have been registered, all of whom have given live birth. Of these women, 436 were registered in the Netherlands. Since the centralization of outpatient care for CIP participants' families in the Netherlands in 2018, a total of 226 children (221 mothers; 5 twins) had been referred to our CIP offspring outpatient clinic (Multimedia Appendix 2). This had already resulted in a combined total of 465 follow-up visits until May 1, 2024 (Figure 2). Of these children, 125 out of 226 (55.33%) were female and 101 (44.7%) were male. The median gestational age at birth was 37.3 (IQR 26.3-41.7) weeks. The distribution of maternal cancers was similar to that in the general population [28]. Disease- and treatment-related characteristics are presented in Table 1. Moreover, we observed an increase in gestational age at birth over time, which is likely attributable in part to the implementation of evidence-based recommendations by the multidisciplinary advisory board aimed at minimizing preterm delivery.

As of May 2024, thirty out of 221 (14%) mothers had died due to cancer early after delivery. Twelve of these mothers died of breast cancer, 5 died of a hematological malignancy, 4 died of gastrointestinal cancer, 3 died of cervical cancer, 3 died of melanoma, 2 died of bone cancer, and 1 died of a rhabdomyosarcoma. Overall, the children appear to be doing well medically. However, of the 226 children, we did observe 1 case of a neuroblastoma (stage IV) in a child at the age of 3 years and treatment was administered. This boy had been born from the mother with a meningioma and had been exposed to surgery and anesthesia in utero (at gestational age 22 weeks). This child is under regular cancer follow-up care after his cancer diagnosis at the Princess Máxima Center now.

We recognized that being diagnosed with cancer during pregnancy is a significant life event for the entire family, which can evoke symptoms of psychological concern. We noticed that the medical care and psychosocial support of the small dedicated core team, the focus on the long-term care plan and surveillance, and attention to the entire family system are highly appreciated by the families in general. Parents particularly appreciate being reassured, especially in the early stages following a stressful pregnancy, that their child is progressing along expected developmental lines. They value being well-informed about their child's development, and the combination of a small, dedicated team and the logistical framework we have developed for our clinic proves to be highly effective in supporting the parents.

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Figure 2. Median gestational age at birth (GAB) of the offspring (n=226).

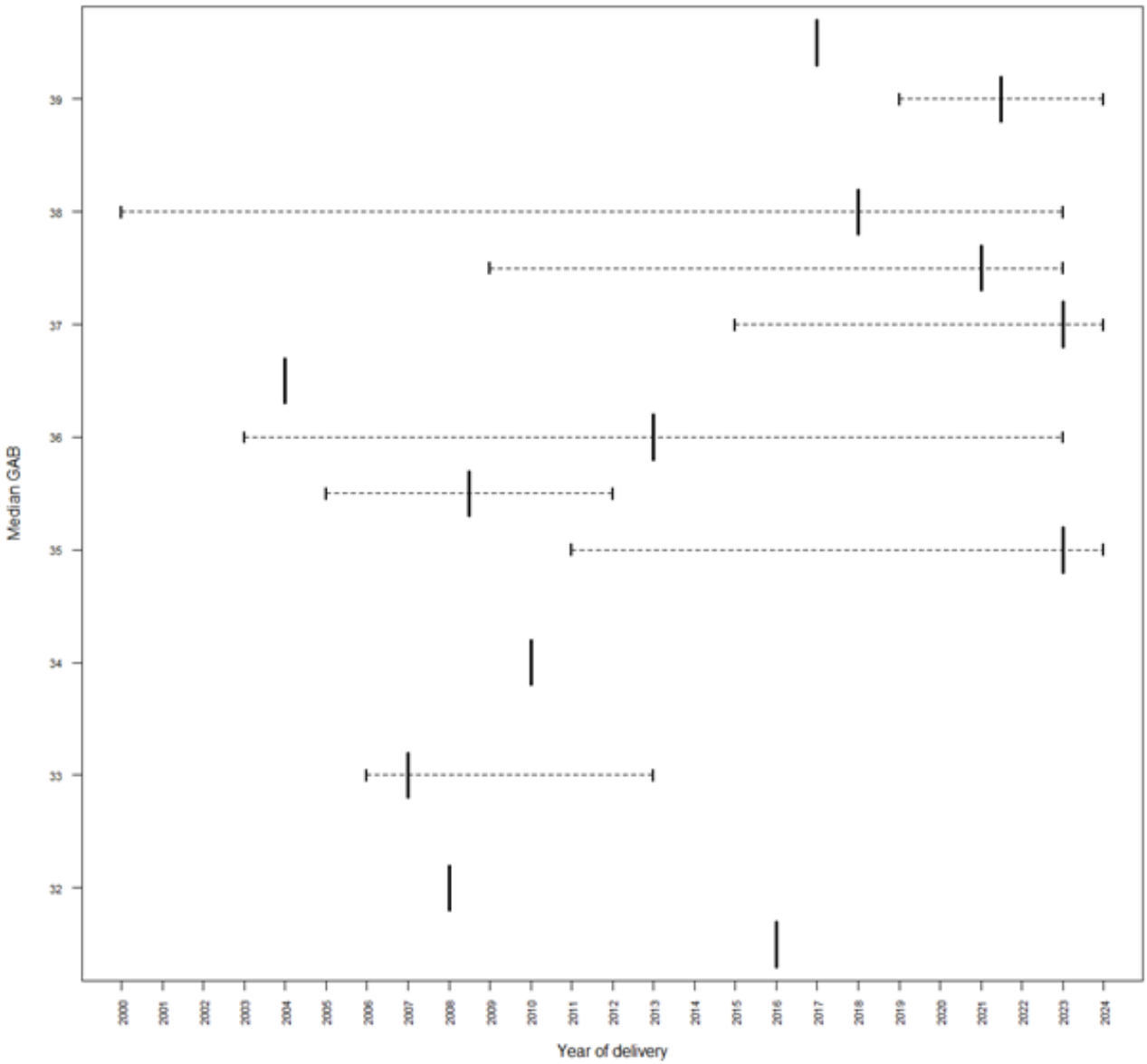

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Table 1. Disease and treatment-related characteristics of the mothers.

Characteristic	Children, n (%)
Maternal cancer diagnosed during pregnancy (n=226; 5 twins)	
Breast	108 (47.78)
Gynecological	40 (17.96)
Hematological	30 (13.27)
Melanoma	21 (9.29)
Gastrointestinal	7 (3.09)
Brain tumor	4 (1.70)[a]
Bone	3 (1.33)
Urothelial	3 (1.33)
Other	10 (4.42)
Chemotherapeutic agent type (n=132)	
Anthracyclines	109 (48.23)
Taxanes	65 (28.76)
Platinum	40 (17.70)
Other	12 (5.31)
Timing radiotherapy (at gestational age in weeks; n=7)	
7-13	1 (14.28)
11-14	1 (14.28)
18-23	1 (14.28)
20-27	1 (14.28)
27-34	1 (14.28)
Unknown	2 (28.57)
Immunotherapy (targeted) type (n=6)	
PEGylated interferon	1 (16.67)
Nilotinib	1 (16.67)
Bosutinib	1 (16.67)
Trastuzumab	1 (16.67)
Trastuzumab + pertuzumab	1 (16.67)
Interferon + nilotinib	1 (16.67)

[a]One (25%) later turned out to be a meningioma.

Peer Support

During the initial years of the CIP offspring outpatient clinic, parents took the initiative to establish a peer support Association—Stichting STER(k). This association provides support to parents and partners through information, a website, and on-demand support activities [29]. Stichting STER(k) provides peer support for women, their partners, and families facing cancer during pregnancy and in the postpartum period, thereby addressing intensive treatment for the mother and the needs of the newborn, which often create logistical challenges. The association strongly collaborates with our CIP offspring outpatient clinic team to disseminate general information by covering topics such as psychological and social issues and logistic aspects of a pregnancy complicated by a cancer (treatment) and practical issues such as breastfeeding, maternity care, and maternal health. Organization of parent-information workshops has been initiated.

Discussion

This paper outlines the mission, design, and logistics of the Dutch CIP offspring outpatient clinic, the first nationally centralized clinic for children exposed to cancer in pregnancy, and shares key lessons learned.

Experiences of the CIP Offspring Team

We consider this teamwork, the establishment of Stichting STER(k), and the continuum with the ABCIP and INCIP groups, which identify the children already during pregnancy, as well

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as the translational set-up, that is, the contribution of the outcome data to the INCIP registry from the CIP offspring outpatient clinic (and the studies carried out in other countries) to provide knowledge that informs the ABCIP [24], as keys to success.

We have learned that gestational age is the most significant independent predictive factor for long-term neurocognitive impairment rather than in utero exposure to cancer treatment. As we currently discourage premature delivery, whenever feasible over time, we observed that prematurity consequently appears to decrease over time. Furthermore, we have observed inconsistent national referrals due to lack of expertise. This requires ongoing effort.

Finally, our nationally centralized structure is unique within the INCIP research framework, as follow-up in other countries is typically decentralized or is currently not taking place. Sharing our experiences as well as international communication may support similar structured follow-up in other countries, ultimately improving global outcomes for children prenatally exposed to maternal cancer.

Limitations

Long-term effects of maternal cancer treatment during pregnancy, especially beyond adolescence, remain largely unknown due to limited very-long-term follow-up data (>10 years). This is crucial, as late effects, such as anthracycline-induced cardiotoxicity, may emerge decades later, similar to what has been observed in children with cancer [30-37]. Ongoing surveillance through adolescence and adulthood is essential to uncover potential risks in physical, cognitive, emotional, and psychosocial development. Collaboration with the INCIP research framework and the advisory board has provided valuable insights, suggesting that early care may be more targeted, focusing on specific evidence-based risk factors, and shifting the emphasis toward the very-long-term effects of prenatal exposure to maternal cancer treatment.

Furthermore, most knowledge about long-term side effects for offspring is available from large cohort studies with childhood cancer survivor with conventional chemotherapeutic agents. The rapid development of novel innovative cancer treatments poses the need for additional risk exploration, as some of them had not been used in children so far [38-41]; hence, in vitro exploration is required before these treatments can be safely applied in pregnant women with cancer [42].

In pediatric oncology, where the median age of the first childhood cancer survivors is now approaching 40 years, the long-term effects of chemotherapy exposure are gradually becoming clear. The CIP offspring outpatient clinic, with shorter follow-up so far, highlights the need for lifelong, individualized monitoring similar to that in childhood cancer survivors. Families often need additional support to cope with the complex postpartum period; referrals are made to specialized care facilities and peer support organizations like Stichting STER(k), in collaboration with general practitioners. To improve care, our goal is full cohort inclusion through increased awareness and standardized, risk-adaptive screening that is timed appropriately for different toxicities. Lifelong multidisciplinary follow-up and further research, including molecular studies, are vital to fully understand and support this unique population.

Conclusions

In conclusion, we have found that the establishment of a dedicated national centralized CIP offspring outpatient clinic for exposed offspring of pregnant women with cancer during their pregnancy who are receiving treatment addresses a clear need for structured care and support for families, while providing standardized long-term surveillance and consistent data collection on the health and development of exposed children. Given the relative rarity of this condition, this setup in the Netherlands, which provides this care in a nationwide expert setting with the aim of providing optimal care for children and their families, may serve as a model for other countries that aim to establish a similar national centralized program. This paper may help enhance connections with other countries that envisage building a similar structure.

Acknowledgments

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Data Availability

All data generated or analyzed during this study are included in this published article.

Authors' Contributions

Writing—original draft: EAH and MMvdHE

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Writing—review and editing: AMK, EJV, SCH, EMvD-L, CARL, MK, FA, MMAvG, and MvG

Conflicts of Interest

None declared.

Multimedia Appendix 1
Design of the LATER-outpatient clinic embedded in the Princess Máxima Center.
[PNG File , 244 KB - resprot_v14i1e71612_app1.png]

Multimedia Appendix 2
Recruitment.
[PNG File , 51 KB - resprot_v14i1e71612_app2.png]

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Abbreviations

ABCIP: Advisory Board on Cancer, Infertility, and Pregnancy
CIP: Cancer in Pregnancy
INCIP: International Network on Cancer Infertility and Pregnancy

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Protocol

Resolving Challenges in HIV Cure–Related Research: Protocol for a Modified Delphi Consensus-Building Process

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Abstract

Background: HIV cure–related research is expanding rapidly, bringing both new opportunities and ethical challenges. Historically, clinical trials for novel HIV treatments have underrepresented populations most affected by HIV, such as Black gay men and transgender women. This disparity is compounded by medical mistrust and historical mistreatment of racially and ethnically diverse individuals in the United States. Addressing these issues is crucial as we plan HIV cure–related clinical trials. We aim to build consensus on how to increase representation of groups most affected by HIV in cure-related trials in the United States.

Objective: We aimed to describe a protocol using a hybrid Delphi consensus-building methodology to build consensus on 3 key research questions: how to better engage populations in HIV cure research who carry the greatest burden of HIV (ie, racial, ethnic, sex, and gender minority groups); how to enhance trust and diminish mistrust in health care and scientific settings that influence willingness to participate; and how to design HIV cure research and analytical treatment interruption protocols that do not limit participation of working adults.

Methods: We used a hybrid Delphi method, involving 4 iterative survey rounds. Initial surveys were open-ended and broad, refining over subsequent rounds into more specific, closed-ended questions based on previous feedback. Between rounds, an independent stakeholder group reviewed interim findings, incorporating a nominal group technique to enhance the process. Panelists represented diverse racial, ethnic, sex, and gender perspectives, including an intentional oversampling of experts on racial and ethnic minority issues. Recruitment was facilitated through partnerships with community-based organizations, such as The Well Project, National Minority AIDS Council, and TruEvolution.

Results: As of December 2024, all 4 Delphi survey rounds and 3 nominal group technique discussions have been completed. The process progressed from broad, open-ended questions in round 1 to structured ranking and rating in rounds 3 and 4. Iterative feedback informed survey refinement between rounds. The final data analysis and synthesis of consensus recommendations are underway and will be reported in a forthcoming results paper.

Conclusions: The hybrid Delphi methodology effectively refined responses and built consensus on engaging priority populations in HIV cure research. Oversampling of diverse participants and the inclusion of independent stakeholder feedback added robustness and inclusivity to the findings. Future steps include detailed data analysis and data dissemination. Consensus recommendations will be reported in subsequent manuscripts to inform more inclusive, trust-centered, and accessible HIV cure trial design.

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KEYWORDS

hybrid Delphi; consensus building; HIV cure research; analytical treatment interruption; recruitment; underrepresented populations; protocol

Introduction

Background

Several major advancements in the areas of therapeutics for the prevention and treatment of HIV have made finding a cure more possible than impossible [1]. However, as the field of HIV cure research grows in the number of conducted and planned studies, and in the complexity and intensity of potential cure-related strategies, ethical and social challenges emerge that must be addressed [2-4]. Furthermore, several HIV cure–related trials require the interruption of HIV antiretroviral treatment (ART)—a process known as analytical treatment interruption (ATI) [5].

Unfortunately, biomedical advancements for ending the HIV epidemic have been associated with a widening of disparities, as people with HIV who carry the greatest disease burden (eg, Black gay men and transgender women) are underrepresented in clinical trials of these advancements. Moreover, they are not the first to benefit once implementation has rolled out. This was true when a new class of combination ART arrived in 1995 [6], which dramatically increased the likelihood of people with HIV achieving viral suppression, and again in 2012, when pre-exposure prophylaxis for HIV prevention was approved. White men who have sex was men were significantly more likely to use pre-exposure prophylaxis than Black men who have sex was men, although Black men represented the population carrying the highest burden of HIV [7-9].

Accurately representing the disease burden and proportionally enrolling people with diverse racial, ethnic, sexual, and gender identities is a key challenge to ending the HIV epidemic. It is well-documented that past demographic characteristics of trial participants do not reflect the diversity of people with HIV in the United States [10-12]. Four reviews or landscape analyses [10-13] reporting on over 100 HIV cure–related studies found that detailed demographic information of trial participants was severely lacking, and in many cases, could not be extracted. When available, almost all racial, ethnic, sex, or gender minority groups made up <20% of trial participants [10]. Furthermore, data on young adults are also limited, as ATI trial participants tend to be older [14,15].

It is important to explore and address sample differences in HIV cure outcomes between demographic subgroups. For example, according to the US Centers for Disease Control and Prevention, 65% of people with HIV in the United States are Black or African American or Latino [16], and although smaller in total numbers, Black or African American cisgender women and transgender women are severely overburdened compared to their White and cisgender counterparts [16]. Currently, HIV cure trial participant samples do not come close to representing the populations carrying the greatest burden of HIV in the United States [17].

Considering the risks posed by HIV cure research, which often involve monitoring interruptions and pauses of HIV ART—also called ATIs [5], additional barriers to participation are likely structural in nature. Recent federal guidance and research on diversifying clinical trial samples identified potential strategies to overcome barriers that exclude certain groups [18-21], such as documenting demographic information, eliminating inclusion and exclusion criteria that are not scientifically justified, listing enrollment targets (eg, by race and ethnicity, as well as sex and gender), and designing study visit schedules that allow for working adults and caregivers to participate [22]. However, given the historical and ongoing maltreatment of people of color in medical settings [23,24], it is important to acknowledge that hesitance to engage in risky research is compounded by issues related to trust and medical mistrust [25-28] and further exacerbated by biases in biomedical teams screening participants based on assumptions about their willingness to participate.

The prevailing call to action as explained by the phrase “nothing about us without us” [12,29-32] makes clear that advancing HIV cure science without the people who are most impacted by HIV in the United States is a major failing of the scientific community. To prepare for the advent of a cure for HIV, we sought to generate consensus on helping address outstanding ethical and social challenges facing the field of HIV cure research regarding priority populations.

Objectives

In 2018, a consensus meeting [5] organized by the Ragon Institute of Massachusetts General Hospital, Massachusetts Institute of Technology, and Harvard Medical School led to key recommendations for future HIV cure research design. A second ATI consensus meeting, organized by the Ragon Institute and the US Military HIV Research Program, occurred in Nairobi, Kenya, in May 2024, with a focus on building consensus for implementing ATIs in resource-limited settings (report forthcoming). However, these meetings were led by researchers who discussed and set current priorities using an invitation-only panel format, which may not fully consider the needs and priorities of potential HIV cure research participants. To build on prior efforts, such as the ATI-focused consensus meetings led by the Ragon Institute, which were conducted through invitation-only expert panels, we adopted a hybrid Delphi consensus-building approach. The Delphi method offers a more inclusive, systematic, and iterative process, allowing integration of community perspectives, diverse stakeholder engagement, and structured feedback across multiple rounds. This approach is particularly well-suited for addressing ethically complex issues in HIV cure research that require consensus from both experts and affected communities [33,34].

Here, we describe a protocol to build consensus on three research questions: (1) how to better engage populations in HIV cure research who themselves carry the greatest burden of HIV (ie, racial, ethnic, sex, and gender minority groups); (2) how to enhance trust and diminish mistrust in health care and scientific

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settings that are associated with lower willingness to participate in HIV cure research; and (3) how to design HIV cure research and ATI protocols that do not limit participation of working adults (Table 1). Notably, we focus this discussion on the United States, given the sample recruitment strategy and the professional connections within the investigators' social networks.

Table 1. Initial unresolved challenges in HIV cure–related research.

Potential challenges	Possible questions to panel
Engaging people with HIV in HIV cure research who have been historically excluded, including Black and African Americans, cisgender women, and sexual and gender minority groups	• What are the reasons for the underrepresentation of diverse people with HIV in HIV cure research? • What are the strategies we can use to engage diverse people with HIV in HIV cure research?
Enhancing trust and minimizing medical mistrust in research, and accepting or tolerating analytical treatment interruptions	• What is medical mistrust to you? • What types of trust influence research? • How does trust and mistrust affect HIV cure research? Analytical treatment interruptions specifically? • Whose responsibility is it to address trust and mistrust in HIV cure research? How would you address it in your specific role?
Meeting the needs of adults with full-time responsibilities	• How should normal work schedules inform trial protocol designs? • How do we operationalize trial activities that do not require extended absences from work?

Methods

Hybrid Delphi Process Study Design

The goal of our hybrid Delphi process was to arrive at consensus around challenges facing HIV cure research participation. On the basis of current published recommendations around Delphi methods [35,36], our study consisted of 4 survey rounds. Each survey contained modules corresponding to each of the 3 challenges listed previously. In this approach, each round of data was rapidly and iteratively analyzed to generate consensus around each challenge. The process repeated until no further refinements or considerations emerged around a challenge. The survey rounds began with open-ended and broad questions, then became narrower and closed-ended, in accordance with previous round responses from the study participants. For example, in round 1, participants provided free-text responses to the question "What barriers stand in the way of recruiting more women into HIV cure trials?." These free-text or qualitative responses were analyzed using a general thematic analysis approach. In round 2, we asked this same question in the following format: "Out of the top five barriers to women being recruited into HIV cure trials your group identified in the previous round, which is most important to you?." Respondents moved toward ranking responses in round 3 and rating them in order of importance in round 4, that is, "If we have to prioritize one barrier to recruiting women into HIV cure trials, is it A, B, or C?." Thus, over the course of this process, a consensus was built.

To further ensure the robustness of findings, in between the survey rounds 1 and 2, 2 and 3, and 3 and 4, we asked an independent stakeholder group to review the interim survey findings. Implementing this group review introduced a hybrid design [37,38] to the Delphi process, capitalizing on the benefits of a diverse survey response panel and ensuring data validation. In this design, an independent (nonpanel) community expert group comprising 8 participants provided feedback on each survey round in meetings structured according to the nominal group technique (NGT) [35,39]. The NGT minimized "loudest voice" bias possible during the traditional free-flowing focus group format by structuring time for each participant to share their contributions. Then, we aggregated feedback to verify findings and identify information gaps in the emerging data from survey rounds [37,38]. This feedback also informed subsequent survey questions (Figure 1).

The hybrid Delphi design conferred numerous advantages not evident in an invitation-only panel format. The methodology decentralized input, prevented confrontation, increased comfort in raising controversial questions, and allowed for giving controlled feedback in each round [36,40]. Importantly, the technique prevented singular views from dominating or less popular perspectives from being marginalized. The online administration of the survey resolved geographic limitations [36,40] and allowed for confidentiality in response submission. Including multiple expert groups increased representation of professional backgrounds, academic disciplines, and community stakeholder input.

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Figure 1. PERSIST Delphi data collection analysis flowchart. NGT: nominal group technique.

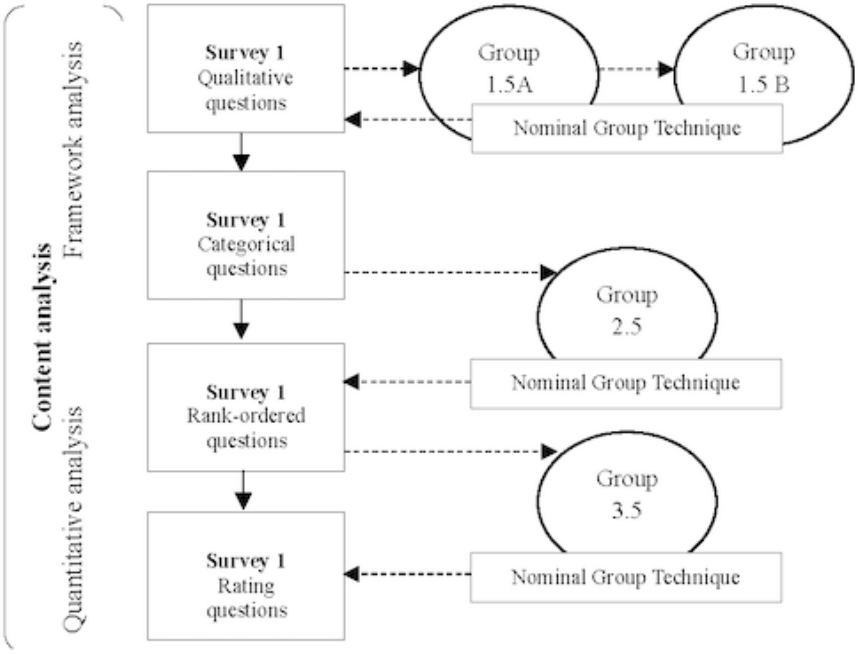

Eligibility, Identification, and Recruitment of Delphi Panel Members

To meet our objectives, we recruited Delphi panel members (ie, survey respondents) representative of racial, ethnic, sex, and gender minority groups, as well as experts in HIV cure in the United States. Expertise was defined as the ability to represent the viewpoint of each group, based on the number of years in a professional field or in the field of HIV cure research. The panelists, although independent, collectively represented 1 of 6 distinct perspectives: A—community experts and members, B—biomedical researchers, C—HIV care providers, D—funders and private industry members, E—bioethicists, regulators, and institutional review board (IRB) members, and F—individuals studying medical mistrust, medical racism, and community engagement (Table 2). Importantly, to correct for the underrepresentation of racial and ethnic minority groups in HIV cure research, we oversampled the group representing expertise in this topic (group A; projected n of 16 rather than 8). This was done to ensure that perspectives from those most disproportionately affected by HIV were meaningfully reflected in the consensus-building process. The overall sample size was selected to ensure broad input, aligned with previous research [36], and helped preserve management of the panel.

To recruit panel members, we leveraged the community and scientific networks of our investigative team. Specifically, we partnered with 3 highly influential organizations in their respective fields (The Well Project, National Minority AIDS Council, and TruEvolution) to identify key panel members representing diverse groups of people with HIV. The Well Project also assisted with identifying racially and ethnically diverse cisgender women and transgender women who systematically reviewed data and provided feedback during the NGT.

Table 2. The initial planned panel composition by the Delphi groups.

Group	Projected, n	Description
A	16	Key persons that represent the *perspectives of people with HIV* across spectrums of age, sex and gender, race and ethnicity, and regions of the United States. Importantly, we oversampled group A to represent the demographic diversity of *people with HIV* (age, race and ethnicity, sex and gender, and US region).
B	8	*Biomedical HIV cure researchers* in the ACTG[a] network and other HIV cure research groups that have used ATIs[b] in the past 5 y.
C	8	*HIV primary care providers* (including those not involved in HIV cure research). The inclusion of HIV primary care providers is important to ensure ATIs remain acceptable, and this group has been underrepresented to date.
D	8	*Funder and industry representatives* who provide funding to support HIV cure research.
E	8	*Bioethicists, regulators, and Institutional review board members* who may review HIV cure research.
F	8	*Individuals studying medical mistrust*, medical racism, and community engagement.

[a]ACTG: AIDS Clinical Trials Group.

[b]ATI: analytical treatment interruption.

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Delphi Survey Procedures

In each round, Delphi panelists received, via email: a survey link; an individually assigned 3-character participant ID (PID) number consisting of their respective group designation (A to F) and 2 digits; and a reminder of their respective study group assignment (A to F). Each survey began with video-recorded messages from the investigative team describing the overall study purpose and the round-specific instructions. In round 1, panelists first completed a standard demographic questionnaire, which also included questions about the number of years of professional experience and the number of years worked in HIV cure–related research or health research. Panelists who missed round 1 and entered the study in subsequent rounds completed informed consent and the demographic form as of their entry round. Panelists entered their PID and selected their study group, then proceeded with each survey. Surveys were programmed in Qualtrics XM.

Contents of Delphi Surveys and Analyses

Overview

Demographic data were compiled in SPSS. Data exports from Qualtrics XM were analyzed in Microsoft Excel. In each survey round, we conducted standard quality checks, checking raw data for duplicates, missingness, partial completion, and skip logic, as needed. Responses were both pooled for overall sample analysis and grouped by respondent expertise category (A to F). Spreadsheets were set up such that each row represented a unique response, and each column a unique code.

Round 1

In round 1, framework analysis guided our analytic approach [41-43]. Framework analysis is useful when there is a need to organize open-ended responses to prespecified questions over a discrete period. Framework analysis consists of (1) deep familiarization with the data; (2) coding raw data based on *a priori* and emergent themes; (3) finalizing codes in an analytic framework; (4) applying the analytic framework to restructure the data to summarize each narrative; and (5) mapping the data to reduce volume, resulting in a matrix view [41,42].

We adopted an inductive coding approach. Coders (AK and LRG) read the responses, created a code per unique concept within the response, and then recorded this code in a column within a Microsoft Excel sheet. If applicable, they then created subsequent codes in an adjacent column. Once a code was created, the column was dedicated to that code, and the code was listed as the column header. The process continued with subsequent codes. Categories were modified as needed to capture greater breadth. New categories were created to minimize overlap of separate concepts. This procedure resulted in a matrix, with each row corresponding to the unique response, parsed into codes, and each column representing the unique code.

We counted the total number of code occurrences, computing the proportion by dividing the total by the sample size. Next, we obtained an ordered list of responses, from most frequent to least, per question, by first flipping the dataset (via the paste transpose function in Microsoft Excel), then sorting the data in descending order on the percentage column. We then created a 3-part item for each question, categorizing the “most reported,” “less reported,” and “unique” responses. We defined “more,” “less,” and “unique” as follows: (1) more frequent codes (occurring in more than 10% of responses), (2) less frequent codes (occurring in 10% or fewer of the codes), and (3) unique codes (occurring only once). Notably, “consensus” varied, ranging from a low of 10% to 18% in categorized responses to one question, to a high of 10% to 71% in another. We then refined the existing code list. Unique items were further consolidated into “more” or “less” frequently occurring codes, as appropriate. Responses were combined into broader thematic categories and synthesized in a Microsoft Word document.

Round 2

On the basis of the round 1 findings, we developed the round 2 survey. We organized the second survey into three main parts: part 1—barriers and burdens to participation in HIV cure research with ATIs, part 2—strategies and solutions to enhance participation in HIV cure research with ATIs, and part 3—general questions and medical mistrust and requiring thresholds in HIV cure research (eg, trials must enroll a minimum percentage of racial and ethnic minority group). In each of parts 1 and 2, the general questions were presented first and the subgroup-specific questions asking about specific populations (ie, Black or African American and Latino populations, cisgender women, and transgender women) followed. In this round, we collapsed the Black or African American and Latino subgroups, given multiple commonalities in respondents’ responses to recognized barriers and proposed solutions within the 2 priority populations.

Respondents were asked a series of bipartite questions. First, select 5 items from the most commonly reported responses; then, select 3 items from the less commonly reported responses. Response items were grouped into topical themes and narrowed down as follows: overall barriers and solutions (Topic 2 from round 1)—8 response items per question and subgroup-specific barriers and solutions (Topic 1 from round 1)—approximately 5 items (notable exceptions: 6 more reported barriers for cisgender women and 4 less reported barriers for transgender women). We rephrased response items for clarity, coherence, and internal consistency, based on reviewer comments.

Once the survey fielding was completed, we analyzed the data. As in round 1, we first conducted standard quality checks. In Microsoft Excel, we sorted and grouped responses by respondent expertise group (A to F). We then calculated raw counts and proportions of responses per response category within each question. This was performed separately for each respondent group (A to F). We then created an overall results display, mapping each response category per question against the quantity and percentage of respondents selecting the relevant response category. Subsequently, we created group-specific results sheets, sorted in descending order. We then conducted a series of data checks, ensuring accuracy in sorting and calculations. Finally, we created bar graphs to visualize the top 5 response categories per question item for each respondent group.

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Round 3

To maintain parallel construction with the round 2 survey, we organized the round 3 survey into three parts: part 1—barriers and burdens; part 2—strategies and solutions; and part 3—general, medical mistrust and participation thresholds. In parts 1 and 2, we presented the general questions first, and the subgroup-specific questions (Black or African American and Latino populations, cisgender women, and transgender women) followed. As described in the previous section, the presented response choices were those selected by survey respondents in round 2 and analyzed for the third round. The response item wording also paralleled round 2, modified only according to the round 2.5 discussion (refer to *Hybrid Group Discussion* section).

In Qualtrics XM, panelists were first presented with a randomized response list, per question item, of each subgroup choice (A to F). To facilitate comparison across subgroups, each item was color-coded and displayed as a column in a table, per respondent group. Participants received information summarizing their group's responses in comparison with those of other groups. To generate consensus, they were instructed to consider the group-specific results before proceeding to ranking. They were then instructed to rank the pooled responses in order of descending importance (from most to least important). Participants ranked 5 answer choices for 2 questions on general barriers and solutions and 3 answer choices each for subgroup-specific questions.

We analyzed round 3 data in Microsoft Excel, first conducting quality checks, and then performing calculations. Per the branching in this round of the Qualtrics XM survey, this process consisted of first analyzing 6 separate datasets, one per group. For each, we calculated the mean value of each item's rank, per group (A to F). Given the need to recategorize participants who misclassified themselves into an incorrect group, this was done using stacked ranges. Once calculated, we then created separate worksheets per question item (Q1-Q10). Within each, we converted the average values back into ranks. We then displayed each group's rankings of each response item, from first to last place. In one case, where only miscategorized (and then reassigned) participants ranked a specific response option, we used counts, rather than averages, to determine rankings. Finally, we created stacked bar charts of the counts of the number of groups selecting each answer choice, from first to last place, for each question item.

Round 4

We organized the final survey into three parts, consistent with the previous round: part 1—barriers and burdens, part 2—strategies and solutions, and part 3—general. We asked the overall population questions first, followed by subgroup-specific questions (Black or African American and Latino populations, cisgender women, and transgender women). Participants also completed an open-ended summary section (refer to *Delphi Survey Progression* section).

In Qualtrics XM, participants viewed previous round survey results in 2 graphics per question: a color-coded bar graph indicating *how many* groups ranked each response choice, from first to last, and a data table displaying *how each group* (A to F) ranked each response choice, from first to last place. In part 1, participants were asked to rate, on a Likert scale, "how important do you believe each barrier is to address on a scale from 1 (equal importance to other items) to 9 (extremely important (highest priority))." In part 2, they were asked to rate, on a Likert scale, "how urgent do you believe each solution is to address on a scale from 1 (equal relative urgency) to 9 (extremely urgent [highest priority])." Scales were presented for each response item within each question.

Participants thus rated 5 answer choices for each of the 2 questions on general barriers and solutions, and 3 answer choices for each of the 6 subgroup-specific questions. Notably, per the prevalence of missing data and several tied responses, we dropped supplementary part 2 questions (Q5a, Q6a, Q7a, and Q8a), which asked participants to rate less frequently recommended solutions in the previous round.

As in previous iterations, we analyzed participant responses, first conducting quality checks, then calculations. After verifying existing PIDs on file, we sorted the dataset by respondent group (A to F), then calculated means and SDs for each numeric-response question item (Q1-Q8) response ratings. In Q1 and Q5, respondents rated 5 responses; in all other questions (Q2-Q4 and Q6-Q8), they rated 3 responses. We then sorted the transposed response lists to obtain a descending ratings list for each item. We performed these operations for the pooled response set and for each subgroup (A to F). We also highlighted the occurrences of tied ratings.

Next, we created combination line and bar charts for each barrier and solution category: overall participation, Black or African American and Latino populations, cisgender women, and transgender women. We represented each group's mean ratings via bar charts and the pooled responses as an average line, within each chart, thus showing both group-specific ratings and overall trends. Separately, we processed the open-ended responses (Q9-Q11), the latter of which is presented here (refer to *Results* section and Multimedia Appendix 1).

NGT: Hybrid Group Discussions

Between each survey round, Delphi panel results were reviewed by an independent group discussion with members referred by The Well Project, an HIV community organization focused on the needs of women, members of which represent the diversity of women living with or affected by HIV in the United States (Figure 1). The discussions were held via teleconference and moderated by a Well Project–affiliated consultant (BP). Participants filled out demographic information and reviewed the study information sheets. As a group, NGT participants reviewed a Microsoft PowerPoint presentation highlighting key survey findings from the previous survey round.

The in-between round 1 and round 2 discussion (round 1.5) centered on general participation issues specific to HIV cure research and ATIs, as well as issues specific to 2 populations of interest: cisgender women and transgender women. This discussion was split into 2 parts, each about 90 minutes in length. Seven participants were involved in the first part of the round 1.5 discussions, 6 of whom also participated in the second

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part. In round 1.5, participants were asked to review findings on barriers and solution to participation in HIV cure research, general and specific to women (cisgender women and transgender women), then select their top 3 to 4 choices. They also identified gaps in round 1 survey results—for example, discussion around "transphobia" (fear) as a barrier to participation expanded to include "transmissia" (hostility). Items emphasized during the in-between group discussion were marked with asterisks (*) in the round 2 survey.

The in-between round 2 and round 3 discussion (round 2.5) consisted of participants ranking their top 3 or 4 choices for top strategies to better engage cisgender women and transgender women in HIV cure research. Six participants reviewed responses from each of the survey respondent groups (A to F) during the 90-minute discussion. While overlap and variation existed, participants generally emphasized centering the study design on each group's specific needs, including prioritizing the meaningful involvement of people with HIV [44]. Insights from the hybrid group discussion led to rephrasing of 3 survey items (overall, cisgender women, and transgender women) to include the word "unique" in the round 3 survey.

Eight participants attended the final, hour-long, in-between round 3 and round 4 discussion (round 3.5). Participants first anonymously ranked strategies for engaging cisgender and transgender women in HIV cure research, then discussed overall and group-specific findings. Participants discussed the practical implementation of "true inclusion" for transgender women and the intersectional identities of cisgender women. They also shared feedback regarding the Delphi consensus-building process and the NGT, noting challenges in ranking and appreciation for a safe space to discuss transgender and cisgender identity.

Ethical Considerations

The hybrid Delphi consensus-building process was approved by the University of California, San Diego IRB (project #805348). All participants provided electronic informed consent before enrollment. Participation was voluntary, and panelists or NGT participants were informed of their right to decline or withdraw at any time without penalty. Data collected during the Delphi rounds and NGT discussions were deidentified before analysis to ensure participant confidentiality. No personally identifying information was retained. Participants received US $100 compensation per completed survey round, and an additional US $100 bonus for completing all 4 rounds, for a maximum of US $500 total. NGT participants were also compensated US $100 per discussion (US $200 for round 1.5 if they participated in both sessions). The funders and government officials who participated were not compensated. These procedures were approved by the IRB as part of the study protocol. To support transparency and completeness in reporting, this protocol has been mapped to the DELPHISTAR (Delphi studies in social and health sciences—recommendations for an interdisciplinary standardized reporting) reporting guidelines for Delphi studies [45].

Recruitment and Enrollment of Delphi Panel Members

Potential panelists received a link to our study website, which provided an overview of the Delphi process. The invitation materials explained the study purpose and expected time commitment (30-60 min per survey round). Panel recruitment lasted 7 weeks, from February 27, 2023, to April 14, 2023. The round 1 survey data collection lasted 4 weeks, from April 10, 2023, to May 9, 2023. Round 2 data collection lasted 6 weeks, from September 15, 2023, to October 20, 2023. Round 3 data collection lasted 6.5 weeks, from March 19, 2024, to May 3, 2024. Round 4 data collection also lasted 6.5 weeks, from July 10, 2024, to August 23, 2024.

We initially invited 85 potential panelists to participate in the Delphi consensus-building panel (Table 3). Of these 85, 58 (68%) accepted the invitation. One panelist later withdrew due to retirement. Of the remaining 57, 52 (91%) completed the round 1 survey. In round 2, 82% (46/56) completed the survey. In rounds 3 and 4, 86% (48/56) completed the survey (Table 4).

Table 3. Delphi panel enrollment (United States, 2023 to 2024).

Group	Group name	Invited (N=85), n (%)	Accepted (n=58), n (%)	Declined (n=12), n (%)	No response (n=14), n (%)	Accepted and withdrew (n=1), n (%)
A	Community experts and members	20 (24)	17 (29)	0 (0)	3 (20)	0 (0)
B	Biomedical researchers	13 (15)	9 (15)	2 (17)	2 (13)	0 (0)
C	HIV care providers	11 (13)	9 (15)	1 (8)	1 (7)	0 (0)
D	Funders and private industry members	14 (16)	7 (12)	4 (33)	3 (20)	1 (100)
E	Bioethicists, regulators, IRB[a] members	15 (18)	8 (14)	4 (33)	3 (20)	0 (0)
F	Individuals studying medical mistrust, medical racism, and community engagement	12 (14)	8 (14)	1 (8)	2 (13)	0 (0)

[a]IRB: institutional review board.

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Table 4. Number of invited and completed panelist surveys.

Group	Round 1			Round 2			Round 3			Round 4		
	Invited (n=57), n (%)	Completed (n=52), n (%)	Completion rate (%)	Invited (n=56), n (%)	Completed (n=46), n (%)	Completion rate (%)	Invited (n=56), n (%)	Completed (n=48), n (%)	Completion rate (%)	Invited (n=56), n (%)	Completed (n=48), n (%)	Completion rate (%)
A	17 (30)	17 (33)	100	17 (30)	16 (35)	94	17 (30)	15 (31)	88	17 (30)	15 (31)	88
B	9 (16)	8 (15)	89	9 (16)	5 (11)	56	9 (16)	6 (13)	67	9 (16)	5 (10)	56
C	9 (16)	9 (17)	100	9 (16)	9 (20)	100	9 (16)	9 (19)	100	9 (16)	9 (19)	100
D	6 (11)	4 (8)	67	5 (9)	4 (9)	80	5 (9)	4 (8)	80	5 (9)	4 (8)	80
E	8 (14)	7 (13)	100	8 (14)	6 (13)	75	8 (14)	7 (15)	88	8 (14)	8 (17)	100
F	8 (14)	7 (13)	88	8 (14)	6 (13)	75	8 (14)	7 (15)	88	8 (14)	7 (15)	88

Delphi Panel Demographics

For descriptive purposes, panelist demographic details are shown in Table 5. The panelists were generally concentrated in the west or northeast regions of the United States (Figure 2).

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Table 5. Demographic characteristics of the Delphi panel (United States, 2023 to 2024; n=54).

Characteristic	Panelists, n (%)
Gender identity	
Cisgender woman	34 (63)
Transgender woman	2 (4)
Cisgender man	15 (28)
Nonbinary or gender queer	2 (4)
Unknown	1 (2)
Sex assigned at birth	
Female	35 (65)
Male	19 (35)
Ethnicity	
Hispanic or Latino	7 (13)
Not Hispanic or Latino	46 (85)
Unknown	1 (2)
Race	
Asian	6 (11)
Black or African American	11 (20)
Mixed or other	3 (6)
Prefer not to answer	1 (2)
Unknown	1 (2)
White	32 (59)
Education level	
High school diploma or General Educational Development	1 (2)
College graduate	10 (19)
Master or equivalent	8 (15)
Doctorate or equivalent	35 (65)
US residence region	
Northeast	19 (35)
Southeast	8 (15)
Southwest	1 (2)
Midwest	2 (4)
West	23 (43)
Prefer not to answer	1 (2)
Number of years worked in the field (HIV research: 19.7 y)	
1 to 10	8 (15)
11 to 20	21 (39)
21 to 30	17 (31)
31 to 40	5 (9)
>41	2 (4)
Prefer not to answer	1 (2)
Number of years in HIV cure–related research (HIV cure research 7.9 y)	
0	9 (17)
1 to 5	13 (24)

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Characteristic	Panelists, n (%)
6 to 10	19 (35)
11 to 15	4 (7)
16 to 20	2 (4)
>21	4 (7)
Prefer not to answer	2 (4)
Unknown	1 (2)

Figure 2. Map of the Delphi participants across the United States (2023 to 2024).

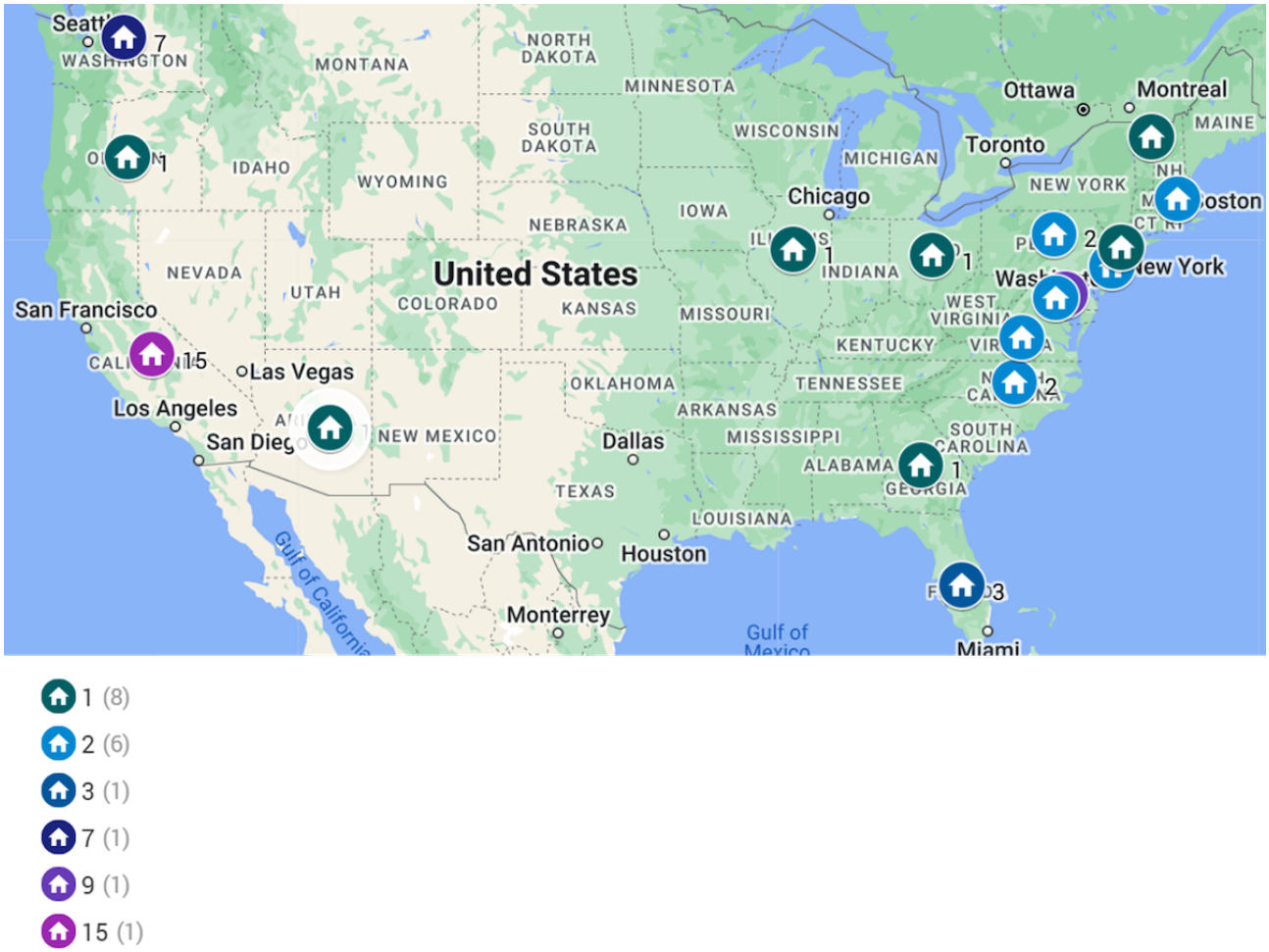

NGT or Hybrid Group Participant Demographics

Table 6 also lists the demographics of 8 participants who participated in the group discussions referred to by The Well Project.

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Table 6. Nominal group technique participants (n=8)—demographic characteristics (United States, 2023 to 2024).

Characteristic	Participants, n (%)
Gender identity	
Cisgender woman	6 (75)
Transgender woman	2 (25)
Sex assigned at birth	
Female	6 (75)
Male	2 (25)
Ethnicity	
Hispanic or Latino	1 (13)
Not Hispanic or Latino	7 (88)
Race	
Black	6 (75)
White	2 (25)
Highest level of education	
High school diploma or General Educational Development	1 (13)
Some college	4 (50)
College or above	2 (25)
Prefer not to answer	1 (13)
US region	
West	1 (13)
Southwest	2 (25)
Midwest	1 (13)
Southeast	1 (13)
Northeast	3 (38)
Occupation or field of work	
Public health	1 (13)
Cashier	1 (13)
Peer navigator	1 (13)
HIV and trans advocacy	3 (38)
HIV clinical work	2 (25)
Years involved or worked in the field of HIV	
0 to 5	3 (38)
6 to 10	1 (13)
11 to 15	2 (25)
16 to 20	2 (25)
Familiarity with the field of research	
Not at all familiar	1 (13)
Somewhat familiar	3 (38)
Moderately familiar	2 (25)
Very familiar	2 (25)

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Results

Delphi Survey Progression

The round 1 survey consisted of 35 free-response questions, organized in 3 topics: engaging underrepresented populations (20), general participation barriers and strategies (16), and medical mistrust (9). Within the first topic, 4 questions (reasons for lack of representation, barriers, recommendations for researchers, and strategies) were repeated for each of the 4 groups: Black or African American individuals, Latino individuals, cisgender women, and transgender women. For each topic, participants were also asked to consider solutions without restrictions on resources, as well as barriers to such solutions (Textbox 1).

Textbox 1. Delphi survey modules, by survey round, with the number of questions.

Round 1 (35 questions)

- Engaging marginalized groups (20 questions)
- Engaging all groups (16 questions)
- Medical mistrust (9 questions)

Round 2 (17 questions)

- Barriers and burdens (8 questions)
- Solutions and strategies (8 questions)
- Medical mistrust and required thresholds (3 questions)

Round 3 (14 questions)

- Barriers and burdens (4 questions)
- Solutions and strategies (8 questions)
- Required thresholds and summary (4 questions)

Round 4 (31 questions)

- Barriers and burdens (14 questions)
- Solutions and strategies (14 questions)
- Required thresholds and summary (3 questions)

In round 2, we consolidated items, halving the number of survey questions (to 17), and changing the question type, such that participants were asked to select from listed categories. We also amended the survey structure: rather than grouping by the original topics, we first presented all questions on barriers (generally and then for underrepresented groups), then on strategies, and finally on a summary section (views on required thresholds—yes, no, maybe, and why; and medical mistrust). As stated earlier, because responses indicated that the 2 groups faced very similar barriers to participation, we collapsed the Black or African American and Latino groups into one; we kept questions on cisgender women and transgender women separate, because responses indicated differences in barriers.

In round 3 (16 questions), we maintained the survey structure from round 2 and asked the participants to rank order the items they previously selected in round 2. In topic 1, we focused only on the more frequently reported barriers. In topic 2, we included supplemental questions for less frequently reported solutions. In topic 3, we expanded the question on required thresholds into a 3-part item, which included a “yes, no, and maybe” response, a free-text response, and a select one item. As noted, while participants were asked to rank the pooled survey results, they were also presented with group-specific response choices.

While we maintained the 3-part survey structure, we made notable revisions in the final survey round, resulting in 31 questions. In both part 1 (barriers and burden) and part 2 (solutions and strategies), we asked participants to assess the relative importance (Q1-Q4) and relative urgency (Q5-Q8) of each survey response item. We asked the participants to indicate their ratings using a 9-point Likert scale, where 1=equal relative importance or urgency and 9=extremely important or urgent (highest priority). Thus, each section was expanded to include 14 questions. Finally, we revised the summary section to include only open-ended questions. Having obtained sufficient data in round 3, we dropped the medical mistrust question. The required threshold question was only asked of respondents who had answered “maybe” or “no” to threshold use in the previous round. All participants were asked the 2 remaining summary questions.

Survey Panel Feedback

As we concluded our last survey round, we asked participants about their experiences as Delphi panelists. A total of 23 participants responded, mostly expressing positive feedback, although 5 highlighted potential areas of improvement (Multimedia Appendix 1). Participants noted that the Delphi consensus-building process was well organized and thought out. The participants were grateful to have been part of a study

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that valued community input and engagement. Many expressed hope that the study results would lead toward advancements in health equity and greater representation of underserved communities, not only in HIV cure–related research, but also in other fields. In reference to critiques, participants shared that the survey duration was quite long, especially in the first 2 rounds. Not only did survey completion seemed longer than anticipated, but some participants were also unaware that one could pause the survey and resume it at a later time. This caused some discontent among those who wanted to answer more thoroughly but felt constrained due to time limitations. Participants also noted some difficulties with having to rate strategies. At times, participants selected multiple strategies as "urgent"—instead of prioritizing one or the other—due to perceived equal importance.

NGT Implementation

In the first NGT meeting, participants openly vocalized their responses, which could have influenced others' responses. To address this, in the second discussion group, the facilitator instructed participants to type in their responses in the Zoom (Zoom Communications, Inc) chat to provide unbiased opinions before engaging in dialogue. In the final discussion group, they were asked to send their chat responses in private messages before discussing openly. Furthermore, our team facilitated a debrief session after the final NGT group. Overall, participants expressed satisfaction, stating how comfortable and safe they felt in sharing their responses. Participants emphasized the importance of continuing conversations around cisgender and transgender women's health; appreciated learning from one another; and valued how unifying and nondivisive the conversation felt. However, participants found it somewhat difficult to rank their top strategies and burdens. They shared feelings that solutions needed to occur as a systemic cascade, rather than highlighting just 1 or 2 strategic recommendations. Similarly, participants noted that impediments to participation may not be limited to 1 or 2 barriers; rather, the intersection between individual and systemic level barriers needed to be addressed.

Discussion

Anticipated Findings

This protocol is designed to yield consensus-driven recommendations informed by both experts and community perspectives on 3 persistent challenges in HIV cure–related research. We anticipate that the findings will offer practical, community-validated strategies to improve equity in trial design, particularly by clarifying how representation, trust, and trial accessibility can be addressed in ATI-inclusive protocols. Given the hybrid Delphi-NGT structure, we also expect insights on how participatory approaches can strengthen consensus-building efforts in ethically complex research domains. This methodology may be transferable to other fields, including oncology, reproductive health, or vaccine research, where inclusion, community engagement, and ethical complexity are similarly critical.

Advantages and Disadvantages of Hybrid Delphi Methodology

The Delphi methodology used in this study conferred several significant advantages. The iterative nature of the Delphi process, involving 4 rounds of surveys, allowed a systematic refinement of responses and a progressive convergence toward consensus around the topic of prioritizing key strategies to engage priority populations in HIV cure research. Initially, broad and open-ended questions facilitated a comprehensive exploration of challenges around the topic of barriers and then solutions to engage populations in this research, which were subsequently distilled into more focused queries as the Delphi consensus-building process progressed [38]. This approach ensured that the resultant consensus was grounded in a thorough and nuanced understanding of the issues surrounding HIV cure research participation. In addition, the recruitment strategy aimed to enhance the study's inclusivity and representativeness. By engaging a diverse panel of stakeholders, including members from underrepresented racial and ethnic groups, community experts, biomedical researchers, and HIV care providers, the study collected a wide range of perspectives. The intentional oversampling of racially and ethnically diverse participants further addressed critical representation gaps, ensuring that the findings reflected a broad spectrum of experiences and viewpoints. Finally, the hybrid design, incorporating feedback from an independent stakeholder group through the NGT, added robustness to the Delphi consensus-building process. This design allowed for the validation of data and the introduction of new insights, thereby mitigating potential biases and enhancing the reliability of the results. The structured nature of the NGT discussions also minimized the risk of dominant voices overshadowing less popular but important viewpoints, fostering a more balanced and comprehensive analysis [35].

Despite these advantages, several limitations of the Delphi methodology were evident. The reliance on online surveys, while facilitating wide geographical and disciplinary participation, may have introduced accessibility barriers for potential respondents, potentially limiting the diversity of input. The initial Delphi survey round was open-ended, and thus more onerous and time-consuming than the subsequent ones. In addition, the iterative rounds of the Delphi process, while beneficial for refining consensus, could have led to survey fatigue among participants, potentially affecting response quality and engagement over time. Another limitation was the potential for bias in the selection and recruitment of panel members. While efforts were made to ensure a diverse and representative panel, the initial sample size and recruitment strategy could have inadvertently excluded some key stakeholders. For instance, the predominance of participants from the west and northeast regions of the United States might not fully capture the perspectives of those from other geographic areas. Furthermore, the high level of education and professional experience among participants may not fully reflect the broader population's views, potentially skewing the findings toward more informed or specialized perspectives. Finally, the Delphi process' complexity and multiple feedback rounds presented challenges in data interpretation and synthesis [46]. The iterative surveys, while enabling a thorough exploration of perspectives

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on HIV cure research participation, also introduced variability in responses, complicating the interpretation and the consistency of consensus signals.

Lessons Learned

In categorizing the survey panel respondent groupings (eg, biomedical researchers vs bioethicists), we learned that the assigned categories were more porous than originally anticipated. As detailed throughout this paper, we divided the sample into 6 groups based on expertise. However, in the third survey round, 3 respondents whom we had categorized as medical mistrust experts (group F) self-identified as community experts and members (group A) and 2 HIV care providers (group C) self-identified as biomedical researchers (group B). While we corrected this by reassigning group membership in the analysis and restructuring subsequent round identification questions, we learned that additional communication with study participants around group membership designation was needed. Moreover, future studies can consider alternative approaches to panel member classification, including asking potential participants to self-identify.

Throughout the data collection period, we allowed multiple survey log-in attempts. In the initial survey round, incomplete entries totaled about a fifth of overall survey attempts; in successive rounds, these dropped to 1 or 2 cases per round. The change in survey format, from primarily open-ended to primarily close-ended questions, likely correlated with initial attempt completion. However, it is worthwhile to consider a single survey log-in to facilitate data processing. This would also serve to eliminate duplicate response entries, although these were not highly prevalent (4 cases in the initial round to 1 or 2 in ensuing surveys). Notably, we recommend communicating with participants regarding the need to save their progress and returning to complete before survey submission.

Previous work, on which our study was primarily modeled [37,38], incorporated “subsequent reduction” of content following initial round open-ended responses. However, in our study an expansion (in round 4) followed the reduction (in rounds 2 and 3). This was due to the change from a ranking of response options in relation to one another to a rating of each individual choice [47]. We did not find this expansion to increase respondent burden. In fact, the round 4 respondent feedback, describing the later rounds of the survey process, was generally positive. Earlier rounds were seen as more time-consuming than expected, which would need to be communicated better in future Delphi studies.

Retention

Our implementation of the Delphi hybrid methodology proved to be an effective means of participant retention over time. Despite some fluctuations, >80% of eligible participants completed each survey round. On the basis of the participant feedback, we can infer that the decrease in participant burden, as surveys shifted from primarily open-ended to primarily close-ended, facilitated renewed participant commitment. Notably, the final completion incentive for those who engaged in all 4 rounds may have also encouraged retention. The participants also commented that the survey reorganization—from subgroup-specific to orientation around challenges and solutions—allowed for simpler navigation. It is likely that the modality—online access through a popular survey application (Qualtrics XM)—also contributed to participant retention [37]. Similarly, survey respondents’ social ties to the investigative team and existing expertise in the topic matter may have also motivated intrinsic interest in survey completion.

Limitations

We acknowledge several limitations of our consensus-building process. First, recruitment through investigative team networks may have introduced sampling bias and limited the representativeness of the panel. While participant lists were reviewed by the study team to maximize diversity, this convenience sampling approach may affect reproducibility. Future studies could consider broader outreach or randomized strategies, although these may be more resource-intensive. Second, despite our efforts to ensure demographic diversity, like other hybrid Delphi studies [37,38], the panel was skewed toward highly educated, White, and female participants, with geographic clustering in the northeastern and western regions of the United States. Oversampling was used to address some gaps, but more structured quotas may help ensure even representation in future studies. Third, participant expertise levels varied, and some individuals reclassified their group affiliations midstudy. We corrected for this in later rounds, but future protocols may benefit from allowing participants to self-identify expertise from the outset. Fourth, although our 68% acceptance rate and our total sample size match what is usually expected in Delphi studies (around 60% to 80%), there is still a chance that people dropping out could affect the results. To help prevent this, we used strategies such as offering incentives, making the surveys easier to complete, and staying in direct contact with participants.

Conclusions

This protocol engaged 6 stakeholder groups to identify barriers to, and strategies for improving, the inclusion of underrepresented demographic groups in HIV cure–related research in the United States. The hybrid Delphi approach, integrating 4 rounds of structured surveys with NGT discussions, proved to be an effective and inclusive method for building consensus across diverse perspectives. Final analysis of consensus findings is underway and will be presented in a separate manuscript. These recommendations will also inform policy briefs, community reports, and presentations at HIV cure research forums. Our team is committed to disseminating these recommendations through academic and community channels to help inform more inclusive HIV cure trial design and implementation.

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Data Availability

Deidentified data, interview guide, and survey instruments used in this study are available upon reasonable request from the corresponding author.

Authors' Contributions

JS and KD are principal investigators of the study and oversaw all aspects of the design of the protocol and writing of this manuscript. AK led the design of the survey process and coled the group discussions and writing of these sections. LRG supported the survey design process and also coled group discussions and revising and writing those sections of this manuscript. BP led the discussion groups and reviewed and edited this complete manuscript. AA was responsible for supporting in the writing of all sections of this manuscript. JS and KD drafted the manuscript and completed all final editing.

Conflicts of Interest

KD provides advisory services to Gilead Sciences, Inc and AbbVie, Inc. All other authors declare no conflict of interest.

Multimedia Appendix 1
Supplementary tables.
[DOCX File , 16 KB - resprot_v14i1e67123_app1.docx]

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Abbreviations

ART: antiretroviral treatment
ATI: analytical treatment interruption
IRB: institutional review board
NGT: nominal group technique
PID: participant ID

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Authors' Reply: Enhancing Patient Support in Digital Inflammatory Bowel Disease Tools: The Need for Medication Guidance and Decision Support

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KEYWORDS

digital health; self-management; electronic medical records; quality of life; diet; mental health; inflammatory bowel disease; social determinants of health; implementation

Thank you for your thoughtful letter regarding our protocol for the MyIBDToolkit study [1,2]. We appreciate your insights from both a clinical and a patient advocacy perspective, which align with our core goal of creating a patient-centered tool that addresses the complexities of inflammatory bowel disease (IBD) care.

We agree that providing comprehensive, patient-specific medication guidance and responsive symptom-based support is crucial for effective self-management. MyIBDToolkit is designed to incorporate these features. The patient-facing tools in our protocol include questionnaires and flowsheets for tracking symptoms and a flare questionnaire that collects patient-reported data to inform responsive decision support. We recognize that decision support tools may help health care provider (HCP) adherence to protocols [3]. Still, we plan to evaluate how HCPs and patients use these tools before exploring the addition of more standardized decision support.

A key challenge with IBD medications is that they are highly individualized for each patient [4]. We have chosen to empower HCPs to manage medication messaging directly. With our tool, doctors can access and customize "smart phrases," or prewritten text templates, to provide precise instructions [5]. To balance the evolving nature of treatments with our capacity to update information, we've created a linked information page on our provincial health website https://myhealth.alberta.ca/HealthTopics/ibd/Pages/Inflammatory-bowel-disease-(IBD)-basics.aspx[6] that provides information on IBD medications and will be updated regularly under the oversight of a team of HCPs. The toolkit also includes mini self-management pathways that offer patients vetted resources for mental health and nutrition. We believe these will provide the self-care suggestions you recommend.

The HCP-targeted tools we are building, such as the "IBD Overview" and "IBD Navigator," are designed to standardize care and facilitate comanagement. This will ensure medication information is consistently recorded and visible to patients on their portal, which we believe may help reduce the information overload patients often feel after appointments.

We trust the feedback from our patient advisory council and physician advisory board to address any future gaps. We continually use their input to refine the MyIBDToolkit. The tiered, phased rollout of our study is designed to collect and analyze this feedback, informing subsequent iterations. We also acknowledge that building within our province's existing electronic health record system limits our ability to add certain features.

We are confident that by working closely with our patient partners and continuously improving the tool based on implementation metrics, we can create a comprehensive resource that improves health care use and empowers patients with the confidence to manage their complex condition.

Thank you again for your valuable feedback. It strengthens our resolve to create a truly impactful digital health solution for the IBD community.

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Conflicts of Interest

None declared.

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Abbreviations

HCP: health care provider
IBD: inflammatory bowel disease

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Enhancing Patient Support in Digital Inflammatory Bowel Disease Tools: The Need for Medication Guidance and Decision Support

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KEYWORDS

digital health; self-management; electronic medical records; quality of life; diet; mental health; inflammatory bowel disease; social determinants of health; implementation

With respect to the article "Developing and Evaluating a Bundled Digital Tool to Improve Complex Care and Self-Management of Patients With Inflammatory Bowel Disease: Protocol for a Hybrid Effectiveness-Implementation Study" [1], I wanted to raise a concern about one important area of patient support that I feel could be strengthened. While the protocol describes an app with potential to help patients manage their inflammatory bowel disease (IBD), I worry that its current design may not provide sufficient decision support in response to patient-reported symptoms.

As a training doctor with a special interest in IBD and digital health solutions, and as a former member of the young adults advisory board for a national IBD charity, I have seen the challenges from both a clinical and a patient advocacy perspective. In my medical training, I have encountered the complexity of modern IBD treatment, particularly the rapidly expanding use of biologics, and the barriers patients face in understanding and adhering to their medication plans. During my time on the advisory board, I listened to the experiences of young adults living with IBD who often felt overwhelmed by their treatment regimens, unsure where to find reliable information, and uncertain about what to do when symptoms changed.

These treatments are quite often complex. Biologics, immunomodulators, and combination therapies require strict adherence, careful monitoring, and awareness of possible side effects. While clinicians aim to cover these points in the clinic, patients may leave with only partial recall of what was discussed. Many turn to the internet for further information, where guidance can be inconsistent or inaccurate [2,3].

A thoughtfully designed IBD self-management app could close this gap by including a dedicated section tailored to each patient's prescribed medications. This section could clearly explain the purpose of each drug, how it works, how and when to take it, and potential side effects. For biologics, in particular, clear instructions on injection schedules, the importance of monitoring blood tests, and what to do if a dose is missed would be especially valuable [2].

Beyond static information, the app could also incorporate responsive decision support. If a patient reports worsening abdominal pain, new bleeding, or unusual fatigue, the app could offer evidence-based prompts such as adjusting self-care, reviewing medication timing, or seeking prompt medical advice [2,4]. This would not replace clinical decision-making, but it could help prevent deterioration, avoid unnecessary emergency visits, and improve patient confidence in managing their condition [4,5].

If these features are not included, the tool risks falling short of its potential, leaving patients without the personalized guidance they need for increasingly complex regimens. On the other hand, integrating clear medication information and responsive symptom-based guidance could improve adherence, strengthen patient-clinician communication, and ultimately lead to better outcomes [4,5].

In summary, I urge the developers and researchers to consider embedding comprehensive, patient-specific medication guidance, particularly for biologics. Responsive decision support should also be considered in this promising tool. These additions would make it a more complete, patient-centered resource, better equipping people with IBD to manage their condition effectively.

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Conflicts of Interest

None declared.

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Abbreviations

IBD: inflammatory bowel disease

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